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Original article

Synthesis of some novel 1-(2-naphthyl)-2-(imidazol-1-yl)ethanone oxime ester derivatives and evaluation of their anticonvulsant activity

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ABSTRACT

Twenty-three new oxime ester derivatives of nafimidone were synthesized with the prospect of potential anticonvulsant activities. MES and ScM tests were employed for their anticonvulsant activities and rotorod test for neurological deficits. Eighteen compounds were found to be protective against MES seizures. Alkyl (**1**–**8**) and arylalkyl (**9**, **10**) oxime ester derivatives were found to be more active than aryl oxime ester derivatives (**11**–**23**). Five compounds (**2**, **3**, **7**, **9**, **10**), which were protective at 0.5 h at the doses of 30 mg/kg and higher in MES test, showed the highest activity. Compound **17** was the most active one in ScM test at all dose levels at 4 h.

1. Introduction

Epilepsy is a neurological disorder which affects more than 50 million people worldwide and becomes manifest by recurring attacks [1]. It usually starts at childhood and continues lifetime. Antiepileptic drug (AED) treatment, which is the main therapeutic option, is mainly symptomatic since the exact reason of this brain pathology is not clear yet. Despite many AEDs present in the market, seizures cannot be taken under control for approximately 30% of the patients [2,3]. Furthermore, AEDs cannot be tolerated well by most of the patients. These drugs not only cause tiredness, neurophysiologic disorders, and weight gain but also affect the metabolism of many drugs. Therefore there is a need to develop more effective, safer, new anticonvulsant compounds controlling all types of epileptic seizures and also decreasing the frequency and/or severity of seizures in people with epilepsy [4,5]. Although there are many strategies ranging from serendipity to genetic approach to develop new AEDs, the complexity of action mechanisms of AEDs makes it difficult to use some rational methodologies of discovery. One of the well-known and productive AED design strategies is molecular modification of existing drugs and potentially active compounds [1,6,7].

The first AEDs were in ureide structure. However, AEDs of different skeletons with various functional groups have been introduced during the last 25 years, which has lead to a remarkable progress in AED therapy. (Arylalkly)azoles are one of the anticonvulsant groups different from the ureide structure; nafimidone and denzimol are the representative molecules of this group of anticonvulsant compounds [8,9] (Formulas 1 and 2).

According to the SAR studies of this group, imidazole ring as an azole group, 2-naphthyl as a lipophilic aryl group, and also a two carbon chain alkylene bridge with a small oxygen functional group (such as carbonyl, ethylene dioxy, methoxy, acyloxy, hydroxyl, amido, and oximino substituents) between these two rings are important for high anticonvulsant activity [8–16]. In one of the recent studies it was shown that nafimidone alcohol esters exhibited significant protection against MES induced seizures [14]. In the literature it was also reported that oxime ether derivatives of nafimidone were found to be active in MES test whereas nafimidone oxime itself does not have any anticonvulsant activity [16].

According to these results, in this study we aimed to prepare some new oxime ester derivatives of nafimidone as potential anticonvulsant compounds and test their anticonvulsant activities. Various carboxylic acids of different sizes and structures were used for preparation of the esters in order to establish the relationships between the activity and structure.

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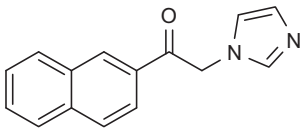


Formula 1. Nafimidone.

2. Results and discussion

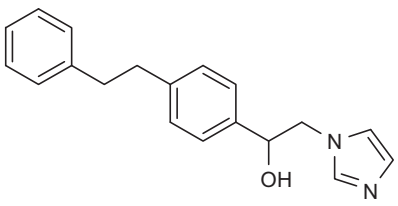
2.1. Chemistry

The total synthesis of the compounds is given in Scheme 1. Nafimidone was obtained by the alkylation of imidazole with 1-(2-naphthyl)-2-bromoethanone [8]. Nafimidone oxime was prepared by the reaction of nafimidone and hydroxylamine hydrochloride [16]. *O*-acylation of nafimidone oxime was realized via four different esterification methods to gain the final oxime ester derivatives: 1) The reaction of nafimidone oxime with appropriate carboxylic acid in the presence of N,N′-dicyclohexylcarbodiimide and 4-dimethylaminopyridine (DCC/DMAP) (Method A), 2) The reaction of nafimidone oxime with acid anhydride (Method B), 3) The reaction of nafimidone oxime with acyl halides in the presence of DMAP (Method C) and 4) The reaction of nafimidone oxime with aromatic acyl halides in the presence of TEA (Method D).

At the end of the reactions the crude products of the most compounds gave very close double spots on TLC plates and the upper one of these two spots was usually much smaller than the lower one. We speculated that these double spots indicated a mixture of *E*/*Z* isomers due to the double bond between the carbon and nitrogen atoms of the oxime group. However the reaction of the crude products with gaseous hydrochloric acid in ether yielded their salt forms as single, pure isomer. This may be explained by probable *E*–*Z* isomerisation caused by solvent and/or pH effect as reported in the literature [16–18]. Another *E*–*Z* isomerisation case was observed for compounds **7** and **8** during the NMR run. TLC results confirmed that gaseous hydrochloric acid treatment yielded isomerically pure products of these compounds just before their NMR run. Nevertheless their NMR spectra proposed a mixture of *E* and *Z* isomers. Accordingly, we performed a TLC run of the samples taken from their NMR tubes and observed double spots on the plates for both compounds just like the double spots of their crude products. Therefore we concluded that this *E*/*Z* isomerisation occurred during the NMR run due to solvent effect.

Structures and some physicochemical properties of the synthesized compounds are given in Table 1. The structures of the compounds were confirmed by IR, ^{1}H NMR, mass spectral and elementary analysis data provided in the experimental section.

Strong C=O and C–O stretching bands around 1793–1731 and 1280–1091 cm^{-1} respectively and the absence of the strong broad –OH band in the 3600–2700 cm^{-1} region in the IR spectra of the compounds indicate the presence of oxime ester group. A singlet around 6.00 ppm which represents the methylene protons of the alkylene bridge in addition to the protons of R/Ar group of the acid in the ^{1}H NMR spectra of the compounds was also another evidence for the formation of the ester group.



Formula 2. Denzimol.

It is known that the configurations of the oxime ester and oxime ester are usually same as the initial oxime configuration [19]. According to the literature, the peak of C$\underline{H}_2$–C=N– protons on the same side with oxime (*Z*-isomer) shifts to a lower field in ^{1}H NMR spectrum because of the electronegativity of the oxygen [20]. In the literature, it was reported that chemical shift values of methylene (C$\underline{H}_2$–C=N–) protons for the *E* and *Z* isomers of some nafimidone oxime ethyl ether derivates obtained separately were 5.50 and 5.80 ppm respectively [16]. Since *Z*-isomer of nafimidone oxime was used for the ester synthesis in this study, the ester derivatives obtained were expected to be in *Z*-configuration. NMR spectra of the aliphatic carboxylic acid esters are in accordance with this expectation. Therefore we can speculate that compounds **1**–**10** are *Z* isomers.

