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# Dihydro-pyrano[2,3-*b*]pyridines and tetrahydro-1,8-naphthyridines as CB1 receptor inverse agonists: Synthesis, SAR and biological evaluation

Christina B. Madsen-Duggan [a,*], John S. Debenham [a,*], Thomas F. Walsh [a], Lin Yan [a], Pei Huo [a], Junying Wang [a], Xinchun Tong [a], Julie Lao [b], Tung M. Fong [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], Mark T. Goulet [a,‡], Jeffrey J. Hale [a]

[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*

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ABSTRACT

Synthesis and structure–activity relationships of cannabinoid-1 receptor (CB1R) inverse agonists based on dihydro-pyrano[2,3-*b*] pyridine and tetrahydro-1,8-naphtyridine scaffolds are presented. Rat food intake and pharmacokinetic evaluation of **13g**, **13i**, **13k** and **17a** revealed these compounds to be highly efficacious orally active modulators of CB1R.

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The cannabinoid-1 receptor is found predominantly in the CNS and is activated by the endocannabinoids.[1] An inverse agonist/antagonist of the cannabinoid-1 receptor (CB1R)[2] has the ability to suppress food intake in both humans[3] and other animals.[4] CB1R inhibition has been demonstrated effective in treating obesity.[3]

Merck Research Laboratories have disclosed several series of CB1R modulators where a central heterobicyclic scaffold was strategically flanked by hydrophobic domains (Fig. 1).[5] Naphthyridinone **1**[5a] was our first bicyclic core and was found to effect in vivo efficacy similar to that of MK-0364/taranabant; which has been extensively studied in preclinical species and in humans (Fig. 1).[6] As compound **1** showed low clearance, an optimization effort in reducing the half-life led to furopyridine **2**.[5b] While **2** had an appropriate pharmacokinetic profile for clinical advancement, it was later found to be a partial agonist of human $GABA_A$ receptors ($EC_{50}$ of about 700 nM with a maximum efficacy of 18% at 3 μM relative to maximum GABA activity). CNS adverse events, presumably related to this GABA activity, were seen at levels 100 times its MED of 0.3 mg/kg.[5b] At the same time efforts to eliminate the off target activity of **2** were underway, we initiated a simultaneous ef-

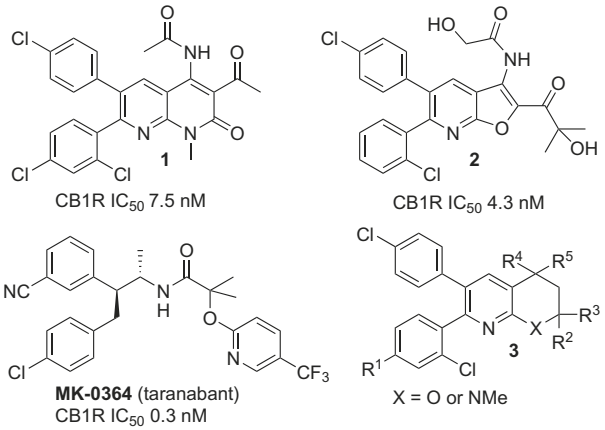


**Figure 1.** Early Merck leads, taranabant and core structure **3**.

* Corresponding authors. Tel.: +1 732 594 5497; fax: +1 732 594 2210.
*E-mail address:* john.debenham@merck.com (J.S. Debenham).
† Present address: Forest Research Institute, Jersey City, NJ 07311, USA.
‡ Present address: Merck Research Laboratories, 33 Avenue Louis Pasteur, Boston, MA 02115, USA.

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fort exploring the structurally related core **3**. Herein, the synthesis and structure–activity relationships (SAR) of the generalized bicyclic core **3** are described.

