*proceedings*

MDPI

*Proceedings*

# *Microwave assisted Synthesis of bis-heterocycles containing the imidazo[1,2-a]pyridine by Groebke-Blackburn- Bienaymé reaction.*

**Sandra C. Ramírez-López[1] and Rocío Gámez-Montaño[1]***

[1] Departamento de Química, Universidad de Guanajuato, Noria Alta S/N, Col. Noria Alta, C.P. 36050, Guanajuato, Gto., México.

* Correspondence: rociogm@ugto.mx (R.G.-M.); Tel.: +52-473-73-20006 ext. 8191 (R.G.-M.)

† Presented at the 23th International Electronic Conference on Synthetic Organic Chemistry.

**Academic editor: Julio A. Seijas**

**Abstract:** A serie of six fused *bis*-heterocycles having imidazo[1,2-*a*]pyridine bound with quinoline were synthesized by microwave assisted Groebke-Blackburn-Bienaymé reaction (GBBR) under green catalysis. The GBB products are privileged scaffolds and their synthesis is of great interest in synthetic and medicinal chemistry.

**Keywords:** imidazo[1,2-a]pyridine; Groebke-Blackburn-Bienaymé reaction (GBBR); 2-Chloro-3-formyl-quinoline.

## 1. Introduction

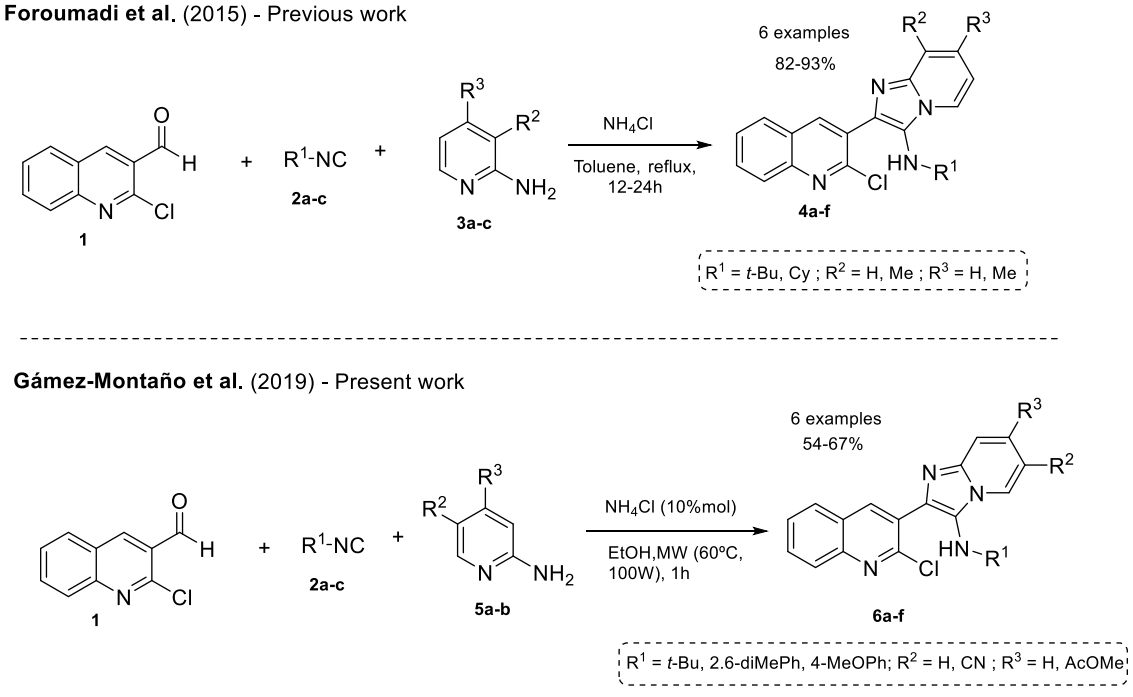
Nitrogen is considered a key element with a vital role in bioactive compounds providing a noticeable range of activities [1]. Heterocycles containing nitrogen atom possess several pharmaceutical properties. For instance, quinoline core has received much attention in medicinal chemistry resulting of their activities e.g. anti-tuberculosis [2], antibacterial [3], antifungal [4], antimalarial [5], anti-HIV [6] and anti-inflammatory [7] activities. As result of their Pharmacological and biological properties of bioactive compounds incorporated quinoline ring system, the 2-chloroquinoline-3-carbaldehyde has been applied as an aldehyde moiety in multicomponent reactions as Ugi-4CR [8-10], Ugi-azide [11] and Groebke-Blackburn-Bienaymé (GBBR)[11-13].

