Synthesis, *In Vitro* Activities of (2-Cyclopropoxyphenyl)piperidine Derivatives for α_{1a} and α_{1d} Adrenergic Receptor Inhibitors

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Abstract: An α_{1a}– and α_{1d}–adrenergic receptor (AR) selective antagonist may be a more efficacious treatment for BPH/LUTS patients and may have fewer side effects than the existing pharmaceuticals. A facile synthesis for a series of (2-cyclopropoxyphenyl)piperidine derivatives has been developed, in which aryl vinyl ether formation and subsequent cyclopropyl formation provide efficient access to key intermediate *N*-Boc-4-(2-cyclopropoxyphenyl)piperidine. The synthesized (2-cyclopropoxyphenyl)piperidine derivatives display high affinity and selectivity for α_{1a}–AR and α_{1d}–AR compared to α_{1b}-AR and D_2 receptor, K_i values for α_{1a}-AR are 0.91 nM to 79.0 nM and α_{1d}-AR are 2.0 nM to 57 nM; K_i values for α_{1b}-AR are 107 nM to 839.8 nM and D_2 receptor are 66.2 nM to 187.1 nM. The selectivity ratios of $Ki(\alpha_{1b})/Ki(\alpha_{1a})$ are 11 to 155 fold, $Ki(\alpha_{1b})/Ki(\alpha_{1d})$ are 6 to 171 fold, $Ki(D_2)/Ki(\alpha_{1a})$ are 2 to 158 fold, and $Ki(D_2)/Ki(\alpha_{1d})$ are 1.2 to 89 fold. Compound **17a** shows improved stability in human liver microsome test ($t_{1/2}$ = 18 minutes).

INTRODUCTION

Our laboratory has recently been engaged in research directed toward treatment of benign prostatic hyperplasia (BPH), a non-malignant enlargement of the prostate characterized by both filling symptoms such as urgency, incontinence, and nocturnia, and voiding symptoms such as weak stream, hesitancy, incomplete bladder emptying, and abdominal straining. BPH is a serious medical problem in a large segment of the elderly male population and is a cause of lower urinary tract symptoms (LUTS), which also develop in women of a certain age [1]. One method of current treatment for BPH/LUTS is administration of non-selective or minimally sub-type selective α_1 adrenergic receptor (AR) antagonists [2]. Studies have suggested that an α_{1a}–AR and α_{1d}–AR selective antagonist may be a more efficacious treatment for BPH/LUTS patients and may have fewer side effects than the existing pharmaceuticals. A program within our drug discovery team has led us to explore a number of chemical series targeted at this kind of antagonist profile. We have reported a series of 1,4-cyclohexylamine-derived compounds that are potent and selective α_{1a}–AR and α_{1d}–AR inhibitors [3-6]. Many of these compounds contain an *iso*-propoxyphenyl moiety that is important for good AR affinity and subtype selectivity. Because *iso*-propoxy may be susceptible to metabolic degradation, we sought to replace it with a less labile group that maintained its attractive AR binding properties.

Because of their unique properties, cyclopropyl groups and substituted cyclopropyl moieties have been implemented in many research drug candidates with broad therapeutic applications. These elements are widely used in fluroquinolones developed for the treatment of infectious diseases. Moxifloxacin, an 8-methoxyfluoroquinolone with a cyclopropyl-moiety at the N1 position of the quinolone core structure, is an inhibitor of DNA gyrase, an enzyme essential for bacterial growth and replication, that has been approved for the treatment of acute respiratory infections such as community-acquired pneumonia, intra-abdominal infections, acute sinusitis and skin infections [7]. N1-cyclopropyl fluoroquinolones having an additional methoxy group at the C8 position show increased ability to prevent wild-type populations of M. tuberculosis from becoming resistant [8]. DW-224a, another fluoroquinolone with a cyclopropyl-moiety at the N1 position , is a promising agent for respiratory tract infections. It has potent activity not only against a battery of 353 quinolone-sensitive pneumonococi but also against 29 quinolone-resistant strains [9]. Sitafloxacin, an 8-chlorofluoroquinolone with a 2'-fluorocyclopropyl-moiety at the N1 position, is one of the most potent quinolones against a broad range of the Gram positive and most of the Gram negative organisms [10]. Other fluoroquinolones with a cyclopropyl-moiety at the N1 position , e.g. ciprofloxacin, moxifloxacin, grepafloxacin, and sparfloxacin, are found to upregulate hematopoiesis, which reveals their immunomodulatory effects [11]. Pitavastatin, the (+)-monocalcium salt of bis [(3R, 5S, 6E)-7-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinolyl]-3,5-dihydroxy-6-heptenoate], is a potent HMG-CoA reductase inhibitor that decreases plasma cholesterol and triglycerides (TG) and inhibits the accumulation of lipids into macrophages and the intimal thickening [12]. NN414, a cyclopro-

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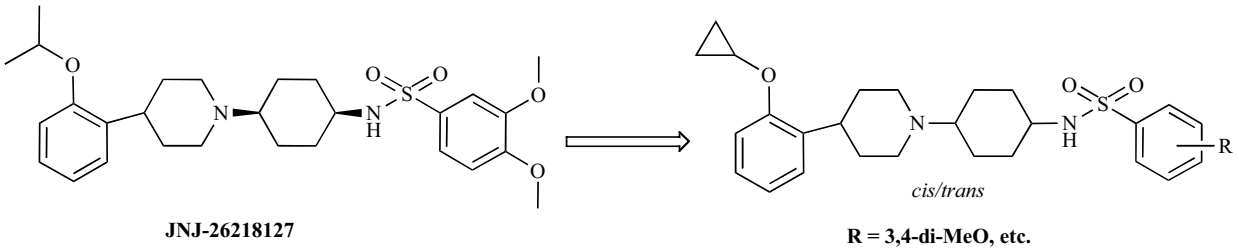


