Synthesis and Evaluation of Dibenzothiazepines: A Novel Class of Selective Cannabinoid-1 Receptor Inverse Agonists

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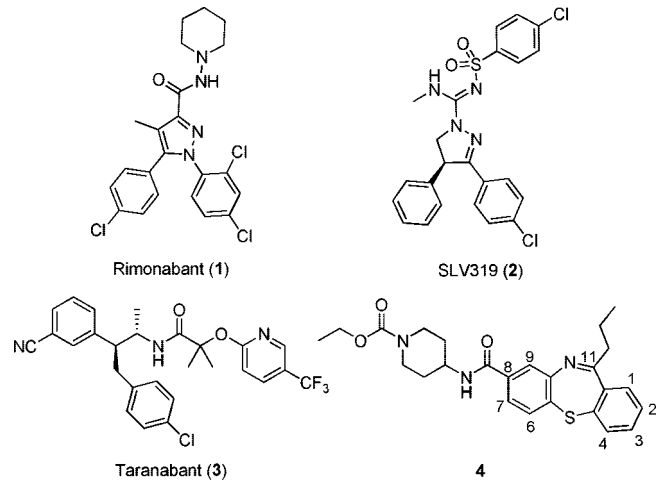
A novel class of CB1 inverse agonists was discovered. To efficiently establish structure−activity relationships (SARs), new synthetic methodologies amenable for parallel synthesis were developed. The compounds were evaluated in a mammalian cell-based functional assay and in radioligand binding assays expressing recombinant human cannabinoid receptors (CB1 and CB2). In general, all of the compounds exhibited high binding selectivity at CB1 vs CB2 and the general SAR revealed a lead compound 11-(4-chlorophenyl)dibenzo[*b*,*f*][1,4]thiazepine-8-carboxylic acid butylamide (**12e**) which showed excellent in vivo activity in pharmacodynamic models related to CB1 receptor activity. The low solubility that hampered the development of **12e** was solved leading to a potential preclinical candidate 11-(3-chloro-4-fluorophenyl)-dibenzo[*b*,*f*][1,4]thiazepine-8-carboxylic acid butylamide (**12h**).

Introduction

The cannabinoid receptor 1 (CB1[a]) is widely expressed in the central nervous system (CNS) and also at significant levels in peripheral tissues and represents a potentially useful therapeutic target for many indications including type II diabetes, obesity, drug addiction, and smoking cessation.[1] Consequently, the development of CB1 antagonists and inverse agonists as therapeutic agents has been the subject of intense research. The majority of compounds that have been described belong to the diarylpyrazole structural class of compounds or derivatives thereof such as inverse agonists rimonabant (**1**)[2,3] and **2** (SLV319)[4] (Chart 1). Rimonabant (**1**) was approved in the European Union (EU) for the treatment of obesity.[5] However, the FDA Advisory Committee did not recommend approval of **1** because of the severe psychiatric side effects in some patients; consequently, the new drug application (NDA) was withdrawn in the U.S.[6] Recently the EU has followed the FDA and removed **1** from the market. Development of another CB1 inverse agonist taranabant (**3**) was discontinued in 2008 because of similar side effects at high doses.[7] Whether the psychiatric side effects arise from the mechanism of action itself or if these are compound specific remains uncertain. It is therefore important to identify and develop novel, structurally unique, and selective CB1 antagonists/inverse agonists that may provide a distinct therapeutic profile.

A high-throughput screen (HTS) of a 270 000 compound library using the proprietary mammalian cell-based functional assay receptor selection and amplification technology (R-SAT) was employed to screen for novel CB1 inverse agonists.[8] A novel CB1 inverse agonist **4** showing affinity for the CB1 receptor in the submicromolar range was identified. Although the tricyclic core is shared with a well-known class of antipsychotic compounds, e.g., quetiapine, clozapine, and olanzapine showing biological activity at CNS targets such as D_2 and $5HT_{2A}$ receptors,[9] it turned out that the scaffold functionalized with an amide side chain and not having a basic amine functionality constituted a unique class of molecules that showed high selectivity toward CB1. Several hundred molecules of this class were synthesized in parallel to establish the SAR. A representative set of compounds stating the most obvious trends in the SAR as well as activities in rodent in vivo models relating to CB1 activity are discussed herein.

Chart 1. Examples of CB1 Antagonists and Initial ACADIA Hit



Chemistry

A synthetic route that enabled the synthesis of a large number of compounds in a combinatorial mode was developed. Lactam **9** was synthesized in multigram scale from commercially available starting materials in a high overall yield (84%) over

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[a] Abbreviations: CB1, cannabinoid receptor 1; CNS, central nervous system; DFT, density functional theory; DIO, diet-induced obese; EU, European Union; HTS, high-throughput screen; ip, intraperitoneal; mCPBA, *m*-chloroperbenzoic acid; NDA, new drug application; NSA mice, non-Swiss albino mice; PEG, polyethylene glycol; po, per oral; qd, quaque die (everyday); R-SAT, receptor selection and amplification technology; SD, standard deviation; SAR, structure−activity relationship.

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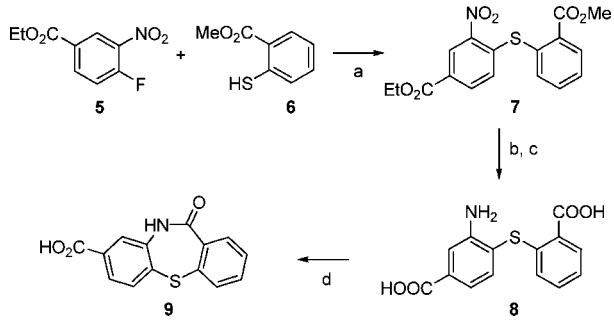
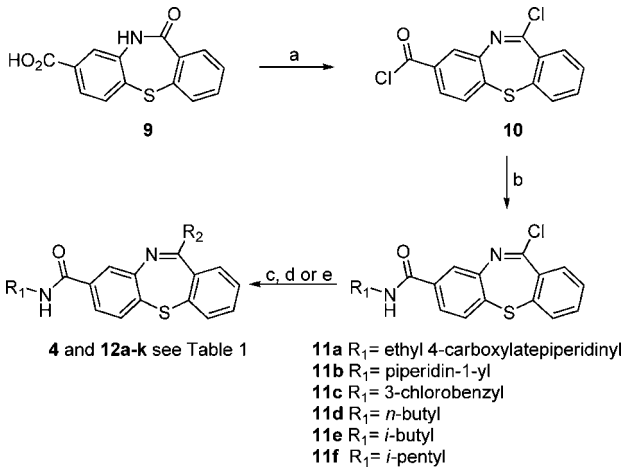
Scheme 1. Synthesis of Key Intermediate **8**[a]



[a] Reagents: (a) Cs_2CO_3, DMF, 40 °C, 45 min (92%); (b) LiOH (aq, 1 M), THF, 60 °C, 2 h (99%); (c) PtO_2, Pd/C, H_2, MeOH, room temp, 16 h (96%); (d) CDI, THF, room temp, 16 h (91%).

