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Synthesis of Imidazole Derivatives and Their Biological Activities

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Abstract

Imidazoles play an important role in medicinal chemistry, because many of its derivatives have demonstrated significant biological activity. This article is a revision of the last years, of the synthesis methods used in the preparation of imidazole derivatives which have shown biological activity as antibacterial, antiinflammatory, analgesic, antifungal, anticancer, antidepressants, including inside the biological activities of different therapeutic diseases.

Keywords: Imidazole, biological activity, synthesis

1. Introduction

The imidazole (1,3-diaza-2,4-cyclopentadiene) is a planar, five membered heteroaromatic molecule with 3C and 2N atom in 1 and 3 positions. It was first named as gluoxaline (first synthesis with glyoxal and ammonia). Amphoteric nature is susceptible to electrophilic and nucleophilic attack. Highly stable to thermal, acid, base, oxidation and reduction conditions. It has extensive intramolecular hydrogen bonding. It exists in two equivalent tautomeric forms because the hydrogen atom can be located on either of the two nitrogen atoms. The compound is classified as aromatic due to the presence of a sextet of π-electrons, consisting of a pair of electrons from the protonated nitrogen atom and one from each of the remaining four atoms of the ring.

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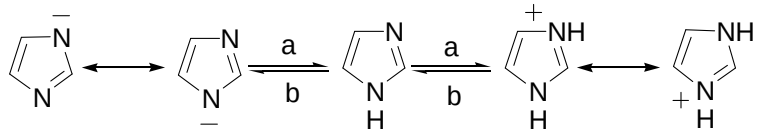
Imidiazole is amphoteric, because it functions as an acid as well as a base. As an acid, the pKa of imidazole is 14.5, making it less acidic than carboxylic acids, phenols and imides, but slightly more acidic than alcohols. The acidic proton is located on N-1. As a base, the pKa of the conjugated acid (cited below as pKBH+ to avoid confusion between the two) is approximately 7, making imidazole approximately sixty times more basic than pyridine. These properties are explained by the resonance interactions, which increase the basicity of the 3-nitrogen atom. Some resonance structures of imidazole are shown in scheme 1.



Scheme 1.Resonance structures of imidazole. Reactions conditions: (a) H^+, (b) $-H^+$.

Imidazole was first reported for Debus et al., in 1858 from diketone an aldehyde and ammonia although various imidazole derivatives had been discovered earlier in the 1840s. Since then, this particular heterocyclic family has hugely expanded and imidazoles are found today in a myriad of applications. They play an important role in areas such as natural products (Brown et al., 1998; Forte et al., 2009), medicinal chemistry (Brown et al., 1998), material sciences for nonlinear optical application (Wang et al., 2002), some imidazole derivatives are used as a catalyst in industrial uses (Louie et al., 2002; Doung et al., 2004) also they have been used as corrosion inhibitors for iron in acidic medium (Abdallah et al., 2012), on certain transition metals, such as copper (Antonijevic et al., 2008) and carbon steel (Bereket et al., 2002). Imidazole can also be found in various compounds which are used for photography(Nakamura et al., 1998; Clark et al., 2005) and these derivatives are used as dopants for doping an organic semiconductor matrix material, organic semiconductor materials and electronic or optoelectronic structural elements(Hartmann et al., 2010).

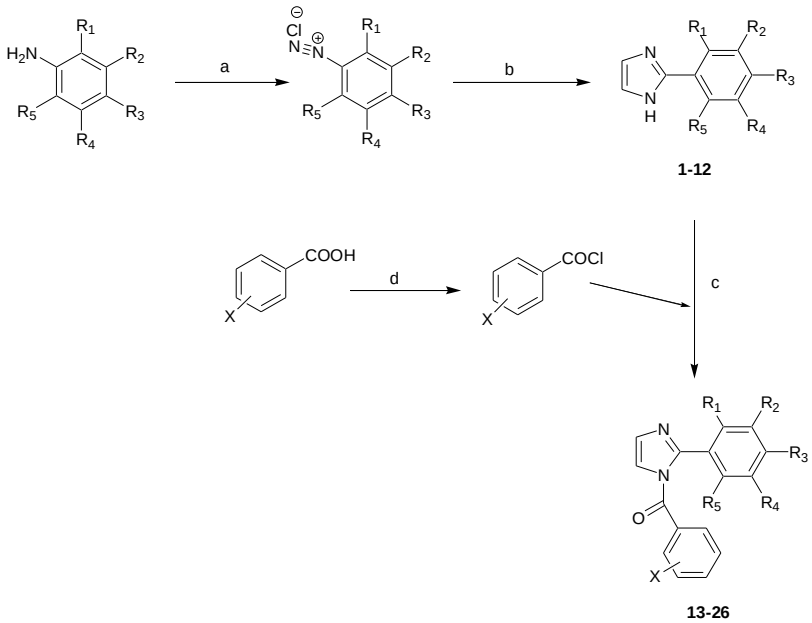
In the last year's reviews of different aspects of compounds, which contain imidazole, have been performed, the most recent is the convenient approach for the synthesis of imidazole derivatives using microwaves for Chawla *et al.,*(2012).

The relevant advances in the design of new multichannel imidazole-based receptors capable of recognizing different types of analytes were reported by Molina *et al.,*(2012). On the other hand the chemistry of imidazole and its pharmacological actions was reported too (Kumar, 2010; Shalini et al., 2010; Bhatnagar et al., 2011). A review focusing only on alkaloids possessing a clear pharmacological value with the total synthesis of the pyrrol imidazole alkaloids (PIAs) originated from marine sponges was reported by Forte *et al*., (2009). The report from Bellina *et al*., (2007) described the synthesis and biological activity of vicinal diaryl-substituted 1H-imidazoles.

This review highlights mainly the synthesis of compounds containing imidazole and his pharmaceutical importance. The derivatives of imidazole have intensive synthetic interest due to their important biological activities, and many of these compounds are candidates for drug development and have therefore drawn the attention of various research groups.

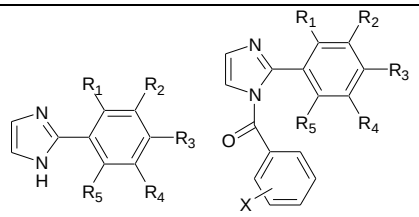
2. Imidazole with Antibacterial and Antiinflammatory Activity

In the synthesis of substituted imidazole derivatives reported for Sharma D. *et al*.,(2009), the intermediates, 2-(substituted phenyl)-1*H*-imidazoles (**1–12**) were the key for the obtention of compounds **13-26**. The compounds (**1-12**) were prepared by the condensation of imidazoles with the corresponding substituted aryldiazonium chlorides, which were prepared by the diazotization of substituted anilines. The coupling with the imidazole was carried out using sodium acetate. The intermediates (**1-12**) were reacted with substituted benzoyl chloride that was prepared by the reaction of substituted benzoic acid with thionyl chloride (scheme 2, table 1).



Scheme 2.Synthetic scheme for the synthesis of 2-(substituted phenyl)-1*H*-imidazoles and (substituted phenyl)-[2-(substituted phenyl)-imidazol-1-yl]-methanones. Reactions conditions: (a) $NaNO_2HCl$ (0-10ºC); (b) Imidazole, 48 h, (yield 12-74%); (c) 24 h, rt (yield 19-76%); (d) $SOCl_2$.

Table 1 Compound synthesized 2-(substituted phenyl)-1*H*-imidazoles and (substituted phenyl)-[2-(substituted phenyl)-imidazol-1-yl]-methanones



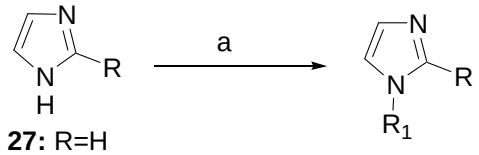
1-12 13-26

Compd	R_1	R_2	R_3	R_4	R_5	X
1	Cl	H	H	H	H	-
2	H	H	Cl	H	H	-
3	H	Cl	H	H	H	-
4	H	NO_2	H	H	H	-
5	NO_2	H	H	H	H	-
6	H	H	NO_2	H	H	-
7	H	H	H	H	H	-
8	COOH	H	H	H	H	-
9	H	H	OCH_3	H	H	-
10	CH_3	CH_3	H	H	H	-
11	CH_3	H	H	CH_3	CH_3	-
12	H	H	Br	H	H	-
13	H	NO_2	H	H	H	4-NO_2
14	NO_2	H	H	H	H	4-NO_2
15	Cl	H	H	H	H	4-NO_2
16	H	H	Cl	H	H	4-NO_2
17	COOH	H	H	H	H	4-NO_2
18	H	Cl	H	H	H	4-NO_2
19	H	H	NO_2	H	H	4-NO_2
20	H	H	OCH_3	H	H	4-NO_2
21	NO_2	H	H	H	H	2-Br
22	H	NO_2	H	H	H	2-Br
23	Cl	H	H	H	H	2-Br
24	H	H	Cl	H	H	2-Br
25	H	H	OCH_3	H	H	2-Br
26	H	H	NO_2	H	H	2-Br

Compounds **15**, **17** and **24** showed appreciable antibacterial activity equivalent to that of the standard drug norfloxacin.

The compounds **14**, **16**, **21** and **26** have antifungal activity significantly active against *A. niger*, and the compounds **22**, **25** and **26** shown activity against *C. albicans* in both casesusing fluconazole as control. Finally the compounds **16** and **19** could be selected as lead compounds for the development of novel antiviral agents because of present antiviral activity equivalent to that of the standard drugs brivudin and cidofovir.

A series of imidazole based compounds were synthesized by Pandey*et al.,* (2009).The synthesis of compounds **29**-**31** starting by reaction of imidazole (**27**) with 3,4-dichlorobenzyl bromide, ethyl bromoacetate and ethyl bromopropionate separately in THF in the presence of NaH/TBAB gave 1-(3,4-dichlorobenzyl)-1*H*-imidazole (**29**), imidazol-1-yl-acetic acid ethyl ester (**30**) and 3-imidazol-1-yl-propionic acid ethyl ester (**31**) respectively in quantitative yield (scheme 3).

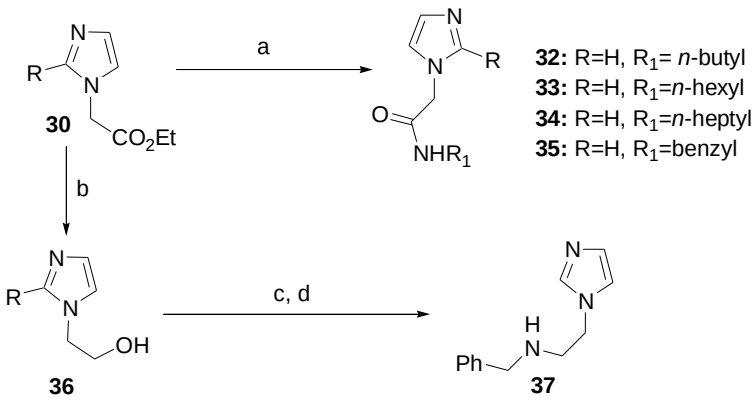


27: R=H

29: R=H, R_1= 3,4-dichlorobenzyl
30: R=H, R_1=CH_2COOEt
31: R=H, R_1=CH_2CH_2COOEt

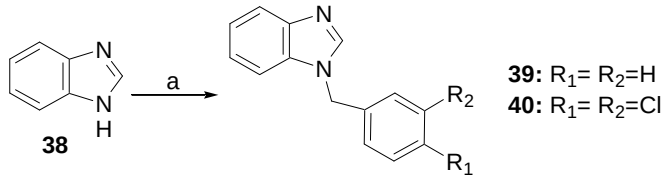
Scheme 3. Synthesis of *N*-alkyl(aralkyl)imidazoles. Reactions conditions: (a) R1-X, THF, NaH/TBAB (yield 65-70%)

Compounds (**32-35)** were prepared by amidation of compound **30** with different amines. *n*-butyl, *n*-hexyl, *n*-heptylamine, and benzylamine under refluxing condition DBU to giverespective carboxamides. $LiAlH_4$ reduction of the above compound **30** gave respective 1-(2-hydroxy ethyl)-1*H*-imidazole**36** in good yield. The latter, on mesylation with methanesulphonyl chloride followed by reaction with benzyl amine in presence of DBU gave 1-(2-benzyl aminoethyl)-1*H*-imidazole **37** in quantitative yield (scheme 4).



