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Drug metabolism-based design, synthesis, and bioactivities of 1-(2,6-dimethylphenoxy)-2-(3,4-dimethoxyphenylethylamino)propane hydrochloride (DDPH) analogs as α_1-adrenoceptors antagonists

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ABSTRACT

1-(2,6-dimethylphenoxy)-2-(3,4-dimethoxyphenylethylamino)propane hydrochloride (DDPH) is a potent α_1-adrenoceptor antagonist that is currently under Phase II clinic trials. However, the fast metabolism has restricted its further use. In this paper, 11 DDPH analogs were designed according to the probable metabolism pathways of DDPH, and featured the structures of halogen, methyl, and cyano groups at the 3-, or 4-position of aromatic ring A to block the hydroxylation, and one hydroxyl group at the 3-, or 4-position of aromatic ring B to extend the duration time. These compounds were synthesized in moderate to good yields from the reductive amination of substituted phenoxyacetones with substituted phenylethylamines, and fully characterized with ^{1}H NMR, IR, and HRMS. Biological evaluation indicated that most of the compounds exhibited strong blocking and moderate to good antihypertensive activities. It is clear that the compounds having 4-OH/3-OMe on group B exhibited higher blocking activities and longer duration time than their corresponding analogs having 4-OMe/3-OMe (and also 3-OH/4-OMe). Among them, compound **13** having bromo group at the 4-position of ring A and 4-OH/3-OMe on group B, exhibited the highest blocking activity, whereas compound **17** that had a methyl group at the 4-position of ring A and a hydroxyl group at the 4-position of ring B, was more active than potent DDPH in terms of both blocking and antihypertensive activities. In addition, the possible correlations between the blocking and antihypertensive activities are also briefly discussed.

1. Introduction

α_1-Adrenoceptors (α_1-ARs) belong to the seven transmembrane-domain receptor super-family and play a crucial role in regulating of the functions of several physiological processes, in particular in the cardiovascular system.[1–5] This biological importance has prompted major efforts to develop new agents that are capable of blocking the function of α_1-ARs. These agents, namely α_1-AR antagonists, can find wide applications as effective therapeutic drugs, for example, for benign prostatic hypertrophy and high blood pressure.[6,7]

In these aspects, readily available phenoxylalkylamines represent one class of α_1-AR antagonists.[8,9] In our previous study, we have shown that some novel phenoxylalkylamines exhibit promising blocking activities,[10–13] remarkable among which is 1-(2,6-dimethyl-phenoxy)-2-(3,4-dimethoxyphenylethylamino)propane hydrochloride (DDPH, Chart 1).[12] DDPH is currently under phase II clinic trials as an antihypertensive drug in China. Recent studies have shown that DDPH has protective effects against neuron damage induced by acute ischemia in mice and rats,[14] and can efficiently cross the blood brain barrier and inhibit the contraction of vascular smooth muscle in the brain.[15]

However, DDPH presented one major problem in phase II clinic trials. That is, it metabolized so fast that patients had to be served 3–4 times daily. This drawback has largely restricted its clinic use. To gain insight into exactly how DDPH was deactivated in vivo, Lu et al. synthesized the probable metabolites of DDPH, that is, **1–8** (Chart 1),[16] among which compounds **1–6** were detected as the actual metabolites by LC–MS and compounds **1–4** were the main metabolites with the contents being in the order of **1** > **2** > **3** > **4**.[17,18] Study on the biological activities indicated that, compared with DDPH, the compounds that were hydroxylated at the 3- or 4-position of ring A, that is, compounds **1**, **3**, **4**, **6**, and **8** (but except **5**), had significantly shorter duration time, whereas the compounds that had no hydroxyl groups on ring A (i.e., compounds **2**