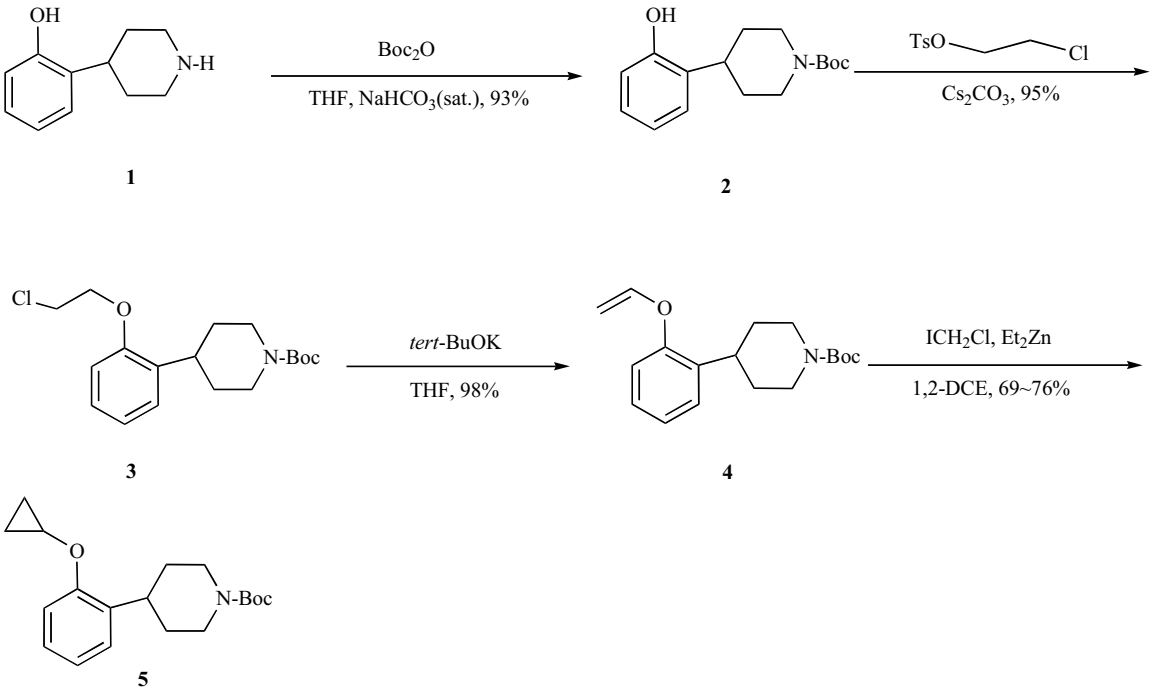
Scheme 1. *N*-{4-[(4-(2-cyclopropoxyphenyl)piperidin-1-yl)cyclohexyl]benzenesulfonamides.

pyl substituted sulfonylurea, is a selective opener of the pancreatic β-cell potassium channel. In a 21-day study in the ZDF (fa/fa) rat model, NN414 reduces fasting blood glucose levels and improves glucose tolerance, thus showing promising for treatment of type 2 diabetes [13]. The cyclopropyl derived bicyclohexyl and bicycloheptyl ureas have demonstrated utility as orally active MCH1-R antagonists in rodent models and may be useful for treatment of obesity [14,15]. Zoniporide or CP-597396, [1-(quinolin-5-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl-guanidine], is a potent and selective inhibitor of the human sodium-hydrogen exchanger isoform 1 (NHE-1). It represents a novel class of potent and selective human NHE-1 inhibitors with potential utility for providing cardioprotection in a clinical setting [16]. Cyclopropyl antiestrogens have demonstrated activity as a new class of antitumor agents for the treatment of breast cancer [17]. The cyclopropylcarboxylic acid derived bicyclohexyl aminoacids, e.g. LY354740 and LY404039, are mGluR2/3 agonists that represent a novel potential treatment of schizophrenia [18].

