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Imidazolylchromanone oxime ethers as potential anticonvulsant agents: Anticonvulsive evaluation in PTZ-kindling model of epilepsy and SAR study

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ABSTRACT

As a continuation of our efforts to develop the azolylchromanone derivatives as potential anticonvulsant agents, we explored (*Z*)- and (*E*)-oxime ether derivatives of imidazolylchromanones bearing different lipophilic *O*-benzyl groups and tested their anticonvulsant activities in PTZ-kindling model of epilepsy. *O*-(2,4-Dichlorobenzyl) oximes **8a**, **16a** and **20a** were significantly effective in delaying the onset of the PTZ-evoked seizures at the dose of 30 mg/kg in kindled animals. The most effective compounds in delaying seizures were 7-chlorochromanone-*O*-(2,4-dichlorobenzyl) oximes **8a** and **20a**. SAR studies showed that introduction of a chlorine atom to the 7-position and/or a methyl group to the 2-position of the chroman ring resulted in an improvement of anti-seizure efficacy in *O*-(2,4-dichlorobenzyl) oxime series.

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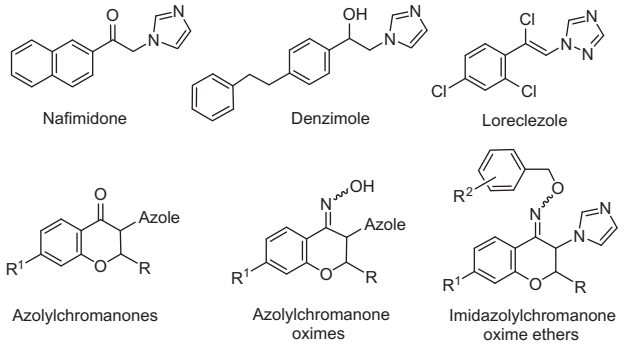
Epilepsy is a general term given to a group of neurological disorders that involve recurrent, spontaneous and abnormal electrical activity in some portion of the brain. These disorders have numerous causes, may occur at any age, and affects approximately 1–2% of the world's population.[1] In addition, about 4% of individuals over their lifetime give a diagnosis of epilepsy.[2] Typically, epileptic disorders require lifelong treatment, and may significantly limit patient autonomy and life quality.[3,4]

Treatment of epilepsy utilizes long-term administration of anticonvulsants with the intent to prevent the occurrence of convulsive seizures.[5] Many of the older generation of anticonvulsants drugs, that is, phenytoin, phenobarbital and carbamazepin were approved before three decades ago. The newer generation of anticonvulsant drugs, such as felbamate, levetiracetam, gabapentin, zonisamide, lamotrigine, rufinamide, remacemide, pregabaline, tiagabine and retigabine has certain advantages that have resulted in increased treatment options for clinicians and patients.[6,7]

Despite the significant advances in our understanding of seizure pathogenesis and considerable progress in the drug treatment of seizures, about 30–40% of patients with epilepsy are resistant to current pharmacotherapy. Likewise, multiple-drug therapies are commonly required for adequate seizure control. Even with adequate seizure control by multiple-drug therapies, there is currently no drug available which prevents the progression of epilepsy.[8] Many of current antiepileptic agents cause serious side effects, which include ataxia, nausea, mental dulling and hepatotoxicity. Moreover, the use of these drugs is often precluded by the occurrence of metabolic and drug interactions.[9,10] Accordingly, the search for more effective drugs that treat or prevent epilepsy with minimal side effects is urgently necessary.

Previously, we described design and synthesis of a series of azolylchromanones and their oxime derivatives as conformationally constrained analogs of (arylalkyl)azole anticonvulsants (e.g., nafimidone, denzimole and loreclezole) (Fig. 1). Preliminary results of PTZ-induced lethal convulsions test revealed that some



Azole = imidazol-1-yl; 1,2,4-triazol-1-yl
R = H; CH_3 R^1 = H; Cl
R^2 = H; Cl; Br; F; 2,4-Cl_2, 3,4-Cl_2

Figure 1.

