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Facile synthesis of new imidazo[1,2-*a*]pyridines carrying 1,2,3-triazoles via click chemistry and their antiepileptic studies

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ABSTRACT

The present article reports the synthesis and anticonvulsant studies of new 2-arylimidazo[1,2-*a*]pyridines carrying suitably substituted 1,2,3-triazoles as well as their intermediates. The structures of newly synthesized compounds were confirmed by various spectroscopic techniques. The anticonvulsant study was carried out by MES and scPTZ screening methods, while their toxicity study was performed following Rotarod method. The active compounds showed enhanced seizure control in scPTZ method when compared with that of MES method. Compounds **3f**, **4c**, **4f**, **5k**, **5p** and **5w** carrying active pharmacophores exhibited complete protection against seizure and their results were comparable with standard drug diazepam. Majority of new compounds were found to be non-toxic, while few of them showed toxicity at 100 mg/kg. The *c*log*P* values of target compounds are in the range of 3.5–5.3, which confirm their lipophilic nature.

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Epilepsy is a chronic neurological disorder, characterized by the episodic and random occurrence of seizures that affects people of all ages.[1] Such recurrent seizures caused by the synchronized discharges of neurons in the brain lead to abnormal behaviour of affected patients.[2] Being one of the oldest recognized disorders, it is bounded by fear, discrimination, social and frightening manifestations.[3] According to a survey by World Health Organization (WHO), approximately 1% of human population is suffering from this neurological disorder, all over the world.[4] Currently, quite a large number of antiepileptic drugs (AEDs) are available in the market. However, these drugs fail to control seizures in about 30–40% of epileptic patients.[5] Moreover, all the existing AEDs involve long-term and consistent administration and such intake of medicines for a long period of time results in various side effects such as ataxia, nausea, sedation, etc.[6,7] As a result, antiepileptic research involving development of new therapeutic agents has gathered momentum and has become an active research area in medicinal chemistry.

It is observed that most of the antiepileptic drugs, which are in clinical use are neither linked with any particular site of action nor with a known mechanism of action.[8] Many AEDs exhibit their potency via many possible mechanisms of action. The lack of understanding and complexity in mechanism of action certainly affect the development of new candidates as possible AEDs through mechanism-driven designs. So, presently the antiepileptic research mainly focuses on investigation of new anticonvulsant agents through conventional screening and structural modifications rather than mechanism based drug design.

Imidazo[1,2-*a*]pyridines are our choice of research interest, due to their significant CNS activities. They were shown to exhibit selective affinity towards benzodiazepine receptors without producing any considerable side effects.[9] As a result, they appear as effective substitutes for trivial benzodiazepine drugs and hence they are generally used as sedatives, anticonvulsants, hypnotics, anxiolytics and muscle relaxants.[10,11] Interestingly, many imidazo[1,2-*a*]pyridine based drugs such as Zolpidem, Alpidem, Saripidem, etc. have been found to exhibit potency against pentylenetetrazole (PTZ) induced seizures.[12] Their CNS application is dose dependant and particularly, Zolpidem has been reported as a potent anticonvulsant drug at a dose of 1–10 mg/kg.[13] Further, imidazo[1,2-*a*]pyridines containing an aryl substituent at 2-position have been reported as highly CNS active scaffolds.[14] Recently, we reported potential anticonvulsant activity for newly synthesized 2,3-disubstituted imidazo[1,2-*a*]pyridines.[15] Keeping this in view, it has been contemplated to design a new series of heterocyclic hybrids carrying 2-arylimidazo[1,2-*a*]pyridine as a core moiety for investigating their anticonvulsant properties.

