Med Chem Res
DOI 10.1007/s00044-013-0887-7

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

New 6-bromoimidazo[1,2-*a*]pyridine-2-carbohydrazide derivatives: synthesis and anticonvulsant studies

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Received: 11 April 2013 / Accepted: 5 December 2013

Abstract In the present work, we report the facile synthesis and anticonvulsant study of new imidazo[1,2-*a*]pyridines carrying biologically active hydrazone functionality (**3a**–**3e**) and suitably substituted 1,2,4-triazole moieties (**4**, **5a**–**5d**, **6**, and **7a**–**7d**). The newly synthesized intermediates and final compounds were characterized by various spectral techniques such as FTIR, ^{1}H NMR, ^{13}C NMR, and mass spectral and elemental analysis studies. The in vivo anticonvulsant study of the target compounds were carried out following maximal electroshock seizure and subcutaneous pentylene tetrazole methods, while their toxicity study was performed following rotarod method by taking 20, 40, and 100 mg/kg dose levels. Most of the new compounds displayed remarkable anticonvulsant properties at these doses. Particularly, compounds **3b** and **4** carrying hydrogen bond donor groups, viz. hydroxyl and amine moieties respectively, exhibited complete protection against seizure and their results are comparable to that of standard drug diazepam. Further, the motor impairment study revealed that all the compounds are nontoxic upto 100 mg/kg.

Keywords Imidazo[1,2-*a*]pyridine · 1,2,4-Triazole · Hydrazone · Anticonvulsant study · Neurotoxicity

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Introduction

Epilepsy is a heterogeneous mixture of disorders characterized by neuronal hyperexcitability and hypersynchronous neuronal firing, which affects about 1 % of the human population (Zhang *et al*., 2012). Regrettably, around 90 % epileptic patients are from developing countries. At present, many antiepileptic drugs (AEDs) are available, but such trivial drugs are able to control the seizure in only about 60 % of patients or they can decrease the incidence in only about 75 % of patients (Gupta *et al*., 2011). In this context, many new generation of AEDs have been developed, which show improved therapeutic actions. But their toxicity and adverse side effects limit their utility (Picot *et al*., 2008; Naithani *et al*., 2010). Moreover, the mechanism of action for many existing drugs is remaining mystery and this significantly affects the development of new anticonvulsants. The discovery of new safer AEDs with proper mechanism of action may circumvent the shortcomings of current anticonvulsants. Due to the lack of knowledge about mechanism of action for various AEDs, structural modification approach appears to be an effective route for the development of new therapeutic agents rather than mechanism-driven design (Obniska *et al*., 2012).

Imidazo[1,2-*a*]pyridines are the important class of CNS agents, acting as the potential sedatives, anticonvulsants, anxiolytics, and hypnotics. They produce relatively less side effects when compared to those of classical benzodiazepines and so, they are claimed to be the efficient substitutes for trivial drugs. Interestingly, the CNS activity of various imidazo[1,2-*a*]pyridine-based drugs are found to be dose dependant and so, they display different CNS activities at various doses. Important imidazo[1,2-*a*]pyridine drugs such as Zolpidem, Alpidem, Saripidem etc. are acting as the potential anticonvulsant agents against PTZ

Published online: 17 December 2013

induced seizures (Tomczuk *et al*., 1991) and particularly, Zolpidem is found to be anticonvulsant active at smaller doses (Vlainic and Pericic, 2010). Recently, we reported significant anticonvulsant activity for new imidazo[1,2-*a*] pyridines carrying aryl substituents at second position (Ulloora *et al*., 2012). Encouraged by this and also, as a part of our continued research on design and synthesis of new antiepileptic agents, in this present work, it has been thought of developing some new anticonvulsants derived from 2-substituted imidazo[1,2-*a*]pyridines.

During the last decade, the 1,2,4-triazole field has grown rapidly, probably owing in part to the medicinal interest which 1,2,4-triazoles command. Several aryl substituted 1,2,4-triazoles were shown to display variety of biological properties. It is well-established that 1,2,4-triazole moiety possesses greater affinity toward epileptic receptors and thereby enhances the anticonvulsant property of its derivatives (Dawood *et al*., 2006; Mokrab *et al*., 2007). The presence of hydrogen bonding donor/acceptor groups on the 1,2,4-triazole moiety and the hydrophobic aryl unit attached to it, are the most probable reasons for their good bio-efficacy (Deng *et al*., 2011). Active anticonvulsant drugs like Alprazolam and Estazolam carry triazole moiety as an important pharmacophore in their structure. Moreover, antiepileptic property of various triazole derivatives were documented in many research articles (Guan *et al*., 2010; Plech *et al*., 2012; Piao *et al*., 2011). In addition to antiepileptic property, they were reported to possess many other pharmacological applications such as antimicrobial (Murthy *et al*., 2012), antiprotozoal (Durust *et al*., 2012), anti-tubercular (Costa *et al*., 2006), anti-inflammatory (Abdel-Megeed *et al*., 2009), and anticancer (Sztanke *et al*., 2008) activities.

