European Journal of Medicinal Chemistry 47 (2012) 360–369

Contents lists available at SciVerse ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Design and synthesis of novel stiripentol analogues as potential anticonvulsants

Mohamed N. Aboul-Enein [a,*], Aida A. El-Azzouny [a], Mohamed I. Attia [a,b], Yousreya A. Maklad [c], Kamilia M. Amin [d], Mohamed Abdel-Rehim [e], Mohammed F. El-Behairy [a]

[a] Medicinal and Pharmaceutical Chemistry Department (Medicinal Chemistry group), Pharmaceutical and Drug Industries Research Division, National Research Centre, 12622 Dokki, Giza, Egypt
[b] Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia
[c] Medicinal and Pharmaceutical Chemistry Department (Pharmacology group), Pharmaceutical and Drug Industries Research Division, National Research Centre, 12622 Dokki, Giza, Egypt
[d] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Cairo University, Cairo, Egypt
[e] Department of Chemistry, Karlstad University, SE-651 88 Karlstad, Sweden

ARTICLE INFO

Article history:
Received 10 June 2011
Received in revised form
21 September 2011
Accepted 2 November 2011
Available online 11 November 2011

Keywords:
Stiripentol
Epilepsy
Semicarbazones
Pyrazolines
Anticonvulsants

ABSTRACT

A series of stiripentol (STP) analogues namely, 2-[(1*E*)-1-(1,3-benzodioxol-5-yl)-4,4-dimethylpent-1-en-3-ylidene]-*N*-(aryl/*H*)hydrazinecarboxamides **7a**–**h**, (±)-(5RS)-*N*-(aryl/*H*)-(1,3-benzodioxol-5-yl)-3-*tert*-butyl-4,5-dihydro-1*H*-pyrazole-1-carboxamides (±)-**8a**–**h**, and (±)-[(5*RS*)-(1,3-benzodioxol-5-yl)-3-*tert*-butyl-4,5-dihydro-1*H*-pyrazol-1-yl](aryl)methanones (±)-**13a**–**f** was synthesized by adopting appropriate synthetic routes and was pharmacologically evaluated in the preliminary anticonvulsant screens. The selected bioactive new chemical entities were subjected to ED_{50} determination and neurotoxicity evaluation. The most active congeners are **7h** in MES screen and (±)-**13b** in scPTZ screen which displayed ED_{50} values of 87 and 110 mg/kg, respectively, as compared to that of STP (ED_{50} = 277.7 and 115 mg/kg in MES and scPTZ, respectively).

1. Introduction

Epilepsy is a group of serious disorders of the brain characterized by excessive temporary neuronal discharge resulting in recurrent unprovoked seizures [1]. It affects approximately 1% of mankind and the majority of cases are in the developing countries [2,3]. Despite the availability of many new antiepileptic drugs (AEDs) and remarkable strides in this research field, estimates suggest that available medication controls the seizures in only 50% of patients or decreases the incidence in only 75% of patients [4]. The currently used antiepileptic drugs like phenytoin, carbamazepine, ethosuximide, valproic acid and barbiturates though widely prescribed, produce adverse effects such as ataxia, hepatotoxicity, gingival hyperplasia and megaloblastic anaemia [5,6]. Accordingly, the search for novel, more effective, more selective antiepileptic agents with lesser side effects continues to be an invaluable area of investigation in medicinal chemistry.

Stiripentol ([3,4-methylenedioxyphenyl]-4,4-dimethyl-1-penten-3-ol, STP, **I**, Diacomit®) is a novel antiepileptic drug produced by Biocodex (Gentilly, France), structurally unrelated to all currently marketed antiepileptic products as it belongs to the group of aromatic allylic alcohols [7]. It has been used as co-therapy for treatment of epilepsy for many years and it has been granted orphan drug status in the European Union for the treatment of severe myoclonic epilepsy in infancy (Dravet syndrome) [8]. Although precise mechanism of action of STP remains unknown, it has long been considered to be indirect, as it inhibits the enzymes responsible for metabolism of other antiepileptic drugs. Nevertheless, a recent report suggested that STP might also act at the neuronal level, increasing inhibitory GABAergic neurotransmission through positive allosteric modulation of $GABA_A$ receptors [9].

Semicarbazones **II** (Fig. 1) have been recognized earlier as a promising pharmacophore for anticonvulsants and a number of semicarbazone derivatives have displayed anticonvulsant activity [10,11]. In the present work, it has been planned to attach semicabazone moiety to the backbone of STP, compound **7h**, aiming to have synergetic effect dealing with treatment of epilepsy. Moreover, the terminal hydrogen of the amidic moiety of **7h** has been replaced with aryl moiety, compounds **7a**–**g**, in order to study the

* Corresponding author. Fax: +2 0237601877.
E-mail address: mnaboulenein@yahoo.com (M.N. Aboul-Enein).

0223-5234/$ – see front matter © 2011 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2011.11.004

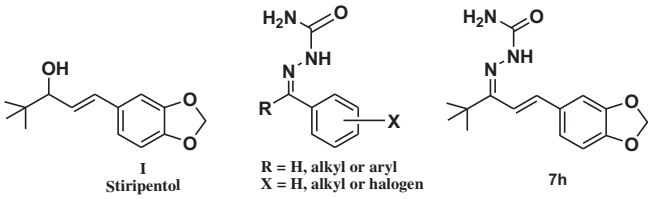


Fig. 1. Structures of stiripentol (**I**), semicarbazons (**II**) and **7h**.

role of the primary amidic group in the anticonvulsant potential of STP derived semicarbazones.

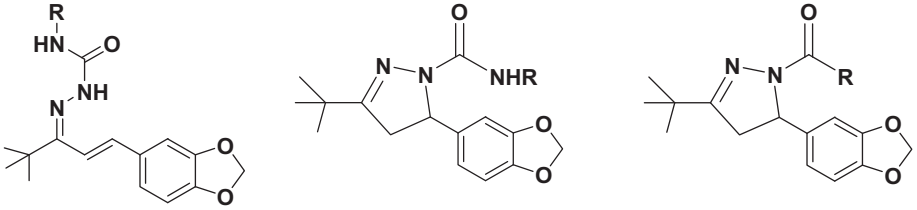
Further, the pyrazoline moiety has been found to exhibit a broad spectrum of biological activities such as antidepressants [12], antibacterial [13], anti-inflammatory [14] analgesic [15], and anticonvulsant [16]. Accordingly, cyclization of the semicarbazones **7a**–**h** afforded the respective racemic pyrazolines (±)-**8a**–**h** to be evaluated as anticonvulsants. Moreover, the influence of removal of the terminal amidic NH group on the anticonvulsant profile of the racemic compounds (±)-**8a**–**f** was explored *via* synthesis and pharmacological evaluation of (±)-**13a**–**f** (Table 1).

2. Chemistry

The synthesis of the target compounds **7a**–**h**, (±)-**8a**–**h**, and (±)-**13a**–**f** and their intermediates were achieved as portrayed in Schemes 1–3. Aryl semicarbazides **3a**–**g** were prepared by adopting new strategy using substituted anilines **1a**–**g** as starting materials. Thus, **1a**–**g** were reacted with ethyl chloroformate in CH_2Cl_2 at room temperature to afford the respective carbamates **2a**–**g**. Subsequently, **2a**–**g** were elaborated to the corresponding aryl semicarbazides **3a**–**g** through reflux in hydrazine hydrate (Scheme 1).

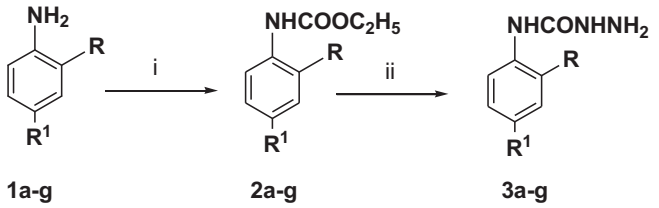
3,4-Dihydroxybenzaldehyde (**4**) was allowed to react with CH_2Cl_2 under reflux conditions to yield piperonal (**5**) [17] which was further subjected to Claisen–Schmidt condensation with pinacolone [18] to afford the pivotal chalcone **6** in good yield. The α,β-unsaturated ketone **6** was reacted with the appropriate aryl semicarbazide **3a**–**g** in ethanol and glacial acetic acid to furnish the

Table 1
Anticonvulsant activity of compounds **7a**–**h**, (±)-**8a**–**h**, and (±)-**13a**–**f**.



Compound no.	R	Dose (μmol/kg)	Anticonvulsant activity[a] (% protection)		
			scPTZ	Relative potency[b]	MES
7a	C_6H_5	410	66	1.30	–
7b	4-Br-C_6H_4	330	66	1.60	16
7c	4-Cl- C_6H_4	370	33	1.15	–
7d	4–CH_3–C_6H_4	390	16	0.98	–
7e	2–CH_3–C_6H_4	390	83	1.48	–
7f	2,4-Cl_2–C_6H_3	340	33	1.26	16
7g	4-F-C_6H_4	390	50	1.26	–
7h	H	346	50	1.42	100
(±)-**8a**	C_6H_5	410	66	1.30	16
(±)-**8b**	4-Br-C_6H_4	330	33	1.29	–
(±)-**8c**	4-Cl- C_6H_4	370	33	1.15	–
(±)-**8d**	4–CH_3–C_6H_4	390	83	1.48	–
(±)-**8e**	2–CH_3–C_6H_4	390	16	0.95	–
(±)-**8f**	2,4-Cl_2–C_6H_3	340	33	1.26	–
(±)-**8g**	4-F-C_6H_4	390	33	1.09	–
(±)-**8h**	H	346	16	1.11	66
(±)-**13a**	C_6H_5	420	66	1.27	–
(±)-**13b**	4-Br-C_6H_4	350	100	2.13	16
(±)-**13c**	4-Cl- C_6H_4	390	50	1.26	–
(±)-**13d**	4–CH_3–C_6H_4	410	33	1.04	33
(±)-**13e**	2–CH_3–C_6H_4	410	–	–	16
(±)-**13f**	2,4-Cl_2–C_6H_3	357	33	1.19	16
Stiripentol (STP)		384	16	1	ND
		427	33	1	ND
		491	50	1	ND
		534	66	1	ND
		576	83	1	ND
		640	83	1	66
		747	100	1	ND
Phenytoin		159	–		100
Phenobarbitone		108	100		ND

[a] Doses were administered i.p. Animals ($n = 6$) were examined at 0.5 h after administration of the test compounds. The dash (–) indicates an absence of anticonvulsant activity at the administered dose. The figures in the table indicate the minimal dose whereby % protection from seizures was demonstrated.
[b] Dose (μmol/kg) of STP/dose (μmol/kg) of the test compound which displayed the same % protection in the scPTZ test. ND: Not determined.



