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2-Substituted piperazine-derived imidazole carboxamides as potent and selective CCK1R agonists for the treatment of obesity

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ABSTRACT

The discovery and structure–activity relationship of 1,2-diarylimidazole piperazine carboxamides bearing polar side chains as potent and selective cholecystokinin 1 receptor (CCK1R) agonists are described. Optimization of this series resulted in the discovery of isopropyl carboxamide **40**, a CCK1R agonist with sub-nanomolar functional and binding activity as well as excellent potency in a mouse overnight food intake reduction assay.

The worldwide incidence of obesity is rising and has reached epidemic levels in Western societies.[1] In the United States, obesity is a leading cause of morbidity and mortality, largely due to the increased risk of type 2 diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, weight-bearing osteoarthritis, and certain types of cancer.[2,3]

Cholecystokinin (CCK) is a peptide hormone secreted by the gut in response to the ingestion of a meal. It promotes satiety and meal termination, resulting in reduced meal size.[4] This physiological effect has been observed in a variety of animal models, including humans, when CCK is administered prior to a meal.[5–8] The CCK peptide interacts with two G-protein coupled receptor subtypes: the CCK1 receptor (CCK1R, also known as CCK-AR) and the CCK2 receptor (CCK2R, also known as CCK-BR).[9] CCK2R is also the gastrin receptor and is located primarily in the stomach and brain and regulates gastric acid secretion and many CNS related functions.[9–11] CCK1R is found in the gallbladder, pyloric smooth muscle, and the enteric vagal afferent nerves.[5,11] Activation of CCK1R mediates physiological effects including gallbladder contraction, gastric emptying, intestinal motility, and satiety.[6]

Two small molecule CCK1R agonists, 1,5-benzodiazepine GI181771X (**1**)[12] and thiazole SR-146131 (**2**),[12b,13] have been disclosed in the literature (Fig. 1). The results of a phase II clinical trial conducted with **1** were also reported.[14] Although statistically significant weight loss relative to placebo was not achieved in patients treated with **1**, this lack of efficacy may be the result of dose-limiting gastrointestinal adverse effects. Moreover, the authors suggest that combination studies with other anorectic agents could be used to maximize the benefits of a small molecule CCK1R agonist.

Previous reports from our laboratories described the discovery of imidazole carboxamides **3**–**5** as potent and selective CCK1R agonists (Fig. 1).[15] Optimization of this structure class revealed that increasing agonist polarity often led to improved CCK1R binding and functional activities. Based on these observations, the effect of appending polar substituents onto the piperazine ring of compounds **3**–**5** was investigated. This letter describes the synthesis and biological profile of a series of imidazole carboxamides represented by general structure **6** (Fig. 1).

The synthesis of a series of methylamine-linked derivatives began with an amide coupling between imidazole carboxylic acid **7**[15b] and the corresponding enantiomerically pure piperazine **8** employing mesyl chloride/1-methylimidazole activation (Scheme 1).[16] The ester was subsequently reduced to the primary alcohol with lithium borohydride, followed by acetylation with acetic anhydride to afford **9**. Removal of the *N*-carbobenzyloxy group