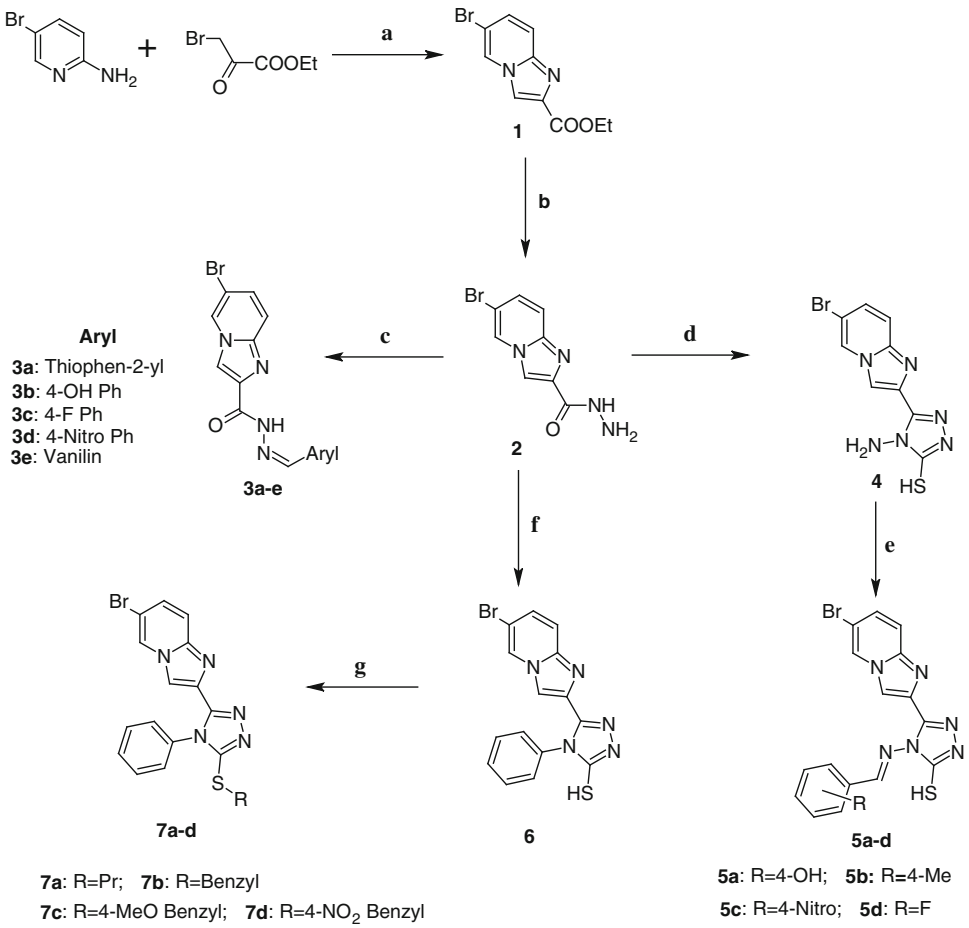
To the best of our knowledge, the synthetic and biological strategy of heterocyclic hybrids containing imidazo[1,2-*a*]pyridine and 1,2,4-triazole moieties in a single organic framework is not reported in the literature. Against this background, it has been contemplated to incorporate a suitably substituted 1,2,4-triazole group at second position of biologically active imidazo[1,2-*a*]pyridine core in our new design, with the expectation of enhanced antiepileptic activity for resulting hybrid molecules. In addition, several heterocyclic hydrazone derivatives were shown to exhibit a good anticonvulsant activity (Kulandasamy *et al*., 2009). Hydrazone linkage possesses hydrogen bond donor, as well as acceptor groups, which are found to enhance the antiepileptic property of resulting molecules, by being involved in hydrogen bonding interactions with receptor site (Dimmock *et al*., 2000). Keeping this in view, it has been also planned to develop new imidazo[1,2-*a*]pyridines carrying hydrazone pharmacophore at second position. Accordingly, new derivatives of imidazo[1,2-*a*]pyridines carrying hydrazone and 1,2,4-triazoles were synthesized following appropriate synthetic routes. The reaction sequence employed for the synthesis of target compounds **3a–3e**, **5a–5d**, and **7a–7d** is given in Scheme 1. The newly synthesized compounds were characterized by FTIR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry followed by elemental analysis studies. Further, the new compounds were screened for their in vivo anticonvulsant properties following maximal electroshock seizure (MES) and subcutaneous pentylene tetrazole (scPTZ) screening methodologies, followed by their Rotarod toxicity study.

Results and discussion

Chemistry

The imidazo[1,2-*a*]pyridine-2-carboxylate derivative **1** was synthesized following reported procedure (Herath *et al*., 2010) by refluxing 5-bromo-2-aminopyridine with ethyl bromopyruvate in ethanol medium. This solid ester product was later reacted with hydrazine hydrate to attain active scaffold hydrazide **2**. The hydrazide **2** was reacted with appropriate aromatic aldehydes in presence of a drop of conc. sulfuric acid as a dehydrating agent, to get a set of hydrazones **3a–3e**. On the other hand, hydrazide **2** was cyclized to 1,2,4-triazole **4**, by stirring hydrazide **2** with carbon disulfide and potassium hydroxide at room temperature followed by reflux with hydrazine hydrate under ethanol media for 6 h. The free amine group of **4** was condensed with different aromatic aldehydes in presence of acidic catalyst to get a set of Schiff bases **5a–5d**. Similarly, hydrazide **2** was refluxed with phenyl isothiocyanate under ethanol medium to get thiosemicarbazide intermediate that later cyclized to 4-phenyl-1,2,4-triazole-3-thiol derivative **6** by stirring with 2 N NaOH at 80 °C. Finally, the free thiol group of **6** was alkylated with appropriate alkyl/benzyl halides in the presence of potassium carbonate to afford **7a–7d**. At the end, all these newly synthesized intermediates and target compounds were purified by recrystallization or column chromatography technique.

The structures of new derivatives were confirmed by their FTIR, ^{1}H NMR, ^{13}C NMR, and mass spectral studies followed by elemental analysis data. The cyclization of 5-bromo-2-aminopyridine into 6-bromoimidazo[1,2-*a*]pyridine-2-carboxylate (**1**) was confirmed by their FTIR and ^{1}H NMR spectral studies. In the FTIR spectrum of compound **1**, the peaks due to amine and ketonic groups of starting materials, viz. 5-bromo-2-aminopyridine and ethyl bromopyruvate, respectively disappeared, while a new peak at 1,697 cm^{-1} corresponding to carboxylate group appeared. Appearance of two singlets in its ^{1}H NMR spectrum at δ 8.94 and 8.37 ppm, corresponding to two aromatic protons present at C-5 and C-3 positions,



Scheme 1 Synthetic routes for target compounds. *a* Ethanol, 80 °C, 6 h; *b* $N_2H_4.H_2O$, Ethanol, 80 °C, 6 h; *c* ArCHO, Ethanol, H^+, 80 °C, 6–8 h, *d*, *i* CS_2, KOH, Ethanol, 25 °C, 8 h; *ii* $N_2H_4.H_2O$, 80 °C, 6 h; *e* ArCHO, Ethanol, H^+, 80 °C, 6–8 h; *f* i PhNCS, Ethanol, 70 °C, 8 h; *ii* 2 N NaOH, 80 °C, 4 h; *g* RBr, K_2CO_3, DMF, 60 °C, 6 h

