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An insight into the recent developments in anti-infective potential of indole and associated hybrids☆

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ABSTRACT

Prevention, accurate diagnosis, and effective treatment of infections are the main challenges in the overall management of infectious diseases. The best example is the ongoing SARs-COV-2(COVID-19) pandemic; the entire world is extremely worried about at present. Interestingly, heterocyclic moieties provide an ideal scaffold on which suitable pharmacophores can be designed to construct novel drugs. Indoles are amongst the most essential class of heteroaromatics in medicinal chemistry, which are ubiquitous across natural sources. The aforesaid derivatives have become invaluable scaffolds because of their wide spectrum therapeutic applications. Therefore, many researchers are focused on the design and synthesis of indole and associated hybrids of biological relevance. Hence, in the present review, we concisely discuss the indole containing natural sources, marketed drugs, clinical candidates, and their biological activities like antibacterial, antifungal, anti-TB, antiviral, antimalarial, and anti-leishmanial activities. The structure-activity relationships study of indole derivatives is also presented for a better understanding of the identified structures. The literature data presented for the anti-infective agents herein covers largely for the last twelve years.

1. Introduction

Adolf von Baeyer synthesised the indole (**1**) (Fig. 1a) for the first time in the year 1866. It gave a faecal odour, but it is used as a perfumery because of its flowery smell at lower concentrations [1].

Indole chemistry came to the limelight with the development of indigo dye. Indigo (**2**) can be easily converted to isatin (**3**) and then to oxindole (**4**). An essential amino acid tryptophan (**5**) found in many natural resources contains an indole ring. It is also a biosynthetic precursor in the synthesis of 5-hydroxy tryptophan (**6**), tryptamine (**7**), an immediate precursor of serotonin (**8**) (5-Hydroxytryptamine), and also melatonin (**9**). Serotonin is an important neurotransmitter associated with the transmission of nerve impulses. It further serves as a precursor to melatonin, a neurohormone secreted by the pineal gland. Indole-3-acetic acid (IAA) (**10**) is the most common and widely studied plant growth hormone of the auxin class containing indole motif [2] (Fig. 1b).

Indole is one of the most important heterocyclic systems and is ubiquitous in natural products. Derivatives of the indole have become a significant motif because of their broad scope of importance in drug discovery, as a building block, crop protection chemicals, material applications etc. Consequently, the production of the indole nucleus and its derivatization is a key objective in heterocyclic chemistry and has attracted many researchers around the globe in the form of many reviews employing the synthetic methodologies and biological activity of the indole derivatives [3–10]. In the sight of the above findings and in the extension of our own research efforts in the field [11–16], the present review is intended to present a significant outline of the various research activities in this intensifying field. There is a scarcity of review reports on research involving the active principle capable of inducing activity on new infective pathogens. In this regard, the aim of this review endows information on the current studies of biologically indispensable indole derivatives. It is fulfilled through the bibliography exploration of scientific articles and pertinent literature identified through the various means of electronic databases.

☆ Dedicated to Prof. M. G. Purohit.

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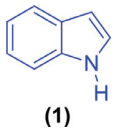

(1)

Fig. 1a. Structure of indole.

2. Indoles of natural product origin

Gunasekera et al. reported the isolation and biological activity of hamacanthin A (**11a**) and hamacanthin B (**11b**) a new species of deep-water marine sponge, *Hamacantha sp*. [17]. These alkaloids act as growth inhibitors of *Candida albicans* and *Cryptocous neoformans*. The isolation and antimicrobial activity of pibocin (**12**) from the Far-Eastern ascidian *Eudistoma sp*. from the Sea of Japan was reported by Makrieve et al. [18]. Stao et al. [19] demonstrated the isolation and spectroscopic studies of four new rhopaladins A-D, a bis(indole) alkaloids (**13 a–d**), from the Okinawan marine tunicate *Rhopalaea sp.* Jasplakinolide (**14**), a naturally occurring cyclic peptide was isolated from the marine sponge, *Jaspis johnstoni* by Holzinger [20]. The same compound is now synthetically prepared and has become commercially available. The jasplakinolide has membrane-permeable potential and it is a normally used tool in cell biology when actin filament stabilization or polymerization has to be achieved. From the root bark of *Tabernaemontana hystrix,* a novel alkaloid hystrixnime was isolated (**15**) by Monnerat et al. [21]. The spectroscopic studies were used to elucidate the structure of the novel compound. Kitajima and co-workers [22] took the advantage of the isolation and structural determination of novel alkaloid, 7-hydroxyspeciociliatine (**16**) from the fruits of Mitragyna speciosa Korth. The opioid agonistic potential of the novel compound was explored in guinea-pig ileum experiments. The 7-hydroxyspeciociliatine exhibited a moderate effect on μ-opioid receptors.

Pedas and Soledad explored [23] the chemistry and biological potential of brassinin (**17**) and cyclobrassinin (**18**) produced by plants of the family brassicaceae. Phytoalexins [24] also reported the isolation, structure elucidation and antifungal activities of three novel alkaloids caulilexins A (**19**), caulilexins B (**20**) and caulilexins C (**21**). The isolated lexins were screened for their antifungal activity against pathogenic fungi *Leptosphaeria maculans, Rhizoctonia solani* and *Sclerotinia sclerotiorum*. A novel indole alkaloid pityriazepin (**22**) was isolated from *malassezia furfur* yeast by Mexia et al. [25]. Lee and co-workers [26] reported the isolation, structural determination and anticancer potential of a novel indole alkaloid macrolepiotin (**23**) from *Macrolepiota neomastoidea*. The isolated compound was screened for *in vitro* anticancer efficacy against A549, SK-OV-3, SK-MEL-2 and HCT15 human cancer cell lines using the SRB assay. The various structures of indoles **(11–23)** isolated from natural sources are presented in Fig. 2a.

Geleganidines A and C (**24 and 25**) were isolated from the roots of *Gelsemium elegans* by Ye and co-workers [27]. The isolated monoterpenoid indole alkaloids were evaluated for their cytotoxic activity against MCF-7 and PC-12 cells. Compound **25** showed moderate cytotoxicity. Fox Ramos et al. [28] isolated a new monoterpene indole alkaloid geissolaevine (**26**) from the bark of *Geissospermum leave*. The isolated alkaloid was tested its antiparasitic activity against *Plasmodium falciparum* and *Leishmania donovani* and anticancer activity against the MRC-5 cell line. Queirozand his co-worker [29] reported the five novel indole alkaloids (**27, 28, 29a, 29b** and **29c**) from the stem bark of *Conchocarpus fontanesianus*. These new indolopyridoquinazolines were tested for their antifungal activity against *Candida albicans* by a bioautography assay method. Also, the author's discussed the effectiveness of molecular networks to target the isolation of novel bioactive natural products and the usefulness of this advanced technic for dereplication. Reyes et al. [30] reported the isolation, structure elucidation and anticancer activities of two novel indolocarbazole alkaloids, 7-oxo-3,8,9-trihydroxystaurosporine (**30a**) and 7-oxo-8,9-dihydroxy-4′-*N*-demethylstaurosporine (**30b**). These alkaloids exhibited potent cytotoxicity against three human tumour cell lines. Mulwa et al. [31] explored the isolation of two novel secondary metabolites, labindole A (**31a**) and labindole B (**31b**) from the myxobacterium Labilithrix luteola (DSM 27648T). The structures of these new compounds were conformed from high-resolution mass spectrometry and 2D NMR. Further, the antimicrobial activities were studied for these novel secondary metabolites and the compounds were found to be highly effective. Ramkissoon et al. [32] isolated three novel indole alkaloids, tris(1*H*-indol-3-yl) methylium (**32a**), bis(indol-3-yl) phenylmethane (**32b**), and indolo (2, 1b) quinazoline-6, 12 dione (**32c**) from a *Pseudomonad bacterium* and *Pseudomonas aeruginosa*. The spectroscopic methods were used to elucidate the structure of the foresaid indole alkaloids and further, the antimicrobial evaluations were carried *in vitro* against an ample variety of microorganisms via the broth microdilution technique.

Sun and co-workers [33] reported the identification of a new indole alkaloid, 17-oxo-19-(*Z*)-naucline **(33)**, from the areal parts of *Nauclea officinalis*. The new alkaloid was evaluated *in*

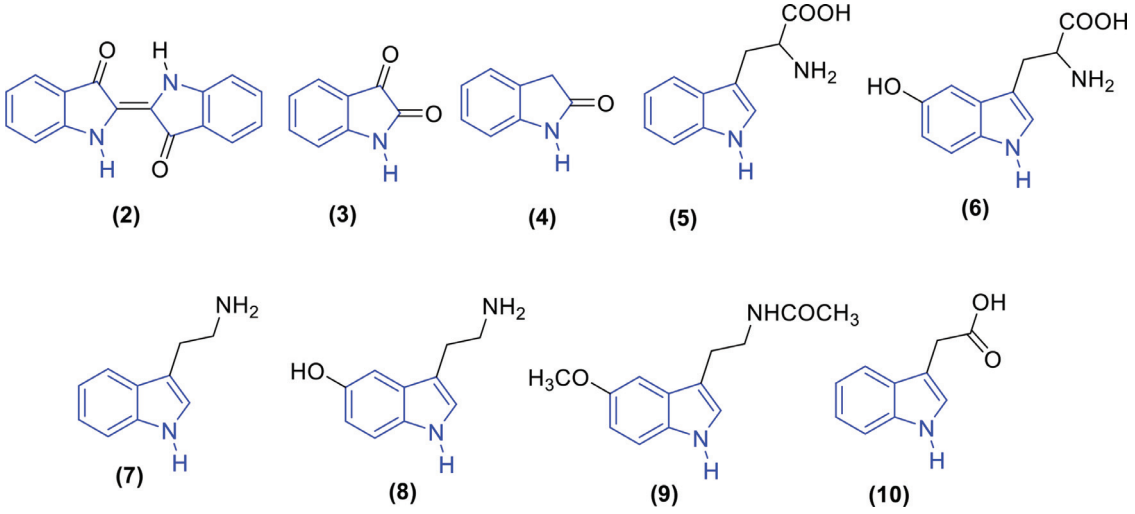

Fig. 1b. Indole associated derivatives of biological relevance.

