Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters 17 (2007) 2031–2035
Bioorganic & Medicinal Chemistry Letters

# Lead optimization of 5,6-diarylpyridines as CB1 receptor inverse agonists

Christina B. Madsen-Duggan,[a,*] John S. Debenham,[a] Thomas F. Walsh,[a] Richard B. Toupence,[a] Song X. Huang,[a] Junying Wang,[a] Xinchun Tong,[a] Julie Lao,[b] Tung M. Fong,[b] Marie-Therese Schaeffer,[b] Jing Chen Xiao,[b] Cathy R.-R. C. Huang,[b] Chun-Pyn Shen,[b] D. Sloan Stribling,[c] Lauren P. Shearman,[c] Alison M. Strack,[c] D. Euan MacIntyre,[c] Lex H. T. Van der Ploeg[d] and Mark T. Goulet[d]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA*
[b]*Department of Metabolic Disorders, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA*
[c]*Department of Pharmacology, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA*
[d]*Merck Research Laboratories, 33 Avenue Louis Pasteur, Boston, MA 02115, USA*

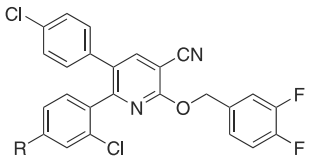
Received 11 December 2006; revised 4 January 2007; accepted 5 January 2007
Available online 13 January 2007

**Abstract**—Optimization of the biological activity for 5,6-diarylpyridines as CB1 receptor inverse agonists is described. Food intake and pharmacokinetic evaluation of **3f** and **15c** indicate that these compounds are effective orally active modulators of CB1.


The discovery of the cannabinoid receptor 1, CB1,[1] (expressed predominantly in the central nervous system) and subsequent elucidation of the CB1 endogenous ligands, the endocannabinoids, has led to the recognition that the cannabinoid system has an important role in food intake modulation.[2] Food intake suppression mediated by CB1 inverse agonists has been demonstrated in animal[3] and human studies[4] and has now been approved as a treatment for obesity.[5]

In our previous report we disclosed the structure–activity relationship (SAR) efforts that led to the identification of diarylpyridine **1a** (Fig. 1), with a 1 nM CB1 binding affinity.[6] Unfortunately, the in vitro potency of **1a** only translated into modest in vivo efficacy, due most likely to less than optimal PK and CNS exposure.[6] Further alteration of structure **1a** led to compounds with improved in vivo efficacy and are described within.

Excellent CB1 binding affinity in the 2-benzyloxypyridine series was observed with 5-(4-chlorophenyl)-6-(2,4-dichlorophenyl)pyridine containing derivatives such as **1a** (CB1, $IC_{50}$ = 1.3 nM). We also recognized that the bis-dichloro derivative **1b** had respectable potency with the benefit of reduced molecular weight (CB1, $IC_{50}$ = 8 nM). Adjacent chlorophenyl groups on a heterocyclic scaffold are a common element of CB1 modulators, and both bis- and tris-chlorophenyl containing ligands have been reported from these and other laboratories.[2] Consequently, we adopted these two aryl chlorination patterns and focused our SAR studies on the pyridine 2 and 3-position substituents.



