Med Chem Res
DOI 10.1007/s00044-017-2010-y

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

# Design and synthesis of novel 2-(5-(4-aryl)-4,5-dihydro-1*H*-pyrazol-3-yl)-1-(substituted aminomethyl)-1*H*-benzimidazole as potent anticonvulsants

**Pullagura Mallikarjuna Krishna Prasad**[1] · **Raja Sundararajan**[2]

Received: 4 April 2017 / Accepted: 27 July 2017


**Abstract** A variety of novel 2-(5-(4-aryl)-4,5-dihydro-1*H*-pyrazol-3-yl)-1-(substitutedaminomethyl)-1*H*-benzimidazole **5a–5l** have been synthesized from *o*-phenylenediamine by a multi-step synthesis. Antiepileptic screening of the title compounds was performed using maximal electroshock and subcutaneous pentylenetetrazole seizures tests while the neurotoxicity was determined by rotorod test. In the preliminary screening, compounds **5d, 5e, 5f** and **5l** were found active in maximal electroshock model; while **5d, 5e, 5f** and **5k** showed significant antiepileptic activity in subcutaneous pentylenetetrazole seizure model. Further all these five compounds were administered to rats at 30 mg/kg dose in oral route and found that compounds **5e** and **5f** showed better activity than Phenytoin. These compounds **5e** and **5f** revealed protection in maximal electroshock after intraperitoneal administration at a dose of 30 mg/kg (0.5 h and 4.0 h). These compounds also provided protection in the subcutaneous pentylenetetrazole seizure at a dose of 100 mg/kg (0.5 h) and 300 mg/kg (4 h).

**Keywords** Benzimidazole · Pyrazole · Epilepsy · In vivo studies · Neurotoxicity

## Introduction

Epilepsy is a collective term given to group of syndromes that involves spontaneous, intermittent, abnormal electrical activity in the brain, which manifests as seizures (Yogeeswari et al. 2005). Epilepsy affects approximately 1% of the world's population according to epidemiological studies, and often, therapeutic regimens for epileptic patients will involve a change of first line and/or add-on antiepileptic drugs (AEDs, McNamara 2001). The currently used AEDs can be broadly classified into four categories on the basis of the main molecular mechanisms of action, as follow: (a) Enhancement of γ-aminobutyric acid (GABA)-mediated inhibition or other effect on the GABA system, (b) Modulation of voltage-dependent $Na^+$ and/or $Ca^{2+}$ channels, (c) Modulation of synaptic release and (d) Inhibition of synaptic excitation mediated by ionotropic glutamate receptors (Pollard and French 2006). The long established AEDs control seizures in 50% of patients developing partial seizures and in 60–70% of those developing generalized seizures (Lopes Lima 2000; Berk et al. 2001; Duncan 2002). The efficacy of many of the marketed AEDs is greatly compromised by severe side effects, such as ataxia, drowsiness, gingival hyperplasia, gastrointestinal disturbances and megaloblastic anaemia (Spear 2001).

Toxicity, intolerance and lack of efficacy are the limitations of the current AEDs. All of these have stimulated intensive research on novel AEDs. The complex mechanism of action of most AEDs and the insufficient information on the cellular mechanism of epilepsy in human makes it difficult to use rational methodologies in the field of drug discovery. Therefore an another design of new AEDs is based on the existence of different pharmacophores that were established through the analysis of structural characteristics of clinically effective drugs as well as other

**Electronic supplementary material** The online version of this article (doi:10.1007/s00044-017-2010-y) contains supplementary material, which is available to authorized users.

✉ Raja Sundararajan
sraja61@gmail.com

[1] Pfizer Limited, Pfizer Center, Mumbai 400 102 Maharashtra, India

[2] Department of Pharmaceutical Chemistry, GITAM Institute of Pharmacy, GITAM University, Gandhi Nagar, Rushikonda, Visakhapatnam 530 045 Andhra Pradesh, India

Published online: 17 August 2017

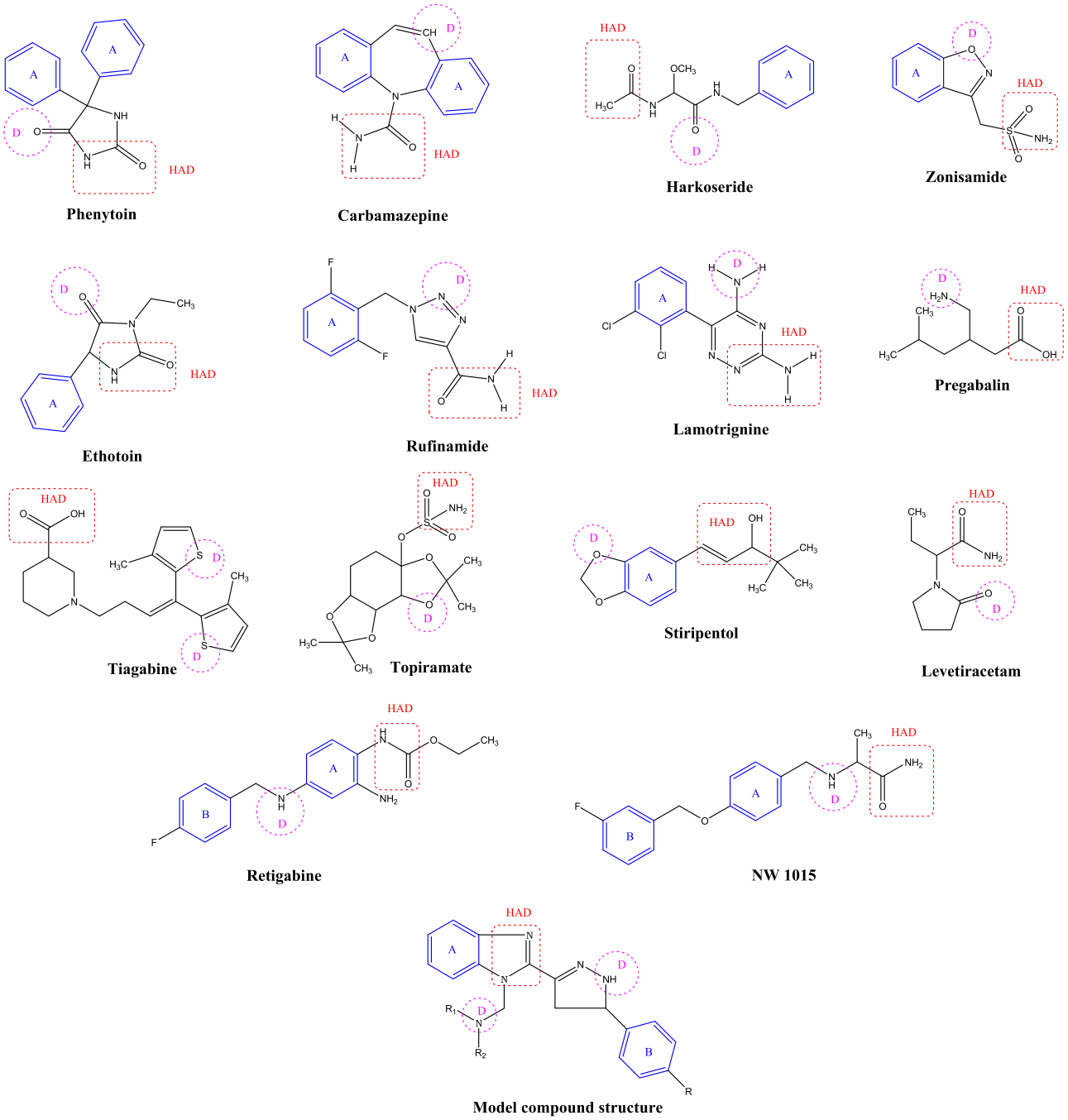



**Fig. 1** Pharmacophonic pattern of well known antiepileptics and model compound with its vital structural features: **a** hydrophobic aryl ring system (HAD) hydrogen bond accepter/donor domain, **d** electron donor moiety and **b** distal aryl ring

antiepileptic compounds (Deng et al. 2010; Karakurt et al. 2010; Alam et al. 2010). In the literatures (Estrada Pena 2000; Bruno-Blanch et al. 2003), it is well documented that one of the important core fragments is defined by presence of (i) Hydrogen acceptor/donor unit (HAD), (ii) One electron donor atom (D) and (iii) A hydrophobic domain (A) (aryl ring substituted/unsubstituted). This common template is found in the structures of well-established first generation AEDs such as phenytoin/carbamazepine or in the second generation AEDs or among the newest drugs (e.g., Felbamate) and the drugs in clinical trial (Fig. 1). Much efforts devoted in the recent years based on the pharmacophore model for the development of novel therapeutics resulted in the availability of several newer drugs (such as tiagabine, lamotrigine, pregabalin, stiripentol, zonisamide, topiramate and levetiracetam) as promising AEDs (Stefan and

Feuerstein 2007). Therefore, continued search for novel AEDs with less toxicity and more selectivity to be an area of investigation in the field of medicinal chemistry.

The importance of heterocyclic compounds has long been recognized in the field of synthetic organic chemistry. Currently, heterocyclic compounds have been extensively studied due to their important properties and applications. It is well known that a number of heterocyclic compounds containing nitrogen exhibited a wide variety of biological activity. Among these compounds, benzimidazole derivatives have become especially noteworthy in recent years due to their wide spectrum of biological activity such as antimicrobial (Sri Krishnanjaneyulu et al. 2014), analgesic (Monika and Chander 2015), anti-inflammatory (Kaur et al. 2014), antiviral (Jun et al. 2005), anticancer (Castro et al. 2011), anti-tubercular (Yoon et al. 2015) and other activities (Siracusa et al. 2008; Salerno et al. 2012; Swiqtkiewicz Olasik 2015; Akhtar et al. 2017). Benzimidazole represents a good template for preparations of some new anticonvulsant agents since such a heterocyclic system possess the required pharmacophoric moiety (Bhrigu et al. 2012; Siddiqui et al. 2016). On the other hand pyrazoles have gained importance because of physiological and pharmacological activities associated with them (Pevarello et al. 2006; Bindi et al. 2010; Alagarsamy and Saravanan 2012; Panneer Selvam et al. 2014). The anticonvulsant action of pyrazole moiety is ascribed to its unique properties of being an electron donor system and ability to act as a constrained pharmacophore at the receptor (GABA, glutamate receptor, and voltage-dependent $Na^+$ channels) site.