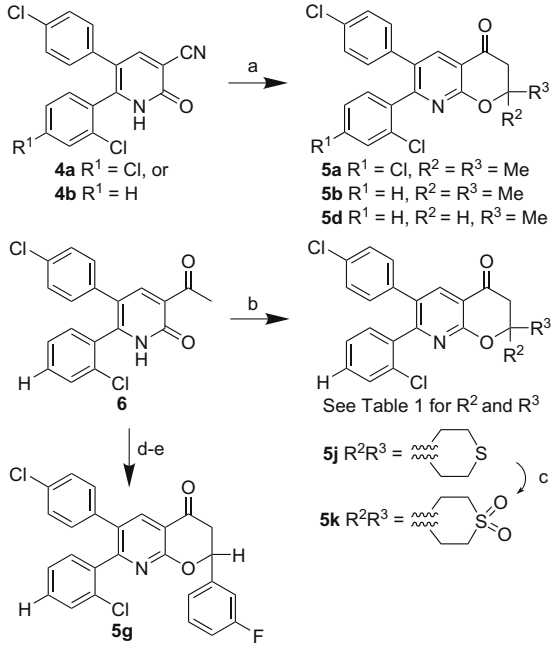
In order to probe the 2-position of the β face of the pyranopyridine scaffold, our initial strategy involved the addition of vinyl Grignard reagents to the cyano group of **4a**[7] or **4b**[5a] (Scheme 1) followed by intramolecular cyclization of the pyridone oxygen onto the resulting vinyl ketone. This generated dimethyl ketones **5a–b**, and the monomethylated ketone **5d**, in yields ranging between 11% and 58% (Table 1).

An alternative approach involved an aldol condensation strategy. 3-Acetylpyridone **6**[5a] was treated with various ketones, and pyrrolidine, at elevated temperatures using either conventional or microwave heating (Scheme 1). This effort led to diethyl **5c**, mono *i*-propyl and *t*-butyl derivatives **5e** and **5f** and also the spiroannulated compounds **5h–j** and **5l** in yields ranging from 8% to 100% (Table 1). Pyridone **6** could also be treated with acetone and DBU at elevated temperature affording **5a** in 37% yield.[8]

Sulfide **5j** was readily oxidized with magnesium bis(monoperoxyphthalate), providing sulfone analog **5k**. To obtain the phenyl derivative **5g**, pyridone **6** was treated with 3-fluoro benzaldehyde and NaOMe, affording the intermediate uncyclized phenyl 3-hydroxypropanoylpyridone. The ketol was treated with tosic acid in toluene at 120 °C, yielding predominantly the α,β-unsaturated ketone product, providing **5g** in low yield (Scheme 1, Table 1).

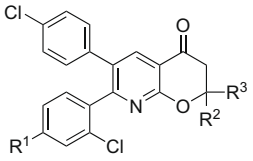
The hydroxy analogs **7a** and **7b** were obtained by reacting **5a** with $NaBH_4$ or methyl Grignard, respectively (Scheme 2, Table 3). Treatment of **7a** with NaH and MeI afforded ether **7c**.

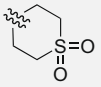
As noted previously,[5] the amides in the structural series represented by **1** and **2** imparted significant potency and efficacy enhancement. In order to evaluate both amide enantiomers, a racemic synthesis was used (Scheme 2). Ketones **5a** or **5i** were first converted to the oxime, followed by reduction with zinc in acetic acid affording the amines in about 80% yield. The spiroannulated cyclohexyl amine was then treated with acid chlorides to generate amides **12a** or **8–10**. Alternatively, either amine underwent PyBOP coupling to yield amides **11**, **12c–h** and **13g–h** (Tables 2 and 4). The hydroxy amides, **12b** and **13a–f**, were synthesized by treating the corresponding acetoxy amides **8–11** with NaOMe in MeOH. In order to obtain 'reversed' amides **14a–d** (Table 5), ketone **5a** was

