Review Article

Thai Journal of Pharmaceutical Sciences

Recent advancements on biological activity of indole and their derivatives: A review

Punet Kumar[1], Md Iftekhar Ahmad[2], Sangam Singh[3], Mohammad Rizki Fadhil Pratama[4], Arun K. Mishra[1]

[1]Department of Pharmaceutical Chemistry, SPS, IFTM University, Moradabad, Uttar Pradesh, India, [2]Department of Pharmaceutics, Shri Gopichand College of Pharmacy, Baghpat, Uttar Pradesh, India, [3]Department of Pharmaceutical Chemistry, Oxford College of Pharmacy, Hapur, Uttar Pradesh, India, [4]Department of Pharmacy, Universitas Muhammadiyah Palangkaraya, Palangka Raya, Central Kalimantan, Indonesia

Corresponding Author:
Punet Kumar, Department of Pharmaceutical Chemistry, SPS, IFTM University, Moradabad, Uttar Pradesh, India
E-mail: punetkumar987@gmail.com

Received: January 27, 2021
Accepted: April 14, 2021
Published: May 27, 2022

ABSTRACT

Indole, a versatile outstanding heterocyclic compound, engaged in numerous pharmacological properties due to their multiple biochemical processes. The remarkable indole moiety resembles with numerous protein structures. The fascinating molecular framework of indole makes its suitable for drug development. Indole derivatives mimic the peptides structure and bind reversibly to several enzymes, which contribute enormous opportunities to develop novel drugs with distinct mechanism of action. The presence of nitrogen-based heterocycles in several compounds has been investigated enormously as the core structures comprise several biologically appropriate molecules found active in different diseases. The investigations conducted worldwide have shown outstanding impact for scientists, working on indole derivatives to formulate commercially approved indole derivatives. Numerous drug molecules having indole moiety are under investigation to control disease. The explicit characteristics with the rationale and foundation of the research topic are to establish and assist the formulator. In this review, we summarized various studies reported on anticancer, antifungal, antiplatelet, antidiabetics, antimalarial, antimicrobial, antidiabetic, antiviral, antifungal, anticonvulsant, antifertility, anti-inflammatory, antidepressant, antioxidant, antiestrogenic, and antitubercular of past several decades. This review article would provide a platform for researchers in tactical outline of novel indole derivatives having numerous encouraging biological activities with decreased toxicity and side effects.

Keywords: Anticancer, Anticonvulsant, Antimicrobial, Antitubercular, Indole derivatives

INTRODUCTION

The most remarkable scaffold which arises in several in alkaloids, peptides, and various synthetic compounds is from those which have indole ring in their nucleus. The heterocyclic property of any phytochemicals nucleus provides a broad scope in pharmaceutical applications such as pharmacological activity and synthetic chemistry. Indole and its derivatives have been utilized as an absolute platform in heterocyclic chemistry containing a nitrogen atom.[1] Indole having a formula of C_8H_7N comprised a bicyclic structure containing benzene merged with pyrrole moiety with derivatives possesses various biological applications in medicinal chemistry.[2] The indole was synthesized by reducing oxindole which has suggested by Adolf Von Baeyer in 1866.[3] In indole, 10 π electrons resonate in a heteroaromatic planar molecule. The delocalization of a lone pair of a nitrogen atom in the π electron system which resonates in an indole ring makes indole a weak base. Consequently, nitrogen's lone pair of an electron does not undergo protonation but attain protonated at C-3 carbon meta position. This place allows the withholding of aromaticity and provides thermodynamic stability. Because of this, indole takes part in numerous chemical synthesis, that is, cycloaddition, carbon lithiation, oxidation, electrophilic substitution, and organometallic indole anion complexes, etc.[4] The indole exists as solid at 23–25°C temperature. Indole exists naturally in the feces of human beings which gives it a peculiar smell. Although at lower concentrations, it has a flowery smell and is the main component of flower scents, coal tar, and perfumes. Besides

this, indole is associated with numerous biological reactions in humans. Indole modulates the physiology of bacteria, which is associated with the stability of plasmid, formation of spore, virulence, biofilm formation, and drug resistance.[5]

Indole is a heteroatomic planar lead molecule. The history of indole use in the chemical industry goes back to dates to the mid-19th century on a wide-ranging investigation on indigo dyes which guides in preparation of indole by zinc distillation of oxindole in1866.[6,7] Hence, in this review, we focused on the various synthetic routes of indole-based scaffold and their pharmacological activity. This moiety is a key bioactive molecule which is a vital part of the pharmacological activity of natural products such as plant growth hormone, 5-hydroxytryptamine (serotonin), vincristine, vinblastine, indole-3-acetic acid (IAA) (antibacterial), and indole alkaloids such as tryptophan (essential amino acid), reserpine, alstonine, and ergotamine. Melatonin is generally used as the neurotransmitter, antipsychotic, migraine, hypertension, cancer chemotherapy, and lowering blood pressure.[3,8-12]

Indole-3-carbinol along with 3,3-diindolylmethane's biological assessment is under-investigated because of their antioxidant, anticancer as well as anti-atherogenic activity.[13-16] Besides, some of the important pharmaceutical lead-containing indole rings are roxindole, indalpine, ondansetron, tadalafil, and fluvastatin, perindopril, reserpine, and pindolol introduced by Novartis in an application intended for hypertension management since 1982.[17] Heart failure and hypertension are treated by indapamide marketed by Servier.[18] The US FDA approved delavirdine and ateviridine against HIV-1.[19] Indomethacin containing the most important promising lead drug molecule for anti-inflammatory and analgesic effects.[20] Besides this, numerous marketed indole derivatives such as apaziquone (anticancer), abridol (anticancer), zafirlukast (antihistaminic), indolmycin (antibiotic), and strychnine are shown in Table 1.[21-25]

In medicinal science, indole-based therapeutic drugs encompass valuable pharmacological activities such as antimalarial, antimicrobial, antiviral, anti-leishmanial, antifungal, antioxidant, anti- human immunodeficiency virus (HIV), and antitubercular.[26-33] Indole is a key structural molecule that elucidates as an affluent scaffold. Evans *et al*. suggested and explained scaffolds of indole which are accomplished by performing as ligand meant for receptors diversity.[33-36] Indole and their derivatives exhibit the special attribute of imitating the structure of proteins and inversely binding with enzymes that offer great scope to discover novel drugs with a propagation mode of action. Various drugs available in the market containing indole have been reported as the "Best Retail" by the USA.[37-41] In this review, we tried to summarize recent advances in the moiety with diverse biological and therapeutic functionality in the health-care domain. We outline to gather the details of indole and their derivatives synthetic form, *in vitro*, *in silico,* and *in vivo* evaluation. It had been completely done on diverse indole molecules by collecting the different research articles survey.

Synthesis of Indole Ring

Various methods have been reported in the literature regarding the conventional synthesis of the indole nucleus. It encompasses indole synthesis (Fischer indole synthesis, Kanematsu indole synthesis, Mori indole synthesis, Buchwald indole synthesis, Madelung indole synthesis, Sundberg indole synthesis, Van Leusen indole synthesis, Nenitzescu indole synthesis, and Hemetsberger indole synthesis).[42-50]

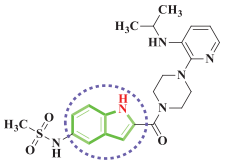
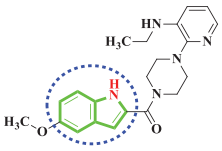
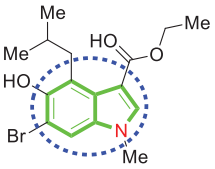
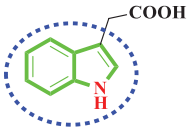
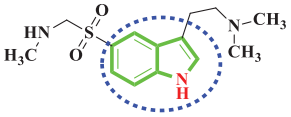
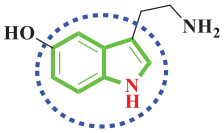
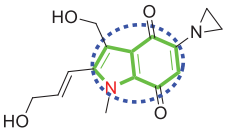
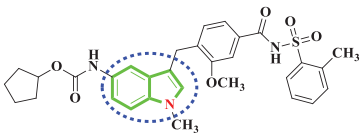
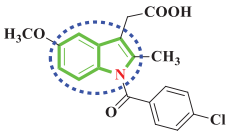
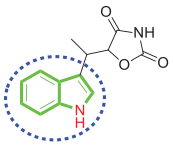
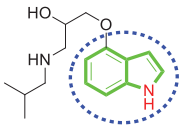
THE PHARMACOLOGICAL ACTIVITY INVOLVED WITH INDOLE COMPOUNDS

Due to the wide distribution of indole derivatives in nature, it has got acceptability among the organic and medicinal industries. Numerous drug molecules having indole moiety are under investigation to control disease conditions such as bacterial, malaria, fungal, viral, tubercular, and HIV infections.

Antimicrobial Activity

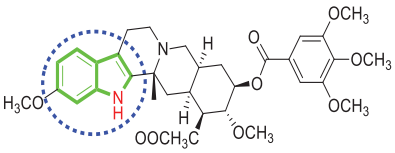
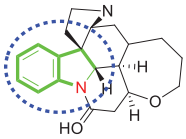
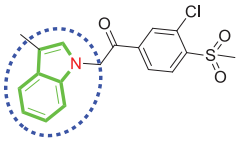
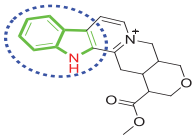
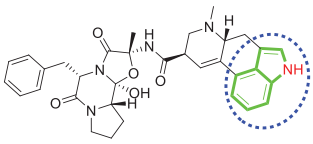
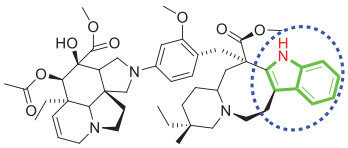
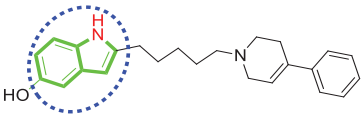
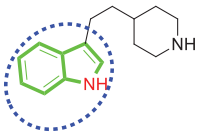
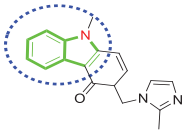
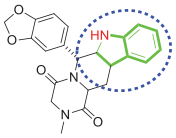
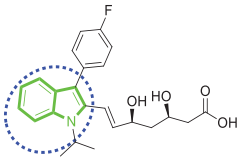
The rapid development of drug resistance has emerged as a serious challenge since the entry of the first agent into the clinical market in the 1940s. To avoid microbial resistance, there is a need to preserve the current antimicrobials through proper use besides developing new lead molecules. The World Health Organization in its latest survey report has confirmed that more than 0.5 million people have developed antibiotics resistance across 22 countries.[51] To control the antibiotics resistance problem, new indole derivatives with a different mechanism of action must be evolved. Nemours derivatives of indole are identified and study as an antimicrobial agent. Sanna *et al*., 2018, synthesized hybrids of indole-thiourea and treated it on a group of Gram-positive and Gram-negative microbes. The synthesized compound **1** (minimum inhibitory concentration <12.5 μg/ml) has reported higher potency compared to reference drug ciprofloxacin (minimum inhibitory concentration <1.0 μg/ml).[52] Since thiazolidine has been reported for its antimicrobial activity, therefore, the scientists tried to combine thiazolidine moiety with other indole derivatives to form a potent antimicrobial agent.[53] Oxindole thiazolidine conjugates were synthesized by Abo-Ashour *et al*., 2018, and were treated against *C. albicans, S. aureus, E. coli, A. fumigatus, M. tuberculosis, and P. aeruginosa.* The compound **2** (minimum inhibitory concentration < 0.98 μg/ml) has been reported very effective in potency as compared to ciprofloxacin (minimum inhibitory concentration <3.90 μg/ml) and amphotericin B (MIC <1.95 μg/ml), reciprocally.[54] In recent times, many indole derivatives with heterocyclic were synthesized and evaluated and examined for antimicrobial properties. The newly synthesized compounds containing thiophene and imidazole ring enhanced the antimicrobial properties. The compound **3** (minimum inhibitory concentration < 8 μg/ml) having demonstrated high antibacterial activity whereas compound **4** (minimum inhibitory concentration< 6 μg/ml) displayed higher antifungal activity.[55] Gani *et al*., 2017, synthesized and evaluated 5-hydroxy indole analogs and treated on *A. niger, B. cirroflagellosus,* and *C. albicans* for their antimicrobial properties. The compound **5** shows a higher potency (zone inhibition = 28 mm) compared to griseofulvin (zone inhibition = 30 mm).[56] Mane *et al*., 2017, synthesized and evaluated numerous 5-substituted indole-2-carboxamide derivatives treated against *A. fumigatus, C. albicans, C. neoformans, C. parapsilosis,* and *E. coli* for antioxidant and antimicrobial activity. The compound **6** with MIC<6.25 μg/ml revealed higher microbial

Table 1: Bioactive molecule containing the indole framework

Name	Chemical Structure	Indication	References
Delavirdine		Antiviral	[19]
Ateviridine		Antiviral	[19]
Abridol		Antiviral	[22]
Indole-3-Acidic acid		Antibacterial	[29]
Sumatriptan		Antimigrain	[10]
Serotonin		Antipsychotric	[11]
Apaziquone		Anticancer	[21]
Zafirlukast		Antihistaminic	[23]
Indomethacin		Anti-inflammatory	[20]
Indolmycin		Antibiotic	[24]
Pindolol		Antihypertensive	[17]

(Contd...)

