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Functionalised alkynes as starting materials to build up valuable organic scaffolds

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Dottorando

Vincenzo Marsicano

Coordinatore del corso

Prof. Antonio Mecozzi

Tutor

Prof. Antonio Arcadi

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The work described in this thesis was carried out at:



DSFC – Dipartimento di Scienze Fisiche e chimiche
Laboratorio di Chimica Organica
Università degli studi dell'Aquila
L'Aquila, Italy



ICN – Institut de Chimie de Nice, CNRS UMR 7272
Equipe Arômes Parfums Synthèse et Modélisation
Université Côte d'Azur
Nice, France



Discovery Section R&D
Chemistry Laboratories
Dompé Farmaceutici S.p.A.
L'Aquila, Italy

Table of Contents

Abstract pag. 8

Chapter 1

Efficient synthetic strategies in organic chemistry

1.1 Multi-Bond Forming Transformations pag. 10
1.2 Microwave-Assisted Organic Synthesis pag. 11
1.3 Transition-metal catalysis pag. 13
1.3.1 Activation of alkynes by transition metals pag. 16

Chapter 2

Aim and outline of the thesis pag. 19

Chapter 3

Product selectivity control in the reaction of 2-alkynylanilines with unactivated carbonyl compounds

3.1 Introduction pag. 22
3.2 Results and discussion pag. 24
3.3 Conclusions pag. 35

Chapter 4

Brønsted acid-promoted reaction of β-(2-aminophenyl)-α,β-ynones with ketones for the synthesis of polycyclic quinolines

4.1 Introduction pag. 38
4.2 Results and discussion pag. 40
4.3 Conclusions pag. 48

Chapter 5

Domino reactions of β-(2-aminophenyl)-α,β-ynones with β-dicarbonyl compounds: divergent synthesis of polycyclic quinolines derivatives

5.1 Introduction pag. 50
5.2 Results and discussion pag. 52
5.2.1 Reaction with β-ketoesters – optimisation and substrate scope pag. 52
5.2.2 Reaction with β-diketones – optimisation and substrate scope pag. 56
5.3 Conclusions pag. 60

Chapter 6

Sequential reactions of β-(2-aminophenyl)-α,β-ynones with isocyanates/isothiocyanates

6.1 Introduction pag. 62
6.2 Results and discussion pag. 65
6.3 Computational investigation pag. 71
6.3.1 Reaction A pag. 71
6.3.2 Effects of the addition of silver cations pag. 73
6.3.3 Reaction B pag. 74
6.4 Conclusions pag. 76

Chapter 7

Gold-catalysed regioselective hydration of phthalimido-protected propargylamines: experimental and computational investigation

7.1 Introduction pag. 78
7.2 Results and discussion pag. 80
7.3 Computational investigation pag. 85
7.4 Conclusions pag. 89

Chapter 8

Gold/Selectfluor partnership in the divergent functionalisation of N-propargyl phthalimides

8.1 Introduction pag. 92
8.2 Results and discussion pag. 93
8.3 Conclusions pag. 100

Chapter 9

Water as reaction medium in the palladium-catalysed hydroarylation of ynamides with arylboronic acids

9.1 Introduction pag. 102
9.2 Results and discussion pag. 104
9.3 Conclusions pag. 110

Chapter 10

Design and synthesis of phenyl thiazoles as potential TRPM8 antagonists

10.1 Introduction pag. 112
10.1.1 Medicinal chemistry of TRPM8 channels pag. 113
10.1.2 TRPM8 antagonists developed by Dompé Farmaceutici S.p.A. pag. 115
10.2 Aim of the work pag. 116
10.3 Results and discussion pag. 119
10.4 Conclusions pag. 128

Concluding remarks pag. 129

Chapter 11

Experimental Section

11.1 General information pag. 132

11.2 Product selectivity control in the reaction of 2-alkynylanilines with unactivated carbonyl compounds pag. 133

11.2.1 Preparation and characterisation of 2-alkynylaniline **1r** pag. 133

11.2.2 Preparation and characterisation of 2,2,3-substituted-2,3-dihydroquinolin-4(1*H*)-ones **10aa-10le** pag. 134

11.2.3 Preparation and characterisation of quinolines **11mb-11qe** pag. 142

11.2.4 Preparation and characterisation of quinolines **11aa-11rd** pag. 144

11.2.5 Preparation and characterisation of 1-*N*-alkenyl indoles **12aa-12sd** pag. 146

11.3 Brønsted acid-promoted reaction of β-(2-aminophenyl)-α,β-ynones with ketones for the synthesis of polycyclic quinolines pag. 148

11.3.1 Preparation and characterisation of β-(2-aminophenyl)-α,β-ynones pag. 148

11.3.2 Preparation and characterisation of polycyclic quinolines **18aa-18kd** pag. 150

11.4 Domino reactions of β-(2-aminophenyl)-α,β-ynones with β-dicarbonyl compounds: divergent synthesis of polycyclic quinolines derivatives pag. 159

11.4.1 Preparation and characterisation of β-(2-aminophenyl)-α,β-ynones pag. 159

11.4.2 Preparation and characterisation of 4*H*-pyrano[3,4-c]quinoline-4-ones **22aa-22pa** pag. 160

11.4.3 Preparation and characterisation of 4*H*-pyrano[3,4-c]quinolines **23aa-23ab** pag. 164

11.4.4 Preparation and characterisation of 4*H*-pyrano[3,4-c]quinolines in alternative alcoholic solvents pag. 168

11.5 Sequential reactions of β-(2-aminophenyl)-α,β-ynones with isocyanates/isothiocyanates pag. 169

11.5.1 Preparation and characterisation of 3,4-dihydroquinazolin-2(1*H*)-ones **35aa-35ha** pag. 169

11.5.2 Preparation and characterisation of **35ce** and **35c** pag. 175

11.5.3 Preparation and characterisation of benzoxazines **36aa** and **36da** pag. 176

11.5.4 Preparation and characterisation of benzo[*d*][1,3]thiazine **37aa** and **37la** pag. 178

11.5.5 Computational details pag. 179

11.5.6 X-ray crystallographic data pag. 179

11.6 Gold-catalysed regioselective hydration of phthalimido-protected propargylamines: experimental and computational investigation pag. 181

11.6.1 Preparation and characterisation of *N*-propargyl phthalimides **42a-n** pag. 181

11.6.2 Preparation and characterisation of ketones **43a-n** pag. 184

11.6.3 Preparation and characterisation of other miscellaneous derivatives pag. 188

11.6.4 Computational details pag. 190

11.7 Gold/Selectfluor partnership in the divergent functionalisation of *N*-propargyl phthalimides pag. 191

11.7.1 Preparation and characterisation of *N*-propargyl phthalimide **42l** pag. 191

11.7.2 Preparation and characterisation of α-fluoro ketones **48a-l** pag. 191

11.7.3 Preparation and characterisation of 1,2-diketones **49a, c, g, h** pag. 194

11.7.4 Preparation and characterisation of α,α-difluoro ketone **50a** pag. 195

11.8 Water as reaction medium in the palladium-catalysed hydroarylation of ynamides with arylboronic acids pag. 196
11.8.1 Preparation and characterization of enamides **53aa-53hb** and **54aa-54hb** pag. 196
11.9 Design and synthesis of phenyl thiazoles as potential TRPM8 antagonists pag. 201
11.9.1 Synthetic procedures and characterisation of **V1** and **V2** pag. 201
11.9.2 Synthetic procedures and characterisation of **V3** pag. 203
11.9.3 Synthetic procedures and characterisation of **V4** pag. 204
11.9.4 Synthetic procedures and characterisation of **V5-V10** pag. 205
11.9.5 General procedure for the metal-free reaction between triflates and amine pag. 208

Abstract

The synthesis of organic compounds is of great interest nowadays, primarily because of their application in multiple fields, even in everyday life. A major concern, however, is the impact that organic synthetic methodologies may have on both environment and human health. Because of this, great effort has been devoted to the development of novel efficient synthetic strategies, with the concept of efficiency shifting from the only consideration of the overall yield to a much more complex definition, including also waste production, energy requirements, toxicity and hazard of chemicals used.

Alkynes are emerging as interesting building blocks in organic synthesis, thanks to their versatility and the ability to act as both nucleophiles and electrophiles, upon activation by Brønsted and Lewis acids. Moreover, the presence of proximal functional groups, such as carbonyl, amino and hydroxy groups, allows alkynes to undergo cascade one-pot reaction to generate complex organic architectures.

The present PhD work is centred on the use of alkynes, in particular nitrogen-containing alkynes, to access valuable organic scaffolds, using efficient synthetic strategies such as multi-bond forming reactions, microwave-assisted organic synthesis and transition-metal catalysis. Four different types of alkyne-containing substrates (2-alkynylanilines, β-(2-aminophenyl)-α,β-ynones, propargylamines and ynamides) have been successfully employed in the synthesis of valuable organic compounds that are expected to have potential applications in medicinal chemistry, material sciences or as intermediates in the synthesis of more complex organic compounds. Moreover, the synthesis of ten new potential TRPM8 antagonists has been carried out in collaboration with Dompé Farmaceutici S.p.A.; the project focused on the design of new phenyl thiazole derivatives and on the planning of the synthetic sequences to obtain them, with a particular attention on the improvement of already-planned strategies, especially in terms of reduction of wastes and sources of potential contamination of the final product. Moreover, the introduction of an alkyne moiety in the thiazole core enabled to access interesting new isocoumarin analogues.

Chapter 1

Efficient synthetic strategies in organic chemistry

Synthetic organic chemistry has progressed enormously since 20th century, so that there are virtually no limits to the type of molecules that can be generated. Indeed, the focus of research in this field has significantly shifted from the question 'can we synthetise this molecule' to the more contemporaneous one 'can we make it in an efficient way?'. The concept of efficiency in organic synthesis [1] is heavily influenced by overall yield and selectivity but, recently, also other parameters, such as waste production, energy requirements, toxicity and hazard of chemicals, are gaining importance. Thus, an efficient organic synthesis should be not only high yielding and selective, but also sustainable and friendly towards human health and environment. Many efforts have been done in the past decades to improve the sustainability of organic reactions, by developing new competitive synthetic methodologies. The ones used in this doctoral thesis will be shortly described in the following sections.

1.1 Multi-Bond Forming Transformations

The classical synthetic strategies used for the synthesis of organic scaffolds have always been based on the general concept of 'one bond at a time'. Nowadays this approach is no longer competitive, especially because the complexity of the organic structures that are being sought would force to plan lengthy and time-consuming sequences. Moreover, the need to isolate each intermediate results in high waste production, posing serious problems on how to deal with them. An easy way to improve the efficiency of synthetic pathways is the use of chemical processes that allow the creation of several covalent C-C and C-heteroatom bonds in a single chemical operation, the so-called Multi-Bond Forming Transformations (MBFTs). [2] In fact, the possibility to synthetise both simple and complex organic architectures from easily accessible building blocks using a single step is an attractive tool for synthetic chemists, minimising the production of waste, the amount of solvents, reagents and adsorbents used but also the cost of the overall procedure.

Three main types of MBFTs have been defined:

- Domino reactions;
- Consecutive reactions;
- Multicomponent reactions.

Domino reactions (also identified as tandem or cascade reactions) have been defined by Tietze as transformations involving the formation of two or more bonds under identical reaction

[1] Sheldon, R.A. *Chem. Soc. Rev*. **2012**, 41, 1437-1451.
[2] Green, N.J.; Sherburn, M.S. *Aust. J. Chem.* **2013**, 66, 267-283.

conditions, in which the latter reaction occurs at the functionalities obtained in the former bond forming event. [3] The quality and usefulness of these processes is determined by the number of bonds formed in a single step (bond-forming efficiency or economy), the increase in structural complexity in the products in comparison to the reagents and the suitability for a general application.

Consecutive reactions are transformations leading to the formation of multiple bonds in a single step but, unlike domino reactions, some kind of change in reaction conditions are required to complete the sequence. Such changes can be, for example, an increase in reaction temperature, the sequential addition of reagents or the change of reaction solvent. [4]

Finally, multicomponent reactions (MCRs) can be defined as the convergent combination of three or more reactants introduced simultaneously to form a single product, regardless of the mechanisms and protocols involved. [5] The first MCRs have been discovered in the 19th century (such as the Strecker, Hantzsch and Biginelli reaction) but are still in use, especially for the combinatorial synthesis of medicinal compounds.

1.2 Microwave-Assisted Organic Synthesis

Microwave-Assisted Organic Synthesis (MAOS) is emerging in recent years as an invaluable technique for promoting organic reactions and it is based on the use of microwave (MW) as a non-conventional heating source. MAOSs have several crucial advantages in comparison to reactions performed under conventional thermal heating (TH), such as a dramatic reduction of reaction times, higher yields and higher product purity. [6] Their first use in organic synthesis dates back to mid-1980s, when domestic MW ovens were used by a couple of pioneering research groups; since then, the introduction of modern MW reactors enabled the diffusion of this technology in both academia and industry so that nowadays synthetic transformations are more and more routinely carried out by MW heating.

MWs are a component of the electromagnetic spectrum, in the frequency range from 0.3 to 300 GHz. All MW ovens (both domestic and chemical reactors) operate at a frequency of 2.45 GHz to avoid interferences with telecommunications and cellular phone frequencies.

In comparison to traditional thermal heating, which is based on the conductive transfer of

[3] Tietze, L.F.; Brasche, G.; Gericke, K.M. *Domino Reactions in Organic Synthesis*. 1st ed, Wiley-VCH: Weinheim, **2006**.
[4] Tietze, L.F.; Beifuss, U. *Angew. Chem. Int. Ed. Engl.* **1993**, 32, 131.
[5] For selected examples, see: a) Insuasty, D.; Castillo, J.; Becerra, D.; Rojas, H.; Abonia, R. *Molecules* **2020**, 25, 505. b) Zhi, S.; Ma, X.; Zhang, W. *Org. Biomol. Chem*. **2019**, 17, 7632-7650. c) Ibarra, I.A.; Islas-Jácome, A.; González-Zamora, E. *Org. Biomol. Chem*. **2018**, 16, 1402-1418. d) Brauch, S.; van Berkel, S.S.; Westermann, B. *Chem. Soc. Rev*. **2013**, 42, 4948-4962.
[6] Kappe, O.C.; Stadler, A.; Dallinger, D. *Microwaves in Organic and Medicinal Chemistry*. 2nd ed, Wiley-VCH: Weinheim, **2005.**

energy from an external heating source, MW irradiation produces efficient internal heating and raises the temperature of the whole volume simultaneously (bulk heating). Moreover, since the materials used to fabricate reaction vessels are MW transparent, an inverted temperature gradient results compared to conventional thermal heating, with minimized wall effects (no hot vessel surface). [7]

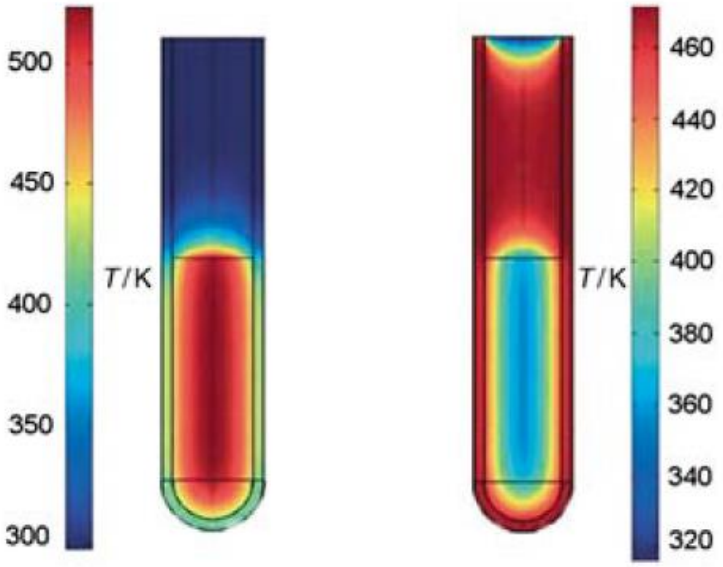


Figure 1.1 Difference in the temperature profiles after 1 min of microwave irradiation (left) and treatment in an oil bath (right).

The heating of materials determined by MW irradiation is caused by the electric component of the electromagnetic field by two distinct mechanisms, dipolar polarisation and ionic conduction. Dipolar polarisation describes the behaviour of polar compounds when irradiated by MW. In fact, for a substance to generate heat when irradiated with MW, it must possess a dipole moment (solvents such as CCl_4, benzene and dioxane are in fact more or less MW transparent due to lack of a permanent dipole). When exposed to MW, the dipoles of the sample irradiated tend to align themselves with the applied field through rotation; as the field oscillates, the dipoles attempt to realign themselves. Under very low frequencies, dipoles rotate in perfect phase with the electric field, while under the influence of high frequencies the dipoles do not have enough time to respond and so do not rotate; under MW irradiation, the frequencies are sufficiently low to enable the rotation but not in perfect phase. Because of this phase difference, energy is lost in the form of heat through molecular frictions and collisions. It should be highlighted that the interaction between MW radiation and polar solvents is not a quantum mechanical resonance phenomenon; transitions between quantised rotational bonds

[7] Kappe, O.C. *Angew. Chem. Int. Ed*. **2004**, 43, 6250-6284.

are not involved. On the contrary, ionic conduction describes the oscillation of the charged particles dissolved in the solvent that is being irradiated under the influence of the electric component of the electromagnetic field; while moving back and forth, these particles collide, liberating energy and causing heat. [8]

While the mechanisms causing heating of materials are well understood, the enhancement of chemical processes by MW irradiation is still a source of debate in the scientific community. Sometimes, in fact, the outcome of a reaction performed under MW irradiation differs from the conventionally heated counterpart at the same measured reaction time, especially in terms of rate, products distribution and by-products formation. To explain this, the existence of 'non-thermal MW effects' has been suggested. Essentially, these effects have been postulated to result from a direct interaction of the electric field with the molecules in the reaction mixture; for example, it has been proposed that, in reactions experiencing an increasing polarity going from the ground state to the transition state, the interaction of MWs with dipolar intermediates lowers the activation energy, resulting in an enhancement of reactivity. [9] The subject is, however, very controversial, with some of the earlier reports on the existence of these effects being not reproduced in later experiments. [10] Nowadays, it is generally agreed that in the vast majority of cases the observed improvements in MW-heated reactions are in fact the result of purely thermal/kinetics effects; in other words, they are the consequence of the heating profiles obtained during MW irradiation that are very different from those accessible by TH techniques. [11]

1.3 Transition-metal catalysis

Catalysis has gained a central role in modern synthetic chemistry: 90% of all commercial chemicals are produced, in fact, by methods that involve at least one catalytic step. [12]

Although known and used in organic chemistry since the 18th century, catalysis is still considered a hot topic in chemical research, especially because it has emerged as a valuable and efficient tool to achieve economical, energy-saving, environmentally benign and sustainable chemical processes. Indeed, a catalyst is used to increase the rate of chemical reactions by lowering the activation energy of the process, without being modified during the reaction. This latter feature enables the use of sub-stoichiometric amounts of catalysts and its

[8] Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, 57, 9225-9283.
[9] Perreux, L.; Loupy, A. *Tetrahedron* **2001**, 57, 9199-9223.
[10] Gedye, R.N.; Wei, J.B. *Can. J. Chem.* **1998**, 76, 525-532.
[11] de la Hoz, A.; Díaz-Ortiz, A.; Moreno, A. *Chem. Soc. Rev.* **2005**, 34, 164-178.
[12] Zhou, Q.-L. *Angew. Chem. Int. Ed*. **2016**, 55, 5352-5353.

recycling, improving enormously the sustainability of chemical processes, especially in terms of cost and consumption of natural resources.

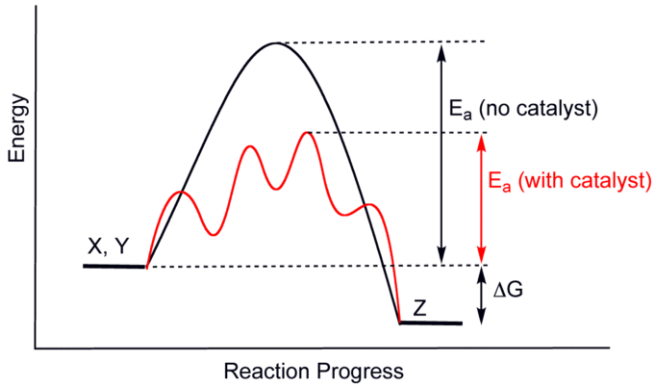


Figure 1.2 Comparison between a catalysed (red) and un-catalysed (black) reaction.

The use of transition metals and their complexes as catalysts has had a great impact on organic synthesis; thanks to their *d*-orbitals, these catalysts can activate various functional groups and accelerate reactions through coordination, ligand exchange, insertion and elimination.

Palladium complexes have been widely used in organic synthetic transformations thanks to their versatility, wide scope and high tolerance to many functional groups. The most versatile and useful application of palladium catalysts lies in cross-coupling reactions, [13] which enable to access highly valuable C-C and C-heteroatom covalent bonds through a general mechanism consisting of oxidative addition, transmetalation and reductive elimination. Since the first reports in 1970s, they have marked a revolution in synthetic organic chemistry and their success and popularity led to the attribution of the Nobel Prize in Chemistry in 2010. [14]

[13] Molnár, Á. *Palladium-Catalyzed Coupling Reactions. Practical Aspects and Future Developments*. Wiley-VCH: Weinheim, **2013.**

[14] Johansson Seechurn, C.C.C.; Kitching, M.O.; Colacot, T.J.; Snieckus, V. *Angew. Chem. Int. Ed*. **2012**, 51, 5062−5085.

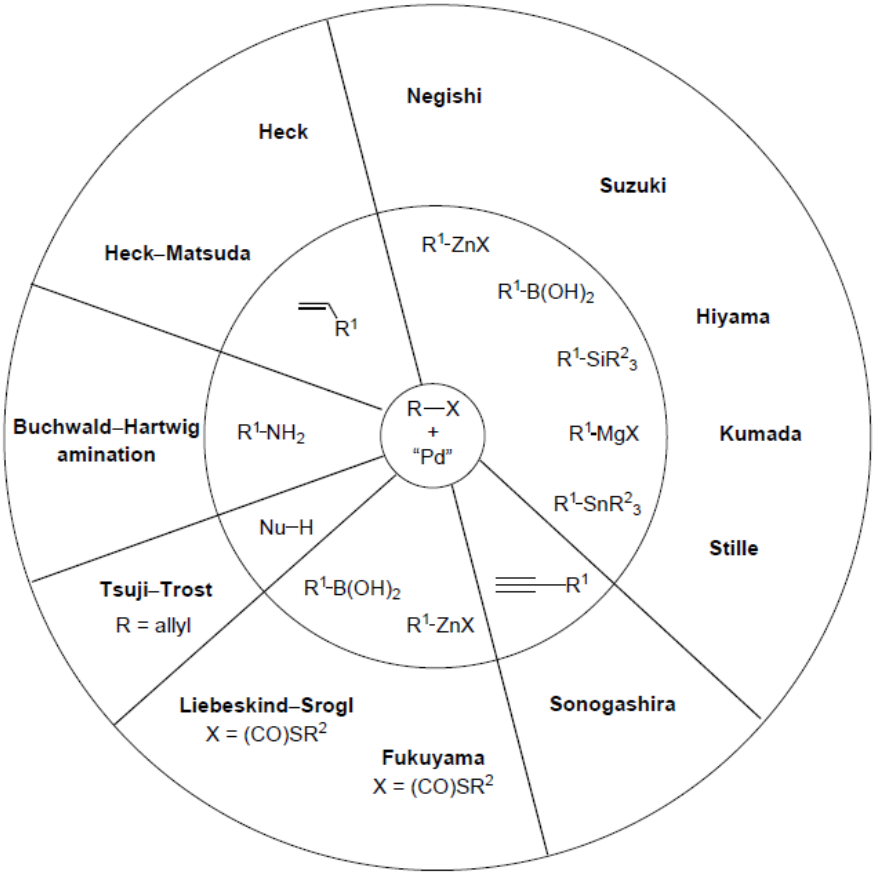


Figure 1.3 Overview of well-established Pd-catalysed cross-coupling reactions.

In recent years, palladium catalysis has also been efficiently applied in cascade reactions, opening new transformations with unexpected activation modes. [15] The almost total economy of these cascade processes and their applications in medicine, biology, agriculture and material sciences make this field very attractive and continuously expanding.

Despite having a shorter history in catalysis than palladium, gold has gained a comparative level of interest in organic synthesis thanks to its ability to activate C-C multiple bonds and C-H bonds of aromatic and heteroaromatic compounds. [16] In fact, although gold has been considered as a purely decorative inert metal for centuries, it has a peculiar reactivity whose origin lies in the relativistic effects; [17] in particular, the most interesting aspects of this metal are the π-Lewis acidity and the good potential to stabilise cationic reaction intermediates.

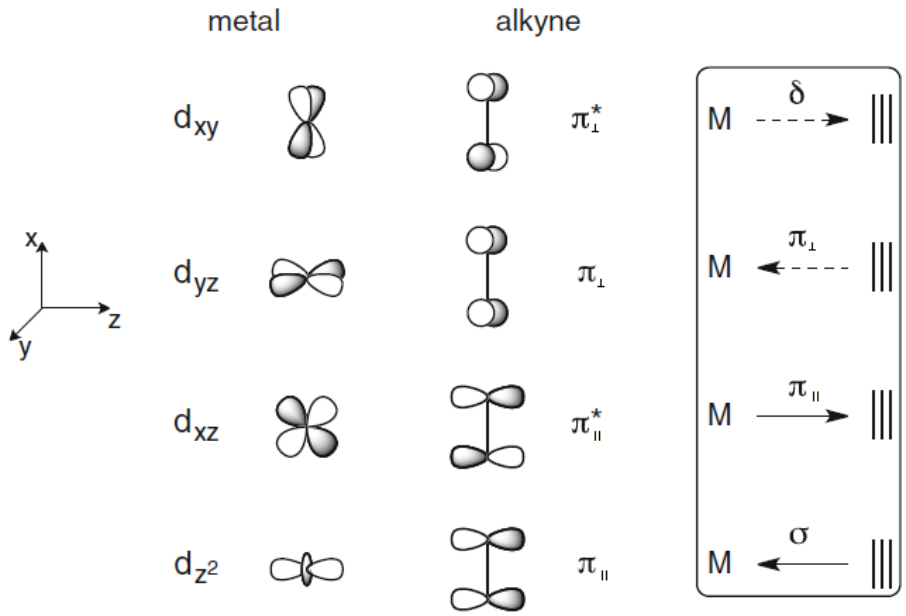
[15] For selected reviews, see: a) Döndaş, H.A.; de Gracia Retamosa, M.; Sansano, J.M. *Organometallics* **2019**, 38, 1828-1867. b) Biemolt, J.; Ruijter, E. *Adv. Synth. Catal.* **2018**, 360, 3821-3871. c) Ohno, H.; Inuki, S. *Synthesis* **2018**, 50, 700-710.
[16] For selected leading reviews, see: a) Meera, G.; Rohit, K.R.; Treesa, G.S.S.; Anilkumar, G. *Asian J. Org. Chem.* **2020**, *9*, 144-161. b) Zhao, X.; Rudolph, M.; Hashmi, A.S.K. *Chem. Commun*. **2019**, 55, 12127-12135. c) Harris, R.J.; Widenhoefer, R.A. *Chem. Soc. Rev*. **2016**, 45, 4533-4551. d) Zi, W.; Toste, F.D. *Chem. Soc. Rev*. **2016**, 45, 4567-4589. e) Rudolph, M.; Hashmi, A.S.K. *Chem. Commun*. **2011**, 47, 6536-6544. f) Bandini, M. *Chem. Soc. Rev*. **2011**, 40, 1358-1367. g) Arcadi, A. *Chem. Rev*. **2008**, 108, 3266-3325. h) Hashmi, A.S.K.; Hutchings, G.J. *Angew. Chem. Int. Ed*. **2006**, 45, 7896-7936.
[17] Pyykkö, P.; Desclaux, J.P. *Acc. Chem. Res.* **1979**, 12, 276-281.

In several types of transformations, gold has demonstrated better performances than other transition metals, especially in terms of robustness, selectivity and mildness of reaction conditions. Moreover, gold has the advantage of being non-toxic, further improving the sustainability of the chemical processes in which it is used. The only drawback is its cost and limited abundance on earth which are, however, better than those of other widely used transition metals (platinum, palladium, rhodium, exc.).

1.3.1 Activation of alkynes by transition metals

Alkynes can behave as both π-donors and π-acceptors, so they can interact with carbophilic transition metals resulting in activation towards novel reactivities. In catalysis, it is well accepted that transition metals behave as π-Lewis acids, interacting with π-systems in a side-on bonding mode. The bonding situation is generally described using the model of Dewar-Chatt-Duncanson (DCD). [18] Basically, the DCD model asserts that a σ bond is formed by overlap of the π-orbital of the ligand (alkyne) with an empty *d* orbital of suitable symmetry of the metal; a π bond then results through back-donation of electron density from a filled metal *d* orbital into an antibonding π* orbital of the alkyne. Although generally accepted as a good model to describe metal-alkyne complexes, much debate has been devoted to disclosing the influences of the single interactions on the overall bond. In fact, as depicted in Scheme 1.1, there are four couples of orbitals of different symmetry that overlap to form the complex, contributing differently to the final bond.

[18] a) Dewar, M.J.S. *Bull. Soc. Chim. Fr.* **1951**, 18, C71. b) Chatt, J.; Duncanson, L.A. *J. Chem. Soc.* **1953**, 2939-2947.



Scheme 1.1 DCD model for a metal-alkyne bond.

In-plane interactions (σ and $\pi_{||}$) between parallel orbitals are the strongest ones and represent the major contributions to the bonding situation, while the other two interactions ($\pi_\perp$ and δ) are weaker, because of a poorer overlap, and therefore lead to a minute contribution to the bonding. [19]

The model thus predicts a net shift of electron density from the bonding π orbital into the antibonding π* orbital of the alkyne; this, in turns, results in an elongation of the C-C multiple bond, with loss of linearity and planarity. Moreover, the loss of electron density from the bonding π orbital results in an increase of the electrophilicity of alkyne, triggering the anti-addition of nucleophiles. This is more pronounced for those metals (such as Au and Pt) behaving as soft Lewis acids; they experience, in fact, a weak back-donation to the ligand because of relativistic effects. [20] Upon complexation with the alkyne, they deprive the latter of a prominent part of its electron density generating a partial positive charge on it, as electron back-donation from the metal is poorly effective (although not negligible).

[19] Fürstner, A.; Davies, P.W. *Angew. Chem. Int. Ed*. **2007**, 46, 3410-3449.
[20] Nechaev, M.S.; Rayón, V.M.; Frenking, G. *J. Phys. Chem. A* **2004**, 108, 3134-3142.

Chapter 2

Aim and outline of the thesis

As already reported in **Chapter 1**, the field of organic chemistry has evolved enormously in the past decades, especially concerning the sustainable synthesis of valuable organic architectures. Due to their high versatility and potential, alkynes represent unvaluable tools for the efficient synthesis of a wide range of organic compounds; in particular, alkynes bearing proximal nitrogen atoms are of great help in the synthesis of nitrogen heterocyclic and non-heterocyclic organic compounds, which are highly sought due to their widespread presence in nature.

As part of the going interest in the synthesis of heterocycles by means of atom-economical methodologies and easily accessible starting materials, the aim of this doctoral thesis consists in the use of a variety of alkynes as useful building blocks to efficiently access valuable organic scaffolds. A great support to this aim has been represented by the combination of the use of the aforementioned alkynes as starting building blocks with more sustainable synthetic strategies such as multi-bond forming reactions, transition metal catalysis and microwave-assisted organic synthesis.

In the first part of this work (**Chapter 3**), the reaction of 2-alkynylanilines with cyclic and acyclic ketones has been explored under different reaction conditions. In a classical DOS-strategy, three distinct organic derivatives could be obtained by changing solvent or/and the catalyst. An extensive mechanistic investigation has been carried out in order to clarify the main factors affecting the product selectivity.

In the second part, β-(2-aminophenyl)-α,β-ynones have been reacted with electrophiles to generate complex heterocyclic structures in a one-pot fashion. The reaction with unactivated cyclic ketones yielded complex polycyclic quinolines under mild reaction conditions, enabling to access also linear and/or angular A-fused steroidal quinolines (**Chapter 4**). The extension of the methodology to β-dicarbonyl compounds allowed the synthesis of more complex polycyclic quinolones (**Chapter 5**). In particular, the *p*-TsOH-catalysed reaction with β-ketoesters gave access to 4*H*-pyrano[3,4-c]quinoline-4-ones in high yields, which are interesting for their structural similarity with natural-occurring alkaloids. On the contrary,

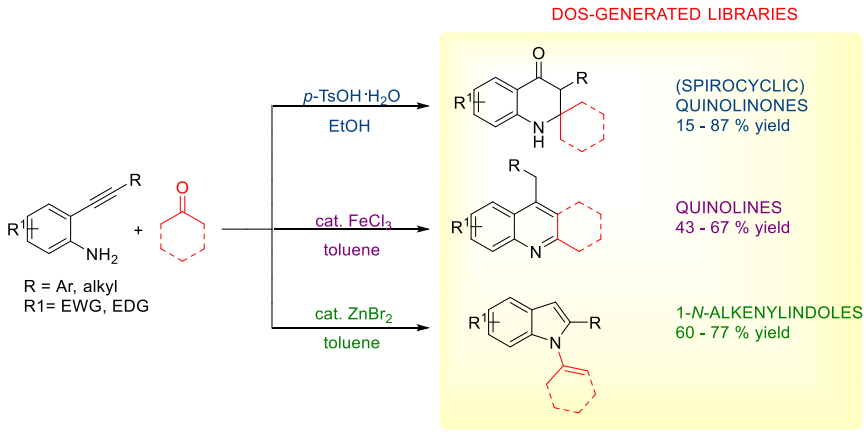
under the promotion of *p*-TsOH, β-(2-aminophenyl)-α,β-ynones and β-diketones underwent a three-component reaction to afford 4*H*-pyrano[3,4-c]quinoline derivatives which showed interesting fluorescent properties. Finally, the base-promoted tandem addition/cyclisation reaction of β-(2-aminophenyl)-α,β-ynones with aryl isocyanates/benzoyl isothiocyanate has been explored under different reaction conditions, to divergently give quinazoline, benzoxazine and benzothiazine derivatives, respectively (**Chapter 6**).

During the six months spent as a visiting PhD Student at Institut de Chimie de Nice (ICN), Université Côte d'Azur, under the supervision of Prof. V. Michelet, the synthesis and the use of *N*-propargyl phthalimides as versatile building blocks in organic synthesis was explored. Firstly, the gold-catalysed hydration of these derivatives has been investigated as an alternative mild way to access valuable β-amino ketones (**Chapter 7**). Then, the well-known partnership between gold catalysts and Selectfluor was exploited to afford α-fluoro- and α,α-difluoro-β-amino ketones. The preliminary data of this latter work, still in progress, are reported in **Chapter 8**. Under the supervision of Prof. V. Michelet, the Pd-catalysed hydroarylation of ynamides in water was also investigated (**Chapter 9**). By a suitable choice of different phosphine ligands, it was possible to selectively isolate the whole panel of the corresponding regio- and stereoisomeric aryl enamides.

Finally, the results of the synthesis of new potential TRPM8 antagonists, carried out under the supervision of Dr. A. Aramini and Dr. G. Bianchini in the chemical laboratories of the Discovery Section of Dompé Farmaceutici S.p.A., in L'Aquila, are described. Ten new chemical entities have been designed and synthetised, with a special focus on how to reduce the use of metals in pharmaceutical industries and on how to increase the structural complexity of the obtained compounds by exploiting the reactivity of alkynes (**Chapter 10**). Some parts of the work carried out at Dompé Farmaceutici S.p.A. are not publishable in relation to the use of data protected by industrial secrecy, pursuant to current legislation.

Chapter 3

Product selectivity control in the reaction of 2-alkynylanilines with unactivated carbonyl compounds

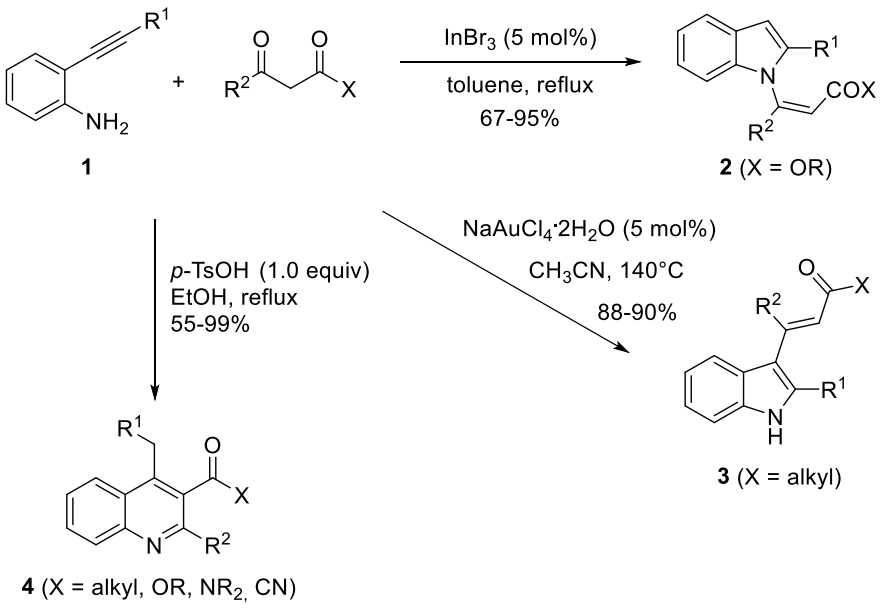


The reaction of 2-alkynylanilines with unactivated ketones was explored under different reaction conditions. In particular, challenging quinolin-4-one derivatives were easily prepared by using *p*-toluenesulfonic acid monohydrate as a promoter of the reaction in refluxing EtOH; the same starting materials gave the corresponding 4-substituted quinolines in Toluene at 110 °C, both in the presence of *p*-toluenesulfonic acid monohydrate as the promoter or $FeCl_3$ as the catalyst. The divergent formation of 1-*N*-alkenylindole derivatives occurred by switching to $ZnBr_2$ as the catalyst under the same reaction conditions. Conversely, only the 4-methylsubstited quinoline derivatives were isolated by reacting 2-ethynylanilines and/or 2-trimethylsylilanilines with ketones, regardless of the reaction conditions. A thorough mechanistical investigation was carried out to shed light on the major factors affecting product selectivity.

Marsicano, V.; Arcadi, A.; Chiarini, M.; Fabrizi, G.; Goggiamani, A.; Iazzetti, A. *Org. Biomol. Chem.* **2021**, 19, 421-438

3.1 Introduction

Cascade reactions of 2-alkynylanilines have recently emerged as an efficient strategy to easily access a wide panel of different N-containing heterocyclic scaffolds. Of particular interest are their reactions with carbonyl compounds; in fact, the enamine that forms *in situ* as intermediate during these reactions can be considerate as a pluripotent reactive species and, therefore, can be converted into several different types of compounds by finely modulating reaction conditions. Thus, the control of product selectivity in these reactions has gained a lot of attention and has been extensively used in the divergent synthesis of chemical libraries. For instance, the reaction of 2-alkynylanilines with activated carbonyl compounds, such as 1,3-dicarbonyls, has been used in the generation of both indoles and quinolines by exploiting both 5-endo-dig and 6-exo-dig cyclisation modes (Scheme 3.1).



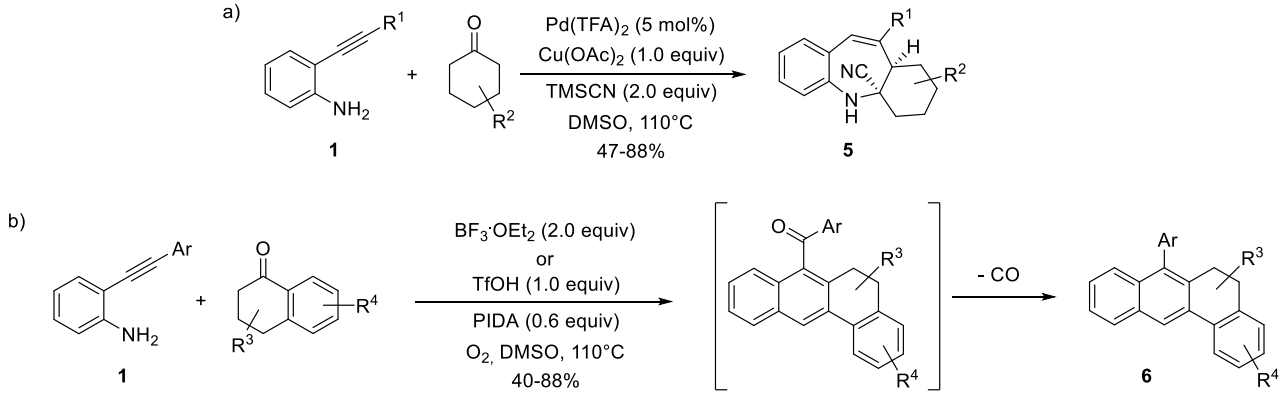
Scheme 3.1 Divergent behaviour of 2-alkynylanilines with activated carbonyl compounds.

By using $InBr_3$ as catalyst, Fujioka and co-workers generated *N*-alkenylindoles **2** by reacting 2-alkynylanilines with β-ketoesters. The products are always obtained with the double bond in Z-geometry, suggesting the involvement of an intramolecular hydrogen bond in the enamine intermediate directing the selectivity of the reaction. [21] On the contrary, the use of a more alkynophilic catalyst such as $NaAuCl_4{\cdot}2H_2O$ led to the regioisomeric 3-alkenyl-substituted indole scaffold **3**; in this case, the formation of enamine intermediate was obviously ruled out, envisaging a mechanism involving a 5-endo-dig cyclisation followed by the alkenylation

[21] Murai, K.; Hayashi, S.; Takaichi, N.; Kita, Y.; Fujioka, H. *J. Org. Chem.* **2009**, 74, 1418-1421.

reaction at position 3. [22] The 6-exo-dig cyclisation has been conversely obtained by using stoichiometric amounts of the Brønsted acid *p*-TsOH, generating 2,3,4-trisubstituted quinolines **4**, bearing at position 3 different types of acyl groups. [23] Interestingly, these reaction conditions were found to be incompatible with simple unactivated ketones, which failed to give the desired quinoline product.

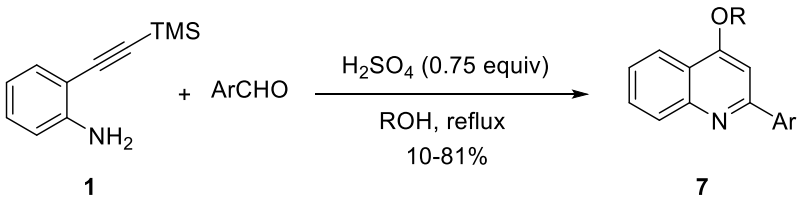
Simple ketones, such as cyclohexanone, have been successfully used in a Pd-catalysed multicomponent reaction in the presence of trimethylsilyl cyanide (TMSCN) as cyanating agent to form 1-benzoazepine carbonitriles **5** through 7-endo-dig cyclization of the *in situ* generated enamine intermediate (Scheme 3.2, a). [24] Later, the same research group developed an acid-promoted cyclisation reaction with unstrained ketones to generate polycyclic quinolines **6**; the addition of electrophilic N-iodo species such as phenyliodine(III) diacetate (PIDA) triggered a sequential aromatisation-induced decarbonylation reaction (Scheme 3.2, b). [25]



Scheme 3.2 Cascade reaction of 2-alkynylanilines **1** with unactivated ketones.

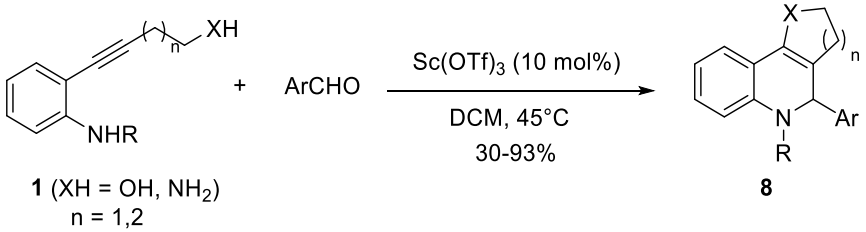
Aldehydes have been used too to convert 2-alkynylanilines in a plethora of different organic architectures. For example, Wang et *al*. have developed a sulfuric acid promoted condensation of 2-[2-(trimethylsilyl)ethynyl]anilines **1** with arylaldehydes in alcoholic solvents to generate 4-alkoxy-2-arylquinolines **7** (Scheme 3.3). The presence of the TMS-group was found to be fundamental for the reaction, which has been proposed to occur *via* formation of a cyclic vinylic cation that is later quenched by the solvent. [26]

[22] Arcadi, A.; Alfonsi, M.; Bianchi, G.; D'Annibale, G.; Marinelli, F. *Adv. Synth. Catal.* **2006**, 348, 331-338.
[23] Peng, C.; Wang, Y.; Liu, L.; Wang, H.; Zhao, J.; Zhu, Q. *Eur. J. Org. Chem.* **2010**, 818-822.
[24] Dhandabani, G.K.; Mutra, M.R.; Wang, J.-J. *Adv. Synth. Catal.* **2018**, 360, 4754-4763.
[25] Dhandabani, G.K.; Shih, C.-L.; Wang, J.-J. *Org. Lett.* **2020**, 22, 1955-1960.
[26] Wang, Y.; Peng, C.; Liu, L.; Zhao, J.; Su, L.; Zhu, Q. *Tetrahedron Lett.* **2009**, 50, 2261-2265.



Scheme 3.3 Brønsted acid promoted reaction of 2-[2-(trimethylsilyl)ethynyl]anilines **1** with arylaldehydes.

The same strategy has been used to generate polycyclic scaffolds by trapping the vinylic cation with extra nucleophilic functionalities of the 2-alkynylaniline reagent (Scheme 3.4). [27]



Scheme 3.4 Formation of tricyclic scaffolds by intramolecular trapping of the *in situ* formed vinylic cation.

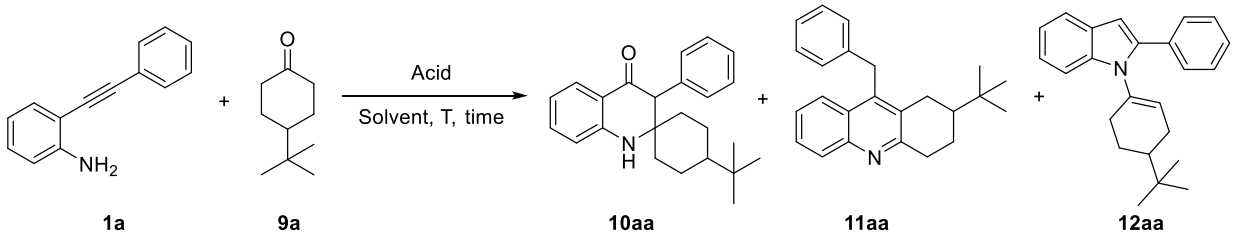
Intrigued by the possibility to divergently generate multiple organic scaffolds form the same reagents by simply changing reaction conditions, the reaction of 2-alkynylanilines **1** with unactivated ketones **9** has been explored, with particular emphasis on the study of the factors affecting product selectivity. Diversity-oriented synthesis (DOS) of N-heterocycles from simple nitrogenated starting materials is still an important challenge in organic synthesis, especially from the point of view of operational simplicity and assembly efficiency. [28]

3.2 Results and discussion

The reaction of 2-(phenylethynyl)aniline **1a** with 4-(*tert*-butyl)cyclohexan-1-one **9a** was explored as model reaction with the aim to depict the role of solvents, catalysts and temperature on the control of product selectivity. The results are reported in Table 3.1.

[27] Zhu, C.; Ma, S. *Angew. Chem. Int. Ed.* **2014**, 53, 13532-13535.
[28] a) Gerry, C.J.; Schreiber, S.L. *Curr. Opin. Chem. Biol.* **2020**, 56, 1-9. b) Mortensen, K.T.; Osberger, T.J.; King, T.A.; Sore, H.F.; Spring, D.R. *Chem. Rev.* **2019**, 119, 10288-10317. c) Pavlinov, I.; Gerlach, E.M.; Aldrich, L.N. *Org. Biomol. Chem.* **2019**, 17, 1608-1623. d) Kidd, S.L.; Osberger, T.J.; Mateu, N.; Sore, H.F.; Spring, D.R. *Front. Chem.* **2018**, 6, 460.

Table 3.1 Optimisation of the reaction conditions for the condensation of **1a** and **9a.**



1a **9a** **10aa** **11aa** **12aa**

Entry	Acid (equiv.)	Solvent	T (°C)	Time (h)	Yield[a] (%) 10aa	11aa	12aa
1	*p*-TsOH·H_2O (1.0)	EtOH	80	8	70	-	-
2	*p*-TsOH·H_2O (0.2)	EtOH	80	24	52	-	-
3	TFA (1.0)	EtOH	80	6	15	-	-
4	HI (1.0)[b]	EtOH	80	5	65	-	-
5	HCl (1.0)[c]	EtOH	80	5	38	-	-
6[d]	AcOH (1.0)	EtOH	80	24	-	-	-
7	TfOH (1.0)	EtOH	80	24	52	22	-
8	*p*-TsOH·H_2O (1.0)	CH_3CN	80	6	15	-	-
9	*p*-TsOH·H_2O (1.0)	EtOH/H_2O (1:1)	80	6	44	-	-
10[d]	*p*-TsOH·H_2O (1.0)	EtOH	rt	24	-	-	-
11[d]	*p*-TsOH·H_2O (1.0)	EtOH	40	24	41	-	-
12[e]	HCl (1.0)[c]	CH_3CN	80	6	-	-	-
13	*p*-TsOH·H_2O (1.0)	Toluene	110	24	22	54	-
14	$FeCl_3$ (0.2)	Toluene	110	24	-	60	5
15	$ZnBr_2$ (0.2)	Toluene	110	6	-	-	62
16	$NaAuCl_4 \cdot 2H_2O$ (0.05)	Toluene	110	3	-	-	36
17	$NaPdCl_4$ (0.05)	Toluene	110	6	-	-	12
18	$CuBr_2$ (0.1)	Toluene	110	8	-	-	34
19[d]	AgOTf (0.05)	Toluene	110	8	-	-	10

Reaction conditions: 1a (0.5 mmol) and **9a** (0.5 mmol) were dissolved in the chosen solvent (2 mL). The reaction was stirred at rt-110°C for 3-24 h. [a)] Isolated yield. [b)] The 55% HI aqueous solution was used. [c)] The 37% HCl aqueous solution was used. [d)] **1a** was recovered unreacted. [e)] 1-(2-aminophenyl)-2-phenylethan-1-one (**13a**) was the major product (44% isolated yield), together with 2-(1-chloro-2-phenylvinyl)aniline (39% yield).

Based on the data reported in literature, the exploration was started by using Brønsted acids as promoters. Interestingly, in contrast with the previously reported results, when the reaction of **1a** and **9a** was performed in refluxing ethanol with *p*-TsOH as promoter, the only obtained product was 4-(*tert*-butyl)-3'-phenyl-1'*H*-spiro[cyclohexane-1,2'-quinolin]-4'(3'*H*)-one **10aa**

in good yield (Table 3.1, entry 1). It should be remarked that it has been previously reported that simple ketones were unable to react with 2-alkynylaniline derivatives in the presence of *p*-TsOH·H_2O as the promoter in ethanol. [23] The use of catalytic amounts of *p*-TsOH·H_2O resulted in a lower yield and in a prolonged reaction time (Table 3.1, entry 2), suggesting that stoichiometric amounts of the Brønsted acid are fundamental to efficiently promote the formation of **10aa**. Worst results were obtained with trifluoroacetic, hydrochloric, acetic and trifluoromethanesulfonic acids while the use of hydroiodic acid resulted in a yield comparable with that obtained with *p*-TsOH·H_2O (Table 3.1, entries 3-7). The effect of temperature was investigated too, with the reaction being completely unsuccessful at room temperature and only moderately successful at 40°C (Table 3.1, entries 10-11). The solvent played a crucial role in the formation of **10aa**, as demonstrated by the fact that lower yields were obtained when switching to less polar solvents such as acetonitrile and toluene (Table 3.1, entries 8 and 13); moreover, the addition of water as cosolvent did not improve the yield of **10aa** but, on the contrary, worsened the outcome of the reaction since it promoted the undesired regioselective hydration of **1a** to 1-(2-aminophenyl)-2-phenylethan-1-one **13a**, which was isolated in 19% yield (Table 3.1, entry 9).

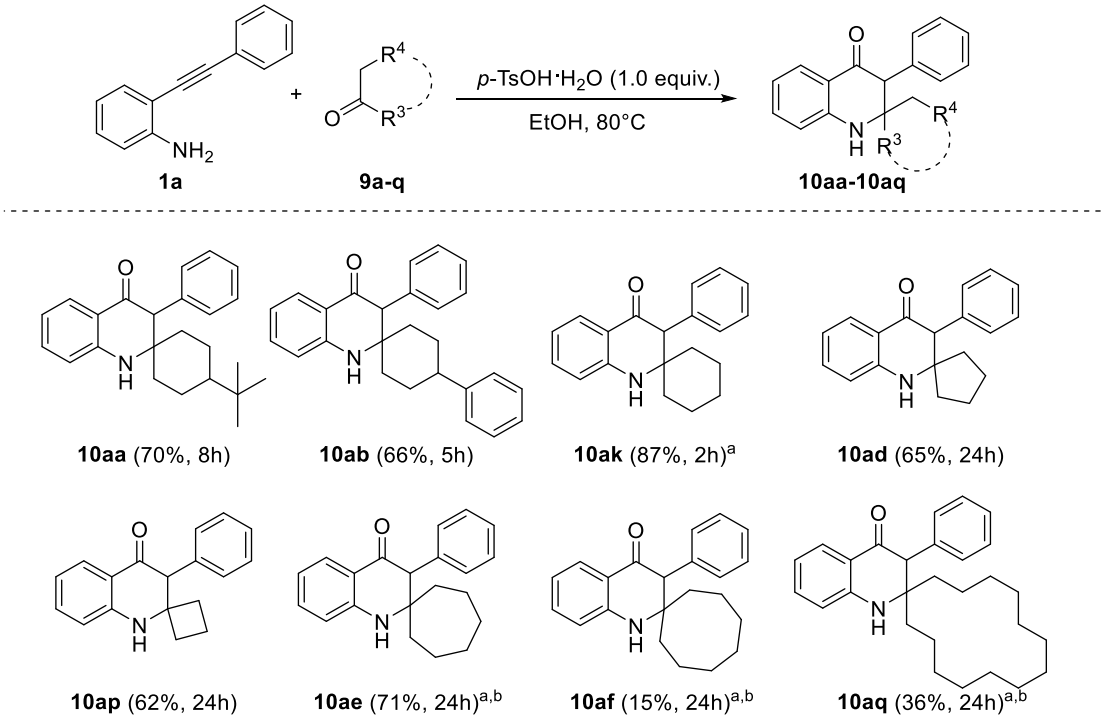
The solvent showed to have an influence not only on the yield of **10aa** but also on product selectivity; in fact, when the reaction was performed with *p*-TsOH·H_2O in toluene, quinoline **11aa** was isolated as the major product (Table 3.1, entry 13). In order to explore this alternative cyclisation mode, several Lewis acids were tested, disclosing an interesting pattern: when using strong σ acids, such as $FeCl_3$, the quinoline **11aa** was the compound predominantly obtained (Table 3.1, entry 14); in contrast, when using π acids, the 5-endo-dig cyclization mode of the *in situ* formed enamine intermediate prevailed, with formation of the *N*-alkenyl indole **12aa** (Table 3.1, entries 15-19). Interestingly, when using alkynophilic π acids as catalyst, 2-phenylindole **15a**, derived from the intramolecular hydroamination reaction of **1a,** has always been isolated as a by-product. [29]

Having found the optimised reaction conditions for the synthesis of the three different scaffolds, the scope and limitations of the methodology have been explored. Using *p*-TsOH·H_2O in refluxing ethanol (Table 3.1, entry 1), the unprecedented Brønsted-acid mediated sequential imination/annulation of 2-alkynylanilines **1a** with ketones to generate valuable 2,2,3-functionalised-2,3-dihydroquinolin-4(1*H*)-ones **10** has been extensively studied. Noteworthily, these compounds have very interesting pharmacological properties: in

[29] The yields of the 2-phenylindole by-product **15a** were 25% when using $ZnBr_2$, 10% when using $CuBr_2$, 39% when using $NaAuCl_4{\cdot}2H_2O$ and, finally, 10% when using $NaPdCl_4$.

general, the hydroquinoline scaffold has been frequently used in medicine as anticancer, antibacterial and antimalarial agent; [30] moreover, spiro junctions are highly sought in medicinal chemistry as an efficient way to introduce conformational rigidity in a molecule [31] and multiple marketed drugs feature this structural motif, such as Irbesartan, Drospirenone and Spironolactone.

Firstly, the influence of the nature of the carbonyl compound on the reaction was investigated by reacting cyclic commercial ketone **9a-q** with **1a**, as reported in Scheme 3.5.



Scheme 3.5 Substrate scope of the of the *p*-TsOH·H_2O promoted reaction of **1a** with different cyclic ketones **9**. [a)] 2 equiv. of ketone were used in the reaction. [b)] The corresponding quinoline was isolated as co-product.

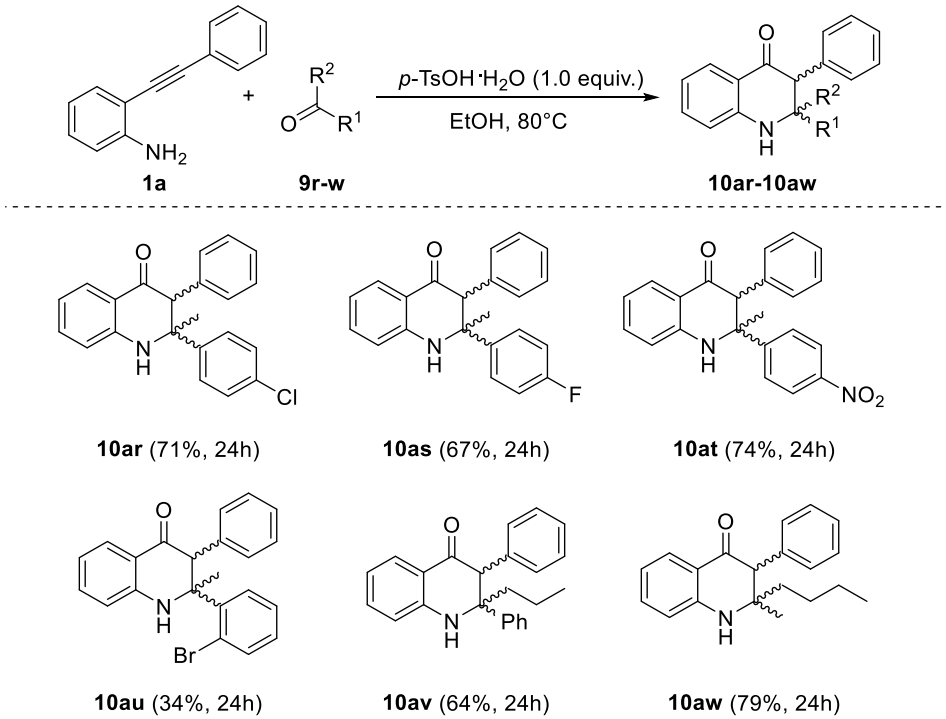
Cyclic ketones of different nature were tolerated, affording the 2-spirofused-quinolin-4(1*H*)-ones **10aa-10aq** from low to high yields. The results of the investigation show that the outcome of the transformation is strongly influenced by the dimension of the ring of the ketone reagent; in general, an increase in the size of the ring translates in poorer yields and selectivity. Indeed, when the reaction is performed using cycloheptanone (**9e**), cyclooctanone (**9f**) and cyclopentadecanone (**9q**), the corresponding quinolin-4(1*H*)-ones were isolated in very low yields; the use of two equivalents of the corresponding ketone resulted in an improvement of

[30] For selected examples, see: a) Ma, Y.; Zhu, Y.; Zhang, D.; Meng, Y.; Tang, T.; Wang, K.; Ma, J.; Wang, J.; Sun, P. *Green Chem.* **2019**, 21, 478-482. b) Politanskaya, L.; Rybalova, T.; Zakharova, O.; Nevinsky, G.; Tretyakova, E. *J. Fluorine Chem.* **2018**, 211, 129-140. c) Gao, C.; Fan, Y.-L.; Zhao, F.; Ren, Q.-C.; Wu, X.; Chang, L.; Gao, F. *Eur. J. Med. Chem.* **2018**, 157, 1981-1095. d) Zhang, G.-F.; Zhang, S.; Pan, B.; Liu, X.; Feng, L.-S. *Eur. J. Med. Chem.* **2018**, 143, 710-723. e) Jiang, D. *J. Heterocyclic Chem.* **2018**, 55, 2003-2018. f) Kotha, S.; Panguluri, N.R.; Ali, R. *Eur. J. Org. Chem.* **2017**, 5316-5342. g) Rios, R. *Chem. Soc. Rev.* **2012**, 41, 1060-1074.

[31] Zheng, Y.; Tice, C.M.; Singh, S.B. *Bioorg. Med. Chem. Lett.* **2014**, 24, 3673-3682.

the yield, which has been more pronounced for **10ae** (from 50% to 71%) in comparison to **10af** (for which the yield did not change) and **10aq** (from 26% to 36%). At the same time, when using these macrocyclic ketones, the reaction appeared to be scarcely selective toward the formation of the spiro quinolin-4(1*H*)-one scaffold. In fact, in all three cases, the corresponding quinoline **11a** could be isolated, which resulted to be the major product in the reaction between **1a** and **9f**. [32] The formation of the quinoline scaffold can be easily imputed to a competing Friedländer reaction between the macrocyclic ketone and the product derived from the hydration of 2-alkynylanilines, which can easily take place in refluxing alcohol under the promotion of Brønsted acids. [33] Indeed, when the reaction between **1a** and **9f** was tested with 1 equivalent of hydroiodic acid in ethanol at 80°C, 1-(2-aminophenyl)-2-phenylethan-1-one (**13a**) was isolated in 27% yield together with quinoline **11af**, supporting the aforementioned hypothesis.

The developed procedure resulted to be even more versatile, as it could be successfully extended to acyclic enolisable ketones too, as reported in Scheme 3.6.



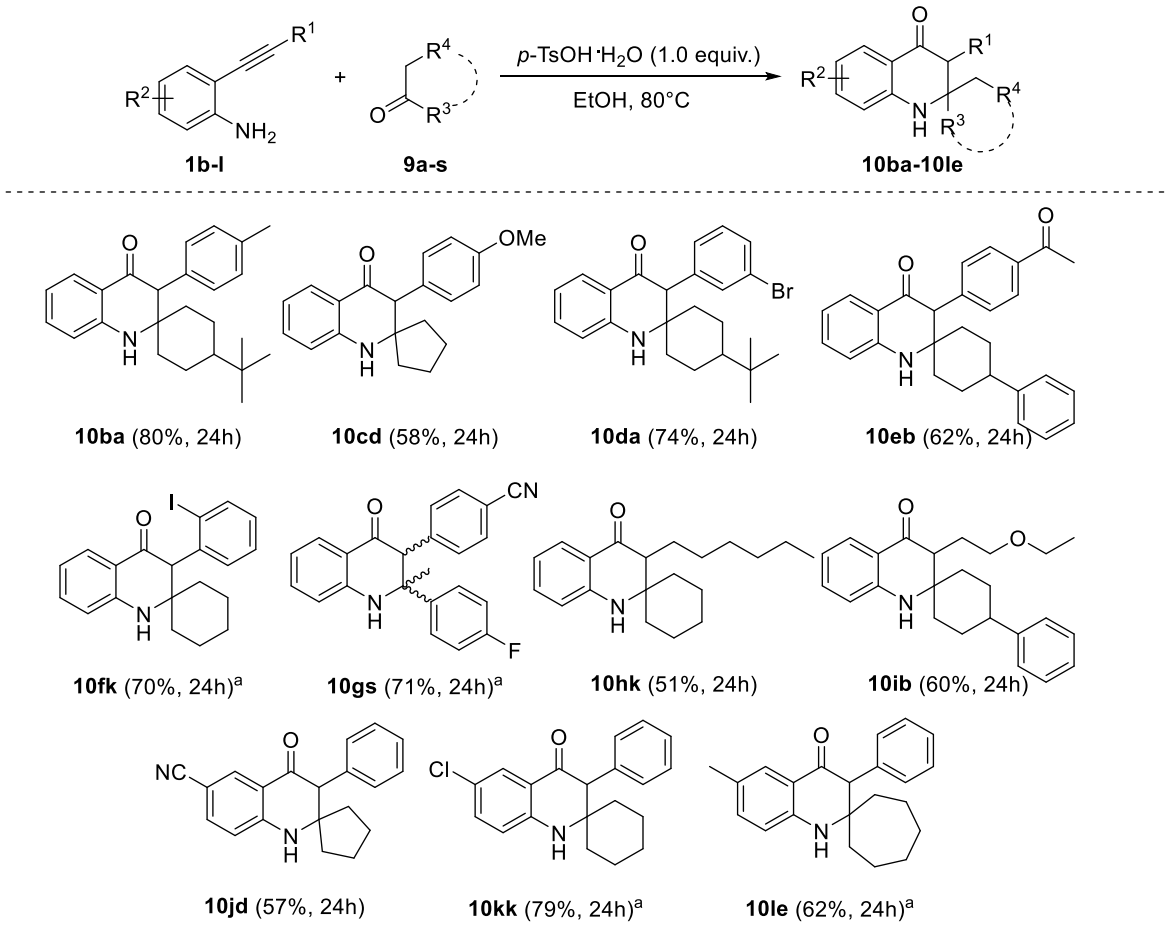
Scheme 3.6 Substrate scope of the of the *p*-TsOH·H_2O promoted reaction of **1a** with acyclic ketones **9**. The yields refer to the mixture of the two diastereoisomers, which were not separable through column chromatography (with the only exception of **10av**).

[32] The yields of the quinolines obtained under the reaction conditions optimised for the synthesis of 2,2,3-functionalised-2,3-dihydroquinolin-4(1*H*)-ones are: **11ae** (11-benzyl-7,8,9,10-tetrahydro-6*H*-cyclohepta[b]quinoline, 22%), **11af** (12-benzyl-6,7,8,9,10,11-hexahydrocycloocta[b]quinoline, 51%) and **11aq** (5-benzyl-7,8,9,10,11,12,13,14,15,16,17,18-dodecahydro-6*H*-cyclopentadeca[b]naphthalene, 29%).

[33] a) Lin, H.-P.; Ibrahim, N.; Provot, O.; Alami, M.; Hamze, A. *RSC Adv.* **2018**, 8, 11536-11542. b) Politanskaya, L.; Shteingarts, V.; Tretyakov, E.; Potapov, A. *Tetrahedron Lett.* **2015**, 56, 5328-5332.

Phenyl methyl ketones bearing different substituents on the phenyl ring were used and proved to be successful in affording the corresponding 2,2-disubstituted-3-phenyl-2,3-dihydroquinolin-4(1*H*)-ones in good yields. The only exception is represented by 2-Br-phenyl methyl ketone **9u**, which generated the dihydroquinolinone **10au** in a very poor yield, probably due to steric hindrance. The increase of the length of the alkyl chain, from methyl to propyl, determined only a slight decrease of the yield, while the use of a dialkyl-ketone such as hexan-2-one (**9w**) caused a more pronounced drop of the yield (but was still compatible with the developed methodology). All derivatives **10ar**-**10aw** have been isolated as unresolved diastereoisomeric mixtures.

After having screened different ketones, changes to the 2-alkynylaniline substrate were probed, as reported in Scheme 3.7.

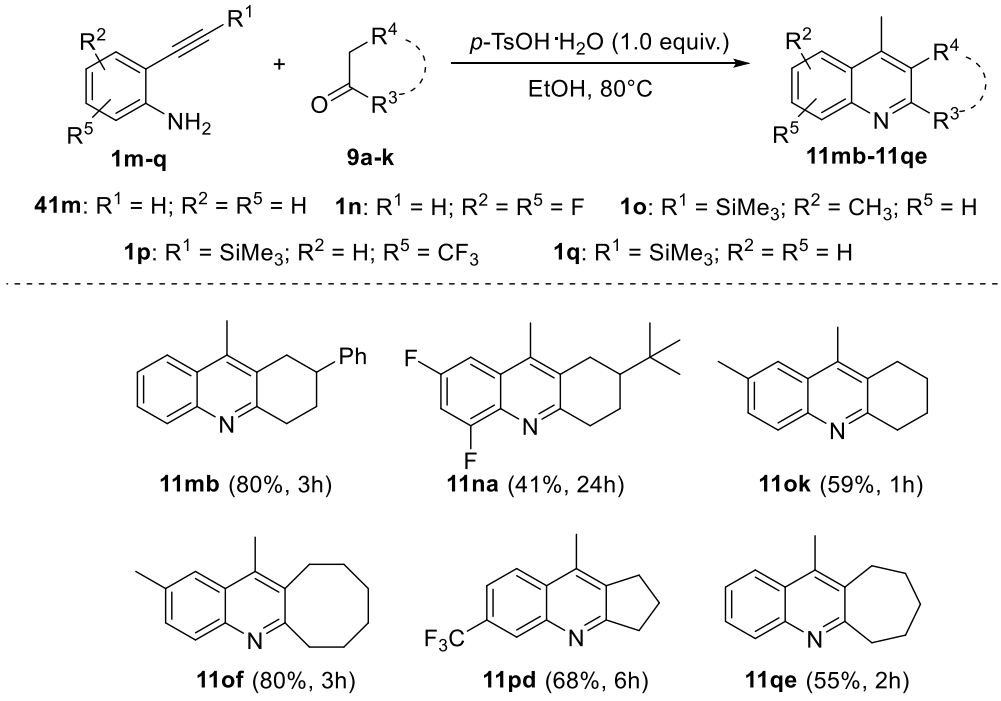


Scheme 3.7 Substrate scope of the of the *p*-TsOH·H_2O promoted reaction of different 2-alkynylanilines **1** with different cyclic ketones **9**. [a)] 2 equiv. of ketone were used in the reaction.

Satisfactory yields were obtained for all the tested 2-alkynylanilines **1b-l**, regardless of the feature of the R^1 substituent and its electronic nature. Phenyl rings bearing both electron-withdrawing and electron-donating groups in *ortho*, *meta* and *para* position were well tolerated (**1b-g**), as well as long alkyl substituents (**1h**, although with a slight decrease of

yield). Interestingly, the 4-(2-aminophenyl)but-3-yn-1-ol **1i**, bearing an extra OH nucleophilic functionality, afforded the quinolone **10ib** with an ethyl ether moiety in place of the hydroxy group, most probably because of the rapid reaction of the free OH group with the solvent ethanol under the optimised reaction conditions. This could explain why the expected poly-heteroannulation, previously reported in literature by Zhu, did not take place in this case. [27]

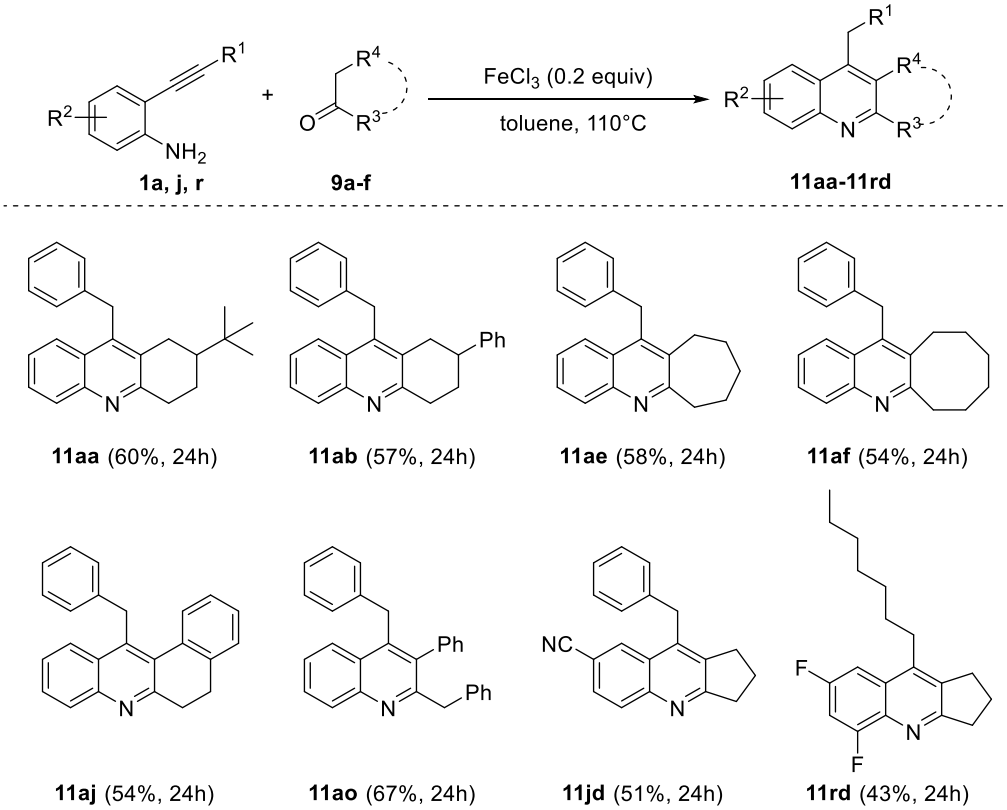
The influence of the nature of the substitution in the aniline ring of the starting 2-alkynylanilines was tested too, showing that even electron-withdrawing groups in *para* position to the amino group are compatible with the methodology. Useful functionalities, such as cyano, chloro and methyl group (**1j-l**) were thus included in the final quinolone derivatives. To fully assess the compatibility of different R^1 substituents on the reaction outcome, even 2-ethynylaniline (R^1 = H) and 2-(trimethylsilyl)ethynylaniline (R^1 = TMS) derivatives were investigated. As reported in Scheme 3.8 and in accordance with literature, only the corresponding 4-methyl quinoline derivatives **11mb-qe** were obtained, instead of the expected quinolinones, under the same reaction conditions, showing a first limitation of the developed methodology. [34]



Scheme 3.8 Results of the *p*-TsOH·H_2O promoted reaction of 2-ethynylanilines **1m-n** and 2-(trimethylsilyl)ethynylanilines **1o-q** with ketones **9**.

[34] The quinoline **11mb** has been isolated as the only product even when the reaction was performed in refluxing toluene, using $FeCl_3$ (0.2 equiv.) and $ZnBr_2$ (0.2 equiv.) as catalysts. In the first case, the isolated yield was 46% after 44h, while in the second one the yield was 40% after 5h of reaction.

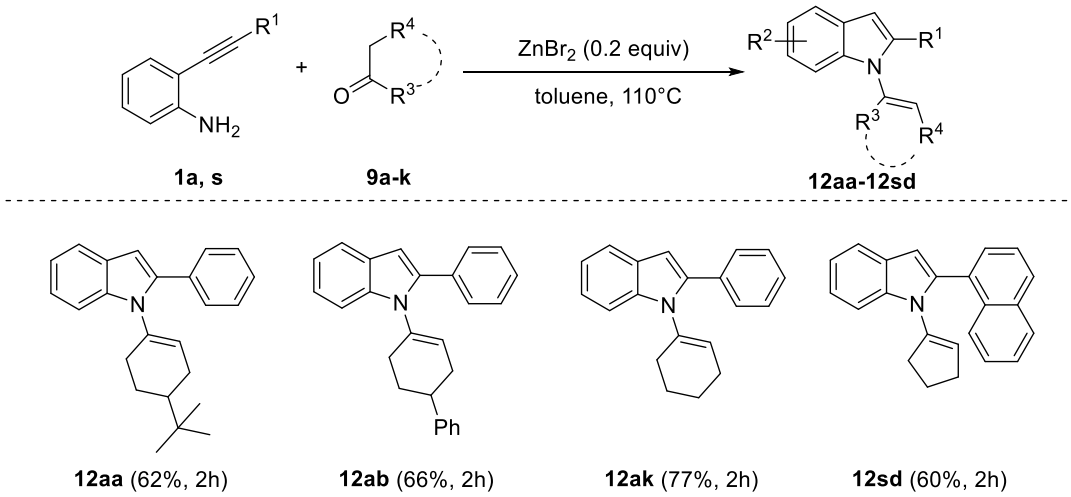
Starting from internal 2-alkynylanilines, the quinoline scaffold was also obtained using toluene as solvent and $FeCl_3$ (0.2 equiv.) as the catalyst (Scheme 3.9). The synthetic procedure appeared to be fairly versatile, being compatible with both cyclic and acyclic ketones and even with 2-alkynylanilines bearing electron-withdrawing groups (such as cyano and fluoro) in *ortho* and *para* positions to the nitrogen atom.



Scheme 3.9 Substrate scope of the $FeCl_3$-catalysed reaction of different 2-alknylanilines **1** with different ketones **9**.

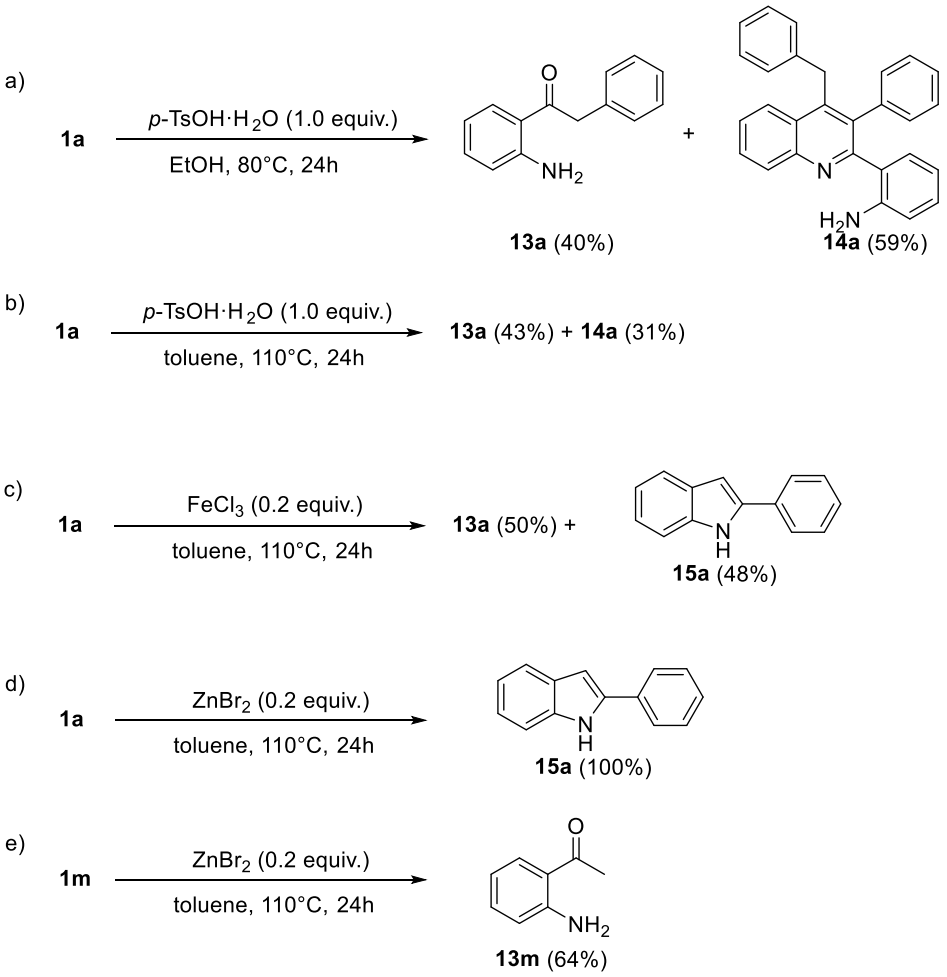
Keeping toluene as solvent but switching to $ZnBr_2$ as catalyst, the reaction of 2-alkynylanilines **1a** and **1s** with cyclic ketones **9a-k** resulted in a different amination/5-endo-dig cyclisation pathway leading to 1-*N*-alkenylindoles **12aa-12sd** in good isolated yields (Scheme 3.10). The use of zinc salts in heterocyclic synthesis, although rather unexplored, is very interesting, especially for large scale applications, because of their inexpensiveness, great abundancy, non-toxicity and eco-friendliness. [35]

[35] a) Ghobadi, M.; Qhazvini, P.P.; Kazemi, M. *Synth. Commun.* **2020**, 50, 3717-3738. b) Neetha, M.; Rohit, K.R.; Saranya, S.; Anilkumar, G. *ChemistrySelect* **2020**, 5, 1054-1070. c) Keerthi Krishnan, K.; Ujwaldev, S.M.; Saranya, S.; Anilkumar, G.; Beller, M. *Adv. Synth. Catal.* **2019**, 361, 382-404.



Scheme 3.10 Substrate scope of the $ZnBr_2$-catalysed reaction of 2-alkynylderivatives **1** with cyclic ketones **9**.

To gain some more information about the plausible reaction mechanism and to clarify the principal factors affecting product selectivity, control experiments were carried out, as summarised below in Scheme 3.11.



Scheme 3.11 Control experiments in the absence of the ketone reagent.

In the absence of the ketone reagent, 2-alkynylaniline **1a** underwent the hydration of the triple bond in the presence of *p*-TsOH·H_2O in both ethanol and toluene at reflux (Scheme 3.11, a and b), affording the 2-aminoaryl ketone **13a** in a comparable yield. Interestingly, in both cases, it was also possible to isolate the 2-(4-benzyl-3-phenylquinolin-2-yl)aniline **14a**, derived from the condensation reaction of the ketone **13a** with **1a**; the rate of the condensation reaction between the carbonyl and the primary amino group appeared, however, to be slower in toluene than in ethanol. [36] The hydration product **13a** was also obtained when the reaction was performed in refluxing toluene but in the presence of 0.2 equivalents of anhydrous $FeCl_3$ (Scheme 3.11, c). Very likely the amount of water contained in the commercial toluene was enough to determine the iron-catalysed hydration of the triple bond; at the same time, the ability of iron to activate the triple bond through a π-complex could explain the formation of 2-phenylindole **15a** in 48% yield. [37] The same derivative was isolated as the sole product and in quantitative yield when the reaction was performed with 0.2 equivalents of $ZnBr_2$, a much more alkynophilic Lewis acid than $FeCl_3$ (Scheme 3.11, d). Surprisingly, under the same reaction conditions, the terminal alkyne **1m** afforded only the hydration product 2'-amino-acetophenone **13m** (Scheme 3.11, e).

The data collected throughout the whole experimental investigation and literature reports helped to rationalise a plausible mechanism to account for the formation of the three scaffolds **10aa**, **11aa** and **12aa**, as summarised in Scheme 3.12. The cascade sequence starts with the amination reaction of **1a** with **9a** to generate the imine intermediate **A**; this reaction is efficiently promoted by Brønsted and Lewis acids, even if, for highly alkynophilic metal catalysts, the competing intramolecular hydroamination of **1a** becomes significant (as experienced especially with gold and palladium), strongly hindering the formation of **A**. The intermediate **A** is at equilibrium with its enamine tautomer **B**; the position of this equilibrium seems to be heavily influenced by the solvent in which the reaction takes place: polar solvents, such as ethanol, favour the tautomer **A** while with apolar solvents, such as toluene, **B** is the predominant form. The imine **A** is the only intermediate that can evolve to the spiroquinolone derivative **10aa**, most probably through a sequence consisting of *aza*-Prins reaction [38] with formation of the cyclic vinylic cation **C**, quenching by ethanol to generate **D** and,

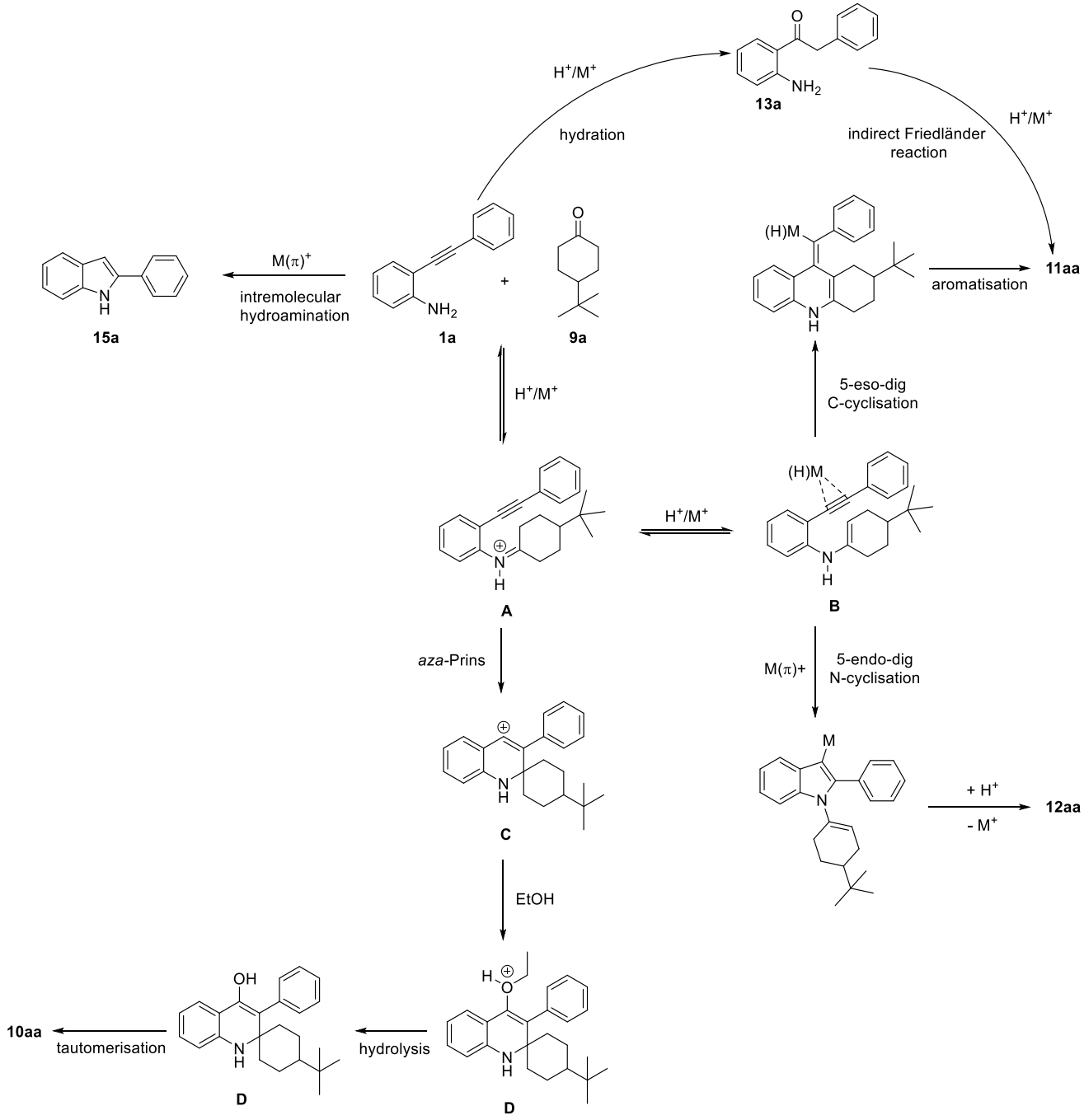
[36] a) Yaragorla, S.; Pareek, A. *Tetrahedron Lett.* **2018**, 59, 909-913. b) Jung, D.-I.; Song, J.-H.; Lee, E.-J.; Kim, Y.-Y.; Lee, D.-H.; Lee, Y.-G.; Hahn, J.-T. *Tetrahedron Lett.* **2009**, 50, 5805-5807.

[37] a) Terrasson, V.; Michaux, J.; Gaucher, A.; Wehbe, J.; Marque, S.; Prim, D.; Campagne, J.-M. *Eur. J. Org. Chem.* **2007**, 5332-5335. b) Michaux, J.; Terrasson, V.; Marque, S.; Wehbe, J.; Prim, D.; Campagne, J.-M. *Eur. J. Org. Chem.* **2007**, 2601-2603.

[38] Bai, J.-F.; Yasumoto, K.; Kano, T.; Maruoka, K. *Chem. Eur. J.* **2018**, 24, 10320-10323.

subsequently, hydrolysis and tautomerisation reactions to afford the quinolinone derivative **10aa**.

The intermediate **B**, conversely, is a bidentate nucleophile that can selectively generate two different derivatives: the indole derivatives **12aa** via a 5-endo-dig cyclisation or the quinoline **11aa** via a regio-divergent 6-exo-dig cyclisation. The cyclisation mode seems to be influenced by the nature of the catalyst used: σ acids favour the C-6-exo-dig cyclisation mode, with generation of the quinoline scaffold while π acids promote the N-5-endo-dig cyclisation that affords *N*-alkenylindoles.



Scheme 3.12 Proposed mechanism to account for the formation of **10aa**, **11aa** and **12aa**.

Even the features of the substituent bonded at the terminal position of the triple bond play a crucial role on the selectivity of the subsequent reaction path. In fact, while internal alkynes undergo all the pathways depicted in the Scheme above (depending on the solvent and the promoter used), terminal or TMS-substituted alkynes exclusively produce the corresponding quinolines in all cases. Moreover, the prevalent formation of the quinoline derivative for certain ketones (especially the macrocyclic ones) and for 2,4-difluoro-6-(oct-1-yn-1-yl)aniline **1r** in the conditions optimised for the formation of the quinolinone scaffold **10** could be easily explained by envisaging that, in the reported reaction conditions, the hydration reaction of the 2-alkynylaniline **1** is faster than the condensation reaction with the ketone**,** generating the corresponding 2-aminoaryl ketone **13** which leads to the formation of the quinoline derivatives via an indirect Friedländer-type reaction (Scheme 3.12, path a). [39]

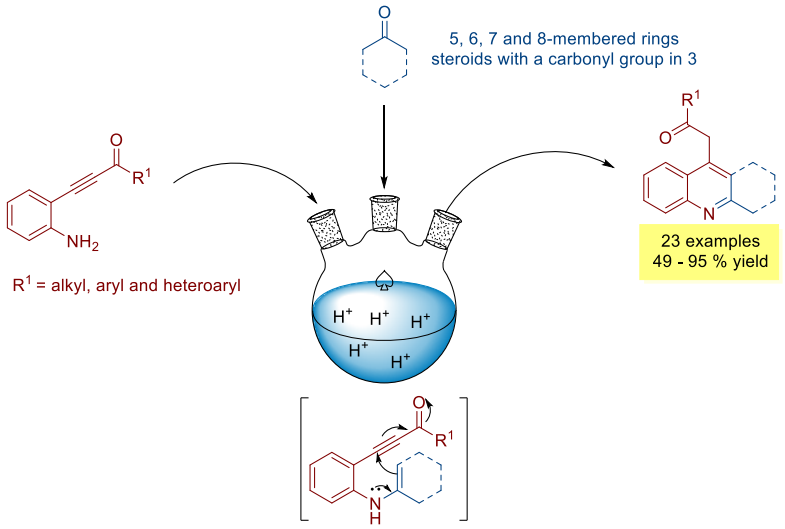
3.3 Conclusions

In conclusion, the reaction of easily accessible 2-alkynylaniline derivatives with commercially available ketones enabled to generate a structurally-variegate library of heterocyclic compounds through a Diversity-Oriented Synthesis approach. In particular, the use of *p*-TsOH·H_2O in refluxing ethanol allows the formation of challenging yet valuable 2,2,3-substituted-2,3-dihydroquinolin-4(*1H*)-ones. By simply switching from EtOH to toluene, the same starting reagents can selectively achieve the synthesis of polyfunctionalised quinolines *vs* the divergent formation of 1-*N*-alkenylindoles by a suitable choice of *p*-TsOH·H_2O or $FeCl_3$ *vs.* $ZnBr_2$ as promotors. On the contrary, only quinolines were isolated from the reaction of ketones with terminal alkynylanilines or with alkynylanilines bearing a trimethylsilyl group as substituent at the terminal position. The attentive examination of the experimental data also enabled to highlight the main features affecting product selectivity and enabled to propose a plausible mechanism accounting for the formation of all the derivatives. These novel synthetic protocols are expected to be of great use in the synthesis of the aforementioned scaffolds, particularly valuable in medicinal chemistry, because of their versatility, controllable selectivity and the use of readily accessible substrates and inexpensive promoters.

[39] a) Rahul, P.; Nitha, P.R.; Omanakuttan, V.K.; Babu, S.A.; Sasikumar, P.; Praveen, V.K.; Hopf, H.; Jubi, J. *Eur. J. Org. Chem.* **2020**, 3081-3089. b) Zhu, Y.; Cai, C. *RSC Adv.* **2014**, 4, 52911-52914.

