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3-Oxo-2-piperazinyl acetamides as potent bradykinin B1 receptor antagonists for the treatment of pain and inflammation

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ABSTRACT

The discovery of novel and highly potent oxopiperazine based B1 receptor antagonists is described. Compared to the previously described arylsulfonylated (*R*)-3-amino-3-phenylpropionic acid series, the current compounds showed improved in vitro potency and metabolic stability. Compound **17**, 2-((2*R*)-1-((4-methylphenyl)sulfonyl)-3-oxo-2-piperazinyl)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)acetamide, showed EC_{50} of 10.3 nM in a rabbit biochemical challenge model. The practical syntheses of chiral arylsulfonylated oxopiperazine acetic acids are also described.

Bradykinin-1 (B1) receptor is a G-protein coupled receptor.[1] It is activated by the longer acting des-Arg [9/10] metabolites of bradykinin (BK) and kallidin (Lys-BK). The receptor is normally absent or expressed at very low levels but is induced during tissue injury and inflammation. Pre-clinical studies suggested that B1 receptor is implicated in establishing and maintaining the signaling of chronic pain.[2,3] The rationale for and discovery of B1 receptor antagonists as potential treatment of pain and inflammation has been extensively discussed in the literature.[4–8]

We recently reported a number of novel B1 antagonists containing bicyclic chromans and tetralins as the key subunit.[9–13] Both acyclic and cyclic arylsulfonylated β-amino acids represented by **1–3**[10,11,13] were investigated. Early leads such as **1–2** suffered from high human microsomal clearance or moderate functional potencies. Dihydroquinoxalinone acetic acid based compounds such as **3** exhibited much improved functional potency and in some cases improved metabolic stability.[13] We prepared the analog of **3** without the fused benzo ring (i.e., compound **4** as a mixture of two diastereomers) and found that both binding and functional potency for B1 receptor was maintained (Table 1). This report discusses the structure–activity relationships (SAR) studies of these oxopiperazine based B1 antagonists, which led to compound **17** with improved in vivo efficacy over initial lead **1**.

In order to facilitate quick exploration of structure–activity relationships we used commercially available ethyl 2-(3-oxopiperazin-2-yl)acetate to prepare analogs of **4** as 1:1 diastereomeric mixtures. The synthesized compounds were tested in a human B1 receptor binding assay to give various K_i values. They were also tested in a human B1 agonist-induced aqueorin-based calcium efflux assay in Chinese hamster ovary cells to measure their functional potency (reported as IC_{50}).[9,11] In this paper we will focus the discussion on functional activities, although similar SAR trends

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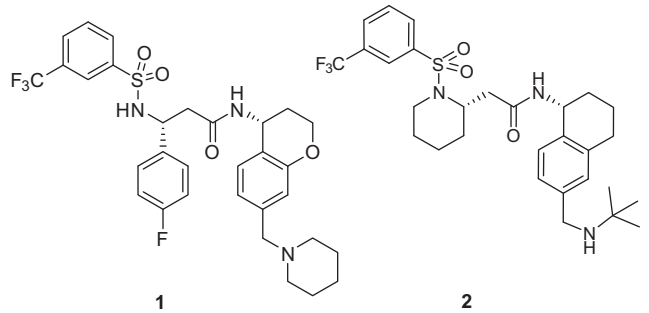
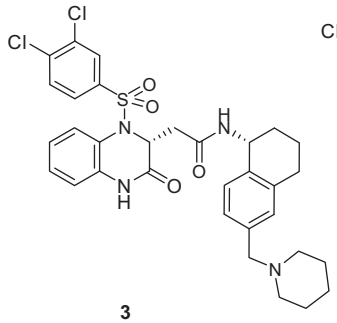
Table 1
Discovery of a new class of oxopiperazine based B1 antagonists



