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Review Article

A Review on Targets and Synthesis Methods of Pyridine Compounds for Anti-Convulsant, Anti-Depressant Actions

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ABSTRACT

Background: The market is overstocked with commercially accessible medications that contain pyridine rings, including abiraterone acetate and crizotinib for cancer, delavirdine for HIV/AIDS, isoniazid and ethionamide for TB, ciclopirox for anthelmintic conditions, and tacrine for Alzheimer's disease. These developments have raised hopes for how pyridine may help treat conditions relating to the central nervous system and caused research into the drug to continue growing. **Objectives:** The objective is to compile and analyze information on various pyridine-based derivatives that target various receptors and ion channels to provide relief from CNS disorders. **Materials and Methods:** To offer a comprehensive overview of the authorized medications and bioactivity data for compounds containing pyridine, research and review papers from PubMed and Google Scholar are integrated with data from other sources. **Results:** The majority of the responses covered in this article have directly provided readers with an understanding of various CNS receptors that pyridine analogs may target, in addition to synthetic methods for creating novel analogs that can be used to create new derivatives with more potent anticonvulsant and antidepressant properties. **Conclusion:** The majority of the responses covered in this article have directly provided readers with an understanding of various CNS receptors that pyridine analogs may target, in addition to synthetic methods for creating novel analogs that can be used to create new derivatives with more potent anticonvulsant and antidepressant properties.

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Rashmi Mishra: She has around 20 years plus experience in teaching and research. Doctorate in Biotechnology from BIT Mesra in 2009 and has passion for microbes. She was formal joint secretary in Swadeshi Science Moment of India (vigyan bharti). She has also two books and around 50 papers to her credit and received Best Teachers Award in 2023 in seeking a responsible position to leverage my skills and experience in fostering an educational atmosphere and aiding students in their intellectual growth across research, academia, or entrepreneurship. He purpose is to stay abreast of cutting-edge technologies and contributes significantly to organizational growth.

Motamarri V. N. Lalitha Chaitanya: He is an academic researcher with teaching as passion having 12 years of experience in teaching, quality control, and research having expertise in natural product drug discovery, ethno-pharmacology, isolation, and characterization. Currently working as associate professor in LPU University, Phagwara, Punjab. His current interest is the discovery of potent anticancer leads and drugs (Human dual Topopoisons) from nature like holistic plants, weeds, algae, crystals, and minerals.

Content

1. Introduction

Pyridine has a chemical formula of C_5H_5N containing a nitrogen atom inside the six-membered ring and it belongs to the class of azaheterocycles [1-3]. Pyridine ring is also found in phytochemicals belonging to the class of alkaloids, vitamins, and coenzymes [4]. Nearly 7000 existing drug moieties consist of pyridine analogs in their pharmacophore [5]. Pyridine molecules are generally sp^2 hybridized containing nitrogen atoms with a lone pair of electrons contributing to the aromaticity of the molecule [6]. The lone pair contribution does not show much effect on the aromatic ring but helps in the characterization of the pyridine motifs. Pyridine structure has an imine moiety

because of the nitrogen atom placed in the plane of the pyridine ring and trigonal with the lone pair in the pyridine ring structure. The nitrogen in the pyridine structure acts as a nucleophilic center due to lone pairs of electrons that are not delocalized. This nucleophilicity characterization allows the pyridine ring to be used as a catalyst in acylation reactions [7]. Also because of their weak basicity and aqueous solubility, pyridine scaffolds are found in many drugs and are known for their antimicrobial, antiviral [8], antioxidant [9], anti-inflammatory [10], antiamoebic [11], antidiabetic [12], antimalarial [13], anti-psychotic [14], and other medicinal properties. With a forecasted compound annual growth rate [CAGR] of 9.5% between 2022 and 2028, the worldwide pyridine market is expected to develop from its 2021 value of over USD 1.1 billion to more than USD 2.4 billion by the end of 2028 [9]. Some examples and percentages of reported pyridine-related patents across the world are shown in **Table 1** and **Figure 1**. All drugs like Isoniazid [tuberculosis] [15], Pyridostigmine [myasthenia gravis] [16], Nicotinamide [pellagra] [17], Piroxicam [arthritis] [18], Enpiroline [malaria] [19], Omeprazole [ulcer] [20], Tacrine [Alzheimer's disease] [21], Tropic Amide [anti-muscarinic] [22], Delavirdin [HIV] [23], and Nilvadipine [hypertension] [24] contains pyridine rings and are commercially available drugs [25]. Many studies, as shown in **Figure 2**, elucidate that adding a pyridine ring in the structure improves or enhances the many pharmacological and pharmacokinetic aspects like permeability, metabolic stability, protein binding, and biological activity of the drug [26]. Pyridine-derived anti-convulsant analogs give their anti-convulsant action by targeting the action of different receptors (as shown in **Figure 3**) like enhancement of GABAergic inhibition [27-29], inhibition of sodium channels [30,31], inhibition of calcium channels [32,33], modulation of glutamate receptors [34,35], enhancement of potassium conductance [36,37], glycine receptor modulation [38-40] and antidepressant action by acting as selective serotonin reuptake inhibitors [SSRIs] [43,44], serotonin-norepinephrine reuptake inhibitors [SNRIs][45,46], tricyclic antidepressants [TCAs] [47,48], monoamine oxidase inhibitors [MAOIs] [49,50], atypical antidepressants [51,52], NMDA receptor antagonists [53,54]. In chemistry, pyridine analogs are advantageous for CNS-acting drug lead development due to their unique structural features, lipophilicity, and electronic characteristics [55-58]. Furthermore, the nitrogen atom in the pyridine ring can serve as a hydrogen bond acceptor or donor, further enhancing the molecule's binding affinity and selectivity. These factors make pyridine analogs valuable in medicinal chemistry for designing and optimizing drug candidates with improved efficacy, specificity, and pharmacokinetic profiles [59,60]. This review article focuses on different targets of pyridine analogs for anti-convulsant and anti-depressant action along with different synthesis methodologies used in the last 10 years for pyridine derivative synthesis.

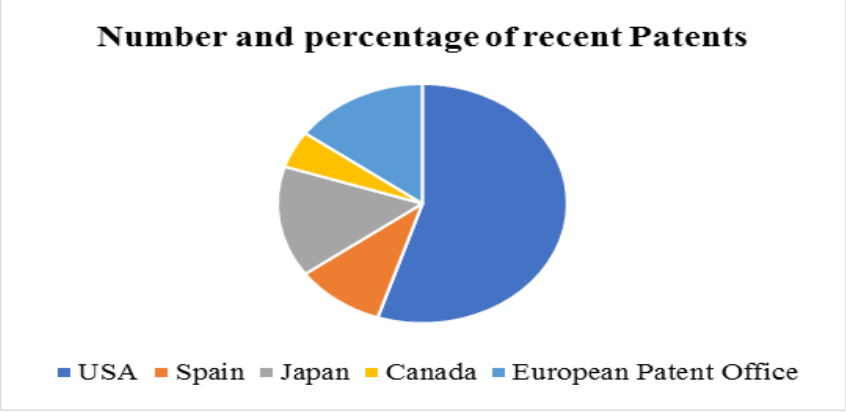


Figure 1. Patents percentage of Pyridine analogs in different countries

Table 1. Patents of pyridine analogs with status [61-80]

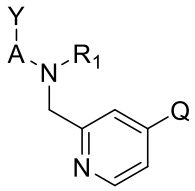
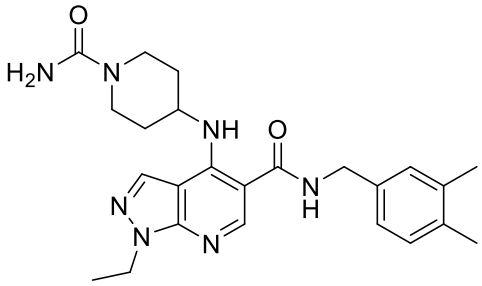
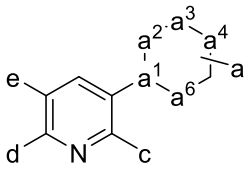
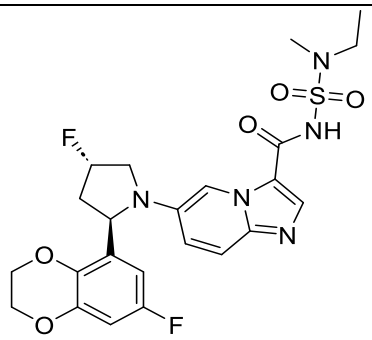
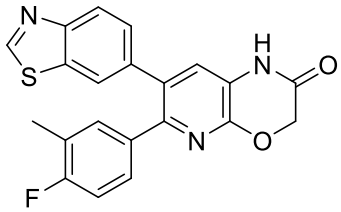
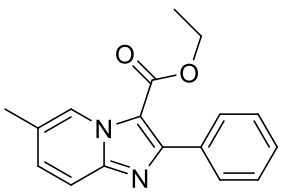
S No.	Patent Number	Title	General Structure	Country	Status
1	CA2901022C	Substituted pyridine compounds as inhibitors of histone demethylases		Canada	Granted
2	US7709497B2	Pyrazolo[3,4-*b*] pyridine compound, and its use as a PDE4 inhibitor		United States	Granted
3	US8609708B2	Synthetic compounds and derivatives as modulators of smoking or nicotine ingestion and lung cancer		United States	Granted
4	US9782391B2	Substituted imidazo[1,2 – *a*] pyridine compounds as tropomyosin receptor kinase a [trka] inhibitors		United States	Granted
5	EP3129367B1	2,3-disubstituted pyridine compounds as tgf-beta inhibitors		European Patent Office	Granted
6	US10913737B2	Imidazo [1,2-*a*] pyridine compounds, synthesis thereof, and methods of using the same		United States	Granted