Table 1: *(Continued)*

Name	Chemical Structure	Indication	References
Reserpine		Antihypertensive	[9]
Strychnine		Antidot	[25]
Indapamide		Antihypertensive	[18]
Alstonine		Antipsychotic	[2]
Ergotamine		Migraine and uterine muscle Contraction	[10]
Vincristine		Anticancer	[2]
Roxindole ((EMD-49,980)		Schizophrenia	[2]
Indalpine		Antidepressant	[2]
Ondansetron		Anti-nausea and vomiting	[2]
Tadalafil		To improve erectile dysfunction	[2]
Fluvastatin		Anti-hyperlipidemia	[2]

potency as equated to reference drug gentamicin MIC<3.0 μg/ml.[57] The pyrazole and imidazole expressed maximum antimicrobial properties because of nitrogen atom presence in their nucleus which functions by restraining DNA synthesis.[58-60] The numerous indole-pyrazole by-products synthesized and investigated for antimicrobial activity by Quazi *et al*., 2017. The compound **7** (zone of inhibition< 0.5 cm) showed higher potency against Gram-positive bacteria.[61] Rajaraman *et al*., 2017, synthesized and performed molecular docking studies of numerous indole derivatives for antimicrobial activity. The compound **8** (minimum inhibitory concentration < 12.5 μg/ml) showed considerable stability bond parameter reactivity due to the existence of negative charges on nitrogen and oxygen atom as compared to standard drug methicillin (minimum inhibitory concentration < 6.25 μg/ml).[62] Yadav *et al*., 2016, synthesized and evaluated 1,2,3,5-substituted indole derivatives for antimicrobial activity and treated against *E. coli, P. aeruginosa, S. aureus,* and *S. pyogenes*. The compound **9** (minimum inhibitory concentration < 37.5 μg/ml) revealed higher potency as equated reference drug gentamicin.[63] In another study, *bis*-indole derivatives were prepared and treated on *E. coli, P. aeruginosa, and K. pneumoniae* by Choppara *et al*. in 2015. The compound **10** (zone of inhibition <24 mm) showed higher potency as equated to reference drug ciprofloxacin (zone of inhibition <27 mm).[64] Gali and their colleagues, 2015, synthesized and investigated the thiazolyl coumarins substituted indole derivatives and treated on *E. coli and B. subtilis*. The compound **11** (zone of inhibition < 18 mm) initiates higher potency as equated to reference drug streptomycin (zone of inhibition < 30 mm).[65] Hydrazone derivatives are widely present in several biological moieties and display innumerable pharmacological actions like anticonvulsant, antiviral, antibacterial, anti-tubercular, and anticancer action.[66,67] Shirizadeeh *et al*., 2011, synthesized and investigated many indole-hydrazone derivatives to combat multidrug-resistant bacteria problems. The compound **12** (MIC < 25 μg/ml) showed higher potent as compared to reference drug fluconazole (MIC < 0.78 μg/ml) and ciprofloxacin (MIC < 0.19 μg/ml).[68] Nassar *et al*., 2010, synthesized and evaluated pyridine, pyrimidine, and pyrazoline indole-substituted derivatives for antibacterial activity against *A. niger, C. albicans, E. coli, P. aeruginosa, and S. aureus*. Compound **13** (zone of inhibition < 34 mm) exhibits higher antimicrobial potency as compared to ciprofloxacin (zone of inhibition < 44 mm) and nystatin (zone of inhibition < 44 mm).[69] A new series of indole derivatives (bisindolyl-substituted cycloalkane indoles) synthesized and evaluated against MRSA (methicillin resistance *S. aureus*) and *S. aureus* for antibacterial activity by El-Sayed and colleagues, 2015. The new active derivative **14** was containing cyclohexane indole moiety when evaluated against *S. aureus* and MRSA (methicillin resistance *S. aureus*).[70] Choppara, *et al.,* 2019, synthesized two classes of new analogs indole and selected for their antimicrobial and antitumor activities. The synthesized compound **15** has shown higher potency.[71] The numerous indole derivatives were prepared and evaluated for antibacterial activity by Shi *et al*., 2015. Ultrasound irradiation was used to synthesize thirteen novel indole derivatives by using *2-mercapto-5-substituted-1,3,4-oxadiazoles* and *4-amino-5-(1H-indol-3-yl)-4H-[1,2,4] trizole-3thiol* out of which two compounds 16 and 17 exhibited exceptional anti-microbial activity against *E. coli* and *S. aureus*.[72] The indole nucleus-based antimicrobial compound structures (1-17) are mentioned in Figure 1.

Antitubercular Activity

Abo-Ashour *et al*., 2018, prepared and investigated numerous oxindole-thiazolidine conjugates treated on bacterial strain (RCMB 010126) of *M. tuberculosis*. The synthesized compound **18** (minimum inhibitory concentration of 0.39 μg/ml) has been found equally potent against reference drug isoniazid, which has shown its minimum inhibitory concentration at 0.78 μg/ml.[54] Trott *et al.*, 2010, prepared and investigated numerous indole derivatives and treated on bacterial strain (MTCC 300), which was further subjected to docking study using AutoDock Vina software (Los Angeles, USA). The compound **19** has shown MIC of 40 μg/ml, which is equivalently effective equated to reference drug isoniazid (MIC = 10 μg/ml). The compound 19 has shown good binding interaction with target protein.[73,74] Based on reported literature, piperazine is also good antitubercular agents.[75,76] Naidu *et al*.,2016, synthesized and investigated numerous indole-piperazine analogs and treated on *Mycobacterium tuberculosis* (H_{37}Rv). The compound 20 has shown the MIC of 6.16 μM which is an appropriately robust antitubercular agent equated to reference drug isonicotinic acid hydrazide (MIC= 91.14 μM).[77] In another study, the numerous indole-carboxamide derivatives were synthesized by Stec *et al*., 2016. The compound was investigated by targeting at $MmpL_3$ protein and investigated for antitubercular activity through *in vitro* and *in vivo* study. The compound **21** (MIC= 0.012 μM) has shown tremendous potency against multidrug-resistant and extensively drug-resistant strains of *M. tuberculosis*.[34] The indole-based 1,3,4-oxadiazole derivatives and pyridine have been reported for antitubercular activity. The evaluation of antitubercular activity on microbial strain *M. tuberculosis* (H_{37}, Ra, and *M. bovis*) was performed by *in vitro* studies. The compound **22** (MIC= 0.094 to 5.17 μg/ml) acknowledged for better activity as equated to reference drug isoniazid (MIC ranging 0.037 μg/ml) and rifampicin (MIC ranging 0.017 μg/ml). The compound **23** revealed higher potency.[78,79] Novel 3-alkylated indole derivatives were synthesized by utilizing CuO (heterogeneous catalyst) by Khan *et al.,* 2016. The compound **24** having MIC of 15 μg/ml revealed remarkable antitubercular activity on bacterial strain (MTCC 300) as compared to reference drug isoniazid (MIC = 10 μg/ml).[80] Ustundag and his colleagues, 2016, prepared and investigated indole-based hydrazide-hydrazone, 4-thiazplidinones treated against tubercular strain (H_{37} Rv). The compound **25** (minimum inhibitory concentration ranging from 6.25 to 25 μg/ml) showed remarkable antitubercular activity as equated to reference drug rifampicin (minimum inhibitory concentration of 25 μg/ml).[81] Numerous Schiff base indole derivatives synthesized and investigated using a microtiter plate on Gram-positive and Gram-negative bacterial stain by Tehrania *et al*., 2014. The compound **26** having MIC of 3.91 μg/ml shown higher potency as equated to reference drug ethambutol (MIC of 0.75 μg/ml).[82] The indole derivatives based antitubercular active compound structure **(18-26)** are mentioned in Figure 2.

Antimalarial Activity

Yadav *et al*., 2016, designed and investigated numerous indole derivatives and treated *P. falciparum* for antimalarial activity. The

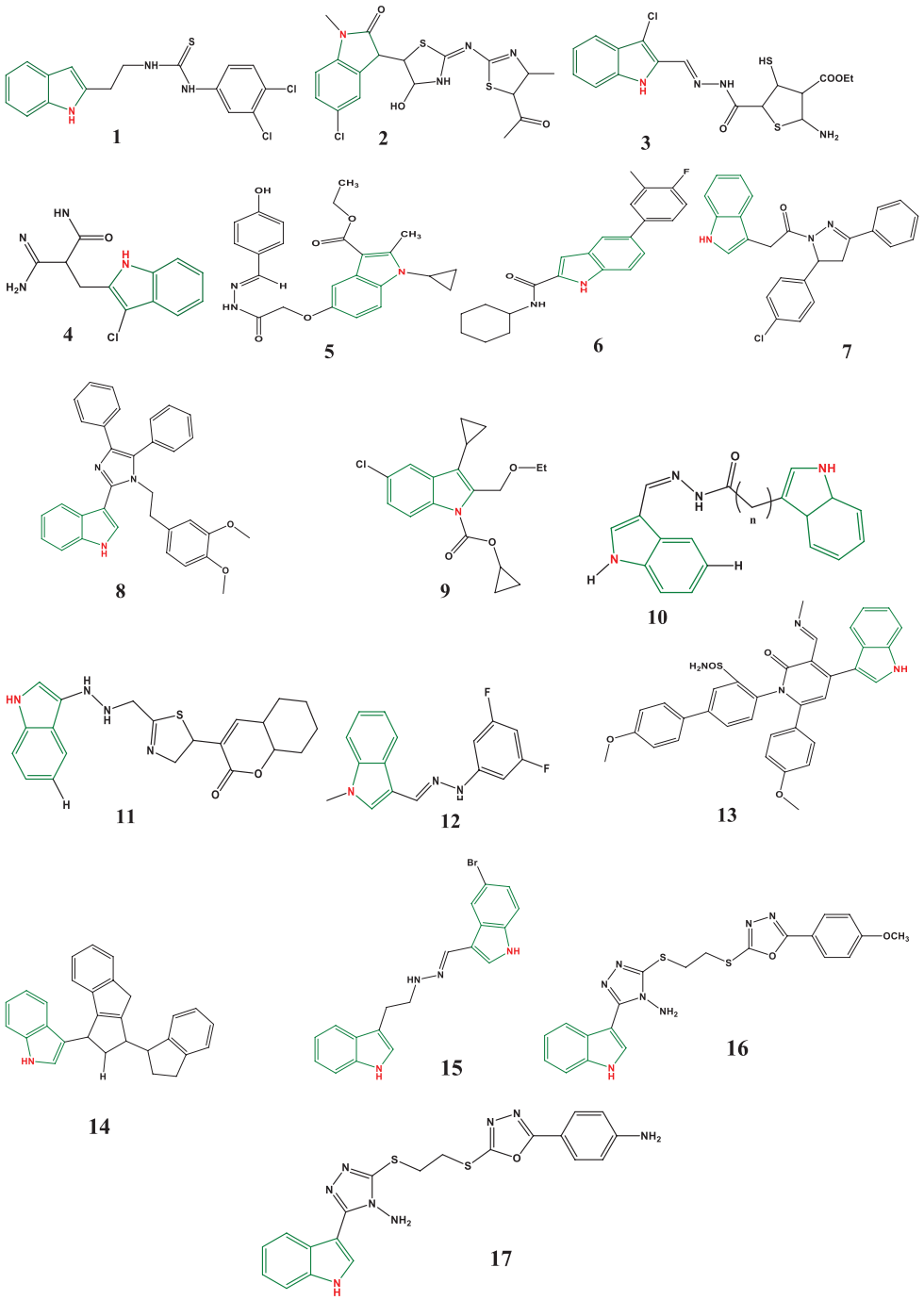


Figure 1: Antimicrobial activity of indole derivatives

compound **27** exhibited higher potency with MIC restricted to 0.70 µg/ml as compared to reference drug quinine (minimum inhibitory concentration of 0.270 µg/ml) and chloroquine (minimum inhibitory concentration of 0.02 µg/ml).[63] Schuck *et al.*, 2014, designed and investigated 1H-indole and melatonin derivatives treated against *P. falciparum* which revealed antimalarial activity. The synthesized compound **28** has shown maximum potency (EC_{50} ~ 3 µM, cLogP = 2.42 and MW = 305) for malaria parasites without showing any resistance compared to reference drug-like chloroquine, artesunate, atovaquone, and amodiaquine with EC_{50} values of 285±58 µM, 1.97±0.43 µM, 0.35±0.14 µM, and 12.30±4.21 µM, consequently.[83] Numerous melatonin-based indole derivatives were prepared and evaluated by Singh *et al.* (2014) which has an inhibitory effect on *P. falciparum* cell cycle. The compound **29** revealed higher antimalarial activity (IC_{50}= 2.93 µM).[84] The different quinoline-indole conjugates were prepared by Teguh and colleagues, 2013, and investigated for antimalarial activity by treating against bacterial strain K1 of *P. falciparum*. The compound 30 has shown increasing antimalarial activity (IC_{50} <0.4±0.2 µg/ml).[85] Numerous meridianin G-based indole derivatives were prepared and evaluated by Bharate *et al.*, 2013, treated against chloroquine-sensitive *P. falciparum* by plasmodial. The synthesized

