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Carboxylate bioisosteres of gabapentin

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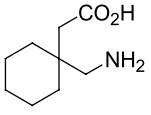
Dedicated to David W. Robertson in memory of his outstanding contributions as a mentor and drug hunter.

Abstract—A series of carboxylate bioisosteres of structures related to gabapentin **1** have been prepared. When the carboxylate was replaced by a tetrazole, this group was recognized by the α_2-δ protein. Further characterization of α_2-δ binding compounds **14a** and **14b** revealed a similar pattern of functional in vitro and in vivo activity to gabapentin **1**.

1. Introduction

Gabapentin **1** has been approved as an add-on therapy for epilepsy and as a treatment for postherpetic neuralgia.[1] More recently, pregabalin **2** has shown more potent and robust activity for these indications[2] and has been approved for use in some jurisdictions. Both compounds bind with high affinity to the α_2-δ subunit of voltage-gated calcium channels.[3] Binding to α_2-δ appears to allosterically modulate neuronal calcium channels, reducing calcium influx into activated neurons.[4] This attenuation of calcium currents in synaptic terminals leads, in turn, to a reduction in the release of neurotransmitters, including norepinephrine, substance P, and glutamate.[5–7] Such a reduction in neurotransmitter release is thought to underlie the in vivo anxiolytic, anticonvulsant, and antihyperalgesic effects observed with pregabalin and gabapentin. Studies of analogs of **1** and **2** have, in fact, shown a correlation between affinity for α_2-δ and in vivo activity.[8,9]



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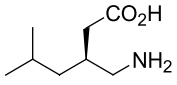

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Carboxylic acid replacements are an important area of investigation in medicinal chemistry.[10] Phosphinates,[11] sulfinates,[12] sulfonates,[13] and tetrazoles[14] have been used successfully as replacements for the carboxylate functionality. In this communication, we detail studies of these carboxylate isosteres in the context of gabapentin **1**.

2. Chemistry

Various acidic groups have been shown to be suitable replacements for the carboxylate functionality in various GABAergic compounds.[12,15] To determine if these replacements would also be recognized by the α_2-δ protein, phosphinate and sulfonate analogs of gabapentin were prepared.

The sulfinic acid derivative was prepared from 1-(aminomethyl)-cyclohexanemethanol **3**[16] according to the

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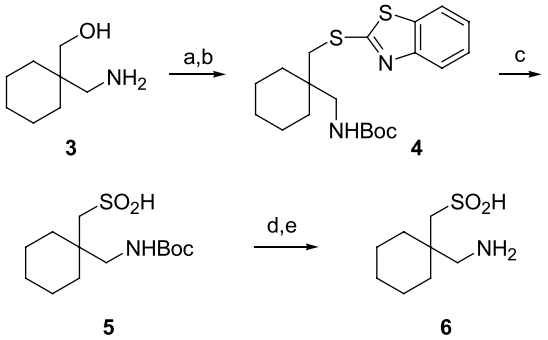
Schering–Plough precedent.[12] Hence, amine protection, followed by Mitsunobu displacement of the hydroxyl group with benzothiazole-2-thiol, proceeded smoothly to provide **4** (Scheme 1). Oxidation at sulfur, followed by reductive benzothiazole cleavage, afforded the free sulfinic acid **5**. The Boc group was removed uneventfully, yielding the desired amino sulfinic acid **6**. The sulfonic acid variant **7** was prepared, as described previously, by Satzinger et al.[17] from amino alcohol **3** via conversion to the hydrogen sulfate derivative and treatment with sodium sulfite.

The phosphinate analog was prepared according to the method developed by Krogsgaard-Larsen and co-workers.[15c] Hence, imidoaldehyde **8**, readily available from amino alcohol **3** via protection and oxidation, underwent addition of ethyl diethoxymethylphosphinate in the presence of triethylamine to give hydroxyimide **9** (Scheme 2). Acylation and subsequent deoxygenation of **10**, followed by hydrolysis, furnished the desired aminophosphinic acid **11**.

