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SAR of biphenyl carboxamide ligands of the human melanin-concentrating hormone receptor 1 (MCH R1): Discovery of antagonist SB-568849

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Abstract—We report here the discovery of a class of MCH R1 ligands based on a biphenyl carboxamide template. A docked-in model is presented indicating key interactions in the putative binding site of the receptor. Parallel high throughput synthetic techniques were utilised to allow rapid exploration of the structure–activity relationship around this template, leading to compound SB-568849 which possessed good receptor affinity and selectivity. This compound proved to be an antagonist with stability in vivo, an acceptable brain–blood ratio and oral bioavailability.

The G-protein coupled receptor MCH R1 (11CBy) was reported as a cognate receptor for the neuropeptide melanin-concentrating hormone (MCH) in 1999.[1,2] MCH has been implicated in signalling cascades related to the stress axis.[3] When administered by intracerebroventricular (icv) dosing, MCH has also been shown to elicit an increased feeding response in rats.[4] Targeted deletion of the MCH gene in mice results in a lean and hypophagic phenotype.[5] Several pieces of data suggest that the effect of MCH on body weight is mediated by MCH R1. Deletion of MCH R1 in mice results in animals that are of normal body weight but reduced fat mass and which are less susceptible to diet-induced obesity than their wild-type counterparts. Furthermore, icv dosing of MCH does not stimulate feeding nor cause obesity in the MCH R1 knockout animals.[6,7] Thus, antagonists of this receptor may have applications in the treatment of obesity, as well as anxiety and depression.[8–15]

A high throughput screen of the company compound bank was conducted using a FLIPR assay, measuring inhibition of calcium mobilisation effected by treatment of the MCH R1 receptor with MCH.[16] This resulted in an antagonist hit, the biphenyl carboxamide **1**, apparent pK_b 7.5. This was found to be consistent with the pK_i from a binding assay, also 7.5.[17]

Compound **1** showed >30-fold selectivity against a range of aminergic receptors but possessed significant affinity for the 5-HT_{2C} receptor subclass with a pK_i of 6.8. The compound was also evaluated in rat liver microsomes and showed a moderate in vitro clearance[18] of 9 mL/min/g and a solubility of 4 μg/mL at physiological pH, which resulted in low oral bioavailability. The structure of **1** was docked into an homology model of MCH R1 based on the electron micrograph of bovine rhodopsin, (a 7-trans-membrane receptor of the same class). Its location was supported by site-directed mutagenesis experiments. The model suggested a linear binding mode (Fig. 1) in a tight, generally lipophilic binding site.[19] An optimisation campaign was therefore initiated to explore the SAR around this lead and to refine our understanding of receptor binding, in order to optimise both the affinity and developability properties of this series.

Keywords: MCH; MCH R1; Biphenylcarboxamide; Antagonist; Melanin-concentrating hormone; Obesity; Feeding; Stress; Anxiety.
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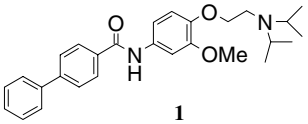

