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Discovery of potent and stable conformationally constrained analogues of the MCH R1 antagonist SB-568849

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Abstract—A strategy of systematically targeting more rigid analogues of the known MCH R1 receptor antagonist, SB-568849, serendipitously uncovered a binding mode accessible to *N*-aryl-phthalimide ligands. Optimisation to improve the stability of this compound class led to the discovery of novel *N*-aryl-quinazolinones, benzotriazinones and thienopyrimidinones as selective ligands with good affinity for human melanin-concentrating hormone receptor 1.

Interest in the 7-transmembrane G-protein coupled receptor MCH R1, a cognate receptor for melanin-concentrating hormone,[1,2] has grown since the discovery of its association with the regulation of feeding activities in rodents.[3] Intracerebroventricular (icv) dosing of MCH elicits a feeding response in wild-type rodents, while MCH knock-out mice are characterized by a lean and hypophagic phenotype.[4] Mice in which the MCH R1 receptor has been deleted, show a reduced susceptibility to diet induced obesity, and do not respond to icv dosing of MCH with feeding behaviours.[5,6] It is conjectured that brain penetrant antagonists of this receptor may have applications in the treatment of human obesity.[7,8]

In the preceding paper we described the discovery of a class of phenyl carboxanilide antagonists of MCH R1, for example, **1a** and **1b** which, through a lead optimisation programme, led to the more soluble and metabolically stable analogue SB-568849 (Fig. 1) incorporating a smaller basic moiety and an *N*-methyl amide.[8] In this paper, we disclose an investigation of conformational constraints, undertaken with the aim of further improving both potency and developability properties.[7,9]

Our strategy was to subject three regions of compound **1** to systematic conformational constraint: the basic side chain **A**, the biphenyl group **B** and the carbonyl moiety **C** (Fig. 2).

Target compounds **8a–e,g**, **11a**, **13b–d**, **15b–d**, **20–24**, **35a–d**, **36b–d**, **39** and **42** (Tables 1 and 2) were prepared by the methods described in Schemes 1–5. Anilides **8a–e** containing O-linked constrained amines were prepared by one of two routes (Scheme 1). Hydroxyl-pyrrolidines **3a–c** were reacted with 4-nitro-2-methoxyphenol **2p** in the presence of tributylphosphine and azodicarbonyl-dipiperidine (ADDP) in a Mitsunobu reaction to afford **4a–c**. Examples **3d** and **3e** were treated with 4-chloronitrobenzene **2q** in DMF with sodium hydride to form **4d** and **4e** by nucleophilic aromatic substitution.[10] Amines **6a–e** were formed by hydrogenation of **4a–e** and were coupled to either 4-cyclohexyl-benzoyl chloride **7m**, (e.g., **8a–d**) or 4-biphenyl-carbonyl chloride **7n** (e.g., **8e**), under conditions of base catalysis. The corresponding piperazines (**8f** and **8g**) were formed in an analogous manner from known piperazine **5** by protection of the basic nitrogen using Boc anhydride to give **4f**, followed by hydrogenation of the nitro group and coupling to 4-cyclohexyl-benzoyl chloride to form protected analogue

Keywords: MCH; MCH R1; Biphenylcarboxamide; Antagonist; Melanin-concentrating hormone; Obesity; Feeding; Stress; Anxiety; Quinazolinone; Benzotriazinone; Thienopyrimidinone; Cyclisation; Bicyclic heterocycle.
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† Dr. Guillaume Hervieu sadly died before publication of this work.

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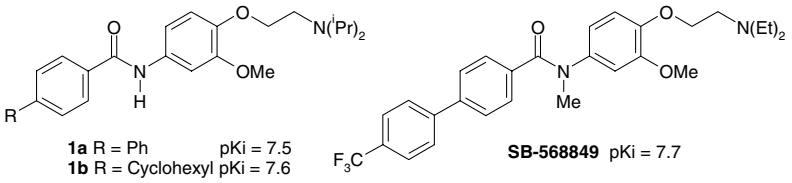


Figure 1. MCH R1 antagonists.

