Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters 17 (2007) 662–667
Bioorganic & Medicinal Chemistry Letters

Synthesis and SAR of novel 2-arylthiazolidinones as selective analgesic N-type calcium channel blockers

Lars J. S. Knutsen,* Christopher J. Hobbs, Christopher G. Earnshaw, Andrea Fiumana, Jenny Gilbert, Sarah L. Mellor, Fleur Radford, Nichola J. Smith, Philip J. Birch, J. Russell Burley, Stuart D. C. Ward and Iain F. James

Ionix Pharmaceuticals Ltd,† 418 Cambridge Science Park, Milton Road, Cambridge CB4 0PA, UK

Received 23 June 2006; revised 30 October 2006; accepted 31 October 2006
Available online 6 November 2006

Abstract—A series of new N-type ($Ca_v2.2$) calcium channel blockers derived from the 'hit' structures 2-(3-bromo-4-fluorophenyl)-3-(2-pyridin-2-ylethyl)thiazolidin-4-one **9** and its 2-[4-(4-bromophenyl)pyridin-3-yl]-3-isobutyl analogue **10** is described. Extensive SAR studies using a range of synthetic approaches resulted in novel, patented compounds with IC_{50} values of up to 0.2 μM in an in vitro IMR32 assay, and selectivities for N/L of up to 30-fold. The new compounds described have potential in treatment of neuropathic pain.

Ion channel blockers are attractive drug targets for an expanding range of therapeutic indications[1] and voltage-dependent Ca^{2+} channels play important roles in critical biological processes.[2] Based on their pharmacological and electrophysiological properties the channels have been classified into several subtypes: N- ($Ca_v2.2$), L- ($Ca_v1.1$-$Ca_v1.4$), P/Q- ($Ca_v2.1$), R- ($Ca_v2.3$) and T-type ($Ca_v3.1$-$Ca_v3.3$). These targets for therapeutic intervention play specialised roles in cellular function.[3,4]

N-type channels are located primarily at pre-synaptic nerve terminals and mediate spinal transmission of pain signals from the periphery to the central nervous system (CNS) by modulating release of nociceptive neuro-transmitters and neuropeptides.[4] Selective Ca^{2+} channel blockers in particular are now emerging as prospective therapeutics for the treatment of neuropathic and inflammatory pain.[5] Mice lacking N-type channels show suppressed response to painful stimuli that induce inflammation, and show reduced neuropathic pain symptoms. This provides evidence that N-type channels may be essential for development of neuropathic pain, that is, pain associated with nerve injury, and control of N-type activity is important in the management of pain.[6]

The recently approved pain drug Ziconotide (Prialt™) is a potent blocker of N-type Ca^{2+} channels.[7] Pre-clinical and clinical studies of Ziconotide conclude that selective blockade of the N-type channel is effective in reducing inflammatory and neuropathic pain in humans.

The market for Ziconotide may be restricted by the need for intrathecal delivery of this new peptide drug, and by a range of neurological and cardiovascular side-effects.[8]

Gabapentin **1** (Fig. 1) was the first drug approved for post-herpetic neuralgia treatment. The cyclic amino acid **1** and Pregabalin **2** are ligands at the $\alpha_2\delta$ domain of $Ca_v2.2$, stimulating interest in Ca^{2+} channels as pain drug targets.[9,10] Flunarizine[11] **3** and Lomerizine[12] **4**, known as L-type ligands, exhibit N-type blockade (Table 1). Given this promising target, we started a search for novel drug-like analgesic N-type blockers.

The objective of Ionix's N-type drug discovery programme was to identify orally active selective small molecule N-type blockers with an acceptable therapeutic index for the treatment of chronic pain. Several patented compounds are claimed to be selective N-type blockers. Examples include NMED 39-45-3 **5** and cinnarizine analogue MC 34D **7**, from a Neuromed piperazine

Keywords: N-type calcium channel; Analgesia; Thiazolidinone.
* Corresponding author. Tel.: +1 610 738 6505; fax: +1 610 738 6558; e-mail: LKnutsen@cephalon.com
† Vernalis PLC, 613 Reading Road, Winnersh, RG41 5UA, UK (www.vernalis.com) acquired Ionix Pharmaceuticals, July 2005.

