A brief review of the biological potential of indole derivatives

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Abstract

Background: Various bioactive aromatic compounds containing the indole nucleus showed clinical and biological applications. Indole scaffold has been found in many of the important synthetic drug molecules which gave a valuable idea for treatment and binds with high affinity to the multiple receptors helpful in developing new useful derivatives.

Main text: Indole derivatives possess various biological activities, i.e., antiviral, anti-inflammatory, anticancer, anti-HIV, antioxidant, antimicrobial, antitubercular, antidiabetic, antimalarial, anticholinesterase activities, etc. which created interest among researchers to synthesize a variety of indole derivatives.

Conclusion: From the literature, it is revealed that indole derivatives have diverse biological activities and also have an immeasurable potential to be explored for newer therapeutic possibilities.

Keywords: Indole, Antiviral, Anti-inflammatory, Anticancer, Anti-HIV, Antioxidant, Antimicrobial, Antitubercular, Antidiabetic, Antimalarial, Anticholinesterase activities

Background

Indole is also known as benzopyrrole which contains benzenoid nucleus and has 10 π-electrons (two from lone pair on nitrogen and double bonds provide eight electrons) which makes them aromatic in nature. Similar to the benzene ring, electrophilic substitution occurs readily on indole due to excessive π-electrons delocalization [1]. Indole is an important heterocyclic system that provides the skeleton to lysergic acid diethylamide (LSD), strychnine, and alkaloid obtained from plants. Physically, they are crystalline colorless in nature with specific odors. The addition of the indole nucleus to medicinal compounds that is bioactively pharmaeophore made it an important heterocyclic compound having broad-spectrum biological activities [2]. Due to this, researchers took interest to synthesize various scaffolds of indole for screening different pharmacological activities. Various natural compounds contain indole as parent nucleus for example tryptophan. Indole-3-acetic acid is a plant hormone produced by the degradation of tryptophan in higher plants. Derivatives of indole are of wide interest because of their diverse biological and clinical applications. Here, we have tried to summarize the important pharmacological activity of indole derivatives [3].

Main text

Biological activities of indole

Antiviral activity

6-Amino-4-substitutedalkyl-1H-indole-2-substituted-carboxylate derivatives were prepared and reported as antiviral agents by Xue et al. In all tested compounds, compound methyl 6-amino-4-isobutoxy-1H-indole-2-carboxylate (1) showed inhibitory activity against influenza A with IC₅₀ = 7.53 μmol/L and the highest selectivity index (SI) value 17.1 to CoxB3 virus [4].
4-Alkyl-1-(5-fluoro-3-phenyl-1H-indole-2-carbonyl)thiosemicarbazide derivatives of indole were prepared and investigated in vitro for antiviral activity in a broad range of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) viruses by Cihan-Üstündag et al. Compounds 1-(5-fluoro-3-phenyl-1H-indole-2-carbonyl)-4-methylthiosemicarbazide (2), 4-ethyl-1-(5-fluoro-3-phenyl-1H-indole-2-carbonyl)thiosemicarbazide (3), 1-(5-fluoro-3-phenyl-1H-indole-2-carbonyl)-4-propylthiosemicarbazide (4), and 4-butyl-1-(5-fluoro-3-phenyl-1H-indole-2-carbonyl)thiosemicarbazide (5) are potent antiviral agents with IC$_{50}$ values ranging from 0.4 to 2.1 μg/mL against Coxsackie B4 virus [5].

Ethyl 1H-indole-3-carboxylates also showed antiviral activity in Huh-7.5 cells explained by Sellitto et al. Compound 4-((3-(ethoxycarbonyl)-1-methyl-5-(pyrrolidin-1-ylmethyl)-1H-indol-2-yl)methyl)benzenesulfinate (6) was the most active compound at low concentration against Hepatitis C virus (HCV) [6].

Giampieri et al. elaborated reaction of indoles and 2-naphthols through Mannich bases and tested against different viruses and compound methyl 1-((1H-indol-3-yl)methyl)-2-naphthoate (7) showed significant activity against Yellow Fever Virus (YFV), Bovine viral diarrhea virus (BVDV), Human immunodeficiency virus-1 (HIV-1), and Respiratory syncytial virus (RSV) [7].

Pyrimidine-derived indole ribonucleosides (2S,3R,4S,5S)-2-(6-chloro-4-(furan-2-yl)-9H-pyrimido[4,5-b]indol-9-yl)-5-(hydroxymethyl)-tetrahydrofuran-3,4-diols were synthesized and tested for in vitro antiproliferative (HL-60 cervical carcinoma HeLaS3, T-lymphoblastic leukemia human cell line CCRF-CEM and promyelocytic leukemia) and antiviral activity (Dengue virus and anti-hepatitis C virus) by Tichy et al. Compound (2S,3R,4S,5S)-2-(6-chloro-4-(furan-2-yl)-9H-pyrimido[4,5-b]indol-9-yl)-5-(hydroxymethyl)-tetrahydrofuran-3,4-diol (8) exhibited the notable cytotoxicity in HepG2 cells and THP-1 with IC$_{50}$ of 0.175 and 1.565 μM [8].

5-Nitro-3-[(5-nonsubstituted/methyl-4-thiazolidinone-2-ylidene) hydrazono]-1H-2-indolinones were prepared and tested for antiviral activities by Terzioglu et al. Compounds (Z)-4-allyl-1-((morpholinomethyl)-5-nitro-2-oxoindolin-3-ylidene)thiosemicarbazide (9), (3Z,3E)-3-(2-(ethyl-4-oxothiazolidin-2-ylidene)hydrazono)-5-nitroindolin-2-one (10), (3Z,3E)-5-nitro-3-(2-(4-oxo-3-phenylthiazolidin-2-ylidene)hydrazono)indolin-2-one (11), (3Z,3E)-3-(2-(3-(4-bromophenyl)-5-methyl-4-oxothiazolidin-2-ylidene)hydrazono)-5-nitroindolin-2-one (12) and (3Z,3E)-3-(2-(3-(4-chlorophenyl)-5-methyl-4-oxothiazolidin-2-ylidene)hydrazono)-5-nitroindolin-2-one (13) prevented the development of bovine viral diarrhea virus in cells [9].
7-Ethoxy-1-methyl-4, 9-dihydro-3H-pyrido [3, 4-b]indole derivatives were reported as anti-Herpes Simplex virus-1(HSV-1) compounds by El-sawy et al. and derivatives ethyl 2-(3-(5-(4-nitrophenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-1H-indol-1-yl)acetate (14), ethyl 2-(3-(6-(4-nitrophenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-1H-indol-1-yl)acetate (15), ethyl 2-(3-(6-(4-nitrophenyl)-2-thioxo-1,2-dihydropyrimidin-4-yl)-1H-indol-1-yl)acetate (16) and ethyl 2-(3-(6-(4-chlorophenyl)-2-imino-1,2-dihydropyrimidin-4-yl)-1H-indol-1-yl)acetate (17) possessed considerable antiviral activity with IC\textsubscript{50} ranged between 5 and 6 μg/ml and substantial therapeutic indices (TI) of 80 and 83 were recorded [10].

