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Original article

Synthesis of some 1-(2-naphthyl)-2-(imidazole-1-yl)ethanone oxime and oxime ether derivatives and their anticonvulsant and antimicrobial activities

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Abstract – In this study, oxime and oxime ether derivatives of anticonvulsant nafimidone [1-(2-naphthyl)-2-(imidozole-1-yl)ethanone] were prepared as potential anticonvulsant compounds. Nafimidone oxime was synthesized by the reaction of nafimidone and hydroxylamine hydrochloride. O-Alkylation of the oxime by various alkyl halides gave the oxime ether derivatives. Anticonvulsant activity of the compounds was determined by maximal electroshock (MES) and subcutaneous metrazole (scMet) tests in mice and rats according to procedures of the Antiepileptic Drug Development (ADD) program of the National Institutes of Health (NIH). In addition to anticonvulsant evaluation, compounds were also screened for possible antibacterial and antifungal activities because of the structural resemblance to the azole antifungals, especially to oxiconazole. All compounds were evaluated against three human pathogenic fungi and four bacteria using the microdilution method. Most of the compounds exhibited both anticonvulsant and antimicrobial activities; the *O*-alkyl substituted compounds (**2**, **3**, **4** and **5**) were found to be more active than the *O*-arylalkyl substituted compounds in both screening paradigms. © 2001 Éditions scientifiques et médicales Elsevier SAS

oxime and oxime ethers / (arylalkyl)imidazoles / anticonvulsant activity / antimicrobial activity / *E*/*Z* isomers / X-ray crystallography

1. Introduction

About 50 million people worldwide suffer from epilepsy [1]. Although there are a number of antiepileptic drugs currently available in the market, uncontrolled seizures and medication toxicity are still the main problems of antiepileptic drug treatment [2, 3]. Therefore the development of new anticonvulsant compounds with greater specificity and fewer toxic side effects is still popular.

One of the structurally distinct class of antiepileptic drugs is the (arylalkyl)imidazoles. Nafimidone (I) and denzimole (II) are two independently discovered representatives of this group and possess a profile of activity similar to that of phenytoin or carbamazepine but distinct from those of barbiturates or valproic acid [4–6]. Structure–activity relationship studies show that anticonvulsant properties of this group are associated with the presence of a small oxygen functional group (such as carbonyl, ethylene dioxy, methoxy, acyloxy and hydroxy substituents) in the alkylene bridge [4, 5, 7–9] in addition to imidazole ring [7] and lipophilic aryl portion facilitating penetration of the blood–brain barrier.

The introduction of oxime and oxime ether groups to the alkylene bridge of (arylalkyl)imidazoles as a small oxygen functional group had not been studied to date.

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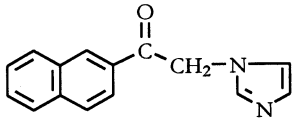
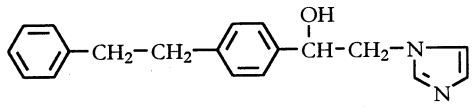
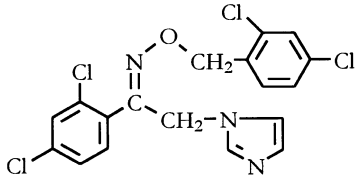


(I) Nafimidone



(II) Denzimol

Therefore, in this study, we aimed to synthesize oxime and some oxime ether derivatives of nafimidone as potential anticonvulsant compounds according to the previous studies in the literature [4–7]. We prepared oxime ethers with different alkyl groups in order to establish the contributions of the type and the size of the alkyl chain to the activity. For this purpose, saturated alkyl groups in different chain length (methyl, ethyl, propyl), an unsaturated alkyl group (allyl), a cyclic alkyl group (cyclohexyl) and arylalkyl groups (benzyl and chloro substituted benzyls) were used to obtain the oxime ethers (*figure 1*). Due to the structural similarities of these compounds with 1-substituted-1*H*-azole antifungals and oxiconazole possessing an oxime ether group (III) [10], we postulated that these compounds might also have antifungal–antibacterial properties in addition to their anticonvulsant activities.



(III) Oxiconazole

o-Chloro and *o*, *p*-dichlorobenzyl groups were chosen especially for antifungal activity since most of the 1-substituted-1*H*-azole antifungal agents and oxiconazole have these moieties in their structure.

2. Chemistry

Nafimidone was obtained by the alkylation of imidazole with 1-(2-naphthyl)-2-bromoethanone, which was prepared by Immediata's method [4, 11]. Nafimidone oxime was synthesized by reaction of nafimidone and hydroxylamine hydrochloride [12]. O-Alkylation of nafimidone oxime with appropriate alkyl halides gave the oxime ether derivatives (*figure 2*). Sodium ethoxide was used as a base to obtain oximates before alkylation. Finally, oxime ethers were treated with hydrogen chloride gas in ether or benzene at 0–5°C to get the salts of the compounds.

Initially, two methods were tried to synthesize nafimidone oxime ether derivatives. Compound **7** was used to test these methods. *O*-Benzyl substituted hydroxylamine was prepared by the reaction of benzyl halide and *N*-hydroxyphthalimide in DMSO in the presence of sodium acetate trihydrate and then hydrolysis of imidic group by hydrazine hydrate according to Favara's method (*figure 3*) [13]. *O*-Benzylhydroxylamine was then reacted with nafimidone [14], but the reaction yield was very low (16%). Contrary to condensation of ketones with O-substituted hydroxylamines, O-alkylation of oxime by alkyl halide significantly improved the yield (97%) to obtain the oxime ether derivatives.

Structure and some physicochemical properties of the compounds are given in *table I*.

The structure of the compounds was confirmed by elementary analysis and IR, ^{1}H-NMR, Mass spectral data which were given in the experimental part. The X-ray crystallographic data of nafimidone oxime **1**, which was obtained as one isomer with high yield, showed that this compound was in *Z* configuration [15]. Only compound **3** could be obtained as two isomers with different physicochemical properties such as solubility and melting point. Isolation of these two isomers was achieved by fractional precipitation with gas HCl. While the first precipitate **3-A** is not

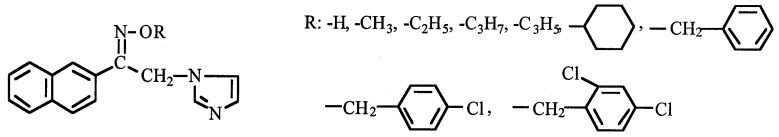


Figure 1. The structure of the synthesized compounds.

