Indolylimidazoles: Synthetic approaches and biological activities

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\textbf{ABSTRACT}

Indolylimidazole compounds that contain both indole and imidazole rings have shown various biological and pharmacological activities. These indolylimidazole compounds have been synthesized and extracted from the plants. In this paper, we have reviewed biological activities of natural and synthesized indolylimidazoles and their various synthetic methods. In recent time, the substituted indolylimidazole derivatives have synthesized and reported in the presence of different kind of the catalysts such as strong protic acid HNO\textsubscript{3}@nano SiO\textsubscript{2}, Zn\textsuperscript{2+}@KSF and acetic acid and Amberlyst A-15. This review paper is divided into two categories bases on bioactivities of natural and synthesized indolylimidazole derivatives.

\textbf{Keywords:} Imidazole, Pharmacological activities, Anticancer, Amberlyst A-15, Microwave irradiation

1. Introduction

Indolylimidazole and its derivatives are an important class of heterocycles. From the literature survey, it followed that the presence of imidazole ring in natural and synthesized compounds have shown significant biological activities. It has also appeared that indole ring-containing natural and synthesized compounds have also shown vast biological activities.

Indolylimidazole compounds that contain both indole and imidazole rings have showed various biological and pharmacological activities such as protein kinase C inhibitor, interleukin-6 production inhibitor, MRSA PK inhibitor, Fms-like tyrosine kinase-1 (Flt-1) and topoisomerase inhibitor, anti-plasmodial, anti-depressants, antimicrobial, antifungal, antibacterial, anti-urease, antioxidant and radio-sensitizing activities. These compounds also showed anticancer, cytotoxicity against murine tumour cells and P388 cells.

1.1. Natural Bioactive Indolylimidazoles

Indolylimidazole structure resembling compounds such as Topsentin was first reported in 1987 and isolated from marine sponges.\textsuperscript{1-4} These Topsentin (Fig. 1) and its derivatives (Fig. 2 to Fig. 5) showed different types of biological activities such as antifungal,\textsuperscript{5} antibacterial,\textsuperscript{6} antiviral,\textsuperscript{6} antitumor,\textsuperscript{7-9} and anti-inflammatory\textsuperscript{10,11}. 
Indolylimidazole skeleton containing Nortopsentins A-C (Fig. 6 to Fig. 8) isolated from the deep sea sponge spongosoritesruetzler and showed in vitro cytotoxicity against P388 cells (IC50 4.0-18.3 μM)\textsuperscript{12} and antifungal properties. Nortopsentin-A exhibited antiplasmodial activity and inhibited parasite growth at the trophozoite stage at submicromolar 50% inhibitory concentrations (IC50).\textsuperscript{13} Nortopsentins-D (Fig. 9) and N-methyl substituted derivatives of Nortopsentin also showed cytotoxicity against P388 cells (IC50 0.6-1.6 μM).\textsuperscript{5}

Discodermindole (Fig. 10) has been isolated and exhibited cytotoxicity against murine tumor cells.\textsuperscript{14} 2-(Dimethylamino)-5-(1H-indol-3-yl)-4H-imidazol-4-one (Fig. 11) has isolated from the tunicate Dendrodoa grossularia and it showed cytotoxicity against murine tumor cells.\textsuperscript{15}
Trachycladindole A–G compounds are the product of southern Australian marine sponge *Trachycladus lae vispirulifer*. The Trachycladindole (Fig. 12) displayed promising selective cytotoxicity against a panel of human cancer cell lines.\textsuperscript{16} 2-(4,5-Dihydro-1H-imidazol-2-yl)-5-fluoro-1-methyl-2,3-dihydro-1H-indole (Fig. 13) has shown anti-depressant activities.\textsuperscript{17} 5-(1H-indol-3-yl)-1-(1-methyl-1H-indol-3-yl)-1,3-dihydro-2H-imidazol-2-one (Fig. 14) has been reported as a protein kinase C inhibitor.\textsuperscript{18,19}
Fig. 14. Structure of 5-(1H-indol-3-yl)-1-(1-methyl-1H-indol-3-yl)-1,3-dihydro-2H-imidazol-2-one