respectively, also supported the proposed structure. These two protons resonated at down field, because of the inductive field effect offered by adjacent electronegative nitrogen atom. Moreover, appearance of a quartet and a triplet at δ 3.98 and 0.96 ppm clearly confirms the presence of ethyl carboxylate group. In the FTIR spectrum of **2**, new peaks at 3,448, 3,256, and 3,159 cm^{-1} have appeared corresponding to hydrazidic NH and NH_2 groups, respectively. On the other hand, a downshift in the carbonyl stretching frequency was observed from 1,697 to 1,677 cm^{-1}, when ester was converted into hydrazide. The ^1H NMR spectrum of compound **2** showed a new peak at δ 9.89 ppm corresponding to CONH proton, while NH_2 peak appeared at δ 4.28 ppm. The complete disappearance of quartet and a triplet peak of ethyl carboxylate group of compound **1** and appearance of two characteristic peaks corresponding to NH and NH_2 protons, clearly confirm the conversion of **1**–**2**. In the FTIR spectrum of **3a**, the peak due to NH_2 group of hydrazide **2** has disappeared, while peak due to NH stretching has shifted from 3,448 to 3,297 cm^{-1}. Similarly, the carbonyl stretching peak has shifted from 1,677 to 1,670 cm^{-1}, upon coupling with thiophene-2-aldehyde, which evidences the formation of hydrazone **3a**. In the same way, a down field shift was observed in the ^1H NMR spectrum of compound **3a** for NH peak, while a new prominent peak has appeared at δ 8.55 ppm corresponding to vinylic proton of imine group, which clearly confirms the proposed structure. This was further evidenced by its mass spectral data, wherein a mass peak of 350.7 (M+1) was observed which is in accordance with its molecular formula $C_{13}H_9BrN_4OS$.

The cyclization of hydrazide **2** into 4-amino-1,2,4-triazole-3-thiol **4** was confirmed by its ^1H NMR spectrum, which showed characteristic peaks at δ 13.88 and 5.91 ppm corresponding to tautomeric NHCS and NH_2 protons, respectively. The appearance of peak at δ 13.88 ppm due to NH group clearly shows that the triazole ring might be stable in the keto (thione) tautomeric form than thiol form. In the ^1H NMR spectrum of **5a**, the amine peak of **4** at δ 5.91 ppm has disappeared, while a new peak has appeared at δ 9.51 ppm that corresponds to CH=N proton, confirming the conversion of amine into imine. Appearance of another new peak at δ 10.41 ppm corresponding to phenolic group further confirms the conversion. Synthesis of 4-phenyl-1,2,4-triazol-3-thiol derivative **6** was evidenced by its ^1H NMR spectrum, where peaks due to NH and NH_2

Table 1 Physical data of target compounds **3a–7d**

Sample	R/Aryl	Molecular formula	Mol. Wt. (g)	Yield (%)	M.P. (°C)
3a	Thiophen-2-yl	$C_{13}H_9BrN_4OS$	349.2	86	277–279
3b	4-Hydroxyphenyl	$C_{15}H_{11}BrN_4O_2$	359.2	88	>300
3c	4-Fluorophenyl	$C_{15}H_{10}BrFN_4O$	361.2	91	>300
3d	4-Nitrophenyl	$C_{15}H_{10}BrN_5O_3$	388.2	82	>300
3e	Vanilinyl	$C_{16}H_{13}BrN_4O_3$	389.2	85	257–259
4	–	$C_9H_7BrN_6S$	311.2	78	239–241
5a	4-Hydroxy	$C_{16}H_{11}BrN_6OS$	415.3	82	213–215
5b	4-Methyl	$C_{17}H_{13}BrN_6S$	413.3	84	231–233
5c	4-Nitro	$C_{16}H_{10}BrN_7O_2S$	444.3	79	>300
5d	4-Fluoro	$C_{16}H_{10}BrFN_6S$	417.3	85	>300
6	–	$C_{15}H_{10}BrN_5S$	372.2	80	138–140
7a	Propyl	$C_{18}H_{16}BrN_5S$	414.3	86	181–183
7b	Benzyl	$C_{22}H_{16}BrN_5S$	462.4	82	163–165
7c	4-Methoxybenzyl	$C_{23}H_{18}BrN_5OS$	492.4	76	207–209
7d	4-Nitrobenzyl	$C_{22}H_{15}BrN_6O_2S$	507.4	75	264–266

protons of hydrazide **2** have disappeared, while new peaks corresponding to phenyl ring and thiol group present on triazole ring have appeared at δ 7.5–7.1 and 2.07 ppm, respectively. Upon alkylation with propyl bromide, the ^{1}H NMR spectrum of product **7a** displayed three characteristic peaks at δ 3.88, 1.67, and 0.97 ppm corresponding to two methylene and the terminal methyl groups of propyl chain. Its ^{13}C NMR spectrum showed peaks at δ 53.0, 20.77, and 10.86 ppm attributing to those alkyl protons, respectively, confirming the conversion. In the same way, the structures of all the final compounds were confirmed by their characterization data and the same is summarized in the experimental section. The physical data of target compounds are given in Table 1.

Anticonvulsant studies

The in vivo animal models are the majorly used and widely accepted methods for the investigation of preliminary anticonvulsant activity in a newly synthesized compound. The MES (Krall *et al*., 1978) and scPTZ (Clerk *et al*., 1984) screening methods are the most important and widely accepted techniques for the antiepileptic evaluation. These two methods can detect new bioactive chemical entities affording protection to seizures. Interestingly, all the active AEDs are found to be active in at least one among these two screening methods (Dawidowski *et al*., 2012). Similarly, compounds found to be effective in either of these screening methods are generally referred as potential anticonvulsants (Więckowski *et al*., 2012). Therefore in our present study, new derivatives were screened for their antiepileptic properties following these two methods. Further, the toxicity profile of new compounds was evaluated by Rotarod method (Dunham and Miya, 1957). These screening results are summarized in Table 2.

Table 2 Anticonvulsant screening results of final compounds **3a–3e**, **4**, **5a–5d**, **6,** and **7a–7d**

Sample	MES[a]		scPTZ[a]		Toxicity results[a]	
	0.5	4.0	0.5	4.0	0.5	4.0
3a	–	–	40	40	–	–
3b	–	40	20	20	–	–
3c	40	–	20	40	–	–
3d	–	–	100	100	–	–
3e	–	–	40	40	–	–
4	20	40	20	20	–	–
5a	–	40	40	40	–	–
5b	–	–	–	100	–	–
5c	–	–	–	–	–	–
5d	40	–	40	100	–	–
6	–	100	40	40	–	–
7a	–	40	40	40	–	–
7b	–	–	100	100	–	–
7c	–	–	–	100	–	–
7d	–	–	–	–	–	–
Phenytoin	20	20	x	x	100	100
Diazepam	x	x	20	20	–	–

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

[a] Doses of 20, 40,and 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 anticonvulsant results indicated that compounds **3b**, **3c**, **4**, **5a**, **5d**, **6**, **7a**, and **7b** were active in MES method, while all the tested compounds except **5c** and **7d** were active in scPTZ method. Among MES active compounds, hydrazones carrying electron donating groups were found to be more active than those containing electron withdrawing substituents. Compound **4** carrying 4-amino-1,2,4-triazole moiety displayed the highest activity at both the intervals (0.5 and 4 h) indicating its fast onset and long duration of action. On the other hand, most of the compounds exhibited prominent activity in both the intervals as indicated by the results of PTZ method. This clearly shows that they can raise seizure threshold effectively (Stables and Kupferberg, 1997). Compounds **3b** and **4** exhibited complete protection from seizure at 20 mg/kg dose and their results are compared to that of standard drug diazepam.

