Biological Importance of the Indole Nucleus in Recent Years: A Comprehensive Review

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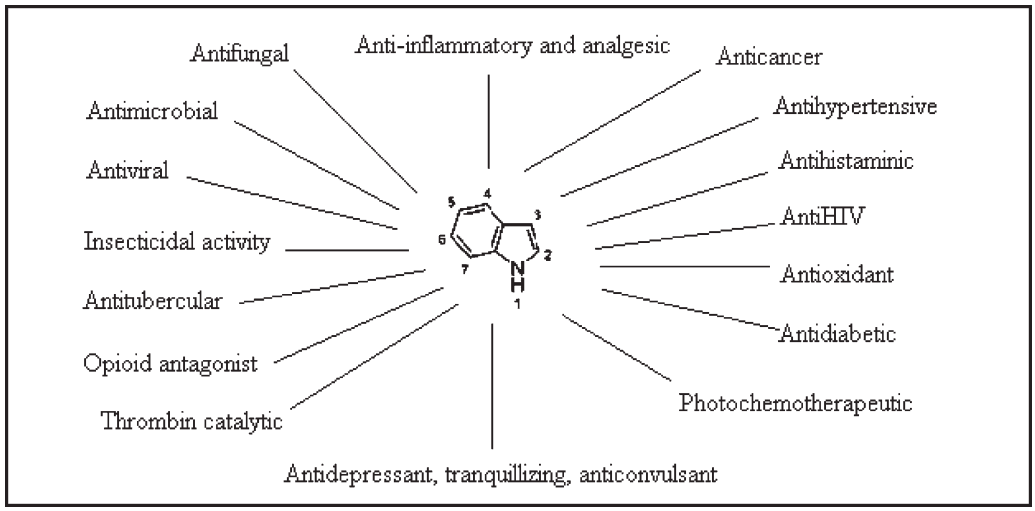

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INTRODUCTION

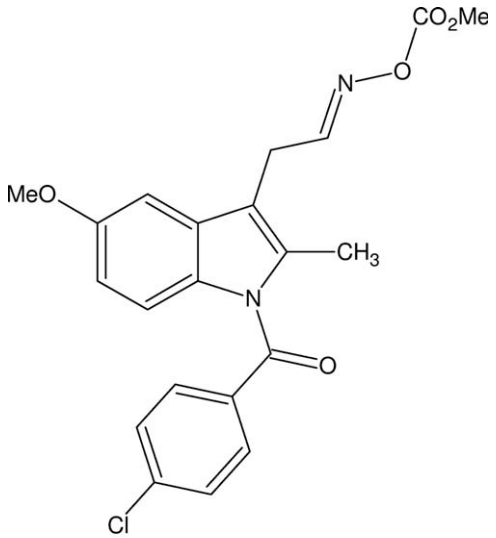
Heterocyclic compounds are those cyclic compounds in which one or more of the ring carbons are replaced by another atom. The non-carbon atoms in such rings are referred to as ''heteroatoms.'' Such bicyclic heterocyclic compounds containing pyrrole ring with benzene ring fused to α,β-position are known as Indoles. Indole has a benzene ring and pyrrole ring sharing one double bond. It is a heterocyclic system with 10 electrons from four double bonds and the lone pair from the nitrogen atom.

Indole is an important heterocyclic system because it is built into proteins in the form of amino acid tryptophan, because it is the basis of drugs like indomethacin and because it provides the skeleton of indole alkaloids—biologically active compounds from plants including strychnine and LSD.

The incorporation of indole nucleus, a biologically accepted pharmacophore in medicinal compounds (Table 1), has made it versatile heterocyclic possessing wide spectrum of biological activities (Table 2). In the present study, we have made an attempt to collect biological properties of imidazole nucleus reported in the new millennium.

BIOLOGICAL ACTIVITIES OF INDOLE NUCLEUS

Anti-inflammatory and analgesic activity. Abele *et al*. synthesized isatin and indole oximes and carried out the chemical reactions and biological activities of the synthesized compounds where the compound (**1**) was found to be most active analgesic and anti-inflammatory agent [1].



(1)

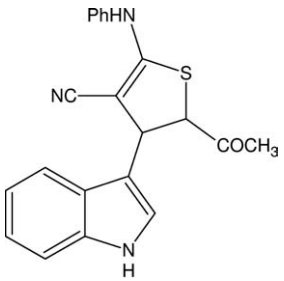
Radwan *et al*. carried out the synthesis and biological evaluation of 3-substituted indole derivatives as potential anti-inflammatory and analgesic agents. They reported 3-(3-indolyl) thiophene derivative (**2**) as a

Table 1

Various biological activities of compounds possessing indole nucleus are as follows.

S. No.	Biological activities	References
1.	Anti-inflammatory and analgesic	[1–5]
2.	Antifungal	[1,6]
3.	Antimicrobial	[7,8]
4.	Insecticidal activity	[1,9]
5.	Anticancer	[1,10–13]
6.	5-Lipoxygenase inhibitors	[14]
7.	AntiHIV	[1,15]
8.	Antioxidant	[16,17]
9.	Antitubercular	[1,18]
10.	Antiviral	[1]
11.	Plant growth regulator	[1]
12.	Antidepressant, tranquillizing, anticonvulsant	[1,19]
13.	Cardiovascular activity	[1,20]
14.	Antihypertensive	[1]
15.	Antihistaminic	[21]
16.	Opioid antagonist	[22]
17.	Photochemotherapeutic activity	[23]
18.	Antidiabetic activity	[24]
19.	LXR receptor agonist	[25]
20.	ACAT inhibitor	[26]
21.	IL-1 inhibitors	[27]
22.	LTB_4 production inhibitor	[28]
23.	Steroid 5α-reductase inhibitor	[29]
24.	Glycoprotein IIb\IIIa inhibitor	[30]
25.	Thrombin catalytic activity	[31]
26.	Peroxisome proliferator-activated receptor agonist	[32]
27.	Cytosolic phospholipase A2α inhibitors	[33]
28.	Galanine GAL_3 receptor antagonist	[34]
29.	Selective CB2 receptor agonist	[35]
30.	Selective dopamine agonist	[36,37]

potent anti-inflammatory compound whereas thiazolidine-4-one derivative (**3**) exhibit analgesic activity [2].