0960-894X/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2006.10.098

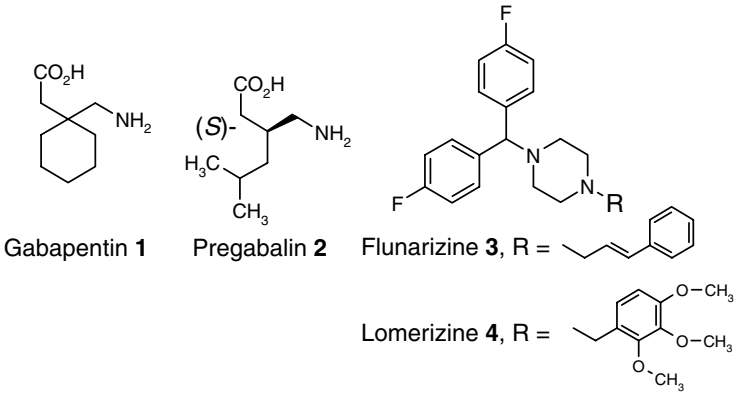
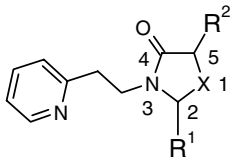


Figure 1. Structures of reference calcium channel modulators.

Table 1. IC_{50} values for 3-(2-pyridin-2-ylethyl)thiazolidine-4-ones in the IMR32 assay[23]



Compound	R^1	R^2	X	N-type IC_{50} (μM)	L-type IC_{50} (μM)	Ratio L-type/N-type
9	3-Br, 4-F–Ph	H	S	1.68	9.51	5.6
26	3-CF_3–Ph	H	S	2.41	11.5	4.8
23	3-Br, 4-F–Ph	*N*-^{i}Bu-acetamide	S	1.34	2.92	2.2
27	3-CF_3–Ph	*N*-^{i}Bu-acetamide	S	1.29	2.08	1.6
28	3-Br, 4-F–Ph	H	SO_2	8.13	>30	—
29	3-Br, 4-F–Ph	H	S=O	29.8	>30	—
3	—	—	—	1.67	0.78	0.5
4	—	—	—	2.43	1.48	0.6

series,[13] as well as the amide **6** with in vivo activity in pain models.[14] The quinoline **8** has reported activity in the late stage formalin paw pain model.[15] We noted the structural diversity in Figure 2, and sought differing starting points as leads in our search for novel blockers.

We utilised a high-throughput in vitro fluorescence-based assay to assess IC_{50} values for blockade of both N- and L-type channels in a human neuroblastoma cell line, IMR32, essentially in a single assay.[16] Evaluation of the Ionix corporate compound library identified 2-arylthiazolidinones, including **9** and **10**, as promising N-type blockers, and both were selected as promising screening 'hit' structures for elaboration of SAR (Fig. 3).

Very few thiazolidinones modulating ion channels are known. Compound **11** is one of a series of Na^+ channel blockers[17] and CP-060S **12** is an anti-ischaemic with Ca^{2+} overload inhibition and antioxidant activity.[18] Thiazolidinones with K^+ modulation are known.[19] Given promising in vitro activity and selectivity of **9** and **10** in the IMR32 assay (Tables 1 and 2), we embarked on a detailed SAR study of 2-arylthiazolidinones. Tables 1–4 summarise SAR studies, focusing on structural features aiming to provide selectivity for N-type over L-type calcium channels, and represent a major chemistry effort. Experimental detail has already been published.[20]

The carbinol **14**, derived from **13**, was converted into the nicotinaldehyde **15** utilising a Vilsmeier reagent, followed by ammonium acetate-induced cyclisation.[21] Aldehyde **15** was cyclocondensed with mercaptoacetic acid and isobutylamine to provide target **10** (Scheme 1).

The intermediate **18** was prepared from aldehyde **17** available from formylation of **16**.[21] Suzuki coupling of **18** with 4-CF_3-phenylboronic acid provided **19** (Scheme 2). A higher yielding method for synthesis of **19** is via aldehyde **21**; Suzuki coupling[22] of **21** afforded **22** and cyclocondensation provided **19**. Syntheses of related thiazolidinones are illustrated in Scheme 3 and 4.

