



## SYNTHESIS AND BIOLOGICAL ACTIVITY OF IMIDAZOLE DERIVATIVES

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**Abstract:** Heterocyclic compounds have various medicinal and pharmaceutical applications. These compounds comprise the major and the most varied family of organic compounds. Imidazole is one of the most important heterocyclic compounds, which possess a wide range of applications in medicine as well as pharmacies. This review includes the various methods for the synthesis of imidazole derivatives and its biological activities.

**Keywords:** Heterocyclic compounds; Imidazole derivatives; Biological activity.

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### 1. Introduction:

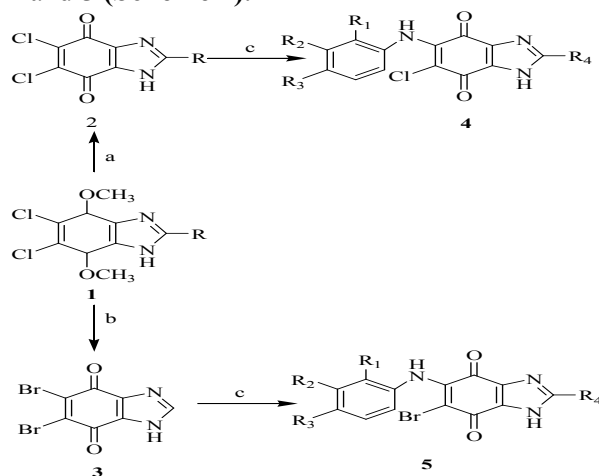
Heterocyclic compounds are the organic compounds containing one or more heteroatoms in their structure. These heterocyclic compounds plays a key role in the biological system because most of the biological molecules like DNA , RNA ,Vit.B<sub>12</sub>, hemoglobin, myoglobin contain heterocyclic compounds in their skeleton. Imidazole constitutes major class of heterocyclic compounds, which are useful in the medicinal field. Imidazole is a five membered ring containing two nitrogen atoms at 1 and 3 position. Many natural products like alkaloids contain imidazole ring. This ring system is present in important biological building blocks, such as histidine and the related hormone histamine. Many drugs like antifungal, nitroimidazole series of antibiotics, and the sedative midazolam contain imidazole ring. The literature survey shows that a lot of work on the imidazole

nucleus have done and continues to study their biological applications. Imidazole derivatives possesses various pharmacological activities such as anti viral, anti inflammatory, analgesic, antidepressant, anti fungal and anti-bacterial, anti cancer, anti-tubercular and anti-leishmanial activity.<sup>1-XXVI</sup> Herein, in continuation of our studies towards imidazole, and since there is a wide range of synthesis methods that include the synthesis of imidazole compounds. This review presents the recent methodologies for synthesis of imidazole derivatives and their biological activities.

## 2. Development in the synthesis of Imidazole derivatives

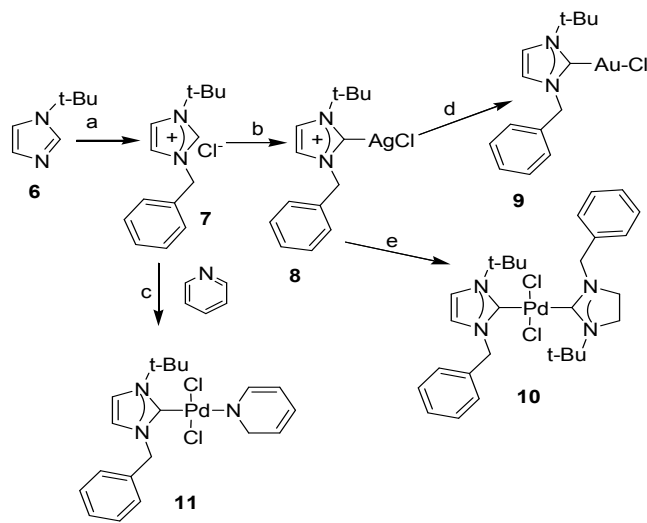
Imidazoles are the invincible class of drug due its wide-ranging medicinal as well as pharmaceutical activities. To raise the activity of Imidazole derivatives the various fictionalization development at various position is still going on. Generally, these procedures involve harsh condition, various name reaction, multicomponent reaction, multi-step strategy, and use of Lewis base and Lewis acid, metal free condition, costly transition metal catalyst or in solvent and solvent-free condition. In this review, we mainly focus on the different route of synthesis part of imidazoles and functionalisation at its various positions.

In 2006, Kwang-Hoe Chung et. al. described the synthesis of 5-Arylamino-1H-benzo[d]imidazole-4,7-diones. A functionalized imidazole derivative **4** and **5** were synthesized on oxidation of the compound **1** and on refluxing with HBr and NaBrO<sub>3</sub> gives **2** and **3** derivatives. These **2** and **3** derivatives on refluxing with aryl amine in ethanol gives the imidazole derivatives **4** and **5** (Scheme 1).<sup>XXVII</sup>



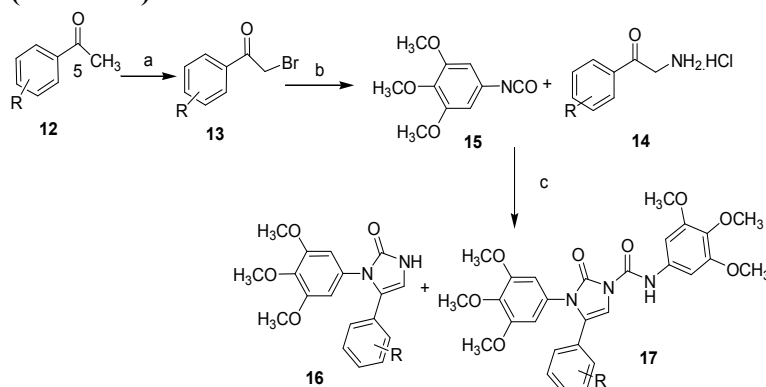
**Scheme 1: Reagents and conditions:** (a) HCl/HNO<sub>3</sub>/reflux/0.5h; (b) HBr/reflux/ 6 h and then; HBr/NaBrO<sub>3</sub>/reflux/1 h; (c) arylamine (1 equiv)/EtOH/ reflux, 5hrs.

Sriparna Ray and coworkers in 2007, synthesized Palladium, Gold, and Silver N-Heterocyclic Carbene Complexes. Trans-[1-benzyl-3-tertbutylimidazol-2-ylidene]Pd(pyridine)Cl<sub>2</sub> **10** was synthesized from the reaction of 1-benzyl-3-tert-butylimidazolium chloride **6** with PdCl<sub>2</sub> in the presence of K<sub>2</sub>CO<sub>3</sub> as a base. The other palladium complex, [1-benzyl-3-tert-butylimidazol-2-ylidene]<sub>2</sub>PdCl<sub>2</sub> **9**, and a gold complex, [1-benzyl-3-tert-butylimidazol-2-ylidene]AuCl **8**, were synthesized by following a transmetalation route from the silver complex, [1-benzyl-3-tertbutylimidazol-2-ylidene]AgCl **7**, by treatment with (COD)PdCl<sub>2</sub> and (SMe<sub>2</sub>)AuCl, respectively(Scheme 2).<sup>XXVIII</sup>



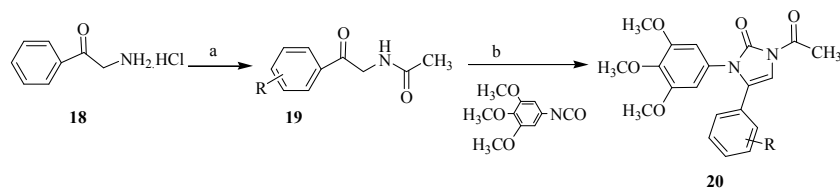
**Scheme 2: Reagent and Conditions:** a) PhCH<sub>2</sub>Cl, b) Ag<sub>2</sub>Cl, c) PdCl<sub>2</sub>, K<sub>2</sub>CO<sub>3</sub>, d) (SMe<sub>2</sub>)AuCl, e) COD, PdCl<sub>2</sub>.

