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Discovery of pyrimidine carboxamides as potent and selective CCK1 receptor agonists

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ABSTRACT

A series of six-membered heterocycle carboxamides were synthesized and evaluated as cholecystokinin 1 receptor (CCK1R) agonists. A pyrimidine core proved to be the best heterocycle, and SAR studies resulted in the discovery of analog **5**, a potent and structurally diverse CCK1R agonist.

Obesity is increasingly prevalent both in the United States and globally. Excess weight and obesity lead to serious health consequences including cardiovascular disease, diabetes, osteoarthritis, sleep apnea, and certain cancers.[1,2] Cholecystokinin (CCK) is the major hormone responsible for gallbladder contraction and pancreatic enzyme secretion. CCK receptors have physiological roles in stimulation of pancreatic and biliary secretions, regulation of gastrointestinal mobility, postprandial inhibition of gastric emptying, and regulation of food intake. Two different CCK receptors have been identified that mediate the biological actions of CCK: in the CCK1 receptor (formerly CCKAR) and the CCK2 receptor (formerly CCKBR). Biological actions mediated by the CCK1R suggest that CCK1R agonists may be used for the treatment of obesity.[3,4]

Efforts to produce CCK1R agonists for treating obesity, resulted in the discovery of 1,5-benzodiazepines GI181771X (**1**) and CE-326597 (**2**), as well as thiazole SR-146131 (**3**)[5–7] (Fig. 1). A Phase II clinical trial with **1** resulted in no body weight loss in obese patients after 24 weeks of treatement.[5] Nevertheless, combination therapy with other anorectic agents was suggested by the authors as a potential means to improve efficacy of this CCK1R agonist.

Imidazole carboxamides (e.g., **4** in Fig. 1) have been reported as potent and selective CCK1R agonists that exhibit in vivo activity in mice typical of CCK1R agonists such as gallbladder emptying and overnight food intake reduction.[8] SAR studies within this series showed that the imidazole ring was the optimal five-membered ring heterocyclic core for CCK1R agonist activity. In order to expand the structural diversity of this new series of CCK1R agonists, we sought to replace the five-membered ring heterocyclic core with six-membered ring heterocycles. Herein, we report the synthesis and optimization of a series of six-membered ring heterocycles designed to replace the imidazole core of **4**. Ultimately, a series of pyrimidine carboxamides (**5** and **6**) were discovered that demonstrate potent and selective activity as CCK1R agonists.

The synthesis of pyrazines **28** and **29** (Fig. 2) is described in Scheme 1. Commercially available 3-methoxy phenylacetic acid was reacted with methyl *p*-toluate in the presence of lithium bis(trimethylsilyl)amide to give ketone **8**.[9a] Oxidation of the benzylic methylene with selenium dioxide in acetic acid at 145 °C provided diketone **9**,[9b] which was cyclized with 2-aminoacetamide to afford both regioisomers **10** and **11**.[9b] Treatment with phosphorus oxychloride in toluene furnished pyrazine chlorides **12** and **13**,[9c] which were converted to carboxylic esters **14** and **15** using a palladium mediated carbonylation reaction.[9d] Saponification of the esters followed by coupling of the resulting acids with 3-naphthyl piperazine yielded the two pyrazine derivatives which were separated using a ChiralCel AD column to give **28** and **29**.

The preparation of 3-pyridine carboxylic amide **30** is outlined in Scheme 2. Intermediate **8** was reacted with DMF dimethyl acetal to give vinylogous amide **16**. Treatment of **16** with cyanoacetamide and sodium hydride in DMF effected ring closure to the 5,6-diaryl-3-cyanopyridine-2-one **17**, which was converted to chloride