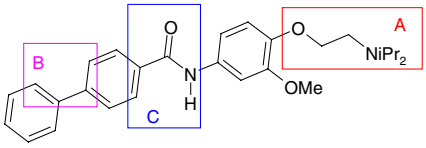
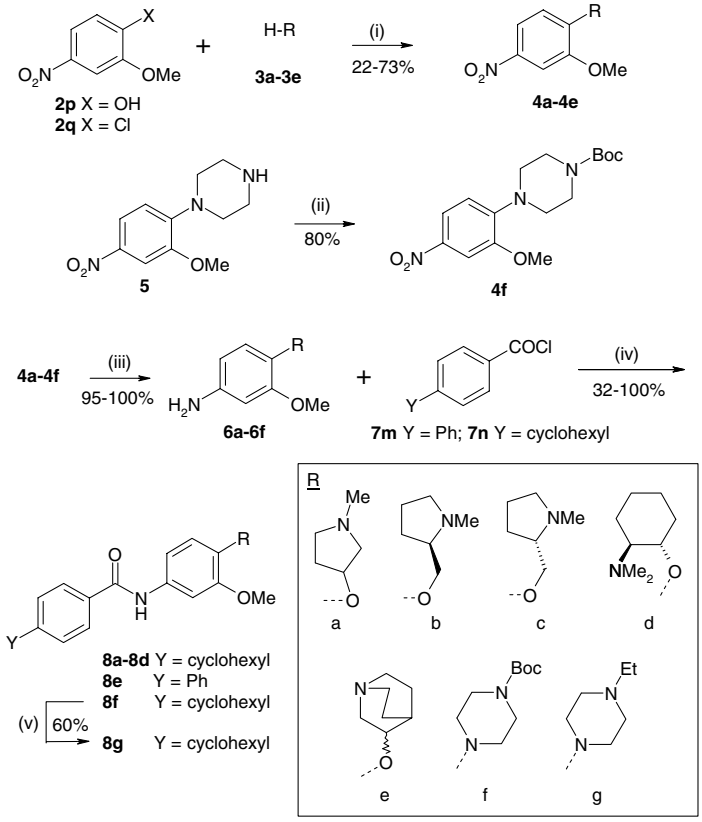


Figure 2. Regions for conformational constraint.

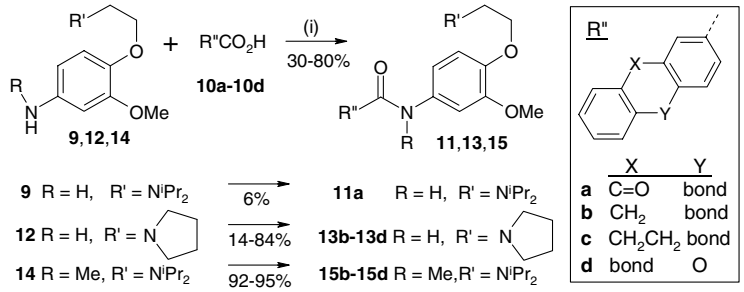
8f, using the process described, for example, **8a**–**e**.[11] Removal of the Boc group of **8f** with hydrochloric acid was followed by alkylation using a resin bound cyanoborohydride as reductant in the presence of acetaldehyde, affording **8g**.

Constrained biphenyl compounds, **11a**, **13b**–**d** and **15b**–**d**, were prepared by coupling the appropriate biphenyl-carboxylic acids (**10a**–**d**) to the diisopropyl-aniline (**9**), the pyrrolidinyl-aniline (**12**) or the *N*-methyl-aniline (**14**).[8] This was achieved either using the coupling agent EDC, or by prior conversion of the acids to the corresponding acid chloride, followed by amide coupling under conditions of base catalysis (Scheme 2).