Scheme 2. Synthesis of Target Molecules **4** and **12**[a]

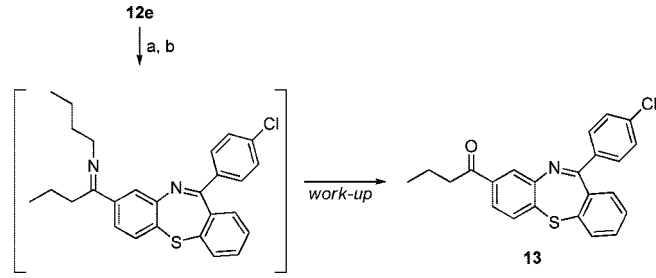


[a] Reagents: (a) $SOCl_2$, DMF, toluene, 80 °C, 17 h, 84%; (b) R_1-NH_2, DCM, 0 °C to room temp, $^1/_2$ h, 72−88% yield; (c) R_2-MgX, $Fe(acac)_3$, THF, NMP, −78 °C to room temp, 2 h; (d) R_2-NH, toluene, 90 °C, overnight, 67% and 99% yields; (e) R_2-ZnX, $PdCl_2(PPh_3)_2$, THF, 2 h.

three steps (Scheme 1). Dichloride **10**, set up to be easily functionalized at both the 8- and the 11-position, was formed in a high yield from lactam **9** via a double chlorination (Scheme 2). A sequential diversification of **10** was possible because of the difference in reactivity between the acid chloride and the imidoyl chloride functionalities. The amides **11a**−**f** containing a reactive imidoyl chloride functionality were isolated by silica gel column chromatography in high yields (72−88%) and stored for days under vacuum, from a reaction between the corresponding amines and the acid chloride (**10**) at 0 °C to room temperature.

As previously reported, imines (e.g., **12**, R_2 = alkyl or aryl) can be obtained by an iron-catalyzed cross-coupling of Grignard reagents with imidoyl chlorides.[10] However, the iron-catalyzed reaction conditions with aromatic Grignard reagents gave poor yields because of an extensive side reaction, a homocoupling forming biaryls. Therefore, in order to synthesize imines with R_2 equaling aryl or R_2 equaling heteroaryl (**12d**−**k**) efficiently, a palladium-catalyzed Negishi cross-coupling reaction using aromatic zinc reagents was developed.[11] This new method turned out to be convenient for parallel synthesis and gave the final products in good to excellent yields in a fast and mild reaction, 30 min, at room temperature. A nucleophilic substitution reaction gave access to a third series of compounds. Piperidines were added to the imidoyl chloride moiety at an elevated temperature (no reaction took place at 0 °C to room temperature), yielding amidines **12b** and **12c** in 99% and 67% yields, respectively.

Scheme 3. Synthesis of Ketone **13**[a]



[a] Reagents: (a) $SOCl_2$, 80 °C, 1 h, quant; (b) PrMgCl, $Fe(acac)_3$, THF/NMP, room temp, 20 min, 78%.

To investigate the amide bond in the 8-position, ketone **13** was synthesized in a high overall yield (78%) over two steps (Scheme 3). The amide **12e** was treated with thionyl chloride at 80 °C for 1 h, the imidoyl chloride formed was concentrated to dryness and reacted with *n*-propylmagnesium chloride in an iron-catalyzed cross-coupling reaction, and the subsequent acidic workup gave ketone **13**. This new amide to ketone transformation is mild, fast, and high yielding.

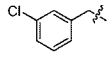
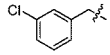
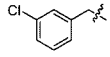
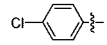
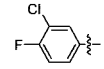
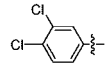
The conformational influence by the heteroatom in the central azepine ring of the tricyclic framework was explored by the synthesis of compounds containing CH_2 (**14a**), O (**14b**), NH (**14c**), SO (**14d**), and SO_2 (**14e**) as replacement of S (e.g., **12a** and **12d**) (Table 2). The CH_2 and O analogues **14a** and **14b**, respectively, were synthesized in the same way as the corresponding S analogue (**12a**), via the lactam, and subsequently similarly sequentially derivatized, as described in the Supporting Information. The NH analogue **14c** was synthesized as described in Scheme 4, starting from the 8-chlorolactam **15**. A coupling reaction with molybdenum hexacarbonyl was used in the final step to introduce the amide bond (**14c**).[12] The sulfoxide **14d** and the sulfone **14e** were obtained by an oxidation of the corresponding S analogue (**12d**) with hydrogen peroxide and mCPBA, respectively.

Results and Discussion

All compounds were evaluated in vitro using the proprietary mammalian cell-based functional assay R-SAT.[8] Binding studies were performed on most of the compounds using HEK293 cells transiently transfected with human CB1 and CB2 receptors. The in vitro activities are summarized in Tables 1 and 2. In general, the compounds were selective, displaying high activity at CB1 and little or no activity at the CB2 receptor. Introducing more lipophilic groups at both R_1 and R_2 increased the biological activity; for example, compounds more lipophilic than **4** exhibited an increased activity (Table 1), which is not surprising because of the lipophilic character of CB1 ligands in general.[13] As soon as the polarity of the compound was increased especially with heteroatoms in the periphery of the structure, the activity decreased (e.g., **4**).

