Global Journal of Science Frontier Research: B
Chemistry
Volume 18 Issue 1 Version 1.0 Year 2018
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4626 & Print ISSN: 0975-5896

Synthesis and Chemistry of Bis-imidazole Derivatives: A Review

By Abdullah Elmorsy, A. M. S. Hebishy, Ahmed Elwahy & M. S. Abdelfattah
Helwan University

Abstract- Imidazole, an important heterocycle, having biological and therapeutic properties prompted various medicinal chemists to develop various synthetic methods to synthesize a large number of novel derivatives used in chemotherapy. This fascinating group of heterocyclic compounds has interesting biological activities such as antimicrobial, anticancer, antiviral, analgesic, anti-inflammatory, anthelmintic, anticonvulsant, antiulcer, and anti-allergic activity. Various bis-imidazole derivatives introduced a great contribution not only in the field of synthetic organic chemistry but also in the field of medicinal chemistry and chemotherapy. This article aims to review the work reported in the synthesis and chemistry of bis-imidazole derivatives during past years.

Keywords: *imidazole, heterocycle, bis-imidazole.*

GJSFR-B Classification: *FOR Code: 039999*

Strictly as per the compliance and regulations of:

Synthesis and Chemistry of Bis-imidazole Derivatives: A Review

Abdullah Elmorsy [α], A. M. S. Hebishy [σ], Ahmed Elwahy [ρ] & M. S. Abdelfattah [ω]

Abstract- Imidazole, an important heterocycle, having biological and therapeutic properties prompted various medicinal chemists to develop various synthetic methods to synthesize a large number of novel derivatives used in chemotherapy. This fascinating group of heterocyclic compounds has interesting biological activities such as antimicrobial, anticancer, antiviral, analgesic, anti-inflammatory, anthelmintic, anticonvulsant, antiulcer, and anti-allergic activity. Various bis-imidazole derivatives introduced a great contribution not only in the field of synthetic organic chemistry but also in the field of medicinal chemistry and chemotherapy. This article aims to review the work reported in the synthesis and chemistry of bis-imidazole derivatives during past years.

Keywords: imidazole, heterocycle, bis-imidazole.

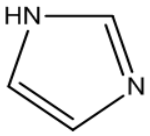
I. Introduction

Imidazole 1, a histidine 2 component, is five membered heterocyclic compound containing nitrogen atoms in 1 and 3 positions. It has fascinating biological activities such as antibacterial [1, 2, 3], anticancer [4], antiviral [5], anti depressant [3, 6]. Bis-imidazole is an important moiety in therapeutic chemistry due to its versatile synthesis methods and biological activities.

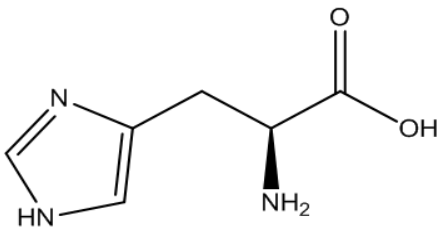
Imidazole is a five membered aromatic heterocyclic compound, categorized as diazole having two nitrogen atoms. Many important drugs contain imidazole ring, such as antifungal drugs, Nitroimidazole [7-12], and Purine 3 which is the most widely occurring nitrogen-containing heterocycle in nature consist of imidazole fused to pyrimidine [3]

Due to the significant biological activity of bis-imidazole derivatives and the rise of practical, safe, and environmentally friendly procedures for the synthesis of bis-imidazoles, [13-15] organic chemists become interested in the development of novel bis-imidazole derivatives.

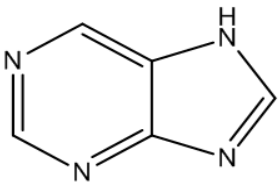
The synthesis of bis-imidazole derivatives in literature does not fit with their increasing biological importance. Herein we try to put in front of organic synthesis community the few novel bis-imidazole derivatives that were synthesized and found a unique application in the last years.



