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# Medicinal chemistry of indole derivatives: Current to future therapeutic prospectives

Archana Kumari[a,1], Rajesh K. Singh[b,*]

[a] Rayat-Bahra Institute of Pharmacy, Dist. Hoshiarpur, 146104 Punjab, India
[b] Department of Pharmaceutical Chemistry, Shivalik College of Pharmacy, Nangal, Dist. Rupnagar, 140126 Punjab, India

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ABSTRACT

Indole is a versatile pharmacophore, a privileged scaffold and an outstanding heterocyclic compound with wide ranges of pharmacological activities due to different mechanisms of action. It is an superlative moiety in drug discovery with the sole property of resembling different structures of the protein. Plenty of research has been taking place in recent years to synthesize and explore the various therapeutic prospectives of this moiety. This review summarizes some of the recent effective chemical synthesis (2014–2018) for indole ring. This review also emphasized on the structure–activity relationship (SAR) to reveal the active pharmacophores of various indole analogues accountable for anticancer, anticonvulsant, antimicrobial, antitubercular, antimalarial, antiviral, antidiabetic and other miscellaneous activities which have been investigated in the last five years. The precise features with motives and framework of each research topic is introduced for helping the medicinal chemists to understand the perspective of the context in a better way. This review will definitely offer the platform for researchers to strategically design diverse novel indole derivatives having different promising pharmacological activities with reduced toxicity and side effects.

## 1. Introduction

Bicyclic heterocyclic structures occur widely in many biologically important molecules, one of them with versatile nature is Indole. Indole or benzo[*b*]pyrrole is an organic chemical compound with formula $C_8H_7N$ containing six-membered benzene ring fused to the five-membered nitrogen-containing pyrrole ring reported as an important building block in the field of medicinal chemistry field [1]. In 1866,

*Abbreviations:* 3D-QSAR, 3-Dimensional quantitative structur-activity relationship; AAPH, 2,2′-Azobis(2-amidinopropane) dihydrochloride; AbI, Abelson interactor 1; ADP, Adenosine diphosphate; AIDS, Acquired immune deficiency syndrome; Akt, Protien kinase B; ALK, Anaplastic lymphoma kinase ; ATR, Ataxia telangiectasia and Rad3; Bcl-2, B-cell lymphoma 2; BHT, Butylatedhydroxytoluene; BVDV, Bovine viral diarrhoea virus; $CC_{50}$, half maximal inhibitory compound concentration; CD38, Cluster of differentiation 38; CDK7, Cyclin-dependent kinase 7; CHIKV, Chikungunya virus; ClogP, Calculated log P; COX-1, Cyclooxygenase-1; COX-2, Cyclooxygenase-2; CVB-2, Coxsackievirus B-2 strain; DCFH-DA, Dichlorodihydrofluorescein diacetate; DNA, Deoxyribonucleic acid; DPPH, 2, 2-diphenyl-1-picrylhydrazyl; $EC_{50}$, 50% effective concentration; EI1, EZH2 inhibitor 1; ER β, Estrogen receptor beta; ERα, Estrogen receptor alpha; EZH2, Enhancer of homology Zesta 2; FABP, Fatty-acid-binding proteins; FAK, Focal adhesion kinase ; FGFR, Fibroblast growth factor receptors; FST, Forced swim test; GABA, gamma-Aminobutyric acid; GSK, GlaxoSmithKline; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HDACs, Histone deacetylases; HDM2, Human double minute 2; HIV-1, Human immunodeficiency virus-1; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-coenzyme A; IAP, Inhibitor of Apoptosis Protein; JAK2, Janus kinase 2; LDH, Lactate dehydrogenase; LOX, Lipoxygenase; LP, Lipid peroxidation; LPS, Lipopolysaccharide; MCF-7, Macrophage colony-stimulating factor-7; MDM2, Mouse double minute 2; MES, Maximal electroshock; MET, Mesenchymal-Epithelial Transition; MIC, Minimum inhibitory concentration; $NAADP^+$, Nicotinic acid adenine dinucleotide phosphate; $NAD(P)^+$, Nicotinamide adenine dinucleotide phosphate; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; NMDA, *N*-methyl-D-aspartate receptor; NNRTIs, Non-nucleoside reverse transcriptase inhibitors; NS5B, Nonstructural protein 5B; PDGFR, Platelet-derived growth factor receptors; PERK, PKR like endoplasmic reticulum kinase; PPARγ, Peroxisomes proliferator-activated receptor-γ; PRC2, Polycomb repressive complex 2; PYK2, Protein tyrosine kinase 2; QP $P_{caco}$, Cell permeability; QPLog$P_{o/w}$, Partition coefficient; QPLogS, Predicted aqueous solubility; RdRp, RNA-dependent RNA polymerase; RNA, Ribonucleic acid; ROS, Reactive oxygen species; SCLC, Small cell lung cancer; ScPTZ, subcutaneous pentylenetetrazol; STAT3, Signal transducer and activator of transcription 3; TFA, Trifluoroacetic acid; TNF-α, Tumor necrosis factor alpha; VEGFR, Vascular endothelial growth factor receptors; VZV, Varicella zoster virus; WT, Wild type; XIAP, X-linked inhibitor of apoptosis protein ; YFV, Yellow fever virus

* Corresponding author.
*E-mail address:* rksingh244@gmail.com (R.K. Singh).
[1] Research Scholar, Faculty of Pharmacy, I.K. Gujral Punjab Technical University, Jalandhar, India.

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Adolf von Baeyer prepared the indole by the reduction of oxindole [2,3]. It is the planar heteroaromatic molecule in which ten π electron moves throughout the structure. Chemically, indole is very weakly basic. This is due to the delocalization of nitrogen lone-pair into the π-electronic system which is free to circulate throughout the indole ring. Therefore, the lone pair of the electron on nitrogen is not available for protonation and get protonated at the C-3 because this position due to retention of aromaticity, is thermodynamically more stable [4,5]. Due to this it is involved in various chemical reactions, i.e. electrophilic substitution [6], organometallic indole anion complexes [7], carbon lithiation [8,9], oxidation [10], cycloaddition [11] etc, occur particularly at C-3 position. Indole is solid at room temperature. It occurs naturally in human faeces providing faecal smell. However, at a lower concentration, it gives the flowery smell and constituent of many flower scents, perfumes and coal tar [12]. Apart from this, indole is also involved in various biochemical reactions in the occurring in the body. It regulates various aspects of bacterial physiology, involving spore formation, plasmid stability, and resistance to drugs, biofilm formation and virulence [13].

### 1.1. Chemical synthesis of the indole ring

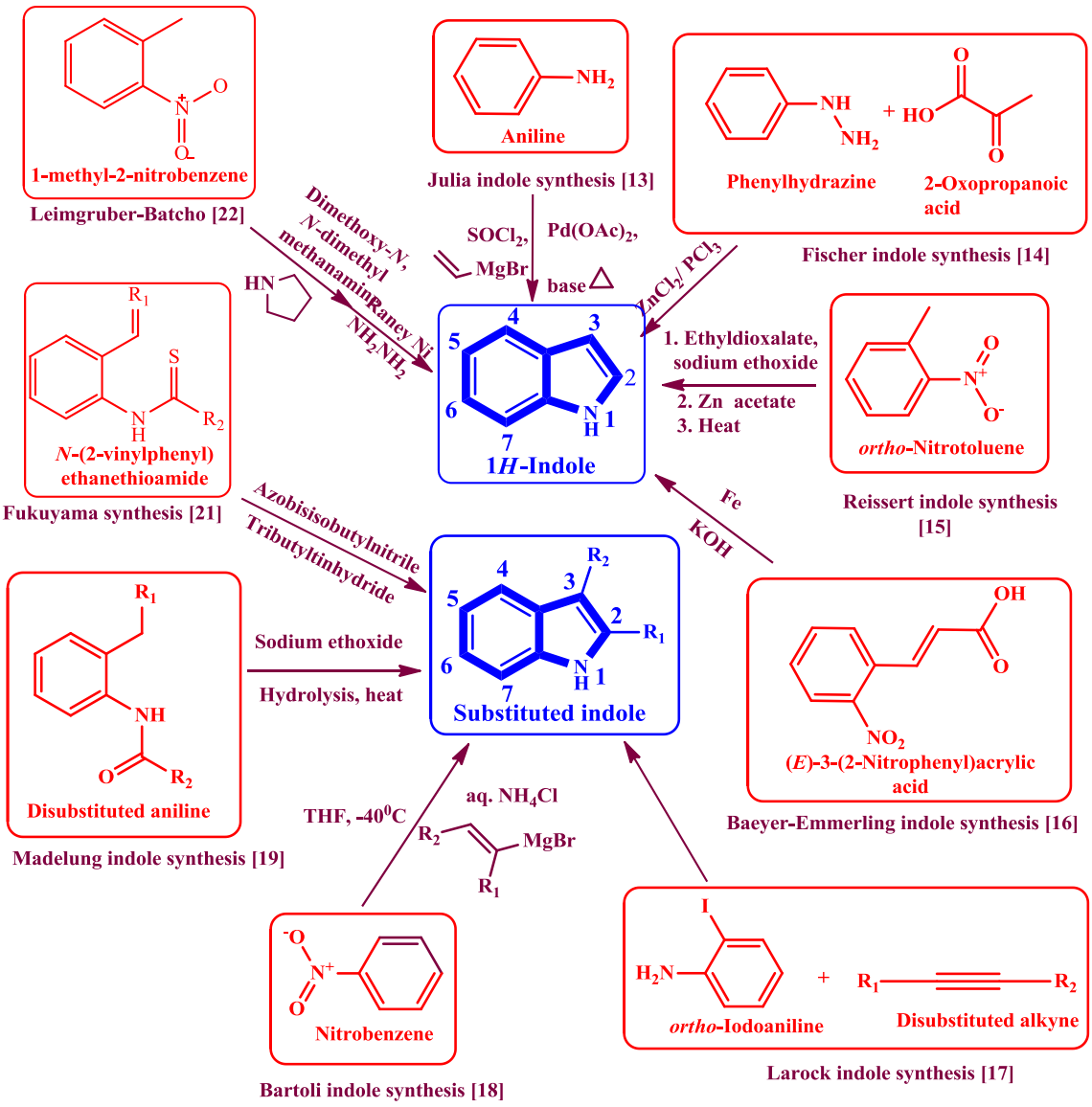
Conventional syntheses of the indole nucleus by various methods are mentioned in the literature. It involves a number of starting materials and different strategies as mentioned in Scheme 1 that includes: Julia indole synthesis [14], Fischer indole synthesis [15], Reissert indole synthesis [16], Baeyer-Emmerling indole synthesis [17], Larock indole synthesis [18], Bartoli indole synthesis [19], Madelung indole synthesis [20], Fukuyama synthesis [21], Leimgruber-Batcho [22]. Recently, some novel methods using various effective catalysts have been explored in the last five years, which have been discussed and presented in Scheme 2.

Recently, Zeidan and coworkers reported the palladium catalyzed 2-gem-dihalovinylanilines conversion into substituted indole. $Zn(TFA)_2$ is added to prolong the catalytic activity and also $Zn(CN)_2$ is used as a source of cyanide. The concentration of cyanide was maintained during the reaction due to the solubility of $Zn(CN)_2$ in two solvent mixtures. Cyano indole derivatives can be seen in various plant sources and pharmaceutical drugs [23]. Shi et al, uses the strategy of C—H activation in the rhodium catalyzed coupling reaction of butyl oxycarbonyl hydrazones with diazodiesters under mild temperature conditions. Trifluoroacetic acid (TFA) acts as a reaction medium, providing the yield of about 45%, which can be further, increased to 82% with higher temperature conditions [24]. In 2017, Yu and others introduced the scheme involving the reaction between aminoarylacetonitriles and arylboronic acid with the use of palladium as a catalyst. This conversion involves the nucleophilic addition followed by intramolecular cyclization. Halogens showed good compatibility providing the path for derivatization broadening [25]. Wang mentioned the formylation of indole in the presence of formaldehyde and ammonia under aerobic conditions involving the time duration of about 1–20 h. The use of oxygen instead of other harmful oxidants makes this reaction economical and environment-friendly. This method can be applied for the synthesis of indole on gram scale [26]. Miao and coworkers in 2016, stated the direct use of alkynylanilines with diethyl zinc under 1 atm with $CO_2$ for synthesis. There is the easy availability of starting material providing a good chance to develop a library of bioactive indole derivatives. This technique is applied for the synthesis of drug “Lotronex” used for irritable bowel syndrome [27]. In the same year, Hu and other researchers reported the role of rhodium-catalyzed cascade cyclization using nitrogen source *N*-pivaloyloxylamides for indole synthesis under mild temperature conditions. This is the novel and efficient method used to synthesize various heterocyclic fused indole nuclei [28]. Similarly, in 2016, Mizukami and coworkers mentioned the synthesis from ethanylanilines and isocyanates using rhodium as a catalyst through the cyclization addition mechanism. It is the high yielding novel technique affording the variety of substrates with different functional groups [29]. Wu et al, give the methodology for the synthesis of indole through the cyclization of vinylanilines in the presence of phenyliodine bis(trifluoroacetate) as oxidant under mild conditions. Due to the good compatibility of electron withdrawing and electron donating groups on the aromatic ring and nitrogen atom of 2-vinylanilines, desired product were produced in high yield [30]. In 2015, Sayyad and colleagues reported the method for the synthesis of substituted indole nucleus. The method involves the simple strategy for the formation of cyclopropyl substituted indole using thiophenol, dichloromethane, boron trifluoride and diethyl ether. The reaction was followed by aromatization and elimination of thiophenol in the presence of copper and dimethylformamide under the temperature conditions of 125 °C maintaining for 5–24 h [31]. In 2015, Ortgies and coworkers reported the one step cyclization method. This strategy entails the use of selenium catalyst for the activation of alkenes and *N*-flourobenzenesulfonimide as terminal oxidant. It requires the temperature conditions of 100 °C required to maintain for 16 h. The main applications of this method were the formation of high yield and excellent functional group tolerance [32]. Li and colleagues provide the scheme for the synthesis of substituted indole employing the C—N bond aromatization with the addition of *N*-iodosuccinimide under the mild temperature conditions and without the use of any catalyst. The major applications of this method were the rapid synthesis and high yield of the products [33]. In the same year, Michalska and colleagues introduced the heterocyclization of alkynylanilines with the use of the small quantity of gold under mild conditions. The major application involves the use of a substrate with a variety of substituents [34]. In 2014, Nallagonda and other researchers designed an efficient strategy for the synthesis of substituted indole from allylanlines through cycloisomerization with the use of palladium acetate or triphenylphosphine as a catalyst and oxygen an oxidizing agent. It illustrates the advantages of high yield and a broad substrate scope [35]. In the same year, Jiao and others reported the method for the synthesis of substituted nitrogen-containing heterocycles i.e., pyrroles, indoles involving the palladium/norbornene catalyzed alkylation at the 2 carbon of these nuclei with a good yield of alkyl substituted indole. The alkyl halide was added as electrophile conducting the reaction smoothly. *N, N*-dimethylformamide acts as a good solvent which is superior in smooth conversion during the reaction [36].

### 1.2. Indole in natural products

This lead compound is a universal constituent of pharmacologically active natural products. Indole alkaloids are broadly occurring in various plant families, i.e., Apocyanaceae, Loganiaceae, Rubiaceae and Nyssaceae [37]. Auxin, a cell growth hormone essential for both cellular division and cellular expansion in plants, is indole-3-acetic acid [38]. Tryptophan (2-amino-3-(1*H*-indol-3-yl)propanoic acid), an essential amino acid, is used as a building block in protein biosynthesis. It is found to be a biochemical precursor for various biological compounds, e.g. serotonin (neurotransmitter), melanin (a neurohormone). Indole alkaloids act on the central and peripheral nervous systems [39]. Some indole alkaloids show interaction with the receptors, e.g. mitragynine for μ-opioid receptors [40], harmala alkaloids for GABA-receptors [41], ibogaine for NMDA-receptors [42] and physostigmine for acetylcholinesterase inhibitor [43] etc.

There are several clinically important indole alkaloids are available. Some of them are (a) ergot alkaloids (ergotamine **1)** (Fig. 1), ergometrine, bromocriptine **2** (Fig. 1) having the action of uterine muscle contraction, migraine relief, lactation suppression, mammary carcinoma treatment [44] (b) vinca alkaloids (vincristine and vinblastine **3** (Fig. 1)) having the hypoglycemic and cytotoxic effects [45] (c) Rauwolfia alkaloids (reserpine **4)** (Fig. 1), reserpine etc with antihypertensive and antiepileptic roles [46] (d) Indole alkaloids obtained from *Alstonia scholaris* contain antibacterial activity [47] (e) *Melodinus*




**Scheme 1.** Chemical reactions for the synthesis of indole by old conventional methods.

*cochinchinensis* fruit provides various indole derivatives (melodinus A-H) **5** (Fig. 1) having cytotoxic effect [48].

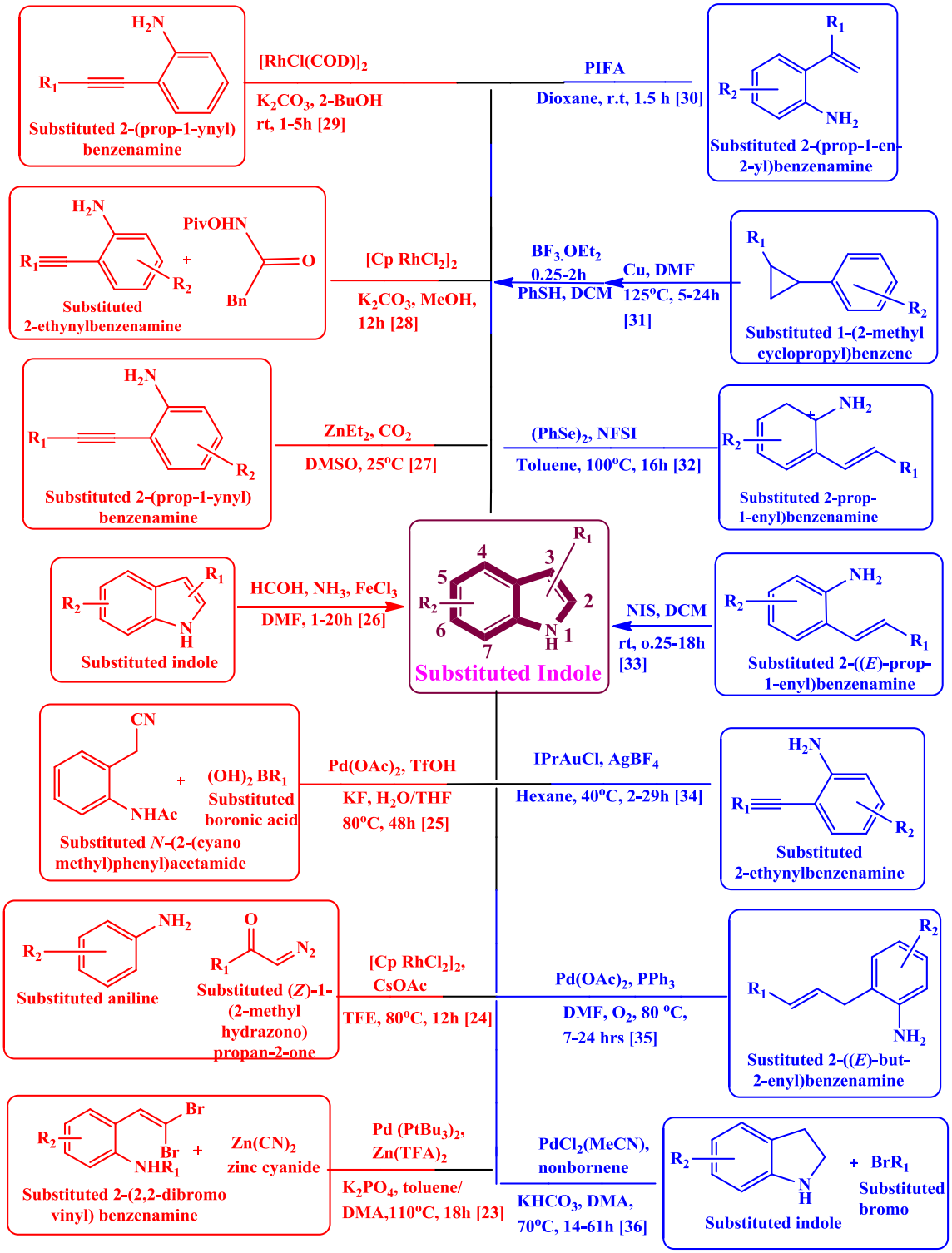
Marine and bacterial indole alkaloids are striking molecules for drug discovery as they have cytotoxic, antibacterial, antimicrobial and antineoplastic activity [49]. Topsentia sponge contains tulongicin indole alkaloid having antibacterial activity obtained from deep water having anti-HIV, cytotoxic and antibiotic effect. Apart from tulongicin **6** (Fig. 1), fractionation gives other indole-containing compounds [50]. Various other indole derivatives such as brasilidine A **7** (Fig. 1), eudistomin K **8** (Fig. 1), gelliusine A **9** (Fig. 1), mitraphylline **10** (Fig. 1) and cediranib **11** (Fig. 1) [13] are mentioned in the Fig. 1.

### 1.3. Indole in synthetic products

The pharmacological activity of various natural indole derivatives motivated many researchers to synthesize various synthetic compounds containing indole. Medicinal chemists are designing various compounds by using the various heterocyclic nucleus with indole against various diseases. Desai et al, synthesized pyridine and oxadiazole derivatives of indole as antitubercular agents [51]. Shakuja et al, synthesized bis spiroindole derivatives as antibacterial agents etc [52]. Various indole derivatives are available in market preparations. Pindolol **12** introduced by Novartis, is used for the treatment of hypertension since 1982 [53]. Indapamide **13** marketed by Servier, used in the treatment of heart failure and hypertension [54]. Others are perindopril [55,56], trandolapril [57] and carvedilol [58] (Fig. 2). delavirdine **14** (Fig. 2), approved by US FDA, used against HIV-1[59]. Indomethacin **15** (Fig. 2) is considered as one of the most promising anti-inflammatory and analgesic drug [60]. Yohimbine **16** (Fig. 2), is considered as an effective drug against sexual dysfunction and also reduces the risks of diabetes 2 [61]. Along with this, various other marketed indole derivatives are illustrated in Fig. 2:

Recently, FDA databases have revealed the significance of nitrogen-containing heterocycles in drug designing. Among these molecules, indole and indole derivatives ranking in the ninth position of the top 25 molecules in 2015, involved in the synthesis of fundamental FDA approved drugs [62]. This class of heterocyclic compounds has great significance in recent years due to their variety of pharmacological activities (Fig. 3) [63].

