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Design, synthesis, and pharmacological evaluation of azetedine and pyrrolidine derivatives as dual norepinephrine reuptake inhibitors and 5-HT$_{1A}$ partial agonists

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ABSTRACT

Compounds with combined norepinephrine reuptake inhibitor (NRI) and serotonin 1A (5-HT$_{1A}$) partial agonist pharmacology may offer a new therapeutic approach for treating symptoms of neuropsychiatric disorders including ADHD, depression, and anxiety. Herein we describe the design and optimization of novel chemical matter that exhibits favorable dual NRI and 5-HT$_{1A}$ partial agonist activity. Lead compounds in this series were found to be devoid of activity at the dopamine transporter and were shown to be brain penetrant with high receptor occupancy.

Pharmacological agents that increase synaptic levels of monoamine neurotransmitters are recognized as effective therapeutics for some neuropsychiatric disorders.[1] Attention Deficit Hyperactivity Disorder (ADHD) has been associated with low levels of dopamine (DA) and norepinephrine (NE) at the synapse in cortical brain regions.[2,3] Treatment for ADHD includes the use of stimulant medications such as amphetamine and methylphenidate, which increase the synaptic concentration of NE and DA.[4] Dopamine signaling is a key component of the reward pathway, and some compounds that rapidly and significantly enhance DA signaling in areas like the nucleus accumbens and substantia nigra have been associated with an increased potential for abuse.[5] Atomoxetine is a norepinephrine reuptake inhibitor that was approved in 2003 as a non-stimulant treatment for ADHD. This compound acts to increase NE signaling globally throughout the brain via blockade of the norepinephrine reuptake transporter (NRI) responsible for the synaptic clearance of released neurotransmitter. In the prefrontal cortex there is negligible expression of the dopamine-specific reuptake transporter (DAT) and released DA is instead cleared by the norepinephrine reuptake transporter (NET), which performs a double duty in this subregion. Thus, NRI inhibition is hypothesized to increase DA signaling in the prefrontal cortex with less impact on reward pathways. In additional to their demonstrated clinical efficacy in ADHD, agents exhibiting NRI activity can be useful for managing additional psychiatric disorders such as depression[6,7] and anxiety.[8] Emerging studies suggest that the ability of NRI's to elevate prefrontal dopamine signaling can be significantly enhanced with agonism or partial agonism at 5-HT$_{1A}$ autoreceptors.[9,10] For example, microdialysis measurement of rodent prefrontal neurotransmission showed a significant, synergistic increase in dopamine levels after dosing a combination of atomoxetine and buspirone.[11] Similarly, preclinical behavioral models of cognition and depression indicate that the combination of NRI and 5-HT$_{1A}$ partial agonist drugs afford greater efficacy than can be obtained with either mechanism dosed alone.[12] On the basis of these theoretical and experimental results, we hypothesized that compounds designed to have appropriately balanced dual NRI and 5-HT$_{1A}$ partial agonist action may offer a new and improved treatment strategy for addressing ADHD and other neuropsychiatric illness.

Toward this end, we recently disclosed the discovery of a series of dual NRI/5-HT$_{1A}$ partial agonists as exemplified by **1**.[13] Encouraged by its excellent profile both in vitro and in vivo, efforts were directed toward further optimization of this series. As depicted in Figure 1, two approaches were pursued in parallel. The first involved replacing one of the phenyl rings with a heterocycle. This

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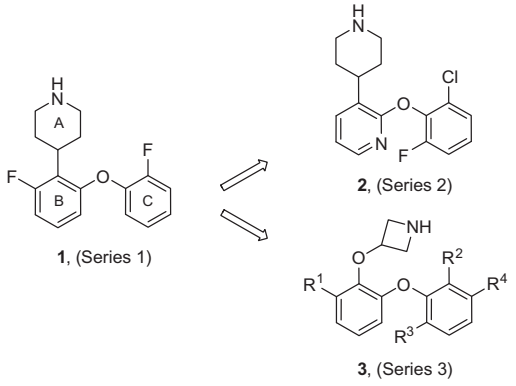