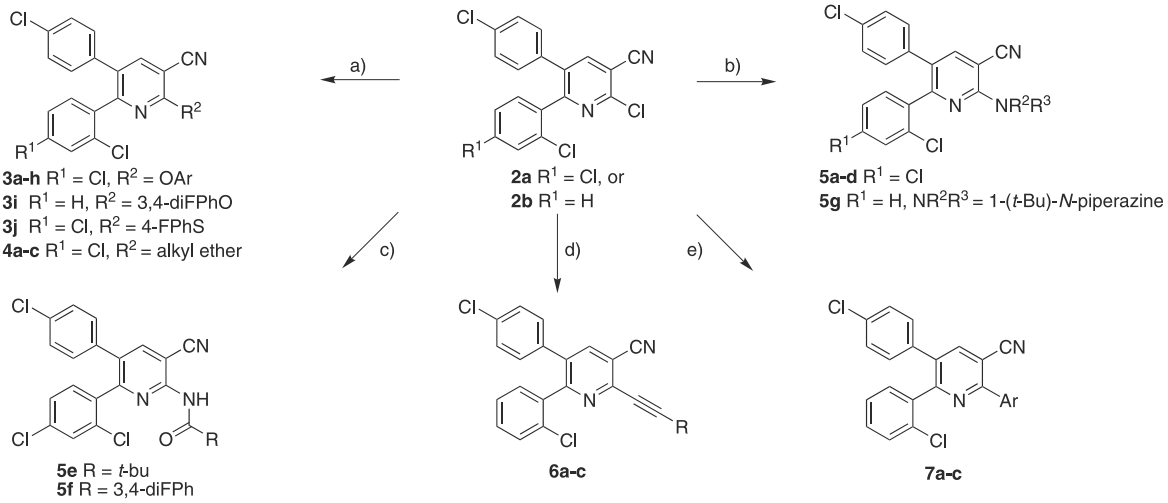
**1a** R = Cl, CB1 $IC_{50}$ = 1.3 nM
**1b** R = H, CB1 $IC_{50}$ = 8 nM

**Figure 1.** Structure of Merck early leads.

In order to probe the SAR of the pyridine 2-position, 2-chloropyridines **2a**,[7] and related **2b** (Scheme 1), were utilized due to their synthetic versatility.

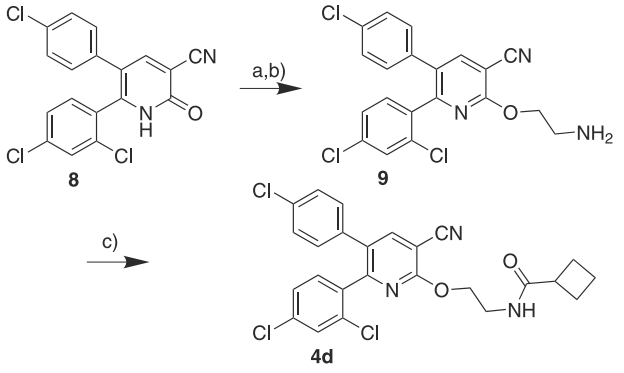
*Keywords*: Cannabinoid; CB1; Inverse agonist; Pyridine; Obesity.
* Corresponding author. E-mail: christina_madsen_duggan@merck.com

0960-894X/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2007.01.005

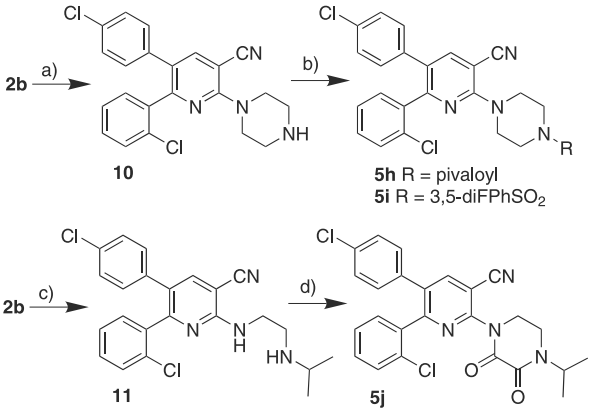



**Scheme 1.** Reagents and conditions: (a) ArOH, ArSH or ROH, $Cs_2CO_3$, toluene, 100 °C, 50–94%; (b) $NHR_2R_3$, THF or toluene, 40–100 °C, 23–89%; (c) $RCONH_2$, $Cs_2CO_3$, DMF, 100 °C, 47–50%; (d) alkyne, $NEt_3$, CuI, $PdCl_2(PPh_3)_2$, DMF, 50 °C, 85–100%; (e) $RB(OH)_2$, $PdCl_2(PPh_3)_2$, $Cs_2CO_3$, DMF, microwave heating, 120 °C, 10–37%.

