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NOVEL INDOLE DERIVATIVES AS A PROMISING SCAFFOLD FOR THE DISCOVERY AND DEVELOPMENT OF POTENTIAL BIOLOGICAL ACTIVITIES: AN OVERVIEW

Jainendra Singh Verma [*1], Renu Singh [1] and Karuna Shankar Shukla [2]

Department of Chemistry [1], Maharishi University of Information Technology, Lucknow - 226013, Uttar Pradesh, India.
Goel Institute of Pharmaceutical Sciences [2], Faizabad Road, Lucknow - 226028, Uttar Pradesh, India.

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Correspondence to Author:
Jainendra Singh Verma

Ph.D. Research Scholar,
Department of Chemistry,
Maharishi University of Information Technology, Lucknow - 226013, Uttar Pradesh, India.

E-mail: jainendraverma1984@gmail.com

ABSTRACT: Various bioactive aromatic compounds containing the indole nucleus showed clinical and biological applications. It has the unique property of mimicking different structures of proteins and binding to enzymes in a reversible manner. Indole scaffold has been found in many of the important synthetic drug molecules which gave a valuable idea for treatment and binds with high affinity to the multiple receptors helpful in developing new useful derivatives. Indole derivatives possess various biological activities, *i.e.*, antiviral, antifungal, antidiabetic, anti-inflammatory, anticancer, antifertility, anti-HIV, antioxidant, antimicrobial, antitubercular, anticonvulsant, antimalarial, anticholinesterase activities, *etc*. which created interest among researchers to synthesize a variety of indole derivatives. This review focussed on recent developments of indole derivatives having different pharmacological profiles as well as different perspectives on how this indole moiety as a privileged structure may be exploited in the future.

INTRODUCTION: Indole is a well-known privileged structure scaffold occurring in numerous natural products such as alkaloids, peptides, and various synthetic compounds [1]. Because of its biodynamic properties; Indole as well as its derivatives has occupied a unique platform in nitrogen heterocyclic chemistry [2]. The heterocyclic property of any phytochemical 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.

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Indole having a formula of C8H7N comprised of a bicyclic structure containing benzene merged with pyrrole moiety with derivatives possesses various biological applications in medicinal chemistry [3]. The indole was synthesized by reducing oxindole which was suggested by Adolf Von Baeyer in 1866 [4]. In indole, 10 π electrons resonate in a heteroaromatic planar molecule. The indole exists as a 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.

The chemistry of indole dates back to the mid-19th century due to extensive research on a natural violet-blue dye named indigo which led to the synthesis of indole in 1866 by zinc distillation of Oxindole.

General Methods for Synthesis of Indole, and its Derivatives: This scaffold is an omnipresent constituent of pharmacologically active natural products such as indole-3-acetic acid (IAA-plant hormone) [5], tryptophan (essential amino acid) [6, 5-hydroxytryptamine (5-HT- neurotransmitter) [7], melatonin [8]. Biological studies of indole-3-carbinol (I3C), and 3,30- diindolylmethane (DIM), (a natural product derived from the digestion of I3C) are under research due to their anti-cancer, anti-oxidant, and anti-atherogenic effects [9-12], Ajmalicine (Indole alkaloid - as antihypertensive drug) [13-14], Reserpine [15] & Vinblastine [16]. Indole finds applications in medical science due to various valuable biological 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 inhibitor and 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 that are capable of acting as ligands for the diversity of receptors [17-19]. They have the exclusive property of mimicking the structure of proteins and bind reversibly to enzymes [20-23] which provide fabulous opportunities to discover novel drugs with dissimilar modes of action [24]. There are also a 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 are listed below.