Furthermore, 1,4-disubstituted 1,2,3-triazoles are an important class of five membered heterocyclic systems and have gained broad range of scope in medicinal chemistry. They display a number of chemotherapeutic properties such as antifungal,[16] anticancer,[17] anti-tubercular,[18] antiviral,[19] antimicrobial,[20] anti-HSV,[21]

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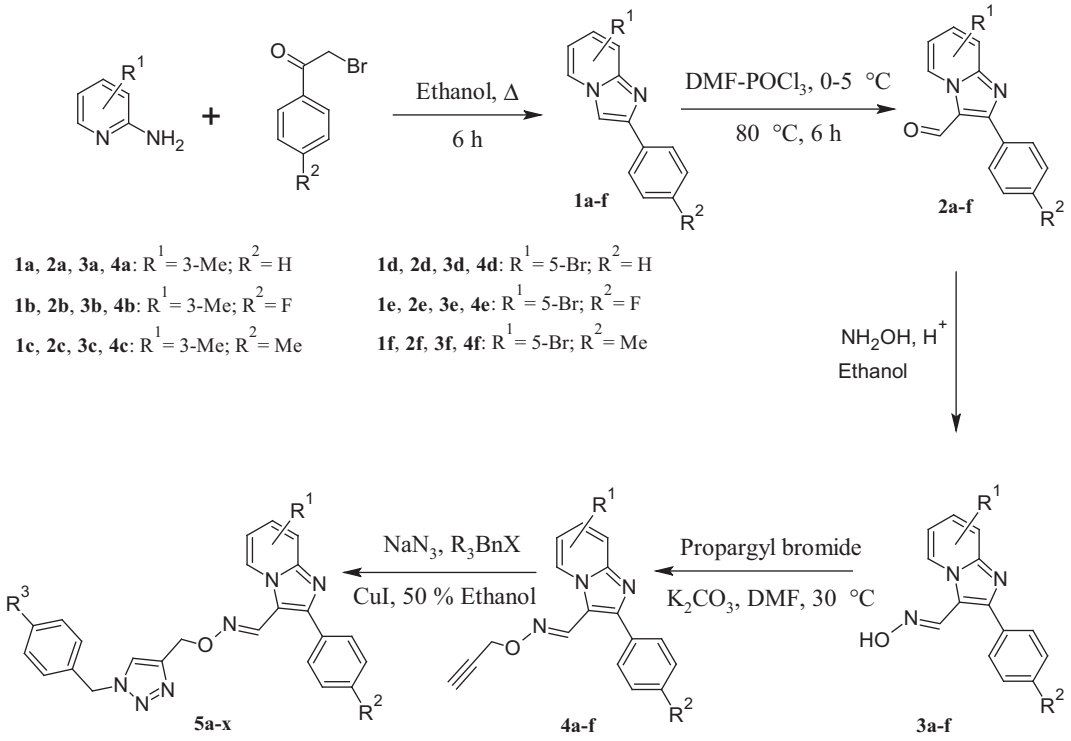
anti-inflammatory,[22] anti-HIV[23] activities along with significant anticonvulsant[24–26] properties. They also find applications as metal binders, agro chemicals, monomers for polymers and bio-medicals.[27,28] Surprisingly, 1,2,3-triazoles are least explored towards antiepileptic research when compared with their structural isomers, 1,2,4-triazole derivatives. Against this background, we have thought of designing new heterocyclic hybrids by incorporating biologically active 1,2,3-triazole system to imidazo[1,2-*a*]pyridine scaffold through imine linkage, with the expectation of enhanced antiepileptic activity for resulting molecules. In this approach, the imidazo[1,2-*a*]pyridine scaffold was conveniently prepared starting from substituted 2-aminopyridines via series of reactions. Later, the required target molecules carrying 1,2,3-triazoles were successfully synthesized by means of 'Click Chemistry' that involves 2+3 cycloaddition of an alkyne and an azide in a cyclic concerted organic reaction sequence. In this reaction, copper iodide was used as a catalyst to get energy efficient and regioselective 1,4-disubstituted 1,2,3-triazole derivatives with high yield.[29] These molecules were later screened for their in vivo antiepileptic properties following MES and scPTZ methods, while neurotoxicity study was performed by Rotarod technique. At the end, their structure–activity relationships (SAR) were established.

