Tetrahedron Letters 52 (2011) 1303–1305

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An expedient atom-efficient synthesis of the cannabinoid CB_1 receptor inverse agonist ibipinabant

Jos H. M. Lange *, Hans J. Sanders, Jeroen van Rheenen

Abbott Healthcare Products B.V., Chemical Design & Synthesis Unit, C.J. van Houtenlaan 36, 1381 CP Weesp, The Netherlands

ARTICLE INFO

Article history:
Received 16 November 2010
Revised 21 December 2010
Accepted 14 January 2011
Available online 21 January 2011

ABSTRACT

A novel synthetic route to the highly selective and orally active cannabinoid CB_1 receptor inverse agonist ibipinabant is described which combines the use of inexpensive, commercially available reagents and mild reaction conditions with a high degree of atom-efficiency. The method is expected to enable the rapid synthesis of a variety of sulfonylguanidines.

The endocannabinoid system plays a key role in many physiological processes.[1] Moreover, cannabinoid CB_1 receptor antagonists/inverse agonists have shown clinical efficacy in the treatment of obesity and related cardiovascular and metabolic risk factors,[2,3] and have been related[4,5] to the potential treatment of addiction,[6,7] cognitive disorders[8] and peripherally mediated disorders, such as liver fibrosis, cancer, arthritis and chronic bronchitis. However, the risk of psychiatric side-effects has led to the termination[9] of many developmental programmes on CB_1 receptor blockers for the treatment of obesity. More recently, suggestions have been made aimed at possible therapeutic applications in peripheral pathologies[10] and continuation of obesity clinical trials, while safeguarding the safety of patients and clinical trial subjects.[11] The majority of the reported[12–14] CB_1 receptor antagonists and inverse agonists can be described in terms of a general pharmacophore model.[15–19]

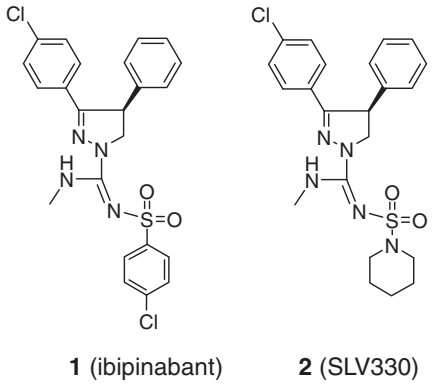
The dihydropyrazole derivative **1** (ibipinabant, SLV319)[20] is a thousand-fold CB_1/CB_2 selective and an orally active cannabinoid CB_1 receptor inverse agonist which constitutes an important pharmacological tool for investigation of the physiological role of the cannabinoid CB_1 receptor in vitro and in vivo (Fig. 1). It should also be noted that **1** showed negligible off-target activities in a panel of more than hundred receptor and enzyme biological targets.

Several synthetic approaches to **1**[20] and **2** (SLV330)[21] and structural analogues[22–24] have been reported, and routes to general structure **3** are summarized in Scheme 1.[20–22] Typically, the key building block **4** was coupled with various electrophilic reagents **5**–**7** to furnish intermediates **8**–**10**, respectively, which were further converted into the racemic CB_1 inverse agonists of general formula **3**.

Although the routes outlined in Scheme 1 are well-suited to produce pyrazolines, such as **1** and **2** on small scale under laboratory conditions, the use of corrosive and highly toxic reagents (e.g., $HgCl_2$) has rendered them less useful for synthesis on a larger scale. For example, in the described[20] synthetic route to **1**, the corrosive chlorinating agent PCl_5 was used at reflux temperature in chlorobenzene. At elevated temperatures, PCl_5 is known to slowly decompose into PCl_3 and highly toxic chlorine gas. Large scale use of such compounds would create considerable safety hazards.

A novel synthetic route to pyrazoline derivatives of the more general formula **3**, under milder reaction conditions, would enable the inclusion of additional sensitive functionalities without the need for complicated protecting group strategies. Furthermore, it should be emphasized that the efficient synthetic methods are characterized by a high degree of atom economy,[25] that is, the maximum number of atoms from the reactants appearing in the product.

