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Azolylimidazoles: Synthetic strategies and medicinal applications

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Abstract: The current review summarizes the known routes to different azoles linked directly to imidazole. This review is divided into classes based on the type of azoles connected to an imidazole ring. Some medical applications are mentioned.

Key words: Imidazoles, azoles, imidazolylthiazoles, imidazolylthiadiazoles, applications

1. Introduction

Imidazole and its derivatives are an important class of heterocycles. Medicinal properties of imidazole compounds include anticancer,[1] antimicrobial,[2–4] antibacterial,[5] antifungal,[6] and antioxidant activities.[7] Molecules having an imidazole ring linked directly to an azole ring find applications in different fields of science. For example, imidazolyl-thiazoles and triazoles have been proved to possess antibacterial, antifungal, antischistosomacidal, protozoacide, and schistosomacide activities.[8–10] Imidazolylpyrazolylvinylpyridine is useful as an inhibitor of ATP-protein kinase interactions.[11] Moreover, imidazolylthiadiazoles showed antibacterial, antifungal, and antiarrhythmic activities.[12,13] In addition, bis(indolyl)imidazole, known as topsentin, is a marine natural product and inhibited the proliferation of cultured human and murine tumor cells.[14–16] Also, indolylimidazoles are useful as an antidepressant,[17] and act as protein kinase C inhibitors.[18,19] As a continuation of our very recently published review article concerning the synthesis of biologically active heterocyclic systems,[20–23] we prepared this review to present for the reader a survey of the literature on different azoles linked directly with an imidazole nucleus. Some of the medicinal applications are also mentioned.

2. Pyrrolylimidazoles

The reaction of imidazo[4,5-*c*]isoxazole-6-carboxylate ester **1** with either acetylenic esters or ketones **2**, in boiling toluene or neat, involved the addition of 2 molecules of an alkyne followed by ring opening and fragmentation, leading to the formation of (2-pyrrol-2-yl)imidazoles **3** in 37%–62% yields (Scheme 1).[24]

2-Pyrrolyloxazolines **5** were readily obtained from 1-methyl-1*H*-pyrrole-2-carboxylic acid **4** by refluxing with thionyl chloride, followed by treatment with 2-amino-2-methylpropan-1-ol and finally reaction with thionyl chloride in boiling toluene. Quaternization of the oxazoline nitrogen followed by reaction with ethylene diamine in boiling acetonitrile gave 2-pyrrolylimidazole **7** in 87% yield. Moreover, oxazoline **5** can be converted directly to **7**, in 79%–92% yield, by refluxing with ethylene diamine and aceteonitrile (Scheme 2).[25,26]

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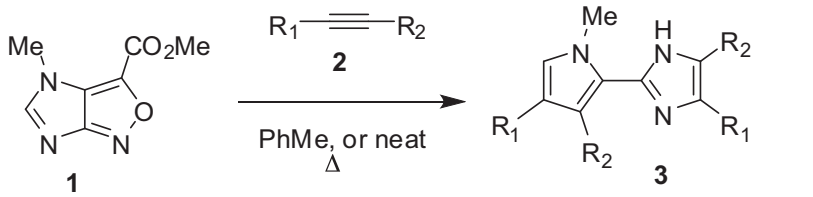
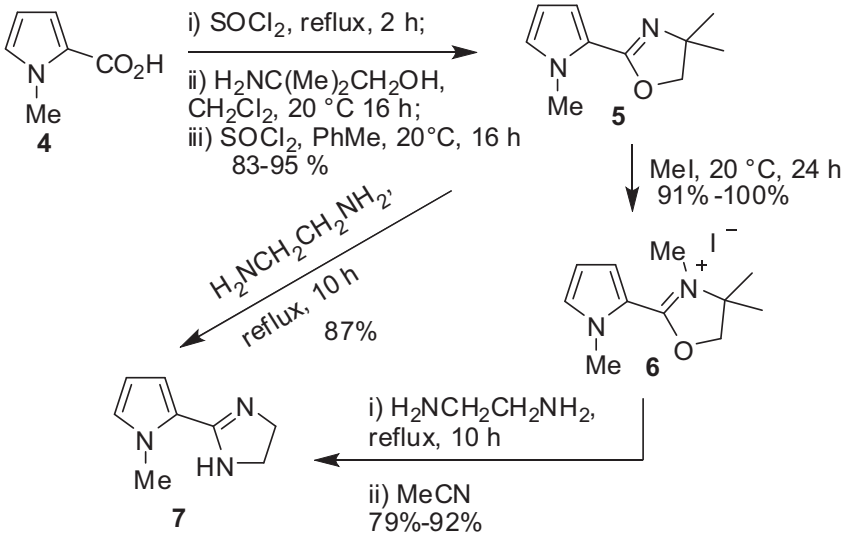


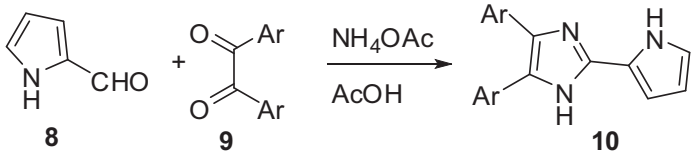
R_1	R_2	Yield %
CO_2Me	CO_2Me	62
CO_2Et	CO_2Et	37
CF_3	CO_2Et	51
COMe	COMe	40

Scheme 1



Scheme 2

The reaction of pyrrole-2-carbaldehyde **8** with benzil derivative **9** in acetic acid in the presence of ammonium acetate led to formation of pyrrolylimidazole **10** in high yield, which was useful as an inflammation inhibitor (Scheme 3).[27]

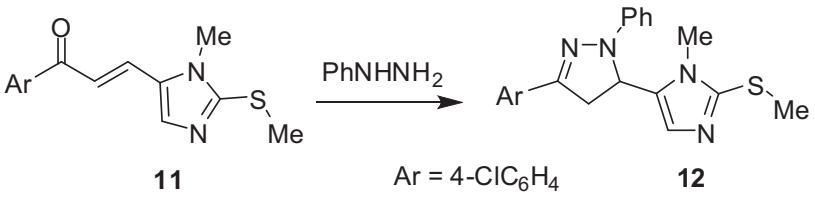


Ar = 4-$MeOC_6H_4$

Scheme 3

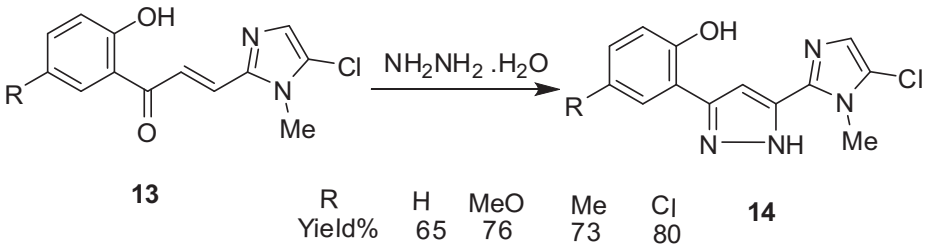
3. Imidazolylpyrazoles

Imidazolyl-2-pyrazoline derivative **12**, having antibacterial and antifungal activities, was prepared starting from chalcone **11** by reaction with phenylhydrazine (Scheme 4).[28]



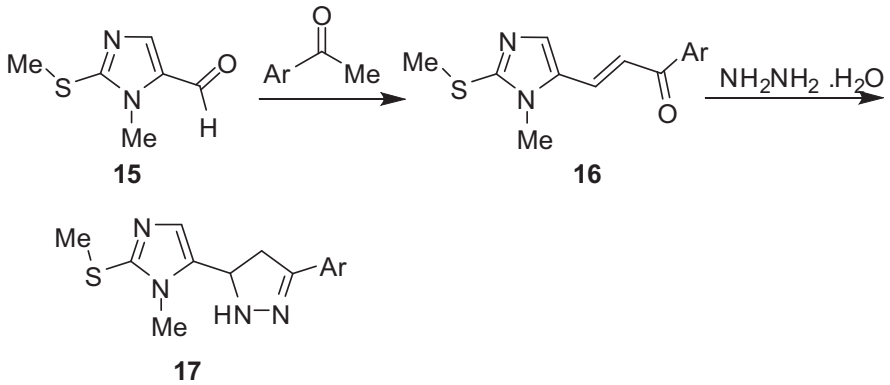
Scheme 4

In the same fashion, imidazolylpyrazoles **14** were prepared, in 65%–80% yields, by reaction of chalcone **13** with hydrazine hydrate in refluxing ethanol for 10–20 h followed by diluting with water (Scheme 5).[29,30]



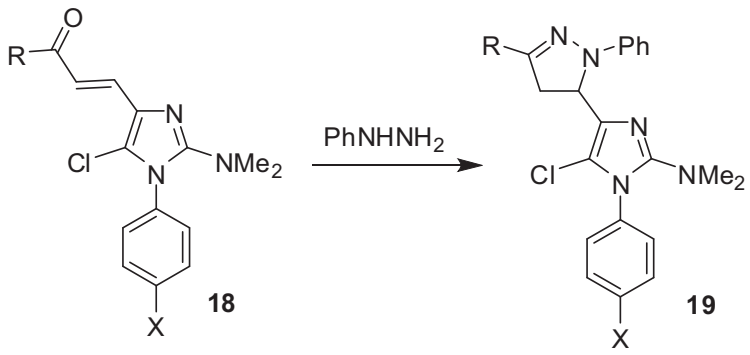
Scheme 5

5-Formyl-1-methyl-2-(methylthio)imidazole **15** reacted with methyl ketones followed by cyclocondensation of **16** with hydrazine hydrate gave imidazolyl-2-pyrazolines **17**, which have antimicrobial activity (Scheme 6).[28]



Scheme 6

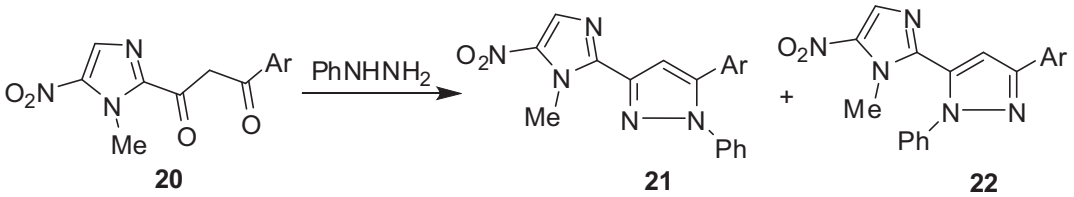
Similarly, imidazolylpyrazolines **19** were prepared by condensation of the corresponding imidazolepropenone**s** **18** with phenylhydrazine (Scheme 7).[31]



R = Ph, 4-BrC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-PhC_6H_4, 2-(5-(2-chlorophenyl)thienyl); X = H, F, Cl, Br

Scheme 7

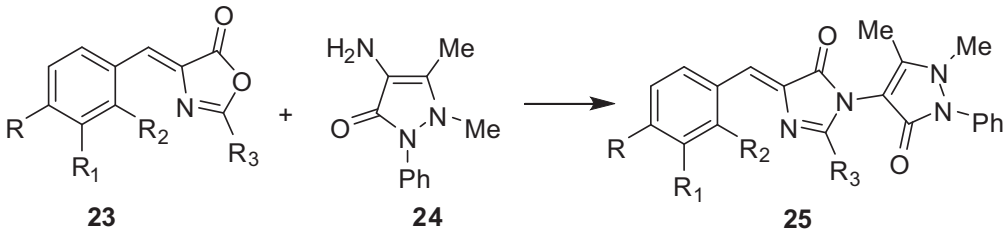
The reaction of β-diketones **20** with phenylhydrazine afforded 5-aryl-3-(1-methyl-5-nitro-2-imidazolyl)-1-phenylpyrazole **21** and 3-aryl-5-(1-methyl-5-nitro-2-imidazolyl)-1-phenylpyrazole **22** (Scheme 8).[32]



