# SCIENTIFIC LETTER 15



## Edito

Dans le contexte sanitaire que nous avons tous connus en 2020 et en ce début 2021 notre équipe a dû et a su s'adapter à ces nouvelles conditions de travail et a continué d'assurer la livraison de vos projets. Ainsi en 2020, 85% des contrats ont été livrés dans les délais impartis et ce malgré un contexte sanitaire très particulier et contraignant.

Nous mesurons pleinement les efforts que vous avez dû réaliser pour maintenir vos projets de recherche et nous sommes fiers d'avoir pu participer à vos côtés à la synthèse de ces nouvelles entités chimiques, qui pour certaines répondent aux défis à relever dans la lutte contre le COVID.

Vous nous avez fait confiance tout au long de cette période aussi nous sommes ravis de vous annoncer l'arrivée ces derniers mois de trois nouveaux chimistes qui ont rejoint l'équipe d'AtlanChim Pharma : Dr.Thibaut Martinez, Anthony Dupont et Dr.Thomas Glachet. Ils nous enrichissent de leurs expériences en synthèse chimique et viennent compléter notre expertise en synthèse organique de petites molécules et en isolement et identification d'impuretés.

Vous pouvez retrouver toute l'actualité de notre société en consultant notre site internet et notre page linkedIn,. Et nous vous donnons rendez-vous le 27 mai 2021 à 15h pour le prochain webinaire de notre directeur scientifique Pr. Jacques Lebreton intitulé « La chimie du noyau isoquinoléine à travers des travaux récents ».

Dans cette attente nous vous proposons la lecture de notre nouvelle lettre scientifique « Traditional methods for synthesis of quinolines ».

Bonne lecture,

L'équipe AtlanChim Pharma

## Editorial

In the health context that we have all experienced throughout 2020 and beginning of 2021, our team had and managed to adapt to these new working conditions and ensured the achievement of your projects. In 2020, 85% of contracts were delivered on time, despite a very specific context.

We fully appreciate the efforts you had to make yourself to maintain your R&D projects and we are proud to have been able to participate alongside you in the synthesis of these new chemical entities, some of which meet the challenges to be taken up in the fight against COVID.

You have trusted us during this period, and we are delighted to announce the new arrival of three chemists who have joined our team : Dr. Thibaut Martinez, Anthony Dupont and Dr. Thomas Glachet. They enrich us with their experiences in chemical synthesis and reinforce our expertise in organic synthesis of small molecules and in the isolation and identification of impurities.

You can find all the latest news from our company by consulting our website or on our linkedIn page. And we look forward to seeing you on May 27th, 2021 at 3 p.m. for the next webinar presented by our scientific director Prof. Jacques Lebreton entitled " La chimie du noyau isoquinoléine à travers des travaux récents ".

In the meantime, we invite you to read our new scientific letter "Traditional methods for synthesis of quinolines".

Enjoy the reading,

The AtlanChim Pharma team

# Traditional methods for synthesis of quinolines*
## *(*The best broths are cooked in the oldest pans*)

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Quinoline represents a privileged framework that occurs in a large variety of biologically active natural products as well as in pharmaceuticals exhibiting a broad range of activities.[1] In view of the importance of quinoline and its derivatives, their preparation has received considerable attention from the organic synthesis community. In this context, numerous improvements of existing methodologies as well as novel pathways have been investigated and published over the last decades. The well-known traditional methods to construct the quinoline core include the Skraup, Skraup-Doebner-von Miller, Gould-Jacobs, Combes, Conrad-Limpach, Povarov, Niementowski, Friedländer and Pfitzinger reaction.[2] Even if, these well-established procedures often suffer from certain drawbacks such as harsh reaction conditions (i.e., strongly acidic media, high temperature, etc.), low functional group tolerance, side reactions and the unsatisfactory yields, they are still largely used.

This new *AtlanChim Pharma Scientific Letters* provides an overview on traditional methods for synthesis of quinolines highlighted through recent examples in Medicinal Chemistry.

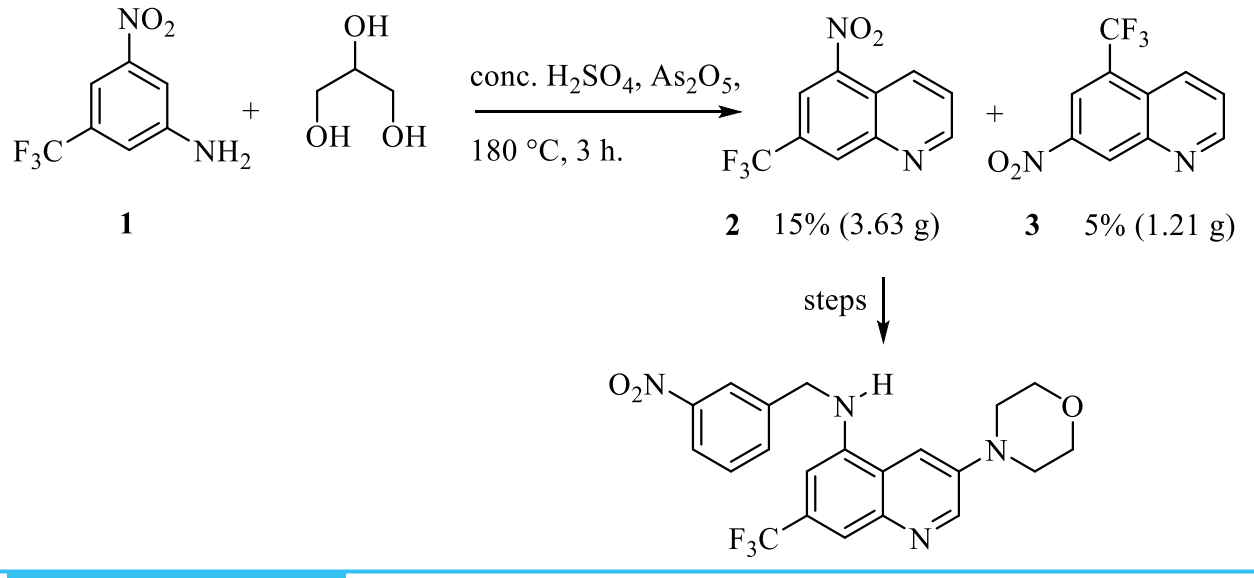
Many methods to prepare substituted quinolines are based on condensation of aniline derivatives with various annulation partners. In some cases, this strategy suffers from low regioselectivity with *meta*-substituted anilines providing after ring closure a mixture of 2,4-substituted quinoline derivatives (*vide supra*).