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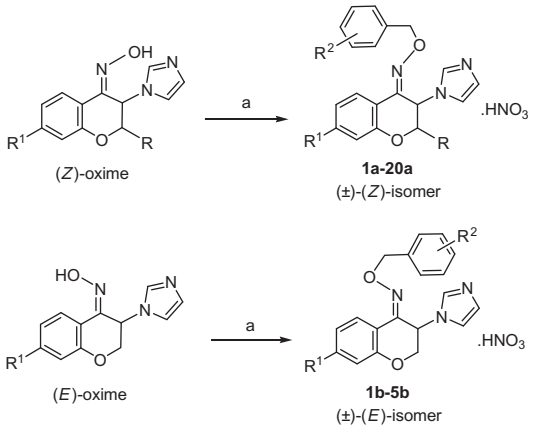
compounds were significantly effective in delaying the onset of the first myoclonic twitches at the dose of 5 mg/kg, and were protective against pentylenetetrazole-induced HLTE and mortality.[11] Based on these results, four promising compounds were subjected to the subsequent experiments including lithium-pilocarpine induced seizure and PTZ-induced kindling models of epilepsy. These compounds exhibited limited effects in PTZ-induced kindling model. However, 7-chloro-3-(1*H*-imidazol-1-yl)chroman-4-one (azole = imidazol-1-yl, R = H; R^1 = Cl), was found to exert respectable action in delaying seizures and reducing seizure index at the dose of 10 mg/kg.[12] Therefore, in the current study, we prepared some new oxime ether derivatives of imidazolylchromanones (Fig. 1) bearing different lipophilic *O*-benzyl groups and tested their anticonvulsant activities in PTZ-kindling model of epilepsy. The introduction of substituted benzyl on the imidazolylchromanone oximes and the variation of substituents on these fragments and chroman ring have allowed us to evaluate the influence of physicochemical parameters at the pharmacophoric part of the molecules.

Imidazolylchromanone oxime ethers **1a**–**20a** and **1b**–**5b** were prepared by reacting (*Z*)- or (*E*)-oximes with substituted benzyl halides in DMF, in the presence of NaH at room temperature according to the general synthetic procedures previously described by us.[13,14] The geometry of oximes was preserved in the course of *O*-benzylation reaction (Scheme 1).

All described compounds **1a**–**20a** and **1b**–**5b** (Scheme 1 and Table 1), which possess one or two chiral centers on their chroman ring on C-2 and C-3 positions, are racemates. In the case of 2-methylchromanone oxime ether derivatives **10a**–**20a**, the configuration of methyl group respect to the imidazole ring was assigned as *trans*-configuration, according to the ^{1}H NMR spectral data.[14]

The use of animal seizure models is prerequisite in the discovery and development of new antiepileptic drugs. There are various animal models including kindling models, post-status epilepticus models and genetic models, with chronic brain dysfunctions thought to reflect the processes underlying human epilepsy. Currently, the kindling and post-status models are the most widely used models for studies on epileptogenesis and on drug targets by which epilepsy can be prevented or modified. Furthermore, the seizures in these models can be used for testing of antiepileptic drug effects.[15] Accordingly, anticonvulsive actions of compounds **1a**–**20a** and **1b**–**5b** were determined by PTZ-induced kindling model.[16] PTZ-kindling was induced as described previously.[12] Briefly, animals were given a repeated sub-convulsive dose of PTZ (35 mg/kg, ip) for kindling acquisition. On the basis of a dose–response study, repeated administration of sub-convulsive PTZ progressively increased seizure susceptibility in animal and after 11 injections of PTZ (Monday, Wednesday and Friday) produced fully kindled animals. After reaching the criterion of kindled seizures, compounds **1a**–**20a** and **1b**–**5b** (30 mg/kg, ip) were administered to animals (n = 6) 30 min before intraperitoneal injection of PTZ (35 mg/kg). After each injection, the rats were placed singly in isolated transparent Plexiglas cages and were observed for 30 min. The onset of seizures (seizure latency) and the duration of behavioral seizure in each group were noted. These results were compared with those of the typical antiepileptic drug sodium valproate (100 and 200 mg/kg, ip) as a standard drug (Table 1).



