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Synthesis, anticonvulsant and antimicrobial activities of some new 2-acetylnaphthalene derivatives

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ABSTRACT

In this study, as a continuation of our research for new (arylalkyl)imidazole anticonvulsant compounds, the design, synthesis and anticonvulsant/antimicrobial activity evaluation of a series of 2-acetylnaphthalene derivatives have been described. Molecular design of the compounds has been based on the modification of nafimidone [1-(2-naphthyl)-2-(imidazol-1-yl)ethanone], which is a representative of the (arylalkyl)imidazole anticonvulsant compounds as well as its active metabolite, nafimidone alcohol (**3**, **4**). In general, these compounds were variously substituted at the alkyl chain between naphthalene and imidazole rings and subjected to some other modifications to evaluate additional structure–activity relationships. The anticonvulsant activity profile of those compounds was determined by maximal electroshock seizure (MES) and subcutaneous metrazol (scM) seizure tests, whereas their neurotoxicity was examined using rotarod test. All the ester derivatives of nafimidone alcohol (**5a–h**), which were designed as prodrugs, showed anticonvulsant activity against MES-induced seizure model. Four of the most active compounds were chosen for further anticonvulsant evaluations. Quantification of anticonvulsant protection was calculated via the ip route (ED_{50} and TD_{50}) for the most active candidate (**5d**). Observed protection in the MES model was 38.46 mg kg^{-1} and 123.83 mg kg^{-1} in mice and 20.44 mg kg^{-1}, 56.36 mg kg^{-1} in rats, respectively. Most of the compounds with imidazole ring also showed antibacterial and/or antifungal activities to a certain extent in addition to their anticonvulsant activity.

1. Introduction

Epilepsy is a disease that affects more than 50 million people worldwide, and the cost of treatment and lost productivity to society is also staggering. So new and better treatments are desperately needed. Many of the older generation of antiepileptic drugs were approved before 1985 (i.e., phenytoin, phenobarbital, carbamazepin). Each of the newer generation anticonvulsants (levetiracetam, lamotrigine, felbamate, gabapentin, etc.) has certain advantages that have resulted in increased treatment options for clinicians and patients. Although some of the newer drugs were purported to have decreased side effects and/or fewer drug–drug interactions, nearly 30–40% of patients remain uncontrolled or suffer breakthrough seizures. While recognizing that the last three decades have brought significant advances in our understanding of seizure propagation and associated pathophysiology of the disease process, it must also be noted that treatments, even achieving seizure control, are less than optimal in terms of both dose-related side effects and breakthrough seizures. For many patients, seizure control is only achieved at a very high price. Therefore, it is critical to continue efforts to find safer and more efficacious drugs and ultimately a treatment for this devastating disease.[1,2]

Many of the newer antiepileptic drugs (post 1990) as well as those currently in clinical development were designed through structural modifications of pre-existing compounds; others were developed with a specific aim to modify neurotransmitter function such as enhancement of inhibitory-mediated neurotransmission or attenuation of excitatory-mediated neurotransmission.[3] Most successful anticonvulsants possess more than one mechanism of action. Having multiple mechanisms or being 'pharmacologically rich' is a characteristic of many AEDs and can be viewed as both a treatment advantage and a disadvantage for patients and their clinicians. The disadvantages include increased potential for side effects and metabolic drug–drug interactions. Some of the advantages can be seen in the form of broad spectrum of actions. Thus, several AEDs can be useful in different syndromes and even other neurological disorders such as neuropathic pain, migraine and bipolar disorder. In general the most common mechanisms

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involved in seizure control can be attributed to a drug's action on ion channels (sodium, potassium), neuronal excitation, and inhibition actions.

GABA is the most common inhibitory neurotransmitter in the central nervous system. Drugs like progabid, gabapentin and vigabatrin were specifically designed as GABA prodrugs or lipophilic GABA analogs.[4] Valproic acid, which has a different chemical structure from classical antiepileptic drugs, was developed as a GABA agonist, but later it was shown that it can also increase GABA levels in different ways.[5] Numerous studies are reported in the literature about valeric, isovaleric, and especially valproic acid esters as potential anticonvulsant agents.[6,7] Loreclazole, one of the (arylalkyl)azole anticonvulsant compounds with broad activity spectrum, has a modulating action on $GABA_A$.[8] Nafimidone and denzimol are the other examples of (arylalkyl)azoles, which possess a profile of activity similar to that of phenytoin or carbamazepine but distinct from barbiturates or valproic acid.[9,10] Nafimidone alcohol, the major metabolite of nafimidone, also has high anticonvulsant activity (Fig. 1).[11] SAR studies of (arylalkyl)azole anticonvulsant compounds have shown that anticonvulsant properties of this group are associated with the presence of a small oxygen functional group (such as carbonyl, ethylene dioxy, methoxy, acyloxy, hydroxyl and oxime ether substituents) in the alkylene bridge in addition to imidazole ring and lipophilic aryl portion facilitating penetration through blood–brain barrier.[9,10,12,13]

In addition to their anticonvulsant activity, many from the chemical class represented by the (arylalkyl)azole compounds show antifungal and/or antibacterial activities largely because of their structural similarities to 1-substituted-1*H*-azole antifungals, which have an important place among the other antifungal groups. Azole antifungals generally possess an imidazole or triazole ring (seen with miconazole, ketoconazole, fluconazole and itraconazole) as an azole group.[13,14]

In this study, in the light of available literature and as a continuation of our previous studies on nafimidone derived (arylalkyl)azole compounds, we aimed to synthesize some new acetylnaphthalene derivatives as potential anticonvulsant compounds and then to evaluate their anticonvulsant and antimicrobial activities in an effort to find more active and less toxic treatment candidates. In the process, we sought to explore potential new relationships between the structure and the activities of this major group. To this end, we prepared some carboxylic acid esters of nafimidone alcohol (**5a–h**) as prodrugs. These esters were designed with various alkyl or aryl groups in order to establish the effects of the size and branching of the alkyl chain on the activity. Among these compounds, GABA (**5f**) and valproic acid (**5e**) esters were also the hybrid molecules of nafimidone alcohol (**4**) and these two acids. Recently it has been shown that coupling of valproic acid with some aromatic amino alkanes and cyclic alkyl analogs improves the pharmacological profile.[15,16] Therefore, valproic, valeric, isovaleric acid and GABA esters (**7a–d**) of 1-(naphthalene-2-yl)ethanol (**6**) without an imidazole ring were prepared by considering the naphthalene ring as a carrier to target the brain. The Schiff base of 2-acetylnaphthalene with GABA was also designed as another CNS-targeted molecule resembling progabid. Since the neurotoxicity is the main problem of nafimidone derivatives, we synthesized 1-hydroxynaphthalene derivatives of nafimidone **11** and its reduction product **12** to decrease neurotoxicity via decreasing the lipophilicity by adding a polar hydroxyl group to the molecule (Table 1).

2. Results and discussion

2.1. Chemistry

The total synthesis of the compounds is given in Scheme 1. Nafimidone **3** was obtained by the alkylation of imidazole with α-bromo-2-acetylnaphthalene **2**.[9,15] Reduction of **3** with sodium borohydride produced nafimidone alcohol **4**. Ester derivatives **5a–h** were prepared by esterification of the alcohol **4** with acid anhydride (method A), acyl chloride (method B), carboxylic acid and dicyclohexilcarbodiimide/4-dimethylaminopyridine (DCC/DMAP) (method C) or pyridine/DMAP (method D). Reduction of 2-acetylnaphthalene **1** with sodium borohydride produced alcohol **6** which reacted with carboxylic acid and DCC/DMAP to have esters **7a–d**. *t*-Boc-GABA was prepared using GABA and di-*tert*-butyl carbamate to synthesize compounds **5f** and **7d** (Scheme 1).

Synthesis of compounds **11** and **12**, which are the 1-hydroxynaphthalene analogous of nafimidone **3** and nafimidone alcohol **4**, respectively, was started by using 1-hydroxy-2-acetylnaphthalene **8**. To obtain 2-bromo-1-(1-acetyloxynaphthalene-2-yl)ethanone **9**, 1-hydroxy-2-acetylnaphthalene **8** was acetylated by acetic anhydride before bromination to protect the hydroxyl group. N-Alkylation of imidazole with **10** produced **11** and its reduction with sodium borohydride yielded **12**. Deprotection of acetyl group of **10** was realized during N-alkylation reaction due to excess basic imidazole. Imine derivative **13** was obtained through Schiff reaction between the ketone group of 1-hydroxy-2-acetylnaphthalene and amino group of GABA sodium salt prepared from the reaction of GABA and sodium ethoxide (Scheme 1).