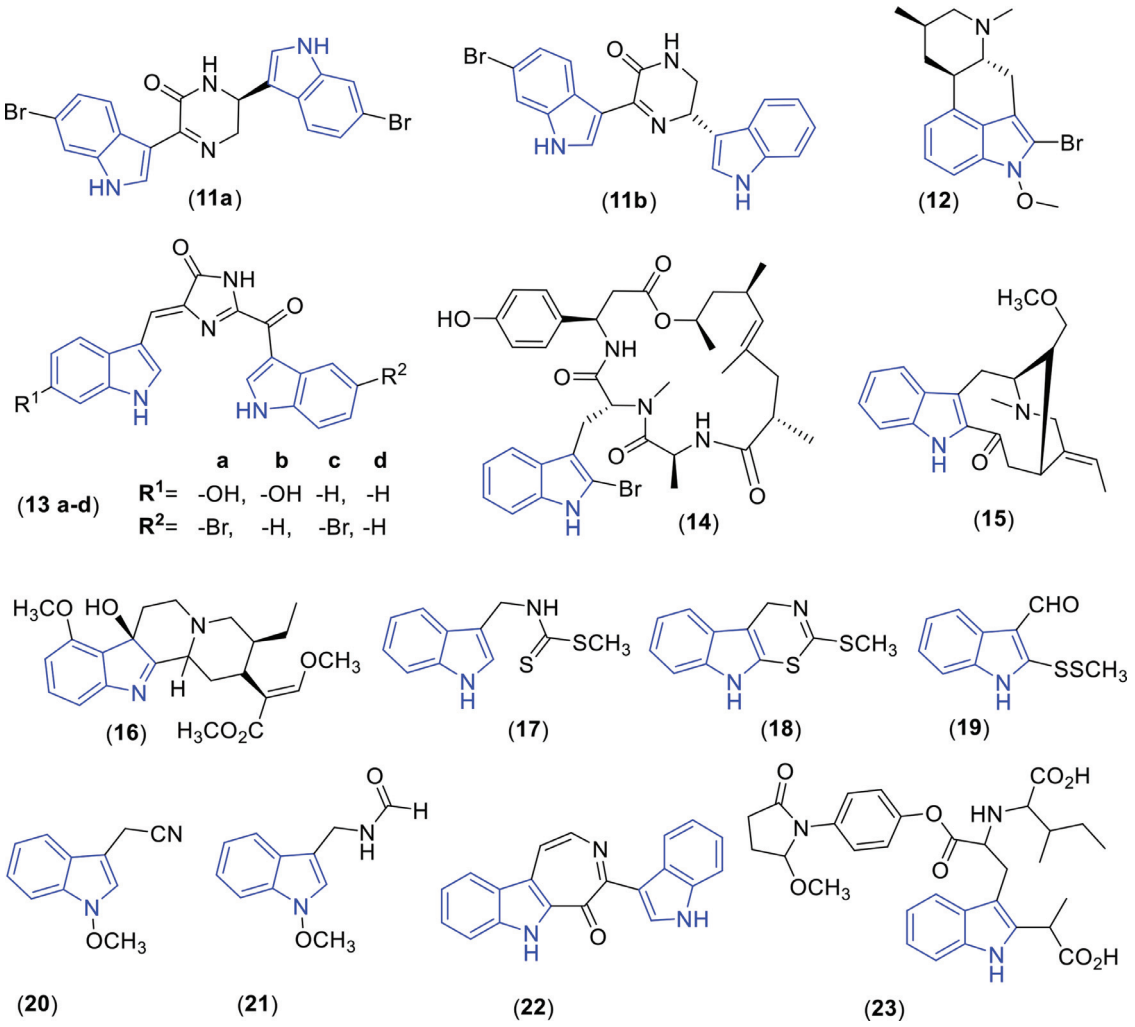

Fig. 2a. Bioactive indoles from natural resources.

*vitro*anti-inflammatory activity, wherein, the compound displayed a decrease in LPS-stimulated production of nitric oxide in RAW264. Christopher et al. [34] investigated a novel indole (*E*)-4-(1*H*-indol-5-yl)-but-3-en-2-one (**34**) from the methanolic extract of Monodora minor Engl. And Diels (Annonaceae) stem bark. The structure of the isolated compound was elucidated based on NMR spectroscopy and high-resolution electron ionization mass spectrometry (HR-EIMS) data. Further, the isolated compound was tested for their antimalarial activity against *Trypanosoma brucei* and *Plasmodium falciparum* at a single concentration of 20 μM. The novel indole alkaloid, Legonimide (**35**) was isolated by Deng and co-workers [35] from the extracts of *Streptomyces* sp. CT37 using bioassay in combination with mass spectrometric molecular networking (MN) driven isolation. The antimicrobial screening was carried out against *Candida albicans* ATCC 10231 which showed moderate activity. Park et al. [36] have isolated a new indole alkaloid, pulveratinol (**36**) from Indigo *Pulverata Levis*. The structure of the novel indole alkaloid was confirmed by spectroscopic methods like NMR and HRMS. Further, the isolated compound was tested for its neuroprotective activity through stimulation of nerve growth factor (NGF) in C6 glioma cells. Riley and his co-workers [37] reported the isolation protocol for akuamma alkaloids. This method gives akuammine (**37**) in high purity and high productivity. Further, compound **37** was tested against a panel of >40 central nervous system receptors to recognize that their primary targets are the opioid receptors. A new cycloheptapeptides, asperheptatides A and B (**38a and 38b**) were isolated from the fungus *Aspergillus Versicolor* by Chao et al. [38]. The structures of these peptides were elucidated by applications of complete spectroscopic methods and these two novel compounds were evaluated for their antitubercular activity against *Mycobacterium tuberculosis* H37Ra. The structures of indoles **(24–38)** isolated from natural sources are depicted in Fig. 2b.

3. Indole based approved drugs and drug candidates under clinical trials

An antiviral drug umifenovir (**39**) is marketed under the brand name Arbidol for the treatment of influenza infection mainly in Russia and China. The mode of action involves inhibition of membrane fusion of influenza virus. Recently it is used in combination with darunavir for treatment of Covid-19 [39]. A non-nucleoside, ateviridine (**40**) has been studied for the treatment of HIV and it acts as a reverse transcriptase inhibitor [40]. The results showed that the plasma concentrations of ateviridine demonstrated considerable interpatient inconsistency which was reduced by the proper maintenance of doses to attain the desired concentrations. Another non-nucleoside antiviral drug delavirdine (**41**) sold under the brand name rescriptor by Viiv Healthcare, acts as a reverse transcriptase inhibitor [41]. In the treatment of the human immunodeficiency virus (HIV), it is used as part of highly active antiretroviral therapy (HAART). A new synthetic dipeptide, golotimod (SCV-

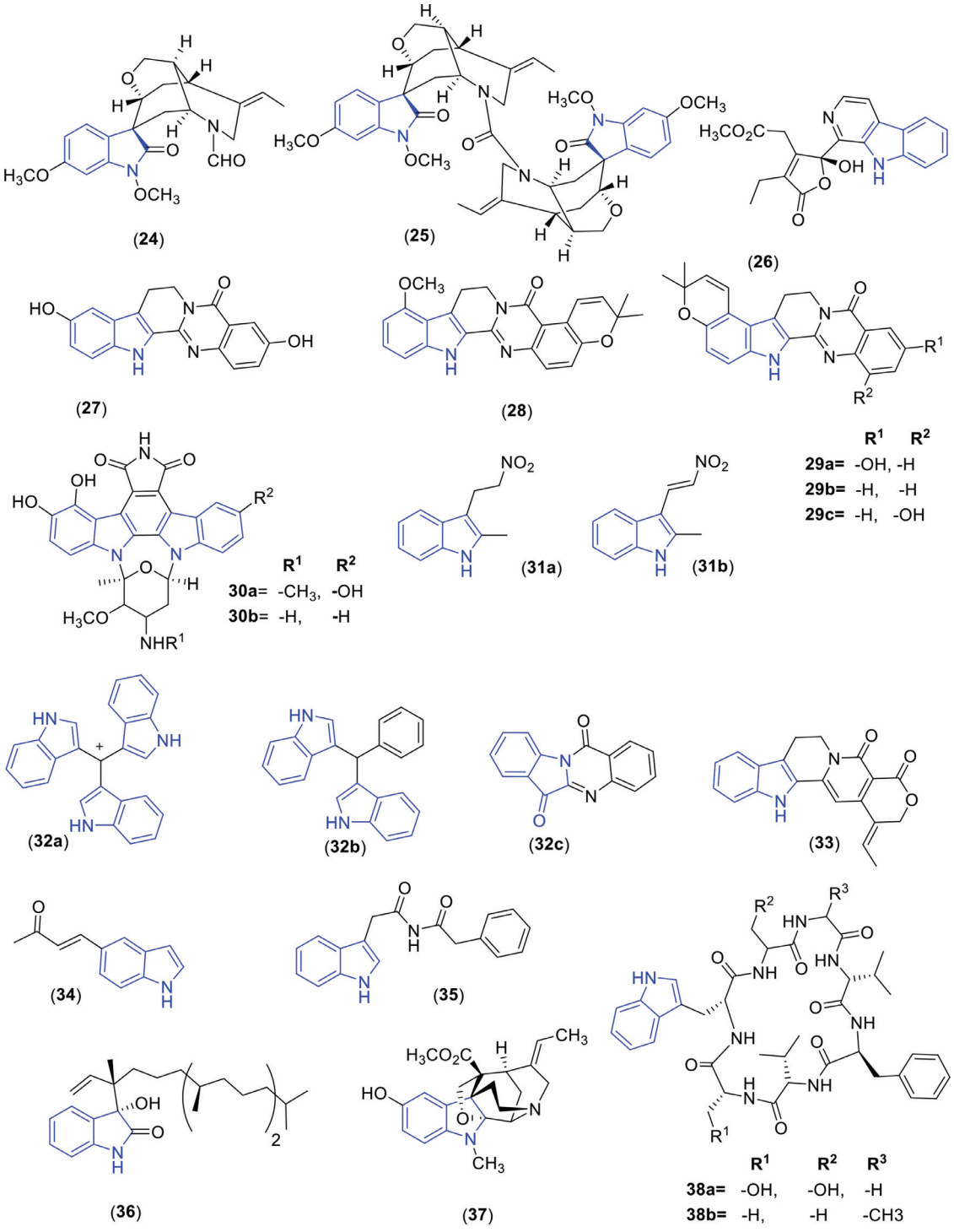

Fig. 2b. Bioactive indole scaffolds of natural origin.

07) (**42**) works principally on the Toll-like receptor pathway. It has been revealed to encourage T-lymphocyte differentiation, macrocytic phagocytosis, specific immune responses, and enhance IL-2 and INF-g production [42]. A non-selective histone deacetylase inhibitor panobinostat (**43**) is used to treat multiple myeloma in combination with other anticancer drugs [43]. Panobinostat is another indole-based drug marketed under the brand name Farydak by Novartis. It works as a non-selective histone deacetylase inhibitor (pan-HDC inhibitor) and compared to other marketed drugs it is more effective.

Prof. Martinez from the French National Centre for Scientific Research (CNRS) at the University of Montpellier investigated the maciorelin (**44**) for the first time. It is sold under brand name Macrilen Aeterna Zentaris, which was approved by the FDA in December 2017 for as an oral solution against adult growth hormone deficiency [44]. A cyclic lipopeptide antibiotic, Daptomycin (**45**) marketed under the brand name cubicin is used for the treatment of systemic and life-threatening infections caused by susceptible Gram-positive bacteria [45]. It is naturally found in the soil saprotroph *Streptomyces roseosporus*. Its diverse mode of action makes it

beneficial in treating infections caused by multiple drug-resistant bacteria. Major depressive disorder (MDD) is treated with an antidepressant agent vilazodone (**46**) and it is sold under the brand name viibryd. The same drug was approved for medical use in the United States in 2011 and in Canada in 2018 [46]. Vilazodone acts as a serotonin reuptake inhibitor (IC_{50} = 2.1 nM) and 5-HT1A receptor partial agonist (IC_{50} = 0.2 nM). A receptor tyrosine kinase inhibitor (RTK), sunitib (**47**) employed for the curative of renal cell carcinoma (RCC) and imatinib-resistant gastrointestinal stromal tumor (GIST). It is approved by US FDA in 2006 [47]. Vertex Pharmaceuticals developed a drug tezacaftor (**48**) to felicitate the cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, class. In 2018, FDA approved the tezacaftor in combination with ivacaftor to manage cystic fibrosis [48]. The movement of charged ions crossways cell membranes is usually accomplished through the performance of the cystic fibrosis transmembrane regulator (CFTR) protein. This protein acts as a channel and permits for the transport of chloride and sodium.