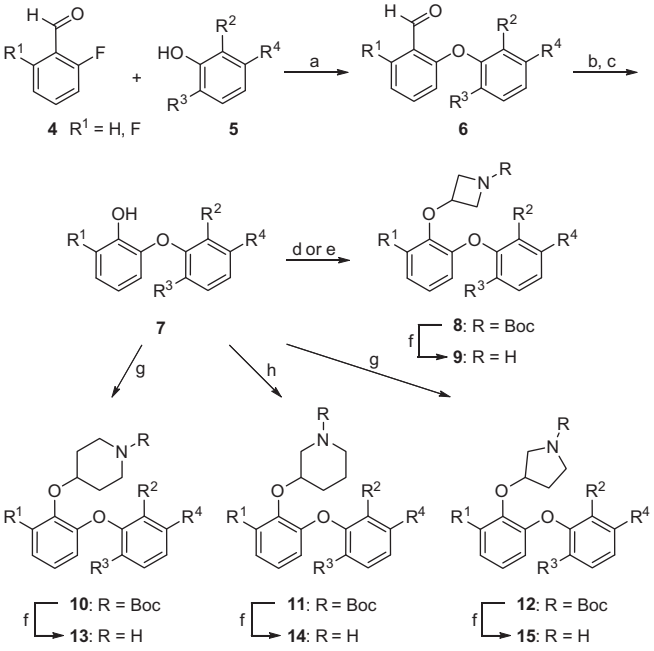
Figure 1

culminated in the discovery of a phenoxy pyridyl series 2 as exemplified by **2**, which exhibits superior NET/DAT-selectivity as compared to **1**.[14] The second avenue, as exemplified by **3**, focused on replacing the piperidine A-ring with a less basic, less lipophilic group, which may help improve safety margins in this series.[15] The primary objective was to reduce potency at DAT while maintaining or improving the 5-HT_{1A} partial agonist activity and retaining drug-like physicochemical properties.[15] In the early part of these optimization efforts, in-house PK/PD modeling suggested that 5-HT_{1A} partial agonist activity was important for elevating maximal monoamine neurotransmission, and that reduced activity at NET would be acceptable.[16]

An azetidine with a one-atom linker was envisioned as a suitable replacement for the piperidine moiety of **1** since it would conserve the distance between the secondary amine and the central phenyl ring. Calculated pK_a values indicated that the introduction of an ether-linked azetedine would result in a 1.5 unit reduction in pK_a of the amine in Series 3 as compared to Series 1. The ether-linkage would confer the additional advantage of enabling the chemistry toward rapid evaluation of additional piperidine replacements in parallel using Mitsunobu chemistry.

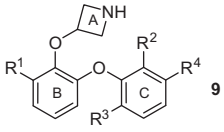
As depicted in Scheme 1, the synthesis of compounds **9** and **13**–**15** commenced with the formation of biaryl ether **6** via S_NAr reaction of various phenols **5** with commercially available 2-fluorobenzaldehydes **4** bearing either a hydrogen or a fluoro-substituent in the R^1-position. Dakin oxidation of the aldehyde function of **6** afforded the corresponding formate ester, which, in turn was hydrolyzed to phenol **7** in excellent yield (85–94% over two steps). We next explored introducing the azetidine moiety via alkylation of phenol **7**. The azetedine ether-linkages of **9a**, **9b**, and **9c** (Table 1) were forged by heating a mixture of requisite phenols **7**, the mesylate derived from *N*-Boc-3-hydroxyazetedine, and Cs_2CO_3 in acetonitrile at 160 °C, in a microwave reactor for 1.5 h. Using these rather forcing reaction conditions, the ether-linkage of **9a** was formed in excellent yield (87%), whereas, the corresponding carbon oxygen bonds of **9b** and **9c** were formed only in lower yield (42%).

To incorporate additional substituents that may not be compatible with the harsh reaction conditions used in this alkylation protocol, we explored the use of Mitsunobu chemistry to carry out the etherification. The coupling of phenol **7** with *N*-Boc-3-hydroxyazetedine proceeded slowly at room temperature and required an excess (3 equiv) of PPh_3 and DIAD to go to completion.[17] Alternatively, warming the reaction to 50 °C significantly increased the reaction rate while only requiring 1.1–1.2 equiv of both DIAD and PPh_3 to afford the desired products in excellent yield (70–96%).[18] These conditions were successfully run on 25 g scale. The Boc-protected pyrrolidine and piperidine rings were also introduced using the Mitsunobu chemistry to afford **10**, and **12**, but in contrast to the azetidines, these reactions did not require heating.



