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Bioorganic & Medicinal Chemistry Letters 16 (2006) 3559–3563
Bioorganic & Medicinal Chemistry Letters

Carboxylate bioisosteres of pregabalin

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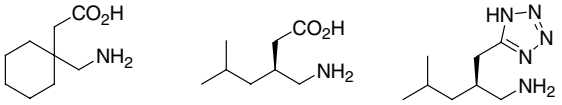
Received 10 February 2006; revised 23 March 2006; accepted 24 March 2006
Available online 18 April 2006

Abstract—Several β-amino tetrazole analogs of gabapentin **1** and pregabalin **2** were prepared by one of two convergent, highly efficient routes, and their affinity for the α_2–δ protein examined. Two select compounds with potent affinity for α_2–δ, **8a** and **16a**, were subsequently tested in vivo in an audiogenic seizure model and found to elicit protective effects.

Recently, we described the preparation and biological activity of a series of analogs of gabapentin **1**, in which the carboxylate had been replaced with various bioisosteres.[1] When the replacement employed for **1** was tetrazole, binding to the α_2–δ protein was conserved, as was the in vivo anticonvulsant activity. Binding to α_2–δ appears to attenuate calcium currents in synaptic terminals,[2] leading to a reduction in the release of neurotransmitters, including norepinephrine, substance P, and glutamate.[3–5] Mindful that pregabalin **2** has shown more potent and robust activity than gabapentin **1** in various models of epilepsy, neuropathic pain, and anxiety,[6] we were interested in subjecting **2** to a similar strategy. However, when the carboxylic acid of **2** was replaced by tetrazole, no significant binding of **3** to the α_2–δ protein was observed. To address this issue, we recalled that a series of constrained β-amino acid analogs of pregabalin **2** demonstrated good potency for the α_2–δ protein.[7] As a result, we were intrigued at the possibility of replacing the carboxylate of β-amino acid analogs of pregabalin **2** with a tetrazole[8] and examining the pharmacological consequences.



1 **2** **3**

In 1995, workers at Novartis showed that 5-lithiotetrazoles added to a variety of electrophiles, including aldehydes, ketones, enones, amides, iodine, and diethyl chlorophosphate.[9] Although they found that no addition to benzyl bromide, *N*-methyl benzylideneamine, or propylene oxide took place, nitroolefins were not examined as a possible electrophilic partner for this useful reagent. We noted that if such an addition were feasible, it might serve as a key step toward a general preparation of β-amino tetrazoles, potentially useful bioisosteres of β-amino acids (Fig. 1, path a).

To initiate the sequence, 1-benzyltetrazole **4** was metalated with *n*-butyllithium at low temperature, and without allowing the mixture to warm, nitroolefin **5** in THF was added (Scheme 1). It had been reported previously that the lithiated tetrazole underwent decomposition with extrusion of N_2 at temperatures above −70 °C. In fact, we observed that a portion of lithiated *N*-benzylcyanamide was formed under the reaction conditions which also added to the nitroolefin to give cyanamide

Keywords: Gabapentin; Pregabalin; α_2–δ Subunit; Tetrazole.
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doi:10.1016/j.bmcl.2006.03.083

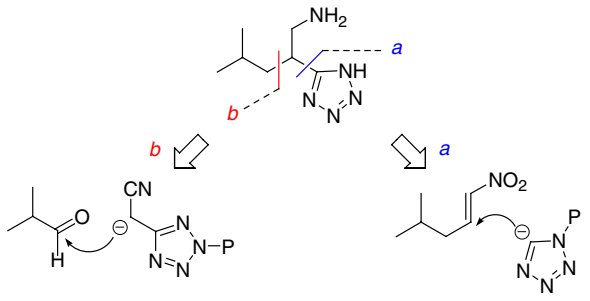
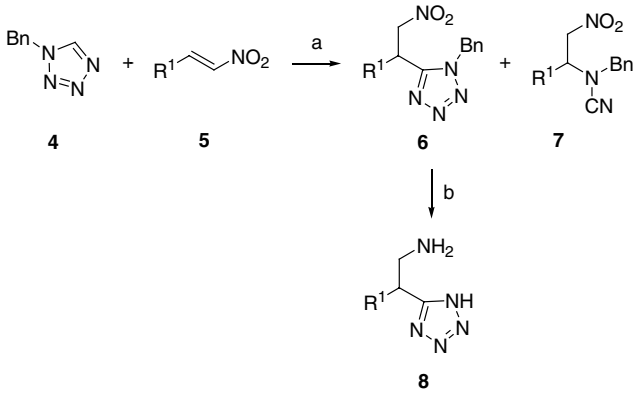