Na Xue and co workers, in 2008 synthesized, a new series of aryl substituted imidazol-2-one derivatives structurally related to combretastatin A-4 (CA-4). Bromination of substituted acetophenones **12** gave substituted 2-bromo-1-phenylethanones **13**, which were treated with hexamethylenetetramine and then hydrolyzed with concd HCl in EtOH to give the corresponding 2-amino-1-phenylethanone hydrochlorides **14** (Scheme 2). Cyclization of 2-amino-1-(4-hydroxyphenyl)ethanone hydrochloride **15** with 3,4,5-trimethoxyphenyl isocyanate in refluxing toluene provided an approximately 1:3 mixture of 1,3-dihydro-3-(3,4,5-trimethoxyphenyl)-4-(4-hydroxyphenyl)-2H-imidazol-2-one **16** and 2,3-dihydro-N,3-bis(3,4,5-trimethoxyphenyl)-4-(4-hydroxyphenyl)-2-oxo-1H-imidazole-1-carboxamide **17** (Scheme 3).<sup>XXIX</sup>



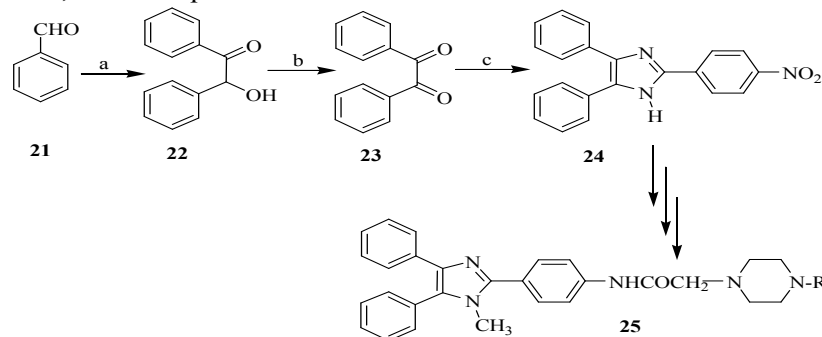
**Scheme 3: Reagents and conditions:** (a) pyridinium hydrobromide perbromide, THF, rt, 3 h; (b) i) hexamethylenetetramine, CHCl<sub>3</sub>, rt, 1 h; ii) C<sub>2</sub>H<sub>5</sub>OH, HCl aq, rt, 1 h; (c) toluene, reflux, 4 h; (d) AcOH, Zn, rt, 2 h; (e) 10% Pd/C, H<sub>2</sub>, rt, 2 h.

Similarly, Na Xue and co workers synthesized the imidazole derivatives **20**, on acetylation of substituted 2-amino-1-phenylethanone hydrochlorides **18** with acetic anhydride resulted in the corresponding N-(2-oxo-2-phenylethyl)acetamides **19** which were then reacted with 3,4,5-trimethoxyphenyl isocyanate to yield desired 1-acetyl-1,3-dihydro-3,4-diaryl-2H-imidazol-2-ones **20** (Scheme 4).<sup>XXIX</sup>



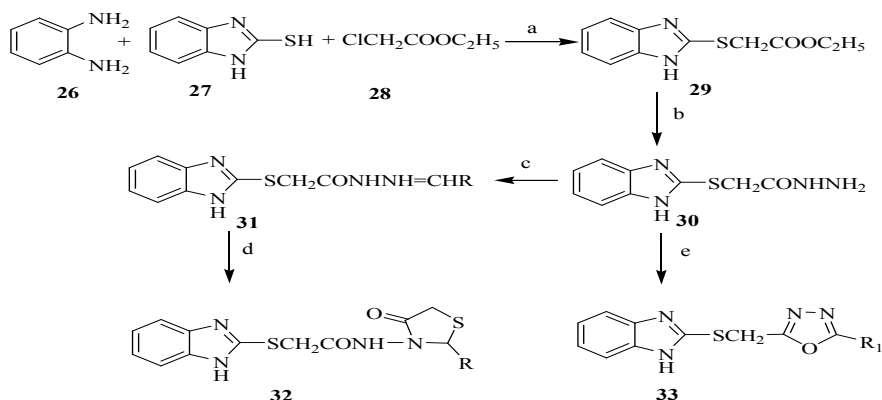
**Scheme 4: Reagents and conditions:** (a)  $(\text{Ac})_2\text{O}$ ,  $\text{H}_2\text{O}$ ,  $\text{NaOAc}/\text{H}_2\text{O}$ ,  $0^\circ\text{C}$  to rt; (b) toluene, reflux, 4 h; (c)  $\text{AcOH}$ ,  $\text{Zn}$ , rt, 2 h.

In 2010, Yusuf Özkay et. al. describe the synthesis of novel imidazole-(benz)azole and imidazole epiperazine derivatives. For the synthesis of the target compounds there, action sequence outlined in the **Scheme 5**.<sup>XXX</sup>



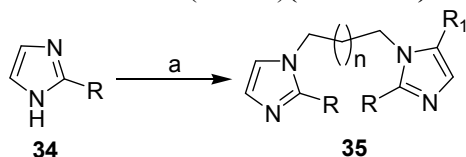
**Scheme 5: Reagents and conditions:** a)  $\text{NaCN}$ ,  $\text{H}_2\text{O}/\text{EtOH}$ , reflux 1h, b)  $(\text{CH}_3\text{COO})_2\text{Cu}$ ,  $\text{NH}_4\text{NO}_3$ ,  $\text{AcOH}$ , reflux 2h, c) 4-Nitrobenzaldehyde,  $\text{CH}_3\text{COONH}_4$ ,  $\text{AcOH}$ , reflux 3h, d) 1)  $\text{NaH}/\text{THF}$ , R.T. 15min. 2)  $\text{CH}_3\text{I}$  reflux 3h, e)  $\text{Zn}$ ,  $\text{EtOH}/\text{HCl}$ , rt, reflux 1h, f)  $\text{TEA}$ ,  $\text{ClCH}_2\text{COCl}$ , benzene, ice bath, rt, 1h, g) Appropriate thiol-(benz)azole,  $\text{K}_2\text{CO}_3$ , acetone, reflux 12h, h) Corresponding 1-substituted piperazine,  $\text{K}_2\text{CO}_3$ , acetone, reflux 24h.