Scheme 1. Preparation of imidazolylchromanone oxime ethers. Reagents and conditions: (a) appropriate benzyl halide, NaH, DMF, rt and then EtOH or *i*-PrOH, HNO_3.

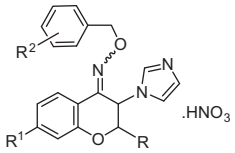
All animals pretreated with vehicle had generalized seizures after intraperitoneal injection of PTZ and the latency to seizure onset was 274 ± 58 s (Table 1). Compounds **7a**, **8a**, **16a** and **20a** were significantly effective in delaying the onset of the PTZ-evoked seizures at the dose of 30 mg/kg. The most effective compounds in delaying seizures were 7-chlorochromanone-*O*-(2,4-dichlorobenzyl) oximes **8a** and **20a**. The latency to seizure onset was moderately increased in animals pretreated with compound **4a** and **17a**. However, pretreatment of animals with remaining compounds had no significant effect on seizure latency at the doses tested. There are not any significant differences in seizure latency between compounds **8a**, **16a** and **20a** (at the dose level of 30 mg/kg) and sodium valproate (100 and 200 mg/kg).

The duration of PTZ-evoked seizures in kindled animals group administered vehicle was 51.7 ± 4.6 s. Pretreatment of kindled animals with compounds **8a**, **16a** and **20a** significantly reduced the seizure duration less than ~43 s. Polyhalogenated-2-methyl analog **20a** had more effective action on reducing seizure duration (~34 s vs ~52 s of control group). There is not any significant difference in seizure duration between compound **20a** (30 mg/kg) and sodium valproate (100 mg/kg). However, pretreatment of the kindled animals with the remaining compounds had no significant effect on seizure duration at the dose of 30 mg/kg.

Since the halogens are very useful to modulate the electronic effects on phenyl rings of drugs and can affect the steric characteristics and the hydrophilic–hydrophobic balance of the molecules, thus a diverse type of halogens like F, Cl, Br were introduced on *O*-benzyl group of imidazolylchromanone oxime ethers. Also, the role of chlorine was investigated by preparing 7-chlorochroman derivatives. For *O*-benzyl group, the better results were obtained with 2,4-dichloro- substituent as exemplified by compounds **4a**, **8a**, **16a** and **20a**. The effect of positional substitution was investigated by preparing 2,4- and 3,4-dichloro-substitutions on benzyl ring attached to the oxime. Replacing the 2,4-dichlorobenzyl group with a 3,4-dichloro benzyl one as in compound **9a** and **17a** resulted in an obvious decrease in the anti-seizure properties. This results maybe due to the steric hindrance of 3-chlorine substitution on *O*-benzyl pendent. As is shown with the comparison of compounds **4a** and **8a** or compounds **16a** and **20a**, introduction of a chlorine to the 7-position of the chroman ring resulted in an improvement of anti-seizure efficacy. The comparison of anticonvulsant activity of 2,4-dichloro-compounds **4a** and **16a** or compounds **8a** and **20a**, appears that introduction of a methyl group to the 2-position of the chroman ring had a positive effect on anti-seizure profile. Moreover, no effective compound was detected in 2-desmethyl- and 7-deschloro-series. By a prompt perusal of biological data, it can be concluded that the un-substituted or mono-halogenated compounds had no significant effects on seizure latency and seizure duration. In general, there was no significant differences between the (*Z*)- and (*E*)-stereoisomers (**1a**–**5a** vs **1b**–**5b**) as regards to the efficacy against the seizure latency and seizure duration.

