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Imidazole: Chemistry and biological activities

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ABSTRACT

Imidazole, a five membered heterocyclic compound, with two nitrogen atoms at positions 1 and 3 respectively exhibits a wide range of pharmacological action such asanti-fungal, anti-bacterial, anti-tubercular, anti-viral, anti-inflammatory, analgesic, anti-depressant, anti-cancer, carbonic anhydrase inhibitor, anti-ulcer, anthelmintic, anti-amoebic, anti-hypertensive, anti-epileptic, anti-psychotic and anti-emetic.A number of drugs having imidazole nucleus are available in the market for clinical use.Some of these marketed drugs are ketoconazole, omeprazole, mebendazole, acyclovir, secnidazolepimozide, and ondansetron.Various derivatives of imidazole nucleus have been synthesized and screened for their pharmacological activities.There are a number of well-established protocols for the synthesis of this heterocyclic ring. This paper summarizes some of the approaches of synthesis of imidazole derivatives having different pharmacological activities.

Key words: *Imidazole; Debus-Radziszewski synthesis; Wallach synthesis; Markwald synthesis*

1. Introduction

Imidazole (1), a planar five-membered heterocyclic ring, consists of two nitrogen atoms in 1 and 3 positions. It exists in two tautomeric forms depending upon the position of hydrogen on the nitrogen atoms. It is a crystalline solid, soluble in polar solvents but almost insoluble in petroleum ether. It is a highly polar compound with dipole moment of 3.61 D. Due to its amphoteric nature; it can act as both acid as well as base. The basic pK_a and acidic pK_a of imidazole ring are 7.2 and 14.5 respectively. The melting point and boiling point of imidazole

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are 90 ^{0}C and 256 ^{0}C respectively. The presence of intermolecular hydrogen bonding is responsible for its high boiling point. The molecular formula is $C_3H_4N_2$ [1].

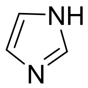

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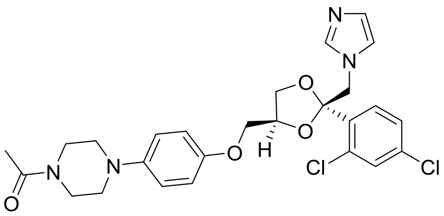
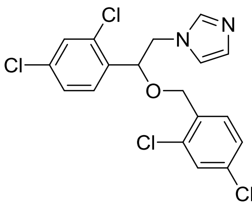
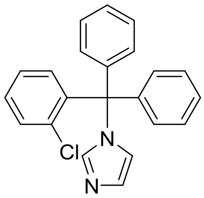
Figure 1: Chemical structure of imidazole ring

The first ever synthesis of imidazole was reported by Heinrich Debus in 1858 from glyoxal and formaldehyde in ammonia, and is called glyoxaline. Although this synthetic approach relatively gives low yields but still it is used for preparing C-substituted imidazole. Now this name is obsolete, and imidazole or iminazole is preferred greatly [2-4].

Imidazole is a versatile nucleus and a number of derivatives of imidazole have been synthesized which exhibited a wide range of pharmacological activities such as antifungal, antibacterial, antitubercular, antiviral, anti-inflammatory, analgesic, antidepressant, anticancer, carbonic anhydrase inhibitor, antiulcer, anthelmintic, anti-amoebic, antihypertensive, anti-epileptic, antipsychotic and anti-emetic. A number of the drugs having imidazole nucleus are available in the market and are summarized in **Table 1** [5, 6].

Table 1: Marketed drugs having imidazole nucleus

Comp. No.	Drug	Chemical structure	Therapeutic class	Reference
2	Ketoconazole		Anti-fungal	[5]
3	Miconazole		Anti-fungal	[7]
4	Clotrimazole		Anti-fungal	[8]

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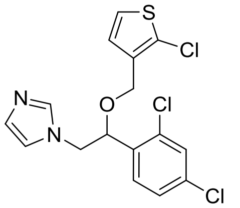
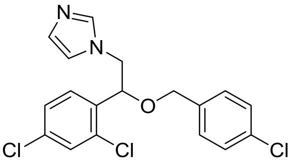
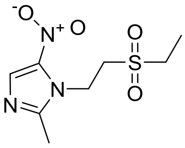
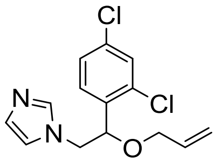
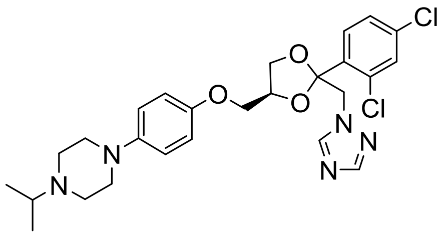
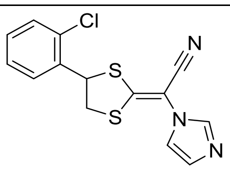
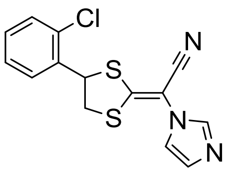
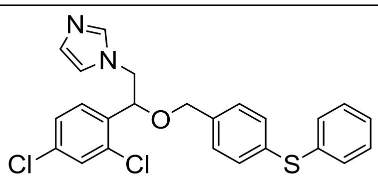
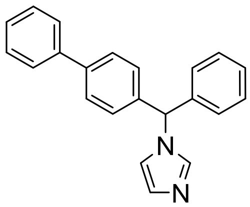
5	Tioconazole		Anti-fungal	[8]
6	Econazole		Anti-fungal	[9]
7	Tinidazole		Anti-fungal	[10]
8	Enilconazole		Anti-fungal	[11]
9	Terconazole		Anti-fungal	[12]
10	Eberconazole		Anti-fungal	[13]
11	Lanoconazole		Anti-fungal	[14]
12	Fenticonazole		Anti-fungal	[15]
13	Bifonazole		Anti-fungal	[16]