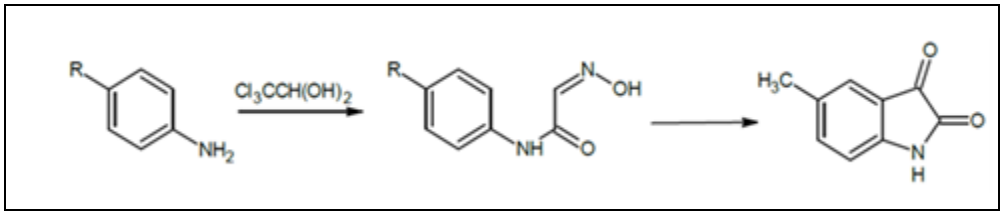


FIG. 1: COMMON METHOD FOR THE SYNTHESIS OF INDOLE AND DERIVATIVES

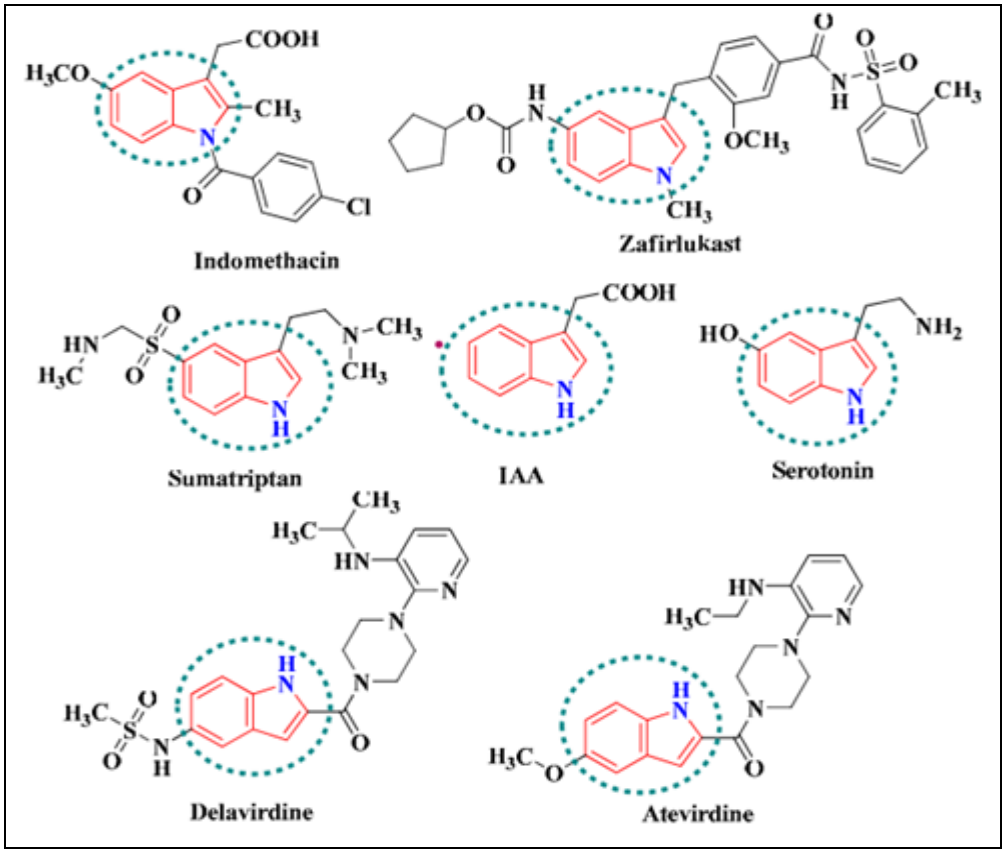
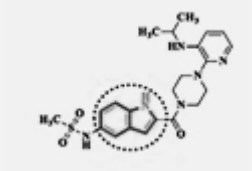
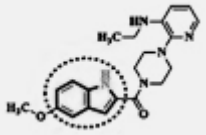
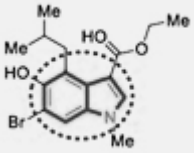
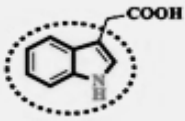
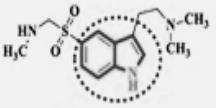
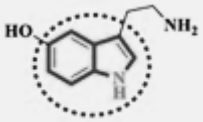
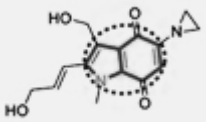
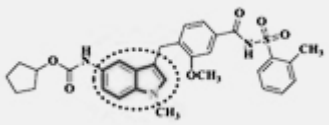
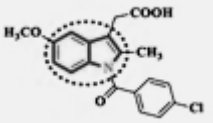
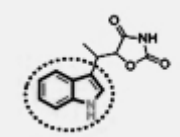