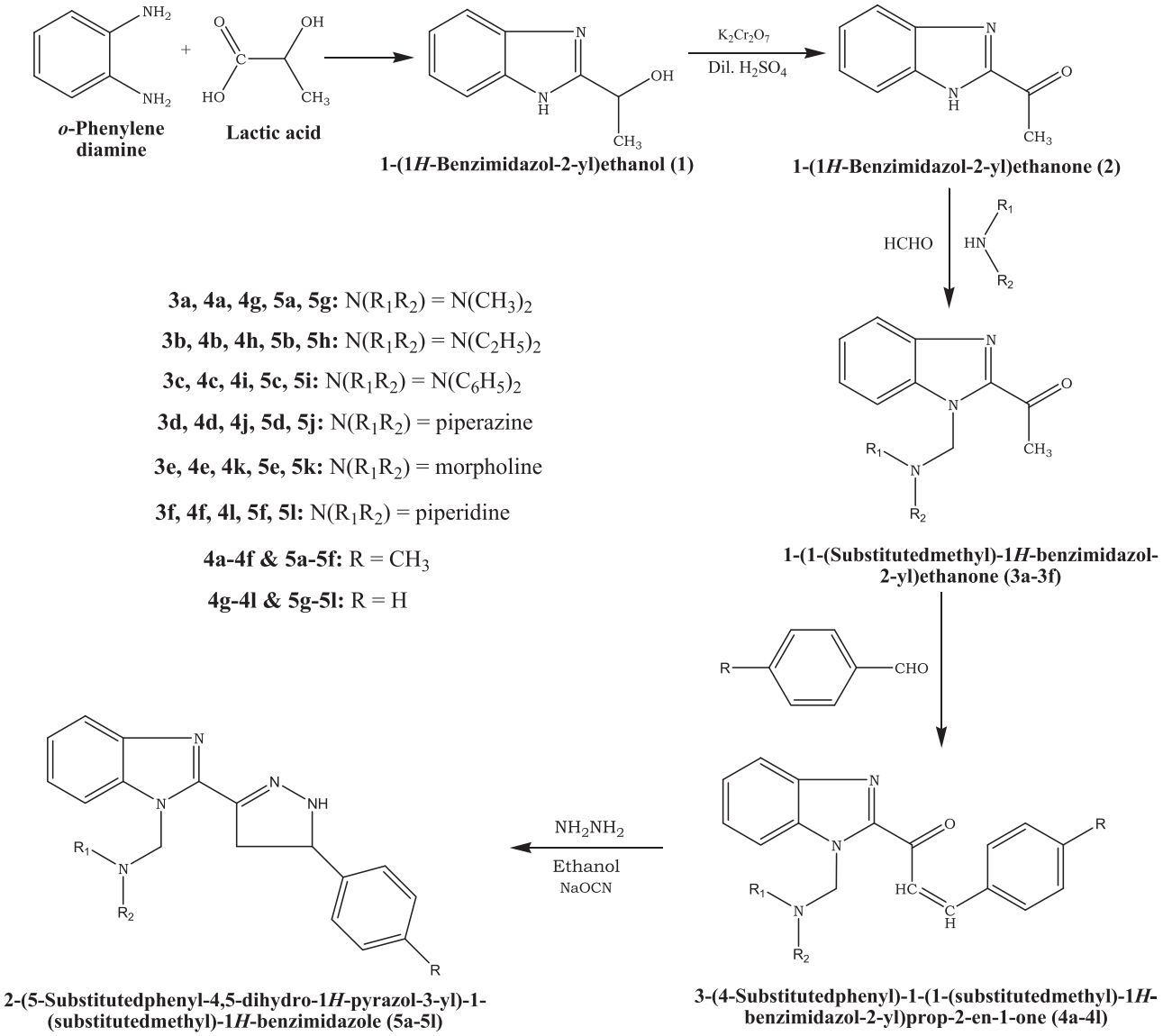
Based on the above findings and considering the wide applications of benzimidazole molecule in medicinal chemistry an attempt has been made to synthesize different benzimidazole derivatives containing 5-(4-aryl)-4,5-dihydro-1*H*-pyrazole moiety as antiepileptic agents.

## Results and discussion

The protocol for the synthesis of target compounds **5a–5l** is shown in Scheme 1. In this study, a series of novel benzimidazole derivatives **5a–5l** were synthesized by substituting different pyrazole at 2-position and various substituted aminomethyl groups at 1-position of benzimidazole. By a multistep synthesis, a sequence of new 2-(5-(4-aryl)-4,5-dihydro-1*H*-pyrazol-3-yl)-1-(substitutedaminomethyl)-1*H*-benzimidazole **5a–5l** were synthesized from *o*-phenylenediamine. Initially *o*-phenylenediamine was treated with lactic acid to obtain 1-(1*H*-benzimidazol-2-yl)ethanol **1** by a ring closure reaction with the elimination of two molecule of water. Latter, obtained 1-(1*H*-benzimidazol-2-yl)ethanol **1** undergone oxidation in presence of potassium dichromate and sulphuric acid and produced 1-(1*H*-benzimidazol-2-yl) ethanone **2**. In the succeeding step, compound **2** was treated with various secondary amines and formaldehyde to produce 1-(1-(substitutedaminomethyl)-1*H*-benzimidazol-2-yl) ethanone **3a–3f** by Mannich base reaction. In the next step, compound **3a–3f** was treated with 4-methylbenzaldehyde/benzaldehyde to get a corresponding chalcone **4a–4l** [3-(4-aryl)-1-(1-(substituted aminomethyl)-1*H*-benzimidazol-2-yl)prop-2-en-1-one]. Finally, title compounds 2-(5-(4-aryl)-4,5-dihydro-1*H*-pyrazol-3-yl)-1-(substitutedaminomethyl)-1*H*-benzimidazole **5a–5l** were synthesized by treating compounds **4a–4l** with hydrazine hydrate by a cyclisation reaction. Thin-layer chromatography (TLC) was performed throughout the reactions to optimize the reactions for purity and completion.

Infrared (IR), nuclear magnetic resonance (NMR), mass spectra, and elemental analyses of the synthesized compounds are in accordance with the assigned structures. The IR spectra of all synthesized compounds showed some characteristic peaks indicating the presence of particular groups. Formation of the 1-(1*H*-benzimidazol-2-yl)ethanol **1** was confirmed by the presence of absorption peak at 3545 and 3356 $cm^{-1}$ in IR due to presence of OH and NH stretching, respectively and appearance of singlet in its $^1$H-NMR spectra at $\delta$ 3.41 and 5.78 ppm for one proton which might be assigned to OH and NH proton, respectively. The formations of oxidized compound **2** was confirmed by the disappearance of absorption peak around 3500 $cm^{-1}$ in IR due to absence of OH stretching and appearance of sharp peak at 1740 $cm^{-1}$ in IR corresponds to C=O stretching. The formation of Mannich base **3a–3f** from compound **2** can be recognized by absence of strong absorption peak around 3350 $cm^{-1}$ in IR due to absence of NH stretching and appearance of singlet in its $^1$H-NMR spectra between $\delta$ 4.42–4.91 ppm for two protons which might be assigned to $CH_2$ linkage. NMR spectrum of compounds **4a–4l** shows two doublets for single protons between $\delta$ 6.20–7.46 ppm corresponds to CH=CH confirms the formation of compounds **4a–4l**. The formation of pyrazole nucleus in title compounds **5a–5l** were confirmed by appearance of absorption bands at 3320–3368 $cm^{-1}$, which can be assignable to NH stretching. This is further supported by a singlet peak in NMR spectrum for a single proton of pyrazole NH at $\delta$ 6.61–6.95 ppm. Further mass spectrum confirmed their purity and molecular weight. The physical characterization of synthesized compounds **5a–5l** is summarized in Table 1.

For the identification of antiepileptic activity in mice, test compounds were administered intraperitoneal (i.p.) and challenged by maximal electroshock (MES) and subcutaneous pentylenetetrazole seizure (*sc*PTZ) test. Compounds found to be active in these seizure challenges are generally regarded to be significantly useful candidates in treatment of partial, generalized and even absence seizures.



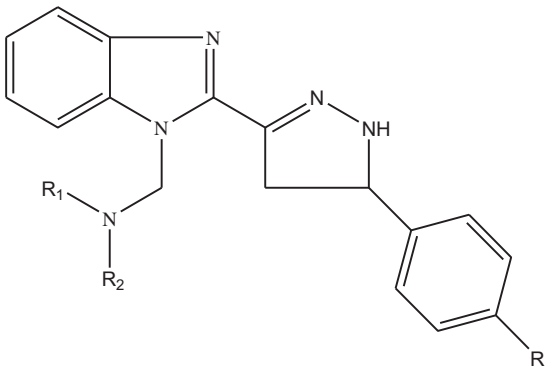

**Scheme 1** Synthesis of 2-(5-Substitutedphenyl−4,5-dihydro-1*H*-pyrazol-3-yl)-1-(substitutedmethyl)-1*H*-benzimidazole

The data regarding the antiepileptic screening of all the compounds are reported in Table 2.

Out of several tested compounds, four compounds **5d, 5e, 5 f** and **5 l** were found to be significantly active in the electroshock investigation as they showed protection at the lowest dose of 30 mg/kg after 0.5 h. But at same dose (30 mg/kg) these compounds continued to show the activity after 4.0 h except **5d** and **5l**, which needs 100 mg/kg, indicating the rapid onset as well as long duration of action of these compounds. The promising activity of the compounds may be attributed to the amines present in substitutedaminomethyl group at 1-position of benzimidazole ring. These compounds contain alicyclic amines such as piperidine, morpholine and piperazine at N-1 of benzimidazole ring. In general it was observed that 5-*p*-tolyl-4,5-dihydro-1*H*-pyrazole derivatives **5a–5f** exhibited better activity than 5-phenyl-4,5-dihydro-1*H*-pyrazole derivatives **5g–5l**. This may be because of the fact that the 5-*p*-tolyl-4,5-dihydro-1*H*-pyrazole derivatives are better fitted into the receptor site. After 0.5 h, at 100 mg/kg compounds **5c, 5j** and **5k** were showed protection indicating the ability of these compounds to protect from seizures at relatively lower dose. These compounds except **5c** were also active after 4.0 h at 100 mg/kg dose; whereas **5c** was found to be active at 300 mg/kg after 4.0 h. Compounds **5a, 5 g** and **5i** were found to be active at a dose of 300 mg/kg either after 0.5 h and/ 4.0 h. Rest of compounds **5b** and **5 h** doesn't showed protection at any of the tested dose.

Most of the compounds exhibited moderate-to-good antiepileptic activity in the *sc*PTZ screening. Compounds

**Table 1** Physical constants of the synthesized compounds **5a–5l**



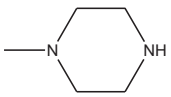
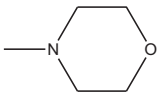
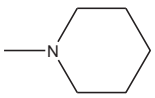
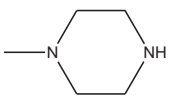
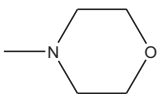
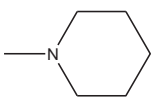

| Compound | –R | –N($R_1R_2$) | Mol. formula | % Yield | mp (°C) |
|---|---|---|---|---|---|
| **5a** | $-CH_3$ | $-N(CH_3)_2$ | $C_{20}H_{23}N_5$ | 82 | 203–205 |
| **5b** | $-CH_3$ | $-N(C_2H_5)_2$ | $C_{22}H_{27}N_5$ | 74 | 230–231 |
| **5c** | $-CH_3$ | $-N(C_6H_5)_2$ | $C_{30}H_{27}N_5$ | 77 | 217–219 |
| **5d** | $-CH_3$ |  | $C_{22}H_{26}N_6$ | 79 | 239–240 |
| **5e** | $-CH_3$ |  | $C_{22}H_{25}N_5O$ | 73 | 196–198 |
| **5f** | $-CH_3$ |  | $C_{23}H_{27}N_5$ | 81 | 245–246 |
| **5g** | –H | $-N(CH_3)_2$ | $C_{19}H_{21}N_5$ | 76 | 222–223 |
| **5h** | –H | $-N(C_2H_5)_2$ | $C_{21}H_{25}N_5$ | 73 | 256–258 |
| **5i** | –H | $-N(C_6H_5)_2$ | $C_{29}H_{25}N_5$ | 72 | 235–236 |
| **5j** | –H |  | $C_{21}H_{24}N_6$ | 78 | 209–211 |
| **5k** | –H |  | $C_{21}H_{23}N_5O$ | 80 | 250–252 |
| **5l** | –H |  | $C_{22}H_{25}N_5$ | 75 | 226–228 |

**Table 2** Antiepileptic activity and neurotoxicity of compounds **5a–5l** administered intraperitoneally to mice

| Compound | MES[a] screening | | *sc*PTZ[b] screening | | NT[c] screening | |
|---|---|---|---|---|---|---|
| | 0.5 h[d] | 4.0 h[d] | 0.5 h[d] | 4.0 h[d] | 0.5 h[d] | 4.0 h[d] |
| **5a** | 300 | 300 | 300 | 300 | ND | ND |
| **5b** | – | – | – | 300 | ND | ND |
| **5c** | 100 | 300 | 300 | – | – | – |
| **5d** | 30 | 100 | 100 | 300 | – | 300 |
| **5e** | 30 | 30 | 100 | 300 | – | – |
| **5f** | 30 | 30 | 100 | 300 | – | – |
| **5g** | 300 | – | 300 | – | ND | ND |
| **5h** | – | – | – | – | ND | ND |
| **5i** | – | 300 | – | 300 | ND | ND |
| **5j** | 100 | 100 | – | 300 | – | 100 |
| **5k** | 100 | 100 | 100 | 300 | 300 | – |
| **5l** | 30 | 100 | 300 | 300 | – | 300 |
| Phenytoin[e] | 30 | 30 | – | – | 100 | 100 |
| Ethosuximide[f] | – | – | 100 | 300 | – | – |

