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Discovery of imidazole carboxamides as potent and selective CCK1R agonists

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ABSTRACT

High-throughput screening revealed diaryl pyrazole **3** as a selective albeit modest cholecystokinin 1 receptor (CCK1R) agonist. SAR studies led to the discovery and optimization of a novel class of 1,2-diaryl imidazole carboxamides. Compound **44**, which was profiled extensively, showed good in vivo mouse gallbladder emptying (mGBE) and lean mouse overnight food intake (ONFI) reduction activities.

Cholecystokinin (CCK) is a peptide hormone secreted by the duodenum in response to intraluminal nutrients (particularly fat and protein). There are two CCK receptors, CCK1R and CCK2R (also known as CCKA and CCKB receptors, respectively), which belong to the G-protein coupled receptor (GPCR) superfamily. CCK1R stimulation causes decreased food intake, delayed gastric emptying, increased gallbladder emptying and increased pancreatic exocrine secretion. CCK2R is the stomach gastrin receptor, mediating gastric acid secretion, and is also widely expressed and functional in the CNS.[1]

Since Gibbs et al. first demonstrated the satiety actions of CCK in rats,[2] CCK has been shown to inhibit food intake in multiple species, including humans.[3] CCK1R agonists, including peptides, peptoids, and small molecules, have been studied as satiety agents for the treatment of obesity.[4] Both the 1,5-benzodiazepine-based GI181771X (**1**) and the thiazole SR-146131 (**2**) reached clinical trials (Fig. 1).[4] Recent phase II studies revealed that GI181771X (**1**) alone did not cause weight loss in overweight or obese patients after 24 weeks, and it was suggested that combination therapy should be assessed in future studies.[5a] Tolerability-limiting gastrointestinal events including vomiting and diarrhea were observed,[5] which might prohibit dosing at a level sufficient to cause robust weight loss.

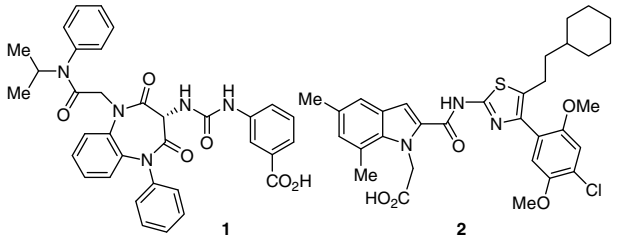

Figure 1. CCK1R agonists GI181771X (**1**) and SR-146131 (**2**).

Through a high-throughput screening campaign, 1,5-diaryl pyrazole carboxamide **3** (Fig. 2) was identified as a selective albeit

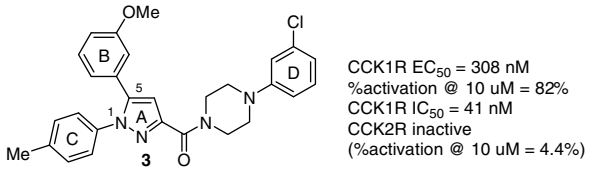

Figure 2. CCK1R agonist hit from high-throughput screening.

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modest CCK1R agonist.[6,7] Herein, we describe the SAR studies around this novel CCK1R agonist scaffold which led to the discovery of a class of highly potent and selective CCK1R agonists.

SAR studies started with replacement of the central 1,5-diaryl pyrazole core A with a variety of 5-membered heteroaromatic rings. A series of isomeric pyrazoles, imidazoles, oxazoles, thiazoles, and triazoles were incorporated as cores in this system, but only 1,2-diaryl imidazole **4** (Fig. 3) was found to have improved potency relative to **3**. All other heterocycles were less active against CCK1R.

The synthesis of 1,2-diaryl imidazoles is outlined in Scheme 1.[8] A variety of aryl groups Ar^1 and Ar^2 were incorporated into the imidazole ring by condensing arylamidine **5** with 3-bromo-2-oxopropanoate in 1,4-dioxane or THF. After saponification, the resulting 1,2-diaryl-1*H*-imidazole carboxylic acid **6** was coupled with aryl piperazine **7** either by EDC/HOBt or MsCl/1-methylimidazole activation.[9]

Pd catalyzed C–N bond formation was utilized for the synthesis of most non-commercially available aryl piperazines **7** (Scheme 2).[10] For some aryl piperazines such as 2-piperazin-1-yl-1*H*-benzimidazole, direct nucleophilic aromatic substitution was utilized (not shown).

