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Novel 4-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)methylbenzofuran derivatives as selective α_{2C}-adrenergic receptor antagonists

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Abstract—The synthesis of a series of 4-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)methyl-2-arylbenzofuran and 4-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)methylbenzofuran-2-carboxamide derivatives as novel α_{2C}-adrenergic receptor antagonists are described. Their affinity at three different human α_2-adrenergic receptors is reported, and some of these compounds exhibited high affinity for the α_{2C}-adrenergic receptor with high subtype selectivity. Among them, compound **10e** has been found to show the anti-L-dopa-induced dyskinetic activity in marmosets. The structure–activity relationship of these compounds is also discussed.

Adrenergic receptors (ARs) are membrane proteins belonging to the superfamily of G-protein-coupled receptors and are pharmacologically classified into α_1-, α_2-, and β-ARs.[1] In particular, α_2-ARs are further subdivided into α_{2A}, α_{2B}, and α_{2C} subtypes, encoded by different genes in different species.[2] This knowledge has led to a search for selective ligands for each subtype.

Parkinson's disease (PD) is the second most common progressive neurological disorder resulting from the degeneration of nerve cells (neurons) in a region of the brain that controls movement. It has been reported that within 5 years of beginning treatment with the L-3,4-dihydroxyphenylalanine (L-dopa), 40–80% of patients develop dyskinesia, a severely disabling condition with chaotic and uncontrollable movements of limbs, face, and mouth, that often necessitates long-term hospitalization or even lifetime nursing home care.[3–5] There are no pharmaceutical agents presently approved for the treatment of dyskinesia.

Idazoxan (**1**) and yohinbine (**2**) are known to be potent and selective α_2-AR antagonists. Henry et al. reported that idazoxan (**1**) and yohinbine (**2**) reduced L-dopa-induced dyskinesia in the MPTP-treated marmoset model of PD. Furthermore, they described that coadministration of idazoxan (**1**) with L-dopa can provide an anti-parkinsonian action more than twice the length of that seen with L-dopa alone.[6] Besides idazoxan (**1**) and yohinbine (**2**), a potent α_2-AR antagonist fipamezole (JP-1730) was recently reported to reduce L-dopa-induced dyskinesia in the MPTP-treated marmoset model of PD.[7] On the other hand, according to studies using the knockout mouse of each subtype of α_2-AR, it was supposed that α_{2A}- and α_{2B}-AR may participate in lowering and raising of blood pressure, respectively, however, α_{2C}-AR probably does not take part in the regulation of blood pressure.[8] Based on the above facts, we assumed that selective α_2-AR antagonists would be anti-dyskinetic and anti-parkinsonian agents with a little influence to the cardiovascular system.

The discovery of a novel series of triazolopyrimidines (e.g. **3**) as α_{2C}-AR antagonists and their structure–activity

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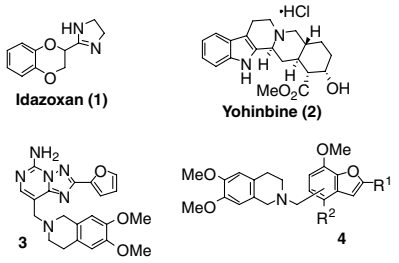
relationship (SAR) were recently reported.[9] During the SAR studies, it was revealed that 6,7-dimethoxy-tetrahydroisoquinoline (6,7-DMTHIQ) structure is important to represent high α_{2C}-AR affinity and subtype selectivity. However, subtype selectivity of **3**, one of the optimized compounds, was insufficient.