The sign '–' (en dash) represents an absence of activity at maximum dose administered (300 mg/kg)

*ND* not determined

[a] Maximal electroshock test (administered intraperitoneally to mice at doses ranging from 30 to 300 mg/kg)

[b] Subcutaneous pentylenetetrazole test (administered intraperitoneally to mice at doses ranging from 30 to 300 mg/kg)

[c] Neurotoxicity (administered intraperitoneally to mice at doses ranging from 30 to 300 mg/kg)

[d] Time of test after drug administration

[f] Reference drug, data for ethosuximide ref (Rajak et al. 2009)

[e] Reference drug, data for phenytoin ref (Yogeeswari et al. 2005)

[f] Reference drug, data for ethosuximide ref (Rajak et al. 2009)

that revealed protection in the *sc*PTZ test indicated the ability of a substance to increase the seizure threshold. At a dose of 100 mg/kg, compounds **5d, 5e, 5 f** and **5k** showed protection after 0.5 h. But at higher doses (300 mg/kg), these compounds continued to show the activity after 4.0 h indicating the rapid onset as well as long duration of action of these compounds. The above results were comparable to results obtained for ethosuximide which is recognized as reference AED for this screen. Compounds **5a** and **5 l** showed protection at 300 mg/kg after 0.5 h and 4.0 h. Except **5 h** rest of compounds **5b**, **5c**, **5 g**, **5i** and **5j** were active at 300 mg/kg either after 0.5 h or 4.0 h. It was observed that in this method, the most active compound have alicyclic amine substitution at N-1 of benzimidazole ring resulted in increased antiepileptic activity.

Many compounds that are, **5a, 5c–5g, 5j, 5k** and **5 l** were showed activity in either MES or *sc*PTZ model at any one of the tested dose after 0.5 h. The study reveals that 83% of the compounds that is **5a**, **5c–5g** and **5i–5l** were shown activity in MES screening, whereas in *sc*PTZ test except **5 h**, rest of 92% of the compounds were active at any one of the tested dose. These reports revealed that maximum of compounds possessed some *sc*PTZ selectivity.

**Table 3** Antiepileptic activity and toxicity of compounds **5d**, **5e**, **5f**, **5k** and **5l** administered orally (30 mg/kg) to rats

| Compound | MES[a] | | | | | TOX[b] |
|---|---|---|---|---|---|---|
| | 0.25 h[c] | 0.5 h[c] | 1 h[c] | 2 h[c] | 4 h[c] | |
| **5d** | 1/4 | 2/4 | 2/4 | 3/4 | 3/4 | 0/4 (–)[d] |
| **5e** | 1/4 | 2/4 | 3/4 | 4/4 | 4/4 | 0/4 (–)[d] |
| **5f** | 1/4 | 2/4 | 3/4 | 4/4 | 4/4 | 0/4 (–)[d] |
| **5k** | 0/4 | 0/4 | 0/4 | 1/4 | 2/4 | 0/4 (–)[d] |
| **5l** | 1/4 | 2/4 | 2/4 | 3/4 | 3/4 | 0/4 (–)[d] |
| Phenytoin[e] | 1/4 | 4/4 | 3/4 | 3/4 | 3/4 | 0/4 (–)[d] |

[a] Maximal electroshock test (dose of 30 mg/kg was administrated. The data indicate: number of rats protected/number of rats tested)

[b] Neurotoxicity (number of rats protected/number of rats tested)

[c] Time after drug administration

[d] (–) No neurotoxicity at dose tested

[e] Reference drug, data for phenytoin ref (Yogeeswari et al. 2005)

Neurotoxicity study was evaluated by rotorod test in mice. The study revealed that most of the candidate compounds exhibited neurotoxicity at doses higher than widely prescribed drugs Phenytoin or Carbamazepine. But while evaluating an antiepileptic compounds, separation between antiepileptic and neurotoxic dose is desirable. All the compounds evaluated for its neurotoxicity study except **5a**, **5b**, **5 g**, **5 h** and **5i**, due to its poor response in antiepileptic activity. In neurotoxic study at 100 mg/kg dose **5j** was found to be neurotoxic. Compounds **5d, 5k** and **5 l** were showed neurotoxicity at 300 mg/kg, while all other compounds **5c, 5e** and **5 f** were not found to be neurotoxic at maximum administered dose.

Ability to inhibit epilepsy when given by the oral route is a valuable property of candidate antiepilepsy. This screen discloses the time of onset, the approximate time of peak effect and the duration of antiepileptic activity or neurotoxicity. We identified five compounds **5d**, **5e**, **5 f**, **5k** and **5 l** from the initial screen that were further evaluated for oral availability using the MES acute seizure model and neurotoxicity in rats at a dose of 30 mg/kg. The results obtained are presented in Table 3.

From these data it was observed that the most active compounds are **5e** and **5 f** which protected 100% (4/4) of rats at time points 2 h and 4 h, 75% (3/4) at 1 h, 50% (2/4) at 0.5 h and 25% (1/4) at 0.25 h. These molecules were more active and showed longer duration of satisfactory action than Phenytoin. While, compounds **5d** and **5l** were found moderately effective in rat MES oral screen and protected

only 75% (3/4) of rats at time points 2 h and 4 h, 50% (2/4) at 0.5 h and 1 h and 25% (1/4) at 0.25 h. Rest of tested compounds i.e. **5k** were less effective and it protected only 50% (2/4) of tested animals at the time point 4 h and 25% (1/4) at 2 h. All derivatives tested were found devoid of neurotoxicity when given orally at a dose of 30 mg/kg. The in vivo data in rats confirmed absorption of compounds from gastrointestinal tract and also their penetration to central nervous system. The inhibition of electrically induced seizures that is characteristic for Phenytoin and Phenytoin-like drugs may indicate the influence of compounds on voltage depended $Na^+$ channels as the most plausible mechanism of antiepileptic action.

On correlating the structures of the sample candidate with their biological activity, it has been observed that, out of several tested compounds **5a–5l**, five compounds **5d**, **5e**, **5 f**, **5k** and **5 l** exhibited better activity in MES and/ *sc*PTZ test. All the above mentioned compounds were alicyclic amine-substituted derivative. The nature of substituted group on $C_2$ of benzimidazole ring appeared to greatly influence the antiepileptic activity; the 5-*p*-tolyl-4,5-dihydro-1*H*-pyrazole derivatives **5a–5f** exhibited higher antiepileptic activity than the 5-phenyl-4,5-dihydro-1*H*-pyrazole derivatives **5g–5l**. At the same 5-*p*-tolyl-4,5-dihydro-1*H*-pyrazole derivatives, the compounds with alicyclic aminomethyl-substituted benzimidazole ring **5d–5f** exhibited higher antiepileptic activity than the compound with alkyl/aryl aminomethyl substituted benzimidazole ring **5a–5c**. Among alicyclic aminomethyl substituted compounds, **5e** and **5 f** exhibited better activity than other compounds **5d** and **5j–5l**. The increases in antiepileptic activity of test compounds with 5-*p*-tolyl-4,5-dihydro-1*H*-pyrazole derivatives may be attributed to the presence of extra one electron releasing group (methyl) on phenyl ring (which is absent in 5-phenyl-4,5-dihydro-1*H*-pyrazole derivatives) might be accountable for additional bonding with the binding site.

In conclusion, a series of 2-(5-(4-aryl)-4,5-dihydro-1*H*-pyrazol-3-yl)-1-(substitutedaminomethyl)-1*H*-benzimidazole derivatives **5a–5l** were synthesized and characterized by IR, NMR, mass spectroscopy, and elemental analyses. Entire test compounds were evaluated for their antiepileptic activity by MES and *sc*PTZ model along with its neurotoxicity. All title compounds exhibited various degree of above mentioned activities. In this series, generally it was found that 5-*p*-tolyl-4,5-dihydro-1*H*-pyrazole analog showed significant antiepileptic activity than corresponding 5-phenyl-4,5-dihydro-1*H*-pyrazole derivative. Out various aminomethyl substituents tested, alicyclic aminomethyl derivative showed superior antiepileptic activity than alkyl and aromatic aminomethyl derivatives. Among the screened compounds **5d, 5e, 5f** and **5l** were exhibited significant activity in MES screening, while compounds **5d, 5e, 5f** and **5k** showed significant antiepileptic activity in *sc*PTZ model. These five compounds **5d, 5e, 5f, 5k** and **5l** were selected for oral administration in rats at 30 mg/kg dose. Compounds **5e** and **5f** exhibited better antiepileptic activity in oral dose than standard drug phenytoin. Among all test compounds, the most active compound was 1-(morpholinomethyl)-2-(5-*p*-tolyl-4,5-dihydro-1*H*-pyrazol-3-yl)-1*H*-benzimidazole **5e** and 1-(piperidin-1-ylmethyl)-2-(5-*p*-tolyl-4,5-dihydro-1*H*-pyrazol-3-yl)-1*H*-benzimidazole **5f** that revealed protection in the electrically induced seizures at a dose of 30 mg/kg (i. p.) after 0.5 h and 4 h. These molecules also provided protection in the *sc*PTZ at a dose of 100 mg/kg and 300 mg/kg after 0.5 h and 4 h, respectively. Thus the compounds **5e** and **5f** emerged out as the lead molecule with a wide spectrum of antiepileptic activity without any neurotoxicity.

## Experimental

### General

The chemicals and reagents used were obtained from various chemical units Qualigens, E. Merck India Ltd., CDH, and SD Fine Chem. These solvents used were of LR grade and purified before their use. The silica gel G used for analytical chromatography (TLC) was obtained from E. Merck India Ltd. All the melting points were taken in open glass capillary and are uncorrected. $^1$H-NMR and $^{13}$C-NMR spectra were recorded at 500 MHz and 125 MHz, respectively on Bruker Avance-500 NMR spectrometer in $CDCl_3$ using tetramethylsilane for $^1$H-NMR and $CDCl_3$ for $^{13}$C-NMR as an internal standard. The chemical shifts are reported in ppm scale. Mass spectra were obtained on a JEOL-SX-102 instrument using electron impact ionization. All the IR spectra were recorded in KBr pellets on a Jasco FT-IR 410 spectrometer. Elemental analyses were performed on a Perkine Elmer model 240 C analyzer and were within $\pm$ 0.4% of the theoretical values.

*Synthesis of 1-(1H-benzimidazol-2-yl)ethanol (**1**)*

A mixture of *o*-phenylene diamine (10.8 g; 0.1 mol) and lactic acid (13.51 g; 0.15 mol) was taken in round-bottomed flask. To this ethanol (20 ml) was added and refluxed for 5 h in a water bath. The resulting solution was cooled and 10% sodium hydroxide was added slowly with stirring until it is alkaline to litmus. The product separated **1** was filtered, dried and recrystallised. Yield = 73%, m.p. 181–183 °C. IR (KBr) $cm^{-1}$: 3545 (OH), 3356 (NH), 3025 (Ar-CH), 2972 ($CH_3$–CH), 1627 (C=N), 1587 (C=C). $^1$H-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 1.75 (d, 3H, $CH_3$), 3.41 (s, 1H, OH), 4.24 (t, 1H, CH), 5.78 (s, 1H, NH), 7.12–7.90 (m, 4H, Ar-CH). $^{13}$C-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 148.4 (C-2), 135.9

(C-8 & C-9), 120.1 (C-5 & C-6), 109.8 (C-4 & C-7), 76.3 (CH(OH)), 25.4 ($CH_3$). EI-MS *m/z*: 162 ($M^+$). Anal. calcd for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.81; H, 6.19; N, 17.25.