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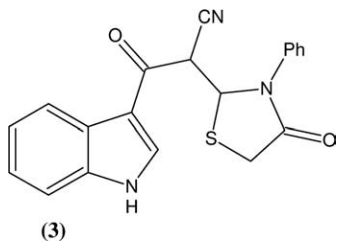
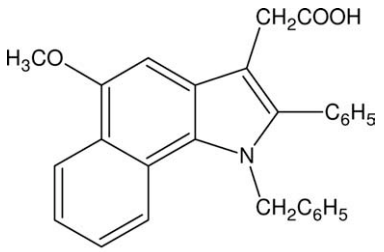


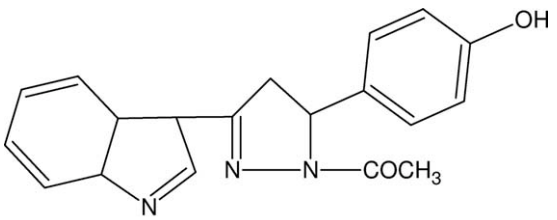
(3)

Kalaskar *et al*. synthesized indole-3-acetic acids and evaluated them for their *in vivo* anti-inflammatory activity. The compound 1,2-disubstituted-5-methoxyindole/benz(g)indole-3-acetic acid (**4**) showed significant activity [3].



(4)

The synthesis and anti-inflammatory activity of heterocyclic indole derivatives was performed by Rani *et al*. The compound **(5)** was found to be most potent (inhibition of oedema at 50 μg/Kg dose) [4].



(5)

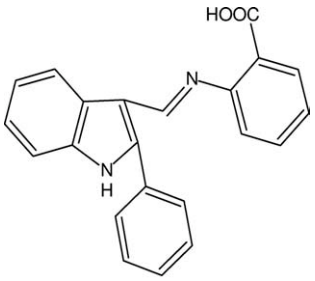
Amir *et al*. carried out synthesis and anti-inflammatory activity of various indole and indazole derivatives where the compounds 2-Phenyl-3-(2′-carboxyphenyliminomethyl)-

Table 2

Importance of indole derivatives in medicinal chemistry.

S.No.	Indole derivative	Biological activity
1.	Indomethacin	Anti-inflammatory and analgesic
2.	Fendosal	Analgesic
3.	Etodolac	Antiarthritis
4.	Sumatriptan	Antimigraine
5.	Besipirdine	Nootropic
6.	Noratriptan	CNS stimulant
7.	Pindolol	Antihypertensive
8.	Indolmycin	Antibiotic
9.	Indigo carmine	As a dye in functional kidney test and in milk testing
10.	Adrenochrome	Hemostatic

indole (**6**) and 2-phenyl-3-(2′-carboxyphenyliminomethyl)-indol-1-acetic acid (**7**) were found to be most potent [5].



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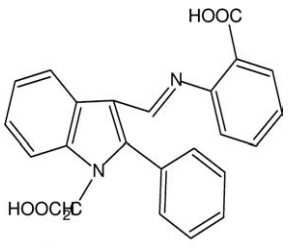
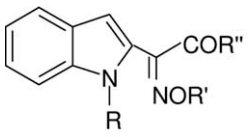


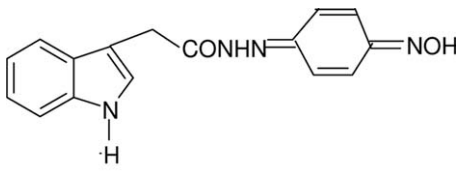
(7)

Antifungal activity. Some of the isatin and indole oximes synthesized by Abele *et al*. were found to be exhibiting high fungicidal activity where the oxime derivates of 2-substituted indoles **(8)** and 3-substituted indoles **(9)** demonstrated significant antifungal activity [1].



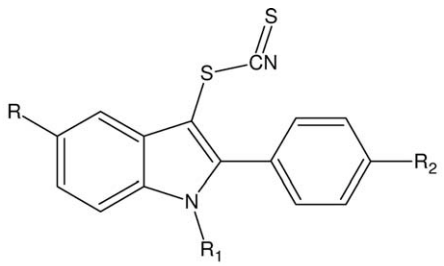
R,R' = Alkyl
R'' = OAlk, SAlk, NHAlk, NAlk

(8)



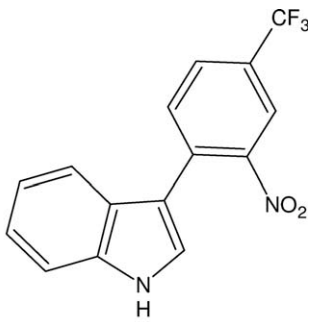
(9)

A series of S-(indolyl-3)diethyl dithiocarbamates was synthesized and evaluated for their activity by Skii *et al*. The compounds (**10a–e**) were found to be exhibiting highest antifungal activity [6].