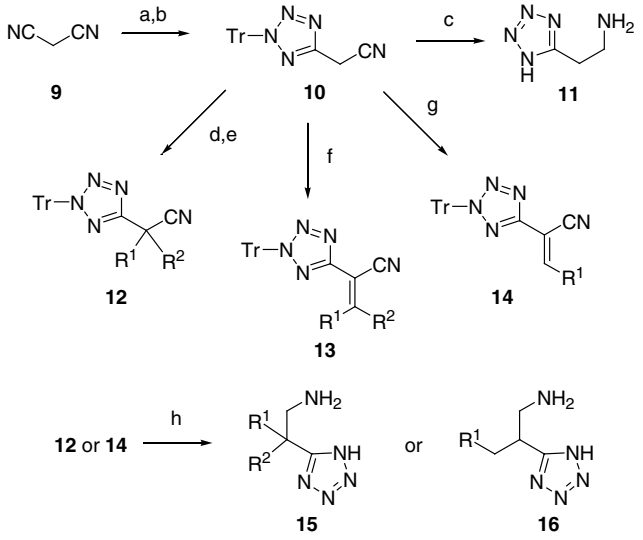
Figure 1. Convergent routes to access β-amino tetrazoles.



Scheme 1. Reagents and conditions: (a) *n*-BuLi, THF, −78 °C; (b) H_2, Pd/C, MeOH, HCl.

7. Fortunately, this byproduct could be easily removed from the desired adduct **6** by chromatography. Hydrogenation of **6** in the presence of acid afforded the target aminotetrazole **8** in just two steps from the nitroolefin. The added acid was essential to effect debenzylation of the azole. Although this route proved very efficient, we decided to examine an alternate approach owing to the fact that nitroolefin preparation, although routine, nevertheless required 2–3 steps.

Guided by the Knoevenagel condensation approach to β-amino acids,[10] it was envisioned that a modification using a cyanotetrazole in place of cyanoacetate would afford the desired framework (Fig. 1, path b). An inspection of the literature found that this type of reagent had indeed been previously prepared and its reactivity examined.[11] Hence, it was reported that *N*-alkyl or *N*–aryl cyanotetrazoles not only underwent condensation with aldehydes, but also S_N2 addition to alkyl halides and Michael addition to ynones. With the ability to perform alkylations as well as condensations, this versatile reagent seemed highly attractive for our purposes. Reaction of malononitrile **9** with sodium azide and ammonium chloride at 80 °C, followed by regioselective tritylation,[12] afforded the appropriately protected cyanomethylated tetrazole **10** (Scheme 2). Direct nitrile reduction of **10** under acidic conditions proceeded with concomitant trityl group cleavage to furnish the tetrazolyl β-alanine derivative **11**.[13] Mild condensation of **10** with aldehydes could be carried out under phase-transfer conditions as outlined previously.[11] However, to effect condensations with ketones or substitutions of

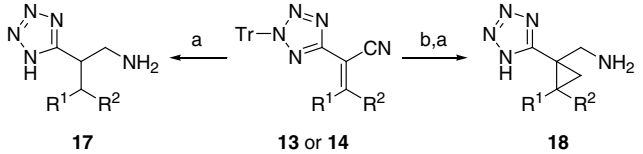


Scheme 2. Reagents and conditions: (a) NaN_3, NH_4Cl, DMF, 80 °C; (b) Ph_3CCl, Et_3N, DMF; (c) H_2, PtO_2; (d) NaH, R^1X, THF; (e) NaH, R^2X, THF; (f) NaH, ketone, THF; (g) Bu_4NBr, aldehyde, PhH, 10% NaOH (aq); (h) H_2, PtO_2, MeOH, HCl.

alkyl halides, direct deprotonation (NaH) was found to be required. If performing an S_N2 displacement, it was found that the sequence could be repeated to form quaternary cyanotetrazoles **12**. The unsaturated cyanotetrazoles **13** and **14** were somewhat sensitive but could be adequately purified by expedient (plug) chromatography on silica gel. Exhaustive reduction under acidic conditions resulted in 1,2- and 1,4-reduction of the nitrile and detritylation as for **11** to furnish the desired aminotetrazoles **15** or **16**.