This whole information proved that indole and indole derivatives are very essential in the drug discovery process and therefore, several reviews have been published so far [64–71]. Some review on the involvement of the indole nucleus in Alzheimer's disease [64], as antiviral [65] and anticancer activity [66] are accessible in the literature.




**Scheme 2.** Chemical reactions for the synthesis of indole by novel methods using various catalysts.

Silakari et al, have reviewed the chemistry of natural indole derivatives [13]. Advancement in spirocyclization of indole [67] and synthesis of phosphorous containing indole have also been published [68]. Recently, a review on current advances in the application of indole in the multicomponent reaction is reported by Ziarani et al [69]. Some compilations of reports on all activities associated with the indole nucleus [70] and especially to 2-aryl indole [71] are also reported, but in recent times, no comprehensive update report on varied activities of indole analogues along with structure–activity relationship (SAR) is available in the literature till date. Hence, in the present review, our main motive is to provide information about the recent advances in the chemistry of indole with various pharmacological activities in the last five years. The changes in the indole ring substitution along with their consequences on the pharmacological activities have also been discussed.

## 2. Pharmacological profile of indole derivatives

Due to the versatile nature of indole, it had gained huge popularity

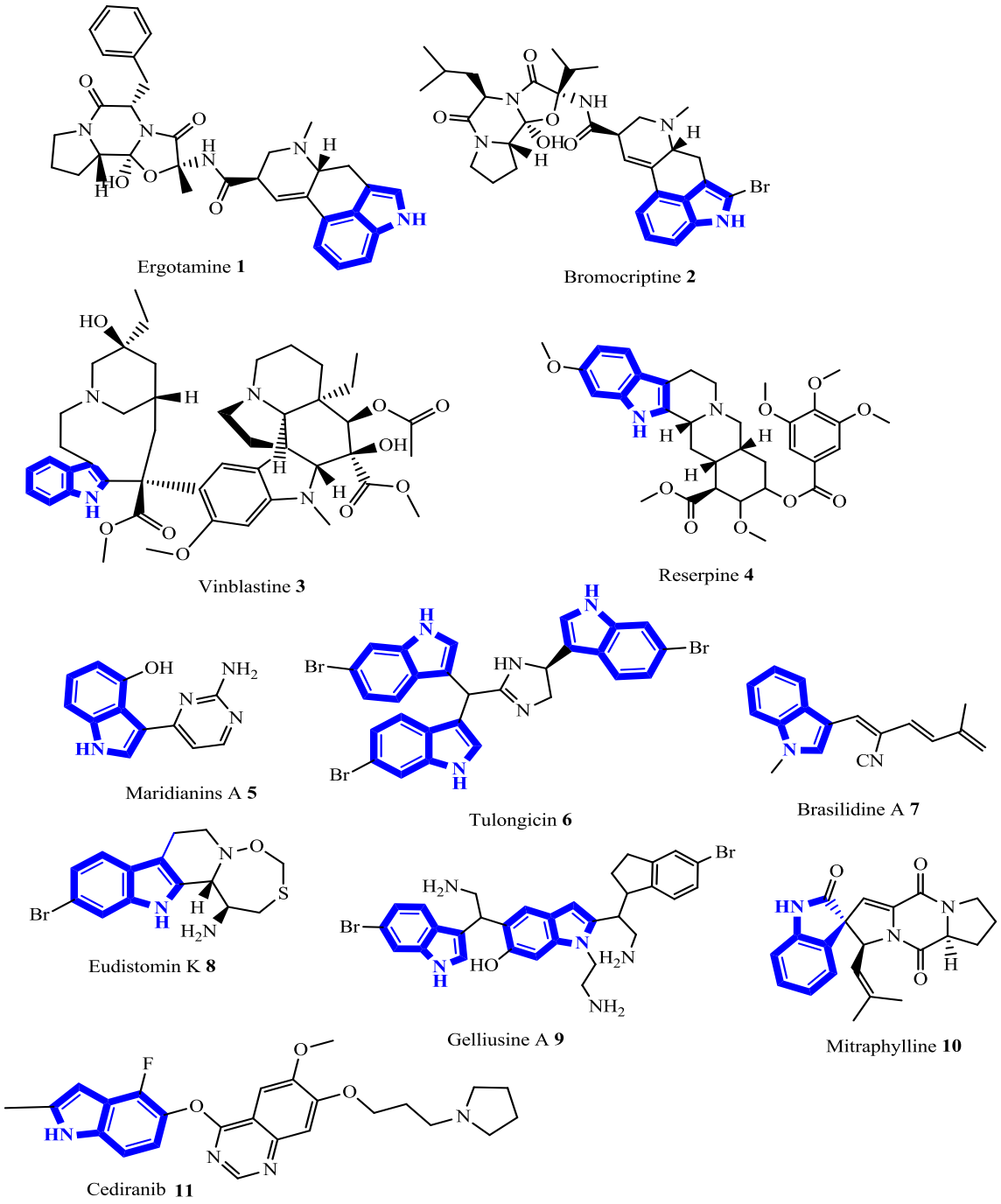



**Fig. 1.** Chemical structures of the compounds **1–11.**

among the organic and medicinal chemists. A number of drug molecules containing indole nucleus are found to be involved in the treatment of various disease conditions as anticancer, antimalarial, antitubercular, anti-HIV agent etc.

### 2.1. Anticancer activity

Cancer is a life-threatening disease characterized by uncontrolled growth and spread of abnormal cells. According to the data of 2018, 609,640 cancer deaths occur in the United States and According to statistics of 2006–2015 death rate declined by 1.5% in both men and women [72]. Hence, it is required to develop novel indole derivatives having a different mechanism of action. Various indole derivatives are designed as an anticancer agent in recent years that act *via* various targets such as histone deacetylases (HDACs), sirtuins, DNA topoisomerase etc [66].

Thiazolidinediones are responsible for the activation of peroxisomes proliferator-activated receptor-γ (PPARγ) affecting the apoptosis, cell cycle and differentiation [73,74]. Based on this fact, Corigliano 2018, designed and synthesized various 2, 4-thiazolidinedione substituted indole derivatives. All the synthesized compounds were further evaluated against two cell line MCF-7 (human breast cancer cells) and PC3 (human prostate cancer cells). SAR study concluded that methoxy at 5th position is most favorable for the activity. Compound **22** ($IC_{50}$ = 5 μM) was found to be the highly potent [75].

Ustundag et al, 2016, mentioned the synthesis and evaluation of hydrazide-hydrazone, thiazolidinones derivatives of indole. SAR study highlighted the role of methyl substitution. Compound **23**

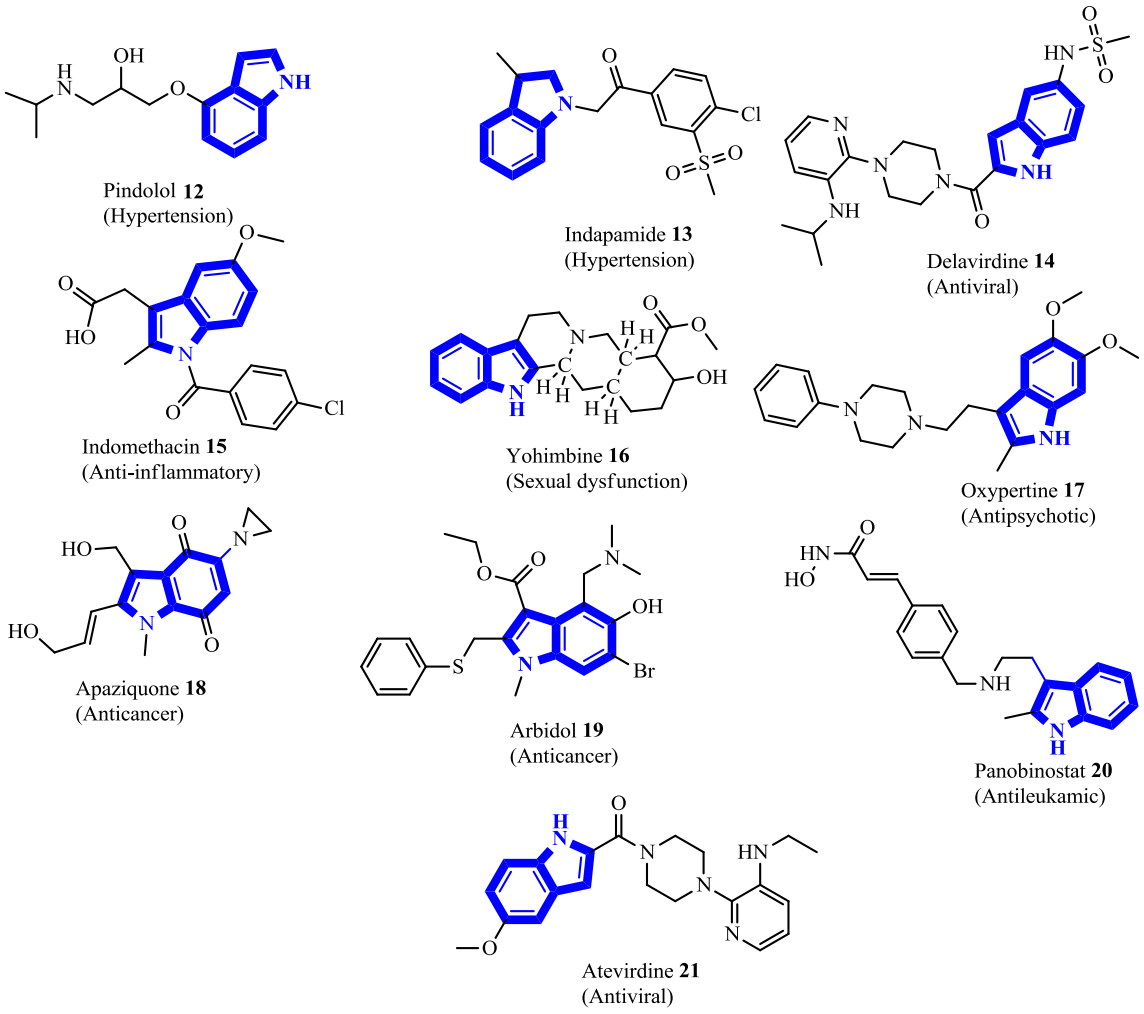



**Fig. 2.** Chemical structures of the compounds **12–21.**

($GI_{50}$ = 0.13–24 μM) has notable anticancer activity as compared with standard drug 5-fluorouracil ($GI_{50}$ = 0.01–79.4 μM) [76]. In 2019, Demurtas and colleagues designed, synthesized hydrazone derivatives of indole and evaluated on K562 (erythroleukemia) and Colo-38 (melanoma) cell lines. SAR studies confirmed the importance of phenol and naphthol substitution. Compounds **24** ($IC_{50}$ < 0.63 ± 0.05 μM) and

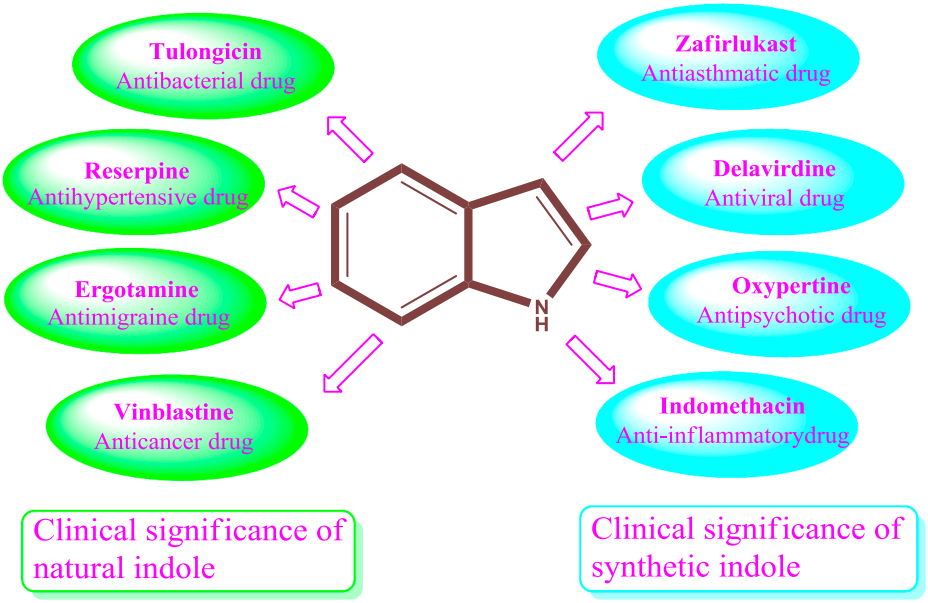



**Fig. 3.** Pharmacological signifance of indole nucleus.

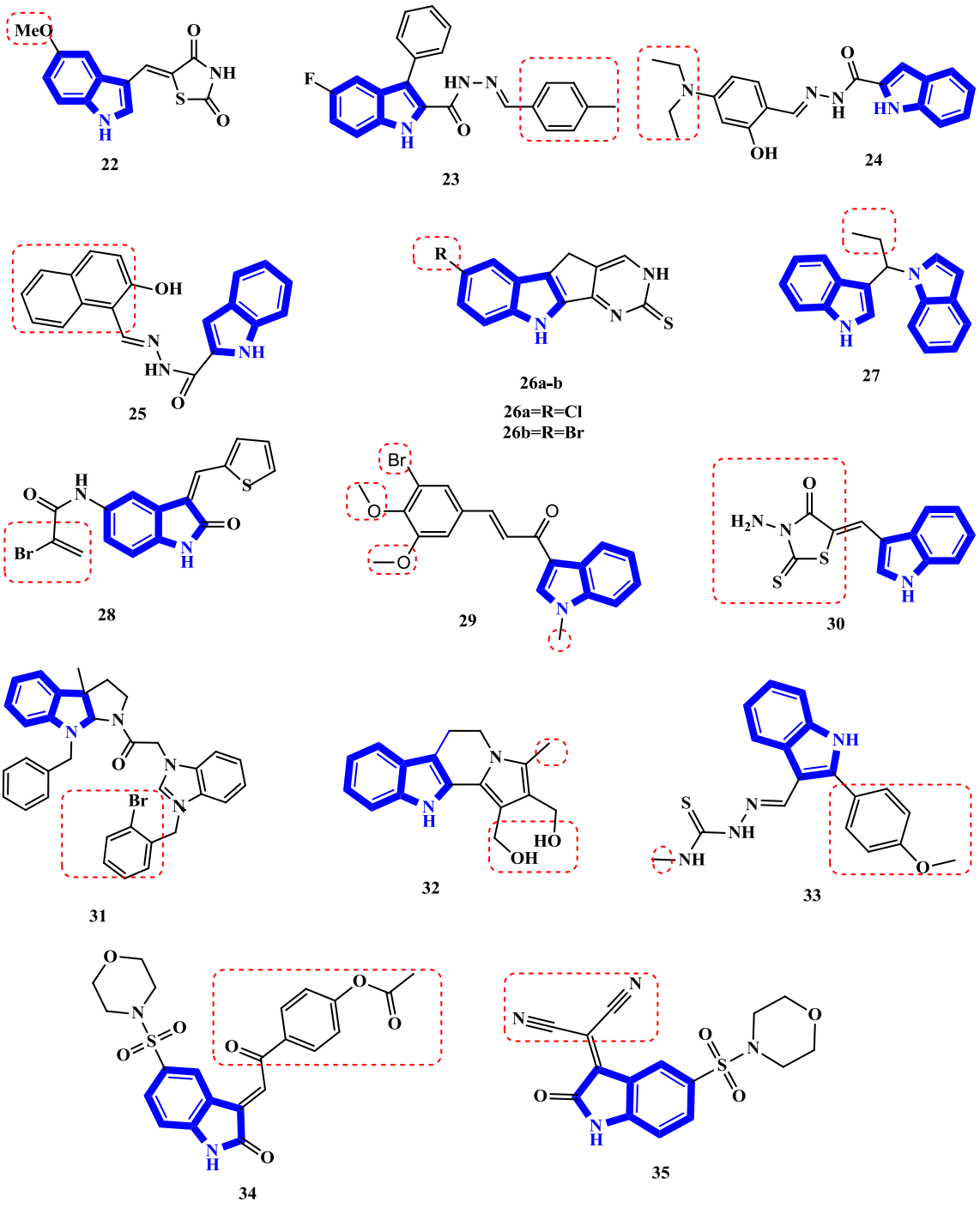



**Fig. 4.** Chemical structures for indole derivatives having anticancer activity **22–35** with active pharmacophores.

**25** ($IC_{50}$ < 0.83 ± 0.09 μM) were found to be highly potent [77].

Parkash et al, 2018, synthesized substituted heteroannulated indole derivatives and evaluated for their cervical anticancer activity. It was observed that electron withdrawing groups were more favorable at the C-8 position and have good interaction with the target receptor due to Van der Waal's and hydrogen bond interaction indicated by docking study. Compounds **26a** (Fig. 4) and **26b** (Fig. 4) show excellent potency ($IC_{50}$ = 13.41 μM) and ($IC_{50}$ = 14.67 μM) respectively, and is close to the activity of standard drug cisplatin ($IC_{50}$ = 13.20) [78]. Bis indoles were synthesized and evaluated against hepatocarcinoma cells by Tocco et al, compound **27** ($IC_{50}$ = 20–100 μM) was found to be more active than standard drug indole 3-carbinol [79]. In the same year, Romagnoli and coworkers synthesized and screened a series of 3-substituted-2-oxindole hybrid derivatives. Compound **28** (Fig. 4) was highly active ($IC_{50}$ < 5500 μM) on HL-60 cells which may be due to more interactions with cellular nucleophiles as compared with the standard drug [80].

Microtubules are one the vital component in cell cytoskeleton participating in mitosis, cell signalling and intracellular transport [81]. Chalcone scaffold was found to be a potent microtubule inhibitor [82]. Based on this fact, Mirzai et al, designed novel indole-based chalconoid derivatives as tubulin-targeting antiproliferative agents. The compound, **29** (Fig. 4) ($IC_{50}$ = 4.3 μg/mL) shows good potency particularly against A549 cell compared to standard etoposide ($IC_{50}$ = 7.8 μg/mL) and docking studies proved that it shows best binding to colchicines binding site [83]. In another study, thiazolidine and imidazolidine rings

were condensed with indole moiety to obtain potent anticancer drugs. Compound **30** (Fig. 4) exhibited significant anticancer activity on breast cancer cell lines (T47D), with $IC_{50}$ value (1.93 μM), lower than the positive control, doxorubicin (4.61 μM). The study showed that the indole nucleus helped with the integration of molecules into the DNA resulting in cell death [84]. Similarly, Zhou et al, studied the molecular hybridization of two potent molecules to synthesize various hexahydropyrrolo [2, 3-b] indole imidazolium derivatives. The compound **31** ($IC_{50}$ < 2.68 μg/mL) (Fig. 4) was found as most selective and potent against all the five cell lines as compared to the standard drug cisplatin ($IC_{50}$ = 10.45 μg/mL) [85].

Chang et al, 2016, synthesized and evaluated novel series of bis-(hydroxymethyl) indolizino [8,7-b] indole hybrids as anti-small cell lung cancer agents. Hybridization of two nuclei leads to the inhibition of tumor cell growth *via* two mechanisms i.e. topoisomerase II inhibition and induction of DNA cross-linking. Compound **32** demonstrated highest potency ($IC_{50}$ = 0.49 μM) (Fig. 4) against the growth of SCLC (small cell lung cancer) H526 cells in xenograft model against cisplatin ($IC_{50}$ = 0.63 μM) [86].

Bakherad et al., also study the anticancer activity. Various thiosemicarbazone derivatives of indole were synthesized and evaluated against MCF-7 (breast cancer), A-549 (lung cancer), Hep-G2 (liver cancer) cell lines. SAR study concluded that methyl and methoxy phenyl substitution is favorable for the activity. Compound **33** was found to be potent against A-549 ($IC_{50}$ = 12.5 μM), Hep-G2 ($IC_{50}$ = 56 ± 6.30 μM) (Fig. 4) cell lines as compared with standard drugs etoposide (A-549 = $IC_{50}$ = 38.23 ± 1.89 μM and Hep-G2 = $IC_{50}$ = 33.17 ± 3.19 μM) and colchicines (A-549 = $IC_{50}$ = 1.9 ± 0.23 μM and Hep-G2 = $IC_{50}$ = 6 ± 0.49 μM) [87].

Similarly, El-Sharief and co-workers prepared and studied isoindole derivatives on three cancer cell lines. SAR study concluded that phenylacetamide and malononitrile substitution is favorable for the activity. Among all the synthesized compounds, **34** ($IC_{50}$ < 6.67 ± 0.36 μM) and **35** ($IC_{50}$ = 6.34 ± 0.21 μM) (Fig. 4) were found to be highly potent as compared with standard drugs isatin ($IC_{50}$ < 41.83 ± 0.67 μM) and doxorubicin ($IC_{50}$ < 7.03 ± 0.21 μM) [88].

In the same year, Jiang and coworkers synthesized various indole derivatives and evaluated against Hela, A-549, ECA-109 cell lines. Compounds **36a** ($IC_{50}$ < 16.65 μM) and **36b** ($IC_{50}$ < 14.74 μM) (Fig. 5) were found have more potency compared to the standard drug cisplatin (($IC_{50}$ < 30.89 μM) [89]. Halogen substitution is found to be favorable for the activity. Similarly, Yan et al, reported indole-chalcone derivatives and evaluated both by *in vivo* and *in vitro* activity. Compound **37** ($IC_{50}$ < 0.009 μM) (Fig. 5) was highly potent as compared with the standard drug ($IC_{50}$ < 0.013 μM) [90].