Among them, *bis*-heterocycles have attracted much attention due to their numerous applications in many fields such as organic synthesis, optics, materials and polymer sciences, agrochemistry, and mainly in medicinal chemistry [14]. The research towards finding novel applications is supported on the basic principle union makes force [15]. Two heterocycles can be suitably placed to construct complex products having potential new or enhanced known properties.

Imidazo[1,2-a]pyridine core is present in a lot of drugs, useful in various treatments of brain diseases and CNS-related disorders. For example, zolpidem is the most prescribed drug for insomnia [15]. The GBBR is one of the highest important class of isocyanide-based multicomponent reactions (I-MCRs) and the most efficient methods for the synthesis of fused imidazole analogues. GBBR usually requires a solvent and catalyst. In this context, GBBR methodologies using various green catalysts, such as, Lewis acids, Bronsted acids, solid supported, organic bases and inorganic salts have been reported [16]. It is highlight that reported methodologies have some drawbacks such high temperature, low yields, expensive catalyst and non-greener solvents.

Microwave irradiation (MW) plays a central role in synthetic organic chemistry mainly to decrease the reaction times. Herein the goal is to develop an efficient protocol for the synthesis of new heterocyclic scaffolds containing imidazole and quinoline cores under ecofriendly conditions. MW offers several benefits over conventional methods including short reaction time and yield enhancements.

Foroumadi and co-workers reported in 2015 the synthesis of imidazo[1,2-a]pyridine in moderate yields (65-93%) via a GBBR using $NH_4Cl$ in stoichiometric quantities and hard conditions (Scheme 1) [17]. Our methodology has some advantages, for example, the synthetic process worked well under green catalyst. Besides short reaction times and MW energy source.



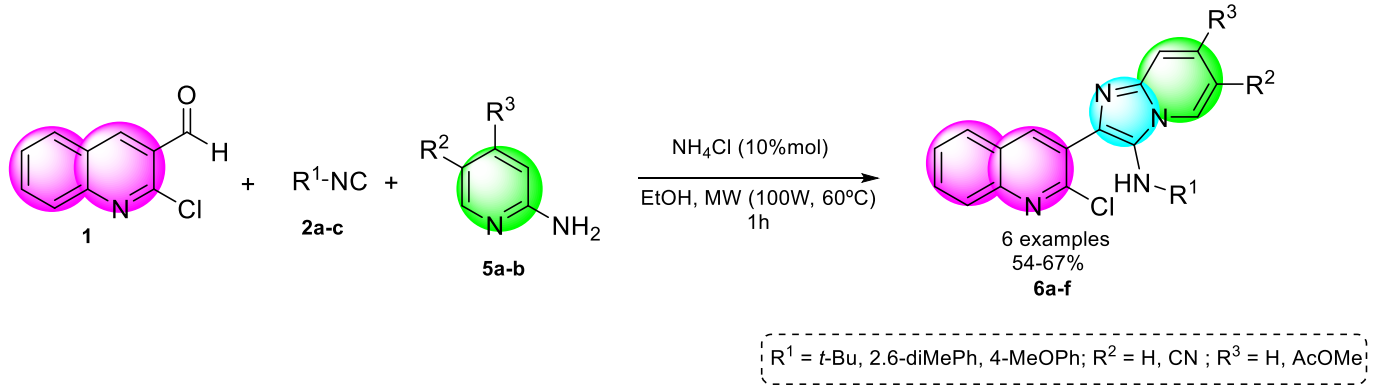

**Scheme 1**. Previous works related to the synthesis of imidazo[1,2-a]pyridines analogues.

The principal objective in our research group during last years has been to develop versatile and efficient I-MCR-based methodologies to synthesize series of novel unsymmetrical *bis*-heterocycles containing privileged nucleus in medicinal chemistry [10-12,18].

