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, antischistosomal, protozoacidal, 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-1H-pyrrole-2-carboxylic acid 4 by refluxing with thionyl chloride, followed by treatment with 2-amino-2-methyloxiran-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 acetonitrile (Scheme 2).25,26

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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).\textsuperscript{27}

3. Imidazolylpyrazoles

Imidazolyl-2-pyrazoline derivative 12, having antibacterial and antifungal activities, was prepared starting from chalcone 11 by reaction with phenylhydrazine (Scheme 4).\textsuperscript{28}
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).\textsuperscript{29,30}

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).\textsuperscript{28}

Similarly, imidazolylpyrazolines 19 were prepared by condensation of the corresponding imidazolepropenones 18 with phenylhydrazine (Scheme 7).\textsuperscript{31}
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

Benzylideneimidazolypyrazolinones 25, as potential antimicrobial and acetylcholinesterase inhibitory agents, were prepared from the corresponding benzylidenoxazolones 23 and the aminopyrazolone 24 (Scheme 9). 33

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
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

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

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-1H-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 POCl3 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-1H-imidazol-2-yl)-1H-pyrazol-4-amine 38, which was used as intermediate for the synthesis of the antipsychotic 1H-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-1H-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-1H-pyrazole-4-carbaldehydes 43, 1,2-diketones 44, and ammonium acetate in acetic acid via the Debus reaction (Scheme 17).42
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-(imidazol-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. 

Ar = Ph, 4-BrC₆H₄, 4-OMeC₆H₄, 4-MeC₆H₄, 3-BrC₆H₄, 3-OMeC₆H₄
R₁ = R₂ = H, Me
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 = NH₂) in refluxing methanol (Scheme 19). 44

\[
\begin{align*}
\text{Scheme 19} \\
\begin{array}{c}
\text{51} \\
\text{R = Me, NH₂} \\
\text{52}
\end{array}
\end{align*}
\]

5-Methyl-1-(3-phenoxy)methyl)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

\[
\begin{align*}
\text{Scheme 20} \\
\begin{array}{c}
\text{53} \\
\text{Me} \\
\text{O \text{Ph} \text{Me}} \\
\text{54} \\
\text{Me} \\
\text{O \text{Ph} \text{Me}}
\end{array}
\end{align*}
\]

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

\[
\begin{align*}
\text{Scheme 21} \\
\begin{array}{c}
\text{55} \\
\text{O₂N} \\
\text{N \text{Me} \text{S}} \\
\text{NH₂} \\
\text{56} \\
\text{R} \\
\text{O \text{Me} \text{EtO}} \\
\text{57} \\
\text{R} \\
\text{O \text{Me} \text{EtO}}
\end{array}
\end{align*}
\]

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

\[
\begin{align*}
\text{Scheme 22} \\
\begin{array}{c}
\text{58} \\
\text{Ar = Ph, 4-MeC₆H₄, 4-MeOC₆H₄, 4-ClC₆H₄, 2-MeC₆H₄}
\end{array}
\end{align*}
\]
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}

\[
\text{R}_1 = \text{Me, Br; R}_2 = 2\text{-furyl-}, \text{Ph-}, 3\text{-pyridyl-}, \text{EtNH}
\]

\text{Scheme 23}

1-(5-Nitro-2-thiazolyl)-\(\Delta^2\)-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}

\text{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}

\text{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}

\text{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-1H-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).

5. Imidazolylisoxazoles

Ceric ammonium nitrate (CAN) acted as an efficient catalyst for the synthesis of 1-(1H-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).
2-(Phenyl)-3-(2-butyl-4-chloro-1H-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](image)

1-Methyl-5-nitro-1H-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 propionate, respectively (Scheme 30).\(^{59}\)

![Scheme 30](image)
Imidazolylisoxazoles 93 were prepared by reaction of C(\(\alpha\))-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).\(^{35,60}\)

\[
\begin{align*}
\text{Ar} & = 4\text{-CH}_3\text{C}_6\text{H}_4, 4\text{-MeOC}_6\text{H}_4, 3,4\text{-}(\text{MeO})_2\text{C}_6\text{H}_3 \\
\end{align*}
\]

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).\(^{29,61}\)

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).\(^{62}\)
7. Imidazolytriazoles

Imidazol-1,2,3-triazolo-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). \(^{63}\)
Imidazolyltriazoles 113 were prepared by cyclocondensation reaction of 4-amino-5-cyanotriazoles 112 with diamines 111 in the presence of P$_2$S$_5$ as catalyst (Scheme 35).

![Scheme 35](image)

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).

