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Synthesis and anticonvulsant activity of new 2-substituted-5-(2-benzyloxyphenyl)-1,3,4-oxadiazoles

Afshin Zarghi,[a,*] Sayyed A. Tabatabai,[a] Mehrdad Faizi,[b] Avideh Ahadian,[a] Parisa Navabi,[a] Vahideh Zanganeh[b] and Abbas Shafiee[c]

[a]*Department of Medicinal Chemistry, Faculty of Pharmacy, Shaheed Beheshti University of Medical Sciences, Tehran 141556153, Iran*
[b]*Department of Pharmacology, Faculty of Pharmacy, Shaheed Beheshti University of Medical Sciences, Tehran 141556153, Iran*
[c]*Department of Medicinal Chemistry, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran 141556451, Iran*

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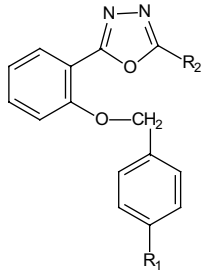
Abstract—A series of new 2-substituted-5-(2-benzyloxyphenyl)-1,3,4-oxadiazoles have been synthesized and evaluated as anticonvulsant agents. Compound **4b** shows considerable anticonvulsant activity both in PTZ and MES models. It seems this effect is mediated through benzodiazepine receptors mechanism.

Benzodiazepines (BZDs) have been widely used to provide anxiolysis and sedation in numerous clinical settings since their discovery over four decades ago.[1] BDZs allosterically enhance the action of γ-aminobutyric acid (GABA) at $GABA_A$ receptors by increasing the frequency of the opening of the chlorine channel, potentiating the inhibitory GABA action in the brain.[2,3] Several pharmacophore models have been proposed for BZDs, and amongst all models that suggest binding to the benzodiazepine receptor at least two features are common: an aromatic ring and a coplanar proton accepting group at a suitable distance. Also, the presence of a second out-of-plane, aromatic ring could potentiate binding to the receptor.[4–8] On this basis, we reported 2-substituted-5-(2-phenoxyphenyl)-1,3,4-oxadiazoles and 1,2,4-triazoles, which had considerable anticonvulsant activity.[9,10]

In the present study some new 2-substituted-5-(2-benzyloxyphenyl)-1,3,4-oxadiazoles with a flexible second out-of-plane aromatic ring, benzyoxy group, have been synthesized (Fig. 1, compounds **4**–**6**) and their anticonvulsant effects have been determined through pentylentetrazole (PTZ)-induced lethal convulsion and maximal electroshock (MES) tests. To clarify the mode of action of the synthesized compounds, the effect of flumazenil, a benzodiazepine receptor antagonist, were determined on the anticonvulsant activity of the compounds.

The designed compounds were synthesized according to Scheme 1. Reaction of methylsalicylate **1** with appropriate benzyl chloride in alkaline hydromethanolic solution afforded corresponding 2-benzyloxy benzoic acid methyl ester **2**.[11] 2-Benzyloxy benzoic acid hydrazides **3** were readily prepared by treatment with hydrazine hydrate in methanol.[12] The hydrazides were converted to 2-amino-5-(2-benzyloxyphenyl)-1,3,4-oxadiazoles **4** using cyanogens bromide in methanol (75–84%).[13]

5-(2-Benzyloxyphenyl)-2-mercapto-1,3,4-oxadiazole **5** was prepared by reaction of hydrazide **3a** with carbon disulfide under basic condition.[14]



4a: R_1=H; R_2=NH_2
4b: R_1=F; R_2=NH_2
4c: R_1=Cl; R_2=NH_2
5: R_1=H; R_2=SH
6a: R_1=H; R_2=SCH_3
6b: R_1=H; R_2=SC_2H_5
6c: R_1=H; R_2=SBz

Figure 1. The structure of designed compounds.

Keywords: Substituted 1,3,4-oxadiazoles; Anticonvulsant; Benzodiazepine receptor.
* Corresponding author. Tel.: +98 2187735215; fax: +98 218795008; e-mail: azarghi@yahoo.com