Chapter 4

Brønsted acid promoted reaction of β-(2-aminophenyl)-α,β-ynones with ketones for the synthesis of polycyclic quinolines



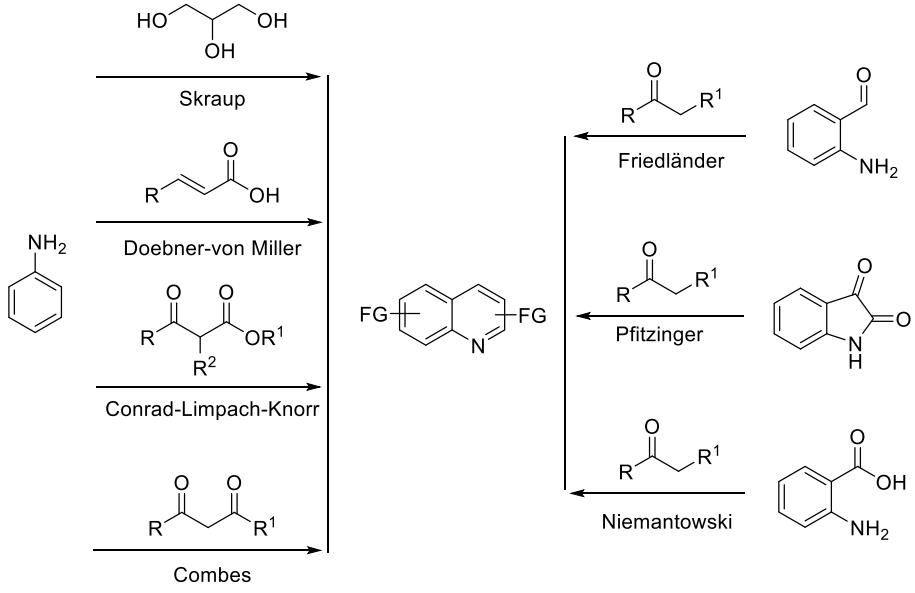
The synthesis of polycyclic quinolines was achieved by the acid-promoted reaction between β-(2-aminophenyl)-α,β-ynones and cyclic α-methylene carbonyl compounds through a tandem amination/annulation/aromatisation sequence. A wide range of quinolines was obtained in high yields by using reaction conditions that were milder than those classically used to generate the quinoline ring. The developed methodology tolerated different functional groups and is characterised by high regio- and chemo-selectivity. A-fused steroidal quinolines could also be easily obtained under the optimised reaction conditions, both as linear and angular isomers depending on the structural features of the starting substrate. The procedure is expected to find practical applications due to its operational simplicity and to the potential applicability of the generated compounds.

Marsicano, V.; Chiarini, M.; Marinelli, F.; Arcadi, A. *Adv. Synth. Catal.* **2019**, 361, 2365-2370.

4.1 Introduction

Quinoline derivatives represent an important class of organic compounds thanks to their multiple properties. Quinoline scaffold is widespread in nature as the central core of numerous chemical products belonging to the family of alkaloids; [40] moreover, it is a crucial pharmacophore in medicinal chemistry as it has been reported to possess several different pharmacological activities such as anticancer, antimalarial, antitubercular, antibacterial, anti-inflammatory, antifungal, antioxidant, antihypertensive, antiviral, exc. [41] Quinolines are also of great interest in material sciences thanks to their chelating abilities [42] and to their interesting optical and electronic properties. [43]

Because of its importance, a multitude of synthetic methods have been developed to construct the quinoline ring. The classical synthetic routes available include the Skraup, Doebner-von Miller, Conrad-Limpach-Knorr and Combes synthesis, using unsubstituted anilines as starting material, and the Friedländer, Pfitzinger and Niemantowski synthesis, using ortho-substituted anilines.



Scheme 4.1 Conventional methods to generate quinolines.

[40] Shang, X.-F.; Morris-Natschke, S.L.; Liu, Y.-Q.; Guo, X.; Xu, X.-S.; Goto, M.; Li, J.-C.; Yang, G.-Z.; Lee, K.-H. *Med Res Rev*. **2018**, 38, 775-828.

[41] For selected reviews on the biological properties of quinolines, see: a) Hu, Y.-Q.; Gao, C.; Zhang, S.; Xu, L.; Xu, Z.; Feng, L.-S.; Wu, X.; Zhao, F. *Eur. J. Med. Chem.* **2017**, 139, 22-47. b) Musiol, R. *Expert Opinion on Drug Discovery* **2017**, 12, 583-597. c) Afzal, O.; Kumar, S.; Haider, M.R.; Ali, M.R.; Kumar, R.; Jaggi, M.; Bawa, S. *Eur. J. Med. Chem.* **2015**, 97, 871-910. d) Keri, R.S.; Patil, S.A. *Biomed. Pharmacother.* **2014**, 68, 1161-1175. e) Mukherjee, S.; Pal, M. *Drug Discov. Today* **2013**, 18, 389-398.

[42] a) Chen, X.; Ma, Y.; Zhang, Y.; Chen, Q.; Wang, H.; Wang, Z. *ChemistrySelect* **2020**, 5, 4017-402. b) Reiersølmoen, A.C.; Fiksdahl, A. *Eur. J. Org. Chem*. **2020**, 2867–2877.

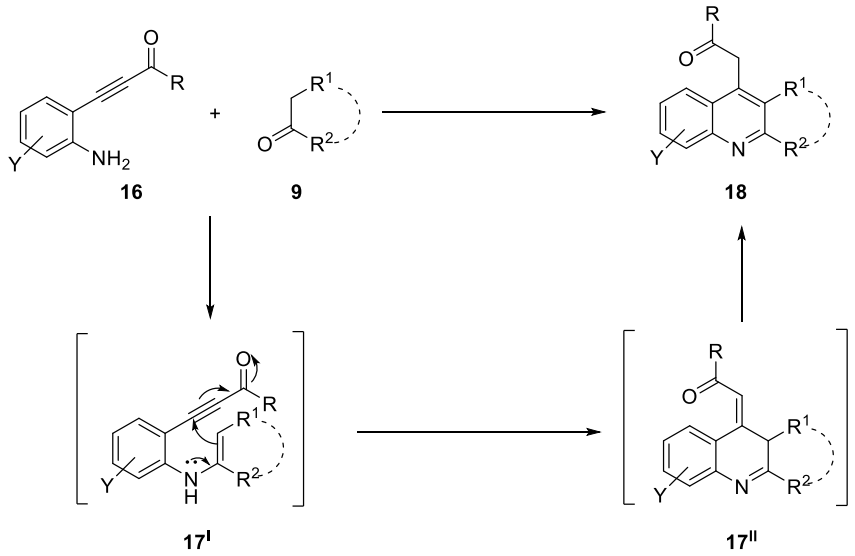
[43] a) Karuppasamy, P.; Kamalesh, T.; Anitha, K.; Pandian, M.S.; Ramasamy, P.; Verma, S. *J. Mol. Struct.* **2020**, 1210, 128036. b) Albrecht, G.; Herr, J.M.; Steinbach, M.; Yanagi, H.; Göttlich, R.; Schlettwein, D. *Dyes and Pigments* **2018**, 158, 334-341.

Even though many of these reactions are very effective, they suffer from several serious drawbacks such as lack of generality, high reaction temperatures, use of strong acids and/or oxidising agents and operational complexity in order to isolate the desired product. Thus, new efficient and sustainable synthetic methodologies are highly requested. In recent years significant progress has been made, especially in terms of functional group tolerance, selectivity and mildness of reactions conditions, by means of transition-metal catalysis, [44] organocatalysis [45] and other green strategies. [46] However, the development of versatile and efficient synthetic strategies, especially aimed at the construction of polycyclic structures similar to those found in nature, is still a centre of significant interest in organic chemistry.

Much work has been done on the use of β-(2-aminophenyl)-α,β-ynones as building blocks for the synthesis of the quinoline scaffold, especially through the reaction with nucleophiles. Although quite effective in generating quinolines in a straightforward way, this strategy has still some limitations on the nature of the substituents that can be introduced in the final scaffold. For example, it is quite difficult to introduce alkyl substituents in position 4, unless using additional activation strategies such as electrochemistry. [47] An interesting approach to further diversify the nature of substituents and the positions accessible on the quinoline core is the cascade reaction of β-(2-aminophenyl)-α,β-ynones with C1 or C2 units; this strategy has already been successfully used to generate 2-aminoquinolines via the gold-catalysed reaction with ynamides as C2 units. [48] In these conditions, in fact, the formation of the quinoline scaffold can derive from the annulation/aromatisation reaction of the enaminic intermediate formed *in situ* through the gold-catalysed hydroamination of β-(2-aminophenyl)-α,β-ynones with ynamides. [49]

It can be easily predicted that the same enaminic intermediate could be generated by reacting β-(2-aminophenyl)-α,β-ynones with enolisable ketones; after the formation of the C-N bond, the desired quinoline derivatives could be easily generated by regioselective 6-exo-dig annulation/aromatisation reaction, as depicted in Scheme 4.2.

[44] Sharma, R.; Kour, P.; Kumar, A. *J. Chem. Soc.* **2018**, 130, 73.
[45] Li, L.-H.; Niu, Z.-J.; Liang, Y.-M. *Chem. Asian J.* **2020**, 15, 231-241.
[46] Nainwal, L.M.; Tasneem, S.; Akhtar, W.; Verma, G.; Khan, M.F.; Parvez, S.; Shaquiquzzaman, M.; Akhter, M.; Alam, M.M. *Eur. J. Med. Chem.* **2019**, 164, 121-170.
[47] Arcadi, A.; Bianchi, G.; Inesi, A.; Marinelli, F.; Rossi, L. *Synlett* **2007**, 07, 1031-1036.
[48] Rode, N.D.; Arcadi, A.; Di Nicola, A.; Marinelli, F.; Michelet, V. *Org. Lett.* **2018**, 20, 5103-5106.
[49] Kramer, S.; Dooleweerdt, K.; Lindhardt, A.T.; Rottländer, M.; Skrydstrup, T. *Org. Lett.* **2009**, 11, 4208-4211.

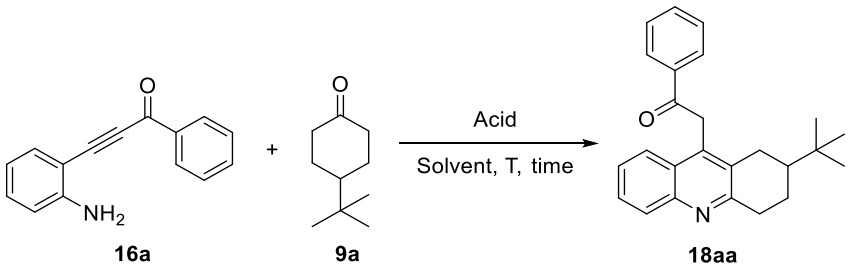


Scheme 4.2 Expected cascade pathway for the reaction of β-(2-aminophenyl)-α,β-ynones with ketones.

4.2 Results and discussion

To test this hypothesis and to explore suitable reaction conditions, the reaction of 3-(2-aminophenyl)-1-phenylprop-2-yn-1-one **16a** with the commercially available 4-(*tert*-butyl)cyclohexan-1-one **9a** was selected as model reaction. Different conditions were tested, examining the influence of solvent, temperature and the type of acid promoter/catalyst used; the results of the screening are reported in Table 4.1.

Table 4.1 Optimisation of the reaction conditions in the reaction between **16a** and **9a.**



Entry	9a/16a	Acid (equiv.)	Solvent	T (°C)	Time (h)	Yield[a] (%)
1	1:1	$FeCl_3$ (0.1)	Toluene	80	24	47
2	1:1	$InCl_3$ (0.1)	Toluene	80	24	50
3	1:1	$Yb(OTf)_3$ (0.1)	-	80	24	45
4	1:1	$Y(OTf)_3$ (0.1)	-	80	24	82
5	1:1	$NaAuCl_4{\cdot}2H_2O$ (0.05)	EtOH	r.t.	24	63 (27)[b]
6	1:1	*p*-TsOH·H_2O (0.2)	EtOH	80	1	60
7	1:1	*p*-TsOH·H_2O (1.0)	EtOH	80	1	95
8	1:1	*p*-TsOH·H_2O (1.0)	EtOH	r.t.	24	89
9	2:1	*p*-TsOH·H_2O (1.0)	EtOH	80	1	90
10	1:1	TFA (1.0)	EtOH	80	3	82
11	1:1	TfOH (1.0)	EtOH	80	1	89
12	1:1	*p*-TsOH·H_2O (1.0)	CH_3CN	80	1	88
13	1:1	*p*-TsOH·H_2O (1.0)	Toluene	80	1	90
14	1:1	*p*-TsOH·H_2O (1.0)	Dioxane	80	1	83

Reaction conditions: to a mixture of **16a** (0.4 mmol) and **9a** (0.4 or 0.8 mmol) in the appropriate solvent (2 mL), the chosen catalyst/promoter was added; the reaction was then performed at 80°C or room temperature for 1-24h. [a)] Isolated yield. [b)] % of unreacted **16a** recovered.

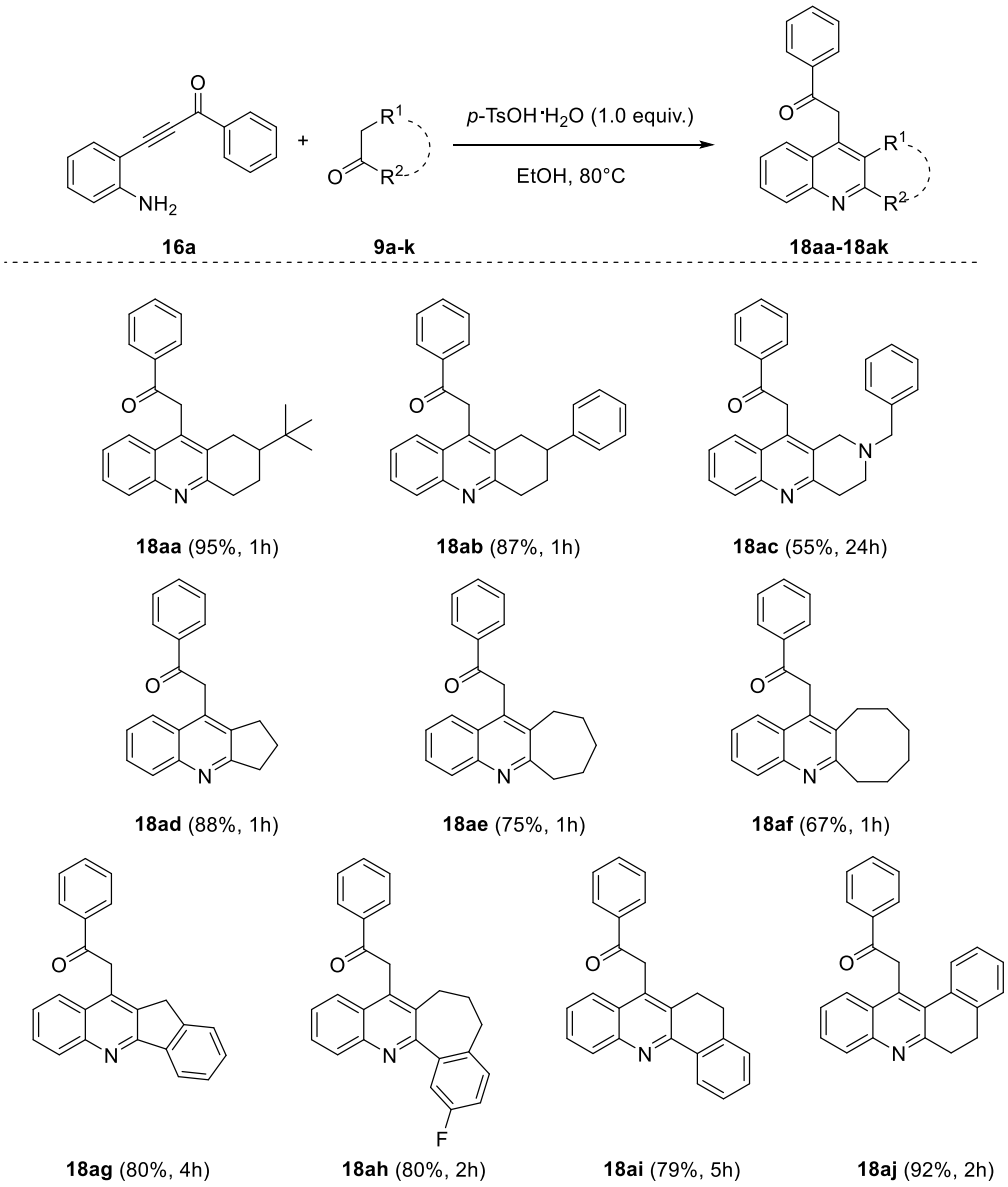
The investigation started with the use of Lewis acids as catalysts, which are well known for their ability to promote the classical Friedländer reaction. [50] The formation of the corresponding quinoline **18aa** occurred only in moderate yield after a prolonged reaction time when using $FeCl_3$, $InCl_3$ and $Yb(OTf)_3$ (Table 4.1, entries 1-3), while the use of $Y(OTf)_3$ under solventless conditions afforded the desired product in better yields (Table 4.1, entry 4). When using $NaAuCl_4{\cdot}2H_2O$ as catalyst, in accordance with previous reported results on its use as an

[50] For selected examples, see: a) Liu, S.; Li, G.; Xu, F. *J. Chin. Chem. Soc*. **2018**, 65, 888-892. b) Tanwar, B.; Kumar, D.; Kumar, A.; Ansari, M.I.; Qadri, M.M.; Vaja, M.D.; Singh, M.; Chakraborti, A.K. *New J. Chem.* **2015**, 39, 9824-9833. c) Sivaraman, M.; Perumal, P.T. *RSC Adv*. **2014**, 4, 52060-52066. d) Chanda, T.; Verma, R.K.; Singh, M.S. *Chem. Asian J*. **2012**, 7, 778-787. e) Genovese, S.; Epifano, F.; Marcotullio, M.C.; Pelucchini, C.; Curini, M. *Tetrahedron Lett.* **2011**, 52, 3474-3477.

alternative efficient catalyst in sequential amination/annulation reactions, [51] good results were obtained, although recovering **16a** partly unreacted (Table 4.1, entry 5). Remarkably, the desired product **18aa** was obtained in comparable yield when using a catalytic amount of *p*-toluenesulfonic acid monohydrate in refluxing ethanol (Table 4.1, entry 6); excellent yields where obtained when performing the reaction in the same conditions but using a stoichiometric amount of the Brønsted acid (Table 4.1, entry 7). It has already been reported, in fact, that stoichiometric *p*-TsOH·H_2O may display better performances than Lewis acids in the Friedländer synthesis of quinolines. [52] Then, a brief exploration of the Brønsted acid-mediated reaction between **16a** and **9a** was made. Doubling the equivalents of **9a** was not effective, not bringing further improvements in the yield of **18aa** (Table 4.1, entry 9); in the same way, the use of other Brønsted acid promoters, such as trifluoroacetic acid (TFA) and trifluoromethanesulfonic acid (TfOH), afforded the desired product in very good yields but lower than those reached with *p*-TsOH·H_2O (Table 4.1, entries 10-11). The reaction was very effective also when performed with *p*-toluenesulfonic acid monohydrate in ethanol at room temperature, (Table 4.1, entry 8) although requesting longer reaction times and generating **18aa** with a slightly inferior yield; this is very interesting as a further potential increase of the sustainability of the process. Subsequent examination of the solvent effect revealed that CH_3CN, toluene and dioxane were also suitable solvents for the reaction (Table 4.1, entries 12–14); ethanol, however, was preferred as reaction medium due to its safer profile in terms of eco- and biocompatibility. [53]

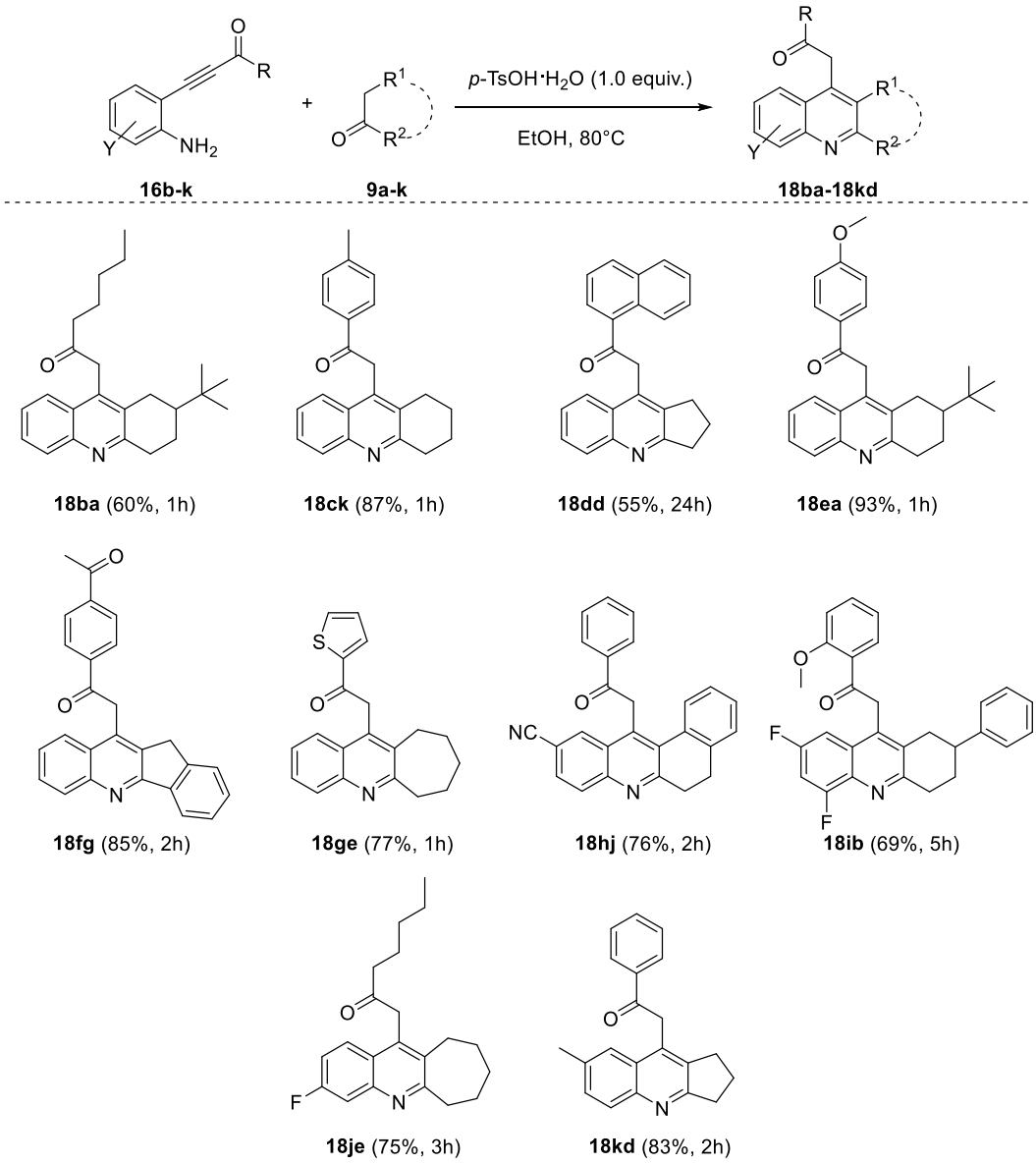
With the best reaction conditions in hands (Table 4.1, entry 7), the scope and the flexibility of the methodology was investigated by reacting **16a** with different types of commercially available ketones **9**. Polycyclic compounds **18aa**-**18ak** bearing five, six, seven or eight membered rings fused at the 2,3-position of the quinoline core were smoothly obtained in good to high yields (Scheme 4.3). In all cases, the ketones used were symmetrical or had only one accessible enolisable position, so preventing regiochemical problems; interestingly, however, when using the unsymmetrical 2-tetralone **9j**, only one regioisomer was obtained [2-(5,6-dihydrobenzo[a]acridin-12-yl)-1-phenylethan-1-one, **18aj**], demonstrating the high regiocontrol that can be achieved through this methodology.

[51] a) Arcadi, A.; Chiarini, M.; Di Giuseppe, S.; Marinelli, F. *Synlett* **2003**, 203-206. b) Arcadi, A.; Bianchi, G.; Di Giuseppe, S.; Marinelli, F. *Green Chem.* **2003**, 5, 64-67. c) Arcadi, A.; Di Giuseppe, S.; Marinelli, F.; Rossi, E. *Tetrahedron Asymmetry* **2001**, 12, 2715-2720. d) Arcadi, A.; Di Giuseppe, S.; Marinelli, F.; Rossi, E. *Adv. Synth. Catal.* **2001**, 343, 443-446.
[52] Jia, C.-S.; Zhang, Z.; Tu, S.-J.; Wang, G.-W. *Org. Biomol. Chem.* **2006**, 4, 104-110.
[53] Byrne, F.P.; Jin, S.; Paggiola, G.; Petchey, T.H.M.; Clark, J.H.; Farmer, T.J.; Hunt, A.J.; McElroy, C.R.; Sherwood, J. *Sustain. Chem. Process*. **2016**, 4, 7.



Scheme 4.3 Substrate scope of the reaction of **16a** with different ketones **9**.

Then, the influence of the substituents of β-(2-aminophenyl)-α,β-ynones on the reaction has been investigated. Ynones **16b-k** were reacted with some of the ketones used in Scheme 4.4 to generate quinolines **18ba**-**18kd**.

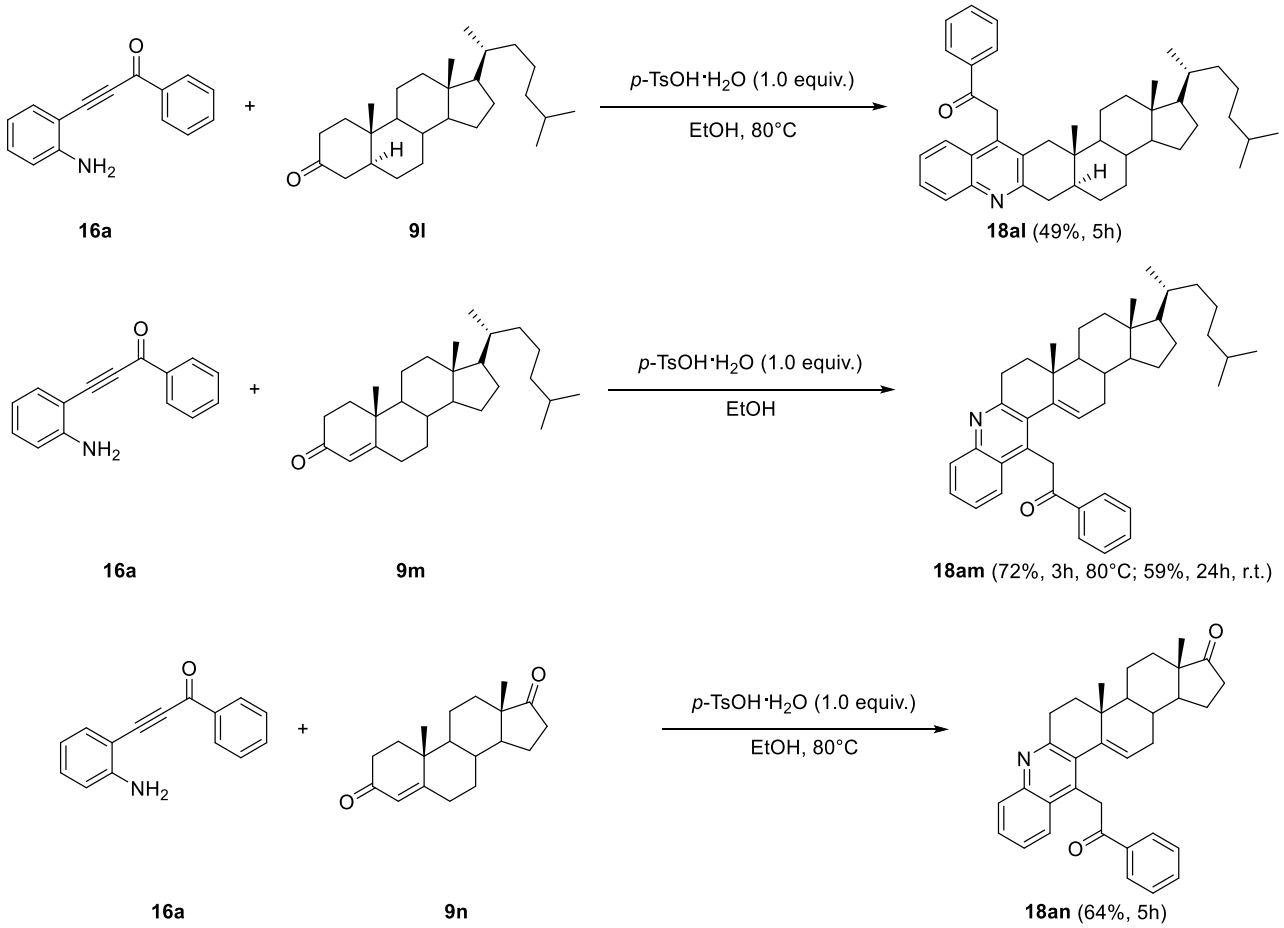


Scheme 4.4 Substrate scope with different β-(2-aminophenyl)-α,β-ynones **16b-k**.

As shown in Scheme 4.4, good to excellent yields have been obtained when using β-(2-aminophenyl)-α,β-ynones bearing alkyl-, aryl- and heteroaryl-substituents in the acyl framework. In particular, the aryl-substituted ones afforded the polycyclic quinolines in better yields, well tolerating both electron-donating and electron-withdrawing groups (**16c-f**). Moreover, bulky substituents such as the naphthalene group (**16d**) did not hinder the reaction, enabling the isolation of the quinoline compound in high yield. Gratifyingly, the optimised reaction conditions resulted compatible with the presence of the thiophene ring on the starting material (**16g**), with the corresponding quinoline being isolated with a good yield. Moreover, the influence of different substituents on the aniline ring of β-(2-aminophenyl)-α,β-ynones has been investigated too. Pleasingly, the method developed appeared to be compatible with different types of substituents (**16h-k**), even with strong electron-withdrawing groups (such

as fluoro and cyano groups) in *ortho* and/or *para* positions to the nitrogen atom of the starting material; this particular pattern of substitution should decrease the nucleophilicity of the nitrogen atom, hindering the amination reaction with the ketone partner. Nevertheless, the reaction was possible and the corresponding quinolines (**18hj** and **18ib**) were isolated with good yields.

As a further extension of the substrate scope, steroidal compounds bearing carbonyl groups have been reacted with **16a**, with the aim to obtain fused steroidal quinoline derivatives (Scheme 4.5). In fact, this type of steroidal derivatives is highly requested since the incorporation of a heterocyclic ring in the steroid backbone can affect the chemical properties of the steroidal compound, often resulting in useful alterations in its biological activities. A- and D-ring fused steroidal quinolines have been extensively synthetised and screened for their antimicrobial activities against a panel of various bacterial and fungal strains, indicating that analogues of these compounds are promising antibacterial agents. [54] Different types of steroidal derivatives were tested under the optimised reaction conditions, collecting some interesting results on their general reactivity.



Scheme 4.5 Synthesis of steroidal quinoline derivatives.

[54] Gogoi, S.; Shekarrao, K.; Duarah, A.; Bora, T.C.; Gogoi, S.; Boruah, R.C. *Steroids* **2012**, 77, 1438-1435.

When the condensation reaction was performed using steroids bearing a simple ketone group at position 3, such as 5α-cholestan-3-one **9l**, the linear cholestanoquinoline derivative **18al** was obtained, although in low yields. On the contrary, different results were obtained when using 3-keto-Δ^4-polycyclic steroidal derivatives as reagents. In these cases, in fact, the optimised methodology allowed the divergent generation of the angular quinoline derivative, whose synthesis is generally considered more challenging and demanding. Satisfactory yields have been obtained when using both 4-cholesten-3-one **9m** and 4-androstene-3,17-dione **9n**.

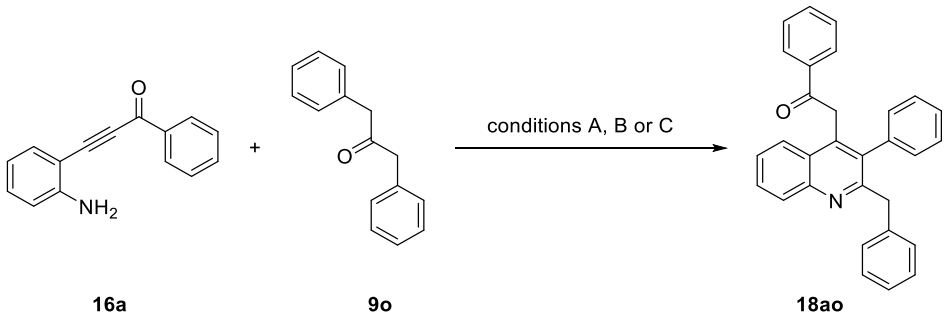
Moreover, it was interesting to note that when reacting steroidal dicarbonyl derivatives like **9n**, the condensation reaction took place selectively only on the conjugated carbonyl group at 3 position, leaving the ketone group at position 17 unreacted. The non-reactivity of this position was further confirmed by testing some steroidal derivatives, such as benzoylandrosterone, 5-androsten-3β-ol-17-one and estrone, bearing only one carbonyl group at position 17. When submitted to the optimised reaction conditions, these steroids did not generate any D-fused steroidal quinolines, further confirming the hypothesis.

The data obtained are in perfect accordance with previously reported results on the sequential amination/cyclization/aromatisation reaction of ketones, [55] showing that the amination reaction occurs preferentially on the conjugated carbonyl group and that the linear *vs.* angular fusion to the cyclic skeleton is purely directed by the presence of a saturated or conjugated carbonyl group in the substrate.

In the attempt to expand the methodology to symmetric acyclic ketones too, **16a** has been reacted with 1,3-diphenylpropan-2-one **9o**. As reported in Table 4.2, the standard reaction conditions allowed to obtain the expected quinoline **18ao** but only with a low yield, recovering **16a** partly unreacted. None of the other conditions tested enabled a substantial increase of the yield, so further investigations are needed.

[55] Abbiati, G.; Arcadi, A.; Bianchi, G.; Di Giuseppe, S.; Marinelli, F.; Rossi, E. *J. Org. Chem*. **2003**, 68, 6959-6966.

Table 4.2 Extension of the procedure to acyclic carbonyls.

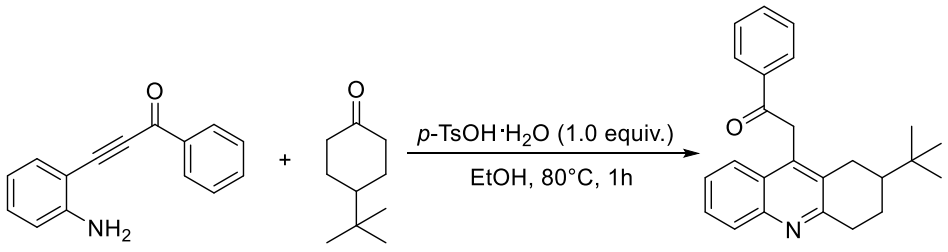


16a 9o 18ao

Entry	Conditions	Yield[a] (%)	16a recovered[a] (%)
A	*p*-TsOH·H_2O (1.0 equiv.), EtOH, 80°C, 24h	35%	36%
B	*p*-TsOH·H_2O (1.0 equiv.), toluene, 80°C, 6h	21%	61%
C	$InCl_3$ (0.2 equiv.), MeCN, 80°C, 6h	-	67%

[a)] Isolated yield.

Finally, to demonstrate the efficiency and practicality of this protocol, a gram-scaled experiment was performed under the optimal reaction conditions. When 1.00 g of **16a** was reacted, **18aa** was obtained in 97% yield (Scheme 4.6).



16a (1.0 g) **9a** (0.7 g) **18aa** (1.56 g, 97%)

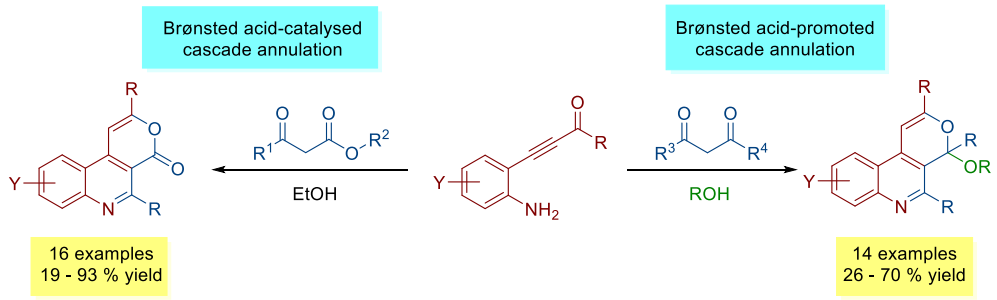
Scheme 4.6 Gram-scale preparation of compound **18aa.**

4.3 Conclusions

In conclusion, the use of the Brønsted acid *p*-TsOH·H_2O as a promoter enabled the reaction between β-(2-aminophenyl)-α,β-ynones and cyclic ketones to generate polycyclic quinoline derivatives in excellent yields. The reaction, occurring through a sequential amination/6-exo-dig annulation/aromatisation mechanism, overcomes the drawbacks of the classical methods usually used to build up the quinoline core, employing much safer chemicals, a highly sustainable solvent and milder reaction conditions. Different types of substituents were well tolerated on both reagents; moreover, when using unsymmetrical carbonyl compounds, complete regiocontrol was achieved. Interesting results have been obtained using steroids as carbonyl reagents, generating A-fused steroidal quinolines in competitive yields. By choosing the right starting material, it has been possible to create both linear and angular steroidal quinolines, the latter being much more difficult to synthetise with classical methods. This seems to be the first report for the synthesis of angular fused steroidal quinolines. The structure-reactivity relationships that can be derived from the investigations done on steroidal reactivity can be very useful in choosing the more suitable reagent when planning the synthesis of steroidal quinolines derivatives.

Chapter 5

Domino reactions of β-(2-aminophenyl)-α,β-ynones with β-dicarbonyl compounds: divergent synthesis of polycyclic quinolines derivatives

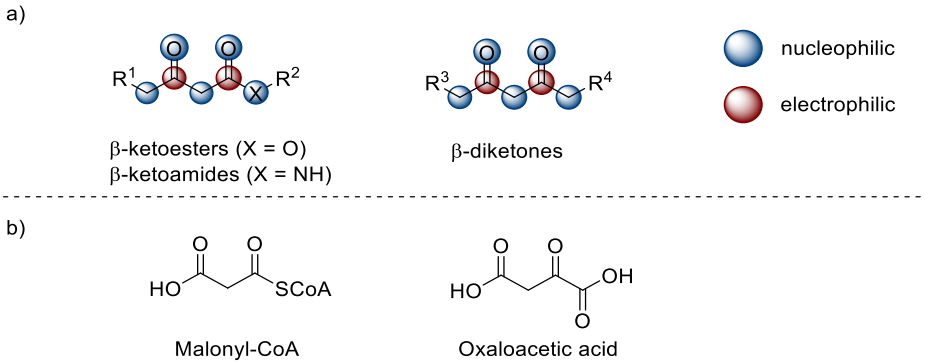


The Brønsted acid-promoted reaction of β-(2-aminophenyl)-α,β-ynones with ketones was expanded to activated carbonyl compounds such as β-ketoesters and β-diketones. For β-ketoesters, a thorough screening of reaction conditions revealed that catalytic amounts of *p*-TsOH·H_2O were sufficient to promote a cascade double-cyclisation leading to 4*H*-pyrano[3,4-c]quinoline-4-one derivatives in a high yielding and operationally simple methodology. On the contrary, with β-diketones, a stoichiometric amount of *p*-TsOH·H_2O triggered a three-component reaction, involving a molecule of the alcoholic solvent too. Although the data are only preliminary, both procedures appear to be simple and versatile and are expected to be of great impact since the multiple potential applications of the obtained organic compounds.

5.1 Introduction

As described in the previous chapter, the use of stoichiometric amounts of *p*-TsOH·H_2O in refluxing ethanol allows to easily generate quinoline derivatives from β-(2-aminophenyl)-α,β-ynones and cyclic ketones. The versatility of the methodology and the high value of the scaffolds obtained makes this procedure a valuable useful alternative for the synthesis of diversified polycyclic quinolines from easily available basic chemical materials. To further expand the array of organic architectures accessible through it, the reactivity of other carbonyl compounds, such as β-dicarbonyl compounds, was tested.

β-dicarbonyl compounds are exceptional synthetic platforms for organic synthesis thanks to the presence of multiple contiguous functional groups with different reactivity; they can display up to five nucleophilic and two electrophilic potential reaction sites (Scheme 5.1, a). Nature itself exploits the reactivity of these substrates in biochemical pathways; malonyl-CoA, for instance, is fundamental in the elongation of fatty acids and in the synthesis of polyketides, while oxaloacetic acid is a central component of Krebs cycle (Scheme 5.1, b).



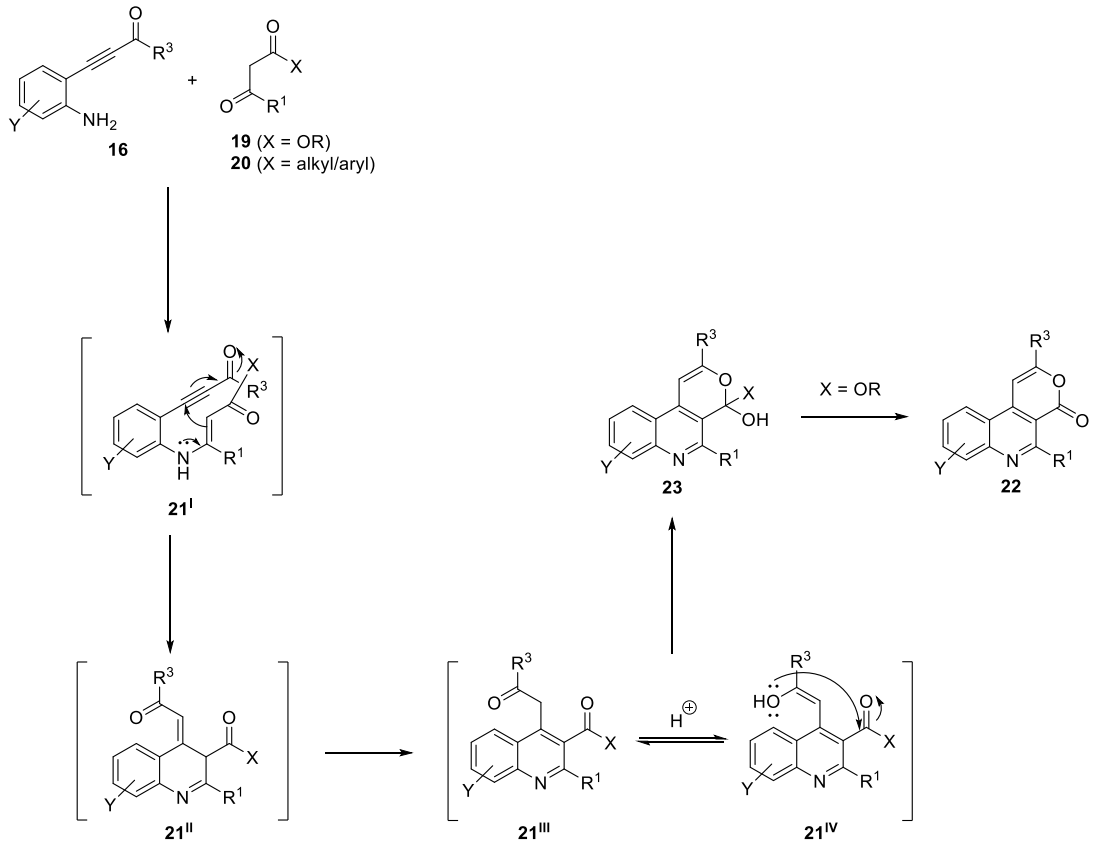
Scheme 5.1 Potential reaction sites in β-dicarbonyls.

Thanks to the high density of potential reaction sites, β-dicarbonyl compounds have been extensively used in MBFTs, especially in MCRs; [56] Biginelli, Hantzsch and Yonemitsu reactions are just few examples of the plethora of synthetic strategies that have been developed with them. A great advantage in the use of these substrates in MBFTs is that regio- and chemoselectivity problems can be easily avoided by modulation of the R^i substituents which strongly influence the reactivity of the carbonyl groups.

In the attempt to generate complex polycyclic structures based on the quinoline core, β-dicarbonyl compounds were reacted with β-(2-aminophenyl)-α,β-ynones. In fact, it is well

[56] a) Bonne, D.; Constantieux, T.; Coquerel, Y.; Rodriguez, J. *Chem. Eur. J.* **2013**, 19, 2218-2231. b) Shokova, E.A.; Kim, J.K.; Kovalev, V.V. *Russ. J. Org. Chem.* **2015**, 51, 773-847.

known that β-dicarbonyl compounds can be efficiently used in the Friedländer reaction with 2-aminobenzoaldehydes or 2-alkynylanilines to generate quinolines bearing a carbonyl substituent in position 3. [57] This type of intermediate **21^{III}** is expected in the reaction with β-(2-aminophenyl)-α,β-ynones too; however, in this case, the carbonyl group at position 3 could further react with the other keto functionality in the alkyl-substituent at position 4, generating an additional [3,4]-fused 6-membered ring whose structure depends on the type of β-dicarbonyl compound used (Scheme 5.2).



Scheme 5.2 Cascade reaction of β-(2-aminophenyl)-α,β-ynones with β-dicarbonyl compounds.

One-pot MBFTs are very interesting means to bust the sustainability and the atom- and step-economy of synthetic procedures, especially when used to generate complex polycyclic structures; moreover, the possibility to obtain different compounds by simply changing the β-dicarbonyl used is appealing, especially in the synthesis of diversified chemical libraries for medicinal uses. Indeed, the 4*H*-pyrano[3,4-c]quinoline-4-one system of compound **22** has an high similarity with the alkaloids extracted from plants belonging to the family of *Annonaceae*, subtropical fruit trees used in folk and traditional medicine. [58]

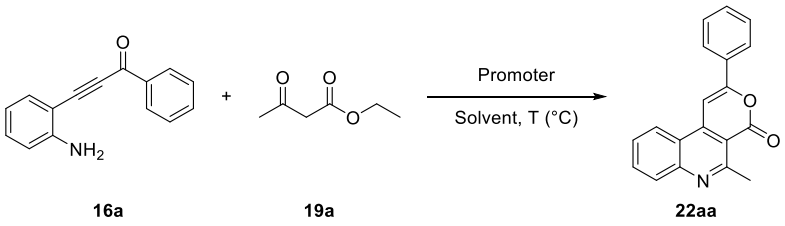
[57] Peng, C.; Wang, Y.; Liu, L.; Wang, H.; Zhao, J.; Zhu, Q. *Eur. J. Org. Chem.* **2010**, 818-822.
[58] Dhoro, F.; Parkin-Gibbs, J.; MeIldowie, M.; Skelton, B.W., Piggot, M.J. *J. Nat. Prod.* **2018**, 81, 1658-1665.

5.2 Results and discussion

5.2.1 Reaction with β-ketoesters – optimisation and substrate scope

To verify the thesis and the possibility to obtain the one-pot double cyclisation, the reaction of 3-(2-aminophenyl)-1-phenylprop-2-yn-1-one **16a** with ethyl 3-oxobutanoate **19a** was investigated under several reaction conditions (Table 5.1).

Table 5.1 Optimisation of the reaction conditions in the reaction between **16a** and **19a.**



16a **19a** **22aa**

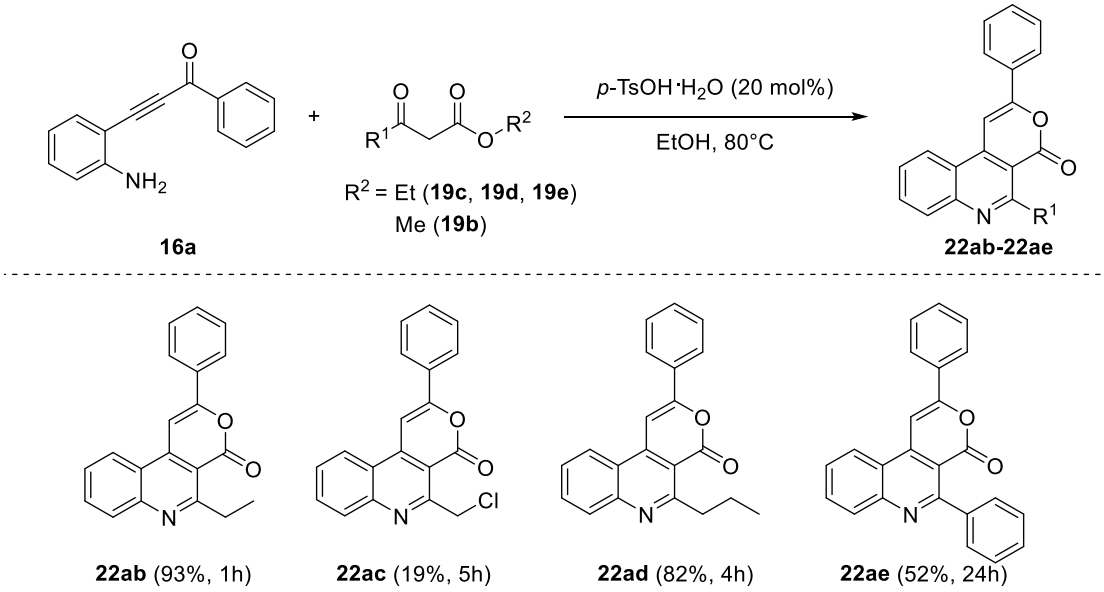
Entry	19a/16a	Promoter (equiv.)	Solvent	T (°C)	Time (h)	Yield[a] (%)
1	1:1	*p*-TsOH·H_2O (1.0)	EtOH	80	1	51
2	2:1	*p*-TsOH·H_2O (1.0)	EtOH	80	1	84
3	2:1	*p*-TsOH·H_2O (1.0)	EtOH	40	7	60
4	2:1	*p*-TsOH·H_2O (1.0)	EtOH	rt	24	41 (49)[b]
5	2:1	*p*-TsOH·H_2O (1.0)	Toluene	110	1	64
6	2:1	*p*-TsOH·H_2O (0.2)	EtOH	80	1	90
7	2:1	*p*-TsOH·H_2O (0.1)	EtOH	80	6	60[d]
8	2:1	H_2SO_4 (1.0)	EtOH	80	1	78
9	2:1	HCl (1.0)[c]	EtOH	80	1	60
10	2:1	AcOH (1.0)	EtOH	80	24	38 (35)[b]
11	2:1	TFA (1.0)	EtOH	80	2	77
12	2:1	TfOH (1.0)	EtOH	80	3	59
13	2:1	Amberlist-15 (1.0)	EtOH	80	24	28 (40)[b,e]
14	2:1	$NaAuCl_4·2H_2O$ (0.05)	EtOH	80	5	46
15	2:1	$InCl_3$ (0.05)	Toluene	110	24	12 (71)
16	2:1	$InCl_3$ (0.2)	Toluene	110	24	83
17	2:1	$FeCl_3$ (0.2)	Toluene	110	6	60
18	2:1	$ZnBr_2$ (0.2)	Toluene	110	6	57

Reaction conditions: to a mixture of **16a** (0.2 mmol) and **19a** (0.2 or 0.4 mmol) in the appropriate solvent (2 mL), the chosen catalyst/promoter was added; the reaction was then performed at rt-110°C for 1-24h. [a)] Isolated yield. [b)] % of unreacted **16a** recovered. [c)] The 37% HCl aqueous solution was used. [d)] 4-ethoxy-2-phenylquinoline was isolated as by-product in 33% yield. [e)] The uncyclised ethyl 2-methyl-4-(2-oxo-2-phenylethyl)quinoline-3-carboxylate was isolated as minor product in 24% yield.

When the reaction was performed under the optimised conditions found for the reaction of β-(2-aminophenyl)-α,β-ynones with cyclic ketones (Chapter 4), the expected polycyclic quinoline **22aa** was obtained in 51% yield (Table 5.1, entry 1). Pleasingly, by increasing the amount of β-ketoester **19a** to 2 equivalents, the yield was further improved to 84% (Table 5.1, entry 2). The influence of the temperature on the reaction outcome was investigated too: the formation of **22aa** occurred in 60% yield at 40°C, with only small traces of unreacted starting material (Table 5.1, entry 3), while when the reaction was performed at room temperature, a major decrease in conversion was observed after a prolonged reaction time, since the 49% of **16a** could be isolated unreacted (Table 5.1, entry 4). The use of toluene as an alternative solvent did not produce any improvement, even if the reaction was performed at a higher temperature (Table 5.1, entry 5). Interestingly, an important increase in the yield of **22aa** was obtained when the reaction was performed with a catalytic amount of *p*-TsOH·H_2O (20 mol%, Table 5.1, entry 6). However, a further reduction of the amount of *p*-TsOH·H_2O, from 20 mol% to 10 mol%, was not helpful and resulted in a reduction of the yield of **22aa** and in the formation of the 4-ethoxy-2-phenylquinoline by-product in 33% yield (Table 5.1, entry 7). In fact, when the reaction between **16a** and **19a** is too slow, the conjugate addition of the nucleophilic solvent on the triple bond of **16a** could be expected, yielding 4-ethoxy-2-phenylquinoline, as already reported in literature. [59] Other Brønsted acids were tested too as promoters of the reaction. H_2SO_4, HCl, TfOH and trifluoro acetic acid were similar in the outcome but generally inferior then *p*-TsOH·H_2O (Table 5.1, entries 8-9 and 11-12). Only acetic acid resulted in a much worst result, generating **22aa** in a very poor yield and with the partial recovering of the unreacted starting material (Table 5.1, entry 10). Even solid Brønsted acids as heterogenous catalysts were compatible with the generation of **22aa**; however, when using Amberlist-15 as promoter, [60] the expected polycyclic quinoline formed only in a poor 28% yield (Table 5.1, entry 14). The formation of quinoline **22aa** occurred only from low to moderate yield when using Lewis acids such as $NaAuCl_4$, $FeCl_3$, $InCl_3$ and $ZnBr_2$ (Table 5.1, entries 14-17) in a slightly increased reaction time.

Consequently, the conditions reported in Table 5.1, entry 4 were selected as optimised reaction conditions to study the scope and flexibility of the methodology. The procedure was firstly investigated by reacting 3-(2-aminophenyl)-1-phenylprop-2-yn-1-one **16a** with different commercial β-ketoesters (Scheme 5.3).

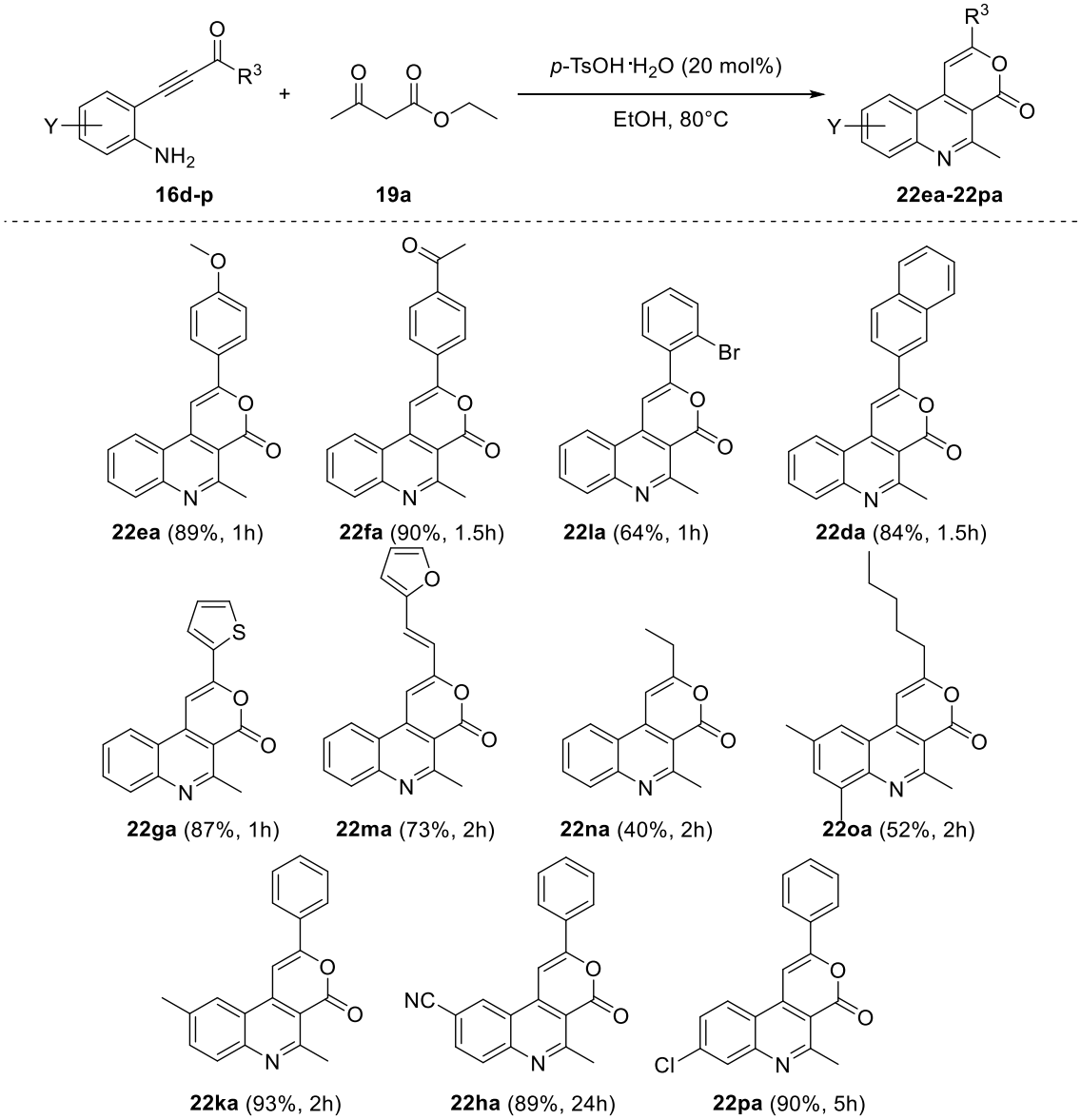
[59] Rode, N.D.; Arcadi, A.; Chiarini, M.; Marinelli, F. *Synthesis* **2017**, 49, 2501-2512.
[60] Sanaboina, C.; Jana, S.; Eppakayala, L. *Synlett* **2014**, 25, 1006-1008.



Scheme 5.3 Substrate scope of the reaction of **16a** with different β-ketoacids **19**.

The procedure seems to be highly versatile, since both methyl (**19b**) and ethyl (**19c**, **19d** and **19e**) β-ketoesters were found to be compatible. As for the substitution pattern, both alkyl- and aryl-groups as R^1 substituents were well tolerated, yielding the corresponding 2-phenyl-4*H*-pyrano[3,4-c]quinolin-4-ones **22ab**, **22ad** and **22ae** with excellent yields. Even ethyl 4-chloro acetoacetate (**19c**), bearing a chloromethyl moiety as R^1 group, managed to generate the expected polycyclic compound **22ac**, although with a much lower yield. The reaction was also tested with fluoro-containing β-ketoesters, such as ethyl 4,4,4-trifluoro-3-oxobutanoate and ethyl 4,4,5,5,5-pentafluoro-3-oxopentanoate, although with mediocre results. In fact, in these cases, no 2-phenyl-4*H*-pyrano[3,4-c]quinolin-4-one derivatives were obtained, recovering only the unreacted **16a** and the 4-ethoxy-2-phenylquinoline by-product in low yield, showing a first limitation of the methodology.

Then, several β-(2-aminophenyl)-α,β-ynones with different substituents on both the acyl moiety and the aniline ring were tested, to study the influence of their substitution pattern on the reaction outcome (Scheme 5.4).



Scheme 5.4 Substrate scope of the reaction of different β-(2-aminophenyl)-α,β-ynones **16** with ethyl 3-oxobutanoate **19a**.

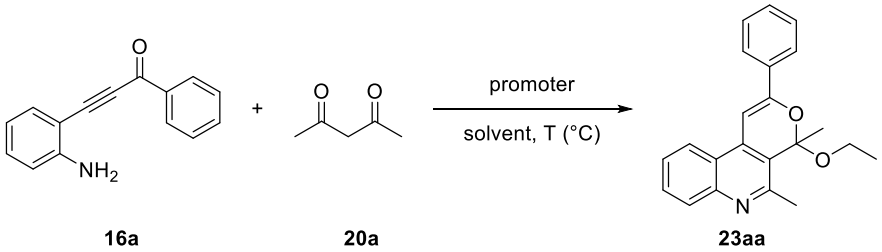
As shown in the scheme above, the methodology is compatible with both aryl- and alkyl-substituted β-(2-aminophenyl)-α,β-ynones. In particular, the aryl-substituted ones yielded the corresponding 2-phenyl-4*H*-pyrano[3,4-c]quinolin-4-ones in excellent yields (**16e**, **f**, **l** and **d**), well tolerating both electron-withdrawing and electron-donating groups. Even the presence of heteroaromatics substituents, such as furan (**16m**) and thiophene (**16g**), was compatible with the selected reaction conditions. Alkyl-substituted β-(2-aminophenyl)-α,β-ynones, such as **16n** and **16o**, were less efficient in generating the corresponding quinolines **22**, which were obtained only in moderate yields. Regarding the influence of the substitution of the aniline ring, both electron-withdrawing (**16h** and **16p**) and electron-donating groups (**16k** and **16o**) were compatible with the methodology. Surprisingly, the quinoline **22ha** was obtained in a

very good yield even in the presence of a strong withdrawing group such as -CN in *para* position to the amino group.

5.2.2 Reaction with β-diketones – optimisation and substrate scope

With the aim to further expand the applicability of the developed methodology, the reaction was also tested with β-diketones, such as pentane-2,4-dione **20a** (Table 5.2). Interestingly, when the reaction between **16a** and **20a** was performed in the same conditions used for β-ketoesters, the ketal **23aa** (4-ethoxy-4,5-dimethyl-2-phenyl-4*H*-pyrano[3,4-c]quinoline) was obtained as the major product in 60% yield, together with the corresponding uncyclised quinoline in 33% yield.

Table 5.2 Optimisation of the reaction conditions in the reaction between **16a** and **20a.**



16a **20a** **23aa**

Entry	20a/16a	Promoter (equiv.)	Solvent	T (°C)	Time (h)	Yield[a] (%)
1	2:1	*p*-TsOH·H_2O (0.2)	EtOH	80	24	60[b]
2	1:1	*p*-TsOH·H_2O (1.0)	EtOH	80	20	41
3	1:1	$NaAuCl_4 \cdot 2H_2O$ (0.05)	EtOH	80	24	51
4	2:1	*p*-TsOH·H_2O (1.0)	EtOH	80	5	67
5	2:1	*p*-TsOH·H_2O (1.0)	Toluene	110	24	-[c]

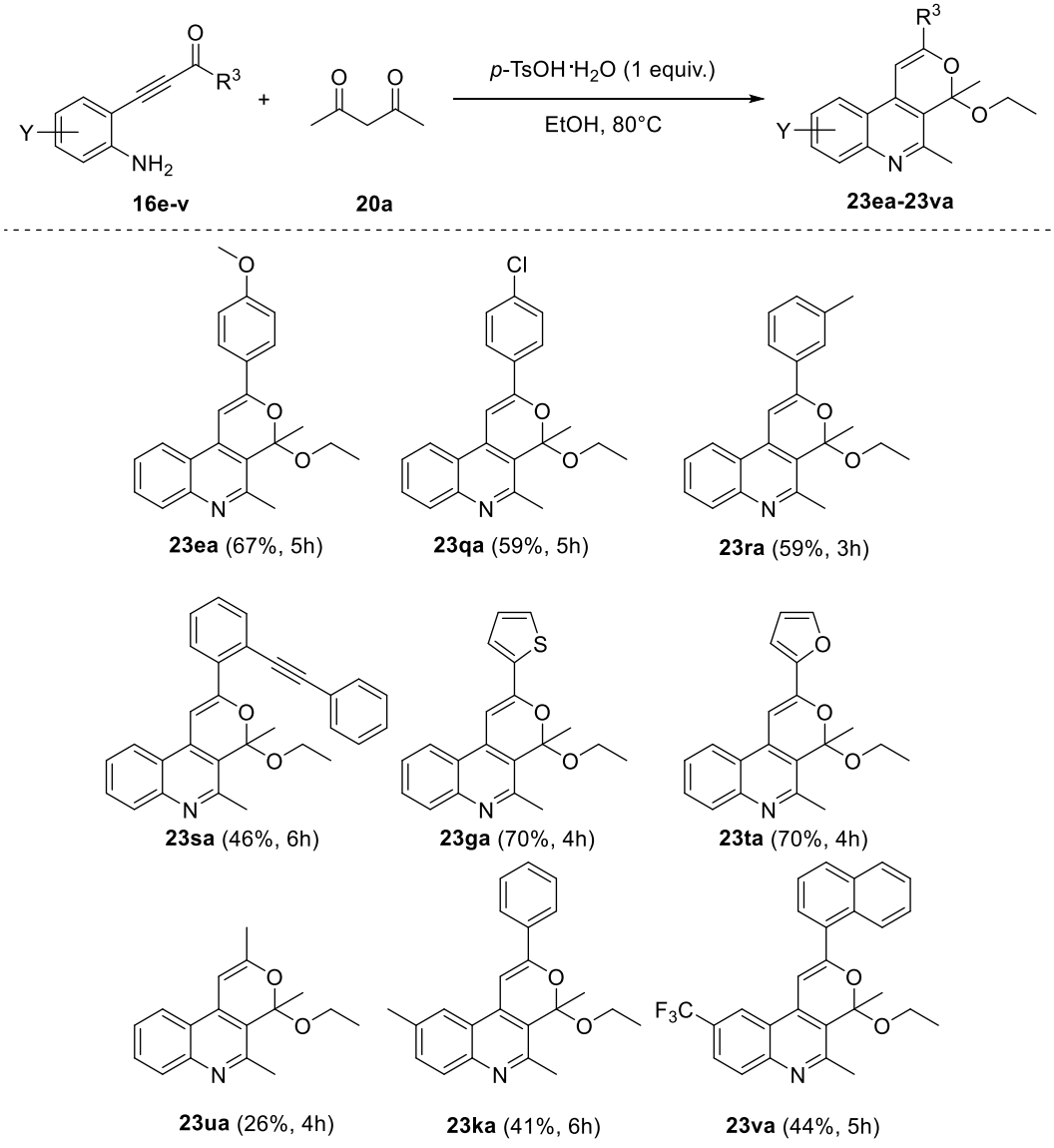
Reaction conditions: to a mixture of **16a** (0.2 mmol) and **20a** (0.2 or 0.4 mmol) in the appropriate solvent (2 mL), the chosen catalyst/promoter was added; the reaction was then performed at 80-110°C for 5-24h. [a)] Isolated yield. [b)] The uncyclised 2-(3-acetyl-2-methylquinolin-4-yl)-1-phenylethan-1-one (**21aa**) was obtained in 33% yield. [c)] The uncyclised 2-(3-acetyl-2-methylquinolin-4-yl)-1-phenylethan-1-one (**21aa**) was obtained in 74% yield.

A rapid optimisation of reaction conditions was therefore performed in order to improve the yield of **23aa**. A pronounced decrease of the yield of the ketal was obtained when the reaction was performed with a stoichiometric amount of *p*-TsOH·H_2O but with only one equivalent of **20a** (Table 5.2, entry 2). The yield increased only slightly when using $NaAuCl_4 \cdot 2H_2O$ as catalyst (Table 5.2, entry 3). On the contrary, when using one equivalent of *p*-TsOH·H_2O but an excess of **20a**, **23aa** was obtained with an interesting 67% yield (Table 5.2, entry 4). The use of ethanol as a solvent was found to be fundamental for the second cyclisation to take

place; in fact, when changing the solvent to toluene, the pyran ring was not obtained and the only isolated product was the uncyclized 2-(3-acetyl-2-methylquinolin-4-yl)-1-phenylethan-1-one (**21aa**) (Table 5.2, entry 5).

The optimised reaction conditions (Table 5.2, entry 4) were therefore used to further test the versatility of the three-component reaction between β-(2-aminophenyl)-α,β-ynones **16**, β-diketones **20** and alcohols.

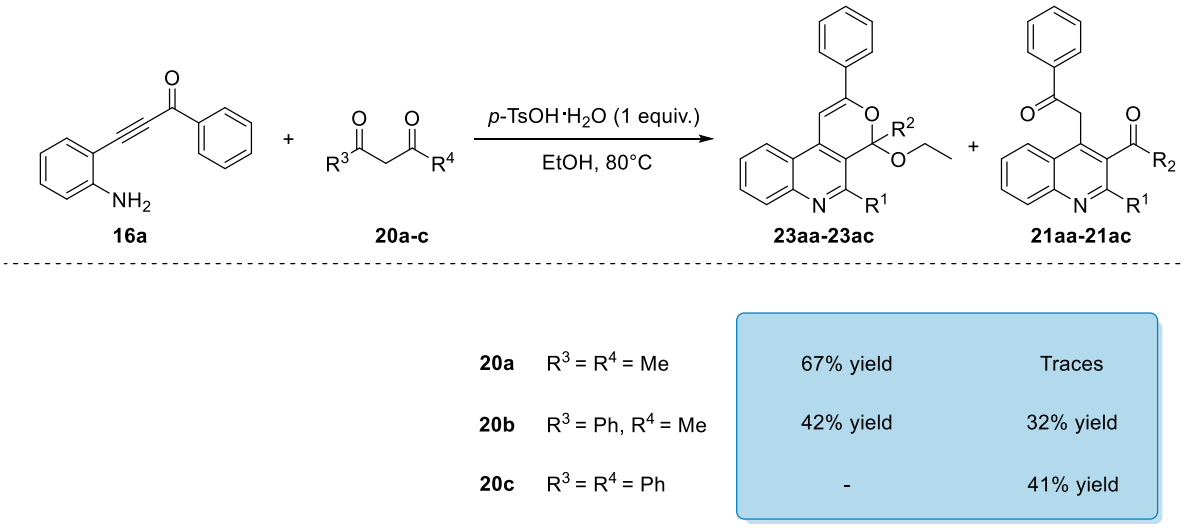
Firstly, the effect of the substitution of β-(2-aminophenyl)-α,β-ynones was investigated by reacting **16e-v** with pentane-2,4-dione **20a** in ethanol under the optimised reaction conditions.



Scheme 5.5 Substrate scope of the reaction of different β-(2-aminophenyl)-α,β-ynones **16** with pentane-2,4-dione **20a** in EtOH.

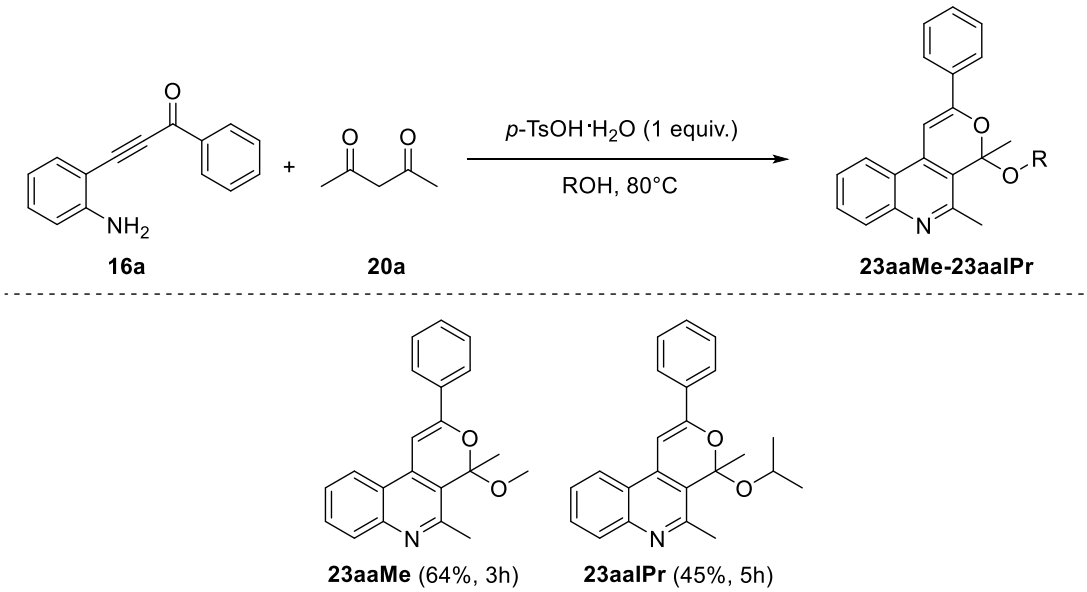
As summarised in Scheme 5.5, the synthetic procedure could be successfully applied on aryl-substituted β-(2-aminophenyl)-α,β-ynones, bearing both electron-withdrawing (**16q**) and electron-donating groups (**16e** and 16**r**). Pleasingly, the reaction conditions were also compatible with the aryl-substituted ynone **16s**, bearing an additional phenylethynyl group in the *ortho* position; the expected ketal **23sa** was obtained in a good yield, leaving the additional triple bond unreacted. Both thiophene (**16g**) and furan (**16t**) as acyl substituents of β-(2-aminophenyl)-α,β-ynones were well tolerated, yielding the corresponding polycyclic quinolines in good yields. Worst results were generally obtained with alkyl-substituted ynones; in fact, only the use of the methyl-substituted one **16u** enabled to isolate the expected ketal **23ua** in a very low yield, while the reaction of 1-(2-aminophenyl)oct-1-yn-3-one **16b** (R^3 = pentyl) and 1-(2-amino-3,5-dimethylphenyl)oct-1-yn-3-one **16o**, in the same conditions, resulted in a very complex mixture (not resolved) with minor traces of the expected product (as detected by ^{1}H NMR analysis of the crude). Regarding the substitution of the aniline ring, both electron-donating (**16k**) and electron-withdrawing (**16v**) groups in *para* position to the amino group are compatible with the developed methodology, although yielding the corresponding ketals in a low yield.

The reaction was also tested with different β-diketones **20**. The preliminary results obtained (Scheme 5.6) showed that the reaction is highly dependent on the nature of both R^1 and R^2 substituents, especially in regard to the ketal-yielding cyclisation. In fact, as seen in Table 5.2, when both R^1 and R^2 substituents were alkyl groups (**20a**), the second cyclisation occurred smoothly with only small traces of the uncyclised 2-(3-acetyl-2-methylquinolin-4-yl)-1-phenylethan-1-one (**21aa**). On the contrary, when using 1-phenylbutane-1,3-dione (**20b**) and 1,3-diphenylpropane-1,3-dione (**20c**), a drastic drop in the yield of the ketal was observed, with the uncyclised quinoline **21ac** being the only isolated product when $R^1 = R^2$ = Ph.



Scheme 5.6 Preliminary results on the reaction of β-(2-aminophenyl)-α,β-ynone **16a** with β-diketones **20b-c** in ethanol.

To further demonstrate the versatility of the methodology, the synthesis of ketals **23** was screened in other alcoholic solvents (Scheme 5.7). Although only preliminarily investigated, the formation of the expected quinolines **23** seemed to occur smoothly in methanol and 2-propanol too.



Scheme 5.7 Substrate scope of the reaction of β-(2-aminophenyl)-α,β-ynone **16a** with pentane-2,4-dione **20a** in different alcoholic solvents.

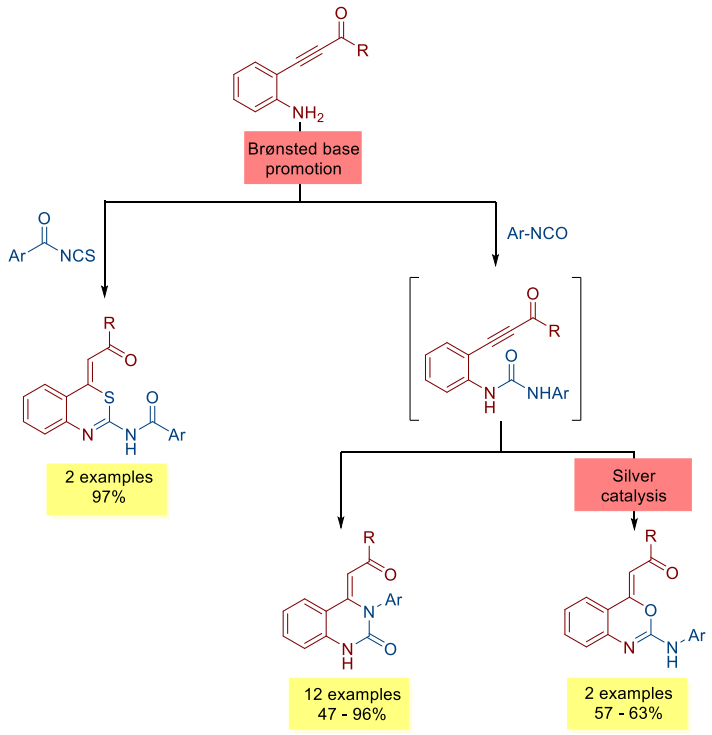
The use of methanol as solvent gave comparable results to the use of ethanol, while the use of the more sterically hindered 2-propanol resulted in a worst result, with the isolation of the expected ketal **23aaIPr** together with the uncyclized quinoline **21aa** in 39% yield. This is a further confirmation that the solvent plays a crucial role in the ketal-forming cyclisation.

5.3 Conclusions

Concluding, in continuation to the work reporter in Chapter 4, the *p*-toluenesulfonic acid promoted reaction of β-(2-aminophenyl)-α,β-ynones with carbonyl compounds has been expanded to activated carbonyl compounds, such as β-ketoesters and β-diketones. For β-ketoesters, the use of catalytic amounts of *p*-TsOH·H_2O enabled to isolate, in excellent yields, 4*H*-pyrano[3,4-c]quinoline-4-one derivatives, very interesting organic scaffolds for their high similarity to natural-occurring compounds. The broad substrate scope showed a high level of compatibility of the methodology with a wide range of substituents on both reagents. β-diketones, on the contrary, requested a stoichiometric amount of *p*-TsOH to efficiently yield 4*H*-pyrano[3,4-c]quinolines; interestingly, these compounds have been isolated only in their ketalic form because of the involvement of the ethanolic solvent in the cyclisation cascade sequence. Indeed, the solvent seemed to play a crucial role in the ketal-forming cyclisation, as demonstrated by the impossibility to generate the ketal ring using other solvents, such as toluene and CH_3CN. The versatility of this three-component reaction has been demonstrated by varying the nature of all the three reagents. Although the results are only preliminary (especially regarding the screening of β-diketones and alcohols), the methodology seems to be robust and compatible with several functional groups. Both methodologies are expected to be of great applicability thanks to the potential application of the obtained polycyclic quinolines in therapy or as fluorescent probes.

Chapter 6

Sequential reactions of β-(2-aminophenyl)-α,β-ynones with isocyanates/isothiocyanates



The tandem addition/cyclisation reaction of β-(2-aminophenyl)-α,β-ynones with aryl isocyanates/benzoyl isothiocyanate was investigated under Brønsted base-promotion. Suitable reaction conditions were found to selectively direct the reaction outcome towards the divergent generation of quinazoline, benzoxazine and benzothiazine derivatives through the 6-*exo-dig* *N*-, *O*-, or *S*-annulation of the *in situ* generated alkynyl urea/thiourea intermediate. Quantum-chemical calculations have been performed in collaboration with Professor Massimiliano Aschi (DSFC, Università degli Studi dell'Aquila, Italy) in order to provide a plausible rationale for the reaction outcome.

Arcadi, A.; Aschi, M.; Chiarini, M.; Marinelli, F.; Marsicano, V.; Portalone, G. *Org. Biomol. Chem.* **2020**, 18, 3177-3189.

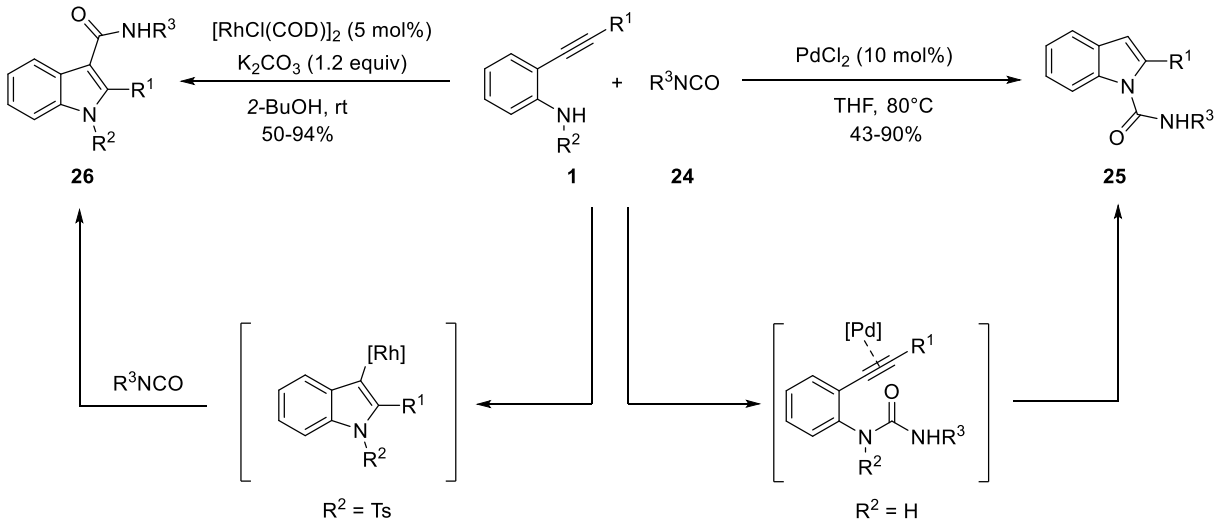
6.1 Introduction

Isocyanates and isothiocyanates represent powerful tools in organic chemistry, especially in cascade reactions, thanks to their peculiar reactivity. In fact, although nitrogen, oxygen and sulphur atoms have a nucleophilic nature, the highly electrophilic character of the central carbon atom makes isocyanates/isothiocyanates particularly reactive electrophilic partners in the presence of nucleophilic entities, such as amines and alcohols. However, after reacting with such nucleophiles, they disclose the masked nucleophilic sites which can be engaged in further reactions. Thus, when reacting with bifunctional compounds (i.e. compounds bearing both electrophilic and nucleophilic moieties), multiple bonds can be formed at the same time, allowing the easy access to complex cyclic structures, especially N-, O- and S-heterocyclic molecules.

Isocyanates/isothiocyanates have been extensively used in MCRs. For example, polysubstituted 4-sulfonyliminotetrahydropyrimidin-2-ones have been recently obtained in moderate to excellent yields under mild copper-catalysed conditions through a three-component sequential reaction employing propargylamines, isocyanates and sulfonyl azides as reagents. [61] A convenient one-pot MCR approach has been developed by Potuganti et al. to obtain spiro-oxazolidinone derivatives from simple ketones, arylacetylenes and isocyanates through sequential catalytic addition, hydroamination and cyclisation. [62] Visible light has been successfully used to promote the three-component assembly of 2-iminothiazolidin-4-ones starting from amines, isothiocyanates and α-bromoesters. [63]

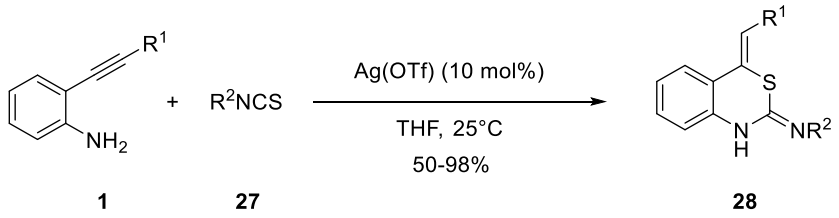
Sequential reactions of isocyanates and isothiocyanates with 2-alkynylaniline derivatives have been widely explored under different reaction conditions to generate several types of heterocyclic scaffolds. Through palladium chloride catalysis, for example, 2-alkynylanilines and phenyl isocyanates have been converted into 2-substituted-*N*-1*H*-indole-1-carboxamides through the regioselective 5-endo-dig cyclisation of the *in situ* formed 2-alkynyl-phenylurea intermediate. [64] The same reaction has been later studied by Inamoto and co-workers who, using rhodium catalysis, obtained the isomeric 2-substituted indole-3-carboxamide scaffold (Scheme 6.1). [65]

[61] Tong, T.; Wu, X.; Li, E.; Kang, H.; Wang, X.; Lv, X. *J. Org. Chem*. **2018**, 83, 15533-15540.
[62] Potuganti, G.R.; Indukuri, D.R.; Nanubolu, J.B.; Alla, M. *J. Org. Chem.* **2018**, 83, 15186-15194.
[63] Guo, W.; Zhao, M.; Tan, W.; Zheng, L.; Tao, K.; Liu, L.; Wang, X.; Chen, D.; Fan, X. *J. Org. Chem*. **2018**, 83, 1402-1413.
[64] Ye, S.; Ding, Q.; Wang, Z.; Zhou, H.; Wu, J. *Org. Biomol. Chem.* **2008**, 6, 4406-4412.
[65] Mizukami, A.; Ise, Y.; Kimachi, T.; Inamoto, K. *Org. Lett*. **2016**, 18, 748-751.



Scheme 6.1 Divergent reactivity of 2-alkynylanilines with isocyanates.

Conversely, the 6-exo-dig cyclisation of the urea intermediate has been efficiently obtained in the reaction of 2-alkynylanilines with isothiocyanates under Ag-catalysis; 2,4-dihydro-1H-benzo[d][1,3]thiazines have been easily obtained at room temperature in moderate to excellent yields. [66] Interestingly, in the reported reaction conditions, the cyclisation of the thiourea intermediate obtained *in situ* occurs always in a 6-exo-dig manner with sulphur acting as nucleophile, regardless of the nature of the substituents on both reagents.



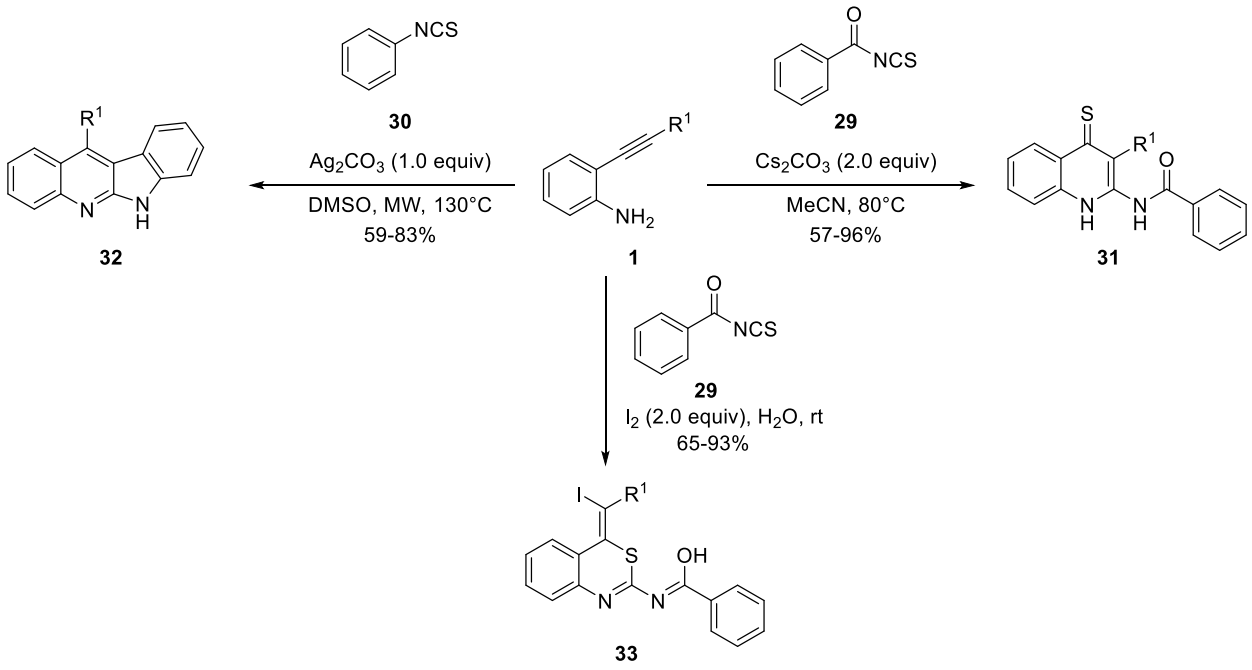
Scheme 6.2 Reaction of 2-alkynylanilines with tosyl isocyanates.

The same research group has later reported an interesting update on the methodology developed, showing that similar results could be obtained by using silica gel as heterogeneous promoter. Silica can be reused up to four times without a significant loss of catalytic activity, which has been ascribed to its mild Lewis acidity. [67]

When performing the same reaction under MW irradiation, using Ag_2CO_3 as catalyst, indolo[2,3-b]quinolines **32** have been obtained, through the desulphurisation of the thiourea intermediate, which subsequently undergoes an intramolecular thermal [3+2] cyclisation generating a carbene-type intermediate which forms the quinoline core by C-H insertion and

[66] Ding, Q.; Wu, J. *J. Comb. Chem.* **2008**, 10, 541-545.
[67] Ding, Q.; Cao, B.; Zong, Z.; Peng, Y. *J. Comb. Chem.* **2010**, 12, 370-373.

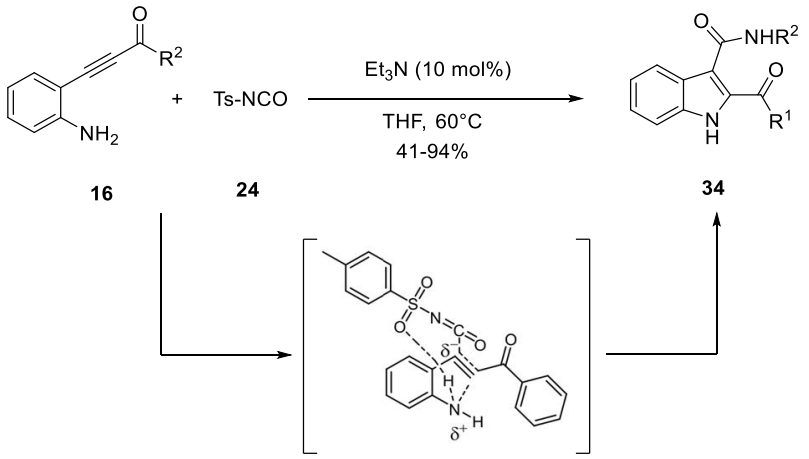
aromatisation. [68] The replacement of aryl/alkyl isothiocyanates with aroyl/acyl isothiocyanates enabled to divergently generate quinoline-4(1*H*)-thiones **31** through a different base-promoted 6-exo-dig S-cyclisation/rearrangement sequence. [69] The reaction of aroyl isothiocyanates and 2-alkynylanilines has been studied also in water, using I_2 as promoter, generating iodo-substituted 1,3-benzothiazines **33**. [70] Benzothiazines have also been obtained in the catalyst-free reaction of phenyl isothiocyanates with 2-amino chalcones; by simply changing the solvent in which the reaction takes place, 3,4-dihydroquinazoline-2-thiones can be divergently generated. [71]



Scheme 6.3 Reaction of 2-alkynylanilines with isothiocyanates.

Because of the great interest in using β-(2-aminophenyl)-α,β-ynones in cascade reactions, the research group in which this thesis has been carried out has previously explored their reactivity with tosyl isocyanates. [72] Using catalytic amounts of triethylamine, an unprecedented 5-endo-dig cycloamination/carboxamidation reaction has been described, achieving an efficient approach for the synthesis of 2-aroyl-*N*-tosyl-1*H*-indole-3-carboxamide. DFT calculations led to speculate that the reaction occurs through a sulfonate-assisted cycloamination reaction followed by a barrier-free carboxamidation at β position of the starting ynone.

[68] Ali, W.; Dahiya, A.; Pandey, R.; Alam, T.; Patel, B.K. *J. Org. Chem*. **2017**, 82, 2089-2096.
[69] Modi, A.; Sau, P.; Patel, B.K. *Org. Lett*. **2017**, 19, 6128-6131.
[70] Saini, K.M.; Saunthwal, R.K.; Kumar, S.; Verma, A.K. *Org. Biomol. Chem*. **2019**, 17, 2657-2662.
[71] Xie, T.; Xiao, Y.; Zhao, S.; Hu, X.-Q.; Xu, P.-F. *J. Org. Chem*. **2016**, 81, 10499-10505.
[72] Rode, N.D.; Aschi, M.; Chiarini, M.; Del Vecchio, L.; Marinelli, F.; Arcadi, A. *Adv. Synth. Catal*. **2018**, 360, 3672-3676.



Scheme 6.4 Reaction of β-(2-aminophenyl)-α,β-ynones with tosyl isocyanates.

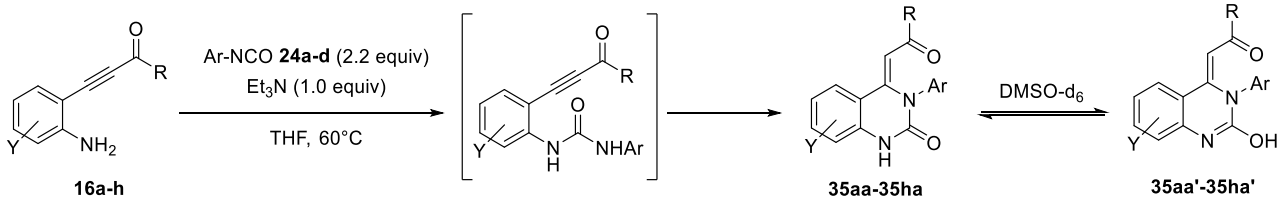
The reaction, however, seemed to work only with tosyl isocyanates under the tested reaction conditions; to expand the methodology towards different types of isocyanates, further studies have been done, discovering a completely different sequence involving N-addition and 6-exo-dig cyclisation when using phenyl isocyanates.