1



2



3

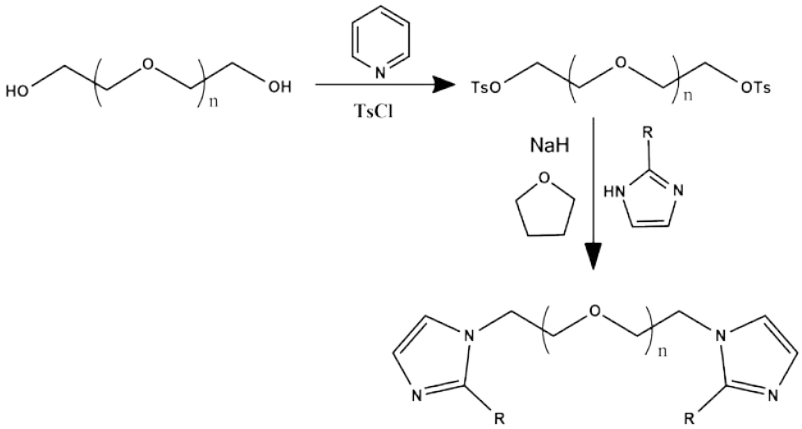
II. General Methods of Synthesis

Imidazole moieties and substituted imidazoles can be formed through various methods. Different synthesis methods include Debus synthesis, Radiszewski synthesis, dehydrogenation of imidazolines, imidazole from alpha halo ketones, Wallach synthesis, from aminonitrile and aldehyde and Marckwald synthesis [12, 16]. Herein we introduce the various methods applied for the synthesis of bis-imidazole derivatives.

III. Synthesis of bis (Imidazole)

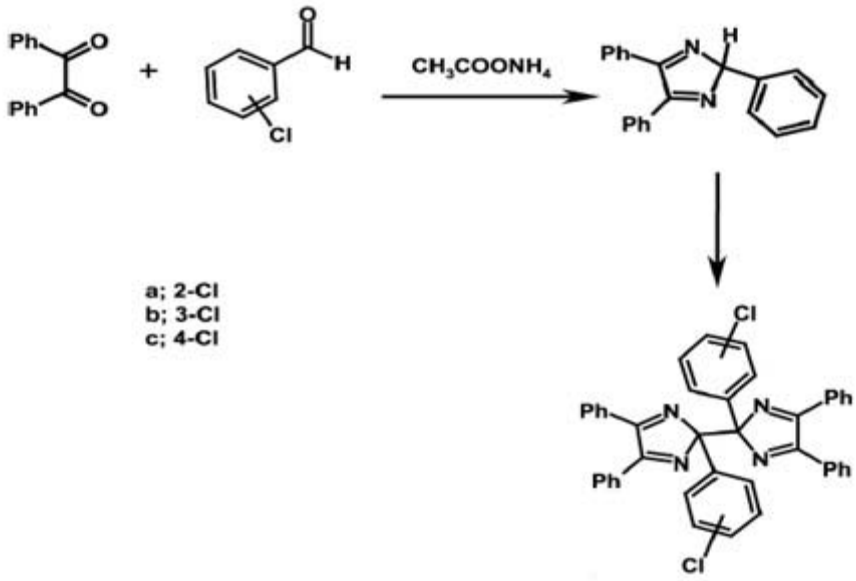
Zhou *et al.* proposed a simple, convenient and efficient method for synthesis of ether bis-imidazoles and their derivatives [17] from oligo-ethyleneglycols, imidazole, and 2-methylimidazole. The synthetic approach is shown in scheme (1).

