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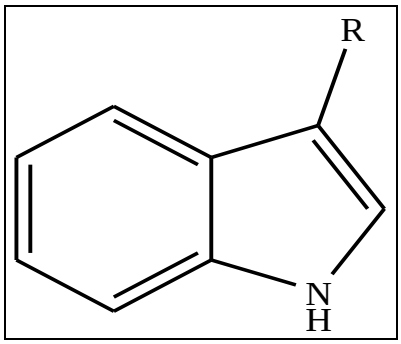
Versatility in pharmacological actions of 3-substituted indoles

Nitish Kumar and Amrita Parle

Abstract
3-substituted indole is a heterocyclic compound having formula C_8H_6NR and has indole as parent moiety. Indole and its derivatives have vital role in medicinal chemistry. They are attaining considerable importance due to their wide range of pharmacological activities viz: antiviral, anti-HIV, antidepressant, antimicrobial, analgesic etc. This review deliberates on pharmacological activities, ongoing clinical trials and current marketed preparations of 3-substituted indole derivatives.

Keywords: Indole, antimicrobial, anticancer, marketed preparations, clinical trials

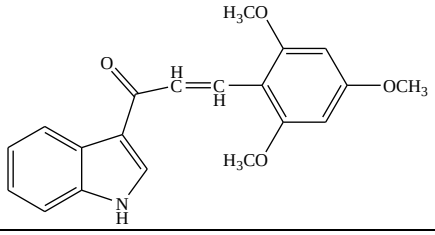
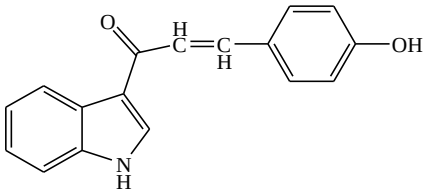
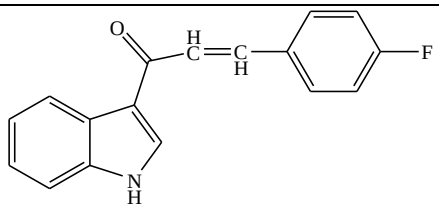
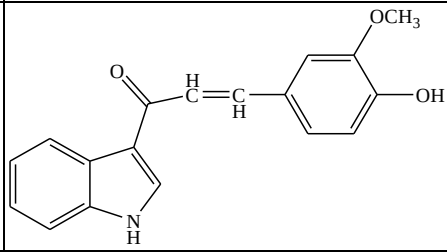
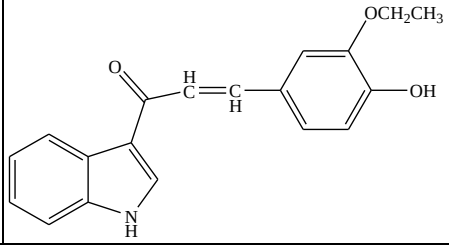
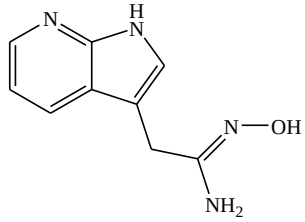
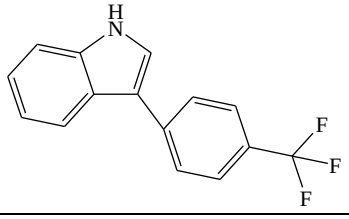
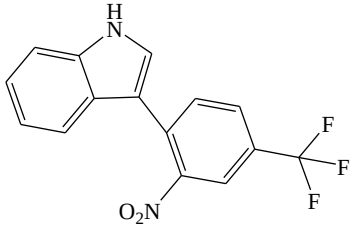
Introduction
Indole is nothing but benzpyrole. It has pyrrole and benzene ring fused at α,β-position. Indole is an important heterocyclic system as it is building block in proteins in the form of amino acid tryptophan. Indole is the parent moiety in drugs like indomethacin, zafirlukast as well as biologically active compounds from plants like strychnine and LSD (Lysergic acid diethylamide). Most indoles are quite stable in air, except 2-methylindoles which are auto oxidized easily even in a dark brown bottle [1].
3-Substituted indole is an aromatic heterocyclic compound having formula C_8H_6NR. It has indole as parent moiety with aromatic or aliphatic substitution at 3rd position. They are widely explored by scientists and found to contain various medicinal activities. The substitutions can be acetyl, methyl, phenyl, carboxy, carbonyl, ester, amido, amino, cyno etc. This review covers on pharmacological activities, ongoing clinical trials and current marketed preparations of 3-substituted indole derivatives.