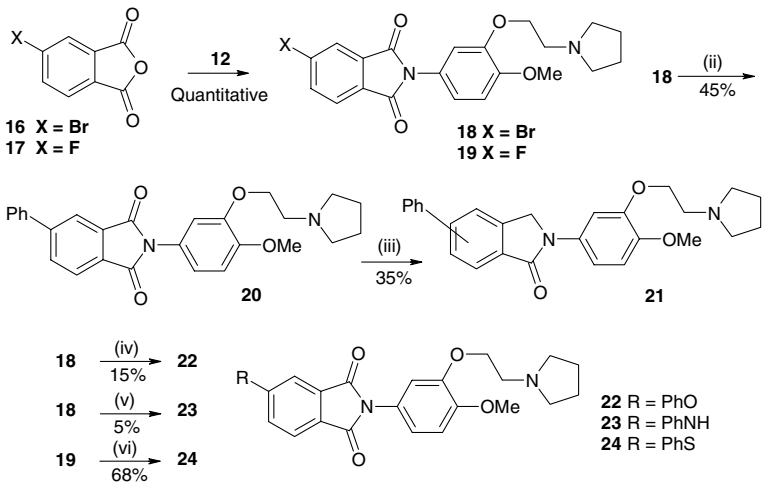
Isoindolone, **21**, was isolated as a mixture of regioisomers as prepared in a four-step process outlined in Scheme 3. Condensation of bromophthalic anhydride (**16**) with aniline **12** in the presence of EDC resin gave phthalimide **18**. A palladium-catalysed Suzuki reaction of this material with benzeneboronic acid afforded the intermediate phenyl-phthalimide (**20**). Reduction of just one of the carbonyl groups proceeded without regioselectivity to give isoindolone **21** as an ~1:1 isomer mixture. Heteroatom-linked analogues (**22** and **23**) were prepared by coupling phenol and aniline to bromophthalimide **18** under conditions of palladium catalysis, albeit in low yield, while the thioether analogue **24** was prepared in a two-step process from fluorophthalic anhydride (**17**). This was coupled to **12** in the same manner as



Scheme 1. Reagents and conditions: (i) either **2p**, Bu_3P, ADDP, THF or **2q** NaH, DMF, 80 °C; (ii) Boc_2O, CH_2Cl_2; (iii) H_2 10% Pd/C, EtOH; (iv) Et_3N or DIEA resin, CH_2Cl_2; (v) 4 M HCl in 1,4-dioxane, 70 °C, 5 min, evaporate, then acetaldehyde, Amberlyst cyanoborohydride resin, AcOH, EtOH.



Scheme 2. Reagents and conditions: (i) either **10a–d**, EDC, DMF, HOBT or 1—**10a–d**, $SOCl_2$, CH_2Cl_2, reflux, 3 h, evaporate then 2. Compounds **9/12/14**, Et_3N, CH_2Cl_2.