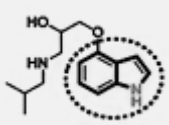
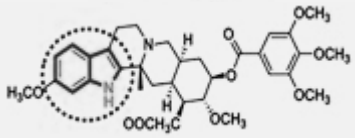
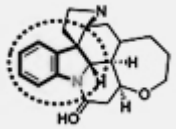
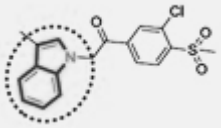
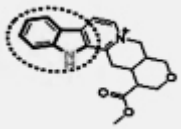
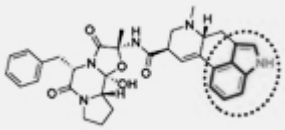
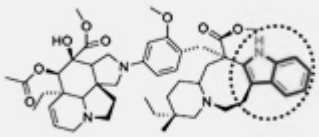
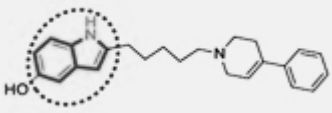
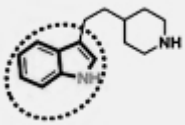
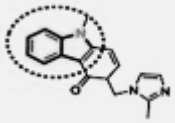
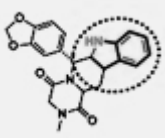
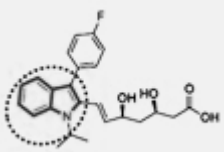
FIG. 2: STRUCTURES OF SOME MARKETED FORMULATIONS AND NATURAL PRODUCTS CONTAINING INDOLE SCAFFOLD

Pharmacological Activity: Due to the wide distribution of indole derivatives in nature, it has 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:

TABLE 1: NOVEL ANTIBACTERIAL AGENTS WITH THE MODE OF ACTION

Delavirdine		Antiviral	19
Areviridine		Antiviral	19
Abridol		Antiviral	22
Indole-3-acidc 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
Reserpine		Antihypertensive	9
Strychnine		Antidote	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

Antiviral Activity: 6-Amino-4-substituted alkyl-1H-indole-2-substituted carboxylate derivatives were prepared and reported as antiviral agents by Xue *et al.* In all tested compounds, compound

methyl 6-amino - 4 – isobutoxy - 1Hindole- 2-carboxylate (1) showed inhibitory activity against influenza A with IC_{50} = 7.53μmol/L and the highest selectivity index (SI) value 17.1 to CoxB3 virus [25]. 4 – Alkyl – 1 - (5 - fluoro-3-phenyl-1H-indole-2-carbonyl) thiosemicarbazide derivatives of indole were prepared and investigated in vitro for antiviral activity in a broad range of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) viruses by Cihan-Üstündag *et al.* Compounds 1-(5-fluoro-3-phenyl-1H-indole-2- carbonyl) – 4 - methyl thiosemicarbazide (2), 4-ethyl-1-(5- fluoro-3-phenyl-1H-indole-2-carbonyl) thiosemicarbazide (3), 1-(5-fluoro-3-phenyl-1H-indole-2-carbonyl)-4-propylthiosemicarbazide (4), and 4-butyl-1-(5-fluoro- 3-phenyl - 1H – indole - 2-carbonyl) thiosemicarbazide (5) are potent antiviral agents with IC_{50} values ranging from 0.4 to 2.1 μg/mL against Coxsackie B4 virus [26].

Ethyl 1*H*-indole-3-carboxylates also showed anti-viral activity in Huh-7.5 cells explained by Sellitto *et al.* Compound 4-((3-(ethoxycarbonyl)-1-methyl-5- (pyrrolidin-1-ylmethyl)-1*H*-indol-2-yl)methyl) benze- nesulfinate (6) was the most active compound at low concentration against hepatitis C virus (HCV) [27].

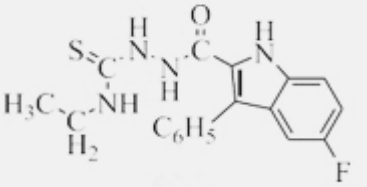
Giampieri et al. elaborated reaction of indoles and 2- naphthols through Mannich bases and tested against different viruses and compound methyl 1-((1*H*-indol-3- yl) methyl)-2-naphthoate (7) showed significant activity against Yellow Fever Virus (YFV), Bovine viral diarrhea virus (BVDV), Human immunodeficiency virus-1 (HIV- 1), and Respiratory syncytial virus (RSV) [28].