Ar = Ph, 4-$O_2NC_6H_4$, 4-BrC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$

Scheme 8

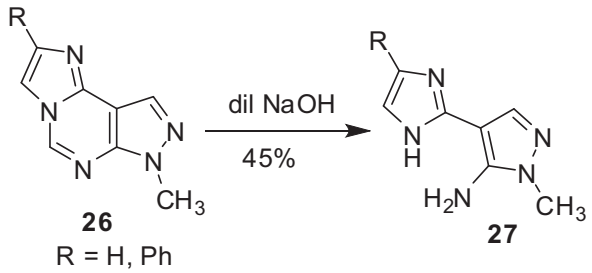
Benzylideneimidazolylpyrazolinone**s** **25**, as potential antimicrobial and acetylcholinesterase inhibitory agents, were prepared from the corresponding benzylideneoxazolones **23** and the aminopyrazolone **24** (Scheme 9).[33]



R = H, Cl, MeO; R_1 = H, MeO; R_2 = H, OH; R_3 = Me, Ph

Scheme 9

By treatment of imidazo[2,1-f]pyrazolo[3,4-d]pyrimidines **26** with diluted sodium hydroxide solution, ring opening took place at the 4-position and 5-amino-4-(imidazol-2-yl)- pyrazoles **27** were obtained in about 45% yields (Scheme 10).[34]

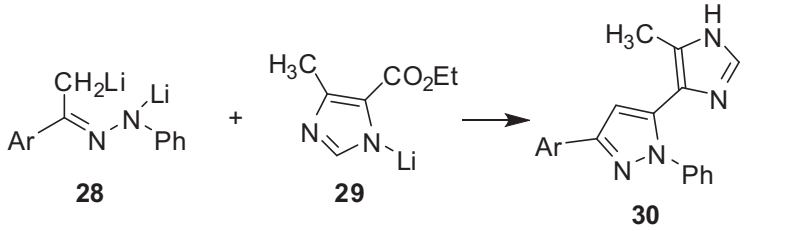


26
R = H, Ph

27

Scheme 10

The reaction of the C(α)-dianions with electrophilic-nucleophilic reagents has extended to the condensation of C(α)-dianions of phenylhydrazoxylate **28** (in the presence of an excess amount of LDA) with ethyl 4-methyl-5-imidazolecarboxylate **29** to give lithiated intermediate, which was cyclized to imidazolylpyrazoles **30** under acidic conditions (Scheme 11).[35]

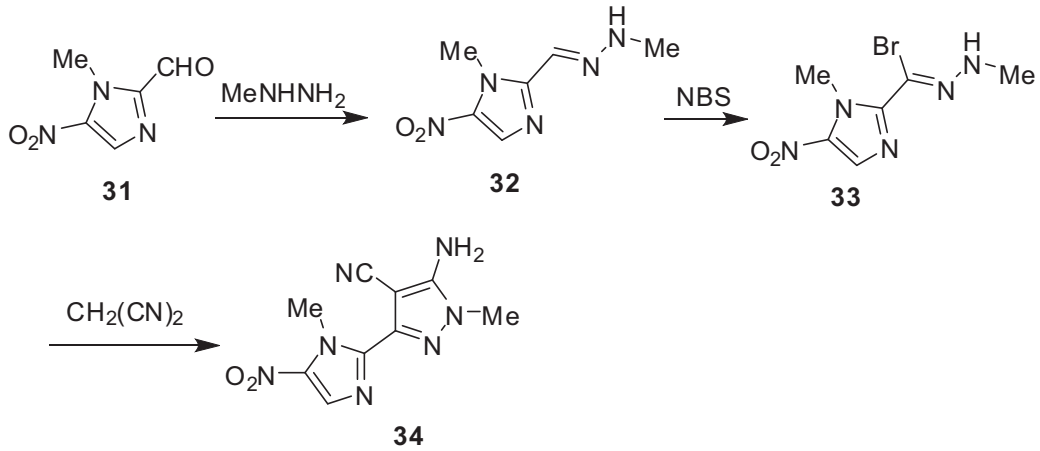


28 **29** **30**

Ar = Ph (20%)
Ar = 4-MeC$_6$H$_4$ (53%)

Scheme 11

The 1-methyl-5-nitro-1H-imidazole-2-carbaldehyde **31** was treated with methylhydrazine to give hydrazone **32**. Bromination of **32** using NBS and cyclization with malononitrile yield **34**, which is used as a bactericide, particularly in animal feeds (Scheme 12).[36]



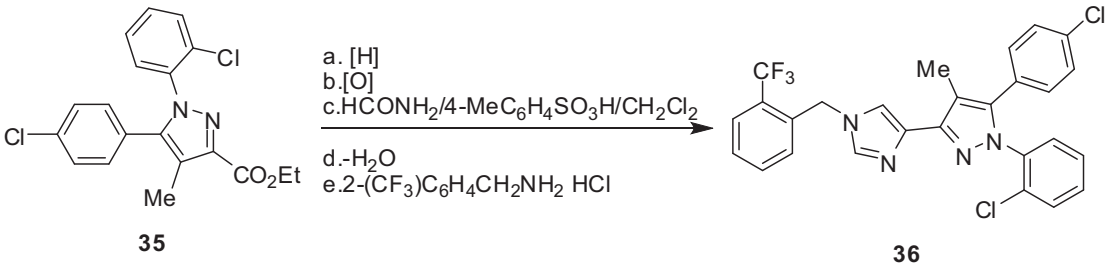
31 **32** **33**

34

Scheme 12

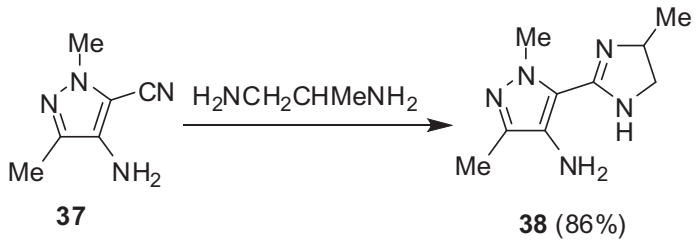
Imidazolylpyrazole hydrochloride **34**, used in the treatment of diseases linked to the modulation of cannabinoid receptors in animals, was prepared from 5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1 *H* -pyrazole-3-carboxylic acid ethyl ester **33**, via reduction with diisobutylaluminum hydride, then Swern oxidation with

oxalyl chloride/DMSO in dichloromethane, followed by reaction with formamide/4-methylbenzenesulfonic acid in dichloromethane containing chlorotrimethylsilane. Then the obtained product was dehydrated with $POCl_3$ in THF, and finally reacted with *o*-trifluoromethyl benzyl amine hydrochloride (Scheme 13).[37]



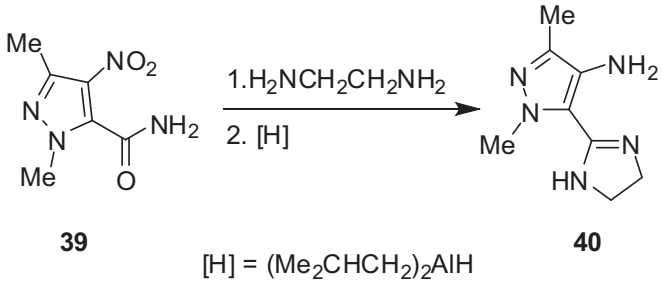
Scheme 13

Cyclocondensation of cyanopyrazole **37** with propane-1,2-diamine gave 1,3-dimethyl-5-(4-methyl-4,5-dihydro-1*H*-imidazol-2-yl)-1*H*-pyrazol-4-amine **38**, which was used as intermediate for the synthesis of the antipsychotic 1*H*-imidazo[1,2-*c*]pyrazolo[3,4-*e*]pyrimidines (Scheme 14).[38,39]



Scheme 14

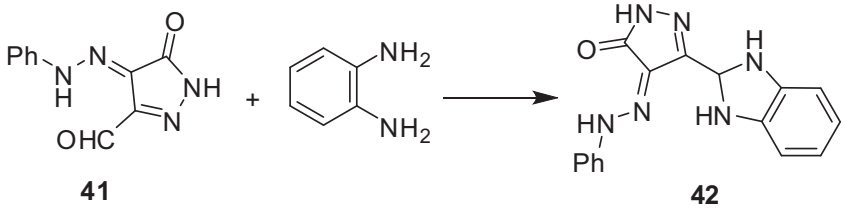
Treatment of 1,3-dimethyl-4-nitro-5-pyrazolecarboxamide **39** with ethane-1,2-diamine, followed by reduction using diisobutylaluminum hydride gave 2-(4-amino-1,3-dimethyl-5-pyrazolyl)imidazoline **40** (Scheme 15).[40]



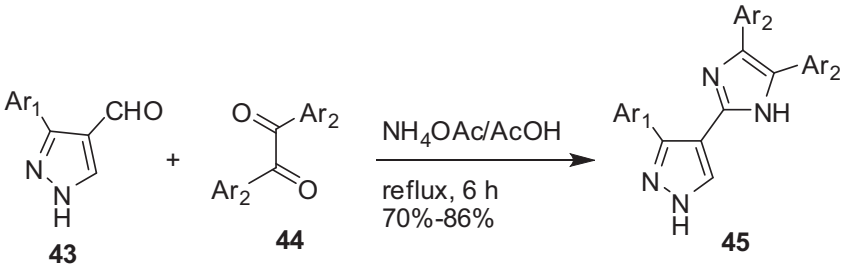
Scheme 15

Imidazole derivative **42** was prepared from 5-oxo-4-(2-phenylhydrazono)-4,5-dihydro-1*H*-pyrazole-3-carbaldehyde **41** in good yield by reaction with *o*-phenylene diamine (Scheme 16).[41]

Imidazolylpyrazoles **45** were obtained in excellent yields by refluxing a mixture of 3-substituted-1*H*-pyrazole-4-carbaldehydes **43**, 1,2-diketones **44**, and ammonium acetate in acetic acid via the Debus reaction (Scheme 17).[42]



Scheme 16

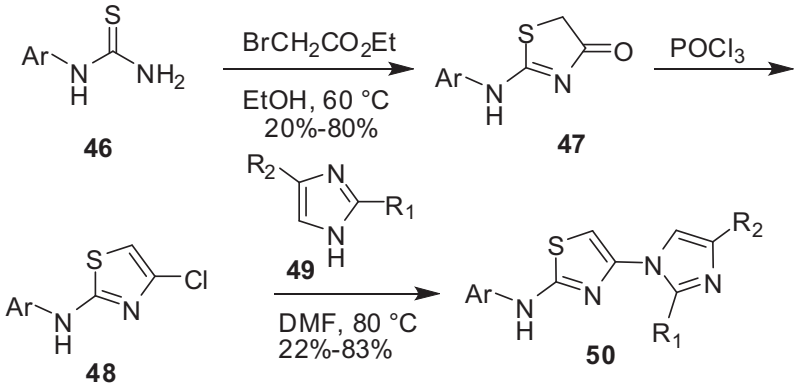


Ar_1 = 4-PhC_6H_4, 2,4-$Cl_2C_6H_3$, 2,5-$Cl_2C_6H_3$, 4-MeC_6H_4, 4-$MeSC_6H_4$;
Ar_2 = Ph, 4-BrC_6H_4