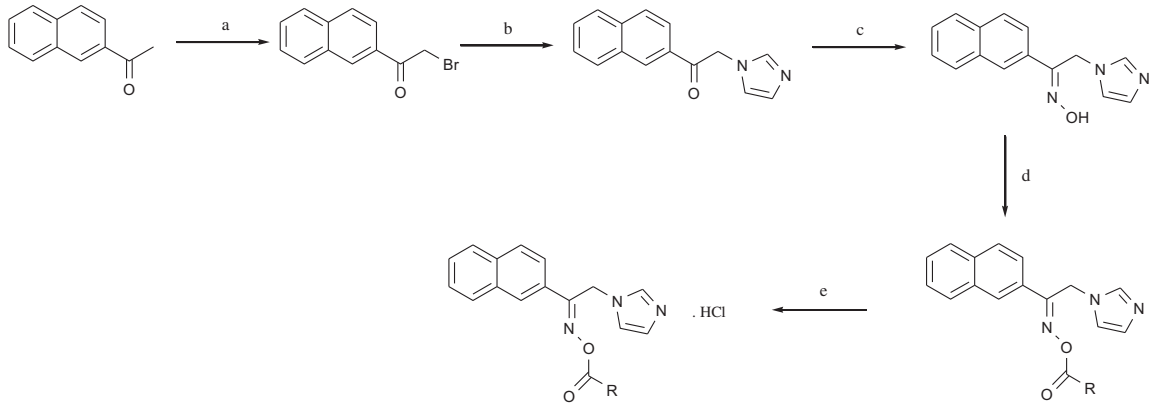
Since the signals for C$\underline{H}_2$–N protons of the aromatic acid esters (compounds **11**–**23**) are quite different and the relationship between the electronic properties and/or locations (*o*-, *m*-, *p*-) of the substituent and the chemical shift values of C$\underline{H}_2$–N protons is unpredictable, it is hard to make any speculation about their configuration.

The ^{1}H NMR spectra of two compounds (compound **7** and **8**) were found to be different from the others due to the duplication of the signals for C$\underline{H}_2$–N, C$\underline{H}$–C=O, and imidazole H^2 protons with different integral values but in the same ratio for three groups of protons. For compound **7** two singlets (total 2H) were observed at 5.80 ppm (31%) and 5.90 ppm (69%) for C$\underline{H}_2$–N protons, two multiplets (total 1H) with the same appearance were observed at 2.21–2.25 ppm (% 31) and 2.58–2.64 ppm (% 69) for C$\underline{H}$–C=O proton and two singlets (total 1H) were observed at 9.28 ppm (31%) and 9.35 ppm (69%) for imidazole H^2 proton. For compound **8** two singlets (total 2H) were observed at 5.92 ppm (34%) and 6.08 ppm (66%) for C$\underline{H}_2$–N protons, two multiples (total 1H) with the same appearance were observed at 2.29–2.36 ppm (% 34) and 2.59–2.66 ppm (% 66) for C$\underline{H}$–C=O proton and two singlets (total 1H) were observed at 10.01 ppm (34%) and 10.31 ppm (66%) for imidazole H^2 proton. According to these ^{1}H NMR data we concluded that compounds **7** and **8** consisted of two isomers (*E* and *Z* together) of different ratios (which was also explained above). Considering the chemical shifts of C$\underline{H}_2$–N protons we suggested that the signals in the lower fields (5.90 ppm and 6.08 ppm) with higher proportion belonged to the *Z* isomers and the others (5.80 ppm and 5.92 ppm) to the *E* isomers. Since both compounds were obtained as pure compounds as salt forms after gaseous hydrochloric acid treatment (one spot in TLC and fine crystal with certain m.p.) it may rather be speculated that one isomer (probably *Z*) converted to another one (*E* isomer) in deuterated solvent during ^{1}H NMR run. The reason for having two isomers for compounds **7** and **8** may be the branching structure of these compounds; in other words only these two compounds have α-methine group in their acid chain.

The molecular ion peak of the compounds in their mass spectra also confirmed the structure of the compounds. The other spectral data were in accordance with the data in the literature and the elemental analysis results were also consistent with the structure.

2.2. Anticonvulsant activity

Anticonvulsant activity and neurotoxicity screening test results (MES, ScM and rotorod) of the synthesized compounds are summarized in Table 2. All of the compounds except compound **6** showed antiMES and/or ScM activity. None of the compounds except **2** showed neurotoxicity in any dose level. Compound **2** caused motor impairment in the rotorod screen at 300 mg/kg dose level at 0.5 h, mice resumed their normal motor activity at 4 h,



a. Br_2 in CH_3COOH, b. Imidazole in DMF, c. 1) $NH_2OH.HCl/NaOH$ in ethanol 2) HCl in H_2O, d. method 1: RCOOH/DCC/DMAP in CH_2Cl_2, method 2: RCOX, method 3: $(RCO)_2O$, method 4: ArCOX/TEA, e. gaseous HCl in ether.

Scheme 1. Synthesis of the compounds.

which is consistent with its activity results. Animal deaths were observed at 300 mg/kg at both time points (0.5 h and 4 h) for compound **10**, which is one of the most active compounds in MES test due to the protection it exhibited at 30 and 100 mg/kg dose levels at 0.5 and 4 h respectively.

Almost half of the compounds (**3**, **4**, **9**, **10**, **12**, **15**, **16**, **19**, **21**–**23**) exhibited MES selective activity whereas only four of the compounds were found to be ScM selective, namely compounds **5**, **13**, and **20** at 300 mg/kg and compound **17** at 30 mg/kg. Although it was reported in the literature [8,9] that the activity of the compounds derived from nafimidone were highly MES specific in mice, some of the oxime ester derivatives in this project exhibited activity against ScM test as well as MES induced seizures. Moreover, a few of them, mainly aromatic acid esters, showed only anti-ScM activity. These data are in accordance with our previous studies including oxime ether and amide derivatives of nafimidone [15,16,21].

Most of the compounds revealed their activity rather at 0.5 h than at 4 h suggesting that they have a rapid onset of action. However compound **17**, which is ScM selective, was active at 4 h at all doses despite no protection at 0.5 h and the activities of compounds **2**, **4**, **7**, **10**–**12**, **16**, and **18** against MES-induced seizures lasted 4 h at least at one of the dose levels. Compounds **2**, **3**, **7**, **9**, **10**, **11**, and **18** were the most active compounds (30 mg/kg) in MES test at 0.5 h and/or 4 h while compound **17** was the most protective one against ScM-induced seizures at all dose levels at 4 h.

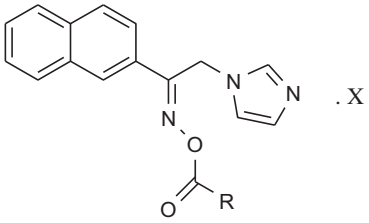
Aliphatic oxime esters proved more effective than aromatic ones in MES tests. This result is in accordance with the literature data for the esters of the nafimidone alcohol [14]. The length of the alkyl chain did not turn out important for the activity unless it is a five-carbon chain since the only inactive compound was **6** which has a six-carbon alkyl chain. Cyclization of the alkyl chain (compound **8**) resulted in increased activity compared to straight chain derivative (compound **6**). Branching of the "R" group in the active aliphatic oxime ester derivatives did not appear to have an important role in the potency but in the prolonged activity duration when the activity of compound **3** (valeric acid ester) compared to the activity of compound **4** (isovaleric acid ester). Incorporation of a double bond and a tertiary alpha-methine group in the alkyl chain (compound **5**) resulted in an inactive compound however, compound **9** (cinnamic acid ester), which also has a double bond in arylalkyl group, is one of the most active MES selective compounds. The other arylalkyl ester derivative (compound **10**) is also another most active compound in MES test. Therefore it may be speculated that arylalkyl groups in the carboxylic acid structure (compounds **9** and **10**) resulted in increased potency and MES selectivity. Various benzoic acid esters (compounds **11**–**23**) were designed to examine if the substitution on the phenyl ring is important in terms of SARs in this group of compounds. But these modifications showed that no correlation between the physicochemical properties of the substituent and/or their position on the ring and the activity, neurotoxicity and the duration of the activity existed.

