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Pharmacological properties of some 3-substituted indole derivatives, a concise overview

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Abstract

Indole is a nitrogen-containing heterocycle. It is a very important motif in agriculture and pharmacy. Many compounds containing indole moiety have been isolated form nature. It is also an important part in natural alkaloids. Tryptophan is an amino acid which posses indole. 3-Sustituted indoles are the main group of its derivatives. Because the wide-spread application of 3-substituted indolic compounds, their synthetic procedures are in demand by organic chemists. In this review, we have focused on about twenty compounds of 3-substituted indole derivatives that showed pharmacological properties. A concise synthetic route for some of them has also been reported. The main pharmaceutical properties of these compounds are antibacterial, anti-cancer and antimicrobial activities.

Keywords: Indole; indolyl; pharmacy; drug; synthesis.

Introduction

The nitrogen containing heterocycles has been an attractive target for synthesis over many years. They are found in various natural products and have been identified as products of chemical and biological importance. Indole is a highly conserved heterocyclic molecule that acts as a free radical scavenger and has a broad-spectrum of antioxidant activity [1]. It has a unique place in the biological systems playing crucial roles in the form of amino acid, growth hormone and alkaloids [2]. Indole core is also an important component in many of recent drugs for

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treatment of chemotherapy-induced nausea and vomiting, cluster headache, or as antihypertensive, antineoplastic and antimitotic agents [3-5]. 3-Substituted indole derivatives play a key role in the synthesis of biologically active compounds especially with anticancer, antitumor, hypoglycemic, anti-inflammatory, analgesic and antipyretic activities [6-8]. Because the mentioned importance of indole compounds, herein, we have focused on some 3-substituted indole derivatives that possess drug potential.

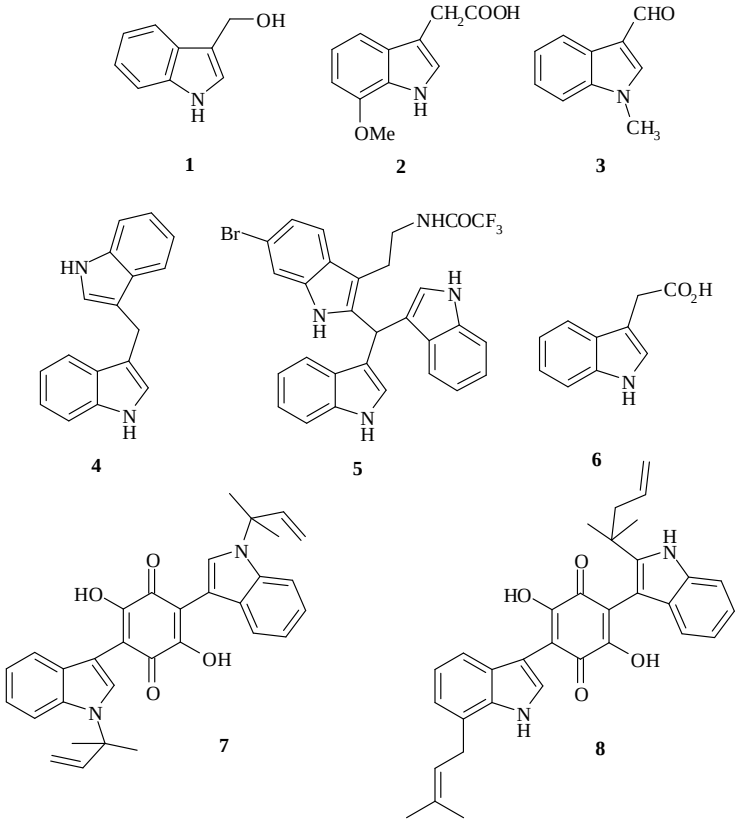
Indole-3-carbinol (I3C) (Scheme 1, **1**) is a potent inhibitor of cyclin dependent kinases (CDKs) [9]. It has also been reported to have anti-inflammatory effects through the inhibition of inflammatory factor production [10]. I3C has shown potential therapeutic effects as a novel treatment for vascular remodeling after injury [11]. This compound has been demonstrated to have inhibitory effects on the growth of a variety of cancer cells, including those of the prostate, breast, colon, lung and endometrium by targeting multiple signaling pathways [12]. **I3C** is a natural phytochemical that has been found in the vegetables of the cruciferous family that suppress the proliferation of cancer cells of breast, colon, prostate, and endometrium [13-14]. Antiobesity activity of indole-3-carbinol in high-fat-diet has been proved [15].

7- Methoxyindole-3-carboxylic acid methyl ester (Scheme 1, **2**) and 1-methylindole-3-carboxaldehyde **3** have been isolated from the mushroom Phellinus lintues [16]. It must be mentioned that mushroom Phellinus linteus has long been used as a traditional medicine in oriental countries for the treatment of stomachache, inflammation, arthritis of the knee, gastrointestinal disorder, lymphatic disease and cancer [17-18]. The chemical synthesis of **2** from enamine in the presence of Pd/C has been reported [19].

Bis-indolylmethanes (BIMs) have been recognized as one of the scaffolds that are found in many natural products isolated from both terrestrial and marine natural sources [20]. Among the family of BIMs, 3,3'-bis-indolylmethane **4** is a major metabolite of the anticancer agent which is found in vegetables of the Brassica genus. It is capable of inhibiting the proliferation of both estrogen-dependent and -independent breast cancer cell lines [21-22].