1,3-Thiazole and 1,2,4-triazolo[3,4-b]1,3,4-thiadiazine containing indole nucleus derivatives were prepared and checked for their antiviral activity against HSV-1(herpes simplex type1) by Abdel-gawad et al. Compounds 5-(1H-indol-3-yl)-1-phenyl-N-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl)-1H-pyrazole-3-carboxamide (18) and 2-(2-(1H-indol-3-yl)ethylidene)hydrazinyl)-5-(1H-(E)-(4-chlorophenyl)diazienyl)-4-methylthiazole (19) showed best activity against HSV-1 [11].

Indole-based spirothiazolidinones also have antiviral activity as discussed by Cihan-Üstündağ et al. Compounds presented inhibitory action in Vero cells against yellow fever and Punta Toro virus. The range of IC\textsubscript{50} values was 1.9–12 μM. Compound 5-chloro-N-((2S,5S,8R)-2,8-dimethyl-3-oxo-1-thia-4-azaspiro[4,5]decan-4-yl)-3-phenyl-1H-indole-2-carboxamide (20) was the most active [12].

Anti-inflammatory and analgesic activities
Indole-based chalcone derivatives reported as COX-1 and COX-2 inhibitor by Ozdemir et al. Compound 3-(5-Bromo-1H-indol-3-yl)-1-(4-cyanophenyl)prop-2-en-1-one (21) and compound 3-(5-methoxy-1H-indol-3-yl)-1-(4-(methylsulfonyl)phenyl)prop-2-en-1-one (22) were found to demonstrate a significant activity [13].

Sarva et al. carried out solvent-free reaction in microwave between indole and substituted aldehydes. The product, bis(indolyl)methane is bioactive. The anti-inflammatory activity was shown by most of the compounds but compounds 3,3’-((1H-imidazol-2-yl)methylene)bis(1H-indole) (23), 3,3’-((1H-imidazol-2-yl)methylene)bis(1H-indole) (24), 3,3’-((5-methylpyridin-2-yl)methylene)bis(1H-indole) (25) and 3,3’-((thiophen-2-ylmethyl)bis(1H-indole) (26) were the most potent [14].
Anti-inflammatory activities of chalcones of indole were elaborated by Rani et al. against carrageenan-induced edema in albino rats. The most effective compound of this series was found to be 4-(3-(1H-indol-3-yl)-4,5-dihydro-1H-pyrazol-5-yl) phenol (27) [15].

Indole containing isoxazole derivatives were reported by Pedada et al. as sPLA₂ inhibitory agents. Compound N-((3-(4-fluoro-3-(trifluoromethyl) phenyl) isoxazol-5-yl) methyl) (5-methyl-1H-indol-3-yl) methanamine hydrochloride (28) showed significant sPLA₂ inhibition activity that is comparable or more to ursolic acid (positive control) [16].

Reactive oxygen species (ROS) generation and nitric oxide release induced through lipopolysaccharide were inhibited free radicals HMPH (1-[(1H-indol-3-yl)methylene]-2-phenylhydrazine scavenged) in RAW cells without any cytotoxicity explained by Misra et al. In all tested compounds, compound (E)-1-((1H-indol-3-yl)methylene)-2-phenylhydrazine (29) showed significant activity [17].

3-(2′-Substituted indolidene aminothiazol-4′-yl)-2-(4-chlorophenyl) indoles derivatives were reported as analgesic and anti-inflammatory agents by Singh et al. Compound (E)-4-(2-(4-chlorophenyl)-1H-indol-3-yl)-N-((2-methyl-1H-indol-3-yl)methylene)thiazol-2-amine (30) showed the better result as anti-inflammatory and analgesic agent [18].

(3-Ethyl-5-(methylsulfonyl)-2-phenyl-1H-indol-1-yl) substitutedphenyl methanones were prepared and tested for their anti-inflammatory activity against COX enzymes. For in vitro studies, all of the tested compounds, especially compounds incorporating SO₂Me moiety as a COX-2 pharmacophoric feature, showed preferential inhibitory activity against COX-2 over COX-1 (SI = 4.02 to 65.71) compared with indomethacin (SI = 0.079). Whereas in vivo anti-inflammatory activity was good for the compound having SO₂Me moiety and compounds (3-ethyl-5-(methylsulfonyl)-2-phenyl-1H-indol-1-y1)(4-fluorophenyl)methanone (31) and (4-chlorophenyl)(3-ethyl-5-(methylsulfonyl)-2-phenyl-1H-indol-1-y1)methanone (32) were more potent than indomethacin. The presence of a carbonyl moiety as a spacer instead of methylene resulted in an increase in the anti-inflammatory activity [19].
3-Methyl-2-phenyl-1-substituted-indole derivatives were synthesized and investigated for anti-inflammatory (in vitro and in vivo) and analgesic activities by Abdellaatif et al. Derivatives (3-methyl-5-(methylsulfonyl)-2-phenyl-1H-indol-1-yl)(phenyl)methanone (33), (4-chlorophenyl)(3-methyl-5-(methylsulfonyl)-2-phenyl-1H-indol-1-yl)methanone (34), and 1-benzyl-3-methyl-5-(methylsulfonyl)-2-phenyl-1H-indole (35) showed the highest anti-inflammatory (in vitro and in vivo) and analgesic activities. The results of molecular docking studies were in agreement with that obtained from the in vitro COX inhibition assays [20].

![Chemical structure of 33](image1)

![Chemical structure of 34](image2)

![Chemical structure of 35](image3)

3-(2-Aminopyrimidin-4-yl) indoles were prepared and investigated for their ulcerogenic, anti-inflammatory, and analgesic activities by Chavan et al. All the synthesized compounds showed alike results with indomethacin. Among the tested compounds, compounds 4-(2-amino-6-(2-(4-chlorophenyl)-1H-indol-3-yl)pyrimidin-4-yl)phenol (36) and 4-(4-aminophenyl)-6-(2-(4-chlorophenyl)-1H-indol-3-yl)pyrimidin-2-amine (37) showed 87.4 and 88.2% inflammation inhibition using paw edema, 78.5 and 76.6% inhibition of acetic acid-induced writhings [21].

![Chemical structure of 36](image4)

![Chemical structure of 37](image5)

Some new derivatives of 3-(2'-carboxy-5'-mehoxyindol-3'-yl)-5-(substituted phenyl)-2-isoxazolines have been prepared with less CVS and CNS activities but good anti-inflammatory activity by Prajapati et al. All the compounds were investigated for anti-inflammatory activity and compound 5-methoxy-3-(3-phenylacryloyl)-1H-indole-2-carboxylic acid (38) showed maximum activity (64.20%) at 50 mg/kg [22].

![Chemical structure of 38](image6)

1, 8-Dihydro-1-aryl-8-alkyl pyrazolo[3,4-b]indoles were synthesized by Mandour et al. that showed remarkable anticonvulsant, analgesic, and anti-inflammatory activities in comparison to diazepam, flufenamic acid, and indomethacin as positive controls. Among the tested compounds, the most potent compounds were found to be (6-chlorocyclohexa-2,4-dienyl)(1-(2,4,6-trichlorophenyl)pyrazolo[3,4-b]indol-8(1H)-yl)methanone (39) and (6-chlorocyclohexa-2,4-dienyl)(1-phenylpyrazolo[3,4-b]indol-8(1H)-yl)methanone (40) with percentage inflammation inhibition 85 and 79% (100 mg kg$^{-1}$) and 70 and 64% (50 mg kg$^{-1}$) respectively [23].