Scheme 17

4. Imidazolylthiazoles

Ring closure of arylthiourea derivatives **46** with ethyl bromoacetate followed by chlorination of the resulting 2-phenylaminothiazol-4-ones **47** with phosphorus oxychloride yielded (4-chlorothiazol-2-yl)phenylamines **48** as intermediates. The latter intermediate was transformed into [4-(imida-zol-1-yl)thiazol-2-yl]phenylamines **50**, in 22%–83% yields, by nucleophilic substitution using an excess amount of imidazoles **49** in the presence of base in DMF at 80 °C (Scheme 18). The obtained imidazolylthiazols **50** were used as potent colchicine site binding tubulin inhibitors.[43]

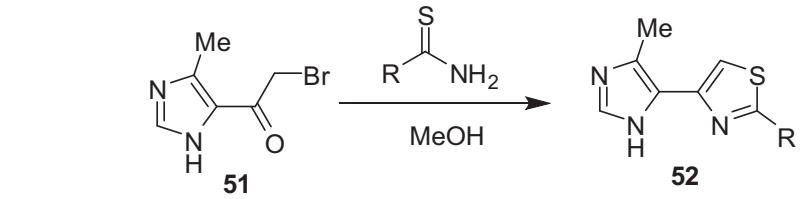


Ar = Ph, 4-BrC_6H_4, 4-$OMeC_6H_4$, 4-MeC_6H_4, 3-BrC_6H_4, 3-$OMeC_6H_4$

R_1 = R_2 = H, Me

Scheme 18

4-(4-Methyl-5-imidazolyl) thiazole **52** was prepared by the reaction of 4-methyl-5-bromoacetylimidazole **51** with either thioacetamide (R = Me) or thiourea (R = NH_2) in refluxing methanol (Scheme 19).[44]

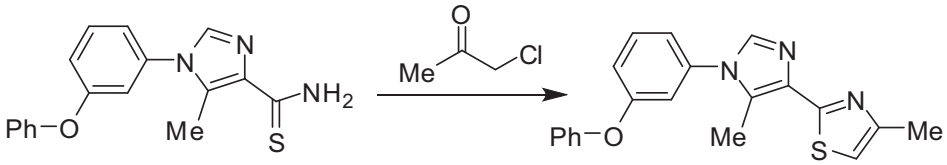


51 **52**

R = Me, NH_2

Scheme 19

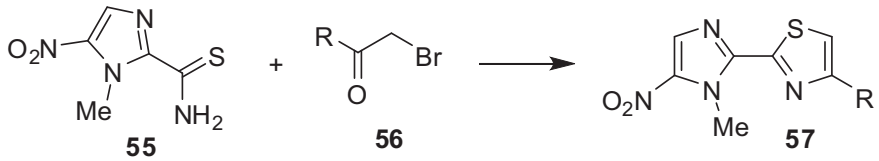
5-Methyl-1-(3-phenoxymethyl)imidazole-4-thiocarboxamide **53** was refluxed with chloroacetone for 13 h to give 4-(4-methylthiazol-2-yl)-5-methyl-1-(3-phenoxyphenyl)imidazole **54**, which acts as a benzodiazepine receptor ligand (Scheme 20).[45]



53 **54**

Scheme 20

2-(1-Methyl-5-nitro-2-imidazolyl)thiazoles **57**, with amebicidal, bactericidal, fungicidal, and trichomonacidal activities, were prepared by cyclocondensation of α-bromoketones **56** with 5-nitro-2-imidazolethiocarboxamide **55** in refluxing protic solvent (Scheme 21).[46]

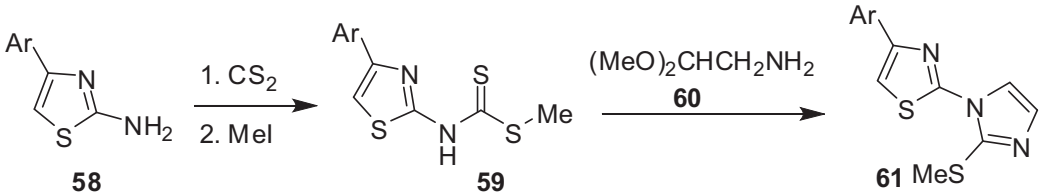


55 **56** **57**

R = Me, EtO_2C

Scheme 21

2-Amino-4-arylthiazoles **58** were reacted with carbon disulfide and then with methyl iodide to give **59**, which underwent cyclocondensation with 2,2-dimethoxyethanamine **60** to give thiazolyl(methylthio)imidazoles **61** (Scheme 22).[47]

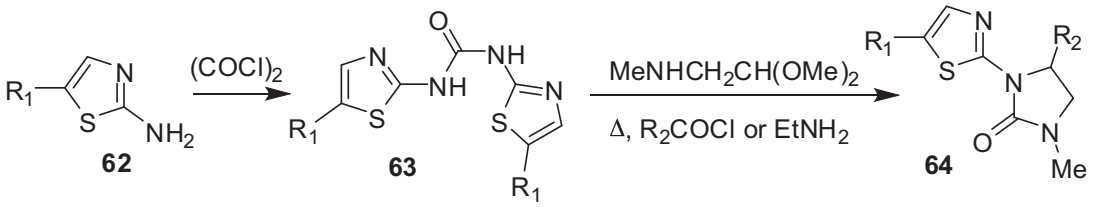


58 **59** **61**

Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 2-MeC_6H_4

Scheme 22

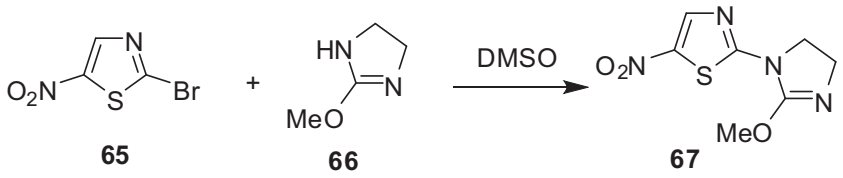
Herbicidal thiazolylimidazolones **64** were prepared by treatment of 2-amino-5-substituted thiazoles **62** with phosgene, which gave 1,3-di(thiazol-2-yl)urea **63**. Reaction of the latter with 2,2-dimethoxy-*N*-methylethanamine followed by cyclization under thermal conditions and acylation afforded **64** (Scheme 23).[48–51]



R_1 = Me, Br; R_2 = 2-furyl-CO_2, $PhOCH_2CO_2$, 3-pyridyl-CO_2, EtNH

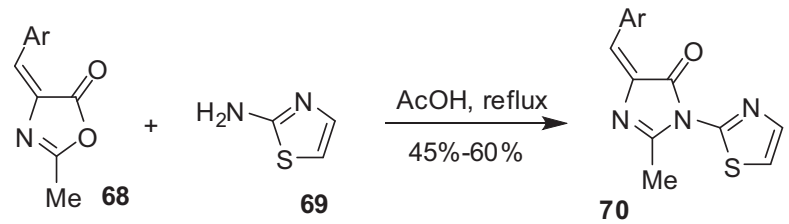
Scheme 23

1-(5-Nitro-2-thiazolyl)-Δ^2-imidazoline derivative **67**, used as schistosomacides, protozoacides, and bactericides, were prepared by the reaction of 2-bromo-5-nitrothiazole **65** with 2-methoxy-2-imidazoline **66** in DMSO (Scheme 24).[52]



Scheme 24

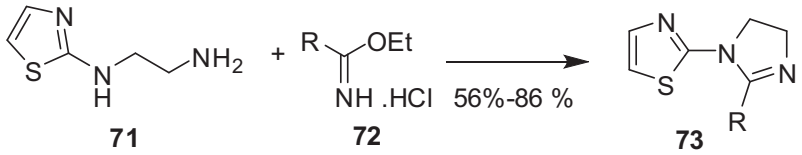
1-(Thiazol-2-yl)-2-methyl-4-(substituted benzylidene)-5-imidazolones **70** were obtained in 45%–60% yield by treatment of the corresponding oxazolones **68** with 2-amino-1,3-thiazole **69** in refluxing galacial acetic acid (Scheme 25).[53]



Ar = 3,4-$Cl_2C_6H_3$, 2,4-$Cl_2C_6H_3$, 2-O_2N-3,4-$(MeO)_2C_6H_2$, 4-ClC_6H_4,
Ph, 3,4-methylenedioxyphenyl, 2-$MeOC_6H_4$, 4-Cl-2-$(MeO)C_6H_3$, 2,4-$(MeO)_2C_6H_3$

Scheme 25

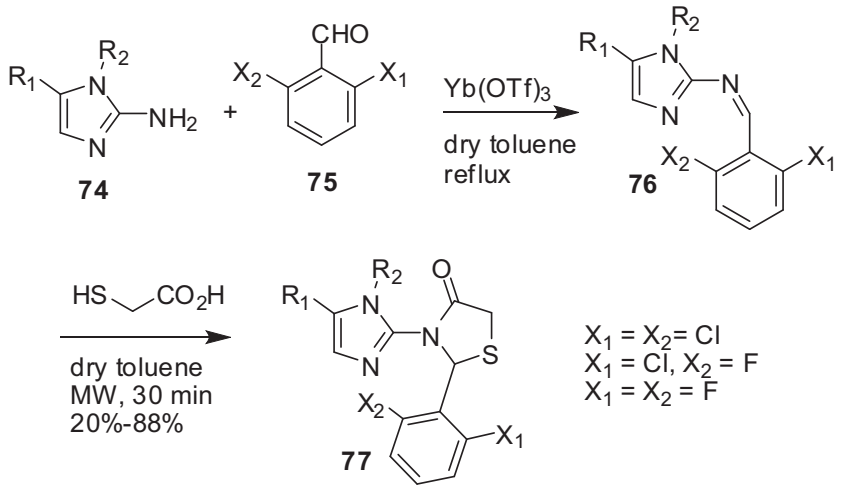
Thiazolylimidazolines **73** were prepared by reaction of *N*-(4-phenylthiazol-2-yl)- ethylenediamine **71** with ethyl alkimidate hydrochloride **72** in 56%–86% yields (Scheme 26).[54]



