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Synthesis and anticonvulsant activity of new 2-substituted-5-[2-(2-fluorophenoxy)phenyl]-1,3,4-oxadiazoles and 1,2,4-triazoles

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Abstract—A series of new 2-substituted-5-[2-(2-fluorophenoxy)phenyl]-1,3,4-oxadiazoles has been synthesized and screened for their anticonvulsant activities. Compound **3** shows considerable anticonvulsant activity both in PTZ and MES models. It seems that this effect is mediated by benzodiazepine receptors and other unknown mechanism, respectively.

Many compounds bearing five-membered heterocyclic rings such as triazoles, oxadiazoles, thiadiazoles and pyrazoles have been synthesized and evaluated for their anticonvulsant and antidepressant activities.[1–3] In our previous works, we reported that 3-amino-5-[4-chloro-2-(2-chlorophenoxy)phenyl]-4H-1,2,4-triazole **1** (Fig. 1) and 2-amino-5-phenyl-1,3,4-thiadiazole **2** (Fig. 1) had considerable anticonvulsant activity.[4,5] These results are in good agreement with the ones reported for some 2-aryl-5-hydrazino-1,3,4-thiadiazole, 5-aryl-3-(alkylthio)-4H-thiadiazole and 2,4-dihydro-3H-1,2,4-triazole-3-thione derivatives.[6,7]

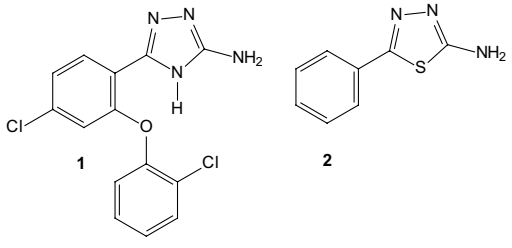

Figure 1.

Moreover we showed that compound **1** exerts its anticonvulsant activity through benzodiazepine receptors but compound **2** did not.

In the present study some new 1,3,4-oxadiazoles and 1,2,4-triazoles have been synthesized (Fig. 2 compounds **3–8**) and their anticonvulsant effects have been determined using pentylenetetrazole (PTZ)-induced lethal convulsion and maximal electroshock (MES) tests. To confirm the mode of action of the synthesized compounds. The effect of flumazenil, a benzodiazepine antagonist, on the anticonvulsant activity of the compounds were determined.

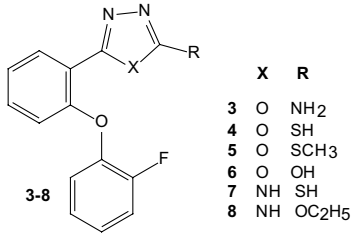

Figure 2.

Keywords: Substituted 1,3,4-oxadiazoles; Anticonvulsant; PTZ; MES.
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Target compounds **3**–**8** were obtained according to Scheme 1. The starting hydrazide **9** and 2-amino-5-[2-(2-fluorophenoxy)phenyl]-1,3,4-oxadiazole **3** were prepared as described previously.[8] Reaction of compound **9** with carbon disulfide under basic condition afforded 5-[2-(2-fluorophenoxy)phenyl]-1,3,4-oxadiazole-2(3H)-thione **4**.[9] Sonication of compound **4** in the presence of methyl iodide in alkaline ethanol gave 2-methyltio-5-[2-(2-fluorophenoxy)phenyl]-1,3,4-oxadiazole **5**.[4] Hydrazide **9** was converted to 5-[2-(2-fluorophenoxy)phenyl]-1,3,4-oxadiazole-2(3H)-one **6** by addition of 1,1′-carbonyldiimidazole in the presence of triethylamine.[10] 5-[2-(2-fluorophenoxy)phenyl]-2,4-dihydro-3H-1,2,4-triazole-3-thione **7** was synthesized by reaction of compound **9** with KSCN followed by cyclization of the thiosemicarbazide intermediate with an aqueous solution of NaOH.[11] Compound **3** was rearranged to 3-ethoxy-5-[2-(2-fluorophenoxy)phenyl]-1,2,4-triazole **8** upon treatment with ethanolic KOH.[4]

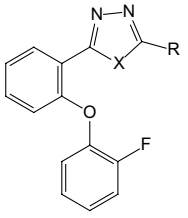
The anticonvulsant activity of the synthesized compounds was determined by evaluation of the ability of the compounds to protect mice against convulsion induced by a lethal dose of PTZ[12] and electroshock[13] as two routine models.

Diazepam was considered as a reference benzodiazepine agonist with anticonvulsant effect in both models. The synthesized compounds, diazepam or vehicle were administered 30 min before injection of PTZ 100 mg/kg or induction of electroshock (60 Hz, 37.2 mA and 0.25 s).

The dead mice were counted in PTZ test and occurrence of HLTE (hind limb tonic extension) were observed in MES Model, 30 min later.