As a part of our research program in the development of green or eco-friendly IMCR strategies herein, we describe the one-pot synthesis of new unsymmetrical *bis*-heterocycles via the GBBR under mild conditions. The target molecules containing two different complex heterocycles such as imidazo[1,2-a]pyridine bound with quinoline moiety.

## 2. Results and Discussion

Following our interests in the efficient synthesis of *bis*-heterocycles containing frameworks of interest in medicinal chemistry, our work consist of the synthesis of six new analogs of 2-chloroquinoline imidazo[1,2-*a*]pyridine which were synthesized in moderate to good yields (54-67%) via GBBR under mild green conditions (Scheme 2).

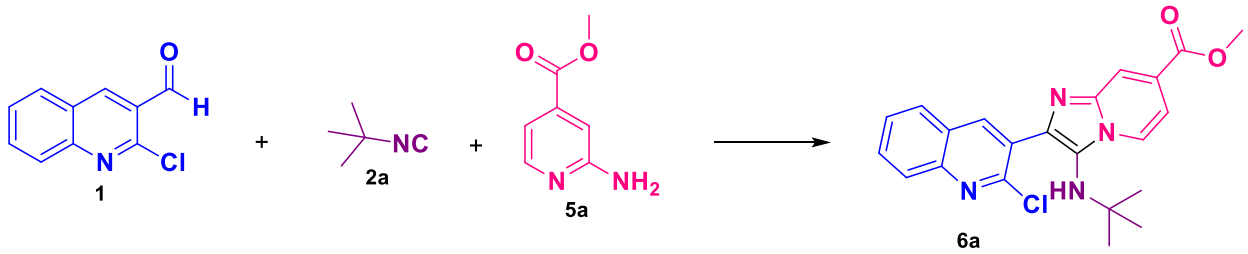



**Scheme 2**. Strategy for the synthesis of analogs of 2-chloroquinoline imidazo[1,2-*a*]pyridine.

In order to find the optimum conditions for the GBBR involved in the synthetic strategy toward unsymmetrical bound-type bis-heterocycles **6a**, 2-chloro-3-formylquinoline (**1**) was reacted sequentially with one equivalent of methyl-2-aminopyridine-4-carboxylate (**5a**), tertbutyl isocyanide (**2a**) which were selected as the model reaction (Table 1). According with our main line research, green solvents, moderate temperatures and green catalyst were studied to optimize the reaction conditions. Firstly, we performed the GBBR at room temperature in water (Table 1, entry 1) but the starting materials remained completely unconsumed. When the reaction was carried out in ethanol without catalyst at r.t (Table 1, entry 3), the product **6a** was obtained in 13% yield. Due to the low yields obtained we decided to use a catalyst and we decided try reaction

