Indole: a multipotent nucleus

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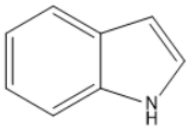
***Abstract*: Indole (1H-indole) is one of the most important heterocyclic rings which offers a privileged scaffold in drug discovery. Indole derivatives have a vast pharmacological significance and provide a huge opportunity for discovering novel drugs with a different mode of action. The indole nucleus has shown its versatility and therapeutic potency in many naturally occurring compounds like alkaloids. In the recent past many studies have been conducted to integrate and explore various therapeutic aspects of this moiety. The indole scaffold found in both natural and synthetic sources is considered to be one of the most promising heterocyclic compounds possessing several biological activities viz. anticonvulsant, antidiabetic, anti-inflammatory, anti-HIV, anticancer, antitubercular, antioxidants, antihypertensive, antimicrobial, antifungal, etc. Indole derivatives have generated larger interest amongst various researchers to discover therapeutic leads to alleviate a large range of human ailments. In the present review, authors have reviewed and interpreted certain aspects and deciphered certain developments in the field of indole derivatives in the biological, chemical, and pharmacological paradigms of drug discovery including a few drug candidates currently under clinical trials.**

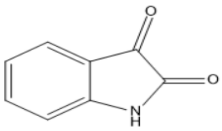
***Keywords:* Indole, 1H-indole, Heterocyclic ring, Anticonvulsant, Antioxidants, Antidiabetic, Anti-inflammatory, Clinical trials.**

1. INTRODUCTION

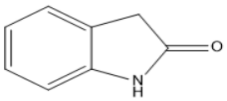
The word indole is a portmanteau of the word ***ind****igo* and ***ole****um* since indole was first isolated by treatment of the indigo dye with oleum. Indole (1H-indole) is the organic compound with the chemical formula C_8H_7N also known as benzopyrrole because the benzene ring and pyrrole rings are fused through the 2- and 3-positions of the pyrrole nucleus. It is one of the most abundant heterocycles in both natural products and biologically active molecules. It can be considered the most important of all privileged structures in medicinal chemistry[1]. Indole is a non-basic nitrogenous compound[2]. The word indole was composed of the word India, a blue dye imported from India which is known as indigo. Indigo can be converted to isatin **(1)** and then to oxindole **(2)**. Adolf von Baeyer, in the year 1866 reduced oxindole to indole with the help of zinc dust. In the year 1869, he proposed the structure for indole. Indole derivatives occur widely in natural products, plants, animals, and marine organisms[3].



Structure proposed by Baeyer's in 1869



Isatin
1



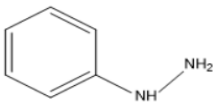
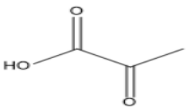
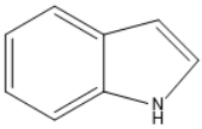
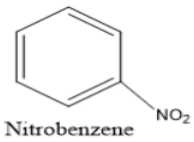
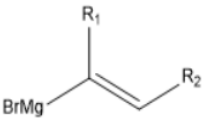
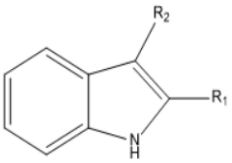
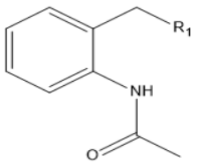
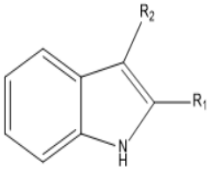
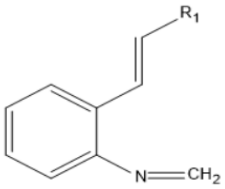
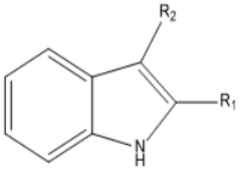
Oxindole
2

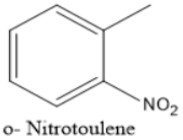
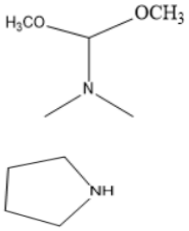
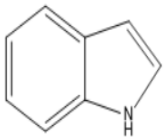
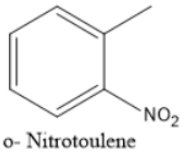
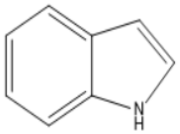
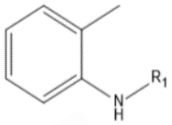
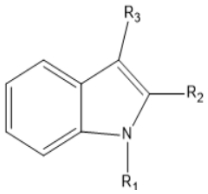
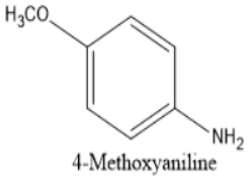
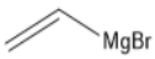
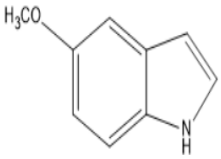
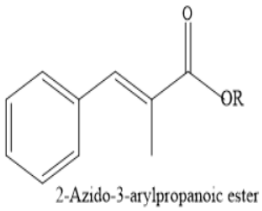
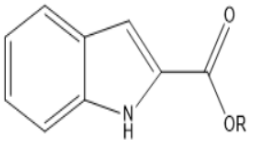
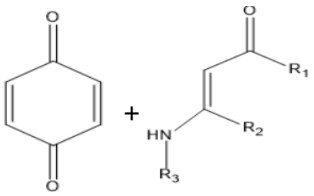
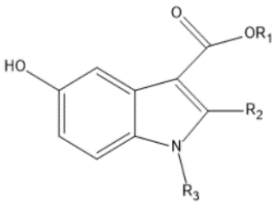
Chemical synthesis of the indole ring

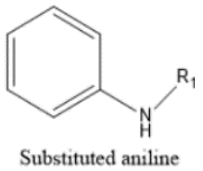
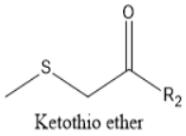
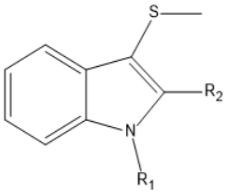
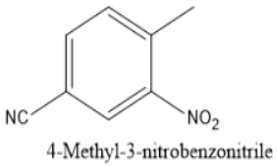
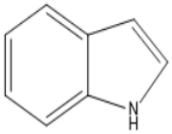
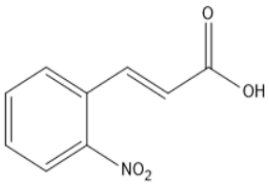
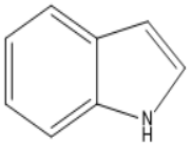
The synthesis of indole has been achieved by using different starting materials and strategies as mentioned in various organic chemistry literature reports which include: Fischer indole synthesis[4], Bartoli indole synthesis[5], Madelung indole synthesis[6], Fukuyama synthesis[7], Leimgruber-Batcho[8], Reissert indole synthesis[9], Larock indole synthesis[10], Julia indole synthesis[11], Hemetsberger indole synthesis[12], Nenitzescu indole synthesis[13], Gassman indole synthesis[14], Sundberg indole synthesis[15], Baeyer-Emmerling indole synthesis[16]

Table 1: Different methods for indole preparations.

Reaction Names	Reactant(s)	Reaction Conditions/Catalyst	Product (Indoles/ Substituted indoles)	References

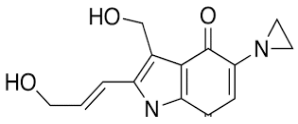
Fischer indole synthesis	 + Phenylhydrazine  2-oxopropanoic	$ZnCl_2/PCl_3$		[4]
Bartoli indole synthesis	 Nitrobenzene	 2. THF, -40˚C		[5]
Madelung indole synthesis		1.Sodium ethoxide 2.Hydrolysis, heat		[6]
Fukuyama synthesis		Azobisisobutyronitrile (AIBN), Tributyltin hydride (Bu_3SnH)		[7]

Leimgruber-Batcho		 o- Nitrotoulene	 , Raney Nickel, hydrazine, water		[8]
Reissert synthesis	indole	 o- Nitrotoulene	1.Ethyl-dioxalate, sodium ethoxide 2. Zn, acetic acid 3. heat		[9]
Larock synthesis	indole	 Disubstitu. alkyne + R_3	$Pd(OAc)_2$, base		[10]
Julia synthesis	indole	 4-Methoxyaniline	$SOCl_2$,  , Heat		[11]
Hemetsberger indole synthesis		 2-Azido-3-arylpropanoic ester	Heat		[12]
Nenitzescu synthesis	indole	 Benzoquinone (β-Amimocrotonic acid)			[13]

Gassman indole synthesis	 Substituted aniline	1.tert-butyl hypochlorite 3. Triethylamine 2.  Ketothio ether		[14]	2.
Sundberg indole synthesis	 4-Methyl-3-nitrobenzonitrile	1. p-substituted benzaldehyde, piperidine,150˚C 2.$P(OEt)_3$, reflux		[15]	
Baeyer-Emmerling indole synthesis		Fe, KOH		[16]	

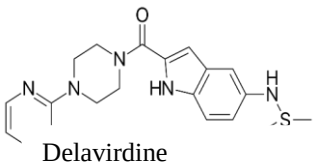
Marketed drugs having indole as the basic nucleus

Marketed drugs containing Indole nucleus and their related pharmacological activities are listed in **Table 2.** The biological profile of the new generation of indoles represents a major advance over the older compounds. Apaziquone (EOquin, **3**) is a type of indoequinone that is a prodrug and a chemical analog of mitomycin C[17]. Delavirdine **(4)**, an inhibitor of the cytochrome P450 isozyme, is a drug that is developed for the treatment of HIV type 1 containing an indole nucleus or ring within it[18]. Many indole-based pharmaceutical drugs comprise a very effective class of therapeutic molecules and are likely to replace many of the existing pharmaceuticals in the near future[19].



