Bioorganic & Medicinal Chemistry Letters 23 (2013) 1502–1506

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

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

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ARTICLE INFO

Article history:
Received 11 September 2012
Revised 29 November 2012
Accepted 12 December 2012
Available online 20 December 2012

Keywords:
Imidazo[1,2-*a*]pyridine
Anticonvulsant activity
Toxicology

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

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http://dx.doi.org/10.1016/j.bmcl.2012.12.035

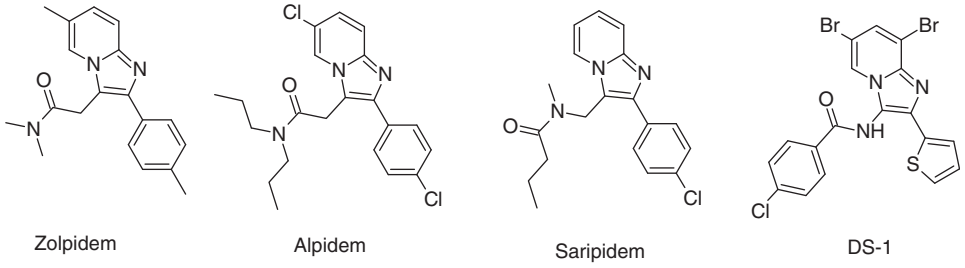
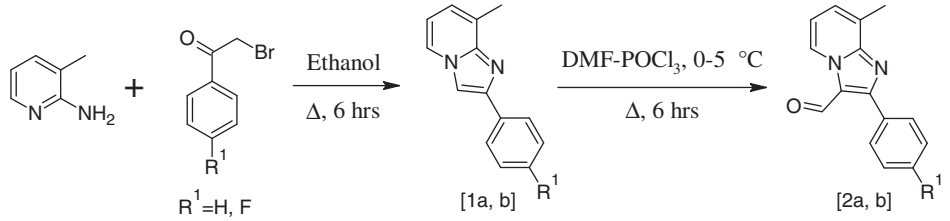


Figure 1. Important imidazo[1,2-*a*]pyridines acting as CNS agents.