Table 1. Continued

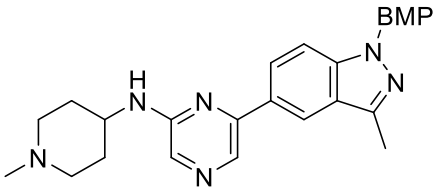
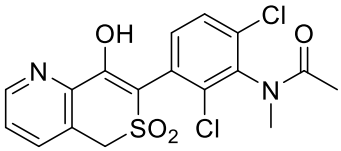
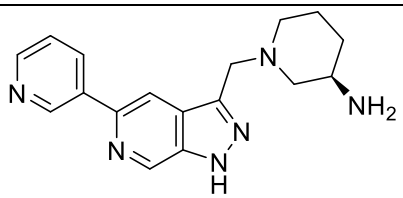
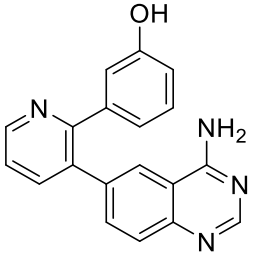
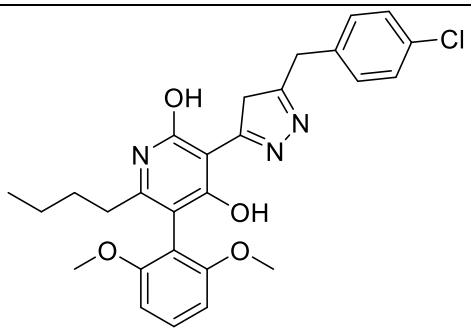
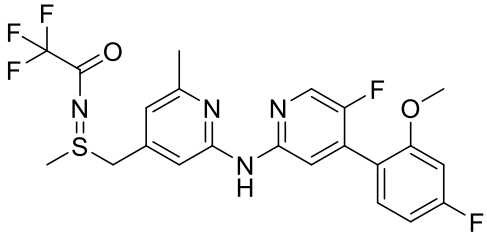
S No.	Patent Number	Title	General Structure	Country	Status
7	US9962382B2	Substituted 5 -[pyrazine- 2 – yl] -1h-pyrazolo [3, 4 - *b*] pyridine and pyrazolo [3, 4- *b*]. pyridine derivatives as protein kinase inhibitors		United States	Granted
8	EP3209668B1	Substituted pyridine compounds having herbicidal activity		European Patent Office	Granted
9	US9850239B2	Pyrazolo[3,4-*c*] pyridine compounds and methods of use		United States	Granted
10	ES2759240T3	2,3-Disubstituted pyridine compounds as TGF-beta inhibitors		Spain	Granted
11	US10336739B2	4-hydroxy-3-[heteroaryl] pyridine -2-one APJ agonists		United States	Granted
12	US9877954B2	5-fluoro-*N*-[pyridine-2-yl] pyridine-2-amine derivatives containing a sulfoximine group		United States	Granted

Table 1. Continued

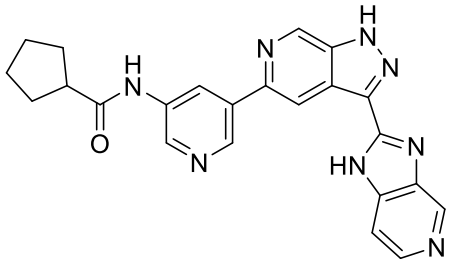
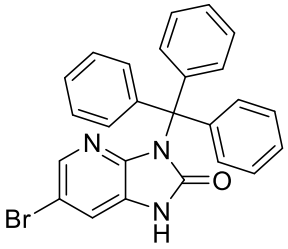
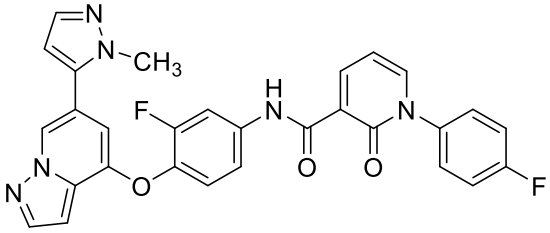
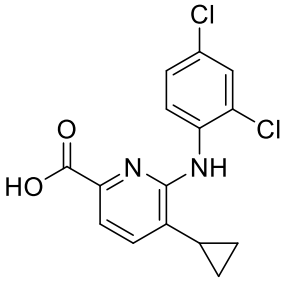
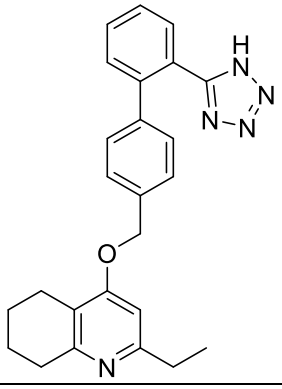
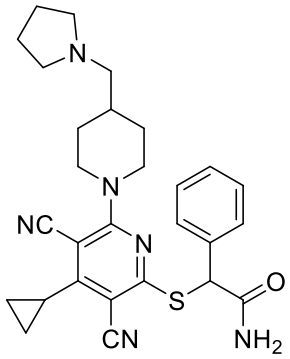
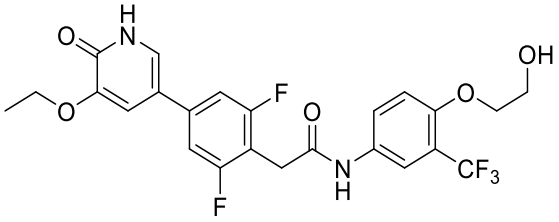
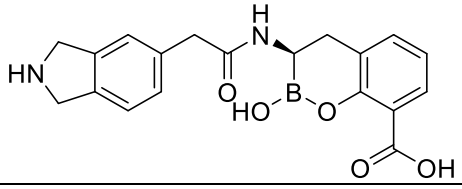
S No.	Patent Number	Title	General Structure	Country	Status
13	US9540398B2	3-[1*h*-imidazo[4,5-*c*] pyridine-2-yl]-1*h*-pyrazolo[3,4-*c*] pyridine and therapeutic uses thereof		United States	Granted
14	JP7001682B2	Substitution 1*H*-imidazole [4,5-*b*] pyridin-2 [3*H*] -one and their use as GLUN2B receptor regulators		Japan	Granted
15	EP3087070B1	Pyrazolo[1,5-*a*] pyridine derivatives and methods of their use		European Patent Office	Granted
16	JP6484746B2	Pyridine-2-amides useful as CB2 agonists		Japan	Granted
17	US8809545B2	Aryl pyridine as aldosterone synthase inhibitors		United States	Granted

Table 1. Continued

S No.	Patent Number	Title	General Structure	Country	Status
18	JP7051829B2	Substituted pyridine as an inhibitor of DNMT1		Japan	Granted
19	ES2616655T3	Pyridine derivatives as reorganized kinase inhibitors during transfection [RET]		Spain	Granted
20	US10125152B2	Beta-lactamase inhibitors		United States	Granted

2. Anti-Convulsant, Anti-Depressant Targets of Pyridine Derivatives

Pyridine is a heterocyclic compound that has been found to have anticonvulsant activity. Pyridine derivatives have been reported to act on various receptors, including GABA-A, NMDA, and nicotinic acetylcholine receptors.

2.1. GABA-A receptors

Anticonvulsant activity of the various pyridine derivatives is converged as acting on the GABA receptors and these are witnessed by various researches like antagonism of yohimbine induced clonic seizures predictive in the mice models and GABA mimetic potential. This module was reported by the tri-substituted pyridines [81]. GABA is associated with the ligand-gated ion channels that respond to the GABA by elevated chloride conduction, resulting in neuronal hyperpolarization. The treatment strategy mentions that binding with the differential allosteric sites of the $GABA_A$ complexes can influence the chloride ion channel with the response to GABA, as depicted in **Figure 4**. Therefore, it may act by delaying the time of opening of the channel and is opened for a longer duration and other drugs may increase the frequency of opening of the channel [82].

O. I. Salam *et al.* (2013) synthesized the pyridine carbohydrate derivative (**Figure 5**) from the basic reaction of derivatives of the isonicotinic acid hydrazide with substituted benzaldehyde. The synthesized compounds were tested for their anticonvulsant properties and compared with the standard drug valdecoxib, carbamazepine. Antagonism to clonic seizures induced by yohimbine in mice is regarded as a predictive model for evaluating the potential of substances to act as

anticonvulsants and mimic GABA activity [83]. Taking the chemistry of the compound into consideration the derivatives were synthesized by the chloro derivative of the 6-hydrazino-isonicotinic acid using $POCl_3$ from the dihydroxy derivative of the isonicotinic acid (as shown in **Scheme 1**).

In the subsequent steps, the dichloro derivative has undergone the substitution reaction with the hydrazine reagent, and the amine hydrogen substitutes with the benzaldehyde derivative used in the last step of the reaction. The evaluation of the tested compounds revealed that the halogen substituents in the compounds showed good inhibitory activity as compared to the carbamazepine, the ED_{50} value of compound 10 was 15 ± 0.0114 and the relative potency was 2.05 ± 0.22 which inhibits yohimbine induced clonic seizure. The electron-withdrawing groups increase the electron density on the cationic polarised group of the compounds which serves as the increasing substituents for the anticonvulsant activity.