Apaziquone

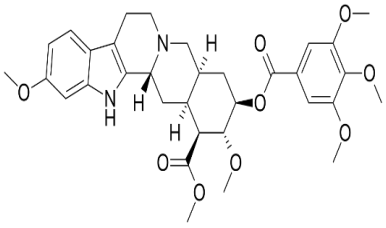
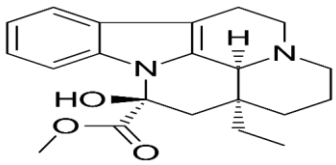
3

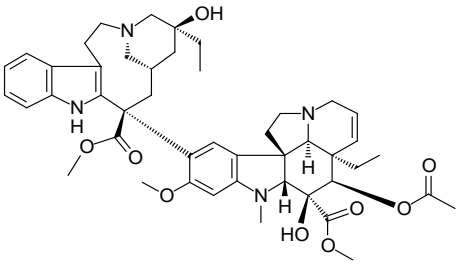
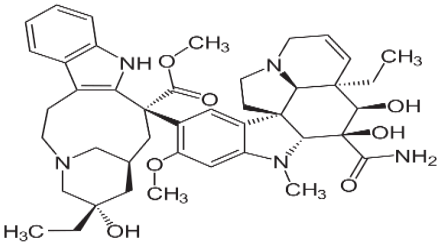
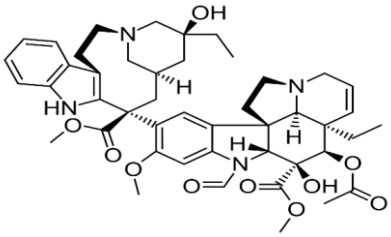
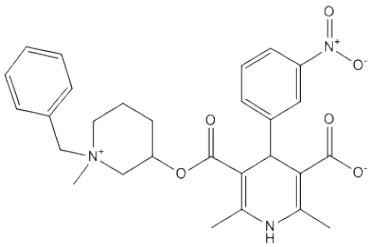
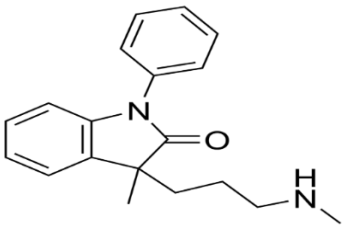
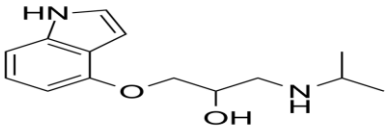


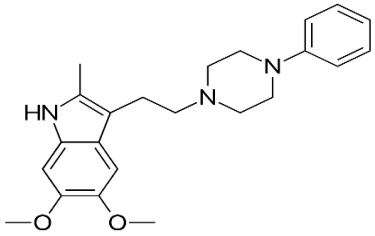
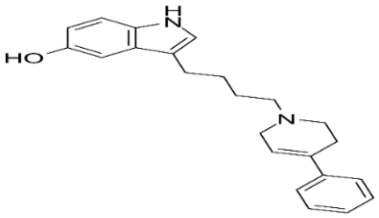
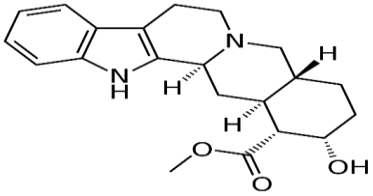
Delavirdine

4

Table2: Some marketed drugs having indole ring and their pharmacological activities

Drug	Brand name	Chemical Structure	Use	Reference
Reserpine	Serpasil		Anti-hypertensive drug	[20]
Vincamine	Oxybral SR		Anti-hypertensive drug	[21]

Vinblastine	Oncovin		Anti-cancer drug	[22]
Vindesine	Eldisine		Anti-cancer drug	[22]
Vincristine	Vincasar		Anti-cancer drug	[23]
Binedaline	Benidipinum		Anti-depressant drug	[24]
Amedalin	Clavam		Anti-depressant drug	[25]
Pindolol	Visken		Anti-depressant drug	[26]

Oxypertine	Equipertine		Anti-psychotic agent	[27]
Roxindole	Roxindole		Schizophrenia	[28]
Yohimbine	Aphrodyne		Sexual dysfunction	[29]

3. Pharmacological profile of indole derivatives

The versatile properties of indoles made them widely popular among different chemists. It has been found to be involved in the treatment of various medical conditions, including anticonvulsant, anticancer, anti-inflammatory, anti-viral, antidepressants, anti-diabetic, etc.,

3.1. Anticonvulsant activity

Priya Ahuja *et al.,* in 2014 proposed a novel series of thirty indoles C-3 substituted 5-amino-6-(5-substituted-2- phenyl-1H-indol-1-yl)-4,5-dihydro-1,2,4-triazine-3(2H)- thione derivatives were explored for possible anticonvulsant agents. The derivative 1-(1-(5-amino-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-yl) -5-fluoro-2-phenyl-1H-indol3-yl)ethenone **(5)** showed significant activity in maximal electroshock (MES) test with a minimum duration of limb extension (5.40-0.61sec) and quantitative median dose of 7 mg/kg. In subcutaneous pentylenetetrazole screening 1-(5- amino-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-yl)-5-fluoro-2-phenyl-1H-indole-3-sulfonamide **(6)** showed an increase in the seizure latency to onset of clonus and was effective at a median dose of 35 mg/kg[30].

Govindaraj Saravanan *et al.,* in 2014 synthesized 1- (morpholinomethyl)-3-substituted isatin **(7)** derivatives and explore them for anticonvulsant activity using MES and scPTZ seizure tests. Among the synthesized analogs, the most active one was (22) which revealed protection in MES at a dose of 30 mg/kg (i.p.) after 0.5 h and 4 h. This molecule also provided protection in the scPTZ at a dose of 100 mg/kg (0.5 h) and 300 mg/kg (4 h)[31].

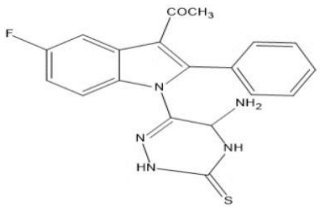
Novel indole derivatives which were having oxazolone/imidazolone moieties were synthesized by MSY Khan *et al.*, in 2012, and they were tested for their anticonvulsant activity in MES and scPTZ animal models. Compounds (**8** and **9**) showed significant anticonvulsant activity in MES animal model whereas compound **(9)** was active in scPTZ animal model. Therefore from the series of novel derivatives one compound, 1-(2-Hydroxypropyl)-2-phenyl-4-[(2-phenylindolin-3-yl)methylene]-1*H*-imidazol-5(4*H*)-one appears to be the lead compound and it could be considered for further studies[32].

A new series of 3-(4- substituted phenyl)-3-(substituted phenyl aminomethylene)-2,3- dihydrobenzoxazepin/benzothiazepin-2-yl)-2,5-disubstituted indoles were proposed by Anil Kumar *et al*., in 2011, and screened them for its anticonvulsant potential. Out of the compounds screened, the compound **(10)** was found most potent anticonvulsant agent than the standard drug phenytoin sodium at a dose of 30 mg/kg i.p. While some other compounds were found to possess activity equipotent to that of reference drugs [33].

Pandeya *et al.,* in 1999 synthesized a series of p-nitrophenyl substituted semicarbazones **(11)** and tested their anticonvulsant activity by using maximal electroshock (MES), subcutaneous pentylenetetrazole (scPTZ), and subcutaneous strychnine (scSTY) methods[34].

Siddiqui et al., in 2008 synthesized 2-(1*H*-indol-3-yl)-N-(substituted phenyl) hydrazine carbothioamides **(12)** and their related heterocyclic derivatives were screened for their anti-convulsant activities and it was found that the showed protection against seizures both after 0.5 h and 4 h at 30 mg/kg body mass[35].

Novel oxa/thiadiazolylazetidinonyl/thiazolidinonylcarbazoles were synthesized by Kumar *et al.,* in 2010 **(13)**. The compounds were screened for their anticonvulsant activity against maximal electroshock-induced seizures. The compound demonstrated different degrees of anticonvulsant activity. The compound exhibited potent 80% anticonvulsant activity by the MES animal model.[36]



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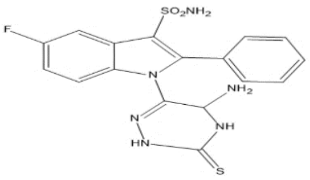

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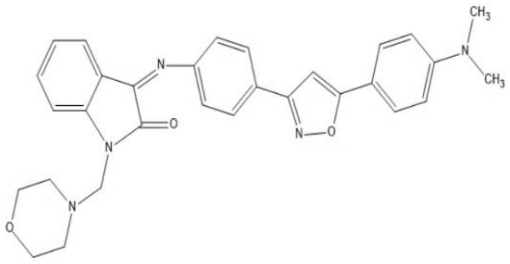

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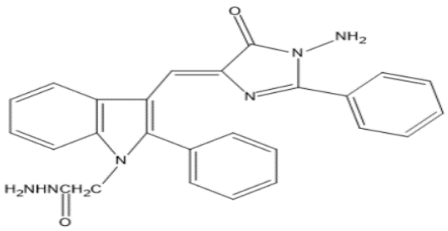

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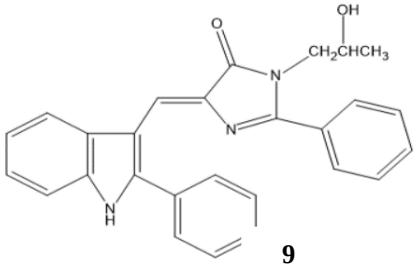

