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Bioorganic & Medicinal Chemistry Letters 17 (2007) 3028–3033
Bioorganic & Medicinal Chemistry Letters

Synthesis and structure–activity relationships of 4-hydroxy-4-phenylpiperidines as nociceptin receptor ligands: Part 2

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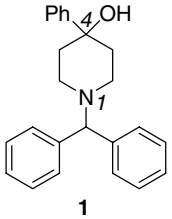
Received 31 January 2007; revised 14 March 2007; accepted 19 March 2007
Available online 21 March 2007

Abstract—A series of 4-[2-(aminomethyl)phenyl]-1-[bis(2-chlorophenyl)methyl]-4-hydroxypiperidine analogs has been identified as nociceptin receptor ligands. These compounds display high affinity and functional activity at the nociceptin receptor. The synthesis and structure–activity relationships at the C-4 phenyl and N-1 positions are described and the antitussive activity of a selected compound is reported.

In the previous communication, we have disclosed the preparation and biological evaluation of a series of *N*-benzhydryl substituted 4-hydroxy-4-phenylpiperidines as nociceptin receptor ligands.[1] The nociceptin receptor, NOP (previously termed ORL-1 (opioid receptor-like-1) or OP_4), is a G protein-coupled receptor that was cloned in 1994.[2] It bears high homology to the classic opioid μ, κ, and δ receptors (MOP, KOP, and DOP), but has little cross-reactivity with their native ligands. Nociceptin (or orphanin FQ), the endogeneous ligand to NOP, was discovered in 1995 and shown to be a peptide ligand that activates the NOP receptor, but not the classic opioid receptors.[3] Therefore, the nociceptin receptor is pharmacologically distinct from the classic opioid receptors. Since the nociceptin receptor is widely distributed throughout the nervous system, it may participate in a broad spectrum of pharmacological processes. In vivo studies with nociceptin and its peptide and non-peptide ligands have demonstrated that the nociceptin/NOP system may have important roles in the regulation of cough, urinary incontinence, pain, stress and anxiety, feeding, learning and memory, locomotor activity, substance abuse, cardiovascular function, sleep disturbance, and Parkinson's disease.[4] Since the nociceptin receptor is pharmacologically distinct from the classic opioid receptors, development of drugs targeting the nociceptin receptor should be devoid of traditional opioid liabilities. Accordingly, we have initiated a program to identify nociceptin receptor agonists for the management of cough. In this communication, we will report the results of an expanded SAR study to identify nociceptin receptor ligands that exhibit enhanced affinity and improved selectivity relative to the lead compound **1**. In addition, we will report the antitussive activity of a selected compound **70**. Our lead compound **1** displays high affinity for NOP with a binding affinity of 13 nM and moderate to excellent selectivity over MOP, KOP, and DOP.



1

NOP K_i= 13 nM
DOP K_i= 1666 nM
KOP K_i= 364 nM
MOP K_i= 233 nM

Schemes 1 and 2 outline the preparation of 4-phenyl modification compounds of types **4** and **7**. Alkylation

Keywords: Nociceptin; Orphnin FQ; Nociceptin receptor (NOP); Opioid receptor-like-1 (ORL-1); G protein-coupled receptor; Opioid receptors (MOP, KOP, DOP).
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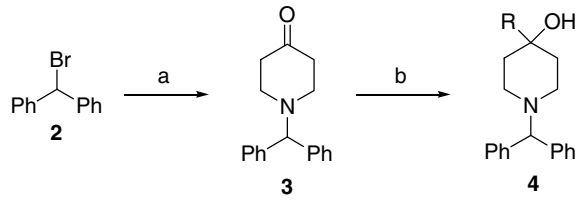
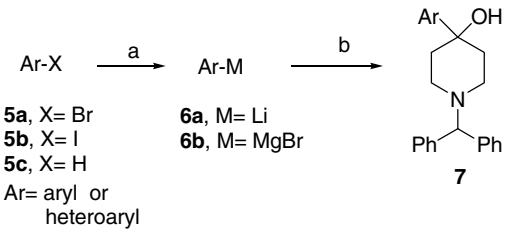
doi:10.1016/j.bmcl.2007.03.062