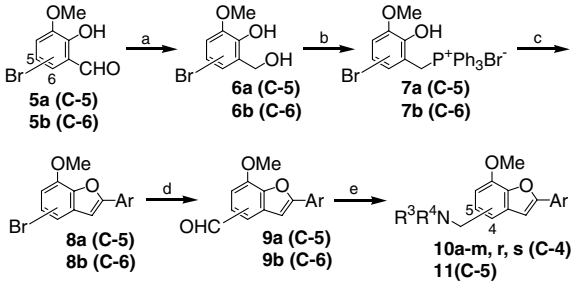
In the drug design approach, replacement of the core scaffold of a known active to another one is known as one of effective techniques to find new active chemotypes. We therefore focused our attention to the structural homology between triazolopyrimidine and other ring systems. With the aim of further enhancing subtype selectivity, we decided to replace the core structure to the benzofuran scaffold which was thought to be easier to introduce functional groups at various positions and make several types of benzofuran analogs which have 6,7-DMTHIQ. We herein describe the synthesis of 4-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)methyl-2-arylbenzofuran, 4-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)methylbenzofuran-2-carboxamide, and their regioisomers (**4**), and the SAR study as novel α_{2C}-AR selective antagonists (see Table 1).[10]

The target compounds were synthesized as shown in Schemes 1–6. 4- or 5-Aminomethyl-2-arylbenzofuran derivatives **10a**–**m**, **r**, **s** and **11** were synthesized as shown in Scheme 1. 2-Arylbenzofurans **8a** and **b** were derived from commercially available bromosalicyl-aldehydes **5a** and **b** by known literature procedures, respectively.[11] Halogen-metal exchange was accomplished by treatment of **8** with butyllithium at −90 °C, and obtained Ar–Li species were quenched quickly with DMF at −90 °C to suppress generation of regioisomers of **9**.[12] Reductive amination of a formyl group with 6,7-DMTHIQ gave target compounds **10a**–**m** and **11**, respectively. Compounds **10r** and **s** were also synthesized by a similar method as above using 1,2,3,4-tetrahydroisoquinoline or 4-phenylpiperadine, respectively.

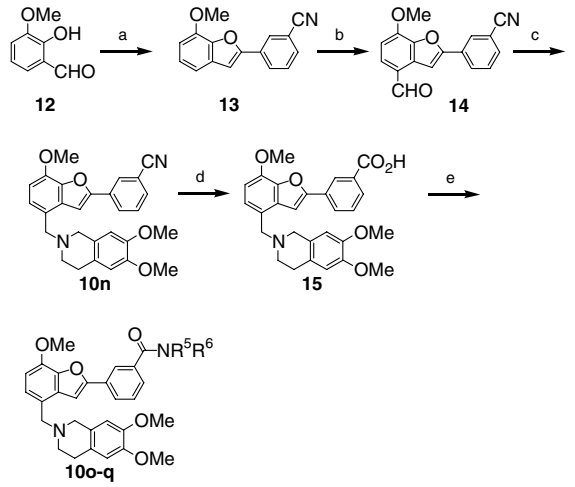
Table 1. Binding activity of α_{2C}-AR antagonists

Compound	Binding affinity (K_i, nM)[a,b]		
	α_{2A}	α_{2B}	α_{2C}
Idazoxan (**1**)	8	100	19
Yohinbine (**2**)	1.8	15	1.9
3	400	370	19

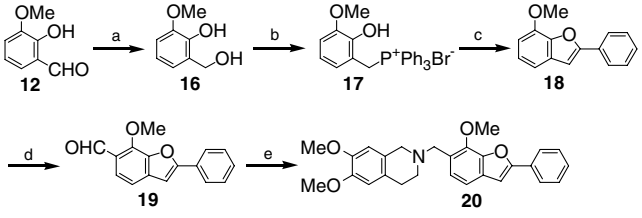
[a] The assay protocol is described in Ref. 18.
[b] Values are means of at least two independent assays.



Scheme 1. Reagents and conditions: (a) $NaBH_4$, MeOH, rt; (b) Ph_3P, aq. HBr, CH_3CN, reflux; (c) ArCOCl, Et_3N, toluene, reflux; (d) *n*-BuLi, THF, −90 °C, then DMF; (e) $NaBH(OAc)_3$, R^3R^4NH, $(CH_2Cl)_2$, rt.

