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Indolylimidazoles: Synthetic approaches and biological activities

Narendra Nirwan[a*], Chandresh Pareek[a] and V. K. Swami[b]

[a]*Heterocyclic research Lab. Department of Chemistry, S. D. Govt. College, Beawar, India*
[b]*Department of Chemistry, Govt. Lohia PG College, Churu, India*

C H R O N I C L E

Article history:
Received June 12, 2019
Received in revised form
June 30, 2019
Accepted July 7, 2019
Available online
July 7, 2019

Keywords:
Imidazole
Pharmacological activities
Anticancer
Amberlyst A-15
Microwave irradiation

A B S T R A C T

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_3@nano SiO_2, Zn^{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.

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.[1-4] These Topsentin **(Fig. 1)** and its derivatives **(Fig. 2 to Fig. 5)** showed different types of biological activities such as antifungal,[5] antibacterial,[6] antiviral,[6] antitumor[7-9] and anti-inflammatory[10,11].

* Corresponding author.
E-mail address: drnirwann@gmail.com (N. Nirwan)

doi: 10.5267/j.ccl.2019.007.001

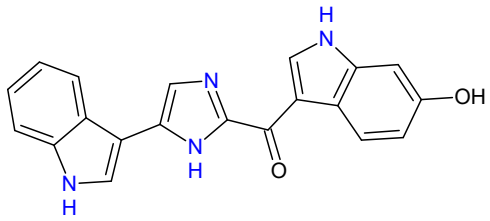


Fig. 1. Structure of Topsentin

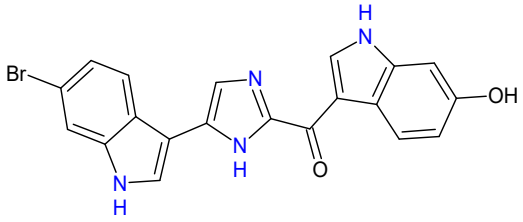


Fig. 2. Structure of Bromotopsentin

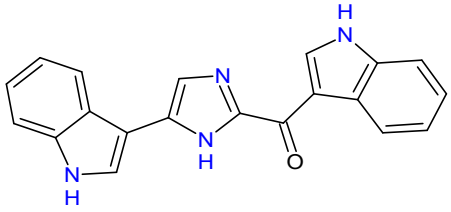


Fig. 3. Structure of Deoxytopsentin

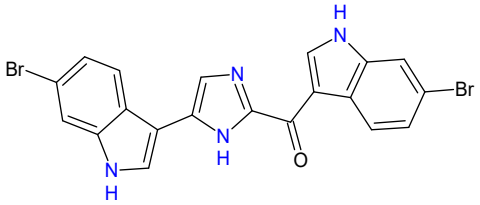


Fig. 4. Structure of Dibromodeoxytopsentin

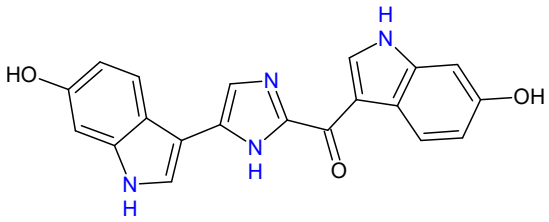


Fig. 5. Structure of Hydroxytopsentin

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)[12] and antifungal properties. Nortopsentin-A exhibited antiplasmodial activity and inhibited parasite growth at the trophozoite stage at submicromolar 50% inhibitory concentrations (IC50).[13] Nortopsentins-D **(Fig. 9)** and *N*-methyl substituted derivatives of Nortopsentin also showed cytotoxicity against P388 cells (IC50 0.6-1.6 μM).[5]

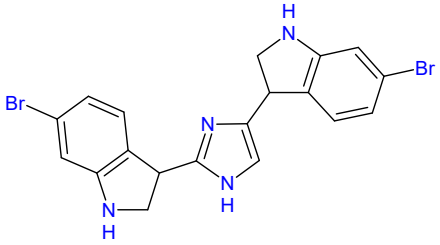


Fig. 6. Structure of Nortopsentin-A

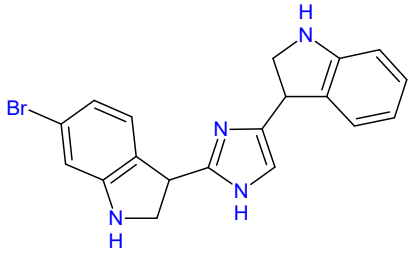


Fig. 7. Structure of Nortopsentin-B

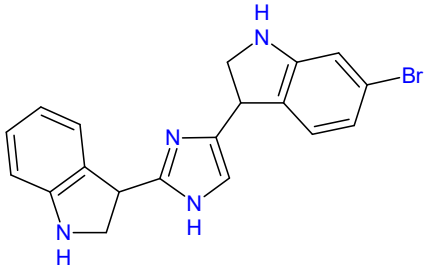


Fig. 8. Structure of Nortopsentin-C

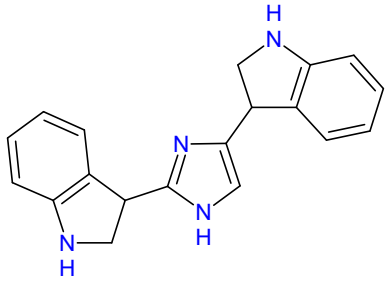


Fig. 9. Structure of Nortopsentin D

Discodermindole **(Fig. 10)** has been isolated and exhibited cytotoxicity against murine tumor cells.[14] 2-(Dimethylamino)-5-(1*H*-indol-3-yl)-4*H*-imidazol-4-one **(Fig. 11)** has isolated from the tunicate *Dendrodoa grossularia* and it showed cytotoxicity against murine tumor cells.[15]

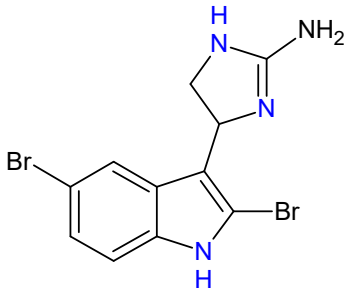


Fig. 10. Structure of Discodermindole

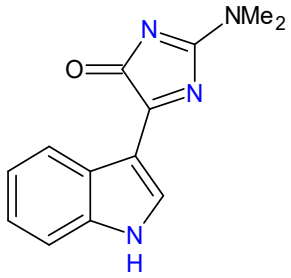


Fig. 11. Structure of 2-(Dimethylamino)-5-(1*H*-indol-3-yl)-4*H*-imidazol-4-one

Trachycladindole A–G compounds are the product of southern Australian marine sponge *Trachycladuslae vispirulifer.* The Trachycladindole **(Fig. 12)** displayed promising selective cytotoxicity against a panel of human cancer cell lines.[16]