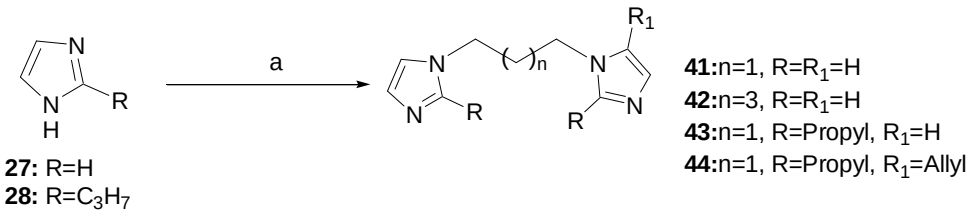
Scheme 4. Synthesis of imidazole derivatives. Reactions conditions: (a) Amines/DBU, Toluene/reflux (yield 78-80%); (b) $LiAlH_4$/THF (yield 46%); (c)$CH_3SO_2Cl/Et_3N/CH_2Cl_2$;(d) Benzylamine/4ÅMS/DBU, Toluene/reflux. (Yield 80%).

On the other side the compounds **39** and **40** were prepared by benzylation of benzimidazole **38** with benzyl bromide and 3,4-dichlorobenzyl bromide respectively (scheme 5).



Scheme 5. Synthesis of benzimidazole derivatives. Reactions conditions: (a) $ArCH_2Br$, THF, NaH/0-30ºC, (yield 70-75%).

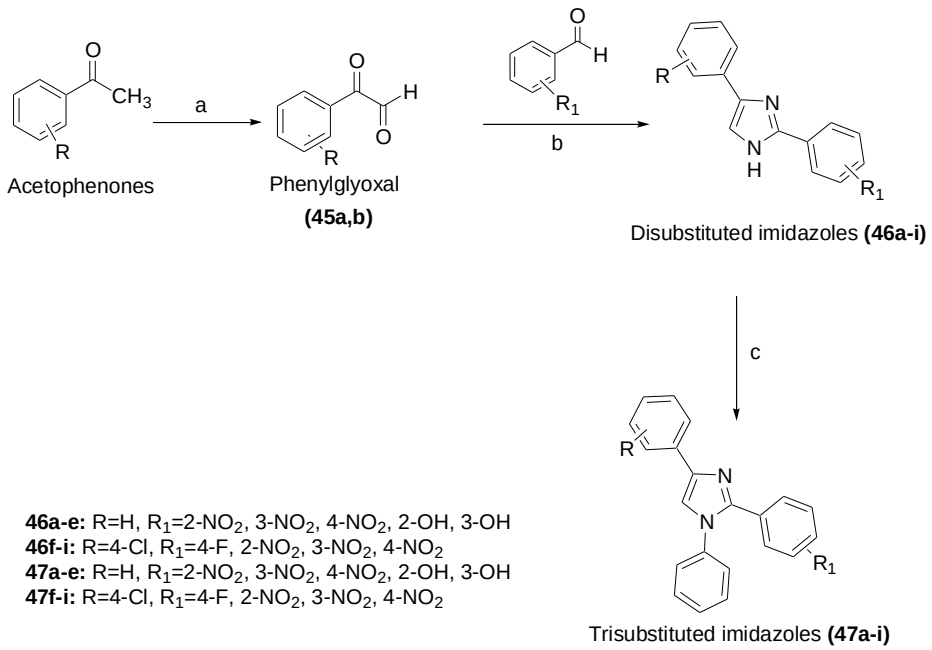
Compounds **41-44** were prepared by the reaction of imidazole (**27** or **28**) with dibromoalkanes in presence of NaH and TBAB in THF (scheme 6). The reaction of 2 eq. of imidazole with 1 eq. of 1,3-dibromopropane and 1,5-dibromopentane separately led to the formation of compounds **41** and **42** respectively in good yields. However, reacting 2 eq. of 2-propylimidazole with 1 eq. of 1,3-dibromopropane gave the expected 1,3-bis-(2-propylimidazol-1-yl)-propane (**43**) as major product along with another unusual minor product, 1-(4-allyl-2-propylimidazol-1-yl)-3-(2-propylimidazol-1-yl)-propane (**44**).



Scheme 6. Synthesis of bis-imidazoly derivatives. Reactions conditions: (a) 1,3-dibromopropane or 1,5-dibromopentane, NaH / THF, TBAB, 0-30ºC, 4h, (yield 45-70%).

The synthesized compounds were screened against *Mycobacterium tuberculosis*, using Ethambutol (EMB) and isoniazid (INH) as control; the compound **43** exhibited very good *in vitro* antitubercular activity and may serve as a lead for further optimization.

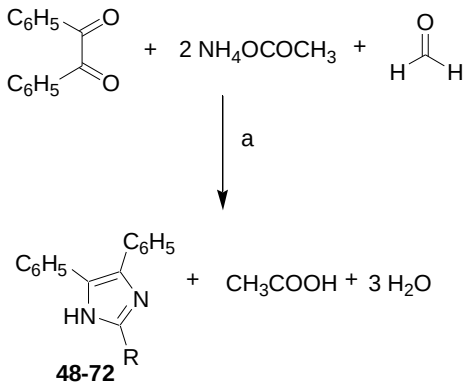
Husain *et al*., (2009) described the synthesis of disubstituted imidazoles (**46a**-**i**). These products were prepared by reacting appropriate phenylglyoxal (**45a**,**b**) with different aryl aldehydes in the presence of ammonium acetate. The required phenylglyoxals (starting material) were prepared by refluxing viastirring acetophenone / 4-chloroacetophenone in dioxane with selenium dioxide. Trisubstituted imidazoles (**47a**-**i**) were prepared by reacting disubstituted imidazole (**46a**-**i**) with chlorobenzene in the presence of catalytic amount of triethylamine (TEA) (scheme 7).



Scheme 7. Protocol for synthesis of substituted imidazoles (46a-i, 47a-i). Reactions conditions: (a) Se_2O, H_2O, Dioxan, (yield 72-78%); (b) Amonium acetate, Glacial acetic acid, (yield 40-74%); (c) Chloro-benzene, Triethylamine, Tetrahidrofuran (yield 40-63%).

The results indicated that compounds **47c** and **47g** showed significant anti-inflammatory activity with very low ulcerogenicity. Some compounds like **46f**, **46i**, **47d**, **47f**, **47h**, and **47i** also showed significant antimicrobial activity.

Puratchikody and Doble, (2007)described the synthesis and pharmacological evaluation pertaining to antinociceptive (hot plate and tail flick) and antiinflammatory (based on Carrageenan-induced paw oedema) activities, and QSAR studies on 2-substituted-4,5-diphenyl-1*H*-imidazoles. The synthesis was performed by condensation of benzil with ammonium acetate and appropriate aldehydes in presence of glacial acetic acid. Substituted benzaldehyde(s) is used to obtain compounds **48**-**68**. Aldehyde containing alkyl, alkenyl or styryl unit were used to give compounds **69**-**72** (scheme 8, table 2).



48-72

Scheme 8. Reactions conditions: (a) glacial acetic acid, stir, rt, 1-2 h (yield 65-82%)

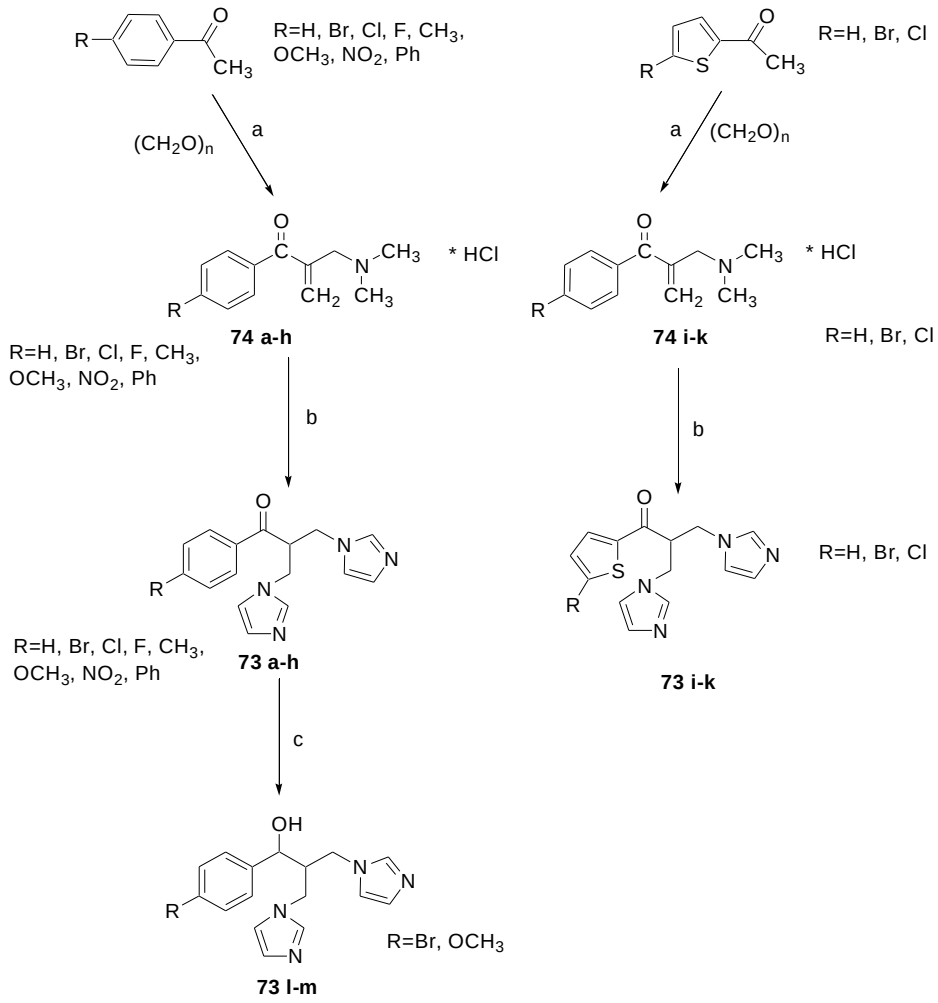
Table 2 Derivatives 2-substituted-4,5-diphenyl-1*H*-imidazoles

Compd	R	Compd	R	Compd	R
48	Phenyl	**57**	3-Methoxyphenyl	**66**	4-Hydroxyphenyl
49	2-Chlorophenyl	**58**	4-Hidroxy-3-methoxyphenyl	**67**	4-Methylphenyl
50	2-Nitrophenyl	**59**	4-Fluorophenyl	**68**	4-Methoxiphenyl
51	2-Hydroxyphenyl	**60**	4-Chlorophenyl	**69**	H
52	2-Methylphenyl	**61**	4- Bromophenyl	**70**	Methyl
53	2-Methoxyphenyl	**62**	4-Iodophenyl	**71**	2-Propenyl
54	3-Chlorophenyl	**63**	4-Nitrophenyl	**72**	2-Styryl
55	3-Nitrophenyl	**64**	4- Aminophenyl		
56	3-Methylphenyl	**65**	4-Dimethylaminophenyl		

For antinociceptive and antiinflamatory activities was used pentazocine and indomethacine as standard respectively, in both the Tween suspension was as control. Compounds with phenyl substitution with –F, –Cl, $–NH_2$, $–N(CH_3)_2$, –OH and $–OCH_3$ at *p*-position (compounds **59**, **60**, **64**, **65**, **66** and **68**, respectively) showed higher activity than all other substitutions in both studies. Electron-donating groups and hydrophilicity play an important role in the biological activity, lowering of activity was observed with hydrophobic groups.

New bis-imidazole derivatives have been synthesized for Zampieri*et al*., (2007) with this synthesis the corresponding substituted arylmethylketones and thienylmethylketones with paraformaldehyde and dimethylamine hydrochloride in acetic acid were prepared the [(dimethylamino) methyl]-propenones **74a-h** and 2-[(dimethylamino)methyl]-1-(thiophene-2-yl)-propenones **74i-k** as hydrochlorides.