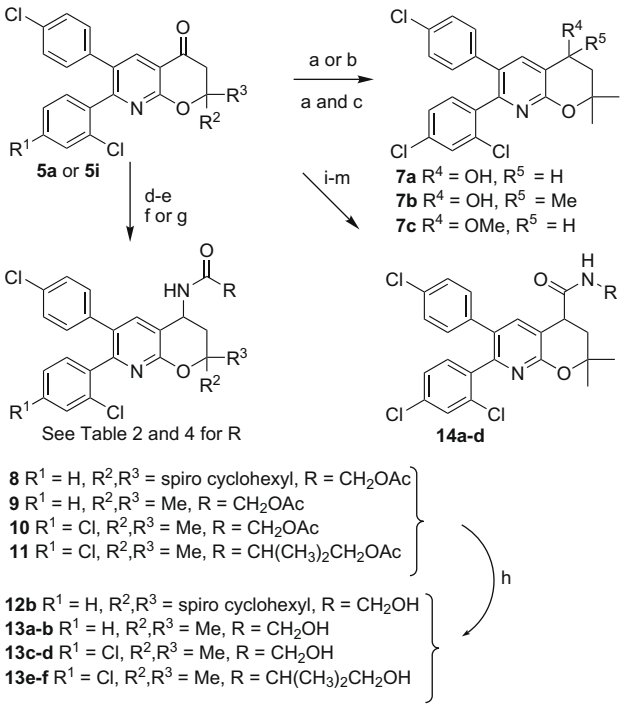



**Scheme 1.** Reagents and conditions: (a) 1 equiv MeMgBr, $R^1R^2C{=}CMgBr$, THF, 2 M HCl, rt, 11–58%; (b) $R^1R^2CO$, pyrrolidine, microwave heating, 150 °C or $R^1R^2CO$, pyrrolidine, MeCN, 60 °C, 8–100%; (c) MMPP, $CH_2Cl_2$, MeOH, rt, 84%; (d) 3-fluorobenzaldehyde, MeONa, THF, MeOH, rt, 75%; (e) TsOH, toluene, 120 °C, 7%.

**Table 1**
Structures and binding affinities of compounds at the human CB1R and CB2R expressed as $IC_{50}$ (nM), of the ketone derivatives **5a–l**[10]

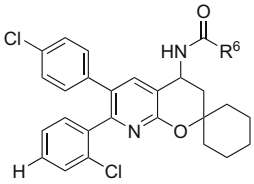


| Compound | $R^1$ | $R^2$ | $R^3$ | CB1R | CB2R |
|---|---|---|---|---|---|
| **5a** | Cl | Me | Me | 47 | 1300 |
| **5b** | H | Me | Me | 120 | 2300 |
| **5c** | H | Et | Et | 15 | 4200 |
| **5d**, racemic | H | H | Me | 21 | 6300 |
| **5e**, racemic | H | H | *i*-Pr | 3.2 | 3300 |
| **5f**, racemic | H | H | *t*-Bu | 1.9 | 3400 |
| **5g**, racemic | H | H | 3-FPh | 1.7 | >2000 |
| **5h** | H | Spiro cyclopentyl | | 23 | 3000 |
| **5i** | H | Spiro-cyclohexyl | | 8.2 | 8300 |
| **5j** | H |  | | 4.9 | 8000 |
| **5k** | H |  | | 15 | 4100 |
| **5l** | H |  | | 790 | >2000 |




**Scheme 2.** Reagents and conditions: (a) $NaBH_4$, THF, 0 °C, 92%; (b) MeMgBr, THF, 0 °C, 14%; (c) MeI, NaH, DMF, rt, 28%; (d) $HONH_2{\cdot}HCl$, TEA, KOAc, MeOH, 70 °C; (e) Zn, AcOH, 95 °C, (two steps), 86–95%; (f) RCOCl, TEA, $CH_2Cl_2$, rt, 40–84%; (g) $RCO_2H$, PyBOP, HOBt, DIPEA, DMF, rt, 39–80%; (h) NaOMe, MeOH, rt, (two steps), 78–81%; (i) phenyl triflate, LiHMDS, DMF, −78 °C, 91%; (j) CO, $Pd(dppf)Cl_2{\cdot}diCH_2Cl_2$, TEA, MeOH, DMF, 70 °C, 81%; (k) Te, $NaBH_4$, EtOH, AcOH, 70–20 °C, 65%; (l) 10% KOH, THF, 70 °C, 96%; (m) $NH_4Cl$ or $RNH_2$, PyBOP, HOBt, DIPEA, DMF, rt, 41–95%.

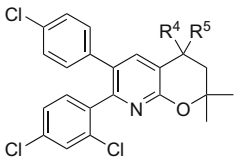
**Table 2**
Structures and binding affinities of compounds at the human CB1R and CB2R expressed as $IC_{50}$ (nM), of the spiro cyclohexyl amide derivatives **12a–h**[10]



| Compound | $R^6$ | CB1R | CB2R |
|---|---|---|---|
| **12a**, racemic | Me | 1.3 | 3900 |
| **12b**, racemic | $CH_2OH$ | 0.3 | 4200 |
| **12c**, E1 | $C(CH_3)_2OH$ | 0.7 | 3200 |
| **12d**, E2 | | 18 | 12,000 |
| **12e**, E1 | (1*S*)-1-Ethanolyl | 0.4 | 1800 |
| **12f**, E2 | | 13 | 10,000 |
| **12g**, E1 | (1*R*)-1-Ethanolyl | 0.2 | 3600 |
| **12h**, E2 | | 2.0 | 3400 |

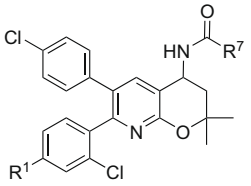
E1 = Enantiomer 1; E2 = enantiomer 2.

