Bioorganic & Medicinal Chemistry Letters 20 (2010) 3540–3544

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

2′ Biaryl amides as novel and subtype selective M_1 agonists. Part I: Identification, synthesis, and initial SAR

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ARTICLE INFO

Article history:
Received 20 March 2010
Revised 26 April 2010
Accepted 27 April 2010
Available online 17 May 2010

Keywords:
Subtype selective M1 muscarinic acetylcholine receptor agonist
Novel M1 agonists
2′ Biaryl amides

ABSTRACT

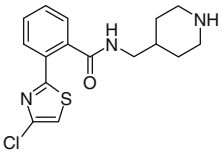
Biaryl amides were discovered as novel and subtype selective M_1 muscarinic acetylcholine receptor agonists. The identification, synthesis, and initial structure–activity relationships that led to compounds **3j** and **4c**, possessing good M_1 agonist potency and intrinsic activity, and subtype selectivity for M_1 over M_{2-5}, are described.

Five muscarinic acetylcholine receptor (mAChR) subtypes, M_1–M_5, are known to date.[1–3] These seven-transmembrane (7TM) receptors share a common orthosteric ligand-binding site with an extremely high sequence homology, which explains why it has been difficult historically to identify subtype selective ligands.[3] M_1–M_5 mAChRs are widely distributed in mammalian organs and the central and peripheral nerve system where they mediate important neuronal and autocrine functions including memory and attention mechanisms, motor control, and nociception.[4,5] In particular, selective M_1 agonism has been suggested as a therapeutic approach in dementia including Alzheimer's disease and age-associated memory impairment or cognitive impairment associated with Schizophrenia.[6] Furthermore, recent clinical results from pan MAChR agonists have resulted in severe GI and CV effects which further demonstrates the need for selective agonists of M_1.[25]

AC-42, the first subtype selective M_1 agonist, achieved the high degree of subtype selectivity via binding to an allosteric binding site unique to M_1 mAChRs.[7] More recently, TBPB and its analogs were also reported as subtype selective M_1 allosteric agonists.[8] We herein describe the identification, synthesis, and initial structure–activity relationships (SAR) of biaryl amides as novel and subtype selective M_1 agonists.

Data mining of the corporate databases resulted in the identification of biaryl amide **1**, a compound prepared for the M_3 antagonist program, as a hit with good M_1 agonist potency and intrinsic activity (IA), and good subtype selectivity for M_1 over M_2 and M_3 (Fig. 1).[9,10] Compound **1** was subsequently found to be also selective for M_1 over M_4 and M_5. On the basis of the good M_1 agonist activity and subtype selectivity, **1** was considered an acceptable starting point for our hit-to-lead chemistry optimization aimed at improving potency and identifying tractable SAR.

We began our initial exploration by replacing the 4-aminomethyl piperidine of **1** using the solution phase route[11] that had been used for the original synthesis of **1** (Scheme 1). Suzuki coupling of pinacol ester **6** with 2,4-dichlorothiazole[12] followed by basic hydrolysis gave acid **7**, which via EDC coupling with



1, M_1 FLIPR pEC_{50} = 6.6, IA = 84 %
M_2 FLIPR pIC_{50} < 5
M_3 FLIPR pIC_{50} < 5
M_4 FLIPR pIC_{50} < 5
M_5 FLIPR pIC_{50} < 5

Figure 1. Structure and in vitro profile of **1**.

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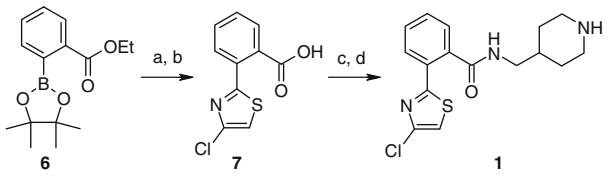
doi:10.1016/j.bmcl.2010.04.128