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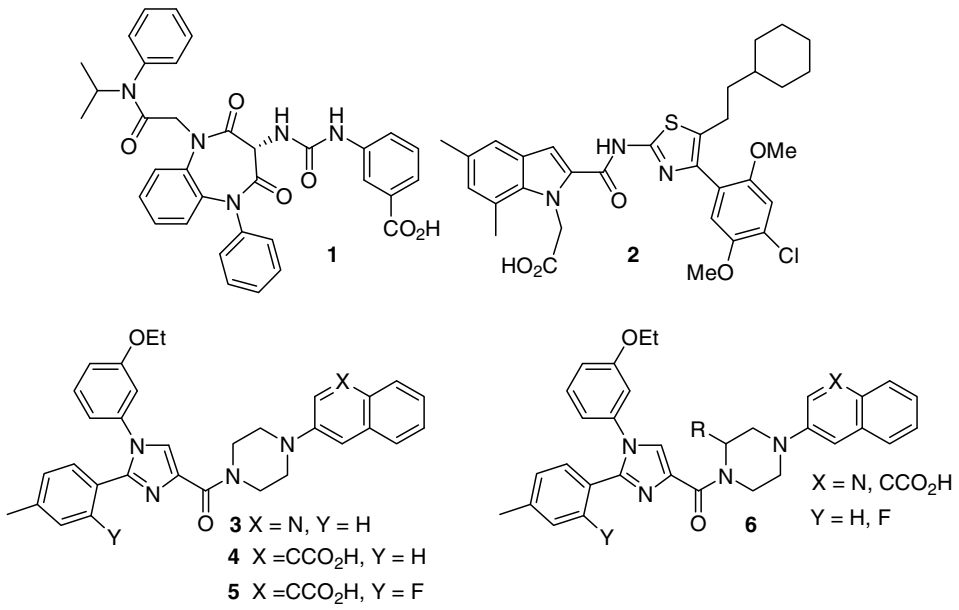
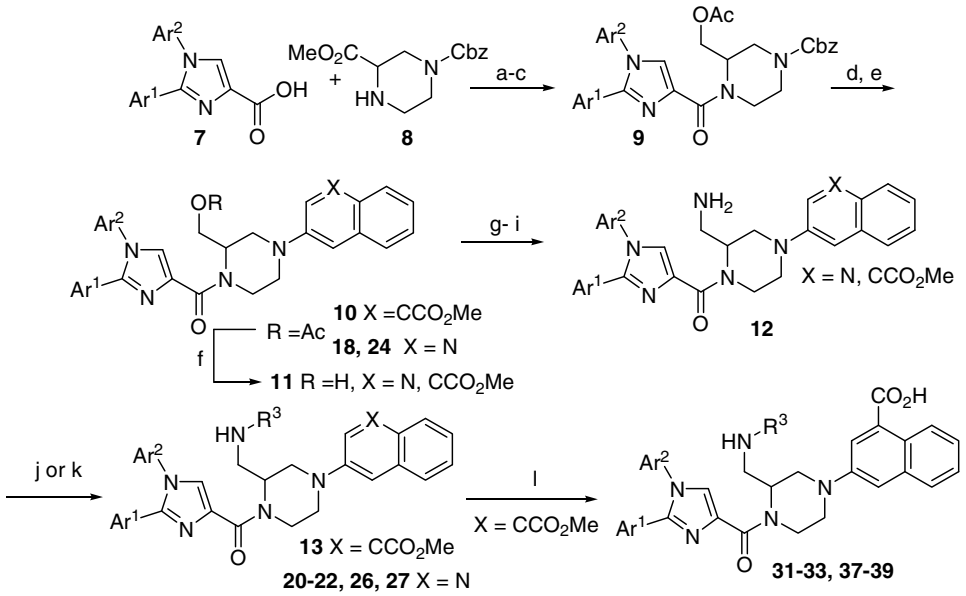


Figure 1. Small molecule CCK1R agonists for the treatment of obesity: GI181771X (**1**), SR-146131 (**2**), and Merck MRL imidazole carboxamides (**3**–**6**).