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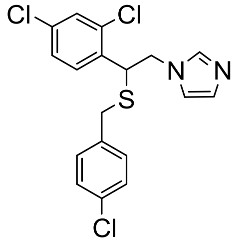
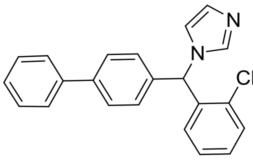
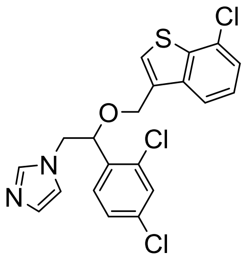
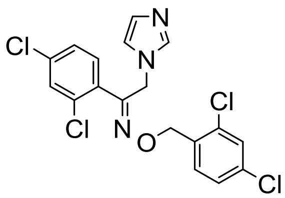
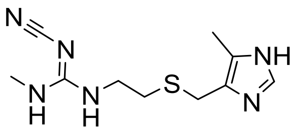
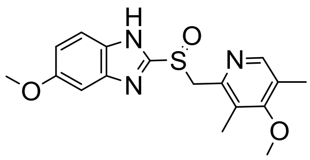
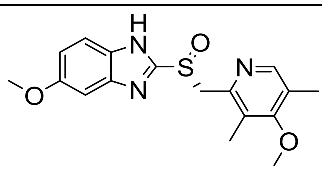
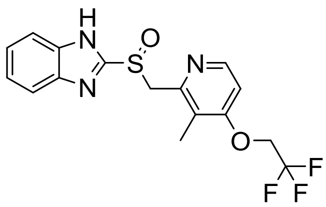
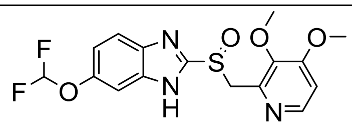
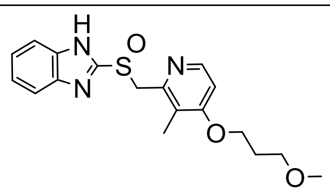
14	Sulconazole		Anti-fungal	[17]
15	Lombazole		Anti-fungal	[18]
16	Sertaconazole		Anti-fungal	[19]
17	Oxiconazole		Anti-fungal	[20]
18	Cimetidine		Anti-ulcer	[21]
19	Omeprazole		Anti-ulcer	[22]
20	Esomeprazole		Anti-ulcer	[23]
21	Lansoprazole		Anti-ulcer	[24]
22	Pantoprazole		Anti-ulcer	[25]
23	Rabeprazole		Anti-ulcer	[26]

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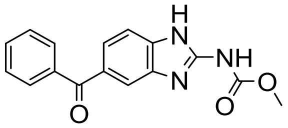
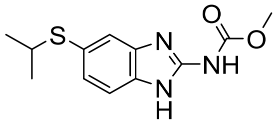
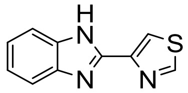
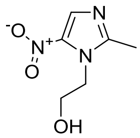
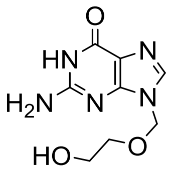
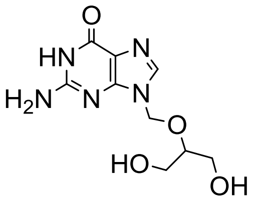
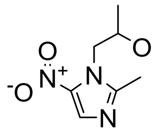
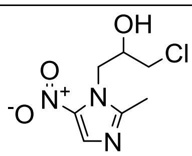
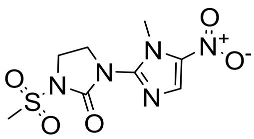
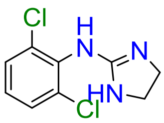
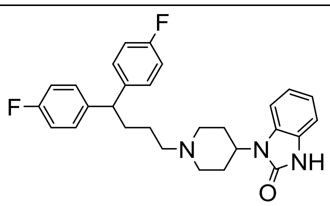
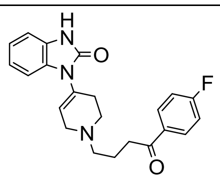
24	Mebendazole		Anti-anthelmintic	[27]
25	Albendazole		Anti-anthelmintic	[28]
26	Thiabendazole		Anti-anthelmintic	[29]
27	Metronidazole		Anti-bacterial	[30]
28	Acyclovir		Anti-viral	[31]
29	Ganciclovir		Anti-viral	[32]
30	Secnidazole		Anti-amoebic	[33]
31	Ornidazole		Anti-amoebic	[34]
32	Satranidazole		Anti-amoebic	[35]
33	Clonidine		Anti-hypertensive	[36]
34	Pimozide		Anti-psychotic	[37]
35	Droperidol		Anti-psychotic	[38]

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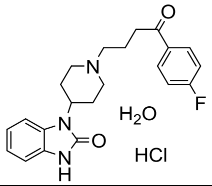
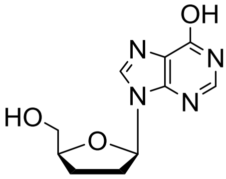
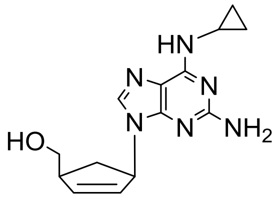
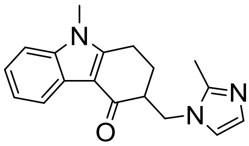
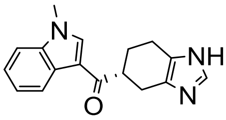
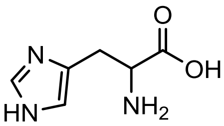
36	Benperidol		Anti-psychotic	[39]
37	Didanosine		Anti-HIV	[40]
38	Abacavir		Anti-HIV	[41]
39	Ondansetron		Anti-emetics	[42]
40	Ramosetron		Anti-emetics	[43]

Imidazole nucleus is also present in some of the natural components of human organisms like histidine (41), histamine (42), adenine (43), guanine (44) and biotin (45). It is also present in alkaloids derived from various plants such as Pilocarpine, Leucetta, Lepidium, Cynometra etc. [44, 45].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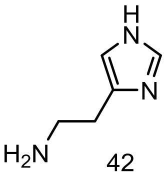
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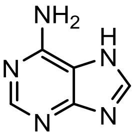
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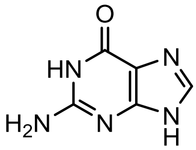
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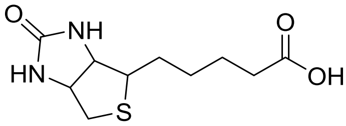
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2. Approaches for the synthesis of imidazoles

Different synthetic approaches have been reported for the preparation of imidazole and substituted imidazoles. Some of the important synthetic approaches have been discussed in the following sections.