Author α σ ρ ω: Helwan University. e-mail: elmorsy3@gmail.com



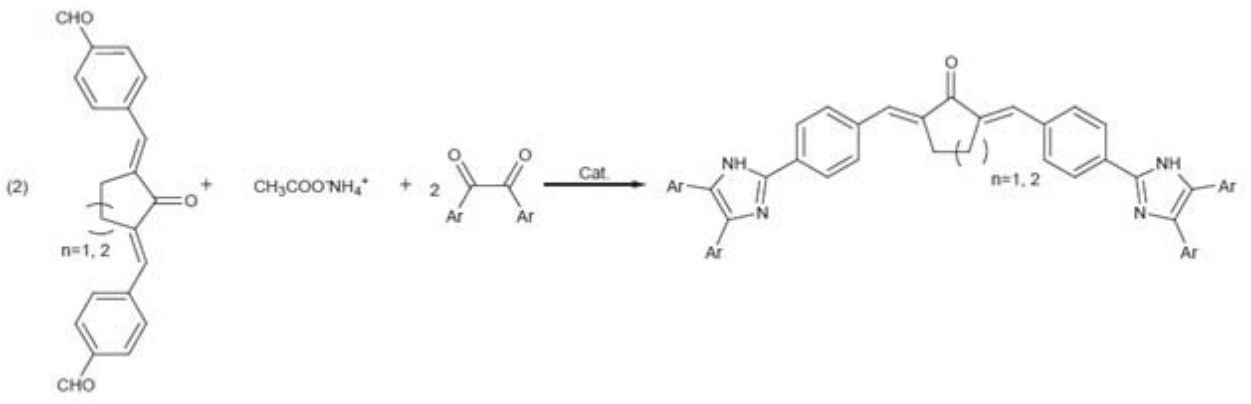
Scheme (1)

Bis-imidazole also synthesized by Asiri *et al.* [18]. He and his coworkers synthesized firstly imidazole from benzyl, ammonium acetate, and one of the three isomers of chlorobenzaldehyde. Then new bis-imidazoles was synthesized by dissolving the imidazole derivative and cooling in ice bath, then adding potassium ferricyanide to the cooled imidazole, the synthesis route is shown in scheme (2).



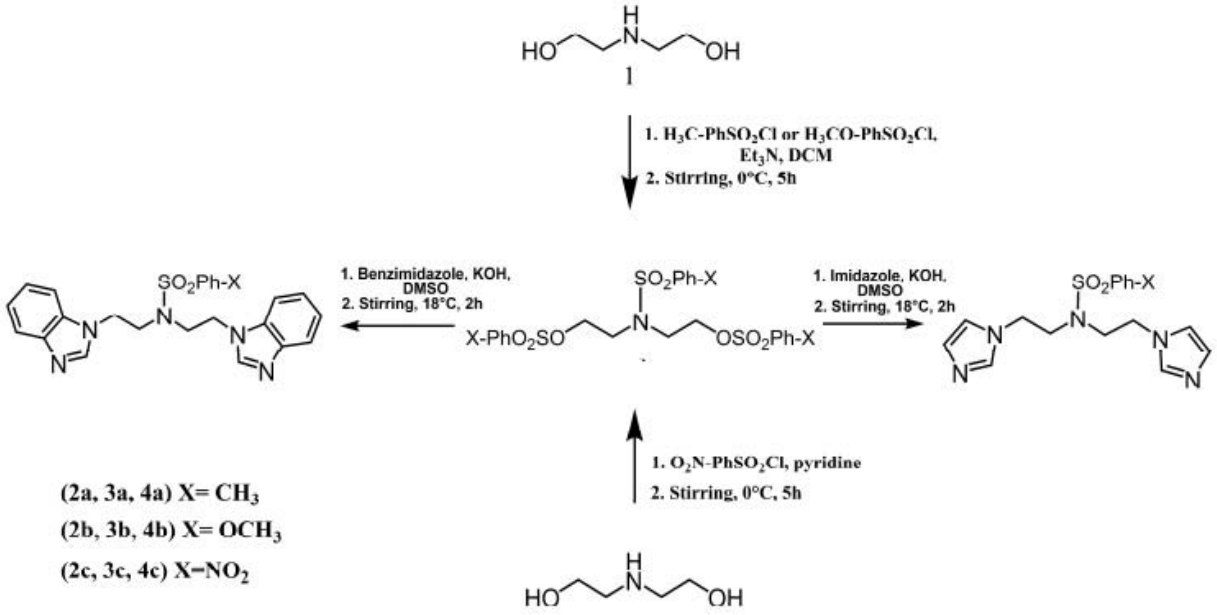
Scheme (2)

Ghazvini *et al.* reported an efficient one-pot synthesis for some novel bis imidazole from 4,4′-(2-oxocycloalkane-1,3-diylidene) bis(methan-1-yl-1-ylidene) dibenzaldehydes derivatives with benzyl and ammonium acetate [15]. The reaction conditions were optimised by changing the type and amount of catalyst, and adjusting reaction temperature. The key advantages of this procedure are environmentally friendly conditions and good yield of products. The synthetic pathway is shown in scheme (3).