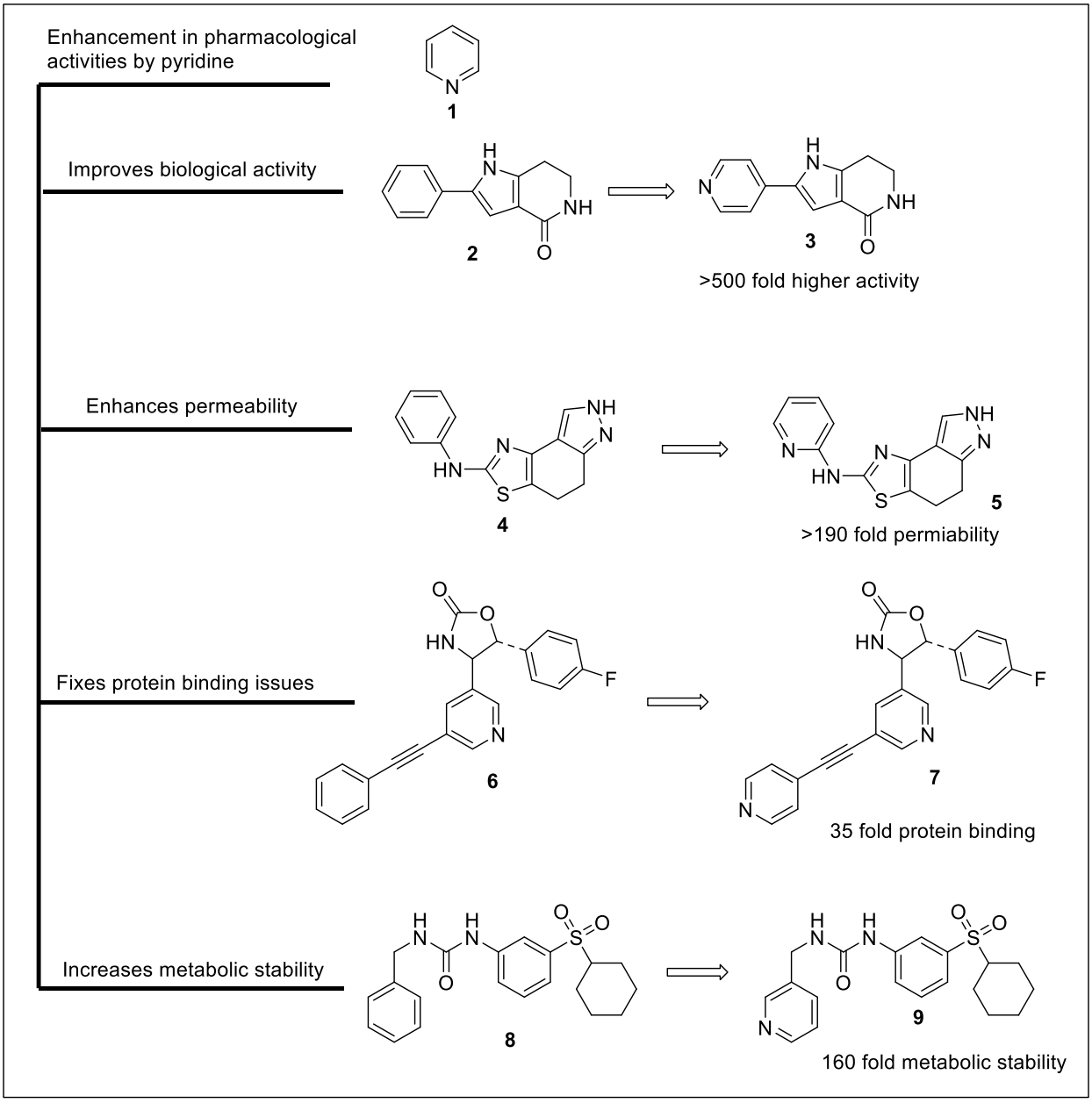


Figure 2. Effect on pharmacological aspects by pyridine derivatization

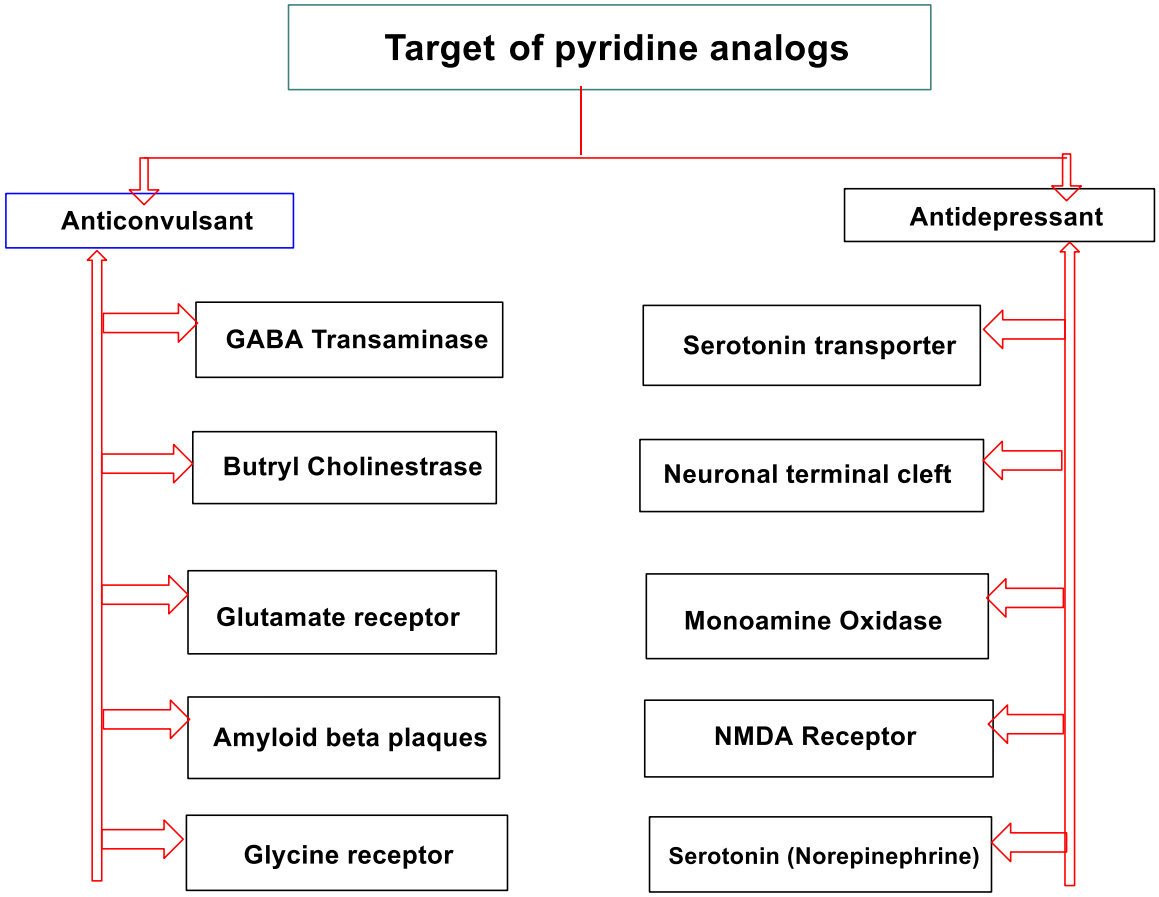


Figure 3. Different Targets of pyridine analogs for anti-convulsant and anti-depressant actions

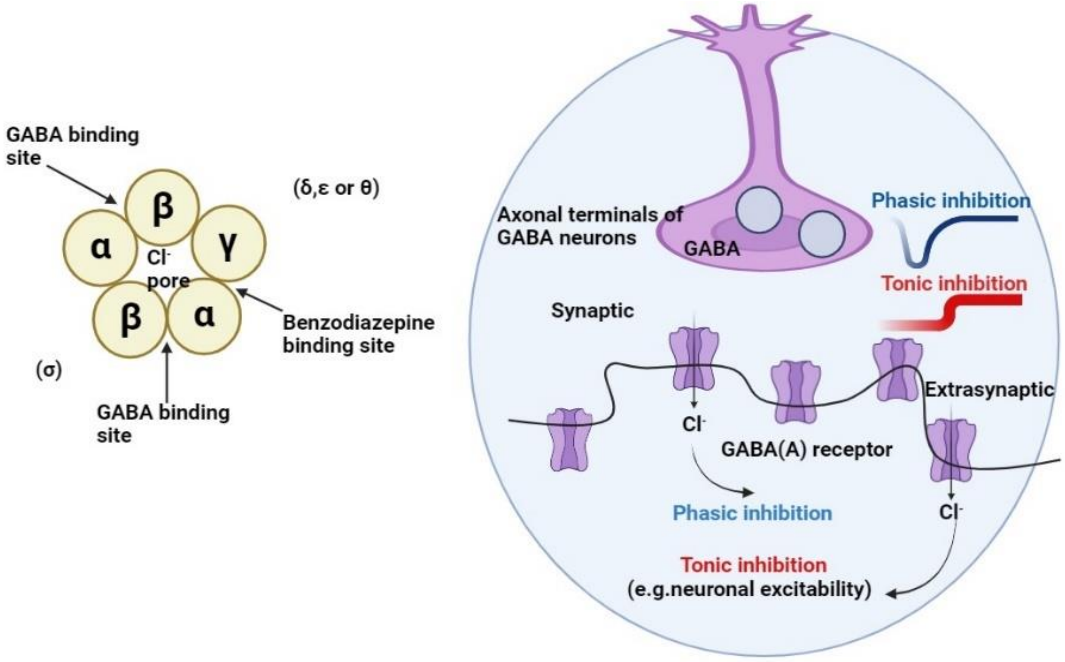


Figure 4. GABA binding sites with the receptors along with the inhibition of the ligands

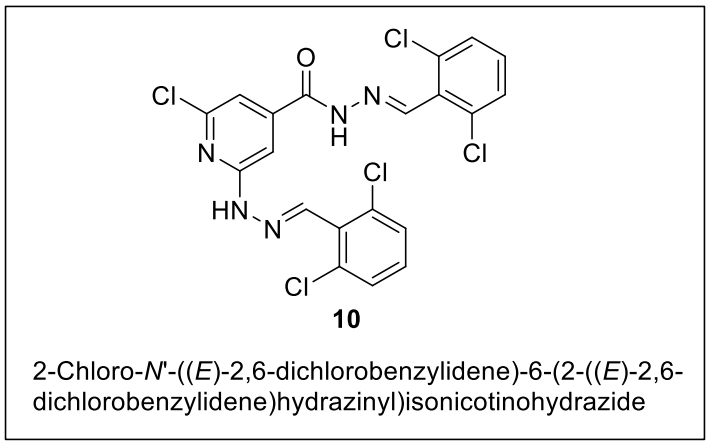
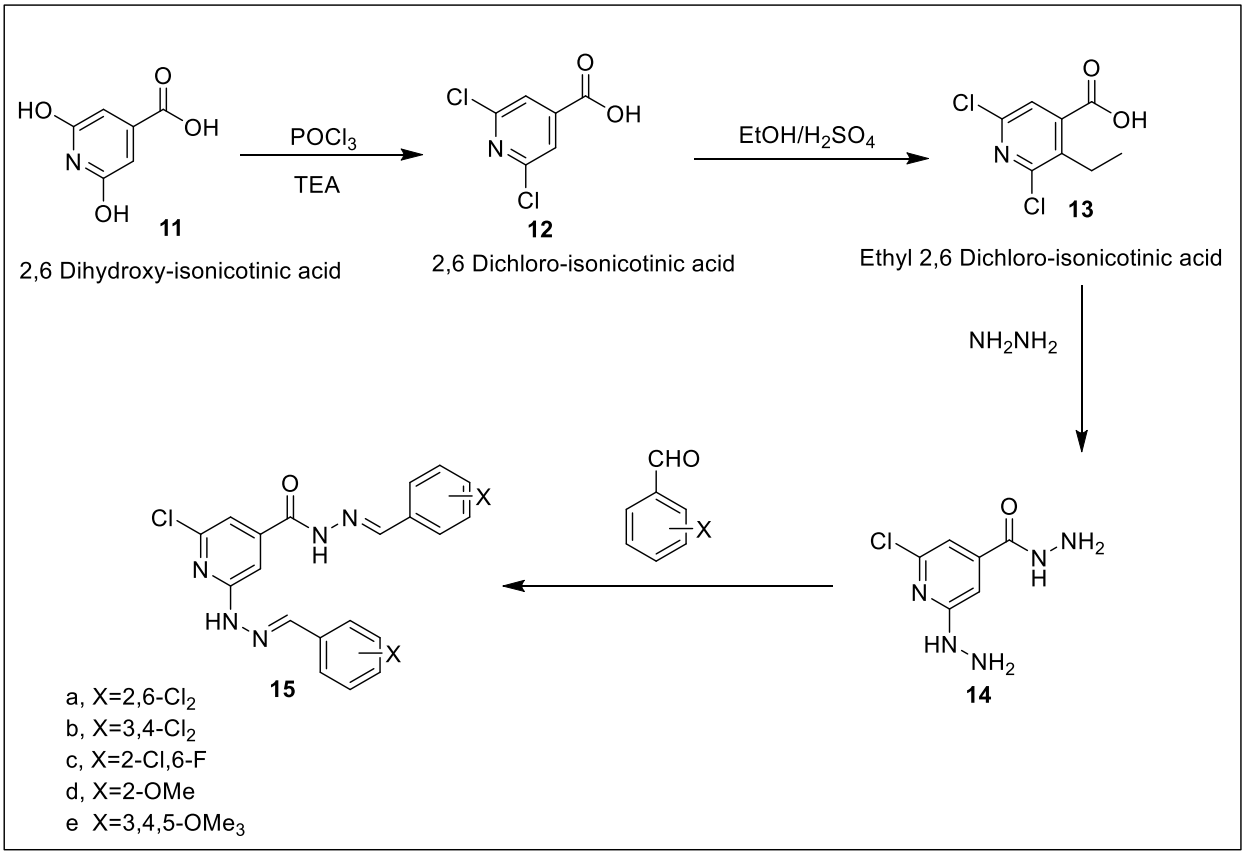
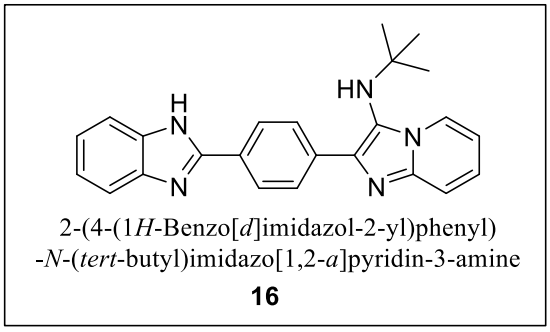


