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Privileged structure-based ligands for melanocortin receptors—tetrahydroquinolines, indoles, and aminotetralines

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Abstract—Substitution of the aryl sulfonamide moiety contained in MC4 agonist **1** with bicyclic heterocycles and aminotetralines produced compounds with MC4 activity. The heterocycles represent alternative privileged structures to that contained in **1**. Compounds in which the polar group of the privileged structure was displayed in an endocyclic fashion were not as active as the parent agonist **1**, while those with an exocyclic polar group afforded activity competitive with **1**.

Melanocortins are a family of bioactive peptides derived from the post-translational modification of proopiomelanocortin (POMC).[1] These substances, whose properties were first described in 1916,[2] are known to possess a fascinating array of physiological functions. Recently, five unique type I G-protein coupled receptors (GPCRs) have been identified and cloned for these peptide ligands.[3] While use of the Melanocortins as pharmacological tools has afforded considerable insight into the functions of each receptor, complete characterization of each member has been hampered by the lack of selective tools.[4]

We have recently described our library-based approach for the generation of ligands for the melanocortin receptors.[5] This effort initially yielded structures of modest potency and selectivity, which were readily optimized for the Human Melanocortin receptor 4 (hMC4). The lead compound (**1**) can be described as being composed of a GPCR privileged structure[6] (**2**) coupled with a dipeptide 'address element' **3** (Fig. 1). Consistent with the literature, we found that optimization of these types of structures benefited from chemical modification of the privileged structure to a greater extent than the address element.[7] This strategy was enhanced further by the fact that our molecules' key components were linked together with an amide bond, thus allowing ready exchange of a variety of privileged structures. Herein, we describe a portion of our efforts to develop and understand new privileged structures that afford melanocortin receptor activity when coupled to the previously described dipeptide address element **3**. Inspection of the privileged structure contained in our lead compound reveals functionality common to other similar motifs; namely, an aryl group and an amine-based polar group.[8] We sought to explore the relationship of these two key elements by constraining the polar group in lead compound **1**. Specifically, we sought to see if the aryl

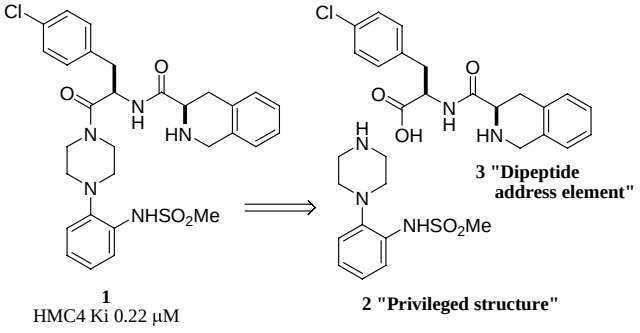

Figure 1.

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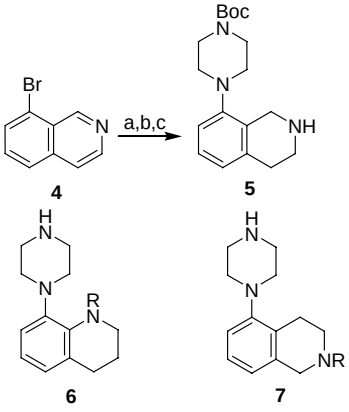
sulfonamide could be replaced with suitably substituted tetrahydroquinolines, indoles, and aminotetralines.

Preparation of the desired isoquinoline intermediates begins by allowing 8-bromoisoquinoline[9] (**4**) to react with excess piperazine in the presence of palladium[10] (Scheme 1). The resulting adduct was protected on the secondary nitrogen with Boc_2O and then partially reduced with Pt_2O, affording tetrahydroisoquinoline **5**. The formed amine was then transformed further either by reductive amination or acylation. Removal of the Boc group from the piperazine was accomplished with TFA. Intermediates containing either an 8-substituted tetrahydroquinoline (**6**) or a 5-substituted tetrahydroisoquinoline (**7**) were prepared from the corresponding bromoquinoline derivatives in a similar fashion.