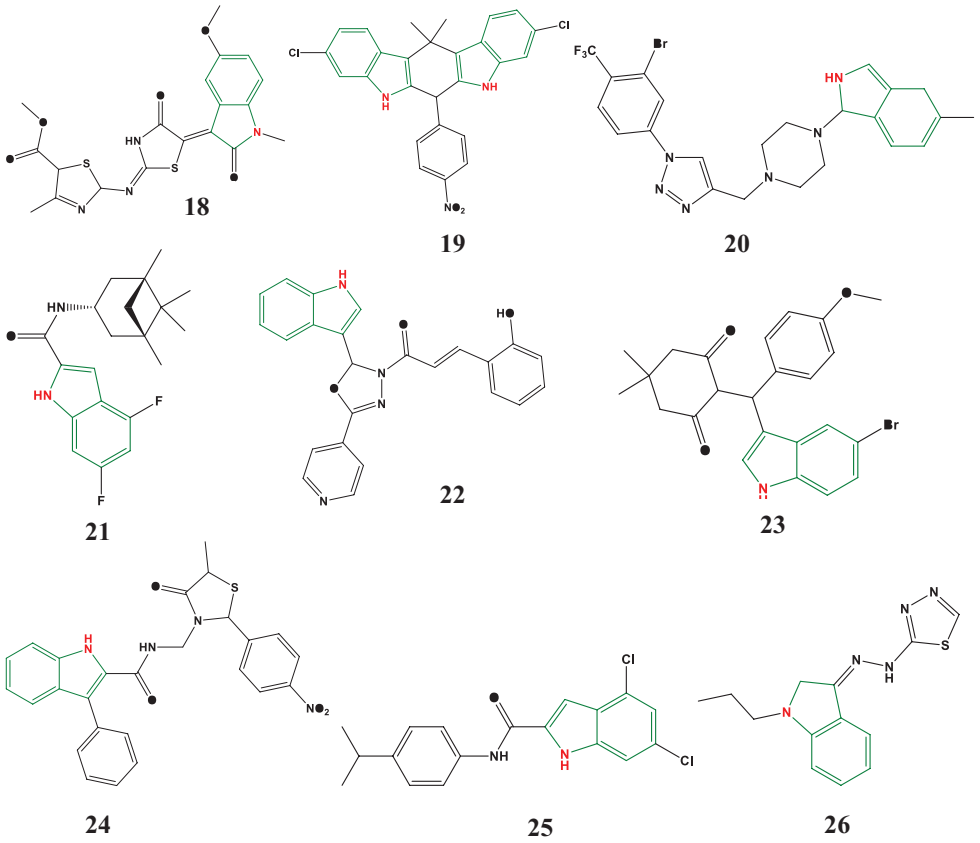


Figure 2: Antitubercular activity of indole derivatives

compound **31** (IC_{50} <4.01μM) has revealed higher efficacy as compared to reference drug chloroquine (IC_{50} <0.72 μM) and artemisinin (IC_{50} <0.09 μM).[86] Santos and colleagues, 2015, prepared 3-piperidin-4-yl-1H-indole containing treated against bacterial strain *P. falciparum* for antiparasitic activity. The new synthesized compound **32** has shown prospective antiparasitic activity.[87] Schuck and colleagues, 2014, synthesized and reported a new series of melatonin analogs that were treated against bacterial strain *P. falciparum* culture. Although the analog of melatonin, derivative compound **33** was found to be active against *P. falciparum* and inhibits its development.[83] The indole derivatives based antimalarial active compound structures[26-32] are mentioned in Figure 3.

Antiviral Activity

A new class of novel indole-3-carboxylate analogs was synthesized and investigated against the chikungunya virus by the CPE reduction method. The compound **34** (EC50 =65±1) shown higher potency as equated to reference drug arbidol.[88] Chen *et al.,* 2017, synthesized and investigated on integrated indoles and spiroindolines. The prepared compounds were, furthermore, investigated by *in vitro* and *in vivo* method tobacco mosaic virus. The compound **35** (% inhibition of 56±2% has shown higher potency as equated to reference drug ribavirin (% inhibition of 36±1%) and harmine (% inhibition of 45±1%) at the concentration of 500 μg/ml.[89] Musella *et al.,* 2016, designed and synthesized amide substituted indole derivatives and treated on the human alphaherpesvirus-3 (HHV-3). The synthesized compound **36** (CC50 = 39 μM) has revealed higher potency as compared to reference drug briuvudine (CC50 = 160 μM) and acyclovir (CC50 = 191 μM).[90] In 2009, Giampieri *et al*. form indole-naphthyl derivatives by fusing indole with naphthalene nucleus. Further, all prepared indole derivatives were treated on a variety of viruses like yellow fever virus (YFV), coxsackievirus B-2 strain (CVB-2), bovine viral diarrhea virus (BVDV), and HIV-1. The synthesized compound **37** (CC50 => 57 μM, SI=<5) has relatively effective as equated to reference drug acyclovir, mycophenolic acid, and ribavirin (CC50 => 100 μM, SI=<50).[30] Sanna and his colleagues, 2018, synthesized and novel-indole thiourea hybrids derivatives investigated on HIV-1. The prepared compound **38** (EC_{50} = 8.7 ± 0.4 μM) has revealed higher potency against standard drug efavirenz (EC_{50} = 0.002 ± 0.0002 μM).[82] A further study conducted by Dussan *et al*., 2016, designed and investigated numerous indole derivatives against HIV activity. The compound **39** (EC_{50} < 0.011 μM) has been reported as highly potent anti-HIV activity.[27] Ravichandran *et al*., 2016, synthesized and investigated numerous indole-7-carboxamide derivatives for anti-HIV activity. The compound 40 has revealed higher potency.[91] Numerous indole-pyrido derivatives were synthesized and investigated for anti-HIV activity. Ashok and his colleagues, 2015, indole-pyrido derivatives, molecular properties were also studied to monitor HIV-infected cells. The synthesized compound **41** (EC_{50}=0.53 μM) has revealed higher potency equated to reference drug zidovudine with EC_{50}=0.002 μM.[92] Jiang and colleagues, 2014, have synthesized trifluoromethyl-indole analogs which have

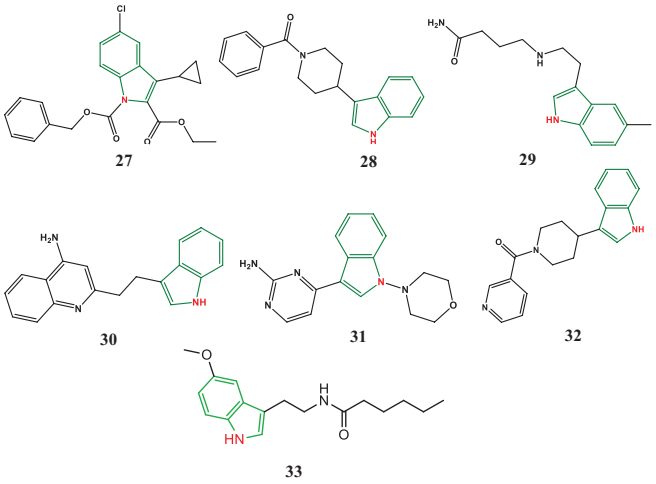


Figure 3: Antimalarial activity of indole derivatives

shown better drug resistance against anti-HIV-1 NNRTIs. The compound **42** (EC_{50}<133.33 μM) has shown better potency as compared to reference drug nevirapine with EC_{50}=0.4 μM and efavirenz with EC_{50}=0.08 μM.[93] Ferro *et al*., 2014, developed and investigated the indole derivatives for HIV-1 integrase through a docking study. The compound **43** (IC_{50} = 0.4 mM) has shown maximum potency.[94] Hassam and colleagues, 2012, synthesized and investigated cyclopropyl indole analog for HIV-1 activity. The compounds **44** (IC50= 0.065 μM) and **45** (IC50= 0.069 μM) have revealed higher potency as compared to reference drug nevirapine (IC50= 0.087 μM).[95] Balupuri and colleagues, 2014, prepared and investigated 1H-indole-piperazine derivatives and screened it through numerous molecular computational techniques (molecular dynamics, combined docking, and 3D-QSAR) study. The compound **45** ((IC50n= 0.005 nM) has revealed higher potency and shown a better binding affinity to the HIV cells receptor.[96] Yeung *et al.,* 2013, synthesized the indole-7-carboxamide derivatives and investigated by cell-based assay against pseudotype virus. The compound **46** found to be very potent (EC50 +0.29 nM).[97] Indole-2-carboxamide derivatives were synthesized, investigated, and treated against HIV-1 Strain (G190A, IRLL98, K101Q, K103N, Y181C, and Y188L) by Regina *et al*., 2012. The compound **47** with EC_{50} = 2.0 ±0.2 nM has shown higher potency as compared to reference drug efavirenz with EC_{50} = 6.3 ±3.2 nM and zidovudine with EC_{50} = 2.0 ±0.2 nM.[98] Regina and colleagues, 2011, prepared and investigated indole-2-carboxamide derivatives and treated against HIV-1 strain (L100I and K103NRT).

The compound **48** with EC50 = 1.3 ±0.0 nM has revealed higher potency as compared to reference drug nevirapine with EC_{50} = 19.2 ±0.2 nM) and efavirenz with EC_{50} = 21.5 ±0.3 nM.[99] Further study in the same year Tichy *et al*. designed and investigated indole-2-carboxylate derivatives for anti-HIV activity. The compound **49** exhibited good anti-HIV activity.[100] Xue *et al*., 2014, synthesized and investigated indole-2-carboxylate derivatives for antiviral potencies. The compound **50** exhibiting a good potency for antiviral effect.[101] The indole derivatives based antiviral active compound structures (34-50) are mentioned in Figure 4.

Hepatitis C Virus Activity

Zhang *et al.,* 2005, reported and prepared a new series of indole derivatives (2-(4-sulfonamidophenyl)-indole 3-carboxamides) and evaluated on the HCV genotype 1b replicon. The synthesized compound **51** exhibits good potency [Figures 5 and 6].[102] The indole derivatives based hepatitis C virus active compound structure is mentioned in Figure 5.

Anti-leishmanial Agents

Porwal *et al*., 2017, designed, synthesized gem-dithioacetylated indole analogs, and investigated against Leishmania Donovan. The compound **52** (% inhibition of 96–99%) revealed higher potency.[103] In 2016, Felix and colleagues designed and investigated thiophene-indole hybrids and treated them on *L. donovani*. The prepared compound **53** (IC_{50}=3.2 μg/mL, SI>124.6) has shown good potency as equated to reference drug amphotericin B (IC_{50}=0.2 μg/mL, SI>124.5).[104] Sharma and colleagues, 2014, synthesized and investigated triazine indole-quinoline hybrid derivatives and treated them against *L. donovani*. The compound **54** (IC_{50}=0.36μM) has revealed higher potency as equated to reference drug miltefosine (IC_{50}=8.10 μM).[105]

Bharate and colleagues, 2013, synthesized and evaluated 3.3-diindolylmethane for anti-leishmanial activity on *L. donovani*. The synthesized compounds **55** (IC_{50}<7.17 μM) and **56** (IC_{50}<8.37 μM) have shown higher potency as equated to reference drug amphotericin B (IC_{50}< 0.17 μM) and pentamidine (IC_{50}<8.39 μM).[106] Singh *et al*., 2012, synthesized and investigated azetidine-indole analogs and screened for *L. promastigotes*. The compound **57 (**056 ± 0.06 μg/mL) has revealed higher potency as equated to reference drug amphotericin B (056 ± 0.001 μg/mL).[107] The indole derivatives based anti-leishmanial active compound structures[51-56] are mentioned in Figure 6.

Antifungal Activity

In recent times, indole derivatives have an achieved acknowledgment due to their exceptional role as an antifungal agent. Kumar *et al.,* 2020, synthesized and investigated 1H-Indole derivatives on fungi, *Aspergillus niger*, and *Candida albicans*. The compound **58** (zone of inhibition 16±2 mM) has revealed better potency as compared to reference drug ampicillin (zone of inhibition 25±2 mM).[108] In 2015, Zhang and colleagues prepared and investigated the antifungal activity of streptochlorin analogs. The compound **59** has shown remarkable potency of 81–100% in controlling the disease.[109] Jia *et al*., 2018, performed an investigation on streptochlorin. The investigation of analogs was performed on *Pythium dissimile, Alternaria solani, Gibberella zeae, Botrytis cinerea, Rhizoctonia solani, Alternaria blotch, and Collecteri chumcapsica*. The compound **60** was established highly potent.[110,111] Mishra *et al.,* 2018, conducted a study to improve the antifungal activity of the indole triazole-amino acid conjugates. The prepared compound **61** has shown better activity equated to reference drugs.[112] Sandmeyer reaction in the presence of tert-butyl nitrite was used to prepare a new class of indole [1,2-c]-1,2,4-benzotriazine analog. A commercial fungicide, hymexazol, and two