R = Me, Ph, benzyl, 5-nitrofur-2-yl

Scheme 26

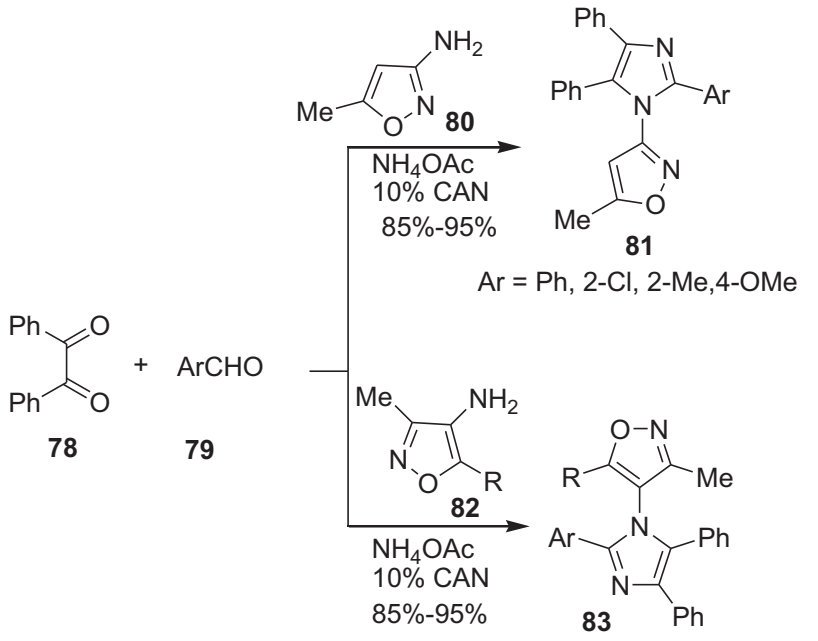
Microwave-assisted synthesis of a novel class of imidazolylthiazolidin-4-ones has been reported, in 2 steps, by reacting a mixture of 5-phenyl-1*H*-imidazol-2-amine **74** and 2,5-disubstituted benzaldehyde **75** in dry toluene using 5 mol% of $Yb(OTf)_3$ as catalyst, followed by reaction with mercaptoacetic acid under microwave irradiation (Scheme 27).[55]



Scheme 27

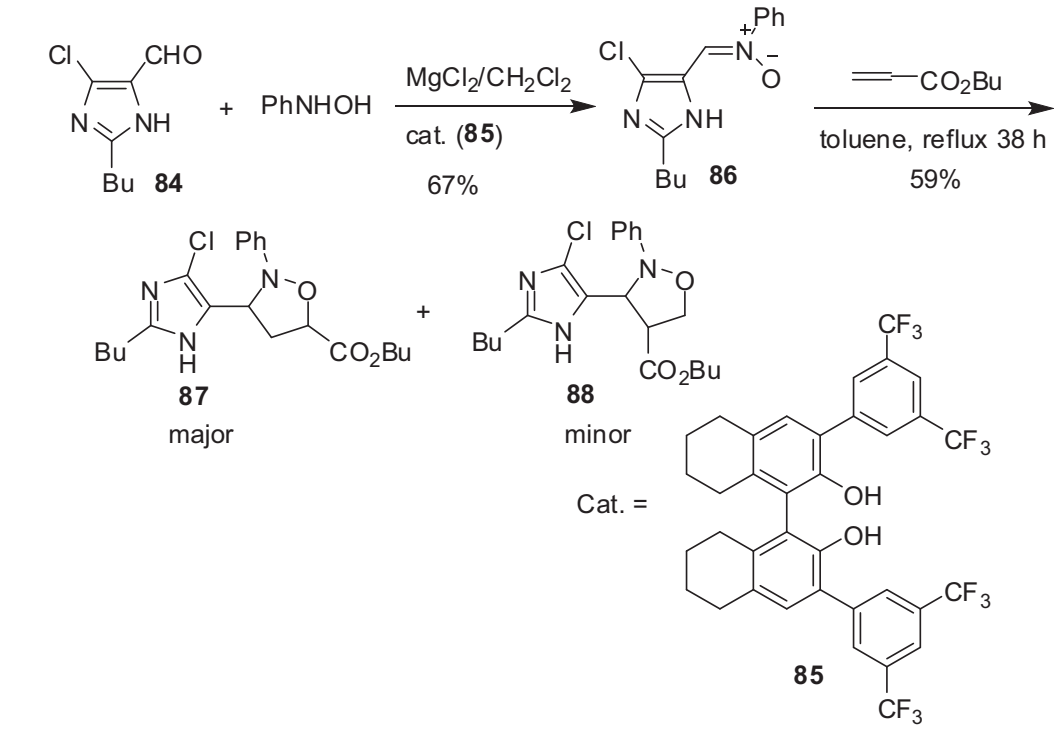
5. Imidazolylisoxazoles

Ceric ammonium nitrate (CAN) acted as an efficient catalyst for the synthesis of 1-(1*H*-imidazol-4-yl)isoxazoles **81** and **83** in a 4-component 1-pot condensation of benzil **78**; aromatic aldehydes **79**; isoxazolamines **80**, **82**; and ammonium acetate, respectively (Scheme 28).[56,57]



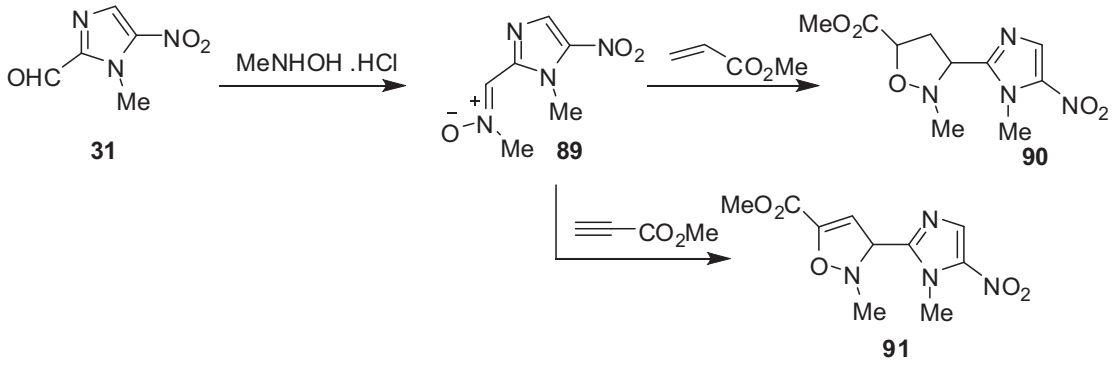
Scheme 28

2-(Phenyl)-3-(2-butyl-4-chloro-1*H*-imidazolyl)-5-butylate isoxazolidine **87** was synthesized by the condensation of *E*− isomer of nitrone **86** with butyl acrylate in an inert solvent. The condensation of *N*-phenylhydroxylamine with aldehyde **84** in the presence of Brønsted acid catalyst **85** yielded *E*− isomer of nitrone **86**. The 1,3-dipolar cycloaddition of nitrone **86** with butyl acrylate gave a mixture of regioisomers, **87** and **88**. The major isomer **87** was separated by column chromatography on silica gel (Scheme 29).[15,58]



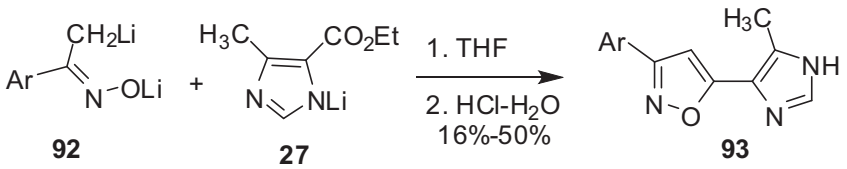
Scheme 29

1-Methyl-5-nitro-1*H*-imidazole-2-carbaldehyde **31** was treated with *N*-methylhydroxylamine hydrochloride to afforded nitrone **89**, which was transformed into **90** and **91** when treated with methyl acrylate and methyl propiolate, respectively (Scheme 30).[59]



Scheme 30

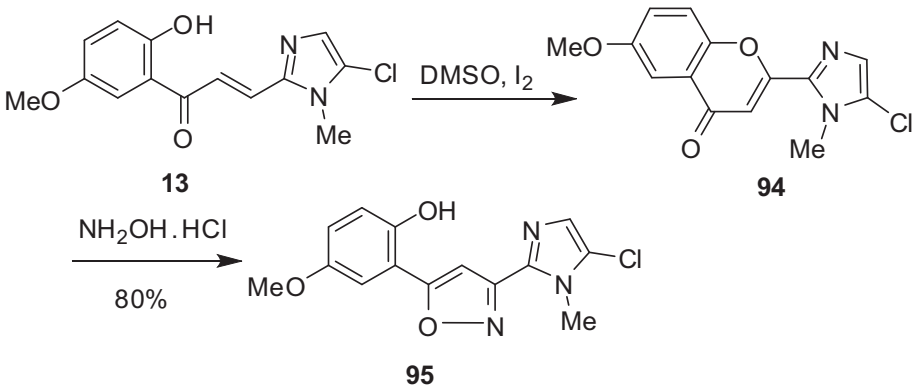
Imidazolylisoxazoles **93** were prepared by reaction of C(α)-dianions of oximes 92 with electrophilic-nucleophilic reagent ethyl 4-methyl-5-imidazolcarboxylate **27** in the presence of an excess amount of LDA (Scheme 31).[35,60]



Ar = 4-$CH_3C_6H_4$, 4-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_3$

Scheme 31

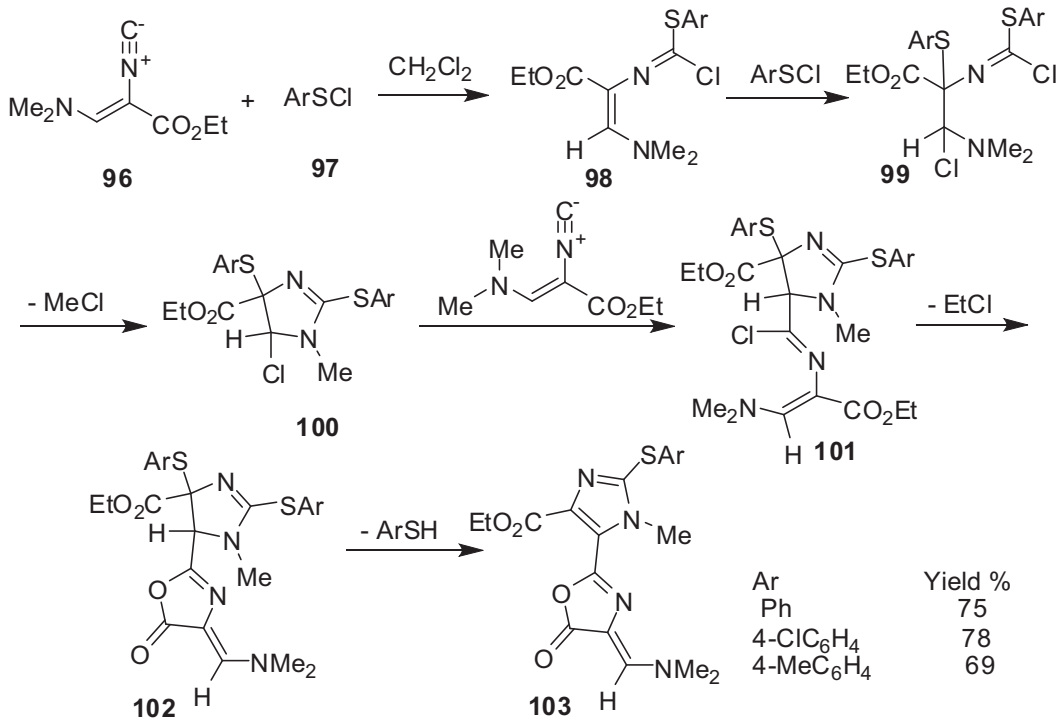
2-Hydroxychalcone **13** underwent oxidative cyclization in treatment with I_2 in refluxing DMSO to produce flavonones **94**. The reaction of **94** with hydroxylamine hydrochloride gave the imidazolylisoxazole **95** in 80% yield (Scheme 32).[29,61]