Pyrimidine-derived indole ribonucleosides (2*S*, 3*R*, 4*S*, 5*S*) – 2 - (6-chloro – 4 - (furan-2-yl)-9*H*-pyrimido [4, 5-b] indol-9-yl)-5-(hydroxymethyl)-tetrahydrofuran-3,4-di- ols were synthesized and tested for in vitro antiproliferative (HL-60 cervical carcinoma HeLaS3, T- lymphoblastic leukemia human cell line CCRF–CEM and promyelocytic leukemia) and antiviral activity (Den- gue virus and anti-hepatitis C virus) by Tichy *et al.* Compound (2*S*, 3*R*, 4*S*, 5*S*)-2-(6-chloro-4-(furan-2-yl)- 9*H*-pyrimido [4, 5-b] indol-9-yl)-5-(hydroxymethyl)-tetra- hydrofuran-3,4-diol (8) exhibited the notable cytotox- icity in HepG2 cells and THP-1 with IC_{50} of 0.175 and 1.565 μM [29].

4 – Nitro – 3 - [(5-nonsubstituted/ methyl-4-thiazolidinone-2- ylidene) hydrazono]-1*H*-2-indolinones were prepared and tested for antiviral activities by Terzioğlu *et al.* Compounds (*Z*)-4-allyl-1-(1-(morpholino ethyl)-5-nitro-2-oxoindolin-3-ylidene) thiosemicarbazide (9), (3*Z*,3*E*)-3-(2-(3-ethyl-4- oxothiazolidin-2-ylidene) hydrazone)-5-nitroindolin-2-one (10), (3*Z*, 3*E*)-5-nitro-3-(2-(4-oxo-3-phenylthiazolidin-2 – yli - dene) hydrazone) indolin – 2 - one (11), (3*Z*, 3*E*) – 3 - (2-(3-(4-bromophenyl) – 5 – methyl - 4-oxothiazolidin-2-ylidene) hydra- zone)-5-nitroindolin-2-one (12) and (3*Z*, 3*E*)-3-(2-(3-(4- chlorophenyl)-5-methyl-4-oxothiazolidin - 2 - ylidene) - hydrazone) - 5-nitroindolin-2-one (13) prevented the development of bovine viral diarrhea virus in cells [30].

7-Ethoxy-1-methyl-4, 9-dihydro-3*H*-pyrido [3, 4-*b*] in- dole derivatives were reported as anti-Herpes Simplex virus-1(HSV-1) compounds by El-sawy *et al.* and derivatives ethyl 2-(3-(5-(4-nitrophenyl)-1-phenyl-4,5-dihydro- 1*H*-pyrazol-3-yl)-1*H*-indol-1-yl)acetate (14), ethyl 2-(3- (6-(4-nitrophenyl)-2-oxo-1, 2-dihydropyrimidin-4-yl)-1*H*- indol-1-yl)acetate (15), ethyl 2-(3-(6-(4-nitrophenyl)-2-thioxo-1, 2-dihydropyrimidin-4-yl)-1*H*-indol-1-yl)acetate (16) and ethyl 2-(3-(6-(4-chlorophenyl)-2-imino-1,2- dihydropyrimidin-4-yl)-1*H*-indol-1-yl)acetate (17) possessed considerable antiviral activity with IC_{50} ranged between 5 and 6 μg/ml and substantial therapeutic indices (TI) of 80 and 83 were recorded [31].

TABLE 2: ANTIMICROBIAL ACTIVITY OF INDOLE DERIVATIVES



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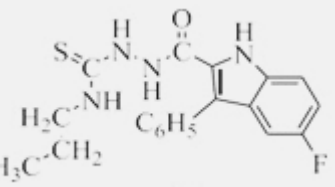

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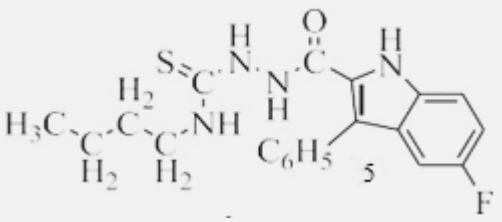

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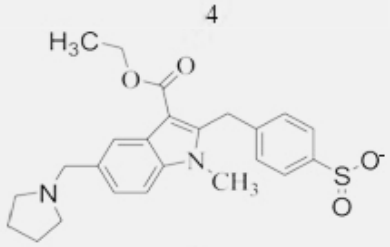