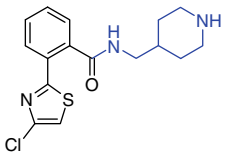


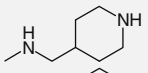
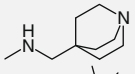
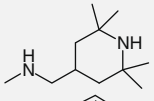
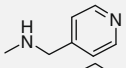
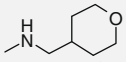
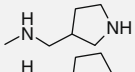
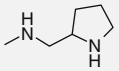
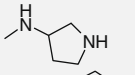
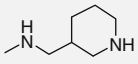
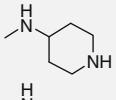
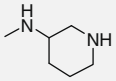
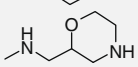
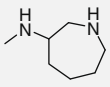
Scheme 1. First generation exploration of diamine region. Reagents and conditions: (a) 2,4-dichlorothiazole, $Pd(PPh_3)_4$, 2 M Cs_2CO_3, DME, 80 °C, 16 h; (b) LiOH, EtOH, rt, 16 h; (c) 1-Boc-4-(aminomethyl)piperidine or various amines or Boc-protected diamines, EDC, HOAt, CH_2Cl_2, rt, 16 h; (d) 4 M HCl, MeOH or 50% TFA/CH_2Cl_2, rt, 16 h (if required).

various mono boc-protected diamines or amines followed by deprotection gave final compounds exemplified by **1**.[13]

As shown in Table 1, replacement of the 4-aminomethyl piperidine with a tertiary amine bridged analogue (**1a**) gave modest activity,[10] while the 2,2,6,6-tetramethyl piperidine analogue (**1b**) was inactive. Substitution of pyridine for piperidine (**1c**), or replacement of nitrogen with oxygen as a nonbasic hydrogen bond acceptor (**1d**) also gave no activity. Pyrrolidines **1e–g** were inactive, as were piperidines **1h–j**, morpholine **1k**, and homopiperazine **1l**.

Table 1
First generation diamine region SAR



Compd	Structure	M_1 pEC_{50} IA%
1		6.6 84
1a		6.1 63
1b		<5.0
1c		<5.0
1d		<5.0
1e		<5.0
1f		<5.0
1g		<5.0
1h		<5.0
1i		<5.0
1j		<5.0
1k		<5.0
1l		<5.0

A first generation study of the activity of simple substituents around the amide phenyl moiety of **1** was conducted by substitution of the appropriate benzoic acid for biaryl acid **7** in Scheme 1. As shown in Figure 2, all such structures were inactive, implying a 2' substituted biaryl structure like that of hit **1** is required for M_1 agonist activity.

After our initial exploration of simple substituents on the amide phenyl yielded no improvements, we developed an efficient and robust solid phase route amenable to rapid modification of the biaryl region for further exploration of this series (Scheme 2). 1-Boc-4-(aminomethyl)piperidine was loaded onto 2,6-dimethoxy-4-polystyrenebenzyloxy benzaldehyde resin (DMHB resin)[14] via reductive amination to give **8**, followed by coupling with a 2-haloaryl acid, affording resin-bound aryl amides **9**. Suzuki coupling of amides **9** with various aryl boronic acids followed by resin cleavage produced the targeted biaryl amides in good yields and purity.[15]

We focused our next generation examination of the biaryl region on exploring 2' biaryls like hit **1**, specifically examining SAR of the lower aryl. For synthesis of these compounds we used the solid phase route of Scheme 2, but also used the route in Scheme 3,[16] where intermediate **10** allowed use of aryl halides to install the lower aryl complementing the use of aryl boronic acids to install the lower aryl in the route of Scheme 2.

As shown in Table 2, in exploration of the lower aryl as a substituted phenyl, a wide variety of substitutions (**2a–m**) gave inactive compounds with the exception of **2d**, its 3-Cl phenyl moiety giving a 0.6 log potency increase over the chlorothiazole of **1**. Several unsubstituted heterocycles were tried, but given unsubstituted thiazole **2n** (des-Cl **1**) was inactive, it is not surprising compounds **2o–u** were also inactive. An alternate Cl-substituted heterocycle was also inactive (**2v**).