1

2



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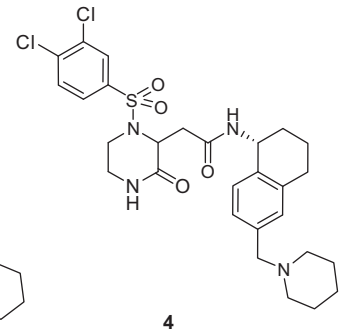
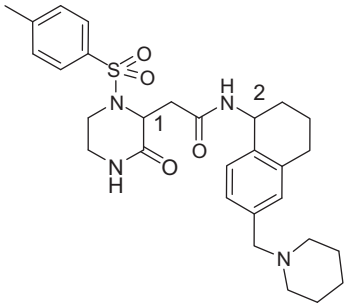


4

Compd #	hB1 K_i[a] (nM)	hB1 IC_{50}[a] (nM)	HLM[b] (μL/min/mg)
1	0.4 ± 0.1	0.8 ± 0.1	330
2	23 ± 8	13 ± 8	900
3	0.1 ± 0.01	0.55 ± 0.08	417
4	0.17 ± 0.03	1.2 ± 0.7	369

[a] K_i and IC_{50} reported are average ± SD of at least two or more determinations.
[b] The experiments are performed wth two replicates for each compound. The percent difference between replicates must be less than or equal to 20% in order for the results to be considered valid.

Table 3
Characterization of the four diastereomers of compound **10**



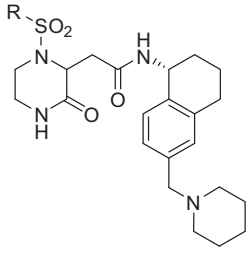
Compd # (stereochemistry at 1, 2)	hB1 K_i[a] (nM)	hB1 IC_{50}[a] (nM)
17 (*R*,*R*)	0.16 ± 0.08	0.22 ± 0.07
18 (*R*,*S*)	31.8 ± 2.8	248 ± 10
19 (*S*,*R*)	5.3 ± 0.1	3.6 ± 0.1
20 (*S*,*S*)	541 ± 129	1165 ± 69

[a] K_i and IC_{50} reported are average ± SD of at least two or more determinations.

were observed in the binding assay. We also assessed the metabolic stability of these compounds by incubation in human liver microsomal preparation. The rate of the disappearance of the parent was measured and expressed in unit of μL/min/mg.

Substitution on the sulfonamide portion was studied (Table 2). In general various mono and disubstitution by halogen, methyl, methoxy, and trifluoromethyl group on benzenesulfonamides were well tolerated. Although more lipophilic groups increased the binding affinity slightly, the functional potency was compromised in certain cases compared to simple phenyl sulfonamide (e.g., compare **14** and **6**). Furthermore these compounds were also metabolically more labile. Substituted thiophene or benzothiophene sulfonamides were also well tolerated. However, replacement of the phenylsulfonamide by methyl sulfonamide resulted in 1000-fold drop in functional potency.

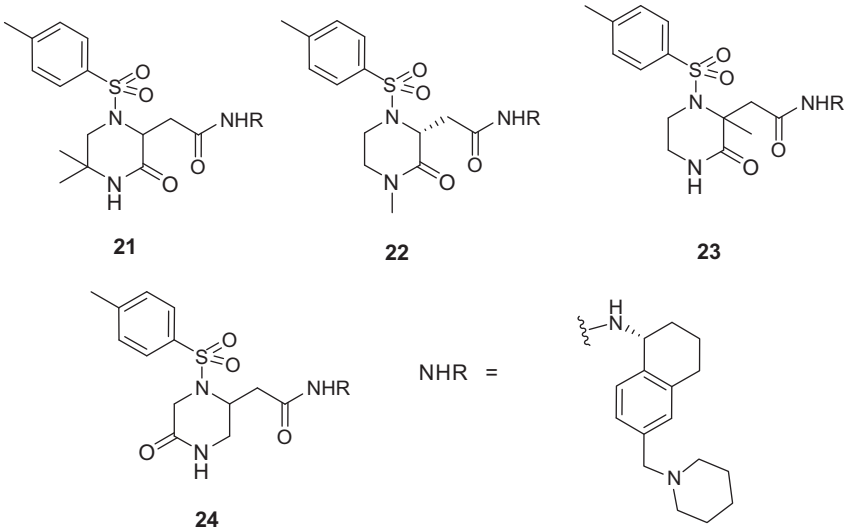
Table 2
SAR studies on the sulfonamide portion