Figure 5. Derivative of pyridine derivative which may serve as GABA mimetic



Scheme 1. Synthesis of analogs with GABA mimetic agents

Al-Tel *et al*. synthesized the imidazo[1,2-*a*] pyridines from 2-aminopyridines, isocyanides, and aldehydic benzylic acid by the procedure of one-pot synthesis of the three compounds, as shown in **Figure 6** [84]. The reaction involves the multicomponent addition reaction (**Scheme 2**) where the derivatives of the benzylic groups involving the heterocyclic pyridine ring also help in the cyclic condensation reaction and the formation of the fusion with the help of the reagent $ScOTf_3$ ring giving the final product as **20**. The synthesized compound was tested for the inhibitor of β-secretase as the potential



2-(4-(1*H*-Benzo[*d*]imidazol-2-yl)phenyl)
-*N*-(*tert*-butyl)imidazo[1,2-*a*]pyridin-3-amine

16

Figure 6. Derivative of imidazo[1,2-*a*]pyridine

candidate for the lead compound in Alzheimer's. The computational value of compound 16 was an IC_{50} value of 5511 ± 248 nm and Ki value was 5312 ± 447nm for the BACE1 and BACE2 values were 5675 and 5509, respectively. The *in silico* screening of the compounds with the β-secretase enzyme gave the structural relationship of different molecules with the synthesized compounds fitting in the pocket of the enzyme compound and gave the above compound **16** which fits the S1-S3 pocket efficiently, by giving the good IC_{50} values.

2.2. Modulation of ion channel

Mono-substituted pyridines also act as sodium channel blockers by acting on the maximal Na^+ channel potential of -65mV. The disopyramide derivatives shared the same potencies by acting as the blockade of the sodium neuronal currents and were established by optimizing the derivatives with the dialkylamino chain. The regulation of the sodium channel is depicted in (**Figure 7**). Not only the sodium channels, but also voltage-gated calcium channels are responsible for the depolarization in the generated action potential. These channels are also important targets in Alzheimer's disease [85].

A.V. Adhikari *et al.* (2013) reported the synthesis of the dimethylpyridine-3-ol (**Figure 8**) from the derivatives of prop-1-en-2-amine and but-3-yn-2-one with ethanol under little

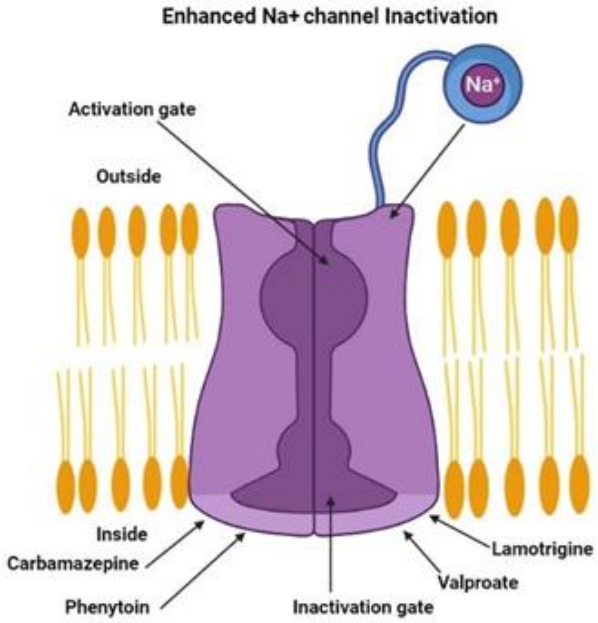
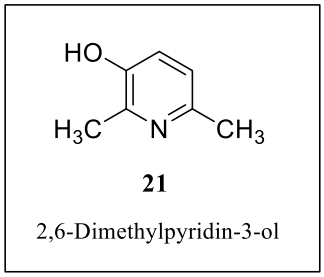


Figure 7. Modulation of Na^+ ion channel



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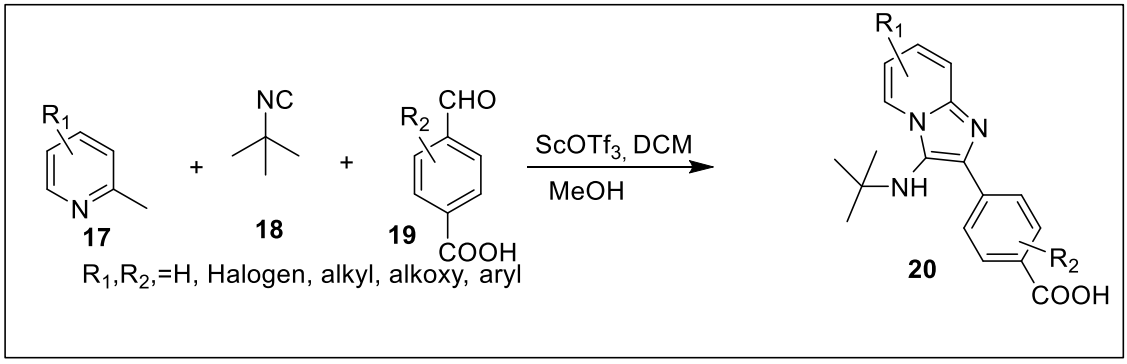
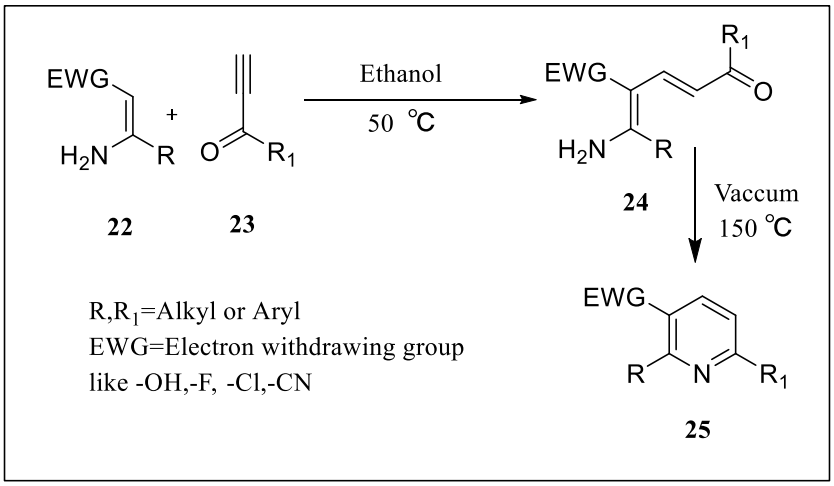
2,6-Dimethylpyridin-3-ol

Figure 8. Dimethylpyridine-3-ol which is tested for the anticonvulsant activity



Scheme 2. Synthesis of imidazo[1,2-*a*]pyridine derivatives



Scheme 3. Synthesis of dimethylpyridine-3-ol derivatives

heated conditions by the aldol condensation process yielding the α,β-unsaturated ketone and which upon the treatment with vacuum condition yields the pyrazoline ring [86]. The reaction of the α,β-unsaturated amine reaction with the ethynylketones which under the vacuum conditions gave the cyclic condensed product of the pyridine ring is known as the Bohlmann-Rahtz pyridine synthesis. This reaction gives the flexibility to synthesize the trisubstituted pyridines (**Scheme 3**). The synthesized compound when tried to fuse with the imidazole ring and the final synthesized compound was tested for the anticonvulsant property and the small doses have shown efficient biological activity.

F. Herold et al. (2012) synthesized the amide derivatives of pyridine (**Figure 9**) from the arylacetonitriles where the starting material is deprotonated with KOH in DMSO which results in the formation of C-arylated along with 2-Bromopyridine through a one-pot synthetic procedure. The subsequent synthetic derivatives were synthesized from the 2-aryl-2-pyridilacetonitriles through hydrolyzation to give the corresponding amides (**Scheme 4**) [87].

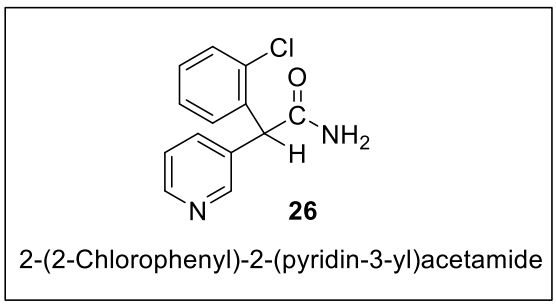
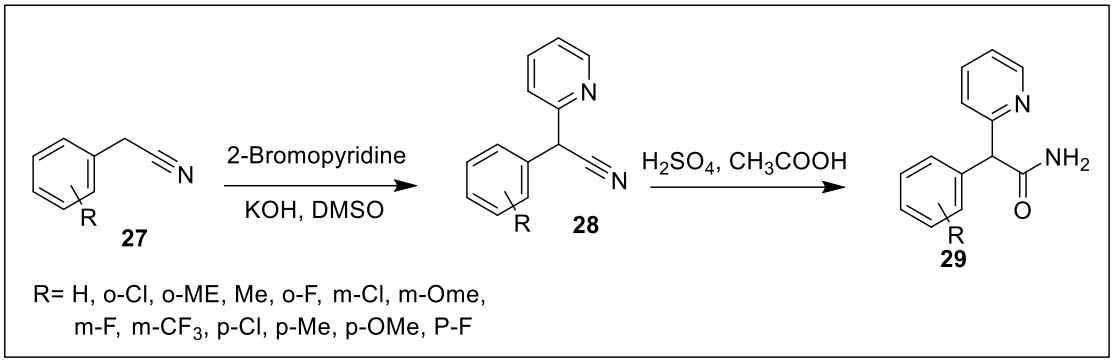


Figure 9. Chloro-substituted pyridines with amide functionality



Scheme 4. Synthesis of mono-substituted pyridines with amide functionality

2.3. Inhibition of the polo-like kinase enzyme activity

Numerous studies have reported that mutation of the pyridoxal kinase [pdxK] gene that codes for the Polo-like kinase enzyme and its activity has been changed during the seizure episodes that are due to the tissue variations in the enzyme activity could be attributed to the polymorphism in the gene promoter regions (Figure 10). Several compounds inhibit the Polo-like kinase activity and are directed at different targets with a concomitant deficiency in PLP, causing unwanted convulsions, and leg paralysis. Natural compounds such as the *Ginkgo biloba* are used in treatments such as asthma, depression, and dizziness. The gingotoxin is structurally like the vitamin B6 primers which have the pyridine rings in them. Research on these ginkogotoxin and theophyllines has a well-established inhibition of the Polo-like kinase inhibitory activity, the ligand interaction with the ligand and activation and inactivation is depicted in (**Figure 14**) and epileptic patients treated with theophylline have shown decreased serum levels of PLP [pyridoxal 5'-phosphate] [88].