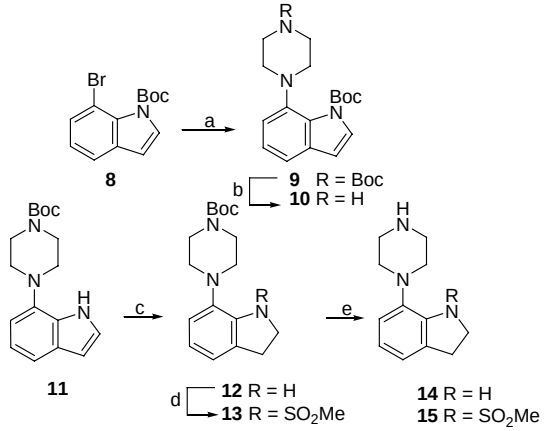
Compounds containing a substituted indole or indolene were prepared from protected indole **8**, as outlined in Scheme 2. The reaction of Boc-protected piperazine with **8** in the presence of palladium affords intermediate **9**, which, upon exposure to TFA, affords amine **10**. Reprotection of the piperazine nitrogen in **10** yields indole **11**, which is then reduced with $NaBH_3CN$ providing indolene **12**. Sulfonamide **13** is readily obtained from this material by exposure to methanesulfonyl chloride. Deprotection of **12** and **13** is easily accomplished by treatment with TFA, affording compounds **14** and **15**.

Substituted 2-aminotetralines were prepared in several ways, as outlined in Scheme 3. In general, 2-amino-8-bromotetralines were coupled with Boc-protected piperazine to form intermediate **16** using the Buchwald conditions described previously. Removal of the Boc group from the piperazine afforded amines **17**. Racemic 2-aminotetralines were prepared either by reductive amination of ketone **18** or by a routine acylation or alkylation of amine **19**. Optically active aminotetralines were prepared from the known bromotetraline **20**.[11]

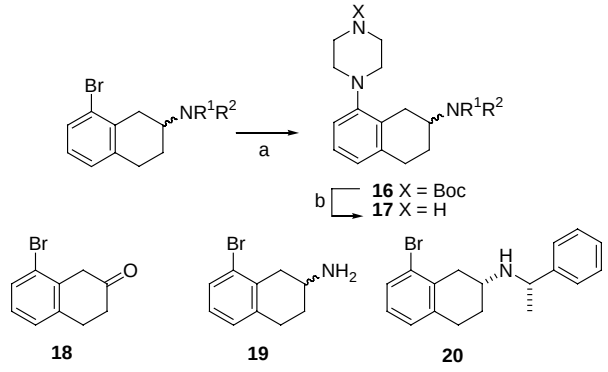
Final compounds for this paper were constructed by coupling the aforementioned piperazine intermediates with the known dipeptide address element **3**. A specific example of this sequence is illustrated with the reaction of intermediate **15** and the previously described dipeptide **3** in the presence of HATU[12] to afford the penultimate derivative **21**. Treatment with TFA provided the desired deprotected compound **22d**, which could be used as the corresponding TFA salt or subjected to salt exchange to obtain the HCl salt (Scheme 4). Coupling of racemic aminotetralines with dipeptide **3** afforded diastereomeric pairs that were not separated for biological evaluation.



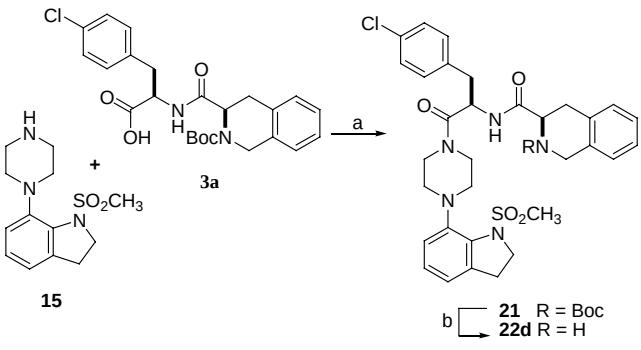
Scheme 1. Reagents: (a) Piperazine, $Pd(dba)_2$, NaOAc, BINAP; (b) Boc_2O; (c) Pt/H_2.