Novartis produced the 5-HT4 agonist, tegaserod (**49**) under the brand name Zelnorm for the treatment of irritable bowel syndrome with constipation. It was approved by US FDA in 2019 [49]. However, voluntarily introverted from widespread usage in the US market in 2007 after the possibility that tegaserod could potentially cause unsafe cardiovascular events in patients. Sloan Pharma then expanded the Zelnorm (tegaserod) by re-approval in April 2019. Setmelanotide (**50**) is used in the treatment of patients with proopiomelanocortin, proprotein subtilisin/Kexin type-I, or leptin deficiencies [50]. Setmelanotide, marketed under the brand name Imcivree, is a drug used for the treatment of genetic obesity. The structures of compounds discussed a **(39–50)** are presented in Fig. 3a**.**

A glucagon-like peptide-1 (GLP-1) receptor agonist, Lixisenatide (**51**) is used as an injection in the medication of non-insulin-dependent or adult-onset diabetes [51]. Chemically, lixisenatixe is made of 44 amino acids, with an amide group on its C terminus. It is marketed under the brand name Adlyxin by Sanofi-Aventis and received approval from FDA in 2016. A peptide drug, octreotide (**52**) used for the treatment of acromegaly as well as diarrhoea associated with metastatic cancers and vasoactive intestinal peptide secreting neoplasms [52]. It is sold under the brand name Bynfezia. Octreotide is a chronic drug with biological activities that imitate those of the usual hormone, somatostatin, which restrains the release of growth hormone. A 5-HT3 antagonist, alosetron (**53**) used for the management of severe diarrhoea-predominant irritable bowel syndrome (IBS) in women and it might amend serotonin-sensitive gastrointestinal (GI) processes [53]. In June 2002, the FDA approved a supplemental new drug application allowing the remarketing of the drug under restricted conditions of use. An oral leukotriene receptor antagonist (LTRA), zafirlukast (**54**) is utilized for the treatment of asthma, regularly used in combination with an inhaled steroid and/or chronic bronchodilator [54]. It is sold under the brand name Accolate. Zafirlukast is a selective and aggressive receptor antagonist of leukotriene D4 and E4 (LTD_4 and LTE4), components of a slow-reacting substance of anaphylaxis (SRSA). Pfizer a pharmaceutical company developed a third-generation selective estrogen receptor modulator (SERM) drug bazedoxifene (**55**). In late 2013, Pfizer received a sanction for bazedoxifene as part of the combination drug in the anticipation of postmenopausal osteoporosis [55]. A non-steroidal anti-inflammatory drug (NSAID), acemetacin (**56**) used for the management of osteoarthritis, rheumatoid arthritis, lower back pain, and relieving postoperative pain [56]. It is manufactured by Merck and sold under the trade name Emflex. Acemetacin is a non-selective inhibitor of the pro-inflammatory mediators imitative from the exploit of the enzyme cyclooxygenase (COX).

Requip, a trading name of ropinirole (**57**), is used for the treatment of Parkinson's disease (PD) and restless legs syndrome (RLS) [57]. It is manufactured by Glaxo Smith Kline Pharmaceuticals and ropinirole was initially approved in 1997 by the FDA. It is available as a generic medicine since 2018. A small indole molecule, flortaucipir F-18 (**58**) used for the management of monoamine oxidase as well as to regions containing high levels of melanin, neuromelanin, and iron [58]. It is marketed under the trade name tauvid by Avid Radiopharmaceuticals and approved by FDA in 2020. Bremelanotide (**59**) was investigated for sexual dysfunction in men and women, however, at present, it is only indicated for women [59]. Bremelanotide is a peptide drug, which acts by triggering melanocortin receptors got approved by FDA in 2019. Indole-3-carbinol (**60**) is under Phase I clinical trials (NCT00033345) [60], to study the effectiveness in preventing breast cancer in non-smoking women who are at high risk. Recently Cannalire et al. [61] synthesised two compounds **61a** (PF-00835231), **61b** (PF-07304814) and evaluated their antiviral activity against Covid-19. The structures **(51-61)** of indole-based drugs are given in Fig. 3b.

4. Anti-infective evaluation

For many decades heterocyclic motifs are employed as a diversity pool for drug design and discovery *viz*., indole, quinoline, coumarin, imidazole, pyrimidine, purine, thiazole, flavones, triazole, etc. [62–70]. The indole ring is renowned as a privileged scaffold that represents a wide variety of beneficial perspectives such as antibacterial, antifungal, antimycobacterial, antiviral, antimalarial, and anti-leishmanial activities [71–74]. Hence, in the following sections, we discuss in detail the contributions of indole-based heterocycles as an anti-infective agent.

4.1. Antibacterial activity

From our own group, 5-substituted-3-phenyl-*Nb*-(substituted-2-oxo-2*H*-pyrano [2, 3-b] quinoline-3-carbonyl)-1*H*-indole-2-carboxy hydrazides (**62**) were synthesized and subjected for antimicrobial activity. All the synthesized compounds are screened for their antibacterial activity against *S. aureus, E. coli* and *B. Subtilus*, antifungal activity against *A. niger* and *C. albicans* and anti-tuberculosis activity against *Mycobacterium tuberculosis* (H37Rv) [75]. The structure-activity relationship studies revealed that the indole derivatives containing halogen substitution exhibited excellent inhibition activity of bacterial growth. Synthesis and anti-microbial activity of some new 5-substituted-*N*-[(1*E*)-(2-hydroxyquinolin-3-yl)methylene]-3-phenyl-1*H*-indole-2-carbohydrazide (**63**) derivatives were reported by our own group [76]. The results of structure-activity relationship studies described that, *N*-(2H-[1, 3]oxazino[6,5-b]quinolin-3(4H)-yl)-5-chloro-3-phenyl-1*H*-indole-2-carboxamide exhibited maximum antibacterial activity with activity index 0.95, as compared to standard drug Gentamycin. Later an antimicrobial activities of 5-substituted-*N*-(substituted-2*H*-[1, 3]oxazino[6, 5-b]quinolin-3(4*H*)-yl)-3-phenyl-1*H*-indole-2-carboxamides (**64**) were also reported by our own group [77]. In 2018, we also disclosed the design, synthesis and antimicrobial activities of a series of novel 6-substituted-3-(5-chloro-3-phenyl-1*H*-indole-2yl)-3,4-dihydro-4-substituted phenacyl-2*H*-1,3-benzoxazine-2ones (**65**) [78]. The compound 6-bromo-3-(5-chloro-3-phenyl-1*H*-indol-2-yl)-4-(2-oxo-2-phenylethyl)-3,4-dihydro-2*H*-benzo[e][1,3]oxazin-2-one showed highest antibacterial activity. The Halawa et al. [79] took the advantage of bis-indole (**66**) synthesis by using facile and efficient condensation of three positional isomeric indole-carboxaldehydes. The structures of these compounds were confirmed by spectroscopic methods like ^{1}H NMR, ^{13}C NMR and HRMS. All the newly synthesised evaluated for their antimicrobial activity

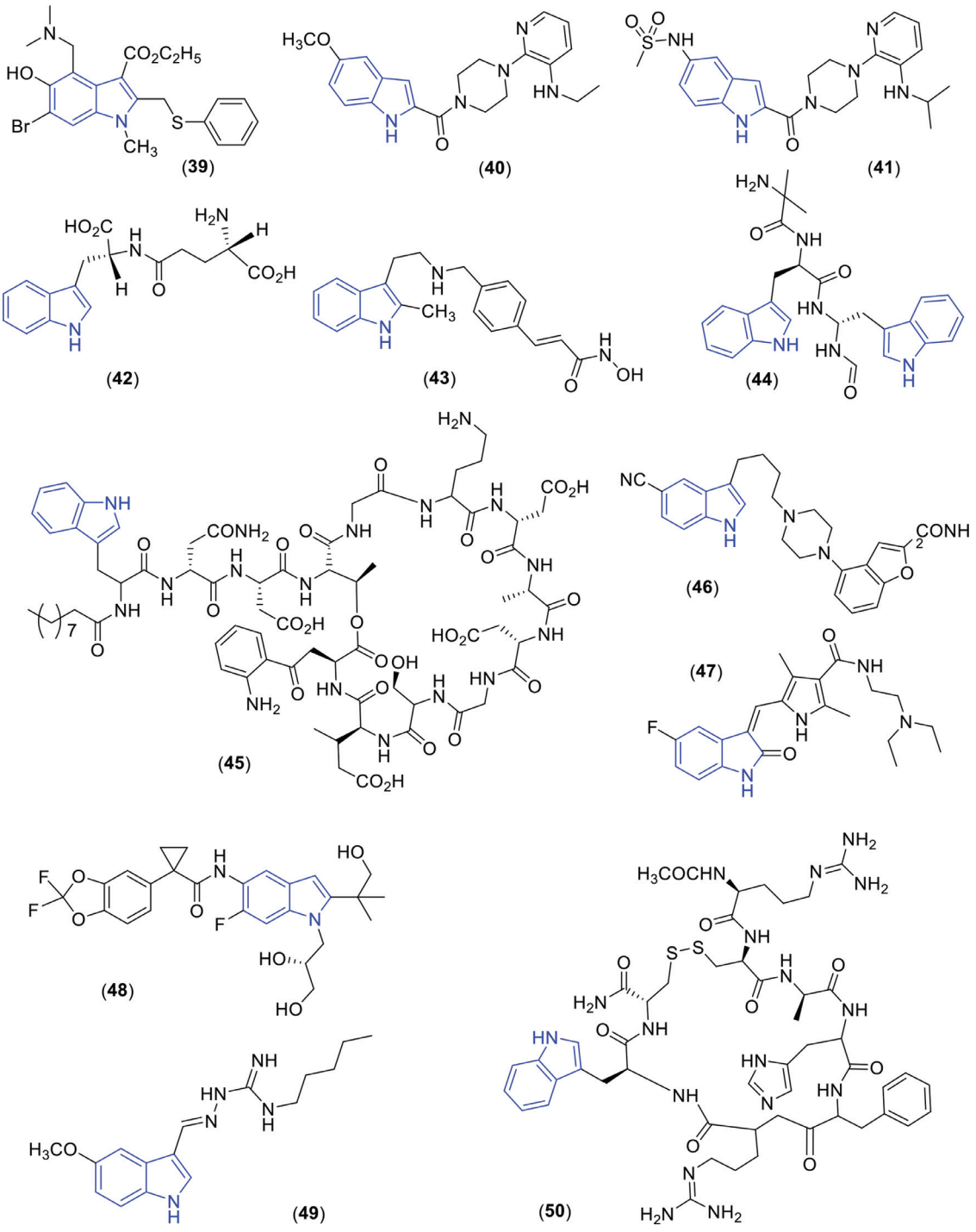

Fig. 3a. Indole based drugs and drug candidates under clinical trial.

by agar diffusion method. The results of antibacterial activity indicated that, *N*-{4-[(-(1*H*-indol-3-yl)methylene) amino]phenyl}-1-(1*H*-indol-5-yl)methanimine exhibited promising antibacterial activity against various gram-positive and negative bacteria, while compound *N,N′*-[ethane-1,2-diylbis(4,1-phenylene)]bis[1-(1*H*-indol-3-yl)methanimine] exhibited moderate activity against several gram-positive bacteria. Mahamadalli Shaikh and Debebe [80] reported the synthesis of novel *N*-substituted indole derivatives (**67**) and tested for their *in vitro* antimicrobial activities by the disc diffusion method against the latest strains of bacteria *Staphylococcus aureus, Escherichia coli*, and *Candida albicans*. Especially, the compound 4-(1-(2-(1*H*-indol-1-yl) ethoxy) pentyl)-*N,N*-dimethyl aniline displayed most effective activity than the other derivatives, which showed higher inhibition than the standard drug chloramphenicol. Shirinzadeh et al. [81] has been investigated the novel indole (**68a** and **b**) derivatives encompassing substituted 1,2,4-triazole, 1,3,4-thiadiazole and evaluated for their antimicrobial activities against Staphylococcus aureus, MRSA, *Escherichia coli, Bacillus subtilis, Candida albicans*, and *Candida krusei*. The derivatives demonstrated a broad spectrum of activity against the tested pathogens with MIC values 3.125-50 μg/mL. The investigation offered important evidence that the indole-triazole derivative,

H–His–Gly–Glu–Gly–Thr–Phe–Thr–Ser–Asp–Leu–Ser–Lys–Gln–Met–Glu–Glu–Glu–Ala–Val–Arg–Leu–Phe–Ile–Glu–Trp–Leu–Lys–Asn–Gly–Gly–Pro–Ser–Ser–Gly–Ala–Pro–Pro–Ser–Lys–Lys–Lys–Lys–Lys–Lys–NH_2

(51)