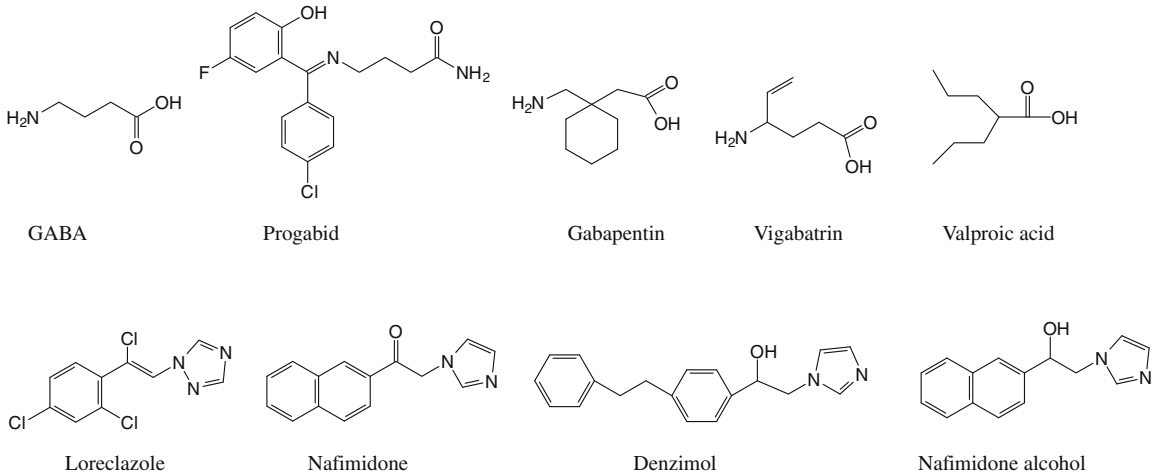
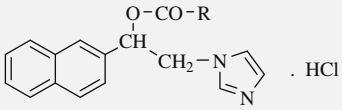
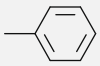
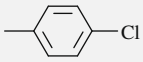
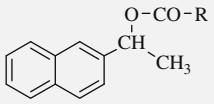
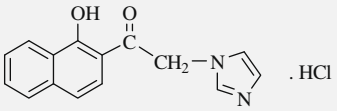
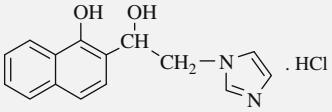
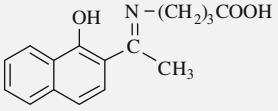


Figure 1. Chemical structure of the compounds.

Table 1
The structures, crystallization solvents, synthesis methods, yields, melting points and *c* log *P* values of the compounds

Compd	R	Crystallization solvent	Method	Yield (%)	Mp (°C)	*c* log *P*
						
5a	$-CH_2CH_2CH_3$	Ethyl acetate/petroleum ether	A	49	155–156	3.80
5b	$-CH(CH_3)_2$	Ethyl acetate	B	57	165–167	3.58
5c	$-CH_2(CH_2)_2CH_3$	Methanol/ethyl acetate	C	71	133–134	4.33
5d	$-CH_2CH(CH_3)_2$	Methanol/ethyl acetate	C	80	135–137	4.20
5e	$-CH(C_3H_7)_2$	Methanol/ethyl acetate	C	75	181–183	5.70
5f	$-(CH_2)_3-NH-COOC(CH_3)_3$	Ethyl acetate	C	68	130–131	4.26
5g		Methanol/ethyl acetate	C	65	215–217	4.59
5h		Ethyl acetate/petroleum ether	D	58	179–181	5.30
						
7a[a]	$-CH_2(CH_2)_2CH_3$	—	C	82	205 (bp)	5.03
7b[a]	$-CH_2CH(CH_3)_2$	—	C	88	208 (bp)	4.90
7c[a]	$-CH(C_3H_7)_2$	—	C	85	223 (bp)	6.40
7d	$-(CH_2)_3-NH-COOC(CH_3)_3$	Methanol/water	C	79	80–82	4.96
11		Methanol/ethyl acetate	E	38	250–252	2.55
12		Chloroform/petroleum ether	F	98	220 (dec.)	1.19
13		Chloroform/petroleum ether	G	79	171–172	2.76

[a] Liquid compounds.

The physical properties of the synthesized compounds are presented in Table 1. The structure of the compounds was confirmed by IR, ^{1}H NMR, mass spectral data and elemental analysis has been provided in Section 4.

2.1.1. X-ray analysis of compound 11

Since the activity of compounds **11** and **12**, which are the 1-hydroxynaphthalene derivatives of nafimidone **3** and its active metabolite nafimidone alcohol **4** were surprisingly found very low or even inactive compared to nafimidone and nafimidone alcohol, we decided to evaluate the three-dimensional structure of compound **11** by X-ray crystallography to determine whether the H-bond between 1-hydroxyl and carbonyl group exists and blocks the carbonyl oxygen, which is probably important for receptor interaction.

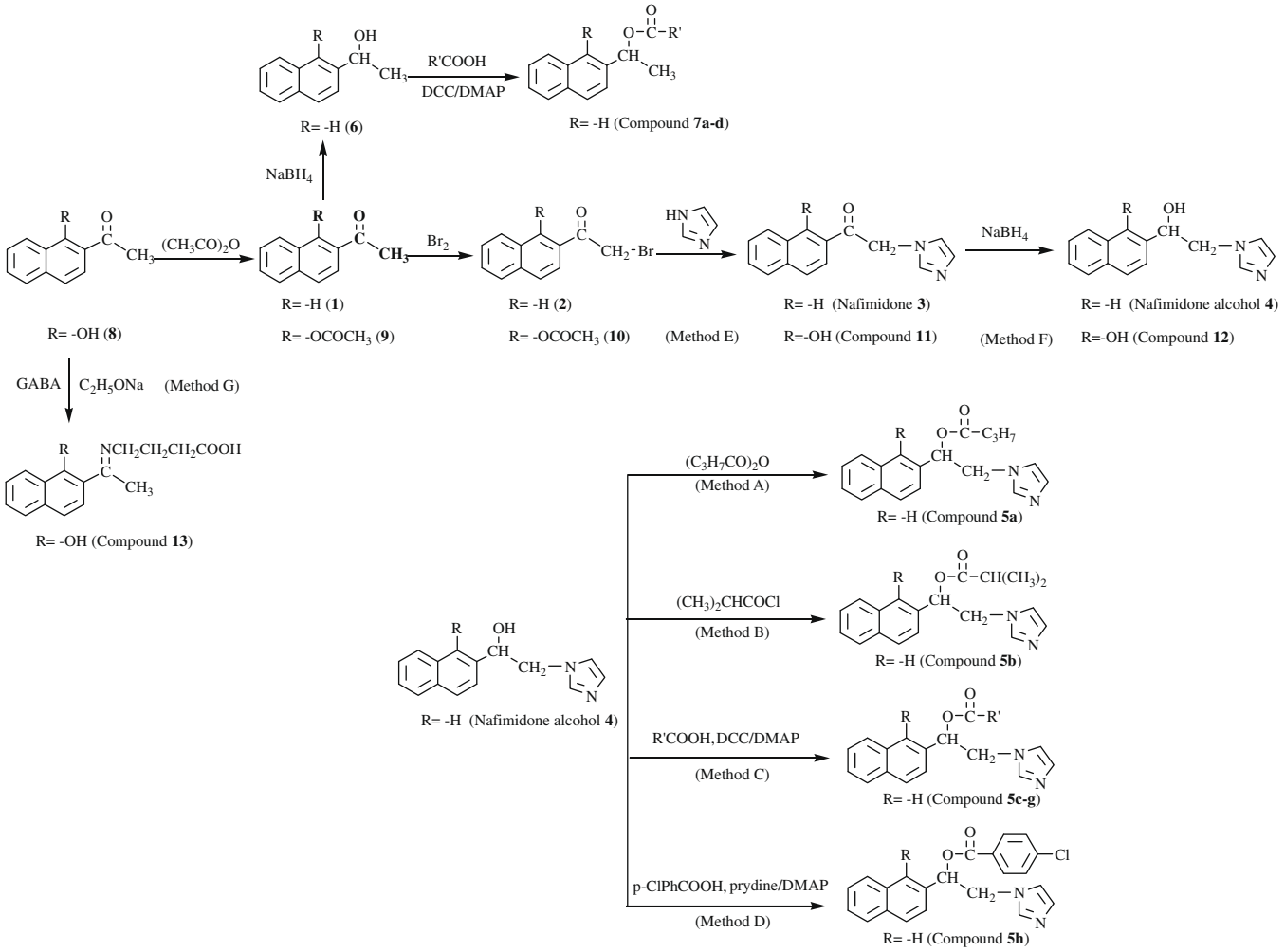
The X-ray crystallographic data of compound **11** demonstrated that there is an intramolecular hydrogen bond between carbonyl and the hydroxyl group on the naphthalene ring (C=O···H–O). A weak intermolecular hydrogen bond between hydroxyl and imidazole H4 (C–H···O–H) was also observed via X-ray crystallographic study.