With the hit **4** in hand, a general structural comparison with rimonabant and taranabant was made. In the place of one of the aryls in rimonabant and taranabant which resides in a hydrophobic pocket engaged in aromatic stacking interactions, hit **4** had an *n*-propyl (see Figure 1, overlays of **12e** with rimonabant and taranabant; **4** has a *n*-propyl in the 11-postion instead of the 4-chlorophenyl (**12e**)). Since *n*-propyl cannot participate in aromatic stacking interactions (e.g., $\pi-\pi$ stacking), its contribution to binding, if any, would be of a lipophilic

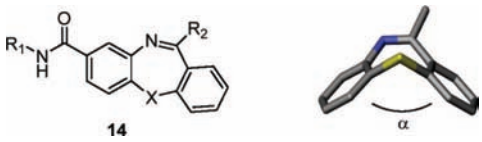
Table 1. In Vitro Results for Inverse Agonist, Binding, and Microsomal Assays[a]

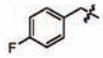
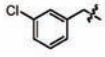
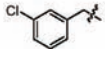
Comp	R_1	R_2	R-SAT pIC_{50}	Binding pK_i		Cl_{int} (μL/min · mg)	
				hCB1	hCB2	Rat	Hum
1	Rimonabant, free base		7.2±0.4	8.7±0.2	6.4±0.3	159	41
2	(+/-)-SLV319		7.7±0.3	8.5±0.1	5.7±0.0	nd	nd
4	See Chart 1		6.5±0.4	nd	nd	539	279
12a			7.6±0.3	8.6±0.0	na	846	84
12b			8.1±0.2	9.5±0.1	na	644	265
12c			7.4±0.2	9.1±0.1	5.9±0.0	66	40
12d			8.0±0.1	nd	nd	127	35
12e			8.1±0.3	9.7±0.5	na	89	24
12f			8.6±0.1	nd	nd	61	35
12g			6.9±0.0	7.6±0.1	5.3±0.0	nd	nd
12h			8.4±0.0	9.7±0.2	6.0±0.2	58	16
12i			8.2±0.0	nd	nd	32	0
12j			8.6±0.1	8.9±0.0	na	77	46
12k			7.6±0.1	8.8±0.0	na	377	114
13	See Scheme 3		nd	7.4±0.0	nd	nd	nd

[a] nd, not determined; na, not active at 10 μM. pIC_{50} and pK_i values are the mean values of at least three experiments ± SD. pIC_{50} (R-SAT inverse agonist assays) was calculated as the negative logarithm of the concentration of test article that repressed the basal activity 50%. pK_i (binding assays) was determined from the pIC_{50} values (concentration of test article that caused 50% displacement of radioligand ^{3}H-SR141716A) using the Cheng−Prusoff correction (see ref 8c).

nature. Introducing the hydrazide side chain (R_1) also found in rimonabant and a cyclohexyl in place of the *n*-propyl gave a compound **12a** equipotent with rimonabant (**1**) and (±)-SLV319 (**2**). Keeping R_1 fixed (3-chlorobenzyl) provided an opportunity to compare amidines **12b** and **12c** and the 4-fluorophenyl **12d**. Compounds **12b** and **12d** were equipotent in the inverse agonist assay; thus, an aromatic substituent in the 11-position did not increase the functional activity compared with an aliphatic one. Geminal 4,4-difluoro substituents in the piperidinyl (**12c**), introduced to increase the metabolic stability, gave a slight decrease in the activity compared with having an unsubstituted piperidinyl (**12b**). Compounds having R_2 equaling an aryl or heteroaryl (**12d**−**k**) generally showed high activity at the CB1 receptor. Changes in CB1 potency depending on the position of the substituent on the phenyl were observed, exemplified by **12e**−**g**. While the 3- and 4-chlorophenyls **12f** and **12e**, respectively, exhibited similar activities, they were at least 10 times more active than the 2-chloro derivative (**12g**). The latter may be the result of a conformational restriction enforced by having the larger chlorine in the 2-position. Changing R_2 from phenyl to a substituted thienyl (**12j**) or a pyridinyl (**12k**) also gave high affinity compounds (pK_i of 8.9 and 8.8, respectively); thus, heteroaryls were well tolerated by the CB1 receptor.

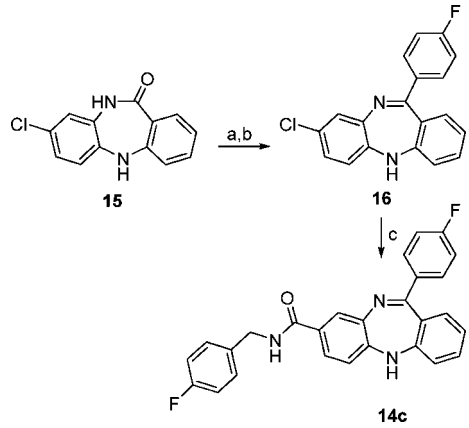
Table 2. Effect of Bridging Atom on the α-Angle



Comp	R_1	R_2	X	Calc. angle[a]	R-SAT pIC_{50}[b]
12a	See Table 1		S	110°	7.6±0.1
14a			CH_2	118°	7.3±0.1
14b			O	121°	7.1±0.1
12d	See Table 1		S	109°	8.0±0.1
14c			NH	135°	6.6±0.0
14d			SO[c]	101°	7.2±0.0
14e			SO_2	112°	7.7±0.2

[a] The α-angle is for C(7)−X−C(3). [b] pIC_{50} values are the mean values of at least three experiments ± SD. [c] The SO oxygen is in pseudoequatorial conformation.

Scheme 4. Synthesis of the NH Analogue **14c**[a]



[a] Reagents: (a) $POCl_3$, *N*-dimethylaniline, toluene, 95 °C, 2 h, 72%; (b) $PdCl_2(PPh_3)_2$, 4-FPhZnBr, THF, room temp, 45 min, 72%; (c) 4-FBnNH_2, $Mo(CO)_6$, cataCXium, $[(CH_3)_3C]_3P\cdot HBF_4$, DBU, THF, 170 °C, microwave, 20 min, 30%.

No apparent trend in activity was observed when R_1, the amide group, was varied. However, the NH in the amides (e.g., **12e**) and the hydrazide (**12a**) was important for activity; replacement of the amide with a ketone functionality reduced the activity (**13**). This suggests that the amide bond is involved in binding either directly via hydrogen bonding or indirectly via the iminol tautomer. In addition, this pharmacophore element is also seen in the clinical compounds (**1** and **2**, Chart 1). It has been suggested in docking studies of rimonabant (**1**) and taranabant (**3**) that the amide bond has great importance for binding to the receptor but to different sites; rimonabant hydrogen-binds via the carbonyl oxygen to a lysine and taranabant via the amide NH to serine.[14a] Molecular mechanical calculations (MMFF force field) were performed on **12e**, and 49 unique conformers were all found within 4 kcal/mol having the central thiazepine ring in a boat conformation. As expected, since most of the structural variations were associated with the butyl part, these conformers could be divided into two subsets depending on the conformation of the amide bond.[15] The energetically more favorable conformation with the carboxamide oxygen pointing toward the sulfur had a 1.5 kcal/mol preference using the MMFF force field. To further look at the amide bond conformers, density functional theory (DFT) calculations (B3LYP/6-31G*) were used. Again, the same conformer was found to be more energetically favorable, but this time the separation between the two was only 0.4 kcal/mol.[16] The conformation of rimonabant (**1**) has been well studied, and the conformer previously used for docking studies was selected and evaluated for overlap with the conformers of **12e**.[17] The conformer deemed the best fit belonged to the energetically less favorable amide bond conformation (Figure 1a). The triad, the two phenyls and the carboxamide oxygen, important for rimonabant binding to the CB1 receptor had a good fit with **12e**. Similarly **12e** was, including both sets of enantiomeric conformers, evaluated with the taranabant conformer D, the conformer used in the docking studies.[14b] As also seen in the rimonabant−**12e** and the taranabant−rimonabant[14a] overlays, the aryls residing in hydrophobic pockets of the CB1 receptor overlapped well in the taranabant−**12e** overlay. However, including the amide NH of taranabant together with the two aryls in the model, all three reported to be important for the binding of taranabant, resulted in a less optimal fit with **12e** compared to the **12e**−rimonabant overlay (Figure 1b).