The in vivo results indicated that the presence of electron donating groups on aryl groups enhances the anticonvulsant property remarkably. This was evidenced by the hydrazone derivatives (**3a**–**3e**), wherein compound **3a**–**3c** and **3e** carrying electron donating groups were more active than compound **3d** that contains nitrophenyl moiety. The compound **3b** carrying 4-hydroxyphenyl group exhibited complete protection from seizure at 20 mg/kg, which may be attributed to the presence of hydrogen bond donating hydroxyl group in the molecule. Similarly, 4-amino-1,2,4-triazole derivative **4** carrying hydrogen bond donor, as well as acceptor groups in the moiety showed similar activity (100 % protection) in scPTZ method. Coupling of the amine group with various aldehydes has led to decrease in anticonvulsant activity. This clearly confirms the importance of amine group for enhanced anticonvulsant activity. In Schiff bases **5a**–**d**, more activity was observed for compounds **5a**, **5b**, and **5d** carrying electron donating groups, viz. hydroxyphenyl, tolyl, and fluorophenyl groups, respectively. In the same way, another 1,2,4-triazole-3-thiol derivative **6** also displayed good activity at 40 mg/kg. The same extent of activity was retained when the thiol group was alkylated with propyl bromide. However, replacement of propyl chain by benzyl rings resulted in considerable decrease in their activity. The reason may be due to the fact that the presence of more bulky groups might disturb the direct ligand-receptor interaction by inducing steric hindrance on the moiety.

The toxicity study revealed that new imidazo[1,2-*a*]pyridines are nontoxic at all tested doses. So, the new compounds can be considered as nontoxic anticonvulsants. In conclusion, the linking of imidazo[1,2-*a*]pyridines with triazole and hydrazone moieties resulted in improved activity without producing any toxicity upto 100 mg/kg. Particularly, those hybrids possessing electron donating and hydrogen bond donor/acceptor groups exhibited pronounced activity. The activity of **3b** and **4** are comparable with those of standard drug diazepam and so, they can be considered as active templates for future developmental studies.

Conclusions

Three new series of imidazo[1,2-*a*]pyridines carrying hydrazone and triazole groups were successfully synthesized. The structures of new derivatives were confirmed by various spectral studies such as FTIR, ^{1}H NMR, ^{13}C NMR, and mass spectral followed by elemental analysis studies. The in vivo anticonvulsant studies of target compounds were performed following MES and scPTZ methods, while their toxicity study was carried out by Rotarod method. The new compounds displayed better activity in scPTZ method than that of MES method, which indicates their ability to raise seizure threshold, effectively. Compounds possessing electron donor groups showed pronounced activity when compared with those of electron acceptor analog. Particularly, compounds **3b** and **4** carrying hydroxyphenyl and 4-amino-1,2,4-triazole-3-thiol groups, respectively, exhibited 100 % protection in scPTZ method, and their results are comparable with those of standard drug diazepam. Moreover, all the final compounds were found to be nontoxic at all tested doses and so, they can be considered as effective anticonvulsant agents.

Experimental

Chemistry

All the chemicals used in the present work were procured from Sigma Aldrich and Lanchaster (UK). All the solvents used were of analytical grade. They were purchased and used as such without any further purification. The progress of the reaction was monitored by thin layer chromatography, performed on a Silica gel 60 F254 coated aluminum sheet. Melting points were determined on open capillaries using a Stuart SMP3 (BIBBY STERLIN Ltd. UK) apparatus and were uncorrected. Infrared spectra were recorded on a Nicolet Avatar 5700 FTIR (Thermo Electron Corporation). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker-400 MHz FT-NMR spectrometer using TMS as internal reference and DMSO-d_6, $CDCl_3$ as solvent. Elemental analyses were performed on a Flash EA1112 CHNS analyzer (Thermo Electron Corporation). Mass spectra (ESI) were recorded on Waters ZQ-4000 liquid chromatography-mass spectrometer. The synthesis of imidazo[1,2-*a*]pyridine-2-carboxylate (**1**), its hydrazide (**2**) and various

hydrazones (**3a**–**3e**) were synthesized following reported procedure (Turan-Zitoni *et al*., 2001).

*Procedure for the synthesis of ethyl 6-bromo-imidazo[1,2-a]pyridine-2-carboxylate (**1**)*

A mixture of 5-bromo-2-aminopyridine (1 g, 5.78 mmol) and ethyl bromopyruvate (1.13 g, 5.78 mmol) in 15 mL of ethanol was refluxed for 6 h. The solvent was removed under reduced pressure, and resulting crude product was quenched into ice cold water with stirring. The solid product was isolated by filtration and dried. The product was later recrystallized from ethyl acetate to obtain pure product.

Yield 84 %, m.p. 63–65 °C. FTIR (ATR, cm^{-1}): 2,897, 2,846, 1,697, 1,538, 1,213. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.94 (s, 1H, ArH), 8.37 (s, 1H, CH), 7.56–7.53 (d, 1H, ArH, $J = 12$ Hz), 7.38–7.35 (d, 1H, ArH, $J = 12$ Hz), 4.00–3.97 (q, 2H, CH_2, $J = 8$, 4 Hz), 0.96–0.91 (t, 3H, CH_3, $J = 10$ Hz). ^{13}NMR (100 MHz, DMSO-d_6): 169.7 (C=O), 150.7 (PyC, C=N), 142.7 (ArC, C=N), 139.3 (PyC, C=N), 124.1(ArC, C=N), 123.3 (PyC), 117.6 (PyC), 115.3 (PyC), 61.8 (OCH_2), 13.8 (CH_3). MS (m/z): 270.3. Anal. Calcd. for $C_{10}H_9BrN_2O_2$: C, 44.63; H, 3.37; N, 10.41. Found: C, 44.59; H, 3.38; N, 10.40.

*Procedure for the synthesis of 6-bromo-imidazo[1,2-a] pyridine-2-carbohydrazide (**2**)*

The ethyl carboxylate derivative **1** (0.8 g, 2.97 mmol) was refluxed with hydrazine hydrate (0.3 g, 6.0 mmol) in ethanolic media for about 6 h. Upon completion of reaction, the reaction mixture was cooled in deep freezer so as to get solid product **2**, that later filtered, dried, and recrystallized from ethanol.