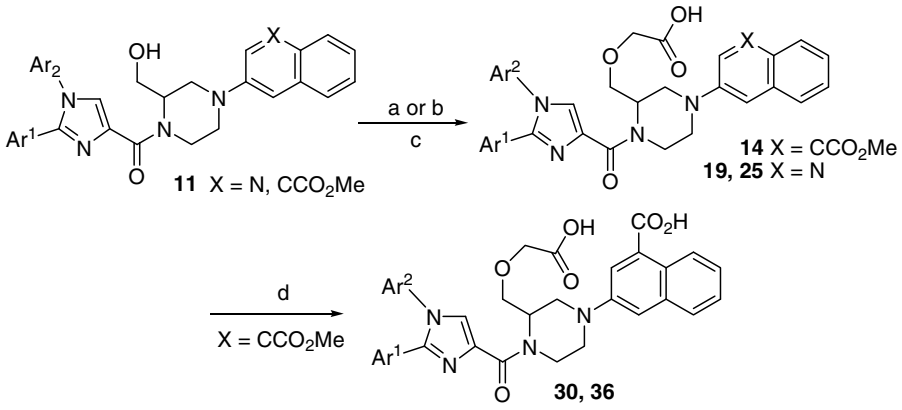


Scheme 1. Synthesis of methylamine-linked derivatives: Ar^1 = 4-MePh or 2-F,4-MePh, Ar^2 = 3-EtOPh. Reagents and conditions: (a) MsCl, 1-methylimidazole, DMAP, 0 °C → rt; (b) $LiBH_4$, MeOH, 0 °C; (c) Ac_2O, $^iPr_2NEt$, DMAP (65–76%, 3 steps); (d) 10% Pd/C, 40 psi H_2, MeOH; (e) ArBr, $Pd_2(dba)_3$, Cs_2CO_3, 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino) biphenyl, 1,4-dioxane, 85 °C (75–80%, 2 steps); (f) NaOMe, MeOH, 0 °C (75–85%); (g) MsCl, $^iPr_2NEt$, CH_2Cl_2, 0 °C → rt; (h) NaN_3, DMF, rt; (i) 20% $Pd(OH)_2$, 40 psi H_2, MeOH (80–85%, 3 steps); (j) RSO_2Cl or RCOCl, $^iPr_2NEt$, CH_2Cl_2, 0 °C → rt (80–95%); (k) triphosgene, $MeNH_2$, CH_2Cl_2, 0 °C (80%); (l) LiOH, THF/MeOH/H_2O (90–95%).

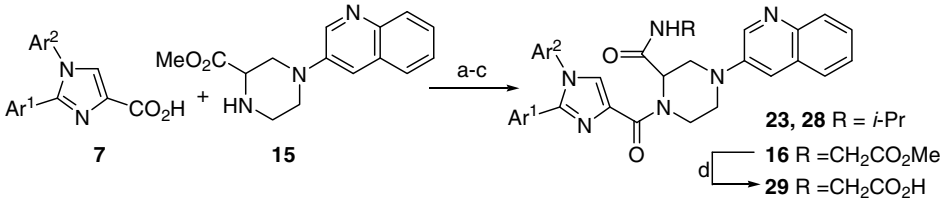
with 10% palladium on activated carbon under an atmosphere of hydrogen, followed by palladium-catalyzed C–N bond formation, with either 3-bromoquinoline or methyl 3-bromo-1-naphthoate, yielded compounds **10**, **18**, and **24**.[17] Subsequent removal of the acetate with sodium methoxide revealed primary alcohol **11**. Amines **12** were prepared by initial mesylation of **11**, followed by nucleophilic displacement with azide and hydrogenation. Treatment of **12** with an acid chloride or sulfonyl chloride in the presence of *N*, *N*-diisopropylethylamine afforded the desired CCK1R agonists **20**, **21**, **26**, and **27**. Alternatively, **12** can be reacted with triphosgene followed by methylamine to yield urea **22**. In the case of ester derivatives **13**, a lithium hydroxide mediated saponification was required to reveal the naphthoic acid derivatives **31**–**33** and **37**–**39**.

A series of alkoxy acetic acids were also prepared from **11** (Scheme 2). Alkylation with bromo *tert*-butyl acetate in the presence of either sodium hydride or potassium carbonate, followed by trifluoroacetic acid mediated deprotection of the ester afforded the corresponding carboxylic acids **14**, **19** and **25**. Ester hydrolysis of **14** revealed the *bis*-acids **30** and **36**.

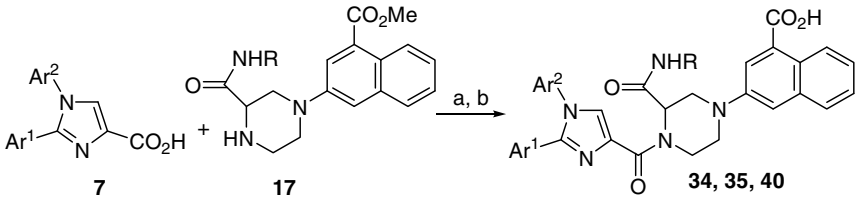
The preparation of the 2-piperazine carboxamides in the quinoline series began with an amide coupling between acid **7**[15b] and the corresponding enantiomerically pure piperazine **15**[15b] (Scheme 3). Saponification followed by a 1-[3-dimethylamino)propyl]-



Scheme 2. Synthesis of acetic acid-linked derivatives: Ar^1 = 4-MePh or 2-F,4-MePh, Ar^2 = 3-EtOPh. Reagents and conditions: (a) NaH *tert*-butyl bromoacetate, DMF, 0 °C; (b) K_2CO_3, *tert*-butyl bromoacetate, DMF (70–80%, 2 steps); (c) TFA, CH_2Cl_2 (quantitative), (d) LiOH, THF/MeOH/H_2O (90–95%).