![Chemical structure of 39](image7)

![Chemical structure of 40](image8)

2-(5-Methoxy-2-methyl-1H-indol-3-yl)-N'-(substituted phenyl)methylidene] acetohydrazide derivatives were reported by Bhat et al. and investigated for cyclooxygenase expression, lipid peroxidation, ulcerogenic, analgesic, and anti-inflammatory activities. Compound (E)-N'-(3-nitrobenzylidene)-2-(5-methoxy-2-methyl-1H-indol-3-yl) acetohydrazide (41) was active as analgesic and anti-inflammatory agents [24].

![Chemical structure of 41](image9)

Benzothiazole containing benzene sulphonamide and carboxamide were prepared by Ugwu et al. and evaluated for their in vivo anti-inflammatory, analgesic, and ulcerogenic activities. Amongst the derivatives, compounds (S)-N-(1-(benzo[d]thiazol-2-ylamino)-3-(1H-indol-2-yl)-1-oxopropan-2-yl)-N-(4-...
nitrophenylsulfonyl)benzamide (42) and (S)-N-(benzo[d]thiazol-2-yl)-1-(4-nitrophenylsulfonyl)pyrrolidine-2-carboxamide (43) showed anti-inflammatory and analgesic activities along with ulcerogenic index (0.82 and 0.89) compared with indomethacin and celecoxib. In molecular docking studies, interaction is excellent with receptors [25].

Indomethacin analogs of 2-(4-(methylsulfonyl)phenyl)-1-substituted-indole were synthesized by Shaker et al. and assessed for their in vitro COX-2 inhibitory activity as well as in vivo anti-inflammatory activity. COX inhibitory activity (in vitro) evaluation showed selective binding with receptor (COX-2) with SI = 30.35–107.63 as compared to standard drug (SI = 0.079) whereas in vivo anti-inflammatory activity studies reported compounds 1-(4-chlorobenzyl)-2-(4-(methylsulfonyl)phenyl)-1H-indole (44) (90.5%), 1-(4-chlorobenzyl)-5-methyl-2-(4-(methylsulfonyl)phenyl)-1H-indole (45) (75.6%), 1-(4-chlorobenzyl)-5-fluoro-2-(4-(methylsulfonyl)phenyl)-1H-indole (46), and (81.1%) as most active. Molecular modeling studies of the compounds 44 and 46 showed excellent binding interaction to COX-2 enzyme [26].

**Anticancer activity**

Zhuang et al. reported a series of 2, 4-disubstituted furo[3,2-b]indoles for anticancer activity against the (human NCI-60) tumor cell lines. Among the tested compounds, compound 5-(2-(hydroxy-methyl)-4H-furo[3,2-b]indol-4-yl)methylfuran-2-ylmethanol (47) demonstrated the best anticancer activity. The analysis of results suggests that the fingerprint of the compound 48 is similar NSC-754549 [27].

2,3-Dimethylindoles and tetrahydrocarbazoles also show anticancer properties against the cancer cell lines such as MCF10A, Calu1, HCT116, Panc1, ACHN, and H460 by using staining assay of propidium iodoide (PI) as reported by Kumar et al. Compounds 2,3-dimethyl-1H-indole (50) and 5-fluoro-2,3-dimethyl-1H-indole (51) were found to be cytotoxic against cancer cell lines [30].
5-(2-Carboxyethenyl) indole derivatives gave antican-
cer response against HT-29 and K562 cell lines as ex-
plained by Han et al. and compounds (E)-methyl 3-(1-
tolyl-1H-indol-5-yl)acrylate (52), (E)-methyl 3-(1-benzyl-
1H-indol-5-yl)acrylate (53) and (E)-methyl 3-(1-(4-(tri-
fluoromethyl)benzyl)-1H-indol-5-yl)acrylate (54) demon-
strated notable activity in cell lines(HT-29) with potency
4.67, 8.24 and 6.73 μM, respectively [31].

3-[(4-Substitutedpiperazin-1-yl)methyl]-1H-indole deriva-
tives were prepared using Mannich reaction by Akkoc et al.
and evaluated for cytotoxic activity. The cytotoxicity of the
compound was dependent on three cell lines: human liver
(HUH7), breast (MCF7), and colon (HCT116). The most po-
tent compound against cancer cell lines was 3-((4-(3,4-
dichlorobenzyl)piperazin-1-yl)methyl)-1H-indole (55) [32].

3, 5-Bis (indolyl)-1, 2, 4-thiadiazoles showed cytotoxicity
against selected human cancer cell lines reported by Kumar
et al. and compound 1-(4-chlorobenzyl)-3-(5-(1-(4-chloro-
benzyl)-4-methoxy-1H-indol-3-yl)-1,2,4-thiadiazol-3-yl)-4-
methoxy-1H-indole (56) gave the most potent activity (anti-
cancer) [33].

N-1 and C-3 substituted indole derivatives also showed
cytotoxic properties as reported by Choppara et al. Com-
ounds (Z)-1-((5-bromo-1-(3-methylbut-2-enyl)-1H-
indol-3-yl)methylene)semicarbazide (57) and (Z)-1-((5-
bromo-1-(3-methylbut-2-enyl)-1H-indol-3-yl)methylene-
ethiosemicarbazide (58) were found to be cytotoxic [34].

Indole hybridized diazenyl derivatives were designed
and reported for cytotoxicity against human cell lines, i.e.,
leukemic cell (K562), normal cell (HEK293), lung cell
(HCT-116), and breast cell (MDAMB231) adopting
MTT assay by Kaur et al. Compounds (R)-5-(((E)-1-(4-
(Z)-(1H-indol-3-yl)diazenyl)phenyl)ethylidene)amino-
cyclohexa-2,4-diene-1-carboxylic acid (59) and N-(2-
((E)-1-(4-(Z)-(1H-indol-3-yl)diazenyl)phenyl)ethylidene-
amino)ethyl)naphthalen-2-amine (60) showed poten-
tial against breast cancer cell line (MDAMB231) [35].

The derivatives of 2-phenylindole containing triazine,
thiazolo-s-triazine, imidazole sugar, imidazolothiazole, and
imidazole were prepared and screened for their anticancer
activity against colorectal carcinoma, liver carcinoma, pro-
tate cancer, and breast adenocarcinoma by Yousif et al. The
compounds 2-chloro-1-(2-phenyl-1H-indol-1-yl)ethanone
(61), 4-(2-phenyl-1H-indol-1-yl)-1H-imidazol-2(5H)-one (62)
and ethyl 2-(2-oxo-4-(2-phenyl-1H-indol-1-yl)-2H-imidazol-
1(5H)-yl)acetate (63) showed high cytotoxic activity [36].

Anti-HIV activity
Kasralikar et al. reported a series of novel indolyl and
oxochromenyl xanthenone derivatives and performed
their molecular docking studies as an anti-HIV-1. In
tested compounds, compounds 9-(1H-indol-3-yl)-7-
methoxy-3,3-dimethyl-3,4-dihydro-2H-xanthen-1(9H)-
one (64), 9-(1H-indol-3-yl)-3,3-dimethyl-3,4-dihydro-2H-xanthen-1(9H)-one (65) and 7-bromo-9-(1H-indol-3-yl)-3,3-dimethyl-3,4-dihydro-2H-xanthen-1(9H)-one (66) were found to be most active compounds [37].