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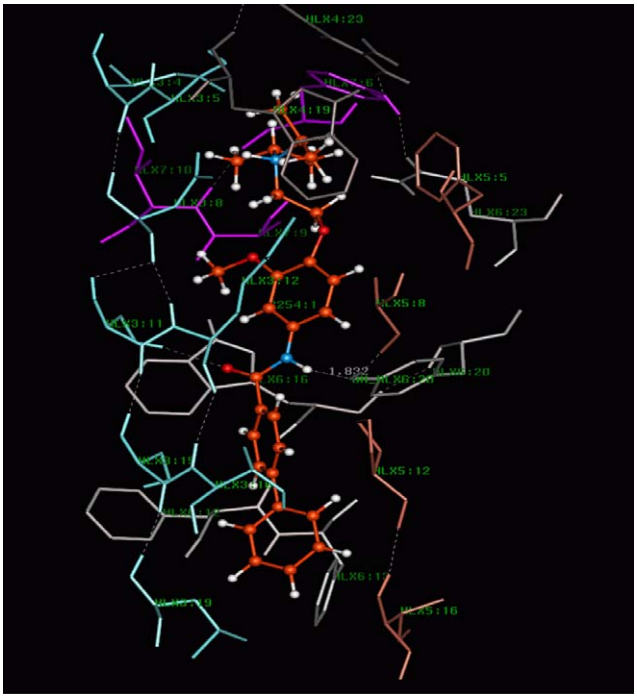
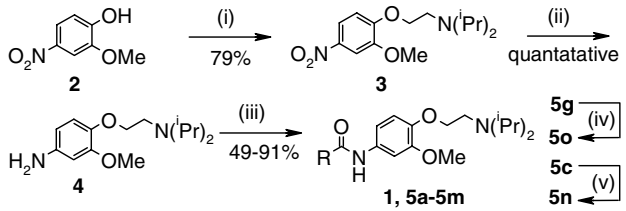


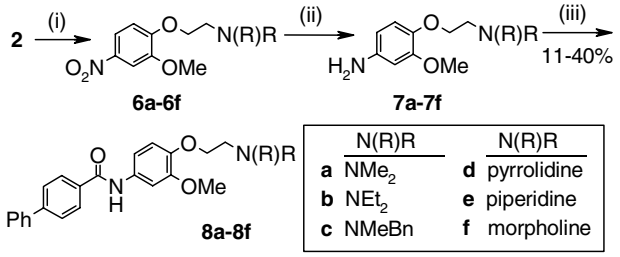
Figure 1. Compound **1** (orange) docked in MCH R1, based on a bovine rhodopsin E-micrograph homology model (only local residues shown).

A outline of the differing routes to analogues of **1** is described below. In addition to **1**, target compounds **5a**–**5o**, **8a**–**8f**, **11a**–**11g**, **12**, **13**, **15a**–**15f**, **15h** and **17** (Tables 1–3) were prepared by the methods described in Schemes 1–4. Amides **5a**–**5o** were prepared by the routes described in Scheme 1: 2-*N*-diisopropyl-1-chloroethane reacted with 4-nitro-2-methoxy-guiacol **2** to form ether **3**. Reduction of this material by hydrogenation over a palladium/carbon catalyst in ethanol at room



	R		R		R
1	4-Ph-Ph	**5f**	4-Bn-Ph	**5l**	(3-Me-4-Ph)-Ph
5a	3-Ph-Ph	**5g**	3-Bz-Ph	**5m**	(2-Me-4-Ph)-Ph
5b	Ph	**5h**	4-(PhO)-Ph	**5n**	4-[4-(CF_3)-Ph]-Ph
5c	4-Br-Ph	**5i**	3-PhO)-Ph	**5o**	3-Bn-Ph
5d	4-[3-(CF_3)Ph]-Ph	**5j**	4-(^{t}Bu)-Ph		
5e	4-(2-Me-Ph)-Ph	**5k**	4-cyclohexyl-Ph		

Scheme 1. Reagents and conditions: (i) (^{i}Pr)$_2$ NCH_2CH_2Cl·HCl, K_2CO_3, H_2O, DME, rt; (ii) H_2, 10% Pd on C, EtOH, rt, 24 h; (iii) RCOCl, CH_2Cl_2, NEt_3, rt or RCO_2H, EDC, HOBT, DMF, rt; (iv) Et_3SiH, TFA, MDC, rt, 66%; (v) $Pd(Ph_3P)_4$, Na_2CO_3, PhH, EtOH, $(HO)_2B$–C_6H_4(4-CF_3), reflux, 75%.