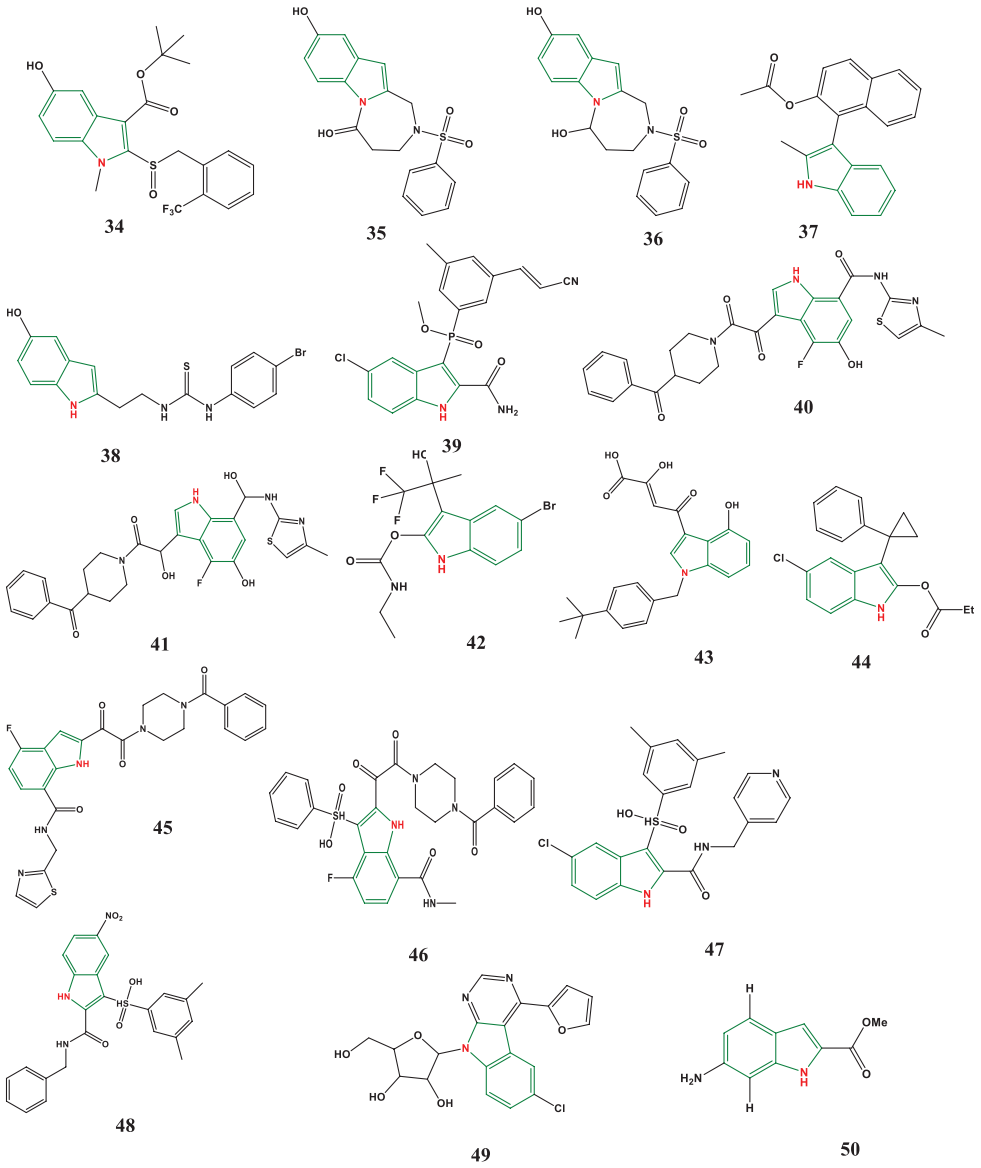


Figure 4: Antiviral activity of indole derivatives

indoles [1,2-c]-1,2,4-benzotriazines at a concentration of 50 mg/ml have shown promising and prominent antifungal activity against phytopathogenic fungi. It concluded that the substitution on indolyl moiety of [1,2-c]-1,2,4-benzotriazines (compound **63**) would form a potent antifungal agent.[113]

Based on the principle of combination of new structural rings, a bespoke and proficient synthetic technique for three classes of new indole-based 1,3,4-oxadiazoles **64** was explained. Biological assay conducted at Syngenta exhibited that more than a few prepared compounds revealed good potency as compared to standard drug pimprinine, the natural compounds which stimulated this synthesis. Two main structural modifications were found to make wider the spectrum of biological activity in most belongings.[114] Song *et al.*, 2015, synthesized 2-(Indole-3-yl)-thiochroman-4-ones **65** and 6-chloro-2(5-chloro-1H-indole-3-yl)-thiochroman-4-one by ionic liquid and investigated for antifungal study through *in vitro* experiment. The compounds **65** and **66** have revealed better antifungal activity as compared to reference drug Fluconazole.[115] Pooja *et al.*, 2014, synthesized amino acid appended indole moiety and investigated against *Candida albicans*. The compound **67** exhibited proficient antifungal activity.[116] The indole derivatives based antifungal activity compound structures[57-66] are mentioned in Figure 7.

Anticancer Activity

Coriglino *et al.*, 2018, synthesized numerous 2,4-thiazolidinedione indole analogs as an anticancer agent. The synthesized compound was analyzed upon human breast cancer cells (MCF-7) and PC3 human prostate cancer cells. The compound **68** (IC_{50}=5 μM) showed high potency.[117] Ustundag *et al.*, 2016, synthesized and biological investigation of 1H-indole hydrazide-hydrazone, thiazolidinones derivatives. In compound 70 has revealed the IC50 values of colo-38 (IC50<0.83 ± 0.09) and K562 (IC50 < 0.63 ± 0.05 μM).[81] Demurtas *et al.*, 2019, prepared indole hydrazone derivatives

and analyzed for erythroleukemia (K562) and melanoma cell lines (Colo-38). In compound **70** (IC_{50} < 0.63 ± 0.05 μM) has revealed higher potency for anticancer activity.[118] The

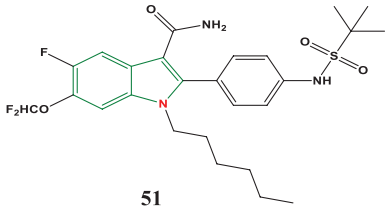


Figure 5: Hepatitis C virus genotype activity of indole derivatives

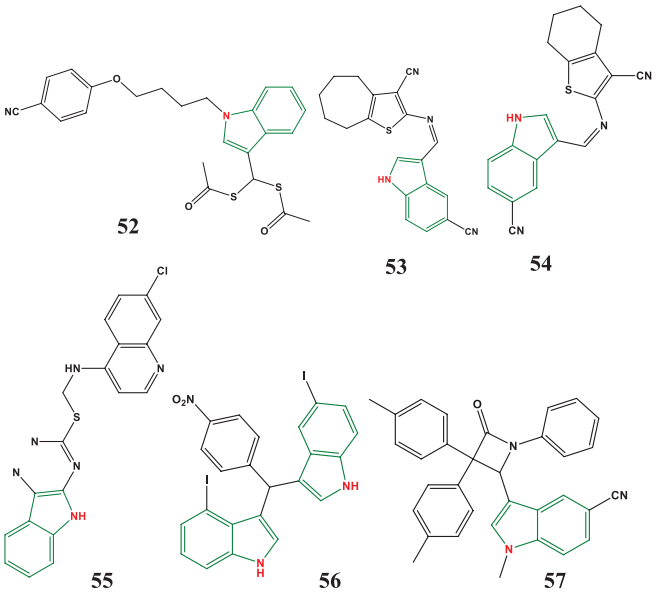


Figure 6: Anti-leishmanial activity of indole derivatives

prepared and investigate reciprocated heteroannulated indole derivative for their cervical anticancer activity was performed by Parkash *et al.*, 2018. The electron-withdrawing group present at the 8th position of carbon showed good association at the target site because of the hydrogen bonding and Van der Waal's interaction, observed in the docking study. The compound **71** (IC_{50} = 13.41 µM) and IC_{50} = 14.67 µM) revealed exceptional anticancer activity, which is equipotent to reference drug cisplatin (IC50 = 13.20 µM) activity.[119] Tocco *et al.,* 2017, prepared and investigated *Bis*-Indole against hepatocarcinoma cell. Compound **72** (IC50 = 20-100 µM) was observed to have better activity than the standard drug indole 3-carbinol.[120] Romagnoli *et al.,* 2017, prepared and evaluated several 3-substituted-2-oxindole hybrid analogs. The prepared compound **73** has shown the highest potency (IC_{50}< 5500 µM) on human leukemia-60 cells. The human leukemia-60 cells showed better interaction with cellular nucleophiles than standard drugs.[121] Lafayette and colleagues, 2017, prepared and investigated indole derivatives as encouraging DNA-binding sites for antitumor and anti-topoisomerase activity. The compound **74** revealed remarkable antitumor activity on cell lines T47D (IC_{50} =1.93 µM).[122] Chang et al. (2016), synthesized a series of bis-(hydroxymethyl) idolizing [8,7-b] indole hybrids compound of β-carboline and bis(hydroxymethyl)pyrrole to evaluate antitumor and lung cancer cell investigation.. The compound **75** (IC_{50} = 0.49 µM) exhibited higher anticancer activity treated equated to the growth of small cell lung cancer (SCLC) H526 cells in xenograft against cisplatin (IC_{50} = 0.63 µM).[123] Bakherad and colleagues, 2019, prepared and investigated numerous thiosemicarbazone indole derivatives on MCF-7 (breast cancer), A-549 (cancer of the lung), and Hep-G2 (liver cancer) cell lines. The compound **76** has shown the potency treated on A-549 (IC_{50} = 12.5 µM) and Hep-G2 (IC_{50} = 56± 6.30 µM) cell lines equated to reference drug etoposide A-549

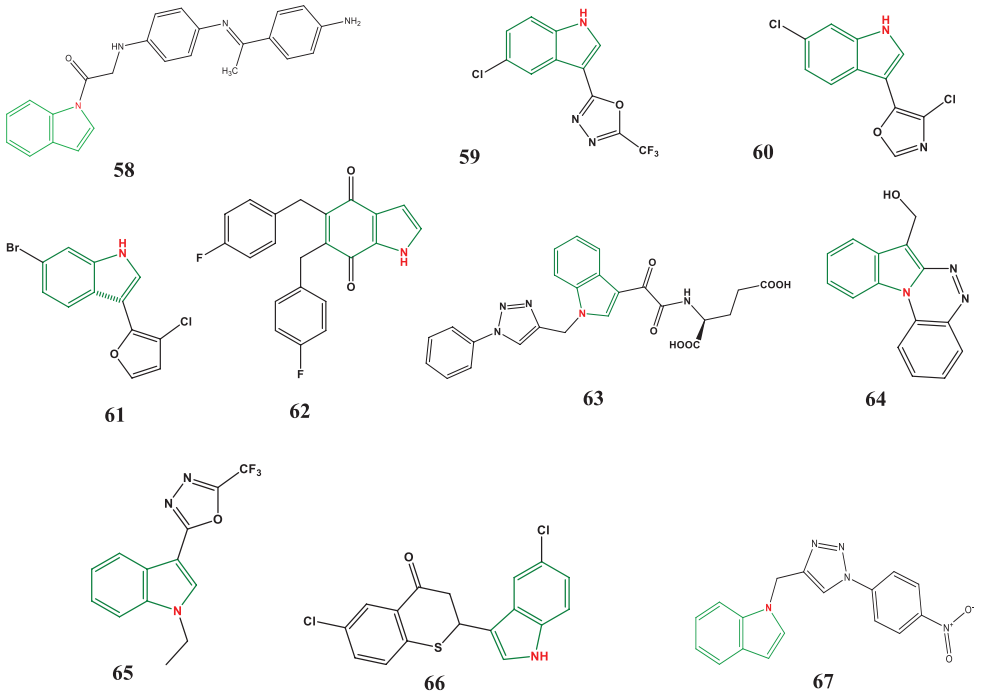


Figure 7: Antifungal activity of indole derivatives

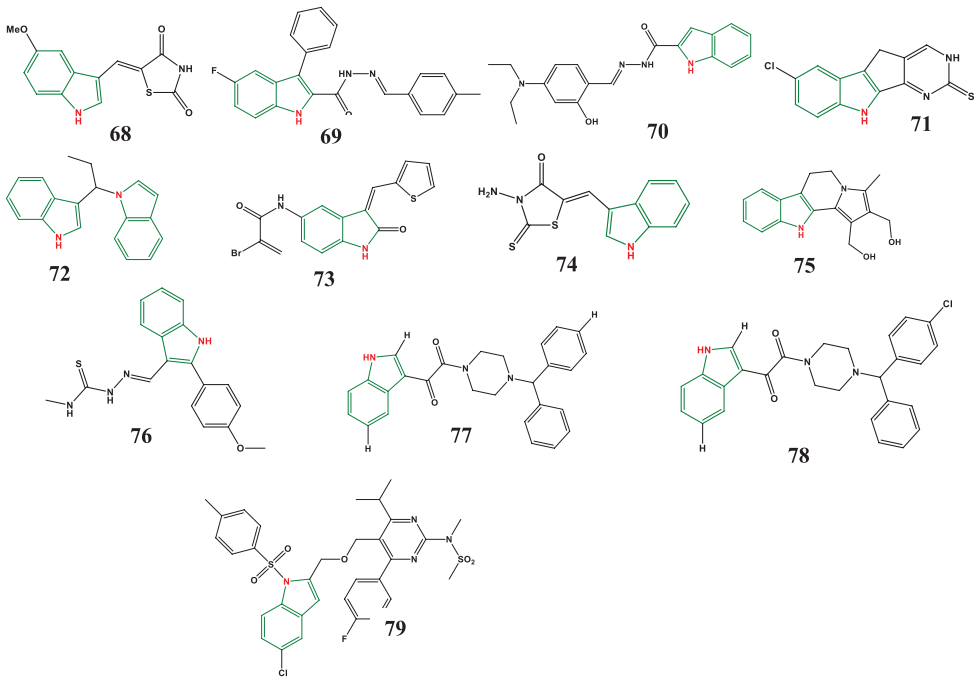


Figure 8: Anticancer activity of indole derivatives

(IC_{50} = 38.23 ± 1.89 μM) and Hep-G2 (IC_{50} = 33.17 ± 3.19 μM), and colchicine A-549 (IC_{50} = 1.9 ± 0.23 μM), Hep-G2 (IC_{50} = 6± 0.49 μM).[124] Jiang and colleagues (2016) prepared and investigated numerous indole derivatives treated on HeLa, A-549, and ECA-109 cell lines. The compound **77a** (IC_{50} < 16.65 μM) and **(77b)** (IC_{50} <14.74 μM) has revealed higher potency than reference drug cisplatin (IC_{50} < 30.89 μM).[125]

Kumar *et al.*, 2016, prepared and investigated numerous rosuvastatin-based indole derivatives for anticancer activities on against A549 and TZMBL cell lines. Compound **78** (IC50<12 μM) has revealed higher potency in comparison to reference drug gemcitabine.[126] Hu and colleagues prepared and investigated numerous new series of 2,5-disubstituted indole derivatives for their anticancer properties. The compound **79** (IC_{50} < 8.70 ± 0.11 μg/mL) has revealed higher potency as compared to reference drug cisplatin (IC_{50} < 6.10 ± 0.09 μg/mL).[127] The indole derivatives based anticancer activity compound structures[54,67-77] are mentioned in Figure 8.