2.1 Debus-Radziszewski synthesis

In Debus-Radziszewski synthesis, an imidazole is synthesized from an α-dicarbonyl (commonly glyoxal), an aldehyde and two equivalents of dry ammonia in alcohol. In addition

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to glyoxal, ketoaldehydes can also be used. The reaction involves two steps. In first step, the dicarbonyl and ammonia condense to give a diamine which further condense with aldehyde to give imidazole. Although a century old method, but it is still commonly used to synthesize various imidazole derivatives [46, 47].

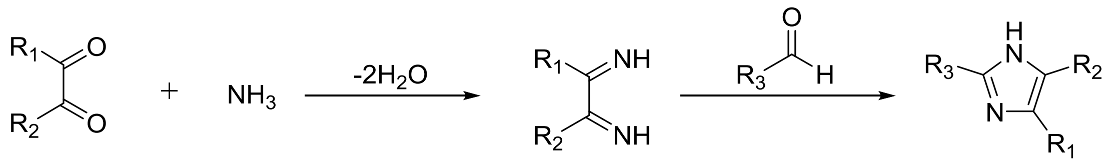


Figure 1: Debus-Radziszewski synthesis

2.2 Dehydrogenation of imidazoline

Dehydrogenation of substituted/unsubstituted 2-imidazolines with nickel-petroleum paste, Pd, or Pt as metal catalyst gave corresponding imidazoles [48]. The other oxidizing agents such as potassium permanganate supported on silica gel can also be used to synthesize imidazoles [49].

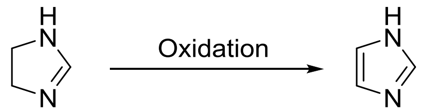


Figure 2: Dehydrogenation of Imidazoline

2.3 Wallach synthesis

In the presence of phosphorous pentachloride, *N*,*N*-dimethyloxamide is converted into a 5-chloro derivative which on reduction with hydrogen iodide gave *N*-methyl imidazole [50].

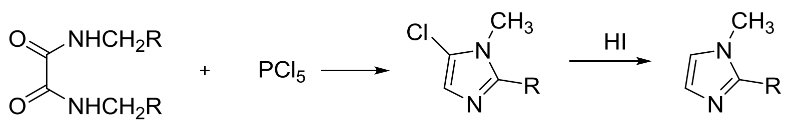
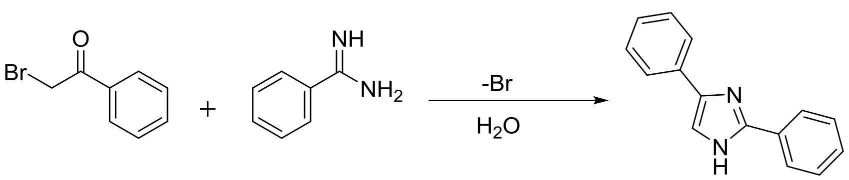


Figure 3: Wallach synthesis of imidazole

2.4 From α-halo ketone

2,4- or 2,5- biphenyl imidazole is synthesized by reaction between α-halo ketone and imidine. In another synthesis, acyloin reacts with amidine or α-halo ketones to yield imidazoles [51].



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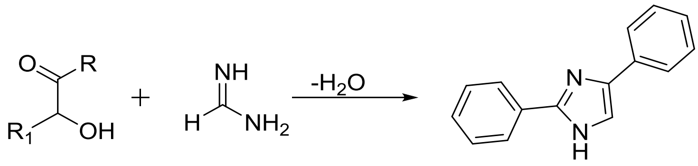

Figure 4: Synthesis of imidazole from α-halo ketone

2.5 Markwald synthesis

In Markwald synthesis, α-amino carbonyl compounds reacts with potassium thiocyanate to give 2-mercaptoimidazoles; which then undergo oxidative cleavage to form substituted imidazole by loss of sulphur[52].

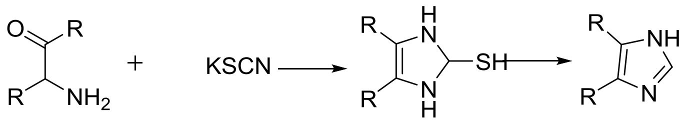

Figure 5: Markwald synthesis of imidazole

2.6 From amino nitrile and aldehyde

In an another approach, condensation of substituted aldehydes with aminonitrile in suitable reaction conditions gave imidazole derivatives [53].

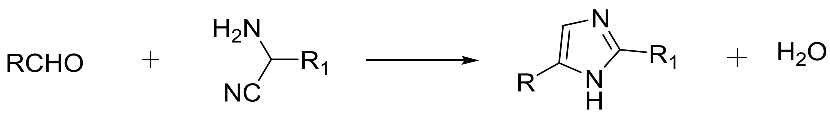

Figure 6: Synthesis of imidazole from amino nitrile and aldehyde

2.7 Microwave assisted synthesis

Qasim and his co-workers reported the synthesis of 2-phenylimidazo [4,5-*f*][1,10] phenanthroline derivatives by using dicarbonyl and *p*-substituted benzaldehyde as starting materials. The microwave reaction provided a number of advantages like easy workup, better yield, and environment friendly reaction conditions [54].

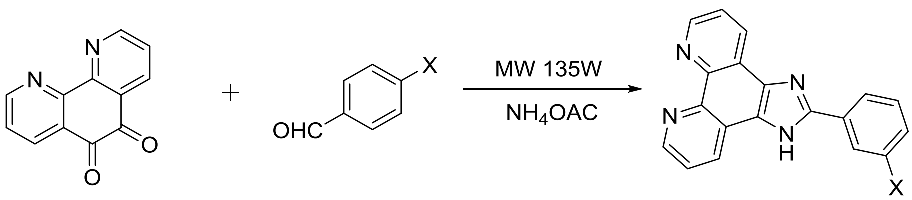

Figure 7: Microwave assisted synthesis of imidazole from dicarbonyl and benzaldehyde

In 2009, Ermolatreported the synthesis of mono and disubstituted-2-amino-1*H* imidazoles from imidazo [1,2*a*] pyrimidines by microwave assisted hydrazinolysis. The method was

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superior to conventional cyclocondensation as it had all the advantages of green synthesis [55].