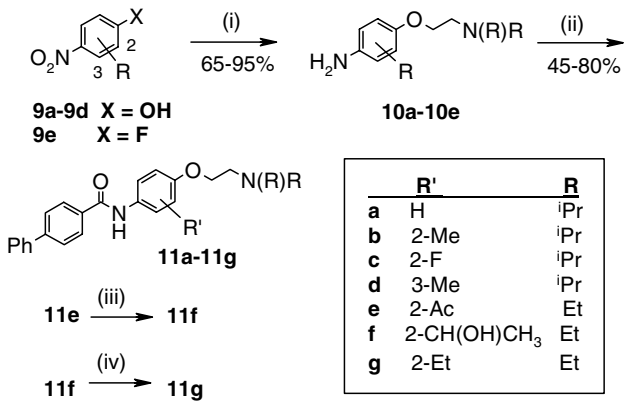
Scheme 2. Reagents and conditions: (i) $RN(R)CH_2CH_2Cl$·HCl, K_2CO_3, H_2O, DME, rt, 15–67% or $Bn(Me)NCH_2CH_2OH$, DPPE, DPPA, THF, 12%; (ii) H_2, 10% Pd on C, EtOH, rt, 24 h, quantitative; (iii) 4-Ph–PhCOCl, CH_2Cl_2, NEt_3, rt, 14 h or 4-Ph–$PhCO_2H$, EDC, HOAT, DMF, rt, 14 h.

temperature and pressure afforded aniline **4**. This was used to form amides **1** and **5a**–**5m** by reaction with selected carboxylic acid chlorides under conditions of base catalysis, or was coupled to the corresponding carboxylic acids directly using EDC in DMF. Compound **5o** was prepared by reduction of the ketone carbonyl of **5g** with triethylsilane in TFA. A Suzuki coupling of bromoamide **5c** with 4-trifluoromethylphenylboronic acid furnished analogue **5n**.

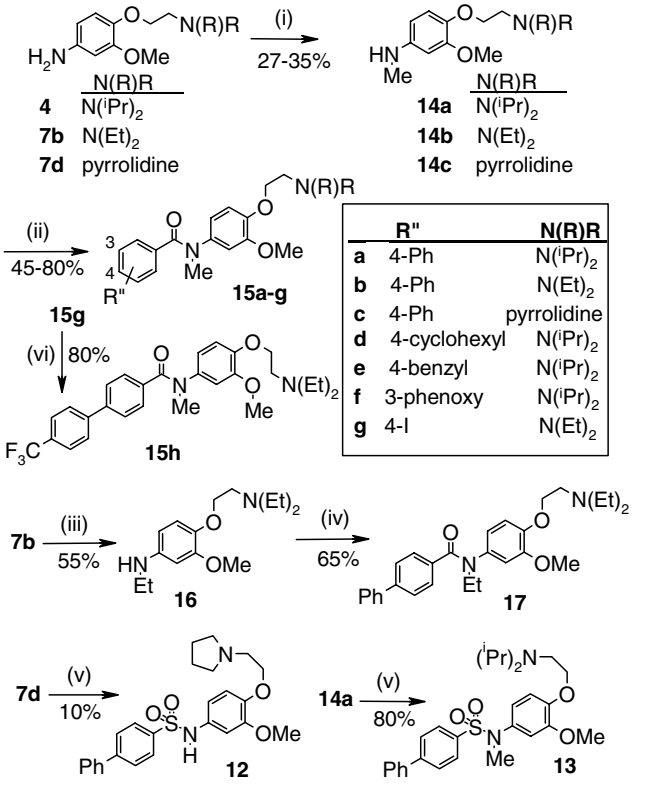
Analogues of **1** bearing varied basic side chains were prepared using the route described in Scheme 2. A set of nitrophenylamines (**6a**–**6f**) was produced by nucleophilic substitution of a range of β-haloamines with 4-nitro-2-methoxyguiacol or, in the case of **6c**, by a Mitsunobu coupling of **2** with the *N*-methyl-*N*-benzylaminoethanol. Hydrogenation of these compounds under conditions of palladium catalysis afforded anilines **7a**–**7f**. These were coupled to 4-biphenylcarboxylic acid using EDC or reacted directly with the corresponding acid chloride under conditions of base catalysis to form amides **8a**–**8f** in low to moderate yields.