The compounds synthesized were examined for their ability to bind and activate CCK1R using a variety of in vitro assays.[6] SAR studies of Ar^3 groups (Table 1) at the piperazine revealed that both the agonist activity (EC_{50}) and binding affinity (IC_{50}) of 3,4-dichlorophenyl **8** (EC_{50} = 25 nM, IC_{50} = 8.0 nM) were improved compared with that of **4**. Further improvements were noted with the 2-naphthyl piperazine derivative **9** (EC_{50} = 9.6 nM and IC_{50} = 2.5 nM) while the 1-naphthyl derivative **10** was much less potent. Benzimidazole **11** had slightly reduced potency compared with the 2-naphthyl derivative **9**. For quinolines and isoquinolines **12**–**16**, the point of attachment had variable affects on CCK1R activities, with quinoline **14** (EC_{50} = 1.1 nM, IC_{50} = 1.3 nM) being the most potent. Carboxylic acid substitution on the naphthyl ring was next explored. Acid **17** was found to possess improved potency (EC_{50} = 0.40 nM, IC_{50} = 1.3 nM) relative to **9**. Acid **18** afforded the greatest improvement in both CCK1R functional and binding activities (EC_{50} = 0.078 nM, IC_{50} = 0.14 nM).

Since the 2-naphthyl compound **9** showed improved CCK1R activities compared with the original 3-chlorophenyl derivative **4**, SAR studies at the B and C rings were performed with 2-naphthylpiperazine derivatives (Tables 2 and 3). The crucial role of the 3-alkoxy group on the B-ring is illustrated in Table 2 by comparing **9** (EC_{50} = 9.6 nM, IC_{50} = 2.5 nM) with the 3-ethyl analog **20**

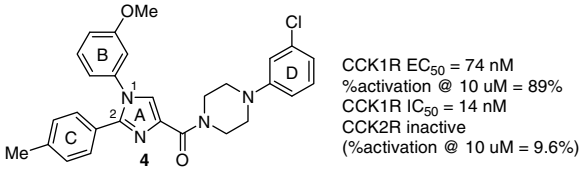
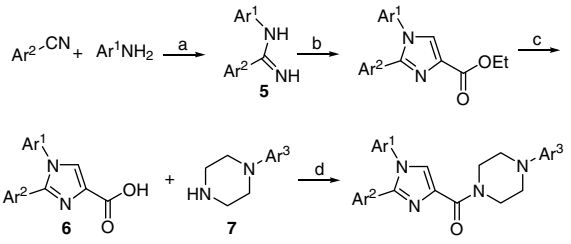
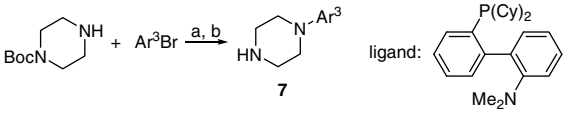


Figure 3. 1,2-Diaryl imidazole core with improved potency.

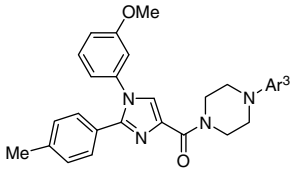


Scheme 1. Synthesis of 1,2-diaryl imidazole carboxamides. Reagents and conditions: (a) NaHMDS, THF; (b) ethyl 3-bromo-2-oxopropanoate, $NaHCO_3$, 1,4-dioxane or THF, Δ; (c) NaOH, THF/MeOH/H_2O; (d) EDC, HOBt, *i*-Pr_2NEt or MsCl, 1-methylimidazole.



Scheme 2. Synthesis of aryl piperazine **7**. Reagents: (a) NaO*t*-Bu, $Pd(dba)_2$, ligand; (b) TFA, CH_2Cl_2.

Table 1
Affects of D-ring modification Ar^3

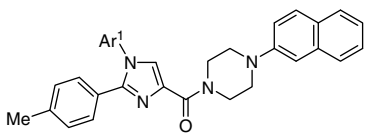


4, **8-18**

Compound	Ar^3 =	EC_{50}[a,b] (nM)	IC_{50}[c] (nM)
4	3-ClPh	74 (89% act)	14
8	3,4-Cl_2Ph	25 (99% act)	8.0
9	2-Naphthyl	9.6 (99% act)	2.5
10	1-Naphthyl	5371 (30% act)	630
11	1*H*-Benzimidazol-2-yl	9.1 (89% act)	17
12	Quinolin-2-yl	43 (89% act)	16
13	Isoquinolin-3-yl	8.4 (89% act)	1.9
14	Quinolin-3-yl	1.1 (92% act)	1.3
15	Quinolin-6-yl	9.3 (108% act)	8.6
16	Isoquinolin-6-yl	106 (86% act)	190
17	2-Naphthoic acid-3-yl	0.40 (92% act)	1.3
18	1-Naphthoic acid-3-yl	0.078 (85% act)	0.14