The nucleophilic attack of imidazole both on carbon bearing the dimethylamino group and α,β-unsaturated ketone moiety via a Michael type reaction, allowed the formation of 1-aryl-3-(1H-imidazol-1-yl)-2-[(1H-imidazol-1-yl) methyl]-propan-1-one derivatives **73a-h** and 3-(1H-imidazol-1-yl)-2-[(1H-imidazol-1-yl)methyl]-1-(thiophen- 2-yl)-propan-1-one derivatives **73i-k**, by microwave (MW) irradiation of the reagent mixture in EtOH–H_2O at room temperature. The reduction of the above obtained ketone derivatives**73a-h** with $NaBH_4$ produced the secondary alcohols **73l-m** (scheme 9).

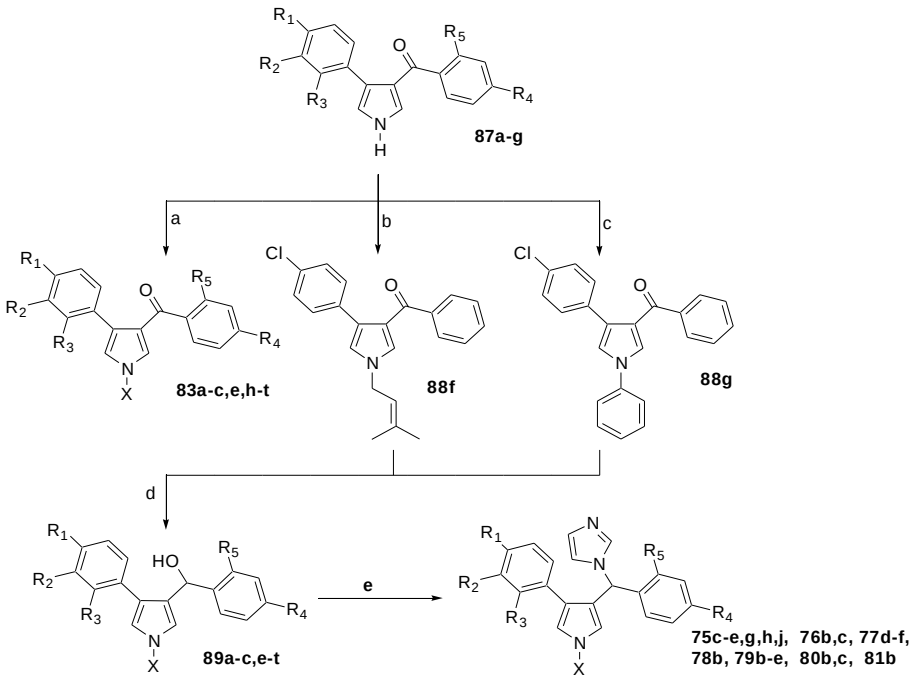


Scheme 9. Reactions conditions: (a) AcOH, Dimethyl-amine, (yield 41-73%); (b) EtOH-H_2O, Imidazole, MW 250w, (yield 5-36%); (c) $NaBH_4$, (yield 30-36%).

All the bis-imidazole derivatives exhibited some degree of antifungal and antimycobacterial activity; compound **73h** in which the biphenylyl moiety is present is the most active antifungal derivative in the series. The activity was higher than that of the reference drug miconazole and similar to the activity of amphotericin B. On the other hand the compound **73a-m** was also tested for antitubercular activity against the reference strain of *M. tuberculosis* H37RV, in comparison with rifampicin. But in this case only exhibited moderate activity, with MIC values in the range of 8-64 mg/mL.

3. Imidazole with Antifungal Activity

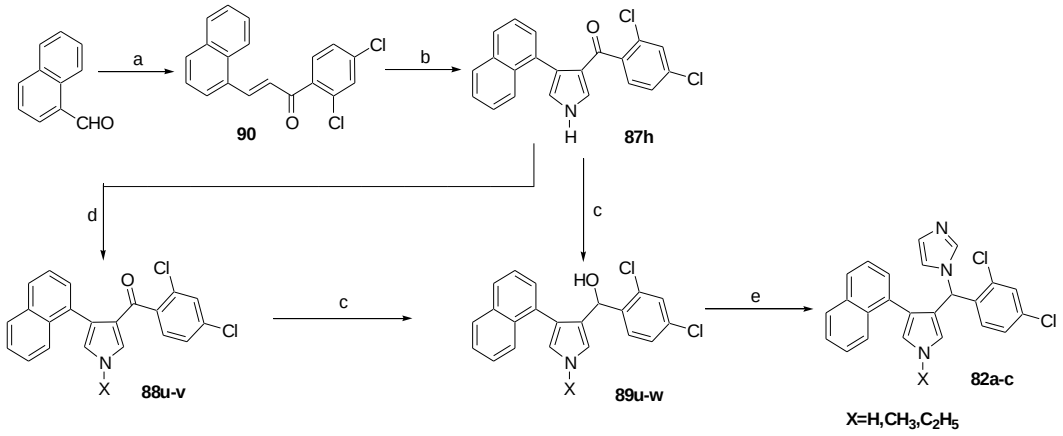
N-Substituted Derivatives of 1-[(Aryl)(4-aryl-1*H*-pyrrol-3-yl)methyl]-1*H*-imidazole were reported by Di Santo *et al*., (2005).The synthesis started with the alkylation of pyrroles **87a-g** (scheme 10, table 3) with the appropriate alkyl halide in alkaline medium (K_2CO_3) to give *N*-alkylpyrrolylmethanones **88a-c,e,h-t**.



Scheme 10. Reactions Conditions: (a) alkyl iodide or bromide, K_2CO_3, DMF, (yield 27-100%); (b) 1-bromo-3-methyl-2-butene, NaH, THF, (yield 91%); (c) $PhB(OH)_2$, $Cu(OAC)_2$, pyridine, NMP, microwave 60 W, 120°C, 3x50 s, (yield 19%); (d) $LiAlH_4$, THF, (yield 74-100%); (e) 1,1´-carbonyldiimidazole, MeCN, (yield 28-99%).

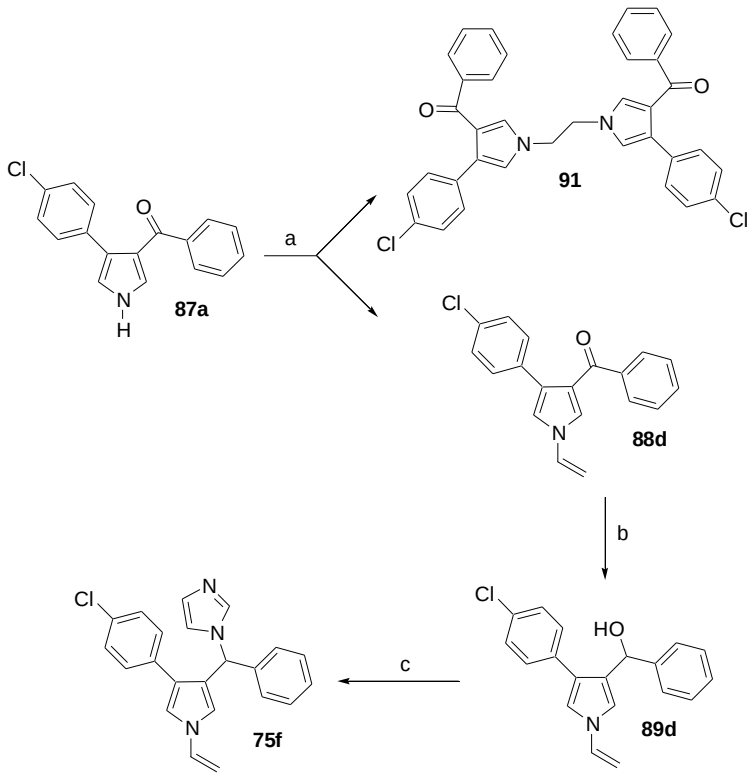
For the compound **88f** it necessary to use NaH as a catalyst by reaction of dimethylallyl bromide with **87a**. The compound **88g** was obtained by Suzuki reaction conditions using phenylboronic acid, Cu(II) acetate, pyridine and *N*-methylpyrrolidone by microwave-assisted. The imidazoles **75c-e**,**g**,**h**,**j**,**76b**,**c**, **77d-f**,**78b**,**79b-e**,**80b**,**c and 81b** (table 3)were afford by reduction of ketones **88a-c, e-t** with $LiAlH_4$ to give compounds **89a-c, e-t** which werethen treated with 1,1'-carbonyldiimidazole (CDI).

The derivatives **82a-c** (scheme 11, table 3) were synthesized by a similar synthetic pathway. The compound **87h** was obtained by the condensation of the naphthalene-1-carboxaldehyde with 2',4'-dichloroacetophenone in aqueous sodium hydroxide to afford propenone **90**, followed by TosMIC cycloaddition in the presence of sodium hydride.



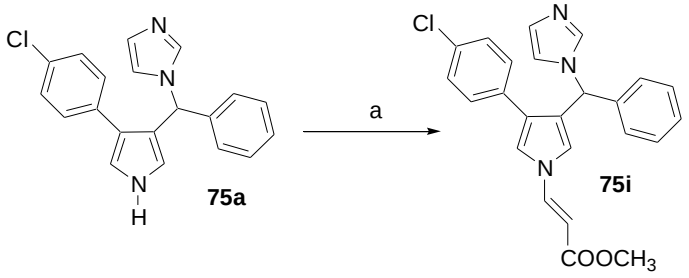
Scheme 11. Reactions Conditions: (a) 2,4-dichloroacetophenone, NaOH, EtOH (yield 76%); (b) toluene-4-sulfonylmethyl isocyanide (TosMIC), NaH, DMSO, Et_2O (yield 82%); (c) $LiAlH_4$, THF, (yield 98-100%); (d) alkyliodide, K_2CO_3, DMF (yield 67-93%); (e) 1,1´-carbonyldiimidazole, MeCN (yield 58-80%).

On the other hand the reaction of **87a** with 1,2-dichloroethane (tetrabutylammonium hydrogen sulfate (Bu_4NHSO_4), aqueous sodium hydroxide and dichloromethane) gave the expected methanone **88d**, reduction of **88d** furnished the corresponding alcohol **89d**, which was condensed with CDI to afford imidazole derivative **75f** (scheme 12).



Scheme 12. ReactionConditions: (a) 1,2-dichloroethane, Bu_4NHSO_4, NaOH, CH_2Cl_2, (yield 6%, 77%); (b) $LiAlH_4$, THF, (yield 100%); (c) 1,1´-Carbonyldiimidazole, MeCN, (Yield 70%).

Finallydirect reaction of **75a** with methyl propiolate in the presence of tetrabutylammonium fluoride (Bu_4NF) (scheme 13), gave derivative **75i**.



Scheme 13. Reactions Conditions: (a) methyl propiolate, Bu_4NF, THF, (yield 37%).