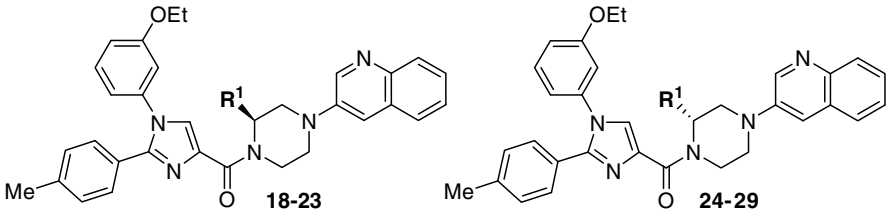


Scheme 3. Synthesis of piperazine carboxamide derivatives: Ar^1 = 4-MePh or 2-F,4-MePh, Ar^2 = 3-EtOPh: (a) MsCl, 1-methylimidazole, DMAP, 0 °C → rt (80–90%); (b) LiOH, THF/MeOH/H_2O; (c) EDC, HOAT, RNH_2 (75–85%, 2 steps); (d) LiOH, THF/MeOH/H_2O (90–95%).



Scheme 4. Synthesis of piperazine carboxamide derivatives: Ar^1 = 4-MePh or 2-F,4-MePh, Ar^2 = 3-EtOPh: (a) MsCl, 1-methylimidazole, DMAP, 0 °C → rt (80–90%); (b) LiOH, THF/MeOH/H_2O (90–95%).

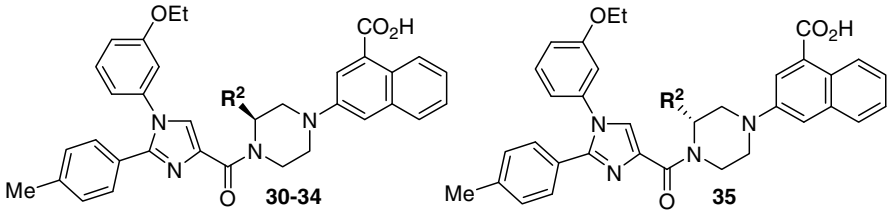
Table 1
Selected 3-quinoline-derived CCK1R agonists



Compound	R^1	EC_{50}[a] (nM)	% Act.	IC_{50}[b,c] (nM)
3	H	0.73	105	0.45
18	CH_2OCOCH_3	0.25	104	0.24
19	$CH_2OCH_2CO_2H$	0.097	96	0.039
20	$CH_2NHCOCH_3$	0.10	91	0.25
21	CH_2NHSO_2Me	0.21	100	0.43
22	$CH_2NHCONHMe$	0.16	70	0.56
23	CONH*i*-Pr	0.18	87	0.21
24	CH_2OCOCH_3	0.77	118	0.47
25	$CH_2OCH_2CO_2H$	0.065	93	0.052
26	$CH_2NHCOCH_3$	0.097	104	0.39
27	CH_2NHSO_2Me	0.46	117	0.73
28	CONH*i*-Pr	0.14	102	0.24
29	$CONHCH_2CO_2H$	0.089	82	0.018

[a] CCK_IP3 (CCK1 Human, NFAT) agonist data, values are means of ⩾3 experiments, with standard deviations <75% of the average.
[b] Values are an average of ⩾3 experiments with standard deviations <75% of the average.
[c] See Supporting information for binding assay protocols.