As an extension of this method, we found that the unsaturated cyanotetrazoles could also be cyclopropanated using a sulfur ylide. Hence, treatment of crude condensation products **13** with the sodium anion of trimethylsulfoxonium iodide at ambient temperature followed by hydrogenation afforded the cyclopropanated aminotetrazole **18** (Scheme 3). Alternately, the unsaturated cyanotetrazoles could be directly reduced and deprotected in one pot to give **17**. The aldehyde-derived unsaturated cyanotetrazoles of type **14** also underwent smooth cyclopropanation by this method.

Unlike the SAR trends observed previously for modifications of the pregabalin backbone, subtle modifications in the β-amino tetrazole series did not have a dramatic



Scheme 3. Reagents: (a) H_2, PtO_2, MeOH, HCl; (b) trimethylsulfoxonium iodide, NaH, DMF.

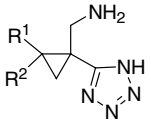
effect on α_2–δ binding using pig brain membranes[7] in the aliphatic series. Noteworthy is the fact that unsubstituted aminotetrazole **11** did not bind to α_2–δ. The direct pregabalin analog **8a** was found to be equipotent to pregabalin **1**, and the truncated structure **8b** was fourfold less potent (entries 3 and 4). However, when the methyls on the isobutyl side chain of **8a** were extended to a (2-ethyl)-butyl group, the most potent compound was obtained (cf. **16a**, 11 nM). In the aromatic series, a more predictable SAR was observed with respect to distance of the phenyl ring from the pharmacophore. Until the ring was separated from the aminotetrazole by at least three methylene units, only micromolar affinity was obtained (entries 12–17). A well seemed to be reached at the four methylene unit distance. Finally, in the quaternary series the optimal combination of substituents was found to be methyl and benzyl, optimally substituted on the ring with an electron-withdrawing group as in **15d** (entries 18–22) (Table 1).

In the case of the cyclopropyl series, the SAR tracked closely with the amino acid series reported previously. For instance, it was found that the binding of *spiro*-fused bicyclic tetrazole **18c** to α_2–δ correlated with the corresponding amino acid,[7] however with somewhat reduced potency. In the case of pregabalin-like substrates **18a**–**b**, only marginal potency was achieved. This observation was in accordance with the amino acid series, where it was found that the opposite relative orientation about the cyclopropyl ring (alkyl and carboxylate *cis*) was required to obtain low nanomolar α_2–δ potency. Not surprisingly, from the sulfur ylide the thermodynamic products containing the alkyl group *cis* to the nitrile (and subsequently the aminomethyl group) were obtained.[16] (Table 2)

Finally, the in vivo activity of this series of heterocyclic derivatives was examined. It was found that, like pregabalin **2** (but unlike γ-amino tetrazole **3**), protection of DBA/2 mice against audiogenic seizures could be achieved after oral dosing with **8a** and **16a**[17] (Table 3).

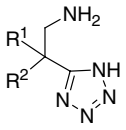
In summary, a series of heterocyclic carboxylate replacements of pregabalin **2** were prepared via two highly convergent routes. The first route employed the addition of

Table 2. α_2–δ Binding affinity of cyclopropyl tetrazoles



Entry	Compound	R^1	R^2	α_2–δ Binding (K_i, μM)
1	**18a**	$CH(CH_3)_2$	H	0.19 ± 0.019
2	**18b**	$CH(CH_2CH_3)_2$	H	4.0 ± 0.15
3	**18c**	$-CH_2CH_2CH_2CH_2CH_2-$		0.033 ± 0.007

Table 1. α_2–δ Binding affinity of β-amino tetrazoles[a]