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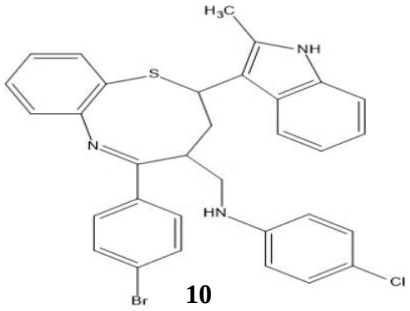

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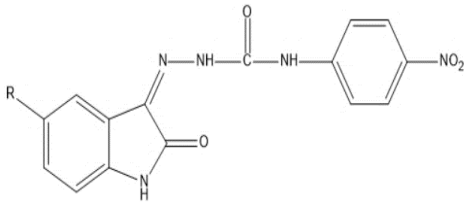
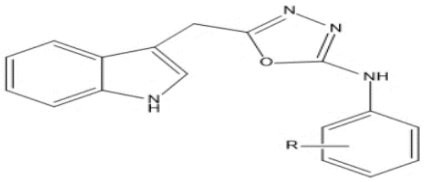


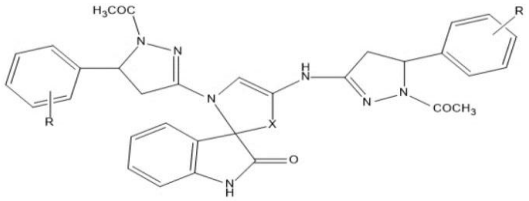
R= H, Cl, NO_2

11



R= H, 2-Cl, 2-OCH_3, 4-OCH_3, 2-CH_3, 3-CH_3, 4-CH_3

12



R= 4-OH, 2,4-OH, 4-OH, 3-OCH_3, 4-$N(CH_3)_2$, 2-Br

X=O, S

13

Fig 1 Indole derivatives with potential Anticonvulsant activity

Anticonvulsant action is increased by the introduction of biphenyl moiety.

The activity is increased by adding an acetyl group to the piperazine or piperidine moiety in the third position.

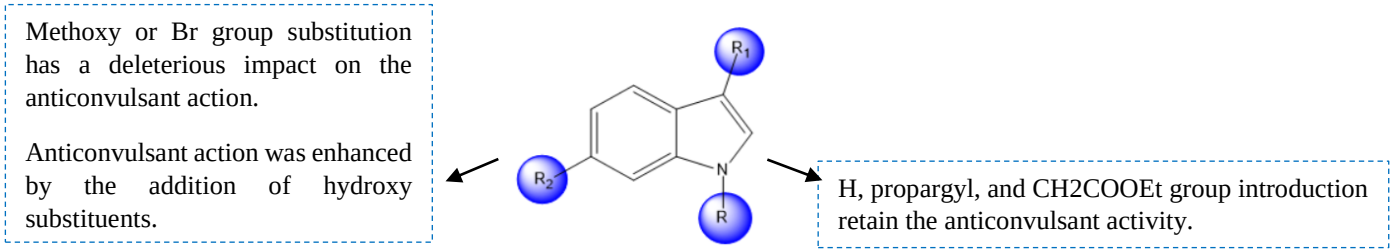


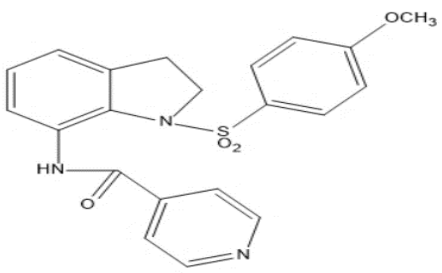
Fig 2 SAR of Anticonvulsant activity

4.2 Anticancer activity

A novel oral indoline-sulfonamide agent, j30 **(14)** were synthesized by Liou *et al*., in 2007, exhibiting potent activity against human cancer cells. The novel sulfonamide-based drug, J30, has been shown to have broad-spectrum *in-vitro* activity by inducing apoptosis and to be effective against tumour xenografts in animal models. Besides that, J30 is efficient when given orally to mice and is less susceptible to drug resistance, at least when brought on by MDR or MRP overexpression. According to their research, J30 has the potential to be an effective oral anti-neoplastic medication for the treatment of many malignancies and tumours that are resistant to other drugs.[37]

Sigman *et al.,* in 2010 synthesized and carried out the preliminary biological studies of 3- substituted Indoles **(15)** accessed by a palladium-catalyzed enantioselective alkene functionalization reaction. Several compounds' evaluations revealed promising anticancer activity against MCF-7 cells[38].

Popp and Pajouhesh *et al.,* in 2017 synthesized 3-o-nitrophenyl hydrazones of isatin **(16)** by condensation of isatin with o-nitrophenyl hydrazine. These compounds were found to be active intramuscularly against Walker carcinoma-256 and inactive against L-1210 lymphoid leukemia[39]



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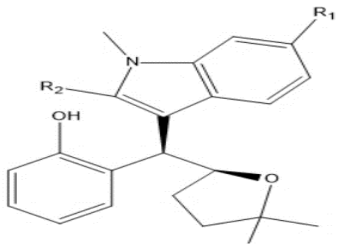
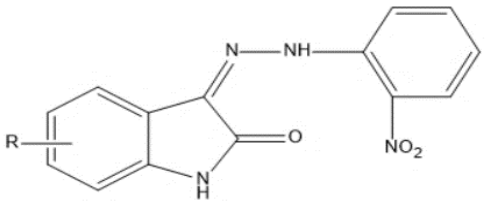


R2 = Ph, R1 = H (G1 phase arrest), **R2** = H, **R1** = COOCH3 (G2 phase arrest)

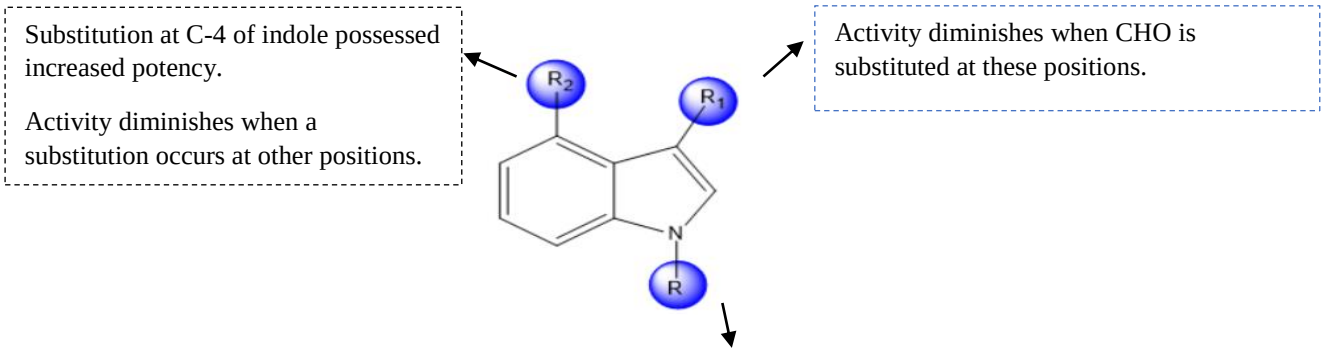
15



R= H, 1-CH3, 1-COCH3, 4-CF3, 5-Br, 5-Cl, 5-SO3H

16

Fig 3 Indole derivatives with potential Anticancer activity



The introduction of methyl diminishes the activity.

Fig 4 SAR of Anticancer activity

4.3 Anti-inflammatory activity

The novel indole-3-guanidine hydrazone hydrochloride **(17)** were synthesized by Sandes et al., in 2018, which showed anti-inflammatory effects in the carrageenan-induced pleurisy model which is proved by increased levels of total leucocyte count and dysregulation of proinflammatory (TNF-α and IL-1β) and anti-inflammatory cytokines (IL-10)[40].

Shin *et al.*, in 2014 synthesized 7-hydroxyl-1-methylindole-3- acetonitrile (7-HMIA) **(18)**. HIMA showed positive inhibitory effects on LPS-induced proinflammatory cytokines such as NO, TNF-α, IL-6, and PGE_2 production in macrophages, and the effect were closely associated with suppression of NF-kB activity assessed through decreased translocation of p65 and Akt phosphorylation. 7-HMIA significantly suppressed the mRNA stability of microsomal prostaglandin E synthase (mPGES-1) without inhibiting cyclooxygenase-2 (COX-2) expression. HMIA had also been shown to possess a 2-fold improvement in anti-inflammatory activity in comparison to parent arvelexin and its derivatives[41]

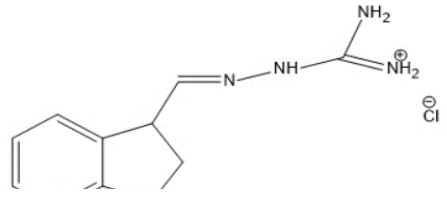
Synthesis of acetohydrazide-indole derivatives was proposed by Bhat *et al.*, in 2016 to check their anti-inflammatory activity. According to the SAR studies substitution of nitrophenol was favorable for COX-2 inhibitory activity. Furthermore, molecular docking studies show that compound (**19**, potency = 0.79%) is found to be the most selective inhibitor and also was potent as compared to the standard drug used which was Indomethacin (potency = 1.0%)[42].

Liu *et al.*, in 2016 designed and evaluated indole-2-carboxamide derivatives for anti-inflammatory activity. Moreover, *in vivo* studies were carried out for screening the biological activity of the potent compounds. SAR studies concluded that oxazole and amine substitution through carboxamide at C-5 had an effect on activity. Also, increasing methoxy substitution enhances the activity. Furthermore, the substitution of 2,6-di-chlorobenzyl, 3-fluorobenzyl, 4-bromobenzyl, and 4-trifluoromethyl benzyl at the N1 position shows good anti-inflammatory activity. Compounds **(20a)** and **(20b)** were found to be highly potent[43]

Shaker *et al.*, in 2020 designed, synthesized, and evaluate the anti-inflammatory activity of methylsulphonyl and aryl-substituted derivatives indole derivatives. SAR studies show the importance of halogen substitution compound **(21a)** and compound **(21b)** showed maximum anti-inflammatory activity as compared to the standard drug indomethacin[44].