	R	R^1
a	H	H
b	H	Br
c	H	Cl
d	H	CH_3
e	CH_3	H
f	Cl	Cl
g	H	F

Scheme 1. Synthesis of semicarbazides **3a**–**g.** Reagents and conditions: i) $ClCOOC_2H_5$, CH_2Cl_2, RT, 0.5-24 h; ii) H_2N-$NH_2.H_2O$, reflux, 1-24 h (c.f. experimental part).

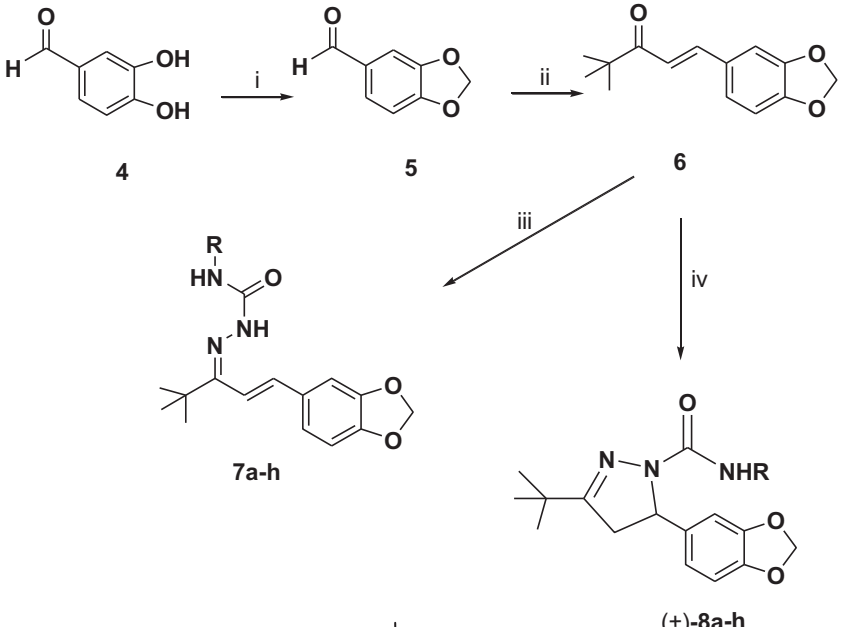
respective semicarbazones **7a**–**g**. Whereas semicarbazone **7h** was synthesized from semicarbazide HCl and ketone **6** in the presence of sodium acetate. Additionally, pyrazolines (±)-**8a**–**h** were obtained from the appropriate semicarbazide **3a**–**g** and **6** in the presence of sodium hydroxide in ethanol under reflux conditions (Scheme 2).

Chalcone **6** was reacted with hydrazine hydrate in ethanol under reflux conditions to yield the pyrazoline derivative (±)-**12.** Acyl azides **11a**–**d**, which were prepared from their corresponding acyl chlorides **10a**–**d** and sodium azide in toluene under reflux conditions, were used as acylating agents for (±)-**12**. Acylation of (±)-**12** using acyl azides **11a**–**d** has been performed in ethanol instead of hazardous pyridine which is the preferred reaction medium for acylation in case of using acyl chlorides as acylating agents. In addition, our trials to acylate (±)-**12** using acyl chlorides **10a**–**d** in ethanol were unsuccessful. Thus, coupling of the appropriate acid azide **11a**–**d** with the amine (±)-**12** in ethanol afforded the respective amides (±)-**13a**–**d**. While for (±)-**13e** and (±)-**13f**, (±)-**12** was acylated through the common coupling procedure in pyridine using acyl chlorides **10e** and **10f**, respectively, due to the unsuccessful acylation *via* corresponding acid azides in ethanol (Scheme 3).

The spectral data of the synthesized compounds in the present investigation were in accordance with their assigned structures.

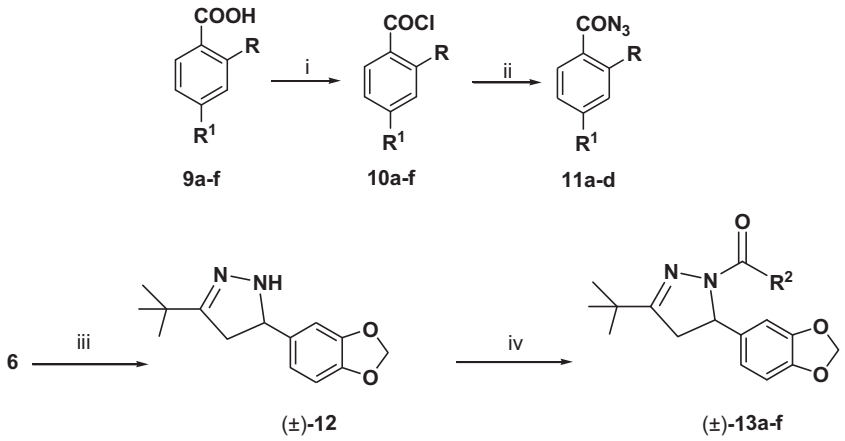
3. Pharmacology

As in many classes of drugs, the preclinical discovery and development of a novel bioactive chemical entity for the treatment of epilepsy rely heavily on the use of predictable animal models. To the best of our knowledge, there are three *in vivo* animal models that are routinely used by most antiepileptic drugs (AEDs) discovery programs. They include subcutaneous pentylenetetrazole (scPTZ), maximal electroshock seizures (MES), and the kindling model. Of these, the scPTZ and MES seizure models, which are recognized as the "gold standards" in the early stages of testing, represent the two animal seizure models most widely used in the search for novel AEDs [19]. These two test systems have been



	R
a	C_6H_5
b	4-Br-C_6H_4
c	4-Cl-C_6H_4
d	4-CH_3-C_6H_4
e	2-CH_3-C_6H_4
f	2,4-Cl_2-C_6H_3
g	4-F-C_6H_4
h	H

Scheme 2. Synthesis of the target compounds **7a**–**h** and (±)**-8a**–**h**. Reagents and conditions: i) CH_2Cl_2, K_2CO_3, DMF, reflux, 4 h; ii) pinacolone 50% KOH, CH_3OH, 70 °C, 5 h; iii) for **7a-g**, glacial acetic acid, **3a-g**, ethanol, reflux, 24-48 h, for **7h**, semicarbazide HCl, sodium acetate, ethanol, RT, 18 h; iv) for (±)-**8a-g**, NaOH, **3a-g**, ethanol, reflux, 1-24 h (c.f. experimental part), for (±)-**8h**, semicarbazide HCl, NaOH, ethanol, reflux, 24 h.



	R	R^1	R^2
a	H	H	C_6H_5
b	H	Br	4-Br-C_6H_4
c	H	Cl	4-Cl-C_6H_4
d	H	CH_3	4-CH_3-C_6H_4
e	CH_3	H	2-CH_3-C_6H_4
f	Cl	Cl	2,4-Cl_2-C_6H_3

Scheme 3. Synthesis of the target compounds (±)-**13a**–**f**. Reagents and conditions: i) $SOCl_2$, reflux, 1 h; ii) NaN_3, toluene, reflux, 1 h; iii) H_2N-NH_2.H_2O, ethanol, reflux, 2 h; iv) for (±)-**13a-d**, absolute ethanol, **11a-d**, reflux, 18 h, for (±)-**13e-f**, pyridine, **10e-f**, reflux, 18 h.

claimed to detect new bioactive chemical entities affording protection to generalized absence ("petit mal") seizures and generalized tonic-clonic ("grand mal") seizures, respectively [20].

All the synthesized compounds **7a**–**h**, (±)-**8a**–**h**, and (±)-**13a**–**f** were evaluated for their initial anticonvulsant activity (Phase 1 screening) according to the protocol given by the epilepsy section of National Institute of Neurological Disorders and Stroke (NINIDS) using the standard protocol adopted by the Antiepileptic Drug Development (ADD) program [21]. Those include the subcutaneous pentylenetetrazole (scPTZ) screen, which is used to identify compounds that elevate seizure threshold, and maximal electroshock seizure (MES) screen, which is indicative of the ability of the test compounds to prevent seizure spread. The selected compounds were subjected to quantitative estimation (median effective dose against seizures, ED_{50}) and to minimal motor impairment (neurotoxicity) test.

4. Results and discussion

In this study, the "gold standards" seizure models were used for preliminary (phase-I) screening of the synthesized compounds **7a**–**h**, (±)-**8a**–**h,** and (±)-**13a**–**f** and the results are presented in Table 1.

STP exhibited anticonvulsant properties in various animal models, including scPTZ and MES tests [22,23]. In addition, it has been demonstrated that a number of aryl semicarbazones displayed anticonvulsant activity in both scPTZ and MES screens [24]. Accordingly, synthesis of compounds as a hybrid structure incorporating STP scaffold and semicarbazone moiety, like compound **7h**, is of considerable importance aiming to get novel bioactive anticonvulsants.

In scPTZ screen, compound **7h** exhibited 50% protection at 346 μmol/kg as compared to STP which showed the same percent protection at 491 μmol/kg. Moreover, **7h** (346 μmol/kg) showed 100% protection in the MES screen whereas STP (640 μmol/kg) displayed only 66% protection in the same screen. Thus, incorporation of semicarbazone moiety into STP scaffold improves its anticonvulsant activity in both scPTZ and MES screens. It has been proposed that aryl semicarbazones exhibiting anticonvulsant activity interact at a putative binding site *in vivo* which was designated as a hydrogen bonding area and an aryl binding site. It is likely that the pharmacophoric descriptors in aryl semicarbazones are thought to be a hydrogen bonding semicarbazone group and a lipophilic aryl ring which align at their complementary areas on the macromolecular complex *in vivo* [25]. However, the aryl moiety in aryl semicarbazones displaying anticonvulsant activity has been replaced with *tert*-butyl group attached directly to the carbimino carbon as in **7h** with retention of anticonvulsant activity. Therefore, the portion of the binding site with which aryl group of aryl semicarbazones interacts will be referred to as a hydrophobic bonding area rather than an aryl binding site. Furthermore, another putative hydrophobic pocket in the receptor binding area can accommodate the hydrophobic β-1,3-benzodioxol-5-ylethylenic moiety as proposed in the literature [26]. The presence of double bond between this hydrophobic moiety and hydrogen bonding area provides vinylgous compounds as in **7h** which could improve binding with the complementary receptor binding area *in vivo*.