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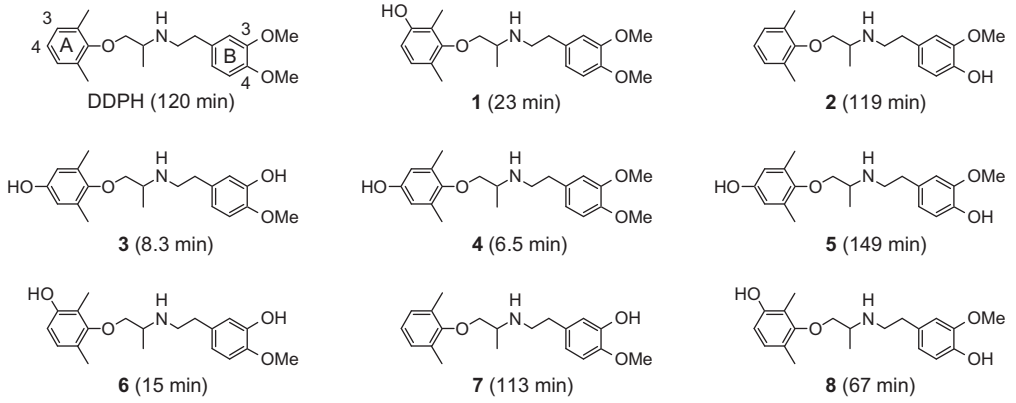


Chart 1. Chemical structures of DDPH and compounds **1–8**. Shown in the parentheses is the duration time of each compound. The data were from Ref. 16, and measured by using the protocols similar to those described in Section 4 of this paper.

and **7**) or one hydroxyl group at the 4-position of ring B (i.e., compounds **2**, **5**, but except **8**), had comparable antihypertensive effects and duration time. These results strongly suggested that DDPH might be metabolized via the hydroxylation at the 3- or 4-position of phenyl ring A and that the demethylation at the 4-position of phenyl ring B may help to extend the duration time. However, how the demethylation at the 3-position of ring B affected the bioactivity is not presently clear.

Based on this result as well as the principles of drug metabolism retardation, we designed 11 DDPH analogs **9–19** (Chart 2) in which halogen, methyl, and cyano groups were introduced to block the hydroxylation at the 3-, or 4-position of aromatic ring A,[19] and one hydroxyl group into the 3- or 4-position of ring B to clarify how the demethylation at one of these two positions affects the bioactivity. Their blocking and antihypertensive activities were evaluated. In addition, the possible correlation between the blocking and antihypertensive activities is also briefly discussed.

2. Results and discussion

2.1. Synthesis of compounds 9–19

The synthetic route of compounds **9–19** is shown in Scheme 1. Thus, these compounds were synthesized in 32–63% from the reductive amination of substituted phenylethylamines **20** with substituted phenoxyacetones **21**, and converted into hydrochloric acid salts by treating with gaseous HCl. It should be noted that all the compounds were racemates and did not be resoluted based on the fact that the stereochemistry of DDPH had no significant influence on the bioactivity.[20] Compounds **20** were prepared from the reaction of substituted benzaldehyde with nitromethane, followed by reduction by Zn/HCl.[21] Compounds **21** were obtained from the alkylation of substituted phenols with bromoacetone in the presence of potassium carbonate, according to reported procedures.[21,22] Compounds **9–19** were fully characterized with ^{1}H NMR, IR, and HRMS. They afforded MS spectra with the *m/z* values corresponding to $[M+H]^+$. Their NMR spectra were also in full agreement with the given structures (see Section 4). The purity was judged from NMR and TLC.

2.2. Biological activities of compounds 9–19

2.2.1. Blocking activities

The blocking activities of compounds **9–19** were evaluated on anococcygeus smooth muscles as the isolated tissues, by using methods similar to those described in the literatures.[21–24] The activity is expressed as $pA_2 = -\log [\mathbf{9–19}]_2$, in which $[\mathbf{9–19}]_2$ is defined as the concentrations of **9–19** that were measured according