Yield 81 %, m.p. 183–186 °C. FTIR (ATR, cm^{-1}): 3,448, 3,256, 3,159, 3,065, 1,677, 1,627, 1,561, 1,476, 1,279. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.89 (s, 1H, NH), 8.60 (s, 1H, ArH), 8.23 (s, 1H, CH), 7.770–7.447 (d, 1H, ArH, $J = 9.2$ Hz), 7.194–7.171 (d, 1H, ArH, $J = 9.2$ Hz), 4.28 (s, 2H, NH_2). ^{13}NMR (100 MHz, DMSO-d_6): 165.3 (C=O), 150.8 (PyC, C=N), 140.3 (ArC C=N), 138.7 (PyC, C=N), 126.3 (ArC, C=N), 124.7 (PyC), 118.7 (PyC), 116.4 (PyC). MS (m/z): 257.3. Anal. Calcd. for $C_8H_7BrN_4O$: C, 37.67; H, 2.77; N, 21.97. Found: C, 37.65; H, 2.75; N, 21.98.

*General procedure for the synthesis of hydrazones (**3a**–**e**)*

The hydrazide **2** (0.5 g, 1.96 mmol) was treated with thiophene-2-aldehyde (0.22 g, 1.96 mmol) in 10 mL of ethanol solution. A drop of concentrated sulfuric acid was added as a dehydrating agent and the solution was refluxed for 6 h. The reaction vessel was cooled to room temperature and the precipitated product was collected by filtration. The product was washed well with ethanol and purified by column chromatographic technique using hexane: ethyl acetate (9:1) eluting system. Other derivatives were also synthesized following similar procedures.

*6-Bromo-N'-(thiophen-2-ylmethylene)-imidazo[1,2-a] pyridine-2-carbohydrazide (**3a**)* FTIR (ATR, cm^{-1}): 3,297, 3,077, 2,925, 1,670, 1,592, 1,549, 1,476, 1,199. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 11.89 (s, 1H, NH), 8.96 (s, 1H, ArH), 8.55 (s, 1H, CH), 8.46 (s, 1H, CH), 7.631–7.608 (d, 1H, ArH, $J = 9.2$ Hz), 7.511–7.486 (d, 1H, ArH, $J = 9.2$ Hz), 7.39–7.18 (m, 3H, ArH). ^{13}NMR (100 MHz, DMSO-d_6): 164.3 (C=O), 158.2 (PyC, C=N), 146.7 (ArC, C=N), 141.8 (PyC, C=N), 139.2 (ArH, C=N), 131.2 (ArC), 129.2 (ArC), 127.1 (ArC), 118.9 (ArC), 117.6 (PyC), 115.8 (PyC), 107.3 (HC=N). MS (m/z): 350.7. Anal. Calcd. for $C_{13}H_9BrN_4OS$: C, 44.71; H, 2.60; N, 16.04. Found: C, 44.73; H, 2.61; N, 16.04.

*N'-(4-Hydroxybenzylidene)-6-bromo-imidazo[1,2-a] pyridine-2-carbohydrazide (**3b**)* FTIR (ATR, cm^{-1}): 3,323, 3,283, 3,092, 1,668, 1,599, 1,516, 1,434, 1,274. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 11.90 (s, 1H, NH), 9.05 (s, 1H, OH), 8.96 (s, 1H, ArH), 8.57 (s, 1H, CH), 8.47 (s, 1H, CH), 7.712–7.692 (d, 2H, ArH, $J = 8.0$ Hz), 7.630–7.609 (d, 1H, ArH, $J = 8.4$ Hz), 7.514–7.493 (d, 1H, ArH, $J = 8.4$ Hz), 7.223–7.203 (d, 2H, ArH, $J = 8.0$ Hz). ^{13}C NMR (100 MHz, DMSO-d_6): 164.3 (C=O), 161.6 (C–OH), 150.2 (PyC, C=N), 146.7 (ArC, C=N), 142.3 (PyC, C=N), 139.0 (ArC, C=N), 130.7 (ArC), 129.3 (ArC), 127.4 (ArC), 118.6 (ArC), 116.1 (ArC), 115.7 (ArC), 107.3 (HC=N). MS (m/z): 360.3. Anal. Calcd. for $C_{15}H_{11}BrN_4O_2$: C, 50.16; H, 3.09; N, 15.60. Found: C, 50. 14; H, 3.09; N, 15.61.

*N'-(4-Fluorobenzylidene)-6-bromo-imidazo[1,2-a] pyridine-2-carbohydrazide (**3c**)* FTIR (ATR, cm^{-1}): 3,300, 3,137, 3,070, 1,665, 1,600, 1,552, 1,488, 1,201. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 11.94 (s, 1H, NH), 8.96 (s, 1H, ArH), 8.58 (s, 1H, CH), 8.46 (s, 1H, CH), 7.766–7.745 (d, 2H, ArH, $J = 8.4$ Hz), 7.631–7.607 (d, 1H, ArH, $J = 9.6$ Hz), 7.511–7.487 (d, 1H, ArH, $J = 9.6$ Hz), 7.309–7.288 (d, 2H, ArH, $J = 8.4$ Hz). ^{13}C NMR (100 MHz, DMSO-d_6): 164.2 (C=O), 161.8 (ArC, C–F), 158.1 (PyC, C=N), 147.0 (ArC, C=N), 142.4 (PyC, C=N), 139.1 (ArC, C=N), 131.0 (ArC), 129.5 (ArC), 127.4 (ArC), 118.3 (ArC), 115.9 (ArC), 107.1 (HC=N). MS (m/z): 361. 9. Anal. Calcd. for $C_{15}H_{10}BrFN_4O$: C, 49.88; H, 2.79; N, 15.51. Found: C, 49.90; H, 2.78; N, 15.51.