The reaction sequence involving the synthesis of required intermediates and title compounds is given in Scheme 1. The core imidazo[1,2-*a*]pyridine nuclei **1a–f** were conveniently synthesized as per procedures followed in our earlier publication,[15] by coupling 2-aminopyridines with different freshly prepared phenacyl bromides[30] under reflux condition. These cyclic products were then made to undergo Vilsmeier–Haack formylation, selectively at free nucleophilic carbon centre on imidazole ring to get the corresponding aldehydes **2a–f** with good yield. These aldehydes were later converted into oximes **3a–f** by reacting them with hydroxyl amine hydrochloride in presence of acid catalyst. The hydroxyl group of oximes **3a–f** was alkylated with propargyl bromide in presence of potassium carbonate to obtain active scaffolds **4a–f**. Finally, the alkyne intermediates **4a–f** were cyclised to new 1,2,3-triazole derivatives **5a–x** by means of one pot multi-component 'Click Chemistry' cyclization, wherein alkynes were treated with sodium azide and an appropriate benzyl halide in presence of 10 mol % of copper iodide as catalyst. These newly synthesized compounds were later purified by column chromatography using methanol and chloroform solvent systems.

The structures of newly synthesized intermediates and target compounds were confirmed by their FTIR, ^{1}H NMR, ^{13}C NMR, mass spectrometry followed by elemental analysis. The analytical data of compounds **1a–f** and **2a–f** are in good agreement with earlier reports. The conversion of aldehyde **2a** into oxime **3a** was confirmed by their FTIR and ^{1}H NMR spectra. In FTIR spectrum of **3a**, the peak due to carboxaldehyde group of **2a** disappeared, while two new prominent peaks at 3112 and 1568 cm^{-1} corresponding to hydroxyl and imine groups, respectively were observed that clearly confirmed the conversion. This conversion was further evidenced by



1a, **2a**, **3a**, **4a**: R^1 = 3-Me; R^2 = H
1b, **2b**, **3b**, **4b**: R^1 = 3-Me; R^2 = F
1c, **2c**, **3c**, **4c**: R^1 = 3-Me; R^2 = Me
1d, **2d**, **3d**, **4d**: R^1 = 5-Br; R^2 = H
1e, **2e**, **3e**, **4e**: R^1 = 5-Br; R^2 = F
1f, **2f**, **3f**, **4f**: R^1 = 5-Br; R^2 = Me

5a: R^1 = 3-Me; R^2 = H; R^3 = Me
5b: R^1 = 3-Me; R^2 = H; R^3 = MeO
5c: R^1 = 3-Me; R^2 = H; R^3 = NO_2
5d: R^1 = 3-Me; R^2 = H; R^3 = CN
5e: R^1 = 3-Me; R^2 = F; R^3 = Me
5f: R^1 = 3-Me; R^2 = F; R^3 = MeO
5g: R^1 = 3-Me; R^2 = F; R^3 = NO_2
5h: R^1 = 3-Me; R^2 = F; R^3 = CN
5i: R^1 = 3-Me; R^2 = Me; R^3 = Me
5j: R^1 = 3-Me; R^2 = Me; R^3 = MeO
5k: R^1 = 3-Me; R^2 = Me; R^3 = NO_2
5l: R^1 = 3-Me; R^2 = Me; R^3 = CN
5m: R^1 = 5-Br; R^2 = H; R^3 = Me
5n: R^1 = 5-Br; R^2 = H; R^3 = MeO
5o: R^1 = 5-Br; R^2 = H; R^3 = NO_2
5p: R^1 = 5-Br; R^2 = H; R^3 = CN
5q: R^1 = 5-Br; R^2 = F; R^3 = Me
5r: R^1 = 5-Br; R^2 = F; R^3 = MeO
5s: R^1 = 5-Br; R^2 = F; R^3 = NO_2
5t: R^1 = 5-Br; R^2 = F; R^3 = CN
5u: R^1 = 5-Br; R^2 = Me; R^3 = Me
5v: R^1 = 5-Br; R^2 = Me; R^3 = MeO
5w: R^1 = 5-Br; R^2 = Me; R^3 = NO_2
5x: R^1 = 5-Br; R^2 = Me; R^3 = CN