Ramya V. Shingalapur and et.al.in 2010 described the synthesis of benzimidazole derivatives. The synthetic routes to compounds **32** and **33** from **26**, **27** and **28** are illustrated in (**Scheme 6**).<sup>XXXI</sup>



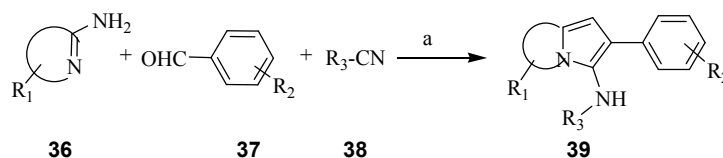
**Scheme 6: Reagent and Conditions:** a)  $\text{CS}_2$ ,  $\text{NaOH}$ ,  $\text{EtOH}$ ; b)  $\text{EtOH}$ ; c)  $\text{EtOH}$ ,  $\text{NH}_2\text{NH}_2$ ,  $\text{H}_2\text{O}$ ; d)  $\text{R-CHO}$ ; e)  $\text{SHCH}_2\text{COOH}$ ,  $\text{DMF}$ ,  $\text{ZnCl}_2$ ; f)  $\text{R}_1\text{-COOH}$ ,  $\text{POCl}_3$ .

A series of imidazole-based compounds were synthesized by Jyoti Pandey and et. al. in 2010, by reacting simple imidazoles with alkyl halides or alkyl halocarboxylate in presence of tetrabutylammonium bromide (TBAB)(**Scheme 7**).<sup>XXXII</sup>



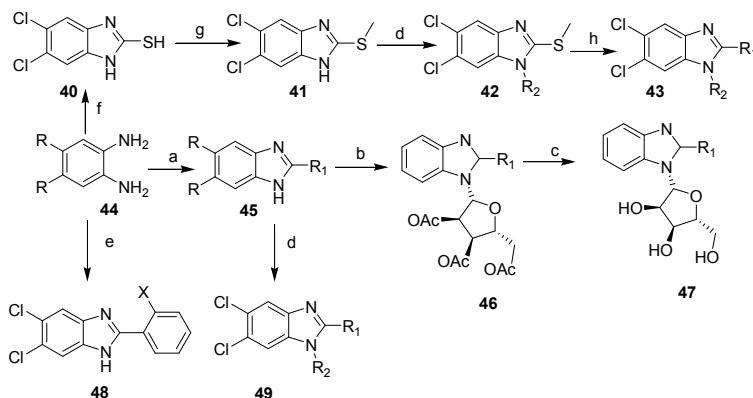
**Scheme 7: Reagent and Conditions:** a) 1,3-dibromopropane/ 1,5-dibromopentane, NaH/THF, TBAB, 0-30°C, 4hr.

Ashish T. Baviskar and et. al. in 2011, synthesis of bicyclic N-fused aminoimidazoles **39** were predicted. The target bicyclic imidazole derivatives **39** were prepared by compound **36** with substituted aldehydes **37** and alkyl cyanide **38** using ZnCl<sub>4</sub> in PEG-400 at different temperature (**Scheme 8**).<sup>XXXIII</sup>



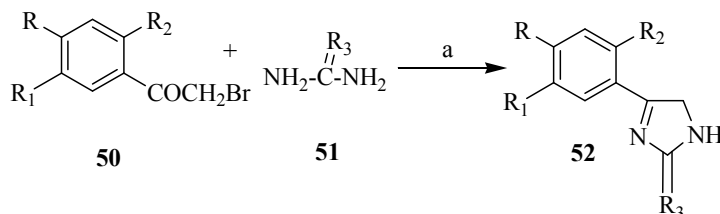
**Scheme 8: Reagent and Conditions:** a) ZnCl<sub>4</sub>, PEG-400, Method A -50°C, Method B-140°C.

In 2012, Hamad M. Alkahtani and co-workers developed the synthesis of benzo[d]imidazole derivatives. Benzo[d]imidazole derivatives **43**, **47**, **48** and **49** were synthesized using the series of reaction steps from substituted aromatic 1,2-diamines (**Scheme 9**).<sup>XXXIV</sup>



**Scheme 9: Reagents and conditions:** a) R<sub>1</sub>COOH, reflux ; 4 h, or R<sub>1</sub>COOH, Discovery Microwave, 145°C, 20 min, (b) (i) BSA, MeCN, reflux, 1 h, (ii) (2S,3R,4R,5R)-5-(acetoxymethyl)tetrahydrofuran-2,3,4-triyl triacetate in MeCN, TMSOTf, reflux, 24 h, (c) NH<sub>3</sub> in MeOH, rt, 24 h; (d) R<sub>2</sub>X, NaOH, MeCN, 24 h, (e) ArCHO, Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub>, EtOH, reflux, (f) CS<sub>2</sub>, KOH, EtOH, reflux, (g) MeI, K<sub>2</sub>CO<sub>3</sub>, reflux, 4 h, (h) DCM, m-CPBA, 40°C. rt.

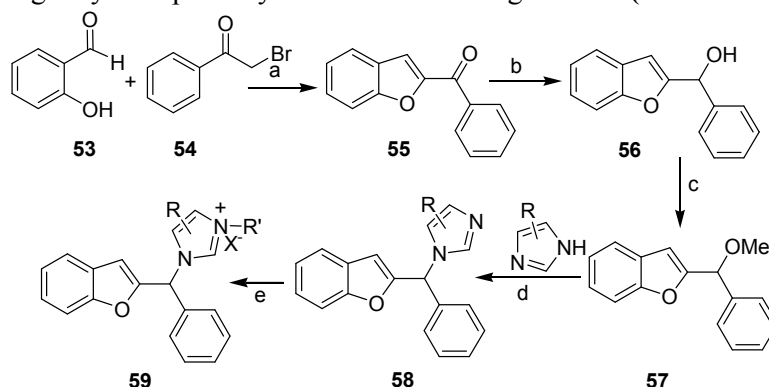
S. G. Dandale and coworkers' in 2012, described the synthesis of 4-(substituted Phenyl)-1H-Imidazol-2(5H)-One/ Thione /Imines **52**. Target compound **52** was synthesized when 2-Bromo-1-(substituted phenyl) ethanone **50** dissolved in ethanol and substituted amide/imidine **51** in water using TEBA as catalyst were irradiated under microwave for 3.5 min at 700W (**Scheme 10**).<sup>XXXV</sup>



**Scheme 10: Reagent and Conditions:** a) TEBA, Ethanol, 3-5 min.

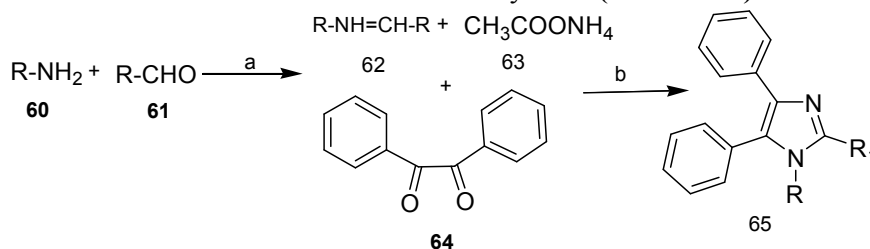
Xue-Quan Wang and co-workers' in 2013, a series of novel hybrid compounds between 2-benzylbenzofuran and imidazole has been prepared. 2-benzylbenzofuran-

imidazole hybrid **59** was readily achieved by reacting salicylaldehydes **53** with phenacyl bromide **54** to produce (benzofuran-2-yl)(phenyl)methanone **55** in base-mediated reaction. Then, **55** were reduced with NaBH<sub>4</sub> to the respective (benzofuran-2-yl)(phenyl)methanol compound **56**. Subsequently, **56** was transformed via themselves to the respective 2-benzylbenzofurane imidazole hybrids **57** with various substituted imidazole by refluxing under acetonitrile. Finally, novel 2-benzylbenzofuran-based imidazolium salts **59** were prepared with excellent yields by reaction of 2-benzylbenzofuraneimidazole hybrids **58** with the corresponding alkyl and phenacyl halides in refluxing acetone (**Scheme 11**).<sup>XXXVI</sup>