Compd #	R	hB1 K_i[a] (nM)	hB1 IC_{50}[a] (nM)	HLM[b] (μL/min/mg)
4	3,4-Cl_2Ph	0.17 ± 0.03	1.2 ± 0.7	369
5	Me	522 ± 75	475 ± 108	<50
6	Ph	1.2 ± 0.2	0.48 ± 0.31	<50
7	2-ClPh	0.41 ± 0.09	0.55 ± 0.06	104
8	4-ClPh	0.60 ± 0.08	0.49 ± 0.05	137
9	2,4-Cl_2Ph	0.21 ± 0.02	0.64 ± 0.08	198
10	4-MePh	0.30 ± 0.18	0.30 ± 0.13	176
11	4-OMePh	0.55 ± 0.04	0.43 ± 0.02	<50
12	4-CF_3Ph	0.46 ± 0.01	1.76 ± 0.3	215
13	3-CF_3Ph	0.15 ± 0.01	0.94 ± 0.46	193
14	4-Me-3-CF_3Ph	0.12 ± 0.02	2.3 ± 0.4	722
15	3-Br-5-Cl-thiophen-2-yl	0.10 ± 0.01	0.33 ± 0.02	415
16	5-Cl-benzothiophen-2-yl	0.10 ± 0.02	3.3 ± 0.01	326

[a] K_i and IC_{50} reported are average ± SD of at least two or more determinations.
[b] The experiments are performed wth two replicates for each compound. The percent difference between replicates must be less than or equal to 20% in order for the results to be considered valid.

Table 4
Modification of the oxopiperazine ring

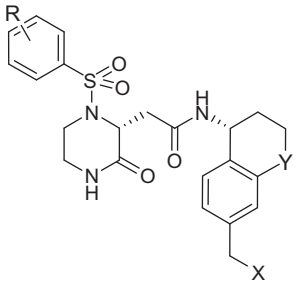


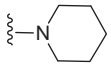
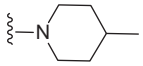
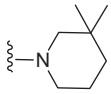
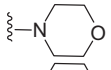
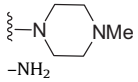
21 **22** **23** **24**

Compd #	hB1 K_i[a] (nM)	hB1 IC_{50}[a] (nM)
10	0.30 ± 0.18	0.30 ± 0.13
21	17.6 ± 1.8	136 ± 40
22	442 ± 255	98.6 ± 34
23	718 ± 79	ND[b]
24	5.10 ± 0.02	2.2 ± 0.7

[a] K_i and IC_{50} reported are average ± SD of at least two or more determinations.
[b] ND: not determined.

Table 5
SAR study of optically pure oxopiperazines



Compd #	R	Y	X	hB1 K_i[a] (nM)	hB1 IC_{50}[a] (nM)	HLM (μL/min/mg)
17	4-Me	CH_2		0.16 ± 0.08	0.22 ± 0.07	<50
25	H	CH_2		0.5 ± 0.2	0.8 ± 0.2	<50
26	4-Cl	CH_2		0.3 ± 0.1	0.2 ± 0.1	124
27	4-Me	O		0.18 ± 0.04	0.4 ± 0.2	<100
28	4-Me	CH_2		0.11 ± 0.11	0.14 ± 0.02	<50
29	4-Me	CH_2		1.98 ± 0.44	2.6 ± 0.1	371
30	4-Me	CH_2		3.0 ± 0.3	1.2 ± 1.4	<100
31	4-Me	CH_2		2.4 ± 0.9	1.46 ± 1.2	<50
32	4-Me	CH_2	$-NH_2$	60 ± 43	238 ± 253	<50
33	4-Me	CH_2	–NHcPr	1.09 ± 0.01	4.3 ± 0.4	<100
34	4-Me	CH_2	$-NH_2$cPen	0.52 ± 0.08	0.60 ± 0.04	<100
35	4-Me	CH_2	–NH*t*Bu	4.1 ± 0.9	1.28 ± 0.22	<5
36	4-Me	CH_2	$-NHCH_2$cPr	0.22 ± 0.07	0.33 ± 0.23	113
37	4-Me	CH_2	$-NHCH_2$*i*Pr	0.29 ± 0.08	0.48 ± 0.46	<100
38	4-Me	CH_2	$-NHCH_2$*t*Bu	1.6 ± 1.5	2.3 ± 1.6	113