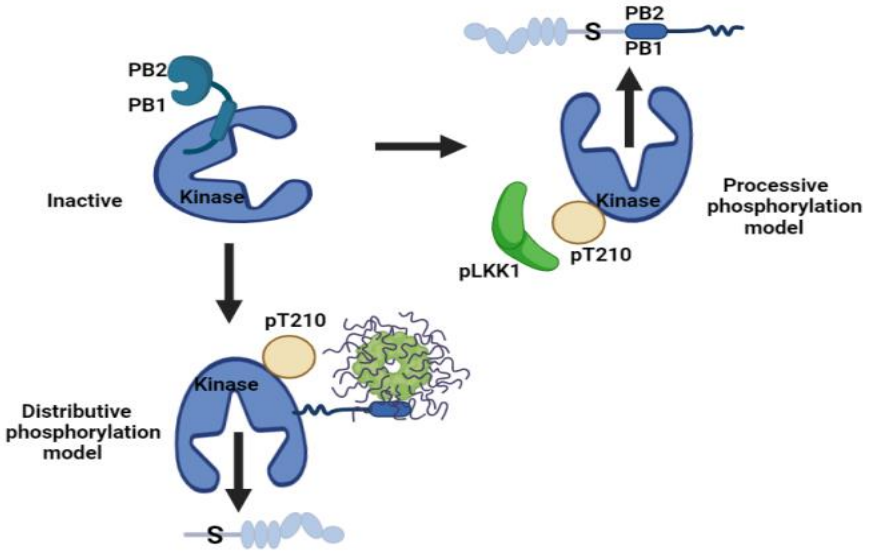
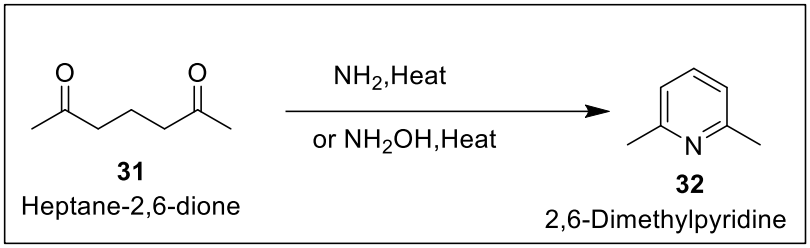


Figure 10. A Framework for Plk Substrate Targeting and Activation. Two potential frameworks illustrate the function of the Polo-box domain in substrate phosphorylation. In the processive phosphorylation framework, the Polo-box domain binds to a pre-phosphorylated site on a substrate, directing it for further phosphorylation by the Plk kinase domain. In the distributive phosphorylation framework, the Polo-box domain attaches to a phosphorylated scaffold, bringing the activated kinase domain in proximity to its substrates



Scheme 5. Synthesis of 2,6-dimethylpyridine

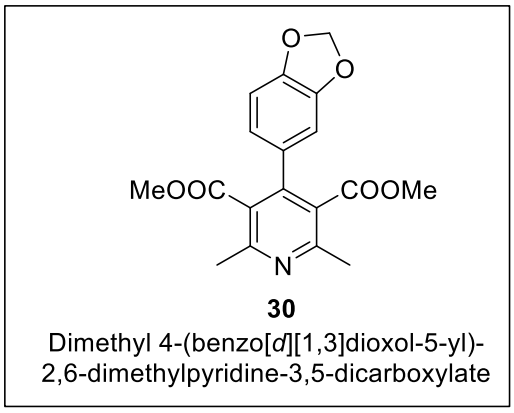


Figure 11. Dimethyl pyridine

C.J. Bataille *et al.* reported the synthesis of the targeted compound 2, 6-dimethylpyridine (**Figure 11**) from the heptane-2,6-dione through the alkaline ammoniacal solution under the heating conditions, by the process of using internal cyclization of 1,5-dicarbonyls [89a]. The synthesized pyridine compound is the basis used as the lead for the development of the anticonvulsant drug (**Scheme 5**). Substitutions at the 3rd and the 5th positions of the dimethyl pyridines with the aryl and the alkyl substitutions were tested for the anticonvulsant activity. The below reaction was used for the synthesis of the derivatives of dimethyl pyridine. The PTZ test was done for the evaluation of the anticonvulsant activity which proved that the aryl substitutions with the electron-withdrawing groups were responsible for the Latency period [s] mean ± SEM 200± 0.33 for the scPTZ test and 15± 1 for the MES test [limb extension test [89b]. S.A.Harris *et al.* (2014) synthesized the lactone pyridine derivatives (**Figure 12**) by oxidation of 2-methyl-3- methoxy-4,5-*bis*-[hydroxymethyl]-pyridine, by potassium permanganate to the lactone of 2-methyl-3-methoxy-4-hydroxymethyl-5-carboxypyridine. Since it has been demonstrated now that pyridoxine is oxidized by permanganate at the 4-hydroxymethyl group to pyridoxal, it is to be expected that the corresponding lactone should be obtainable by the same treatment. A new compound, the lactone of 2-methyl-3-hydroxy-4-carboxy-5-hydroxymethyl pyridine, has been synthesized (**Scheme 6**) [90].

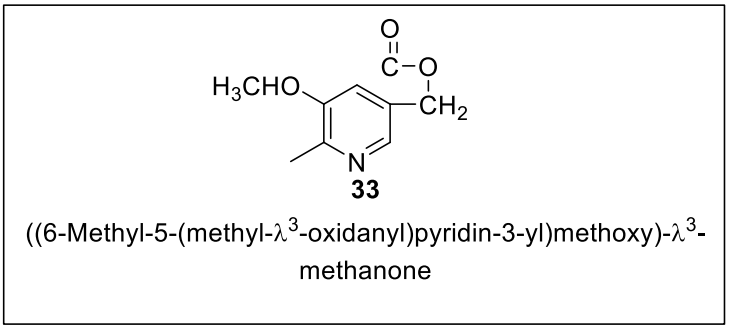
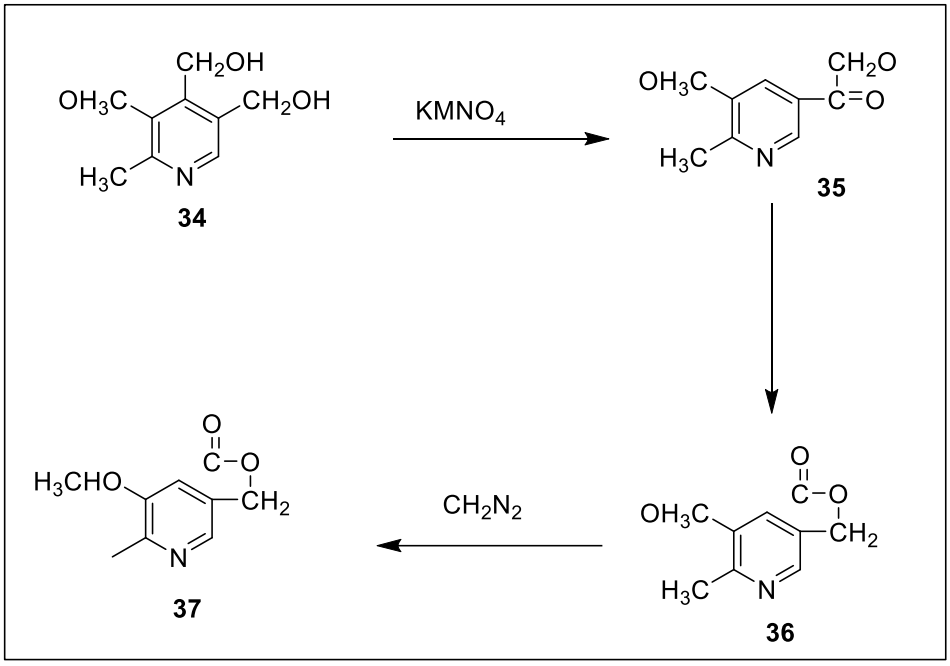


Figure 12. Methyl-λ3-oxidanyl] pyridine-3-yl analog which was tested for the 5-HT receptor and SERT analog



Scheme 6. Synthesis of [6-methyl-5-[methyl-λ³-oxidanyl] pyridine-3-yl]methoxy]- λ³-methanone

Various researches on the pyridine analogs have stated that some of the drugs such as trazodone have shown antidepressant activity by antagonizing the 5-hydroxytryptamine [5-HT2] receptors and inhibiting their function. These drugs also block the Serotonin reuptake transporter [SERTs] but inhibition of 5-HT by pyridine derivatives is reported to have a 100-fold potential more than Serotonin reuptake transporter [SERTs]. Both actions together contribute to the antidepressant efficacy of the drug and are classified as serotonin antagonist reuptake inhibitors [90]. Other clinically important receptor binding that are associated with these are blocking of the α-1 adrenergic receptors and H_1 histamine receptors. When administered at higher doses may act on other ones such as α-2 and 5-HT_{2c} receptors. Action on 5-HT_{2c} is relevant because newer-generation antidepressants act on this receptor such as mirtazapine, trazodone, quetiapine, and tricyclic antidepressants. Therefore, it may be helpful for novel drug delivery approaches for medicinal chemists that pyridine antagonists can be developed through the targeting of 5-HT_{2c} receptors [91].

2.4. Regulation of the glutamate ionotropic receptors [NMDA, AMPA]

In context to the rapid antidepressant activity regulation, the glutamate receptors are the important targets. Glutamate is one of the excitatory neurotransmitters in the brain which involves one-third of the CNS neurons and plays a major role in the learning and memory processes changes in the levels of glutamate could uphold the abnormalities in the dendritic spines which represent a target for rapidly acting glutamate modulators (Figure 13).