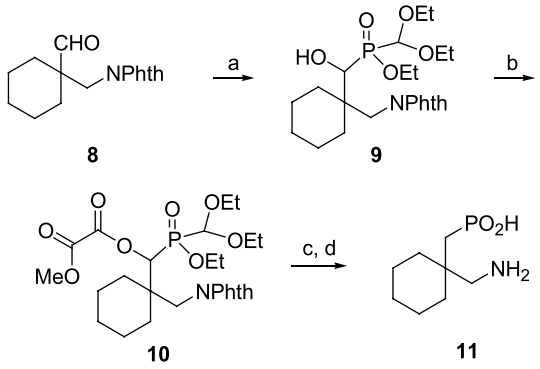
Next, we decided to examine the effect of replacing the carboxylate function with a tetrazole (Scheme 3). Typically the approach commenced with Knoevenagel condensation of the appropriate cyclic ketone **12**, followed by cyanide addition and decarboxylation in the same pot to afford **13**. Tetrazole formation was effected with azidotrimethylsilane in the presence of tributyltin oxide, and subsequent nitrile reduction gave the desired γ-amino tetrazoles **14a**–**c**. Unlike the γ-amino acids, no undesired lactam formation was possible with the tetrazole replacements.

Next, the effect of eliminating the acidic tetrazole hydrogen on α_2-δ binding was examined (Scheme 4). Hence, 1,5-dimethyltetrazole was lithiated[18] and added to nitroolefin **15**[19], affording adduct **16** in moderate yield. To our knowledge, the addition of metalated 5-alkyl-tetrazoles to nitroolefins is unprecedented. Hydrogenation of the resultant nitrotetrazole furnished the desired *N*-1-methylated derivative **17**.

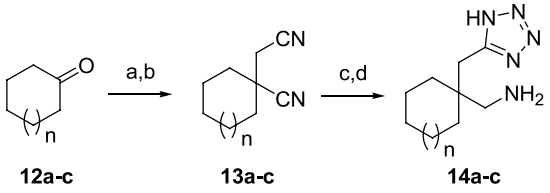
Finally, a synthesis of the tetrazole replacement of pregabalin **2** was undertaken (Scheme 5). Starting with *N*-Boc pregabalin **18**,[20] formation of the mixed anhydride was followed by amidation with 3-aminopropionitrile to yield **19**. Tetrazole formation, according to the du Pont Pharma protocol,[21] proceeded smoothly at ambient temperature to furnish **20**. Sequential deprotection of the tetrazole and amine moieties was



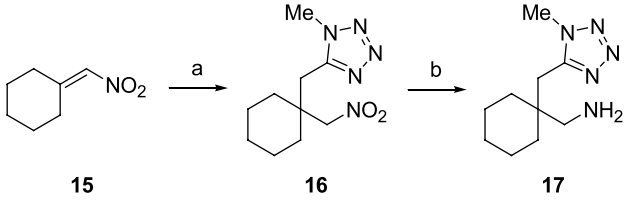
Scheme 1. Reagents and conditions: (a) Boc_2O, THF, 77%; (b) benzothiazole-2-thiol, DEAD, THF, 62%; (c) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 64%; (d) $NaBH_4$, EtOH, 47%; (e) 4 M HCl, Et_2O, ~100%.



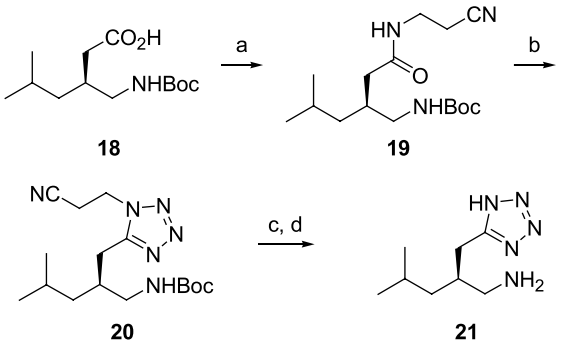
Scheme 2. Reagents and conditions: (a) $(EtO)HP(O)CH(OEt)_2$, Et_3N, 41%; (b) methyl oxalyl chloride, DMAP, CH_3CN, 87%; (c) Bu_3SnH, AIBN, toluene, reflux, 29%; (d) 4 M HCl, Et_2O, dioxane.