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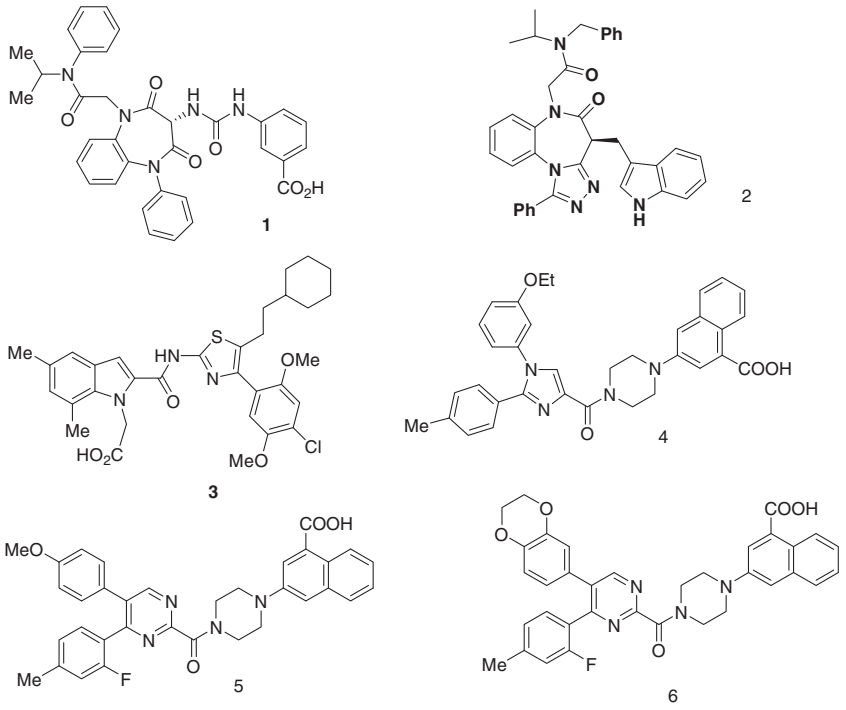


Figure 1. CCK1R agonists GI181771X (**1**), CE-326597 (**2**), SR-146131 (**3**), imidazole carboxamide (**4**) and pyrimidine carboxamides (**5** and **6**).[5–8]

18 using phosphorus oxychloride in toluene. Conversion of nitrile **18** to the corresponding carboxylic acid was achieved by heating with sulfuric acid, and the methyl ester **19**[10] was then formed by treatment with diazomethane. Hydrogenation to remove the chloride then afforded **20**. Saponification followed by coupling with 3-naphthyl piperazine yielded pyridine analog **30**.

Scheme 3 describes the synthesis of 2-pyridine carboxylic amide **31**. Cinnamic acid **21** was converted to the corresponding aldehyde in a two step process via reduction to the alcohol followed by oxidation to aldehyde **22**. The aldehyde was reacted with azidoacetate to give azido intermediate **23** which was then reacted with triphenylphosphine in ether to yield intermediate **24**. Subsequent cyclization with *p*-tolualdehyde in acetonitrile afforded pyridine carboxylic ester **25**.[10] Saponification followed by coupling with 3-naphthyl piperazine then furnished the 3-pyridine analog **31** (Fig. 2).