**Table 3**
Structures and binding affinities of compounds at the human CB1R and CB2R expressed as $IC_{50}$ (nM), of the gem-dimethyl amide derivatives **7a–d**[10]



| Compound | $R^4$ | $R^5$ | CB1R | CB2R |
|---|---|---|---|---|
| **7a**, racemic | H | OH | 130 | 4950 |
| **7b**, racemic | Me | OH | 80 | 2920 |
| **7c**, racemic | H | OMe | 19 | 3790 |
| **7d**, racemic | H | $NH_2$ | 110 | 7760 |

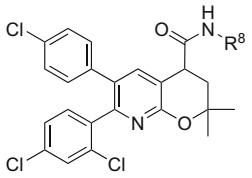
**Table 4**
Structures and binding affinities of compounds at the human CB1R and CB2R expressed as $IC_{50}$ (nM), of the gem-dimethyl amide derivatives **13a–l**[10]



| Compound | $R^1$ | $R^7$ | CB1R | CB2R |
|---|---|---|---|---|
| **13a**, E1 | H | $CH_2OH$ | 46 | >2000 |
| **13b**, E2 | | | 360 | 10,130 |
| **13c**, E1 | Cl | $CH_2OH$ | 1.7 | 4780 |
| **13d**, E2 | | | 670 | 6610 |
| **13e**, E1 | Cl | $CH(CH_3)_2CH_2OH$ | 2.1 | 570 |
| **13f**, E2 | | | 34 | 7600 |
| **13g**, E1 | Cl | $(CH_3)_2OH$ | 1.7 | 2460 |
| **13h**, E2 | | | 14 | 5400 |
| **13i**, E1 | |  | 4.8 | 2260 |
| **13j**, E2 | Cl | | 78 | 5310 |
| **13k**, E1 | |  | 3.0 | 4750 |
| **13l**, E2 | Cl | | 16 | 3450 |

E1 = Enantiomer 1; E2 = enantiomer 2.

**Table 5**
Structures and binding affinities of compounds at the human CB1R and CB2R expressed as $IC_{50}$ (nM), of the gem-dimethyl amide derivatives **14a–d**[10]



| Compound | $R^8$ | CB1R | CB2R |
|---|---|---|---|
| **14a**, E1 | H | 97 | 2480 |
| **14b**, E2 | | 220 | >2000 |
| **14c**, E1 | $CH(CH_3)_2CH_2OH$ | 14 | 5150 |
| **14d**, E2 | | 150 | 7450 |

E1 = Enantiomer 1; E2 = enantiomer 2.

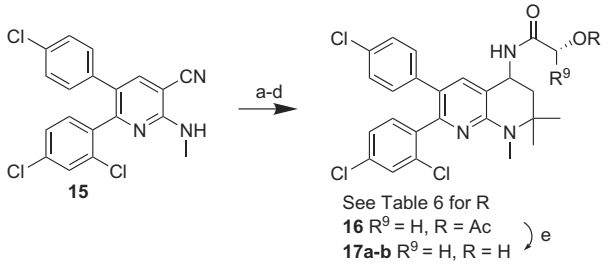
initially converted to the triflate and then carboxylated yielding the unsaturated methyl ester. The unsaturated ester was reduced with tellurium[9] and $NaBH_4$ and then saponified. The resulting saturated acid was coupled to various amines with PyBOP yielding **14a–d**.

It was of interest to examine the importance of the pyran oxygen and its impact on binding affinity. The *N*-methyl amino derivatives (tetrahydro-1,8-naphthyridine) **17a–d** were readily prepared as described previously except starting with the *N*-methyl pyridine **15**[5a] instead of pyridone **4a** or **4b** (Scheme 3, Table 6).