[a] K_i and IC_{50} reported are average ± SD of at least two or more determinations.

Table 6
PK profiles of representative oxopiperazines

Compd #	Rat IV Cl[a] (L/h/kg)	Rat IV V_{ss}[a] (L/kg)	Rat F%[b]	CYP 3A4 IC_{50} (μM) no incubation	CYP 3A4 IC_{50} (μM) 30-min pre-incubation
17	7.4	9.3	6	>30	>30
25	5.4	9.9	NA	NA	NA
26	6.7	11.9	19	NA	NA
27	6.7	12.5	6.5	NA	NA
35	3.4	8.34	0.3	>30	>30
31	6.1	15.2	NA	NA	NA
38	1.8	3.4	16	>30	2.2

[a] After IV bolus dose of 1 mg/kg in DMSO to Sprague–Dawley rats ($n = 2$).
[b] After po administration of 10 mg/kg in 2% HPMC/1% Tween 80 to Sprague–Dawley rats ($n = 2$). NA: not available.

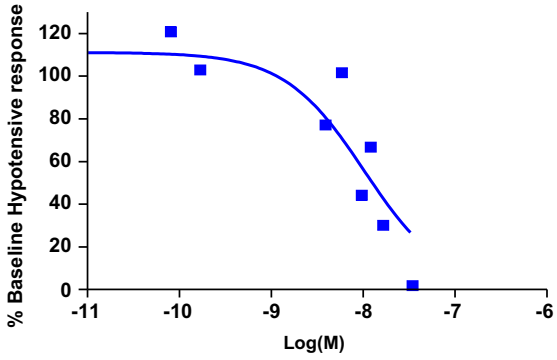


Figure 1. Effect of compound **17** on B1 agonist DAK induced hypotension. Each data point represented the % hypotensive response due to DAK administration either at 30- or 75-min post subcutaneous dose of **17**. The *x*-axis represented the measured plasma concentration of **17** at different doses or time points.

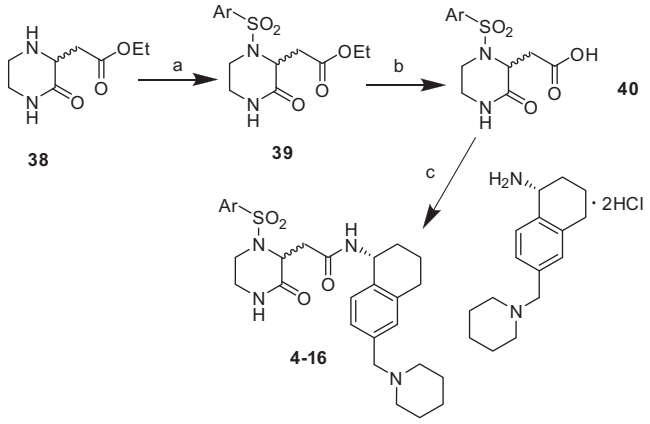
Table 7
Pharmacokinetic profiles of **17** in pre-clinical species

Species	CL[a] (L/h/kg)	V_{ss}[a] (L/kg)	$t_{1/2}$[a] (h)	F[b] (%)
Mouse	8.0	6.0	1.4	6
Rat	7.4	9.3	4.8	6
Rabbit	3.2	6.4	2.4	5[c]
Cynomolgus monkey	0.6	1.6	5.6	17
Rhesus monkey	1.8	5.9	3.2	23[c]
Dog	3.8	16.2	4.6	24[e]

[d] Dosed orally 5 mg/kg in 2% HPMC/1% Tween 80.
[a] Dosed iv at 1 mg/kg in 100% DMSO (rat) or PBS (other species).
[b] Dosed orally 10 mg/kg (rat and Rat) in 2% HPMC/1% Tween 80 (rat) or PBS (mouse).
[c] Dosed orally 5 mg/kg po in PBS.
[e] Dosed orally at 3 mg/kg in 2% HPMC/1% Tween 80.