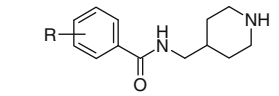
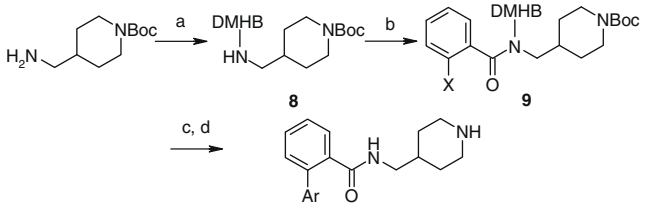
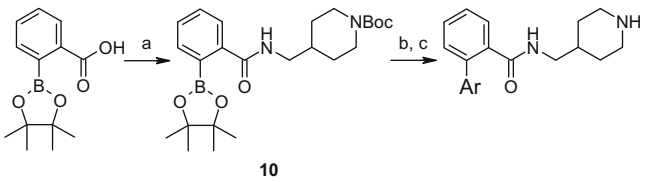


Figure 2. Activity with simple substituents on amide phenyl.

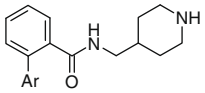


Scheme 2. Solid phase synthesis of biaryl amides. Reagents and conditions: (a) 2,6-dimethoxy-4-polystyrenebenzyloxybenzaldehyde (DMHB resin), $Na(OAc)_3BH$, DIEA, 10% AcOH in NMP, rt, 16 h; (b) various substituted 2-haloaryl acids, DIC, NMP, rt, 16 h; (c) $ArB(OH)_2$, $Pd(PPh_3)_4$, 2 M Cs_2CO_3, DME, 80 °C; (d) 50% TFA/DCE, rt, 1 h.



Scheme 3. Installation of lower aryl via aryl halides. Reagents and conditions: (a) 1-Boc-4-(aminomethyl)piperidine, EDC, HOAt, CH_2Cl_2, rt, 16 h; (b) various aryl halides, $Pd(PPh_3)_4$, 2 M Cs_2CO_3, DME, 80 °C, 3 h; (c) 50% TFA/DCE or 4 M HCl, MeOH, rt.

Table 2
SAR of lower aryl



Compd	Ar = Ph, Ph substituent=	M_1 pEC_{50} IA%
2a	3-F	<5.0
2b	4-F	<5.0
2c	2-Cl	<5.0
2d	3-Cl	7.2 86
2e	4-Cl	<5.0
2f	3-Me	<5.0
2g	4-Me	<5.0
2h	2-OMe	<5.0
2i	3-OMe	<5.0
2j	4-OMe	<5.0
2k	3-CF_3	<5.0
2l	4-CF_3	<5.0
2m	3-Ac, NAc, Ph, COOH, CN, N(CH_3)$_2$, OCF_3, SO_2Me, $CONH_2$, CON(CH_3)$_2$, CH_2OMe, SO_2NH_2	All <5.0
	Ar = Heterocyclic	
1	4-Chloro-1,3-thiazol-2-yl	6.6 84
2n	1,3-Thiazol-2-yl	<5.0
2o	Thien-2-yl	<5.0
2p	Thien-3-yl	<5.0
2q	Pyridin-3-yl	<5.0
2r	Pyridin-4-yl	<5.0
2s	2-Furyl	<5.0
2t	1-Naphthyl	<5.0
2u	2-Naphthyl	<5.0
2v	5-Chlorothien-2-yl	<5.0

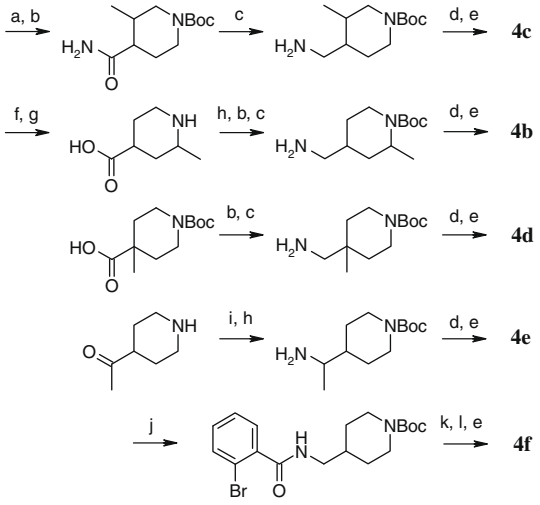
After discovery of the 3-Cl phenyl of **2d** as a potency enhancing replacement for the chlorothiazole of **1**, we pursued a second generation lower phenyl disubstituted array where the 3-Cl was held fixed and a second substituent added systematically to the four remaining positions, shown in Table 3.