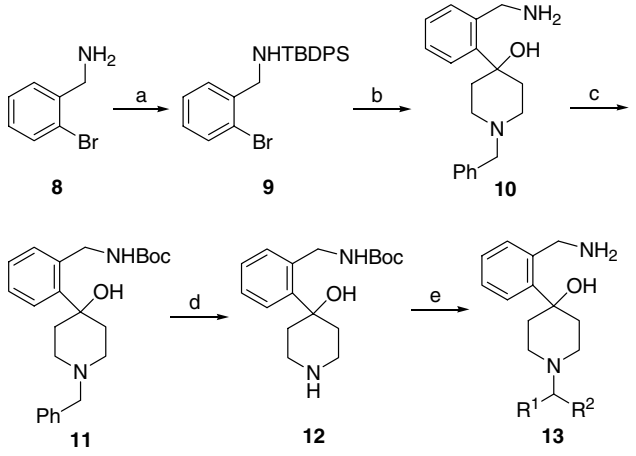
Scheme 1. Reagents: (a) 4-piperidone monohydrate hydrochloride, K_2CO_3, MeCN; (b) RLi or RMgBr, THF or Et_2O.



Scheme 2. Reagents: (a) *n*-BuLi/hexanes or *t*-BuLi/pentane (**5a**, **5c**) or *i*-PrMgCl/Et_2O (**5b**), THF or ether; (b) **3**, THF or Et_2O.

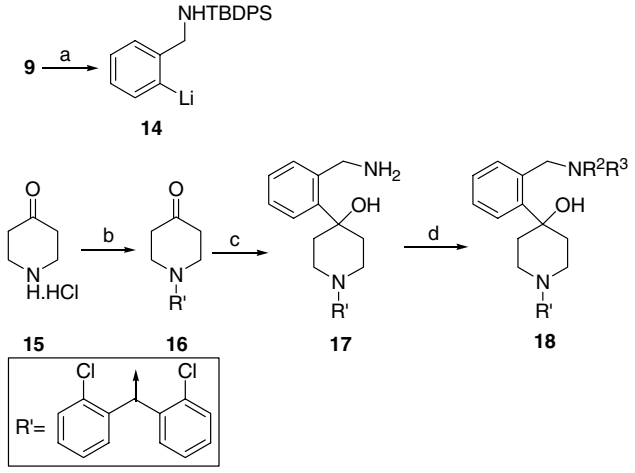
of 4-piperidone hydrochloride with bromodiphenylmethane (**2**) produces the 4-piperidone intermediate **3**. Treatment of **3** with an appropriate lithium or Grignard reagent affords the 4-alkyl analogs of type **4**. The 4-aryl analogs of type **7** are prepared by reaction of **6a** or **6b** with **3**. The lithium reagents **6a** are either purchased or prepared from lithium–halogen exchange of aryl bromides or iodides or deprotonation of the appropriate heteroaryls with *n*-butyllithium or *tert*-butyllithium. The Grignard reagents **6b** are either purchased or prepared by Grignard exchange of the aryl or heteroaryl iodides with isopropylmagnesium chloride.

The synthesis of 4-(2-aminomethyl)phenyl analogs of type **13** is diagrammed in Scheme 3. 2-Bromobenzylamine (**8**) is protected as its *tert*-butyldiphenylsilyl ether

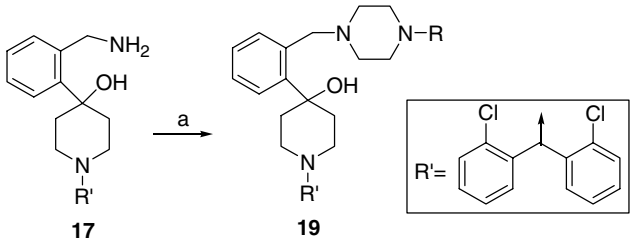


Scheme 3. Reagents: (a) $Ph_2Si(t\text{-}Bu)Cl$, Et_3N or imidazole, CH_3CN; (b) i—*n*-BuLi, 1-benzyl-4-piperidone, THF; ii—NH_4Cl (aq); (c) di-*tert*-butyl dicarbonate, CH_2Cl_2; (d) $Pd(OH)_2/C$, HCO_2NH_4, MeOH; (e) i—R^1R^2CHX (X=Cl or Br), K_2CO_3, NaI (X=Cl), CH_3CN or R^1CHO, $NaBH(OAc)_3$, THF; ii—4 M HCl/dioxane, CH_2Cl_2.