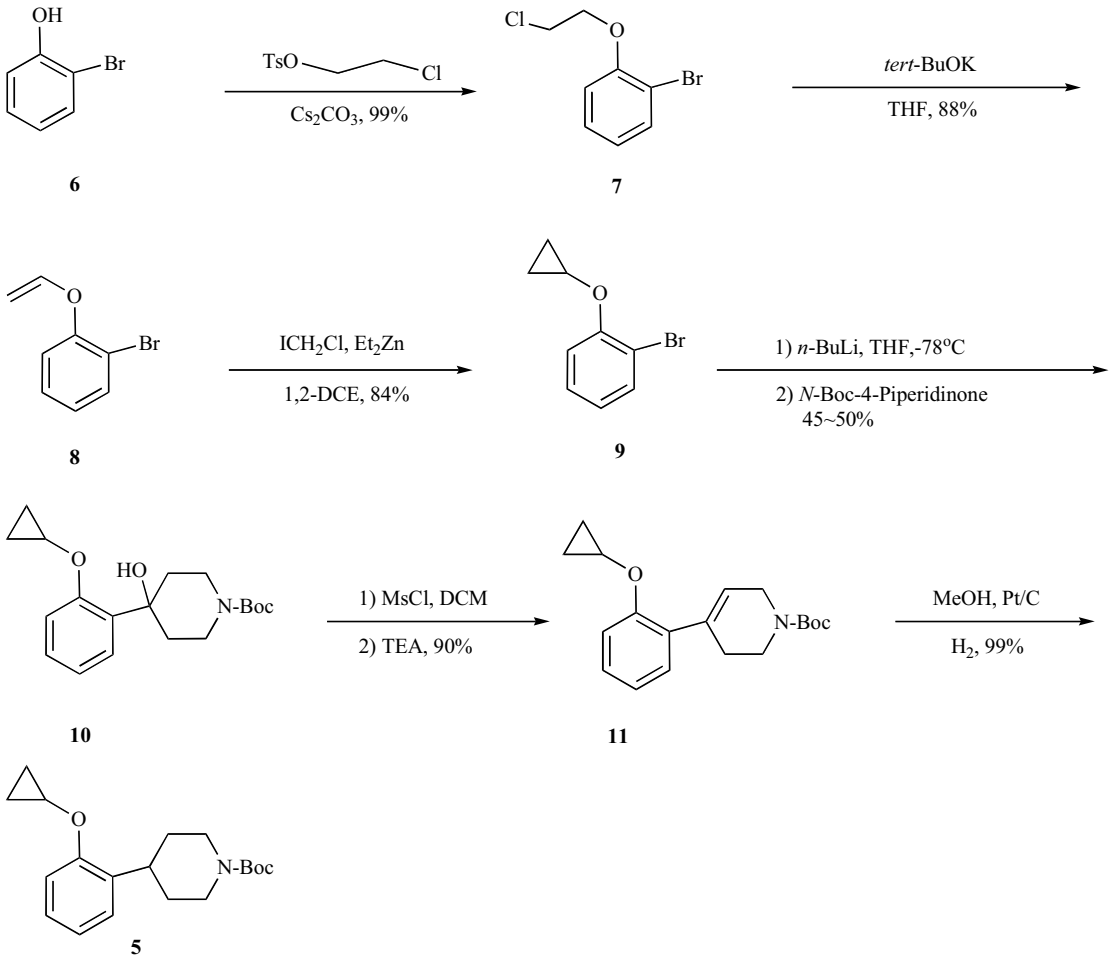
As demonstrated in the literature, cyclopropyl is a useful replacement for an alkyl group, especially for the *iso*-propyl group. One of its most important applications is replacing an alkyl group attached to a heteroatom (e.g., O, N, etc.) to reduce the liability for metabolic dealkylation. Nevertheless, very few precedents incorporating a cyclopropyl group in an adrenergic receptor antagonist for BPH treatment have been reported. As an expansion of structure-activity relationship (SAR) studies for the cyclohexylamine derived α_{1a}–AR and α_{1d}–AR selective inhibitors such as **JNJ-26218127**, we have designed the *N*-{4-[(4-(2-cyclopropoxyphenyl)piperidin-1-yl)]-1-cyclohexyl}benzenesulfonamide series (Scheme **1**). To enable this work, we needed to develop readily access to 4-(2-cyclopropoxyphenyl)piperidine to synthesize such targets. Herein we describe the facile synthesis of *N*-Boc-4-(2-cyclopropoxyphenyl)piperidine (Scheme**s 2**-**3**) and its application to the synthesis of the designed *N*-{4-[(4-(2-cyclopropoxyphenyl)-piperidin-1-yl)]-1-cyclohexyl}benzenesulfonamides (Scheme **4**) by a few steps of simple chemical transformations. This series of compounds has demonstrated potent and selective α_{1a}–AR and α_{1d}–AR inhibitory activity *in vitro* (Table **1**).

SYNTHESIS OF *N*-BOC-4-(2-CYCLOPROPOXYPHENYL)PIPERIDINE

In general, three major approaches may be used to make aryl cyclopropyl ethers. The most direct route is *via* reaction



Scheme 2. Synthesis of *N*-Boc-4-(2-cyclopropoxyphenyl)piperidine from (2-hydroxyphenyl)piperidine.