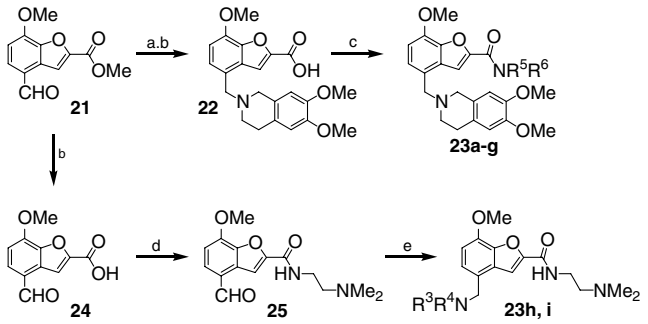


Scheme 2. Reagents and conditions: (a) K_2CO_3, KI, 3-(bromomethyl)-benzonitrile, DMF, reflux; (b) MFA, $(Cl_2PO)_2O$, rt; (c) $NaBH(OAc)_3$, 6,7-DMTHIQ, $(CH_2Cl)_2$, rt; (d) 5 mol/L aq. NaOH, $(CH_2OH)_2$, 150 °C; (e) R^5R^6NH, EDCI, HOBt, DMF, rt.

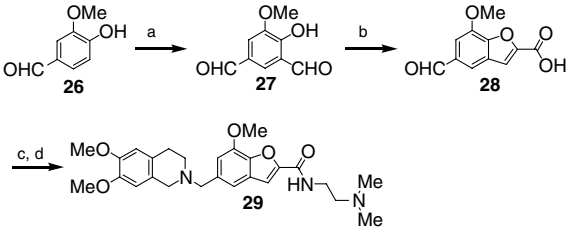


Scheme 3. Reagents and conditions: (a) $NaBH_4$, MeOH, rt; (b) Ph_3P, aq. HBr, CH_3CN, reflux; (c) PhCOCl, Et_3N, toluene, reflux; (d) $TiCl_4$, Cl_2CHOCH_3, CH_2Cl_2, −20 °C to rt; (e) $NaBH(OAc)_3$, 6,7-DMTHIQ, $(CH_2Cl)_2$, rt.

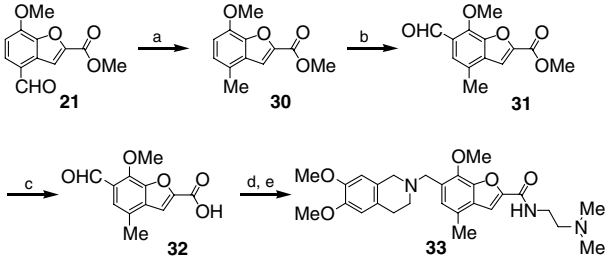
Compounds **10n**–**q** were prepared as shown in Scheme 2. *O*-Alkylation of *ortho*-vanillin **12** followed by intra-molecular cyclizaion in basic condition gave cyano-phenylbenzofuran **13** at one effort. Formylation using *N*-methylformanilide (MFA) and $(Cl_2PO)_2O$[13] proceeded regioselectively to give **14**. Other formylation conditions, such as using DMF-$POCl_3$,[13] $(CH_3)S^+S(CH_3)BF_4^-$-$(PhS)_3CH$,[14] TFA–hexamethylene-tetramine (HMT),[15] and $TiCl_4$-Cl2CHOCH$_3$,[16] were not effective due to low regioselectivity and low yield.



Scheme 4. Reagents and conditions: (a) 6,7-DMTHIQ, $NaBH(OAc)_3$, $(CH_2Cl)_2$, rt; (b) aq. NaOH, MeOH–H_2O, rt; (c) R^5R^6NH, EDCI, HOBt, DMF or $CHCl_3$, rt; (d) $Me_2NCH_2CH_2NH_2$, EDCI, HOBt, DMF, rt; (e) R^3R^4NH, $NaBH(OAc)_3$, $(CH_2Cl)_2$, rt.



Scheme 5. Reagents and conditions: (a) HMT, TFA, reflux; (b) Cs_2CO_3, $BrCH_2CO_2Et$, DMF, reflux; (c) $Me_2NCH_2CH_2NH_2$, EDCI, HOBt, DMF, rt; (d) 6,7-DMTHIQ, $NaBH(OAc)_3$, $(CH_2Cl)_2$, rt.