It should be noted that a perusal of the CNS-active structures will reveal a noticeable range of molecular weights, topologies

Table 1
Chemical structure and anticonvulsant activity of imidazolylchromanone oxime ether derivatives



Compound[a]	R	R^1	R^2	Geometery	Seizure latency (s)[b]	Seizure duration (s)
1a	H	H	H	Z	274 ± 73	49.8 ± 3.8
1b	H	H	H	E	288 ± 70	50.8 ± 6.0
2a	H	H	4-Cl	Z	237 ± 26	52.0 ± 3.1
2b	H	H	4-Cl	E	258 ± 26	51.0 ± 4.4
3a	H	H	4-Br	Z	268 ± 54	54.8 ± 5.4
3b	H	H	4-Br	E	261 ± 66	56.5 ± 5.3
4a	H	H	2,4-Cl_2	Z	358 ± 47	49.2 ± 3.2
4b	H	H	2,4-Cl_2	E	293 ± 55	49.3 ± 6.2
5a	H	H	3,4-Cl_2	Z	285 ± 51	50.3 ± 7.6
5b	H	H	3,4-Cl_2	E	266 ± 56	51.8 ± 5.3
6a	H	Cl	H	Z	323 ± 59	46.7 ± 6.8
7a	H	Cl	4-Cl	Z	467 ± 112	47.0 ± 5.5
8a	H	Cl	2,4-Cl_2	Z	715 ± 153	40.3 ± 4.7
9a	H	Cl	3,4-Cl_2	Z	271 ± 49	48.5 ± 5.4
10a	Me	H	H	Z	259 ± 49	52.7 ± 3.9
11a	Me	H	4-Cl	Z	286 ± 51	49.7 ± 5.9
12a	Me	H	4-Br	Z	305 ± 70	51.3 ± 3.9
13a	Me	H	4-F	Z	263 ± 43	52.3 ± 5.3
14a	Me	H	3-F	Z	321 ± 59	51.5 ± 4.9
15a	Me	H	2-F	Z	254 ± 44	51.7 ± 1.8
16a	Me	H	2,4-Cl_2	Z	644 ± 128	42.8 ± 4.3
17a	Me	H	3,4-Cl_2	Z	367 ± 69	47.5 ± 6.0
18a	Me	Cl	H	Z	282 ± 52	50.7 ± 4.0
19a	Me	Cl	4-Cl	Z	286 ± 58	45.5 ± 4.8
20a	Me	Cl	2,4-Cl_2	Z	776 ± 97	342 ± 4.9
Control					274 ± 58	51.7 ± 4.6
Sodium valproate 100 mg/kg					817 ± 196	40.5 ± 8.1
Sodium valproate 200 mg/kg					900 ± 208	26.5 ± 3.9

[a] Compounds **1a**–**20a** and **1b**–**5b** were administered ip at the dose of 30 mg/kg.
[b] Data are shown as means ± SE ($n = 6$). $P < 0.05$ was considered as statistically significant.

and functional groups. In general, drugs that treat CNS disorders tend to be at the balanced physicochemical properties, with proportionally heteroatoms and polar functional groups. This may be in part due to the additional constraint of having to pass through the BBB.[17] Since, the physicochemical properties are crucial for CNS drugs to pass BBB, some quantitative parameters including constitutional (octanol–water partition coefficient, log *P*; molar refractivity, MR), topological (molecular topological index, MTI) and geometrical (connolly accessible area, CAA; connolly molecular area, CMA) values of the compounds were calculated by Chem 3D Ultra version 8.0.[18] The In silico physicochemical parameters of compounds **1a**–**20a** and **1b**–**5b** were summarized in Table 2.

The introduction of substituted benzyl on the imidazolylchromanone oximes and the variation of substituents on these fragments and chroman ring have allowed us to evaluate the influence of lipophilicity and steric parameters at the pharmacophoric part of the molecules. Within the series of compounds **1a**–**20a** and **1b**–**5b**, we have observed respectable anti-seizure activity of compounds **7a**, **8a**, **16a** and **20a** with the increase in MR from 91.00 cm^3/mol (**1a** and **1b**) to >100 cm^3/mol and with the increase in log *P* from 2.66 to >3.7. Although the predicted molar refractivity and lipophilicity of compounds **4a**,**b**, **5a**,**b**, **9a**, **12a**, **17a** and **19a** were in the range, but could not improved their efficacies. It is well known that high log *P* values are important for BBB passage, but lipophilicity is not the only parameter for the activity and some other properties are also responsible from the activity. Regarding other parameters from the data summarized in Table 2, there is a clear influence of topological (MTI) and geometrical (CAA, CMA) parameters of compounds **7a**, **8a**, **16a** and **20a** on anti-seizure activity compared with less active compounds **1a**–**5a** and **1b**–**5b**. For example, the optimal CAA and CMA for the most active compounds were found to be more than 580 and 330 $Å^2$, respectively. Also, active compounds exert molecular topological index more than 12,100.

