RECENT REVIEW ON INDOLE: A PRIVILEGED STRUCTURE SCAFFOLD

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Abstract

Indole is abicyclic aromatic heterocyclic organic compound comprising of a six membered benzene ring fused to a five-membered nitrogen-containing pyrrole ring. It is an excellent scaffold in drug discovery which provides numerous opportunities in the discovery of novel drugs with different mechanism of action. It has a very unique property of mimicking different structures of proteins and binding to enzymes in a reversible manner. A vast research has occurred on indole and its derivatives which resulted in many approved indole containing drugs in the world market as well as many are in the pipeline stages. This reviewfocussed on recent developments of indole derivatives having different pharmacological profiles as well as different perspectives on how this indole moiety as a privilege structure may be exploited in the near future.

Keywords: Indole; Anti-cancer activity; Anti-malarial activity and Anti-viral activity.

Introduction

Indole is a well-known privileged structure scaffold occurring in numerous natural products such as alkaloids, peptides and various synthetic compounds. Because of its biodynamic properties; Indole as well as its derivatives has occupied a unique platform in nitrogen heterocyclic chemistry [1, 2].It is a hetero-atomic planar molecule comprising of benzene ring fused to a pyrrole ring at -2 & -3 position.[3]. The chemistry of indole dates back to mid-19th century due to an extensive research on a natural violet-blue dye named indigo which leads to the synthesis of indole in 1866 by zinc distillation of Oxindole [4-6].

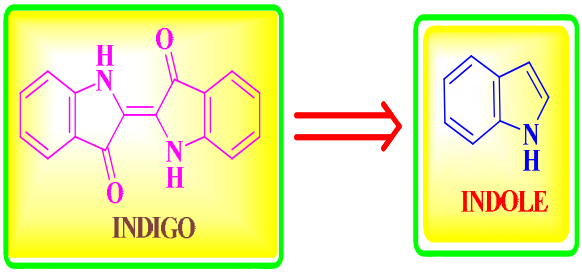


Fig. 1: Discovery of indole

Thisscaffold is an omnipresent constituent of pharmacologically active natural products such as indole-3-acetic acid (IAA-plant hormone)[7], tryptophan (essential amino acid)[8], 5-hydroxytryptamine (5-HT-neurotransmitter) [9], melatonin [10]. Biological studies of indole-3-carbinol (I3C), and 3,30-diindolylmethane(DIM), (natural product derived from the digestion of I3C)are under research due to their anti-cancer, anti-oxidant, and anti-atherogenic effects [11-14], Ajmalicine (Indole alkaloid - as antihypertensivedrug)[15-16],

Reserpine [17]&Vinblastine [18]etc.Indole finds applications in medical science due tovarious valuable biologic activities such as Antiviral, Anti-inflammatory, Anti-cancer, Anti-microbial, Anti-malarial, Anti-asthmatic, ACE inhibitor,Anti-oxidant, Anti-fungal, Aromatase inhibitor, CB1 receptor allosteric modulator, Chelating agent, Glucagon receptor antagonist, Hepatitis C virus genotype activity, Hepsin inhibitor, Histone deacetylase inhibitor, PDE4 inhibitor, Urease inhibitorand VEGFR-2 kinase inhibitor.Indole is a chief structural motif described as privileged scaffolds, a term introduced by Evans and co-workers to define scaffolds which are capable of acting as ligand for diversity of receptors [19-21]. They have the exclusive property of mimicking structure of proteins and bind reversibly to enzymes [22-25] which provide fabulous opportunities to discover novel drugs with dissimilar modes of action. Many of the synthesized indole-containing commercial drugs are

reported as among best Selling Drugs by US Retail. [26]. There are also large number of approved indole containing drugs in the market as well as compounds currently going through different clinical phases. Some indole containing marketed drugs is listed below.