Scheme 1 illustrates the elaboration of **2a** and **2b** into several new classes of compounds. Nucleophilic aromatic substitution of the 2-chloropyridines **2a** or **2b** by treatment with phenols, 4-fluorothiophenol, 4-fluoroaniline or alcohols with cesium carbonate in refluxing toluene, afforded the aryl ethers **3a**–**i**, the 4-fluorophenylthio ether **3j**, the 4-fluoroaniline **3k**, and the alkyl ethers **4a**–**c**, respectively (Tables 1 and 2). The 2-aminopyridine derivatives, **5a**–**b** (Table 3), were obtained by heating **2a** with *iso*-butylamine or piperidine in THF. Imidazole **5c**, benzotriazole **5d**, and the piperazine derivative **5g** were generated when **2a** or **2b** was refluxed in toluene with the appropriate heterocyclic amine, and amides **5e** and **5f** were synthesized by heating **2a** with either pivalamide or 3,4-difluorobenzamide in the presence of cesium carbonate at 100 °C (Table 3). Incorporation of carbon substituents at the pyridine 2-position was achieved by coupling **2b** with acetylenes under Sonagashira conditions to produce the alkynes **6a**–**c** (Table 4) or by Suzuki coupling of **2b** with heterocyclic boronic acids to afford the 3-pyridyl (**7a**), 5-pyrimidinyl (**7b**), and 1-methyl-4-pyrazolyl (**7c**) derivatives (Table 5). The cyclobutylamido ethyl ether **4d** (Table 2, Scheme 2) was obtained when pyridone **8**[6] was treated with *N*-bromoethyl phthalimide, then deprotected with hydrazine to provide amine **9**, followed by treatment with cyclobutanecarbonyl chloride at room temperature.



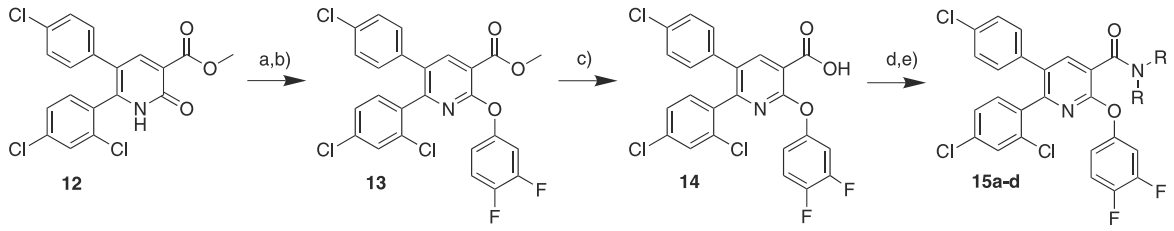

**Scheme 2.** Reagents and conditions: (a) *N*-bromoethyl phthalimide, $K_2CO_3$, DMF, 70 °C; (b) $NH_2NH_2$, MeCN, EtOH, 80 °C, 80% (two steps); (c) cyclobutanecarbonyl chloride, $NEt_3$, $CH_2Cl_2$, rt, 68%.




**Scheme 3.** Reagents and conditions: (a) piperazine, toluene, 100 °C, 99%; (b) RCOCl or $RSO_2Cl$, $NEt_3$, $CH_2Cl_2$, rt, 25–46%; (c) *N*-*iso*-propylethylenediamine, $Cs_2CO_3$, DMF, 96%; (d) $(COCl)_2$, MeCN, 15%.

Scheme 3 illustrates the synthesis of piperazine derivatives **5h** and **5i** (Table 3). The 2-chloropyridine **2b** was initially reacted with piperazine in refluxing toluene to afford **10**. This material was then either reacted with pivaloyl chloride to yield **5h**, or treated with 3,5-difluorobenzenesulfonyl chloride to generate sulfonamide **5i**. The preparation of piperazine-2,3-dione **5j** (Table 3) is also shown in Scheme 3. Initial treatment of **2b** with *N*-*iso*-propylethylenediamine led to **11**, which underwent a ring-closure with oxalyl chloride affording the desired compound **5j**.