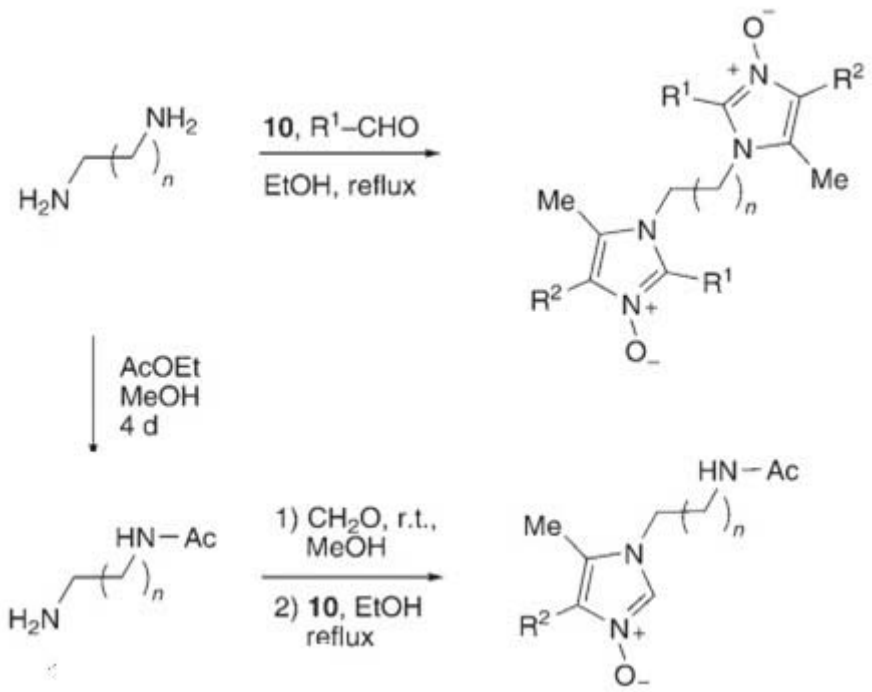
Scheme (3)

Nassir *et al.* synthesized some novel bisimidazole sulfonamide compounds [19]. The bis-imidazole sulfonamides compounds were obtained by treating imidazole with tris-(4-substituted benzensulfonate)-diethanolamine under basic conditions to form the corresponding bis imidazole as shown in scheme (4).



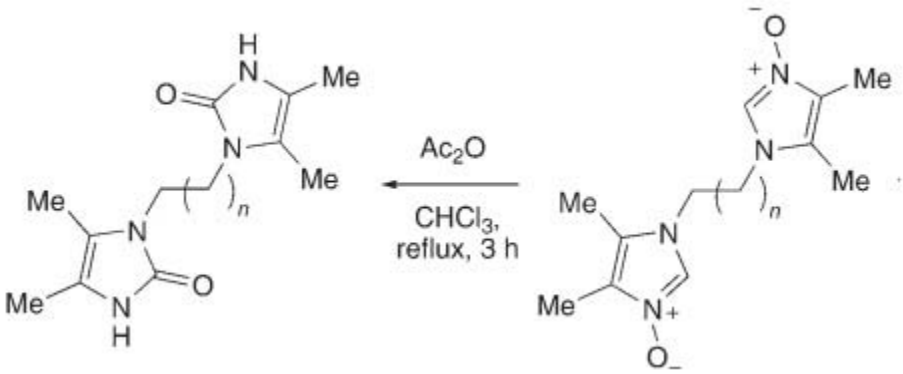
Scheme (4)

Jasinski *et al.* afford an interesting method for synthesis of some novel bis-imidazoles [20]. The synthesis procedure involved the formation of bis-imidazole oxide compounds that were converted finally to bis-imidazole. The bis-imidazole oxide derivatives synthesis step was carried out according to scheme (5).