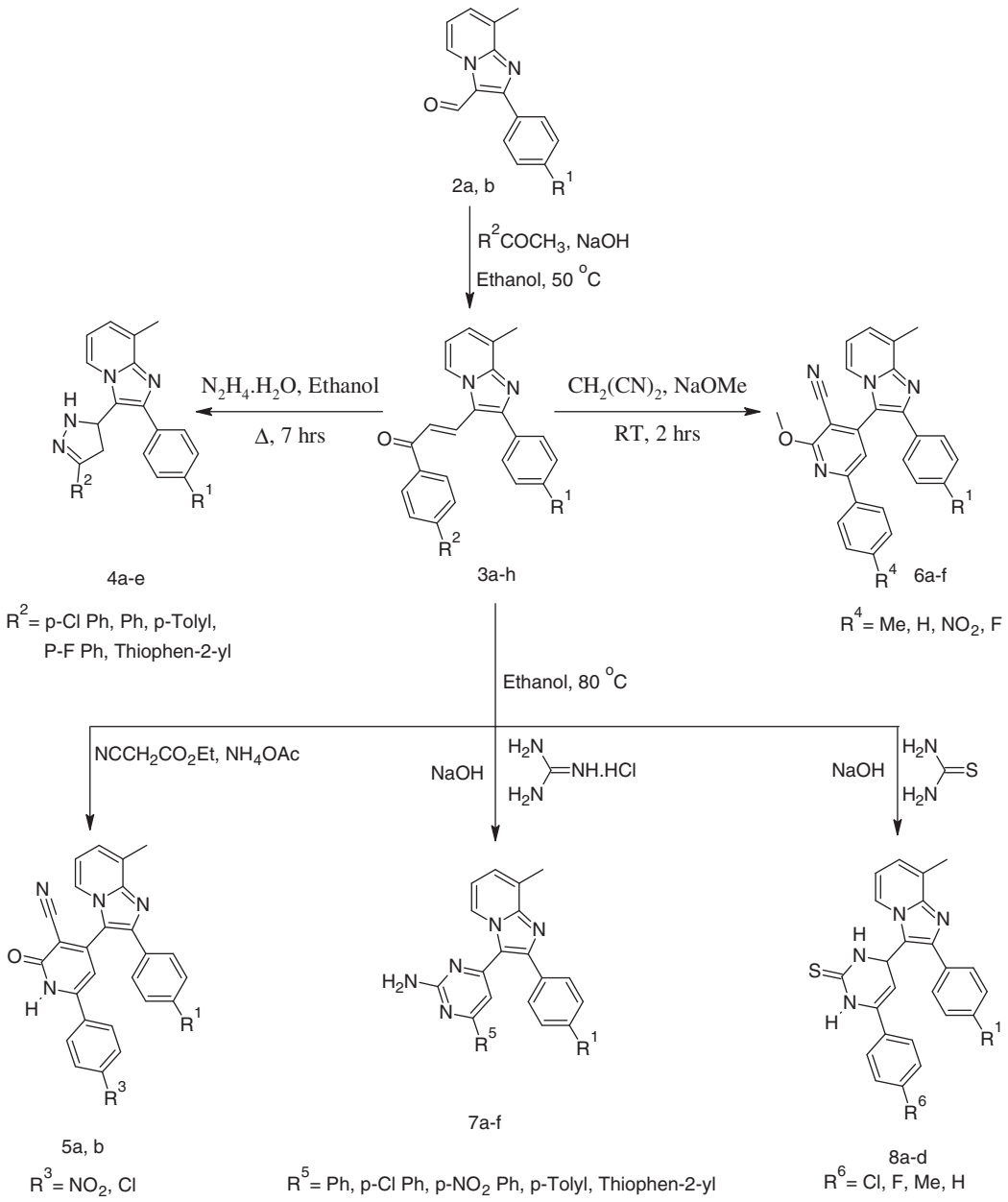
Scheme 1. Synthesis of imidazo[1,2-*a*]pyridine-3-carboxaldehydes.

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



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

protection to generalized tonic–clonic seizures and generalized absence seizures, respectively. Almost all clinically significant AEDs are protective in at least one of these two models.[22] In the same way compounds found to be effective in either of these seizure methods are termed as potential anticonvulsants.[23] In our study also, target compounds were screened for their antiepileptic properties following these methods by administering a single dose (10 mg/kg) of test samples, 0.5 h prior to the study. Further, their toxicity study was carried out by Rotarod method,[24] that measures motor impairment. The toxicity profiles of tested compounds was evaluated after 0.5 and 4 h, by taking three different test doses (10, 50 and 100 mg/kg). The screening results of MES, scPTZ and Rotarod toxicity studies are summarized in Table 1. The experimental protocols used for these in vivo studies are described in Supplementary data.

In MES method, among pyrazoline derivatives **4a**–**e**, compound **4b** carrying fluoro substituent at *para* position on aryl ring attached to 2nd position of imidazo[1,2-*a*]pyridine nuclei displayed enhanced activity with latency period of 10.97 ± 1.74 s, which is significant when compared with that of control (2.18 ± 0.47). Similarly, another fluoro derivative **4a** also showed good anticonvulsant activity (9.15 ± 1.01). However, replacement of fluoro by hydrogen as in **4c**, **4d** and **4e** resulted in decreased anti-epileptic efficacy of the molecules. The cyanopyridone derivatives **5a**, **b** displayed better activity irrespective of substituents present on the molecule indicating that cyanopyridone is an active moiety.[25] In contrast, little less activity was observed for 2-methoxy-3-cyanopyridines **6a**–**f** when compared with cyanopyridone analogues. Here also, compounds **6a** and **6b** displayed good results owing to the presence of fluoro substituent on aryl ring (halo-aryl) attached to imidazopyridine moiety. In spite of halo-aryl group present in **6c**, it resulted relatively less activity which may be attributed to the presence of electron withdrawing nitro group.[26] Further, 2-amino pyrimidine **7a**–**f** and pyrimidine 2-thiones **8a**–**d** exhibited