3-{2-(4-Methylphenyl)-5-[4-(trifluoromethyl)-phenyl]-1H-imidazol-4-yl}-1H-indole (Fig. 15) has been reported as interleukin 6-production inhibitor. 20 3-(1-Alkyl-1H-imidazol-4-yl)-1H-indole (Fig. 16) and 3-(1-alkoxyalkyl-1H-imidazol-4-yl)-1H-indole derivatives (Fig. 17) have been reported as Flt-1 and topoisomerase inhibitor. 21

Fig. 15. Structure of 3-{2-(4-Methylphenyl)-5-[4-(trifluoromethyl)-phenyl]-1H-imidazol-4-yl}-1H-indole

Fig. 16. Structure of 3-(1-Alkyl-1H-imidazol-4-yl)-1H-indole

Fig. 17. Structure of 3-(1-alkoxyalkyl-1H-imidazol-4-yl)-1H-indole
Rhopaladins A-D (Fig. 18) compounds have been isolated from Okinawan tunicate Rhopalaea sp. in 1998. These compounds reported as an antibacterial agent against Sarcinalutea, Corynebacterium xerosis and showed inhibiting activity against cyclin-dependent kinase-4 and cerb β-2 kinase. 

![Image of Rhopaladins A-D](image.png)

\[
\begin{align*}
R^1 = \text{OH}, & \quad R^2 = \text{Br}; \quad \text{Rhopaladin-A} \\
R^1 = \text{OH}, & \quad R^2 = \text{H}; \quad \text{Rhopaladin-B} \\
R^1 = \text{H}, & \quad R^2 = \text{Br}; \quad \text{Rhopaladin-C} \\
R^1 = \text{H}, & \quad R^2 = \text{H}; \quad \text{Rhopaladin-D}
\end{align*}
\]

Fig. 18. Structure of Rhopaladins A-D

5-(benzyloxy)-3-[1-(1,2,3,4-tetrahydronaphthalen-1-yl)-1H-imidazol-5-yl]-1H-pyrrolo[2,3-c]pyridine (Fig. 19) acted as antibiotic and antitumor agent.

![Image of indolylimidazole derivative](image.png)

Fig. 19. Structure of indolylimidazole derivative

1.2. Synthesized Bioactive Indolylimidazoles

(5Z)-5-[(1-Benzyl-1H-indol-3-yl)-methylidene]-imidazolidine-2,4-dione (Fig. 20) has been synthesized and reported as radio-sensitizer against HT-29 cell line. (5Z)-5-[(1-(4-substitutedbenzyl)-1H-indol-3-yl)-methylidene]-imidazolidine-2,4-dione (Fig. 21) derivative also exhibited strong radio-sensitizing activities.

![Image of (5Z)-5-[(1-Benzyl-1H-indol-3-yl)-methylidene]-imidazolidine-2,4-dione](image.png)

Fig. 20. Structure of (5Z)-5-[(1-Benzyl-1H-indol-3-yl)-methylidene]-imidazolidine-2,4-dione
Fig. 21. Structure of (5Z)-5-[(1-(4-substitutedbenzyl)-1\textit{H}-indol-3-yl)-methylidene]-imidazolidine-2,4-dione

5-(Aziridin-1-yl)-3-(1\textit{H}-imidazol-2-yl)-1-methyl-1\textit{H}-indole-4,7-dione (Fig. 22) has shown good cytotoxicity via forming Hoogsteen-type of hydrogen bonds with DNA and involved DNA cleavage as a result of binding to the major-groove followed by phosphate backbone alkylation.\textsuperscript{25} Spongotine-A (Fig. 23) has also shown MRSA PK inhibitory activity.\textsuperscript{26}

Fig. 22. Structure of 5-(Aziridin-1-yl)-3-(1\textit{H}-imidazol-2-yl)-1-methyl-1\textit{H}-indole-4,7-dione

3-(4,5-Diphenyl-1\textit{H}-imidazol-2-yl)-1\textit{H}-indole (Fig. 24) has shown antioxidant activities.\textsuperscript{27} 3-(1-(1,2,3,4-Tetrahydronaphthalen-1-yl)-1\textit{H}-imidazole)-5-(benzyloxy)-1\textit{H}-pyrrolo[2,3-c]-pyridine (Fig. 25) has reported as an antibiotic and antitumor agent.\textsuperscript{28}