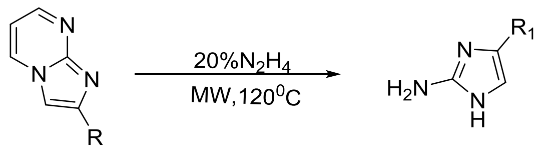


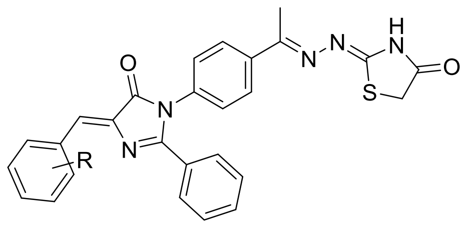
Figure 7: Microwave assisted synthesis of imidazole from imidazo [1,2*a*] pyrimidines

3. Pharmacological activities of imidazole derivatives

3.1 Antifungal

Imidazoles are mainly used as antifungal and a number of imidazole derivatives are available in clinical practice for the treatment of fungal diseases. They are used for both superficial and deep fungal infections. Imidazoles impair ergosterol synthesis by inhibition of fungal lanosterol l4-demethylase (cytochrome P450 enzyme), thus lead to membrane abnormalities [1].

New series of imidazole derivatives (46) with 4-thiazolididone motifs was synthesized by multiple chemical reactions like condensation, cycloaddition etc. The synthesized compounds were evaluated for antifungal potential against *Candida albicans*, *Aspergillus niger* and *A. clavatus* by serial broth dilution method. Substituents at 2 and 4-positions on the benzene ring of imidazole were found to affect antimicrobial potency significantly [30].



46

New heterocyclic compound having imidazole ring, anthracene ring and thiadiazole ring (47) had been synthesized by condensation reaction of *N*-anthracen-9(10*H*)-ylidenehistidine with thiosemicarbazide in phosphorusoxy chloride. Preliminary *in vitro* screening revealed that the synthesized derivatives exhibited potent fungicidal activity [56].

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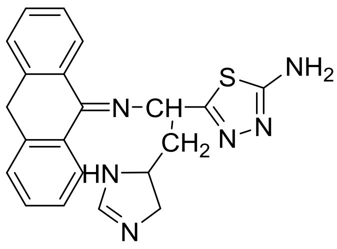
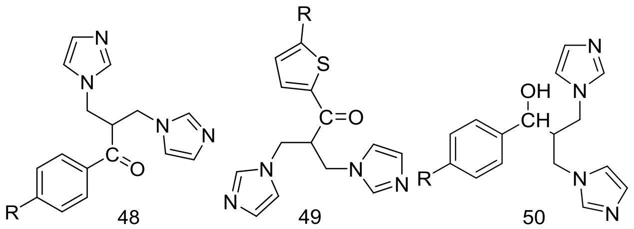


47

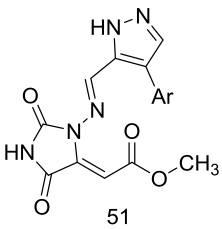
Derivatives of bis-imidazole had been synthesized by Zampieri and his co-workers in 2007. The anti-fungal property of the synthesized compounds was evaluated against *Candida albicans*3038 and *C. glabrata* 123 using miconazole and amphotericin B as standard drugs. All the synthesized compounds exhibited moderate to good activity against both the strains of fungi [57].



48 49 50

3.2 Antibacterial

Anti-bacterial potential of imidazole derivatives (51) substituted with pyrazole moiety was determined against *Staphylococcus aureus*, *Bacillus subtillis* and *Escherichia coli*. The various derivatives of imidazoles was synthesized via Debus reaction between 3-substituted-1*H*-pyrazole-4-carbaldehydes, 1,2-diketones and ammonium acetate in acetic acid. Among the synthetized derivatives, the compound having 4-thioanisyl was found to be most potent antimicrobial [58].



51

The anti-tubercular potential of imidazole was explored by Patel and his co-workers in 2017. They synthesized a new series of fused imidazole and thiadiazole derivatives (52) and evaluated for *in vitro*antitubercular activity against *Mycobacterium tuberculosis*. The compound having 4-nitro group was found to be most active among the different derivatives with MIC of 3.14 µg/ml [59].

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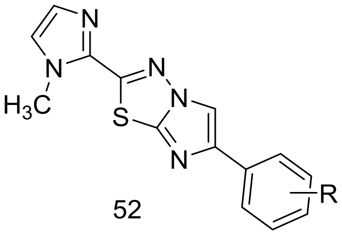
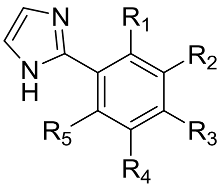


52

The anti-bacterial and anti-fungal potential of 2-substituted imidazole derivatives were explored by Sharma et. al. in 2009. Structure activity relationship studies revealed that the presence of electron withdrawing groups enhance the anti-microbial potential of synthesized derivatives [60].



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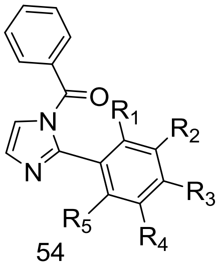
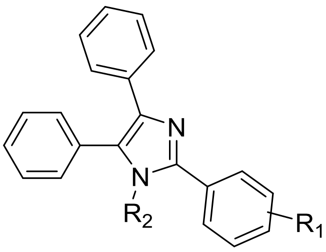


54

In an another study, 2,4,5-triphenyl-*N*-substituted imidazoles were evaluated for anti-bacterial effect against *S. aureus*, *E.coli* and *B. subtilis*. All the synthesized derivatives were found to be effective against bacterial infections as evaluated in in vitro studies [61].



55

3.3 Anti-convulsant

A novel oxime and oxime ether derivatives of nafimidone (56) were synthesized and evaluated for anti-convulsant potential. Reaction between nafimidone and hydroxylamine hydrochloride gave oxime derivatives while *O*-alkylation with alkyl halide gave oxime ethers. In addition to anti-convulsant activity, the compounds were screened for anti-bacterial and anti-fungal activities also. Most of the synthesized derivatives exhibit potent anti-convulsant and anti-microbial activities, *O*-alkyl substituted derivatives were found to be more potent than *O*-arylalkyl substituted derivatives [62].