Next we prepared the four single diastereomers of compound **10** to study the effect of stereochemistry at the amino acid and amine sites (Table 3). Consistent with previous SAR the (*R*) stereochemistry is preferred at both sites.[9] Switching the stereochemistry at either site reduced the functional potency by at least 10-fold. The potency was reduced further when both centers were changed to (*S*) configuration.

The oxopiperazine portion of compound **10** was examined (Table 4). Introduction of the gem-dimethyl group at the carbon adjacent to the internal amide NH to give compound **21** reduced the functional potency by 412-fold. N-Methylation of the ring amide NH in **10** also decreased the potency by 300-fold. The α-methylation of the carbon next to the internal carbonyl group to give **23** adversely impacted the binding affinity. The translocation of the



Scheme 1. Synthetic sequence for oxopiperazine acetamides. Reagents and conditions: (a) RSO_2Cl, pyridine; (b) LiOH, water, methanol and dioxane (1:1:1); (c) DIPEA, EDCI, HOAt, IPA.

3-oxo in **10** to 5-oxo analog **24** reduced the functional potency by sixfold. These data indicated the modification of oxopiperazine ring dramatically affected the affinity for the B1 receptor and the parent 3-oxopiperazine core provided the highest antagonistic potency at the B1 receptor.

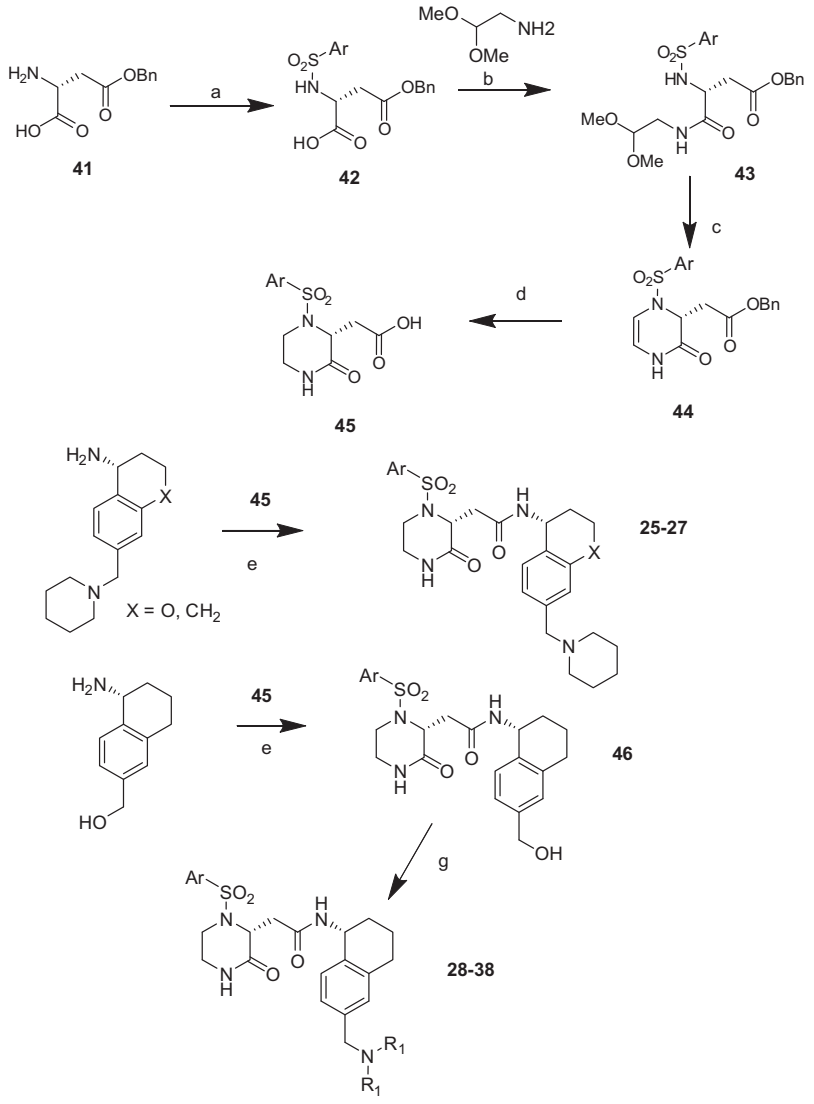
We subsequently prepared a number of optically pure (*R*)-2-oxopiperazine acetamides with modifications at aryl sulfonamide, bicyclic and terminal amine portions to establish the SAR pattern in the series (Table 5).