Thiazolidinone **9** proved to be one of the more selective examples with a selectivity ratio for the N-/L-type of >5, with promising solubility and physical properties. However, N-type potency of >1 μM was not improved in any of the analogues of **9** in Table 1, and dropped away markedly upon oxidation of the sulfur. Selectivity could not be readily improved, even by probing neighbouring areas of the binding site with bulky R^2 groups at the thiazolidinone 5-position, for example, the acetamide **23** (Scheme 3).

We opted therefore to focus on an SAR study around 2-[4-(4-bromo-phenyl)pyridin-3-yl]-3-isobutylthiazolidin-4-one **10**, which proved to be robustly selective with an

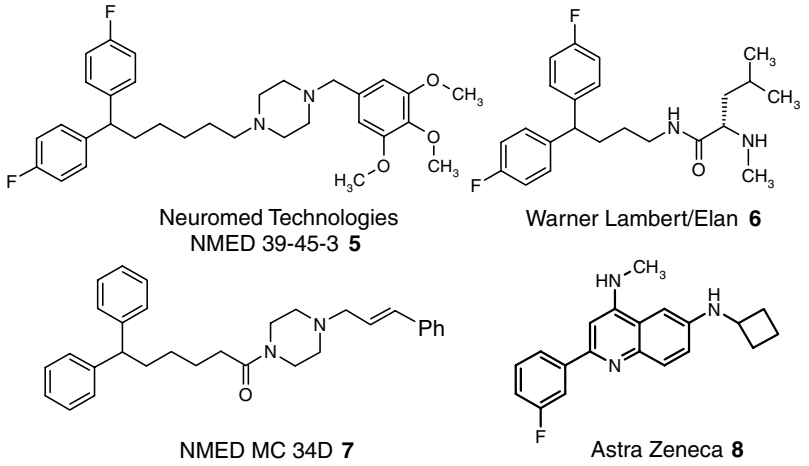


Figure 2. Structures of reference N-type blockers.

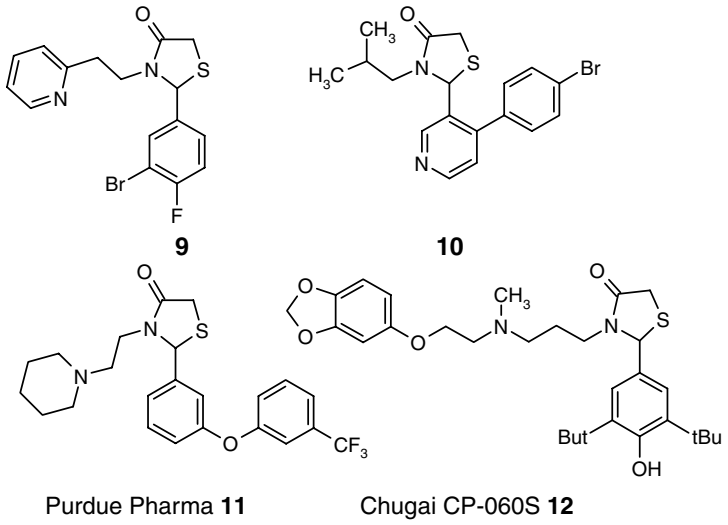
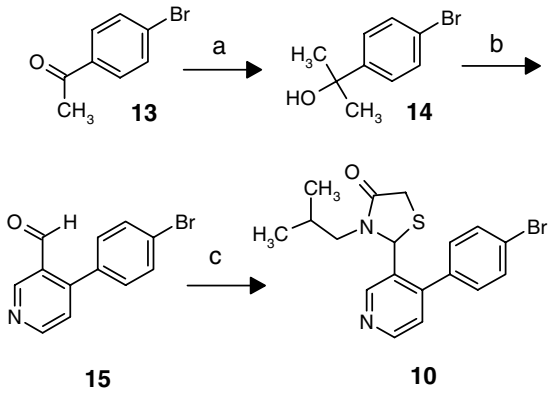


Figure 3. Structures of reference and 'hit' thiazolidin-4-ones.



Scheme 1. Reagents and conditions: (a) MeMgI, C_6H_6, 0 °C, 80%; (b) i—$POCl_3$, DMF, 0–60 °C, 18 h; ii—NH_4OAc, 60 °C, 39%; (c) $HSCH_3CO_2H$, isobutylamine, C_6H_6, 70 °C, 18 h, 99%.

