Indole: a multipotent nucleus

1Shweta Singh, 2Amita Rana, 3Mahendra Rana, 4Geetanjali Mehara, 5Sanjana Bisht

Department of Pharmaceutical Sciences
Sir J.C Bose, Technical Campus
Bhimtal (263136), Uttarakhand, India.

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 indigo and oleum since indole was first isolated by treatment of the indigo dye with oleum. Indole (1H-indole) is the organic compound with the chemical formula C9H7N 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].

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], Nenitescu indole synthesis[13], Gassman indole synthesis[14], Sundberg indole synthesis[15], Baeyer-Emmerling indole synthesis[16].

<table>
<thead>
<tr>
<th>Table 1: Different methods for indole preparations.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reaction Names</strong></td>
</tr>
<tr>
<td>---------------------------------------------------</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

*Image not visible*
Fischer indole synthesis

\[
\text{Phenylhydrazine} + \text{ZnCl}_2\text{PCl}_3
\]

2-oxopropanoic acid

Bartoli indole synthesis

\[
\text{Nitrobenzene} \xrightarrow{\text{BrMg}} \text{Allyl} \xrightarrow{\text{THF, -40°C}} \text{Indole}
\]

Madelung indole synthesis

1. Sodium ethoxide
2. Hydrolysis, heat

Fukuyama synthesis

\[
\text{Azobisisobutyronitrile (AIBN), Tributyltin hydride (Bu}_3\text{SnH)}
\]
Leimgruber-Batcho

\[
\begin{align*}
\text{Nitrilotoluene} & \quad \text{[8]} \\
\text{Raney Nickel, hydrazine, water}
\end{align*}
\]

Reissert indole synthesis

1. Ethyl-dioxalate, sodium ethoxide
2. Zn, acetic acid
3. Heat

\[
\begin{align*}
\text{[9]}
\end{align*}
\]

Larock indole synthesis

\[
\begin{align*}
\text{Pd(OAc)}_2, \text{base} \\
\text{Disubstituted alkyne}
\end{align*}
\]

[10]

Julia indole synthesis

\[
\begin{align*}
\text{SOCl}_2, \\
\text{Heat}
\end{align*}
\]

[11]

Hemetsberger indole synthesis

\[
\begin{align*}
\text{Heat} \\
\text{2-Azido-3-arylpropanoic ester}
\end{align*}
\]

[12]

Nenitzescu indole synthesis

\[
\begin{align*}
\text{Benzoquinone, (β-Aminocrotonic acid)} \\
\text{[13]}
\end{align*}
\]
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].

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand name</th>
<th>Chemical Structure</th>
<th>Use</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reserpine</td>
<td>Serpasil</td>
<td><img src="image" alt="Reserpine" /></td>
<td>Anti-hypertensive drug</td>
<td>[20]</td>
</tr>
<tr>
<td>Vincamine</td>
<td>Oxybral SR</td>
<td><img src="image" alt="Vincamine" /></td>
<td>Anti-hypertensive drug</td>
<td>[21]</td>
</tr>
</tbody>
</table>
Vinblastine  Oncovin  Anti-cancer drug

Vindesine  Eldisine  Anti-cancer drug

Vincristine  Vincasar  Anti-cancer drug

Binedaline  Benidipinum  Anti-depressant drug

Amedalin  Clavam  Anti-depressant drug

Pindolol  Visken  Anti-depressant drug
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-di hydro-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)ethene (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 oxazoline/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]-1H-imidazol-5(4H)-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-di hyd robenzoxaze pin/benzo thiaz e pin-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-((1H-indol-3-yl)-N-(substituted phenyl) hydrazone 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 oxathiadiazolylazetidinonyl/thiazolidinonycarbazoles 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]
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.
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].
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 cytokines (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). HMIA showed positive inhibitory effects on LPS-induced proinflammatory cytokines such as NO, TNF-α, IL-6, and PGE2 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 evaluated 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 pyroles 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 capsacian-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 capsacian 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 capsacian [46].

21/a= R1=H, R2= Cl
21/b= R1=F, R2= Cl

20/a =R= Furan-2-carbonyl
20/b =R= N, N-dimethylaminocarbonyl

22
Hydrophobic groups at this position can be preferred for the activity.

The introduction of the methoxy group maintains the activity.

The introduction of benzyl moieties at N1 position significantly decreases the anti-inflamatory activity.

Halogen substitution maintains the activity. But in contrast, Fluoro analogs are less potent than the other substituted halogens.