In order to reveal the importance of the primary amidic group in the anticonvulsant activity of STP derived semicarbazones, the terminal hydrogen of the amide moiety of **7h** has been replaced with aryl moiety containing substituents endowed with different electronic and steric properties. These substituents may be able to favour interaction with the structures of the target macromolecule *in vivo*, which in turn could lead to the development of new potent anticonvulsants. Substitution of the terminal hydrogen of the amidic group of **7h** with various aryl moieties gave compounds **7a-g**. In general, **7a-g** retained the anticonvulsant activity only in the scPTZ screen with exception of compounds **7b** and **7f** which showed also a weak anticonvulsant activity in MES screen. Compounds **7b** (330 μmol/kg, 66% protection) and **7e** (390 μmol/kg, 83% protection) are the most active congeners in the **7a**–**g** series and being 1.60 and 1.48, respectively, more potent than STP in scPTZ screen. Accordingly, it is conceivable from the present study

Table 2
ED_{50} and neurotoxicity of compounds **7h**, (±)-**13b**, and stiripentol.

Compound no.	ED_{50}[a] (mg/kg)	Neurotoxicity[b]	
		Grip strength	Wire mesh grasping test
7h	87 (71.85–105.35)	8/8	8/8
(±)–**13b**	110 (93.19–129.85)	0/8	0/8
STP[c]	115 (99.14–133.39)	0/8	0/8

[a] Data in parentheses are the confidence limit.
[b] Number of animals exhibiting neurotoxicity/number of animals tested at the dose level which displays 100% protection in MES (for **7h**) and in scPTZ (for (±)-**13b** and STP) screens.
[c] STP showed ED_{50} in MES screen = 277 ± 12.1 [23].

that substitution of terminal primary amidic group with different aryl moieties decreased the anticonvulsant potential significantly in MES screens which is in agreement with proposition of Puthucode *et al.* [26].

Pyrazolines (±)-**8a**–**h** could be considered as cyclic analogues of the aryl semicarbazones **7a**–**h**. Compounds (±)-**8a**–**h** displayed anticonvulsant activity in scPTZ screen where (±)-**8d** (390 μmol/kg, 83% protection) is the most potent candidate. While anticonvulsant activity of (±)-**8h** (346 μmol/kg) has been decreased as compared with its respective aryl semicabazone **7h** in both scPTZ and MES screens. Therefore, cyclization of **7a**–**h** to give (±)-**8a**–**h** did not significantly affect the anticonvulsant activity of **7a**–**h** indicating that the NH group proximal to the carbimino group of semicarbazone moiety did not play a crucial role in the anticonvulsant activity rather it could be only a hydrogen bonding entity. Additionally, variation in the biological activity of (±)-**8a**–**g** with different substituents at the aromatic ring could be due to the pharmacokinetic influence of these substituents on the anticonvulsant activity in scPTZ screen.

Removal of the terminal amidic NH group from compounds (±)-**8a**–**f** gave compounds (±)-**13a**–**f** in which (±)-**13b** exhibited the best anticonvulsant activity in the whole synthesized series in scPTZ screen with 100% protection at dose level of 350 μmol/kg being 2-fold more potent than STP in the same screen.

The most potent surrogates in the adopted anticonvulsant screens, compounds **7h** and (±)-**13b**, were subjected to quantitative estimation (median effective dose against seizures, ED_{50}) and to minimal motor impairment (neurotoxicity) tests (Table 2). Compound (±)-**13b** displayed a promising anticonvulsant profile in the whole synthesized compounds of the present investigation with ED_{50} = 110 mg/kg (256.8 μmol/kg) as compared with stiripentol (ED_{50} = 115 mg\kg, 490 μmol/kg) in the scPTZ screen without any neurotoxicity.

5. Conclusion

The synthesis of a number of stiripentol (STP) derived analogues as anticonvulsant candidates is reported in this study. Anticonvulsant evaluation of the new compounds in mice using gold standards (scPTZ and MES screens) revealed that most of the synthesized compounds afforded greater protection than STP in the scPTZ screen. The present results indicate that substitution of the terminal primary amidic group of the semicarbazone moiety with aryl moiety decreases the anticonvulsant activity in MES test without significant effect on scPTZ screen. Additionally, the hydrophobic binding area at the putative binding site *in vivo* could accommodate *tert*-butyl group instead of aryl rings. Also, the presence of double bond between the hydrophobic bonding area and hydrogen bonding area provides vinylgous compounds as in **7h** which could improve binding with the complementary receptor binding area *in vivo*. The most active compounds in the present investigation are 2-[(1*E*)-1-(1,3-benzodioxol-5-yl)-4,4-dimethylpent-1-en-3-ylidene]hydrazinecarboxamide (**7h**) at dose level of 346 μmol/kg in MES screen and (±) [(5*RS*)-(1,3-benzodioxol-5-yl)-3-*tert*-butyl-4,5-dihydro-1*H*-pyrazol-1-yl](4-bromophenyl)methanone (±)-(**13b**) at dose level of 350 μmol/kg in scPTZ screen displaying 100% protection in the preliminary (phase-I) screens. Compound (±)-(**13b**) is a promising anticonvulsant new chemical entity exhibiting ED_{50} = 110 mg/kg (256.8 μmol/kg) without any neurotoxicity. The results of this logical sequence of studies may permit the rational design of additional novel anticonvulsants.

6. Experimental protocols

6.1. Chemistry

All melting points were determined using Electrothermal Capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded as thin film (for oils) in NaCl discs or as KBr pellets (for solids) with JASCO FT/IR-6100 Spectrometer and values are represented in cm^{-1}. ^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were carried out on Jeol ECA 500 MHz spectrometer using TMS as internal standard and chemical shift values were recorded in ppm on δ scale. The ^1H NMR data were represented as follows: chemical shifts, multiplicity (s. singlet, d. doublet, dd. doublet of doublet, t. triplet, m. multiplet, br. broad), number of protons, and type of protons. The ^{13}C NMR data were represented as chemical shifts and type of carbons. HRMS was conducted on Agilent 6520 connected to Agilent LC 1200 ionization ESI spectrometer. Silica gel TLC (thin layer chromatography) cards from Merck (silica gel precoated aluminium cards with fluorescent indicator at 245 nm) were used for thin layer chromatography. Visualization was performed by illumination with UV light source (254 nm). Column chromatography was carried out on silica gel 60 (0.063–0.200 mm) obtained from Merck.

6.1.1. General procedure for synthesis of N-phenylhydrazinecarboxamides *3a–g*

A solution of the appropriate aniline **1a**–**g** (2.0 mol) in CH_2Cl_2 (120 mL) was added dropwise to a stirred solution of ethyl chloroformate (1.0 mol) in CH_2Cl_2 (30 mL). The reaction mixture was stirred at room temperature for 0.5 h (**2a**, **2b**, and **2d**–**f**) and 24 h (for **2c** and **2g**). After completion of the reaction, the reaction mixture was filtered and the filtrate was washed with 1N HCl, dried (Na_2SO_4) and evaporated under vacuum to afford the respective crude carbamates **2a**–**g**. A mixture of the appropriate carbamate **2a**–**g** (10 g) and hydrazine hydrate (50 mL) was stirred under reflux for sufficient time (TLC controlled). After completion of the reaction, the reaction mixture was cooled and filtered to afford the corresponding crude carboxamides **3a**–**g**. The crude products were used as such for the next reactions.

*6.1.1.1. N-Phenylhydrazinecarboxamide (**3a**).* Solid, mp 146–148 °C, (Lit [27]. mp 122–123 °C); reaction time 24 h; yield 80%.

*6.1.1.2. N-(4-Bromophenyl)hydrazinecarboxamide (**3b**).* Solid, mp 254 °C, (Lit [28]. mp 254 °C); reaction time 2 h; yield 87%.

*6.1.1.3. N-(4-Chlorophenyl)hydrazinecarboxamide (**3c**).* Solid, mp 260 °C, (Lit [27]. mp 190 °C); reaction time 24 h; yield 82%.

*6.1.1.4. N-(4-Methylphenyl)hydrazinecarboxamide (**3d**).* Solid, mp 208–210 °C, (Lit [29]. mp 212 °C); reaction time 24 h; yield 72%.

*6.1.1.5. N-(2-Methylphenyl)hydrazinecarboxamide (**3e**) [30].* Solid, mp 154–156 °C; reaction time 24 h; yield 49%.

*6.1.1.6. N-(2,4-Dichlorophenyl)hydrazinecarboxamide (**3f**) [31].* Solid, mp 160–162 °C; reaction time 1 h; yield 43.5%.

*6.1.1.7. N-(4-Fluorophenyl)hydrazinecarboxamide (**3g**).* Solid, mp 182–184 °C, (Lit [29]. mp 185 °C); reaction time 24 h; yield 90%.

*6.1.2. Synthesis of 1,3-benzodioxole-5-carbaldehyde (**5**, Piperonal) [17]*

A solution of 3,4-dihydroxybenzaldehyde (10 g, 0.073 mol) in DMF (150 mL) was added dropwise to a suspension of CH_2Cl_2 (7 mL, 0.108 mol) and K_2CO_3 (20 g, 0.144 mol) in DMF (300 mL). The mixture was stirred and heated to reflux for 4 h then cooled and filtered. The filtrate was concentrated, diluted with water and extracted with diethyl ether (3 × 100 mL). The filtered cake was washed with diethyl ether (100 mL). The ethereal extracts were combined, washed with 10% NaOH (100 mL), water (100 mL), dried (Na_2SO_4) and evaporated to afford 7.0 g (64%) of **5** as light brown solid mp 37 °C. The crude **5** was used in the next step without any further purification.

*6.1.3. Synthesis of (1E)-1-(1,3-benzodioxol-5-yl)-4,4-dimethylpent-1-en-3-one (**6**) [7]*

50% Aqueous solution of KOH (78.5 mL) was added to a stirred solution of piperonal (**5**, 11.0 g, 0.074 mol) and pinacolone [18] (10.2 mL, 7.4 g, 0.074 mol) in methanol (200 mL). The reaction mixture was stirred and heated at 70 °C for 5 h. The reaction mixture was cooled to room temperature and diluted with water (150 mL). The precipitated solid was filtered off, washed with water (50 mL) and air dried to afford 13 g (78%) of **6** as pale yellow crystals mp 92 °C. The crude **6** was pure enough to be used in the next step. Analytical sample of **6** was obtained by recrystallization from ethanol to give **6** mp 93 °C (Lit [7]. mp 93 °C). The spectral data of **6** were compatible with the reported spectral data [32].