### Skraup reaction

The Skraup reaction was first described in 1880 and relies on the treatment of aniline with glycerol, to form by dehydration acrolein, with an oxidizing agent in concentrated sulfuric acid at high temperature.[3] Under these harsh reaction conditions large amounts of waste are formed leading to a tedious isolation of the desired quinoline in poor yields. The preparation of the quinoline derivative **2**, reported in Scheme 1, illustrated these limitations.

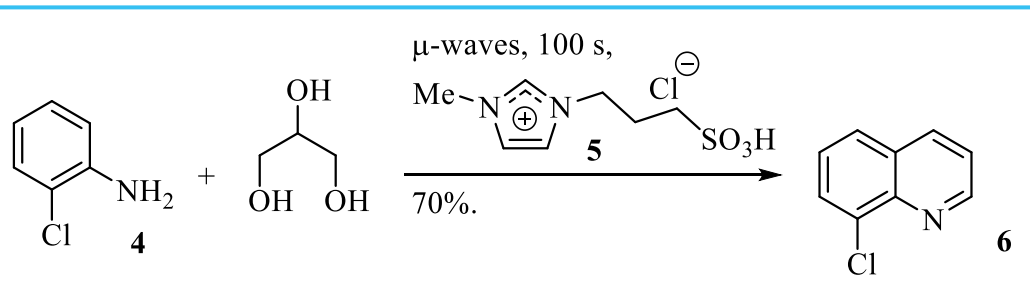
[1] A. Weyesa, E. Mulugeta, *RSC Adv.* **2020**, *10*, 20784-20793 and cited literature.
[2] (a) R. A. Mekheimer, M. A. Al-Sheikh, H. Y. Medrasi, K. U. Sadek, *RSC Adv.* **2020**, *10*, 19867-19935 and cited literature. (b) G. A. Ramann, B. J. Cowen, *Molecules* **2016**, *21*, 986; doi:10.3390/molecules21080986. (c) V. V. Kouznetsov, L. Y. Vargas Méndez, C. M. Meléndez Gómez, *Curr. Org. Chem.* **2005**, *9*, 141-161.
[3] Z. H. Skraup, *Ber. Dtsch. Chem. Ges.* **1880**, *13*, 2086.

Treatment of the commercially available 3-nitro-5-(trifluoromethyl)aniline **1** with glycerol, sulfuric acid, and arsenic pentoxide as oxidizing agent gave massive gummy reaction complex in which the targeted quinoline **2** was isolated in low yield accompanied with the other regioisomer **3**.[4] Attempts to perform this Skraup reaction with other oxidizing agents such as sodium 3-nitrobenzenesulfinate or green vitriol ($FeSO_4$,$7H_2O$) were not successful.




SCHEME 1

Several recent modifications have been addressed to avoid these harsh reaction conditions. In a recent report, Brönsted acidic ionic liquid 1-(1-propylsulfonic)-3-methylimidazolium chloride **5** has been used as catalyst and solvent to prepare the 8-subtituted quinoline **6** from the corresponding aniline **4** with glycerol under microwave irradiation to generate *in situ* acrolein (see Scheme 2).[5] It should be pointed out that under these reaction conditions the use of oxidizing agents, such as nitrobenzene or metal catalysts, is not necessary. The relative molar ratio between the three components, aniline, glycerol and ionic liquid, is 1/3/1.5.

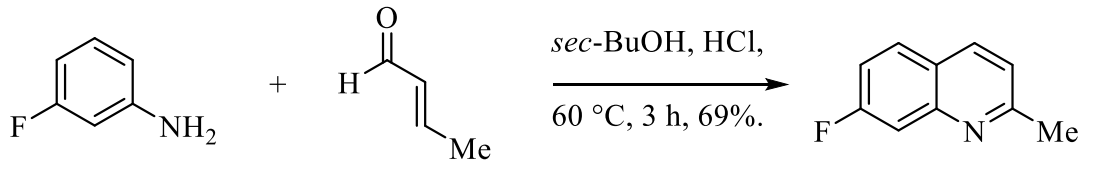



SCHEME 2

[4] Y. Wang, J. Ai, Y. Wang, Y. Chen, L. Wang, G. Liu, M. Geng, A. Zhang, *J. Med. Chem*. **2011**, *54*, 2127-2142.
[5] A. S. Amarasekara, M. A. Hasan, *Tetrahedron Letters* **2014**, *55*, 3319-3321.

**Skraup-Doebner-Von Miller quinoline synthesis**

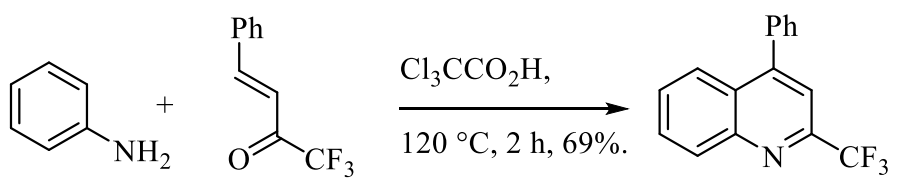
A variation of the Skraup procedure, the Doebner-Von Miller reaction was introduced in 1881 and uses α,β-unsaturated aldehydes or ketones, instead of glycerol, leading the preparation of quinolines with substituents on the pyridine ring, as presented in Scheme 3.[6]




SCHEME 3

It should be noted that the mechanism of this Skraup-Doebner-Von Miller quinoline synthesis was fully investigated by Denmark[7] using $^{13}C$-labelled substrates, but remains controversial and not well understood.[8]

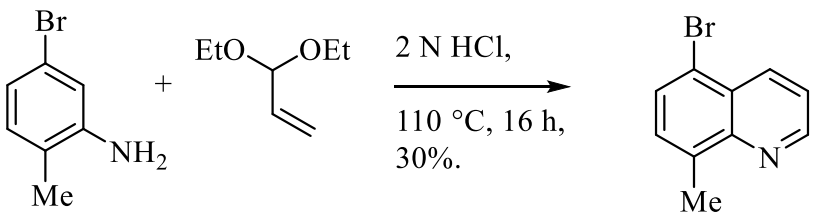
It is important to notice that a reversal of the standard regiochemistry of the Skraup-Doebner-Von Miller quinoline synthesis is observed when anilines have been condensed with β-phenyl-α,β-unsaturated trifluoromethyl ketone in hot trichloroacetic acid (TCA) (see Scheme 4).[9] The proposed mechanism involves 1,2-addition of the anilines to β-phenyl-α,β-unsaturated trifluoromethyl ketone to provide the corresponding Schiff's base adducts, followed by cyclization and oxidation.