The results of the disubstitution study in Table 3 show clear SAR trends for adding another substituent to the 3-chlorophenyl moiety. Additional substitution at the 4 (**3d–f**) or the 6 (**3j–k**) position gave disubstituted compounds of good activity, while substitution at the 2 (**3a–c**) or 5 (**3g–i**) position caused large activity losses.

After our broad initial exploration of the diamine region with a diverse set of replacements (Table 1) resulted in no improvements, we turned our attention to a precision study of the effect of adding a single methyl group at each position around the 4-aminomethyl piperidine moiety, using the 3-Cl biphenyl from **2d** in the biaryl. In Scheme 4, $LiAlH_4$ reduction of a primary amide,[17] obtained via EDC coupling of NH_3 with the appropriate acid, gave Boc-protected diamines required for the syntheses of **4b–d**. Reductive amination[18] of the appropriate ketone gave the Boc-protected diamine needed for **4e**, while **4f** was obtained by N-methylation of the secondary amide.

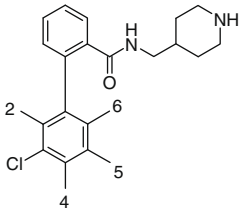
We found addition of a single methyl at each position[19] (Table 4, positions 1–6) gave an inactive compound, with the exception of compound **4c**. We were delighted to find addition of a 3 methyl on the piperidine in **4c** gave a 0.5 log potency increase over the unsubstituted piperidine of **2d** (data for **2d** also shown for reference).

Encouraged by compound **4c**, we carried out a third generation study of the diamine region. In Scheme 5, reductive cyanation of the appropriate ketone[20] via tosylmethyl isocyanide (TosMIC), followed by $LiAlH_4$ reduction to obtain the required diamine, and then amide coupling led to **5a**, **5c**, and **5e**, while $LiAlH_4$ reduction of the appropriate primary amide[20] followed by amide coupling led to **5d**.



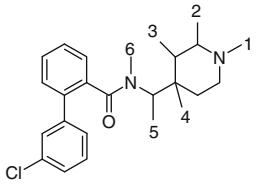
Scheme 4. Syntheses of **4b-f**.[17–19] Reagents and conditions: (a) 3-Me-4-carboxyl piperidine HCl, Boc_2O, Et_3N, CH_2Cl_2, rt; (b) 2 M NH_3 in MeOH, EDC, HOAt, CH_2Cl_2, rt, 16 h; (c) (i) $LiAlH_4$, −78 °C to rt, THF; (ii) $Na_2SO_4{\cdot}10H_2O$; (d) 3′-chloro-1,1′-biphenyl-2-carboxylic acid, EDC, HOAt, CH_2Cl_2, rt, 16 h; (e) 4 M HCl, MeOH, rt; (f) 2,4-lutidine, SeO_2, pyridine, 90 °C, 1 h; (g) PtO_2, H_2 (60 psi), AcOH, 16 h; (h) Boc_2O, Et_3N, CH_2Cl_2, rt, 15 min; (i) NH_4HCO_2, 10% Pd/C, MeOH/H_2O 9:1, rt, 16 h; (j) 2-Br benzoic acid, 1-Boc-4-(aminomethyl)piperidine, EDC, HOAt, CH_2Cl_2, rt, 16 h; (k) 3-Cl phenylboronic acid, $Pd(PPh_3)_4$, 2 M Cs_2CO_3, DME, 80 °C, 4 h; (l) powdered KOH, MeI, DMSO, rt, 10 min.

