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Bioorganic & Medicinal Chemistry Letters 16 (2006) 4668–4673
Bioorganic & Medicinal Chemistry Letters

Design and synthesis of potent and selective 1,3,4-trisubstituted-2-oxopiperazine based melanocortin-4 receptor agonists

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Received 8 May 2006; revised 23 May 2006; accepted 30 May 2006
Available online 12 June 2006

Abstract—The design and synthesis of a series of potent 1,3,4-trisubstituted-2-oxopiperazine based MC4 agonists are described. The tripeptidomimetic analogs (**12a**,**b** and **23**) and the dipeptidomimetic **27** displayed single-nanomolar binding affinity and agonist potency for MC4R and excellent selectivity for MC4R relative to MC1R.
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The melanocortin receptors (MCRs) belong to a family of 7-transmembrane G-protein coupled receptors. Five different subtypes (MC1R–MC5R) have been identified and are activated by the peptide ligands: α,β,γ-melanocyte stimulating hormones (MSH) and adrenocorticotrpin (ACTH). These endogenous ligands are derived from a common precursor protein, proopiomelanocortin (POMC) by post-translational cleavage.[1] Over the last decade, significant progress has been made toward the design of peptidic and non-peptidic ligands as potential therapeutic agents for melanocortin-mediated diseases.[2–4] In particular, MC4R has attracted an enormous level of attention as a therapeutic target for obesity, sexual dysfunction, and involuntary weight loss associated diseases.[5,6] The intensive efforts targeted at MC4R have led to the discovery of a number of selective, non-peptide small molecule MC4 agonists.[7–19]

We recently reported the design of a series of proline and pyrrolidine based melanocortin agonists using a conformationally constrained dipeptide mimic approach.[20] The design was based on the coupling of Xaa-D-Phe dipeptide, corresponding to two amino acids at the left side of early tetrapeptide leads, to a five-membered ring constrained Arg-Nal dipeptide mimic and led to the discovery of a number of pyrrolidine analogs that exhibited single-nanomolar binding affinity and agonist potency at MC4R. These results further demonstrated that the approach of using a conformationally constrained dipeptide mimic to replace the Arg-Trp dipeptide of the tetrapeptide leads is a viable design strategy to develop peptidomimetic MCR agonists. Our quest for more potent and selective small molecule MC4R agonists prompted us to extend this strategy to other scaffolds as conformational control elements for the Arg and Trp side chain, that is, guanidine moiety and naphthyl ring. One type of Arg-2-Nal dipeptide mimitic we have investigated contained a more flexible six-membered ring 2-oxopiperazine (Fig. 1), which was derived by inserting a CH_2–CH_2 unit between the amide nitrogen atoms of the two amino acids. The 2-oxopiperazine template has been explored in the design of thyrotropin releasing hormone (TRH)[21] and in non-peptide fibrinogen receptor antagonists.[22] During the course of our program to develop constrained peptidomimetic MCR agonists, we have investigated this scaffold as a conformational constraining element to design Arg-2-Nal dipeptide mimics, based on our success achieved with the pyrrolidine scaffold. In comparison with the pyrrolidine scaffold (**3**), the targeted 1,3,4-trisubstituted 2-oxopiperazine analogs **2** (Fig. 1) contain a C-terminus (carboxamide moiety), in addition to the expanded ring size and the amide moiety in the ring, thus providing opportunity to probe the role of the

Keywords: 2-Oxopiperazine; Peptidomimetics; Melanocortin-4; Agonists.

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doi:10.1016/j.bmcl.2006.05.087

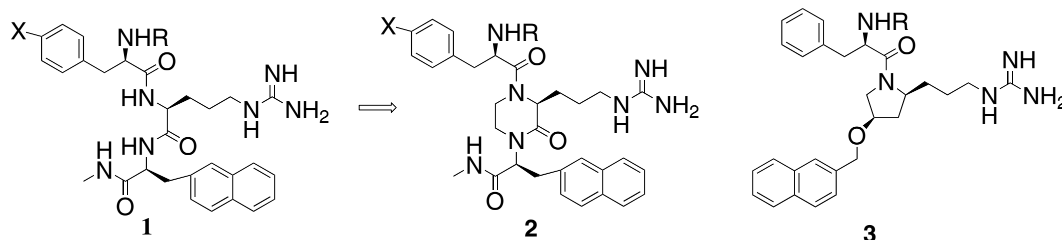


Figure 1. Design of 1,3,4-trisubstituted 2-oxopiperazine analogs.