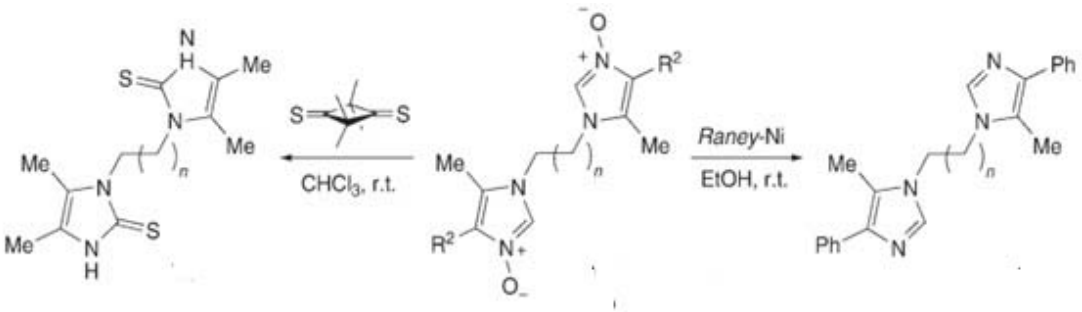


Scheme (5)

The prepared bis[imidazole 3-oxides] was isomeried with Ac_2O to give the bis[2H-imidazol-2-one] as shown in scheme (6). Finally bis[imidazole 3-oxides] derivatives was converted to 2H-imidazole-2- thiones and bis-imidazole derivatives using 2,2,4,4-tetramethylcyclobutane-1,3-dithione and Raney-Ni respectively according to scheme (7).

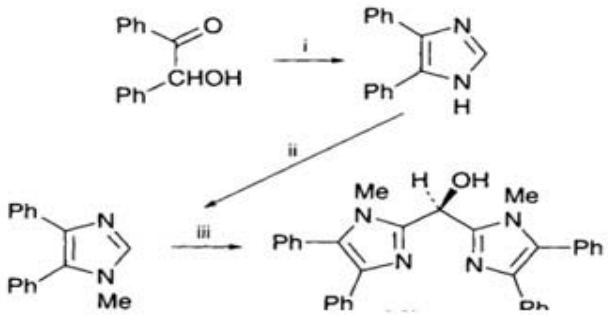


Scheme (6)



Scheme (7)

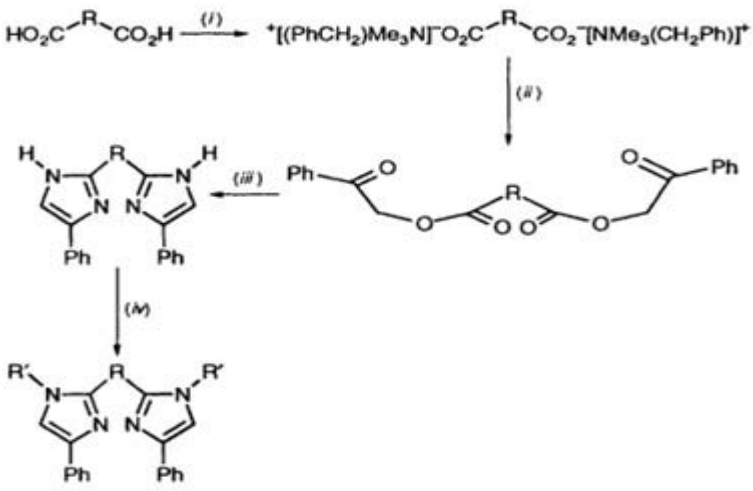
Bhalla *et al.* studied the coordination ability bis-imidazole, to achieve their goal they prepared Bis(1-methyl-4,5-diphenylimidaz-2-oyl) (benzyloxy) methane ligand [21, 22] using the conditions followed in scheme (8).



Synthesis of bis(1-methyl-4,5-diphenylimidaz-2-oyl)carbinol, BimOH. *Reagents and conditions*: i, H_2NCHO; ii, NaH then MeI, thf; iii, BuLi then 0.5 HCO_2Et, thf, −78 °C.