N-arylsulfonyl-3-acetylindole derivative was prepared and evaluated as HIV-1 inhibitors analogs by Ran et al. Compounds 1-(4-methyl-1-(phenylsulfonyl)-1H-indol-3-yl)ethanone (67) and 1-(1-(4-ethylphenylsulfonyl)-4-methyl-1H-indol-3-yl)ethanone (68) were the most effective against the anti-HIV-1 activity. SAR showed that acetyl group derivatives were more active [38].

4-[(1,2-Dihydro-2-oxo-3H-indol-3-ylidene)amino]N(4,6-dimethyl-2-pyrimidinyl)-benzene derivatives were synthesized and screened for their anti-HIV activity against HIV-1 (IIIB) and HIV-2 (ROD) strains replication in acutely infected cells (MT-4) by Selvam et al. Compounds (Z)-3-(4-(4,6-dimethylpyrimidin-2-ylamino)methylsulfonyl)phenylimino)indolin-2-one (69), (Z)-5-chloro-3-(4-((4,6-dimethylpyrimidin-2-ylamino)methylsulfonyl)phenylimino)indolin-2-one (70), (Z)-5-bromo-3-(4-((4,6-dimethylpyrimidin-2-ylamino)methylsulfonyl)phenylimino)indolin-2-one (71), (Z)-3-(4-((4,6-dimethylpyrimidin-2-ylamino)methylsulfonyl)phenylimino)-5-methylindolin-2-one (72) and (Z)-1-acetyl-3-(4-((4,6-dimethylpyrimidin-2-ylamino)methylsulfonyl)phenylimino)Indolin-2-one (73) were found to be most effective [39].

N-Arylsulfonyl-3-acetylindole benzoyl hydrazone derivatives were reported as HIV-1 inhibitors by Che et al. Among the reported analogs, compounds (E)-N’-(1-(1-(3-nitrophenylsulfonyl)-1H-indol-3-yl)ethylidene)benzo-hydrazide (74) and (E)-2-methyl-N’-(1-(1-(3-nitrophenyl-sulfonyl)-1H-indol-3-yl)ethylidene)benzohydrazide (75) displayed the highest IC50 and therapeutic index (TI) values 0.26, 769.23, and 0.31, 645.16 in microgram for anti-HIV-1 respectively [40].

1-(Thiophen-2-yl)-9H-pyrido[3,4-b]indole derivatives were synthesized and screened for their anti-HIV activity by Ashok et al. and structure–activity relationship (SAR) studies stated that electron-withdrawing group and electron-donating ortho, para directing groups increases the antiviral activities. Among the synthesized derivatives, derivative (4-(3-methoxyphenyl)piperazin-1-yl)(1-(thiophen-2-yl)-9H-pyrido[3,4-b]indol-3-yl)methanone (76) showed significant anti-HIV activity with selectivity index (SI) 483 and IC50 (0.53 μM). Lipinski rule is followed by these compounds in the molecular predication studies (In-silico) [41].

Indole-based reverse transcriptase inhibitors (non-nucleoside) were prepared and tested for anti-HIV virus type HIV-1IIIB using TZM-bl cell assay by Han et al. SAR studies showed that substituent affects the potency. From the synthesized compounds, compounds methyl 2-amino-3, 3, 3-trifluoro-2-(6-fluoro-1H-indol-3-yl) propanoate (77) and methyl 3-(2-amino-3-ethoxy-1, 1, 1-trifluoro-3-oxopropan-2-yl)-1H-indole-5-carboxylate (78) were most active with IC50 values (0.060 μM and 0.045 μM respectively) [42].

2-(1H-Indol-3-yl) ethylthiourea derivatives were explained as anti-HIV agents by Sanna et al. The
compound 1-(2-(1H-indol-3-yl)ethyl)-3-(4-bromophenyl)thiourea (79) showed potent activity against HIV-1 [43].

(79)

Indolyl aryl sulfones were discussed through molecular modeling studies using 3-D QSAR model as new anti-HIV agents by Ragno et al. From the screened compounds, compounds 5-chloro-3-(o-tolylsulfonyl)-1H-indole-2-carboxyhydrazide (80) and 5-chloro-N'-isopropyl-3-(o-tolylsulfonyl)-1H-indole-2-carboxyhydrazide (81) were found to be the most potent compound against C-8166 and MT-4 cell [44].

(80) (81)

Ethyl 6-bromo-5-hydroxy-1H-indole-3-carboxylates derivatives were prepared and investigated for anti-hepatic activities by Chai et al. Compounds ethyl 6-bromo-1-cyclopropyl-2-((3,4-difluorophenylsulfinyl)methyl)-5-hydroxy-4-(1H-imidazol-1-yl)-1H-indole-3-carboxylate (82), ethyl 6-bromo-2-((3,4-difluorophenylsulfinyl)methyl)-5-hydroxy-1-methyl-4-(5-methyl-1H-imidazol-1-yl)-1H-indole-3-carboxylate (83), ethyl 6-bromo-1-cyclopropyl-2-((4-fluorophenyl)sulfinyl)methyl)-5-hydroxy-4-(((guanidinoselanyl)(imino)methyl)amino)-5-hydroxy-1H-indole-3-carboxylate (84), and ethyl 6-bromo-1-cyclopropyl-2-((3,4-difluorophenylsulfinyl)methyl)-5-hydroxy-4-((methylpiperazin-1-yl)-1H-indole-3-carboxylate (85) possessed significant activities with IC₅₀ (3.6, 6.37, 5.2, and 5.4 μg/ml) against hepatitis B virus (HBV) [45].

(82) (83) (84) (85)

Indole sulfonamides derivatives were designed and evaluated as non-nucleoside reverse transcriptase inhibitors (NNRTIs) by Zhao et al. Among all, the analogs N-(2-chloro-6-fluorobenzyl)-5-bromo-3-(pyrrolidin-1-ylsulfonyl)-1H-indole-2-carboxamide (89), N-(2-hydroxybenzyl)-5-bromo-3-(pyrrolidin-1-ylsulfonyl)-1H-indole-2-carboxamide (90), and 5-bromo-2-(5-methyl-1H-imidazol-2-yl)-3-(pyrrolidin-1-ylsulfanyl)-1H-indole (91) improved the activities against HIVRT mutants Y181C and K103N which retain potent cellular activity [48].

(89) (90) (91)

(R)-N-(3-(1H-indol-5-yl oxy)-2-hydroxypropyl)-N-isobutyl benzenesulfonamide derivatives were screened for anti-HIV activity by Chiummiento et al. Among all compounds in this series, compounds (R)-N-(3-(1H-indol-5-yl oxy)-2-hydroxypropyl)-N-isobutyl-4-nitrobenzenesulfonamide (92), (R)-N-(3-(1H-indol-5-yl oxy)-2-hydroxypropyl)-N-isobutyl-3,4-dimethoxybenzenesulfonamide (93), activities in cells by Zhao et al. The structures ethyl 1-cyclopropyl-5-hydroxy-4-((5-methyl-1H-imidazol-1-yl)methyl)-2-(phenylsulfonylmethyl)-1H-indole-3-carboxylate (86) and ethyl 5-hydroxy-2-((3-methoxyphenylsulfonyl)methyl)-1-methyl-4-(pyrrolidin-1-ylmethyl)-1H-indole-3-carboxylate (87) exhibited significant activity against hepatitis B virus (HBV) with the IC₅₀ values of compounds (24.90 μg/ml) and (15.41 μg/ml) higher than those of the used of reference drug lamivudine (228.00 μg/ml) [46].

