Available online at www.sciencedirect.com
SCIENCE DIRECT®
ELSEVIER
Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 16 (2006) 2329–2332

Heteroaromatic side-chain analogs of pregabalin

Robert M. Schelkun, Po-wai Yuen,* David J. Wustrow, Jack Kinsora, Ti-Zhi Su and Mark G. Vartanian

PGRD Michigan Laboratories, Ann Arbor, MI 48105, USA

Received 16 February 2005; revised 27 June 2005; accepted 29 June 2005
Available online 15 August 2005

Dedicated to the memory of David W. Robertson in recognition of his outstanding accomplishments in drug discovery and research.

Abstract—A series of heteroaromatic analogs of pregabalin has been identified that possess anticonvulsant activity in the DBA/2 mouse model. The methods of synthesis and preliminary pharmacology are discussed herein.
© 2005 Elsevier Ltd. All rights reserved.

The γ-amino acid pregabalin (**1**) (Fig. 1) is known to bind to the gabapentin binding site on the α_2-δ subunit of voltage sensitive calcium channels in the CNS.[1] Binding to the α_2-δ protein by pregabalin is proposed to modulate the functional effects these proteins have on calcium currents in activated neurons[2] and on stimulated neurotransmitter release.[3] Reduced release of excitatory neurotransmitters and peptide neuromodulators (especially under conditions of hyperexcitability) is thought to account for the anticonvulsant, anxiolytic, and analgesic effects of these compounds. Pregabalin has been shown to reduce the frequency of partial seizures, reduce pain from post-herpetic neuralgia[4] and diabetic peripheral neuropathy,[5] and reduce symptoms of generalized anxiety disorder[6] in placebo-controlled studies. Sustained efficacy in these indications was associated with a favorable safety profile, with the most common side effects including dizziness and somnolence.[7]

As part of a program to identify the scope of substituents recognized by the α_2-δ protein, we were interested in replacing the isobutyl side chain of pregabalin with other groups such as aromatic or heteroaromatic rings.

The synthesis of a series of heteroaromatic-substituted analogs of pregabalin is depicted in Scheme 1. Starting with either 2 or 3-furaldehyde (**4a** and **4b**), or 3-thiophene carboxaldehyde (**4d**), and treating with either trimethylphosphono acetate or triethylphosphono acetate (1.1 equiv) and NaH in THF at 0 °C, gave the acrylic acid ester as only the (*E*) isomer (**5a**, **b**, and **d**). The double bond was reduced with H_2 (50 psi) using Wilkinson's catalyst in THF at 45 °C in the case of the furans (**5a** and **b**), and 20%Pd/C in methanol for the 3-thienyl compound (**5d**), giving **6a**, **6b**, and **6d**. The resulting saturated ester (**6a**, **6b**, **6d**) was alkylated with *tert*-butyl bromoacetate and LDA in THF at −78 °C. The methyl or ethyl ester in **7a**, **7b**, and **7d** could be selectively hydrolyzed using 1 N LiOH in THF/*i*-PrOH. The carboxylic acid in **8a**, **8b**, and **8d** was reduced to the alcohol using borane dimethyl sulfide complex in THF at 0 °C. The tosylate was obtained from the alcohol by treatment with *para*-toluenesulfonyl chloride and triethyl amine in CH_2Cl_2 at 0 °C. Conversion to the azide (**9a**, **9b**, and **9d**) was carried out using sodium azide in DMSO at 60 °C. For the furan analogs (**9a** and **9b**), the azide was selectively hydrogenated to the amine using $Pd/CaCO_3$ in EtOAc[8] prior to hydrolyzing the *tert*-butyl ester using TFA/CH_2Cl_2. The free base was isolated using ion exchange chromatography to give compounds **11a** and **11b**. For the 3-thienyl analog (**9d**), the *tert*-butyl ester was hydrolyzed first, followed by hydrogenation of the azide to the amine using 10%Pd/C in THF. The amino acid (**10d**) was recrystallized from methanol/EtOAc.