*6.1.4. General procedure for synthesis of 2-[(1E)-1-(1,3-benzodioxol-5-yl)-4,4-dimethylpent-1-en-3-ylidene]-N-arylhydrazinecarboxamides **7a–g***

Glacial acetic acid (1 mL) was added to a solution of **6** (1.0 g, 0.0043 mol) and the appropriate aryl semicarbazide **3a–g** (0.0043 mol) in absolute ethanol (40 mL). The reaction mixture was stirred under reflux for the appropriate time (TLC controlled). The solvent was evaporated under reduced pressure to afford the respective crude *N*-arylhydrazinecarboxamides **7a–g**.

*6.1.4.1. 2-[(1E)-1-(1,3-Benzodioxol-5-yl)-4,4-dimethylpent-1-en-3-ylidene]-N-phenyl- hydrazinecarboxamide (**7a**).* Canary yellow Solid, mp 90 °C; reaction time 24 h; purified by column chromatography using silica gel and petroleum ether/ethyl acetate (9/1 then 8/2); yield 40%. IR (KBr, cm^{-1}): 3373 (NH), 3200 (NH), 2975 (C=C), 1682 (C=O), 1598 (C=N). ^1H NMR ($CDCl_3$): δ 1.2 (s, 9H, *t*-butyl), 5.9 (s, 2H, O–CH_2–O), 6.25 (d, J = 16.9 Hz, 1H, C*H* = CHph), 6.65 (d, J = 16.8 Hz, 1H, CH = C*H*ph), 6.81 (d, J = 4.3 Hz, 1H, H-7), 6.99 (d, J = 4.2 Hz, 1H, H-6), 7.3 (s, 1H, H-4), 7.33 (t, J = 3.9, 3.8 Hz, 1H, H-4′), 7.49 (t, J = 4.2, 3.8 Hz, 2H, H-3′, H-5′), 7.5 (d, J = 4.3 Hz, 2H, H-2′, H-6′), 7.98 (s, 1H, CONHph), 8.2 (s, 1H, NNHCO) ppm. ^{13}C NMR ($CDCl_3$): δ 28.3 (C(*C*H_3)$_3$), 38.4 (*C*(CH_3)$_3$), 101 (CH_2), 105, 108, 115, 119, 122, 123, 129, 129.5 (CH_{ar}, C_{ar}), 137 (*C*H = CHph), 138 (CH = *C*Hph), 148.4, 148.7 (C_{ar}), 153 (C=N), 155 (C=O) ppm. HRMS: for $C_{21}H_{23}N_3O_3.H^+$, calcd. 366.1812, found 366.1806.

*6.1.4.2. 2-[(1E)-1-(1,3-Benzodioxol-5-yl)-4,4-dimethylpent-1-en-3-ylidene]-N-(4-bromophenyl)hydrazinecarboxamide (**7b**).* Brown solid, mp 144 °C; reaction time 24 h; purified by recrystallization from methanol; yield 30%. IR (KBr, cm^{-1}): 3352 (NH), 3186 (NH), 2963 (C=C), 1681 (C=O), 1590 (C=N). ^1H NMR ($CDCl_3$): δ 1.2 (s, 9H, *t*-butyl), 6.0 (s, 2H, O–CH_2–O), 6.25 (d, J = 16.8 Hz, 1H, C*H* = CHph), 6.65 (d, J = 16.9 Hz, 1H, CH = C*H*ph), 6.77–6.90 (m, 2H, H-6, H-7), 6.97 (s, 1H, H-4), 7.37–7.47 (m, 4H, H-2′, H-3′, H-5′, H-6′), 8.0 (s, 1H, CONHph), 8.2 (s, 1H, NNHCO) ppm. ^{13}C NMR ($CDCl_3$): δ 28.1 (C(*C*H_3)$_3$), 38.3 (*C*(CH_3)$_3$), 101 (CH_2), 105, 108, 115.4, 115.6, 120, 122, 129, 131 (CH_{ar}, C_{ar}), 137,2 (*C*H = CHph), 137.6 (CH = *C*Hph), 148.3, 148.6 (C_{ar}), 153 (C=N), 156 (C=O) ppm. HRMS: for $C_{21}H_{22}BrN_3O_3.H^+$, calcd. 444.0917, found 444.0917.

*6.1.4.3. 2-[(1E)-1-(1,3-Benzodioxol-5-yl)-4,4-dimethylpent-1-en-3-ylidene]-N-(4- chlorophenyl)hydrazinecarboxamide (**7c**).* Yellow solid, mp 127 °C; reaction time 24 h; purified by column chromatography using silica gel and petroleum ether/ethyl acetate/chloroform (8/1/1) then petroleum ether/ethyl acetate (8/2) followed by recrystallization from ethanol; yield 42%. IR (KBr, cm^{-1}): 3346 (NH), 3196 (NH), 2963 (C=C), 1683 (C=O), 1592 (C=N). ^1H NMR ($CDCl_3$): δ 1.2 (s, 9H, *t*-butyl), 6.0 (s, 2H, O–CH_2–O), 6.27 (d, J = 17.2 Hz, 1H, C*H* = CHph), 6.66 (d, J = 17.2 Hz, 1H, CH = C*H*ph), 6.78–6.81 (m, 1H, H-7), 6.80–6.88 (m, 1H, H-6), 6.99 (d, J = 6.3 Hz, 1H, H-4), 7.24–7.27 (m, 2H, H-2′, H-6′), 7.42–7.45 (m, 2H, H-3′, H-5′),8.0 (s, 1H, CONHph), 8.2 (s, 1H, NNHCO) ppm. ^{13}C NMR ($CDCl_3$): δ 28.2 (C(*C*H_3)$_3$), 38.3 (*C*(CH_3)$_3$), 101 (CH_2), 105, 108, 115, 120, 122, 128, 128.8, 129.3 (CH_{ar}, C_{ar}), 136 (*C*H = CHph), 137 (CH = *C*Hph), 148.3, 148.6 (C_{ar}), 153 (C=N), 156 (C=O) ppm. HRMS: for $C_{21}H_{22}ClN_3O_3.H^+$ calcd. 400.1422, found 400.1410.

*6.1.4.4. 2-[(1E)-1-(1,3-Benzodioxol-5-yl)-4,4-dimethylpent-1-en-3-ylidene]-N-(4-methylphenyl)hydrazinecarboxamide (**7d**).* Brown solid, mp 111 °C; reaction time 24 h; purified by column chromatography using silica gel and ethyl acetate/chloroform (9/1) followed by recrystallization from methanol; yield 32%. IR (KBr, cm^{-1}): 3368 (NH), 3179 (NH), 2959 (C=C), 1692 (C=O), 1590 (C=N). ^1H NMR ($CDCl_3$): δ 1.15 (s, 9H, *t*-butyl), 2.22 (s, 3H, CH_3), 5.93 (s, 2H, O–CH_2–O), 6.2 (d, 17.6, 1H, C*H* = CHph), 6.59 (d, J = 16.8 Hz, 1H,CH = C*H*ph), 6.74 (d, J = 8.5 Hz, 1H, H-7), 6.81 (d, J = 7.7, 1H, H-6), 6.92 (d, J = 1.6 Hz, 1H, H-4), 7.0 (d, J = 8.5 Hz, 2H, H-2′, H-6′), 7.3 (d, J = 7.6 Hz, 2H, H-3′, H-5′), 7.8 (s, 1H, CONHph), 8.0 (s, 1H, NNHCO) ppm. ^{13}C NMR ($CDCl_3$): δ 20.7 (CH_3), 28.3 (C(*C*H_3)$_3$), 38.3 (*C*(CH_3)$_3$), 101 (CH_2), 105, 108, 115, 119, 119.5, 122, 129, 132 (CH_{ar}, C_{ar}), 135 (*C*H = CHph), 137 (CH = *C*Hph), 148.3, 148.6 (C_{ar}), 153 (C=N), 155 (C=O) ppm. HRMS: for $C_{22}H_{25}N_3O_3.H^+$, calcd. 380.1969, found 380.1962.

*6.1.4.5. 2-[(1E)-1-(1,3-Benzodioxol-5-yl)-4,4-dimethylpent-1-en-3-ylidene]-N-(2-methylphenyl)hydrazinecarboxamide (**7e**).* Light brown solid, mp 126 °C; reaction time 24 h; purified by recrystallization from methanol; yield 46%. IR (KBr, cm^{-1}): 3349 (NH), 3197 (NH), 2963 (C=C), 1652 (C=O), 1590 (C=N). ^1H NMR ($CDCl_3$): δ 1.2 (s, 9H, *t*-butyl), 2.3 (s, 3H, CH_3), 5.99 (s, 2H, O–CH_2–O), 6.3 (d, J = 16.8 Hz, 1H, C*H* = CHph), 6.7 (d, J = 16.8 Hz, 1H, CH = C*H*ph), 6.8 (d, J = 7.7 Hz, 1H, H-7), 6.9 (dd, J = 7.7, 1.5 Hz, 1H, H-6), 6.99 (t, J = 6.9, 6.9 Hz, 1H, H-4′), 7.0 (s, 1H, H-4), 7.16 (d, J = 6.9 Hz, 1H, H-5′), 7.2 (t, J = 7.7, 7.7 Hz, 1H, H-3′), 8.0 (d, J = 8.4 Hz, 1H, H-2′), 8.3 (s, 1H, CONH ph), 8.5 (s, 1H, NNHCO) ppm. ^{13}C NMR ($CDCl_3$): δ 20.7 (phCH_3), 28.3 (C(*C*H_3)$_3$), 38.3 (*C*(CH_3)$_3$), 101 (CH_2), 105, 108, 115, 119, 119.5, 122, 129, 132 (CH_{ar}, C_{ar}), 135 (*C*H = CHph), 137 (CH = *C*Hph), 148.3, 148.6 (C_{ar}), 153 (C=N), 155 (C=O) ppm. HRMS: for $C_{22}H_{25}N_3O_3.H^+$ calcd. 380.1969, found 380.1961.