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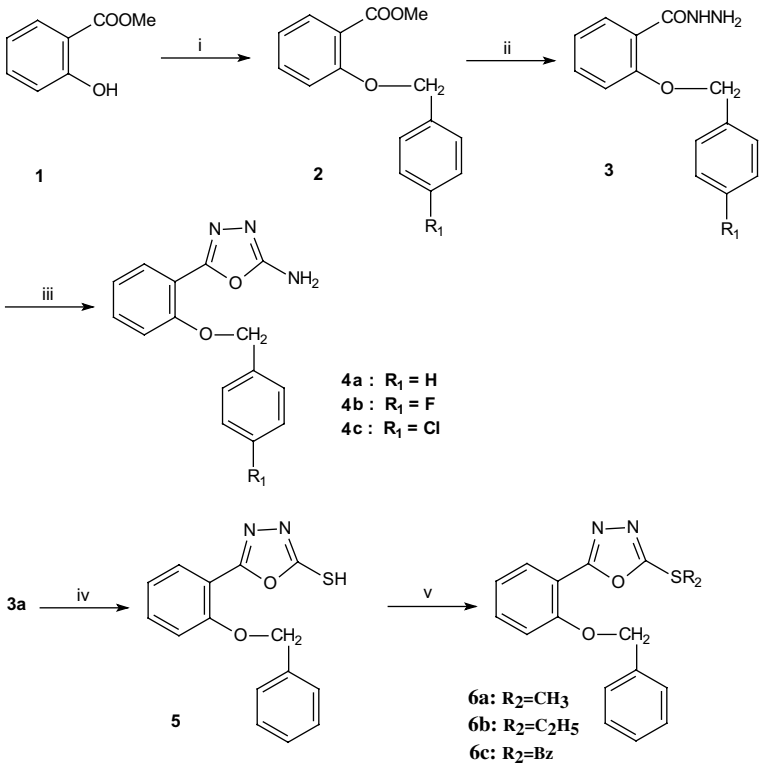


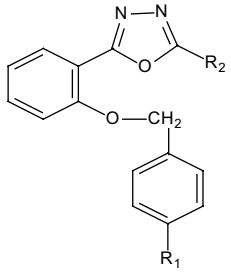
Scheme 1. Reagents and conditions: (i) BzCl, KOH 10%; MeOH, rt, 6 h; (ii) $NH_2NH_2{\cdot}H_2O$; MeOH, rt, 5 h; (iii) BrCN, $NaHCO_3$; MeOH, rt, 3 h; (iv) CS_2, KOH, EtOH, reflux, 6 h; (v) RI, NaOH 10%, EtOH, sonication, 20 min.

Sonication of compound **5** in the presence of suitable alkyl halide in alkaline media afforded 2-alkylthio-5-(2-benzyloxyphenyl)-1,3,4-oxadiazoles **6a**–**c** (78–95%).[15] The compounds were characterized by ^1H nuclear magnetic resonance, infrared, mass spectrometry and CHN analysis.

Benzodiazepine activity of the synthesized compounds was determined through the evaluation of the ability of the compounds to protect mice against convulsion induced by a lethal dose of PTZ[16] and electroshock[17] 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 indication of electroshock (60 Hz, 37.2 mA and 0.25 s). After 30 min, the dead mice were counted in PTZ test and occurrences of HLTE (hind limb tonic extension) were observed in MES Model.

As shown in Table 1, compound **4b** with amino group on position 2 of oxadiazole ring and fluoro substituent at the *para* position of benzyloxy group has the best anticonvulsant activity in both PTZ and MES models. The activity was antagonized with flumazenil, a benzodiazepine antagonist, which establishes the involvement of benzodiazepine receptors in this effect. However, replacement of the fluoro substituent with a larger electron withdrawing group such as Cl (**4c**) abolished the activity. This effect appears to be steric since the unsubstituted analogue **4a** had a moderate anticonvulsant activity. These results are in good agreement with the classical SAR of BZDs[18] and our previous studies on 1,3,4-oxadiazole and 1,2,4-triazole derivatives.[9,10] In the series of 2-alkylthio oxadiazoles, only compound **6a** had a weak anticonvulsant activity but the

Table 1. Pharmacological evaluation of the synthesized compounds



Compd	R_1	R_2	ED_{50} mg/kg[a]	
			PTZ	MES
4a	H	NH_2	85.2 (62.1–125.9)[b]	63.2 (41.9–82.9)[b]
4b	F	NH_2	2.5 (1.5–4.1)[b]	3.3 (2.1–5.1)[b]
4c	Cl	NH_2	>100	>100
5	H	SH	>100	>100
6a	H	SCH_3	91.2 (55.1–196.4)[b]	>100
6h	H	SC_2H_5	>100	>100
6c	H	SBz	>100	>100
Diazepam			1.4 (1.1–2.0)[b]	1.8 (1.1–2.6)[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 ($P < 0.05$).

compounds **5**, **6b** and **6c** did not have any significant anticonvulsant activities in both models.

In conclusion, the results of this investigation indicates that some synthesized 2-amino-5-aryl-1,3,4-oxadiazoles with a simple nonrigid structure in which the second out-of-plane aromatic ring, benzyloxy group, with a suitable substituent could show benzodiazepine activity comparable with diazepam confirms the suggested SARs for benzodiazepine agonists.

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