Heterocycle-containing oxindoles derivatives were prepared and evaluated for their anti-HIV activity by Jiang et al. In this series, compound (1S,2S)-5'-chloro-2-(pyridin-2-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (88) exhibited potent inhibitory activities against viruses [47].

(88)
and \((R)-N-(3-(1H\text{-}indol-5\text{-}yloxy})\text{-}2\text{-}hydroxypropyl)\text{-}4\text{-}amino-N\text{-}isobutylbenzenesulfonamide\) (94) demonstrated the best results [49].

\((E)-4\text{-}(1\text{-}(\text{Substitutedbenzyl})\text{-}4\text{-}methoxy\text{-}1H\text{-}indol-3-y)\text{-}2\text{-}hydroxy\text{-}4\text{-}oxobut-2\text{-}enoic\text{ acid}\) derivatives were reported as new HIV inhibitor (integrase strand-transfer inhibitors) by Ferro et al. The binding modes of the compounds were studied by induced-fit docking (IFD). Among all compounds, \((E)-4\text{-}(1\text{-}(4\text{-}chlorobenzyl)\text{-}4\text{-}methoxy\text{-}1H\text{-}indol-3-y)\text{-}2\text{-}hydroxy\text{-}4\text{-}oxobut-2\text{-}enoic\text{ acid}\) (95), \((E)-4\text{-}(1\text{-}(3\text{-}chloro\text{-}5\text{-}fluorobenzyl)\text{-}4\text{-}methoxy\text{-}1H\text{-}indol-3-y)\text{-}2\text{-}hydroxy\text{-}4\text{-}oxobut-2\text{-}enoic\text{ acid}\) (96), and \((E)-4\text{-}(1\text{-}(4\text{-}chloro\text{-}3\text{-}fluorobenzyl)\text{-}4\text{-}methoxy\text{-}1H\text{-}indol-3-y)\text{-}2\text{-}hydroxy\text{-}4\text{-}oxobut-2\text{-}enoic\text{ acid}\) (97) showed inhibition (in strand-transfer) in respect to elvitegravir [50].

\((E)-1\text{-}(\text{Substitutedphenyl})\text{-}2\text{-}(2\text{-}(4\text{-}fluorophenyl)\text{-}1H\text{-}indol-3-y)\text{methylene})\text{hydrazine}\) (101), and \((E)-1\text{-}(2\text{-}fluorophenyl)\text{-}2\text{-}(2\text{-}(4\text{-}fluorophenyl)\text{-}1H\text{-}indol-3-y)\text{methylene})\text{hydrazine}\) (102) exhibited significant activity [52].

\((E)-5\text{-}(1\text{-}(\text{Substitutedphenyl})\text{-}3\text{-}(1H\text{-}indol-3-y)\text{allylidene})\text{pyrimidine}\text{-}2,\text{4,}\text{6}(1H,3H,5H)\text{-trione}\) derivatives containing barbitone moiety were reported as DNA cleavage and antioxidant agents by Biradar et al. The compounds \((E)-5\text{-}(3\text{-}(1H\text{-}indol-3-y)\text{-}1\text{-}p\text{-}tolylallylidene)\text{pyrimidine}\text{-}2,\text{4,}\text{6}(1H,3H,5H)\text{-trione}\) (103), \((E)-5\text{-}(3\text{-}(1H\text{-}indol-3-y)\text{-}1\text{-}p\text{-}tolylallylidene)\text{pyrimidine}\text{-}2,\text{4,}\text{6}(1H,3H,5H)\text{-trione}\) (104) and \((E)-5\text{-}(1\text{-}(4\text{-}chlorophenyl})\text{-}3\text{-}(1H\text{-}indol-3-y)\text{allylidene})\text{pyrimidine}\text{-}2,\text{4,}\text{6}(1H,3H,5H)\text{-trione}\) (105) exhibited excellent antioxidant and DNA cleavage activities [53].

Antioxidant activity
Di(1H- indol-3-yl)sulfane derivatives were prepared and evaluated as antioxidants agents by Silveira et al. Compound di(1H- indol-3-yl)sulfane (98) exhibited antioxidant activity in ferric reducing ability of plasma (FRAP), 2,2-Diphenyl-1-picrylhydrazyl (DPPH) and 2,2’-Azinobis(3-ethylbenzothiazoline-6-sulfonic acid ) (ABTS) assays at micromolar concentration [51].

\((E)-1\text{-}(\text{Substitutedphenyl})\text{-}2\text{-}(2\text{-}(4\text{-}fluorophenyl)\text{-}1H\text{-}indol-3-y)\text{methylene})\text{hydrazine}\) (101), and \((E)-1\text{-}(2\text{-}fluorophenyl)\text{-}2\text{-}(2\text{-}(4\text{-}fluorophenyl)\text{-}1H\text{-}indol-3-y)\text{methylene})\text{hydrazine}\) (102) exhibited significant activity [52].

\((E)-5\text{-}(1\text{-}(\text{Substitutedphenyl})\text{-}3\text{-}(1H\text{-}indol-3-y)\text{allylidene})\text{pyrimidine}\text{-}2,\text{4,}\text{6}(1H,3H,5H)\text{-trione}\) derivatives containing barbitone moiety were reported as DNA cleavage and antioxidant agents by Biradar et al. The compounds \((E)-5\text{-}(3\text{-}(1H\text{-}indol-3-y)\text{-}1\text{-}p\text{-}tolylallylidene)\text{pyrimidine}\text{-}2,\text{4,}\text{6}(1H,3H,5H)\text{-trione}\) (103), \((E)-5\text{-}(3\text{-}(1H\text{-}indol-3-y)\text{-}1\text{-}p\text{-}tolylallylidene)\text{pyrimidine}\text{-}2,\text{4,}\text{6}(1H,3H,5H)\text{-trione}\) (104) and \((E)-5\text{-}(1\text{-}(4\text{-}chlorophenyl})\text{-}3\text{-}(1H\text{-}indol-3-y)\text{allylidene})\text{pyrimidine}\text{-}2,\text{4,}\text{6}(1H,3H,5H)\text{-trione}\) (105) exhibited excellent antioxidant and DNA cleavage activities [53].

Indole derivatives like tryptophan and tryptamine were investigated for DNA clevaging activity by Estêvão et al. Compounds 2-amino-3-\((1\text{-}(3\text{-}methylbut-2-enyl})\text{-}1H\text{-}indol-3-yl)propanoic acid (106) \((IC_{50}4.13 \pm 0.17 \mu M)\), 2-amino-3-(2-(3-methylbut-2-enyl)\text{-}1H\text{-}indol-3-yl)propanoic acid (107) \((IC_{50}4.56 \pm 0.48 \mu M)\), and methyl 2-(1,3-dioxoisimidolin-2-yl)-3-(2-isopentyl\text{-}1H\text{-}indol-3-yl)propanoate (108) \((IC_{50}14.0 \pm 6.8 \mu M)\) showed significant activity [54].
(E)-1-((2-Phenyl-3H-inden-1-yl) methylene)-4-substitutedthiosemicarbazides, a new class of antioxidant agents, were synthesized by Bakherad et al. and compounds exhibited better anti-oxidant activities. Compound (E)-1-((2-phenyl-3H-inden-1-yl)methylene)-4-p-tolylthiosemicarbazide (109) found to be the most potent compound [55].