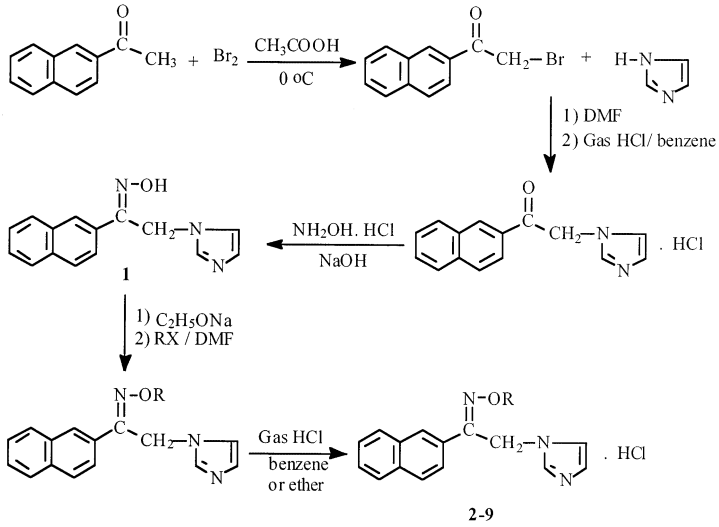


Figure 2. Synthesis of nafimidone oxime and the oxime ethers by O-alkylation of the oxime with alkyl halide.

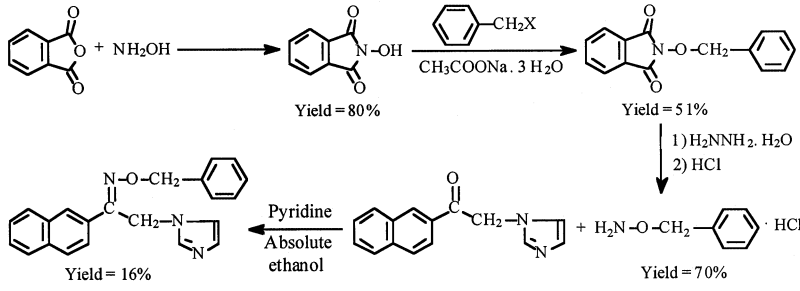
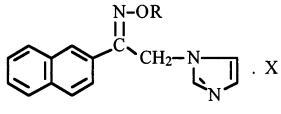


Figure 3. Synthesis of nafimidone *O*-benzyloxime (**7**) by condensation of ketone with O-substituted hydroxylamine.

Table I. The structures, crystallization solvents, yields (%) and melting points of the compounds



Compound	*R*	*X*	Crystallization solvent	Yield (%)	MP (°C)
1	–H		Methanol	82	193–6
2	$-CH_3$	HCl	Methanol/ethylacetate	47	167–8
3-A (*E*)	$-C_2H_5$	HCl	(1) Methanol/water, (2) Ethylacetate	46	92–4
3-B (*Z*)	$-C_2H_5$	HCl	Methanol/ethylacetate	33	82–4
4	$-C_3H_7$	HCl	(1) Methanol/water, (2) Methanol/ethylacetate	84	170–2
5	$-CH_2-CH=CH_2$	HCl	Methanol/ethylacetate	58	164–6
6	$-C_6H_{11}$ (cyclo)	HCl	(1) Ethylacetate, (2) Benzene	34	179–81
7	$-CH_2C_6H_5$	HCl	(1) Methanol/water, (2) Benzene	97	158–60
8	$4\text{-}CH_2C_6H_4Cl$	HCl	(1) Methanol/water, (2) Dioxan/water	87	188–90
9	$2,4\text{-}CH_2C_6H_3Cl_2$	HCl	Dioxan/ether	56	186–7

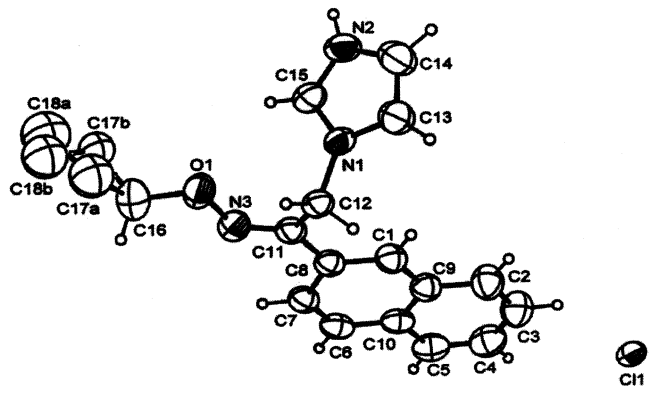
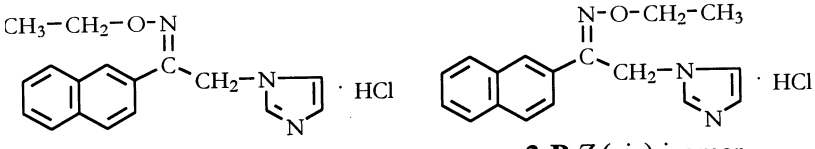


Figure 4. An ORTEPII drawing of compound **5** with the displacement ellipsoids drawn at the 50% probability level.

soluble in cold water and melts at 92–94°C, the second one **3-B** is readily soluble in cold water and melts at 82–84°C. *E*/*Z* configuration of these isomers (**3-A** and **3-B**) was assigned to the chemical shift of the singlet of methylene protons between oxime group and imidazole ring (–C(=N–O)–C*H*$_2$–N–) and to the chemical shift of the singlet of imidazole H^2 between two nitrogens (=N–C*H*=N–) since these protons are unshielded by the near presence of the oxime oxygen in *Z* isomer. One of the isomers **3-A** differed from the other **3-B** by displacement of CH_2 singlet from 5.5 to 5.8 ppm and imidazole H^2 singlet from 7.0–8.1 to 9.8 ppm. Based on the ^{1}H-NMR data and literature [12], we decided that the first precipitate **3-A** was *E* isomer and the second one **3-B** was *Z* isomer (IV).



3-A *E* (trans) isomer **3-B** *Z* (cis) isomer

(IV)

^{1}H-NMR data of **2**, **4**, **5**, **6**, **7** and **9** showed that they were in *Z* configuration too. This result is in accordance with the literature that the oxime ethers obtained by the alkylation of oxime with alkyl halides are generally expected to have the same configuration of the oxime [16]. As an exception, compound **8** was probably in *E* configuration because the methylene and H^2-imidazole protons appeared at 5.3 and <8.0 ppm, respectively.

Since we obtained a fine crystal of **5** (salt form) for X-ray analysis, we were able to prove the configuration of this compound and to confirm the configuration of the others by analogy between the ^{1}H-NMR data of this compound and of the others.

Table II. Experimental details of the X-ray analysis of compound **5**.