The above mentioned considerations prompted the design of a general and easily scalable route toward sulfonylguanidines,[26] in particular those in which one of the guanidine nitrogen atoms is part of a heterocyclic ring,[27] such as **1** and **2**, combining the use of mild reaction conditions and inexpensive, commercially available reactants with a high degree of atom-efficiency.[28] Such an

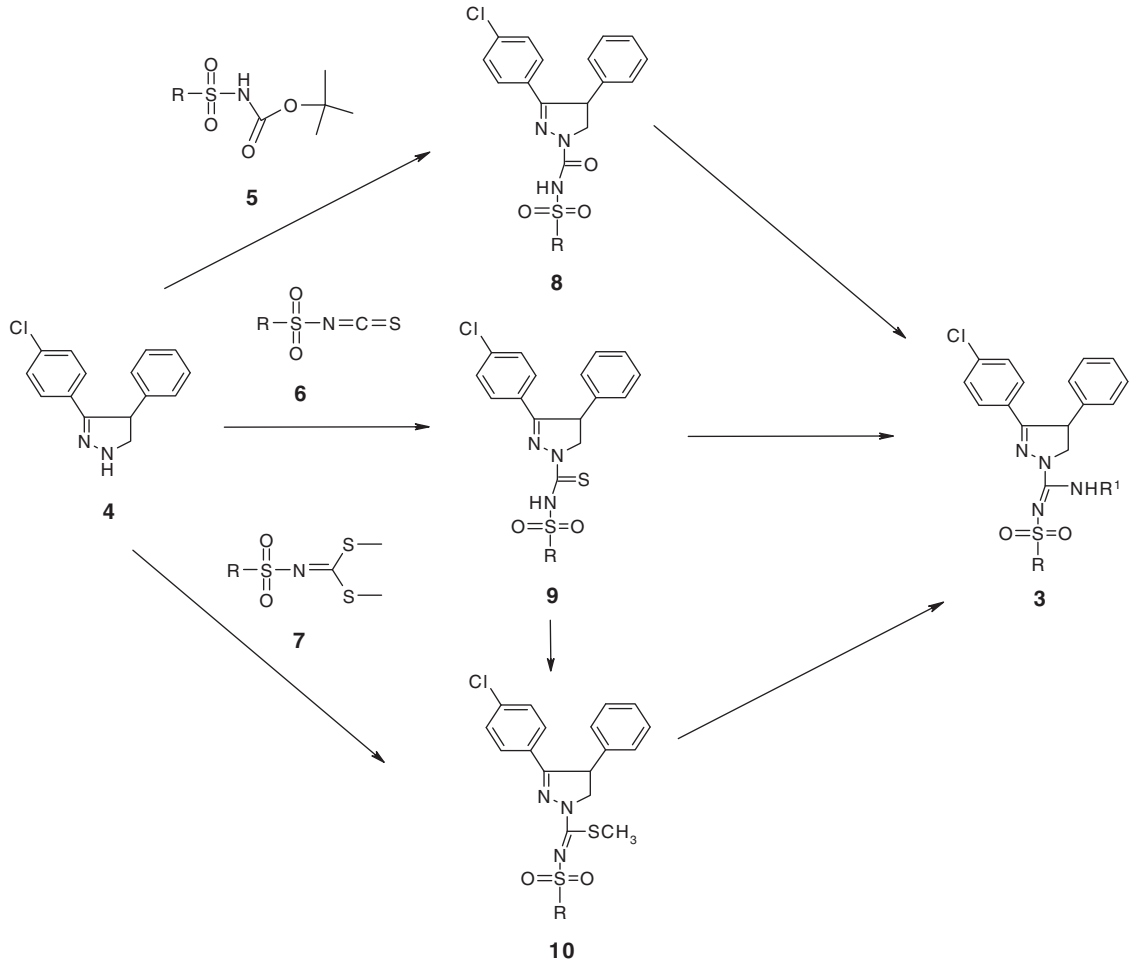


1 (ibipinabant) **2** (SLV330)

Figure 1. CB_1 receptor inverse agonists **1** and **2**.