Fig. 23. Structure of Spongotine-A

Fig. 24. Structure of 3-(4,5-Diphenyl-1\textit{H}-imidazol-2-yl)-1\textit{H}-indole
Fig. 25. Structure of 3-(1-(1,2,3,4-Tetrahydronaphthalen-1-yl)-1H-imidazole)-5-(benzyloxy)-1H-pyrrolo[2,3-c]-pyridine

Rajaramana D., Sundararajana G. et al.\textsuperscript{29} described the synthesis of 3-{1-[2-(3,4-dimethoxyphenyl)ethyl]-4,5-diphenyl-1H-imidazol-2-yl]-1H-indole (Fig. 26) catalysed by SO\textsubscript{4}\textsuperscript{2-}/Y\textsubscript{2}O\textsubscript{3} and reported as antimicrobial agent.

Fig. 26. Structure of 3-{1-[2-(3,4-dimethoxyphenyl)ethyl]-4,5-diphenyl-1H-imidazol-2-yl]-1H-indole

Naureen S., Ijaz F., et al.\textsuperscript{30} synthesized 3-[1-(4-substitutedphenyl)-4,5-diphenyl-1H-imidazol-2-yl]-2-(4-substitutedphenyl)-5-substituted-1H-indole derivatives 4 by refluxed of substituted-indole-3-carboxaldehyde 1, benzil 2, substituted-aniline 3 and ammonium acetate in the presence of acetic acid for 5-6 hours (Scheme 1). These synthesized compounds showed significant biological activities such as 3-[1-(4-methoxyphenyl)-4,5-diphenyl-1H-imidazol-2-yl]-2-(4-methylphenyl)-1H-indole (Fig. 27) and compound 2-(4-bromophenyl)-3-[1-(4-methylphenyl)-4,5-diphenyl-1H-imidazol-2-yl]-1H-indole (Fig. 28) exhibited potent antiurease activity good antioxidant inhibition of 90.3 ± 0.57% at 0.5mM respectively. 3-[1,4,5-Triphenylimidazole-2-yl]-2-phenylindole (Fig. 29) derivatives have been reported as antiurease and antioxidant agent.

Scheme 1. Synthesis of indolylimidazole derivatives
Mahmoodia N. O., Nikokarb I., et al. synthesized substituted-indolylimidazole derivatives by condensation of mixture of substituted-indole-3-carboxaldehyde, benzil, substituted-aniline and ammonium acetate in the presence of Zn$^{2+}$@KSF at 70°C for 40 minute (Scheme 2). These synthesised compounds 3-(1,4,5-triphenyl-1H-imidazol-2-yl)-1H-indole (Fig. 30), 1-Methyl-3-(1-methylphenyl-4,5-diphenyl-1H-imidazol-2-yl)-1H-indole (Fig. 31) and 1,4-bis-[3-(1,4,5-triphenyl-1H-imidazol-2-yl)-1H-indole]-butane (Fig. 32) showed good antibacterial activities against Micrococcus luteus, Bacillus subtilis and Salmonella enteritis respectively.
Scheme 2. Synthesis of indolylimidazole derivatives

Fig. 30. Structure of 3-(1,4,5-triphenyl-1H-imidazol-2-yl)-1H-indole

Fig. 31. Structure of 1-Methyl-3-(1-methylphenyl-4,5-diphenyl-1H-imidazol-2-yl)-1H-indole

Fig. 32. Structure of 1,4-bis-[3-(1,4,5-triphenyl-1H-imidazol-2-yl)-1H-indole]-butane
Nirwan N., Pareek C., et al. synthesized 5-substituted-3-(4,5-diphenyl-1H-imidazol-2-yl)-1H-indole derivatives and 3-(4,5-diphenyl-1-substituted-1H-imidazol-2-yl)-1H-indole derivatives by the irradiation with microwaves of a mixture of 5-substituted-indole-3-aldehyde, benzil, substituted-aniline, NH₄OAc, and Amberlyst A-15 at a constant temperature (Scheme 3). These compounds (Fig. 33) showed good antibacterial activities against *E. coli* and *P. aeruginosa*.