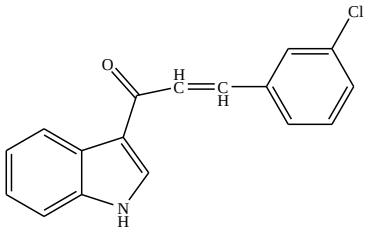
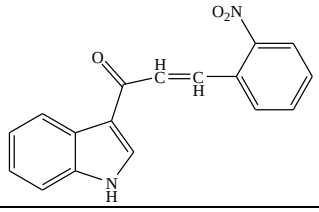
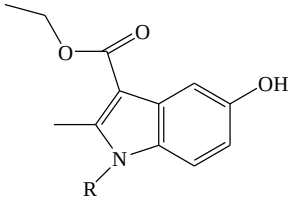
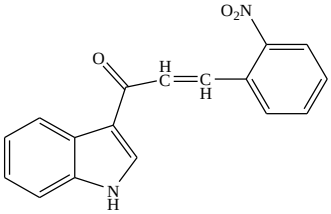
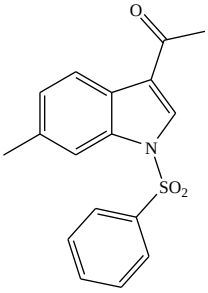
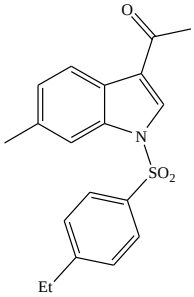


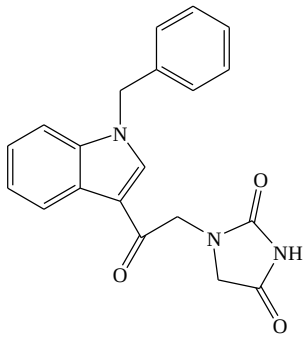
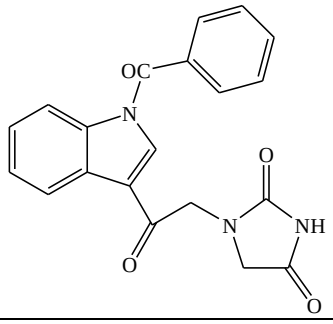
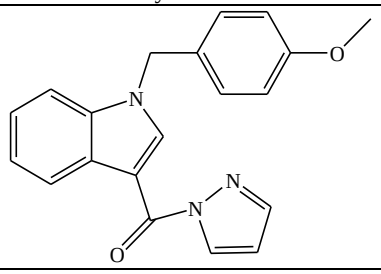
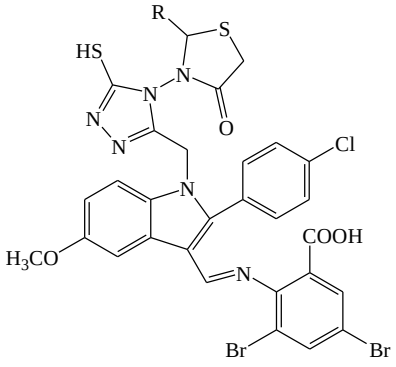
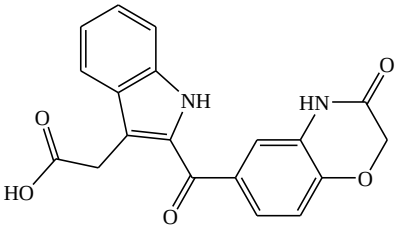
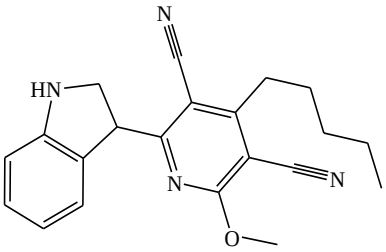
3-substituted indole