* Corresponding author. Tel.: +31 294 479731; fax: +31 294 477138.

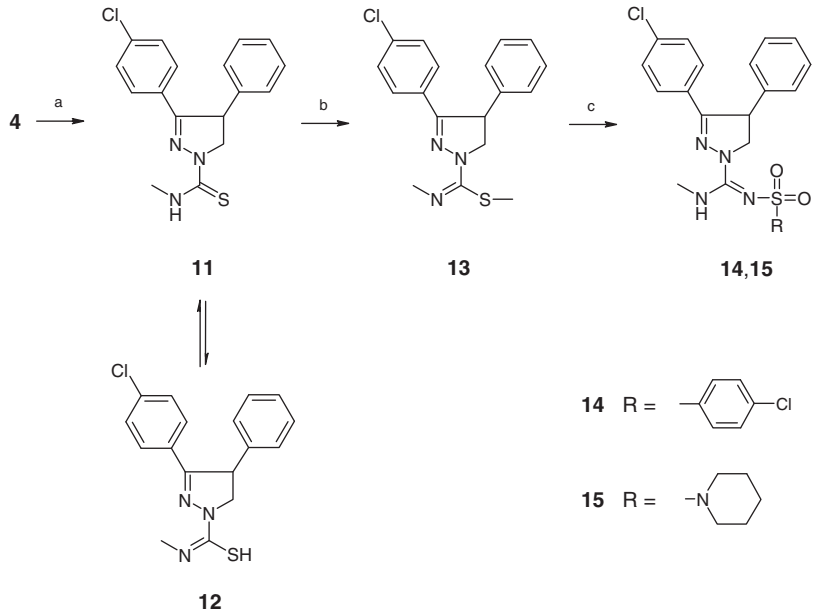
0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.01.068



Scheme 1. Reported synthetic conversions of **4** into compounds of general structure **3**.

improvement in synthetic access will be of importance since the (sulfonyl)guanidine moiety constitutes a key structural element in many biologically active compounds[29] and natural products.[30]

The resulting novel synthetic route starts from commercially available **4**[31] which was reacted with methylisothiocyanate in ethanol to furnish the corresponding carbothioamide **11** in 90% yield,



Scheme 2. Reagents and conditions: (a) $CH_3N{=}C{=}S$, EtOH, N_2, reflux, 3 h (90%); (b) MeI, MeOH, N_2, 40 °C, 16 h (99%); (c) RSO_2NH_2, MeCN, reflux, 16 h (82–87%).

which can equilibrate with its tautomer **12** (Scheme 2). Subsequent reaction of **11** with methyl iodide in methanol gave **13** in almost quantitative yield (99%). Gratifyingly, no chromatographic purification was required for these first two steps. The racemic target compound **14** was obtained[32] in 87% yield by the reaction of **13** with commercially available 4-chlorophenylsulfonamide in acetonitrile. The overall yield of this reaction sequence was 78% which is substantially higher than the original route[20] (~60%). The atom-efficiency of this novel route was 75% which is considerably higher than those of the previously described routes. Analogously, piperidine analogue **15** was prepared in 82% yield from **13** and commercially available piperidine-1-sulfonamide. The resultant overall yield in this sequence was 73% being much higher than the original route[21] (~45%).

Application of preparative chiral HPLC enabled the active 4*S* enantiomers **1** and **2** to be obtained[20,21] in multi-kilogram amounts after scale-up.

A crucial step herein constituted racemisation of the corresponding 4*R* enantiomers, which were also collected during the preparative chiral HPLC procedure, under basic conditions and subsequently recycling the respective racemates **14** and **15** in the chiral HPLC separation process. It was found that treatment with 2 N NaOH in ethanol at room temperature for 20 h resulted in clean racemisation which is in line with the observed epimerization[33] in structural analogues of **1** and **2**.