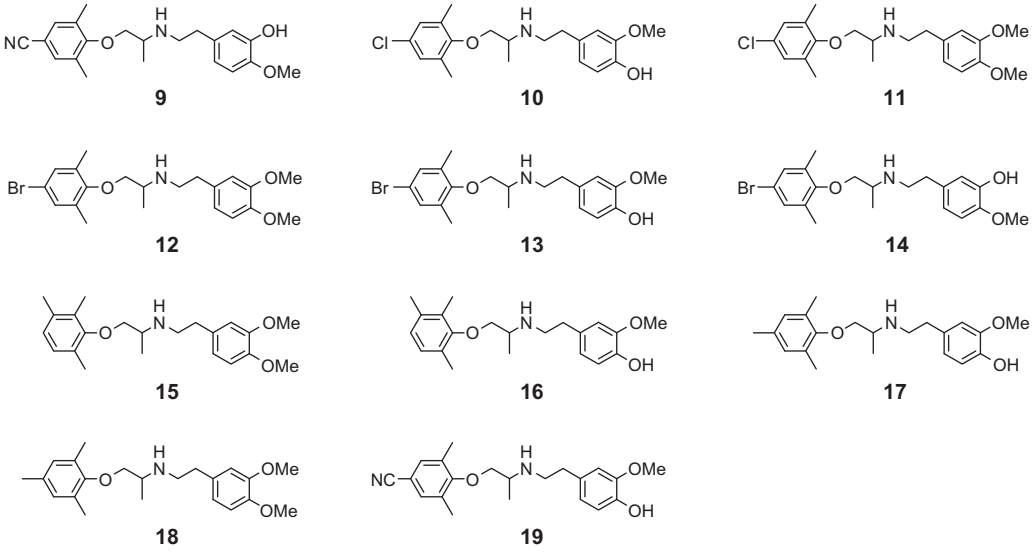
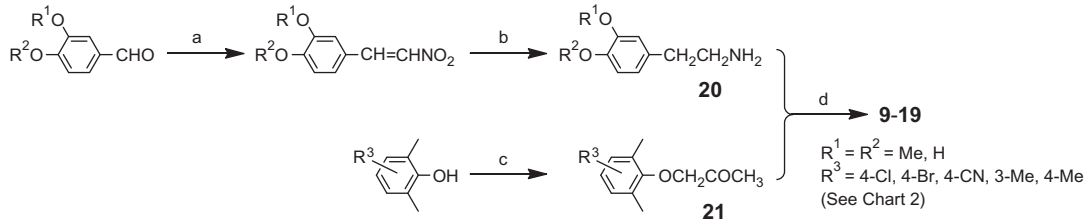


Chart 2. Chemical structures of compounds **9–19**. All the compounds were hydrochloride salt.



Scheme 1. Synthetic route for compounds **9–19**. Reagents and conditions: (a) CH_3NO_2, CH_3NH_2, MeOH; (b) Zn/HCl; (c) $BrCH_2COCH_3$, K_2CO_3, acetone, reflux; and (d) KBH_4, MeOH, HCl.

to Schild's methods.[25] The obtained pA_2 values of compounds **9–19**, together with that of DDPH as a positive control, are listed in Table 1.

It can be seen from Table 1 that most of the compounds exhibited strong blocking activities, among which compounds **13** and **17** were more active than potent DDPH, and that the pA_2 values varied with the structures of both aromatic groups A and B. The compounds having 4-OH/3-OMe on group B, that is, **10**, **13**, **16**, **17**, and **19**, exhibited higher activities than their corresponding analogs having 4-OMe/3-OMe (and also 3-OH/4-OMe), that is, **11**, **12** (**14**), **15**, **18**, and **9**. However, the activities of such compounds were also dependent on the structures of aromatic group A. For example, compound **17** showed up to 10^2-fold higher activity than compound **19**. It is clear that cyanated analogs had the lowest activity. However, other analogs having halogen and methyl groups did not show clear trend in their activities that varied in a large range, suggesting that blocking of α_1-AR might be modulated by multiple factors.

2.2.2. Antihypertensive activities of compounds 9–19

The antihypertensive activities of compounds **9–19** were evaluated by using methods similar to those described in the literatures.[16] The obtained values for pre-treated blood pressures (mmHg) in terms of systolic arterial pressures (SAP), mean arterial pressures (MAP), and diastolic arterial pressures (DAP), heart ratios (HR, BMP) and duration time, together with those of DDPH and 5% DMSO (background) for comparison, are listed in Table 2.

