Bioorganic & Medicinal Chemistry Letters 19 (2009) 5351–5354

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Bioisosteric replacement of the hydrazide pharmacophore of the cannabinoid-1 receptor antagonist SR141716A. Part I: Potent, orally-active 1,4-disubstituted imidazoles

Robert L. Dow *, John R. Hadcock, Dennis O. Scott, Steven R. Schneider, Ernest S. Paight, Philip A. Iredale, Philip A. Carpino, David A. Griffith, Marlys Hammond †, Paul DaSilva-Jardine

Pfizer Global Research and Development, Groton, CT 06340, USA

ARTICLE INFO

Article history:
Received 12 June 2009
Revised 25 July 2009
Accepted 28 July 2009
Available online 6 August 2009

Keywords:
Cannabinoid-1 receptor antagonist
SR-141716
Imidazole isostere
Food intake inhibition

ABSTRACT

A new series of CB_1 receptor antagonists incorporating an imidazole-based isosteric replacement for the hydrazide moiety of rimonabant (SR141716) is disclosed. Members of this imidazole series possess potent/selective binding to the rCB_1 receptor and exhibit potent hCB_1 functional activity. Isopropyl analog **9a** demonstrated activity in the tetrad assay and was orally-active in a food intake model.

The endocannabinoid system (ECS), and specifically the cannabinoid type 1 (CB_1) receptor, plays a pivotal role in energy homeostasis.[1–3] As such, stimulation of the ECS promotes food intake and energy storage and may be chronically overactive in obese subjects.[4–7] In contrast, blockade of the CB_1 receptor in the central nervous system decreases food intake and increases energy expenditure, leading to a reduction in body weight.[8–11]

CB_1 receptor antagonists may provide effective therapy options for the management of metabolic disorders, such as obesity. It was hoped that CB_1 receptor antagonists might provide effective therapy options for the management of metabolic disorders, such as obesity. Unfortunately, several CB_1 receptor inverse agonists/antagonists were recently withdrawn from clinical development including the diarylpyrazole rimonabant[12] (**1**, SR141716A), the acyclic amide taranabant **2** (MK-0364)[13] and otenabant **3** (CP-945,598).[14]

In considering options for designing agents that would potentially have an improved profile relative to **1**, one of the elements we chose to focus on is the hydrazide functionality. While during its early clinical testing there were no reports of toxicity resulting from the hydrazide functionality present in **1**, there is the possibility that this chemotype could prove problematic upon longer term exposure in humans. Our concerns were based on reports that certain hydrazide-containing drugs, such as isoniazid and iproniazid, are hepatotoxic.[15,16] Mechanistic studies on these drugs concluded that the observed hepatotoxicity is likely driven by free radical formation via oxidation of the hydrazine core. Based on this chemotype toxicity concern, efforts in our laboratory focused on designs that would eliminate this potential issue.

Based on their precedent as isosteric equivalents of amides we chose to focus on nitrogen-containing heterocycles as replacements for the hydrazide functionality in **1**.[17] Our design approach focused on two key pharmacophore elements present in **1**. The first of these is incorporation of a hydrogen bond acceptor feature that could mimic the carbonyl oxygen of **1**. It has been hypothesized that a hydrogen bond between Lys192 of the CB_1 receptor and this oxygen is a significant component of the binding affinity and the expression of inverse agonist activity of **1**.[18–20] The second pharmacophore element taken into account is proper disposition of the substituents so as to attain good overlap with the piperidinyl substituent of **1**.

From the various heterocyclic options, 1,4-disubstituted imidazoles **4** met the pharmacophore criteria cited above and are the focus of this communication.[21] Subsequent to the studies reported here on imidazoles, both oxadiazole[22] and tetrazole[23] replacements for the amide functionality of **1** have been reported (Fig. 1).

An overlay of the minimized conformations of **8a** and **1** suggests that the N-3 imidazole nitrogen atom of **8a** is positioned to serve

* Corresponding author. Tel.: +1 860 441 4423; fax: +1 860 441 0548.
E-mail address: robert.l.dow@pfizer.com (R.L. Dow).
† Present address: GlaxoSmithKline Pharmaceuticals, Metabolic Pathways Centre for Excellence in Drug Discovery, 709 Swedeland Road, King of Prussia, PA 19406, USA.