The crystal data and a summary of intensity data collections and structural refinements, bond lengths, bond angles and torsion angles are given in the tables below (Tables 2–4).

2.2. Anticonvulsant activity

Anticonvulsant activity and neurotoxicity screening test results (MES, scM and rotarod) are summarized in Table 5. None of the compounds are found to be active against scM test. According to these screening results (Table 5), it can be concluded that anticonvulsant activities of these compounds are MES specific. This result is in accordance with the findings obtained from other (arylalkyl)azole derivatives.[9,10,13,14]

All the ester derivatives with imidazole ring **5a–h**, which were designed as prodrugs of nafimidone alcohol **4**, showed anti-MES activity at either 30 or 100 mg kg^{-1} at 0.5 h except **5h** which is active only at 300 mg kg^{-1}. These compounds are more active at the 0.5th h than at the 4th h, indicating that they have a rapid onset of action; they also display toxicity at 0.5 h at 300 mg kg^{-1}. Therefore, although they were designed as prodrugs, they probably do not act as prodrugs or they are metabolized very fast. The size and branching of the 'R' group in the active ester derivatives **5a–h** did not appear to have an important role in the activity but *p*-chlorophenyl ester derivative **5h** was the least active one with activity only at 300 mg/kg. This decreased activity is most probably caused by steric hindrance of chloro substituent rather than lipophilicity because the compound **5h** (*c* log *P*: 5.30) is more lipophilic than phenyl ester derivative **5g** (*c* log *P*: 4.59).



Scheme 1. Synthesis of the compounds.

Table 2
Hydrogen bonding geometry (Å, °)

Donor–H···acceptor	[Symmetry code]	D–H	H···A	D···A	D–H···A
O(2)–H(7O)···O	[Intra]	0.82	1.85	2.573(3)	147
C(1)–H(1)···Cl	[7545.02]	0.93	2.55	3.398(4)	152
C(2)–H(2)···O	[6545.01]	0.93	2.53	3.242(4)	134
C(3)–H(3)···Cl	[4655.02]	0.93	2.80	3.503(4)	133
C(4)–H(4B)···Cl	[1655.02]	0.97	2.72	3.599(3)	150

Symmetry code:
[7545.] = 1/2 − *x*, −1/2 + *y*, *z*.
[6545.] = 1/2 + *x*, −1/2 + *y*, 1/2 − *z*.
[4655.] = 1 − *x*, *y*, 1/2 − *z*.
[1655.] = 1 + *x*, *y*, *z*.

Since the lipophilicity (log *P* >2) is crucial for CNS drugs to pass BBB, *c* log *P* values of the compounds were calculated by ChemDraw Ultra 8.0. The predicted *c* log *P* values of these ester derivatives **5a–h** were in the range of 3.58–5.70 which are much higher than 2. But an increase in the lipophilicity from isopropyl ester derivative **5b** (*c* log *P*: 3.58) to valproyl ester derivative **5e** (*c* log *P*: 5.70) did not result in an increase in the activity. Because an increase in lipophilicity does not result in an increased activity after a point and, sometimes even an activity drop or loss may be seen depending on the optimal log *P* value.

Although it is well known that high log *P* values are important for BBB passage, lipophilicity is not the only parameter for the activity and some other properties are also responsible from the activity. For example, the absence of the imidazole ring brings about the lack of the activity in compounds **7a–d** and **13** with very high log *P* values (*c* log *P*: 2.76–6.40). The valproic acid ester **5e**, which was designed also as a hybrid molecule, did not provide an advantage in the activity compared to the other esters probably because the dose used was not high enough to provide effective dose of valproic acid (MES ED_{50} in mice ip: 263 mg kg^{-1}).[17]

On the other hand, ester derivatives without imidazole ring **7a–d** and Schiff base derivative **13**, which were designed as brain targeted molecules of valproic, valeric, isovaleric acids and GABA, did not show any significant efficacy or toxicity in the MES and ScM models at the times and doses used in these assays (neither anticonvulsant activity nor neurotoxicity) probably because of the high effective dose level of these acids and also metabolic decomposition (hydrolysis or reduction) problems of ester and azomethine (C=N) groups.

Although the nafimidone dose providing anti-MES activity in mice is 15 mg kg^{-1} ip, compound **11**, which has only an extra hydroxyl group on the naphthalene ring compared to nafimidone, has activity at 300 mg kg^{-1} and unfortunately shows neurotoxicity at the same dose level as well.[9] Lipophilicity is not the cause of the drop in the activity since *c* log *P* is 2.55 for compound **13** and 2.22 for nafimidone. Therefore, it may be speculated that this is probably because of the hydrogen bond between hydroxyl on the naphthalene ring and carbonyl group, which is also important for the receptor interaction (Fig. 2). Moreover, differences in some other

Table 3
Geometric parameters (Å, °, °)

Bond length (Å)		Bond angle (°)		Torsion angle (°)	
N2–C1	1.337(4)	C1–N2–C3	106.9(3)	C1–N2–C4–C5	91.2(4)
N2–C3	1.371(4)	C1–N2–C4	127.1(3)	C3–N2–C4–C5	−84.5(4)
N2–C4	1.451(3)	C3–N2–C4	125.9(3)	C7–C6–C11–O2	−179.3(3)
O1–C5	1.235(4)	C11–C6–C7	117.7(3)	C5–C6–C11–O2	0.9(4)
C6–C11	1.393(4)	C11–C6–C5	120.1(3)	C7–C6–C11–C10	−0.2(4)
C6–C7	1.417(4)	C7–C6–C5	122.2(3)	C5–C6–C11–C10	−180.0(3)
C6–C5	1.445(4)	C1–N1–C2	106.5(3)	C12–C10–C11–O2	0.8(4)
N1–C1	1.317(4)	N2–C4–C5	112.2(3)	C9–C10–C11–O2	179.5(3)
N1–C2	1.374(4)	C12–C10–C9	119.6(3)	C12–C10–C11–C6	−178.4(3)
O2–C11	1.357(3)	C12–C10–C11	122.8(3)	C9–C10–C11–C6	0.3(4)
C4–C5	1.522(4)	C9–C10–C11	117.6(3)	C2–N1–C1–N2	0.6(4)
C10–C12	1.411(4)	C14–C15–C9	120.2(4)	C3–N2–C1–N1	−0.8(4)
C10–C9	1.417(4)	O2–C11–C6	121.3(3)	C4–N2–C1–N1	−177.1(3)
C10–C11	1.419(4)	O2–C11–C10	116.2(3)	C9–C10–C12–C13	−0.2(4)
C15–C14	1.368(4)	C6–C11–C10	122.5(3)	C11–C10–C12–C13	178.6(3)
C15–C9	1.399(5)	N1–C1– N2	110.8(3)	C11–C6–C7–C8	−0.1(5)
C12–C13	1.354(4)	C13–C12–C10	119.5(3)	C5–C6–C7–C8	179.7(3)
C7–C8	1.346(4)	C8–C7–C6	121.6(3)	C14–C15–C9–C10	0.9(5)
C9–C8	1.419(4)	C15–C9–C10	118.9(3)	C14–C15–C9–C8	−178.4(3)
C3–C2	1.341(5)	C15–C9–C8	121.7(4)	C12–C10–C9–C15	−0.7(4)
C13–C14	1.395(4)	C10–C9–C8	119.4(3)	C11–C10–C9–C15	−179.5(3)
		O1–C5–C6	123.6(3)	C12–C10–C9–C8	178.6(3)
		O1–C5–C4	118.4(3)	C11–C10–C9–C8	−0.2(4)
		C6–C5–C4	118.0(3)	C11–C6–C5–O1	−2.9(5)
		C2–C3–N2	107.2(3)	C7–C6–C5–O1	177.3(3)
		C7–C8–C9	121.2(3)	C11–C6–C5–C4	176.6(3)
		C3–C2–N1	108.6(3)	C7–C6–C5–C4	−3.2(5)
		C12–C13–C14	121.3(3)	N2–C4–C5–O1	−1.3(5)
		C15–C14–C13	120.4(4)	N2–C4–C5–C6	179.2(3)
				C1–N2–C3–C2	0.6(4)
				C4–N2–C3–C2	177.0(3)
				C6–C7–C8–C9	0.2(5)
				C15–C9–C8–C7	179.2(3)
				C10–C9–C8–C7	0.0(5)
				N2–C3–C2–N1	−0.2(4)
				C1–N1–C2–C3	−0.3(4)
				C10–C12–C13–C14	1.0(5)
				C9–C15–C14–C13	−0.1(5)
				C12–C13–C14–C15	−0.8(5)

properties of compound **13** compared to nafimidone may also play a role in the activity loss.