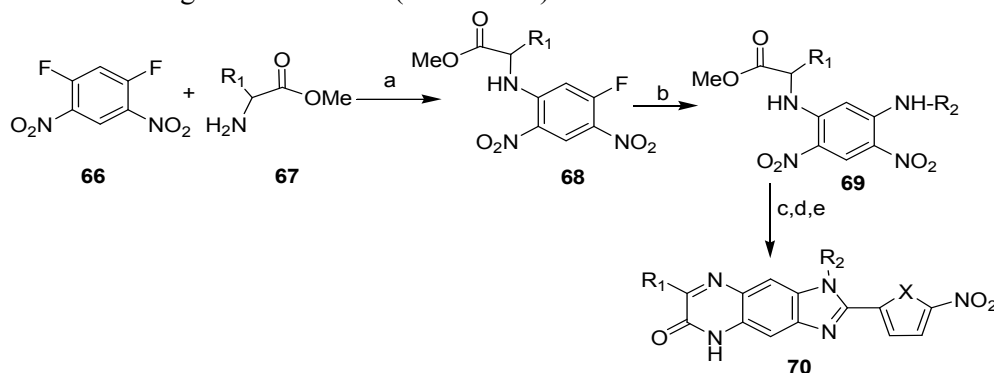
**Scheme 11: Reagent and Conditions:** a) Acetone, K<sub>2</sub>CO<sub>3</sub>, rt, 12hr, b) NaBH<sub>4</sub>, DCM/MeOH, rt, 2hr, c) MsCl, Et<sub>3</sub>N, reflux, DCM; d) MeCN, reflux, 24-48hrs; e) R'-X, Method A: Acetone, reflux, 8-2hr, Method B:DMF, rt, 12hr.

Gyanendra kumar Sharma and co-workers' in 2013 synthesized aryl imidazole derivatives **65** by reacting 1,3-dicarbonyl compound **64**, ammonium acetate **63** and Schiff bases **62** which is obtained from amine **60** and aldehyde **61** (**Scheme 12**).<sup>XXXVII</sup>



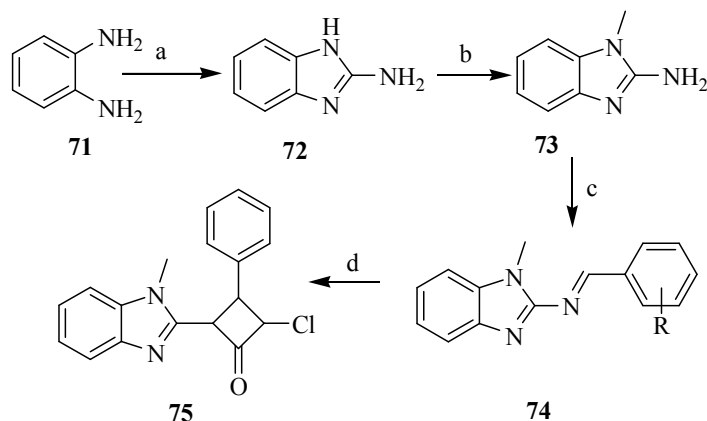
**Scheme 12: Reagent and Conditions:** a) AcOH, reflux, 7hrs, MW, activated silica gel, 1000W, 8min; b) reflux, 12-15hrs, MW, 1000W, 13-16min.

Yaling Gong and coworkers synthesized Benzimidazole-based compounds **70** in 2014. Target compound **70** was prepared from **69** by a series of reactions. **69** was obtained by treating **68** with substituted amines in the presence of DIPEA in THF and **68** was obtained from **66** and **67** using DIPEA in THF (**Scheme 13**).<sup>XXXVIII</sup>



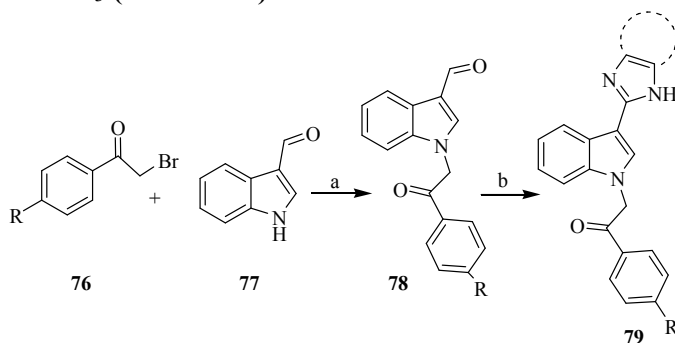
**Scheme 13: Reagents and Conditions:** a) DIPEA, THF, rt; b) R<sub>2</sub>NH<sub>2</sub>, DIPEA, THF, rt; c) Pd/C, HCOONH<sub>4</sub>, THF, EtOH, rt; d) 5-nitrofuraldehyde or 5-nitrothiophenolaldehyde, dioxane, THF, EtOH, 5% AcOH, rt; e) 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), reflux.

In 2014, Malleshappa Noolvi and coworkers synthesized, a series of 1-methyl-N-[(substituted-phenylmethylidene)-1H-benzimidazol-2-amines **74** were prepared via the formation of 1-methyl-1H-benzimidazol-2-amine **73**, which was prepared by the cycloaddition of o-phenylenediamine **71** with cyanogen bromide in the presence of aqueous base followed by N-methylation with methyl iodide in the presence of anhydrous potassium carbonate in dry acetonitrile. Moreover, the four-membered b-lactam ring was introduced by the cycloaddition of **74** and chloroacetyl chloride in the presence of triethylamine catalyst to give 3-chloro-1-(1-methyl-1H-benzimidazol-2-yl)-phenylazetid-2-one **75** (Scheme 14).<sup>XXXIX</sup>



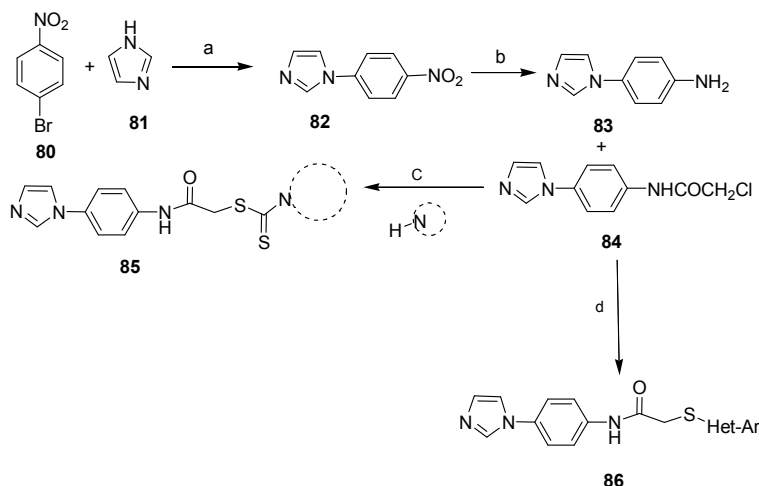
**Scheme 14: Reagent and conditions:** a) CNBr, THF, aq. NaOH; b) CH<sub>3</sub>I, K<sub>2</sub>CO<sub>3</sub>, acetonitrile; (c) C<sub>2</sub>H<sub>5</sub>OH, substituted aldehydes, CH<sub>3</sub>COOH; (d) ClCH<sub>2</sub>COCl, N(C<sub>2</sub>H<sub>5</sub>)<sub>3</sub>, dioxane.