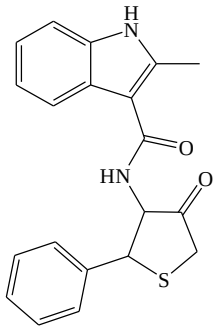
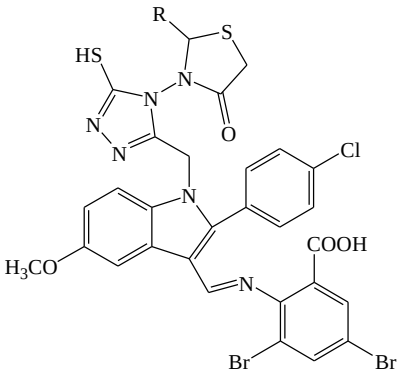
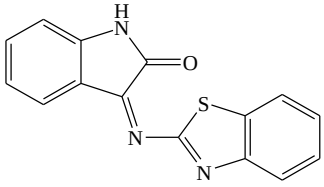
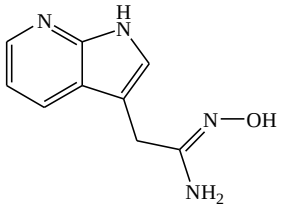
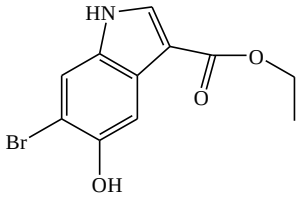
Pharmacological activity
Researchers have found that indole derivatives posses wide range of pharmacological activity.

Table 1: Pharmacological activity of 3-substituted indole

S. No.	Compound	Structure	Activity against	Reference
Antimicrobial Activity				
3-Substittuted acetyl indole				
1.	3-(1*H*-indol-3-yl)-3-(2, 4, 6-trimethoxyphenyl) prop-2-en-1-one		*Bacillus subtilis, Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa*	[2]
2.	3-(4-hydroxyphenyl)-1-(1*H*-indol-3-yl) prop-2-en-1-one		*B. subtilis, E. coli, S.aureus, P. aeruginosa*	[2]
3.	3-(4-flurophenyl)-1-(1*H*-indol-3-yl) prop-2-en-1-one		*B. subtilis, E. coli, S.aureus, P. aeruginosa*	[2]
4.	3-(4-hydroxy-3-methoxyphenyl)-1-(1*H*-indol-3-yl) prop-2-en-1-one		*B. subtilis, E. coli, S.aureus, P. aeruginosa*	[2]
5.	3-(3-ethoxy-4-hydroxyphenyl)-1-(1*H*-indol-3-yl) prop-2-en-1-one		*B. subtilis, E. coli, S.aureus, P. aeruginosa*	[2]
3-Substituted ethyl indole				
6.	7-azaindole-3-acetamidoxime		*Bacillus megaterium, Bacillus subtilis*	[3]
3-Substituted phenyl indole				
7.	3-(4-trifluoromethylphenyl) Indole		*Escherichia coli, Staphylococcus bacteria*	[3]
8.	3-(2-nitro-4-(trifluoromethyl)phenyl)-1*H*-indole		*Escherichia coli, Staphylococcus bacteria*	[4]

Antifungal Activity				
3-Substituted acetyl indole				
8.	3-(3-chlorophenyl)-1-(1*H*-indol-3-yl)-prop-2-ene-1-one		*Candida albicans, Asperigillus niger*	[1]
9.	1-(1*H*-indol-3-yl)-3-(2-nitrophenyl) prop-2-en-1-one		*Candida albicans, Asperigillus niger*	[1]
3-Ssubstituted carboxy ester indole				
10.	1-aryl-2-methyl-3-carboethoxy-5-hydroxy indole	 R= substituted phenyl	*Aspergillus awamori, Aspergillus arogens*	[3]
Antioxidant				
3- Substituted acetyl indole				
11.	1-(1*H*-indol-3-yl)-3-(2-nitrophenyl) prop-2-en-1-one			[2]
Antitumor Activity				
3- Substituted acetyl indole				
12.	*N*-phenylsulfonyl-3-acetyl-6-methylindole			[5]
13.	*N*-(p-ethyl)phenylsulfonyl3-acetyl-6-methylindole			[5]