Rosuvastatins and other HMG-CoA reductase inhibitors have attracted enormous interest as potential anticancer agents [91]. Based on this fact, Kumar et al, 2016 reported various rosuvastatin based indole derivatives and evaluated for anticancer activities against A549, TZM-BL cell lines. The presence of phenyl sulphonyl and fluoro substitution was vital for modulating cytotoxic activity. Among all the compounds, **38** ($IC_{50}$ < 12 μM) (Fig. 5) was found to be an active compound as compared with standard drug gemcitabine [92]. Hu et al, 2016 developed and evaluated various novel 2, 5-disubstituted indole derivatives as anticancer agents. SAR studies concluded that alkyl substituted phenyl is favorable for the activity. Among all the compounds, **39** ($IC_{50}$ < 8.70 ± 0.11 μg/mL) (Fig. 5) was found to be an most effective compound as compared with the standard drug cisplatin ($IC_{50}$ < 6.10 ± 0.09 μg/mL) [93]. Various bis-indole derivatives have been synthesized and evaluated against Hela, Colo-205, Hep G2 cell lines. Compounds **40a** ($IC_{50}$ < 43.1 μg/mL) (Fig. 5) and **40b** ($IC_{50}$ < 64 μg/mL) (Fig. 5) were found to be more active as compared with standard drug curcumin ($IC_{50}$ < 36.65 μg/mL). The activity was increased by introducing 5-bromo substituent [94]. Similarly, Kamath et al, combined the indole and coumarin moieties to synthesize indole-coumarin derivatives. All the synthesized compounds were further evaluated against MCF-7. SAR studies concluded that acid and aldehyde substitution on the indole and the halogen atom on coumarin ring attached with indole leads to an increase in activity. The compound **41** ($IC_{50}$ = 7.4 μM) (Fig. 5) showed the best results in cytotoxicity and docking studies, compared to standard drug vincristine ($IC_{50}$ < 0.3 μM). Bromo group substitution was found to be favorable in forming halogen bond in the docking studies [95]. Various pyranochalcone derivatives of indole were synthesized and evaluated against HepG2 cancer cell line. SAR studies concluded the key role propionyl substituents for the inhibitory activity. Compound **42** ($IC_{50}$ = 0.22 ± 0.03 μM) (Fig. 5) was found to be highly potent as compared with the standard drug colchicine ($IC_{50}$ = 2.5 μM) (Fig. 5) and paclitaxel ($IC_{50}$ = 2.5 μM) [96]. In the same year, Kumar and the coworkers mentioned the synthesis of chalcone substituted indole derivatives having the property of enhancing tubulin polymerization. SAR study concluded the role of methoxy and fluoro group for the activity. Compound **43** (Fig. 5) exhibited significant potency ($IC_{50}$ = 0.8 μM) as compared with the standard drug ($IC_{50}$ = 0.45 μM) and selective against A549 lung cancer cell line [97]. Indole-thiazolylcoumarin analogues were synthesized and evaluated against a panel of human tumor cell lines. SAR study demonstrated the role of unsubstituted thiazolylcoumarins as anticancer agents. Compounds **44** ($GI_{50}$ = 1.18–2.44 μM) (Fig. 5) were reported as the most active compound of the series as compared with the standard drug [98]. Various sulfonamide derivatives of mono-indole, bis-indole, tris-indole were synthesized and evaluated against various cancer cell lines HuCCA-1, HepG2, A549, MOLT-3. SAR study concluded the significance of chloro substitution. Among all the synthesized compounds, **45** ($IC_{50}$ < 8.74 ± 0.79 μM) (Fig. 5) was found to be most active as compared with standard drugs etoposide ($IC_{50}$ < 30.92 ± 5.35 μM) and doxorubicin ($IC_{50}$ < 1.01 ± 0.13 μM) [99].

### 2.2. Anticonvulsant activity

Convulsion is a central nervous system (CNS) disorder due to paroxysmal cerebral dysrhythmia with brief episodes of seizures and /or loss of consciousness. Approximately 50 million people worldwide have epilepsy, making it one of the most common neurological diseases globally [100]. Researchers have synthesized and evaluated various indole derivatives as anticonvulsant agents [101].

Swathi and Saragapani in 2017 designed, synthesized and evaluated dialkylaminoalkoxy-oxindole derivatives. SAR studies suggested that semicarbazone substitution at the 3rd position of indole and alkyl substitution at the nitrogen atom present in the side chain of the indole were favorable for the activity. Compounds, **46** (67.18 ± 0.23) (Fig. 6) was found to be highly potent as compared with standard drug phenytoin (1 0 0) [102]. The literature survey suggested that benzohydrazide moiety exhibits a significant anticonvulsant activity by binding to GABA receptors [103]. This idea leads to the synthesis of benzohydrazide-oxindole derivatives by Madhira et al, in 2017 [104]. Methyl and propyl substitution at the indole ring were favorable for the activity. Compound, **47** (% protection = 83.19%) (Fig. 6) exhibited significant anticonvulsant activity as compared to standard drug phenytoin (% protection = 100%) [69]. Raju and coworkers synthesized and conducted anticonvulsant activity of novel indole carboxylate derivatives by MES method. SAR studies concluded that phenyl and piperazine substitution at the indole were responsible for the favorable activity. The compound, **48** (108.3 ± 0.7) (Fig. 6) was found to be the most effective as compared with standard drug phenytoin (100%) [105].

A huge data suggested the pyrazole has potent anticonvulsant properties [106–108]. This suggested the idea for Patil and Bari to synthesize some novel indole derivatives having pyrazole moiety. SAR studies revealed that the electron withdrawing group at the phenyl ring of indole is effective for the activity. The compound, **49a** (116.3 ± 1.54 s) (Fig. 6) and **49b** (109.8 ± 2.86 s) (Fig. 6) were found

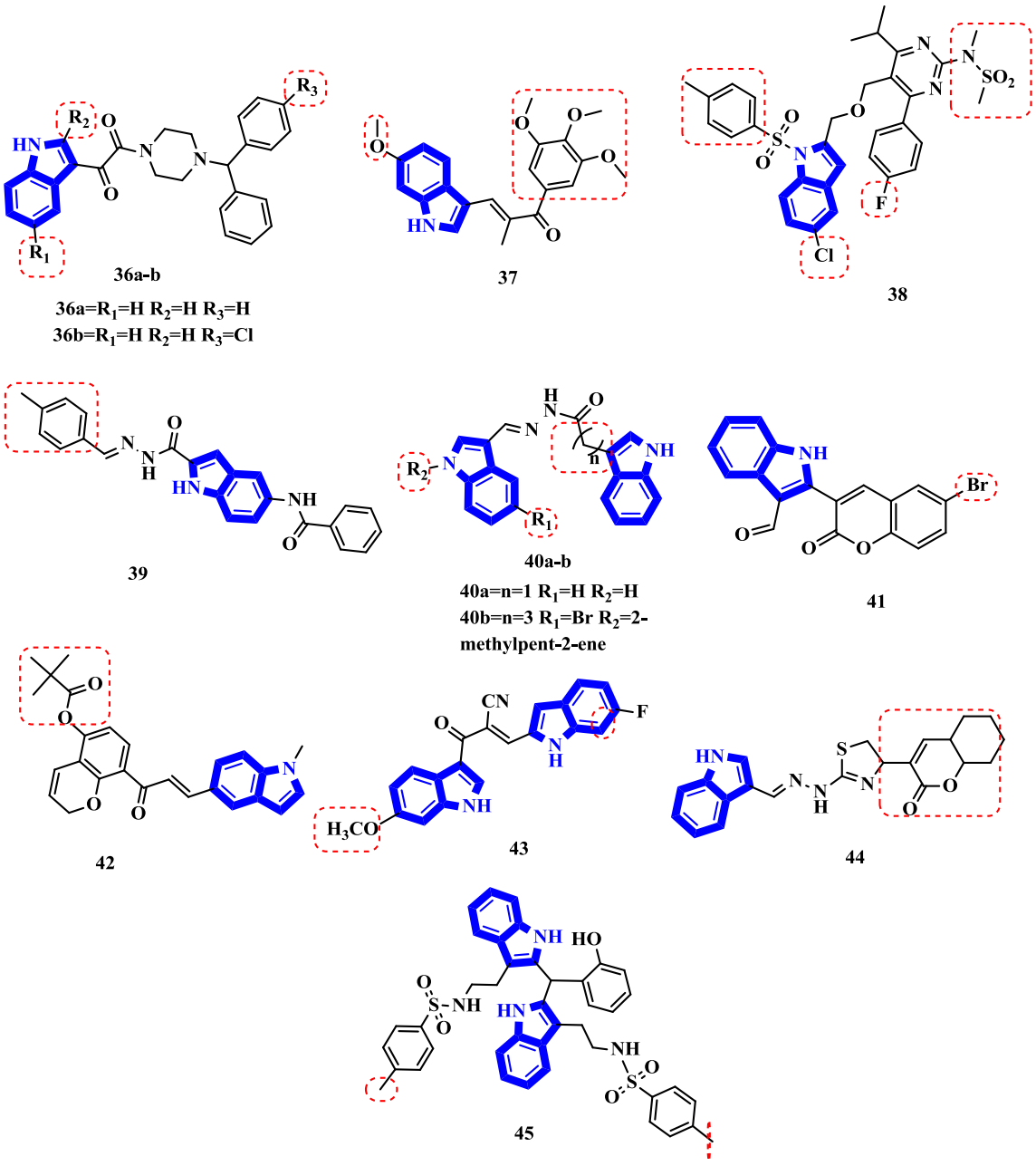



**Fig. 5.** Chemical structures for indole derivatives having anticancer activity **36–45** with active pharmacophores.

to be most effective as compared with standard drug diazepam (128. ± 2.33) [109]. In 2015, Zhen and coworkers designed acetamide derivatives of oxindole. SAR studies concluded the role of halogen substituent for the activity. **50a** and **50b** were found to be highly active (seizure test < 2/3) on comparing with standard drug carbamazepine (seizure test = 3/3) [110]. Indole-hydrazide derivatives were synthesized as new dual binding site cholinesterase inhibitors involving *in vitro* and docking studies. Most of the tested compounds were found to be actively involved in the inhibition of acetylcholinesterase and butyrylcholinesterase. SAR study suggested that aryl and aryl halide substitution on indole enhances the activity. Compound **51** (Fig. 6) ($IC_{50}$ = 91.21 ± 0.06 μM) and compound **52** (Fig. 6) ($IC_{50}$ = 68.52 ± 0.04 μM) exhibited promising acetylcholinesterase inhibitory activity as compared with standard drug eserine ($IC_{50}$ < 0.85 ± 0.0001). Additionally, the activity of compound **52** (Fig. 6) was also found to be due to two point attachment with acetylcholinesterase. In the case of butyrylcholinesterase, **51** (Fig. 6) was highly potent due to the presence of amide linkage [111]. In the same year, Ahuja and Siddiqui, synthesized and evaluated indole-1, 2, 4-triazine derivatives and screened against maximal electroshock (MES) test and subcutaneous pentylenetetrazole (scPTZ). Electron withdrawing groups such as trifluoromethyl and chloro were more effective in modulating anticonvulsant activity as compared to electron donating groups i.e. thiomethyl and methoxy. On the other hand, sulfonamide derivatives of indole-containing halogens, $CF_3$ showed good activity as compared to $OCH_3$ and $SCH_3$. Among the carboxamide derivatives, compound **53** (% protection = 100%) (Fig. 6) exhibited maximum potency which studied to be due to the presence of nitro group which helps in the binding with receptor [112].

Imidazole-indole derivatives were synthesized and evaluated against two seizure models *viz* MES (maximal electroshock seizure) and scPTZ (subcutaneous pentylenetetrazole. SAR studies suggest that substitution at the $N^1$ of imidazole substituted at the 3rd position of indole has marked role in enhancing anticonvulsant activity. To get

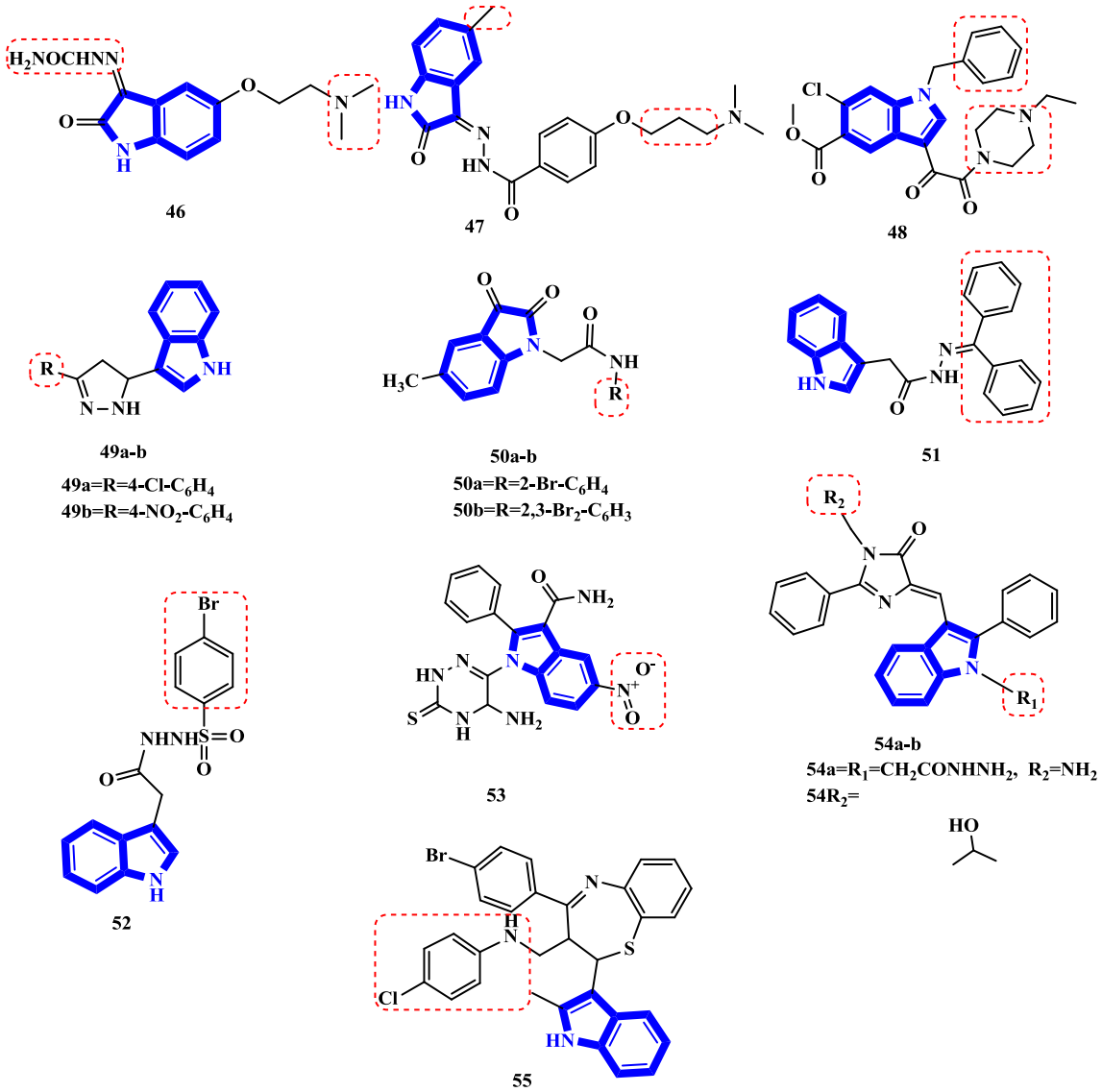



**Fig. 6.** Chemical structures for indole derivatives having anticonvulsant activity **46–55** with active pharmacophores.

potential anticonvulsant agents, these derivatives can be further tailored. Compounds **54a** and **54b** (Fig. 6) were found to be highly potent in MES [113]. A series of indole derivatives were synthesized by Kumar et al, and conducted *in vivo* study for anticonvulsant activity and acute toxicity studies. All the synthesized compounds were screened against maximal electroshock-induced seizure. SAR studies concluded that 1. Chloro group at the 4th position of phenyl attached to indole 3-yl is favorable for the anticonvulsant activity. 2. Presence of benzothiazepine nucleus is better as compared to the benzoxapine nucleus. 3. Substitution of *p*-chloro methylene aminophenyl group at the 4th position of benzothiazepine is good for activity. Out of the entire derivatives, compound **55** (Fig. 6) was found to be highly potent. Whereas, other compounds were also equally potent [114].

### 2.3. Antimicrobial activity

Antimicrobial resistance has been an issue since the introduction into the clinical use of the first agents in the 1940 s. To curtail the development and spread of antimicrobial resistance, it requires the preservation of current antimicrobials through their appropriate use, as well as the discovery and development of new agents. A higher rate of mortality and cost is observed in the treatment of microbial disease and that further amplified with an increase in antimicrobial resistance [115]. The WHO's latest survey reveals that among patients suffering from bacterial infection, 500,000 people are antibiotic resistant across 22 countries [116]. To combat the problem of antimicrobial resistance new indole derivatives targeting microorganism through different mechanism should be developed. Various indole derivatives are diagnosed and evaluated as antimicrobial agents that are discussed below.

Sanna and colleagues mentioned the synthesis of indole-thiourea hybrids and evaluated against about a pool of microbes containing both Gram-positive and Gram-negative type. Compound **56** (MIC < 12.5 μg/mL) (Fig. 7) was found to be highly potent as compared with standard drug ciprofloxacin (MIC < 1.0 μg/mL) [117]. Thiazolidine is also known for its activity as an antimicrobial agent. Various researchers are enduring to combine thiazolidine moiety with others to design potent antimicrobial agents [118]. These prompted, Abo-Ashour and coworker to design and synthesize oxindole-thiazolidine conjugates. All the synthesized derivatives were evaluated against *S. aureus*, *P. aerugenosa*, *E. coli*, *M. tuberculosis*, *A. fumigates*, *C. albicans*. SAR study concluded that chloro and methyl substitution is favorable for the activity. Compound **57** (MIC < 0.98 μg/mL) (Fig. 7) was found to be most active with equal potency both as antimicrobial and antifungal as compared with standard drug ciprofloxacin (MIC < 3.90 μg/

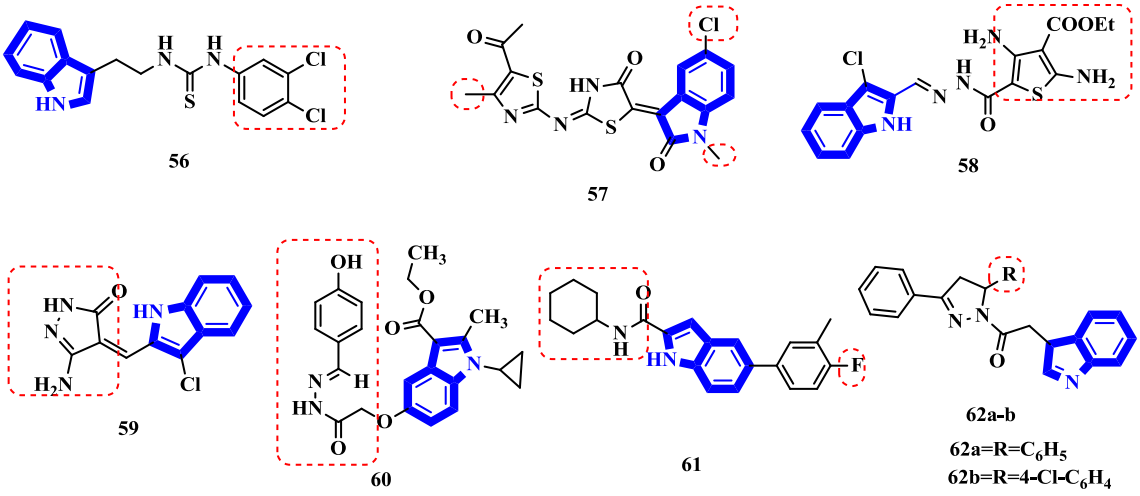



**Fig. 7.** Chemical structures of the antimicrobial indole derivatives **56–62** with active pharmacophores.

mL) and amphotericin B (MIC < 1.95 μg/mL) respectively [119]. Recently, Sayed et al, 2018 synthesized and evaluated various indole derivatives containing heterocyclic nucleus as antimicrobial agents. The presence of thiophene and imidazole rings enhances the antimicrobial activity of synthesized compounds. It was observed that compound **58** (MIC < 8 μg/mL) (Fig. 7) showed high antibacterial activity, whereas compounds **59** (MIC < 6 μg/mL) (Fig. 7) showed high antifungal activity [120]. Various 5-hydroxy-indole derivatives were synthesized and evaluated against *C. albicans, A. niger, E. coli, B. cirroflagellosus*. Compounds **60** (zone of inhibiton = 28 mm) (Fig. 7) showed maximum potency as compared with standard drug griseofulvin (zone of inhibiton = 30 mm) [121]. Mane et al, 2016 synthesized and evaluated various indole-2-carboxamide derivatives on the basis of research that various ester and amide derivatives of indole-2-carboxylic acid as found to be potent antioxidant and antimicrobial properties. All the synthesized compounds were evaluated against *K. pneumonia, E. coli, P. aeruginosa, S. typhi, C. albicans, C. neoformans, A. fumigates, C. parapsilosis.* SAR studies suggested that the alkyl and halogen substituted phenyl and cyclohexylcarboxamide derivatives are favorable for the activity. Compound **61** (MIC < 6.25 μg/mL) (Fig. 7) exhibited maximum antimicrobial activity compared with standard drug gentamicin (MIC < 3.0 μg/mL) [122].