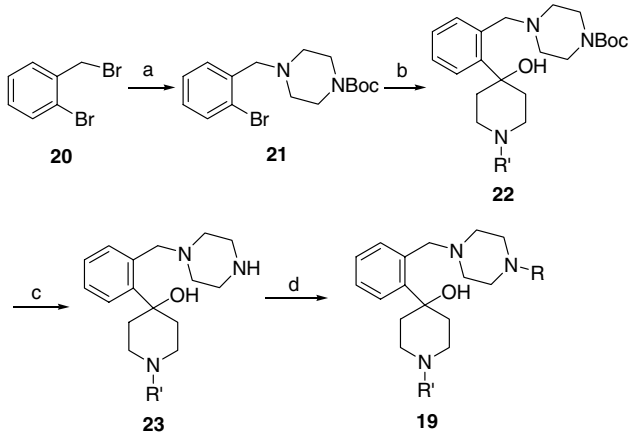
9. The lithium anion is generated and reacted with 1-benzyl-4-piperidone to produce **10** after aqueous work-up and chromatographic purification on silica gel. Compound **10** is protected as its *tert*-butyl carbamate **11** followed by debenzylation to give **12** as an advantaged intermediate for parallel synthesis. Alkylation of **12** with an appropriate alkyl halide or reductive amination with an aldehyde followed by deprotection provides **13**.



Scheme 4. Reagents and condition: (a) *n*-BuLi, THF; (b) $(2\text{-}ClPh)_2CHBr$, K_2CO_3, MeCN, 80 °C; (c) i—**14**, THF; ii—NH_4Cl (aq); (d) R^4SO_2Cl, Et_3N, CH_2Cl_2 ($R^2 = SO_2R^4$, R^3 = H), or R^4NCO ($R^2 = CONHR^4$, R^3 = H).

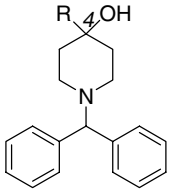


Scheme 5. Reagents and condition: (a) $RN(CH_2CH_2Cl)_2.HCl$ (R = CH_3, CH_2Ph), DMF, 135 °C.



Scheme 6. Reagents: (a) 1-Boc-piperazine, $(i\text{-}Pr)_2NEt$, CH_2Cl_2; (b) i—*n*-BuLi, THF; ii—**16**; (c) 4 M HCl/dioxane; (d) R^4SO_2Cl, EtN, CH_2Cl_2($R = SO_2R^4$).

Table 1. SAR of 4-phenyl modification analogs



Compound	R	K_i (nM)[a]			
		NOP	DOP	KOP	MOP
24	2-F–Ph	34	6990	1738	589
25	3-F–Ph	23	5610	1994	705
26	4-F–Ph	14	3325	759	771
27	4-Cl–Ph	24	6364	1702	936
28	4-Br–Ph	51	15,240	2612	1057
29	2-Me–Ph	11	1668	818	74
30	3-Me–Ph	27	7796	1151	273
31	4-Me–Ph	55	12,115	4054	940
32	4-Et–Ph	1281	24,900	11,355	3433
33	4- *n*-Pr–Ph	1745	33,345	19,695	11,430
34	4-*n*-Bu–Ph	9155	nd	nd	nd
35	2-MeO–Ph	85	4392	4160	983
36	3-MeO–Ph	180	9585	3668	2988
37	4-MeO–Ph	588	19,220	10,928	11,050
38	4-Me_2N–Ph	4544	nd	nd	nd
39	4-CN–Ph	1449	28,380	61,045	8382
40	2-$HOCH_2$–Ph	16	4363	2769	186
41	**2-H_2NCH_2–Ph**	**1.6**	**13,905**	**1658**	**125**
42	*c*-Pr	376	130,550	26,405	18,365
43	*i*-Pr	433	52,825	7390	13,230
44	*n*-Bu	23	18,800	4563	272
45	*t*-Bu	62	56,600	1073	3599
46	*n*-Hex	1147	17,865	9221	8899
47	*c*-Hex	17	8105	387	407
48	$PhCH_2$	2176	15,010	1438	10,390
49	$Ph(CH_2)_3$	1667	13,750	1801	3364
50	2-Furanyl	136	14,455	9644	4554
51	2-Thienyl	48	8446	3412	1734
52	3-Me–2-thienyl	15	8885	2574	756
53	2-Thiazolyl	1273	nd	nd	nd
54	2-Pyridinyl	313	45,590	13,180	11,540

[a] Values are means of two and three experiments (nd, not determined).