It can be seen that most of the compounds showed moderate to good antihypertensive activities. They were capable of reducing the SAP, MAP, and DAP by 3–36%, 7–46%, and 8–49%, respectively, while without signification effect on the heart ratios. Note worthy among them was compound **17**. Compared with DDPH, this compound showed higher antihypertensive activity in terms of SAP, MAP, and DAP. More importantly, its duration time was about twofold longer than that of DDPH. This result, together with the high blocking activity, suggests that compound **17** may be exploitable as a potent antihypertensive agent.

Further analyses could afford some interesting structure–activity correlations. Firstly, as similar to those observed in the blocking activities of compounds **9–19** (Table 1), the compounds having the same aromatic groups A had duration times in the order of 4-OH/3-OMe > 4-OMe/3-OMe > 3-OH/4-OMe on group B, that is, **13** > **12** (>**14**), **10** > **11**, **17** > **18**, and **19** > **9**. Secondly, for the analogs having 4-OH/3-OMe on group B, the duration time increased in the order of Me > Cl > Br > CN, that is, **17** > **10** > **13** > **19**.

2.2.3. Is there any correlation between the blocking and antihypertensive activities of compounds 9–19?

From the standpoint of new drug discovery for clinic use, it is ideal for an α_1-AR antagonist to boast of both potent blocking activity and long duration time. Thus, how to develop such an α_1-AR antagonist represents a challenging topic. The aforementioned results, taken together, may provide some guidances for future rational design. It is clear that the compounds having low blocking activities (e.g., pA_2 <7.5), that is, **9**, **12**, **14**, **18**, and **19**, had very short duration time being 4, 12, 4, 33, and 6 min, respectively. However, it should be noted that this correlation may not be necessarily positive. In other words, an analog having high blocking activity may have short duration time, as evident from the fact that compound **13** had the highest pA_2 value of 9.94, but short duration time of 23 min.

Table 1
Blocking activities (pA_2) of compounds **9–19** and DDPH[a]

Compound	pA_2
9	5.61 ± 0.50
10	8.60 ± 0.81
11	8.18 ± 0.19
12	6.93 ± 1.26
13	9.94 ± 0.46
14	7.02 ± 0.69
15	7.71 ± 0.70
16	8.02 ± 0.50
17	8.86 ± 0.07
18	7.25 ± 1.24
19	6.65 ± 0.34
DDPH	8.07 ± 0.29

[a] pA_2 values, expressed as means ± SEM, each tested at least three times.

3. Concluding remarks

In this paper, 11 DDPH analogs were designed according to the probable metabolism pathways of DDPH, synthesized in good yields from the reductive amination of substituted phenols with substituted phenylethylamines, and fully characterized with ^{1}H NMR, IR, and HRMS. Most of the compounds exhibited strong blocking and moderate to good antihypertensive activities. Their SAR indicated that the compounds having 4-OH/3-OMe on group B exhibited higher activities and longer duration time than their corresponding analogs having 4-OMe/3-OMe (and also 3-OH/4-OMe). Among them, the compound having bromo group at the 4-position of ring A and 4-OH/3-OMe on group B, exhibited the highest blocking activity, whereas the compound that was methylated at the 4-position of ring A and hydroxylated at the 4-position of ring B, was more active than potent DDPH in terms of both blocking and antihypertensive activities, thus may be exploitable as a potent antihypertensive.

4. Experimental section

General. Melting points (mp) were measured on RDCSY-I, and the temperature was uncorrected. IR spectra were recorded on a Nicolet Impact 410 spectrophotometer as KBr pellets. NMR spectra were recorded on Bruker AM-500 (300) MHz spectrometer with TMS as an internal standard. HRMS spectra were mea-

Table 2
Effects of compounds **9–19**, DDPH and DMSO on SAP, MAP, DAP, HR, and duration time