0960-894X/$ - see front matter © 2009 Published by Elsevier Ltd.
doi:10.1016/j.bmcl.2009.07.130

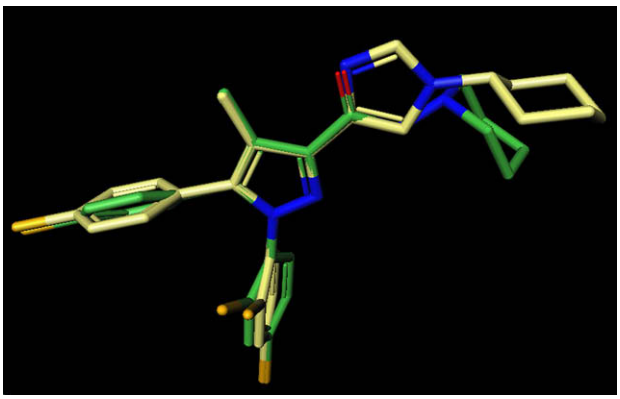
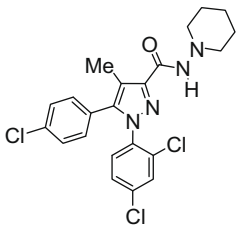
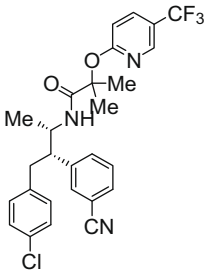


Figure 1. Overlay of minimized conformations of **1**[14] (green) and **8a** (yellow).

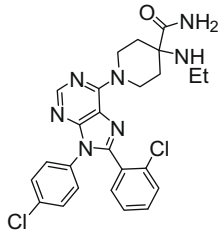
the same hydrogen bond acceptor role with the CB_1 receptor hypothesized for the carbonyl oxygen of **1**. Also, the N-1 substituent vector of **8a** is reasonably well aligned with the piperdinyl moiety of **1**.



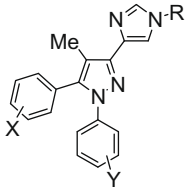
1 (SR141716)



2 (MK-0364)



3 (CP-945598)

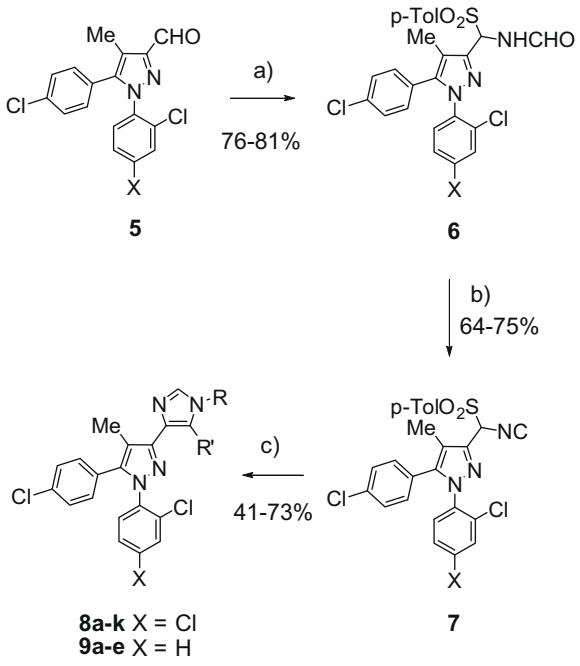


4

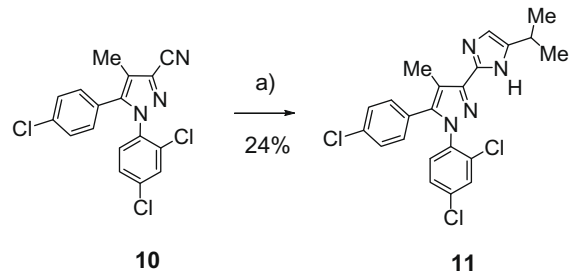
The synthetic route utilized to prepare derivatives **8a–k** and **9a–e** employed the tosylmethyl isocyanide-based approach to imidazole ring formation (Scheme 1).[24] Pyrazole carboxaldehyde **5**[21] was condensed with formamide in the presence of *p*-toluenesulfinic acid to afford intermediate **6**, which was dehydrated to provide tosylmethyl isocyanide **7**. Imidazole ring formation was accomplished either with the requisite amine and glyoxylic acid in the case of the 1,4-disubstituted analogs (R′ = H) or with an amine and an aldehyde in the case of 1,4,5-trisubstituted analogs **8** and **9** (Schemes 2 and 3).