C-terminus in potency and selectivity. Herein, we report on the synthesis and evaluation of 1,3,4-trisubstituted 2-oxopiperazine based melanocortin-4 receptor agonists.

The 2-oxopiperazine guanidine analogs were synthesized using a route similar to one reported by Just and co-workers.[21,23,24] In the case of analogs containing Arg-2-Nal residues, the synthesis began with H-Orn(Cbz)-OH, which was converted to 2-nitrobenzenesulfonamide **5**, Scheme 1. The coupling of **5** with **6** under EDCI activation afforded dipeptide **7**. The oxopiperazine ring was assembled by treatment of **7** with 1,2-dibromoethane in the presence of potassium carbonate in DMF at 75 °C. Cleavage of the NOS group of **8** afforded **9**, which was then coupled with Boc-D-Phe-OH or Boc-D-(4-F)-Phe-OH to produce **10**. Reductive cleavage of the Cbz group of **10** followed by guanidination and removal of Boc groups yielded tripeptidomimetics **12a**,**b**. For the synthesis of N-capped tripeptidomimetics or tetrapeptidomimetics, **10** was treated with trifluoroacetic acid and the primary amine was then coupled with acetic acid or amino acids to give **14a**,**b** and **18a**–**f**, which were then converted to the guanidine analogs **17a**,**b** and **21a**–**f** by means of a three-step sequence as described above.

Analog **23** containing a shorter C-3 guanidino side chain was prepared from H-DAB(Cbz)-OH (**22**) using the reaction sequences described for **12b** (Scheme 1).

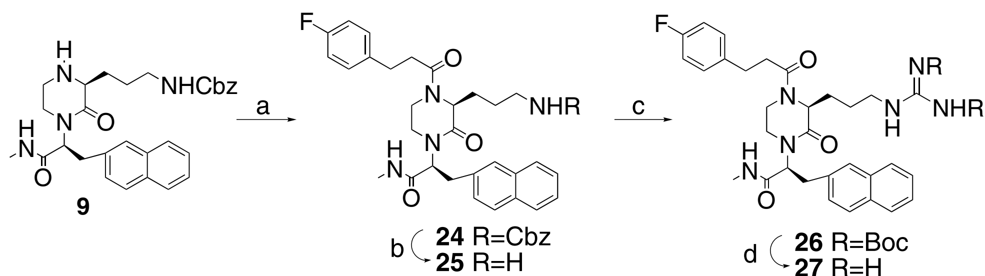
N-Terminus truncated analog **27** was synthesized from intermediate **9** (Scheme 2). The coupling of **9** with 3-(4-fluorophenyl)propanoic acid afforded **24**, which was converted to the guanidine analog **27** using reaction sequences as described above.

Our early efforts directed toward the development of melanocortin agonists on the basis of the His-D-Phe-Arg-His tetrapeptide led to the discovery of a series of MC4R agonists which possess a D-Phe-Arg-2-Nal-$NHCH_3$ tripeptide fragment, as exemplified by Ac-His-D-Phe-Arg-2-Nal-$NHCH_3$ (**28**) and Ac-Tyr-D-Phe-Arg-2-Nal-$NHCH_3$ **29** (Table 1). We also found that tripeptide D-Phe-Arg-2-Nal-$NHCH_3$ (**30**) itself had weak affinity and agonist potency at MC4R. However, substitution of the D-Phe residue of the tripeptide for D-Phe (D-(4-F)-Phe-Arg-2-Nal-$NHCH_3$, **31**) resulted in ~6-fold increase in binding and agonist potency at MC4R. Similarly, the enhancement in potency by incorporating D-(4-F)Phe was observed with the pseudo-tetrapeptide and pyrrolidine based analogs as well.[26] Therefore, both D-Phe and 4-F-D-Phe residues were employed in our research efforts of designing 2-oxopiperazine based MCR agonists. Along this line, we initially synthesized and screened tripeptidomimetic, **12a** (Table 2), and remarkably found that this tripeptide analog showed single-nanomolar binding and agonist potency at MC4R, representing a 480-fold improvement in potency as compared to linear tetrapeptide **30**. More importantly, **12a** was selective for MC4R relative to MC1R and MC3R (116- and 42-fold, respectively, based on binding affinity). In contrast with the previous SAR observations with the linear peptides, 4-F-D-Phe analog **12b** was found to exhibit similar binding affinity and functional potency at MC1R and MC4R to those of **12a**.