Novel N-acyl substituted indole-linked benzimidazoles **79** were synthesized by Rajan Abraham and coworkers in 2017. To get the intermediate **78**, the mixture of substituted phenacyl bromide **76** and indole-3-carbaldehyde **77** was stirred in the presence of K<sub>2</sub>CO<sub>3</sub> in THF. A mixture of 1-(2-oxo-2-(p-tolyl)ethyl)-1H-indole-3-carbaldehyde **78** and o-phenylenediamine or naphthalene-2,3-diamine was refluxed in DMF in the presence of NaHSO<sub>3</sub> (Scheme 15).<sup>XLI</sup>



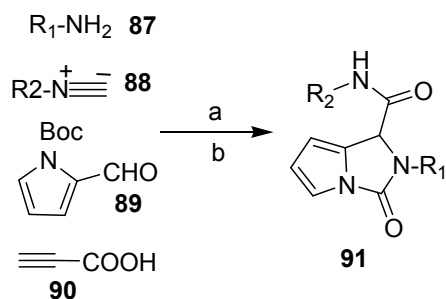
**Scheme 15: Reagents and conditions:** a) THF, K<sub>2</sub>CO<sub>3</sub>, RT, 12h; b) DMF, NaHSO<sub>3</sub>, o-phenylenediamine (or) naphthalene-2,3-diamine, 12h, reflux.

Aysen Isik and coworkers' in 2018 developed, two novel series of imidazole derivatives containing dithiocarbamate **85** and (benz)azolethiol **86** using a series of steps (Scheme 16).<sup>XLI</sup>



**Scheme 16: Reagent and conditions:** a)  $K_2CO_3$ /DMF, MW; b)  $SnCl_2 \cdot H_2O$ , EtOH; c)  $ClCOCH_2Cl$ , TEA/THF.c)  $CS_2$ , NaOH ;d) SH-Het-Ar.

In 2019, Ming Zhang et.al. synthesized the pyrrole-imidazole derivatives **91** from Amine **87**, Alkylcyanide **88**, Boc-protected pyrrole aldehyde **89** and propylcyanoic acid **90**(Scheme 17).<sup>XLII</sup>

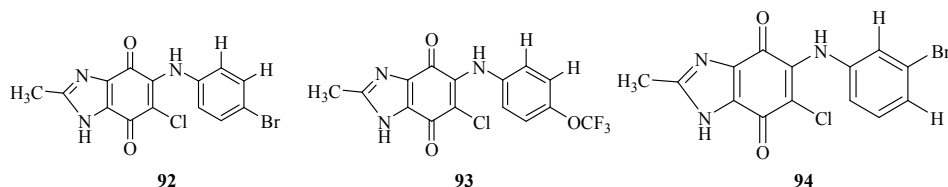


**Scheme 17: Reagent and Conditions:** a) MeOH, rt; b)  $K_2CO_3$ , MeCN.

### 3. Biological activities of imidazole derivatives

#### 3.1 As an anticancer agent:

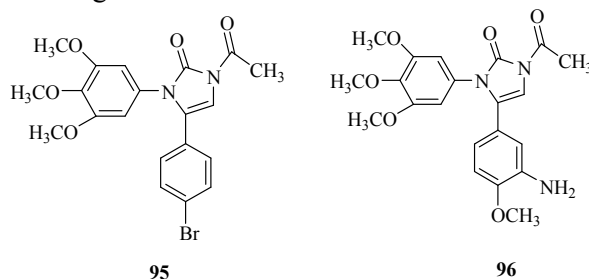
Imidazole plays a very important role as an anticancer agent. A series of 5-Arylamino-1H-benzo[d]imidazole-4,7-dione was synthesised and tested for their inhibitory activities on the proliferation of human umbilical vein endothelial cell and the smooth muscle cells. Among them several compounds exhibited the selective anti-proliferative activity on the of human umbilical vein endothelial cell .The compound **92**, **93**, **94** are found to be selective inhibitor of HUVECs and thus may be the promising lead in the inhibition of HUVECs proliferation.<sup>XXVII</sup>



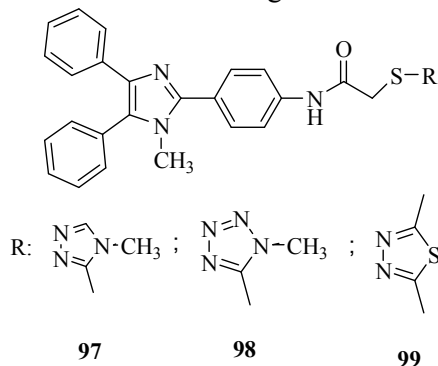
A series of aryl substituted imidazol-2-one derivatives was synthesised and evaluated for their cytotoxic activities in vitro against various human cancer cell lines including MCF-7, human myeloid leukemia cell HL-60, K562, K562R, lung cancer cells A549 taking Docataxel as a positive control. It was found that compounds **95** and **96** showed similar or



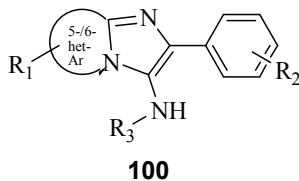
greater potent cytotoxic activity than that of docetaxel. Compound **95** exhibited excellent inhibitory activity on tumour growth in vivo.<sup>XXIX</sup>



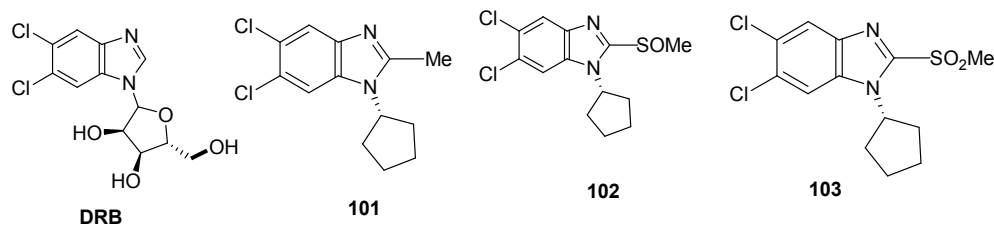
A series of novel imidazole-(benz)azole and imidazole piperazine derivatives was synthesised to investigate their probable anticancer activity. Most of the derivatives are active against HT-29 cells than MCF-7 cells. Anticancer activity screening revealed that the compounds **97**, **98** and **99** were most active in the series and exhibited significant cytotoxicity against carcinogenic cell lines and caused DNA fragmentation of the HT-29 cells.<sup>XXX</sup>