The 2,4-disubstituted imidazole **11** was prepared by cyclization of the imidate derived from nitrile **10**[21] with the requisite bromoketone. Regioisomeric imidazole **13** was prepared via condensation of the bromoketone derived from **12**[21] with isopropylcarboxamidine.

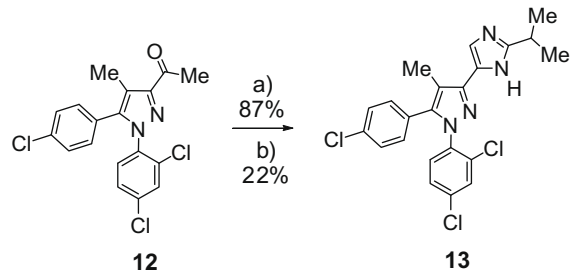
Rat CB_1 receptor binding affinities for the imidazole-based isosteres are detailed in Table 1. The rat receptor assay serves as a good surrogate for the human form given their high sequence



Scheme 1. Reagents and conditions: (a) H_2NCHO, *p*-toluenesulfinic acid, Me_3SiCl, toluene, 50 °C; (b) $POCl_3$, 2,6-lutidene, THF; (c) when R′ = H:RNH_2, $HCOCO_2H$, K_2CO_3, DMF; when *R* is other than H:RNH_2, R′CHO, K_2CO_3, DMF.



Scheme 2. Reagents and conditions: (a) $LiN(TMS)_2$, THF, then $Me_2C(O)CH_2Br$.



Scheme 3. Reagents and conditions: (a) Br_2, $CHCl_3$; (b) isopropylcarboxamidine HCl, K_2CO_3, DMF, 80 °C.

homology.[25] Inhibition of GTPγ [^{35}S] binding to the human CB_1 receptor was also determined for key analogs. Though the data is not shown, all of the imidazoles in Table 1 possess greater than 100-fold binding selectivity versus the human CB_2 receptor.

Cyclohexylimidazole **8a** was selected as an initial probe compound to examine the feasibility of this approach. While **8a** is ~10-fold less potent than **1** in binding to the rat receptor, there is only a threefold difference in the human CB_1 functional response. While this initial result was very encouraging, there are multiple

Table 1
Biochemical profiles for compounds **1**, **8a**–**k**, **9a**–**e**, **11** and **13**

Compd	R	R′	rCB$_1$ K_i[a] (nM)	hGTPγ[^{35}S] K_i[b] (nM)
1			0.9	1.6
8a	Cyclohexyl	H	8.6	4.7
8b	Cyclobutyl	H	10	5.0
8c	*t*-Butyl	H	14	ND[c]
8d	*i*-Propyl	H	4.9	9.0
8e	Ethyl	H	20	ND
8f	4-Tetrahydropyranyl	H	25	ND
8g	Benzyl	H	14	ND
8h	C(Me)$_2$Ph	H	1.8	0.1
8i	*i*-Propyl	Methyl	5.7	9.0
8j	*i*-Propyl	Ethyl	38	ND
8k	*i*-Propyl	CH_2OH	19	ND
9a	*i*-Propyl	H	5.3	7.6
9b	C(Me)$_2$Ph	H	1.1	0.1
9c	Cyclopropyl	H	7.4	7.9
9d	Phenyl	H	19	3.8
9e	H	*i*-Propyl	31	ND
11			9.5	5.2
13			7.2	9.5

[a] Rat brain tissue preparation used for CB1 receptor assay.[14] These data were obtained from a single determination run in triplicate.
[b] Human CB$_1$ receptor stably transfected into CHO cells.[14] These data were obtained from a single determination run in triplicate.
[c] ND = Value not determined.

imidazole regioisomers that could potentially fulfill the CB$_1$ receptor pharmacophore and it was important to optimize this feature before investigating finer structure–activity relationships.