It is found that pyrazole and imidazole have the broad spectrum of antimicrobial activity which may be due to the presence of nitrogen atom in five-membered rings which act by inhibiting cell wall synthesis or DNA damage [123–125]. The antimicrobial activity of these heterocyclics attracted various scientists to attach pyrazole and imidazole rings with the indole nucleus to prevent the problem of microbial resistance. In 2017, Quazi and coworkers, synthesized and evaluated various indole-pyrazole derivatives. Among all the compounds, **62a** (zone of inhibition < 0.5 cm) (Fig. 7) showed good activity against gram-positive bacteria and compounds **62b** (zone of inhibition < 0.1 cm) (Fig. 7), has good activity against fungal strain *Macrophomina phaseolina* and *Sclerotium rolfsii* [126]. A series of imidazole-based indole derivatives were synthesized and assayed against bacterial strains *S. aureus, S. pyogenes, Shigella flexneri, Proteus mirabilis*, *Vibrio cholera* and also on fungal strains *Candida albicans, C. glubrate* and *C. crusei.* The antibacterial activity trend of synthesized compounds were found to be **60** > **61** > **62** > **63**. Apart from this, density functional theory, computational method, X-ray crystallographic analysis and molecular docking study were also performed. Compound **63** (MIC < 12.5 μg/mL) (Fig. 8) showed good chemical stability, reactivity and bond parameters due to the presence of negative charges on oxygen and nitrogen atoms when compared with methicillin standard drug (MIC < 6.25 μg/mL) (Fig. 8) [127]. In the same year, Yadav 2016, reported the role antibacterial activity of 1,2,3,5 substituted indole derivatives and evaluated against *S. aureus, S. pyogenes, E. coli, P. aerugenosa.* Compounds **64** (MIC = 37.5 μg/mL) (Fig. 8) was found to be most active [128]. Choppara et al, 2015 have designed and synthesized bis-indole derivatives and evaluated against *B. subtilis, E. coli, K. pneumonia, P. aerugenosa*. SAR study concluded the role of prenyl system for the activity. Compound **65a** (Fig. 8) (zone of inhibition < 24 mm), **65b** (Fig. 8) (zone of inhibition < 21 mm) and **65c** (Fig. 8) (zone of inhibition < 20 mm) were found to be the most active as compared with standard drug ciprofloxacin (zone of inhibition < 27 mm)[94]. Gali and coworkers, mentioned the synthesis of thiazolylcoumarins substituted indole derivatives and further evaluated against *B. subtilis, E. coli.* SAR highlighted that the presence of unsubstituted thiazolylcoumarins was favorable for the activity. Compound **66** (zone of inhibition < 18 mm) was found to be highly potent as compared to standard drug streptomycin (zone of inhibition < 30 mm)[98].

Hydrazone is another moiety having immense antimicrobial activity due to inhibition of microbial cell wall synthesis described in a large literature data [129,130]. Based on this, Shirinzadeh et al, synthesized and evaluated various indole-hydrazone derivatives to cope with the problem of multidrug-resistant bacterias. SAR studies suggested that activity increased with the introduction of halogen atoms into the phenyl ring especially at the *ortho* position. **67a** (3,5-difluoro) (MIC < 100 μg/mL) (Fig. 8), **67b** (MIC < 50 μg/mL) (3,5-dichloro) (Fig. 8), showed the highest activity when compared to standard drugs sultamicillin (MIC < 25 μg/mL), ampicillin (MIC < 50 μg/mL), fluconazole (MIC < 0.78 μg/mL) and ciprofloxacin (MIC < 0.19 μg/mL) [131]. Nassar et al, also reported the synthesis of pyrazoline, pyridine, pyrimidine substituted indole derivatives as antimicrobial agents. All the synthesized compounds were evaluated against *S. aureus, E. coli, P.aerugenosa, Fusarium A. niger, C. albicans.* SAR study indicated the role of methoxyphenyl substitution. Compound **68** (Fig. 8) (zone of inhibition < 34 mm) exhibited promising antibacterial activity when compared to standard drug ciprofloxacin (zone of inhibition < 44 mm) and nystin (zone of inhibition < 44 mm) [132].

Recently, indole subunits have gained wide-spread concern due to their remarkable role as antifungal agents. In this perspective, Zhang et al., have done noticeable work in the area of antifungal drug development. In 2012, analogues of pimpirinine, an indole alkaloid obtained from streptomyces species, were synthesized and bioassay was conducted on *Pythium dissimile, Alternaria solani, Botyyotinia fuckeliana and Gibberella zeae* by Zhang and coworkers. SAR study concluded that bromo and acetyl chloride substitutions were favorable for the activity. Among all **69a** and **69b** was found to be highly potent **(**Fig. 8**)** [133]. Further, the same researchers in 2013, synthesized and studied the

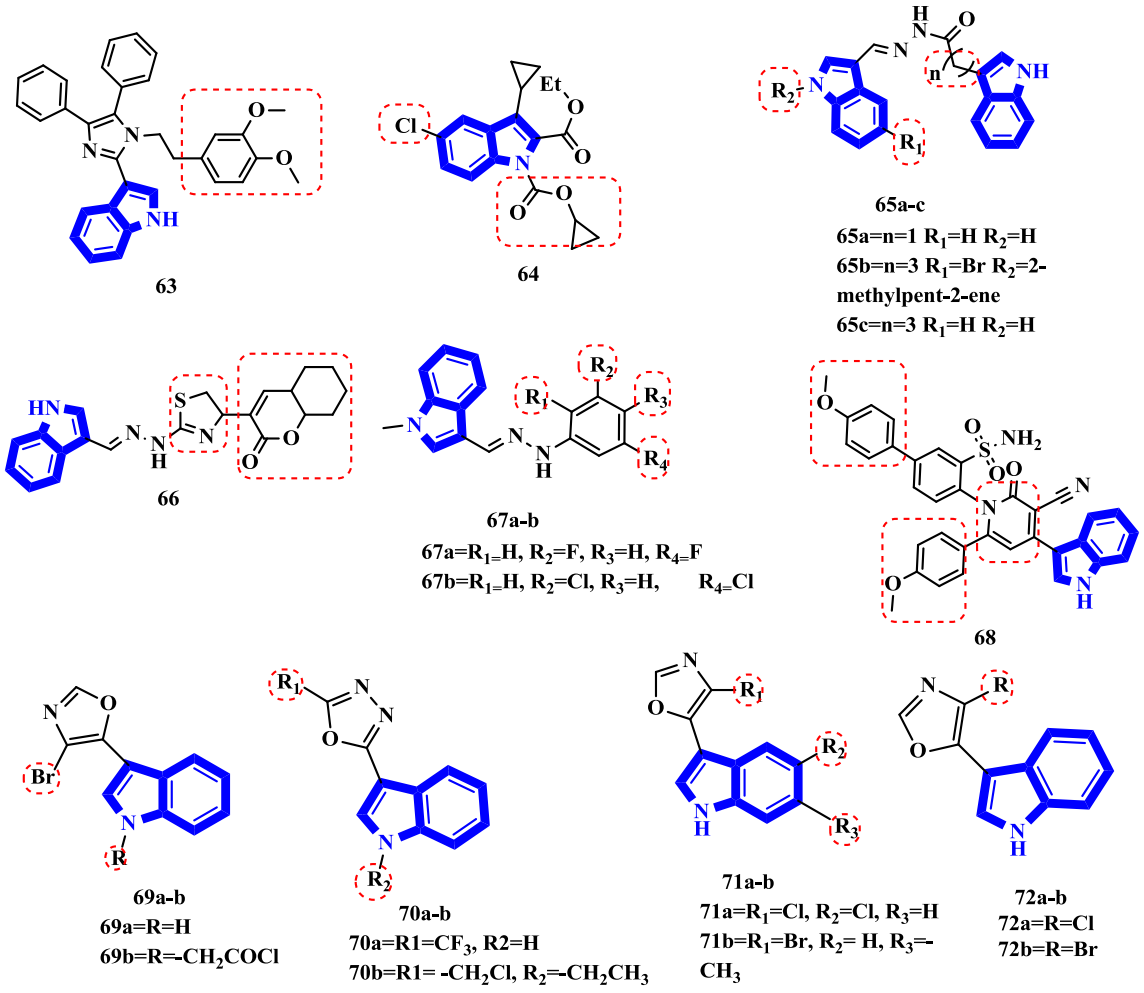



**Fig. 8.** Chemical structures of the antimicrobial indole derivatives **63–72** with active pharmacophores.

oxadiazole derivatives of indole. All the synthesized compounds were evaluated against *Pythium dissimile, Septoria tritici* and *Uromyces viciae-fabae* and also compared with pimpirine alkaloid as already reported in the previous article. SAR study concluded that halogen substitution is favorable for the activity. Compounds **70a** and **70b** (Fig. 8) were found to be potent [134]. Motivated by the promising results, this study was further extended with streptochlorin, an indole alkaloid obtained from marine actinomycetes. Synthesized streptochlorin analogues were evaluated against *Pythium dissimile, Alternaria solani,* Uromyces viciae-fabae, *Gibberella zeae, Alternaria solani, Phytophthora infestans, Zymoseptoria tritici and A. Solani.* The introduction of chloro and bromo substitution at the 4th position of oxazole ring increases the activity. Compounds **71a** and **71b** (Fig. 8) were found to be highly potent analogs showing 81–100% control of disease [135]. Similarly, novel derivatives of streptochlorin were synthesized with more active heterocycles having improved antifungal activity. All analogues were studied against *Pythium dissimile, Alternaria solani, Uromyces viciae-fabae, Gibberella zeae, Alternaria solani, Phytophthora infestans, Zymoseptoria tritici.* SAR study marked the importance of indole moiety in streptochlorin [136]. Due to the high potency of streptochlorin as antibiotic, extensive study on the derivatization of streptochlorin is also conducted by other researchers. Recently, Jia et al., 2018 also conducted the study on streptochlorin, natural antifungal constituents extracted from marine streptomyces species. Evaluation of analogues was conducted on *Pythium dissimile, Alternaria solani, Gibberella zeae, Botrytis cinerea, Rhizoctorzia solani, Alternaria blotch and Collecterichum capsica.* Chloro and bromo substitution were favorable for the activity. Compounds **72a** and **72b** were found to be highly potent (Fig. 8) [137].

### 2.4. Antitubercular activity

Tuberculosis is caused due to the infection spread by *Mycobacterium tuberculosis* affecting lungs as well as other parts of the body [138]. According to the 2016 data, among 10 million cases of TB, 1.3 million were died [139]. Tuberculosis is considered the most life-threatening disease that causes about 100 million deaths worldwide [140]. About 9093 cases of tuberculosis were identified in the United States having a rate of 2.8 over 100,000 which is decreased by 1.8% from 2016 to 2017 [141]. A number of indole derivatives are mentioned here having advanced antitubercular activity.

In 2018, Abo-Ashour with colleagues synthesized and evaluated various oxindole-thiazolidine conjugates active against *M. tuberculosis bacterial strain* RCMB 010126. The methoxy, ethoxy, alkyl groups were found to be favorable for the activity. Compounds **73a** (Fig. 9) (MIC = 0.39 μg/mL) and **73b** (Fig. 9) (MIC = 0.39 μg/mL) were more and equally potent compared to standard drug isoniazid (MIC = 0.78 μg/mL) [119]. Various indole derivatives were synthesized using Knoevenagel and Michael reaction mechanism and *in vitro* study was conducted to evaluate the antitubercular activity against *M. tuberculosis* bacterial strain (MTCC CODE 300). Docking study was also performed to further detect the affinity between the synthesized compound and enoyl-acyl carrier protein reductase using AutoDock-Vina software (Los Angeles, USA) [142]. SAR studies concluded that chloro and nitro substituent at the *para* and *ortho* positions of phenyl ring were favorable for the activity. Compound, **74** (Fig. 9) has

comparable activity (MIC = 40 μg/mL) to standard drug isoniazid (MIC = 10 μg/mL) and also good binding affinity (-11.6) with target

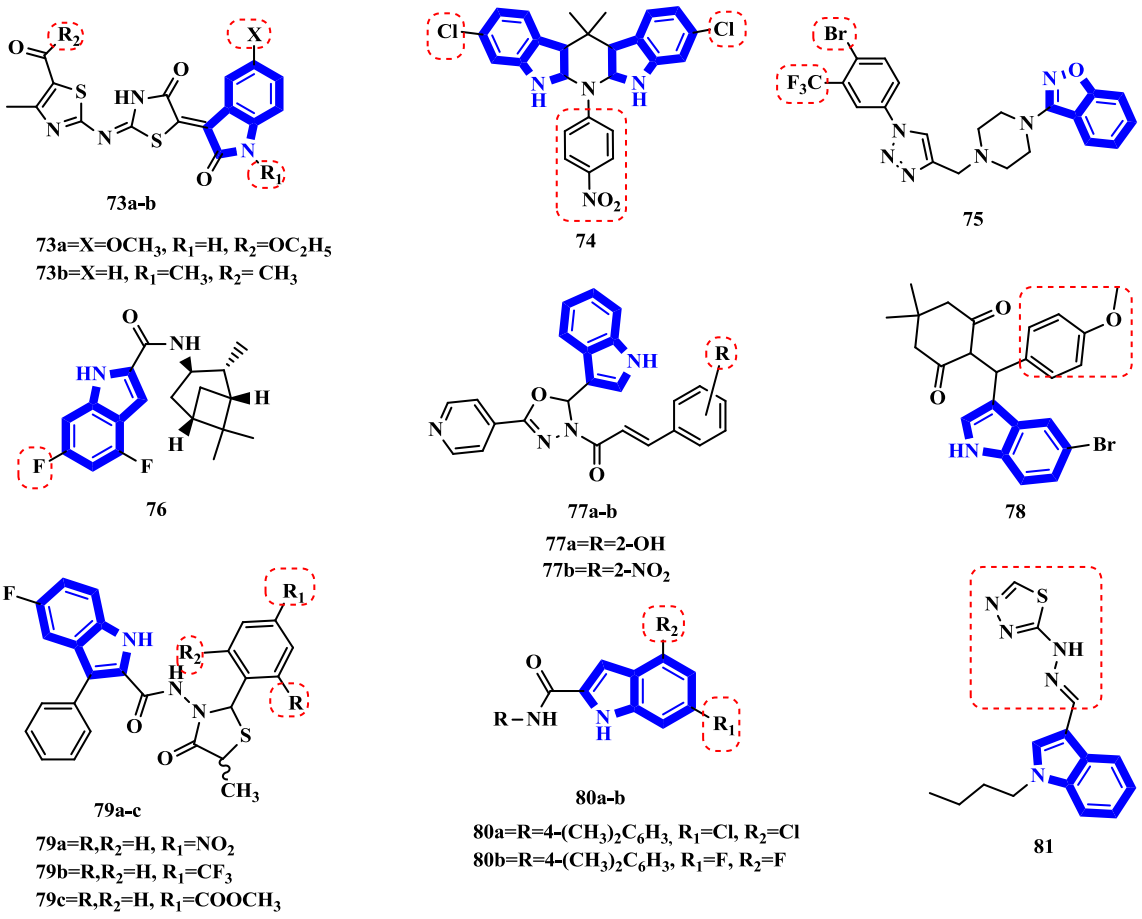



**Fig. 9.** Chemical structures for indole derivatives having antitubercular activity **73–81** with active pharmacophores.

protein [143].

Based on an enormous data of piperazine as antitubercular agents [144,145], Naidu and coworkers, 2016 reported various indole-piperazine derivatives and evaluated against *Mycobacterium tuberculosis*, bacterial strain H37Rv, Spec. 210, Spec. 192. The introduction of electron withdrawing groups such as Br, $CF_3$ leads to increase in antitubercular activity. Compounds, **75** (MIC = 6.16 μM) (Fig. 9) was showed the highly potent antitubercular activity compared to standard drug isonicotinic acid hydrazide (MIC = 91.14 μM) [146]. In the same year, Stec J, et al, designed, synthesized various indole-carboxamide derivatives targeting MmpL3 protein and were further evaluated for antitubercular activity by conducting *in vivo* and *in vitro* studies. Lipophilic compounds exhibited higher activity compared to hydrophilic derivatives. The compound, **76** (Fig. 9) was found to have excellent activity (MIC = 0.012 μM) against multidrug-resistant and extensively drug-resistant *M. tuberculosis* strains. Apart from this, docking studies were also conducted showing the maximum binding of **76** (MIC = 0.29 μM) (Fig. 9) with MmpL3 protein [147]. Some novel indole and pyridine based 1, 3, 4-oxadiazole derivatives having antitubercular activity was reported. The *in vitro* studies were conducted to evaluate the antitubercular activity against *M. tuberculosis* $H_{37}Ra$ and *M. bovis* BCG. However, the antiproliferative activities of synthesized derivatives were also evaluated using three cell lines- HeLa, A549 and PANC-1. According to SAR, the substitution pattern at the phenyl ring of chalcone significantly modulates the activity. At the 2nd positions of the phenyl ring, –OH and $–NO_2$ functional group are favorable for the activity. Compound, **77a** (Fig. 9) and **77b** (Fig. 9) were recognized as the most active compounds with MIC ranging from 0.94 to 5.17 μg/mL compared to isoniazid (MIC = 0.037 μg/mL) and rifampicin (MIC = 0.017 μg/mL). Docking studies were also conducted using Grid–Based Ligand Docking [148]. Compounds **77a** (Fig. 9) and **77b** (Fig. 9) exhibited maximum docking in the active site of mycobacterial enoyl reductase (InhA) [51]. Khan et al, 2016 have synthesized novel 3-alkylated indole derivatives using mpCuO as a heterogeneous catalyst having high catalytic efficiency, maximum surface area and recyclability. Among all the synthesized compounds, **78** (Fig. 9) (MIC = 15 μg/mL) containing *p*-methoxy phenyl derivative at the 3rd position of indole exhibited significant antitubercular activity against *M. tuberculosis* bacterial strain (MTCC CODE 300) in comparison to the isoniazid taken as a standard drug (MIC = 10 μg/mL). Docking studies were also conducted using enoyl-acyl carrier protein reductase and the binding score was calculated for each derivative. Among all the synthesized derivatives, **78** (Fig. 9) showed maximum binding score [149].

Various organic moieties containing a hetero atom, the double bond between carbon and nitrogen, are found to be a potent inhibitor of DNA gyrase enzyme causing the bacterial death.

Hydrazone and thiazolidinones falling under this category are found to be potent antitubercular agents [150–152]. Because of this, Ustundag et al, 2016 investigated and designed indole-based hydrazide-hydrazone, 4-thiazolidinones derivatives and screened for *in vitro* antitubercular activity against *M. tuberculosis* H37Rv. SAR studies concluded that substitutions on the phenyl ring have a major impact on the activity. Substitution of F, CN, $NO_2$, $CF_3$ and $COOCH_3$ at the *para* position were favorable for the activity. Compound, **79a** (MIC = 12.5 μg/mL) (Fig. 9) and **79b** (MIC = 12.5 μg/mL). (Fig. 9), **79c** (MIC = 25 μg/mL) (Fig. 9) demonstrated notable anti-TB activity ranging from 6.25 to 25 mg/mL compared to rifampicin as standard drug (MIC = 25 μg/mL). However, anticancer activity is also evaluated using the colon cancer cell line COLO 205 [76]. Various indole-2-carboxamide derivatives were also reported. SAR studies revealed that -Cl, -F, –CN substituents

at the 4th and 6th position of indole and methyl substitution on phenyl ring attached with indole leads to increase in potency. All the synthesized derivatives were tested against *M. tuberculosis* H37Rv strain. The compound, **80a** ($MIC_{50}$ = 0.15 μM) (Fig. 9) and **80b** ($MIC_{50}$ = 0.23 μM) (Fig. 9) were found to be highly potent as compared to the standard drug isoniazid ($MIC_{50}$ = 0.33 μM) [153]. Later in 2014, Tehrania and colleagues, synthesized and evaluated various Schiff' base based indole derivatives. All the synthesized compounds are further evaluated using a microtiter plate on gram positive and gram negative strain. SAR studies concluded that urea-based derivatives were highly potent. Compounds **81** (MIC = 3.91 μg/mL) (Fig. 9) exhibited maximum potency as compared with standard drug ethambutol ((MIC = 0.75 μg/mL) [154].

### 2.5. Antimalarial activity

Malaria is an infectious disease caused by *Plasmodium* parasite. Malaria is a chronic disease that leads to thousands of deaths annually [155]. According to the 2016 data, among the 216 million reported cases of malaria, 731,000 died worldwide. Maximum cases were appeared in Africa [156]. It is required to develop antimalarial drugs at a fast rate to combat this problem. A few of indole derivatives as antimalarial agents are discussed below.

Yadav et al, 2016 synthesized and evaluated various novel indole derivatives and evaluated against *P. falciparum*. SAR studies explained that alkyl substitution with carboxylate at 1st and 2nd position and aryl at the 3rd position of indole were favorable for the activity. Compounds **82a** and **82b** (Fig. 10) showed high potency, having MIC value not > 0.70 μg/mL on comparing to the standard drugs quinine (MIC = 0.270 μg/mL) and chloroquine (MIC = 0.02 μg/mL) [128]. Various indole-based piperidine derivatives were synthesized and *in vitro* studies were conducted in *P. falciparum* culture and activity was measured in terms of $EC_{50}$. Lipophilicity was also calculated in terms of the partition coefficient (clogP), to further access the activity of synthesized derivatives. Piperidinyl moiety was found to be critical for the activity. Compound **83** (Fig. 10) was obtained having selectivity for malaria parasites, no drug resistance and better activity ($EC_{50}$ ~ 3 μM, cLogP = 2.42 and MW = 305) as compared to most of the standard drugs chloroquine, atovaquone, amodiaquine, artesunate with $EC_{50}$ value 285 ± 58 μM, 0.35 ± 0.14 μM, 12.30 ± 4.21 μM, 1.97 ± 0.43 μM respectively [157].

Melatonin is an indole-derived hormone secreted by the pineal gland. It is involved in various signalling pathways involving the *Plasmodium* cell cycle and major role in the replication of *Plasmodium*. Inhibition of this hormone can be used to inhibit the growth of *Plasmodium*. Keeping this in mind, Schuck and coworkers have investigated various melatonin based indole derivatives. The synthesized derivatives have an inhibitory effect on the cell cycle of *P. falciparum*. The *in vitro* studies were conducted in *P. falciparum* culture and flow cytometer was used for activity calculation. SAR studies explained that carboxamide at the C-3 position of indole was decisive for the activity. Compounds **84a** ($IC_{50}$ = 19.17 μM) and **84b** ($IC_{50}$ = 19.10 μM), **84c** ($IC_{50}$ = 2.93 μM) (Fig. 10) exhibited maximum antimalarial activity. Alkyl and aryl substitution with carboxamide at the C-3 and methoxy group at the C-5 gave maximum potency [158]. Among the entire major heterocyclic nucleus, quinoline derivatives are the well known antimalarial agents acting through the inhibition of DNA synthesis of microorganism [159,160]. It could be a wonderful idea to combine this moiety with indole. This prompted Teguh et al, to synthesize various quinoline-indole conjugates and tested against *P. falciparum* using K1 strain. SAR studies concluded that the amino group and alkyl-substituted amino group were favorable for the activity. Compound **85** ($IC_{50}$ < 0.4 ± 0.2 μg/mL) (Fig. 10) demonstrated promising antimalarial activity [161].