Anticonvulsant Activity

Dialkylaminoalkoxy-oxindole analogs were prepared and investigated by Swathi and Saragapani in 2017. Synthesized compounds were investigated for anticonvulsant activity by the pentylenetetrazole (PTZ) induced convulsion method and maximal electroshock seizure (MES). The compound 80 has shown (IC50 < 67.18 ± 0.23 μg/mL) better anticonvulsant activity compared to the standard drug Phenytoin.[128] Madhira *et al.*, 2017, prepared and evaluated benzohydrazide-oxindole derivatives to anticonvulsant activity. The compound **81** (%protection=83.19%) [Figure 9] showed higher potency equated to reference drug phenytoin (%protection=100%).[129] Raju and colleagues, 2016, prepared and investigated novel indole carboxylate derivative for anticonvulsant activity by the MES method. The compound **82** (108.3 ± 0.7) [Figure 10] has revealed higher potency as compared to reference drug phenytoin (100%).[130] Indole-1,2,4-triazine analogs were synthesized, evaluated against maximal electric shock (MES), and subcutaneous pentylenetetrazole (scPTZ), by Ahuja and Siddiqui. The compound **(83)** (% protection=100%) revealed higher potency upon study due to the presence of nitro groups binding with the receptor.[131] The indole derivatives based anticonvulsant activity compound structures[34,78-80] are mentioned in Figure 9.

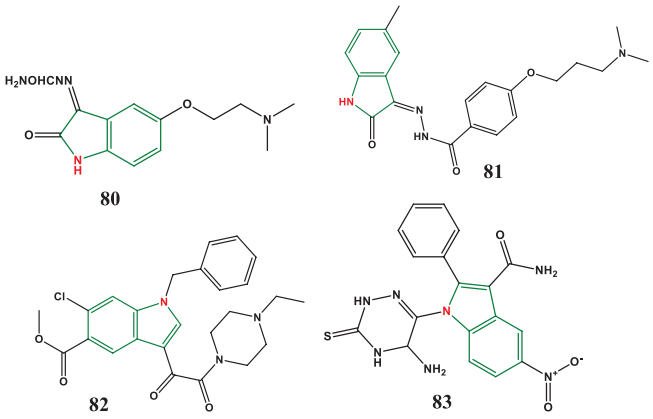


Figure 9: Anticonvulsant activity of indole derivatives

Antidiabetic Activity

The novel indole-triazole derivatives were prepared and investigated for antidiabetic properties by Rajan and colleagues in 2018. Syrian Golden Hamster model was used for evaluating all the synthesized compounds. The compound **84** [Figure 10] showed maximum potency.[132] Nazir and colleagues, 2018, prepared and investigated indole-oxadiazole hybrids analogs for inhibiting α-glucosidase activity. The compounds **85** (IC_{50} = 9.46 ± 0.03 μM)

[Figure 10] and **86** (IC_{50} = 9.37 ± 0.03 µM) [Figure 10] revealed high potency as compared to acarbose (IC_{50} = 37.38 ± 0.12 µM).[133] The diabetes-induced chick model was investigated in the *in vivo* study, for the synthesized indole derivatives by Srividya and Reddy, 2017. The compound **87 (**29.6-38.6%) [Figure 10] demonstrate very good antidiabetic activity against standard drug glibenclamide (57.10%).[134] Taha *et al.*, 2017, combined indole and oxadiazole to attain a new chain of tris-indole-oxadiazole analogs. The prepared compound **88** (IC_{50}=2.00 ± 0.001mM) [Figure 10] revealed high potency as compared to reference drug acarbose (IC_{50}=895.09 ± 2.04 mM).[135] The indole derivatives based antidiabetic activity compound structures (84-88) are mentioned in Figure 10.

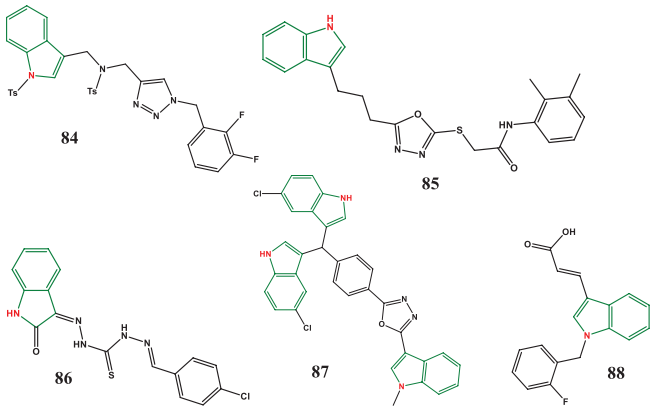


Figure 10: Antidiabetic activity of indole derivatives

Anti-inflammatory Activity

1H-indole capsaicin derivatives and nitro-indole derivatives were synthesized and investigated on the pro-inflammatory cytokinase TNF-α by Mukhtung *et al.,* 2018. The compound **89a** showed a value % relative inhibition of 47.65% and **89b** % relative inhibition of 51.95%) [Figure 11] revealed high potency in comparison to standard drug capsaicin (relative % inhibition = 65.55%).[136] Bhat and colleagues, 2018, prepared and investigated acetohydrazide-indole hybrid derivatives COX-2 inhibitory activity. The docking study of compound **(90)** (potency 0.79%) [Figure 11] revealed potent selective inhibition as equated to reference drug Indomethacin (potency = 1.0%).[137] In the same year, Shaker *et al.* conducted the prepared and investigated of indole derivatives containing methyl sulfonyl and aryl-substituted derivative for COX-2 inhibition activity. The compound **91a** (IC_{50}=0.11 µM, SI=107.63) and **(91b)** (IC_{50}=0.15 µM, SI=76.6) [Figure 11] demonstrates higher potency as equated to reference drug

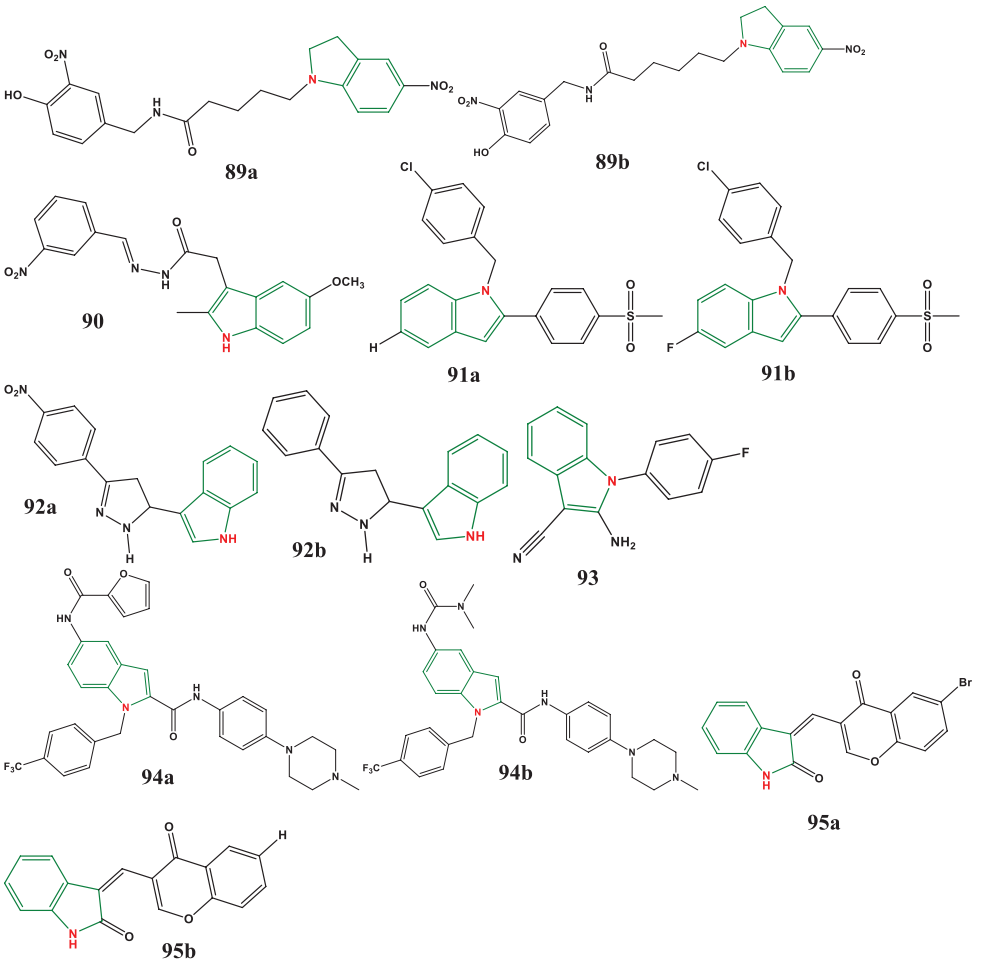


Figure 11: Anti-inflammatory activity of indole derivatives

indomethacin (IC_{50}=0.49 μM, SI=0.079).[138] The novel indolyl-pyrazoline derivatives were prepared and investigated to inhibit inflammation using the Carrageenan-induced paw edema method by Shroff and Daharwal in 2017. The compound **92a** (% of inhibition=63.90%) and **92b** (% of inhibition = 57.46%) [Figure 11] showed higher potency as compared to reference drug indomethacin (% of inhibition=61.36%).[139] Numerous indole derivatives were prepared and investigated for an anti-inflammatory property using the paw edema method by Fatahala *et al*. in 2017. The highest potency was shown by compound **(93)** (%inhibition = 92%) [Figure 12] in comparison to ibuprofen (% of inhibition=69.84%) and indomethacin (% of inhibition = 78.58%).[140] Xu and colleagues, 2019, prepared and investigated indole-2-carboxamide derivatives for the identification of potent anti-inflammatory agents. The compound **94a** (% of inhibition < 2.90 ± 0.73%) and **94b** ((% of inhibition < 2.67 ± 0.76%) has revealed better potency.[141] Numerous chromone-substituted oxindole was synthesized by Shaveta and colleagues in 2014 and investigated on COX-1, COX-2, and 5-LOX. The compound **95a** (IC_{50} = 9.5 ± 0.8 μg/mL) and **95b** (IC_{50}= 10.0 ± 4.2 μg/mL) [Figure 11] has shown higher potency in comparison to reference drug indomethacin (IC_{50} = 0.7 ± 0.2 μg/mL).[142] The indole derivatives based anti-inflammatory activity compound structures (89a-95b) are mentioned in Figure 11.

Antidepressant Activity

Oxindole derivatives having azetidinone moiety were synthesized and analyzed by Kerazare *et al*. in 2018 which further undergone animal study using a forced swim test. The compound **96a** showed a reduction in immobility to 66.82% and compound **96b** to 65.61% [Figure 12] has revealed high potency as compared to reference drug fluoxetine reduction in immobility to 70.93%.[143] The numerous indole derivatives having dihydropyrazole moiety were synthesized and investigated for antidepressant activity using a forced swim test by Patil and Bari 2013. The compound **97a** (116.3 ± 1.54) and **97b** (109.8 ± 2.86) [Figure 12] demonstrated higher potency as equated to reference drug fluoxetine reduction in immobility to 77.4% and imipramine to 75.5%.[144] The indole derivatives based antidepressant activity compound structures **(96a-97b)** are mentioned in Figure 12.

Antioxidant Activity

Melatonin analogs with indole moiety were synthesized and investigated for antioxidant and protective effects against damage induced β-amyloid by Orhan *et al*., 2016. The compound **98a** (IC_{50} = 38.3 ± 8.9 μM) and **98b** (IC_{50} = 37.0 ± 2.0 μM) was screened against ROS-induced oxidation and it was found very effective against the standard drug melatonin.[145] Silveira *et al*., 2013, conducted a study on C-3 sulfenyl indoles for antioxidant activity. The compound **99** (activity <96.8%) showed higher potency.[146] The indole derivatives based antioxidant active compound structures (98a-99) are mentioned in Figure 13a.

Anticholinergic Activity

Parveen *et al*., 2018, demonstrated that the synthesized indole analogs on molecular docking and *in vitro* study showed anticholinergic activity. The compound **100** has revealed higher potency.[147] Farani *et al*., 2013, synthesized numerous indole derivatives by investigating *in vitro* and docking study for anticholinergic activity. The compound **101** (IC_{50}=1.1 ± 0.25 μM) has revealed high potency against the reference drug donepezil (IC_{50}=0.41 ± 0.12 μM).[148] The indole derivatives based anticholinergic active compound structures (100-101) are mentioned in Figure 13b.