Table 3 Chemical of Derivatives 75c-j, 76b,c, 77d-f, 78b, 79b-e, 80b,c, 81b, 82a-c 87a-h, 88a-v, 89a-w, 90, and 91

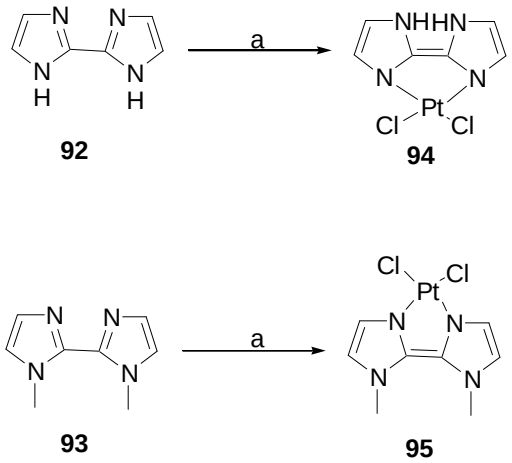
Compd	R_1	R_2	R_3	R_4	R_5	X	Compd	R_1	R_2	R_3	R_4	R_5	X
75c	Cl	H	H	H	H	C_2H_5	**88i**	Cl	H	Cl	H	H	C_2H_5
75d	Cl	H	H	H	H	C_3H_7	**88j**	Cl	H	H	Cl	Cl	C_3H_7
75e	Cl	H	H	H	H	CH_2-c-C_3H_5	**88k**	Cl	H	H	Cl	Cl	$CH_2CH=CH_2$
75f	Cl	H	H	H	H	$CH=CH_2$	**88l**	Cl	H	H	Cl	Cl	$CH_2CH(OCH_3)_2$
75g	Cl	H	H	H	H	$CH_2CH=CH_2$	**88m**	H	H	Cl	Cl	Cl	CH_3
75h	Cl	H	H	H	H	$CH_2CH=C(CH_3)_2$	**88n**	Cl	H	Cl	Cl	Cl	CH_3
75i	Cl	H	H	H	H	$CH=CHCOOCH_3$	**88o**	Cl	H	Cl	Cl	Cl	C_2H_5
75j	Cl	H	H	H	H	Ph	**88p**	Cl	H	Cl	Cl	Cl	C_3H_7
76b	Cl	H	Cl	H	H	CH_3	**88q**	Cl	H	Cl	Cl	Cl	$CH_2CH=CH_2$
76c	Cl	H	Cl	H	H	C_2H_5	**88r**	Cl	Cl	H	CH_3	H	CH_3
77d	Cl	H	H	Cl	Cl	C_3H_7	**88s**	Cl	Cl	H	CH_3	H	C_2H_5
77e	Cl	H	H	Cl	Cl	$CH_2CH=CH_2$	**88t**	1-pyrrolyl	H	H	Cl	Cl	CH_3
77f	Cl	H	H	Cl	Cl	$CH_2CH(OCH_3)_2$	**88u**	-	-	-	-	-	CH_3
78b	H	H	Cl	Cl	Cl	CH_3	**88v**	-	-	-	-	-	C_2H_5
79b	Cl	H	Cl	Cl	Cl	CH_3	**89a**	Cl	H	H	H	H	C_2H_5
79c	Cl	H	Cl	Cl	Cl	C_2H_5	**89b**	Cl	H	H	H	H	C_3H_7
79d	Cl	H	Cl	Cl	Cl	C_3H_7	**89c**	Cl	H	H	H	H	CH_2-c-C_3H_5
79e	Cl	H	Cl	Cl	Cl	$CH_2CH=CH_2$	**89d**	Cl	H	H	H	H	$CH=CH_2$
80b	Cl	Cl	H	CH_3	H	CH_3	**89e**	Cl	H	H	H	H	$CH_2CH=CH_2$
80c	Cl	Cl	H	CH_3	H	C_2H_5	**89f**	Cl	H	H	H	H	$CH_2CH=C(CH_3)_2$
81b	1-pyrrolyl	H	H	Cl	Cl	CH_3	**89g**	Cl	H	H	H	H	Ph
82a	-	-	-	-	-	H	**89h**	Cl	H	Cl	H	H	CH_3
82b	-	-	-	-	-	CH_3	**89i**	Cl	H	Cl	H	H	C_2H_5
82c	-	-	-	-	-	C_2H_5	**89j**	Cl	H	H	Cl	Cl	C_3H_7
87a	Cl	H	H	H	H	-	**89k**	Cl	H	H	Cl	Cl	$CH_2CH=CH_2$
87b	Cl	H	Cl	H	H	-	**89l**	Cl	H	H	Cl	Cl	$CH_2CH(OCH_3)_2$
87c	Cl	H	H	Cl	Cl	-	**89m**	H	H	Cl	Cl	Cl	CH_3
87d	H	H	Cl	Cl	Cl	-	**89n**	Cl	H	Cl	Cl	Cl	CH_3
87e	Cl	H	Cl	Cl	Cl	-	**89o**	Cl	H	Cl	Cl	Cl	C_2H_5
87f	Cl	Cl	H	CH_3	H	-	**89p**	Cl	H	Cl	Cl	Cl	C_3H_7
87g	1-pyrrolyl	H	H	Cl	Cl	-	**89q**	Cl	H	Cl	Cl	Cl	$CH_2CH=CH_2$
87h	-	-	-	-	-	-	**89r**	Cl	Cl	H	CH_3	H	CH_3
88a	Cl	H	H	H	H	C_2H_5	**89s**	Cl	Cl	H	CH_3	H	C_2H_5
88b	Cl	H	H	H	H	C_3H_7	**89t**	1-pyrrolyl	H	H	Cl	Cl	CH_3
88c	Cl	H	H	H	H	CH_2-c-C_3H_5	**89u**	-	-	-	-	-	H
88d	Cl	H	H	H	H	$CH=CH_2$	**89v**	-	-	-	-	-	CH_3
88e	Cl	H	H	H	H	$CH_2CH=CH_2$	**89w**	-	-	-	-	-	C_2H_5
88h	Cl	H	Cl	H	H	CH_3							

Derivatives **75c-j**, **76b**,**c**, **77d-f**, **78b**, **79b-e**, **80b**,**c, 81b** and**82a-c** showed high potency against *Candida albicans*, and the most active derivative was compound **75d**, which was more potent than the reference.

4. Imidazole with Antiparasiticactivity

The effect of *cis*-2-(1*H*-imidazole-2-yl)-1*H*-imidazole dichloro platinum (II) on the *in-vitro* formation of β-Hematin was reported by Akkawi*et al*., (2012).

The compound *cis*-2-(1*H*-imidazol-2-yl)-1*H*-imidazole Dichloro Platinum (ll) **94**complex was prepared by mixing two solutions of 1N HCl, the first one containing potassium tetrachloroplatinate (K_2PtCl_4) and the second containing 2,2'-Biimidazole **92**. On the other hand the compound *cis*-1-methyl-2-(1-methyl-1*H*-imidazole-2-yl)-1*H*-imidazole dichloro platinum (II) **95** was prepared in a similar way as the above compound but using 1,1'-dimethyl-2,2'-Biimidazole **93**(scheme 14).



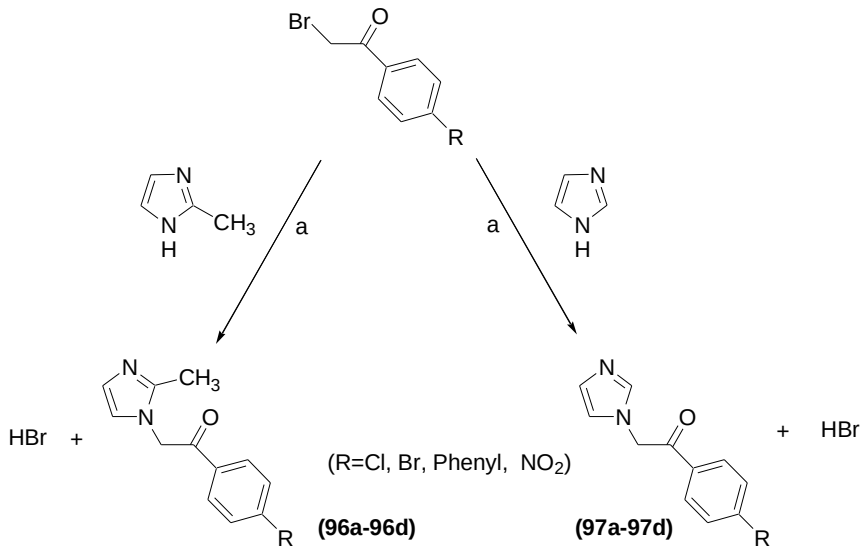
92 **94**

93 **95**

Scheme 14. Reactions Conditions: (a) K_2PtCl_4, HCl 1N.

Cisplatin complexes not only have anti-tumor activity, as proposed by others, but also they have the ability to inhibit the formation of β-hematin in *in-vitro* systems. The study revealed that *cis*-2-(1*H*-imidazol-2-yl)-1*H*-imidazole dichloro platinum (ll) was more effective against β-hematin formation than *Cis*-1-methyl-2-(1-methyl-1*H*-imidazole-2-yl)-1*H*-imidazole dichloro Platinum (ll).

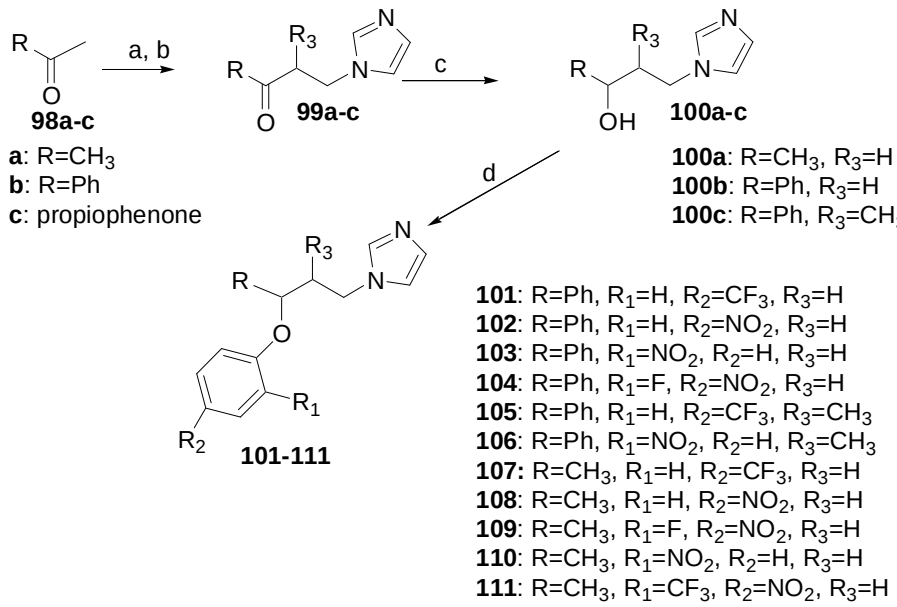
Lakshmanan*et al*., (2011)reported the synthesisof1-substituted imidazole derivatives, the *N*-phenacyl 2-methyl imidazole derivatives**96a-d** were obtained for treatment of 2-methyl imidazole with the appropriate *para* substituted phenacyl bromides in presence of dry DMF in cold stirring (5-10°C) for 3-6 h. On the other hand the *N*-phenacyl imidazole derivatives **97a-d** were synthetized for treatment of imidazole and of appropriate *para* substituted phenacyl bromides in the same conditions that **96a-d** (scheme 15).



Scheme 15. Reactions Conditions: (a) DMF, 5-10 ºC, 3-5 h,stir.

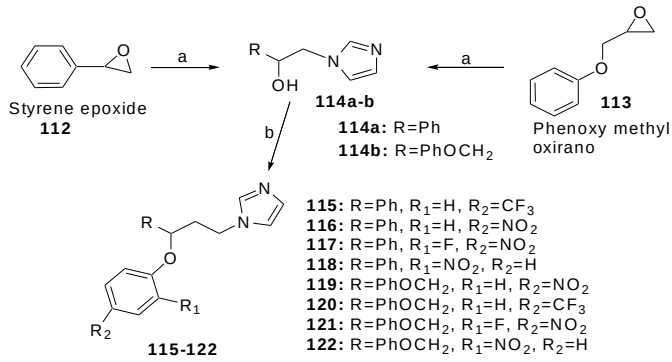
The derivatives **97a-d** containing imidazole moiety possesses greater anthelmintic activity compared to similar analogs containing 2-methyl imidazole **96a-d**. Compound **97d** showed the better activity compared with the standard drugs albendazole and piperazine citrate.

The synthesis of substituted aryloxy alkyl and aryloxy aryl alkyl imidazoles were reported by Bhandari *et al*., (2010).Ketone (acetone, acetophenone or propiophenone) **98a-98c** was reacted with pyrrolidine and paraformaldehydeunder asymmetric Mannich conditions in the presence of L-proline to give the corresponding Mannichproducts. Subsequent replacement of the pyrrolidine with imidazole (amine exchange reaction to give **99a and 99b**, **99c**) followed by sodium borohydridereduction gave the hydroxyl intermediates **100a-100c.** Condensation of the hydroxyl intermediates **100a**, **100b** and *cis* **100c** isomer (major product) with substituted aryl halides furnished the required ethers **101-111** (**105**and**106** were obtained as *cis* diastereomers) scheme 16.