Empirical formula	$(C_{18}H_{18}N_3O)^+$ Cl^-
Formula weight	327.82
Temperature (K)	293
Radiation/wavelength (Å)	Mo K$\alpha/\lambda = 0.71073$
Crystal system	triclinic
Space group	*P*-1
Unit cell dimensions	
a (Å)	8.737(1)
b (Å)	9.499(1)
c (Å)	11.050(1)
α (°)	101.93(1)
β (°)	107.33(1)
γ (°)	92.10(1)
V (Å^3)	851.7(2)
Z	2
D_{calc}(g cm^{-3})	1.280
Absorption coefficient (mm^{-1})	0.23
Crystal size (mm)	$0.12 \times 0.30 \times 0.48$
Diffractometer/scan	Enraf–Nonius CAD4/ω–2θ
Maximum 2θ (°)	52.6
Reflections collected	3473
Reflections observed [$I > 2\sigma(I)$]	2325
Solution	Direct Methods, SIR88 in MOLEN [18]
Final *R* indices	0.045
Goodness-of-fit on F_o	0.81
Final shift/error	0.00
Largest difference peak and hole (e Å^{-3})	0.35 and −0.08

The X-ray structure of **5** showed that the configuration of the compound was *Z* (*figure 4*). This result was in accordance with the ^{1}H-NMR data of the compound (a singlet at 5.84 ppm for methylene protons between oxime and imidazole and a singlet at 9.93 ppm for imidazole H^2). The crystal data and the refinement details are given in *table II*. The fractional coordinates and mean temperature factors with estimated standard deviations for non-hydrogen atoms are listed in *table III* and selected bond lengths, bond angles and torsion angles are given in *table IV*.

The imidazole ring is planar. The deviations of each atom of the imidazole ring from the mean plane were very small (0.004 Å maximum for C13) thus indicating some π delocalization over this ring. The imidazole ring could be thought to exhibit both aromatic and polar non-aromatic behavior depending on its environment. The C12 atom was −0.071(2) Å out of the imidazole plane. Two C–N bond distances in the imidazole ring were intermediate between the expected single- and double-bond lengths as was shown in other imidazole oxime derivative [17]. The planar naphthalene moiety at C11 makes a dihedral angle of 69.0(1)° with the imidazole ring. The orientation of the naphthalene was defined by the torsion angles C8–C11–C12–N1 = 91.5(3)° for imidazole ring and C1–C8–C11–N3 = 162.8(2)° for oxime. In 1-(2-naphthyl)-2-(imidazole-1-yl)ethanone oxime, the oxime was twisted with the torsion angle of 36.2(1)° out of naphthalene plane [15]. C11–N3 [1.285(4) Å] and N3–O1 [1.402(3) Å] bond distance were similar to those found in two-reported imidazole oxime derivatives [15, 17]. The imidazole N2 atom was protonated and the positive charge of N2 occurs with proton transfer from the HCl. Atoms C17 and C18 show disorder with occupancy factors of 0.5 for both atoms.

Table III. Fractional atomic coordinates and Beq [a] values (Å^2) for non-hydrogen atoms (atoms with asterix were refined isotropically).

	X	*Y*	*Z*	B_{eq}
C11	0.47104(7)	0.12861(7)	0.18647(6)	4.30(1)
O1	0.1777(2)	0.6808(2)	1.1789(2)	4.71(4)
N1	0.1276(2)	0.8101(2)	0.9237(2)	3.20(4)
N2	−0.1189(2)	0.8525(2)	0.8525(2)	4.38(5)
N3	0.2123(3)	0.5642(2)	1.0938(2)	4.07(5)
C1	0.2992(3)	0.5175(3)	0.7911(2)	3.66(5)
C2	0.3357(4)	0.4338(3)	0.5757(3)	4.88(7)
C3	0.3634(4)	0.3262(4)	0.4846(3)	5.35(7)
C4	0.3873(4)	0.1892(3)	0.5092(3)	5.24(8)
C5	0.3849(3)	0.1612(3)	0.6247(3)	4.55(7)
C6	0.3499(3)	0.2460(3)	0.8413(3)	3.78(6)
C7	0.3204(3)	0.3522(3)	0.9317(2)	3.59(5)
C8	0.2919(3)	0.4917(3)	0.9072(2)	3.28(5)
C9	0.3297(3)	0.4087(3)	0.6955(2)	3.68(5)
C10	0.3547(3)	0.2699(3)	0.7206(2)	3.61(5)
C11	0.2573(3)	0.6061(3)	1.0052(2)	3.36(5)
C12	0.2771(3)	0.7625(3)	0.9998(2)	3.32(5)
C13	0.1194(3)	0.8933(3)	0.8358(3)	5.06(7)
C14	−0.0355(4)	0.9203(3)	0.7924(3)	5.59(7)
C15	−0.0190(3)	0.7868(3)	0.9312(3)	4.23(6)
C16	0.1668(4)	0.6344(4)	1.2925(3)	5.62(8)
C17a	0.1790(9)	0.7686(8)	1.4006(7)	6.9(2)*
C17b	0.0810(7)	0.7338(6)	1.3574(5)	4.6(1)*
C18b	0.1469(9)	0.8094(8)	1.4849(7)	6.7(2)*
C18a	0.081(1)	0.8043(9)	1.4642(8)	7.9(2)*

[a] $B_{eq} = (8\pi^2/3)\Sigma_i\Sigma_j U_{ij}\ a_i{*}a_j{*}a_i\,a_{j.}$

3. Pharmacology and microbiology

3.1. Anticonvulsant activity

The anticonvulsant activity and neurotoxicity tests of the compounds were carried out at laboratories located at the University of Utah under the contract with the Anticonvulsant Screening Project (ASP) of National Institute of Neurological Disorders and Stroke (NINDS) at National Institutes of Health (NIH) using the methods described by Stables and Kupferberg [19, 20]. The anticonvulsant activity of the compounds was tested against maximal electroshock (MES) and subcutaneous metrazole (scMet) induced seizures in mice and rats. Rotorod, positional sense, gait and stance tests were used to evaluate the neurotoxicity. The suspension of the compounds in methylcellulose was administered to test animals for anticonvulsant and neurotoxicity screening tests. Compounds were administered to mice by intraperitoneal route half or four hours before evaluation of their activities. Oral evaluation of anti-MES and neurotoxic activity in rats and pharmacological quantitations were performed for selected compounds only.