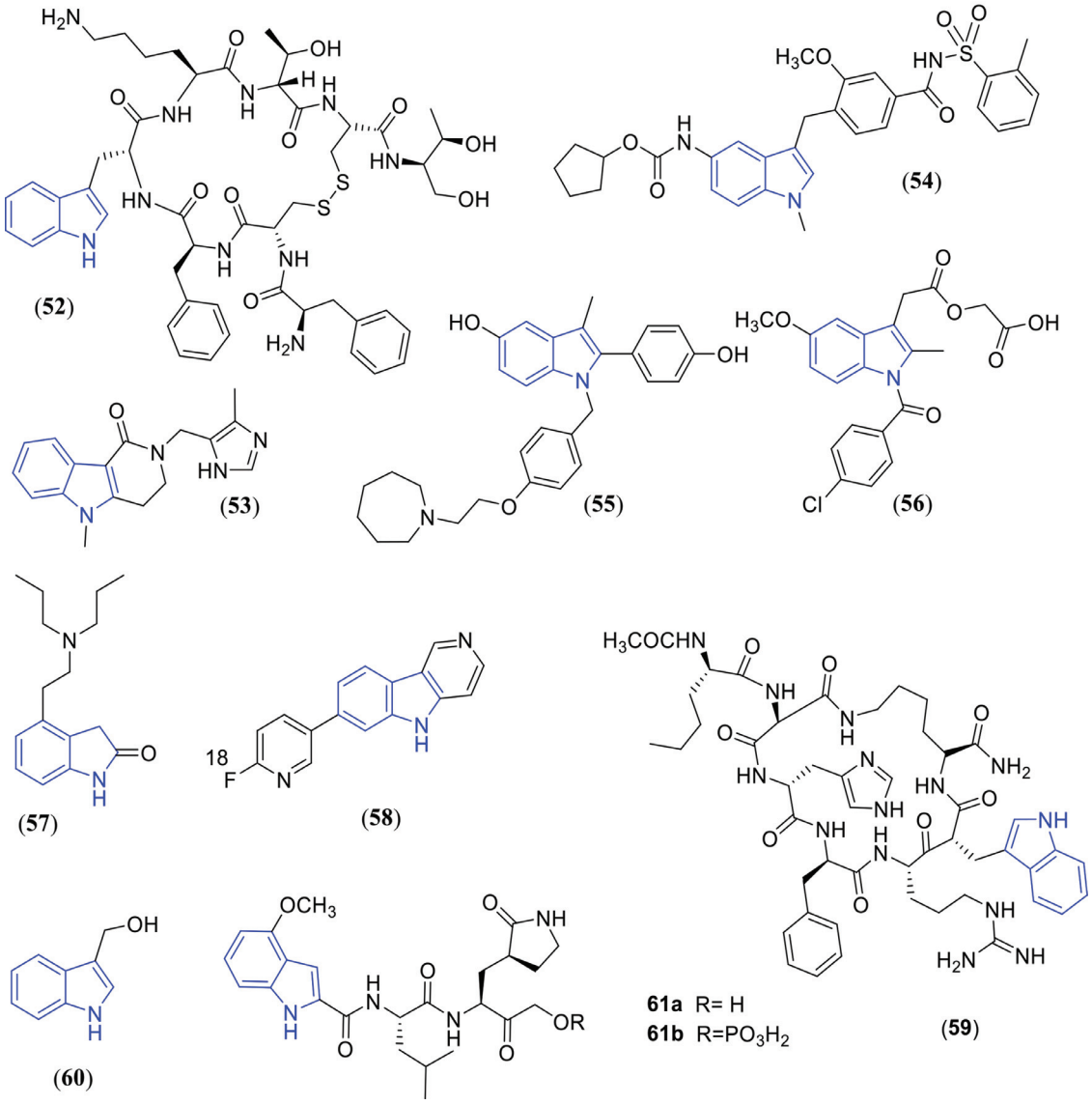

Fig. 3b. Structures of indole-based drugs.

5-((1*H*-indol-3-yl)methyl)-4-phenyl-4*H*-1,2,4-triazole-3-thiol holds significant promise as a novel antibacterial and antifungal lead analogue. The various poly substituted indole derivatives (**69**) were synthesised and screened for their antimicrobial activities against human pathogens like *Streptococcus pyogenes, Streptococcus aureus, Escherichia coli, Candida albicans, Aspergillus niger*, and *Aspergillus clavatus* by Yadav et al. [82]. Further, they studied the MIC values and mean half-maximal inhibitory concentration (IC_{50}) values of newly designed heterocyclic compounds. Mane et al. [83] disclosed the synthesis and antimicrobial activities of various novel substituted indole derivatives (**70**). The newly synthesised compounds were tested *in vitro*, antibacterial activity against pathogenic bacteria *Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa*, and *Salmonella typhi* using gentamicin/ciprofloxacin as standard drugs.

These compounds displayed maximum antibacterial inhibitory activity with MIC values in the range of 0.12–6.25 μg/mL. The synthesis and antimicrobial activity of diverse 1-[(3,5 diphenyl substituted) -4,5-dihydro-1*H*-pyrazol-1-yl]-2-(3*H*-indol-3-yl) ethan-1-ones (**71**) were reported by Quazi et al. [84]. One of the analogues compounds 1-[5-(4-chlorophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl]-2-(3*H*-indol-3-yl) ethan-1-one showed maximum antibacterial activity. Rajaraman et al. [85] disclosed the synthesis and characterisation of novel 3-(1-(3,4-dimethoxyphenethyl)-4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole (**72**). Further, the structures of compounds were confirmed by single-crystal XRD analysis and density functional theory (DFT) for optimized bond parameters calculations. The authors also evaluated the antibacterial activity of the synthesized derivatives and studied using molecular docking studies and compared with their experimental results. The structures of indole derivatives (**62–72**) with antibacterial activity were depicted in Fig. 4.1a.

Gani et al. [86] reported the chemo-selective synthesis of 1-cyclopropyl-3-ethoxycarbonyl-2-methylindole-5-(1-

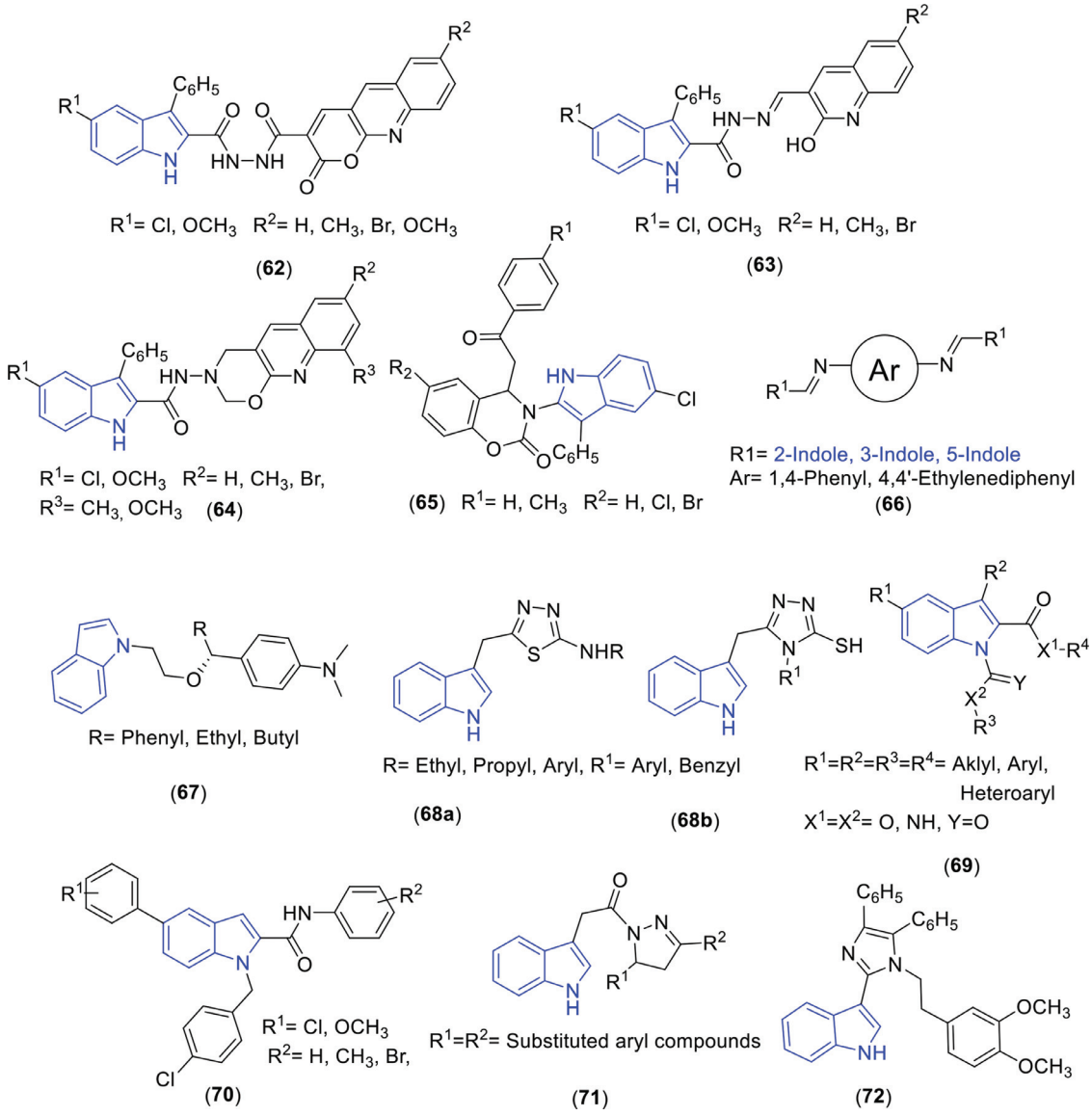

Fig. 4.1a. Structures of indole derivatives exhibiting antibacterial activity.

methylethoxyaceticacidhydrazide) derivatives (**73**). Further, the authors investigated the antimicrobial potential of synthesized derivatives to identify the hit/lead molecules. The novel 1-cyclopropyl-2- methyl-3-ethoxycarbonyl-5-hydroxyindole derivatives were subjected for *in vitro* antimicrobial activity against *Escherichia coli* and *Bacillus cirroflagellosus* using Norfloxacin as a standard drug. Amongst all Schiff bases, nitrobenzaldehyde derivatives showed the highest antibacterial activity against *E. coli* and *B. cirroflagellosus*. This may be due to the effect of electron-withdrawing groups such as NO_2 and electron-donating groups such as OH and thiazole moiety, also this variation is due to change in inductive effect of substituents. Synthesis and spectral studies of a series of novel 2-(1*H*-indol-3-yl)ethylthiourea (**74**) derivatives were reported by Sanna et al. [87]. Evaluation of the antibacterial activity of all the newly synthesized compounds was also carried out against S. aureus and S. cocci. The structure-activity relationship studies indicated that the compound 1-(2-(1H-indol-3-yl)ethyl)-3-(3,4-dichlorophenyl)thiourea showed maximum antibacterial activity. Abo-Ashour et al. [88] reported the design, synthesis and antibacterial activity of two series of indole appended thiazolidinone derivatives (**75a and b**). The targeted compounds were evaluated for their *in vitro* antibacterial activity against pathogenic Staphylococcus aureus, *Pseudomonas aeruginosa*, and *Escherichia coli*. The structure-activity relationship studies clearly indicated that the compound (2*E*, 5*Z*)-2-((5-acetyl-4-methylthiazol-2-yl)methylene)-5-((1-methyl-1*H*-indol-3-yl)methylene)thiazolidin-4-one exhibited potent broad-spectrum antibacterial activity with MIC value 0.98 μg/mL. Synthesis and structure elucidation of some new indole derivatives containing thiazolyl (**76a**) and pyrazolyl (**76b**) motifs were reported by Sayed et al. [89]. All synthesized derivatives were assessed for their antimicrobial activity. The compound (*E*)-2-(2-((3-chloro-1*H*-indol-2-yl)methylene)hydrazinyl)-4-methylthiazole exhibited excellent antibacterial activity against all tested pathogens. Kaur et al. [90] reported the efficient synthesis and antibacterial activity of indole hybridized diazenyl derivatives (**77**). The structures of all the newly synthesised compounds were characterised by various spectroscopic techniques. The antibacterial evaluation of indole compounds was done by tube dilution method against pathogens *E. coli* and *Klebsiella pneumonia*. These synthesized compounds exhibited excellent activity against gram-negative bacteria with MIC values ranging from 1.95 to7.81 μg/ml. The