In the sulfonamide portion, removal of 4-Me from **17** to give **25** resulted in threefold drop in potency. The 4-Cl analog **26** is equally potent to the 4-Me analog **17**. Changing the tetralin in **17** to chroman had only minor effect on potency (see **27**). Modification of the piperidine in **17** was studied next. Adding a methyl group at 4-position slightly increased the functional potency. Addition of gem-dimethyl group at 3-position, however, reduced the potency by 10-fold. Changing the piperidine ring to a more polar group such as morpholine or *N*-methylpiperazine ring decreased the potency by four to fivefold. Truncation of piperidine to simple amino group dramatically reduced the potency. The potency could be restored by introduction of a lipophilic alkyl or cycloalkyl group on the nitrogen. The cyclopropylmethylamine and isobutylamine analogs (**36–37**) were almost equally potent to the piperidine analog **17**. Most compounds in the series, except **29**, had dramatically reduced human microsomal clearance compared to earlier leads **1–3**.

The in vivo pharmacokinetics of representative examples of oxopiperazines in rat are shown in Table 6. Generally most compounds in this series possessed high IV clearance and high V_{ss}. Compound **38** had the lowest in vivo clearance among the compounds profiled. Additional PK experiments on **38** showed the compound to be a time dependent CYP 3A4 inhibitor (TDI, see Table 6).

Several analogs of **38** were screened for TDI and *N*-neopentyl group was identified to be responsible for the observed TDI. Replacing neopentylamino group by tertbutylamino (compound **35**) or piperidine (compound **17**) solved the TDI issue (see Table 6).

We next examined the in vivo activity of **17**. Several B1 antagonists such as **1** were previously tested in a rabbit biochemical challenge model.[11,12] Briefly, treatment with lipopolysaccharide upregulates B1 receptors in animals like rabbits and subsequent injection with a B1 agonist such as DAK (des-Arg10-Kallidin) induces hypotensive response. This effect could be reversed by administration of B1 antagonists in a pharmacodynamic assay of in vivo activity.[11,12]



