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New imidazo[1,2-*a*]pyridines carrying active pharmacophores: Synthesis and anticonvulsant studies

Shrikanth Ulloora [a], Ramakrishna Shabaraya [b], Syed Aamir [b], Airody Vasudeva Adhikari [a,*]

[a] Department of Chemistry, National Institute of Technology Karnataka, Surathkal, Mangalore 575 025, Karnataka, India
[b] Srinivas College of Pharmacy, Valachil, Mangalore, Karnataka, India

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ABSTRACT

Five new series of imidazo[1,2-*a*]pyridines carrying biologically active pyrazoline (**4a**–**e**), cyanopyridone (**5a**, **b**), cyanopyridine (**6a**–**f**), 2-aminopyrimidine (**7a**–**f**) and pyrimidine-2-thione (**8a**–**d**) systems were designed and synthesized as prominent anticonvulsant agents. The target compounds were screened for their in vivo anticonvulsant activity following maximal electroshock (MES) and subcutaneous pentylene tetrazole (scPTZ) methods at a small test dose of 10 mg/kg. Further, Rotarod toxicity method was used to study the toxicity profile of selected compounds. Compounds **4b**, **5a**, **5b**, **6a**, **7e** and **8d** possessing 4-fluorophenyl substituent at 2nd position of imidazo[1,2-*a*]pyridine ring displayed potent anticonvulsant activity without displaying any toxicity. Enhanced activity profile was observed for new compounds in PTZ method over MES method.

Epilepsy is a collective term used for about 40 different types of human seizure disorders.[1] It is a major health problem that affects approximately 1% of world population.[2] Also, the cellular mechanism of human epilepsy is still uncertain and hence the present drug therapy is rather concerned only with control of epilepsy symptoms than curing.[3] Moreover, about 40% of patients are found to experience uncontrolled seizure and is resistant to present antiepileptic drugs (AEDs),[4] which are the only choice of medication for epilepsy. Further, an ideal AED should keep the patient free from any seizures without any considerable adverse effects. However, present therapy for seizure is associated with various adverse side effects such as ataxia, hyperplasia and anaemia.[5,6] Consequently, development of new antiepileptic agents having improved seizure control along with better tolerability is a major goal in epilepsy research.

The non-benzodiazepines are generally used as sedatives, anticonvulsants, hypnotics, anxiolytics and muscle relaxants as they show less adverse effects compared to classical benzodiazepines.[7] In fact, imidazopyridines are the major class of non-benzodiazepines, acting upon various central nervous systems (CNS) disorders. Interestingly, several imidazopyridine based drugs such as Zolpidem, Alpidem, Saripidem, etc. exhibit potency against pentylenetetrazole (PTZ) induced seizures.[8] The chemical structure of some important imidazo[1,2-*a*]pyridine based CNS agents are given in Figure 1. In addition to their CNS activity, recent literatures also revealed various other applications of imidazopyridine derivatives in medicinal chemistry. They were reported as potential antiprotozoal,[9] antimicrobial,[10] antiherpetic,[11] anti-HIV,[12] antiviral,[13] anticancer[14] and anti-inflammatory[15] agents.

Design of new synthetic compounds with appropriate therapeutic importance is a major challenge in medicinal chemistry. Molecular modification could be a productive source for new biologically active molecules.[16] Recently, imidazopyridines containing an aryl substituent at 2nd position were reported as highly CNS active scaffolds.[17] Further, it is also revealed that, selectivity of imidazo[1,2-*a*]pyridines towards benzodiazepine receptors can be enhanced by incorporating a 4-halophenyl ring at 2nd position and a hydrophobic unit at 8th position.[18] Inspired by this observation, it has been planned to design new series of imidazo[1,2-*a*]pyridines containing 4-fluoro substituted aryl ring at 2nd position and a methyl group as a hydrophobic unit at 8th position of the ring, with the expectation of improved pharmacological activity.