Antifertility Agents

Bhowal*et al*., 2008, synthesized and evaluated 2-(2"-chloroacetamidobenzyl)-3-(3'-indolyl) quinoline as a contraceptive agent by measuring the level of sexual hormones and spermatogenesis. The compound **102** [Figure 14a] has demonstrated good potency.[149]

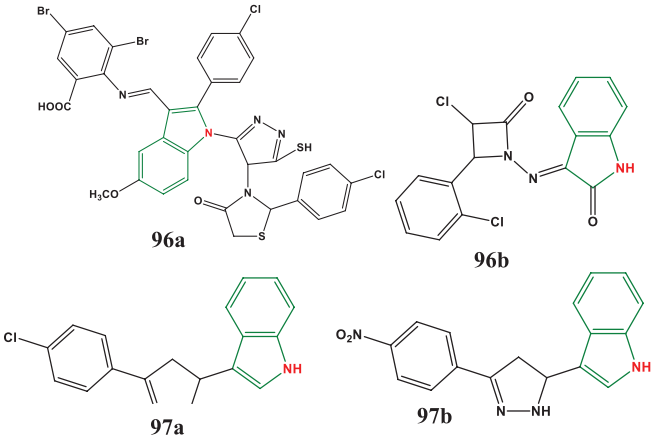


Figure 12: Antidepressant activity of indole derivatives

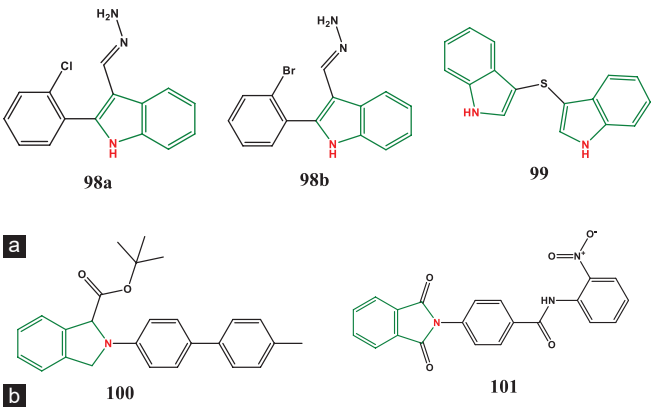


Figure 13: (a) Antioxidant activity of indole derivatives and (b) anticholinergic activity of indole derivatives

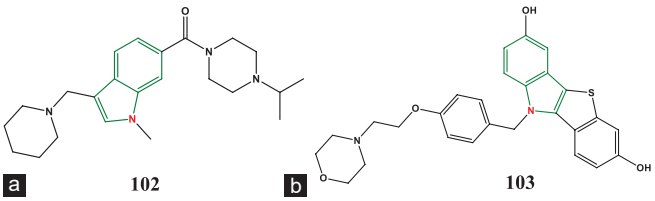


Figure 14: (a) Antifertility activity of indole derivatives and (b) antiestrogenic activity of indole derivatives

Antiestrogenic Activity

Ji *et al.*, 2005, synthesized and evaluated benzothieno[3,2-b] indole derivatives which were effective estrogen receptor modulators. The synthesized compound was treated with estrogen receptor (ERσ, ER β), and their action on bone and uterus was observed. The compounds **103** [Figure 14b] revealed higher potency.[150]

FUTURE PROSPECTS OF INDOLE DERIVATIVES DRUGS IN THERAPEUTICS

The clinical trial used to be performed for diagnosing, treating, and preventing diseases. A huge amount of data is pending with the FDA for approval of indole containing drug's clinical trial. Indole is found to be an encouraging biologically active molecule, due to its reactivity which can be modified to obtain a variety of lead molecules for the treatment of different diseases. Therefore, indole derivatives are a potential drug for clinical trial study. Most of the drugs have cleared the different phases of clinical trials and revealed its high efficacy. Although, few compounds revealed significant ill effect and no furthermore screened. The various indole derivatives are undergoing the examination and structural alterations are being done to conduct a clinical trial.

CONCLUSION

Various drugs bearing indole moiety acquired from nature or by synthesis are under clinical investigation. Besides, investigator and analyst are cooperating their research work on indole containing novel compounds intended for a few ailing conditions including infection and malignancy. Although, the least symptoms and improving the pharmacological action remained a crucial challenge. Evidence collected from the literature review showed variability in the indole core practically touches all the diseased states. A great deal of escalated research should be done by looking at the capability of indole with other synthetic substances. It is imperative to realize that different potential indole derivatives should be affirmed for its pharmacodynamics profile utilizing appropriate animal models in preclinical data. There is a shortage of preclinical and clinical data of recently synthesized indole derivatives with anticipated diversified therapeutic action and strong antimicrobial adequacy.

ACKNOWLEDGMENT

The authors would like to thank Dr. Arun K. Mishra, Faculty of Pharmacy, IFTM University, Moradabad, Uttar Pradesh, India, for valuable scientific suggestions in writing the manuscript.

AUTHORS' CONTRIBUTIONS

P.K. Conceptualization; data curation; and writing – original draft; M.I.A. Visualization; review and editing; S.S. Writhing – review and editing; M.R.F.P Review, editing, and checking the English language; and A.K.M Supervision.

CONFLICTS OF INTEREST

None.

FINANCIAL SUPPORT

All authors are declared no financial support or otherwise.

REFERENCES

1. Knepper K, Vanderheiden S, Brase S. Synthesis of diverse indole libraries on polystyrene resin-Scope and limitations of an organometallic reaction on solid supports. J Org Chem 2012;8:1191.
2. Thanikachalam PV, Maurya RK, Garg V, Monga V. An insight into the medicinal perspective of synthetic analogs of indole: A review. Eur J Med Chem 2019;180:562-612.
3. Baeyer A. Ueber die reduction aromatischer verbindungen mittelst zinkstaub. Justus Liebigs Annalen der Chem 1866;140:295-6.
4. Kumari A, Singh RK. Medicinal chemistry of indole derivatives: Current to future therapeutic prospectives. Bioorg Chem 2019;89:103021.
5. Chadha N, Silakari O. Indoles as therapeutics of interest in medicinal chemistry: Bird's eye view. Eur J Med Chem 2017;134:159-84.
6. Von-Sundberg RJ. The Chemistry of Indoles. Organic Chemistry, a Series of Monographs. Vol. 18. New York, London: Academic Press; 1970.
7. Joule JA, Mills K, Smith GF. Heterocyclic Chemistry. New Delhi: Chapman and Hall; 1995.
8. Won C, Shen X, Mashiguchi K, Zheng Z, Dai X, Cheng Y, *et al*. Conversion of tryptophan to indole-3-acetic acid by tryptophan aminotransferases of arabidopsis and YUCCAs in arabidopsis. Proc Natl Acad Sci U S A 2011;108:18518-23.
9. Zhang MZ, Mulholland N, Beattie D, Irwin D, Gu YC, Chen Q, *et al.* Synthesis and antifungal activity of 3-(1,3,4-oxadiazol-5-yl)-indoles and 3-(1,3,4-oxadiazol-5-yl) methyl-indoles. Eur J Med Chem 2013;63:22-32.
10. Leon F, Habib E, Adkins JE, Furr EB, McCurdy CR, Cutler SJ. Phytochemical characterization of the leaves of *Mitragyna speciosa* grown in the U.S.A. Nat Prod Commun 2009;4:907-10.
11. Chen FE, Huang J. Reserpine: A challenge for the total synthesis of natural products. Chem Rev 2005;105:4671-706.
12. Young SN. How to increase serotonin in the human brain without drugs. J. Psychiatry Neurosci 2007;32:394-9.
13. Diss LB, Robinson SD, Wu Y, Fidalgo S, Yeoman MS, Patel BA. Age-related changes in melatonin release in the murine distal colon. ACS Chem Neurosci 2013;4:879-87.
14. Patil SA, Patil R, Miller D. Indole molecules as inhibitors of tubulin polymerization: Potential new anticancer agents. Future Med Chem 2012;4:2085-115.
15. Higdon JV, Delage B, Williams DE, Dashwood RH. Cruciferous vegetables and human cancer risk: Epidemiologic evidence and mechanistic basis. Pharmacol Res 2007;55:224-36.
16. Rogan EG. The natural chemopreventive compound indole-3-carbinol: State of the science. *In Vivo* 2006;20:221-8.
17. Kim YS, Milner JA. Targets for indole-3-carbinol in cancer prevention. J Nutr Biochem 2005;16:65-73.
18. Atterhog JH, Duner H, Pernow B. Experience with pindolol, a beta-receptor blocker, in the treatment of hypertension. Am J Med 1976;60:872-6.
19. London GM, Asmar RG, O'Rourke MF, Safar ME. Project investigators, mechanism of selective systolic blood pressure reduction after a low dose combination of perindopril/indapamide in hypertensive subjects: Comparison with atenolol. J Am Coll Cardiol 2004;43:92-9.
20. Chen X, Zhan P, Li D, Liu X. Recent advances in DAPYs and related analogs as HIV-1 NNRTIs. Curr Med Chem 2011;18:359-76.
21. Jacobi H, Dell HD. On the pharmacodynamics of acemetacin (author's transl). Arzneimittelforschung 1980;30:1348-62.
22. Srivastava G, Somasundaram RT, Walfish PG, Ralhan R.