The benzylamine modification analogs of type **18** are prepared as shown in Schemes 4–6. Scheme 4 illustrates the preparation of the sulfonamide and urea analogs. The construction of piperazine analogs is outlined in Schemes 5 and 6. The *N*-methyl and *N*-benzylpiperizine analogs are prepared by reaction of **17** with an appropriate bis(2-chloroethyl)amine (Scheme 5). The sulfonamide and *tert*-butyl carbamate analogs are achieved by the procedures summarized in Scheme 6.

Target compounds have been tested for affinity at the cloned human nociceptin receptor expressed in CHO cell membranes by measuring their ability to compete with [^{125}I][Tyr^{14}]nociceptin FQ. The opioid receptor binding assays are performed with CHO cell membranes expressing the human opioid receptors using [^{3}H]-diprenorphine as the radioligand. The K_i values are determined from dose–response curves. The functional activities of selected compounds are evaluated by their ability to enhance the binding of [^{35}S]GTPγS in the presence of GDP, using membranes isolated from cells transfected with the nociceptin receptor.[5]

The SAR of 4-phenyl modifications is delineated in Table 1. The methyl, methoxy, trifluoromethyl, fluorine, chlorine, and bromine substitutions are tolerated at the *ortho*, *meta*, or *para* position of the C-4 phenyl ring. Moving the methyl or methoxy from the *ortho* to the *meta* or *para* position reduces affinity at the NOP receptor (**29**, **30**, **31**, and **35**, **36**, **37**). In contrast, moving the fluorine from the *ortho* to the *meta* or *para* enhances the potency (**24**, **25**, **26**). Increasing the size of the substituent at the *para* position of the C-4 phenyl leads to decreases in affinity at the NOP receptor (**26**, **27**, **28**, and **31**, **32**, **33**, **34**). Introduction of an *N*,*N*-dimethyl or cyano substituent at the *para* position of the C-4 phenyl results in a substantial loss of potency (**38** and **39**). The 2-hydroxymethylphenyl analog **40** displays comparable NOP affinity to compound **1** with ~11-fold selectivity over MOP and greater than 100-fold selectivity

Table 2. Functional activity of selected 4-phenyl modification analogs

Compound	GTPγS % Stim at [μM]	Compound	GTPγS % Stim at [μM]
1	107 at 10	**40**	87 at 10
25	61 at 100	**41**	94 at 10
26	104 at 10	**44**	69 at 10
27	103 at 10	**47**	121 at 100
29	69 at 100	**52**	96 at 10

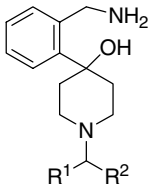
over DOP and KOP. Introduction of an aminomethyl at the *ortho* position of the C-4 phenyl enhances affinity at NOP and shows a dramatic improvement in selectivity over DOP, KOP, and MOP (**41**). Lower alkyl and cycloalkyl moieties are tolerated at the C-4 of the piperidine (**42**–**47**). The 4-*n*-butyl and 4-cyclohexyl analogs **44** and **47** have comparable NOP affinity to compound **1** and exhibit excellent selectivity over DOP and KOP, and moderate selectivity over MOP. Replacement of the C-4 phenyl with a benzyl or phenethyl decreases potency at the NOP receptor (**48** and **49**). The oxygen and nitrogen containing heteroaryl at the C-4 of piperidine reduces affinity at NOP (**50**, **53**, **54**). The 4-thienyl analogs (**51** and **52**) have improved potency compared to the oxygen and nitrogen containing heteroaryl analogs. Table 2 tabulates the functional activity of the 4-phenyl modification analogs when the nociceptin receptor binding is less than 25 nM.

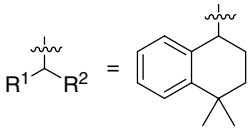
Table 4. Functional activity of selected *N*-benzhydryl modification analogs

Compound	GTPγS % Stim at [μM]	Compound	GTPγS % Stim at [μM]
55	97 at 10	**17**	102 at 1
56	92 at 10	**63**	119 at 10
57	119 at 0.1	**64**	86 at 10
58	116 at 0.1	**65**	104 at 1
59	115 at 1	**66**	67% inh. at 1
60	94 at 1	**67**	43% inh. at 10

Encouraged by the potency and selectivity of compound **41**, we have further examined variations of the piperidine nitrogen substitution in **41**. Table 3 catalogs the SAR of the analogs modified at the *N*-benzhydryl group. Removal of one of the phenyl groups leads to a ~28-fold loss of potency at the NOP receptor and produces a partial agonist response (compound **10**). The *N*-benzyl analogs generally are less potent and possess antagonist or weak agonist response. Replacement of one of phenyls on **41** with *n*-butyl or *n*-pentyl produces high affinity for NOP, KOP, and MOP, but weaker affinity for DOP (**55** and **56**). The methyl, chlorine, bromine, and fluorine are well tolerated at the *ortho* position(s) of one or both of the phenyls (**57–65** and**17**). The 2,2′-dichloro, 2,2′-dimethyl, and 2,2′-dibromo analogs display a dramatic improvement in the selectivity over the MOP receptor compared with the corresponding 2-chloro, 2-methyl,