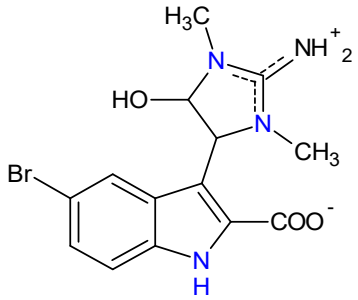


Fig. 12. Structure of Trachycladindole

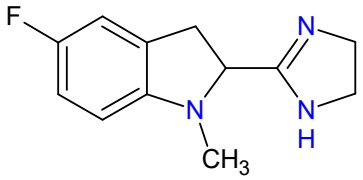


Fig. 13. Structure of 2-(4,5-Dihydro-1*H*-imidazol-2-yl)-5-fluoro-1-methyl-2,3-dihydro-1*H*-indole

2-(4,5-Dihydro-1*H*-imidazol-2-yl)-5-fluoro-1-methyl-2,3-dihydro-1*H*-indole **(Fig. 13)** has shown anti-depressant activities.[17] 5-(1*H*-indol-3-yl)-1-(1-methyl-1*H*-indol-3-yl)-1,3-dihydro-2*H*-imidazol-2-one **(Fig. 14)** has been reported as a protein kinase C inhibitor.[18,19]

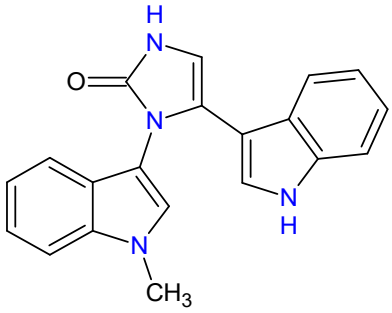


Fig. 14. Structure of 5-(1*H*-indol-3-yl)-1-(1-methyl-1*H*-indol-3-yl)-1,3-dihydro-2*H*-imidazol-2-one

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

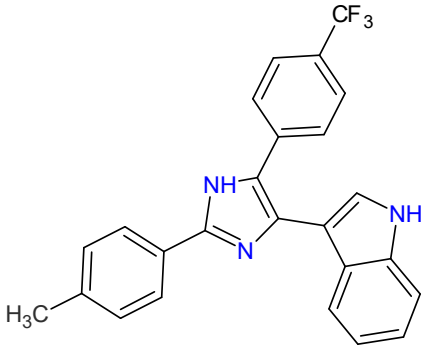
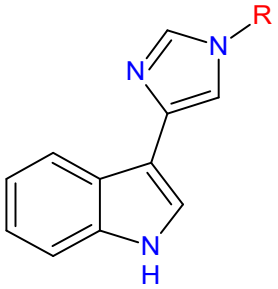
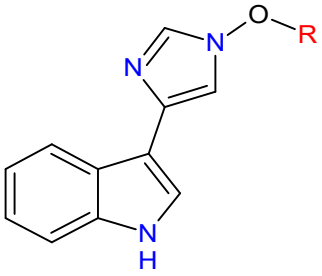


Fig. 15. Structure of 3-{2-(4-Methylphenyl)-5-[4-(trifluoromethyl)-phenyl]-1*H*-imidazol-4-yl}-1*H*-indole



R = Alkyl

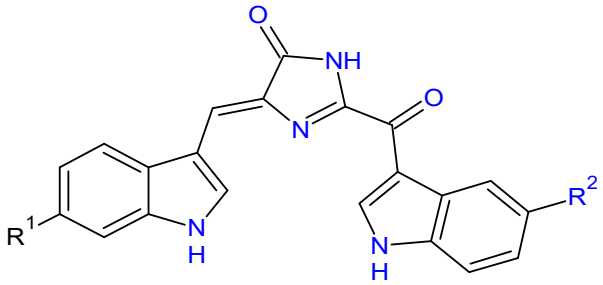
Fig. 16. Structure of 3-(1-Alkyl-1*H*-imidazol-4-yl)-1*H*-indole



R = Alkyl

Fig. 17. Structure of 3-(1-alkoxyalkyl-1*H*-imidazol-4-yl)-1*H*-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.*[22]



R^1 = OH, R^2 = Br; Rhopaladin-A
R^1 = OH, R^2 = H; Rhopaladin-B
R^1 = H, R^2 = Br; Rhopaladin-C
R^1 = H, R^2 = H; Rhopaladin-D

Fig. 18. Structure of Rhopaladins A-D

5-(benzyloxy)-3-[1-(1,2,3,4-tetrahydronaphthalen-1-yl)-1*H*-imidazol-5-yl]-1*H*-pyrrolo[2,3-c]pyridine **(Fig. 19)** acted as antibiotic and antitumor agent.[23]

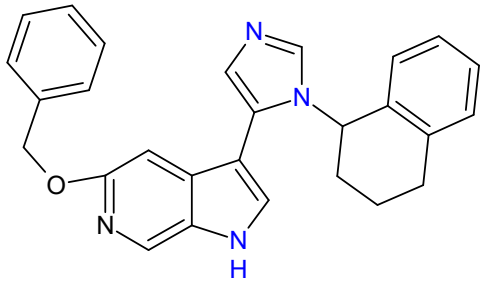


Fig. 19. Structure of indolylimidazole derivative

1.2. Synthesized Bioactive Indolylimidazoles

(*5Z*)-5-[(1-Benzyl-1*H*-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)-1*H*-indol-3-yl)-methylidene]-imidazolidine-2,4-dione **(Fig. 21)** derivative also exhibited strong radio-sensitizing activities.[24]

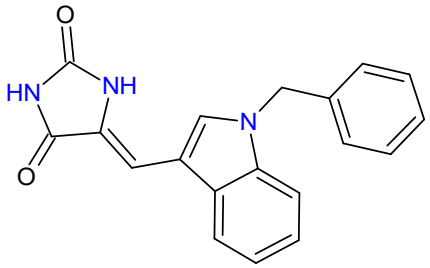
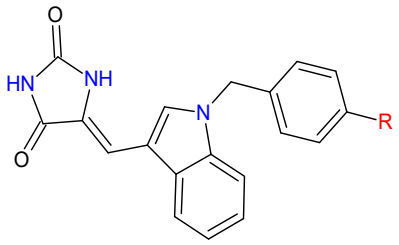


Fig. 20. Structure of (*5Z*)-5-[(1-Benzyl-1*H*-indol-3-yl)-methylidene]-imidazolidine-2,4-dione



R = CH, -NO_2, -$COOCH_3$

Fig. 21. Structure of (*5Z*)-5-[(1-(4-substitutedbenzyl)-1*H*-indol-3-yl)-methylidene]-imidazolidine-2,4-dione