Anilines **10a**–**10e** were prepared in two steps from the corresponding substituted 4-nitrophenols (**9a**–**9d**) by nucleophilic displacement of *N*-(2-chloroethyl)diisopropylamine in the presence of aqueous potassium carbonate, or in the case of **10e**, by nucleophilic aromatic substitution of 3-acetyl-4-fluoro-nitrobenzene (**9f**) with 2-diethyamino-ethanol and sodium hydride in DMF (Scheme 3). The nitro-ethers were either hydrogenated under conditions of palladium catalysis, or reduced by iron powder in an aq ammonium chloride buffer to afford anilines **10a**–**10e**. Reaction with 4-biphenylcarboxylic acid chloride in dichloromethane and triethylamine afforded amides **11a**–**11e**. The acetyl compound **11e** was reduced to the alcohol (**11f**) using sodium borohydride in ethanol in quantitative yield. Further reduction to the ethyl compound (**11g**) was effected using triethylsilane in the presence of trifluoroacetic acid.

N-Methyl amide analogues of **1**, and **15a**–**15g** were prepared from the unsubstituted anilines in a three step process (Scheme 4). Reaction of the corresponding unsubstituted aniline (**4**, **7b** or **7d**) with triethyl orthoformate under conditions of acid catalysis formed an imidate, which was reduced using sodium borohydride to



Scheme 3. Reagents and conditions: (i) 1—$(Et)_2NCH_2CH_2OH$, NaH, DMF, 60 °C, 14 h or $(^iPr)_2NCH_2CH_2Cl{\cdot}HCl$, K_2CO_3, H_2O, DME, rt. 2—H_2, 10% Pd on C, rt, EtOH, 24 h or Fe, aq NH_4Cl, CH_2Cl_2; (ii) 4-(Ph)–PhCOCl, CH_2Cl_2, NEt_3, rt, 14 h; (iii) $NaBH_4$, EtOH, 5h, rt; (iv) $(Et)_3SiH$, TFA, CH_2Cl_2, rt.



Scheme 4. Reagents and conditions: (i) $(EtO)_3CH$, TFA, 60 °C, 3 h, then $NaBH_4$, EtOH, rt, 5 h; (ii) R-PhCOCl, CH_2Cl_2, NEt_3, rt, 14 h or R-$PhCO_2H$, EDC, HOBT, DMF, rt, 14 h; (iii) $CH_3C(OEt)_3$, TFA then, EtOH, $NaBH_4$; (iv) 4-(Ph)–PhCOCl, CH_2Cl_2, NEt_3, rt, 14 h; (v) 4-(Ph)–$PhSO_2Cl$, pyridine, rt, 12 h; (vi) 4-(CF_3)–$PhB(OH)_2$, PhH, EtOH, Na_2CO_3, $Pd(Ph_3P)_4$, reflux.

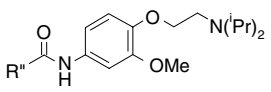
give the monomethyl anilines **14a**–**14c**. These were linked to a range of substituted benzoic acids either through an EDC coupling or by reaction with the corresponding acid chlorides, to afford amides **15a**–**15g**. Iodobenzamide **15g** was converted to the 4-CF_3-Ph derivative **15h** by a Suzuki coupling with the corresponding boronic acid. Reaction of aniline **7b** with triethylorthoacetate and trifluoroacetic acid followed by reduction with sodium borohydride afforded monoethylaniline **16**, which was coupled with 4-biphenylcarboxylic acid chloride to form tertiary amide **17**. The N–H and *N*-methyl sulfonamides (**12** and **13**) were prepared by coupling the anilines (**7d** and **14a**, respectively) with 4-biphenylsulfonyl chloride under conditions of base catalysis.