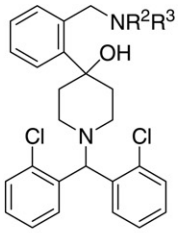
Table 3. SAR of *N*-benzhydryl modification analogs

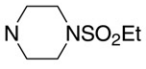
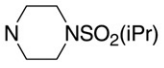


Compound	R^1	R^2	K_i(nM)[a]			
			NOP	DOP	KOP	MOP
10	Ph	H	455	nd	nd	nd
55	Ph	*n*-Bu	0.4	1212	15	2
56	Ph	*n*-Pent	0.5	606	30	2
41	Ph	Ph	1.6	13,905	1658	125
57	Ph	2-Me–Ph	0.7	2867	725	28
58	Ph	2-Cl–Ph	0.5	3702	425	72
59	Ph	2-Br–Ph	1.1	3291	279	83
60	2-Me–Ph	2-Me–Ph	0.5	8435	450	190
61	4-Me–Ph	4-Me–Ph	110	8900	1056	502
17	**2-Cl–Ph**	**2-Cl–Ph**	**0.5**	**2998**	**747**	**249**
62	4-Cl–Ph	4-Cl–Ph	674	3990	2092	3085
63	2-F–Ph	2-F–Ph	0.5	3702	116	37
64	3-F–Ph	3-F–Ph	9.6	9383	771	530
65	2-Br–Ph	2-Br–Ph	1.8	3204	278	614
66		H	4.6	99,505	664	452
67			5.5	23,400	1354	181

[a] Values are means of two-three experiments (nd, not determined).

Table 5. SAR of benzylic nitrogen modification analogs



Compound	NR^2R^3	K_i (nM)[a]			
		NOP	DOP	KOP	MOP
17	NH2	0.5	2998	747	249
68	NHMe	0.7	3818	255	167
69	$NHSO_2$(*n*-Pr)	15	777	122	271
70	$NHSO_2$(*i*-Pr)	4.1	518	174	163
71	NHCONHMe	2	1992	215	198
72	NHCONHEt	12	2445	330	304
73		5.9	2911	323	120
23		1.9	1167	261	145
74		2.2	1705	139	190
75		0.9	1585	146	351
76		0.6	3159	186	353

[a]Values are means of two-three experiments (nd, not determined).

and 2-bromo analogs (**57** and **60**, **58** and **17**, **59**, and **65**). Moving the fluorine from the *ortho* to the *meta* (**63** and **64**) or moving the methyl or chlorine from the *ortho* to the *para* (**60** and **61**, **17** and **62**) reduces affinity at NOP. The cyclooctylmethyl analog **66** and the tetralinyl analog **67** provide high affinity at NOP and good to excellent selectivity over MOP, KOP, and DOP, and also produce an antagonist response. Table 4 shows the functional activity of the benzhydryl modification analogs when the nociceptin receptor binding is less than 10 nM. With the exception of **66** and **67**, these compounds in Table 3 display a potent agonist response.

Additional SAR work on the potent and selective NOP agonist **17** centers on the benzylic nitrogen modification of the C-4 phenyl. Table 5 includes the binding affinity of representative compounds. In general, this modification yields high affinity NOP agonists. The 1°-, 2°-, and 3°-amines, sulfonamides, and ureas are well tolerated. A number of these compounds also display good selectivity over the MOP, KOP, and DOP receptors. Table 6 shows the functional activity of the benzylic

Table 6. Functional activity of selected benzylic nitrogen modification analogs

Compound	GTPγS % Stim at [μM]	Compound	GTPγS % Stim at [μM]
68	95 at 10	**23**	122 at 10
69	114 at 10	**74**	123 at 10
70	146 at 10	**75**	126 at 10
71	120 at 10	**76**	124 at 10
72	118 at 10		

nitrogen modification analogs. All of these compounds exhibit a good nociceptin receptor agonist activity.