Scheme 2. Reagents: (a) Boc piperazine, $Pd(dba)_2$, NaOAc, BINAP; (b) TFA; (c) $NaBH_3CN$; (d) $MeSO_2Cl$; (e) HCl.



Scheme 3. Reagents: (a) Boc piperazine, $Pd(dba)_2$, NaOMe, BiNap; (b) HCl.



Scheme 4. Reagents: (a) HATU, (b) TFA or HCl.

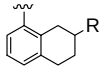
Compounds synthesized for this study were evaluated for binding affinity, across human melanocortin receptors 1, 3, 4, and 5, by determining the competitive inhibition of [^{125}I]NDP MSH binding.[13,14] Compound specific data obtained with these assays are given in Tables 1–3.

Tetrahydroquinoline derivatives **22a–c**, which represent direct cyclic analogs of our lead compound **1**, were the first series examined (see Table 1). The sulfonyl substituted analog **22c** afforded 3.8-fold less potency than its acyclic congener **1**. Exchange of the sulfonyl group with an acetyl moiety (**22b**) resulted in further erosion of activity (7.7 μM K_i). The nonsubstituted compound (**22a**) had similar potency (1.6 μM) as the acetyl analog. Contracting the nitrogen-containing ring by one atom provided indolene **22d**, which has similar activity (0.94 μM) as the tetrahydroquinoline **22c**. A comparison of compounds **22e** and **22f** suggests that unsaturation in the 5-membered ring had little impact on activity. Surprisingly, the sulfonyl-capped isoquinoline analog **22h** was 2-fold more potent than its tetrahydroquinoline analog **22c**. Interestingly, in this series, the acetyl and sulfonyl groups provide similar activities (compare **22g** and **22h** with **22b** and **22c**). Changing the polar group from acetyl to *N*-alkyl had a positive impact in this series, as exemplified by compounds **22k** and **22l**, which displayed binding affinities more potent than our lead, compound **1**. Isomeric isoquinoline analogs **22m** and **22n** were in each case less potent than there direct comparators **22h** and **22l**, respectively.

Table 1. Fused heterocycle analogs **22a–n**

Privileged structure	Compound	R	hMC4R (μM) K_i[13,15]
	**22a**	H	1.6
	22b	$COCH_3$	7.7
	22c	SO_2CH_3	0.9
	**22d**	SO_2CH_3	0.9
	22e	H	2.1
	**22f**	—	4.8
	22g	$COCH_3$	0.5
	22h	SO_2CH_3	0.6
	**22i**	SO_2iPr	0.95
	22j	SO_2Ph	2.5
	22k	CH_3	0.28
	22l	CH_2CH_3	0.19
	**22m**	CH_2CH_3	0.7
	22n	SO_2CH_3	3.9

Table 2. Tetraline analogs **22o–z**



Compound	R	hMC4 (μM) K_i[13,15]
22o	H	4.2
22p	NH_2	0.24
22q	NHAc	0.41
22r	$N(CH_3)SO_2CH_3$	0.53
22s	$NHCH_3$	0.15
22t	$N(CH_3)_2$	0.07
22u	$N(CH_2CH_3)_2$	0.17
22v	$N(CH_2CH_2CH_3)_2$	0.18
22w	$N(CH_2)_4$	0.14
22x	$N(CH_2)_2O$	0.23
22y	*R* $(NCH_3)_2$	0.05
22z	*S* $(NCH_3)_2$	0.08

Table 3. Representative binding selectivities

Compound	K_i (μM) (Fold selectivity relative to MC4)		
	hMC1[13,15]	hMC3[13,15]	hMC5[13,15]
22b	20 (23)	0.5 (0.6)	4.0 (5)
22j	7 (23)	1.2 (4)	0.7 (2.6)
22t	4 (72)	8.2 (164)	0.28 (5.6)
22o	3 (47)	1.2 (181)	0.26 (3.8)