Lipophilicity (log *P* 2) is important for CNS drugs to pass BBB, thus clog *P* values of the compounds were calculated by ChemDraw Ultra 8.0 (Table 1). As can be seen in Table 1, increased clog *P* values of compound **23** (clog *P*: 6.36) and compound **6** (clog *P*: 5.20) resulted in decreased and lost MES activity respectively, when compared to more active compounds with less clog *P* values (clog *P*: 3.61 for compound **1** and clog *P*: 4.14 for compound **2**). This is explained by the fact that increased lipophilicity does not necessarily enhance anticonvulsant properties; conversely it may sometimes even lead to reduced or lost activity. Therefore lipophilicity is not considered the only parameter but some additional properties and action mechanisms of the compounds account for the anticonvulsant activity as well.

3. Conclusion

As a continuation of our research interest in developing novel nafimidone-like anticonvulsant compounds and establishing new relationships between their structure and activity, we designed and synthesized a series of nafimidone oxime ester derivatives and evaluated their anticonvulsant activities according to the screening tests of ASP. We found that most of the ester derivatives of nafimidone oxime showed MES and/or ScM activity to some extent with almost no neurotoxicity; this result is in consistence with the results of oxime ether derivatives except their higher neurotoxicity compared to that of oxime esters [16]. So we concluded that it was worth to continue to study on this group; firstly selecting the most promising compounds according to the criteria of ASP for further tests, for example, activity tests for p.o. administration in rats, determination of TPE and quantification of the pharmacological parameters (ED_{50} and TD_{50}) and also to design new derivatives with better activity profiles.

Table 1
The structures, *c*log *P* values, yields, melting points of the synthesized compounds.



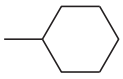
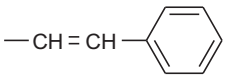
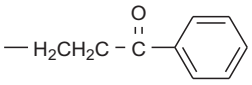
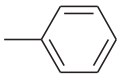
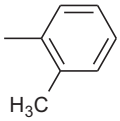
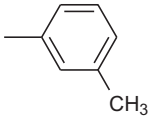
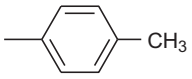
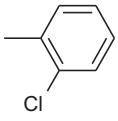
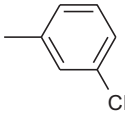
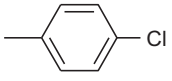
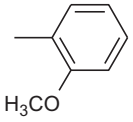
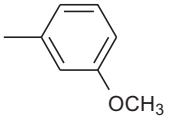
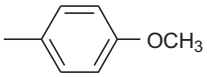
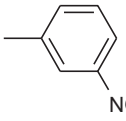
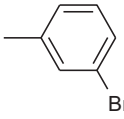
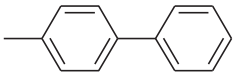
Comp.	R	X	Method	*c*log *P*	Yield (%)	M.p. (°C)
1	$-CH_2CH_3$	HCl	A	3.61	66.80	150
2	$-CH_2CH_2CH_3$	HCl	B	4.14	59.28	144–5
3	$-CH_2(CH_2)_2CH_3$	HCl	A	4.67	96.44	102–5
4	$-CH_2CH(CH_3)_2$	HCl	A	4.54	53.45	141–3
5	$-C(CH_3)=CHCH_3$	HCl	A	4.33	82.79	132–3
6	$-CH_2(CH_2)_3CH_3$	HCl	B	5.20	56.71	95–8
7	$-CH(CH_2CH_2CH_3)_2$	HCl	A	6.04	55.54	105–8
8		HCl	A	5.12	87.73	120–1
9		HCl	C	5.44	62.14	155–8
10		–	A	4.50	53.18	165–7
11		–	D	4.48	76.25	149–51
12		–	D	4.98	59.28	132–3
13		–	D	4.98	79.58	128–30
14		–	D	4.98	74.44	153–4
15		–	D	5.19	69.51	157–9
16		–	D	5.19	51.81	153–5
17		–	D	5.19	76.44	152–4
18		–	D	4.40	64.86	145–7

Table 1 (*continued*)

Comp.	R	X	Method	*c*log *P*	Yield (%)	M.p. (°C)
19		–	D	4.40	58.89	135–6
20		–	D	4.40	76.54	156–7
21		–	D	4.22	74.17	149–50
22		–	D	5.34	66.77	124–6
23		HCl	A	6.36	79.84	175

4. Experimental part

4.1. Chemistry

All chemicals used in this study were purchased from E. Merck, Fluka AG, A. Aesar, and Aldrich. Purity of the compounds was checked by TLC with Merck Kieselgel 60 F254 aluminum plates. Column chromatography for purification of the compounds was performed on Kieselgel 60 (0.040–0.063 mm) (230–400 mesh ASTM) (Merck). Melting points were determined with a Thomas Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded in KBr disks with a Jasco 420 Fourier FT-IR Spectrometer or ATR method with a Perkin Elmer Spectrometer.

^{1}H NMR spectra were recorded on a Varian Mercury 400 MHz FT-NMR spectrometer or a Brucker Avance Ultrashield FT-NMR spectrometer in DMSO or $CDCl_3$ at 300 MHz. All the chemical shifts are expressed in δ (ppm) values. Splitting patterns are designated as follows: s: singlet; d: doublet; dd: doublet of doublets; t: triplet; q: quartet; and m: multiplet. Mass spectra were obtained by 73DIP-1 Direct Insertion Probe and Agilent 5973-network Mass Selective Detector (EI) or by Agilent 1100 HPLC and ACE 5C18 detector (ES-API). Elemental analysis was performed on Leco 982 CHNS elemental analysis apparatus at TUBITAK (Scientific and Technical Research Council of Turkey) and Leco 932 CHNS elemental analysis apparatus at Ankara University Faculty of Pharmacy Center Laboratory or at Inonu University, Malatya.

2-bromo-1-(naphthalene-2-yl)ethanone [22], 1-(2-naphthyl)-2-(imidazol-1-yl)ethanone [8], 1-(2-naphthyl)-2-(imidazol-1-yl) ethanone oxime [16] were prepared according to the procedures described in the relevant literature.

4.1.1. Preparation of the compounds. 1-(2-naphthyl)-2-(imidazol-1-yl) ethanone oxime esters

Method A: Appropriate carboxylic acids (3.5 mmol), DCC (3.5 mmol) and DMAP (0.17 mmol) were stirred in dry methylene chloride and 1-(2-naphthyl)-2-(imidazol-1-yl)ethanone oxime (1.5 mmol) was added. Reaction mixture was stirred for 18–36 h at

Table 2
Anticonvulsant and neurotoxicity screening data in mice dosed ip with the compounds.