Table 2
Selected 3-(1-naphthoic acid)-derived CCK1R agonists



Compound	R^2	EC_{50}[a] (nM)	% Act.	IC_{50}[b,c] (nM)
4	H	0.094	105	0.12
30	$CH_2OCH_2CO_2H$	0.097	85	0.14
31	$CH_2NHCOCH_3$	0.04	67	0.08
32	CH_2NHSO_2Me	0.095	72	0.12
33	$CH_2NHCONHMe$	0.13	74	0.08
34	CONH*i*-Pr	0.082	94	0.11
35	CONH*i*-Pr	0.053	103	0.016

[a] CCK_IP3 (CCK1 Human, NFAT) agonist data, values are means of ⩾3 experiments, with standard deviations <75% of the average.
[b] Values are an average of ⩾3 experiments with standard deviations <75% of the average.
[c] See Supporting information for binding assay protocols.

3-ethylcarbodiimide (EDC)-mediated amide coupling afforded the desired compounds **23** and **28**. Hydrolysis of methyl ester **16** then afforded glycine derivative **29**.

The naphthoic acid derivatives were prepared by first reacting acid **7**[15b] with enantiomerically pure piperazine **17**[15b] using mesyl chloride/1-methylimidazole activation (Scheme 4). Methyl ester saponification with lithium hydroxide yielded the desired CCK1R agonists **34**, **35**, and **40**.

The activities of selected 3-quinoline-derived CCK1R agonists are reviewed in Table 1.[18] Enantiomeric pairs generally had comparable EC_{50}s and IC_{50}s, with neither enantiomer showing significantly greater CCK1R activity. Acetate **18** displayed improved potency relative to **3**, but was not pursued further due to the potential metabolic liability of the ester functionality. Incorporating similar polar functional groups such as sulfonamides, ureas, and amides led to the identification of acetamides **20** and **26** as potent CCK1R agonists. In addition, the incorporation of the glycine carboxamide **29** afforded an 8-fold improvement in EC_{50} and a 25-fold boost in binding IC_{50} relative to the unsubstituted parent **3**.

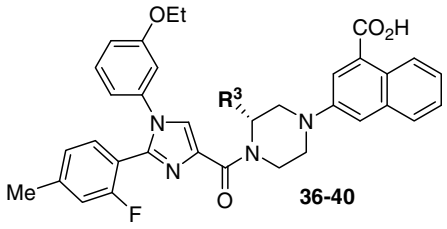
Selected alterations in the 3-quinoline series were also incorporated into the 1-naphthoic acid derivative **4** with a minimal loss of CCK1R activity (Table 2).[18] For example, diacid **30** was almost identical to **4** in terms of CCK1R EC_{50} and IC_{50}. Isopropyl carboxamide **35** possessed the best overall in vitro profile in this series, with excellent functional activity and binding at the CCK1 receptor (EC_{50} = 0.053 nM, IC_{50} = 0.016 nM).

It was previously reported that incorporation of a 2-fluoro-4-methylphenyl moiety (**5**) improved CCK1R potencies in the 3-(1-naphthoic acid) series.[15] This effect was subsequently investigated with the substituted piperazines (Table 3).[18] These analogs maintained a similar in vitro profile to the parent **5**, displaying excellent potencies at the CCK1R in terms of functional activity and binding.

Compounds with superior activities at the CCK1 receptor were evaluated for activity at the CCK2 receptor. Analogs **4**, **5**, **19**, **29**, **35**, **37**, and **40** all showed EC_{50}s greater than 6000, nM and less than 60% activation at the human CCK2R. Additionally, these analogs showed binding IC_{50}s > 10000 nM against the human CCK2R.[19]

The in vivo efficacies of these 2-substituted-piperazine-derived imidazole carboxamides were also evaluated (Table 4). The overnight food intake (ONFI) of lean mice, dosed orally with CCK1R agonists at 0.3 and 3.0 mg/kg, was measured relative to those dosed with vehicle.[20] Similar to previous reports,[15a] neither of the potent CCK1R agonists **19** or **29** in the 3-quinoline series exhib-

Table 3
Effects of 2-fluoro,4-methylphenyl substituent in 3-(1-naphthoic acid) series



Compound	R^3	EC_{50}[a] (nM)	% Act.	IC_{50}[b,c] (nM)
5	H	0.055	73	0.040
36	$CH_2OCH_2CO_2H$	0.034	106	0.041
37	$CH_2NHCOCH_3$	0.033	70	0.058
38	CH_2NHSO_2Me	0.10	97	0.067
39	$CH_2NHCONHMe$	0.074	90	0.097
40	CONH*i*-Pr	0.071	94	0.010

[a] CCK_IP3 (CCK1 Human, NFAT) agonist data, values are means of ⩾ 3 experiments, with standard deviations <75% of the average.
[b] Values are an average of ⩾3 experiments with standard deviations <75% of the average.
[c] See Supporting information for binding assay protocols.