The discovery of tripeptide mimetics **12a**,**b** as potent and selective MC4R agonists provided additional compelling evidence for our strategy of conformationally constraining the Arg-2-Nal dipeptide region. To further explore this oxopiperazine based Arg-Nal dipeptide mimetic in the design of MCR agonists, we then moved on to investigate tetrapeptide mimetics to gain SAR of the top side chain. The corresponding constrained analogs of linear tetrapeptides **28** and **29** (**17a,b**), were first synthesized. It was interesting to find that capping the D-Phe residue of **12a** with the His residue resulted in 1650-, 240-, and 7-fold increased binding affinity, respectively, at MC1R, MC3R, and MC4R along with similar magnitude of increase in functional activity across the three MCRs tested (Table 2). The analog **17a** showed sub-nanomolar binding affinity and agonist potency at MC1R and MC4R, and was significantly less selective for MC4R relative to MC1R as compared to **12a**. The Tyr analog **17b** had also sub-nanomolar binding and potency at MC4R and single-nanomolar binding and potency at MC1 and MC3R. Both analogs were significantly more potent than the corresponding linear analogs **28** and **29** across the three MCRs.

Tetrapeptide analogs containing the D-(4-F) Phe residue revealed slightly different SAR insights. The capping of the D-Phe of **12b** with the His residue (**21a**) did not affect binding affinity and agonist potency at MC4R but led to only 190- and 2-fold increase in binding affinity at MC1 and MC3R, versus 1650- and 240-fold in the case of **17a**, respectively. On the other hand, Tyr analog **21b** showed similar affinity and agonist potency at MC3R and MC4R to those of D-Phe analog **17b** but was ~14-fold less potent at MC1R (K_i, 14 nM vs 1 nM).

Scheme 1. Reagents and conditions: (a) 2-nitrobenzenesulfonyl chloride, Et_3N, THF/H_2O; (b) EDCI, HOBt, NMM, DMF; (c) 1,2-dibromoethane, K_2CO_3, 75 °C, DMF; (d) 4-mercaptophenol, K_2CO_3, CH_3CN; (e) Boc-D-Phe(4-F)-OH, EDCI, NMM, HOBt; (f) H_2, Pd/C, CH_3OH; (g) 1,3-bis(*tert*-butoxycarbonyl)2-methyl-2-thiopseudourea, $HgCl_2$, Et_3N, DMF; (h) TFA, CH_2Cl_2; (i) R^2OH(Ac-His(Trt)-OH, Ac-Tyr-OH), EDCI, HOBt, NMM, DMF; (j) R^2OH (Ac-His(Trt)-OH, Ac-Tyr-OH, Boc-Tic-OH, Boc-Pip-OH, Ac-Gln-OH, AcOH), EDCI, HOBt, NMM, DMF.



Scheme 2. Reagents and conditions: (a) 3-(4-fluorophenyl)propanoic acid, EDCI, NMM, HOBt, DMF; (b) H_2, Pd/C, CH_3OH; (c) 1,3-bis(*tert*-butoxycarbonyl)2-methyl-2-thiopseudourea, $HgCl_2$, Et_3N, DMF; (d) TFA, CH_2Cl_2.

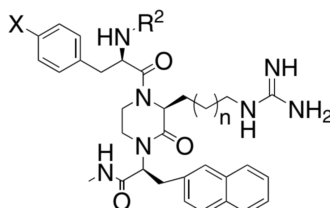
Additional tetrapeptide analogs were synthesized using **12b** as a template to expand SAR of the top side chain. Incorporation of the Tic residue to **12b** did not affect potency at MC1R and MC4R but led to a ~4-fold loss in potency at MC4R. This result was not expected as significant enhancement in potency has been observed

Table 1. Binding affinity and agonist potency for peptides **28**–**31**[a,b]