Table 1
Anticonvulsant and toxicity screening results of target compounds

Sample	R^1	$R^2/R^3/R^4/R^5/R^6$	MES test[a]		scPTZ test[a]		Toxicity studies[b]	
			Duration of tonic extension (s)	Latency (onset of clonus)	Onset times in s (mean ± SEM)		0.5 h	4.0 h
					Conic	Tonic		
Control			15.35 ± 0.60	02.18 ± 0.47	59.2 ± 1.11	385.5 ± 10.90	x	x
Diazepam			—	13.17 ± 1.29	—	—	—	—
4a	F	4-Cl Ph	07.21 ± 1.30	09.45 ± 1.01	158.7 ± 1.54	542.2 ± 6.74	—	—
4b	F	Ph	06.54 ± 1.14	10.97 ± 1.74	149.3 ± 2.24	528.2 ± 4.85	—	—
4c	H	4-Me Ph	07.22 ± 1.32	09.28 ± 1.11	126.7 ± 1.74	532.5 ± 4.81	x	x
4d	H	4-F Ph	07.15 ± 1.07	09.25 ± 1.15	79.32 ± 1.23	426.8 ± 3.23	x	x
4e	H	Thiophen-2-yl	07.27 ± 1.11	09.33 ± 1.25	117.7 ± 1.05	530.8 ± 5.51	—	—
5a	F	NO_2	06.61 ± 1.21	10.88 ± 1.31	171.8 ± 2.22	641.5 ± 6.07	—	100
5b	F	Cl	06.54 ± 1.14	10.97 ± 1.74	129.2 ± 4.17	544.7 ± 8.77	—	—
6a	F	Me	09.84 ± 1.17	07.94 ± 1.53	335.3 ± 4.58	611.5 ± 8.45	—	—
6b	F	H	07.77 ± 1.01	09.90 ± 1.41	171.5 ± 1.83	596.0 ± 9.64	—	—
6c	F	NO_2	07.01 ± 1.15	09.13 ± 1.01	115.7 ± 0.84	469.2 ± 6.09	x	x
6d	H	F	06.96 ± 1.23	10.77 ± 1.33	90.87 ± 1.70	456.7 ± 4.55	—	—
6e	H	NO_2	08.52 ± 1.41	08.72 ± 1.36	79.32 ± 1.23	426.8 ± 3.23	—	—
6f	H	Me	06.85 ± 1.06	10.90 ± 1.44	170.7 ± 1.74	595.7 ± 8.46	—	—
7a	F	4-Cl Ph	09.88 ± 0.98	07.95 ± 1.50	109.7 ± 1.60	480.2 ± 3.84	x	x
7b	F	4-NO_2 Ph	08.67 ± 1.01	08.80 ± 1.32	85.33 ± 1.70	435.8 ± 3.73	x	x
7c	F	4-Me Ph	08.15 ± 1.71	08.16 ± 1.21	171.4 ± 1.74	593.2 ± 8.47	—	—
7d	F	Ph	08.27 ± 1.37	08.11 ± 1.43	115.7 ± 0.85	469.2 ± 6.09	—	—
7e	H	Thiophen-2-yl	08.71 ± 1.25	08.86 ± 1.50	79.50 ± 1.23	426.8 ± 3.22	—	—
7f	H	4-Me Ph	08.52 ± 1.41	08.72 ± 1.36	90.83 ± 1.70	454.7 ± 4.55	—	—
8a	F	Cl	07.77 ± 1.01	09.90 ± 1.41	82.50 ± 1.70	435.0 ± 3.94	x	x
8b	F	H	08.13 ± 1.76	08.04 ± 1.25	107.0 ± 4.32	479.7 ± 7.22	—	—
8c	H	Me	07.45 ± 1.51	09.75 ± 1.32	79.34 ± 1.23	426.5 ± 3.23	—	—
8d	H	F	06.87 ± 1.12	10.91 ± 1.45	90.83 ± 1.70	454.7 ± 4.55	—	—

[a] Results are expressed as mean ± SEM; ($n = 6$). MES and PTZ tests were carried out at 10 mg/kg dose. The mice were examined 0.5 h post ip injection of test samples.
[b] Toxicity study was carried out by Rotarod method at a 10, 50 and 100 mg/kg doses. The values indicate the minimum dose required to exhibit toxicity in at least 50% of mice. (—) indicates the absence of toxicity, while (x) means not tested.

similar trend in their results, wherein compounds **7e** and **8d** containing thiophene and fluoro groups displayed enhanced activity.