Test	MES						ScM						Tox					
Time	0.5 h			4 h			0.5 h			4 h			0.5 h			4 h		
Dose (mg/kg)	30	100	300	30	100	300	30	100	300	30	100	300	30	100	300	30	100	300
1	0/1	**1/1**	**1/1**	0/1	0/1	0/1	0/1	0/1	**1/1**	0/1	0/1	0/1	0/4	0/4	0/4	0/2	0/2	0/2
2	**1/1**	**1/1**	**1/1**	0/1	0/1	**1/1**	0/1	0/1	0/1	0/1	0/1	**1/1**	0/4	0/4	**4/4**	0/2	0/2	0/2
3	**1/1**	**1/1**	**1/1**	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/4	0/4	0/4	0/2	0/2	0/2
4	0/1	**1/1**	**1/1**	0/1	**1/1**	**1/1**	0/1	0/1	0/1	0/1	0/1	0/1	0/4	0/4	0/4	0/2	0/2	0/2
5	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	**1/1**	0/4	0/4	0/4	0/2	0/2	0/2
6	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/4	0/4	0/4	0/2	0/2	0/2
7	**1/1**	**1/1**	**1/1**	0/1	0/1	**1/1**	0/1	0/1	**1/1**	0/1	0/1	**1/1**	0/4	0/4	0/4	0/2	0/2	0/2
8	0/1	**1/1**	**1/1**	0/1	0/1	0/1	0/1	**1/1**	**1/1**	0/1	0/1	0/1	0/4	0/4	0/4	0/2	0/2	0/2
9	**1/1**	**1/1**	**1/1**	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/4	0/4	0/4	0/2	0/2	0/2
10	**1/1**	**1/1**	*	**1/1**	**1/1**	*	0/1	0/1	*	0/1	0/1	*	0/4	0/4	*	0/2	0/2	*
11	0/1	**1/1**	**1/1**	**1/1**	**1/1**	**1/1**	0/1	0/1	0/1	0/1	0/1	**1/1**	0/4	0/4	0/4	0/2	0/2	0/2
12	0/1	0/1	**1/1**	0/1	0/1	**1/1**	0/1	0/1	0/1	0/1	0/1	0/1	0/4	0/4	0/4	0/2	0/2	0/2
13	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	**1/1**	0/1	0/1	**1/1**	0/4	0/4	0/4	0/2	0/2	0/2
14	0/1	**1/1**	**1/1**	0/1	0/1	0/1	0/1	**1/1**	**1/1**	0/1	0/1	**1/1**	0/4	0/4	0/4	0/2	0/2	0/2
15	0/1	**1/1**	**1/1**	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/4	0/4	0/4	0/2	0/2	0/2
16	0/1	**1/1**	**1/1**	0/1	**1/1**	**1/1**	0/1	0/1	0/1	0/1	0/1	0/1	0/4	0/4	0/4	0/2	0/2	0/2
17	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	**1/1**	**1/1**	**1/1**	0/4	0/4	0/4	0/2	0/2	0/2
18	0/1	**1/1**	**1/1**	**1/1**	**1/1**	**1/1**	0/1	**1/1**	**1/1**	0/1	0/1	0/1	0/4	0/4	0/4	0/2	0/2	0/2
19	0/1	0/1	**1/1**	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/4	0/4	0/4	0/2	0/2	0/2
20	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	**1/1**	0/1	0/1	0/1	0/4	0/4	0/4	0/2	0/2	0/2
21	0/1	0/1	0/1	0/1	0/1	**1/1**	0/1	0/1	0/1	0/1	0/1	0/1	0/4	0/4	0/4	0/2	0/2	0/2
22	0/1	**1/1**	**1/1**	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/4	0/4	0/4	0/2	0/2	0/2
23	0/1	0/1	0/1	0/1	0/1	**1/1**	0/1	0/1	0/1	0/1	0/1	0/1	0/4	0/4	0/4	0/2	0/2	0/2
Phenytoin	**1/1**	**1/1**	**1/1**	**1/1**	**1/1**	**1/1**	0/1	0/1	0/1	0/1	0/1	0/1	0/4	0/4	**4/4**	0/2	**2/2**	**2/2**
Carbamazepine	**1/1**	**1/1**	**1/1**	**0/1**	**1/1**	**1/1**	0/1	0/1	**1/1**	0/1	**1/1**	**1/1**	0/4	0/4	**4/4**	0/2	0/2	0/2
Sodium Valproate	0/1	0/1	**1/1**	0/1	0/1	0/1	0/1	0/1	**1/1**	0/1	0/1	0/1	0/4	0/4	0/4	0/2	0/2	0/2

MES: Maximal electroshock seizure test (number of animal protected/number of animal tested). ScM: Subcutaneous metrazole seizure test (number of animal protected/number of animal tested). Tox: rotarod test (number of animal exhibiting toxicity/number of animal tested). 0/1: no activity at dose level. 1/1: noticeable activity at dose level (given in bold). * Animal death.

room temperature. The precipitate was filtered off; the solution was dried over anhydrous sodium sulphate and then was evaporated to dryness. The residue was dissolved in ether and treated with etheral hydrochloric acid to obtain the hydrochloric acid salt of the compounds. The precipitated salt was filtered and washed with appropriate solvents.

Method B: Appropriate acid anhydride (3.5 mmol) and 1-(2-naphthyl)-2-(imidazol-1-yl)ethanone oxime (1.5 mmol) were stirred for 6 h. Ether was added to the reaction mixture, which then treated with etheral hydrochloric acid. The compounds were crystallized from appropriate solvents.

Method C: Appropriate acid chloride (3.5 mmol), 1-(2-naphthyl)-2-(imidazol-1-yl)ethanone oxime (0.24 g, 1 mmol), and DMAP (0.17 mmol) were stirred at room temperature for 12 h. Ether was added to the reaction mixture; the precipitate was filtered off, treated with etheral hydrochloric acid and crystallized from the appropriate solvents.

Method D: 1-(2-naphthyl)-2-(imidazol-1-yl)ethanone oxime (0.01 mol) was resolved in dry acetone (20 ml) and then triethylamine (TEA) (0.015 mol) was added drop wise to the solution at 0 °C and then reaction mixture was stirred for 5 min at 0 °C, for 6 h at room temperature. Appropriate acid chloride (0.01 mol) was added to the mixture and then reaction mixture was stirred for 10–30 min at 0 °C. Acetone was evaporated to dryness. The residue was washed with cold ether (5 ml) and hot water and then purified by column chromatography on silica gel eluting with chloroform or/and crystallized from the appropriate solvents.