No activity (neither anticonvulsant nor neurotoxicity) was observed in compound **12**, which is the reduction product of compound **11** (1-hydroxynaphthalene analog of nafimidone), mainly due to its very low log *P* value (*c* log *P*: 1.19), which is not enough to pass BBB and, less likely due to the hydrogen bond between both hydroxyl groups on the naphthalene ring and alkyl chain (nafimidone alcohol anti-MES ED_{50}: 34 mg kg^{-1}, TD_{50}: 89 mg kg^{-1} and *c* log *P*: 1.91).[9] Finally, the results obtained from the screening tests have revealed that anticonvulsant activity mainly depends on the existence of azole ring and the ester group on the alkyl chain.

Among these potent ester derivatives with imidazole ring, four compounds **5b**, **5d**, **5e** and **5g** were selected for evaluation of their oral anti-MES activity and neurotoxicity in rats at several time points (Table 6). The compounds were dosed at 30 mg kg^{-1}. At this dose level, none of the candidates exhibited neurotoxicity. The activity spectrum of compound **5d** was non-linear probably because of poor oral absorption.

Anti-MES activity and neurotoxicity of compounds **5d** and **5e** were also evaluated intraperitoneally in rats at 30 mg kg^{-1} (Table 7). Both of these compounds were found to be active at this dose level and no toxicity was observed at any of the time points used.

Compound **5d** was selected for quantification of its pharmacological parameters (Tables 8 and 9). Time to peak effect (TPE) test results in mice and rats dosed ip with compound **5d** are presented in Table 8. According to the ED_{50} biological response data in mice and rats dosed ip with compound **5d** at TPE (0.5 h), quantitative anticonvulsant data in mice for compound **5d** were found to be MES ED_{50} 38.46 mg kg^{-1}, ScM ED_{50} >138 mg kg^{-1} and MES TD_{50} 123.83 mg kg^{-1}; therefore, therapeutic index (TI) of this compound is 3.22 (ip). In the rat model (ip), MES ED_{50}, TD_{50} and TI values were 20.44 mg kg^{-1}, 56.36 mg kg^{-1} and 2.76, respectively (Table 9).

This compound was also tested in the hippocampal kindled rat model at a dose of 300 mg kg^{-1} (ip); but it did not have any apparent activity in this model in the single animal tested.

2.3. Antifungal and antibacterial activities

Antifungal and antibacterial activities of the compounds with imidazole ring were evaluated since the structure of these compounds resembles azole antifungals. The antimicrobial activity test results of these compounds are given in Table 10.

Most of the compounds (**5a–h**, **11**) were found to be active against Gr (+) bacteria especially *Staphylococcus aureus* at 8–64 μg/ml concentration. Compounds **5c–e** and **5g** were also found to be active against *Enterococcus faecalis* at 16–64 μg/ml concentration. All of the compounds were found to be inactive against Gr (−) bacteria.

Compounds **5a–d** were active against *Candida albicans* at 8–64 μg/ml concentration. Some of the compounds (**5a**, **5d** and **11**) showed antifungal activity against *Candida parapsilosis*. Only compound **11** was active against *Candida krusei* at 64 μg/ml concentration. Surprisingly, chloro substituted benzyl derivative **5h** was found to be inactive against fungi, while alkyl derivatives **5a–d** were active.

Table 4
Crystal data and details of the structure determination of compound **11**

Formula	$C_{15}H_{13}ClN_2O_2$
Molecular weight	288.72
Crystal system	Orthorhombic
Space group	*Pbcn*
a (Å), *b* (Å), *c*(Å)	10.742(1), 11.542(1), 22.075(2) 22.075(2)
α (°), β (°), γ (°)	90, 90, 90
Volume (Å^3)	2737.0(5)
Z	8
D (calculated) (g cm^{-3})	1.369
F 0 0 0	1192
Linear absorption coefficient (mm^{-1})	0.281
Absorption correction type	Integration (X-RED32)
Crystal size (mm)	0.580 × 0.343 × 0.110
Diffractions radiation type	MoKα
λ (Å)	0.71073
Monochromator	Graphite
Diffractions measurement device type	Stoe IPDS-II (Image Plate)
Diffractions measurement device	φ scans
Total reflection number	11521
Independent reflection number	2258
Collected reflection for $I > 2\sigma(I)$	979
R_{int}	0.0492
h, *k*, *l* ranges	−12→12, −10→13, −22→25
θ_{min} , θ_{max} range (°)	2.59, 24.54
Solution	Direct methods, SHELXS-97, SHELXL-97, WINGX
Least squares refine weighting details	$w = 1/\sigma^2(F)^2$
Number of variable	181
R	0.0397
wR	0.0506
$S(F^2)$	0.701
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e/Å^3)	0.254, −0.168

3. Conclusion

As a continuation of our interest in developing nafimidone-like anticonvulsant compounds we designed and synthesized a series of (arylalkyl)azole derivatives with different functional groups at the alkyl chain between aryl and azole rings and evaluated their anticonvulsant, antifungal and antibacterial activities. The results obtained revealed that most of the ester derivatives with imidazole ring were found to be active in MES screen. Nafimidone alcohol esters **5a–g**, which were designed as its prodrug, did not provide an advantage in the activity compared to nafimidone alcohol since ED_{50} of nafimidone alcohol (34 mg kg^{-1}) is lower than that of ester derivatives. In this group, not only lipophilicity but also the presence of imidazole ring is essential for the anti-MES activity. A hydroxyl group at α-position of the naphthalene ring caused loss in the activity probably because of the hydrogen bond with carbonyl (in nafimidone) or hydroxyl group (in nafimidone alcohol) on the alkyl chain as well as the reduction in the lipophilicity. Anticonvulsant activities of these compounds appear to be MES selective. Some of the ester derivatives were selected for further investigations in addition to the screening tests; according to these results, compound **5d** (isovaleric acid ester of nafimidone alcohol) was selected for quantification of its pharmacological parameters and the findings were as follows: MES ED_{50} 38.46 mg kg^{-1}, TD_{50} 123.83 mg kg^{-1} and TI 3.22 in mice (ip).

Concerning the antifungal and antibacterial activities of the compounds with imidazole ring, it can be concluded that these compounds were more active against Gr (+) bacteria than Gr (−) bacteria and some of the ester derivatives also showed antifungal activities to some extent especially against *C. albicans*.

4. Experimental part

4.1. Chemistry

All the chemicals used in this study were purchased from E. Merck, Fluka AG and Aldrich. Purity of all the compounds was checked by using TLC with Merck Kieselgel 60 F254 aluminum plates. Column chromatography 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 were uncorrected. Boiling points were determined by distillation. IR spectra were recorded on KBr disks with a Bruker Vector 22 IR (Opus Spectroscopic Software Version 2.0) Spectrometer. ^{1}H NMR spectra were recorded on a Bruker 80 MHz and Bruker Avance 400 MHz FT NMR spectrometer. All the chemical shifts were 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 using 73DIP-1 Direct Insertion Probe and Agilent 5973-network Mass Selective Detector. Elemental analysis was performed on Leco 982 CHNS elemental analysis apparatus at TUBITAK (Scientific and Tech-

Table 5
Anticonvulsant and neurotoxicity screening data in mice dosed ip with the compounds

Tests	Hours	Dose (mg kg^{-1})	Compound														
			5a	**5b**	**5c**	**5d**	**5e**	**5f**	**5g**	**5h**	**7a**	**7b**	**7c**	**7d**	**11**	**12**	**13**
MES[a]	1/2	30	0/1	1/1	1/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
		100	3/3	3/3	3/3	3/3	3/3	3/3	3/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
		300	1/1[c]	0/0	1/1	1/1	1/1	1/1	1/1	1/1	0/1	0/1	0/1	0/1	1/1	0/1	0/1
MES	4	30	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
		100	0/3	1/3	1/3	1/3	1/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
		300	1/1	1/1	0/0	1/1	1/1	1/1	0/1	0/1	0/1	0/1	0/1	0/1	1/1	0/1	0/1
Toxicity[b]	1/2	30	0/4	0/4	0/4	0/4	0/4	0/4	1/4[e]	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
		100	6/8	1/8	0/8	0/8	0/8	3/8[e]	2/8[e]	0/8	0/8	0/8	0/8	1/8	0/8	0/8	1/8
		300	4/4[d]	4/4[d,e,f]	4/4[d,g]	4/4[d,g]	4/4[d,e]	3/4[d,e]	4/4[c,d,e]	1/4	0/4	0/4	0/4	0/4	2/4[d,e]	1/4	4/4
Toxicity	4	30	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
		100	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
		300	0/2	0/2	2/2[d,f]	2/2[d,f]	2/2[d,e]	0/2	1/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2

[a] Maximal electroshock test (number of animal protected/number of animal tested).
[b] Toxicity (number of animal exhibiting toxicity/number of animal tested).
[c] Clonic seizures.
[d] Unable to grasp rotarod.
[e] Muscle spasms.
[f] Dead.
[g] Hiperactivity.