[a] CCK_IP3 (CCK1 human, NFAT) agonist data, values are mean of ⩾3 experiments except compound **18** (n = 2), standard deviations are ⩽82% of the mean. % Activation at 10,000 nM is given in parentheses.[6]
[b] CCK2R inactive (% activations are ⩽20% at 10,000 nM).[6]
[c] Mean of ⩾3 experiments, standard deviations are ⩽92% of the mean.

Table 2
Affects of B-ring modification Ar^1

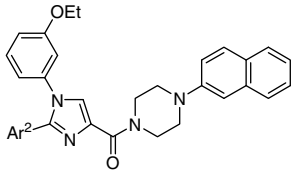


9, **19-28**

Compound	Ar^1 =	EC_{50}[a,b] (nM)	IC_{50}[c] (nM)
9	3-MeOPh	9.6 (99% act)	2.5
19	4-MeOPh	20 (110% act)	6.9
20	3-EtPh	65 (101% act)	43
21	3-HOPh	82 (102% act)	22
22	3-EtOPh	6.6 (93% act)	2.3
23	3-*n*-PrOPh	962 (89% act)	160
24	3-*i*-PrOPh	53 (94% act)	30
25	3-CF_3OPh	3152 (66% act)	130
26	3-CF_3CH_2OPh	1349 (95% act)	200
27	3,4-(OCH_2CH_2O)Ph	0.99 (89% act)	0.42
28	2,3-(OCH_2CH_2O)Ph	471(70% act)	140

[a] CCK_IP3 (CCK1 human, NFAT) agonist data, values are mean of ⩾3 experiments, standard deviations are ⩽71% of the mean. % Activation at 10,000 nM is given in parentheses.[6]
[b] CCK2R inactive (% activations are ⩽21% at 10,000 nM).[6]
[c] Mean of ⩾3 experiments, standard deviations are ⩽86% of the mean.

Table 3
Affects of C-ring modification Ar^2



22, 29-37

Compound	Ar^2 =	EC_{50}[a,b] (nM)	IC_{50}[c] (nM)
22	4-MePh	6.6 (93% act)	2.3
29	Ph	7.4 (100% act)	3.4
30	4-EtPh	175 (83% act)	43
31	4-FPh	2.9 (96% act)	1.9
32	4-ClPh	5.5 (119% act)	5.6
33	3-FPh	105 (106% act)	35
34	2-FPh	6.3 (110% act)	1.9
35	2,6-F_2Ph	4.4 (109% act)	1.9
36	2,4-F_2Ph	1.1 (103% act)	1.0
37	2-F,4-MePh	1.9 (116% act)	0.56

[a] CCK_IP3 (CCK1 human, NFAT) agonist data, values are mean of ⩾3 experiments, standard deviations are ⩽66% of the mean. % Activation at 10,000 nM is given in parentheses.[6]
[b] CCK2R inactive (% activations are ⩽12% at 10,000 nM).[6]
[c] Mean of ⩾3 experiments, standard deviations are ⩽68% of the mean.

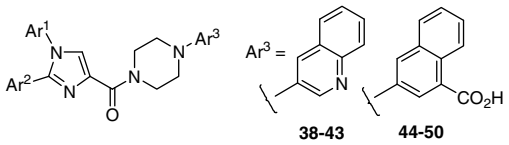
(EC_{50} = 65 nM, IC_{50} = 43 nM). Additionally, the 4-methoxy compound **19** was ~2-fold less potent than the 3-methoxy derivative **9**. Methoxy and ethoxy appeared to be optimal at the 3-position of the B-ring as the 3-hydroxy (**21**), the 3-propoxy (**23**), and the 3-isopropoxy (**24**) derivatives were less potent than **9** and **22**. Electron withdrawing alkyl groups connected to the 3-alkoxy position such as OCF_3 (**25**) and OCH_2CF_3 (**26**) also reduced the potency. The biggest improvement in binding and functional activity was observed with 1,4-benzodioxane compound **27** (EC_{50} = 0.99 nM, IC_{50} = 0.42 nM) while regioisomer **28** was much less potent.