6.2 Results and discussion

When 3-(2-aminophenyl)-1-phenylprop-2-yn-1-one **16a** was reacted with phenyl isocyanate **24a** under the reaction conditions optimised for tosyl isocyanates, no appreciable reaction occurred. Conversely, when the reaction was performed using a large excess of phenyl isocyanate (2.2 equiv.) and a stoichiometric amount of triethylamine (Et_3N), in anhydrous THF at 60°C, it was possible to isolate the 3,4-dihydroquinazolin-2(1*H*)-one derivative **35aa** as the only product (Table 6.1, entry 1). It could be easily inferred that, under these conditions, the reaction proceeds firstly through the addition of the isocyanate to the amino group of β-(2-aminophenyl)-α,β-ynone, with *in situ* generation of an urea intermediate, which then undergoes an intramolecular 6-exo-dig conjugate addition, affording the isolated product. Noteworthy, in these conditions the cyclisation occurs always through attack of the nitrogen atom; the formation of the benzoxazine scaffold derived from the oxygen attack over the conjugated triple bond was never observed. [73]

[73] Costa, M.; Della Ca', N.; Gabriele, B.; Massera, C.; Salerno, G.; Soliani, M. *J. Org. Chem*. **2004**, 69, 2469-2477.

Table 6.1 Substrate scope of the reaction between β-(2-aminophenyl)-α,β-ynones **16a-h** and isocyanates **24a-d.**



Entry	R	Ar	Y	Time (h)	Yield[a] (%)	35/35' [b]
1	Ph	Ph	H	3	69	**35aa/35aa'** (81/19)
2	Ph	*p*-NO_2-C_6H_4	H	2	90	**35ab/35ab'** (60/40)
3	Ph	*p*-CH_3O-C_6H_4	H	24	47	**35ac/35ac'** (83/17)
4	C_5H_{11}	Ph	H	6	96	**35ba/35ba'** (81/19)
5	C_5H_{11}	*p*-Cl-C_6H_4	H	6	82	**35bd/35bd'** (67/33)
6	*p*-CH_3-C_6H_4	Ph	H	5	70	**35ca/35ca'** (79/21)
7	*p*-CH_3-C_6H_4	*p*-Cl-C_6H_4	H	6	81	**35cd/35cd'** (66/34)
8	1-naphtyl	Ph	H	5	75	**35da/35da'** (82/18)
9	1-naphtyl	*p*-Cl-C_6H_4	H	6	90	**35dd/35dd'** (62/38)
10	*p*-CH_3O-C_6H_4	Ph	H	5	87	**35ea/35ea'** (80/20)
11	2-thyenyl	Ph	H	6	59	**35ga/35ga'** (86/14)
12	Ph	Ph	CN	5	72	**35ha/35ha'** (74/26)

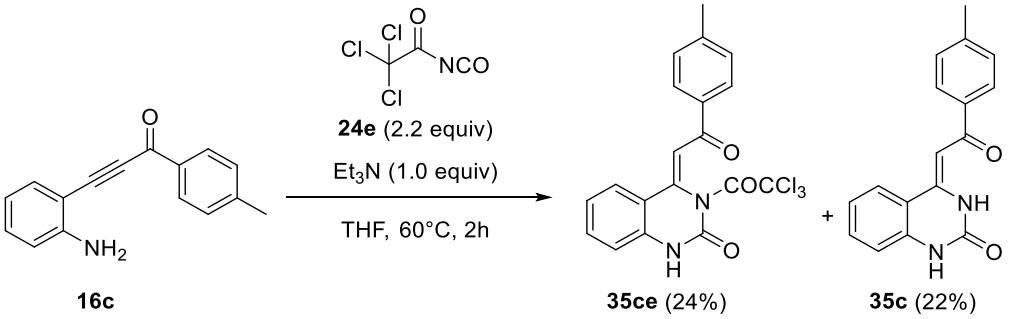
Reaction conditions: to a solution of **16** (0.5 mmol) in anhydrous THF, Et_3N (0.5 mmol) and aryl isocyanate **24** (1.1 mmol) were added, at rt and under N_2 purging. The mixture was brought at 60°C and stirred for 3-24 h. [a] Isolated yield. [b] Determined by ^1H NMR.

As shown by the data reported in Table 6.1, the reaction of β-(2-aminophenyl)-α,β-ynones **16a-h** with isocyanates **24a-d** afforded the 3,4-dihydroquinazolin-2(1*H*)-one products **35aa-35ha** in moderate to excellent yields. Aryl, heteroaryl and alkyl substituents were well tolerated in the acyl framework of ynones, with better results obtained with the *n*-pentyl-substituted ynone **16b** (Table 6.1, entry 4). The introduction of substituents in the aniline ring was well tolerated too; the methodology was also compatible with the presence of strong electron-withdrawing groups (such as the cyano group) in *para* position to the nitrogen atom, which should decrease the nucleophilicity of the amino group, hindering the addition reaction with isocyanates (Table 6.1, entry 12).

Isocyanates bearing both electron-withdrawing (**24b** and **24d**) and electron-donating (**24c**) substituents on the aryl group were tested too. Both types of substituents were well tolerated, showing a peculiar pattern of reactivity: phenyl isocyanates with electron-withdrawing groups

generally afforded the corresponding products with higher yields, while the *p*-MeO-substituted one required prolonged reaction times to generate the corresponding 3,4-dihydroquinazolin-2(1H)-one **135ac** only in moderate yield.

The reaction was also performed using isocyanates bearing different substituents than aryl groups. The reaction conditions were partly compatible with the use of trichloroacetyl isocyanate **24e**; in fact, when it was reacted with 3-(2-aminophenyl)-1-(p-tolyl)prop-2-yn-1-one **16c**, the trichloroacetyl quinazolin-2-one **35ce** was isolated in low yield but together with the trichlorodeacetylated derivative **35c** (Scheme 6.5). On the contrary, the reaction did not work at all with alkyl-substituted isocyanates, such as cyclohexyl isocyanate, with complete recovery of the unreacted starting materials.



Scheme 6.5 Reaction of **16c** with trichloroacetyl isocyanate **24e**.

All the 3,4-dihydroquinazolin-2(1H)-one derivatives were selectively obtained as Z isomers. The configuration of the double bond was assigned by 2D-NOESY experiments, after having unambiguously assigned all the ^{1}H and ^{13}C NMR resonances though 2D-COSY, HMBC and HSQC. As shown in Figure 6.1, for **35aa** (chosen as model compound), the analysis of NOESY spectrum showed proximity of the ethylidene proton H(18a) with the proton H(10) of the dihydroquinazolin-2(1H)-one ring and with the protons H(22,26) of the phenyl substituent in the acyl moiety, confirming the Z geometry of the double bond.

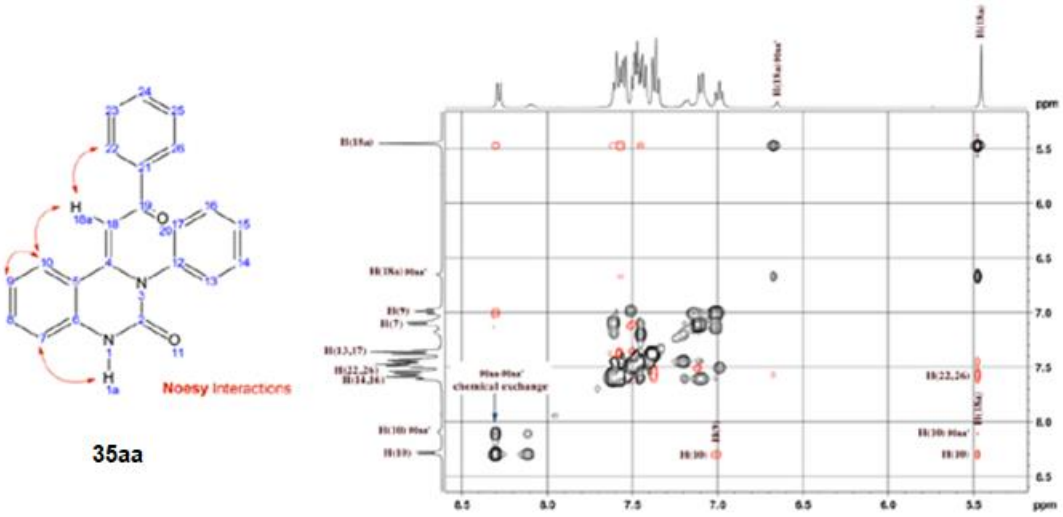


Figure 6.1 NOESY correlations for **35aa**, with an enlargement of the key portion of the spectrum.

For all the compounds obtained, the NMR analysis in DMSO-d_6 showed the presence of mixtures of both the NH tautomer **35** and the OH tautomer **35'**. In all the examined cases, the predominant form was the NH tautomer **35**; however, the compounds obtained with isocyanates bearing electron-withdrawing groups showed an increased amount of the OH tautomer **35'** at equilibrium, with ratios shifting approximately from 8:2 to 6:4 (Table 6.1). This tautomeric equilibrium was expected only in solution; in fact, X-ray crystallographic analysis of compounds **35aa** and **35ca** revealed that, in the solid state, only the NH form is present, which is highly stabilised by the formation of strong N–H···O intermolecular hydrogen bonds (2.807 (3)–2.865(3) Å) between centrosymmetric molecules (Figure 6.2).

The tautomeric behaviour of 2-substituted-4(3H)-quinazolinones has already been investigated through a combination of theoretical calculations and experiments [74] and has also been observed in the functionalisation of 2-methyl-3-o-tolyl-4(3H)quinazolinone. [75]

[74] Sim, Y.-L.; Omer, N.; Khan, M.N.; Pratt, L.M. *Tetrahedron* **2013**, 69, 2524-2533.
[75] Rathman, T.L.; Sleevi, M.C.; Krafft, M.E.; Wolfe, J.F. *J. Org. Chem*. **1980**, 45, 2169-2176.

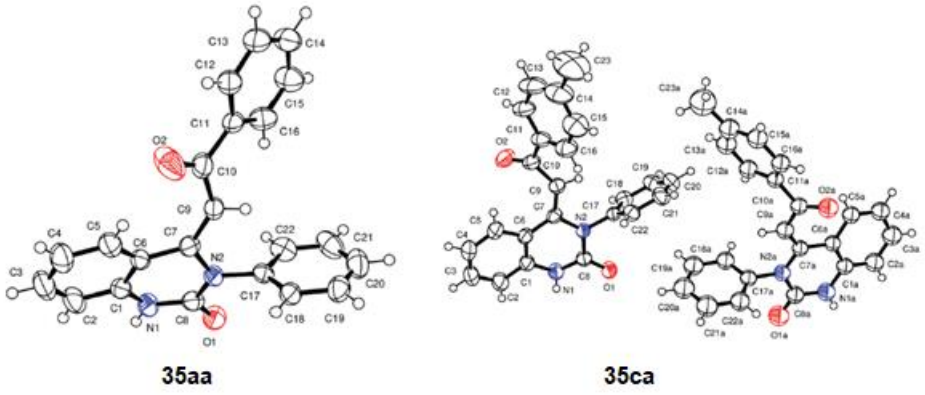
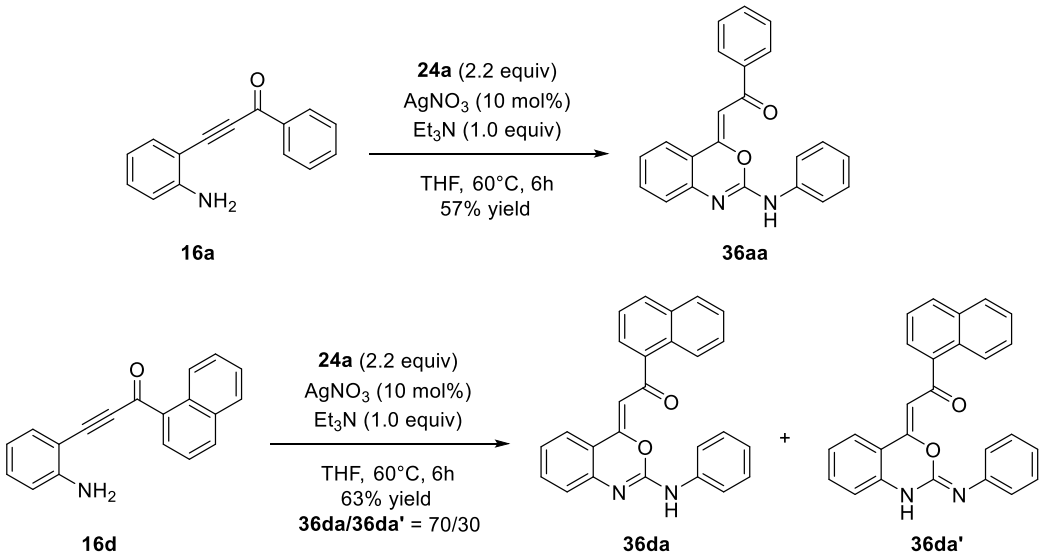


Figure 6.2 Asymmetric units of **35aa** and **35ca**, showing the atomic crystallographic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

The 2-alkynylurea intermediate that originates after addition of aryl isocyanates to the amino group of β-(2-aminophenyl)-α,β-ynones possesses both N- and O-nucleophilic sites, thus can be considered as a bidentate nucleophile. It has already been demonstrated that, by correctly choosing reaction conditions and catalysts, it is possible to selectively direct the cyclisation of alkynyl ureas toward the only formation of N- or O-cyclised derivatives. [76] For example, in the gold-catalysed cycloisomerization of N-substituted-2-alkynyl-1H-indole-1-carboxamides, the two isomeric products have been divergently obtained by simply changing the silver salt additive, with the N-cyclised derivative isolated when using AgOTf and the O-cyclised one when using $AgNO_3$. [77] Indeed, the role of coinage metals on directing the selectivity of the cycloisomerization reactions of alkynyl ureas and other substrates has been already widely explored. [78]

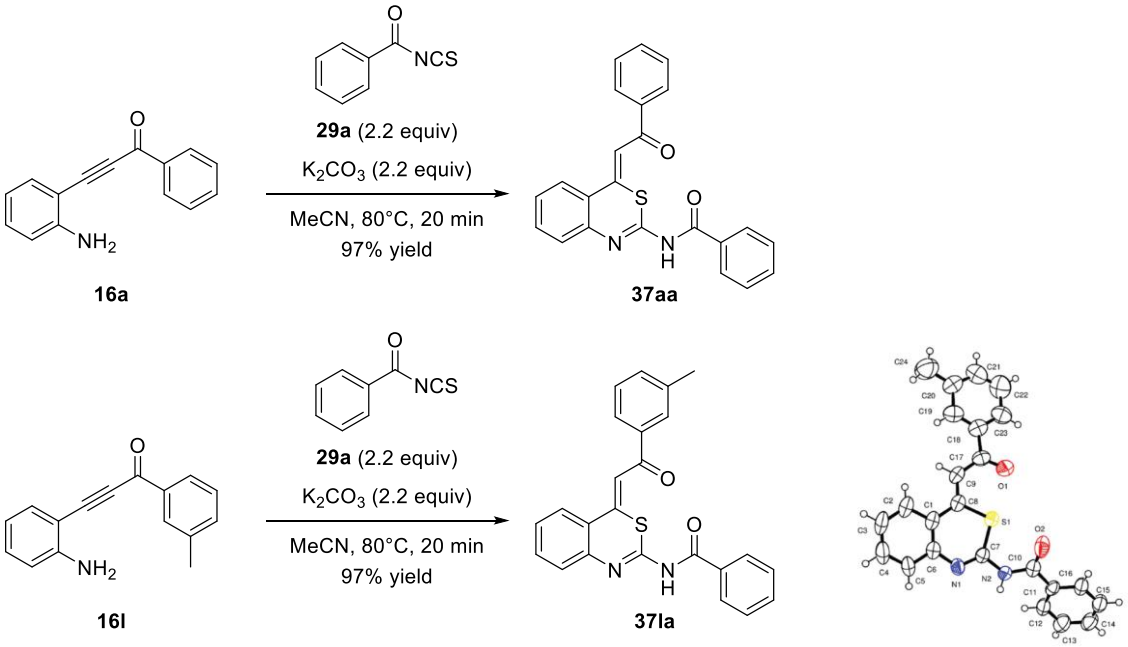
Consequently, $AgNO_3$ was chosen as catalyst in order to selectively access the O-cyclised products. When the reaction of 3-(2-aminophenyl)-1-phenylprop-2-yn-1-one **16a** with phenyl isocyanate **24a** has been performed in the presence of catalytic amounts of $AgNO_3$, the O-cyclised (2Z)-2-(2-anilino-4H-3,1-benzoxazin-4-ylidene)-1-phenylethanone **36aa** was isolated in moderate yield; this compound does not show a tautomeric equilibrium in DMSO-d_6 solution. Conversely, **36da**, obtained in the reaction of 3-(2-aminophenyl)-1-(naphthalen-1-yl)prop-2-yn-1-one **16d** with **24a**, resulted in a 70:30 mixture of both tautomers when analysed by NMR in DMSO-d_6 (Scheme 6.6).

[76] a) Peshkov, V.A.; Pereshivko, O.P.; Nechaev, A.A.; Peshkovc, A.A.; Van der Eycken, E.V. *Chem. Soc. Rev.* **2018**, 47, 3861-3898. b) Bianchi, G.; Chiarini, M.; Marinelli, F.; Rossi, L.; Arcadi, A. *Adv. Synth. Catal.* **2010**, 352, 136-142.
[77] Gupta, S.; Koley, D.; Ravikumar, K.; Kundu, B. *J. Org. Chem.* **2013**, 78, 8624-8633.
[78] Boyle, J.W.; Zhao, Y.; Chan, P.W.H. *Synthesis* **2018**, 50, 1402-1416.



Scheme 6.6 Silver-catalysed divergent access to O-cyclised scaffolds.

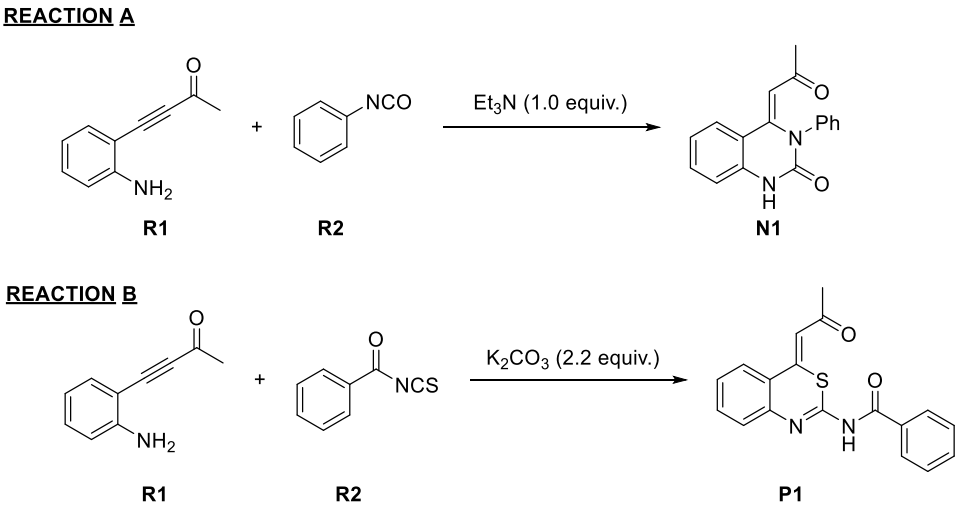
The methodology was expanded also to the use of aroyl isothiocyanates **29**. The optimised reaction conditions already used throughout the whole investigation resulted unsuccessful in the isolation of the cyclised product; on the contrary, the use of conditions similar to those already reported in literature for the reaction of 2-alkynylanilines and aroyl isothiocyanates enabled to isolate the S-cyclisation products **37aa** and **37la** in good yields and in short reaction times. The structure of the benzo[*d*][1,3]thiazine **37la** was also confirmed by X-ray crystallographic analysis (Scheme 6.7).



Scheme 6.7 Synthesis of benzo[*d*][1,3]thiazines through reaction of β-(2-aminophenyl)-α,β-ynones **16** with aroyl isothiocyanates **29**.

6.3 Computational investigation

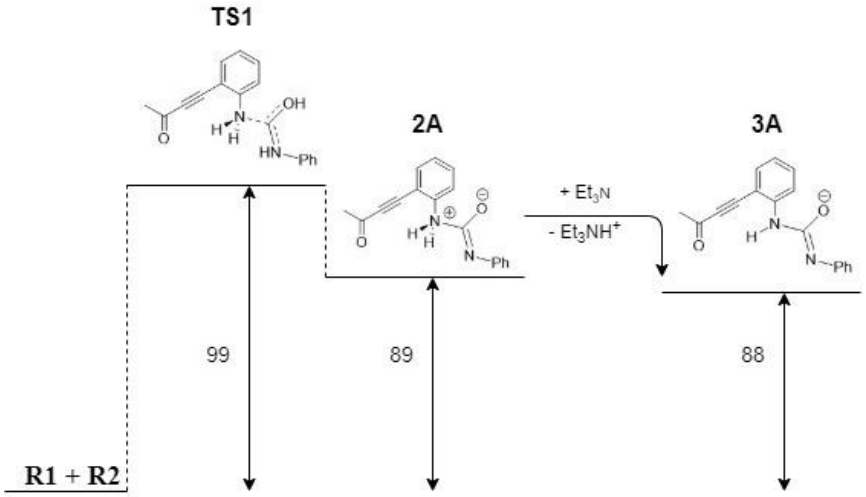
In order to better understand the reaction mechanism and to provide an insight into the factors determining the product selectivity of the tandem addition/cyclisation reactions of β-(2-aminophenyl)-α,β-ynones **16** with aryl isocyanates **24**/ benzoyl isothiocyanate **29**, quantum-chemical calculations have been performed. Because of the high computational costs associated with the analysis of the whole repertoire of the systems experimentally investigated, the attention was limited to two model reactions (Scheme 6.8).



Scheme 6.8 Model reactions investigated computationally.

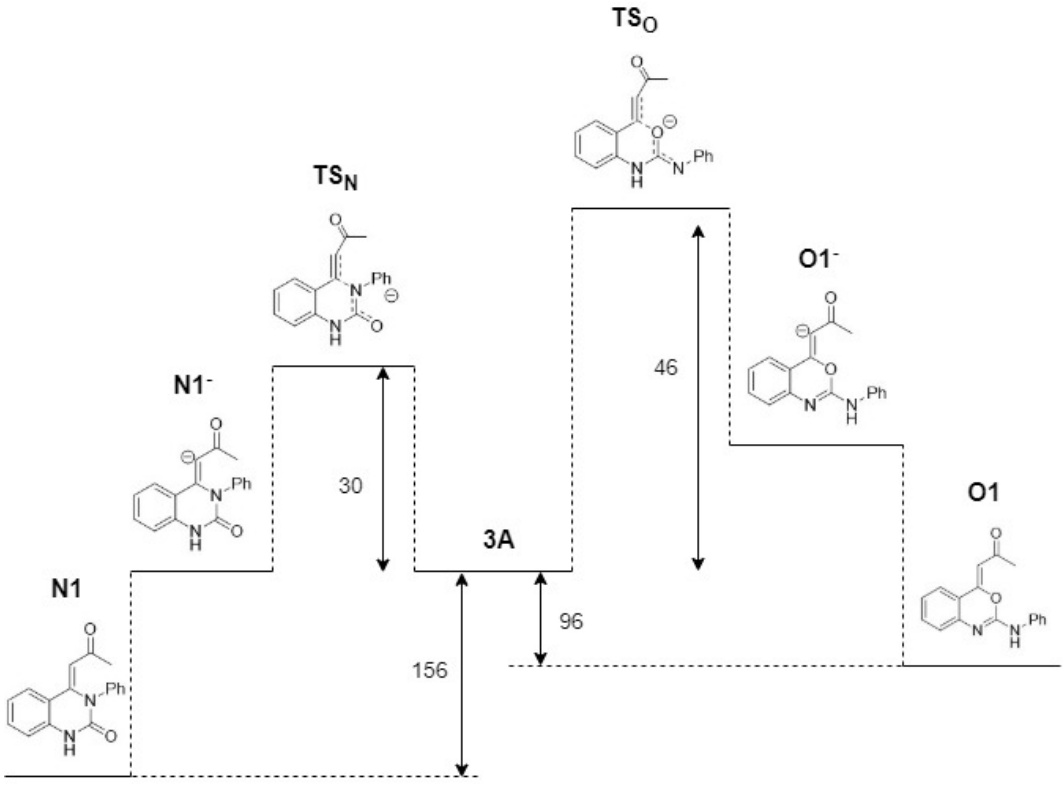
6.3.1 Reaction A

The results obtained with the computational analysis show that reaction A occurs firstly with the N-addition of phenyl isocyanate **R2** to the β-(2-aminophenyl)-α,β-ynone **R1** leading to the 2-alkynylurea intermediate **2A** in a zwitterionic form; any other attempt of finding plausible alternative pathways of **R1** addition, e.g. directly on the alkynyl moiety, turned out to be unproductive as they were characterised by very high-energy structures. The formation of **2A** is characterised by relatively high values of both the activation and reaction (standard) free energies at 60 °C (the temperature at which the reaction was experimentally performed), thus indicating that this initial step is neither kinetically nor thermodynamically favoured; moreover, **2A** can easily restore the reactants through a low barrier energy. However, the high-energy intermediate **2A** can be efficiently deprotonated by the Brønsted base present in stoichiometric amount, producing the anionic species **3A**.



Scheme 6.9 Free-energy diagram (at 60 °C in THF in kJ mol^{-1}) for the initial stage of Reaction A.

Once formed, **3A** can irreversibly interconvert either into the N-cyclised derivative **N1**$^{-}$ or into the O-cyclised one **O1**$^{-}$. These two anionic species are then transformed into their conjugated acids, i.e. the final product **N1** or **O1**, through the bimolecular reaction with the just-formed ammonium species. As shown in Scheme 6.10, N-cyclisation has a lower free-energy barrier than the competing O-cyclisation, in agreement with the experimentally observed formation of the sole **N1** product under the examined reaction conditions.



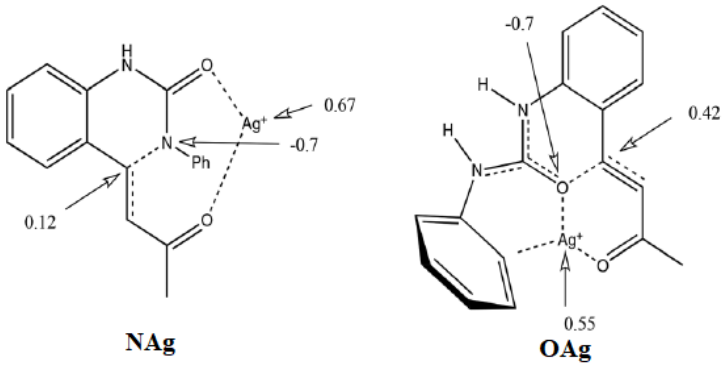
Scheme 6.10 Free-energy diagram (at 60 °C in THF in kJ mol^{-1}) for the alternative channels involving **3A.**

The tautomeric behaviour of **N1** has been addressed too. When the calculations were performed in THF as solvent, the OH tautomer **N1'** was revealed to be less stable than the NH one **N1**; however, when the solvent was switched to DMSO, the **N1'** species turns out to be more stable than **N1** of 10 kJ mol^{-1}, in qualitative agreement with the experimental observations.

Finally, the sequential regioselective 5-endo-dig cycloamination/carboxamidation pathway, that emerged from the previous investigation on tosyl isocyanates, was investigated too. The corresponding transition state showed an activation free energy more than 80 kJ mol^{-1} higher than **TS1** (Scheme 6.9), clearly indicating that this reaction channel, although able to lead to thermodynamically stable species, is kinetically irrelevant if compared to the other reaction route.

6.3.2 Effects of the addition of silver cations

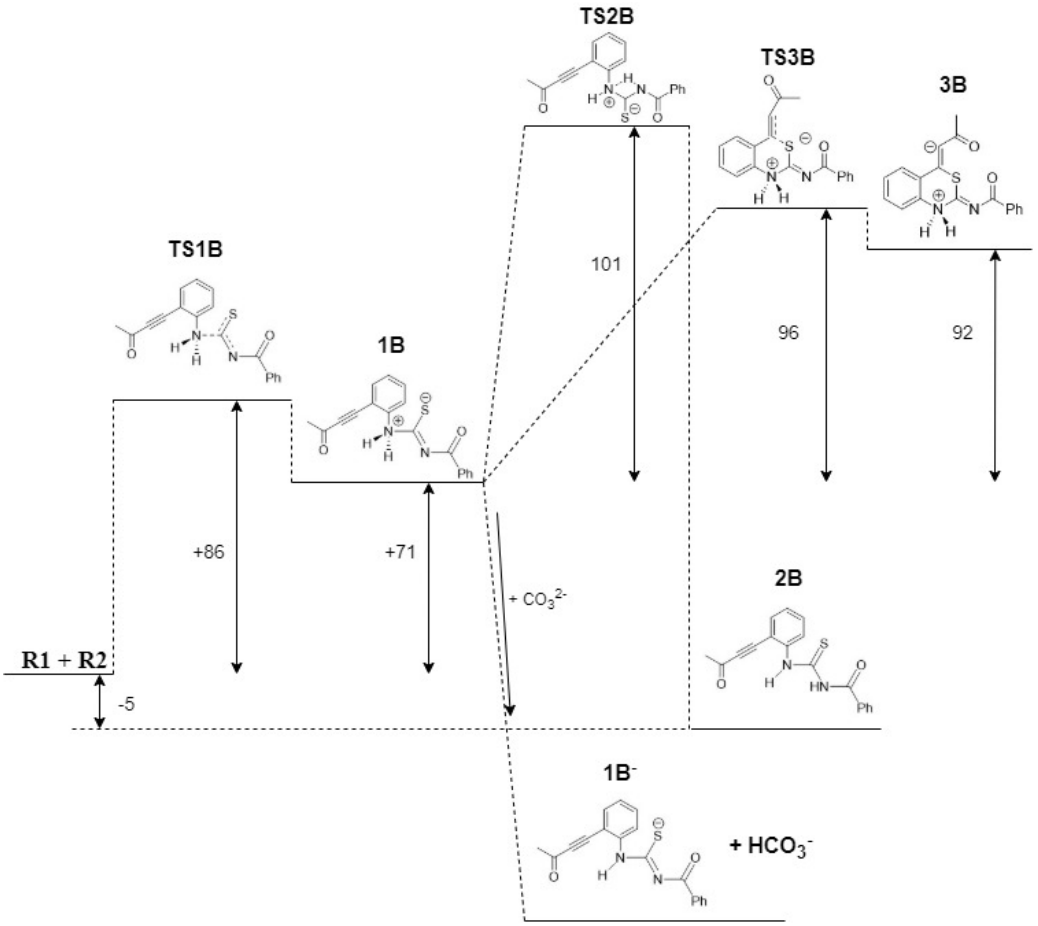
As stated above, the calculations performed revealed that O-cyclisation is less favourable than N-cyclisation under the optimised reaction conditions because of a much higher free-energy barrier. However, as demonstrated by the experimental results, the addition of $AgNO_3$ to the reaction mixture changed the reactivity profile, allowing the generation of the less favourable O-cyclised derivative. In order to rationalise the effects observed for the addition of silver cations, the transition states of both cyclisation modes have been studied in the presence of Ag^+. The results obtained show that the addition of silver cations determines a stabilisation of the transitions states, which is more pronounced for the O-cyclisation (OAg is 15 kJ mol^{-1} more stable than NAg). This results in a more pronounced lowering of free-energy barrier for O-cyclisation. Electronic effect appears to be very important. In fact, analysis of the atomic charges of the two TS structures, reported in Scheme 6.11, shows bigger enhancement of the partial (positive) charge on the electrophilic alkynyl carbon when O-cyclisation is concerned.



Scheme 6.11 Atomic charges calculated for the transition structures for N-cyclisation (**NAg**) and O-cyclisation (**OAg**) in the presence of the silver cation.

6.3.3 Reaction B

The mechanism concerning reaction B resulted to be much more diversified than that of reaction A, involving a higher number of low energy intermediates. Also in this case the interaction between **R1** [β-(2-aminophenyl)-α,β-ynone] and **R2** (benzoyl isothiocyanate) occurs primarily through N-addition, generating the zwitterionic intermediate **1B** with an activation energy similar to that of the initial step of reaction A.



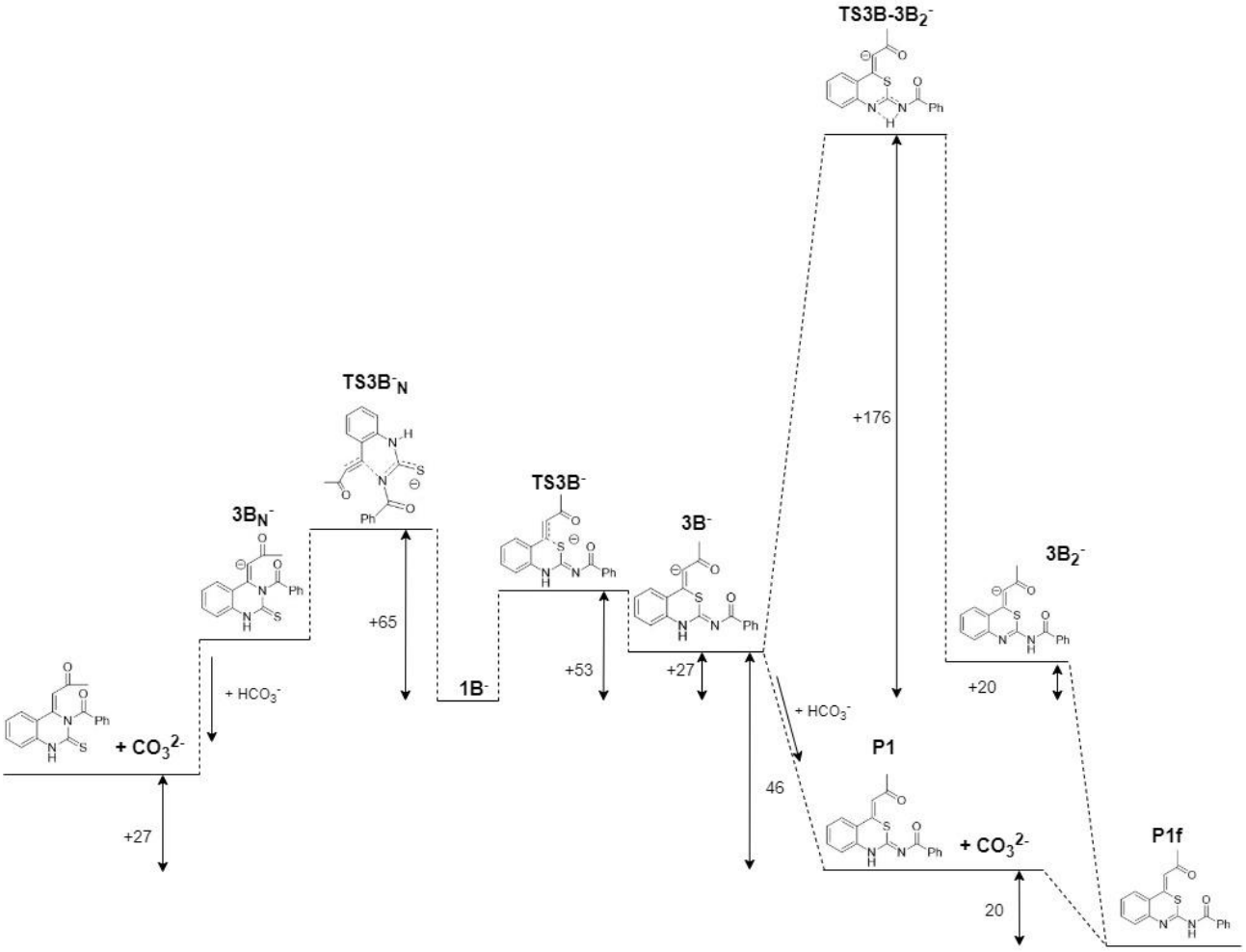
Scheme 6.12 Free-energy diagram (at 80 °C in acetonitrile in kJ mol^{-1}) for the initial stage of Reaction B.

Three different species can be generated from this intermediate (Scheme 6.12):

- **3B**, the zwitterionic product of the unimolecular S-cyclisation;
- **2B**, the neutral 2-alkynylurea, generated by unimolecular proton transfer;
- **$1B^-$**, the anionic species formed through the bimolecular, and practically irreversible, proton-transfer reaction with the carbonate ion.

Similar to Reaction A, also in this case the only route that is able to compete with the restoration of reagents is the one leading to **$1B^-$**. This anionic species subsequently undergoes the unimolecular S-cyclisation reaction generating the intermediate **$3B^-$** which irreversibly

forms the final product **P1** through a series of proton transfer reactions involving the CO_3^{2-}/HCO_3^- buffer. The alternative channel, leading to the formation of the N-cyclisation product from $\mathbf{1B}^-$, appears to be neither kinetically nor thermodynamically competitive with the S-cyclisation channel, in good qualitative agreement with the experimental outcome (Scheme 6.13).



Scheme 6.13 Free-energy diagram (at 80 °C in acetonitrile in kJ mol^{-1}) of the plausible evolution channels of intermediate $\mathbf{1B}^-$.

The S-cyclisation product can exist in two tautomeric forms, **P1** and **P1f**; however, differently from N-cyclisation products, only **P1f**, with the H atom bound to the N atom external to the cycle, has been experimentally observed. In accordance with the experimental data, **P1f** resulted to be approximately 20 kJ mol^{-1} more stable than **P1**. In theory, **P1f** can be directly generated form $\mathbf{3B}^-$ *via* an alternative pathway involving the transition state **TS3B-3B2**$^-$; however, because of the excessive height of the barrier associated with such a process, the formation of **P1f** must be rationalised through a sequence of bimolecular proton-transfer steps involving **P1** and CO_3^{2-}/HCO_3^- (Scheme 6.13).

6.4 Conclusions

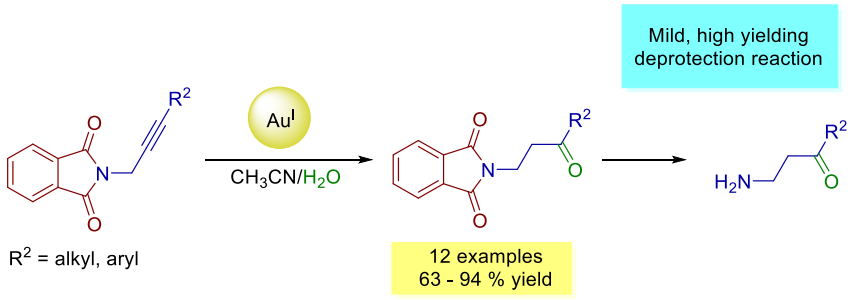
In conclusion, the reaction of a variety of β-(2-aminophenyl)-α,β-ynones with aryl isocyanates/benzoyl isothiocyanate has been explored under different reaction conditions, allowing the divergent generation of quinazoline, benzoxazine and benzothiazine derivatives, which are important organic scaffolds because of their medicinal properties. [79] A thorough investigation has been performed to confirm the structures obtained, both through bidimensional NMR analysis and X-ray crystallography of selected representative compounds. Isocyanates with both electron-withdrawing and electron-donating groups on the aryl substituent were tolerated by the reaction conditions; trichloroacetyl isocyanate can be used too but alkyl isocyanates resulted to be incompatible.

Quantum-chemical calculations have been performed to shed a light on the factors affecting the reaction, especially on the factors influencing the divergency in N-cyclisation vs. X-cyclisation (X = O, S) experimentally observed. From the mechanistic hypothesis done, it emerges that the key reactive species are, respectively, **3A** and **1B**$^{-}$. Their calculated atomic charges show a very good correlation with the calculated barriers, hence suggesting that electronic effect plays a central role in these reactions.

[79] a) Dohle, W.; Jourdan, F.L.; Menchon, G.; Prota, A.E.; Foster, P.A.; Mannion, P.; Hamel, E.; Thomas, M.P.; Kasprzyk, P.G.; Ferrandis, E.; Steinmetz, M.O.; Leese, M.P.; Potter, B.V.L. *J. Med. Chem.* **2018**, 61, 1031-1044. b) Pham, T.T.; Walden, M.; Butler, C.; Diaz-Gonzalez, R.; Pérez-Moreno, G.; Ceballos-Pérez, G.; Gomez-Pérez, V.; García-Hernández, R.; Zecca, H.; Krakoff, E.; Kopec, B.; Ichire, O.; Mackenzie, C.; Pitot, M.; Ruiz, L.M.; Gamarro, F.; González-Pacanowska, D.; Navarro, M.; Dounay, A.B. *Bioorg. Med. Chem. Lett.* **2017**, 27, 3629-3635. c) Sawant, R.T.; Stevens, M.Y.; Odell, L.R. *Eur. J. Org. Chem.* **2015**, 7743-7755.

Chapter 7

Gold-catalysed regioselective hydration of phthalimido-protected propargylamins: experimental and computational investigation



The regioselective hydration of *N*-protected propargylamines was investigated with the aim to find an easy way to access β-amino ketones, which are very interesting intermediates in organic synthesis. Gold catalysis appeared to be the elective choice to obtain phthalimido-protected β-amino ketones in high yields and under mild reaction conditions. Both aryl- and alkyl-groups were well tolerated. The removal of the phthalimido protecting group was achieved at room temperature and with a high yield. A thorough DFT investigation was performed in collaboration with Professor Massimiliano Aschi (DSFC, Università degli Studi dell'Aquila, Italy) to qualitatively support the obtained experimental data, especially regarding regioselectivity.

Marsicano, V.; Arcadi, A.; Aschi, M.; Michelet, V. *Org. Biomol. Chem.* **2020**, 18, 9438-9447.

7.1 Introduction

The hydration reaction of alkynes is an important reaction in synthetic organic chemistry since it can be efficiently used to convert alkynes into carbonyl compounds which are much more versatile building blocks and have multiple interesting biological and chemical properties. Moreover, the hydration is characterised by a high value of atomic efficiency, which is one of the fundamental principles of green chemistry.

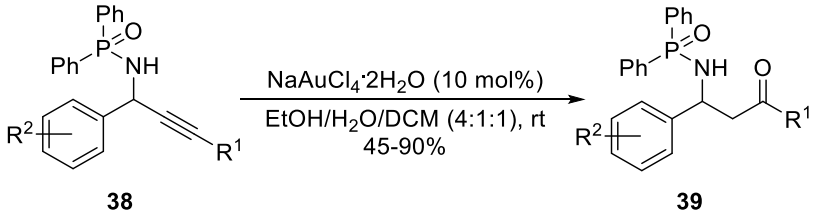
The first reported reactions involved very harsh conditions such as prolonged reaction times, great quantities of strong Brønsted acids, high temperatures; in 1881, Kucherov discovered that the reaction could be considerably improved by the addition of mercury salts such as $HgCl_2$, $HgBr_2$ or HgO. [80] Although very effective in promoting the reaction, mercury salts are highly toxic and tend to rapidly convert into inert metallic mercury. Because of this, new catalytic systems able to efficiently promote this reaction are still sought and studied. Gold has emerged as a valuable alternative of mercury thanks to its low toxicity and to the ability to catalyse the reaction at mild conditions. Different types of alkynes have been efficiently hydrated using gold as catalyst, [81] showing good to high levels of regioselectivity when using unsymmetrical internal alkynes as starting materials.

Propargylamines too have been submitted to gold-catalysed hydration with the aim to generate β-amino ketones, that are not only important for their pharmaceutical properties (i.e. bupropion, pyrovalerone, falicaine, moban) but also very interesting as reactive intermediates. For example, they can be easily converted in β-amino alcohols which are a widespread structural motif in natural and synthetic biologically active molecule (i.e. fluoxetine and duloxetine); [82] moreover, they can also be used as versatile chiral building blocks or auxiliaries in a variety of asymmetric synthesis such as enantioselective dialkylzinc addition to aldehydes [83] and in Henry reactions. [84]

Recently, Ying et *al*. reported the $NaAuCl_4$-catalysed hydration of *N*-(diphenylphosphinoyl)propargyl amines **38** (Scheme 7.1). [85] Although characterised by limited substrate scope to only alkyl-substituted propargylamines, the methodology developed

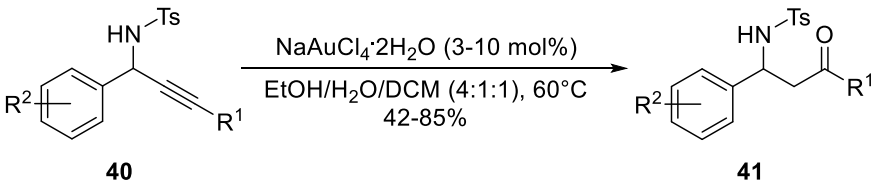
[80] Ponomarev, D.A.; Shevchenko, S.M. *J. Chem. Educ.* **2007**, 84, 1725-1726.
[81] For selected examples of recent literature, see: a) Lima, S.R.; Coelho, F. *ACS Omega* **2020**, 5, 8032-8045. b) Kuang, J.; Zhou, T.; You, T.; Chen, J.; Su, C.; Xia, Y. *Org. Biomol. Chem.* **2019**, 17, 3940-3944. c) Cloutier, M.; Roudias, M.; Paquin, J.-F. *Org. Lett.* **2019**, 21, 3866-3870. d) Li, F.; Wang, N.; Lu, L.; Zhu, G. *J. Org. Chem.* **2015**, 80, 3538-3546. e) Ghosh, N.; Nayak, S.; Prabagar, B.; Sahoo, A.K. *J. Org. Chem.* **2014**, 79, 2453-2462. f) Xie, L.; Wu, Y.; Yi, W.; Zhu, L.; Xiang, J.; He, W. *J. Org. Chem.* **2013**, 78, 9190-9195. g) Ghosh, N.; Nayak, S.; Sahoo, A.K. *J. Org. Chem.* **2011**, 76, 500-511. h) Marion, N.; Ramón, R.S.; Nolan, S.P. *J. Am. Chem. Soc.* **2009**, 131, 448-449.
[82] Calow, A.D.J.; Fernández, E.; Whiting, A. *Org. Biomol. Chem.* **2014**, 12, 6121-6127.
[83] Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, 101, 757-824.
[84] Palomo, C.; Oiarbide, M.; Laso, A. *Angew. Chem. Int. Ed.* **2005**, 44, 3881-3884.
[85] Ying, J.; Pu, L. *J. Org. Chem.* **2016**, 81, 8135-8141.

was regiospecific towards the formation of β-amino ketones **39** under very mild conditions. The regiochemistry was ascribed to the directing effect of the N-diphenylphosphinoyl group through formation of a six-membered cyclic intermediate.



Scheme 7.1 Gold-catalysed hydration of N-(diphenylphosphinoyl)propargyl amines.

Later, Ying et *al*. expanded the methodology to *N*-tosyl protected propargylamines **40**. [86] In this case too, the regiospecificity was linked to the formation of a six-membered cyclic intermediate through the attack of one of the oxygen atoms of the tosyl group.



Scheme 7.2 Gold-catalysed hydration of N-tosyl propargylamines.

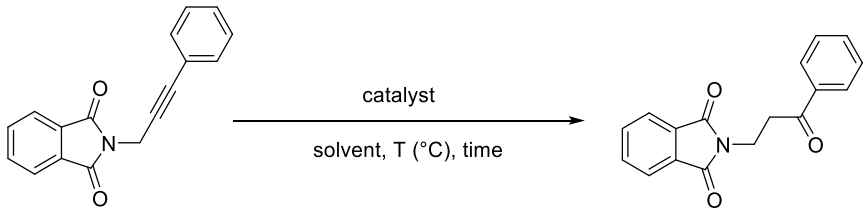
Although the above-reported methodologies allowed to easily generate β-amino ketones, the *N*-protecting groups chosen in both cases to direct the regiochemical outcome of the reaction were not easily removable from the final products. As the absence of protecting groups may hinder the reaction, it would be desirable to use a protecting group that could be later removed under mild conditions. For this purpose, the phthalimido group has been selected as a useful alternative protecting group to direct the regioselective atom-economical functionalisation of non-symmetrical alkynes by means of gold catalysis. The phthalimido moiety can be, in fact, easily removed from the obtained derivatives using bases or hydrazine. Moreover, phthalimide is an interesting pharmacophoric scaffold that is present in several drugs and bioactive molecules, [87] so increasing the potential applicability of the synthetised derivatives. For example, 2-(3-oxo-3-phenylpropyl)isoindoline-1,3-dione (**43a**) has been recognised as a potential non-glycosidic inhibitor of β-D-galactosidase. [88]

[86] Ying, J.; Wang, H.; Qi, X.; Peng, J.-B.; Wu, X.-F. *Organometallics* **2018**, 37, 2837-2841.
[87] a) Mahlooji, I.; Shokri, M.; Manoochehri, R.; Mahboubi-Rabbani, M.; Rezaee, E.; Tabatabai, SA. *Arch. Pharm*. **2020**, 353, e2000052. b) Tehrani, M.B.; Emani, P.; Rezaei, Z.; Khoshneviszadeh, M.; Ebrahimi, M.; Edraki, N.; Mahdavi, M.; Larijani, B.; Ranjbar, S.; Foroumadi, A.; Khoshneviszadeh, M. *J. Mol. Struct.* **2019**, 1176, 86-93. c) Zahran, M.A.H.; El-Aarag, B.; Mehany, A.B.M.; Belal, A.; Younes, AS. *Arch. Pharm. Chem. Life Sci*. **2018**; 351, e1700363.
[88] Abdula, A.M.; Khalaf, R.A.; Mubarak, M.S.; Taha, M.O. *J. Comput. Chem*. **2010**, 32, 463-482.

7.2 Results and discussion

To test the feasibility of the regioselective hydration reaction using phthalimide as protecting group, the readily available *N*-propargyl phthalimide **42a** was selected as a model substrate for the screening of catalysts and reaction conditions. The results of the investigation are summarised in Table 7.1.

Table 7.1 Optimisation of the reaction conditions for the hydration of *N*-propargyl phthalimide **42a**.



42a **43a**

Entry	Catalyst	Solvent	T (°C)	time (h)	Yield [a] (%) (Conv.) [b]
1	$NaAuCl_4 \cdot 2H_2O$	EtOH/H_2O/DCM (4:1:1)	r.t.	24	19 (20)
2	$NaAuCl_4 \cdot 2H_2O$	EtOH	80	19	64 (88)
3 [c]	*p*-TsOH·H_2O	EtOH	80	24	12 (15)
4	$IPrAuNTf_2$	EtOH	80	24	79 (-)
5	$IPrAuNTf_2$	H_2O	80	24	43 (49)
6	$IPrAuNTf_2$	CH_3CN/H_2O (10:1)	80	24	86 (88)
7	$IPrAu(CH_3CN)BF_4$	CH_3CN/H_2O (10:1)	80	24	60 (90)
8	$AgNTf_2$	CH_3CN/H_2O (10:1)	80	24	- (0)
9 [d]	$AgNO_3$	CH_3CN/H_2O (10:1)	80	24	- (0)
10	PPh_3AuNTf_2	CH_3CN/H_2O (10:1)	80	24	60 (-)
11	PPh_3AuNTf_2	CH_3CN/H_2O (10:1)	r.t.	24	16 (18)
12	$XPhosAu(CH_3CN)SbF_6$	CH_3CN/H_2O (10:1)	80	24	17 (32)

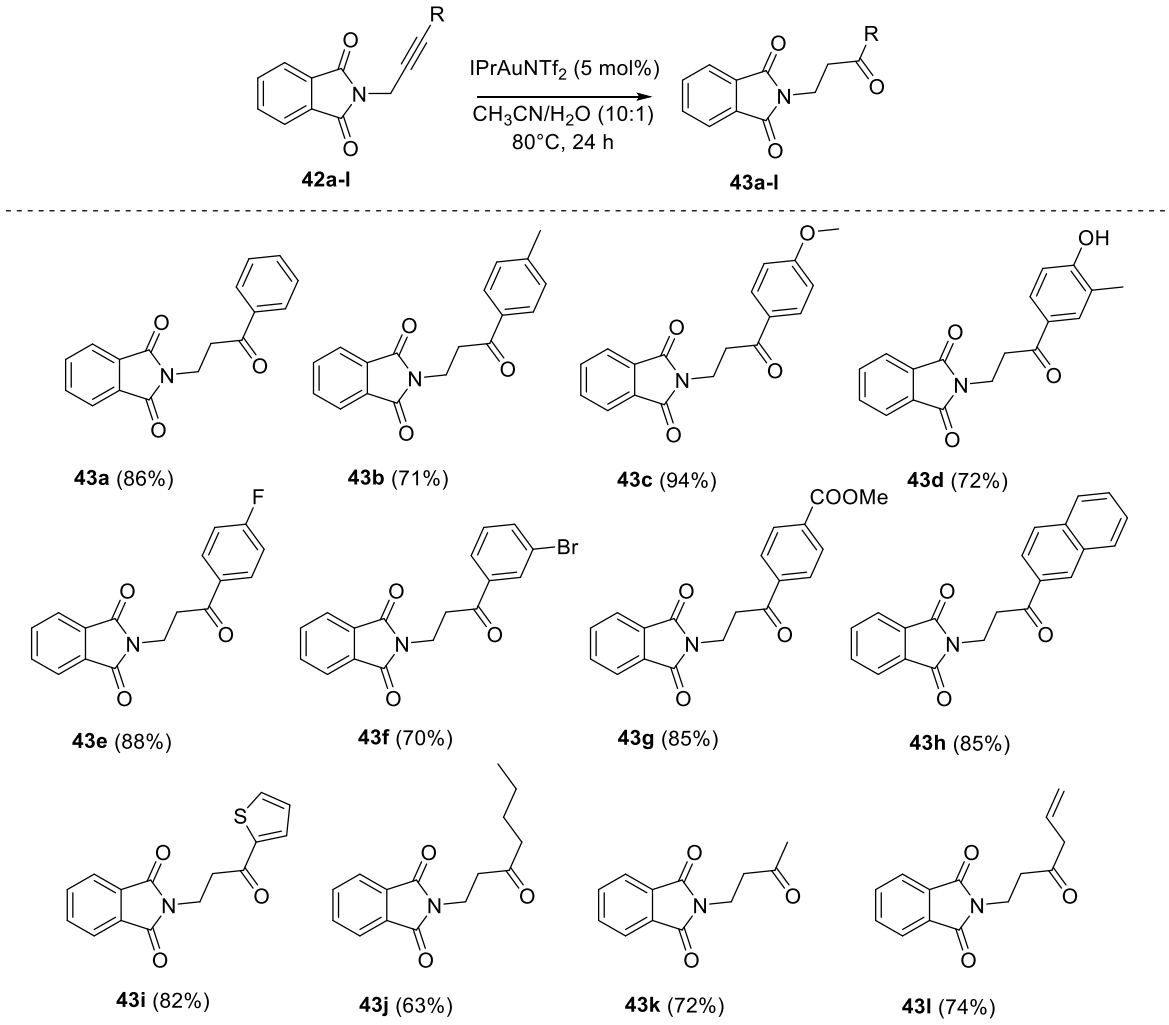
Reaction conditions: to a solution of **42a** (0.191 mmol) in 3 mL of solvent, the catalyst (5 mol%) was added. The mixture was stirred at the appropriate temperature (rt-80°C) for 19-24 h. [a)] Isolated yield. [b)] Conversion. [c)] *p*-TsOH was used in stoichiometric amount. [d)] 10 mol% of the catalyst were used.

The investigation was started by testing the conditions previously reported for the hydration of *N*-diphenylphosphinoyl propargylamines. [85] Only a single regioisomeric hydration product (the β-phthalimido derivative **43a**) was isolated, although in low yield and with the recovery of the unreacted starting material (80%) (Table 7.1, entry 1). The formation of **43a** occurred in 64% yield in the presence of the same catalyst in absolute ethanol at 80 °C, with a drastic

improvement of the conversion too (Table 7.1, entry 2). The use of stoichiometric amount of *p*- toluenesulfonic acid in refluxing ethanol failed to give **43a** in synthetic useful yield (Table 7.1, entry 3). [89] Pleasingly, the use of $IPrAuNTf_2$ as catalyst under the same reaction conditions resulted in the formation of the desired product in 79% isolated yield with complete conversion of the starting material (Table 8.1, entry 4). [90] In further optimisation of the reaction outcome, other reaction media were tested with the same catalyst. Pure water proved to be less suitable for the formation of the hydration product, with a drop of both yield and conversion (Table 7.1, entry 5); the use of CH_3CN and water in a 10:1 ratio provided very good results, with the formation of **43a** in 86% yield (Table 7.1, entry 6). Further investigations to find the more efficient catalytic system showed that the choice of the ligand L and anion X^- in complexes L-Au-X can play an effective role in the reaction outcome. [91] Changing the counter anion of the cationic gold(I) from NTf_2^- to BF_4^- resulted in a decreasing yield of **43a** to 60% yield (Table 7.1, entry 7). When using gold(I) catalysts bearing phosphines as ligands, poorer results were obtained: a slightly lower yield was obtained when using PPh_3AuNTf_2 in refluxing ethanol (Table 7.1, entry 10), while a dramatic decrease of yield was observed with $XPhosAu(CH_3CN)SbF_6$ (Table 7.1, entry 12). Finally, the use of silver(I) catalysts such as $AgNTf_2$ and $AgNO_3$ resulted in the recovery of the starting alkyne **42a** completely unchanged (Table 7.1, entries 8-9).

The optimised reaction conditions (Table 7.1, entry 6) were therefore used to study the scope and limitations of the methodology, by reacting a variety of *N*-propargyl phthalimides **42a-l** with different R groups at the terminal alkynyl position (Scheme 7.3). Both aryl- and alkyl-groups were well tolerated, giving only the corresponding β-phthalimido ketones **43a-l** in good to very good yields.

[89] Politanskaya, L.; Tretyakov, E. *Synthesis* **2018**, 555-564.
[90] Nun, P.; Ramon, R.S.; Gaillard, S.; Nolan, S.P. *J. Organomet. Chem.* **2011**, 696, 7-11.
[91] (a) Zuccaccia, D.; Del Zotto, A.; Baratta, W. *Coord. Chem. Rev.* **2019**, 396, 103-116. [b)] Jia, M.; Bandini, M. *ACS Catal*. **2015**, 5, 1638-1652.

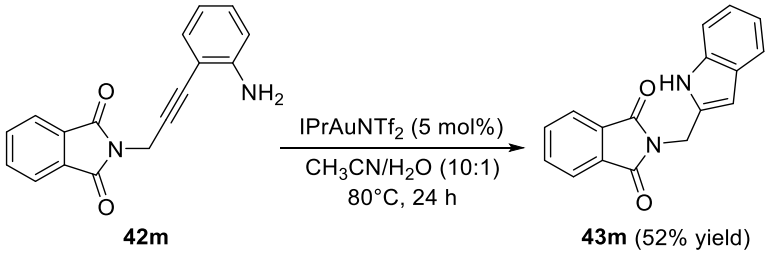


Scheme 7.3 Substrate scope of the gold-catalysed hydration of *N*-propargyl phthalimides **42**.

Both electron-donating and electron-withdrawing substituents on the aryl moiety were compatible with the developed methodology, with *p*-MeO group (**42c**) showing the best results in terms of yield. The thiophenyl- group was well tolerated too, affording the corresponding β-phthalimido ketone **43e** in good yield; on the contrary, when the reaction was performed using a *N*-propargyl phthalimide bearing a 2-pyridinyl substituent (structure not shown), no reaction occurred, probably because of the strong coordination of the heteroatom with the gold catalyst. [92] The reaction resulted successful for the compounds bearing a linear alkyl group at terminal alkynyl position too; gratifyingly, the hydration of **42l**, having an allyl group on the triple bond, afforded the desired product **43l** in good yield without participation of the double bond in the reaction. Interestingly, when the optimised reaction conditions were applied to the 2-aminophenyl substituted *N*-propargyl phthalimide **42m**, only the gold-catalysed

[92] a) Chen, X.; Martini, S.; Michelet, V. *Adv. Synth. Catal*. **2019**, 361, 3612-3618. b) Cacchi, S.; Fabrizi, G.; Fochetti, A.; Ghirga, F.; Goggiamani, A.; Iazzetti, A. *Org. Biomol. Chem.* **2019**, 17, 527-532.

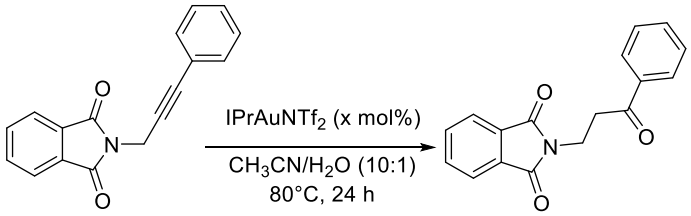
intramolecular hydroamination occurred, affording the 2-((1*H*-indol-2-yl)methyl)isoindoline-1,3-dione **43m** in 52 % yield (Scheme 7.4).



42m **43m** (52% yield)

Scheme 7.4 Gold-catalysed intramolecular hydroamination of **42m**.

To further demonstrate the versatility of the developed methodology, the hydration of **42a** was conducted on 1 g scale in the presence of a smaller amount of catalyst. When the reaction was performed with 2 mol% of $IPrAuNTf_2$ at 80 °C in CH_3CN/H_2O (10:1), the desired ketone **43a** was obtained in 69% isolated yield in 48h; a further reduction of the catalyst loading to 1 mol% resulted in the isolation of **43a** in a very poor yield (Scheme 7.5).

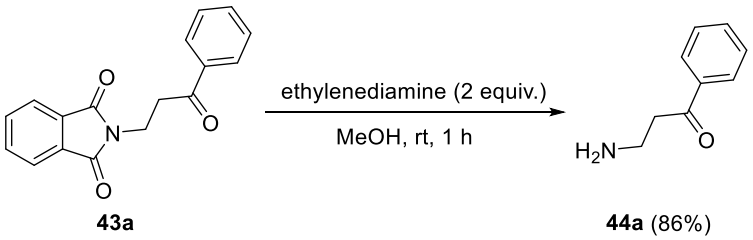


42a (1.00 g) **43a** (0.735 g, 69%, 2 mol%)
(0.136 g, 13%, 1 mol%)

Scheme 7.5 Scale-up of the hydration of the *N*-propargyl phthalimide **42a**.

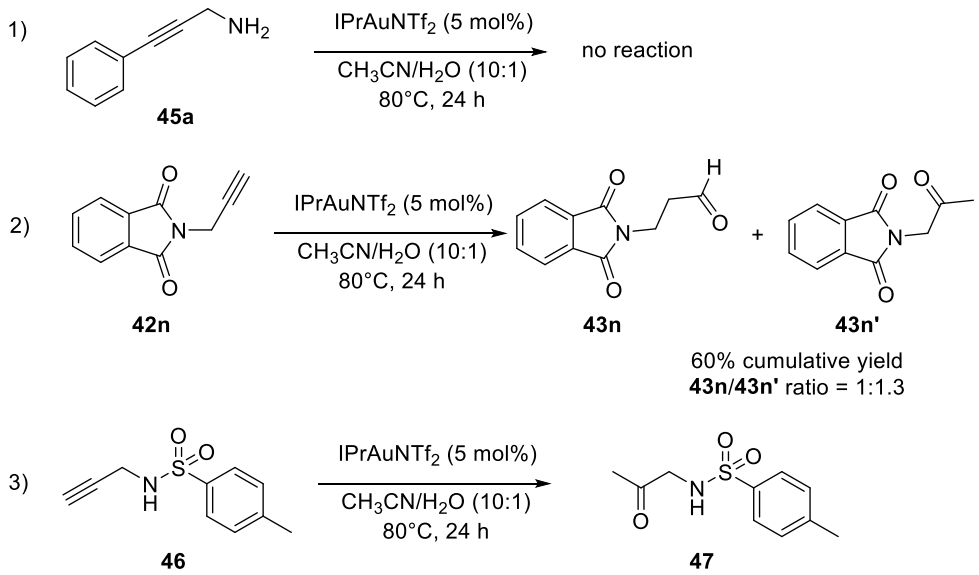
As already stated above, the great advantage of this procedure in comparison to the ones previously reported is the easiness with which the phthalimido protecting group can be removed, obtaining the valuable β-amino ketones. It was envisaged that the conditions classically used to remove the phthalimido moiety (excess of hydrazine in refluxing ethanol) would not have been compatible with the studied β-phthalimido ketones; in fact, when the reaction was explored using hydrazine hydrate, both in stoichiometric amount and in excess, a complex mixture of products was obtained. Interestingly, when using ethylenediamine in MeOH as deprotecting agent, [93] the corresponding primary amine derivative **44a** was easily obtained in very good yield and at much milder conditions (Scheme 7.6).

[93] Wang, Q.; Jiang, Y.; Sun, R.; Tang, X.-Y.; Shi, M. *Chem. Eur. J.* **2016**, 22, 14739-14745.



Scheme 7.6 Deprotection of the phthalimido derivative **43a**.

To investigate the mechanism of the reaction, some control experiments have been performed. Firstly, to demonstrate the role of the phthalimido group in the reaction outcome, the reaction was investigated using 3-phenylprop-2-yn-1-amine **45a** as substrate. When this compound, lacking the phthalimido protecting group, was reacted under the optimised reaction conditions, no desired hydration was observed (Scheme 7.7, Eq. 1), confirming its importance in controlling both the reactivity and the regiochemical outcome of the reaction. Subsequently, the reaction of the terminal *N*-propargyl phthalimide **42n** under the standard reaction conditions was investigated (Scheme 7.7, Eq. 2). A lack of regioselectivity was observed, with the reaction affording a mixture of **44n** and **44n'** in a 1:1.3 ratio and in 60% cumulative yield. Anticipating that this unusual regioselectivity could be due to the protective group, the hydration reaction was performed on the *N*-tosyl protected compound **46**. With this starting material, a total regioselectivity was observed leading to the formation of only the α-tosylamido ketone **47** in 77% yield (Scheme 7.7, Eq. 3). All the results obtained suggests that the phthalimido group plays indeed a crucial role in directing the regioselectivity of the hydration reaction but in a slightly less efficient way than the tosyl group, especially for terminal alkynes, indicating a potential influence of other parameters on the reaction outcome such as the electronic effects of the R substituent on the alkyne moiety.



Scheme 7.7 Control experiments on the effect of directing groups.

7.3 Computational investigation

Although several DFT calculations [94] and theoretical papers [95] have already appeared in literature aimed to clarify the mechanism of gold-catalysed alkyne hydration under apolar, aprotic and neutral conditions, further computational calculations have been performed to shed additional light on the key factors determining the regioselective outcome of the hydration of *N*-propargyl phthalimides. All the performed calculations suffer from some intrinsic limitations that do not allow to extract a fully quantitative information from the obtained free-energy profiles and from the QTAIMS analysis. However, they could be actually considered as a qualitative support to the experimental observations.

The hydration of 2-(3-phenylprop-2-yn-1-yl)isoindoline-1,3-dione **42a** was studied as model reaction, in acetonitrile at 80°C and in the presence of the complex of Au(I) with 1,3-dimethyl-imidazol-4,5-2-ylidene, as a simplified but still realistic model of the catalyst used in the experimental investigation. The results of the computational study are summarised in Figure 7.1. The reaction starts with the addition of water to the adduct between the gold active catalyst (indicated as R_1-Au^+) and the propargyl triple bond. The nucleophile can attack both the α and β positions of the triple bond, resulting, respectively, in the transition structures **TSα** and **TSβ**.

[94] a) Cordón, J.; Jiménez-Osés, G.; López-de-Luzuriaga, J.M.; Monge, M.; Olmos, M.E.; Pascual, D. *Organometallics* **2014**, 33, 3823-3830. b) Zuccaccia, D.; Belpassi, L.; Tarantelli, F.; Macchioni, A. *Eur. J. Inorg. Chem.* **2013**, 4121-4135. c) Mazzone, G.; Russo, N.; Sicilia, E. *J. Chem. Theory Comput.* **2010**, 6, 2782-2789. d) Krauter, C.M.; Hashmi A.S.K.; Pernpointner, M. *ChemCatChem* **2010**, 2, 1226-1230.

[95] Gatto, M.; Belanzoni, P.; Belpassi, L.; Biasiolo, L.; Del Zotto, A.; Tarantelli, F.; Zuccaccia, D. *ACS Catal.* **2016**, 6, 7363-7376.

As clearly depicted in Figure 7.1, **TSα** has a higher free energy than **TSβ**, with the β-addition appearing therefore as the kinetically more favoured initial step. Such a difference was also observed in the calculations performed in gas-phase (i.e., in the absence of possible solvent effects), thus suggesting that its origin should be related to intrinsic effects, such as electronic or steric effects.

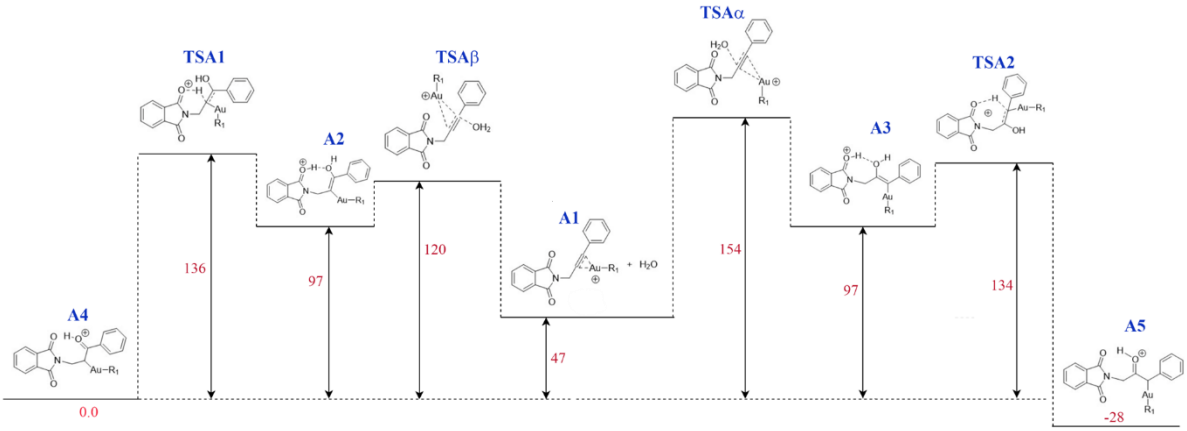


Figure 7.1 Free energy (kJ/mol) diagram at 80°C in acetonitrile for the gold-catalysed hydration of **42a**.

Hence, it could be easily inferred from the obtained data that the experimentally observed regioselectivity should be determined by the different free energy barrier between the α- and β-addition. In contrast with other gold-catalysed regioselective hydration reactions reported in literature, [96] the possible involvement of a cyclisation intermediate was discarded because of the very high positive free energy (ΔG° of +40 kJ/mol at 80°C, at the same level of the theory) associated with the related reaction. However, in both α- and β-addition, a sharp H-bond between the water molecule and the phthalimido moiety was found (in the intermediate complexes **A2** and **A3**), producing a zwitterionic pseudo-cyclic species in both cases. Such a proton was then transferred, through **TSA1** and **TSA2**, to the other carbon of the triple bond to irreversibly produce the protonated form of the final product. Therefore, this H-bond seems to be a key catalytic event for the whole process but, apparently, does not play any relevant role in the observed regioselectivity. The same shuttling role of the phthalimido group was observed when the reaction of *N*-propargyl phthalimide **42n** was investigated at the same level of theory (Figure 7.2). In this case, however, the relative height of the barriers of the α- and β-addition appeared to be lower and reversed in comparison to the hydration of **42a**, suggesting

[96] a) Goodwin, J.A.; Aponick, A. *Chem. Commun.* **2015**, 51, 8730-8741. b) Jeong, J.; Ray, D.; Oh, C.H. *Synlett*, **2012**, 897-902. c) Wang, W.; Xu, B.; Hammond, G.B. *J. Org. Chem.* **2009**, 74, 1640-1643.

a reduced degree of regioselectivity, in nice qualitative agreement with the experimental results.

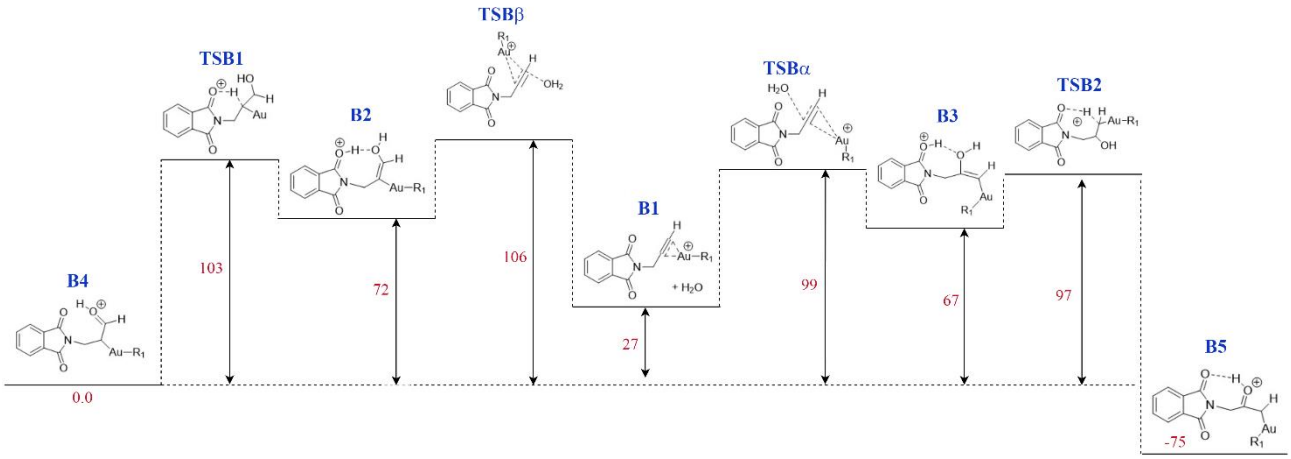


Figure 7.2 Free energy (kJ/mol) diagram at 80°C in acetonitrile for the gold-catalysed hydration of **42n**.

To verify the importance of the phthalimido shuttling group, the hydration of 3-phenylprop-2-yn-1-amine **45a** was investigated too. Although experimentally found to be completely inefficient, the analysis of the free-energy diagram showed that the hydration reaction could be considered as kinetically feasible through a relatively low energy-barrier α-addition thanks to the stabilising effect of the basic amino group in the intermediate **E2** (Figure 7.3). However, for this system, a very stable N-Au complex was identified, [97] which was found to be 75 kJ/mol more stable than the initial adduct between the gold catalyst and the propargylic triple bond. Further analysis of the data obtained revealed that this huge free energy difference could be entirely ascribed to non-intrinsic electronic effects and, in particular, to the higher polarity of the N-Au complex, whose dipole moment (4.0 Debye), is exactly twice bigger than that of the π-complex. Hence, in the presence of a polar solvent such as acetonitrile, the more polar N-Au complex is highly stabilised through electrostatic effects, resulting in the inhibition of the hydration reaction.

[97] a) Kovács, G.; Lledòs, A.; Ujaque, G. *Angew. Chem. Int. Ed.* **2011**, 50, 11147-11151. b) Lavallo, V.; Frey, G.D.; Donnadieu, B.; Soleilhavoup, M.; Bertrand, G. *Angew. Chem. Int. Ed.* **2008**, 47, 5224-5228.

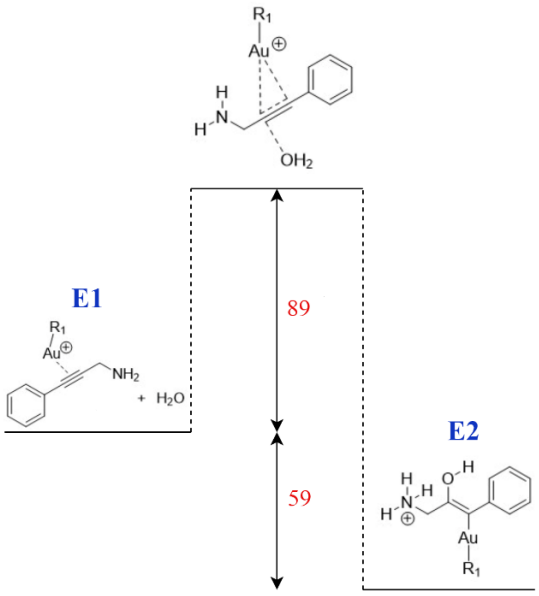


Figure 7.3 Free energy (kJ/mol) diagram at 80°C in acetonitrile for the gold-catalysed hydration of **45a**.

To better understand the factors influencing the observed regioselectivity, a comparative investigation was carried out on the main electronic features of the initial π-adduct and the hydration TSs, using both Natural Bond Order [98] and QTAIMS (Quantum Theory of Atoms In Molecules) [99] analysis. The first approach enables to calculate atomic charges, while the second is a density-based topological approach for studying the chemical bonds and the boundaries of the atoms forming a molecular system. The data obtained show that the gold(I) atom interacts, through a transit interaction (order of 50-60 kJ/mol), only with the C_α atom in substrate **42a**, probably because of the intrinsic electronic features of the π-adducts (Figure 7.4). As a consequence of such interaction, the metal induces an electronic vacancy on the adjacent Csp atom, which, in turns, results to be more electrophilic and more prone to be attacked by water. For this reason, only the C_β atom in **42a** always shows the kinetically more accessible hydration site, thus generating the observed regioselectivity.

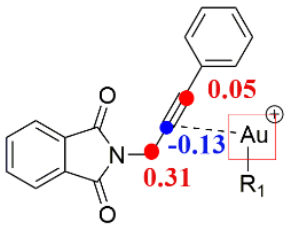


Figure 7.4 Schematic picture of the NBO charges (in atomic units) for the atoms mainly involved in the hydration process of **42a**. The presence or the absence of a dotted line between gold atom and the alkyne carbon atoms indicates the presence or the absence of an interaction as emerged from QTAIMS analysis.

[98] Foster, F.P.; Weinhold, F. *J. Am. Chem. Soc.* **1980**, 102, 7211-7218.
[99] Bader, R. *Chemical Reviews* **1991**, 91, 893-928.

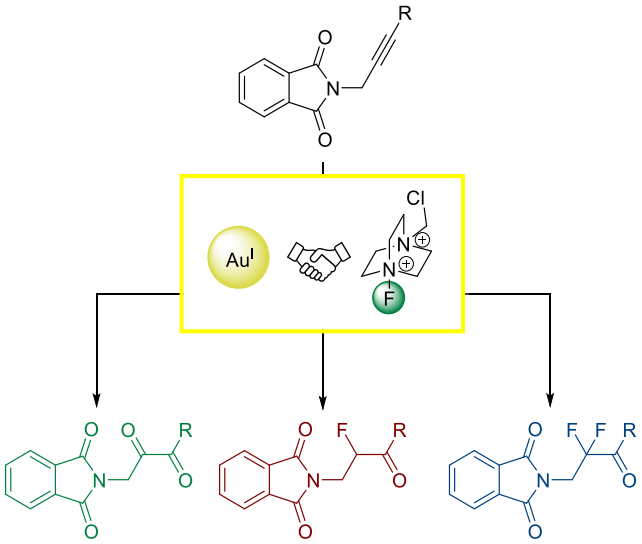
7.4 Conclusions

Concluding, the vast array of the gold-catalysed reactions has been further broadened by studying and optimising the hydration process of *N*-propargyl phthalimides towards the synthesis of valuable β-amino ketones. The commercially available IPrAuNTf$_2$ was found very effective in promoting such a reaction, under mild reaction conditions and in a regioselective way, regardless of the substituents of the alkynyl moiety. Furthermore, the presence of phthalimide as the amino-protecting group enabled to easily generate the corresponding primary amine at room temperature, in sharp contrast with the synthetic approaches previously reported in literature.

Computational calculations have been performed to clarify the factors influencing the regioselectivity and the results obtained for the hydration of substrates **42a**, **42n** and **45a** were found to be in satisfactory agreement with the experimental findings. Electronic effects appeared to be as the most relevant in influencing the reaction outcome and the selectivity, especially the intrinsic electronic features of the initial π-adduct and external electronic characteristics such as solvent effect. The phthalimido moiety was also found to be kinetically relevant for the irreversibility of the formation of the final product thanks to its ability to establish a H-bond with the entering molecule of water.

Chapter 8

Gold/Selectfluor partnership in the divergent functionalization of *N*-propargyl phthalimides

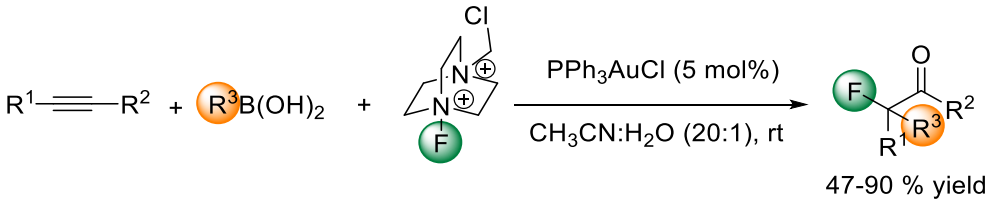


The well-known partnership between gold catalysis and Selectfluor was exploited to divergently generate three distinct chemical entities from the same *N*-propargyl phthalimide starting materials through the "functionalised hydration" strategy. By modifying the catalyst used, the equivalents of Selectfluor and the solvent mixture, very interesting fluoro- and difluoro ketones were generated, alongside with 1,2-diketones, which could be employed in the synthesis of interesting heterocyclic compounds. Although the work is only at a preliminary stage, the data collected so far suggested a good functional groups tolerance and a good versatility of the methodology.

8.1 Introduction

Gold catalysts have undoubtedly widened the range of organic architectures accessible from simple starting materials such as alkynes. However, certain transformations are not easily achievable with them, especially those involving changes in the oxidation state of the metal, because of the high redox potential showed by the Au(I)/Au(III) redox couple. A significant improvement in the field has been done through the association of the metal with other reactive partners, such as Selectfluor.

Selectfluor is an electrophilic fluorinating agent with R_3N^+-F general structure that, in comparison to the previous fluorinating reagents, is milder, safer, more stable and less expensive to produce. Since its discovery in 1992, Selectfluor has been extensively used in the fluorination of several different types of chemical functionalities, such as carbonyl compounds, thioethers, aromatic compounds, alkenes, exc. [100] Moreover, in partnership with gold, both C-C and C-O reductive elimination reactions have been described, further demonstrating its potential and versatility. [101] For example, Hammond and Xu have reported an elegant strategy to convert simple alkynes into α-substituted ketones, called "functionalised hydration". [102] In a domino sequence, water addition on the triple bond, oxidative coupling with phenyl boronic acids and fluorination allowed to generate α-fluoro-α-aryl ketones in one-pot (Scheme 8.1). Although obtaining good to excellent yields, regioselectivity was poor for asymmetrically substituted alkynes.



Scheme 8.1 Functionalised hydration of alkynes by Hammond and Xu.

The same approach has been successfully applied to other alkynylic substrates, such as terminal alkynes, [103] propargyl acetates, [104] *o*-alkynyl phenols, [93] and most recently *o*-alkynyl

[100] For selected examples, see: Nyffeler, P.T.; Gonzalez Durón, S.; Burkart, M.D.; Vincent, S.P.; Wong, C.-H. *Angew. Chem. Int. Ed.* **2005**, 44, 192-212 and references therein.
[101] For selected reviews on the association of Selectfluor with gold, see: a) Miró, J.; del Pozo, C. *Chem. Rev.* **2016**, 116, 11924-11966. b) Engle, K.M.; Mei, T.-S.; Wang, X.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2011**, 50, 1478-1491.
[102] a) Xu, B.; Wang, W.; Hammond, G.B. *J. Fluorine Chem.***2011**, 132, 804-810. b) Wang, W.; Jasinski, J.; Hammond, G.B.; Xu, B. *Angew. Chem. Int. Ed.* **2010**, 49, 7247-7252.
[103] de Haro, T.; Nevado, C. *Adv. Synth. Catal.* **2010**, 352, 2767-2772.
[104] a) de Haro, T.; Nevado, C. *Chem. Commun.* **2011**, 47, 248-249. b) Hopkinson, M.N.; Giuffredi, G.T.; Gee, A.D.; Gouverneur, V. *Synlett* **2010**, 18, 2737-2742.

benzaldehydes. [92a] In all the cases, α-fluoro ketones have been obtained in high yields and with good levels of regioselectivity.

The possibility to easily introduce fluorine atoms into organic molecules is of great appeal in the fields of organic and medicinal chemistry. [105] Fluorine can be considered, in fact, as a bioisoster of hydrogen: when introduced in an organic molecule in place of hydrogen, it induces only small steric changes but it determines great alteration of the electronic properties of the system, because of its high electronegativity and the strong covalent bond it can create with carbon. Moreover, in drugs, it has been demonstrated that fluorine is able to increase metabolic stability, especially reducing the susceptibility of nearby chemical groups to the enzymatic oxidation performed by cytochrome P450. [106] Furthermore, molecules bearing radioactive ^{18}F atoms are widely used in diagnosis, for example in Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI). [107] Consequently, the development of new, mild and highly regioselective methodologies to incorporate fluorine atoms in organic molecules is of great interest in modern organic chemistry.

Following the work reported in Chapter 7 on the regioselective hydration of *N*-propargyl phthalimides, it was anticipated that α-fluoro-β-amino ketones could be straightforwardly obtained with the same catalytic system by simply adding an excess of Selectfluor. α-Fluoro ketones are interesting organic compounds, both as building blocks in the synthesis of fluorinated organic architectures and as potential drugs, being analogues of α-hydroxy ketones, which are ubiquitous in nature. [108]

8.2 Results and discussion

The investigation was started by employing 2-(3-phenylprop-2-yn-1-yl)isoindoline-1,3-dione **42a** as model starting material in the screening of the suitable reaction conditions to achieve the selective formation of the monofluoro derivative. Different catalysts, solvent mixtures and amounts of Selectfluor were tested, as reported in Table 8.1.

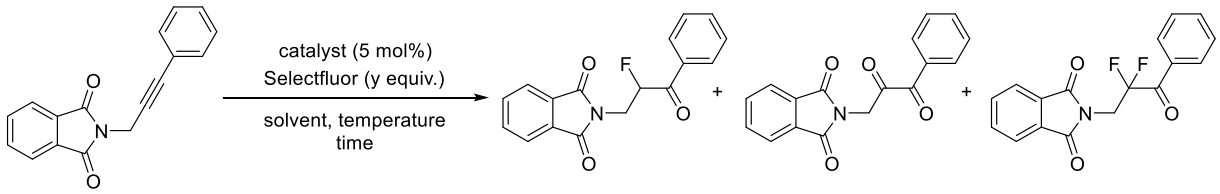
[105] a) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J.L.; Soloshonok, V.A.; Izawa, K.; Liu, H. *Chem. Rev.* **2016**, 116, 422-518. b) Yerien, D.E.; Bonesi, S.; Postigo, A. *Org. Biomol. Chem.* **2016**, 14, 8398-8427. c) Gouverneur, V.; Seppelt, K. *Chem. Rev.* **2015**, 115, 563-565. xx) O'Hagan, D. *Chem. Soc. Rev.* **2008**, 37, 308-319. xx) Purser, S.; Moore, P.R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, 37, 320-330.

[106] Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, 317, 1881-1886.

[107] a) Preshlock, S.; Tredwell, M.; Gouverneur, V. *Chem. Rev.* **2016**, 116, 719-766. b) Chansaenpak, K.; Vabre, B.; Gabbaï, F.P. *Chem. Soc. Rev.* **2016**, 45, 954-971. c) Buckingham, F.; Gouverneur, V. *Chem. Sci.* **2016**, **7**, 1645-1652. d) Tirotta, I.; Dichiarante, V.; Pigliacelli, C.; Cavallo, G.; Terraneo, G.; Baldelli Bombelli, F.; Metrangolo, P.; Resnati, G. *Chem. Rev.* **2015**, 115, 1106-1129.

[108] a) Fan, J.; Peng, Y.; Xu, W.; Wang, A.; Xu, J.; Yu, H.; Lin, X.; Wu, Q. *Org. Lett.* **2020**, 22, 5446-5450. b) Trost, B.M.; Tracy, J.S.; Yusoontorn, T.; Hung, C.-I J. *Angew. Chem. Int. Ed.* **2020**, 59, 2370-2374. c) Gonzalez, C.; de Cabrera, M.; Wnuk, S.F. *Nucleosides, Nucleotides & Nucleic Acids*, **2018**, 37, 248-260.

Table 8.1 Optimisation of the reaction conditions for the fluorination of *N*-propargyl phthalimide **42a**.



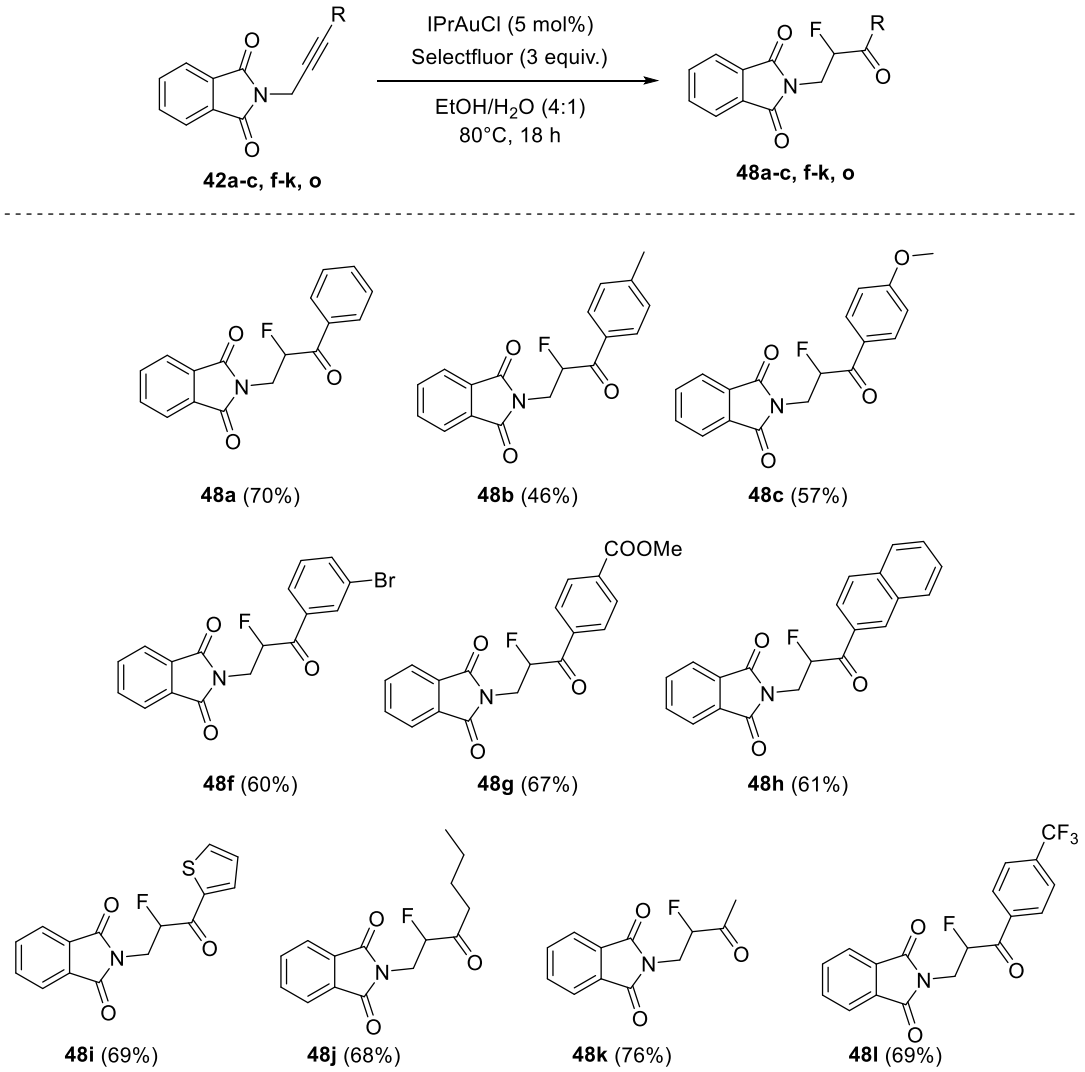
42a **48a** **49a** **50a**

Entry	Catalyst	y equiv.	Solvent	T (°C)/ Time (h)	Conv. (%)	Yield[a] (%)		
						113a	114a	115a
1	PPh_3AuCl	1.5	CH_3CN/H_2O (10:1)	rt/24	85	-	51	-
2	IPrAuCl	1.5	CH_3CN/H_2O (10:1)	80/24	68	-	66	-
3	PPh_3AuNTf_2	1.5	CH_3CN/H_2O (10:1)	80/24	88	-	82	-
4	PPh_3AuNTf_2	1.5	$EtOH/H_2O$ (4:1)	rt/24	61	22	12	-
5	PPh_3AuCl	3.0	$EtOH/H_2O$ (4:1)	rt/24	38	35	3	-
6[b]	PPh_3AuCl	3.0	$EtOH/H_2O$ (4:1)	80/24	79	56	20	-
7	PPh_3AuNTf_2	3.0	$EtOH/H_2O$ (4:1)	80/24	83	60	21	-
8[b]	PPh_3AuCl	3.0	$Acetone/H_2O$ (4:1)	80/24	ND	31	27	-
9[b]	PPh_3AuCl	3.0	DMF/H_2O (4:1)	80/24	49	-	23	-
10[b]	PPh_3AuCl	3.0	$MeOH/H_2O$ (4:1)	80/24	79	57	18	-
11[b]	PPh_3AuCl	3.0	$Dioxane/H_2O$ (4:1)	80/24	ND	34	46	-
12[b]	PPh_3AuCl	3.0	H_2O	80/24	41	6	-	-
13	IPrAuCl	3.0	$EtOH/H_2O$ (4:1)	80/18	98	70	9	-
14[c]	IPrAuCl	3.0	$EtOH/H_2O$ (4:1)	80/24	ND	-	-	-
15	-	3.0	$EtOH/H_2O$ (4:1)	80/24	0	-	-	-
16	AuCl	3.0	$EtOH/H_2O$ (4:1)	80/24	ND	-	43	-
17[d]	$AgNO_3$	3.0	$EtOH/H_2O$ (4:1)	80/24	52	-	46	-
18	$PdCl_2$	3.0	$EtOH/H_2O$ (4:1)	80/24	ND	-	39	-
19	$NaAuCl_4{\cdot}2H_2O$	3.0	$EtOH/H_2O$ (4:1)	80/24	98	38	-	59
20	$NaAuCl_4{\cdot}2H_2O$	3.0	$EtOH/H_2O$ (4:1)	rt/24	0	-	-	-
21	$NaAuCl_4{\cdot}2H_2O$	1.5	$EtOH/H_2O$ (4:1)	80/24	98	15	-	42
22	$NaAuCl_4{\cdot}2H_2O$	5.0	$EtOH/H_2O$ (4:1)	80/24	78	22	-	55
23	$NaAuCl_4{\cdot}2H_2O$	5.0	$EtOH/H_2O$ (4:1)	50/24	98	18	-	62

Reaction conditions: to a solution of **42a** (0.191 mmol) in 3 mL of solvent mixture, the catalyst (5 mol%) and Selectfluor (y equiv.) were added. The mixture was stirred at the appropriate temperature (rt-80°C) for 18-24 h. [a)] Isolated yields. [b)] Yields determined by ^1H NMR, using 3,4,5-tricholoropyridine as internal standard. [c)] NFSI was used as fluorinating agent. [d)] 10 mol% of the catalyst were used. ND = not determined.