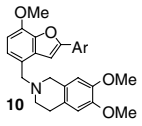
Scheme 6. Reagents and conditions: (a) H_2, $Pd(OH)_2/C$, EtOH, rt; (b) $TiCl_4$, Cl_2CHOCH_3, CH_2Cl_2, −20 °C to rt; (c) aq. NaOH, MeOH–H_2O, rt; (d) $Me_2NCH_2CH_2NH_2$, EDCI, HOBt, DMF, rt; (e) 6,7-DMTHIQ, $NaBH(OAc)_3$, $(CH_2Cl)_2$, rt.

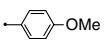
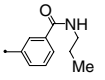
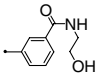
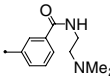
Reductive amination with 6,7-DMTHIQ and hydrolysis of a cyano group afforded carboxylic acid **15**, which was transferred to amides **10o–q** by the standard peptide coupling method (EDCI and HOBt).

6-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)-methyl-2-arylbenzofuran **20** was synthesized as shown in Scheme 3. Formylation of **18**, which was derived from *ortho*-vanillin **12**, gave a mixture of 3-, 4-, and 6-formyl-2-phenylbenzofurans. Compound **19** was isolated from the mixture by silica gel column chromatography and gave **20** by same method described in Scheme 1.

Scheme 4 shows the preparation of various 4-aminomethylbenzofuran-2-carboxamide derivatives. Reductive amination of **21**[17] with 6,7-DMTHIQ and following hydrolysis of the ester group afforded carbox-

Table 2. Binding affinity of 2-arylbenzofuran derivatives



Compound	Ar	Binding affinity (K_i, nM)[a,b]		
		α_{2A}	α_{2B}	α_{2C}
10a		204	160	8.0
10b		135	330	9.6
10c		NT[d]	NT[d]	62%[c]
10d		NT[d]	NT[d]	35%[c]
10e		1742	752	20
10f		11%[c]	20%[c]	54%[c]
10g		2552	804	19
10h		NT[d]	NT[d]	56%[c]
10i		857	299	11
10j		3%[c]	13%[c]	52%[c]
10k		NT[d]	NT[d]	41%[c]
10l		304	949	18
10m		NT[d]	NT[d]	18%[c]
10n		NT[d]	NT[d]	42%[c]
10o		NT[d]	NT[d]	48%[c]
10p		29%[c]	31%[c]	54%[c]
10q		216	584	9.4

[a] The assay protocol is described in Ref. 18.
[b] Values are means of at least two independent assays.
[c] %Inhibition at 0.1 μM ($n = 2$).
[d] Not tested.

ylic acid **22**, which was converted to amides **23a**–**g**. Amidation of **24**, derived by hydrolysis of ester **21**, with *N*,*N*-dimethylethylenediamine using EDCI and HOBt proceeded cleanly to give **25** without affecting a formyl group. Reductive amination of the formyl group afforded **23h** and **i**.

5-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)-methylbenzofuran-2-carboxamide derivative **29** was synthesized as illustrated in Scheme 5. Formylation of vanillin **26** using HMT–TFA[15] gave dialdehyde **27** in moderate yield. The benzofuran scaffold was synthesized by using ethyl bromoacetate and cesium carbonate in DMF to afford **28**. Compound **29** was derived from **28** by a similar manner as that described above.

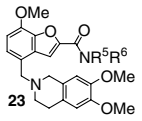
Introduction of 6,7-DMTHIQ at the C-6 position was performed as illustrated in Scheme 6. C-4 Position of the benzofuran scaffold was blocked by a methyl group to introduce a formyl group regioseletively. The formyl group was introduced at *ortho*-position of the methoxy group to afford **31**, which was transferred by the same method as that shown in Scheme 4 to give the target compound **33**. All substances we prepared were characterized by ^{1}H NMR and mass spectroscopy.

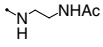
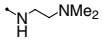
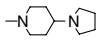
[^{3}H]MK-912 binding experiments were conducted using membranes from human hepatoma cells HepG2. In addition, in order to determine the selectivity over the other α_2 receptor subtypes, [^{3}H]MK-912 binding experiments using membranes from human colon cells HT-29 expressing the α_{2A} receptors and COS-7 cells transfected with the human α_{2B} receptors were performed.[18] The α_2-AR affinity data of the benzofuran derivatives are shown in Tables 2–6.