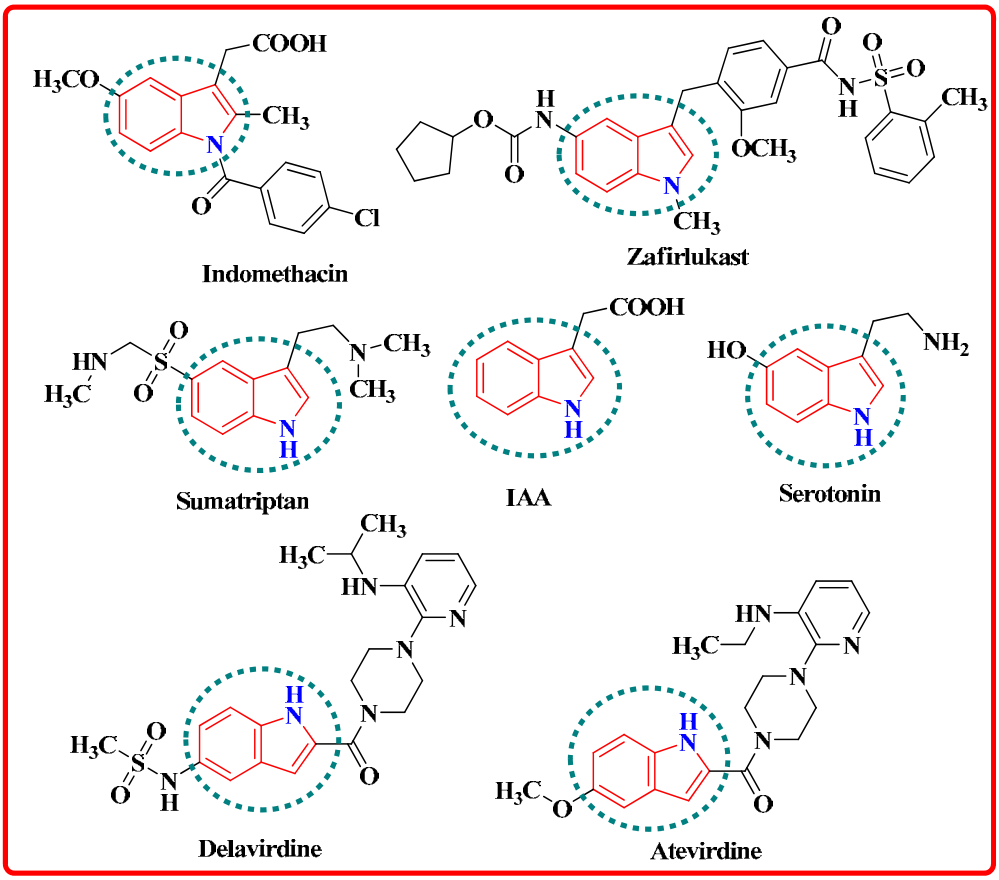


Fig. 2: Structures of some marketed formulations and natural products containing Indole scaffold.

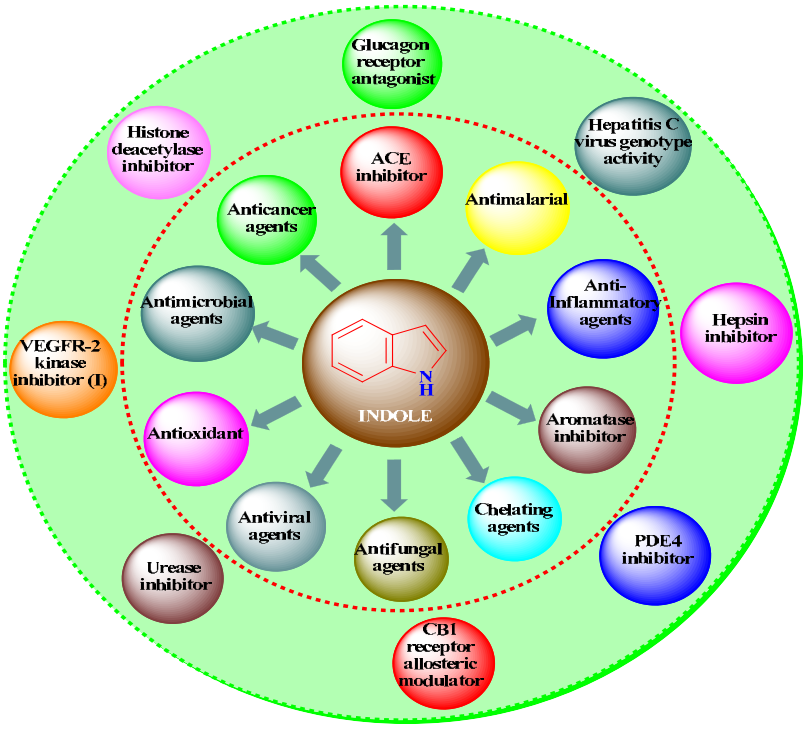
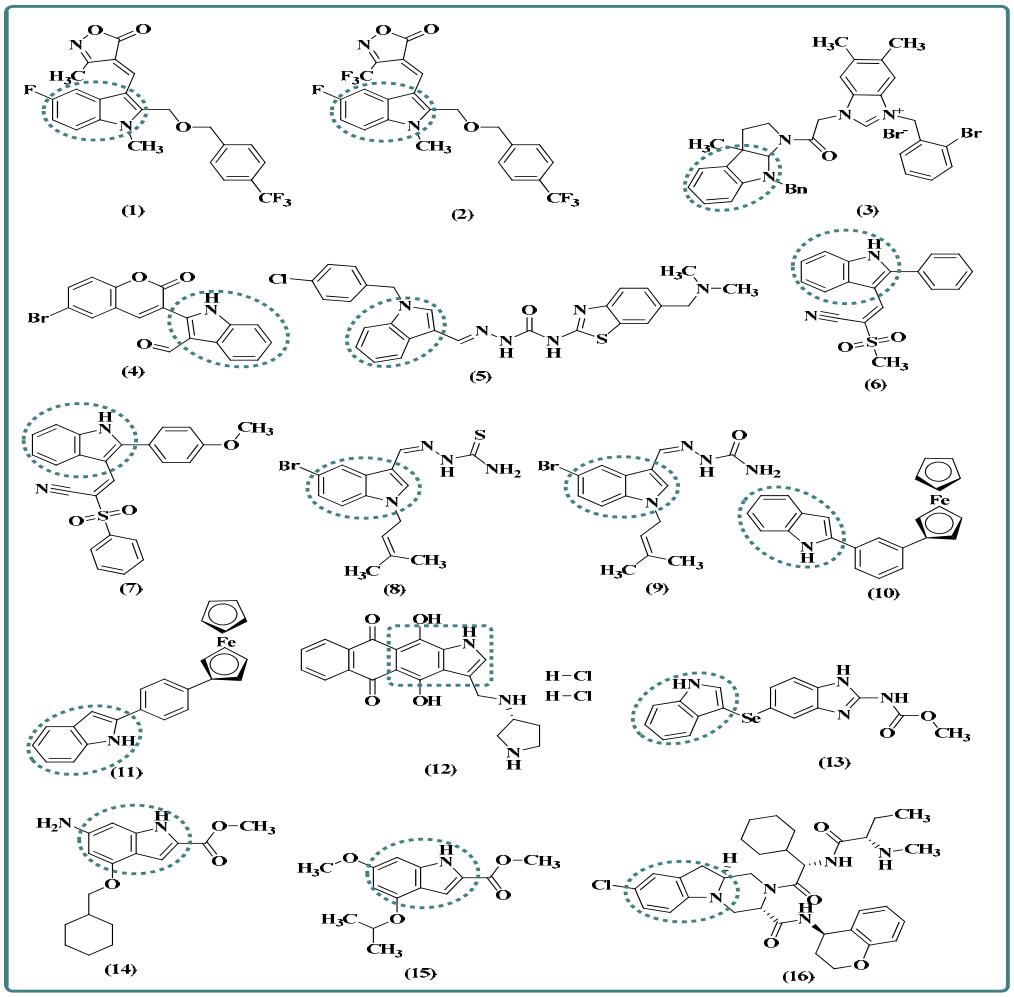