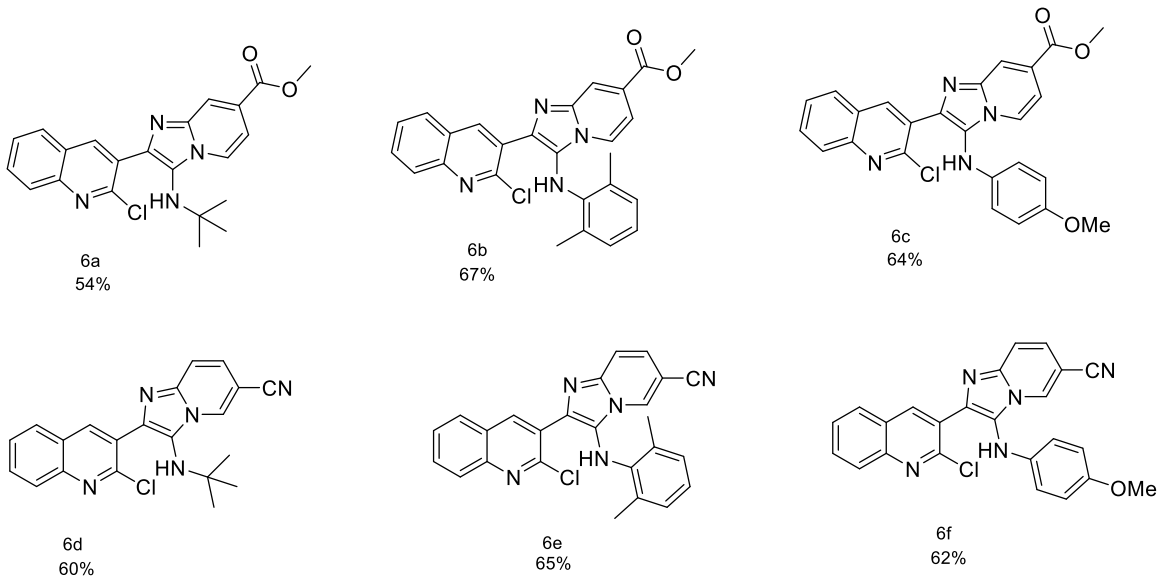
using $NH_4Cl$ in 10% mol which is a green, inexpensive and easily available catalyst. In the literature there are many reports of use of $NH_4Cl$ in GBBR in stoichiometric amount and longer reaction times were required. In 2018 we reported for first time $NH_4Cl$ in GBBR in catalytic amount [18]. The TLC of the reaction with $NH_4Cl$ revelated that the product yield was increased. Under MW at 60°C in EtOH and $NH_4Cl$ the yield was better that USI 54 and 42% of **6a** respectively. The course of reaction was monitored by TLC and characterized by $^1H$ y $^{13}C$ NMR.

**Table 1**. Reaction optimizing conditions **6a.**




| Entry | Solvent | Catalyst | T (°C) | Time(h) | Yield (%) |
|---|---|---|---|---|---|
| 1 | $H_2O$ | ---------- | r.t | 8 | n.r |
| 2 | $H_2O$ | ---------- | r.t USI | 3 | n.r |
| 3 | EtOH | ---------- | r.t | 8 | 13 |
| 4 | EtOH | ---------- | r.t USI | 4 | 18 |
| 5 | EtOH | | 60 USI | 4 | 26 |
| 6 | EtOH | $NH_4Cl$ | USI | 4 | 35 |
| 7 | EtOH | $NH_4Cl$ | 60 USI | 2 | 42 |
| **8** | **EtOH** | **$NH_4Cl$** | **60 MW** | **1** | **54** |

Using optimized conditions, a serie of six new 2-chloroquinoline imidazo[1,2-*a*]pyridine were synthesized (shown in scheme 3). The versatility of the developed methodology was examined using different isocyanides as aryl and alkyl (**2a-c**) and two different aminoazines with withdrawing groups. The respective products **6a–f** were obtained in moderate to good yields (54-67%).



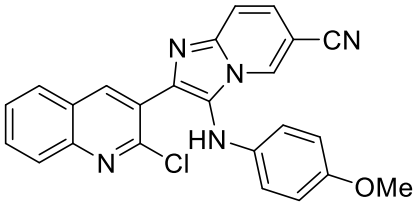

**Scheme 3.** Substrate scope

## 3. Experimental Section

General Information. $^{1}H$ and $^{13}C$ NMR spectra were acquired on a 500 MHz spectrometer. The solvent for NMR samples was $CDCl_3$. Chemical shifts are reported in parts per million (δ/ppm). Internal reference for NMR spectra is tetramethylsilane at 0.00 ppm. Coupling constants are reported in Hertz (J/Hz). Multiplicities of the signals are reported using the standard abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). NMR spectra were analyzed using the MestreNova software version 10.0.1-14719. The reaction progress was monitored by TLC and the spots were visualized under UV light (254 or 365 nm). Flash column chromatography was performed using silica gel (230-400 mesh) and mixtures in different proportions of hexanes with ethyl acetate as mobile phase. Chemical names and drawings were obtained using the ChemBioDraw Ultra 13.0.2.3020 software package.