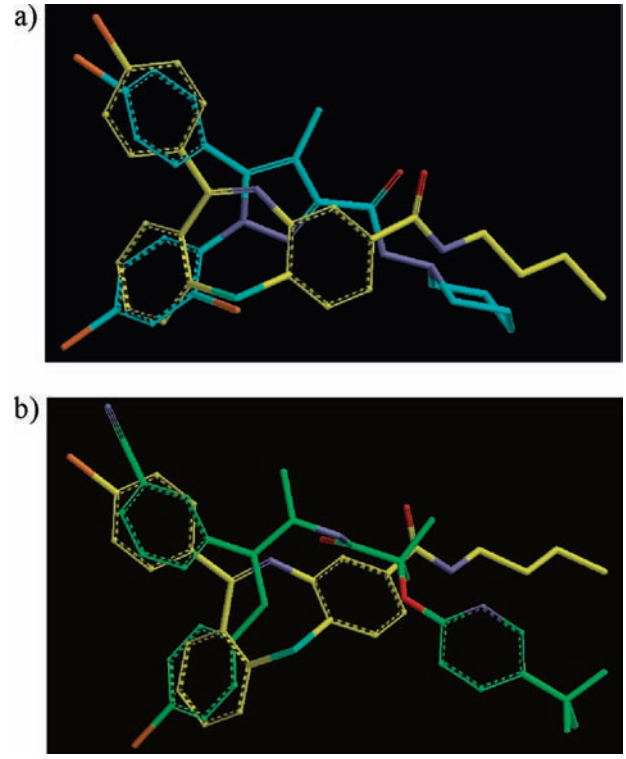


Figure 1. (a) Overlay of **12e** (yellow) with rimonabant (cyan). (b) Overlay of **12e** (yellow) and taranabant (green).

Exchanging the heteroatom in the central azepine ring changed the dihedral angle between the two planar aryls in the tricyclic framework. DFT calculations (B3LYP/6-31G*) showed

that the angle increased when going from S to C, from C to O, and from O to N (Table 2).[18,19] By comparison of **12a** with **14a** and **14b**, it is seen that increasing the dihedral angle between the two aryls, which results in a more planar structure, significantly reduces activity. This is further emphasized by the N-analogue **14c**. In contrast, decreasing the angle when replacing S with SO in the ring also gave a reduction in activity (**12d** and **14d**). This may indicate that the optimum α-angle for activity at the CB1 receptor is around 110°; however, **14d** was tested as a racemic mixture which made it difficult to draw a definitive conclusion from this experiment. A small shift in the α-angle was seen when replacing S with SO_2, which correlates with the observed change in activity (**12d** and **14e**).

Metabolic Stability. The stability in human and rat microsomes was analyzed for a representative set of compounds (Table 1). Introducing an aryl group at R_2 not only improved activity, it also appeared to have a positive influence on the stability in microsomes. As seen in Table 1, the compounds having R_2 equaling alkyl (**4**, **12a**) or piperidinyl (**12b**) showed high in vitro clearance values, especially in rat but also in human microsomes, compared to the compounds having R_2 equaling aryl (**12d**−**j**). However, the clearance was significantly reduced in the piperidinyl series by introducing geminal fluorines in the 4-position (**12c**). In vitro clearance values of less than 75 and 50 μL/(min·mg) represent moderate to low clearance compounds (less than 70% liver blood flow) in rat and human, respectively. An exception to the general trend that an aryl group at R_2 improved the microsomal stability significantly was the pyridinyl **12k**; however, this was also the only aryl in the experimental set not having a halogen substituent, and in addition, the aromatic nitrogen is a potential oxidation site.

The major problem with this lipophilic class of compounds is the low solubility not only in phosphate buffer solution but also in other formulations frequently used in in vivo pharmacology. Compound **12e**, the first selected lead compound, has excellent CB1 activity and reasonable metabolic stability in both rat and human microsomes but has moderate solubility, for example, in polyethylene glycol (PEG) (3.7 mg/mL). One potential rationale for this low solubility is $\pi-\pi$ stacking between molecules, giving stable crystals.[20] Therefore, two halogens were added to the R_2 phenyl as a way to try to disrupt the $\pi-\pi$ stacking between the molecules. The melting point and the solubility in PEG were measured, and a correlation between the melting point and the solubility in PEG was found; thus, the melting points were indicative of the solubility. Introduction of two halogens at the 3- and 4-position in the aryl **12h** (mp 154−157 °C, solubility (PEG) of >13 mg/mL) and **12i** (mp 168−172 °C, solubility (PEG) of >14 mg/mL) lowered the melting point and increased the solubility in PEG compare with **12e** (mp 217−219 °C, solubility (PEG) of >3.7 mg/mL). Besides improving solubility, this change maintained/slightly improved CB1 activity and significantly increased metabolic stability in both rat and human microsomes.

Hypothermia Assay. The compounds from Table 1 showing promise as drug-like molecules were also tested in hypothermia assays, a convenient in vivo measurement of CB1-receptor activation or blockade for CB1 agonists and CB1 antagonists, respectively.[21] Hypothermia assays were performed as follows: administration of a 1 mg/kg dose of the potent CB1 agonist CP55940 caused a body temperature drop of approximately 6 °C in male, NSA mice. Test compounds were administered ip in NSA mice 30 min prior to ip administration of CP55940. After 60 min the body core temperature was measured to test to what extent the test compound could reverse the CP 55940 induced hypothermia. As seen in Table 3, several compounds showed good to excellent in vivo activity in a dose-dependent manner comparable to rimonabant and SLV-319, especially compounds **12e** and **12h**.