Table 3
Disubstitution SAR of lower phenyl with 3-Cl fixed

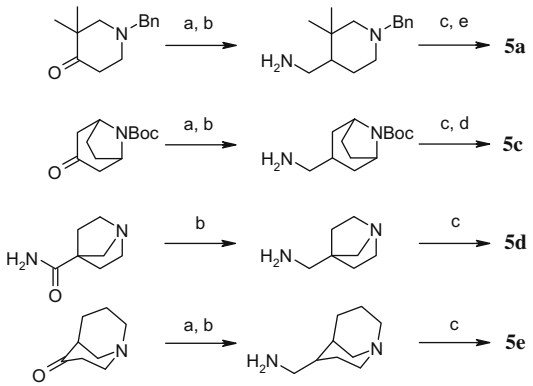


Compd	M_1 pEC_{50} IA%	F		Cl		Me	
2		**3a**	6.0 66	**3b**	<5.0 16	**3c**	<5.0 5
4		**3d**	7.6 76	**3e**	7.3 59	**3f**	7.9 91
5		**3g**	<5.0 17	**3h**	<5.0 24	**3i**	5.8 52
6		**3j**	8.0 111	**3k**	7.4 100	**3l**	6.8 86

Table 4
Mono-methylation SAR of diamine region



Compd	**4a** **1**	**4b** **2**	**4c** **3**	**4d** **4**	**4e** **5**	**4f** **6**	**2d** n/a
M_1 pEC_{50} IA%	<5.0 16	<5.0 28	7.7 99	<5.0 45	<5.0 26	<5.0 2	7.2 86

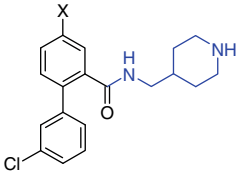


Scheme 5. Syntheses of 5a, 5c-e.[22] Reagents and conditions: (a) tosylmethyl isocyanide (TosMIC), KO^{t}Bu, DME, 0 °C, 45 min, rt 1 h; (b) (i) $LiAlH_4$, THF, rt, 16 h; (ii) $Na_2SO_4{\cdot}10H_2O$; (c) 3′-chlorobiphenyl-2-carboxylic acid (**5c**–**e**) or 3′,4-dichloro-1,1′-biphenyl-2-carboxylic acid[23] (**5a**), EDC, HOAt, CH_2Cl_2, rt, 16 h; (d) 4 M HCl, MeOH, 16 h; (e) (i) α-chloroethyl chloroformate, K_2CO_3, DCE, reflux 1 h; (ii) MeOH, reflux 1 h.

We found (Table 5) that although the 3 methyl in **4c** was beneficial, geminal dimethyl **5a**[21] was inactive. Other modifications including moving the N outside the ring (**5b**[22]), and a bridged piperidine (**5c**) also destroyed activity. Bicyclic tertiary amines **5d** and **5e** were inactive, as was **5f**[22] despite the fact the same moiety showed modest activity with the 4-chloro-1,3-thiazol-2-yl of **1** as the lower aryl (compound **1a** in Table 1).

Promising compounds were evaluated in M_{2-5} selectivity assays. We were pleased to find as we improved M_1 agonist potency and intrinsic activity, we were able to maintain subtype selectivity (Table 6). For example, compounds **3j** and **4c** were potent full agonists with 100-fold or greater selectivity for M_1 over M_{2-5}.

Table 5
Third iteration diamine region SAR



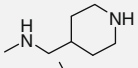
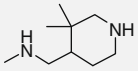
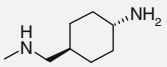
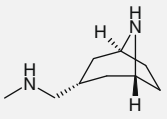
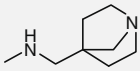
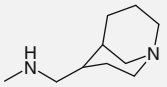
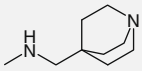
Compd	X=	Structure	M_1 pEC_{50} IA%
2d (ref.)	H		7.2 86
5a	Cl		<5.0
5b[22]	H		<5.0
5c	H		<5.0
5d	H		<5.0
5e	H		<5.0
5f	H		<5.0

Table 6
Subtype selectivity profiles of selected compounds[24]

Compd	M_1 pEC_{50} IA%	M_2 pIC_{50}	M_3 pIC_{50}	M_4 pIC_{50}	M_5 pIC_{50}
1	6.6 84	<5.0	<5.0	<5.0	<5.0
2d	7.2 86	5.1	5.4	5.3	<5.0
3f	7.9 96	6.4	6.6	6.4	6.1
3j	8.0 111	5.7	6.0	5.8	5.3
4c	7.7 99	5.4	5.9	5.5	<5.0

In conclusion, we have identified a novel biphenyl amide series as potent and subtype selective M_1 agonists. Initial optimization of the series resulted in compounds such as **3j** and **4c** with good M_1 agonist potency and intrinsic activity, and up to 100-fold selectivity for M_1 over M_{2-5}. Additional SAR and optimization of this series, including further exploration of the upper aryl, middle linker, and diamine regions, as well as rat PK profiles of optimized compounds, shall be reported.