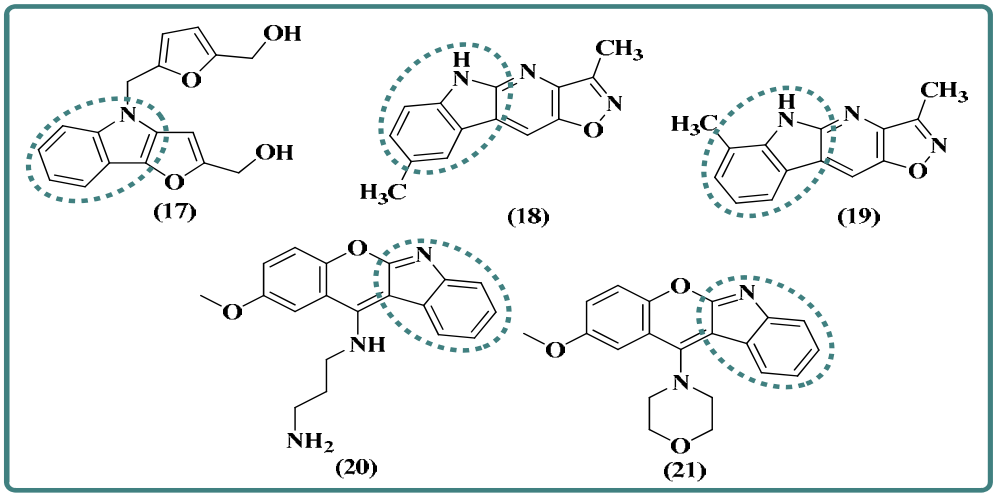
Fig. 3: Pharmacological profile of Indole scaffold.