Meridianin G, is an indole alkaloid obtained from marine invertebrate *Aplidium meridianum*. It is found to be the inhibitor of cyclin-dependent protein kinase, involved in the progression of malaria. Based on this fact, Bharate et al, reported various meridianin G-based indole derivatives and evaluated against chloroquine sensitive and resistant clones of *P. falciparum* through plasmodial LDH (lactate dehydrogenase) activity. Compound, **86** ($IC_{50}$ < 4.01 μM) (Fig. 10) was found to be most effective as compared with standard drug artemisin ($IC_{50}$ < < 0.09 μM) and chloroquine ($IC_{50}$ < 0.72 μM) [162].

### 2.6. Antidiabetic activity

Diabetes mellitus is identified by a high blood sugar level over a long period of time. Diabetes is linked with the high rate of mortality causes renal and eye problems [163]. The global prevalence (age-standardized) of diabetes has nearly doubled since 1980, rising from 4.7% to 8.5% in the adult population. According to the 2014 data, 422 million adult's cases of diabetes were obtained [164]. Novel antidiabetic drugs are required to tackle this problem. Large pools of indole derivatives are available in the literature with antidiabetic activity. Derivatives of some nitrogen-containing heterocyclic nuclei are identified as antidiabetic agents. Oxadiazole derivatives manage the type-II diabetes mellitus condition through α-glucosidase inhibitory activity [165]. Another nucleus, triazole showed antiadipogenic and antidyslipidemic activity through Wnt3a/β-catenin pathway [166]. Prompted by these facts, Rajan et al, synthesized and evaluated novel indole-triazole derivatives. All the synthesized compounds were evaluated by the Syrian Golden Hamster model. SAR studies concluded that

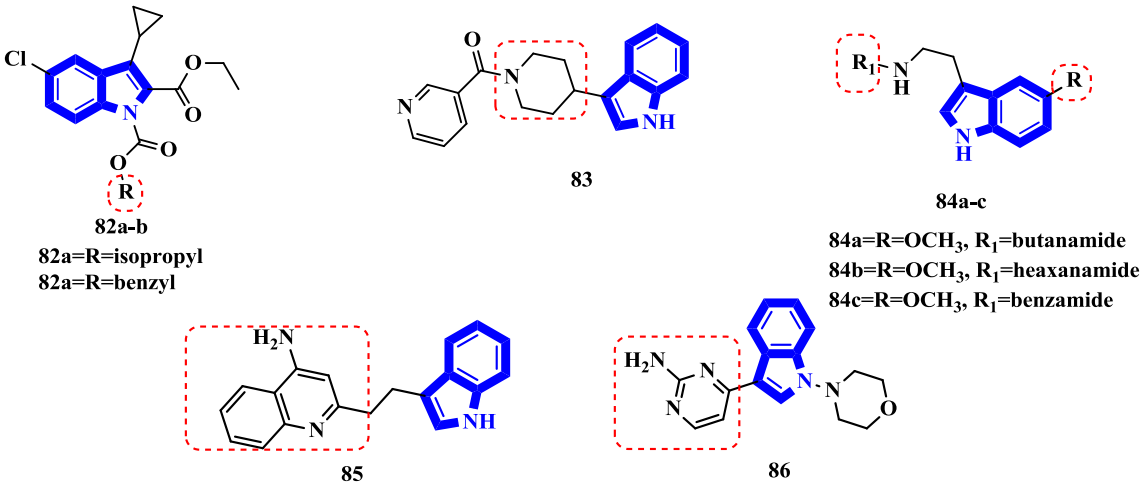



**Fig. 10.** Chemical structures for indole derivatives having antimalarial activity **82–86** with active pharmacophores.

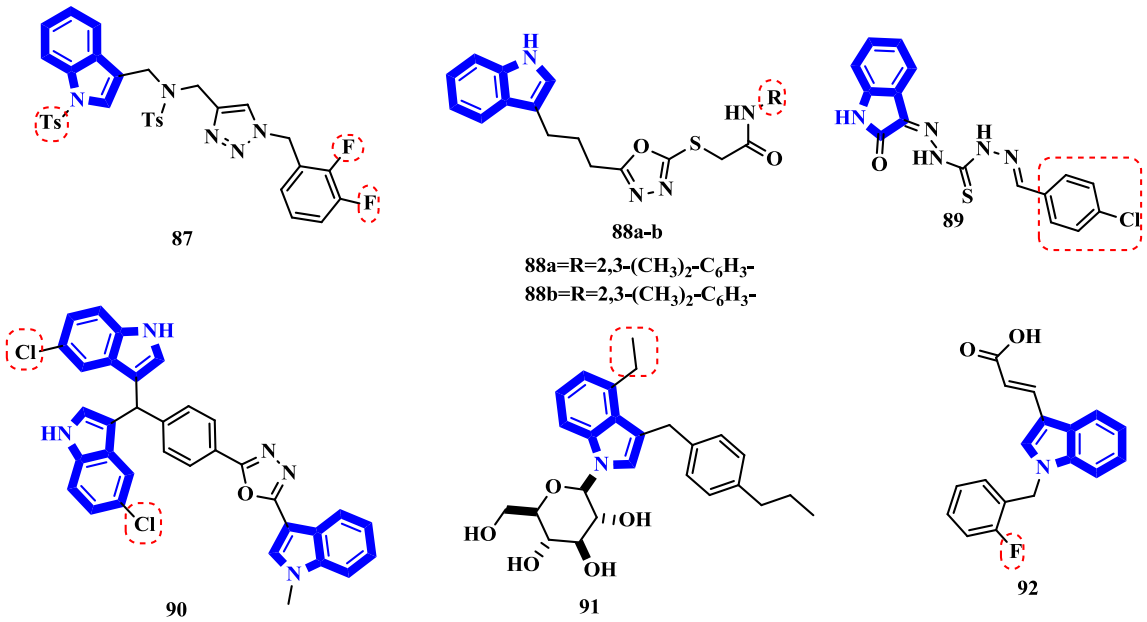



**Fig. 11.** Chemical structures for indole derivatives having antidiabetic activity **87**–**92** with active pharmacophores.

difluoro and tosyl substitution is favorable for the activity. Compound **87** (Fig. 11) was found to be the highly potent [167]. Similarly, various indole-oxadiazole hybrids were synthesized by Nazir and coworkers and tested as α-glucosidase enzyme inhibitory activity. SAR study concluded that 2,3 and 2,4-dimethyl substituted phenyl were favorable derivatives. Compounds **88a** ($IC_{50}$ = 9.46 ± 0.03 μM) (Fig. 11) and **88b** ($IC_{50}$ = 9.37 ± 0.03 μM) (Fig. 11) were found to be highly potent as compared with the standard drug acarbose ($IC_{50}$ = 37.38 ± 0.12 μM) [168].

Srividya and Reddy, 2017 designed, synthesized and evaluated indole derivatives as antidiabetic agents. *In vivo* study was conducted on diabetes-induced chick model to evaluate all the derivatives. The test compound **89** (Fig. 11) was found to have a good reduction potential of sugar level (29.6–38.6%) on comparing with the standard drug glibenclamide (57.10%) [169]. Combining oxadiazole with indole was carried out in 2017, by Taha and coworkers in which oxadiazole ring was attached to indole to obtain a series of tris indole-oxadiazole hybrid analogues. Synthesized derivatives showed their antidiabetic effect through the inhibition of α-glucosidase. Chloro substitution at R5 leads to highly potent compounds as seen in compound **90** ($IC_{50}$ = 2.00 ± 0.001 mM) (Fig. 11) compared to standard acarbose ($IC_{50}$ = 895.09 ± 2.04 mM) (Fig. 11). High activity may be due to the maximum binding affinity of the chloro group to the active site of an enzyme. The molecular docking studies were also performed with the binding site of α-glucosidase and binding affinity is measured from the QPLog$P_{o/w}$ (partition coefficient), QPLogS (predicted aqueous solubility), QP $P_{caco}$ (cell permeability), and Glide Score. All the synthesized derivatives were in the range and form hydrogen bonds with catalytic residue. Compound **90** (Fig. 11) was completely fit into the whole furrow of the binding site of the protein [170].

Novel indole *N*-glucoside derivatives were synthesized and evaluated on high-fat diet fed mice. SAR studies concluded that methyl and halogen substitution is favorable for the activity. Compound **91** ($IC_{50}$ = 1.1 μM) (Fig. 11) was found to be highly potent [171]. A series of thiazole and indole-based derivatives were reported by Xu and coworkers. *In vivo* study was conducted in diet-induced obese rats. All the synthesized compounds were evaluated for the inhibitory effect on the production of LPS-stimulated TNF-α. A complete SAR study revealed that *ortho* and *para*-substitutions on the phenyl ring at the first position showed good activity and no activity was observed at the *meta* position. Whereas, the substitution of strongly electron withdrawing groups gave only moderate activity. Compound, **92** (Fig. 11) was found to have an excellent inhibitory effect (95%) that is more than standard drug BMS309403 (85.13%) and also it was observed that oral administration of compound **92** (Fig. 11) significantly reduce the levels of plasma blood glucose, triglycerides, total cholesterol in diabetic induced model. Docking studies were also conducted with fatty acid binding protein 4 (A-FABP) which proved that of compound **92** (Fig. 11) has a good binding affinity for the protein having $K_i$ value 33Nm [172].

### 2.7. Antiviral activity

A viral infection is spread by pathogenic viruses and infectious virus particles when entering inside the body. Various antiviral drugs are available in the market against HIV, Herpes viruses, hepatitis B and C viruses. Among all the infections, viral is the fastest spreading, creating about 60% illness in Developed countries [173]. Due to the fast replication rate, it is required to design safe and efficacious antiviral drugs. Researchers are working to design novel antiviral drugs with a wide range of activities [65].

Scuotto et al, 2016 designed a series of novel multi-target indole-3-carboxylate derivatives as antiviral agents. All the synthesized compounds were evaluated against Chikungunya virus in Vero cell culture by a CPE reduction assay. SAR studies suggested that the hydroxyl group at the 5th position is found to be most favorable. Compounds, **93** (Fig. 12) was found to be most active ($EC_{50}$ = 6.5 ± 1) which is 10 fold more as compared to the standard drug arbidol. Further docking studies were also performed by using the crystal structure of CHIKV glycoprotein complex. Maximum derivatives inserted into the lateral sites of the active site whereas in compound **93** (Fig. 12) indole got deeply inserted into the cavity and thiophenol ring occupy solvent exposed portions showing maximum bonding. The antiviral effect is due to the inhibition of an earlier viral life cycle [174].

Spiroindolines, like indole, have the property to inhibit the viral protein synthesis, nucleic acid synthesis, receptor recognition. With these diversified mechanisms, spiroindoline and indole combination can be the best strategy to control viral action [175]. Based on these facts, Chen and other researchers, designed, synthesized and evaluated fused indoles and spiroindolines. All the synthesized compounds were further screened by *in vivo* and *in vitro* assays against *Tobacco mosaic* virus. SAR studies concluded that in the case of fused indole derivatives,

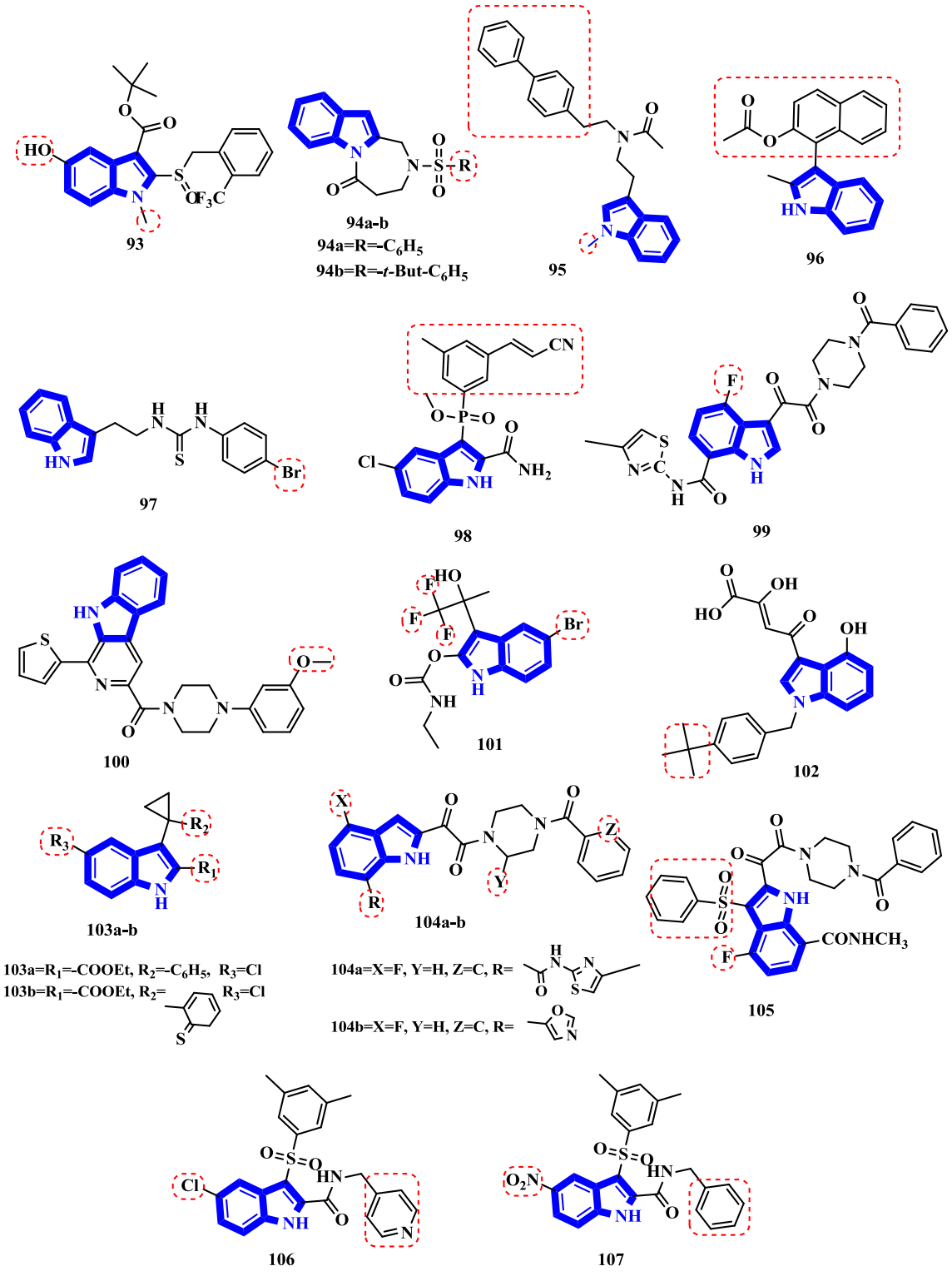



**Fig. 12.** Chemical structures for indole derivatives having antiviral **93–107** with active pharmacophores.

phenylsulfonyl, 4-*tert*-butylsulphonyl, 4-chlorophenylsulphonyl groups are favorable for the activity whereas C ring is crucial for the activity. In case of spiroindolines, electron withdrawing groups i.e., -Cl, –CN, -$CF_3$ etc on quinolone phenyl ring were vital for activity. Derivatives **94a** (% inhibition = 48 ± 1%) and **94b** (% inhibition = 56 ± 2%) (Fig. 12) exhibited maximum potency as compared to standard drug ribavirin (% inhibition = 36 ± 1%) and harmin (% inhibition = 45 ± 1%) at the concentration of 500 μg/mL [176]. Similarly, Musella and coworkers also reported the synthesis of amide substituted indole derivatives and tested against human *Varicella zoster* virus (VZV). SAR studies concluded that substitution of biphenyl ethyl moiety and acetylation at the amino group of tryptamine is required for the activity against VZV. Compound, **95** ($CC_{50}$ = 39 μM) (Fig. 12) was found to be highly potent as compared with standard drug acyclovir ($CC_{50}$ = 191 μM) and biuvudin ($CC_{50}$ = 160 μM) [177].

Naphthalene derivatives are also observed against a variety of viral

disease conditions. Inhibition of viral replication is the main mechanism used by these derivatives [178]. Prompted by these, Giampieri et al, in 2009 fused the indole with naphthalene nucleus to form indole-naphthyl derivatives. All the synthesized derivatives were screened against a variety of viruses i.e., HIV-1 (human immunodeficiency virus-1), BVDV (bovine viral diarrhoea virus), YFV (yellow fever virus), CVB-2 (coxsackie virus B-2 strain). Presence of carboxylate, indole and naphthol were found to be imperative for the antiviral activity. Compound **96** ($CC_{50}$ = > 57 μM, SI = < 5) (Fig. 12) was quite active among all the compounds and compared to the standard drugs acyclovir, mycophenolic acid, ribavirin, 6-azauridine ($CC_{50}$ = > 100, SI = < 50) [179].

AIDS is a very dreadful disease occurring due to the infection by human immunodeficiency virus (HIV) [180]. According to 2016 data, 36.7 million people are diagnosed with HIV worldwide in 2016 [181]. Thus, the advancement of anti-HIV drugs should emphasize on the favorable structural modifications and its mechanism of action. Some novel indole derivatives as anti-HIV agents are mentioned here.

In 2018 Sanna, with other researchers mentioned the synthesis of novel indole-thiourea hybrids and evaluated against HIV-1. SAR studies reported the importance of 4-bromophenyl moiety. Among all the synthesized compounds, **97** ($EC_{50}$ = 8.7 ± 0.4 μM) (Fig. 12) was found to be highly potent as compared with standard drug efavirenz ($EC_{50}$ = 0.002 ± 0.0002 μM) [117]. In 2016, Doussan with other researchers, synthesized and evaluated various indole derivatives for anti-HIV activity. Compounds, **98** ($EC_{50}$ < 0.011 μM) (Fig. 12) was found to be highly potent as compared [182]. Various indole-7-carboxamide derivatives were also reported by Ravichandran. Computational techniques were used to screen the synthesized derivatives, thereby calculated various properties to evaluate the indole-7-carboxamide analogues i.e., physicochemical, steric, electrostatic and hydrophobic properties. SAR studies revealed that bulky and electronegative groups were favorable at the 3rd position of indole-7-carboxamide groups present on benzamido and pyrazine nucleus contribute hydrogen acceptance property which facilitates binding with HIV-1. Compound **99** (Fig. 12) was found to be highly potent [183]. Ashok et al, 2014, studied and reported the synthesis and evaluation of various indole-pyrido derivatives. *In vitro* study was conducted on HIV-1 infected cells and molecular properties were also calculated to further screen the synthesized analogues. SAR studies were conducted on the basis of substitutions present on the phenyl ring attached to piperazine which is further attached with indole. The studies concluded that *ortho* and *para* directing substitutions on 4th position of phenyl ring leads to no anti-HIV activity. Whereas, the 2-3rd position of phenyl favors the activity. Replacement of phenyl with benzyl moiety leads to increase in potency. The compound, **100** ($EC_{50}$ = 0.53 μM) (Fig. 12) was found to be highly potent whereas others have moderate activity compared to standard drug zidovudine ($EC_{50}$ = 0.002 μM) [184]. In the same year, trifluoromethyl-indole derivatives having improved drug resistance with anti-HIV-1 NNRTIs were reported by Jiang and coworkers. All the synthesized derivatives were screened against WT (wild-type) HIV-1 strain. SAR studies revealed that the presence of Cl or Br at C-5 improved the activity and presence of nitro at C-7 reduced the activity. Substitution of alkyl chain substituted with halogen at C-3 leads to potent compound **101** ($EC_{50}$ < 133.33 μM) (Fig. 12) on basis of the comparison with standard drug nevirapine ($EC_{50}$ = 0.4 μM) and efavirenz ($EC_{50}$ = 0.08 μM). Further docking analysis gave the idea about the binding mode of various derivatives with HIV reverse transcriptase enzyme [185]. Ferro et al, 2014 designed, synthesized and evaluated indole derivatives by performing the docking study with HIV-1 integrase. Docking studies concluded that bulkier substituent on the benzyl group, i.e. *tert*-butyl, trifluoromethyl group, is favorable for the interaction with HIV-1 integrase protein. Compound, **102** ($IC_{50}$ = 0.4 mM) (Fig. 12) was found to be highly potent [186]. Hassam and coworkers synthesized and evaluated cylopropyl indole derivatives as HIV non-nucleoside reverse transcriptase inhibitors. All the synthesized compounds were evaluated by using HIV-1 retroviral vector system. SAR studies concluded that C-1 position of propanoic acid and amides were favorable for the activity. At the C-2 position, cyclic groups, i.e., phenyl and thiophene enhance the activity and finally, at the C-3 position, Cl and Br groups are favorable. Compounds **103a** ($IC_{50}$ = 0.085 μM) and **103b** ($IC_{50}$ = 0.065 μM) (Fig. 12) were highly potent on the basis of the comparison with standard drug nevirapine ($IC_{50}$ = 0.087 μM). Docking studies were also conducted to further evaluate the activity using HIV non-nucleoside reverse transcriptase enzyme which confirmed that compound **103b** (Fig. 12) well accommodated within the active site [187].

Various indole-piperazine derivatives were also synthesized and screened using various molecular computational techniques, i.e., combined docking, molecular dynamics and 3D-QSAR study. SAR studies suggested that small bulky substituents were required for the activity and also smaller substituents having balanced steric and electrostatic properties are highly desirable at 7 positions of the indole ring. However, activity reduced in the order of primary > secondary > tertiary amine. Compounds, **104a** ($EC_{50}$ = 0.006 nM) and **104b** ($EC_{50}$ = 0.005 nM) (Fig. 12) were found to be highly potent, having good binding affinity with receptor [188]. In the same year, indole-7-carboxamide derivatives were synthesized by Yeung and coworkers. All the synthesized compounds were evaluated by cell-based assay against a pseudotype virus expressing a JRFL envelope. SAR studies concluded that 4-fluoro substitution is favorable for the activity. Among all the compounds, **105** ($EC_{50}$ = 0.29 nM) (Fig. 12) was found to be highly potent [189]. Regina et al, 2012 synthesized and evaluated nitrogen-containing indole 2-carboxamide derivatives. All the synthesized derivatives were evaluated against mutant Y181C, Y188L, K103N, K101Q, IRLL98 AND G190A HIV-1 strain. SAR studies concluded that pyridine-4-yl methyl substituent is favorable for the activity. Compound **106** ($EC_{50}$ = 2.0 ± 0.2 nM) (Fig. 12), as compared with standard drug zidovudine ($EC_{50}$ = 2.0 ± 0.2 nM) and efavirenz ($EC_{50}$ = 6.3 ± 3.2 nM) was found to be highly potent [190]. Regina et al, also studied the synthesized and evaluated indole 2-carboxamide derivatives with different substitutions. All the synthesized compounds were further evaluated against mutant L100I and K103N RT HIV-1 strains. SAR studies concluded that nitro and pyrrole substituted carboxamide is favorable for the activity. Compound **107** ($EC_{50}$ = 1.3 ± 0.0 nM) (Fig. 12) was found to be highly potent than standards, nevirapine ($EC_{50}$ = 19.2 ± 0.2 nM) and efavirenz ($EC_{50}$ = 1.5 ± 0.3 nM) [191].