Acknowledgments

We thank Bing Wang for NMR and Qian Jin for LC/MS support.

Supplementary data

Supplementary data (experimental procedures detailing the preparation of **1** via the route outlined in Scheme 1) associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.04.128.

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9. Fluorometric imaging plate reader (FLIPR) assays were used to measure M_1 agonist potency and intrinsic activity, and M_{2-5} subtype selectivity. For FLIPR assay details, see: Budzik, B. W; Cooper, D. G.; Forbes, I. F.; Jin, J.; Shi, D.; Smith, P. W.; Walker, G. R. WO Patent 2007036711-A1, 2007; *Chem. Abstr.* **2007**, *146*, 401966.
10. The biological assay results in the paper are a mean of at least two determinations with standard deviation of <±0.3. We report agonist potency in pEC_{50} defined as the negative log of the EC_{50} value in molarity.
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13. All new compounds in this paper were characterized via LC/MS and ^{1}H NMR.
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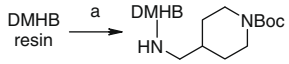
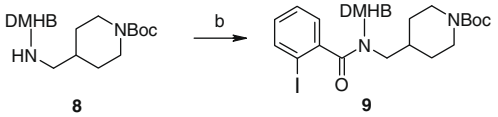
15. Experimental procedures exemplifying use of the solid phase route of Scheme 2 to produce **2d** and **3f**:
DMHB resin-bound 1-Boc-4-(aminomethyl)piperidine **8**:



8

To a 250 mL shaker vessel was added 2,6-dimethoxy-4-polystyrenebenzyloxy-benzaldehyde[14] (DMHB resin) (10 g, 1.5 mmol/g, 15 mmol) and 150 mL of 1-methyl-2-pyrrolidinone (NMP). 1-Boc-4-(aminomethyl)piperidine (16.1 g, 75 mmol), AcOH (15 mL), and $Na(OAc)_3BH$ (19.1 g, 90 mmol) was then added. The resulting mixture was shaken briefly and then immediately vented, this procedure being repeated until no more pressure builds up in the vessel, then the mixture was shaken for 15 min, vented again, then shaken at rt overnight. The mixture was then washed with NMP (150 mL × 2), DCM (150 mL × 2), MeOH (150 mL × 2) and DCM (150 mL × 2). The resulting resin was dried in a vacuum oven at 35 °C overnight to yield DMHB resin-bound 1-Boc-4-(aminomethyl)piperidine **8** (15 mmol, loading 100%).

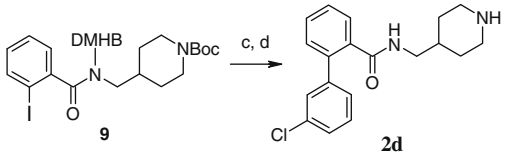
DMHB resin-bound t-butyl 4-{[(2-iodobenzoyl)amino] methyl}piperidine-1-carboxylate **9**:



8 **9**

To DMHB resin-bound 1-Boc-4-(aminomethyl) piperidine **8** [5 g, 1.16 mmol/g (theoretical loading), 5.8 mmol] in DCE/DMF (1:1, 150 mL) was added 2-iodobenzoic acid (14.4 g, 58 mmol) and DIC (9.1 mL, 58 mmol). The mixture was shaken at rt 16 h and then washed with DMF (100 mL × 2), DCM (100 mL × 2), MeOH (100 mL × 2) and DCM (100 mL × 2). The resulting resin was dried in a vacuum oven at 35 °C overnight to yield DMHB resin-bound *t*-butyl 4-{[(2-iodobenzoyl)amino] methyl} piperidine-1-carboxylate (**9**, 5.8 mmol). An analytical amount of the resin was cleaved with 50% TFA/DCE for 10 min. The resulting solution was concentrated in vacuo and dissolved in 0.5 mL of MeOH. MS (ES+) 345 $[M-Boc+H]^+$.