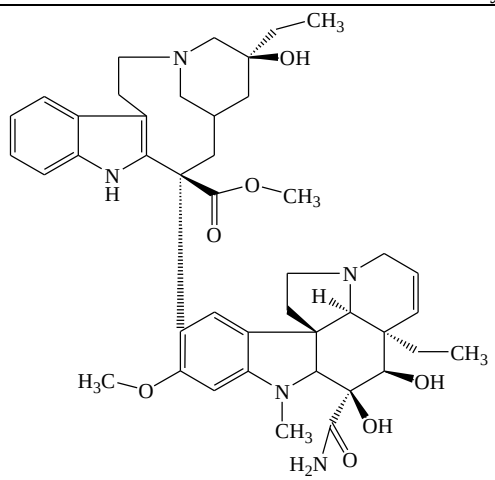
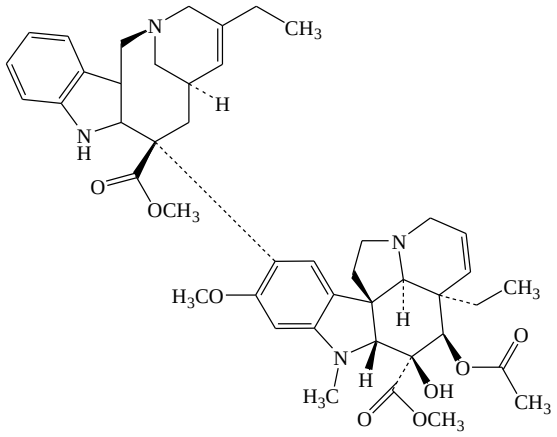
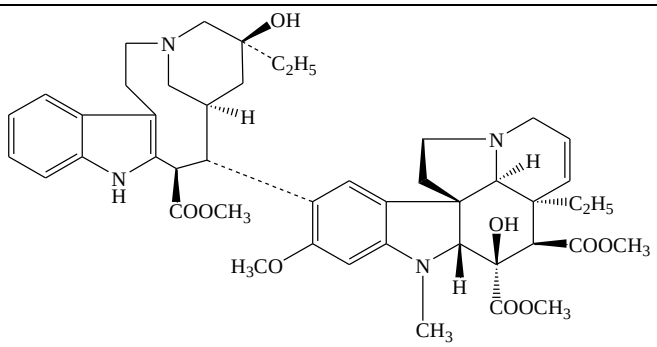
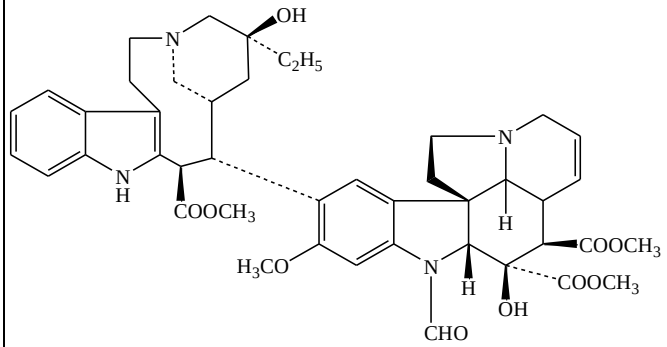
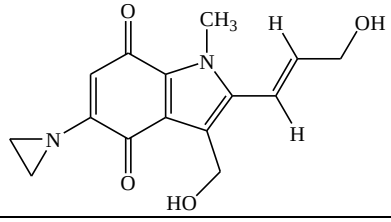
14	1-[(1-benzyl indol-3-yl) carbomethyl]-2-thioxoimidazolidine-4-one			[3]
15.	1-[(1--benzoyl indol-3-yl) carbomethyl]-2-thioxoimidazolidine-4-one			[3]
3-Substituted carbonyl indole				
16.	(1-(4-methoxybenzyl)-1*H*-indol-3-yl)(1*H*-pyrazol-1-yl)methanone			[3]
Anti-inflammatory activity				
3-Substituted methyl indole				
17.	2-(*p*-chlorophenyl)-1-[4-(2-(*p*-chorophenyl)-4-oxo-thiazolidin-3-yl]-5-mercapto[1,2,4,]-trizole-3-yl-methyl]-3[4,6-dibromo-2-carboxyphenyliminomethyl]-5-methoxyindole	 R= chlorobenzylidene amino		[3]
3-Substituted carboxy methyl indole				
18.	[2-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-carbonyl)-1*H*-indol-3yl]acetic acid		COX-2 inhibitor properties	[3]
3-Substituted heterocyclic indoline				
19.	2-(1*H*-indol-3-yl)-6-methoxy-4-pentylpyridine-3,5-dicarbonitrile			[3]