Compound	MC1R		MC3R		MC4R	
	K_i (nM)	EC_{50} (E_{max}, %) (nM)	K_i (nM)	EC_{50} (E_{max}, %) (nM)	K_i (nM)	EC_{50} (E_{max}, %), (nM)
28	13 ± 2	14 ± 1 (98)	1195 ± 326	541 ± 88 (106)	29 ± 5	5.7 ± 0.7 (101)
29	4520 ± 1257	20,000 (83)	1727 ± 67	20,000 (51)	104 ± 10	44 ± 5 (84)
30	4384 ± 820	20,000 ± 0 (26)	22,562 ± 108,74	20,000 ± 0 (20)	1248 ± 185	809 ± 122 (77)
31	4058 ± 942	21,667 ± 1667(46)	1143 ± 207	20,000 ± 0(32)	225 ± 15	140 ± 20(93)

[a] The analogs were screened against the human MC1R, MC3R, and MC4R as previously reported.[25]
[b] The data represent means of at least three experiments ± SEM.

Table 2. Binding affinity and agonist activity of 2-oxopiperazine guanidine analogs[a,b]



Compound	n	X	R^2	MC1R		MC3R		MC4R	
				K_i (nM)	EC_{50} (E_{max}, %) (nM)	K_i (nM)	EC_{50} (E_{max}, %) (nM)	K_i (nM)	EC_{50} (E_{max}, %) (nM)
12a	1	H	H	659 ± 187	526 ± 78 (108)	239 ± 46	41 ± 3.6 (102)	5.7 ± 1.7	1.7 ± 0.7 (105)
12b	1	F	H	366 ± 18	317 ± 67 (106)	75 ± 7	37 ± 10 (113)	7.0 ± 0.6	1.6 ± 0.3 (98)
17a	1	H	Ac-His	0.4 ± 0.1	0.07 ± 0.02 (92)	1 ± 0	0.4 ± 0.1 (152)	0.8 ± 0.3	0.3 ± 0.1 (149)
17b	1	H	Ac-Tyr	1 ± 0	1.7 ± 0.7 (99)	1 ± 0	1 ± 0 (133)	0.6 ± 0.2	0.2 ± 0.1 (149)
21a	1	F	Ac-His	2.0 ± 0.6	1.7 ± 0.6 (106)	35 ± 8	6.0 ± 1.5 (105)	5 ± 2	2 ± 0 (110)
21b	1	F	Ac-Tyr	14 ± 6	30 ± 12 (122)	1.1 ± 0.5	2 ± 0 (77)	0.4 ± 0.1	8.7 ± 2.3 (98)
21c	1	F	Tic	313 ± 4	104 ± 29 (120)	352 ± 114	163 ± 39 (108)	6 ± 1	1.6 ± 0.3 (110)
21d	1	F	Pip	4.3 ± 0.3	3.7 ± 0.9 (102)	17 ± 2	5.6 ± 0.3 (103)	1.3 ± 0.4	1.6 ± 0.3 (103)
21e	1	F	Ac-Gln	2 ± 0	0.37 ± 0.03 (96)	3.3 ± 0.9	0.5 ± 0.1 (100)	1.1 ± 0.4	0.34 ± 0.03 (110)
21f	1	F	Ac	18 ± 5	2.3 ± 0.9 (103)	7 ± 1	10 ± 0 (64)	1.3 ± 0.3	0.5 ± 0.2 (98)
23	0	F	H	1120 ± 151	353 ± 6 (105)	470 ± 50	84 ± 15 (86)	11 ± 1	2.2 ± 0.2 (106)
27				958 ± 7	1391 ± 136 (96)	206 ± 76	142 ± 57 (69)	5.3 ± 1.2	9 ± 3 (91)

[a] The analogs were screened against the human MC1R, MC3R, and MC4R as previously reported.[25]
[b] The data represent means of at least three experiments ± SEM.

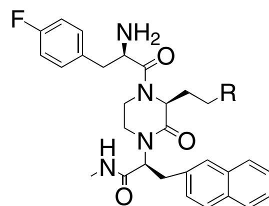
when the Tic moiety was introduced into linear tripeptide D-Phe-Arg-2-Nal (**30**).[26] However, substitution of Tic moiety for a less sterically bulky Pip residue (**21d**) resulted in increase in binding affinity (85-, 4-, and 5-fold, respectively) and agonist potency across three MCRs as compared to **12b**. Similarly, appending of a linear amino acid, Ac-Gln, to the D-Phe of **12b** afforded an analog (**21e**) showing sub-nanomolar functional activity across three MCR receptors.