As shown in Table 1, compound **3** with amino substituent on position 2 of oxadiazole ring has the best anticonvulsant activity in both PTZ and MES models. The effect was antagonized with flumazenil, a benzodiazepine antagonist, in PTZ test which verifies the involvement of benzodiazepine receptors in this effect. These results are in good agreement with our pervious studies on 1,2,4-triazole derivatives with the same activity.

Table 1. Pharmacological evaluation of the synthesized compounds

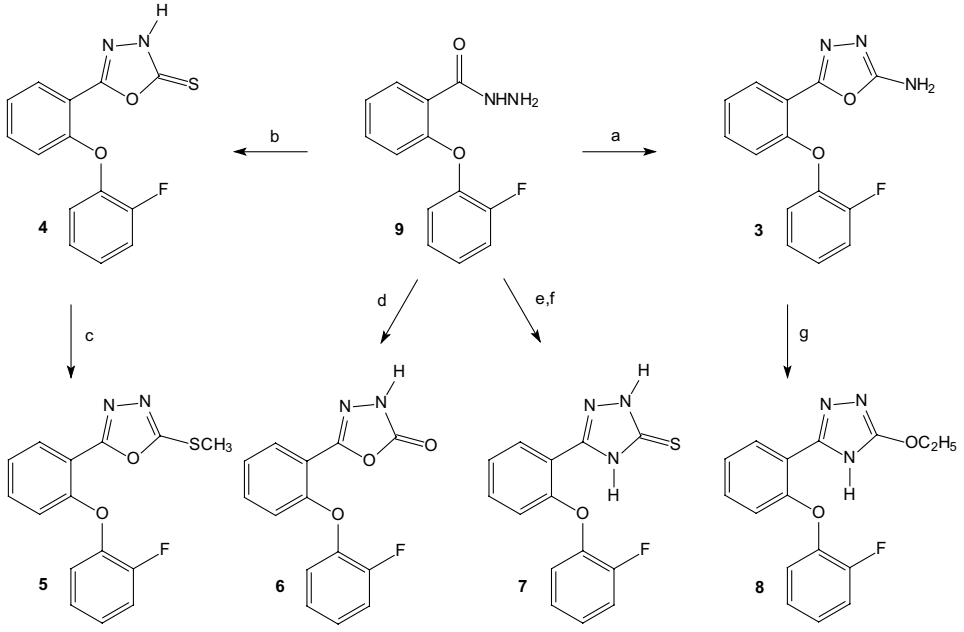


Compd	X	R	ED_{50} mg/kg[a]	
			PTZ	MES
3	O	NH_2	39.21 (32.69–45.49)[b]	9.57 (6.30–13.88)
4	O	SH	>100	43.11 (27.37–70.06)
5	O	SCH_3	>100	>100
6	O	OH	>100	>100
7	N	SH	>100	92.00 (78.96–107.18)
8	N	OEt	84.84 (73.96–97.02)[b]	ND[c]
Diazepam			1.87 (1.30–2.60)[b]	1.57 (1.16–2.14)[b]

[a] $n = 10$, 95% confidence limits in parentheses, LD_{50} of all compounds >300 mg/kg.

[b] ED_{50} significantly increased in the presence of flumazenil 10 mg/kg ($P < 0.05$).

[c] Not determined.



Scheme 1. Reagents and conditions: (a) BrCN, $NaHCO_3$, dioxane, rt, 3 h; (b) CS_2, KOH, EtOH, reflux, 7 h; (c) MeI, NaOH 10%, EtOH, sonication, 20 min; (d) 1,1′-carbonyldiimidazole, THF, rt, 18 h; (e) KSCN, HCl, H_2O, reflux, 3 h; (f) aq NaOH, reflux, 4 h; (g) EtOH, KOH, reflux, 15 h.

However, in MES model the anticonvulsant activity of compound **3** was not reduced by flumazenil. These interesting results show that other mechanisms may be involved in this effect and support the diversity of receptors that induce convulsion in MES and PTZ models. Since other receptors such as NMDA, AMPA or Kainic acid and voltage-regulated ion channels including those gating K^+, Na^+ and Ca^{2+} may be involved in convulsion[14], the mechanism of the anticonvulsant activity of the synthesized compounds in MES model need to be clarified in future studies.

Moreover PTZ and MES tests are the experimental models of absence and grand mal seizures, respectively.[15–18] Therefore, it seems that compound **3** may be effective in both type of seizure by a rather different mechanism.

The compounds with substituents other than amino group did not have significant activity in PTZ and MES models. Only compounds with OEt (compound **8**) and SH (compounds **4** and **7**) showed mild effects in PTZ and MES tests, respectively.

In conclusion a group of agents with wide anticonvulsant activity both mediated through benzodiazepine receptors and another unknown mode of action is introduced.

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