Scheme 32

6. Oxazolylimidazoles

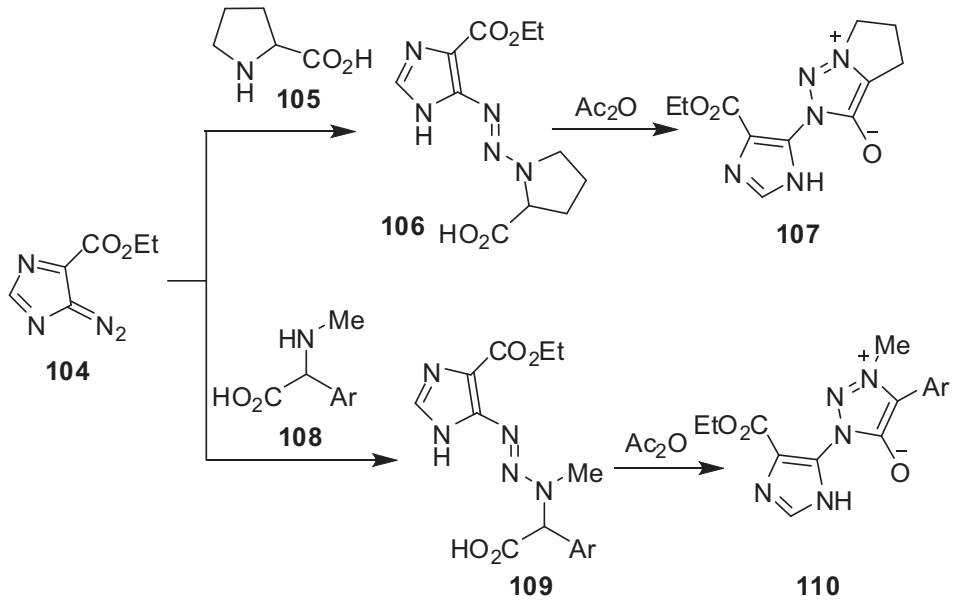
The reaction between ethyl (*Z*)-3-dimethylamino-2-isocyanoacrylate **96** and arenesulfenyl chlorides **97** gave (oxazolidinyl)imidazolecarboxylates **103** in 69%–78% yields via the intermediates **98**–**102** (Scheme 33).[62]



Scheme 33

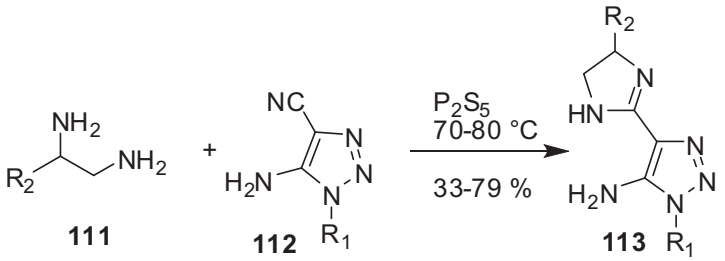
7. Imidazolyltriazoles

Imidazolyl-1,2,3-triazolio-5-olates **107** or **110** were obtained in about 80% yield by the reaction of ethyl 4-diazo-4*H*-imidazole-5-carboxylate **104** with proline **105** or *p*-tolyl-*N*-methylglycine **108** followed by the reaction of the obtained **106** or **109** with acetic anhydride, respectively (Scheme 34).[63]



Scheme 34

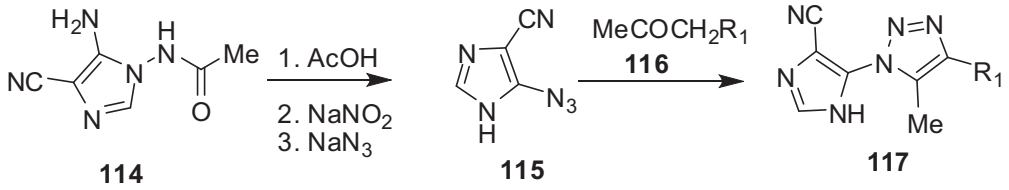
Imidazolyltriazoles **113** were prepared by cyclocondensation reaction of 4-amino-5-cyanotriazoles **112** with diamines **111** in the presence of P_2S_5 as catalyst (Scheme 35).[64]



R_1 = $PhCH_2$, 4-$ClC_6H_4CH_2$, 2,4-$Cl_2C_6H_3CH_2$, R_2 = H, Me

Scheme 35

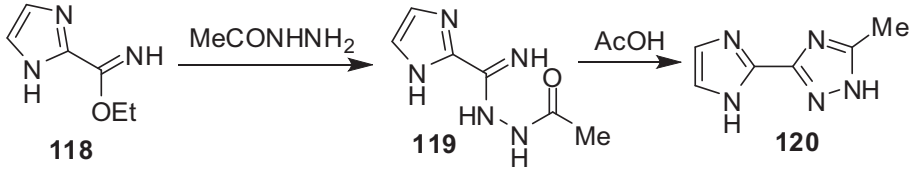
Diazotization of 1-acetamido-5-amino-4-cyanoimidazole **114** using sodium nitrite in aqueous acetic acid followed by reaction with sodium azide gave 5-azido-4-cyanoimidazole **115** in 94% yield. Reaction of **115** with active methylene compounds **116** in the presence of a base led to imidazolyltriazoles **117** (Scheme 36).[65]



R_1 = COMe, COPh,CO_2Et

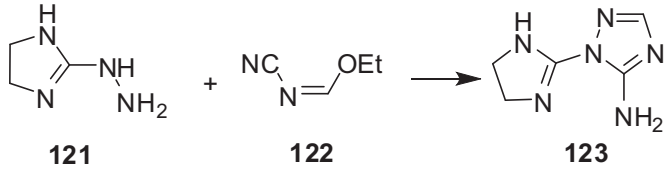
Scheme 36

The imidazolyltriazole **120** was prepared by treatment of ethyl 1*H*-imidazole-2-carbimidate **118** with acetohydrazide to give **119**, which was then cyclized in acetic acid (Scheme 37).[66]



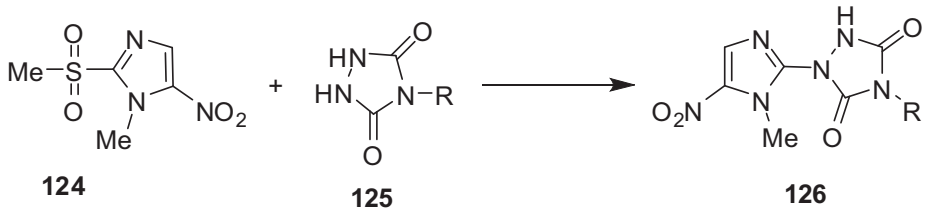
Scheme 37

The reaction of 2-hydrazino-2-imidazoline **121** with ethyl *N*-cyanoformimidate **122** gave triazoleamine derivative **123** (Scheme 38).[67]



Scheme 38

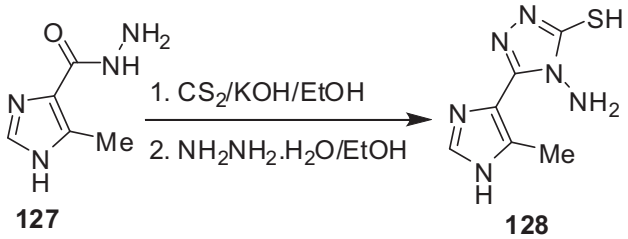
Condensation of 1-methyl-2-methylsulfonyl-5-(nitro)imidazole **124** with the sodium salts of triazolidinediones **125** gave the imidazolyltriazolidinediones **126** (Scheme 39).[68]



R = Me, Et, allyl,Pr, Bu, 3,4,5-$(MeO)_3C_6H_2$, PhCH=CH, $PhCH_2CH_2$, 2-phenylcyclopropyl

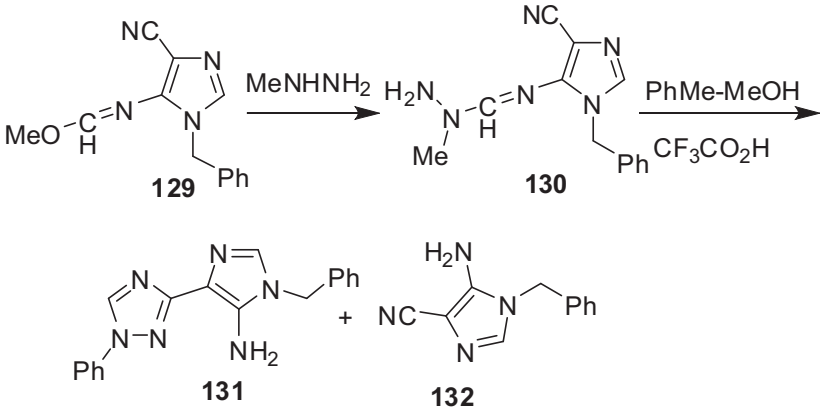
Scheme 39

The synthesis of substituted 4*H*-1,2,4-triazole **128** from 5(4)-methyl-1(3)*H*-imidazole-4(5)-carboxylic acid hydrazide **127** was reported via reaction with carbon disulfide followed by hydrazine hydrate (Scheme 40).[69]



Scheme 40

Reaction of imidazole **129** with methyl hydrazine gave **130**. Thermolysis of **130** in refluxing PhMe-MeOH containing trifluroactic acid gave an equimolar mixture of 5-amino-1-benzyl-4-cyanoimidazole **131** and triazole **132** (Scheme 41).[70]

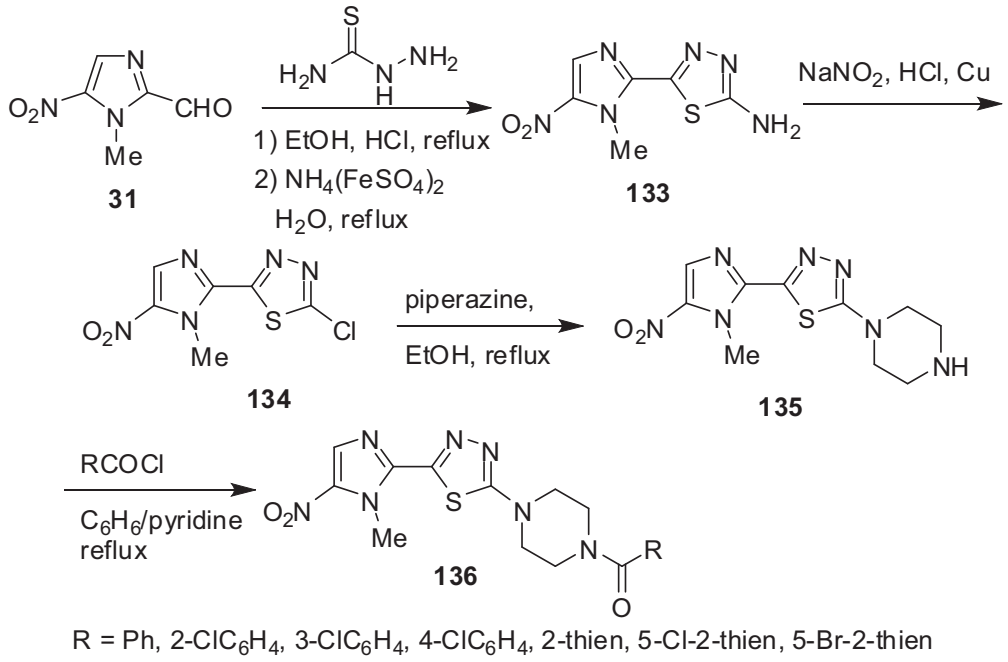


Scheme 41

8. Imidazolylthiadiazoles

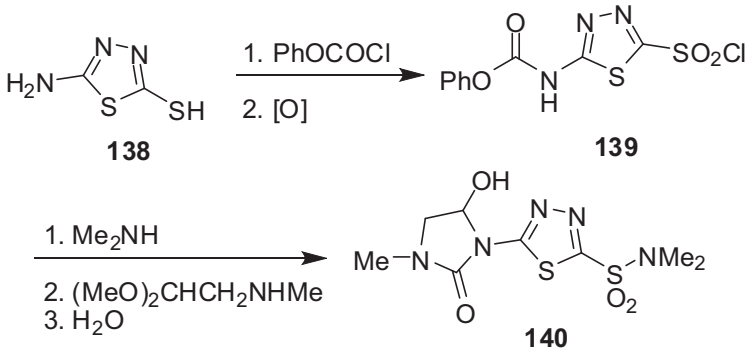
2-Chloro-1,3,4-thiadiazole **134** was obtained from 1-methyl-5-nitroimidazole-5-carbaldehyde **31** by reacting with thiosemicarbazide in the presence of HCl to afford the corresponding thiosemicarbazone, which upon cyclization