Scheme 1. Reagents and conditions: (a) K_2CO_3, DMA, reflux, 2.5 h (53–61%); (b) *m*CPBA, $CHCl_3$, 30 °C, 18 h; (c) KOH, MeOH/THF, 0 °C, (85–94% yield, two-steps); (d) *tert*-butyl-3-(methylsulfonyloxy)azetidine-1-carboxylate, Cs_2CO_3, CH_3CN, microwave, 160 °C, 15 bar, 1.5 h, (42–86% yield); (e) *tert*-butyl-3-hydroxyazetidine-1-carboxylate, DIAD, PPh_3, THF, 50 °C, 16 h, (70–96%); (f) AcCl, MeOH, (67–89%); (g) *tert*-butyl-4-hydroxypiperidine-1-carboxylate or *tert*-butyl-3-hydroxypyrrolidine-1-carboxylate, DIAD (1.2 equiv), PPh_3, THF, rt 16 h, (69–72%); (h) *N*-*tert*-butyl-3-(methylsulfonyloxy)-piperidine-1-carboxylate, Cs_2CO_3, CH_3CN, reflux, 5 h, (43% yield).

Table 1
Binding and selectivity of ether-linked azetidine analogs



CP	R^1	R^2	R^3	R^4	5-HT_{1A} K_i[a] (nM)	NET K_i[b] (nM)	DAT K_i[b] (nM)	SERT K_i[b] (nM)	*c* log *P*
1	—	—	—	—	4.6	32	278	1260	4.1
2	—	—	—	—	11	33	>6180	194	3.0
9a	H	H	H	H	57	1640	2090	2670	3.4
9b	H	F	H	H	22	528	2040	>4710	3.3
9c	F	F	H	H	12	507	>4860	>4710	3.4
9d	F	Cl	H	H	14	198	4700	1710	4.0
9e	F	F	Cl	H	1	138	>6460	>4900	3.9
9f	F	F	Me	H	3	116	>6460	1160	3.9
9g	F	F	F	H	<3	482	>6410	>4620	3.4
9h	F	Cl	Cl	H	6	164	>5940	>4620	4.5
9i	F	Cl	Me	H	16	433	>6410	>4610	4.5
9j	F	Cl	H	Cl	16	374	312	94	4.6

[a] 5-HT_{1A} RBSHA binding assay; K_i values are the mean of at least two experiments carried out in duplicate.[20]

[b] Monoamine transporter binding scintillation proximity assay (SPA); K_i values are the mean of at least two experiments carried out in duplicate.[21]

Initial attempts to install the 3-hydroxypiperidine group of **11** using Mitsunobu chemistry resulted in low yields. This problem was circumvented by using the corresponding mesylate and forming the ether-linkage by alkylation of phenol **7**. The final step in the syntheses involved removal of the Boc-group by treating **8**, **10**, **11** and **12** with methanolic HCl[19] at room temperature to deliver the target secondary amines in good yield.

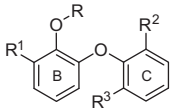
Biological characterization of this series began by assessing the unsubstituted azetidine analog **9a** (Table 1). As observed in our previously described series (e.g., **1** and **2**, Fig. 1) only moderate 5-HT_{1A} activity and weak NET activity could be attained with unsubstituted B- and C-rings (**9a**).[13,14] Introduction of a fluoro-substituent on the C-ring R^2 position (**9b**) increased both 5-HT_{1A} and NET activity (two- and three-fold increase, respectively). This result was further improved by installing a fluoro-substituent on the B-ring (**9c**) which afforded an additional two-fold increase in 5-HT_{1A} binding affinity. While the 5-HT_{1A} activity of **9c** is comparable to that of **2**, potency at NET was approximately 20-fold weaker. Previous SAR studies in series 2 demonstrated that larger substituents such as a chloro-, methyl-substituent in the R^2 position of the C-ring afforded improved activity at NET while being well tolerated by 5-HT_{1A}. Accordingly, **9d** was prepared which demonstrated that this SAR trend holds true for the ether-linked azetedine series as well, providing a 2.5-fold increase in NET potency over **9c**.