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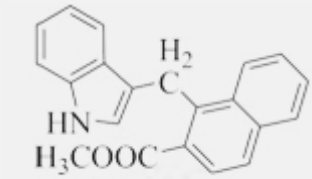

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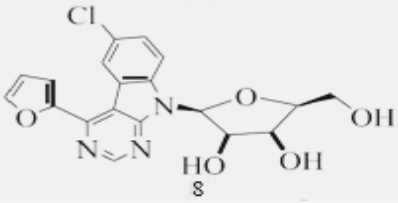

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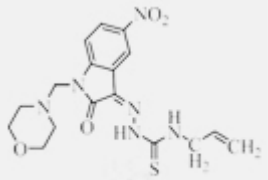

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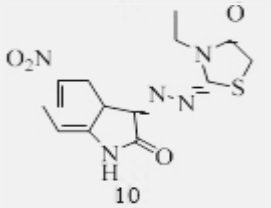

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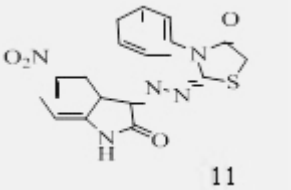

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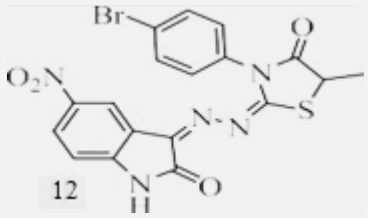

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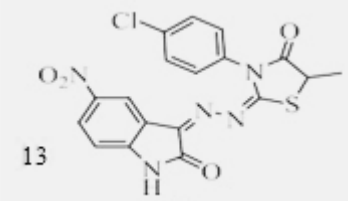

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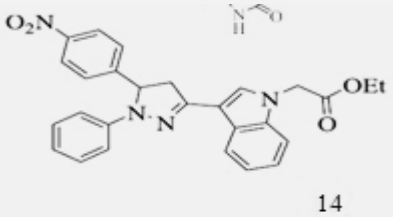

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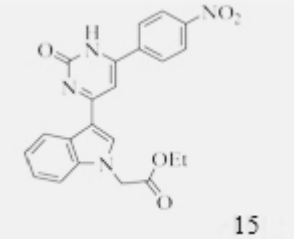

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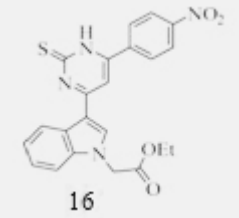

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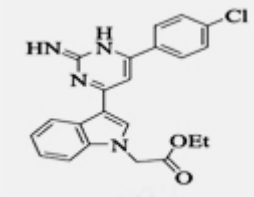

17

Anticancer Activity: Spallarossa*et al* [32] synthesized a new series of indole-based analog's potential anticancer agents. Compounds (E)-2-(methylsulfonyl) – 3 - (2 – phenyl - 1H-indol-3-yl) acrylonitrile and (E)-3-(2-(4-methoxyphenyl)-1H-indol-3-yl)-2- (phenylsulfonyl) acrylonitrile was found to be most active and highlighted a pro-apoptotic potential. Choppara *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 (Z)-2-((5-bromo-1-(3-methylbut-2-enyl)-1H- indol-3-yl) methylene) hydrazine carbothioamide and (Z)-2-((5-bromo-1-(3-methylbut-2-enyl)-1H-indol-3- yl) methylene) hydrazine carboxamide was found to be most potent with an LC_{50} of 6.49 µM (8) and with an IC_{50} of 33.69 µm.

Radulovic *et al.* [34] designed and synthesized two new ferrocene–indole hybrids, 2-(3-ferrocenylphenyl)-1H-indole and 2-(4-ferrocenylphenyl)-1H-indole, utilizing the Fischer indole synthesis as the key step. Both compounds showed significant myeloperoxidase inhibiting activity, and 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 naphtha [2,3-*f*] indole- 5,10-diones bearing the cyclic diamine in the position 3 of the indole ring. Compound (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 sulfur 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 methyl 5-(1H-indol-3-ylselanyl) - 1H-benzo [d] imidazol-2-ylcarbamate showed most promising results. Ji *et al* 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 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* developed hexahydropyrazino [1,2-a] indole scaffold using a structure-based drug design. Compound (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. Compounds (18) & (19) showed potential anticancer activity as compared to Cisplatin. Peng *et al* [41] synthesized a series of 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).