with ammonium ferric sulfate gave 2-amino-1,3,4-thiadiazole **133** followed by diazotization of amine **133** in HCl solution, in the presence of copper powder. The reaction of compound **134** with piperazine in refluxing ethanol gave *N*-piperazinyl compound **135**. *N*-Aroylation of the piperazine **135** with appropriate benzoyl chlorides or thiophen-2-carbonyl chlorides afforded **136** in 77%–85% yields, which are useful as anti-leishmanial agents (Scheme 42).[71]



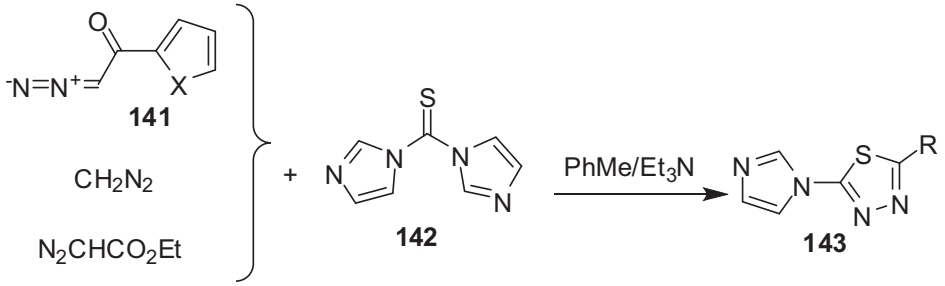
Scheme 42

Thiol **138** was treated with phenylchloroformate and then oxidized to give **139**, which was aminated with dimethyl amine and treated with 2,2-dimethoxy-*N*-methylethanamine and then hydrolysis of the acetal group was followed by cyclization to give **140**, which is useful as a herbicide (Scheme 43).[72]



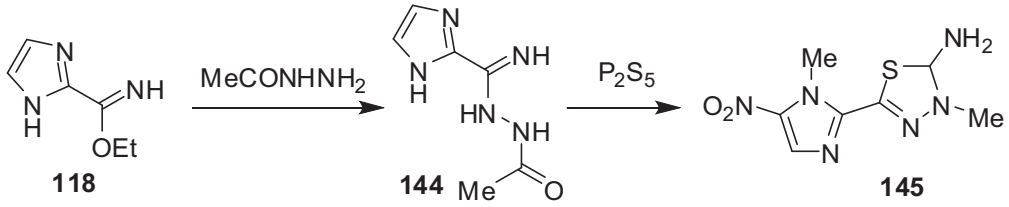
Scheme 43

5-Substituted 2-(1-imidazolyl)-1,3,4-thiadiazoles **143** were prepared in 30%–74% yield by treating *N*,*N*'-(thiocarbonyl)diimidazole **142** in dry toluene with an equimolar amount of diazomethane, diazoethyl acetate, 2-furyl diazomethyl ketone, or 2-thienyl diazomethyl ketone **141** in the presence of triethyl amine (Scheme 44).[73–76]



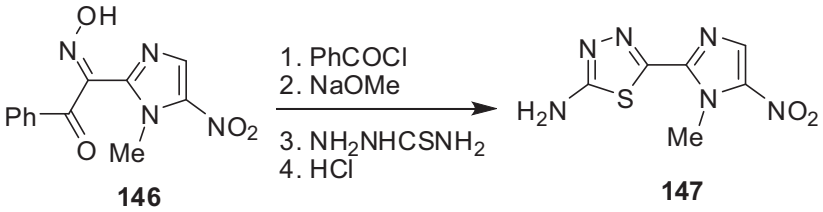
Scheme 44

The synthesis of 3-methyl-5-(1-methyl-5-nitro-1*H*-imidazol-2-yl)-2,3-dihydro-1,3,4-thiadiazol-2-amine **145** was conducted by treating ethyl 1*H*-imidazole-2-carbimidate **118** with acetohydrazide to give **144**, followed by cyclization with P_2S_5 (Scheme 45).[77]



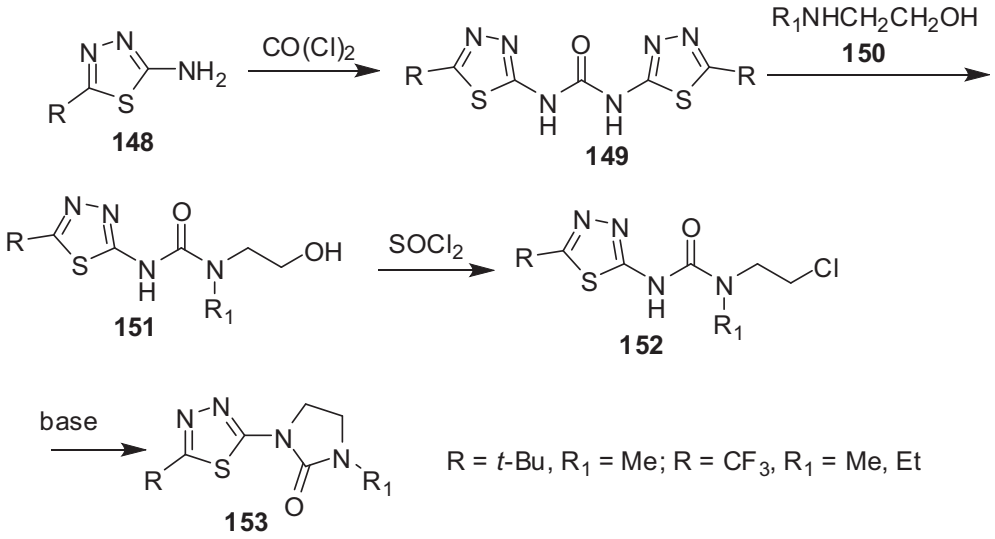
Scheme 45

2-Amino-5-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole **147** was prepared by treatment of 1-oximino-1-(1-methyl-5-nitro-2-imidazolyl)-2-phenylglyoxal **146** with benzoyl chloride, followed by treatment with sodium methoxide and thiosemicarbazide and cyclization of the intermediate with HCl (Scheme 46).[78]



Scheme 46

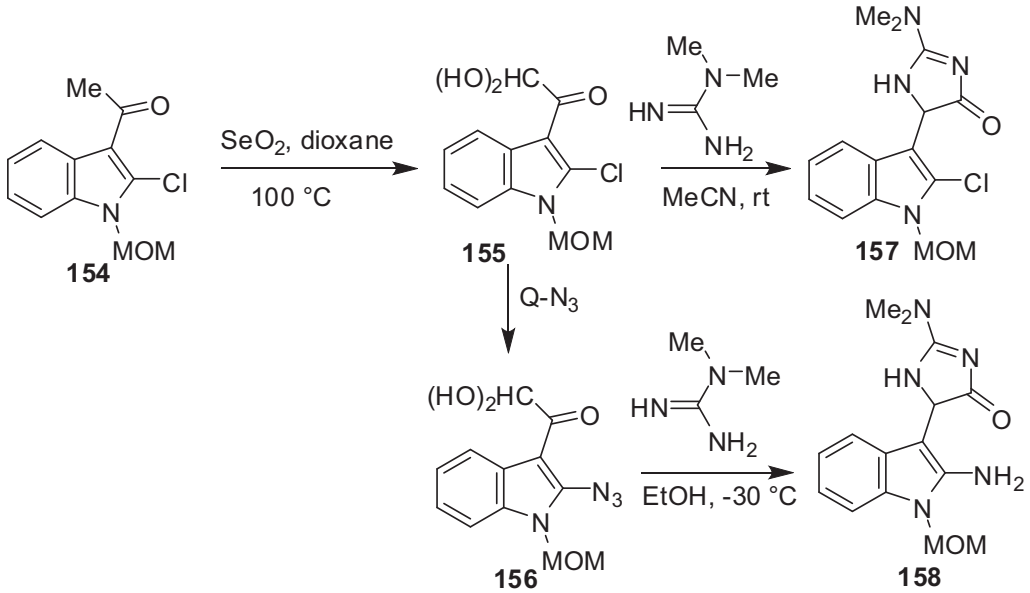
Herbicidal thiadiazole derivatives **153** were prepared by treating the amines **148** with phosgene, followed by reacting with aminoethanols **150** followed by chlorination and then cyclization with base (Scheme 47).[79]



Scheme 47

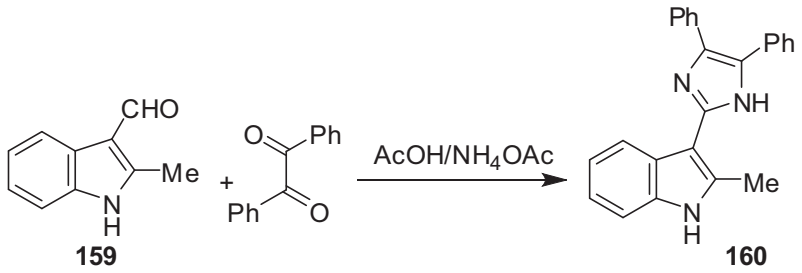
9. Indolylimidazoles

Oxidation of 1-methoxymethyl-3-acetyl-2-chloroindole **154** with selenium dioxide afforded the 3-indolylglyoxal hydrate **155** in 96% yield, which was converted into the corresponding azide **156** in 80% yield by treatment with polymeric quaternary ammonium azide (QN_3). The reaction of **155** and **156** with N,N-dimethylguanidine in ethanol at –30 °C gave **157** and **158** in 91% and 95% yields, respectively (Scheme 48).[80]



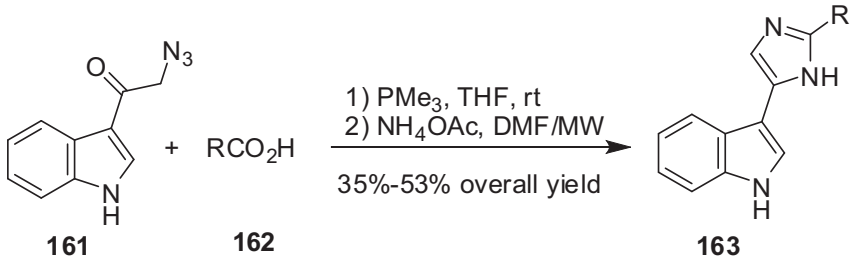
Scheme 48

2-Methyl-1H-indole-3-carbaldehyde **159** was condensed with benzil in the presence of ammonium acetate in refluxing AcOH to yield 3-(4,5-diphenyl-1H-imidazol-2-yl)-2-methyl-1H-indole **160** (Scheme 49).[81]