3′-Chloro-N-(piperidin-4-ylmethyl)-1,1′-biphenyl-2-carbox amide trifluoroacetate (**2d**):



9 **2d**

To resin **9** [140 mg, 0.91 mmol/g (theoretical loading), 0.13 mmol] in 7 mL of DME was added 3-chlorophenyl boronic acid (60 mg, 0.38 mmol), 2 M Cs_2CO_3 (190 μL, 0.38 mmol), and $Pd(PPh_3)_4$ (8 mg, 0.0065 mmol). After purging with Ar for 30 s, the mixture was shaken at 80 °C under Ar for 16 h. The resulting resin was washed with THF (10 mL × 2), THF–H_2O (1:1, 10 mL × 2), H_2O (10 mL × 2), THF–H_2O (1:1, 10 mL × 2), THF (10 mL × 2), DCM (10 mL × 2). The washed resin was cleaved [2 × (4 mL of 50% TFA/DCE, 30 min)], combined cleavage solution evaporated and the residue purified via HPLC to produce 3′-chloro-*N*-(piperidin-4-ylmethyl)-1,1′-biphenyl-2-carbox amide trifluoroacetate **2d** (35 mg, 61%). ^1H NMR (400 MHz, DMSO-d_6) δ 8.46 (m, 1H), 8.34 (t, J = 5.8 Hz, 1H), 8.14 (m, 1H), 7.52 (m, 1H), 7.48–7.39 (m, 6H), 7.34 (m, 1H), 3.20 (m, 2H), 2.96 (m, 2H), 2.73 (m, 2H), 1.56 (m, 1H), 1.50 (m, 2H), 1.13 (m, 2H). MS (ES+) 329 $[M+H]^+$.

3′-Chloro-4′-methyl-*N*-(piperidin-4-ylmethyl)-1,1′-bi-phenyl-2-carboxamide trifluoroacetate **3f** was likewise produced by substitution of 3-chloro-4-methylphenyl-boronic acid in step c.

^1H NMR (400 MHz, DMSO-d_6) δ 8.56–8.43 (m, 1H), 8.30 (t, J = 6.1 Hz, 1H), 8.26–8.13 (m, 1H), 7.53–7.47 (m, 1H), 7.46–7.36 (m, 5H), 7.25 (dd, J = 7.8, 1.8 Hz, 1H), 3.19 (d, J = 12.6 Hz, 2H), 2.95 (t, J = 6.4 Hz, 2H), 2.77–2.64 (m, 2H), 2.36 (s, 3H), 1.62–1.41 (m, 3H), 1.19–1.05 (m, 2H). MS (ES+) 343 $[M+H]^+$.

The compounds of Figure 2, and most of the compounds of Tables 2 and 3 were produced likewise by substitution of the appropriate aryl boronic acid in step c (or benzoic acid in step b for the compounds of Figure 2). The remainder of the compounds were made via the route of Scheme 3 using aryl halides (see note[16] below).