Scheme 1. Synthesis of new intermediates and target compounds.

its ^{1}H NMR spectrum, wherein it showed two singlet peaks at δ 11.38 and 8.42 ppm, corresponding to hydroxyl and CH=N protons, respectively. Also, its mass spectrum showed molecular ion peak at 252.8, which is corresponding to M+1 peak of the molecule. Disappearance of hydroxyl peak and appearance of a new peak at 3229 cm^{-1} corresponding to alkyne CH stretching in FTIR spectrum of compound **4a** clearly confirmed the alkylation of **3a** with propargyl bromide. Another prominent peak at 2203 cm^{-1} corresponding to C–C triple bond stretching in its FTIR spectrum further confirmed its formation. ^{1}H NMR spectrum of **4a** displayed two new singlets at δ 4.85 and 3.53 ppm corresponding to CH_2 and CH protons of propargyl group, respectively. Furthermore, the ^{13}C NMR spectrum of **4a** showed peaks at δ 79.8, 77.6 and 61.4 ppm corresponding to two alkyne carbons and one methylene carbon, respectively. Similarly, the cyclization of alkyne **4a** to 1,2,3-triazole **5a** was confirmed by their spectral analysis. Its ^{1}H NMR spectrum showed two singlets at δ 8.48 and 8.35 ppm, corresponding to CH=N and a single aromatic proton of 1,2,3-triazole moiety, respectively. Also, two more characteristic singlets at δ 5.77 and 5.33 ppm, corresponding to two methylene groups present in the molecule were observed. Its ^{13}C NMR spectrum displayed two typical peaks at δ 66.8 and 51.7 ppm attributing to two methylene carbons, which further support the proposed structure. Similarly, structures of other new intermediates **3b–f**, **4b–f** and target molecules **5b–x** were also confirmed based on their spectroscopic analysis. The analytical and characterization data of the intermediates and the final compounds are summarised in the Supplementary data, while their physical data are tabulated in Table 1.

The in vivo animal models are the majorly used and widely accepted methods for the identification of preliminary anticonvulsant property in a newly synthesized compound. The maximal electroshock (MES)[31] and subcutaneous pentylene tetrazole (scPTZ)[32] screening methods are the two most important and routinely used animal models for the anticonvulsant studies. They are believed to detect new bioactive chemical entities affording protection to generalized tonic–clonic seizures as well as absence seizures. It is observed that, almost all clinically significant AEDs are protective in at least one of these two models.[33] In the same way, compounds found to be effective in either of these seizure methods are termed as potential anticonvulsants.[34] As a result, these two methods are recognized as the 'gold standards' in the preliminary screening. Keeping this in view, all the newly synthesized compounds were evaluated for their antiepileptic properties following these methods by taking three different test doses, viz. 20, 40 and 100 mg/kg. Anticonvulsant evaluation was carried out after 0.5 and 4 h of sample administration by inducing convulsion either by electrical shock or PTZ injection. Furthermore, their toxicity study was performed by Rotarod method[35] by taking the same test doses as used for screening studies. These animal studies were performed in accordance with the ethical standards on animal experimentations. The in vivo results of MES, scPTZ and Rotarod toxicity studies are summarized in Table 2. The procedures used for these in vivo studies are given in the Supplementary data.