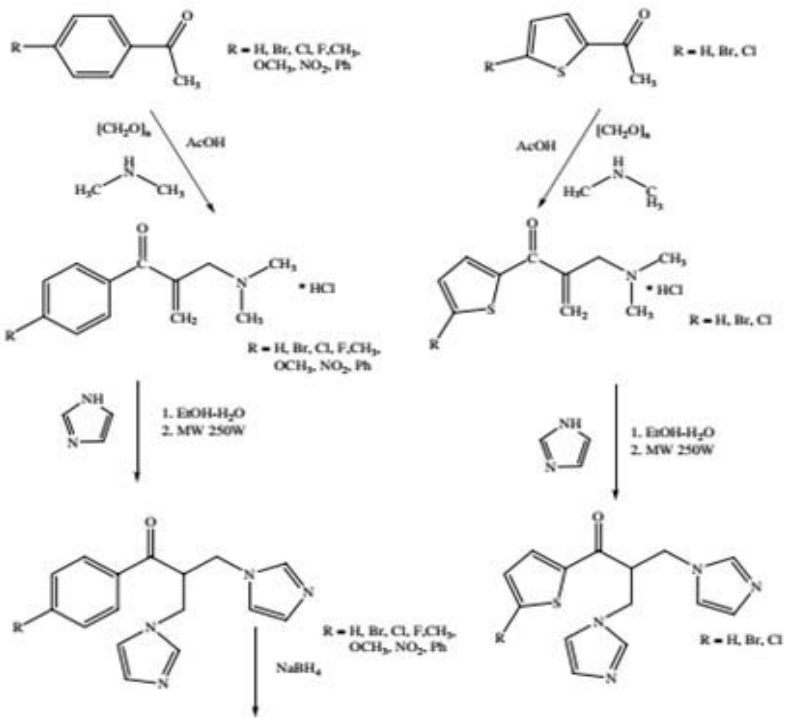
Scheme (8)

Due to presence of donor nitrogen atoms, imidazole heterocycle is of great interest in the coordination chemistry. To be used as a proligands, Higgs *et al. reported the synthesis* of new sterically hindered bis(imidazo1e). The authors followed a multi step synthesis as shown in scheme (9), which lead to the formation of 1,2-bis- (4-phenylimidazol-2-yl)ethane [23]. The first step involves dissolving succinic acid in MeOH *and* neutralised to pH 7.5 using $[NMe_2(CH_2Ph)][OMe]$ (40% solution in MeOH). In the following step Formamide was then added to the reaction mixture and the solution stirred for 5 min before bromoacetophenone was added. In the third step ammonium acetate is introduced to the reaction liquor and refluxed for 48 hours. Here we have prepared Dimethylbis(4-phenylimidazol-2-yl)lmethan. The authors extended their work to another final step which involves the use of sodium hydride to achieve deprotonation of the obtained bis(imidazo1e).



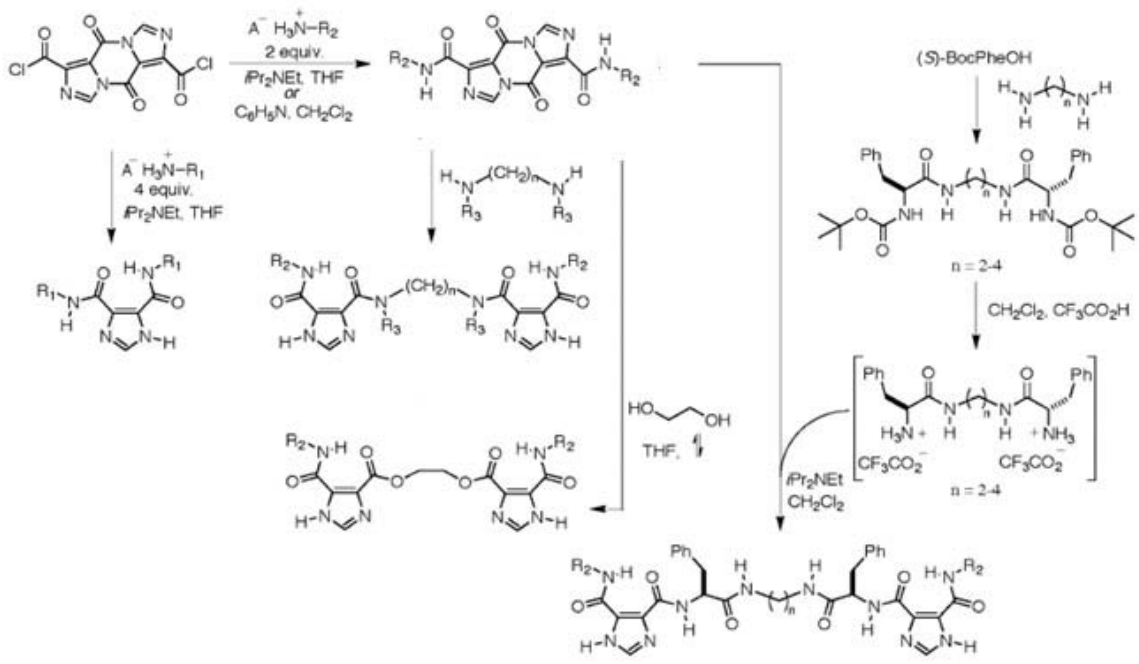
Scheme (9)