Pharmacological profile

Anticancer

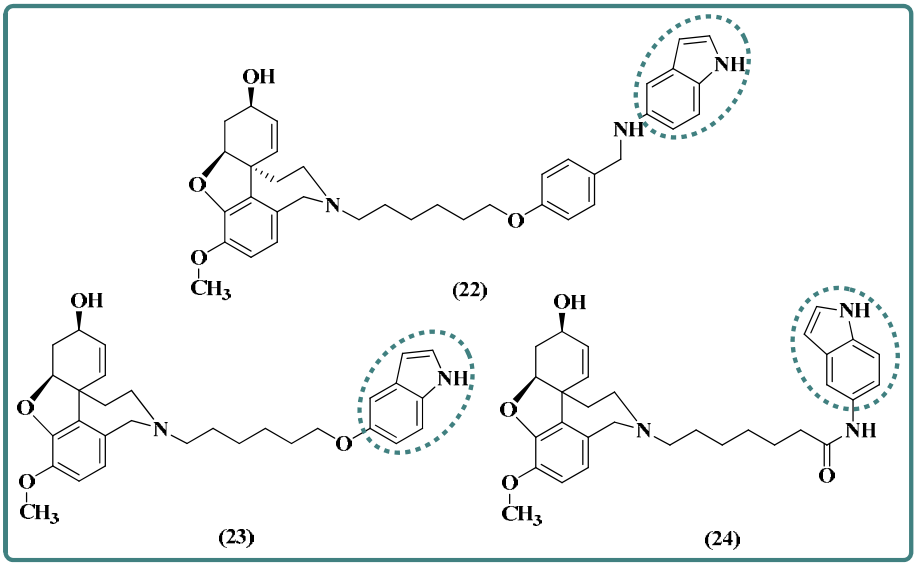
Panathur*et al* [28] synthesized a new series of indole–isoxazolone hybrids using a facile synthetic route and were screened against three human cancer cell lines to evaluate their in vitro cytotoxic property. Compound (**1**) (E)-4-((5-fluoro-1-methyl-2-((4-(trifluoromethyl) benzyloxy)methyl)-1H-indol-3-yl)methylene)-3-methylisoxazol-5(4H)-one and (**2**) (E)-4-((5-fluoro-1-methyl-2-((4-(trifluoromethyl)benzyloxy)methyl)-1H-indol-3-yl)methylene)-3-(trifluoromethyl)isoxazol-5(4H)-one found to be most potent inhibitors of SIRT1 with IC_{50} values of 35.25 and 37.36 lM, respectively. Zhou *et al* [29] synthesized a novel series of hexahydropyrrolo[2,3-*b*]indole–1*H*-imidazolium salts and evaluated them against human tumor cell lines *in vitro*. Compound **(3)** 1-(2-(8-benzyl-3a-methyl-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indol-1(2H)-yl)-2-oxoethyl)-3-(2-bromo benzyl)-5,6-dimethyl-1H-benzo[d]imidazol-3-iumbromide was found to be most potent with IC_{50} values below 2.68 µM and is more selective towards SMMC-7721, A549 and SW480 cell lines. Kamath *et al* [30] synthesized three series of indole–coumarin hybrids – 3-(1-benzyl-1H-indol-2-yl)-2H-chromen-2-ones, 2-(2-oxo-2H-chromen-3-yl)-1H-indole-3-carbaldehydes and 2-(2-oxo-2H-chromen-3-yl)-1H-indole-3-carboxylic acids and characterized by spectral techniques like IR, ^{1}H NMR, ^{13}C NMR, Mass spectrometry and elemental analysis. Compound (**4**) 2-(6-bromo-2-oxo-2H-chromen-3-yl)-1H-indole-3-carbaldehyde was found to be most active.Ma *et al* [31] designed and synthesized a series of novel benzothiazole derivatives bearing indole-based moiety and screened against HT29, H460, A549 and MDA-MB-231 cancer cell lines for in vitro antitumor activity. Compound (**5**) (E)-2-((1-(4-chlorobenzyl)-1H-indol-3-yl)methylene)-N-(6-((dimethylamino)methyl)benzo[d]thiazol-2-yl)hydrazinecarboxamide showed excellent antitumor activity with IC_{50} values of 0.024, 0.29, 0.84 and 0.88 Mm against HT29, H460, A549 and MDA-MB-231.Spallarossa*et al* [32] synthesized a new series of indole-based analogues potential anticancer agents. Compounds (**6**) (E)-2-(methylsulfonyl)-3-(2-phenyl-1H-indol-3-yl)acrylonitrile and (**7**) (E)-3-(2-(4-methoxyphenyl)-1H-indol-3-yl)-2-(phenylsulfonyl)acrylonitrile was found to be most active and highlighted a pro-apoptotic potential.Chopparа*et al* [33] designed and synthesized a series of novel N-1 and C-3 substituted indole derivatives and evaluated them for their cytotoxic properties, viz Brine Shrimp Lethality Bioassay (BSLB) besides 5-Lipoxygenase (5-LOX) inhibitory activities through in vitro assays. Compound (**8**) (Z)-2-((5-bromo-1-(3-methylbut-2-enyl)-1H-indol-3-yl) methylene) hydrazinecarbothioamide and (**9**) (Z)-2-((5-bromo-1-(3-methylbut-2-enyl)-1H-indol-3-yl) methylene) hydrazinecarboxamide was found to be most potent with an LC_{50} of 6.49 µM (**8**) and with an IC_{50} of 33.69 µm (**9**). Radulovic*et al* [34] designed and synthesized two new ferrocene–indole hybrids, (**10**)2-(3-ferrocenylphenyl)-1H-indole and (**11**) 2-(4-ferrocenylphenyl)-1H-indole, utilizing the Fischer indole synthesis as the key step. Both compounds showed significant myeloperoxidase inhibiting activity, weak anticholinesterase activity but high cytotoxicity against rat peritoneal macrophages & the crustacean Artemiasalina and possible cytotoxic activities of these compounds against human cancer cell lines.Shchekotikhin*et al* [35] synthesized a series of new 3-aminomethyl-4,11-dihydroxy naphtho[2,3-*f*]indole-5,10-diones bearing the cyclic diamine in the position 3 of the indole ring. Compound (**12**) (R)-4,11-dihydroxy-3-((pyrrolidin-3-ylamino)methyl)-1H-naphtho[2,3-f]indole-5,10-dione dihydrochloride was found to be most active.Guan *et al* [36] synthesized a series of novel benzimidazole carbamates bearing indole moieties with sulphur or selenium atoms connecting the aromatic rings and evaluated them for their anti-proliferative activities against SGC-7901, A-549 and HT-1080 human cancer cell lines by using an MTT assay. Compounds (**13**) methyl 5-(1H-indol-3-ylselanyl)-1H-benzo[d]imidazol-2-ylcarbamate showed most promising results.Ji *et al* [37] designed and synthesized a novel class of indole-2-carboxylate derivatives which is based on the chemical structure of Pyrroloquinolinequinone (PQQ) and assayed for anti-proliferative activity in cancer cells *in vitro*. Compound (**14**) methyl 6-amino-4-cyclohexylmethoxy-1Hindole-2-carboxylate and (**15**) methyl 4-isopropoxy-6-methoxy-1H-indole-2-carboxylate were found to be more potent anti-proliferative agent than the reference drugs PQQ and etoposide *in vitro*, with IC_{50} values ranging from 3.78 _ 0.58 to 24.08 _ 1.76 µM. Shiokawa*et al* [38] developed hexahydropyrazino [1,2-a]indole scaffold using structure-based drug design. Compound (**16**) (3S,10aS)-8-Chloro-2-[(2S)-2-cyclohexyl-2-{[(2S)-2-(methylamino)butanoyl]amino}acetyl]-N-[(4R)-3,4-dihydro-2H-chromene-4-yl]-1,2,3,4, 10,10a-hexahydropyrazino[1,2-a]indole-3-carboxamide showed strong inhibition of IAP binding (X chromosome-linked IAP [XIAP]: IC_{50} 23 µM and cellular IAP [cIAP]: IC_{50} 1.1 µM) and cell growth inhibition (MDA-MB-231 cells: GI_{50} 2.8 µM) with high permeability and low potential of MDR1 substrate.Zhuang *et al* [39] synthesized and evaluated a series of 2,4-disubstituted furo[3,2-*b*]indole derivatives for anticancer activity. Compound (**17**) (5-((2-(hydroxymethyl)-4H-furo[3,2-b]indol-4-yl)methyl)furan-2-yl)methanol was found to be the most promising agent. Rajanarender*et al* [40] synthesized a series of novel isoxazolo[50,40:5,6]pyrido[2,3-b]indoles and evaluated them for their *in vitro* and *in vivo* anticancer activities. Compound (**18**) & (**19**) had shown potential anticancer activity as compared to Cisplatin. Peng *et al* [41] synthesized a series 11-amino derivatives of chromeno[2,3-b]indoles. Compound (**20**) N1-(2-methoxychromeno[2,3-b]indol-11-yl)propane-1,3-diamine and (**21**) 2-methoxy-11-morpholinochromeno[2,3-b]indole showed excellent anti-proliferative activity against MV4-11 (human leukemia), A549 (lung cancer), HCT116 (colon cancer), and the normal mice fibroblast (BALB/3T3).