The synthetic tris-indolylmethane **5**, which is bengacarboline analog, has been shown to exhibit anti-cancer activity as well as the ability to induce the accumulation of cells in the S phase of DNA synthesis [23]. Indole 3-acetic acid **6** is the principle hormone which regulates various developmental and physiological processes in plants [24]. It has been isolated form the tryptophan cata-

bolize in purple bacteria [25]. Purple bacteria help growth enhancement and productivity of rice [26]. Asterriquinone A1 **7** and demethylasterriquinones **8** have recently been isolated from a wide range of fungi, including Aspergillus terreus, Chaetomium sp. and Pseudomassaria sp. [27-29]. They exhibit a wide range of biological activities including antitumor properties and are inhibitors of HIV reverse transcriptase [30]. Compound **7** has been shown to arrest the cell cycle in G1 and promote apoptotic cell death [31]. It has also been reported as an orally active non-peptidyl mimetic of insulin with anti-diabetic activity [32]. These derivatives possessed 3-indolylbenzoquinone nucleus.

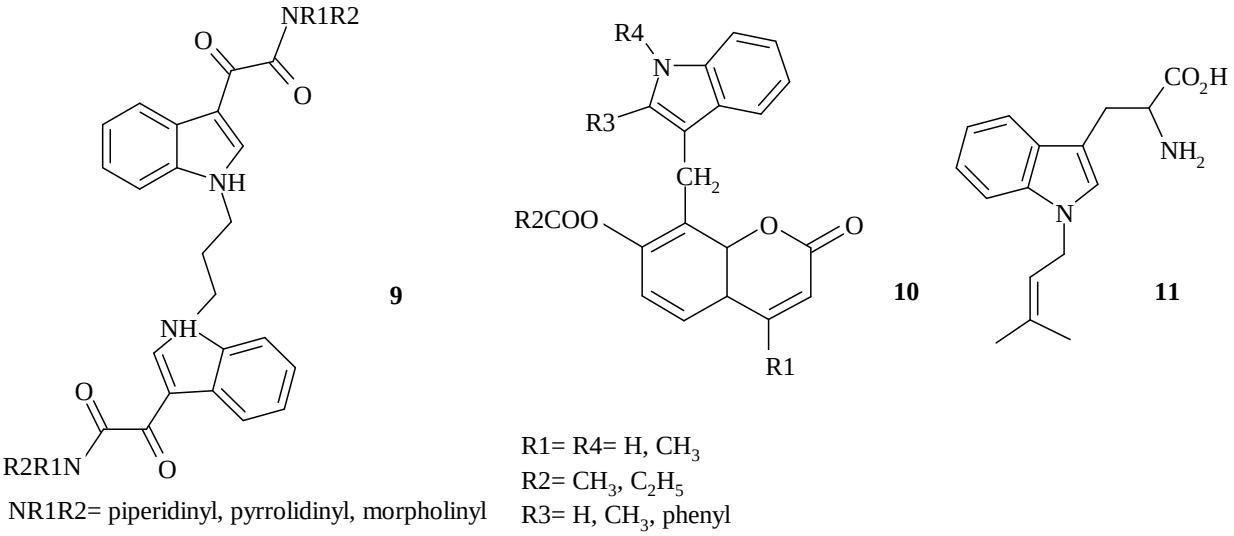


Scheme 1.

A series of *N*-1, C-3 and C-5 substituted bisindoles (Scheme 2, **9**) have been identified as highly potent antifungal and antibacterial compounds. Dockings of these molecules in the active sites of lanosterol demethylase, dihydrofolate reductase and topoisomerase II indicate their strong interactions with these enzymes [33].

A class of compounds (Scheme 2, **10**) which contain two heterocycle moieties, indole and coumarin, linked by a methylene bridge, were tested for cytotoxicity and anti-

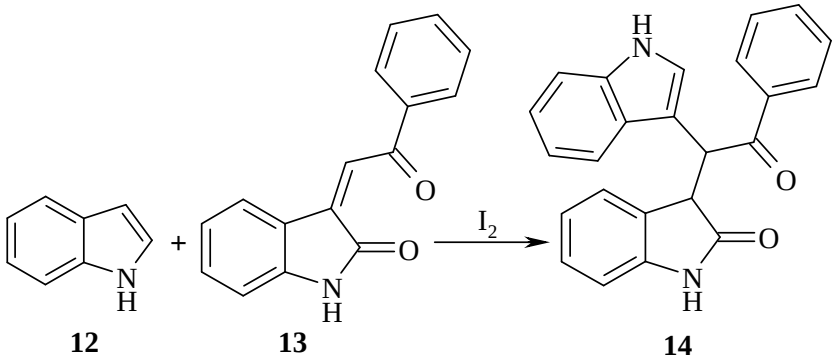
viral activity and showed successive results against Flaviviruses (yellow fever virus, YFV) and Pestiviruses (bovine viral diarrhea virus, BVDV) [34]. Prenylated indole compounds show scavenging activity for reactive oxygen species (ROS) and reactive nitrogen species (RNS). *N*-prenyl tryptophan 11 is an example of this class that is very active against peroxyl radical ($ROO^{\cdot}$). It showed scavenging of hypochlorous acid (HOCl). The radical stabilization was performed by the allylic double bond as well as by dissipation into the indole ring [35]. So, they are good candidates to be used as antioxidant drugs.