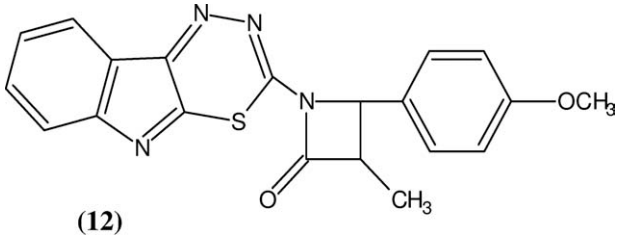
10a: R= R_1 = R_2 = H
10b: R = H, R_1 =CH_2Ph
10c: R = R_2 = H, R_1 = Ph
10d: R = R_1 = H, R_2 = Br
10e: R = R_2 = Br, R_1 = H

Antimicrobial activity. The synthesis and antibacterial activity of some substituted 3-(aryl) and 3-(heteroaryl) indoles were reported by Hiari *et al*. The most active compound was reported to be 3-(4-trifluoromethyl-2-nitrophenyl) indole **(11)** exhibiting MIC $\approx$ 7 μg/cm^3 against *Escherichia coli* and *Staphylococcus aureus* [7].



(11)

Panwar *et al*. synthesis substituted azetidonyl and thiazolidinonyl-1,3,4-thiadiazino[6,5-b]indoles as prospective antimicrobial agents. The compounds (**12**) and (**13**) were found to exhibit most inhibitory effect against *E. coli* and *S. aureus* [8].



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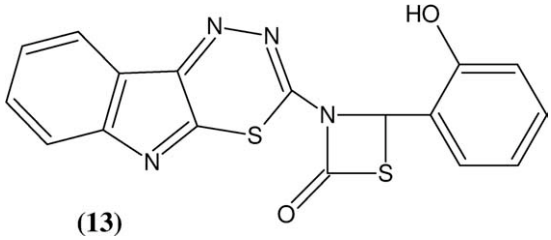
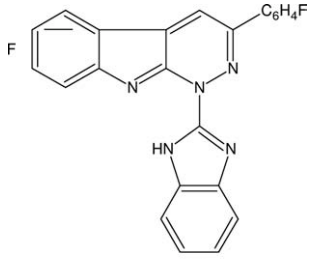


(13)

Insecticidal activity. Sharma *et al*. investigated the insecticidal activity of synthesized novel indole derivatives. The compounds **(14)** and **(15)** exhibited promising results against *Spodoptera liture* (eighth instar larvae) and *Jeliothis armigera* [9].



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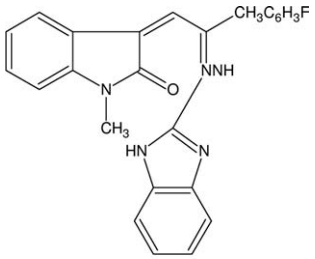
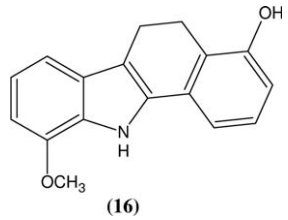


(15)

Anticancer activity. The series of various tricyclic and tetracyclic indoles synthesized by Hong *et al*. were evaluated for their anticancer activity where the compounds **16, 17, 18,** and **19** were found to exhibit highest *in vitro* activity against human nasopharyngeal carcinoma (HONE-1) and gastric adenocarcinoma (NUGC-3) cell lines [10].



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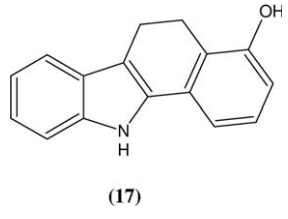

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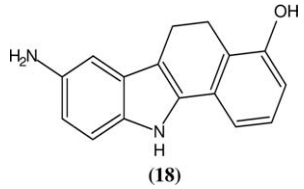

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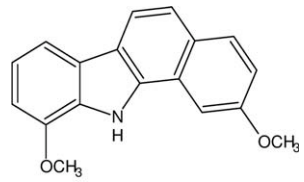
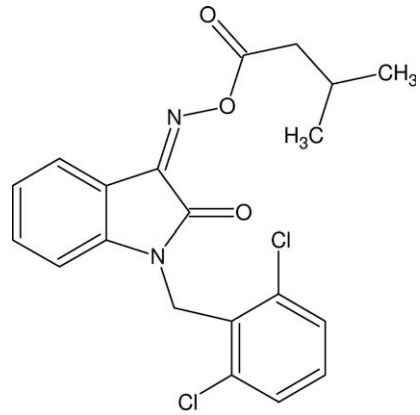


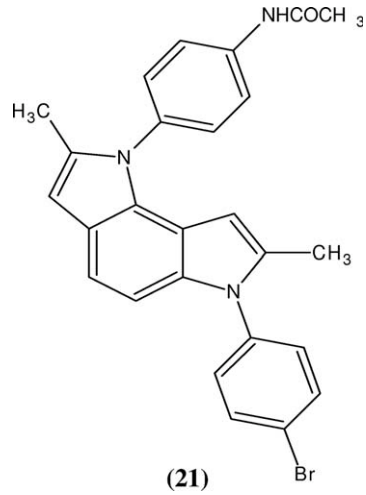
(19)

The compound **(20)** synthesized by Abele *et al*. was reportedly showing highest anticancer activity [1].



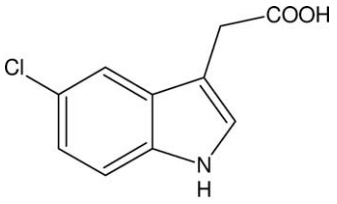
(20)

Garcia *et al*. synthesized pyrrolo[2,3-e] indole derivatives and evaluated them for possible *in vitro* cytotoxic activity. The most active compound was found to be (**21**), which shows best result in PC-3 (prostate) cell line [11].