New bis-imidazole derivatives have been synthesized by Zampieri *et al.* [24]. The synthesis was achieved using via a Michael type reaction by nucleophilic attack of imidazole to 1-Aryl-2-[(dialkylamino)methyl]-propenone hydrochlorides or and 2-[(dimethylamino)methyl]-1-(thiophene-2-yl)-propenones under microwave (MW) irradiation of the reagent mixture in EtOH–H_2O at room temperature.



Scheme (10)

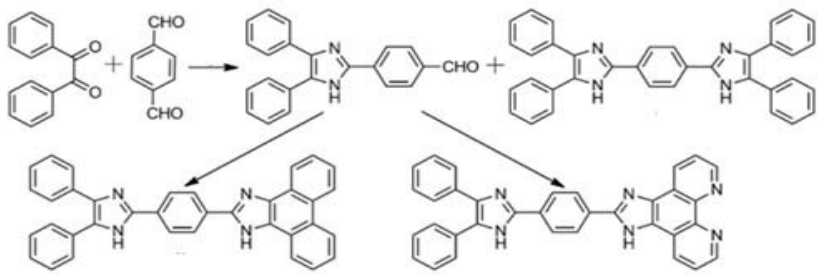
Wiznycia *et al.* prepared a series of symmetric bis(imidazole-4,5-dicarboxamides) with amino acid esters and a variety of linker groups [25]. The bis-imidazole derivatves in this study were obtained by reacting a symmetric pyrazine derivative bearing reactive acid chloride and acyl imidazole functionalities with 2 equiv of an amino acid salt along with a base scheme (11).



Scheme (11)

Zhang *et al.* reported a scheme involves the synthetic procedure for the synthesis of bis-imidazole compounds according to previous studies [26, 27, 28] as illustrated in scheme (12). In this study, the authors synthesized one symmetrical structure called 1,4-bis(4,5-diphenyl- 1*H*-imidazol-2-yl)benzene and two

asymmetrical structures, namely 2-(4-(4,5-diphenyl- 1*H*-imidazol-2-yl)phenyl)-1*H*-phenanthro (9,10-*d*) imidazole and 2-(4-(4,5-diphenyl-1*H*-imidazol-2-yl)phenyl)-1*H*-imidazo(4,5-*f*)(1,10)phenanthroline. The synthetic route of bis-imidazole compounds begins with terephthaldehyde, benzyl, and ammonium acetate in presence of glacial acetic acid.



Scheme (12)

IV. Conclusion

Bis-imidazoles are an important heterocyles having great biological activities and used as an important precursor for the synthesis of various other bioactive compounds. Several synthetic routes and methods have been introduced to achieve the synthesis of these compounds. This review highlighted the strategies and synthetic routes for the bis-imidazole synthesis.

Conflict of Interest

The authors confirm that this article content has no conflict of interest.