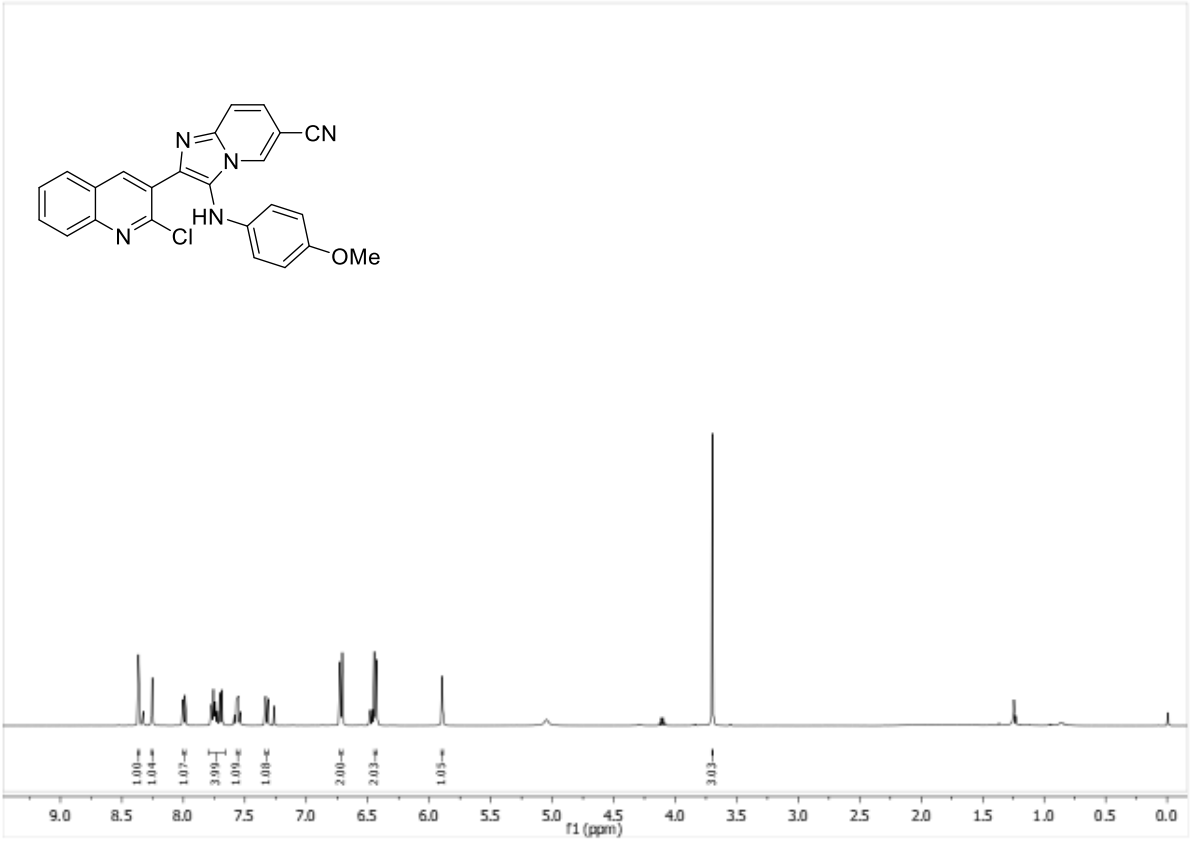
**General method**: 2-Chloroquinoline-3-carboxaldehyde **1** (0.365 mmol, 1.0 equiv), 2-aminopyridine derivatives with withdrawing groups **5 a-b** (0.365 mmol, 1 equiv), isocyanide **2 a-c** (0.365 mmol, 1 equiv) and $NH_4Cl$ 10%mol in MeOH (1M) were placed in a 10 mL vial equipped with a magnetic stirring bar. The reaction mixture was MW-heated at 60 °C (100W) for 1h. Then, the solvent was removed to dryness and the crude was purified by silica-gel column chromatography using mixtures of hexanes with ethyl acetate (1/1; *v*/*v*) to afford products **6 a-f**.

