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Azolylchromans as a novel scaffold for anticonvulsant activity

Saeed Emami,[a,*] Abbas Kebriaeezadeh,[b] Mohammad Jafar Zamani[b] and Abbas Shafiee[c]

[a]*Department of Medicinal Chemistry, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran*
[b]*Department of Toxicology and Pharmacology, Pharmaceutical Sciences Research Center, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran*
[c]*Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Iran*

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Abstract—A series of azolylchroman derivatives were prepared as conformationally constrained analogs of (arylalkyl)azole anticonvulsants. The anticonvulsant activities of the compounds were evaluated by determining seizure latency and protective effect against pentylenetetrazole (PTZ)-induced lethal convulsions in mice at a dose of 5 mg/kg. Among these compounds, 7-chloro-3-(1*H*-imidazol-1-yl)chroman-4-one and 3-(1*H*-1,2,4-triazol-1-yl)chroman-4-one exhibited significant action in delaying seizures as well as effective protection against PTZ-induced seizures and deaths.
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Epilepsy is a major neurological disorder and up to 5% of the world population develop epilepsy in their lifetime.[1] It is a chronic and often progressive disorder characterized by recurrent transient attacks which are caused by an abnormal discharge of cerebral neurons.[2,3]

However, with the available antiepileptic drugs on the market, about 70% of the people with epilepsy achieve satisfactory seizure control and approximately 30% of patients are refractory to first-line antiepileptic drugs. Furthermore, even though ten new antiepileptic drugs have been licensed for clinical use during the last decade, these drugs have had little impact on the prognosis of intractable epilepsy. Consequently, the chances of seizure freedom with monotherapy for these patients are low, and invariably they are prescribed polytherapy in an attempt to enhance seizure control.[2,4] There is continuing demand for new anticonvulsant agents, as it has not been possible to control every kind of seizure with the currently available antiepileptic drugs. Moreover, the current therapy of epilepsy with modern antiepileptic drugs is associated with side effects, dose-related and chronic toxicity, and teratogenic effects.[4,5] Therefore, the development of new antiepileptic agents with approved therapeutic properties is still popular.[2,4,6]

One of the structurally distinct classes of antiepileptic drugs is the (arylalkyl)azoles. In recent years, loreclezole **1** has emerged as a structurally novel 1,2,4-triazole anticonvulsant with broad-spectrum activity. Loreclezole potentiates $GABA_A$ receptor-mediated Cl^- currents through a site present on the β2 and β3 (but not β1) subunits of $GABA_A$ receptors.[7,8] Furthermore, several 1,2,4-triazole derivatives have been proven to exhibit anticonvulsant properties.[9–12] Another structure among the azoles that were studied for anticonvulsant activity is imidazole nucleus. Nafimidone **2** and denzimole **3** are the examples of imidazole analogs, which possess a profile of activity similar to that of phenytoin or carbamazepine but distinct from those of barbiturates or valproic acid.[13–16]

In addition, certain azolylchromanone derivatives were synthesized in our laboratory, as intermediates for achieving some antifungal agents.[17–19] These compounds can be considered as conformationally constrained analogs of (arylalkyl)azoles (loreclezole **1**, nafimidone **2**, and denzimole **3**) (Fig. 1) and consist of a chroman ring that, in itself, shows some anticonvulsant activity.[20,21]

In view of the above observations, the preparation of azolylchromanone derivatives **4**, and related compounds **5** and **6** was aimed at investigating anticonvulsant activity (Table 1).

As illustrated in Scheme 1, 3-azolylchroman-4-ones **4** were obtained from 2′-hydroxy-2-azolylacetophenones **7** according to the method reported in the literature.[17–19]

Keywords: Anticonvulsant; Azole; Chroman.
* Corresponding author. E-mail: sd_emami@yahoo.com

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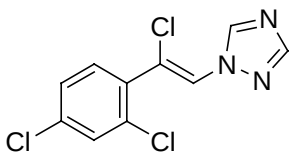
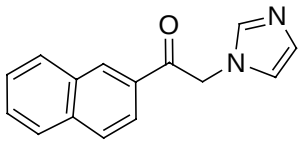


1, Loreclezole



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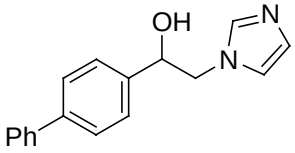
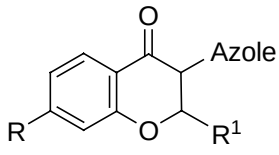