SCHEME 4

[6] A. von Sprecher, M. Gerspacher, A. Beck, S. Kimmel, H. Wiestner, G. P. Anderson, U. Niederhauser, N. Subramanian, M. A. Bray, *Bioorg. Med. Chem. Lett*. **1998**, *8*, 965-970.
[7] S. E. Denmark, S. Venkatraman, *J. Org. Chem*. **2006**, *71*, 1668-1676.
[8] J. Fotie, H. V. K. Wangun, F. R. Fronczek, N. Massawe, B. T. Bhattarai, J. L. Rhodus, T. A. Singleton, D. S. Bohle, *J. Org. Chem*. **2012**, *77*, 2784-2790.
[9] Q.-W. Pan, J.-H. Wang, Q. Wang, H.-J. Li, Y.-C. Wu, *Chemistry Select* **2020**, *5*, 4099-4103.

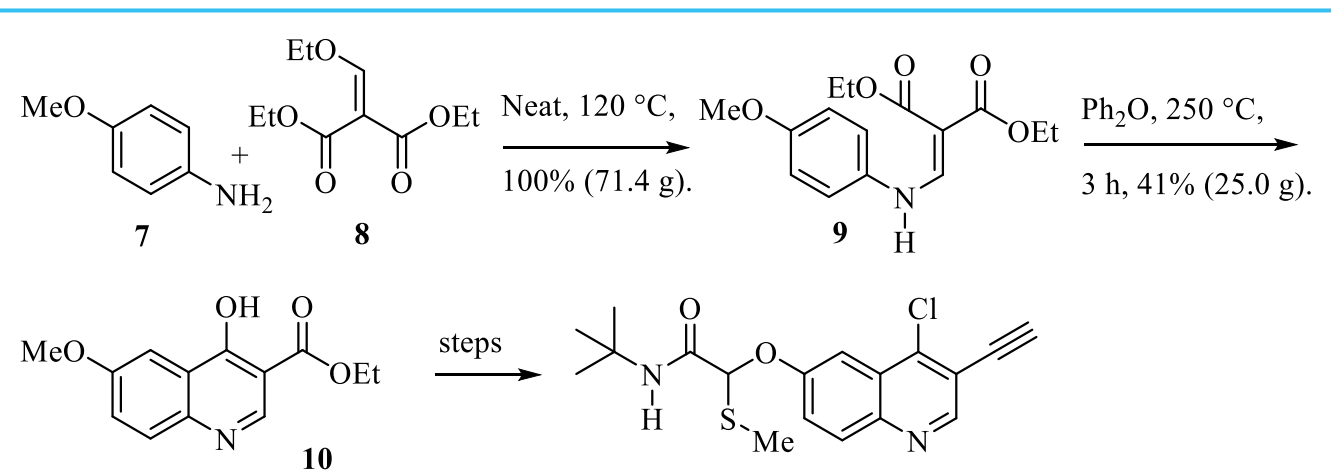
An improvement to this Skraup-Doebner-Von Miller quinoline synthesis was the use of acrolein diethyl acetal[10] as annulation partner, instead of acrolein, as described in Scheme 5.[11] If compared to pure acrolein, commercially available acrolein diethyl acetal is less costly and has no potency to oligomerize, nevertheless yields are still modest in the range of 30-40%.




SCHEME 5

**Gould-Jacobs reaction**

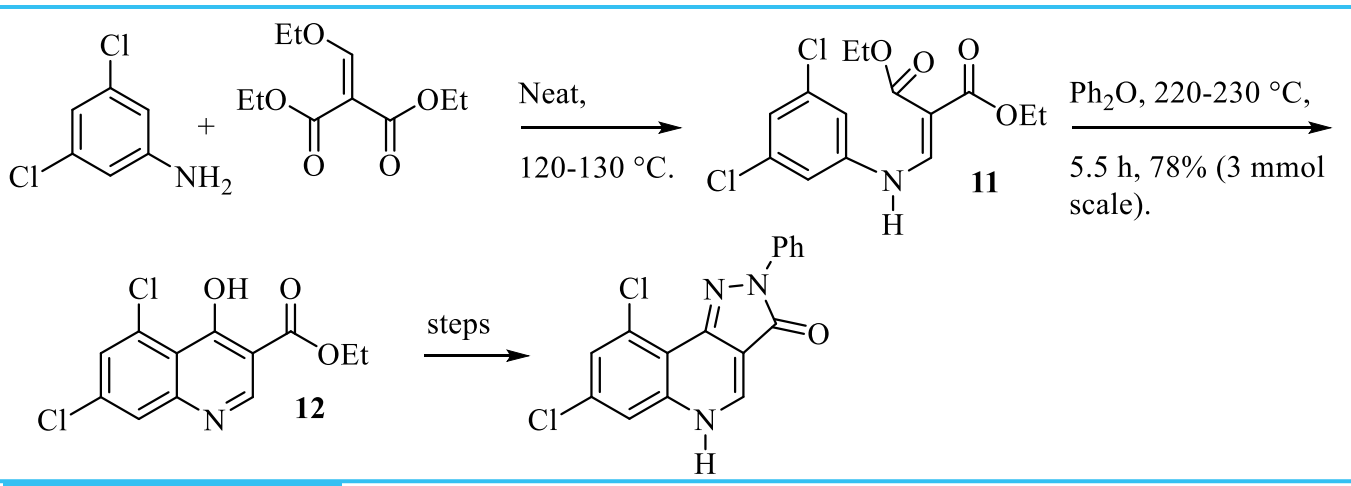
Pericyclic annulations of aniline derivatives with diethyl ethoxymethylenemalonate **8** to provide quinolin-4-ol nucleus is known as Gould-Jacobs reaction.[12] This cyclization is a versatile tool which is largely applied to the preparation of quinoline scaffolds offering various possibilities for the introduction of an additional substituent at C-4 position. This efficient method was used with success to obtain 3,4,6-trisubstituted quinoline derivatives as outlined in Scheme 6.[13] Condensation of diethyl ethoxymethylenemalonate **8** and *para*-anisidine **7** without solvent afforded the anilinodiester intermediate **9** which was subsequently submitted to Gould-Jacobs cyclization to provide the 3,4,6- trisubstituted quinoline derivative **10**.