### 2.8. Antiinflammatory activity

Inflammation is a complex body response towards the harmful stimuli, i.e., pathogens, damaged cells, irritants. Inflammation is involved in tissue repairment. But in the chronic form, it has negative effects on the body. Antiinflammatory agents treat inflammation reducing swelling and pain. The indole is found to be a major inhibitor of cyclooxygenase [192].

In 2018, Mukthung and coworkers developed various capsaicins based indole and nitroindole derivatives and evaluated against the proinflammatory kinase TNF-α. SAR study highlighted the role of capsaicin alkyl chain system and nitro substitution for favorable activity. Compound **108a** (relative % inhibition = 47.65%) and **108b** (relative % inhibition = 51.95%) (Fig. 13) were the highly potent as the relative % inhibition compared with standard drug capsaicin [193]. In the same year, Bhat and colleagues reported the acetohydrazide-indole hybrids for COX-2 inhibitory activity. SAR studies suggested the role of nitrophenol substituent favorable for the activity. Docking studies revealed that compound **109** (potency = 0.79%) (Fig. 13) found to be a most selective inhibitor and also potent as compared to standard drug indomethacin (potency = 1.0%) [194]. Similarly, Shaker and colleagues discussed the synthesis and evaluation of COX-2 inhibitory activity of indole derivatives having methylsulphonyl and aryl substituted derivatives. SAR highlighted the importance of halogen substitution.

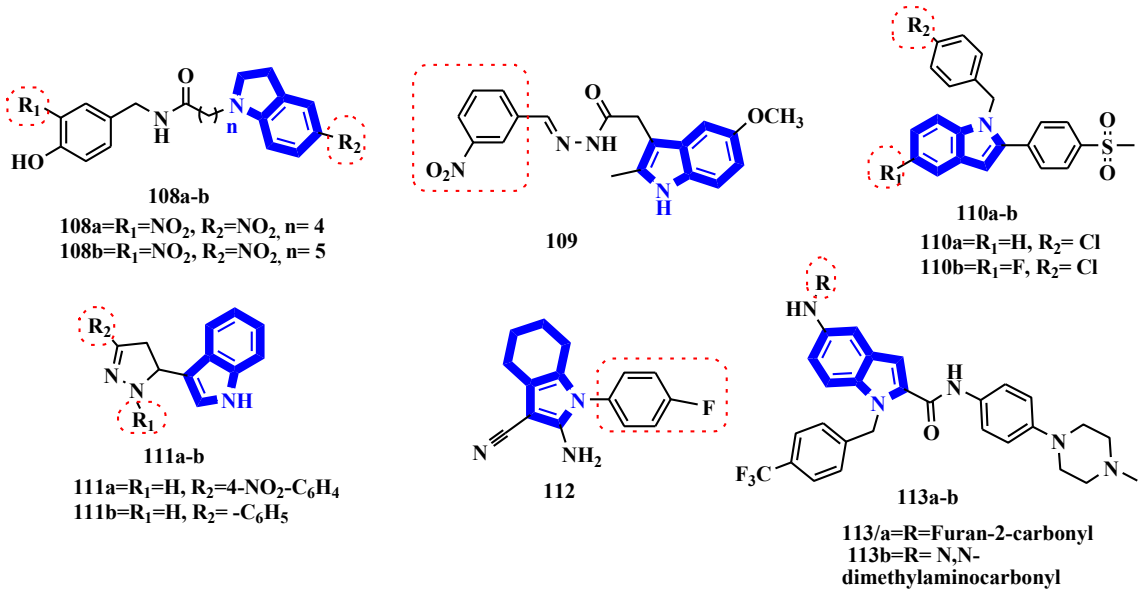



**Fig. 13.** Chemical structures for indole derivatives having antiinflammatory activity **108–113** with active pharmacophores.

Compound **110a** ($IC_{50}$ = 0.11 μM, SI = 107.63) and **110b** ($IC_{50}$ = 0.15 μM, SI = 76.6) (Fig. 13) showed maximum anti-inflammatory activity as compared to standard drug indomethacin ($IC_{50}$ = 0.49 μM, SI = 0.079) [195].

Indole derivatives such as indomethacin and melatonin reduce the inflammation and oxidation process [196–198]. Hence, it is required to develop novel indole derivatives with potent antiinflammatory activity. Shroff and Daharwal, synthesized and evaluated novel indolyl-pyrazoline derivatives as anti-inflammatory agents. *In vivo* study was conducted using carrageenan-induced paw edema method. SAR studies concluded that phenyl and *p*-nitro phenyl substitution at C-3 and unsubstitution at N1 gave best results. Compounds **111a** (%inhibition = 63.97%) and **111b** (%inhibition = 57.46%) (Fig. 13) were the highly potent when compared to standard drug indomethacin (%inhibition = 61.36%) [199]. Similarly, Fatahala et al, in 2017 reported a series of indole derivatives and screened for antiinflammatory activity using rat paw edema method and docking analysis. The addition of hydrophobic ring coplanar with the original ring, the substitution of *p*-fluorophenyl leads to increased activity. Compound, **112** (%inhibition = 92%) (Fig. 13) showed maximum activity to standard drugs ibuprofen (%inhibition = 69.84%) and indomethacin (%inhibition = 78.58%) [200].

In 2016, Liu et al, studied and designed indole-2-carboxamide derivatives. Further, *in vivo* study was conducted for screening the biological activity resulted in the identification of potent compounds. SAR concluded that oxazole and amine substitution through carboxamide at C-5 has a marked effect on activity. With the increase in methoxy substitution leads to an increase in activity. Substitution of 2, 6-dichlorobenzyl, 3-fluorobenzyl, 4-chlorobenzyl, 4-bromobenzyl and 4-trifluoromethylbenzyl at N1 leads to the compounds having good anti-inflammatory activity. Compounds **113a** (%inhibition < 2.90 ± 0.73%) and **113b** (%inhibition < 2.67 ± 0.76%) (Fig. 13) were found to be highly potent [201]. In 2015, indole-chalcone derivatives were reported by Ozdemir and other researchers. All the synthesized compounds are evaluated against COX-1, COX-2. SAR studies concluded that methoxy, bromo groups and sulphonyl substituted chalcone derivative is favorable for the activity. Among all the synthesized compounds **114a** and **114b** (Fig. 14) were found to be the highly potent [202].

Chromone derivatives are found to be potent inhibitors of ROS dependent activation of TRAF6-ASK1-p38 pathway which is particularly involved in the inflammation process. A combination of two mechanisms involving different pathways can be the best approach to design potent anti-inflammatory agents [203]. Based on this concept, Shaveta et al, designed, synthesized and evaluated various chromone substituted oxindole derivatives. All the synthesized compounds were evaluated against COX-1, COX-2 and 5-LOX. SAR studies concluded that halogen substituted chromone derivative was favorable for the activity. Compounds **115a** (IC50 = 9.5 ± 0.8 μg/mL) and **115b** (IC50 = 10.0 ± 4.2 μg/mL) (Fig. 14) demonstrated maximum potency as compared with standard drug indomethacin ($IC_{50}$ = 0.7 ± 0.2 μg/mL) [204]. Sharath and colleagues also reported various pyrazole substituted indole derivatives. All the synthesized compounds were evaluated by the anti-lipoxygenase assay. SAR studies concluded that anisole substituted pyrazole is favorable for the activity. Compound **116** ($IC_{50}$ = 18 ± 0.45) (Fig. 14) was found to be highly potent as compared with standard drug ascorbic acid ($IC_{50}$ = 10 ± 0.11) [205]. A series of isoxazole-fused indole derivatives were synthesized and *in vivo* study was conducted for anti-inflammatory activity using carrageenan-induced rat paw edema model. SAR studies concluded that C-3 substituted indole derivatives have a significant role. i.e., 4-chlorophenyl, 4-trifluoromethyl phenyl and 4-iodo phenyl substituted isoxazole, phenyl. Compounds, **117a** (paw edema volume = 1.51 ± 0.08 mL) and **117b** (paw edema volume = 1.47 ± 0.05 mL) (Fig. 14) were found to be highly potent as compared to indomethacin standard (paw edema volume = 1.31 ± 0.06 mL) [206]. Various indole-imidazolidine derivatives were synthesized and evaluated using an air pouch and carrageenan-induced, acetic acid induced vascular permeability models. Compound **118** (percentage inhibition = 72.1%) as compared with standard drug indomethacin (percentage inhibition = 86.7%) (Fig. 14) was found to be potent [207]. A series of carboxyphenyl imino indole derivatives were mentioned by Chandra and coworkers. Substitution of the halogen group on phenyl ring was found to be favorable for the activity. All the synthesized compounds were further evaluated by carrageenan-induced paw edema. Among all the synthesized compounds, **119** (% inhibition = 67.9%) (Fig. 14) showed maximum potency as compared with standard drugs, phenylbutazone (% inhibition = 65.6%) and indomethacin (% inhibition = 92.3%) [208].

### 2.9. Antidepressant activity

Depression affects the person's thought, behavior, tendencies, potential feelings characterized by the low mood [209]. Depression is the leading cause of ill health and disability worldwide. At this time about

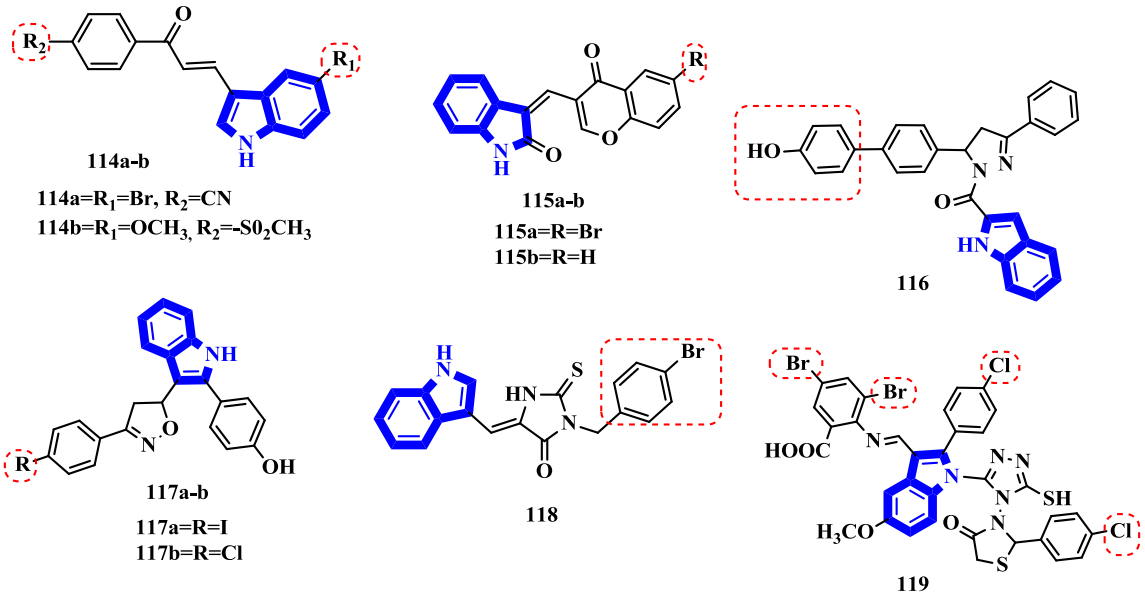



**Fig. 14.** Chemical structures for indole derivatives having antiinflammatory activity **114–119** with active pharmacophores.

300 million people are suffering from depression and there is the increment of 18% between 2005 and 2015 [210]. Recent data shows that 8.1% American adults over had depression in the 2-week period. Women are suffering more as compared to men [211]. Researchers are involved in the discovery of drugs with advanced structural modifications having a potent effect on the brain. Various indole derivatives are reported as antidepressant agents.

Latest literature survey finds out azetidinone and derivatives have potent antidepressant acting *via* cholinergic and NMDA receptor inhibition [212]. This finding motivated to combined derivatives of indole and azetidinone. Kerazare et al, 2017 synthesized oxindole derivatives bearing azetidinone moiety and conducted *in vivo* study using a forced swim test (FST). Finally, SAR study concluded that $-NO_2$ and -Cl group substitution at the *ortho* position of the phenyl ring system are better for potency. Also, highly lipophilic group, i.e., *para*-substituted hydroxyl, dimethylamino, trimethoxy and dimethoxy group in the phenyl ring, leads to the compounds with good hydrophobic interaction with the enzyme. Compounds **120a** (immobility reduced to 66.82%). and **120b** (immobility reduced to 65.61%). (Fig. 15) were found to be highly potent on comparing with standard drug fluoxetine (immobility reduced to 70.93%) [213]. Further molecular docking studies were also conducted which identify the potent compound **120a** and **120b** on the basis of the maximum binding score. Both the compounds showed binding with the enzyme through a hydrogen bond, hydrophobic and Van Der Waal's interactions [213]. In 2015, Zhen and coworkers introduced a series of 2-(5-methyl-2, 3-dioxoindolin-1-yl) acetamide derivatives. All the synthesized compounds were further screened for antidepressant activity using FST. SAR study concluded that only 3-Br-phenyl, 4-Br-phenyl, 3-$CF_3$-phenyl and benzyl group attachment with acetamide gives potent compounds. Compounds, **121a** (65.77 ± 17.8) and **121b** (75.77 ± 18.7) (Fig. 15) exhibited good potency when compared to standard drug fluoxetine (58.5 ± 9.3) [110].

Another mechanism involved in the treatment of depression is MAO-A inhibition. This mechanism is particularly seen in dihydropyrazole derivatives [214]. Hence, potent indole-dihydropyrazole derivatives can be synthesized to inhibit depression. Patil and Bari et al, 2016, synthesized and screened a series of indole derivatives bearing dihydropyrazole moiety and evaluated for antidepressant activity using FST. The presence of electron donating groups on the phenyl ring of indolylpyrazoline has marked role in the activity. Finally, it was concluded from the *in vivo* study that **122a** (116.3 ± 1.54) and **122b** molecules (109.8 ± 2.86) (Fig. 15) were found to be highly potent when compared to standard drug fluoxetine (immobility reduced to 77.4%) and imipramine (immobility reduced to 75.5%) [109]. The same group previously synthesized the isoxazoline fused indole derivatives, as antidepressant agents. A detailed SAR was also conducted which proved that the activity of these compounds is due to the presence of heterocyclic rings i.e., pyridine, pyrrole. Also, the substitution of electron withdrawing system (F, Br, Cl) at the *para* position resulted in the good activity. Similarly, electron releasing groups ($CH_3$, OH, $OCH_3$) decreases the activity. Compounds **123a** and **123b** (Fig. 15) were found to be the highly potent [215].

### 2.10. Antioxidant activity

Antioxidant agents inhibit the oxidation reactions ultimately

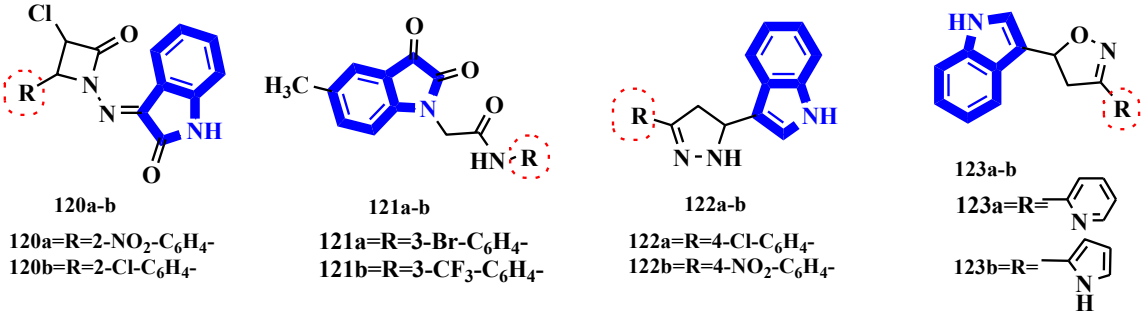



**Fig. 15.** Chemical structures for indole derivatives haviing antidepressant activity **120–123** with active pharmacophores.

prevent the free radical formation and cell damage. Thiols and ascorbic acid are found to be responsible for the termination of these reactions. Apart from this, antioxidants have also effect on the neurodegenerative diseases, i.e. Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis etc [216]. Indole derivatives are found to be very effective antioxidizing agent protecting biomolecules from the peroxidation [217].

Melatonin, found in almost every cell, promotes the synthesis of superoxide dismutase, glutathione peroxidase which acts as antioxidant enzymes. It scavenges various reactive oxygen species such as peroxyl radical, peroxynitrite anion etc. Orhan et al, 2016 synthesized and evaluated indole-based melatonin derivatives. SAR studies concluded that hydrazone derivatives of indole bearing *o*-halogenphenyl and 3, 5-difluorophenyl substituents are favorable for the activity. All the synthesized derivatives were screened against ROS-induced DCFH-DA oxidation. Compounds, **124a** ($IC_{50}$ = 38.3 ± 8.9 μM) and **124b** ($IC_{50}$ = 37.0 ± 2.0 μM) (Fig. 16) were found to be the highly potent antioxidant and cytoprotective in neuronal and non neuronal cells as compared with standard drug melatonin [218]. In 2013, Silveira and colleagues reported the study on the antioxidant activity of C-3 sulfenyl indoles. SAR studies concluded that increased potency is due to the presence of bis-indole system connected through sulfide group at the C-3 position. The substitution at the C-3 position leads to the better stabilization of indole ring and delocalization of electrons. Compounds, **125** (activity < 96.8%) (Fig. 16) exhibited the highly potent antioxidant activity [219]. Various triazole substituted indole derivatives were synthesized by Baytas and coworkers and were tested for DPPH and superoxide radical scavenging activities. SAR studies concluded that unsubstituted 1, 2, 4-triazole-5(4H)-thione ring attached at the 2nd position of indole is found to be favorable for the activity. Compounds, **126a** (% inhibition = 87 ± 3) and **126b** (% inhibition = 88 ± 4) (Fig. 16) were found to be highly potent as compared with standard drug butylatedhydroxytoluene (BHT) [220]. In the same year, Suzen et al, investigated the antioxidant activity of indole-based melatonin derivatives and evaluated by LP (lipid peroxidation) inhibition and DPPH radical scavenging activities. SAR studies concluded that benzoylpyrrolidine is favorable for activity. The compound, **127** (Fig. 16) showed better results [221].

In another study, various aminomethyl-indole derivatives were synthesized and evaluated for superoxide radical scavenging activity and anti LP (lipid peroxidation) activities. Electron withdrawing groups, phenyl and pyrrole substitution were found to be favorable for the activity. Among all the synthesized derivatives, **128a** and **128b** having % inhibition of 36–42%, as compared with standard drug butylated hydroxyl toluene (Fig. 16) were found to be highly potent [222]. Melatonin based indole derivatives were also synthesized by Shirinzadeh et al, and screened by evaluating their reducing effect against the oxidation of the redox-sensitive fluorescent probe, by examining their protective effect against $H_2O_2$ and by determining the inhibitory effect on AAPH. SAR studies disclosed that halogen substitution impacts a marked effect on activity, i.e., *o*- and *m*- halogens in the aromatic side chain increase the antioxidant activity. Substitution of methyl at indole nitrogen and halogenated side chain leads to highly potent compounds. Among all the entire series, **129a** and **129b** (Fig. 16) were found to be the most promising compounds [223]. In the same year, Estevao et al, synthesized and evaluated tryptophan and tryptamine derivatives of indole with the prenylated system. The scavenging activity of all the synthesized compounds was checked against superoxide, hydrogen peroxide, hypochlorous acid radical. SAR studies reveal that carbomethoxy group, free amine group in the side chain and free indolic nitrogen are favorable for the activity. Compounds, **130** ($IC_{50}$ = 4.13 0.17 mM) and **131** ($IC_{50}$ = 4.56 0.48 mM)

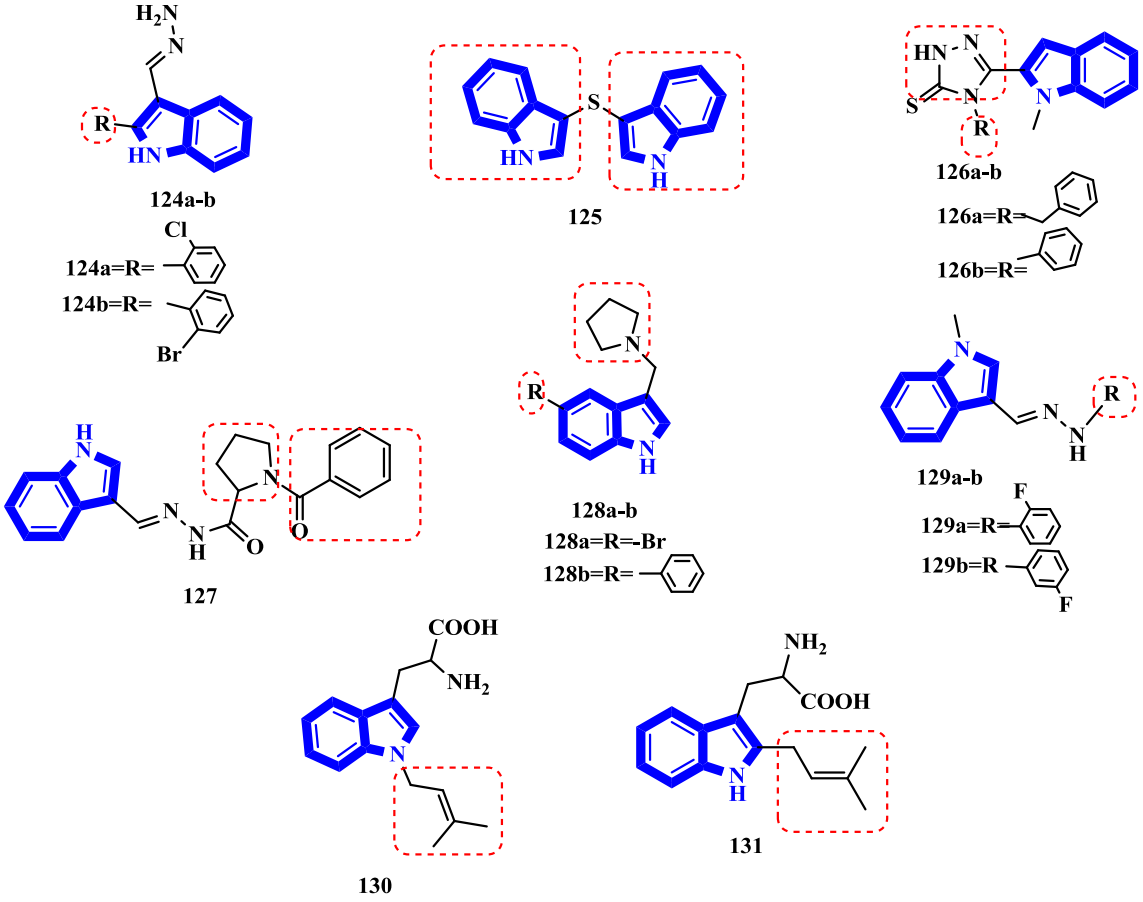



**Fig. 16.** Chemical structures for indole derivatives having antioxidant activity **124–131** with active pharmacophores.