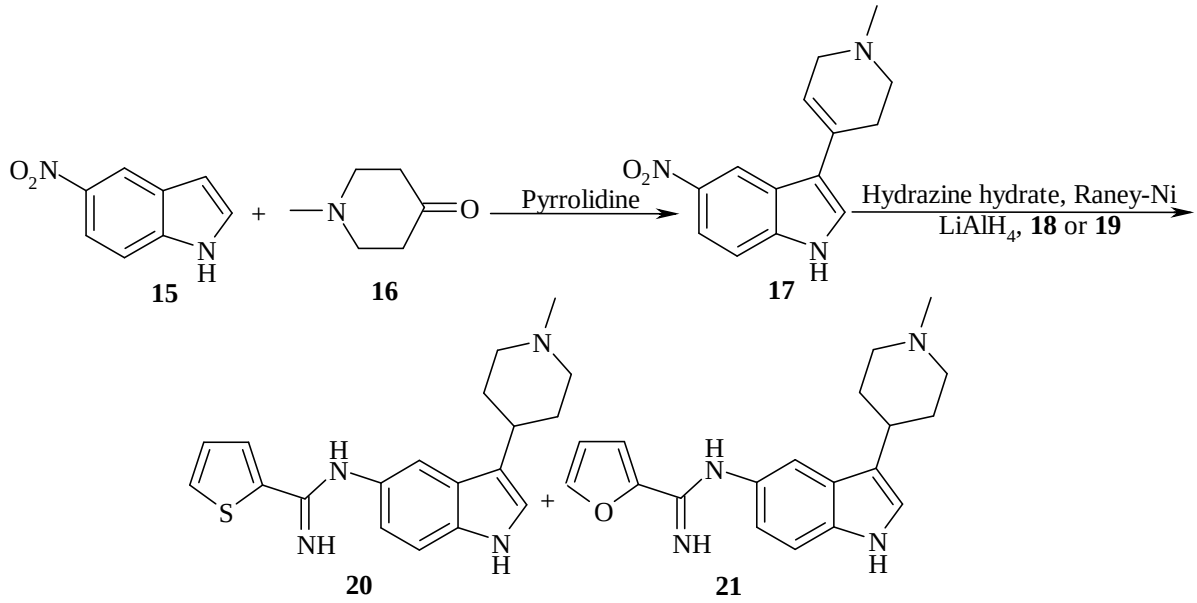
Scheme 2.

3-(1-(1H-indol-3-yl)-2-oxo-2-phenylethyl)indolin-2-one **14** exhibited antibacterial and antifungal properties. It has been prepared from iodine catalyzed smooth conjugate addition of indole **12** onto en-1,4-dione **13** (Scheme 3) [36]. The minimum inhibitory concentrations (MIC) of these compounds against three representative Gram-positive organisms viz. Bacillus subtilis (MTCC 441), Staphylococcus aureus (MTCC 96), Staphylococcus epidermidis and Gram negative organisms viz. Escherichia coli (MTCC 443), Pseudomonas aeruginosa (MTCC 741), and Klebsiella pneumoniae (MTCC 618) by National Committee for Clinical Laboratory (NCCL) standards confirmed their antimicrobial activity. In vitro antifungal activity of the newly synthesized compounds has also been studied against the fungal strains such as Candida albicans (MTCC 227), Saccharomyces cerevisiae (MTCC 36), Rhizopus oryzae (MTCC 262),

and Aspergillus niger (MTCC 282) by Agar Well Diffusion Method [37]. 3-(*N*-methylpiperidine)indoles that possess two of the guanidine isosteric groups (2-thiophene amidine and 2-furanyl amidine) at 5-position of indole ring (Scheme 4, **20**, **21**) were synthesized from carbon–carbon bond formation of 5-nitroindole 15 reaction with *N*-methyl-4-piperidone 16 under basic conditions [38] yield the corresponding amine **17**. Reduction of the nitro group under hydrogenation conditions followed by coupling to methyl thiophene-2-carbimidothioate hydroiodide **18** or benzyl furan-2-carbimidothioate hydrobromide **19**, afforded **20** and **21**, respectively (Scheme 4) [39]. These 3,5- indoles have been evaluated as inhibitors of human nitric oxide synthase (NOS) [40]. The NOS has important roles in controlling blood pressure and in immune response. The important contributing factor of a guanidine group in these compounds for NOS inhibition has become one of the most promising strategies for early selective NOS inhibition design [41]. The drug-drug interaction potential as well as the cardiovascular liabilities in these compounds is due to the indole moiety.



Scheme 3. 3-(1-(1H-indol-3-yl)-2-oxo-2-phenylethyl)indolin-2-one synthesis



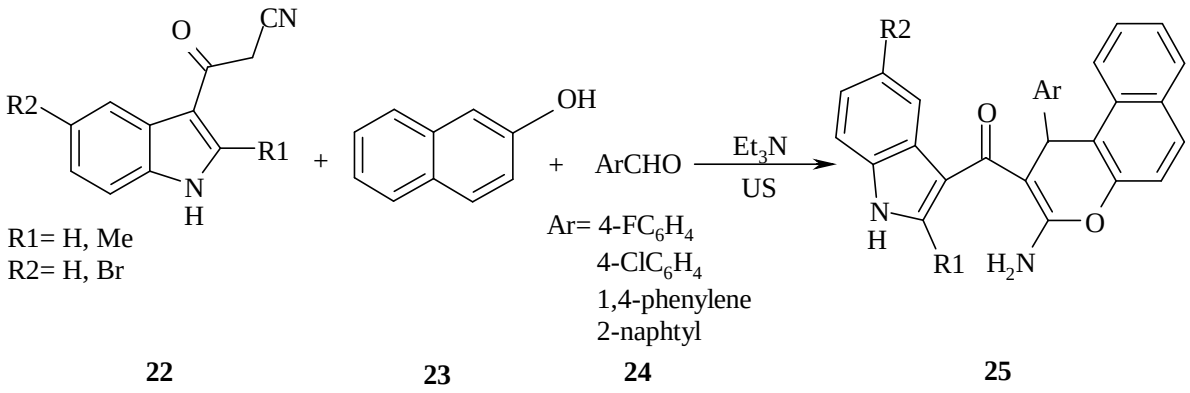
Scheme 4. 3-(*N*-methylpiperidine)indoles synthesis