Among the analogs prepared, the best C-ring substitution patterns were 2-fluoro-6-chloro (**9e**) and 2-fluoro-6-methyl (**9f**). These compounds were selected for further evaluation in vivo (vide infra). It is noteworthy that careful selection of the substitution pattern on the B- and C-ring resulted in significant gains in 5-HT_{1A} and NET activity, while the potency at DAT and SERT generally did not increase. In particular, key analog **9e** is devoid of DAT and SERT activity while **9f** exhibited weak potency at SERT. This stands in contrast to **1**, which displays a DAT K_i of 278 nM. Furthermore, DAT and SERT selectivities are particularly sensitive to substitution on the C-ring R^4 position as exemplified by **9j** in which selectivity for NET over DAT and SERT is completely lost.

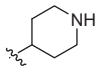
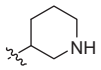
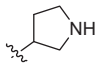
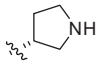
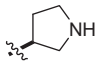
We next turned our attention to examining the effect of changing the size of the A-ring heterocycles (Table 2). While piperidine analogs **13b–d** displayed similar binding affinity at 5-HT_{1A} as the corresponding azetidines **9c**, **9e**, **9f**, their functional 5-HT_{1A} activity was considerably lower (data not shown). Moving the piperidine nitrogen from the 4-position to the 3-position (e.g., **14a**) resulted in significantly less in potency at both NET and 5-HT_{1A} as compared to the corresponding 4-piperidine **13b** and 3-azetidine **9c**. The pyrrolidine derivatives **15a–g** on the other hand appeared more promising (Table 2). In particular, racemic pyrrolidine **15e**, which incorporates a 2-chloro-6-fluoro substitution pattern on the C-ring exhibited K_i of 3 nM at 5-HT_{1A} and 226 nM at NET. The pure enantiomers of **15e** were then prepared starting from commercially available (*R*)- and (*S*)-*N*-Boc-3-hydroxypyrrolidine using Mitsunobu chemistry as in Scheme 1. Interestingly, the *S*-enantiomer **15g** was approximately 10-fold more potent than the *R*-enantiomer **15f** at both 5-HT_{1A} and NET while maintaining excellent selectivity against DAT and SERT.

Having established that ether-linked azetidines and pyrrolidines are suitable A-ring piperidine replacements with improved 5-HT_{1A}/DAT selectivity, we next sought to further improve physicochemical properties by incorporating a pyridyl nitrogen in the B-ring, as this was a successful strategy in Series 2. Heating a mixture of 3-bromo-2-chloropyridine (**16**) and phenol **17** in the presence of cesium carbonate delivered pyridyl ether **18** in 80% yield (Scheme 2). Halogen-metal exchange followed by addition of triisopropyl borate gave **19** (40% yield),[22] which upon oxidation with 30% hydrogen peroxide furnished the requisite phenol **20** in 86% yield. The remainder of the syntheses was carried out as described in Scheme 1, the only difference being that the Mitsunobu reaction of phenol **20** with *N*-Boc-azetedinol required heating to 70 °C to reach completion. Introduction of a pyridyl nitrogen into the B-ring provides improved physicochemical properties (e.g., *c* log *P*). Pyrrolidine **22** exhibited weaker affinity for both 5-HT_{1A} and NET whereas azetedine **24** showed an improvement in potency at NET as compared to the corresponding biaryl ethers **9a–j** (Table 3).

Table 2
Binding and selectivity of ether-linked pyrrolidine and piperidine analogs