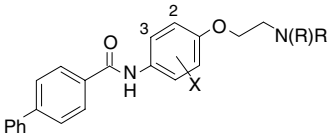
A strategy was adopted of modifying the left-hand side (LHS) aryl group and right-hand side (RHS) aniline independently. An initial array of carboxamides (**5a**–**5o**) was therefore targeted; specifically compounds retaining the RHS aniline portion of compound **1**. pK_i values are shown in the left column of Table 1. Disappointingly, no compounds with significantly higher affinity for MCH R1 were discovered, however several trends became apparent. Affinity for the *para* biphenyl **1** was much greater than for *meta* example **5a** (pK_i 5.3). Truncation to the unsubstituted benzamide (**5b**) also reduced affinity by >100-fold. Substitution around the terminal aromatic ring led to a modest reduction in affinity, thus a *para* CF_3 substituent (**5n**, pK_i 7.1) was more tolerated than *meta* (**5d**, pK_i 6.6). A methyl group was tolerated at the *ortho* position (**5e**, pK_i 7.4). Generally the LHS favoured lipophilic substituents, thus the carbonyl containing 3-benzyl analogue (**5g**) showed low affinity. In contrast, the *para* benzyl (**5f**, pK_i 7.4) and *meta* phenyl ether (**5i**, pK_i 7.1) substituents retained affinity. Respective *meta* (**5o**) and *para* (**5h**) isomers bound slightly more weakly. Affinity was lost if the terminal benzene ring was replaced by a bromine (**5c**) or an acyclic alkyl group such as *t*-Bu (**5j**). However, a *para* cyclohexyl substituent (**5k**, pK_i 7.6) afforded comparable affinity to **1**. Both *ortho* and *meta* (**5m**, **5l**) methyl substituents in the benzoyl ring of the biphenyl led to reduced affinity.

Four LHS groups: 4-biphenylcarboxylic acid, 4-benzylbenzoic acid, 3-phenoxybenzoic acid and 4-cyclohexylbenzoic acid (present in **1**, **5f**, **5i**, and **5k**) were selected to prepare a two-dimensional array by coupling with a group of substituted anilines. Over 300 analogues were prepared, utilising Myriad™ and Bohdan™ technologies. The resulting compounds showed a consistent profile with the 4-biphenyl-carboxamide and 4-cyclohexylbenzamides exhibiting approximately equivalent affinity for the receptor. The benzyl and phenyl ether analogues were between 0.2 and 0.6 log units less potent. The RHS SAR is therefore adequately illustrated by consideration of the biphenylcarboxamides, examples of which, **8a**–**8f** and **11a**–**11g**, are shown in Table 1 (right column).

First, the influence of changing the alkylamino substitution pattern was investigated. Holding the biphenylcarboxamide LHS group constant, the RHS diisopropyl group could be effectively replaced by other lipophilic amines such as a diethyl group (**8b**) or by a cyclic amine such as pyrrolidine (**8d**) with little loss of binding affinity. Larger or smaller alkyl groups resulted in only marginally reduced affinity, a property also observed with a relatively polar morpholine group (**8f**) (pK_i 7.2). This was shown across all amide series.

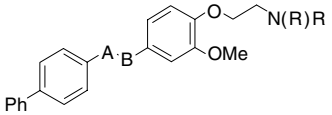
Table 1. Affinities of dialkylaminoethoxy-aniline amides for MCH R1