*6.1.4.6. 2-[(1E)-1-(1,3-Benzodioxol-5-yl)-4,4-dimethylpent-1-en-3-ylidene]-N-(2,4-dichlorophenyl)hydrazinecarboxamide (**7f**).* Yellow solid, mp 157 °C; reaction time 48 h; purified by recrystallization

from methanol; yield 29%. IR (KBr, cm^{-1}): 3334 (NH), 3199 (NH), 2962 (C=C), 1692 (C=O), 1575 (C=N). ^1H NMR ($CDCl_3$): δ 1.2 (s, 9H, *t*-butyl), 5.99 (s, 2H, O–CH_2–O), 6.29 (d, J = 17.2 Hz, 1H, C*H* = CHph), 6.68 (d, J = 17.2 Hz, 1H, CH = C*H*ph), 6.79 (d, J = 8.0 Hz, 1H, H-7), 6.88 (dd, J = 8.1, 1.7 Hz, 1H, H-6), 6.99 (d, J = 1.7 Hz, 1H, H-4), 7.19 (dd, J = 8.6, 2.3 Hz, 1H, H-5′), 7.36 (d, J = 2.2 Hz, 1H, H-3′), 8.30 (d, J = 9.2 Hz, 1H, H-6′), 8.2 (s, 1H, CONHph), 9.0 (s, 1H, NNHCO) ppm. ^{13}C NMR ($CDCl_3$): δ 28.2 (C(CH_3)$_3$), 38.5 (*C*(CH_3)$_3$), 101 (CH_2), 105, 108, 115, 120, 122, 127.2, 127.7, 128.5, 129.3 (CH_{ar}, C_{ar}), 134 (*C*H = CHph), 137 (CH = *C*Hph), 148.3, 148.6 (C_{ar}), 152.8 (C=N), 156.5 (C=O) ppm. HRMS: for $C_{21}H_{21}Cl_2N_3O_3.H^+$, calcd. 434.1033, found 434.1024.

*6.1.4.7. 2-[(1E)-1-(1,3-Benzodioxol-5-yl)-4,4-dimethylpent-1-en-3-ylidene]-N-(4-fluorophenyl)hydrazinecarboxamide (**7g**).* Yellow solid, mp 110 °C; reaction time 24 h; purified by column chromatography using silica gel and chloroform followed by recrystallization from methanol; yield 25%. IR (KBr, cm^{-1}): 3346 (NH), 3211 (NH), 2965 (C=C), 1679 (C=O), 1610 (C=N). ^1H NMR ($CDCl_3$): δ 1.15 (s, 9H, *t*-butyl), 5.9 (s, 2H, O–CH_2–O), 6.2 (d, J = 17.6 Hz, 1H, C*H* = CHph), 6.59 (d, J = 17.6 Hz, 1H, CH = C*H*ph), 6.73 (d, J = 8.4 Hz, 1H, H-7), 6.8 (dd, J = 7.7, 1.6 Hz, 1H, H-6), 6.92 (d, J = 1.6 Hz, 1H, H-4), 6.95 (d, J = 8.4 Hz, 2H, H-2′, H-6′), 7.36–7.39 (m, 2H, H-3′, H-5′), 7.93 (s, 1H, CONH ph), 8.1 (s, 1H, NNHCO) ppm. ^{13}C NMR ($CDCl_3$): δ 28.3 (C(*C*H_3)$_3$), 38.4 (*C*(CH_3)$_3$), 101 (CH_2), 105, 108, 115.4, 115.6, 115.7, 121, 122, 129 (CH_{ar}, C_{ar}), 134 (*C*H = CHph), 137 (CH = *C*Hph), 148.3, 148.6 (C_{ar}), 153 (C=N), 156 (C=O) ppm. HRMS: for $C_{21}H_{22}FN_3O_3.H^+$, calcd. 384.1718, found 384.1715.

*6.1.5. Synthesis of 2-[(1E)-1-(1,3-benzodioxol-5-yl)-4,4-dimethylpent-1-en-3-ylidene]hydrazinecarboxamide (**7h**)*

A solution of **6** (1.0 g, 0.0043 mol), semicarbazide hydrochloride (0.5 g, 0.0043 mol) and anhydrous sodium acetate (0.35 g, 0.0043 mol) in absolute ethanol (40 mL) was stirred at room temperature for 18 h. The reaction mixture was filtered and the filtrate was evaporated under vacuum to afford 0.65 g (46%) of crude **7h**. The solid was recrystallized from ethanol to afford 0.54 g (38%) of pure **7h** as a yellowish white solid mp 144 °C. IR (KBr, cm^{-1}): 3373(NH), 3266, 3201 (NH_2), 2970 (C=C), 1684 (C=O), 1581 (C=N). ^1H NMR ($CDCl_3$): δ 1.1 (s, 9H, *t*-butyl), 5.9 (s, 2H, O–CH_2–O), 6.25 (d, J = 17.2 Hz, 1H, C*H* = CHph), 6.61 (d, J = 17.2 Hz, 1H, CH = C*H*ph), 6.77 (d, J = 8.1 Hz, 1H, H-7), 6.84 (dd, J = 1.7, 8.0 Hz, 1H, H-6), 6.98 (d, J = 1.1 Hz, 1H, H-4), 8.0 (s, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ 28.3 (C(*C*H_3)$_3$), 38.3 (*C*(CH_3)$_3$), 101 (CH_2), 105, 108, 115 (CH_{ar}), 122 (C_{ar}), 129 (*C*H = CHph), 137 (CH = *C*Hph), 148.3, 148.5 (C_{ar}), 155 (C=N), 157 (C=O) ppm. HRMS: for $C_{15}H_{19}N_3O_3.H^+$, calcd. 290.1499, found 290.1501.

*6.1.6. General procedure for synthesis of (±)-N-aryl-(5RS)-(1,3-benzodioxol-5-yl)-3-tert-butyl-4,5-dihydro-1H-pyrazole-1-carboxamides (±)-**8a**–**h***

20% Aqueous NaOH (1 mL) was added to a solution of **6** (1.0 g, 0.0043 mol) and the appropriate arylsemicarbazide **3a**–**g** or semicarbazide hydrochloride (0.004 mol) in ethanol (10 mL). The reaction mixture was stirred under reflux for appropriate time (TLC controlled). The solvent was evaporated under vacuum to afford crude (±)-**8a**–**h**. The crude products were recrystallized from ethanol to afford (±)-**8a**–**h** as pure solids.

*6.1.6.1. (±)-(5RS)-(1,3-Benzodioxol-5-yl)-3-tert-butyl-N-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide ((±)-**8a**).* Yellow solid, mp 138 °C; reaction time 24 h; yield 23%. IR (KBr, cm^{-1}): 3382 (NH), 2961 (C=C), 1689 (C=O), 1597 (C=N). ^1H NMR ($CDCl_3$): δ 1.2 (s, 9H, *t*-butyl), 2.77 (dd, J = 5.4, 17.6 Hz, 1H, CH*C*H_2), 3.4 (dd, J = 12.3, 18.4 Hz, 1H, CH*C*H_2), 5.3 (t, J = 6.1, 4.6 Hz, 1H, *C*HCH$_2$), 5.9 (s, 2H, O–CH_2–O), 6.68–6.74 (m, 3H, H-4, H-6, H-7), 6.98 (s, 1H, H-4′), 7.2 (d, J = 7.7 Hz, 2H, H-3′, H-5′), 7.4 (d, J = 6.9 Hz, 2H, H-2′, H-6′), 7.95 (s, 1H, CONHph) ppm. ^{13}C NMR ($CDCl_3$): δ 28.1 (C(*C*H_3)$_3$), 38.1 (*C*(CH_3)$_3$), 42.5 (CH*C*H_2), 59.9 (*C*HCH$_2$), 101 (O–CH_2–O), 105, 108, 118.9, 119, 122, 128, 137, 138, 147, 148 (CH_{ar}, C_{ar}), 152 (C=O), 163 (C=N) ppm. HRMS: for $C_{21}H_{23}N_3O_3.H^+$, calcd. 366.1812, found 366.1803.

*6.1.6.2. (±)-(5RS)-(1,3-Benzodioxol-5-yl)-N-(4-bromophenyl)-3-tert-butyl-4,5-dihydro-1H-pyrazole-1-carboxamide ((±)-**8b**).* Off-white solid, mp 141 °C; reaction time 1 h; yield 56%. IR (KBr, cm^{-1}): 3394 (NH), 2959 (C=C), 1687 (C=O), 1588 (C=N). ^1H NMR ($CDCl_3$): δ 1.2 (s, 9H, *t*-butyl), 2.79 (dd, J = 5.4, 18.3 Hz, 1H, CH*C*H_2), 3.4 (dd, J = 10.7, 17.6 Hz, 1H, CH*C*H_2), 5.3 (dd, J = 5.4, 11.5 Hz, 1H, *C*HCH$_2$), 5.9 (s, 2H, O–CH_2–O), 6.65–6.73 (m, 3H, H-4, H-6, H-7), 7.32–7.36 (m, 4H, H-2′, H-3′, H-5′, H-6′), 7.9 (s,1H, CONHph) ppm. ^{13}C NMR ($CDCl_3$): δ 28.1 (C(*C*H_3)$_3$), 34.1 (*C*(CH_3)$_3$), 42.5 (CH*C*H_2), 59.9 (*C*HCH$_2$), 101 (O–CH_2–O), 105, 108, 115, 118, 120, 131, 136, 137, 147, 148 (CH_{ar}, C_{ar}), 151 (C=O), 164 (C=N) ppm. HRMS: for $C_{21}H_{22}BrN_3O_3.H^+$, calcd. 444.0917, found 444.0908.

*6.1.6.3. (±)-(5RS)-(1,3-Benzodioxol-5-yl)-3-tert-butyl-N-(4-chlorophenyl)-4,5-dihydro-1H-pyrazole-1-carboxamide ((±)-**8c**).* White solid, mp 141 °C; reaction time 8 h; yield 40%. IR (KBr, cm^{-1}): 3397 (NH), 2963 (C=C), 1658 (C=O), 1590 (C=N). ^1H NMR ($CDCl_3$): δ 1.2 (s, 9H, *t*-butyl), 2.79 (dd, J = 5.4, 18.4 Hz, 1H, CH*C*H_2), 3.4 (dd, J = 12.3, 18.4 Hz, 1H, CH*C*H_2), 5.3 (dd, J = 5.4, 12.2 Hz, 1H, *C*HCH$_2$), 5.9 (s, 2H, O–CH_2–O), 6.66–6.73 (m, 3H, H-4, H-6, H-7), 7.2 (t, J = 6.9, 1.6 Hz, 2H, H-2′, H-6′), 7.4 (t, J = 6.9, 2.3 Hz, 2H, H-3′, H-5′), 7.9 (s, 1H, CONHph) ppm. ^{13}C NMR ($CDCl_3$): δ 28.1 (C(*C*H_3)$_3$), 34.1 (*C*(CH_3)$_3$), 42.5 (CH*C*H_2), 59.9 (*C*HCH$_2$), 101 (O–CH_2–O), 105, 108, 118, 120.6, 127.7, 128, 136, 137, 147, 148 (CH_{ar}, C_{ar}), 151 (C=O), 164 (C=N) ppm. HRMS: for $C_{21}H_{22}ClN_3O_3.H^+$, calcd. 400.1422, found 400.1409.