![Scheme 36](image)

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).

![Scheme 37](image)

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

![Scheme 38](image)
Condensation of 1-methyl-2-methylsulfonyl-5-(nitro)imidazole 124 with the sodium salts of triazolidinediones 125 gave the imidazolyltriazolidinediones 126 (Scheme 39).

\[
\begin{align*}
\text{Me-SO} & \quad + \quad \text{HN-N=O-R} \\
\text{124} & \quad \longrightarrow \\
\text{125} & \quad \text{126}
\end{align*}
\]

\( R = \text{Me, Et, allyl,Pr, Bu, 3,4,5-(MeO)}_3\text{C}_6\text{H}_2, \text{PhCH} = \text{CH, PhCH}_2\text{CH}_2, 2\text{-phenylcyclopropyl} \)

Scheme 39

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

\[
\begin{align*}
\text{O} & \quad \text{NH}_2 \\
\text{127} & \quad \longrightarrow \\
\text{128}
\end{align*}
\]

Scheme 40

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

\[
\begin{align*}
\text{NC} & \quad \text{MeO} \quad \text{C}=\text{N} \\
\text{129} & \quad \text{MeNHNH}_2 \\
\text{130} & \quad \text{PhMe-MeOH}
\end{align*}
\]

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](image)

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](image)

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

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

Herbicidal thia diazole 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
9. Indolylimidazoles

Oxidation of 1-methoxymethyl-3-acetyl-2-chloroindole \(154\) with selenium dioxide afforded the 3-indolyglyoxal 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).

2-Methyl-1\(H\)-indole-3-carbaldehyde \(159\) was condensed with benzil in the presence of ammonium acetate in refluxing AcOH to yield 3-(4,5-diphenyl-1\(H\)-imidazol-2-yl)-2-methyl-1\(H\)-indole \(160\) (Scheme 49).
A 2-step regioselective synthesis of indolyl imidazole 163 was reported by the reaction of \( \alpha \)-azidoacetyl indole 161 with carboxylic acids 162 in the presence of trimethyl phosphines followed by cyclization using ammonium acetate under microwave irradiation (Scheme 50).\(^{82}\)

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).\(^{83-85}\)

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).

Indolylimidazolinones **173** were prepared from the reaction between 3-amino-2-phenylindole **171** and the oxazolones **172** (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).
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).\(^\text{89}\)

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).\(^\text{90}\)

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).\(^\text{91}\)
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

11. Medicinal applications
5-Oximidazoline 192 showed antibacterial and antifungal activity,8 and imidazole 193 showed pronounced antischistosomical activity.9 Also 1-(5-nitro-2-thiazolyl)imidazolinyl derivatives 194 and their salts were used as bactericides, protozoacides, and schistosomacides (Figure 1).10

3-(2-Butyl-4-chloro-1H-imidazolyl)-isoxazoline 195 was used as a cholinesterase inhibitor.17 Imidazolylpyrazolylvinylpyridine 196 was useful as an inhibitor of ATP-protein kinase interactions.11 Thiadiazolyl-oxophenylurea 197 was used as a protein kinase inhibitor.93 4-Substituted-3(1H)-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

Figure 1. Chemical structures of compounds 192–194.
199 showed significant antibacterial and antifungal activity. Also imidazolylthiadiazoles 200 are useful as potent anti-Trypanosoma cruzi drugs (Figure 2).

![Compounds 195-200](image)

Figure 2. Chemical structures of compounds 195–200.

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

![Compounds 201-205](image)

Figure 3. Chemical structures of compounds 201–205.

5-Imidazol-1-yl-1H-benzimidazoles 206 act as interleukin-1 inhibitors. Imidazolylbenothiazole derivatives 207 are used as antithrombotics and inhibited collagen-induced blood platelet aggregation in platelet-rich plasma of a rabbit (Figure 4).
Substituted imidazolylthiadiazoles are useful as antipROTOZOAL agents\textsuperscript{101} and bactericides and are effective against ascarids.\textsuperscript{102} Thiazolylimidazoles \textbf{208} act as microsomal triglyceride transfer protein (MTP) and/or apoprotein B (ApoB) inhibitors useful in the treatment of dyslipidemia and related diseases.\textsuperscript{103} Pyrrolylimidazole \textbf{209} was used as an antibiotic and antitumor agent.\textsuperscript{26} Also, 4,5-dichloroimidazole-2-carboxylic acid derivative \textbf{210} is useful as an herbicidal and fungicidal (Figure 5).\textsuperscript{62}

\textbf{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.

\textbf{References}

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