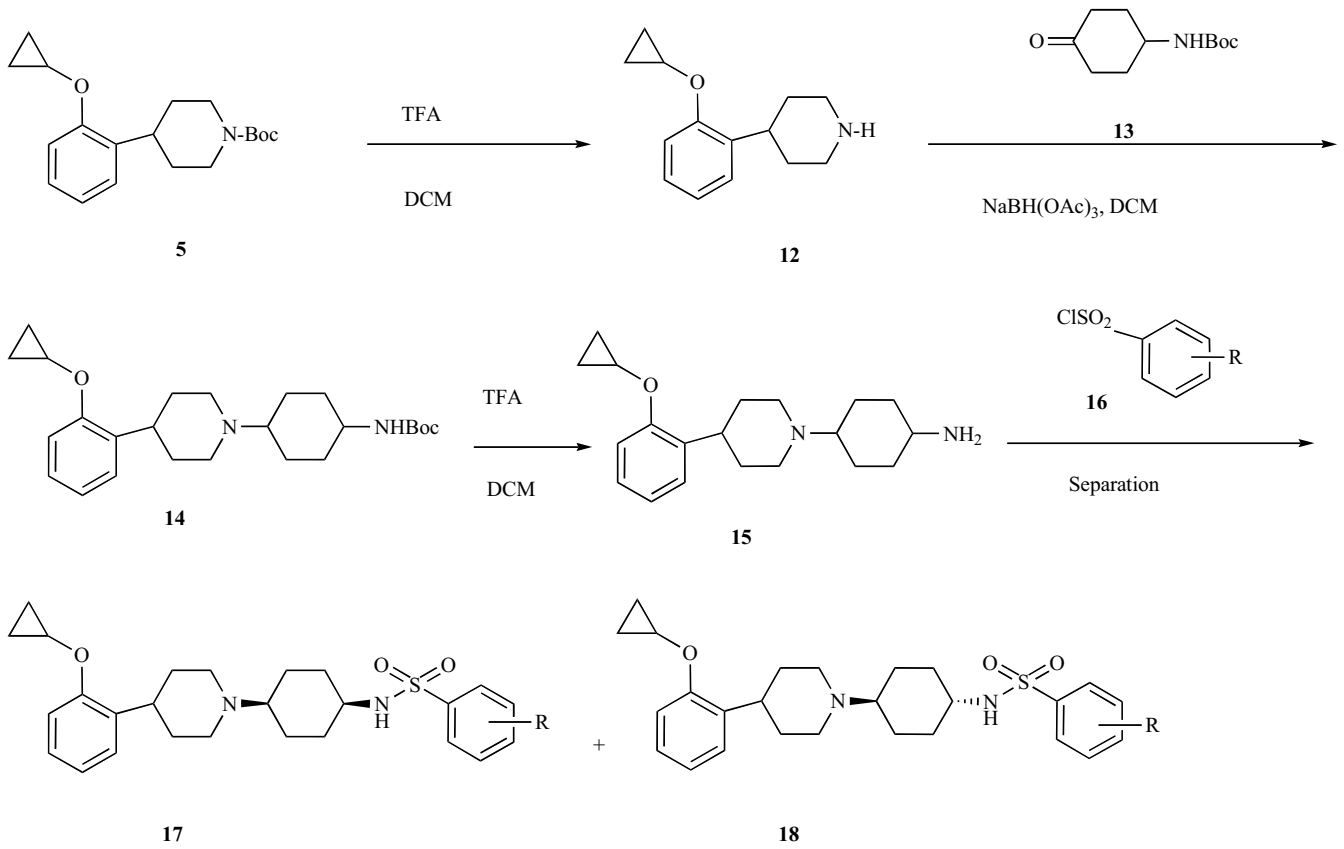


Scheme 3. Synthesis of *N*-Boc-4-(2-cyclopropoxyphenyl)piperidine from 2-bromophenol.

of a phenolic alcohol with cyclopropyl bromide. Although some additives such as silver carbonate/KI/I_2 may facilitate the cyclopropanation, this strategy essentially failed in our hands for substrates such as *N*-Boc-4-(2-hydroxyphe-nyl) piperidine. A minimal modification of this strategy uses an activated cyclopropyl halide such as 1-iodocyclopropyl-phenylthioether [19]. After formation of the aryl cyclopropyl ether, the activating group is removed by oxidation to SO_2Ph and subsequent chemical reduction. However, this method also proved to be inefficient. We observed only trace amounts of *N*-Boc-4-[2-(1-phenylsulfanyl-cycloproxy)phe-nyl]piperidine. A second strategy involves reaction of cyclo-propanol with a phenolic alcohol under either Mitsunobu reaction conditions [20] or Whitesides oxidative cross cou-pling conditions [21,22]. Unfortunately, this approach is lim-ited by the reagent, cyclopropanol, which is not readily available. Although ethyl 1-hydroxycyclopropyl-carboxylate [23] may be used as an alternative, thermal decarboxylation of the resultant aryloxy-cyclopropyl carboxylate is an extra step and is sometimes problematic. A third approach builds the cyclopropyl group adjacent to aryl oxide. In principle the cyclopropyl group can be formed by the reaction of carbene and an alkene [24,25]. Schollkopf described the method util-izing arylether carbenoids, which can be generated by the reaction of aryl chloromethyl ethers with *n*-BuLi [26]. This method may be an option if an ethylene cylinder is readily available. On the other hand, the Simmons-Smith reaction [27,28] and its Furukawa variation [29,30] provide a general way to make the cyclopropyl ring, in which the *in situ* gener-ated carbenoids react with an aryl vinyl ether to form the desired aryl cyclopropyl ether. The required aryl vinyl ether can be formed by β-elimination of an aryl 2-chloroethyl ether.

Based on this analysis, we chose to pursue the Simmons Smith/Furukawa route shown in Scheme **2**. Commercially available (2-hydroxyphenyl)piperidine (**1**) was selectively protected in THF to form *N*-Boc-4-(2-hydroxyphenyl)piperi-dine (**2**, 93% yield), which was then alkylated by 2-chloro-ethyl-*p*-toluenesulfonate in the presence of cesium carbonate in DMF at 50°C to give the product, *N*-Boc-4-[2-(2-chloro-ethoxy)phenyl]- piperidine (**3**), in high yield (95%). Subse-quent β-elimination to form the aryl vinyl ether (**4**) pro-ceeded uneventfully at room temperature using *tert*-BuOK in THF. The product *N*-Boc-4-(2-vinyloxyphenyl)-piperidine (**4**) was isolated in almost quantitative yield (98%). This aryl vinyl ether was then treated with Et_2Zn and ICH_2Cl at –40 °C to –15 °C in dry 1,2-dichloroethane to form *N*-Boc-4-(2-cyc-lopropoxyphenyl)piperidine (**5**) in 69-76% yield (Scheme **2**).

Similarly, the cyclopropanation route can be applied to simple phenols. The synthesis starting from 2-bromophenol is outlined in Scheme **3**, in which 2-cyclopropoxyphenyl-



Scheme 4. Synthesis of *N*-{4-[(4-(2-cyclopropoxyphenyl)piperidin-1-yl)]-1-cyclohexyl}benzenesulfonamides.

bromide (**9**) was prepared in 73% overall yield *via* the Simmons Smith/Furukawa cyclopropanation methodology. Compound **9** was subsequently introduced onto the 4-position of *N*-Boc-piperidine by a few straightforward chemical transformations [14] to form *N*-Boc-4-(2-cyclopropoxyphenyl) piperidine (**5**) (Scheme **3**).