3, Denzimole



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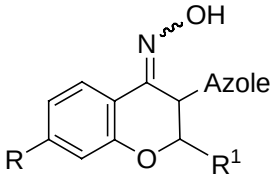

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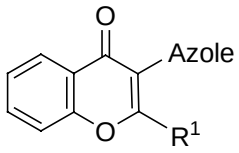
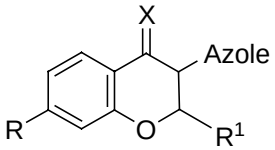


6

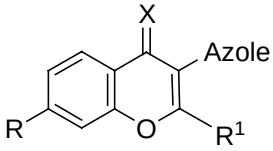
Azole = 1*H*-imidazol-1-yl; 1*H*-1,2,4-triazol-1-yl; 4*H*-1,2,4-triazol-4-yl
R = H; Cl R^1 = H; CH_3 (*trans* respect to Azole)

Figure 1.

Table 1. Anticonvulsant effects of compounds **4**–**6** in the PTZ-induced lethal convulsions test



4, **5**



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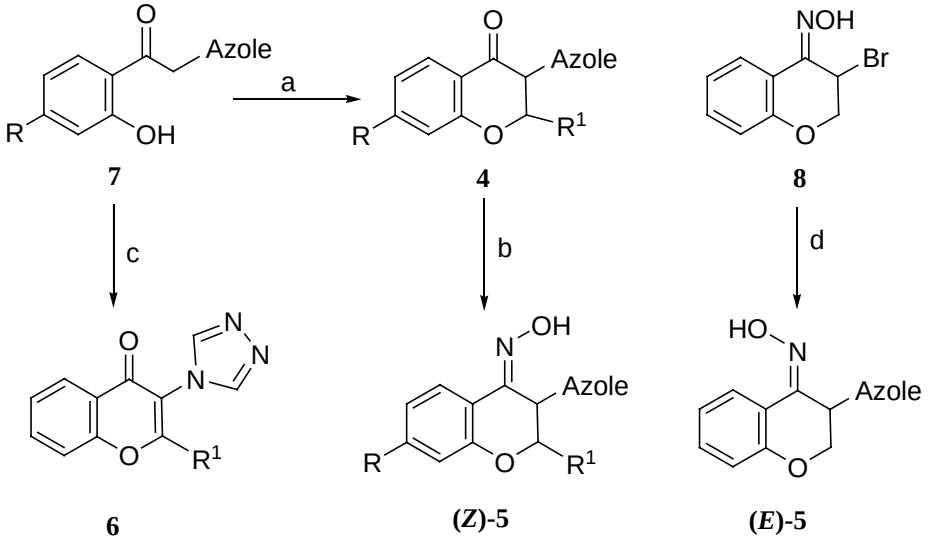
Compound[a]	Azole[b]	X	R	R^1	Seizure latency (min)[c]	HLTE (%)	Mortality (%)
4a	Im-1-yl	O	H	H	2.00 ± 0.32	83	83
4b	Im-1-yl	O	Cl	H	23.50 ± 3.08*	00	00
trans-**4c**	Im-1-yl	O	H	Me	17.00 ± 5.33*	100	67
trans-**4d**	Im-1-yl	O	Cl	Me	18.60 ± 5.41*	67	67
4e	Tz-1-yl	O	H	H	22.00 ± 4.11*	17	17
4f	Tz-1-yl	O	Cl	H	2.50 ± 0.56	100	100
4g	Tz-4-yl	O	H	H	2.83 ± 1.08	100	100
4h	Tz-4-yl	O	Cl	H	4.67 ± 1.14	100	83
trans-**4i**	Tz-4-yl	O	H	Me	7.17 ± 2.75	100	100
trans-**4j**	Tz-4-yl	O	Cl	Me	10.00 ± 4.28	83	83
(*Z*)-**5a**	Im-1-yl	NOH	H	H	7.80 ± 1.02	83	00
(*Z*)-**5b**	Im-1-yl	NOH	Cl	H	5.83 ± 2.23	100	100
(*Z*)-**5c**	Tz-1-yl	NOH	H	H	4.00 ± 1.09	100	100
(*Z*)-**5d**	Tz-4-yl	NOH	Cl	H	2.50 ± 0.67	100	100
(*E*)-**5a**	Im-1-yl	NOH	H	H	5.50 ± 1.98	100	100
(*E*)-**5c**	Tz-1-yl	NOH	H	H	7.17 ± 4.04	100	100
6a	Tz-4-yl	O	H	H	10.00 ± 2.74	100	100
6b	Tz-4-yl	O	H	Me	5.00 ± 0.57	100	100
Sodium valproate					15.65 ± 4.37	00	00
Control					4.80 ± 0.86	100	100

[a] Compounds **4**–**6** were administered ip at the dose of 5 mg/kg. Sodium valproate was administered at the dose of 150 mg/kg as reference drug.
[b] Azole: Im-1-yl = imidazol-1-yl; Tz-1-yl = 1,2,4-triazol-1-yl; Tz-4-yl = 1,2,4-triazol-4-yl.
[c] Mean ± SEM.
* $P < 0.05$.