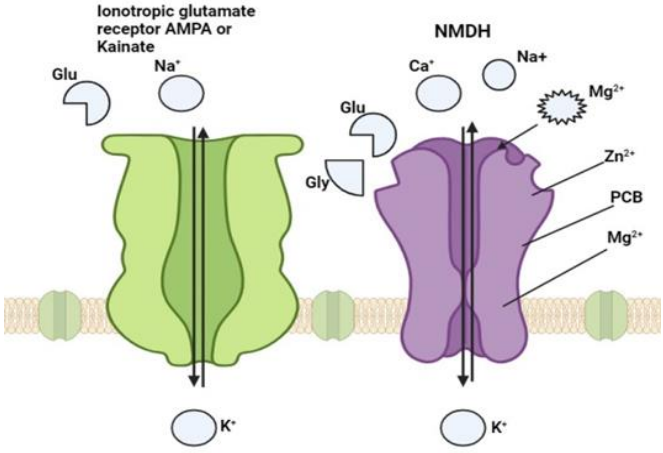
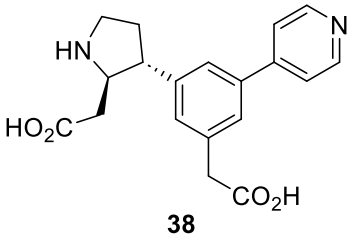


Figure 13. Regulation of the glutamate ionotropic receptors [NMDA, AMPA]

Glutamate is not easily metabolized by any process and its concentration is concerned with the glutamate reuptake transporters which is localized on the neurons and glia. Indeed, glutamate is complex and related to other *N*-methyl-D-aspartate [NMDA] receptors amino-3- and *α*-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA] receptors, and includes a combination of GluN1, GluN2, GluN2B, and GluN2D receptor subunits. Glycine and Glutamate are responsible for the activation of the ion channel activation and phencyclidine sites. Ionotropic glutamate receptors and mGluRs have various effects, and the regulation of the glutamate ionotropic enzyme, as shown in the regulation, and proposed models. Therefore, these complex cycles of the glutamate somehow help act as the target for antidepressant activity [92]. S. Kayser *et al.* (2020) synthesized the 3-[carboxyphenyl]pyrrolidine-2-carboxylic acid derivatives (**Figure 14**) through the benzylic alcohol derivative aromatic bromo-alkoxy derivatives with the palladium catalyst. Structure–activity relationship [SAR] study of the parental scaffold 2,3-trans-3-carboxy-3-phenyl-proline was done in the experiment for the anticonvulsant property [93]. The synthesized compound (synthesis as shown in **Scheme 7**) with the COOH group at the benzene ring with the pyridine ring has shown good activity with the ionotropic glutamate receptors and other groups which are electron-hdrawing groups and the triazole ring at the acetic acid groups with the good IMPA IC_{50} 4.581 ± 0.07 and KA IC_{50} 4.61 ± 0.05 and NMDA Ki 5.76 ± 0.01 values for the compound **38**.



38

2-((2*R*,3*R*)-3-(3-(carboxymethyl)-5-(pyridin-4-yl)phenyl)pyrrolidin-2-yl)acetic acid

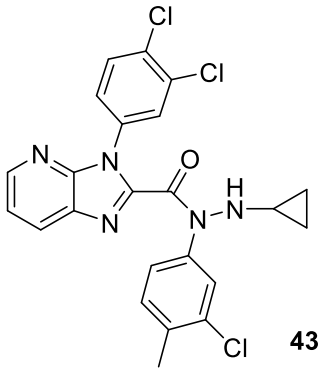
Figure 14. 3-[6-Methylpyridin-2-ylethynyl]-5-bromopyridine derivative which was having good IMPA IC_{50} and KA IC_{50} value

2.5. mGluR7 Coupled to the inhibitory cyclic AMP signal transduction

The diseased model was developed for the rat metabotropic glutamate receptor isolated through PCR-mediated DNA amplified by primer sequence among the metabotropic receptor. This group of mGluR family receptors corresponds to the putative L-2-amino-4-phosphonobutyrate receptor which plays an important role in the modulation of transmission of glutamate in the CNS [94].

Various drug development-acting allosteric agonists have made neuropharmacological and neurochemical studies in the functions of mGluR7 feasible as the target for optimizing new agents for the antidepressive agent as the regulation of the mGluR7 coupled with the AMP signal transduction, as illustrated in (**Figure 15**). For the *in vitro* assays, cAMP and GTPγS binding were evaluated for various parameters in recombinant cells expressing mGluR7 inhibitory effect [95].

A.K.Vadukoot *et al.* (2020) reported the synthesis, SAR, and biological evaluation of a series of 1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxamide derivatives (Figure 16) as



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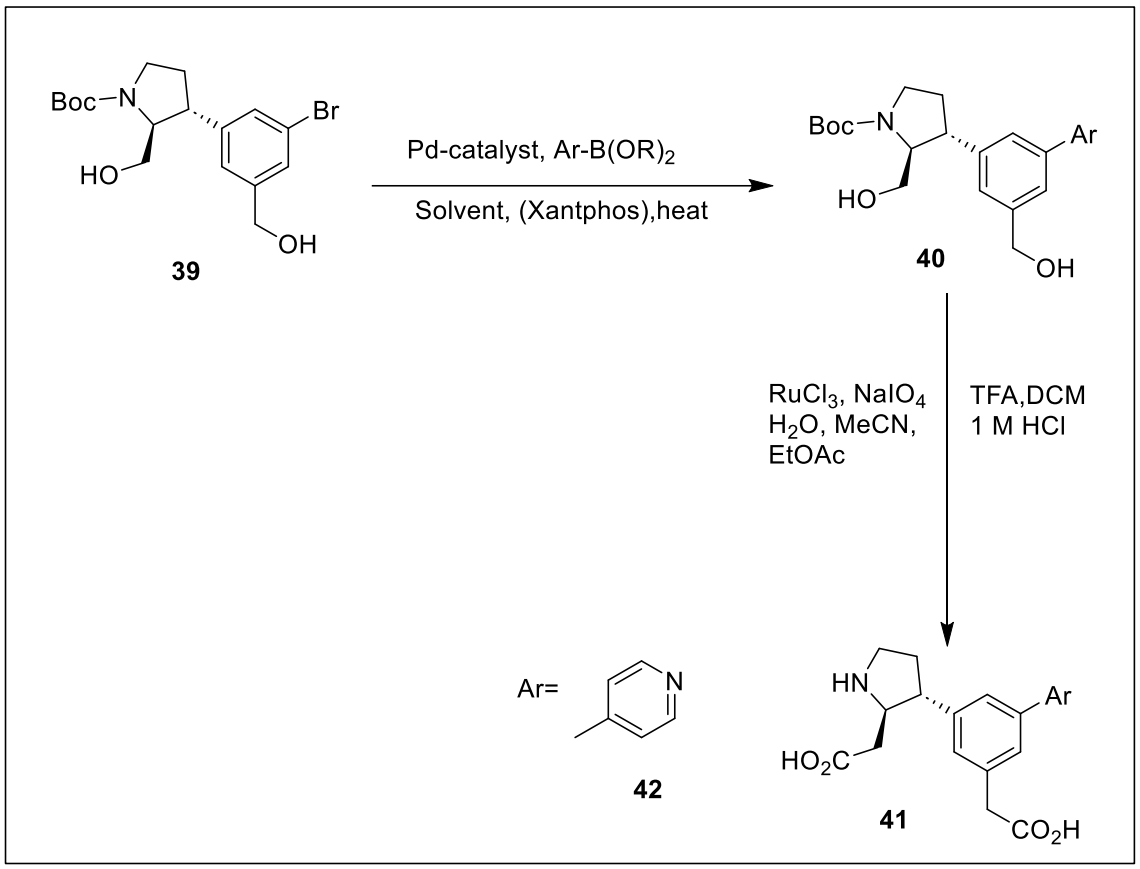
N-(3-Chloro-4-methylphenyl)-*N*'-cyclopropyl-3-(3,4-dichlorophenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carbohydrazide

Figure 16. Halogenated benzene substituted pyridine derivative which was tested against the PDE4B and PDE4D enzyme for the CNS activity



Scheme 7. Synthesis of 3-[6-methylpyridin-2-ylethynyl]-5-bromopyridine

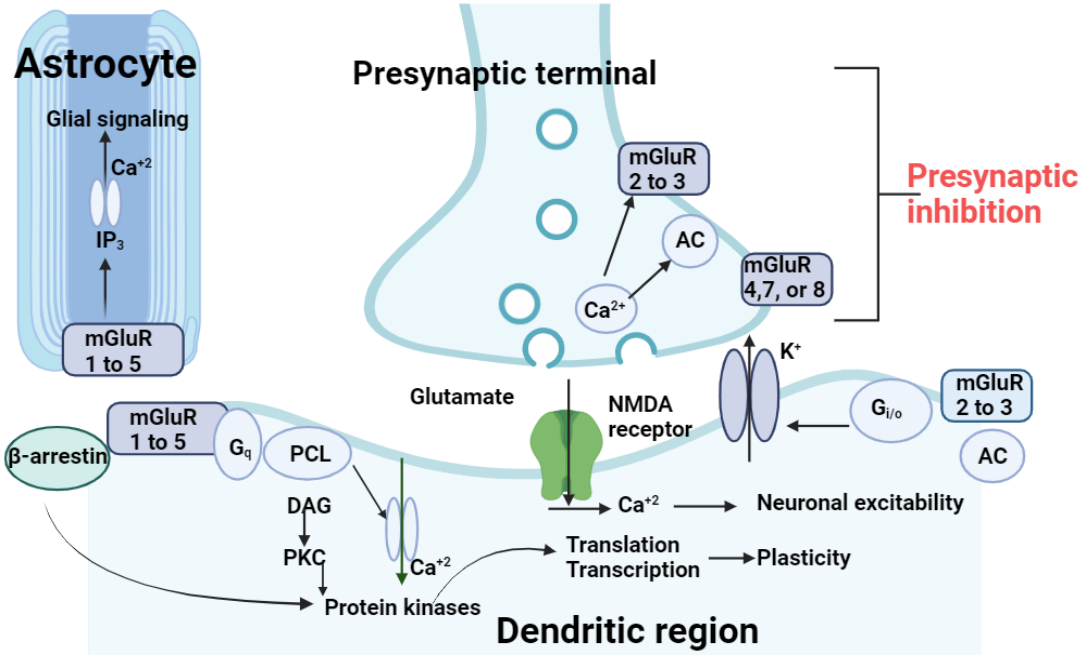
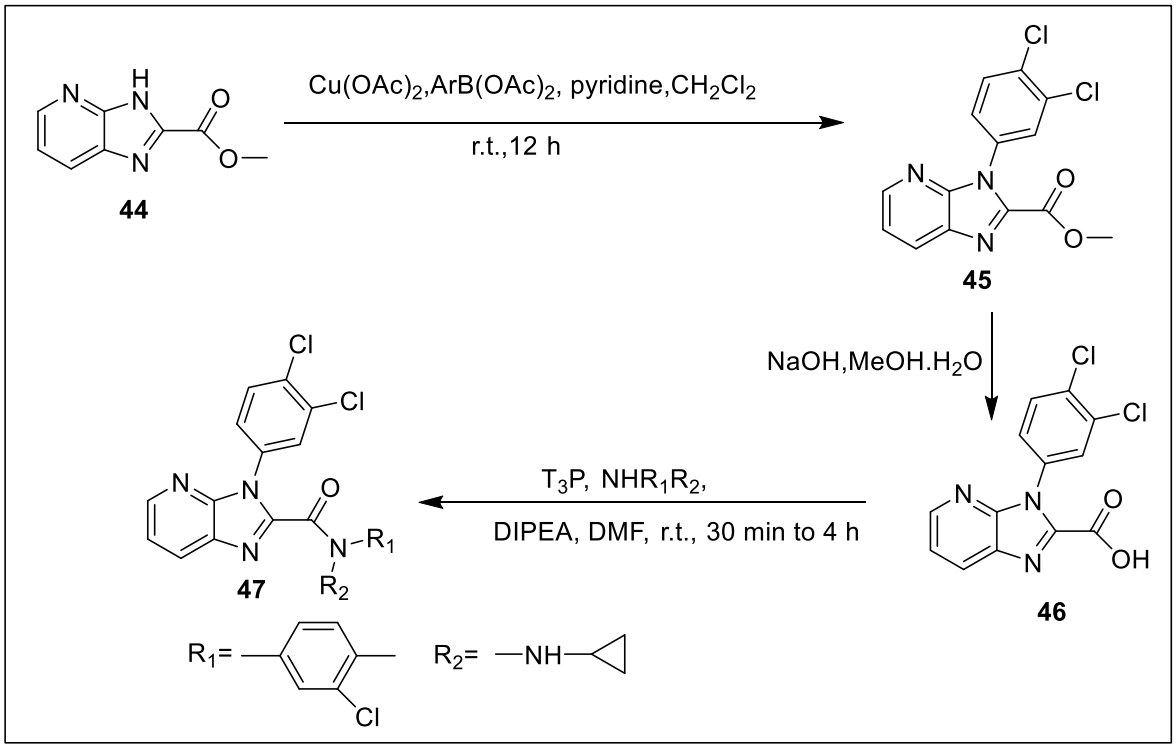