SCHEME 6

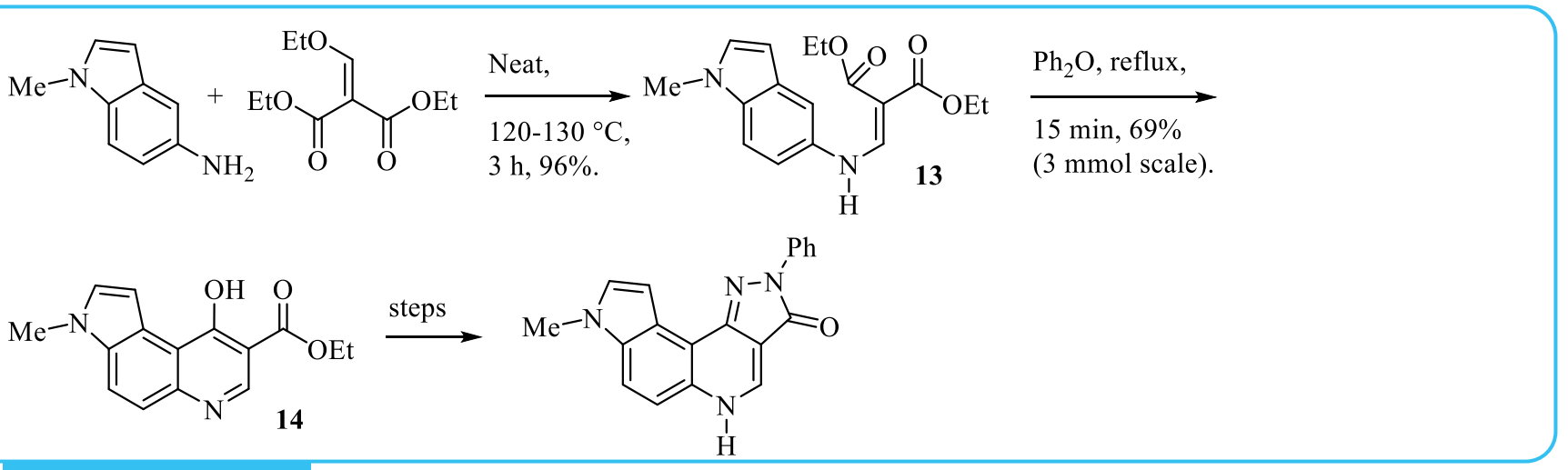
[10] G. A. Ramann, B. J. Cowen, *Tetrahedron Letters* **2015**, *56*, 6436-6439.
[11] B. A. Sherer, Brian *et al*, WO **2019**/018354 Al.
[12] R. Gould, W. Jacobs, *J. Am. Chem. Soc*. **1939**, *61*, 2890-2895.
[13] S. Trah, C. Lamberth, *Tetrahedron Letters* **2017**, *58*, 794-796.
.

It is worth noting that the intramolecular thermal Gould-Jacobs cyclization in diphenyl ether could be problematic as depicted in Scheme 7.[14] At 220-230 °C, and with strict control of the temperature, the cyclization of the enamine intermediate **11** proceeded efficiently to give the desired quinolin-4-ol **12** in 78% yield. At 180-210 °C, the product was formed in low yields (20-30%) and at refluxing diphenyl ether (257°C), the decomposition of the solvent with prolonged reaction times considerably complicates the purification process.




SCHEME 7

In the preparation of pyrazolo[4,3-c]pyrrolo[3,2-f]quinolin-3-one derivatives, the key intramolecular thermal Gould-Jacobs cyclization was performed efficiently by adding portions of anilinodiester intermediate **13** to refluxing phenyl ether, for 15 minutes to afford the corresponding tricyclic pyrroloquinoline 8-ethyl ester **14** in 69% yield as reported in Scheme 8.[15] It should be pointed out that the cyclization of the enamine **13** led exclusively to the formation of one regioisomer.

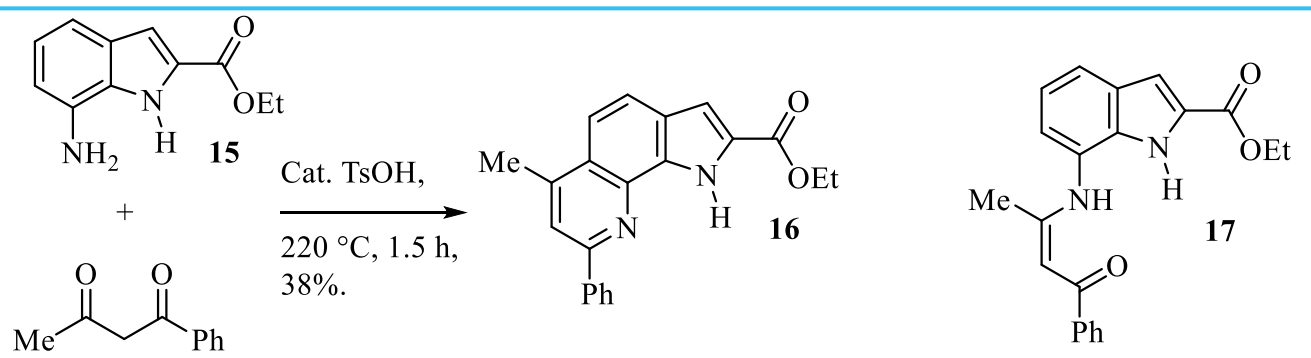



SCHEME 8

[14] M. J. López Rivilli, E. L. Moyano, G. I. Yranzo, *Tetrahedron Letters* **2010**, *51*, 478-481.
[15] M. G. Ferlin, G. Chiarelotto, S. Dall'Acqua, E. Maciocco, M. P. Mascia, M. G. Pisu, G. Biggio, *Bioorg. Med. Chem.* **2005**, *13*, 3531-3541.