3.2. Antifungal and antibacterial activities

The compounds were evaluated in vitro against three human pathogenic fungi, *Candida albicans* (ATCC 90028), *C. krusei* (ATCC 6258) and *C. parapsilosis* (ATCC 22019) [21] and, against four bacteria, *Staphylococcus aureus* (ATCC 25923), *Enterococcus faecalis* (ATCC 29212), *Escherichia coli* (ATCC 25922) and *Pseudomonas aeruginosa* (ATCC 27853) by using broth microdilution method [22]. Fluconazole and amikacin sulphate were used as reference drugs for antifungal and antibacterial activities, respectively.

4. Results and discussion

4.1. Anticonvulsant activity

Anticonvulsant and neurotoxicity screening data are summarized in *table V*.

Table IV. Selected geometric parameters (Å, °) of compound **5**.

O1	N3	1.402(3)	N3	C11	1.285(4)		
O1	C16	1.440(4)	C11	C12	1.504(4)		
N1	C12	1.471(3)	C13	C14	1.348(4)		
N1	C13	1.362(4)	C16	C17a	1.533(8)		
N1	C15	1.322(3)	C16	C17b	1.435(7)		
N2	C14	1.347(5)	C17a	C18a	1.27(1)		
N2	C15	1.311(3)	C17b	C18b	1.378(8)		
N3	O1	C16	109.0(2)	N1	C12	C11	112.5(2)
C12	N1	C13	124.7(2)	N1	C13	C14	106.9(3)
C12	N1	C15	127.4(2)	N2	C14	C13	107.4(3)
C13	N1	C15	107.9(2)	N1	C15	N2	109.2(3)
C14	N2	C15	108.6(2)	O1	C16	C17a	108.7(4)
O1	N3	C11	111.5(2)	O1	C16	C17b	108.8(3)
N3	C11	C8	116.3(2)	C16	C17a	C18a	129.2(7)
N3	C11	C12	123.2(2)	C16	C17b	C18b	122.6(5)
C8	C11	C12	120.5(2)				
C16	O1	N3	C11	−166.1(2)			
N3	O1	C16	C17a	163.5(4)			
N3	O1	C16	C17b	−161.0(3)			
C13	N1	C12	C11	−136.5(2)			
C12	N1	C13	C14	−176.6(2)			
C12	N1	C15	N2	176.8(2)			
C15	N2	C14	C13	0.5(3)			
C14	N2	C15	N1	−0.1(3)			
O1	N3	C11	C8	−178.1(2)			
C1	C8	C11	N3	162.8(2)			
C8	C11	C12	N1	91.5(3)			
O1	C16	C17a	C18a	123.7(8)			
O1	C16	C17b	C18b	−121.6(6)			

Surprisingly, nafimidone oxime **1** was found to be devoid of activity in both MES and scMet tests and showed no neurotoxicity at any of the doses administered (30, 100, 300 mg kg^{-1}) although oxime group is a small oxygen functional group and nafimidone alcohol is the active metabolite of nafimidone.

All of the oxime ether derivatives except **9** showed anti-MES activity based on the data in *table V*. Increasing the size of the O-substituents of oxime ethers from alkyl group to arylalkyl group reduced both anticonvulsant activity and neurotoxicity. This may be due to steric hindrance for approaching to the receptor site or owing to excess lipophilicity of the molecules. Anti-MES activity at 300 mg kg^{-1} was recorded for compound **8**, with neurotoxicity at the half-hour time point. Compounds **2**, **3-B** and **5** (salt) were found to be active at 30 mg kg^{-1} (1/3, mice protected/mice tested) at the half-hour time point without neurotoxicity (0/8) at the same dose level. Compounds **4**, **5** (base), **6**, **7** were active in the MES test using 100 mg kg^{-1} at half-hour while compound **3-A** had a protective effect at both time points at the same dose level. Compound **5** in salt form was fully protective at 100 mg kg^{-1} whereas base form of the same compound was fully protective at 300 mg kg^{-1} (*table V*). We assume that this resulted from the better pharmacokinetic properties of salt form than that of the base form. Although it has been reported [4–7] that the activity of nafimidone and denzimol as well as the other (arylalkyl)imidazoles are highly MES-specific in mice, some of these oxime ether derivatives (**2**, **3**, **4**, **5**) exhibited some activity against scMet as well as MES-induced seizures. The scMet activity was observed at doses, which also elicited toxic effects in test animals. Thus, the protective effects observed may, if real, have been a manifestation of toxicity and the presence of severe toxicity may interfere with animal's ability to respond to elicitation of seizure activity. Since there was almost no difference between the activity of the *E* and *Z* isomers of compound **3**, the anticonvulsant activity appeared to be not stereoselective.

Compounds **3**, **4** and **5** (salt) were the most active compounds from the group tested based on the level of

Table V. Anticonvulsant and neurotoxicity screening data in mice dosed intraperitoneally with the compunds.

Compounds	Dose (mg kg^{-1})	Activity					
		MES [a]		scMet [b]		Toxicity [c]	
		0.5 h	4 h	0.5 h	4 h	0.5 h	4 h
1	10	– [i]	–	–	–	–	–
	30	0/1	0/1	0/1	0/1 [d]	0/4	0/2
	100	0/3	0/3	0/1	0/1 [d]	0/8	0/4
	300	0/1	0/1	0/1	0/1	0/4	0/2
2	10	0/1	0/1	0/1	0/1	0/4	0/2
	30	1/3	0/3	0/1	0/1	0/8	0/4
	100	1/1	1/1	1/1	0/1	3/4	1/2
	300	–	–	–	–	–	–
3-A	10	–	–	–	–	–	–
	30	0/1	0/1	0/1	0/1	0/4	0/2
	100	3/3	2/3	3/5	0/1	5/8	0/4
	300	1/1	1/1	1/1	1/1	4/4 [e]	2/2 [e]
3-B	10	0/1	0/1	0/1 [d]	0/1	0/4	0/2
	30	1/3	0/3	0/1	0/1	0/8	0/4
	100	1/1	1/1	1/1	0/1	4/4 [f]	0/2
	300	–	–	–	–	–	–
4	10	–	–	–	–	–	–
	30	0/1	0/1	0/1	0/1	0/4	0/2
	100	2/3	0/3	1/5	0/1	1/8	0/4
	300	1/1	1/1	5/5	1/1	4/4 [f]	1/2
5 (base)	10	–	–	–	–	–	–
	30	0/1	0/1	0/1	0/1	0/4	0/2
	100	1/3	0/3	0/1	0/1	0/8	0/4
	300	1/1	0/1	1/1	1/1	3/4	1/2
5 (salt)	10	0/1	0/1	0/1	0/1	0/4	0/2
	30	1/3	0/3	0/1	0/1	0/8	0/4
	100	1/1	0/1	0/1	0/1	1/4	0/2
	300	–	–	–	–	–	–
6	10	0/1	0/1	0/1 [g]	0/1	0/4	0/2
	30	0/3	0/3	0/1	0/1	0/8	0/4
	100	1/1	0/1	0/1	0/1	0/4	0/2
	300	–	–	–	–	–	–
7	10	0/1	0/1	0/1	0/1	0/4	0/2
	30	0/3	0/3	0/1 [h]	0/1	0/8	0/4
	100	1/1	0/1	0/1	0/1 [h]	1/4	0/2
	300	–	–	–	–	–	–
8	10	–	–	–	–	–	–
	30	0/1	0/1	0/1	0/1	0/4	0/2
	100	0/3	0/3	0/1	0/1	0/8	0/4
	300	1/1	1/1	0/1	0/1	1/4	0/2
9	10	–	–	–	–	–	–
	30	0/1	0/1	0/1	0/1 [d]	0/4	0/2
	100	0/3	0/3	0/1	0/1	2/8	0/4
	300	0/1	0/1	0/1	0/1	0/4	0/2