SYNTHESIS OF *N*-{-4-[(4-(2-CYCLOPROPOXYPHENYL)}PERIDIN-1-YL)]-1-CYCLOHEXYL}-BENZENESULFONAMIDES

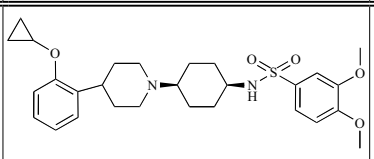
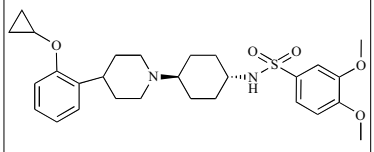
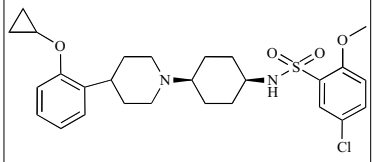
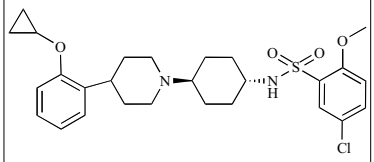
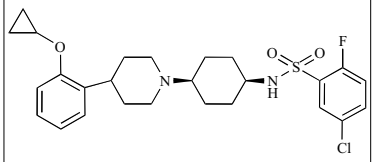
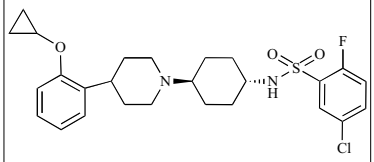
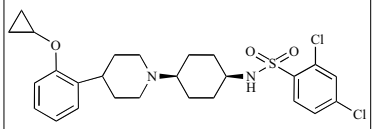
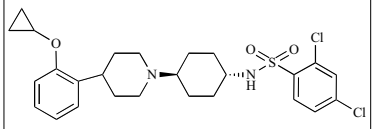
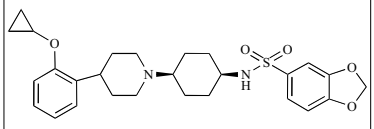
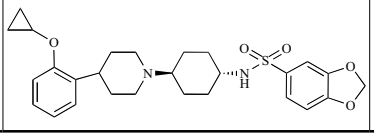
As outlined in Scheme **4**, *N*-Boc-4-(2-cyclopropoxyphenyl)piperidine (**5**) was used for the synthesis of the designed α_{1a}–AR and α_{1d}–AR inhibitors. The cyclopropoxide group of *N*-Boc-4-(2-cyclopropoxyphenyl)piperidine (**5**) was found to be stable to Boc deprotecting conditions with TFA in dichloromethane and reductive alkylation of the resultant 4-(2-cyclopropoxyphenyl)piperidine (**12**) with 4-*N*-Boc-amino-cyclohexanone (**13**) and sodium triacetoxyborohydride. No de-alkylation or decomposition of the cyclopropyl group was observed in these processes. Advanced intermediate 4-[4-(2-cyclopropoxyphenyl)piperidin-1-yl]cyclohexylamine (**15**) that was obtained from **14** in high yield was reacted with arylsulfonyl chlorides (**16**) to form *N*-{4-[4-(2-cyclopropoxyphenyl)piperidin-1-yl]cyclohexyl}benzenesulfonamides (**17**/**18**) in good yields. The *cis* isomers (**17**, with higher R_f value) and *trans* isomers (**18**, with lower R_f value) of the final product were readily separated by silica gel chromatography (5% MeOH/DCM), and their structures were confirmed by comparison of the NMR spectra with those of known compounds that have been assigned *cis* and *trans* configurations by 2-D NMR and X-ray structure.

IN VITRO ACTIVITIES

The binding affinities of **17** and **18** for α_1-adrenergic receptors were determined utilizing a ^{125}I HEAT [(±)-(β-(([^{125}I] 3-iodo-4-hydroxyphenyl)-ethyl)-aminomethyl)-tetralone] radioligand binding assay. In this assay the binding affinities of the synthesized compounds to COS cell membranes expressing the human adrenergic receptor subtypes (α_{1a}-AR, α_{1b}-AR and α_{1d}-AR) were evaluated [3]. The binding affinities for dopamine D_2 receptor using ^{125}I-spiperone were also screened as an indicator of potential CNS effects of this series of compounds. The K_i (nM) values of the synthesized compounds binding to α_{1a}-AR, α_{1b}-AR, α_{1d}-AR, and D_2 receptor, the ratios of $K_i(\alpha_{1b})$ over $K_i(\alpha_{1a})$ and $K_i(\alpha_{1d})$ as well as the ratios of $K_i(D_2)$ over $K_i(\alpha_{1a})$ and $K_i(\alpha_{1d})$ are summarized in Table **1**.