*6.1.6.4. (±)-(5RS)-(1,3-Benzodioxol-5-yl)-3-tert-butyl-N-(4-methylphenyl)-4,5-dihydro-1H-pyrazole-1-carboxamide ((±)-**8d**).* White Solid, mp 131 °C; reaction time 1 h; yield 58%. IR (KBr, cm^{-1}): 3399 (NH), 2963 (C=C), 1681 (C=O), 1590 (C=N). ^1H NMR ($CDCl_3$): δ 1.2 (s, 9H, *t*-butyl), 2.3 (s, 3H, CH_3), 2.77 (dd, J = 6.1, 12.2 Hz, 1H, CH*C*H_2), 3.4 (dd, J = 12.9,18.4 Hz, 1H, CH*C*H_2), 5.3 (dd, J = 4.2, 11.5 Hz, 1H, *C*HCH$_2$), 5.9 (s, 2H, O–CH_2–O), 6.67–6.74 (m, 3H, H-4, H-6, H-7), 7.0 (d, J = 8.4 Hz, 2H, H-2′, H-6′), 7.3 (d, J = 6.1 Hz, 2H, H-3′, H-5′), 7.8 (s, 1H, CONHph) ppm. ^{13}C NMR ($CDCl_3$): δ 20.0 (CH_3), 28.1 (C(*C*H_3)$_3$), 34.1 (*C*(CH_3)$_3$), 42.5 (CH*C*H_2), 60.0 (*C*HCH$_2$), 101 (*C*H_2), 105, 108, 118, 126, 129, 132, 136, 137, 146, 148 (CH_{ar}, C_{ar}), 153 (C=O), 163 (C=N) ppm. HRMS: for $C_{22}H_{25}N_3O_3.H^+$,calcd. 380.1969, found 380.1975.

*6.1.6.5. (±)-(5RS)-(1,3-Benzodioxol-5-yl)-3-tert-butyl-N-(2-methylphenyl)-4,5-dihydro-1H-pyrazole-1-carboxamide ((±)-**8e**).* White solid, mp 122 °C; reaction time 1 h; yield 50%. IR (KBr, cm^{-1}): 3401 (NH), 2965 (C=C), 1688 (C=O), 1588 (C=N). ^1H NMR ($CDCl_3$): δ 1.2 (s, 9H, *t*-butyl), 2.3 (s, 3H, CH_3), 2.77 (dd, J = 5.4, 17.6 Hz, 1H, CH*C*H_2), 3.4 (dd, J = 12.2,18.4 Hz, 1H, CH*C*H_2), 5.3 (dd, J = 5.4, 11.5 Hz, 1H, *C*HCH$_2$), 5.9 (s, 2H, O*C*H_2O), 6.7–6.74 (m, 3H, H-4, H-6, H-7), 6.9–7.9 (m, 4H, H-2′, H-3′, H-4′, H-5′), 8.0 (s, 1H, CONHph) ppm. ^{13}C NMR ($CDCl_3$): δ 17.0 (CH_3), 28.1 (C(*C*H_3)$_3$), 34.1 (*C*(CH_3)$_3$), 42.5 (CH*C*H_2), 60.0 (*C*HCH$_2$), 101 (*C*H_2), 105, 108, 119, 119.8, 122, 126, 126.8, 130, 137, 137.1, 147, 148 (CH_{ar}, C_{ar}), 152 (C=O), 163 (C=N) ppm. HRMS: for $C_{22}H_{25}N_3O_3.H^+$, calcd. 380.1969, found 380.1961.

*6.1.6.6. (±)-(5RS)-(1,3-Benzodioxol-5-yl)-3-tert-butyl-N-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazole-1-carboxamide ((±)-**8f**).* White solid, mp 150 °C; reaction time 1 h; yield 47%. IR (KBr, cm^{-1}): 3399 (NH), 2963 (C=C), 1681 (C=O), 1590 (C=N). ^1H NMR ($CDCl_3$): δ 1.2 (s, 9H, *t*-butyl), 2.79 (dd, J = 5.3, 18.4 Hz, 1H, CH*C*H_2), 3.4 (dd, J = 12.2, 18.4 Hz, 1H, CH*C*H_2), 5.3 (dd, J = 4.6, 11.5 Hz, 1H, *C*HCH$_2$), 5.9 (s, 2H,

O–CH_2–O), 6.68–6.75 (m, 3H, H-4, H-6, H-7), 7.1 (d, $J = 8.4$ Hz, 1H, H-6′), 7.3 (s, 1H, H-3′), 8.2 (d, $J = 9.2$ Hz, 1H, H-5′), 8.7 (s, 1H, CONHph) ppm. ^{13}C NMR ($CDCl_3$): δ 28.1 (C(CH_3)$_3$), 34.1 (*C*(CH_3)$_3$), 42.5 (CH*C*H_2), 60.0 (*C*HCH_2), 101 (O–CH_2–O), 105, 108, 119, 120, 122, 126, 127, 128, 134, 136, 147, 148 (CH_{ar}, C_{ar}), 151 (C=O), 164 (C=N) ppm. HRMS: for $C_{21}H_{21}Cl_2N_3O_3.H^+$, calcd. 434.1033, found 434.1034.

*6.1.6.7. (±)-(5RS)-(1,3-Benzodioxol-5-yl)-3-tert-butyl-N-(4-fluorophenyl)-4,5-dihydro-1H-pyrazole-1-carboxamide ((±)-**8g**).* White solid, mp 144 °C; reaction time 1 h; yield 64%. IR (KBr, cm^{-1}): 3403 (NH), 2965 (C=C), 1682 (C=O), 1613 (C=N). ^{1}H NMR ($CDCl_3$): δ 1.2 (s, 9H, *t*-butyl), 2.79 (dd, $J = 5.4$, 18.4 Hz, 1H, CHCH_2), 3.4 (dd, $J = 11.5$, 17.6 Hz, 1H, CHCH_2), 5.3 (dd, $J = 5.4$, 12.3 Hz,1H, C*H*CH_2), 5.9 (s, 2H, O–CH_2–O), 6.67–6.73 (m, 3H, H-4, H-6, H-7), 6.9 (t, $J = 8.5$, 9.2 Hz, 2H, H-2′, H-6′), 7.4 (dd, $J = 4.6$, 9.2 Hz, 2H, H-3′, H-5′), 7.88 (s, 1H, CONHph) ppm. ^{13}C NMR ($CDCl_3$): δ 28.1 (C(CH_3)$_3$), 34.1 (*C*(CH_3)$_3$), 42.5 (CH*C*H_2), 60.0 (*C*HCH_2), 101 (O–CH_2–O), 105, 108, 115.3, 115.4, 118, 120.6, 120.7, 134, 136, 147, 148 (CH_{ar}, C_{ar}), 152 (C=O), 163.8 (C=N) ppm. HRMS: for $C_{21}H_{22}FN_3O_3.H^+$, calcd. 384.1718, found 384.1710.

*6.1.6.8. (±)-(5RS)-(1,3-Benzodioxol-5-yl)-3-tert-butyl-4,5-dihydro-1H-pyrazole-1- carboxamide ((±)-**8h**).* Solid, mp 160 °C; reaction time 24 h; yield 64%. IR (KBr, cm^{-1}): 3458 (NH), 2966 (C=C), 1681 (C=O), 1606 (C=N). ^{1}H NMR ($CDCl_3$): δ 1.1 (s, 9H, *t*-butyl), 2.69 (dd, $J = 2.3$, 17.6 Hz, 1H, CHCH_2), 3.3 (dd, $J = 13.8$, 17.6 Hz, 1H, CHCH_2), 5.2 (dd, $J = 9.9$, 12.2 Hz, 1H, C*H*CH_2), 5.3 (s, 2H, NH_2), 5.9 (s, 2H, O–CH_2–O), 6.61–6.71 (m, 3H, H-4, H-6,H-7) ppm. ^{13}C NMR ($CDCl_3$): δ 28.0 (C(CH_3)$_3$), 33.9 (*C*(CH_3)$_3$), 42.4 (CH*C*H_2), 59.6 (*C*HCH_2), 101 (O–CH_2–O), 105, 108, 118.7, 137, 146.8, 148 (CH_{ar}, C_{ar}), 155(C=O), 163 (C=N) ppm. HRMS: for $C_{15}H_{19}N_3O_3.H^+$, calcd. 290.1499, found 290.1497.

*6.1.7. General procedure for synthesis of substituted acid chlorides **10a–f** and substituted acid azides **11a–d***

A solution of the appropriate benzoic acid **9a–f** (0.006 mol) in thionyl chloride (10 mL) was refluxed for 1 h, diluted with dry toluene and evaporated to afford the respective acid chlorides **10a–f**. Crude **10a–d** were dissolved in dry toluene (10 mL) and NaN_3 (1.17 g, 0.018 mol) was added to the reaction mixture. The reaction mixture was refluxed for 1 h, filtered and evaporated under reduced pressure to afford **11a–d**. The crude products **10e**,**f** and **11a–d** were used in the next step without any further purification.

*6.1.8. Synthesis of (±)-(5RS)-(1,3-benzodioxol-5-yl)-3-tert-butyl-4,5-dihydro-1H-pyrazole ((±)-**12**)*

Hydrazine hydrate (0.62 mL, 0.64 g, 0.012 mol) was added to a solution of **6** (1.0 g, 0.0043 mol) in absolute ethanol (30 mL). The reaction mixture was stirred under reflux for 2 h, and evaporated under vacuum to afford 1.0 g (90%) of (±)-**12** as yellowish oil. The oil was dissolved in methanolic HCl, cooled and filtered to afford 1.15 g (100%) of hydrochloride salt of (±)-**12** as white powder, mp 120 °C ^{1}H NMR ($CDCl_3$) of (±)-**12** (base): 1.0 (s, 9H, *t*-butyl), 2.3 (dd, $J = 10.7$, 16.1 Hz, 1H, CHCH_2), 2.9 (dd, $J = 9.95$, 16.1 Hz, 1H,CHCH_2), 4.5 (t, $J = 9.9$, 10.7 Hz, 1H, C*H*CH_2), 5.9 (s, 2H, O–CH_2–O), 6.7 (s, 1H, NH), 6.75 (dd, $J = 1.5$, 7.6 Hz, 1H, H-6), 6.7 (d, $J = 8.4$ Hz,1H, H-7), 6.8 (s, 1H, H-4) ppm.^{13}C NMR ($CDCl_3$) of (±)-**12** (base): 27.9 (C(CH_3)$_3$), 35.5 (*C*(CH_3)$_3$), 40.0 (CH*C*H_2), 60.0 (*C*HCH_2), 101 (OCH_2O) 107, 108, 120 (CH_{ar}), 137 (C_{ar}), 146, 147 (C_{ar}), 160 (C=N) ppm.