5-(Aziridin-1-yl)-3-(1*H*-imidazol-2-yl)-1-methyl-1*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.[25] Spongotine-A **(Fig. 23)** has also shown MRSA PK inhibitory activity.[26]

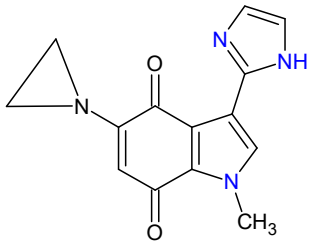


Fig. 22. Structure of5-(Aziridin-1-yl)-3-(1*H*-imidazol-2-yl)-1-methyl-1*H*-indole-4,7-dione

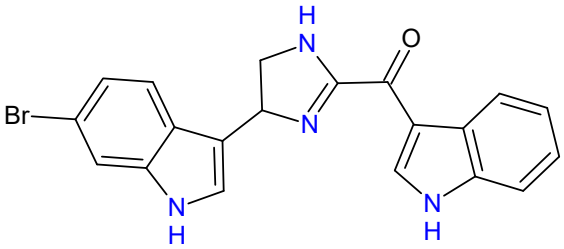


Fig. 23. Structure of Spongotine-A

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

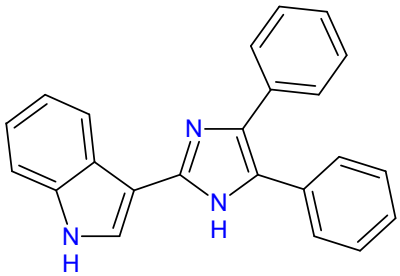


Fig. 24. Structure of 3-(4,5-Diphenyl-1*H*-imidazol-2-yl)-1*H*-indole

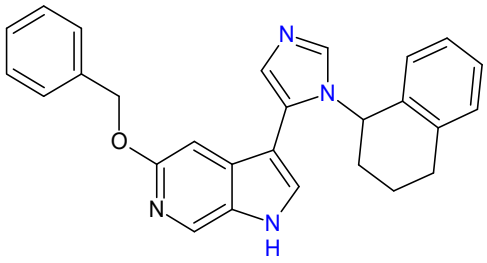


Fig. 25. Structure of 3-(1-(1,2,3,4-Tetrahydronaphthalen-1-yl)-1*H*-imidazole)-5-(benzyloxy)-1*H*-pyrrolo[2,3-c]-pyridine

Rajaramana D., Sundararajana G. et al.[29] described the synthesis of 3-{1-[2-(3,4-dimethoxyphenyl)ethyl]-4,5-diphenyl-1*H*-imidazol-2-yl}-1*H*-indole **(Fig. 26)** catalysed by SO_4^{2-}/Y_2O_3 and reported as antimicrobial agent.

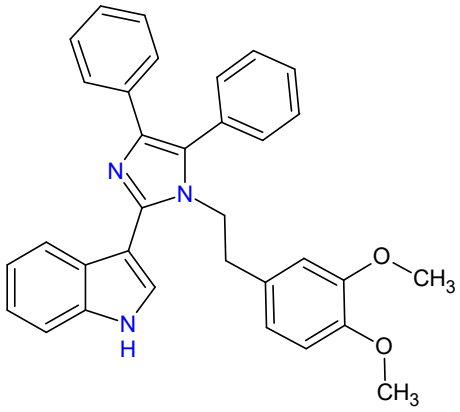
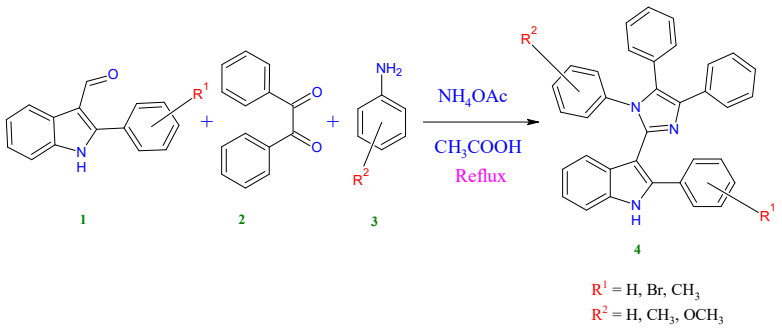


Fig. 26. Structure of 3-{1-[2-(3,4-dimethoxyphenyl)ethyl]-4,5-diphenyl-1*H*-imidazol-2-yl}-1*H*-indole

Naureen S., Ijaz F., et al.[30] synthesized 3-[1-(4-substitutedphenyl)-4,5-diphenyl-1*H*-imidazol-2-yl]-2-(4-substitutedphenyl)-5-substituted-1*H*-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-1*H*-imidazol-2-yl]-2-(4-methylphenyl)-1*H*-indole **(Fig. 27)** and compound 2-(4-bromophenyl)-3-[1-(4-methylphenyl)-4,5-diphenyl-1*H*-imidazol-2-yl]-1*H*-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

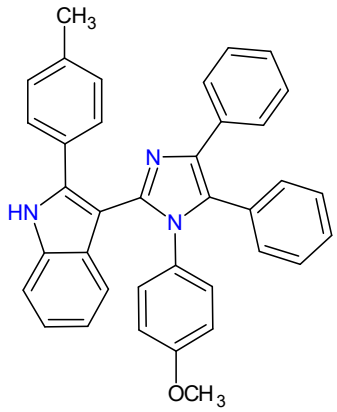


Fig. 27. Structure of 3-[1-(4-methoxyphenyl)-4,5-diphenyl-1*H*-imidazol-2-yl]-2-(4-methylphenyl)-1*H*-indole

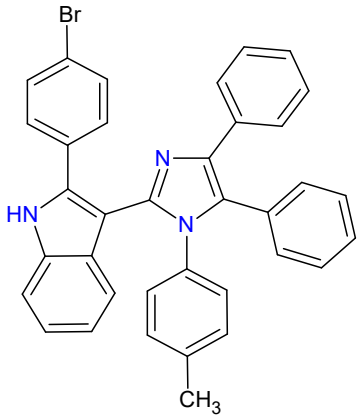


Fig. 28. Structure of 2-(4-bromophenyl)-3-[1-(4-methylphenyl)-4,5-diphenyl-1*H*-imidazol-2-yl]-1*H*-indole