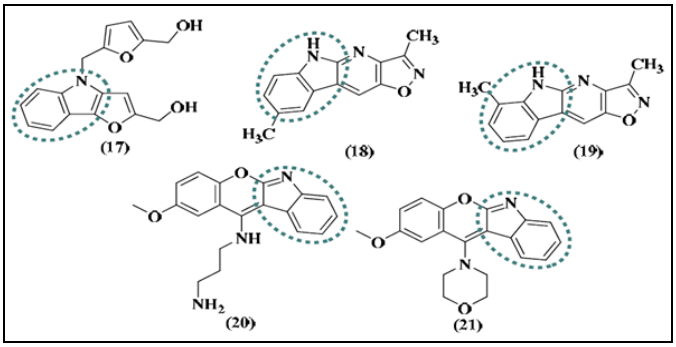

FIG. 3: COMMON ANTICANCER AGENTS

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- amino) 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.

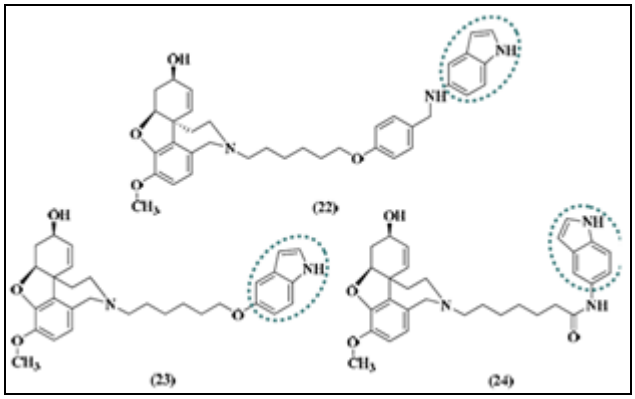

FIG. 4: A NOVEL ACETYLCHOLINESTERASE INHIBITOR

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

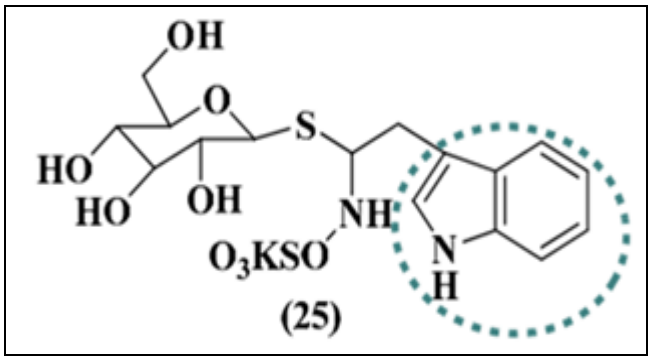

FIG. 5: ANTI-INFLAMMATORY AGENT

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 for antiparasitic 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) could inhibit the *P. falciparum* growth and thereby found to be most active.