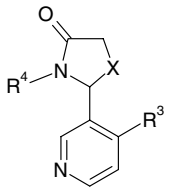
N/L ratio of 12 (Table 2). It was possible to retain selectivity by altering substituents at the 3-position, replacing the isobutyl group in **10** progressively by 2-butyl, cyclopropyl, cyclopentyl and cyclohexyl. The 2-butyl derivative **30** exhibited the highest potency at the N-type channel in this whole series (IC_{50} 210 nM); and cyclopentyl **32** retained good selectivity (>16) while the selectivity of cyclohexyl derivative **33** fell away.

We next replaced 4-bromophenyl with alternative aryl functions while retaining an *N*-isobutyl; potency and selectivity was retained in 4-toluyl, 4-ethenylphenyl and 4-CF_3-phenyl derivatives. When sulfur was replaced by sulfinyl or oxygen, the potency fell away.

2-[3-(4-Bromophenyl)pyridin-4-yl]-3-isobutylthiazolidin-4-one **41**, the pyridine-4-yl isomer of **10**, showed similar properties to of its parent, so SAR of these analogues was elucidated (Table 3). In contrast to the 3-pyridyl series, simple replacement of bromine with chlorine did not decrease selectivity, and beneficial changes in terms of selectivity were 4-methoxy-, 4-methyl- and 4-ethenylphenyl.

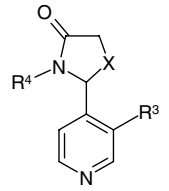
Unlike the 3-pyridyl series, *N*-cyclopentyl in place of isobutyl did not confer any improvement, and was deleterious to activity when a basic substituent such as 4-dimethylamino was introduced in place of bromine.

Table 2. IC_{50} values for (4-phenylpyridin-3-yl)-thiazolidine-4-ones



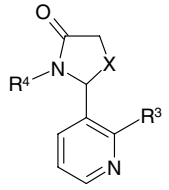
Compound	R^3	R^4	X	N-type IC_{50} (μM)	L-type IC_{50} (μM)	Ratio L-type/N-type
10	4-Br–Ph	Isobutyl	S	0.66	8.41	12.8
30	4-Br–Ph	2-Butyl	S	0.21	2.33	11.2
31	4-Br–Ph	Cyclopropyl	S	1.30	4.69	3.6
32	4-Br–Ph	Cyclopentyl	S	0.63	10.3	16.3
33	4-Br–Ph	Cyclohexyl	S	1.32	2.01	1.5
34	Ph	Isobutyl	S	3.98	16.4	4.1
35	4-Cl–Ph	Isobutyl	S	0.60	2.18	3.6
36	4-F–Ph	Isobutyl	S	1.29	6.66	5.2
37	4-CH_3–Ph	Isobutyl	S	0.49	8.20	16.7
38	4-Ethyl-Ph	Isobutyl	S	0.88	5.54	6.3
39	4-Ethenyl-Ph	Isobutyl	S	0.51	9.99	19.5
19	4-CF_3–Ph	Isobutyl	S	1.07	10.3	9.6
40	4-Br–Ph	Isobutyl	S=O	3.97	15.0	3.8
24	4-Br–Ph	Isobutyl	O	4.42	29.3	6.6