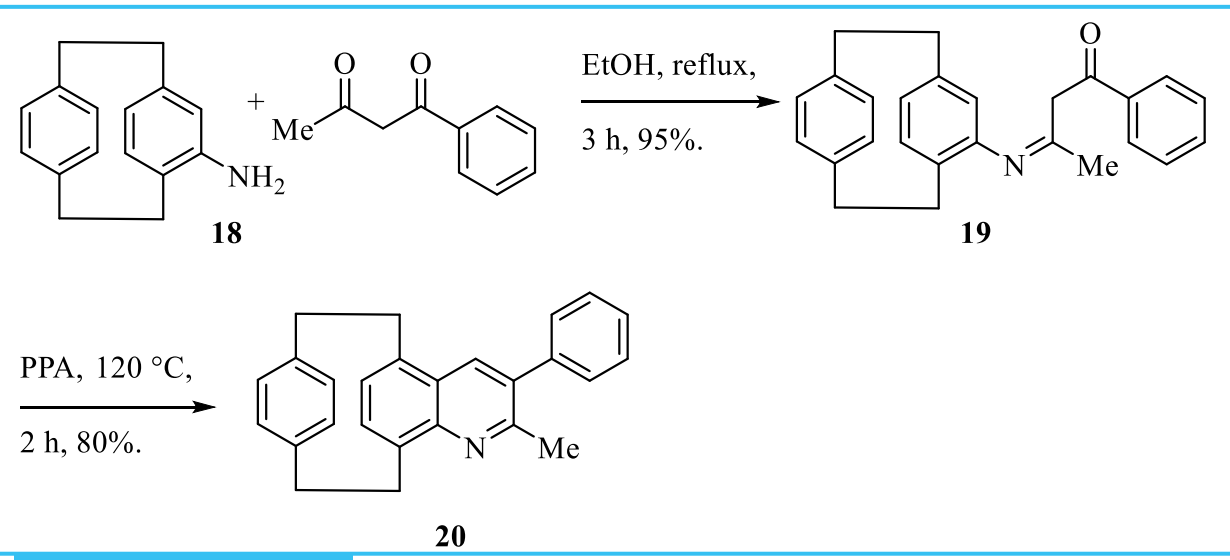
**Combes quinoline synthesis**

The preparation of quinolines by condensation of anilines with β-diketones followed by cyclization in the presence of sulfuric acid was first reported by Combes in 1888.[16] Hamelin applied this Combes condensation to the preparation of 1H-pyrrolo[3,2-h]quinoline derivative as presented in Scheme 9.[17] Treatment of ethyl 7-aminoindole-2-carboxylate **15** with benzoylacetone at 220 °C without solvent in the presence of a catalytic amount of TsOH afforded the desired quinoline derivative **16** in a modest yield of 38%. It is worth noting that this transformation carried out at 80 °C gave the enamine intermediate **17** which was unable to undergo cyclization. This annulation process was pointed out as rate-limiting step.[18]




SCHEME 9

A two-step sequence Combes quinoline synthesis was used to prepare [2.2]paracyclophane derivatives as presented in Scheme 10.[19] Treatment of 4-amino-[2.2]paracyclophane **18** with benzoylacetone in refluxing ethanol furnished chemoselectively the imine **19** in 95% yield. This latter intermediate **19** was heated in polyphosphoric acid (PPA) at 120 °C giving the targeted disubstituted-[2]paracyclo-[2](5,8)-quinolinophane **20** in 80% yield after purification on silica gel column. Polyphosphoric acid (PPA) used in this transformation was freshly prepared from 89% phosphoric acid and $P_2O_5$.



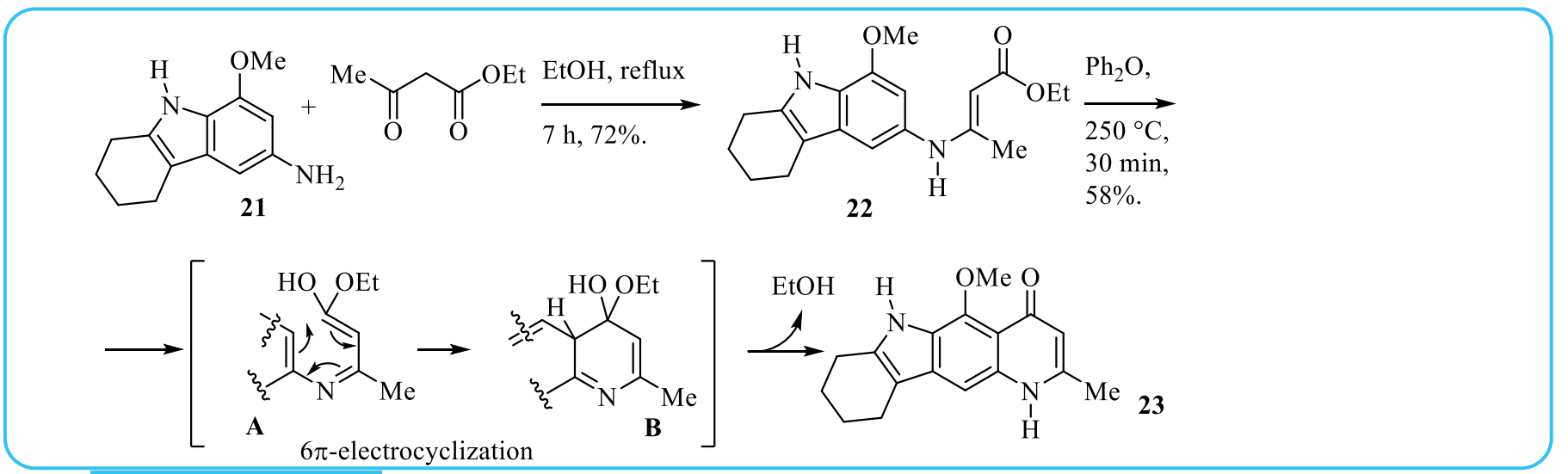

SCHEME 10

[16] A. Combes, *Bull. Chim. Soc. Fr.* **1888**, 49, 89.
[17] M. El Ouar, N. Knouzi, J. Hamelin, *J. Chem. Research (S)*, **1998**, 92-93.
[18] For a recent mechanistic investigation on Combes quinoline synthesis, see: J. C. Sloop, *J. Phys. Org. Chem*. **2009**, *22*, 110-117.
[19] A. A. Aly, *Tetrahedron* **2003**, *59*, 1739–1747.