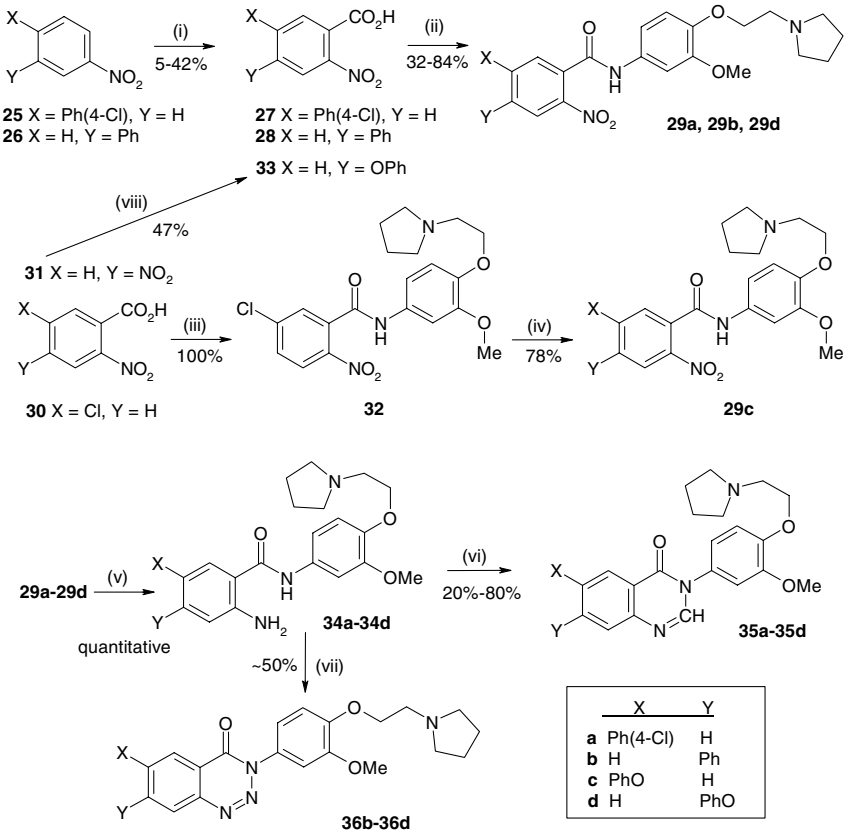


Scheme 3. Reagents and conditions: (i) EDC resin, CH_2Cl_2, 12 h; (ii) $Pd(PPh_3)_4$, toluene, Cs_2CO_3, $PhB(OH)_2$; (iii) 1—$NaBH_4$, EtOH then 2—DIBAL-H, MDC; (iv) PhOH, $Pd(PPh_3)_4$, toluene, Cs_2CO_3; (v) $PhNH_2$, BINAP, toluene, Cs_2CO_3; (vi) PhSH, NaH, DMF.

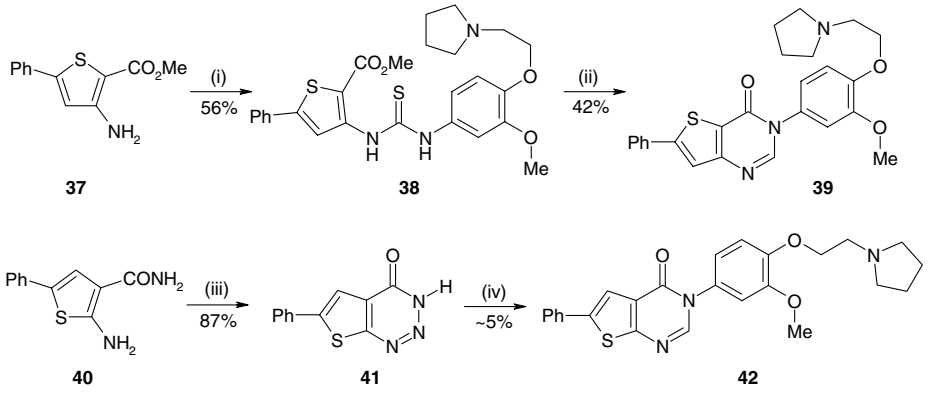
compound **16**, then imide **19** subjected to a nucleophilic aromatic substitution of fluoride by thiophenol to afford **24**.

Quinazolinones (**35a–d**) and benzotriazinone-linked compounds (**36b–d**) were prepared by the methods outlined in Scheme 4. For the aryl-substituted heterocyclic precursors (**29a** and **29b**), the parent substitution pattern was established using a vicarious nucleophilic substitution (VNS) reaction on 4-chloro-4′-nitrobiphenyl (**25**) and 3-nitrobiphenyl (**26**). Reaction of the nitroaromatics with the chloroform anion, generated using potassium *tert*-butoxide in THF/DMF, in both cases, gave a dichloromethyl moiety *ortho* to the nitro group. In the case of **25**, the 4′-chloro substituent blocked an alternative VNS reaction in the distal ring. The $CHCl_2$ group was hydrolysed in the presence of wet silver triflate to form aldehydes which were oxidised to the corresponding acids (**27** and **28**) using sodium perborate in acetic acid. These were converted to their acid chlorides using oxalyl chloride and a trace of DMF in dichloromethane, then coupled to aniline **12** to afford nitroamides **29a** and **29b**, respectively. Analogous aryloxy compound **29c** was prepared from 5-chloro-2-nitrobenzoic acid (**30**) by conversion to the acid chloride, as described previously, then coupling to amine **12** under conditions of base catalysis to form amide **32**. This material reacted with sodium phenoxide in DMF to give the 4-phenoxyl-substituted analogue (**29c**). The fourth substitution pattern was established by conversion of the dinitrobenzoic acid **31** to the phenyl ester. This was treated with sodium phenoxide to give predominant displacement of the 4-nitro group such that hydrolysis of the ester gave acid **33**. This was converted to the nitroamide **29d** using the same protocol as for **29a** and **29b**. Nitroamides **29a–d** were then converted to the corresponding *ortho*-amino amides (**34a–d**) by hydrogenation over a palladium catalyst. Ring closures to the quinazolinones (**35a–d**) were effected with trimethyl orthoformate, while the corresponding benzotriazinones (**36b–d**) were prepared by treatment of the amino amides with butyl nitrite in the presence of TFA.