Replacement of the amine moiety in these tetrahydroquinoline analogs with a methylene provides tetraline derivative **22o**[16] (Table 2), which is significantly less active (4.2 μM) than any analog in the above series. Addition of a substituted amine to the tetraline ring of **22o** affords analog **22p**, which has a K_i of 0.24 μM. Primary amide **22q** was 2-fold less active (0.41 μM) than amine **22p** and similar in activity to tertiary sulfonamide **22r** (0.53 μM). In contrast to the aforementioned amide derivatives, alkylation of the amine appeared to provide better activity. For example, relative to primary amine **22p**, monomethylation (**22s**) increased affinity slightly (0.15 μM), and dimethylation (**22t**) afforded a 4-fold increase in activity (0.07 μM). The diethyl (**22u**) and the dipropyl analogs (**22v**) were similar in activity with K_i's of 0.17 and 0.14 μM, respectively. Cyclic amines (**22w** and **22x**) did not appear to provide any advantage relative to their dialkyl counterparts. Compounds **22y** and **22z** illustrate the activity contribution of each diastereomer of the diethyl analog. The *R* containing enantiomer **22y** was modestly more potent (0.05 μM) than the *S* containing enantiomer **22z** (0.08 μM).

In addition to MC4 activity, compounds were screened for binding affinity at human melanocortin receptors 1, 3, and 5. Data for select compounds, which represent the selectivity trends, observed for the series of compounds described above, are given in Table 3. In general, the compounds we prepared were inherently selective for MC4, with the greatest selectivity ratios seen between MC1 and MC3 (~20-fold). Selectivity between MC4 and MC5 was modest, favoring the former roughly by 3-fold. Selectivity for MC5 versus MC1 and MC3 was slightly less than that observed for MC4 with average ratios of 5- to 10-fold. Compounds with selectivity for MC1 or MC3 were not observed for the series reported in this paper.

The data highlighted in this report demonstrate that fused ring systems, which incorporate separate aromatic and polar functionalities, can be employed as privileged structures in this series. Within the constrained analogs

prepared, we noticed sensitivity in regard to placement and type of the polar group. Locating the polar group adjacent to the aromatic ring apparently afforded too much conformational restraint, resulting in lower affinity, relative to its acyclic congener. This activity was somewhat restored by moving the polar group one atom over to the benzylic position. Further movement within the ring proved to be less optimal. Movement of the polar group from an endocyclic to an exocyclic position presumably provided additional conformational flexibility, which leads to an increase in activity. Interestingly, in the one example shown, enantiomeric configuration had little impact on overall activity. Consistent with earlier findings, activity was higher with alkyl amine substitution.[5]

Finally, compound **22o** illustrates an important finding of this paper. A comparison of compounds **22b** and **22c** with compound **22o** illustrates the fact that mere incorporation of a polar group into a privileged structure motif does not always lead to expected or enhanced activity. Rather, the data suggest that placement and orientation of this functionality are important aspect to consider during the exploration and optimization of an initial privileged structure containing hits. Once the general location of the polar group has been identified, there is usually some latitude with regard to functional group identity and orientation that should allow further refinement of either potency or overall properties of the molecule.