Next we elaborated the 3-cyano group of the pyridine to prepare more polar structures in an attempt to lower the log *D*[8] and improve physicochemical properties such as vehicle solubility. The primary amide **15a**, *iso*-propyl




**Scheme 4.** Reagents and conditions: (a) $POCl_3$, reflux, 78%; (b) 3,4-di-fluorophenol, $Cs_2CO_3$, toluene, 100 °C, 86%; (c) 3 N NaOH, MeOH, 50 °C,100%; (d) $(COCl)_2$, $CH_2Cl_2$, DMF, rt; (e) NHRR, $CH_2Cl_2$, $NEt_3$, rt, 52–92% (two steps).

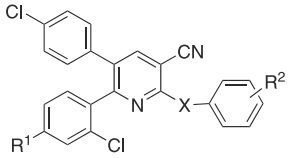
amide **15b**, 1,1-dimethylhydrazide **15c**, and sym-dimethylhydrazide **15d**, all bearing the 3,4-difluorophenoxy group at the 2-position, were made as illustrated in Scheme 4. Ester **12**[6] was treated sequentially with phosphorus oxychloride and then 3,4-difluorophenol to yield the desired ether **13**. Compound **13** underwent saponification to give acid **14**, which was then treated with oxalyl chloride and the appropriate amine or hydrazine to afford **15a–d** (Table 6).

Binding affinities were determined using a standard protocol[9] and all compounds tested were found to be functional inverse agonists.

Our initial SAR efforts focused on comparing phenoxy, phenylthio, and phenylamino alternatives to the benzyloxy group of **1a** as shown in Table 1.

The monohalo phenyl compounds, 3-fluoro **3a**, 4-fluoro **3b**, 3-chloro **3c**, and 4-chloro **3d**, showed good potency (CB1, $IC_{50}$ = 4–14 nM), while the 4-methoxyphenoxy analog **3e** was less potent (CB1, $IC_{50}$ = 26 nM). Aryl halogen disubstitution enhanced potency as seen with 3,4-difluoro **3f**, 3,5-difluoro **3g**, and 3,5-dichloro **3h** (CB1, $IC_{50}$ = 3.7, 0.91, and 3.9 nM, respectively). There was a 6-fold drop in potency with the bis-chloro analog **3i**, relative to the tris-chloro **3f**, which was consistent with our previous observation that the tris-chloro substitution pattern was favored over the bis-chloro in the benzyloxy series (**1a** vs **1b**).

**Table 1.** Structures and binding affinities (CB1; CB2) expressed as $IC_{50}$ (nM), of the 2-phenoxy derivatives **3a–k**



| Compound | X | $R^1$ | $R^2$ | CB1; CB2 |
|---|---|---|---|---|
| **3a** | O | Cl | 3-F | 11; 2300 |
| **3b** | O | Cl | 4-F | 14; 4400 |
| **3c** | O | Cl | 3-Cl | 4; 4100 |
| **3d** | O | Cl | 4-Cl | 7; 4200 |
| **3e** | O | Cl | 4-OMe | 26; 3800 |
| **3f** | O | Cl | 3,4-diF | 3.7; 4100 |
| **3g** | O | Cl | 3,5-diF | 0.91; 320 |
| **3h** | O | Cl | 3,5-diCl | 3.9; 5600 |
| **3i** | O | H | 3,4-diF | 25; 5700 |
| **3j** | S | Cl | 4-F | 154; 5200 |
| **3k** | NH | Cl | 4-F | 50; 2800 |

Diminished potency was observed when the oxygen at the pyridine 2-position was exchanged with sulfur or nitrogen. The 4-fluorophenyl thioether **3j** showed an 11-fold drop, while the 4-fluoroaniline **3k** had a 3-fold drop relative to the phenoxy ether **3b**. Alkyl ethers were also well tolerated ($IC_{50}$ = 5.7–11 nM at CB1) as shown in Table 2.

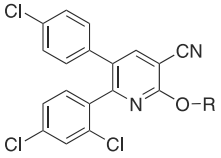
An array of nitrogen linked compounds at the pyridine 2-position are illustrated in Table 3. In general the potency of these compounds was considerably less than the dihalophenoxy compounds of Table 1.