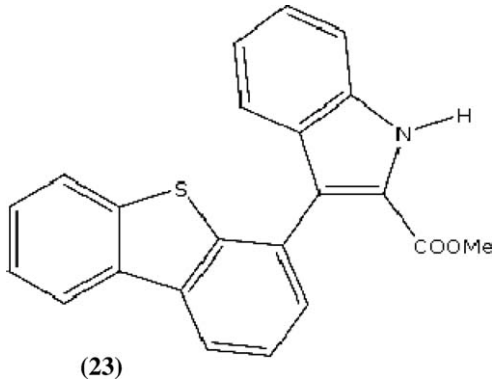
(21)

A series of halogenated indole-3-acetic acids as oxidatively activated prodrugs with potential for targeted cancer therapy were reported by Rossiter *et al*. These derivatives were oxidized by horse radish peroxidase (HRP) and toxicity against V79 Chinese hamster lung fibroblasts was determined and the compound (**22**) was found to possess highest cytotoxicity and it was the best drug for targeted cancer therapy [12].



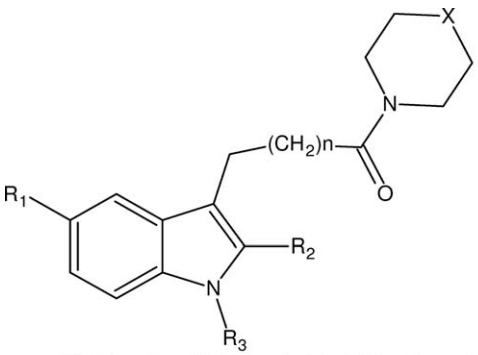
(22)

Queiroz *et al*. studied the inhibitory activity of the heteroarylindoles and of the phenylbenzothienoindole on the growth of human tumor cell lines, MCF-7 (breast adenocarcinoma), NCI-H460 (non-small cell lung cancer), and SF-268 (CNS cancer). The results showed that the methyl 3-(dibenzothien-4-yl)indole-2-carboxylate (**23**) had most potent growth inhibitory activity in all the tumor cell lines tested (with GI_{50} values ranging from11 to 17 μ*M*) [13].



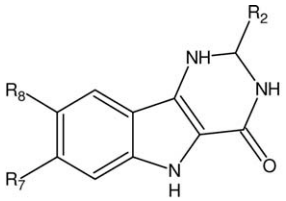
(23)

Lipoxygenase inhibitor. Zheng *et al*. synthesized a series of indole derivatives as possible 5-lipoxygenase inhibitors. In all, four compounds **24, 25, 26,** and **27** exhibited the most potent inhibitory activity with IC_{50} values ranging from 0.74 μ*M* to 3.17 μ*M* [14].

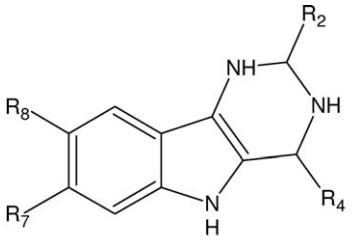


24: $R_1 = R_2 = H$, R_3 = 3, 4-Dichlorobenzyl, X = O, n = 0
25: R_1 = Cl, $R_2 = CH_3$, R_3 = Benzyl, X = O, n = 2
26: $R_1 = R_2 = R_3 = H$, X = BocN, X = O, n = 2
27: $R_1 = R_2 = H$, R_3 = Benzyl, X = NH, n = 2

HIV inhibitors. The analogs of pyrimido[5,4-b]indoles were synthesized and biologically evaluated by Merino *et al*. for their possible HIV inhibitory activity. The derivative **(28)** formed by substitution at position 2 in analog-I and derivative **(29)** at position 2, 4 in analog II (formed in 65% and 64% maximum yield) were reported to be the inhibitors of wild and mutant HIV-1 RT types in an ''*in vitro*'' recombinant HIV-1 RT screening assay as well as anti-infectives in $HLT4lacZ\text{-}1_{IIIB}$ cells [15].



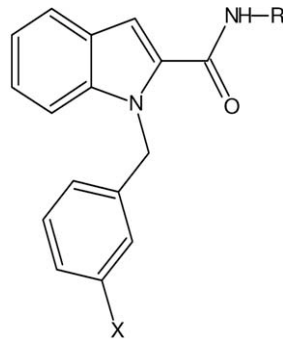
Analog I
28: R_2 = methyl-N-[4-(2′-methoxyphenyl)]piperazinyl, $R_7 = R_8 = H$



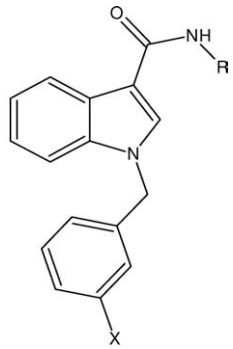
Analog II
29: R_2 = 2′-pyridyl, R_4 = N-morpholinyl, $R_7 = R_8 = H$

Antioxidant activity. A series of indole derivatives were synthesized and biologically evaluated by Enien *et al*., and found that Indole-2 and 3-carboxamides were having antioxidant properties by Chemoluminesence and Electron spin resonance spin trapping. They further reported that the derivatives **30** and **31** have strongest scavenging effect on OH^- radicals, *i.e*., quenching >30%

and the derivatives **31** and **32** have strongest effect on scavenging of superoxide radicals [16].

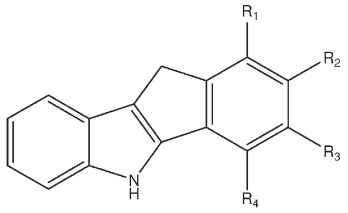


Indole-2-carboxamide
30: X=H, R=Phenyl



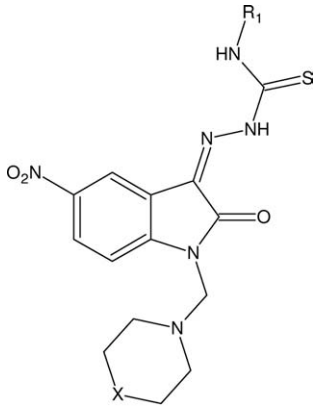
Indole-3-carboxamide
31: X=H, R=Thiazolyl
32: X=F, R=Thiazolyl

Talaz *et al*. described the synthesis of 5,10-dihydroindeno[1,2-b]indoles containing substituents such as methoxy, hydroxyl, and halogen (F, Cl, and Br) on indeno part and their antioxidant activity and radical scavenging activities were assessed by various *in vitro* assays and compared with the activities of synthetic and standard antioxidant compounds. The compounds **(33)** and **(34)** were found to have maximum Fe^{3+}–Fe^{2+} reducing ability whereas compound **(35)** was found to have maximum Cu^{2+}–Cu^{+} reducing ability [17].