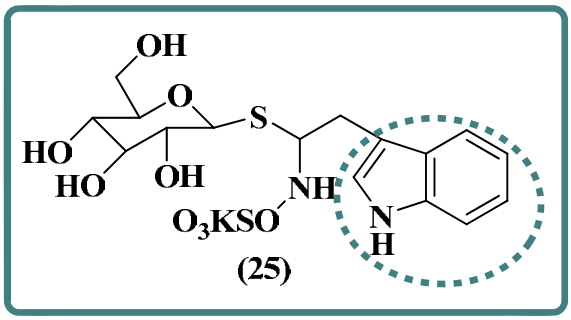
Acetylcholinesterase inhibitor

Atanasova*et al* [42]synthesized galantamine derivatives with indole moiety in the side chain which were 11-95 times more active than galantamine. Compound (**22**) (4aS,6R,8aS)-11-(6-(4-((1H-Indol-5-ylamino)methyl)phenoxy) hexyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]-benzofuro[4,3-cd]azepin-6-ol, (**23**) (4aS,6R,8aS)-11-(6-(1H-Indol-5-yloxy) hexyl)-3-methoxy-5,6,9,10,11,12-hexa hydro-4aH-benzo[2,3]benzofuro[4,3-*cd*]azepin-6-ol and (**24**) N-(1H-Indol-5-yl)-6-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]-benzofuro[4,3-cd]azepin-11(12H)-yl)hexanamide were found to be most potent.



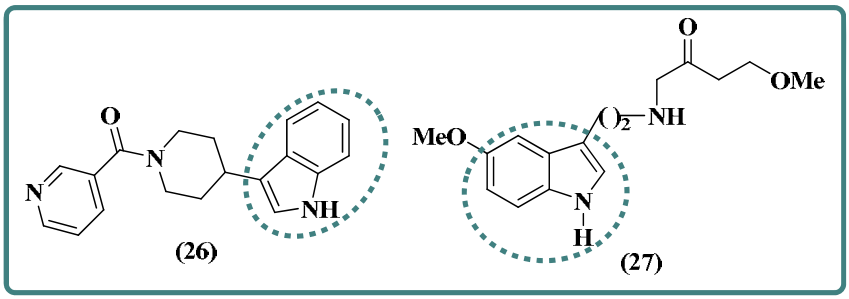
Anti-inflammatory

Vo *et al* [43] in this work synthesized indole glucosinolates(GLs) through nitronate and nitrovinyl methods and evaluated for their anti-inflammatory activity which was determined by inhibition of TNF-α secretion in LPS-stimulated THP-1 cells. The compound (**25**) Glucobrassin was found to be most potent.



Antimalarial

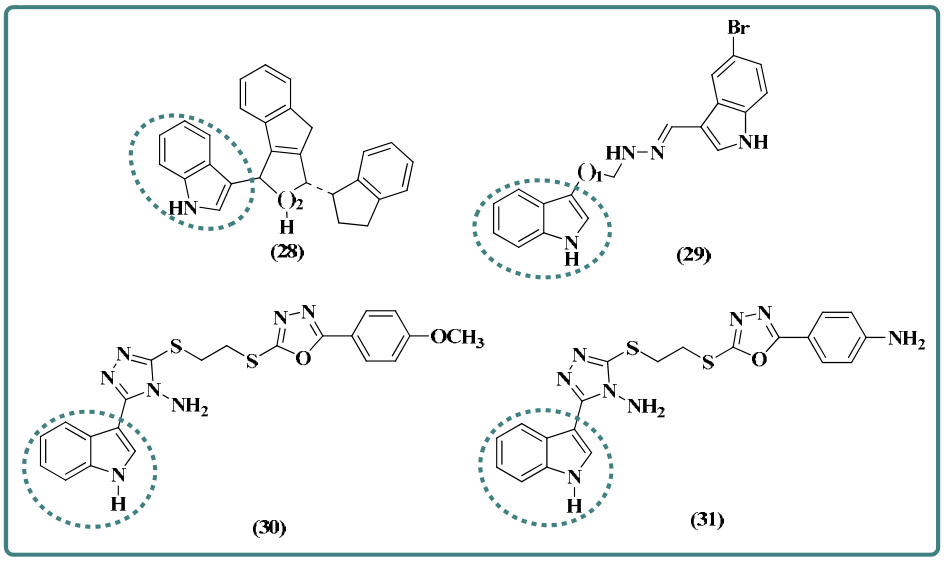
Santos *et al* [44] in their study examined a series of 3-piperidin-4-yl-1H-indoles based on a hit derived from an HTS whole-cell screen against Plasmodium falciparum and evaluated forantiparasitic activity. SAR study was carried out which shows that 3-piperidin-4-yl-1H-indole is intolerant to most N-piperidinyl modifications. Compounds (**26**) (4-(1H-indol-3-yl)piperidin-1-yl) (pyridin-3-yl) methanone exhibits potential antimalarial activity.Schuck *et al* [45] have synthesized two families of structurally-related melatonin compounds which were assayed in P. falciparum culture and their antimalarial activities were measured by flow cytometry. Among the melatonin derivatives, Compounds (**27**) was capable of inhibiting the P. falciparum growth and thereby found to be most active.