derivatives have demonstrated very little activity against tested Gram-positive bacterial and fungal strains. The preliminary inhibition studies by targeting at Fts Z and followed by its antibacterial screening of novel indole (**78**) derivatives was reported by Yuan et al. [91]. The synthesised compounds showed promising antibacterial activity against, tested Gram-positive bacteria, such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus*. The result of antibacterial activity showed that (Z)-2-((1-(phenylsulfonyl)-5-(4-(trifluoromethyl) phenyl)-1*H*-indol-3-yl)methylene)hydrazinecarboximidamide with MIC 2 μg/mL is able to disrupt FtsZ polymerization and inhibit GTPase activity and cell division. Salimova et al. [92] disclosed the synthesis and antibacterial activity of novel indole (**79**) derivatives of fusidic acid by using the Fischer indolisation process. Further, the compounds were evaluated for antibacterial activity against *Staphylococcus aureus* (MRSA, strain ATCC 43300) and the results were found to be comparable with fusidic acid. The design, synthesis and structure elucidation of indole derivatives (**80**) were explored by Jia et al. [93]. Some compounds exhibited the potent activity, with minimum inhibitory concentrations (MIC) values in the range of 0.94–3.87 μM (0.39–1.56 μg/mL) against the four tested bacteria viz. *Staphylococcus aureus, Bacillus subtilis, Pseudomonas aeruginosa*, and *Escherichia coli*. Asghari et al. [94] took the advantage of a multi-component reaction strategy for the synthesis of novel indole-hydrazono thiazolidinones (**81**) in productive yield. These compounds were tested for their antibacterial activity against bacteria *viz. Staphylococcus aureus, Bacillus subtilis, Escherichia coli* and *Pseudomonas aeruginosa* at different concentrations. The result of antibacterial activity clearly indicated that the compounds with the amide group in their skeleton exhibited superior activity than compounds with the ester group. A series of novel pyrimido[4,5-b]indole (**82**) derivatives were synthesised by Kong et al. [95] and evaluated for their *in vitro* and *in vivo* antibacterial activity against multidrug-resistant pathogenic *Acinetobacter baumannii*. Amongst, The compound (*R*)-4-(3-(3-aminobutan-2-ylidene)azetidin-1-yl)-6-fluoro-*N*-methyl-2-((2-methylpyrimidin-5-yl)oxy)-9*H*-pyrimido[4,5-b] indol-8-amine represented excellent broad-spectrum antibacterial activity against both gram-positive and gram-negative bacteria. The structures of indole derivatives (**73–82**) with antibacterial activity were presented in Fig. 4.1b

4.2. Antifungal activity

Xu and Fan [96] exploited, the Sandmeyer reaction to report the synthesis and antifungal activity of novel indole[1,2-c]-1,2,4-benzotriazine (**83**) derivatives in quantitative yields. These newly synthesized compounds showed more potential and prominent *in vitro* antifungal activities against five phytopathogenic fungi. The efficient and modified method for synthesis of new indole (**84**) encompassing 1,3,4-oxadiazoles is investigated by Zhang et al. [97] and evaluated for antifungal activity. A few of the examined derivatives exhibited enhanced antifungal activity. The authors also studied the structure-activity relationships of the pimprinine analogues. The structure-activity relationship studies indicated that the compound 2-(1*H*-indol-3-yl)-5-(trifluoromethyl)-1,3,4-oxadiazole exhibited the highest antibacterial activity. Zhang et al. [98] took the advantage of bioisosterism approach to develop novel indole (**85**) derivatives. Their antifungal activity against *Alternaria solani* was also demonstrated. The structure-activity relationships studies clearly indicate that the indole ring system is very important for antifungal activity. A new series of substituted indole (**86**) encircling thiochroman derivatives were synthesized by Song et al. [99] and these novel compounds were evaluated for their *in vitro* antifungal activity by microdilution broth method against *Candida albicans* and *Cryptococcus neoformans*. Molecular docking studies of novel compounds were also disclosed. The compound 2-chloro-11-(2-(pyrrolidin-1-yl)ethyl)-5,11-dihydroisothiochromeno[4,3-b]indole showed the excellent antifungal activity, with MIC of 4 μg/mL. Xu et al. [100] investigated the design, synthesis and antifungal activity of novel indole (**87**) compounds bridged with the 1,2,3-triazole motif. The newly synthesises derivatives were tested for their antifungal activity against pathogens *Colletotrichum capsici* and cotton *Physalospora*. The authors also reported the preliminary structure-activity relationship studies of the new compounds. Altuntas et al. [101] investigated the antifungal activity of previously reported indole (**88**) compounds against *Candida albicans* (ATTC 10231), sultamacillin T, ampicillin, ciprofloxacin and fluconazole were used as standards. The new hybrid molecules with indole and imidazole were designed and synthesized by Sumiya et al. [102] using camalexin as a molecular scaffold. The antifungal activity of novel indole (**89**) derivatives was tested against *Magnaporthe oryzae* by using the agar cup plate method. Structure-activity relationship studies of these molecules were also discussed and the compound 6-(3-imidazol-1-ylmethyl-indol-1-yl)-hexanoic acid ethyl ester displays the most potent inhibition activity with 38.8 ± 2.5% on the inhibition of the diameter of the mycelial mat of *Magnaporthe oryzae* while the positive control of propiconazole was found 39.3 ± 2.9%. Abo-Salem et al. [103] developed a new series of 3-indolylthiophene (**90**) derivatives. The newly synthesized compounds were evaluated for their antifungal activity against two strains of fungi, namely, *Candida albicans* (ATCC-10231) and *Aspergillus niger* (ATCC-10535). The mechanism of action of the highly potent antifungal compounds was examined by docking with cytochrome P450 14 α-sterol demethylase (CYP51) (PDB ID: 1EA1).

Design, synthesis and antifungal activity of a new series of 1,2,4-triazole-indole hybrid molecules were reported by Pagniez et al. [104]. A new hybrid molecule (2-(2,4-dichlorophenyl)-3-(1*H*-indol-1-yl)-1-(1,2,4-1*H*-triazol-1-yl)propan-2-ol (**91**) was tested for antifungal activity against pathogens viz. *Candida glabrata, Candida krusei*, and *Candida albicans* with MIC values 0.25, 0.125 and 0.5 μg/mL, respectively. The derivatives displayed more promising activity than fluconazole and were comparable to voriconazole drug. Song et al. [105] reported the efficient synthesis of new indole (**92**) derivatives with 1,3,4-oxadiazole-5-thioether moieties via diversity-oriented synthesis of natural product streptochlorin. Antifungal activity of a diverse library of derivatives was evaluated against the *Pythium dissimile*. Further structural optimization of pimprinine and streptochlorin derivatives aiming to discover synthetic analogues with improved antifungal activity was also disclosed. Al-Wabli et al. [106] designed and synthesised the novel indole containing triazole motifs (**93**) as a new antifungal agent. These novel derivatives were evaluated for their *in vitro* antifungal activity against *Candida tropicalis* and *Candida albicans*. Some of the compounds exhibited excellent antifungal activity. The compound 2-(5-((3,4-dichlorobenzyl)thio)-4-phenyl-4*H*-1,2,4-triazol-3-yl)-1*H*-indole exhibited most effective antifungal activity with MIC value of 2 μg/mL against Candida albicans. Gao et al. [107] took advantage of indole alkaloid streptochlorin, to design the novel indole (**94**) derivative with imidazole motif. These new molecules synthesized were subjected for the antifungal activity against *Alternaria Leaf Spot* and *Rhizoctorzia solani*. The authors also disclosed the mode of action of antifungal activity via molecular docking studies. Simple, expedient and one-pot synthetic route for production of 3-(1*H*-indole-3-carbonyl)-2*H*-chromen-2-one (**95**) derivatives were developed by Umar Basha et al. [108] *in vitro* antifungal activity of novel compounds was tested against *Candida albicans*. Compound 6-chloro-3-(2-methyl-1*H*-indole-3-carbonyl)-2H-chromen-2-one exhibited good antifungal activity against *Candida albicans*. Fig. 4.2 illustrates the structures (**83–95**) of indole and its derivatives showing antifungal activity.

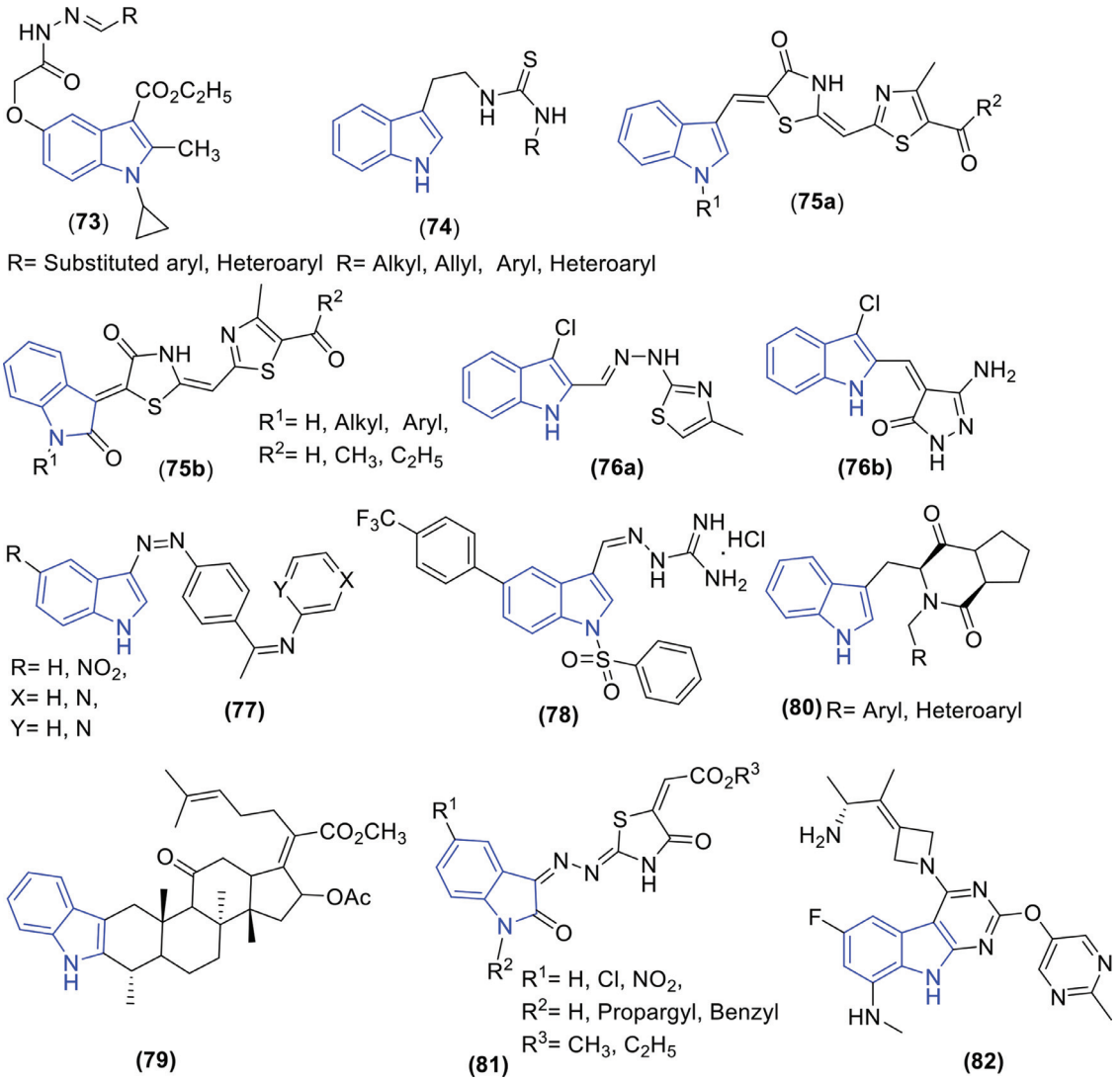

Fig. 4.1b. Structures of indole derivatives with antibacterial activity.