For the lead CB$_1$ receptor antagonist **1** there is the potential for a hydrogen bond to be formed between the N–H of the hydrazide and N-2 of the pyrazole ring. If this arrangement is an important determinate of conformational stabilization resulting in enhanced receptor binding or alternatively the N–H provides a key interaction with the CB$_1$ receptor, incorporation of a similar hydrogen bond donor feature could provide enhanced affinity for the imidazole series.[26] This led to the preparation of the regioisomeric 2,4-disubstituted imidazoles **11** and **13**. Both of these imidazoles contain a free N–H and would thus have the potential to mimic the hydrazide N–H of **1**. However, when compared to the corresponding lead imidazole **8d**, neither **11** nor **13** provide a potency advantage. In addition, in vitro human microsomal analysis suggested series **8** (**8d**, hCL_{int} = 14 mL/min/kg) would have a threefold lower hepatic clearance potential relative to the two N–H containing imidazole series (**11**/**13**, hCL_{int} = 42,50 mL/min/kg, respectively). Based on these results further optimization efforts were focused on the 1,4-substituted imidazoles.

Since the overlap of the cyclohexyl ring of **8a** extends beyond the space occupied by the piperidinyl group of **1** in the respective minimized structures, analogs possessing smaller N-1 alkyl substituents were evaluated. Reducing the steric bulk of the N-1 substituent by incorporation of smaller carbocyclic (**8b**) or simple branched alkyl (**8c**–**e**) substituents has less than a twofold impact on CB$_1$ binding/functional activities. Introduction of heteroatoms (e.g., **8f**) as a means of further improving the clearance profile of this series was successful (hClint <7 mL/min/kg), though in all cases reduced CB$_1$ potency is observed. While *N*-benzyl analog **8g** is significantly less potent than **1**, findings from related CB$_1$ series pursued in our laboratory (unpublished data) suggested that α,α-dimethylbenzyl analog **8h** would have improved potency. This trend did translate between series with **8h** being approximately sevenfold more potent than **8g** and potently inhibits GTP binding (0.1 nM). However, the hydrochloride salt of **8h** fails to exhibit significant in vivo responses in either the tetrad or fasted-induced refeeding assays.[27] Pharmacokinetic analysis revealed very low free plasma and brain exposures, which is driven by the low solubility (<5 μg/mL-kinetic) and high clearance associated with these highly lipophilic analogs.

In order to explore the vector off the imidazole 5-position (R′ in **8**) a small set of trisubstituted analogs were prepared. Incorporation of a methyl group (**8i**) has no impact on the biochemical profile. This result was somewhat surprising based on the negative impact of N-methylation of the N–H of a homolog of **1**[26] and an expectation that the methyl group of **8i** should induce a significantly altered conformation around the pyrazole-imidazole bond. Attempts to incorporate larger substituents (**8j**) or polar functionality (**8k**) resulted in diminished activity against the CB$_1$ receptor.

Because the CB$_1$ receptor antagonist pharmacophore apparently requires highly lipophilic chemical matter (**1**/**8d**, clog $D_{7.4}$ = 5.8/5.9), modifications to **8** that reduced lipophilicity were of interest. Replacement of the pyrazole methyl group of **8d** with a hydrogen resulted in a sixfold reduction in CB$_1$ inhibitory activity and significantly lower aqueous solubility.[28] An alternative approach, based on other CB$_1$ chemical series identified in our laboratories, is to remove the para chlorine atom from the N-1 pyrazole phenyl substituent. Comparison of des-chloro analogs **9a** and **9b** with **8d** and **8h**, respectively, confirmed the expectation that there would be little or no impact on their in vitro profiles. This modification results in a one log unit reduction in the clog $D_{7.4}$ relative to their structural counterparts in series **8**.

Since significant structure–activity analysis has been carried out on series **8** and the initial potency trends between **8** and **9** were comparable, further efforts with **9** focused on a small number of analogs directed towards improving potency. Given the potential for cyclopropyl groups to serve as enhanced replacements[29] for dimethyl or isopropyl substituents, compound **9c** was prepared, but did not show any potency advantage. Analog **9d** was prepared to determine whether a phenyl group could mimic the interactions of the α,α-dimethylbenzyl substituent present in **9b**. This modification leads to an approximate 30-fold loss in functional activity relative to **9b**. The final modification pursued is that in which the isopropyl substituent of **9a** is moved into the 5-position of the imidazole ring, producing the free N–H imidazole **9e**. In analogy to the earlier studies on series **8**, substitution in the 5-position led to a significant reduction in activity.