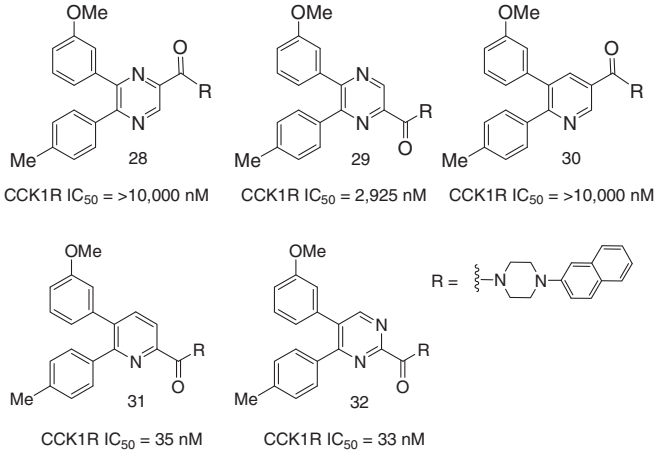


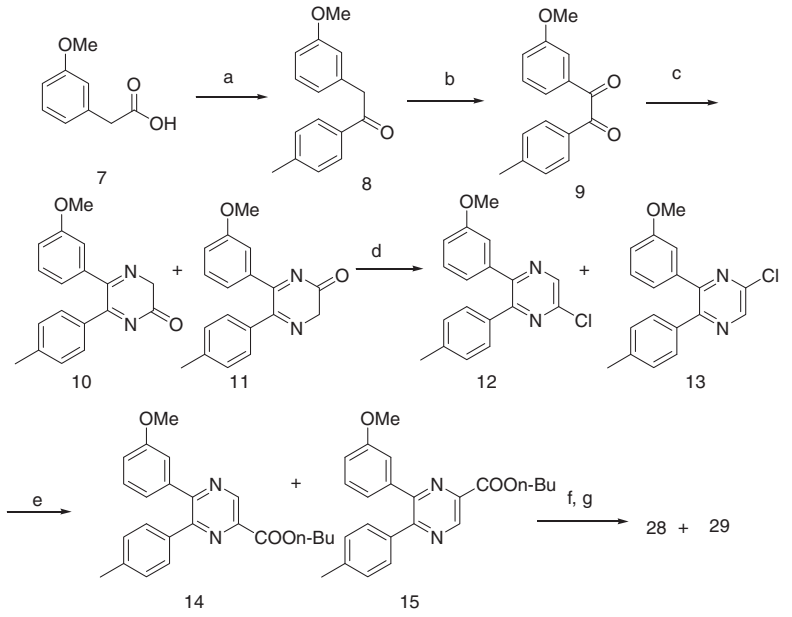
Figure 2. Binding affinities for six-membered heterocyclic aromatic carboxamides at the human CCK1R. IC50s are an average of ⩾2 assays with a standard deviations <78%. See Supplementary data for assay protocols.[14]

The synthesis of 5,6-diaryl pyrimidine carboxamide derivatives is outlined in Scheme 4. Enamide **16** was reacted with acetamidine in the present of sodium ethoxide to yield methyl pyrimidine **26**. The methyl group was next oxidized using selenium oxide in pyridine to give the corresponding acid **27**.[11] Exposure of the aryl piperazines with acid **27** under standard amide bond coupling conditions then afforded diaryl pyrimidine derivatives **5**, **6**, and **33**–**57**.

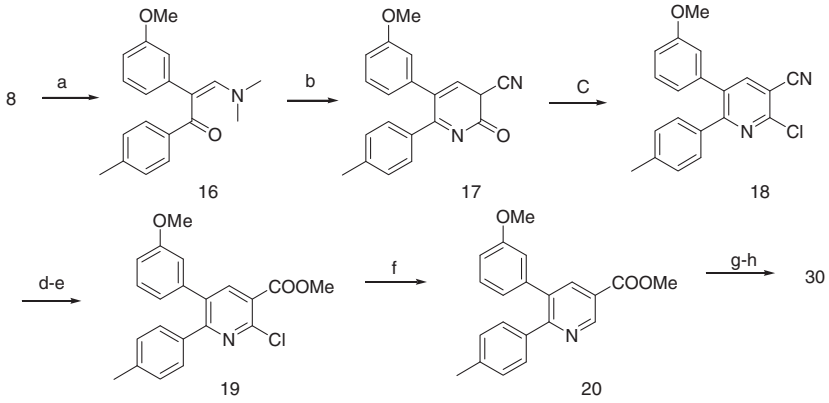
The in vitro human CCK1R binding activities[8] of various six-membered heterocyclic carboxamides **28**–**32** are displayed in Figure 2. The pyrazine 5-carboxamide **28** and pyridine 5-carboxamide **30** display insignificant binding affinity for the CCK1 receptor (IC_{50} >10 μM), while the pyrazine 6-carboxamide **29** possesses modest potency (IC_{50} = 2.9 μM). In contrast, pyridine 6-carboxamide **31** and pyrimidine 2-carboxamide **32** are significantly more potent at CCK1R binding. The substitution pattern on the six-membered ring heterocyclic core plays an important role for CCK1R binding potency. It appears that three contiguous moieties are important for maintaining CCK1R potency: the *para*-methyl phenyl substituent, the embedded nitrogen in the six-membered ring heterocycle core, and the carboxamide substituent. Although the origin of these receptor/ligand relationships is not well understood, it is noteworthy that this is consistent with SAR reported in the five-membered ring cores.[8a] Both **31** and **32** provided excellent lead structures for the development of novel CCK1R agonists, but only the pyrimidine analogs (i.e., **32**) were further pursued due to CCK1R potency, synthetic accessibility, and the paucity of patent publications on this structure class.