1H-benzo[f]chromen-2-yl)(1H-indol-3-yl)methanones **25** are bi-functional heterocycles. They contain indole moiety that exhibit antibacterial and antifungal activities [42] and chromen motif that shows high antifungal, antibacterial [43-44] and also anti-picornavirus properties [45]. These classes of compounds have been synthesized from the triethylamine catalyzed condensation of 3-cyanoacetylindoles **22**, β-naphthol **23** and aryl aldehydes **24** under ultrasonic irradiations [46] (Scheme 5).

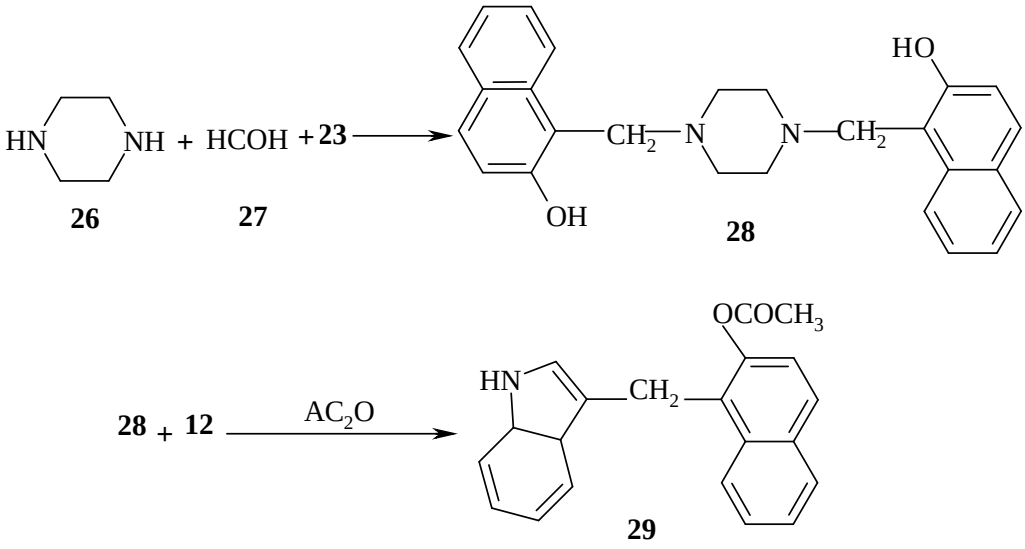
3-(2-Acetoxynaphthalen-1-yl)methylindole **29** is an unsymmetrical methylene derivative of indole which is synthesized from Mannich base **28** and **12**, that examined in vitro in parallel cell-based assays for cytotoxicity and antiviral activity. The results confirmed that this novel compound showed a significant activity against respiratory syncytial virus (RSV), human immunodeficienc virus type-1 (HIV-1) and antiviral activity against flaviviridae family i.e. flaviviruses (YFV) and pestiviruses (BVDV) (Scheme 6) [47]. It is interesting to know that many of the emerging infections in humans and animals are caused by RNA viruses.

Sigma receptors are classified into two sub types denoted sigma-1 and sigma-2. Sigma-1 is expressed in the central nervous system and is also widely distributed in peripheral organs and tissues such as heart and spleen [48]. The sigma-2 receptors are associated with functions and disorders such as inflammation [49], depression and Alzheimer