A series of fused pyrroles were synthesized by Fatahala *et al.*, in 2017, and screened there *in-vivo* anti-inflammatory activity by using the rat paw edema method and performed molecular docking analysis. According to SAR studies the addition of hydrophobic ring coplanar with the original ring, and substitution of p-fluorophenyl leads to increased anti-inflammatory activity. Compound **(22)** (% inhibition=92%) showed maximum activity to a standard drug used which is indomethacin (% inhibition= 78.58%)[45].

A capsaicin-based indole and nitro-indole derivatives were synthesized by Mukthung *et al.*, in 2018 and screened them against the proinflammatory kinase TNF-α. SAR studies showed the role of capsaicin alkyl chain system and nitro substitution for favorable activity. Compounds **(23a)** (relative % inhibition = 47.65%) and **(23b)** (relative % inhibition = 51.95%) were the most potent compounds as the relative % inhibition compared with standard drug capsaicin[46].



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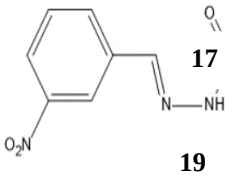

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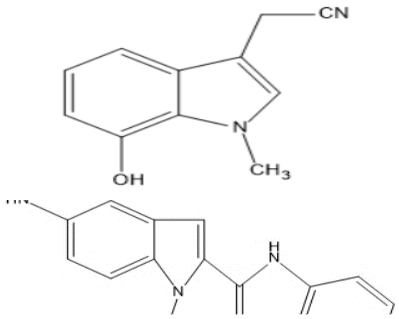
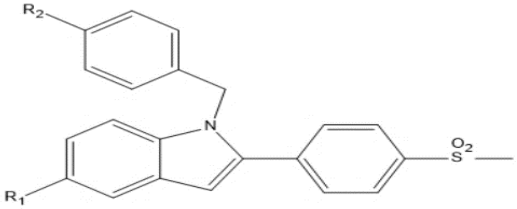


20/a =R= Furan-2-carbonyl

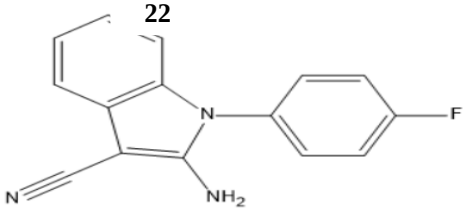
20/b =R= N, N-dimethylaminocarbonyl

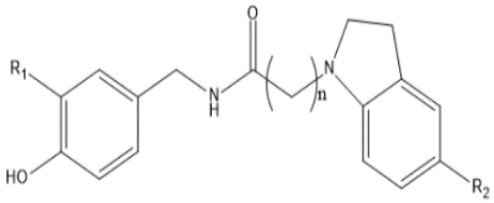


21/a=R1=H, R2= Cl

21/b=R1=F, R2= Cl

22





23a= **R_1**= NO_2, **R_2**=NO_2, n= 4
23b= **R_1**= NO_2, **R_2**=NO_2, n= 5

Fig 5 Indole derivatives with potential Anti-inflammatory activity

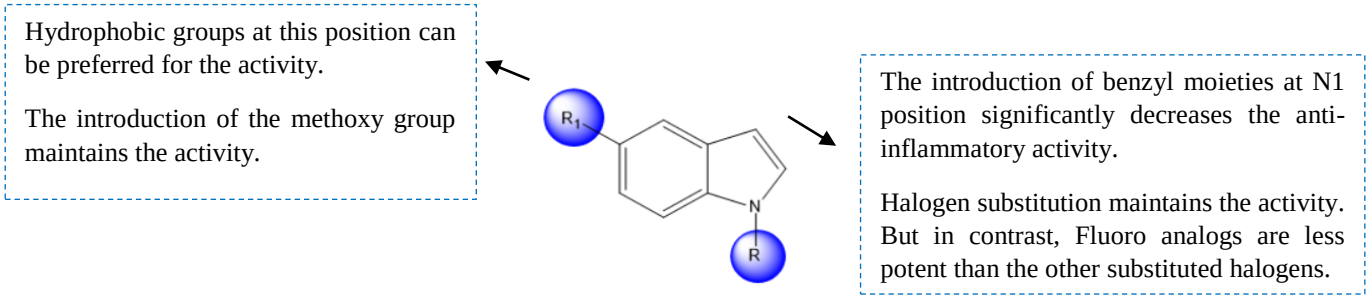


Fig 6 SAR of Anti-inflammatory activity

4.4 Antiviral activity

Musella *et al.*, in 2016 synthesized amide-substituted indole derivatives and evaluated them against the human *Varicella zoster virus* (VZV). SAR studies show that substituting biphenyl ethyl moiety and acetylation at the amino group of tryptamines is required for the activity against VZV. Compound **(24)** (Cytotoxic concentration, CC_{50} = 39µM) was found to be highly potent as compared with standard drug acyclovir (CC_{50} = 191µM) and biuvudin (CC_{50} = 160 µM)[47].

A novel indole-thiourea hybrids were synthesized by Sanna *et al.*, in 2018 and evaluated them against HIV-1 (human immunodeficiency virus). SAR studies show the importance of 4-bromophenyl moiety. Among all the synthesized compounds, **(25)** (EC_{50} = 8.7 ± 0.4µM) was found to be highly potent as compared with the standard drug efavirenz (EC_{50} = 0.002 ± 0.0002 µM)[48].

Ferro *et al.*, in 2013 designed, synthesized, and evaluated indole derivatives by performing the docking study with HIV-1 integrase. Docking studies showed that bulkier substituent on the benzyl group, i.e., *tert*-butyl, trifluoromethyl group, is desirable for the interaction with HIV-1 integrase protein. Compound, **(26)** (IC_{50} = 0.4Mm) was found to be highly potent[49].

Balupuri *et al.*, in 2014 synthesized and screened using various molecular dynamics and 3D-QSAR studies. SAR studies showed that small bulky substituents were required for the activity and also smaller substituents having balanced electrostatic and steric properties are highly desirable at the 7th position of the indole ring. However, activity reduced in the order of primary > secondary > tertiary amine. Compounds **(27a)** (EC50 = 0.006 nM) and **(27b)** (EC50 = 0.005 nM) were found to be highly potent, having a good binding affinity with a receptor[50].

Selvam *et al.*, in 2006 synthesized 4-[(1,2dihydro-2-oxo-3H-indol-3-ylidene)amino]-N-(4,6-dimethyl-2-pyrimidin-2-yl)benzenesulphonamide and its derivatives **(28a, 28b, 28c)**. These compounds were tested for antiviral activity against influenza A (H1H1, H3N2, and H5N1) and B viruses in the Madin Darby canine kidney (MDCK) cell culture[51].

A novel derivative of 3-ethoxycarbonyl-6-bromo-5-hydroxyindoles **(29)** was synthesized by Dun Wang *et al.*, in 2014. Moreover, their antiviral activity was determined in cell culture with virus cytopathic effect assay[52].

Synthesis and evaluation of cyclopropyl indole derivatives as HIV non-nucleoside reverse transcriptase inhibitors was performed by Hassam *et al.*, in 2012. SAR studies showed that the C-1 position of propanoic acid groups, i.e., phenyl and thiophene increases the activity and at the C-3 position, Cl and Br (halogen groups) are desirable for the activity. Compounds **(30a)** (IC_{50} = 0.085µM) and **(30b)** (IC_{50} = 0.065µM) were highly potent as compared to the standard drug nevirapine (IC_{50} = 0.087 µM). Molecular docking studies were performed to evaluate the activity using HIV non-nucleoside reverse transcriptase enzyme which confirmed that compound **(30b)** was well accommodated within the active site[53].

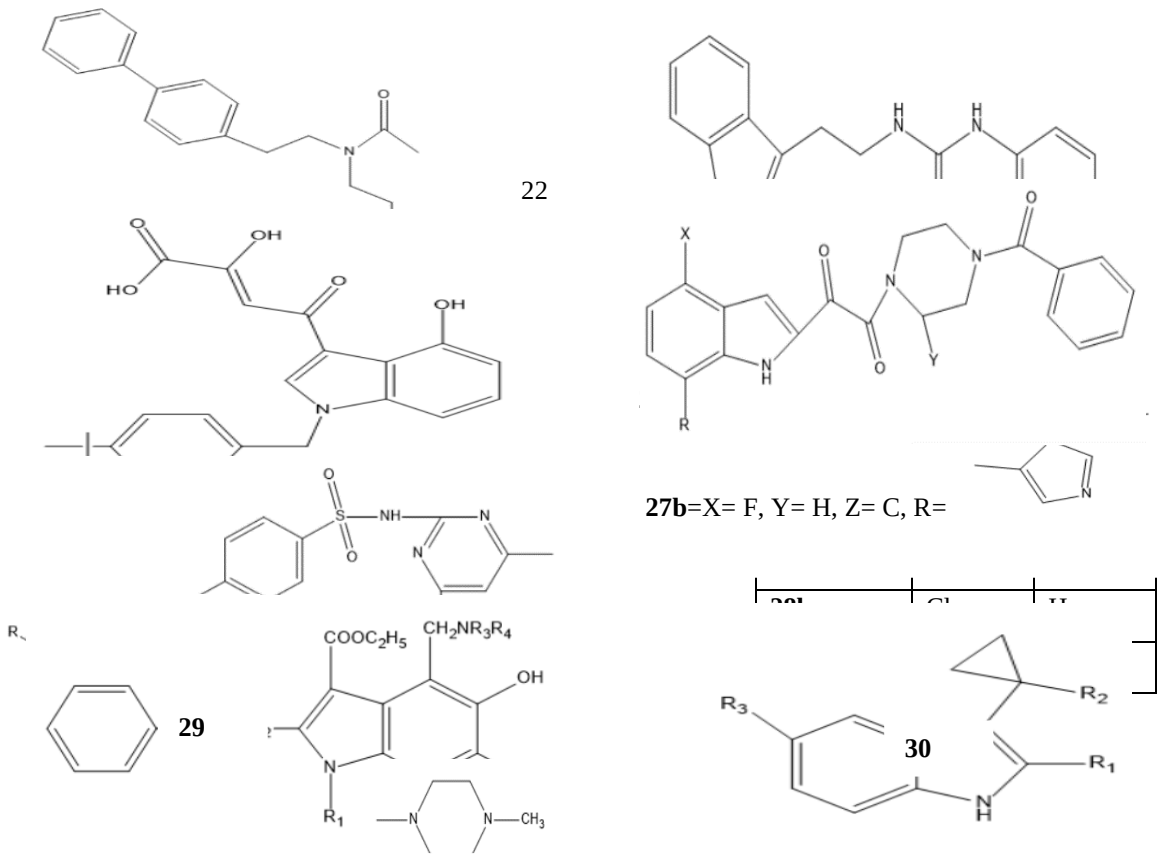


Fig 7 Indole derivatives with potential Anti-viral activity

The activity is increased when halogen is substituted.