Binding affinities were determined using a standard protocol[10] and all compounds tested were found to be functional inverse agonists.

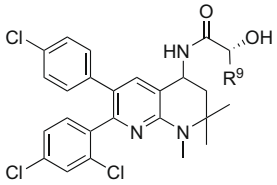
Our initial efforts focused on optimization of the $R^2$ and $R^3$ positions of **3**. In general, as the size and hydrophobicity of these positions increased from methyl, so did the potency at CB1R (Table 1). When $R^2$ and $R^3$ were both methyl there was little difference (2.6-fold) in activity when $R^1$ was chlorine **5a** or hydrogen **5b**. Interestingly, the monomethylated **5d** showed about a sixfold increase compared to the corresponding **5b** and an eightfold potency increase was observed going from the dimethyl of **5b**, to the diethyl of **5C**. Mono *iso*-propyl **5e**, mono *tert*-butyl **5f** and aryl **5g** were most potent at about 2–3 nM. The spiroannulated **5h**, **5i**, **5j** and **5k** all had potency in the 5–23 nM range while the spiroannulated methyl piperidine was over 50-fold less active than sulfone **5k**, indicated a strong intolerance for basic groups at this position.

Even though **5e**, **5f**, and **5g** showed a little more potency at CB1R than achiral **5i**, we wanted to minimize the complications of including an extra chiral center. This led us to evaluate amides in the spiro-cyclohexyl series first (Table 2). Racemic acetamide showed a sixfold (relative to **5i**) increase in potency to 1.3 nM while the racemic glycolamide **12b** exhibited a 27-fold CB1R po-




**Scheme 3.** Reagents and conditions: (a) $(CH_3)_2C{=}CHMgBr$ or $CH_3C{=}CHMgBr$, THF, 2 M HCl, rt, 59 %; (b) $HONH_2HCl$, TEA, KOAc, MeOH, 70 °C; (c) Zn, AcOH, 95 °C, (two steps), 88%; (d) AcOAcCl, TEA, $CH_2Cl_2$, rt, or D-lactic acid, PyBOP, HOBt, DIPEA, DMF, rt, 60%; (e) NaOMe, MeOH, rt, (two steps), 70%.

**Table 6**
Structures and binding affinities of compounds at the human CB1R and CB2R expressed as $IC_{50}$ (nM), of the gem-dimethyl amide derivatives **17a–d**[11]




| Compound | $R^9$ | CB1R | CB2R |
|---|---|---|---|
| **17a**, E1 | H | 3.7 | 801 |
| **17b**, E2 | | 76 | 3390 |
| **17c**, E1 | Me | 1.8 | 1280 |
| **17d**, E2 | | 29 | 2330 |

E1 = Enantiomer 1; E2 = enantiomer 2.

tency enhancement. Additionally, **12b** also displayed a 14,000-fold selectivity over CB2R. Upon resolution of hydroxy amide analogs **12c–h** a 10–30-fold preference for one enantiomer was observed with the more active enantiomers all subnanomolar in activity at CB1R. In the case of **12h** even the less active enantiomer was still quite potent at 2 nM for CB1R.

The compounds of Table 3 confirm the need for substitution at the 4-position of the dihydropyrano ring. Hydroxy and amino compounds **7a**, **7b** and **7d** were poorly tolerated at about 80–130 nM CB1R. Even methylation of the heteroatom such as methoxy **7c** showed improvement to 19 nM CB1R.

To determine if the spiro-cyclohexyl ring of amides **12a–h** was required for good binding, the gem-dimethyl pyranopyridine **5a** and **5b** were also examined. There was a strong preference for the tri-chloro substitution pattern (Table 4) as shown by the 25-fold potency enhancement of **13c** over the dichloro **13a**. As was the case for the spiroannulated series (Table 2), the hydroxy amides with the gem-dimethyl substitution showed excellent activity with a strong preference for one enantiomer (Table 4). The 2-hydroxyacetamide **13c**, 3-hydroxy-2,2-dimethylpropanamide **13e**, dimethyl hydroxy **13g**, L-lactic acid derivative **13i** and the D-lactic acid analog **13k** all showed similar activity (CB1R, $IC_{50}$ = 2–5 nM).