Compound	*n*	Item	Blood pressures and HR before treated $x \pm s$	Changes after treated (%) $x \pm s$	Duration time/min $x \pm s$
9	3	SAP	126 ± 17.7	−8.2 ± 12.5	4 ± 4.0
		MAP	107 ± 13.2	−11.0 ± 12.4	
		DAP	85 ± 10.5	−14.2 ± 11.8	
		HR	315 ± 30.0	−6.4 ± 5.8	
10	6	SAP	126 ± 11.9	−12.1 ± 5.1	61 ± 44.4
		MAP	100 ± 10.4	−20.2 ± 8.1	
		DAP	84 ± 9.9	−25.1 ± 10.5	
		HR	352 ± 33.8	−6.6 ± 4.8	
11	6	SAP	120 ± 10.7	−13.3 ± 3.5	34 ± 16.4
		MAP	89 ± 9.3	−15.9 ± 6.4	
		DAP	84 ± 7.6	−18.5 ± 10.3	
		HR	338 ± 43.9	−8.78 ± 11.5	
12	3	SAP	125 ± 10.6	−9.2 ± 4.1	12 ± 4.0
		MAP	100 ± 9.9	−8.5 ± 3.2	
		DAP	75 ± 9.6	−7.8 ± 2.1	
		HR	323 ± 36	−8.3 ± 2.3	
13	3	SAP	113 ± 4.2	−7.6 ± 2.2	23 ± 2.9
		MAP	89 ± 7.1	−15.5 ± 2.0	
		DAP	71 ± 7.1	−19.1 ± 4.9	
		HR	331 ± 38.9	−1.7 ± 3.1	
14	3	SAP	130 ± 13.8	−3.5 ± 3.8	4 ± 3.5
		MAP	107 ± 12.3	−7.5 ± 2.4	
		DAP	89 ± 5.3	−12.8 ± 5.0	
		HR	359 ± 43.2	−2.3 ± 4.7	
15	6	SAP	124 ± 12.0	−17.4 ± 7.3	57 ± 19.5
		MAP	102 ± 11.6	−27.1 ± 5.0	
		DAP	85 ± 9.1	−34.2 ± 2.1	
		HR	315 ± 39.0	−16.6 ± 3.6	
16	6	SAP	136 ± 9.5	−7.9 ± 3.9	80 ± 25.0
		MAP	110 ± 9.0	−14.6 ± 7.5	
		DAP	89 ± 6.5	−20.5 ± 8.9	
		HR	342 ± 53.5	−0.96 ± 2.4	
17	6	SAP	129 ± 4.4	−36.45 ± 8.7	205 ± 77.0
		MAP	98 ± 10.5	−45.92 ± 9.5	
		DAP	82 ± 10.7	−48.99 ± 7.2	
		HR	365 ± 29.7	−23.52 ± 15.8	
18	6	SAP	127 ± 12.7	−19.03 ± 9.2	33 ± 11.6
		MAP	96 ± 11.6	−27.86 ± 14.5	
		DAP	78 ± 11.7	−28.23 ± 24.2	
		HR	342 ± 32.6	−16.3 ± 3.6	
19	3	SAP	131 ± 8.3	−17.3 ± 13.1	6 ± 1.5
		MAP	98 ± 9.3	−24.9 ± 18.6	
		DAP	87 ± 7.4	−29.61 ± 20.1	
		HR	344 ± 19.2	−2.33 ± 3.6	
DDPH	6	SAP	127 ± 12.8	−19.79 ± 5.6	120 ± 4.5
		MAP	105 ± 9.6	−30.40 ± 6.1	
		DAP	87 ± 10.2	−26.0 ± 11.0	
		HR	321 ± 38.0	−16.04 ± 5.3	
DMSO	4	SAP	130 ± 7.6	−8.44 ± 5.1	9 ± 4.2
		MAP	107 ± 9.5	−10.49 ± 9.4	
		DAP	92 ± 7.1	−10.06 ± 10.4	
		HR	320 ± 37.0	−1.99 ± 2.7	

sured on an Agilent 1100 LC–MS instrument. Chromatographic separations were performed on silica-gel 60 (200–300 mesh). Compounds **20–21** were prepared according to the reported procedures.[21,22] All other reagents and chemicals were obtained from commercial sources and used as received unless otherwise stated.