[a] Maximal electroshock test (number of animal protected/number of animal tested).
[b] Subcutaneous metrazole test (number of animal protected/number of animal tested).
[c] Toxicity (number of animal exhibiting toxicity/number of animal tested).
[d] Tonic extension.
[e] Loss of righting reflex.
[f] Unable to grasp rotorod.
[g] Dead following tonic extension.
[h] Continuous seizure activity.
[i] "–"; not determined

Table VI. Anticonvulsant [anti-MES] and toxicity qualitative screening data in rats dosed orally with the selected compounds [a].

Compounds	Test	Time in hours				
		0.25	0.50	1.00	2.00	4.00
3-A	MES [b]	0/4	1/4	0/4	1/4	2/4
	TOX [c]	0/4	0/4	0/4	0/4	0/4
4	MES	0/4	1/4	0/4	3/4	2/4
	TOX	0/4	0/4	0/4	0/4	0/4
5 (salt)	MES	2/4	3/4	1/4	2/4	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.
[b] Maximal electroshock seizures test (number of animal protected/ number of animal tested).
[c] Toxicity (number of animal exhibiting toxicity/number of animal tested).

seizure protection and were selected for quantitation of their pharmacological parameters [20]. For oral evaluation of anti-MES and neurotoxic activity of compound **3-A**, **4** and **5** (salt) in rats, compounds were administered per os at 30 mg kg^{-1} at a particular time point from one quarter to four hours (*table VI*). None of the compounds were neurotoxic at this dose (30 mg kg^{-1}).

Quantitative evaluations were performed for the same compounds (**3**, **4** and **5** salt) in mice or rats dosed orally or intraperitoneally. Median effective doses (ED_{50}'s) evaluated against MES- and scMet-induced convulsions and median toxic doses (TD_{50}'s) determined by the rotorod procedure for assessing neurologic deficit are given in *table VII*.

Quantitative anticonvulsant data showed that compound **4** was the most active compound with ED_{50} 17.95 and $TD_{50}<150$ when drug was administered intraperitoneally in rats. When the same compound was administered orally to rats we were unable to obtain a linear dose effect. An equal protection was found at 40 mg kg^{-1} (3/8, protected animals/tested animals) and 320 mg kg^{-1} (3/8, protected animals/tested animals). The most likely reason was due to poor absorption in this model. There was no observable toxicity ($TD_{50}>320$ mg kg^{-1}) in the oral screen of **4** could be considered a positive finding but again this may be due to poor absorption of the compound. Blood levels should have to be determined to confirm this statement. Instead, we used the i.p. route in mice for the same compound. PI values of **3-A** and **4** in mice via the i.p. route showed that effective and toxic doses were not much separated. The PI value of **5** (>2.420) was much better than **3-A** and **4**.

Table VII. Quantitative anticonvulsant data in mice dosed intraperitoneally and in rats dosed intraperitoneally or orally with the selected compounds [a].

Compound		Test	ED_{50}	PI	TPE
3-A	mouse, i.p.	MES	36.99 (26.798–49.938)	1.411	0.25
		scMet	>60.00 (0.000–0.000)	<0.870	
		Tox (TD_{50})	52.19 (30.520–73.763)		0.25
4	mouse, i.p.	MES	46.77 (42.075–58.628)	1.417	0.25
		scMet	71.64 (51.917–88.746)	0.925	0.25
		Tox (TD_{50})	66.30 (55.590–80.052)		0.25
4	rat, i.p.	MES	17.95 (13.37–23.35)		0.5
		scMet	<125		
		Tox (TD_{50})	<150		0.5
4	rat, p.o.	MES	>320.00 (0.000–0.000)	0.000	6.00
		scMet			
		Tox (TD_{50})	>320.00 (0.000–0.000)		0.00
5	rat, p.o.	MES	70.24 (42.648–114.385)	>2.420	2.00
		scMet			
		Tox (TD_{50})	>170.00 (0.000–0.000)		0.00

[a] Pharmacological values given in this table: the ED_{50}, dose of drug required to assure anticonvulsant protection in 50% of animals; the TD_{50}, dose eliciting minimal neurological toxicity in 50% of animals; the PI, protection index ($PI = TD_{50}/ED_{50}$), and the time of peak effect (TPE). ED_{50} and TD_{50} values are expected as mg kg^{-1}, and TPE as hours.

Table VIII. Antibacterial and antifungal activity of the compounds (MIC in μg mL^{-1}).

Compound no.	Bacteria (MIC-μg mL^{-1})				Fungi (MIC-μg mL^{-1})		
	S. aureus ATCC 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
1	>64	>64	>64	>64	>64	>64	>64
2	32	16	>64	>64	64	32	64
3-A	0.5	16	>64	>64	1	1	2
3-B	8	16	>64	>64	2	4	4
4	8	4	>64	>64	16	32	32
5	>64	>64	>64	>64	8	16	8
6	1	>64	>64	>64	>64	>64	>64
7	0.5	>64	>64	>64	>64	>64	>64
8	0.5	>64	>64	>64	>64	>64	>64
9	2	4	32	>64	>64	>64	>64
Fluconazole					0.25	16	1
Amikacin	4	64	1	2			

4.2. Microbiology

The antimicrobial activity results are given in *table VIII*. Nafimidone oxime **1** was the only compound, which was found to be inactive against both the bacteria and fungi at the doses tested. Most of the compounds (**2**, **3-A**, **3-B**, **4**, **6**, **7**, **8**, **9**) were found to be active against Gr (+) bacteria especially *S. aureus* in low MIC values. **2**, **3-A**, **3-B**, **4** and **9** were also found to be active against *E. faecalis* at 4–16 $\mu g\,mL^{-1}$ concentration while amikacin was active at 64 $\mu g\,mL^{-1}$. All oxime ethers (except **9** against *E. coli*) were found to be inactive against Gr (−) bacteria. The antibacterial activity of compound **3-A** against *S. aureus* and **3-A**, **3-B** and **4** against *E. faecalis* was higher than amikacin. Only five of the compounds (**2**, **3-A**, **3-B**, **4**, **5**) were active against fungi and the most active one was **3-A**. Compound **3-A** and **3-B** were more active than fluconazole against *C. krusei*. Unexpectedly, chloro substituted benzyl derivatives (**8** and **9**) were found to be inactive against fungi whereas small alkyl derivatives were active. The difference between the activity of **3-A** and **3-B** may indicate that the antibacterial activity against *S. aureus* and the antifungal activity were stereoselective.