4.3. Anti-tubercular activity

Haj Mohammad Ebrahim Tehrani et al. [109] reported the synthesis and spectral studies of novel substituted indoles (**96**) derived from thiocarbohydrones. The newly synthesised compounds were evaluated for their antimicrobial activity against *Mycobacterium bovis*. The studies revealed that the thiadiazole motif acts as a critical pharmacophore in exhibiting antimycobacterial activity. Design, synthesis and *in vitro* antimycobacterial evaluation of indole (**97**) derived thiazolidinones was reported by Cihan-Ustundag et al. [110]. The newly synthesised compounds were evaluated for *in vitro* antitubercular activity against *Mycobacterium tuberculosis* H37Rv. Naidu et al. [111] explored the synthesis, structure determination and antimycobacterial activity of 1-(4-(benzo[d]isoxazol-3-yl)piperazin-1-yl/1,4-diazepan-1-yl)-2-(1*H*-indol-3-yl)substituted-1-one (**98**) derivatives. The novel compounds were tested for *in vitro* anti-tubercular activity against *Mycobacterium tuberculosis* H37Rv strain and two 'wild' strains Spec. 210 and Spec. 192. The synthesised derivatives displayed minimum inhibitory concentration (MIC) ranging from 6.16 to >200 μM. The design, synthesis and antimycobacterial activity of various indoleamides (**99**) were investigated by Stec and co-workers [112] in 2016. The newly synthesised compounds were evaluated for *in vitro* anti-TB activity against multidrug-resistant and extensively drug-resistant *M. tuberculosis* pathogens. Cao et al. [113] developed novel and effective anti-mycobacterial agent's *viz*. indole-2-carboxamides (**100**). The investigations disclosed that the new indoleamides possess less toxicity, low side effects and desirable ADME properties with more efficacies against both multidrug resistance and extensively drug-resistant tuberculosis. Khan et al. [114] took advantage of synchronized Knoevenagel and Michael-type reactions to synthesis a novel series of 5,5-dimethyl-11-phenyl-4b,5,5a,10,10a,11,11a,12-octahydro-10,11,12-triaza-indeno[2,1-b]fluorenes (**101**) by utilising oxindole, arylamines and acetone in presence of an organocatalyst, dibutyl amine. The structures of newly synthesised compounds were confirmed by various spectroscopic techniques and evaluated for antimycobacterial activity against *M. Tuberculosis.* From the same group, in the year 2018, [115] utilised the earlier strategy to synthesize novel 2-(1*H*-Indol-3-ylmethyl)-5,5-dimethylcyclohexane-1,3-diones (**102**). The binding affinity values against enoyl acyl carrier protein reductase of new compounds were studied via docking studies. The authors also evaluated the antimycobacterial activity of indole derivatives against *M. Tuberculosis* H37Rv. A series of new indole derived spirochromene analogues (**103**) were synthesized in acceptable yields by Dogamanti et al. [116]. These novel compounds were evaluated for *in vitro* antimycobacterial activity against *Mycobacterium tu-*

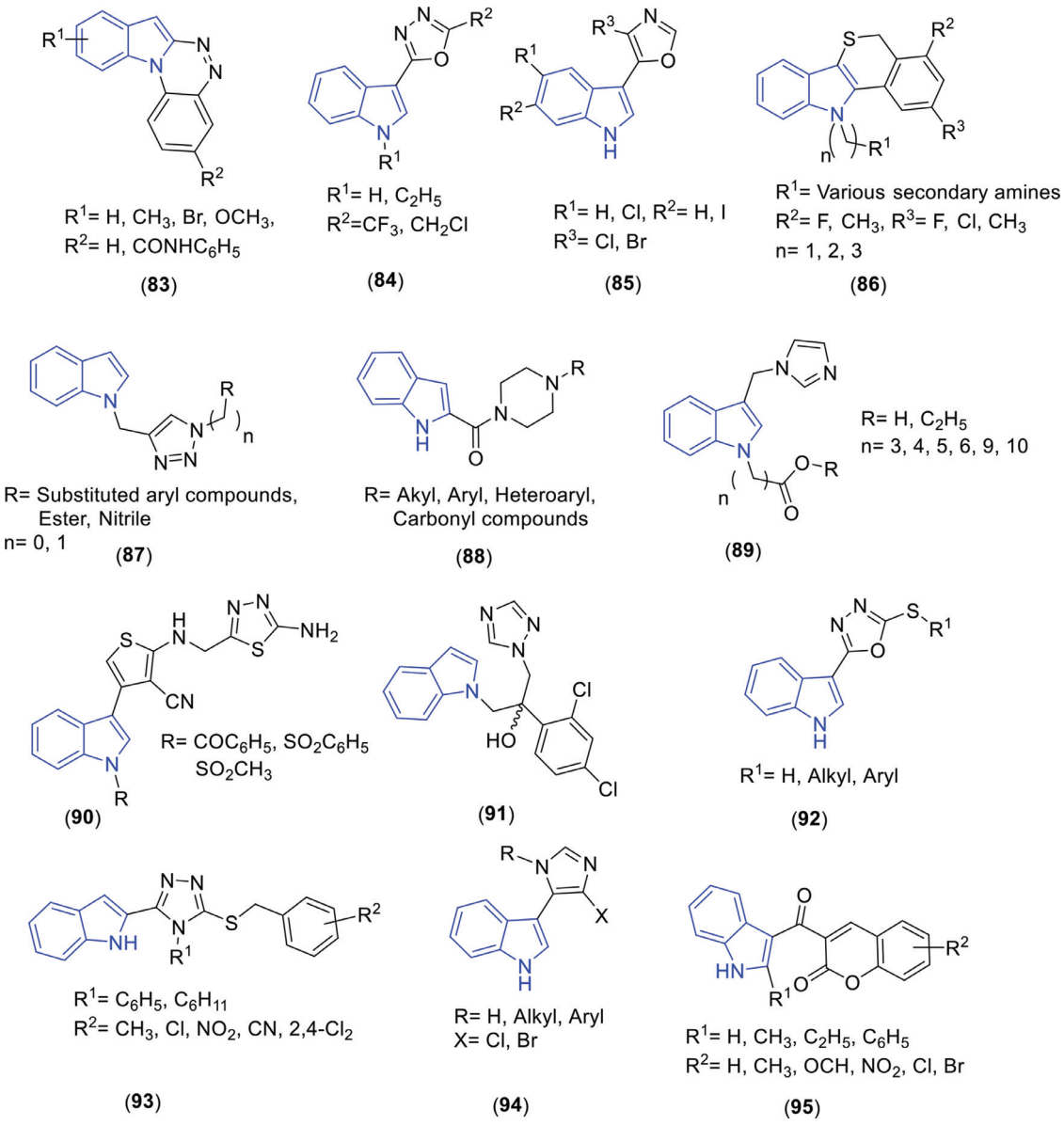

Fig. 4.2. Structures of indole derivatives with antifungal potential.

berculosis (ATCC 27294) strain. The structure-activity relationship studies revealed that the compound 7′-chloro-6′-methyl-1,2,4,9-tetrahydrospiro[carbazole-3,2′-chromene]-6-carbonitrile exhibited excellent anti-TB activity with MIC value 1.56 g/ml. Champciaux et al. [117] developed a simple and efficient method for the synthesis of indole-fused lactones (**104**). The *in vitro* anti-TB activity of these novel compounds were evaluated against *M. Tuberculosis*. The compound (*E*)-7-iodo-3-(5-methylhex-2-yn-1-ylidene)-3,4-dihydro-1*H*-[1,4]oxazepino[6,5,4-hi]indol-1-one showed good antimycobacterial activity with MIC value 0.2 g/ml.

A design and synthesis of *N*-benzylated indole (**105**) Mannich bases were developed by Muthyala et al. [118]. These novel compounds were tested for antimycobacterial activity against *Mycobacterium tuberculosis* by MABA assay method. The structure-activity studies revealed that the compound 4-((1-(3,4-dichlorobenzyl)-1*H*-indol-3-yl)methyl)morpholine exhibited excellent anti-TB activity with MIC value 6.25 g/ml. Cihan-Üstündağ et al. [119] reported the design, synthesis and anti-TB activity of indole derived spirothiazolidinones (**106**). The structures of the new compounds were established by various spectral techniques, EIMS, and microanalysis. The structure relationship studies indicate that the compounds bearing a phenyl substituted spiro ring, displayed remarkable antitubercular activity against *Mycobacterium tuberculosis* H37Rv ATCC 27294 at concentrations of 3.9 μM. The tetracyclic pyrido-carbazole (**107**) hybrids were synthesized by Schmidt et al. [120]. These novel compounds were evaluated for anti-tuberculosis activity against *Mycobacterium tuberculosis*. The anti-TB activity evaluation results showed that the compound 9-methoxyolivacine exhibited the most notable inhibitory activity against Mycobacterium tuberculosis, with MIC value 1.5 μM. The structures of indole compounds (**96-107**) showing antimycobacterial activities are depicted in Fig. 4.3.

4.4. Antiviral activity

Design, synthesis and docking studies of novel indole (**108**) derivatives were reported by Ferro et al. [121]. These new compounds were evaluated for the antiviral activity against HIV-1.

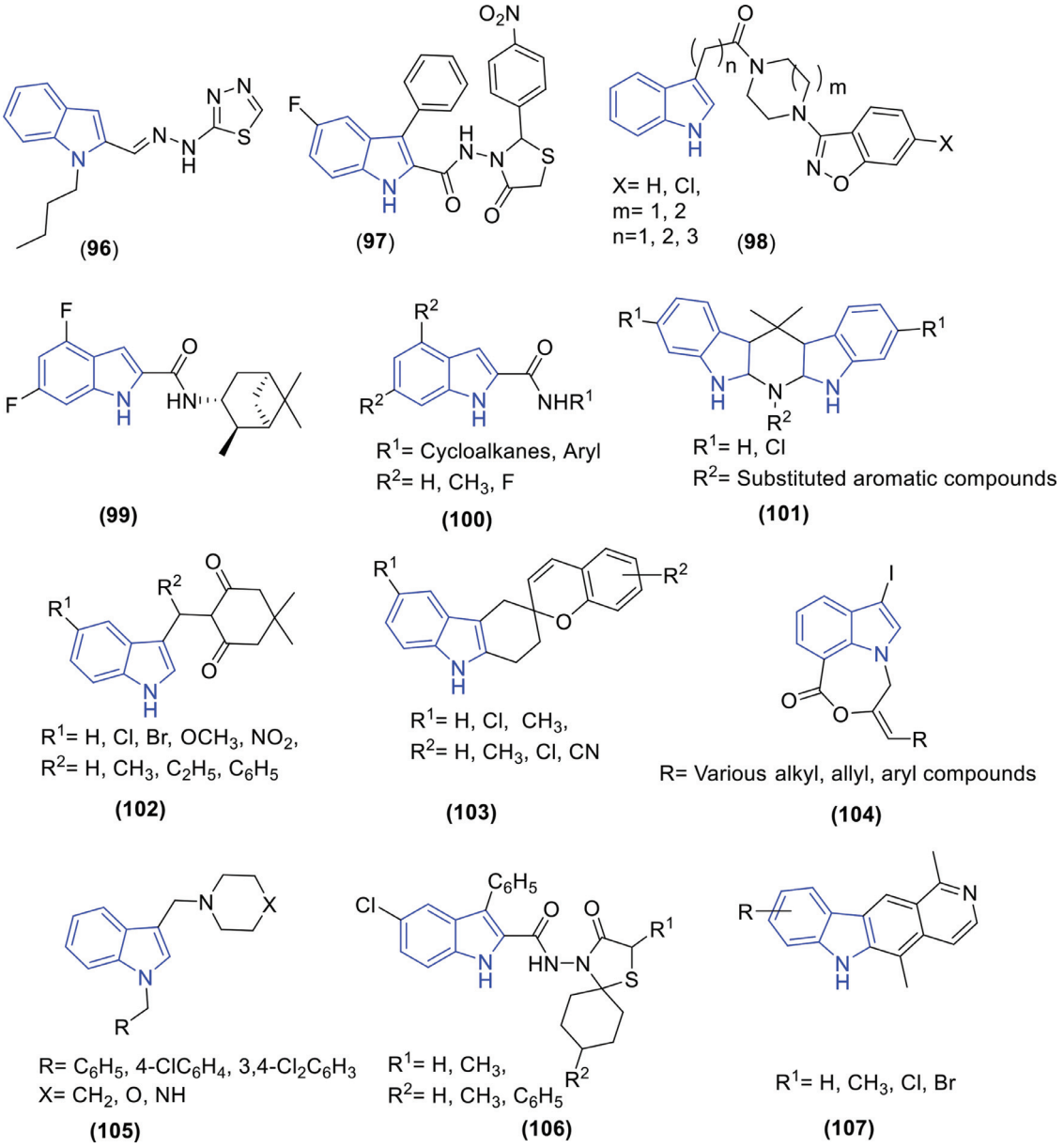

Fig. 4.3. Structures of indole (96-107) derivatives showing antimycobacterial activity.