4.1. Synthesis of compounds 9–19

4.1.1. *N*-(3-Hydroxy-4-methoxyphenethyl)-1-(4-cycno-2,6-dimethylphenoxy)propan-2-amine hydrochloride 9

A mixture of 3,5-dimethyl-4-(2-oxopropoxy)benzonitrile (0.39 g, 1.9 mmol), 2-(3-hyroxy-4-methoxyphenyl)ethylamine (0.32 g, 0.19 mmol) and a catalytic amount of TsOH in methanol (10 mL) was refluxed for 3 h. After cooled to room temperature, KBH_4 (0.2 g) was added portion wise over a period of 1 h. The resulting mixture was stirred at room temperature for another 2 h, and concentrated under reduced pressure. The obtained residue was partitioned between H_2O (10 mL) and ethyl acetate (10 mL). After the organic layer was separated, the aqueous layer was extracted with ethyl acetate (10 mL × 2). The combined organic solution was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The obtained residue was purified by chromatography on a silica-gel column (petroleum ether/ethyl acetate/triethylamine, 20:20:1 by volume) to afford an oil residue that was dissolved in anhydrous methanol and saturated with HCl to afford compound **9** (0.31 g, 42%) as a white crystal having mp 173–175 °C; IR (KBr, cm^{-1}) ν 3380, 2952, 1620, 1540, 1278, 1207, 1045; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.42 (d, 3H, J = 6.60 Hz, CHCH_3), 2.28 (s, 6H, 2 × ArCH_3), 2.98 (t, 2H, J = 8.15 Hz, ArCH_2), 3.25 (br s, 2H, NCH_2), 3.64 (br s, 1H, CHN), 3.79 (s, 3H, ArOCH_3), 3.95–4.02 (m, 2H, OCH_2), 6.59–7.21 (m, 5H, ArH), 8.96 (s, 1H,

OH), 10.21 (br s, 2H, NH_2^+) and HRMS calcd for $C_{21}H_{26}N_2O_3{\cdot}HCl$ ($[M-HCl+H]^+$): 355.20217, found: 355.20194.

4.1.2. *N*-(4-Hydroxy-3-dimethoxyphenethyl)-1-(4-chloro-2,6-dimethylphenoxy)propan-2-amine hydrochloride 10

Similar procedures. 0.28 g (37%) from 1-(4-chloro-2,6-dimethylphenoxy) propan-2-one (0.40 g, 0.19 mmol) and 2-(4-hydroxy-3-methoxyphenyl)ethylamine (0.32 g, 0.19 mmol). Mp 149–151 °C; IR (KBr, cm^{-1}) ν 3420, 2961, 1603, 1522, 1275, 1200, 1038; ^1H NMR (DMSO-d_6, 500 MHz) δ 1.44 (d, 3H, J = 6.60 Hz, CHCH_3), 2.27 (s, 6H, 2 × ArCH_3), 2.96 (t, 2H, J = 8.10 Hz, ArCH_2), 3.22 (br s, 2H, NCH_2), 3.64 (br s, 1H, C*H*N), 3.77 (s, 3H, ArOCH_3), 3.98 (br s, 2H, OCH_2), 6.65–7.14 (m, 5H, ArH), 8.85 (s, 1H, OH), 9.32 (br s, 2H, NH_2^+) and HRMS calcd for $C_{20}H_{26}ClNO_3{\cdot}HCl$ ($[M-HCl+H]^+$): 364.16740, found: 364.16404.

4.1.3. *N*-(3,4-Dimethoxyphenethyl)-1-(4-chloro-2,6-dimethylphenoxy)propan-2-amine hydrochloride 11

Similar procedures. 0.25 g (32%) from 1-(4-chloro-2,6-dimethylphenoxy)propan-2-one (0.40 g, 1.9 mmol) and 2-(3,4-dimethoxyphenyl)ethylamine (0.34 g, 0.19 mmol). Mp 126–130 °C; IR (KBr, cm^{-1}) ν 3425, 2955, 1589, 1516, 1261, 1200, 1026; ^1H NMR (DMSO-d_6, 500 MHz) δ 1.43 (d, 3H, J = 6.71 Hz, CHCH_3), 2.27 (s, 6H, 2 × ArCH_3), 2.97 (t, 2H, J = 8.13 Hz, ArCH_2), 3.30 (br s, 2H, NCH_2), 3.55 (br s, 1H, CHN), 3.73, 3.76 (2s, 6H, 2 × ArOCH_3), 3.96–4.07 (m, 2H, OCH_2) 6.78–7.14 (m, 5H, Ar*H*), 9.18 (br s, 2H, NH_2^+) and HRMS calcd for $C_{21}H_{28}ClNO_3{\cdot}HCl$ ($[M-HCl+H]^+$): 378.18305; found: 378.18009.

