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Oxadiazolone bioisosteres of pregabalin and gabapentin

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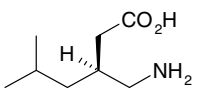
ABSTRACT

A series of oxadiazolone bioisosteres of pregabalin **1** and gabapentin **2** were prepared, and several were found to exhibit similar potency for the α_2-δ subunit of voltage-gated calcium channels. Oxadiazolone **9** derived from **2** achieved low brain uptake but was nevertheless active in models of osteoarthritis. The high clearance associated with compound **9** was postulated to be a consequence of efflux by OAT and/or OCT, and was attenuated on co-administration with cimetidine or probenecid.

Pregabalin **1**[1] was approved in the U. S. and Europe as an add-on therapy for epilepsy, and also for the treatment of neuropathic pain.[2] In June 2007 it became the first medication approved in the U. S. for the treatment of fibromyalgia,[3] and it has also been approved in the E. U. for the treatment of generalized anxiety disorder.[4] The therapeutic efficacy of **1** has been linked to binding at the α_2-δ subunit of voltage-gated calcium channels.[5] Recently, we reported that the carboxylate functions of pregabalin **1**[6] and gabapentin **2**[7] may be replaced by tetrazole, affording compounds that demonstrated similar in vitro and in vivo pharmacology to the parent amino acids. It was subsequently communicated that this approach could be extended to replacement with an oxadiazolone,[8] which has previously been shown to be a viable replacement for carboxylic acids.[9] Herein we wish to disclose additional SAR and biological data of γ-amino oxadiazolones that target the α_2-δ protein.



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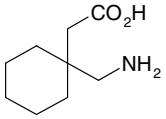
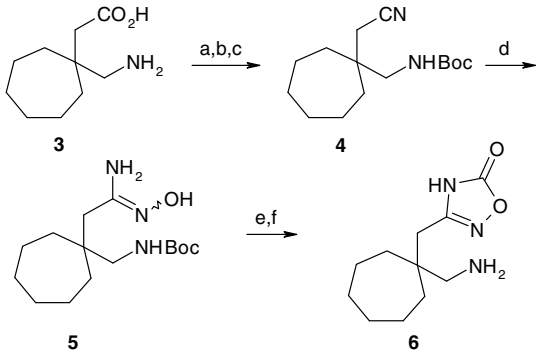


2

The synthetic route used to access oxadiazolones from the corresponding γ-amino acids is shown in Scheme 1.[10] N-protection and amidation of cycloheptane **3** via the mixed anhydride was followed by dehydration with cyanuric chloride[11] to afford nitrile **4**. Treatment of the nitrile with hydroxylamine under alkaline conditions furnished *N*-hydroxyamidine **5** as a ca. 1:1 mixture of *E*:*Z* isomers. Cyclization was effected with CDI, and finally acidic deprotection gave amino oxadiazolone **6**.



Scheme 1. Synthesis of oxadiazolone **6** from amino acid **3**. Reagents and conditions: (a) Boc_2O, 1 N NaOH, THF; (b) *i*-BuOCOCl, Et_3N, THF, then NH_3; (c) cyanuric chloride, DMF (65%, 3 steps); (d) NH_2OH-HCl, KOH, EtOH (78%); (e) CDI, THF (52%); (f) HCl; (g) dioxane (100%).

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We had previously reported that the affinity of tetrazole derivative **7** was found to be comparable to that for **1** and **2**, and that elimination of the acidic function via alkylation as in **8** resulted in complete reduction of potency for α_2-δ (Table 1).[7] [1,2,4]Oxadiazolones **9** and **10** derived from **2** gave results consistent with the tetrazoles, suggesting that this heterocycle was in fact a suitable carboxylic acid replacement for gabapentin.[8] Importantly, neither the tetrazole **7** or oxadiazolone **9** were substrates for the system L amino acid transporter, previously shown to facilitate entry of amino acids such as **1** and **2** into the brain.[12]