Docking experiments indicates the bulkier substituent on the benzyl group is encouraging for the interfacing with HIV-1 integrase protein. The structure activity relationship studies indicated that ethyl (5, 7-dichloro-3-(1,1,1-trifluoro-2-hydroxypropan-2-yl)-1*H*-indol-2-yl)carbamate displayed highest efficacy towards virus infection. Jiang et al. [122] disclosed the synthesis and structure activity relationship studies of trifluromethyl-indole (**109**) derivatives. The antiviral acitvity of newly synthesised compounds were evaluated againsit WT (wild-type) HIV-1 strain. Ashok et al. [123] explored the synthesis and structure elucidation of a novel series of 1-(thiophen-2-yl)-9H-pyrido [3,4-b]indole (**110**) derivatives. The antiviral activity revealed that these scaffolds have the potential for futuristic studies. Authors also reported the physicochemical properties of aforesaid derivatives. Amongst all the synthesised derivatives, compound (4-(2-methoxyphenyl)piperazin-1-yl)(1-(thiophen-2-yl)-9H-pyrido[3,4-b]indol-3-yl) methanone exhibited significant anti-HIV activity with EC_{50} 0.53 µm and selectivity index 483. The design, synthesis and antiviral activity of novel indole-aryl-phosphate (**111**) derivatives were investigated by Doussan et al. [124]. These synthesised compounds were identified as a clinical candidate for non-nucleoside reverse transcriptase inhibitors (NNRTIs) and also proposed elements of extremely potent antiretroviral therapy (HAART) for the management of HIV-1. The compound (*E*)-methyl (2-carbamoyl-5-chloro-1*H*-indol-3-yl)(3-(2-cyanovinyl)-5-methylphenyl)phosphinate showed excellent anti-HIV activity with EC_{50} 11 nM. Chen et al. [125] explored the synthesis of anti-HIV-1 inhibitors, *N*-arylsulfonyl-3-formylindoles (**112**). Some of the synthesized compounds exhibited significant anti-HIV-1 activity. The authors also demonstrated the structure-activity relationship studies of newly synthesized indole derivatives. Amongst all the tested derivatives, the compound *N*-m-nitrophenylsulfonyl-6-methyl-3-formylindole exhibited imperative anti-HIV-1 activity, with EC_{50} value 5.02 µM, and TI value 81.69. Ravichandran et al. [126] took the advantage of combinatorial chemistry to develop a series of novel indole-7-carboxamides (**113**) as potential antiviral agents. The physicochemical properties of new indole derivatives and QSAR models were demonstrated. The antiviral activity for indoleamides

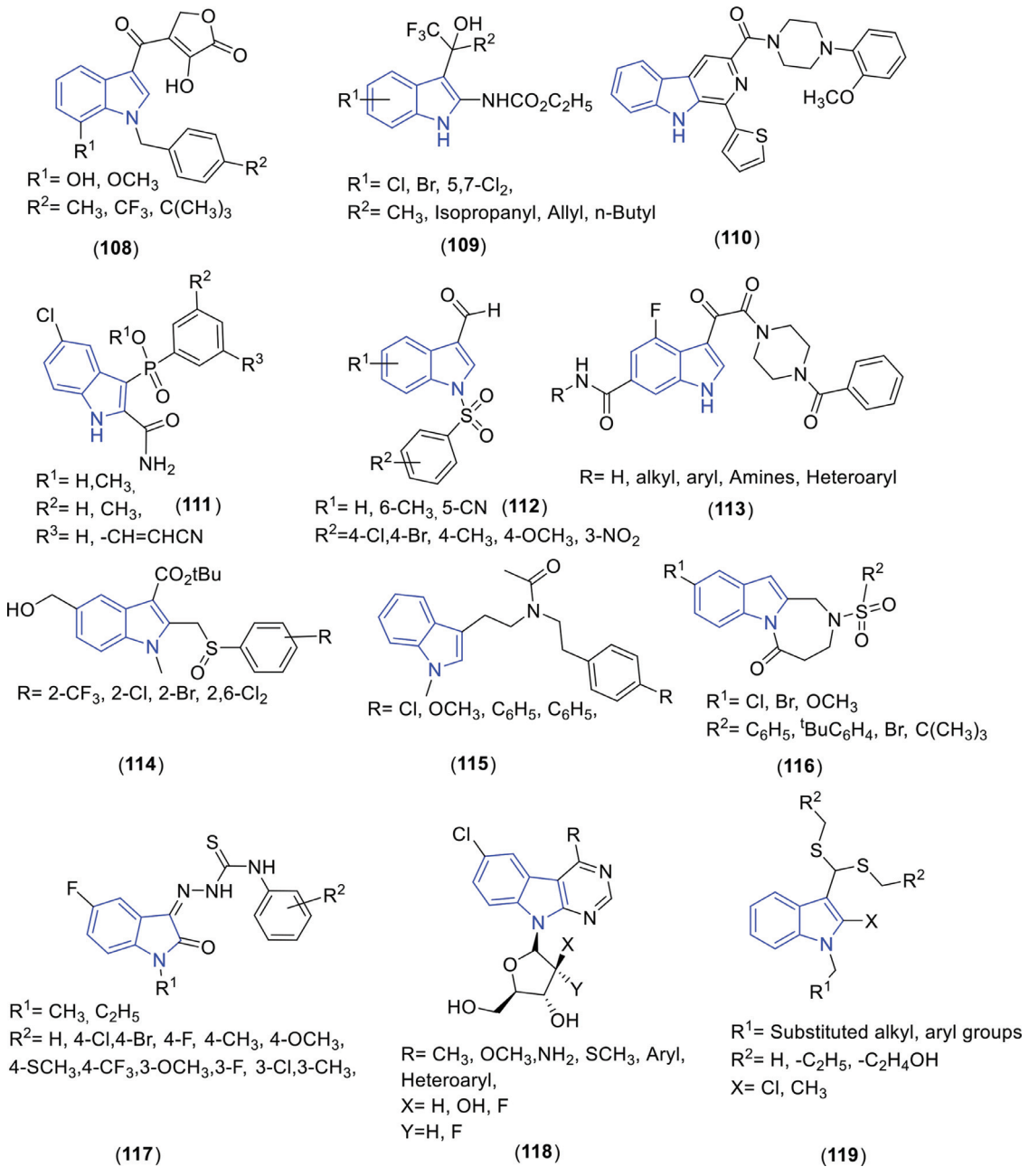

Fig. 4.4. Structures of indole and its derivatives showing antiviral activity.

revealed promising results against HIV-1. The design, synthesis and antiviral activity of novel arbidol based indole (**114**) derivatives have been disclosed by Scuotto et al. [127]. The antiviral activity of indole derivatives was evaluated against the anti-chikungunya virus (CHIKV) in Vero cell culture by a CPE reduction assay and systematic optimization of the lead compounds were also demonstrated. The compound tert-butyl-5-hydroxy-1-methyl-2-(2-trifluoromethysulfynyl)methyl)-indole-3-carboxylate exhibited ten folds enhanced anti-CHIKV inhibitory activity with EC_{50} value 6.5 ± 1 μM as compared to standard drug Arbidol. Novel non-nucleoside antiviral agents of the indole (**115**) motif have been developed by Musella et al. [128]. The antiviral activity of indole derivatives tested against the human *varicella-zoster virus* (VZV) and the structure-activity relationship study was also disclosed. The presence of *N*-acetyl group of tryptamine and a biphenyl ethyl moiety are minimum requirements for anti-VZV activity. The fused indoles (**116**) were developed and assessed for antiviral activity by Chen et al. [129]. *In vivo* and *in vitro* antiviral activities of all the synthesized compounds were evaluated against the *Tobacco mosaic virus*. The structure-activity relationship study indicates that the compounds substituted with *N*-Tosyl and *N*-Sulfonyl groups are exhibited excellent antiviral activity. Sevinçli et al. [130] reported the synthesis and antiviral activity of novel 5-Fluro indole-substituted-thiosemicarbzones (**117**). All the synthesised compounds were tested for antiviral activity against HSV-1 (KOS), HSV-2 (G) HSV-1 TK- KOS ACVr and VV in HEL cell cultures. The compound (Z)-2-(1-ethyl-5-fluoro-2-oxoindolin-3-ylidene)-N-(4-(trifluoromethyl)phenyl)hydrazinecarbothioamide possesses excellent inhibitory activity against tested viral organisms.

Importance of modified nucleosides as antiviral agents were disclosed by Knoc et al. [131] via sugar modified indolo-pyrimido nucleosides (**118**). All the synthesised compounds were tested for

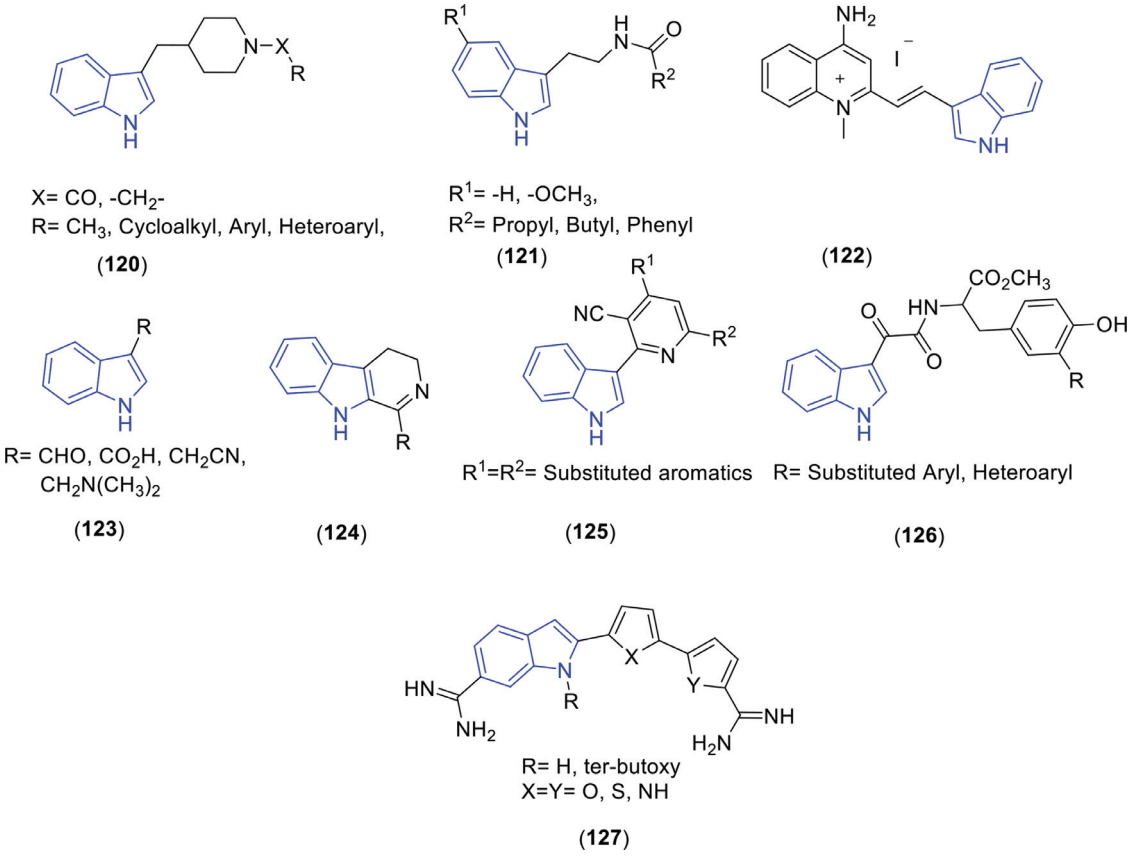

Fig. 4.5. Structures of indole and its derivatives exhibiting antimalarial activity.