4.1.4. *N*-(3,4-Dimethoxyphenethyl)-1-(4-bromo-2,6-dimethylphenoxy)propan-2-amine hydrochloride 12

Similar procedures. 0.55 g (63%) from 4-bromo-2,6-dimethylphenoxyacetone (0.49 g, 0.19 mmol) and 2-(3,4-dimethoxyphenyl)ethylamine(0.34 g, 0.19 mmol). Mp 171–173 °C; IR (KBr, cm^{-1}) ν 3441, 2951, 1593, 1518, 1265, 1200, 1030; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.64 (d, 3H, J = 6.42 Hz, CHCH_3), 2.24 (s, 6H, 2 × ArCH_3), 3.27 (br s, 2H, ArCH_2), 3.40 (br s, 2H, NCH_2), 3.65 (br s, 1H, C*H*N), 3.82, 3.85 (2s, 6H, 2 × ArOCH_3), 3.92–4.28 (m, 2H, OCH_2), 6.73–7.09 (m, 5H, ArH), 9.95 (d, 2H, J = 46.68 Hz, NH_2^+) and HRMS calcd for $C_{21}H_{28}BrNO_3{\cdot}HCl$ ($[M-HCl+H]^+$): 422.13253, found: 422.13091.

4.1.5. *N*-(4-Hydroxy-3-methoxyphenethyl)-1-(4-bromo-2,6-dimethylphenoxy)propan-2-amine hydrochloride 13

Similar procedures. 0.29 g (34%) from 4-bromo-2,6-dimethylphenoxy-acetone (0.49 g, 0.19 mmol) and 2-(4-hydroxy-3-methoxyphenyl)ethylamine (0.32 g, 0.19 mmol). Mp 150–152 °C; IR (KBr, cm^{-1}) ν 3420, 2926, 1605, 1524, 1279, 1207, 1032; ^1H NMR (DMSO-d_6, 500 MHz) δ 1.43 (d, 3H, J = 6.47 Hz, CHCH_3), 2.26 (s, 6H, 2 × ArCH_3), 2.94 (t, 2H, J = 8.10 Hz, ArCH_2), 3.21 (br s, 2H, NCH_2), 3.63 (br s, 1H, C*H*N), 3.76 (s, 3H, ArOCH_3), 3.98 (br s, 2H, OCH_2), 6.65–7.27 (m, 5H, ArH), 8.85 (s, 1H, OH), 9.34 (br s, 2H, NH_2^+) and HRMS calcd for $C_{20}H_{26}BrNO_3{\cdot}HCl$ ($[M-HCl+H]^+$): 408.11688, found: 408.11425.

4.1.6. *N*-(3-Hydroxy-4-methoxyphenethyl)-1-(4-bromo-2,6-dimethylphenoxy)propan-2-amine hydrochloride 14

Similar procedures. 0.38 g (45%) from 4-bromo-2,6-dimethylphenoxyacetone (0.49 g, 0.19 mmol) and 2-(3-hydroxy-4-methoxyphenyl)ethylamine (0.32 g, 0.19 mmol). Mp 157–159 °C; IR (KBr, cm^{-1}) ν 3410, 2924, 1603, 1524, 1275, 1208, 1034; ^1H NMR (DMSO-d_6, 500 MHz) δ 1.44 (d, 3H, J = 6.51 Hz, CHCH_3), 2.25 (s, 6H, 2 × ArCH_3), 2.95 (t, 2H, J = 8.08 Hz, ArCH_2), 3.22 (br s , 2H, NCH_2), 3.54 (br s, 1H, CHN), 3.76 (s, 3H, ArOCH_3), 4.13–4.23 (m, 2H, OCH_2), 6.69–7.30 (m, 5H, ArH), 8.88 (s, 1H, OH), 9.41 (br s, 2H, NH_2^+) and HRMS calcd for $C_{20}H_{26}BrNO_3{\cdot}HCl$ ($[M-HCl+H]^+$): 408.11688, found: 408.11427.