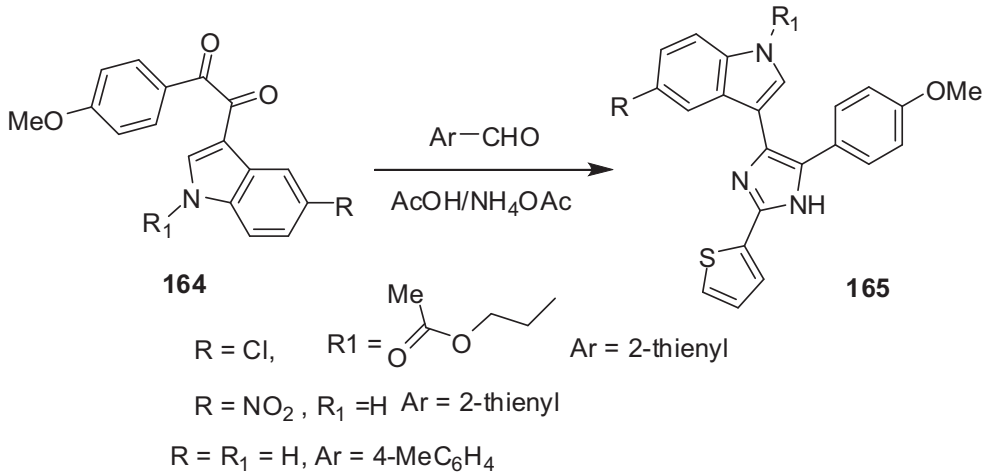
Scheme 49

A 2-step regioselective synthesis of indolyl imidazole **163** was reported by the reaction of α-azidoacetyl indole **161** with carboxylic acids **162** in the presence of trimethyl phosphines followed by cyclization using ammonium acetate under microwave irradiation (Scheme 50).[82]



Scheme 50

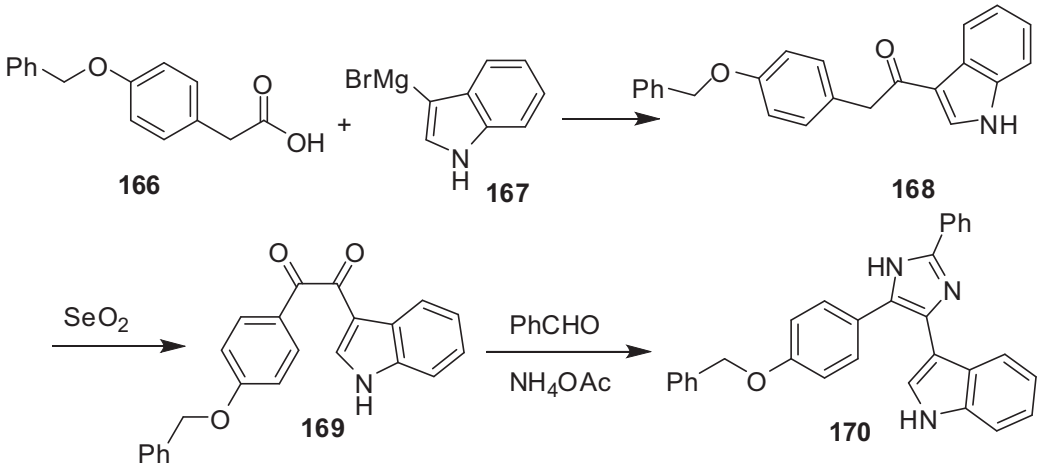
The preparation of 4-(3-indolyl)imidazoles **165** as phosphodiesterase inhibitors has been reported. Refluxing *N*-(2-acetoxyethyl)-3-(4-methoxyphenylglyoxylyl)indoles **164** with aldehydes in acetic acid in the presence of ammonium acetate gave 3-(5-(4-methoxyphenyl)-2-(thiophen-2-yl)-1*H*-imidazol-4-yl)-1*H*-indoles **165** (Scheme 51).[83–85]



Scheme 51

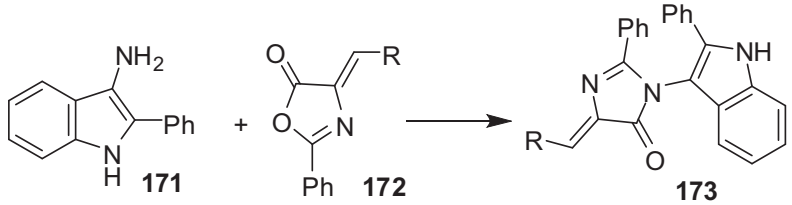
Preparation of 5-(substituted phenyl)-4-(3-indolyl)imidazoles **170** as phosphodiesterase inhibitors was reported by reaction of 4-(benzyloxy)phenylacetic acid **166** with indolylmagnesium bromide **167** to give 2-(4-benzyloxyphenyl)-1-(3-indolyl)ethanone **168**. Then oxidation of **168** with selenium dioxide followed by

reaction with benzaldehyde and ammonium acetate gave 5-(4-benzyloxyphenyl)-4-(3-indolyl)-2-phenylimidazole **170** (Scheme 52).[86]



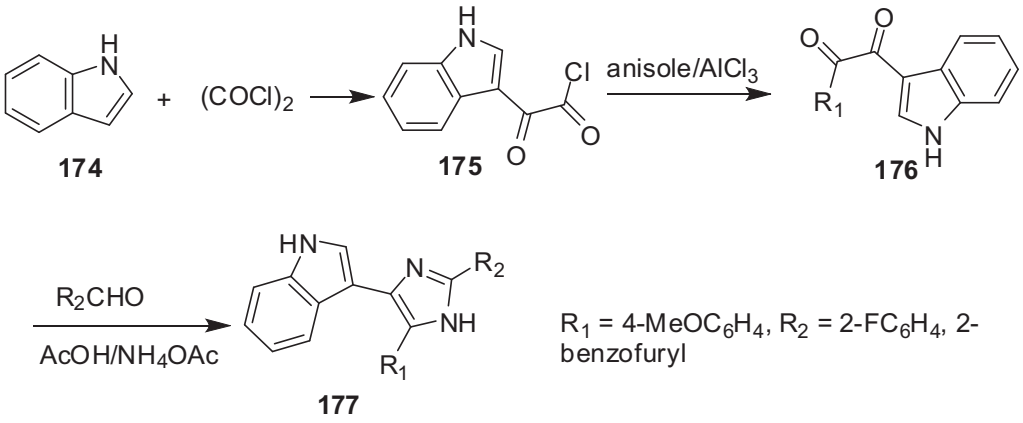
Scheme 52

Indolylimidazolinones **173** were prepared from the reaction between 3-amino-2-phenylindole **171** and the oxazolones **172** (Scheme 53).[56]



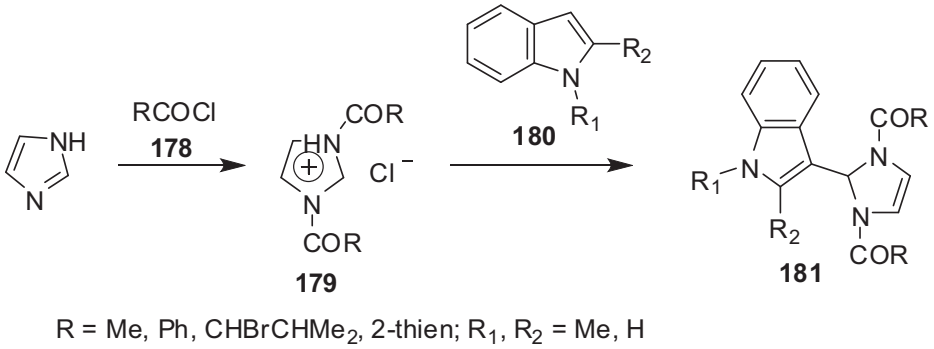
Scheme 53

4-(3-Indolyl)-5-(hetero)aryl-2-substituted-imidazoles **177**, as anti-inflammatory, analgesic, and antipyretic agents, were prepared by treatment of oxalyldichloride with indole **174** followed by reaction of the obtained **175** with anisole to give 1-(3-indolyl)-2-(4-methoxyphenyl)ethanedione **176**. Reaction of **176** with 2-fluorobenzaldehyde in acetic acid and in the presence of ammonium acetate under reflux conditions gave **177** (Scheme 54).[87,88]



Scheme 54

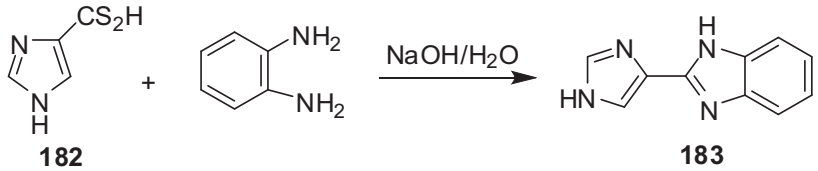
Indolylimidazoles **181** were obtained by heating a mixture of imidazole with acyl chlorides **178** to afford the diacetyl imidazolium salts **179** in 7%–95% yields. Treatment of **179** with indoles **180** in acyl chloride as solvent for 2 h afforded the 1,3-diacyl-2-(3'-indolyl)-4-imidazoles **181** after dilution with water (Scheme 55).[89]



Scheme 55

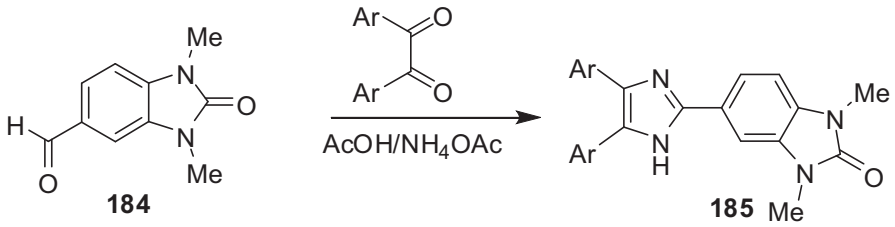
10. Imidazolylbenzimidazoles

2-(Imidazol-4-yl-4')benzimidazole **183** was synthesized by the reaction of imidazole-4-dithiocarboxylic acid **182** with an equimolar amount of *o*-phenylenediamine (Scheme 56).[90]