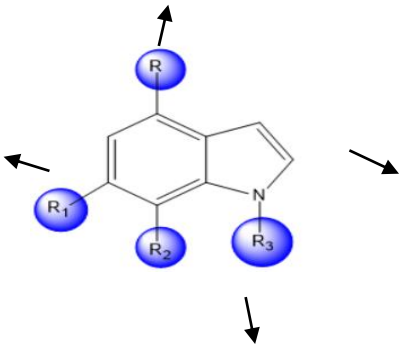
The activity is maintained by substitution with methoxy, ethoxy, and nitro groups.

The activity decreases when the alkyl chain increases.

The activity gets decreased when the hydroxy group is substituted.

The activity is seven times greater when a F atom is substituted.

The antiviral activity was lost when the Cl and OCH3 substitutions were replaced.



Replacement with methyl maintains the activity

Alkyl substitution is less effective than alkoxy substitution.

The size of the substituent has an impact on the compound's potency.

Strong activity is displayed when hetrocyclic moeities like tetraozole or a five-membered ring are substituted.

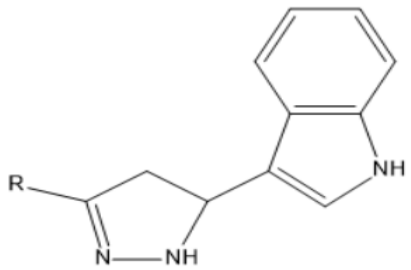
The strong action was likewise seen when a primary or secondary amide was substituted.

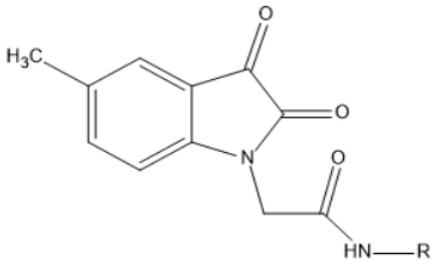
Fig 8 SAR of Anti-viral activity

4.5 Antidepressant activity

Synthesis and screening of a series of indole derivatives bearing dihydropyrazoline moiety was performed by Patil and Bari *et al.*, in 2016, and evaluated them for antidepressant activity using a forced swimming test. SAR studies show that the presence of electron-donating groups on the phenyl ring of indolylpyrazoline has a big role in the activity. Finally, it was concluded from the *in vivo* study that compounds **(31a)** (116.3 ± 1.54) and **(31b)** (109.8 ± 2.86) were found to be highly potent when compared to the standard drug fluoxetine (immobility reduced to 77.4%) and imipramine (immobility reduced to 75.5%)[54].

Zhen *et al.*, in 2015 synthesized a series of 2-(5-methyl-2,3-dioxoindolin-1-yl) acetamide derivatives. The compounds were further screened for antidepressant activity using a forced swim test. SAR studies show that only 3-Br-phenyl, 4-Br-phenyl, 3-CF_3-phenyl, and benzyl group attachment with acetamide gives potent compounds. Compounds, **(32a)** (65.77 ± 17.8) and **(32b)** (75.77 ± 18.7) show good potency when compared with the standard drug fluoxetine (58.5 ± 9.3)[55]





31a=R=4-Cl-C_6H_4-

31b=R=4-NO_2- C_6H_4-

32a=R=3-Br-C_6H_4-

32b=R=3-CF_3-C_6H_4-

Fig 9 Indole derivatives with potential Anti-depressant activity

The affinity for the 5-HT_{2A} receptor was made stronger by C-2 methylation.

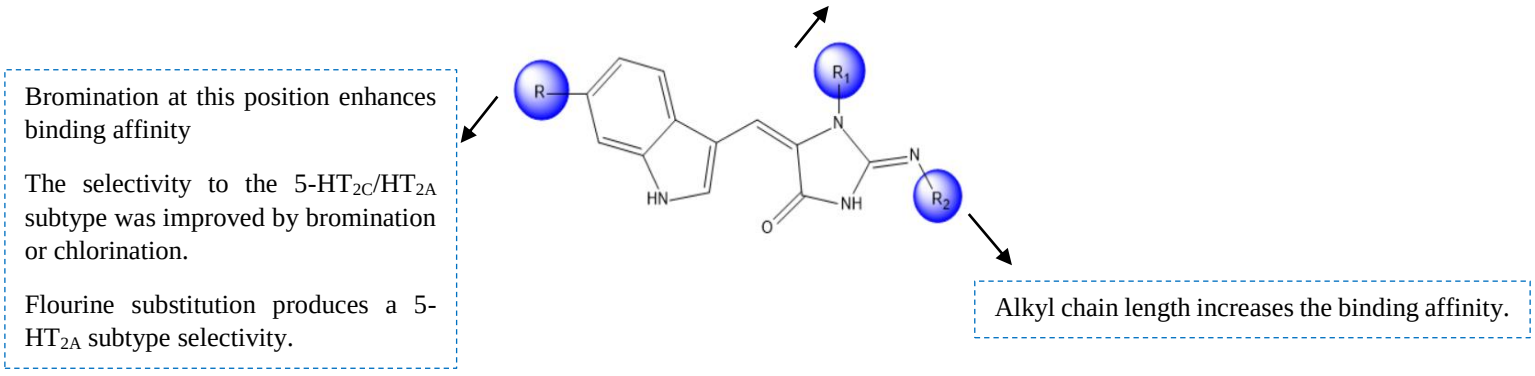


Fig 10 SAR of Anti-depressant activity

4.6 Anti-diabetic activity

Mohler *et al.,* in 2009 discovered a site at the monomer interface is known as the indole inhibitor site. Compound **(33)** inhibited liver and muscle GP in the nM range in enzyme kinetics and was active in forskolin-induced, cell-based glycogenolysis in the mM range (1.9Mm)[56].

Synthesis of novel indole N-glucoside derivatives was proposed by Nomura *et al.,* in 2014, and evaluated them on high-fat diet-fed mice. SAR studies show that methyl and halogen substitution is desirable for the activity. Compound **(34)** (IC_{50} =1.1µM) was found to be highly potent[57].

Synthesis and evaluation of novel indole-triazole derivatives was conducted by Rajan *et al.,* in 2017. All the synthesized compounds were evaluated by the Syrian Golden Hamster model. SAR studies show that difluoro and tosyl substitution is desirable for the activity. The compound **(35)** was found to be highly potent[58].