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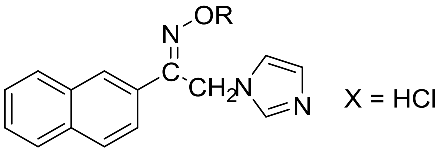
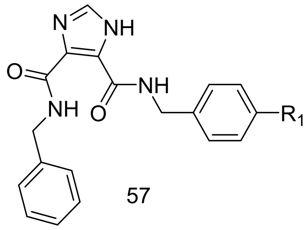


56

3.4 Antiviral

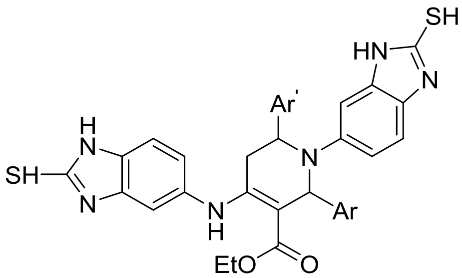
A novel class of disubstituted imidazole 4,5-dicarboxamide (57) was synthesized from imidazole 4,5-dicarboxylic acid. In *in vitro* screening, the synthesized compounds exhibited inhibitory activity against virus [63].



57

3.5 Anti-inflammatory and antioxidant

One-pot synthesis of a series of benzo[*d*]imidazolyltetrahydropyridine carboxylates (58) has been carried by reaction between (*E*)-5-(benzylidene-amino)-1*H*-benzo[*d*]imidazole-2-thiole, 5-amino-2-thiobenzimidazole, aldehydes and ethyl acetoacetate. All the synthesized compounds exhibited significant anti-inflammatory and antioxidant activities [64].



58

New series benzothiazoles derivatives with imidazole ring have been synthesized from substituted 2-aminobenzothiazoles. Pharmacological evaluation studies indicated the anti-inflammatory potential of synthesized derivatives [65].

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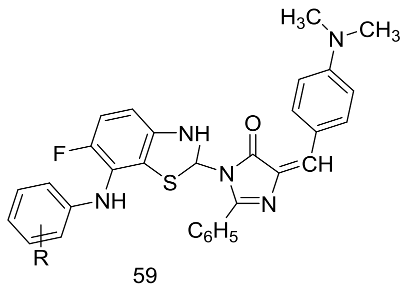
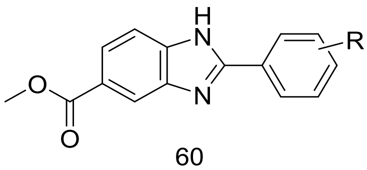


59

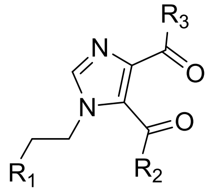
3.6 Anticancer

Karthikeyan and his co-workers synthesized a new series of ester derivatives of substituted 2-(phenyl)-3*H*-benzo[*d*]imidazole-5-carboxylic acids. The synthesized compounds were examined for *in vitro* anti-proliferative effects against breast cancer cell lines. The synthesized compounds exhibited comparable or greater anti-proliferative effects than cisplatin. However the compound with 3,4-dihydroxy substitution in the aryl ring was found to be most active in all the three cell lines [66].



60

A series of novel imidazole derivatives were synthesized by reaction of 4,5-dimethyl 1*H*-imidazole-dicarboxylate with potassium carbonate and different 2-chloroalkylamine hydrochlorides. The compounds were screened for anti-proliferative assays on selected tumor cell lines. Although the derivative have cytostatic effect against HeLa cells but no effect was observed against normal fibroblasts [67].



61

3.7 Anthelmintic

The condensation of primary aromatic amines with aryl halides gave Schiff bases which on subsequent reaction with ammonium acetate and isatin gave aryl imidazole derivatives (62). All the synthesized compounds exhibited good anthelmintic activity in comparison to standard drug mebendazole[68].

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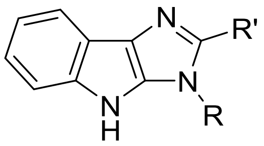

62

3. CONCLUSION

Imidazole is a versatile nucleus possessing a wide range of pharmacological activities. A number of derivatives of imidazole have been synthesized and marketed as drugs for various diseases such as anti-fungal, anti-ulcer, anthemintic, anti-viral, anti-amoebic, anti-psychotic and anti-emetic. Some of the synthesized molecules are in the pre-clinical phase and can be a future drug after the clinical and toxicity studies. Quantitative structural activity relationship studies can be used to design the more potent imidazole derivatives with minimal side effects.

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Vol-22-Issue-37-December -2019

4. REFERENCE

[1] A. Bhatnagar, P. Sharma, and N. Kumar, “A review on imidazoles: Their chemistry and pharmacological potentials,” Int. J. PharmTech Res., vol. 3, pp. 268-282, Jan. 2011.

[2] R. Ghosh, and D. Biplab, “Review on: synthesis, chemistry and therapeutic approaches of imidazole derivatives,” Int. J. PharmTech Res., vol. 45, pp. 237-246, Dec. 2014.

[3] B. Ashish, and S. Pandeya, “Various approaches for synthesis of imidazole derivatives,” Int. J. Res. Ayurveda Pharm., vol. 2, pp. 1124-1129, Mar. 2011.

[4] S. Ahmed, B. Pochaiah, and M. Harikishan, “Synthesis and screening of 1H-substituted 2,4,5-triphenyl imidazole derivatives,” Pharma. Scient., vol. 1, pp. 8-11, 2012.

[5] C. Liu, C. Shi, F. Mao, Y. Xu, J. Liu, B. Wei, J. Zhu, M. Xiang, and J. Li, “Discovery of new imidazole derivatives containing the 2, 4-dienone motif with broad-spectrum antifungal and antibacterial activity,” Molecules, vol. 19, pp. 15653-15672, 2014.

[6] A. Verma, S. Joshi, and D. Singh, “Imidazole: Having versatile biological activities,” J. Chem., vol. 2013, 2013.