Table 3. IC_{50} values for (3-phenylpyridin-4-yl)thiazolidinones

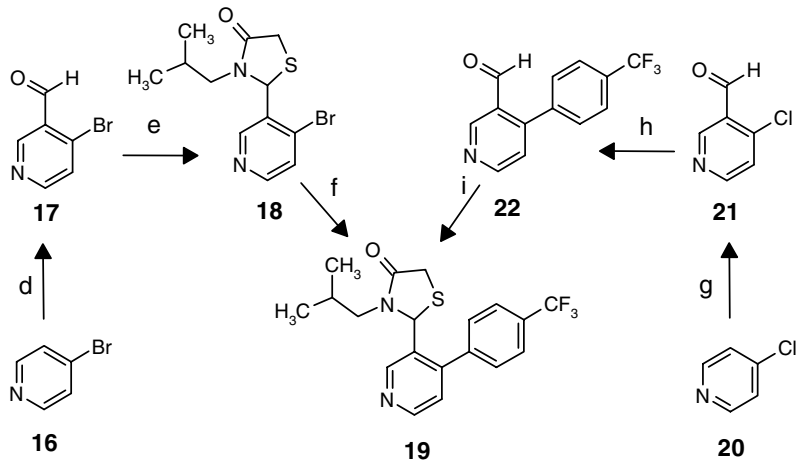


Compound	R^3	R^4	N-type IC_{50} (μM)	L-type IC_{50} (μM)	Ratio L-type/N-type
41	4-Br–Ph	Isobutyl	0.50	3.08	6.1
42	4-Cl–Ph	Isobutyl	0.58	4.58	7.9
43	4-F–Ph	Isobutyl	4.15	11.7	2.8
44	4-CH_3O–Ph	Isobutyl	1.40	13.7	9.5
45	4-CH_3–Ph	Isobutyl	0.59	8.03	13.6
46	4-Ethenyl-Ph	Isobutyl	0.53	4.16	7.8
47	4-(CH_3)N–Ph	Cyclopentyl	10.7	18.2	1.7
48	4-(CF_3)–Ph	Cyclopentyl	1.37	4.25	3.1

Table 4. IC_{50} values for (2-phenylpyridin-3-yl)thiazolidinones



Compound	R^3	R^4	N-type IC_{50} (μM)	L-type IC_{50} (μM)	Ratio L-type/ N-type
49	4-Br–Ph	Isobutyl	0.70	6.20	8.9
50	4-Cl–Ph	Isobutyl	1.26	7.49	5.9
51	4-F–Ph	Isobutyl	4.92	12.9	2.6
52	4-MeO–Ph	Isobutyl	8.93	20.6	2.3
53	4-Me–Ph	Isobutyl	1.96	12.5	6.4
54	4-(CF_3)–Ph	Isobutyl	0.56	5.44	9.7
55	4-Ethenyl-Ph	Isobutyl	1.33	4.23	3.2

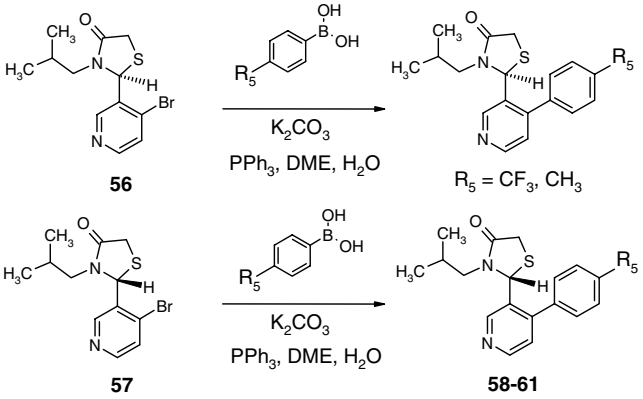


Scheme 2. Reagents and conditions: (d) i—LDA, THF, −78 °C, 30 min; ii—DMF, −78 °C, 15 min, to rt 25%; (e) $HSCH_3CO_2H$, isobutylamine, C_6H_6, 70 °C, 18 h, 41%; (f) 4-$CF_3PhB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3 aq, DME, 85 °C, 18 h, 29%; (g) i—LDA, THF, −78 °C, 1.5 h; ii—*N*-CHO-piperidine, −78 °C, 1 h, 63%; (h) 4-$CF_3PhB(OH)_2$, $Pd(OAc)_2$, PPh_3, K_2CO_3 aq, DME, 85 °C, 18 h, 81%; (i) $HSCH_3CO_2H$, isobutylamine, $(EtO)_3CH$, C_6H_6, 80 °C, 75%.

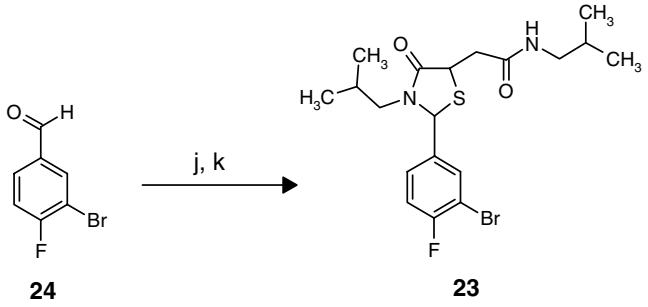
In the series featuring 2-[2-(4-bromophenyl)pyridin-3-yl]-3-isobutylthiazolidin-4-ones (Table 4), no real improvement in potency was recorded despite changing the aromatic functionality at the pyridyl 2-position.