Entry	Compound	R^1	R^2	α_2–δ Binding (K_i, μM)[b]
1	**2**	—	—	0.019 ± 0.003
2	**11**	H	H	>10
3	**8a**[14]	$CH_2CH(CH_3)_2$	H	0.017 ± 0.004
4	**8b**	$CH(CH_3)_2$	H	0.13 ± 0.016
5	**8c**	$CH_2CH_2CH(CH_3)_2$	H	0.21 ± 0.058
6	**8d**	$CH_2(CH_2)_4CH_3$	H	0.33 ± 0.058
7	**16a**	$CH_2CH(CH_2CH_3)_2$	H	0.011 ± 0.001
8	**16b**[15]	$CH_2CH(CH_2CH_2CH_3)_2$	H	0.28 ± 0.040
9	**17a**	*c*-C_5H_9	H	0.018 ± 0.003
10	**17b**	*c*-C_6H_{11}	H	0.15 ± 0.009
11	**16c**	CH_2-*c*-C_6H_{11}	H	0.57 ± 0.072
12	**8e**	Ph	H	>10
13	**16d**	CH_2Ph	H	7.6
14	**16e**	CH_2CH_2Ph	H	3.1
15	**16f**	$CH_2CH_2CH_2Ph$	H	2.1 ± 0.25
16	**16g**	$CH_2(CH_2)_2CH_2Ph$	H	0.13 ± 0.019
17	**16h**	$CH_2(CH_2)_3CH_2Ph$	H	0.50 ± 0.13
18	**15a**	CH_3	CH_3	>10
19	**15b**	CH_2Ph	CH_3	0.90 ± 0.18
20	**15c**	CH_2–*m*,*p*-di-F–C_6H_3	CH_3	0.52 ± 0.089
21	**15d**	CH_2–*m*-CF_3–C_6H_4	CH_3	0.16 ± 0.020
22	**15e**	CH_2Ph	CH_2Ph	>10

[a]For clarity, R^1 and R^2 have been modified to fit the generic structure above the table. The compound number only reflects method of preparation.
[b]Data reported as means ± SEM ($N = 4$ experiments).

Table 3. Anticonvulsant activity of **2**, **3**, **8a**, and **16a**

Compound	α_2–δ Binding (K_i, μM)	DBA/2 anticonvulsant assay (% protection)[a]	
		t = 1 h	t = 2 h
2	0.019	100	100
3	0.38	0	0
8a	0.017	40	80
16a	0.011	60	100

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

a metalated tetrazole to a nitroolefin, followed by reduction to yield β-amino tetrazoles in two steps. Alternately, a Knoevenagel-type condensation of a malononitrile-derived cyanotetrazole with carbonyl compounds afforded an intermediate that could be hydrogenated to the desired target structures. This second method obviated the need for nitroolefin preparation, and could be extended to give quaternary substituted aminotetrazoles through double alkylation. A wide range of substitution on the β-aminotetrazole template was tolerated by the α_2–δ protein, and two representative substrates **8a** and **16a** were also found to have in vivo protective activity against seizures.