(E)-1-(Substitutedphenyl)-2-((1-methyl-1H-indol-2-yl)methylene)hydrazines were synthesized and reported as antioxidant agents by Suzen et al., and compounds (E)-1-(2,5-difluorophenyl)-2-((1-methyl-1H-indol-2-yl)methylene)hydrazine (110), (E)-1-(2,5-dichlorophenyl)-2-((1-methyl-1H-indol-2-yl)methylene)hydrazine (111) and (E)-1-(2,6-dichlorophenyl)-2-((1-methyl-1H-indol-2-yl)methylene)hydrazine (112) were the most promising compounds [56].

5-Chloroindole hydrazide/hydrazone derivatives were prepared and evaluated for antioxidant activity by Yılmaz et al. 2,2-Diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity (IC50 2 to 60 μM) was shown by all compounds. Compound (E)-1-((5-chloro-1H-indol-2-yl)methylene)-2-(2-chlorophenyl) hydrazine (113) possessed high inhibitory activities in assay (LP) against melatonin at 0.1 mM [57].

3-(1-(4-(4-chlorophenyl)thiazol-2-yl)-3-(substituted-phenyl)-1H-pyrazol-5-yl)-1H-indole derivatives were reported as antioxidant agents by Ummadi et al. Compounds 3-(1-(4-(4-chlorophenyl)thiazol-2-yl)-3-p-tolyl-1H-pyrazol-5-yl)-1H-indole (114) and 3-(1-(4-(4-chlorophenyl)thiazol-2-yl)-3-(4-methoxyphenyl)-1H-pyrazol-5-yl)-1H-indole (115) showed excellent antioxidant activity in comparison to ascorbic acid. Structural activity relationship (SAR) stated that OCH3, CH3 groups showed higher activity (scavenging) as compared to NO2, Cl, Br groups [58].

Melatonin retinamide derivatives were synthesized through reaction between the melatonin and tetrathymethylnaphthalene carboxylic acid and screened for antioxidant activity by Ates-Alagoz et al. The compounds have weak 2,2-Diphenyl-1-picrylhydrazyl (DPPH) inhibition activity pattern and some of the compounds N-(2-(1H-indol-3-yl)ethyl)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydroindole-2-carboxamide (116), N-(2-(5-methoxy-1H-indol-3-yl)ethyl)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydroindole-2-carboxamide (117), N-(1H-indol-5-yl)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydroindole-2-carboxamide (118), N-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydroindole-2-carboxamide (119), 4-(1H-indol-3-yl)-N-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydroindole-2-carboxamide (120), and 5-(1H-indol-3-yl)-N-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydroindole-2-carboxamide (121) possessed a strong inhibition of lipid peroxidation (88, 96, 90, 94, 93, and 86%) [59].

N-((10-nitro-1H-indolo[1,2-c]quinazolin-12-yl)methylene)benzenamines were prepared and tested for their anti-oxidant activity by Dixit et al. Nearly all derivatives have shown good antioxidant activity at all the concentrations, but compounds 4-nitro-N-((10-nitro-1H-indolo[1,2-c]quinazolin-12-yl)methylene)benzenamine (122), 4-fluoro-N-((10-nitroH-indolo[1,2-c]quinazolin-12-yl)methylene)benzenamine (123), and 4-chloro-2-nitro-N-((10-nitroH-indolo[1,2-c]quinazolin-12-yl)methylene)benzenamine (124) were found to be the best free radical scavengers [60].

Antimicrobial activity
Indole[1,2-c]-1,2,4- butynitrite benzotriazine derivatives were prepared using Sandmeyer reaction and screened...
for the antifungal activity by Xu et al. Compound indole[1,2-c]-1,2,4-butylnitrite benzotriazine (125) was more potent derivative [61].

![Image of compound 125]

3-(2-(5-(Substitutedphenyl)-1,3,4-oxadiazol-2-ylthio)ethylthio)-5-(1H-indol-3-yl)-4H-1,2,4-triazol-4-amine were prepared by Shi et al. using special technique, i.e., ultrasonic. Compounds 3-(2-(5-(2-ethoxyphenyl)-1,3,4-oxadiazol-2-ylthio)ethylthio)-5-(1H-indol-3-yl)-4H-1,2,4-triazol-4-amine (126), and 3-(2-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-ylthio)ethylthio)-5-(1H-indol-3-yl)-4H-1,2,4-triazol-4-amine (127) exhibited excellent activity against Staphylococcus aureus and Escherichia coli strains [62].

![Image of compounds 126 and 127]

Substituted 1, 2, 3, 4-tetrahydropyrazino[1,2-a]indole derivatives were reported by Tiwari et al. as antimicrobial agents against bacteria (both Gram positive and negative). Compounds 1-(4-fluorophenyl)-10-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indole (128), 10-methyl-1-p-tolyl-1,2,3,4-tetrahydropyrazino[1,2-a]indole (129), and 10-methyl-1-(4-nitrophenyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole (130) exhibited significant activity [63].

![Image of compounds 128, 129, and 130]

Methyl (E)-1-(substitutedbenzyl)-3-((2-(4, 5-dihydro-1H-imidazol-2-yl)hydrazono)methyl)-1H-indole-5-carboxylate derivatives were reported as antimicrobial agents by Hong et al. Compounds (131), (132), (133), and (134) showed activity against Mycobacterium tuberculosis, multidrug-resistant Acinetobacter baumanii, and Gram-negative bacteria [64].

![Image of compounds 131 to 134]

Azo dye of indoles were prepared by Ozturk et al. and evaluated in vitro against yeast Saccharomyces cerevisiae, Gram (+), and (-) bacteria. Compounds (E)-ethyl 4-((1H-indol-3-yl) diazenyl) benzoate (135), (E)-ethyl 4-((1-methyl-1H-indol-3-yl) diazenyl) benzoate (136) and (Z)-1-(4-methoxyphenyl)-2-(3-methyl-1H-indol-2-yl)diazene (137) showed good activity [65].

![Image of compounds 135 to 137]

2, 3-Diarylindoles derivatives containing amine substituent at the 5 and 6 positions of indole were prepared and screened as anticoccidial agents by Scribner et al. Compound 2-((4-fluorophenyl)-6-((piperidin-4-yl)-3-(pyridin-3-yl)-1H-indole (138) showed the best activity [66].

![Image of compound 138]

A series of nitrogen and carbon substituted bisindoles were synthesized and investigated for antimicrobial agents by Singh et al. The N-benzyl moiety or
morpholine or pyrrolidine at position 3 and xylidine or butane or propane as the bridge between the indoles were good for activity. Dockings studies showed strong interactions in the active sites of topoisomerase II lanosterol demethylase and dihydrofolate reductase. Compounds (139) and (140) were more active [67].