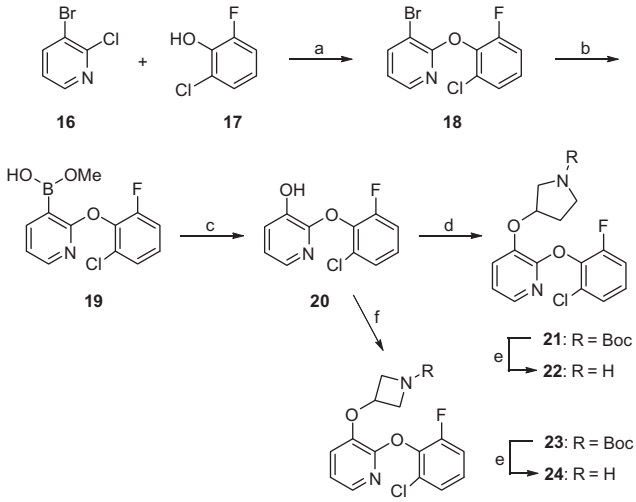


13-15

	R	R^1	R^2	R^3	5-HT_{1A} K_i[a] (nM)	NET K_i[b] (nM)	DAT K_i[b] (nM)	SERT K_i[b] (nM)
13a		H	F	H	693	1000	4510	>4710
13b		F	F	H	30	489	2190	>4650
13c		F	F	Cl	8	218	>6370	2040
13d		F	F	Me	4	323	>6460	3250
14a		F	F	H	90	1950	>5590	>4710
15a		H	F	H	193	1350	>6220	>4710
15b		F	F	H	8	1020	3880	>4710
15c		F	Cl	H	19	192	2030	2230
15d		F	F	Me	4	328	>6460	>4690
15e		F	F	Cl	3	226	>6460	>4900
15f		F	F	Cl	13	1010	>5870	>4530
15g		F	F	Cl	1	110	>5870	>4530

[a] 5-HT_{1A} RBSHA binding assay; K_i values are the mean of at least two experiments carried out in duplicate.[20]

[b] Monoamine transporter binding scintillation proximity assay (SPA); K_i values are the mean of at least two experiments carried out in duplicate.[21]

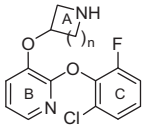


Scheme 2. Reagents and conditions: (a) Cs_2CO_3, DMSO, 140 °C, 80%; (b) *n*BuLi −78 °C; then $B(OiPr)_3$, −78 °C to rt; MeOH, 40%; (c) 30% H_2O_2, CH_2Cl_2, 86%; (d) *tert*-butyl-3-(methylsulfonyloxy)pyrrolidine-1-carboxylate, Cs_2CO_3, CH_3CN, reflux, 56%; (e) AcCl, MeOH, (89–94%); (f) *tert*-butyl-3-azetidine-1-carboxylate, DIAD, PPh_3, THF, 70 °C, 83%.

Without the B-ring fluoro-substituent, however, only moderate affinity for 5-HT_{1A} was observed. Introduction of the B-ring fluoro-substituent *para* to the pyridyl nitrogen was therefore attempted, but these efforts were hampered by chemical instability.

A subset of these compounds with promising activity and selectivity in the monoamine and 5-HT_{1A} in vitro binding and functional assays were selected for further profiling using ex vivo receptor

Table 3
Binding and selectivity of pyridyl analogs **22** and **24**



	n	5-HT$_{1A}$ K_i[a] (nM)	NET K_i[b] (nM)	DAT K_i[b] (nM)	SERT K_i[b] (nM)	*c* log *P*
22	2	203	1140	>4620	>6130	2.84
24	1	64	73	>4260	>6280	2.83

[a] 5-HT$_{1A}$ RBSHA binding assay; K_i values were determined in a single experiment carried out in duplicate.[20]
[b] Monoamine transporter binding scintillation proximity assay (SPA); K_i values were determined in a single experiment carried out in duplicate.[21]

Table 4
Functional activity and in vivo occupancy at 5-HT$_{1A}$ receptor and NET

	5-HT$_{1A}$ EC$_{50}$[a] (nM)	5-HT$_{1A}$ % IA[a]	NET EC$_{50}$ (nM)[b]	Receptor occupancy (% at 10 mg/kg s.c.)[27]	
				5-HT$_{1A}$	NET
1	341	84	28	62 ± 3	80 ± 2
9e	197	88	40	81 ± 1	87 ± 2
9f	225	84	239	76 ± 2	84 ± 1
15e/g	77[c]	79[c]	97[d]	73 ± 2[d]	54 ± 1[d]

[a] 5-HT$_{1A}$ GTPγS functional assay; EC$_{50}$ and intrinsic activity (IA) values are the mean of at least two experiments carried out in duplicate.[28]
[b] NET functional assay; EC$_{50}$ values are the mean of at least two experiments carried out in duplicate.[29]
[c] Determined for single enantiomer **15g**.
[d] Determined for racemate **15e**.