Scheme 3. Reagents and conditions: (a) ethyl cyanoacetate, NH_4OAc, toluene, reflux, 87%; (b) KCN, EtOH, H_2O, reflux, 69%; (c) $TMSN_3$, Bu_3SnO, toluene, reflux, 70%; (d) H_2/PtO_2, MeOH, recrystallization from MeOH/EtOAc, 39% (yields reflect preparation of **14a**, i.e., $n = 1$).



Scheme 4. Reagents and conditions: (a) 1,5-dimethyl-1*H*-tetrazole, *n*-BuLi, THF, −78 °C to rt, 43%; (b) H_2, Pd/C, MeOH/THF, 44%.



Scheme 5. Reagents and conditions: (a) *i* = BuCOCl, 3-aminopropionitrile fumarate, 71%; (b) $TMSN_3$, DEAD, Ph_3P; (c) 2 N NaOH, THF, 57% (2 steps); (d) HCl, dioxane (89%).

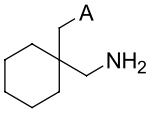
effected with base and acid, respectively, and the resultant tetrazole **21** was determined to be >99% ee following derivatization with Marfey's reagent[22] and HPLC analysis.

3. Results and discussion

The sulfinate **6**, sulfonate **7**, and phosphinate **11** analogs of gabapentin **1** did not bind to the α_2-δ subunit, as evidenced by their inability to displace [^{3}H]gabapentin from pig brain membranes (Table 1).[3] However, the tetrazole analog **14a** displayed affinity for α_2-δ similar to that of gabapentin. The *N*-methyl analog **17** was inactive, suggesting the importance of acidic functionality toward achieving affinity for α_2-δ as observed for **14a**.

When the ring size was varied on the aminotetrazole backbone, nearly equal potency was observed for the six-membered ring **14a** and the homolog **14b** (Table 2). However, expanding the ring by one more carbon resulted in marked decrease in α_2-δ binding affinity (cf. **14c**). Similarly, when the acyclic pregabalin derivative **21** was examined, no appreciable affinity for α_2-δ was observed. These differences in affinity at α_2-δ were manifested in the ability of the compounds to prevent audiogenic seizures in DBA/2 mice.[23] For instance, while α_2-δ ligands **14a** and **14b** demonstrated robust anticonvulsant activity, compounds **14c** and **21** displaying weak (μM) affinity for α_2-δ did not show any protective effects. Hence, the direct tetrazole replacement strategy that was successful for gabapentin **1** was not as promising for pregabalin **2**.

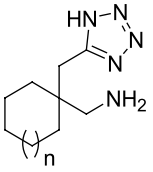
Table 1. Affinity for α_2-δ of a series of gabapentin carboxylate replacements



Compound	A	α_2-δ binding IC_{50} (nM)[a]
1	CO_2H	70 (±2)
6	SO_2H	>10,000
7	SO_3H	>10,000
11	PO_2H	>10,000
14a	tetrazole	100 (±23)
17	*N*-1-Me-tetrazole	>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. 3).

Table 2. α_2-δ Binding and anticonvulsant activity of a series of γ-amino tetrazoles



Compound	*n*	α_2-δ binding IC_{50} (nM)[a]	DBA/2 seizure % protection[b]
14a	1	108	80
14b	2	100	100
14c	3	2357	0
21	—	1587	0

[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. 3.

[b] % protection is the fraction of DBA/2 mice (N = 5 animals) protected from audiogenically induced tonic seizures by a 30 mg/kg p.o. dose of the test compound.

Compound **14b** was further characterized in in vitro and in vivo assays. Previously, gabapentin and pregabalin have been shown to decrease K^+-evoked [^{3}H]norepinephrine release from superfused rat neocortical slices, and this inhibitory effect is considered to be a functional consequence of α_2-δ binding.[5] Using the same assay conditions[5] and as shown in Figure 1, tetrazole **14b** produced a submaximal, concentration-dependent decrease of norepinephrine release with an IC_{50} [95% CI] = 5.7 [2.6–12.3] μM, being of similar potency to gabapentin (IC_{50} = 8.9 [2.9–27.5] μM).