Early structure–activity studies of CCK1R agonists in the imidazole carboxamide structure class identified the 3-quinoline as a preferred piperazine substitutent.[8] Consequently, this moiety was maintained in SAR studies of the pyrimidine series in order to properly evaluate the relative potencies of these compounds.

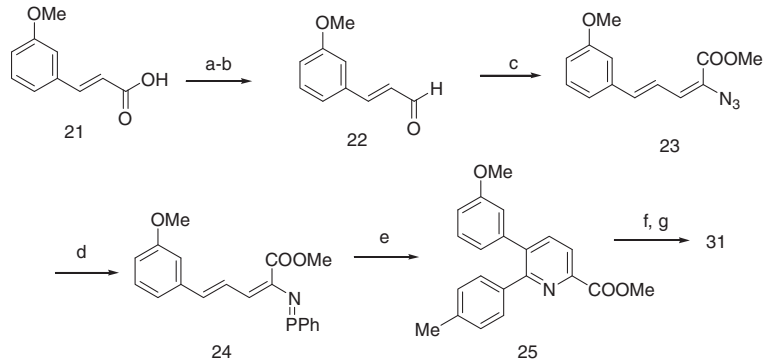
Initially, our efforts focused on optimization of the C-5 aromatic group Ar[1] (Table 1). Various 2-, 3- and 4-substituted phenyl derivatives were prepared which included methoxyphenyl (**33**, **34**, **36**),



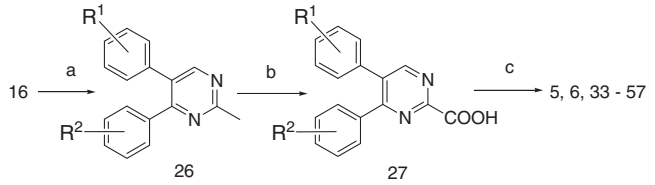
Scheme 1. Synthesis of 1,2-diaryl pyrazine carboxamides. Reagents: (a) methyl *p*-toluate, LiHMDS, THF (72%); (b) SeO_2, AcOH, Δ (71%); (c) 2- aminoacetamide, NaOH, EtOH (53%); (d) $POCl_3$, toluene, Δ (73%); (e) *n*-BuOH, CO gas, $PdCl_2$(dppf), NEt_3 (95%); (f) LiOH, MeOH; (g) substituted piperazine, EDC, HOBt, *i*Pr_2NEt, DMF, separation of isomers by Chiral AD column (34%).



Scheme 2. Synthesis of 1,2-diaryl pyridine 4-carboxamide. Reagents: (a) 2-cyanoacetamide, DMF-acetal, DMF (100%); (b) 2-cyanoacetamide, NaH, MeOH, DMF (66%); (c) $POCl_3$, toluene, Δ (64%); (d) 50% H_2SO_4, Δ; (e) $TMSCN_2$, MeOH (55%, two steps); (f) $PdCl_2$, MeOH (83%); (g) LiOH, THF, water, MeOH; (h) substituted piperazine, EDC, HOBt, *i*Pr_2NEt, DMF.

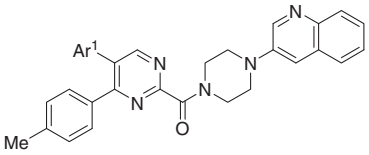


Scheme 3. Synthesis of 1,2-diaryl pyridine 5-carboxamides. Reagents: (a) isopropyl chloroformate, NEt_3, $NaBH_4$, THF (51%); (b) Swern oxidation; (c) methyl diazoacetate in DCM, NaOMe, MeOH; (d) PPh_3, ether, *p*-tolualdehyde; (e) AcCN, Δ (7%, three steps); (f) LiOH, MeOH; (g) 3-naphthyl piperazine, EDC, HOBt, *i*Pr_2NEt, DMF (37%, two steps).



Scheme 4. Synthesis of 5, 6-diaryl pyrimidine carboxamides. Reagents: (a) acetamidine, NaOEt in 20% EtOH, EtOH; (b) SeO_2, pyridine, Δ; (c) substituted piperazine, EDC, HOBt, iPr_2NEt, DMF.