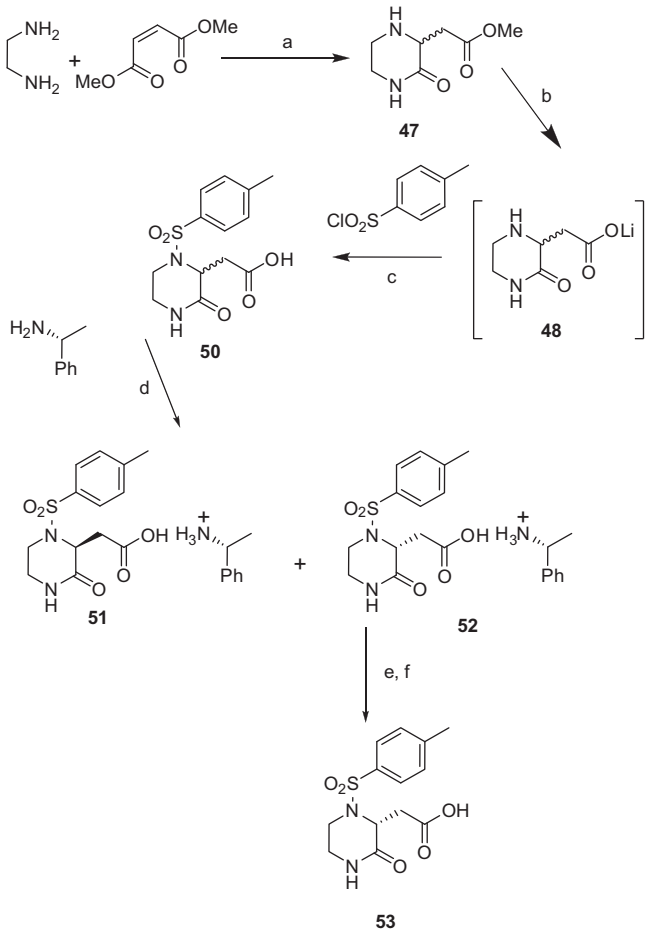
Scheme 2. Chiral synthesis of oxopiperazines. Reagents and conditions: (a) Na_2CO_3, THF/water; (b) EDCI, HOBt, THF; (c) *p*-TsOH, dioxane, 60 °C; (d) TFA, Et_3SiH, CH_2Cl_2, then 10% Pd/C, EtOAc; (e) EDCI, HOBt, DMF; (f) MnO_2, CH_2Cl_2, then R_1R_2NH, $CHCl_3$, $NaBH(OAc)_3$.

Compound **17** had functional IC_{50} of 4.1 nM against rabbit B1 receptor. In the rabbit biochemical challenge model it was able to reduce the B1 agonist (DAK) induced hypotension in rabbit in a plasma-concentration dependent manner (see Fig. 1). In contrast to compound **1** (only 47% reduction in the hypotensive response at the highest plasma concentration tested with the calculated EC_{50} of 1700 nM)[11] it almost completely reversed the hypotension at a much lower concentration. From Fig 1, the EC_{50} value was calculated to be 10.3 nM (R^2 = 0.81, 95%$_{CI}$: 4.3–24.7 nM). This correlated well with IC_{50} value in the rabbit functional assay divided by the free fraction (4.1 nM/0.28 f_u = 14.6 nM). Since the difference in functional IC_{50} against rabbit B1 receptor was only 2.5-fold (4.1 nM for **17** vs 10.4 nM for **1**) the enhanced PD effect of **17** could be partially attributed to significantly lower plasma protein binding (72% for **17** vs 94.5% for **1**).

Based on the close correlation between rabbit PD EC_{50} and in vitro functional potency it is reasonable to assume that in human the EC_{50} for **17** could be approximated by its functional potency divided by its free fraction in human plasma. In order to obtain more relevant functional activity of **17** we tested its activity in an ex vivo isolated tissue bath assay using human umbilical vein (HUV).[14] The stress of tissue isolation up-regulated the B1 receptor in umbilical vein segments and administration of a B1 agonist produced smooth muscle contractions in a dose-dependent manner. In this native tissue preparation, **17** had K_b value of 0.34 nM (n = 3). Using this value we could estimate the human EC_{50} of 1.21 nM.

The pharmacokinetics of **17** was profiled in several pre-clinical species (Table 7). In mouse, rat, rabbit and dog, CL of **17** was very high, with a large volume of distribution and a terminal half-life ranging from 1.4 to 4.8 h (see Table 7). In cynomolgus monkey, it had lower clearance, and a moderate volume of distribution, with a 5.6 h terminal half-life. In rhesus monkey, clearance was higher compared to cynomolgus monkey. The oral bioavailability of **17** ranged from low in rodents to moderate in dog and monkey (Table 7). In allometric scaling a more conservative estimate (excluding non-human primate data) provided 1.2 L/h/kg of human clearance and 6.5 L/kg of volume distribution. Using these projected human PK values and assuming oral bioavailability of 10% in humans, it was estimated that either 100 mg QD or 20 mg BID would allow 24 h coverage of estimated human EC_{50} of 1.21 nM.