Based on a balance of in vitro CB$_1$ receptor antagonist potency and physical properties, **9a** was selected for in vivo profiling. Pharmacokinetic analysis of the crystalline hydrochloride salt of **9a** in the rat revealed moderate clearance, half-life and volume of distribution (21 mL/min/kg, 1.5 h, 2.5 L/kg, 2 mg/kg, iv), in addition to moderate bioavailability (42%, 5 mg/kg, po). Based on this profile **9a** was advanced to testing in in vivo models of functional CB$_1$ antagonism.[27] In the hot plate/hypothermia legs of the tetrad assay, **9a** (10 mg/kg; ip) partially reversed the effects of the CB agonist CP-55940, 56% (p <0.01) and 33% (p <0.01), respectively. In comparison, SR141716 is able to completely reverse the agonism induced by CP-55940 at 3 mg/kg, ip (p <0.01). In a rat model of CB$_1$ receptor-mediated fast-induce refeeding, **9a** (10 mg/kg; po) produces a statistically significant reduction (44%, p <0.01) in food intake over a 4 h test period, when compared to SR141716 at 3 mg/kg (−31%, p <0.01).

Though our expectation was that the 1,4-disubstitution pattern of the imidazole ring would mitigate any CYP inhibition risk associated with the imidazole functionality present in **9a**, inhibition studies employing the major isoforms were carried out. Compound **9a** showed no significant inhibitory activity (IC_{50}'s >10 μM) against the CYP isoforms 3A4, 1A2, 2C9, 2C19 and 2D6.

In summary, isosteric replacement of the hydrazide pharmacophore of **1** with a 1,4-disubstituted imidazole moiety has been shown to be a viable isosteric substitution. Analogs from this imidazole series exhibited potent CB$_1$ antagonism both in vitro and in vivo. Conformational restriction of these and related heterocyclic isosteres will be the subject of a future publication.

Acknowledgments

We thank Shawn Black, Denise Gautreau, Jeffrey Lizano, Dawn Kelly-Sullivan, Rebecca O'Connor, Meihua Tu and Karen Ward for their contributions to this work.