On the other hand, the title compounds exhibit better results in PTZ induced anticonvulsant screening test than that of MES method. Many compounds especially, **4a**, **4b**, **5a**, **6a**, **7e** and **8d** exhibit good protection against epilepsy at tested dose (10 mg/kg). In PTZ method also, compounds with fluoro substituent on aryl ring displays delayed onset of clonus–tonus phases, indicating their anticonvulsant efficacy. Particularly, a cyanopyridine derivative **6a**, possessing an electron donating methyl group along with fluoro-aryl moiety exhibit the highest activity with complete protection against seizures. Further, 2-amino pyrimidine derivatives are found to be more active analogues than corresponding pyrimidine-2-thiones, possibly due to more hydrogen bond donor capacity of amine group.

The toxicity study was carried out for most of the compounds by Rotarod method. The study was performed by observing the mice after 0.5 and 4 h of test sample administration. None of the tested samples exhibited toxicity at both the intervals except **5a**, which showed toxicity at a high dose of 100 mg/kg (after 4 h). The toxicity of **5a** is might be due to the presence of nitro group in the molecule. This compound remained non-toxic at 0.5 h interval, indicating that the compound has slow onset of toxicity. Other tested compounds were non-toxic at all tested doses (10, 50 and 100 mg/kg) and at both the intervals, thereby appears to be potential candidates for anticonvulsants.

When we correlate the structures of the test samples and their activity, it appears that presence of 4-fluorophenyl group at 2nd position of imidazo[1,2-*a*]pyridine ring is responsible for enhanced anticonvulsant activity. Additionally, the in vivo results also indicate that the presence of heterocyclic systems at 3rd position improves their efficacy. Further, significant influence on the activity is observed when different substituents are present on these heterocyclic ring systems. The presence of electron rich aryl and halophenyl substituents on these heterocyclic systems has resulted in improved activity whereas less activity has been observed for those possessing electron withdrawing groups. Similarly, motor impairment study shows that electron withdrawing groups such as nitro substituent induces toxicity. Despite the good activity of **4a**, **4b**, **5a**, **5b**, **6a**, **7e** and **8d**, they are less potent when compared with standard drug, diazepam. Nevertheless, the compounds display prominent activity at a small dose of 10 mg/kg without producing toxicity. This clearly indicates that there is a good scope for the development of new imidazo[1,2-*a*]pyridine based potent antiepileptic agents through suitable structural modifications.

In conclusion, new series of imidazo[1,2-*a*]pyridines carrying various heterocyclic systems were conveniently designed and synthesized. These target compounds were confirmed by FTIR, ^{1}H NMR, ^{13}C NMR, mass spectral followed by elemental analyses studies. The final compounds were screened for their in vivo anticonvulsant activities following MES and scPTZ methodologies. Additionally, toxicity study was carried out following Rotarod method and they are found to be non-toxic at all tested doses. Many compounds such as **4a**, **4b**, **5a**, **5b**, **6a**, **7e** and **8d** exhibit the prominent anticonvulsant activity in very small dose, that is at 10 mg/kg. Particularly, compounds possessing 4-fluorophenyl ring attached at 2nd position of imidazo[1.2-*a*]pyridine moiety resulted in enhanced activity. These results confirms that imidazo[1,2-*a*]pyridines carrying 4-fluorophenyl substituent at 2nd position is an appropriate structural feature for significant anticonvulsant properties and it can be used as a template for further modifications and investigations to get new active analogues.

Acknowledgments

The authors are thankful to National Institute of Technology Karnataka, India for financial support, Indian Institute of Science, Bangalore, India for NMR facilities and SAIF, Punjab, SAIF, Shillong for mass spectral facilities.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.12.035.

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