antiviral activity against Hepatitis C (HCV) and all these compounds displayed interesting anti-HCV activities with an IC_{50} value in the range between 1.6–20 μM. Wei et al. [132] reported the synthesis and anti-plant viral activity of novel indole (**119**) derivatives attached dithioacetal motif. All the synthesised compounds evaluated antiviral activity with tobacco mosaic virus (TMV). In particular, the compound 2,2′-(((2-chloro-1-(2,4-dichlorobenzyl)-1H-indol-3-yl)methylene)bis(sulfanediyl))diethanol showed anti-TMV curative (55.1%), protective (57.2%) and inactivating activity (80.3%) and EC_{50} value for inactivating activity was 88.5 μg/mL. The structures of indole and its derivatives (**108-119**) screened for antiviral activities are depicted in Fig. 4.4.

4.5. Antimalarial activity

Santos et al. [133] took the advantage of high-throughput screening to develop a series of novel indole-linked-piperidins (**120**) and evaluated them for their anti-parasitic activity. All the synthesised compounds were evaluated for antimalarial activity against *Plasmodium falciparum* and the authors also demonstrated the physicochemical properties of the novel indole derivatives. The structure-activity relationship study indicated that the compound (4-((1*H*-indol-3-yl)methyl)piperidin-1-yl)(pyridin-3-yl)methanone exhibited excellent antimalarial activity with EC_{50} value 3 nM. Design, synthesis and antimalarial activity of novel indole (**121**) derivatives were explored by Schuck et al. [134]. These melatonin analogues were tested for their antimalarial activity against P. falciparum. Amongst, all the synthesised melatonin derivatives, only the compounds *N*-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)benzamide, *N*-(2-(5-methoxy-1H-indol-3-yl)ethyl)hexanamide, and *N*-(2-(5-methoxy-1H-indol-3-yl)ethyl)butyramide were capable of inhibiting the P. falciparum growth IC_{50} values 2.93, 19.10 and 19.17 M, respectively. Teguh et al. [135] demonstrated the design and synthesis of novel indole derivatives linked with quinolines. The newly developed compounds were tested for (**122**) antimalarial activity against *Plasmodium falciparum*. The indole-quinoline salt (**122**) exhibited the inhibitory concentration for 50% population of *Plasmodium falciparum* with 0.1-0.4 M, 0.2-4 M and 1-4 M at asexual stages, gametocyte stage (I-III), and gametocyte stage (IV-V), respectively. Synthesis of various indole (**123**) derivatives have been reported by Zhao et al. [136] and tested for antiviral activity against a broad spectrum of influenza A viruses. Among these derivatives, 3-indoloacetonitrile exhibited insightful viral inhibition against a broad spectrum of influenza A viruses, as examined in A549 cells.

Nayak et al. [137] described the synthesis and antimalarial activity of novelb-carbolines (**124**) via diversity-oriented synthesis. All these novel compounds tested for antimalarial activity and 1-aryltetrahydro-β-carbolines displayed significant anti-plasmodial activity against both the artemisinin-sensitive and artemisinin-resistant strain of *Plasmodium falciparum*. Elshemy et al. [138] took the advantage of a fragment-based approach to produce novel indole-pyridyl (**125**) analogues for malarial infection management. The newly developed compounds were assessed for antimalarial activity against chloroquine-sensitive (D6) and chloroquine-resistant (W2) strains of *Plasmodium falciparum*. Numerous derivatives revealed antimalarial action with IC_{50} values in the range of 1.47–9.23 μM, and 1.16–7.66 μM, for D6 and W2 strains, respectively. Stefani and co-workers [139] developed a convenient and proficient synthesis of indole-3-glyoxyl (**126**) derivatives for antimalarial drug discovery. All the synthesized compounds were evaluated for antimalarial activity against *Plasmodium falciparum*. The design, synthesis and antimalarial activity of indole and benzimidazole derivatives have been reported by Farahat et al. [140].

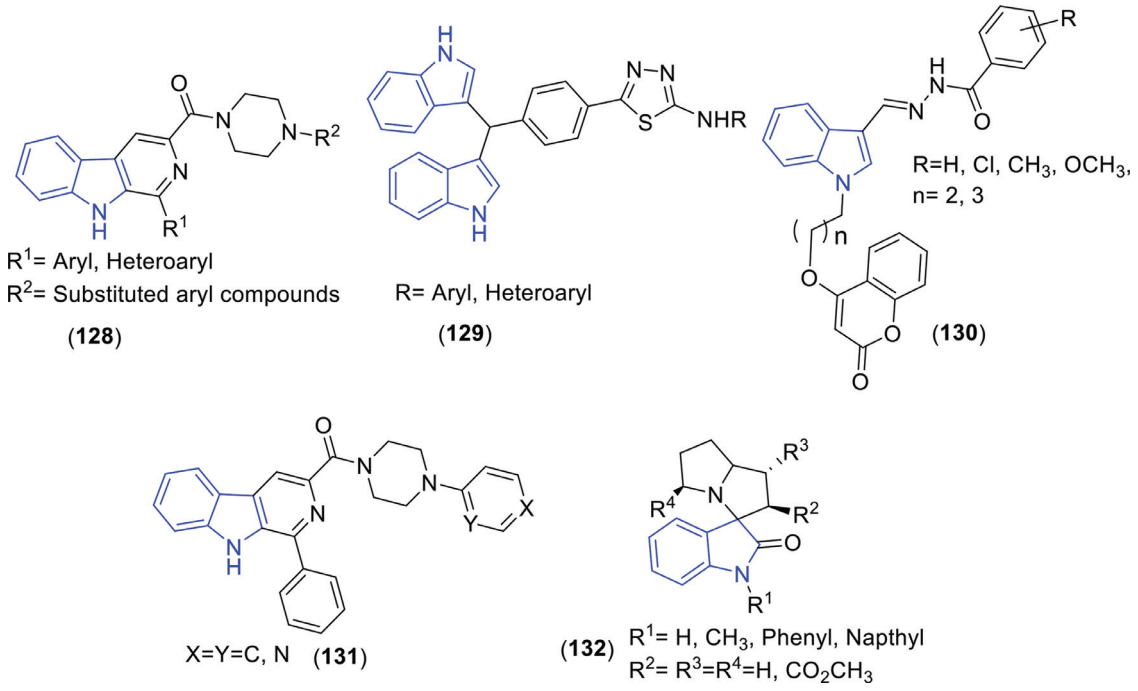

Fig. 4.6. Structures of indole and its derivatives with Anti-leishmanial activity.

Antimalarial activity of novel compounds evaluated against the tropical parasites causing African sleeping sickness and malaria. The SAR studies revealed that the benzimidazole equivalents were generally less active while their diamidino-indole derivatives also exhibited admirable *in vitro* antimalarial activity. Fig. 4.5 indicates the structures of indole derivatives (**120–127**) exhibited antimalarial activity.

4.6. Anti-leishmanial activity

Ashok et al. [141] explored the design, synthesis and antiparasitic activity of a novel 3-substituted-1-(substituted-2-yl)-9*H*-pyrido[3,4-b]indole (**128**) derivatives. All the synthesised indole motifs were evaluated for *in vitro* anti-leishmanial activity against both *Leishmania donovani* and *Leishmania Amazonensis*. These accounted derivatives, displayed potent activity 15.6 to 3.1 μM against *L. donovani* promastigotes than standard drugs miltefosine (15.7 μM) and pentamidine (32.7 μM) with superior selectivity manifestation. An inventive series of bisindole containing thiadiazoles (**129**) were reported by Taha et al. [142]. All the structures of synthesised compounds were confirmed by spectral techniques and tested for anti-leishmanial activity. The IC_{50} values were demonstrated and all derivatives exhibited more effectiveness than the standard drug. Singh and his research group [143] accounted for new, efficient and simple *N*-substituted indole (**130**) scaffolds for the treatment of leishmaniasis infections. The structure of all the newly synthesised compounds was characterised by spectral methods viz. FT-IR, NMR and Mass spectrometry. The anti-leishmanial potential was evaluated for these compounds against promastigotes of *Leishmania donovani*. The authors also disclosed the understandings of structural features of these derivatives for the anti-infection activity via *in silico* binding interactions with nitric oxide synthase. The compounds, (*E*)-4-chloro-N'-((1-(2-((2-oxo-2H-chromen-4-yl)oxy)propyl)-1*H*-indol-3-yl)methylene)benzohydrazide and (*E*)-4-methoxy-N'-((1-(2-((2-oxo-2H-chromen-4-yl)oxy)propyl)-1*H*-indol-3-yl)methylene)benzohydrazide showed maximum inhibitory activity with IC_{50} values 21.5 and 24.2 M in the antileishmanial assay. Ashok et al. [144] took the advantage of the molecular hybridization approach for the design and synthesis of novel piperazinyl-β-carboline-3-carboxamides (**131**). The anti-leishmanial activities of all the compounds were evaluated against *Leishmania donovani* and *Leishmania infantum*. The demonstrations of structure-activity relationship studies were also disclosed and suggested that para substitution of methoxy group, para and meta substitution of chloro groups and benzyl substitutes essential for significant anti-leishmanial against *L. donovani*. The synthesis and biological potential of new spirooxindole derivatives have been reported by Saha et al. [145]. The anti-leishmanial activity of all derivatives evaluated against Leishmania donovani and the drug-protein interaction and molecular docking studies. The structures of indole and its derivatives (**128-132**) exhibiting anti-leishmanial activities are shown in Fig. 4.6.

5. Conclusion

Indole and its derivatives are extremely notable heterocyclic compounds in the field of drug design and development. There has been increasing interest in the management of indole scaffolds as drug molecules against pathogens and various kinds of other disorders. Therefore, in this review, we have presented the prominent literature results pertaining to the indole hybrids, *viz.* from natural sources, marketed drugs, clinical candidates, synthetic derivatives; as antibacterial, antifungal, anti-TB, antiviral, antimalarial, and anti-leishmanial agents. we also briefly discussed the structure-activity relationships study of indole appended scaffolds responsible for their biological potential. We emphasize that the data summarized herein for the anti-infective potential of indole and associated scaffolds will aid in the design and development of novel leads and clinical candidates against various infectious diseases.

Dedication

The authors would like to dedicate the present review article to Prof. M.G. Purohit of Gulbarga University, Kalaburagi-585 106. In the memory of his long and productive career in Organic

and Medicinal Chemistry, he produced many doctoral students and published more than 100 research articles in national and international peer-reviewed journals.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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