Thienopyrimidines **39** and **42** were prepared from commercial aminothiophenes as described in Scheme 5. 3-Amino-4-phenylthiophene-1-carboxylic acid methyl ester (**37**) was treated with di-2-pyridyl thionocarbonate in dichloromethane to form the 3-isothiocyanate. This was reacted with compound **12** to form thiourea **38**. Treatment of the thiourea with methyl iodide and base resulted in alkylation on sulfur to give the imidothiocarbamate, which, on warming, cyclised to the desired substituted heterocycle with a



Scheme 4. Reagents and conditions: (i) 1—$CHCl_3$, KO^{t}Bu, THF, DMF; 2—AgOTf, aq MeCN reflux; 3—$NaBO_3$, AcOH 60 °C 16 h; (ii) 1—$(COCl)_2$, CH_2Cl_2, DMF; 2—**12**, DIEA resin, MDC; (iii) 1—$(COCl)_2$, CH_2Cl_2, DMF; 2—**12**, DIEA resin, MDC; (iv) PhONa, DMF; (v) H_2, Pd/C, EtOH; (vi) $HC(OMe)_3$, 100 °C, 24 h; (vii) BuONO, TFA then DBU; (viii) 1—$(COCl)_2$, CH_2Cl_2, DMF; 2—PhOH, DIEA resin 1 h; 3—NaH, DMF; 4—aq NaOH, EtOH then aq HCl.



Scheme 5. Reagents and conditions: (i) 1—S=C(OPy)$_2$, CH_2Cl_2 0 °C then 2—**12**, CH_2Cl_2, rt; (ii) 1—MeI, K_2CO_3, THF; 2—toluene reflux; 3—Raney-Ni, methanol, rt; (iii) $NaNO_2$, aq HCl 1,4-dioxane (iv) 1—**12**, *p*-xylene, reflux; 2—$HC(OEt)_3$, 100 °C, 24 h.

2-methylthio substituent. Synthesis was completed by desulfurisation to compound **39** with Raney-nickel in methanol. The isomeric compound was prepared from 2-amino-4-phenyl-thiophene-3-carboxamide (**40**) which was cyclised to the thienotriazinone (**41**) by treatment with aqueous nitrous acid. The carbonyl was sufficiently activated to react directly with compound **12** at high temperature to give an amino amide, which was closed to form compound **42** by triethylorthoformate.

Compounds modified in each of the regions **A**–**C** were assessed for receptor affinity in a binding assay.[12]

A—*Basic side-chain constraint.* In earlier studies, effective basic side chains were found to include 2-*N*-di alkylamino-ethoxy and 2-*N*-pyrrolidine-ethoxy groups.[8] Fusion of this basic side chain was therefore investigated by linking specific cyclic 2-aminoethoxy groups onto the core aniline template, retaining the tertiary amine by N-alkylation, to give amides **8a**–**e** and **8g** (Table 1).

Cyclisation from the nitrogen, whether onto the linker position next to the oxygen (**8a**), or next to the nitrogen (**8b** and **8c**), slightly reduced receptor affinity, but little discrimination: both *R* and *S* isomers (**8b** and **8c**) gave similar pK_i values. The bridged piperidine (**8e**) substantially retained affinity (pK_i 7.3), and only the *trans*-fusion of a hexyl ring on the ethyl group (**8d**) significantly reduced the pK_i to 5.6. Replacement of the aminoethoxy group with a piperazine gave, in **8g**, a compound which retained some receptor affinity (pK_i 7.1). However, disappointingly, no fusion showed improved potency relative to the parent template of **1b**.