References and notes

1. Burgos-Lepley, C. E.; Thompson, L. R.; Kneen, C. O.; Osborne, S. A.; Bryans, J. S.; Capiris, T.; Suman-Chauhan, N.; Dooley, D. J.; Donovan, C. M.; Field, M. J.; Vartanian, M. G.; Kinsora, J. J.; Lotarski, S. M.; El-Kattan, A.; Walters, K.; Cherukury, M.; Taylor, C. P.; Wustrow, D. J.; Schwarz, J. B. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2333.
2. Fink, K.; Dooley, D. J.; Meder, W. P.; Suman-Chauhan, N.; Duffy, S.; Clusmann, H.; Gothert, M. *Neuropharmacology* **2002**, *42*, 229.
3. Dooley, D. J.; Donovan, C. M.; Pugsley, T. A. *J. Pharmacol. Exp. Ther.* **2000**, *295*, 1086.
4. Maneuf, Y. P.; Hughes, J.; McKnight, A. T. *Pain* **2001**, *93*, 191.
5. Dooley, D. J.; Mieske, C. A.; Borosky, S. A. *Neurosci. Lett.* **2000**, *280*, 107.
6. Lauria-Horner, B. A.; Pohl, R. B. *Expert Opin. Investig. Drugs* **2003**, *12*, 663.
7. Schwarz, J. B.; Gibbons, S. E.; Graham, S. R.; Colbry, N. L.; Guzzo, P. R.; Le, V.-D.; Vartanian, M. G.; Kinsora, J.; Lotarski, S. M.; Li, Z.; Dickerson, M. R.; Su, T.-Z.; Weber, M. L.; El-Kattan, A.; Thorpe, A. J.; Donevan, S. D.; Taylor, C. P.; Wustrow, D. J. *J. Med. Chem.* **2005**, *48*, 3026.
8. (a) Herr, R. J. *Bioorg. Med. Chem.* **2002**, *10*, 3379; (b) Yuan, H.; Silverman, R. B. *Bioorg. Med. Chem.* **2006**, *14*, 1331.
9. Satoh, Y.; Marcopulos, N. *Tetrahedron Lett.* **1995**, *36*, 1759.
10. Lee, J.; Gauthier, D.; Rivero, R. A. *J. Org. Chem.* **1999**, *64*, 3060.
11. Brekhov, Y. V.; Buzilova, S. R.; Vereshchagin, L. I. *Zh. Org. Khim.* **1992**, *28*, 1921.
12. Huff, B. E.; LeTourneau, M. E.; Staszak, M. A.; Ward, J. A. *Tetrahedron Lett.* **1996**, *37*, 3655.
13. McManus, J. M.; Herbst, R. M. *J. Org. Chem.* **1959**, *24*, 1643.
14. Representative procedure for addition of lithiated tetrazole to nitroolefin and subsequent hydrogenation: To a solution of 1-benzyl-1*H*-tetrazole **4** (0.25 g, 1.56 mmol) in 7.0 mL THF at −78 °C was added *n*-butyllithium (1.6 M solution in hexanes, 1.17 mL, 1.87 mmol) slowly dropwise over 5 min until the yellow color persisted (ca. 1.0 equiv). The mixture was stirred at −78 °C for 15 min at which time 4-methyl-1-nitropent-1-ene **5a** (0.20 g, 1.56 mmol) in 1 mL THF was added dropwise. The mixture was stirred at −78 °C for 20 min, then warmed directly to ambient temperature and quenched with satd NH_4Cl (aq). The mixture was extracted with EtOAc, and the organic phase dried (Na_2SO_4) and concentrated. Flash chromatography of the residue (15%→20%→25% EtOAc/hexanes) provided 0.27 g (60%) of 1-benzyl-5-(3-methyl-1-nitromethyl-butyl)-1*H*-tetrazole **6a** as well as 0.058 g (14%) of benzyl-(3-methyl-1-nitromethyl-butyl)-cyanamide **7a** as colorless oils. Nitrotetrazole **6a**: ^{1}H NMR ($CDCl_3$) δ 7.37 (m, 3H), 7.22 (m, 2H), 5.72 (d, J = 15.6 Hz, 1H), 5.50 (d, J = 15.6 Hz, 1H), 4.69 (dd, J = 14.6, 9.8 Hz, 1H), 4.56 (dd, J = 14.6, 5.1 Hz, 1H), 3.72 (m, 1H), 1.47 (m, 2H), 1.19 (hept, J = 6.6 Hz, 1H), 0.65 (d, J = 6.6 Hz, 3H), 0.62 (d, J = 6.6 Hz, 3H). Cyanamide **7a**: ^{1}H NMR ($CDCl_3$) δ 7.37 (m, 3H), 7.31 (m, 2H), 4.51 (dd, J = 13.2, 8.8 Hz, 1H), 