When using PPh_3AuCl as catalyst, in the presence of 1.5 equivalents of Selectfluor, in a mixture of acetonitrile and water (10:1) at room temperature, no fluorination product **48a** was observed; instead, the over-oxidation product 2-(2,3-dioxo-3-phenylpropyl)isoindoline-1,3-dione **49a** was isolated in 51% of yields (Table 8.1, entry 1). Better yields of the same derivative were obtained when IPrAuCl or PPh_3AuNTf_2 were used as catalysts, in the same mixture of solvents at 80°C (Table 8.1, entries 2-3). Interestingly, when switching from acetonitrile to ethanol, the oxyfluorination product **48a** could be obtained, although together with the dioxo derivative **49a** (Table 8.1, entries 5-7). A rapid exploration of other solvent mixtures showed that alcoholic solvents allowed to obtain the best results, with ethanol being the best one. The reaction was also investigated in plain water but resulted in a very poor conversion (Table 8.1, entries 8-12). The investigation on the amount of Selectfluor indicated that the use of 3 equivalents was the best compromise to obtain the highest yield of **48a**, while the use of other fluorinating agents such as *N*-Fluorobenzenesulfonimide (NFSI) yielded the hydrated derivative **43a** as the sole product with 41% yield (Table 8.1, entry 14). As for the nature of the catalyst, IPrAuCl showed the best results when used in $EtOH/H_2O$ at 80°C while PPh_3AuCl and PPh_3AuNTf_2 resulted in a worse selectivity under the same reaction conditions (Table 8.1, entries 6-7 and 13). The presence of the gold catalyst was demonstrated to be fundamental, as the reaction did not take place at all when omitting IPrAuCl in the reaction system (Table 8.1, entry 15). Other metal catalysts, such as $AgNO_3$, AuCl and $PdCl_2$, were also ineffective for the formation of **48a** in refluxing wet ethanol (Table 8.1, entries 16-18). Interestingly, when using $NaAuCl_4$ in $EtOH/H_2O$ at 80°C, the difluoro derivative **50a** could be obtained as the major product in the reaction mixture (Table 9.1, entry 19). A rapid screening of the reaction conditions showed that product selectivity was influenced by both the temperature and the equivalents of Selectfluor used, with the best yield of **50a** being obtained with 5.0 equivalents of the fluorinating agent at 50°C (Table 9.1, entry 23).

Subsequently, the substrate scope of the gold/Selectfluor promoted oxyfluorination reaction was investigated using differently substituted *N*-propargyl phthalimides **42** under the optimized reaction conditions (Table 8.1, entry 13), as reported in Scheme 8.2.

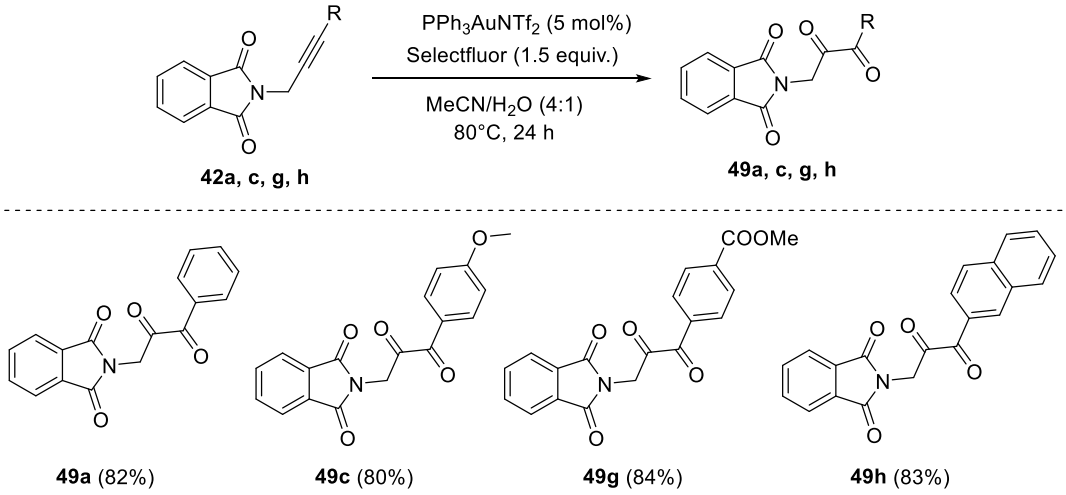


Scheme 8.2 Substrate scope of the gold/Selectfluor promoted oxyfluorination of *N*-propargyl phthalimides **42**.

The procedure showed to be very versatile, being compatible with both aryl- and alkyl-substituted *N*-propargyl phthalimides; in all the examined cases, complete regioselectivity was obtained. Both electron-donating (**42b-c**) and electron-withdrawing (**42f-g**) groups on the aryl moiety are well tolerated, with better yields obtained for the electron-withdrawing ones. Interestingly, even strongly withdrawing groups, such as the -CF_3 group in *para* position (**42l**), are compatible with the developed methodology. The heteroaryl substituted derivative **42i** gave the desired α-fluoro ketone **48i** in a satisfactory 69% yield. Furthermore, when the aromatic alkynes were switched to the aliphatic alkynes, the corresponding derivatives **48j-k** were isolated in good yields.

Having found reaction conditions that allow to selectively obtain 1,2-diketone derivatives, the substrate scope was investigated for these derivatives too. 1,2-diketones are, in fact, very interesting organic scaffolds, especially as intermediates in organic synthesis since they can

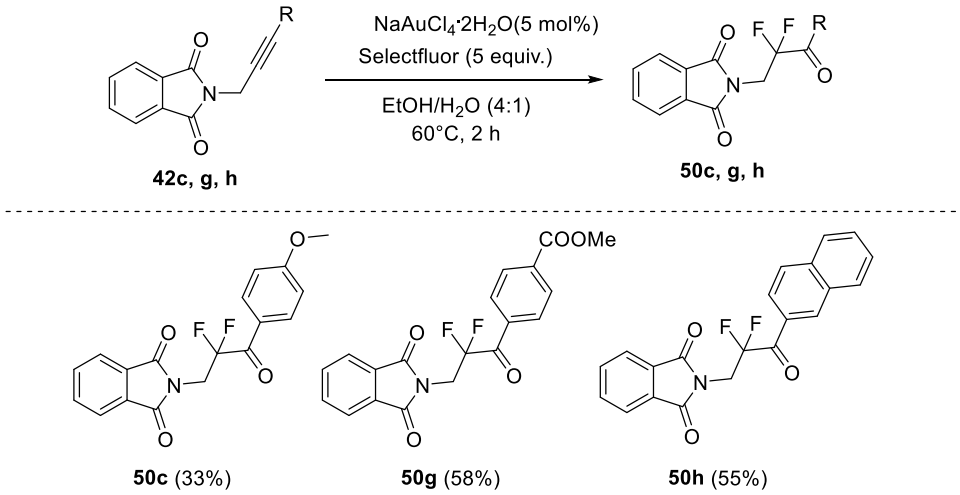
be converted in a plethora of different heterocyclic compounds. [109] Although the synthesis of these derivatives has already been successfully accomplished in several different ways, [110] the methodology developed in this study could be expected to be of great help in the synthesis of heterocycles containing aminomethyl-pendants, which could be interesting on a medicinal/biochemical point of view. [111] As reported in Scheme 8.3, the methodology was only marginally investigated, but showed an interesting compatibility with different aryl-substituted derivatives.



Scheme 8.3 Substrate scope of the gold/Selectfluor promoted oxidation of *N*-propargyl phthalimides **42**.

Regarding the use of $NaAuCl_4$ for the synthesis of α-difluoro ketones from *N*-propargyl phthalimides, the substrate scope was not examined in too depth since it was practically impossible to separate the desired derivative from the monofluoro analogue, using classical purification techniques. The yields reported below in Scheme 8.4 were determined by means of ^1H NMR and the obtained derivatives were not further characterised.

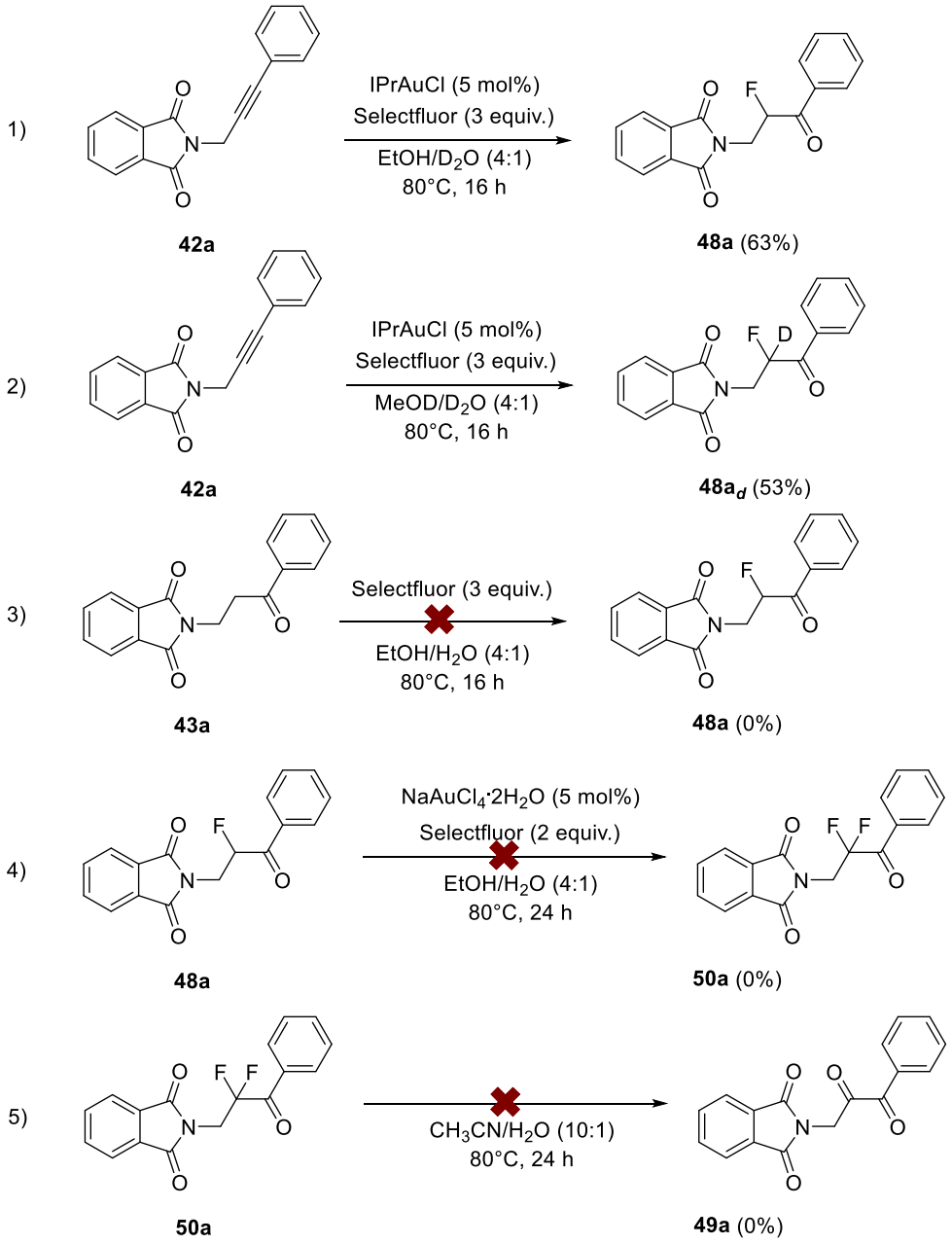
[109] Dubovtsev, A.Y.; Dar'in, D.V.; Krasavin, M.; Kukushkin, V.Y. *Eur. J. Org. Chem.* **2019**, 1856-1864.
[110] For selected examples, see: a) Dubovtsev, A.Y.; Shcherbakov, N.V.; Dar'in, D.V.; Kukushkin, V.Y. *J. Org. Chem.* **2020**, 85, 745-757. b) Dubovtsev, A.Y.; Dar'in, D.V.; Kukushkin, V.Y. *Org. Lett.* **2019**, 21, 4116-4119. c) Xia, X.-F.; Gu, Z.; Liu, W.; Wang, N.; Wang, H.; Xia, Y.; Gao, H.; Liu, X. *Org. Biomol. Chem.* **2014**, 12, 9909-9913. d) Jung, M.E.; Deng, G. *Org. Lett.* **2014**, 16, 2142-2145. e) Shi, S.; Wang, T.; Yang, W.; Rudolph, M.; Hashmi, A.S.K. *Chem. Eur. J.* **2013**, 19, 6576-6580. f) Xu, C.-F.; Xu, M.; Jia, Y.-X.; Li, C.-Y. *Org. Lett.* **2011**, 13, 1556-1559.
[111] a) Ma, S.; Wang, L.; Ouyang, B.; Fan, M.; Qi, J.; Yao, L. *Bioorg. Med. Chem.* **2020**, 28, 115683. b) Kahler, J. P.; Lenders, S.; de Plassche, M.A.T.; Verhelst, S.H.L. *ACS Med. Chem. Lett.* **2020**, 11, 1739-1744. c) Tsuchihira, T.; Kajino, R.; Maeda, Y.; Ueno, Y. *Bioorg. Med. Chem.* **2020**, 28, 115611.



Scheme 8.4 Substrate scope of the gold/Selectfluor promoted oxydifluorination of *N*-propargyl phthalimides **42**.

In order to clarify the possible reaction pathways taking place in the reported conditions, some control experiments have been performed. In the presence of D_2O, non-deuterated product **48a** was isolated, most probably because of the fast proton exchange between EtOH and D_2O; on the contrary, when using MeOD and D_2O as solvent mixture, the deuterated fluoro derivative **48a*d*** could be isolated, suggesting that the formation of α-fluoro ketones should occurs through protodeauration step or tautomerisation of a fluoro-enol intermediate (Scheme 8.5, Eq. 1-2). It is well known that Selectfluor is capable to directly fluorinate the α position of preformed ketones under metal-free conditions; [112] under the optimised reaction conditions, however, the formation of **48a** from **43a** was not achievable, thus excluding the possible mechanism involving gold-catalysed hydration of **42a** and α-fluorination of the *in situ* formed ketone (Scheme 8.5, Eq. 3). Moreover, the difluoro derivative **50a** was not obtained when **48a** was submitted to the optimised reaction conditions (Scheme 8.5, Eq. 4), suggesting a much more complex mechanism for the formation of these derivatives. Regarding the formation of **49a**, it is reported in literature that 1,2-diketones could be obtained through hydrolysis of α,α-difluoro ketones. [113] However, when **50a** was treated with the solvent mixture of the optimised conditions for the generation of **49a** (Scheme 8.5, Eq. 5), at 80°C, no hydrolysis was recorded, suggesting either an involvement of gold catalyst and/or Selectfluor in the generation of the 1,2-diketo moiety from **50a** or a different reaction pathway involving the oxidative properties of the fluorinating agent used in this study.

[112] a) Souz, L.G.; de O. Domingos, J.L.; de A. Fernandes, T.; Renno, M.N.; Sansano, J.M.; Najera, C.; Costa, P.R.R. *J. Fluo. Chem.* **2019**, 217, 72-79. b) Liu, J.; Chan, J.; Bryant, C.M.; Duspara, P.A.; Lee, E.E.; Powell, D.; Yang, H.; Liu, Z.; Walpole, C.; Roberts, E.; Batey, R.A. *Tetrahedron Lett*. **2012**, 53, 2971-2975.
[113] Liu, Y.; Chen, X.; Zhang, J.; Xu, Z. *Synlett* **2013**, 24, 1371-1376.



Scheme 8.5 Control experiments.

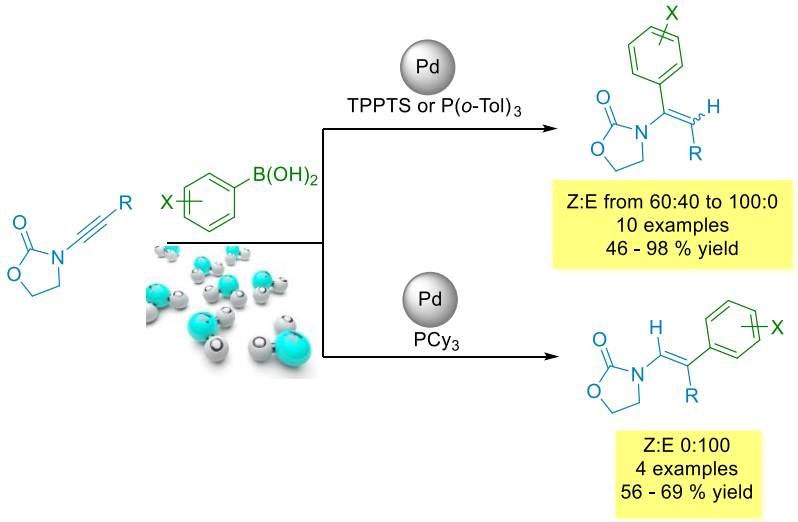
8.3 Conclusions

The divergent generation of different types of ketones starting from the same reagent has been obtained by employing the partnership between gold catalysis and Selectfluor, a benchmark and stable electrophilic fluorinating agent. A thorough optimisation of reaction conditions allowed to selectively obtain α-fluoro-, α,α-difluoro ketones and 1,2-diketones, which are very interesting organic scaffolds in both organic and medicinal chemistry. Furthermore, the presence of phthalimide as the amino-protecting group could be expected to be not only fundamental for the regioselectivity of the reaction, but also for the possibility to easily access the corresponding primary amines. The scope for both α-fluoro ketones and 1,2-diketones has been explored, while the difficulties in the separation of mono from difluoro derivatives were the main reason in the shallow exploration of the substrate scope for α,α-difluoro ketones. A further optimisation of reaction conditions towards a major selectivity in the formation of the latter could be useful, as well as the use of more exotic purification techniques.

Control experiments have been performed to shed light on the plausible reaction mechanism; although helpful in clarifying some aspects of the reactivity of **42a** in the reported reaction conditions, more investigation should be done in order to gain a better understanding.

Chapter 9

Water as reaction medium in the palladium-catalysed hydroarylation of ynamides with arylboronic acids



The Pd-catalysed hydroarylation of ynamides with aryl boronic acids was studied in pure water in the presence of the water-soluble industrial TPPTS ligand in comparison with the use of PCy_3 or P(*o*-Tol)$_3$. The use of $Pd(OAc)_2$/TPPTS catalytic system exhibited high activity for the conversion of various aryl- and alkyl-ynamides with arylboronic acids bearing both electron-donating and electron-withdrawing groups; (*Z*)-α,β-disubstituted enamides were obtained as the major compounds in the case of arylynamides and as unique isomer in the case of alkylynamides. Conversely, α,β-disubstituted or β,β′-disubstituted enamides were isolated as major single stereoisomers and at room temperature in water in the absence of any additive by using PCy_3 or P(*o*-Tol)$_3$, respectively.

Di Nicola, A.; Marsicano, V.; Arcadi, A.; Michelet, V. *Tetrahedron Lett.* **2020**, 61, 151725.

9.1 Introduction

The solvent is often an indispensable component in an organic transformation; in fact, it allows the creation of a homogeneous reaction mixture by dissolving or solvating the reactants, also enabling the fine control of reaction temperatures as well as the moderation of exothermic reactions. However, the use of organic solvents brings out some drawbacks, especially regarding safety issues and environmentally concerns (pollution, toxicity, treatment of wastes). In the last decades, organic chemists have been interested in finding alternative and safer reaction media and water has emerged as a highly promising solvent for organic transformations. [114]

Water is indeed cheap, nontoxic, eco-friendly and non-flammable, so it could be considered as the perfect green solvent; however, it should be remarked that the replacement of an organic solvent with water does not automatically improve the environmental impact of the process, especially on a small laboratory-scale point of view, because many other criteria have to be taken in consideration, such as the efficiency of the reaction, the work-up procedures to separate and purify the products and the contamination of water by residual organics or metal complexes. Nevertheless, water can offer additional advantages when used as solvent in organic transformations, thanks to its highly structured nature and its peculiar physico-chemical properties. In particular, it has been discovered that water can increase reaction rates and alter product selectivity through the so-called "hydrophobic effect", observed for the first time by Rideout and Breslow in 1980s. [115] Although the origins of this phenomenon have not been fully understood yet, it has been shown that different types of reactions can benefit from this effect, such as cycloadditions, Claisen rearrangement and nucleophile-mediated ring opening of epoxides. [116]

Interested in the exploration of the reactivity of organic molecules in aqueous systems, the hydroarylation reaction of ynamides with aryl boronic acids in water has been studied. Hydroarylation reactions of alkynes have been largely explored with different types of catalytic systems as an efficient way to access Csp^2-Csp^2 covalent bonds. [117] When performed

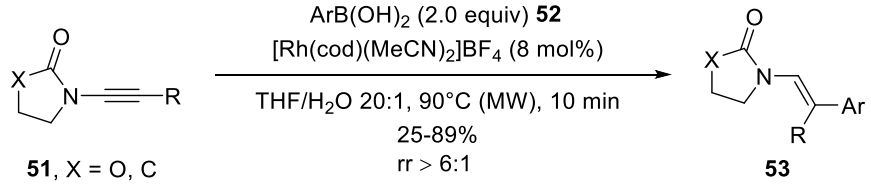
[114] For selected reviews, see: a) Butler, R.N.; Coyne, A.G. *Chem. Rev.* **2010**, 110, 6302-6337. b) Li, C.-J.; Chen, L. *Chem. Soc. Rev.* **2006**, 35, 68-82. c) Li, C.-J. *Chem. Rev.* **2005**, 105, 3095-3166. d) Pinault, N.; Bruce, D.W. *Coord. Chem. Rev.* **2003**, 241, 1-25. e) Lindström, U.M. *Chem. Rev.* **2002**, 102, 2751-2772.

[115] Rideout, D.C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, 102, 7816-7817.

[116] Narayan, S.; Muldoon, J.; Finn, M.G.; Fokin, V.V.; Kolb, H.C.; Sharpless, K.B. *Angew. Chem. Int. Ed.* **2005**, 44, 3275-3279.

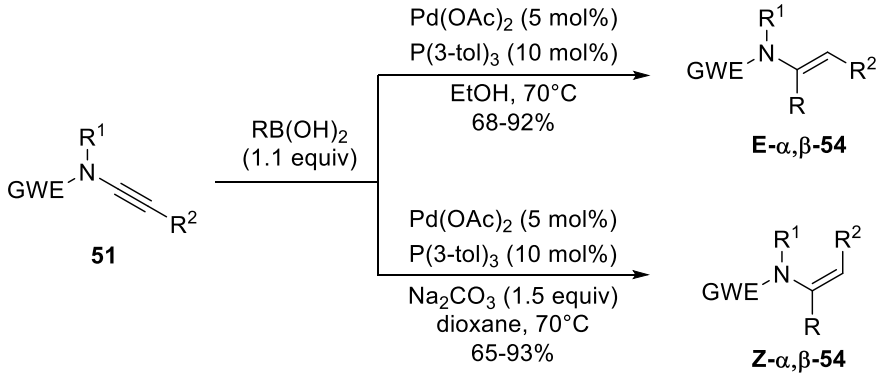
[117] For selected examples, see: a) Corpas, J.; Quirós, M.T.; Mauleón, P.; Arrayás, R.G.; Carretero, J.C. *ACS Catal.* **2019**, 9, 10567-10574. b) Hanna, L.E.; Konev, M.O.; Jarvo, E.R. *Eur. J. Org. Chem.* **2019**, 184-187. c) Yan, Z.; Yuan, X.-A.; Zhao, Y.; Zhu, C.; Xie, J. *Angew. Chem. Int. Ed.* **2018**, 57, 12906-12910. d) Xu, X.; Chen, J.; Gao, W.; Wu, H.; Ding, J.; Su, W. *Tetrahedron* **2010**, 66, 2433-2438. e) Yamamoto, Y.; Asatani, T.; Kirai, N. *Adv. Synth. Catal.* **2009**, 351, 1243-1249.

using ynamides as starting materials, hydroarylation reactions allow to access di- or trisubstituted enamides, which are interesting building blocks in synthetic organic chemistry and can be used as intermediates in the synthesis of heterocycles and bioactive molecules. [118] For example, Lam and co-workers have reported the Rh-catalysed carbometallation of ynamides with boronic acids, boronic esters and triaryl boroxines to generate β,β'-disubstituted enamides **53** as the major regioisomer. The high levels of regioselectivity achieved were ascribed to the directing effect of the carbonyl group of the oxazolidinone protecting group. [119]



Scheme 9.1 Rh-catalysed hydroarylation of ynamides reported by Lam et *al*.

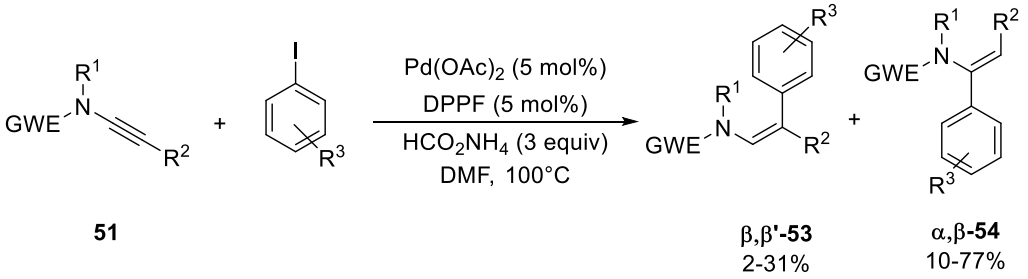
Later, the group of Zhou proposed two different methods, both based on Pd-catalysis, to selectively access regioisomeric α,β-disubstituted enamides **54**; by using the same catalytic system but changing solvent and additives, they managed to divergently generate both E- and Z-geometries of the double bond. [120]



Scheme 9.2 Pd-catalysed hydroarylation of ynamides reported by Zhou et *al*.

[118] For selected reviews on the use of enamides as building blocks in organic synthesis, see: a) Cai, X.; Yang, M.; Guo, H. *Curr. Org. Synth.* **2019**, 16, 70-97. b) Courant, T.; Dagousset, G.; Masson, G. *Synthesis* **2015**, 47, 1799-1856. c) Gopalaiah, K.; Kagan, H.B. *Chem. Rev.* **2011**, 111, 4599-4657. d) Carbery, D.R. *Org. Biomol. Chem.* **2008**, 6, 3455-3460.
[119] Gourdet, B.; Smith, D.L.; Lam, H.W. *Tetrahedron* **2010**, 66, 6026-6031.
[120] a) Yang, Y.; Wang, L.; Zhang, F.; Zhu, G. *J. Org. Chem.* **2014**, 79, 9319-9324. b) Yang, Y.; Wang, L.; Zhang, J.; Jin, Y.; Zhu, G. *Chem. Commun.* **2014**, 50, 2347-2349.

Although boronic acids are the most employed reagents in hydroarylation reactions, other types of derivatives have been used too. For example, the Pd-catalysed hydroarylation of ynamides with aryl iodides has been described by Wakamatsu et *al*. [121]



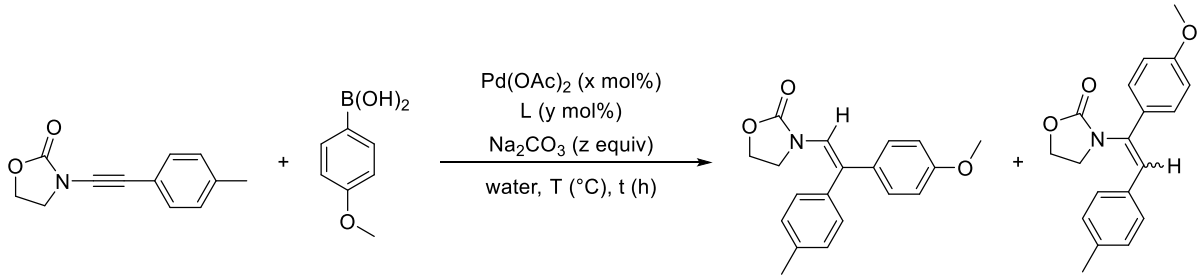
Scheme 9.3 Pd-catalysed hydroarylation of ynamides with aryl iodides.

9.2 Results and discussion

To test the reactivity of ynamides in water, the reaction between 3-(*p*-tolylethynyl)oxazolidin-2-one **51a** and 4-methoxyphenyl boronic acid **52a** was studied in the presence of $Pd(OAc)_2$ as catalyst, as reported in Table 9.1. In accordance with previous reports on C-C bond forming transformations in water, [122] water-soluble ligands were chosen to promote the solubility of the catalytic system in the selected reaction medium. TPPTS [3,3′,3″-phosphanetriyltris(benzenesulfonic acid) trisodium salt] [123] and *m*-TPPTC [triphenylphosphane-3,3′,3″-tricarboxylate] [124] were picked as ligands for the optimisation of reaction conditions because of their good water-solubility and their commercial availability.

[121] Wakamatsu, H.; Yanagisawa, R.; Kimura, S.; Osawa, N.; Natori, Y.; Yoshimura, Y. *Synlett* **2017**, 28, 2135-2138.
[122] a) Çakır, S.; Türkmen, H. *Appl. Organometal. Chem*. **2020**, 34, e5499. b) Rao, K.U.; Appa, R.M.; Lakshmidevi, J.; Vijitha, R.; Rao, K.S.V.K.; Narasimhulu, M.; Venkateswarlu, K. *Asian J. Org. Chem*. **2017**, 6, 751-757. c) Chatterjee, A.; Ward, T.R. *Catal. Lett.* **2016**, 146, 820-840. d) Steeples, E.; Kelling, A.; Schilde, U.; Esposito, D. *New J. Chem.* **2016**, 40, 4922-4930. e) Seva, L.; Hwang, W.-S.; Sabiah, S. *J. Mol. Catal. A, Chem*. **2016**, 418, 125-131.
[123] a) Shaughnessy, K.H. *Eur. J. Org. Chem*. **2006**, 1827-1835. b) Michelet, V.; Savignac, M.; Genêt, J.-P. in: Paquette, L.; Fuchs, P.; Crich, D.; Wipf, P. (Eds.), *Electronic Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, **2004**.
[124] a) Neaţu, F.; Ciobanu, M.; Ştoflea, L.E.; Frunză, L.; Pârvulescu, V.I.; Michelet, V. *Catal. Today* **2015**, 247, 155-162. b) Leseurre, L.; Püntener, K.; Genêt, J.-P.; Scalone, M.; Michelet, V. *Adv. Synth. Catal.* **2011**, 353, 3269-3277. c) Genin, E.; Amengual, R.; Michelet, V.; Savignac, M.; Jutand, A.; Neuville, L.; Genêt, J.-P. *Adv. Synth. Catal.* **2004**, 346, 1733-1741.

Table 9.1 Optimisation of the reaction conditions in pure water with water-soluble ligands (Procedure A).



51a **52a** **53aa** **54aa**

Entry	x	L (y)	z	T (°C)	t (h)	Yield[a] (%)	53aa:54aa	Z:E (54aa)[b]
1	3	TPPTS (9)	1.5	80	1	65	25:75	7:3
2	3	TPPTS (9)	1.5	50	4	88	35:65	7:3
3	3	TPPTS (9)	1.5	rt	24	98	20:80	7:3
4	3	TPPTS (15)	1.5	80	24	80	8:92	6:4
5	3	TPPTS (15)	1.5	50	24	74	28:72	6:4
6	3	TPPTS (15)	1.5	rt	24	98	10:90	7:3
7	3	*m*-TPPTC (9)	1.5	50	4	55	40:60	ND
8	3	*m*-TPPTC (9)	-	50	4	57	40:60	ND
9	3	-	1.5	80	2	75	55:45	ND
10	3	-	1.5	50	24	81	50:50	ND
11	3	-	1.5	rt	24	60	58:42	ND
12	3	-	0.5	80	1	77	50:50	ND
13	3	TPPTS (9)	-	50	24	88	30:70	1:1
14	3	TPPTS (9)	1	50	6	92	35:65	7:3
15	3	TPPTS (9)	0.5	50	6	90	10:90	1:1
16	1.5	-	1.5	80	24	67	55:45	ND
17	1.5	TPPTS (6)	1.5	80	2	62	40:60	6:4
18	3[c]	-	1.5	rt	48	-	-	-

Reaction conditions: 52a (2.5 equiv., 1.07 mmol), $Pd(OAc)_2$, the chosen ligand and Na_2CO_3 were placed were placed in a round-bottomed flask with a magnetic stir-bar under N_2, then **51a** (0.427 mmol) and water (1 mL) were added. The mixture was stirred at the appropriate temperature (rt-80°C) for 1-48 h. [a] Isolated yield of **53aa + 54aa**. [b] Determined by ^1H NMR. [c] $Pd(PPh_3)_4$ used instead of $Pd(OAc)_2$. ND = not determined.

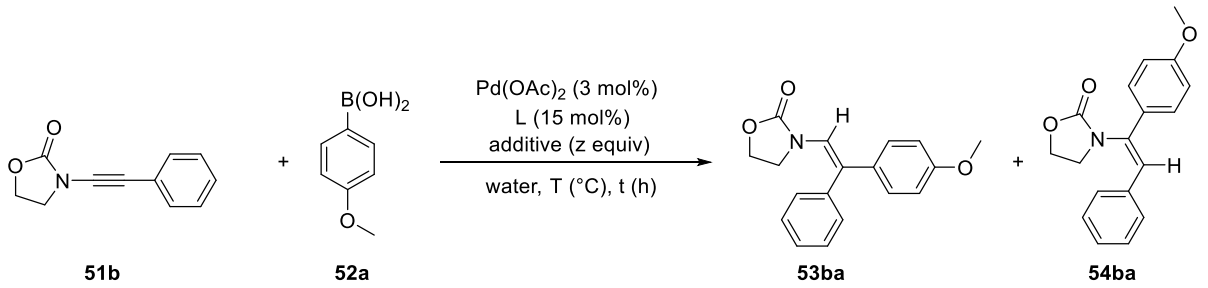
Pleasingly, the hydroarylation of **51a** with **52a** in the presence of TPPTS as ligand and Na_2CO_3 as basic additive was possible in water both under heating (80 and 50°C) and at room temperature, although with prolonged reaction time (Table 9.1, entries 1-3). A mixture of both regioisomeric disubstituted enamides **53aa** and **54aa** was obtained, with the α,β-derivative being the major component in all the examined cases; **54aa** was always isolated as a mixture

of both E- and Z-stereoisomers, with the latter being the predominant one, as determined by ^{1}H NMR analysis of the mixture. The ligand plays an important role in influencing the reaction outcome, as demonstrated by the fact that the increase of its molar percentage to 15 mol% led to an improvement of overall yield (calculated as the sum of the isolated **53aa** and **54aa**) and of the ratio between the two regioisomeric products, although it did not affect the Z:E ratio for **54aa** (Table 9.1, entries 4-6). The efficiency and selectivity of TPPTS was further confirmed by the poorer results, both in terms of yield and regioselectivity, obtained when switching to *m*-TPPTC (Table 9.1, entries 7-8) or when completely omitting the ligand (Table 9.1, entries 9-12). Lowering the amount of palladium catalyst or using $Pd(PPh_3)_4$ resulted in lower yields or no reactivity at all (Table 9.1, entries 16-18). Regarding the influence of the quantity of the base, a rapid screening demonstrated that 1.5 equivalents of Na_2CO_3 were the optimal to achieve the best ratio for regio- and stereoselectivities (Table 9.1, entries 13-15). In conclusion, under the optimised reaction conditions for Procedure A (Table 10.1, entry 6), **Z-54aa** resulted to be the major product obtained, with **E-54aa** and **53aa** as minor by-products, in accordance with the data previously reported by Zhu. [120]

With the aim to further expand the methodology toward the access of the β,β'-disubstituted regioisomer **53aa**, other types of water-insoluble phosphine ligands were investigated. On the basis of previous results on Rh- and Pd-catalysed hydroarylation of propargylamines with aryl boronic acids, [125] tricyclohexylphosphine PCy_3 and tri(*o*-tolyl)phosphine $P(o\text{-Tol})_3$ were tested in water in the presence of acidic and basic additives, as reported in Table 9.2. The choice of using insoluble ligands was mostly dictated by the possibility to exploit the hydrophobic effect, thus increasing reaction speed.

[125] Arcadi, A.; Aschi, M.; Chiarini, M.; Ferrara, G.; Marinelli, F. *Adv. Synth. Catal.* **2010**, 352, 493-498.

Table 9.2 Optimisation of the reaction conditions in pure water with water-insoluble ligands (Procedure B/C).



51b **52a** **53ba** **54ba**

Entry	L	Additive (z)	T (°C)	t (h)	53ba Yield[a] (%)	54ba Yield[a] (%)
1	TPPTS	AcOH (1.3)	50	24	-	-
2	PCy_3	AcOH (1.3)	50	0.7	29	55
3	PCy_3	-	50	1	49	50
4	PCy_3	-	rt	1	69	22
5	PCy_3	Na_2CO_3 (1.5)	rt	24	30	43
6	P(*o*-Tol)$_3$	-	rt	6	17	66

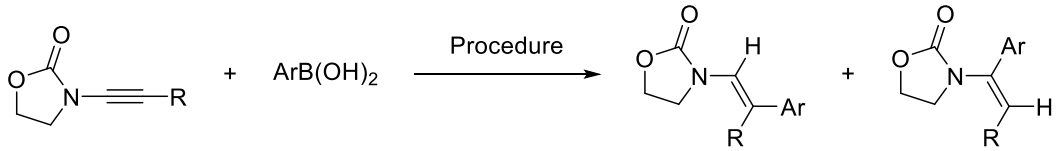
Reaction conditions: 51b (0.6 mmol), **52a** (1.8 mmol), L (0.045 mmol, 15 mol%), $Pd(OAc)_2$ (0.018 mmol, 3 mol%) and the chosen additive (AcOH, 0.78 mmol or Na_2CO_3, 0.9 mmol) were suspended in 1 mL water and stirred at 50°C or rt for 0.7-24 h. [a)] Isolated yield.

In the presence of TPPTS as ligand, the use of acetic acid instead of Na_2CO_3 as additive resulted in the recovery of the unreacted starting materials without the formation of the expected hydroarylated products (Table 9.2, entry 1). On the contrary, when switching to PCy_3 as ligand, both regioisomers **53ba** and **54ba** could be isolated with only slightly inferior yield and ratio in comparison to Procedure A but in shorter reaction times (Table 9.2, entry 2); moreover, both hydroarylated compounds were isolated as pure stereoisomers, E and Z respectively. By contrast with the expected results and the data reported in literature, [126] it was found that the addition of AcOH was not necessary to promote the hydroarylation reaction but influenced the regioselective outcome of the procedure since its omission resulted in better yields but in a poorer **53**:**54** ratio (Table 9.2, entry 2 *vs* entry 3). Surprisingly, the temperature seemed to play a key role on influencing the **53:54** ratio; in fact, when performing the reaction at room temperature, in the presence of PCy_3 as ligand and without additives, the β,β'-disubstituted regioisomer **53ba** was obtained as the prevalent regioisomer (Table 9.2, entry 4, Procedure B). In contrast, the use of P(*o*-Tol)$_3$ as ligand (Table 9.2, entry 6, Procedure c) enabled the formation of **54ba** as the prevalent regioisomer; in contrast with Procedure A, however, **54ba** was obtained as single Z stereoisomer. The structure of all the products

[126] (a) Kocięcka, P.; Trzeciak, A.M. *Appl. Catal. A, General* **2020**, 589, 117243; (b) Zeng, H.; Hua, R. *J. Org. Chem.* **2008**, 73, 558-562.

obtained during the optimisation of reaction conditions were unambiguously assigned on the basis of the chemical shift of the vinylic proton (which is expected to have an higher chemical shift for the β,β'-regioisomer because of its closer proximity to the nitrogen atom) and by comparison with the data reported in literature. The three optimised procedures A, B and C were then used to synthetise a small library of enamides **53** and **54** using both aryl- and alkyl-substituted ynamides **51a-g**. For aryl-substituted ynamides, the three procedures have been successfully applied with divergent generation of both regioisomers, as reported in Table 9.3.

Table 9.3 Scope of the hydroarylation reaction of aryl-ynamides in water.



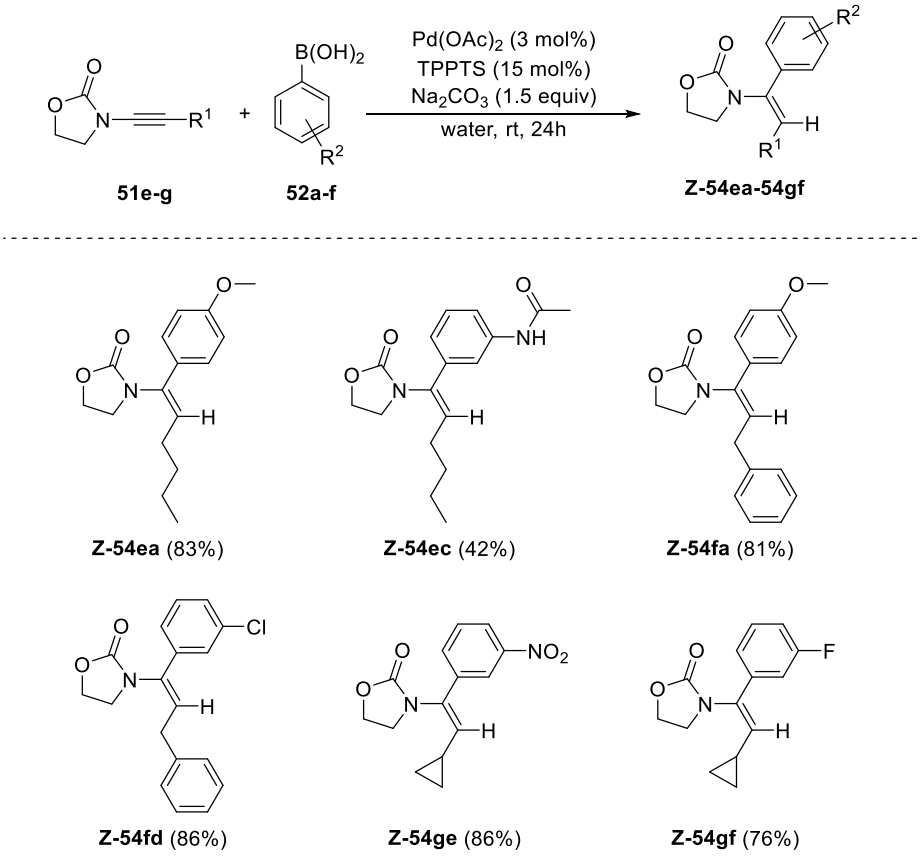
51b-d **52a-b** **53ba-bb** **54ba-bb**

Entry	Procedure	R	Ar	53 Yield (%)	54 Yield (%)
	A	Ph	*p*-CH_3O-C_6H_4	**53ba** (19)	**54ba** (74)[a]
1	**B**	Ph	*p*-CH_3O-C_6H_4	**E-53ba** (69)	**Z-54ba** (22)
	C	Ph	*p*-CH_3O-C_6H_4	**E-53ba** (17)	**Z-54ba** (66)
	A	Ph	Ph	**53bb** (11)	**54bb** (61)[b]
2	**B**	Ph	Ph	**53bb** (56)	**Z-54bb** (19)
	C	Ph	Ph	**53bb** (13)	**Z-54bb** (77)
	A	*p*-CH_3O-C_6H_4	*p*-CH_3O-C_6H_4	**53ca** (9)	**54ca** (53)[c]
3	**B**	*p*-CH_3O-C_6H_4	*p*-CH_3O-C_6H_4	**53ca** (64)	**Z-54ca** (11)
	C	*p*-CH_3O-C_6H_4	*p*-CH_3O-C_6H_4	**53ca** (17)	**Z-54ca** (68)
	A	*p*-Cl-C_6H_4	*p*-CH_3O-C_6H_4	**53da** (-)	**54da** (46)[d]
4	**B**	*p*-Cl-C_6H_4	*p*-CH_3O-C_6H_4	**Z-53da** (60)	**Z-54da** (9)
	C	*p*-Cl-C_6H_4	*p*-CH_3O-C_6H_4	**Z-53da** (13)	**Z-54da** (63)

[a] Z:E ratio = 7:3. [b] Z:E ratio = 7:3. [c] Z:E ratio = 7:3. [d] Z:E ratio = 6:4.

When using Procedure A, the α,β-disubstituted enamides **54** were always obtained as the major regioisomer, in a mixture of both Z- and E-geometries, with the first one being the predominant in all the examined cases. The overall yields for Procedure A were generally modest to good (from 46% to 93%) but the Z/E stereoisomers could unfortunately not be separated. The application of the other two procedures B and C enabled to overcome this problem, since in all cases only one stereoisomer was obtained (the *trans*-addition of boronic acids **52** to ynamides **51** was never observed when applying these two procedures). In accordance with

the data collected during the optimisation of reaction conditions, the predominant regioisomer obtained with Procedure B was always the β,β'-disubstituted derivative **53**, allowing the divergent access of both regioisomeric products. The overall yields for Procedure B and C were comparable with those obtained with Procedure A (69-91% and 76-90%, respectively). Then, the hydroarylation reaction was explored for alkyl-substituted ynamides too. Surprisingly, when applying Procedure A, the (Z)-α,β-disubstituted enamides **54** were the only obtained isomers, in contrast with the results attained with aryl-substituted ynamides. Differently, when applying both Procedures B and C, a complex inseparable mixture of both regioisomers **53** and **54** was obtained; [127] for this reason, the scope with alkyl-substituted ynamides was explored only with Procedure A, as reported in Scheme 9.4.

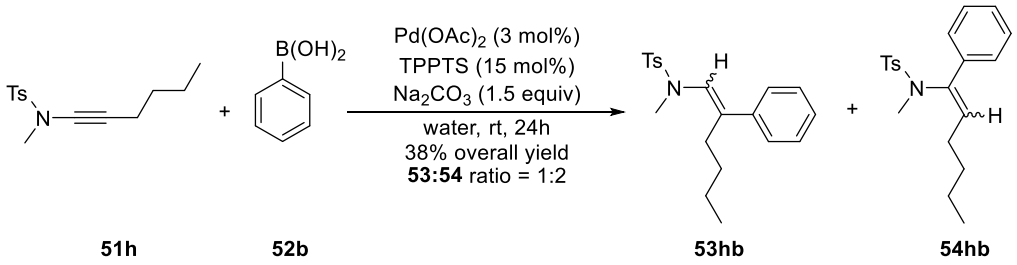


Scheme 9.4 Scope of the hydroarylation reaction of alkyl-ynamides in water using Procedure A.

The hydroarylation was efficiently conducted in the presence of aryl boronic acids **52** bearing electron-withdrawing and electron-donating groups, leading to enamides **54ea**-**54gf** within 42% to 86% isolated yield. Interestingly, when aryl boronic acids with strong electron-

[127] When the reaction was performed between ynamide **51f** and 4-methoxyphenyl boronic acid **52a**, both regioisomer **53fa** and **54fa** were obtained in an inseparable mixture when using Procedure B and C. The regiochemistry obtained was, however, in accordance with the data obtained for aryl-substituted ynamides, with the α,β-regioisomer being predominant with Procedure C (64% overall yield, **53:54** ratio of 28:72) and the β,β'-regioisomer with Procedure B (62% overall yield, **53:54** ratio of 71:29).

withdrawing groups (such as *m*-bromo-phenyl boronic acid and 2,3-difluoro-phenyl boronic acid) were used with aryl-substituted ynamides, the hydroarylation reaction did not occur and the only isolated product was the amide derived from the hydration of the ynamide reagent.
To further investigate the influence of the structural features of ynamides on the reaction, Procedure A was applied to *N*-(hex-1-yn-1-yl)-*N*,4-dimethylbenzenesulfonamide **51h**, bearing the tosyl group as N-protecting group. The presence of the oxazolidine-2-one was found to be crucial for this process, as an inseparable mixture of **53hb** and **54hb** was obtained in this case, with a low overall yield of 38% (Scheme 9.5).



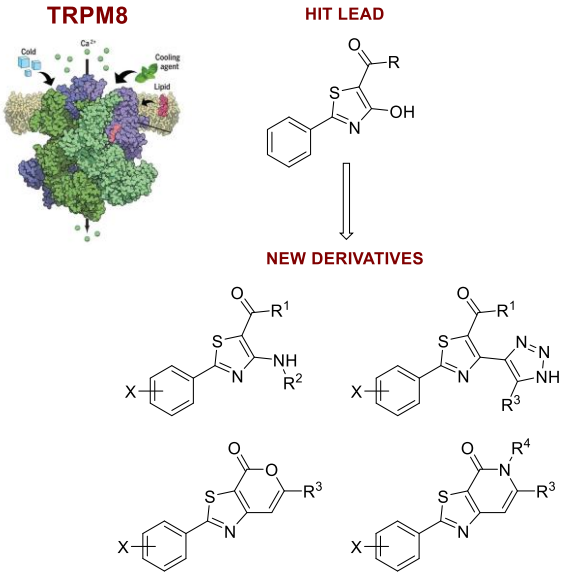
Scheme 9.5 Hydroarylation of *N*-tosyl protected ynamide **51h** with Procedure A.

9.3 Conclusions

Concluding, it has been demonstrated that the Pd-catalysed hydroarylation reaction of ynamides with phenyl boronic acids can be efficiently performed in water, both in the presence of the water-soluble industrial ligand TPPTS and of classical phosphine ligands, such as PCy_3 and $P(o\text{-}Tol)_3$. The optimisation of reaction conditions showed that, independently of the ligand used, the reaction could nicely be conducted at room temperature, allowing the generation of disubstituted enamides at much milder conditions in comparison to those previously reported in literature. Three distinct procedures have been developed, which can be considered as complementary to access the whole panel of the expected regio- and stereoisomers. In fact, the use of TPPTS or P(*o*-Tol)$_3$ as ligands enabled to selectively obtain α,β-disubstituted enamides **54**, as Z/E inseparable mixtures in the first case and as single Z stereoisomers in the second one; on the contrary, the employment of PCy_3 allowed the access to β,β'-disubtituted enamides **53**, always as a single stereoisomer. The exploration of the substrate scope also demonstrated that the performance of each procedure, especially in terms of regio- and stereoselectivity, is highly dependent on the nature of the ynamide used: aryl-substituted ynamides tend to afford better results when using PCy_3 and $P(o\text{-}Tol)_3$ as ligands, while the alkyl-substituted ones show better hydroarylation reactions with the catalytic system $Pd(OAc)_2$/TPPTS.

Chapter 10

Design and synthesis of phenyl thiazoles as potential TRPM8 antagonists



Ten new potential TRPM8 antagonists were synthetised in the chemical laboratories of the Discovery Section R&D of Dompé Farmaceutici S.p.A. with the aim to expand the SAR of the 2-phenyl thiazole scaffold which was already discovered as an interesting TRPM8 antagonist. The bioisosteric substitution of the hydroxy group with a secondary amino group was performed, as well as the molecular hybridisation with triazoles. In order to generate analogues of the natural-occurring isocumarins, bicyclic compounds were designed and synthetised. Moreover, the optimisation of the metal-free nucleophilic substitution of aryl triflates with amines was successfully performed in order to avoid the use of metals in the synthesis of API, which represents a primary source of contamination of pharmaceuticals.

10.1 Introduction

The evolution of molecular biology and biochemistry has been of considerable help in better understanding diseases, enabling to discover how receptors, enzymes and channels are involved in pathological pathways. This has led to an increase in the number of the so-called "druggable targets", i.e. cellular structures that have the ability to bind small, drug-like molecules with a high affinity and that can be therefore used for the discovery of new therapeutic agents. [128]

Transient Receptor Potential (TRP) channels are an interesting example of such newly discovered druggable targets and have gained a lot of attention in medical sciences thanks to their involvement in several physio-pathological processes. They are a large family of cation channels located on the plasma membrane of different cell types consisting of six transmembrane subdomains flanked by C- and N-terminal regions and are capable of homo- or hetero-tetramerisation to form ion-permeable pores. [129] TRP channels have a polymodal nature: in fact, they can be activated by several different stimuli such as voltage, pressure, temperature and the binding of ions, lipids and other ligands. Eight members of the family are recognised as thermo-TRPs in that they are expressed in primary somatosensory neurons and are activated at specific temperatures ranging from painful cold to noxious heat. The first channel to be identified as a sensor for cold temperatures (8-28°C) has been TRPM8 (Transient Receptor Potential Melastatin type 8). [130] TRPM8 is a non-selective cation channel, with a certain preference for Ca^{2+} permeation. Besides cold temperatures, it is activated also by membrane depolarisation, changes in extracellular osmolarity and different cooling compounds such as menthol and icilin. [131] Other endogenous factors, such as PIP_2, [132] endocannabinoids [133] and testosterone [134] also participate in the regulation of the channel.

These channels are highly expressed in peripheral sensory neurons (Aδ and C fiber afferents) but also on deep visceral afferents in prostate, bronchopulmonary tissue, bladder and the urogenital tract. This body-wide diffusion explains why TRPM8 has been found to be implied in several pathological conditions. For example, it is well known that the channel is involved

[128] Liu, T.; Altman, R.B. *CPT: Pharmacometrics Systems Pharmacology* **2014**, 3, e93.
[129] Ramsey, I.S.; Delling, M.; Clapham, D.E. *Annu. Rev. Physiol.* **2006**, 68, 619-647.
[130] a) McKemy, D.D.; Neuhausser, W.M.; Julius, D. *Nature* **2002**, 416, 52-58. b) Peier, A.M.; Moqrich, A.; Hergarden, A.C.; Reeve, A.J.; Andersson, D.A.; Story, G.M.; Earley, T.J.; Dragoni, I.; McIntyre, P.; Bevan, S.; Patapoutian, A. *Cell* **2002**, 108, 705-715.
[131] Liu, Y.; Qin, N. *Adv. Exp. Med. Biol.* **2011**, 704, 185-208.
[132] Daniels, R.L.; Takashima, Y.; McKemy, D.D. *J. Biol. Chem.* **2009**, 284, 1570-1582.
[133] De Petrocellis, L.; Starowicz, K.; Moriello, A.S.; Vivese, M.; Orlando, P.; Di Marzo, V. *Exp Cell Res.* **2007**, 313, 1911-1920.
[134] Asuthkar, S.; Demirkhanyan, L.; Sun, X.; Velpula, K.K.; Zakharian, E.; Elustondo, P.A.; Krishnan, V.; Baskaran, P.; Thyagarajan, B.; Pavlov, E.V. *J. Biol. Chem.* **2015**, 290, 2670-2688.

in the abnormally cold sensitivity in some pathologic states such as the cold allodynia (i.e. the pain induced by a normally innocuous cold temperature) that is often experienced by patients undergoing chemotherapy or with other conditions such as diabetic neuropathy, fibromyalgia and traumatic neuropathy. [135]

Dysfunction of TRPM8-mediated sensing of evaporation-induced temperature and osmolarity change in the corneal surface has been suggested as a possible pathophysiological mechanism in dry eye disease (DED), which is a growing problem in our society and causes pain on the ocular surface. The use of TRPM8 agonists could be beneficial in this pathology through an increase in the production of tears. [136]

Several experimental findings suggest a correlation between the expression of TRPM8 and tumour progression. The upregulation of this channel in different types of cancers, such as prostate, pancreas, colon, breast, lung and skin, is well documented and, in most cases, it correlates with tumour aggressiveness. [137]

In addition, TRPM8 channels have been also implicated in other diseases such as migraine, bladder painful disorders, irritable bowel syndrome, oropharyngeal dysphagia and chronic cough.

10.1.1 Medicinal chemistry of TRPM8 channels

Altogether, the findings reported above suggest that TRPM8 channels could be promising targets to develop novel drugs to treat painful pathologies and it is not surprising that numerous research groups, both in academia and in pharmaceutical companies, have become interested in the development of small molecules interacting with these receptors. An interesting feature of TRPM8 channels is that both their activation and inhibition may be beneficial, highly depending on the type of pathology and symptoms experienced by the patient. Because of this, both agonists and antagonists have been designed and synthetised. [138] Antagonists may find an application in the treatment of diseases associated with overexpression and/or hyperactivity of TRPM8 such as neuropathic pain, inflammation, migraine and cancer. Different types of organic architectures have shown the capability to bind and antagonise these channels; a summary of the most potent lately described TRPM8 antagonists is reported in Figure 10.1. For example, De Petrocelli and coworkers have reported two distinct families of antagonists,

[135] Weyer, A.D.; Lehto, S.G. *Pharmaceuticals* **2017**, 10, 37.
[136] Yang, J.M.; Wei, E.T.; Kim, S.J.; Yoon, K.C. *Pharmaceuticals* **2018**, 11, 125.
[137] Liu, Z.;Wu, H.;Wei, Z.;Wang, X.; Shen, P.;Wang, S.;Wang, A.; Chen,W.; Lu, Y. *J. Cancer Res. Clin. Oncol*. **2016**, 142, 1871-1881.
[138] González-Muñiz, R.; Bonache, M.A.; Martín-Escura, C.; Gómez-Monterrey, I. *Int. J. Mol. Sci*. **2019**, 20, 2618 and references therein.

tetrahydroisoquinoline-derived ureas **55** (symmetric and asymmetric) and pyrazino[1,2-*b*]isoquinolin-1-ones **56**, both showing good potency and selectivity. [139] A related tetrahydronaphthyridine-based asymmetric urea **57** has been reported by Amgen; [140] the same company discovered that the linear urea derivatives used as intermediate in the synthesis of tetrahydronaphthyridines, such as **58**, were effective as TRPM8 antagonists. A thorough SAR investigation led to the discovery of AMG-333 (**59**), a potent amide derivative which was elected as a clinical candidate for the treatment of migraine and entered clinical trials. [141] Other potent antagonists based on the carboxamide moiety are PF-05105679 **60** by Pfizer [142] and **61** by Mitsubishi Tanabe Pharma Corporation. [143]

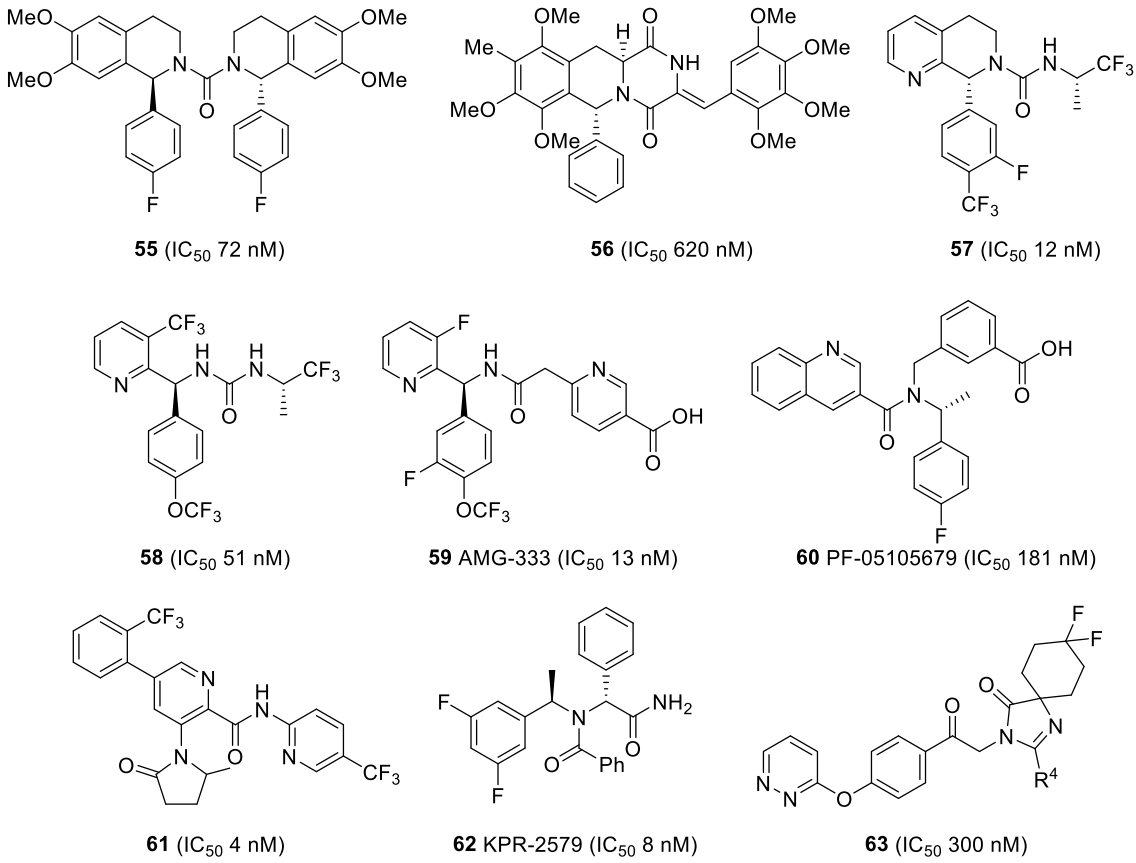


Figure 10.1 Recently described TRPM8 antagonists.

[139] De Petrocellis, L.; Arroyo, F.J.; Orlando, P.; Schiano Moriello, A.; Vitale, R.M.; Amodeo, P.; Sánchez, A.; Roncero, C.; Bianchini, G.; Martín, M.A.; López-Alvarado, P.; Menéndez, J.C. *J. Med. Chem.* **2016**, 59, 5661-5683.
[140] Horne, D.B.; Tamayo, N.A.; Bartberger, M.D.; Bo, Y.; Clarine, J.; Davis, C.D.; Gore, V.K.; Kaller, M.R.; Lehto, S.G.; Ma, V.V.; Nishimura, N.; Nguyen, T.T.; Tang, P.; Wang, W.; Youngblood, B.D.; Zhang, M.; Gavva, N.R.; Monenschein, H.; Norman, M.H. *J. Med. Chem.* **2014**, 57, 2989-3004.
[141] Horne, D.B.; Biswas, K.; Brown, J.; Bartberger, M.D.; Clarine, J.; Davis, C.D.; Gore, V.K.; Harried, S.; Horner, M.; Kaller, M.R.; Lehto, S.G.; Liu, Q.; Ma, V.V.; Monenschein, H.; Nguyen, T.T.; Yuan, C.C.; Youngblood, B.D.; Zhang, M.; Zhong, W.; Allen, J.R.; Chen, J.J.; Gavva, N.R. *J. Med. Chem.* **2018**, 61, 8186-8201.
[142] Andrews, M.D.; af Forselles, K.; Beaumont, K.; Galan, S.R.G.; Glossop, P.A.; Grenie, M.; Jessiman, A.; Kenyon, A.S.; Lunn, G.; Maw, G.; Owen, R.M.; Pryde, D.C.; Roberts, D.; Tran, T.D. *ACS Med. Chem. Lett.* **2015**, 6, 419-424.
[143] Kato, T.; Sakamoto, T.; Niwa, Y.; Sawamoto, D.; Otani, N.K.M. *Patent Number JP2017214290*, **7 December 2017**.

Another interesting class of antagonist is represented by the α-arylglycinamides reported by Kissei Pharmaceutical Co. as potential therapeutics in urological disorders. The structure-activity relationships of several different derivatives led to compound KPR-2579 **62**, with good potency and selectivity. [144] Other related compounds have been later reported by the same company. [145] RaQualia Pharma Inc. synthetised some imidazolinone derivatives of general formula **63**, with good pharmacokinetic properties, low toxicity and IC_{50} values in the μM range. [146]

To date, only three of the antagonists reported above have reached clinical trials, two of which (PF-05105679 and AMG-333) did not pass phase I studies. Moreover, one of the major drawbacks of most antagonists described in literature is the lack of selectivity for TRPM8, being able to interact with other TRP channels, especially TRPV1 and TRPA1. The interaction with other TRP channels has been associated with side effects, such as burning sensations. Because of this, new potent and selective scaffolds are needed and many companies and researchers across the globe are working on this target.

10.1.2 TRPM8 antagonists developed by Dompé Farmaceutici S.p.A.

Dompé Farmaceutici S.p.A. has been very active in the last decade in the development of new TRPM8 antagonists, reporting interesting molecules with IC_{50} values in the nM range.

By using a combination of ligand- and structure-based virtual screening strategies, a new family of naphthyl derivatives acting as potent and selective TRPM8 antagonists has been discovered. [147] More than 120.000 compounds have been virtually screened, identifying 11.725 promising active molecules that were pharmacologically characterised among which DFL14817 (**64**) was selected as the most promising one as clinical candidate. DFL14817 shows, in fact, nanomolar potency, selectivity towards TRPA1, TRPV1 and TRPV3, good pharmacokinetic properties and in vivo efficiency in an overreactive bladder rat model.

The pharmacophore mapping performed in the study also enabled to rationalise which are the structural features that are fundamental for the antagonism. All the examined chemotypes showed suitably spaced hydrogen bond acceptor (HBA) and hydrogen bond donor (HBD) systems which interact, respectively, with Tyr745 and Asp802 that are key residues of the menthol binding site of TRPM8 channels.

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[144] Kobayashi, J.; Hirasawa, H.; Ozawa, T.; Ozawa, T.; Takeda, H.; Fujimori, Y.; Nakanishi, O.; Kamada, N.; Ikeda, T. *Bioorg. Med. Chem*. **2017**, 25, 727-742.

[145] Hirasawa, H.; Kawamura, N.; Kobayashi, J. *Patent Number JP 2016094407*, **26 May 2016**.

[146] Shishido, Y.; Ohmi, M. *Patent Number WO2017043092*, **16 March 2017**.

[147] Beccari, A.R.; Gemei, M.; Lo Monte, M.; Menegatti, N.; Fanton, M.; Pedretti, A.; Bovolenta, S.; Nucci, C.; Molteni, A.; Rossignoli, A.; Brandolini, L.; Taddei, A.; Za, L.; Liberati, C.; Vistoli, G. *Sci. Rep*. **2017**, 7, 10999.

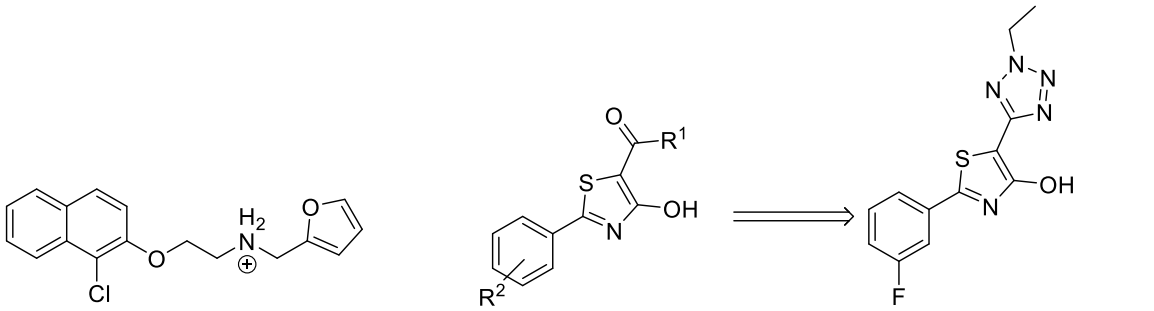


Figure 10.2 TRPM8 antagonists reported by Dompé Farmaceutici S.p.A.

4-hydroxy-2-phenyl-1,3-thiazol-5-yl methanone derivatives of general structure **65** have also demonstrated a great potential as TRPM8 antagonists and could be efficiently used in the treatment of pain, neurodegeneration, ischemia and psychiatric disorders. Several different derivatives have been synthetised where R^1 were (un)substituted 5-7 membered aliphatic or aromatic heterocyclic groups, containing 1-4 heteroatoms selected from S, O and N and R^2 are H, alkyl, F, Cl or OH. [148] The exploration of thiazole derivatives bearing an ester moiety and other bioisosteric groups led to the discovery of DFL23448 (**66**) as a selective blocker of TRPM8. [149] In vivo experiments showed good performances of this molecule in reducing orofacial and neuropathic pain in acute and chronic pain models in rat [150] and in blocking bladder overactivity. [151]

11.2 Aim of the work

In order to further improve the SAR of phenyl thiazoles and to expand the library of potential TRPM8 antagonists, three different sets of new derivatives have been synthetised during a six-months internship in the chemical laboratories of the Discovery Section of Dompé Farmaceutici S.p.A. in L'Aquila.

The first library has been synthetised through the bioisosteric substitution of the hydroxy group with an amino group. This substitution introduces only a small distortion in the three-dimensional geometry of the molecule but can induce large shifts in its electro-chemical features, especially in terms of HBD/HBA capability and acid/basic properties. In particular, the four derivatives **V1-V4** (Figure 10.3) have been synthetised replacing the hydroxy group

[148] Aramini, A.; Bianchini, G.; Lillini, S. *Patent Number WO2017108632*, **29 June 2017**.
[149] Moriconi, A.; Bianchini, G.; Colagioia, S.; Brandolini, L.; Aramini, A.; Liberati, C.; Bovolenta, S. *Patent Number WO2013092711*, **27 June 2013**.
[150] De Caro, C.; Russo, R.; Avagliano, C.; Cristiano, C.; Calignano, A.; Aramini, A.; Bianchini, G.; Allegretti, M.; Brandolini, L. *Br. J. Pharmacol*. **2018**, 175, 1691-1706.
[151] Mistretta, F.A.; Russo, A.; Castiglione, F.; Bettiga, A.; Colciago, G.; Montorsi, F.; Brandolini, L.; Aramini, A.; Bianchini, G.; Allegretti, M.; Bovolenta, S.; Russo, R.; Benigni, F.; Hedlund, P. *J. Pharmacol. Exp. Ther*. **2016**, 356, 200-211.

with the 3-aminopyrrolidine moiety. Interestingly, the presence of the additional amino groups allows to isolate the desired products as their corresponding hydrochloric salts, improving water solubility and facilitating their formulation and administration. The structure of compounds V3 and V4 could not be shown because of patent issues. These four molecules will converge in a larger library of 4-amino-2-phenyl thiazoles derivatives previously synthetised at Dompé Farmaceutici S.p.A.

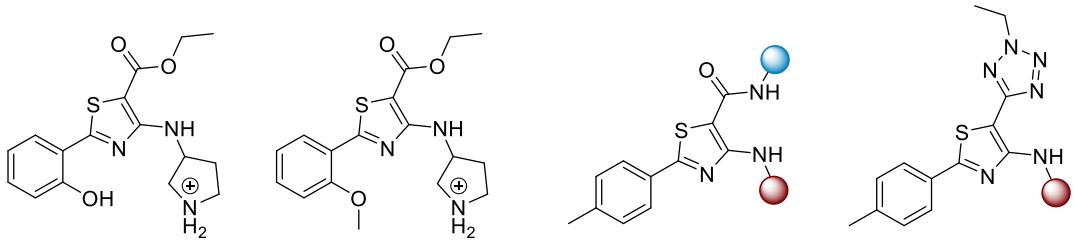


Figure 10.3 Structure of compounds **V1-V4**.

The second library has been obtained with the same strategy but replacing the hydroxy group with an alkyne moiety [compounds **V5** and **V6** (Figure 10.4)]. The linear geometry of the triple bond allows, in fact, to place the two substituents at a distance that is comparable to that of two groups in a *para* arrangement on a phenyl ring. Noteworthy, when using an alkyne in place of a para-disubstituted aromatic ring, the carbon count is only raised by two units, with beneficial effects on both MW and octanol-water partition coefficient (logP) and, consequently, on oral bioavailability. [152] The butanoic acid fragment introduced in **V5** has been found as a key structural feature in other derivatives synthetised by Dompé Farmaceutici S.p.A.; likewise, the *m*-fluoro phenyl substituent on the thiazole ring was chosen based on the good results obtained by this fragment in TRPM8 antagonism. As for **V1**-**V4**, the presence of an acidic moiety enables the formulation of the compound as a salt, improving water solubility. Obviously, at this stage of drug development it could not be clearly anticipated if the presence of the free carboxylic group is beneficial or not for the biological activity; for this reason, the corresponding ethyl ester **V6** has been synthetised, in order to gain a deeper insight on this aspect. Moreover, it should be highlighted that esters can be easily hydrolysed in our organisms by esterases and that esters prodrugs are commonly designed as a strategy to

[152] MW and logP are two of the five molecular properties that have been defined by Lipinski as strongly influencing solubility and permeability of drug candidates (Lipinski's rule of five). Although several other molecular features have been taken in consideration in last years, the original five principle of Lipinski are still used nowadays to determine if a chemical compound with biological activity has the right physical and chemical properties to likely be an orally active drug in humans. For references, see: a) Leeson, P.D.; Springthorpe, B. *Nat. Rev. Drug Discov*. **2007**, 6, 881-890. b) Lipinski, C.A. *Drug Discov. Today Technol*. **2004**, 337-341. c) Veber, D.F.; Johnson, S.R.; Cheng, H.-Y.; Smith, B.R.; Ward, K.W.; Kopple, K.D. *J. Med. Chem*. **2002**, 45, 2615-2623.

improve solubility, stability, bioavability and selectivity of drugs. [153] The versatility of the triple bond allowed to further increase the complexity of the organic architectures obtained. In particular, the presence of an ester nucleophilic group in close proximity to the alkyne moiety made possible to perform intramolecular 6-endo-dig cyclisation reactions to generate the bicyclic derivatives **V7**-**V10**, which can be considered as bioisosters of natural isocoumarins. Isocoumarins are isomers of coumarins with an inverted lactone ring and most of the natural isocoumarins possess a 3-alkyl (C_1-C_{17}) or a (un)substituted 3-phenyl ring on the α-pyranone moiety. [154] An ever-increasing number of naturally occurring isocoumarins have been isolated from various natural sources (fungi, lichens, sponges, bacteria, molds and to a lesser extent in higher plants) exhibiting a broad range of pharmacological properties including antiallergic and antimicrobial, antifungal, antiinflammatory, immunomodulatory, cytotoxic and antiangiogenic activity. [155] The inclusion of such a potent pharmacological nucleus in the molecules synthetised could be beneficial in broadening their therapeutic potential, also against different biological targets.

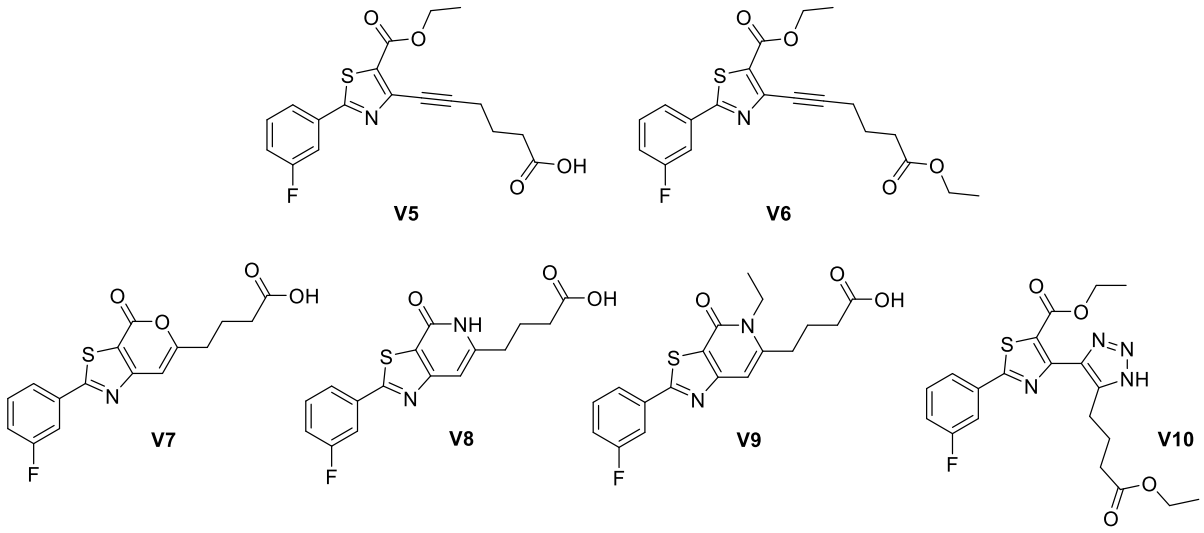


Figure 10.4 Structure of compounds **V7-V10.**

The nitrogen-containing derivatives **V8** and **V9** have been easily obtained from **V7**; recently, pyridin-2(1H)-one/thiazole hybrid compounds have been found as promising anticancer small-molecule drugs. [156] **V9**, with a *N*-ethyl substituent, has been designed to test whether the

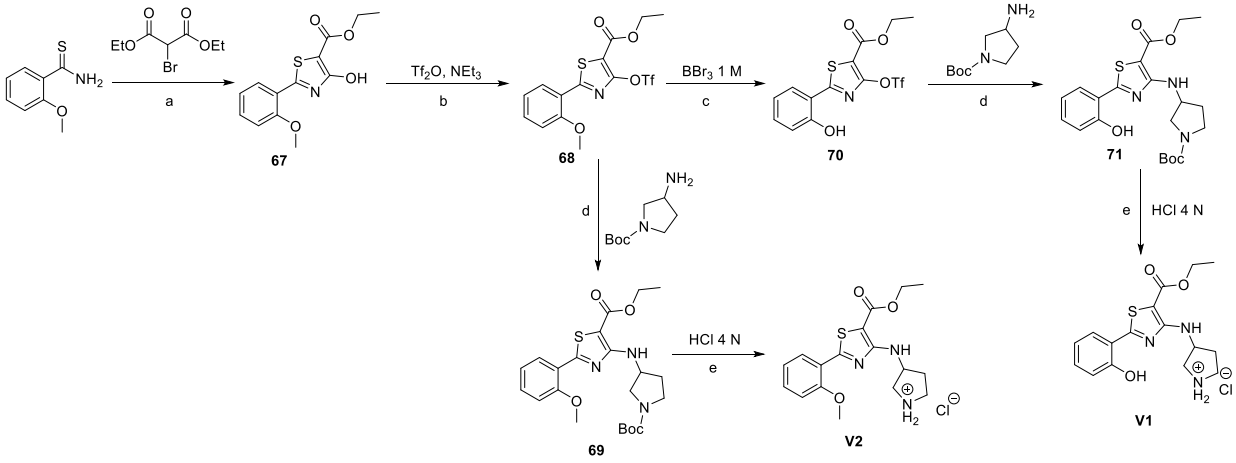
[153] a) Zheng, Y.; Yu, B.; Ji, K.; Pan, Z.; Chittavong, V.; Wang, B. *Angew. Chem. Int. Ed*. **2016**, 55, 4514-4518. b) Perez, C.; Daniel, K.B.; Cohen, S.M. *ChemMedChem*, **2013**, 8, 1662-1667. c) Yang, Y.-H.; Aloysius, H.; Inoyama, D.; Chen, Y.; Hu, L.-Q. *Acta Pharm. Sin. B* **2011**, 143-159. d) Beaumont, K.; Webster, R.; Gardner, I.; Dack, K. *Curr. Drug Metab*. **2003**, 4, 461-485.
[154] Pal, S.; Chatare, V.; Pal, M. *Curr. Org. Chem.* **2011**, 15, 782-800.
[155] Saeed, A. *Eur. J. Med. Chem.* **2016**, 116, 290-317.
[156] Xie, W.; Wu, Y.; Zhang, J.; Mei, Q.; Zhang, Y.; Zhu, N.; Liu, R.; Zhang, H. *Eur. J. Med. Chem.* **2018**, 145, 35-40.

free amino group has an influence on the biological activity and to introduce an additional point of differentiation among the derivatives.

Finally, the triazole-thiazole hybrid **V10** has been obtained through a classic Huisgen cycloaddition reaction with sodium azide. Molecular hybridisation has emerged, in recent years, as a new tool in drug design and development based on the incorporation of two or more pharmacophores into a single entity to produce a new hybrid compound with improved affinity and efficacy, when compared to the parent drugs. Additionally, this strategy can result in compounds presenting modified selectivity profiles, different and/or dual modes of action and reduced undesired side effects. [157]

10.3 Results and discussion

All the designed derivatives have been obtained following the same general strategy consisting of the generation of the 2-phenyl thiazole core followed by its functionalisation to introduce the desired substituents.



Scheme 10.1 Reaction conditions: a) Diethyl 2-bromomalonate (1 equiv.), EtOH, MW (110°C). b) Tf_2O (2 equiv.), NEt_3 (1.5 equiv.), DCM dry, -15°C to rt. c) BBr_3 (4 equiv.), DCM dry, 0°C to rt. d) Xantphos (10 mol%), $Pd(dba)_2$ (5 mol%), Cs_2CO_3 (1.4 equiv.), tert-butyl 3-aminopyrrolidine-1-carboxylate (1.2 equiv.), THF dry, MW (135°C). e) HCl 4 N (20 equiv.), Dioxane, rt.

As depicted in Scheme 10.1, **V1** and **V2** were synthetised according to a common procedure. The 2-phenyl thiazole scaffold **67** was obtained through the reaction of 2-methoxybenzothioamide with diethyl 2-bromomalonate; the generated ethyl 4-hydroxy-2-(2-methoxyphenyl)thiazole-5-carboxylate was then converted in the corresponding triflate derivative **68**, as triflates are known to be very good leaving groups.

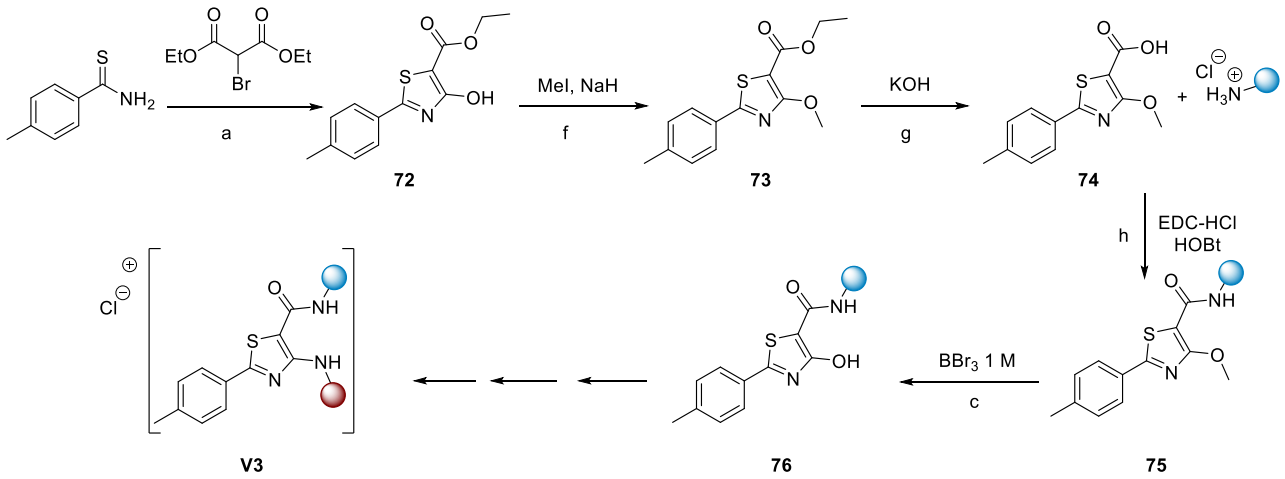
[157] Viegas-Junior, C.; Danuello, A.; da Silva Bolzani, V.; Barreiro, E.J.; Manssour Fraga, C.A. *Curr. Med. Chem.* **2007**, 14, 1829-1852.

For the synthesis of **V2**, **68** was directly submitted to a microwave-assisted Buchwald-Hartwig reaction with tert-butyl 3-aminopyrrolidine-1-carboxylate to generate **69** which, upon hydrolysis of the Boc-protecting group by means of HCl, yielded the derivative **V2** as hydrochloric salt.

For the synthesis of **V1**, bearing a hydroxy group instead of the methoxy substituent in *ortho* position on the phenyl ring, the triflate **68** was converted in the derivative **70** through an O-demethylation reaction promoted by boron tribromide (BBr_3). [158] Then, **70** was submitted to the Buchwald-Hartwig with tert-butyl 3-aminopyrrolidine-1-carboxylate and the subsequent hydrolysis with HCl achieved the isolation of the desired product as a hydrochloric salt.

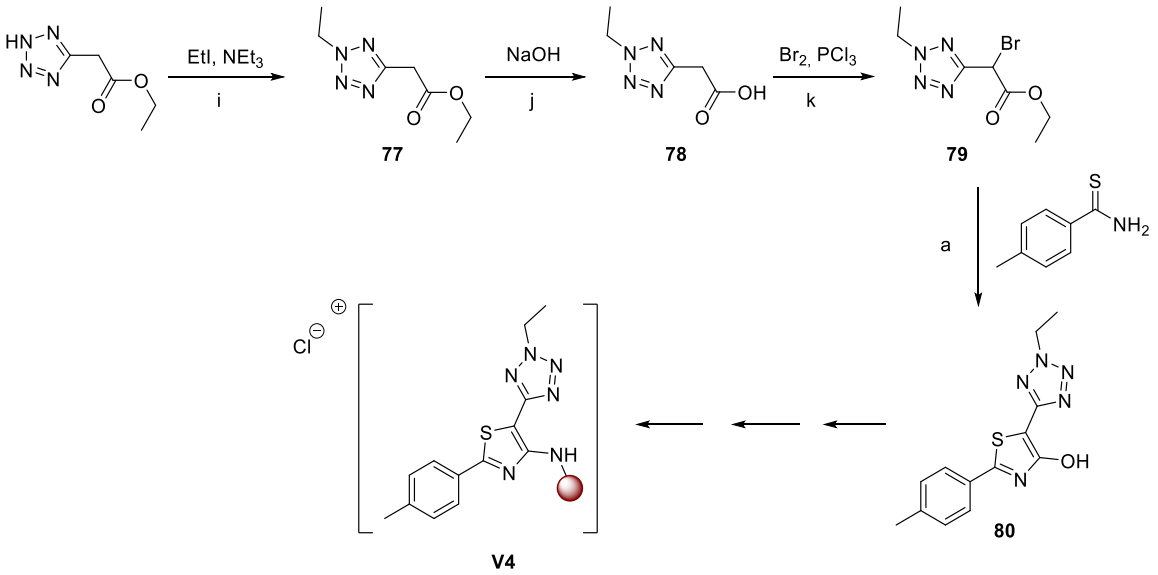
V3 was synthetised starting from 4-methylbenzothioamide and diethyl 2-bromomalonate, similarly to **V1** and **V2**. As depicted in scheme 10.2, the main difference with the analogues previously described is the presence, in **V3**, of an amide group at position 5 in place of the ester group; ethyl 4-hydroxy-2-(*p*-tolyl)thiazole-5-carboxylate (**72**) was therefore converted in derivative **76** through a synthetic sequence consisting of 1) methylation of the hydroxy group at position 4 as a way to protect it against undesired reactions; 2) KOH-mediated saponification of the ester group; 3) reaction between the newly formed carboxylic group and the appropriate amine in the presence of N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (EDC·HCl) and 1-hydroxybenzotriazole (HOBt) as coupling reagents; 4) restoration of the hydroxy group through O-demethylation mediated by BBr_3. Derivative **76** was planned to be transformed in the desired product **V3** by a sequence not shown here because of patent issues.

[158] Kosak, T.M.; Conrad, H.A.; Korich, A.L.; Lord, R.L. *Eur. J. Org. Chem.* **2015**, 7460-7467.



Scheme 10.2 Reaction conditions: f) MeI (20 equiv.), NaH (2 equiv.), THF/DMSO (6:1), 0°C to 60°C. g) KOH (10 equiv.), H_2O/EtOH (1:1), 40°C. h) EDC·HCl (1.1 equiv.), HOBt (1.1 equiv.), NEt_3 (5 equiv.), amine hydrochloride (1.5 equiv.), DMF dry, 0°C to rt. For the conditions of steps a, see scheme 10.1.

The synthesis of **V4**, with a tetrazole ring in place of the carbonyl moiety at position 4, has been more complicated due to the fact that ethyl 2-bromo-2-(2-ethyl-2*H*-tetrazol-5-yl)acetate (**77**), fundamental for the generation of the thiazole scaffold, was commercially unavailable.



Scheme 10.3 Reaction conditions: i) EtI (2 equiv.), NEt_3 (1.2 equiv.), CH_3CN, 0°C to rt. j) NaOH (2 equiv.), Dioxane/EtOH (1:1), rt. k) PCl_3 (0.5 equiv.), Br_2 (1 equiv.), DCM, 0°C to rt, then quenching with EtOH. For the conditions of steps a, see scheme 10.1.

This latter derivative **77** was synthetised starting from ethyl 2-(2*H*-tetrazol-5-yl)acetate, which was initially ethylated on the nitrogen at the 2 position of the tetrazole ring. The ester was then saponificated with NaOH in a mixture of 1,4-dioxane and ethanol and the obtained carboxylic acid **78** was brominated at α position with molecular bromine and phosphorus trichloride (PCl_3). The ester **79** was finally obtained by quenching the reaction mixture with

ethanol and was then used to synthetise the desired derivative **V4** (synthetic sequence not shown here because of patent issues) (Scheme 10.3).

The triflate group has already been recognised as an outstanding leaving group; there are, for example, several reports in literature regarding the possibility to perform nucleophilic substitutions on aryl triflates without the need of metal catalysts. [159] The possibility to avoid the use of palladium and other metals in the synthesis of pharmaceuticals is very appealing; in fact, while largely used in the synthesis of active pharmaceutical ingredients (APIs), any remaining metal can interfere with subsequent steps and, importantly, should never reach the patient. Stringent guidelines are in place for the presence of elemental impurities in pharmaceuticals for human use, with palladium being controlled to the demanding limit of 10 ppm in drug products, drug substances and excipients (according to the "*ICH guideline Q3D (R1) on elemental impurities*" published by EMA in 2019). [160,161] The metal is generally quantified by atomic absorption spectrometry or inductively coupled plasma mass spectrometry. These techniques are tedious and require expensive instruments that are operated mostly off site, with a consequent increase in the time and cost needed to produce APIs.

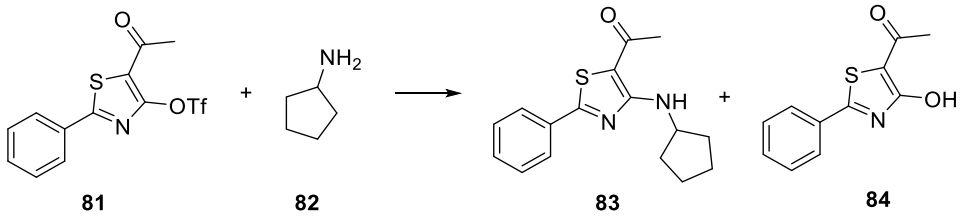
With the aim to improve the methodology used for the generation of the designed derivatives, the possibility to bypass the Buchwald-Hartwig used for the synthesis of **V1** and **V2** and to directly introduce the desired amine into the 2-phenyl thiazole scaffold by a simple nucleophilic substitution of triflate was investigated. The model reaction between 5-acetyl-2-phenylthiazol-4-yl trifluoromethanesulfonate (**81**) and cyclopentanamine (**82**) was studied under different conditions, as reported in Table 10.1.