Table 3. In Vivo Results for Hypothermia and Anorexia Assays[a]

compd	hypothermia, % inhibition 3 mg/kg ip	hypothermia, % inhibition 1 mg/kg ip	food intake, % inhibition, 10 mg/kg po
1	nd	70	55
2	82	51	nd
12e	82	71	69
12h	94	70	59
12i	58	nd	nd
12j	73	nd	54

[a] nd, not determined.

Anorexia Assay. Given the interest in developing CB1 antagonists for treating obesity, we tested several of the compounds that displayed good activity in the hypothermia assays for inhibition of feeding in fasted male Sprague Dawley rats. Rats were fasted for a period of 18 h (water was always available). After the fasting period, test compounds were administered orally (po). Dosed animals were immediately returned to their home cage for 30 min following compound administration, after which the rats were removed from their home cages and placed individually into clean cages with a premeasured amount of food. Food consumption was monitored for a period of 2 h (i.e., 2.5 h after test compound administration) and expressed as percent inhibition of food consumption in vehicle-treated animals. As shown in Table 3, compounds **12e**, **12h**, and **12j** had activity that was comparable to or better than that of rimonabant (**1**) in suppressing food intake. In addition, these experiments showed that these compounds are orally active.

Weight Loss Assay. Male C57BL/6 diet-induced obese (DIO) mice (Taconic Laboratories, Oxnard, CA), approximately 16−17 weeks old and within a weight range of approximately 40−45 g, were maintained on a high-fat diet (Research Diets D12492) and had access to food and water ad libitum. Mice were housed individually and were allowed to acclimate to the vivarium for a period of at least 3 days, during which body weight was monitored. Test article was prepared in a lipid based formulation at a concentration of 8 mg/mL and dosed at a volume of 1.25 mL/kg for a final dose concentration of 10 mg/kg. Oral administration of vehicle or test compound occurred once daily, between 1500 and 1600 h each day, beginning on day 1 through day 15, the end of the study, as indicated. Additionally, a "no-treatment" group was included in which only body weights were monitored. As shown in Figure 2, **12h** dosed at 10 mg/kg produced robust weight loss of approximately 13% of initial body weight compared to vehicle-treated animals. There was no animal loss and no clinical observations noted for the duration of the study. Similar results were observed with **12e** (data not shown).

Conclusion

In summary, we have developed new synthetic routes to a novel class of CB1 inverse agonists involving sequential addition of substituents to a reactive bifunctionalized intermediate, amenable for combinatorial chemistry. A large number of compounds in this class were synthesized, and a general SAR was established. All compounds exhibited high CB1 vs CB2 receptor subtype selectivity, and the lead compounds showed excellent in vivo activities. Subsequent experiments demonstrated that both **12e** and **12h** promoted weight loss in rodents in chronic (multiday) dosing experiments. The solubility of the

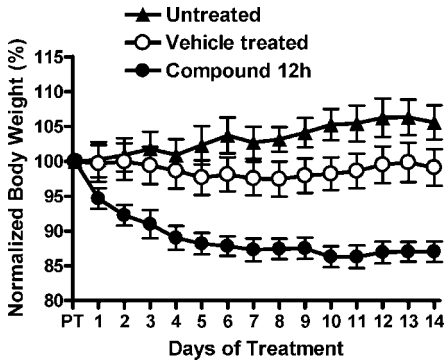


Figure 2. Weight-loss-promoting effects of compound **12h**. Compound **12h** was administered orally, qd, at 10 mg/kg to DIO mice as described above. Body weights were measured daily and are reported as normalized to initial body weight. Body weights for the animals used in these studies were between 40 and 44 g at the start of the study.

lead compound **12e** was improved by the introduction of a 3,4-dihalogenated phenyl group, which resulted in compound **12h**, a potential preclinical candidate as a CB1 inverse agonist.

Experimental Section

Chemistry. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian mercury 400 VX (^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz) spectrometer with solvent resonance as the internal standard: $CDCl_3$ (δ_H 7.26, δ_C 77.16); DMSO-d_6 (δ_H 2.50, δ_C 39.52); acetone-d_6 (δ_H 2.05, δ_C 29.84, 206.26); MeOH-d_4 (δ_H 3.31, δ_C 49.00). ^{1}H NMR are reported as follows: chemical shifts in ppm, coupling constants in Hz, multiplicity (s = singlet, br s = broad singlet, d = doublet, dd = double doublet, dt = double triplet, t = triplet, tt = triple triplet, m = multiplet). Unless otherwise mentioned, purities were determined by LCMS, equipped with 996 photodiode array detector (190−450 nm) and run in 10 mM NH_4OAc buffer with H_2O/MeCN gradient (0−0.5 min 30% MeCN, 0.5−5.5 min 30−100% MeCN, 5.5−7 min 100% MeCN). The column was am Xterra MS C18 3.5 μm 30 × 4.6 mm i.d., and elemental analysis results were obtained from a "2400 CHN elemental analyzer" by Perkin-Elmer in the microanalytical laboraties of Fakultät für Chemie, Universität Wien. The microwave-assisted reactions were carried out using a SmithCreator single mode cavity, producing continuous irradiation at 2450 MHz. Reaction temperature and pressure were determined using the built-in, online IR and pressure sensors. Analytical thin layer chromatography (TLC) was performed on silica gel 60 F_{254}. Visualization was accomplished with UV light. Purification of the reaction products was carried out by column chromatography using SiO_2 (60 Å, 200 μm). Melting points were obtained using SMP3 melting point apparatus with an open capillary tube and are uncorrected. HRMS analyses were recorded in FAB(+) mode using direct inlet at the University of Lund, Sweden. Unless otherwise noted, all reagents were obtained from commercial sources and used without further purification.

General Procedure for Iron-Catalyzed Alkylimidoyl Chloride Cross-Coupling. A flame-dried flask was charged under argon with the imidoyl chloride (0.05 mmol), $Fe(acac)_3$ (0.9 mg, 0.0025 mmol), tetrahydrofuran (1 mL), and NMP (0.1 mL). A solution of alkylmagnesium halide (2 M in Et_2O, 100 μL, 0.20 mmol) was slowly added to the resulting red solution, causing an immediate color change to dark brown. The resulting mixture was stirred for 10 min, and the reaction was then carefully quenched with NH_4Cl (aq) and diluted with Et_2O. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated to give the crude product. Purification by column chromatography (ethyl acetate/heptane/MeOH 1:1:0.05) gave the product (27−77%).