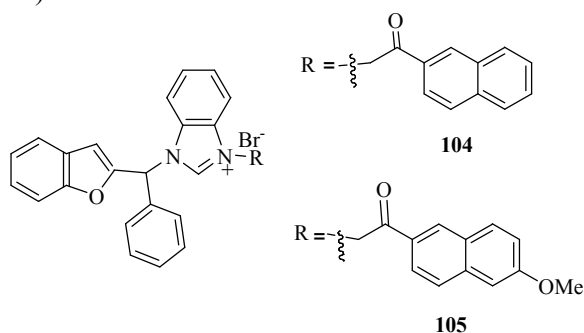
Near about 31 compounds of bicyclic N- fused amino-imidazoles were synthesised and out of these, eight different bicyclic scaffolds, imidazopyridine, imidazopyrazole, and imidazopyrazine with suitable substituent showed potent inhibition of catalytic activity of hTopoII $\alpha$ . N-Fused amino-imidazoles **100** showed potent anticancer activities in kidney and breast cancer cell lines with low toxicity to normal cells, relatively higher potency compared to etoposide and 5-fluorouracil in kidney cancer cell lines, and potent inhibition in cell migration. These compounds were found to exert apoptotic effect in G1/S phase. N-Fused imidazoles as novel anticancer agents inhibit catalytic activity of Topoisomerase II $\alpha$  and induce Apoptosis in G1/S Phase.<sup>XXXIII</sup>



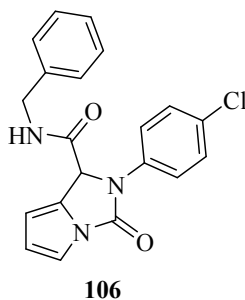
5,6 dichloro-1- $\beta$ -D ribofuranosylbenzimidazole (DRB), is an analogue of adenosine which inhibits RNAPII transcription in vivo and vitro. A series of analogues of DRB and benzo[d]imidazole was reported and found that the compounds **101**, **102**, **103** possessed potent antiproliferative activity in cancer cell lines.<sup>XXXIV</sup>



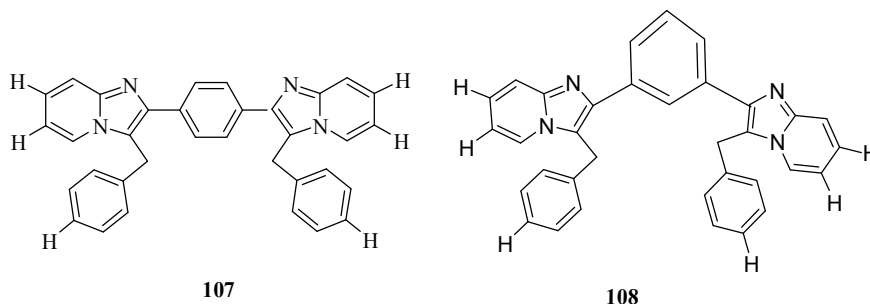
A series of compounds between 2-benzylbenzofuran and imidazole were synthesised and evaluated against a panel of human tumor cell lines. The result showed that the presence of benzimidazole ring plays a vital role for the cytotoxic activity. The hybrid compounds **104** and **105** bearing 4-methoxyphenacyl or naphthylacyl at position-3 of benzimidazole were found potent against human tumor cell lines and more potent than cisplatin. These compounds shows the cytotoxic activity against breast carcinoma (MCF-7) and Myeloid liver carcinoma (SMMC-7721).<sup>XXXVI</sup>



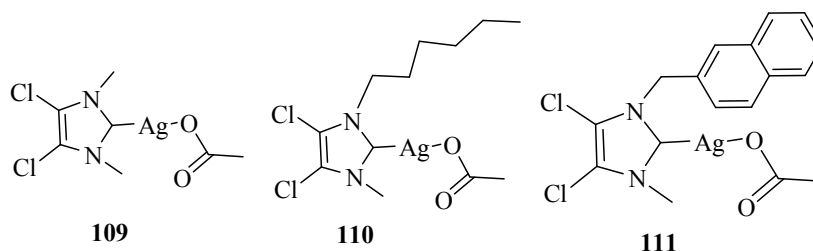
One pot synthesis of substituted pyrrole–imidazole was reported via a post –Ugi cascade reaction. Compound **106** exhibited a high potency of anticancer activity in human pancreatic cancer cell lines PANC and ASPC-1.<sup>XLII</sup>



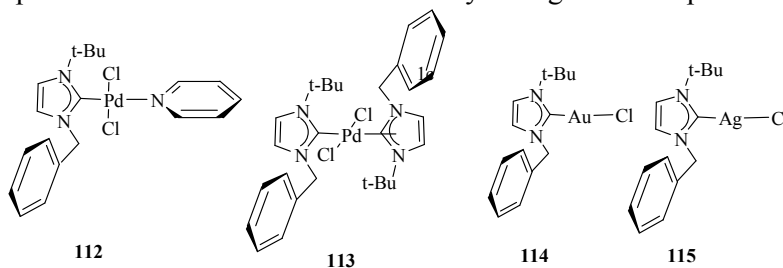
A novel series of bis-imidazoles and bis-imidazo[1,2-*a*]pyridines from Schiff base dimmers was synthesised and screened for their anticancer activities against three cancer cell lines, including cervical (He-La), breast (MDA-MB-231), and renal cancer (ACHN). Compounds **107** and **108** exhibit the best inhibitory activities against all three cell lines. Both these compounds were very effective against the breast cancer cell exceeding the activity of adriamycin. Vivo anticancer activity of these compounds was compared with the standard tamoxifen drug.<sup>XLIII</sup>



Metal complexes of imidazole also act as an effective anticancer agent. A class of silver (I) complexes, (109, 110, 111) derived from 4,5-dichloro-1H-imidazole has been evaluated for their anticancer activity against the human cancer cell lines OVCAR-3 (ovarian), MB157 (breast), and Hela (cervical) and found to be active against the ovarian and breast cancer cell lines.<sup>XLIV</sup>

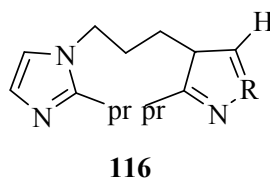


Palladium, silver and gold complexes of 1-benzyl-3-tert-butylimidazole-2-ylidene were reported. Biomedical studies of these complexes revealed that the palladium complexes 112 and 113 displayed potent anticancer activity, the gold 114 and silver 115 complexes exhibited significant antimicrobial properties. Similarly complex 113 showed strong antiproliferative activity against three types of human tumor cells, namely, cervical cancer (HeLa), breast cancer (MCF-7), and colon adenocarcinoma (HCT 116). The antiproliferative activity of complex 113 was found to be considerably stronger than cisplatin.<sup>XXVIII</sup>



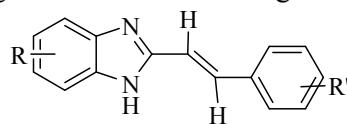
### 3.2 Imidazole as an anti-tubercular agent:

A series of new imidazoles have been synthesized and screened against Mycobacterium tuberculosis. Imidazole derivative 116 exhibits good in vitro antitubercular activity and may serve as a lead for further optimization.<sup>XXXII</sup>



A new series of twelve novel 5-(nitro/bromo)-styryl-2-benzimidazoles were synthesised and screened for anti-tubercular activity against M. tuberculosis H<sub>37</sub> Rv, anti-bacterial

activity and anti-fungal activity. Compounds **117**, **118**, **119**, **120**, **121** showed higher anti-tubercular activity and emerged as lead molecules against a panel of microorganisms.<sup>XXXI</sup>



**117** R=-NO<sub>2</sub> and R'- 2,4-Cl

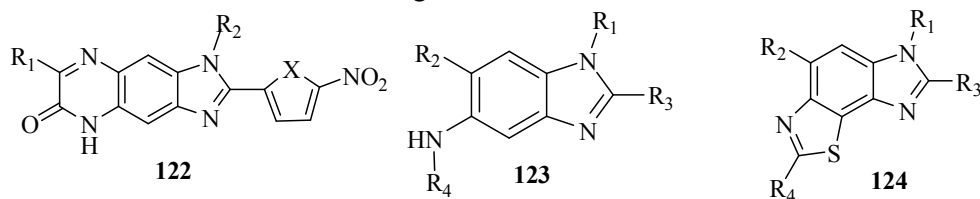
**118** R=-Br and R'-H

**119** R=-Br and R'- 3,4-OCH<sub>3</sub>

**120** R=-Br and R'- 4-CH<sub>3</sub>

**121** R=-Br and R'- 2,4-Cl

A new series of derivatives of three benzimidazole scaffolds viz ,1*H*-imidazo[4,5-*g*]quinoxalin-6(5*H*)-ones (**122**) , 1,2,5,6-tetrasubstituted benzimidazoles (**123**) and 6*H*-imidazo[4',5':3,4]benzo[1,2-*d*]thiazolo (**124**) were synthesised and their activity against mycobacterium tuberculosis in replicating and physiologically induced non replicating state was studied . Compounds **125 to 130** of scaffold 2, which shared a 5-nitrofuranyl moiety, exhibited high potency and acceptable selectivity indices (SI). Compound **126** having 5-nitrofuranyl group was compatible with minimal cytotoxicity and good intra-macrophage killing, although it lacked non-replicating activity, when assessed by CFU assays and also had low mutagenic potential by SOS Chromotest assay, making this class of compounds good candidates for further evaluation and target identification.<sup>XXXVlll</sup>

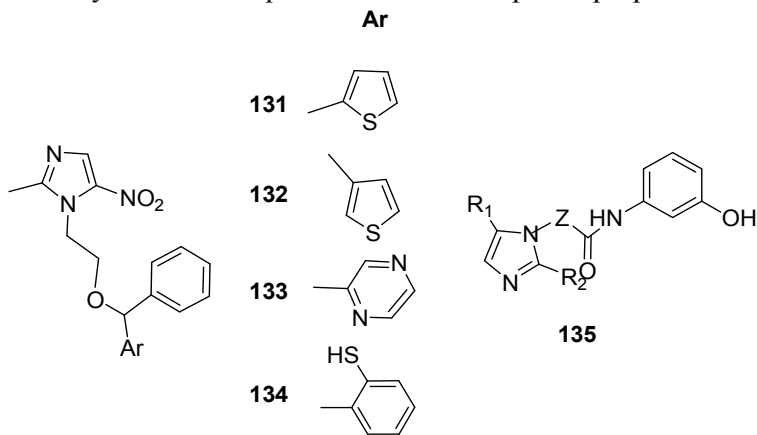


| Compounds  | R <sub>1</sub>   | R <sub>2</sub> | R <sub>3</sub>   |
|------------|------------------|----------------|------------------|
| <b>125</b> |                  |                | -CH <sub>3</sub> |
| <b>126</b> |                  |                | -CH <sub>3</sub> |
| <b>127</b> |                  |                | -CH <sub>3</sub> |
| <b>128</b> |                  |                | -CH <sub>3</sub> |
| <b>129</b> |                  |                | -CH <sub>3</sub> |
| <b>130</b> | -CH <sub>3</sub> |                | -CH <sub>3</sub> |

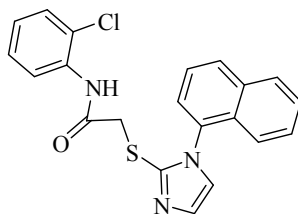
### 3.3 Imidazole as an anti HIV agent:

A series of Imidazolyl derivatives were synthesized and evaluated for their anti-HIV and antibacterial activities. The synthesized imidazole derivatives **131**, **132**, **133** and **134** revealed moderate anti-bacterial and weak anti-HIV activity. N-(3-hydroxyphenyl)-2-(substituted imidazol-1-yl) alkanamides **135** also exhibited significant antibacterial activities. It is

concluded that, these series of imidazoles and nitro-imidazoles might be useful as starting moieties that can be further exploited synthetically for the discovery of analogues with more potent anti-HIV activity with broad-spectrum chemotherapeutic properties.<sup>XLV</sup>



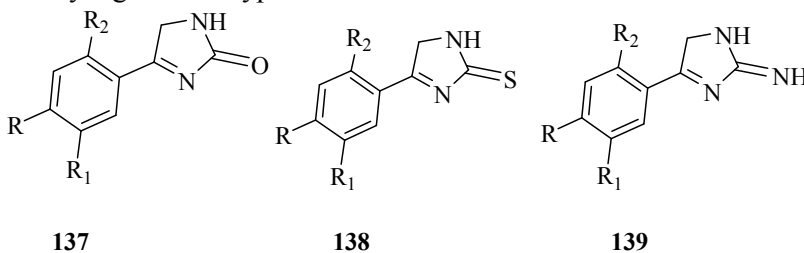
A series of Imidazole thioacetanilide (ITA) derivatives were synthesized and evaluated as potent inhibitors of HIV-1. Among these ITA, the most potent HIV-1 inhibitors was compound **136** which was more effective than the lead compound **L1** ( $EC_{50} = 2.053 \mu\text{M}$ ) and the reference drugs nevirapine and delavirdine.<sup>XLVI</sup>



**136**

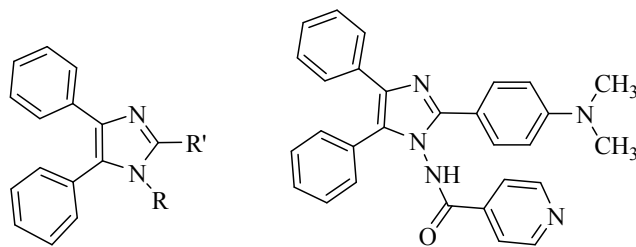
### 3.4 Imidazole as an anti-microbial agent:

4-(substituted phenyl)-1H-imidazol-2(5H)-one **137**/thione **138** / imine **139** was synthesized and evaluated for their anti-microbial activity against *Staphylococcus aureus*, *Escherichia coli*, *Salmonella typhi*, *Proteus vulgaris*. The results showed that *P. vulgaris* was sensitive to all the synthesized compounds, less activity against *S. aureus*, good activity against *E. coli*, and average activity against *S. Typhi*.<sup>XXXV</sup>