To investigate the in vivo pharmacology of nociceptin receptor agonists, selected compounds have been evaluated for their antitussive activity in a capsaicin-induced guinea pig model.[4a,b] The most potent antitussive compound in the 4-hydroxy-4-phenyl series is compound **70**. Compound **70** exhibits oral antitussive activity with an ED_{50} of 0.06 mg/kg at 2 h and 0.15 mg/kg at 6 h.

In summary, the SAR development of *N*-benzhydryl substituted 4-hydroxy-4-phenylpiperidines has identified a series of 4-[2-(aminomethyl)phenyl]-1-[bis(2-chlorophenyl)methyl]-4-hydroxypiperidine analogs that exhibit enhanced affinity and functional activity and improved selectivity relative to the lead compound **1**. Compound **70** exhibits an good excellent in vivo efficacy in the guinea pig model of capsaicin-induced cough.

Acknowledgments

The authors would like to thank Dr. Jesse Wong and his group for the preparation of intermediates **12** and **16**; Drs. Michael Czarniecki, Ashit Ganguly, John Hey, John Hunter, John Piwinski, and Catherine Strader for helpful discussions.

References and notes

1. Please see the preceding paper in this journal.
2. (a) Mollereau, C.; Parmentier, M.; Mailleux, P.; Butour, J.; Moisand, C.; Chalon, P.; Caput, D.; Vassart, G.; Meunier, J.-C. *FEBS Lett.* **1994**, *341*, 33; (b) Fukada, k.; Kato, S.; Mori, K.; Nishi, M.; Takeshima, H.; Iwabe, N.; Miyata, T.; Houtani, T.; Sugomoto, T. *FEBS Lett.* **1994**, *343*, 42; (c) Chen, Y.; Fan, Y.; Liu, J.; Mestek, A.; Tian, M.; Kozak, C. A.; Yu, L. *FEBS Lett.* **1994**, *347*, 279; (d) Wang, J. B.; Johnson, P. S.; Imai, Y.; Persico, A. M.; Ozenberger, B. A.; Eppler, C. M.; Uhl, G. R. *FEBS Lett.* **1994**, *348*, 75.
3. (a) Meunier, J.-C.; Mollereau, C.; Toll, L.; Suaudeau, C.; Moisand, C.; Alvinerie, P.; Butour, J.-L.; Guillemot, J.-C.; Ferrara, P.; Monsarrat, B.; Mazarguil, H.; Vassart, G.; Parmentier, M.; Costentin, J. *Nature* **1995**, *377*, 532; (b) Reinscheid, R. K.; Nothacker, H. P.; Bourson, A.; Ardati, A.; Henningsen, R. A.; Bunzow, J. R.; Grandy, D. K.; Langen, H.; Monsma, F. J., Jr.; Civelli, O. *Science* **1995**, *270*, 792.
4. (a) Mcleod, R. L.; Parra, L. E.; Mutter, J. C.; Erickson, C. H.; Carey, G. J.; Tulshian, D. B.; Fawzi, A. B.; Smith-Torhan, A.; Egan, R. W.; Cuss, F. M.; Hey, J. *Br. J. Pharmacol.* **2001**, *132*(6), 1175; (b) Mcleod, R. L.; Bolster, D. C.; Jia, Y.; Parra, L. E.; Mutter, J. C.; Wang, X.; Tulshian, D. B.; Egan, R. W.; Hey, J. A. *Pulm. Pharmacol. Ther.* **2002**, *15*(3), 213; (c) Meunier, J.-C. *Expert Opin. Ther. Patents* **2000**, *10*, 371, and references cited therein; (d) Bignan, G. C.; Connolly, P. J.; Middleton, S. A. *Expert Opin. Ther. Patents* **2005**, *15*(4), 357, and references cited therein; (e) Calo, G.; Guerrini, R.; Rizzi, A.; Salvadori, S.; Regoli, D. *Br. J. Pharmacol.* **2000**, *129*(7), 1261, and references cited therein; (f) Allen, C. N.; Jiang, Z.-G.; Teshima, K.; Darland, T.; Ikeda, M.; Nelson, C. S.; Quigley, D. I.; Yoshioka, T.; Allen, R. G.; Rea, M. A.; Grandy, D. K. *J. Neurosci.* **1999**, *2152*; (g) Teshima, K.; Minoguchi, M. World Patent 2003082333, 2003; *Chem. Abstr*. **2003**, *139*, 302062.
5. Fawzi, A. B.; Zhang, H.; Weig, B.; Hawes, B.; Graziano, M. P. *Eur. J. Pharmacol.* **1997**, *336*, 233.