**Conrad-Limpach reaction**

Condensation of anilines with β-ketoesters followed by the cyclization of Schiff base intermediates to afford 4-oxoquinolines is known as Conrad-Limpach quinoline synthesis. In the context of the synthesis and the biological evaluation of ellipticine analogues as anticancer agents, the 7*H*-pyrido [2,3-c]carbazole intermediate **23** was prepared as presented in Scheme 11.[20] By refluxing in ethanol, a mixture of aniline derivative **21** and ethyl acetoacetate provided the corresponding enamine intermediate **22**, which was cyclized at 250 °C in diphenylether giving the desired 7*H*-pyrido [2,3-c]carbazole intermediate **23** in 45% overall yield.

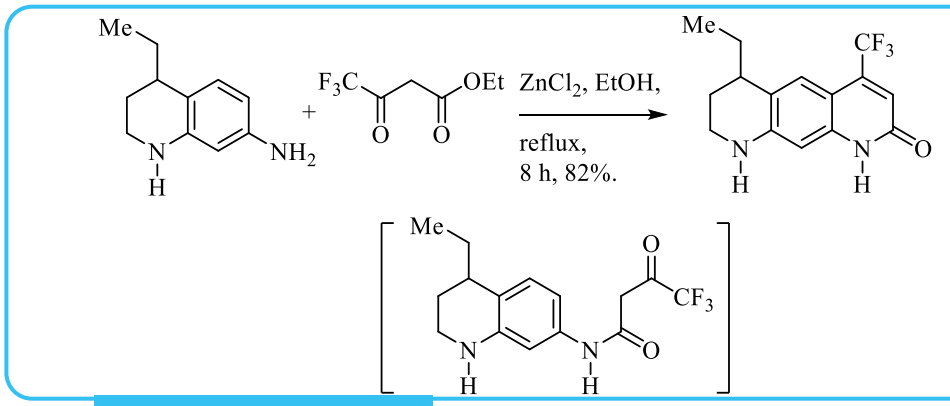
It should be pointed out that this latter pericyclic annulation reaction required high temperatures mainly due to breaking of aromaticity of the phenyl ring during the 6-$\pi$-electrocyclization process from the imine-enol tautomer intermediate (**A**) into the hemiketal (**B**).




SCHEME 11

**Knorr quinoline synthesis**

The Knorr quinoline refers to the preparation 2-hydroxyquinolines from anilines and β-ketoesters, *via* the cyclization by dehydration of aβ-ketoacetamide intermediates, under strong acidic conditions at high temperatures. To avoid these harsh reaction conditions, Lewis acid promoted Knorr quinoline synthesis has been described as outlined in Scheme 12.[21]

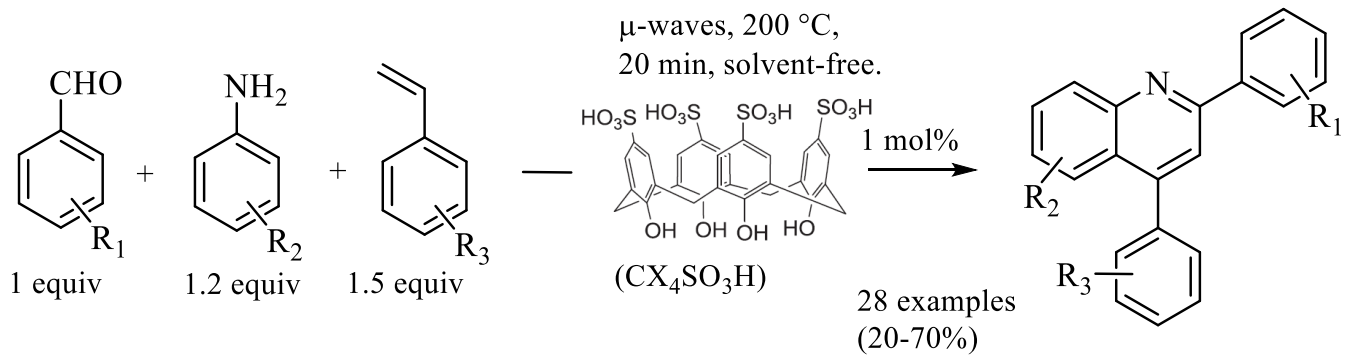



SCHEME 12

[20] M. Grazia Ferlin *et al.*, *ChemMedChem.* **2009**, *4*, 363-377.
[21] T. K. Jones *et al.*, *J. Med. Chem.* **1999**, *42*, 210-212.

## Povarov quinoline synthesis

Povarov quinoline synthesis is a three-component reaction involving an aniline, an aldehyde and an electron rich alkene. This one-pot process implies the acid-catalyzed formation of an imine which *via* an inverse electron-demand aza-Diels-Alder reaction with the electron rich alkene provides the corresponding dihydro intermediate and subsequent oxidation by ambient atmosphere gives the desired quinoline. A simple and efficient protocol for the synthesis of a series of 2,4-disubstituted quinolines under solvent-free conditions was recently published to evaluate their potential antifungal, anticancer and antioxidant properties. This Povarov quinoline synthesis was carried out under microwave irradiation with a catalytic amount of *para*-sulfonic acid calix[4]arene ($CX_4SO_3H$) as reported in Scheme 13.[22] It should be noted that reactions under microwave irradiation furnished the desired quinolines more rapidly with better yields compared to conventional thermal heating (reflux in acetonitrile).