Table 1
5-Pyrimidyl substituent (Ar^1) modifications



Compd	Ar^1	EC_{50}[a] (nM)	% Act.	IC_{50}[b,c] (nM)
33	2-MeOPh	286	94	165
34	3-MeOPh	42	102	35
35	3-EtOPh	34	100	25
36	4-MeOPh	1.3	97	2.4
37	4-EtOPh	21	92	2.4
38	3,4-$(MeO)_2$Ph	256	83	857
39	3,4-$(HO)_2$Ph	88	90	1632
40	3,4-(OCH_2CH_2O)Ph	0.73	91	0.18

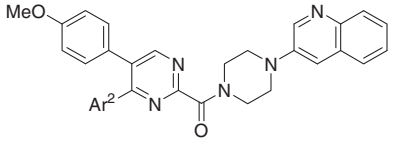
[a] CCK_IP3 (IP3 assay of a CHO cell line expressing human CCK1R) agonist data,[8] values are means of ⩾3 experiments, with standard deviations <77% of the average.
[b] Values are an average of ⩾3 experiments with standard deviations <75% of the average.
[c] See Supplementary data for assay protocols.[14]

ethoxyphenyl (**35**, **37**), 3,4-dimethoxyphenyl **38**, 3,4-dihydroxyphenyl **39** and 3,4-dioxanephenyl **40**. The 4-methoxyphenyl analog **36** displays the most potent in vitro profile of the mono-substituted derivatives. This is a departure from the imidazole carboxamides where the 3-ethoxyphenyl substituent was optimal. Interestingly, the disubstituted 1,4-benzodioxane derivative **40** dramatically improves CCK1R in vitro potencies, affording a 13-fold improvement in functional activity and a two-fold improvement in binding activity relative to the corresponding 4-methoxyphenyl compound **36**.

Selected modifications to the C-6 aromatic substituent (Ar^2) in the pyrimidine series were also evaluated (Table 2). The 4-fluorophenyl derivative **46** displays minimal loss of CCK1R functional and binding activity relative to the 4-methylphenyl derivative **36**, while the 2-fluorophenyl derivative **47** displays approximately a two-fold improvement in both potencies. The 2-fluoro-4-methylphenyl derivative **48** possesses the best overall in vitro profile in this series, with excellent functional and binding activities at the CCK1 receptor (EC_{50} = 0.24 nM, IC_{50} = 0.26 nM).

It was previously reported by our laboratories that quinoline-3-yl and 1-naphthoic acid-3-yl piperazine amides in the imidazole carboxamide structure class afforded excellent potency in CCK1R functional and binding activities.[8] This effect was also observed with the 5,6-diarylpyrimidine 2-carboxamides (Table 3). Although incorporation of a variety of biaryl groups is well tolerated, quinoline-3-yl (**36**) and 1-naphthoic acid-3-yl (**57**) remain the optimal aryl substituents. Indeed, analog **57** exhibits >10-fold increase in potency compared to the corresponding naphthyl compound **49**.

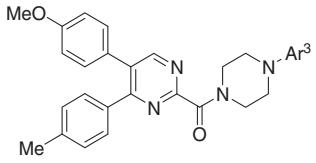
Table 2
4-Pyrimidyl substituent (Ar^2) modifications



Compd	Ar^2	EC_{50}[a] (nM)	% Act.	IC_{50}[b,c] (nM)
36	4-MePh	1.3	97	2.4
41	Ph	6.1	101	17.9
42	2-MePh	37	96	55
43	3-MePh	196	86	174
44	2-ClPh	61	105	35
45	3-FPh	38	72	51
46	4-FPh	1.8	103	6.7
47	2-FPh	0.71	92	1.4
48	2-F,4-MePh	0.24	98	0.26

[a] CCK_IP3 (IP3 assay of a CHO cell line expressing human CCK1R) agonist data,[8] values are means of ⩾2 experiments, with standard deviations <77% of the average.
[b] Values are an average of ⩾2 experiments with standard deviations <75% of the average.
[c] See Supplementary data for binding assay protocols.[14]