Figure 15. mGluR7 Coupled to the inhibitory cyclic AMP signal transduction

selective and potent PDE4B inhibitors. In addition, 11 h was found to be a selective molecule against a panel of CNS receptors and represents an excellent lead for further optimization and preclinical testing in combating CNS diseases [96]. The synthesized derivatives (synthesis carried out as per Scheme 8) have some activity against the PDE4B which have IC_{50} value 630 and PDE4D enzymes which have IC_{50} value 59 and were tested for CNS disorders and the compounds with the triazole ring with fluorine have shown decreased activity against the inhibition of the PDE4B and PDE4D enzyme activity.

2.6. Other synthesis approaches for pyridine derivatives

As discussed above in the review, the anticonvulsant and antidepressant profile of the drugs used or patented have the importance of the heterocyclic ring system in the area, and prevailing the use of pyridine ring derivatives the use of DHP, imidazole-pyridine, triazole, pyrimidine, pyrazole, oxazole, and various amides and hydrazones are used. Focusing on the pyridine heterocyclic system, it displayed various CNS-related activities including anticonvulsant activity. Epilepsy therapy continues for a longer duration and has associated side effects such as drowsiness, ataxia, hyperplasia, and ataxia. These observations demonstrate the scope and need for the development of newer anticonvulsant and antidepressant drugs with better tolerance levels and with lesser side effects [97]. Ulloora S. *et al.* (2013) worked on new imidazo[1,2, a-] pyridine derivatives (**Figure 17**) which were found to be an active pharmacophore and were active with anticonvulsant properties. Designing of new chemical entity for drug development is a complex procedure, therefore molecule modification is a better task to perform. The chemistry about the synthesis of the compound derivatives of the imidazo[1,2]pyridine derivatives which is attached with the chalcone derivative upon the treatment with the hydrazine undergoes the aldol condensation and forms the pyrazoline ring compound, whereas the treatment of the methyl di-cyanide which gave the formation of the dihydropyridine ring and which gave out various derivatives of the compound.



Scheme 8. Synthesis of *N*-[3-chloro-4-methylphenyl]-*N*'-cyclopropyl-3-[3,4-dichlorophenyl]-3*H*-imidazo[4,5-*b*]pyridine-2-carbohydrazide

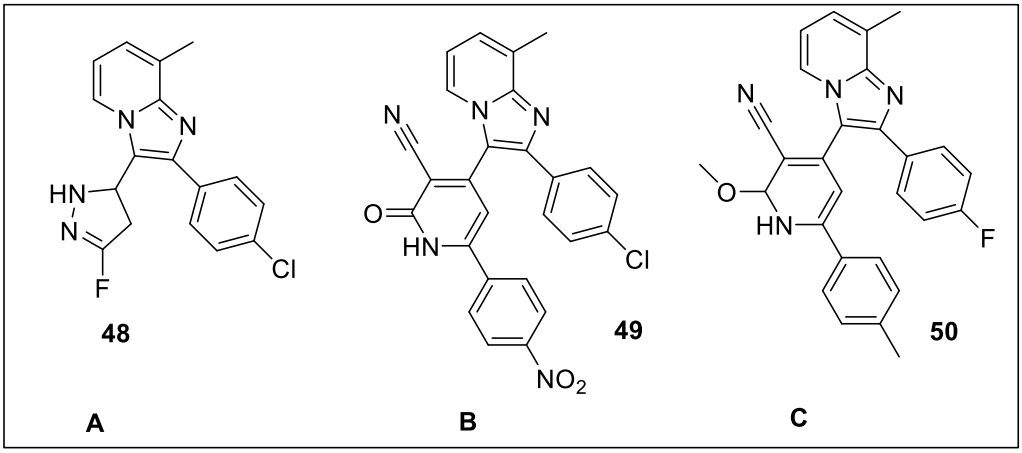
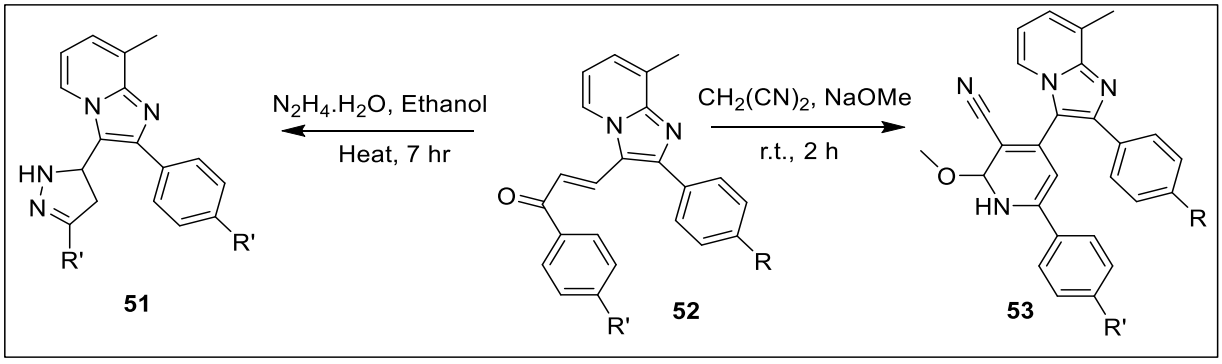


Figure 17. The tested derivatives for the MES and scPTZ test for the CNS activity

These derivatives were active against benzodiazepine derivatives along with potent CNS activity. The activity was tested for the derivatives and their activity by MES test with IC_{50} values for the compound **48** were 07.15 ± 1.07 µM and scPTZ values 79.32 ± 1.23, for **49** were 06.61 ± 1.21 µM and 171.8 ± 2.22, respectively, and **50** 09.84 ± 1.17 µM and 335.3 ± 4.58, respectively. Among all synthesized compounds (Synthesis as shown in **Scheme 9**), Compound C was found as the most potential compound [98]. Abd El-Galil E. *et al.* (2005) carried out various experiments for the anticonvulsant property of the drugs derived from pyridine and after the structural activity relationship studies on *N*-[7-[6-[3-chloro-5-ethoxyphenyl]-3-cyano-2-[thiophen-2-yl]isonicotinamido]-1,3,6,8-tetraoxo-3,6,7,8 tetrahydrobenzo[lmn][3,8]phenanthroline 2[1*H*]-yl]-5-cyano-2'-ethoxy-6'-methyl-6-[thiophen-2-yl]-[2,4'-bipyridine]-4-carboxamide (Structure demosntrated in **Figure 18**) which was synthesized from 6-amino-2'-chloro-6'-ethoxy-4-[thiophen-2-yl]-[2,4'-bipyridine]-5-carbonitrile and 1H,3H-benzo[1,2-c:4,5-c']difuran-1,3,5,7-tetraone highly potent and selective for the antagonize yohimbine-induced clonic seizure with the values ED_{50} 53 ± 0.41 mg/kg and relative potency 0.67 ± 0.008 for the anticonvulsant activity and taking as the carbamazepine with the property of crossing BBB and *in vivo* receptor occupancy in the rat model with oral bioavailability [99]. The synthetic chemistry of the compounds (**Scheme 10**) is the reaction of the aryl chloride with the amino substituted pyridine and benzne malonic ester along with the dioxane, TBAB solvent which gives the compound pyridine ring which has the amine substitution and the alkyl which upon treatment with the diketo carbonyl product gives the cycloaddition product of the pyridine fused thiazole ring with some R substitutions.