*4.1.1.1. 1-(2-naphthyl)-2-(imidazol-1-yl)ethanone O-propanoyl oxime hydrochloride (**1**).* Compound was purified by precipitation with acetone. IR (ν cm^{-1}, KBr): 1793 (C=O), 1602 (C=N), 1108 (C–O); ^{1}H NMR (DMSO-d$_6$, 300 MHz): δ 1.14 (t, 3H, J = 7.4 Hz, –C$\underline{H}_3$), 2.59–2.66 (q, 2H, J = 7.4 Hz, –C$\underline{H}_2$–C=O), 5.92 (s, 2H, –C$\underline{H}_2$–N), 7.58 (s, 1H, imidazole H^4), 7.75 (s, 1H, imidazol H^5), 7.62–8.47 (m, 7H, naphthalene protons), 9.34 (s, 1H, imidazole H^2); ^{13}C NMR (DMSO-d$_6$): δ 9.19 (1C; CH$_3$), 25.97 (1C; C$\underline{H}_2$–C=O), 44.35 (1C; CH$_2$–N), 120.44–136.79 (13C, naphthalene and imidazole), 159.32 (C=N), 171.32 (C=O); Mass (API-ES): m/e 307 (M$^+$, % 100); Anal. Calcd. for $C_{18}H_{18}ClN_3O_2$. 2H$_2$O (379.13): C, 56.92; H, 5.84; N, 11.06. Found: C, 56.18; H, 5.01; N, 10.65.

*4.1.1.2. 1-(2-naphthyl)-2-(imidazol-1-yl)ethanone O-butanoyl oxime hydrochloride (**2**).* Compound was purified by precipitation with acetone. IR (ν cm^{-1}, KBr): 1758 (C=O), 1570 (C=N), 1148 (C–O); ^{1}H NMR (DMSO-d$_6$, 300 MHz): δ 0.96 (t, 3H, J = 7.3 Hz, –C$\underline{H}_3$), 1.62–1.69 (m, 2H, –C$\underline{H}_2$–CH$_3$), 2.57 (t, 2H, J = 7.3 Hz, –C$\underline{H}_2$–C=O), 5.88 (s, 2H, –C$\underline{H}_2$–N), 7.58 (s, 1H, imidazole H^4), 7.72 (s, 1H, imidazol H^5), 7.61–8.42 (m, 7H, naphthalene protons), 9.25 (s, 1H, imidazole H^2); ^{13}C NMR (DMSO-d$_6$): δ 13.71 (1C; CH$_3$), 18.16 (1C; C$\underline{H}_2$–CH$_3$), 34.22 (1C; C$\underline{H}_2$–C=O), 44.45 (1C; CH$_2$–N), 120.66–136.79 (13C, naphthalene and imidazole), 159.37 (C=N), 170.29 (C=O); Mass (API-ES): m/e 321 (M$^+$, % 100); Anal. Calcd. for $C_{19}H_{20}ClN_3O_2$ (357.12): C, 63.77; H, 5.63; N, 11.74. Found: C, 63.23; H, 5.54; N, 11.53.

*4.1.1.3. 1-(2-naphthyl)-2-(imidazol-1-yl)ethanone O-pentanoyl oxime hydrochloride (**3**).* IR (ν cm^{-1}, KBr): 1770 (C=O), 1600 (C=N), 1091 (C–O); ^{1}H NMR (DMSO-d$_6$, 300 MHz): δ 0.91 (t, 3H, J = 7.3 Hz, –C$\underline{H}_3$), 1.30–1.40 (m, 2H, –C$\underline{H}_2$–CH$_3$), 1.56–1.66 (m, 2H, –C$\underline{H}_2$–CH$_2$), 2.59 (t, 2H, J = 7.3 Hz, –C$\underline{H}_2$–C=O), 5.89 (s, 2H, –C$\underline{H}_2$–N), 7.58 (s, 1H, imidazole H^4), 7.73 (s, 1H, imidazol H^5), 7.61–8.44 (m, 7H, naphthalene protons), 9.28 (s, 1H, imidazole H^2); ^{13}C NMR (DMSO-d$_6$): δ 14.10 (1C; CH$_3$), 22.08 (1C; C$\underline{H}_2$–CH$_3$), 26.72 (1C; C$\underline{H}_2$–CH$_2$), 32.11 (1C; C$\underline{H}_2$–C=O), 44.43 (1C; CH$_2$–N), 120.97–136.88 (13C, naphthalene and imidazole), 159.35 (C=N), 170.37 (C=O); Mass (API-ES): m/e 335 (M$^+$, % 100); Anal. Calcd. for $C_{20}H_{22}ClN_3O_2$. H$_2$O

(389.15): C, 61.61; H, 6.20; N, 10.78. Found: C, 61.30; H, 6.02; N, 10.70.

*4.1.1.4. 1-(2-naphthyl)-2-(imidazol-1-yl)ethanone O-3-methylbutanoyl oxime hydrochloride (**4**).* Compound was recrystallized from acetone/petroleum ether. IR (ν cm^{-1}, KBr): 1766 (C=O), 1568 (C=N), 1151 (C–O); ^1H NMR (DMSO-d_6, 300 MHz): δ 0.98 (d, 6H, J = 6.6 Hz, –C$\underline{H}_3$), 2.06–2.10 (m, 1H, –C$\underline{H}$), 2.47 (d, 2H, J = 7.0 Hz, –C$\underline{H}_2$–C=O), 5.88 (s, 2H, –C$\underline{H}_2$–N), 7.57 (s, 1H, imidazole H^4), 7.71 (s, 1H, imidazol H^5), 7.58–8.43 (m, 7H, naphthalene protons) and 9.25 (s, 1H, imidazole H^2); Mass (API-ES): m/e 335 (M^+, % 100); Anal. Calcd. for $C_{20}H_{22}ClN_3O_2$. 1/2H_2O (380.15): C, 63.07; H, 6.09; N, 11.03. Found: C, 63.01; H, 6.08; N, 11.35.

*4.1.1.5. 1-(2-naphthyl)-2-(imidazol-1-yl)ethanone O-2-methylbut-2-enoyl oxime hydrochloride (**5**).* Compound was purified by precipitation with acetone. IR (ν cm^{-1}, ATR): 1745 (C=O), 1646 (C=N), 1299 (C–O); ^1H NMR ($CDCl_3$-d, 300 MHz): δ 1.79 (d, 3H, J = 6.1 Hz, –C(C$\underline{H}_3$)=CHC$\underline{H}_3$), 1.86 (s, 3H, –C(C$\underline{H}_3$)=CHCH$_3$), 5.99 (s, 2H, –C$\underline{H}_2$–N), 6.91–6.94 (q, 1H, J = 5.7 Hz, –C(CH$_3$)=C$\underline{H}$CH$_3$), 7.13 (s, 1H, imidazole H^4), 7.18 (s, 1H, imidazole H^5), 7.39–8.43 (m, 7H, naphthalene protons), 9.86 (s, 1H, imidazole H^2); Mass (API-ES): m/e 334 (M + H, % 100); Anal. Calcd. for $C_{20}H_{20}ClN_3O_2$. 4/3H_2O (393.12): C, 60.99; H, 5.80; N, 10.67. Found: C, 60.56; H, 5.57; N, 11.65.