On the other hand, from the study of parameters related to CNS activity or inactivity of commercially available drugs, a very simple prediction rule has been described. Based on this rule, if N + O (the number of nitrogen and oxygen atoms) in a molecule is less than or equal to five, it has a high chance of entering the brain.[19] According to this rule it was predicted that the examined compounds could be transported across the blood-brain barrier.

Recently, for rapidly improving the lead structures into the drug candidates with reduced mammalian toxicity, the definition of drug-likeness in physicochemical terms has drawn considerable attention.[20] There are several approaches that predict a compound's drug-likeness and toxicity partially based on topological descriptors, fingerprints of molecular drug-likeness structure keys or other properties such as MW and *c* log *P*.[21] In our study, the toxicity prediction, drug-likeness and drug-score of the compounds were calculated using online Osiris property explorer.[22] The prediction in the Osiris calculations is fragment-based approach and the occurrence frequency of each fragment is determined within the collection of traded drugs and within the supposedly non-drug-like collection of commercially available chemicals. A positive drug-likeness value (0.1–10) states that a molecule contains predominantly fragments which are frequently present in traded drugs.[22] The Osiris calculations allow us to predict the toxicity risks, like mutagenicity, tumorigenicity, irritating and reproductive

Table 2
In silico physicochemical parameters of compounds **1a**–**20a** and **1b**–**5b**

Compound	MF	MW	log *P*	MR	CAA	CMA	MTI
1a	$C_{19}H_{17}N_3O_2$	319.36	2.66	91.00	535.93	300.94	10457
1b	$C_{19}H_{17}N_3O_2$	319.36	2.66	91.00	543.45	299.10	10457
2a	$C_{19}H_{16}ClN_3O_2$	353.81	3.21	95.80	557.66	314.78	11349
2b	$C_{19}H_{16}ClN_3O_2$	353.81	3.21	95.80	567.39	314.02	11349
3a	$C_{19}H_{16}BrN_3O_2$	398.26	3.49	98.62	568.05	320.93	11349
3b	$C_{19}H_{16}BrN_3O_2$	398.26	3.49	98.62	573.68	318.91	11349
4a	$C_{19}H_{15}Cl_2N_3O_2$	388.25	3.77	100.61	566.66	323.10	12083
4b	$C_{19}H_{15}Cl_2N_3O_2$	388.25	3.77	100.61	575.17	322.01	12083
5a	$C_{19}H_{15}Cl_2N_3O_2$	388.25	3.77	100.61	579.97	330.05	12164
5b	$C_{19}H_{15}Cl_2N_3O_2$	388.25	3.77	100.61	584.71	327.79	12164
6a	$C_{19}H_{16}ClN_3O_2$	353.81	3.21	95.80	558.21	315.07	11218
7a	$C_{19}H_{15}Cl_2N_3O_2$	388.25	3.77	100.61	584.73	331.08	12136
8a	$C_{19}H_{14}Cl_3N_3O_2$	422.70	4.33	105.41	591.92	338.73	12892
9a	$C_{19}H_{14}Cl_3N_3O_2$	422.70	4.33	105.41	596.96	342.5	12975
10a	$C_{20}H_{19}N_3O_2$	333.39	2.98	95.42	539.15	306.17	11415
11a	$C_{20}H_{18}ClN_3O_2$	367.84	3.53	100.22	561.27	320.59	12362
12a	$C_{20}H_{18}BrN_3O_2$	412.29	3.80	103.04	569.44	325.50	12362
13a	$C_{20}H_{18}FN_3O_2$	351.38	3.13	95.63	547.46	311.35	12362
14a	$C_{20}H_{18}FN_3O_2$	351.38	3.13	95.63	545.97	311.53	12274
15a	$C_{20}H_{18}FN_3O_2$	351.38	3.13	95.63	543.49	310.13	12186
16a	$C_{20}H_{17}Cl_2N_3O_2$	402.28	4.09	105.03	580.31	332.69	13141
17a	$C_{20}H_{17}Cl_2N_3O_2$	402.28	4.09	105.03	567.44	330.40	13227
18a	$C_{20}H_{18}ClN_3O_2$	367.84	3.53	100.22	564.22	322.17	12206
19a	$C_{20}H_{17}Cl_2N_3O_2$	402.28	4.09	105.03	586.47	336.47	13179
20a	$C_{20}H_{16}Cl_3N_3O_2$	436.73	4.65	109.83	604.74	347.84	13980