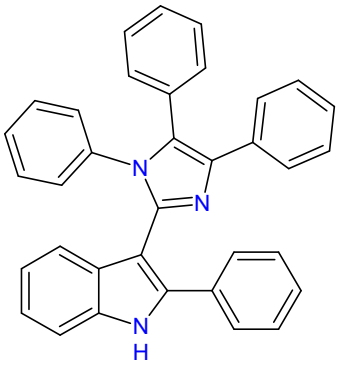
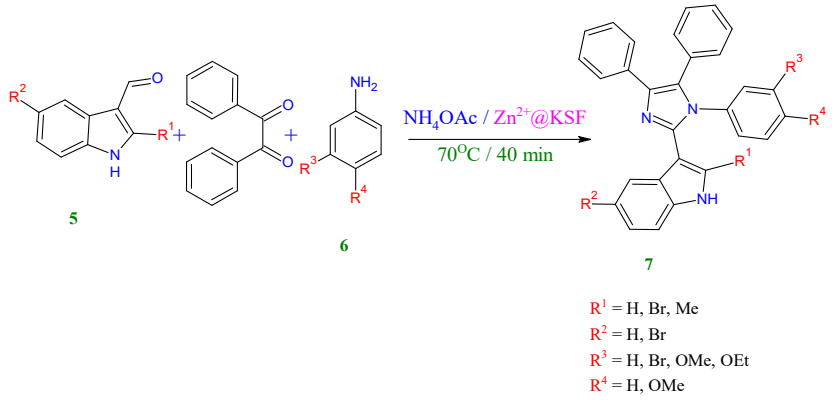


Fig. 29. Structure of 3-[1,4,5-Triphenylimidazole-2-yl]-2-phenylindole

Mahmoodia N. O., Nikokarb I., et al.[31] synthesized substituted-indolylimidazole derivatives **7** by condensation of mixture of substituted-indole-3-carboxaldehyde **5**, benzil, substituted-aniline **6** and ammonium acetate in the presence of Zn^{2+}@KSF at 70^{O}C for 40 minute **(Scheme 2)**. These synthesised compounds 3-(1,4,5-triphenyl-1*H*-imidazol-2-yl)-1*H*-indole **(Fig. 30)**, 1-Methyl-3-(1-methylphenyl-4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole **(Fig. 31)** and 1,4-bis-[3-(1,4,5-triphenyl-1*H*-imidazol-2-yl)-1*H*-indole]-butane **(Fig. 32)** showed good antibacterial activities against *Micrococcus luteus*, *Bacillus subtilis and Salmonella enteritis* respectively.



Scheme 2. Synthesis of indolylimidazole derivatives

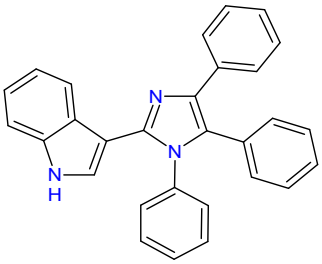


Fig. 30. Structure of 3-(1,4,5-triphenyl-1*H*-imidazol-2-yl)-1*H*-indole

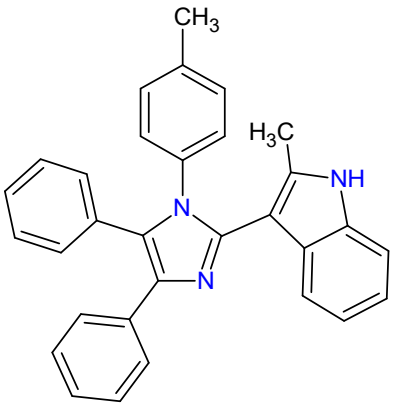


Fig. 31. Structure of 1-Methyl-3-(1-methylphenyl-4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole

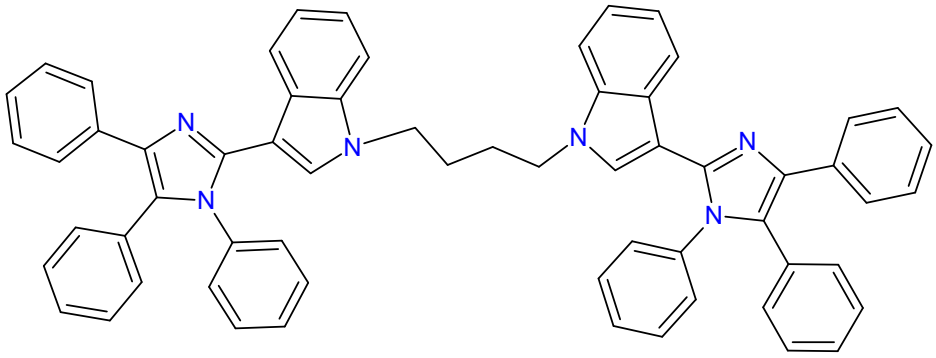
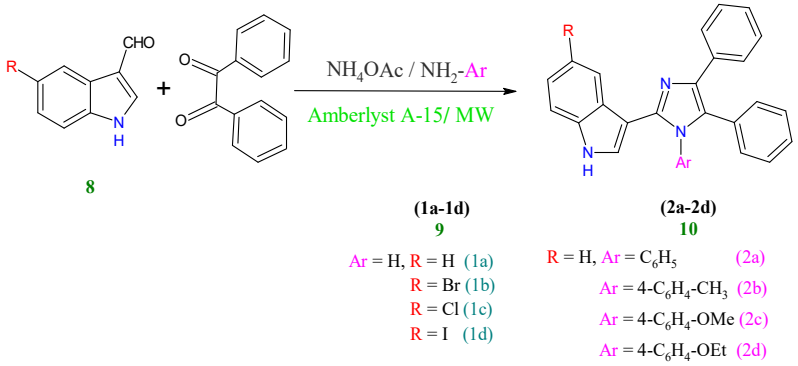
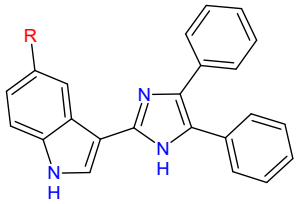


Fig. 32. Structure of 1,4-bis-[3-(1,4,5-triphenyl-1*H*-imidazol-2-yl)-1*H*-indole]-butane

Nirwan N., Pareek C., et al.[32,33] synthesized 5-substituted-3-(4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole derivatives **9** and 3-(4,5-diphenyl-1-substituted-1*H*-imidazol-2-yl)-1*H*-indole derivatives **10** by the irradiation with microwaves of a mixture of 5-substituted-indole-3-aldehyde **8**, benzil, substituted-aniline, NH_4OAc, and Amberlyst A-15 at a constant temperature **(Scheme 3)**. These compounds **(Fig. 33)** showed good antibacterial activities against *E. coli and P. aeruginosa.*[34]



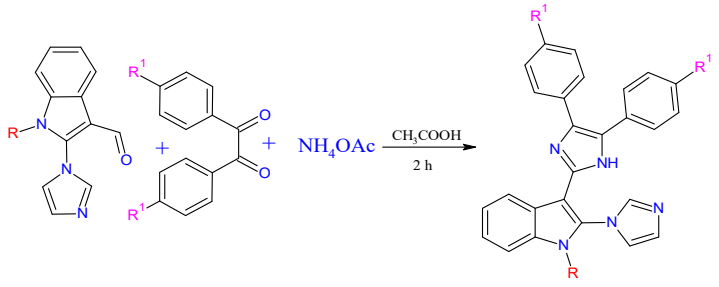
Scheme 3. Synthesis of indolylimidazole derivatives