Scheme 16 .Reactions Conditions: (a) pyrrolidine, (HCHO)n, L-proline / DMSO, 6-8 h; (b) corresponding Mannich salt, imidazole / ethanol: H_2O (3:2), 5 h; (c) $NaBH_4$ / MeOH, 2 h; (d) K(*t*-OBu), DMSO, substitute aryl halides, 2-3 h.

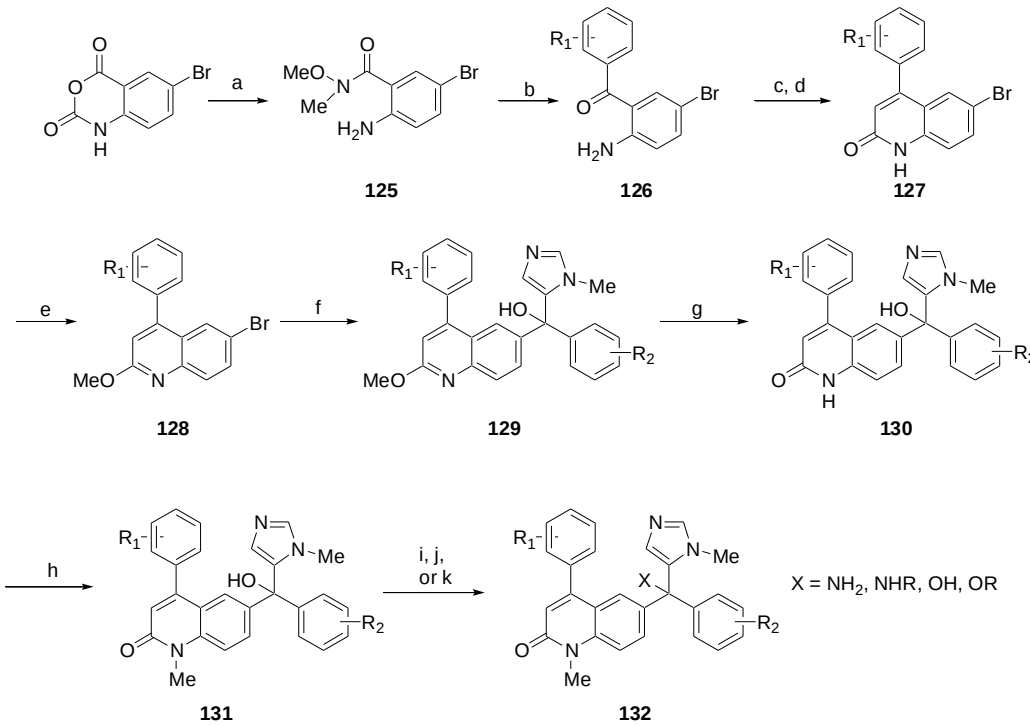
For the formation of final compounds aryloxy aryl alkyl imidazoles (**115-118**) and diaryloxy alkyl imidazoles (**119-122**), following it was used the regioselective ring opening of styrene epoxide (**112)** or phenoxy methyl oxirane (**113)**with imidazole gave the corresponding alcohols **114a** and **114b**, SN_{Ar} substitution with an aryl fluoride generated the targeted aryloxy ethers **115-122**scheme 17.



Scheme 17. Reactions Conditions: (a) imidazole / abs ethanol, reflux, 5 h; (b) K(*t*-OBu), DMSO, substitute aryl halides, 2-3 h.

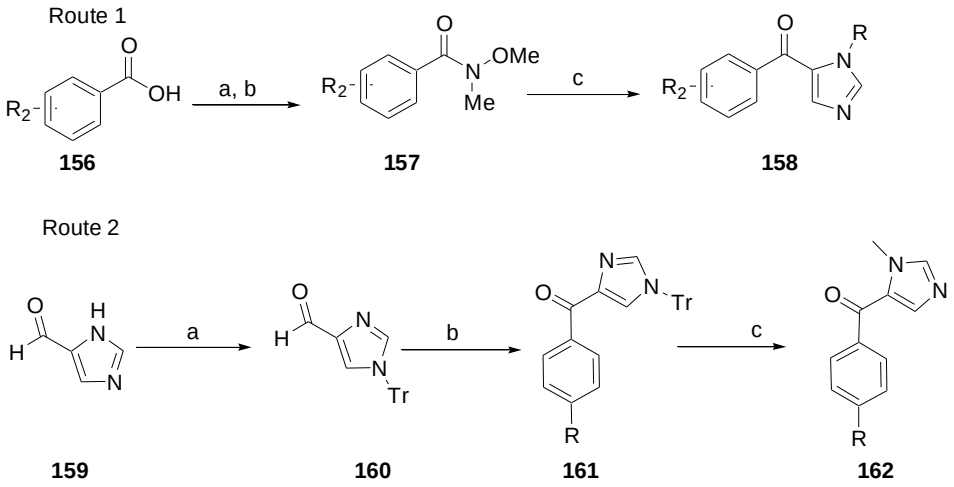
All the 19 compounds exhibited 94–100% inhibition at 10 μg/mL against promastigotes and 12 compounds exhibited high inhibition with an IC_{50} in the range of 0.47–4.85 μg/mL against amastigotes. Promising compounds were tested further *in vivo*. Among all, compounds **101** and **120** with 4-CF_3 aryloxy moiety exhibited medium *in vivo* inhibition of 58–60%, thus providing new structural lead for antileishmanials.

The synthesis of analogs of tipifarnib (**123,** table 4) as inhibitors of Tc-L14DM and as anti-*T.cruzi* agents was reported for Kraus *et al*., (2010). The synthesis started with the formation of Weinreb amide **125**from 5-bromoisatoic anhydride in presence of pyridine, this amide reacts with a variety of phenyl lithiums to give ketone **126.** Acetylation of the amino group followed by intramolecular ring closure using *t*-BuOK gives quinolone **127**. Conversion of **127** to the set of compounds **132**was carried out as described in earlier study (Kraus et al., 2009). The compound **128** was obtained by reaction of quinolone **127**with BF_4OMe_3 and after base. The compound **129**was prepared from **128**by bromide-lithium exchange and subsequent addition of intermediated N(Me)Imidazole-CO-PhenylR_2**162**. The compound **130**was obtained by deprotection of **129** with 6N HCl at reflux, the *N*-alquilation with CH_3I in presence of *N,N,N'*-Triethylbenzenemethanaminium chloride (BTEAC)and NaOH gave the compound **131**. Finally the compound **132a-b** was formed from intermediate **131** by substitution of alkyl chloride by gaseous ammonia or CH_3NH_2. The compound **132d** was obtained from**131**via an acid catalyzed dehydrationetherification in methanol as solvent (scheme 18).



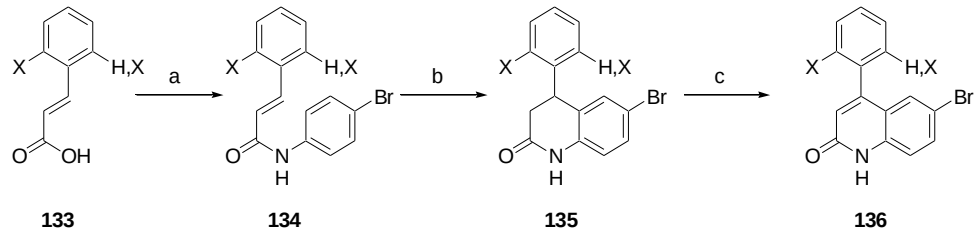
Scheme 18. Synthesis of tipifarnib analogs from 5-bromoisatoic anhydride. Reactions Conditions: (a) CH_3ONHCH_3 HCl, pyridine, CH_2Cl_2, (yield 89%); (b) R_1PhBr (2eq), *n*-BuLi (2eq), THF, (yield 85%); (c) Ac_2O, toluene, reflux; (d) *t*-BuOK, 1,2-dimethoxyethane, (yield 66%); (e) 1) BF_4OMe_3, CH_2Cl_2, 2) NaOH, (yield 63%); (f) 1) *n*-BuLi, THF, −78 °C, 2) N(Me)Imidazole-CO-PhenylR_2, (yield 60%); (g) 6N HCl, THF, reflux, (yield 62%); (h) CH_3I, NaOH, BTEAC, THF (yield 59%); (i) $SOCl_2$, neat, 12 h; (j) NH_3 (or CH_3NH_2), THF, rt; (k) tosic acid 1eq+cat, MeOH, reflux, (yield 9%).

Scheme 19 shows two routes to make the methanones needed for step f in scheme 18. The synthesis of methanones started with the reaction of 4-chlorobenzoic acid **156** with thionyl chloride. This product reacts with *N*-dimethylhydroxylamine to give 4-Chloro-*N*-methoxy-*N*-methylbenzamide **157**. The methanone **158** was obtained for the formation in situ of C-2 triethylsilyl protected *N*-methylimidazole and finally reaction with **157**. The synthesis of methanone for route 2, started with the protection of 3H-imidazole-4-carbaldehyde with trityl chloride to give the compound **160**. The compound **161**was obtained by reaction of *p*-bromotoluene with magnesium turnings and a pinch of iodine and after addition of **160** and finally addition of MnO_2. The methanone **162** was obtained by reaction of **161** with methyltrifluoromethane sulfonate.



Scheme 19. Synthesis of substituted 5-benzoyl-*N*1-alkyl-imidazoles. Route 1: (a) $SOCl_2$, neat; (b) CH_3ONHCH_3, pyridine, CH_2Cl_2, (yield 90%); (c) *N*-alkyl-imidazole, 1) *n*-BuLi, THF, −78°C, 2) Et_3SiCl, −78 °C, 3) *n*-BuLi, THF, −78 °C, (yield 76.6%). Route 2: (a) TrCl, Et_3N, CH_3CN, (yield 94%); (b) 1) Mg, I_2, ether, RC_6H_4Br, rt to reflux 2) MnO_2, dioxane, reflux, (yield 94%); (c) MeOTf, CH_2Cl_2, (yield 89.6%).

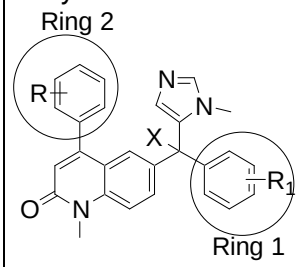
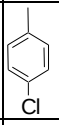
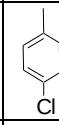
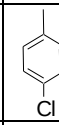
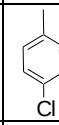
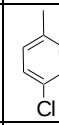
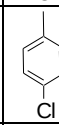
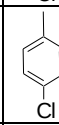
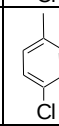
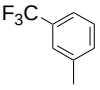
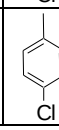
The synthesis of tipifarnib analogs is depicted in scheme 20. Commercially available halogenated cinnamic acid **133** was converted to the acid chloride and thenreacted with 4-bromoaniline to give amide **134**. IntramolecularFriedel-Crafts alkylation proceeded smoothly with concentratedH_2SO_4 to give lactam **352**. Conversion to the quinolonewas accomplished by oxidation of **135** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone to give **136**. The latter was convertedto the desired tipifarnib analogues by using steps fromscheme 18.