References Références Referencias

1. Sharma D, Narasimhan B, Kumar P, Judge V, Narang RE, De Clercq J. Balzarini, European Journal of Medicinal Chemistry. 2009; 44:2347-2353
2. Shingalapur RV, Hosamani KM, Keri RS. European Journal of Medicinal Chemistry. 2009; 44: 4244-4248.
3. P. Manocha, SR Wakode, A. Kaur, K. Anand, H. Kumar. International Journal of Pharmaceutical Science and Research 2016; 12-16
4. Ozkay Y, Iskar I, Incesu Z, Akalın Ge. European Journal of Medicinal Chemistry. 2010, 1-9.
5. Luo, M.-M., Guo, S.-J., Zhou, C.-H. and Xie, R.-G., *Heterocycles* 1995, 41, 1421
6. Hadizadeh F, Hosseinzadeh H, Sadat Motamed-Shariaty V, Seifi M, Kazemi S. Iranian Journal of Pharmaceutical Research. 2008; 7(1):29-33.
7. A.R. Katritzky, Rees. *Comprehensive Heterocyclic Chemistry.,*1984, 5, 469-498
8. M.R. Grimmett. *Imidazole and Benzimidazole Synthesis.,*1997, Academic Press
9. E.G. Brown, *Ring Nitrogen and Key Biomolecules.,* 1998, Kluwer Academic Press.
10. A.F. Pozharskii, *Heterocycles in Life and Society.,*1997, John Wiley & Sons.
11. TL Gilchrist, Heterocyclic Chemistry The Bath press 1985.
12. A. Chawla, A. Sharma and A. Sharma, derpharmachemica 2012 4 (1):116-140
13. L.H. Zhang, Y.Y. Liu, J.F. Ma, J. Yang, L.G. Zhang, J. Li and Y.W. Li, *Polyhedron*, 2011, 30, 764
14. Y. Wang, F.H. Zhao, A.H. Shi, Y.X. Che and J.M. Zheng, *Inorg. Chem. Commun.*, 2012, 20, 23.
15. M. H. Ghazvini and A. Mobinikhaledi, JOURNAL OF CHEMICAL RESEARCH 2014, (38) 648–650
16. A. Bhatnagar, P.K. Sharma, N. Kumar. *Inter. J. Pharm Tech Res*., 2011, 3(1), 268-282.
17. C. Zhou, X. Gu, R. Xie, M. Cai Synthetic Communications 1999, 29(7), 1217-1222
18. A. M. Asiri, K. Badahdah, Pigment & Resin Technology, · 2006 , 35 (4) · 200–2043.
19. N. Al-Mohammed, Y. Alias, Z. Abdullah, R. M. Shakir, E. M. Taha, A. Abdul Hamid, *Molecules* 2013, *18*, 11978-11995
20. M. Jasinski1, G. Mloston, P. Mucha, Helvetica Chimica Acta, 2007 (90) 1765-1780
21. R. Bhalla, M. Helliwell, C. D. Garner, *Chem. Commun.,* 1996, 921-922
22. R. Bhalla, M. Helliwell, C. D. Garner, *Inorg. Chem.* 1997, *36,* 2944-2949
23. T. C. Higgs, M. Helliwell, C. D. Garner, *J. Chem. SOC.,*Dalton *Trans., 1996, Puges 2101-2/10*
24. D. Zampieri, M. Mamolo, L. Vio, E. Banfi,G. Scialino, M. Fermeglia, M. Ferrone, S. Pricl. Bioorganic & Medicinal Chemistry 15 (2007) 7444–7458
25. A. V. Wiznycia, J. R. Rush, P. W. Baures, *J. Org. Chem.* 2004, *69*, 8489-8491
26. Tian, M.; Wang, C.; Wang, L.; Luo, K.; Zhao, A.; Guo, C. 2014, *29*, 540–548.
27. Gao, F.; Chen, X.; Zhou, F.; Weng, L.-P.; Guo, L.-T.; Chen, M.; Chao, H.; Ji, L.-N. *Inorg. Chim. Acta* 2009, *362*, 4960–4966.
28. L. Zhang, F. Liu. *Molecules* 2017, *22*, 1519.

Global Journals Guidelines Handbook 2018

www.GlobalJournals.org