Table 4
Effect of orally dosed CCK1R agonists on 18-h overnight food intake reduction (ONFI)[a] in mice

Compound	mEC_{50} (nM)[b]	% Act.	Suppression of food intake[a]	
			@ 0.3 mpk	@ 3 mpk
4	1.30	103	18%	82%
5	0.30	56	13%	86%
19	0.50	84	ns[c]	ns[c]
29	0.11	99	ns[c]	ns[c]
35	0.11	110	19%	45%
37	0.13	77	ns[c]	18%
40	0.034	94	32%	92%

[a] Compared with vehicle (10% Tw80 in water).
[b] CCK_IP3 (CCK1 Mouse, K1) agonist data, values are means of ⩾ 3 experiments, with standard deviations <75% of the average.
[c] ns, not significant.

Table 5
Effect of **40** on 18- and 48-h ONFI[a] in wild-type and CCK1R$^{-/-}$mice

Mouse	Suppression of food intake @ 3 mpk[a]	
	18 h	48 h
Wild-type	89%	85%
CCK1R$^{-/-}$	ns[b]	ns[b]

[a] Compared with vehicle (10% Tw80 in water).
[b] ns, not significant.

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

Compound	Clp (ml/min/kg)	V_d (L/kg)	PO AUC (μM-h)	$t_{1/2}$ (h)	F (%)	C_{max} (μM)	T_{max} (h)
4	5.3	0.47	0.39	3.5	7	0.28	6.7
5	10.4	0.59	0.61	1.7	22	0.82	0.6
35	20.4	3.7	0.15	2.5	11	0.18	5.5
40	9.7	0.42	0.1	2.3	4	0.18	8.0

[a] IV administration dosed at 1.0 mpk, PO administration dosed at 10 mpk.

ited any in vivo activity. On the other hand, compounds **4**, **5**, **35**, **37**, and **40** containing the 3-(1-naphthoic acid) all displayed a statistically significant decrease in food intake relative to vehicle. Based on these results, it seems that both incorporation and positioning of the carboxylic acid moiety are critical factors that determine the magnitude of in vivo potency in this structure class. The isopropyl carboxamide **40** had the most significant effect on the reduction of overnight food intake in mice at both doses. Additionally, at an oral dose of 3.0 mg/kg, **40** had no effect on food intake in CCK1R$^{-/-}$ mice[21] while inducing a significant reduction in food intake in wild-type mice (Table 5). Although these results indicate that food intake reduction observed in wild-type mice dosed with **40** is CCK1R-mediated, it should be noted that the anorectic effects may not be solely attributed to an increased satiety effect due to CCK1R activation.[22] Nevertheless, the ONFI reduction provides a quantifiable method to evaluate the *in vivo* effects of CCK1R agonists.

Table 6 presents the mouse pharmacokinetic profile of compounds active in the ONFI assay. The most potent compound (**40**) had the lowest oral exposure, oral bioavailability, and C_{max}, suggesting that systemic exposure may not be necessary for efficacy.[23]

In conclusion, a series of 2-substituted piperazine derived 1,2-diarylimidazole carboxamides were found to be highly potent and selective CCK1R agonists. Although several compounds possessed comparable sub-nanomolar in vitro activities, these activities did not always translate into *in vivo* efficacy. The isopropylcarboxamide **40** exhibited one of the most potent in vitro and *in vivo profiles observed in this structure class to date.*

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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.2008.07.083.

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19. All CCK2R EC_{50} values are human IP3 agonist data and are an average of $\geqslant 3$ experiments with standard deviations <75% of the average. CCK2 % activations are expressed as the % of activation relative to CCK-8. CCK2R IC_{50}s are an average of $\geqslant 3$ experiments with standard deviations <75% of the average. Additional assay protocols are given in the Supporting information.
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