The synthesized *N*-{4-[(4-(2-cyclopropoxyphenyl)piperidin-1-yl)]-1-cyclohexyl}benzenesulfonamides display selective binding affinities for α_{1a}-AR and α_{1d}-AR compared to α_{1b}-AR and D_2 receptor. K_i values for α_{1a}-AR are 0.91 nM to 79.0 nM and α_{1d}-AR are 2.0 nM to 57 nM; K_i values for α_{1b}-AR range from 107 nM to 839.8 nM and D_2 receptor range from 66.2 nM to 187.1 nM. The selectivity ratios $Ki(\alpha_{1b})/Ki(\alpha_{1a})$ are 11 to 155 fold; $Ki(\alpha_{1b})/Ki(\alpha_{1d})$ are 6 to 171 fold; $Ki(D_2)/Ki(\alpha_{1a})$ are 2 to 158 fold; and $Ki(D_2)/Ki(\alpha_{1d})$ are 1.2 to 89 fold. The *cis* isomers (**17a**-**17e**) show stronger binding affinities for α_{1a}-AR and α_{1d}-AR as well as better selectivity

Table 1. ***In Vitro*** **Binding Profile (Ki, nM) of *N*-{4-[4-(2-cyclopropoxyphenyl)piperidin-1-yl]cyclohexyl}benzenesulfonamides**

Compd.	Structure	α_{1a} (K_i, nM)	α_{1b} (K_i, nM)	α_{1d} (K_i, nM)	D_2 (K_i, nM)	α_{1b}/α_{1a}	α_{1b}/α_{1d}	D_2/α_{1a}	D_2/α_{1d}
17a		0.91	141	2	144.2	155	71	158	72
18a		10.8	133	33.6	133.1	12	4	12	4
17b		1.3	82	2.6	129.5	63	32	100	2
18b		4.5	305	47	154.3	68	6	34	3
17c		1.8	107	2.1	187.1	59	51	104	89
18c		3.8	337	32	158.6	89	11	42	5
17d		79.0	839.8	6.0	174.3	11	140	2	29
18d		30.4	411.1	2.4	84.5	14	171	3	35
17e		15.6	275	13	66.2	18	21	4	5
18e		14	340	57	70.7	24	6	5	1.2

against α_{1b}-AR and D_2 receptor than the corresponding *trans* isomers (**18a**-**18e**). This trend is consistent with the SAR (structure activity relationship) observed for other series of analogues that are derived from 1,4-cyclohexyldiamine. The 3,4-dimeoxybenzenesulfonyl group, which has been used as the bench mark group for other series of analogues, has also

been incorporated into a 4-(2-cyclopropoxyphenyl)piperidine derivative (**17a**); this compound is the most potent and selective inhibitor among the synthesized compounds. Its half life ($t_{1/2}$) in a human liver microsomal stability assay has been enhanced to 18 minutes, while the corresponding *iso*-propoxy analogue, *N*-{4-[(4-(2-isopoxyphenyl)piperidin-1-yl)]-1-cyclohexyl}benzenesulfonamide (**JNJ-26218127**), has a half life ($t_{1/2}$) of only 4.9 minutes[6]. This preliminary result suggests that the activity and selectivity of this series are closely related to the functional groups on the benzenesulfonyl moiety and that microsomal stability may be enhanced by replacing the *iso*-propoxy group with cyclopropoxy. In previous work, we reported that replacement of *iso*-propoxy with fluorinated ethoxy groups also improves metabolic stability [6]. In the best example, the analog of **17a** having 2,2,2-trifluoroethoxy in place of cyclopropoxy has a half-life in human microsomes of 56 minutes. Despite its increased stability, however, the 2,2,2-trifluoroethoxy substitution cannot be improved, whereas the cyclopropoxy ring can be further substituted to provide additional analogs that may increase metabolic stability and receptor selectivity, as well as improve other properties beyond that of **17a**. Therefore, the results obtained for **17a-e** and **18a-e** provide a valuable starting point for additional modifications.

CONCLUSION

In summary, we have described the facile synthesis of *N*-{4-[(4-(2-cyclopropoxyphenyl)piperidin-1-yl)]-1-cyclohexyl} benzenesulfonamides from the key intermediate *N*-Boc-4-(2-cyclopropoxyphenyl)piperidine starting from either 4-(2-hydroxyphenyl)piperidine or 2-bromophenol. In the *in vitro* binding assays, the synthesized (2-cyclopropoxyphenyl) piperidine derivatives have demonstrated potent and selective inhibitors of α_{1a}-AR and α_{1d}-AR compared to α_{1b}-AR and D_2 receptor with improved stability in a human liver microsome test.

EXPERIMENTAL SECTION

General

^{1}H NMR spectra were recorded on a Bruker AC-400 (400 MHz) spectrometer using tetramethylsilane(TMS) as an internal standard MS/LCMS data were obtained from Agilent LC/MSD SL or 1000 series LC/MSD instrument.

N-Boc-4-(2-cyclopropoxyphenyl)piperidine (5)

From 4-(2-hydroxyphenyl)-piperidine

The hydrobromide salt of 4-(2-hydroxyphenyl)piperidine **1** (5.00 g, 19.37 mmol) was dissolved in 80 mL of THF, followed by addition of $NaHCO_3$ (sat., 30 mL). The mixture was stirred with Boc_2O (5.07 g, 23.24 mmol) at room temperature overnight (18 h). The reaction mixture was extracted with dichloromethane (DCM, 150 mL X 3) and dried over Na_2SO_4. After column chromatography (silica gel, 10% AcOEt/Hexane), compound **2** (4.56 g, 16.44 mmol) was obtained as a colorless oil in 85% yield.

Compound **2** (0.67 g, 2.42 mmol), 2-chloroethyl-*p*-toluenesulfonate (1.13 g, 4.84 mmol), Cs_2CO_3 (1.60 g, 4.84 mmol), and DMF (20 mL) were heated and stirred at 50 ^{o}C overnight (18 h). The excess DMF was removed under reduced pressure and the white residue was mixed with AcOEt (100 mL), washed with H_2O, and dried over Na_2SO_4. Crude product was obtained by evaporating the filtered dry solution, which was purified using flash chromatography (silica gel, 25% AcOEt/Hexane). Pure compound **3** (0.78 g, yield 95%) was obtained as a colorless sticky oil. LC-MS at 3.943 minutes, m/z 362.1 ($M + Na^+$). Compound **3** (0.78 g, 2.3 mmol) was dissolved in dry THF (20 mL) and cooled to 0 ^{o}C; *tert*-BuOK (1.03 g, 9.2 mmol) was added to the stirring solution. The yellow clear solution was stirred at 0 ^{o}C for 0.5 h and then at r.t. for 2 h until TLC analysis (25% AcOEt/Hexane) indicated that compound **3** had disappeared, whereupon the solution was cooled to 0 ^{o}C again. H_2O (10 mL) was added and the excess THF was removed on a rotary evaporator. The aqueous solution was extracted with AcOEt and dried over Na_2SO_4. Compound **4** (0.72 g, yield 98%) was obtained as colorless oil. LC-MS at 3.863 minutes, m/z 326.1 ($M + Na^+$).