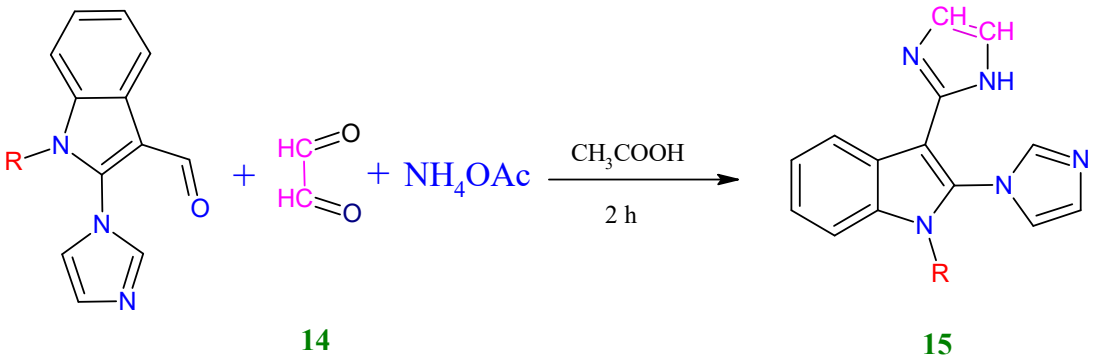
R = H, Br

Fig. 33. Structure of indolylimidazole derivatives

Benkli K., Demirayak S. et al.[35] synthesized 1-substituted-2-(1*H*-imidazol-1-yl)-3-(4,5-di-[4-substituted]phenyl-1*H*-imidazol-2-yl)-1*H*-indole derivatives **13 (Fig. 34 to Fig. 39)** by refluxed of 2-(1*H*-imidazol-1-yl)-1*H*-indole-3-carbaldehyde **11**, substituted-benzil **12** and ammonium acetate in presence of acetic acid for 2 hours **(Scheme 4)**. Indolylimidazoles **15** such as 1-substituted-2-(1*H*-imidazol-1-yl)-3-(1*H*-phenantho[5,6-*d*]-imidazol-2-yl)-1*H*-indole derivatives **(Fig. 40)** and 1-substituted-2-[2-(1*H*-imidazol-1-yl)-1*H*-indol-3-yl]-1*H*-benzimidazole derivatives **(Fig. 41)** also produced via above described method by using 2-(1*H*-imidazol-1-yl)-1*H*-indole-3-carbaldehyde, ammonium acetate and 1,2-diole **14** reactants **(Scheme 5)**. These compounds reported as antifungal and antimicrobial.



Scheme 4. Synthesis of indolylimidazole derivatives



14 **15**

15 R = CH_3, C_2H_5, C_6H_5, CH(O)=CH(O) = Phenanthrene-9,10-dione **(Fig. 40)**
R = CH_3, C_2H_5, C_6H_5, CH(O)=CH(O) = Cyclohexa-3,5-diene-1,2-dione **(Fig. 41)**

Scheme 5. Synthesis of indolylimidazole derivatives

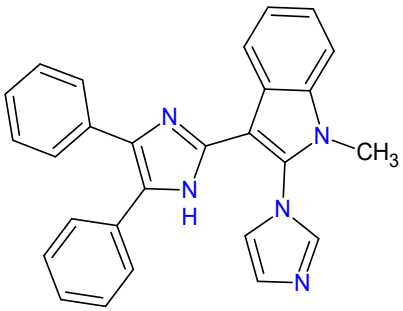
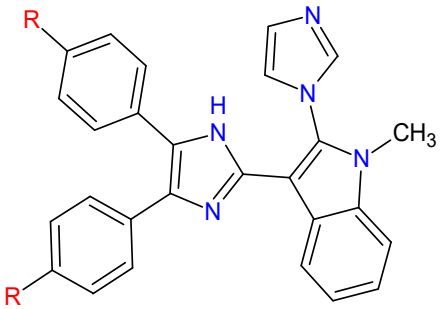
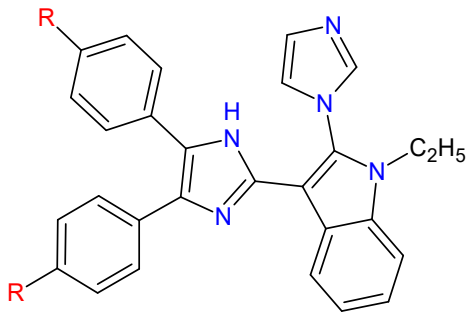


Fig. 34. Structure of 2-(1*H*-imidazol-1-yl)-1-methyl-3-(4,5- diphenyl-1*H*-imidazol-2-yl)-1*H*-indole



R = CH_3,OCH_3,Cl

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



R = CH_3,OCH_3,Cl

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

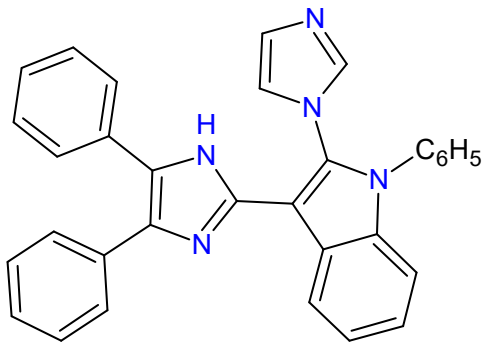
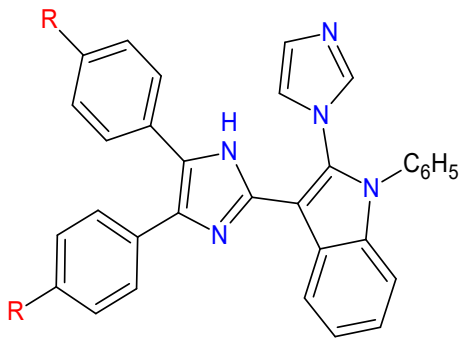
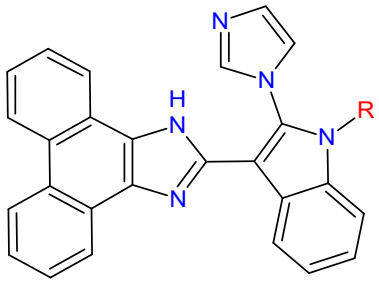


Fig. 38. Structure of 2-(1*H*-Imidazol-1-yl)-1-phenyl-3-(4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole



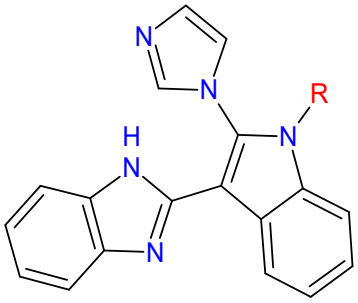
R = CH_3,OCH_3,Cl

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



R = CH_3, C_2H_5, C_6H_5

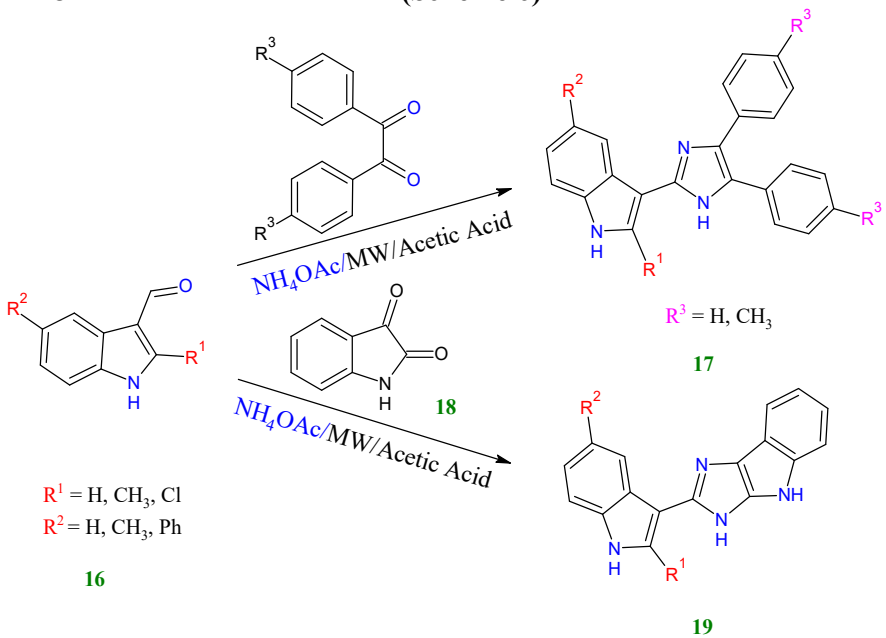
Fig. 40. Structure of 2-(1*H*-Imidazol-1-yl)-1-substituted-3-(1*H*-phenantho[5,6-*d*]imidazol-2-yl)-1*H*-indole



R= CH_3, C_2H_5, C_6H_5

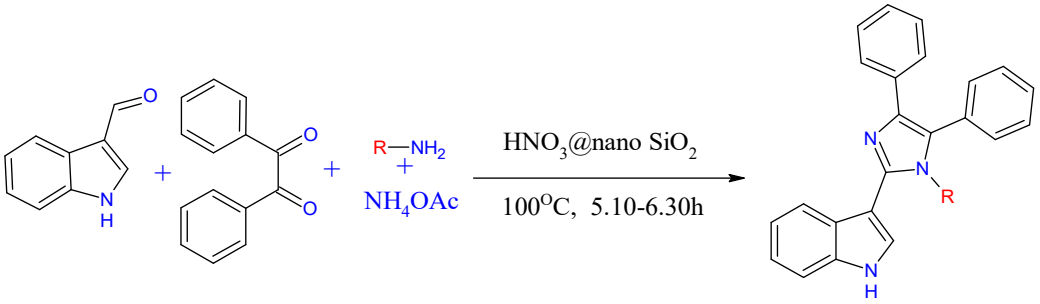
Fig. 41. Structure of 1-Substituted-2-[2-(1*H*-imidazol-1-yl)-1*H*-indol-3-yl]-1*H*-benzimidazole

Biradar J. S., Somappa S. B., et al.[36] synthesized 2,5-disubstituted-3-(4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-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-1*H*-indol-3-yl)-3,4-dihydroimidazo[4,5-b]indole derivatives **19** were also synthesized by using 1*H*-indole-2,3-dione **18** in same reaction condition **(Scheme 6)**.



Scheme 6. Synthesis of indolylimidazole derivatives

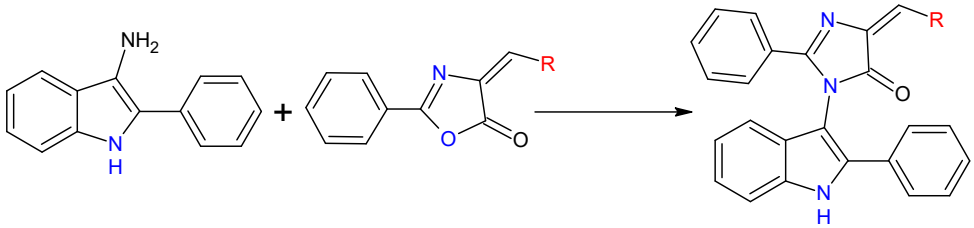
Nikoofar K, Dizgarani S. M., et al.[37] described the synthesis of 3-(4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole **20** and 3-(1,4,5-triphenyl-1*H*-imidazol-2-yl)-1*H*-indole **21** by condensation of benzil, indole-3-carbaldehyde, amine and ammonium acetate in the presence of HNO_3@nano SiO_2 at 100^{O}C for 6.30 hours and 5.10 hours in 74% and 76% yields respectively **(Scheme 7)**.