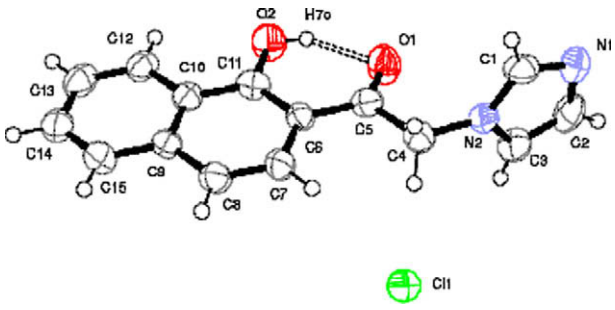


Figure 2. An ORTEPII drawing of compound **11**, showing 50% probability displacement ellipsoids and atom-numbering scheme.

Table 6
Anticonvulsant (anti-MES) and toxicity qualitative screening data in rats dosed orally with selected compounds[a]

Compound	Test	Time in hours				
		0.25	0.5	1	2	4
5b	MES	0/4	1/4	1/4	1/4	1/4
	TOX	0/4	0/4	0/4	0/4	0/4
5d	MES	0/4	3/4	0/4	0/4	2/4
	TOX	0/4	0/4	0/4	0/4	0/4
5e	MES	0/4	0/4	1/4	2/4	0/4
	TOX	0/4	0/4	0/4	0/4	0/4
5g	MES	1/4	0/4	0/4	1/4	0/4
	TOX	0/4	0/4	0/4	0/4	0/4

[a] At each time point, rats were given a single dose of 30 mg of compound per kg of body weight.

Table 7
Anticonvulsant (anti-MES) and toxicity qualitative screening data in rats dosed ip with selected compounds[a]

Compound	Test	Time in hours				
		0.25	0.5	1	2	4
5d	MES	3/4	3/4	3/4	1/4	1/4
	TOX	0/4	0/4	0/4	0/4	0/4
5e	MES	—	2/2	3/4	3/4	—
	TOX	—	0/2	0/4	0/4	—

[a] At each time point, rats were given a single dose of 30 mg of compound per kg of body weight.

Table 8
Time to peak effect test results in mice and rats dosed ip

Compd		Test	Dose (mg/kg)	0.25 h	0.5 h	1 h	2 h	4 h	6 h
5d	Mice	MES	23	1/8	2/8	0/8	—	—	
	ip	MES	35	—	2/4	2/4	0/4	—	
		MES	70	3/4	4/4	4/4	2/4	0/4	
		TOX	150	8/8[a,b]	3/8[a]	0/8	0/8	—	
	Rats	MES	30	3/4	4/4	3/4	—	—	
	ip	TOX	10	0/2	0/2	0/2	0/2	0/2	
		TOX	30	0/2	0/2	0/2	0/2	0/2	
		TOX	50	2/8	3/8	3/8	0/8	0/8	0/8
		TOX	75	—	8/8	6/8	—	—	

[a] Unable to grasp rotarod.
[b] Muscle spasms.

nical Research Council of Turkey). 2-Bromo-1-(naphthalene-2-yl)ethanone **1**,[18] 2-(imidazol-1-yl)-1-(naphthalene-2-yl)ethanone **2**,[9] 2-(imidazol-1-yl)-1-(naphthalene-2-yl)ethanol **3**,[9] 1-(1-acetyloxynaphthalene-2-yl)ethanone **4**,[19] 2-bromo-1-(1-acetyloxy-naphthalene-2-yl)ethanone **5**,[19] 1-(naphthalene-2-yl)ethanol **6**[9] were prepared according to the procedures described in relevant literature.

4.1.1. Preparation of the compounds. 2-(Imidazol-1-yl)-1-(naphthalene-2-yl)ethanol esters and 1-(naphthalene-2-yl)ethanol esters (compounds 5a–h, 7a–d)

4.1.1.1. Method A. Appropriate acid anhydride (1 mmol) and 2-(imidazol-1-yl)-1-(naphthalene-2-yl)ethanol (0.24 g, 1 mmol) were refluxed for 4 h in dry ether (25 ml). After ether was evaporated, the residue was purified by column chromatography on silica gel eluting with chloroform/methanol (90:10), dissolved in ether, and treated with etheral hydrochloric acid crystallized from the appropriate solvents.

4.1.1.2. Method B. Appropriate acid chloride (1 mmol), 2-(imidazol-1-yl)-1-(naphthalene-2-yl) ethanol (0.24 g, 1 mmol) and pyridine (4 ml) were stirred at room temperature for 4 h. The mixture was poured onto ice, extracted with ethyl acetate, and the solvent was evaporated to dryness. The residue was purified by column chromatography on silica gel eluting with chloroform/methanol (90:10), dissolved with ether, and treated with etheral hydrochloric acid crystallized from the appropriate solvents.

4.1.1.3. Method C[20]. Appropriate carboxylic acids (2.5 mmol) and 2-(imidazol-1-yl)-1-(naphthalene-2-yl)ethanol (0.60 g, 2.5 mmol) or 1-(naphthalene-2-yl)ethanol (0.43 g, 2.5 mmol) were stirred in dry methylene chloride under nitrogen atmosphere at 0 °C. *N,N′*-Dicyclohexylcarbodiimide (DCC) (0.52 g, 2.5 mmol) and 4-dimethylaminopyridine (DMAP) (0.02 g, 0.17 mmol) in dry methylene chloride were added drop wise to the mixture at 0 °C, and then, reaction mixture was stirred for 5 min at 0 °C, for 6 h at room temperature. The precipitate was filtered off; the solvent was dried over anhydrous sodium sulfate and then was evaporated to dryness. The residue was purified by column chromatography on silica gel eluting with chloroform/methanol (90:10) or chloroform. The eluent was evaporated under reduced pressure, and then the residue was dissolved in ether and treated with etheral hydrochloric acid. Precipitated hydrochloric acid salt of the compound was crystallized from the appropriate solvents. Purification of liquid compounds (**7a–c**) was realized by distillation in vacuo.

4.1.1.4. Method D[19]. Appropriate acid chloride (1.25 mmol), 2-(imidazol-1-yl)-1-(naphthalene-2-yl)ethanol (0.29 g, 1 mmol), pyridine (0.10 g, 1.25 mmol) and DMAP (0.003 g, 0.025 mmol) were stirred in dichloromethane at room temperature for 4 h. The mixture was poured onto ice, extracted with chloroform, dried at sodium sulfate and the solvent was evaporated to dryness. The residue was purified by column chromatography on silica gel eluting with chloroform/methanol (90:10) after evaporation, dissolved with ether and treated with etheral hydrochloric acid crystallized from the appropriate solvents.