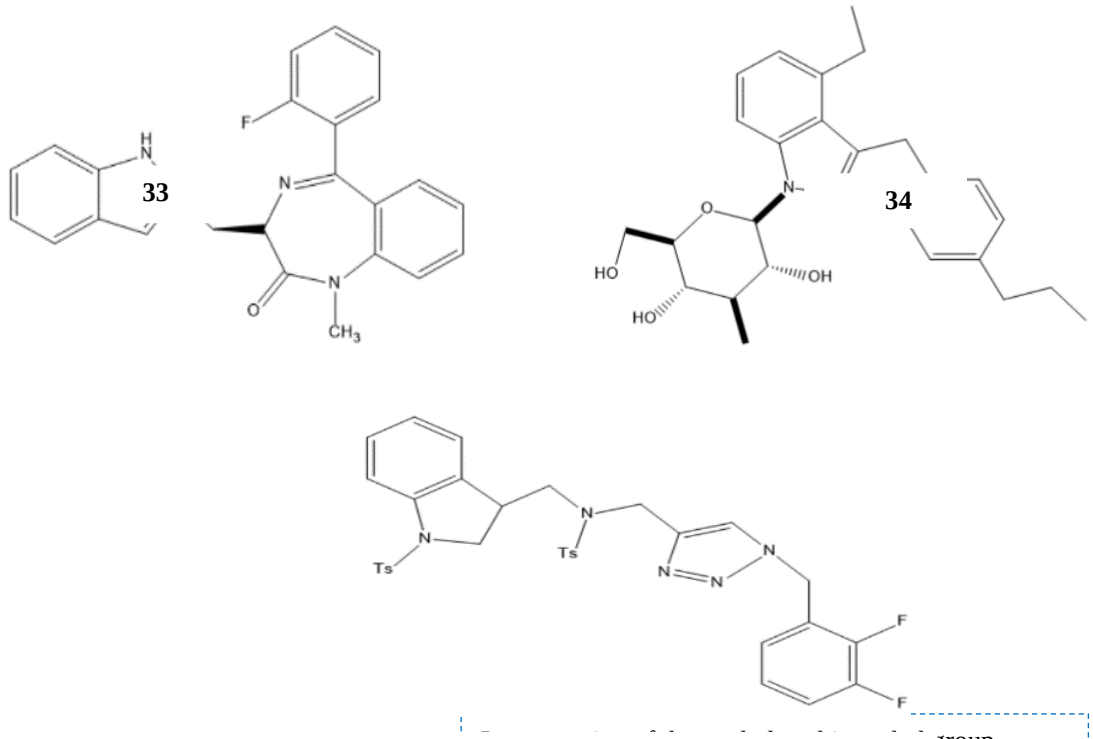
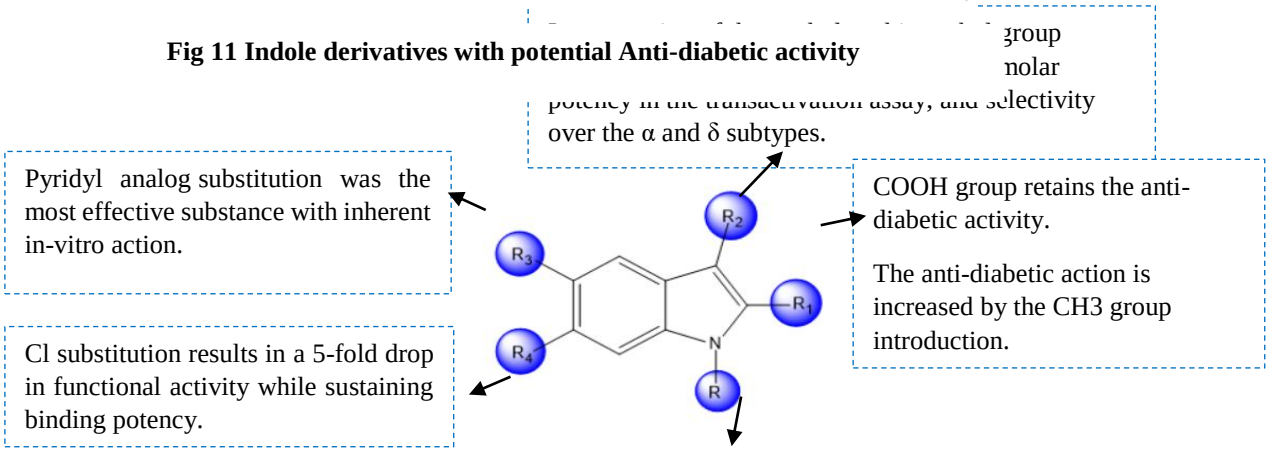


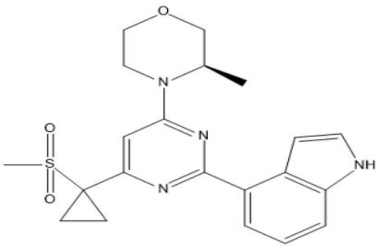
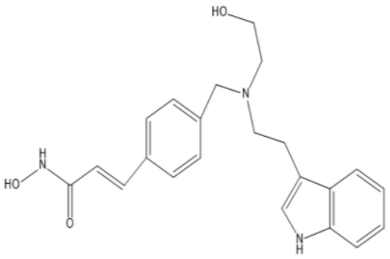
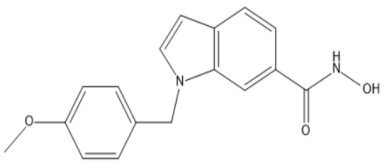
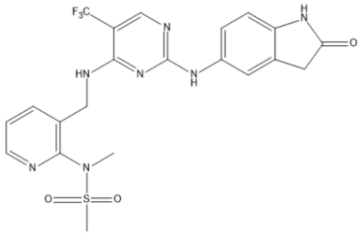
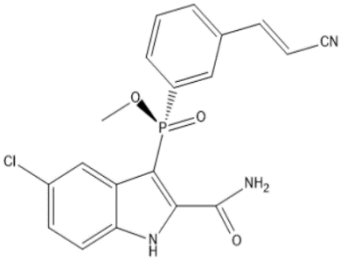
Fig 11 Indole derivatives with potential Anti-diabetic activity

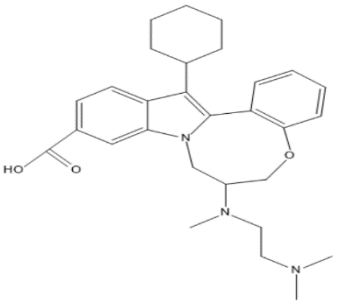
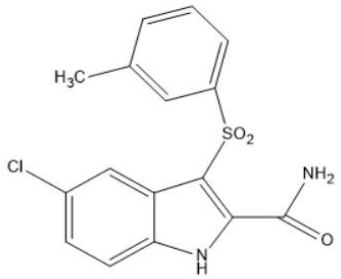


The binding and functional activity was reduced when benzyl, tBu, or biphenyl carboxylic acid was substituted.

Fig 12 SAR of Anti-diabetic activity

4. **Drugs under clinical trials having indole nucleus.**

Drug	Pharmacological activity	Developed by	Structure	Reference
ATR/mTOR inhibitor (AZ- 20)	Anticancer activity (showed activity against HT29 tumor cancer cell line)	AstraZeneca's		[59]
Dacinostat (LAQ-824)	Anticancer	Novartis		[60]
PCI-34051	Anticancer	-		[61]
Serdemetan (JNJ-26854165)	Anticancer	Johnson and Johnson Pharmaceutical and Research Development Pvt. Ltd.		[62]
Fosdevirine* (GSK2248761)	Anti-viral activity (NNRTI resistant mutant HIV)	GlaxoSmithKline		[63]

MK-3281*	Anti-viral activity (second-generation tetracyclic allosteric finger-loop inhibitor of the Hepatitis C Virus NS5B polymerase)	Merck Research Laboratories		[64]
Sulfonylindolecarboxamide (L-737126)	Anti-viral activity (non-nucleoside reverse transcriptase inhibitors (NNRTIs) active against NNRTI-resistant mutant)	Merck Research Laboratories		[65]

***phase 2 clinical trial drug candidate**

Conclusion

Indole is a highly versatile nucleus in the pharmaceutical and biomedical field. Due to its prevalence in several natural products and manufactured medications, indole synthesis is still an important topic of research. Its derivatives are widely used as anticancer agents, anti-inflammatory agents, antiviral agents, anti-depressant agents, etc., Many of these molecules have been approved by the FDA and are currently used in drug therapy. Despite the extensive research in the molecule, the potential of newer indole-based drug molecules is still available. The structure activity relationship reveals that position N-1, C-3, and C-5 of indole shows effective anti-convulsant action as mentioned above in anticonvulsant study e.g., the compound **5 and 6** (5-amino-6-(5-substituted-2- phenyl-1H-indol-1-yl)-4,5-dihydro-1,2,4-triazine-3(2H)- thiones). Substituting N-1 with halogens maintains the anti-inflammatory activity moreover substituting hydrophobic groups at the C-5 position of indole gives potent anti-inflammatory agents e.g. the compound **20a** and **20b** indole-2-carboxamide derivatives. Substitution on N-1, C-4, C-6, and C-7 positions of indole gives promising anti-viral e.g., the compound **29**, agents3-ethoxycarbonyl-6-bromo-5-hydroxyindoles. Position C-3 of indole when substituted by a long alkyl chain increases the binding affinity and the C-6 position of indole when undergoing bromination and chlorination enhances anti-depressant activity e.g., the compound **32a** and **32b** 2-(5-methyl-2,3-dioxoindolin-1-yl) acetamide derivatives. For anti-diabetic action methyl group substitution at the C-2 position increases the anti-diabetic activity, substitution of methyl or thiomethyl group at C-3 position shows high affinity in a binding assay, at C-5 position, substitution with pyridyl analogues gives the most potent compounds also by substituting Cl at C-6 position reduces the activity e.g., the compound **35** indole-triazole derivatives. The review represents a piece of concise information regarding the utilization of indole nucleus by a medicinal chemist for the design and development of therapeutically active drug candidates and also an overview of their pharmacological activities.

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REFERENCES:

[1] F. Bouchikhi *et al.*, "Synthesis and biological evaluation of diversely substituted indolin-2-ones," *Eur J Med Chem*, vol. 43, no. 11, pp. 2316–2322, Nov. 2008, doi: 10.1016/J.EJMECH.2008.01.010.

[2] Srivastava and S. N. Pandeya, "'INDOLE' A VERSATILE NUCLEUS IN PHARMACEUTICAL FIELD," *Available online on www.ijcpr.com International Journal of Current Pharmaceutical Review and Research*, vol. 1, no. 3, 2010, Accessed: Feb. 16, 2023. [Online]. Available: www.ijcpr.com

[3] S. Samala, R. K. Arigela, R. Kant, and B. Kundu, "Diversity-oriented synthesis of ketoindoloquinoxalines and indolotriazoloquinoxalines from 1-(2-nitroaryl)-2-alkynylindoles," *Journal of Organic Chemistry*, vol. 79, no. 6, pp. 2491–2500, Mar. 2014, doi: 10.1021/JO402783P/SUPPL_FILE/JO402783P_SI_002.CIF.

[4] E. Fischer, F. J. deutschen chemischen Gesellschaft, and undefined 1883, "Ueber die hydrazine der brenztraubensäure," *scholar.archive.org*, Accessed: Feb. 16, 2023. [Online]. Available: https://scholar.archive.org/work/sd7td3snrralxpusd7thbe5ppe/access/ia_file/crossref-pre-1909-scholarly-works/10.1002%252Fcber.188201502279.zip/10.1002%252Fcber.188301602141.pdf

[5] G. Bartoli, G. Palmieri, M. Bosco, R. D.-T. Letters, and undefined 1989, "The reaction of vinyl grignard reagents with 2-substituted nitroarenes: A new approach to the synthesis of 7-substituted indoles," *Elsevier*, Accessed: Feb. 16, 2023. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S004040390193730X

[6] W. Madelung, "Über eine neue Darstellungsweise für substituierte Indole. I," *Berichte der deutschen chemischen Gesellschaft*, vol. 45, no. 1, pp. 1128–1134, 1912, doi: 10.1002/CBER.191204501160.