*Synthesis of 1-(1H-benzimidazol-2-yl)ethanone (**2**)*

To a solution of 1-(1*H*-benzimidazol-2-yl)ethanol **1** (8.1 g, 0.05 mol) in dilute sulphuric acid (40 ml), a solution of potassiumdichromate (9.8 g, 0.05 mol) in water (60 ml) was added at room temperature. To this mixture, concentrated sulphuric acid (20 ml) was added in a dropwise fashion, over a period of 20 min. The reaction mixture was stirred vigorously during addition. The separated solid was filtered and wash with water (30 ml). The precipitate obtained was re-suspended in water (50 ml) and treated very carefully with aqueous ammonia to obtain a pH 6.0–6.5. The suspension was stirred for 0.5 h and filtered. The residue **2** was washed with water (3 × 10 ml) and dried. Yield = 70%, m. p. 189–191 °C. IR (KBr) $cm^{-1}$: 3358 (NH), 3024 (Ar-CH), 2971 ($CH_3$-CH), 1740 (C=O), 1647 (C=N), 1601 (C=C). $^1$H-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 2.31 (s, 3H, $CH_3$), 5.19 (s, 1H, NH), 7.342–7.86 (m, 4H, Ar-CH). $^{13}$C-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 195.4 (C=O), 154.8 (C-2), 140.5 (C-8 & C-9), 129.6 (C-5 & C-6), 117.2 (C-4 & C-7), 29.7 ($CH_3$). EI-MS *m/z*: 160 ($M^+$). Anal. calcd for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.68; H, 5.04; N, 17.44.

*Synthesis of 1-(1-(substitutedaminomethyl)-1H-benzimidazol-2-yl)ethanone (**3a–3f**)*

A mixture of 1-(1*H*-benzimidazol-2-yl)ethanone **2** (3.2 g; 0.02 mol), formaldehyde (0.9 g; 0.03 mol) and secondary amine (0.03 mol) in ethanol (30 ml) were stirred mechanically for the period of 1 h. The obtained mixture was then refluxed in a water bath for 4 h. The resulting reaction mixture was cooled and poured in ice cold water with vigorous stirring. The obtained product **3a–3f** was filtered and recrystallised using methanol.

*1-(1-((Dimethylamino)methyl)-1H-benzimidazol-2-yl) ethanone (**3a**)*

Yield = 76%, m.p. 163–165 °C. IR (KBr) $cm^{-1}$: 3014 (Ar-CH), 2950 ($CH_3$–CH), 1734 (C=O), 1670 (C=N), 1614 (C=C). $^1$H-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 1.93 (s, 6H, N($CH_3$)$_2$), 2.87 (s, 3H, $CH_3$), 4.42 (s, 2H, $CH_2$), 6.90–7.65 (m, 4H, Ar-CH). $^{13}$C-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 194.5 (C=O), 148.2 (C-2), 136.7 (C-9), 130.8 (C-8), 125.3 (C-5 & C-6), 119.1 (C-4 & C-7), 73.4 ($CH_2$), 48.5 (N($CH_3$)$_2$), 26.6 ($CH_3$). EI-MS *m/z*: 217 ($M^+$). Anal. calcd for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.13; H, 6.98; N, 19.38.

*1-(1-((Diethylamino)methyl)-1H-benzimidazol-2-yl) ethanone (**3b**)*

Yield = 72%, m.p. 149–151 °C. IR (KBr) $cm^{-1}$: 3037 (Ar-CH), 2958 ($CH_3$–CH), 1718 (C=O), 1643 (C=N), 1609 (C=C). $^1$H-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 1.43 (t, 6H, $CH_3$), 2.87 (t, 4H, $CH_2$), 3.14 (s, 3H, $CH_3$), 4.79 (s, 2H, $CH_2$), 6.74–7.51 (m, 4H, Ar-CH). $^{13}$C-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 187.8 (C=O), 146.0 (C-2), 139.6 (C-9), 134.1 (C-8), 128.2 (C-5 & C-6), 116.5 (C-4 & C-7), 65.3 ($CH_2$), 49.1 (N($\underline{C}H_2CH_3$)$_2$), 24.9 ($CH_3$), 17.8 (N($CH_2\underline{C}H_3$)$_2$). EI-MS *m/z*: 245 ($M^+$). Anal. Calcd for $C_{14}H_{19}N_3O$: C, 68.54; H, 7.81; N, 17.13. Found: C, 68.72; H, 7.82; N, 17.08.

*1-(1-((Diphenylamino)methyl)-1H-benzimidazol-2-yl) ethanone (**3c**)*

Yield = 75%, m.p. 157–158 °C. IR (KBr) $cm^{-1}$: 3051 (Ar-CH), 2974 ($CH_3$–CH), 1720 (C=O), 1648 (C=N), 1617 (C=C). $^1$H-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 2.58 (s, 3H, $CH_3$), 4.91 (s, 2H, $CH_2$), 6.93–8.37 (m, 14H, Ar-CH). $^{13}$C-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 196.1 (C=O), 149.6 (C-2), 149.0 (C-1 of phenyl), 136.8 (C-9), 128.1 (C-3 & C-5 of phenyl), 128.3 (C-8), 120.7 (C-5 & C-6), 119.5 (C-2 & C-6 of phenyl), 118.3 (C-4 of phenyl), 108.4 (C-4 & C-7), 74.8 ($CH_2$), 28.2 ($CH_3$). EI-MS *m/z*: 341 ($M^+$). Anal. Calcd for $C_{22}H_{19}N_3O$: C, 77.40; H, 5.61; N, 12.31. Found: C, 77.16; H, 5.63; N, 12.35.

*1-(1-(Piperazin-1-ylmethyl)-1H-benzimidazol-2-yl) ethanone (**3d**)*

Yield = 70%, m.p. 170–171 °C. IR (KBr) $cm^{-1}$: 3389 (NH), 3017 (Ar-CH), 2950 ($CH_3$–CH), 1735 (C=O), 1661 (C=N), 1626 (C=C). $^1$H-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 2.41 (s, 1H, NH of piperazine), 2.88 (s, 3H, $CH_3$), 2.93–3.40 (m, 8H, $CH_2$ of piperazine), 4.67 (s, 2H, $CH_2$), 7.01–7.78 (m, 4H, Ar-CH). $^{13}$C-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 192.7 (C=O), 152.5 (C-2), 135.3 (C-9), 131.2 (C-8), 126.4 (C-5 & C-6), 117.9 (C-4 & C-7), 64.3 ($CH_2$), 52.4 (C-2 & C-6 of piperazine), 46.8 (C-3 & C-5 of piperazine), 25.0 ($CH_3$). EI-MS *m/z*: 258 ($M^+$). Anal. calcd for $C_{14}H_{18}N_4O$: C, 65.09; H, 7.02; N, 21.69. Found: C, 64.87; H, 7.04; N, 21.75.

*1-(1-(Morpholinomethyl)-1H-benzimidazol-2-yl)ethanone (**3e**)*

Yield = 74%, m.p. 142–144 °C. IR (KBr) $cm^{-1}$: 3049 (Ar-CH), 2934 ($CH_3$–CH), 1726 (C=O), 1653 (C=N), 1607

(C=C), 1084 (C–O–C). $^1$H-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 2.60 (s, 3H, $CH_3$), 2.75–3.38 (m, 8H, $CH_2$ of morpholine), 4.82 (s, 2H, $CH_2$), 6.85–7.42 (m, 4H, Ar-CH). $^{13}$C-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 189.6 (C=O), 150.9 (C-2), 134.4 (C-9), 129.7 (C-8), 122.8 (C-5 & C-6), 109.1 (C-4 & C-7), 67.9 ($CH_2$), 65.0 (C-3 & C-5 of morpholine), 51.6 (C-2 & C-6 of morpholine), 23.3 ($CH_3$). EI-MS *m/z*: 259 ($M^+$). Anal. Calcd for $C_{14}H_{17}N_3O_2$: C, 64.85; H, 6.61; N, 16.20. Found: C, 64.67; H, 6.62; N, 16.25.

*1-(1-(Piperidin-1-ylmethyl)-1H-benzimidazol-2-yl)ethanone (**3f**)*

Yield = 71%, m.p. 175–177 °C. IR (KBr) cm$^{-1}$: 3073 (Ar-CH), 2961 ($CH_3$–CH), 1735 (C=O), 1640 (C=N), 1616 (C=C). $^1$H-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 1.83–2.89 (m, 10H, $CH_2$ of piperidine), 3.25 (s, 3H, $CH_3$), 4.56 (s, 2H, $CH_2$), 7.26–7.99 (m, 4H, Ar-CH). $^{13}$C-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 197.4 (C=O), 145.3 (C-2), 142.1 (C-9), 133.9 (C-8), 124.0 (C-5 & C-6), 113.6 (C-4 & C-7), 64.7 ($CH_2$), 53.1 (C-2 & C-6 of piperidine), 26.3 (C-3 & C-5 of piperidine), 25.7 (C-4 of piperidine), 22.7 ($CH_3$). EI-MS *m/z*: 257 ($M^+$). Anal. calcd for $C_{15}H_{19}N_3O$: C, 70.01; H, 7.44; N, 16.33. Found: C, 70.23; H, 7.42; N, 16.28.

*Synthesis of 3-(4-aryl)-1-(1-(substitutedaminomethyl)-1H-benzimidazol-2-yl)prop-2-en-1-one (**4a-4l**)*

1-(1-(Substitutedaminomethyl)-1*H*-benzimidazol-2-yl)ethanone **3a–3f** (0.01 mol) and 4-methylbenzaldehyde/benzaldehyde (0.01 mol) were dissolved in ethanol (25 ml). To this mixture, 10% sodium hydroxide solution (catalytic quantity) was added slowly and stirred for 4 h in magnetic stirrer. The resulting mixture was then poured into cold water (400 ml) with constant stirring and left overnight in refrigerator. The precipitate obtained **4a–4l** was filtered, washed and recrystallised from ethanol.

*1-(1-((Dimethylamino)methyl)-1H-benzimidazol-2-yl)-3-p-tolylprop-2-en-1-one (**4a**)*

Yield = 79%, m.p. 274–275 °C. IR (KBr) cm$^{-1}$: 3058 (Ar-CH), 2933 ($CH_3$–CH), 1722 (C=O), 1654 (C=N), 1607 (C=C). $^1$H-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 2.15 (s, 6H, N($CH_3$)$_2$), 2.71 (s, 3H, $CH_3$), 4.76 (s, 2H, $CH_2$), 6.68 (d, 1H, –CO–C<u>H</u> = CH–), 7.14 (d, 1H, –CO–CH = C<u>H</u>–), 7.32–7.97 (m, 8H, Ar-CH). $^{13}$C-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 189.1 (C=O), 152.6 (CH=<u>C</u>H), 148.6 (C-2), 145.4 (C-9), 140.2 (C′-4), 138.7 (C-8), 136.5 (C′-1), 132.4 (C′-3 & C′-5), 129.0 (C′-2 & C′-6), 124.9 (C-5 & C-6), 122.3 (<u>C</u>H=CH), 119.5 (C-4 & C-7), 72.8 ($CH_2$), 46.1 (N($CH_3$)$_2$), 28.3 ($CH_3$). EI-MS *m/z*: 319 ($M^+$). Anal. calcd for $C_{20}H_{21}N_3O$: C, 75.21; H, 6.63; N, 13.16. Found: C, 75.07; H, 6.65; N, 13.20.

*1-(1-((Diethylamino)methyl)-1H-benzimidazol-2-yl)-3-p-tolylprop-2-en-1-one (**4b**)*

Yield = 71%, m.p. 285–287 °C. IR (KBr) cm$^{-1}$: 3075 (Ar-CH), 2849 ($CH_3$–CH), 1735 (C=O), 1645 (C=N), 1608 (C=C). $^1$H-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 1.62 (t, 6H, $CH_3$), 2.25 (s, 3H, $CH_3$), 2.74 (t, 4H, $CH_2$), 4.41 (s, 2H, $CH_2$), 6.39 (d, 1H, –CO–C<u>H</u>=CH–), 7.28 (d, 1H, –CO–CH=C<u>H</u>–), 7.43–8.07 (m, 8H, Ar-CH). $^{13}$C-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 192.4 (C=O), 154.7 (CH=<u>C</u>H), 145.7 (C-2), 143.3 (C-9), 139.5 (C′-4), 138.1 (C-8), 135.4 (C′-1), 134.9 (C′-3 & C′-5), 130.6 (C′-2 & C′-6), 127.0 (C-5 & C-6), 126.2 (<u>C</u>H=CH), 124.1 (C-4 & C-7), 74.9 ($CH_2$), 53.0 (N(<u>C</u>H$_2$CH$_3$)$_2$), 26.5 ($CH_3$), 19.4 (N(CH$_2$<u>C</u>H$_3$)$_2$). EI-MS *m/z*: 347 ($M^+$). Anal. calcd for $C_{22}H_{25}N_3O$: C, 76.05; H, 7.25; N, 12.09. Found: C, 76.31; H, 7.23; N, 12.05.