*4.1.1.6. 1-(2-naphthyl)-2-(imidazol-1-yl)ethanone O-hexanoyl oxime hydrochloride (**6**).* Compound was purified by precipitation with acetone. IR (ν cm^{-1}, KBr): 1765 (C=O), 1603 (C=N), 1134 (C–O); ^1H NMR (DMSO-d_6, 300 MHz): δ 0.88 (t, 3H, J = 7.0 Hz, –C$\underline{H}_3$), 1.30–1.34 (m, 4H, –C$\underline{H}_2$–C$\underline{H}_2$–CH$_3$), 1.60–1.65 (m, 2H, –C$\underline{H}_2$–CH$_2$–C=O), 2.58 (t, 2H, J = 7.3 Hz, –C$\underline{H}_2$–C=O), 5.90 (s, 2H, –C$\underline{H}_2$–N), 7.58 (s, 1H, imidazole H^4), 7.73 (s, 1H, imidazol H^5), 7.59–8.44 (m, 7H, naphthalene protons), 9.30 (s, 1H, imidazole H^2); Mass (API-ES): m/e 349 (M^+, % 100); Anal. Calcd. for $C_{21}H_{24}ClN_3O_2$. H_2O (403.17): C, 62.45; H, 6.49; N, 10.40. Found: C, 61.96; H, 6.36; N, 10.16.

*4.1.1.7. (E/Z)-1-(2-naphthyl)-2-(imidazol-1-yl)ethanone O-2-propylpentanoyl oxime hydrochloride (**7**).* Compound was purified by precipitation with acetone. IR (ν cm^{-1}, ATR): 1758 (C=O), 1577 (C=N), 1089 (C–O); ^1H NMR (DMSO-d_6, 300 MHz): δ 0.66 (% 31) and 0.88 (% 69) (t, 6H, J = 7.3 Hz, –C$\underline{H}_3$), 1.02–1.09 (% 31) and 1.43–1.62 (% 69) (m, 4H, –C$\underline{H}_2$–CH$_3$), 1.19–1.38 (m, 4H, –C$\underline{H}_2$–CH), 2.21–2.25 (% 31) vs 2.58–2.64 (% 69) (m, 1H, –C$\underline{H}$–C=O), 5.80 (% 31) and 5.90 (% 69) (s, 2H, –C$\underline{H}_2$–N), 7.58 (s, 1H, imidazole H^4), 7.71 (s, 1H, imidazol H^5), 7.59–8.45 (m, 7H, naphthalene protons), 9.28 (% 31 *E* isomer) and 9.35 (s, 1H, imidazole H^2); Mass (API-ES): m/e 377 (M^+, % 100); Anal. Calcd. for $C_{23}H_{28}ClN_3O_2$. 1/2H_2O (422.19): C, 65.31; H, 6.91; N, 9.94. Found: C, 65.18; H, 6.71; N, 9.90.

*4.1.1.8. (E/Z)-1-(2-naphthyl)-2-(imidazol-1-yl)ethanone O-cyclohexanecarbonyl oxime hydrochloride (**8**).* IR (ν cm^{-1}, ATR): 1781 (C=O), 1682 (C=N), 1113 (C–O); ^1H NMR ($CDCl_3$-d, 300 MHz): δ 1.18–2.12 (m, 10H, cyclohexane C$\underline{H}_2$ protons), 2.29–2.36 (34%) and 2.59–2.66 (66%) (m, 1H, cyclohexane C$\underline{H}$ protons), 5.92 (% 34) and 6.08 (% 66) (s, 2H, –C$\underline{H}_2$–N), 7.09–8.58 (m, 7H, imidazole H^2 and naphthalene protons), 10.01 (34%) and 10.31 (66%) (1H, s, imidazole H^2), and 15.88 (s, 1H, N^+–H); ^{13}C NMR (DMSO-d_6): δ 25.38 (2C; cyclohexyl C3 and C5), 25.66 (2C; cyclohexyl C4), 28.91 (2C; cyclohexyl C2 and C6), 44.66 (1C; CH_2–N), 115.98 (1C; C$\underline{H}$=CH–C=O), 120.59–136.74 (13C, naphthalene and imidazole), 147.11 (1C; CH=C$\underline{H}$–C=O), 159.78 (C=N), 171.93 (C=O); Mass (API-ES): m/e 361 (M^+, % 100); Anal. Calcd. for $C_{22}H_{24}ClN_3O_2$. 1/2H_2O (406.16): C, 64.94; H, 6.19; N, 10.33. Found: C, 64.43; H, 5.99; N, 9.98.

*4.1.1.9. 1-(2-naphthyl)-2-(imidazol-1-yl)ethanone O-cinnamoyl oxime hydrochloride (**9**).* IR (ν cm^{-1}, ATR): 1725 (C=O), 1634 (C=N), 1111 (C–O); ^1H NMR ($CDCl_3$-d, 300 MHz): δ 6.02 (s, 2H, –C$\underline{H}_2$–N), 6.76 (d, 1H, J = 16.0 Hz, =C$\underline{H}$–C=O), 7.28–7.45 (m, 15H, =C$\underline{H}$–Ph, naphthalene, phenyl protons and imidazole $H^{4,5}$), 9.55 (s, 1H, imidazole H^2); ^{13}C NMR (DMSO-d_6): δ 44.44 (1C; CH_2–N), 115.98 (1C; C$\underline{H}$=CH–C=O), 120.60–136.88 (19C, naphthalene, benzene and imidazole), 147.11 (1C; CH=C$\underline{H}$–C=O), 159.81 (C=N), 163.53 (C=O); Mass (API-ES): m/e 381 (M^+, % 100); Anal. Calcd. for $C_{24}H_{20}ClN_3O_2$. 1/3H_2O (423.89): C, 68.00; H, 4.91; N, 9.91. Found: C, 68.05; H, 4.81; N, 9.64.

*4.1.1.10. 1-(2-naphthyl)-2-(imidazol-1-yl)ethanone O-(4-oxo-4-phenyl)butanoyl oxime (**10**).* IR (ν cm^{-1}, ATR): 1779, 1682 (C=O), 1596 (C=N), 1111 (C–O); ^1H NMR ($CDCl_3$-d, 300 MHz): δ 3.04 (t, J = 6.4 Hz, 2H, –COC$\underline{H}_2$CH$_2$COC$_6$H$_5$), 3.49 (t, 2H, J = 6.4 Hz, –COCH$_2$C$\underline{H}_2$COC$_6$H$_5$), 5.49 (s, 2H, –C$\underline{H}_2$–N), 7.00 (s, 1H, imidazole H^4), 7.05 (s, 1H, imidazole H^5), 7.49–8.04 (12H, m, naphthalene and phenyl protons), 8.15 (1H, s, imidazole H^2); ^{13}C NMR (DMSO-d_6): δ 27.23 (1C; C$\underline{H}_2$–(C=O)–O), 33.55 (1C; C$\underline{H}_2$–(C=O)–Ph), 41.61 (1C; CH_2–N), 120.16–136.88 (13C, naphthalene, benzene and imidazole), 161.33 (C=N), 170.43 (O–C=O), 198.76 (Ph–C=O); Mass (API-ES): m/e 412 (M^+, % 100); Anal. Calcd. for $C_{25}H_{21}N_3O_3$. H_2O (429.17): C, 69.92; H, 5.40; N, 9.78. Found: C, 70.49; H, 5.21; N, 9.83.

*4.1.1.11. 1-(2-naphthyl)-2-(imidazol-1-yl)ethanone O-benzoyloxime (**11**).* Compound was recrystallized from acetone and ethyl acetate. IR (ν cm^{-1}, KBr): 1749 (C=O), 1652 (C=N), 1240 (C–O); ^1H NMR ($CDCl_3$-d): δ 5.55 (s; 2H; –C$\underline{H}_2$–N), 6.98–8.17 (m; 15H; naphthalene, benzene and imidazole); Mass (EI, 70 eV): m/e 355 [M^+] (34%), 332, 301, 233, 206, 179, 153, 122, 105 (base peak, 100%), 77, 51; Anal. Calcd. for $C_{22}H_{17}N_3O_2$. 1/5H_2O (358.73): C, 73.60; H, 4.89; N, 11.71. Found: C, 73.88; H, 5.39; N, 11.72.