5. Conclusions

Although many of the most active (arylalkyl)imidazole anticonvulsants such as denzimol and nafimidone alcohol (reduced nafimidone) have hydroxy group in their alkylene bridge as a small oxygen containing group, nafimidone oxime **1** did not show any anticonvulsant activity. O-Alkylation of nafimidone oxime, i.e. introduction of an oxime ether functional group to the alkylene bridge of nafimidone, resulted in new compounds with anticonvulsant activity. Considering the activity results of the nafimidone oxime ethers, we may conclude that the size of the alkyl moiety on the oxime group appears to be important for the activity since compound **8** and **9**, which have chloro-substituted benzyl groups did not display any anticonvulsant and neurotoxic activities. But no relation was found between the activity and the nature of the alkyl moiety such as unsaturation or cyclization. We may also conclude that anticonvulsant activity is not stereoselective based on the activity results of the *E* and *Z* isomers.

Additionally, the oxime ether derivatives showed either antibacterial or antifungal activity. Gr (+) bacteria especially *S. aureus* were very sensitive against to this group of compounds. The size of the molecule appears to be important for antimicrobial activity since compound **3** was the most active one and **6**–**9** were inactive up to 64 $\mu g\,mL^{-1}$ against most of the bacteria and fungi. Antibacterial activity of the compounds against *S. aureus* and antifungal activity were stereoselective.

6. Experimental part

6.1. Chemistry

All chemicals used in this study were purchased from E. Merck, Fluka AG and Aldrich. Purity of all compounds was checked by TLC with Merck Kieselgel GF 254 plates. Melting points were determined with a Thomas Hoover capillary melting point apparatus and were uncorrected. UV spectra were obtained by Shimadzu UV-160A UV–vis spectrometer in methanol. IR spectra were recorded in KBr disks with a Perkin–Elmer FT-IR Spectrometer 1720 X. ^{1}H-NMR spectra were recorded on a Bruker 80 MHz and Bruker Gmbtt DPX-400 MHz FT-NMR spectrometer. All chemical shifts were reported as δ (ppm) values. Splitting patterns were designated as follows: s: singlet; d: doublet; dd: doublet of doublets; t: triplet; q: quartet; and m: multiplet. Mass spectra were obtained by HP series II plus 5890 GC-HP 5972 Mass and VG platform II LC-MS. Elementary analysis were performed on Leco 982 CHNS elementary analysis apparatus at TÜBITAK (Scientific and Technical Research Council of Turkey). Enraf–Nonius CAD4/w–2θ was used for X-ray crystallographic study.

6.1.1. Synthesis of the compounds

6.1.1.1. 1-(2-Naphthyl)-2-bromoethanone and 1-(2-naphthyl)-2-(imidazole-1-yl)ethanone

These compounds used in nafimidone oxime synthesis, were prepared according to the literature procedures [4, 11].

6.1.1.2. 1-(2-Naphthyl)-2-(imidazole-1-yl)ethanone oxime ***1***

About 0.015 mol nafimidone and 0.03 mol hydroxylamine hydrochloride were dissolved in 75 mL ethanol and the pH of the mixture was adjusted to 11 with 15 N NaOH. The solution was refluxed for 3 h and then the

precipitate was removed by filtration. The solvent was evaporated to dryness. The residue was dissolved in water and acidified to pH 5 with hydrochloric acid. The compound was precipitated out of solution and recrystallized from methanol.

6.1.1.3. Oxime ethers ***2–9***

0.01 Mol nafimidone oxime was added to a solution of 0.011 mol sodium in 25 mL of ethanol. The resulting solution was refluxed for 30 min. Ethanol was evaporated in vacuo. The residue was dissolved in 10 mL anhydrous DMF and 0.01 mol appropriate alkyl halide was added. The solution was stirred at room temperature for 2–3 h (only **4** was stirred at 70°C). After DMF was evaporated, the oily residue was dissolved with benzene or ether and treated with gas HCl. The precipitate was filtered off, dried and crystallized from the appropriate solvents.

Isolation of E/Z isomers of ***3***. After DMF was evaporated, the oily residue was dissolved in ether. The ethereal solution was cooled in an ice bath and HCl gas was passed through the etheral solution. The precipitate (**3-A**) was filtered off and then the ethereal solution was retreated with gas HCl. The second isomer precipitated (**3-B**) was removed by filtration.

Z-(1-(2-naphthyl)-2-(imidazole-1-yl)ethanone) oxime ***1***. UV: λ_{max} (nm) ($\log \varepsilon$) (MeOH): 283.4 (3.76), 240.4 (4.18). IR (KBr, cm^{-1}): *v* (C–H aromatic) 3124, (O–H oxime) 2607, (N–O) 931, (C–H naphthalene A) 864, 822, (C–H naphthalene B) 755. ^{1}H-NMR (DMSO-d_6, 80 MHz): δ 5.50 (s, 2H, CH_2), 6.80–8.30 (m, 10H, aromatic rings), 12.15 (s, 1H, O–H). EIMS (70 eV): *m/e* 235 (base peak, 100%), 207, 195, 180, 154, 139, 127, 109, 82, 54 and 41. Anal. Found: C, 71.87; H, 5.03; N, 16.49. Calc. for $C_{15}H_{13}N_3O$ (251.29): C, 71.70; H, 5.21; N, 16.72%.