Piperidine derivative **5b** (CB1, $IC_{50}$ = 19 nM) showed 5-fold better binding affinity than the *iso*-butyl derivative **5a**. The aromatic nitrogen linked compounds, **5c** and **5d**, showed improvement in potency, with **5d** displaying an $IC_{50}$ value of 5.7 nM. The pivalamido and 3,4-difluorobenzamido derivatives **5e** and **5f** displayed more modest activity (CB1, $IC_{50}$ = 29 and 20 nM), while in the piperazine series, the sulfonamide **5i** showed excellent activity (CB1, $IC_{50}$ = 3.8 nM).

Carbon linked substituents at the pyridine 2-position are shown in Tables 4 and 5. In the alkynyl series, the *tert*-butyl alkyne **6a** was potent (CB1, $IC_{50}$ = 5.9 nM), while the hydroxy and the amino substituted alkynes **6b** and **6c** displayed modest activity.

Of the heteroaryl analogs, the 3-pyridyl (**7a**) and the 3,5-pyrimidinyl (**7b**) derivatives showed modest activity,

**Table 2.** Structures and binding affinities (CB1; CB2) expressed as $IC_{50}$ (nM), of 2-alkyl ethers **4a–d**



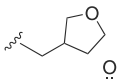
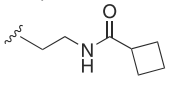
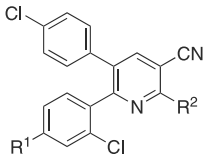
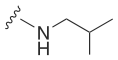
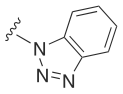
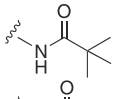
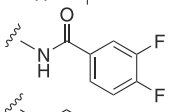
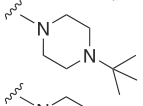
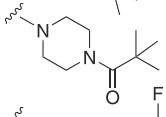
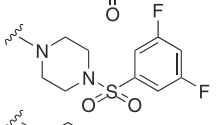
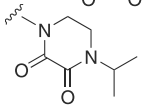
| Compound | R | CB1; CB2 |
|---|---|---|
| **4a** |  | 10; 860 |
| **4b** |  | 11; 730 |
| **4c** |  | 6.6; 430 |
| **4d** |  | 5.7; 450 |

**Table 3.** Structures and binding affinities (CB1; CB2) expressed as $IC_{50}$ (nM), of 2-aminopyridine derivatives **5a–j**



| Compound | $R^1$ | $R^2$ | CB1; CB2 |
|---|---|---|---|
| **5a** | Cl |  | 89; 1800 |
| **5b** | Cl |  | 19; 4000 |
| **5c** | Cl |  | 12; 310 |
| **5d** | Cl |  | 5.7; 465 |
| **5e** | Cl |  | 29; 1700 |
| **5f** | Cl |  | 20; 315 |
| **5g** | H |  | 108; 2600 |
| **5h** | H |  | 37; 1100 |
| **5i** | H |  | 3.8; 1400 |
| **5j** | H |  | 12; 715 |

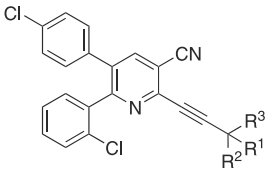
while the 1-methyl-4-pyrazolyl **7c** had diminished potency (CB1, $IC_{50}$ = 165 nM).

Finally, the 3-carboxamidopyridine and 3-hydrazidopyridine analogs were examined as shown in Table 6. Binding activity of the *iso*-propylamide **15b** (CB1, $IC_{50}$ = 3.5 nM) showed a small improvement over the primary amide **15a**. The hydrazide **15c** (CB1, $IC_{50}$ = 5.6 nM) was found to be similar to **15b**, but superior to the sym-hydrazide **15d**.

Compounds **3f** and **15c** were selected for evaluation of their effects on food intake and body weight changes in diet-induced obese (DIO) rats fed overnight ad libitum on a moderate high fat, high sucrose diet.[7] Data for compound **1a** are included for comparison.[6] All compounds were dosed orally at 10 mg/kg.