[159] For selected examples, see: a) Reichelt, A.; Bailis, J.M.; Bartberger, M.D.; Yao, G.; Shu, H.; Kaller, M.R.; Allen, J.G.; Weidner, M.F.; Keegan, K.S.; Dao, J.H. *Eur. J. Med. Chem.* **2014**, 80, 364-382. b) Jeankumar, V.U.; Renuka, J.; Santosh, P.; Soni, V.; Sridevi, J.P.; Suryadevara, P.; Yogeeswari, P.; Sriram, D. *Eur. J. Med. Chem.* **2013**, 70, 143-153. c) Ronkin, S.M.; Badia, M.; Bellon, S.; Grillot, A.-L.; Gross, C.H.; Grossman, T.H.; Mani, N.; Parsons, J.D.; Stamos, D.; Trudeau, M.; Wei, Y.; Charifson, P.S. *Bioorg. Med. Chem. Lett*. **2010**, 20, 2828-2831. d) Arcadi, A.; Attanasi, O.A.; Guidi, B.; Rossi, E.; Santeusanio, S. *Eur. J. Org. Chem*. **1999**, 3117-3126.

[160] a) Bu, X.; Koide, K.; Carder, E.J.; Welch, C.J. *Org. Process Res. Dev*. **2013**, 17, 108-113. b) Forfar L.C.; Murray P.M. *Meeting Metal Limits in Pharmaceutical Processes*. In: Colacot T., Sivakumar V. (eds) Organometallics in Process Chemistry. Topics in Organometallic Chemistry, **2018**, vol 65. Springer, Cham

[161] https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-32.pdf.

Table 10.1 Optimisation of the conditions for the reaction of **81** with **82.**



81 82 83 84

Entry	Solvent	Temp. (°C)	Time (h)	150 (equiv.)	83 Yield[a] (%)	84 Yield[a] (%)	Conversion[b] (%)
1	Toluene	130	2	6	71	28	>99
2	Dioxane	130	2	6	85	13	>99
3[c]	DMF	130	2	6	32	27	>99
4	DMSO	130	2	6	96	traces	>99
5	DME	130	2	6	80	12	>99
6	CH_3CN	130	2	6	73	15	>99
7	DMSO	130	2	1	19	16	38
8	DMSO	130	2	1.5	68	12	90
9	DMSO	130	2	2	93	ND	>99
10	DMSO	50	2	2	43	45	89
11	DMSO	70	2	2	92	ND	>99
12	DMSO	90	2	2	92	ND	>99
13	DMSO	110	2	6	95	ND	>99
14[d]	DMSO	100	2	2	96	ND	ND

Reaction conditions: 81 (0.18 mmol) and **82 (**from 0.18 to 1.08 mmol) were dissolved in the selected solvent in a microwave vial equipped with a magnetic stirrer bar and irradiated at the selected temperature for 2 h. [a)] Isolated yield. [b)] Determined by UPLC. [c)] 1-(4-(dimethylamino)-2-phenylthiazol-5-yl)ethan-1-one was isolated as major product (89% yield). [d)] The reaction was performed under conventional heating. ND = not determined.

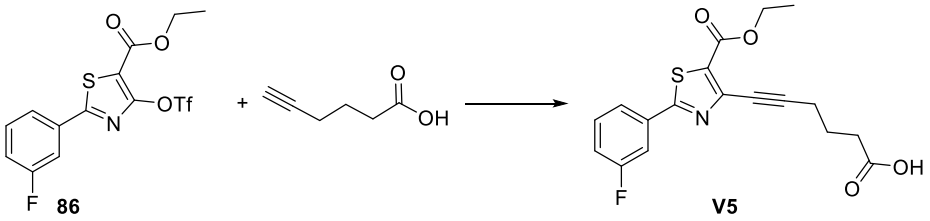
The reaction was firstly examined with different solvents (Table 10.1, entries 1-6); complete conversion of the starting material was obtained in all the cases although the desired derivative **83** was always isolated together with 1-(4-hydroxy-2-phenylthiazol-5-yl)ethan-1-one **84**, derived from the hydrolysis of the triflate **81**. The best selectivity was achieved employing DMSO and DMF (Table 10.1, entries 3-4); however, when the reaction was performed in DMF, 1-(4-(dimethylamino)-2-phenylthiazol-5-yl)ethan-1-one was isolated as the major product, probably because of the reaction between **81** and dimethylamine (DMA), which is

known to be a common impurity of dimethylformamide. [162] For this reason, DMSO has been chosen as elected solvent for all the subsequent investigations. Then, the role of the number of equivalents of the amine reagent was investigated (Table 10.1, entries 7-9), showing that an excess of amine is fundamental to achieve the complete conversion of the starting material even if a large excess is not necessary (the differences in the yield between the use of 2 or 6 equivalents of amine are in fact only marginal). In the end, the effects of temperature were investigated (Table 10.1, entries 10-13). The reaction can be efficiently performed even at 70°C under MW irradiation without a significant impairment of conversion, selectivity and yield. The reaction can be performed also under conventional heating with comparable results (Table 10.1, entry 14), showing the versatility of the methodology.

The creation of the second library of compounds (Scheme 10.4) started with the synthesis of ethyl 2-(3-fluorophenyl)-4-hydroxythiazole-5-carboxylate **85**, through the classic coupling between the appropriate thiobenzamide and diethyl 2-bromomalonate, followed by the conversion in the corresponding triflate derivative **86**, by means of triflic anhydride and triethylamine. Then, **86** was submitted to Sonogashira coupling with hex-5-ynoic acid to generate 6-(5-(ethoxycarbonyl)-2-(3-fluorophenyl)thiazol-4-yl)hex-5-ynoic acid (**V5**), from which all the other designed derivative could be easily obtained. Different reaction conditions were tested for the Sonogashira coupling, as summarised in Table 10.2, but the best yield was obtained when the reaction was left stirring overnight at room temperature, using triethylamine as base and THF as solvent (Table 10.2, entry 5).

[162] Magtaan, J.K.; Devocelle, M.; Kelleher, F. *J Pep Sci*. **2019**, 25, e3139.

Table 10.2 Optimisation of the Sonogashira coupling between **86** and hex-5-ynoic acid.



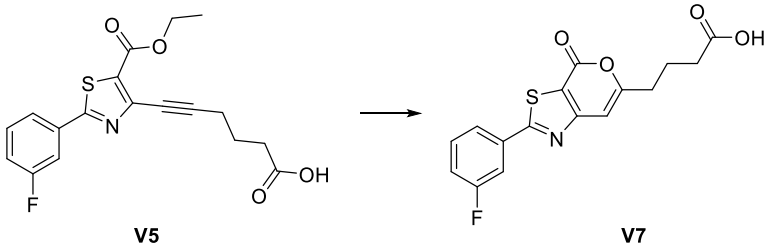
Entry	Conditions	Yield[a] (%)
1	$Pd(PPh_3)_4$ (10 mol%), CuI (10 mol%), K_2CO_3 (3.5 equiv.), DME/H_2O (1:1), MW, 80°C, 2 h	15%
2	$PdCl_2(PPh_3)_2$ (10 mol%), CuI (20 mol%), K_2CO_3 (3.5 equiv.), DME/H_2O (1:1), MW, 80°C, 2 h	61%
3	$PdCl_2(PPh_3)_2$ (10 mol%), CuI (20 mol%), K_2CO_3 (3.5 equiv.), DME/H_2O (1:1), rt, overnight	-
4	$PdCl_2(PPh_3)_2$ (3 mol%), CuI (2 mol%), TEA (20 equiv.), THF dry, MW, 100°C, 1 h	77%
5	$PdCl_2(PPh_3)_2$ (3 mol%), CuI (2 mol%), TEA (20 equiv.), THF dry, rt, overnight	86%

[a)] Isolated yield.

The 6-endo-dig cyclisation of **V5** was subsequently attempted in order to generate the pyran-2-one scaffold. Alkynes bearing proximal carboxylic groups have been successfully cyclised into pyran-2-one containing derivatives and several methodologies have been already reported in literature; [163] different procedures were thus tested for the substrate of interest **V5**, as reported in Table 10.3.

[163] For selected examples, see: a) Domaradzki, M.E.; Liu, X.; Ong, J.; Yu, G.; Zhang, G.; Simantov, A.; Perl, E.; Chen, Y. *Tetrahedron* **2020**, 76, 131437. b) Zhang, X.; Wan, X.; Cong, Y.; Zhen, X.; Li, Q.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. *J. Org. Chem.* **2019**, 84, 10402-10411. c) Curti, F.; Tiecco, M.; Pirovano, V.; Germani, R.; Caselli, A.; Rossi, E.; Abbiati, G. *Eur. J. Org. Chem.* **2019**, 9, 1904-1914. d) Lin, H.-P.; Ibrahim, N.; Provot, O.; Alami, M.; Hamze, A. *RSC Advances* **2018**, 8, 11536-11542. e) Kita, Y.; Yata, T.; Nishimoto, Y.; Chiba, K.; Yasuda, M. *Chem. Sci.* **2018**, 9, 6041-6052. f) Zhu, Y.; Shen, Z. *Adv. Synth. Catal.* **2017**, 359, 3515-3519. g) Speranca, A.; Godoi, B.; Pinton, S.; Back, D.F.; Menezes, P.H.; Zeni, G. *J. Org. Chem.* **2011**, 76, 6789-6797. h) Hellal, M.; Bourguignon, J.-J.; Bihel, F.J.-J. *Tetrahedron Lett*. **2008**, 49, 62-65.

Table 10.3 Optimisation of the intramolecular cyclisation of **V5**.



V5 **V7**

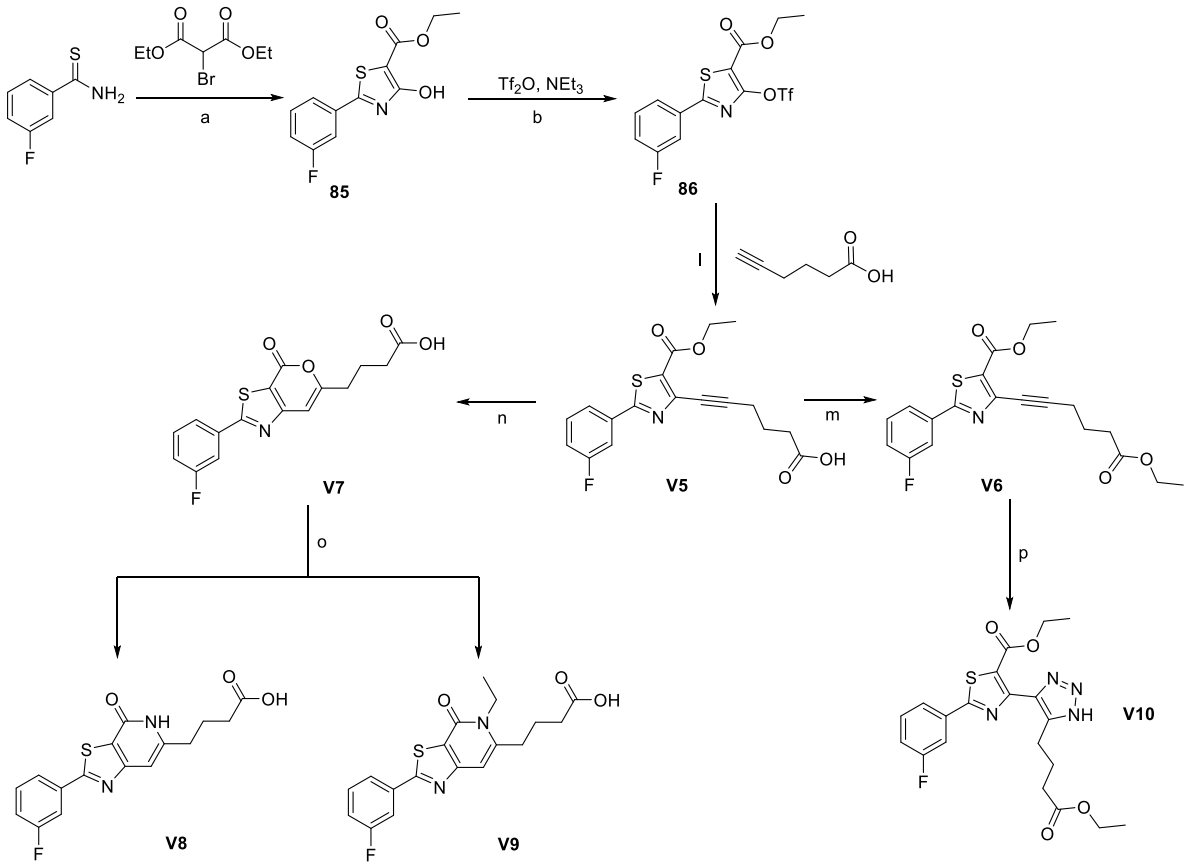
Entry	Conditions	Yield[a] (%)
1	*p*-TsOH·H_2O (20 mol%), EtOH, 160°C, MW, 4h	-
2	*p*-TsOH·H_2O (1 equiv.), EtOH, 160°C, MW, 4h	-
3	*p*-TsOH·H_2O (1.5 equiv.), EtOH, 160°C, MW, 4h	-
4	*p*-TsOH·H_2O (30 mol%), $Ag(OTf)_2$ (5 mol%), DCM, 130°C, MW, 4h	-
5	TEA (2 equiv.), toluene, 150°C, MW, 2h	-
6	KOH (10 equiv.), H_2O + MeOH (1:1), rt, 1h	-
7	1) KOH (10 equiv.), H_2O + MeOH (1:1), rt, 1h 2) Ag_2CO_3 (10 mol%), H_2O + MeOH (1:1), rt, 1h	59%
8	1) KOH (10 equiv.), H_2O + MeOH (1:1), rt, 1h 2) TBAF·$3H_2O$ (5 mol%), H_2O, 100°C, MW, 1h	77%

a) Isolated yield.

The use of *p*-TsOH, both in catalytic and stoichiometric amounts, did not allow to obtain the 6-endo-dig cyclisation of **V5** under microwave irradiation (Table 10.3, entries 1-3); in all cases, on the contrary, ethyl 4-(6-ethoxy-6-oxohex-1-yn-1-yl)-2-(3-fluorophenyl)thiazole-5-carboxylate **V6**, derived from the acid-promoted esterification of the hex-5-ynoic acid, was detected, with the best yield obtained when using a catalytic amount of the Brønsted acid (76%, Table 10.3, entry 1). Likewise, the addition of a catalytic amount of $Ag(OTf)_2$ did not cause any improvement on the reaction. No cyclisation was obtained in the presence of Brønsted bases too; however, when using a large excess of the inorganic base KOH, the quantitative hydrolysis of the ester group was obtained, yielding the 6-(5-(ethoxycarbonyl)-2-(3-fluorophenyl)thiazol-4-yl)hex-5-ynoic acid derivative (Table 10.3, entries 5-6). When the free carboxylic acid intermediate was stirred in a mixture of methanol and water with a catalytic amount of $AgCO_3$, at room temperature, **V7** was obtained in 59% of yield (Table 10.3, entry 7). Silver salts are in fact well-known for their ability to promote this type of cyclisation; [164] however, to avoid the use of metal salts, the same reaction was tested with a catalytic amount of tetra-*n*-butylammonium fluoride (TBAF) in plain water under microwave irradiation, obtaining **V7** in a good 77% yield (Table 10.3, entry 8). Fluoride catalysts, such

[164] a) Gianni, J.; Pirovano, V.; Abbiati, G. *Org. Biomol. Chem.* 2018, 16, 3213-3219. b) Godet, T.; Vaxelaire, C.; Michel, C.; Milet, A.; Belmont, P. *Chem. Eur. J.* **2007**, 13, 5632-5641.

as TBAF, are being widely used in organic synthesis as catalysts or promoters for several C–N, C–O, and C–C bond forming reactions. [165]



Scheme 10.5 Reaction conditions: l) alkyne (1.05 equiv.), $PdCl_2(PPh_3)_2$ (3 mol%), CuI (2 mol%), NEt_3 (20 equiv.), THF dry, rt. m) *p*-TsOH·H_2O (1.5 equiv.), EtOH, 160°C, MW. n) KOH (10 eq), H_2O + MeOH (1:1), rt, 1h, then TBAF·$3H_2O$ (5 mol%), H_2O, 100°C, MW. o) Amine (2 mL), MeOH or H_2O, 50°C. p) NaN_3 (2 equiv.), DMSO, 100°C, MW. For the conditions of steps a and b, see scheme 10.1.

The 4-(2-(3-fluorophenyl)-4-oxo-4*H*-pyrano[4,3-d]thiazol-6-yl)butanoic acid derivative **V7** was further used as starting material for the synthesis of the lactams derivatives **V8** and **V9**. In both cases, the pyran-2-one derivative was stirred in the presence of a large excess of the corresponding amine (ammonia and ethylamine, respectively) at 50°C under metal-free conditions.

Finally, the triazole derivative **V10** was directly obtained from **V6** through a classical Huisgen cycloaddition, under microwave irradiation. [166]

[165] a) Zhao, Y.; Guo, X.; Wang, Z.; Shen, D.; Chen, T.; Wu, N.; Yan, S.; You, J. *Eur. J. Org. Chem*. **2020**, 978-984. b) Wu, A.; Sun, J. *Synlett* **2019**, 30, 515-518. c) Watanabe, K.; Mino, T.; Masuda, C.; Yoshida, Y.; Sakamoto, M. *Eur. J. Org. Chem.* **2019**, 1635-1645. d) Lanari, D.; Piermatti, O.; Morozzi, C.; Santoro, S.; Vaccaro, L. *Synthesis* **2017**, 49, 973-980. e) Prasad, P.; Shobhashana, P.G.; Patel, M.P. 2017 *R. Soc. Open Sci.* **2017**, 4, 170764. f) De Nisi, A.; Sierra, S.; Ferrara, M.; Monari, M.; Bandini, M. *Org. Chem. Front*. **2017**, 4, 1849-1853. g) Nagy, E.; Lepore, S.D. *Org. Lett.* **2017**, 19, 3695-3698. h) Zhang, P.; Ye, D.; Chu, Y. *Tetrahedron Lett.* **2016**, 57, 3743-3745.

[166] Kumar, P.; Garg, V.; Verma, A.K. *Tetrahedron Lett*. **2019**, 60, 1854-1859.

10.4 Conclusions

During a six-months internship in the chemical laboratories of the Discovery Section of Dompé Farmaceutici S.p.A. in L'Aquila, ten new chemical entities belonging to the family of 2-phenyl thiazole were designed and synthetised, in order to find new and potent hit compounds as antagonists of TRPM8 channels, which are involved in several important pathologies. Six of the obtained derivatives (**V1-V6**) are analogues of compounds that have been previously synthetised and tested by Dompé Farmaceutici S.p.A, with the substitution of the hydroxy group with amines or alkynes; the other four have been obtained exploiting the versatility and reactivity of alkynes bearing proximal ester groups. In particular, bioisosters of isocoumarin were obtained in good yields, which could be expected to have promising biological activities. Moreover, to avoid the Buchwald-Hartwig reaction, a crucial step in the synthesis of **V1-V4**, a thorough investigation was carried out in order to optimise the metal-free coupling of triflates with amines under microwave irradiation. The results obtained could be expected to be of great help in avoiding the use of palladium catalysts in pharmaceutical industry, which could represent a potential source of metal contamination of the final medicinal product.

Concluding remarks

The work done in this PhD thesis demonstrated the versatility of alkynes as starting materials in the synthesis of complex organic architectures. In particular, four different types of nitrogen-containing alkynes have been successfully converted into valuable organic scaffolds by means of efficient synthetic strategies such as domino reactions, diversity-oriented synthesis and metal catalysis.

2-alkynylanilines have been efficiently converted into three distinct heterocyclic scaffolds through the reaction with cyclic and acyclic ketones. By simply changing the solvent and/or the catalyst, quinolinones, quinolines and 1-*N*-alkenylindoles have been generated in a straightforward way from the same starting materials. Interestingly, spirocyclic quinolinones could be easily obtained when reacting 2-alkynylanilines with cyclic ketones in the presence of stoichiometric amounts of *p*-TsOH in refluxing ethanol. The spiro junction is of great interest in medicinal chemistry but particularly difficult to create; the developed methodology offered a simple and efficient way to introduce it in pharmacologically active quinolinones.

The *p*-TsOH-promoted reaction of cyclic ketones with β-(2-aminophenyl)-α,β-ynones, close analogues of 2-alkynylanilines, enabled the one-pot synthesis of polycyclic quinolines. The reaction has been successfully expanded to the use of steroids bearing a carbonyl group at position 3, accessing therefore A-fused steroidal quinolines. Both linear and angular steroidal quinolines could be accessed through the developed methodology, depending on the structure of the steroidal reagent. By using pluripotent β-dicarbonyl compounds as reaction partners, β-(2-aminophenyl)-α,β-ynones have been converted into pyrano-fused quinolines, interesting for their medicinal and fluorescent properties. In the presence of β-ketoesters, under the catalysis of *p*-TsOH, 4*H*-pyrano[3,4-c]quinoline-4-ones have been obtained in high yields, through a cascade bicyclisation process; on the contrary, when using β-diketones, a three-component reaction took place, generating 4*H*-pyrano[3,4-c]quinoline derivatives in their ketalic form. Finally, the reaction with aryl isocyanates/benzoyl isothiocyanate has been explored under basic conditions, allowing the divergent generation of quinazoline, benzoxazine and benzothiazine derivatives. A thorough DFT investigation has been performed to clarify the factors influencing the product selectivity experimentally observed.

N-propargyl phthalimides, as protected analogues of propargylamines, have been the focus of the project developed at the Institut de Chimie de Nice (ICN), Université Côte d'Azur, under the supervision of Prof. V. Michelet. Their gold-catalysed hydration has been studied to easily

access valuable β-amino ketones, which can be obtained by removing the phthalimido protecting group under very mild reaction conditions. The reaction proceeded with complete regioselectivity, which was attributed to the intrinsic electronic features of the initial π-adduct between gold and the alkyne substrate through a computational investigation. To further expand the range of chemicals accessible from N-propargyl phthalimide derivatives, gold catalysis has been used in partnership with Selectfluor. In particular, by changing the nature of the gold catalysts, the solvent and the amount of Selectfluor, three different scaffolds have been generated. Although the results are only preliminary, the methodology seems to be particularly interesting for the synthesis of α-fluoro- and/or α,α-difluoro-β-amino ketones. Because of the multiple properties of fluoro-organic compounds, new simple synthetic methodologies to introduce fluorine atoms in organic compounds are always sought.

Under the supervision of Prof. V. Michelet, an additional project on the Pd-catalysed hydroarylation of ynamides in water has been carried out. Independently of the ligand used, enamides could be easily obtained at room temperature, at much milder conditions in comparison to those already reported in literature. Three distinct ligands have been used, the water soluble TPPTS and the classic $P(o\text{-Tol})_3$ and PCy_3, allowing to access the whole panel of the expected regio- and stereoisomers.

Finally, the synthesis of ten new potential TRPM8 antagonists has been carried out in collaboration with the Discovery Section of Dompé Farmaceutici S.p.A., in L'Aquila, under the supervision of Dr. A. Aramini and Dr. G. Bianchini. The versatility of alkynes helped in the synthesis of very interesting isocoumarin analogues. Moreover, an extensive investigation on the direct substitution of aryl triflates with amines avoided the use of metal catalysts in the synthetic sequence of four derivatives. This is of great importance on an industrial perspective, as it removes a source of potential contamination of the final product. The obtained molecules will be tested to assess their pharmacological potential.

Chapter 11

Experimental Section

11.1 General Information

All reactions were carried out with magnetic stirring and were monitored by TLC on silica gel 60 Å (Fluorochem, SigmaAldrich or Macherey-Nagel GmbH & Co. KG, Düren, Germany). Unless otherwise stated, all starting materials, catalysts, and solvents were commercially available and were used as purchased. Reaction products were purified by flash chromatography on silica gel (60-200 μm) by elution with n-hexane/EtOAc mixtures or using Isolera One (Biotage) with prepacked SNAP cartridges containing silica, eluting with n-hexane/EtOAc mixtures. Reactions under microwaves irradiation were performed with the Initiator + microwave synthetiser (Biotage), equipped with an automated system.

^{1}H NMR spectra were recorded at 400 MHz on a Bruker Avance III spectrometer. Chemical shifts (in ppm) were referenced to tetramethylsilane (δ = 0 ppm) or $CDCl_3$ (δ = 7.25 ppm) or dimethyl sulfoxide-d_6 (δ = 2.49 ppm) as an internal standard. ^{13}C NMR spectra were taken on the same machine at 101 MHz and were calibrated with tetramethylsilane (δ = 0 ppm) or $CDCl_3$ (δ = 77.0 ppm) or dimethyl sulfoxide-d_6 (δ = 39.50 ppm) as an internal standard. ^{19}F NMR spectra were taken on the same machine at 376 MHz and were calibrated with trifluoroacetic acid (δ = - 76.55 ppm) as an internal standard. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; q, quartet; br, broad. The coupling constants, J, are reported in Hertz [Hz] and result from averaging the experimentally found values. The stereochemistry in the solution for **10ar-10aw**, **35aa**, **35ca**, **36aa** and **37aa** was assigned by performing COSY, NOESY, HSQC and HMBC NMR experiments using Bruker standard parameters. Analytical GC-MS analyses were performed for all compounds on a Shimadzu QP2010S- MS chromatograph (EI, 70 eV), equipped with an SLB-5ms capillary column (thickness 0.25 mm, length 30 m, and inside diameter 0.25 mm) while UPLC-MS analysis were performed on a Waters ACQUITY UPLC-MS chromatograph. High resolution mass spectroscopy (HRMS) analyses for new compounds were performed using a MALDI-TOF spectrometer AB SCIEX TOF/TOF 5800 System using matrix in combination with KI for the ionization (11.2, 11.3, 11.4 and 11.5) or a Thermo Vanquish UHPL-Q-Exactive Focus Mass Spectrometer equipped with H-ESI source (11.6 and 11.7), both operated in a positive mode.

11.2 Product selectivity control in the reaction of 2-alkynylanilines with unactivated carbonyl compounds

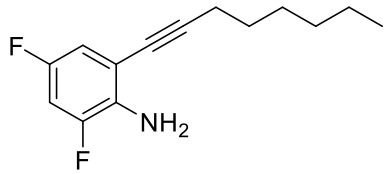
2-Alkynylanilines **1a-q**, **s** were prepared following the procedures already reported in literature. [167]

The spectroscopic data for 1-(2-aminophenyl)-2-phenylethan-1-one (**13a**), [168] 2-phenylindole (**15a**), [169] 2-aminoacetophenone (**13m**), [170] and 2-(4-Benzyl-3-phenylquinolin-2-yl)aniline (**14a**) [171] matched the values previously reported in literature.

11.2.1 Preparation and characterisation of 2-alkynylaniline **1r**

To a stirring solution of 2-bromo-4,6-difluoroaniline (4.8 mmol) in dry DMF (1 mL) under nitrogen atmosphere at room temperature, anhydrous triethylamine (9 mL), $PdCl_2(PPh_3)_2$ (2 mol%) and CuI (1 mol%) were added. Then, oct-1-yne (5.77 mmol, 1.2 equiv.) was added dropwise and the resulting solution was heated at 50°C for 24 hours. After completion, as monitored by TLC, the solution was diluted with a saturated aqueous solution of NH_4Cl and extracted with AcOEt (3 x 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The obtained crude was purified by column chromatography over silica gel using PE/AcOEt 98:2 v/v obtaining **1r** as a yellow oil.

2,4-difluoro-6-(oct-1-yn-1-yl)aniline (1r)



Yellow oil. (72% yield, 822 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.78 (ddd, *J* = 8.9, 2.8, 1.7 Hz, 1H), 6.71 (ddd, *J* = 11.0, 8.4, 2.8 Hz, 1H), 3.95 (br, 2H, NH_2), 2.45 (t, *J* = 7.1 Hz, 2H), 1.65-1.57 (m, 2H), 1.48-1.41 (m, 2H), 1.36-1.30 (m, 4H), 0.90 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 153.8 (dd, *J* = 237.4, 12.5 Hz, Cq-F), 150.5 (dd, *J* = 241.0, 12.8 Hz, Cq-F), 132.8 (dd, *J* = 13.5, 3.1 Hz, Cq-NH_2), 113.2 (dd, *J* = 23.2, 3.6 Hz, CH), 110.9 (dd, *J* = 11.0, 6.7 Hz, Cq), 103.7 (dd, *J* = 26.8, 22.9 Hz, CH), 98.0 (Cq), 75.3 (dd, *J* = 5.2, 3.6 Hz, Cq), 31.3 (CH_2), 28.7 (CH_2), 28.6 (CH_2), 22.5 (CH_2), 19.5 (CH_2), 14.0 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -125.1 (d, *J* = 1.5 Hz), -130.5 (d, *J* = 1.5 Hz). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{14}H_{17}F_2NNa$: $[M+Na]^+$ 260.1227, Found: 260.1227.

[167] a) Arcadi, A.; Chiarini, M.; Del Vecchio, L.; Marinelli, F.; Michelet, V. *Eur. J. Org. Chem.* **2017**, 16, 2214-2222. b) Shen, J.; Yuan, D.; Qiao, Y.; Shen, X.; Zhang, Z.; Zhong, Y.; Yi, Y.; Zhu, X. *Org. Lett.* **2014**, 16, 4924-4927. c) Gabriele, B.; Veltri, L.; Salerno, G.; Mancuso, R.; Costa, M. *Adv. Synth. Catal.* **2010**, 352, 3355-3363. d) Tseng, K.-F.; Lin, C.-F.; Lo, Y.-H.; Hu, Y.-L.; Chen, L.-Y.; Yang, S.-H.; Lin, S.-R.; Chang, L.-S.; Wu, M.-J. *Eur. J. Med. Chem.* **2009**, 44, 35-41. e) Sakai, N.; Annaka, K.; Fujita, A.; Sato, A.; Konakahara, T. *J. Org. Chem.* **2008**, 73, 4160-4165. f) Arcadi, A.; Bianchi, G.; Marinelli, F. *Synthesis* **2004**, 4, 610-618. g) Cacchi, S.; Fabrizi, G.; Marinelli, F. *Synlett* **1999**, 4, 401-404.

[168] Ferrini, S.; Ponticelli, F.; Taddei, M. *J. Org. Chem.* **2006**, 71, 9217-9220.

[169] Jang, Y.H.; Youn, S.W. *Org. Lett.* **2014**, 16, 3720-3723.

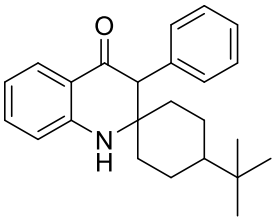
[170] Tan, D.-W.; Li, H.-X.; Zhang, M.-J.; Yao, J.-L.; Lang, J.-P. *ChemCatChem* **2017**, 9, 1113-1118.

[171] Jia, R.; Li, B.; Zhang, X.; Fann, X. *Org. Lett.* **2020**, 22, 6810-6815.

11.2.2 Preparation and characterisation of 2,2,3-substituted-2,3-dihydroquinolin-4(1*H*)-ones **10aa-10le**

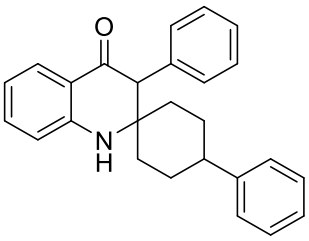
General procedure. To a solution of 2-(phenylethynyl)aniline **1** (0.53 mmol, 1 equiv.) in EtOH (2 mL), ketone **9** (0.53 mmol, 1 equiv.) and *p*-TsOH·H_2O (0.53 mmol, 1 equiv.) were added. The mixture was heated to 80°C and stirred for 8-24 hours. After the completion of the reaction, as monitored by TLC, the mixture was diluted with a saturated solution of $NaHCO_3$ and extracted with AcOEt (20 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4. After removal of the solvent at reduced pressure, the crude was further purified by column chromatography on silica gel with mixtures of *n*-hexane–EtOAc from 95:5 to 60:40 v/v.

4-tert-butyl-3'-phenyl-1'*H*-spiro[cyclohexane-1,2'-quinolin]-4'(3'*H*)-one (10aa)



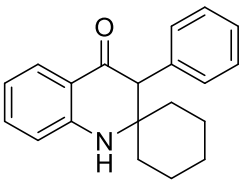
White solid. (70% yield, 129 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.84 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.35 (ddd, *J* = 8.5, 6.9, 1.3 Hz, 1H), 7.25-7.22 (m, 3H), 7.17-7.15 (m, 2H), 6.75-6.71 (m, 2H), 4.68 (br, 1H, NH), 3.39 (d, *J* = 0.9 Hz, 1H), 2.26 (dq, *J* = 13.1, 3.0 Hz, 1H), 1.67-1.58 (m, 2H), 1.50 (dq, *J* = 13.7, 3.0 Hz, 1H), 1.30 (td, *J* = 13.5, 4.1 Hz, 1H), 1.25 (td, *J* = 13.2, 3.1 Hz, 1H), 1.20-0.95 (m, 3H), 0.84 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 194.1 (CO), 148.7 (Cq), 135.5 (CH), 135.3 (Cq), 129.6 (2CH), 128.3 (2CH), 128.0 (CH), 127.2 (CH), 118.1 (Cq), 117.7 (CH), 115.8 (CH), 64.2 (CH), 56.0 (Cq), 47.1 (CH), 34.6 (CH_2), 32.9 (CH_2), 32.3 (Cq), 27.4 ($3CH_3$), 22.5 (CH_2), 21.8 (CH_2). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{24}H_{29}KNO$: $[M+K]^+$ 386.1886, Found: 386.1887.

3',4-diphenyl-1'*H*-spiro[cyclohexane-1,2'-quinolin]-4'(3'*H*)-one (10ab)



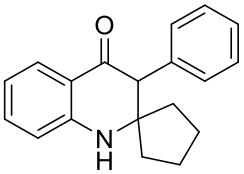
Yellow solid. (66% yield, 120 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.86 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.37 (ddd, *J* = 8.4, 7.0, 1.6 Hz, 1H), 7.30-7.17 (m, 10H), 6.79 (dq, *J* = 8.3, 0.5 Hz, 1H), 6.75 (ddd, *J* = 8.3, 7.0, 1.0 Hz, 1H), 4.86 (br, 1H, NH), 3.46 (d, *J* = 0.7 Hz, 1H), 2.50 (dt, *J* = 11.8, 3.5 Hz, 1H), 2.35 (dq, *J* = 13.5, 3.0 Hz, 1H), 1.84-1.40 (m, 7H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 193.9 (CO), 148.6 (Cq), 146.0 (Cq), 135.6 (CH), 135.1 (Cq), 129.6 (2CH), 128.44 (2CH), 128.40 (2CH), 128.1 (CH), 127.4 (CH), 126.6 (2CH), 126.3 (CH), 118.1 (Cq), 117.9 (CH), 115.9 (CH), 64.2 (CH), 55.8 (Cq), 43.0 (CH), 34.3 (CH_2), 32.9 (CH_2), 29.0 (CH_2), 28.7 (CH_2). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{26}H_{25}KNO$: $[M+K]^+$ 406.1573, Found: 406.1576.

3'-phenyl-1'*H*-spiro[cyclohexane-1,2'-quinolin]-4'(3'*H*)-one (10ak)



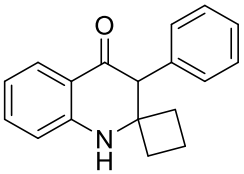
Pale yellow solid. (87% yield, 172 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.82 (ddd, *J* = 7.9, 1.6, 0.6 Hz, 1H), 7.37 (ddd, *J* = 8.5, 6.9, 1.6 Hz, 1H), 7.25-7.19 (m, 5H), 6.74 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H), 6.72 (ddd, *J* = 8.2, 1.1, 0.6 Hz, 1H), 4.49 (br, 1H, NH), 3.55 (s, 1H), 1.96 (dd, *J* = 12.7, 5.5 Hz, 1H), 1.68-1.25 (m, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 193.9 (CO), 148.8 (Cq), 135.6 (CH), 135.3 (Cq), 129.5 (2CH), 128.4 (2CH), 128.2 (CH), 127.3 (CH), 117.81 (Cq), 117.76 (CH), 115.7 (CH), 62.3 (CH), 56.6 (Cq), 34.6 (CH_2), 33.4 (CH_2), 25.2 (CH_2), 21.7 (CH_2), 21.3 (CH_2). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{20}H_{21}KNO$: $[M+K]^+$ 330.1260, Found: 330.1265.

3'-phenyl-1'*H*-spiro[cyclopentane-1,2'-quinolin]-4'(3'*H*)-one (10ad)



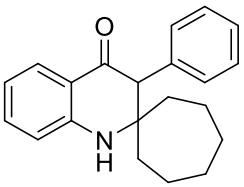
Yellow solid. (65% yield, 93 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.76 (ddt, *J* = 7.9, 1.6, 0.6 Hz, 1H), 7.26 (ddd, *J* = 8.4, 7.0, 1.6 Hz, 1H), 7.19-7.13 (m, 5H), 6.78 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 6.61 (d, *J* = 8.2 Hz, 1H), 4.26 (br, 1H, NH), 3.43 (s, 1H), 1.83-1.61 (m, 7H), 1.37-1.29 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 193.9 (CO), 149.8 (Cq), 136.5 (Cq), 135.4 (CH), 129.1 (2CH), 128.4 (2CH), 128.3 (CH), 127.3 (CH), 118.2 (Cq), 117.9 (CH), 115.9 (CH), 67.1 (Cq), 61.6 (CH), 38.7 (CH_2), 35.7 (CH_2), 23.4 (CH_2), 22.7 (CH_2). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{19}H_{19}KNO$: $[M+K]^+$ 316.1104, Found: 316.1116.

3'-phenyl-1'*H*-spiro[cyclobutane-1,2'-quinolin]-4'(3'*H*)-one (10ap)



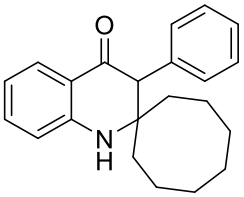
Yellow solid. (62% yield, 60 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.83 (ddt, *J* = 8.0, 1.6, 0.5 Hz, 1H), 7.35 (ddd, *J* = 8.3, 7.0, 1.6 Hz, 1H), 7.31-7.22 (m, 5H), 6.74 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H), 6.70 (ddd, *J* = 8.2, 1.0, 0.5 Hz, 1H), 4.54 (br, 1H, NH), 3.82 (s, 1H), 2.42-2.35 (m, 1H), 2.28-2.20 (m, 1H), 2.07-1.99 (m, 1H), 1.96-1.79 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 193.9 (CO), 149.0 (Cq), 135.6 (CH), 135.5 (Cq), 129.1 (2CH), 128.4 (2CH), 128.2 (CH), 127.4 (CH), 118.4 (Cq), 118.3 (CH), 115.9 (CH), 60.12 (CH), 60.07 (Cq), 36.3 (CH_2), 32.1 (CH_2), 13.1 (CH_2). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{18}H_{17}KNO$: $[M+K]^+$ 302.0947, Found: 302.0950.

3'-phenyl-1'*H*-spiro[cycloheptane-1,2'-quinolin]-4'(3'*H*)-one (10ae)



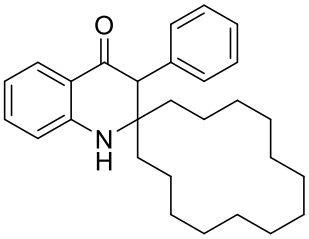
Yellow solid. (71% yield, 89 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.72 (ddt, *J* = 7.9, 1.1, 0.6 Hz, 1H), 7.25 (ddd, *J* = 8.3, 7.0, 1.6 Hz, 1H), 7.15-7.10 (m, 5H), 6.65-6.60 (m, 2H), 4.50 (br, 1H, NH), 3.47 (s, 1H), 1.98-1.92 (m, 1H), 1.81-1.75 (m, 1H), 1.51-1.16 (m, 10H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 194.0 (CO), 149.0 (Cq), 135.8 (Cq), 135.5 (CH), 129.5 (2CH), 128.4 (2CH), 128.0 (CH), 127.2 (CH), 117.8 (Cq), 117.5 (CH), 115.7 (CH), 62.7 (CH), 60.6 (Cq), 37.8 (CH_2), 36.9 (CH_2), 29.8 (CH_2), 29.6 (CH_2), 22.0 (CH_2), 21.9 (CH_2). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{21}H_{23}KNO$: $[M+K]^+$ 344.1417, Found: 344.1423.

3'-phenyl-1'*H*-spiro[cyclooctane-1,2'-quinolin]-4'(3'*H*)-one (10af)



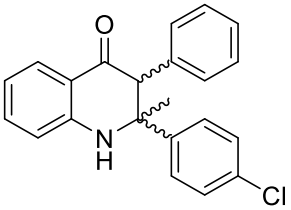
Yellow solid. (15% yield, 26 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.73 (ddd, *J* = 8.0, 1.7, 0.4 Hz, 1H), 7.29 (ddd, *J* = 8.4, 7.0, 1.6 Hz, 1H), 7.16-7.11 (m, 5H), 6.66 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.61 (ddd, *J* = 8.3, 1.0, 0.5 Hz, 1H), 3.48 (s, 1H), 2.03-1.97 (m, 1H), 1.82-1.75 (m, 1H), 1.48-1.38 (m, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 193.9 (CO), 148.8 (Cq), 135.9 (Cq), 135.6 (CH), 129.4 (2CH), 128.5 (2CH), 128.2 (CH), 127.3 (CH), 117.8 (Cq), 117.7 (CH), 115.6 (CH), 61.4 (CH), 60.3 (Cq), 32.3 (CH_2), 31.5 (CH_2), 28.6 (CH_2), 27.9 (CH_2), 25.2 (CH_2), 22.1 (CH_2), 21.4 (CH_2). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{22}H_{25}KNO$: $[M+K]^+$ 358.1573, Found: 358.1570.

3'-phenyl-1'*H*-spiro[cyclopentadecane-1,2'-quinolin]-4'(3'*H*)-one (10aq)



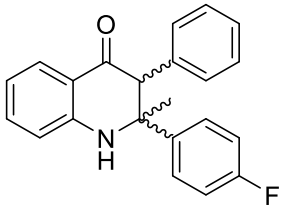
Pale yellow solid. (36% yield, 87 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.79 (ddt, *J* = 8.0, 1.7, 0.5 Hz, 1H), 7.35 (ddd, *J* = 8.5, 7.0, 1.7 Hz, 1H), 7.24-7.20 (m, 5H), 6.73 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 6.67 (ddd, *J* = 8.5, 1.1, 0.5 Hz, 1H), 4.25 (br, 1H, NH), 3.50 (d, *J* = 1.7 Hz, 1H), 1.89-1.81 (m, 1H), 1.62-1.56 (m, 2H), 1.38-1.12 (m, 25H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 193.9 (CO), 148.9 (Cq), 135.7 (Cq), 135.6 (CH), 129.2 (2CH), 128.6 (2CH), 128.3 (CH), 127.3 (CH), 117.7 (CH), 117.6 (Cq), 115.5 (CH), 60.9 (CH), 59.9 (Cq), 34.3 (CH_2), 33.8 (CH_2), 27.5 (CH_2), 27.3 (CH_2), 27.0 (CH_2), 26.9 (CH_2), 26.8 (CH_2), 26.7 (CH_2), 26.6 ($2CH_2$), 26.2 (CH_2), 26.1 (CH_2), 21.5 (CH_2), 21.0 (CH_2). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{29}H_{39}KNO$: $[M+K]^+$ 456.2669, Found: 456.2669.

(2R, 3S / 2S, 3R) (Major Isomer) + (2S, 3S / 2R, 3R) (Minor Isomer) 2-(4-chlorophenyl)-2-methyl-3-phenyl-2,3-dihydroquinolin-4(1*H*)-one (10ar)



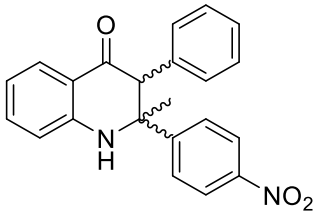
Brown solid. (71% yield, 126 mg). **Ratio Major/Minor:** 1.00/0.55. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.83 (ddt, *J* = 7.9, 1.6, 0.5 Hz, 1H, minor), 7.67 (ddt, *J* = 7.9, 1.6, 0.5 Hz, 1H, major), 7.36 (ddd, *J* = 8.4, 7.0, 1.6 Hz, 1H, minor), 7.33 (ddd, *J* = 8.4, 7.0, 1.6 Hz, 1H, major), 7.27-7.24 (m, 2H, major), 7.18-7.13 (m, 5H, major), 7.08-7.06 (m, 2H, major), 7.04 (m, 4H, minor), 7.00-6.96 (m, 1H, minor), 6.95-6.91 (m, 2H, minor), 6.79-6.73 (m, 2H minor + 1H major), 6.70-6.66 (m, 2H minor + 1H major), 4.64 (br, 1H, NH), 4.45 (br, 1H, NH), 4.01 (s, 1H, major), 3.59 (s, 1H, minor), 1.74 (s, 3H, minor), 1.29 (s, 3H, major). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 193.1 (minor, CO), 192.5 (major, CO), 149.41 (major, Cq), 149.40 (minor, Cq), 143.9 (major, Cq), 141.6 (minor, Cq), 135.9 (major, CH), 135.8 (minor, CH), 135.3 (minor, Cq), 134.8 (major, Cq), 133.12 (major, Cq), 133.09 (minor, Cq), 130.0 (major, 2CH), 129.3 (minor, 2CH), 128.7 (major, 2CH), 128.4 (major, 2CH), 128.2 (major, CH), 128.1 (minor, 2CH), 128.04 (minor, 2CH), 128.03 (minor, CH), 127.54 (major, CH), 127.52 (major, 2CH), 127.2 (minor, CH), 127.0 (minor, 2CH), 118.8 (major, Cq), 118.6 (minor, CH), 118.3 (major, CH), 118.2 (minor, Cq), 116.4 (minor, CH), 115.3 (major, CH), 64.6 (minor, CH), 63.1 (major, CH), 62.0 (minor, Cq), 61.8 (major, Cq), 26.5 (minor, CH_3), 26.0 (major, CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{22}H_{18}ClKNO$: $[M+K]^+$ 386.0714, Found: 386.0714.

(2R, 3S / 2S, 3R) (Major Isomer) + (2S, 3S / 2R, 3R) (Minor Isomer) 2-(4-fluororophenyl)-2-methyl-3-phenyl-2,3-dihydroquinolin-4(1*H*)-one (10as)



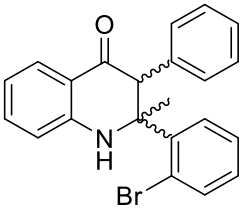
Yellow solid. (67% yield, 82 mg). **Ratio Major/Minor:** 1.00/0.30. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.92 (ddd, *J* = 8.0, 1.7, 0.5 Hz, 1H, minor), 7.77 (ddd, *J* = 7.9, 1.6, 0.5 Hz, 1H, major), 7.45 (ddd, *J* = 8.5, 6.9, 1.7 Hz, 1H, minor), 7.42 (ddd, *J* = 8.5, 6.9, 1.6 Hz, 1H, major), 7.39-7.35 (m, 2H, major), 7.24-7.23 (m, 3H, major + minor), 7.18-7.16 (m, 2H, minor), 7.14-7.12 (m, 2H, major), 7.06-6.98 (m, 3H, minor), 6.97-6.92 (m, 2H, major), 6.88-6.83 (m, 2H, minor), 6.82 (ddd, *J* = 8.2, 1.0, 0.5 Hz, 1H, major), 6.77 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, major), 6.75 (ddd, *J* = 8.3, 1.5, 0.5 Hz, 1H, minor), 4.65 (br, 1H, NH, major + minor), 4.11 (s, 1H, major), 3.66 (s, 1H, minor), 1.85 (s, 3H, minor), 1.41 (s, 3H, major). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 193.2 (CO, minor), 192.5 (CO, major), 161.86 (d, *J* = 246.6 Hz, CF, major), 161.84 (d, *J* = 246.7 Hz, CF, minor), 149.5 (Cq, minor), 149.4 (Cq, major), 141.0 (d, *J* = 3.2 Hz, Cq, major), 138.8 (d, *J* = 3.3 Hz, Cq, minor), 135.9 (CH, major), 135.8 (CH, minor), 135.5 (Cq, minor), 134.9 (Cq, minor), 130.1 (2CH, major), 129.3 (2CH, minor), 128.3 (2CH, major), 128.2 (CH, major), 128.1 (CH, minor), 128.0 (2CH, minor), 127.8 (d, *J* = 8.1 Hz, 2CH, major), 127.5 (CH, major), 127.3 (d, *J* = 8.0 Hz, 2CH, minor), 127.1 (CH, minor), 118.8 (Cq, major), 118.6 (CH, minor), 118.30 (CH, major), 118.26 (Cq, minor), 116.3 (CH, minor), 115.34 (d, *J* = 21.4 Hz, 2CH, major), 115.29 (CH, major), 114.8 (d, *J* = 21.3 Hz, 2CH, minor), 64.9 (d, *J* = 0.9 Hz, CH, minor), 63.5 (d, *J* = 0.7 Hz, CH, major), 62.0 (Cq, minor), 61.9 (Cq, major), 26.6 (CH_3, minor), 25.9 (CH_3, major). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -115.3 (minor), -115.5 (major). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{22}H_{18}FKNO$: $[M+K]^+$ 370.1009, Found: 370.1010.

(2R, 3S / 2S, 3R) (Major Isomer) + (2S, 3S / 2R, 3R) (Minor Isomer) 2-methyl-(4-nitrophenyl)-3-phenyl-2,3-dihydroquinolin-4(1*H*)-one (10at)



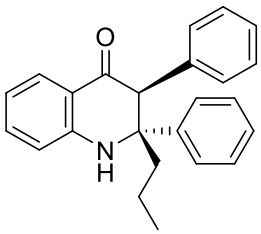
Yellow solid. (74% yield, 106 mg). **Ratio Major/Minor:** 1.00/0.30. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.12-8.10 (m, 2H, major), 8.01-7.98 (m, 2H, minor), 7.92 (ddd, *J* = 7.7, 1.6, 0.8 Hz, 1H, minor), 7.75 (ddd, *J* = 7.9, 1.6, 0.5 Hz, 1H, major), 7.61-7.58 (m, 2H, major), 7.48 (ddd, *J* = 8.5, 6.9, 1.6 Hz, 1H, minor), 7.45 (ddd, *J* = 8.5, 6.9, 1.6 Hz, 1H, major), 7.42-7.38 (m, 2H, minor), 7.27-7.25 (m, 1H major + 1H minor), 7.19-7.15 (m, 2H, major), 7.09-7.05 (m, 2H, major), 7.02-6.98 (m, 2H, minor), 6.92-6.87 (m, 1H major + 2H minor), 6.82-6.76 (m, 1H major + 2H minor), 4.76 (br, 1H, NH, major), 4.51 (br, 1H, NH, minor), 4.12 (s, 1H, major), 3.72 (s, 1H, minor), 1.90 (s, 3H, minor), 1.44 (s, 3H, major). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 192.2 (CO, minor), 191.8 (CO, major), 153.0 (Cq, major), 150.5 (Cq, minor), 149.0 (Cq, major+minor), 147.1 (Cq, major), 147.0 (Cq, minor), 136.2 (CH, major), 136.1 (CH, minor), 134.8 (Cq, minor), 134.2 (Cq, major), 130.0 (2CH, major), 129.1 (2CH, minor), 128.6 (2CH, major), 128.4 (CH, major), 128.3 (2CH, minor), 128.2 (CH, minor), 127.9 (CH, major), 127.5 (CH, minor), 127.2 (2CH, major), 126.6 (2CH, minor), 123.8 (2CH, major), 123.2 (2CH, minor), 119.3 (CH, minor), 119.0 (Cq, major), 118.9 (CH, major), 118.2 (Cq, minor), 116.5 (CH, minor), 115.3 (CH, major), 64.5 (CH, minor), 62.9 (CH, major), 62.5 (Cq, minor), 62.3 (Cq, major), 26.6 (CH_3, minor), 26.0 (CH_3, major). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{22}H_{18}N_2NaO_3$: $[M+Na]^+$ 381.1215, Found: 381.1217.

(2R, 3S / 2S, 3R) (Major Isomer) + (2S, 3S / 2R, 3R) (Minor Isomer) 2-(2-bromophenyl)-3-phenyl-2,3-dihydroquinolin-4(1*H*)-one (10au)



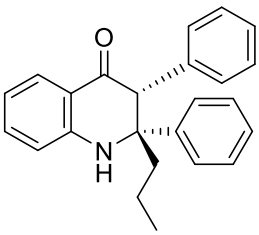
Yellow solid. (34% yield, 48 mg). **Ratio Major/Minor:** 1.00/0.50. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.79 (ddd, *J* = 8.0, 1.6, 0.5 Hz, 1H, minor), 7.67 (ddd, *J* = 7.9, 1.6, 0.5 Hz, 1H, major), 7.53 (dd, *J* = 7.9, 1.4 Hz, 1H, major), 7.48 (ddd, *J* = 7.9, 1.4, 0.3 Hz, 1H, minor), 7.45 (dd, *J* = 8.0, 1.7 Hz, 1H, major), 7.40-7.27 (m, 1H, major + minor), 7.24-7.16 (m, 5H, major + minor), 7.13-7.09 (m, 1H, major + minor), 7.06-7.04 (m, 1H, minor), 7.01-6.96 (m, 1H, major) 6.92-6.87 (m, 1H, minor) 6.83-6.79 (m, 1H, minor) 6.76 (ddd, *J* = 8.3, 1.0, 0.5 Hz, 1H, major), 6.71-6.65 (m, 1H, minor), 6.67 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H, major), 5.25 (br, 1H, NH, major + minor), 4.72 (s, 1H, major), 3.48 (s, 1H, minor), 1.48 (s, 3H, major), 1.06 (s, 3H, minor). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 193.8 (CO, minor), 193.2 (CO, major), 149.5 (Cq, minor), 149.2 (Cq, major), 142.2 (Cq, major), 141.7 (Cq, minor), 136.7 (CH, minor), 136.6 (CH, major), 135.9 (CH, major), 135.7 (Cq, minor), 135.5 (CH, minor), 135.2 (Cq, major), 130.0 (2CH, major), 129.7 (2CH, minor), 129.12 (CH, major), 129.10 (CH, major), 128.7 (CH, minor), 128.52 (CH, minor), 128.48 (2CH, major), 128.3 (2CH, minor), 128.2 (CH, minor), 128.10 (CH, major), 128.07 (CH, minor), 127.62 (CH, major), 127.58 (CH, major), 127.3 (CH, minor), 121.53 (Cq, minor), 121.48 (Cq, major), 119.10 (Cq, minor), 119.05 (CH, minor), 118.5 (Cq, major), 118.4 (CH, major), 115.7 (CH, minor), 115.1 (CH, major), 63.4 (CH, minor), 62.5 (Cq, major), 59.1 (CH, major), 56.0 (Cq, minor), 25.2 (CH_3, minor), 24.4 (CH_3, major). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{22}H_{18}BrKNO$: $[M+K]^+$ 430.0209, Found: 430.0207.

(2*R*, 3*S* / 2*S*, 3*R*)-2,3-diphenyl-2-propyl-2,3-dihydroquinolin-4(1*H*)-one (10av)



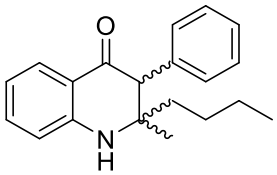
Yellow solid. (33% yield, 46 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.72 (ddt, *J* = 7.9, 1.6, 0.6 Hz, 1H), 7.40 (ddd, *J* = 8.5, 6.9, 1.6 Hz, 1H), 7.36-7.33 (m, 2H), 7.28-7.17 (m, 8H), 6.84 (ddd, *J* = 8.3, 1.1, 0.5 Hz, 1H), 6.73 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 4.89 (br, 1H, NH), 4.18 (d, *J* = 1.0 Hz, 1H), 1.74 (ddd, *J* = 13.7, 12.0, 4.4 Hz, 1H), 1.61 (ddd, *J* = 13.7, 12.0, 5.0 Hz, 1H), 1.09-0.86 (m, 2H), 0.70 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 192.8 (CO), 149.6 (Cq), 142.8 (Cq), 135.8 (CH), 134.9 (Cq), 130.0 (2CH), 128.5 (2CH), 128.4 (2CH), 128.2 (CH), 127.5 (CH), 127.1 (CH), 126.7 (2CH), 119.1 (Cq), 118.1 (CH), 115.3 (CH), 64.5 (Cq), 62.9 (CH), 39.6 (CH_2), 16.4 (CH_2), 14.1 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{24}H_{23}KNO$: $[M+K]^+$ 380.1417, Found: 380.1418.

(2*S*, 3*S* / 2*R*, 3*R*)-2,3-Diphenyl-2-propyl-2,3-dihydroquinolin-4(1*H*)-one (10av)



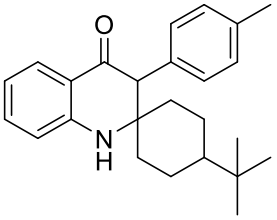
Yellow solid. (31% yield, 41 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.90 (ddd, *J* = 7.8, 1.2, 1.0 Hz, 1H), 7.44 (ddd, *J* = 8.2, 7.1, 1.6 Hz, 1H), 7.39-7.29 (m, 1H), 7.17-7.10 (m, 4H), 7.00-6.91 (m, 3H), 6.86-6.84 (m, 2H), 6.79-6.77 (m, 2H), 3.69 (s, 1H), 2.38 (ddd, *J* = 14.2, 11.7, 5.0 Hz, 1H), 2.05 (ddd, *J* = 14.2, 11.8, 4.0 Hz, 1H), 1.19-0.99 (m, 2H), 0.80 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 193.7 (CO), 149.2 (Cq), 140.7 (Cq), 135.8 (CH), 135.4 (Cq), 129.2 (2CH), 128.2 (2CH), 128.1 (CH), 127.8 (2CH), 126.9 (CH), 126.8 (CH), 125.5 (2CH), 118.4 (CH), 118.3 (Cq), 116.2 (CH), 65.1 (Cq), 64.7 (CH), 38.5 (CH_2), 17.2 (CH_2), 14.1 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{24}H_{23}NNaO$: $[M+Na]^+$ 364.1677, Found: 364.1675.

(2R, 3S / 2S, 3R) (Minor Isomer) + (2S, 3S / 2R, 3R) (Major Isomer) 2-butyl-2-methyl-3-phenyl-2,3-dihydroquinolin-4(1*H*)-one (10aw)



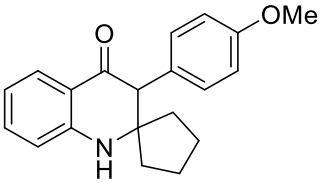
Yellow solid. (79% yield, 52 mg). **Ratio Major/Minor:** 1.00/0.50. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.83 (ddd, *J* = 7.9, 1.6, 0.5 Hz, 1H, major), 7.82 (ddd, *J* = 7.9, 1.6, 0.4 Hz, 1H, minor), 7.36-7.32 (m, 1H, major + minor), 7.26-7.17 (m, 5H, major + minor), 6.75-6.71 (m, 1H, major + minor), 6.67 (ddd, *J* = 8.3, 1.0, 0.5 Hz, 1H, minor), 6.66 (ddd, *J* = 8.3, 1.0, 0.5 Hz, 1H, major), 4.31 (br, 1H, NH, minor), 4.27 (br, 1H, NH, major), 3.58 (s, 1H, minor), 3.52 (s, 1H, major), 1.85-1.77 (m, 1H, major + minor),1.54-1.47 (m, 1H, major + minor), 1.44-1.36 (m, 1H, major + minor), 1.32 (s, CH_3, minor), 1.30-1.22 (m, 2H, major + minor), 1.21-1.12 (m, 1H, major + minor), 1.01 (s, CH_3, major), 0.85 (t, *J* = 7.1 Hz, 3H, major), 0.79 (t, *J* = 7.1 Hz, 3H, minor). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 194.1 (CO, major), 193.8 (CO, minor), 149.2 (Cq, major), 149.1 (Cq, minor), 135.9 (Cq, major), 135.6 (CH, major), 135.5 (CH, minor), 135.4 (Cq, minor), 129.7 (2CH, minor), 129.6 (2CH, major), 128.41 (2CH, major), 128.35 (2CH, minor), 128.1 (CH, minor), 128.0 (CH, major), 127.32 (CH, minor), 127.29 (CH, major), 117.714 (CH, minor), 117.705 (Cq, major), 117.68 (Cq, minor), 117.66 (CH, major), 115.7 (CH, minor), 115.6 (CH, major), 62.7 (CH, minor), 62.1 (CH, major), 58.0 (Cq, minor), 57.8 (Cq, major), 38.7 (CH_2, major), 36.7 (CH_2, minor), 26.0 (CH_2, major), 25.3 (CH_2, minor), 24.7 (CH_3, minor), 22.92 (CH_2, minor), 22.91 (CH_2, major), 22.86 (CH_3, major), 14.0 (CH_3, major), 13.9 (CH_3, minor). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{20}H_{23}KNO$: $[M+K]^+$ 332.1417 Found: 332.1419.

4-(*tert*-Butyl)-3'-(*p*-tolyl)-1'*H*-spiro[cyclohexane-1,2'-quinolin]-4'(3'*H*)-one (10ba)



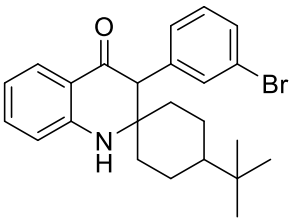
White solid. (80% yield, 99 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.83 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.35 (ddd, *J* = 8.4, 6.9, 1.6 Hz, 1H), 7.02 (br, 4H), 6.76-6.72 (m, 2H), 4.59 (br, 1H, NH), 3.37 (s, 1H), 2.28 (s, 3H), 2.24 (dq, *J* = 13.2, 3.1 Hz, 1H), 1.69-1.59 (m, 2H), 1.53 (dq, *J* = 13.7, 3.2 Hz, 1H), 1.34-0.94 (m, 5H), 0.85 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 194.1 (CO), 148.6 (Cq), 136.9 (Cq), 135.4 (CH), 132.2 (Cq), 129.5 (2CH), 129.0 (2CH), 128.1 (CH), 118.2 (Cq), 117.7 (CH), 115.8 (CH), 63.9 (CH), 56.0 (Cq), 47.1 (CH), 34.6 (CH_2), 32.8 (CH_2), 32.3 (Cq), 27.4 ($3CH_3$), 22.5 (CH_2), 21.9 (CH_2), 21.0 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{25}H_{31}KNO$: $[M+K]^+$ 400.2043, Found: 400.2044.

3'(4-methoxyphenyl)-1'*H*-spiro[cyclopentane-1,2'-quinolin]-4'(3'*H*)-one (10cd)



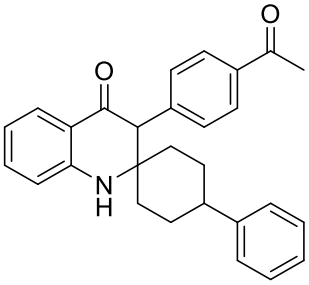
Yellow solid. (58% yield, 41 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.83 (ddd, *J* = 7.9, 1.6, 0.5 Hz, 1H), 7.34 (ddd, *J* = 8.5, 6.9, 1.6 Hz, 1H), 7.20-7.16 (m, 2H), 6.80-6.76 (m, 2H), 6.74 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 6.67 (ddd, *J* = 8.3, 1.1, 0.5 Hz, 1H), 4.34 (br, 1H, NH), 3.75 (s, 3H), 3.46 (s, 1H), 1.87-1.69 (m, 8H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 194.1 (CO), 158.8 (Cq), 149.8 (Cq), 135.4 (CH), 130.1 (2CH), 128.7 (Cq), 128.4 (CH), 118.1 (Cq), 117.9 (CH), 115.8 (CH), 113.9 (2CH), 67.2 (Cq), 60.7 (CH), 55.2 (OCH_3), 38.6 (CH_2), 35.7 (CH_2), 23.4 (CH_2), 22.8 (CH_2). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{20}H_{21}KNO_2$: $[M+K]^+$ 346.1209, Found: 346.1203.

3'-(3-bromophenyl)-4-*tert*-butyl-1'*H*-spiro[cyclohexane-1,2'-quinolin]-4'(3'*H*)-one (10da)



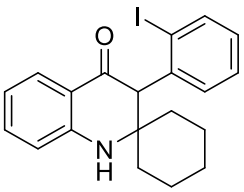
Pale yellow solid. (74% yield, 53 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.84 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.40-7.34 (m, 3H), 7.14-7.09 (m, 2H), 6.79-6.75 (m, 2H), 4.60 (br, 1H, NH), 3.36 (s, 1H), 2.25 (dq, *J* = 13.2, 3.0 Hz, 1H), 1.71-1.50 (m, 4H,) 1.33-0.98 (m, 4H), 0.85 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 193.2 (CO), 148.5 (Cq), 137.5 (Cq), 135.8 (CH) 132.7 (CH), 130.4 (CH), 129.8 (CH), 128.1 (CH+CH), 122.3 (Cq), 118.0 (CH), 117.8 (Cq), 115.9 (CH), 63.8 (CH), 56.1 (Cq), 47.0 (CH), 34.5 (CH_2), 32.7 (CH_2), 32.3 (Cq), 27.4 ($3CH_3$), 22.4 (CH_2), 21.8 (CH_2). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{24}H_{28}BrKNO$: $[M+K]^+$ 464.0991, Found: 464.0991.

3'-(4-acetylphenyl)-4-phenyl-1'*H*-spiro[cyclohexane-1,2'-quinolin]-4'(3'*H*)-one (10eb)



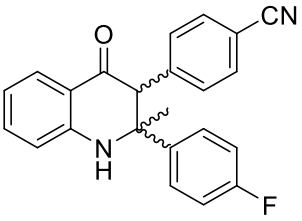
Yellow solid. (62% yield, 112 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.87-7.84 (m, 3H), 7.41 (ddd, *J* = 8.5, 6.9, 1.6 Hz, 1H), 7.33-7.27 (m, 4H), 7.22-7.17 (m, 3H), 6.83-6.80 (m, 1H), 6.79 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 3.55 (s, 1H), 2.55 (s, 3H), 2.56-2.48 (m, 1H), 2.39 (dd, *J* = 13.4, 2.5 Hz, 1H), 1.87-1.80 (m, 2H), 1.70-1.42 (m, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 197.7 (CO), 192.9 (CO), 148.4 (Cq), 145.7 (Cq), 140.7 (Cq), 136.2 (Cq), 135.9 (CH), 130.0 (2CH), 128.5 (2CH), 128.4 (2CH), 128.2 (CH), 126.6 (2CH), 126.4 (CH), 118.3 (CH), 118.0 (Cq), 116.0 (CH), 64.2 (CH), 56.1 (Cq), 42.9 (CH), 34.4 (CH_2), 32.8 (CH_2), 28.9 (CH_2), 28.7 (CH_2), 26.5 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{28}H_{27}KNO_2$: $[M+K]^+$ 448.1679, Found: 448.1677.

3'-(2-iodophenyl)-1'*H*-spiro[cyclohexane-1,2'-quinolin]-4'(3'*H*)-one (10fk)



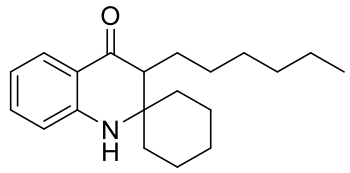
Pale yellow solid. (70% yield, 59 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.89 (ddd, *J* = 7.9, 1.3, 0.5 Hz, 1H), 7.83 (ddd, *J* = 7.8, 1.6, 0.7 Hz, 1H), 7.36 (ddd, *J* = 8.5, 6.9, 1.6 Hz, 1H), 7.22-7.16 (m, 2H), 6.90 (ddd, *J* = 8.0, 6.7, 2.3 Hz, 1H), 6.77 (m, 2H), 4.63 (br, 1H, NH), 4.30 (s, 1H), 2.18-2.14 (m, 1H), 1.63-1.25 (m, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 193.1 (CO), 148.5 (Cq), 140.0 (CH), 138.7 (Cq), 135.6 (CH), 129.4 (CH), 128.8 (CH), 128.3 (CH), 128.2 (CH), 118.0 (CH), 117.7 (Cq), 115.9 (CH), 104.5 (Cq), 64.8 (CH), 57.5 (Cq), 34.6 (CH_2), 31.8 (CH_2), 25.1 (CH_2), 21.5 (CH_2), 21.1 (CH_2). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{20}H_{20}IKNO$: $[M+K]^+$ 456.0227, Found: 456.0232.

(2R, 3S / 2S, 3R) (Major Isomer) + (2S, 3S / 2R, 3R) (Minor Isomer) 4-(2-(4-fluorophenyl)-2-methyl-4-oxo-1,2,3,4-tetrahydroquinolin-3-yl)benzonitrile (10gs)



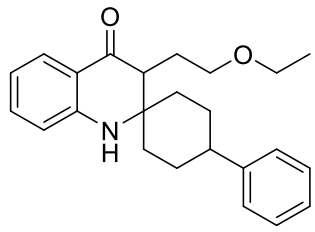
Yellow solid. (71% yield, 87 mg). **Ratio Major/Minor:** 1.00/0.40. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.91 (ddd, *J* = 8.0, 1.6, 0.5 Hz, 1H, minor), 7.78 (ddd, *J* = 7.9, 1.6, 0.5 Hz, 1H, major), 7.53-7.51 (m, 2H, major), 7.48 (ddd, *J* = 8.5, 6.9, 1.6 Hz, 1H, minor), 7.44 (ddd, *J* = 8.5, 6.9, 1.6 Hz, 1H, major), 7.37-7.29 (m, 1H major + 2H minor), 7.32-7.29 (m, 2H, minor), 7.21-7.19 (m, 2H, major), 7.17-7.14 (m, 2H, minor), 6.98-6.94 (m, 2H, major), 6.91-6.78 (m, 3H major + 4H minor), 4.73 (br, 1H, NH, major), 4.52 (br, 1H, NH, minor), 4.18 (s, 1H, major), 3.72 (s, 1H, minor), 1.85 (s, 3H, minor), 1.44 (s, 3H, major). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 191.8 (CO, minor), 191.1 (CO, major), 162.04 (d, *J* = 247.6 Hz, CF, major), 161.95 (d, *J* = 248.0 Hz, CF, minor), 149.3 (Cq, minor), 149.2 (Cq, major), 141.0 (Cq, minor), 140.2 (Cq, major), 140.1 (d, *J* = 3.2 Hz, Cq, major), 138.1 (d, *J* = 3.3 Hz, Cq, minor), 136.4 (CH, minor), 136.3 (CH, major), 131.9 (2CH, major), 131.7 (2CH, minor), 131.1 (2CH, major), 130.1 (2CH, minor), 128.2 (CH, major), 128.1 (CH, minor), 127.8 (d, *J* = 8.1 Hz, 2CH, major), 127.0 (d, *J* = 8.0 Hz, 2CH, minor), 119.2 (CH, minor), 118.7 (CH, major), 118.63 (Cq, major), 118.60 (Cq, minor), 118.3 (Cq, major), 117.8 (Cq, minor), 116.6 (CH, minor), 115.6 (CH, major), 115.5 (d, *J* = 21.4 Hz, 2CH, major), 115.2 (d, *J* = 21.3 Hz, 2CH, minor), 111.5 (Cq, major), 111.1 (Cq, minor), 64.8 (d, *J* = 0.9 Hz, CH, minor), 63.8 (d, *J* = 0.5 Hz, CH, major), 62.2 (Cq, major), 62.0 (Cq, minor), 26.6 (CH_3, minor), 24.4 (CH_3, major). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -114.2 (minor), -114.5 (major). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{23}H_{17}FKN_2O$: $[M+K]^+$ 395.0962, Found: 395.0957.

3'-hexyl-1'*H*-spiro[cyclohexane-1,2'-quinolin]-4'(3'*H*)-one (10hk)



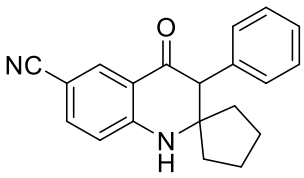
Brown solid. (51% yield, 38 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.75 (ddd, *J* = 7.9, 1.6, 0.4 Hz, 1H), 7.27 (ddd, *J* = 8.4, 7.0, 1.6 Hz, 1H), 6.67 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H), 6.61 (ddd, *J* = 8.3, 1.0, 0.4 Hz, 1H), 4.32 (br, 1H, NH), 2.29 (dd, *J* = 10.4, 4.4 Hz, 1H), 1.75-1.21 (m, 20H), 0.84 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 197.6 (CO), 148.2 (Cq), 134.9 (CH), 127.6 (CH), 117.5 (Cq), 117.1 (CH), 115.2 (CH), 56.3 (Cq), 54.8 (CH), 33.4 (CH_2), 32.9 (CH_2), 31.7 (CH_2), 29.5 (CH_2), 27.4 (CH_2), 25.5 (CH_2), 24.7 (CH_2), 22.6 (CH_2), 21.6 (CH_2), 21.4 (CH_2), 14.1 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{20}H_{29}KNO$: $[M+K]^+$ 338.1886, Found: 338.1889.

3'-(2-ethoxyethyl)-4-phenyl-1'*H*-spiro[cyclohexane-1,2'-quinolin]-4'(3'*H*)-one (10ib)



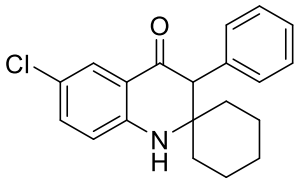
Yellow solid. (60% yield, 105 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.78 (ddd, *J* = 7.8, 1.6, 0.6 Hz, 1H), 7.31-7.26 (m, 3H), 7.22-7.17 (m, 3H), 6.71-6.66 (m, 2H), 4.74 (br, 1H, NH), 3.44 (q, *J* = 7.0 Hz, 2H), 3.44-3.38 (m, 2H), 2.52 (tt, *J* = 12.0, 3.5 Hz, 1H), 2.35 (dd, *J* = 10.4, 3.7 Hz, 1H), 2.16-2.09 (m, 2H), 2.01-1.75 (m, 4H), 1.68-1.55 (m, 2H), 1.53-1.44 (m, 2H), 1.16 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 196.7 (CO), 147.9 (Cq), 146.0 (Cq), 135.0 (CH), 128.4 (2CH), 127.5 (CH), 126.5 (2CH), 126.2 (CH), 117.5 (Cq), 117.2 (CH), 115.4 (CH), 68.5 (CH_2), 66.1 (CH_2), 55.4 (Cq), 53.9 (CH), 43.1 (CH), 32.8 (CH_2), 31.7 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 25.1 (CH_2), 15.1 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{24}H_{29}KNO_2$: $[M+K]^+$ 402.1835, Found: 402.1832.

4'-oxo-3'-phenyl-3',4'-dihydro-1'*H*-spiro[cyclopentane-1,2'-quinolin]-6'carbonitrile (10jd)



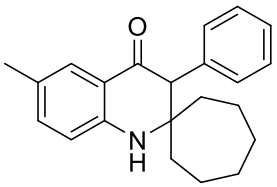
Yellow solid. (57% yield, 85 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 2.0 Hz, 1H), 7.50 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.27-7.15 (m, 3H), 7.20-7.18 (m, 2H), 6.75 (dd, *J* = 8.6, 0.4 Hz, 1H), 5.10 (br, 1H, NH), 3.56 (s, 1H), 1.88-1.73 (m, 8H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 191.9 (CO), 151.8 (Cq), 137.3 (CH), 135.4 (Cq), 133.8 (CH), 128.8 (2CH), 128.7 (2CH), 127.8 (CH), 119.1 (Cq), 117.4 (Cq), 116.4 (CH), 100.3 (Cq), 67.1 (Cq), 60.7 (CH), 38.9 (CH_2), 35.4 (CH_2), 23.3 (CH_2), 22.7 (CH_2). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{20}H_{18}KN_2O$: $[M+K]^+$ 341.1056, Found: 341.1056.

6'-chloro-3'-phenyl-1'*H*-spiro[cyclohexane-1,2'-quinolin]-4'(3'*H*)-one (10kk)



Yellow solid. (79% yield, 105 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.28 (d, *J* = 2.6 Hz, 1H), 7.30 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.26-7.23 (m, 3H), 7.20-7.17 (m, 2H), 6.70 (dt, *J* = 8.7, 0.4 Hz, 1H), 4.52 (br, 1H, NH), 3.54 (s, 1H), 1.93 (dd, *J* = 12.6, 4.5 Hz, 1H), 1.62-1.33 (m, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 192.8 (CO), 147.2 (Cq), 135.5 (CH), 134.8 (Cq), 129.4 (2CH), 128.5 (2CH), 127.5 (CH), 127.3 (CH), 123.1 (Cq), 118.5 (Cq), 117.3 (CH), 61.8 (CH), 56.7 (Cq), 34.5 (CH_2), 33.2 (CH_2), 25.1 (CH_2), 21.6 (CH_2), 21.2 (CH_2). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{20}H_{20}ClKNO$: $[M+K]^+$ 364.0870, Found: 364.0868.

6'-methyl-3'-phenyl-1'*H*-spiro[cycloheptane-1,2'-quinolin]-4'(3'*H*)-one (10le)

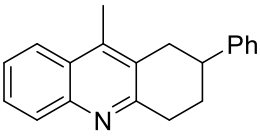


Yellow solid. (62% yield, 109 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.62-7.61 (m, 1H), 7.24-7.17 (m, 6H), 6.62 (dd, *J* = 8.3, 0.3 Hz, 1H), 4.28 (br, 1H, NH), 3.53 (s, 1H), 2.24 (s, 3H), 2.03 (ddd, *J* = 14.7, 7.9, 2.1 Hz, 1H), 1.84 (ddd, *J* = 14.7, 8.9, 2.6 Hz, 1H), 1.63-1.32 (m, 10H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 194.1 (CO), 147.1 (Cq), 136.8 (CH), 136.0 (Cq), 129.5 (2CH), 128.4 (2CH), 127.5 (CH), 127.2 (CH), 126.9 (Cq), 117.8 (Cq), 115.8 (CH), 62.9 (CH), 60.7 (Cq), 37.7 (CH_2), 37.1 (CH_2), 29.8 (CH_2), 29.6 (CH_2), 22.1 (CH_2), 22.0 (CH_2), 20.3 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{22}H_{25}KNO$: $[M+K]^+$ 358.1573, Found: 358.1568.

11.2.3 Preparation and characterisation of quinolines **11mb-11qe**

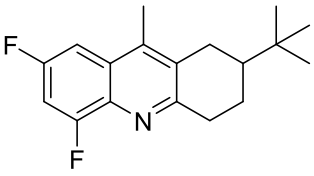
General procedure. To a solution of 2-ethynylaniline **1m** or 2-(trimethylsilyl)ethynylaniline **1q** (0.8 mmol, 1 equiv.) in EtOH (2 mL), ketone **9** (0.8 mmol, 1 equiv.) and *p*-TsOH·H_2O (0.8 mmol, 1 equiv.) were added. The mixture was heated to 80°C and stirred for 3-24 hours. After the completion of the reaction, as monitored by TLC, the mixture was diluted with a saturated solution of $NaHCO_3$ and extracted with AcOEt (20 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4. After removal of the solvent at reduced pressure, the crude was further purified by column chromatography on silica gel with mixtures of *n*-hexane–EtOAc.

9-methyl-2-phenyl-1,2,3,4-tetrahydroacridine (11mb)



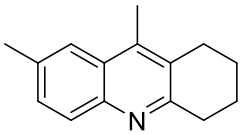
White solid. (80% yield, 174 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 8.5 Hz, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.57 (t, *J* = 7.3 Hz, 1H), 7.42 (t, *J* = 7.4 Hz, 1H), 7.36-7.22 (m, 5H), 3.32-3.15 (m, 3H), 3.01 (tdd, *J* = 11.5, 5.2, 2.6 Hz, 1H), 2.83-2.76 (m, 1H), 2.43 (s, 3H), 2.25-2.19 (m, 1H), 2.03 (qd, *J* = 12.1, 5.5 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 157.6 (Cq), 146.04 (Cq), 145.97 (Cq), 141.3 (Cq), 128.9 (CH), 128.6 (2CH), 128.2 (CH), 128.0 (Cq), 126.8 (2CH), 126.7 (Cq), 126.5 (CH), 125.3 (CH), 123.3 (CH), 40.8 (CH), 35.7 (CH_2), 34.4 (CH_2), 29.5 (CH_2), 13.5 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{20}H_{19}KN$: $[M+K]^+$ 312.1155, Found: 312.1160.

2-(*tert*-butyl)-5,7-difluoro-9-methyl-1,2,3,4-tetrahydroacridine (11na)



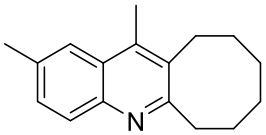
White solid. (41% yield, 33 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.30 (ddd, *J* = 10.4, 2.6, 1.6 Hz, 1H), 7.05 (ddd, *J* = 10.3, 8.6, 2.7 Hz, 1H), 3.23 (ddd, *J* = 17.6, 4.6, 2.6 Hz, 1H), 3.03-2.92 (m, 2H), 2.46 (dd, *J* = 17.0, 11.7 Hz, 1H), 2.44 (s, 3H), 2.11-2.05 (m, 1H), 1.50 (tdd, *J* = 12.0, 5.1, 2.3 Hz, 1H), 1.40 (td, *J* = 12.4, 4.6 Hz, 1H), 0.95 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 158.8 (dd, *J* = 246.6, 12.1 Hz, CF), 158.5 (dd, *J* = 2.6, 1.7 Hz, CF), 158.2 (dd, *J* = 258.4, 13.5 Hz, Cq), 141.2 (dd, *J* = 5.8, 2.5 Hz, Cq), 133,4 (d, *J* = 10.9 Hz, Cq), 131.2 (Cq), 128.4 (dd, *J* = 10.3, 3.3 Hz, Cq), 103.7 (dd, *J* = 29.6, 23.0 Hz, CH), 102.8 (dd, *J* = 22.2, 4.8 Hz, CH), 44.6 (CH), 35.1 (CH_2), 32.7 (Cq), 28.9 (CH_2), 27.3 ($3CH_3$), 23.9 (CH_2), 14.1 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -102.5 (d, *J* = 7.9 Hz), -121.2 (d, *J* = 7.9 Hz). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{18}H_{21}F_2KN$: $[M+K]^+$ 328.1279, Found: 328.1273.

2-(*tert*-butyl)-5,7-difluoro-9-methyl-1,2,3,4-tetrahydroacridine (11ok)



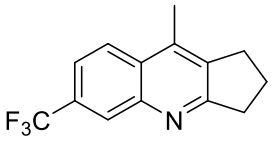
Pale brown solid. (59% yield, 47 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.85 (dt, *J* = 8.6, 0.3 Hz, 1H), 7.71-7.70 (m, 1H), 7.42 (ddd, *J* = 8.6, 1.9, 0.4 Hz, 1H), 3.10-3.07 (m, 2H), 2.88-2.86 (m, 2H), 2.52 (m, 3H), 2.51 (s, 3H), 1.93-1.90 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 157.5 (Cq), 144.5 (Cq), 140.5 (Cq), 134.8 (Cq), 130.3 (CH), 128.7 (CH), 128.6 (Cq), 126.9 (Cq), 122.3 (CH), 34.4 (CH_2), 27.1 (CH_2), 23.3 (CH_2), 22.8 (CH_2), 21.9 (CH_3), 13.4 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{15}H_{18}N$: $[M+H]^+$ 212.1439, Found: 212.1437.

2,12-dimethyl-6,7,8,9,10,11-hexahydrocycoocta[*b*]quinoline (11of)



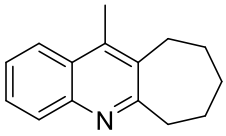
White solid. (49% yield, 46 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.90 (dt, *J* = 8.5, 0.5 Hz, 1H), 7.71-7.70 (m, 1H), 7.43 (ddd, *J* = 8.5, 1.9, 0.5 Hz, 1H), 3.18-3.15 (m, 2H), 3.04-3.01 (m, 2H), 2.61 (m, 3H), 2.53 (s, 3H), 1.90-1.83 (m, 2H), 1.76-1.70 (m, 2H), 1.51-1.46 (m, 2H), 1.32-1.26 (m, 2H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ 162.1 (Cq), 144.8 (Cq), 139.4 (Cq), 134.9 (Cq), 131.8 (Cq), 130.0 (CH), 129.0 (CH), 127.2 (Cq), 122.5 (CH), 36.9 (CH_2), 31.3 (CH_2), 29.9 (CH_2), 27.2 (CH_2), 26.7 (CH_2), 25.8 (CH_2), 21.9 (CH_3), 14.0 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{17}H_{22}N$: $[M+H]^+$ 240.1752, Found: 240.1756.

9-methyl-6-(trifluoromethyl)-2,3-dihydro-1*H*-cyclopenta[b]quinoline (11pd)



White solid. (68% yield, 80 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.30 (s, 1H), 8.00 (d, *J* = 8.7 Hz, 1H), 7.62 (d, *J* = 8.7 Hz, 1H), 3.18 (t, *J* = 7.7 Hz, 2H), 3.06 (t, *J* = 7.4 Hz, 2H), 2.58 (s, 3H), 2.21 (qt, *J* = 7.6 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 168.6 (Cq), 146.3 (Cq), 138.3 (Cq), 136.3 (Cq), 129.9 (q, *J* = 32.7 Hz, Cq), 128.8 (Cq), 126.7 (q, *J* = 4.2 Hz, CH), 124.5 (CH), 124.2 (q, *J* = 272.2 Hz, CF_3), 121.0 (CH), 35.0 (CH_2), 29.7 (CH_2), 22.8 (CH_2), 14.9 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -62.5. **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{14}H_{13}F_3N$: $[M+H]^+$ 252.1000, Found: 252.0997.

11-methyl-7,8,9,10-tetrahydro-6*H*-cyclohepta[b]quinoline (11qe)

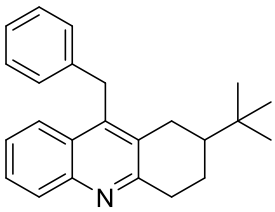


Brown solid. (55% yield, 61 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.96 (ddd, *J* = 8.4, 1.4, 0.6 Hz, 1H) 7.89 (ddd, *J* = 8.4, 1.4, 0.6 Hz, 1H), 7.56 (ddd, *J* = 8.3, 6.9, 1.4 Hz, 1H), 7.42 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 3.19-3.17 (m, 2H), 2.95-2.92 (m, 2H), 2.56 (s, 3H), 1.86-1.79 (m, 2H), 1.78-1.72 (m, 2H), 1.68-1.62 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 164.2 (Cq), 145.5 (Cq), 138.9 (Cq), 134.0 (Cq), 129.1 (CH), 127.7 (CH), 127.0 (Cq), 125.3 (CH), 123.7 (CH), 39.8 (CH_2), 31.6 (CH_2), 29.1 (CH_2), 27.6 (CH_2), 26.9 (CH_2), 14.0 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{15}H_{18}N$: $[M+H]^+$ 212.1439, Found: 212.1441.

11.2.4 Preparation and characterisation of quinolines **11aa-11rd**

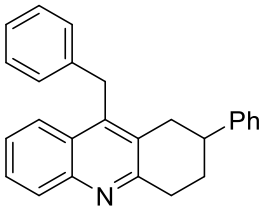
General procedure. To a solution of 2-(phenylethynyl)aniline **1** (0.53 mmol, 1 equiv.) in toluene (2 mL), ketone **9** (0.53 mmol, 1 equiv.) and $FeCl_3$ (0.11 mmol, 20 mol%) were added. The mixture was heated to 110°C and stirred for 24 hours. After the completion of the reaction, the mixture was directly purified by column chromatography on silica gel with *n*-hexane–EtOAc mixtures.

12-benzyl-2-(*tert*-butyl)-1,2,3,4-tetrhydroacridine (11aa)



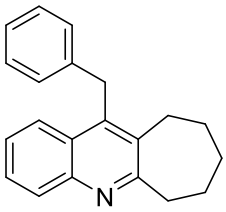
Brown solid. (60% yield, 108 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.01 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.88 (d, *J* = 9.1 Hz, 1H), 7.56 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.36 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.20-7.17 (m, 2H), 7.14-7.10 (m, 1H), 7.03-7.01 (m, 2H), 4.39 (d, *J* = 16.0 Hz, 1H, AB system), 4.36 (d, *J* = 16.0 Hz, 1H, AB system), 3.29-3.24 (m, 1H), 3.11-2.96 (m, 1H), 2.44 (dd, *J* = 16.4, 11.2 Hz, 1H), 2.11-2.07 (m, 2H), 1.52-1.42 (m, 2H), 0.91 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.1 (Cq), 146.4 (Cq), 142.9 (Cq), 138.5 (Cq), 129.6 (Cq), 129.1 (CH), 128.5 (2CH), 128.09 (CH), 128.05 (2CH), 126.7 (Cq), 126.2 (CH), 125.6 (CH), 123.7 (CH), 44.6 (CH), 35.1 (CH_2), 33.0 (CH_2), 32.6 (Cq), 28.2 (CH_2), 27.2 ($3CH_3$), 24.0 (CH_2). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{24}H_{27}KN$: $[M+K]^+$ 368.1781, Found: 368.1782.

9-benzyl-2-phenyl-1,2,3,4-tetrahydroacridine (11ab)



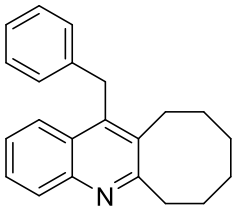
Yellow solid. (57% yield, 126 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.04 (dd, *J* = 8.5, 1.3 Hz, 1H), 7.85 (dd, *J* = 8.5, 1.3 Hz, 1H), 7.57 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.35 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.29-7.25 (m, 2H), 7.21-7.08 (m, 6H), 6.97-6.95 (m, 2H), 4.37 (d, *J* = 16.3 Hz, 1H, AB system), 4.34 (d, *J* = 16.3 Hz, 1H, AB system), 3.37-3.19 (m, 3H), 3.07-2.99 (m, 1H), 2.91-2.84 (m, 1H), 2.26-2.22 (m, 1H), 2.11-2.00 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 158.2 (Cq), 146.5 (Cq), 145.7 (Cq), 142.7 (Cq), 138.1 (Cq), 129.1 (CH), 128.8 (Cq), 128.54 (2CH), 128.51 (2CH), 128.4 (CH), 127.9 (2CH), 126.8 (2CH), 126.7 (Cq), 126.4 (CH), 126.2 (CH), 125.8 (CH), 123.9 (CH), 40.5 (CH), 34.9 (CH_2), 34.4 (CH_2), 32.9 (CH_2), 29.7 (CH_2). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{26}H_{24}N$: $[M+H]^+$ 350.1909, Found: 350.1917.

11-benzyl-7,8,9,10-tetrahydro-6*H*-cyclohepta[b]quinoline (11ae)



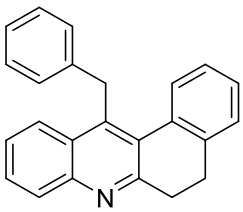
Yellow solid. (58% yield, 29 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 8.1 Hz, 1H), 7.87 (ddd, *J* = 8.5, 1.4, 0.6 Hz, 1H), 7.57 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.40 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.19-7.14 (m, 2H), 7.13-7.10 (m, 1H), 6.98-6.96 (m, 2H), 4.46 (s, 2H), 3.30-3.27 (m, 2H), 2.93-2.90 (m, 2H), 1.78-1.76 (m, 4H), 1.53-1.48 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 164.3 (Cq), 144.5 (Cq), 142.8 (Cq), 138.8 (Cq), 135.5 (Cq), 128.9 (CH), 128.7 (2CH), 128.2 (CH), 128.0 (2CH), 127.1 (Cq), 126.6 (CH), 126.4 (CH), 124.3 (CH), 38.9 (CH_2), 33.7 (CH_2), 31.6 (CH_2), 29.5 (CH_2), 27.6 (CH_2), 26.8 (CH_2). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{21}H_{22}N$: $[M+H]^+$ 288.1752, Found: 288.1754.

12-benzyl-6,7,8,9,10,11-hexahydrocycloocta[b]quinoline (11af)



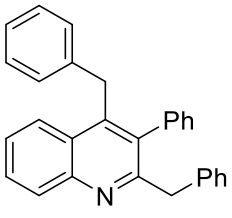
White solid. (54% yield, 86 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.04 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.82 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.58 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.36 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.25-7.13 (m, 3H), 7.02-7.00 (m, 2H), 4.51 (s, 2H), 3.25-3.21 (m, 2H), 3.03-3.00 (m, 2H), 1.95-1.89 (m, 2H), 1.70-1.64 (m, 2H), 1.51-1.45 (m, 2H), 1.37-1.31 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 163.6 (Cq), 146.9 (Cq), 141.6 (Cq), 139.4 (Cq), 132.9 (Cq), 129.3 (CH), 128.5 (2CH), 128.1 (CH), 128.0 (2CH), 127.1 (Cq), 126.2 (CH), 125.7 (CH), 124.2 (CH), 36.8 (CH_2), 33.5 (CH_2), 31.3 (CH_2), 30.5 (CH_2), 27.4 (CH_2), 26.7 (CH_2), 25.9 (CH_2). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{22}H_{24}N$: $[M+H]^+$ 302.1909, Found: 302.1914.