occupancy.[23] Table 4 highlights functional and receptor occupancy data for azetidines **9e** and **9f** and pyrrolidine **15e/g**. High 5-HT$_{1A}$ intrinsic activity was observed for all three compounds with 88%, 84%, and 79% agonism, respectively, which compares well to **1**. Following 10 mg/kg subcutaneous dosing, the three lead compounds were shown to be brain penetrant and exhibiting excellent binding to the target receptors in vivo. A dose–response was generated for azetidine **9e** indicating a NET ID$_{50}$,[24] of 1.2 mg/kg and a 5-HT$_{1A}$ ID$_{10}$,[25] of less than 1 mg/kg. Additionally, compounds **9e**, **9f**, and **15g** were shown to have good oral exposure as determined in a dog pharmacokinetic study.[26]

In summary, we have developed a novel biaryl-ether series displaying dual NRI and 5-HT$_{1A}$ partial agonist pharmacology. Our main design objective was to identify a replacement for the A-ring piperidine of **1** that would drive reduced potency at the dopamine transporter while maintaining or improving 5-HT$_{1A}$ partial agonist pharmacology. This goal was achieved through the identification of an oxygen-linked azetidine or pyrrolidine moiety as a suitable piperidine A-ring replacement. It is noteworthy that in the case of azetedine lead compound **9e**, optimization of the pharmacological profile relative to **1** was achieved without an increase *c* log *P* while also affording a reduction in the pK_a. As observed in Series 1 and 2, selectivity for NET over DAT and SERT was found to be highly dependent on the sterics and electronics associated with the C-ring substitution pattern. Finally, key compounds were evaluated in vivo and were shown to be brain penetrant and to display excellent receptor occupancy at 5-HT$_{1A}$ and NET.

Acknowledgments

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17. 1.5 equiv of each reagent were initially added, and an additional 1.5 equiv of each reagent were added at the 8 h time point.
18. The reactions were complete after stirring at 50 °C overnight (ca. 16 h).
19. Anhydrous HCl was generated by the addition of AcCl to MeOH at 0 °C.
20. Assay conducted as described in Graham, J. M.; Coughenour, L. L.; Barr, B. M.; Rock, D. L.; Nikam, S. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 489.
21. The affinity of test compounds for binding to human NET, DAT, and SERT were assessed by measuring inhibition of binding to [^{3}H]nisoxetine, [^{3}H]WIN 35,428, and [^{3}H]citalopram, respectively, using a scintillation proximity assay. Assay protocol is described in Ref. 14
22. While the boronic acid was isolated upon aqueous work-up, following purification by column chromatography on silica eluting with 20–45% ethyl acetate in heptane, concentration of the solvents under reduced pressure, and co-evaporation from methanol, the mixed boronate ester **19** was obtained as the sole product.
23. Grimwood, S.; Hartig, P. R. *Pharmacol. Ther.* **2009**, *122*, 281.
24. Dose at which 50% receptor occupancy was observed.
25. Dose at which 10% receptor occupancy was observed. The minimal pharmacologically active dose is typically observed at 5–10% 5-HT$_{1A}$ receptor occupancy using competitive agonist binding assays.
26. Dog plasma exposures (C_{max}) for **9e**, **9f**, **15g** at the 1 h time point (T_{max}) following 5 mg/kg p.o. dosing were = 919, 525, and 146 ng/ml (n = 2), respectively. The corresponding AUC exposures (extrapolated from 0–24 h) for **9e**, **9f**, **15g** were = 3480, 2800, and 560 ng h/ml, and the half-life in dog plasma was 2.35, 3.01, and 1.85 h (n = 2), respectively.
27. Ex vivo receptor occupancy data were collected at 1 h post-dose for **1**, **9e**, **9f**, **15e** following subcutaneous administration. Total brain drug concentration for **1**, **9e**, **9f**, **15e** were = 2230 ± 179, 5900 ± 585, 5690 ± 370, 5620 ± 555 ng/ml (mean ± SEM, n = 4), respectively.
28. Assay conducted as described in published protocol: Newman-Tancredi, A.; Assie, M.-B.; Martel, J.-C.; Cosi, C.; Slot, L. B.; Palmier, C.; Rauly-Lestienne, I.; Colpaert, F.; Vacher, B.; Cussac, D. *Br. J. Pharmacol.* **2007**, *151*, 237.
29. Monoamine functional assay conducted as described in Ref. 13