A dose–response study of compound **14b** in the DBA/2 mouse anticonvulsant model was also carried out. Compound **14b** showed greater potency than gabapentin in this assay (ED_{50} = 3.1 mg/kg for **14b** vs 12.5 mg/kg for **1**) (see Fig. 2).

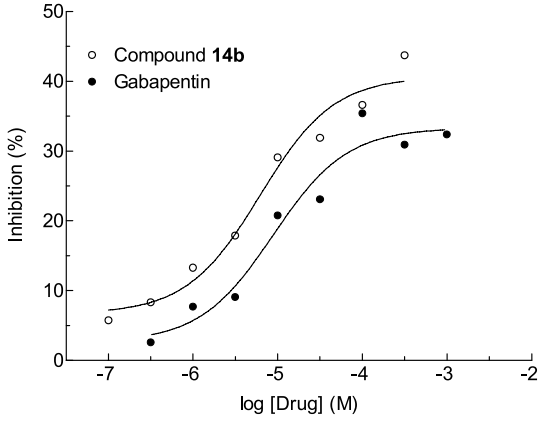


Figure 1. Inhibition of K^+-evoked [^{3}H]norepinephrine release from rat neocortical slices by gabapentin **1** and compound **14b**.

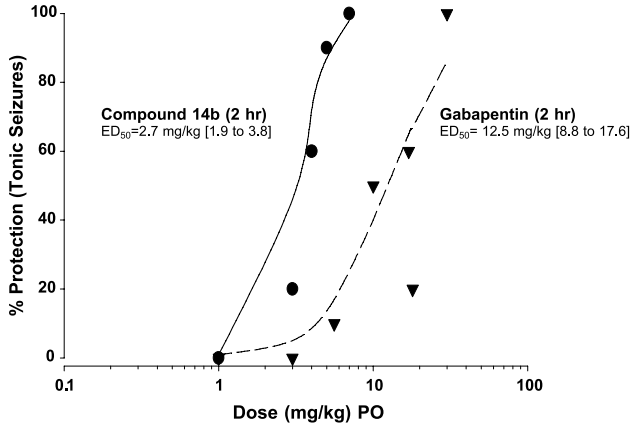


Figure 2. Comparison of gabapentin **1** and tetrazole **14b** in the DBA/2 mouse anticonvulsant assay.

Table 3. Rat pharmacokinetic parameters for gabapentin **1** and tetrazole **14b**

Parameter	Gabapentin **1**	Tetrazole **14b**
Bioavailability (%F)	76	85
Clearance (mL/min/kg)	6.0	10.6
Plasma half-life ($t_{1/2}$)	1.5	1.0
AUC[a] (μg h/mL)	8.6	5.2
Vd[b] (L/kg)	0.65	0.38

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

A comparison of rat pharmacokinetic data for compound **14b** and gabapentin **1** is outlined in Table 3. Like gabapentin, compound **14b** had good oral bioavailability. However, the tetrazole **14b** was more rapidly cleared from plasma and as a consequence had a shorter plasma half-life than gabapentin.

4. Conclusion

Bioisosteric replacements have been commonly used in drug discovery to optimize drug-like properties such as solubility, absorption, distribution, and/or clearance. Attempts to introduce a traditional carboxylic acid replacement to gabapentin **1** such as sulfinate, phosphinate, or sulfonate were unsuccessful, in that binding of these analogs to the α_2-δ protein was abolished. However, when a tetrazole group was employed as the isostere, affinity for α_2-δ was retained, as demonstrated by **14a**. In addition, comparable efficacy against seizures was observed in vivo for **14a** and **14b** compared to pregabalin **2**. However, when the acidic tetrazole proton was replaced by *N*-Me (cf. **17**), no binding to α_2-δ was observed, underscoring the importance of the acidic functionality for activity. Similarly, acyclic tetrazole **21** had approximately 16-fold weaker affinity for α_2-δ than **14b**. Further characterization of compound **14b** revealed it had similar in vitro and in vivo potency, as well as bioavailability when compared to gabapentin **1**.

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