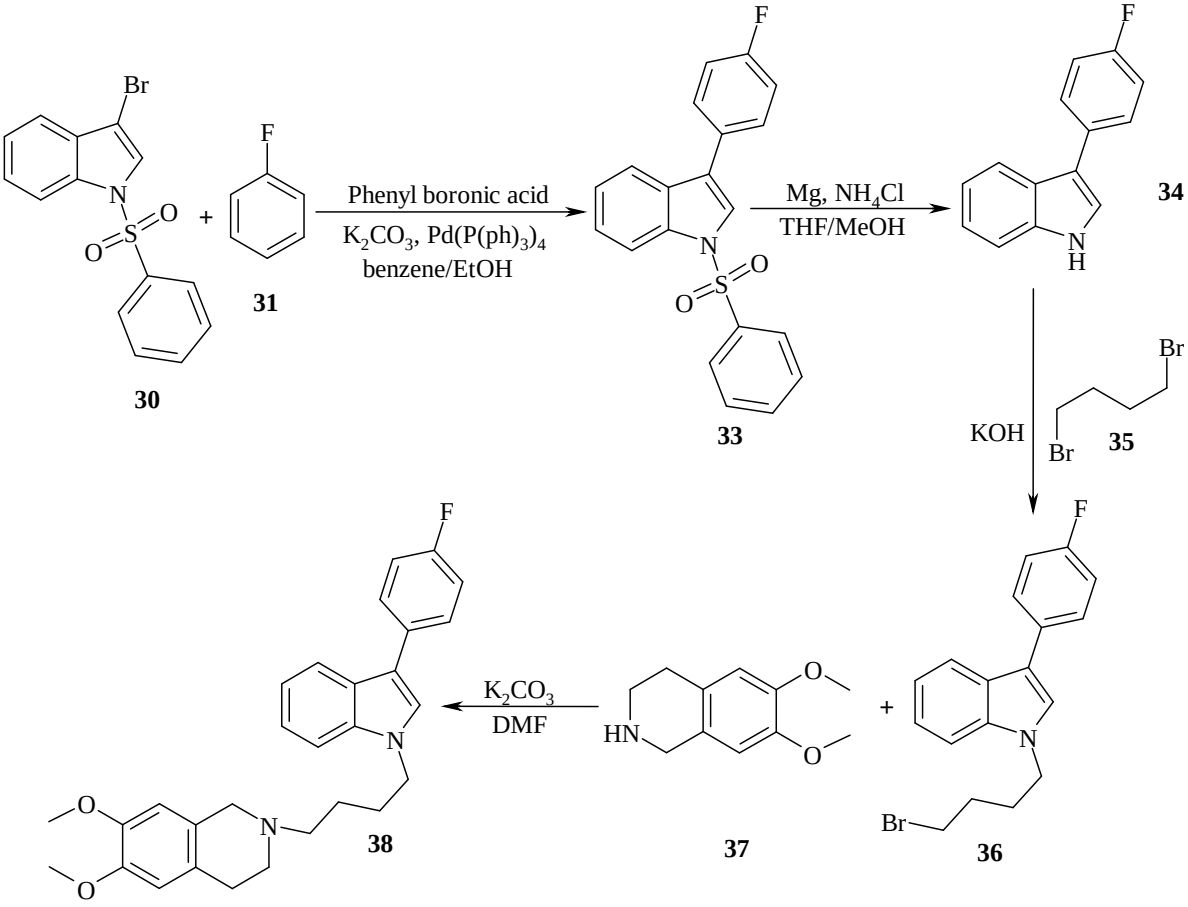
disease [50]. A series of 4-(indol-1-yl)butan-1-amines were synthesized evaluating their binding affinity for sigma receptors. 2-(4-(3-(4-Fuorophenyl)indol-1-yl)butyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **38** is one of this class of compounds identified as a high-affinity for sigma-2 receptor and a weak affinity for the sigma-1 receptor. This compound has been synthesized from the Suzuki reaction of 3-bromo-1-(phenylsulfonyl)indole **30** with phenyl boronic acid **32** [51] followed by the deprotection with magnesium and ammonium chloride to give **34**. *N*-alkylation with 1,4-dibromobutane **35** gave the bromo intermediate **36** which reacted with amine **37** to give 3-substituted-indole **38** (Scheme 7).



Scheme 5. 1H-benzo[f]chromen-2-yl)(1H-indol-3-yl)methanones synthesis



Scheme 6. 3-(2-Acetoxynaphthalen-1-yl)methylindole synthesis

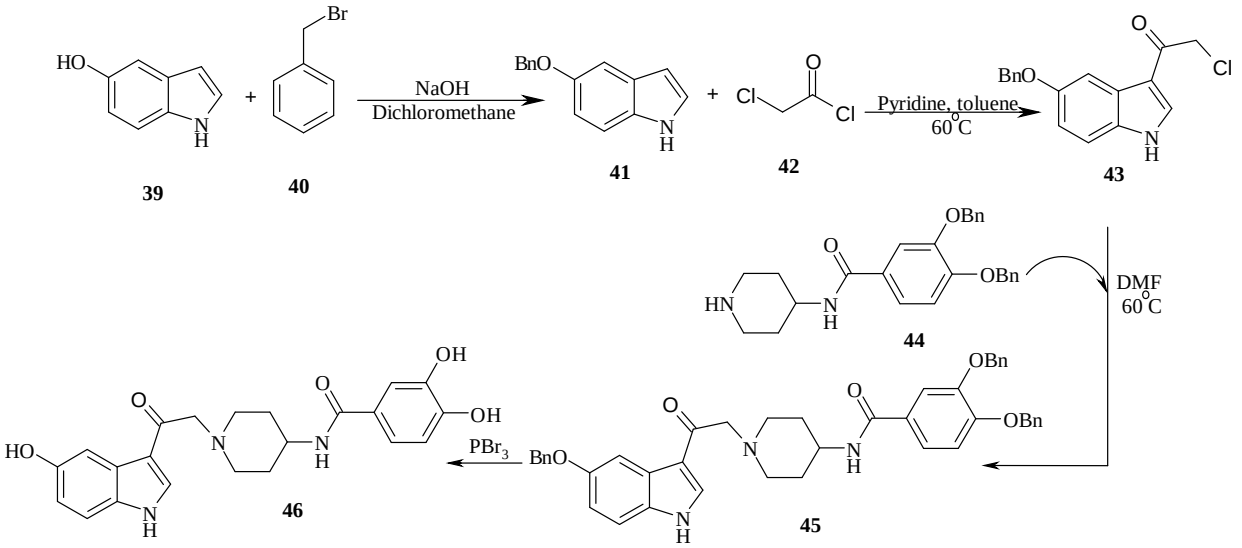


Scheme 7. 2-(4-(3-(4-fluorophenyl)indol-1-yl)butyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline synthesis

3,4-Dihydroxy-*N*-[1-[2-(5-hydroxy-1H-indol-3-yl)-2-oxoethyl]piperidin-4-yl]benzamide **46** was the most effective antioxidant agent. This antioxidant has been synthesized from the reaction of 5-hydroxy-1H-indole **39** with benzyl bromide **40** that reacted with chloro acetylchloride **42** to give the 1-[5-(benzyloxy)-1H-indol-3-yl]-2-chloroethanone 43 that was coupled with the 3,4-bis(benzyloxy)-*N*-piperidin-4-yl-benzamide 44 giving the triple benzyl protected 1H-indol-3-substituted derivative 45. Finally, reacting with boron tribromide, the cleavage of protecting benzyl group was successfully carried out giving **46** (Scheme 8) [52]. It must be mentioned that antioxidants which decrease the free radical generation could be used as protective agents against excitotoxic injuries [53].