![Scheme 3. Synthesis of indolylimidazole derivatives](image)

Benkli K., Demirayak S. et al. synthesized 1-substituted-2-(1H-imidazol-1-yl)-3-(4,5-di-[4-substituted]phenyl-1H-imidazol-2-yl)-1H-indole derivatives (Fig. 34 to Fig. 39) by refluxed of 2-(1H-imidazol-1-yl)-1H-indole-3-carbaldehyde, substituted-benzil and ammonium acetate in presence of acetic acid for 2 hours (Scheme 4). Indolylimidazoles such as 1-substituted-2-(1H-imidazol-1-yl)-3-(1H-phenanthro[5,6-d]-imidazol-2-yl)-1H-indole derivatives (Fig. 40) and 1-substituted-2-[2-(1H-imidazol-1-yl)-1H-indol-3-yl]-1H-benzimidazole derivatives (Fig. 41) also produced via above described method by using 2-(1H-imidazol-1-yl)-1H-indole-3-carbaldehyde, ammonium acetate and 1,2-diole reactants (Scheme 5). These compounds reported as antifungal and antimicrobial.

![Scheme 4. Synthesis of indolylimidazole derivatives](image)
Scheme 5. Synthesis of indolylimidazole derivatives

15 R = CH₃, C₂H₅, C₆H₅, CH(O)=CH(O) = Phenanthrene-9,10-dione (Fig. 40)
R = CH₃, C₂H₅, C₆H₅, CH(O)=CH(O) = Cyclohexa-3,5-diene-1,2-dione (Fig. 41)

Fig. 34. Structure of 2-(1H-imidazol-1-yl)-1-methyl-3-(4,5-diphenyl-1H-imidazol-2-yl)-1H-indole

Fig. 35. Structure of 2-(1H-imidazol-1-yl)-1-methyl-3-(4,5-di-[4-substitutedphenyl]-1H-imidazol-2-yl)-1H-indole
**Fig. 37.** Structure of 1-Ethyl-2-(1H-imidazol-1-yl)-3-(4,5-di-[4-substitutedphenyl]-1H-imidazol-2-yl)-1H-indole

\( R = \text{CH}_3, \text{OCH}_3, \text{Cl} \)

**Fig. 38.** Structure of 2-(1H-Imidazol-1-yl)-1-phenyl-3-(4,5-diphenyl-1H-imidazol-2-yl)-1H-indole

**Fig. 39.** Structure of 2-(1H-Imidazol-1-yl)-1-phenyl-3-(4,5-di-[4-substitutedphenyl]-1H-imidazol-2-yl)-1H-indole

\( R = \text{CH}_3, \text{OCH}_3, \text{Cl} \)
Fig. 40. Structure of 2-(1H-Imidazol-1-yl)-1-substituted-3-(1H-phenanthro[5,6-d]imidazol-2-yl)-1H-indole

\[
\text{R} = \text{CH}_3, \text{C}_2\text{H}_5, \text{C}_6\text{H}_5
\]

Fig. 41. Structure of 1-Substituted-2-[2-(1H-imidazol-1-yl)-1H-indol-3-yl]-1H-benzimidazole

\[
\text{R}= \text{CH}_3, \text{C}_2\text{H}_5, \text{C}_6\text{H}_5
\]

Biradar J. S., Somappa S. B., et al. synthesized 2,5-disubstituted-3-(4,5-diphenyl-1H-imidazol-2-yl)-1H-indole derivatives 17 by microwave irradiation of the mixture of 2,5-disubstituted-indole-3-carboxaldehydes 16, substituted-benzil and ammonium acetate in acetic acid. 2-(2`,5`-Disubstituted-1H-indol-3-yl)-3,4-dihydroimidazo[4,5-b]indole derivatives 19 were also synthesized by using 1H-indole-2,3-dione 18 in same reaction condition (Scheme 6).