*N'-(4-Nitrobenzylidene)-6-bromo-imidazo[1,2-a]pyridine-2-carbohydrazide (**3d**)* FTIR (ATR, cm^{-1}): 3,297, 3,077, 2,925, 1,670, 1,592, 1,549, 1,476, 1,334, 1,199. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 11.95 (s, 1H, NH), 8.96 (s, 1H, ArH), 8.59 (s, 1H, CH), 8.46 (s, 1H, CH), 8.124–8.103 (d, 2H, ArH, J = 8.4 Hz), 7.632–7.609 (d, 1H, ArH, J = 9.2 Hz), 7.51–7.48 (m, 3H, ArH). ^{13}C NMR (100 MHz, DMSO-d_6): 164.3 (C=O), 161.9 (ArC, C–NO_2), 160.2 (PyC, C=N), 147.3 (ArC, C=N), 142.6 (PyC, C=N), 139.3 (ArC, C=N), 131.4 (ArC), 128.9 (ArC), 127.4 (ArC), 118.7 (ArC), 116.1 (ArC), 107.2 (HC=N). MS (m/z): 389.2. Anal. Calcd. for $C_{15}H_{10}BrN_5O_3$: C, 46.41; H, 2.60; N, 18.04. Found: C, 46.39; H, 2.60; N, 18.03.

*N'-(4-Hydroxy-3-methoxybenzylidene)-6-bromo-imidazo [1,2-a]pyridine-2-carbo hydrazide (**3e**)* FTIR (ATR, cm^{-1}): 3,382, 3,327, 3,063, 2,934, 1,670, 1,583, 1,464, 1,231. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 11.93 (s, 1H, NH), 9.10 (s, 1H, OH), 8.96 (s, 1H, ArH), 8.58 (s, 1H, CH), 8.45 (s, 1H, CH), 7.632–7.610 (d, 1H, ArH, J = 8.8 Hz), 7.511–7.489 (d, 1H, ArH, J = 8.8 Hz), 7.462–7.443 (d, 1H, ArH, J = 7.6 Hz), 7.36 (s, 1H, ArH), 7.289–7.270 (d, 1H, ArH, J = 7.6 Hz), 3.98 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): 164.2 (C=O), 161.4 (ArC), 154.3 (PyC, C=N), 150.2 (ArC, C=N), 146.8 (PyC, C=N), 142.3 (ArC), 139.4 (ArC, C=N), 130.6 (ArC), 129.9 (ArC), 129.2 (ArC), 120.3 (ArC), 118.6 (ArC), 117.9 (ArC), 107.2 (HC=N), 64.2 (OCH_3). MS (m/z): 390.8. Anal. Calcd. for $C_{16}H_{13}BrN_4O_3$: C, 49.38; H, 3.37; N, 14.40. Found: C, 49.35; H, 3.38; N, 14.40.

*Procedure for the synthesis of 4-amino-5-(6-bromoimidazo[1,2-a]pyridin-2-yl)-4H-1,2,4-triazole-3-thiol (**4**)*

An ethanolic solution of KOH was prepared by dissolving 0.2 g (3.6 mmol) of KOH in 10 mL of ethanol. To this solution, hydrazide **2** (0.5 g, 1.96 mmol) and carbon disulfide (0.3 g, 3.94 mmol) were added and the resulting mixture was stirred at ambient temperature for about 8 h to get potassium salt. Later, this mixture was stirred with hydrazine hydrate (0.2 g, 4 mmol) at reflux condition for 6 h. Upon completion of reaction, the solvent was removed and quenched into ice cold water. The mixture was neutralized with hydrochloric acid to get solid product that later isolated by filtration. The product was recrystallised with ethanol-chloroform mixture.

FTIR (ATR, cm^{-1}): 3,174, 3,098, 2,916, 2,771, 1,636, 1,591, 1,410, 1,319, 1,223, 1,167. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 13.88 (s, 1H, H–NC=S), 9.06 (s, 1H, ArH), 8.55 (s, 1H, CH), 7.768–7.747 (d, 1H, ArH, J = 8.4 Hz), 7.164–7.143 (d, 1H, ArH, J = 8.4 Hz), 5.91 (s, 2H, NH_2). ^{13}C NMR (100 MHz, DMSO-d_6): 166.1 (C=S), 142.7 (PyC, C=N), 131.4 (PyC, C=N), 129.3 (ArC, C=N), 127.5 (ArC), 118.4 (ArC), 114.9 (ArC), 106.8 (C–N). MS (m/z): 313.5. Anal. Calcd. for $C_9H_7BrN_6S$: C, 34.74; H, 2.27; N, 27.01. Found: C, 34.71; H, 2.26; N, 27.02.

*General procedure for the synthesis of Schiff bases (**5a**–**5d**)*

A mixture of triazole **4** (0.4 g, 1.29 mmol) with 4-hydroxy benzaldehyde (0.19 g, 1.5 mmol) in 10 mL of ethanol was refluxed for 6 h in presence of a drop of concentrated sulfuric acid. The product **5a** that precipitated out during the course of reaction was filtered, washed with ethanol and dried. The crude product was recrystallized from ethylene dichloride to obtain pure compound. Similarly, other derivatives were also synthesized.

*4-((3-(6-Bromo-imidazo[1,2-a]pyridin-2-yl)-5-mercapto-4H-1,2,4-triazol-4-ylimino) methyl)phenol (**5a**)* FTIR (ATR, cm^{-1}): 3,412, 3,068, 2,884, 2,740, 1,620, 1,502, 1,417, 1,319, 1,148, 1,109. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 14.12 (s, 1H, NH), 10.41 (s, 1H, OH), 9.51 (s, 1H, CH), 9.07 (s, 1H, ArH), 8.40 (s, 1H, CH), 7.861–7.839 (d, 2H, ArH, J = 8.8 Hz), 7.755–7.734 (d, 1H, ArH, J = 8.4 Hz), 7.667–7.645 (d, 2H, ArH, J = 8.8 Hz), 7.454–7.433 (d, 1H, ArH, J = 8.4 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): 177.1 (C=S), 163.2 (ArC, C–OH), 161.9 (PyC, C=N), 144.2 (PyC, C=N), 132.0 (ArC, C=N), 130.1 (ArC), 129.1 (ArC), 127.5 (ArC), 122.7 (ArC), 118.4 (ArC), 115.7 (N=C–N), 107.5 (HC=N). MS (m/z): 416.3. Anal. Calcd. for $C_{16}H_{11}BrN_6OS$: C, 46.28; H, 2.67; N, 20.24. Found: C, 46.25; H, 2.66; N, 20.24.