Antimicrobial

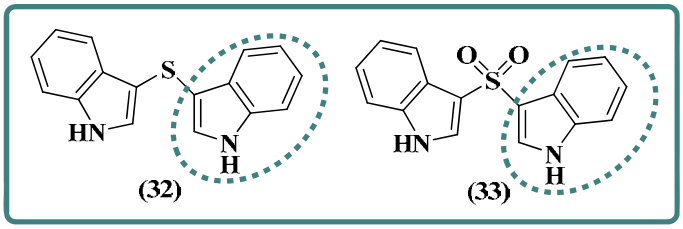
El-Sayed *et al* [46] in this present work synthesized bisindolyl-substituted cycloalkane-anellated indoles as novel class of antibacterial agents. The most active compound (**28**) was found to be cyclohexane indole when tested against against S. aureus and MRSA.Chopparaet *al* [47] in this present work synthesized two series of novel bis(indole) analogues and were screened for their antimicrobial, anticancer activities and structure and

activity relationship (SAR) was also investigated. Compound (**29**) N(-((5-bromo-1H-indol-3-yl)methylene)-2-(1H-indol-3-yl)acetohydrazide) was found to be most potent.Shi *et al* [48] discussed the synthesis and antibacterial activities of novel indole derivatives containing 1,3,4-oxadiazole and 1,2,4-triazole moieties through ultrasound irradiation. In this series two optimized inhibitors (**30**) 3-(1H-indol-3-yl)-5-[[2-[[5-(4-methoxyphenyl)- 1,3,4-oxadiazol-2-yl]thio]ethyl]thio]-4H-1,2,4-triazol- 4-amine and (**31**)3-(1H-indol-3-yl)-5-[[2-[[5-(4-aminophenyl)-1,3,4- oxadiazol-2-yl]thio]ethyl]thio]-4H-1,2,4-triazol-4- amine shows excellent intrinsic potency.



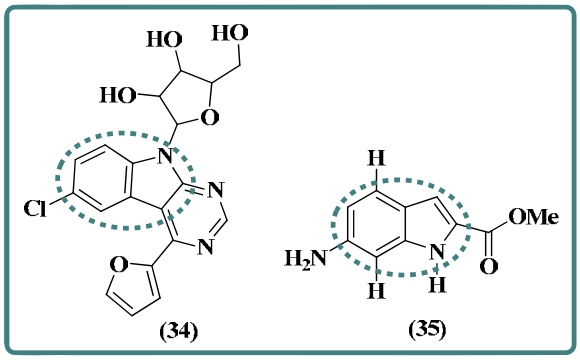
Antioxidant

Silveira*et al* [49] was designed new C-3 sulfur-substituted indoles and evaluated for antioxidant activity at the low micromolar level, in DPPH, ABTS, and FRAP assays. The compounds (**32**) bis(indol-3-yl)sulphide and (**33**) bis(indol-3-yl)sulfone proved to display potent antioxidant activity.



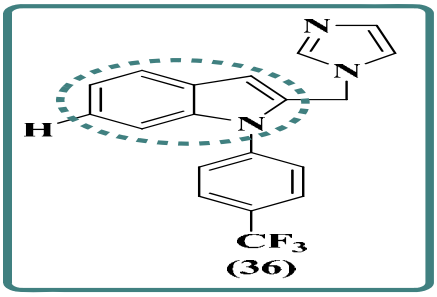
Antiviral

Tichy*et al* [50] synthesized some novel indole-2-carboxylate derivatives which was assayed for antiviral activities. Their relation with activity was carried out through SAR study was performed to get the biological activity. Compound (**34**) 2-(6-chloro-4-(furan-2-yl)-9H-pyrimido[4,5-b]indol-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diolshows potent inhibitory activity.Xue*et al* [51] synthesized a series of novel indole-2-carboxylate derivatives and were assayed to determine their in vitro broad spectrum antiviral activities. SAR study was also carried out .When tested against influenza A virus, compound (**35**) methyl 6-amino-1H-indole-2-carboxylate showed most potent inhibitory activity.



Aromatase inhibitors

Wang *et al* [52] the aromatase inhibitory activity was performed to the synthesized novel indole-imidazole derivatives. Among the series of compounds, the most active compound was found to be (**36**) 2-((1H-imidazol-1-yl)methyl)-1-(4-(trifluoromethyl)phenyl)-1H-indole.



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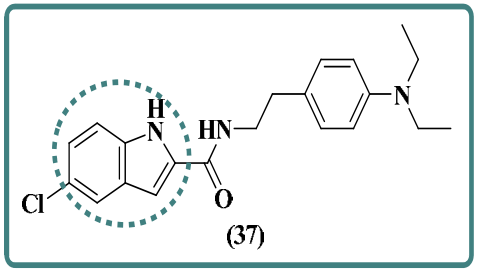
CB1 receptor allosteric modulators

Nguyen *et al* [53] synthesized a series of substituted 1H-indole-2-carboxamides and evaluated them for CB1 allosteric modulating activity in calcium mobilization assays along with the SAR study. The most potent compound (**37**) 5-Chloro-N-{2-[4-(diethylamino)phenyl]ethyl}-1H-indole-2-carboxamide had an IC_{50} value of 79 µM which is 2.5 and 10 fold more potent than the parent compounds.