[7] J. H. Davis Jr, K. J. Forrester, and T. Merrigan, “Novel organic ionic liquids (OILs) incorporating cations derived from the antifungal drug miconazole,” Tetrahedron Lett., vol. 39, pp. 8955-8958,Dec. 1998.

[8] G. E. Stein, S. Christensen, and N. Mummaw, “Comparative study of fluconazole and clotrimazole in the treatment of vulvovaginal candidiasis,” DICP, Ann. Pharmacother., vol. 25, pp. 582-585,Jun. 1991.

[9] L. Li, H. Kankaanranta, K. Vaali, I. Paakkari, and H. Vapaatalo, “Econazole, miconazole and SK&F 96365 inhibit depolarization-induced and receptor-operated contraction of guinea-pig isolated trachea in vitro,” Eur. J. Pharmacol., vol. 331, pp. 221-225,Jul. 1997.

ISSN:0971-1260
Vol-22-Issue-37-December -2019

[10] J. R. Villagrana-Zesati, F. M. Guerra-Infante, and I. E. Sosa-González, “Clinical efficacy of fluconazole, tinidazole and clindamycin vs fluconazole, tinidazole and azithromycin in the treatment of mixed cervical-vaginal infections, included those caused by Mycoplasma and Chlamydia trachomatis,” Ginecol. Obstet. Mex., vol. 81, pp. 231-238, 2013.

[11] M. Sharman, Z. Lenard, G. Hosgood, and C. Mansfield, “Clotrimazole and enilconazole distribution within the frontal sinuses and nasal cavity of nine dogs with sinonasal aspergillosis,” J. Small Anim. Pract., vol. 53, pp. 161-167, Mar. 2012.

[12] M. Weisberg, “Terconazole--a new antifungal agent for vulvovaginal candidiasis,” Clin. Ther., vol. 11, pp. 659-668, 1989.

[13] B. Fernández-Torres, I. Inza, and J. Guarro, “In vitro activities of the new antifungal drug eberconazole and three other topical agents against 200 strains of dermatophytes,” J. Clin. Microbiol., vol. 41, pp. 5209-5211, 2003.

[14] Y. Niwano, M. Matsui, T. Tabuchi, K. Kanai, H. Hamaguchi, T. Miyazaki, K. Uchida, and H. Yamaguchi, “Studies on the antifungal activity of the new imidazole antimycotic lanoconazole in infected sites. Distribution in the skin and in vitro activity in the presence of stratum corneum,” Arzneim. Forsch., vol. 47, pp. 1056-1060, Sep. 1997.

[15] M. Veronese, M. Salvaterra, and D. Barzaghi, “Fenticonazole, a new imidazole derivative with antibacterial and antifungal activity. In vitro study,” Arzneim. Forsch.,vol. 31, pp. 2133-2137, 1981.

[16] A. Carrilo-Munoz, C. Tur, J. Torres, and A. Seymour, “In-vitro antifungal activity of sertaconazole, bifonazole, ketoconazole, and miconazole against yeasts of the Candida genus,” J. Antimicrob. Chemother., vol. 37, pp. 815-819, Apr. 1996.

[17] H. Y. Aboul-Enein, and I. Ali, “Comparative study of the enantiomeric resolution of chiral antifungal drugs econazole, miconazole and sulconazole by HPLC on various cellulose chiral columns in normal phase mode,” J. Pharm. Biomed. Anal., vol. 27, pp. 441-446, Jan. 2002.

ISSN:0971-1260
Vol-22-Issue-37-December -2019

[18] D. Barug, H.B. Bastiaanse, J.M. van Rossum, and A. Kerkenaar, “Action of lombazole, and inhibitor of fungal ergosterol biosynthesis, on Staphylococcus epidermidis,” Antimicrob. Agents Chemother., vol. 30, pp. 238-244, Aug. 1986.

[19] A. J. Carrillo-Muñoz, G. Giusiano, P. A. Ezkurra, and G. Quindós, “Sertaconazole: updated review of a topical antifungal agent,” Expert Rev. Anti-Infect. Ther., vol. 3, pp. 333-342, Jun. 2005.

[20] A. Polak, “Oxiconazole, a new imidazole derivative. Evaluation of antifungal activity in vitro and in vivo,” Arzneim. Forsch.,vol. 32, pp. 17-24, 1982.

[21] A. Sancho, J. Borras, L. Soto, and E. Colacio-Rodriguez, “Thermal decomposition of metal complexes of cimetidine,” Thermochim. Acta, vol. 130, pp. 213-220, Aug. 1988.

[22] S. Jiang, J. Meadows, S. A. Anderson, and A. J. Mukkada, “Antileishmanial activity of the antiulcer agent omeprazole,” Antimicrob. Agents Chemother.,vol. 46, pp. 2569-2574, Aug. 2002.

[23] A. Morgner, S. Miehlke, and J. Labenz, “Esomeprazole: prevention and treatment of NSAID-induced symptoms and ulcers,” Expert Opin. Pharmacother., vol. 8, pp. 975-988, May 2007.

[24] Y. Matsukawa, Y. Tomita, S. Nishinarita, T. Horie, K. Kato, Y. Arakawa, K. Ko, H. Shimada, M. Nakano, and Y. Kitami, “Efficacy of lansoprazole against peptic ulcers induced by nonsteroidal anti-inflammatory drugs: Endoscopic evaluation of ulcer healing,” J. Int. Med. Res., vol. 25, pp. 190-195, Jul. 1997.

[25] P. W. Jungnickel, “Pantoprazole: a new proton pump inhibitor,” Clin. Ther., vol. 22, pp. 1268-1293, Nov. 2000.

[26] B. Singh, H. Lal, L. Pal, and V. Sharma, “In vitro release profile of anti-ulcer drug rabeprazole from biocompatible psyllium-PVA hydrogels,” J. Mater. Sci.: Mater. Med., vol. 23, pp. 1021-1032, Apr. 2012.

[27] J. Laclette, G. Guerra, and C. Zetina, “Inhibition of tubulin polymerization by mebendazole,” Biochem. Biophys. Res. Commun., vol. 92, pp. 417-423, Jan. 1980.

[28] V. Kalra, T. Dua, and V. Kumar, “Efficacy of albendazole and short-course dexamethasone treatment in children with 1 or 2 ring-enhancing lesions of

ISSN:0971-1260
Vol-22-Issue-37-December -2019

neurocysticercosis: a randomized controlled trial," J. Pediatr., vol. 143, pp. 111-114, Jul. 2003.