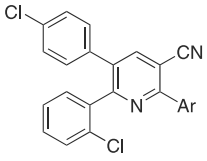
Compound **3f** suppressed cumulative food intake by 48% after 18-h post-dosing ($p$ = 0.0014) resulting in an 8 g decrease in body weight, while vehicle treated

**Table 4.** Structures and binding affinities (CB1; CB2) expressed as $IC_{50}$ (nM), of 2-alkynyl derivatives **6a-c**



| Compound | $R^1$ | $R^2$ | $R^3$ | CB1; CB2 |
|---|---|---|---|---|
| **6a** | Me | Me | Me | 5.9; 2100 |
| **6b** | OH | Me | Me | 44; 1800 |
| **6c** | $NH_2$ | Et | Et | 39; 1100 |

**Table 5.** Structures and binding affinities (CB1; CB2) expressed as $IC_{50}$ (nM), of 2-heteroaryl derivatives **7a–c**



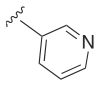
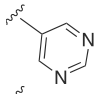
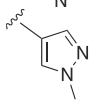
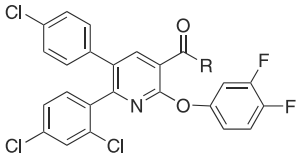
| Compound | Ar | CB1; CB2 |
|---|---|---|
| **7a** |  | 27; 3700 |
| **7b** |  | 38; 4300 |
| **7c** |  | 165; 3300 |

**Table 6.** Structures and binding affinities (CB1; CB2) expressed as $IC_{50}$ (nM), of 3-amido and 3-hydrazido derivatives **15a–d**



| Compound | R | CB1; CB2 |
|---|---|---|
| **15a** | $NH_2$ | 11; 4900 |
| **15b** | NH*i*-Pr | 3.5; 1600 |
| **15c** | $NHNMe_2$ | 5.6; 1800 |
| **15d** | NMeNHMe | 80; 650 |

controls gained 7 g overnight ($p$ < 0.001) as shown in Table 7. Compound **15c** also inhibited feeding by 45% ($p$ = 0.009) and decreased overnight body weight gain by 5 g versus a 4 g increase for vehicle treated controls ($p$ = 0.007). In contrast, compound **1a** had a non-significant reduction in food intake (−22%; $p$ > 0.05), but had a modest, yet statistically significant, reduction in overnight body weight gain (−1 g vs +8 g for vehicle treated controls; $p$ < 0.05).

Pharmacokinetic properties for compounds **3f** and **15c** were determined in Sprague–Dawley rats and compared to those reported for compound **1a**[6] as shown in

**Table 7.** Rat food intake/body weight change overnight (18 h) for **3f**, **15c**, and **1a**[6]

| Compound | Dose (mg/kg) | Δ Body weight (g) | % FI suppression |
|---|---|---|---|
| Vehicle (for **3f**) | | +7 | |
| **3f** | 10 | −8 ($p < 0.001$) | −48 ($p = 0.0014$) |
| Vehicle (for **15c**) | | +4 | |
| **15c** | 10 | −5 ($p = 0.007$) | −45 ($p = 0.009$) |
| Vehicle (for **1a**) | | +8 | |
| **1a** | 10 | −1 ($p < 0.05$) | −22 ($p > 0.05$) |

**Table 8.** Pharmacokinetic profiles for **3f**, **15c**, and **1a**[6]

| Compound | **3f** | **15c** | **1a** |
|---|---|---|---|
| $F$ (%) | 66 | 26 | 27 |
| Clp (mL/min/kg) | 3.5 | 24 | 3.6 |
| $t_{1/2}$ (h) | 5.6 | 4.1 | 3.6 |
| $V_d$ (L/kg) | 1.5 | 6.7 | 0.77 |
| Brain/plasma ratio 0.25 h; 4 h post iv dosing | 0.10; 0.61 | 1.2; 3.0 | 0.03; 0.26 |

Table 8. All three compounds showed similar half-lives, but **3f** had about 2.5 times the bioavailability of **15c** or **1a**. Of note was that **15c** was the least restricted to plasma with a volume of distribution almost nine times that of **1a**. Of greatest importance for efficacy was the higher brain to plasma ratios observed for **3f** and **15c**. While **15c** had lower bioavailability than **3f**, the fact that it had a larger $V_d$, and was better brain penetrant than **3f**, accounts for its similar efficacy in vivo.