Scheme 6. Synthesis of indolylimidazole derivatives
Nikoofer K, Dizgarani S. M., et al.\textsuperscript{37} described the synthesis of 3-(4,5-diphenyl-1\textit{H}-imidazol-2-yl)-1\textit{H}-indole 20 and 3-(1,4,5-triphenyl-1\textit{H}-imidazol-2-yl)-1\textit{H}-indole 21 by condensation of benzil, indole-3-carbaldehyde, amine and ammonium acetate in the presence of HNO\textsubscript{3}@nano SiO\textsubscript{2} at 100\textdegree C for 6.30 hours and 5.10 hours in 74\% and 76\% yields respectively (Scheme 7).

\begin{scheme}
\centering
\begin{align*}
\text{Scheme 7. Synthesis of indolylimidazole derivatives}
\end{align*}
\end{scheme}

Kelarev V. I., Remezov A. S., et al.\textsuperscript{38} synthesized 5-(substituted-methylidene)-2-phenyl-3-(2-phenyl-1\textit{H}-indol-3-yl)-3,5-dihydro-4\textit{H}-imidazol-4-one derivatives 24 by the reaction of 2-phenyl-1\textit{H}-indol-3-amine 22 and 4-(substituted-methylidene-2-phenyl-1,3-oxazol-5(4\textit{H})-one 23 (Scheme 8).

\begin{scheme}
\centering
\begin{align*}
\text{Scheme 8. Synthesis of indolylimidazole derivatives}
\end{align*}
\end{scheme}

Molina P., Fresneda P. M., et al.\textsuperscript{39} produced 3-(1\textit{H}-imidazol-2-yl)-1\textit{H}-indole 27 by two steps region-selective method by reaction of 2-azido-1-(1\textit{H}-indol-3-yl)-ethan-1-one 25 and substituted-carboxylic acid 26 in the presence of tri-methyl phosphine followed by cyclization using ammonium acetate under microwave irradiation and obtained 35-53\% yield (Scheme 9).

\begin{scheme}
\centering
\begin{align*}
\text{Scheme 9. Synthesis of indolylimidazole derivatives}
\end{align*}
\end{scheme}

Kobori T., Hatanaka Y., et al.\textsuperscript{40} prepared 2-(1\textit{H}-indol-3-yl)-1\textit{H}-imidazole-1,3(2\textit{H})-substituted-dicarbaldehyde derivatives 31 by heating imidazole 28 and acyl chloride 29 mixture followed by reaction of obtained diacetyl imidazolium salts 30 with 1,2-disubstituted-indole in the presence of acyl chloride for 2 hours (Scheme 10).
Scheme 10. Synthesis of indolylimidazole derivatives

Kobori T., Hatanaka Y., et al.\textsuperscript{41} synthesized 3-\{5-[4-(benzyloxy)-phenyl]-2-phenyl-1\textsubscript{H}-imidazol-4-yl\}-1\textsubscript{H}-indole 36 by reaction of indolylmagnesium bromide 32 with [4-(benzyloxy)-phenyl]-acetic acid 33 followed by oxidation of obtained 2-[4-(benzyloxy)phenyl]-1-(1\textsubscript{H}-indol-3-yl)ethan-1-one 34 with selenium dioxide. Then reaction of 1-[4-(benzyloxy)-phenyl]-2-(1\textsubscript{H}-indol-3-yl)-ethane-1,2-dione 35 with benzaldehyde and ammonium acetate (Scheme 11). This Compound 36 reported as phosphodiesterase inhibitors.

Scheme 11. Synthesis of indolylimidazole derivatives

Ota T., Nakanishi M., et al.\textsuperscript{42,43} synthesized 3-[2-substituted-5-(4-methoxyphenyl)-1\textsubscript{H}-imidazol-4-yl]-1\textsubscript{H}-indole 41 by reaction of indole 37 with ethanediol dichloride 38 followed by reaction of obtained (1\textsubscript{H}-indol-3-yl)(oxo)acetyl chloride 39 and anisole in the presence of aluminium chloride to form 1-(1\textsubscript{H}-indol-3-yl)-2-(4-methoxyphenyl)ethane-1,2-dione 40. Then the refluxed of product 40, aldehyde, ammonium acetate in the presence of acetic acid (Scheme 12). The compounds 41 reported as anti-inflammatory, analgesic, and antipyretic agents.
Scheme 12. Synthesis of indolylimidazole derivatives