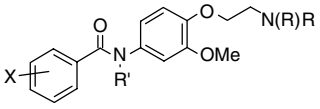




Compound	R″	pK_i	Compound	N(R)R	X	pK_i
5a	3-Ph–Ph	5.3	**1**	$N(^iPr)_2$	2-OMe	7.5
5b	Ph	<5	**8a**	$N(Me)_2$	2-OMe	7.3
5c	4-Br–Ph	<5.2	**8b**	$N(Et)_2$	2-OMe	7.5
5d	4-[3-(CF_3)-Ph]–Ph	6.6	**8c**	NMeBn	2-OMe	7.3
5e	4-(2-Me–Ph)–Ph	7.4	**8d**	1-Pyrrolidine	2-OMe	7.5
5f	4-Bn–Ph	7.4	**8e**	1-Piperidine	2-OMe	7.4
5g	3-Bz–Ph	<5	**8f**	1-Morpholine	2-OMe	7.2
5h	4-(PhO)–Ph	6.7	**11a**	$N(^iPr)_2$	H	7.2
5i	3-(PhO)–Ph	7.1	**11b**	$N(^iPr)_2$	2-Me	7.2
5j	4-(^{t}Bu)–Ph	<5	**11c**	$N(^iPr)_2$	2-F	6.4
5k	4-Cyclohexyl–Ph	7.6	**11d**	$N(^iPr)_2$	3-Me	7.6
5l	(3-Me-4-Ph)–Ph	6.8	**11e**	$N(Et)_2$	2-Ac	7.5
5m	(2-Me-4-Ph)–Ph	6.9	**11f**	$N(Et)_2$	2-CH(OH)Me	6.6
5n	4-[4-(CF_3)–Ph]–Ph	7.1	**11g**	$N(Et)_2$	2-Et	7.3
5o	3-Bn–Ph	6.8				

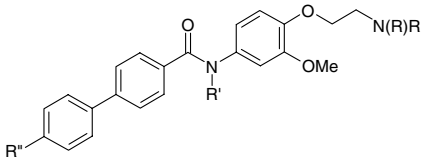
Table 2. Affinity of substituted amides and sulfonamides





Compound	A	B	N(R)R	pK_i	Compound	X	R′	R	pK_i
12	SO_2	NH	Pyrrolidine	<5	**15d**	4-*c*-Hexyl	Me	^{i}Pr	7.0
13	SO_2	NMe	N^iPr_2	<5	**15e**	4-Benzyl	Me	^{i}Pr	7.1
15a	C=O	NMe	N^iPr_2	7.8	**15f**	3-Phenoxy	Me	^{i}Pr	6.4
15b	C=O	NMe	NEt_2	7.7	**15h**	4-(4-CF_3)–Ph	Me	Et	7.7
15c	C=O	NMe	Pyrrolidine	7.7	**17**	4-Ph	Et	Et	6.6

Table 3. Series pharmacokinetic parameters



Compound	R″	R′	N(R)R	$CL_{i(rat)}$ (mL/min/g)	$CL_{b(rat)}$[22] (mL/min/kg)	Brain–blood Ratio[23]
1	H	H	$N(^iPr)_2$	9	67	2.7
8b	H	H	$N(Et)_2$	4	Not done	Not done
8d	H	H	Pyrrolidine	2	Not done	Not done
15a	H	Me	$N(^iPr)_2$	19	Not done	Not done
15b	H	Me	$N(Et)_2$	5	51	0.1
15c	H	Me	Pyrrolidine	2	57	0.1
15h	CF_3	Me	$N(Et)_2$	4	16	1

Next, the SAR around the aniline ring was investigated. Differing LHS amide series indicated that the methoxy group *meta* to the aniline nitrogen in **1** conferred a slightly higher affinity for the receptor compared with the unsubstituted analogue. For example, with the biphenylcarboxamide group fixed, **11a** showed a pK_i of 7.2. This trend was also true for the methyl (**11b**) and ethyl (**11g**) analogues, though affinity was retained if the methoxy moiety was replaced by acetyl (**11e**). Both a hydrogen bond donor in the side chain (**11f**, pK_i 6.6), and an electron withdrawing fluorine substituent in the ring (**11c**, pK_i 6.4), markedly reduced affinity. A

methyl substituent *ortho* to the aniline nitrogen (**11d**) was tolerated (Table 1, right column).