**Spectral data**

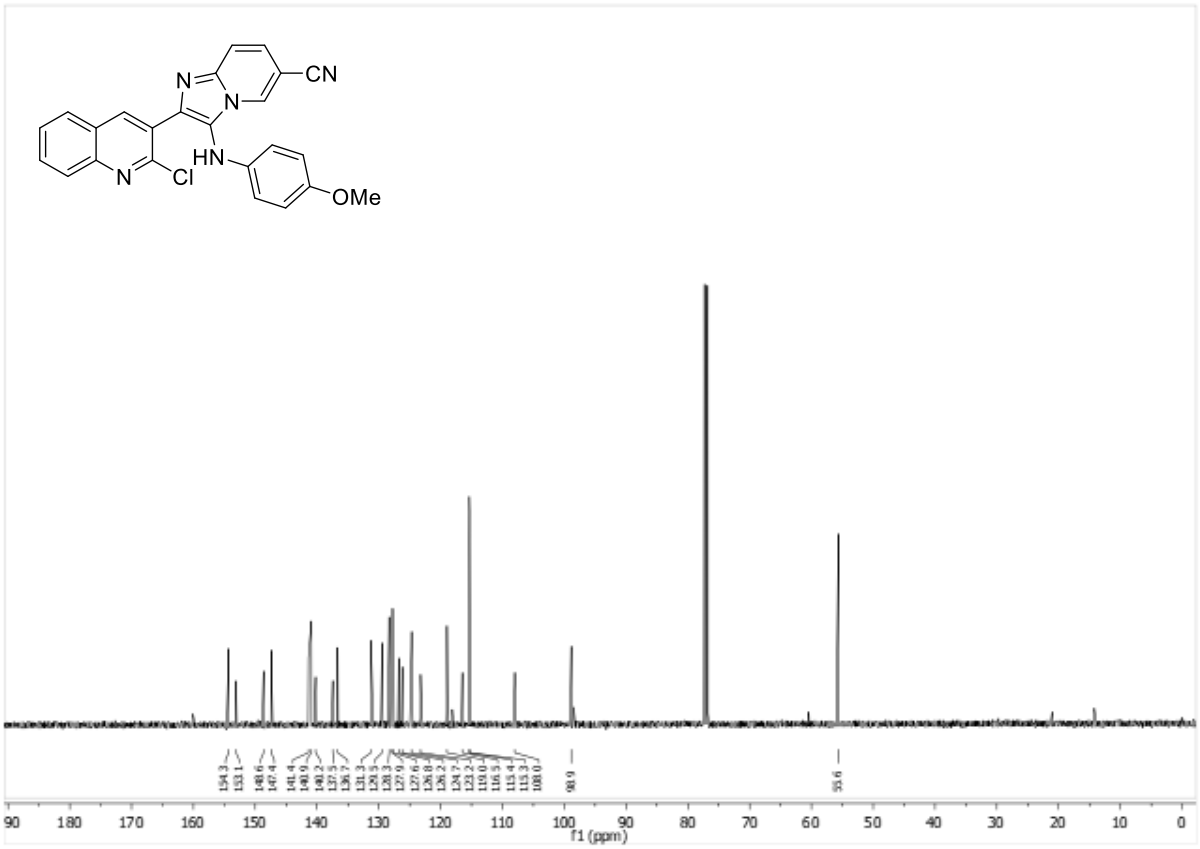



**2-(2-chloroquinolin-3-yl)-3-((4-methoxyphenyl)amino)imidazo[1,2-a]pyridine-6-carbonitrile (6f)**

yellow solid (97.0 mg, 62%); Rf = 0.32 (Hexanes-EtOAc = 1/1 v/v); $^{1}$H NMR (500 MHz, CDCl3) δ 8.36 (s, 1H), 8.25 (s, 1H), 8.0–7.98 (m, 1H), 7.78–7.68 (m, 1H), 7.57–7.54 (m, 1H), 7.34–7.31 (m, 1H), 6.73–6.70 (m, 2H), 6.45–6.43 (m, 2H), 3.70 (s, 3H); $^{13}$C NMR (126 MHz, CDCl3) δ 154.3, 153.1, 148.6, 147.4, 141.4, 140.9, 140.2, 137.5, 136.7, 131.3, 129.5, 128.3, 127.9, 127.6, 126.8, 126.2, 124.7, 123.2, 119.0, 116.5, 115.4,115.3,108.0, 98.9, 56.6.




$^{1}$H NMR spectrum of compound **6f.**




$^{13}$C NMR spectrum of compound **5c**

## 4. Conclusions

In conclusions, herein we described GBBR protocol under green catalyst for the synthesis of *bis*-heterocycles containing privileged nucleus in medicinal chemistry. Additionally, this strategy has advantages in comparation with previous works due the strategy herein described take place under mild and green conditions.

**Author Contributions:** All authors contributed equally to this work.

**Acknowledgments:** R.G.-M. is grateful for CONACYT-México (CB-2016-285622) and DAIP-UG (CIIC 154/2019) for financial support, . S.C.R.-L. acknowledges CONACYT-México for scholarship (701343/582679), the Laboratorio Nacional de Caracterización de Propiedades Fisicoquímícas y Estructura Molecular (CONACYT-México, Project: 123732) for the instrumentation time provided.