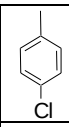
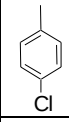
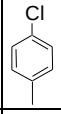
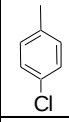
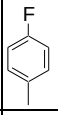
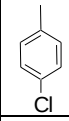
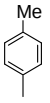
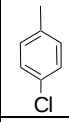
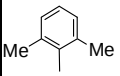
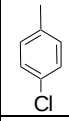
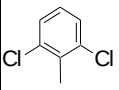
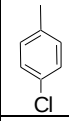
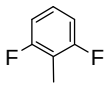
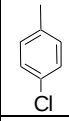
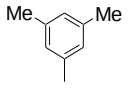
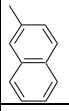
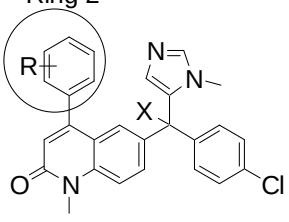
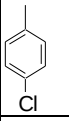
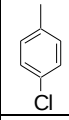
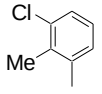
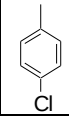
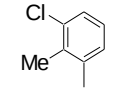


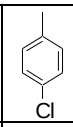
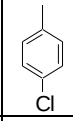
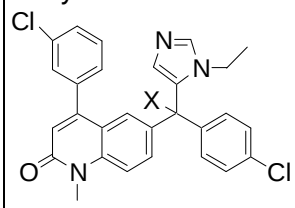
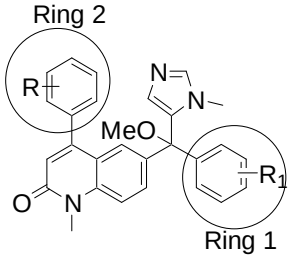
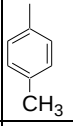
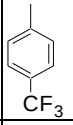
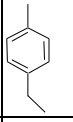
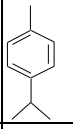
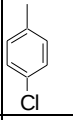
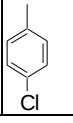
Scheme 20. Synthesis of tipifarnib analogs. Reactions Conditions: (a) $SOCl_2$, (neat), reflux, 6 hours then 4-bromoaniline, DIEA (1.5 eq), CH_2Cl_2, 0 °C, (yield 76%); (b) H_2SO_4 (conc.), 105 °C, yield (79%); (c) DDQ, dioxane, reflux, (yield 68%).

The compound **132**, which lacks an *ortho* substituent (so no rotamers are possible) and also lacks the 3-chloro group, which is important for binding to protein farnesyltransferase. This compound ranks among the most potent of the compounds against *T. cruzi* and displays an intermediate loss in affinity for protein farnesyltransferase. The posaconazole was used as standard.

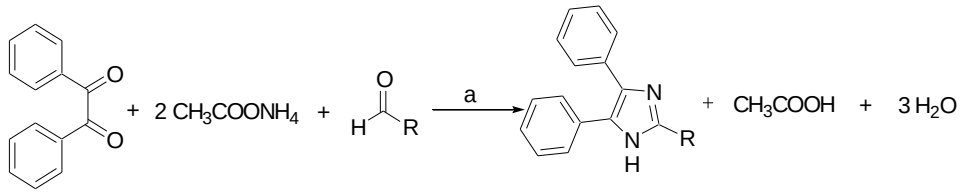
Table 4 Entry 1: Tipifarnib Analogues with Ring 1 and Ring 2 Modifications.Entry2: Tipifarnib Analogues with X Group Modifications.Entry 3: Tipifarnib Analogues with Imidazole and X Group Modifications.Entry 4: Tipifarnib Analogues with Additional Ring 1 and Ring 2 Modifications

	Compd	Ring 1	Ring 2	X
Entry 1 	**123**			-NH_2
	124			-OMe
	125			-OMe
	126			-OMe
	127			-OMe
	128			-OMe
	129			-OMe
	130			-OMe
	131			-OMe

	132			-OMe
	133			-OMe
	134			-OMe
	135			-OMe
	136			-OMe
	137			-OMe
	138			-OMe
	139			-OMe
	140			-OMe
Entry 2 Ring 2 	**141**			-OH
	142			-OH
	143			-OEt

	144			-OPr
	145			-NHMe
Entry 3 	**146**	-		-NH_2
	147	-		-NHMe
	148	-		-OMe
	149	-		-OH
Entry 4 	**150**			-OMe
	151			-OMe
	152			-OMe
	153			-OMe
	154			-OMe
	155			-OMe

The synthesis of 2-substituted-4,5-diphenyl imidazoles **163a-j** was reported by Dutta *et al*., (2010) the compounds were synthetized by refluxing benzyl with different substituted aldehydes in the presence of ammonium acetate and glacial acetic acid (scheme 21).



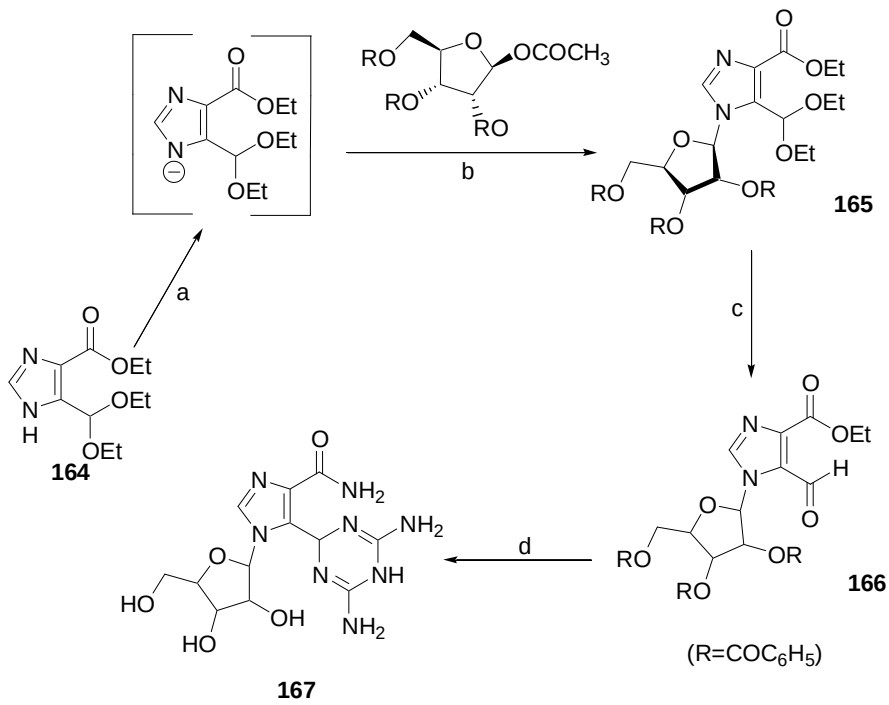
163a R= phenyl
163b R= 2-hidroxiphenyl
163c R= 3-methoxyphenyl
163d R= 4-hidroxi-3-methoxyphenyl
163e R= 2-phenylethenyl
163f R= 2-chlorophenyl
163g R= 4-fluorophenyl
163h R= 3-nitrophenyl
163i R= H
163j R= methyl

Scheme 21. (a) Refluxing, CH_3CO_2H, (yield 32-80%)

The compound **163b, 163c, 3163e, 163g, 163h** were found to have improved anthelmintic activity compared to albendazole and piperazine citrate.

6. Imidazole with Antiviral Activity

The synthesis of 4-carbamoyl-5-(4,6-diamino-2,5-dihydro-1,3,5-triazin 2-yl) imidazole-1–β-*D*-ribofuranoside was reported by Ujjinamatada*et al*., (2007). The synthesis started with ethyl 5-diethoxymethylimidazole-4-carboxylate **164** by reaction with NaH to convert in sodium salt and was further reacted with 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl-1-iodide under standard conditions of glycosylation to give ethyl 1-(2,3,5-tri-*O*-benzoyl-β-*D*-ribofuranosyl)-5-(diethoxymethyl)imidazole- 4-carboxylate**165**. The acetal **165** was reacted with 80% aqueous acetic acid to obtain the corresponding carboxaldehyde **166**. The reaction of the latter with excess guanidine in ethanol at reflux provided the target nucleoside **167**(scheme 22).



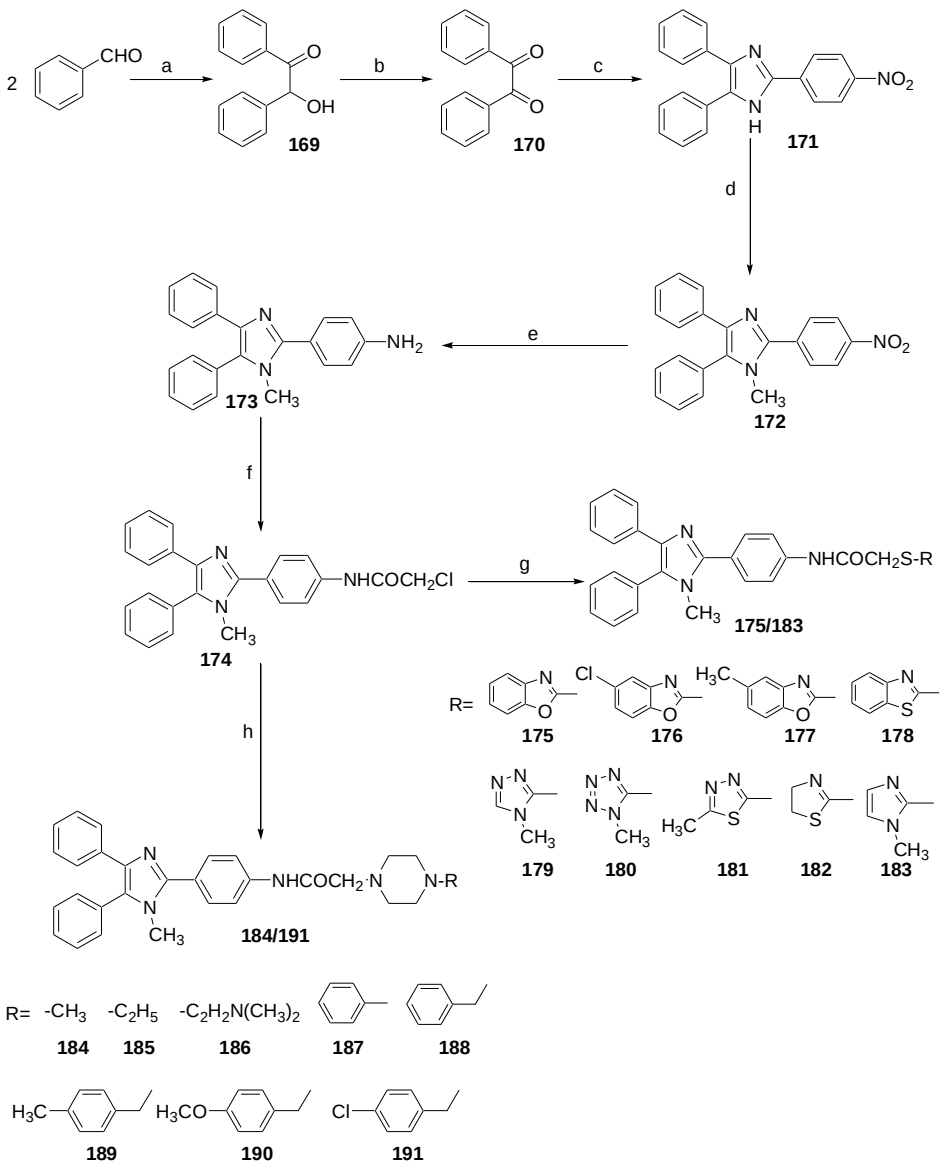
Scheme 22. Synthesis of the target nucleoside 167. Reaction conditions: (a) NaH, CH_3CN, 50ºC, 2h; (b) $(CH_3)_3SiI$/Benzene, (yield 87%); (c) AcOH 80%, (yield 78%); (d) EtOH, excess guanidine, reflux, 12h, (yield 61%).

Compound**167** was evaluated *in vitro* against NTPases/helicases of four different viruses of the Flaviviridae family, including the West Nile virus (WNV), hepatititis C virus (HCV), dengue virus (DENV), and the Japanese encephalitis virus (JEV), employing both RNA and a DNA substrate. The compound showed activity against NTPase/helicase of WNV and HCV with an IC_{50} of 23 and 37 μM, respectively, when a DNA substrate was employed; while no activity was observed when an RNA substrate was used.

7. Imidazole with Anticancer activity

Özkay*et al*.,(2010)reported the synthesis of 2-substituted-*N*-[4-(1-methyl-4,5-diphenyl-1*H*-imidazole-2-yl) phenyl]acetamide derivatives.