In conclusion, a novel synthetic approach to the highly selective and orally active cannabinoid CB_1 receptor inverse agonist ibipinabant (**1**) and a structural analogue **2** is disclosed. This route combines the use of inexpensive, commercially available reagents and mild reaction conditions with a high degree of atom-efficiency. It can be anticipated that the outlined synthetic methodology will enable easy access to a wide variety of sulfonylguanidine derivatives. Work in this area is currently in progress.

Acknowledgements

Chris Kruse, Fabrice Guillier and Uwe Schön are gratefully acknowledged for their helpful suggestions and Syncom BV (The Netherlands) for synthetic support. Belal Shadid is thanked for his contribution to the described racemisation procedure.

References and notes

1. Lambert, D. M.; Fowler, C. J. *J. Med. Chem.* **2005**, *48*, 5059–5087.
2. Van Gaal, L. F.; Rissanen, A. M.; Scheen, A. J.; Ziegler, O.; Rössner, S. *Lancet* **2005**, *365*, 1389–1397.
3. Antel, J.; Gregory, P. C.; Nordheim, U. *J. Med. Chem.* **2006**, *49*, 4008–4016.
4. Lange, J. H. M.; Kruse, C. G. *Chem. Rec.* **2008**, *8*, 156–168.
5. Di Marzo, V. *Nat. Rev. Drug Disc.* **2008**, *7*, 438–455.
6. Beardsley, P. M.; Thomas, B. F.; McMahon, L. R. *Int. Rev. Psychiatry* **2009**, *21*, 134–142.
7. De Bruin, N. M. W. J.; Lange, J. H. M.; Kruse, C. G.; Herremans, A. H.; Schoffelmeer, A. N. M.; van Drimmelen, M.; de Vries, T. J. *Behav. Brain Res.* **2011**, *217*, 408–415.
8. De Bruin, N. M. W. J.; Prickaerts, J.; Lange, J. H. M.; Akkerman, S.; Andriambeloson, E.; de Haan, M.; Wijnen, J.; van Drimmelen, M.; Hissink, E.; Heijink, L.; Kruse, C. G. *Neurobiol. Learn. Mem.* **2010**, *93*, 522–531.
9. Jones, D. *Nat. Rev. Drug Disc.* **2008**, *7*, 961–962.
10. Bifulco, M.; Pisanti, S. *Nat. Rev. Drug Disc.* **2009**, *8*, 594.
11. Le Foll, B.; Gorelick, D. A.; Goldberg, S. R. *Psychopharmacology* **2009**, *205*, 171–174.
12. Högenauer, E. K. *Expert Opin. Ther. Patents* **2007**, *17*, 1457–1476.
13. Jagerovic, N.; Fernandez-Fernandez, C.; Goya, P. *Curr. Top. Med. Chem.* **2008**, *8*, 205–230.
14. Janero, D. R.; Makriyannis, A. *Expert Opin. Emerg. Drugs* **2009**, *14*, 43–65.
15. Reggio, P. H. *Curr. Pharm. Des.* **2003**, *9*, 1607–1633.
16. Lange, J. H. M.; Kruse, C. G. *Curr. Opin. Drug Discov. Devel.* **2004**, *7*, 498–506.
17. Lange, J. H. M.; Kruse, C. G. *Drug Discovery Today* **2005**, *10*, 693–702.
18. Wang, H.; Duffy, R. A.; Boykow, G. C.; Chackalamannil, S.; Madison, V. S. *J. Med. Chem.* **2008**, *51*, 2439–2446.
19. Foloppe, N.; Benwell, K.; Brooks, T. D.; Kennett, G.; Knight, A. R.; Misra, A.; Monck, N. J. T. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4183–4190.
20. Lange, J. H. M.; Coolen, H. K. A. C.; van Stuivenberg, H. H.; Dijksman, J. A. R.; Herremans, A. H. J.; Ronken, E.; Keizer, H. G.; Tipker, K.; McCreary, A. C.; Veerman, W.; Wals, H. C.; Stork, B.; Verveer, P. C.; den Hartog, A. P.; de Jong, N. M. J.; Adolfs, T. J. P.; Hoogendoorn, J.; Kruse, C. G. *J. Med. Chem.* **2004**, *47*, 627–643.