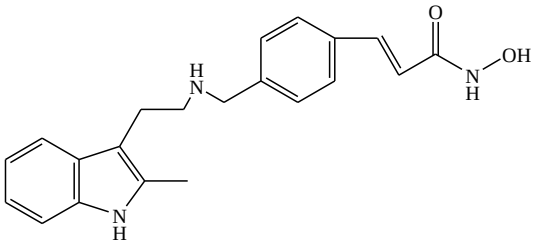
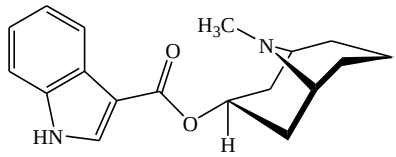
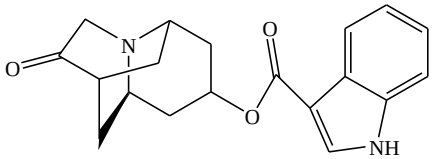
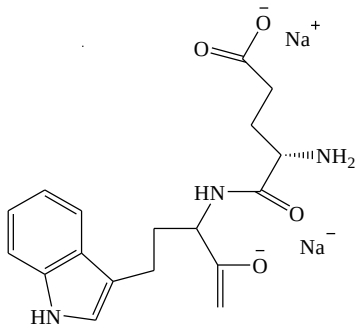
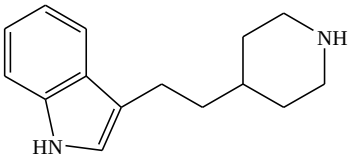
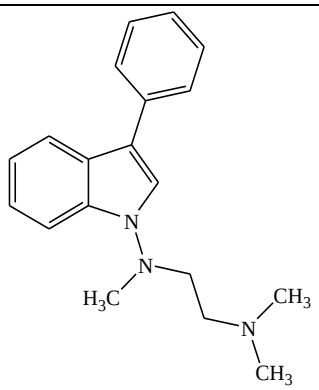
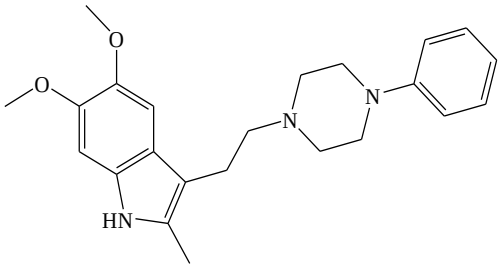
Analgesic Activity				
3- Substituted amido indole				
20.	2-methyl-1*H*-indole-3-carboxylic acid[2-(2-substitutedphenyl)-4-oxo-thiazolidin-3-yl]amide	 R= alkyl or heterocyclic nucleus		[3]
3-Substituted methyl indole				
21.	2-(*p*-chlorophenyl)-1-[4-(2-(*p*-chorophenyl)-4-oxo-thiazolidin-3-yl]-5-mercapto[1,2,4,]-trizole-3-yl-methyl]-3[4,6-dibromo-2-carboxyphenyliminomethyl]-5-methoxyindole	 R= chlorobenzylidene amino		[3]
Anticonvulsant Activity				
3-Substituted imino indole				
22.	3-(1,3-benzothiazol-2-ylimino)-1,3-dihydro-2*H*-indol-2-one			[3]
Antihypertensive Activity				
3- Substituted ethyl indole				
23.	7-azaindole-3-acetamidoxime			[3]
Antiviral Activity				
3-Substituted carboxy ester indole				
24.	3-ethoxycarbonyl-6-bromo-5-hydroxyindole		Laboratory-passaged isolates of human influenza A3 and respiratory syncytial virus(RSV)	[3]