Unlike the N-linked amides of Tables 2 and 4, the C-linked amides of Table 5 were less well tolerated with the best, **14c**, at 14 nM CB1R. The primary amides **14a** and **14b** ranged from about 100 to 220 nM.

Table 6 showed that the oxygen of the dihydropyrano ring could be readily exchanged with *N*-methyl, as the resultant glycolamide **17a** and (2*R*)-2-hydroxypropanamide **17c** showed equivalent potency with the pyran series analogs. Again there was a large preference for one enantiomer as has been shown with the other N-linked amides.

Several compounds were selected for evaluation of their effects on food intake (FI) and body weight (BW) changes in diet-induced obese (DIO) rats.[5a] The compounds were all dosed orally at 3 mg/kg and the rats were monitored for 18 h and compared to vehicle treated animals (Table 7). The cyclohexyl spiroannulated series amide **12c** showed a 28% reduction in suppressing overnight FI. All of the dimethyl series amides showed very robust effects at reducing BW and suppressing FI with **13i** and structurally similar **13k** showing a remarkable 72% suppression of FI. The tetrahydro-1,8-naphthyridines, **17a** and **17c** were also effective at suppressing FI and BW with the glycolamide showing a more robust FI suppression. As a comparison, taranabant elicited a FI suppression of 49%[6] at 3 mg/kg.

**Table 7**
Rat food intake/body weight change (g) overnight (18 h)[a]

| Compound | Δ Body weight (control) | Δ Body weight (compound) | % Food intake suppression |
|---|---|---|---|
| **12c** | +7 | +3 | 28 |
| **13g** | +5 | −11 | 48 |
| **13i** | +5 | −19 | 72 |
| **13k** | +5 | −16 | 72 |
| **17a** | +6 | −8 | 55 |
| **17c** | +6 | −5 | 24 |
| Taranabant | +10 | −10 | 49 |

[a] All rats were dosed at 3 mg/kg. The effects of all compounds were significant compared to control ($p$ <0.05).

**Table 8**
Pharmacokinetic profiles (rats)

| Compound | *F* (%) | $T_{1/2}$ (h) | Cl*p* (mL/min/kg) | Brain/plasma levels at 4 h (μM)<br>Brain/plasma ratio |
|---|---|---|---|---|
| **12b** | 13 | 0.8 | 34 | 0.027/0.016<br>1.7 |
| **12c** | 6 | 1.9 | 62 | 0.116/0.033<br>3.5 |
| **13g** | 85 | 13 | 3 | —<br>— |
| **13k** | 100 | 7.9 | 4 | 0.122/0.321<br>0.38 |
| **17**[a] | 25 | 4.2 | 12 | 0.076/0.086<br>0.88 |

Brain/plasma concentrations were determined at 4 h following 1 mg/kg IV dosing.

The pharmacokinetic properties for selected compounds are displayed in Table 8.[6] The cyclohexyl spiroannulated series represented by **12b** and **12c** had high clearance and poor oral bioavailability (6–13%). Of note was compound **12c**. Even though it had the worst bioavailability (6%), and most rapid clearance (62 mL/min/kg) of the group, its favorable B/P ratio (3.5) allowed for sufficient CNS permeation to show FI and BW effects. Tetrahydro-1,8-naphthyridine **17a** showed somewhat improved bioavailibity (25%), while compounds **13g** and **13k** both had high oral bioavailability (>80%) and robust half-lives (8–13 h). Not surprisingly these compounds showed very robust actions on FI suppression and BW changes.

Counterscreening of lead compounds **13g**, **13i**, **13k** and **17a** revealed them to have potent activity in the hERG potassium ion channel assay (380, 340, 120 and 40 nM $IC_{50}$, respectively). Other amides represented by Tables 2, 4 and 6 also had strong hERG affinity (most <500 nM $IC_{50}$). It should be noted that the hERG activity of the amides was largely absent from the ketones of Table 1, many of which were >3–10 μM $IC_{50}$.

In summary, we have shown that both dihydro-pyrano[2,3-*b*]pyridine and tetrahydro-1,8-naphthyridine bicyclic core structures, (exemplified by **13g**, **13i**, **13k** and **17a**) are orally effective modulators of food intake and body weight in a rodent model of feeding. While these compounds have excellent CB1R activity, they also possess considerable hERG affinity as well. Our efforts to attenuate this hERG activity will be the subject matter of another report.[11]

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