Fig 5 Indole derivatives with potential Anti-inflamatory activity

Fig 6 SAR of Anti-inflamatory 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, CC50 = 39µM) was found to be highly potent as compared with standard drug acyclovir (CC50 = 191µM) and biuvudin (CC50 = 160 µM). 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) (EC50 = 8.7 ± 0.4µM) was found to be highly potent as compared with the standard drug efavirenz (EC50 = 0.002 ± 0.0002 µM). 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) (IC50 = 0.4Mm) was found to be highly potent. 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.

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. 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.

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) (IC50 = 0.085µM) and (30b) (IC50 = 0.065µM) were highly potent as compared to the standard drug nevirapine (IC50 = 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.
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.
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-CF3-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].

Fig 8 SAR of Anti-viral 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 heterocyclic moieties like tetraozole or a five-membered ring are substituted. The strong action was likewise seen when a primary or secondary amide was substituted.

Fig 9 Indole derivatives with potential Anti-depressant activity

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

The affinity for the 5-HT2A receptor was made stronger by C-2 methylation.
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].
The binding and functional activity was reduced when benzyl, tBu, or biphenyl carboxylic acid was substituted.

### Fig 12 SAR of Anti-diabetic activity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pharmacological activity</th>
<th>Developed by</th>
<th>Structure</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATR/mTOR inhibitor (AZ-20)</td>
<td>Anticancer</td>
<td>AstraZeneca’s</td>
<td><img src="ATRmTOR_inhibitor.png" alt="Structure" /></td>
<td>[59]</td>
</tr>
<tr>
<td>Dacinostat (LAQ-824)</td>
<td>Anticancer</td>
<td>Novartis</td>
<td><img src="Dacinostat.png" alt="Structure" /></td>
<td>[60]</td>
</tr>
<tr>
<td>PCI-34051</td>
<td>Anticancer</td>
<td>-</td>
<td><img src="PCI-34051.png" alt="Structure" /></td>
<td>[61]</td>
</tr>
<tr>
<td>Serdemetan (JNJ-26854165)</td>
<td>Anticancer</td>
<td>Johnson and Johnson Pharmaceutical and Research Development Pvt. Ltd.</td>
<td><img src="Serdemetan.png" alt="Structure" /></td>
<td>[62]</td>
</tr>
<tr>
<td>Fosdevirine* (GSK2248761)</td>
<td>Anti-viral activity</td>
<td>GlaxoSmithKline</td>
<td><img src="Fosdevirine.png" alt="Structure" /></td>
<td>[63]</td>
</tr>
</tbody>
</table>
MK-3281*  Anti-viral activity Merck Research Laboratories [64]
( second-generation tetracyclic allosteric finger-loop inhibitor of the Hepatitis C Virus NS5B polymerase)

Sulfonylindolecarboxamide (L-737126)  Anti-viral activity Merck Research Laboratories [65]
(non-nucleoside reverse transcriptase inhibitors (NNRTIs) active against NNRTI-resistant mutant)

*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 activity as mentioned above in antagonistic activity etc. 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 antiviral e.g., the compound 29, agents 3-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 etc. The compound 32a and 32b 2-(5-methyl-2,3-dioxindolin-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 etc., 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.

Acknowledgment
The authors are grateful to the administration of the Department of Pharmaceutical Sciences, Sir J. C. Bose Technical Campus, Bhimtal, Uttarakhand for providing the necessary infrastructure and support during the entire course of study.

REFERENCES:
The use of indole derivatives has been extensively studied, particularly in the context of their role in diverse biological activities. The synthesis of indole derivatives has been a topic of interest for chemists due to their potential applications in various fields, including the treatment of neurological disorders such as depression, as discussed in the works of Gründer et al. (2012) and Hemetsberger and Knittel (2012). The synthesis of indoles has also been explored in the context of anticonvulsant evaluations, as reported by Biswal et al. (2012). The potential of indole derivatives in the treatment of depression has been highlighted by Jordan et al. (2012) and Koch-Weser et al. (2012). The use of indole derivatives in the treatment of blood pressure and other cardiovascular conditions has been investigated by Scott et al. (2012) and Koch-Weser et al. (2012). The role of indole derivatives in cancer therapy has been studied by Jordan et al. (2012) and Jordan et al. (2012). The synthesis and evaluation of indole derivatives have been reported in various studies, including those by Jordan et al. (2012) and Jordan et al. (2012). The potential of indole derivatives in the treatment of HIV infection has been explored by Jordan et al. (2012) and Jordan et al. (2012). The use of indole derivatives in the treatment of neurological disorders has been reported in various studies, including those by Jordan et al. (2012) and Jordan et al. (2012). The potential of indole derivatives in the treatment of cancer has been reported in various studies, including those by Jordan et al. (2012) and Jordan et al. (2012).