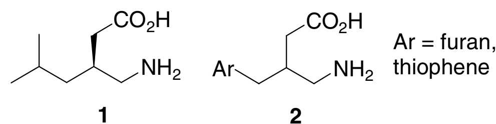
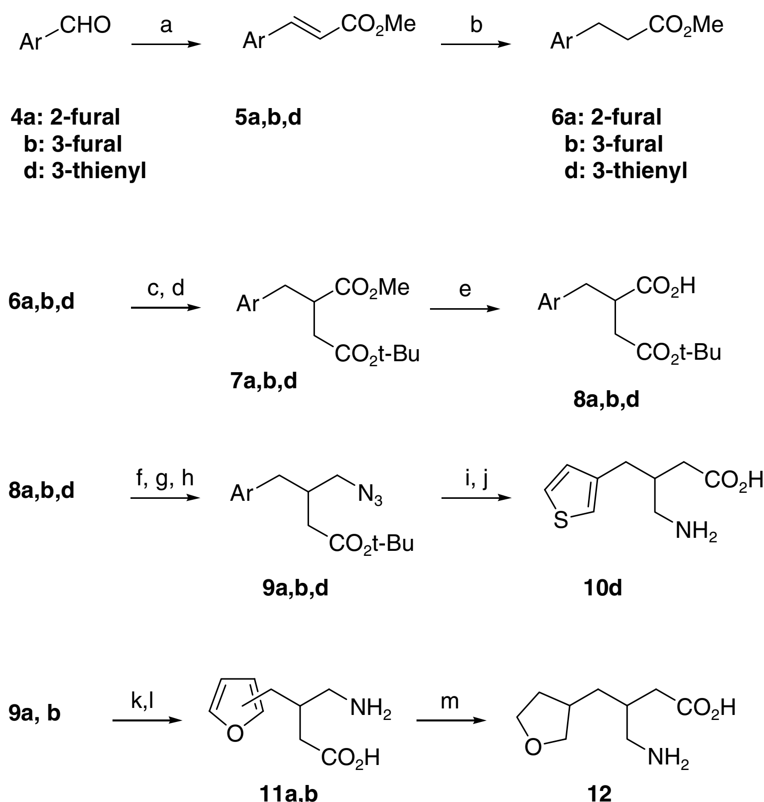


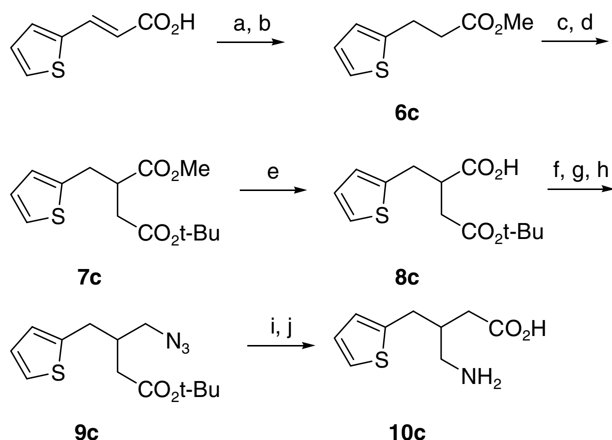
Figure 1.

* Corresponding author. Tel.: +1 734 622 1979; fax: +1 734 622 5165; e-mail: po-wai.yuen@pfizer.com

0960-894X/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2005.06.090



Scheme 1. Reagents and conditions: (a) trimethylphosphono acetate, NaH, THF, 100%; (b) Wilkinson's catalyst, H_2, THF, 45 °C, 97%, or 20% Pd/C/H_2, MeOH, 89%; (c) LDA, THF, −78 °C; (d) *tert*-butyl bromoacetate, 44–54%; (e) LiOH, H_2O, THF, *i*-PrOH, 90%; (f) $BH_3{\cdot}SMe_2$, THF, 0 °C, 55–80%; (g) TsCl, TEA, CH_2Cl_2, 90%; (h) NaN_3, DMSO, 60 °C, 85–95%; (i) TFA, CH_2Cl_2, 95%; (j) 10% Pd/C/H_2, MeOH, 60–70%; (k) 10% Pd/$CaCO_3$, EtOAc, 77%; (l) TFA, CH_2Cl_2, 100%; (m) 20% Pd/C/H_2, MeOH.