We initially examined the effect of replacement from the triazolopyrimidine to the benzofuran (Table 2). Compound **10a** showed a slight increase in potency (α_{2C}-AR K_i = 7.7 nM) and retained α_2-subtype selectivity compared to those of the original compound **3**. 2-(Pyridyl)benzofuran **10b** retained α_{2C}-AR affinity and subtype selectivity. Other 2-pyridyl derivatives **10c** and **d** exhibited reduced affinity for α_{2C}-AR. 2-Phenyl derivative **10e** exhibited substantial improvement in subtype selectivity. Encouraged by these results, we investigated the effect of substituents on the phenyl ring of **10e**. Introduction of a *meta*-methoxy group (**10g**) was accompanied by an increase in subtype selectivity for α_{2A}-AR affinity, whereas introduction of a methoxy group at the *ortho*- or *para*-position (**10f** and **h**) resulted in reduction of the activity for α_{2C}-AR. On the other hand, the *ortho*-fluorophenyl (**10i**) and *ortho*-CF_3 (**10l**) groups were both effective comparing with the corresponding *meta*- or *para*-substitution in terms of potency. The *meta*-cyano group (**10n**) also reduced α_{2C}-AR affinity. Among the *meta*-amide groups (**10o**–**q**), only *N*-[2-(*N*,*N*-dimethylamino)ethyl]amide (**10q**) was found to retain α_{2C}-AR affinity and subtype selectivity.

However, we found it interesting that the activity of those derivatives with *meta*-amide groups (**10o**–**q**) varied depending on the substituents.

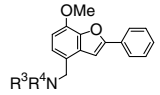
Table 3. Binding affinity of benzofuran-2-carboxamide derivatives

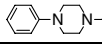


Compound	NR^5R^6	Binding affinity (K_i, nM)[a,b]		
		α_{2A}	α_{2B}	α_{2C}
23a		NT[c]	NT[c]	20%[d]
23b		NT[c]	NT[c]	6%[d]
23c		NT[c]	NT[c]	9%[d]
23d		454	2068	9.4
23e		141	1535	4.2
23f		42	857	0.8
23g		186	1364	3.5

[a] The assay protocol is described in Ref. 18.
[b] Values are means of at least two independent assays.
[c] Not tested.
[d] %Inhibition at 0.1 μM (n = 2).

Table 4. Binding inhibitory activity of benzofuran derivatives

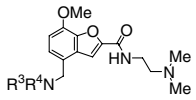


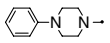
Compound	R^3R^4N	Inhibition % at 0.1 μM[a,b]		
		α_{2A}	α_{2B}	α_{2C}
10r		30	51	54
10s		NT[c]	NT[c]	29

[a] The assay protocol is described in Ref. 18.
[b] Values are means of at least two independent assays.
[c] Not tested.

The results of **10o**–**q** prompted us to design less complex benzofuran derivatives in which an amide moiety is attached to the C-2 position directly. We therefore synthesized a set of benzofuran-2-carboxamide derivatives having a similar side chain as those of **10o**–**q**. The binding affinity for these compounds is shown in Table 3. Compounds **23a**–**c** exhibited significant loss of potency for α_{2C}-AR, however, **23d** showed high affinity. These results were parallel to those of compounds **10o**–**q**. Compounds with various diamino side chains **23e**–**g** also showed the potent affinity; especially, compound **23f** having a quinuclidinyl group showed the potent activity

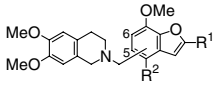
Table 5. Binding inhibitory activity of benzofuran derivatives

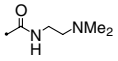
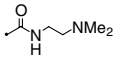


Compound	R^3R^4N	Inhibition % at 0.1 μM[a,b]		
		α_{2A}	α_{2B}	α_{2C}
23h		88	51	94
23i		80	33	68

[a] The assay protocol is described in Ref. 18.
[b] Values are means of at least two independent assays.