Amino acids were not the only capping groups that produced analogs with significantly increased affinity and functional activity. A simple acetylation of **12b** resulted in 5- to 20-fold increase in affinity at the three MCRs tested and the resulting analog **21f** exhibited an EC_{50} value of 0.52 nM and a K_i value of 1.3 nM at MC4R. Furthermore, **21f** had better affinity and agonist potency at MC3R and MC4R than His and Tic analogs and comparable potency for MC3R and MC4R to those of Pip and Ac-Gln analogs. These results might suggest that H-bond capacity and steric bulk of amino acids in comparison with the acetyl group were not key factors contributing to the enhancement of potency across the three receptors observed when **12a** or **12b** was capped.

To further optimize this novel 2-oxopiperazine dipeptide mimetic, we have briefly investigated the effect of the space between the guanidine moiety and the six-membered piperazine ring. The shortening of the linkage length by one methylene unit led to only a marginal change for MC4 activity but the resulting analog **23** had 4- and 5-fold reduced binding for MC1 and MC3R, thus improving the selectivity for MC4R.

We have previously demonstrated within the class of pyrrolidine based MCR agonists that presence of the N-terminus on the D-Phe side chain was critical for the binding affinity and functional potency.[20] To further explore the 2-oxopiperazine based tripeptide mimetics and to better understand the minimal structural fragment required for significant binding affinity and functional activity, we then investigated the effect of removal of the N-terminus from D-Phe on the biological activity. Surprisingly, the resulting dipeptide mimetic **27** showed single-nanomolar binding affinity (K_i, 5 nM), comparable to those of D-Phe analog **12b**, with an EC_{50} of 9 nM at MC4R. Furthermore, it was more selective for MC4R relative to MC1R and MC3R than **12b**. This result is remarkable, given that a majority of small

Table 3. Binding affinity and agonist activity of non-guanidino 2-oxopiperazine analogs[a,b]



Compound	R	MC1R K_i (nM)	MC3R K_i (nM)	MC4R K_i (nM)	MC4R EC_{50} (E_{max}, %) (nM)
31	NH_2	5000 ± 0	3237 ± 679	85 ± 19	62 ± 18 (98)
32	NH_2	5820 ± 514	4122 ± 240	189 ± 59	45 ± 9 (105)
33	$NHC(O)NH_2$	2132 ± 142	461 ± 183	261 ± 61	12 ± 2 (85)
34	$NHC(O)NH_2$	21,703 ± 1696	6107 ± 189	365 ± 72	18 ± 2 (94)

[a] The analogs were screened against the human MC1R, MC3R, and MC4R as previously reported.[25]
[b] The data represent means of at least three experiments ± SEM.

molecule MC4 agonists reported to date possesses a D-Phe residue. Compound **27** might serve as a new template for the design of potent MC4R agonists with reduced peptide character and molecular weight.

The basic guanidine moiety contained in tripeptidomimetics discussed above seems to be important for binding affinity and agonist potency. The amino analogs **31** and **32**, precursors for guanidine analogs **12b** and **23**, were found to have K_i values of 89 nM and 189 nM (Table 3) as well as EC_{50}s <100 nM, significantly less potent than the corresponding guanidine analogs. Use of a neutral urea moiety to replace the guanidine of **12b** and **23** led to ~35-fold reduced binding affinity at MC4R (**33** and **34**).

In summary, we have demonstrated that 1,3,4,-trisubstituted 2-oxopiperazine based Arg-2-Nal dipeptide mimic is an effective replacement for Arg-2-Nal for designing potent MC4R agonists. The coupling of the appropriate D-Phe residue to this novel dipeptide mimic led to potent and selective MC4R agonists **12a**,**b**. Furthermore, capping the D-Phe of **12a**,**b** with an acetyl group or amino acids (with the exception of Tic) resulted in significant increase in binding affinity and agonist potency at MC1R and MC3R, thus reducing selectivity for MC4R over MC1R and MC3R. Another notable SAR finding was that truncation of the N-terminus from **12b** led to **27**, which displayed single-nanomolar affinity and agonist potency at MC4R. We have subsequently incorporated these findings into the design of the orally active ketopiperazine based MC4R agonists and details will be reported in due course.

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