1,2-Dichloroethane (DCE, 20 mL) was cooled to –40 ^{o}C; $ZnEt_2$ (14 mL, 1.0 M hexane) was added to the continuously stirring solution until the white smoke disappeared. Then compound **4** (0.68 g, 2.23 mmol, dissolved into 30 mL of DCE) was added and the mixture was stirred for a few minutes, the solution becoming almost colorless and clear. Chloroiodomethane (1.63 mL, 22 mmol) was added dropwise. The mixture was stirred at –40 ^{o}C to –15 ^{o}C for 8 h. The white turbid mixture was diluted with AcOEt (100 mL) and cooled to –40 ^{o}C; then NH_4Cl (sat., 30 mL) was added, the two layers were separated, and the organic extracts were dried over Na_2SO_4. Crude product was obtained by evaporating the solvent from the filtered dry solution. Pure compound **5** (0.488 g, yield 69%) was obtained as a colorless oil by flash chromatography (silica gel, 10 % AcOEt/Hexane). LC-MS at 4.291 minutes, m/z 262.2 ($M^+ + 1 - 56$). ^{1}H NMR ($CDCl_3$, TMS), δ 0.65-0.85 (m, 3 H), 0.85-0.95 (m, 1 H), 1.48 (s, 9 H), 1.55-1.65 (m, 2 H), 1.68-1.90 (m, 2 H), 2.70-2.92 (m, 2 H), 2.92-3.15 (m, 1 H), 3.68-3.85 (m, 1 H), 4.10-4.35 (br s, 2 H), 6.85-7.00 (m, 1 H), 7.05-7.15 (m, 1 H), 7.15-7.35 (m, 3 H).

From 2-bromophenol

2-Bromophenol **6** (10.00 g, 57.8 mmol), 2-chloroethyl-*p*-toluenesulfonate (13.56 g, 57.8 mmol), Cs_2CO_3 (18.83 g, 57.8 mmol), and DMF (100 mL) were heated and stirred at 70 ^{o}C overnight (18 h). The reaction mixture was cooled to room temperature, diluted with AcOEt (500 mL), washed with water and dried over Na_2SO_4. Evaporation of the filtered dry solution gave crude product as brownish oil. Pure compound **7** (13.51 g, 57.4 mmol) was obtained as a colorless oil in 99% yield from bulb to bulb distillation (120 ^{o}C/0.1 torr.). Compound **7** (13.51 g, 57.4 mmol) was dissolved into dry THF (150 mL) and cooled to 0 ^{o}C; *tert*-BuOK (25.75 g, 229.5 mmol) was added into the stirring solution. The mixture was stirred at 0 ^{o}C for 0.5 h and then at r.t. for 3 h until HPLC analysis indicated that compound **7** disappeared, whereupon the solution was cooled to 0 ^{o}C again. H_2O (65 mL) was added, stirred for 15 min. and upper organic layer was isolated. The aqueous solution was extracted with AcOEt (200 mL) and the combined organic layers were dried over Na_2SO_4. Pure compound **8** (10.02 g, 50.3

mmol) was obtained as colorless oil in 88% yield from bulb to bulb distillation (60-80 °C/0.1 torr.).

$ZnEt_2$ (106.5 mL, 1.0 M in hexane) was cooled to –40 °C and stirred, then compound **8** (3.53 g, 17.72 mmol, dissolved into 40 mL of DCE) was added. The mixture was stirred for 10 minutes, then chloroiodomethane (25 g, 141.7 mmol) was added to form a white suspension that was stirred at –40 °C to r.t. overnight. The white turbid mixture was diluted with AcOEt (200 mL) and cooled to –40 °C; then NH_4Cl (sat., 80 mL) was added, the two layers were separated, and the organic extracts were dried over Na_2SO_4. Crude product was obtained from evaporation. Pure compound **9** (3.17 g, yield 84%) was obtained by column chromatography (silica gel, 100 % Hexane).

Compound **9** (7.44 g, 34.89 mmol) was dissolved into dry THF (120 mL) and cooled to –78 °C. Into the stirring solution, *n*-BuLi (13.9 mL, 2.5 M in hexane) was added. The yellow solution was stirred at –78 °C for another 30 min, then *N*-Boc-4-piperidone (6.954 g, 34.89 mmol) in 50 mL of dry THF was added. The final mixture was stirred and warmed to r.t. gradually (ca. 18 h). The usual aqueous workup gave crude product as yellowish solid. Pure compound **10** (5.83 g, yield 50%) was obtained as a white powder by column chromatography (silica gel, 30 % AcOEt/ Hexane).

Compound **10** (7.00 g, 20.99 mmol) was dissolved into dry DCM (100 mL) and cooled to –78 °C. Into the stirring solution, MsCl (3.25 mL, 41.98 mmol) was added. The yellowish solution was stirred at –78 °C for another 30 min, then NEt_3 (5.84 mL, 41.98 mmol) was added. The final mixture was stirred and warmed to r.t. overnight (ca. 18 h). The usual aqueous workup gave crude product as yellowish oil. Pure compound **11** (5.958 g, yield 90%) was obtained as a colorless oil by column chromatography (silica gel, 30 % AcOEt/Hexane).