Next, the effects of ring C modification (Ar^2 groups, Table 3) were investigated. Unlike the B-ring which required a 3-alkoxyphenyl group for good potency, several different sterically small substituents such as hydrogen (**29**), methyl (**22**), fluorine (**31**), and chlorine (**32**) were well tolerated at the 4-position of the ring C phenyl group. The 4-fluorophenyl compound **31** (EC_{50} = 2.9 nM, IC_{50} = 1.9 nM) had slightly improved CCK1R activities compared to 4-methyl **22** (EC_{50} = 6.6 nM, IC_{50} = 2.3 nM). Additionally, fluorine substitution was also tolerated at the 2-position (**34** and **35**). The 2,4-disubstituted compounds **36** (EC_{50} = 1.1 nM, IC_{50} = 1.0 nM) and **37** (EC_{50} = 1.9 nM, IC_{50} = 0.56 nM) had the most improved potency. In contrast, 3-fluoro substitution (**33**) and more sterically demanding substituents such as 4-ethyl (**30**) reduced potency against CCK1R.

After we discovered that quinolin-3-yl **14** and 1-naphthoic acid-3-yl **18** (Table 1) improved CCK1R functional and binding activities compared to **9**, piperazines bearing these two aryl groups were incorporated into the imidazole core with optimized B- and C-rings (Table 4). Compounds **38**–**50** all possessed subnanomolar EC_{50} and IC_{50} values. Furthermore, it was notable that they maintained excellent selectivity over CCK2R.[11] In general, the acid bearing naphthalenes afforded superior in vitro profiles compared to the quinoline derivatives, with **44**–**47**, **49**, and **50** all showing extremely potent functional activity and binding at the CCK1 receptor.

One of the CCK1R agonist mediated physiological effects is the stimulation of gallbladder emptying.[1] Consequently, the in vivo activities of CCK1R agonists presented here were first evaluated in a mouse gallbladder emptying (mGBE) assay (see Supporting Information). To facilitate interpretation of these data, mouse CCK1R EC_{50} values of selected compounds were measured (Table 5). At an oral dose of 0.3 mg/kg, quinoline **38** reduced mouse gallbladder weight by 59% compared with vehicle (Table 5). However, it was ineffective at an oral dose of 0.1 mg/kg. Much greater in vivo mGBE activities were observed with the naphthoic acid derivatives **44**, **45**, **46**, and **49** which all showed >50% reductions in gallbladder weight at oral doses as low as 0.001 mg/kg (Table 5). Thus, carboxylic acid substitution improved not only the in vitro CCK1R functional and binding activities, but also the in vivo activities. Compounds **44**, sodium salt **44a** (Fig. 4), **45**, **46**, and **49** also caused robust overnight food intake (ONFI) reduction in lean mice at oral doses of 3 mg/kg. Moreover, **44**, **44a**, **46**, and **49** were effective at oral doses of 0.3 mg/kg.[12]

Table 4
Quinolin-3-yl and 1-naphthoic acid-3-yl with optimized Ar^1 and Ar^2



38-43 **44-50**

Compound	Ar^1	Ar^2	EC_{50}[a,b] (nM)	IC_{50}[c,d] (nM)
38	3-EtOPh	4-MePh	0.73 (105%)	0.45
39	3-EtOPh	4-FPh	0.25 (92%)	0.60
40	3-EtOPh	2-FPh	0.53 (89%)	0.57
41	3-EtOPh	2-F,4-MePh	0.13 (86%)	0.24
42	3,4-(OCH_2CH_2O)Ph	4-MePh	0.12 (94%)	0.20
43	3,4-(OCH_2CH_2O)Ph	4-FPh	0.26 (101%)	0.12
44	3-EtOPh	4-MePh	0.094 (105%)	0.12
45	3-EtOPh	4-FPh	0.048 (95%)	0.08
46	3-EtOPh	2-F,4-MePh	0.056 (73%)	0.06
47	3-EtOPh	2,4-F_2Ph	0.053 (76%)	0.07
48	3,4-(OCH_2CH_2O)Ph	4-MePh	0.14 (107%)	0.14
49	3,4-(OCH_2CH_2O)Ph	4-FPh	0.093 (97%)	0.03
50	3,4-(OCH_2CH_2O)Ph	2-F,4-MePh	0.077 (71%)	0.03

[a] CCK_IP3 (CCK1 human, NFAT) agonist data, values are mean of ⩾3 experiments, standard deviations are ⩽72% of the mean. % Activation at 10,000 nM is given in parentheses.[6]
[b] CCK2R inactive (% activations are ⩽36% at 10,000 nM).[6]
[c] Mean of ⩾3 experiments, standard deviations are ⩽88% of the mean.
[d] CCK2R IC_{50} are >10,000 nM; % inhibitions are ⩽24% at 10,000 nM.