[7] T. Fukuyama, X. Chen, and G. Peng, "A Novel Tin-Mediated Indole Synthesis," *J Am Chem Soc*, vol. 116, no. 7, pp. 3127–3128, Apr. 1994, doi: 10.1021/JA00086A054/SUPPL_FILE/JA3127.PDF.

[8] "A.D. Batcho, W. leimgruber, U.s. Patent 3,732,245... - Google Scholar." https://scholar.google.com/scholar?hl=en&as_sdt=0%2C5&q=A.D.+Batcho%2C+W.+leimgruber%2C+U.s.+Patent+3%2C732%2C245+and+U.S.+Patent+3%2C976%2C639&btnG= (accessed Feb. 16, 2023).

[9] A. R.-B. der deutschen chemischen Gesellschaft and undefined 1897, "Einwirkung von oxalester und natriumäthylat auf nitrotoluole. synthese nitrirter phenylbrenztraubensäuren," *scholar.archive.org*, Accessed: Feb. 16, 2023. [Online]. works/10.1002%252Fcber.18960290244.zip/10.1002%252Fcber.189703001200.pdf

[10] R. C. Larock and E. K. Yum, "Synthesis of Indoles via Palladium-Catalyzed Heteroannulation of Internal Alkynes," *J Am Chem Soc*, vol. 113, no. 17, pp. 6689–6690, Aug. 1991, doi: 10.1021/JA00017A059.

[11] J. Baudin, S. J.-T. letters, and undefined 1986, "Synthesis of indoles from N-aryl-1-alkenylsulphinamides," *Elsevier*, Accessed: Feb. 16, 2023. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S0040403900841143

[12] H. Hemetsberger and D. Knittel, "Synthese und Thermolyse von α-Azidoacrylestern - Enazide, 4. Mitt.," *Monatsh Chem*, vol. 103, no. 1, pp. 194–204, Jan. 1972, doi: 10.1007/BF00912944.

[13] "Nenitzescu, C.D., Derivatives of 2-methyl-5-hydroxyindole... - Google Scholar." accessed Feb. 17, 2023).

[14] N. Chadha and O. Silakari, "Indoles as therapeutics of interest in medicinal chemistry: Bird's eye view," *Eur J Med Chem*, vol. 134, pp. 159–184, Jul. 2017, doi: 10.1016/J.EJMECH.2017.04.003.

[15] R. Sundberg, *The chemistry of indoles*. 2012. Accessed: Feb. 16, 2023. [Online].

[16] A. Baeyer, A. E. chemischen Gesellschaft, and undefined 1869, "Synthese des indols," *scholar.archive.org*, Accessed: Feb. 17, 2023. [Online].

[17] V. Yutkin and J. Chin, "Apaziquone as an intravesical therapeutic agent for urothelial non-muscle-invasive bladder cancer," *Expert Opin Investig Drugs*, vol. 21, no. 2, pp. 251–260, Feb. 2012, doi: 10.1517/13543784.2012.646081.

[18] L. Scott, C. P.- Drugs, and undefined 2000, "Delavirdine: a review of its use in HIV infection," *Springer*, Accessed: Feb. 16, 2023. [Online]. Available: https://link.springer.com/article/10.2165/00003495-200060060-00013

[19] S. Biswal, S. Biswal, U. Sahoo, S. Sethy, H. K. S. Kumar, and M. Banerjee, "Indole: the molecule of diverse biological activities," *researchgate.net*, 2012, Accessed: Feb. 16, 2023. [Online]. Available: https://www.researchgate.net/profile/Sabyasachi-Biswal/publication/283857931_Indole_The_molecule_of_diverse_biological_activities/links/5f699006a6fdcc00863431ac/Indole-The-molecule-of-diverse-biological-activities.pdf

[20] A. v. Chobanian *et al.*, "Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure," *Hypertension*, vol. 42, no. 6, pp. 1206–1252, Dec. 2003, doi: 10.1161/01.HYP.0000107251.49515.C2.

[21] J. Koch-Weser, P. Cook, and I. James, "Cerebral Vasodilators," *New England Journal of Medicine*, vol. 305, no. 26, pp. 1560–1564, Dec. 1981, doi: 10.1056/NEJM198112243052604.

[22] M. Jordan, L. W.-N. reviews cancer, and undefined 2004, "Microtubules as a target for anticancer drugs," *nature.com*, doi: 10.1038/nr1317.

[23] J. Hooker and W. Bogdanich, "Tainted Drugs Linked to Maker of Abortion Pill; Big Company in China; Cancer Drugs Marred--RU-486 Problems Are Not Evident," 2008, Accessed: Feb. 17, 2023. [Online]. Available: https://repository.library.georgetown.edu/handle/10822/959058

[24] F. Faltus, F. G.- Neuropsychobiology, and undefined 1984, "A controlled double-blind study comparing binedaline and imipramine in the treatment of endogenous depression," *karger.com*, Accessed: Feb. 16, 2023. [Online]. Available: https://www.karger.com/Article/Abstract/118107

[25] A. Cañas-Rodriguez and P. R. Leeming, "N-Phenyl-2-indolinones and N-Pheny lindo lines. a New Class of Antidepressant Agents†," *J Med Chem*, vol. 15, no. 7, pp. 762–770, Jul. 1972, doi: 10.1021/JM00277A017.

[26] M. I.-E. mental health and undefined 2004, "combining pindolol with an SSRI improves early outcomes in people with depression," *pubmed.ncbi.nlm.nih.gov*, Accessed: Feb. 17, 2023. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/15504795/

[27] Chapman and Hall., "Dictionary of organic compounds.," 1996.

[28] G. Gründer, H. Wetzel, E. Hammes, and O. Benkert, "Roxindole, a dopamine autoreceptor agonist, in the treatment of major depression," *Psychopharmacology (Berl)*, vol. 111, no. 1, pp. 123–126, Apr. 1993, doi: 10.1007/BF02257418.

[29] S. Biswal, S. Biswal, U. Sahoo, S. Sethy, H. K. S. Kumar, and M. Banerjee, "Indole: the molecule of diverse biological activities," *researchgate.net*, 2012, Accessed: Feb. 17, 2023. [Online]. Available: https://www.researchgate.net/profile/Sabyasachi-Biswal/publication/283857931_Indole_The_molecule_of_diverse_biological_activities/links/5f699006a6fdcc00863431ac/Indole-The-molecule-of-diverse-biological-activities.pdf

[30] P. Ahuja and N. Siddiqui, "Anticonvulsant evaluation of clubbed indole-1,2,4-triazine derivatives: A synthetic approach," *Eur J Med Chem*, vol. 80, pp. 509–522, Jun. 2014, doi: 10.1016/J.EJMECH.2014.04.043.

[31] G. Saravanan, V. Alagarsamy, and P. Dineshkumar, "Anticonvulsant activity of novel 1-(morpholinomethyl)-3-substituted isatin derivatives," *Bulletin of Faculty of Pharmacy, Cairo University*, vol. 52, no. 1, pp. 115–124, Jun. 2014, doi: 10.1016/J.BFOPCU.2014.02.001.

[32] M. Khan, N. Dhar, A. H.- Pharmacophore, and undefined 2012, "Indole derivatives with anticonvulsant activity against two seizure models," *pharmacophorejournal.com*, vol. 3, no. 1, pp. 55–61, 2012, Accessed: Feb. 16, 2023. [Online].

[33] A. Kumar, D. Kumar, M. Akram, H. K.- IJPBA, and undefined 2011, "Synthesis and evaluation of some newer indole derivatives as anticonvulsant agents," *Citeseer*, vol. 2, no. 2, pp. 744–750, 2011, Accessed: Feb. 16, 2023. [Online]. Available: https://citeseerx.ist.psu.edu/document?repid=rep1&type=pdf&doi=72f973a8ff9af570bd324e54d5bdf12438d392d5

[34] S. Pandeya, I. Ponnilavarasan, … A. P.-D., and undefined 1999, "Evaluation of p-nitrophenyl substituted semicarbazones for anticonvulsant properties.," *europepmc.org*, Accessed: Feb. 16, 2023. [Online]. Available: https://europepmc.org/article/med/10631757

[35] N. Siddiqui, M. Alam, W. A.-A. Pharmaceutica, and undefined 2008, "Synthesis, anticonvulsant and toxicity evaluation of 2-(1H-indol-3-ylacetyl)-N-(substituted phenyl) hydrazinecarbothioamides and their related heterocyclic derivatives," *hrcak.srce.hr*, doi: 10.2478/v10007-008-0025-0.

[36] H. Kaur, S. Kumar, P. Vishwakarma, … M. S.-E. J. of, and undefined 2010, "Synthesis and antipsychotic and anticonvulsant activity of some new substituted oxa/thiadiazolylazetidinonyl/thiazolidinonylcarbazoles," *Elsevier*, Accessed: Feb. 16, 2023. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S0223523410001923

[37] J. Liou, K. Hsu, C. Kuo, … C. C.-J. of P., and undefined 2007, "A novel oral indoline-sulfonamide agent, J30, exhibits potent activity against human cancer cells in vitro and in vivo through the disruption of microtubule," *ASPET*, Accessed: Feb. 16, 2023. [Online]. Available: https://jpet.aspetjournals.org/content/early/2007/07/27/jpet.107.126680.short

[38] T. P. Pathak, K. M. Gligorich, B. E. Welm, and M. S. Sigman, "Synthesis and preliminary biological studies of 3-substituted indoles accessed by a palladium-catalyzed enantioselective alkene difunctionalization reaction," *J Am Chem Soc*, vol. 132, no. 23, pp. 7870–7871, Jun. 2010, doi: 10.1021/JA103472A.