1-(2-Naphthyl)-2-(imidazole-1-yl)ethanone O-methyloxime hydrochloride ***2***. UV: λ_{max} (nm) ($\log \varepsilon$) (MeOH): 296.8 (3.68), 285.6 (3.74), 242.6 (4.31). IR (KBr, cm^{-1}): *v* (N^+–H) 3440, (C–H aromatic) 3020, (C–H aliphatic) 2816, (C–O) 1045, (N–O) 908, (C–H naphthalene A) 858, 822, (C–H naphthalene B) 743. ^{1}H-NMR ($CDCl_3$-*d*): δ 4.10 (s, 3H, CH_3), 5.70 (s, 2H, CH_2–N), 7.10–8.20 (m, 8H, naphthalene H^{3-8} and imidazole H^4, H^5), 8.45 (s, 1H, naphthalene H^1), 9.90 (s, 1H, imidazole H^2). EIMS (70 eV): *m/e* 265 (63%, M^+), 234, 207, 169, 153 (base peak, 100%), 81 and 54. Anal. Found: C, 63.16; H, 4.92; N, 13.54. Calc. for $C_{16}H_{16}ClN_3O$ (301.78): C, 63.68; H, 5.34; N 13.92%.

E-(1-(2-naphthyl)-2-(imidazole-1-yl)ethanone) O-ethyloxime hydrochloride ***3-A***. UV: λ_{max} (nm) ($\log \varepsilon$) (MeOH): 297.0 (4.21), 286.0 (4.25), 243.8 (4.53), 212.6 (4.44). IR (KBr, cm^{-1}): *v* (N^+–H) 3446, (C–H aromatic) 3117, (C–H aliphatic) 2891, (C–O) 1045, (N–O) 928, (C–H naphthalene A) 858, 819, (C–H naphthalene B) 756. ^{1}H-NMR ($CDCl_3$-*d*): δ 1.40 (t, 3H, CH_3), 4.40 (q, 2H, CH_2–O), 5.50 (s, 2H, CH_2–N), 7.00–8.10 (m, 9H, naphthalene H^{3-8} and imidazole protons), 8.50 (s, 1H, naphthalene H^1). EIMS (70 eV): *m/e* 279 (66% M^+), 250, 234, 207, 170, 153 (base peak, 100%), 127, 81, 69, 54, 53. Anal. Found: C, 63.07; H, 5.17; N, 12.86. Calc. for $C_{17}H_{18}ClN_3O{\cdot}1/2H_2O$ (324.8): C, 62.86; H, 5.90; N, 12.94%.

Z-(1-(2-naphthyl)-2-(imidazole-1-yl)ethanone) O-ethyloxime hydrochloride ***3-B***. UV: λ_{max} (nm) ($\log \varepsilon$) (MeOH): 297.2 (4.19), 286.2 (4.22), 243.2 (4.50), 212.4 (4.40). IR (KBr, cm^{-1}): *v* (N^+–H) 3447, (C–H aromatic) 3117, (C–H aliphatic) 2891, (C–O) 1045, (N–O) 928, (C–H naphthalene A) 858, 819, (C–H naphthalene B) 756. ^{1}H-NMR ($CDCl_3$-*d*): δ 1.40 (t, 3H, –CH_3), 4.40 (q, 2H, CH_2–O), 5.80 (s, 2H, CH_2–N), 7.10–8.10 (m, 8H, naphthalene H^{3-8} and imidazole H^4, H^5), 8.40 (s, 1H, naphthalene H^1), 9.80 (s, 1H, imidazole H^2). EIMS (70 eV): *m/e* 279 (63% M^+), 250, 234, 207, 180, 170, 153 (base peak, 100%), 127, 81, 69, 54, 53. Anal. Found: C, 64.27; H, 5.30; N, 13.15. Calc. for $C_{17}H_{18}ClN_3O$ (315.8): C, 64.66; H, 5.75; N, 13.31%.

1-(2-Naphthyl)-2-(imidazole-1-yl)ethanone O-propyloxime hydrochloride ***4***. UV: λ_{max} (nm) ($\log \varepsilon$) (MeOH): 297.2 (4.14), 286.0 (4.17), 243.6 (4.47), 212.6 (4.38). IR (KBr, cm^{-1}): *v* (C–H aromatic) 3147, (C–H aliphatic) 2962, 2880, (N^+–H) 2412, (C–O) 1032, (N–O) 934, (C–H naphthalene A) 871, 830, (C–H naphthalene B) 761. ^{1}H-NMR ($CDCl_3$-*d*): δ 1.00 (t, 3H, –CH_3), 1.8 (m, 2H, CH_2–CH_3), 4.35 (t, 2H, CH_2–O), 5.70 (s, 2H, CH_2–N), 7.10–8.10 (m, 8H, naphthalene H^{3-8} and imidazole H^4, H^5), 8.40 (s, 1H, naphthalene H^1), 9.60 ppm (s, 1H, imidazole H^2). EIMS (70 eV): *m/e* 293 (78% M^+), 262, 234, 207, 195, 170, 153 (base peak, 100%), 127, 81, 69, 43. Anal. Found: C, 63.33; H, 5.77; N, 12.21. Calc. for $C_{18}H_{20}ClN_3O{\cdot}1/2H_2O$ (338.84): C, 63.81; H, 6.25; N, 12.40%.

1-(2-Naphthyl)-2-(imidazole-1-yl)ethanone O-(2-propen)oxime hydrochloride ***5***. UV: λ_{max} (nm) ($\log \varepsilon$) (MeOH): 296.4 (3.59), 285.4 (3.63), 244.4 (4.11). IR (KBr, cm^{-1}): *v* (N^+–H) 3436, (C–H aromatic and allylic) 3084, (C–H aliphatic) 2950, (C–O) 1083, (N–O) 918, (C–H naphthalene A) 861, 821, (C–H naphthalene B) 748. ^{1}H-NMR ($CDCl_3$-*d*, 400 MHz): δ 4.85 (d, 2H,

O–CH_2), 5.37 (dd, 2H, =CH_2), 5.84 (s, 2H, CH_2–N), 5.96–6.19 (m, 1H, CH), 7.28 (d, 2H, naphthalene H^5, H^8) 7.48 (m, 2H, naphthalene H^6, H^7), 7.82 (t, 2H, naphthalene H^3, H^4), 7.94 (d, 1H, imidazole H^4), 8.07 (d, 1H, imidazole H^5), 8.47 (s, 1H, naphthalene H^1), 9.93 (s, 1H, imidazole H^2). EIMS (70 eV): *m/e* 291 (58% M^+), 234, 207, 194, 180, 154, 153, 127, 122, 81 (base peak, 100%), 77, 69, 41. Anal. Found: C, 74.22; H, 5.72; N, 14.25. Calc. for $C_{18}H_{17}N_3O$ (base form)(291.35): C, 74.20; H, 5.88; N, 14.42%.