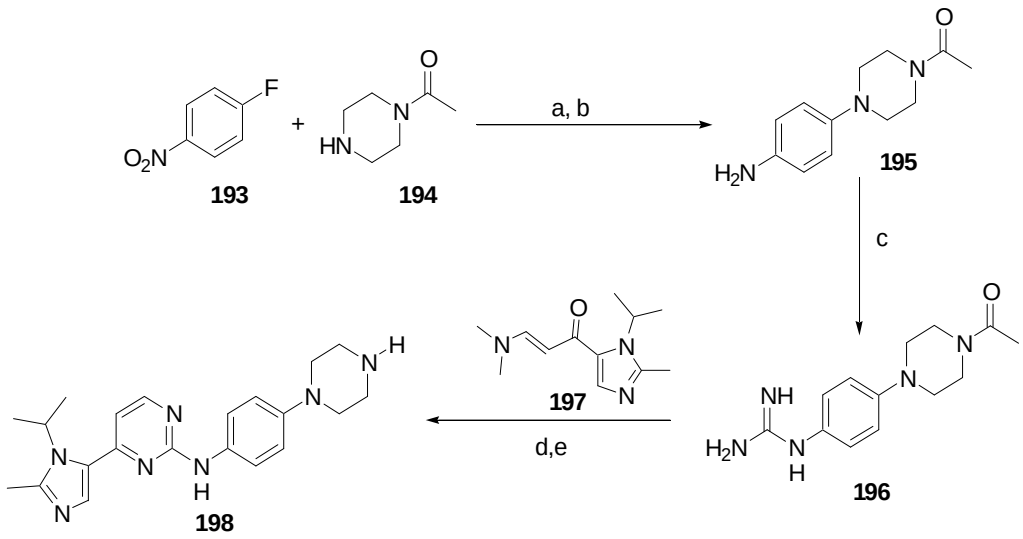
The synthesis started with dimerization of benzaldehyde in presence of NaCN to give benzoin **169**, oxidation of the **169** with $(CH_3COO)_2Cu$ and NH_4NO_3 gave benzyl **170**, cyclisation of **170** with 4-nitrobenzaldehyde and CH_3COONH_4 permitted the formation of 2-(4-nitrophenyl)-4,5-diphenyl-1*H*-imidazole **171** and N-methylation of the **171**with NaH and MeI gave 1-methyl-2-(4-nitrophenyl)-4,5-diphenyl-1*H*-imidazole **172**. Reduction of the **172** with Zn/HCl produced 1-methyl-2-(4-aminophenyl)-4,5-diphenyl-1*H*-imidazole **173**. 2-Chloro-N-[4-(1-methyl-4,5-diphenyl-1*H*-imidazole-2-yl)phenyl]acetamide**174** was prepared via acetylation of the **173** with chloroacetylchloride. At final step the **174** was reacted with appropriate thiol-(benz)azoles or corresponding piperazine derivatives to give 2-substituted-N-[4-(1-methyl-4,5-diphenyl-1*H*-imidazole-2-yl)phenyl]acetamide derivatives **175-191**(scheme 23).



Scheme 23 .Synthesis of 2-substitued-*N*-[4-(1-methyl-4,5-diphenyl-1*H*-imidazole-2-yl)phenyl]acetamide derivatives (173-191) Reagents and conditions; (a) NaCN,H_2O/EtOH, reflux 1 h; (b) $(CH_3COO)_2Cu$, NH_4NO_3, AcOH, reflux 2h; (c) 4-Nitrobenzaldehyde,CH_3COONH_4, AcOH, reflux 3h; (d) NaH/THF, rt, 15min; CH_3I reflux 3h; (e) Zn, EtOH/HCl, rt and then reflux 1h; (f) TEA,$ClCH_2COCl$, benzene, ice bath and then rt. 1h; (g) Appropriate thiol-(benz)azole, K_2CO_3, acetone, reflux 12h; (h) Corresponding 1-substituted piperazine, K_2CO_3, acetone, reflux 24h.

Anticancer agent cisplatin was used as a positive control. The **175, 179, 180** and **181**are the most cytotoxic compounds in the series. Specially the compounds **179**, **180**and**181**indicated significant anticancer activity against colon carcinoma cell line. These three compounds showed substantial cytotoxicity and caused DNA fragmentation of the HT-29 cells.

Finlay *et al*., (2008) reported obtaining of imidazole piperazines, the synthesis began with the coupling of4-fluoro-nitrobenzene**193** with 1-acetylpiperazine **194** under basic conditions. Following reduction of the nitro group, the resulting aniline **195** was reacted with cyanamide to produce guanidine **196** as the bicarbonate salt. Cyclisation with the known aminopropenone **197**followed by hydrolysis gave the piperazine **198** (scheme 24).

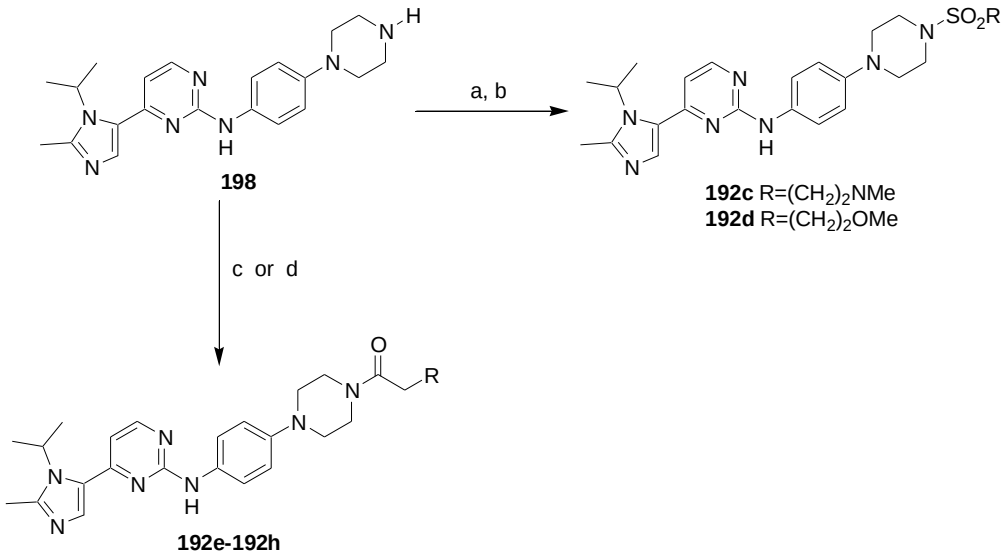


Scheme 24 . Synthesis of piperazine intermediate 198. Reaction conditions: (a) K_2CO_3, NMP, 120ºC, 2 h, (yield 80%); (b) H_2 gas, 10% Pd/C, EtOH, (yield 99%); (c) $NCNH_2$, HCl, Dioxane, EtOH, 90°C, 30 h, (yield 70%); (d) 2-Methoxyethanol, 110°C, (yield 75%); (e) concd. HCl, *iso*-propanol, (yield 28%).

Further reaction with 2-chloro-1-ethanesulfonyl chloride followed by *in situ* elimination gave the vinyl sulfonamide.

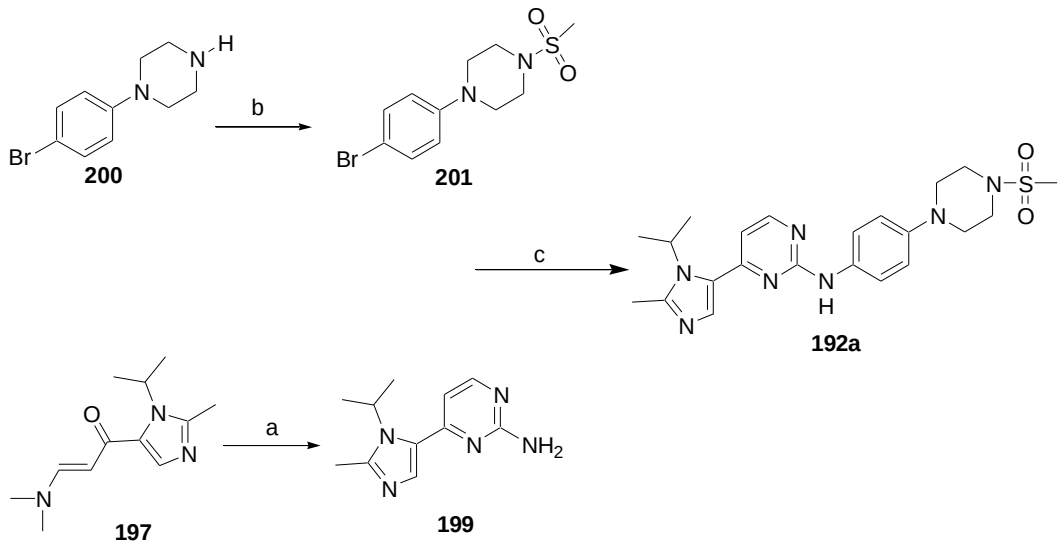
This could undergo conjugate addition with both sodium methoxide and dimethylamine to give **192c** and **192d**, respectively.

The compounds **192e** and **192f** were obtained by coupling with activated carboxylic acids (e.g., glycolic acid or *S*-lactic acid) leading to amides **192e**and **192f**.Basic amides (**192g** and**192h**) were accessed by reaction with chloro-acetyl chloride followed by displacement with dimethylamine or diethylamine(scheme 25, table 5).



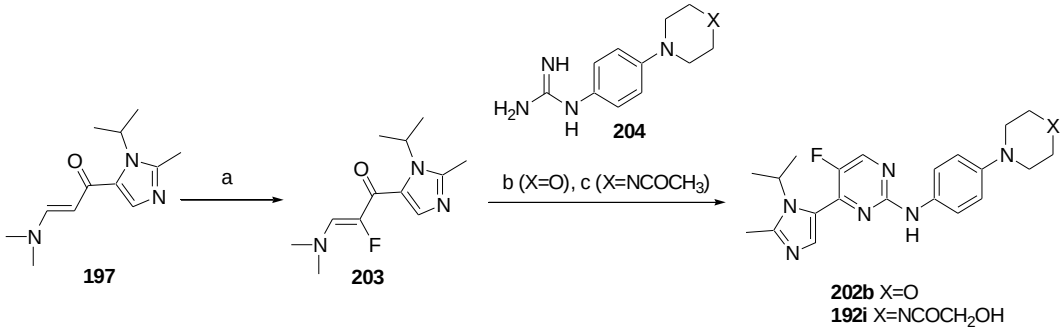
Scheme 25 . Synthesis of piperazine amides and sulfonamides 192. Reaction conditions: (a) $ClSO_2CH_2CH_2Cl$, Et_3N, CH_2Cl_2, (yield 31%); (b) NMe_2, THF (yield 80%) or NaOMe, Methanol (yield 28%); (c) Carboxylic acid, HATU, DIPEA, DMF (yield 20-95%); (d) i-chloroacetyl chloride, *i*-Pr_2EtN, CH_2Cl_2, (yield 87%); ii-amine, THF, (yield 80-90%).

Methyl sulfonamide **192a** was prepared in a slightly different way as shown in scheme 26. Reaction of guanidine with aminopropenone **197**gave the amino pyrimidine **199**. Buchwald coupling with bromocompound **201** (derived from sulfonylation of commercialpiperazine **200**) then provided the required compound**192a**.



Scheme 26 . Synthesis of piperazine 192a. Reaction conditions: (a) Guanidine hydrochloride, NaOMe, Butanol, reflux, (yield 40%); (b) $MeSO_2Cl$, CH_2Cl_2, (yield 80%); (c) $Pd_2(DBA)_3$, 2-(ditertbutylphosphino)biphenyl, NaO*t*-Bu, 1,4-dioxane (yield 15%).

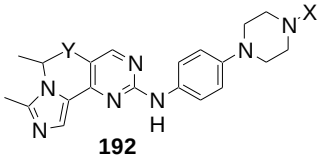
Fluorination of **197** was achieved using select fluor in ACN to give the product **203** as a golden crystalline solid. The compounds**202b** and **192i** were obtained by cyclisation of **203** and guanidine derivative **204**(scheme 27).



Scheme 27 .Synthesis of 5-fluoropiperazines and morpholines 192i and 202b. Reagents and conditions: (a) Selectfluor, MeCN, (yield 52%); (b) 2-methoxyethanol, 110ºC, (yield 85%); (c) i-2-methoxyethanol, 110ºC, (yield 83%); ii-IPA, concd HCl, 85ºC, (yield 91%); iii-acetoxyacetyl chloride, Et_3N, CH_2Cl_2, rt then 20% NH_3 in MeOH, rt, (yield 81% over two steps).