Anticancer activity of apaziquone in oral cancer cells and xenograft model: Implications for oral cancer therapy. PLoS One 2015;10:33735.
23. Boriskin YS, Leneva IA, Pecheur EI, Polyak SJ. Arbidol: A broad-spectrum antiviral compound that blocks viral fusion. Curr Med Chem 2008;15:997-1005.
24. Battaglia S. Indole amide derivatives: Synthesis, structure-activity relationships, and molecular modeling studies of a new series of histamine H1-receptor antagonists. Eur Jour Med Chem 1999;20:93-105.
25. Sharma V, Kumar P, Pathaka D. Biological Importance of the indole nucleus in recent years: A comprehensive review. J Heterocyclic Chem 2010;47:491.
26. El-Gendy AA, Said MM, Ghareb N, Mostafa YM, El-Ashry ES. Synthesis and biological activity of functionalized indole-2-carboxylates triazino-and pyridazino indoles. Arch Pharm (Weinheim) 2008;341:294-300.
27. Dousson C, Alexandre FR, Amador A, Bonaric S, Bot S, Caillet C, *et al*. Discovery of the Aryl-phosphoindole IDX899, a highly potent anti-HIV non-nucleoside reverse transcriptase inhibitor. J Med Chem 2016;59:1891-8.
28. Gomha SM, Riyadh SM. Synthesis under microwave irradiation of [1, 2, 4] triazolo[3,4-b] [1,3,4]thiadiazoles and other diazoles bearing indole moieties and their antimicrobial evaluation. Molecules 2011;16:8244-56.
29. Yadav RR, Khan SI, Singh S, Khan IA, Vishwakarma RA, Bharate SB. Synthesis, anti-malarial and anti-tubercular activities of meridianin derivatives. Eur J Med Chem 2015;98:160-9.
30. Giampieri M, Balbi A, Mazzei M, La Colla P, Ibba C, Loddo R. Antiviral activity of indole derivatives. Antiviral Res 2009;83:179-85.
31. Zhang MZ, Jia CY, Gu YC, Mulholland N, Turner S, Beattie D, *et al*. Synthesis and antifungal activity of novel indole-replaced streptochlorin analogs. Eur J Med Chem 2017;126:669-74.
32. Mishra BB, Singh RK, Srivastava A, Tripathi VJ, Tiwari VK. Fighting against leishmaniasis: Search of alkaloids as future true potential anti-leishmanial agents. Mini-Re. Med Chem 2009;9:107-23.
33. Estevão MS, Carvalho LC, Ribeiro D, Couto D, Freitas M, Gomes A, *et al*. Antioxidant activity of unexplored indole derivatives: Synthesis and screening. Eur J Med Chem 2010;45:4869-78.
34. Stec J, Onajole OK, Lun S, Guo H, Merenbloom B, Vistoli G, *et al*. Indole-2-carboxamide-based mmpl3 inhibitors show exceptional antitubercular activity in an animal model of tuberculosis infection. J Med Chem 2016;59:6232-47.
35. Ishikawa H, Colby DA, Boger DL. Direct coupling of catharanthine and vindoline to provide vinblastine: Total synthesis of (þ)- and ent-(-)-vinblastine. J Am Chem Soc 2008;130:420-1.
36. Desa-Alves FR, Barreiro EJ, Fraga C. From nature to drug discovery: The indole scaffold as a 'privileged structure. Mini Rev Med Chem 2009;9:782-93.
37. Evans BE, Rittle KE, Bock MG, DiPardo RM, Freidinger RM, Whitter WL, *et al*. Methods for drug discovery: Development of potent, selective, orally effective cholecystokinin antagonists. J Med Chem 1988;31:2235-46.
38. Welsch ME, Snyder SA, Stockwell BR. Privileged scaffolds for library design and drug discovery. Curr Opin Chem Biol 2010;14:347-61.
39. Kaushik NK, Kaushik N, Attri P, Kumar N, Kim CH, Verma AK, *et al*. Biomedical importance of indoles. Molecules 2013;18:6620-62.
40. Dolle RE, Nelson KH Jr. A comprehensive survey of combinatorial library synthesis. J Comb Chem 1999;1:235-82.
41. Franzen RG. Recent advances in the preparation of heterocycles on solid support: A review of the literature. J Comb Chem 2000;2:195-214.
42. Dolle RE. A comprehensive survey of combinatorial library synthesis. J Comb Chem 2001;3:477-517.
43. Cao C, Shi Y, Odom AL. Intermolecular alkyne hydroamination by 1, 1-disubstituted hydrazines. Org Lett 2002;4:2853-6.
44. Buchwald CJ, Buchwald SL. Palladium-catalyzed regioselective hydrodebromination of dibromoindoles: Application to the enantioselective synthesis of indolodioxane U86192A. J Org Chem 2004;69:3336-9.
45. Sundberg RJ, Laurino JP, Laurino JP. Cyclization of 2-[N-(methylsulfonyl)anilino]acetaldehyde diethyl acetals to indoles. Evidence for stereoelectronic effects in intramolecular electrophilic aromatic substitution. J Org Chem 1984;49:249-54.
46. Hemetsberger H, Knittel D, Weidmann H. Enazide, 3. Mitt.: Thermolyse von α-Azidozimtestern; Synthese von Indolderivaten. Monatshefte für Chem 1970;101:161-5.
47. Hayakawa K, Yasukouchi T, Kanematsu K. A new approach to the efficient indole synthesis by allene intramolecular cycloaddition. Tetrahedron Lett 1986;27:1837-40.
48. Moskal J, Van Leusen AM. A new synthesis of indoles by electrocyclic ring closure of dialkenylpyrroles. Synthesis of alkenylpyrroles from 1-tosylalkenyl isocyanides and Michael acceptors. J Org Chem 1986;51:4131-9.
49. Ketcha DM, Wilson LJ, Portlock DE. The solid-phase nenitzescu indole synthesis. Tetrahedron Lett 2000;41:6253-7.
50. Tabbi A, Kaplancikli ZA, Tebbani D, Yurttas L, Canturk Z, Atli O, *et al* Synthesis of novel thiazolylpyrazoline derivatives and evaluation of their antimicrobial activities and cytotoxicities. Turk J Chem 2016;40:641-54.
51. World Health Organization. Available from: http://www.who.int/mediacentre/news/releases/2018/antibiotic-resistance-found/en [Last accessed on 2018 Aug 30].
52. Sanna G, Madeddu S, Giliberti G, Piras S, Struga M, Wrzosek MG, *et al*. Synthesis and biological evaluation of novel indole-derived thioureas. Molecule 2018;10:2554.
53. Hafez NA, Elsayed MA, El-Shahawi MM, Awad GE, Alia KA. Synthesis and antimicrobial activity of new thiazolidine-based heterocycles as rhodanine. J Heterocyclic Chem 2018;55:685-91.
54. Abo-Ashour MF, Eldehna WM, George RF, Abdel-Aziz MM, Elaasser MM, Abdel Gawad NM, *et al*. Novel indole-thiazolidinone conjugates: Design, synthesis and whole-cell phenotypic evaluation as a novel class of antimicrobial agents. Eur J Med Chem 2018;160:49-60.
55. Sayed M, El-Dean AM, Ahmed M, Hassanien R. Synthesis of some heterocyclic compounds derived from indole as antimicrobial agents. Synt Commun 2018;48:413-21.
56. Gani RS, Karabasanagouda T, Kumari S, Chalannavar RK, Malabadi RB, Chougale RB, *et al*. Chemoselective synthesis and evaluation of the antimicrobial activity of novel 5-hydroxy indole derivatives. Der Pharm Sin 2017;8:1-9.
57. Mane YD, Sarnikar YP, Surwase S, Biradar DO, Gorepatil PB, Shinde VS, *et al*. Design, synthesis, and antimicrobial activity of novel 5-substituted indole-2-carboxamide derivatives. Res Chem Intermed 2017;43:1253-75.
58. Badgujar JR, More DH, Meshram JS. Synthesis, antimicrobial and antioxidant activity of pyrazole-based sulfonamide derivatives. Ind J Microbiol 2018;58:93-9.
59. Faria JV, Vegi PF, Miguita AG, Dos Santos MS, Boechat N, Barnardino AM. Recently reported biological activities of pyrazole compounds. Bioorg Med Chem 2017;25:5891-903.
60. Skocibusic M, Odžak R, Ramić A, Smolić T, Hrenar T, Primožič I. Novel imidazolaldoximes with broad-spectrum antimicrobial potency against multidrug-resistant gramnegative bacteria. Molecules 2018;23:1212.
61. Quazi I, Sastry VG, Ansari JA. Synthesis and antimicrobial activity of indole derivative bearing the pyrazole moiety. IJPSR 2017;8:1145-52.
62. Rajaraman DM, Sundararajan G, Loganath NK, Krishnasamy K. Synthesis, molecular structure, DFT studies and antimicrobial activities of some novel

3-(1-(3,4-dimethoxyphenethyl)-4,5-diphenyl-1H-imidazol-2-yl)-1H-indole derivatives and its molecular docking studies. J Mol Struct 2017;1127:597-610.
63. Yadav BP, Ahmad I, Thakur M. Synthesis of some novel indole derivatives as potential antibacterial, antifungal and antimalarial agents. IOSR J Pharm 2016;6:27-33.
64. Choppara P, Bethu MS, Prasad YV, Rao JV, UdayRanjan TJ, Siva Prasad GV, *et al*. Synthesis, characterization and cytotoxic investigations of novel bis(indole) analogs besides antimicrobial study. Arab J Chem 2015;51:15.
65. Gali R, Banothu J, Gondru R, Bavantula R, Velivela Y, Crooks PA. One pot multicomponent synthesis of indole incorporated thiazolylcoumarins and their antibacterial, anticancer and DNA cleavage studies. Bioorg Med Chem Lett 2015;25:106-12.
66. Popiołek L. Hydrazide-hydrazones as potential antimicrobial agents: Overview of the literature since 2010. Med Chem Res 2017;26:287-301.
67. Neeraj K, Chauhan LS. Antimicrobial potential of hydrazide-hydrazone derivatives: Review. Int J Pharm Clin Res 2015;7:154-61.
68. Shirinzadeh H, Altanlar H, Altanlar N, Yucel N, Ozden S, Suzen S. Antimicrobial evaluation of indole-containing hydrazone derivatives. Z. Naturforsch C J Biosci 2011;66:340-4.
69. Nassar E. Synthesis, (*in vitro*) antitumor and antimicrobial activity of some pyrazoline, pyridine, and pyrimidine derivatives linked to indole moiety. J Am Sci 2010;6:338-47.
70. El-Sayed MT, Suzen S, Altanlar N, Ohlsen K, Hilgeroth A. Discovery of bisindolyl-substituted cycloalkane-anellated indoles as novel class of anti-bacterial agents against *S. aureus* and MRSA. Bioorg Med Chem Lett 2015;26:218-21.
71. Praveen C, Bethu MS, Prasad YV, Rao JV, Ranjan TJ, Siva Prasad GV, *et al*. Synthesis, characterization and cytotoxic investigations of novel bis (indole) analogues besides antimicrobial study. Arab J Chem 2019;12:2721-31.
72. Shi Z, Zhao Z, Huang M, Fu X. Ultrasound-assisted, one-pot, three-component synthesis and antibacterial activities of novel indole derivatives containing 1,3,4-oxadiazole and 1,2,4-triazole moieties.CR Chim 2015;18:1320-7.
73. Trott O, Olson AJ. AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. J Comput Chem 2010;31:455-61.
74. Khan GA, Warb JA, Kumar IA, Sheikh A, Saxenaa R, Das A. Facile synthesis of novel indole derivatives as potential antitubercular agents. J Taib Univ Sci 2017;11:921.
75. Rohde KH, Michaels HA, Nefzi A. Synthesis and antitubercular activity of 1,2,4-trisubstituedpiperazines. Bioorg Med Chem Lett 2016;26:2206-9.
76. Patel KN, Telvekar VN. Design, synthesis and antitubercular evaluation of novel series of N-[4-(piperazin-1-yl) phenyl] cinnamamide derivatives. Eur J Med Chem 2014;75:43-56.
77. Naidu KM, Srinivasarao S, Agnieszka N, Ewa AK, Kumar MM, Chandra KV. Seeking potent anti-tubercular agents: Design, synthesis, anti-tubercular activity and docking study of various (triazoles/indole)-piperazin-1-yl/1, 4-diazepan-1-yl) benzo [d] isoxazole derivatives. Bioorg Med Chem Lett 2016;26:2245-50.
78. Schrödinger Release 2019-4. New York: BioLuminate, Schrödinger, LLC; 2019.
79. Desai NC, Somani H, Trivedi A, Bhatt K, Nawale L, Khedkar VM, *et al*. Synthesis, biological evaluation and molecular docking study of some novel indole and pyridinebased 1.3.4-oxadiazole derivatives as potential antitubercular agents. Bioorg Med Chem Lett 2016;26:1776-83.
80. Khan GA, War JA, Naikoo GA, Pandit UJ, Das R. Porous CuO catalyzed green synthesis of some novel 3-alkylated indoles as potent antitubercular agents. J Saudi Chem Soc 2018;22:6-15.
81. Üstündağ GC, Şatana D, Özhan G, Çapan G. Indole-based hydrazide-hydrazones and 4-thiazolidinones: Synthesis and evaluation as antitubercular and anticancer agents. J Enzyme Inhib Med Chem 2016;31:369-80.
82. Tehrani KH, Mashayekhi V, Azerang P, Sardari S, Kobarfard F, Ostamizadeh KR. Synthesis and antimycobacterial activity of novel thiadiazolylhydrazones of 1-substituted indole- 3-carboxaldehydes. Chem Biol Drug Des 2014;83:224-36.
83. Schuck DC, Jordao AK, Nakabashi M, Cunha AC, Ferreira VF, Garcia CR. Synthetic indole and melatonin derivatives exhibit antimalarial activity on the cell cycle of the human malaria parasite *Plasmodium falciparum*. Eur J Med Chem 2014;78:375-82.
84. Singh SK, Singh S. A brief history of quinoline as antimalarial agents. Int J Pharm Sci Rev Res 2014;25:295-302.
85. Teguh SC, Klonis N, Duffy S, Lucantoni L, Avery VM, Hutton CA, *et al*. Novel conjugated quinoline-indoles compromise plasmodium falciparum mitochondrial function and show promising antimalarial activity. J Med Chem 2013;56:6200-15.
86. Bharate SB, Yadav RR, Khan SI, Tekwani BL, Jacob MR, Khan IA, *et al*. Meridianin and its analogs as antimalarial agents. Med Chem Commun 2013;4:1042-8.
87. Santos SA, Lukens AK, Coelho L, Nogueira F, Dyann F, Wirth Mazitschek R, *et al.* Exploring the 3-piperidin-4-yl-1H-indole scaffold as a novel antimalarial chemotype. Eur J Med Chem 2015;102:320-33.
88. Scuotto M, Abdelnabi R, Collarile S, Schiraldi C, Delang L, Massa A, *et al.* Discovery of novel multi-target indole-based derivatives as potent and selective inhibitors of chikungunya virus replication. Bioorg Med Chem 2016;25:327-37.
89. Chen L, Liu Y, Song H, Liu Y, Wang L, Wang Q. Expanding indole diversity: Direct 1-step synthesis of 1,2-fused indoles and spiroindolines from 2-halo anilines for fast SAR antiviral elucidation against tobacco mosaic virus (TMV). Mol Divers 2017;21:61-8.
90. Musella S, di Sarno V, Ciaglia T, Sala M, Spensiero A, Scala MC, *et al*. Identification of an indole-based derivative as potent and selective Varicella-zostervirus (VZV) inhibitor. Eur J Med Chem 2016;124:773-81.
91. Ravichandran VS, Shalini K, Venkateskuma S, Dhanaraj A. Exploring the structuralinsights of Indole-7-carboxamides as anti-HIV agents. FARMACIA 2016;64:745-56.
92. Ashok CL, Chander S, Zheng YT. Murugesan S. Design, synthesis, and biologicalevaluation of 1-(thiophen-2-yl)-9H-pyrido [3,4-b] indole derivatives as anti-HIV agents. Chem Biol Drug Des 2015;85:722-8.
93. Jiang HX, Zhuang DM, Huang XX, Cao JY, Zhang CB, Jiang B. Design, synthesis, and biological evaluation of novel trifluoromethyl indoles as potent HIV-1 NNRTIs with animproved drug resistance profile. Org Biomol Chem 2014;12:3446-58.
94. Ferro S, Morreale LS, Christ F, Debyser Z, Gitto R, Chimirri A. Synthesis and biologicalevaluation of novel antiviral agents as protein-protein interaction inhibitors. J Enzyme Inhib Med Chem 2014;29:237-42.
95. Hassam M, Basson AE, Liotta DC, Morris L, Van Otterlo WA, Pelly SC. Novel cyclopropyl-indole derivatives as HIV non-nucleoside reverse transcriptase inhibitors. ACS Med Chem Lett 2012;3:470-5.
96. Balupuri A, Gadhe CG, Balasubramanian PK, Cho G, Kothandan SJ. *In silico* study onindole derivatives as anti HIV-1 agents: A combined docking, molecular dynamics and 3DQSARstudy. Arch Pharm Res 2014;37:1001-15.
97. Yeung KS, Qiu ZQ, Fang H, Yang Z, Zadjura L, Eggers CD, *et al.* Inhibitors of HIV-1 attachment. Part 7: Indole-7-carboxamides as potent and orally bioavailable antiviral agents. Bioorg Med Chem Lett 2013;23:198-202.
98. La G, Regina A, Brancale A, Piscitelli F, Amiglini V, Cosconati SG, *et al.* New nitrogen containing substituent at the indole-2-carboxamide yield high potent and broad spectrum indolylarylsulfone HIV-1 non-nucleoside reverse transcriptase