4.1.2. 2-(1*H*-Imidazol-1-yl)-1-(naphthalene-2-yl)ethyl butyrate hydrochloride (5a)

Yield: 49%; mp: 155–6 °C; IR (ν cm^{-1}, KBr): 3150–2550 (N^+–H), 3051 (C–H aromatic), 2963 (C–H aliphatic), 1743 (C=O); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.90 (t, 3H, CH_3), 1.59–1.65 (m, 2H, CH_2–CH_3), 2.38 (t, 2H, CH_2–C=O), 4.74–4.76 (dd, 1H, CH_2–N H_A, J_{AB}: 14.46 Hz, J_{AX}: 7.62 Hz), 4.84–4.89 (dd, 1H, CH_2–N H_B, J_{AB}: 14.37 Hz, J_{BX}: 3.70 Hz), 6.34–6.36 (dd, 1H, CH–O H_X, J_{AX}: 7.45 Hz, J_{BX}: 3.64 Hz), 7.04 (s, 1H, imidazole H^4), 7.30 (s, 1H, imidazole H^5), 7.45–7.55 (m, 3H, naphthalene H^3, H^6, H^7), 7.80–7.90 (m, 4H, naphthalene H^1, H^4, H^5, H^8), 9.49 (s, 1H, imidazole H^2), 15.96 (1H, s, N^+–H); EIMS (70 eV): *m/e* 308 [M^+] (55%), 240, 227, 221, 194, 181, 170, 152, 127, 115, 82 (base peak, 100%), 71, 43 and

Table 9
Anticonvulsant quantification test results-mice and rats ip[a]

Compd		Test	Time (h)	ED_{50}	95% Confidence interval low		Slope	Std. err
					Low	High		
5d	Mice	MES	0.5	38.46	25.25	55.32	3.97	1.17
		Toxicity	0.25	123.83	109.85	133.83	16.21	4.88
	Rats	MES	0.5	20.44	16.32	24.78	7.23	2.47
		Toxicity	0.5	56.36	41.57	64.36	10.88	4.27

[a] The reference compound was valproic acid and the values were: MES ED_{50}: 263 mg kg^{-1}(237–282), TD_{50}: 398 mg kg^{-1} (356–445) in mice ip and MES ED_{50} : 485 mg kg^{-1}(324–677), TD_{50}: 784 mg kg^{-1} (503–1176) in rat ip.[17]

Table 10
Antibacterial and antifungal activities of the compounds **5a–h**, **11** and 1**2** (MIC in μg/ml)

Compound	Bacteria (MIC-μg/ml)				Fungi (MIC-μg/ml)		
	S. aureus ATCC[a] 25923	*E. faecalis* ATCC 29212	*E. coli* ATCC 25922	*P. auruginosa* ATCC 27853	*C. albicans* ATCC 90028	*C. krusei* ATCC 6258	*C. parapsilosis* ATCC 22019
5a	8	128	>1024	>1024	8	256	64
5b	16	128	>1024	>1024	64	256	256
5c	8	32	>1024	>1024	16	128	128
5d	8	64	>1024	>1024	32	128	64
5e	8	16	>1024	>1024	1024	1024	1024
5f	16	128	>1024	>1024	>1024	>1024	>1024
5g	8	32	>1024	>1024	1024	512	1024
5h	32	128	1024	1024	512	512	512
11	64	64	1024	>1024	>1024	64	32
12	512	256	>1024	>1024	512	512	512
Fluconazole	—	—	—	—	1	64	8
Ampicilline	1	2	8	—	—	—	—

[a] ATCC is the registered trademark of 'American Type Culture Collection'.

41. Anal. Calcd for $C_{19}H_{21}ClN_2O_2{\cdot}1/2H_2O$ (353.85): C, 64.49; H, 6.27; N, 7.92. Found: C, 64.12; H, 6.36; N, 8.00.

4.1.3. 2-(1*H*-Imidazol-1-yl)-1-(naphthalene-2-yl)ethyl 2-methylpropionate hydrochloride (5b)

Yield: 57%; mp: 165–7 °C; IR (ν cm^{-1}, KBr): 3094 (C–H aromatic), 2979, 2910 (C–H aliphatic), 2820–2250 (N^+–H), 1713 (C=O); ^{1}H NMR ($CHCl_3$, 80 MHz), δ 1.20 (d, 6H, CH_3), 2.30–2.90 (m, 1H, CH–CH_3), 4.90 (d, 2H, CH_2–N), 6.40 (t, 1H, CH–O), 7.00 (s, 1H, imidazole H^4), 7.30 (s, 1H, imidazole H^5), 7.35–7.70 (m, 3H, naphthalene H^3, H^6, H^7), 7.70–8.00 (m, 4H, naphthalene H^1, H^4, H^5, H^8), 9.45 (s, 1H, imidazole H^2); EIMS (70 eV): *m*/*e* 308 [M^+] (55%), 241, 240, 221, 194, 181, 170, 152, 127, 115, 82 (base peak, 100%), 71, 43 and 41. Anal. Calcd for $C_{19}H_{21}ClN_2O_2$ (344.84): C, 66.18; H, 6.14; N, 8.12. Found: C, 65.94; H, 5.86; N, 8.19.

4.1.4. 2-(1*H*-Imidazol-1-yl)-1-(naphthalene-2-yl)ethyl pentanoate hydrochloride (5c)

Yield: 71%; mp: 133–4 °C; IR (ν cm^{-1}, KBr): 3200–2680 (N^+–H), 3057 (C–H aromatic), 2958 (C–H aliphatic), 1742 (C=O); ^{1}H NMR ($CDCl_3$, 80 MHz): δ 0.85 (t, 3H, CH_3), 1.00–1.80 (m, 4H, (CH_2)$_2$–CH_3), 2.40 (t, 2H, CH_2–C=O), 4.25 (d, 2H, CH_2–N), 6.15 (t, 1H, CH–O), 6.75 (s, 1H, imidazole H^4), 7.00 (s, 1H, imidazole H^5), 7.10–7.90 (m, 8H, naphthalene and imidazole H^2); EIMS (70 eV): *m*/*e* 322 [M^+] (41%), 293, 280, 254, 241, 221, 194, 180, 166, 153, 127, 82 (base peak, 100%) and 57. Anal. Calcd for $C_{20}H_{23}ClN_2O_2{\cdot}1/2H_2O$ (367.87): C, 65.30; H, 6.58; N, 7.62. Found: C, 64.85; H, 6.07; N, 7.68.

4.1.5. 2-(1*H*-Imidazol-1-yl)-1-(naphthalene-2-yl)ethyl 3-methylbutanoate hydrochloride (5d)

Yield: 80%; mp: 135–7 °C; IR (ν cm^{-1}, KBr): 3050–2320 (N^+–H), 3017 (C–H aromatic), 2957 (C–H aliphatic), 1721 (C=O); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.80 (d, 6H, CH_3), 1.92–2.01 (m, 1H, CH–CH_2), 2.18 (d, 2H, CH_2–(C=O)), 4.64–4.69 (dd, 1H, CH_2–N H_A, J_{AB}: 14.30 Hz, J_{AX}: 7.61 Hz), 4.75–4.79 (dd, 1H, CH_2–N H_B, J_{AB}: 14.34 Hz, J_{BX}: 3.45 Hz), 6.25–6.32 (dd, 1H, CH–O H_X, J_{AX}: 7.01 Hz, J_{BX}: 3.19 Hz), 6.95 (s, 1H, imidazole H^4), 7.20 (s, 1H, imidazole H^5), 7.37–7.46 (m, 3H, naphthalene H^3, H^6, H^7), 7.70–7.80 (m, 4H, naphthalene H^1, H^4, H^5, H^8), 9.43 (s, 1H, imidazole H^2), 16.02 (s, 1H, N^+–*H*); EIMS (70 eV): *m*/*e* 322 [M^+] (46%), 241, 221, 194, 180, 166, 153, 127, 82 (base peak, 100%), 57 and 41. Anal. Calcd for $C_{20}H_{23}ClN_2O_2$ (358.86): C, 66.94; H, 6.46; N, 7.81. Found: C, 66.28; H, 6.47; N, 7.67.

4.1.6. 2-(1*H*-Imidazol-1-yl)-1-(naphthalene-2-yl)ethyl 2-propylpentanoate hydrochloride (5e)

Yield: 75%; mp: 181–3 °C; IR (ν cm^{-1}, KBr): 3070 (C–H aromatic), 2953, 2927 (C–H aliphatic), 2850–2400 (N^+–H), 1718 (C=O); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.74 (t, 3H, CH_3), 0.78 (t, 3H, CH_3), 1.00–1.09 (m, 4H, CH_2–CH_3), 1.30–1.40 (m, 2H, CH_2–CH_2), 1.40–1.50 (m, 2H, CH_2–CH_2), 2.35–2.39 (m, 1H, (C=O)–CH), 4.73 (d, 2H, CH_2–N), 6.25 (t, 1H, CH–O), 7.04 (s, 1H, imidazole H^4), 7.22 (s, 1H, imidazole H^5), 7.40–7.46 (m, 3H, naphthalene H^3, H^6, H^7), 7.72–7.80 (m, 4H, naphthalene H^1, H^4, H^5, H^8), 9.45 (s, 1H, imidazole H^2), 16.06 (s, 1H, N^+–*H*); EIMS (70 eV): *m*/*e* 364 [M^+] (52%), 322, 297, 283, 237, 220, 170, 156, 127, 99, 82 (base peak, 100%), 57, 43 and 41. Anal. Calcd for $C_{23}H_{29}ClN_2O_2{\cdot}1/2H_2O$ (409.95): C, 67.39; H, 7.38; N, 6.83. Found: C, 67.91; H, 8.08; N, 7.06.