*6.1.9. General procedure for synthesis of (±)-[(5RS)-(1,3-benzodioxol-5-yl)-3-tert-butyl-4,5-dihydro-1H-pyrazol-1-yl](aryl) methanones (±)-**13a–d***

The appropriate acid azide **11a–d** (0.004 mol) was added to a solution of (±)-**12** (1.0 g, 0.004 mol) in absolute ethanol (30 mL). The reaction mixture was stirred under reflux for 18 h, and the solvent was evaporated under vacuum to afford crude (±)-**13a–d** which were recrystallized from ethanol.

*6.1.9.1. (±)-[(5RS)-(1,3-Benzodioxol-5-yl)-3-tert-butyl-4,5-dihydro-1H-pyrazol-1-yl](phenyl)-methanone ((±)-**13a**).* White solid, mp 172 °C; yield 45%. IR (KBr, cm^{-1}): 2965 (C=C), 1686 (C=O), 1626 (C=N). ^{1}H NMR ($CDCl_3$): δ 1.1 (s, 9H, *t*-butyl), 2.7(dd, $J = 4.6$, 18.4 Hz, 1H, CHCH_2), 3.4 (dd, $J = 11.5$, 18.4 Hz, 1H, CHCH_2), 5.4 (dd, $J = 3.9$, 11.5 Hz, 1H, C*H*CH_2), 5.9 (d, $J = 3.1$ Hz, 2H, O–CH_2–O), 6.65 (d, $J = 7.7$ Hz, 1H, H-2), 6.7 (s, 1H, H-3), 6.8 (d, $J = 7.7$ Hz, 1H, H-1), 7.38–7.44 (m, 3H, H-3′, H-4′, H-5′), 7.7 (d, $J = 6.9$Hz, 2H, H-2′, H-6′) ppm. ^{13}C NMR ($CDCl_3$): δ 28.1 (C(CH_3)$_3$), 34.1 (*C*(CH_3)$_3$), 40.0 (CH*C*H_2), 60.0 (*C*HCH_2), 101 (O–CH_2–O), 106, 108, 119, 128, 130, 131, 135, 137, 146, 148 (CH_{ar}, C_{ar}), 165 (C=O), 167 (C=N) ppm. HRMS: for $C_{21}H_{22}N_2O_3.H^+$, calcd. 351.1703, found 351.1695.

*6.1.9.2. (±)-[(5RS)-(1,3-Benzodioxol-5-yl)-3-tert-butyl-4,5-dihydro-1H-pyrazol-1-yl] (4-bromophenyl)methanone ((±)-**13b**).* Off-white solid, mp 131 °C; yield 43%. IR (KBr, cm^{-1}): 2964 (C=C), 1687 (C=O), 1625 (C=N). ^{1}H NMR ($CDCl_3$): δ 1.2 (s, 9H, *t*-butyl), 2.7 (dd, $J = 4.6$, 18.4 Hz, 1H, CHCH_2), 3.3 (dd, $J = 11.5$, 17.6 Hz, 1H, CH CH_2), 5.5 (dd, $J = 4.6$, 11.5 Hz, 1H, C*H*CH_2), 5.9 (d, $J = 2.3$ Hz, 2H, O–CH_2–O), 6.67–6.74 (m, 3H, H-4,H-6, H-7), 7.5 (d, $J = 8.4$ Hz, 2H, H-3′, H-5′), 7.9 (d, $J = 8.4$ Hz, 2H, H-2′, H-6′) ppm. ^{13}C NMR ($CDCl_3$): δ 28.0 (C(CH_3)$_3$), 34.1 (*C*(CH_3)$_3$), 40.0 (CHCH_2), 60.0 (*C*HCH_2), 101 (O–CH_2–O), 105, 108, 119, 125, 130, 132, 133, 136, 147, 148 (CH_{ar}, C_{ar}), 164 (C=O), 166 (C=N) ppm. HRMS: for $C_{21}H_{21}BrN_2O_3.H^+$, calcd. 429.0808, found 429.0798.

*6.1.9.3. (±)-[(5RS)-(1,3-Benzodioxol-5-yl)-3-tert-butyl-4,5-dihydro-1H-pyrazol-1-yl](4-chlorophenyl)methanone ((±)-**13c**).* Yellow solid, mp 120 °C; yield 25%. IR (KBr, cm^{-1}): 2966 (C=C), 1693 (C=O), 1625 (C=N). ^{1}H NMR ($CDCl_3$): δ 1.2 (s, 9H, *t*-butyl), 2.7 (dd, $J = 4.6$, 18.4 Hz, 1H, CHCH_2), 3.3 (dd, $J = 11.5$, 17.6 Hz, 1H, CH CH_2), 5.5 (dd, $J = 7.6$, 11.5 Hz, 1H, C*H*CH_2), 5.9 (d, $J = 2.3$ Hz, 2H, O-*C*H_2-O), 6.67–6.74 (m, 3H,H-4, H-6, H-7), 7.3 (d, $J = 8.4$ Hz, 2H, H-3′, H-5′), 7.9 (d, $J = 8.4$ Hz, 2H, H-2′, H-6′)ppm. ^{13}C NMR ($CDCl_3$): δ 28.1 (C(CH_3)$_3$), 34.1 (*C*(CH_3)$_3$), 40.0 (CHCH_2), 60.0 (*C*HCH_2), 101 (O–CH_2–O), 106, 108, 119, 128, 130, 131, 135, 137, 146, 148 (CH_{ar}, C_{ar}), 165 (C=O), 167 (C=N) ppm. HRMS: for $C_{21}H_{21}ClN_2O_3.H^+$, calcd. 385.1313, found 385.1308.

*6.1.9.4. (±)-[(5RS)-(1,3-Benzodioxol-5-yl)-3-tert-butyl-4,5-dihydro-1H-pyrazol-1-yl](4-methylphenyl)methanone ((±)-**13d**).* Off-white solid, mp 126 °C; yield 35%. IR (KBr, cm^{-1}): 2964 (C=C), 1693 (C=O), 1634 (C=N). ^{1}H NMR ($CDCl_3$): δ 1.2 (s, 9H, *t*-butyl), 2.3 (s, 3H, CH_3), 2.7 (dd, $J = 4.6$, 17.6 Hz, 1H, CHCH_2), 3.3 (dd, $J = 11.5$,17.6 Hz, 1H, CHCH_2), 5.5 (dd, $J = 3.8$, 11.5 Hz, 1H, C*H*CH_2), 5.9 (s, 2H, O–CH_2–O), 6.7–6.74 (m, 3H, H-4, H-6, H-7), 7.1 (d, $J = 8.4$ Hz, 2H, H-3′, H-5′), 7.9 (d, $J = 7.7$ Hz, 2H, H-2′, H-6′) ppm. ^{13}C NMR ($CDCl_3$): δ 21.4 (CH_3), 27.9 (C(CH_3)$_3$), 34.1 (*C*(CH_3)$_3$), 40.0 (CH*C*H_2), 60.0 (*C*HCH_2), 100 (O–CH_2–O), 105, 108, 118, 128, 130, 131, 136, 137, 141, 146, 147 (CH_{ar}, C_{ar}), 165 (C=O), 166 (C=N) ppm. HRMS: for $C_{22}H_{24}N_2O_3.H^+$, calcd. 365.1860, found 365.1852.

*6.1.10. General procedure for synthesis of (±)-[(5RS)-(1,3-benzodioxol-5-yl)-3-tert-butyl-4,5-dihydro-1H-pyrazol-1-yl](aryl) methanones (±)-**13e,f***

The appropriate acid chloride **10e**,**f** (0.004 mol) was added to a solution of (±)-**12** (1.0 g, 0.004 mol) in pyridine. The reaction mixture was stirred under reflux for 18 h, cooled, poured into aqueous HCl (10%, 200 mL), extracted with diethyl ether (2 × 50 mL), dried (Na_2SO_4) and evaporated under vacuum to afford crude (±)-**13e**,**f**.

*6.1.10.1. (±)-[(5RS)-(1,3-Benzodioxol-5-yl)-3-tert-butyl-4,5-dihydro-1H-pyrazol-1-yl](2-methylphenyl)methanone ((±)-**13e**).* Off-white solid, mp 112 °C; purified by column chromatography using silica gel and chloroform/ethyl acetate (9/1); yield 33%. IR (KBr, cm^{-1}): 2960 (C═C), 1640 (C═O), 1600 (C═N). ^1H NMR ($CDCl_3$): δ 1.1 (s, 9H, *t*-butyl), 2.3 (s, 3H, CH_3), 2.7 (dd, $J = 4.3, 17.9$ Hz, 1H, CHCH_2), 3.4 (dd, $J = 11.5, 17.9$ Hz, 1H, CHCH_2), 5.5 (dd, $J = 4.2, 11.5$ Hz, 1H, CHCH_2), 5.9 (s, 2H, O–CH_2–O), 6.72–6.76 (m, 3H, H_{ar}), 7.14–7.34 (m, 4H, H_{ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.0 (CH_3), 28.0 (C(CH_3)$_3$), 34.0 ($C(CH_3)_3$), 42.0 ($CHCH_2$), 60.0 ($CHCH_2$), 101 (O–CH_2–O), 105, 109, 119, 125, 128, 129, 130, 136, 137, 147, 148 (CH_{ar}, C_{ar}), 166 (C═O), 168 (C═N) ppm. HRMS: for $C_{22}H_{24}N_2O_3.H^+$, calcd 365.1860, found 365.1851.