21. Lange, J. H. M.; van Stuivenberg, H. H.; Veerman, W.; Wals, H. C.; Stork, B.; Coolen, H. K. A. C.; McCreary, A. C.; Adolfs, T. J. P.; Kruse, C. G. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4794–4798.
22. Lange, J. H. M.; van der Neut, M. A. W.; den Hartog, A. P.; Wals, H. C.; Hoogendoorn, J.; van Stuivenberg, H. H.; van Vliet, B. J.; Kruse, C. G. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1752–1757.
23. Lange, J. H. M.; den Hartog, A. P.; van der Neut, M. A. W.; Kruse, C. G. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5675–5678.
24. Lange, J. H. M.; Coolen, H. K. A. C.; van der Neut, M. A. W.; Borst, A. J. M.; Stork, B.; Verveer, P. C.; Kruse, C. G. *J. Med. Chem.* **2010**, *53*, 1338–1346.
25. Trost, B. M. *Science* **1991**, *254*, 1471–1477.
26. (a) Thai, K.; Gravel, M. *Tetrahedron: Asymmetry* **2010**, *21*, 751–755; (b) Shi, Y.; Li, C.; O'Connor, S. P.; Zhang, J.; Shi, M.; Bisaha, S. N.; Wang, Y.; Sitkoff, D.; Pudzianowski, A. T.; Huang, C.; Klei, H. E.; Kish, K.; Yanchunas, J.; Liu, E. C.-K.; Hartl, K. S.; Seiler, S. M.; Steinbacher, T. E.; Schumacher, W. A.; Atwal, K. S.; Stein, P. D. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6882–6889; (c) Qin, C.; Li, J.; Fan, E. *Synlett* **2009**, 2465–2468; (d) Martin, N. I.; Liskamp, R. M. J. *J. Org. Chem.* **2008**, *73*, 7849–7851; (e) Flemer, S.; Madalengoitia, J. S. *Synthesis* **2007**, *12*, 1848–1860; (f) Shepherd, J.; Gale, T.; Jensen, K. B.; Kilburn, J. D. *Chem. Eur. J.* **2006**, *12*, 713–720; (g) Gluszok, S.; Goossens, L.; Depreux, P.; Hénichart, J.-P. *Tetrahedron Lett.* **2006**, *47*, 6087–6090; (h) Jensen, K. B.; Braxmeier, T. M.; Demarcus, M.; Frey, J. G.; Kilburn, J. D. *Chem. Eur. J.* **2002**, *8*, 1300–1309; (i) Zhang, J.; Shi, Y. *Tetrahedron Lett.* **2000**, *41*, 8075–8078; (j) Bonnat, M.; Bradley, M.; Kilburn, J. D. *Tetrahedron Lett* **1996**, *37*, 5409–5412; (k) Deprez, P.; Vevert, J.-P. *Synth. Commun.* **1996**, 4299–4310.
27. (a) Zhang, Y.; Kennan, A. J. *Org. Lett.* **2001**, *3*, 2341–2344; (b) Levallet, C.; Lerpiniere, J.; Ko, S. Y. *Tetrahedron* **1997**, *53*, 5291–5304; (c) Himbert, G.; Schwickerath, W. *Liebigs Ann. Chem.* **1982**, *12*, 2105–2118.
28. Sheldon, R. A. *Pure Appl. Chem.* **2000**, *72*, 1233–1246.
29. (a) Saczewski, F.; Balewski, L. *Expert Opin. Ther. Patents* **2009**, *19*, 1417–1448; (b) Hirsh, A. J.; Sabater, J. R.; Zamurs, A.; Smith, R. T.; Paradiso, A. M.; Hopkins, S.; Abraham, W. M.; Boucher, R. C. *J. Pharmacol. Exp. Ther.* **2004**, *311*, 929–938; (c) Tsuji, S.; Kawano, S.; Tsujii, M.; Kawai, N.; Gunawan, E. S.; Sun, W. H.; Hori, M. *Arzneimittelforschung* **2001**, *51*, 46–50.
30. Berlinck, R. G. S.; Burtoloso, A. C. B.; Trindade-Silva, A. E.; Romminger, S.; Morais, R. P.; Bandeira, K.; Mizuno, C. M. *Nat. Prod. Rep.* **2010**, *27*, 1871–1907.
31. Grosscurt, A. C.; Van Hes, R.; Wellinga, K. *J. Agric. Food Chem.* **1979**, *27*, 406–409.