The reaction sequence involving the synthesis of required imidazo[1,2-*a*]pyridine-3-carboxaldehydes and subsequent final compounds are given in Schemes 1 and 2, respectively. The compounds **1a**, **b** and **2a**, **b** were synthesized following reported procedure.[19] These aldehydes **2a**, **b** were stirred at 50 °C for about 4 h with different acetophenones under alcoholic NaOH media to obtain the key chalcone intermediates **3a**–**h**. Later on, these chalcones were used as active scaffolds for the synthesis of target compounds **4a**–**e**, **5a**, **b**, **6a**–**f**, **7a**–**f** and **8a**–**d** carrying different heterocyclic systems. Pyrazolines **4a**–**e** were synthesized by refluxing appropriate chalcones **3a**–**h** with hydrazine hydrate under ethanolic media. Further, 3-cyano-2-pyridones **5a**, **b** were conveniently obtained

* Corresponding author. Tel.: +91 8242474000x3203; fax: +91 8242474033.
E-mail addresses: avadhikari123@yahoo.co.in, avchem@nitk.ac.in (A.V. Adhikari).

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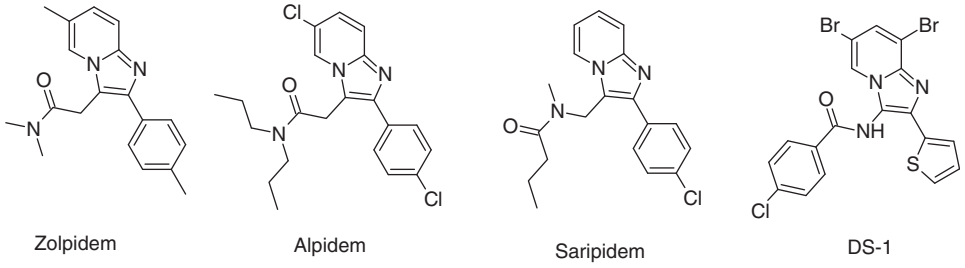
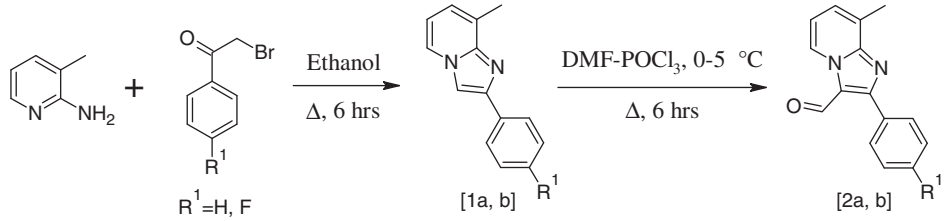


Figure 1. Important imidazo[1,2-*a*]pyridines acting as CNS agents.



Scheme 1. Synthesis of imidazo[1,2-*a*]pyridine-3-carboxaldehydes.

by refluxing chalcones with ethyl cyanoacetate and ammonium acetate under alcoholic media for about 12 h. Similarly, 2-methoxy-3-cyano pyridines **6a**–**f** were synthesized with good yield by stirring chalcones **3a**–**h** with malononitrile at room temperature in sodium methoxide solution. The latter two reactions involve the Michael addition of active methylene compounds to conjugated double bond, followed by internal cyclization. Finally, 2-amino pyrimidines **7a**–**f** and pyrimidin-2-thiones **8a**–**d** were obtained by refluxing chalcones **3a**–**h** with guanidine hydrochloride and thiourea, respectively in presence of alc. NaOH. Further, all the newly synthesised final compounds were purified by either recrystallization or column chromatographic techniques.