Syntheses of compounds mentioned in this manuscript are described in Scheme 1–3. Compounds **4–16** were made from commercially available ethyl 2-(3-oxopiperazin-2-yl)acetate (**38**)



Scheme 3. Chiral resolution approach to prepare oxopierazine acetic acid. Reagents and conditions: (a) *i*PrOH, 50 °C, 73%; (b) LiOH·H_2O, H_2O, 40 °C; (c) Na_2CO_3, H_2O, acetone, 77% (from 47) (d) MeOH (9.5 × volume); (e) H_2SO_4, H_2O; (f) MeOH, 50 °C, 31% (from 50).

as mixture of 1:1 diastereomers. Compound **38** was sulfonylated with various sulfonyl chlorides to give the ester **39**. Basic hydrolysis of the ester **39** gave the corresponding acid **40**. Coupling of the acid **40** with (*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-amine[13] gave amides **4–16**. Compounds **21**, **23**, and **24** were prepared similarly from the corresponding oxopiperazines: ethyl 2-(5,5-dimethyl-3-oxopiperazin-2-yl)acetate,[15] ethyl 2-(2-methyl-3-oxopiperazin-2-yl)acetate,[16] and ethyl 2-(5-oxopiperazin-2-yl)acetate.[17]

Optically pure aryl sulfonylated 2-oxopiperazine acetic acids were first prepared from the chiral aspartic acid derivative **41** (Scheme 2). Compound **41** was sulfonylated with aryl sulfonyl chloride in THF/water in the presence of sodium carbonate to give **42**. EDCI-mediated coupling of **42** with 2,2-dimethoxyethanamine afforded amide **43**. The *p*-toluenesulfonic acid (PTSA) catalyzed cyclization of **43** gave the dehydrooxopiperazine **44**. Sequential reduction of the dehydrooxopiperazine double bond (Et_3SiH/TFA) followed by removal of the benzyl ester through hydrogenolysis afforded **45** in high enantioselectivity (>99.5% ee).

(*R*)-6-(Piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-amine or (*R*)-7-(piperidin-1-ylmethyl)chroman-4-amine was coupled with acid **45** gave the amides **25–35**. Alternatively, acid **45** was coupled to (*R*)-(5-amino-5,6,7,8-tetrahydronaphthalen-2-yl)methanol to give the alcohol intermediate **46**. It was oxidized with MnO_2 to give the aldehyde which was reductively aminated with various amines to give the final compounds **36–46**. Similarly (*R*)-2-(4-methyl-3-oxo-1-tosylpiperazin-2-yl)acetic acid was prepared and coupled with (*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-amine to give compound **22**.

An alternative chiral resolution based synthesis was developed for arylsulfonylated oxopiperazine acetic acids (Scheme 3). The racemic methyl 2-(3-oxopiperazin-2-yl)acetate **47** was prepared from ethylenediamine and dimethyl maleate. Hydrolysis followed by tosylation efficiently gave the racemic acid **50**. Salt pairs were formed from **50** and (*R*)-1-phenylethanamine. The (*R*)-oxopiperazine and (*R*) amine complex **52** was significantly less soluble (16.5 mg/mL in MeOH, 28 °C) than the (*S*)-oxopiperazine and (*R*) amine complex. The crystallized material (**52**) was obtained in good ee (>98.5%). The complex **52** was treated with sulfuric acid to afford the acid **53**, which was recrystallized from methanol to further improve the ee (>99.9%). Other arylsulfonylated oxopiperazine acetic acids were also similarly prepared with high ee %.

In summary, a series of highly potent B1 antagonists with improved metabolic stability were identified. Based on in vitro potency, protein binding, in vivo pharmacokinetics, and pre-clinical animal safety assessment compound **17** was chosen for further pre-clinical evaluation.

References and notes

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