32. Yields refer to isolated pure products unless otherwise noted and were not optimized. Selected data for compounds **14** and **15**. *Synthesis of compound* **14**: A mixture of **4** (30 g, 117 mmol), absolute EtOH (180 ml) and methyl isothiocyanate (11.1 g, 152 mmol) was stirred under an N_2 atmosphere at reflux temperature for 3 h. The resulting solid was filtered off and washed with EtOH (3 × 70 ml) and dried under vacuum to give **11** as a white solid (35 g, 90% yield). Melting point: 181–183 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.25 (d, J = 5 Hz, 3H), 4.33–4.45 (m, 1H), 4.63–4.73 (m, 2H), 7.12–7.18 (m, 2H), 7.22–7.36 (m, 5H), 7.44 (br s, 1H), 7.56 (d, J = 8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.5, 50.6, 58.6, 127.2 (2C), 127.8, 128.5 (2C), 128.85, 128.88 (2C), 129.4 (2C), 136.2, 139.6, 155.9, 177.0. To a stirred solution of **11** (5 g, 15.2 mmol) in MeOH (150 ml) was added MeI (9.5 ml, 152 mmol). The mixture was heated at 40 °C (oil bath temperature) overnight under an N_2 atmosphere. The solution was concentrated in vacuum with an oil bath temperature below 45 °C. The residue was dissolved in CH_2Cl_2 (300 ml) and washed with saturated aqueous $NaHCO_3$ solution (70 ml) and brine (70 ml), dried over Na_2SO_4, filtered and concentrated under vacuum to afford **13** (5.2 g, 99% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.64 (s, 3H), 3.25 (s, 3H), 3.88 (dd, J = 11 and 4.5 Hz, 1H), 4.37 (t, J = 11 Hz, 1H), 4.56 (dd, J = 11 and 4.5 Hz, 1H), 7.15–7.33 (m, 7H), 7.56 (d, J = 8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.7, 38.5, 49.8, 58.1, 127.2 (2C), 127.4, 127.7 (2C), 128.6 (2C), 129.1 (2C), 130.1, 134.7, 140.0, 152.5, 154.1. A stirred solution of **13** (4.00 g, 11.62 mmol) and 4-chlorobenzenesulfonamide (2.34 g, 12.20 mmol) in MeCN (90 ml) was heated at reflux temperature for 16 h. The resulting mixture was evaporated under vacuum. The obtained crude residue was further purified by flash chromatography [silica gel, eluent gradient: petroleum ether/EtOAc = 90:10→60:40 (v/v/)] to afford **14** (4.93 g, 87% yield) as a solid. The ^{1}H NMR spectrum and other analytical data of **14** were in accordance with reported data.[20] *Synthesis of compound* **15**: A solution of **13** (5.0 g, 14.5 mmol) and piperidine-1-sulfonamide (2.5 g, 15.23 mmol) in MeCN (110 ml) was stirred at reflux temperature overnight. The resulting yellow solution was evaporated under vacuum. Purification by column chromatography on alumina (Act. III) eluting with an heptane/EtOAc gradient from 3:1 to 1:1 gave **15** (5.5 g, 82% yield, 99% HPLC purity) as a white solid. Compound **15** crystallized in the test tubes upon collection from the column (heptane/EtOAc, 2:1). Melting point: 175–177 °C. The ^{1}H NMR spectrum and other analytical data of **15** were in accordance with reported data.[21]
33. Donohue, S. R.; Pike, V. W.; Finnema, S. J.; Truong, P.; Andersson, J.; Gulyás, B.; Halldin, C. *J. Med. Chem.* **2008**, *51*, 5608–5616.