Compound **11** (1.00 g, 3.17 mmol) was dissolved into MeOH (30 mL) and Pd/C 10% (0.15 g) was added. The black suspension was shaken under 50 psi of H_2 in a Parr apparatus for 4 h. whereupon the bottle was flushed with N_2 and filtered through Celite. Pure compound **5** (0.991 g, yield 99%) was obtained as colorless oil.

General Procedure for Synthesis of (2-cyclopropoxyphenyl)piperidine Derivatives

Synthesis of *N*-{4-[4-(2-cyclopropoxyphenyl)-piperidin-1-yl]-(*cis*)-cyclohexyl}-3,4-dimethoxybenzene- sulfonamide (**17a**, R = 3,4-di-MeO) and *N*-{4-[4-(2-cyclopropoxyphenyl)-piperidin-1-yl]-(*trans*)-cyclohexyl}-3,4-dimethoxybenzene-sulfonamide (**18a**, R = 3,4-di-MeO) serves as the representative procedure.

Compound **5** (0.48 g, 1.5 mmol) was dissolved into DCM and stirred with TFA and catalytic amount of H_2O at room temperature for 1.0 hr. The volatiles were removed using a rotary evaporator. The residue was mixed with DCM and treated with 1 N NaOH to adjust the pH to ~14. The organic layer was dried over K_2CO_3. The free amine intermediate **12** (0.233 g) was obtained as a yellowish oil by evaporating solvent from the dry solution and it was used directly for the next step reaction without purification.

Free amine intermediate **12** (0.233 g, 1.1 mmol), *N*-Boc-4-aminocyclohexanone (0.26 g, 1.2 mmol), $NaBH(OAc)_3$ (0.70 g, 3.4 mmol), HOAc (2 drops), and anhydrous DCM (30 mL) were mixed together and stirred under nitrogen atmosphere until no free amine was detected by TLC (the white slurry became a yellowish solution). The reaction mixture was diluted with AcOEt (80 mL), washed with NH_4Cl (sat.), 1 N NaOH, H_2O, and dried over Na_2SO_4. Crude product was obtained by removing solvent from the filtered dry solution using a rotary evaporator. Pure product **14** (0.325 g, yield 71%) was obtained by flash chromatography (100% AcOEt, silica gel) as a white sticky oil. LC-MS at 2.863 minutes, m/z 415.2 ($M^+ + 1$). The product was dissolved into DCM and stirred with TFA (0.5 mL) at room temperature for 0.5 h. The volatiles were removed using a rotary evaporator. The residue was mixed with DCM and treated with 1 N NaOH to adjust the pH to ~14. The organic layer was dried over K_2CO_3. The free amine **15** [0.234 g, yield 99.6%, LC-MS at 2.356 minutes, m/z 315.1 ($M^+ + 1$)] was obtained as a colorless sticky oil by evaporating solvent from the dry solution, and it was used directly for next step reaction without purification.

Compound **15** (0.030 g, 0.096 mmol) and 3,4-dimethoxybenzenesulfonyl chloride (0.034 g, 0.143 mmol) were dissolved into DCM (3 mL); K_2CO_3 (0.040 g) was added to the yellowish solution. The yellowish turbid solution was stirred at room temperature and monitored by TLC (5% MeOH/ DCM) and LC-MS. When no compound **15** was detected, the mixture was filtered and the solution was loaded onto a preparative TLC plate, which was developed using 5% MeOH/DCM. In addition to their R_f values, the *cis*-/*trans*-isomers are determined by comparison of their NMR spectra with those of the known compounds which have been confirmed by 2-D NMR and X-ray structure. Compound **17a** (R = 3,4-di-MeO, yellowish oil, 0.023 g) was isolated from the spot of bigger R_f value and was assigned as the *cis* isomer. LC-MS at 2.990 minutes, m/z 515.1 (100, $M^+ + 1$). ^1H NMR ($CDCl_3$, TMS) δ 0.65-0.85 (m, 4 H), 1.10-1.35 (m, 2 H), 1.35-1.84 (m, 10 H), 2.22-2.42 (m, 3 H), 2.78-2.92 (m, 1 H), 3.05 (d, J = 11.2 Hz, 2 H), 3.38-3.53 (m, 1 H), 3.68-3.80 (m, 2 H), 3.94 (s) & 3.96 (s, 6 H), 6.88-7.00 (m, 2 H), 7.12-7.26 (m, 3 H), 7.41 (d, J = 2.0 Hz, 1 H), 7.53 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1 H). Compound **18a** (R = 3,4-di-MeO, yellowish oil, 0.012 g) was isolated from the spot of smaller R_f value and was assigned as the *trans* isomer. LC-MS at 2.763 minutes, m/z 515.1 (100, $M^+ + 1$). ^1H NMR ($CDCl_3$, TMS), δ 0.65-0.82 (m, 4 H), 1.19-1.50 (m, 5 H), 1.75-2.15 (m, 7 H), 2.35-2.70 (m, 3 H), 2.82-2.98 (m, 1 H), 2.98-3.30 (m, 3 H), 3.65-3.79 (m, 2 H), 3.92 (s) & 3.96 (s, 6 H), 6.80-7.00 (m, 2 H), 7.07-7.25 (m, 3 H), 7.37 (d, J = 2.4 Hz, 1 H), 7.50 (dd, J_1 = 2.4 Hz, J_2 = 8.6 Hz, 1 H).

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