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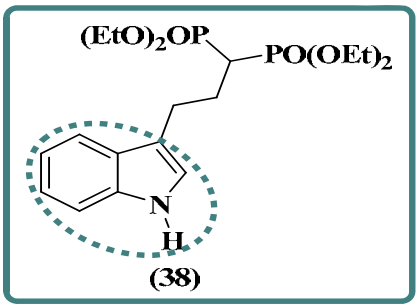
Chelating agents

Palmerini*et al* [54] reported the synthesis of new indole-based bisphosphonates and evaluated osteoclast-mediated bone loss. Preliminary in silico and in vitro ADME studies were also performed and the results suggested that the compound (**38**) tetraethyl 3-(1H-indol-3-yl)propane-1,1-diyldiphosphonate was an indole based bisphosphonates showed highest activity.



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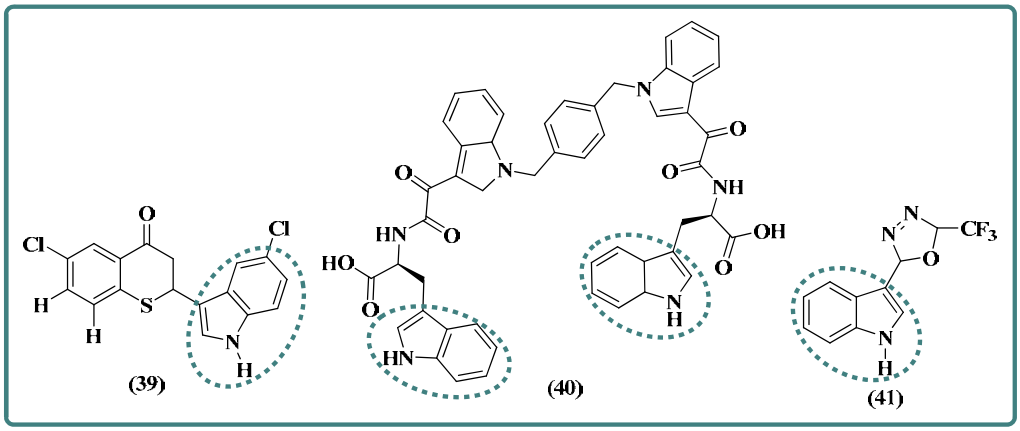
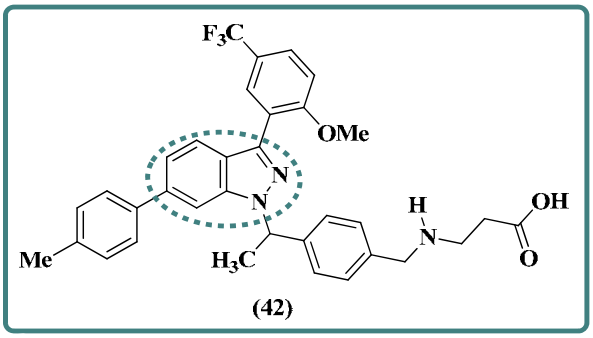
.**Antifungal**

Song *et al* [55] reported the synthesis of 2-(Indole-3-yl)-thiochroman-4-ones and evaluated them for in vitro antifungal activity. The derivatives showed better activity than fluconazole. Compound (**39**) 6-chloro-2-(5-chloro-1H-indol-3-yl)thiochroman-4-one showed potent antifungal activity.Pooja *et al* [56] carried out the synthesis ofamino acid appended indoles and tested against Candida albicans with their MIC_{80} in µg/ml range. Compound (**40**) (2R)-2-(2-(1-(4-((3-(2-((S)-1-carboxy-2-(1H-indol-3-yl)ethylamino)-2-oxoacetyl)-2,7a-dihydro-1H-indol-1-yl) methyl)benzyl)-1H-indol-3-yl)-2-oxoacetamido)-3-(3a,7a-dihydro-1H-indol-3-yl)propanoic acid showed good activity.Zhang*et al* [57] synthesized three series of novel indole-based 1,3,4-oxadiazoles. Bioassaysshowed that several of the synthesized compounds exhibit higher antifungal activity than pimprinine. .Compounds (**41**) 2-(1H-indol-3-yl)-5-(trifluoromethyl)-2,5-dihydro-1,3,4-oxadiazole was found to be most active most active on the biological assays.



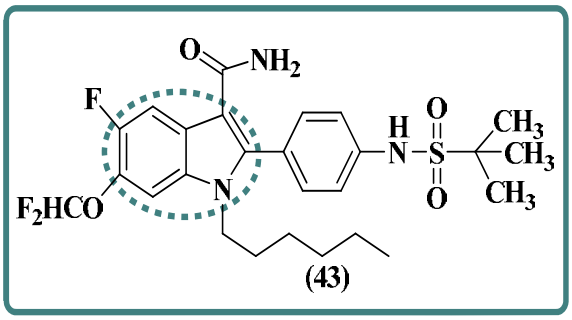
Glucagon receptor antagonist

Lin *et al* [58] carried out the synthesis of a novel series of indazole-/indole-based glucagon receptor antagonists. Compound (**42**) 3-(4-(1-(3-(2-methoxy-5-(trifluoromethyl) phenyl) -6-p-tolyl-1H-indazol-1-yl)ethyl)benzylamino)propanoic acidexhibited significant growth inhibition.



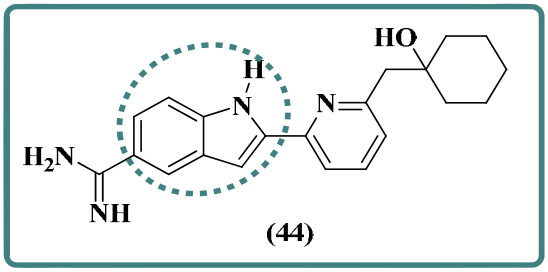
Hepatitis C virus genotype activity

Zhang *et al* [59] synthesized a novel series of 2-(4-sulfonamidophenyl)-indole 3-carboxamides derivatives and was tested against the HCV genotype 1b replicon. Compound (**43**) 6-(difluoromethoxy)-2-(4-(1,1-dimethylethylsulfonamido)phenyl)-5-fluoro-1-hexyl-1H-indole-3-carboxamide showed excellent activity.