[29] P. M. Allen, and D. Gottlieb, "Mechanism of action of the fungicide thiabendazole, 2-(4′-thiazolyl) benzimidazole," Appl. Environ. Microbiol.,vol. 20, pp. 919-926, Dec. 1970.

[30] N. C. Desai, V. V. Joshi, K. M. Rajpara, and A. H. Makwana, "A new synthetic approach and in vitro antimicrobial evaluation of novel imidazole incorporated 4-thiazolidinone motifs," Arabian J. Chem., vol. 10, pp. S589-S599, Feb. 2017.

[31] J. Yao, Y. Zhang, S. Ramishetti, Y. Wang, and L. Huang, "Turning an antiviral into an anticancer drug: nanoparticle delivery of acyclovir monophosphate," J. Controlled Release, vol. 170, pp. 414-420, Sep. 2013.

[32] D. Faulds, and R. C. Heel, "Ganciclovir," Drugs, vol. 39, pp. 597-638, Apr. 1990.

[33] J. C. Gillis, and L. R. Wiseman, "Secnidazole," Drugs, vol. 51, pp. 621-638, Apr. 1996.

[34] T. Chintana, P. Sucharit, V. Mahakittikun, C. Siripanth, and W. Suphadtanaphongs, "In vitro studies on the sensitivity of local Entamoeba histolytica to anti-amoebic drugs," Southeast Asian J. Trop. Med. Public Health, vol. 17, pp. 591-594, Dec. 1986.

[35] S. Shashiprabha, K. S. Rao, K. Nagarajan, K. Shridhara, E. Torreele, and B. Trunz, "Nitroimidazooxazoles# part xxiv, search for antileishmanial agents: 2, 3-dihydro-6-nitroimidazo [2, 1-b] oxazoles as potential antileishmanial agents," Indian J. Pharm. Sci., vol. 76, pp. 92, Jan. 2014.

[36] B. Xu, A. Makris, C. Thornton, R. Ogle, J. S. Horvath, and A. Hennessy, "Antihypertensive drugs clonidine, diazoxide, hydralazine and furosemide regulate the production of cytokines by placentas and peripheral blood mononuclear cells in normal pregnancy," J. Hypertens., vol. 24, pp. 915-922, May 2006.

[37] P. Morris, D. MacKenzie, and H. Masheter, "A comparative double blind trial of pimozide and fluphenazine in chronic schizophrenia," Br. J. Psychiatry, vol. 117, pp. 683-684, Dec. 1970.

[38] R. A. Chambers, and B. G. Druss, "Droperidol: Efficacy and side effects in psychiatric emergencies," J. Clin. Psychiatry,vol. 60, pp. 664-667, Oct. 1999.

ISSN:0971-1260
Vol-22-Issue-37-December -2019

[39] N. Nedopil, E. Eben, H. Klein, R. Krüger, E. Rüther, and M. Schmauss, "High-dosage neuroleptic therapy for acute schizophrenic patients-two double-blind studies with benperidol," Pharmacopsychiatry, vol. 18, pp. 63-66, Jan. 1985.

[40] D. Sriram, P. Yogeeswari, N. Raveendra Babu, and P. Nagashree Kurre, "Synthesis and in vitro anti-HIV activities of didanosine prodrugs," J. Enzyme Inhib. Med. Chem., vol. 22, pp. 51-55, Jan. 2007.

[41] C. Charneira, N. Grilo, S. Pereira, A. Godinho, E. Monteiro, M. Marques, and A. Antunes, "N- terminal valine adduct from the anti- HIV drug abacavir in rat haemoglobin as evidence for abacavir metabolism to a reactive aldehyde in vivo," Br. J. Pharmacol., vol. 167, pp. 1353-1361, Nov. 2012.

[42] S. Kathirvel, D. Shende, and R. Madan, "Comparison of anti-emetic effects of ondansetron, metoclopromide or a combination of both in children undergoing surgery for strabismus," Eur. J. Anaesthesiol., vol. 16, pp. 761-765, Nov. 1999.

[43] S. Yano, K. Makino, H. Nakamura, Y. Kai, M. Morioka, J.I. hamada, M. Kochi, and J.I. Kuratsu, "Comparative clinical study of the anti-emetic effects of oral ramosetron and injected granisetron in patients with malignant glioma undergoing ACNU chemotherapy," Neurologia. medico-chirurgica., vol. 45, pp. 294-299. 2005.

[44] W. H. Hassan, A. M. Al-Taweel, and P. Proksch, "Two new imidazole alkaloids from Leucetta chagosensis sponge," Saudi Pharm. J., vol. 17, pp. 295-298, Oct. 2009.

[45] R. C. De Souza, J. B. Fernandes, P. C. Vieira, M. F. d. G. da Silva, M. F. Godoy, F. C. Pagnocca, O. C. Bueno, M. J. A. Hebling, and J. R. Pirani, "A new imidazole alkaloid and other constituents from Pilocarpus grandiflorus and their antifungal activity," Zeitschrift für Naturforschung B, vol. 60, pp. 787-791, Jul. 2005.

[46] S. Saxer, C. Marestin, R. Mercier, and J. Dupuy, "The multicomponent Debus–Radziszewski reaction in macromolecular chemistry," Polym. Chem., vol. 9, pp. 1927-1933, 2018.

[47] X. Zhao, S. Guo, H. Li, J. Liu, X. Liu, and H. Song, "In Situ Synthesis of Imidazolium-Crosslinked Ionogels via Debus–Radziszewski Reaction Based on PAMAM Dendrimers in Imidazolium Ionic liquid," Macromol. Rapid Commun., vol. 38, pp. 1700415, Nov. 2017.

ISSN:0971-1260
Vol-22-Issue-37-December -2019

[48] Y. Amemiya, D. D. Miller, and F.-L. Hsu, “Dehydrogenation of Imidazolines to Imidazoles with Pd-Carbon,” Synth. Commun., vol. 20, pp. 2483-2489, Aug. 1990.