In MES method, compounds **3c**, **3f**, **4c**, **4f**, **5b**, **5j**, **5k**, **5o**, **5p**, **5s**, **5t** and **5w** were found to be active antiepileptic agents. Amongst them, compounds **4c**, **5k** and **5w** displayed reasonably good activity in both the durations 0.5 and 4 h indicating that they possess rapid onset and long duration of action. Other active compounds showed their activity only after 4 h, which demonstrates their slow onset of action. The final compounds exhibited more activity in

Table 1
Physical data of target compounds **3a–f**, **4a–f** and **5a–x**

Sample	R^1	R^2	R^3	Mol. formula	Mol. wt	Mp (°C)	Yield (%)
3a	3-Me	H	—	$C_{15}H_{13}N_3O$	251.3	251–254	87
3b	3-Me	F	—	$C_{15}H_{12}FN_3O$	269.3	227–229	90
3c	3-Me	Me	—	$C_{16}H_{15}N_3O$	265.3	261–263	83
3d	5-Br	H	—	$C_{14}H_{10}BrN_3O$	316.1	241–243	90
3e	5-Br	F	—	$C_{14}H_9BrFN_3O$	334.1	251–253	90
3f	5-Br	Me	—	$C_{15}H_{12}BrN_3O$	330.2	244–246	88
4a	3-Me	H	—	$C_{18}H_{15}N_3O$	289.3	161–163	92
4b	3-Me	F	—	$C_{18}H_{14}FN_3O$	307.3	151–154	92
4c	3-Me	Me	—	$C_{19}H_{17}N_3O$	303.3	145–147	89
4d	5-Br	H	—	$C_{17}H_{12}BrN_3O$	354.2	164–166	94
4e	5-Br	F	—	$C_{17}H_{11}BrFN_3O$	372.2	158–160	94
4f	5-Br	Me	—	$C_{18}H_{14}BrN_3O$	368.2	155–157	92
5a	3-Me	H	Me	$C_{26}H_{24}N_6O$	436.5	157–159	82
5b	3-Me	H	MeO	$C_{26}H_{24}N_6O_2$	452.5	197–199	84
5c	3-Me	H	NO_2	$C_{25}H_{21}N_7O_3$	467.5	224–226	80
5d	3-Me	H	CN	$C_{26}H_{21}N_7O$	447.5	232–234	91
5e	3-Me	F	Me	$C_{26}H_{23}FN_6O$	454.5	163–165	87
5f	3-Me	F	MeO	$C_{26}H_{23}FN_6O_2$	470.5	213–216	84
5g	3-Me	F	NO_2	$C_{25}H_{20}FN_7O_3$	485.5	207–209	78
5h	3-Me	F	CN	$C_{26}H_{20}FN_7O$	465.5	>300	87
5i	3-Me	Me	Me	$C_{27}H_{26}N_6O$	450.5	149–151	80
5j	3-Me	Me	MeO	$C_{27}H_{26}N_6O_2$	466.5	155–157	78
5k	3-Me	Me	NO_2	$C_{26}H_{23}N_7O_3$	481.5	208–210	76
5l	3-Me	Me	CN	$C_{27}H_{23}N_7O$	461.5	232–235	80
5m	5-Br	H	Me	$C_{25}H_{21}BrN_6O$	501.4	214–216	84
5n	5-Br	H	MeO	$C_{25}H_{21}BrN_6O_2$	517.4	218–220	90
5o	5-Br	H	NO_2	$C_{24}H_{18}BrN_7O_3$	532.4	219–221	82
5p	5-Br	H	CN	$C_{25}H_{18}BrN_7O$	512.4	227–229	89
5q	5-Br	F	Me	$C_{25}H_{20}BrN_6O$	519.4	233–235	85
5r	5-Br	F	MeO	$C_{25}H_{20}BrFN_6O_2$	535.4	161–163	82
5s	5-Br	F	NO_2	$C_{24}H_{17}BrFN_7O_3$	550.4	209–211	81
5t	5-Br	F	CN	$C_{25}H_{17}BrFN_7O$	530.3	235–237	88
5u	5-Br	Me	Me	$C_{26}H_{23}BrN_6O$	515.4	141–143	80
5v	5-Br	Me	MeO	$C_{26}H_{23}BrN_6O_2$	531.4	173–175	84
5w	5-Br	Me	NO_2	$C_{25}H_{20}BrN_7O_3$	546.4	207–209	86
5x	5-Br	Me	CN	$C_{26}H_{20}BrN_7O$	526.4	212–215	91