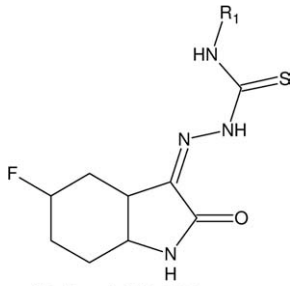


33: R_1=OMe, R_2= H, R_3= H, R_4= OMe
34: R_1=OH, R_2= OH, R_3= H, R_4= H
35: R_1=OH, R_2= H, R_3= H, R_4= OH

Antituberculosis activity. A new series of 1H-indole-2,3-dione derivatives were synthesized and evaluated for *in vitro* antituberculosis activity against *Mycobacterium tuberculosis* H37Rv by Karali *et al*. Among the tested compounds, 5-nitro-1H-indole-2,3-dione-3-thiosemicarbazones and its 1-morpholinomethyl (**36, 37, 38,** and **39**) derivatives exhibited significant inhibitory activity with MIC values $\geq$ 75% [18].

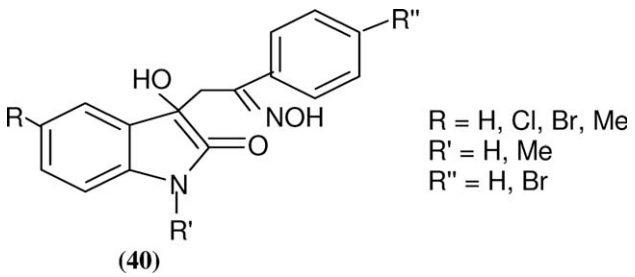


36: $R_1 = CH_3$
37: $R_1 = C_6H_5$
38: $R_1 = 4\text{-}CH_3C_6H_4$



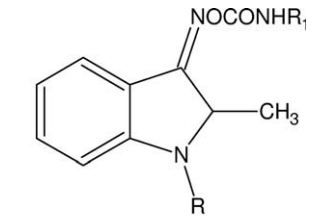
39: $R_1 = 4\text{-}CH_3C_6H_4$

Among the series of isatin and indole oximes synthesized and evaluated by Abele *et al*., the highest broad spectrum antibacterial activity was exhibited by oxime derivatives of 2-indolinone **(40)** against *M. tuberculosis* [1].



(40)

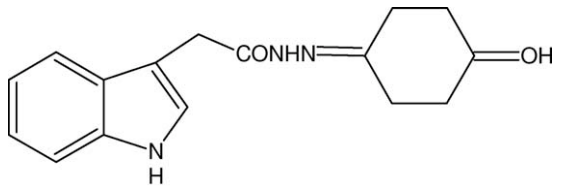
Antiviral activity. The indole oxime, carbamoyl derivative of indole-3-oxime **(41),** exhibited the most potent antiviral activity among the isatin and indole oximes synthesized by Abele *et al*. [1].



(41)

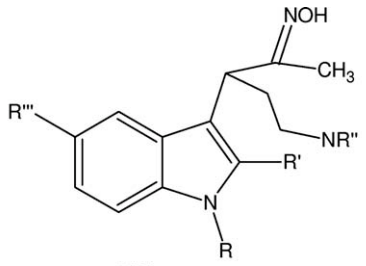
R = H, methyl, ethyl
R_1 = methyl, phenyl

Plant growth regulator. The 3-substituted indole **(42)** was reported to be a plant growth regulator by Abele *et al*. among the various isatin and indole oximes synthesized and evaluated by them [1].



(42)

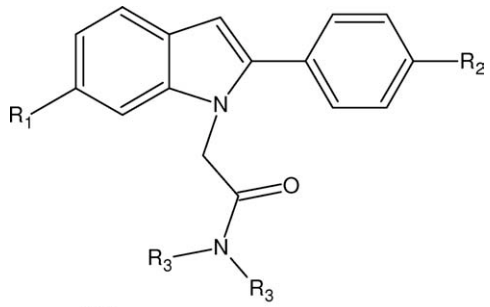
Antidepressant, tranquillizing, and anticonvulsant activity. The oxime of indole aminoketone **(43)** exhibited high antidepressant activity among the isatin and indole oximes synthesized and evaluated for their biological activity by Abele *et al*. [1].



(43)

R = H R' = H, methyl R'' = methyl, ethyl R''' = H, Cl, OMe

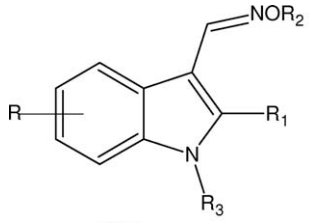
A series of N-substituted indoles were synthesized by Falco *et al*., and afterwards, *in vitro* screening and *in vivo* spontaneous motor activity in mice had revealed molecules with good *in vitro* affinities for the α_1-subunit of $GABA_A$ receptor and potent *in vivo* induction of sedation and **(44)** was found most potent compounds [19].



(44)

$R_1 = R_2$ = methyl, R_3 = propyl

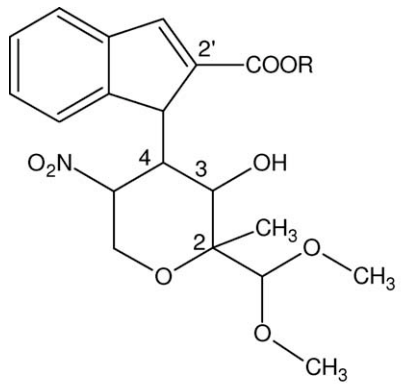
Cardiovascular activity. The isatin oxime **(45)** exhibited the highest antiarrhythmic activity among the isatin and indole oximes synthesized by Abele *et al*. [1].