(Fig. 16) were found to be highly potent [224].

### 2.11. Antihepatitis activity

Hepatitis involves the inflammation of liver tissues due to the infection by Hepatitis C virus characterized by yellow coloration of the skin, the whiteness of the eyes, poor appetite, vomiting, tiredness, abdominal pain, and diarrhea. Estimated 325 million people were living with chronic hepatitis infections i.e., hepatitis B virus (HBV) or hepatitis C virus (HCV) worldwide in 2015. Globally, 1.34 million people died of viral hepatitis in 2015 [225–227]. Only a few vaccines are available in the market as anti-hepatitis agents which are not much more effective [228]. Thus, the development of anti-hepatitis drugs is required at a fast pace. Some of the newly synthesized anti-hepatic indole derivatives with the structure–activity relationship are discussed below.

In 2016, annulated indole derivatives were studied against influenza endonuclease and HCV by Zoidis G and colleagues. SAR studies concluded that substitution of *N*-hydroxyimides resulted in the compounds having potent activity against PA endonuclease. Fluoro and chloro group substitution leads to active derivatives whereas, removal of hydroxyl group from imido nitrogen leads to the compounds with complete loss of activity. Docking studies were also conducted between the active site HCV polymerase and ligands and it was found that compound, **132a** ($EC_{50}$ = 83.8 ± 4.8 μM) and **132b** (**$EC_{50}$** = 10.5 ± 3.1 μM) (Fig. 17) show better hydrophobic interaction with the active site of the protein. Compounds, **132a**and **132b** (Fig. 17) were found to be highly potent whereas other compounds have the least activity towards HCV as compared with standard drug 2,4-dioxo-4-phenylbutanoic acid ($EC_{50}$ > 200 μM) [229]. In the same year, various indole-pyrazole derivatives as antihepatitis agents were also reported by Han and coworkers. SAR studies concluded that substitution of *p*-Me-phenyl, *p*-MeO phenyl, *p*-flouro phenyl and *m*-fluoro phenyl attached with indole at C-3 through pyrazole increases the activity. R-enantiomer of compound **133** ($EC_{50}$ = 1.02 ± 0.10 μM) (Fig. 17) was found to be the highly potent [230]. In another study, Andreev et al, 2015 synthesized and evaluated indole-phenyl derivatives. All the synthesized compounds were screened for anti-hepatitis activity using NS5B RdRp assay ns5b. SAR studies revealed that *N*-benzyl substitution at the tetrahydroindole core, found to be favorable for the activity, whereas *para*-fluorophenyl substitution at the nitrogen atom leads to 3–4 fold reduction in activity. Compound **134** (**$EC_{50}$** < 7.9 μM) (Fig. 17) was found to be highly potent [231]. In the same year, Zang and coworkers reported the synthesis of indole-3-carboxamide and screened against HCV genotype. SAR studies concluded that *t*-butylsulfonamide substitution as compared to *n*-propyl sulfonamide was favorable for the activity. Further alkyl and alkoxy group substitution at the 6th position leads to the analogues having good activity. Among all, compound **135** (**$EC_{50}$** < 831 μM) (Fig. 17) showed the maximum potency [232].

Various pyridine based indole derivatives synthesized and evaluated using pharmacophore modelling and 3D-QSAR study as hepatitis C virus NS5B polymerase inhibitors by Varun G and coworkers. All the synthesized derivatives were evaluated as using pharmacophore modelling and 3D-QSAR study. Compounds, **136** ($_pIC_{50}$ = 4.67) (Fig. 17) having –OH group at the C-5 position of indole with pyridine at C-1 and C-3 position was found to be highly potent [233]. In the same year, Jin and colleagues, synthesized and evaluated various chemical genetics based indole derivatives. All the synthesized compounds were evaluated against HCV NS5B polymerase. SAR studies concluded that acrylamide and cyano group substitution were favorable for the activity. The compound, **137** ($CC_{50}$ = 61.8 μM) (Fig. 17) was found to be highly potent as compared with standard drug clemizole ($CC_{50}$ = 8.0 μM) [234].

### 2.12. Antileishmanial agents

Leishmaniasis is a parasitic disease spread by female Sandfly belonging to genus *Leishmania* which can be appeared in the visceral, cutaneous, diffuse and mucocutaneous form [235]. According to the recent data by WHO, nearly 88 developing and developed countries are affected with leishmaniasis. Every New Year, nearly 1.5–2.0 million cases are reported [236]. As Leishmania causes a wide range of health problems, it is imperative to develop effective drugs.

Recently, Porwal et al, synthesized and evaluated gem-dithioacetylated indole derivatives. All the synthesized compounds were screened through *in vivo* study against *Leishmania donovani.* SAR study revealed that the presence of $H_2S$ at the C-3 and *p*-cyanophenoxy, *N*-phenyl, pentyl chain at nitrogen atom and dimethylsulphoxide at 3rd position of indole were most important for the activity. Compound, **138** (% inhibition = 96–99%) (Fig. 18) showed maximum activity [237]. Felix and coworkers reported the synthesis of thiophene-indole hybrids and evaluation against *L. donovani.* SAR study concluded the role of 5-cyano, 5-methyl were found to be favorable for the activity. Compounds **139a** ($IC_{50}$ = 2.1 μg/mL, SI. > 193.2), **139b** ($IC_{50}$ = 2.3 μg/mL, SI. > 172.4), and **140** ($IC_{50}$ = 3.2 μg/mL, SI. > 124.6) (Fig. 18) were

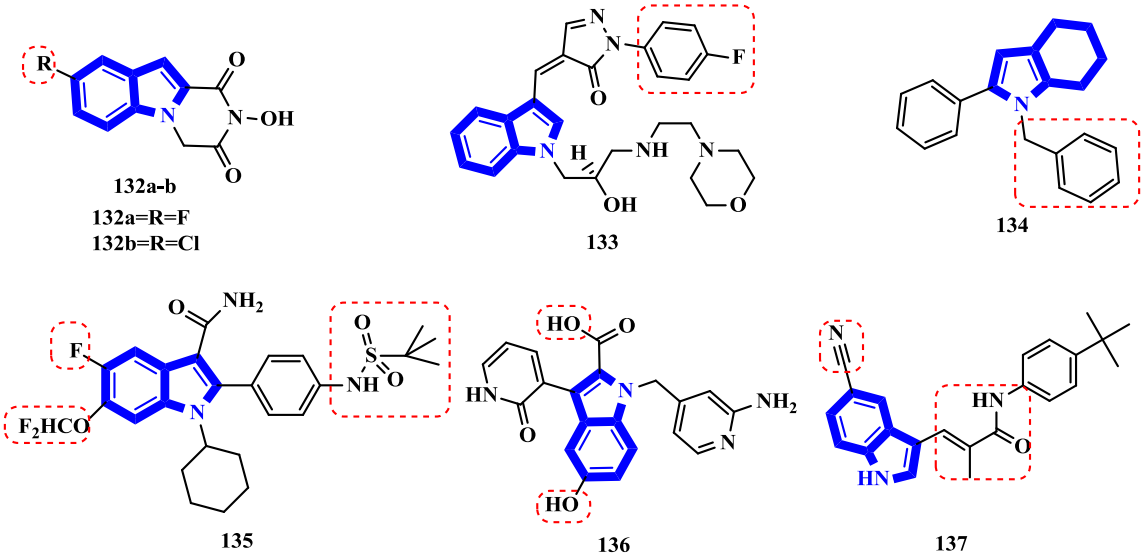



**Fig. 17.** Chemical structures for indole derivatives having antihepatitis activity **132–137** with active pharmacophores.

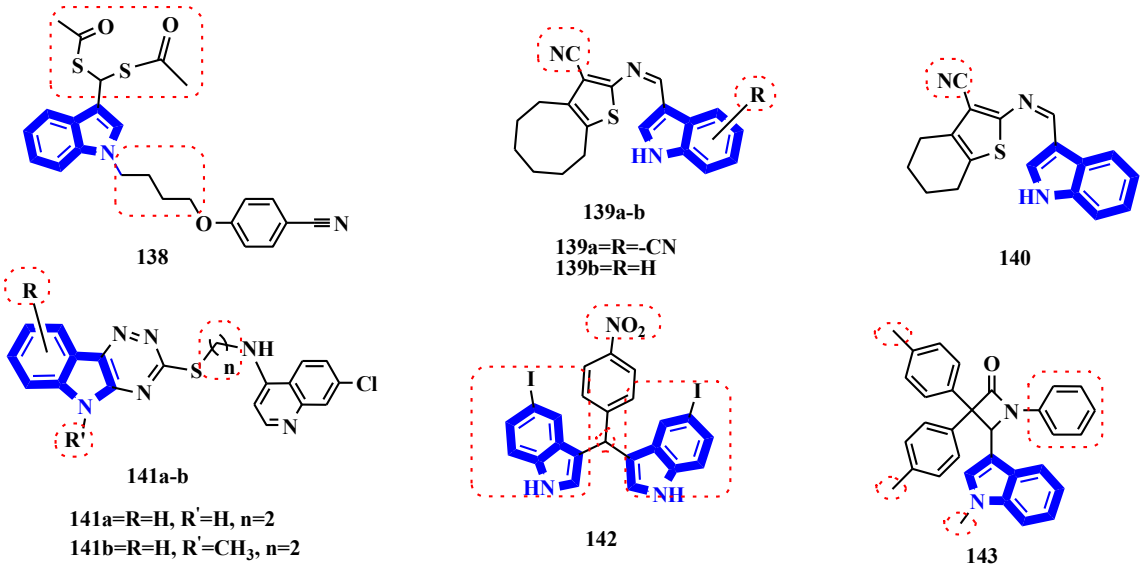



**Fig. 18.** Chemical structures for indole derivatives having antileishmanial activity **138–143** with active pharmacophores.

found to be highly potent with as compared to standard drug amphotericin B ($IC_{50}$ = 0.2 μg/mL, SI. > 124.5) [238]. In 2014, triazino indole-quinoline hybrid derivatives were synthesized and evaluated by Sharma and coworkers. All the synthesized compounds were screened through *in vitro* study against *L. donovani*. SAR studies suggested that at the nitrogen atom of indole hydrogen, methyl, ethyl, isopropyl, isobutyl, allyl, benzyl were favorable for the activity. Alkyl chain length connecting triazino indole and quinoline should contain a maximum of two carbons. Compounds, **141a** ($IC_{50}$= 1.11 μM) and **141b** ($IC_{50}$= 0.36 μM) (Fig. 18) were found to be highly potent as compared with standard drug miltefosine ($IC_{50}$= 8.10 μM) [239]. The antileishmanial activity of 3,3-diindolylmethane was investigated by Bharate and coworkers. All the synthesized compounds were screened through *in vitro* study against *L. donovani*. Pharmacophore model was also developed for diindolyl methane derivatives showed excellent statistical parameters. SAR studies concluded that 4-nitroaryl substitution was favorable for the activity. Compound **142** ($IC_{50}$ < 8.37 μM) (Fig. 18) was found to be highly potent as compared with pentamidine ($IC_{50}$ < 8.39 μM) and amphotericin B ($IC_{50}$ < 0.17 μM) [240].

*Leishmania* cysteine protease is essential for the growth, differentiation and multiplication of parasite. Azetidine derivatives are one of the prominent inhibitors of this enzyme. Based on this fact, Singh and colleagues synthesized and evaluated azetidine-indole derivatives. All the synthesized compounds were screened through *in vitro* study using *Leishmania major promastigotes*. SAR studies concluded that methyl substitution to the imine attached to the indole enhanced the activity. Conversion of imine into azetidin-2-one resulted in the drastic increase in the activity. Among all, compound **143** (0.56 ± 0.06 μg/mL) (Fig. 18) was found to be highly potent as compared with standard drug amphotericin B (0.56 ± 0.001 μg/mL) [241].

### 2.13. Miscellaneous activity

#### 2.13.1. Enzyme inhibitory activity

*2.13.1.1. CD38 enzyme inhibition.* CD38 (cluster of differentiation 38) is a multifunctional enzyme which is ubiquitously distributed in mammalian tissues. It is involved in the conversion of $NAD(P)^+$ into cyclic ADP-ribose, $NAADP^+$ and ADP-ribose and the role of these metabolites in multiple $Ca^{2+}$ signalling pathways makes CD38 a novel potential pharmacological target. The dire lack of CD38 inhibitors, however, renders the search for new molecular tools are highly desirable [242]. Wu et al, 2013 synthesized and evaluated novel indole derivatives. *In vitro* studies and docking procedures were applied to screen the synthesized compounds. SAR studies concluded that substitution of pyridine, and aryl halide, alkyl chain through carboxamide at 5th position and phenyproipionyl moiety were required for the activity of indole. Compounds, **144a** ($IC_{50}$ = 4.7 μM) and **144b** ($IC_{50}$ = 52 μM) (Fig. 19) showed moderate activity [243].

*2.13.1.2. Tyrosinase inhibition.* For the past few decades, tyrosinase inhibitors have been a great concern solely due to the key role of tyrosinase enzymes in both mammalian melanogenesis and fruit or fungi enzymatic browning [244]. Based on this, Ferro et al, in 2016, synthesized and evaluated various indole derivatives. All the synthesized compounds were assayed by *in vitro* technique. SAR studies concluded that a fluorobenzyl derivative at the nitrogen atom of indole was found to be highly potent. The compound, **145** ($IC_{50}$ = 224 ± 1.23 μM) (Fig. 19) was found to be highly potent as compared with standard drug Kojic acid ($IC_{50}$ = 17.76 ± 0.18 μM) [245].

*2.13.1.3. Lysozyme inhibition.* Lysozyme is part of the immune system. Lysozyme inhibition leads to the prevention of cell lysis [246]. Shinitzky et al, evaluated various indole derivatives and concluded that inhibition is due to bond formation between histidine and lysine residue of lysozyme and indole. Two indole derivatives, i.e. **146a** and **146b** (Fig. 19) were evaluated against lysozyme and found to be active [247].

*2.13.1.4. Hyaluronidase inhibitor.* Hyaluronidase enzyme is responsible for the degradation of hyaluronic acid and increasing cell permeability. Hyaluronidase inhibitors are responsible for the antiinflammatory, antiaging, antimicrobial, anticancer and antivenom properties [248]. The hyaluronidase inhibiting effect of various amino methyl indole derivatives was reported by Olegan et al. The synthesized compounds were evaluated by using stain-all assay method. SAR studies concluded that a compound with piperazine derivative and phenyl group at the 5th position of indole was favorable for the activity. For better results, more lipophillic compounds were required. Compound **147** (% inhibition = 23%) (Fig. 19) was found to be highly potent [249]. Previously, the same group also synthesized various novel indole derivatives and evaluated various parameters by turbidimetric, viscometric and colorimetric methods. SAR studies concluded that substitution of choro and fluoro at the *para* position of benzamide attached at the 3rd position of indole were favorable for the activity. Compounds, **148a** (% inhibition = 23%) and **148b** (%

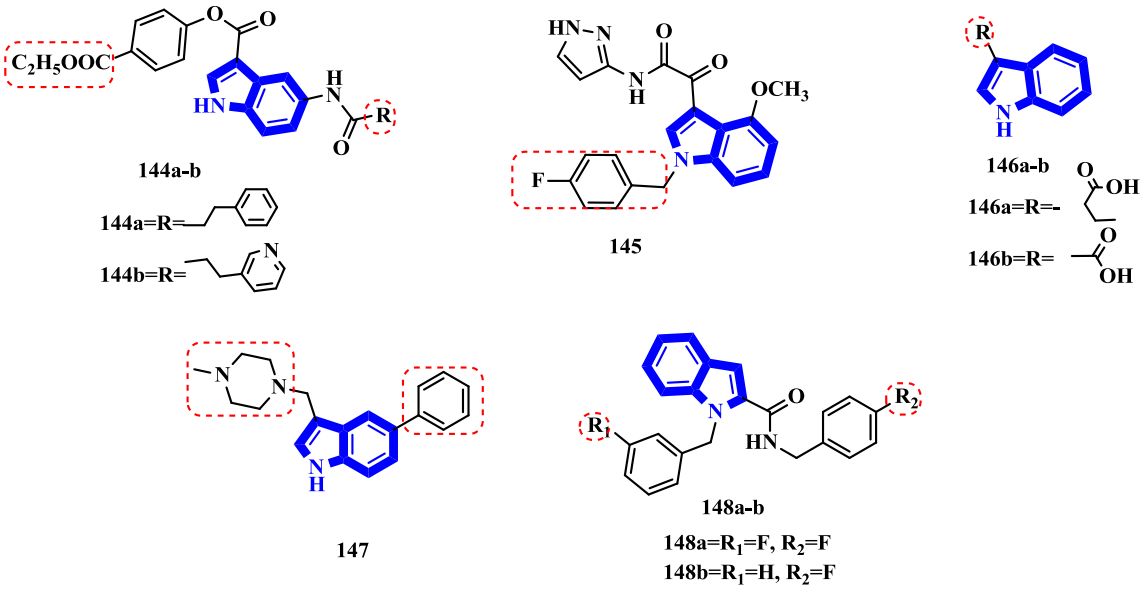



**Fig. 19.** Chemical structures of the enzyme inhibitors indole derivatives **144–148** with active pharmacophores.

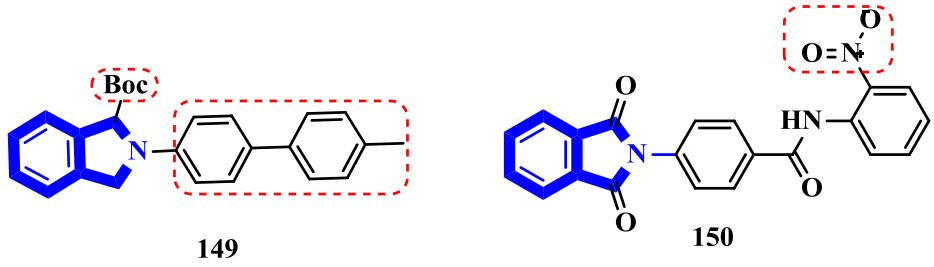



**Fig. 20.** Chemical structures of the anticholinergic indole derivatives **149–150** with active pharmacophores.

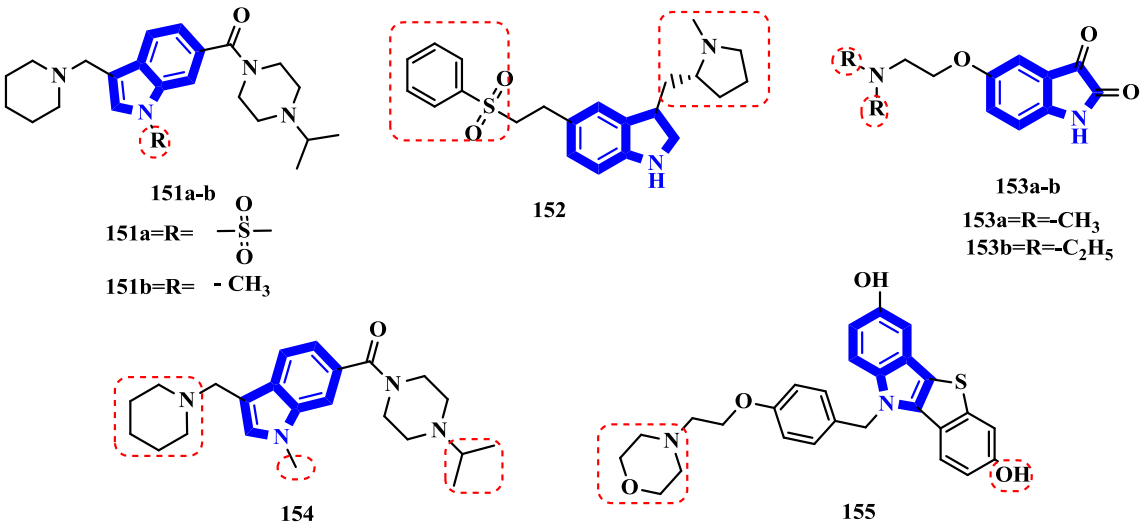


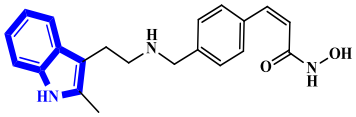
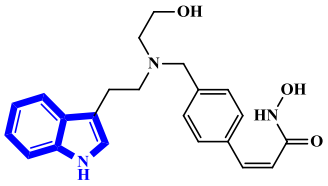
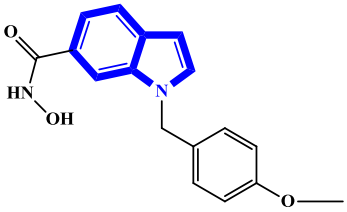
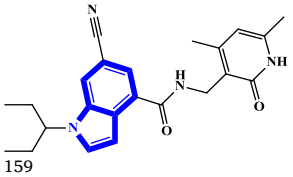
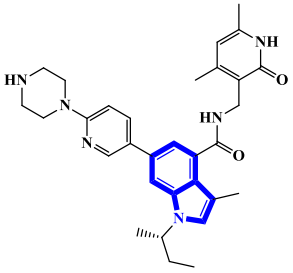
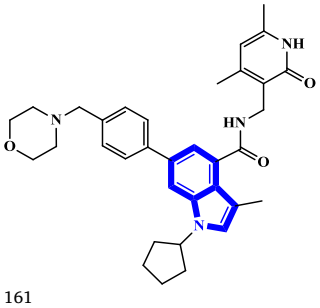
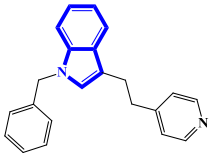
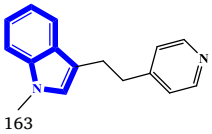

**Fig. 21.** Chemical structures of the indole derivatives with other activities **151–155** with active pharmacophores.

inhibition = 23%) (Fig. 19) were found to be highly potent at the 7 pH, as compared with standard drug vcpal (6-palmitoyl-L-ascorbic acid) (% inhibition = 23%) [250].