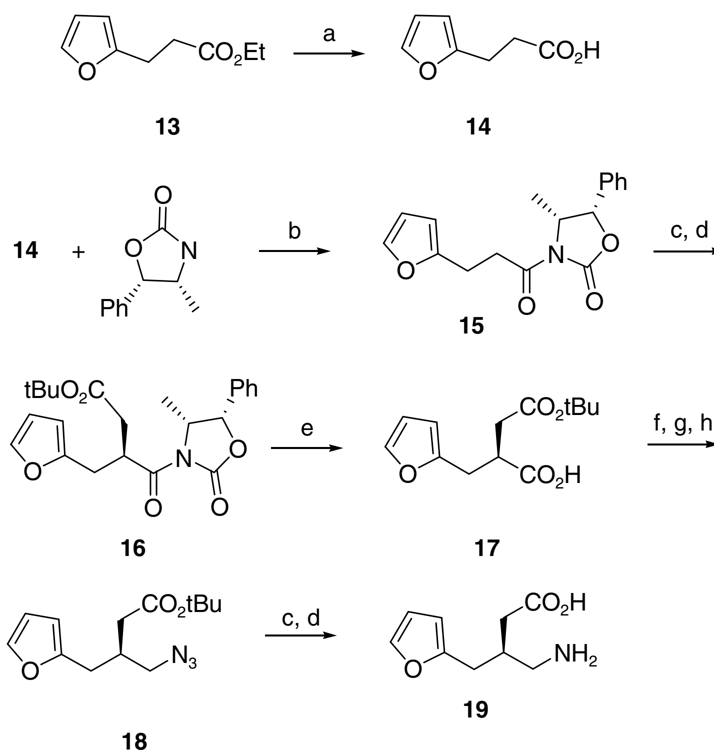


Scheme 2. Reagents and conditions: (a) 20% Pd/C/H_2, MeOH, 100%; (b) $MeCO_2Cl$, TEA, DMAP, 73%; (c) LDA, THF, −78 °C; (d) *tert*-butylbromoacetate, 54%; (e) LiOH, H_2O, THF, *i*-PrOH, 94%; (f) $BH_3{\cdot}SMe_2$, THF, 0 °C, 70%; (g) TsCl, TEA, CH_2Cl_2, 90%; (h) NaN_3, DMSO, 60 °C, 95%; (i) formic acid (88%), 30 °C, 97%; (j) 10% Pd/C/H_2, THF, 58%.

The tetrahydrofuran analog (**12**) could be obtained from the corresponding furan amine *tert*-butyl ester (**11b**) by a subsequent hydrogenation using 20% Pd/C in methanol. The final amino acid was isolated using ion-exchange chromatography.

The synthesis of the 2-thienyl analog (**10c**) is depicted in Scheme 2. Starting with commercially available 3-(2-thienyl)acrylic acid, the double bound was hydrogenated using 20%Pd/C in methanol and H_2 (50 psi). The acid was esterified using methyl chloroformate (1 equiv), triethylamine (1.1 equiv), and catalytic DMAP in CH_2Cl_2 at 0 °C to give the ester (**6c**). The saturated ester (**6c**) was alkylated with *tert*-butyl bromoacetate and LDA in THF at −78 °C. The methyl ester could be selectively hydrolyzed using 1 N LiOH in THF/*i*-PrOH. The carboxylic acid (**8c**) was reduced to the alcohol using borane dimethyl sulfide complex in THF at 0 °C. The tosylate was obtained from the alcohol by treatment with *para*-toluenesulfonyl chloride and triethyl amine in CH_2Cl_2 at 0 °C. Conversion to the azide (**9c**) was carried out using sodium azide in DMSO at 60 °C. The *tert*-butyl ester was hydrolyzed using formic acid, followed by hydrogenation of the azide to the amine using 10% Pd/C in THF, to give the amino acid (**10c**). This was purified using ion exchange chromatography.

The (*R*)- and (*S*)-enantiomers of the racemic 2-furan analog (**11a**) were synthesized stereospecifically. The synthesis used for the (*S*)-enantiomer (**19**) is shown in Scheme 3. The 3-furan-2-yl-propionic acid ethyl ester (**13**) was hydrolyzed to the acid using 1 N LiOH in THF/*i*-PrOH. The resulting acid (**14**) was coupled with the chiral auxiliary (4*R*,5*S*)-(+)-4-methyl-5-phenyl-2-oxazolidinone (1.02 equiv) using trimethylacetyl chloride (1.5 equiv)



Scheme 3. Reagents and conditions: (a) LiOH, H_2O, THF, *i*-PrOH, 100%; (b) trimethylacetyl chloride, TEA, LiCl, THF, 66%; (c) LDA, THF, −78 °C; (d) *tert*-butyl bromoacetate, 75%; (e) LiOH, H_2O_2, THF, H_2O, 78%; (f) BH_3SMe_2, THF, 0 °C, 75%; (g) TsCl, TEA, CH_2Cl_2, 95%; (h) NaN_3, DMSO, 60 °C, 90%; (i) 10% Pd/$CaCO_3$, EtOAc, 84%; (j) TFA, CH_2Cl_2, 50–70%.