(45)

R = H, Alkyl, OH, Halogen, NO_2, NH_2
R_1 = Halogen, OH, SH, NH_2
R_2 = H, Alkyl, Ar
R_3 = H

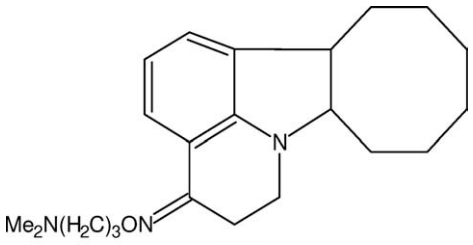
A number of benzopyranyl indoline and indole analogs were synthesized and evaluated for Cardioselective anti-ischemic ATP-sensitive potassium channel (K_{ATP}) opener activity by Lee *et al*. The compounds **(46)** and **(47)** showed the best cardioprotective activity [20].



46: (2-S, 3-R, 4-S, 2'-S) = R= Ethyl
47: (2-R, 3-S, 4-R, 2'-R) = R= Ethyl

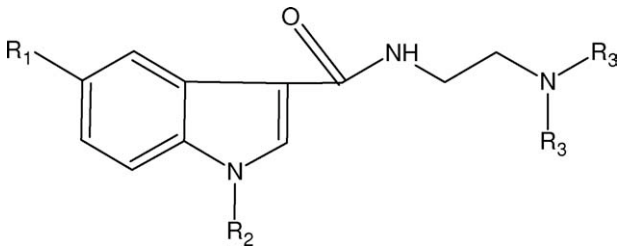
Antihypertensive activity. Among the various isatin and indole oximes reported by Abele *et al*., compound

(**48**), a tetracyclic derivatives of indole oximes, was found to have hypotensive activity lowering the blood pressure in rats by 28% [1].



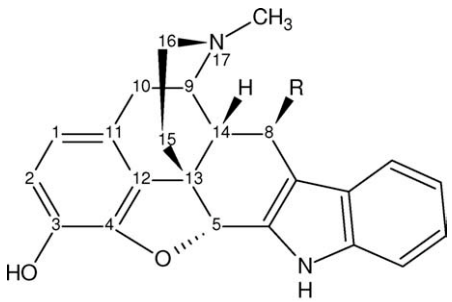
(48)

Antihistaminic activity. A number of indole amide derivatives bearing a side chain, in which the indole ring replaces the isoster benzimidazole nucleus typical of some well known antihistamines, were prepared and tested for the antihistaminic activity by Battaglia *et al*. The most active compounds **49, 50, 51, 52, 53,** and **54** were tested *in vivo* for their ability to antagonize histamine induced cutaneous vascular permeability in rats [21].



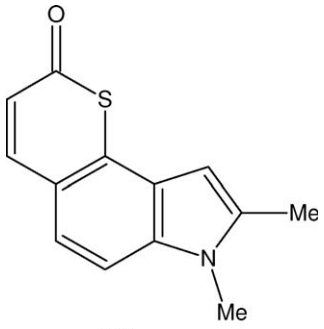
Compound No.	R_1	R_2	R_3-N-R_3
49	H	$CH_2C_6H_5$	CH_3/CH_3
50	H	$CH_2C_6H_5$	Piperidine
51	H	$CH_2C_6H_4$-p-F	CH_3/CH_3
52	H	$CH_2C_6H_4$-p-F	Piperidine
53	H	$CH_2C_6H_4$-p-Cl	CH_3/CH_3
54	H	$CH_2C_6H_4$-p-Cl	Piperidine

Opioid antagonist. The synthesis and biological activity of 8β-substituted hydromorphone indole derivatives were carried out by Yu *et al*. The compound 6,7-dehydro-4,5α-epoxy-8β-methyl-6,7,2′,3′-indolomorphinan **(55)** was found to be a δ antagonist with submolar affinity (0.7 n*M*) for the opioid receptor, and to have good δ-selectivity (μ/δ = 322 n*M*) [22].



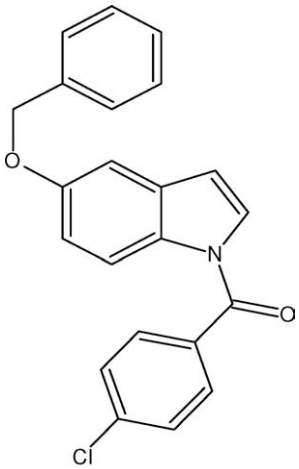
(55)

Photochemotherapeutic activity. The synthesis and photochemotherapeutic activity of thiopyrano[2,3-e]indol-2-ones was performed by Barraja *et al*., wherein the compound thiopyrano[2,3-e]-indol-2-ones **(56)** showed the maximum phototoxicity on two cultured cell lines: HL-60 and LoVo [23].



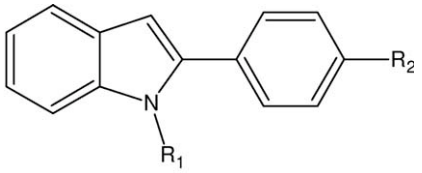
(56)

Antidiabetic activity. Some of the indole derivatives were evaluated for their insulin sensitizing and glucose lowering effects by Li *et al*. The indole derivative **(57)** showed increase in activity of PPARγ agents, which shows decreased serum glucose and contributing to antidiabetic activity [24].