12-benzyl-5,6-dihydrobenzo[a]acridine (11aj)



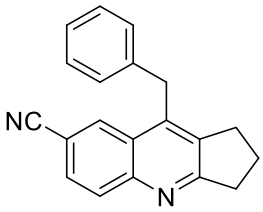
White solid. (54% yield, 39 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.07 (ddd, *J* = 8.4, 1.3, 0.6 Hz, 1H), 7.77 (ddd, *J* = 8.5, 1.4, 0.6 Hz, 1H), 7.60 (ddd, *J* = 8.3, 6.9, 1.4 Hz, 1H), 7.46 (ddd, *J* = 7.8, 1.3, 0.4 Hz, 1H), 7.33 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.33-7.30 (m, 1H), 7.29-7.27 (m, 2H), 7.24-7.20 (m, 1H), 7.23 (td, *J* = 7.4, 1.3 Hz, 1H), 7.15-7.13 (m, 2H), 7.10 (td, *J* = 7.6, 1.4 Hz, 1H), 4.69 (s, 2H), 3.26-3.22 (m, 2H), 2.97-2.94 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 161.0 (Cq), 146.3 (Cq), 140.13 (Cq), 140.10 (Cq), 139.4 (Cq), 133.0 (Cq), 128.9 (CH), 128.8 (2CH), 128.72 (CH), 128.71 (Cq), 128.5 (CH), 128.2 (2CH), 128.1 (Cq), 128.0 (CH), 127.7 (CH), 126.3 (CH), 126.2 (CH), 125.9 (CH), 125.3 (CH), 36.1 (CH_2), 34.8 (CH_2), 29.3 (CH_2). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{24}H_{20}N$: $[M+H]^+$ 322.1596, Found: 322.1597.

2,4-dibenzyl-3-phenylquinoline (11ao)



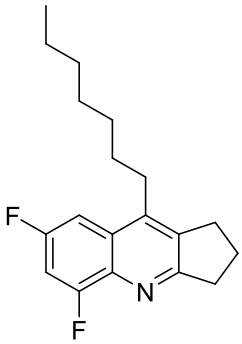
White solid. (67% yield, 94 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.19 (d, *J* = 8.4 Hz, 1H), 7.87 (ddd, *J* = 8.5, 1.4, 0.6 Hz, 1H), 7.68 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.43 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.33-7.29 (m, 1H), 7.26-7.22 (m, 2H), 7.15-7.07 (m, 6H), 6.90-6.84 (m, 6H), 4.18 (s, 2H), 4.15 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.5 (Cq), 147.3 (Cq), 143.6 (Cq), 139.7 (Cq), 139.2 (Cq), 137.9 (Cq), 135.9 (Cq), 129.7 (3CH), 128.93 (CH), 128.90 (2CH), 128.3 (2CH), 128.1 (2CH), 128.0 (2CH), 127.9 (2CH), 127.5 (CH), 126.5 (Cq), 126.3 (CH), 125.9 (CH), 125.8 (CH), 125.1 (CH), 43.9 (CH_2), 35.2 (CH_2). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{29}H_{23}KN$: $[M+K]^+$ 424.1468, Found: 424.1471.

9-benzyl-2,3-dihydro-1*H*-cyclopenta[b]quinolone-7-carbonitrile (11jd)



White solid. (51% yield, 39 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.29 (dd, *J* = 1.8, 0.6 Hz, 1H), 8.09 (dd, *J* = 8.6, 0.6 Hz, 1H), 7.74 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.29-7.19 (m, 3H), 7.07-7.04 (m, 2H), 4.40 (s, 2H), 3.24 (t, *J* = 7.8 Hz, 2H), 3.09 (t, *J* = 7.5 Hz, 2H), 2.25 (qt, *J* = 7.7 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 171.1 (Cq), 149.3 (Cq), 140.4 (Cq), 137.6 (Cq), 137.0 (Cq), 130.8 (CH), 130.3 (CH), 129.1 (CH), 128.9 (2CH), 128.0 (2CH), 126.8 (CH), 126.4 (Cq), 119.2 (Cq), 109.1 (Cq), 35.4 (CH_2), 34.8 (CH_2), 29.8 (CH_2), 22.9 (CH_2). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{20}H_{16}KN_2$: $[M+K]^+$ 323.0951, Found: 323.0948.

5,7-difluoro-9-heptyl-2,3-dihydro-1H-cyclopenta[b]quinoline (11rd)

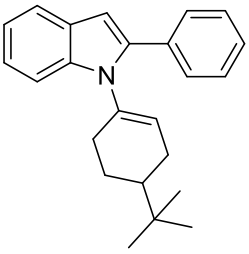


Brown solid. (43% yield, 51 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.27 (dt, *J* = 10.2, 2.0 Hz, 1H), 7.05 (ddd, *J* = 10.5, 8.4, 2.6 Hz, 1H), 3.11 (t, *J* = 7.7 Hz, 2H), 2.98 (t, *J* = 7.4 Hz, 2H), 2.82 (t, *J* = 8.0 Hz, 2H), 2.13 (quint, *J* = 7.6 Hz, 2H), 1.58-1.50 (m, 2H), 1.39-1.17 (m, 8H), 0.81 (t, *J* = 6.8 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.0 (dd, *J* = 2.6, 1.5 Hz, Cq), 157.8 (dd, *J* = 245.5, 12.3 Hz, CF), 157.6 (dd, *J* = 257.1, 13.6 Hz, CF), 141.3 (dd, *J* = 5.6, 2.8 Hz, Cq), 134.8 (t, *J* = 0.7 Hz , Cq), 134.3 (dd, *J* = 11.1, 1.7 Hz, Cq), 127.0 (dd, *J* = 10.2, 3.3 Hz, Cq), 102.4 (dd, *J* = 29.3, 23.2 Hz, CH), 102.0 (dd, *J* = 22.1, 4.7 Hz, CH), 34.0 (CH_2), 30.7 (CH_2), 28.9 (CH_2), 28.7 (CH_2), 28.5 (CH_2), 28.4 (CH_2), 28.1 (CH_2), 22.0 (CH_2), 21.6 (CH_2), 13.1 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -112.4 (d, *J* = 6.6 Hz), -120.2 (d, *J* = 6.6 Hz). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{19}H_{23}F_2NNa$: $[M+Na]^+$, 326.1696 Found: 326.1702.

11.2.5 Preparation and characterisation of 1-*N*-alkenyl indoles **12aa-12sd**

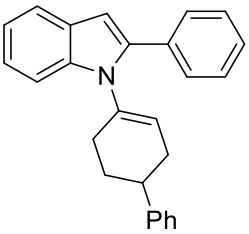
General procedure. To a solution of 2-(phenylethynyl)aniline **1** (0.62 mmol, 1 equiv.) in toluene (2 mL), ketone **9** (0.62 mmol, 1 equiv.) and $ZnBr_2$ (0.12 mmol, 20 mol%) were added. The mixture was heated to 110°C and stirred for 2 hours. After the completion of the reaction, the mixture was directly purified by column chromatography on silica gel with mixtures of *n*-hexane–EtOAc from 95:5 to 90:10 v/v.

1-(4-*tert*-butyl)cyclohex-1-en-1-yl)2-phenyl-1*H*-indole (12aa)



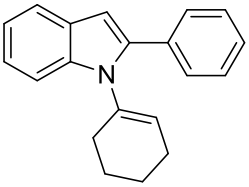
White solid. (62% yield, 126 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.62-7.59 (m, 3H), 7.39-7.35 (m, 3H), 7.31-7.27 (m, 1H), 7.17 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H), 7.11 (ddd, *J* = 8.7, 7.1, 1.1 Hz, 1H), 6.66 (d, *J* = 0.5 Hz, 1H), 6.01 (d, *J* = 5.7 Hz, 1H), 2.34-2.28 (m, 1H), 2.08-1.91 (m, 3H), 1.79-1.75 (m, 1H), 1.40-1.18 (m, 2H), 0.89 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 139.7 (Cq), 138.4 (Cq), 135.7 (Cq), 133.5 (Cq), 128.3 (2CH), 128.1 (Cq), 127.9 (2CH), 127.6 (CH), 127.4 (CH), 121.8 (CH), 120.3 (CH), 120.1 (CH), 110.6 (CH), 102.5 (CH), 43.6 (CH), 32.2 (Cq), 30.4 (CH_2), 27.2 ($3CH_3$), 26.5 (CH_2), 24.3 (CH_2). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{24}H_{27}N$: $[M^*]^+$ 329.2143, Found: 329.2147.

2-phenyl-1-(1,2,3,6-tetrahydro-[1,1'-biphenyl]-1*H*-indole (12ab)



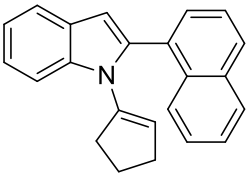
Pale yellow solid. (66% yield, 148 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.66-7.61 (m, 3H), 7.45-7.39 (m, 3H), 7.35-7.29 (m, 3H), 7.25-7.18 (m, 4H), 7.14 (ddd, *J* = 7.9, 7.0, 1.1 Hz, 1H), 6.68 (d, *J* = 0.8 Hz, 1H), 6.11 (dt, *J* = 5.1, 2.6 Hz, 1H), 2.92-2.85 (m, 1H), 2.62-2.55 (m, 1H), 2.48-2.40 (m,1H), 2.20-2.14 (m, 1H), 2.02-1.98 (m, 1H), 1.92-1.78 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 145.8 (Cq), 139.8 (Cq), 138.3 (Cq), 135.8 (Cq), 133.4 (Cq), 128.5 (2CH), 128.4 (2CH), 128.2 (Cq), 127.9 (2CH), 127.5 (CH), 127.0 (CH), 126.8 (2CH), 126.3 (CH), 121.9 (CH), 120.4 (CH), 120.2 (CH), 110.6 (CH), 102.8 (CH), 39.3 (CH), 32.8 (CH_2), 29.9 (CH_2), 29.6 (CH_2). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{26}H_{23}N$: $[M^*]^+$ 349.1830, Found: 349.1831.

1-(cyclohex-1-en-1-yl)-2-phenyl-1*H*-indole (12ak)



White solid. (77% yield, 139 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.64-7.60 (m, 3H), 7.40-7.36 (m, 3H), 7.33-7.29 (m, 1H), 7.18 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H), 7.12 (ddd, *J* = 8.0, 6.9, 1.0 Hz, 1H), 6.67 (d, *J* = 0.8 Hz, 1H), 6.05-6.02 (m, 1H), 2.31-2.27 (m, 2H), 1.97-1.93 (m, 2H), 1.67-1.63 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 139.7 (Cq), 138.3 (Cq), 135.8 (Cq), 133.5 (Cq), 128.3 (2CH), 128.1 (Cq), 127.9 (2CH), 127.7 (CH), 127.4 (CH), 121.8 (CH), 120.3 (CH), 120.1 (CH), 110.6 (CH), 102.5 (CH), 29.2 (CH_2), 24.9 (CH_2), 22.8 (CH_2), 21.8 (CH_2). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{20}H_{19}N$: $[M^*]^+$ 273.1517, Found: 273.1524.

1-(cyclopent-1-en-1-yl)-2-(naphthalen-1-yl)-1H-indole (12sd)



White solid. (60% yield, 65 mg). **^{1}H NMR** (400 MHz, DMSO): δ 8.03-7.99 (m, 2H), 7.83-7.80 (m, 1H), 7.65 (ddd, *J* = 7.8, 1.3, 0.8 Hz, 1H), 7.62-7.57 (m, 2H), 7.55 (dd, *J* = 2.6, 1.5 Hz, 1H), 7.52 (ddd, *J* = 8.0, 2.1, 0.9 Hz, 1H), 7.48 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.24 (ddd, *J* = 8.3, 7.1, 1.3 Hz, 1H), 7.16 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1H), 6.72 (d, *J* = 0.8 Hz, 1H), 5.73 (dt, *J* = 4.0, 2.1 Hz, 1H), 2.24-2.19 (m, 2H), 2.02-1.98 (m, 2H), 1.61 (dt, *J* = 14.7, 7.4 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 138.5 (Cq), 137.6 (Cq), 136.9 (Cq), 133.0 (Cq), 131.7 (Cq), 130.4 (Cq), 128.6 (CH), 128.2 (CH), 128.1 (CH), 127.8 (Cq), 126.4 (CH), 126.1 (CH), 125.5 (CH), 125.1 (CH), 124.9 (CH), 122.0 (CH), 120.24 (CH), 120.21 (CH), 111.1 (CH), 104.8 (CH), 33.2 (CH_2), 29.8 (CH_2), 22.0 (CH_2). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{23}H_{19}N$: $[M^*]^+$ 309.1517, Found: 309.1515.

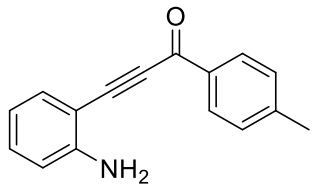
11.3 Brønsted acid-promoted reaction of β-(2-aminophenyl)-α,β-ynones with ketones for the synthesis of polycyclic quinolines

11.3.1 Preparation and characterisation of β-(2-aminophenyl)-α,β-ynones

β-(2-aminophenyl)-α,β-ynones **16a-b** and **16d-i** were prepared according to the procedures already reported in literature. [59,172]

General procedure for the preparation of 3-(2-aminophenyl)-1-(*p*-tolyl)prop-2-yn-1-one (16c). To a solution of 2-ethynylaniline (0.8 g, 6.8 mmol) in anhydrous THF (15 mL), 1-iodo-4-methylbenze (1.56 g, 7.14 mmol), triethylamine (4.77 mL, 34 mmol), $PdCl_2$ (0.024 g, 0.14 mmol) and dppf (0.075 g, 0.14 mmol) were added. The flask was purged with carbon monoxide for few second and connected to a balloon of carbon monoxide. The mixture was stirred at room temperature overnight, then extracted with 0.1 M HCl and ethyl acetate. The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by chromatography on silica gel, using n-hexane/EtOAc 60/40 v/v as eluting mixture, to give **16c**.

3-(2-aminophenyl)-1-(*p*-tolyl)prop-2-yn-1-one (16c)



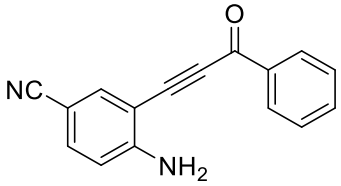
Yellow solid. (65% yield, 1.040 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.03-8.01 (m, 2H), 7.39 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.23-7.21 (m, 2H) 7.18-7.17 (m, 1H), 6.67-6.63 (m, 2H), 4.63 (br, 2H, NH_2), 2.35 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 177.6 (CO), 150.2 (Cq), 145.1(Cq), 134.7 (Cq), 133.8 (CH), 132.5 (CH), 129.6 (2CH), 129.4 (2CH), 118.1 (CH), 114.9 (CH), 104.1 (Cq), 93.4 (Cq), 90.7 (Cq), 21.9 (CH_3). **HRMS** (ESI, positive ion): m/z calculated for $C_{16}H_{13}KNO$: $[M+K]^+$ 274.0634, Found: 274.0631.

General procedure for preparation of β-(2-aminophenyl)-α,β-ynone 16h-j: preparation of 4-amino-3-(3-oxo-3-phenylprop-1-yn-1yl)benzonitrile (16h). To a solution of 4-amino-3-iodobenzonitrile (0.714 g, 2.93 mmol) in THF (7 mL) and *i*-Pr_2NH (2.05 mL, 14.65 mmol), 1-phenylprop-2-yn-1-ol (0.464 g, 3.51 mmol), $PdCl_2(PPh_3)_2$ (0.044 g, 0.044 mmol), and CuI (0.017 g, 0.88 mmol) were added. The mixture was stirred at room temperature under N_2 for 4 h. After completion, AcOEt and water were added, and the organic layer was separated, washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel, using PE/EtOAc, 70:30 v/v as eluting

[172] a) Rode, N.D.; Arcadi, A.; Chiarini, M.; Marinelli, F.; Portalone, G. *Adv.Synth. Catal*. **2017**, 359,3371-3377. b) Arcadi, A.; Aschi, M.; Marinelli, F.; Verdecchia, M. *Tetrahedron* **2008**, 64, 5354-5361. c) Arcadi, A.; Marinelli, F.; Rossi, E. *Tetrahedron* **1999**, 55, 13233-13250.

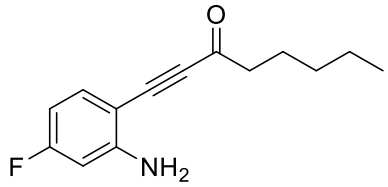
mixture, to give the corresponding propargylic alcohol derivative **4-amino-3-(hydroxyl-3-phenylprop-1-yn-1-yl)benzonitrile** (0.572 g, 79% yield). Then, the propargylic alcohol was dissolved in $CHCl_3$ (8 mL) and activated MnO_2 (5 equiv.) was added. The heterogeneous mixture was refluxed for 1.5 h. The crude mixture was filtered through a short pad of Celite using EtOAc as eluent. The solvent was removed under reduced pressure and the residue was purified by column chromatography over silica gel, with PE/EtOAc 60:40 v/v, to give the 4-amino-3-(3-oxo-3-phenylprop-1-yn-1yl)benzonirtile (**16h**) (84% yield, 0.438 g).

4-amino-3-(3-oxo-3-phenylprop-1-yn-1yl)benzonitrile (16h)



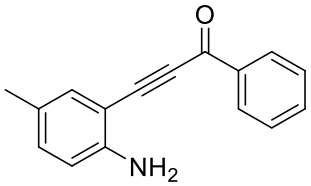
Yellow solid. (84% yield, 438 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.10 (d, *J* = 7.5 Hz, 2H), 7.69 (s, 1H), 7.59 (t, *J* = 7.1 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 1H), 6.70 (d, *J* = 8.5 Hz, 1H), 4.91 (br, 2H, NH_2). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 177.4 (CO), 153.1 (Cq), 138.1 (CH), 136.5 (Cq), 135.4 (CH), 134.5 (CH), 129.5 (2CH), 128.8 (2CH), 118.7 (CN), 114.8 (CH), 104.1 (Cq), 100.5 (Cq), 93.7 (Cq), 87.5 (Cq). **HRMS** (ESI, positive ion): m/z calculated for $C_{16}H_{10}KN_2O$: $[M+K]^+$ 285.0430, Found: 285.0433.

1-(2-amino-4-fluorophenyl)oct-1-yn-3-one (16j)



Yellow sticky solid. (84% yield, 97 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.28-7.24 (m, 1H), 6.36-6.31 (m, 2H), 4.53 (br, 2H, NH_2), 2.58 (t, *J* = 7.5 Hz, 2H), 1.70-1.63 (m, 2H), 1.29-1.25 (m, 4H), 0.84 (t, *J* = 6.9 Hz, 3H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 187.9 (CO), 165.6 (d, *J* = 251.4 Hz, Cq, CF), 152.2 (d, J=12.5 Hz, Cq), 135.9 (d, J=11.1 Hz, CH), 105.8 (d, J=23.2 Hz, CH), 101.2 (d, J=25.6 Hz, CH), 99.89 (Cq), 94.3 (Cq), 87.85 (Cq), 45.34 (CH_2), 31.17 (CH_2), 24.06 (CH_2), 22.41 (CH_2), 13.89 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -104.9. **HRMS** (ESI, positive ion): m/z calculated for $C_{14}H_{16}FKNO$: $[M+K]^+$ 272.0853, Found: 272.0852.

3-(2-amino-5-methylphenyl)-1-phenylprop-2-yn-1-one (16k)

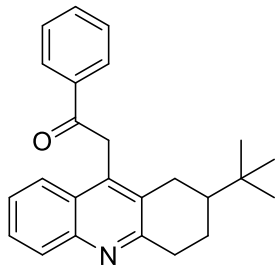


Brown solid. (69% yield, 813 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.13-8.11 (m, 2H), 7.53 (tt, *J* = 7.4, 1.4 Hz, 1H), 7.45-7.41 (m, 2H), 7.22 (dd, *J* = 1.9, 0.6 Hz, 1H), 7.00 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.66 (d, *J* = 8.3 Hz, 1H), 4.66 (br, 2H, NH_2), 2.17 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 177.8 (CO), 147.2 (Cq), 137.0 (Cq), 134.6 (Cq), 134.0 (CH), 133.7 (CH), 133.6 (CH), 129.5 (2CH), 128.6 (2CH), 115.5 (CH), 104.5 (Cq), 93.2 (Cq), 91.3 (Cq), 20.2 (CH_3). **HRMS** (ESI, positive ion): m/z calculated for $C_{16}H_{13}KNO$: $[M+K]^+$ 274.0634, Found: 274.0636.

11.3.2 Preparation and characterisation of polycyclic quinolines **18aa-18kd**

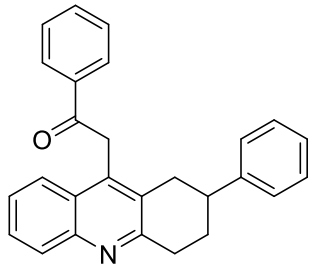
General procedure. A mixture of β-(2-aminophenyl)-α,β-ynones **16** (0.4 mmol, 1.0 equiv.), ketone **79** (0.4 mmol, 1.0 equiv.), and *p*-TsOH·H_2O (0.4 mmol, 1.0 equiv.) in EtOH (2 mL) was stirred at 80 °C for 1–5 h. After completion, the mixture was diluted with a saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2 (25 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4. After the removal of the solvent at reduced pressure, the crude product was purified by column chromatography over silica gel, using *n*-hexane/EtOAc 80:20 v/v as eluting mixture, to give the title compound **18**.

2-(2-(*tert*-butyl)-1,2,3,4-tetrahydracrin-9-yl)-1-phenylethan-1-one (18aa)



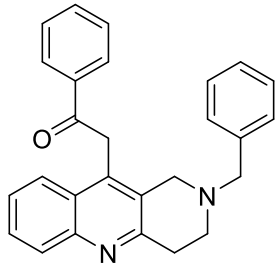
White solid. (97% yield, 1.56 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.13-8.11 (m, 2H), 8.01 (dd, *J* = 8.5, 1.3 Hz, 1H), 7.67-7.53 (m, 5H), 7.39 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 4.75 (d, *J* = 17.9 Hz, AB system, 1H), 4.73 (d, *J* = 17.9 Hz, AB system, 1H), 3.28 (ddd, *J* = 17.4, 4.7, 2.6 Hz, 1H), 3.09 (ddd, *J* = 17.5, 12.2, 5.4 Hz, 1H), 2.88 (ddd, *J* = 16.2, 4.9, 2.2 Hz, 1H), 2.48 (dd, *J* = 16.1, 11.6 Hz, 1H), 2.14-2.11 (m, 1H), 1.60-1.53 (m, 1H), 1.47 (td, *J* = 12.2, 4.9 Hz, 1H), 0.93 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 195.7 (CO), 158.9 (Cq), 146.2 (Cq), 138.7 (Cq), 136.6 (Cq), 133.7 (CH), 130.0 (Cq), 129.2 (CH), 128.9 (2CH), 128.2 (3CH), 126.7 (Cq), 125.7 (CH), 122.9 (CH), 44.6 (CH), 37.5 (CH_2), 35.1 (CH_2), 32.6 (Cq), 28.5 (CH_2), 27.2 ($3CH_3$), 23.9 (CH_2). **HRMS** (ESI, positive ion): m/z calculated for $C_{25}H_{27}KNO$: $[M+K]^+$ 396.1730, Found: 396.1733.

1-phenyl-2-(2-phenyl-1,2,3,4-tetrahydroacridin-9-yl)ethan-1-one (18ab)



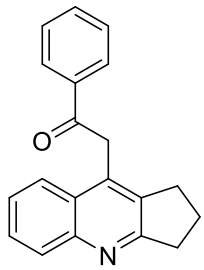
White solid. (87% yield, 145 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.45 (d, *J* = 8.5 Hz, 1H), 8.00-7.98 (m, 2H), 7.58-7.53 (m, 3H), 7.45-7.41 (m, 2H), 7.33 (ddd, *J* = 8.4, 7.0, 1.3 Hz, 1H), 7.25-7.12 (m, 5H), 4.69 (d, *J* = 18.0 Hz, AB system, 1H), 4.65 (d, *J* = 18.0 Hz, AB system, 1H), 3.34 (ddd, *J* = 17.9, 5.4, 3.2 Hz, 1H), 3.23 (ddd, *J* = 17.8, 11.8, 5.7 Hz, 1H), 3.09-2.99 (m, 2H), 2.85-2.72 (m, 1H), 2.23-2.17 (m, 1H), 2.05 (qd, *J* = 12.1, 5.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 195.0 (CO), 157.7 (Cq), 145.6 (Cq), 145.5 (Cq), 139.4 (Cq), 136.3 (Cq), 133.7 (CH), 129.5 (Cq), 128.84 (2CH), 128.76 (CH), 128.66 (CH), 128.60 (2CH), 128.2 (2CH), 126.8 (2CH), 126.6 (Cq), 126.5 (CH), 126.2 (CH), 122.9 (CH), 40.6 (CH_2), 37.7 (CH), 35.4 (CH_2), 34.0 (CH_2), 29.4 (CH_2). **HRMS** (ESI, positive ion): m/z calculated for $C_{27}H_{23}KNO$: $[M+K]^+$ 416.1417, Found: 416.1415.

2-(2-benzyl-1,2,3,4-tetrahydrobenzo[b]naphthyridin-10-yl)-1-phenylethan-1-one (18ac)



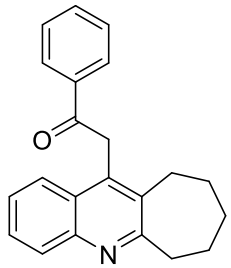
Sticky yellow solid. (55% yield, 103 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 7.6 Hz, 2H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.61-7.44 (m, 4H), 7.35-7.16 (m, 7H), 4.57 (s, 2H), 3.68 (s, 2H), 3.64 (s, 2H), 3.20 (t, *J* = 6.0 Hz, 2H), 2.83 (t, *J* = 6.0 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 195.1 (CO), 156.2 (Cq), 146.5 (Cq), 137.8 (Cq), 137.0 (Cq), 136.4 (Cq), 133.7 (CH), 129.2 (CH), 129.1 (Cq), 129.0 (2CH), 128.9 (2CH), 128.6 (CH), 128.3 (2CH), 128.2 (2CH), 127.2 (CH), 126.5 (Cq), 126.0 (CH), 122.9 (CH), 62.4 (CH_2), 54.0 (CH_2), 49.6 (CH_2), 37.0 (CH_2), 33.6 (CH_2). **HRMS** (ESI, positive ion): m/z calculated for $C_{27}H_{24}KN_2O$: $[M+K]^+$ 431.1526, Found: 431.1525.

2-(2,3-dihydro-1*H*-cyclopenta[b]quinnolin-9-yl)-1-phenylethan-1-one (18ad)



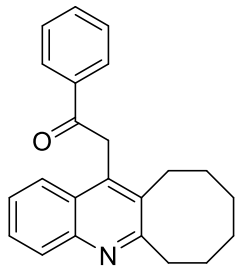
Yellow solid. (88% yield, 115 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.02-7.99 (m, 3H), 7.62 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.57-7.50 (m, 2H), 7.46-7.42 (m, 2H), 7.34 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 4.60 (s, 2H), 3.14 (t, *J* = 7.7 Hz, 2H), 2.91 (t, *J* = 7.4 Hz, 2H), 2.12 (dt, *J* = 15.1, 7.6 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 195.3 (CO), 166.8 (Cq), 147.3 (Cq), 136.5 (Cq), 135.73 (Cq), 135.68 (Cq), 133.62 (CH), 129.1 (CH), 128.8 (2CH), 128.3 (CH), 128.2 (2CH), 126.6 (Cq), 125.8 (CH), 123.1 (CH), 39.1 (CH_2), 34.9 (CH_2), 29.7 (CH_2), 22.9 (CH_2). **HRMS** (ESI, positive ion): m/z calculated for $C_{20}H_{17}KNO$: $[M+K]^+$ 326.0947, Found: 326.0947.

1-phenyl-2-(7,8,9,10-tetrahydro-6*H*-cyclohepta[b]quinolin-11-yl)ethan-1-one (18ae)



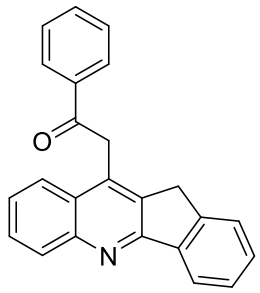
White solid. (75% yield, 112 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 7.3 Hz, 2H), 8.07 (d, *J* = 8.3 Hz, 1H), 7.69-7.53 (m, 5H), 7.42 (ddd, *J* = 8.4, 6.9, 1.2 Hz, 1H), 4.83 (s, 2H), 3.30-3.27 (m, 2H), 2.89-2.86 (m, 2H), 1.87-1.82 (m, 4H), 1.68 (dt, *J* = 9.9, 5.0 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 195.6 (CO), 164.2 (Cq), 145.5 (Cq), 137.0 (Cq), 136.5 (Cq), 135.8 (Cq), 133.7 (CH), 129.2 (CH), 128.9 (2CH), 128.25 (CH), 128.23 (2CH), 126.9 (Cq), 126.2 (CH), 123.3 (CH), 39.7 (CH_2), 38.1 (CH_2), 31.7 (CH_2), 30.1 (CH_2), 27.7 (CH_2), 26.9 (CH_2). **HRMS** (ESI, positive ion): m/z calculated for $C_{22}H_{22}NO$: $[M+H]^+$ 316.1701, Found: 316.1703.

2-(6,7,8,9,10,11-hexahydrocycloocta[b]quinolin-12-yl)-1-phenylethan-1-one (18af)



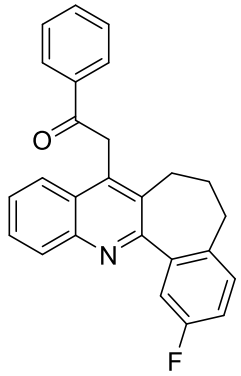
White solid. (67% yield, 88 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.15-8.13 (m, 2H), 8.08 (dd, *J* = 8.8, 1.2 Hz, 1H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.62-7.54 (m, 4H), 7.39 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 4.84 (s, 2H), 3.26-3.23 (m, 2H), 2.99-2.96 (m, 2H), 1.95-1.89 (m, 2H), 1.72-1.66 (m, 2H), 1.53-1.48 (m, 2H), 1.36-1.33 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 195.9 (CO), 163.1 (Cq), 146.3 (Cq), 138.0 (Cq), 136.6 (Cq), 133.7 (CH), 133.3 (Cq), 129.3 (CH), 128.9 (2CH), 128.24 (CH), 128.22 (2CH), 127.1 (Cq), 126.0 (CH), 123.2 (CH), 38.1 (CH_2), 36.8 (CH_2), 31.2 (CH_2), 30.4 (CH_2), 27.7 (CH_2), 26.7 (CH_2), 25.7 (CH_2). **HRMS** (ESI, positive ion): m/z calculated for $C_{23}H_{23}KNO$: $[M+K]^+$ 368.1417, Found: 368.1418.

2-(11*H*-indeno[1,2-b]quinolin-10-yl)-1-phenylethan-1-one (18ag)



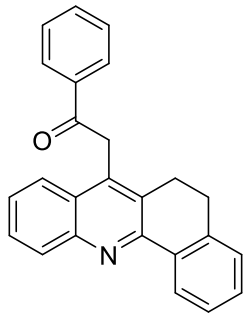
White solid. (80% yield, 97 mg). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 8.21-8.12 (m, 4H), 8.00 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.75-7.70 (m, 2H), 7.67-7.61 (m, 3H), 7.54-7.50 (m, 3H), 5.14 (s, 2H), 4.00 (s, 2H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 196.1 (CO), 160.0 (Cq), 147.7 (Cq), 144.8 (Cq), 140.0 (Cq), 137.1 (Cq), 136.5 (Cq), 134.8 (Cq), 133.6 (CH), 130.0 (CH), 129.2 (CH), 128.8 (2CH), 128.5 (CH), 128.3 (2CH), 127.4 (CH), 126.8 (Cq), 125.7 (CH), 125.6 (CH), 124.3 (CH), 121.3 (CH), 38.9 (CH_2), 33.0 (CH_2). **HRMS** (ESI, positive ion): m/z calculated for $C_{24}H_{18}NO$: $[M+H]^+$ 336.1388, Found: 336.1386.

2-(2-fluoro-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-b]quinolin-8-yl)-1-phenylethan1-one (18ah)



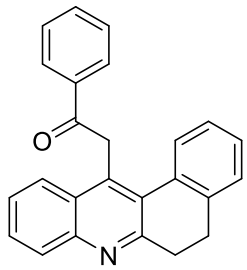
Sticky yellow solid. (80% yield, 122 mg). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 8.23-8.20 (m, 2H), 8.07 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.97 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.74-7.69 (m, 2H), 7.63-7.60 (m, 2H), 7.57-7.52 (m, 2H), 7.34 (dd, *J* = 8.4, 5.8 Hz, 1H), 7.25 (td, *J* = 8.6, 2.8 Hz, 1H), 5.17 (s, 2H), 2.55 (t, *J* = 6.8 Hz, 2H), 2.47 (t, *J* = 6.9 Hz, 2H), 2.04 (quint, *J* = 6.9 Hz, 2H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 196.8 (CO), 161.0 (d, J = 241.8 Hz, CF), 158.2 (d, J = 2.2 Hz, Cq), 146.1 (Cq), 142.3 (d, J = 7.4 Hz, Cq), 138.9 (Cq), 136.2 (Cq), 134.7 (d, J = 3.0 Hz, Cq), 133.6 (CH), 131.7 (Cq), 130.1 (d, J = 7.9 Hz, CH), 129.6 (CH), 128.8 (2CH), 128.5 (CH), 128.3 (2CH), 127.1 (Cq), 126.6 (CH), 124.3 (CH), 115.6 (d, *J* = 20.9 Hz, CH), 115.0 (d, *J* = 22.1 Hz, CH), 37.8 (CH_2), 30.4 (CH_2), 29.4 (CH_2), 26.1 (CH_2). **^{19}F NMR** (376 MHz, DMSO-d_6): δ -116.7. **HRMS** (ESI, positive ion): m/z calculated for $C_{26}H_{21}FNO$: $[M+H]^+$ 382.1607, Found: 382.1610.

2-(5,6-dihydrobenzo[c]acridin-7-yl)-1-phenylethan-1-one (18ai)



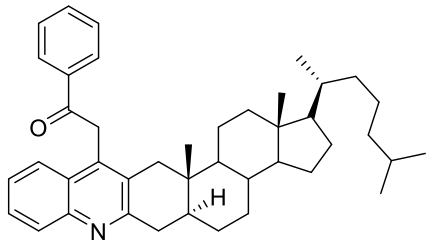
White solid. (79% yield, 69 mg). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 8.48-8.46 (m, 1H), 8.21-8.19 (m, 2H), 8.06 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.95 (dd, *J* = 8.5, 1.2 Hz, 1H), 7.74-7.66 (m, 2H), 7.63-7.60 (m, 2H), 7.50 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.44-7.37 (m, 2H), 7.34-7.31 (m, 1H), 5.13 (s, 2H), 3.00-2.96 (m, 2H), 2.93-2.91 (m, 2H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 196.3 (CO), 151.8 (Cq), 146.3 (Cq), 139.0 (Cq), 138.5 (Cq), 136.3 (Cq), 134.3 (Cq), 133.6 (CH), 129.8 (Cq), 129.6 (CH), 129.5 (CH), 128.8 (CH), 128.5 (CH), 128.3 (CH), 127.8 (CH), 127.4 (Cq), 126.9 (CH), 126.2 (CH), 125.7 (CH), 124.2 (CH), 37.7 (CH_2), 27.2 (CH_2), 25.0 (CH_2). **HRMS** (ESI, positive ion): m/z calculated for $C_{25}H_{20}NO$: $[M+H]^+$ 350.1545, Found: 350.1544.

2-(5,6-dihydrobenzo[a]acridin-12-yl)-1-phenylethan-1-one (18aj)



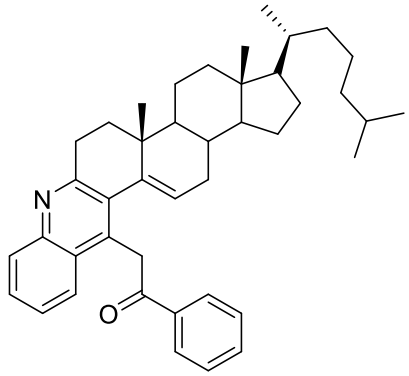
Brown solid. (92% yield, 135 mg). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 8.22-8.19 (m, 2H), 7.98-7.96 (m, 1H), 7.78-7.61 (m, 5H), 7.49 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.45-7.43 (m, 1H), 7.31 (td, *J* = 7.4, 1.4 Hz, 1H), 7.28-7.25 (m, 1H), 7.18 (td, *J* = 7.5, 1.4 Hz, 1H), 5.13 (s, 2H), 3.10-3.07 (m, 2H), 2.92-2.89 (m, 2H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 198.4 (CO), 160.8 (Cq), 146.1 (Cq), 140.7 (Cq), 137.1 (Cq), 136.3 (Cq), 134.5 (CH), 132.9 (Cq), 129.5 (2CH), 129.4 (CH), 129.1 (CH), 128.9 (2CH), 128.8 (CH), 128.7 (Cq), 128.5 (CH), 128.19 (Cq), 128.18 (CH), 127.0 (CH), 126.6 (CH), 125.6 (CH), 41.7 (CH_2), 34.4 (CH_2), 29.0 (CH_2). **HRMS** (ESI, positive ion): m/z calculated for $C_{25}H_{19}KNO$: $[M+K]^+$ 388.1104, Found: 388.1101.

2-((1S,5aS,13aS,15aR)-13a,15a-dimethyl-1-(6-methylhepptan-2-yl)-2,3,3a,3b,4,5,5a,6,13,13a,13b,14,15,15a-tetradecahydro-1*H*-cyclopent[5,6]naptho[1,2-b]acridin-12-yl)-1-phenylethan-1-one (18al)



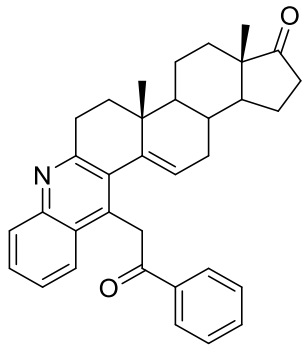
Sticky yellow solid. (49% yield, 69 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.09-8.05 (m, 2H), 7.81-7.77 (m, 2H), 7.66 (tt, *J* = 7.5, 1.4 Hz, 1H), 7.61-7.52 (m, 4H), 4.91 (d, *J* = 17.5 Hz, AB system, 1H), 4.86 (d, *J* = 17.5 Hz, AB system, 1H), 3.71 (d, *J* = 18.0 Hz, 1H), 3.11 (dd, *J* = 19.7, 13.9 Hz, 1H), 2.86 (d, *J* = 16.4 Hz, 1H), 2.37 (d, *J* = 16.4 Hz, 1H), 1.90-1.87 (m, 1H), 1.75-1.66 (m, 4H), 1.57-1.50 (m, 2H), 1.47-1.41 (m, 1H), 1.36-1.23 (m, 8H), 1.20-1.16 (m, 2H), 1.05-0.87 (m, 7H), 0.80 (d, *J* = 3.8 Hz, 3H), 0.79 (s, 3H), 0.78 (d, *J* = 2.1 Hz, 3H), 0.74 (s, 3H), 0.58 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 193.4 (CO), 155.0 (Cq), 135.7 (Cq), 134.5 (CH), 131.2 (Cq), 130.6 (Cq), 129.2 (2CH), 128.9 (CH), 128.32 (2CH), 128.31 (CH), 127.7 (Cq), 127.1 (Cq), 125.7 (CH), 123.4 (CH), 56.20 (CH), 56.18 (CH), 53.3 (CH), 42.3 (Cq), 40.3 (CH_2), 40.0 (CH), 39.7 (CH_2), 39.4 (CH_2), 38.7 (CH_2), 36.1 (CH_2), 35.7(CH), 35.2 (CH), 34.9 (Cq), 32.4 (CH_2), 31.2 (CH_2), 28.1 (CH_2), 28.0 (CH), 27.8 (CH_2), 24.1 (CH_2), 23.8 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 21.2 (CH_2), 18.6 (CH_3), 12.0 (CH_3), 11.9 (CH_3). **HRMS** (ESI, positive ion): m/z calculated for $C_{42}H_{56}NO$: $[M+H]^+$ 590.4362, Found: 590.4360.

2-((3S,3aR,5bR)-3a,5b-dimethyl-3-(6-methylhepptan-2-yl)-2,3,3a,4,5,5a,5b,6,7,15a,15b-dodecahydro-1*H*-cyclopent[5,6]naptho[2,1-a]acridin-13-yl)-1-phenylethan-1-one (18am)



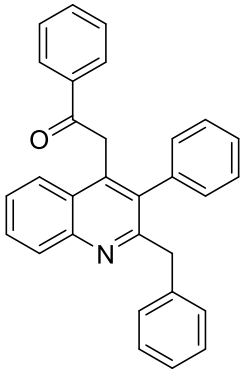
Sticky yellow solid. (72% yield, 89 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.13-8.10 (m, 1H), 8.08-8.05 (m, 2H), 7.60 (tt, *J* = 7.4, 1.3 Hz, 1H), 7.57-7.47 (m, 5H), 7.38-7.35 (m, 1H), 5.59 (dd, *J* = 5.1, 2.3 Hz, 1H), 4.92 (d, *J* = 17.4 Hz, AB system, 1H), 4.76 (d, *J* = 17.4 Hz, AB system, 1H), 3.02-2.96 (m, 1H), 2.85-2.77 (m, 1H), 2.15-2.09 (m, 1H), 2.02-1.96 (m, 2H), 1.82-1.73 (m, 1H), 1.66-1.56 (m, 3H), 1.44-1.42 (m, 3H), 1.32-1.18 (m, 7H), 1.08-0.99 (m, 7H), 0.86 (d, *J* = 6.5 Hz, 3H), 0.84 (s, 3H), 0.80 (d, *J* = 1.7 Hz, 3H), 0.78 (d, *J* = 1.7 Hz, 3H), 0.65 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 196.7 (CO), 160.8 (Cq), 144.2 (Cq), 139.4 (Cq), 138.3 (Cq), 136.2 (Cq), 133.9 (Cq), 133.7 (CH), 129.1 (CH), 128.9 (2CH), 128.7 (CH), 128.3 (2CH), 127.9 (CH), 127.6 (Cq), 126.4 (CH), 124.4 (CH), 56.6 (CH), 56.0 (CH), 47.1 (CH), 42.5 (Cq), 39.81 (CH_2), 39.80 (CH_2), 39.5 (CH_2), 37.9 (Cq), 36.1 (CH_2), 35.8 (CH), 34.1 (CH_2), 32.0 (CH), 31.9 (CH_2), 31.2 (CH_2), 28.2 (CH_2), 28.0 (CH), 24.1 (CH_2), 23.81 (CH_3), 23.80 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 22.0 (CH_2), 18.7 (CH_3), 12.0 (CH_3). **HRMS** (ESI, positive ion): m/z calculated for $C_{42}H_{54}NO$: $[M+H]^+$ 588.4205, Found: 588.4205.

(3aS,3aS,5bR,15bS)-3a,5b-dimethyl-13-(2-oxo-2-phenylethyl)-1,2,3,3a,4,5,5a,5b,6,7,15,15a,15b-dodecahydro-3*H*-cyclopent[5,6]naptho[2,1-a]acridin-3-one (18an)



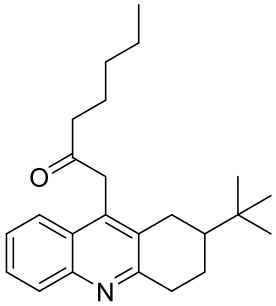
Sticky yellow solid. (64% yield, 70 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.17-8.11 (m, 2H), 8.05 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.71-7.65 (m, 2H), 7.63-7.55 (m, 3H), 7.43-7.39 (m, 1H), 5.68 (dd, *J* = 5.1, 2.0 Hz, 1H), 5.01 (d, *J* = 17.5 Hz, AB system, 1H), 4.80 (d, *J* = 17.5 Hz, AB system, 1H), 2.96-2.82 (m, 2H), 2.62-2.55 (m, 1H), 2.47 (dd, *J* = 19.2, 8.6 Hz, 1H), 2.23-2.19 (m, 1H), 2.09 (dd, *J* = 19.1, 9.1 Hz, 1H), 1.97-1.81 (m, 5H), 1.63-1.21 (m, 6H), 0.95 (s, 3H), 0.93 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 220.6 (CO), 197.0 (CO), 161.0 (Cq), 146.1 (Cq), 140.3 (Cq), 136.6 (Cq), 133.8 (Cq), 133.7 (CH), 133.4 (Cq), 129.2 (CH), 128.9 (2CH), 128.5 (CH), 128.4 (2CH), 127.5 (Cq), 127.0 (CH), 126.0 (CH), 124.3 (CH), 53.4 (CH), 51.7 (CH), 47.3 (Cq), 39.6 (Cq), 38.1 (CH_2), 35.9 (CH_2), 34.4 (CH), 32.1 (CH_2), 31.7 (CH_2), 31.6 (CH_2), 30.8 (CH_2), 24.0 (CH_3), 21.8 (CH_2), 21.4 (CH_2), 13.7 (CH_3). **HRMS** (ESI, positive ion): m/z calculated for $C_{34}H_{36}NO_2$: $[M+H]^+$ 490.2746, Found: 490.2743.

2-(2-benzyl-3-phenylquinolin-4-yl)-1-phenylethanone (18ao)



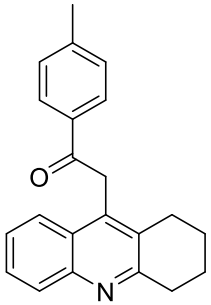
White solid. (35% yield, 64 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.12 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.73-7.71 (m, 2H), 7.62-7.56 (m, 2H), 7.46-7.41 (m, 1H), 7.37 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.32-7.28 (m, 2H), 7.21-7.12 (m, 3H), 7.01-6.97 (m, 3H), 6.88-6.86 (m, 2H), 6.80-6.77 (m, 2H), 4.37 (s, 2H), 4.08 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 196.1 (CO), 159.0 (Cq), 146.9 (Cq), 139.9 (Cq), 139.0 (Cq), 137.9 (Cq), 136.3 (Cq), 136.2 (Cq), 133.4 (CH), 129.8 (CH), 129.6 (2CH), 129.0 (CH), 128.9 (2CH), 128.7 (2CH), 128.5 (Cq), 128.3 (2CH), 128.0 (2CH), 127.9 (2CH), 127.7 (CH), 126.6 (CH), 125.8 (CH), 124.0 (CH), 43.8 (CH_2), 39.7 (CH_2). **HRMS** (ESI, positive ion): m/z calculated for $C_{30}H_{23}KNO$: $[M+K]^+$ 452.1417, Found: 452.1416.

1-(2-(*tert*-butyl)-1,2,3,4-tetrahydroacridin-9-yl)hepthan-2-one (18ba)



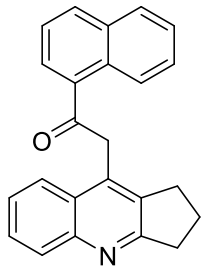
White solid. (60% yield, 61 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.99 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.69 (dd, *J* = 8.5, 1.3 Hz, 1H), 7.56 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.40 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 4.11 (s, 2H), 3.25 (ddd, *J* = 17.5, 4.7, 2.6 Hz, 1H), 3.02 (ddd, *J* = 17.6, 12.2, 5.3 Hz, 1H), 2.86 (ddd, *J* = 16.3, 4.8, 5.2 Hz, 1H), 2.45-2.38 (m, 3H), 2.10-2.06 (m, 1H), 1.57-1.47 (m, 3H), 1.43 (td, *J* = 12.2, 4.7 Hz, 1H), 1.24-1.14 (m, 4H), 0.93 (s, 9H), 0.79 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 206.5 (CO), 158.8(Cq), 145.5(Cq), 138.9(Cq), 129.9 (Cq), 128.7 (CH), 126.5 (Cq), 126.1 (CH), 122.9 (CH), 44.5 (CH), 42.5 (CH_2), 42.4 (CH_2), 34.7 (CH_2), 32.6 (Cq), 31.3 (CH_2), 28.5 (CH_2), 27.2 ($3CH_3$), 23.8 (CH_2), 23.5 (CH_2), 22.4 (CH_2), 13.8 (CH_3). **HRMS** (ESI, positive ion): m/z calculated for $C_{24}H_{33}KNO$: $[M+K]^+$ 390.2199, Found: 390.2201.

2-(1,2,3,4-tetrahydroacridin-9-yl)-1-(*p*-tolyl)ethan-1-one (18ck)



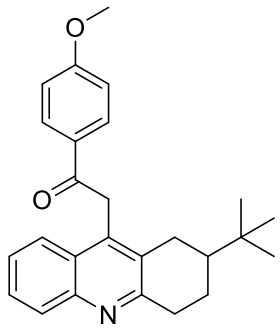
Sticky yellow solid. (87% yield, 110 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.09 (dd, $_J$ = 8.5, 0.9 Hz, 1H), 8.00-7.98 (m, 2H), 7.64 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.58 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.37 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.33-7.31 (m, 2H), 4.69 (s, 2H), 3.19 (t, *J* = 6.3 Hz, 2H), 2.77 (t, *J* = 6.3 Hz, 2H), 2.44 (s, 3H), 1.93-1.84 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 194.8 (CO), 158.4 (Cq), 144.9 (Cq), 144.6 (Cq), 140.0 (Cq), 133.9 (Cq), 130.0 (Cq), 129.5 (2CH), 128.6 (CH), 128.2 (2CH), 127.8 (CH), 126.8 (Cq), 125.9 (CH), 122.9 (CH), 37.4 (CH_2), 33.1 (CH_2), 26.7 (CH_2), 22.6 (CH_2), 22.2 (CH_2), 21.6 (CH_3). **HRMS** (ESI, positive ion): m/z calculated for $C_{22}H_{21}KNO$: $[M+K]^+$ 354.1260, Found: 354.1260.

2-(2,3-dihydro-1*H*-cyclopenta[b]quinolin-9-yl)-1-(naphtyalen-1-yl)ethan-1-one (18dd)



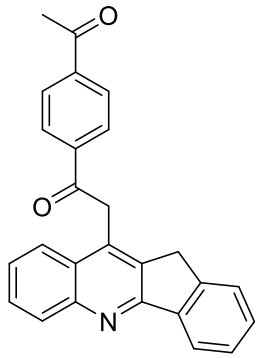
Sticky yellow solid. (88% yield, 92 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.52-8.48 (m, 1H), 8.23 (d, *J* = 8.3 Hz, 1H), 8.12 (dd, *J* = 7.2, 1.2 Hz, 1H), 8.06 (dt, *J* = 8.3, 1.0 Hz, 1H), 7.92-7.88 (m, 2H), 7.68 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.59-7.53 (m, 3H), 7.50 (ddd, *J* = 8.5, 7.1, 1.5 Hz, 1H), 4.85 (s, 2H), 3.32 (t, *J* = 7.8 Hz, 2H), 3.06 (t, *J* = 7.4 Hz, 2H), 2.24 (quint, *J* = 7.6 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 198.8 (CO), 166.2 (Cq), 145.5 (Cq), 136.5 (Cq), 135.0 (Cq), 134.1 (Cq), 133.6 (CH), 130.7 (Cq), 130.2 (Cq), 129.2 (CH), 128.6 (CH), 128.4 (CH), 127.8 (2CH), 126.80 (Cq), 126.78 (CH), 126.6 (CH), 125.5 (CH), 124.3 (CH), 123.4 (CH), 42.8 (CH_2), 34.4 (CH_2), 29.9 (CH_2), 23.1 (CH_2). **HRMS** (ESI, positive ion): m/z calculated for $C_{24}H_{19}KNO$: $[M+K]^+$ 376.1104, Found: 376.1101.

2-(2-(*tert*-butyl)-1,2,3,4-tetrahydroacridin-9-yl)-1-(4-methoxyphenyl)ethan-1-one (18ea)



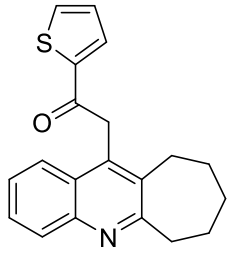
White solid. (93% yield, 83 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.12-8.09 (m, 2H), 8.06 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.69 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.60 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.40 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.03-7.00 (m, 2H), 4.72 (d, *J* = 17.7 Hz, AB system, 1H), 4.70 (d, *J* = 17.7 Hz, AB system, 1H), 3.91 (s, 3H), 3.32 (ddd, *J* = 17.5, 4.6, 2.6 Hz, 1H), 3.10 (ddd, *J* = 17.5, 12.2, 5.3 Hz, 1H), 2.90 (ddd, *J* = 16.2, 4.8, 2.1 Hz, 1H), 2.49 (dd, *J* = 16.2, 11.6 Hz, 1H), 2.17-2.10 (m, 1H), 1.61-1.54 (m, 1H), 1.49 (qd, *J* = 12.2, 4.6 Hz, 1H), 0.93 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 194.1 (CO), 164.0 (Cq), 158.7 (Cq), 145.6 (Cq), 139.9 (Cq), 130.6 (2CH), 130.2 (Cq), 129.7 (Cq), 128.7 (CH), 128.5 (CH), 126.8 (Cq), 125.9 (CH), 123.1 (CH), 114.1 (2CH), 55.6 (OCH_3), 44.6 (CH), 37.2 (CH_2), 34.8 (CH_2), 32.6 (Cq), 28.5 (CH_2), 27.2 ($3CH_3$), 23.9 (CH_2). **HRMS** (ESI, positive ion): m/z calculated for $C_{26}H_{29}KNO_2$: $[M+K]^+$ 426.1835, Found: 426.1834.

1-(4-acetylphenyl)-2-(11*H*-indeno[1,2-b]quinolin-10-yl)ethan-1-one (18fg)



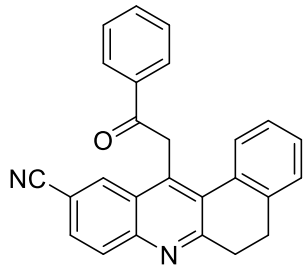
Sticky yellow solid. (85% yield, 84 mg). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 8.31-8.29 (m, 2H), 8.16-8.12 (m, 4H), 8.02 (dd, *J* = 8.5, 1.3 Hz, 1H), 7.73 (td, *J* = 7.6, 1.4 Hz, 1H), 7.67-7.65 (m, 1H), 7.55-7.51 (m, 3H), 5.19 (s, 2H), 4.02 (s, 2H), 2.67 (s, 3H). **^{13}C NMR** (100.6 MHz, DMSO-d_6): δ 197.7 (CO), 196.0 (CO), 160.0 (Cq), 147.7 (Cq), 144.8 (Cq), 140.2 (Cq), 140.0 (Cq), 139.5 (Cq), 136.8 (Cq), 134.9 (Cq), 130.0 (CH), 129.2 (CH), 128.6 (2CH), 128.5 (CH), 128.4 (2CH), 127.4 (Cq), 126.7 (CH), 125.74 (CH), 125.67 (CH), 124.3 (CH), 121.4 (CH), 39.3 (CH_2), 33.0 (CH_2), 27.1 (CH_3). **HRMS** (ESI, positive ion): m/z calculated for $C_{26}H_{20}NO_2$: $[M+H]^+$ 378.1494, Found: 378.1495.

2-(7,8,9,10-tetrahydro-6*H*-cyclohepta[b]quinolin-11-yl)-1-(thiophen-2-yl)ethan-1-one (18ge)



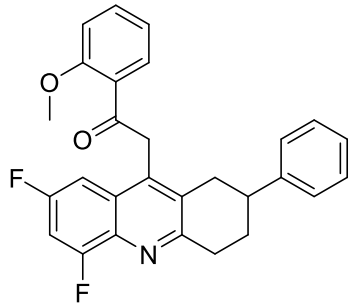
Brown solid. (77% yield, 55 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.09 (d, *J* = 8.2 Hz, 1H), 7.94 (dd, *J* = 3.8, 0.8 Hz, 1H), 7.77 (d, *J* = 8.3 Hz, 1H), 7.72 (dd, *J* = 5.0, 0.9 Hz, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.21 (dd, *J* = 5.0, 3.8 Hz, 1H), 4.77 (s, 2H), 3.30-3.28 (m, 2H), 2.94-2.91 (m, 2H), 1.90-1.80 (m, 4H), 1.72-1.69 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 188.4 (CO), 164.2 (Cq), 145.1 (Cq), 143.4 (Cq), 136.7 (Cq), 136.0 (Cq), 134.4 (CH), 132.3 (CH), 128.9 (CH), 128.5 (CH), 128.4 (CH), 126.9 (Cq), 126.4 (CH), 123.4 (CH), 39.5 (CH_2), 38.8 (CH_2), 31.6 (CH_2), 30.1 (CH_2), 27.7 (CH_2), 26.8 (CH_2). **HRMS** (ESI, positive ion): m/z calculated for $C_{20}H_{20}NOS$: $[M+H]^+$ 322.1266, Found: 322.1264.

12-(2-oxo-2-phenylethyl)-5,6-dihydrobenzo[a]acridine-10-carbonitrile (18hj)



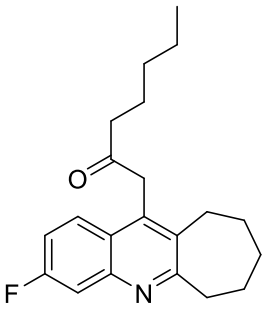
White solid. (76% yield, 60 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.07-8.03 (m, 3H), 7.93 (dd, *J* = 1.7, 0.5 Hz, 1H), 7.68 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.51-7.47 (m, 2H), 7.30-7.28 (m, 1H), 7.23 (td, *J* = 7.4, 1.3 Hz, 1H), 7.19-7.17 (m, 1H), 7.07 (td, *J* = 7.6, 1.5 Hz, 1H), 4.91 (s, 2H), 3.16-3.13 (m, 2H), 2.89-2.86 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 195.7 (CO), 163.2 (Cq), 145.6 (Cq), 139.3 (Cq), 135.8 (Cq), 134.5 (Cq), 133.3 (CH), 130.8 (Cq), 129.94 (CH), 129.85 (Cq), 129.0 (CH), 128.8 (CH), 128.11 (2CH), 128.10 (CH), 127.53 (2CH), 127.48 (CH), 127.1 (CH), 127.0 (Cq), 125.8 (CH), 117.9 (CN), 108.9 (Cq), 40.4 (CH_2), 33.3 (CH_2), 27.7 (CH_2). **HRMS** (ESI, positive ion): m/z calculated for C26H19N2O: [M+H]+ 375.1497, Found: 375.1500.

2-(5,7-diflluoro-2-phenyl-1,2,3,4-tetrahydoacridin-9-yl)-1-(2-methoxyphenyl)ethan-1-one (18ib)



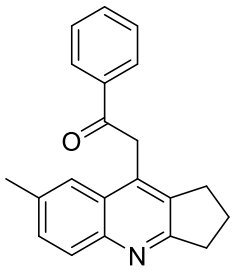
White solid. (69% yield, 58 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.61 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.45-7.41 (m, 1H), 7.26-7.12 (m, 6H), 7.04 (ddd, *J* = 10.2, 8.6, 2.6 Hz, 1H), 6.95-6.91 18 (m, 2H), 4.64 (d, *J* = 18.6 Hz, AB system, 1H), 4.59 (d, *J* = 18.6 Hz, AB system, 1H), 3.85 (s, 3H), 3.37 (ddd, *J* = 18.0, 5.2, 3.0 Hz, 1H), 3.22 (ddd, *J* = 18.0, 11.9, 5.8 Hz, 1H), 3.10 (ddd, *J* = 16.3, 5.0, 1.7 Hz, 1H), 3.06-2.98 (m, 1H), 2.81 (dd, *J* = 16.4, 11.0 Hz, 1H), 2.21-2.17 (m, 1H), 2.09-1.98 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 196.6 (CO), 159.2 (dd, *J* = 246.8, 12.0 Hz, Cq), 158.7 (Cq), 158.1 (dd, *J* = 259.1, 13.6 Hz, Cq), 157.8 (dd, *J* = 2.7, 1.6 Hz, Cq), 145.5 (Cq), 139.7 (dd, *J* = 5.9, 3.3 Hz, Cq), 134.3 (CH), 133.5 (dd, *J* = 11.4, 1.1 Hz, Cq), 131.7 (Cq), 130.5 (CH), 128.6 (2CH), 128.4 (dd, *J* = 10.4, 3.1 Hz, Cq), 127.2 (Cq), 126.8 (2CH), 126.6 (CH), 120.9 (CH), 111.6 (CH), 104.0 (dd, *J* = 29.5, 22.9 Hz, CH), 103.1 (dd, *J* = 22.4, 4.8 Hz, CH), 55.5 (OCH_3), 43.3 (CH), 40.4 (CH_2), 35.5 (CH_2), 34.1 (CH_2), 29.3 (CH_2). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -122.1 (d, *J* = 1.5 Hz), -133.5 (d, *J* = 1.5 Hz). **HRMS** (ESI, positive ion): m/z calculated for $C_{28}H_{23}F_2KNO_2$: $[M+K]^+$ 482.1334, Found: 482.1334.

1-(3-fluoro-7,8,9,10-tetrahydro-6*H*-cyclohepta[b]quinolin-11-yl)heptan-2-one (18je)



Sticky brown solid. (75% yield, 39 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.74 (dd, *J* = 8.9, 6.8 Hz, 1H), 7.57 (dd, *J* = 9.6, 2.4 Hz, 1H), 7.28 (td, *J* = 8.9, 2.7 Hz, 1H), 4.21 (s, 2H), 3.68-3.63 (m, 2H), 2.95-2.87 (m, 2H), 2.59 (t, *J* = 7.4 Hz, 2H), 1.67-1.51 (m, 4H), 1.50-1.43 (m, 2H), 1.37-1.24 (m, 4H), 1.08-0.95 (m, 2H), 0.83 (t, *J* = 6.5 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 206.1 (CO), 163.2 (d, *J* = 258.8 Hz, Cq), 157.2 (Cq), 153.5 (d, *J* = 7.8 Hz, Cq), 138.3 (Cq), 131.6 (d, *J* = 2.3 Hz, Cq), 127.7 (d, *J* = 13.6 Hz, CH), 123.9 (Cq), 119.6 (d, *J* = 25.4 Hz, CH), 106.8 (d, *J* = 26.3 Hz, CH), 43.1 (CH_2), 42.7 (CH_2), 35.9 (CH_2), 32.5 (CH_2), 31.39 (CH_2), 31.36 (CH_2), 29.7 (CH_2), 27.3 (CH_2), 23.4 (CH_2), 22.4 (CH_2), 14.0 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -106.2. **HRMS** (ESI, positive ion): m/z calculated for $C_{21}H_{27}FNO$: $[M+H]^+$ 328.2077, Found: 328.2079.

2-(7-methyl-2,3-dihydro-1*H*-cyclopenta[b]quinolin-9-yl)-1-phenylethan-1-one (18kd)



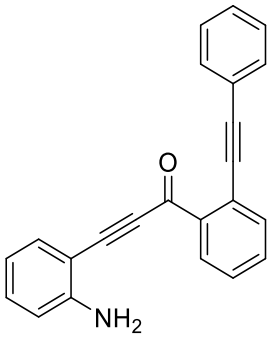
White solid. (83% yield, 59 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.04-8.02 (m, 2H), 7.88-7.86 (m, 1H), 7.57 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.48-7.44 (m, 2H) 7.37-7.32 (m, 2H), 4.60 (s, 2H), 3.10 (t, *J* = 7.7 Hz, 2H), 2.89 (t, *J* = 7.4 Hz, 2H), 2.37 (s, 3H), 2.10 (quint, *J* = 7.5 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 195.4 (CO), 165.8 (Cq), 146.0 (Cq), 136.5 (Cq), 135.6 (Cq), 135.5 (Cq), 133.6 (CH), 130.4 (CH), 129.1 (Cq), 128.9 (CH), 128.8 (2CH), 128.2 (2CH), 126.6 (Cq), 122.1 (CH), 39.1 (CH_2), 34.8 (CH_2), 29.7 (CH_2), 22.9 (CH_2), 21.8 (CH_3). **HRMS** (ESI, positive ion): m/z calculated for $C_{21}H_{19}KNO$: $[M+K]^+$ 340.1104, Found: 340.1102.

11.4 Domino reactions of β-(2-aminophenyl)-α,β-ynones with β-dicarbonyl compounds: divergent synthesis of polycyclic quinolines derivatives

11.4.1 Preparation and characterisation of β-(2-aminophenyl)-α,β-ynones

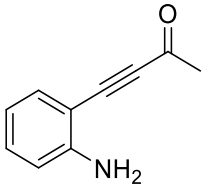
All the β-(2-aminophenyl)-α,β-ynones used were prepared according to the procedures already reported in literature and in Section 11.3.1. Only **16s**, **16u** and **16v** were newly prepared, according to the same procedures, and therefore characterised.

3-(2-aminophenyl)-1-(2-(phenylethynyl)phenyl)prop-2-yn-1-one (16s)



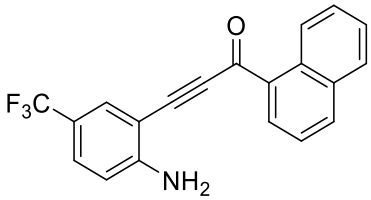
Brown solid. (53% yield, 673 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.14 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.70 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.63-7.53 (m, 3H), 7.48 (td, *J* = 7.8, 1.4 Hz, 1H), 7.42 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.36-7.29 (m, 3H), 7.26-7.19 (m, 1H), 6.73-6.64 (m, 2H), 4.53 (br, 2H, NH_2). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 177.5 (CO), 150.5 (Cq), 138.9 (Cq), 134.3 (CH), 133.9 (CH), 132.7 (CH), 132.3 (CH), 131.9 (2CH), 131.1 (CH), 128.7 (CH), 128.3 (2CH), 128.1 (CH), 117.9 (CH), 114.6 (CH), 103.9 (Cq), 95.8 (Cq), 94.8 (Cq), 91.8 (Cq), 88.2 (Cq). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{23}H_{16}NO$: $[M+H]^+$ 322.1232, Found: 322.1231.

4-(2-aminophenyl)but-3-yn-2-one (16u)



Brown solid. (40% yield, 222 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.38 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.25 (ddd, *J* = 8.0, 7.4, 1.6 Hz, 1H), 6.76-6.66 (m, 2H), 4.44 (br, 2H, NH_2), 2.48 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 184.2 (CO), 150.2 (Cq), 133.9 (CH), 132.7 (CH), 117.9 (CH), 114.6 (CH), 103.5 (Cq), 94.7 (Cq), 88.4 (Cq), 32.7 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{10}H_9KNO$: $[M+K]^+$ 198.0321, Found: 198.0320.

3-(2-amino-5-(trifluoromethyl)phenyl)-1-(naphthalen-1-yl)prop-2-yn-1-one (16v)

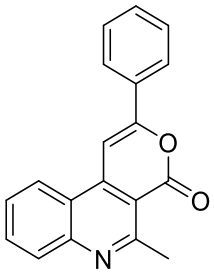


Yellow solid. (83% yield, 248 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.21 (dd, *J* = 8.7, 1.0 Hz, 1H), 8.62 (dd, *J* = 7.3, 1.3 Hz, 1H), 8.15 (d, *J* = 8.0 Hz, 1H), 7.99-7.92 (m, 1H), 7.76 (d, *J* = 1.5 Hz, 1H), 7.72 (ddd, *J* = 8.7, 6.9, 1.5 Hz, 1H), 7.68-7.65 (m, 1H), 7.62 (ddd, *J* = 8.7, 6.9, 1.5 Hz, 1H), 7.49 (dd, *J* = 8.7, 2.2 Hz, 1H), 6.81 (d, *J* = 8.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 179.3 (CO), 152.4 (Cq), 135.9 (Cq), 135.3 (CH), 134.2 (CH), 133.9 (Cq), 132.9 (Cq), 131.0 (q, *J* = 33.5 Hz, Cq), 130.7 (Cq), 129.1 (CH), 129.0 (2CH), 128.7 (CH), 126.9 (CH), 125.9 (CH), 125.3 (q, *J* = 272 Hz, CF_3), 124.6 (CH), 114.3 (CH), 103.7 (Cq), 95.1 (Cq), 87.4 (Cq). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -61.7. **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{20}H_{13}F_3NO$: $[M+H]^+$ 340.0949, Found: 340.0950.

11.4.2 Preparation and characterisation of 4*H*-pyrano[3,4-c]quinoline-4-ones **22aa-22pa**

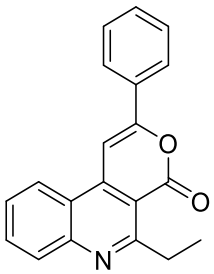
General procedure. A mixture of β-(2-aminophenyl)-α,β-ynones **16** (0.2 mmol, 1.0 equiv.), β-ketoester **19** (0.4 mmol, 2.0 equiv.), and *p*-TsOH·H_2O (0.04 mmol, 20 mol%) in EtOH (2 mL) was stirred at 80 °C for 1–24 h. After completion, the mixture was diluted with a saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2 (25 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4. After the removal of the solvent at reduced pressure, the crude product was purified by column chromatography over silica gel using mixture of *n*-hexane–EtOAc from 80:20 to 60:40 v/v to give the title compound **22**.

5-methyl-2-phenyl-4*H*-pyrano[3,4-c]quinolin-4-one (22aa)



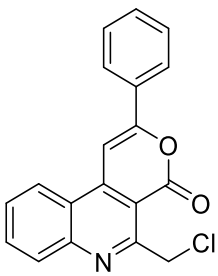
White solid. (90% yield, 54 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.24 (dd, *J* = 8.4, 1.3 Hz, 1H), 8.12-8.03 (m, 1H), 8.01-7.94 (m, 2H), 7.84 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.63 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.56 (s, 1H), 7.54-7.48 (m, 3H), 3.13 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.4 (2Cq), 159.2 (Cq), 148.2 (Cq), 144.9 (Cq), 132.6 (CH), 131.3 (CH), 131.2 (Cq) 129.5 (CH), 129.1 (2CH), 126.8 (CH), 125.9 (2CH), 123.4 (CH), 120.9 (Cq), 110.8 (Cq), 96.1 (CH), 27.1 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{19}H_{14}NO_2$: $[M+H]^+$ 288.1025, Found: 288.1028.

5-ethyl-2-phenyl-4*H*-pyrano[3,4-c]quinolin-4-one (22ab)



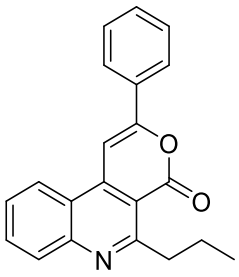
Pale brown solid. (93% yield, 42 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.32 (dd, *J* = 8.3, 1.4 Hz, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 8.05-8.00 (m, 1H), 7.89 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.73-7.63 (m, 2H), 7.55 (dd, *J* = 5.0, 1.8 Hz, 3H), 3.60 (q, *J* = 7.4 Hz, 2H), 1.46 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 164.9 (Cq), 160.0 (Cq), 158.8 (Cq), 148.5 (Cq), 145.1 (Cq), 132.4 (CH), 131.2 (CH), 129.8 (CH), 129.0 (2CH), 126.7 (CH), 125.9 (2CH), 123.4 (CH), 120.8 (Cq), 110.2 (Cq), 96.1 (CH), 32.3 (CH_2), 13.2 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{19}H_{13}ClNO_2$: $[M+H]^+$ 322.0635, Found: 322.0633.

5-(chloromethyl)-2-phenyl-4*H*-pyrano[3,4-c]quinolin-4-one (22ac)



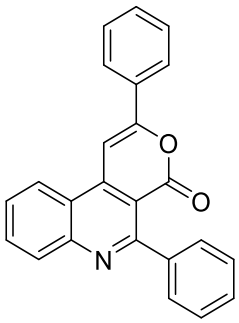
Yellow solid. (19% yield, 12 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.35 (dd, *J* = 8.4, 1.3 Hz, 1H), 8.19 (dd, *J* = 8.3, 1.3 Hz, 1H), 8.09-8.01 (m, 2H), 7.94 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.76 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.66 (s, 1H), 7.59-7.53 (m, 3H), 5.45 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.6 (Cq), 156.9 (Cq), 148.2 (Cq), 145.9 (Cq), 132.9 (CH), 131.6 (CH), 131.0 (Cq), 130.5 (CH), 129.2 (2CH), 128.2 (CH), 126.1 (2CH), 123.6 (CH), 121.7 (Cq), 109.6 (Cq), 96.1 (CH), 47.4 (CH_2). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{20}H_{15}NNaO_2$: $[M+Na]^+$ 324.1000, Found: 324.0999.

2-phenyl-5-propyl-4*H*-pyrano[3,4-c]quinolin-4-one (22ad)



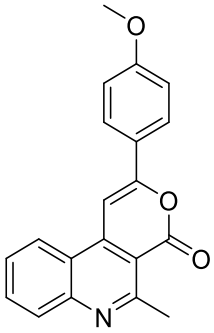
Pale yellow solid. (82% yield, 41 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.26 (dd, *J* = 8.4, 1.3 Hz, 1H), 8.09 (dd, *J* = 8.5, 1.2 Hz, 1H), 8.02-7.93 (m, 2H), 7.85 (ddd, *J* = 8.4, 7.0, 1.3 Hz, 1H), 7.63 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.59 (s, 1H), 7.56-7.47 (m, 3H), 3.62-3.36 (m, 2H), 1.95-1.79 (m, 2H), 1.14 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 163.9 (Cq), 160.1 (Cq), 158.9 (Cq), 148.3 (Cq), 145.2 (Cq), 132.5 (CH), 131.3 (CH), 129.7 (CH), 129.1 (2CH), 126.8 (CH), 125.9 (2CH), 123.4 (CH), 120.9 (Cq), 110.3 (Cq), 96.1 (CH), 40.9 (CH_2), 22.7 (CH_2), 14.4 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{21}H_{18}NO_2$: $[M+H]^+$ 316.1338, Found: 316.1339.

2,5-diphenyl-4*H*-pyrano[3,4-c]quinolin-4-one (22ae)



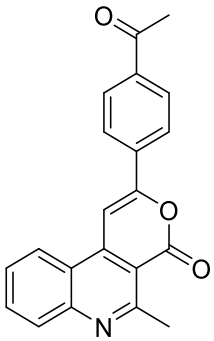
Brown solid. (52% yield, 54 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.44 (d, *J* = 8.3 Hz, 2H), 8.15-8.04 (m, 2H), 7.98 (t, *J* = 7.7 Hz, 1H), 7.80 (d, *J* = 7.7 Hz, 1H), 7.77 (s, 1H), 7.67 (dd, *J* = 6.7, 2.9 Hz, 2H), 7.60-7.49 (m, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.6 (Cq), 159.3 (Cq), 146.2 (Cq), 133.2 (CH), 131.7 (CH), 131.2 (Cq), 129.9 (Cq), 129.2 (2CH), 129.0 (CH), 128.7 (2CH), 128.0 (2CH) 127.9 (CH), 126.2 (2CH), 123.6 (CH), 121.3 (Cq), 109.8 (Cq), 96.1 (CH). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{24}H_{16}NO_2$: $[M+H]^+$ 350.1181, Found: 350.1183.

2-(4-methoxyphenyl)-5-methyl-4*H*-pyrano[3,4-c]quinolin-4-one (22ea)



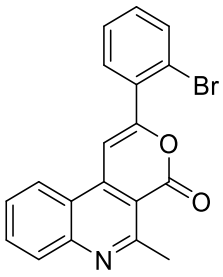
Yellow solid. (89% yield, 39 mg). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 8.73 (dd, *J* = 8.4, 1.3 Hz, 1H), 8.08 (d, *J* = 8.9 Hz, 2H), 8.01 (s, 1H), 7.96 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.90 (ddd, *J* = 8.2, 6.7, 1.3 Hz, 1H), 7.69 (ddd, *J* = 8.2, 6.7, 1.3 Hz, 1H), 7.11 (d, *J* = 8.9 Hz, 2H), 3.88 (s, 3H), 2.98 (s, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 162.3 (Cq), 160.4 (Cq), 159.6 (Cq), 158.9 (Cq), 148.3 (Cq), 145.9 (Cq), 133.1 (CH), 129.1 (CH), 128.3 (2CH), 127.1 (CH), 125.6 (CH), 123.9 (Cq), 121.4 (Cq), 115.1 (2CH), 110.3 (Cq), 95.9 (CH), 56.0 (CH_3), 27.0 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{20}H_{16}NO_3$: $[M+H]^+$ 318.1130, Found: 318.1129.

2-(4-acetylphenyl)-5-methyl-4*H*-pyrano[3,4-c]quinolin-4-one (22fa)



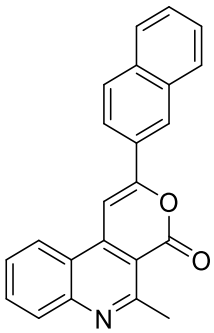
Pale yellow solid. (90% yield, 65 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.34 (dd, *J* = 8.4, 1.4 Hz, 1H), 8.17 (t, *J* = 6.9 Hz, 1H), 8.13 (s, 4H), 7.93 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.76 (s, 1H), 7.71 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 3.21 (s, 3H), 2.69 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 196.9 (Cq), 160.5 (Cq), 160.1 (Cq), 138.9 (Cq), 135.2 (Cq), 132.8 (CH), 129.7 (CH), 128.9 (2CH), 127.1 (CH), 126.2 (2CH), 123.4 (CH), 120.9 (Cq), 111.3 (Cq), 97.8 (CH), 29.6 (CH_3), 26.6 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{21}H_{16}NO_3$: $[M+H]^+$ 330.1130, Found: 330.1136.

2-(2-bromophenyl)-5-methyl-4*H*-pyrano[3,4-c]quinolin-4-one (22fa)



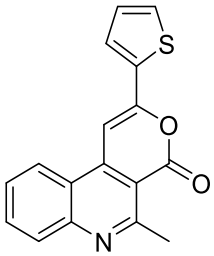
Pale brown solid. (64% yield, 42 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.23 (dd, *J* = 8.4, 1.3 Hz, 1H), 8.13 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.89 (ddd, *J* = 8.4, 7.0, 1.3 Hz, 1H), 7.75 (dt, *J* = 7.6, 1.2 Hz, 2H), 7.69-7.61 (m, 2H), 7.48 (td, *J* = 7.6, 1.2 Hz, 1H), 7.40-7.33 (m, 1H), 3.19 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.6 (Cq), 160.5 (Cq), 158.5 (Cq), 148.4 (Cq), 144.5 (Cq), 134.2 (CH), 133.2 (Cq), 132.8 (CH), 131.8 (CH), 131.0 (CH), 129.5 (CH), 127.8 (CH), 127.1 (CH), 123.7 (CH), 121.7 (Cq), 121.0 (Cq), 111.1 (Cq), 102.1 (CH), 27.2 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{19}H_{13}BrNO_2$: $[M+H]^+$ 366.0130, Found: 366.0127.

5-methyl-2-(naphthalen-2-yl)-4*H*-pyrano[3,4-c]quinolin-4-one (22da)



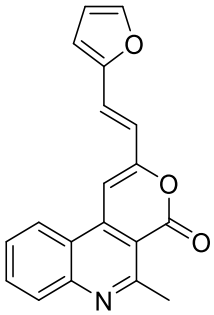
Pale yellow solid. (84% yield, 82 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.36-8.30 (m, 1H), 8.28 (dd, *J* = 8.5, 1.3 Hz, 2H), 8.09-8.04 (m, 1H), 8.02-7.92 (m, 2H), 7.89 (dd, *J* = 7.1, 1.2 Hz, 1H), 7.70 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.67-7.59 (m, 3H), 7.58 (s, 1H), 3.29 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.9 (Cq), 160.6 (Cq), 148.4 (Cq), 145.0 (Cq), 133.8 (Cq), 132.8 (CH), 131.5 (CH), 130.5 (Cq), 130.2 (Cq), 129.5 (Cq), 128.8 (CH), 128.1 (CH), 127.6 (CH), 127.0 (CH), 126.6 (CH), 125.0 (CH), 124.8 (CH), 123.7 (CH), 120.9 (Cq), 110.9 (Cq), 101.7 (CH), 27.3 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{23}H_{16}NO_2$: $[M+H]^+$ 338.1181, Found: 338.1182.

5-methyl-2-(thiophen-2-yl)-4*H*-pyrano[3,4-c]quinolin-4-one (22ga)



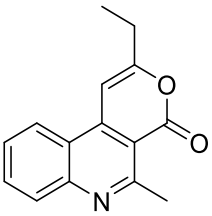
Yellow solid. (87% yield, 79 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.26 (dd, *J* = 8.2, 1.3 Hz, 1H), 8.09 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.89 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.81 (dd, *J* = 3.8, 1.2 Hz, 1H), 7.67 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H), 7.57 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.45 (s, 1H), 7.21 (dd, *J* = 5.0, 3.8 Hz, 1H), 3.16 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.5 (Cq), 160.0 (Cq), 154.8 (Cq), 148.5 (Cq), 145.1 (Cq), 135.0 (Cq), 132.6 (CH), 129.7 (CH), 129.6 (CH), 128.6 (CH), 128.3 (CH), 126.8 (CH), 123.5 (CH), 120.8 (Cq), 110.6 (Cq), 95.3 (CH), 27.3 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{17}H_{12}NO_2S$: $[M+H]^+$ 294.0589, Found: 294.0595.

(E)-2-(2-(furan-2-yl)vinyl)-5-methyl-4*H*-pyrano[3,4-c]quinolin-4-one (22ma)



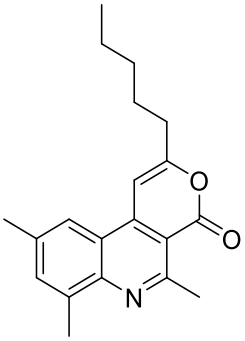
Brown solid. (73% yield, 71 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.18 (dd, *J* = 8.3, 1.3 Hz, 1H), 8.12 (d, *J* = 8.3 Hz, 1H), 7.86 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.64 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.52 (d, *J* = 1.8 Hz, 1H), 7.40 (d, *J* = 15.5 Hz, 1H), 7.11 (s, 1H), 6.76 (d, *J* = 15.5 Hz, 1H), 6.62 (d, *J* = 3.4 Hz, 1H), 6.52 (dd, *J* = 3.4, 1.8 Hz, 1H), 3.16 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.5 (Cq), 160.2 (Cq), 157.9 (Cq), 151.8 (Cq), 145.2 (Cq), 144.4 (CH), 132.9 (CH), 129.3 (CH), 126.8 (CH), 123.4 (CH), 123.3 (CH), 120.9 (Cq), 116.8 (CH), 113.9 (CH), 112.5 (CH), 110.9 (Cq), 99.9 (CH), 26.9 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{19}H_{14}NO_3$: $[M+H]^+$ 304.0974, Found: 304.0978.

2-ethyl-5-methyl-4*H*-pyrano[3,4-c]quinolin-4-one (22na)



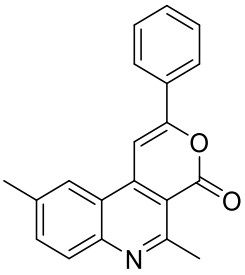
White solid. (40% yield, 65 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.25-8.17 (m, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.89 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.65 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.01 (s, 1H), 3.16 (s, 3H), 2.74 (q, *J* = 7.5 Hz, 2H), 1.40 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.4 (Cq), 161.2 (Cq), 160.6 (Cq), 147.9 (Cq), 145.4 (Cq), 132.7 (CH), 129.3 (CH), 126.8 (CH), 123.6 (CH), 120.7 (Cq), 110.7 (Cq), 97.0 (CH), 27.5 (CH_2), 27.1 (CH_3), 11.2 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{15}H_{13}NNaO_2$: $[M+Na]^+$ 262.0844, Found: 262.0842.

5,7,9-trimethyl-2-pentyl-4*H*-pyrano[3,4-c]quinolin-4-one (22oa)



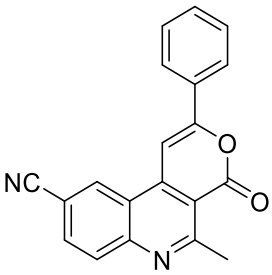
White solid. (52% yield, 45 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.80 (s, 1H), 7.57 (s, 1H), 6.98 (s, 1H), 3.17 (s, 3H), 2.82 (s, 3H), 2.72-2.61 (m, 2H), 2.57 (s, 3H), 1.82 (qd, *J* = 9.6, 8.5, 5.9 Hz, 2H), 1.43 (dq, *J* = 7.3, 3.4 Hz, 4H), 0.95 (t, *J* = 4.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 164.6 (Cq), 161.7 (Cq), 158.4 (Cq), 145.4 (Cq), 144.7 (Cq), 137.0 (Cq), 136.2 (Cq), 135.1 (Cq), 120.5 (CH), 110.4 (Cq), 98.2 (CH), 34.3 (CH_2), 31.3 (CH_2), 27.3 (CH_2), 26.7 (CH_2), 22.4 (CH_3), 21.8 (CH_3), 18.1 (CH_3), 13.9 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{20}H_{23}NNaO_2$: $[M+Na]^+$ 332.1626, Found: 332.1622.

5,9-dimethyl-2-phenyl-4*H*-pyrano[3,4-c]quinolin-4-one (22ka)



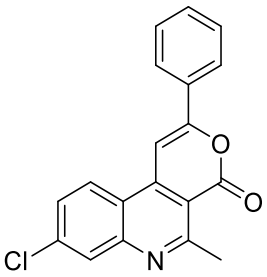
Yellow solid. (93% yield, 81 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.04 (ddd, *J* = 4.7, 2.4, 1.4 Hz, 4H), 7.72 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.63 (s, 1H), 7.56 (dt, *J* = 4.7, 2.4 Hz, 3H), 3.17 (s, 3H), 2.65 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.6 (Cq), 159.5 (Cq), 159.1 (Cq), 144.6 (Cq), 137.1 (CH), 134.9 (Cq), 129.1 (4CH), 126.0 (2CH), 122.6 (CH), 120.9 (Cq), 110.8 (Cq), 96.2 (CH), 26.9 (CH_3), 21.9 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{20}H_{15}NNaO_2$: $[M+Na]^+$ 324.1000, Found: 324.0996.

5-methyl-4-oxo-2-phenyl-4*H*-pyrano[3,4-c]quinoline-9-carbonitrile (22ha)



Pale yellow solid. (89% yield, 45 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.71 (d, *J* = 1.8 Hz, 1H), 8.26 (d, *J* = 8.7 Hz, 1H), 8.13-8.00 (m, 3H), 7.70-7.56 (m, 3H + 1H), 3.24 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 164.1 (Cq), 160.9 (Cq), 159.7 (Cq), 145.3 (Cq), 133.4 (CH), 132.1 (CH), 130.9 (Cq), 130.7 (Cq), 129.6 (CH), 129.3 (3CH), 126.3 (2CH), 120.9 (Cq), 118.2 (Cq), 111.8 (Cq), 110.6 (Cq), 95.4 (CH), 27.4 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{20}H_{13}N_2O_2$: $[M+H]^+$ 313.0977, Found: 313.0979.

8-chloro-5-methyl-2-phenyl-4*H*-pyrano[3,4-c]quinolin-4-one (22pa)

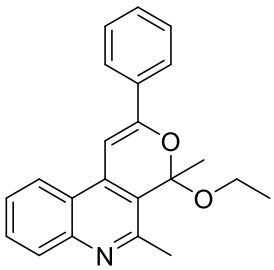


White solid. (90% yield, 46 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.22 (d, *J* = 8.9 Hz, 1H), 8.13-8.09 (m, 1H), 8.02 (dd, *J* = 6.7, 2.9 Hz, 2H), 7.61 (dd, *J* = 8.9, 2.2 Hz, 1H), 7.58-7.54 (m, 3H + 1H), 3.16 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 161.4 (Cq), 160.0 (Cq), 159.3 (Cq), 148.5 (Cq), 145.7 (Cq), 138.2 (Cq), 131.9 (CH), 131.4 (Cq), 129.5 (2CH), 127.9 (CH), 127.76 (CH), 127.67 (CH), 126.6 (2CH), 120.3 (Cq), 111.1 (Cq), 97.5 (CH), 26.9 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{19}H_{13}ClNO_2$: $[M+H]^+$ 322.0635, Found: 322.0630.

11.4.3 Preparation and characterisation of 4*H*-pyrano[3,4-c]quinolines **23aa-23ab**

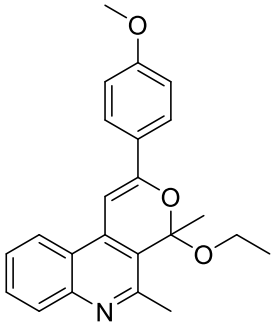
General procedure. A mixture of β-(2-aminophenyl)-α,β-ynones **16** (0.2 mmol, 1.0 equiv.), β-diketone **20** (0.4 mmol, 2.0 equiv.) and *p*-TsOH·H_2O (0.2 mmol, 1 equiv.) in EtOH (2 mL) was stirred at 80 °C for 3–6 h. After completion, the mixture was diluted with a saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2 (25 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4. After the removal of the solvent at reduced pressure, the crude product was purified by column chromatography over silica gel using mixture of *n*-hexane–EtOAc from 80:20 to 60:40 v/v to give the title compound **23**.

4-ethoxy-4,5-dimethyl-2-phenyl-4*H*-pyrano[3,4-c]quinoline (23aa)



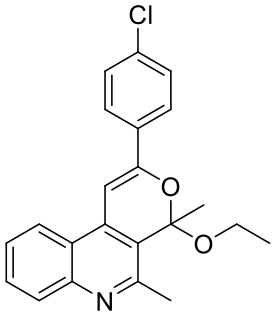
Yellow solid. (67% yield, 50 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.15 (dd, *J* = 8.5, 1.4 Hz, 1H), 8.06 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.96-7.89 (m, 2H), 7.73 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.56 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.53-7.40 (m, 3H), 6.96 (s, 1H), 3.70 (dq, *J* = 9.3, 7.0 Hz, 1H), 3.34 (dq, *J* = 9.3, 7.0 Hz, 1H), 2.93 (s, 3H), 1.94 (s, 3H), 1.28 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 155.5 (Cq), 155.4 (Cq), 147.2 (Cq), 137.2 (Cq), 133.6 (Cq), 130.1 (CH), 129.8 (CH), 128.7 (2CH), 128.6 (CH), 125.9 (CH), 125.6 (2CH), 122.9 (CH), 121.2 (Cq), 119.2 (Cq), 105.6 (Cq), 91.5 (CH), 59.6 (CH_2), 28.2 (CH_3), 24.4 (CH_3), 15.4 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{22}H_{22}NO_2$: $[M+H]^+$ 332.1651, Found: 332.1656.

4-ethoxy-2-(4-methoxyphenyl)-4,5-dimethyl-4*H*-pyrano[3,4-c]quinoline (23ea)



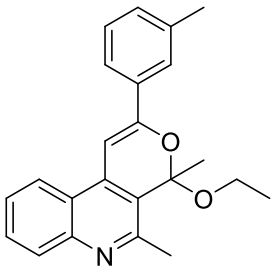
Yellow solid. (67% yield, 48 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.12 (dd, *J* = 8.5, 1.3 Hz, 1H), 8.03 (dd, *J* = 8.5, 1.3 Hz, 1H), 7.87 (d, *J* = 8.9 Hz, 2H), 7.71 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.54 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.00 (d, *J* = 8.9 Hz, 2H), 6.85 (s, 1H), 3.88 (s, 3H), 3.68 (dq, *J* = 9.4, 7.1 Hz, 1H), 3.33 (dq, *J* = 9.4, 7.1 Hz, 1H), 2.90 (s, 3H), 1.92 (s, 3H), 1.27 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 161.3 (Cq), 155.5 (Cq), 155.3 (Cq), 147.0 (Cq), 137.7 (Cq), 129.8 (CH), 128.6 (CH), 127.2 (2CH), 126.1 (Cq), 125.8 (CH), 122.9 (CH), 121.2 (Cq), 118.7 (Cq), 114.0 (2CH), 105.5 (Cq), 89.9 (CH), 59.5 (CH_2), 55.4 (CH_3), 28.1 (CH_3), 24.4 (CH_3), 15.3 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{23}H_{24}NO_3$: $[M+H]^+$ 362.1756, Found: 362.1758.