*4.1.1.12. 1-(2-naphthyl)-2-(imidazol-1-yl)ethanone O-(2-methylbenzoyl)oxime (**12**).* Compound was recrystallized from ethanol/water and acetone/water. IR (ν cm^{-1}, KBr): 1759 (C=O), 1652 (C=N), 1228 (C–O); ^1H NMR (DMSO-d_6): δ 2.59 (s; 3H; –C$\underline{H}_3$), 5.75 (s; 2H; –C$\underline{H}_2$–N), 6.79–8.42 (m; 14H; naphthalene, benzene and imidazole); Mass (EI, 70 eV): m/e 369 [M^+] (23%), 332, 301, 273, 233, 206, 153, 136, 127, 119 (base peak, 100%), 91, 77, 68; Anal. Calcd. for $C_{23}H_{19}N_3O_2$ (369.41): C, 74.78; H, 5.18; N, 11.37. Found: C, 74.43; H, 4.96; N, 11.38.

*4.1.1.13. 1-(2-naphthyl)-2-(imidazol-1-yl)ethanone O-(3-methylbenzoyl)oxime (**13**).* Compound was recrystallized from ethanol/water. IR (ν cm^{-1}, KBr): 1745 (C=O), 1652 (C=N), 1265 (C–O); ^1H NMR (DMSO-d_6): δ 2.44 (s; 3H; –C$\underline{H}_3$), 5.59 (s; 2H; –C$\underline{H}_2$–N), 6.99–8.20 (m; 14H; naphthalene, benzene and imidazole); Mass (EI, 70 eV): m/e 369 [M^+] (8%), 332, 301, 273, 233, 206, 179, 153, 136, 119 (base peak, 100%), 91, 68, 41; Anal. Calcd. for $C_{23}H_{19}N_3O_2$. 1/3H_2O (375.15): C, 73.58; H, 5.28; N, 11.19. Found: C, 73.48; H, 5.39; N, 10.89.

*4.1.1.14. 1-(2-naphthyl)-2-(imidazol-1-yl)ethanone O-(4-methylbenzoyl)oxime (**14**).* Compound was washed with ethylacetate and recrystallized from acetone. IR (ν cm^{-1}, KBr): 1741 (C=O), 1652 (C=N), 1250 (C–O); ^1H NMR (DMSO-d_6): δ 2.08 (s; 3H; –C$\underline{H}_3$), 6.08 (s; 2H; –C$\underline{H}_2$–N), 7.42–9.24 (m; 14H; naphthalene, benzene and imidazole); Mass (EI, 70 eV): m/e 369 [M^+] (18%), 233, 206, 191, 179, 166, 153, 136, 127, 119 (base peak, 100%), 111, 91, 68, 53, 41; Anal.

Calcd. for $C_{23}H_{19}N_3O_2$ (369.41): C, 74.60; H, 5.18; N, 11.37. Found: C, 74.43; H, 4.67; N, 11.10.

*4.1.1.15. 1-(2-naphthyl)-2-(imidazol-1-yl)ethanone O-(2-chlorobenzoyl)oxime (**15**).* Compound was recrystallized from chloroform/n-hexane. IR (ν cm^{-1}, KBr): 1743 (C=O), 1652 (C=N), 1232 (C–O); ^1H NMR (DMSO-d_6): δ 6.00 (s; 2H; $-CH_2-$N), 7.53–9.23 (m; 14H; naphthalene, benzene and imidazole); ^{13}C NMR (DMSO-d_6): δ 45.42 (1C; CH_2–N), 121.02–137.07 (19C, naphthalene, benzene and imidazole), 161.47 (C=N), 162.29 (C=O); Mass (EI, 70 eV): *m/e* 389 [M^+] (17%), 332, 301, 233, 207, 194, 180, 166, 153, 139 (base peak, 100%), 126, 111 75, 63, 41; Anal. Calcd. for $C_{22}H_{16}ClN_3O_2$. 1/3H_2O (395.09): C, 66.75; H, 4.24; N, 10.62. Found: C, 66.54; H, 3.78; N, 10.48.

*4.1.1.16. 1-(2-Naphthyl)-2-(imidazol-1-yl)ethanone O-(3-chlorobenzoyl)oxime (**16**).* Compound was purified by column chromatography and then recrystallized from acetone. IR (ν cm^{-1}, KBr): 1748 (C=O), 1652 (C=N), 1238 (C–O); ^1H NMR (DMSO-d_6): δ 6.12 (s; 2H; $-CH_2-$N), 7.53–9.22 (m; 14H; naphthalene, benzene and imidazole); Mass (EI, 70 eV): *m/e* 389 [M^+] (10%), 332, 301, 233, 207, 194, 179, 153, 139 (base peak, 100%), 111 75, 50, 41; Anal. Calcd. for $C_{22}H_{16}ClN_3O_2$. 1/5H_2O (392.69): C, 67.16; H, 4.20; N, 10.68. Found: C, 66.94; H, 4.08; N, 10.68.

*4.1.1.17. 1-(2-naphthyl)-2-(imidazol-1-yl)ethanone O-(4-chlorobenzoyl)oxime (**17**).* Compound was purified by column chromatography and then recrystallized from ethanol. IR (ν cm^{-1}, KBr): 1750 (C=O), 1590 (C=N), 1258 (C–O); ^1H NMR (DMSO-d_6): δ 6.11 (s; 2H; $-CH_2-$N), 7.55–9.27 (m; 14H; naphthalene, benzene and imidazole); Mass (EI, 70 eV): *m/e* 389 [M^+] (15%), 301, 233, 206, 194, 179, 166, 153, 139 (base peak, 100%), 126, 111, 75, 50, 41; Anal. Calcd. for $C_{22}H_{16}ClN_3O_2$. 1/10H_2O (391.63): C, 67.47; H, 4.17; N, 10.73. Found: C, 67.14; H, 4.18; N, 10.74.

*4.1.1.18. 1-(2-naphthyl)-2-(imidazol-1-yl)ethanone O-(2-methoxybenzoyl)oxime (**18**).* Compound was recrystallized from acetone. IR (ν cm^{-1}, KBr): 1742 (C=O), 1601 (C=N), 1290 (C–O); ^1H NMR (DMSO-d_6): δ 3.89 (s; 3H; O–CH_3), 5.64 (s; 2H; $-CH_2-$N), 7.03–8.26 (m; 14H; naphthalene, benzene and imidazole); Mass (EI, 70 eV): *m/e* 385 [M^+] (18%), 332, 301, 233, 206, 180, 153, 135 (base peak, 100%), 105, 77, 51, 41; Anal. Calcd. for $C_{23}H_{19}N_3O_3$ (385.42): C, 71.67; H, 4.97; N, 10.90. Found: C, 71.42; H, 4.74; N, 10.86.