MF, molecular formula; MW, molecular weight; MR, molar refractivity; CAA, connolly accessible area; CMA, connolly molecular area; MTI, molecular topological index.

effects (Table 3). The Osiris study revealed that all compounds are supposed to be non-mutagenic, non-tumorigenic, with no irritating effects. However, compound **1a**–**9a**, **1b**–**5b** and **14a** showed medium risk of reproductive effect. Moreover, all compounds with the exception of compounds **6a** and **18a** had positive drug-likeness values and the fragments of these compounds had a contribution for drug-like activities. In the Osiris explorer tool, the drug-score is calculated based on the combination of toxicity risks (mutagenicity, tumorogenicity, irritation, reproduction), drug-likeness and some physicochemical parameters such as *c* log *P*, log *S* (solubility) and molecular weight in one handy value than may be used to judge the compound's overall potential to qualify for a drug.[22] The target compounds showed moderate to good drug-score (0.33–0.71) that revealed their potential as safe lead compounds.

Table 3
Drug-likeness properties of target compounds predicted by Osiris property explorer tool

Compound	Toxicity risks[a]				Drug-likeness	Drug-score
	M[b]	T[c]	I[d]	R[e]		
1a	(−)	(−)	(−)	(±)	0.76	0.54
1b	(−)	(−)	(−)	(±)	0.76	0.54
2a	(−)	(−)	(−)	(±)	4.2	0.55
2b	(−)	(−)	(−)	(±)	4.2	0.55
3a	(−)	(−)	(−)	(±)	1.48	0.47
3b	(−)	(−)	(−)	(±)	1.48	0.47
4a	(−)	(−)	(−)	(±)	4.54	0.45
4b	(−)	(−)	(−)	(±)	4.54	0.45
5a	(−)	(−)	(−)	(±)	3.8	0.45
5b	(−)	(−)	(−)	(±)	3.8	0.45
6a	(−)	(−)	(−)	(±)	−1.07	0.35
7a	(−)	(−)	(−)	(±)	2.35	0.43
8a	(−)	(−)	(−)	(±)	2.28	0.33
9a	(−)	(−)	(−)	(±)	1.87	0.33
10a	(−)	(−)	(−)	(−)	1.47	0.69
11a	(−)	(−)	(−)	(−)	4.87	0.63
12a	(−)	(−)	(−)	(−)	2.21	0.56
13a	(−)	(−)	(−)	(−)	3.2	0.71
14a	(−)	(−)	(−)	(±)	1.5	0.53
15a	(−)	(−)	(−)	(−)	2.9	0.7
16a	(−)	(−)	(−)	(−)	5.18	0.5
17a	(−)	(−)	(−)	(−)	4.49	0.5
18a	(−)	(−)	(−)	(−)	−0.08	0.47
19a	(−)	(−)	(−)	(−)	3.28	0.49
20a	(−)	(−)	(−)	(−)	3.2	0.37

[a] Ranked according to: (−) no bad effect, (±) medium bad effect, (+) bad effect.
[b] M, mutagenic effect.
[c] T, tumorigenic effect.
[d] I, irritating effect.
[e] R, reproductive effect.