Thus, ring closure of compound **7** by paraformaldehyde or acetaldehyde in acetic acid at 90–100 °C gave the corresponding 3-azolylchroman-4-one derivatives **4**. In the case of 2-methylchromanone derivatives **4c**, **4d**, **4i**, and **4j**, the configuration of methyl group respect to azole ring was assigned as trans-configuration, according to the large ^{1}H NMR coupling constant (J = 11.6–12.0 Hz). On the other hand, cyclization of compound



Azole = 1*H*-imidazol-1-yl; 1*H*-1,2,4-triazol-1-yl; 4*H*-1,2,4-triazol-4-yl
R = H; Cl R^1 = H; CH_3 (*trans* respect to Azole)

Scheme 1. Synthesis of compounds **4**–**6**. Reagents and conditions: (a) paraformaldehyde or acetaldehyde, AcOH, 90–100 °C; (b) $HONH_2$·HCl, K_2CO_3 (used only in the case of triazole derivatives), MeOH, rt; (c) triethyl orthoformate or triethyl orthoacetate, reflux; (d) imidazole, DMF, rt or 1,2,4-triazole, K_2CO_3, CH_3CN, rt.

7 by refluxing with triethyl orthoformate or triethyl orthoacetate afforded 3-(1,2,4-triazol-4-yl)chromen-4-ones **6**. Ketones **4** were converted to the pure (*Z*)-oxime derivatives (*Z*)-**5** by stirring with 3 equiv of $HONH_2$·HCl in methanol at room temperature.[17–19]

Another stereoselective synthetic pathway was used to obtain the (*E*)-stereoisomers of oximes **5**. Thus, reaction of 3-bromo-4-chromanone oxime **8** with imidazole or 1,2,4-triazole afforded (*E*)-oximes (*E*)-**5**.[17,18] The configuration of the oxime derivatives **5a**–**d** was assigned by ^{1}H NMR spectroscopy. According to our previous papers, the configurational assignment of the oxime geometry was simple due to the strong anisotropic deshielding by the oxime oxygen on the H-3 or H-5 proton on chroman ring in the (*Z*)- or (*E*)-oximes, respectively.[17–19]

The anticonvulsant activities of the compounds **4**–**6** were determined against pentylenetetrazole (PTZ)-induced lethal convulsions in mice. All compounds were suspended in water and Tween 80 (3%, w/v), and administered intraperitoneally (ip) at the dose of 5 mg/kg into a group of six mice. Control animals were injected with vehicle only. Thirty minutes after the administration of either vehicle or test compounds, the animals were injected with pentylenetetrazole (110 mg/kg, sc). This dose of pentylenetetrazole was shown to produce convulsions in all untreated mice and these animals exhibited 100% mortality during 30 min. After injection of PTZ, mice were observed for 30 min to detect the seizure latency, hind limb tonic extension (HLTE), and mortality. Seizure latency was defined as the time elapsed from the injection of PTZ to the first two myoclonic jerks of the forelimbs. This has been concluded to be the first sign of the beginning of the seizure activity. These results were compared with that of sodium valproate (150 mg/kg, ip) as a standard pharmacological drug for PTZ-induced convulsions.

Compounds **4b**–**e** were significantly effective in delaying the onset of the first myoclonic twitches at the dose of 5 mg/kg, the most effective compounds in delaying seizures being **4b** and **4e**. In addition, compounds **4b** and **4e** were protective against pentylenetetrazole-induced HLTE and compound **4b** showed maximum protection. No mortality was detected with compounds **4b** and (*Z*)-**5a**, and compound **4e** significantly reduced mortality rate. However, no mortality was detected with (*Z*)-**5a**, but this compound afforded no significant protection against HLTE and delaying seizures. In contrast, compounds **4c** and **4d** showed significant action in delaying seizures without effective protection against HLTE and deaths. As is shown with the comparison of compounds **4a** and **4c**, introduction of a methyl group to the 2-position of the chroman ring resulted in the ability for delaying seizures. In addition, it seems that chloro-substitution has a different effect in imidazole compound **4a** and triazole derivative **4e**. The comparison of anticonvulsant activity of triazole compounds **4e** and **4f** appears that introduction of a 7-chloro substituent resulted in a loss of protection properties. In contrast, this alteration in imidazole compound **4a** had a positive effect and produced a very effective compound **4b**. Moreover, no effective compound was detected in triazol-4-yl series.