11-Cyclohexyl-*N*-(piperidin-1-yl)dibenzo[*b,f*][1,4]thiazepine-8-carboxamide (12a). The title compound was synthesized according to the general procedure using **11b** (530 mg, 1.43 mmol), $Fe(acac)_3$ (26 mg, 0.075 mmol), cyclohexylmagnesium chloride in diethyl ether (2M, 1.5 mL, 3.0 mmol), NMP (3 mL), and tetrahydrofuran (30 mL). The product was purified by silica gel column chromatography (0−50% ethyl acetate in heptane) to afford **12a** (460 mg, 77%): mp 123−136 °C; LCMS t_R = 4.98 min, *m/z* 420 $[M + H]^+$, purity (UV) 100%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.27 (m, 7H), 6.74 (br s, 1H), 2.92−2.74 (m, 5H), 2.16 (d, 1H, J = 13.6 Hz), 1.93 (d, 1H, J = 13.6 Hz), 1.86−1.64 (m, 8H), 1.48−1.24 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8, 164.6, 148.8, 140.2, 139.1, 134.9, 132.7, 132.6, 131.9, 130.5, 128.8, 127.3, 123.8, 123.3, 57.3, 49.0, 32.5, 30.1, 26.8, 26.3, 26.0, 25.4, 23.4; HRMS *m/e* calcd, 419.2031; found, 420.2106.

General Procedure for Amidine Formation. The appropriate imidoyl chloride (5 mg, 0.013 mmol) was mixed with an excess of the appropriate amine in dry toluene. The mixture was shaken for 18 h at 80 °C. Concentration of the reaction mixture at reduced pressure gave a crude product, which was purified by column chromatography (ethyl acetate/heptane 1:1 to 3:1).

***N*-(3-Chlorobenzyl)-11-(piperidin-1-yl)-dibenzo[*b,f*][1,4]thiazepine-8-carboxamide (12b).** The title compound was synthesized according to the general procedure for amidine formation using **11c** (840 mg, 2.0 mmol), piperidine (1.0 mL, 10 mmol), and toluene (25 mL). The product was purified by silica gel column chromatography (1:1 ethyl acetate/heptane) to give **12b** (911 mg, 99%) as a white solid: LCMS t_R = 5.27 min, *m/z* 462 $[M + H]^+$, purity (UV) 97; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.49 (m, 1H), 7.45 (dd, 1H, J = 0.3, 8.0 Hz), 7.41 (d, 1H, J = 1.9 Hz), 7.36−7.23 (m, 7H), 7.21−7.16 (m, 1H), 6.37 (br s, 1H), 4.55 (dd, 2H, J = 2.8, 6.0 Hz), 3.48 (br s, 4H), 1.80−1.50 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 161.3, 149.4, 140.3, 138.8, 134.9, 134.5, 134.4, 132.5, 132.2, 131.8, 130.8, 129.9, 128.8, 128.5, 127.8, 127.7, 125.9, 123.2, 120.9, 43.4, 25.0. Anal. ($C_{26}H_{24}ClN_3OS$) C, H, N.

***N*-(3-Chlorobenzyl)-11-(4,4-difluoropiperidin-1-yl)dibenzo-[*b,f*][1,4]thiazepine-8-carboxamide (12c).** The title compound was synthesized according to the general procedure for amidine formation using **11c** (400 mg; 0.97 mmol), 4,4-difluoropiperidine hydrochloride (700 mg, 4.4 mmol), and toluene (10 mL). Since the hydrochloride of the amine was used, triethylamine (1.2 mL) was also added to the mixture. The product was purified by silica gel column chromatography (1:9 ethyl acetate/heptane to pure ethyl acetate) to give **12c** (326 mg, 67%): LCMS t_R = 5.02 min, *m/z* 498 $[M + H]^+$, purity (UV) 100%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−7.50 (m, 1H), 7.46 (dd, 1H, J = 0.4, 8.0 Hz), 7.43 (d, 1H, J = 2.0 Hz), 7.40−7.27 (m, 5H), 7.25−7.22 (m, 2H), 7.20−7.16 (m, 1H), 6.37 (br s, 1H), 4.56 (d, 2H, J = 6.0 Hz), 4.00−3.60 (br s, 2H), 3.56−3.43 (br s, 2H), 2.20−1.88 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 160.7, 148.8, 140.2, 139.0, 135.0, 133.7, 132.5, 132.5, 131.8, 131.3, 130.0, 128.8, 128.7, 127.8, 127.7, 125.9, 123.3, 121.5, 43.4, 31.9, 22.7, 14.1; HRMS *m/e* calcd, 497.1140; found, 498.1219.

General Procedure for Palladium Catalyzed Negishi Cross-Coupling. The arylzinc halide (3−5 equiv) was added to the imidoyl chloride (10 mg) and $PdCl_2(PPh_3)_2$ (10 mol%) in dry tetrahydrofuran (1 mL) at room temperature. After 30 min saturated aqueous NH_4Cl and ethyl acetate was added and the aqueous phase was extracted once with ethyl acetate. The combined organic phases were washed with water, brine and then dried (Na_2SO_4). Filtration and concentration under reduced pressure of the organic phase followed by purification of the crude product by column chromatography (ethyl acetate/heptane, 1:1) gave the product.

***N*-(3-Chlorobenzyl)-11-(4-fluorophenyl)-dibenzo[*b,f*][1,4]thiazepine-8-carboxamide (12d).** The title compound was synthesized according to the general procedure using **11c** (681 mg, 1.65 mmol), 4-fluorophenylzinc iodide (0.5 M in tetrahydrofuran, 13.2 mL, 6.6 mmol), $PdCl_2(PPh_3)_2$ (70 mg, 0.10 mmol), and tetrahydrofuran (20 mL). Purification was by silica gel column chromatography (4:1 to 1:1, ethyl acetate/tetrahydrofuran). The isolated solid was recrystallized from ethyl acetate to give **12d** (514 mg, 66%) as light-yellow crystals: LCMS t_R = 5.32 min, *m/z* 473 $[M + H]^+$, purity (UV) 98%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85−7.80 (m, 2H), 7.73−7.70 (m, 2H), 7.58−7.51 (m, 3H), 7.44 (dt, 1H, J =

1.6, 7.4 Hz), 7.34−7.29 (m, 2H), 7.28−7.20 (m, 3H), 7.18 (dd, 1H, J = 1.6, 7.7 Hz), 7.15−7.09 (m, 2H), 6.45 (br s, 1H), 4.60 (d, 2H, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 166.6, 140.3, 134.9 (d, J = 210), 135.3, 133.0, 132.2, 132.1, 131.9, 130.8, 130.3, 128.4, 128.1 (d, J = 9), 126.2, 124.7, 123.9, 115.6 (d, J = 22), 43.8; HRMS *m*/*e* calcd, 472.0812; found, 473.0891.