**Conflicts of Interest:** The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

## References


1. Fan, H.; Peng, J.; Hamann, M.T.; Hu, J. F. Lamellarins and related pyrrole-derived alkaloids from marine organisms., *Chem Rev*, **2018,** 108, 264–287. DOI: 10.1021/cr078199m.
2. Desai, N. C.; Kotadiya, G. M.; Trivedi, A. R., Studies on molecular properties prediction, antitubercular and antimicrobial activities of novel quinoline based pyrimidine motifs. *Bioorg.Med. Chem. Lett.* **2014**, *24* (14), 3126-3130. DOI: 10.1016/j.bmcl.2014.05.002.
3. S. Pramilla, S.P. Garg and S.R. Nautiyal, Indian J. Heterocycl. Chem. 1998, 7, 201-204
4. Vandekerckhove, S.; D'hooghe, M., Quinoline-based antimalarial hybrid compounds. *Bioorg Med Chem* **2015**, 23 (16), 5098-5119. DOI: 10.1016/j.bmc.2014.12.018
5. Ahmed, N.; Brahmbhatt, K. G.; Sabde, S.; Mitra, D.; Singh, I. P.; Bhutani, K. K., Synthesis and anti-HIV activity of alkylated quinoline 2,4-diols. *Bioorg Med Chem* **2010**, 18 (8), 2872-2879. DOI: 10.1016/j.bmc.2010.03.015.
6. El-Feky, S. A. H.; Abd El-Samii, Z. K.; Osman, N. A.; Lashine, J.; Kamel, M. A.; Thabet, H. K., Synthesis, molecular docking and anti-inflammatory screening of novel quinoline incorporated pyrazole derivatives using the Pfitzinger reaction II. *Bioorganic Chemistry* **2015**, 58, 104-116.DOI: 10.1016/j.bioorg.2014.12.003.
7. Asthana, M.; Sharma, N.; Singh, R. M., Densely functionalized 1,2-dihydrobenzo[b][1,6]naphthyridines: one-pot synthesis via sequential Ugi and Heck reactions. Tetrahedron **2014**, 70 (43), 7996-8003. DOI: 10.1016/j.tet.2014.08.046.
8. Asthana, M.; Kumar, R.; Gupta, T.; Singh, R. M., Facile synthesis of functionalized 1H-pyrrolo[2,3-b]quinolines via Ugi four-component reaction followed by Cu-catalyzed aryl-amide, C–N bond coupling. Tetrahedron Letters **2015**, 56 (7), 907-912. DOI: 10.1016/j.tetlet.2014.12.140
9. Ghandi, M.; Zarezadeh, N.; Abbasi, A., One-pot synthesis of spiropyrroloquinoline-isoindolinone and their aza-analogs via the Ugi-4CR/metal-free intramolecular bis-annulation process. Organic & Biomolecular Chemistry **2015**, 13 (30), 8211-8220. DOI: 10.1039/C5OB01095K