The initial SAR around **1** was consistent with the suggested linear binding mode, but offered few clues to improving the affinity of the ligand. However, a modest trend for both higher binding affinity and receptor selectivity was found for compounds in which the amide nitrogen was methylated, for example, **15a**, **15b** and **15c**, all with measured pK_i values $\geqslant$7.7 (Table 2). Interestingly, this change also resulted in significantly higher selectivity over related classes of 7TM receptors.

One possible explanation for the effect on affinity is that the methyl substituent changes the conformational preferences of the carboxamide group. Both NMR studies on **15a** and **1**, and ab initio calculations on model series (Fig. 2), indicated that the lowest energy amide bond dihedral angles differ for N–H and *N*-methyl amides: *transoid* and *cisoid*, respectively.

Although bis-aryl sulfonamides are known to favour a *cisoid* conformation between flanking aromatic groups,[20] sulfonyl analogues **12** and **13** proved to have poor affinity for the receptor. Increasing the size of the *N*-alkyl substituent to ethyl (**17**) (pK_i 6.6) led to diminished affinity, suggesting tight steric constraints. Curiously, the affinity enhancing effects of *N*-methylation were not observed with more flexible LHS benzoyl substituents such as 4-cyclohexyl (**15d**), 4-benzyl (**15e**), or 3-phenoxy (**15f**). It was interesting to note that, unlike the *trans* forms, the *cis* forms of the *N*-methyl amides could not be docked into the receptor model in a low energy conformation.

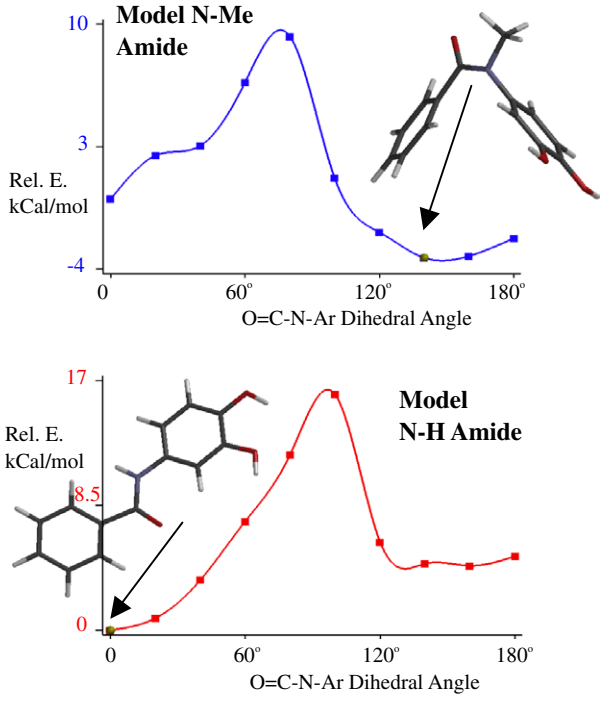


Figure 2. Amide bond ab initio calculations (RHF/6-31G*).

We refined our binding model using a model based on the X-ray structure of bovine rhodopsin.[21] Receptor docking studies suggested that linear amides, whether N-methylated or not, might bind in a twisted-*trans* conformation in which neither the rings nor amide bond lies in the same plane.

This hypothesis would be in agreement with the fact that N-methylation benefits only the biphenyl series in which the minimum energy conformation involves a dihedral angle of ~30° between the phenyl rings. Further calculations suggested that N-methylation would favour an additional twist at the carbonyl, ('twisted-*trans*', Fig. 3) enabling the terminal ring of **15a** to adopt a conformation orthogonal to the C=O group without a large energy penalty.