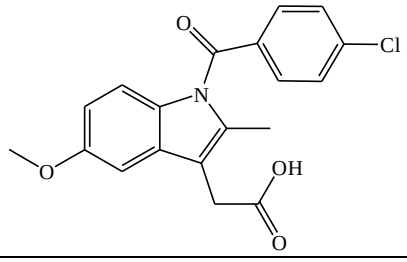
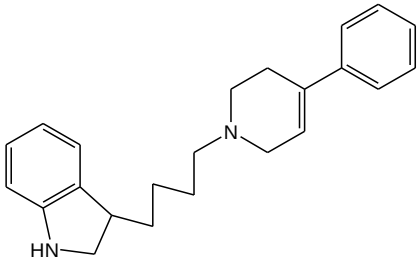
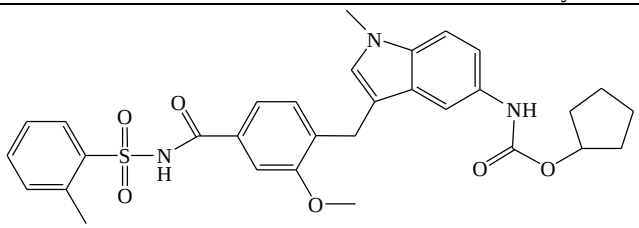
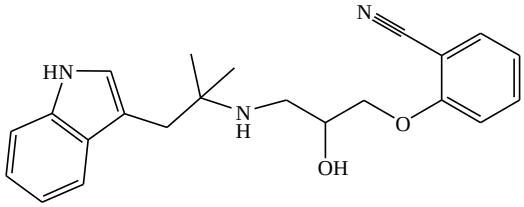
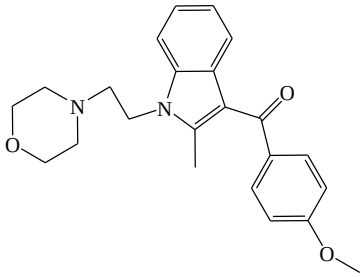
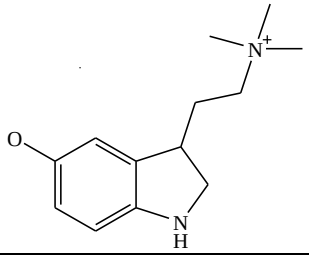
Currently marketed preparations of 3-substiuted indoles

Table 2 summarizes the currently available marketed preparations of 3-substiuted indoles with their name, structure, pharmacological activity, mechanism of action, manufacturer and dosage form.

Table 2: Current marketed preparations of 3-substiuted indoles (*6*)

S. No.	Drug	Structure	Company	Mechanism of action	Dosage form
Anticancer					
3-Substituted methyl indole					
1.	Vindesine		Genus Pharma-ceuticals Limited	Vindesine acts by causing the arrest of cells in metaphase mitosis through its inhibition tubulin mitotic functioning.	Powder for injection
2.	Vinorelbine		Abbott India Limited	Inhibits, mitosis at metaphase through its interaction with tubulin	Solution for injection
3.	Vinblastine		Bedford Laboratories	Inhibits, mitosis at metaphase through its interaction with tubulin	Solution for injection
4.	Vincristine		Alkem Laboratories Ltd., Biochem Pharma-ceutical Industries Ltd., Sun Pharma-ceuticals Industries Ltd.. Intas Pharma-ceutical Ltd.	Inhibits, mitosis at metaphase through its interaction with tubulin	Solution for injection
5.	Apaziquone		Avanscure Lifesciences Pvt. Ltd	Apaziquone is converted to active metabolites by intracellular reductases. The active metabolites alkylate DNA and lead to apoptosis	

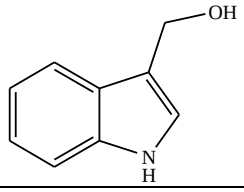
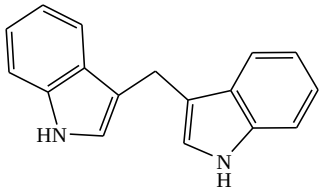
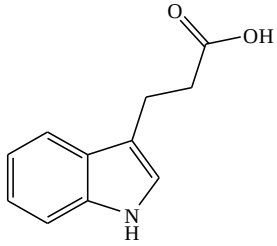
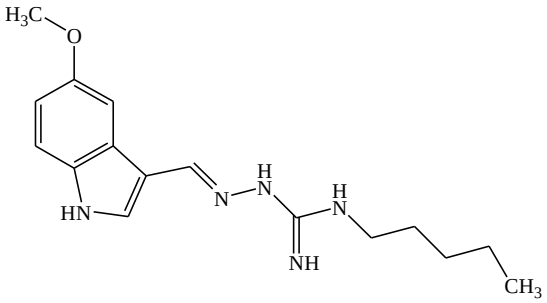
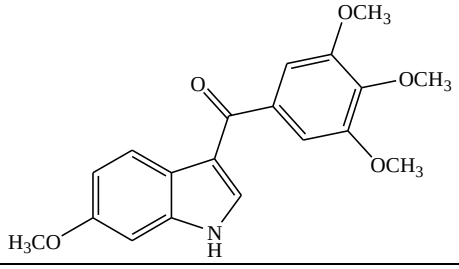
6.	Panobinostat		Novartis	Inhibits, histone deacetylation, damages DNA and upregulates proteins that promote apoptosis and cell-cycle arrest.	Capsule
Antiemetic					
3-Ssubstituted carboxy ester indole					
7.	Tropisetron		Novartis		Solution for injection
8.	Doleasetron		Sanofi, Aventis	5-HT3 receptor antagonist	Solution for injection
Immunomodulatory					
3-Substituted ethyl indole					
9.	Oglufanide		Johnson & Johnson		
Antidepressant					
3-Substituted ethyl indole					
10.	Indalpine		Pharmuka	Selective serotonin reuptake inhibitor (SSRI)	Tablet
3- Substituted phenyl indole					
11.	Binedaline			Selective norepinephrine reuptake inhibitor	
Antipsychotic					
3-Substituted ethyl indole					
12.	Oxypertine		Health Care Formulations Pvt. Ltd.		Tablet