Table 2
Antiepileptic and toxicity data of final compounds **3a–f**, **4a–f** and **5a–x**

Sample	MES[a]		scPTZ[a]		Toxicity results[a]		*c*log*P*
	0.5	4.0	0.5	4.0	0.5	4.0	
3a	—	—	—	—	—	—	4.04
3b	—	—	—	40	—	—	4.19
3c	—	40	20	40	—	—	4.54
3d	—	—	—	—	—	—	4.42
3e	—	—	40	40	—	—	4.56
3f	—	100	20	20	—	—	4.91
4a	—	—	—	100	—	—	3.83
4b	—	—	—	100	—	—	3.97
4c	20	40	20	20	—	—	4.33
4d	—	—	—	—	—	—	4.20
4e	—	—	40	—	—	—	4.35
4f	—	20	20	40	—	—	4.70
5a	—	—	—	—	—	—	4.49
5b	—	40	40	100	—	—	3.91
5c	—	—	—	—	—	—	3.73
5d	—	—	—	40	—	—	3.42
5e	—	—	—	40	—	—	4.64
5f	—	—	40	40	—	—	4.06
5g	—	—	—	40	100	100	3.88
5h	—	—	—	40	100	100	3.57
5i	—	—	—	—	—	—	4.99
5j	—	100	40	100	—	—	4.41
5k	40	40	20	20	—	—	4.23
5l	—	—	—	100	—	100	3.92
5m	—	—	—	—	—	—	4.86
5n	—	—	—	40	—	—	4.28
5o	—	40	20	40	—	—	4.11
5p	—	100	20	20	—	—	3.80
5q	—	—	—	100	—	—	5.01
5r	—	—	—	—	—	—	4.43
5s	—	100	40	100	—	100	4.25
5t	—	100	—	100	—	100	3.94
5u	—	—	40	100	—	—	5.36
5v	—	—	—	40	—	—	4.78
5w	40	100	20	20	—	—	4.61
5x	—	—	40	40	—	—	4.30
Phenytoin	20	20	x	x	100	100	2.08
Diazepam	x	x	20	20	—	—	3.17

[a] Doses of 20, 40, 100 mg/kg of the compounds were administered and the protection as well as toxicity were measured after 0.5 and 4.0 h. The figures indicate the minimal concentration of sample required to cause either protection or toxicity in more than 50% of mice. The dash (—) indicates the absence of activity/toxicity, while (x) denotes not tested.

scPTZ method than that of MES method, indicating their ability to raise the seizure threshold effectively.[36] In scPTZ method, many tested compounds exhibited rapid onset and long duration of action by displaying activity in both 0.5 and 4 h durations. Particularly, compounds **3f**, **4c**, **4f**, **5k**, **5p** and **5w** exhibited complete protection against seizure and their activity at 20 mg/kg are comparable with that of standard drug diazepam.