4.33 (dd, J = 13.2, 4.6 Hz, 1H), 4.27 (d, J = 13.7 Hz, 1H), 4.14 (d, J = 13.9 Hz, 1H), 3.72 (m, 1H), 1.60 (m, 2H), 1.28 (m, 1H), 0.86 (d, J = 6.4 Hz, 3H), 0.73 (d, J = 6.6 Hz, 3H); LRMS: m/z 262.0 (M+1). To a solution of 1-benzyl-5-(3-methyl-1-nitromethyl-butyl)-1*H*-tetrazole **6a** (1.41 g, 4.87 mmol) in MeOH (50 mL) were added 20% Pd/C (0.20 g) and concentrated HCl (0.6 g). The mixture was hydrogenated in a Parr shaker at 48 psi for 70 h, filtered, and concentrated. The residue was dissolved in 5 mL H_2O and loaded onto a plug of DOWEX-50WX4-100 ion exchange resin. The column was eluted with 100 mL H_2O, then 50 mL of 5% NH_4OH (aq), and finally with 50 mL of 10% NH_4OH (aq). The alkaline fractions were concentrated, and the solid dissolved in the minimum amount of MeOH. Precipitation with EtOAc and filtration afforded 0.33 g (40%) of 4-methyl-2-(1*H*-tetrazol-5-yl)-pentylamine **8a** as a colorless solid, mp > 240 °C (dec). ^{1}H NMR (D_2O) δ 3.31 (m, 1H), 3.10 (m, 2H), 1.53 (m, 1H), 1.35 (m, 1H), 1.03 (m, 1H), 0.66 (d, J = 6.6 Hz, 3H), 0.61 (d, J = 6.6 Hz, 3H). LRMS: m/z 168.0 (M−1). Anal. Calcd for $C_7H_{15}N_5$: C, 49.68; H, 8.93; N, 41.38. Found: C, 49.51; H, 8.90; N, 41.20.
15. Representative procedure for condensation of **10** with an aldehyde and subsequent hydrogenation: To a solution of (2-trityl-2*H*-tetrazol-5-yl)-acetonitrile **10** (2.0 g, 5.69 mmol) in 25 mL benzene were added 2-*n*-propylvaleraldehyde (0.87 g, 6.79 mmol), 25 mL of 10% NaOH (aq), and tetrabutylammonium bromide (50 mg). The mixture was stirred for 1 h and then poured into EtOAc. The phases were separated, and the organic phase dried ($MgSO_4$) and concentrated. Flash chromatography of the residue (10%→15% EtOAc/hexanes) furnished 1.66 g (64%) of 4-propyl-2-(2-trityl-2*H*-tetrazol-5-yl)-hept-2-enenitrile **14b** as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 7.34 (m, 10H), 7.09 (m, 6H), 2.86 (m, 1H), 1.30–1.59 (m, 8H), 0.90 (t, J = 7.1 Hz, 6H). To a solution of 4-propyl-2-(2-trityl-2*H*-tetrazol-5-yl)-hept-2-enenitrile **14b** (1.60 g, 3.47 mmol) in 50 mL 1:1 MeOH/THF were added PtO_2 (0.1 g), concentrated HCl (1.09 g), and the mixture was hydrogenated in a Parr shaker at 48 psi for 30 h. The mixture was filtered and concentrated. Flash chromatography of the residue on silica gel (0.25:1.25:3.5 concd NH_4OH (aq)/MeOH/CH_2Cl_2), followed by a second

column using the same conditions, yielded 0.40 g (51%) of 4-propyl-2-(1*H*-tetrazol-5-yl)-heptylamine **16b** as a colorless solid. ^{1}H NMR (D_2O) δ 3.29 (m, 1H), 3.09 (m, 2H), 1.56 (m, 1H), 1.37 (m, 1H), 0.80–1.07 (m, 9H), 0.58 (t, J = 6.6 Hz, 3H), 0.47 (t, J = 6.6 Hz, 3H). Anal. Calcd for $C_{11}H_{23}N_5$: C, 58.63; H, 10.29; N, 31.08. Found: C, 57.87; H, 10.04; N, 30.73.

16. As determined by 1D ^{1}H NMR, and 2D NOESY and COSY spectra obtained with compound **18a**.
17. (a) Schlesinger, K.; Greik, B. J. In *Contributions to Behavior-Genetic Analysis: The Mouse as a Prototype*; Lindzey, G., Theissen, D. D., Eds.; Appleton-Century-Crofts: New York, 1970; pp 219–257; (b) Seyford, T. N. *Fed. Proc.* **1979**, *38*, 2399.