PTZ-induced lethal convulsions test is the most commonly used initial screening test for characterizing potential anticonvulsant drugs. It has been often stated 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 neuro-transmission, such as benzodiazepines and phenobarbital.[22] So, it is possible that the azolylchromans exert their anticonvulsant action by modulation of Ca^{2+} currents or $GABA_A$ receptor. Antiepileptic drugs that inhibit seizures induced by PTZ are effective in the treatment of generalized myoclonic and absence seizures.

In conclusion, compounds **4b** and **4e** may be considered promising for the development of new anticonvulsant agents. These compounds provided significant action in delaying seizures as well as effective protection against PTZ-induced seizures and deaths.

References and notes

1. Sander, J. W. A. S.; Shorvon, S. D. *J. Neurol. Neurosurg. Psychiat.* **1996**, *61*, 433.
2. Löscher, W. *Eur. J. Pharmacol.* **1998**, *342*, 1.
3. Gringauz, A. *Introduction to Medicinal Chemistry*, 1st ed.; Wiley-VCH: New York, 1997, pp 589–593.
4. Brodie, M. J. *Epilepsy Res.* **2001**, *45*, 3.
5. Mattson, R. H. *Epilepsia* **1995**, *36*, S13.
6. Lin, Z.; Kadaba, P. K. *Med. Res. Rev.* **1997**, *17*, 537.
7. Johnston, G. A. R. *Curr. Top. Med. Chem.* **2002**, *2*, 903.
8. Ashton, D.; Fransen, J.; Heeres, J.; Clincke, G. H.; Janssen, P. A. *Epilepsy Res.* **1992**, *11*, 27.
9. Akbarzadeh, T.; Tabatabai, S. A.; Khoshnoud, M. J.; Shafaghi, B.; Shafiee, A. *Bioorg. Med. Chem.* **2003**, *11*, 769.
10. Kane, J. M.; Baron, B. M.; Dudley, M. W.; Sorensen, S. M.; Staeger, M. A.; Miller, F. P. *J. Med. Chem.* **1990**, *33*, 2772.
11. Kehne, J. H.; Kane, J. M.; Chaney, S. F.; Hurst, G.; McCloskey, T. C.; Petty, M. A.; Senyah, Y.; Wolf, H. H.; Zobrist, R.; White, H. S. *Epilepsy Res.* **1997**, *27*, 41.
12. Chimirri, A.; Gitto, R.; Quartarone, S.; Orlando, V.; De Sarro, A.; De Sarro, G. B. *Il Farmaco* **2002**, *57*, 759.
13. Walker, K. A. M.; Wallach, M. B.; Hirschfeld, D. R. *J. Med. Chem.* **1981**, *24*, 67.
14. *Drugs Fut.* **1983**, *8*, 689.
15. Nardi, D.; Tajana, A.; Leonardi, A.; Pennini, R.; Portioli, F.; Magistretti, M. J.; Subissi, A. *J. Med. Chem.* **1981**, *24*, 727.
16. Graziani, G.; Cazzulini, P.; Luca, C.; Nava, G.; Testa, R. *Arzneim.-Forsch./Drug Res.* **1983**, *33*, 1161.
17. Emami, S.; Falahati, M.; Banifatemi, A.; Moshiri, K.; Shafiee, A. *Arch. Pharm. Pharm. Med. Chem.* **2002**, *335*, 318.
18. Emami, S.; Falahati, M.; Banifatemi, A.; Amanlou, M.; Shafiee, A. *Bioorg. Med. Chem.* **2004**, *12*, 3971.
19. Emami, S.; Falahati, M.; Banifatemi, A.; Shafiee, A. *Bioorg. Med. Chem.* **2004**, *12*, 5881.
20. Arnold, A.; Merlini, L.; Quadri, M. L.; Bonsignori, A.; Melloni, P.; Varasi, M. *Farmaco* **1991**, *46*, 629.
21. Arnold, A.; Bonsignori, A.; Melloni, P.; Merlini, L.; Quadri, M. L.; Rossi, A. C.; Valsecchi, M. *J. Med. Chem.* **1990**, *33*, 2865.
22. Mac Donald, R. L.; Kelly, K. M. *Epilepsia* **1995**, *36*, S2.