References and notes

1. Kershaw, E. E.; Flier, J. S. *J. Clin. Endocrinol. Metab.* **2004**, *89*, 2548.
2. Kirkham, T. C. *Behav. Pharmacol.* **2005**, *16*, 297.
3. Pagotto, U.; Marsicano, G.; Cota, D.; Lutz, B.; Pasquali, R. *Endocrinol. Rev.* **2006**, *27*, 73.
4. Matias, I.; Gonthier, M. P.; Orlando, P.; Martiadis, V.; De Petrocellis, L.; Cervino, C.; Petrosino, S.; Hoareau, L.; Festy, F.; Pasquali, R.; Roche, R.; Maj, M.; Pagotto, U.; Monteleone, P.; Di Marzo, V. *J. Clin. Endocrinol. Metab.* **2006**, *91*, 3171.
5. Hao, S.; Avraham, Y.; Mechoulam, R.; Berry, E. M. *Eur. J. Pharmacol.* **2000**, *392*, 147.
6. Engeli, S.; Böhnke, J.; Feldpausch, M.; Gorzelniak, K.; Janke, J.; Bátkai, S.; Pacher, P.; Harvey-White, J.; Luft, F. C.; Sharma, A. M.; Jordan, J. *Diabetes* **2005**, *54*, 2838.
7. Kirkham, T. C.; Williams, C. M.; Fezza, F.; Di Marzo, V. *Br. J. Pharmacol.* **2002**, *136*, 550.
8. Jbilo, O.; Ravinet-Trillou, C.; Arnone, M.; Buisson, I.; Bribes, E.; Péleraux, A.; Pénarier, G.; Soubrié, P.; Le Fur, G.; Galiègue, S.; Casellas, P. *J. FASEB* **2005**, *19*, 1567.
9. Thornton-Jones, Z. D.; Kennett, G. A.; Benwell, K. R.; Revell, D. F.; Misra, A.; Sellwood, D. M.; Vickers, S. P.; Clifton, P. G. *Pharmacol. Biochem. Behav.* **2006**, *84*, 353.
10. Vickers, S. P.; Webster, L. J.; Wyatt, A.; Dourish, C. T.; Kennett, G. A. *Psychopharmacology (Berl.)* **2003**, *167*, 103.
11. Hildebrandt, A. L.; Kelly-Sullivan, D. M.; Black, S. C. *Eur. J. Pharmacol.* **2003**, *462*, 125.
12. Rinaldi-Carmona, M.; Barth, F.; Héaulme, M.; Shire, D.; Calandra, B.; Congy, C.; Martinez, S.; Maruani, J.; Néliat, G.; Caput, D., et al *FEBS Lett.* **1994**, *350*, 240.
13. Lin, L. S.; Lanza, T. J., Jr.; Jewell, J. P.; Liu, P.; Shah, S. K.; Qi, H.; Tong, X.; Wang, J.; Xu, S. S.; Fong, T. M.; Shen, C. P.; Lao, J.; Xiao, J. C.; Shearman, L. P.; Stribling, D. S.; Rosko, K.; Strack, A.; Marsh, D. J.; Feng, Y.; Kumar, S.; Samuel, K.; Yin, W.; Van der Ploeg, L. H.; Goulet, M. T.; Hagmann, W. K. *J. Med. Chem.* **2006**, *49*, 7584.
14. Griffith, D. A.; Hadcock, J. R.; Black, S. C.; Iredale, P. A.; Carpino, P. A.; DaSilva-Jardine, P.; Day, R.; DiBrino, J.; Dow, R. L.; Landis, M. S.; O'Connor, R. E.; Scott, D. O. *J. Med. Chem.* **2009**, *52*(2), 234.
15. Timbrell, J. A. *Drug Metab. Rev.* **1979**, *10*, 125.
16. Zolla, L.; Timperio, A. M. *Biochem. Cell Biol.* **2005**, *83*, 166.
17. Patani, G. A.; LaVoie, E. *J. Chem. Rev.* **1996**, *96*, 3147.
18. Shim, J.-Y.; Welsh, W. J.; Cartier, E.; Edwards, J. L.; Howlett, A. C. *J. Med. Chem.* **2002**, *45*, 1447.
19. Lange, J. H. M.; Kruse, C. G. *Drug Discovery Today* **2005**, *10*, 693.
20. Hurst, D.; Umejiego, U.; Lynch, D.; Seltzman, H.; Hyatt, S.; Roche, M.; McAllister, S.; Fleischer, D.; Kapur, A.; Abood, M.; Shi, S.; Jones, J.; Lewis, D.; Reggio, P. *J. Med. Chem.* **2006**, *49*, 5969.
21. Dow, R. L. U.S. Patent Application 2004/077650A1, 2004; *Chem. Abstr.* **2003**, *140*, 331785.
22. a Barth, F.; Congy, C.; Gueule, P.; Rinaldi-Carmona, M.; Van Broeck, D. PCT Patent Application WO2006/087480A1, 2006.; (b) Lee, S. H.; Seo, H. J.; Lee, S.-H.; Jung, M. E.; Park, J.-H.; Park, H.-J.; Yoo, J.; Yun, H.; Na, J.; Kang, S. Y.; Song, K.-S.; Kim, M.; Chang, C.-H.; Kim, J.; Lee, J. *J. Med. Chem.* **2008**, *51*, 7216.
23. Kang, S. Y.; Lee, S.-H.; Seo, H. J.; Jung, M. E.; Ahn, K.; Kim, J.; Lee, J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2385.
24. Sisko, J.; Kassick, A. J.; Mellinger, M.; Filan, J. J.; Allen, A.; Olsen, M. A. *J. Org. Chem.* **2000**, *65*, 1516.
25. Matsuda, L. A.; Lolait, S. J.; Brownstein, M. J.; Young, A. C.; Bonner, T. I. *Nature* **1990**, *346*, 561.
26. A recent report confirms that blocking (N-methylation) of the hydrazide nitrogen of **1** results in a moderate reduction (4.5-fold) in potency: Chen, J. Z.; Han, X.-W.; Liu, Q.; Makriyannis, A.; Wang, J.; Xie, X.-Q. *J. Med. Chem.* **2006**, *49*, 625.
27. In vivo protocols are reported in the Supplementary data of Ref. 14.
28. This analog (data not shown) was prepared in analogy to **6** and has a K_i of 31 nM against the rat CB_1 receptor.
29. *Topics in Current Chemistry*; Salaun, J., Ed.; Springer: Berlin, Heidelberg, 2000; Vol. 207, pp 1–67.