20 R = H
21 R = Ph

Scheme 7. Synthesis of indolylimidazole derivatives

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



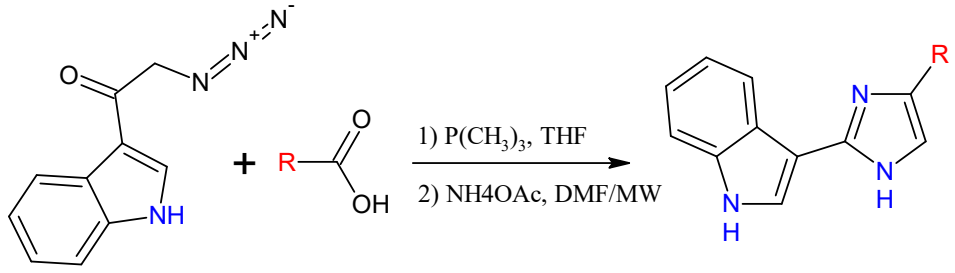
22 **23**

R = Ph, Ph-CH=CH

24

Scheme 8. Synthesis of indolylimidazole derivatives

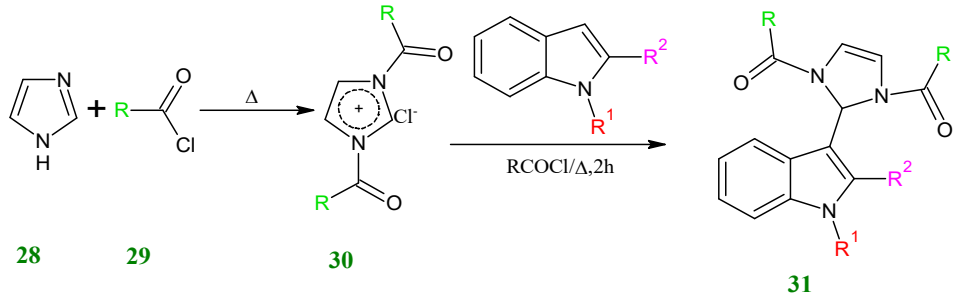
Molina P., Fresneda P. M., et al.[39] produced 3-(1*H*-imidazol-2-yl)-1*H*-indole **27** by two steps region-selective method by reaction of 2-azido-1-(1*H*-indol-3-yl)-ethan-1-one **25** and substituted-carboxylic acid **26** in the presence of tri-methyl phosphine followed by cyclization using ammonium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



25 **26** **27**

Scheme 9. Synthesis of indolylimidazole derivatives

Kobori T., Hatanaka Y., et al.[40] prepared 2-(1*H*-indol-3-yl)-1*H*-imidazole-1,3(2*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)**.

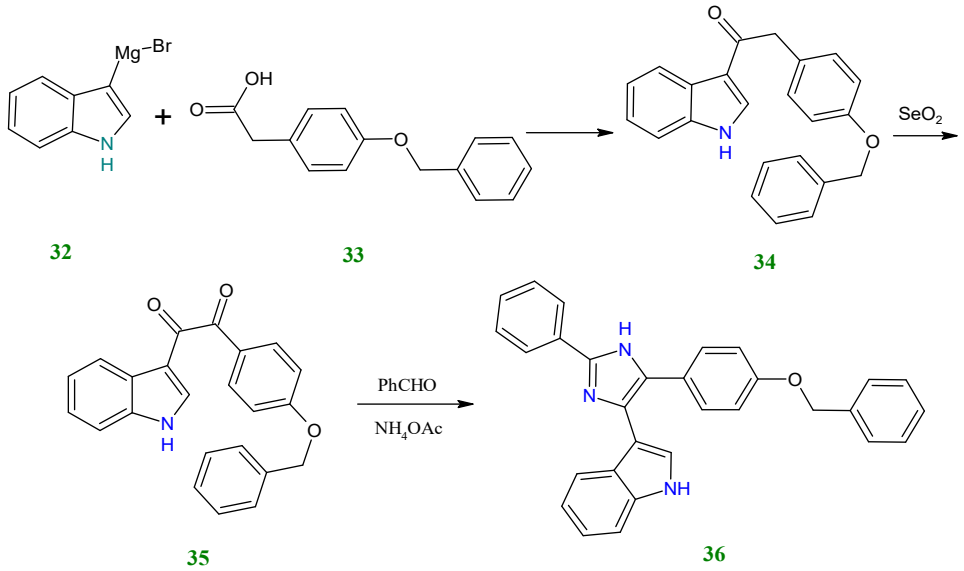


28 29 30 31

31 R = Me, Ph, -CH(Br)-CH(CH$_3$)$_2$, 2-Thein
R^1 = H, Me
R^2 = H, Me

Scheme 10. Synthesis of indolylimidazole derivatives

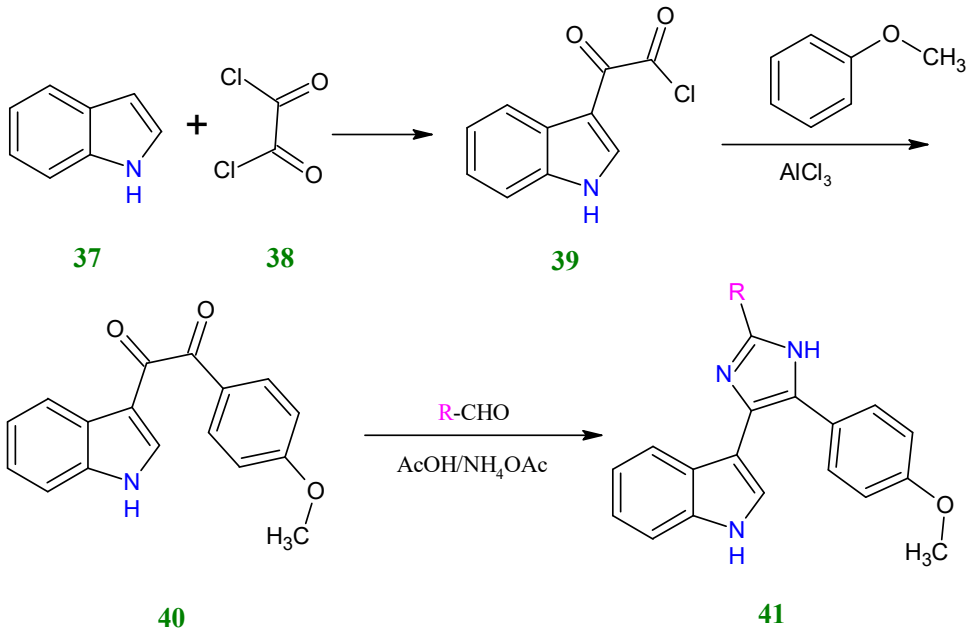
Kobori T., Hatanaka Y., et al.[41] synthesized 3-{5-[4-(benzyloxy)-phenyl]-2-phenyl-1*H*-imidazol-4-yl}-1*H*-indole **36** by reaction of indolylmagnesium bromide **32** with [4-(benzyloxy)-phenyl]-acetic acid **33** followed by oxidation of obtained 2-[4-(benzyloxy)phenyl]-1-(1*H*-indol-3-yl)ethan-1-one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



32 33 34 35 36

Scheme 11. Synthesis of indolylimidazole derivatives

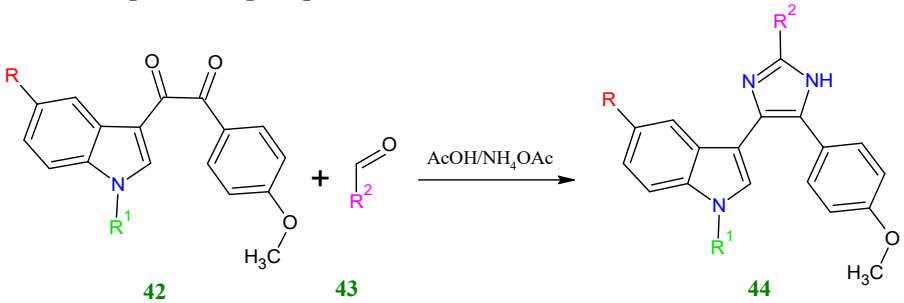
Ota T., Nakanishi M., et al.[42,43] synthesized 3-[2-substituted-5-(4-methoxyphenyl)-1*H*-imidazol-4-yl]-1*H*-indole **41** by reaction of indole **37** with ethanedioyl dichloride **38** followed by reaction of obtained (1*H*-indol-3-yl)(oxo)acetyl chloride **39** and anisole in the presence of aluminium chloride to form 1-(1*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.