and triethylamine (3.75 equiv) in THF at 0 °C. This acyl oxazolidinone (**15**) was alkylated with *tert*-butyl bromoacetate and LDA in THF at −78 °C. The desired product (**16**) was isolated as a single diastereomer as evidenced by ^{1}H NMR.[9] The chiral auxiliary was cleaved using 1 N LiOH (2 equiv) and H_2O_2 (2 equiv) in THF. This carboxylic acid *tert*-butyl ester (**17**) was then carried on to amino acid (**19**) using the previously described chemistry for the racemic analog (**11a**). The (*R*)-enantiomer (**20**) was synthesized using the (4*S*,5*R*)-(−)-4-methyl-5-phenyl-2-oxazolidione in place of the (+)-chiral auxiliary, and the same synthetic steps already described.

Compounds were tested for their ability to displace [^{3}H]gabapentin (10 nM final concentration) from the α_2-δ subunit of CNS calcium channels ([^{3}H]GPB) (Table 1) similar to previously published methods,[10] and for their potency to inhibit the uptake of [^{3}H]leucine into CHO cells.[11] System L affinity (SYS L) is thought to be important for allowing these molecules to cross the blood brain barrier. Results for these two tests are expressed as an IC_{50} ± SEM. In vivo profiling of compounds entailed evaluation of their ability to elicit anticonvulsant and anxiolytic like effects in animal models (Table 1). The DBA/2 strain of mice was used to evaluate

Table 1. In vitro and in vivo profiling of pregabalin and test compounds

HO_2C–CH_2–CH(R)–CH_2–NH_2

Compound	R	Stereochemistry	[^{3}H]GBP Binding IC_{50} (μM)[a,d]	SYS L IC_{50} (μM)[b,d]	WLC %[c]	DBA/2 % protection (2 h)
1	Isobutyl	*S*	0.073 (±0.035)	284 (±214)	100	100
3	Ph-CH_2–	—	>10,000			0
10c	2-Thienyl-CH_2–	—	2.14 (±1.38)	2936	10.3	40
10d	3-Thienyl-CH_2–	—	0.832 (±0.291)	7034	−3	60
11a	2-Furanyl-CH_2–	—	0.421 (±0.001)	10,000	5.3	20
11b	3-Furanyl-CH_2–	—	0.518 (±0.039)	1422	−17	0
19	2-Furanyl-CH_2–	*S*	0.178 (±0.031)	10,000		40
20	2-Furanyl-CH_2–	*R*	1.46 (±0.359)	10,000	0.28	0
12	3-THF-CH_2–	—	>10,000			0

[a] IC_{50} is the concentration (μM) producing half-maximal inhibition of the specific binding of [^{3}H]gabapentin to pig brain membranes.
[b] IC_{50} is the concentration (μM) producing half-maximal inhibition of the uptake of [^{3}H]Leucine in CHO cells.
[c] Activity of pregabalin at 30 mg/kg defined as 100%.
[d] Values are means of three experiments; standard deviation is given in parentheses. Values without ±SEM are from $n = 1$.

anticonvulsant activity of the compounds after inducing seizures in the mice using an audio stimulus.[12] Results are expressed as a percentage of mice protected (out of five animals) from tonic seizures 2 h post dose at 30 mg/kg administered orally. The anxiolytic effect of compounds was evaluated by measuring their ability to reverse shock-induced suppression of drinking in the Vogel water lick conflict assay (WLC %) in rats at a dose of 30 mg/kg administered orally.[13] Activity in this assay is expressed as a percentage of pregabalin's ability to restore punished drinking behavior at a dose of 30 mg/kg.

Compared to pregabalin, the phenyl analog[14] (**3**) was completely inactive in the α_2-δ assay, as well as the DBA/2 model. Surprisingly, replacement of the phenyl group with either a furan or thiophene ring resulted in compounds with α_2-δ binding affinity. Activity in the α_2-δ binding assay followed the trend 2-furan ~ 3-furan > 3-thiophene > 2-thiophene. The 3-THF analog (**12**) was inactive. While a number of compounds (**10d**, **11a**, **11b**, and **19**) possessed sub-micro molar binding, none of the compounds had better binding than pregabalin (**1**). All of the compounds tested in the System L assay were extremely weak when compared to pregabalin (**1**). The 2-fural analog (**11a**) was chosen for stereoselective synthesis of its enantiomers based on its α_2-δ binding, and consistent with the stereochemistry of pregabalin, the (*S*)-enantiomer (**19**) was more potent in the α_2-δ assay.[9] In the DBA/2 mouse model, the 3-thienyl analog (**10d**) was most active, followed by the 2-thienyl analog (**10c**) and the 2-fural analog (**10b**).