The SAR of various oxadiazolone analogs is shown in Table 2. Contraction of the carbocycle to the cyclopentane **11** resulted in a marked loss of potency for α_2-δ relative to **2**. However, expansion as in cycloheptane **6** resulted in enhanced affinity. Complete loss of potency was observed on further expansion to cyclooctane **12**. Presumably this was a consequence of the inability of the ring to support the axial positioning of the carboxylate required for α_2-δ activity.[13] With respect to substitution about the carbocyclic ring of **9**, similar to our previous observations[14] incorporation of a 3-methyl group with the appropriate stereochemistry as in **13** relative to the amino acid bearing carbon resulted in increased affinity for α_2-δ. Incorporation of a second methyl group at the 5-position as in **14** further enhanced potency for α_2-δ, although the diastereomer **15** was devoid of activity. The synthetic route used to access the amino acid precursors to **14** and **15** have previously been reported.[13] Finally, the oxadiazolone analog **16** of pregabalin **1** showed reduced potency in comparison to the gabapentin oxadiazolone **9**, a similar result to that obtained for the tetrazole replacement.[7]

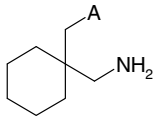
The oxadiazolone **9** was inactive in animal models where brain penetration is a requirement. These include the DBA/2 audiogenic seizure model and the water lick conflict test for anxiety (Table 3).[15] This profile is consistent with the reduced affinity of **9** for the system L transporter that facilitates brain uptake of amino acid drugs such as pregabalin **1**[16] and the tenfold lower brain levels observed for **9** in comparison to **1** (Table 4). However, oxadiazolone **9** has been shown to reduce progression of cartilage damage in a dog model of osteoarthritis.[17,18] It has recently been suggested that α_2-δ subunit ligands may influence the availability of calcium channel complexes at the plasma membrane via an action in the intracellular compartment, and that access to this compartment is gained via the system L transporter.[19] As compound **9** had low affinity for system L, it suggests that either it does not require access to this compartment, or that other transporters may permit access. The significance of this for the actions of these ligands in different animal models remains to be established.

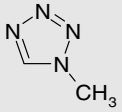
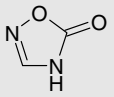
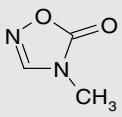
Consistent with its hydrophilic physicochemical properties and low molecular weight, compound **9** demonstrated only minimal protein binding (Fu > 0.9). It was not significantly metabolized, and once absorbed was excreted predominantly in the urine as unchanged parent drug. In addition, unbound renal clearance of **9** was significantly higher than the rat renal glomerular filtration rate of 5.2 mL/min/kg (Table 5). This suggested that compound **9** underwent net renal secretion,[20] possibly mediated by transporter(s) located on the renal proximal tubules such as organic cation transporter (OCT) and organic anionic transporter (OAT).

When compound **9** was co-administered intravenously with probenecid or cimetidine (known inhibitors for OAT and OCT transporters, respectively), its clearance was reduced by 57% and 35% relative to control.[21] This may suggest that OCT and OAT transporters were playing a role in the renal excretion of compound **9** and thereby contributed to the observed renal clearance (Fig. 1).[22]

In summary, oxadiazolone replacements of pregabalin **1** and gabapentin **2** were prepared and some displayed affinity for the α_2-δ subunit. Unlike **1** and **2**, however, oxadiazolone **9** was inactive at the system L transporter which resulted in poor brain uptake. As a result, in vivo activity was limited to models of osteoarthritis. Finally, the high clearance associated with oxadiazolone **9** was

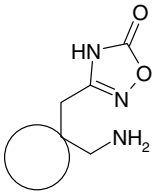
Table 1
Affinity of gabapentin carboxylate replacements for α_2-δ and system L transporter (LST).