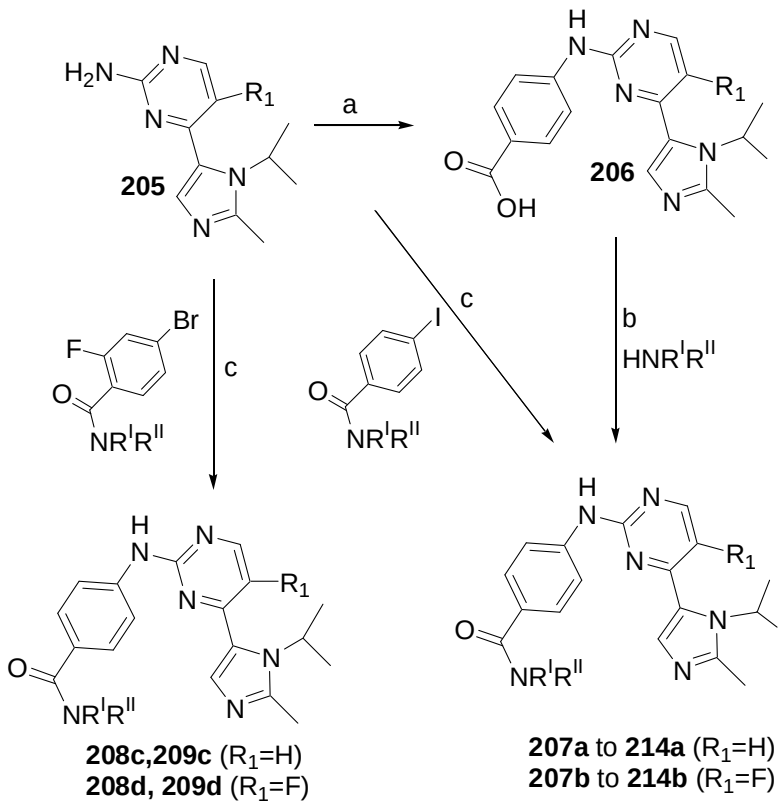
Piperazines **192e** and **192i** were subsequently shown to inhibit tumour growth when dosed orally in a nude mouse xenograft study.

Table 5 Structures for piperazines 192

	compd	X	Y
 **192**	**192c**	$SO_2(CH_2)_2NMe_2$	H
	192d	$SO_2(CH_2)_2OMe_2$	H
	192e	$COCH_2OH$	H
	192f	$COCH(S\text{-}CH_3)OH$	H
	192g	$COCH_2NMe_2$	H
	192h	$COCH_2NEt_2$	H
	192i	$COCH_2OH$	F

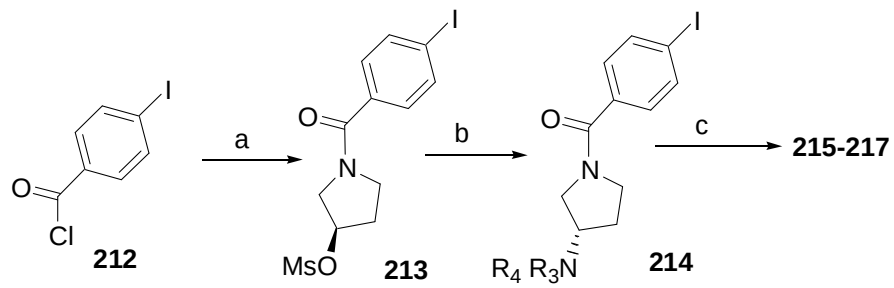
Jones *et al*., (2008) described the synthesis of novel series of imidazole pyrimidine amides, the route developed to obtain these compounds is shown in scheme 28. Palladium catalysed coupling with ethyl 4-iodobenzoate followed by hydrolysis gave the corresponding acids **206**. These acid intermediates were subject to late stage diversification by coupling with amines to give the amides (**207a-214a** and**207b-214b**).

Alternatively, for larger scale work it proved more convenient to couple the 4-iodoarylamides directly with the aminopyrimidines **205** using palladium catalysis (scheme 28). The 4-iodoarylamides were readily obtained by reaction of the required amine with 4-iodobenzoyl chloride. Similar routes using 4-bromo-2-fluoroarylamides were used to obtain the ortho-fluoro substituted amides (**208c**,**d** and**209c**,**d,** table 6**)**.



Scheme 28 . Synthesis of imidazole amides. Reaction conditions: (a) 1) ethyl-4-iodobenzoate, $Pd(OAc)_2$, Xantphos, Cs_2CO_3, 1,4-dioxane, (yield 32-67%); 2) NaOH, THF/water, (yield 94%); (b) HATU, DIPEA, DMF, (yield 49%); (c) $Pd(OAc)_2$, Xantphos, Cs_2CO_3, 1,4-dioxane, (yield 34-78%).

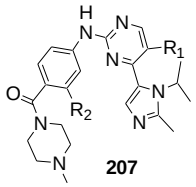
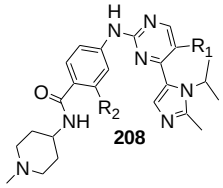
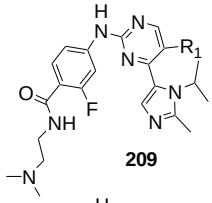
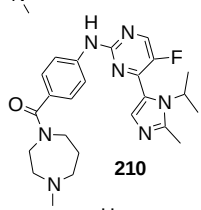
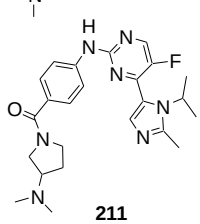
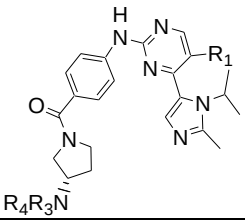
The 4-bromo-2-fluoroarylamides were obtained by reacting the corresponding acid under standard amide coupling conditions (HATU, NEt_3, DMF) with the requisite amine. For the compounds **215-217** the commercially available (*R*)-3-hydroxypyrrolidine was used and it was coupled with 4-iodobenzoyl chloride **212** then activated as the methanesulfonyl ester **213**. Displacementwith inversion of stereochemistry occurred smoothly with a range of primary and secondary amines to give the (*S*)-4-iodoarylamide coupling partners **214**. Subsequent coupling with the appropriate aminopyrimidine under Buchwald–Hartwig conditions, gave the chiral, non-racemic pyrrolidine products in good yield (scheme 29).



Scheme 29 . Synthesis of (*S*)-pyrrolidine imidazole amides 215-217. Reaction conditions: (a) (*R*)-3-hydroxypyrrolidine, Et_3N, CH_2Cl_2 then $MeSO_2Cl$, Et_3N, CH_2Cl_2 (yield 81% over 2 steps); (b) amine, 1,4-dioxane, sealed tube (yield 64-73%); (c) 205, $Pd(OAc)_2$, Xantphos, Cs_2CO_3, 1,4-dioxane, (yield 46-78%).

The imidazole pyrimidine amides possess excellent levels of anti-proliferative potency against cancer cell lines. A lead compound, (*S*)-q2 **217b** (AZD5597), was selected from the series for further development as a CDK inhibitor suitable for intravenous dosing.

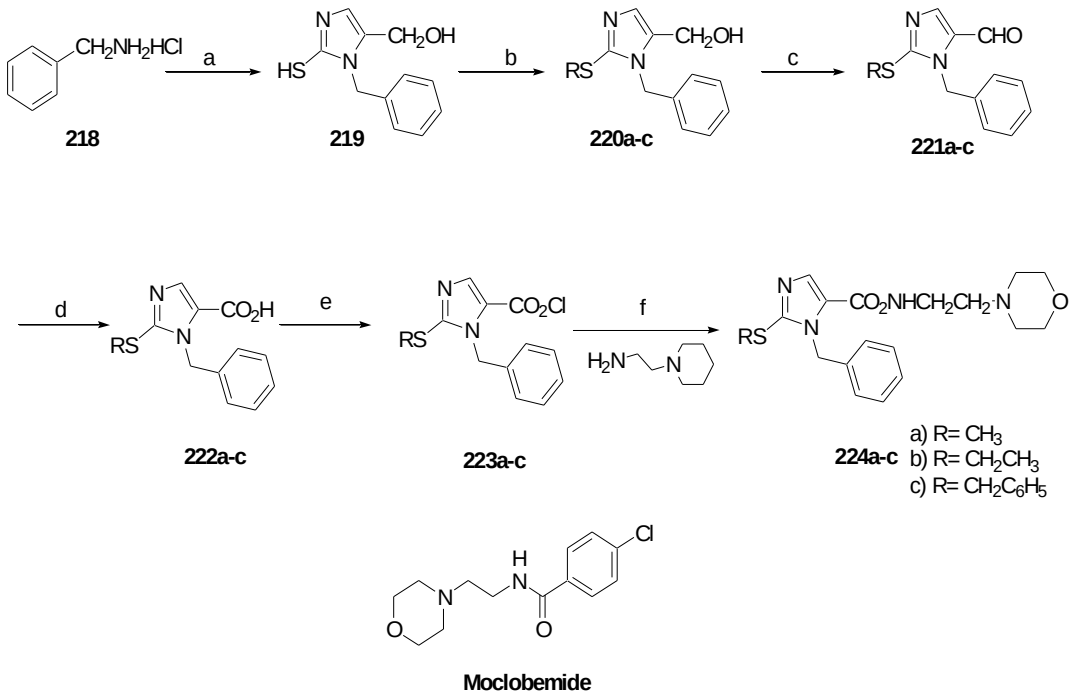
Table 6 Compounds 207-211 and 215, 216 and 217

	Compd	R_1	R_2	NR_3R_4
 **207**	**207a**	H		-
	207b	F	H	-
	208a	H	H	-
	208b	F	H	-
	208c	H	F	-
	208d	F	F	-
 **208**				
 **209**	**209c**	H	-	-
	209d	F		
	(*S*)-210b	F	-	-
	(*R*)-210b	F	-	-
	211b	F	-	-
 **210**				
 **211**				
	**(*S*)-215a**	H	-	NMe, *n*Pr
	(*S*)-216a	H	-	NH^{c}Pr
	(*S*)-217a	H	-	NHMe
	(*S*)-217b	F	-	NHMe

8. Imidazole with Antidepressant Activity

Hadizadeh *et al*.,(2008)reported the synthesis of *N*-Substituted Imidazole-5-Carboxamides.

Benzylamine hydrochloride **218** was stirred with 1, 3-dihydroxyacetone dimmer and potassium thiocyanate to give 5-hydroxymethyl-2-mercapto-1-benzylimidazole **219**. Subsequent alkylation of compound **219** with alkyl halides resulted in 2-alkylthio-1-benzyl-5-hydroxymethylimidazole **220**. Oxidation of **220** with manganese dioxide gave **221**, which was further oxidized by being boiled in alkaline solution of silver nitrate to give 2-alkylthio-1-benzylimidazole-5-carboxylic acid **222**. Compound **222**was converted to its acid halide **223**. 2-Morpholinoethylamie was added dropwise to a solution of **223** in dry THF (tetrahydrofuran) to give *N*-[2-(4-morpholinyl)ethyl)]-1-benzyl-2-(alkylthio)-1H-imidazole-5-carboxamides **224a-c** (scheme 30).



Scheme 30 . (a) DHA, KSCN (b) RX; (c) MnO_2; (d) NaOH,$AgNO_3$, (yield 68-90%); (e) $SOCl_2$, refluxed1 h; (f) THF

The analogs **224a-c** increased antidepressant potency and also toxicity with respect to standard antidepressant moclobemide.

9. Conclusion

Developed approaches have been amplified for the synthesis of different imidazole derivatives with important biological activities as antibacterial, anti-inflammatory, analgesic, antifulgal, antiparasitic, antiviral, anticancer, antidepressant, etc. The modifications in the substituents at 1, 2, 4 and 5 position of the basic imidazole nucleus results in the potent biological activities. The challengefor prospective research in this area of syntheticorganic chemistry involves the optimization of known procedureson the one hand, and the development of newuseful synthetic approaches on the other.

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