**Antitubercular activity**

(\(E\))-1-\((2-(1H\text{-}indol\text{-}3-yl)-5\text{-}(pyridin\text{-}4-yl)\text{-}1,3,4\text{-}oxadiazol\text{-}3(2H\text{-})\text{-}yl)\text{-}3\text{-}(substitutedphenyl)\text{prop-2-en-1-one} derivatives derived from pyridine and Indole were prepared and investigated in active and dormant state against \(H_{37Ra} \text{MTB (Mycobacterium tuberculosis)} \) and \(\text{BCG (Mycobacterium bovis)} \) for their in vitro antitubercular activity by Desai et al. Compounds (\(E\))-1-\((2-(1H\text{-}indol\text{-}3-yl)-5\text{-}(pyridin\text{-}4-yl)\text{-}1,3,4\text{-}oxadiazol\text{-}3(2H\text{-})\text{-}yl)\text{-}3\text{-}(2\text{-}hydroxyphenyl)\text{prop-2-en-1-one} (141), (\(E\))-1-\((2-(1H\text{-}indol\text{-}3-yl)-5\text{-}(pyridin\text{-}4-yl)\text{-}1,3,4\text{-}oxadiazol\text{-}3(2H\text{-})\text{-}yl)\text{-}3\text{-}(2\text{-}nitrophenyl)\text{prop-2-en-1-one} (142), (\(E\))-1-\((2-(1H\text{-}indol\text{-}3-yl)-5\text{-}(pyridin\text{-}4-yl)\text{-}1,3,4\text{-}oxadiazol\text{-}3(2H\text{-})\text{-}yl)\text{-}3\text{-}(4\text{-}nitrophenyl)\text{prop-2-en-1-one} (143), and (\(E\))-1-\((2-(1H\text{-}indol\text{-}3-yl)-5\text{-}(pyridin\text{-}4-yl)\text{-}1,3,4\text{-}oxadiazol\text{-}3(2H\text{-})\text{-}yl)\text{-}3\text{-}(2,4\text{-}dichlorophenyl)\text{prop-2-en-1-one} (144) exhibited effective antitubercular activity [68].

6-Cyano-5-methoxyindolo-[2, 3-\(a\)] carbaazole derivatives were designed and screened for their moderate inhibitory activities against \(H_{37Rv} \text{Mycobacterium tuberculosis)} \) and \(\text{Bacillus anthracis (ANR)} \) strain by Guo et al. to combat tuberculosis and anthrax infections. Compounds 6-methoxy-11,12-dihydroindolo[2,3-\(a\)]carbaazole-5-carbonitrile (145), 11,12-dihydroindolo[2, 3-\(a\)]carbaazole-5-carbonitrile (146), and 11-benzyl-11,12-dihydroindolo[2,3-\(a\)]carbaazole-5-carbonitrile (147) displayed moderate activity against \(\text{Mycobacterium tuberculosis} \) and good activity against \(\text{Bacillus anthracis} \) [69].

Indole and pyridine nuclei combined through hydrazones-hydrazide and hydrazides were evaluated their in vitro antimycobacterial activity by Velezheva et al. In these series, the most potent compound was ethyl (\(E\))-3-\(-(2\text{-isonicotinoylhydrazono)methyl}\)-5\text{-}methyl-1\text{-}H\text{-}indole-2-carboxylate (148) (MIC value of 0.05 \(\mu\text{g/mL} \) and selectivity index 300) was active against \(\text{Mycobacterium tuberculosis} \) \(H_{37Rv} \) [70].

Walmik et al. synthesized several novel \(N'\text{-}(2\text{-phenyl-1H-indol-3-yl) methylene), substituted phenyl-1H-indole-2-carboxyhydrazide derivatives, and screened for their in vitro antimycobacterial activity. The antitubercular result showed that chlorine derivatives were most active. Compound 5-chloro-3-phenyl-\(N'\text{-}((2\text{-phenyl-1H-indol-3-yl)methylene})-1H-indole-2-carboxyhydrazide (149) (MIC = 0.2 \(\mu\text{g/mL} \) possessed potent growth inhibitory effect against \(H_{37Rv} \text{Mycobacterium tuberculosis} \) [71].

3-(1\text{-Isonicotinoyl-3-(substituted-2-phenyl-1H-indol-3-yl)-1H-pyrazol-5-yl)-2H-chromen-2-one derivatives were synthesized and reported as antimycobacterial agents by Rathod et al. In molecular docking studies, the mode of action of these active derivatives were studied and compounds 3-(1\text{-isonicotinoyl-3-(5-methyl-2-phenyl-1H-...}
indol-3-yl)-1H-pyrazol-5-yl)-2H-chromen-2-one (150) and 3-[3-(1H-indol-3-yl)-1-isonicotinoyl-1H-pyrazol-5-yl)-2H-chromen-2-one (151) gave the promising effect with *Mycobacterium tuberculosis* H₃₇Rv strain at 12.5 and 25 μg/ml respectively [72].

\[
\text{CH}_3
\]

\[
\text{H}
\]

(150)

(151)

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\text{H}
\]

\[
\text{N}
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\[
\text{Cl}
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\text{H}
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\text{O}
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\text{O}
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N-(4, 4-dimethylcyclohexyl)-substituted indole-2-carboxamides were reported as antituberculosis agents by Kondreddi et al. Structure-activity relationship (SAR) studies revealed that alkyl groups reduced solubility and increased *Mycobacterium tuberculosis* activity. Compounds 4,6-dichloro-N-(4,4-dimethylcyclohexyl)-1H-indole-2-carboxamide (152) and N-(4,4-dimethylcyclohexyl)-4,6-difluoro-1H-indole-2-carboxamide (153) active compounds displayed improved in vitro activity [73].

\[
\text{Cl}
\]

(152)

(153)

Spirothiazolidinone derivatives of 5-chloro-3-phenyl-1H-indoles were synthesized by Cihan-Üstündağ et al. and evaluated for their in vitro antitubercular activity. Among all, compounds 5-chloro-3-phenyl-N-(8-phenyl-3-oxo-1-thia-azaspiro[4.5]-decan-4-yl)-3-phenyl-1H-indole-2-carboxamide (154) (MIC = 3.9 μM) and 5-chloro-N-(2-methyl-8-phenyl-3-oxo-1-thia-4-azaspiro[4.5]-decan-4-yl)-3-phenyl-1H-indole-2-carboxamide (155) (MIC = 7.8 μM) were the most active compounds having 8-phenyl spiro ring against H₃₇Rv ATCC 27294 (*Mycobacterium tuberculosis*) [12].

\[
\text{Cl}
\]

(154)

(155)

A library of indole chalcones was made by Ramesh et al. and screened for their antimycobacterial activity opposite H₃₇Rv strain. Compounds (E)-1-(furan-3-yl)-3-(1H-indol-3-yl)-prop-2-en-1-one (156) (MIC = 210 μM), (E)-3-(1H-indol-3-yl)-1-(thiophen-2-yl)prop-2-en-1-one (157) MIC = 197 μM) and (E)-2-((1H-indol-2-yl)methylene)cyclopentan-1-one (158) (MIC = 236 μM) were found to be potent drug against *Mycobacterium tuberculosis* [74].

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\text{F}
\]

(156)

(157)

(158)

Naidu et al. synthesized various 3-(4-((1-(4-bromo-3-substitutedphenyl)-1H-1, 2, 3-triazol-4-yl) methyl)piperazin-1-yl) benz[d]isoxazole derivatives as antitubercular agents against H₃₇Rv strain *Mycobacterium tuberculosis*. Among the tested compound, compound 3-(4-((1-(4-bromo-3-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-4-yl)methyl)piperazin-1-yl)benzo[d]isoxazole (159) (MIC = 6.16 μM) exhibited best antitubercular activity. Receptor interactions were studied by docking to pantothenate synthetase enzyme [75].

\[
\text{Br}
\]

(159)

**Anticholinesterase activity**

Bingul et al. synthesized a novel 4, 6-dimethoxyindole-based hydrazide hydrazones and evaluated their anticholinesterase activity towards cholinesterase (AChE and BuChE) enzymes. Compound methyl (E)-7-((2-benzoylhydrazono)methyl)-6, 6-dimethoxy-1H-indole-2-carboxylate (160) was most active [76].

\[
\text{CH}_3
\]

(160)

Prochnow et al. prepared 2-substituted-N-alkynylindoles and screened for anticholinesterase activity. Derivatives (2-fluoro-6-methoxyphenyl)(1-(2-phenylethynyl)-1H-indol-2-yl)methanol (161) and (1-(2-phenylethynyl)-1H-indol-2-yl)methanol (162) were
found as potential inhibitors of cholinesterase activity [77].