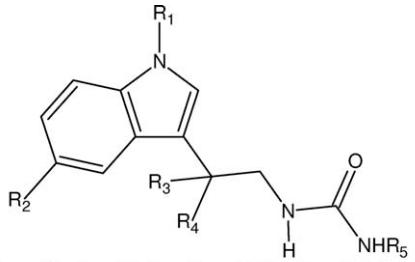
(57)

LXR receptor agonist. A series of 2-Aryl-*N*-acyl indole derivatives was synthesized and biologically evaluated as liver X receptor (LXR) agonists by Kher *et al*. The compound **(58)** was found to be most active with $EC_{50} = 0.012$ μ*M* [25].



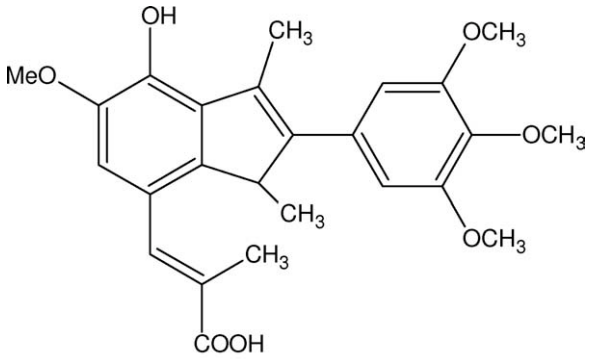
(58)
$R_1 = COPh$, $R_2 = (CH_2)_2CN$

ACAT inhibitors (hypocholestrolemic activity). The indole derivatives synthesized by Bellemin *et al*., were evaluated for their hypocholestrolemic activity. The compounds **(59)** and **(60)** were found to be most effective ACAT inhibitor with ED_{25} values of 0.098 and 0.063 mg/Kg, respectively [26].



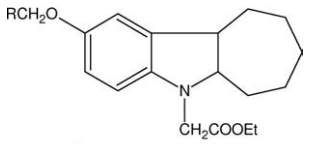
(59): $R_1 = CH_3$, $R_2 = H$, $R_3 = R_4 = (CH_2)_4$, $R_5 = 2,6\text{-}(i\text{-}Pr)_2C_6H_3$
(60): $R_1 = (CH_3)_2N(CH_2)_2$, $R_2 = H$, $R_3 = R_4 = (CH_2)_4$, $R_5 = 2,6\text{-}(i\text{-}Pr)_2C_6H_3$

IL-1 inhibitors. Among the series of hydroxyindole derivatives synthesized and evaluated for IL-1 generation inhibitors by Tanaka *et al*., the compound **(61)** was found to be potent inhibitors of IL-1 generation with IL-1α = 6.4 μ*M* and IL-2 = 8.6 μ*M* [27].

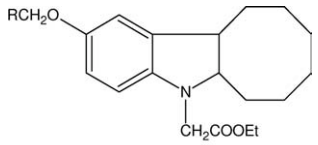


(61)

LTB_4 production inhibitor. The compounds **(62)** and **(63)** exhibited the highest inhibitory activity against LTB_4 production among the series of novel thiopyrano[3,2-b] and cycloalkeno[1,2-b]indole derivatives synthesized and evaluated by Caubere *et al*. [28].

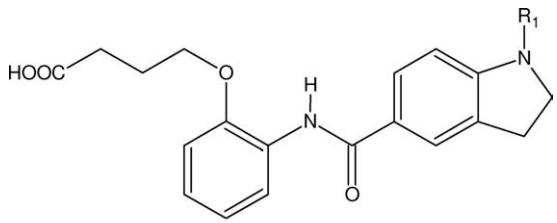


(62)
R = 2-quinolyl

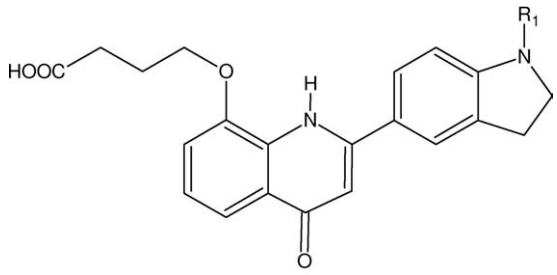


(63)
R = 2-quinolyl

Steroid 5α-reductase inhibitor. A class of indole and benzimidazole derivatives were synthesized and evaluated for their inhibitory activity against rat prostatic 5α-reductase by Takami *et al*. The compounds **(64)** and **(65)** were found to be showing most potent inhibitory activity against rat prostatic 5α-reductase with $IC_{50} = 9.6 \pm 1.0$ n*M* and 19 ± 6.2 n*M*, respectively [29].

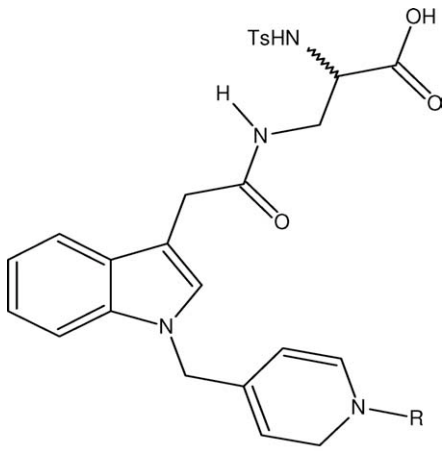


(64)
R_1 = 4, 4′-dipropylbenzhydryl



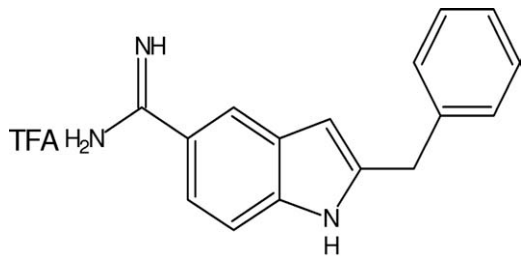
(65)
R_1 = 4-isobutyl-α-methylbenzyl

Glycoprotein IIb\IIIa inhibitors. Grumel *et al*. synthesis 1,3-disubstituted indole derivatives as glycoprotein IIb/IIIa antagonists wherein the compound **(66)** was found to exhibit highest Glycoprotein IIb/IIIa inhibitory activity with $IC_{50} = 4.5$ μ*M* [30].