Thiazolidinones prepared by the methods outlined in Schemes 1–4 are racemic mixtures. In order to compare the N-type selectivity and potency between enantiomers, racemic intermediate **18** was separated by chiral LC[24] to provide the enantiomers **56** and **57**, which were converted into enantiomerically pure compounds **58–61** (Scheme 5).

It is clear from Table 5 that there are large differences in in vitro activity between enantiomers, illustrated by the



Scheme 5. Synthesis of single enantiomer sets of **19** and **37**.

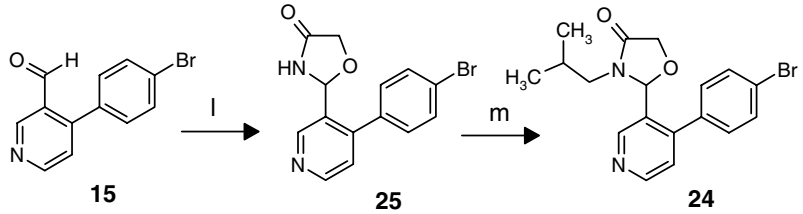


Scheme 3. Reagents and conditions: (j) mercaptosuccinic acid, 2-(2-aminoethyl)pyridine, C_6H_6, 80 °C, 18 h, 82%; (k) i—isobutylamine, EDC, HOBT, NEM, THF, 40 °C, 18 h; ii—HCl, Et_2O, rt, 56%.

Table 5. IC_{50} values for single enantiomer 3-(4-phenylpyridin-3-yl)-thiazolidine-4-ones

Compound	R_5	N-type IC_{50} (μM)	L-type IC_{50} (μM)	Ratio L-type/N-type
58	4-CF_3	3.32	12.9	3.9
59	4-CF_3	0.77	22.9	29.1
60	4-CH_3	4.44	12.9	2.9
61	4-CH_3	0.73	23.2	31.8

selectivity of **59** and **61**, both of which are derived from the same precursor single enantiomer of **18**. Compounds **59** and **61** exhibit a selectivity ratio for N-/L-type of



Scheme 4. Reagents and conditions: (l) glycolamide, $BF_3{\cdot}OEt_2$, THF, 65 °C, 48 h, 85%; (m) NaH, 1-Br-2-CH_3-propane, DMF, 70 °C, 18 h, 43%.

~30, and represent the most selective examples in this series of thiazolidinone N-type Ca^{2+} channel blockers.

In conclusion, we have identified a series of novel 3-arylthiazolidin-4-ones derived from the initial HTS 'hits' **9** and **10**. By analysis of SAR, we have identified compound **30** (Table 2) as the most potent, and single enantiomer **61** (Table 5) as the most selective compounds in this series. These compounds show promise as lead structures in the quest for clinically effective N-type blockers in the treatment of pain.