Table 6. Binding inhibitory activity of benzofuran derivatives



Compound	R^1	R^2	Position[a]	Inhibition % at 0.1 μM[b,c]		
				α_{2A}	α_{2B}	α_{2C}
11		H	5	NT[d]	NT[d]	19
20		H	6	NT[d]	NT[d]	39
29		H	5	NT[d]	NT[d]	41
33		Me	6	20	15	65

[a] Substituted position on benzofuran.
[b] The assay protocol is described in Ref. 18.
[c] Values are means of at least two independent assays.
[d] Not tested.

against α_{2C}-AR (K_i = 0.8 nM). Subtype selectivity was obviously different to that of 2-arylbenzofurans.

Next, we examined the effect of the 6,7-DMTHIQ moiety on the potency and subtype selectivity (Tables 4, 5). Compound **10r** retained potency against α_{2C}-AR. However, subtype selectivity was lower than that of the 6,7-DMTHIQ derivative **10e**. Replacement with 1-phenylpiperazinyl (**10s**) showed a loss of potency. Compounds **23h** and **i** showed potent activity against α_{2C}-AR, however, subtype selectivity of these compounds was low. Therefore, it was verified that the 6,7-DMTHIQ group is important to show high subtype selectivity as well as potency against α_{2C}-AR. Furthermore, we examined the substitution pattern of the 6,7-DMTHIQ moiety. Substitution of the moiety at the C-5 or C-6 position was not effective to exhibit high activity against α_{2C}-AR (Table 6).

In vivo activity of the compounds **10e** and **23d** against L-dopa-induced dyskinesia in MPTP-treated common marmosets, previously primed by exposure to L-dopa to exhibit dyskinesia, was assessed.[19] Compound **10e** showed potent anti-L-dopa-induced dyskinetic activity (2.5 mg/kg, po) without influence to the cardiovascular system. However, significant activity was not observed in the case of compound **23d** (30 mg/kg, po). The PK study of **10e** and **23d** by cassette dosing in marmosets (at 2.5 mg/kg each) revealed that AUC of **23d** (144 ng h/mL) was low in comparison with that of **10e** (11 ng h/mL).[20] Low intestinal absorption of **23d** due to the presence of two basic nitrogen atoms would be one of the reasons for low anti-L-dopa-induced dyskinetic activity of **23d**. We are estimating that selective α_{2C}-AR antagonists will have therapeutic potential for the treatment of L-dopa-induced dyskinesia. Detailed pharmacological properties of these compounds will be reported elsewhere.

In conclusion, a novel class of α_{2C}-AR antagonists has been identified by exploration of the benzofuran derivatives by replacement of core structure. 2-Arylbenzofuran derivatives and benzofuran-2-carboxamide derivatives were shown to have potent α_{2C}-AR affinity. Compound **10e** exhibited anti-L-dopa-induced dyskinetic activity in the MPTP-treated marmoset model.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2006.12.094.

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18. α_2-AR binding was evaluated in in vitro assay to define their affinity at the three subtypes. Cell membrane was prepared from HepG2, which is a human hepatoma cell line and has been reported that only the α_{2C} receptor subtype among three α_2 receptor subtypes is expressed, a human colon cell line HT-29 expressing the α_{2A} receptors, and COS-7 cells transfected with the human α_{2B} receptors, according to description by Schaak et al.[21] Competition assays were started by mixing 1 nmol/L [^{3}H]MK-912 with or without test compounds and the perspective membranes (50 μg for α_{2A}, 1 μg for α_{2B}, and 100–150 μg for α_{2C}), in assay buffer [50 mmol/L Tris–HCl (pH 7.5), 0.5 mmol/L $MgCl_2$]. The assays were incubated at 25 °C for 30 min and terminated by filtration through Whatman GF/C filters under reduced pressure using a MT-24 cell harvester. Filters were washed three times with ice-cold assay buffer and placed in scintillation vials. Bound radioactivity was determined using a liquid scintillation counter, Packard TRI-CARB 4530. Non-specific binding was assessed in the presence of 1 μmol/L phentolamine for α_{2A} and 10 μmol/L yohimbin for α_{2B} and α_{2C} adrenergic receptors.
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