*4.1.1.19. 1-(2-naphthyl)-2-(imidazol-1-yl)ethanone O-(3-methoxybenzoyl)oxime (**19**).* Compound was recrystallized from ethanol/water and acetone. IR (ν cm^{-1}, KBr): 1752 (C=O), 1599 (C=N), 1267 (C–O); ^1H NMR (DMSO-d_6): δ 3.87 (s; 3H; O–CH_3), 5.80 (s; 2H; $-CH_2-$N), 6.78–8.45 (m; 14H; naphthalene, benzene and imidazole); Mass (EI, 70 eV): *m/e* 385 [M^+] (4%), 332, 301, 273, 233, 206, 194, 152 (base peak, 100%), 135, 107, 92, 77, 68, 53, 41; Anal. Calcd. for $C_{23}H_{19}N_3O_3$ (385.42): C, 71.67; H, 4.97; N, 10.90. Found: C, 71.31; H, 4.98; N, 10.65.

*4.1.1.20. 1-(2-naphthyl)-2-(imidazol-1-yl)ethanone O-(4-methoxybenzoyl)oxime (**20**).* Compound was recrystallized from ethanol/water. IR (ν cm^{-1}, KBr): 1731 (C=O), 1604 (C=N), 1253 (C–O); ^1H NMR (DMSO-d_6): δ 3.90 (s; 3H; O–CH_3), 5.53 (s; 2H; $-CH_2-$N), 6.98–8.16 (m; 14H; naphthalene, benzene and imidazole); Mass (EI, 70 eV): *m/e* 385 [M^+] (18%), 301, 273, 233, 206, 179, 153, 154, 135 (base peak, 100%), 107, 77, 53, 41; Anal. Calcd. for $C_{23}H_{19}N_3O_3$ (385.42): C, 71.67; H, 4.97; N, 10.90. Found: C, 71.31; H, 5.06; N, 10.86.

*4.1.1.21. 1-(2-naphthyl)-2-(imidazol-1-yl)ethanone O-(4-nitrobenzoyl) oxime (**21**).* Compound was recrystallized from ethanol/water and acetone. IR (ν cm^{-1}, KBr): 1749 (C=O), 1652 (C=N), 1280 (C–O); ^1H NMR (DMSO-d_6): δ 6.15 (s; 2H; $-CH_2-$N), 7.30–9.50 (m; 14H; naphthalene, benzene and imidazole); Mass (EI, 70 eV): *m/e* 400 [M^+] (3%), 332, 301, 273, 233, 206, 179, 165, 153 (base peak, 100%), 137, 121, 104, 81, 65, 41; Anal. Calcd. for $C_{22}H_{16}N_4O_4$. H_2O (418.40): C, 63.15; H, 4.34; N, 13.39. Found: C, 63.46; H, 3.67; N, 13.04.

*4.1.1.22. 1-(2-naphthyl)-2-(imidazol-1-yl)ethanone O-(3-bromobenzoyl) oxime (**22**).* Compound was purified by column chromatography and then recrystallized from acetone. Yield: 66.77%; mp: 124–6 °C; IR (ν cm^{-1}, KBr): 1753 (C=O), 1571 (C=N), 1231 (C–O); ^1H NMR (DMSO-d_6): δ 5.74 (s; 2H; $-CH_2-$N), 7.03–8.39 (m; 14H; naphthalene, benzene and imidazole); Mass (EI, 70 eV): *m/e* 435 [M^{+1}] (12%), 433 (M^{-1} 12%), 339, 301, 273, 251, 233, 202, 200, 185, 183, 166, 153 (base peak, 100%), 139, 126, 101, 76, 68, 50, 41; Anal. Calcd. for $C_{22}H_{16}BrN_3O_2$. 1/4H_2O (442.05): C, 59.61; H, 3.87; N, 9.48. Found: C, 59.86; H, 3.54; N, 9.53.

*4.1.1.23. 1-(2-naphthyl)-2-(imidazol-1-yl)ethanone O-4-phenylbenzoyl oxime hydrochloride (**23**).* Compound was recrystallized from methanol/petroleum ether, IR (ν cm^{-1}, ATR): 1742 (C=O), 1606 (C=N), 1247 (C–O); ^1H NMR (DMSO-d_6, 300 MHz): δ 6.09 (s, 2H, $-CH_2-$N), 6.97–8.43 (m, 18H, naphthalene, benzene protons and imidazole $H^{4,5}$), 9.08 (s, 1H, imidazole H^2); Mass (API-ES): *m/e* 431 (M^+, % 100); Anal. Calcd. for $C_{28}H_{22}ClN_3O_2$. 3/2H_2O (494.15): C, 67.94; H, 5.09; N, 8.49. Found: C, 67.55; H, 4.97; N, 9.02.

4.2. Anticonvulsant activity

The present study was approved by the Ethics Committee of Hacettepe University, (Date: 27/12/2006, Number: 2006/72-2) and the Ethics Committee of Inonu University, School of Medicine (Date: 24/05/2010, Number: 2010/31).

The compounds were tested for anticonvulsant activity according to the phase I tests of ASP (Antiepileptic Drug Screening Programme) which were developed by National Institutes of Health (NIH), National Institute of Neurological Disorders and Stroke (NINDS) [23,24].

Stimulator (Grass S88, Astro-Med., Grass Instrument Division, W. Warwick, RI, USA), constant current unit (Grass CCU1A, Grass Medical Instrument, Quincy, MA, USA), and corneal electrodes were used for the evaluation of anticonvulsant activity. Suspension of the compounds in 30% aqueous of PEG 400 were administered intraperitoneally at three dose levels (30,100 and 300 mg/kg) 30 min and 4 h after the administration. Twelve Swiss albino mice (20–24 g) were used for each compound (in other words 4 mice at each dose level or 6 mice for MES test and 6 mice for ScM test) (mice were obtained from the Hacettepe University Animal Farm and Laboratory Animals Research Center of Inonu University). Phase I evaluation was designed to identify anticonvulsant activity and neurotoxicity with three tests: MES, ScM, and rotorod. Pentylenetetrazole was supplied by Sigma Chemical Co. and was administered subcutaneously over the back of the neck. The rotorod toxicity test was performed for neurological deficits.

4.2.1. Maximal electroshock seizure (MES) test

MES seizures were elicited with a 60 Hz alternating current of 50 mA intensity delivered for 0.2 s via corneal electrodes. A drop of 0.9% saline was instilled in the eyes prior to the application of the electrodes in order to prevent the death of the animal. Abolition of the hind limb tonic extension component of the seizure was defined as protection.

4.2.2. Subcutaneous pentylenetetrazole (metrazol) (ScM) test

Pentylenetetrazole (85 mg/kg) (which produces seizures in greater than 95% of mice) was administered as a 0.5% solution subcutaneously. The animals were observed for 30 min, failure to

observe even a threshold seizure (a single episode of clonic spasms of at least 5 s duration) was defined as protection.

4.2.3. Neurotoxicity test

The rotorod test was used to evaluate neurotoxicity. The animals were placed on a 1-inch-diameter knurled wooden rod rotating at 6 rpm. Normal mice remain on a rod rotating at this speed indefinitely. Neurotoxicity was indicated by the inability of the animal to maintain equilibrium on the rod for at least 1 min in each of the three trials. In rats, neurological deficit is indicated by ataxia and loss of placing response and muscle tone.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2012.08.037.

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