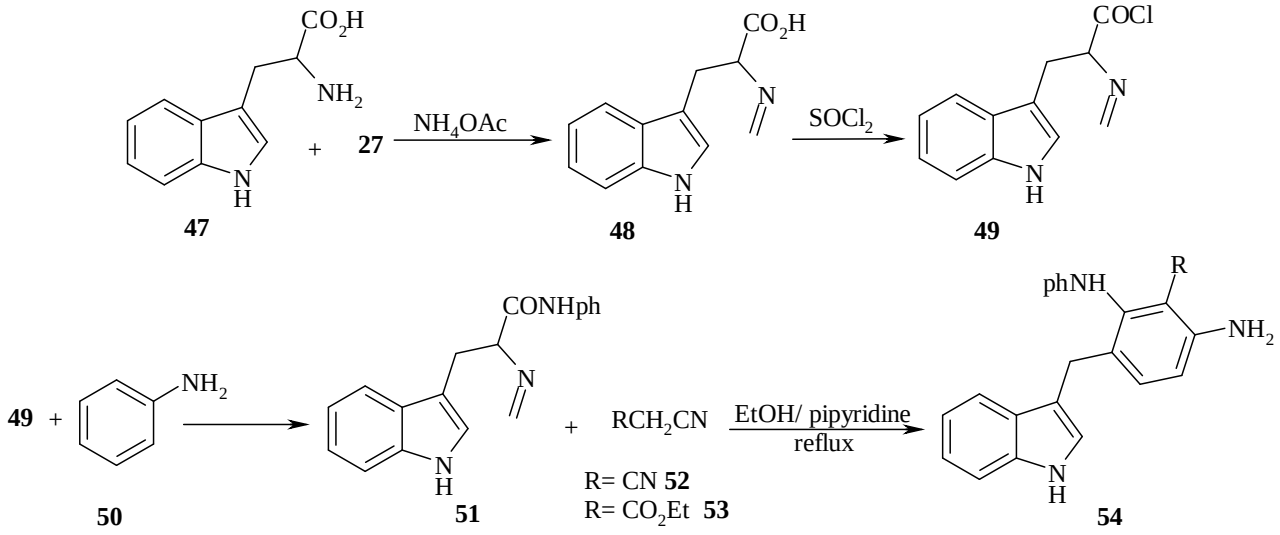
The novel indole derivatives, indolylmethyl pyridine derivatives **54**, which are neuroprotective agents, resulted in significant

increase in brain malondialdehyde level (MDA) and lactate dehydrogenase (LDH) activity whereas it caused significant decrease in brain monoamines levels and antioxidant enzymes activity [54]. This class of compounds can be synthesized from the reaction of l-tryptophan (TRP) **47** with formaldehyde **27** in the presence of ammonium acetate to afford *Nb*-formaltryptophan derivative 48. Reaction of **48** with thionyl chloride gave indolyl methylenaminopropanyl chloride 49 that reacted with aniline **50** to give the corresponding **51**. The reaction of **51** with either malononitrile **52** or ethyl cyanoacetate **53** in refluxing ethanolic/piperidine solution gave the corresponding indolylmethyl aminopyridine derivatives 54 respectively (Scheme 9) [55].

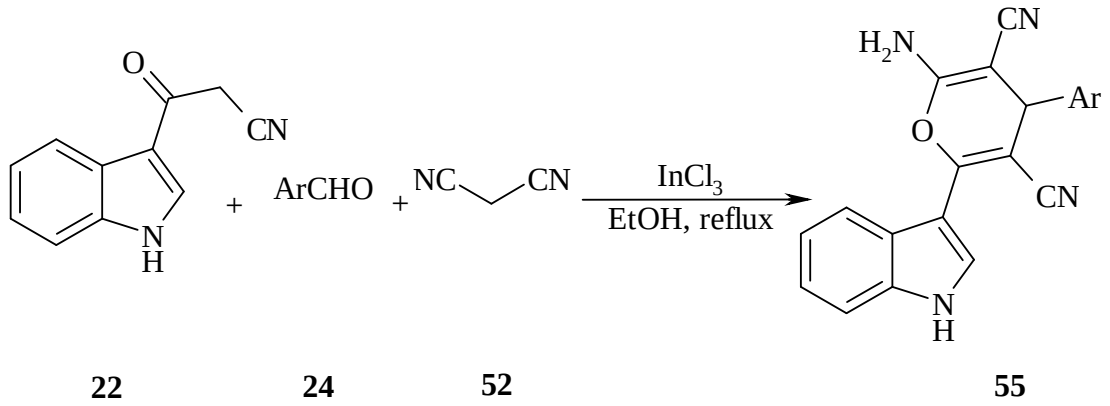


Scheme 8. 3,4-Dihydroxy-*N*-[1-[2-(5-hydroxy-1H-indol-3-yl)-2-oxoethyl]piperidin-4-yl]benzamide synthesis

Polyfunctionalized 3-pyranyl indoles **55** were evaluated for anti-microbial, antioxidant, and anticancer activities. Some of the compounds showed good anticancer activity against MCF-7 breast cancer cell lines in comparison with ~~of~~ standard drug. These privileged medicinal scaffolds have been synthesized through a three component reaction of 3-cyanoacetyl indole **22**, benzaldehydes **24** and malononitrile **52** (Scheme 10) [56]. Antibacterial activity of novel Schiff bases 61 from dimers of 4-amino-3-[3-(1-benzyl)indole]-5-thiomethyl-1,2,4-triazole, against three bacterial strains was studied by the disk diffusion method.