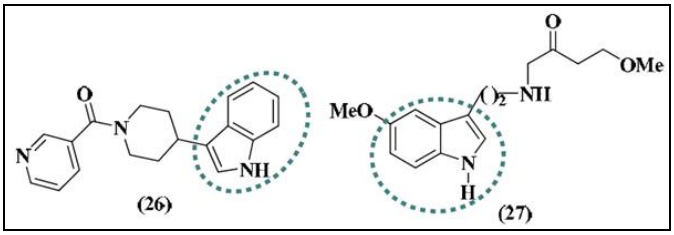

FIG. 6: NOVEL ANTIMALARIAL AGENT

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

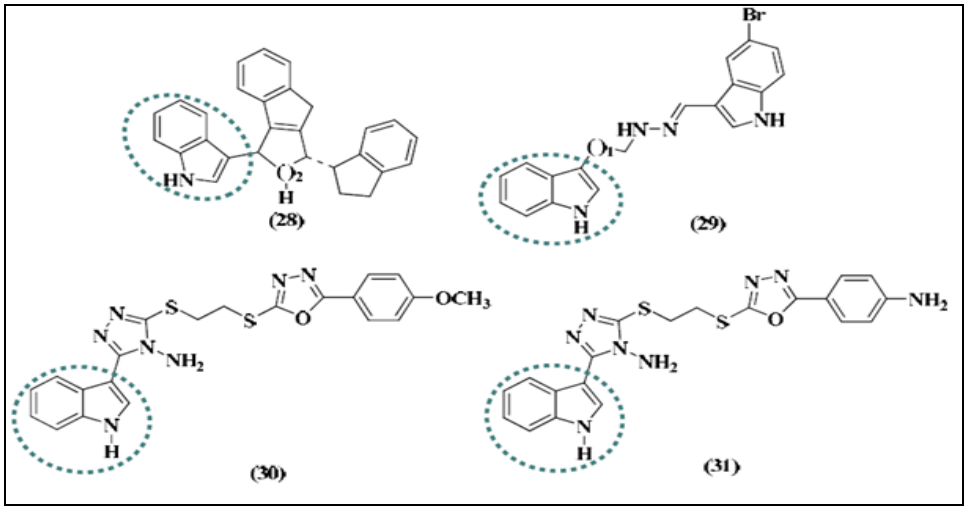

FIG. 7: ANTIMICROBIAL AGENT

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

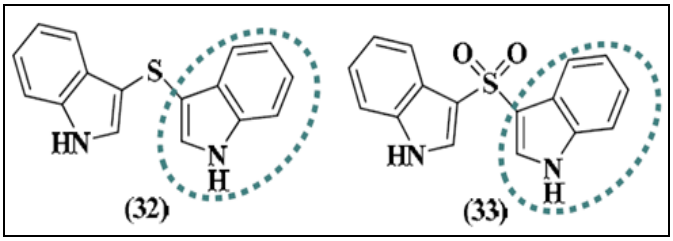

FIG. 8: A POTENT ANTIOXIDANT AGENT

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

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 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.

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 tetraethyl 3-(1H-indol-3-yl) propane-1,1-diyldiphosphonate was an indole-based bisphosphonate showed highest activity.

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 6-chloro-2-(5- chloro-1H-indol-3-yl) thiochroman-4-one showed potent antifungal activity. Pooja *et al* [56] carried out the synthesis of amino acid appended indoles and tested against *Candida albicans* with their MIC_{80} in µg/ml range. Compound (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. Bioassays showed that several of the synthesized compounds exhibit higher antifungal activity than pimprinine.

Compounds 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 3-(4-(1-(3-(2-methoxy-5-(trifluoromethyl) phenyl) -6-p-tolyl-1H-indazol-1-

yl) ethyl) benzylamine) propanoic acid exhibited 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 6-(difluoro-methoxy) – 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 2-(6-((1-hydroxycyclohexyl) methyl) pyridin-2-yl)- 1H-indole-5-carboximidamide showed good activity.

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

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 3-chloro-N-((5-fluoro- 1-tosyl-1H-indol-2-yl) methyl) – N - (4-fluorophenyl) quinoxalin-2-amine showed excellent results.

Urease Inhibitor: Naureen *et al* [63] carried out the synthesis of a series of tetraaryl imidazoles (5A-5O). When compared with thiourea the synthesized compounds exhibited potent anti-urease activity with IC50 values ranging from 0.12 ± 0.06 μM to 29.12 ± 0.18 μM. Compound 3-(4,5-diphenyl-1-p-tolyl - 1H - imidazol-2-yl)-2-(4- (trifluoromethyl) phenyl)-1H-indole was found to be a most potent inhibitor of urease enzyme.

CONCLUSION: Clinical research is being done on several medications that have an indole moiety that can be found in nature or synthesized. Also, researchers and analysts are collaborating on research on novel compounds containing indole that are meant to treat a variety of ailments, such as infection and cancer. Nonetheless, reducing symptoms and enhancing pharmaceutical action continue to be major obstacles. Data gathered from the literature research revealed that virtually all sick states are impacted by the indole core's fluctuation. In-depth research should be conducted by examining indole's compatibility with other synthetic compounds. It is crucial to understand that many possible indole derivatives should have their pharmacodynamics profile confirmed using the relevant animal models in preclinical data. Recently synthesized indole compounds with anticipated varied medicinal activity and potent antibacterial capabilities lack preclinical and clinical data.

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