4.1.7. 2-(1*H*-Imidazol-1-yl)-1-(naphthalene-2-yl)ethyl 4-(*tert*-butoxycarbonyl) aminobutanoate hydrochloride (5f)

Yield: 68%; mp: 130–1 °C; IR (ν cm^{-1}, KBr): 3405 (N–H), 3094 (C–H aromatic), 2974, 2924 (C–H aliphatic), 2750–2300 (N^+–H), 1721 and 1678 (C=O); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.40 (s, 9H,

CH_3), 1.73–1.79 (m, 2H, CH_2–CH_2), 2.37–2.51 (m, 2H, CH_2–NH), 3.09 (t, 2H, CH_2–C=O), 4.70–4.75 (dd, 1H, CH_2–N H_A, J_{AB}: 14.35 Hz, J_{AX}: 7.30 Hz), 4.89–4.94 (dd, 1H, CH_2–N H_B, J_{AB}: 14.45 Hz, J_{BX}: 3.55 Hz), 6.36–6.38 (dd, 1H, CH–O H_X, J_{AX}: 7.30 Hz, J_{BX}: 3.60 Hz), 7.07 (s, 1H, imidazole H^4), 7.25 (s, 1H, imidazole H^5), 7.44–7.50 (m, 3H, naphthalene H^3, H^6, H^7), 7.76–7.82 (m, 4H, naphthalene H^1, H^4, H^5, H^8), 9.65 (s, 1H, imidazole H^2), 15.85 (s, 1H, N^+–H); EIMS (70 eV): *m/e* 423 [M^+] (2%), 350, 323, 280, 157, 129, 127, 82 (base peak, 100%), 71, 57 and 41. Anal. Calcd for $C_{24}H_{30}ClN_3O_4 \cdot 1/2H_2O$ (468.98): C, 61.47, H, 6.66; N, 8.96. Found: C, 61.82; H, 7.14; N, 9.00.

4.1.8. 2-(*1H*-Imidazol-1-yl)-1-(naphthalene-2-yl)ethyl benzoate hydrochloride (5g)

Yield: 65%; mp: 215–7 °C; IR (ν cm^{-1}, KBr): 3126, 3094 (C–H aromatic), 2979 (C–H aliphatic), 2800–2250 (N^+–H), 1713 (C=O); ^1H NMR (DMSO-d_6, 80 MHz): δ 4.90 (d, 2H, CH_2–N), 6.50 (t, 1H, CH–O) 7.20–8.20 (m, 10H, benzene, naphthalene and imidazole), 9.20 (s, 1H, imidazole H^2); EIMS (70 eV): *m/e* 342 [M^+] (46%), 274, 261, 238, 219, 186, 155, 127, 105 (base peak, 100%), 77, 51 and 36.

4.1.9. 2-(1*H*-Imidazol-1-yl)-1-(naphthalene-2-yl)ethyl 4-chlorobenzoate (5h)

Yield: 58%; mp: 179–181 °C; IR (ν cm^{-1}, KBr): 3097 (C–H aromatic), 2920 (C–H aliphatic), 1720 (C=O), ^1H NMR ($CDCl_3$, 80 MHz): δ 5.00 (d, 2H, CH_2–N), 6.60 (t, 1H, CH–O), 7.00–8.10 (m, 13H, benzene, naphthalene and imidazole), 9.60 (s, 1H, imidazole H^2); EIMS (70 eV): *m/e* 378 [M+2] (9%), 376 [M^+] (26%), 295, 220, 192, 156, 139 (base peak, 100%), 111, 75 and 54. Anal. Calcd for $C_{22}H_{17}ClN_2O_2 \cdot H_2O$ (base) (394.85): C, 66.92; H, 4.85; N, 7.09. Found: C, 67.39; H, 5.62; N, 6.88.

4.1.10. 1-(Naphthalene-2-yl)ethyl pentanoate (7a)

Yield: 82%; bp: 205 °C; IR (ν cm^{-1}, KBr): 3056 (C–H aromatic), 2960, 2932 (C–H aliphatic), 1739 (C=O); ^1H NMR ($CDCl_3$, 400 MHz): δ 0.80 (t, 3H, CH_3–CH_2), 1.20–1.26 (m, 2H, CH_3–CH_2), 1.48–1.56 (m, 2H, CH_2–CH_2), 1.51 (d, 3H, CH_3–CH), 2.25 (t, 2H, CH_2–C=O), 5.96 (q, 1H, CH–O), 7.33–7.38 (m, 3H, naphthalene H^3, H^6, H^7), 7.69–7.73 (4H, m, naphthalene H^1, H^4, H^5, H^8); EIMS (70 eV): *m/e* 256 [M^+] (14%), 172, 155 (base peak, 100%), 127, 115, 57 and 41. Anal. Calcd for $C_{17}H_{20}O_2.H_2O$ (274.35): C, 74.42; H 8.08. Found: C, 74.38, H, 7.48.

4.1.11. 1-(Naphthalene-2-yl)ethyl 3-methylbutanoate (7b)

Yield: 88%; bp: 208 °C; IR (ν cm^{-1}, KBr): 3058 (C–H aromatic), 2962, 2933 (C–H aliphatic), 1731 (C=O); ^1H NMR ($CDCl_3$, 400 MHz): δ 0.83 (d, 3H, CH_3–CH–CH_2), 0.85 (d, 3H, CH_3–CH–CH_2), 1.51 (d, 3H, CH_3–CH–O), 2.02–2.08 (m, 1H, CH–CH_2), 2.13 (d, 2H, CH_2–C=O), 6.07 (q, 1H, CH–O), 7.33–7.38 (m, 3H, naphthalene H^3, H^6, H^7), 7.68–7.73 (m, 4H, naphthalene H^1, H^4, H^5, H^8); EIMS (70 eV): *m/e* 256 [M^+] (7%), 225, 172, 155 (base peak, 100%), 127, 85, 57 and 41. Anal. Calcd for $C_{17}H_{20}O_2 \cdot 1/4H_2O$ (260.84): C, 78.28; H, 7.92. Found: C, 78.39; H, 8.55.

4.1.12. 1-(Naphthalene-2-yl)ethyl 2-propylpentanoate (7c)

Yield: 85%; bp: 223 °C; IR (ν cm^{-1}, KBr): 3056 (C–H aromatic), 2963 (C–H aliphatic), 1738 (C=O); ^1H NMR ($CDCl_3$, 400 MHz): δ 0.73 (t, 3H, CH_3–CH_2), 0.78 (t, 3H, CH_3–CH_2), 1.09–1.22 (m, 4H, CH_2–CH_2), 1.23–1.36 (m, 2H, CH_2–CH), 1.45–1.56 (m, 2H, CH_2–CH), 1.49 (d, 3H, CH_3–CH) 2.28–2.35 (m, 1H, CH–C=O), 5.97 (q, 1H, CH–O), 7.30–7.35 (m, 3H, naphthalene H^3, H^6, H^7), 7.66–7.69 (m, 4H, naphthalene H^1, H^4, H^5, H^8); EIMS (70 eV): *m/e* 298 [M^+] (10%), 172, 155 (base peak, 100%), 127, 99, 87, 57 and 41. Anal. Calcd for $C_{20}H_{26}O_2$ (298.42): C, 80.50; H, 8.78. Found: C, 80.57; H, 8.73.

4.1.13. 1-(Naphthalene-2-yl)ethyl 4-(*tert*-butoxycarbonyl) aminobutanoate (7d)

Yield: 79%; mp: 80–2 °C; IR (ν cm^{-1}, KBr): 3363 (N–H), 3048 (C–H aromatic), 2985, 2972 (C–H aliphatic), 1708 (C=O); ^1H NMR ($CDCl_3$, 80 MHz): δ 1.40 (s, 9H, CH_3–C–O), 1.60 (d, 3H, CH_3–CH), 1.70–2.00 (m, 2H, CH_2–CH_2), 2.40 (t, 2H, CH_2–C=O), 3.20 (q, 2H, CH_2NH), 4.40–4.70 (s br, 2H, N–H), 6.10 (q, 1H, CH–O), 7.30–8.00 (m, 7H, naphthalene); EIMS (70 eV): *m/e* 357 [M^+] (1%), 301, 172, 155 (base peak, 100%), 127, 102, 86, 57 and 41. Anal. Calcd for $C_{21}H_{27}NO_4$ (357.44): C, 70.56; H, 7.61; N, 3.92. Found: C, 70.00; H, 7.02; N, 3.96.