At an oral dose of 10 mg/kg, compounds **44** and**46** did not affect overnight food intake in $CCK1R^{-/-}$ mice while inducing robust food intake reduction in the wild type mice, indicating that the observed food intake reduction with these compounds is CCK1R mechanism-based.[13] Although the food intake reduction observed in this mouse model is CCK1R mediated, it is important to note that these anorectic effects may not be solely attributed to an increased satiety effect due to CCK1R activation.[12] Nevertheless, the relative magnitude of ONFI reduction provides a measurable method to rank order CCK1R agonists' effects in vivo.

Table 5
In vivo mouse gallbladder emptying (mGBE) and lean mouse overnight food intake (ONFI) reduction

Compound[a]	mEC_{50}[b] (nM)	mGBE[c,d]	ONFI reduction[c]	
		po doses (mg/kg) with >50% reduction	0.3 po at mg/kg	3 po at mg/kg
38	2.1	0.3 (59%)	—	—
44	1.3	0.001 (72%)	18%	82%
44a	0.78	—	29%	78%
45	1.5	0.001 (69%)	ns	73%
46	0.30	0.001 (77%)	13%	86%
49	0.14	0.001 (88%)	16%	96%

[a] CF_3COOH salts, except **44a** which is sodium salt of **44**.
[b] Mouse CCK_IP3 agonist data, values are mean of ⩾3 experiments. Standard deviations are less than 70% of the mean.
[c] Compared with vehicle (10% Tween® 80 in water), ns, not significant.
[d] Mouse gallbladder weight % reduction is given in parentheses.

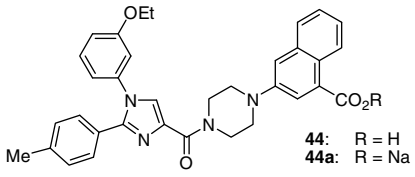


Figure 4. Compound **44** (free acid) and sodium salt **44a**.

Table 6
Active in vivo CCK1R agonists pharmacokinetic profile[a]

Compound	Species	Clp (mL/min/kg)	V_d (L/kg)	po AUC_N (μM h)	$t_{1/2}$ (h)	F (%)	C_{max} (μM)
44	Mouse	5.3	0.47	0.39	3.5	7	0.28
44a	Mouse	3.1	0.56	4.2	3.4	43	4.9
45	Mouse	6.4	0.73	1.5	2.7	33	1.1
46	Mouse	10.4	0.59	0.61	1.7	22	0.82

[a]iv administration dosed at 1.0 mg/kg, po administration dosed at 10 mg/kg.

The mouse pharmacokinetic profiles of selected compounds are shown in Table 6. Compound **45** had higher oral exposure and bioavailability than **44**, however, **45** was not more active in vivo toward mouse ONFI reduction. It is notable that compounds **44** (mouse EC_{50} = 1.3 nM, % activity at 10 μM = 103%) and **45** (mouse EC_{50} = 1.5 nM, % activity at 10 μM = 101%) had similar in vitro mouse CCK1R activities (Table 5). The sodium salt form **44a** increased the plasma exposure after an oral dose relative to the trifluoroacetic acid salt of **44**. Additionally, C_{max} and oral bioavailability increased. Paradoxically, however, **44a** exhibited similar ONFI reduction as the corresponding acid form **44**. These results suggest that systemic exposure of the compound may not play an important role for in vivo efficacy.[14]

In conclusion, optimization of the heterocyclic core of HTS hit **3** led to the identification of a novel series of 1,2-diaryl imidazole carboxamides. Further optimization of the B, C, and D rings led to the discovery of a class of highly potent and selective CCK1R agonists. Quinoline **38** showed only modest in vivo mGBE activity in spite of potent in vitro CCK1R functional and binding activities. Introduction of a carboxylic acid group at the 1-position of the naphthyl ring not only further improved the in vitro profile, but most importantly also improved the in vivo CCK1R mediated activities in mice such as gallbladder emptying and overnight food intake reduction. Compounds **44**, **44a**, **46**, and **49** all exhibited excellent in vivo mouse gallbladder emptying (mGBE) activity and lean mouse overnight food intake (ONFI) reduction. Since **44**/**44a** (Fig. 4) showed a superior in vitro, in vivo, and pharmacokinetic profile, this compound was selected for extensive in vivo testing, and those results will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2008.06.057.