1,5-disubstitutes-3-[5-(4-methoxyphenyl)-2-substitutes-1H-imidazol-4-yl]-1H-indole derivatives 44 synthesized by reflux of 1-(1,5-disubstituted-1H-indol-3-yl)-2-(4-methoxyphenyl)ethane-1,2-dione 42, substituted-aldehyde 43 and ammonium acetate in the presence of acetic acid44-46 (Scheme 13). These compounds 44 reported as phosphodiesterase inhibitors.

Scheme 13. Synthesis of indolylimidazole derivatives

3-(4,5-diphenyl-1H-imidazol-2-yl)-2-methyl-1H-indole 46 synthesized by reflux of 2-methyl-1H-indole-3-carbaldehyde 45, benzil and ammonium acetate in the presence of acetic acid47 (Scheme 14).

Scheme 14. Synthesis of indolylimidazole derivatives
1-[2-Azido-1-(methoxymethyl)-1H-indol-3-yl]-2,2-dihydroxyethan-1-one 49 prepared by oxidation of 1-[2-chloro-1-(methoxymethyl)-1H-indol-3-yl]ethan-1-one 47 by the selenium dioxide followed by reaction of obtained 96% yield of 1-[2-chloro-1-(methoxymethyl)-1H-indol-3-yl]-2,2-dihydroxyethan-1-one 48 with polymeric quaternary ammonium azide (QN3) in 80% yield. 5-[2-chloro-1-(methoxymethyl)-1H-indol-3-yl]-2-(dimethylamino)-1,5-dihydro-4H-imidazol-4-one 50 and 5-[2-amino-1-(methoxymethyl)-1H-indol-3-yl]-2-(dimethylamino)-1,5-dihydro-4H-imidazol-4-one 51 synthesized by reaction of compounds 48 and 49 with N,N-dimethylguanidine in 91% and 95% yields respectively (Scheme 15).

Scheme 15. Synthesis of indolylimidazole derivatives

Shaterian H.R., Ranjbar M., et al.9 described the synthesis of 3-[1-(4-methylphenyl)-4,5-diphenyl-1H-imidazol-2-yl]-1H-indole 52 by condensation reaction of benzil with indole-3-carbaldehyde, 4-methylaniline, ammonium acetate in the presence of triphenyl(propyl-3-sulphonyl)phosphonium toluenesulfonate at 100°C for 35 minute in 82% yields. Benzoin was used for same reaction for 40 minute, 89% yields was obtained (Scheme 16).

Scheme 16. Synthesis of indolylimidazole derivatives

2. Conclusion

Indolylimidazole compounds play an important role in the field of medicinal science because of their wide spectrum of pharmacological activities as reported in the reviewed article. Many bioactive natural and synthesized compounds have been reported which contain the important structural moiety of indolylimidazole. These kinds of compounds synthesized by using different types of catalyst, such as strong protic acid HNO₃@nano SiO₂, Zn²⁺@KSF, acetic acid, QN3, Amberlyst A-15 and
microwave irradiation. The compounds that comprise the core of indolylimidazole skeleton have shown various bioactivities such as inhibitor against protein kinase C, interleukin-6 production, topoisomerase, phosphodiesterase and cyclin-dependent kinase-4 and cerb β-2 kinase. These compounds also exhibit cytotoxicity against a panel of human cancer cell lines, good cytotoxicity by forming Hoogsteen-type hydrogen bonds with DNA and good antibacterial activities against E. coli and P. aeruginosa, M. luteus, B. subtilis, S. enteritis, Sarcinalutea, and C. xerosis. These compounds also show anti-plasmodial, antidepressants, antimicrobial, antiurease, radio sensitizing, antifungal, antioxidants, anti-inflammatory, analgesic, antipyretic, phosphodiesterase and anticancer activities. Thus, this review paper reports about different kinds of synthetic methods and valuable bioactivities of indolylimidazole derivatives.

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References

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