4.1.14. 1-(1-Hydroxynaphthalene-2-yl)-2-(1*H*-imidazol-1-yl)ethanone hydrochloride (11)

A stirred, ice-cooled solution of imidazole (1.02 g, 15 mmol) in DMF (2.5 ml) was added drop wise onto 2-bromo-1-(1-acetyloxynaphthalene-2-yl)ethanone (1.53 g, 5 mmol) in DMF (2.5 ml). The mixture was stirred for 2 h at 0 °C and overnight at room temperature. The solution was poured onto ice. The precipitate which formed as a result was filtered, washed with water, and dissolved in benzene. The benzene solution was then treated with gas hydrochloric acid. The precipitated salt was filtered, and recrystallized through methanol/ethyl acetate. Yield: 38%; mp: 250–2 °C; IR (ν cm^{-1}, KBr): 3700–3240 (O–H), 3021 (C–H aromatic), 2919 (C–H aliphatic), 2900–2460 (N^+–H), 1632 (C=O); ^1H NMR (DMSO-d_6, 400 MHz): δ 6.16 (s, 2H, CH_2), 7.55 (d, 1H, imidazole H^4), 7.63 (t, 1H, imidazole H^5), 7.74–7.77 (m, 3H, naphthalene H^4, H^6, H^7), 7.90 (d, 1H, naphthalene H^5), 7.97 (d, 1H, naphthalene H^3), 8.38 (d, 1H, naphthalene H^8), 9.11 (s, 1H, imidazole H^2), 12.87 (s, 1H, N^+–H); EIMS (70 eV): *m/e* 252 [M^+] (94%), 184, 171 (base peak, 100%), 143 and 82. Anal. Calcd for $C_{15}H_{13}ClN_2O_2$ (288.73): C, 62.40; H, 4.54; N, 9.70. Found: C, 62.23; H, 5.03; N, 9.69.

4.1.15. 1-(1-Hydroxynaphthalene-2-yl)-2-(1*H*-imidazol-1-yl)ethanol hydrochloride (12)

1-(1-Hydroxynaphthalene-2-yl)-2-(1*H*-imidazol-1-yl)ethanone hydrochloride (0.500 g, 1.5 mmol) was dissolved in methanol (25 ml). Sodium borohydride (0.170 g, 4.5 mmol) was added to the solution and stirred at 0 °C for 1 h. The solvent was evaporated; the residue was dissolved in water (100 ml) and acidified with hydrochloric acid until the precipitation was complete. The precipitate was filtered off, washed with water and recrystallized through chloroform/petroleum ether. Yield: 98%; mp: 220 °C (dec.); IR (ν cm^{-1}, KBr): 3700–2700 (O–H and N^+–H), 3050 (C–H aromatic), 2926 (C–H aliphatic); ^1H NMR (DMSO-d_6, 80 MHz): δ 2.40 (s, 1H, CH–O*H*), 4.10 (d, 2H, CH_2), 4.90 (t, 1H, C*H*), 5.20 (s, 1H, Ar–O*H*), 6.50–8.20 (10H, m, aromatic); EIMS (70 eV): *m/e* 236 [M^+−18] (7%), 218, 168 (base peak, 100%), 139, 127, 115, 89, 68 and 41. Anal. Calcd for $C_{15}H_{15}ClN_2O_2$ (290.74): C, 61.97; H, 5.20; N, 9.64. Found: C, 61.90; H, 4.66; N, 9.73.

4.1.16. 4-(1-(1-Hydroxynaphthalene -2-yl)ethylideneamino) butanoic acid (13)

GABA (0.515 g, 5 mmol) was added to a solution of sodium (0.115 g, 5 mmol) in ethanol (25 ml). 1-Hydroxy-2-acetylnaphthalene (0.465 g, 2.5 mmol) was added into this solution. The solution was then refluxed for 2 h. Ethanol was evaporated in vacuo. The residue was dissolved in water and acidified to pH 3 with citric acid. The compound was precipitated out of solution and recrystallized through chloroform/petroleum ether. Yield: 79%; mp: 171–2 °C; IR (ν cm^{-1}, KBr): 3700–2700 (O–H), 3062 (C–H aromatic), 2926 (C–H aliphatic), 1702 (C=O), 1597 (C=N), 1226 (C–O); ^1H NMR ($CHCl_3$, 80 MHz): δ 1.90–2.20 (m, 2H, CH_2–CH_2), 2.25–2.70 (t, 2H, CH_2–COOH), 2.45 (s, 3H, CH_3), 3.70 (t, 2H, CH_2–N), 6.60–8.50 (m, 6H, naphthalene); EIMS (70 eV): *m/e* 271 [M^+] (base peak, 100%), 270, 236, 226, 212,198, 185, 170, 141, 128, 115 and 87. Anal.

Calcd for $C_{16}H_{17}NO_3$ (271.31): C, 70.83; H, 6.32; N, 5.16. Found: C, 71.49; H, 5.92; N, 5.21.

4.1.17. X-ray crystallography

Data collection: X-AREA[21]; cell refinement: X-AREA; data reduction: X-RED32[21]; program used to solve structure: SHELXS97[22]; programs used to refine structure: SHELXL97[22]; molecular graphics: ORTEPIII[23]: software used to prepare material for publication: WINGX[24] and PARST.[25]

4.2. Anticonvulsant activity

The anticonvulsant activity and neurotoxicity evaluations of the compounds were sponsored by the National Institutes of Health (NIH) and long-standing translational drug development program of National Institutes of Neurological Disorders and Stroke (NINDS), known as the Anticonvulsant Screening Program (ASP), using the procedures described by Stables and Kupferberg.[26,27] The anticonvulsant activity of the compounds were tested against various seizure models including MES and scM-induced seizures model. Testing was undertaken in two rodent species: CF#1 mice and Sprague-Dawley rats. Male albino animals were used for all the experiments. The animals had free access to food and water except during actual times of testing. Policies and protocols for the ethical treatment of the animals were strictly enforced under IACUC, AAALAC, PHS and USDA policies and registrations. A topical anesthetic (0.5% tetracaine HCl in normal saline) was applied to the eyes of each test animal prior to MES stimulation. At 60 Hz, a stimulus of 150 mA and 50 mA for 0.2 s was used for the rats and mice, respectively. The apparatus for current was similar to that of Woodbury and Davenport.[28]

To measure potential neurotoxicity, the rotarod test was used in mice, while the positional sense, gait, and stance tests were used for rat evaluations. All the compounds were suspended in methylcellulose 0.5% prior to administration of a candidate drug to the test animals. The weight of the animals ranged from 105 to 130 g for rats and from 18 to 25.5 g for mice. The compounds were administered to the mice by ip route, 0.5 h and 4 h before the evaluation. The endpoint in evaluation of anti-MES action in the mice was inhibition of hindlimb tonic extension.

All the quantitative anticonvulsant/toxicity evaluations of the most active compounds were conducted at the time of peak pharmacodynamic activity (TPE) of the compound. Groups of at least eight mice or rats were tested with various doses of the candidate drug until at least two points were established between the limits of 100 per cent protection or toxicity and 0 per cent protection or minimal toxicity. Slope of the regression lines and standard errors of the slopes were calculated for each quantitative determination. ED_{50} and TD_{50} values were then calculated by a computer program based on the method described by Finney.[29]

4.3. Antibacterial and antifungal activity

The minimal inhibitory concentration (MIC) values of the compounds were determined against yeast-like fungi (*C. albicans* ATCC 90018, *C. krusei* ATCC 6258 and *C. parapsilosis* ATCC 22019), gram positive bacteria (*S. aureus* ATCC 25923, *E. faecalis* ATCC 29212) and gram negative bacteria (*Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853) by using broth microdilution method.[30,31] The tests were carried out using Mueller Hinton broth (BBL, MD, USA) for bacteria and RPMI-1640 medium buffered with MOPS [3-(*N*-morpholino)propane sulfonic acid] (ICN-Flow, Aurora, OH, USA) for fungi. (Final concentration: 0.165 mol/l at pH 7.0). Ampicillin and fluconazole were used as the reference compounds for antibacterial and antifungal activity, respectively. The stock solutions of the compounds were prepared in dimethylsulfoxide. The solution in the test medium furnished the required concentration ranging from 64 μg/ml to 0.06 μg/ml. The microtiter plates were incubated at 35 °C and read visually after 24 h. but for *Candida* species, after 48 h. The MIC values were recorded as the lowest concentrations of the substances that inhibit the visible growth of microorganisms.

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