*1-(1-((Diphenylamino)methyl)-1H-benzimidazol-2-yl)-3-p-tolylprop-2-en-1-one (**4c**)*

Yield = 75%, m.p. 253–254 °C. IR (KBr) cm$^{-1}$: 3030 (Ar-CH), 2965 ($CH_3$–CH), 1736 (C=O), 1656 (C=N), 1610 (C=C). $^1$H-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 2.59 (s, 3H, $CH_3$), 4.83 (s, 2H, $CH_2$), 6.64 (d, 1H, –CO–C<u>H</u>=CH–), 7.45 (d, 1H, –CO–CH=C<u>H</u>–), 7.51–8.76 (m, 18H, Ar-CH). $^{13}$C-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 190.6 (C=O), 156.0 (CH=<u>C</u>H), 147.1 (C-2), 146.9 (C-1 of phenyl), 146.7 (C-9), 143.7 (C-3 & C-5 of phenyl), 141.2 (C′-4), 137.6 (C-8), 135.4 (C′-1), 132.0 (C′-3 & C′-5), 129.2 (C′-2 & C′-6), 128.5 (C-5 & C-6), 128.1 (C-2 & C-6 of phenyl), 126.9 (C-4 of phenyl), 125.8 (<u>C</u>H=CH), 121.3 (C-4 & C-7), 68.4 ($CH_2$), 23.8 ($CH_3$). EI-MS *m/z*: 443 ($M^+$). Anal. calcd for $C_{30}H_{25}N_3O$: C, 81.24; H, 5.68; N, 9.47. Found: C, 81.48; H, 5.67; N, 9.49.

*1-(1-(Piperazin-1-ylmethyl)-1H-benzimidazol-2-yl)-3-p-tolylprop-2-en-1-one (**4d**)*

Yield = 82%, m.p. 291–293 °C. IR (KBr) cm$^{-1}$: 3326 (NH), 3075 (Ar-CH), 2916 ($CH_3$–CH), 1735 (C=O), 1644 (C=N), 1608 (C=C). $^1$H-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 1.84 (s, 1H, NH of piperazine), 2.10 (s, 3H, $CH_3$), 2.73–3.85 (m, 8H, $CH_2$ of piperazine), 4.97 (s, 2H, $CH_2$), 6.46 (d, 1H, –CO–C<u>H</u>=CH–), 7.12 (d, 1H, –CO–CH=C<u>H</u>–), 7.40–8.19 (m, 8H, Ar-CH). $^{13}$C-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 185.1 (C=O), 152.8 (CH=<u>C</u>H), 149.4 (C-2), 145.7 (C-9), 138.0 (C′-4), 137.2 (C-8), 136.7 (C′-1), 131.9 (C′-3 & C′-5), 128.7 (C′-2 & C′-6), 126.3 (C-5 & C-6), 123.6 (<u>C</u>H=CH), 118.5 (C-4 & C-7), 78.0 ($CH_2$), 50.1 (C-2 & C-6 of piperazine), 44.9 (C-3 & C-5 of

piperazine), 25.2 ($CH_3$). EI-MS *m/z*: 360 ($M^+$). Anal. calcd for $C_{22}H_{24}N_4O$: C, 73.31; H, 6.71; N, 15.54. Found: C, 73.47; H, 6.69; N, 15.50.

*1-(1-(Morpholinomethyl)-1H-benzimidazol-2-yl)-3-p-tolylprop-2-en-1-one (**4e**)*

Yield = 72%, m.p. 241–243 °C. IR (KBr) $cm^{-1}$: 3062 (Ar-CH), 2987 ($CH_3$–CH), 1748 (C=O), 1641 (C=N), 1624 (C=C), 1079 (CO-C). $^1$H-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 2.38 (s, 3H, $CH_3$), 2.69–3.46 (m, 8H, $CH_2$ of morpholine), 4.72 (s, 2H, $CH_2$), 6.27 (d, 1H, –CO–C<u>H</u>=CH–), 7.30 (d, 1H, –CO–CH=C<u>H</u>–), 7.55–8.34 (m, 8H, Ar-CH). $^{13}$C-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 188.7 (C=O), 150.2 (CH=<u>C</u>H), 146.0 (C-2), 143.7 (C-9), 139.4 (C′-4), 136.5 (C-8), 135.8 (C′-1), 130.2 (C′-3 & C′-5), 127.9 (C′-2 & C′-6), 125.6 (C-5 & C-6), 124.1 (<u>C</u>H=CH), 122.8 (C-4 & C-7), 75.5 ($CH_2$), 69.0 (C-3 & C-5 of morpholine), 52.4 (C-2 & C-6 of morpholine), 20.3 ($CH_3$). EI-MS *m/z*: 361 ($M^+$). Anal. calcd for $C_{22}H_{23}N_3O_2$: C, 73.11; H, 6.41; N, 11.63. Found: C, 73.34; H, 6.42; N, 11.59.

*1-(1-(Piperidin-1-ylmethyl)-1H-benzimidazol-2-yl)-3-p-tolylprop-2-en-1-one (**4f**)*

Yield = 77%, m.p. 262–264 °C. IR (KBr) $cm^{-1}$: 3046 (Ar-CH), 2958 ($CH_3$–CH), 1749 (C=O), 1658 (C=N), 1615 (C=C). $^1$H-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 2.01–2.75 (m, 10H, $CH_2$ of piperidine), 2.93 (s, 3H, $CH_3$), 4.50 (s, 2H, $CH_2$), 6.59 (d, 1H, –CO–C<u>H</u>=CH–), 7.46 (d, 1H, –CO–CH=C<u>H</u>–), 7.62–8.58 (m, 8H, Ar-CH). $^{13}$C-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 194.4 (C=O), 152.6 (CH=<u>C</u>H), 148.6 (C-2), 146.3 (C-9), 142.9 (C′-4), 139.2 (C-8), 137.1 (C′-1), 132.4 (C′-3 & C′-5), 128.5 (C′-2 & C′-6), 124.8 (C-5 & C-6), 122.0 (<u>C</u>H=CH), 120.9 (C-4 & C-7), 69.2 ($CH_2$), 52.3 (C-2 & C-6 of piperidine), 29.1 (C-3 & C-5 of piperidine), 27.6 (C-4 of piperidine), 24.7 ($CH_3$). EI-MS *m/z*: 359 ($M^+$). Anal. calcd for $C_{23}H_{25}N_3O$: C, 76.85; H, 7.01; N, 11.69. Found: C, 76.62; H, 7.03; N, 11.72.

*1-(1-((Dimethylamino)methyl)-1H-benzimidazol-2-yl)-3-phenylprop-2-en-1-one (**4g**)*

Yield = 81%, m.p. 248–250 °C. IR (KBr) $cm^{-1}$: 3070 (Ar-CH), 2914 ($CH_3$–CH), 1730 (C=O), 1641 (C=N), 1607 (C=C). $^1$H-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 2.80 (s, 6H, N($CH_3$)$_2$), 4.72 (s, 2H, $CH_2$), 6.37 (d, 1H, –CO–C<u>H</u>=CH–), 7.15 (d, 1H, –CO–CH=C<u>H</u>–), 7.302–8.18 (m, 9H, Ar-CH). $^{13}$C-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 192.0 (C=O), 156.5 (CH=<u>C</u>H), 151.3 (C-2), 145.9 (C-9), 141.7 (C′-4), 140.4 (C-8), 138.9 (C′-1), 137.6 (C′-3 & C′-5), 134.2 (C′-2 & C′-6), 131.8 (C-5 & C-6), 130.5 (<u>C</u>H=CH), 126.2 (C-4 & C-7), 73.1 ($CH_2$), 47.9 (N($CH_3$)$_2$). EI-MS *m/z*: 305 ($M^+$). Anal. calcd for $C_{19}H_{19}N_3O$: C, 74.73; H, 6.27; N, 13.76. Found: C, 74.47; H, 6.28; N, 13.81.

*1-(1-((Diethylamino)methyl)-1H-benzimidazol-2-yl)-3-phenylprop-2-en-1-one (**4h**)*

Yield = 73%, m.p. 281–282 °C. IR (KBr) $cm^{-1}$: 3085 (Ar-CH), 2952 ($CH_3$–CH), 1724 (C=O), 1642 (C=N), 1613 (C=C). $^1$H-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 1.95 (t, 6H, $CH_3$), 2.88 (t, 4H, $CH_2$), 4.68 (s, 2H, $CH_2$), 6.51 (d, 1H, –CO–C<u>H</u>=CH–), 7.24 (d, 1H, –CO–CH=C<u>H</u>–), 7.56–8.23 (m, 9H, Ar-CH). $^{13}$C-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 193.8 (C=O), 153.7 (CH=<u>C</u>H), 150.4 (C-2), 147.6 (C-9), 140.1 (C′-4), 139.5 (C-8), 137.9 (C′-1), 134.3 (C′-3 & C′-5), 130.6 (C′-2 & C′-6), 126.0 (C-5 & C-6), 123.4 (<u>C</u>H=CH), 119.2 (C-4 & C-7), 70.6 ($CH_2$), 48.1 (N(<u>C</u>$H_2$$CH_3$)$_2$), 21.8 (N($CH_2$<u>C</u>$H_3$)$_2$). EI-MS *m/z*: 333 ($M^+$). Anal. calcd for $C_{21}H_{23}N_3O$: C, 75.65; H, 6.95; N, 12.60. Found: C, 75.91; H, 6.93; N, 12.61.

*1-(1-((Diphenylamino)methyl)-1H-benzimidazol-2-yl)-3-phenylprop-2-en-1-one (**4i**)*

Yield = 70%, m.p. 258–259 °C. IR (KBr) $cm^{-1}$: 3032 (Ar-CH), 2974 ($CH_3$–CH), 1737 (C=O), 1653 (C=N), 1627 (C=C). $^1$H-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 4.46 (s, 2H, $CH_2$), 6.20 (d, 1H, –CO–C<u>H</u>=CH–), 7.38 (d, 1H, –CO–CH=C<u>H</u>–), 7.44–8.02 (m, 19H, Ar-CH). $^{13}$C-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 186.2 (C=O), 150.4 (CH=<u>C</u>H), 142.7 (C-2), 141.2 (C-1 of phenyl), 140.4 (C-9), 137.3 (C-3 & C-5 of phenyl), 134.8 (C′-4), 132.1 (C-8), 129.2 (C′-1), 125.6 (C′-3 & C′-5), 123.0 (C′-2 & C′-6), 120.3 (C-5 & C-6), 120.0 (C-2 & C-6 of phenyl), 119.2 (C-4 of phenyl), 118.5 (<u>C</u>H=CH), 116.8 (C-4 & C-7), 75.1 ($CH_2$). EI-MS *m/z*: 429 ($M^+$). Anal. calcd for $C_{29}H_{23}N_3O$: C, 81.09; H, 5.40; N, 9.78. Found: C, 81.35; H, 5.38; N, 9.75.