Scheme 56

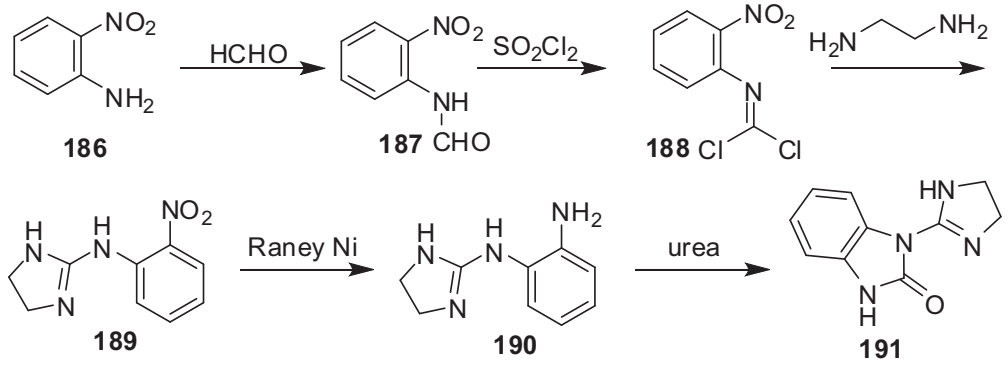
2-(*N*,*N*'-dimethylbenzimidazolon-5-yl)-4,5-diarylimidazoles **185** were prepared by cyclocondensation of 5-formyl-1,3-dimethyl-2-benzimidazolinone **184** with the corresponding diketones in boiling acetic acid containing ammonium acetate in 49%–80% yields (Scheme 57).[91]



Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 4-$EtOC_6H_4$, 4-$NO_2C_6H_4$

Scheme 57

Antihypertensive benzimidazolones **191** were prepared by *N*-formylation of 2-nitroaniline followed by treatment with sulfurylchloride to give 2-nitrophenylcarbonimidic dichloride **188**. Reaction of **188** with ethane-1,2-diamine followed by reduction with Raney Ni gave **190**, which then was cyclized with urea to produce **191** (Scheme 58).[92]



Scheme 58

11. Medicinal applications

5-Oxoimidazoline **192** showed antibacterial and antifungal activity,[8] and imidazoline **193** showed pronounced antischistosomacidal activity.[9] Also 1-(5-nitro-2-thiazolyl)imidazolinyl derivatives **194** and their salts were used as bactericides, protozoacides, and schistosomacides (Figure 1).[10]

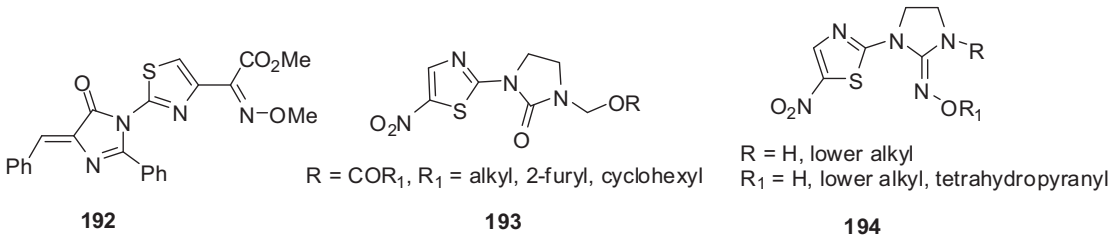


Figure 1. Chemical structures of compounds **192**–**194**.

3-(2-Butyl-4-chloro-1*H*-imidazolyl)-isoxazoline **195** was used as a cholinesterase inhibitor.[17] Imidazolylpyrazolylvinylpyridine **196** was useful as an inhibitor of ATP-protein kinase interactions.[11] Thiadiazolyloxyphenylurea **197** was used as a protein kinase inhibitor.[93] 4-Substituted-3(1*H*)-imidazol-1,2,5-thiadiazoles **198** were useful as antiarrhythmic agents.[12] 2-(Methylsulfonyl)-5-(1-methyl-5-nitro-2-imidazolyl)1,3,4-thiadiazole

199 showed significant antibacterial and antifungal activity.[13] Also imidazolylthiadiazoles **200** are useful as potent anti-Trypanosoma cruzi drugs (Figure 2).[94–96]

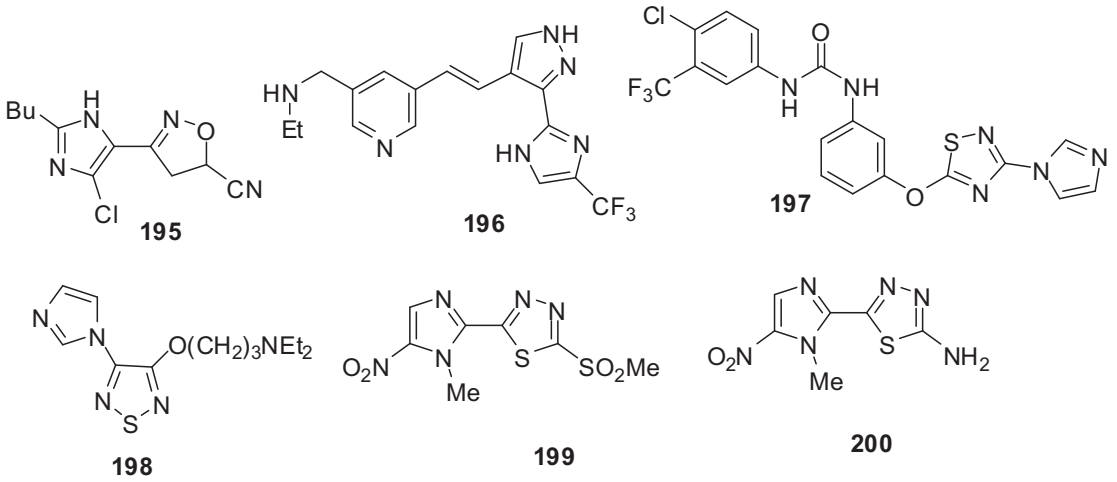


Figure 2. Chemical structures of compounds **195**–**200**.

2-(4,5-Dihydro-1*H*-imidazolyl)-dihydro-1*H*-indoles **201** are antidepressants.[17] Topsentin **202**, a bis(indolyl)imidazole marine natural product, inhibited the proliferation of cultured human and murine tumor cells at micromolar concentrations.[14–16] Indolylimidazolone **203** acts as a protein kinase C inhibitor.[18,19] 4-(3-Indolyl)imidazole derivatives **204** are useful as interleukin 6 production inhibitors.[97] Indolylimidazole derivatives **205** are used as Flt-1 and topoisomerase inhibitors (Figure 3).[98]

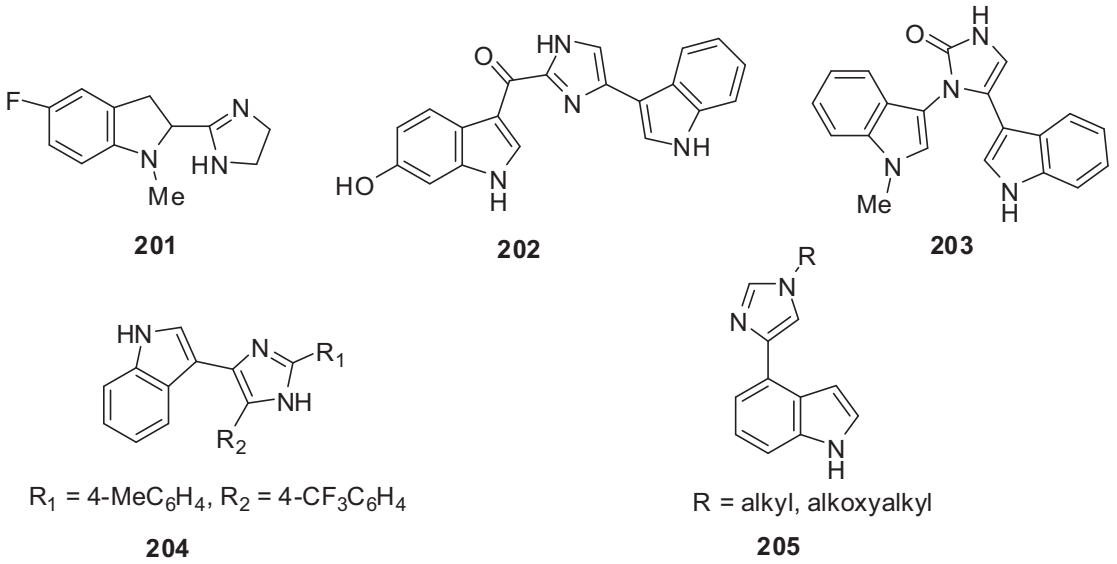


Figure 3. Chemical structures of compounds **201**–**205**.

5-Imidazol-1-yl-1*H*-benzimidazoles **206** act as interleukin-1 inhibitors.[99] Imidazolylbenzothiazole derivatives **207** are used as antithrombotics and inhibited collagen-induced blood platelet aggregation in platelet-rich plasma of a rabbit (Figure 4).[100]

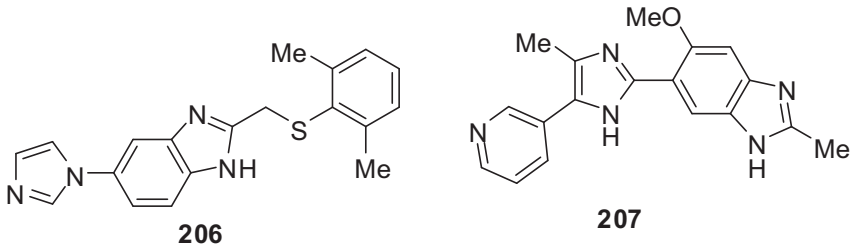


Figure 4. Chemical structures of compounds **206** and **207**.

Substituted imidazolylthiadiazoles are useful as antiprotozoal agents[101] and bactericides and are effective against ascarids.[102] Thiazolylimidazoles **208** act as microsomal triglyceride transfer protein (MTP) and/or apoprotein B (ApoB) inhibitors useful in the treatment of dyslipidemia and related diseases.[103] Pyrrolylimidazole **209** was used as an antibiotic and antitumor agent.[26] Also, 4,5-dichloroimidazole-2-carboxylic acid derivative **210** is useful as an herbicidal and fungicidal (Figure 5).[62]

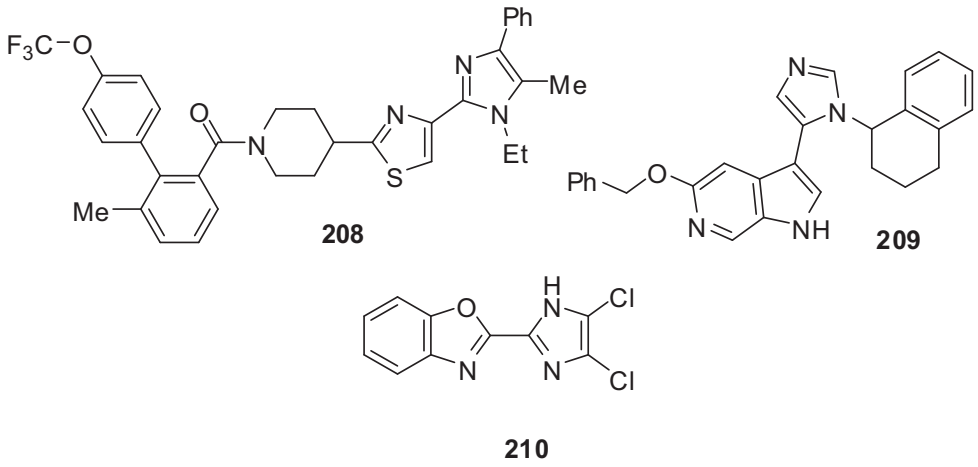


Figure 5. Chemical structures of compounds **208**–**210**.

12. Conclusion

This survey has attempted to summarize the synthetic methods and medicinal applications of different azoles directly attached to an imidazole nucleus in recent years. In the future we will publish a review article covering the fused imidazole nucleus with different azoles.

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