Table 3
5-Pyrimidyl substituent (Ar^3) modifications



Compd	R^1	EC_{50}[a] (nM)	% Act.	IC_{50}[b,c] (nM)
49	Naphthyl-2-yl	27	105	16.9
50	Isoquinoline-3-yl	17	115	13
51	Quinoline-6-yl	7.5	86	19
52	1-Benzofuran-6-yl	10	91	9.9
53	1*H*-Indole-6-yl	41	91	66
54	Methyl-2-naphthate-3-yl	5020	78	587
55	2-Naphthoic acid-3-yl	59	94	95
56	Methyl-1-naphthate-3-yl	9.6	95	4.7
57	1-Naphthoic acid-3-yl	0.20	104	2.0

[a] CCK_IP3 (IP3 assay of a CHO cell line expressing human CCK1R) agonist data,[8] values are means of ⩾3 experiments, with standard deviations <77% of the average.
[b] Values are an average of ⩾3 experiments with standard deviations <75% of the average.
[c] See Supplementary data for binding assay protocols.[14]

Combining all of the optimal substituents with the pyrimidine carboxamide core resulted in analogs **5** and **6**, which demonstrate excellent functional and binding activities at the human CCK1R (Table 4). Furthermore, these analogs exhibit potent functional activity and full receptor activation at the mouse CCK1R (Table 4). Representative compound **5** was further evaluated in an in vivo mouse gallbladder emptying (mGBE) assay in order to confirm a pharmacodynamic effect typical of CCK1R agonists.[6a,8,14] At an oral dose of 0.3 mg/kg, compound **5** reduced mouse gallbladder weight by 63% compared with vehicle. In a second study, the overnight food intake (ONFI) of lean mice dosed orally with **5** was measured relative to those dosed with vehicle.[8] This compound

Table 4
Compounds **5** and **6** in vitro activities at human and mouse CCK1 receptors[a,b,14]

Compd	hEC_{50} (nM)	% Act. hCCK1R	IC_{50} (nM)	mEC_{50} (nM)	% Act. hCCK1R
5	0.063	116	0.22	0.60	86
6	0.065	89	0.034	0.12	102

[a] IP3 assay of a CHO cell line expressing mouse CCK1R,[8] values are means of ⩾2 experiments. Standard deviations are less than 70% of the mean.
[b] Values are an average of ⩾2 experiments with standard deviations <75% of the average.

Table 5
Off-target activities of potent pyrimidine derived CCK1R agonists

Compd	IC_{50}s (nM)			EC_{50} (nM)
	CCK2R	IKr	Cox-1	CB2
5	>10,000	>9000	130	38 (−57%)
6	>10,000	>10,000	240	61 (−94%)

showed a significant effect on food intake reduction in mice at both doses, affording a 95% reduction at 3 mg/kg and a 36% reduction at 0.3 mpk as compared with vehicle. The overall potency and efficacy of **5** in these in vivo assays is comparable to that observed with previously reported CCK1R agonist **4**.[8a]

Selected off-target activities for potent CCK1R agonists **5** and **6** are illustrated in Table 5. Although the pyrimidine series shows excellent selectivity over CCK2R binding, some of these compounds are active as inhibitors of cyclooxygenase-1 (Cox-1)[12] and as inverse agonists at the cannabinoid receptor type 2 (CB2).[9a,13] For example, compound **5** showed an IC_{50} = 130 nM for Cox-1 and an EC_{50} = 38 nM at −57% activation at the CB2 receptor.

In summary, the six-membered ring heterocyclic carboxamides provide a diverse core for sub-type selective CCK1R agonists compared to a previously reported imidazole carboxamide series. In order to improve the potency of this new series of CCK1R agonists, it was necessary to re-optimize the SAR of the substituents at both Ar^1 and Ar^2. Ultimately, a pyrimidine series emerged that yielded potent CCK1R agonists **5** and **6**. Furthermore, analog **5** exhibited potent pharmacodynamic activity characteristic of CCK1R agonists in mice. Unfortunately, the discovery of some undesirable off-target activities in this novel series of CCK1R agonists prevented further development of these compounds.

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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.2011.03.069.

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14. Assay protocols are provided in Supplementary data. Activation of the CCK1 and CCK2 receptors are reported relative to 100% receptor activation.