The neurological toxicity (e.g., ataxia, sedation, hyperexcitability) of the most effective compounds **8a** and **20a** was evaluated in mice using rotarod test at the doses of 30 and 100 mg/kg.[23,24] The test compounds did not show any sign of neurotoxicity at the dose of 30 mg/kg. The neurotoxicity aggravated with increasing dose from 30 to 100 mg/kg, and 25% and 50% motor impairment was expressed in tested animals by compounds **8a** and **20a**, respectively.

Previous studies have shown that seizures induced by PTZ can be blocked by drugs that reduce T-type Ca^{2+} currents, such as ethosuximide, and drugs that enhance $GABA_A$ receptor-mediated inhibitory neurotransmission, such as benzodiazepines and phenobarbital.[25] The representative arylalkylazole loreclezole potentiates $GABA_A$ receptor-mediated chloride currents through a site present on the β2 and β3 (but not β1) subunits of $GABA_A$ receptors.[26] Thus, it is possible that the imidazolylchromanone oxime ethers exert their activity by modulation of $GABA_A$ receptor.

In conclusion, we explored oxime ether derivatives of imidazolylchromanones with different lipophilic *O*-benzyl groups as potential anticonvulsant agents by evaluation in PTZ-kindling model of epilepsy. *O*-(2,4-Dichlorobenzyl) oximes **8a**, **16a** and **20a** were significantly effective in delaying the onset of the PTZ-evoked seizures at the dose of 30 mg/kg in kindled animals. The most effective compounds in delaying seizures were 7-chlorochromanone-*O*-(2,4-dichlorobenzyl) oximes **8a** and **20a**. SAR studies showed that introduction of a chlorine to the 7-position and/or a methyl group to the 2-position of the chroman ring resulted in an improvement of anti-seizure efficacy in *O*-(2,4-dichlorobenzyl) oxime series. Overall, as described by Löscher,[15] chronic epilepsy models in

which animals exhibit long term enhanced seizure susceptibility and spontaneous seizures are preferred to acute models such as the MES and PTZ tests, in which normal animals are induced to have seizures. Thus, effectual profile of promising compounds **8a**, **16a** and **20a** in PTZ-kindling model (as chronic model of epilepsy) predicts potential clinical efficacy of these compounds in epileptic disorders.

Acknowledgments

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16. *Materials:* PTZ and sodium valproate were purchased from Sigma–Aldrich Co. All other solvents and chemicals were of analytical grade and were obtained from Merck. All compounds were suspended in water and Tween 80 (3% w/v) and administered intraperitoneally. Solutions were prepared on a weight/volume basis on the day of use. All drugs were administered in volume of 0.1 ml/10 g of animal body weight. Sodium valproate and PTZ was dissolved in physiologic saline and administered ip. *Animals:* Adult male Wistar rats, weighting 120–150 g at the beginning of the experiment were used in the PTZ-induced kindling model. The animals were housed in standard Plexiglas cages with free access to food (standard laboratory rodent's chow) and water. The animal house temperature was maintained at 23 ± 2.0 °C with a 12 h light/dark cycle. Each animal was tested once. They were fasted overnight before the experiments and were transferred to the laboratory at least 1 h before the start of the experiment. The experiments were performed during the light portion.
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18. The geometries of the target compounds were optimized, using MM2 in the Chem 3D Ultra version 8.0 software (CambridgeSoft). An RMS gradient of 0.100 was used to minimize energy. The optimized geometry was used to calculate 2D and 3D molecular descriptors.
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23. 23. *The neurological toxicity*[24]*:* The rotarod test was performed to evaluate neurotoxicity. The mice were divided in groups of 4 animals and trained to stay on rotating rod (3.2 cm diameter) that rotates at 10 rpm. Trained animals were treated with test compounds at the doses of 30 and 100 mg/kg administered ip. Thirty minutes after ip administration the mice were placed on the rotating rod. Neurotoxicity was determined by the inability of the animal to remain on the rod at least for 1 min.
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