Scheme 9. Synthesis of pyridine-imidazole analogs

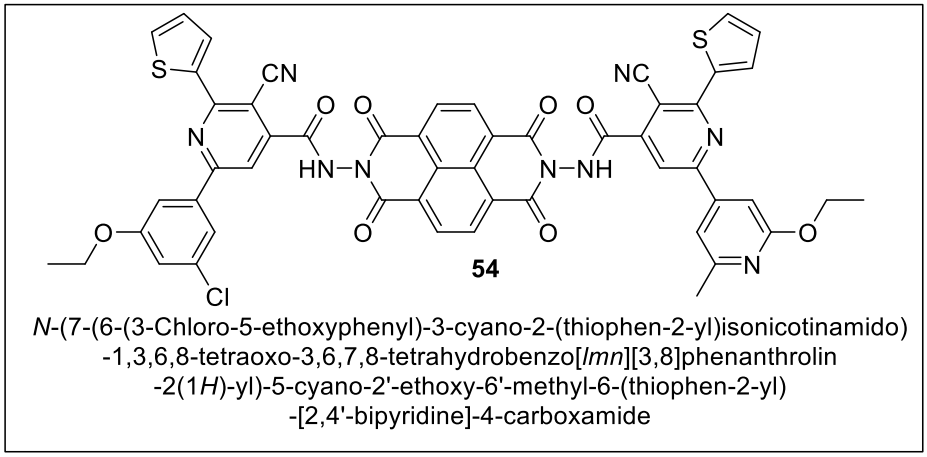
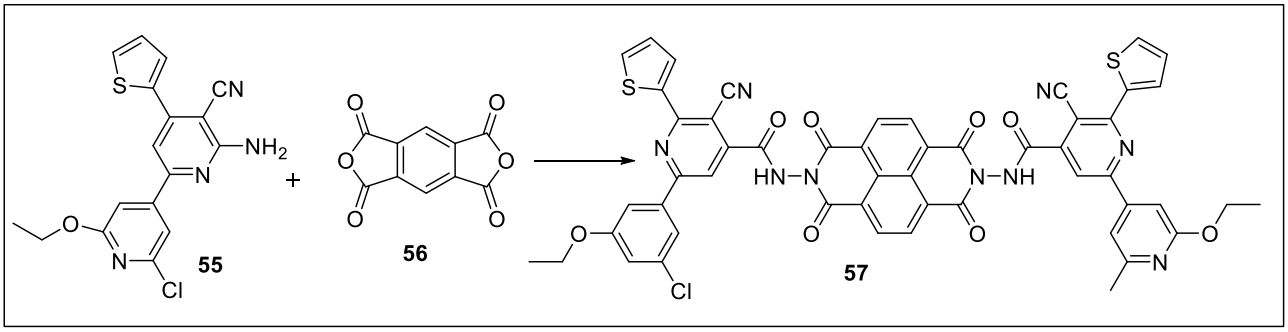


Figure 18. Pyridine derivatives tethered with the isonicotinamide and benzene rings



Scheme 10. Synthesis of tetrazole-pyridine derivatives

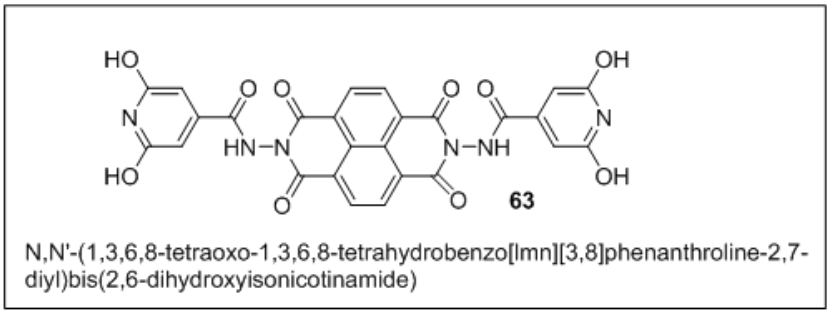
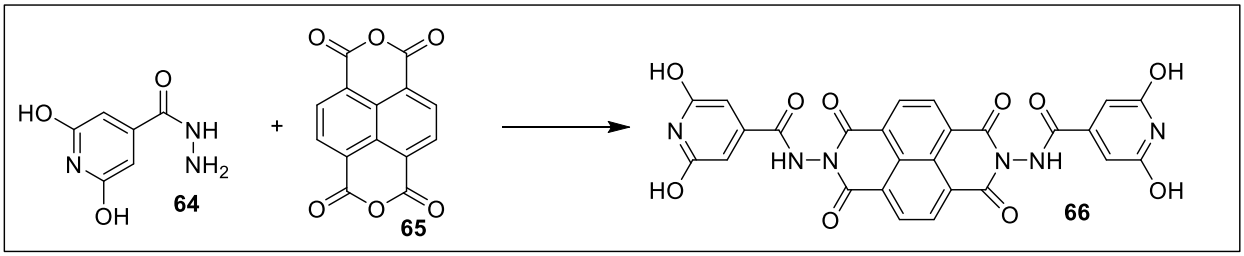


Figure 19. Dipyridine derivatives with the tetrahydrobenzene-phenanthroline ring tested for the anticonvulsant activity for the yohimbine-induced clonic seizures



Scheme 11. Synthesis of tetrahydrobenzo,phenantroline, isonicotinamide substituted pyridine derivatives

Mohamed A. *et al.* (2010) synthesized some novel thiazole derivatives (**Figure 19**) using disubstituted isonicotinic acid hydrazides with screening for anticonvulsant activity. The synthesis of the compounds involves the reaction of the 2,6-dihydroxyisonicotinohydrazide and isochromene-1,3,6,8-tetraone (**Scheme 11**) under the selective reaction condition, as mentioned in the schematic requirements for the better yield of the product. This reaction gives the insertion reaction in the compound synthesis which is highly cyclized compound. The symmetry of the compound fixes the receptor site and a good candidate for the further anticonvulsant property. The anticonvulsant activity of the synthesized compounds as compared with carbamazepine had very excellent activity towards the receptor and had lesser side effects, having ID_{50} value of 2034.89 ± 0.12 mg/kg potent as an anticonvulsant agent and yohimbine-induced clonic seizures [100]. Mitali N. Naik. *et al.* (2017) performed the synthesis of pyridine derivatives (**Figure 20**) with the docking of the synthesized compounds against different targets. Synthesis was done from benzaldehyde, acetophenone, and malonitrile with a multicomponent reaction (**Scheme 12**) which gives the tetra substituted pyridine ring which

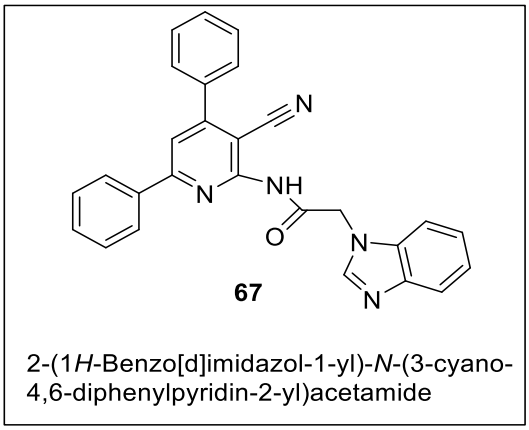
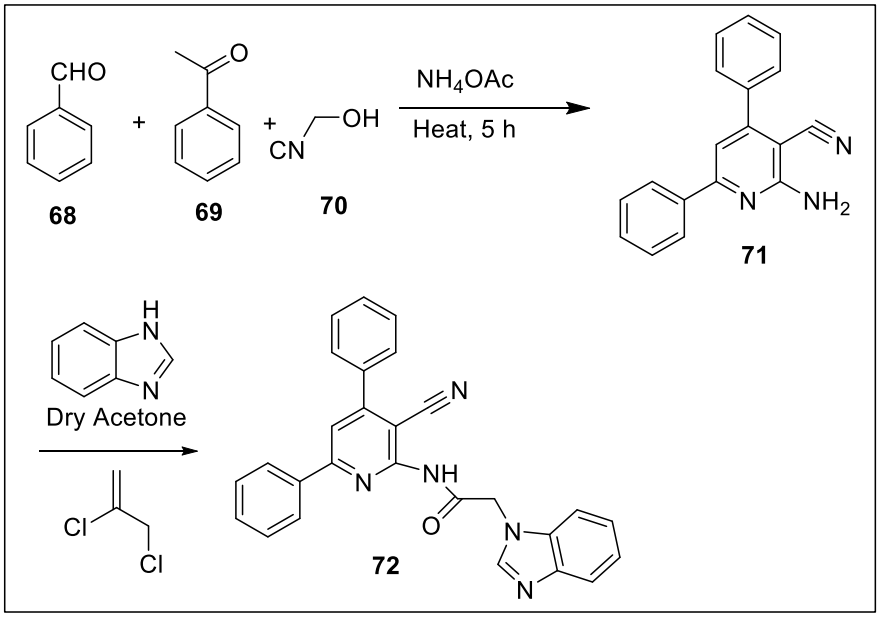


Figure 20. Pyridine derivative substituted with the benzimidazole ring which was tested for the antidepressant activity

can further give the reaction with benzimidazole and which attaches at the amine site and gives the targeted compound.

The used animal model was male albino mice and the standard drug from which the activity of the compound was tested was imipramine and tests were locomotor activity with the values of 169.2 ± 4.286 and forced swim test with values 621.8 ± 18.31. The lead molecule exhibited better antidepressant activity by docking results further verified from *in vivo* testing [101].



Scheme 12. Pyridine derivatives synthesised from benzaldehyde substituted with the benzimidazole ring, diphenyl and cyanide groups

3. Conclusion

To sum up, this comprehensive review illuminates the dual therapeutic potential of pyridine derivatives, offering a nuanced understanding of their anti-convulsant and anti-depressant actions in neurological disorders. The diverse structural modifications of pyridine analogs, as explored in the literature, reveal a remarkable capacity to modulate intricate neurochemical pathways, providing a foundation for their dual efficacy. The anticonvulsant effects, involving mechanisms such as GABAergic enhancement, sodium and calcium channel inhibition, and glutamate receptor modulation, demonstrate the multifaceted nature of pyridine compounds in mitigating aberrant neuronal activity. Simultaneously, their antidepressant properties, encompassing selective serotonin and norepinephrine reuptake inhibition, receptor binding affinity, and modulation of neurotransmitter systems, highlight the potential of pyridine derivatives to address mood disorders. The synergistic impact on both anticonvulsant and antidepressant pathways positions pyridine-based compounds as promising candidates for novel, integrative therapeutic strategies. Despite these promising insights, challenges persist, including the need to optimize selectivity, manage individual variabilities, and minimize potential side effects. Ongoing research efforts are crucial to refining the pharmacological profiles of pyridine analogs, ensuring their safety and efficacy in diverse patient populations. As we navigate the complex landscape of neuropsychopharmacology, the dual-action paradigm of pyridine derivatives emerges as a beacon of hope, offering a potential breakthrough in the development of tailored interventions for individuals facing simultaneous anticonvulsant and antidepressant needs. The reviewed evidence sets the stage for future advancements, inspiring a new wave of research aimed at harnessing the therapeutic potential of pyridine compounds and ultimately improving the lives of those affected by neurological disorders.

Future Perspectives

In future perspectives, the continued exploration of pyridine derivatives in neurological disorders holds great promise. Further research should focus on enhancing the selectivity of these compounds, minimizing potential side effects, and addressing individual variabilities. Advances in understanding the intricate neurochemical pathways involved in anticonvulsant and antidepressant actions will guide the development of more targeted pyridine analogs. In addition, exploring innovative drug delivery systems and combination therapies may optimize treatment outcomes. Collaborative efforts between researchers, clinicians, and pharmaceutical industries will be instrumental in translating these findings into clinically effective, personalized interventions, marking a transformative era in the management of complex neurological conditions.

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Conflict of Interest

There is no related conflict among the authors.

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