### 2.13.2. Anticholinergic activity

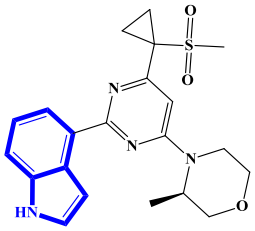
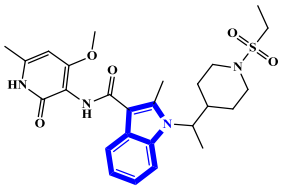
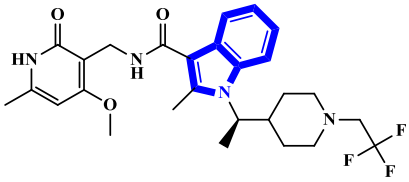
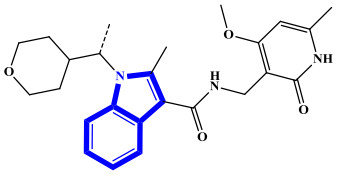
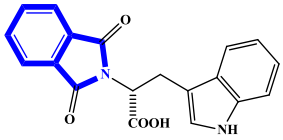
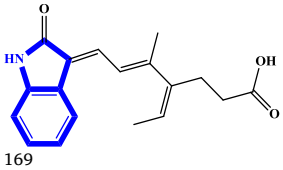
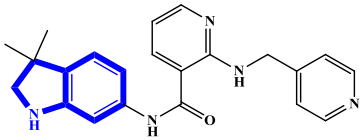
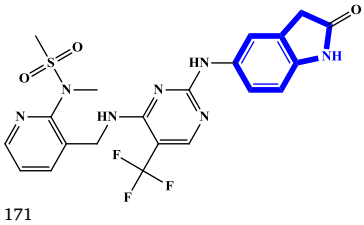
An anticholinergic agent is the inhibitor of acetylcholine present in the central and peripheral nervous system [251]. Parveen et al, 2018 synthesized and evaluated indole derivatives. *In vitro* study and molecular docking, the study was conducted to screen the synthesized derivatives using cholinesterase enzyme. SAR studies concluded that carbonyl and biphenyl substitutions are favorable for the activity. The compound, **149** (Fig. 20) was found to be the highly potent [252]. Farani et al, synthesized and evaluated oxindoline derivatives by *in vitro* and docking analysis. SAR studies concluded that Cl, F, $NO_2$, at the *ortho* and *para* position and methoxy at the *meta* position of phenyl were favorable for the activity. Compound, **150** ($IC_{50}$ = 1.1 ± 0.25 μM) (Fig. 20) was found to be highly potent compared with standard drug donepezil ($IC_{50}$ = 0.41 ± 0.12 μM) [253].

**Table 1**
Chemical structure and mechanism of action of indole containing drugs which are in advanced stages of development.

| S. No. | Indole drugs | Structure | Mechanism of action/Use | References |
|---|---|---|---|---|
| 1 | Panobinostat |  156 | Panobinostat inhibits multiple histone deacetylase enzymes (HDAC), leading to apoptosis of malignant cells *via* multiple pathways. Developed by Novartis for treatment of various cancers and recently approved by FDA and European medicines Agencies in 2015. | [262] |
| 2 | Dacinostat (LAQ-824) |  157 | It is hydroxamate HDAC inhibitor with potential anticancer activity. When tested on a variety of solid tumour cell lines, NVP-LAQ824 exhibited selective anti-proliferative effects, inducing cell growth inhibition in some, while inducing cell death in others. | [263] |
| 3 | PCI-34051 |  158 | It selectively inhibit HDAC8 and treat *T*-cell malignancies. | [264] |
| 4 | EI1 |  159 | It inhibits histone-lysine-*N*-methyltransferase enzyme which inhibits the methyltransferase activity of the EZH2 (Enhancer of zeste homolog 2) /PRC2 (Polycomb repressive complex 2) thereby blocking tumor cells proliferation. | [265] |
| 5 | GSK 126 |  160 | GSK126 is a potent, highly selective EZH2 methyltransferase inhibitor. It block proliferation in *in vitro* and *in vivo* models of diffuse large B-cell lymphoma. | [266] |
| 6 | EPZ005687 |  161 | It is a potent and selective inhibitors of lysine methyltranferase EZH2 to control non-Hodgkin's lymphoma and other cancers. | [267] |
| 7 | IN461 |  162 | Suppress the spontaneous motor activity and act as anticonvulsant. | [268] |
| 8 | IN399 |  163 | Suppress the spontaneous motor activity and act as anticonvulsant. | [269] |

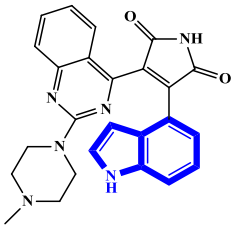
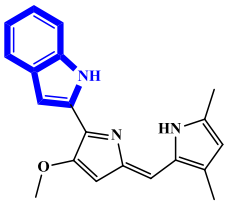
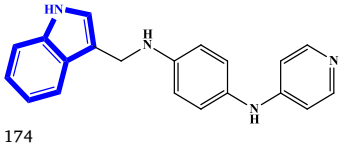
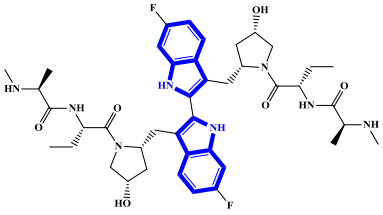
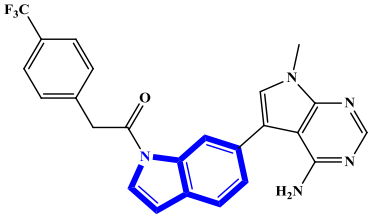
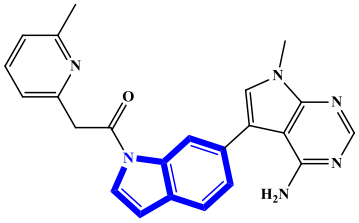
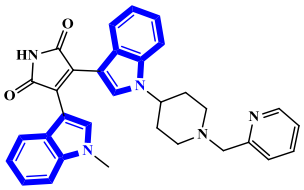
(*continued on next page*)

**Table 1** (*continued*)

| S. No. | Indole drugs | Structure | Mechanism of action/Use | References |
|---|---|---|---|---|
| 9 | AZ20 |  164 | AZ20 is the first reported inhibitor of ATR(ataxia telangiectasia and Rad3) protein kinase demonstrating tumor growth inhibition *in vivo*. It is a promising anticancer agent. | [270] |
| 10 | CPI-169 |  165 | Potent and selective EZH2 inhibitor having microsomal stability and treat lymphoma xenograft, bladder cancer. | [271] |
| 11 | CPI-1205 |  166 | CPI-1205 is a highly potent and selective inhibitor of EZH2. This decrease in histone methylation, alters gene expression patterns associated with cancer pathways and results in decreased proliferation of EZH2-expressing cancer cells. | [272] |
| 12 | CPI-360 |  167 | CPI-360 is a potent, selective, and SAM-competitive EZH1 inhibitor. Effective against non-Hodgkin's lymphoma. | [273] |
| 13 | RG-108 |  168 | This oxoindole derivative is DNA methyltransferase inhibitor and promsing anticancer agent. | [274] |
| 14 | Orantinib |  169 | This oxoindole derivative is VEGFR2 (Vascular endothelial growth factor receptors type 2), PDGFR (Platelet-derived growth factor receptors), FGFR(Platelet-derived growth factor receptors) inhibitor and treat hepatocellular carcinoma. | [275] |
| 15 | Motesanib |  170 | This indoline derivative is VEGFR2, PDGFR, stem cell factor receptor and used to treat breast cancer. | [276] |
| 16 | PF-00562271 |  171 | This oxoindole derivative is FAK (Focal adhesion kinase) and PYK2 (Protein tyrosine kinase 2) inhibitor and treat hepatocellular carcinoma. | [277] |

(*continued on next page*)

**Table 1** (*continued*)

| S. No. | Indole drugs | Structure | Mechanism of action/Use | References |
|---|---|---|---|---|
| 17 | Sotrastaurin |  172 | It acts through protein kinase C (PKCs) inhibition. PKCs are vital in the activation of nuclear factor-kappaB (NF-kB) mediated signaling and treat B-cell lymphomas. | [278] |
| 18 | Obatoclax (GX15-070) |  173 | It acts through Bcl-2 (B-cell lymphoma 2) inhibition. It induces apoptosis in cancer cells thereby preventing tumor growth. Effective in various cancerous conditions. | [279] |
| 19 | JNJ-26854165 (Serdemetan) |  174 | It acts through the inhibition of HDM2 (Human double minute 2) ubiquitin ligase. It inhibits cell growth and induces apoptosis in leukemia cell lines and treat solid tumors. | [280] |
| 20 | TL32711 (Birinapant) |  175 | It is a potent antagonist for XIAP (X-linked inhibitor of apoptosis protein) and IAP (Inhibitor of apoptosis protein) family proteins, with potential antineoplastic activity. It also inactivate the nuclear factor-kappa B (NF-kB)-mediated signaling and treat myelogenous leukemia. | [281] |
| 21 | GSK2606414 |  176 | The first selective inhibitor discovered for the enzyme protein kinase R (PKR) like endoplasmic reticulum kinase (PERK), which is involved in various processes related to cancer and neurodegenerative disorders. | [282] |
| 22 | GSK2656157 |  177 | It is a selective first in class PERK inhibitor and stop the tumor growth | [283] |
| 23 | Enzastaurin |  178 | It is as selective Protien kinase C β inhibitor an enzyme involved in the induction of vascular endothelial growth factor (VEGF) and developed as an antiangiogenic cancer therapy | [284] |

(*continued on next page*)

**Table 1** (*continued*)

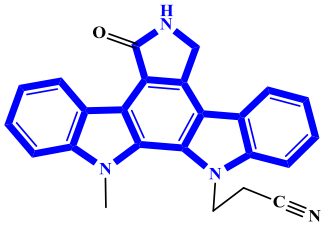
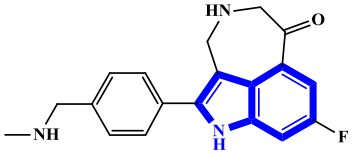
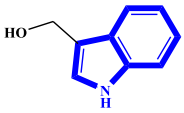
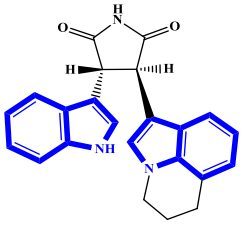
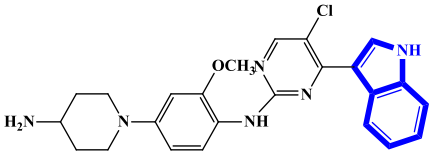
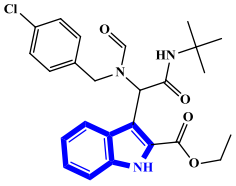
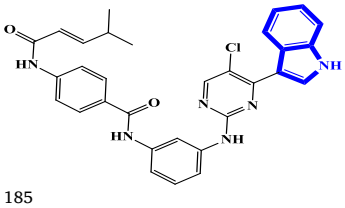
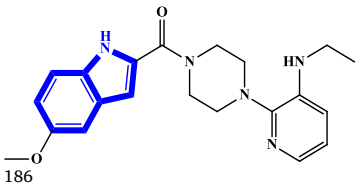
| S. No. | Indole drugs | Structure | Mechanism of action/Use | References |
|---|---|---|---|---|
| 24 | Go6976 |  179 | Potent, selective PKC inhibitor. Selectively inhibits $Ca^{2+}$-dependent PKC isoforms over $Ca^{2+}$-independent. Promising antitumor agent. | [285] |
| 25 | Rucaparib |  180 | It is first-in-class pharmaceutical drug targeting the DNA repair enzyme i.e. poly (ADP-ribose) polymerase enzyme and treat breast, ovarian cancer. | [286] |
| 26 | Indole-3-carbinol |  181 | It prevents the development of estrogen-enhanced cancers including breast, endometrial and cervical cancers | [287] |
| 27 | ARQ-197 (tivantinib) |  182 | It is the first selective non-ATP-competitive c-MET inhibitor and treat hepatocellular, coloreactal, breast, prostate cancer. | [288] |
| 28 | AZD-3463 |  183 | ALK (Anaplastic lymphoma kinase) has been shown to promote cell survival and growth. AZD-3463 is potent ALK inhibitor and therefore effective against drug resistance cancer cell lines. | [289] |
| 29 | YH-239-EE |  184 | P53-MDM2 (Mouse double minute 2) antagonist and treat myeloid leukemia. | [290] |
| 30 | THZ1 |  185 | It selectively inhibit CDK7 (Cyclin-dependent kinase 7) dependent transcriptional addictions in pancreatic cancer | [291] |
| 31 | Atervirdine |  186 | It is novel nonnucleoside reverse transcriptase inhibitor (NNRTI) and acts as antiviral drug. | [292] |

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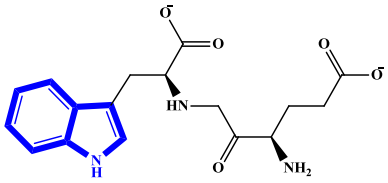
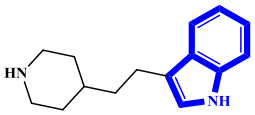
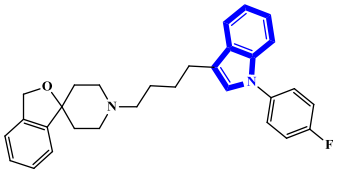
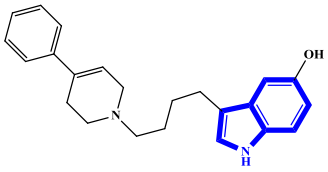
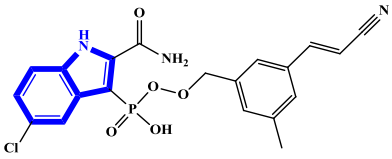
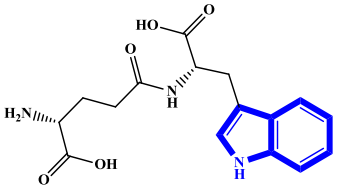
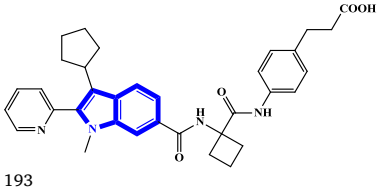
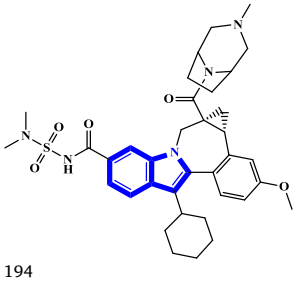
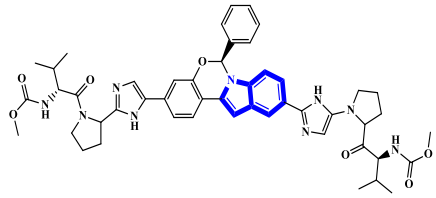
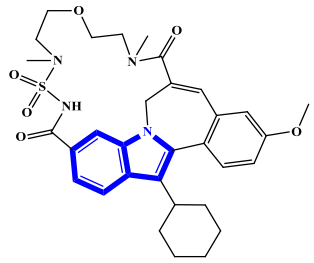
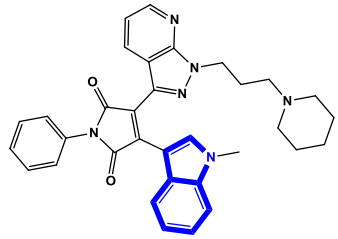
**Table 1** (*continued*)

| S. No. | Indole drugs | Structure | Mechanism of action/Use | References |
|---|---|---|---|---|
| 32 | Oglufanide |  187 | Inhibit vascular endothelial growth factor which may inhibit angiogenesis and acts against hepatitis C. | [293] |
| 33 | Indalpine (LM-5008) |  188 | Indalpine, recently entered in the market, acts through serotonin reuptake inhibiton. Potent antidepressant.. | [294] |
| 34 | LU 28-179 (Siramesine) |  189 | It acts as sigma2 receptor agonist and used as anticancer, antidepressants. | [295] |
| 35 | Roxindole |  190 | Acts as dopamine D2 receptor agonist and treat depression. | [296] |
| 36 | GSK2248761 |  191 | GSK2248761 is a novel, next-generation NNRTI with activity against efavirenz-resistant strains. Promising anti-HIV agent. | [297] |
| 37 | Golotimod (SV-07) |  192 | Inhibit the STAT3 transcription factor. STAT-3 transcription factor upregulated in many cancer cell types, tumor cell growth and survival and immunosuppression. | [298] |
| 38 | BILB-1941 |  193 | Acts as non-nucleoside inhibitor of HCV-NS5B (Hepatitis C virus Nonstructural protein 5B) polymerase. Promising anti-HCV agent. | [299] |
| 39 | BMS-791325 |  194 | It acts as HCV NS5B RNA dependent polymerase inhibitor and acts as potent antihepatitis agent. | [300] |

(*continued on next page*)

**Table 1** (*continued*)

| S. No. | Indole drugs | Structure | Mechanism of action/Use | References |
|---|---|---|---|---|
| 40 | MK-8742 |  195 | HCV-NS5A (Hepatitis C virus Nonstructural protein 5A) inhibitor. Acts against genotype 1a, 1b, and 2a. Promising antihepatitis agent. | [301] |
| 41 | TMC647055 |  196 | Non-nucleoside inhibitor of the hepatitis C virus NS5B polymerase. Promising antihepatitis agent. | [302] |
| 42 | YQ36 |  197 | Antiproliferative agents and acts through the caspase dependant apoptosis induction. | [303] |

### 2.13.3. Antihistaminic agents

Mast cells secrete the histamine which increases the cell permeability that causes the hypersensitivity reactions. Hence antihistaminic agents are used to treat various allergic conditions [254].

Santillan et al, synthesized and evaluated various indole derivatives. SAR studies concluded that alkylpiperdinyl substitutions are most favorable for antihistaminic activity. Also, the substitution of indole nitrogen with methyl and methyl sulphonyl leads to a decrease in activity. Human $H_3$ binding affinity data showed that compounds, **151a** (affinity = 1.9 ± 1.8 nM) and **151b** (affinity = 15 ± 10 nM) (Fig. 21) were highly potent [255]. Various novel indole derivatives were reported by Madasu et al. All the derivatives are synthesized on the basis of the basic scaffold of eletriptan having antimigraine activity i.e. compound **152** (Fig. 21) [256]. Swathi and coworkers have designed, synthesized and evaluated various oxindole derivatives. SAR studies concluded that substitution of dimethyl and diethyl amino ethyl chain at the fifth position of indole was favorable for the activity. All the synthesized derivatives were evaluated by the histamine chamber method. Derivatives, **153a** (% protection = 74%) and **153b** (% protection = 80%) (Fig. 21) were found to be highly potent as compared with standard drug chlorpheniramine (% protection = 83%) [257].

### 2.13.4. Antifertility agents

A vast increase in population is a barrier for the social, economic and technological development of the human race and country [258]. Hence, various synthetic and natural products are designed as antifertility agents. Bhowal et al, designed, synthesized and evaluated indole derivative. Synthesized compounds were evaluated by measurement of level sexual hormones and spermatogenesis by *in vivo* method. Compound **154** (Fig. 21) has shown good activity [259].

### 2.13.5. Antiestrogen activity

An antiestrogen agent acts as the inhibitors of the sex hormone, estrogen. It is used in the treatment of infertility and breast cancer [260]. Ji et al, designed, synthesized and evaluated indole derivatives as antiestrogen agents acting on uterine and mammary tissues. All the synthesized derivatives were evaluated by examining binding affinity with estrogen receptors (ERσ, ER β). Effect on mouse uterus and bone were also evaluated. SAR studies concluded that substitution of piperidine at the nitrogen atom and hydroxy at the 5th position of indole were favorable for the activity. Among all the synthesized compounds, **155** (Fig. 21) was found to be the highly potent [261].

## 3. Indole containing drugs under advanced stage of developments

The clinical trial is to effectively prevent, diagnose and treat disease. A large pool of data is available of the FDA approved and under clinical trial indole containing drugs. Along with indole, various other isoforms of indole i.e. oxindole and indoline, due to similar mechanism of action, have distinct biological significance in the variety of disease conditions. They are, therefore, also among the potential drug candidates which are under clinical trial. Maximum drugs have successfully passed the various phases of clinical trial considered to be very effective. However, a few of them, having serious side effects are not further screened. These indole containing drugs are under study and proper structural modifications are applied to bring them under clinical trial. Some of these drugs are mentioned below in Table 1.

## 4. Conclusion

A large pool of drugs posses' indole nucleus involved in the treatment of various diseases conditions from acute to the chronic state. This ring can be traced in a commercially available marketed drug approved by FDA which are being therapeutically utilized. A number of drugs with indole nucleus obtained from natural origin and synthetic process are under clinical trial. Researchers are still working on non-marketed

indole containing drugs targeting different disease, by removing side effects and improving the biological activity. Data obtained from the extensive literature survey concluded that indole is a versatile nucleus touching almost all the disease conditions. In the present article, maximum information regarding the indole nucleus was tried to be covered including natural and synthetic indole containing drugs, pharmacological activity, drugs under clinical trial with pharmacological effects and mechanism of action. In this work, we also discussed on SAR of indole nucleus which will help to medicinal chemist and researchers to develop safe and efficacious drugs.

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## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2019.103021.

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