References and notes

1. Gribkoff, V. K.; Starrett, J. E. *Expert Opin. Pharmacother.* **1999**, *1*, 61.
2. Cox, B.; Denyer, J. C. *Expert Opin. Ther. Patents* **1998**, *8*, 1237; Elmslie, K. S. *J. Neurosci. Res.* **2004**, *75*, 733.
3. Spafford, J. D.; Zamponi, G. W. *Curr. Opin. Neurobiol.* **2003**, *13*, 308.
4. Catterall, W. A. *Cell Calcium* **1998**, *24*, 307.
5. Dickenson, A. H.; Matthews, E. A.; Diaz, A. M. *Pain* **2003**, 619; Sabido-David, C.; Faravelli, L.; Salvati, P. *Expert Opin. Investig. Drugs* **2004**, *13*, 1249; McGivern, J. G.; McDonough, S. I. *Curr. Drug Targets CNS Neurol. Disord.* **2004**, *3*, 457.
6. Saegusa, H.; Kurihara, T.; Zong, S.; Kazuno, A.; Matsuda, Y.; Nonaka, T.; Han, W.; Toriyama, H.; Tanabe, T. *EMBO J.* **2001**, *20*, 2349.
7. Miljanich, G. P. *Curr. Med. Chem.* **2004**, *11*, 3029; Matthews, E. A.; Dickenson, A. H. *Pain* **2001**, *92*, 235.
8. Atanassoff, P. G.; Hartmannsgruber, M. W. B.; Thrasher, J.; Wermeling, D.; Pharm, D.; Longton, W.; Gaeta, R.; Singh, T.; Mayo, M.; McGuire, D.; Luther, R. R. *Reg. Anesth. Pain. Med.* **2000**, *25*, 274.
9. Sills, G. J. *Curr. Opin. Pharmacol.* **2006**, *6*, 108;; Canti, C.; Davies, A.; Dolphin, A. C. *Curr. Neuropharmacol.* **2003**, *1*, 209.
10. Stahl, S. M. *J. Clin. Psychiatry* **2004**, *65*, 1033.
11. Pauwels, P. J.; Leysen, J. E.; Janssen, P. A. J. *Life Sci.* **1991**, *48*, 1881.
12. Hara, H.; Morita, T.; Sukamoto, T.; Cutrer, F. M. *CNS Drug Rev.* **1995**, *1*, 204.
13. Snutch, T. P. PCT Int. Appl. WO 01/45709, 2001; *Chem. Abstr.* **2001**, *135*, 61354.
14. Song, Y.; Bowersox, S. S.; Connor, D. T.; Dooley, D. J.; Lotarski, S. M.; Malone, T.; Miljanich, G.; Millerman, E.; Rafferty, M. F.; Rock, D.; Roth, B. D.; Schmidt, J.; Stoehr, S.; Szoke, B. G.; Taylor, C.; Vartanian, M.; Wang, Y.-X. *J. Med. Chem.* **2000**, *43*, 3474.
15. Chapdelaine, M.; Kemp, L.; McCauley, J. PCT Int. Appl. WO 02/36567, 2002; *Chem. Abstr.* **2002**, *136*, 369614.
16. Takahara, A.; Fujita, S.; Moki, K.; Ono, Y.; Koganei, H.; Iwayama, S.; Yamamoto, H. *Hypertens. Res.* **2003**, *26*, 743.
17. Sun, Q.; Tafesse, L.; Limberis, J. T.; Islam, K.; Kyle, D. J. *Comb. Chem. High Throughput Screening* **2003**, *6*, 481; Sun, Q.; Kyle, D. J. PCT Int. Appl. WO 03/008398, 2003; *Chem. Abstr.* **2003**, *138*, 131144.
18. Kato, T.; Ozaki, T.; Tamura, K.; Suzuki, Y.; Akima, M.; Ohi, N. *J. Med. Chem.* **1999**, *42*, 3134.
19. Castle, N. A.; Gross, M.; Mendoza, J. S. PCT Int. Appl. WO 99/62891, 1999; *Chem. Abstr.* **1999**, *132*, 12317.
20. Knutsen, L. J. S.; Hobbs, C. J.; Radford, F.; Fiumana, A. PCT Int. Appl. WO 04/17965, 2004; *Chem. Abstr.* **2004**, *140*, 217639; Knutsen, L. J. S.; Hobbs, C. J.; Radford, F.; Fiumana, A.; Earnshaw, C. G.; Mellor, S. L.; Smith, N. J. PCT Int. Appl. WO 04/17966, 2004; *Chem. Abstr.* **2004**, *140*, 217640.
21. Thomas, A. D.; Asokan, C. V. *J. Chem. Soc., Perkin Trans. 1* **2001**, *20*, 2583.
22. Lohse, O.; Thevenin, P.; Waldvogel, E. *Synlett* **1999**, *1*, 45.
23. Reference compound data in the IMR32 assay were obtained as the following pIC_{50} values: ω-Conotoxin GVIA: 8.42 ± 0.22 at N-type, no measurable block at L-type. Nimodipine: 4.97 ± 0.26 at N-type and 7.87 ± 0.27 at L-type. See Ward, S. D. C.; Hick, C. A.; Thomas, D. Online Abstract Viewer/Itinerary Planner, Society for Neuro-science Annual Meeting, New Orleans, Louisiana, November 8–12, 2003; Society for Neuroscience, Washington, DC; Program No. 165.7.
24. The HPLC separation method utilised was Chiralpak® 50801 (20 μm) as chiral stationary phase. Mobile phase CH_3OH; UV detection at 280 nm. Analysis conditions: Chiralcel® OD-H; mobile phase—95% heptane/5% isopropanol; UV detection at 225 nm. Flow rate—1 ml/min, at 25 °C.