1-(2-Naphthyl)-2-(imidazole-1-yl)ethanone O-cyclohexyloxime hydrochloride ***6***. UV: λ_{max} (nm) (log ε) (MeOH): 297.8 (4.02), 286.8 (4.04), 244.0 (4.41). IR (KBr, cm^{-1}): *v* (N^+–H) 3400, (C–H aromatic) 3122, (C–H aliphatic) 2931, 2857, (C–O) 1041, (N–O) 922, (C–H naphthalene A) 859, 822, (C–H naphthalene B) 760. ^{1}H-NMR ($CDCl_3$-*d*): δ 1.15–2.20 (m, 10H, cyclohexyl CH_2), 4.20–4.60 (m, 1H, cyclohexyl CH–O), 5.80 (s, 2H, CH_2–N), 7.00–8.10 (m, 8H, naphthalene H^{3-8} and imidazole H^4, H^5), 8.40 (s, 1H, naphthalene H^1), 9.90 (s, 1H, imidazole H^2). EIMS (70 eV): *m/e* 333 (40% M^+), 304, 265, 250, 207, 195, 153 (base peak, 100%), 127, 81, 55. Anal. Found: C, 67.56; H, 6.23; N, 11.04. Calc. for $C_{21}H_{24}ClN_3O$ (369.89): C, 68.19; H, 6.54; N, 11.36%.

1-(2-Naphthyl)-2-(imidazole-1-yl)ethanone O-benzyloxime hydrochloride ***7***. UV: λ_{max} (nm) (log ε) (MeOH): 297.6 (4.01), 286.4 (4.04), 253.6 (4.32), 211.6 (4.28). IR (KBr, cm^{-1}): *v* (N^+–H) 3430, (C–H aromatic) 3100, (C–H aliphatic) 2927, 2853, (C–O) 1015, (N–O) 920, (C–H naphthalene A) 857, 822, (C–H naphthalene B) 751, (C–H mono substituted benzene) 898, 748, 699. ^{1}H-NMR (DMSO-d_6): δ 5.30 (s, 2H, CH_2–O), 5.70 (s, 2H, CH_2–N), 7.10–8.10 (m, 13H, naphthalene H^{3-8}, benzene and imidazole H^4, H^5), 8.40 (s, 1H, naphthalene H^1), 9.30 (s, 1H, imidazole H^2). EIMS (70 eV): *m/e* 341 (23% M^+), 340, 324, 250, 235, 234, 207, 181, 180, 172, 171, 154, 153, 127, 107, 98, 91(base peak, 100%), 81, 76. Anal. Found: C, 67.92; H, 5.85; N, 10.48. Calc. for $C_{22}H_{20}ClN_3O{\cdot}1/2H_2O$ (386.88): C, 68.30; H, 5.47; N, 10.86%.

1-(2-Naphthyl)-2-(imidazole-1-yl)ethanone O-(4-chlorobenzyl)oxime hydrochloride ***8***. UV: λ_{max} (nm) (log ε) (MeOH): 297.4 (4.30), 286.0 (4.32), 252.0 (4.63). IR (KBr, cm^{-1}): *v* (C–H aromatic) 3067, (C–H aliphatic) 2941, (N^+–H) 2704, (C–O) 1012, (N–O) 992, (C–H naphthalene A) 857, 819, (C–H naphthalene B) 741. ^{1}H-NMR ($CDCl_3$-*d*): δ 5.30(s, 4H, CH_2–O and CH_2–N), 6.80–8.00 (m, 14H, naphthalene, benzene and imidazole). EIMS (70 eV): *m/e* 377 (11% M^{+2}), 375 (31 % M^+), 250, 233, 154, 153, 127, 125 (base peak, 100%), 111, 82, 81. Anal. Found: C, 62.69; H, 5.01; N, 9.51. Calc. for $C_{22}H_{19}Cl_2N_3O{\cdot}1/2H_2O$ (421.32): C, 62.72; H, 4.78; N, 9.97%.

1-(2-Naphthyl)-2-(imidazole-1-yl)ethanone O-(2,4-dichlorobenzyl)oxime hydrochloride ***9***. UV: λ_{max} (nm) (log ε) (MeOH): 297.6 (4.29), 286.2 (4.33), 253.6 (4.59), 213.2 (4.52). IR (KBr, cm^{-1}): *v* (N^+–H) 3392, (C–H aromatic) 3068, (C–H aliphatic) 2926, 2852, (C–O) 1016, (N–O) 902, (C–H naphthalene A) 859, 818, (C–H naphthalene B) 743. ^{1}H-NMR ($CDCl_3$-*d*): δ 5.40 (s, 2H, CH_2–O), 5.80 (s, 2H, CH_2–N), 7.00–8.10 (m, 11H, naphthalene H^3, H^4, H^5, H^6, H^7, H^8, benzene and imidazole H^4, H^5), 8.50 (s, 1H, naphthalene H^1), 10.00 (s, 1H, imidazole H^2). EIMS (70 eV): 176, 159, 153, 141, 126, 111, 77. Anal. Found: C, 59.08; H, 3.95; N, 9.18. Calc. for $C_{22}H_{18}Cl_3N_3O$ (446.76): C, 59.15; H, 4.06; N, 9.41%.

6.2. Pharmacology

Anticonvulsant activities of the compounds were determined by MES and scMet seizure tests and rotorod test for neurotoxicity according to testing procedures utilized by ASP and the ADD program [19, 20].

6.3. Microbiology

The minimal inhibitory concentration (MIC) values of the compounds were determined against yeast like fungi (*Candida albicans* ATCC 90018, *C. krusei* ATCC 6258 and *C. parapsilosis* ATCC 22019), gram-positive bacteria (*Staphylococcus aureus* ATCC 25923, *Enterococcus faecalis* ATCC 29212) and gram-negative bacteria (*Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853) by using broth microdilution method. Tests were carried out using Mueller Hinton broth (BBL, MD, USA) and RPMI-1640 medium buffered with MOPS [3-(*N*-morfolino)propane sulphonic acid] (ICN-Flow, Aurora, OH, USA) (Final concentration 0.165 mol L^{-1} at pH 7.0). Amikacin sulphate 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 to 0.06 μg mL^{-1}. The microtiter plates were incubated at 35°C and read visually after 24 h. but for Candida species 48 h. The MIC values were recorded as the lowest concentrations of the substances that had no visible turbidity.

6.4. X-ray crystallography

Crystallographic and refinement parameters are summarized in *table II*. The data were collected on a Nonius CAD4 diffractometer using graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). Three standard reflections were measured every two hours. The structure was solved by direct methods. The refinement was made with anisotropic displacement factors for all non-hydrogen atoms except for the C17a, C17b, C18a and C18b. The hydrogen atoms were generated geometrically and refined riding on the C atoms. An empirical ψ scan absorption correction was applied from the MO1EN [18], which has been used to carry out all calculations. The view of the molecule was performed using ORTEPII [23].

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