*6.1.10.2. (±)-[(5RS)-(1,3-Benzodioxol-5-yl)-3-tert-butyl-4,5-dihydro-1H-pyrazol-1-yl](2,4-dichlorophenyl)methanone ((±)-**13f**).* Off-white solid, mp 91 °C; purified by column chromatography using silica gel and chloroform/ethyl acetate (9/1); yield 43%. IR (KBr, cm^{-1}): 2960 (C═C), 1690 (C═O), 1620 (C═N). ^1H NMR ($CDCl_3$): δ 1.1 (s, 9H, *t*-butyl), 2.8 (dd, $J = 4.4, 17.9$ Hz, 1H, CHCH_2), 3.3 (dd, $J = 11.5, 17.9$ Hz, 1H, CHCH_2), 5.5 (dd, $J = 4.4, 11.4$ Hz, 1H, CHCH_2), 5.9 (s, 2H, O–CH_2–O), 7.24–7.37 (m, 3H, H-3′, H-5′, H-6′) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.9 (C(CH_3)$_3$), 34.1 ($C(CH_3)_3$), 41.8 ($CHCH_2$), 60.2 ($CHCH_2$), 101.0 (O–CH_2–O), 106.0, 108.6, 119.3, 126.7, 129.1, 130.0, 132.5, 134.9, 135.3, 135.6, 147.2, 148.2 (CH_{ar}, C_{ar}), 164.2 (C═O), 167.3 (C═N) ppm. HRMS: for $C_{21}H_{20}Cl_2N_2O_3.H^+$, calcd 419.0924, found 419.0929.

6.2. Pharmacology

6.2.1. Anticonvulsant screening

Adult male Swiss albino mice weighting 18–25 g were used in this study and were purchased from Animals House Colony of the National Research Centre, Cairo, Egypt. Animals were housed under standardized conditions (room temperature 23 + 2 °C; relative humidity 55 + 5%; 12 h-light/dark cycle) and had free access to tap water and standard rat chow throughout the whole experimental period. All animal procedures were performed after the Ethics Committee of the National Research Center and in accordance with the recommendations for the proper care and use of laboratory animals "Canadian Council on Animal Care Guidelines, 1984". After seven days of adaptation to laboratory conditions, the animals were randomly assigned to experimental groups consisting of 6 mice. All the test compounds were suspended in 7% tween-80 saline solutions. Tween-80 (Sigma, St. Louis, HO, USA), Pentylenetetrazole (Sigma, St. Louis, USA), stiripentol (STP) was synthesized according to the reported procedure [7].

6.2.1.1. Subcutaneous pentylenetetrazole (scPTZ) screen. This test produces threshold or minimal (clonic) seizures. Aqueous solution of PTZ at a dose of 85 mg/kg is administered sc in a loose fold of skin on the back of the mice neck and causes seizures in more than 97% of animals. This dose is called convulsive dose 97 (CD_{97}). Six mice were used in the control group and in the experimental groups. The test is carried out by scPTZ injection half an hour after intraperitoneally (i.p.) injection of the test compounds and observing the animals during the following 0.5 h for the occurrence of seizures. A threshold convulsion was defined as one episode of clonic convulsions which persisted for at least a 5 s period. Absence of a single 5 s episode of clonic spasms during the period of observation is taken as the end point in this test [20,33].

6.2.1.2. Maximal electroshock seizure (MES) screen. Electroconvulsions were produced, half an hour after i.p. injection of the test compounds, by a current (fixed current intensity of 25 mA, 0.2 s stimulus duration) delivered *via* earclip electrodes by a Rodent Shocker generator (constant-current stimulator Type 221, Hugo Sachs Elektronik, Freiburg, Germany). Six mice were used in the control group and in the experimental groups. The criterion for the occurrence of seizure activity was the tonic hind limb extension (i.e., the hind limbs of animals outstretched 180° to the plane of the body axis) [34].

6.2.2. Neurotoxicity

6.2.2.1. Grip strength. In a preliminary experiment the animals were tested for their normal reactivity. The animals were exposed to a horizontal thin metallic wire suspended about 30 cm into the air which they immediately grasp with the forepaws. The mouse is released to hang on with its forelimbs. Normal animals are able to catch the thin wire with the hind limbs and to climb up within 5 s. Only animals that fulfill this criterion were included into the experiment. Eight mice were used in the control group and in the experimental groups. The animals were tested directly after subcutaneous administration of the tested compounds and every 15 min for 2 h. Animals which were not able to catch the thin wire with the hind limbs within 5 s or fell off from the wire were considered to be impaired [35].

6.2.2.2. The wire mesh grasping test "the inverted screen test". Animals were tested for their normal reactivity. Mouse was placed on the center of a wire mesh (20 × 30 cm). After few seconds, the mesh was turned 180°, normal animals are able to climb the top of the wire mesh within 60 s after inversion. Only animals that fulfill this criterion were included into the experiment. Eight mice were used in the control group as well as in the experimental groups. After 30 min from subcutaneous administration of the tested compounds, the animals were tested directly after subcutaneous administration of the tested compounds and every 15 min for 2 h. The animal that either fell off the inverted mesh or did not climb the top of the screen within 60 s was considered to be impaired [36].

References

[1] N. Pessah, M. Bialer, B. Wlodarczyk, R.H. Finnell, B. Yagen, J. Med. Chem. 52 (2009) 2233–2242.
[2] S. Jain, Epilepsia 46 (Suppl 1) (2005) 46–47.
[3] M.T. Medina, R.M. Duron, L. Martinez, J.R. Osorio, A.L. Estrada, C. Zuniga, D. Cartagena, J.S. Collins, K.R. Holden, Epilepsia 46 (2005) 124–131.
[4] N. Siddiqui, W. Ahsan, Eur. J. Med. Chem. 45 (2010) 1536–1543.
[5] M.J. Brodie, M.A. Dichter, N. Engl. J. Med. 334 (1996) 168–175.
[6] W.J. Curry, D.L. Kulling, Am. Fam. Physician 57 (1998) 513–520.
[7] F.M.J. Vallet, US Patent 3,910,959 A, 1975.
[8] C. Chiron, Neurotherapeutics 4 (2007) 123–125.
[9] J.L. Fisher, Neuropharmacology 56 (2009) 190–197.
[10] J.R. Dimmock, S.C. Vashishtha, J.P. Stables, Eur. J. Med. Chem. 35 (2000) 241–248.
[11] O. Alam, P. Mullick, S.P. Verma, S.J. Gilani, S.A. Khan, N. Siddiqui, W. Ahsan, Eur. J. Med. Chem. 45 (2010) 2467–2472.
[12] Y.R. Prasad, A.L. Rao, L. Prasoona, K. Murali, P.R. Kumar, Bioorg. Med. Chem. Lett. 15 (2005) 5030–5034.
[13] B.S. Holla, P.M. Akberali, M.K. Shivananda, Farmaco 55 (2000) 256–263.
[14] O.M. Khalil, Arch. Pharm. Chem. Life Sci. 344 (2011) 242–247.
[15] A. Gursoy, S. Demirayak, G. Capan, K. Erol, K. Vural, Eur. J. Med. Chem. 35 (2000) 359–364.
[16] (a) Z. Ozdemir, H.B. Kandilci, B. Gumusel, U. Calis, A.A. Bilgin, Eur. J. Med. Chem. 42 (2007) 373–379;
(b) N. Siddiqui, P. Alam, W. Ahsan, Arch. Pharm. Chem. Life Sci. 342 (2009) 173–181.
[17] J.W. Cornforth, J.E. Hawes, GB Patent 1,538,214 A, 1975.
[18] D.E. Badertscher, F.C. Whitmore, J. Am. Chem. Soc. 54 (1932) 825–826.
[19] H.S. White, Epilepsia 44 (Suppl 7) (2003) 2–8.
[20] R.L. Krall, J.K. Penry, B.G. White, H.J. Kupferberg, E.A. Swinyard, Epilepsia 19 (1978) 409–428.
[21] R.J. Porter, J.J. Cereghino, G.D. Gladding, B.J. Hessie, H.J. Kupferberg, B. Scoville, B.G. White, Cleve. Clin. Q. 51 (1984) 293–305.
[22] J.J. Luszczki, M.K. Trojnar, N. Ratnaraj, P.N. Patsalos, S.J. Czuczwar, Epilepsy Res. 90 (2010) 188–198.

[23] M. Poisson, F. Huguet, A. Savattier, F. Bakri-Logeais, G. Narcisse, Arzneimittelforschung 34 (1984) 199–204.
[24] J.R. Dimmock, R.N. Puthucode, J.M. Smith, M. Hetherington, J.W. Quail, U. Pugazhenthi, T. Lechler, J.P. Stables, J. Med. Chem. 39 (1996) 3984–3997.
[25] J.R. Dimmock, S.N. Pandeya, J.W. Quail, U. Pugazhenthi, T.M. Allen, G.Y. Kao, J. Balzarini, E. DeClercq, Eur. J. Med. Chem. 30 (1995) 303–314.
[26] R.N. Puthucode, U. Pugazhenthi, J.W. Quail, J.P. Stables, J.R. Dimmock, Eur. J. Med. Chem. 33 (1998) 595–607.
[27] M.W. Beukers, M.J. Wanner, J.K. Von Frijtag, A.P. IJzerman, G.J. Koomen, J. Med. Chem. 46 (2003) 1492–1503.
[28] A.S. Wheeler, J. Am. Chem. Soc. 51 (1929) 3653–3655.
[29] P. Yogeeswari, j.V. Ragavendran, R. Thirumurugan, S. Induja, D. Sriram, J.P. Stables, J. Med. Chem. 2 (2006) 55–62.
[30] S.K. Kashaw, V. Kashaw, P. Mishra, N.K. Jain, J.P. Stables, Eur. J. Med. Chem. 44 (2009) 4335–4343.
[31] M. Cugnon de Sevricourt, C. Dacquet, M. Finet, F. Le Marquer, M. Robba, N.O. Tembo, S. Yannic-Arnoult, J.-L. Torregrosa, EP Patent 0,566,445 A1, 1993.
[32] C. Alvarez-Ibarra, M.S.A. Perez, M.J. Fernandez, D. Serrano, V. Sinisterra, J. Chem. Res. 10 (1992) 2674–2686.
[33] O. Alam, P. Mullick, S.P. Verma, S.J. Gilani, S.A. Khan, N. Siddiqui, W. Ahsan, Eur. J. Med. Chem. 45 (2010) 2467–2472.
[34] J.J. Luszczki, M. Czuczwar, P. Gawlik, G. Sawiniec-Pozniak, K. Czuczwar, S.J. Czuczwar, J. Neural Transm. 113 (2006) 1157–1168.
[35] J.R. Boissier, P. Simon, Therapie 15 (1960) 1170–1174.
[36] H. Singh, J. Sattayasai, P. Lattmann, Y. Boonprakob, E. Lattmann, Sci. Pharm. 78 (2010) 155–169.