*4-(4-Methylbenzylideneamino]-5-(6-bromoH-imidazo[1,2-a] pyridin-2-yl)-4H-1,2,4-triazole-3-thiol (**5b**)* FTIR (ATR, cm^{-1}): 3,343, 2,978, 2,885, 2,765, 1,629, 1,521, 1,418, 1,319, 1,259, 1,148. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 14.12 (s, 1H, NH), 9.51 (s, 1H, CH), 9.10 (s, 1H, ArH), 8.41 (s, 1H, CH), 7.75–7.70 (m, 3H, ArH), 7.457–7.437 (d, 1H, ArH, J = 8.0 Hz), 7.234–7.213 (d, 2H, ArH, J = 8.4 Hz), 2.34 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): 176.5 (C=S), 163.2 (PyC, C=N), 161.7 (PyC, C=N), 145.0 (ArC), 143.4 (ArC), 131.4 (ArC), 129.4 (ArC), 127.5 (ArC), 122.3 (ArC), 121.1 (ArC), 118.4 (ArC), 116.1 (N=C–N), 107.5 (HC=N), 14.3 (CH_3). MS (m/z): 414.1. Anal. Calcd. for $C_{17}H_{13}BrN_6S$: C, 49.40; H, 3.17; N, 20.33. Found: C, 49.38; H, 3.16; N, 20.34.

*4-(4-Nitrobenzylideneamino)-5-(6-bromo-imidazo[1,2-a] pyridin-2-yl)-4H-1,2,4-triazole-3-thiol (**5c**)* FTIR (ATR, cm^{-1}): 3,189, 3,031, 2,954, 2,834, 2,772, 1,618, 1,545, 1,247, 1,164. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 14.15 (s, 1H, NH), 9.52 (s, 1H, CH), 9.17 (s, 1H, ArH),

8.41 (s, 1H, CH), 8.176–8.154 (d, 2H, ArH, $J = 8.8$ Hz), 7.59–7.43 (d, 4H, ArH). ^{13}C NMR (100 MHz, DMSO-d_6): 176.5 (C=S), 164.3 (PyC, C=N), 161.8 (PyC, C=N), 160.4 (ArC, C=NO_2), 144.5 (ArC, C=N), 143.2 (ArC, C=N), 131. 8 (ArC), 131.0 (ArC), 128.9 (ArC), 127.8 (ArC), 122.8 (ArC), 116.7 (N=C–N), 107.6 (HC=N). MS (m/z): 445.7. Anal. Calcd. for $C_{16}H_{10}BrN_7O_2S$: C, 43.26; H, 2.27; N, 22.07. Found: C, 43.25; H, 2.25; N, 22.06.

*4-(4-Fluorobenzylideneamino)-5-(6-bromo-imidazo[1,2-a] pyridin-2-yl)-4H-1,2,4-triazole-3-thiol (**5d**)* FTIR (ATR, cm^{-1}): 3,203, 3,048, 2,950, 2,803, 2,734, 1,631, 1,587, 1,510, 1,417, 1,237. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 14.12 (s, 1H, NH), 9.51 (s, 1H, CH), 9.12 (s, 1H, ArH), 8.41 (s, 1H, CH), 7.864–7.843 (d, 2H, ArH, $J = 8.4$ Hz), 7.516–7.494 (d, 1H, ArH, $J = 8.8$ Hz), 7.453–7.431 (d, 1H, ArH, $J = 8.8$ Hz), 7.332–7.311 (d, 2H, ArH, $J = 8.4$ Hz). ^{13}C NMR (100 MHz, DMSO-d_6): 174.1 (C=S), 165.4 (PyC), 163.1 (PyC), 159.6 (ArC, C–F), 144.5 (ArC, C=N), 142.7 (ArC, C=N), 134.6 (ArC), 129.7 (ArC), 123.4 (ArC), 121.3 (ArC), 119.4 (ArC), 115.4 (N=C–N), 107.6 HC=N). MS (m/z): 418.4. Anal. Calcd. for $C_{16}H_{10}BrFN_6S$: C, 46.06; H, 2.42; N, 20.14. Found: C, 46.04; H, 2.43; N, 20.14.

*Procedure for the synthesis of 5-(6-bromoimidazo[1,2-a] pyridin-2-yl)-4-phenyl-4H-1,2,4-triazole-3-thiol (**6**)*

The hydrazide **2** (0.5 g, 1.96 mmol) was refluxed with phenyl isothiocyanate (0.27 g, 1.96 mmol) in ethanol (10 mL) medium for 8 h. The resulting thiosemicarbazide derivatives was isolated through filtration, washed well with ethanol and dried. This intermediate was later treated with 2 N NaOH and stirred the resulting solution at 80 °C for about 4 h. The reaction mixture was cooled to room temperature and quenched to ice cold water while stirring. The mixture was neutralized with conc. hydrochloric acid and the precipitate thus obtained was filtered, washed with excess of cold water. The pure product **6** was obtained by recrystalising crude compound from ethanol.

FTIR (ATR, cm^{-1}): 3,073, 2,361, 1,648, 1,595, 1,529, 1,501, 1,454, 1,357, 1,232. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.96 (s, 1H, ArH), 8.42 (s, 1H, CH), 7.635–7.611 (d, 1H, ArH, $J = 9.6$ Hz), 7.53–7.10 (m, 6H, ArH), 2.07 (s, 1H, SH). ^{13}C NMR (100 MHz, DMSO-d_6): 142.3 (PyC, C=N), 139.2 (PyC, C=N), 138.6 (C–S), 129.4 (ArC), 128.6 (ArC), 127.6 (ArC), 124.7 (ArC), 118.4 (ArC), 115.7 (ArC), 107.0 (C=N). MS (m/z): 372.9. Anal. Calcd. for $C_{15}H_{10}BrN_5S$: C, 48.40; H, 2.71; N, 18.81. Found: C, 48.37; H, 2.70; N, 18.80.

*General procedure for the synthesis of **7a–7d***

A mixture of **6** (0.4 g, 1.07 mmol), propyl bromide (0.2 g, 1.6 mmol) and potassium carbonate (0.3 g, 2.17 mmol) in dry DMF (10 mL) was stirred at 60 °C for 6 h. The reaction mixture was later quenched into ice water with stirring. The precipitated product was filtered, washed with water, and dried. The compound was purified by column chromatography using hexane: ethyl acetate eluent system. In the same way, other compounds were also synthesized.

*6-Bromo-2-(4-phenyl-5-(propylthio)-4H-1,2,4-triazol-3-yl) -imidazo[1,2-a]pyridine (**7a**)* FTIR (ATR, cm^{-1}): 3,091, 2,966, 2,873, 1,577, 1,494, 1,387, 1,229. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.88 (s, 1H, ArH), 8.40 (s, 1H, CH), 7.60–7.18 (m, 7H, ArH), 3.884–3.839 (t, 2H, SCH_2, $J = 9.0$ Hz), 1.67–1.59 (m, 2H, CH_2), 0.975–0.937 (t, 3H, CH_3, $J = 7.6$ Hz). ^{13}C NMR (100 MHz, DMSO-d_6): 162.6 (PyC, C=N), 154.6 (PyC, C=N), 148.1 (C–S), 143.6 (ArC, C=N), 141.2 (ArC, C=N), 130.7 (ArC), 129.8 (ArC), 126.0 (ArC), 124.8 (ArC), 122.6 (ArC), 118.1 (ArC), 113.7 (ArC), 107.1 (C=N), 53.0 (SCH_2), 20.77 (CH_2), 10.86 (CH_3). MS (m/z): 415.3. Anal. Calcd. for $C_{18}H_{16}BrN_5S$: C, 52.18; H, 3.89; N, 16.90. Found: C, 52.16; H, 3.88; N, 16.90.