*3-Phenyl-1-(1-(piperazin-1-ylmethyl)-1H-benzimidazol-2-yl)prop-2-en-1-one (**4j**)*

Yield = 78%, m.p. 269–271 °C. IR (KBr) $cm^{-1}$: 3323 (NH), 3068 (Ar-CH), 2955 ($CH_3$–CH), 1694 (C=O), 1642 (C=N), 1607 (C=C). $^1$H-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 2.46 (s, 1H, NH of piperazine), 3.01–3.78 (m, 8H, $CH_2$ of piperazine), 4.63 (s, 2H, $CH_2$), 6.45 (d, 1H, –CO–C<u>H</u>=CH–), 7.16 (d, 1H, –CO–CH=C<u>H</u>–), 7.49–8.31 (m, 9H, Ar-CH). $^{13}$C-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 195.7 (C=O), 155.3 (CH=<u>C</u>H), 148.6 (C-2), 144.0 (C-9), 140.9 (C′-4), 138.2 (C-8), 136.8 (C′-1), 134.3 (C′-3 & C′-5), 128.8 (C′-2 & C′-6), 125.2 (C-5 & C-6), 122.5 (<u>C</u>H=CH), 120.4 (C-4 & C-7), 68.5 ($CH_2$), 51.7 (C-2 & C-6 of piperazine), 45.3 (C-3 & C-5 of piperazine). EI-MS *m/z*: 346 ($M^+$). Anal. calcd for

$C_{21}H_{22}N_4O$: C, 72.81; H, 6.40; N, 16.17. Found: C, 72.38; H, 6.38; N, 16.20.

*1-(1-(Morpholinomethyl)-1H-benzimidazol-2-yl)-3-phenylprop-2-en-1-one (**4k**)*

Yield = 74%, m.p. 277–279 °C. IR (KBr) $cm^{-1}$: 3051 (Ar-CH), 2946 ($CH_3$–CH), 17,215 (C=O), 1647 (C=N), 1612 (C=C), 1065 (C–O–C). $^1$H-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 2.15–3.20 (m, 8H, $CH_2$ of morpholine), 4.80 (s, 2H, $CH_2$), 6.28 (d, 1H, –CO–C<u>H</u>=CH–), 7.31 (d, 1H, –CO–CH=C<u>H</u>–), 7.62–8.55 (m, 9H, Ar-CH). $^{13}$C-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 188.6 (C=O), 153.1 (CH=<u>C</u>H), 147.3 (C-2), 145.2 (C-9), 139.1 (C′-4), 138.8 (C-8), 136.5 (C′-1), 135.7 (C′-3 & C′-5), 133.2 (C′-2 & C′-6), 130.4 (C-5 & C-6), 128.6 (<u>C</u>H=CH), 125.3 (C-4 & C-7), 79.7 ($CH_2$), 68.7 (C-3 & C-5 of morpholine), 51.4 (C-2 & C-6 of morpholine). EI-MS m/z: 347 ($M^+$). Anal. calcd for $C_{21}H_{21}N_3O_2$: C, 72.60; H, 6.09; N, 12.10. Found: C, 72.38; H, 6.11; N, 12.13.

*3-Phenyl-1-(1-(piperidin-1-ylmethyl)-1H-benzimidazol-2-yl)prop-2-en-1-one (**4l**)*

Yield = 76%, m.p. 296–298 °C. IR (KBr) $cm^{-1}$: 3044 (Ar-CH), 2970 ($CH_3$–CH), 1743 (C=O), 1655 (C=N), 1628 (C=C). $^1$H-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 1.93–3.07 (m, 10H, $CH_2$ of piperidine), 4.53 (s, 2H, $CH_2$), 6.36 (d, 1H, –CO–C<u>H</u>=CH–), 7.29 (d, 1H, –CO–CH=C<u>H</u>–), 7.37–8.10 (m, 9H, Ar-CH). $^{13}$C-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 191.5 (C=O), 151.9 (CH=<u>C</u>H), 145.2 (C-2), 142.6 (C-9), 137.5 (C′-4), 136.2 (C-8), 134.3 (C′-1), 131.9 (C′-3 & C′-5), 129.1 (C′-2 & C′-6), 125.8 (C-5 & C-6), 120.4 (<u>C</u>H=CH), 117.0 (C-4 & C-7), 71.3 ($CH_2$), 54.7 (C-2 & C-6 of piperidine), 31.0 (C-3 & C-5 of piperidine), 28.4 (C-4 of piperidine). EI-MS *m/z*: 345 ($M^+$). Anal. calcd for $C_{22}H_{23}N_3O$: C, 76.49; H, 6.71; N, 12.16. Found: C, 76.70; H, 6.69; N, 12.12.

*Synthesis of 2-(5-(4-ary)-4,5-dihydro-1H-pyrazol-3-yl)-1-(substitutedaminomethyl)-1H-benzimidazole (**5a-5l**)*

A mixture of 3-(4-aryl)-1-(1-(substitutedaminomethyl)-1*H*-benzimidazol-2-yl)prop-2-en-1-one **4a–4l** (0.05 mol) and hydrazine hydrate (0.1 mol) were dissolved in *N, N*-dimethyl formamide (30 ml). The mixture was refluxed at 120–140 °C for a period of 8–10 h. The resulting mixture was cooled and then poured into cold water containing ice with constant stirring. The precipitate obtained **5a–5l** was separated by filtration, dried over the filter paper and recrystallised using alcohol.

*N,N-Dimethyl(2-(5-p-tolyl-4,5-dihydro-1H-pyrazol-3-yl)-1H-benzimidazol-1-yl)methanamine (**5a**)*

Yield = 82%, m.p. 203–205 °C. IR (KBr) $cm^{-1}$: 3341 (NH), 3064 (Ar-CH), 2938 ($CH_3$–CH), 1640 (C=N), 1615 (C=C). $^1$H-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 1.92 (s, 6H, N($CH_3$)$_2$), 2.34 (d, 2H, $CH_2$ of pyrazole), 2.79 (s, 3H, $CH_3$), 4.21 (t, 1H, CH of pyrazole), 4.90 (s, 2H, $CH_2$), 6.87 (s, 1H, NH of pyrazole), 7.15–7.96 (m, 8H, Ar-CH). $^{13}$C-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 159.5 (C-3 of pyrazole), 140.4 (C-2), 137.5 (C′-1), 135.0 (C-9), 131.7 (C′-4), 129.6 (C-8), 125.9 (C′-3 & C′-5), 123.1 (C′-2 & C′-6), 117.8 (C-5 & C-6), 109.2 (C-4 & C-7), 71.9 ($CH_2$), 47.1 (C-5 of pyrazole), 41.6 (C-4 of pyrazole), 43.4 (N($CH_3$)$_2$), 25.3 ($CH_3$). EI-MS *m/z*: 333 ($M^+$). Anal. calcd for $C_{20}H_{23}N_5$: C, 72.04; H, 6.95; N, 21.00. Found: C, 72.31; H, 6.93; N, 20.95.

*N-Ethyl-N-((2-(5-p-tolyl-4,5-dihydro-1H-pyrazol-3-yl)-1H-benzimidazol-1-yl)methyl)ethanamine (**5b**)*

Yield = 74%, m.p. 230–231 °C. IR (KBr) $cm^{-1}$: 3365 (NH), 3050 (Ar-CH), 2954 ($CH_3$–CH), 1632 (C=N), 1609 (C=C). $^1$H-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 1.45 (t, 6H, $CH_3$), 2.18 (d, 2H, $CH_2$ of pyrazole), 2.43 (s, 3H, $CH_3$), 2.93 (t, 4H, $CH_2$), 4.09 (t, 1H, CH of pyrazole), 4.72 (s, 2H, $CH_2$), 6.61 (s, 1H, NH of pyrazole), 6.98–7.70 (m, 8H, Ar-CH). $^{13}$C-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 156.3 (C-3 of pyrazole), 144.7 (C-2), 141.9 (C′-1), 139.2 (C-9), 133.1 (C′-4), 130.2 (C-8), 128.6 (C′-3 & C′-5), 122.8 (C′-2 & C′-6), 117.0 (C-5 & C-6), 113.6 (C-4 & C-7), 72.0 ($CH_2$), 45.4 (C-5 of pyrazole), 42.8 (C-4 of pyrazole), 44.1 (N(<u>C</u>H$_2$CH$_3$)$_2$), 27.5 ($CH_3$), 20.7 (N(CH$_2$<u>C</u>H$_3$)$_2$). EI-MS *m/z*: 361 ($M^+$). Anal. calcd for $C_{22}H_{27}N_5$: C, 73.10; H, 7.53; N, 19.37. Found: C, 72.88; H, 7.54; N, 19.43.

*N-Phenyl-N-((2-(5-p-tolyl-4,5-dihydro-1H-pyrazol-3-yl)-1H-benzimidazol-1-yl)methyl)benzenamine (**5c**)*

Yield = 77%, m.p. 217–219 °C. IR (KBr) $cm^{-1}$: 3337 (NH), 3072 (Ar-CH), 2949 ($CH_3$–CH), 1635 (C=N), 1614 (C=C). $^1$H-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 2.20 (d, 2H, $CH_2$ of pyrazole), 2.67 (s, 3H, $CH_3$), 4.24 (t, 1H, CH of pyrazole), 4.61 (s, 2H, $CH_2$), 6.83 (s, 1H, NH of pyrazole), 7.09–8.32 (m, 18H, Ar-CH). $^{13}$C-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 155.0 (C-3 of pyrazole), 146.6 (C-2), 144.3 (C-1 of phenyl), 142.9 (C′-1), 139.1 (C-3 & C-5 of phenyl), 136.8 (C-9), 134.0 (C′-4), 131.3 (C-8), 125.7 (C′-3 & C′-5), 120.5 (C′-2 & C′-6), 119.1 (C-5 & C-6), 118.0 (C-2 & C-6 of phenyl), 116.5 (C-4 of phenyl), 115.4 (C-4 & C-7), 69.4 ($CH_2$), 48.7 (C-5 of pyrazole), 38.2 (C-4 of pyrazole), 24.8 ($CH_3$). EI-MS *m/z*: 457 ($M^+$). Anal. calcd for $C_{30}H_{27}N_5$: C, 78.75; H, 5.95; N, 15.31. Found: C, 78.98; H, 5.93; N, 15.26.

*1-(Piperazin-1-ylmethyl)-2-(5-p-tolyl-4,5-dihydro-1H-pyrazol-3-yl)-1H-benzimidazole (**5d**)*

Yield = 79%, m.p. 239–240 °C. IR (KBr) $cm^{-1}$: 3342 & 3255 (NH), 3056 (Ar-CH), 2953 ($CH_3$–CH), 1648 (C=N), 1620 (C=C). $^1$H-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 1.70 (s, 1H, NH of piperazine), 2.13 (d, 2H, $CH_2$ of pyrazole), 2.36 (s, 3H, $CH_3$), 2.95–3.61 (m, 8H, $CH_2$ of piperazine), 4.02 (t, 1H, CH of pyrazole), 4.94 (s, 2H, $CH_2$), 6.67 (s, 1H, NH of pyrazole), 6.85–8.08 (m, 8H, Ar-CH). $^{13}$C-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 157.6 (C-3 of pyrazole), 142.8 (C-2), 140.5 (C′-1), 137.9 (C-9), 133.1 (C′-4), 129.2 (C-8), 124.3 (C′-3 & C′-5), 121.2 (C′-2 & C′-6), 114.0 (C-5 & C-6), 110.4 (C-4 & C-7), 70.2 ($CH_2$), 54.9 (C-2 & C-6 of piperazine), 51.0 (C-5 of pyrazole), 48.3 (C-3 & C-5 of piperazine), 43.7 (C-4 of pyrazole), 25.4 ($CH_3$). EI-MS *m/z*: 374 ($M^+$). Anal. calcd for $C_{22}H_{26}N_6$: C, 70.56; H, 7.00; N, 22.44. Found: C, 70.21; H, 7.02; N, 22.49.