[49] I. Mohammadpoor-Baltork, M. A. Zolfigol, and M. Abdollahi-Alibeik, “Novel and chemoselective dehydrogenation of 2-substituted imidazolines with potassium permanganate supported on silica gel,” Tetrahedron Lett., vol. 45, pp. 8687-8690, Nov. 2004.

[50] T. Benincori, E. Brenna, and F. Sannicolo, “Studies on Wallach's imidazole synthesis,” J. Chem. Soc., Perkin Trans. 1, pp. 675-679, Jan. 1993.

[51] A. W. Erian, S. M. Sherif, and H. M. Gaber, “The Chemistry of α-Haloketones and Their Utility in Heterocyclic Synthesis,” Molecules, vol. 8, pp. 793-865, Nov. 2003.

[52] S. Y. Atanasova-Stamova, S. F. Georgieva, and M. B. Georgieva, “Reaction strategies for synthesis of imidazole derivatives: a review,” Scripta. Scientifica. Pharmaceutica., vol. 5, pp. 7-13, Nov. 2018.

[53] S. Sheik Mansoor, K. Aswin, K. Logaiya, and S. P. N. Sudhan, “An efficient one-pot three-component synthesis of α-amino nitriles via Strecker reaction catalysed by bismuth(III) nitrate,” J. Saudi Chem. Soc., vol. 20, pp. S202-S210, Sep. 2016.

[54] S. Qasim, S. Ali, and S. Ahmed, “$SnCl_2$. $2H_2O$ catalyzed one-pot synthesis of 2-phenylimidazo [4, 5-f][1, 10] phenanthroline,” Res. J. Pharm. Biol. Chem. Sci., vol. 2, pp. 423-428, 2011.

[55] A. Chawla, A. Sharma, and A. kumar Sharma, “A convenient approach for the synthesis of imidazole derivatives using microwaves,” Synthesis, vol. 5, pp. 7, 2012.

[56] S. Jumat, and S. Nadia, “New Schiff bases derivatives containing anthracene and 1, 3, 4-thidiazole moieties: synthesis and fungicidal activity,” Int. J. PharmTech Res., vol. 2, pp. 205-208, 2010.

[57] D. Zampieri, M. G. Mamolo, L. Vio, E. Banfi, G. Scialino, M. Fermeglia, M. Ferrone, and S. Pricl, “Synthesis, antifungal and antimycobacterial activities of new bis-imidazole derivatives, and prediction of their binding to P45014DM by molecular docking and MM/PBSA method,” Bioorg. Med. Chem., vol. 15, pp. 7444-7458, Dec. 2007.

ISSN:0971-1260
Vol-22-Issue-37-December -2019

[58] A. M. Vijesh, A. M. Isloor, S. Telkar, T. Arulmoli, and H.-K. Fun, “Molecular docking studies of some new imidazole derivatives for antimicrobial properties,” Arabian J. Chem., vol. 6, pp. 197-204, Apr. 2013.

[59] H. M. Patel, M. N. Noolvi, N. S. Sethi, A. K. Gadad, and S. S. Cameotra, “Synthesis and antitubercular evaluation of imidazo[2,1-b][1,3,4]thiadiazole derivatives,” Arabian J. Chem., vol. 10, pp. S996-S1002, Feb. 2017.

[60] D. Sharma, B. Narasimhan, P. Kumar, V. Judge, R. Narang, E. De Clercq, and J. Balzarini, “Synthesis, antimicrobial and antiviral evaluation of substituted imidazole derivatives,” Eur. J. Med. Chem., vol. 44, pp. 2347-2353, Jun. 2009.

[61] A. K. Jain, V. Ravichandran, M. Sisodiya, and R. K. Agrawal, “Synthesis and antibacterial evaluation of 2–substituted–4,5–diphenyl–N–alkyl imidazole derivatives,” Asian Pac. J. Trop. Med., vol. 3, pp. 471-474, Jun. 2010.

[62] A. Karakurt, S. Dalkara, M. Ozalp, S. Ozbey, E. Kendi, and J. P. Stables, “Synthesis of some 1-(2-naphthyl)-2-(imidazole-1-yl)ethanone oxime and oxime ether derivatives and their anticonvulsant and antimicrobial activities,” Eur. J. Med. Chem., vol. 36, pp. 421-33, May. 2001.

[63] M. Saudi, J. Zmurko, S. Kaptein, J. Rozenski, J. Neyts, and A. Van Aerschot, “Synthesis and evaluation of imidazole-4,5- and pyrazine-2,3-dicarboxamides targeting dengue and yellow fever virus,” Eur. J. Med. Chem.,vol. 87, pp. 529-539, Nov. 2014.

[64] A. Ravindernath, and M. S. Reddy, “Synthesis and evaluation of anti-inflammatory, antioxidant and antimicrobial activities of densely functionalized novel benzo [d] imidazolyl tetrahydropyridine carboxylates,” Arabian J. Chem.,vol. 10, pp. S1172-S1179, Feb. 2017.

[65] H. Shameer, N. Rao, V. K. Mmj, and E. Ran, “Synthesis, characterization and anti-inflammatory activity of novel *N*-substituted-5-oxa-imidazole.”Indian J. Res. Pharm. Biotechnol.,vol. 1, pp. 50-53, 2013.

[66] C. Karthikeyan, V. R. Solomon, H. Lee, and P. Trivedi, “Synthesis and biological evaluation of 2-(phenyl)-3H-benzo[d]imidazole-5-carboxylic acids and its methyl

ISSN:0971-1260
Vol-22-Issue-37-December -2019

esters as potent anti-breast cancer agents," Arabian J. Chem., vol. 10, pp. S1788-S1794, May 2017.

[67] K. Wittine, K. Poljak, M. Kovac, D. Makuc, J. Plavec, J. Balzarini, T. Martinovic, S. K. Pavelic, K. Pavelic, and M. Mintas, "The novel [4,5-e][1,3]diazepine-4,8-dione and acyclic carbamoyl imino-ureido derivatives of imidazole: synthesis, anti-viral and anti-tumor Activity evaluations," Molecules, vol. 18, pp. 13385-13397, Oct. 2013.

[68] M. Prabhu, and R. Radha, "Synthesis, characterization and evaluation of anti-bacterial and antihelmintic activity of some novel aryl imidazole derivatives," Asian J. Pharm. Clin. Res., vol. 5, pp. 154-159, 2012.