[39] H. Pajouhesh, R. Parson, and F. D. Popp, "Potential anticonvulsants VI: Condensation of isatins with cyclohexanone and other cyclic ketones," *J Pharm Sci*, vol. 72, no. 3, pp. 318–321, 1983, doi: 10.1002/JPS.2600720330.

[40] S. M. S. Sandes *et al.*, "Evidence for the involvement of TNF-α, IL-1β and IL-10 in the antinociceptive and anti-inflammatory effects of indole-3-guanylhydrazone hydrochloride, an aromatic aminoguanidine, in rodents," *Chem Biol Interact*, vol. 286, pp. 1–10, Apr. 2018, doi: 10.1016/J.CBI.2018.02.026.

[41] J. S. Shin, H. E. Choi, S. D. Kim, Y. S. Lee, Y. W. Cho, and K. T. Lee, "Anti-inflammatory effects of 7-hydroxyl-1-methylindole-3-acetonitrile, a synthetic arvelexin derivative, on the macrophages through destabilizing mPGES-1 mRNA and suppressing NF-κB activation," *Chem Biol Interact*, vol. 224, pp. 68–77, Dec. 2014, doi: 10.1016/J.CBI.2014.10.004.

[42] M. Ahmad Bhat *et al.*, "Indole derivatives as cyclooxygenase inhibitors: synthesis, biological evaluation and docking studies," *mdpi.com*, doi: 10.3390/molecules23061250.

[43] Z. Liu *et al.*, "Design, Synthesis, and Structure-Activity Relationship Study of Novel Indole-2-carboxamide Derivatives as Anti-inflammatory Agents for the Treatment of Sepsis," *J Med Chem*, vol. 59, no. 10, pp. 4637–4650, May 2016, doi: 10.1021/ACS.JMEDCHEM.5B02006.

[44] A. M. M. Shaker, E. K. A. Abdelall, K. R. A. Abdellatif, and H. M. Abdel-Rahman, "Synthesis and biological evaluation of 2-(4-methylsulfonyl phenyl) indole derivatives: Multi-target compounds with dual antimicrobial and anti-inflammatory activities," *BMC Chem*, vol. 14, no. 1, Mar. 2020, doi: 10.1186/S13065-020-00675-5.

[45] S. Fatahala, M. Khedr, M. M.-A. C. Slovenica, and undefined 2017, "Synthesis and structure activity relationship of some indole derivatives as potential anti-inflammatory agents," *journals.matheo.si*, vol. 64, pp. 865–876, 2017, doi: 10.17344/acsi.2017.3481.

[46] C. Mukthung, S. Chancharunee, F. Kielar, S. Pongcharoen, and U. Wichai, "Capsaicin derivatives containing indole and nitroindole for improved anti-inflammatory activity," *journal.nu.ac.th*, no. 26, p. 3, 2018, Accessed: Feb. 16, 2023. [Online]. Available: https://www.journal.nu.ac.th/NUJST/article/view/Vol-26-No-3-2018-157-169

[47] S. Musella *et al.*, "Identification of an indol-based derivative as potent and selective varicella zoster virus (VZV) inhibitor," *Eur J Med Chem*, vol. 124, pp. 773–781, Nov. 2016, doi: 10.1016/J.EJMECH.2016.09.014.

[48] G. Sanna *et al.*, "Synthesis and biological evaluation of novel indole-derived thioureas," *mdpi.com*, doi: 10.3390/molecules23102554.

[49] S. Ferro *et al.*, "Synthesis and biological evaluation of novel antiviral agents as protein–protein interaction inhibitors," *Taylor & Francis*, vol. 29, no. 2, pp. 237–242, 2013, doi: 10.3109/14756366.2013.766609.

[50] A. Balupuri, C. G. Gadhe, P. K. Balasubramanian, G. Kothandan, and S. J. Cho, "In silico study on indole derivatives as anti HIV-1 agents: A combined docking, molecular dynamics and 3D-QSAR study," *Arch Pharm Res*, vol. 37, no. 8, pp. 1001–1015, Dec. 2014, doi: 10.1007/S12272-013-0313-1/METRICS.

[51] P. Selvam, N. Murugesh, M. Chandramohan, R. W. Sidwell, M. K. Wandersee, and D. F. Smee, "Anti-influenza virus activities of 4-[(1,2-dihydro-2-oxo-3H-indol-3- ylidene)amino]-N-(4,6-dimethyl-2-pyrimidin-2-yl)benzenesulphonamide and its derivatives," *Antivir Chem Chemother*, vol. 17, no. 5, pp. 269–274, 2006, doi: 10.1177/095632020601700504.

[52] S. Xue, L. Ma, R. Gao, Y. Li, and Z. Li, "Synthesis and antiviral activity of some novel indole-2-carboxylate derivatives," *Acta Pharm Sin B*, vol. 4, no. 4, pp. 313–321, Aug. 2014, doi: 10.1016/J.APSB.2014.06.003.

[53] M. Hassam, A. E. Basson, D. C. Liotta, L. Morris, W. A. L. van Otterlo, and S. C. Pelly, "Novel cyclopropyl-indole derivatives as HIV non-nucleoside reverse transcriptase inhibitors," *ACS Med Chem Lett*, vol. 3, no. 6, pp. 470–475, May 2012, doi: 10.1021/ml3000462.

[54] P. O. Patil and S. B. Bari, "Synthesis, characterization and screening for antidepressant and anticonvulsant activity of 4,5-dihydropyrazole bearing indole derivatives," *Arabian Journal of Chemistry*, vol. 9, no. 4, pp. 588–595, Jul. 2016, doi: 10.1016/J.ARABJC.2013.08.027.

[55] X. Zhen, Z. Peng, S. Zhao, Y. Han, Q. Jin, and L. Guan, "Synthesis, potential anticonvulsant and antidepressant effects of 2-(5-methyl-2,3-dioxoindolin-1-yl)acetamide derivatives," *Acta Pharm Sin B*, vol. 5, no. 4, pp. 343–349, Jul. 2015, doi: 10.1016/J.APSB.2015.01.008.

[56] M. L. Mohler, Y. He, Z. Wu, J. H. Dong, and D. D. Miller, "Recent and emerging anti-diabetes targets," *Med Res Rev*, vol. 29, no. 1, pp. 125–195, Jan. 2009, doi: 10.1002/MED.20142.

[57] S. Nomura *et al.*, "Novel indole-N-glucoside, TA-1887 As a sodium glucose cotransporter 2 inhibitor for treatment of type 2 diabetes," *ACS Med Chem Lett*, vol. 5, no. 1, pp. 51–55, Jan. 2014, doi: 10.1021/ML400339B.

[58] S. Rajan *et al.*, "Novel indole and triazole based hybrid molecules exhibit potent anti-adipogenic and antidyslipidemic activity by activating Wnt3a/β-catenin pathway," *Eur J Med Chem*, vol. 143, pp. 1345–1360, Jan. 2018, doi: 10.1016/J.EJMECH.2017.10.034.

[59] K. M. Foote *et al.*, "Discovery of 4-{4-[(3R)-3-methylmorpholin-4-yl]-6-[1-(methylsulfonyl) cyclopropyl]pyrimidin-2-yl}-1H-indole (AZ20): A potent and selective inhibitor of ATR protein kinase with monotherapy in vivo antitumor activity," *J Med Chem*, vol. 56, no. 5, pp. 2125–2138, Mar. 2013, doi: 10.1021/JM301859S.

[60] L. Ellis, M. Bots, R. L.- Blood, T. Journal, and undefined 2009, "The histone deacetylase inhibitors LAQ824 and LBH589 do not require death receptor signaling or a functional apoptosome to mediate tumor cell death or therapeutic," *ashpublications.org*, Accessed: Feb. 16, 2023. [Online]. Available: https://ashpublications.org/blood/article-abstract/114/2/380/26257

[61] J. A. Ramos *et al.*, "A novel histone deacetylase 8 (HDAC8)-specific inhibitor PCI-34051 induces apoptosis in T-cell lymphomas," *nature.com*, vol. 22, pp. 1026–1034, 2008, doi: 10.1038/leu.2008.9.

[62] J. Tabernero *et al.*, "Phase I pharmacokinetic (PK) and pharmacodynamic (PD) study of HDM-2 antagonist JNJ-26854165 in patients with advanced refractory solid tumors," *Journal of Clinical Oncology*, vol. 27, no. 15_suppl, pp. 3514–3514, May 2009, doi: 10.1200/JCO.2009.27.15_SUPPL.3514.

[63] S. Castellino *et al.*, "Central nervous system disposition and metabolism of Fosdevirine (GSK2248761), a non-nucleoside reverse transcriptase inhibitor: An LC-MS and matrix-assisted laser desorption/ionization imaging MS investigation into central nervous system toxicity," *Chem Res Toxicol*, vol. 26, no. 2, pp. 241–251, Feb. 2013, doi: 10.1021/TX3004196.

[64] F. Narjes *et al.*, "Discovery of (7 R)-14-Cyclohexyl-7-{[2-(dimethylamino)ethyl](methyl) amino}-7,8-dihydro-6 H -indolo[1,2- e][1,5]benzoxazocine-11-carboxylic Acid (MK-3281), a potent and orally bioavailable finger-loop inhibitor of the hepatitis C virus NS5B polymerase," *J Med Chem*, vol. 54, no. 1, pp. 289–301, Jan. 2011, doi: 10.1021/JM1013105.

[65] R. Silvestri *et al.*, "Simple, short peptide derivatives of a sulfonylindolecarboxamide (L-737,126) active in vitro against HIV-1 wild type and variants carrying non-nucleoside reverse transcriptase inhibitor resistance mutations," *J Med Chem*, vol. 47, no. 15, pp. 3892–3896, Jul. 2004, doi: 10.1021/JM031147E.