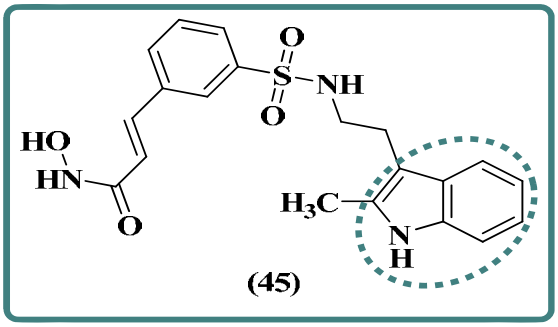
Hepsin inhibitors

Goswami*et al* [60] discovered 2-aryl/pyridin-2-yl-1H-indole derivatives as potent and selective hepsin inhibitors and characterized by X-ray crystallography. Compound (**44**) 2-(6-((1-hydroxycyclohexyl)methyl)pyridin-2-yl)-1H-indole-5-carboximidamide showed good activity.



Histone deacetylase inhibitor

Mehndiratta*et al* [61] have synthesized a series of 2-methyl-1H-indol-3-ethylsulfamoylphenylacrylamides and evaluated for their histone deacetylase (HDAC) inhibitory and anti-inflammatory activity. Compound (**45**) (E)-N-hydroxy-3-(3-(N-(2-(2-methyl-1H-indol-3-yl)ethyl)sulfamoyl)phenyl)acrylamide showed good results and can serve as lead compound.



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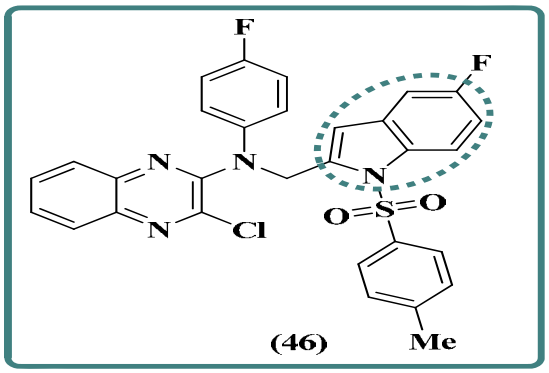
PDE4 inhibitor

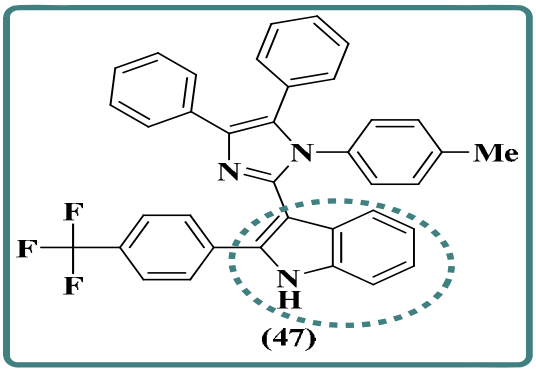
Luther *et al* [62] reported the synthesis of novel indole-quinoxaline hybrids by connecting an indole moiety with a quinoxaline ring through a linker to target phosphodiesterase 4 PDE4). Compound (**46**) 3-chloro-N-((5-fluoro-1-tosyl-1H-indol-2-yl)methyl)-N-(4-fluorophenyl) quinoxalin-2-amine showed excellent results.



(46)

Urease inhibitor

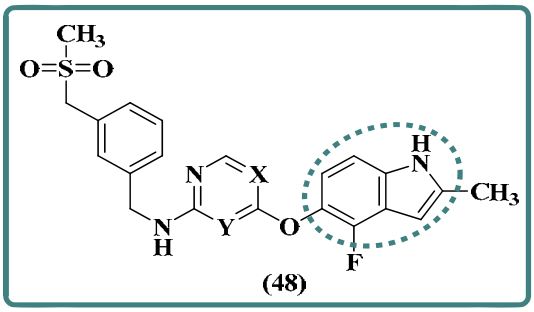
Naureen*et al* [63] carried out the synthesis of a series of tetraarylimidazoles (5A-5O). When compared with thiourea the synthesized compounds exhibited potent anti-urease activity with IC_{50} values ranging from 0.12 ± 0.06 µM to 29.12 ± 0.18 µM. Compound (**47**) 3-(4,5-diphenyl-1-p-tolyl-1H-imidazol-2-yl)-2-(4-(trifluoromethyl)phenyl)-1H-indole was found to be most potent inhibitor of urease enzyme.



(47)

VEGFR-2 kinase inhibitors (I)

Gao *et al* [64] synthesized O-linked indoles and were evaluated by enzymatic proliferation assays as potent inhibitors of VEGFR-2. Compound (**48**) showed significant anti-angiogenesis activities with IC_{50} value of 3.8 nmol/L.



(48)

Conclusion

Indole is an abundant heterocycle which is commonlyfound in pharmacologically active natural products, agrochemicals &pharmaceuticals. Because of its vast biological profile, researchers found interest in the use ofindole derivatives as bioactive molecules against variousdiseases. This review defines recent developments of indole as an important scaffoldin novel drugdiscovery.

Conclusion

The article is focused on different targets of morpholine derivatives which can be explored with different inhibitors/activators for better treatment of lifestyle diseases.

Conflict of interest

The authors confirm that this article content has no conflicts of interest.

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