Anti-inflammatory					
3-Substituted carboxy methyl indole					
13.	Indomethacin		Cipla, Sun pharma, Zydus Cadila Healthcare Ltd.	Cyclo-oxygenase (COX) inhibitor	Capsule, Tablet, Drops
Schizophrenia					
3-Substituted butyl indoline					
14.	Roxindole		Shanghai PI Chemicals Ltd.	Autoreceptor-selective dopamine agonist with additional properties as a serotonin reuptake inhibitor and 5-HT1A agonist	
Anti-Asthmatic					
3-Substituted methyl indole					
15.	Zafirlukast		Astra Zeneca	Blocks the action of the cysteinylleukotrienes on the CysLT1 receptors	Tablet
β-adrenergic Blockers					
3-Substituted ethyl indole					
16.	Bucindolol		ARCA biopharma	Non-selective β-adrenergic receptor blocker with α-1 blocker properties and mild intrinsic sympatholytic activity.	
Analgesic					
3-Substituted carbonyl phenyl indole					
17.	Pravadoline			Cyclo-oxygenase (COX) inhibitor	
Toxin					
3-Substituted ethyl indoline					
18.	Bufotenidine		Triveni Interchem Pvt. Ltd.	Selective 5-HT3 receptor agonist	

3-Substiuted Indoles Undergoing Clinical Trial Studies

Table 3 covers the ongoing clinical trials of 3-substiuted indoles with their name, structure, study, phase status and mechanism of action

Table 3: Ongoing clinical trials of 3-substiuted indoles

S. No.	Drug	Structure	study	status	Reference
3-Substituted methyl indole					
1.	Indole-3-carbinol		Obesity	Phase 2 (Terminated)	[7]
			Breast cancer	Phase 1	[8]
			Unspecified Adult Solid Tumor	Phase 1	[9]
			Biochemical Failure	Phase 3	[10]
2.	BR DIM [3,3'-Diindolyl-methane]		Systemic Lupus Erythematosus	Phase 1	[11]
3.	VP 20629 [Indole-3-propionic acid]		Friedreich's Ataxia	Phase 1	[12]
4.	Tegaserod [1-[[(Z)-(5-methoxyindol-3-ylidene) methyl] amino]-2-pentyl guanidine]		Chronic Constipation	Phase 4	[13]
3-Substituted carbonyl phenyl indole					
5.	SCB01A [6-methoxy-3-(3',4',5'-trimethoxy benzoyl) Indole]		Head and Neck Neoplasms	Phase 2	[14]

Conclusion

3-Substituted indoles have wide range of pharmacological acvities like antimicrobial, antifungal, antioxidant, antitumor, anti-inflammatory, analgesic, anticonvulsant, antihypertensive and antiviral activity. Thus we can say that 3-substituted indole is a moiety which has exhibited versatility in pharmacological action and has further potential for exploring its unexplored pharmacological activities.

Reference

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14. To Evaluate the Efficacy and Safety of SCB01A in Subjects With r/m Squamous Cell Head and Neck Cancer. Available from: https://clinicaltrials.gov/ct2/show/NCT03020823.