*2-(5-(Benzylthio)-4-phenyl-4H-1,2,4-triazol-3-yl)-6-bromo-imidazo[1,2-a]pyridine (**7b**)* FTIR (ATR, cm^{-1}): 3,056, 2,916, 1,634, 1,578, 1,492, 1,213. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.88 (s, 1H, ArH), 8.39 (s, 1H, CH), 7.54–7.10 (m, 12H, ArH), 4.84 (s, 2H, SCH_2). ^{13}C NMR (100 MHz, DMSO-d_6): 162.3 (PyC, C=N), 160.2 (PyC, C=N), 154.7 (C–S), 148.6 (ArC, C=N), 143.3 (ArC, C=N), 130.6 (ArC), 129.5 (ArC), 127.4 (ArC), 126.3 (ArC), 125.0 (ArC), 123.5 (ArC), 118.7 (ArC), 117.0 (ArC), 115.6 (ArC), 107.2 (C=N), 68.4 (SCH_2). MS (m/z): 463.6. Anal. Calcd. for $C_{22}H_{16}BrN_5S$: C, 57.15; H, 3.49; N, 15.15. Found: C, 57.12; H, 3.48; N, 15.14.

*2-(5-(4-Methoxybenzylthio)-4-phenyl-4H-1,2,4-triazol-3-yl)-6-bromo-imidazo[1,2-a]pyridine (**7c**)* FTIR (ATR, cm^{-1}): 3,000, 2,938, 2,834, 1,632, 1,579, 1,503, 1,238. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.87 (s, 1H, ArH), 8.39 (s, 1H, CH), 7.641–7.620 (d, 2H, ArH, $J = 8.4$ Hz), 7.543–7.520 (d, 1H, ArH, $J = 9.2$ Hz), 7.51–7.08 (m, 8H, ArH), 4.82 (s, 2H, SCH_2), 4.03 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6): 162.3 (PyC, C=N), 159.6 (ArC, C–OMe), 153.9 (PyC, C=N), 147.6 (C–S), 140.4 (ArC, C=N), 138.7 (ArC, C=N), 130.3 (ArC), 128.7 (ArC), 127.5 (ArC), 124.3 (ArC), 122.6 (ArC), 121.0 (ArC), 119.8 (ArC), 107.6 (C=N), 68.5 (SCH_2), 63.7 (OCH_3). MS (m/z): 493.5. Anal. Calcd. for $C_{23}H_{18}BrN_5OS$: C, 56.10; H, 3.68; N, 14.22. Found: C, 56.11; H, 3.69; N, 14.22.

*2-(5-(4-Nitrobenzylthio)-4-phenyl-4H-1,2,4-triazol-3-yl)-6-bromoH-imidazo[1,2-a]pyridine (**7d**)* FTIR (ATR, cm^{-1}): 3,066, 1,638, 1,585, 1,503, 1,334, 1,279. ^{1}H NMR (DMSO-d_6,

400 MHz, δ ppm): 8.89 (s, 1H, ArH), 8.40 (s, 1H, CH), 8.145–8.124 (d, 2H, ArH, $J = 8.4$ Hz), 7.643–7.622 (d, 2H, ArH, $J = 8.4$ Hz), 7.545–7.521 (d, 1H, ArH, $J = 9.6$ Hz), 7.47–7.09 (m, 6H, ArH), 4.85 (s, 2H, SCH_2). ^{13}C NMR (100 MHz, DMSO-d_6): 163.2 (PyC, C=N), 161.4 (ArC, C–NO_2), 158.7 (PyC, C=N), 154.6 (ArC, C=N), 146.8 (C–S), 140.1 (ArC, C=N), 131.9 (ArC), 129.8 (ArC), 127.5 (ArC), 125.4 (ArC), 123.5 (ArC), 123.0 (ArC), 120.3 (ArC), 119.5 (ArC), 107.3 (C=N), 68.6 (SCH_2). MS (m/z): 508.6. Anal. Calcd. for $C_{22}H_{15}BrN_6O_2S$: C, 52.08; H, 2.98; N, 16.56. Found: C, 52.06; H, 2.99; N, 16.55.

Anticonvulsant studies

Maximal electroshock seizure (MES) test

The samples were injected to mice by suspending them in 2 % solution of Tween-80. Phenytoin was used as standard drug to compare the effectiveness of target samples. Groups of 6–10 male NMRI mice (18–30 g each) were used to screen the samples. Electrical stimuli of 0.2 s in duration (50 mA at 60 Hz) were delivered via corneal electrodes. Animals were previously administered with the test compound by taking doses of 20, 40, and 100 mg/kg. Anticonvulsant activity was assessed 0.5 and 4 h after i.p. injection of test samples. Reduction in the duration of the hindlimb tonic extensor phase was used as positive criterion. Percent inhibition of seizures relative to control was later calculated.

Pentylene tetrazole (PTZ) test

Similar to MES method, a group of six to ten mice were taken for scPTZ screening by using diazepam as a standard drug. Animals were pretreated with various doses (20, 40, and 100 mg/kg) of the test compound. A standard dose of 85 mg/kg of Metrazol (Tetrazole) was injected subcutaneously after 0.5 and 4 h of drug administration. These animals were placed in isolation cages to minimize stress, and observed for the next 30 min to see the absence of a seizure. Delay in onset of clonic phase was taken as criterion for anticonvulsant evaluation.

Toxicity studies

Animals were divided in groups of four animals and trained to stay on an accelerating rotarod that rotates at 10 revolutions per minute. The rod diameter was 3.2 cm. Trained animals (able to stay on the rotarod for at least two consecutive periods of 90 s) were given an i.p injection of the test compounds at doses of 20, 40, and 100 mg/kg. Neurological deficit was indicated by the inability of the animal to maintain equilibrium on the rod for at least 1 min in each of the three trials. The dose at which animal fell off the rod, was determined. These experimental data are presented in Table 2.

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

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