Compound **15a** proved to have good solubility both in water and artificial cerebrospinal fluid (ACSF) (both >0.5 mg/mL), but suffered from lower in vitro microsomal stability than the initial lead (CL_i = 19 mL/min/g, Table 3).[17] Analogues of **1** containing smaller basic moieties such as diethylamino (**8b**) and pyrrolidinyl (**8d**) in place of the diisopropylamino group had retained receptor affinity and had also afforded greater in vitro microsomal stability. This trend persisted with *N*-methyl analogues **15b** and **15c**. Unfortunately both of these compounds showed a poor brain to blood ratio in the rat, so a range of compounds was prepared bearing additional lipophilic substituents on the biphenyl group. Of these, the trifluoromethyl analogue **15h** retained affinity, demonstrated greater in vivo stability (CL_b = 16 mL/min/kg) and showed an acceptable brain–blood ratio of 1.

Compound **15h**, designated **SB-568849**, also showed >30-fold selectivity over a wide range of monoamine receptors and was an antagonist in the FLIPR assay with a pK_b of 7.7. Studies indicated that **SB-568849** antagonised the effects of MCH on the neuronal hormone CRF in rat brain tissue.[24] This compound had a solubility of 16 mg/mL in water and >6 mg/mL in ACSF as the maleate salt, and showed 30% oral bioavailability with an AUC of 142 ± 34 μM min determined in an iv/po crossover study.[25]

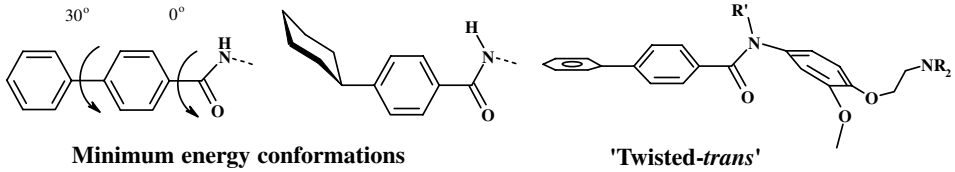


Figure 3. Suggested biphenyl amide binding conformation.

A series of biphenylcarboxamide ligands of MCH has been discovered with good affinity for the MCH R1 receptor. Modelling of receptor–ligand interactions is reflected in calculated conformational preferences and aspects of the binding affinity SAR. **SB-568849** is an effective MCH R1 antagonist which exhibits low in vivo clearance, and demonstrates both a good brain–blood ratio and oral bioavailability in the rat.

Acknowledgments

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17. Compounds were evaluated using displacement of radio-labelled iodo-MCH from the human receptor MCH R1 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.
18. Intrinsic clearance (CL_i) 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 1st order elimination rate constant (K) is determined from the profile and CL_i is then calculated using the relationship $CL_i = KV$, scaled appropriately and reported in units of mL/min/g liver.
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22. CL_b is the initial rate of elimination of the test compound from the blood per unit body mass, following iv dosing as indicated below.
23. CNS penetration at steady state was investigated in the rat. Compounds were dissolved in 2% (v/v) DMSO in 5% (w/v) dextrose aq and administered iv at a constant infusion rate over 12 h at a target dose of 0.3 mg free base/kg/h. Blood samples were removed during the latter part of the infusion to confirm steady-state blood concentrations. Blood and brain samples were analysed by LC/MS/MS.
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25. This study incorporated oral suspension and iv infusion legs on two study days. Cannulated SD rats ($n \geqslant 3$) were dosed with an iv infusion of the buffered test compound at a constant infusion rate of 10 mL/kg/h at a target dose rate of 1.0 mg pfb/kg. Blood samples were taken at intervals after the start of infusions up to 24 h. Following a recovery of at least 2 days, the same rats were given an oral gavage of the same test compound as a suspension in aq methylcellulose at a concentration of 1.5 mg pfb/mL and administered (2 mL/kg) at a target dose of 3 mg pfb/kg. Blood samples were taken pre-dose and at interval post-dose up to 27 h. Blood samples were analysed by LC/MS/MS.