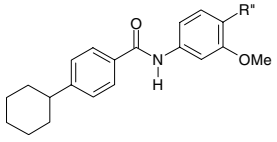
B—*Biphenyl group constraint.* The constraints applied to the biphenyl group were bridging substituents. In the case of the *para*-biphenyl these comprised a methylene (**13b** and **15b**), a carbonyl (**11a**) or an ethyl group (**13c** and **15c**). For the *meta*-biphenyl, a *para*-oxygen linker (**13d** and **15d**) was introduced. Amides in which the amide nitrogen was N-methylated (series **15**) were assessed in comparison with the NH analogues (series **13**) as this modification had proved advantageous in unfused series.

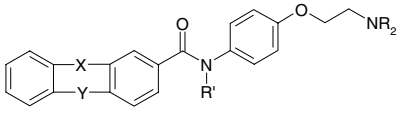
Due to synthetic availability, examples were prepared with two basic side-chain variants (diisopropyl and pyrrolidinyl groups). Compounds with these groups had been shown to differ little in potency in the original unfused series.[8] Although some affinity was retained, most noticeably with the carbonyl-linked **11a** (pK_i 6.7), in all cases, constraining the biphenyl rings to a near planar conformation led to a significant (~10-fold) loss of affinity for MCH R1 (Table 1). This trend was independent of the basic side chain and whether or not the amide nitrogen was methylated. Fused *meta*-substituted examples, such as **15d** (pK_i 5.7), were especially poor, confirming the previously observed preference for a *para*-biphenyl scaffold.

C—*Carbonyl moiety constraint.* Previous studies had indicated that while an *N*-methyl substituent on the amide nitrogen was advantageous, larger groups were detrimental to potency.[8] Therefore, a fusion from the anilide nitrogen to the 2-position on the benzoyl ring was of particular interest. Disappointingly, the first compound with this feature, **21**, prepared as a mixture of regioisomers, also showed a reduction in affinity (pK_i 6.4, Table 2). Surprisingly, the synthetic intermediate, phthalimide **20**, exhibited relatively higher receptor binding (pK_i 6.9). This discovery led to the preparation of corresponding O-, N- and S-linked aryl-phthalimides: **22** (pK_i 7.7), **23** (pK_i 7.8) and **24** (pK_i 7.5), respectively, all of which demonstrated improved affinity for the receptor. Unfortunately, stability studies indicated that this class of *N*-aryl-phthalimides decomposed in aqueous phosphate buffer at ~pH 7, due to hydrolytic phthalimide ring-opening.

We reasoned that the improved affinity could relate to an additional hydrogen bonding, or polar interaction with the lone pair on the second carbonyl group. A series of alternative heterocycles was therefore

Table 1. MCH R1 affinities of aniline-benzamides





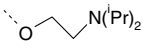
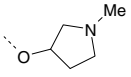
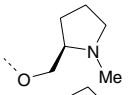
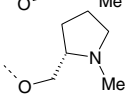
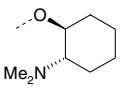
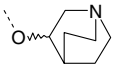
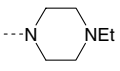
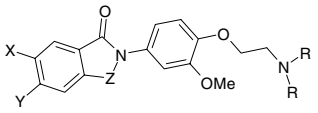
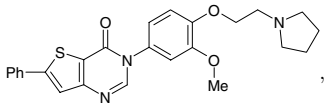
Compound	R″	pK_i	Compound	N(R)R	R′	X	Y	pK_i
1b		7.6	**11a**	$N(^iPr)_2$	H	C=O	Bond	6.7
8a		7.2	**13b**	1-Pyrrolidine	H	CH_2	Bond	6.3
8b		7.1	**15b**	$N(^iPr)_2$	Me	CH_2	Bond	6.4
8c		7.4	**13c**	1-Pyrrolidine	H	$CHCH_2$	Bond	6.0
8d		5.6	**15c**	$N(^iPr)_2$	Me	CH_2CH_2	Bond	6.5
8e		7.3	**13d**	1-Pyrrolidine	H	Bond	O	5.6
8g		7.1	**15d**	$N(^iPr)_2$	H	Bond	O	5.7