By looking at the screening results, it can be seen that substitution by electron donating methyl group on phenyl ring present at 2-position of imidazo[1,2-*a*]pyridine enhances the anticonvulsant property of new oximes **3c**, **3f** and their alkylated derivatives **4c**, **4f**. Substitution of phenyl ring by fluoro group as in compounds **3b**, **3e**, **4b**, **4e** resulted in moderate activity, whereas less activity was observed for unsubstituted phenyl derivatives **3a**, **3d**, **4a**, and **4d**. Similar trend was observed for 1,2,3-triazole derivatives **5a–x** also. Interestingly, when electron donating methyl group was introduced to imidazo[1,2-*a*]pyridine nuclei, the enhanced antiepileptic property was observed for compounds **5a–l** carrying electron rich benzyl substituted triazoles. Amongst **5a–l**, the triazoles carrying methoxybenzyl analogues **5b**, **5f** and **5j** were found to be more active than corresponding methyl derivatives **5a**, **5e** and **5i**, while less activity was observed for those containing electron withdrawing groups such as nitro and cyanobenzyl moieties. However, compound **5k** carrying nitro group showed complete protection from seizures and its result was comparable to standard drug diazepam. On the other hand, contradictory results were observed for 6-bromoimidazo[1,2-*a*]pyridine carrying triazoles **5m–x**, wherein presence of electron withdrawing substituents such as 4-nitrobenzyl (**5o**, **5s** and **5w**) or 4-cyanobenzyl group (**5p**, **5t** and **5x**) on triazole moiety enhanced the activity. Here also substitution of imidazo[1,2-*a*]pyridine ring by 4-methylphenyl ring at 2-position resulted in improved antiepileptic activity. Complete protection was observed for compounds **5p** and **5w** containing cyanobenzyl and nitrobenzyl substituents, respectively.

The neurotoxicity study revealed that majority of tested compounds were non-toxic at all the tested doses. However, compounds **5g**, **5h**, **5l**, **5s** and **5t** were found to be toxic at relatively high dose (100 mg/kg). From the screening results, it can be concluded that neither imidazo[1,2-*a*]pyridine nucleus nor 1,2,3-triazole ring was responsible for their toxicity, but their neurotoxic nature is mainly attributed to the presence of substituents in the hybrid molecules. Also, it has been observed that molecules containing electron withdrawing nitro (**5g**, **5s**) and nitrile substitutents (**5h**, **5l**, **5t**) attached to benzyl ring he exhibited toxicity.

The lipophilicity (*c*log*P*) and hydrophilicity of a molecule play an important role in deciding its drug-likeness, particularly in case of AEDs.[37] It is well-established that there is a direct correlation between anticonvulsant efficiency and lipophilicity data, as compounds with higher lipophilicity can easily penetrate blood–brain barrier (BBB).[38,39] In general, a minimum *c*log*P* value of 2 is very much essential for any good CNS agent to cross BBB effectively.[40] In order to explore the relationship between lipophilicity of the newly synthesized compounds and their antiepileptic activity, their *c*log*P* values were obtained by using ChemDraw Ultra 8.0 Software.[41] The observed values are in the range of 3.5–5.3, indicating that all the compounds are quite lipophilic in nature. Interestingly, the oxime **3f**, that exhibited complete protection against epilepsy possesses higher *c*log*P* value of 4.91. Similarly, oximes **3c** and **3e** with almost equal activity have very close *c*log*P* values of 4.54 and 4.56, respectively. Also, the alkyne **4f** which exhibited complete protection in scPTZ method has high *c*log*P* value of 4.71. However, in case of triazole derivatives no significant correlation could be established between their anticonvulsant efficacy and *c*log*P* values. This clearly suggests that lipophilicity itself is not a sole criterion for a molecule to establish better antiepileptic properties.[42]

In conclusion, new imidazo[1,2-*a*]pyridines carrying suitably substituted 1,2,3-triazoles exhibited enhanced activity in scPTZ method when compared to results of MES method. Further, the majority of tested compounds were found to be non-toxic up to 100 mg/kg. The *c*log*P* values of target compounds are in the range of 3.5–5.3, which clearly indicate the lipophilic nature of final compounds. Amongst tested compounds, **3f**, **4c**, **4f**, **5k**, **5p** and **5w** displayed complete protection against seizures and so, they can be considered as non-toxic lead derivatives.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2013.03.086.

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