2-(2-(4-(Substituted benzyl) piperazin-1-yl) ethyl) isoindoline-1, 3-dione derivatives were reported as anti-cholinesterase agents by Mohammadi-Faran et al. Among synthesized derivatives, 2-(2-(4-(2-chlorobenzyl) piperazin-1-yl) ethyl) isoindoline-1, 3-dione (163) (IC50 = 0.91 ± 0.045 μM) exhibited the highest activity with respect to the standard drug (IC50 = 0.14 ± 0.03 μM) [78].

A novel 4, 6-dimethoxyindole-7-thiosemicarbazone derivatives were designed through Schiff base condensation reaction of indole carbaldehydes and thiosemicarbazides and evaluated for anticholinesterase properties by Bingül et al. Compound methyl (E)-4,6-dimethoxy-7-{(2-(methylcarbamothioyl)hydrazono)methyl}-1H-indole-2-carboxylate (164) exhibited moderate inhibition towards acetylcholinesterase and butyrylcholinesterase enzyme [79].

Various urea and carbamates derived indole derivatives were reported for the inhibition of human monoamine oxidase-A (hMAO-A), human monoamine oxidase-B (hMAO-B), acetylcholinesterase (AChE), and butyrylcholinesterase (BuChE) by Denya et al. Molecular modeling showed significant interactions on active site of the enzyme. Compound N, N-Diethyl-N′-[1-(prop-2-yn-1-yl)-1H-indol-6-yl] urea (167) was most potent [82].

**Antimalarial activity**

Indole-3-glyoxyl tyrosine derivatives were reported by Vasconcelos et al. as antimalarial agents against the pathogen *Plasmodium falciparum*. Compounds (S)-methyl 2-(2-(1H-indol-3-yl)-2-oxoacetamido)-3-(4′-fluoro-6-hydroxy-[1, 1′-biphenyl]-3-yl)propenoate (168) and (S)-methyl 2-(2-(1H-indol-3-yl)-2-oxoacetamido)-3-(4′-bromo-6-hydroxy-[1,1′-biphenyl]-3-yl)propenoate (169) were favorable to antimalarial activity [83].
The potent antimalarial compounds were reported by Luthra et al. and compound (Z)-methyl 2-(2-(methylamino) (phenyl) methyl)-1H-indol-3-yl ethylcarbamate (170) was active at the trophozoite stage of the parasite growth [84].

\[
\text{H}_3\text{COOCHN}
\]

(170)

Schuck et al. synthesized melatonin compounds and assayed in *Plasmodium falciparum* culture for the measurement of antimalarial activities. Structural-activity relationship (SAR) showed that carboxamide group derivatives of indole gave a good result. Derivatives \(N-(2-(5\text{-methoxy-1H-indol-3-yl)}\text{-ethyl})\text{butyramide (171),} \ N-(2-(5\text{-methoxy-1H-indol-3-yl)}\text{-ethyl})\text{hexanamide (172),} \) and \(N-(2-(5\text{-methoxy-1H-indol-3-yl)}\text{-ethyl})\text{-2-phenylacetamide (173) were active at low concentration against the Plasmodium falciparum [85].}

\[
\begin{aligned}
\text{O} \\
\text{N} \\
\text{O} \\
\end{aligned}
\]

(171)

\[
\begin{aligned}
\text{H}_3\text{CO} \\
\text{N} \\
\text{O} \\
\end{aligned}
\]

(172)

\[
\begin{aligned}
\text{H}_3\text{CO} \\
\text{N} \\
\text{O} \\
\end{aligned}
\]

(173)

2-(1H-indol-3-yl)-4, 6-diphenylnicotonitrile derivatives containing pyridine were made by Elshemy et al. and screened for antimalarial activity against *Plasmodium falciparum*. Among all the tested compounds, compounds 4-(4-fluorophenyl)-2-(1H-indol-3-yl)-6-phenylnicotinonitrile (174), 4-(3,4-difluorocyclohexa-1,5-dienyl)-2-(1H-indol-3-yl)-6-phenylnicotinonitrile (175), and 2-(3H-inden-1-yl)-6-phenyl-4-(3,4,5-trimethoxy-cyclohexa-1,5-dienyl)nicotinonitrile (176) exhibit the highest selectivity index (S.I. ranged 3.8–10). Docking studies explained the interaction between compound and active site of the enzyme (quadruple mutant *Plasmodium falciparum* dihydrofolate reductase) [86].

Conclusion

Indole moiety is present in many compounds possessing various biomedical applications. Various synthetic drug molecules contain an indole nucleus as a part of their pharmacophore structure and it helps in affixing drugs to the residues of the binding site of desired targets.

Derivatives holding indole core exhibit different biological activities namely antidiabetic, anticancer, antimicrobial, anti-HIV, antiviral, anti-inflammatory, antioxidant, anticholinesterase, antitubercular, and antimalarial activities, etc. Due to these activities, indole has attracted the attention of researchers in the discovery of novel chemical entities. These chemical entities may be safer and effective drugs for various ailments. Summarizing the literature reports described above, we can say that indole displays a diverse spectrum of biological activities. Indole has an immense potential to be investigated for newer therapeutic possibilities. Chemistry of indole derivatives described in this review would help the researchers worldwide in the design and synthesis of novel drugs useful in the mitigation of various disorders.

Abbreviations

LSD: Lysergic acid diethylamide; YFV: Yellow fever virus; BVDV: Bovine viral diarrhea virus; HIV-1: Human immunodeficiency virus; RSV: Respiratory syncytial virus; COX: Cyclooxygenase; FRAP: Ferric reducing ability of plasma; DPPH: 2,2-Diphenyl-1-picrylhydrazyl; ABTS: 2,2’-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid; viz.: Specifically or namely; SAR: Structural activity relationship; IC\text{50}: IC\text{50} is the concentration required to kill 50% of cell population; hMAO-A: Human monoamine oxidase-A; hMAO-B: Human monoamine oxidase-B; AChE: Acetylcholinesterase; BuChE: Butyrylcholinesterase; MIC: Minimum inhibitory concentration; ‘YM: Micromole; SI: Selectivity index; RNS: Reactive nitrogen species; ROS: Reactive oxygen species; MLT: Melatonin; DNA: Deoxyribonucleic acid; RNA: Ribonucleic acid; IFD: Induced-fit docking; HIV: Human immunodeficiency viruses; NNRTIs: Non-nucleoside reverse transcriptase inhibitors; HBV: Hepatitis B virus; QSAR: Quantitative structure-activity relationship; PI: Propidium iodide; CVS: Cardiovascular system; CNS: Central nervous system; GIT: Gastrointestinal tract; HMPH: 1-[(1H-indol-3-yl)methylene]-2-phenylhydrazone; HSV-1: Herpes simplex type-1; sPLA\text{2} inhibitory: Secretary phospholipase A\text{2} inhibitory

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