SCHEME 13

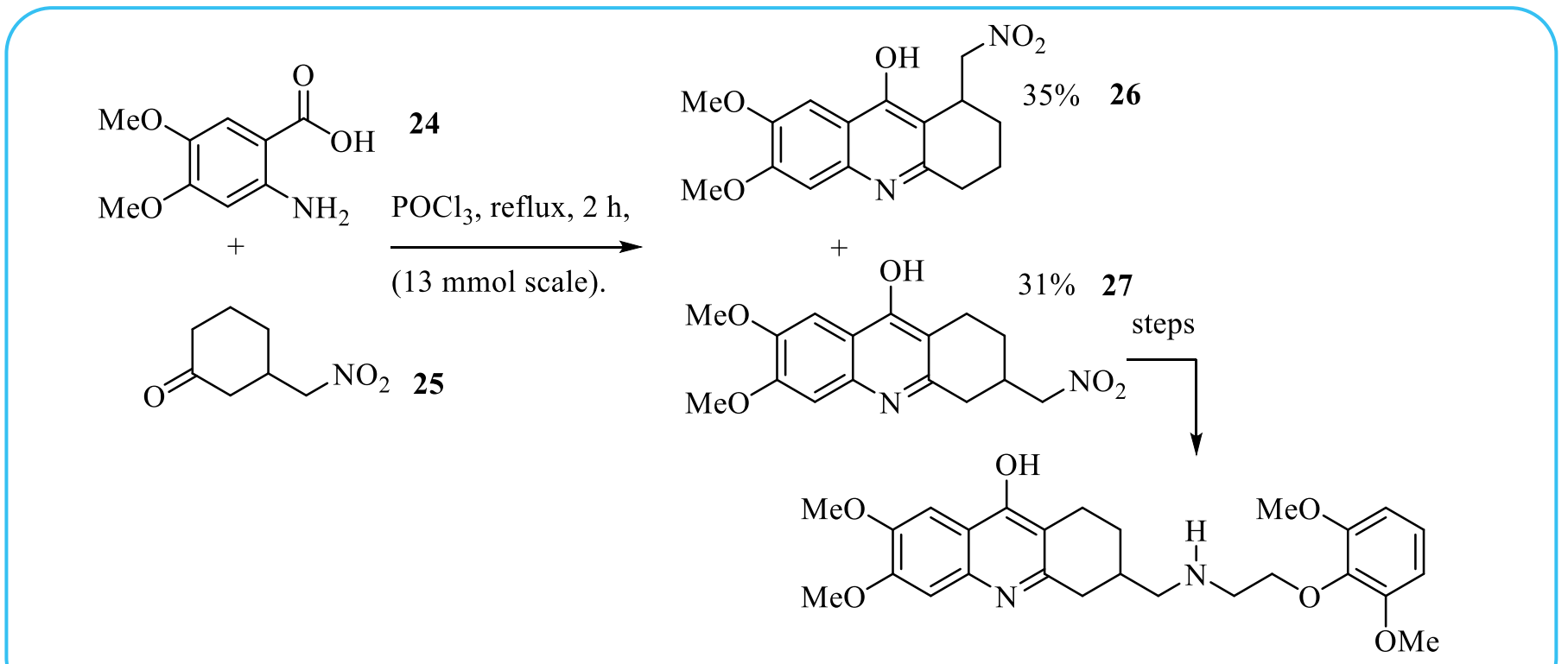
These following methodologies, starting from *ortho*-functionalized anilines, provided the desired quinoline derivatives without any other regioisomers.

[22] S. A. Fernandes *et al*., *Bioorg. Med. Chem*. **2017**, *25*, 1153-1162.

**Niementowski quinoline synthesis**

The Niementowski quinoline synthesis involves a condensation between anthranilic acids and ketones (or aldehydes) followed by a cyclodehydratation.[23] Only a limited number of recent publications have reported the synthesis of quinoline derivatives based on the use of the Niementowski reaction. Nevertheless, Niementowski quinazoline synthesis using amides instead of ketones (or aldehydes) found more application in organic synthesis.[24]

It is obvious that the Niementowski quinoline synthesis suffers from harsh reaction conditions as outlined in Scheme 14.[25] Treatment of the anthranilic acid **24** with the cyclohexanone derivative **25** in refluxing phosphoryl chloride (106 °C) for 2 hours provided the two possible regioisomers **26** and **27**, in respectively 35 and 31% yields.



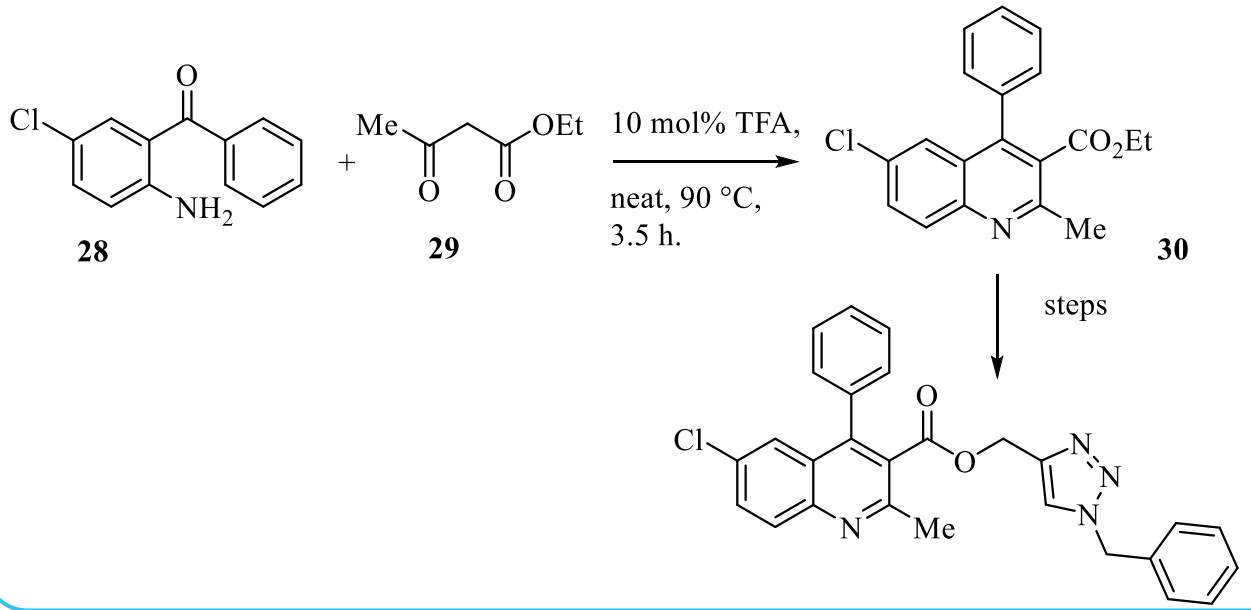

SCHEME 14

**Friedländer reaction**

The Friedländer reaction is a base- or acid-prompted condensation followed by a cyclodehydration between a 2-aminoaryl carbonyl derivative and a reactive α-methylene ketone partner.[26] As reported in Scheme 15, stirring a mixture of 2-aminoaryl ketone **28** and a slight excess of 1,3-dicarbonyl compound **29** at 90 °C in the