Scheme 9. Indolylmethyl pyridine derivatives synthesis

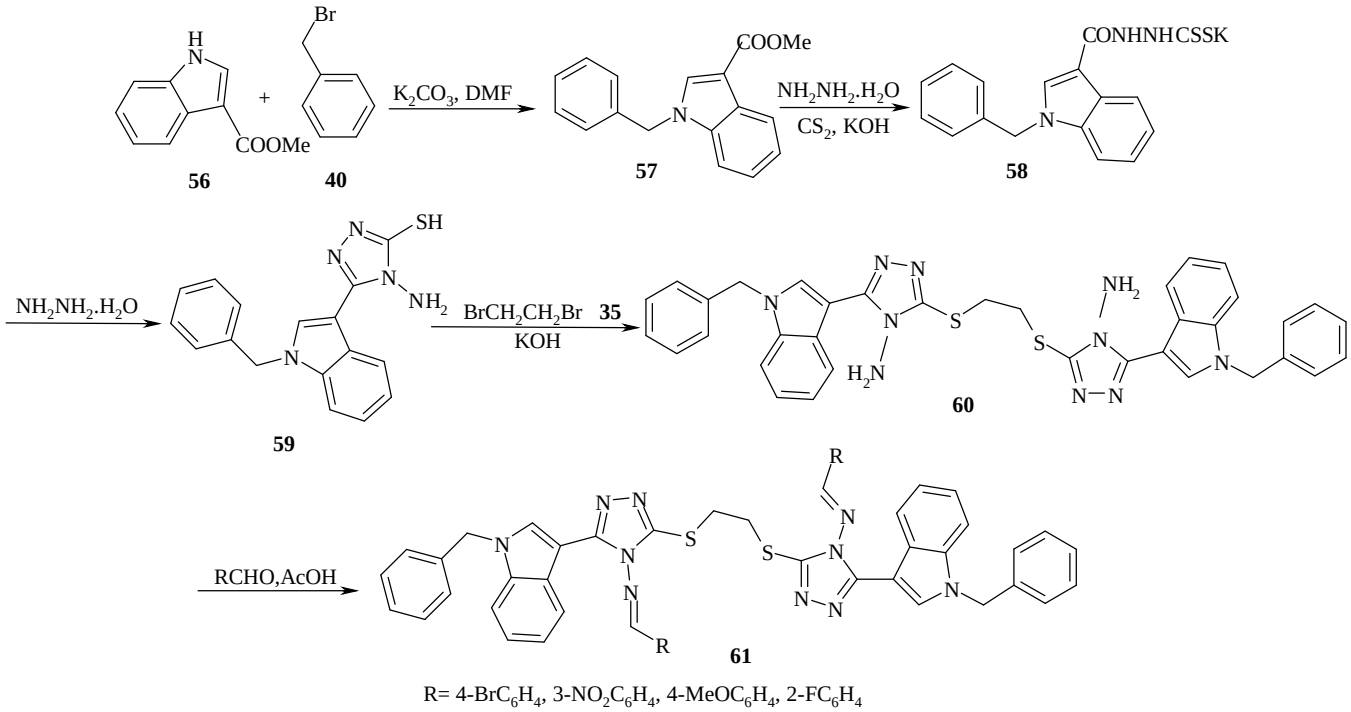


Ar= 2-ClC_6H_4, 4-FC_6H_4, 3-$NO_2C_6H_4$, 4-$MeOC_6H_4$

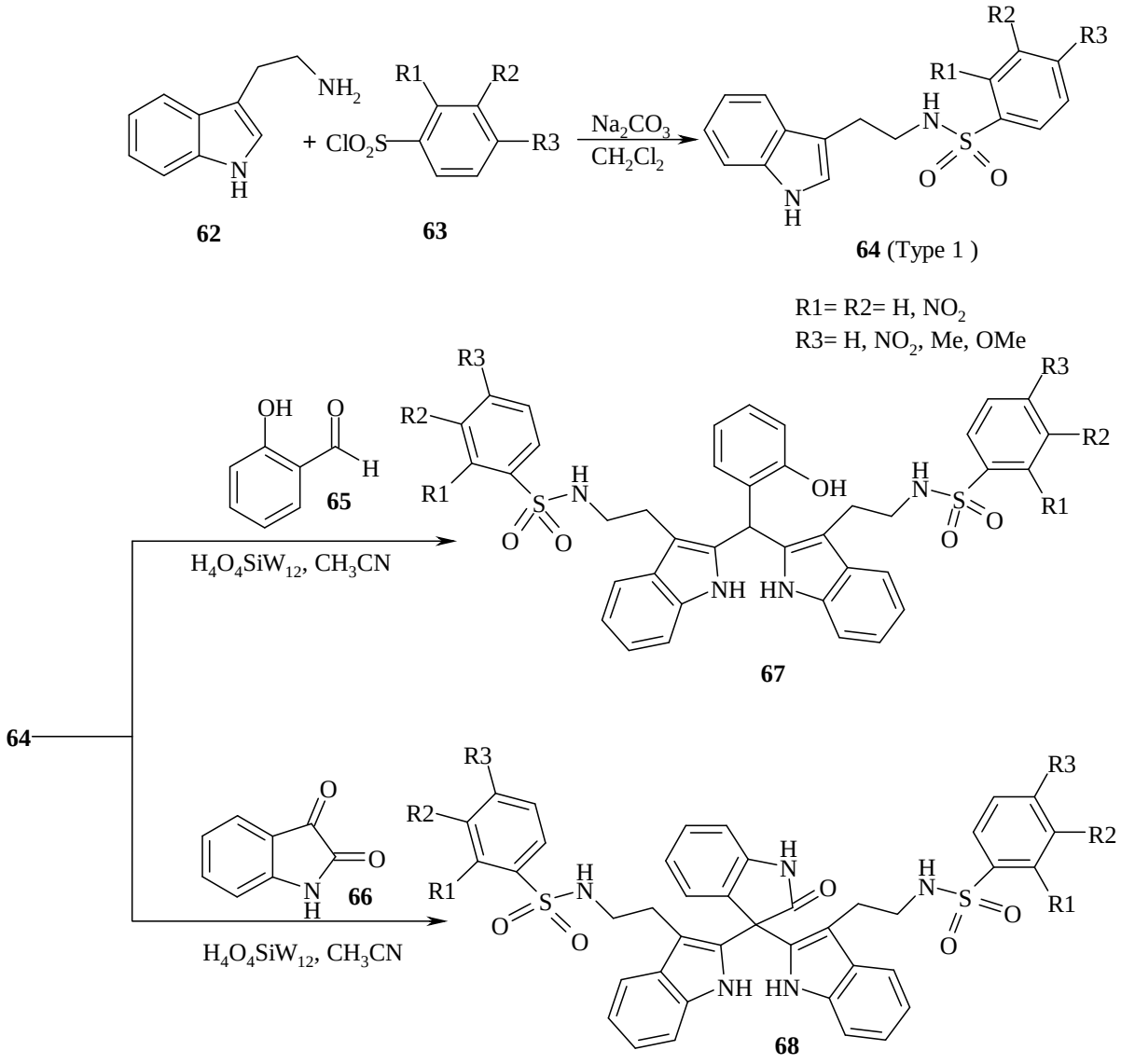
Scheme 10. Polyfunctionalized 3-pyranyl indoles synthesis

Preliminary results indicated that these compounds had strong antibacterial activity. They can be gained from 3-acetoxy indole **56** with benzylbromide **40** to yield **57** followed by the reaction with carbon disulfide and hydrazine to get **59**. Oxidation with 1,2-dibromothane 35 yield dimer **60**. The Schiff bases **61** were obtained via the reaction of **60** with appropriate aldehyde **24** [57]. It must be mentioned that the triazole structure is occured widely in natural medicines and synthetic drugs. Currently available antimicrobial [58] or antitumor [59] drugs such as terconazole, itraconazole contain the tri-

azole ring. So, compound 61 that contain both indole and triazole moieties show very good antibacterial properties, especially those containing methoxyphenyl and halogen substituents (Scheme 11). A series of arylsulfonyl mono-indoles 64, bis-indoles 67, and tris-indoles 68 have been evaluated for their cytotoxicity toward four human cancer cell lines including HuCCA-1 (cholangiocarcinoma), HepG2 (hepatocellular carcinoma), A-549 (lung carcinoma), and MOLT-3 (lymphoblastic leukemia). They showed high antiproliferative activity against the mentioned cells. Among these three classes, *N*-arylsulfonyl bisindoles 67 bearing phenolic groups are potentially interesting that lead to pharmacophores of anticancer agents. Type 1 has been synthesized via the reaction of tryptamine 62 with appropriate