A series of novel aryl imidazoles which are incorporated with the chemotherapeutic pharmacophores such as PABA (p-amino-benzoic acid), INH (isoniazid) and p-amino-phenol as possible anti-bacterial and anti-cancer agents, were synthesized by one pot multicomponent reaction and screened for their short term anticancer activity as well as anti-bacterial activity against two gram positive bacterial strains *B. subtilis* (NCIM 2063), *S. aureus* (NCIM 2079) and two gram negative bacterial strains *K. pneumonia* (NCIM 2087), *E. coli* (NCIM 2065). Almost all the newly synthesized substituted imidazoles showed good

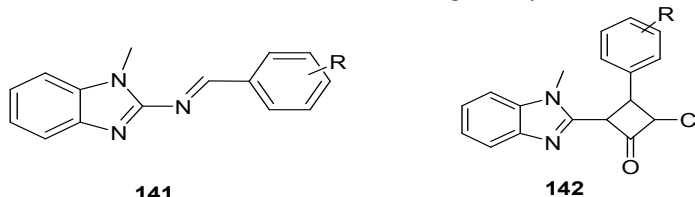
antibacterial activity against gram-negative bacterial strains E.coli and K.pneumonia. and the compound **140** showed most potent anti-cancer activity against DLA and EAC cell line.  
XXXVII



Substituted aryl imidazoles

**140**

A series of 1-methyl-N-(substituted-phenylmethylidene)-1-H-benzimidazol-2-amine **141** (**a-f**) and 3-chloro-1-(1-methyl-1H-benzimidazol-2-yl)-(4'-substituted)-phenylazetid-2-one **142** (**a-f**) were synthesized and screened for antibacterial and cytotoxic activities. Antibacterial activity was studied against S.aureus, B.pumilus, E.coli and P.aeruginosa. It was found that all substituted derivative of compound **141** and **142** exhibited good antibacterial activity while compounds **141 e**, **141f**, **142e** and **142f** exhibit good cytotoxic activity.<sup>XXXIX</sup>



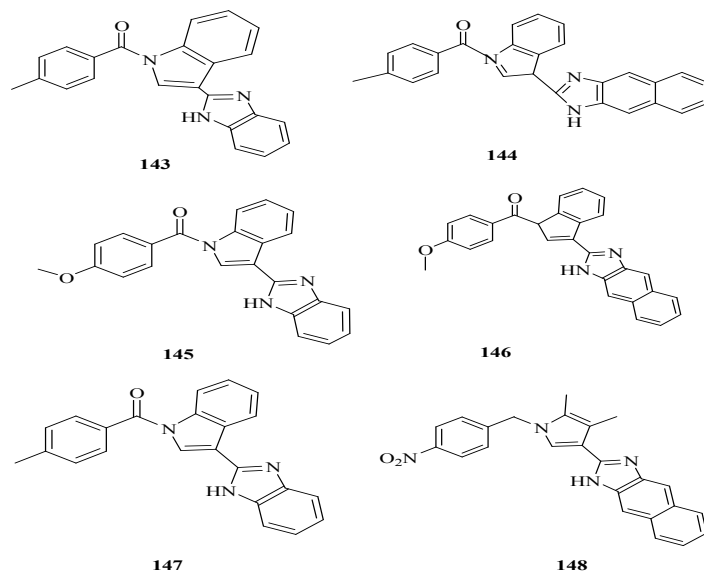
**141**

**142**

**R**

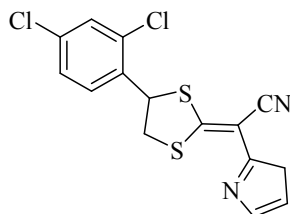
- a = 4 -Chloro
- b = 4-Nitro
- c = 4 -Chloro
- d = 4-Nitro
- e = 2,5 dimethoxy
- f = 2- chloro

A novel N-acyl substituted indole linked benzimidazoles were synthesised and antimicrobial activities were studied for all the compounds **143-148**. The synthesized compounds hinder the biofilm formation and control the growth of the pathogens Staphylococcus epidermis. Anti microbial Activity of the compounds was evaluated against both Gramnegative and Gram positive bacteria such as Staphylococcus aureus (MTCC 2940), Pseudomonas aeruginosa (MTCC424), Escherchia coli (MTCC 443) and Enterococcus fecalis.<sup>XL</sup>



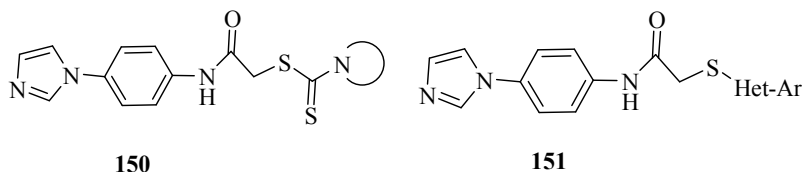
### 3.5 Imidazole as an antifungal activity:

Luliconazole, (R)-(-)-(E)-[4(2,4-dichlorophenyl)-1,3-dithiolan-2-ylidene]-1 imidazolyl-acetonitrile **149** is a novel optically active antifungal imidazole compound. In vitro activity of this luliconazole (NND-502), against dermatophytes and several other groups of medically important fungi was studied. Luliconazole was highly active against all fungal strains and species except zygomycetous fungi, inhibiting the growth of dermatophytes, dematiaceous fungi, hyaline hyphomycetes, and yeast like fungi. Such activity was superior to that of BFZ and TBF, and almost identical in potency to LCZ, which is known as the most potent topically applied antifungal drug currently available. The similarity in both antifungal spectrum and potency between luliconazole and LCZ is probably due to the analogous structures of the two compounds. The results suggested that this compound is a promising candidate for the clinical development of a novel antifungal agent particularly useful in the treatment of dermatomycoses.<sup>XLVII</sup>



149

Two novel series of imidazole derivatives viz, 2-substituted ,N-[4-(1H-imidazole-1-yl ) phenyl]acetamide were synthesized. One series contain dithiocarbamate (57) and the second series contain (benz)azolethiol (58) side chains that are structurally related to the famous antifungalazole pharmacophore. The synthesized compounds were screened in vitro antifungal activity against pathogenic strains fungi like *C. albicans*, *C. krusei*, *C. parapsilosis*, and *C. glabrata*. The result showed that, the first series displayed better antifungal activity than the second series compounds. Compound of first series with 4-methoxybenzyl piperazine scaffolds, showed the most promising antifungal activity with an MIC<sub>50</sub> value of 0.78 µg/mL against *C. krusei*.<sup>XLI</sup>



### Conclusion:

The above -mentioned information about imidazole ring containing compounds has clearly shown that the simple imidazole moiety plays a significant role in medicine as well as in pharmaceuticals. It is observed that, imidazole derivatives possess extensive spectrum of biological activities such as antibacterial, anticancer, anti-tubercular, antifungal, analgesic, and anti-HIV activities. A Series of compounds can be synthesized, characterized, and evaluated for desire pharmacological activity with high potency and low toxicity. By slight modifications in the substituents on the imidazole, improvements in the activity can be achieved. Though a lot of work was done on pharmacological properties of imidazoles, it is still important to carry out research in the development of drugs to show better effect and less toxicity.

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