Acknowledgment

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References and notes

1. Strand, F. L. *Ann. N.Y. Acad. Sci.* **1999**, *897*, 1.
2. Smith, P. E. *Science* **1916**, *44*, 280.
3. Cone, R. D.; Mounthoy, K. G.; Robbins, L. S.; Nadu, J. H.; Johnson, K. R.; Roselli-Rehfuss, L.; Mortund, M. T. *Ann. N.Y. Acad. Sci.* **1993**, *680*, 342.
4. For examples of efforts directed at the preparation of selective ligands see: (a) Pan, K.; Scott, M. K.; Lee, D. H. S.; Fitzpatrick, L. J.; Crooke, J. J.; Rivero, R. A.; Rosenthal, D. I.; Vaidya, A. H.; Zhao, B.; Reita, A. B. *Biorg. Med. Chem. Lett.* **2003**, *11*, 185; (b) Sebhat, I. K.; Martin, W. J.; Ye, S.; Marakat, K.; Mosley, R. T.; Johnston, D. B. R.; Bakshi, R.; Palucki, B.; Weinberg, D. H.; MacNeil, T.; Kalyani, R. N.; Tang, R.; Sterns, R. A.; Tamvakopoulos, C.; Strack, A. M.; McGowan, E.; Cashen, D. E.; Drisko, J. E.; Hom, G. J.; Howard, A. D.; MacIntyre, D. E.; van der Ploeg, L. H. T.; Patchett, A. A.; Nargund, R. P. *J. Med. Chem.* **2002**, *45*, 4589; (c) Dyck, B.; Parfker, J.; Phillips, T.; Carter, L.; Murphy, B.; Summers, R.; Hermann, J.; Baker, T.; Cismowski, M.; Saunders, J.; Goodfellow, V. *Biorg. Med. Chem. Lett.* **2003**, *13*, 3793; (d) Jhang, J.; Xiong, C.; Ying, J.; Wamg, W.; Hrubt, V. J. *Org. Lett.* **2003**, *5*, 3115; (e) Fotsch, C.; Smith, D. M.; Adams, J. A.; Cheetham, J.; Croghan, M.; Dorhety, E. M.; Hale, C.; Jarosinski, M. A.; Kelly, M. G.; Norman, M. H.; Tamayo, N. A.; Xi, N.; Baumgartner, J. W. *Biorg. Med. Chem. Lett.* **2003**, *13*, 2337.
5. Richardson, T. I.; Ornstein, P. L.; Briner, K.; Fisher, M. J.; Backer, R. T.; Biggers, C. K.; Clay, M. P.; Emmerson, P. J.; Hertel, L. W.; Hsiung, H. M.; Husain, S.; Kahl, S. D.; Lee, J. A.; Lindstrom, T. D.; Martinelli, M. J.; Mayer, J. P.; Mullaney, J. T.; O'Brien, T. P.; Pawlak, J. M.; Revell, K. D.; Shah, J.; Zgombick, J. M. *J. Med. Chem.* **2004**, *47*, 744.
6. Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfield, J. *J. Med. Chem.* **1988**, *31*, 2235.
7. For examples of this phenomenon, compare the ligands for growth hormone secretagogues outlined in the following papers: (a) Patchett, A. A.; Nargund, R. P.; Tata, J. R.; Chen, M.-H.; Barakat, K. J.; Johnston, D. B. R.; Cheng, K.; Chan, W. W.-S.; Butler, B. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *79*, 7001; (b) Seyler, D. E.; Dodge, J. A.; Osborne, J. J.; Cox, K. L.; Viswanath, D.; Wilmot, A. F.; Keaton, M. J.; Heiman, M. L.; Bryant, H. U. *Drug Dev. Res.* **2000**, *49*, 260; (c) MacAndrew, J. T.; Ellery, S. S.; Parry, M. A.; Pan, L. C.; Black, S. C. *Eur. J. Pharmacol.* **2001**, *432*, 195.
8. Bondensgaard, K.; Ankersen, M.; Thogersen, H.; Hansen, B. S.; Wulff, B. S.; Bywater, R. P. *J. Med. Chem.* **2004**, *47*, 488.
9. Brown, W. D.; Gouliaev, A-H. *Synthesis* **2002**, 83.
10. Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144.
11. Romero, A. G.; Leiby, J. A.; McCall, R. B.; Piercey, M. F.; Smith, M. W.; Han, F. *J. Med. Chem.* **1993**, *36*, 2066.
12. Speicher, A.; Klaus, T.; Eicher, T. *J. Prakt. Chem./Chem-Ztg* **1998**, *340*, 581.
13. The details of the binding assay have been recently described. See Ref. 5.
14. Functional activity was determined by measuring the cAMP release with a standard luciferase assay employing HEK 293 cells stably transfected with hMC4 (data not shown). Compounds of this paper were agonists with relative efficacies 60–100% of the maximum response obtained with NDP-α-MSH.
15. Each data point represents the average of at least two determinations with an average error of the binding assay being 15%.
16. Boninell, W.E.; Neeb, M.J. WO 02/05819, 2002; *Chem. Abstr*. **2002**, 136, 134783.