References and notes

1. Wank, S. A. *Am. J. Physiol.* **1998**, *274*, G607.
2. Gibbs, J.; Young, R. C.; Smith, G. P. *J. Comp. Physiol. Psychol.* **1973**, *84*, 488.
3. For recent reviews see (a) Little, T. J.; Horowitz, M.; Feinle-Bisset, C. *Obes. Rev.* **2005**, *6*, 297; (b) Moran, T. H.; Kinzig, K. P. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2004**, *286*, G183; (c) Chandra, R.; Little, T. J. *Curr. Opin. Endocrinol. Diabetes Obes.* **2007**, *14*, 63; (d) Dufresne, M.; Seva, C.; Fourmy, D. *Physiol. Rev.* **2006**, *86*, 805.
4. For lead CCK1R medicinal chemistry reviews see (a) Szewczyk, J. R.; Laudeman, C. *Curr. Top. Med. Chem.* **2003**, *3*, 837; (b) García-López, M. T.; González-Mu ñiz, R.; Martín-Martínez, M.; Herranz, R. *Curr. Top. Med. Chem.* **2007**, *7*, 1180.
5. (a) Jordan, J.; Greenway, F. L.; Leiter, L. A.; Li, Z.; Jacobson, P.; Murphy, K.; Hill, J.; Kler, L.; Aftring, R. P. *Clin. Pharmacol. Ther.* **2008**, *83*, 281; (b) Castillo, E. J.; Delgado-Aros, S.; Camilleri, M.; Burton, D.; Stephens, D.; O'Connor-Semmes, R.; Walker, A.; Shachoy-Clark, A.; Zinsmeister, A. R. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2004**, *287*, G363.
6. Pan, J.; Weingarth, D. T.; Qian, S.; Morin, N.; Edmondson, S. D.; Zhu, C.; Berger, R.; Hansen, A. R.; Lee, S. J.; Hubert, J. A.; Strack, A. M.; MacNeil, D. J., in preparation. All CCK1R EC_{50} values are human IP3 (NFAT) agonist data except in Table 6 which are mouse CCK1R IP3 data. Both CCK1 and CCK2 % activation are expressed as the % of activation relative to CCK-8. Additional assay protocols are given in Supporting Information.
7. A series of 1,2-diary imidazoles have recently been reported as CCK1R antagonists: (a) McClure, K.; Hack, M.; Huang, L.; Sehon, C.; Morton, M.; Li, L.; Barrett, T. D.; Shankley, N.; Breitenbucher, J. G. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 72; (b) Sehon, C.; McClure, K.; Hack, M.; Morton, M.; Gomez, L.; Li, L.; Barrett, T. D.; Shankley, N.; Breitenbucher, J. G. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 77; (c) Gomez, L.; Hack, M. D.; McClure, K.; Sehon, C.; Huang, L.; Morton, M.; Li, L.; Barrett, T. D.; Shankley, N.; Breitenbucher, J. G. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6493.
8. Lange, J. H. M.; van Stuivenberg, H. H.; Coolen, H. K. A. C.; Adolfs, T. J. P.; McCreary, A. C.; Keizer, H. G.; Wals, H. C.; Veerman, W.; Borst, A. J. M.; de Looff, W.; Verveer, P. C.; Kruse, C. G. *J. Med. Chem.* **2005**, *48*, 1823.
9. Ueki, H.; Ellis, T. K.; Martin, C. H.; Boettiger, T. U.; Bolene, S. B.; Soloshonok, V. A. *J. Org. Chem.* **2003**, *68*, 7104.
10. Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722.
11. CCK2R % activation and CCK2R % inhibition at 10,000 nM data for compounds **38**–**50** are given in Supporting Information.
12. No distinguishable behavioral features were noted between treatment and vehicle control groups of the ONFI mice at both administered doses (0.3 and 3 mg/kg). Subsequent manuscripts describing the in vivo characteristics (tolerability and efficacy) are in preparation.
13. Kopin, A. S.; Mathes, W. F.; McBride, E. W.; Nguyen, M.; Al-Haider, W.; Schmitz, F.; Bonner-Weir, S.; Kanarek, R.; Beinborn, M. *J. Clin. Invest.* **1999**, *103*, 383.
14. Sugg, E. E.; Birkemo, L.; Gan, L.-S. L.; Tippin, T. K. *Pharm. Biotechnol.* **1998**, *11*, 507.