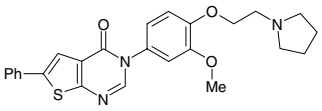
Table 2. MCH R1 affinities of heterocycle-linked anilides



Compound	N(R)R	X	Y	Z	pK_i
21	N(^{i}Pr)$_2$	Ph:H	H:Ph	–CH_2–	6.4
		1:1 Isomer mix			
20	N(^{i}Pr)$_2$	H	Ph	C=O	6.9
22	1-Pyrrolidine	H	PhO	C=O	7.7
23	1-Pyrrolidine	H	PhNH	C=O	7.8
24	1-Pyrrolidine	H	PhS	C=O	7.5
35a	1-Pyrrolidine	4-Cl-Ph–	H	–N=CH–	6.0
35b	1-Pyrrolidine	H	Ph	–N=CH–	7.7
35c	1-Pyrrolidine	PhO	H	–N=CH–	6.5
35d	1-Pyrrolidine	H	PhO	–N=CH–	7.3
36b	1-Pyrrolidine	H	Ph	–N=N–	7.6
36c	1-Pyrrolidine	PhO	H	–N=N–	7.4
36d	1-Pyrrolidine	H	PhO	–N=N–	7.1



39 pKi 7.7



42 pKi 6.1

investigated in which there was a hydrogen bond accepting group at both sides. The terminal aryl group (phenyl or 4-chlorophenyl for **35a**) was linked either directly or by an oxygen linker. Three phenyl-substituted ring systems showed particular promise: 7-quinazolinone, 7-benzotriazinone and 6-thienopyrimidinone. The relative orientation of the carbonyl group and aryl substituent was important—in the case of the quinazolinone, a *para*-relationship was preferred (**35b**, pK_i 7.7; **35d**, pK_i 7.3). This was reversed for the benzotriazinone examples (**36c**, pK_i 7.4 and **36d**, pK_i 7.1). The most potent examples (**35b** and **36b**, pK_i 7.6) shared a common feature in the 7-phenyl group, and both compounds demonstrated low intrinsic clearance in human liver microsome preparations (CLi <1.5 mL/min/g).[13]

This substitution pattern was therefore applied to related heterocycles. The isomeric thienopyrimidines **39** and **42** showed a marked difference in receptor affinity, suggesting a subtle preference for the substitution geometry of the thieno[3,2-*d*]pyrimidin-4(1*H*)-one (**39**, pK_i 7.7). Unlike the phthalimides, all three substituted heterocycles **35b**, **36b** and **39** proved stable to phosphate buffer.

The 4-phenyl-*N*-methyl benzamide moiety found in lead MCH R1 antagonist **1a** can be effectively replaced with conformationally constrained amide isosteres: the 7-phenyl-4(3*H*)-quinazolinone, 7-phenyl-2,3-benzotriazin-4(1*H*)-one and 6-phenyl-thieno[3,2-*d*]pyrimidin-4(1*H*)-one ring systems, leading to compounds with comparable binding affinity such as **35b**, **36b** and **39**. The substitution pattern and consequent geometry around these molecules is consistent with a linear binding mode for the constitutive ring systems. Molecules containing all three classes of heterobicycle have good aqueous stability, and both the quinazolinone and benzotriazinone compounds showed low in vitro susceptibility to metabolism by liver microsomes.

Acknowledgments

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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.2006.06.061.

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12. Compounds were evaluated using displacement of radiolabelled iodo-MCH from the human receptor $MCHR_1$ expressed in HEK-293 cells. All pK_i values reported are given for an n of $\geqslant 3$ and a standard error of the mean of <0.25.
13. Intrinsic clearance (CLi) assay: a liver microsomal incubation of known volume (V) at an initial compound concentration of 0.5 μM with a microsomal protein concentration of 0.5 mg/mL is carried out to characterise the compound loss in the form of a concentration–time profile. The first-order elimination rate constant (K) is determined from the profile and CLi is then calculated using the relationship CLi = KV, scaled appropriately and reported in units of milliliters per minute per gram liver.