***N*-Butyl-11-(4-chlorophenyl)dibenzo[*b*,*f*][1,4]thiazepine-8-carboxamide (12e).** The title compound was synthesized according to the general procedure using **11d** (530 mg, 1.5 mmol), 4-chlorophenylzinc iodide (0.5 M in tetrahydrofuran, 6.0 mL, 3.0 mmol), $PdCl_2(PPh_3)_2$ (55 mg, 0.078 mmol), and tetrahydrofuran (15 mL). Purification was by silica gel column chromatography (5−10% ethyl acetate in heptane). The isolated solid was recrystallized from ethyl acetate to give **12e** (383 mg, 59%) as light-yellow crystals: mp 217−219 °C; LCMS t_R = 5.35 min, *m*/*z* 421 $[M + H]^+$, purity (UV) 99%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77−7.73 (m, 2H), 7.64 (m, 1H), 7.56−7.53 (m, 1H), 7.51−7.48 (m, 2H), 7.45−7.38 (m, 3H), 7.30 (dt, 1H, J = 1.6, 7.6 Hz), 7.16 (dd, 1H, J = 1.6, 7.6 Hz), 6.06 (br s, 1H), 3.46−3.40 (m, 2H), 1.62−1.53 (m, 2H), 1.45−1.34 (m, 2H), 0.94 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 166.8, 148.72, 140.5, 138.6, 137.5, 137.0, 136.1, 132.8, 132.5, 132.2, 131.7, 131.2, 130.5, 128.7, 128.3, 124.5, 123.9, 40.1, 31.9, 20.3, 13.9. Anal. ($C_{24}H_{21}ClN_2OS$) C, H, N.

11-(3-Chlorophenyl)-*N*-isobutyldibenzo[*b*,*f*][1,4]thiazepine-8-carboxamide (12f). The title compound was synthesized according to the general procedure using **11e** (243 mg, 0.7 mmol), 3-chlorophenylzinc iodide (0.5 M in tetrahydrofuran, 3.0 mL, 1.5 mmol), $PdCl_2(PPh_3)_2$ (28 mg, 0.040 mmol), and tetrahydrofuran (8 mL). Purification was by silica gel column chromatography (0−10% ethyl acetate in toluene). The isolated solid was recrystallized from ethyl acetate/heptane to give **12f** (103 mg, 35%) as light-yellow crystals: LCMS t_R = 5.25 min, *m*/*z* 421 $[M + H]^+$, purity (UV) 100%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, 1H, J = 1.8, 1.8 Hz), 7.67−7.60 (m, 2H), 7.56 (dd, 1H, J = 1.1, 7.8 Hz), 7.52 (d, 2H, J = 1.2 Hz), 7.50−7.41 (m, 2H), 7.36 (dd, 2H, J = 7.7, 7.7 Hz), 7.32 (dd, 1H, J = 1.3, 7.5 Hz), 7.18 (dd, 1H, J = 1.4, 7.7 Hz), 6.13 (br s, 1H), 3.34−3.23 (m, 2H), 1.89 (dt, 1H, J = 6.7, 13.4 Hz), 0.98 (d, 6H, J = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 166.6, 148.5, 141.9, 140.3, 136.7, 135.9, 134.5, 132.7, 132.3, 132.0, 131.5, 130.8, 130.2, 129.5, 128.2, 127.9, 124.4, 123.5, 47.4, 28.6, 20.2; HRMS *m*/*e* calcd, 420.1063; found, 421.1144.

***N*-Butyl-11-(2-chlorophenyl)dibenzo[*b*,*f*][1,4]thiazepine-8-carboxamide (12g).** The title compound was synthesized according to the general procedure for palladium catalyzed cross coupling using **11d** (40 mg, 0.11 mmol), 2-chlorophenylzinc iodide (0.5 M in tetrahydrofuran, 880 μL, 0.44 mmol), $PdCl_2(PPh_3)_2$ (8.3 mg, 0.011 mmol), and tetrahydrofuran (2 mL). The crude was purified by silica gel column chromatography (5−10% ethyl acetate in heptane) to give **12g** (27.5 mg, 59%) as a red solid: LCMS t_R = 4.88 min, *m*/*z* 421 $[M + H]^+$, purity (UV) 99; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82−7.78 (m, 1H), 7.70 (d, 1H, J = 1.8 Hz), 7.55 (dd, 1H, J = 1.9, 8.1 Hz), 7.53 (s, 1H), 7.52−7.49 (m, 1H), 7.42−7.39 (m, 3H), 7.37 (dd, 1H, J = 1.4, 7.6 Hz), 7.22 (ddd, 1H, J = 1.3, 7.6, 7.6 Hz), 6.18 (s, 1H), 3.42 (dd, 2H, J = 7.1, 12.9 Hz), 1.62−1.52 (m, 2H), 1.33−1.44 (m, 2H), 0.94 (t, 3H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 166.5, 148.1, 140.5, 139.7, 138.7, 135.8, 133.2, 132.8, 132.2, 132.0, 131.5, 131.3, 130.8, 130.3, 129.2, 128.4, 126.8, 125.0, 124.1, 39.8, 31.7, 20.1, 13.7; HRMS *m*/*e* calcd, 420.1063; found, 421.1145.

***N*-Butyl-11-(3-chloro-4-fluorophenyl)dibenzo[*b*,*f*][1,4]thiazepine-8-carboxamide (12h).** The title compound was synthesized according to the general procedure using **11d** (100 mg;, 0.29 mmol), 3-chloro-4-fluorophenylzinc iodide (0.5 M in tetrahydrofuran, 2.4 mL, 1.2 mmol), $PdCl_2(PPh_3)_2$ (20 mg, 0.029 mmol), and tetrahydrofuran (10 mL). Purification by silica gel column chromatography (0−5% ethyl acetate in toluene) gave **12h** (120 mg, 94%) as a crystalline solid: mp 154−157 °C; LCMS t_R = 5.42 min, *m*/*z* 439 $[M + H]^+$, purity (UV) 100; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (dd, 1H, J = 2.2, 7.2 Hz, ArH), 7.67−7.63 (m, 1H, ArH), 7.63−7.62 (m, 1H, ArH), 7.55 (dd, 1H, J = 0.9, 7.8 Hz, ArH), 7.51−7.50 (m, 2H, ArH), 7.43 (ddd, 1H, J = 1.5, 7.4, 7.8 Hz, ArH), 7.33 (ddd, 1H, J = 1.3, 7.5, 7.7 Hz, ArH), 7.21−7.15 (m, 2H, ArH), 6.03 (br m, 1H, NH), 3.46−3.41 (m, 2H, NCH_2), 1.62−1.55 (m, 2H, CH_2), 1.45−1.36 (m, 2H, CH_2), 0.95 (t, 3H, J = 7.3 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 148.4, 140.3, 136.4, 135.9, 132.7, 132.5, 131.9, 131.9, 131.7, 130.1, 129.8, 129.7, 128.2, 124.4, 123.6, 116.4, 116.2, 77.3, 77.0, 76.7, 39.8, 31.7, 20.1, 13.7. Anal. ($C_{24}H_{20}ClFN_2OS$) C, H, N.