2-(4-chlorophenyl)-4-ethoxy-4,5-dimethyl-4*H*-pyrano[3,4-c]quinoline (23qa)



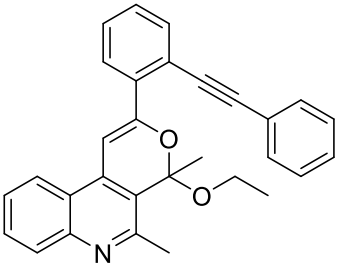
Yellow solid. (59% yield, 35 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.18-8.05 (m, 2H), 7.92-7.83 (m, 2H), 7.75 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.58 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.49-7.45 (m, 2H), 6.95 (s, 1H), 3.68 (dq, *J* = 9.3, 7.1 Hz, 1H), 3.35 (dq, *J* = 9.3, 7.1 Hz, 1H), 2.94 (s, 3H), 1.94 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 155.2 (Cq), 154.7 (Cq), 153.6 (Cq), 146.7 (Cq), 136.2 (Cq), 131.9 (CH), 130.1 (CH), 128.9 (2CH), 126.9 (2CH), 126.2 (CH), 122.8 (CH), 121.2 (Cq), 119.2 (Cq), 105.7 (Cq), 91.8 (CH), 59.7 (CH_2), 28.2 (CH_3), 26.1 (CH_3), 15.3 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{22}H_{21}ClNO_2$: $[M+H]^+$ 366.1261, Found: 366.1262.

4-ethoxy-4,5-dimethyl-2-(*m*-tolyl)-4*H*-pyrano[3,4-c]quinoline (23ra)



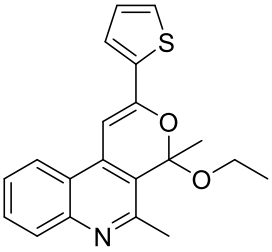
Pale brown solid. (59% yield, 18 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.16 (dd, *J* = 8.4, 1.3 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.83-7.70 (m, 3H), 7.57 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.46-7.36 (m, 1H), 7.32-7.26 (m, 1H), 6.95 (s, 1H), 3.71 (dq, *J* = 9.3, 7.1 Hz, 1H), 3.35 (dq, *J* = 9.3, 7.1 Hz, 1H), 2.92 (s, 3H), 2.48 (s, 3H), 1.95 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 155.8 (Cq), 155.4 (Cq), 146.9 (Cq), 138.4 (Cq), 137.5 (Cq), 133.6 (Cq), 130.9 (CH), 129.9 (CH), 128.6 (2CH), 126.2 (CH), 125.9 (CH), 122.9 (CH), 122.8 (CH), 121.2 (Cq), 119.1 (Cq), 105.6 (Cq), 91.4 (CH), 59.6 (CH_2), 28.2 (CH_3), 24.3 (CH_3), 21.6 (CH_3), 15.3 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{23}H_{24}NO_2$: $[M+H]^+$ 346.1807, Found: 346.1802.

4-ethoxy-4,5-dimethyl-2-(2-(phenylethynyl)phenyl)-4*H*-pyrano[3,4-c]quinoline (23sa)



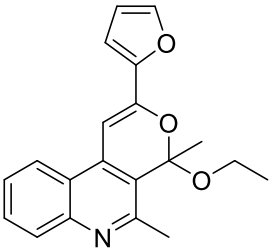
Yellow solid. (46% yield, 61 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.01 (ddd, *J* = 8.3, 4.5, 1.3 Hz, 2H), 7.94 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.74 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.70-7.63 (m, 2H), 7.58-7.52 (m, 2H), 7.46 (dtd, *J* = 20.8, 7.7, 1.5 Hz, 2H), 7.39-7.32 (m, 3H), 7.29 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 3.78 (dq, *J* = 9.2, 7.0 Hz, 1H), 3.38 (dq, *J* = 9.2, 7.0 Hz, 1H), 2.93 (s, 3H), 1.98 (s, 3H), 1.28 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 155.4 (Cq), 153.9 (Cq), 147.3 (Cq), 137.1 (Cq), 134.9 (Cq), 134.3 (CH), 131.7 (2CH), 129.7 (CH), 129.1 (CH), 128.7 (2CH), 128.5 (CH), 128.4 (2CH), 127.8 (CH), 125.8 (CH), 123.4 (CH), 122.9 (Cq), 121.4 (Cq), 120.8 (Cq), 119.4 (Cq), 105.8 (Cq), 96.5 (CH), 95.0 (Cq), 89.2 (Cq), 59.7 (CH_2), 28.0 (CH_3), 24.5 (CH_3), 15.3 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{30}H_{26}NO_2$: $[M+H]^+$ 432.1964, Found: 432.1965.

4-ethoxy-4,5-dimethyl-2-(thiophen-2-yl)-4*H*-pyrano[3,4-c]quinoline (23ga)



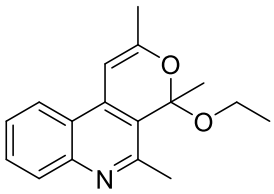
Brown solid. (70% yield, 49 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.09 (dd, *J* = 8.5, 1.3 Hz, 1H), 8.03 (dd, *J* = 8.5, 1.3 Hz, 1H), 7.72 (ddd, *J* = 8.3, 6.8, 1.4 Hz, 1H), 7.63 (dd, *J* = 3.7, 1.2 Hz, 1H), 7.55 (ddd, *J* = 8.3, 6.8, 1.4 Hz, 1H), 7.44 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.15 (dd, *J* = 5.0, 3.7 Hz, 1H), 6.83 (s, 1H), 3.71 (dq, *J* = 9.2, 7.1 Hz, 1H), 3.35 (dq, *J* = 9.2, 7.1 Hz, 1H), 2.90 (s, 3H), 1.92 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 155.2 (Cq), 151.3 (Cq), 147.0 (Cq), 137.8 (Cq), 137.3 (Cq), 129.9 (CH), 128.6 (CH), 128.0 (CH), 127.7 (CH), 126.2 (CH), 125.9 (CH), 122.9 (CH), 121.1 (Cq), 119.2 (Cq), 105.8 (Cq), 90.9 (CH), 59.7 (CH_2), 28.0 (CH_3), 24.4 (CH_3), 15.3 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{20}H_{20}NO_2S$: $[M+H]^+$ 338.1215, Found: 338.1220.

4-ethoxy-2-(furan-2-yl)-4,5-dimethyl-4*H*-pyrano[3,4-c]quinoline (23ta)



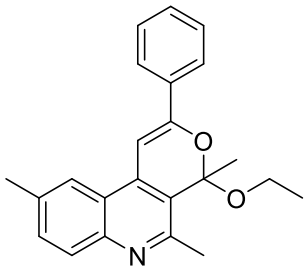
Yellow solid. (70% yield, 98 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.16-8.09 (m, 1H), 8.07-8.00 (m, 1H), 7.72 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.59-7.52 (m, 2H), 6.92 (s, 1H), 6.91 (dd, *J* = 3.5, 0.8 Hz, 1H), 6.57 (dd, *J* = 3.5, 1.4 Hz, 1H), 3.69 (dq, *J* = 9.3, 7.1 Hz, 1H), 3.33 (dq, *J* = 9.3, 7.1 Hz, 1H), 2.90 (s, 3H), 1.90 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.2 (Cq), 148.6 (Cq), 147.8 (Cq), 146.9 (Cq), 144.2 (CH), 137.2 (Cq), 129.9 (CH), 128.4 (CH), 125.9 (CH), 123.1 (CH), 121.2 (Cq), 119.3 (Cq), 112.0 (CH), 110.3 (CH), 105.5 (Cq), 90.6 (CH), 59.9 (CH_2), 28.0 (CH_3), 24.3 (CH_3), 15.3 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{20}H_{20}NO3$: $[M+H]^+$ 322.1443, Found: 322.1435.

4-ethoxy-2,4,5-trimethyl-4*H*-pyrano[3,4-c]quinoline (23ua)



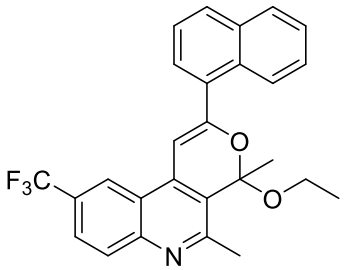
Yellow solid. (26% yield, 43 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.00-7.97 (m, 1H), 7.75-7.67 (m, 2H), 7.54-7.50 (m, 1H), 6.19 (d, *J* = 1.1 Hz, 1H), 3.60 (dq, *J* = 9.2, 7.1 Hz, 1H), 3.25 (dq, *J* = 9.2, 7.1 Hz, 1H), 2.89 (s, 3H), 2.15 (s, 3H), 1.85 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 155.2 (Cq), 137.3 (Cq), 135.4 (Cq), 128.8 (Cq), 126.4 (CH), 123.1 (CH), 122.9 (CH), 120.96 (CH), 120.59 (Cq), 117.9 (Cq), 105.2 (Cq), 92.3 (CH), 59.4 (CH_2), 28.5 (CH_3), 25.8 (CH_3), 20.7 (CH_3), 15.2 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{17}H_{19}KNO_2$: $[M+K]^+$ 308.1053, Found: 308.1055.

4-ethoxy-4,5,9-trimethyl-2-phenyl-4*H*-pyrano[3,4-c]quinoline (23ka)



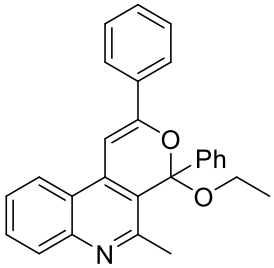
Brown solid. (41% yield, 54 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.00-7.92 (m, 3H), 7.92-7.87 (m, 1H), 7.57 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.54-7.46 (m, 3H), 6.95 (s, 1H), 3.70 (dq, *J* = 9.2, 7.0 Hz, 1H), 3.34 (dq, *J* = 9.2, 7.0 Hz, 1H), 2.90 (s, 3H), 2.61 (s, 3H), 1.94 (s, 3H), 1.28 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 155.3 (Cq), 154.3 (Cq), 145.5 (Cq), 136.7 (Cq), 135.8 (Cq), 133.7 (Cq), 132.1 (CH), 130.0 (CH), 128.6 (2CH), 128.3 (CH), 125.6 (2CH), 121.9 (CH), 121.2 (Cq), 119.2 (Cq), 105.6 (Cq), 91.5 (CH), 59.6 (CH_2), 28.2 (CH_3), 24.2 (CH_3), 21.9 (CH_3), 15.3 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{23}H_{24}NO_2$: $[M+H]^+$ 346.1807, Found: 346.1797.

4-ethoxy-4,5-dimethyl-2-(naphthalen-1-yl)-9-(trifluoromethyl)-4*H*-pyrano [3,4-c]quinoline (23va)



Yellow solid. (44% yield, 52 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.42-8.37 (m, 1H), 8.36-8.32 (m, 1H), 8.18 (d, *J* = 8.8 Hz, 1H), 8.10-7.98 (m, 1H), 7.98-7.95 (m, 1H), 7.91 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.66-7.52 (m, 3H), 6.74 (s, 1H), 3.83 (dq, *J* = 9.2, 7.0 Hz, 1H), 3.47 (dq, *J* = 9.2, 7.0 Hz, 1H), 2.99 (s, 3H), 2.10 (s, 3H), 1.31 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 158.8 (Cq), 157.9 (Cq), 148.1 (Cq), 138.1 (Cq), 133.9 (Cq), 132.4 (Cq), 130.9 (Cq), 130.6 (CH), 129.7 (CH), 128.7 (CH), 127.8 (q, *J* = 30.0 Hz, Cq), 127.0 (CH), 126.9 (CH), 126.3 (CH), 125.6 (CH), 125.5 (q, *J* = 271.1 Hz, CF_3), 125.2 (CH), 125.1 (CH), 121.2 (q, *J* = 4.5 Hz, CH), 120.2 (Cq), 119.6 (Cq), 106.0 (Cq), 95.9 (CH), 59.9 (CH_2), 28.3 (CH_3), 24.5 (CH_3), 15.2 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -62.1. **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{27}H_{23}F_3NO_2$: $[M+H]^+$ 450.1681, Found: 450.1675.

4-ethoxy-5-methyl-2,4-diphenyl-4*H*-pyrano[3,4-c]quinoline (23ab)

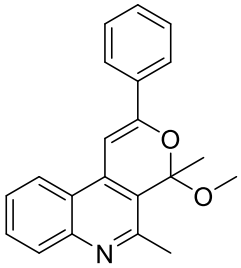


Yellow solid. (42% yield, 47 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.26 (dd, *J* = 8.4, 1.4 Hz, 1H), 8.06 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.89-7.82 (m, 2H), 7.78 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.63 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.56-7.52 (m, 2H), 7.43 (dd, *J* = 5.0, 2.0 Hz, 3H), 7.41-7.32 (m, 3H), 7.06 (s, 1H), 3.73 (dq, *J* = 9.2, 7.0 Hz, 1H), 3.36 (dq, *J* = 9.2, 7.0 Hz, 1H), 2.39 (s, 3H), 1.32 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.2 (Cq), 155.3 (Cq), 147.5 (Cq), 143.7 (Cq), 137.6 (Cq), 133.5 (Cq), 129.98 (CH), 129.93 (CH), 128.9 (CH), 128.6 (3CH), 128.2 (2CH), 126.2 (2CH), 125.9 (CH), 125.7 (2CH), 122.9 (CH), 121.0 (Cq), 117.2 (Cq), 104.9 (Cq), 90.6 (CH), 59.4 (CH_2), 24.7 (CH_3), 15.4 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{27}H_{24}NO_2$: $[M+H]^+$ 394.1807, Found: 394.1805.

11.4.4 Preparation and characterisation of 4*H*-pyrano[3,4-c]quinolines in alternative alcoholic solvents

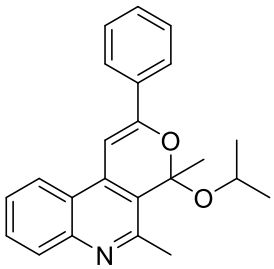
General procedure. A mixture of β-(2-aminophenyl)-α,β-ynone **16a** (0.2 mmol, 1.0 equiv.), β-diketone **20a** (0.4 mmol, 2.0 equiv.), and *p*-TsOH·H_2O (0.2 mmol, 1 equiv.) in alcohol (2 mL) was stirred at 80 °C for 3–5 h. After completion, the mixture was diluted with a saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2 (25 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4. After the removal of the solvent at reduced pressure, the crude product was purified by column chromatography over silica gel using mixture of *n*-hexane–EtOAc from 80:20 to 60:40 v/v to give the title compound **23**.

4-methoxy-4,5-dimethyl-2-phenyl-4*H*-pyrano[3,4-c]quinoline (23aaMe)



Yellow solid. (64% yield, 49 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.19-8.13 (m, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.98-7.91 (m, 2H), 7.74 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.58 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.54-7.47 (m, 3H), 6.99 (s, 1H), 3.33 (s, 3H), 2.91 (s, 3H), 1.93 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 155.6 (Cq), 155.3 (Cq), 147.1 (Cq), 137.7 (Cq), 133.5 (Cq), 130.2 (CH), 129.9 (CH), 128.7 (3CH), 125.9 (CH), 125.6 (2CH), 122.9 (CH), 121.3 (Cq), 118.5 (Cq), 106.1 (Cq), 91.7 (CH), 51.3 (CH_3), 27.8 (CH_3), 24.3 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{21}H_{20}NO_2$: $[M+H]^+$ 318.1494, Found: 318.1494.

4-isopropoxy-4,5-dimethyl-2-phenyl-4*H*-pyrano[3,4-c]quinoline (23aaIPr)



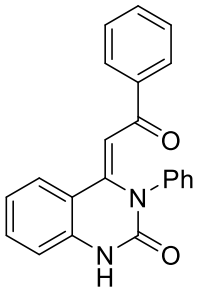
Yellow solid. (45% yield, 58 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.18 (dd, *J* = 8.5, 1.3 Hz, 1H), 8.15-8.11 (m, 1H), 8.00-7.93 (m, 2H), 7.76 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.59 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.55-7.47 (m, 3H), 7.02 (s, 1H), 4.01 (p, *J* = 6.2 Hz, 1H), 2.99 (s, 3H), 2.06 (s, 3H), 1.23 (d, *J* = 6.2 Hz, 3H), 1.08 (d, *J* = 6.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 155.6 (Cq), 146.2 (Cq), 137.4 (Cq), 137.3 (Cq), 133.5 (Cq), 130.2 (CH), 129.8 (CH), 128.7 (2CH), 128.0 (CH), 126.2 (CH), 125.54 (2CH), 122.9 (CH), 121.1 (Cq), 119.6 (Cq), 104.9 (Cq), 90.9 (CH), 67.7 (CH), 29.4 (CH_3), 24.7 (CH_3), 24.3 (CH_3), 23.6 (CH_3). **HRMS** (MALDI-TOF, positive ion): m/z calculated for $C_{23}H_{24}NO_2$: $[M+H]^+$ 346.1807, Found: 346.1807.

11.5 Sequential reactions of β-(2-aminophenyl)-α,β-ynones with isocyanates/isothiocyanates

11.5.1 Preparation and characterisation of 3,4-dihydroquinazolin-2(1H)-ones **35aa-35ha**

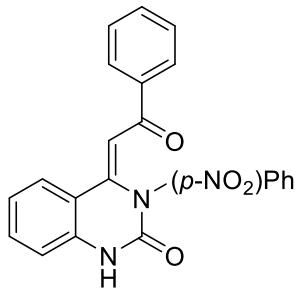
General procedure. Phenyl isocyanate **24** (1.104 mmol, 2.2 equiv.) and Et_3N (0.502 mmol, 1.0 equiv.) were added to a solution of β-(2-aminophenyl)-α,β-ynones **16** (0.502 mmol, 1.0 equiv.) in anhydrous THF (3 mL) at room temperature. The mixture was stirred and purged with N_2, and the temperature was raised to 60°C in 10 minutes. After the completion of the reaction, the mixture was evaporated under reduced pressure. The residue was purified by flash chromatography over silica gel using mixture of *n*-hexane–EtOAc 60:40 v/v to afford 3,4-dihydroquinazolin-2(1H)-one derivatives as a mixture of tautomers **35/35'** when analysed in DMSO-d_6.

(Z)-4-(2-oxo-2-phenylethylidene)-3-phenyl-3,4-dihydroquinazolin-2(1*H*)-one (35aa) + (Z)-2-(2-hydroxy-3-phenylquinazolin-4(3*H*)-ylidene)-1-phenylethan-1-one (35aa′)



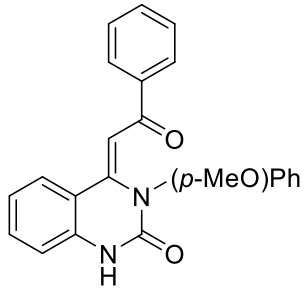
White solid. (69% yield, 122 mg). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 11.14 (br, 1H, NH, major), 10.81 (br, 1H, OH, minor), 7.28 (d, *J* = 8.1 Hz, 1H, major), 8.09 (d, *J* = 7.2 Hz, 1H, minor), 7.61-7.54 (m, 4H, major + minor), 7.50-7.42 (m, 5H, major + minor), 7.38-7.34 (m, 2H, major + minor), 7.20-7.17 (m, 2H, minor), 7.11-7.05 (m, 1H, major + minor), 7.01-6.97 (m, 1H, major + minor), 6.65 (s, 1H, minor), 5.45 (s, 1H, major). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 188.3 (CO, major), 188.2 (CO, minor), 151.6 (Cq, major), 149.3 (Cq, minor), 148.9 (Cq, major), 146.5 (Cq, minor), 140.6 (Cq, minor), 139.9 (Cq, major), 138.3 (Cq, major), 137.9 (Cq, minor), 137.7 (Cq, major), 136.5 (Cq, minor), 133.1 (CH, major), 132.14 (CH, major), 132.10 (CH, minor), 131.6 (CH, minor), 130.1 (2CH, major), 129.9 (CH, major), 129.1 (2CH, major), 128.63 (CH, major), 128.58 (2CH, minor), 128.5 (2CH, major), 128.2 (2CH, minor), 127.8 (2CH, minor), 127.7 (2CH, minor), 127.4 (2CH, major), 126.1 (CH, minor), 124.3 (CH, minor), 122.7 (CH, minor), 121.2 (CH, major), 117.4 (Cq, minor), 114.9 (CH, minor), 114.7 (CH, major), 113.7 (Cq, major), 102.2 (CH, major), 101.3 (CH, minor). **HRMS** (ESI, positive ion): m/z calculated for $C_{22}H_{16}KN_2O_2$: $[M+K]^+$ 379.0849, found: 379.0842.

(4Z)-3-(4-nitrophenyl)-4-(2-oxo-2-phenylethylidene)-3,4-dihydroquinazolin-2(1*H*)-one (35ab) + (2Z)-2-[2-hydroxy-3-(4-nitrophenyl)quinazolin-4(3*H*)-ylidene]-1-phenylethanone (35ab′)



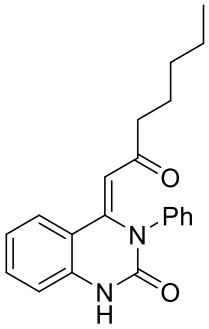
Yellow solid. (90% yield, 67 mg). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 11.17 (br, 1H, OH, minor), 11.04 (br, 1H, NH, major), 8.43-8.40 (m, 2H, minor), 8.23 (dd, *J* = 8.2, 1.2 Hz, 1H, major), 8.09 (dd, *J* = 8.4, 1.2 Hz, 1H, minor), 8.00-7.96 (m, 2H major), 7.81-7.78 (m, 2H, minor), 7.65-7.61 (m, 2H, major + minor), 7.57-7.53 (m, 2H, major), 7.52-7.45 (m, 2H, major + minor), 7.39-7.35 (m, 2H, major + minor), 7.17 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H, major), 7.11-7.09 (m, 1H, major + minor), 6.97 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H, minor), 6.85 (s, 1H, major), 5.35 (s, 1H, minor). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 189.4 (CO, minor), 188.0 (CO, major), 150.1 (Cq, major), 148.8 (Cq, major), 148.7 (Cq, minor), 147.3 (Cq, minor), 146.71 (Cq, minor), 146.68 (Cq, major), 144.8 (Cq, major), 144.3 (Cq, minor), 139.4 (Cq, minor), 137.9 (Cq, major), 137.5 (Cq, minor), 136.3 (Cq, major), 133.1 (CH, minor), 132.6 (CH, major), 132.5 (CH, minor), 132.1 (CH, major), 131.1 (2CH, minor), 129.6 (2CH, major), 128.6 (2CH, minor), 128.4 (CH, major), 127.83 (2CH, major), 127.76 (CH, major), 125.4 (CH, major), 125.1 (CH, minor), 124.5 (2CH, minor), 123.08 (2CH, major), 123.05 (2CH, minor), 118.1 (CH, minor), 117.4 (Cq, major), 115.1 (CH, major), 115.0 (CH, minor), 113.8 (Cq, minor), 103.5 (CH, minor), 102.0 (CH, major). **HRMS** (ESI, positive ion): m/z calculated for $C_{22}H_{15}KN_3O_4$: $[M+K]^+$ 424.0700, found: 424.0700.

(Z)-3-(4-methoxyphenyl)-4-(2-oxo-2-phenylethylidene)-3,4-dihydroquinazolin-2(1*H*)-one (35ac) + (Z)-2-[2-hydroxy-3-(4-methoxyphenyl)quinazolin-4(3*H*)-ylidene]-1-phenylethanone (35ac′)



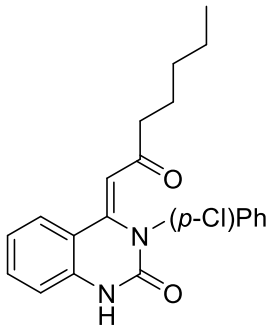
Yellow solid. (47% yield, 64 mg). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 11.06 (br, 1H, NH, major), 10.72 (br, 1H, OH, minor), 8.35 (s, 1H, minor), 8.25 (dd, *J* = 8.3 Hz, 1.3 Hz, 1H, major), 8.05 (d, *J* = 7.7 Hz, 1H, minor), 7.62-7.58 (m, 2H, major + minor), 7.50-7.44 (m, 2H, major + minor), 7.40-7.32 (m, 4H, major + minor), 7.12-7.08 (m, 3H, major), 6.97 (ddd, *J* = 8.3 Hz, 7.2 Hz, 1.3 Hz, 1H, major), 6.85-6.83 (m, 2H, minor), 6.60-6.58 (m, 2H, minor), 6.57 (s, 1H, minor), 5.53 (s, 1H, major), 3.80 (s, 3H, major), 3.70 (s, 3H, minor). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 188.7 (CO, minor), 188.6 (CO, major), 159.0 (Cq, major), 157.2 (Cq, minor), 154.3 (Cq, minor), 152.9 (Cq, minor), 151.8 (Cq, major), 149.5 (Cq, minor), 149.0 (Cq, major), 146.1 (Cq, minor), 139.9 (Cq, major), 137.6 (Cq, major), 133.0 (CH, major), 132.1 (CH, major), 131.5 (CH, minor), 130.7 (Cq, major), 130.1 (2CH, major), 129.81 (CH, major), 129.80 (CH, minor), 128.5 (2CH, major), 128.1 (2CH, minor), 127.9 (2CH, minor), 127.4 (2CH, major), 124.2 (CH, minor), 122.5 (CH, minor), 121.1 (CH, major), 119.9 (2CH, minor), 117.3 (Cq, minor), 115.2 (2CH, major), 114.8 (CH, minor), 114.7 (CH, major), 114.0 (CH, minor), 113.9 (2CH, minor), 113.7 (Cq, major), 102.2 (CH, major), 101.0 (CH, minor), 55.4 (OCH_3, major), 55.1 (OCH_3, minor). **HRMS** (ESI, positive ion): m/z calculated for $C_{23}H_{18}KN_2O_3$: $[M+K]^+$ 409.0954, found: 409.0951.

(4Z)-4-(2-oxoheptylidene)-3-phenyl-3,4-dihydroquinazolin-2(1*H*)- one (35ba) + (1Z)-1-(2-hydroxy-3-phenylquinazolin-4(3*H*)-ylidene) heptan-2-one (35ba′)



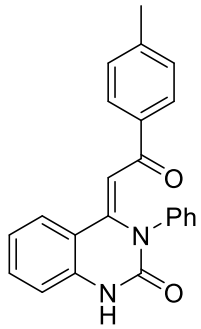
Yellow solid. (96% yield, 148 mg). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 11.03 (br, 1H, NH, major), 10.73 (br, 1H, OH, minor), 8.64 (s, 2H, minor), 8.42-8.40 (m, 1H, major), 7.56 (t, *J* = 7.6 Hz, 2H, major), 7.50-7.39 (m, 2H, major + minor), 7.32-7.25 (m, 2H, major + minor), 7.08-7.01 (m, 1H, major + minor), 6.95 (tq, *J* = 7.4 Hz, 1.2 Hz, 1H, major), 6.20 (s, 1H, minor), 4.97 (s, 1H, major), 2.13 (t, *J* = 7.2 Hz, 2H, major), 2.03 (t, *J* = 7.1 Hz, 2H, minor), 1.36-1.29 (m, 2H, major + minor), 1.18-1.02 (m, 4H, major + minor), 0.78 (t, *J* = 7.0 Hz, 3H, major + minor). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 197.1 (CO, major), 196.7 (CO, minor), 149.7 (Cq, major), 149.4 (Cq, minor), 149.0 (Cq, major), 144.5 (Cq, minor), 141.0 (Cq, major), 139.7 (CH, major), 138.2 (Cq, major), 137.4 (Cq, major), 136.5 (Cq, minor), 132.9 (CH, major), 131.4 (Cq, minor), 129.93 (CH, major), 129.89 (2CH, major), 129.1 (2CH, major), 128.5 (CH, major), 128.4 (2CH, minor), 127.6 (2CH, minor), 126.0 (CH, minor), 123.7 (CH, minor), 122.5 (CH, minor), 121.0 (CH, major), 114.8 (CH, minor), 114.5 (CH, major), 113.9 (Cq, major), 105.2 (CH, major), 104.4 (CH, minor), 44.4 (CH_2, major), 42.5 (CH_2, minor), 30.62 (CH_2, major), 30.55 (CH_2, minor), 24.3 (CH_2, major), 23.0 (CH_2, minor), 21.9 (CH_2, minor), 21.8 (CH_2, major), 13.73 (CH_3, minor), 13.71 (CH_3, major). **HRMS** (ESI, positive ion): m/z calculated for $C_{21}H_{22}KN_2O_2$: $[M+K]^+$ 373.1318, found: 373.1813.

(4Z)-3-(4-chlorophenyl)-4-(2-oxoheptylidene)-3,4-dihydroquinazolin-2(1*H*)-one (35bd) + (1Z)-1-[3-(4-chlorophenyl)-2-hydroxyquinazolin-4(3*H*)-ylidene]heptan-2-one (35bd′)



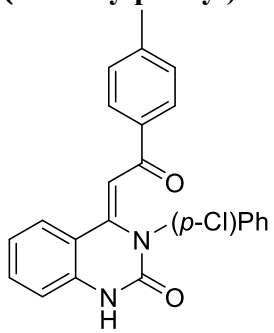
White solid. (82% yield, 68 mg). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 11.01 (br, 1H, NH, major), 10.78 (br, 1H, OH, minor), 8.36 (dd, *J* = 8.2 Hz, 1.1 Hz, 1H, major), 7.93 (dd, *J* = 8.3 Hz, 1.5 Hz, 1H, minor), 7.89 (dd, *J* = 8.1 Hz, 0.8 Hz, 1H, minor), 7.63-7.59 (m, 2H, major), 7.55-7.51 (m, 2H, minor), 7.48 (ddd, *J* = 8.2 Hz, 7.1 Hz, 1.4 Hz, 1H, major), 7.42 (td, *J* = 7.6 Hz, 1.1 Hz, 1H, minor), 7.37-7.34 (m, 2H, major), 7.31-7.27 (m, 2H, minor), 7.26-7.20 (m, 1H, major), 7.12-7.08 (m, 1H, minor), 7.07-7.05 (m, 1H, major), 7.04-7.01 (m, 1H, minor), 6.24 (s, 1H, minor), 4.96 (s, 1H, major), 2.18 (t, *J* = 7.3 Hz, 2H, major), 2.10 (t, *J* = 7.1 Hz, 2H, minor), 1.38-1.30 (m, 2H, major), 1.17-1.06 (m, 4H major + minor, 2H minor), 0.79 (t, *J* = 7.3 Hz, 3H, minor), 0.78 (t, *J* = 7.1 Hz, 3H, major). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 197.9 (CO, major), 197.1 (CO, minor), 150.5 (Cq, minor), 149.8 (Cq, major), 149.7 (Cq, minor), 149.5 (Cq, major), 140.3 (Cq, minor), 137.8 (Cq, major), 137.6 (Cq, major), 136.9 (Cq, minor), 135.1 (Cq, minor), 133.6 (Cq, major), 133.5 (CH, major), 132.1 (CH, minor), 131.6 (2CH, major), 131.5 (2CH, minor), 130.6 (CH, major), 130.5 (2CH, major), 130.3 (CH, major), 129.3 (2CH, minor), 128.0 (CH, minor), 124.3 (CH, minor), 123.2 (CH, minor), 121.6 (CH, major), 117.8 (Cq, minor), 114.3 (Cq, major), 105.9 (CH, major), 104.5 (CH, minor), 44.9 (CH_2, major), 43.1 (CH_2, minor), 31.1 (CH_2, major), 31.0 (CH_2, minor), 24.7 (CH_2, major), 23.5 (CH_2, minor), 22.4 (CH_2, minor), 22.3 (CH_2, major), 14.19 (CH_3, minor), 14.16 (CH_3, major). **HRMS** (ESI, positive ion): m/z calculated for $C_{21}H_{22}ClN_2O_2$: $[M+H]^+$ 369.1370, found: 369.1371.

(Z)-4-[2-(4-methylphenyl)-2-oxoethylidene]-3-phenyl-3,4-dihydroquinazolin-2(1*H*)-one (35ca) + (2Z)-2-(2-hydroxy-3-phenylquinazolin-4(3*H*)-ylidene)-1-(4-methylphenyl) ethanone (35ca′)



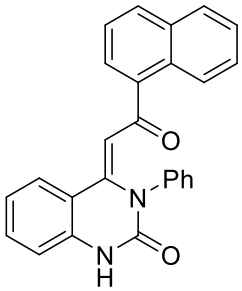
Brown solid. (70% yield, 92 mg). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 11.11 (br, 1H, NH, major), 10.79 (br, 1H, OH, minor), 8.26 (d, *J* = 8.1 Hz, 1H, major), 8.07 (d, *J* = 6.3 Hz, 1H, minor), 7.60-7.57 (m, 1H, major + minor), 7.51-7.41(m, 5H, major + minor), 7.28-7.24 (m, 2H, minor), 7.17-7.15 (m, 2H, major), 7.10-7.06 (m, 3H, major + minor), 7.00-6.96 (m, 1H, major + minor), 6.62 (s, 1H, minor), 5.43 (s, 1H, major), 2.29 (s, 3H, minor), 2.27 (s, 3H, major). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 188.2 (CO, major), 188.0 (CO, minor), 150.9 (Cq, major), 149.3 (Cq, minor), 148.9 (Cq, major), 146.0 (Cq, minor), 142.44 (Cq, major), 142.40 (Cq, minor), 140.5 (Cq, minor), 138.4 (Cq, major), 137.6 (Cq, major), 137.3 (Cq, major), 136.4 (Cq, minor), 135.5 (Cq, minor), 133.0 (CH, major), 131.5 (2CH, minor), 130.0 (2CH, major), 129.7 (CH, major), 129.1 (2CH, major), 129.0 (2CH, major), 128.73 (CH, minor), 128.70 (2CH, minor), 128.6 (CH, major), 128.0 (2CH, minor), 127.6 (2CH, minor), 127.5 (2CH, major), 126.1 (CH, minor), 124.2 (CH, minor), 122.6 (CH, minor), 121.2 (CH, major), 117.5 (Cq, minor), 114.8 (CH, minor), 114.7 (CH, major), 113.8 (Cq, major), 102.5 (CH, major), 101.6 (CH, minor), 21.1 (CH_3, minor), 21.0 (CH_3, major). **HRMS** (ESI, positive ion): m/z calculated for $C_{23}H_{19}N_2O_2$: $[M+H]^+$ 355.1447, found: 355.1450.

(4Z)-3-(4-chlorophenyl)-4-[2-(4-methylphenyl)-2-oxoethylidene]-3,4-dihydroquinazolin-2(1*H*)-one (35cd) + (2Z)-2-[3-(4-chlorophenyl)-2-hydroxyquinazolin-4(3*H*)-ylidene]-1-(4-methylphenyl)ethenone (35cd′)



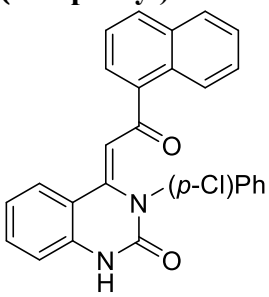
Yellow solid. (81% yield, 120 mg). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 11.15 (br, 1H, NH, major), 10.92 (br, 1H, OH, minor), 8.23 (d, *J* = 8.2 Hz, 1H, major), 8.16 (d, *J* = 7.9 Hz, 1H, minor), 7.71-7.69 (m, 2H, major), 7.62-7.60 (m, 2H, minor), 7.58-7.50 (m, 4H, major + minor), 7.28-7.25 (m, 3H, major + minor), 7.21-7.17 (m, 1H, major), 7.16-7.12 (m, 2H, minor), 7.03 (t, *J* = 7.8 Hz, 1H, major), 6.74 (s, 1H, minor), 5.45 (s, 1H, major), 2.38 (s, 3H, minor), 2.36 (s, 3H, major). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 189.1 (CO, major), 188.4 (CO, minor), 150.8 (Cq, major), 149.6 (Cq, minor), 149.3 (Cq, major), 146.6 (Cq, minor), 143.13 (Cq, major), 143.09 (Cq, minor), 139.9 (Cq, minor), 137.9 (Cq, major), 137.7 (Cq, major), 137.6 (Cq, major), 136.84 (Cq, minor), 136.75 (Cq, minor), 136.0 (Cq, minor), 133.7 (Cq, major), 133.4 (2CH, minor), 132.2 (CH, minor), 131.7 (2CH, major), 130.8 (CH, major), 130.6 (2CH, major), 130.1 (2CH, minor), 129.6 (2CH, major), 129.31 (CH, major), 129.29 (CH, minor), 128.5 (CH, major), 128.2 (2CH, major), 128.1 (2CH, minor), 124.8 (CH, minor), 123.2 (CH, minor), 121.8 (CH, major), 117.8 (Cq, minor), 115.2 (2CH, minor), 114.3 (Cq, major), 103.4 (CH, major), 101.9 (CH, minor), 21.6 (CH_3, minor), 21.5 (CH_3, major). **HRMS** (ESI, positive ion): m/z calculated for $C_{23}H_{18}ClN_2O_2$: $[M+H]^+$ 389.1057, found: 389.1057.

(4Z)-4-[2-(1-naphthyl)-2-oxoethylidene]-3-phenyl-3,4-dihydroquinazolin-2(1*H*)-one (35da) + (2Z)-2-(2-hydroxy-3-phenylquinazolin-4(3*H*)-ylidene)-1-(1-naphthyl)ethenone (35da′)



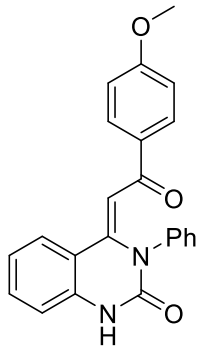
Yellow solid. (75% yield, 98 mg). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 11.19 (br, 1H, NH, major), 10.95 (br, 1H, OH, minor), 8.41 (dd, *J* = 8.3 Hz, 1.0 Hz, 1H, major), 8.30-8.28 (m, 1H, major), 8.05-8.02 (m, 1H, minor), 8.00-7.98 (m, 1H, minor), 7.95-7.01 (m, 2H, major), 7.90-7.85 (m, 2H, minor), 7.79-7.77 (m, 1H, minor), 7.56-7.46 (m, 6H, major + minor), 7.42-7.32 (m, 4H, major + minor), 7.15-7.09 (m, 1H, major + minor), 7.02-6.98 (m, 1H, minor), 6.91 (ddd, *J* = 8.3 Hz, 7.2 Hz, 1.2 Hz, 1H, major), 6.66 (s, 1H, minor), 5.34 (s, 1H, major). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 191.9 (CO, major), 190.0 (CO, minor), 152.3 (Cq, major), 149.8 (Cq, minor), 149.4 (Cq, major), 147.9 (Cq, minor), 141.3 (Cq, minor), 139.8 (Cq, major), 138.6 (Cq, major), 138.2 (Cq, major), 137.1 (Cq, minor), 133.78 (CH, major), 133.75 (CH, major), 132.4 (Cq, minor), 131.9 (CH, minor), 131.6 (CH, major), 130.6 (CH, major), 130.4 (2CH, major), 130.1 (Cq, major), 130.0 (Cq, minor), 129.5 (2CH, major), 129.0 (CH, major), 128.9 (CH, minor), 128.8 (2CH, minor), 128.6 (CH, minor), 128.5 (CH, minor), 128.1 (CH, minor), 127.6 (CH, major), 127.4 (CH, minor), 126.9 (CH, major), 126.74 (CH, minor), 126.67 (CH, major), 126.5 (CH, minor), 125.9 (Cq, minor), 125.6 (CH, major), 125.24 (CH, major), 125.17 (CH, minor), 124.8 (CH, minor), 123.2 (CH, minor), 121.5 (CH, major), 115.4 (Cq, minor), 115.1 (CH, major), 114.2 (Cq, major), 106.5 (CH, major), 104.2 (CH, minor). **HRMS** (ESI, positive ion): m/z calculated for $C_{26}H_{19}N_2O_2$: $[M+H]^+$ 391.1447, found: 391.1447.

(4Z)-3-(4-chlorophenyl)-4-[2-(1-naphthyl)-2-oxoethylidene]-3,4-dihydroquinazolin-2(1*H*)-one (35dd) + (2Z)-2-[3-(4-chlorophenyl)-2-hydroxyquinazolin-4(3*H*)-ylidene]-1-(1-naphthyl)ethanone (35dd′)



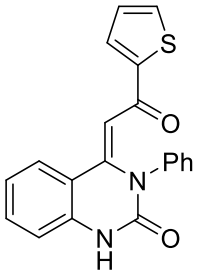
Yellow solid. (90% yield, 141 mg). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 11.26 (br, 1H, NH, major), 11.09 (br, 1H, OH, minor), 8.43 (d, *J* = 8.0 Hz, 1H, major), 8.37-8.34 (m, 1H, major), 8.12-8.06 (m, 1H, major + minor), 8.03-7.96 (m, 2H, major + minor), 7.90-7.87 (m, 1H, major + minor), 7.68-7.36 (m, 7H, major + minor), 7.40-7.36 (m, 2H, minor), 7.24-7.22 (m, 2H, minor), 7.20-7.14 (m, 1H, major + minor), 6.96 (t, *J* = 7.2 Hz, 1H, major), 6.76 (s, 1H, minor), 5.39 (s, 1H, major). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 191.5 (CO, major), 189.7 (CO, minor), 151.3 (Cq, major), 149.1 (Cq, minor), 148.8 (Cq, major), 147.3 (Cq, major), 139.7 (Cq, minor), 139.1 (Cq, major), 137.6 (Cq, major), 137.0 (Cq, major), 136.7 (Cq, minor), 136.6 (Cq, minor), 136.0 (Cq, minor), 133.29 (Cq, minor), 133.27 (CH, major), 133.1 (CH, minor), 132.1 (CH, minor), 131.6 (CH, minor), 131.3 (CH, major), 131.1 (2CH, major), 130.7 (Cq, major), 130.1 (2CH, minor), 130.03 (CH, major), 129.97 (CH, major), 129.6 (CH, minor), 129.4 (Cq, minor), 128.4 (CH, major), 128.1 (2CH, minor), 128.0 (CH, minor), 127.6 (CH, major), 127.2 (2CH, major), 126.9 (CH, minor), 126.6 (CH, major), 126.2 (CH, minor), 126.1 (Cq, major), 125.2 (CH, minor), 125.1 (CH, major), 124.8 (CH, major), 124.7 (CH, minor), 124.4 (CH, minor), 122.8 (Cq, major), 121.1 (CH, major), 117.2 (Cq, minor), 115.0 (CH, minor), 114.7 (CH, major), 113.7 (Cq, minor), 106.1 (CH, major), 103.5 (CH, minor). **HRMS** (ESI, positive ion): m/z calculated for $C_{26}H_{17}ClKN_2O_2$: $[M+K]^+$ 463.0616, found: 463.0611.

(4Z)-4-[2-(4-methoxyphenyl)-2-oxoethylidene]-3-phenyl-3,4-dihydroquinazolin-2(1*H*)-one (35ea) + (2Z)-2-(2-hydroxy-3-phenylquinazolin-4(3*H*)-ylidene)-1-(4-methoxyphenyl)ethenone (35ea′)



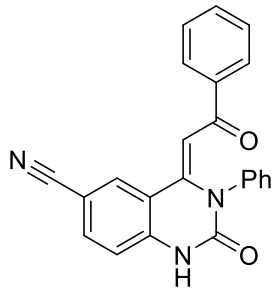
Yellow solid. (87% yield, 55 mg). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 11.02 (br, 1H, NH, major), 10.72 (br, 1H, OH, minor), 8.15 (dd, *J* = 8.3 Hz, 1.1 Hz, 1H, major), 8.06 (dd, *J* = 8.3 Hz, 0.9 Hz, 1H, minor), 7.61-7.56 (m, 2H), 7.52-7.40 (m, 6H), 7.16-7.06 (m, 3H), 6.99-6.87 (m, 2H), 6.59 (s, 1H, minor), 5.40 (s, 1H, major), 3.78 (s, 3H, CH_3, minor), 3.76 (s, 3H, CH_3, major). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 187.7 (CO, major), 187.5 (CO, minor), 162.51 (Cq, major), 162.45 (Cq, minor), 153.5 (Cq, minor), 149.9 (Cq, major), 149.4 (Cq, minor), 149.0 (Cq, major), 148.9 (Cq, minor), 139.7 (Cq, major), 138.4 (Cq, major), 138.1 (Cq, minor), 137.5 (Cq, major), 136.4 (Cq, minor), 134.8 (Cq, major), 132.7 (CH, minor), 130.1 (CH, minor), 130.0 (CH, major), 129.7 (CH, major), 129.6 (CH, minor), 129.1 (CH, major), 128.9 (2CH, major), 128.8 (2 CH, major), 128.7 (CH, major), 128.6 (2CH, minor), 128.5 (2CH, minor), 121.2 (CH, major), 120.9 (CH, minor), 114.7 (CH, minor), 113.9 (Cq, major), 113.7 (CH, major), 113.3 (Cq, major), 102.8 (CH, major), 102.0 (CH, minor), 55.4 (OCH_3, major), 55.3 (OCH_3, minor). **HRMS** (ESI, positive ion): m/z calculated for $C_{23}H_{18}KN_2O_3$: $[M+K]^+$ 409.0954, found: 409.0956.

(4Z)-4-[2-oxo-2-(2-thienyl)ethylidene]-3-phenyl-3,4-dihydroquinazolin-2(1*H*)-one (35ga) + (2Z)-2-(2-hydroxy-3-phenylquinazolin4(3*H*)-ylidene)-1-(2-thienyl)ethanone (35ga′)



Orange solid. (59% yield, 52 mg). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 11.28 (br, 1H, NH, major), 10.81 (br, 1H, OH, minor), 8.70 (s, 1H, minor), 8.67-8.65 (m, 1H, major), 8.20-8.18 (m, 1H, minor), 7.86-7.84 (m, 1H, major), 7.83-7.82 (m, 1H, minor), 7.70-7.66 (m, 1H, major + minor), 7.61-7.56 (m, 2H, major + minor), 7.51-7.47 (m, 2H, major + minor), 7.35-7.30 (m, 1H, major + minor), 7.18-7.14 (m, 1H, major), 7.12-7.11 (1H, major + minor), 7.10-7.09 (m, 1H, major), 7.01 (tt, *J* = 7.4 Hz, 1.2 Hz, 1H, major), 6.74 (s, 1H, minor), 5.59 (s, 1H, major). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 180.7 (CO, minor), 180.0 (CO, major), 153.0 (Cq, minor), 152.5 (Cq, major), 149.8 (Cq, minor), 149.3 (Cq, major), 148.3 (Cq, major), 147.0 (Cq, minor), 141.1 (Cq, minor), 140.2 (CH, minor), 138.8 (Cq, major), 138.3 (Cq, major), 137.0 (Cq, minor), 134.0 (CH, minor), 133.9 (CH, major), 133.8 (CH, major), 132.3 (2CH, minor), 130.7 (CH, major), 130.6 (2CH, major), 130.2 (CH, major), 129.6 (2CH, major), 129.5 (CH, minor), 129.2 (CH, major), 129.0 (2CH, minor), 128.91 (CH, minor), 128.86 (CH, major), 123.2 (Cq, minor), 122.3 (Cq, major), 121.7 (CH, major), 121.5 (CH, minor), 118.6 (CH, major), 118.2 (CH, minor), 115.4 (CH, minor), 115.2 (CH, major), 114.1 (CH, minor), 101.5 (CH, major), 101.0 (CH, minor). **HRMS** (ESI, positive ion): m/z calculated for $C_{20}H_{15}N_2O_2S$: $[M+H]^+$ 347.0854, found: 347.0856.

(4Z)-2-oxo-4-(2-oxo-2-phenylethylidene)-3-phenyl-1,2,3,4-tetrahydroquinazoline-6-carbonitrile (35ha) + (4Z)-2-hydroxy-4-(2-oxo2-phenylethylidene)-3-phenyl-3,4-dihydroquinazoline-6-carbonitrile (35ha′)

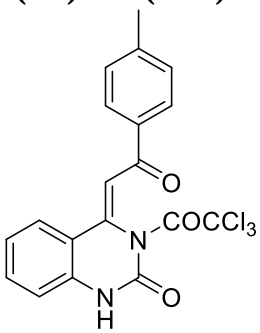


Yellow solid. (72% yield, 86 mg). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 11.56 (br, 1H, NH, major), 10.14 (br, 1H, OH, minor), 8.92 (d, *J* = 1.8 Hz, 1H, major), 8.69 (d, *J* = 1.6 Hz, 1H, minor), 7.89 (dd, *J* = 8.5 Hz, 1.8 Hz, 1H, major), 7.82 (dd, *J* = 8.4 Hz, 1.7 Hz, 1H, minor), 7.64-7.58 (m, 2H, major + minor), 7.54-7.42 (m, 5H, major + minor), 7.39-7.35 (m, 2H, major), 7.34-7.31 (m, 1H, minor), 7.21 (d, *J* = 8.5 Hz, 1H, major), 7.18-7.14 (m, 1H, major), 7.08-7.05 (m, 2H, minor), 6.99-6.95 (m, 1H, minor), 6.81 (s, 1H, minor), 5.61 (s, 1H, major). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 188.8 (CO, minor), 188.2 (CO, major), 150.1 (Cq, major), 150.0 (Cq, minor), 149.1 (Cq, minor), 148.6 (Cq, major), 143.9 (Cq, minor), 141.5 (Cq, major), 140.2 (Cq, minor), 140.0 (Cq, minor), 139.8 (Cq, major), 137.9 (Cq, major), 137.4 (Cq, minor), 135.9 (CH, major), 134.8 (CH, major), 134.6 (CH, minor), 132.6 (CH, minor), 132.5 (CH, major), 130.3 (2CH, major), 129.3 (CH, minor), 129.0 (2CH + CH, major), 128.9 (CH, minor), 128.62 (2CH, major), 128.57 (2CH, minor), 128.2 (2CH, minor), 128.1 (2CH, minor), 127.9 (2CH, minor), 127.5 (2CH, major), 118.7 (Cq, major), 118.5 (Cq, minor), 116.0 (CH, major), 115.9 (CH, minor), 114.2 (Cq, major), 105.0 (Cq, minor), 104.1 (CH, minor), 103.9 (CH, major), 103.3 (Cq, major). **HRMS** (ESI, positive ion): m/z calculated for $C_{23}H_{16}N_3O_2$: $[M+H]^+$ 366.1243, found: 366.1238.

11.5.2 Preparation and characterisation of **35ce** and **35c**

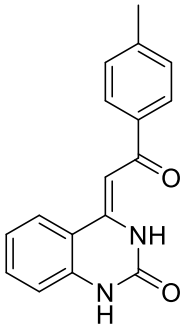
General procedure. Trichloroacetyl isocyanate **24e** (0.1 mL, 0.84 mmol, 2.2 equiv.) and Et_3N (0.054 mL, 0.38 mmol, 1.0 equiv.) were added to a solution of 3-(2-aminophenyl)-1-(p-tolyl)prop-2-yn-1-one **16c** (0.09 g, 0.38 mmol, 1.0 equiv.) in anhydrous THF (3 mL) at room temperature. The mixture was stirred and purged with N_2, and the temperature was raised to 60°C in 10 minutes. After the completion of the reaction, the mixture was evaporated under reduced pressure. The residue was purified by flash chromatography over silica gel, using *n*-hexane–EtOAc 60:40 v/v as eluting mixture, to afford both (4Z)-4-[2-(4-methylphenyl)-2-oxoethylidene]-3-(trichloroacetyl)-3,4-dihydroquinazolin-2(1*H*)-one **35ce** and (4Z)-4-[2-(4-methylphenyl)-2-oxoethylidene]-3,4-dihydroquinazolin-2(1*H*)-one **35c**.

(4Z)-4-[2-(4-methylphenyl)-2-oxoethylidene]-3-(trichloroacetyl)-3,4-dihydroquinazolin-2(1*H*)-one (35ce)



White solid. (24% yield, 40 mg). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 11.03 (br, 1H), 7.87 (dd, *J* = 7.9 Hz, 1.1 Hz, 1H), 7.61 (s, 1H), 7.55 (ddd, *J* = 8.2 Hz, 7.1 Hz, 1.6 Hz, 1H), 7.38-7.36 (m, 2H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.14-7.12 (m, 2H), 2.32 (s, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 196.8 (CO), 175.5 (CO), 156.4 (Cq), 140.4 (Cq), 140.0 (Cq), 138.3 (Cq), 132.6 (CH), 130.2 (Cq), 128.48 (2CH + CH), 128.46 (2CH), 125.9 (CH), 124.0 (Cq), 122.9 (CH), 116.7 (CH), 100.9 (Cq), 21.5 (CH_3). **HRMS** (ESI, positive ion): m/z calculated for $C_{17}H_{14}KN_2O_2$: $[M-COCCl_3+H+K]^+$ 317.0692, found: 317.0695.

(4Z)-4-[2-(4-methylphenyl)-2-oxoethylidene]-3,4-dihydroquinazolin-2(1*H*)-one (35c)

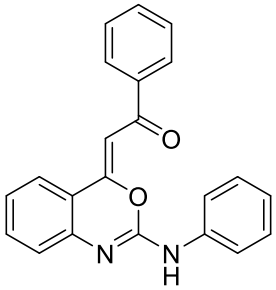


Yellow solid. (22% yield, 23 mg). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 13.21 (s, 1H, NH), 11.16 (s, 1H, NH), 8.27 (d, *J* = 7.8 Hz, 1H), 8.03-8.01 (m, 2H), 7.56 (d, *J* = 7.2 Hz, 1H), 7.30-7.28 (m, 2H), 7.17 (t, *J* = 7.7 Hz, 1H), 7.13 (d, *J* = 8.1 Hz, 1H), 6.92 (s, 1H), 2.37 (s, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 189.1 (CO), 151.8 (Cq), 147.5 (Cq), 142.1 (Cq), 139.3 (Cq), 136.2 (Cq), 133.8 (CH), 128.9 (2CH), 127.6 (2CH), 125.1 (CH), 122.7 (CH), 115.8 (CH), 112.8 (Cq), 87.5 (CH), 21.1 (CH_3). **HRMS** (ESI, positive ion): m/z calculated for $C_{17}H_{14}N_2NaO_2$: $[M+Na]^+$ 301.0953, found: 301.0949.

11.5.3 Preparation and characterisation of benzoxazines **36aa** and **36da**

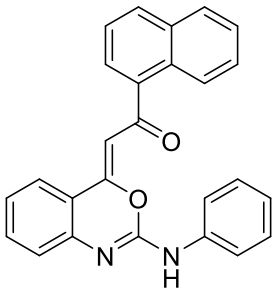
General procedure. Phenyl isocyanate **24a** (0.754 mmol, 2.2 equiv.), Et_3N (0.343 mmol, 1.0 equiv.) and $AgNO_3$ (0.0343 mmol, 10 mol%) were added to a solution of β-(2-aminophenyl)-α,β-ynones **16** (0.343 mmol, 1.0 equiv.) previously dissolved in anhydrous THF (3 mL) at room temperature. The mixture was stirred and purged with N_2, and the temperature was raised to 60 °C in 10 minutes. The formation of a suspension was observed. After the completion of the reaction, the suspension of the crude mixture in CH_2Cl_2 was filtered over paper and the mixture was evaporated under reduced pressure. The residue was purified by flash chromatography over silica gel with a mixture of *n*-hexane–EtOAc 80:20 v/v to afford the O-cyclisation products **36aa** and **36da** (the latter as mixture of tautomers in DMSO-d_6).

(2Z)-2-(2-anilino-4*H*-3,1-benzoxazin-4-ylidene)-1-phenylethanone (36aa)



Yellow solid. (57% yield, 60 mg). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 10.04 (br, 1H), 8.16-8.13 (m, 1H), 8.11-8.09 (m, 2H), 7.86-7.84 (m, 2H), 7.61-7.57 (m, 1H), 7.54-7.50 (m, 3H), 7.35-7.31 (m, 2H), 7.20-7.16 (m, 2H), 7.11 (s, 1H), 7.04 (tt, *J* = 7.4 Hz, 1.1 Hz, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 186.1 (CO), 156.8 (Cq), 148.2 (Cq), 143.4 (Cq), 139.3 (Cq), 138.3 (Cq), 133.8 (CH), 132.2 (CH), 128.58 (2CH), 128.55 (2CH), 127.8 (2CH), 124.5 (CH), 124.4 (CH + CH), 122.8 (CH), 119.9 (2CH), 116.0 (Cq), 94.3 (CH). **^{1}H NMR** (400 MHz, acetone-d_6): δ 10.19 (br, 1H), 8.11-8.08 (m, 2H), 8.05 (dd, *J* = 8.0 Hz, 1.3 Hz, 1H), 7.90-7.87 (m, 2H), 7.60-7.49 (m, 4H), 7.36-7.32 (m, 2H), 7.24 (ddd, *J* = 8.1 Hz, 1.2 Hz, 0.5 Hz, 1H), 7.19 (ddd, *J* = 8.2 Hz, 7.1 Hz, 1.3 Hz, 1H), 7.09 (s, 1H), 7.05 (tt, *J* = 7.4 Hz, 1.1 Hz, 1H). **^{13}C NMR** (101 MHz, acetone-d_6): δ 187.7 (CO), 158.8 (Cq), 149.1 (Cq), 144.9 (Cq), 140.9 (Cq), 139.6 (Cq), 134.7 (CH), 132.9 (CH), 129.5 (2CH), 129.3 (2CH), 128.7 (2CH), 125.8 (CH), 125.3 (CH), 125.0 (CH), 123.7 (CH), 120.2 (2CH), 117.0 (Cq), 94.5 (CH). **HRMS** (ESI, positive ion): m/z calculated for $C_{22}H_{16}KN_2O_2$: $[M+K]^+$ 379.0849, found: 379.0853.

(2Z)-2-(2-anilino-4*H*-3,1-benzoxazin-4-ylidene)-1-(1-naphthyl) ethenone (36da) + (2Z)-1-(1-naphthyl)-2-[(2E)-2-(phenylimino)-1,2-dihydro-4*H*-3,1-benzoxazin-4-ylidene]ethenone (36da′)

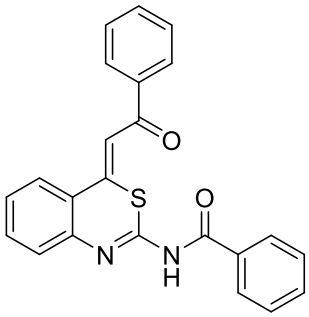


Orange solid. (67% yield, 55 mg). **^{1}H NMR** (400 MHz, acetone-d_6): δ 9.49 (bs, 1H, minor), 9.15 (bs, 1H, major), 8.51-8.49 (m, 2H, minor), 8.08-8.04 (m, 2H, major), 8.00-7.98 (m, 2H, minor), 7.93-7.91 (m, 2H, major), 7.61-7.52 (m, 4H, major + minor), 7.47-7.45 (m, 2H, minor), 7.37-7.33 (m, 2H, major), 7.30-7.24 (m, 4H, major + minor), 7.18-7.14 (m, 1H, major + minor), 7.09-7.05 (m, 1H, major + minor), 6.98-6.95 (m, 1H, major + minor), 6.81 (s, 1H, major). **^{13}C NMR** (101 MHz, acetone-d_6): δ 191.2 (CO, major), 191.0 (CO, minor), 157.8 (Cq, major), 154.5 (Cq, minor), 153.3 (Cq, minor), 149.0 (Cq, major), 144.7 (Cq, minor), 140.9 (Cq, major), 140.6 (Cq, minor), 139.4 (Cq, major), 139.0 (Cq, minor), 136.2 (Cq, major), 135.9 (Cq, minor), 134.8 (Cq, major), 134.6 (CH, major), 134.5 (Cq, major), 132.7 (Cq, minor), 131.7 (CH, major), 131.1 (CH, minor), 130.7 (CH, minor), 129.53 (2CH, minor), 129.49 (2CH, major), 129.48 (CH, major), 129.3 (CH, major), 127.8 (CH, minor), 127.2 (CH, major), 127.1 (CH, major + minor), 126.5 (CH, major), 125.9 (CH, major + minor), 125.8 (CH, minor), 125.5 (CH, major + minor), 124.8 (CH, major + minor), 124.7 (CH, minor), 123.8 (CH, major), 123.3 (Cq, major), 122.88 (CH, major + minor), 122.86 (CH, minor), 121.6 (CH, minor), 120.3 (2CH, minor), 119.6 (Cq, minor), 119.4 (CH, major), 119.3 (CH, minor), 99.3 (CH, major). **HRMS** (ESI, positive ion): m/z calculated for $C_{26}H_{18}KN_2O_2$: $[M+K]^+$ 429.1005, found: 429.1002.

11.5.4 Preparation and characterisation of benzo[*d*][1,3]thiazine **37aa** and **37la**

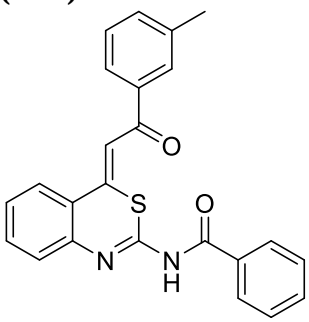
General procedure. Benzoyl isothiocyanate **29a** (0.858 mmol, 2.2 equiv.) and K_2CO_3 (0.858 mmol, 2.2 equiv.) were added to a solution of β-(2-aminophenyl)-α,β-ynones **16** (0.390 mmol, 1.0 equiv.) previously dissolved in anhydrous CH_3CN (4 mL) at room temperature. The mixture was stirred and purged with N_2, and the temperature was raised to 60 °C in 10 minutes. After the completion of the reaction, the mixture was filtered through a short pad of Celite with EtOAc and the solvents were evaporated under reduced pressure to obtain the S-cyclised products **37aa** and **37la**.

N-[(4Z)-4-(2-oxo-2-phenylethylidene)-4*H*-3,1-benzothiazin-2-yl]benzamide (37aa)



Orange solid. (97% yield, 140 mg). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 8.10-8.03 (m, 3H), 7.85-7.82 (m, 2H), 7.69 (s, 1H), 7.55-7.50 (m, 2H), 7.45 (ddd, *J* = 8.2 Hz, 7.0 Hz, 1.4 Hz, 1H), 7.39-7.34 (m, 2H), 7.27-7.22 (m, 3H), 7.12 (ddd, *J* = 8.2 Hz, 6.9 Hz, 1.4 Hz, 1H), 4.27 (br, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 186.4 (CO), 170.2 (Cq), 160.6 (Cq), 157.4 (CO), 148.4 (Cq), 140.7 (Cq), 140.2 (Cq), 139.7 (Cq), 132.2 (CH), 131.8 (CH), 129.8 (CH), 128.72 (2CH), 128.70 (2CH), 128.3 (CH), 127.8 (2CH), 127.6 (2CH), 124.2 (CH), 123.2 (CH), 116.3 (Cq), 107.5 (CH). **HRMS** (ESI, positive ion): m/z calculated for $C_{23}H_{16}N_2NaO_2S$: $[M+Na]^+$ 407.0830, found: 407.0826.

N-{(4Z)-4-[2-(3-methylphenyl)-2-oxoethylidene]-4*H*-3,1-benzothiazin-2-yl}benzamide (37la)



Yellow solid. (76% yield, 171 mg). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 11.73 (br, 1H, NH), 8.36-8.34 (m, 1H), 8.07-8.05 (m, 2H), 8.02 (s, 1H), 7.97 (s, 1H), 7.94 (t, *J* = 3.5 Hz, 1H), 7.68-7.66 (m, 1H), 7.65-7.61 (m, 1H), 7.55-7.51 (m, 1H), 7.46-7.43 (m, 4H), 7.28-7.24 (m, 1H), 2.41 (s, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 187.5 (CO), 152.5 (CO), 148.6 (Cq), 139.6 (Cq), 138.11 (Cq), 138.06 (Cq), 133.2 (CH), 132.9 (CH), 132.6 (CH), 128.7 (CH), 128.6 (CH), 128.50 (CH), 128.47 (CH), 128.4 (CH), 127.0 (CH), 125.3 (CH), 125.1 (CH), 121.7 (CH), 118.1 (CH), 117.3 (Cq), 112.0 (CH), 20.9 (CH_3). **HRMS** (ESI, positive ion): m/z calculated for $C_{24}H_{18}KN_2O_2S$: $[M+K]^+$ 437.0726, found: 437.0723.

11.5.5 Computational details

All the calculations were performed in the framework of density functional theory (DFT) using the CAM-B3LYP functional in conjunction with the 6-31G* basis set. When the silver atom was present, the Los Alamos National Laboratory Effective Core Potential with a double-ζ basis set (lanl2dz) was used. All the structures were first optimised and then characterised as minima or first order saddle points by calculating the harmonic frequencies. A larger basis set, 6-311+G*, was then used for performing single point calculations onto the optimised structures. Free energy calculations were finally obtained at the temperatures of interest (60 °C and 80 °C) by calculating for each structure the partition function in the ideal-gas approximation using the geometries and the associated frequencies and considering as a reference state the concentration of 1.0 mol per litre at a pressure of 1.0 bar. The excess free energy, i.e., the effect of the solvent, was taken into account using a mean-field approach according to the Polarizable Continuum Model (PCM) as implemented in the Gaussian 09 software using the same functional and larger basis set previously reported. Tetrahydrofuran and acetonitrile were used as solvents. The choice of the above level of theory has been only driven by its good performances in previous studies. No check of the effects of the functional and/or basis set on the obtained results has been performed. For this reason, all the data reported are affected by an unknown uncertainty and hence the emerged picture should be taken at a semi-quantitative (if not qualitative) level.

11.5.6 X-ray crystallographic data

The X-ray crystallographic analysis has been performed in collaboration with Professor Gustavo Portalone (Dipartimento di Chimica, Sapienza Università di Roma, Italy). For all the crystal structures, the diffraction data were collected at T = 298.0 K on an Oxford Diffraction Xcalibur S CCD diffractometer equipped with a graphite monochromator (Mo Kα radiation, λ = 0.710689 Å).

Crystal data for 35aa. Light yellow tablets obtained by solvent evaporation technique form a CH_2Cl_2 solution. $C_{22}H_{16}N_2O_2$, Mr = 340.38, monoclinic, a = 5.6311(5) Å, b = 16.1768(13) Å, c = 18.5883(14) Å, β = 90.132(7)°, V = 1693.3(2) $Å^3$, space group $P2_1/n$, Z = 4, μ(MoKα) = 0.087 mm^{-1}, 2959 reflections collected, 1688 independent reflections (Rint = 0.061). The final R_1 and $wR(F^2)$ values were 0.0552 and 0.1007, respectively ($I > 2\sigma(I)$), and 0.1089 and 0.1226, respectively (all data). The goodness of fit on F^2 was 0.951. The crystallographic data

for the structure have been deposited at the Cambridge Crystallographic Data Centre (deposition number: CCDC 1989173).

Crystal data for 35ca. Light yellow tablets obtained by solvent evaporation technique form a DMSO solution. $C_{23}H_{18}N_2O_2$, Mr = 354.39, monoclinic, a = 19.7918(6) Å, b = 8.1770(2) Å, c = 24.1081(7) Å, β = 107.785(3)°, V = 3715.15(19) $Å^3$, space group $P2_1/c$, Z = 8, μ(MoKα) = 0.082 mm^{-1}, 6683 reflections collected, 5177 independent reflections (Rint = 0.0284). The final R_1 and $wR(F^2)$ values were 0.0424 and 0.1043, respectively ($I > 2\sigma(I)$), and 0.0586 and 0.1148, respectively (all data). The goodness of fit on F^2 was 1.054. The crystallographic data for the structure have been deposited at the Cambridge Crystallographic Data Centre (deposition number: CCDC 1989174).

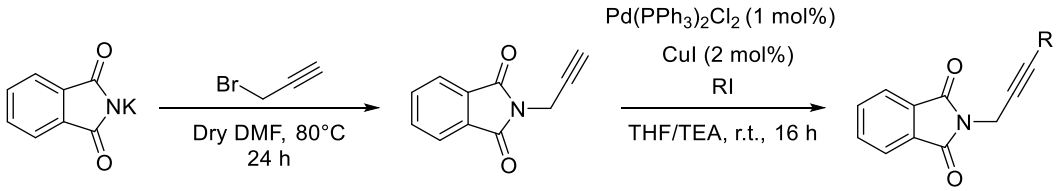
Crystal data for 37la. Light yellow tablets obtained by solvent evaporation technique form a DMSO solution. $C_{24}H_{18}N_2O_2S$, Mr = 398.46, orthorhombic, a = 6.5760(4) Å, b = 16.9049(10) Å, c = 17.5937(8) Å, V = 1955.8(2) $Å^3$, space group $P2_12_12_1$, Z = 4, μ(MoKα) = 0.189 mm^{-1}, 3540 reflections collected, 2627 independent reflections (Rint = 0.0417). The final R_1 and $wR(F^2)$ values were 0.0594 and 0.1246, respectively ($I > 2\sigma(I)$), and 0.0869 and 0.1399, respectively (all data). The goodness of fit on F^2 was 1.040. The crystallographic data for the structure have been deposited at the Cambridge Crystallographic Data Centre (deposition number: CCDC 1989175).

11.6 Gold-catalysed regioselective hydration of phthalimido-protected propargylamines: experimental and computational investigation

11.6.1 Preparation and characterisation of *N*-propargyl phthalimides **42a-n**

The compounds **42a**, **42c**, **42i**, **42j**, **42k**, **42l** and **42n** have been obtained as already reported and their NMR spectra are in accordance with those reported in literature.

General procedure for the synthesis of *N*-propargyl phthalimide derivatives (42a-i, m-n) **173, 174**

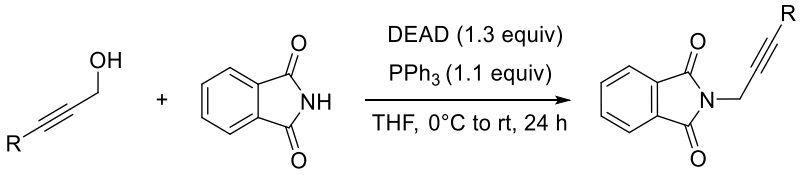


Step 1: To a stirred solution of potassium phthalimide (27 mmol) in dry DMF (40 mL) under nitrogen atmosphere at room temperature, propargyl bromide (80%) (32.4 mmol) was added and the resulting solution was heated to 80°C. The reaction mixture was maintained at 80°C for 24 hours and cooled to room temperature. The reaction mass was added to ice cold water and stirred for an additional hour. The obtained solid was filtered and dissolved in dichloromethane. The dichloromethane solution was dried using $MgSO_4$ and the organic layer was evaporated under high vacuum. The obtained solid (**42n**) was used for the next reaction without further purification.

Step 2: To a stirring solution of *N*-propargyl phthalimide **42n** (10.8 mmol) in dry THF (15 mL), anhydrous triethylamine (15 mL), iodoaryl derivative (14.04 mmol, 1.30 equivalents) and $PdCl_2(PPh_3)_2$ (1 mol%) were added. After stirring for 15 min, CuI (2 mol%) was added and the reaction was stirred at room temperature overnight. After completion, as monitored by TLC and GC, the reaction mass was filtered through Celite bed, washed with ethyl acetate and the filtrate was evaporated under reduced pressure. The crude was purified by column chromatography over silica gel using PE/AcOEt 80:20 v/v.

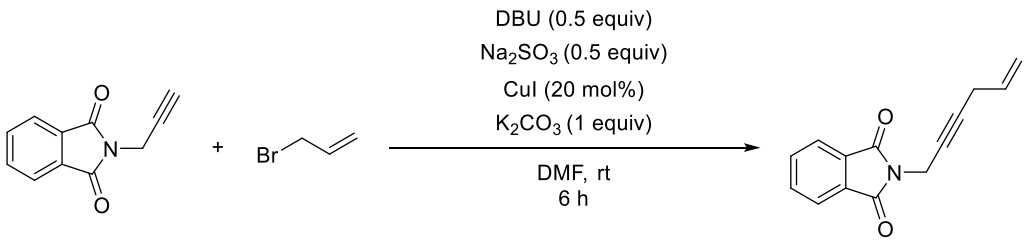
[173] Achard, T.; Lepronier, A.; Gimbert, Y.; Clavier, H.; Giordano, L.; Tenaglia, A.; Buono, G. *Angew. Chem. Int. Ed.* **2011**, 50, 3552-3556.
[174] Sakthivel, S.; Sharma, A.; Balamurugan, R. *Eur. J. Org. Chem.*, **2017**, 3941-3946.

Procedure for the synthesis of 42j-k [175]



To a solution of propargyl alcohol (4.46 mmol) in THF (10 mL) at 0°C were added triphenylphosphine (4.9 mmol), phthalimide (4.9 mmol) and DEAD (5.79 mmol). The reaction mixture was then stirred at room temperature for 24h. When the reaction was complete (as monitored by TLC), the solvent was evaporated and the triphenylphosphine oxide precipitated by addition of a mixture of PE/Et_2O 1:1 (40 mL). The precipitate was filtered through a plug of Celite and the solvent was evaporated under reduced pressure to afford a crude residue which was purified by column chromatography over silica gel with mixtures of PE/AcOEt from 98:2 to 90:10 v/v.

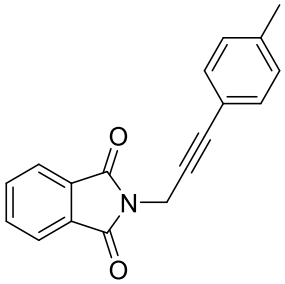
Procedure for the synthesis of 2-(hex-5-en-2-yn-1-yl)isoindoline-1,3-dione (42l) [176]



A mixture of propargyl phthalimide (3.78 mmol), allyl bromide (5.67 mmol), Na_2SO_3 (1.89 mmol), K_2CO_3 (3.78 mmol), DBU (2 mmol), and CuI (0.756 mmol) was stirred at room temperature in DMF (3 mL) for 4 h. The solution was then diluted with Et_2O (70 mL) and washed with H_2O (25 mL × 5). The organic phase was dried over dry $MgSO_4$, filtered, and evaporated, obtaining the desired product as a white solid in 56% of yield. Both ^1H and ^{13}C spectra are in accordance with the data reported in literature.

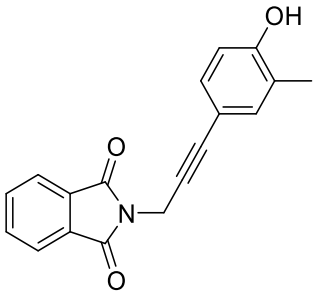
[175] Balducci, E.; Bellucci, L.; Petricci, E.; Taddei, M.; Tafi, A. *J. Org. Chem.* **2009**, 74, 1314-1321.
[176] McNulty, J.; Zepeda-Velazquez, C. *Angew. Chem., Int. Ed.* **2014**, 53, 8450-8454.

2-(3-(*p*-Tolyl)prop-2-yn-1-yl)isoindoline-1,3-dione (42b)



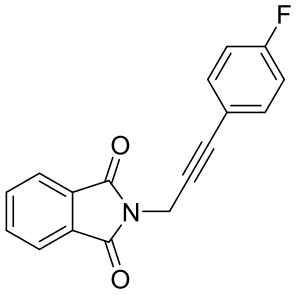
Pale brown solid. (51% yield, 800 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.90 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.74 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 7.07 (d, *J* = 7.9 Hz, 2H), 4.67 (s, 2H), 2.32 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 167.2 (2CO), 138.6 (Cq), 134.1 (2CH), 132.2 (2Cq), 131.8 (2CH), 129.0 (2CH), 123.6 (2CH), 119.3 (Cq), 83.1 (Cq), 81.9 (Cq), 27.9 (CH_2), 21.5 (CH_3). **GC-MS** (EI, 70 eV): m/z(%) calculated for $C_{18}H_{13}NO_2$: 275. 276 (43), 275 (M^+, 100), 247 (88), 246 (47), 233 (27), 232 (79), 218 (27), 204 (48), 115 (58), 102 (37).

2-(3-(4-hydroxy-3-methylphenyl)prop-2-yn-1-yl)isoindoline-1,3-dione (42d)



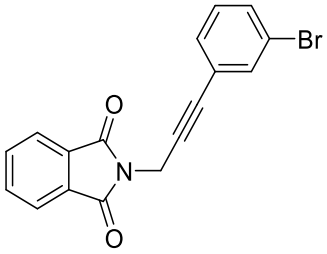
Pale brown solid. (39% yield, 310 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.89 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.74 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.23-7.19 (m, 1H), 7.13 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.66 (d, *J* = 8.2 Hz, 1H), 4.65 (s, 2H), 2.18 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 167.3 (2CO), 154.3 (Cq), 134.8 (CH), 134.2 (2CH), 132.2 (2Cq), 131.1 (CH), 123.9 (Cq), 123.5 (2CH), 114.9 (CH), 114.4 (Cq), 83.0 (Cq), 80.9 (Cq), 28.0 (CH_2), 15.5 (CH_3). **GC-MS** (EI, 70 eV): m/z(%) calculated for $C_{18}H_{13}NO_3$: 291. Found: 291 (M^+, 100).

2-(3-(4-Fluorophenyl)prop-2-yn-1-yl)isoindoline-1,3-dione (42e)



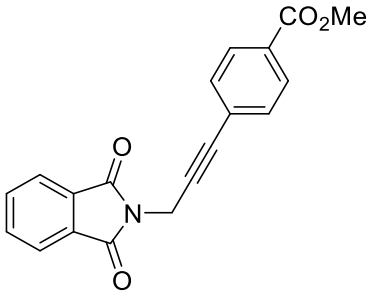
White solid. (35% yield, 112 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.90 (dd, *J* = 5.6, 3.0 Hz, 2H), 7.75 (dd, *J* = 5.6, 3.0 Hz, 2H), 7.40 (dd, *J* = 8.8, 5.4 Hz, 2H), 6.97 (t, *J* = 8.8 Hz, 2H), 4.67 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 167.2 (2CO), 162.6 (d, *J* = 249.6 Hz, CF), 134.2 (2CH), 133.9 (d, *J* = 8.4 Hz, 2CH), 132.1 (2Cq), 123.6 (2CH), 118.4 (Cq), 115.5 (d, *J* = 22.1 Hz, 2CH), 82.4 (Cq), 82.0 (Cq), 27.8 (CH_2). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -110.5. **GC-MS** (EI, 70 eV): m/z(%) calculated for $C_{17}H_{10}FNO_2$: 279. Found: 280 (28), 279 (M^+, 100), 252 (14), 251 (75), 250 (74), 249 (24), 223 (18), 222 (35), 221 (21), 196 (13).

2-(3-(3-Bromophenyl)prop-2-yn-1-yl)isoindoline-1,3-dione (42f)



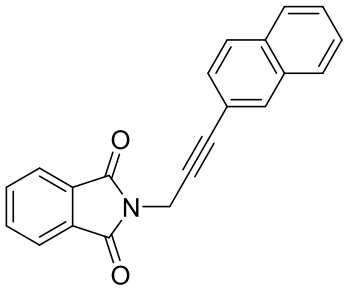
Brown solid. (95% yield, 870 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.90 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.75 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.57 (t, *J* = 1.6 Hz, 1H), 7.43 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.34 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.14 (t, *J* = 8.0 Hz, 1H), 4.67 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 167.1 (2CO), 134.7 (CH), 134.2 (2CH), 132.1 (2Cq), 131.7 (CH), 130.5 (CH), 129.7 (CH), 124.3 (Cq), 123.6 (2CH), 122.0 (Cq), 84.0 (Cq), 81.5 (Cq), 27.8 (CH_2). **GC-MS** (EI, 70 eV): m/z(%) calculated for $C_{17}H_{10}BrNO_2$: 339. Found: 342 (30), 341 (100), 340 (40), 339 (M^+, 93), 313 (32), 312 (29), 311 (36), 310 (22), 233 (15), 232 (51), 206 (14), 205 (43), 204 (73), 203 (44), 202 (20), 177 (15), 176 (25), 114 (13), 113 (29), 102 (23).

Methyl 4-(3-(1,3-dioxoisoindolin-2-yl)prop-1-yn-1-yl)benzoate (42g)



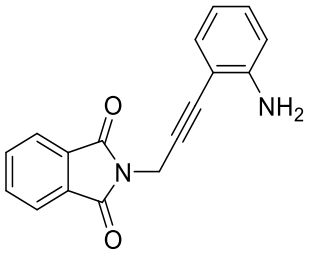
White solid. (78% yield, 670 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.98-7.92 (m, 2H), 7.91 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.76 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.50-7.44 (m, 2H), 4.70 (s, 2H), 3.90 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 167.1 (2CO), 166.5 (CO), 134.3 (2CH), 132.1 (2Cq), 131.9 (2CH), 129.8 (Cq), 129.9 (2CH), 127.0 (Cq), 123.6 (2CH), 85.6 (Cq), 82.3 (Cq), 52.2 (OCH_3), 27.8 (CH_2). **GC-MS** (EI, 70 eV): m/z(%) calculated for $C_{19}H_{13}NO_4$: 319. Found: 320 (43), 319 (M^+, 100), 291 (46), 232 (58), 204 (39), 104 (32).

2-(3-(Naphthalen-2-yl)prop-2-yn-1-yl)isoindoline-1,3-dione (42h)



Pale brown solid. (25% yield, 298 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.96-7.94 (m, 1H), 7.91 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.80-7.71 (m, 5H), 7.49-7.43 (m, 3H), 4.73 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 167.2 (2CO), 134.2 (2CH), 132.9 (Cq), 132.8 (Cq), 132.2 (2Cq), 132.0 (CH), 128.5 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 126.8 (CH), 126.5 (CH), 123.6 (2CH), 119.6 (Cq), 83.3 (Cq), 83.0 (Cq), 28.0 (CH_2). **GC-MS** (EI, 70 eV): m/z(%) calculated for $C_{21}H_{13}NO_2$: 311. Found: 311 (M^+, 100).

2-(3-(2-aminophenyl)prop-2-yn-1-yl)isoindoline-1,3-dione (42m)

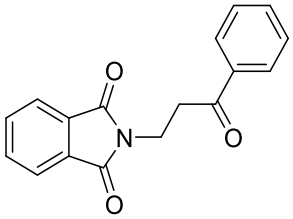


Yellow solid. (77% yield, 577 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.88 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.74 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.23 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.09 (td, *J* = 8.2, 1.6 Hz, 1H), 6.64 (ddd, *J* = 8.2, 7.7, 1.6 Hz, 2H), 4.72 (s, 2H), 4.30 (br, 2H, NH_2). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 167.2 (2CO), 148.7 (Cq), 134.2 (2CH), 132.2 (CH), 132.1 (2Cq), 130.0 (CH), 123.6 (2CH), 117.6 (CH), 114.2 (CH), 106.7 (Cq), 87.9 (Cq), 80.3 (Cq), 28.3 (CH_2). **GC-MS** (EI, 70 eV): m/z(%) calculated for $C_{17}H_{12}N_2O_2$: 276. Found: 277 (20), 276 (M^+, 100), 275 (26), 131 (16), 130 (47), 129 (12).

11.6.2 Preparation and characterisation of ketones **43a-n**

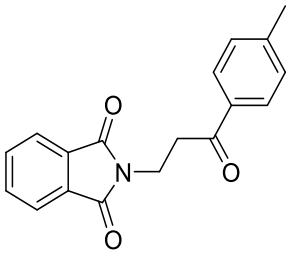
General Procedure. To a stirring solution of phthalimidic derivative **42a-n** (0.191 mmol) in CH_3CN (3 mL), 0.3 mL of H_2O and $IPrAuNTf_2$ (5 mol%) were added. The reaction was stirred at 80°C for 24 h. Then, a saturated aqueous solution of NH_4Cl was added. The organic layer was separated and the aqueous one was extracted with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The obtained crude was purified by column chromatography over silica gel using PE/AcOEt 90:10 v/v.

2-(3-Oxo-3-phenylpropyl)isoindoline-1,3-dione (43a)



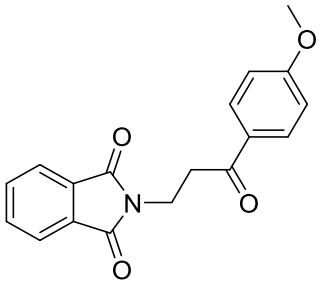
White solid. (86% yield, 46 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.94 (dt, *J* = 7.0, 1.4 Hz, 2H), 7.85 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.72 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.59-7.53 (m, 1H), 7.45 (dd, *J* = 8.4, 7.0 Hz, 2H), 4.15 (dd, *J* = 8.0, 6.8 Hz, 2H), 3.43 (dd, *J* = 8.0, 6.8 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 197.4 (CO), 168.2 (2CO), 136.4 (Cq), 134.0 (2CH), 133.4 (CH), 132.1 (2Cq), 128.7 (2CH), 128.1 (2CH), 123.3 (2CH), 36.8 (CH_2), 33.6 (CH_2). **HRMS** (H-ESI): m/z calculated for $C_{17}H_{14}NO_3$: $[M+H]^+$ 280.0974, Found: 280.0965.

2-(3-Oxo-3-(*p*-Tolyl)propyl)isoindoline-1,3-dione (43b)



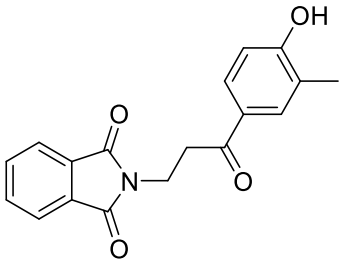
Pale brown solid. (71% yield, 38 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.88-7.81 (m, 4H), 7.72 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.26-7.21 (m, 2H), 4.14 (dd, *J* = 8.0, 6.9 Hz 2H), 3.40 (dd, *J* = 8.0, 6.9 Hz, 2H), 2.40 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 197.0 (CO), 168.2 (2CO), 144.2 (Cq), 134.0 (2CH), 132.2 (2Cq), 129.4 (2CH), 128.2 (2CH), 123.3 (2CH), 36.7 (CH_2), 33.7 (CH_2), 21.7 (CH_3). **HRMS** (H-ESI): m/z calculated for $C_{18}H_{16}NO_3$: $[M+H]^+$ 294.1130, Found: 294.1120.

2-(3-(4-Methoxyphenyl)-3-oxopropyl)isoindoline-1,3-dione (43c)



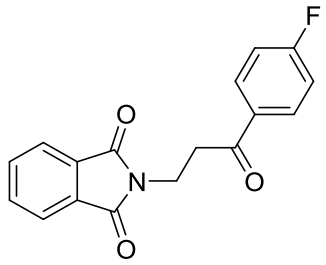
White solid. (94% yield, 50 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.9 Hz, 2H), 7.85 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.72 (dd, *J* = 5.4, 3.0 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 4.13 (dd, *J* = 7.9, 6.8 Hz, 2H), 3.86 (s, 3H), 3.37 (dd, *J* = 7.9, 6.8 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 195.9 (CO), 168.2 (2CO), 163.7 (Cq), 134.0 (2CH), 132.1 (2Cq), 130.3 (2CH), 129.6 (Cq), 123.3 (2CH), 113.8 (2CH), 55.5 (CH_3), 36.5 (CH_2), 33.7 (CH_2). **HRMS** (H-ESI): m/z calculated for $C_{18}H_{16}NO_4$: $[M+H]^+$ 310.1079, Found: 310.1066.

2-(3-(4-Hydroxy-3-methylphenyl)-3-oxopropyl)isoindoline-1,3-dione (43d)



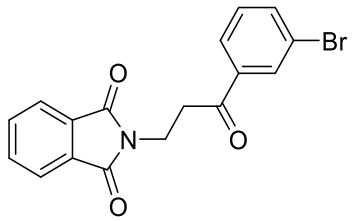
White solid. (72% yield, 38 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.85 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.77-7.66 (m, 3H), 7.68 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.79 (d, *J* = 8.4 Hz, 1H), 4.13 (dd, *J* = 7.9, 6.8 Hz, 2H), 3.35 (dd, *J* = 7.9, 6.8 Hz, 2H), 2.25 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 193.5 (CO), 168.3 (CO), 167.5 (CO), 158.6 (Cq), 134.4 (2CH), 134.0 (CH), 131.9 (2Cq), 131.6 (Cq), 128.2 (Cq), 123.7 (2CH), 123.3 (CH), 114.8 (CH), 36.5 (CH_2), 33.8 (CH_2), 15.7 (CH_3). **HRMS** (H-ESI): m/z calculated for $C_{18}H_{16}NO_4$: $[M+H]^+$ 310.1079, Found: 310.1069.

2-(3-(4-Fluorophenyl)-3-oxopropyl)isoindoline-1,3-dione (43e)



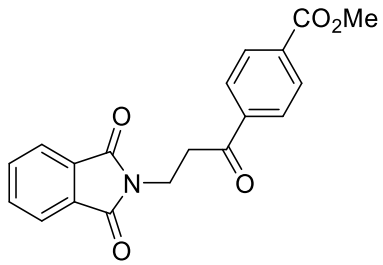
White solid. (88% yield, 47 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.01-7.95 (m, 2H), 7.86 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.73 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.16-7.09 (m, 2H), 4.14 (dd, *J* = 8.0, 6.8 Hz, 2H), 3.40 (dd, *J* = 8.0, 6.8 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 195.7 (CO), 168.2 (2CO), 165.92 (d, *J* = 255.2 Hz, CF), 134.1 (2CH), 132.9 (d, *J* = 3.0 Hz, Cq), 132.1 (2Cq), 130.7 (d, *J* = 9.4 Hz, 2CH), 123.3 (2CH), 115.8 (d, *J* = 22.0 Hz, 2CH), 36.8 (CH_2), 33.5 (CH_2). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -104.6. **HRMS** (H-ESI): m/z calculated for $C_{17}H_{13}FNO_3$: $[M+H]^+$ 298.0879, Found: 298.0871.

2-(3-(3-Bromophenyl)-3-oxopropyl)isoindoline-1,3-dione (43f)



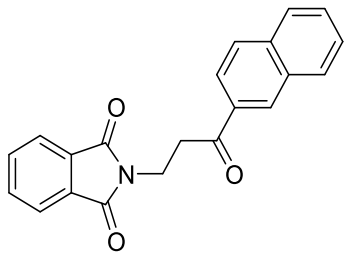
Brown solid. (70% yield, 37 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.07 (t, *J* = 1.8 Hz, 1H), 7.88-7.84 (m, 3H), 7.73 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.69 (dq, *J* = 8.0, 1.0 Hz, 1H), 7.34 (t, *J* = 8.0 Hz, 1H), 4.14 (dd, *J* = 7.9, 6.8 Hz, 2H), 3.40 (dd, *J* = 7.9, 6.8 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 196.0 (CO), 168.2 (2CO), 138.1 (Cq), 136.3 (CH), 134.1 (2CH), 132.1 (2Cq), 131.2 (CH), 130.3 (CH), 126.6 (CH), 123.4 (2CH), 123.1 (Cq), 36.9 (CH_2), 33.4 (CH_2). **HRMS** (H-ESI): m/z calculated for $C_{17}H_{13}BrNO_3$: $[M+H]^+$ 358.0079, Found: 358.0070.

Methyl 4-(3-(1,3-dioxoisoindolin-2-yl)propanoyl)benzoate (43g)



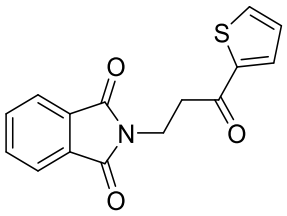
White solid. (85% yield, 45 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.14-8.08 (m, 2H), 8.02-7.96 (m, 2H), 7.85 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.73 (dd, *J* = 5.5, 3.1 Hz, 2H), 4.15 (dd, *J* = 7.9, 6.8 Hz, 2H), 3.95 (s, 3H), 3.46 (dd, *J* = 7.9, 6.8 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 196.9 (CO), 168.2 (2CO), 166.1 (CO), 139.5 (Cq), 134.1 (Cq), 134.0 (2CH), 132.1 (2Cq), 129.9 (2CH), 128.0 (2CH), 123.3 (2CH), 52.5 (OCH_3), 37.2 (CH_2), 33.4 (CH_2). **HRMS** (H-ESI): m/z calculated for $C_{19}H_{16}NO_5$: $[M+H]^+$ 338.1028, Found: 338.1016.

2-(3-(Naphthalen-2-yl)-3-oxopropyl)isoindoline-1,3-dione (43h)



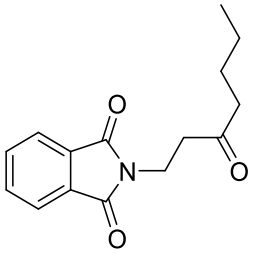
Pale brown solid. (85% yield, 45 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.49-8.43 (m, 1H), 8.01 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.94 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.89 (d, *J* = 8.6 Hz, 2H), 7.86 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.72 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.57 (dtd, *J* = 24.6, 7,4, 1.4 Hz, 2H), 4.21 (dd, *J* = 8.0, 6.8 Hz, 2H), 3.57 (dd, *J* = 8.0, 6.8 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 197.3 (CO), 168.3 (2CO), 135.7 (Cq), 134.0 (2CH), 133.8 (Cq), 132.5 (Cq), 132.1 (2Cq), 129.9 (CH), 129.6 (CH), 128.6 (CH), 127.8 (CH), 126.9 (CH), 123.6 (CH), 123.3 (2CH), 36.9 (CH_2), 33.7 (CH_2). **HRMS** (H-ESI): m/z calculated for $C_{21}H_{16}NO_3$: $[M+H]^+$ 330.1130, Found: 330.1120.