inhibitors. J Med Chem 2012;55:6634-8.
99. La Regina G, Coluccia A, Brancale A, Piscitelli F, Gatti V, Maga G, *et al.* Indolylarylsulfones as HIV-1nonnucleoside reverse transcriptase inhibitors: New cyclic substituents at indole-2-carboxamide. J Med Chem 2011;54:1587-98.
100. Tichy M, Pohl R, Xu HY, Chen Y, Yokokawa F, Shi P. Synthesis and antiviral activity of 4,6-disubstituted pyrimido[4,5-b] indole ribonucleosides. Bioorg Med Chem 2012;20:6123-33.
101. Xue S, Ma L, Gao R, Li Y. Synthesis and antiviral activity of some novel indole-2-carboxylate derivatives. Acta Pharm Sin B 2014;4:313-21.
102. Zhang N, Turpoff A, Zhang X, Huang S, Liu Y, Almstead N, *et al.* Discovery of 2-(4-sulfonamidophenyl)-indole 3-carboxamides as potent and selective inhibitors with broad hepatitis C virus genotype activity targeting HCV NS4B. Bioorg Med Chem Letts 2016;26:594-601.
103. Porwal S, Gupta S, Chauhan PM. Gem-dithioacetylated indole derivatives as novel antileishmanial agents. Bioorg Med Chem Lett 2017;27:4643-6.
104. Félix MB, de Souza ER, de Lima MD, Frade DK, Serafim KA, Rodrigues PL, *et al.* Antileishmanial activity of new thipheneindole hybrids: Junior, design, synthesis, biological and cytotoxic evaluation, and chemometricstudies. Bioorg Med Chem 2016;24:3972-7.
105. Sharma R, Pandey AK, Shivahare R, Srivastava K, Gupta S, Chauhan PM. Triazino indole-quinoline hybrid: A novel approach to antileishmanial agents. Bioorg Med Chem Lett 2014;24:298-301.
106. Bharate SB, Bharate JB, Khan SI, Tekwani BL, Jacob MR, Mudududdla R, *et al.* Discovery of 3,3'-diindolylmethanes as potent antileishmanial agents. Eur J Med Chem 2013;63:435-43.
107. Singh GS, Al-Kahraman YM, Mpadi D, Yasinzai M. Synthesis of N-(1-methyl-1H-indol- 3-yl) methyleneamines and 3,3-diaryl-4-(1-methyl-1H-indol-3-yl) azetidin-2-ones as potential antileishmanial agents. Bioorg Med Chem Lett 2012;22:5704-6.
108. Kumar P, Singh S, Rizki M, Pratama F. Synthesis of some novel 1H-indole derivatives with antibacterial activity and antifungal activity. Lett Appl NanoBioSci 2020;9:961-7.
109. Zhang MZ, Chen Q, Xie CH, Mulholland N, Turner S, Irwin D, *et al*. Synthesis and antifungal activity of novel streptochlorin analogues. Eur J Med Chem 2015;92:776-83.
110. Jia CY, Xu LY, Yu X, Ding YB, Jin B, Zhang MZ, *et al.* An efficient synthesis and antifungal evaluation of natural product streptochlorin and its analogues. Fitoterapia 2018;125:106-10.
111. Ryu CK, Lee JY, Park RE, Ma MY, Nho JH. Synthesis and antifungal activity of 1H-indole-4,7-diones. Bioorg Medi Chem Lett 2007;17:127-31.
112. Mishra S, Kaur M, Singh P. Rational modification of a lead molecule: Improving the antifungal activity of indole triazole-amino acid conjugates. Eur J Med Chem 2018;155:658-69.
113. Xu H, Fan L. Synthesis and antifungal activities of novel indole [1,2-c]-1,2,4-benzotriazine derivatives against phytopathogenic fungi *in vitro*. Eur J Med Chem 2011;46:364-9.
114. Ming-Zhi Z, Mulholland N. Synthesis and antifungal activity of 3-(1,3,4-oxadiazol-5-yl)-indoles and 3-(1,3,4-oxadiazol-5-yl) methyl-indoles. Eur J Med Chem 2013;63:22-32.
115. Song Y, Wu F, Zhang C, Liang G, Zhou G, Yu J. Ionic liquid catalyzed synthesis of 2-(indole-3-yl)-thiochroman-4-ones and their novel antifungal activities. Bioorg Med Chem Lett 2015;25:259-61.
116. Pooja P, Singh P, Pawar K, Vikramdeo KS, Mondal N, Komath SS. Synthesis of amino acid appended indoles: Appreciable anti-fungal activity and inhibition of ergosterol biosynthesis as their probable mode of action. Eur J Med Chem 2014;80:325-39.
117. Corigliano DM, Syed R, Messineo S, Lupia A, Patel R, Reddy CV, *et al*. Brunetti, Indole and 2,4-Thiazolidinedione conjugates as potential anticancer modulators. Peer J 2018;6:5386.
118. Demurtas M, Baldisserotto A, Lampronti I, Moi D, Balboni G, Pacifico S, *et al*. Indole derivatives as multifunctional drugs: Synthesis and evaluation of antioxidant, photoprotective and antiproliferative activity of indole hydrazones. Bioorg Chem 2019;85:568-76.
119. Prakash BN, Amuthavalli A, Edison D, Sivaramkumar MS, Velmurugan R. Novel indole derivatives as potential anticancer agents: Design, synthesis and biological screening. Med Chem Res 2018;27:321-31.
120. Tocco G, Zedda G, Casu M, Simbula G, Begala M. Solvent-free addition of indole to aldehydes: Unexpected synthesis of novel 1-[1-(1h-indol-3-yl) alkyl]-1hindoles and preliminary evaluation of their cytotoxicity in hepatocarcinoma cells. Molecules 2017;22:1747.
121. Romagnoli R, Baraldi PG, Prencipe F, Oliva P, Baraldi S, Salvador MK, *et al*. Design, synthesis and biological evaluation of 3-substituted-2-oxindole hybrid derivatives as novel anticancer agents. Eur J Med Chem 2017;134:258-70.
122. Lafayette EA, de Almeida SM, Cavalcanti Santos RV, de Oliveira JF, Amorim CA, da Silva RM, *et al*. Synthesis of novel indole derivatives as promising DNA binding agents and evaluation of antitumor and antitopoisomerase I activities. Eur J Med Chem 2017;136:511-22.
123. Chang SM, Christian W, Wu MH, Chen TL, Lin YW, Suen CS, *et al*. Novel indolizino[8,7-b] indole hybrids as anti-small cell lung cancer agents: Regioselective modulation of topoisomerase II inhibitory and DNA cross-linking activities. Eur J Med Chem 2017;127:235-49.
124. Bakherad Z, Safavi M, Fassihi A, Sadeghi-Aliabadi H, Bakherad M, Rastegar H, *et al*. Anti-cancer anti-oxidant and molecular docking studies of thiosemicarbazone indole-based derivatives. Res Chem Int 2019;45:2827-54.
125. Jiang JR, Xu F, Wu HG. Synthesis and anticancer activity of 1-(1H-indol-3-yl)- 2-(4-diarylmethylpiperazine-1-yl) ethane-1, 2-dione derivatives. J Chem 2016;2016:4617454.
126. Kumar KS, Rajesham B, Ramulu MS, Bhaskar B, Dash SN, Ashfaq MA, *et al*. Cu-catalyzed ligand-free synthesis of rosuvastatin based novel indole derivatives as potential anticancer agents. RSC Adv 2016;6:100487-93.
127. Hu H, Wu J, Au M, Wang H, Zhou T, Xue Y, *et al*. Synthesis, structure-activity relationship studies and biological evaluation of novel 2,5-disubstituted indole derivatives as anticancer agents. Chem Biol Drug Des 2016;88:766-78.
128. Swathi K, Sarangapani M. Synthesis and antiepileptic activity of schiff's bases of dialkylamino alkoxy isatin derivatives. Adv Exp Med Biol 2015;822:119-28.
129. Madhira S, Mandava K, Mandab S, Prasanna SR, Vijayalaxmi T. Synthesis and evaluation of some novel N, N-dialkylaminoalkoxy-2-oxo-indole-3-ylidene benzohydrazides as anticonvulsant agents. IOSR JPBS 2017;2:84-93.
130. Raju GN, Sai KB, Naveen KT, Nadenla RR. Synthesis, characterization and anticonvulsant activity of novel benzyl-6-chloro Indole carboxylate derivatives. J Basic Appl Res 2016;2:437-41.
131. Ahuja P, Siddiqui N. Anticonvulsant evaluation of clubbed indole-1,2,4-triazine derivatives: a synthetic approach. Eur J Med Chem 2014;2:509-22.
132. Rajan S, Puri S, Kumar D, Babu MH, Shankar K, Varshney S, *et al*. Gaikwad, Novel indole and triazole based hybrid molecules exhibit potent anti-adipogenic and antidyslipidemic activity by activating Wnt3a/β-catenin pathway. Eur J Med Chem 2018;143:1345-60.
133. Nazir M, Abbasi MA, Rehman AU, Siddiqui SZ, Khan KM, Salar U, *et al*. New indole-based hybrid oxadiazole scaffolds with N-substituted acetamides: As potent anti-diabetic agents. Bioorg Chem 2018;81:253-63.
134. Srividya LL, Reddy AR. Antidiabetic activity of 1-(4-chloro

benzylidene)-5-(2-oxoindolin-3-ylidene) thiocarbohydrazone in chick model. Asian J Biol Sci 2017;10:126-9.
135. Taha M, Rahim F, Imran S, Ismail NH, Ullah H, Selvaraj M, *et al*. Synthesis α-glucosidase inhibitory activity and *in silico* study of tris-indole hybrid scaffold with oxadiazole ring: As potential leads for the management of type-II diabetes mellitus. Bioorg Chem 2017;74:30-40.
136. Mukthung C, Chancharunee S, Kielar F, Pongcharoen S, Wichai U. Capsaicin derivatives containing indole and nitroindole for improved anti-inflammatory activity. Naresuan Univ J Sci Technol 2018;26;157-69.
137. Bhat MA, Al-Omar MA, Raish M, Ansari MA, Abuelizz HA, Bakheit AH, *et al*. Indole derivatives as cyclooxygenase inhibitors: synthesis biological evaluation and docking studies. Molecules 2018;23:1250.
138. Shaker AM, Abdelall EK, Abdellatif KR, Abdel-Rahman HM. Design, synthesis, and biological evaluation of 2-(4-(methylsulfonyl) phenyl) indole derivatives with promising COX-2 inhibitory activity. J Appl Pharma Sci 2018;8:1-8.
139. Shroff M, Daharwal SJ. Newer substituted indolyl-pyrazoline derivatives as antiinflammatory agents. Br Biomed Bull 2017;5:298.
140. Fatahala S, Khedr MA, Mohamed MS. Synthesis and structure activity relationship of some indole derivatives as potential anti-inflammatory agents. Acta Chim Slov 2017;64:865-76.
141. Xu X, Rajamanickam V, Shu S, Liu Z, Yan T, He J, *et al*. Indole-2-carboxamide derivative LG25 inhibits triple-negative breast cancer growth by suppressing Akt/mTOR/NF-κB signalling pathway. Drug Design Dev Ther 2019;13:3539.
142. Shaveta SA, Kaur M, Sharma S, Bhatti R, Singh P. Rational design, synthesis and evaluation of chromone-indole and chromone-pyrazole based conjugates: Identification of a lead for anti-inflammatory drug. Eur J Med Chem 2014;77:185-92.
143. Kerzare DR, Menghani SS, Khedekar PB. Synthesis, characterization, antidepressant activity and docking studies of some novel indole bearing azetidinone derivatives. Indian J Pharm Educ Res 2018;52:110-20.
144. Patil PO, Bari SB. Synthesis, characterization and screening for antidepressant and anticonvulsant activity of 4, 5-dihydropyrazole bearing indole derivatives. Arab J Chem 2013;59:588-95.
145. Gurer-Orhan H, Karaaslan C, Ozcan S, Firuzi O, Tavakkoli M, Saso L, *et al*. Novel indole-based melatonin analogues: Evaluation of antioxidant activity and protective effect against amyloid β-induced damage. Bioorg Med Chem 2016;24:1658-64.
146. Silveira CC, Mendes SR, Soares JR, Victoria FN, Martinez DM, Savegnago L. Synthesis and antioxidant activity of new C-3 sulfenyl indoles. Tetrahedron Lett 2013;54:4926-9.
147. Parveen S, Riaz N, Saleem M, Ashraf M, Khatoon T, Nisar F, *et al*. Noropacursane: A new nortriterpenoid from the methanolic extract of *Carissa opaca*. Rec Nat Prod 2018;12:512-7.
148. Mohammadi-Farani A, Ahmadi A, Nadri H, Aliabadi A. Synthesis, docking and acetylcholinesterase inhibitory assessment of 2-(2-(4-Benzylpiperazin-1-yl)ethyl) isoindoline-1,3-dione derivatives with potential anti-Alzheimer effects. DARU 2013;21:47.
149. Bhowal SK, Lala S, Hazra A, Paira P, Banerjee S, Mondal NB, *et al*. Synthesis and assessment of fertility-regulating potential of 2-(2”-chloroacetamidobenzyl)-3-(3’-indolyl) quinoline in adult rats as a male contraceptive agent. Contraception 2008;77:214-22.
150. Ji Q, Gao J, Wang J, Yang C, Hui X, Yan X, *et al*. Benzothieno [3,2-b]indole derivatives as potent selective estrogen receptor modulators. Bioorg Med Chem Lett 2005;15:2891-3.