*1-(Morpholinomethyl)-2-(5-p-tolyl-4,5-dihydro-1H-pyrazol-3-yl)-1H-benzimidazole (**5e**)*

Yield = 73%, m.p. 196–198 °C. IR (KBr) $cm^{-1}$: 3329 (NH), 3081 (Ar-CH), 2956 ($CH_3$–CH), 1640 (C=N), 1622 (C=C), 1095 (C-O-C). $^1$H-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 2.06 (d, 2H, $CH_2$ of pyrazole), 2.72 (s, 3H, $CH_3$), 2.81–3.47 (m, 8H, $CH_2$ of morpholine), 4.28 (t, 1H, CH of pyrazole), 4.65 (s, 2H, $CH_2$), 6.89 (s, 1H, NH of pyrazole), 7.20–8.13 (m, 8H, Ar-CH). $^{13}$C-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 158.0 (C-3 of pyrazole), 146.2 (C-2), 137.8 (C′-1), 132.0 (C-9), 130.2 (C′-4), 123.5 (C-8), 122.3 (C′-3 & C′-5), 119.1 (C′-2 & C′-6), 114.8 (C-5 & C-6), 108.7 (C-4 & C-7), 71.5 ($CH_2$), 68.3 (C-3 & C-5 of morpholine), 53.8 (C-2 & C-6 of morpholine), 49.6 (C-5 of pyrazole), 40.9 (C-4 of pyrazole), 26.1 ($CH_3$). EI-MS *m/z*: 375 ($M^+$). Anal. calcd for $C_{22}H_{25}N_5O$: C, 70.38; H, 6.71; N, 18.65. Found: C, 70.16; H, 6.72; N, 18.71.

*1-(Piperidin-1-ylmethyl)-2-(5-p-tolyl-4,5-dihydro-1H-pyrazol-3-yl)-1H-benzimidazole (**5f**)*

Yield = 81%, m.p. 245–246 °C. IR (KBr) $cm^{-1}$: 3368 (NH), 3044 (Ar-CH), 2922 ($CH_3$–CH), 1643 (C=N), 1631 (C=C). $^1$H-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 1.92–2.69 (m, 10H, $CH_2$ of piperidine), 2.82 (d, 2H, $CH_2$ of pyrazole), 3.04 (s, 3H, $CH_3$), 4.16 (t, 1H, CH of pyrazole), 4.87 (s, 2H, $CH_2$), 6.78 (s, 1H, NH of pyrazole), 7.03–8.21 (m, 8H, Ar-CH). $^{13}$C-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 163.7 (C-3 of pyrazole), 145.7 (C-2), 140.1 (C′-1), 136.9 (C-9), 131.3 (C′-4), 129.4 (C-8), 127.2 (C′-3 & C′-5), 120.6 (C′-2 & C′-6), 115.8 (C-5 & C-6), 112.6 (C-4 & C-7), 73.2 ($CH_2$), 55.1 (C-2 & C-6 of piperidine), 50.3 (C-5 of pyrazole), 41.0 (C-4 of pyrazole), 29.4 (C-4 of piperidine), 28.7 (C-3 & C-5 of piperidine), 25.6 ($CH_3$). EI-MS *m/z*: 373 ($M^+$). Anal. calcd for $C_{23}H_{27}N_5$: C, 73.96; H, 7.29; N, 18.75. Found: C, 74.19; H, 7.28; N, 18.70.

*N,N-Dimethyl(2-(5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-1H-benzimidazol-1-yl)methanamine (**5g**)*

Yield = 76%, m.p. 222–223 °C. IR (KBr) $cm^{-1}$: 3356 (NH), 3065 (Ar-CH), 2932 ($CH_3$–CH), 1637 (C=N), 1613 (C=C). $^1$H-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 1.89 (s, 6H, N($CH_3$)$_2$), 2.09 (d, 2H, $CH_2$ of pyrazole), 4.20 (t, 1H, CH of pyrazole), 4.73 (s, 2H, $CH_2$), 6.61 (s, 1H, NH of pyrazole), 6.95–7.84 (m, 9H, Ar-CH). $^{13}$C-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 159.2 (C-3 of pyrazole), 143.7 (C-2), 139.8 (C′-1), 137.9 (C-9), 133.1 (C′-4), 131.6 (C-8), 126.5 (C′-3 & C′-5), 124.0 (C′-2 & C′-6), 119.4 (C-5 & C-6), 115.6 (C-4 & C-7), 68.1 ($CH_2$), 46.8 (C-5 of pyrazole), 39.3 (C-4 of pyrazole), 42.5 (N($CH_3$)$_2$). EI-MS *m/z*: 319 ($M^+$). Anal. calcd for $C_{19}H_{21}N_5$: C, 71.45; H, 6.63; N, 21.93. Found: C, 71.70; H, 6.61; N, 21.87.

*N-Ethyl-N-((2-(5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-1H-benzimidazol-1-yl)methyl)ethanamine (**5h**)*

Yield = 73%, m.p. 256–258 °C. IR (KBr) $cm^{-1}$: 3333 (NH), 3079 (Ar-CH), 2951 ($CH_3$–CH), 1644 (C=N), 1618 (C=C). $^1$H-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 1.76 (t, 6H, $CH_3$), 2.31 (d, 2H, $CH_2$ of pyrazole), 2.98 (t, 4H, $CH_2$), 4.07 (t, 1H, CH of pyrazole), 4.82 (s, 2H, $CH_2$), 6.95 (s, 1H, NH of pyrazole), 7.33–8.14 (m, 9H, Ar-CH). $^{13}$C-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 158.8 (C-3 of pyrazole), 144.5 (C-2), 139.7 (C′-1), 135.5 (C-9), 132.7 (C′-4), 129.3 (C-8), 126.4 (C′-3 & C′-5), 118.6 (C′-2 & C′-6), 114.2 (C-5 & C-6), 111.0 (C-4 & C-7), 70.4 ($CH_2$), 48.9 (C-5 of pyrazole), 38.1 (C-4 of pyrazole), 45.2 (N($\underline{C}H_2CH_3$)$_2$), 17.6 (N($CH_2\underline{C}H_3$)$_2$). EI-MS *m/z*: 347 ($M^+$). Anal. calcd for $C_{21}H_{25}N_5$: C, 72.59; H, 7.25; N, 20.16. Found: C, 72.81; H, 7.24; N, 20.11.

*N-Phenyl-N-((2-(5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-1H-benzimidazol-1-yl)methyl)benzenamine (**5i**)*

Yield = 72%, m.p. 235–236 °C. IR (KBr) $cm^{-1}$: 3368 (NH), 3043 (Ar-CH), 2935 ($CH_3$–CH), 1636 (C=N), 1612 (C=C). $^1$H-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 2.17 (d, 2H, $CH_2$ of pyrazole), 4.10 (t, 1H, CH of pyrazole), 4.92 (s, 2H, $CH_2$), 6.76 (s, 1H, NH of pyrazole), 7.13–8.54 (m, 19H, Ar-CH). $^{13}$C-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 162.4 (C-3 of pyrazole), 147.3 (C-2), 145.1 (C-1 of phenyl), 142.4 (C′-1), 141.7 (C-3 & C-5 of phenyl), 140.1 (C-9), 136.9 (C′-4), 133.6 (C-8), 132.4 (C′-3 & C′-5), 126.0 (C′-2 & C′-6), 122.7 (C-5 & C-6), 120.5 (C-2 & C-6 of phenyl), 119.6 (C-4 of phenyl), 117.5 (C-4 & C-7), 73.7 ($CH_2$), 50.2 (C-5 of

pyrazole), 41.5 (C-4 of pyrazole). EI-MS *m/z*: 443 ($M^+$). Anal. calcd for $C_{29}H_{25}N_5$: C, 78.53; H, 5.68; N, 15.79. Found: C, 78.27; H, 5.70; N, 15.84.

*2-(5-Phenyl-4,5-dihydro-1H-pyrazol-3-yl)-1-(piperazin-1-ylmethyl)-1H-benzimidazole (**5j**)*

Yield = 78%, m.p. 209–211 °C. IR (KBr) $cm^{-1}$: 3354 & 3276 (NH), 3051 (Ar-CH), 2947 ($CH_3$–CH), 1633 (C=N), 1609 (C=C). $^1$H-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 1.90 (s, 1H, NH of piperazine), 2.21 (d, 2H, $CH_2$ of pyrazole), 2.68–3.26 (m, 8H, $CH_2$ of piperazine), 4.03 (t, 1H, CH of pyrazole), 4.75 (s, 2H, $CH_2$), 6.92 (s, 1H, NH of pyrazole), 7.24–8.17 (m, 9H, Ar-CH). $^{13}$C-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 157.9 (C-3 of pyrazole), 144.4 (C-2), 141.3 (C′-1), 136.1 (C-9), 133.8 (C′-4), 131.7 (C-8), 128.5 (C′-3 & C′-5), 121.8 (C′-2 & C′-6), 117.0 (C-5 & C-6), 110.5 (C-4 & C-7), 69.3 ($CH_2$), 49.5 (C-2 & C-6 of piperazine), 45.7 (C-5 of pyrazole), 42.1 (C-3 & C-5 of piperazine), 40.2 (C-4 of pyrazole). EI-MS *m/z*: 360 ($M^+$). Anal. calcd for $C_{21}H_{24}N_6$: C, 69.97; H, 6.71; N, 23.32. Found: C, 69.76; H, 6.73; N, 23.38.

*1-(Morpholinomethyl)-2-(5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-1H-benzimidazole (**5k**)*

Yield = 80%, m.p. 250–252 °C. IR (KBr) $cm^{-1}$: 3352 (NH), 3003 (Ar-CH), 2921 ($CH_3$–CH), 1641 (C=N), 1611 (C=C), 1017 (C-O-C). $^1$H-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 2.05 (d, 2H, $CH_2$ of pyrazole), 2.50–3.78 (m, 8H, $CH_2$ of morpholine), 4.27 (t, 1H, CH of pyrazole), 4.63 (s, 2H, $CH_2$), 6.84 (s, 1H, NH of pyrazole), 7.12–8.41 (m, 9H, Ar-CH). $^{13}$C-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 160.2 (C-3 of pyrazole), 149.8 (C-2), 144.5 (C′-1), 138.0 (C-9), 135.9 (C′-4), 133.9 (C-8), 129.9 (C′-3 & C′-5), 125.2 (C′-2 & C′-6), 118.3 (C-5 & C-6), 114.3 (C-4 & C-7), 72.8 ($CH_2$), 70.4 (C-3 & C-5 of morpholine), 55.0 (C-2 & C-6 of morpholine), 51.5 (C-5 of pyrazole), 43.1 (C-4 of pyrazole). EI-MS *m/z*: 361 ($M^+$). Anal. calcd for $C_{21}H_{23}N_5O$: C, 69.78; H, 6.41; N, 19.38. Found: C, 69.96; H, 6.40; N, 19.34.

*2-(5-Phenyl-4,5-dihydro-1H-pyrazol-3-yl)-1-(piperidin-1-ylmethyl)-1H-benzimidazole (**5l**)*

Yield = 75%, m.p. 226–228 °C. IR (KBr) $cm^{-1}$: 3320 (NH), 3074 (Ar-CH), 2909 ($CH_3$–CH), 1659 (C=N), 1612 (C=C). $^1$H-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 1.73–2.41 (m, 10H, $CH_2$ of piperidine), 2.87 (d, 2H, $CH_2$ of pyrazole), 4.15 (t, 1H, CH of pyrazole), 4.89 (s, 2H, $CH_2$), 6.90 (s, 1H, NH of pyrazole), 7.34–8.06 (m, 9H, Ar-CH). $^{13}$C-NMR ($CDCl_3$, 500 MHz) $\delta$ ppm: 156.1 (C-3 of pyrazole), 145.1 (C-2), 142.7 (C′-1), 141.0 (C-9), 138.2 (C′-4), 134.0 (C-8), 132.6 (C′-3 & C′-5), 126.2 (C′-2 & C′-6), 122.5 (C-5 & C-6), 113.8 (C-4 & C-7), 68.6 ($CH_2$), 51.3 (C-2 & C-6 of piperidine), 47.9 (C-5 of pyrazole), 39.4 (C-4 of pyrazole), 28.0 (C-4 of piperidine), 26.8 (C-3 & C-5 of piperidine). EI-MS *m/z*: 359 ($M^+$). Anal. calcd for $C_{22}H_{25}N_5$: C, 73.51; H, 7.01; N, 19.48. Found: C, 73.77; H, 7.00; N, 19.42.