2-(3-Oxo-3-(thiophen-2-yl)propyl)isoindoline-1,3-dione (43i)



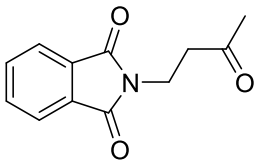
Brown solid. (82% yield, 44 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.85 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.75-7.70 (m, 3H), 7.64 (dd, *J* = 4.9, 1.1 Hz, 1H), 7.12 (dd, *J* = 4.9, 3.8 Hz, 1H), 4.13 (dd, *J* = 8.0, 6.8 Hz, 2H), 3.36 (dd, *J* = 8.0, 6.8 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 190.1 (CO), 168.1 (2CO), 143.6 (Cq), 134.0 (2CH), 132.2 (CH), 132.1 (2Cq), 128.2 (CH), 123.3 (2CH), 37.5 (CH_2), 33.6 (CH_2). **HRMS** (H-ESI): m/z calculated for $C_{15}H_{12}NO_3S$: $[M+H]^+$ 286.0538, Found: 286.0529.

2-(3-Oxoheptyl)isoindoline-1,3-dione (43j)



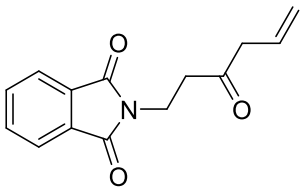
White solid. (63% yield, 34 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.84 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.71 (dd, *J* = 5.4, 3.1 Hz, 2H), 3.96 (dd, *J* = 7.9, 6.9 Hz, 2H), 2.85 (dd, *J* = 7.9, 6.9 Hz, 2H), 2.43 (t, *J* = 7.5 Hz, 2H), 1.62-1.50 (m, 2H), 1.37-1.26 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 208.3 (CO), 168.1 (2CO), 134.0 (2CH), 132.1 (2Cq), 123.3 (2CH), 42.6 (CH_2), 40.6 (CH_2), 33.1 (CH_2), 25.7 (CH_2), 22.3 (CH_2), 13.8 (CH_3). **HRMS** (H-ESI): m/z calculated for $C_{15}H_{18}NO_3$: $[M+H]^+$ 260.1287, Found: 260.1279.

2-(3-Oxobutyl)isoindoline-1,3-dione (43k)



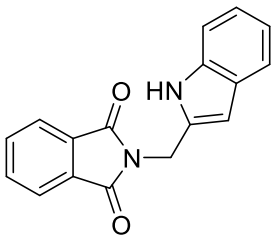
White solid. (72% yield, 39 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.84 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.72 (dd, *J* = 5.4, 3.1 Hz, 2H), 3.96 (dd, *J* = 7.9, 6.9 Hz, 2H), 2.88 (dd, *J* = 7.9, 6.9 Hz, 2H), 2.19 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 205.8 (CO), 168.1 (2CO), 134.0 (2CH), 132.0, (2Cq) 123.3 (2CH), 41.6 (CH_2), 33.0 (CH_2), 29.9 (CH_3). **HRMS** (H-ESI): m/z calculated for $C_{12}H_{11}NO_3$: $[M+H]^+$ 218.0871, Found: 218.0810.

2-(3-Oxohex-5-en- 1-yl)isoindoline-1,3-dione (43l)



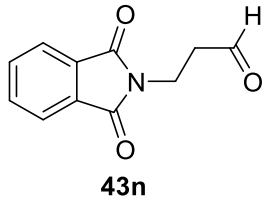
White solid. (54% yield, 29 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.84 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.72 (dd, *J* = 5.5, 3.0 Hz, 2H), 5.91 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H), 5.23-5.10 (m, 2H), 3.96 (dd, *J* = 7.9, 6.9 Hz, 2H), 3.21 (dt, *J* = 7.0, 1.4 Hz, 2H), 2.89 (dd, *J* = 7.9, 6.9 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 205.8 (CO), 168.1 (2CO), 134.0 (2CH), 132.1 (2Cq), 129.9 (CH), 123.3 (2CH), 119.4 (CH_2), 47.7 (CH_2), 40.2 (CH_2), 33.0 (CH_2). **HRMS** (H-ESI): m/z calculated for $C_{14}H_{14}NO_3$: $[M+H]^+$ 244.0974, Found: 244.0965.

2-((1*H*-indol-2-yl)methyl)isoindoline-1,3-dione (43m)



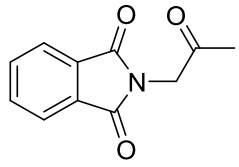
White solid. (52% yield, 26 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.83 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.70 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.55 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.32 (dd, *J* = 8.1, 1.1 Hz, 2H), 7.15 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 7.06 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 2H), 6.55 (d, *J* = 2.1 Hz, 1H), 4.98 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 168.4 (2CO), 136.4 (Cq), 134.3 (2CH), 132.9 (Cq), 131.9 (2Cq), 127.7 (Cq), 123.5 (2CH), 122.5 (CH), 120.8 (CH), 119.9 (CH), 111.0 (CH), 102.7 (CH), 34.9 (CH_2). **HRMS** (H-ESI): m/z calculated for $C_{17}H_{13}N_2O_2$: $[M+H]^+$ 277.0977, Found: 277.0968.

3-(1,3-dioxoisoindolin-2-yl)propanal (43n) + 2-(2oxopropyl)isoindoline-1,3-dione (43n')



43n

+

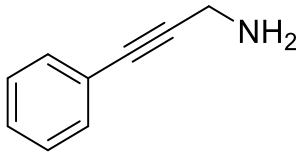


43n'

White solid. (66% cumulative yield, 36 mg). **110n/110n' ratio** (calculated by NMR): 2.27/2.89 = 1/1.3. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.83 (s, 1H, 43n), 7.86 (m, 4H, 43n+43n'), 7.74 (m, 4H, 43n+43n'), 4.50 (s, 2H, 43n'), 4.04 (t, J = 7.0 Hz, 2H, 43n), 2.88 (td, J = 7.0, 1.4 Hz, 2H, 43n), 2.27 (s, 3H, 43n'). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 199.6 (CHO, 43n), 199.4 (CO, 43n'), 168.0 (Cq, 43n), 167.7 (Cq, 43n'), 134.2 (2CH, 43n'), 134.1 (2CH, 43n), 132.1 (2Cq, 43n'), 131.9 (2Cq, 43n), 123.6 (2CH, 43n'), 123.4 (2CH, 43n), 47.1 (CH_2, 43n'), 42.4 (CH_2, 43n), 31.7 (CH_2, 43n), 27.0 (CH_3, 43n').

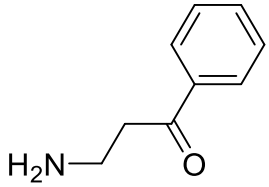
11.6.3 Preparation and characterisation of other miscellaneous derivatives

Synthesis of 3-phenylprop-2-yn-1-amine (45a)



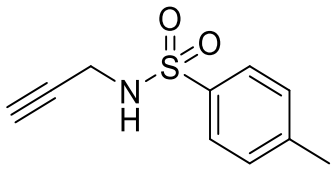
To a solution of phthalimide **42a** (7,65 mmol, 2 g) in EtOH (60 mL) was added hydrazine hydrate (45,93 mmol, 2,28 mL) drop wise and the resulting mixture was stirred at reflux for 4 hours. After completion of the reaction, as monitored by TLC, the reaction mass was filtered through a plug of Celite, washed with diethyl ether (20 mL) and the solvent was evaporated under reduced pressure. The obtained crude residue was finally purified by column chromatography over silica gel with a mixture of PE/AcOEt 50:50 v/v and then 100% AcOEt, obtaining the product as a pale-yellow oil (624 mg, 62% yield). The spectra are in accordance with the data reported in literature. [174] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.48-7.36 (m, 2H), 7.35-7.18 (m, 3H), 3.65 (s, 2H).

Synthesis of 3-amino-1-phenylpropan-1-one (44a)



To a stirring solution of 2-(3-oxo-3-phenylpropyl)isoindoline-1,3-dione **43a** (2.4 mmol, 0.7 g) in MeOH, ethylenediamine (4.8 mmol, 0.32 mL) was added. The obtained suspension was stirred at room temperature for 1 hour until complete homogenisation. After completion (as shown by TLC analysis), the volatiles have been removed by concentration under reduced pressure and the crude has been further purified by column chromatography over silica gel with $CHCl_3$/Acetone 90:10 v/v to give the (3-amino-1-phenylpropan-1-one) **44a** as a yellow oil (86% yield, 0.33 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.00-7.93 (m, 2H), 7.68-7.56 (m, 1H), 7.52-7.45 (m, 2H), 3.79 (q, *J* = 5.9 Hz, 2H), 3.31 (t, *J* = 5.9 Hz, 2H). [177]

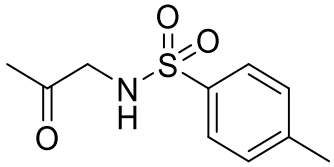
Synthesis of 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (46)



Propargylamine (18.16 mmol, 1.5 mL) was dissolved in DCE (40 mL) and the solution was cooled to 0 °C. To this solution were added triethylamine (43.21 mmol, 6.02 mL) and then *p*-toluenesulfonyl chloride (17.25 mmol, 3.29 g), previously dissolved in DCE (10 mL). The solution was stirred overnight while the ice bath was allowed to warm to room temperature. Then the reaction mixture was dissolved in Et_2O (200 mL), first washed with a solution of HCl (1M) and then with a satured solution of NH_4Cl. The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated, obtaining 3.31 g (87% yield) of the product as a white solid. The spectra are in accordance with the data reported in literature. [173] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 3.83 (dd, *J* = 6.0, 2.5 Hz, 2H), 2.44 (s, 3H), 2.11 (t, *J* = 2.5 Hz, 1H).

[177] Velingkar, V. S.; Dandekar, V. D. *Chin. J. Chem*. **2011**, 29, 504-510.

Synthesis of 4-methyl-*N*-(2-oxopropyl)benzenesulfonamide (47)



To a stirring solution of 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide **46** (0.239 mmol, 0.05 g) in CH_3CN (3 mL), 0.3 mL of H_2O and $IPrAuNTf_2$ (0.012 mmol, 0.01 g) were added. The reaction was stirred at 80°C for 24 h. Then, a saturated aqueous solution of NH_4Cl was added. The organic layer was separated and the aqueous one was extracted with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The obtained crude was purified by column chromatography over silica gel using PE/AcOEt 80:20 v/v to give the 4-methyl-*N*-(2-oxopropyl)benzenesulfonamide **47** as a white solid (77% yield, 0.042 g,). [176] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 5.45 (t, *J* = 4.8 Hz, 1H), 3.85 (d, *J* = 4.8 Hz, 2H), 2.42 (s, 3H), 2.11 (s, 3H).

11.6.4 Computational details

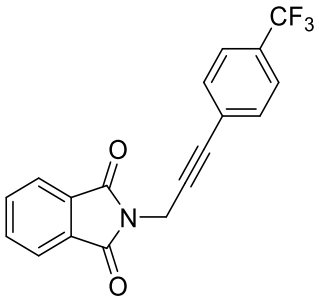
All the calculations were performed in the framework of density functional theory (DFT) using the CAM-B3LYP functional. All the structures were first optimised using the 6-31+G* basis set for all the (light) atoms the Los Alamos National Laboratory Effective Core Potential with a double-ζ basis set (lanl2dz) for gold. The same level of theory was employed for calculating the frequencies and, hence, the free energy correction at the temperature of interest by evaluating for each structure the partition function in the ideal-gas approximation using the geometries and the associated frequencies and considering as a reference state the concentration of 1.0 mole/litre. A larger basis set, 6-311+G*, was then used for all the light atoms to perform single point calculations, atomic charge estimations and to calculate the excess free energy, i.e., the effect of the solvent (acetonitrile at the temperature of 80°C), using a mean-field approach according to the Polarizable Continuum Model (PCM) as implemented in the Gaussian 09 software. Atomic charges were also calculated at the same level of theory, on a selected number of species, using the Natural Bond Order analysis. QTAIMS (quantum theory of atoms in molecules) analysis was finally carried out on the DFT "wavefunction" using the Multiwfn package.

11.7 Gold/Selectfluor partnership in the divergent functionalisation of *N*-propargyl phthalimides

11.7.1 Preparation and characterisation of *N*-propargyl phthalimide **42l**

N-propargyl phthalimides **42a-c** and **42f-k** have been prepared according to the general procedure reported in Section 11.6.1. Only 2-(3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-yl)isoindoline-1,3-dione **42l** was newly synthetised, according to the same methodology.

2-(3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-yl)isoindoline-1,3-dione (42l)

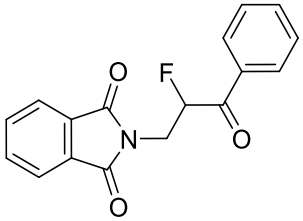


White solid. (96% yield, 699 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.91 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.76 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.57-7.46 (m, 4H), 4.70 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 167.1 (2CO), 134.3 (2CH), 132.2 (2CH), 132.0 (2Cq), 130.3 (q, *J* = 32.6 Hz, Cq), 126.1 (Cq), 125.2 (q, *J* = 3.7 Hz, 2CH), 124.8 (q, *J* = 272.2 Hz, CF_3), 123.6 (2CH), 85.2 (Cq), 81.9 (Cq), 27.8 (CH_2). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -62.9. **GC-MS** (EI, 70 eV): m/z(%) calculated for $C_{18}H_{10}F_3NO_2$: 329. Found: 329 (M^+, 100).

11.7.2 Preparation and characterisation of α-fluoro ketones **48a-l**

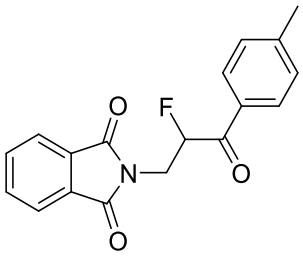
General Procedure. To a stirring solution of phthalimidic derivative **42** (0.191 mmol) in EtOH (2 mL), 0.5 mL of H_2O, Selectfluor (3 equiv.) and IPrAuCl (5 mol%) were added. The reaction was stirred at 80°C for 16-18 h. Then, a saturated aqueous solution of NH_4Cl was added. The organic layer was separated and the aqueous one was extracted with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The obtained crude was purified by column chromatography over silica gel using PE/AcOEt from 90:10 to 80:20 v/v.

2-(2-fluoro-3-oxo-3-phenylpropyl)isoindoline-1,3-dione (48a)



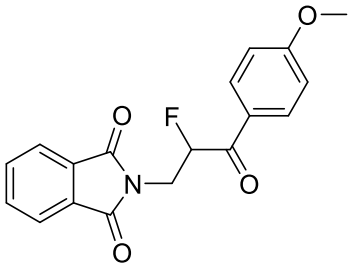
White solid. (69% yield, 39 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.08 (d, *J* = 7.4 Hz, 2H), 7.88 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.76 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.66-7.60 (m, 1H), 7.52 (dd, *J* = 8.3, 7.0 Hz, 2H), 5.99 (ddd, *J* = 49.3, 9.0, 3.4 Hz, 1H), 4.35 (td, *J* = 14.8, 9.0 Hz, 1H), 4.25-4.10 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 193.8 (d, *J* = 18.2 Hz, CO), 167.8 (2CO), 134.33 (CH), 134.31 (2CH), 134.0 (Cq), 131.9 (2Cq), 129.07 (CH), 129.03 (CH), 128.9 (2CH), 128.0 (Cq), 123.6 (2CH), 89.5 (d, *J* = 187.9 Hz, CHF), 39.5 (d, *J* = 22.8 Hz, CH_2). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -194.1. **HRMS** (H-ESI): m/z calculated for $C_{17}H_{13}FNO_3$: $[M+H]^+$ 298.0879, Found: 298.0870.

2-(2-fluoro-3-oxo-3-(*p*-tolyl)propyl)isoindoline-1,3-dione (48b)



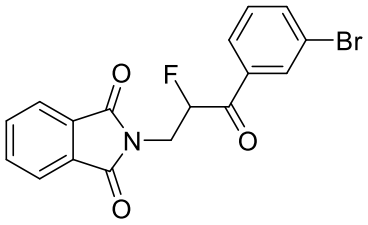
Pale yellow solid. (46% yield, 26 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.98 (d, *J* = 8.2 Hz, 2H), 7.89 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.76 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 5.97 (ddd, *J* = 49.3, 9.1, 3.3 Hz, 1H), 4.34 (td, *J* = 14.7, 9.1 Hz, 1H), 4.16 (ddd, *J* = 30.5, 14.8, 3.4 Hz, 1H), 2.43 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 193.3 (d, *J* = 17.9 Hz, CO), 167.8 (2CO), 145.4 (Cq), 134.3 (2CH), 134.0 (Cq), 131.9 (2Cq), 129.2 (2CH), 129.1 (2CH), 123.6 (2CH), 89.5 (d, *J* = 187.8 Hz, CHF), 39.6 (d, *J* = 22.9 Hz, CH_2), 21.8 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -194.1. **HRMS** (H-ESI): m/z calculated for $C_{18}H_{15}FNO_3$: $[M+H]^+$ 312.1036, Found: 312.1038.

2-(2-fluoro-3-(4-methoxyphenyl)-3-oxopropyl)isoindoline-1,3-dione (48c)



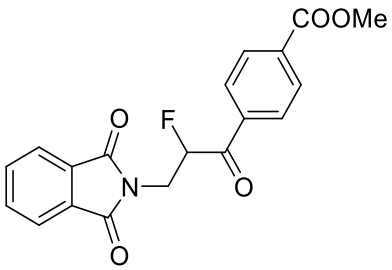
White solid. (57% yield, 32 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.08 (d, *J* = 8.9 Hz, 2H), 7.89 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.76 (dd, *J* = 5.5, 3.1 Hz, 2H), 6.98 (d, *J* = 8.9 Hz, 2H), 5.94 (ddd, *J* = 49.5, 9.2, 3.2 Hz, 1H), 4.35 (td, *J* = 14.7, 9.2 Hz, 1H), 4.15 (ddd, *J* = 31.0, 14.9, 3.2 Hz, 1H), 3.89 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 191.9 (d, *J* = 17.8 Hz, CO), 167.9 (2CO), 164.4 (Cq), 134.3 (2CH), 131.9 (2Cq), 131.5 (2CH), 130.0 (Cq), 123.6 (2CH), 114.2 (2CH), 89.5 (d, *J* = 187.5 Hz, CHF), 55.6 (CH_3), 39.7 (d, *J* = 22.8 Hz, CH_2). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -193.5. **HRMS** (H-ESI): m/z calculated for $C_{18}H_{15}FNO_4$: $[M+H]^+$ 328.0985, Found: 328.0982.

2-(3-(3-bromophenyl)-2-fluoro-3-oxopropyl)isoindoline-1,3-dione (48f)



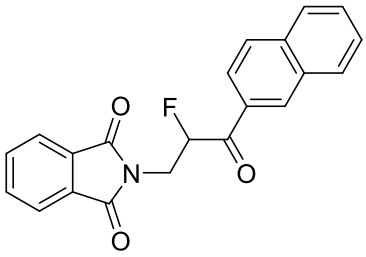
White solid. (60% yield, 33 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.19 (t, *J* = 1.9 Hz, 1H), 8.04-7.98 (m, 1H), 7.89 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.76 (dd, *J* = 5.5, 3.1 Hz, 3H), 7.40 (t, *J* = 7.9 Hz, 1H), 5.91 (ddd, *J* = 48.9, 8.8, 3.6 Hz, 1H), 4.35 (td, *J* = 14.8, 8.8 Hz, 1H), 4.19 (ddd, *J* = 29.2, 14.8, 3.5 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 192.8 (d, *J* = 19.0 Hz, CO), 167.8 (2CO), 137.1 (CH), 135.6 (Cq), 134.4 (2CH), 132.1 (2Cq), 131.8 (CH), 130.5 (CH), 127.7 (CH), 123.7 (2CH), 123.3 (CBr), 89.6 (d, *J* = 188.8 Hz, CHF), 39.2 (d, *J* = 22.9 Hz, CH_2). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -193.4. **HRMS** (H-ESI): m/z calculated for $C_{17}H_{12}BrFNO_3$: $[M+H]^+$ 375.9985, Found: 375.9982.

Methyl 4-(3-(1,3-dioxoisoindolin-2-yl)-2-fluoropropanoyl)benzoate (48g)



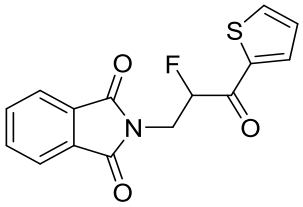
White solid. (67% yield, 37 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.23-8.08 (m, 4H), 7.89 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.76 (dd, *J* = 5.5, 3.0 Hz, 2H), 5.96 (ddd, *J* = 48.9, 8.8, 3.6 Hz, 1H), 4.36 (td, *J* = 14.8, 8.8 Hz, 1H), 4.21 (ddd, *J* = 29.2, 14.8, 3.6 Hz, 1H), 3.96 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): 193.7 (d, *J* = 19.1 Hz, CO), 167.8 (2CO), 165.9 (CO), 137.1 (Cq), 134.8 (Cq), 134.4 (2CH), 131.8 (2Cq), 130.0 (2CH), 129.07 (CH), 129.03 (CH), 123.6 (2CH), 89.7 (d, *J* = 188.7 Hz, CHF), 52.6 (CH_3), 39.2 (d, *J* = 22.6 Hz, CH_2). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -193.6. **HRMS** (H-ESI): m/z calculated for $C_{19}H_{15}FNO_5$: $[M+H]^+$ 356.0934, Found: 356.0933.

2-(2-fluoro-3-(naphthalen-2-yl)-3-oxopropyl)isoindoline-1,3-dione (48h)



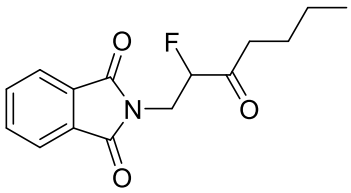
Yellow solid. (61% yield, 34 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.67 (d, *J* = 1.8 Hz, 1H), 8.08 (dd, *J* = 8.6, 1.8 Hz, 1H), 8.01 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.93 (d, *J* = 8.6 Hz, 1H), 7.90-7.84 (m, 3H), 7.74 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.63 (ddd, *J* = 8.2, 6.9, 1.4 Hz, 1H), 7.57 (ddd, *J* = 8.2, 6.9, 1.4 Hz, 1H), 6.13 (ddd, *J* = 49.3, 9.0, 3.4 Hz, 1H), 4.41 (td, *J* = 14.8, 9.0 Hz, 1H), 4.25 (ddd, *J* = 30.3, 14.8, 3.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 193.6 (d, *J* = 18.0 Hz, CO), 167.9 (2CO), 136.1 (CH), 134.3 (2CH), 132.4 (Cq), 131.9 (2Cq), 131.5 (2Cq), 129.9 (CH), 129.3 (CH), 128.9 (CH), 127.8 (CH), 127.1 (CH), 124.0 (CH), 123.6 (2CH), 89.7 (d, *J* = 187.9 Hz, CHF), 39.7 (d, *J* = 22.9 Hz, CH_2). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -193.6. **HRMS** (H-ESI): m/z calculated for $C_{21}H_{15}FNO_3$: $[M+H]^+$ 348.1036, Found: 348.1025.

2-(2-fluoro-3-oxo-3-(thiophen-2-yl)propyl)isoindoline-1,3-dione (48i)



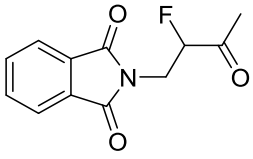
Pale yellow solid. (69% yield, 39 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 3.9 Hz, 1H), 7.91-7.85 (m, 2H), 7.78-7.75 (m, 3H), 7.23-7.13 (m, 1H), 5.71 (ddd, *J* = 49.6, 8.9, 3.7 Hz, 1H), 4.36 (td, *J* = 14.6, 8.9 Hz, 1H), 4.21 (ddd, *J* = 29.5, 14.8, 3.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 187.0 (d, *J* = 20.5 Hz, CO), 167.8 (2CO), 140.2 (Cq), 137.1 (CH), 135.9 (CH), 134.3 (2CH), 131.8 (2Cq), 128.7 (CH), 123.6 (2CH), 90.8 (d, *J* = 190.8 Hz, CHF), 39.7 (d, *J* = 22.7 Hz, CH_2). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -192.3. **HRMS** (H-ESI): m/z calculated for $C_{15}H_{11}FNO_3S$: $[M+H]^+$ 304.0444, Found: 304.0438.

2-(2-fluoro-3-oxoheptyl)isoindoline-1,3-dione (48j)



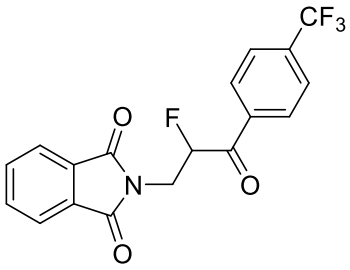
White solid. (68% yield, 39 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.88 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.75 (dd, *J* = 5.5, 3.0 Hz, 2H), 5.25-4.89 (m, 1H), 4.19-4.02 (m, 2H), 2.68 (tq, *J* = 7.2, 1.4 Hz, 2H), 1.73-1.55 (m, 2H), 1.36 (q, *J* = 7.4 Hz, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 207.4 (d, *J* = 23.1 Hz, CO), 167.8 (2CO), 134.3 (2CH), 131.9 (2Cq), 123.6 (2CH), 91.6 (d, *J* = 189.9 Hz, CHF), 38.6 (d, *J* = 22.8 Hz, CH_2), 38.1 (CH_2), 24.6 (d, *J* = 1.9 Hz, CH_2), 22.2 (CH_2), 13.8 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -196.6. **HRMS** (H-ESI): m/z calculated for $C_{15}H_{17}FNO_3$: $[M+H]^+$ 278.1192, Found: 278.1187.

2-(2-fluoro-3-oxobutyl)isoindoline-1,3-dione (48k)



White solid. (76% yield, 45 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.81 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.68 (dd, *J* = 5.5, 3.1 Hz, 2H), 5.00 (dt, *J* = 49.6, 7.3, Hz, 1H), 4.12-3.96 (m, 2H), 2.28 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 204.3 (d, *J* = 24.6 Hz, CO), 166.7 (2CO), 133.3 (2CH), 130.8 (2Cq), 122.6 (2CH), 90.6 (d, *J* = 190.0 Hz, CHF), 37.3 (d, *J* = 23.0 Hz, CH_2), 25.0 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -194.40. **HRMS** (H-ESI): m/z calculated for $C_{12}H_{11}FNO_3$: $[M+H]^+$ 236.0723, Found: 236.0720.

2-(2-fluoro-3-oxo-3-(4-(trifluoromethyl)phenyl)propyl)isoindoline-1,3-dione (48l)

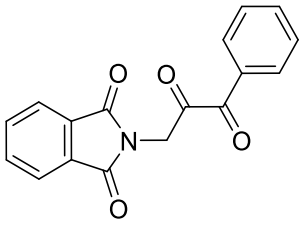


White solid. (69% yield, 38 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.18 (d, *J* = 8.1 Hz, 2H), 7.88 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.77 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.75-7.64 (m, 2H), 5.95 (ddd, *J* = 48.8, 8.7, 3.7 Hz, 1H), 4.36 (td, *J* = 14.8, 8.7 Hz, 1H), 4.23 (ddd, *J* = 29.2, 14.8, 3.5 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 193.4 (d, *J* = 19.4 Hz, CO), 167.8 (2CO), 136.6 (Cq), 135.4 (q, *J* = 33.0 Hz, Cq), 134.4 (2CH), 131.8 (2Cq), 129.5 (2CH), 125.9 (q, *J* = 3.8 Hz, 2CH), 124.3 (q, *J* = 272.2 Hz, CF_3), 123.6 (2CH), 89.8 (d, *J* = 189.0 Hz, CHF), 39.1 (d, *J* = 22.8 Hz, CH_2). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -63.3 (CF_3), -193.5 (CHF). **HRMS** (H-ESI): m/z calculated for $C_{18}H_{12}F_4NO_3$: $[M+H]^+$ 366.0753, Found: 366.0752.

11.7.3 Preparation and characterisation of 1,2-diketones **49a, c, g, h**

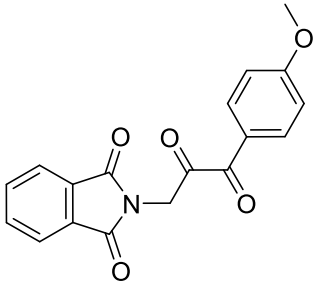
General Procedure. To a stirring solution of phthalimidic derivative **42** (0.383 mmol) in CH_3CN (2 mL), 0.2 mL of H_2O, PPh_3AuNTf_2 (5 mol%) and Selectfluor (0.575 mmol) were added. The reaction was stirred at 80°C for 24 h. At the end, as monitored by TLC and GC-MS, a saturated aqueous solution of NH_4Cl was added. The organic layer was separated and the aqueous one was extracted with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The obtained crude was purified by column chromatography over silica gel using PE/AcOEt 80:20 v/v.

2-(2,3-dioxo-3-phenylpropyl)isoindoline-1,3-dione (49a)



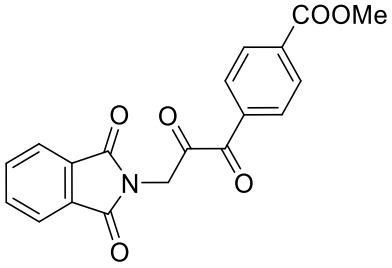
White solid. (82% yield, 92 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.10 (dt, *J* = 7.0, 1.3 Hz, 2H), 7.91 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.77 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.72-7.61 (m, 1H), 7.62-7.46 (m, 2H), 5.06 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 193.3 (CO), 189.4 (CO), 167.6 (2CO), 135.1 (Cq), 134.3 (2CH), 132.1 (CH), 131.7 (2Cq), 130.6 (2CH), 128.9 (2CH), 123.7 (2CH), 44.4 (CH_2). **HRMS** (MALDI-TOF): m/z calculated for $C_{17}H_{12}NO_4$: $[M+H]^+$ 294.0766, Found: 294.0765.

2-(3-(4-methoxyphenyl)-2,3-dioxopropyl)isoindoline-1,3-dione (49c)



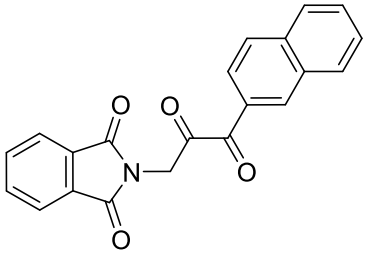
White solid. (80% yield, 73 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 9.0 Hz, 2H), 7.93 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.79 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.00 (d, *J* = 9.0 Hz, 2H), 5.06 (s, 2H), 3.92 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 193.8 (CO), 187.7 (CO), 167.6 (2CO), 165.3 (Cq), 134.3 (2CH), 133.2 (2CH), 132.8 (Cq), 132.1 (2Cq), 124.7 (Cq), 123.6 (2CH), 114.4 (2CH), 55.6 (CH_3), 44.5 (CH_2). **HRMS** (MALDI-TOF): m/z calculated for $C_{18}H_{14}NO_5$: $[M+H]^+$ 324.0872, Found: 324.0871.

Methyl 4-(3-(1,3-dioxoisoindolin-2-yl)-2-oxopropanoyl)benzoate (49g)



White solid. (84% yield, 76 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.19 (d, *J* = 0.8 Hz, 4H), 7.94 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.80 (dd, *J* = 5.5, 3.0 Hz, 2H), 5.09 (s, 2H), 3.99 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 192.5 (CO), 188.4 (CO), 167.5 (2CO), 165.9 (CO), 135.4 (Cq), 134.9 (Cq), 134.4 (2CH), 132.0 (2Cq), 130.5 (2CH), 129.9 (2CH), 123.7 (2CH), 52.6 (CH_3), 44.3 (CH_2). **HRMS** (MALDI-TOF): m/z calculated for $C_{19}H_{14}NO_6$: $[M+H]^+$ 352.0821, Found: 352.0822.

2-(3-(naphthalen-2-yl)-2,3-dioxopropyl)isoindoline-1,3-dione (49h)

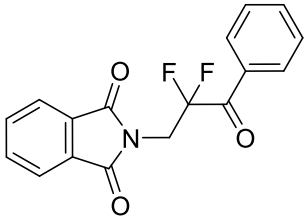


Yellow solid. (83% yield, 48 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.96-8.62 (m, 1H), 8.11 (dd, *J* = 8.7, 1.8 Hz, 1H), 8.08-8.00 (m, 1H), 8.00-7.94 (m, 3H), 7.93-7.89 (m, 1H), 7.81 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.68 (ddd, *J* = 8.1, 6.9, 1.3 Hz, 1H), 7.60 (ddd, *J* = 8.1, 6.9, 1.3 Hz, 1H), 5.14 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 193.5 (CO), 189.1 (CO), 167.6 (2CO), 136.4 (Cq), 134.5 (CH), 134.3 (2CH), 132.4 (2Cq), 132.1 (2Cq), 130.3 (CH), 129.7 (CH), 129.0 (CH), 127.9 (CH), 127.1 (CH), 124.2 (CH), 123.7 (2CH), 44.5 (CH_2). **HRMS** (MALDI-TOF): m/z calculated for $C_{21}H_{14}NO_4$: $[M+H]^+$ 344.0923, Found: 344.0919.

11.7.4 Preparation and characterisation of α,α-difluoro ketone **50a**

General Procedure. To a stirring solution of N-propargyl phthalimide **42a** (0.29 mmol) in EtOH (2 mL), 0.5 mL of H_2O, $NaAuCl_4$•$2H_2O$ (5 mol%) and Selectfluor (1.45 mmol) were added. The reaction was stirred at 50°C for 24 h. At the end, as monitored by TLC and GC-MS, a saturated aqueous solution of NH_4Cl was added. The organic layer was separated and the aqueous one was extracted with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The obtained crude was purified by column chromatography over silica gel using PE/AcOEt 80:20 v/v.

2-(2,2-difluoro-3-oxo-3-phenylpropyl)isoindoline-1,3-dione (50a)



White solid. (62%, 57 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.19-8.06 (m, 2H), 7.93 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.79 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.73-7.61 (m, 1H), 7.53 (dd, *J* = 8.5, 7.2 Hz, 2H), 4.52 (t, *J* = 15.8 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 188.1 (t, *J* = 29.1 Hz, CO), 167.4 (2CO), 134.8 (CH), 134.4 (2CH), 131.9 (Cq), 130.2 (2Cq), 128.8 (4CH), 123.7 (2CH), 115.59 (t, *J* = 258.6 Hz, CF_2), 39.85 (t, *J* = 24.6 Hz, CH_2). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -103.29 (CF_2). **HRMS** (MALDI-TOF): m/z calculated for $C_{17}H_{12}F_2NO_3$: $[M+H]^+$ 316.0785, Found: 316.0788.

11.8 Water as reaction medium in the palladium-catalysed hydroarylation of ynamides with arylboronic acids

Ynamides **51a-h** were obtained according to the method described by Stahl. [178] The analytical data of the synthethized compounds (^{1}H and ^{13}C NMR, MS) were in accordance with the data already reported in literature.

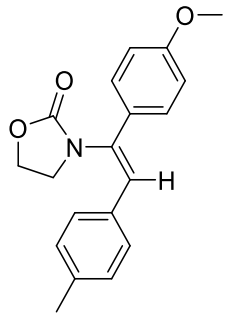
11.8.1 Preparation and characterisation of enamides **53aa-53hb** and **54aa-54hb**

General procedure A. Aryl boronic acid **52** (1.07 mmol, 2.5 equiv.), $Pd(OAc)_2$ (0.012 mmol, 3 mol%), TPPTS (0.064 mmol, 15 mol%) and Na_2CO_3 (0.641 mmol, 1.5 equiv.) were placed in a round-bottomed flask with a magnetic stir-bar under nitrogen atmosphere. Ynamide **51** (0.427 mmol, 1 equiv.) and 1 mL of water, previously deionised and degassed, were added and the solution was stirred at room temperature for 24h, until completion (as monitored by TLC). At the end of the reaction, the mixture was extracted with AcOEt (3 mL x 3); the organic phases were washed with brine, dried over MgSO4, filtered and concentrated under vacuum. The obtained crude was purified by flash chromatography over silica gel with mixtures of *n*-hexane–EtOAc, 60:40 v/v to afford both α,β- and β,β'-disubtituted enamides.

General procedure B/C. Aryl boronic acid **52** (1.29 mmol, 3 equiv.), $Pd(OAc)_2$ (0.013 mmol, 3 mol%) and ligand (15 mol%, for procedure B: PCy_3 0.065 mmol; for procedure C: P(*o*-Tol)$_3$ 0.065 mmol.) were placed in a round-bottomed flask with a magnetic stir-bar under argon atmosphere. Ynamide **51** (0.43 mmol, 1 equiv.) and 1 mL water, previously deionised and degassed, were added and the solution was stirred at room temperature for 3-24 h, until completion (as monitored by TLC). At the end of the reaction, the mixture was extracted with AcOEt (3 mL x 3); the organic phases were washed with brine, dried over MgSO4, filtered and concentrated under vacuum. The obtained crude was purified by flash chromatography over silica gel with mixtures of *n*-hexane–EtOAc, 60:40 v/v to afford the α,β-disubstituted enamides (for Procedure C) and the β,β'-disubtituted enamides (for Procedure B), both as single stereoisomers.

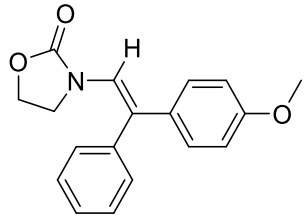
[178] Hamada, T.; Ye, X.; Stahl, S.S. *J. Am. Chem. Soc*. **2008**, 130, 833-835.

(Z)-3-(1-(4-methoxyphenyl)-2-(*p*-tolyl)vinyl)oxazolidin-2-one (Z-54aa) (Procedure A)



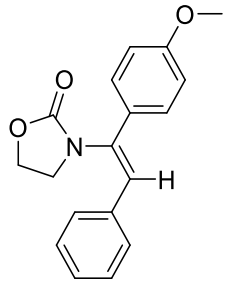
Yellow oil. (45% yield, 49 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.38 (*d*, J = 8.9 Hz, 2H), 7.29 (*d*, J = 8.5 Hz, 2H), 7.17 (*d*, J = 8.5 Hz, 2H), 6.93 (*d*, J = 8.9 Hz, 2H), 6.73 (s, 1H), 4.46-4.42 (m, 2H), 3.63 (s, 3H), 3.70-3.66 (m, 2H), 2.36 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.1 (Cq), 156.4 (CO), 137.8 (Cq), 133.5 (Cq), 132.6 (Cq), 129.5 (2CH), 129.0 (Cq), 128.2 (2CH), 127.2 (2CH), 125.1 (CH), 114.3 (2CH), 62.6 (OCH_2), 55.4 (OCH_3), 45.4 (NCH_2), 21.4 (CH_3). **LC-MS:** m/z 310.26 $[M+H]^+$; 327.34 $[M+NH_4]^+$. **HRMS** (EI): m/z, calculated for $C_{19}H_{19}NO_3$: $[M]^+$ 309.1365, found: 309.1363.

(E)-3-(2-(4-methoxyphenyl)-2-phenylvinyl)oxazolidin-2-one (E-53ba) (Procedure B)



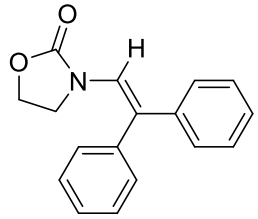
Pale yellow solid. (69% yield, 88 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.44-7.33 (m, 3H), 7.31-7.24 (m, 2H), 7.13 (*d*, J = 8.9 Hz, 2H), 7.06 (s, 1H), 6.83 (*d*, J = 8.9 Hz, 2H), 4.38-4.04 (m, 2H), 3.81 (s, 3H), 3.45-3.01 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 158.9 (Cq), 157.4 (CO), 138.3 (Cq), 133.5 (Cq), 130.8 (2CH), 128.3 (2CH), 128.2 (2CH), 127.8 (CH), 126.2 (Cq), 121.1 (CH), 113.7 (2CH), 62.6 (OCH_2), 55.3 (OCH_3), 44.9 (NCH_2). **LC-MS:** m/z calculated for $C_{18}H_{17}NO_3$: 295.12. Found: 296.24 $[M+H]^+$; 313.30 $[M+NH_4]^+$.

(Z)-3-(1-(4-methoxyphenyl)-2-phenylvinyl)oxazolidin-2-one (Z-54ba) (Procedure C)



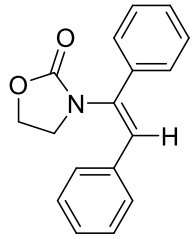
Yellow solid. (66% yield, 55 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.47-7.36 (m, 6H), 7.34-7.21 (m, 1H), 6.95 (*d*, J = 8.9 Hz, 2H), 6.78 (s, 1H), 4.53-4.35 (m, 2H), 3.85 (s, 3H), 3.76-3.65 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.2 (Cq), 156.4 (CO), 135.5 (Cq), 134.2 (Cq), 128.8 (2CH), 128.2 (2CH), 127.9 (CH), 127.3 (2CH), 125.1 (CH), 114.3 (2CH), 62.6 (OCH_2), 55.4 (OCH_3), 45.4 (NCH_2). **LC-MS:** m/z calculated for $C_{18}H_{17}NO_3$: 295.12. Found: 296.24 $[M+H]^+$; 313.30 $[M+NH_4]^+$.

3-(2,2-diphenylvinyl)oxazolidin-2-one (53bb) (Procedure B)



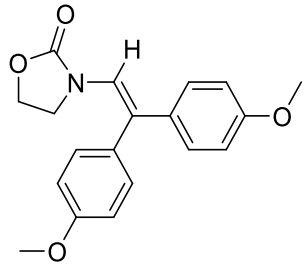
Pale yellow oil. (56% yield, 90 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.44-7.38 (m, 3H), 7.33-7.23 (m, 5H), 7.23-7.19 (m, 2H), 7.17 (s, 1H), 4.80-4.04 (m, 2H), 3.18-3.14 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 157.3 (CO), 140.9 (Cq), 138.0 (Cq), 130.9 (2CH), 128.3 (2CH), 128.2 (2CH), 127.9 (CH), 127.1 (3CH), 126.1 (Cq), 122.5 (CH), 62.7 (OCH_2), 44.9 (NCH_2). **LC-MS:** m/z calculated for $C_{17}H_{15}NO_2$: 265.11. Found: 266.46 $[M+H]^+$.

(Z)-3-(1,2-diphenylvinyl)oxazolidin-2-one (Z-54bb) (Procedure C)



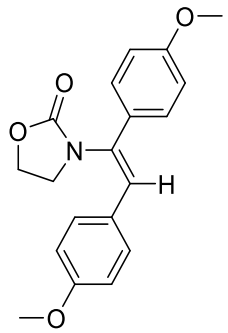
Pale yellow oil. (77% yield, 49 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.50-7.45 (m, 2H), 7.45-7.35 (m, 7H), 7.32-7.27 (m, 1H), 6.87 (s, 1H), 5.14-4.22 (m, 2H), 3.94-3.46 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 156.4 (CO), 136.4 (Cq), 135.3 (Cq), 134.6 (Cq), 128.9 (3CH), 128.8 (2CH), 128.3 (2CH), 128.2 (CH), 127.0 (CH), 125.9 (2CH), 62.6 (OCH_2), 45.4 (NCH_2). **LC-MS:** m/z calculated for $C_{17}H_{15}NO_2$: 265.11. Found: 266.46 $[M+H]^+$.

3-(2,2-bis(4-methoxyphenyl)vinyl)oxazolidin-2-one (53ca) (Procedure B)



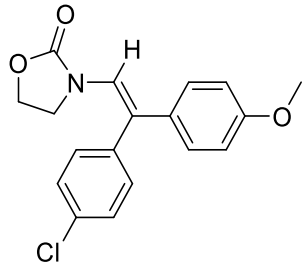
Yellow oil. (64% yield, 71 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.17 (*d*, J = 8.7 Hz, 2H), 7.13 (*d*, J = 8.9 Hz, 2H), 7.00 (s, 1H), 6.92 (*d*, J = 8.7 Hz, 2H), 6.81 (*d*, J = 8.9 Hz, 2H), 4.25-4.14 (m, 2H), 3.85 (s, 3H), 3.80 (s, 3H), 3.20-3.16 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.1 (Cq), 158.9 (Cq), 157.5 (CO), 133.8 (Cq), 131.8 (2CH), 130.3 (Cq), 128.3 (2CH), 126.2 (Cq), 120.9 (CH), 113.6 (4CH), 62.7 (OCH_2), 55.3 ($2OCH_3$), 45.0 (NCH_2). **LC-MS:** m/z calculated for $C_{19}H_{19}NO_4$: 325.13. Found: 326.17 $[M+H]^+$; 343.20 $[M+NH_4]^+$.

(Z)-3-(1,2-bis(4-methoxyphenyl)vinyl)oxazolidin-2-one (Z-54ca) (Procedure C)



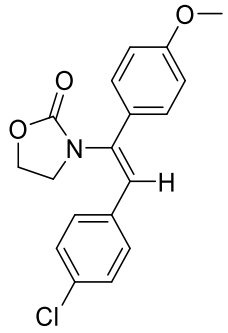
Pale yellow solid. (68% yield, 76 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.44-7.35 (m, 4H), 6.99-6.87 (m, 4H), 6.74 (s, 1H), 4.74-4.40 (m, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.80-3.32 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.9 (Cq), 159.2 (Cq), 156.5 (CO), 132.5 (Cq), 130.8 (Cq), 130.4 (Cq), 129.6 (2CH), 127.0 (2CH), 124.9 (CH), 114.3 (2CH), 114.2 (2CH), 62.6 (OCH_2), 55.4 (OCH_3), 55.3 (OCH_3), 45.3 (NCH_2). **LC-MS:** m/z calculated for $C_{19}H_{19}NO_4$: 325.13. Found: 326.17 $[M+H]^+$; 343.20 $[M+NH_4]^+$.

(Z)-3-(2-(4-chlorophenyl)-2-(4-methoxyphenyl)vinyl)oxazolidin-2-one (Z-53da) (Procedure B)



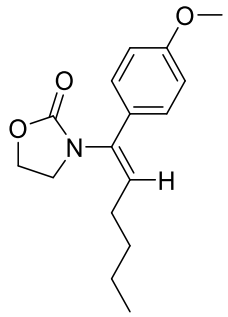
Yellow solid. (60% yield, 69 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.38 (*d*, J = 8.4 Hz, 2H), 7.21 (*d*, J = 8.4 Hz, 2H), 7.10 (*d*, J = 8.8 Hz, 2H), 7.05 (s, 1H), 6.83 (*d*, J = 8.8 Hz, 2H), 4.30-4.21 (m, 2H), 3.81 (s, 3H), 3.29-3.14 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.1 (Cq), 157.3 (CO), 136.9 (Cq), 133.8 (Cq), 133.1 (Cq), 132.1 (2CH), 128.5 (2CH), 128.3 (2CH), 124.9 (Cq), 121.7 (CH), 113.8 (2CH), 62.6 (OCH_2), 55.3 (OCH_3), 45.1 (NCH_2). **LC-MS:** m/z calculated for $C_{18}H_{16}ClNO_3$: 329.08. Found: 330.12 $[M+H]^+$; 347.16 $[M+NH_4]^+$.

(Z)-3-(2-(4-chlorophenyl)-1-(4-methoxyphenyl)vinyl)oxazolidin-2-one (Z-54da) (Procedure C)



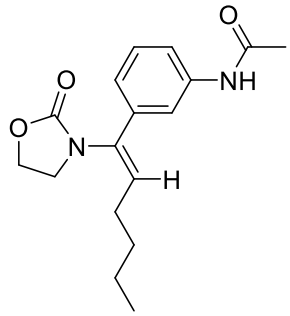
Pale yellow solid. (63% yield, 78 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.41 (*d*, J = 8.8 Hz, 2H), 7.35 (s, 4H), 6.95 (*d*, J = 8.8 Hz, 2H), 6.71 (s, 1H), 4.58-4.40 (m, 2H), 3.85 (s, 3H), 3.75-3.67 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.4 (Cq), 156.2 (CO), 134.8 (Cq), 134.0 (Cq), 133.5 (Cq), 129.5 (2CH), 128.9 (2CH), 128.4 (Cq), 127.4 (2CH), 123.9 (CH), 114.4 (2CH), 62.5 (OCH_2), 55.4 (OCH_3), 45.4 (NCH_2). **LC-MS:** m/z calculated for $C_{18}H_{16}ClNO_3$: 329.08. Found: 330.12 $[M+H]^+$; 347.16 $[M+NH_4]^+$.

(Z)-3-(1-(4-methoxyphenyl)hex-1-en-1-yl)oxazolidin-2-one (Z-54ea) (Procedure A)



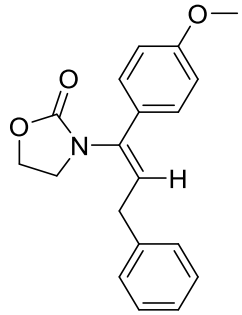
Yellow oil. (83% yield, 134 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.27-7.23 (m, 2H), 6.86-6.83 (m, 2H), 5.87 (*t*, J = 7.1, 1H), 4.47-4.41 (m, 2H), 3.79 (s, 3H), 3.66-3.60 (m, 2H), 2.20-2.15 (m, 2H), 1.46-1.24 (m, 4H), 0.92 (*t*, J =6.5 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.6 (Cq), 156.6 (CO), 133.2 (Cq), 128.9 (Cq), 127.8 (2CH), 113.7 (2CH), 108.8 (CH), 62.3 (OCH_2), 55.3 (OCH_3), 45.8 (NCH_2), 31.3 (CH_2), 27.9 (CH_2), 22.6 (CH_2), 14.2 (CH_3). **LC-MS:** m/z calculated for $C_{16}H_{21}NO_3$: 275.15. Found: 275.19 $[M]^+$; 292.25 $[M+NH_4]^+$.

(Z)-N-(3-(1-(2-oxooxazolidin-3-yl)hex-1-en-1-yl)phenyl)acetamide (Z-54ec) (Procedure A)



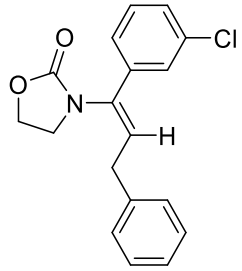
White solid. (42% yield, 73 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.40 (s, 1H), 7.41 (*dt*, J = 7.9, 1.2 Hz, 1H), 7.31 (s, 1H), 7.13 (*t*, J = 7.9 Hz, 1H), 6.98 (*dt*, J = 7.9, 1.2 Hz, 1H), 5.95 (*t*, J = 7.2, 1H), 4.44-4.40 (m, 2H), 3.64-3.60 (m, 2H), 2.12 (*q*, J = 7.3 Hz, 2H), 2.00 (s, 3H), 1.45-1.34 (m, 2H), 1.34-1.25 (m, 1H), 0.84 (*t*, J = 7.3 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 169.2 (CO), 157.1 (CO), 138.9 (Cq), 136.0 (Cq), 133.3 (Cq), 130.9 (CH), 129.2 (CH), 121.0 (CH), 119.8 (CH), 116.9 (CH), 62.6 (OCH_2), 45.9 (NCH_2), 31.00 (CH_2), 28.0 (CH_2), 24.3 (CH_3), 22.6 (CH_2), 13.9 (CH_3). **LC-MS:** m/z 303.17 $[M+H]^+$; 320.22 $[M+NH_4]^+$. **HRMS** (EI): m/z, calculated for $C_{19}H_{19}NO_3$: $[M]^+$ 309.1365, Found: 309.1360.

(Z)-3-(1-(4-methoxyphenyl)-3-phenylprop-1-en-1-yl)oxazolidin-2-one (Z-54fa) (Procedure A)



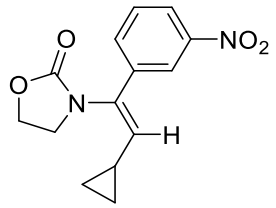
Yellow oil. (81% yield, 133 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.42-7.05 (m, 7H), 6.67 (*d*, J = 8.8 Hz, 2H), 5.96 (*t*, J = 7.1 Hz, 1H), 4.26-4.21 (m, 2H), 3.68 (s, 3H), 3.47-3.41 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.7 (Cq), 155.9 (CO), 147.8 (Cq), 141.3 (Cq), 139.9 (Cq), 129.7 (2CH), 128.8 (4CH), 126.5 (CH), 114.9 (2CH), 103.9 (CH), 65.9 (OCH_2), 55.0 (OCH_3), 44.1 (NCH_2), 29.9 (CH_2). **LC-MS:** m/z calculated for $C_{19}H_{19}NO_3$: 309.14. Found: 310.06 $[M+H]^+$; 327.17 $[M+NH_4]^+$.

(Z)-3-(1-(3-chlorophenyl)-3-phenylprop-1-en-1-yl)oxazolidin-2-one (Z-54fd) (Procedure A)



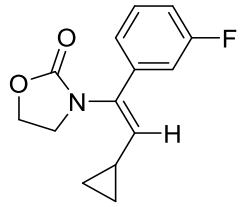
White solid. (86% yield, 144 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.40-7.36 (m, 1H), 7.30 (*dd*, J = 7.1, 1.5 Hz, 3H), 7.25-7.20 (m, 5H), 6.90 (s, 1H), 4.35-4.30 (m, 2H), 4.00 (s, 2H), 3.91-3.86 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 156.9 (CO), 143.1 (Cq), 138.9 (Cq), 134.4 (Cq), 129.7 (Cq), 128.8 (2CH), 128.6 (CH), 127.8 (2CH), 127.2 (CH), 126.5 (CH), 126.4 (CH), 125.0 (CH), 124.5 (CH), 62.4 (OCH_2), 45.4 (NCH_2), 35.2 (CH_2). **LC-MS:** m/z 314.06 $[M+H]^+$; 331.10 $[M+NH_4]^+$. **HRMS** (EI): m/z, calculated for $C_{18}H_{16}ClNO_2$: $[M]^+$ 313.0870, Found: 313.0870.

(Z)-3-(2-cyclopropyl-1-(3-nitrophenyl)vinyl)oxazolidin-2-one (Z-54ge) (Procedure A)



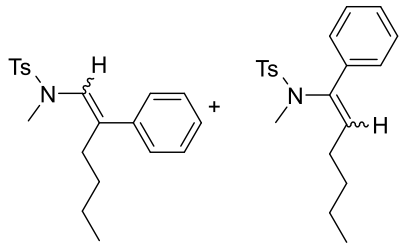
White solid. (54% yield, 79 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.10 (*t*, J = 2.0 Hz, 1H), 8.06 (*dq*, J = 8.0, 1.1 Hz, 1H), 7.55 (*dq*, J = 8.0, 1.1 Hz, 1H), 7.45 (*t*, J = 8.0 Hz, 1H), 5.54 (*d*, J = 10.0 Hz, 1H), 4.66-4.41 (m, 2H), 3.87-3.67 (m, 2H), 1.61-1.53 (m, 1H), 1.07-0.90 (m, 2H), 0.64-0.60 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 156.6 (CO), 148.7 (Cq), 138.1 (Cq), 137.7 (CH), 131.5 (Cq), 130.8 (CH), 129.8 (CH), 122.5 (CH), 119.9 (CH), 62.5 (OCH_2), 45.9 (NCH_2), 11.5 (CH), 8.1 ($2CH_2$). **LC-MS:** m/z 275.06 $[M+H]^+$; 292.08 $[M+NH_4]^+$. **HRMS** (EI): m/z, calculated for $C_{14}H_{14}N_2O_4$: $[M]^+$ 274.0954, Found: 274.0950.

(Z)-3-(2-cyclopropyl-1-(3-fluorophenyl)vinyl)oxazolidin-2-one (Z-54gf) (Procedure A)



White solid. (76% yield, 44 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.22 (*td*, J = 8.0, 5.9 Hz, 1H), 7.01 (*dt*, J = 8.0, 1.3 Hz, 1H), 6.96-6.79 (m, 2H), 5.41 (*d*, J = 10.0 Hz, 1H), 4.47-4.43 (m, 2H), 3.90-3.43 (m, 2H), 1.58-1.49 (m, 1H), 1.04-0.73 (m, 2H), 0.56-0.52 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 163.2 (*d*, J = 245.9 Hz, CF), 156.7 (CO), 138.2 (Cq), 135.9 (CH), 131.6 (*d*, J = 2.5 Hz, Cq), 130.3 (*d*, J = 8.5 Hz, CH), 120.7 (CH), 114.7 (*d*, J = 21.3 Hz, CH), 112.1 (*d*, J = 22.7 Hz, CH), 62.4 (OCH_2), 45.8 (NCH_2), 11.3 (CH), 7.8 ($2CH_2$). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -103.4. **LC-MS:** m/z 248.16 $[M+H]^+$; 265.19 $[M+NH_4]^+$. **HRMS** (EI): m/z, calculated for $C_{14}H_{14}FNO_2$: $[M]^+$ 247.1009, Found: 247.1005.

***N*,4-dimethyl-*N*-(2-phenylhex-1-en1-yl)benzenesulfonamide (53hb) + *N*,4-dimethyl-*N*-(1-phenylhex-1-en-1-yl)benzenesulfonamide (54hb) (Procedure A)**

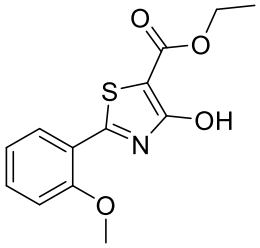


White sticky solid. (38% yield, 49 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.69 (*d*, J = 8.3 Hz, 2H, 53hb), 7.65 (*d*, J = 8.3 Hz, 1H, 53hb), 7.38-7.11 (m, 10H, 53hb + 54hb), 6.04 (*t*, J = 7.3 Hz, 0.5H, 53hb), 5.41 (*t*, J = 7.7 Hz, 1H, 54hb), 3.13 (s, 1.5H, 53hb), 2.99 (s, 3H, 54hb), 2.44 (s, 3H, 54hb), 2.42 (s, 1.5H, 53hb), 2.14-1.93 (m, 3H, 53hb + 54hb), 1.41-1.08 (m, 6 H, 53hb + 54hb), 0.87 (*t*, J = 7.2 Hz, 1.5H, 53hb), 0.82 (*t*, J = 7.1 Hz, 3H, 54hb). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 143.2 (Cq, 54hb), 143.2 (Cq, 53hb), 139.4 (Cq, 54hb), 138.9 (Cq, 53hb), 137.9 (Cq, 53hb), 137.2 (Cq, 53hb), 136.4 (Cq, 54hb), 136.1 (Cq, 54hb), 129.8 (3CH, 53hb), 129.4 (3CH, 54hb), 129.1 (2CH, 54hb), 128.3 (2CH, 53hb), 128.0 (2CH, 54hb), 127.9 (2CH, 53hb), 127.8 (2CH, 54hb), 127.6 (CH, 53hb), 127.5 (2CH, 53hb), 126.0 (CH, 54hb), 38.1 (NCH_3, 54hb), 37.7 (NCH_3, 53hb), 31.8 (CH_2, 54hb), 31.2 (CH_2, 53hb), 28.6 (CH_2, 53hb), 28.3 (CH_2, 54hb), 22.6 (CH_2, 53hb), 22.2 (CH_2, 54hb), 21.6 (CH_3, 54hb), 21.5 (CH_3, 53hb), 13.9 (CH_3, 53hb), 13.8 (CH_3, 54hb). **GC-MS** (EI, 70 eV): m/z calculated for $C_{20}H_{25}NO_2S$: $[M]^+$ 343.16. Found: 343.25.

11.9 Design and synthesis of phenyl thiazoles as potential TRPM8 antagonists

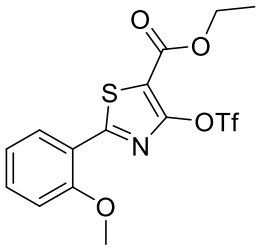
11.9.1 Synthetic procedures and characterisation of **V1** and **V2**

Ethyl 4-hydroxy-2-(2-methoxyphenyl)thiazole-5-carboxylate (67)



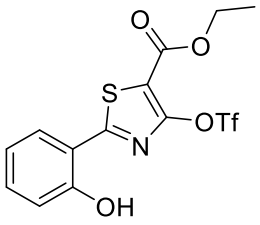
2-methoxybenzothioamide (17.9 mmol) was dissolved in ethanol (54 mL) in a microwave vessel, equipped with a magnetic stirrer bar; the solution was then added with diethyl 2-bromomalonate (17.94 mmol). The vessel was sealed and stirred under microwave irradiation at 110°C for 30 minutes. Upon cooling down to room temperature, the product **67** precipitated from the reaction mixture and was collected by filtration under vacuum. Pale brown solid. (2.005 g, 50% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.90 (br, 1H, OH), 8.49 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.48 (ddd, *J* = 8.4, 7.9, 1.7 Hz, 1H), 7.11 (ddd, *J* = 8.4, 7.9, 1.1 Hz, 1H), 7.06 (dd, *J* = 8.4, 1.0 Hz, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 4.09 (s, 3H), 1.43 (t, *J* = 7.1 Hz, 3H).

Ethyl 2-(2-methoxyphenyl)-4-(((trifluoromethyl)sulfonyl)oxy)thiazole-5-carboxylate (68)



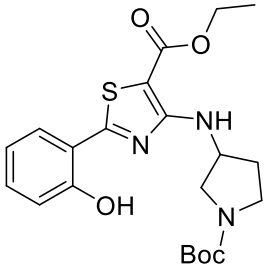
To a solution of **67** (4.36 mmol, 1 equiv.) in CH_2Cl_2 dry (20 mL), under inert atmosphere and at -15°C, triethylamine (6.54 mmol, 1.5 equiv.) and triflic anhydride (8.72 mmol, 2 equiv.) were sequentially added. The reaction mixture was slowly brought to room temperature and left stirring overnight. After completion, as monitored by TLC and GC-MS analysis, water was added and the aqueous phase was extracted with CH_2Cl_2. The organic phases were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude was purified by column chromatography over silica gel with hexane/AcOEt from 95:5 to 90:10 v/v. White solid. (1.687 g, 94% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.35 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.51 (ddd, *J* = 8.4, 7.3, 1.7 Hz, 1H), 7.13 (ddd, *J* = 8.0, 7.3, 1.1 Hz, 1H), 7.08 (dd, *J* = 8.4, 1.1 Hz, 1H), 4.45 (q, *J* = 7.1 Hz, 2H), 4.11 (s, 3H), 1.45 (t, *J* = 7.2 Hz, 3H).

Ethyl 2-(2-hydroxyphenyl)-4-(((trifluoromethyl)sulfonyl)oxy)thiazole-5-carboxylate (70)



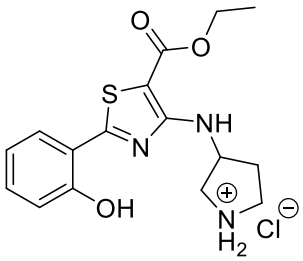
To a solution of **68** (1.75 mmol, 1 equiv.) in CH_2Cl_2 dry (15 mL), under inert atmosphere and at 0°C, a solution of BBr_3 (1M in CH_2Cl_2 dry, 7 mmol, 4 equiv.) was added dropwise. The solution turns to yellow. After the addition is completed, the reaction mixture was warmed to room temperature and left stirring for 4 hours. At the end of the reaction, as monitored by TLC, the mixture was quenched with water and the left stirring for an addition 30 minutes. The aqueous phase was separated and extracted with AcOEt. The organic phases were united, dried over Na_2SO_4 and concentrated under vacuum. The crude was further purified by column chromatography over silica gel with hexane/AcOEt from 95:5 to 90:10 v/v. Yellow solid. (361 mg, 52% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.49 (s, br, 1H), 7.63 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.45 (ddd, *J* = 8.6, 7.2, 1.6 Hz, 1H), 7.09 (dd, *J* = 8.6, 1.1 Hz, 1H), 6.98 (td, *J* = 7.2, 1.1 Hz, 1H), 4.47 (q, *J* = 7.1 Hz, 2H), 1.45 (t, *J* = 7.1 Hz, 3H).

Ethyl 4-((1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)amino)-2-(2-hydroxyphenyl)thiazole-5-carboxylate (71)



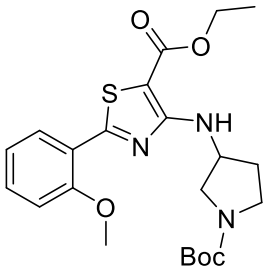
THF dry (2.5 mL) was added in a microwave vessel, equipped with a magnetic stirrer bar and previously dried by heating. Under inert atmosphere, Xantphos (0.025 mmol, 10 mol%) and $Pd_2(dba)_3$ (0.0125 mmol, 5 mol%) were added. The mixture was left stirring for 20 minutes at room temperature. Then, **70** (0.25 mmol, 1 equiv.) was added and the mixture was stirred for 10 minutes at room temperature. At the end, Cs_2CO_3 (0.35 mmol, 1.5 equiv.) and *tert*-butyl 3-aminopyrrolidine-1-carboxylate (0.3 mmol, 1.2 equiv.) were added. The vessel was sealed and stirred under microwave irradiation at 135°C for 1 hour. At the end, the solvent was removed under vacuum and the crude was purified by column chromatography over silica gel using hexane/AcOEt from 95:5 to 90:10 v/v. White solid. (27 mg, 23% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.61 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.39 (ddd, *J* = 8.6, 7.3, 1.6 Hz, 1H), 7.05 (dd, *J* = 8.6, 1.1 Hz, 1H), 6.97-6.85 (m, 1H), 4.60-4.49 (m, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.77 (dd, *J* = 11.3, 6.3 Hz, 1H), 3.52 (ddt, *J* = 15.6, 10.7, 6.3 Hz, 2H), 3.36 (s, 2H), 2.43-2.20 (m, 1H), 2.01 (dq, *J* = 12.8, 6.3 Hz, 1H), 1.49 (s, 9H), 1.38 (t, *J* = 7.1 Hz, 3H).

3-((5-(ethoxycarbonyl)-2-(2-hydroxyphenyl)thiazol-4-yl)amino)pyrrolidin-1-ium chloride (V1)



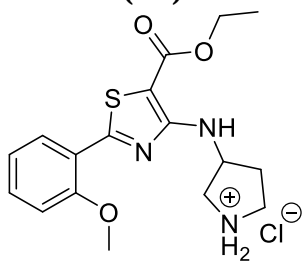
71 (0.056 mmol, 1 equiv.) was dissolved in dioxane (3 mL) and then HCl 4N (1.12 mmol, 20 equiv.) was added dropwise. The reaction was stirred at room temperature for 24 hours. At the end, as monitored by TLC, the mixture was concentrated under vacuum, yielding the desired product without further purification. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 9.60 (br, 1H, NH_2), 9.47 (br, 1H, NH_2), 7.82-7.46 (m, 1H), 7.27 (d, *J* = 8.3 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 6.8 Hz, 1H), 4.79 (q, *J* = 6.4 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.52 (d, *J* = 9.1 Hz, 1H), 3.36 (d, *J* = 9.9 Hz, 2H), 3.30-3.02 (m, 2H), 2.34 (dq, *J* = 13.9, 7.0 Hz, 1H), 2.03 (dq, *J* = 13.9, 7.0 Hz, 1H), 1.29 (t, *J* = 7.0 Hz, 3H). **UPLC-MS** (Esi, positive ion): m/z calculated for $C_{23}H_{30}N_4O_4S$: 458.58. Found: 458.61.

Ethyl 4-((1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)amino)-2-(2-methoxyphenyl)thiazole-5-carboxylate (69)



THF dry (2.5 mL) was added in a microwave vessel, equipped with a magnetic stirrer bar and previously dried by heating. Under inert atmosphere, Xantphos (0.024 mmol, 10 mol%) and $Pd_2(dba)_3$ (0.012 mmol, 5 mol%) were added. The mixture was left stirring for 20 minutes at room temperature. Then, **68** (0.24 mmol, 1 equiv.) was added and the mixture was stirred for 10 minutes at room temperature. At the end, Cs_2CO_3 (0.34 mmol, 1.5 equiv.) and *tert*-butyl 3-aminopyrrolidine-1-carboxylate (0.29 mmol, 1.2 equiv.) were added. The vessel was sealed and stirred under microwave irradiation at 135°C for 1 hour. At the end, the solvent was removed under vacuum and the crude was purified by column chromatography over silica gel using hexane/AcOEt from 95:5 to 90:10 v/v. White solid. (71 mg, 64% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.44 (dt, *J* = 7.9, 1.7 Hz, 1H), 7.42 (ddd, *J* = 8.5, 5.2, 1.7 Hz, 1H), 7.08 (tt, *J* = 7.9, 1.2 Hz, 1H), 7.02 (dt, *J* = 8.5, 1.2 Hz, 1H), 4.75 (t, *J* = 6.1 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 4.04 (s, 3H), 3.83 (d, *J* = 9.1 Hz, 1H), 3.57 (dt, *J* = 11.0, 5.6 Hz, 1H), 3.53-3.41 (m, 1H), 3.37-3.17 (m, 1H), 2.29 (dq, *J* = 13.9, 7.0 Hz, 1H), 1.98 (dq, *J* = 13.9, 7.0 Hz, 1H), 1.48 (s, 9H), 1.38 (t, *J* = 7.2 Hz, 3H).

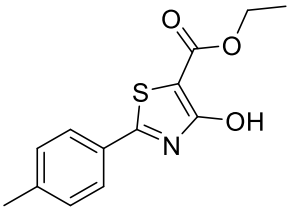
3-((5-(ethoxycarbonyl)-2-(2-methoxyphenyl)thiazol-4-yl)amino)pyrrolidin-1-ium chloride (V2)



69 (0.16 mmol, 1 equiv.) was dissolved in dioxane (3 mL) and then HCl 4N (3.2 mmol, 20 equiv.) was added dropwise. The reaction was stirred at room temperature for 21 hours. At the end, as monitored by TLC, the mixture was concentrated under vacuum, yielding the desired product without further purification. White solid. (60 mg, 99% yield). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 9.60 (br, 1H, NH_2), 9.47 (br, 1H, NH_2), 7.82-7.46 (m, 1H), 7.27 (d, *J* = 8.3 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 6.8 Hz, 1H), 4.79 (q, *J* = 6.4 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 4.04 (s, 3H), 3.52 (d, *J* = 9.1 Hz, 1H), 3.36 (d, *J* = 9.9 Hz, 2H), 3.30-3.02 (m, 2H), 2.34 (dq, *J* = 13.9, 7.0 Hz, 1H), 2.03 (dq, *J* = 13.9, 7.0 Hz, 1H), 1.29 (t, *J* = 7.0 Hz, 3H). **UPLC-MS** (ESI, positive ion): m/z calculated for $C17H22ClN_3O_3S$: 383.89, Found: 383.87.

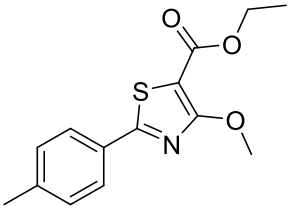
11.9.2 Synthetic procedures and characterisation of **V3**

Ethyl 4-hydroxy-2-(*p*-tolyl)thiazole-5-carboxylate (72)



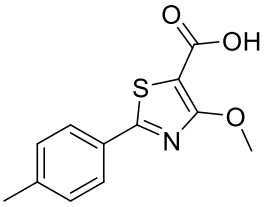
4-methylbenzothioamide (19.83 mmol) was dissolved in ethanol (54 mL) in a microwave vessel, equipped with a magnetic stirrer bar; the solution was then added with diethyl 2-bromomalonate (19.83 mmol). The vessel was sealed and stirred under microwave irradiation at 110°C for 30 minutes. Upon cooling down to room temperature, the product **72** precipitated from the reaction mixture and was collected by filtration under vacuum. Yellow solid. (2.672 g, 51% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.87 (br, 1H, OH), 8.70-7.56 (m, 2H), 7.49-6.91 (m, 2H), 4.32 (q, *J* = 7.1 Hz, 2H), 2.34 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H).

Ethyl 4-methoxy-2-(*p*-tolyl)thiazole-5-carboxylate (73)



72 (4.56 mmol, 1 equiv.) was dissolved in a mixture of THF (9 mL) and DMSO (1.5 mL), at 0°C and in an inert atmosphere. NaH (9.12 mmol, 2 equiv.) was slowly added and then MeI (91.2 mmol, 20 equiv.) was added dropwise. At the end of the addition, the solution was slowly warmed to 60°C and left stirring for 3 hours. At the end, as monitored by TLC and GC-MS analysis, the mixture was diluted with water and AcOEt. The organic phase was separated and sequentially washed with HCl 1N, a saturated solution of $Na_2S_2O_5$ and brine. The organic phase was dried over Na_2SO_4 and concentrated under vacuum. The crude was further purified by column chromatography over silica gel with hexane/AcOEt from 95:5 to 90:10 v/v. Yellow solid. (764 mg, 60% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.02-7.66 (m, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 4.34 (q, *J* = 7.1 Hz, 2H), 4.24 (s, 3H), 2.42 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H).

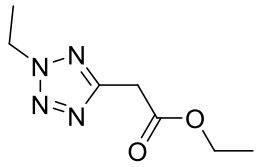
4-methoxy-2-(*p*-tolyl)thiazole-5-carboxylic acid (74)



To a solution of **73** (2.7 mmol, 1 equiv.) in EtOH (20 mL) and H_2O (20 mL), KOH (27 mmol, 10 equiv.) was added. The obtained suspension was heated to 40°C and stirred for 5 hours. At the end, as monitored by TLC, the solution was diluted with water and the pH was adjusted to approximately 1 using HCl 37%. The product precipitated and was recovered by filtration. White solid. (593 mg, 80% yield). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 12.81 (s, 1H), 9.25-7.53 (m, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 4.10 (s, 3H), 2.36 (s, 3H).

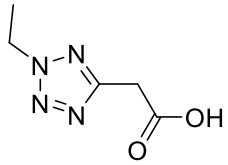
11.9.3 Synthetic procedures and characterisation of **V4**

Ethyl 2-(2-ethyl-2*H*-tetrazol-5-yl)acetate (77)



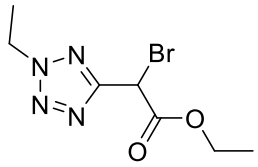
Ethyl 2-(2*H*-tetrazol-5-yl)acetate (32 mmol, 1 equiv.) was dissolved in CH_3CN dry (20 mL). The solution was cooled to 0°C and, in an inert atmosphere, triethylamine (38 mmol 1.2 equiv.) and EtI (64 mmol, 2 equiv.) were sequentially added. Then, the mixture was brought to room temperature and left stirring overnight. At the end of the reaction, as monitored by TLC, the mixture was extracted with brine and AcOEt. The organic phases were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude was purified by column chromatography over silica gel with hexane/AcOEt from 70:30 to 50:50 v/v. Yellow oil. (2.8 g, 48% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.66 (q, *J* = 7.4 Hz, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.97 (s, 2H), 1.64 (t, *J* = 7.4 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H).

2-(2-ethyl-2*H*-tetrazol-5-yl)acetic acid (78)



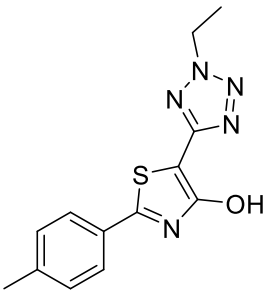
To the solution obtained dissolving **77** (12 mmol, 1 equiv.) in dioxane (10 mL) and EtOH (10 mL), a solution of NaOH (24 mmol, 2 equiv.) in H_2O (5 mL) was added dropwise. The reaction proceeded at room temperature overnight. At the end, as monitored by TLC, the pH of the reaction mixture was adjusted to approximately 1 using HCl 37% and then it was extracted using brine and AcOEt. The organic phases were dried over Na_2SO_4, filtered and concentrated under vacuum. White solid. (1.299 g, 69%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.66 (q, *J* = 7.4 Hz, 2H), 4.04 (s, 2H), 1.63 (t, *J* = 7.4 Hz, 3H).

Ethyl 2-bromo-2-(2-ethyl-2*H*-tetrazol-5-yl)acetate (79)



To the solution obtained dissolving **78** (7.9 mmol, 1 equiv.) in CH_2Cl_2 (20 mL), at 0°C and in an inert atmosphere, PCl_3 (3.95 mmol, 0.5 equiv.) and Br_2 (7.9 mmol, 1 equiv.) were added dropwise. The reaction mixture was brought to room temperature and left stirring for 24 hours. At the end, as monitored by GC-MS, the mixture was quenched with 20 mL of EtOH and then concentrated under reduced pressure. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.72 (s, 1H), 4.33 (q, *J* = 7.4 Hz, 2H), 3.88 (q, *J* = 7.1 Hz, 2H), 1.68 (t, *J* = 7.4 Hz, 3H), 1.37 (t, *J* = 7.1 Hz, 3H).

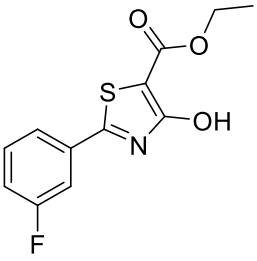
5-(2-ethyl-2*H*-tetrazol-5-yl)-2-(*p*-tolyl)thiazol-4-ol (80)



79 (5.7 mmol) was dissolved in ethanol (15 mL) in a microwave vessel, equipped with a magnetic stirrer bar; the solution was then added with diethyl 2-bromomalonate (5.7 mmol). The vessel was sealed and stirred under microwave irradiation at 110°C for 30 minutes. Upon cooling down to room temperature, the product **80** precipitated from the reaction mixture and was collected by filtration under vacuum. Pale yellow solid. (300 mg, 18% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 7.8 Hz, 2H), 4.72 (q, *J* = 7.4 Hz, 2H), 2.42 (s, 3H), 1.71 (t, *J* = 7.4 Hz, 3H).

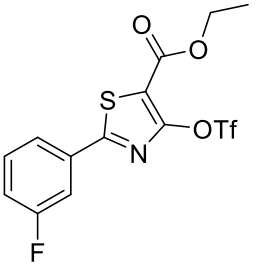
11.9.4 Synthetic procedures and characterisation of **V5-V10**

Ethyl 2-(3-fluorophenyl)-4-hydroxythiazole-5-carboxylate (85)



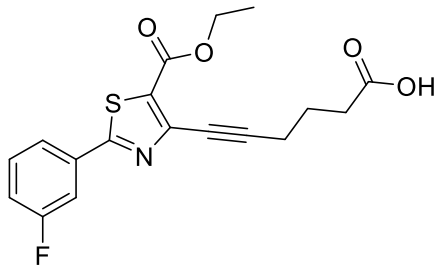
3-fluorobenzothioamide (19.32 mmol) was dissolved in ethanol (54 mL) in a microwave vessel, equipped with a magnetic stirrer bar; the solution was then added with diethyl 2-bromomalonate (19.32 mmol). The vessel was sealed and stirred under microwave irradiation at 110°C for 30 minutes. Upon cooling down to room temperature, the product **153** precipitated from the reaction mixture and was collected by filtration under vacuum. White solid. (2.947 g, 57% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.94 (br, 1H, OH), 8.16-7.64 (m, 2H), 7.45 (td, *J* = 8.0, 5.6 Hz, 1H), 7.21 (tdd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H).

Ethyl 2-(3-fluorophenyl)-4-(((trifluoromethyl)sulfonyl)oxy)thiazole-5-carboxylate (86)



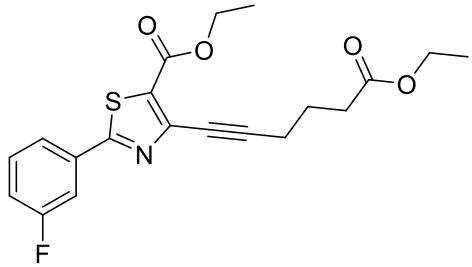
To a solution of **85** (3.08 mmol, 1 equiv.) in CH_2Cl_2 dry (20 mL), under inert atmosphere and at -15°C, triethylamine (4.62 mmol, 1.5 equiv.) and triflic anhydride (6.16 mmol, 2 equiv.) were sequentially added. The reaction mixture was slowly brought to room temperature and left stirring overnight. After completion, as monitored by TLC and GC-MS analysis, water was added and the aqueous phase was extracted with CH_2Cl_2. The organic phases were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude was purified by column chromatography over silica gel with hexane/AcOEt from 95:5 to 90:10 v/v. White solid. (1.165 g, 95% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.72 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.67 (ddd, *J* = 9.2, 2.5, 1.4 Hz, 1H), 7.48 (td, *J* = 8.1, 5.6 Hz, 1H), 7.25 (tdd, *J* = 8.1, 2.5, 0.9 Hz, 1H), 4.46 (q, *J* = 7.1 Hz, 2H), 1.45 (t, *J* = 7.1 Hz, 3H).

6-(5-(ethoxycarbonyl)-2-(3-fluorophenyl)thiazol-4-yl)hex-5-ynoic acid (V5)



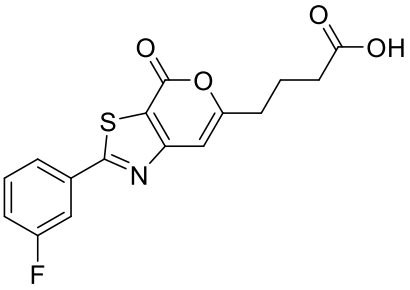
To a solution of **86** (0.52 mmol, 1 equiv.) in THF dry (20 mL), under inert atmosphere and at room temperature, triethylamine (10.4 mmol, 20 equiv.) and hex-5-ynoic acid (0.55 mmol, 1.05 equiv.) were added. Then, $PdCl_2(PPh_3)_2$ (0.0156 mmol, 3 mol%) was added and, after 10 minutes of stirring, CuI (0.0104 mmol, 2 mol%) was added too. The reaction mixture was left stirring overnight at room temperature. After completion, as monitored by TLC and UPLC-MS analysis, HCl 1N was added and the aqueous phase was extracted with AcOEt. The organic phases were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude was purified by column chromatography over silica gel with hexane/AcOEt from 80:20 to 50:50 v/v. White solid. (161 mg, 86% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.65 (dd, *J* = 7.0, 4.8 Hz, 2H), 7.40-7.28 (m, 1H), 7.11 (dd, *J* = 9.4, 6.9 Hz, 1H), 4.46 (q, *J* = 7.1 Hz, 2H), 2.66 (td, *J* = 7.0, 1.9 Hz, 2H), 2.59 (td, *J* = 7.0, 1.9 Hz, 2H), 2.05 (qd, *J* = 7.2, 1.9 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H). **UPLC-MS** (Esi, positive ion): m/z calculated for $C_{18}H_{16}FNO_4S$: 361.08. Found: 361.9 $[M+H]^+$, 383.72 $[M+Na]^+$.

Ethyl 4-(6-ethoxy-6-oxohex-1-yn-1-yl)-2-(3-fluorophenyl)thiazole-5-carboxylate (V6)



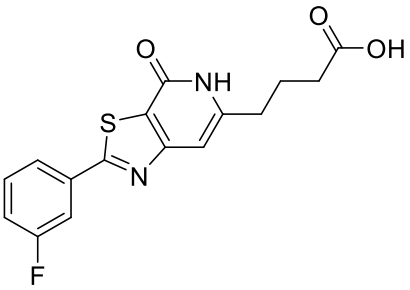
V5 (0.055 mmol, 1 equiv.) was dissolved in EtOH (1 mL) in a microwave vial, equipped with a magnetic stirrer bar. The vial was sealed after the addition of *p*-TsOH·H_2O (0.011 mmol, 20 mol%) and stirred under microwave irradiation at 160°C for 30 minutes. At the end of the reaction, as monitored by TLC and UPLC-MS, HCl 1 N was added and the mixture was extracted with CH_2Cl_2. The organic phases were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude was purified by column chromatography over silica gel with hexane/AcOEt 80:20 v/v. Pale brown solid. (16 mg, 76% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.80-7.71 (m, 2H), 7.54-7.39 (m, 1H), 7.21 (td, *J* = 8.2, 7.3, 4.0 Hz, 1H), 4.46 (q, *J* = 7.1 Hz, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.66 (td, *J* = 7.0, 1.9 Hz, 2H), 2.59 (td, *J* = 7.0, 1.9 Hz, 2H), 2.05 (qd, *J* = 7.2, 1.9 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H). **UPLC-MS** (Esi, positive ion): m/z calculated for $C_{20}H_{20}FNO_4S$: 389.11. Found: 390.16 $[M+H]^+$, 412.17 $[M+Na]^+$.

4-(2-(3-fluorophenyl)-4-oxo-4*H*-pyrano[4,3-d]thiazol-6-yl)butanoic acid (V7)



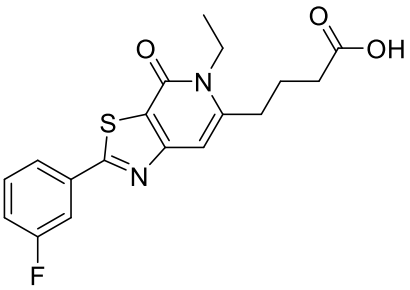
V5 (0.28 mmol, 1 equiv.) was dissolved in MeOH (2 mL); then, a solution obtained by dissolving KOH (2.8 mmol, 10 equiv.) in H_2O (2 mL) was added dropwise. The mixture was stirred at room temperature for 1 hour. At the end, as monitored by TLC and UPLC-MS, the mixture was brought to pH 1 with HCl 37% and then extracted with AcOEt. The carboxylic acid obtained (0.18 mmol, 1 equiv.) was dissolved in H_2O (1.5 mL) in a microwave vial equipped with a magnetic stirrer bar. After the addition of TBAF·$3H_2O$ (0.009 mmol, 5 mol%), the vial was sealed and stirred under microwave irradiation at 100°C for 1 hour. At the end of the reaction, as monitored by TLC and UPLC-MS, the precipitated product was recovered by vacuum filtration. White solid. (46 mg, 77% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.98 (d, *J* = 7.8 Hz, 1H), 7.94 (dd, *J* = 9.8, 2.2 Hz, 1H), 7.66 (q, *J* = 7.8 Hz, 1H), 7.52 (t, *J* = 8.6 Hz, 1H), 7.03 (s, 1H), 2.66 (td, *J* = 7.0, 1.9 Hz, 2H), 2.33 (td, *J* = 7.0, 1.9 Hz, 2H), 1.89 (qd, *J* = 7.2, 1.9 Hz, 2H). **UPLC-MS** (Esi, positive ion): m/z calculated for $C_{16}H_{12}FNO_4S$: 333.05. Found: 333.88 $[M+H]^+$, 666.93 $[2M+H]^+$.

4-(2-(3-fluorophenyl)-4-oxo-4,5-dihydrothiazolo[5,4-c]pyridin-6-yl)butanoic acid (V8)



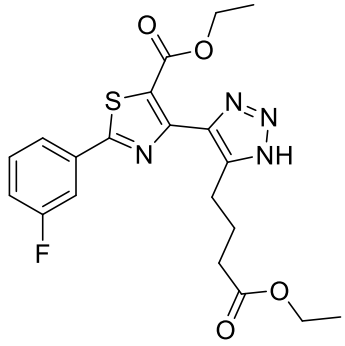
To a solution of **V7** (0.036 mmol) in MeOH (2 mL), NH_4OH 25% (14 mmol) was added. The reaction was stirred at 50°C overnight. At the end of the reaction, as monitored by TLC and UPLC-MS, the reaction mixture was concentrated under reduced pressure, dissolved in H_2O and acidified to pH 1 with HCl 37%. A white precipitate formed, which was recovered by vacuum filtration. White solid. (6 mg, 50% yield). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 12.17 (br, 1H, OH), 8.00 (d, *J* = 7.8 Hz, 1H), 7.96 (dd, *J* = 9.8, 2.2 Hz, 1H), 7.69 (q, *J* = 7.8 Hz, 1H), 7.53 (t, *J* = 8.6 Hz, 1H), 6.81 (s, 1H), 2.67 (td, *J* = 7.0, 1.9 Hz, 2H), 2.32 (td, *J* = 7.0, 1.9 Hz, 2H), 1.95 (qd, *J* = 7.2, 1.9 Hz, 2H). **UPLC-MS** (Esi, positive ion): m/z calculated for $C_{16}H_{13}FN_2O_3S$: 332.06. Found: 333.08 $[M+H]^+$, 663.26 $[2M+H]^+$.

4-(5-ethyl-2-(3-fluorophenyl)-4-oxo-4,5-dihydrothiazolo[5,4-c]pyridin-6-yl)butanoic acid (V9)



To a solution of **V7** (0.051 mmol) in H_2O (2 mL), $EtNH_2$ 2 M in THF (78 mmol) was added. The reaction was stirred at 50°C for 5 hours. At the end of the reaction, as monitored by TLC and UPLC-MS, the reaction mixture was concentrated under reduced pressure, dissolved in H_2O and acidified to pH 1 with HCl 37%. The aqueous phase was extracted with AcOEt. The organic phases were dried over Na_2SO_4, filtered and concentrated under vacuum. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 8.00 (d, *J* = 7.8 Hz, 1H), 7.96 (dd, *J* = 9.8, 2.2 Hz, 1H), 7.69 (q, *J* = 7.8 Hz, 1H), 7.53 (t, *J* = 8.6 Hz, 1H), 6.81 (s, 1H), 3.72 (q, *J* = 7.1 Hz, 2H), 2.67 (td, *J* = 7.0, 1.9 Hz, 2H), 2.32 (td, *J* = 7.0, 1.9 Hz, 2H), 1.95 (qd, *J* = 7.2, 1.9 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H). **UPLC-MS** (Esi, positive ion): m/z calculated for $C_{18}H_{17}FN_2O_3S$: 360.40. Found: 360.91 $[M+H]^+$, 720.80 $[2M+H]^+$.

Ethyl 4-(5-(4-ethoxy-4-oxobutyl)-1*H*-1,2,3-triazol-4-yl)-2-(3-fluorophenyl)thiazole-5-carboxylate (V10)

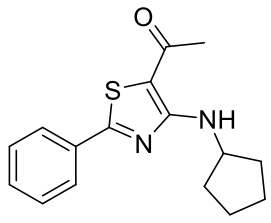


V5 (0.074 mmol, 1 Equiv.) was dissolved in DMSO (2 mL) in a microwave vial equipped with a magnetic stirrer bar. Then, NaN_3 (0.148 mmol, 2 equiv.) was added, the vial was sealed and stirred under microwave irradiation at 100°C for 5 hours. At the end, as monitored by TLC and UPLC-MS, the mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic phases were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude was purified by column chromatography over silica gel with hexane/AcOEt from 80:20 to 60:40 v/v. Yellow solid. (19 mg, 59% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 12.09 (s, br, 1H), 7.80-7.71 (m, 2H), 7.54-7.39 (m, 1H), 7.21 (td, *J* = 8.2, 7.3, 4.0 Hz, 1H), 4.46 (q, *J* = 7.1 Hz, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.66 (td, *J* = 7.0, 1.9 Hz, 2H), 2.59 (td, *J* = 7.0, 1.9 Hz, 2H), 2.05 (qd, *J* = 7.2, 1.9 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H). **UPLC-MS** (Esi, positive ion): m/z calculated for $C_{20}H_{21}FN_4O_4S$: 432.13. Found: 432.93 $[M+H]^+$, 454.85 $[M+Na]^+$.

11.9.5 General procedure for the metal-free reaction between triflates and amine

General procedure. In a microwave vial, equipped with a magnetic stirrer bar, triflate (0.18 mmol, 1 equiv.) was dissolved in DMSO (2 mL). Then, the appropriate amine (0.36 mmol, 2 equiv.) was added and the vial was sealed and stirred under microwave irradiation at 100°C for 30 minutes. After completion of the reaction, as monitored by TLC and UPLC-MS, water was added to the mixture and was extracted with CH_2Cl_2. The organic phases were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude was purified by column chromatography over silica gel with hexane/AcOEt from 90:10 to 50:50 v/v.

1-(4-(cyclopentylamino)-2-phenylthiazol-5-yl)ethan-1-one (83)



Yellow solid. (50 mg, 96% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.85 (dt, *J* = 7.8, 1.5 Hz, 2H), 7.57-7.52 (m, 2H), 7.46-7.43 (m, 1H), 2.75 (dd, *J* = 8.1, 7.0 Hz, 1H), 2.22 (s, 3H), 1.85-1.53 (m, 8H). **UPLC-MS** (Esi, positive ion): m/z calculated for $C16H18N_2O_2$: 286.11. Found: 287.16 $[M+H]^+$.

Acknowledgments

What an amazing journey this PhD has been! First of all, I would like to thank my supervisor, Prof. Antonio Arcadi, for giving me this great opportunity and for believing in me. The suggestions and the constant support I have received from him allowed me to grow both on a personal and professional point of view. I am also very grateful to Prof. Marco Chiarini, for his fundamental help in NMR acquisition and interpretation; without his help, this thesis would have not been possible and my knowledge on the field would have not increased so much.

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Beside chemistry, the most important thing that this PhD let me experience has been friendship. I am so much grateful to the people I met and worked with at University of L'Aquila which have been of unvaluable support. Making a list of people would fill up other 200 pages but, if you are reading this part, you know you are one of those.

Finally, I would like to thank my family, for always supporting me, even without a clear understanding of what I do for a living.

And then, the very last person to thank it's me, for never giving up, for always being so passionate about what I do and for always keeping a smile, even in the darkest time.

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