[23] S. von Niementowski, *Chem. Ber.* **1894**, *27*, 1394-1403.
[24] L. He, H. Li, J. Chen, X.-F. Wu, *RSC Adv*. **2014**, *4*, 12065-12077.
[25] C. Melchiorre *et al*., *J. Med. Chem.* **2003**, *46*, 4895-4903,
[26] For an excellent review, see: J. Marco-Contelles, E. Perez-Mayoral, A. Samadi, M. do Carmo Carreiras, E. Soriano, *Chem. Rev*. **2009**, *109*, 2652-2671.

presence of a catalytic amount of TFA under solvent free condition provided the desired quinoline **30** in good yield.[27]

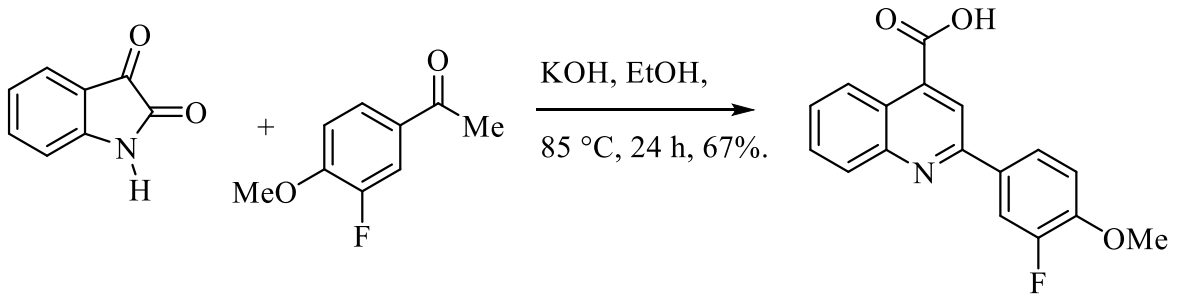



SCHEME 15

**Pfitzinger reaction**

The Pfitzinger reaction is a condensation of an α-methylene carbonyl partner with an isatin derivative in the presence of base, mainly aqueous solution of NaOH or KOH, to give a substituted quinoline-4-carboxylic acid.[28]

The Pfitzinger reaction has been successfully applied in the synthesis of around 50 2-substituted quinoline-4-carboxylic acid derivatives from isatin and various aromatic methyl ketones as exemplified in Scheme 16.[29] It should be noted that various substituted isatins are now commercially available greatly expanding the scope of this transformation.



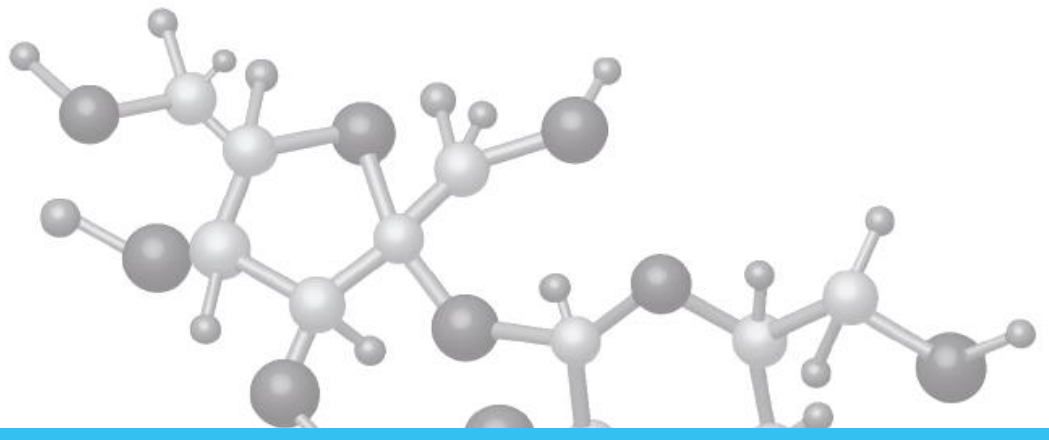

SCHEME 16

[27] A. Upadhyay, P. Kushwaha, S. Gupta, R. P. Dodda, K. Ramalingam, R. Kant, N. Goyal, K. V.Sashidhara, *Eur. J. Med. Chem*. **2018**, *154*, 172-181.
[28] J. N. Sangshetti, A. S. Zambare, I. Gonjari, D. B. Shinde, *Mini-Rev. Org. Chem*. **2014**, *11*, 225-250.
[29] X. Chen, W. Sun, S. Huang, H. Zhang, G. Lin, H. Li, J. Qiao, L. Li, S. Yang, *J. Med. Chem.* **2020**, *63*, 10474-10495.

All these methodologies still have an enormous potential for the preparation of polyfunctionalized quinoline derivatives and new protocols involving microwave activation, flow chemistry, metal-free and/or solventfree[30] will greatly increase their utility.

[30] For green chemistry approaches to quinolines, see: M. Mumtaz Alam *et al*., *Eur. J. Med. Chem.* **2019**, *164*, 121-170.

I would like to thank Johann Leblanc for fruitful discussions and comments. I also warmly thank my colleagues, Dr. Sylvie Archambaud, Dr. Thibaut Martinez, Dr. Thomas Glachet and Dr. Julien Farard from AtlanChim Pharma for their valuable suggestions during the preparation of this manuscript. A special thanks to Lionel Bidet for linguistic assistance.



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