The structures of new intermediates and final compounds synthesized by above mentioned routes were confirmed by various spectral techniques like FTIR, ^{1}H NMR, ^{13}C NMR, mass spectroscopy followed by elemental analysis. Synthesis of core imidazo[1,2-*a*]pyridine derivative **1a**, was confirmed by its FTIR spectrum, where the peak corresponding to amine group of 2-amino-3-picoline and carbonyl functionality of phenacyl bromide disappeared. Also, a new characteristic peak at 1638 cm^{-1} corresponding to C=N stretching of the ring was observed, which clearly demonstrate the cyclization. Similarly, the ^{1}H NMR spectrum of **1a** displayed a singlet at δ 2.65 ppm corresponding to CH_3 group attached to pyridine ring along with other required aromatic peaks, but no peaks corresponding to amine group was observed. Formylation of core ring was clearly established by the observation of new carbonyl stretching peak at 1678 cm^{-1} in FTIR spectrum of **2a**. This was further confirmed by its ^{1}H NMR spectrum, wherein it displayed a singlet at δ 9.98 ppm, corresponding to aldehydic proton. Moreover, a peak at δ 8.34 ppm that corresponds to CH proton at 3rd position of the ring disappeared upon formylation, indicating the electrophilic attack at 3rd position. The shift in carbonyl stretching frequency from 1678 to 1647 cm^{-1} upon reacting aldehyde **2a** with acetophenone, confirmed the formation of chalcone **3a**. Also, appearance of two doublets in ^{1}H NMR spectrum at δ 7.95 and 7.83 ppm correspond to protons of conjugated alkenes, further supported the proposed structure of chalcone. The coupling constant value (J) for these olifinic protons was found to be 15.2 Hz. Similarly, for all other chalcones (**3b**–**h**), the 'J' values are in the range of 14.4–16 Hz, indicating that they are stereoselective and attained trans (E) configuration.

FTIR spectrum of pyrazoline analogue **4a** showed a new peak at 3241 cm^{-1} for NH stretching. Also, its ^{1}H NMR spectrum displayed a singlet at δ 9.34 ppm, corresponding to pyrazoline NH proton. Moreover, three doublets of doublets (dd) were observed for ABX type of pyrazoline ring protons at δ 5.63, 3.38 and 3.03 ppm, which is a characteristic feature of pyrazoline systems that reveals the proposed structure. Formation of 3-cyano-2-pyridone derivative **5a** was well documented from its FTIR spectrum, which showed characteristic peaks at 2213 cm^{-1} corresponding to nitrile functionality and at 1637 cm^{-1} for cyclic amide carbonyl group. Similarly, FTIR spectrum of 3-cyano-2-methoxypyridine analogue **6a** exhibited appropriate peaks at 2220 and 1582 cm^{-1}, respectively, for nitrile and pyridine C=N stretching. Conversion of chalcone **3a** into 2-amino pyrimidine derivative **7a** was evidenced by the appearance of a new peak in its FTIR spectrum at 3306 cm^{-1} corresponding to amine group. Also, its ^{1}H NMR spectrum showed a singlet at δ 5.24 ppm confirming the proposed structure. However, treatment of chalcones **3a**–**h** with thiourea resulted in non-aromatic pyrimidine thiones **8a**–**d**. This was confirmed by FTIR spectrum of **8a** wherein, a signal at 3176 cm^{-1} that corresponds to NH stretching frequency was observed. Furthermore, its ^{1}H NMR spectrum displayed two singlets at δ 10.02 and 9.07 ppm confirming the presence of two NH groups. Also, two doublets at δ 6.06 and 5.12 ppm were observed for vinylic and allylic protons, respectively of the pyrimidine ring which further supported the proposed structure. Moreover, in all above conversions, the cyclization was evidenced by the complete disappearance of two singlets corresponding to conjugated alkenyl protons of chalcones. In the same way, the synthesis of other derivatives was also confirmed. Additionally, the structures of all target compounds were further established by ^{13}C NMR, mass spectral and elemental analyses. The detailed synthetic procedure and characterization data of all these individual compounds are given as Supplementary data.

The preclinical discovery and development of a new bioactive chemical entity for the treatment of epilepsy rely heavily on the use of predictable animal models. The maximal electroshock (MES)[20] and subcutaneous pentylenetetrazole (scPTZ)[21] screening methods are the two important and routinely used in vivo animal models for the anticonvulsant studies. These two methods are recognized as the 'gold standards' in the early stages of testing. They are claimed to detect new bioactive chemical entities affording