***N*-Butyl-11-(3,4-dichlorophenyl)dibenzo[*b*,*f*][1,4]thiazepine-8-carboxamide (12i).** The title compound was synthesized according to the general procedure using **11d** (100 mg, 0.29 mmol), 3,4-dichlorophenylzinc iodide (0.5 M in tetrahydrofuran, 2.4 mL, 1.2 mmol), $PdCl_2(PPh_3)_2$ (20 mg, 0.029 mmol), and tetrahydrofuran (10 mL). Purification was by silica gel column chromatography (0−5% ethyl acetate in toluene), and **12i** (120 mg, 94%) was isolated as a crystalline solid: mp 168−172 °C; LCMS (10 mM NH_4OAc buffer MeCN/H_2O, 0−0.5 min 50% MeCN, 0.5−10.5 min 50−100% MeCN, 10.5−12 min 100% MeCN) t_R = 6.83 min, *m*/*z* 455 $[M + H]^+$, purity (UV) 100; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, 1H, J = 2.0 Hz, ArH), 7.63 (d, 1H, J = 1.1 Hz, ArH), 7.60 (dd, 1H, J = 2.0, 8.4 Hz, ArH), 7.56 (d, 1H, J = 7.8 Hz, ArH), 7.51 (m, 3H Hz, ArH), 7.44 (ddd, 1H, J = 1.2, 7.5, 7.7 Hz, ArH), 7.32 (ddd, 1H, J = 1.2, 7.5, 7.7 Hz, ArH), 7.15 (dd, 1H, J = 1.3, 7.7 Hz, ArH), 6.04 (br m, 1H Hz, NH), 3.46−3.41 (m, 2H, NCH_2), 1.62−1.53 (m, 2H, CH_2), 1.45−1.36 (m, 2H, CH_2), 0.95 (t, 3H, J = 7.4 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 148.3, 140.4, 139.9, 136.3, 132.8, 132.5, 131.7, 131.3, 130.2, 130.0, 128.8, 128.2, 124.5, 123.6, 47.4, 28.6, 20.1. Anal. ($C_{24}H_{20}Cl_2N_2OS$) C, H, N.

11-(5-Chlorothiophen-2-yl)-*N*-isobutyldibenzo[*b*,*f*][1,4]thiazepine-8-carboxamide (12j). The title compound was synthesized according to the general procedure using **11e** (0.38 g, 1.1 mmol), 5-chloro-2-thienylzinc bromide (0.5 M in tetrahydrofuran, 8.8 mL, 4.4 mmol), $PdCl_2(PPh_3)_2$ (78 mg, 0.11 mmol), and dry tetrahydrofuran (10 mL). The mixture was purified by silica gel column chromatography (toluene) and crystallized from toluene to give **12j** (88 mg, 19%) as a yellow solid: mp 217−219 °C; LCMS t_R = 5.37 min, *m*/*z* 427 $[M + H]^+$, purity (UV) 97%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (ddd, 2H, J = 0.7, 1.4, 7.7 Hz), 7.50 (d, 2H, J = 1.6 Hz), 7.47 (dd, 1H, J = 1.7, 7.5 Hz), 7.43 (dd, 1H, J = 1.7, 7.6 Hz), 7.37 (ddd, 1H, J = 1.3, 7.5, 7.5 Hz), 6.91 (dd, 2H, J = 4.0, 15.8 Hz), 6.12 (br s, 1H), 3.36−3.18 (m, 2H), 1.87 (dt, 1H, J = 6.7, 13.5 Hz), 0.96 (d, 6H, J = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 162.4, 148.2, 144.9, 140.2, 136.8, 136.0, 135.1, 132.8, 132.6, 131.8, 131.7, 131.7, 130.0, 128.1, 127.1, 124.4, 123.6, 47.4, 28.6, 20.1; HRMS *m*/*e* calcd, 426.0627; found, 427.0704.

***N*-Isopentyl-11-(pyridin-2-yl)dibenzo[*b*,*f*][1,4]thiazepine-8-carboxamide (12k).** The title compound was synthesized according to the general procedure using **11f** (220 mg, 0.61 mmol), $PdCl_2(PPh_3)_2$ (28 mg, 0.04 mmol), 2-pyridylzinc bromide (0.5 M in tetrahydrofuran, 2.8 mL, 1.4 mmol), and tetrahydrofuran (10 mL). Purification by silica gel column chromatography (25% ethyl acetate in toluene) followed by ion exchange on an acidic SPE column, eluting with 1 M NH_3 in MeOH, gave **12k** (127 mg, 52%) as a yellow solid: LCMS t_R = 4.17 min, *m*/*z* 402 $[M + H]^+$, purity (UV) 99%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69−8.66 (m, 1H), 8.63−8.59 (m, 1H), 8.30−8.25 (m, 1H), 7.84 (dt, 1H, J = 1.7, 7.6 Hz), 7.72−7.81 (m, 1H), 7.56−7.50 (m, 2H), 7.42−7.18 (m, 5H), 6.16 (br s, 1H), 3.44 (q, 2H, J = 6.8 Hz), 1.66 (m, 1H, J = 6.8 Hz), 1.48 (q, 2H, J = 6.8 Hz), 0.93 (d, 6H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 166.6, 157.2, 149.1, 148.5, 139.9, 136.9, 136.7, 135.8, 132.8, 132.5, 132.4, 131.5, 130.9, 127.9, 124.9, 124.9, 124.2, 124.1, 38.6, 38.6, 26.0, 22.6. Anal. ($C_{24}H_{23}N_3OS$) C, H, N.

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Supporting Information Available: Synthetic procedures, characterization for all exemplified compounds, biological methods,

and receptor selectivity for **12a**, **12e**, and **12h** and PK data (rat) for compounds **12a** and **12e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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