16. Experimental procedures exemplifying use of the route of Scheme 3 to produce **3j**:
Preparation of t-butyl 4-({[2-(4,4,5,5-tetramethyl-1,3,2-di oxaborolan-2-yl) benzoyl] amino} methyl)piperidine-1-carboxylate ***10*** *(step a)*: 2-Carboxyphenylboronic acid pinacol ester (33 g, 0.13 mol, 1 equiv), 1-Boc-4-(aminomethyl)piperidine (28.5 g, 0.13 mol, 1 equiv), HOAt (18.1 g, 0.13 mol, 1 equiv), EDC (25.5 g, 0.13 mol, 1 equiv), and DCM (900 mL) were combined at rt and stirred overnight. The reaction was washed 3 × 500 mL H_2O, dried Na_2SO_4, and evaporated, the residue mixed with 750 mL DME, then evaporated again on a 50 °C water bath for 1 h, followed by drying in vacuo overnight to give **10** which was used without further purification (27.8 g, 47%).
^1H NMR (400 MHz, DMSO-d_6) δ 9.43 (m, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.48 (m, 1H), 7.39 (m, 2H), 3.92 (m, 2H), 3.28 (m, 2H), 2.70 (m, 2H), 1.77 (m, 1H), 1.65 (m, 2H), 1.39 (s, 9H), 1.21 (s, 12H), 1.07 (m, 2H). MS (ES+) 445 $[M+H]^+$.
Preparation of ***3j*** *from* ***10*** *(steps b, c)*: **10** (75 mg, 0.17 mmol, 1 equiv), 2-bromo-4-chloro-1-fluorobenzene (36 mg, 0.17 mmol, 1 equiv), 2 M Cs_2CO_3 (188 μL, 0.38 mmol, 2.2 equiv), and DME (10 mL) were combined. The mixture was sparged with Ar for 30 s, then $Pd(PPh_3)_4$ (10 mg, 0.009 mmol, 0.05 equiv) added. The mixture was refluxed overnight under Ar with stirring. Aqueous layer was discarded, and DME layer evaporated and the residue treated with 50% TFA/DCM to deprotect Boc, followed by evaporation, the residue purified via HPLC to yield 5′-chloro-2′-fluoro-*N*-(piperidin-4-ylmethyl)-1,1′-bi phenyl-2-carboxamide trifluoroacetate **3j** (42 mg, 54%).
^1H NMR (500 MHz, $CDCl_3$) δ 8.52 (m, 1H), 8.16 (m, 1H), 7.53 (m, 2H), 7.43 (m, 1H), 7.35 (d, J = 7.5 Hz, 1H), 7.33–7.28 (m, 2H), 7.05 (m, 1H), 6.35 (t, J = 5.8 Hz, 1H), 3.37 (m, 2H), 3.18 (m, 2H), 2.84 (m, 2H), 1.78–1.64 (m, 3H), 1.41 (m, 2H). MS (ES+) 347 $[M+H]^+$.
17. Significant amounts of byproduct with reduction of Boc to methyl was produced in step(s) c of Scheme 4.
18. For method of step (i) in Scheme 4, see: Allegretti, M.; Berdini, V.; Cesta, M. C.; Curti, R.; Nicolini, L.; Topai, A. *Tetrahedron Lett.* **2001**, *42*, 4257.
19. Compound **4c** was ~50:50 *cis* to *trans*, **4b** was 80:20 *cis* to *trans* (by NMR studies). Compound **4a** was made in one step by EDC, HOAt coupling of commercially available 3′-chlorobiphenyl-2-carboxylic acid and 1-methyl-4-(aminomethyl)piperidine.
20. For preparation of the amide starting material for **5d** in Scheme 5, see: Jenkins, S. M.; Wadsworth, H. J.; Bromidge, S.; Orlek, B. S.; Wyman, P. A.; Riley, G. J.; Hawkins, J. *J. Med. Chem.* **1992**, *35*, 2392; For preparation of the ketone starting material for **5e** in Scheme 5, see: Myoung, G. K.; Bodor, E. T.; Wang, C.; Harden, T. K.; Kohn, H. *J. Med. Chem.* **2003**, *46*, 2216.
21. The proper comparison compound to **5a**, that is, the compound with the 5-Cl present on upper phenyl but without the geminal dimethyl on piperidine, had M_1 pEC_{50} = 7.0, IA = 74%.
22. Compound **5b** was made via EDC, HOAt coupling of commercially available 3′-chlorobiphenyl-2-carboxylic acid and *t*-butyl-*trans*-4-aminomethyl cyclohexylcarbamate followed by deprotection with 4 M HCl. Compound **5f** was prepared by reduction of commercially available 4-cyanoquinuclidine ((i) $LiAlH_4$, THF, rt, 16 h; (ii) $Na_2SO_4 \cdot 10H_2O$) followed by EDC, HOAt coupling with 3′-chlorobiphenyl-2-carboxylic acid.
23. 3′,4-Dichloro-1,1′-biphenyl-2-carboxylic acid was easily made by Suzuki coupling of methyl 2-bromo-5-chlorobenzoate (3-Cl phenylboronic acid, $Pd(PPh_3)_4$, 2 M Cs_2CO_3, DME, 80 °C, 4 h) followed by hydrolysis (NaOH, MeOH, reflux 1 h).
24. Compounds were also tested in agonist mode for $M_{2\text{-}5}$ and showed no agonist activity.
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