41 R = 4-C_6H_4Me, 4-C_6H_4F, 2-Benzofuranyl

Scheme 12. Synthesis of indolylimidazole derivatives

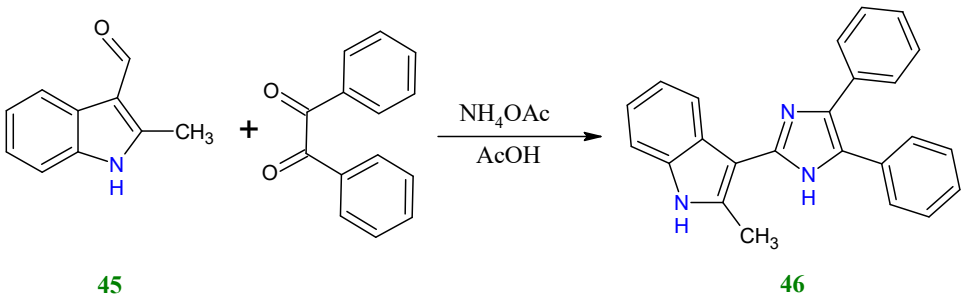
1,5-disubstitutes-3-[5-(4-methoxyphenyl)-2-substitutes-1*H*-imidazol-4-yl]-1*H*-indole derivatives **44** synthesized by reflux of 1-(1,5-disubstituted-1*H*-indol-3-yl)-2-(4-methoxyphenyl)ethane-1,2-dione **42**, substituted-aldehyde **43** and ammonium acetate in the presence of acetic acid[44-46] **(Scheme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



44	R	R^1	R^2
	H	H	4-C_6H_4Me
	Cl	H	2-Thienyl
	NO_2	Propyl acetate	2-Thienyl

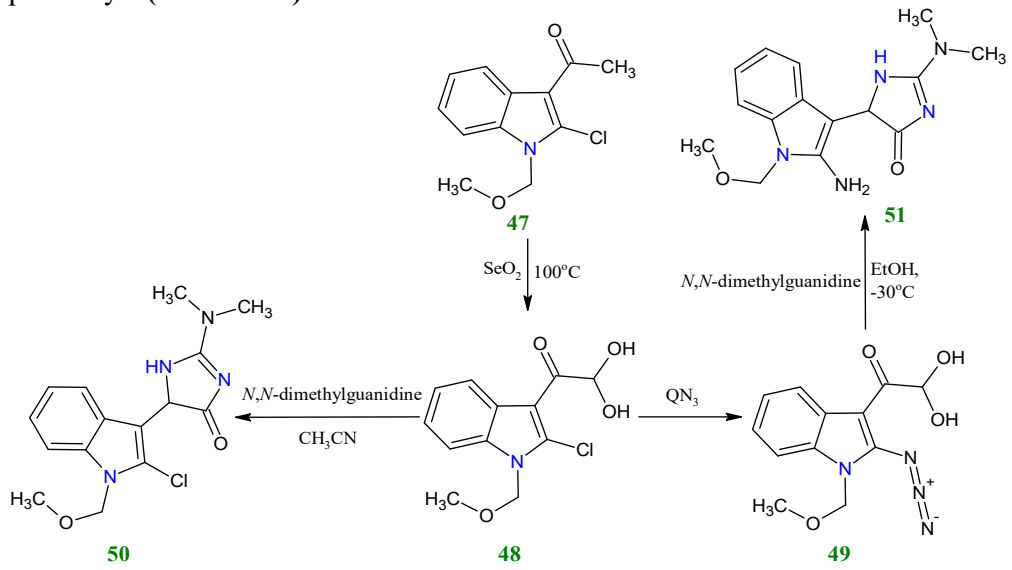
Scheme 13. Synthesis of indolylimidazole derivatives

3-(4,5-diphenyl-1*H*-imidazol-2-yl)-2-methyl-1*H*-indole **46** synthesized by reflux of 2-methyl-1*H*-indole-3-carbaldehyde **45**, benzil and ammonium acetate in the presence of acetic acid[47] **(Scheme 14)**.



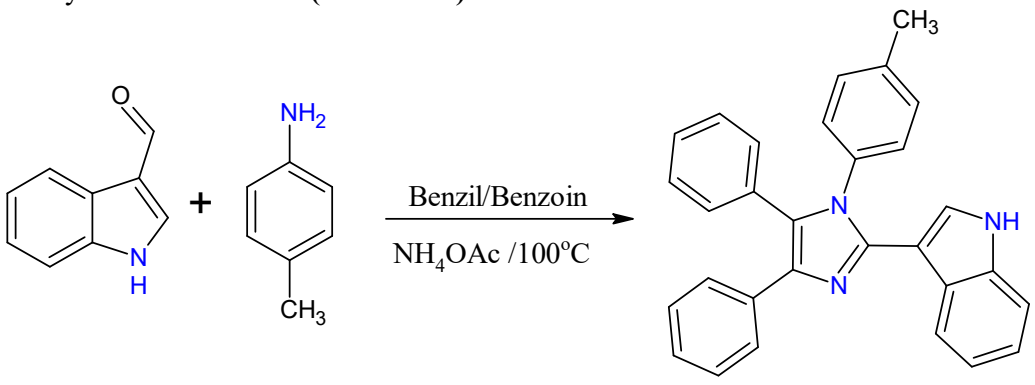
Scheme 14. Synthesis of indolylimidazole derivatives

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



Scheme 15. Synthesis of indolylimidazole derivatives

Shaterian H.R., Ranjbar M., et al[49]. described the synthesis of 3-[1-(4-methylphenyl)-4,5-diphenyl-1*H*-imidazol-2-yl]-1*H*-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^{O}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 HNO_3@nano SiO_2, Zn^{2+}@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.

Acknowledgments

The authors would like to express their sincere thanks to Dr. K.K. Verma, Assistant Professor, SNKP Govt. College, Neem Ka Thana, Dr. Rohitash Sharma, Assistant Professor, Department of Microbiology, JLN Medical College, Ajmer and Mr. Hemant Kumar for their valuable criticism and helpful discussions. One of the authors Narendra Nirwan is thankful to Dr. G.S. Chauhan, Deputy Secretary, UGC, Bhopal for his help and motivation and to UGC-CSIR for granting TRF to him.

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