benzenesulfonyl chloride 63 and sodium carbonate. The reaction of type I with *o*-salisylaldehyde 65 or isatin 66 yields arylsulfonyl bis-indoles 67, and tris-indoles 68. A significant antiproliferative activity was observed for bis- and tris-indole core structures endowed with a phenolic group or with a functional group that can form H-bonding together with the highly hydrophobic *p*-substituent on the benzenesulfonamide moiety (Scheme 12) [60].



Scheme 11. Indole-based Schiff bases synthesis



Scheme 12. Arylsulfonyl mono-indoles, bis-indoles, and tris-indoles synthesis

A series of 5-indolylpyrimido[4,5-d]pyrimidinones **72** were obtained by multi-component reaction of 3-formylindole **69**, thiobarbituric acid/barbituric acid **70** and thiourea/urea **71** under microwave irradiation in dry media. Representative compounds were also evaluated for their antimicrobial activity against Rhizopus stolonifer, Fusarium oxysporum, Escherichia coli, and Pseudomonas aeruginosa at different concentrations. The compounds showed promising antimicrobial activity (Scheme 13) [61].

Conclusion

In this review, we have implied some 3-substituted indole derivatives that comprised pharmaceutical properties, some of them can

be used as drugs. In some of the compounds, there are two different heterocyclic moieties that multiply their therapeutic properties. Some of the mentioned kinds have been isolated from natural sources. Synthetic procedure of some derivatives has also been shown. This overview denotes the importance of 3-substituted indole derivatives in increasing health level of routine life.

Acknowledgments

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