Optimization of the 5,6-diarylpyridine lead revealed that great diversity in structure at the pyridine 2-position is tolerated and affords compounds with high potency for CB1 ($IC_{50} \leqslant 10$ nM) and excellent specificity with respect to CB2. Both **3f** and **15c** effectively suppressed food intake and body weight increases following oral administration in a DIO rat model of food intake. Further SAR focusing on the 2- and 3-position substituents of our diarylpyridine lead will be reported from these laboratories in due course.

## References and notes


1. Devane, W. A.; Dysarz, F. A.; Johnson, M. R.; Melvin, L. S.; Howlett, A. C. *Mol. Pharmacol.* **1988**, *34*, 605.
2. For extensive reviews in this area, see the following: Muccioli, G. G.; Lambert, D. M. *Curr. Med. Chem.* **2005**, *12*, 1361; Hertzog, D. L. *Expert Opin. Ther. Patents* **2004**, *14*, 1435; Smith, R. A.; Fathi, Z. *Idrugs* **2005**, *8*, 53; Lange, J. H. M.; Kruse, C. G. *Curr. Opin. Drug Discov. Devel.* **2004**, *7*, 498; Lange, J. H. M.; Kruse, C. G. *Drug Discovery Today* **2005**, *10*, 693.
3. Cota, D.; Marsicano, G.; Tschöp, M.; Grübler, Y.; Flachskamm, C.; Schubert, M.; Auer, D.; Yassouridis, A.; Thöne-Reinecke, C.; Ortmann, S.; Tomassoni, F.; Cervino, C.; Nisoli, E.; Linthorst, A. C. E.; Pasquali, R.; Lutz, B.; Stalla, G. K.; Pagotto, U. *J. Clin. Invest.* **2003**, *112*, 423.
4. Després, J.-P.; Golay, A.; Sjöström, L. *N. Eng. J. Med.* **2005**, *353*, 2121.
5. ACOMPLIA® (rimonabant) approved in the European Union, June 21, 2006, www.sanofi-aventis.com.
6. Meurer, L. C.; Finke, P. E.; Mills, S. G.; Walsh, T. F.; Toupence, R. B.; Debenham, J. S.; Goulet, M. T.; Wang, J.; Tong, X.; Fong, T. M.; Lao, J.; Schaeffer, M.-T.; Chen, J.; Shen, C.-P.; Stribling, D. S.; Shearman, L. P.; Strack, A. M.; Van der Ploeg, L. H. T. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 681, 1755.
7. Debenham, J. S.; Madsen-Duggan, C. B.; Walsh, T. F.; Wang, J.; Tong, X.; Doss, G. A.; Lao, J.; Fong, T. M.; Schaeffer, M.-T.; Xiao, J. C.; Huang, C. R.-R. C.; Shen, C.-P.; Feng, Y.; Marsh, D. J.; Stribling, D. S.; Shearman, L. P.; Strack, A. M.; MacIntyre, D. E.; Van der Ploeg, L. H. T.; Goulet, M. T. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 681.
8. For comparison the calculated log $D$ for **1a**, **3f**, and **15c** is 8.35, 8.08, and 6.19, respectively (Advanced Chemistry Development log $D$ software version 8.07).
9. The reported binding results were an average of 2–8 independent determinations (each done in replicate), which were normally within 50% of the average value. For both binding and functional assay conditions, see: Felder, C. C.; Joyce, K. E.; Briley, E. M.; Mansouri, J.; Mackie, K.; Blond, O.; Lai, Y.; Ma, A. L.; Mitchell, R. L. *Mol. Pharmacol.* **1995**, *48*, 443.