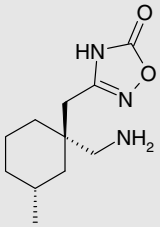
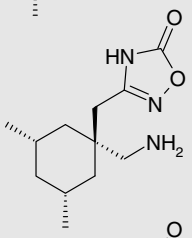
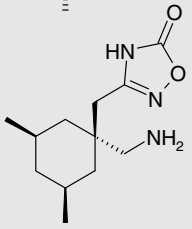
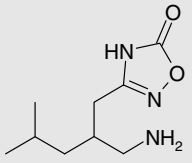


Compound	A	α_2-δ binding IC_{50}, nM[a]	LST binding IC_{50}[b] (μM)
1	Pregabalin	80	158
2 (Gabapentin)	CO_2H	70	30
7		100	>10,000
8		>10,000	
9 (PD 200347)		210	>10,000
10		>10,000	

[a] IC_{50} is the concentration (nM) producing half-maximal inhibition of the specific binding of [^{3}H]gabapentin binding to pig brain membranes, see Ref. 5.
[b] IC_{50} is the concentration (nM) producing half-maximal inhibition of the uptake of [^{3}H]leucine into CHO cells, see Ref. 12.

Table 2
SAR of carbocyclic portion of amino oxadiazolones.



Compound	Carbocycle	α_2-δ IC_{50}[a] (nM)
9	Cyclohexyl	210
11	Cyclopentyl	1140
6	Cycloheptyl	158
12	Cyclooctyl	5600
13		84
14[b]		70
15[b]		>10,000
16[b]		1500

[a] IC_{50} is the concentration (nM) producing half-maximal inhibition of the specific binding of [^{3}H]gabapentin binding to pig brain membranes, see Ref. 5.
[b] Compound is racemic.

Table 3
In vivo profile of compounds **1**, **2**, and **9**.

Compound	DBA/2 mouse anticonvulsant assay (% protected)[a]	Vogel conflict rat anxiolytic assay (% reference activity)[b]
1	100	100
2	100	60
9	20	11

[a] % Protection is the fraction of DBA/2 mice ($n = 5$) protected from audiogenically-induced tonic seizures by a 30 mg/kg PO dose of test compound at $t = 1$ h.
[b] The ability of a 30 mg/kg PO dose of test compound to restore punished drinking behavior in rats compared to a 30 mg/kg dose of **1** which is defined as 100%.

postulated to occur via efflux via the OAT and/or OCT transporters and was moderated on co-administration with cimetidine and probenecid.

Table 4
Exposure of compounds **1** and **9** at 2 h post 30 mg/kg PO dosing in Sprague–Dawley rats.

Compound	System L IC_{50} (μM)	Brain levels (ng/mL)	Plasma levels (ng/mL)	B/P
1	158	7360	25,643	0.29
9	>10,000	750	15,000	0.05

Table 5
Rat pharmacokinetic parameters for compounds **1**, **2**, and **9**.

Parameter	Pregabalin **1**	Gabapentin **2**	PD 200347 **9**
Bioavailability (%*F*)	83	76	97
Clearance (mL/min/kg)	2.9	6.0	20.3
Plasma half-life ($t_{1/2}$) (h)	2.7	1.5	1.6
AUC[a] (μg h/mL)	14.8	8.6	2.2
Vdss[b] (L/kg)	0.79	0.65	1.25

[a] Area under the concentration vs time curve.
[b] Volume of distribution.

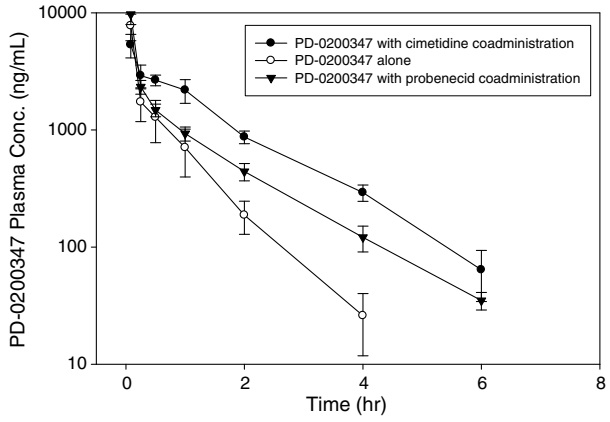


Figure 1. Average plasma concentration vs. time profiles for Wistar rats treated with PD 200347 alone (open circles, $n = 7$), and co-administered with probenecid (closed triangles, $n = 3$) or cimetidine (closed circles, $n = 3$) after 3 mg/kg IV infusion over 5 min.

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