Consistent with what was observed with α_2-δ binding, the (*S*)-enantiomer (**19**) was more active in the DBA/2 model than the corresponding (*R*)-enantiomer (**20**). In the WLC anxiety model, the compounds tested were all devoid of any anxiolytic properties relative to pregabalin. It is believed that the poor System L binding affinity of these compounds accounts for their poor in vivo activity when compared to pregabalin (**1**).

In summary, a series of novel analogs of pregabalin have been synthesized where the isobutyl side chain in pregabalin has been replaced with a heteroaromatic group. These compounds showed activity in both in vitro and animal models. Surprisingly, only the furan and thiophene replacements possessed biological activity, albeit it modest when compared to pregabalin, whereas the phenyl and THF replacements were completely inactive both in vitro and in vivo. These results were unexpected given the inactivity of phenyl analog (**3**). While none of the compounds synthesized possessed a better biological profile than pregabalin, they do provide an expanded understanding of the SAR requirements for future development.

Acknowledgments

The authors wish to acknowledge the late Stephen Johnson for synthesizing the phenyl analog **3**, Nirmala Suman-Chauhan for providing the α_2-δ binding data, and Don Johnson for running the hydrogenation reactions.

References and notes

1. (a) Gee, N. S.; Brown, J. P.; Dissanayake, V. U. K.; Offord, J.; Thurlow, R.; Woodruff, G. N. *J. Biol. Chem.*, *271* 5768; (b) Marias, E.; Klugbauer, N.; Hofmann, F. *Mol. Pharmacol.* **2001**, *59*, 1243.
2. (a) Martin, D. J.; McClelland, D.; Herd, M. B.; Sutton, K. G.; Hall, M. D.; Lee, K.; Pinnock, R. D.; Scott, R. H. *Neuropharmacology* **2002**, *42*, 353; (b) Sutton, K. G.; Martin, D. J.; Pinnock, R. D.; Lee, K.; Scott, R. H. *Br. J. Pharmacol.* **2002**, *135*, 257; (c) Stefani, A.; Hainsworth, A. H. *Curr. Neuropharmacol.* **2003**, *1*, 237.
3. Dooley, D. J.; Donovan, C. M.; Pugsley, T. A. *J. Pharmacol. Exp. Ther.* **2000**, *295*, 1086.
4. Hill, C. M.; Balkenohl, M.; Thomas, D. W.; Walker, R.; Mathe, H.; Murray, G. *Eur. J. Pain* **2001**, *5*, 119.
5. Rosenstock, J.; Tuchman, M.; LaMareaux, L.; Sharma, U. *Pain* **2004**, *110*, 628.
6. Pande, A. C.; Crockatt, J. G.; Feltner, D. E.; Janney, C. A.; Smith, W. T.; Weisler, R.; Londborg, P. D.; Bielski, R. J.; Zimbroff, D. L.; Davidson, J. R. *Am. J. Psychiat.* **2003**, *160*, 533.
7. Lauria-Horner, B. A.; Pohl, R. B. *Expert Opin. Invest. Drugs* **2003**, *12*, 663.
8. The 3-furan **9b** gave a mixture of desired furan-amine and THF-amine, which could be separated by chromatography. For the 2-furan **9a**, no reduction of the furan was observed.
9. Stereochemistry assigned based on previously published results on the chiral synthesis of pregabalin: Yuen, P.-W.; Kanter, G. D.; Taylor, C. P.; Vartanian, M. G. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 823.
10. Suman-Chauhan, N.; Webdale, L.; Hill, D. R.; Woodruff, G. N. *Eur. J. Pharmacol., Mol. Pharmacol.* **1993**, *244*, 293.
11. Su, T.-Z.; Lunney, E.; Campbell, G.; Oxender, D. *J. Neurochem.* **1995**, *64*, 2125.
12. (a) Schlesinger, K.; Greik, B. J. The Genetics and Biochemistry of Audiogenic Seizures. In *Contributions to Behavior-Genetic Analysis: The Mouse as a Prototype*; Lindzey, G., Theissen, D. D., Eds.; Appleton-Centruy-Crofts: New York, 1970, pp 219–257; (b) Seyford, T. N. *Fed. Proc.* **1979**, *38*, 2399.
13. Milan, M. J. *Prog. Neurobiol. (Amsterdam, Netherlands)* **2003**, *70*, 83.
14. Kori, S.; Tokuhisa, T. JP Patent 45,028,769.