10. Unnamatla, M. V. B.; Islas-Jácome, A.; Quezada-Soto, A.; Ramírez-López, S. C.; Flores-Álamo, M.; Gámez-Montaño, R., Multicomponent One-Pot Synthesis of 3-Tetrazolyl and 3-Imidazo[1,2-a]pyridin Tetrazolo[1,5-a]quinolines. *J .Org. Chem* **2016**, 81 (21), 10576-10583. DOI : 10.1021/acs.joc.6b01576.
11. Kishore, K. G.; Islas-Jácome, A.; Rentería-Gómez, A.; Conejo, A. S.; Basavanag, U. M. V.; Wrobel, K.; Gámez-Montaño, R., Synthesis of unsymmetrical bis-heterocycles containing the imidazo[2,1-b]thiazole framework and their benzo[d]fused analogues by an acid-free Groebke–Blackburn–Bienaymé reaction. Tetrahedron Letters **2016**, 57 (31), 3556-3560.DOI: 10.1016/j.tetlet.2016.06.120.
12. Claudio-Catalán, M. Á.; Pharande, S. G.; Quezada-Soto, A.; Kishore, K. G.; Rentería-Gómez, A.; Padilla-Vaca, F.; Gámez-Montaño, R., Solvent- and Catalyst-Free One-Pot Green Bound-Type Fused Bis-Heterocycles Synthesis via Groebke–Blackburn–Bienaymé Reaction/SNAr/Ring-Chain Azido-Tautomerization Strategy. *ACS Omega* **2018,** 3 (5), 5177-5186. DOI: 10.1021/acsomega.8b00170.
13. Premakumari, C.; Muralikrishna, A.; Padmaja, A.; Padmavathi, V.; Park, S. J.; Kim, T.-J.; Reddy, G. D., Synthesis, antimicrobial and anticancer activities of amido sulfonamido methane linked bis heterocycles. *Arabian Journal of Chemistry* **2014**, 7 (4), 385-395. DOI: 10.1016/j.arabjc.2013.10.024
14. Murru, S.; Nefzi, A., Combinatorial Synthesis of Oxazol-Thiazole Bis-Heterocyclic Compounds. ACS Combinatorial Science 2014, 16 (1), 39-45. DOI: 10.1021/co400133a
15. Harrison, T. S.; Keating, G. M., Zolpidem. *CNS Drugs* **2005**, 19 (1), 65-89. DOI: 10.2165/00023210-200519010-00008.
16. Shaaban, S.; Abdel-Wahab, B. F. Groebke-Blackburn-Bienaymé multicomponent reaction: emerging chemistry for drug discovery. *Mol. Divers* **2016**, 20, 233–254. DOI: 10.1021/co400133a.

17. Dianat, S.; Mahdavi, M.; Moghimi, S.; Mouradzadegun, A.; Shafiee, A.; Foroumadi, A. Combinated isocyanide-based multi-component Ullmann-type reaction:an efficient access to novel nitrogen-containing pentacyclic compouds **2015**, 19, 797-805. DOI: 10.1007/s11030-015-9622-2.
18. Mahanandaiah, K.; Pharande, S. G.; Quezada-Soto A.; Gámez-Montaño, R. Ultrasound assisted green synthesis of bound type bis-heterocyclic carbazolyl imidazo[1, 2-a]pyridines via Groebke-Blackburn-Bienaymé reaction. *Tetrahedron Letters* **2018**, 59, 1596-1599. DOI: 10.1016/j.tetlet.2018.03.031.