## Pharmacology

All the synthesized compounds were evaluated for their antiepileptic effects using male albino mice (Swiss, 18-25 g) and rat (Wistar 100–150 g). The primary qualitative evaluations were performed in mice involved two epilepsy tests (MES and *sc*PTZ test). Acute neurological toxicity induced by the compounds in mice was assessed through standardized rotorod test. In the initial screening, candidate compounds were screened for their antiepileptic potential through MES and *sc*PTZ models in mice at a dose level of 30, 100 and 300 mg/kg by i.p. route and the groups of mice are tested at different time points (i.e., 0.5 and 4 h) post administration of the test candidate. It is generally acknowledged that the MES model, which uses an electrical stimulus, induces generalized tonic-clonic seizures. Through electrical induction, it is used to help recognize those compounds which prevent seizure spread. The *sc*PTZ is a model where the myoclonic seizures induced by chemical induction. It helps in identifying those compounds that might act by increasing seizure threshold. Each group consisted of six animals. The animals were maintained in colony cages at 25 ± 2 °C, relative humidity of 45–55%, under a 12 h light and dark cycle; were fed standard animal feed (Olfert et al. 1993). All the animals were acclimatized for a week before use. The Institutional Animal Ethics committee approved the protocol adopted for the experimentation of animals.

## Antiepileptic activity

### *The MES test*

The MES is a model for generalized tonic-clonic seizures and provides a hint of a compound's ability to stop seizure spread when all neuronal circuits in the brain are maximally active. These seizures are extremely reproducible and are electro physiologically reliable with human seizures. For the MES, a drop of anesthetic and electrolyte solution (tetracaine hydrochloride (0.5%) in saline (0.9%)) was applied to the eyes of individual animal before to placement of the corneal electrodes. The electrical stimulus in the MES test was 50 mA, 60 Hz, for mice and 150 mA, 60 Hz, for rats delivered for 0.2 s by an apparatus similar to previously reported method (Woodbury and Davenport 1952; White et al. 1995). Abolition of the hindleg tonic extensor component of the seizure was used as the endpoint. Mice are initially tested with different doses of 30, 100 and 300 mg/kg

of test compound given by i.p. injection at various intervals while rats are initially screened at a fixed dose of 30 mg/kg given by oral route.

*The scPTZ test*

Subcutaneous injection of the convulsant Pentylenetetrazole produces clonic seizures in laboratory animals. The scPTZ test detects the ability of test compounds to raise the seizure threshold of an animal and thus protect it from exhibiting a clonic seizure. Animals are pretreated with various doses of the test compound given by i.p. injection. The dose of Pentylenetetrazole which induces convulsions in 97% of animals ($CD_{97}$: 85 mg/kg mice) is injected into a loose fold of skin in the midline of the neck. The animals are placed in isolation cages to minimize stress (Swinyard et al. 1961) and observed for the next 30 min for the presence or absence of a seizure. An episode of clonic spasms, approximately 3–5 s, of the fore and/or hindlimbs, jaws, or vibrissae is taken as the endpoint. Animals which do not meet this criterion are considered protected.

*Acute toxicity-minimal motor impairment*

To assess a compound's undesirable side effects (toxicity), animals are monitored for overt signs of impaired neurological or muscular function. In mice, the rotorod (Dunham and Miya 1957) procedure is used to disclose minimal muscular (MMI) or neurological impairment. When a mouse is placed on a rod that rotates at a speed of 6 rpm, the animal can maintain its equilibrium for long periods of time. The animal is considered toxic if it falls off this rotating rod three times during a 1 min period. In addition to MMI, animals may exhibit a circular or zigzag gait, abnormal body posture and spread of the legs, tremors, hyperactivity, lack of exploratory behavior, somnolence, stupor, catalepsy, loss of placing response and changes in muscle tone.

**Acknowledgements** The authors gratefully acknowledge the Pfizer limited and GITAM University for providing infrastructure facilities to carry out this research work.

**Compliance with ethical standards**

**Conflict of interests** The authors declares that they have no competing interests.

## References

Akhtar W, Khan MF, Verma G, Shaquiquzzaman M, Rizvi MA, Mehdi SH, Akhter M, Alam MM (2017) Therapeutic evolution of benzimidazole derivatives in the last quinquennial period. Eur J Med Chem 126:705–753

Alagarsamy V, Saravanan G (2012) Synthesis and anticonvulsant activity of novel quinazolin-4(3*H*)-one derived pyrazole analogs. Med Chem Res 22:1711–1722

Alam O, Mullick P, Verma SP, Gilani SJ, Khan SA, Siddiqui N, Ahsan W (2010) Synthesis, anticonvulsant and toxicity screening of newer pyrimidine semicarbazone derivatives. Eur J Med Chem 45:2467–2472

Berk M, Segal J, Janet L, Vorster M (2001) Emerging options in the treatment of bipolar disorders. Drugs 61:1407–1414

Bhrigu B, Siddiqui N, Pathak D, Alam MS, Ali R, Azad B (2012) Anticonvulsant evaluation of some newer benzimidazole derivatives: design and synthesis. Acta Pol Pharm 69: 53–62

Bindi S, Fancelli D, Alli C, Berta D, Bertrand JA, Cameron AD, Cappella P, Carpinelli P, Cervi G, Croci V, D'anello M, Forte B, Giorgini M, Marsiglio A, Moll J, Pesenti E, Pittala V, Pulici M, Riccardi-Sirtori F, Roletto F, Soncini C, Storici P, Varasi M, Volpi D, Zugnoni P, Vianello P (2010) Thieno[3,2-*c*]pyrazoles: a novel class of aurora inhibitors with favorable antitumor activity. Bioorg Med Chem 18:7113–7120

Bruno-Blanch L, Galvez J, Garcia-Domenach R (2003) Topological virtual screening: a way to find new anticonvulsant drugs from chemical diversity. Bioorg Med Chem Lett 13:2749–2754

Castro AR, Rivera IL, Rojas LC, Vazquez GN, Rodríguez AN (2011) Synthesis and preliminary evaluation of selected 2-aryl-5 (6)-nitro-1*H*-benzimidazole derivatives as potential anticancer agents. Arch Pharm Res 34:181–189

Deng XQ, Wei CX, Li FN, Sun ZG, Quan ZS (2010) Design and synthesis of 10-alkoxy-5,6-dihydro-triazolo-[4,3-d]benzo-[f]-[1,4]oxazepine derivatives with anticonvulsant activity. Eur J Med Chem 45:3080–3086

Duncan JS (2002) The promise of new antiepileptic drugs. Br J Clin Pharmacol 53:123–131

Dunham MS, Miya TA (1957) A note on a simple apparatus for detecting neurological deficit in rats and mice. J Am Pharm Assoc Sci 46:208–209

Estrada E, Pena A (2000) In silico studies for the rational discovery of anticonvulsant compounds. Bioorg Med Chem 8:2755–2770

Jun C, Jiangtao X, Xianjin L (2005) Synthesis and antiviral activity against *Coxsackie* virus B3 of some novel benzimidazole derivatives. Bioorg Med Chem Lett 15:267–269

Karakurt A, Ozalp M, Isik S, Stables JP, Dalkara S (2010) Synthesis, anticonvulsant and antimicrobial activities of some new 2-acetylnaphthalene derivatives. Bioorg Med Chem 8:2902–2911

Kaur G, Kaur M, Silakari O (2014) Benzimidazoles: An ideal privileged drug scaffold for the design of multitargeted anti-inflammatory ligands. Mini Rev Med Chem 14:747–767

Lopes Lima JM (2000) The new drugs and the strategies to manage epilepsy. Curr Pharm Des 6:873–878

McNamara JO (2001) Drugs effective in the therapy of the epilepsies. In: Hardman JG, Limbird LE, Gilman AG (Eds.) The pharmacological basis of therapeutics. McGraw-Hill, New York, NY, p 521–548

Monika G, Chander M (2015) Design, synthesis and biological evaluation of novel 1,2,5-substituted benzimidazole derivatives as gastroprotective anti-inflammatory and analgesic agents. Med Chem 5:58–63

Olfert ED, Cross BM, McWilliam AA (1993) Guide to the care and use of experimental animals, Vol 1, 2nd edn. Canadian council of animal care, Canada, p 1–201

Panneer Selvam T, Vijayaraj Kumar P, Saravanan G, Prakash CR (2014) Microwave-assisted synthesis, characterization and biological activity of novel pyrazole derivatives. J Saudi Chem Soc 18:1015–1021

Pevarello P, Fancelli D, Vulpetti A, Amici R, Villa M, Pittala V, Vianello P, Cameron A, Ciomei M, Mercurio C, Bischoff J,

Roletto F, Varasi M, Brasca MG (2006) 3-Amino-1,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazoles: a new class of CDK2 inhibitors. Bioorg Med Chem Lett 16:1084–1090

Pollard JR, French J (2006) Antiepileptic drugs in development. Lancet Neurol 5:1064–1067

Rajak H, Deshmukh R, Aggarwal N, Kashaw S, Kharya MD, Mishra P (2009) Synthesis of novel 2,5-disubstituted-1,3,4-thiadiazoles for their potential anticonvulsant activity: pharmacophoric model studies. Arch Pharm 342:453–461

Salerno L, Modica MN, Romeo G, Pittala V, Siracusa MA, Amato ME, Acquaviva R, Di Giacomo C, Sorrenti V (2012) Novel inhibitors of nitric oxide synthase with antioxidant properties. Eur J Med Chem 49:118–126

Siddiqui N, Alam MS, Ali R, Yar SM, Alam O (2016) Synthesis of new benzimidazole and phenylhydrazinecarbothiomide hybrids and their anticonvulsant activity. Med Chem Res 25:1390–1402

Siracusa MA, Salerno L, Modica MN, Pittala V, Romeo G, Amato ME, Nowak M, Bojarski AJ, Mereghetti I, Cagnotto A, Mennini T (2008) Synthesis of new arylpiperazinylalkylthiobenzimidazole, benzothiazole, or benzoxazole derivatives as potent and selective 5-HT1A serotonin receptor ligands. J Med Chem 51:4529–4538

Spear BB (2001) Pharmacogenetics and antiepileptic drug. Epilepsia 42:31–34

Sri Krishnanjaneyulu I, Saravanan G, Vamsi J, Supriya P, Udaya Bhavana J, Venkata Sunil Kumar M (2014) Synthesis, characterization and antimicrobial activity of some novel benzimidazole derivatives. J Adv Pharm Technol Res 5:21–27

Stefan H, Feuerstein TJ (2007) Novel anticonvulsant drugs. Pharmacol Ther 113:165–183

Swinyard EA, Clark LD, Miyahara JT, Wolf HH (1961) Studies on the mechanism of amphetamine toxicity in aggregated mice. J Physiol 132:97–102

Swiqtkiewicz KB, Olasik EM (2015) Some characteristics of activity of potential chemotherapeutics-benzimidazole derivatives. Adv Med Sci 60:125–132

White HS, Johnson M, Wolf HH, Kupferberg HJ (1995) The early identification of anticonvulsant activity: the role of maximal electroshock and subcutaneous pentylenetetrazole seizure models. Ital J Neurol Sci 16:73–77

Woodbury LA, Davenport VD (1952) Design and use of a new electroshock apparatus, and analysis of factors altering seizure threshold and pattern. Arch Int Pharmacodyn Ther 92: 97–107

Yogeeswari P, Sriram D, Ragavendran JV, Thirumurugan R (2005) The GABA shunt: an attractive and potential therapeutic target in the treatment of epileptic disorders. Curr Drug Metab 6:127–139

Yogeeswari P, Sriram D, Thirumurugan R, Raghavendran JV, Sudhan K, Pavana RK, Stables JP (2005) Discovery of *N*-(2,6-dimethylphenyl)-substituted semicarbazones as anticonvulsants: hybrid pharmacophore based design. J Med Chem 48:6202–6211

Yoon YK, Ali MS, Wei AC, Choon TS, Ismail R (2015) Synthesis and evaluation of antimycobacterial activity of new benzimidazole aminoesters. Eur J Med Chem 93:614–624