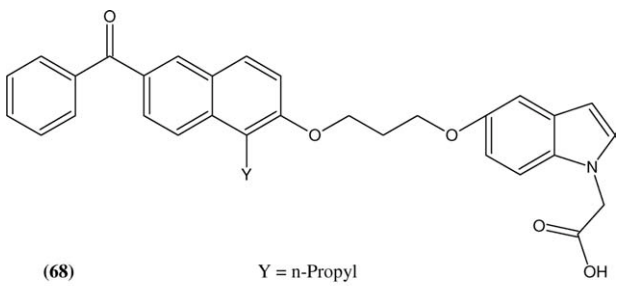
(66)
R = H, HCl

Thrombin catalytic activity. The substituted 5-amide indoles were evaluated as inhibitors of thrombin catalytic activity by Iwanowicz *et al*. The compound **(67)** was found to be the most potent inhibitor of thrombin catalytic activity with an inhibition constant, $K_i = 260$ n*M* [31].



(67)

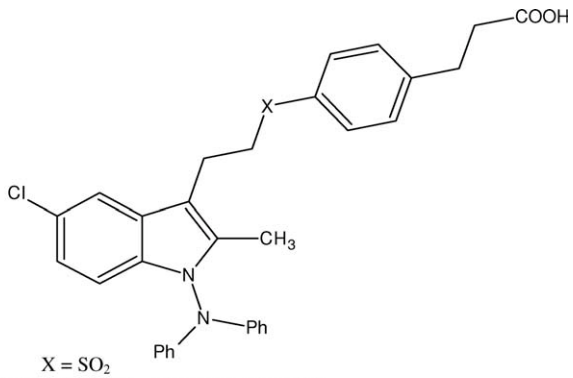
Peroxisome proliferator-activated receptor agonist. A series of indole based PPAR agonist were synthesized and biologically evaluated by Mahindroo *et al*. [32]. The compound **(68)** was found to be most potent PPAR agonist with $IC_{50} = 0.050$ μ*M* and $EC_{50} = 0.070$ μ*M*.



(68) Y = n-Propyl

1.2.27 Cytosolic Phospholipase A2α inhibitors

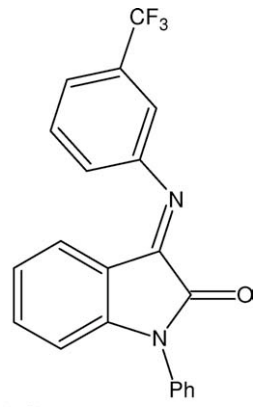
Cytosolic phospholipase A2α inhibitors. The potential of indole nucleus as Cytosolic Phospholipase A2α inhibitors was evaluated by Mckew *et al*. The compound **(69)** was found to be most potent $IC_{50} = 0.5$ μ*M* in the GLU assay and $IC_{50} = 0.8$ μ*M* in the rat whole blood assay [33].



(69) X = SO_2

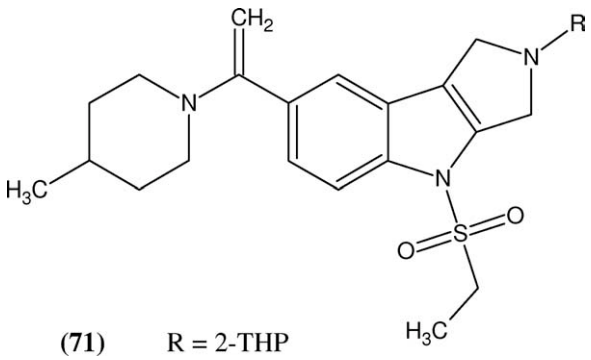
1.2.28 Galanine GAL_3 receptor antagonist

Galanine GAL_3 receptor antagonist. A series of 3-arylimino-2-indolones were reported to be as Galanine GAL_3 receptor antagonists by Konkel *et al*. The compound **(70)** was found to be most potent antagonist with $K_b = 29$ n*M* [34].



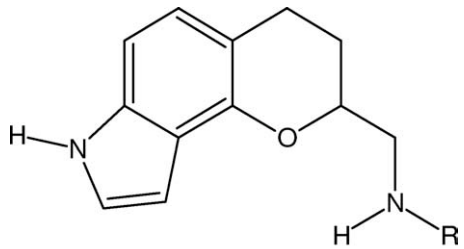
(70)

Selective CB2 receptor agonist. The preparation and evaluation of a class of CB2 receptor agonist based on a 1,2,3,4-tetrahydropyrrolo[3,4-b] indole moiety were reported by Page *et al*. The compound **(71)** showed to be most potent CB2 receptor agonist [35].



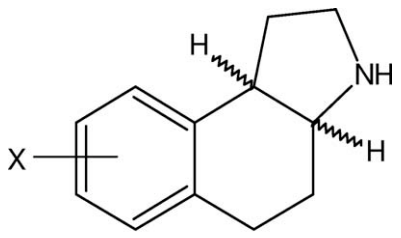
(71) R = 2-THP

Selective dopamine agonist. A series of 2-(aminomethyl)-3,4,7,9-tetrahydro-2H-pyrano[2,3-e]indole and indole-8-one derivatives were synthesized and evaluated by Mewshaw *et al*. The compound **(72)** was found to be most potent agonist [36].



(72) R = Benzyl

The class of cis- and trans-2,3,3a,4,5,9b-hexahydro-1H-binz[e]indoles synthesized by Song *et al*. were evaluated for dopamine D_2 and D_3 receptor binding affinity. The cis-diastereoisomer **(73)** was found to be more potent among the synthesized compounds [37].



(73) X = 8-OH

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