4.1.7. *N*-(3,4-Dimethoxyphenethyl)-1-(2,3,6-trimethylphenoxy)-propan-2-amine hydrochloride 15

Similar procedures. 0.40 g (53%) from 2,3,6-trimethylphenoxyacetone (0.36 g, 0.19 mmol) and 2-(3,4-dimethoxyphenyl)ethylamine (0.34 g, 0.19 mmol). Mp 144–148 °C; IR (KBr, cm^{-1}) ν 3421, 2953, 1591, 1516, 1258, 1207, 1026; ^1H NMR (DMSO-d_6, 500 MHz) δ 1.45 (d, 3H, J = 6.70 Hz, CHCH_3), 2.16, 2.19, 2.24 (3s, 9H, 3 × ArCH_3), 2.96–3.03 (t, 2H, J = 8.10 Hz, ArCH_2), 3.26 (br s, 2H, NCH_2), 3.65–3.67 (m, 1H, CHN), 3.75, 3.76 (2s, 6H, 2 × ArOCH_3), 3.88–3.94 (m, 2H, OCH_2), 6.77–6.95 (m, 5H, ArH), 7.93(s, 1H, OH), 9.19 (d, 2H, J = 26.6 Hz, NH_2^+) and HRMS calcd for $C_{22}H_{31}NO_3{\cdot}HCl$ ($[M-HCl+H]^+$): 358.23767, found: 358.23437.

4.1.8. *N*-(4-Hydroxy-3-methoxyphenethyl)-1-(2,3,6-trimethylphenoxy) propan-2-amine hydrochloride 16

Similar procedures. 0.33 g (46%) from 2,3,6-trimethylphenoxyacetone (0.36 g, 0.19 mmol) and 2-(4-hydroxy-3-methoxyphenyl)-ethylamine (0.32 g, 0.19 mmol). Mp 206–207 °C; IR (KBr, cm^{-1}) ν 3433, 2947, 1598, 1520, 1261, 1217, 1036; ^1H NMR (DMSO-d_6, 500 MHz) δ 1.43 (d, 3H, J = 6.70 Hz, CHCH_3), 2.15, 2.17, 2.25 (3s, 9H, 3 × ArCH_3), 3.01 (br s, 2H, ArCH_2), 3.28 (br s, 2H, NCH_2), 3.65 (br s, 1H, CHN), 3.75, 3.77 (2s, 6H, 2 × ArOCH_3), 3.92–4.01 (m, 2H, OCH_2), 6.74–7.05 (m, 5H, ArH), 8.78(s, 1H, OH), 9.27 (s, 2H, NH_2^+) and HRMS calcd for $C_{21}H_{29}NO_3{\cdot}HCl$ ($[M-HCl+H]^+$): 344.22202, found: 344.22243.

4.1.9. *N*-(4-Hydroxy-3-methoxyphenethyl)-1-(2,4,6-trimethylphenoxy)-propan-2-amine hydrochloride 17

Similar procedures. 0.26 g (36%) from 2,4,6-trimethylphenoxyacetone (0.36 g, 0.19 mmol) and 2-(4-hydroxy-3-methoxyphenyl)-ethylamine (0.32 g, 0.19 mmol). Mp 164–166 °C; IR (KBr, cm^{-1}) ν 3427, 2934, 1610, 1524, 1269, 1217, 1034; ^1H NMR (DMSO-d_6, 500 MHz) δ 1.43 (d, J = 6.70 Hz, 3H, CHCH_3), 2.19 (s, 3H, ArCH_3), 2.22 (s, 6H, 2 × ArCH_3), 2.93–2.97 (m, 2H, ArCH_2), 3.21 (br s, 2H, NCH_2), 3.63 (br s, 1H, CHN), 3.73, 3.76 (2s, 6H, 2 × ArOCH_3), 3.91 (m, 2H, OCH_2), 6.29–6.93 (m, 5H, ArH), 8.56(s, 1H, OH), 9.06 (d, 2H, J = 37.35 Hz, NH_2^+) and HRMS calcd for $C_{21}H_{29}NO_3{\cdot}HCl$ ($[M-HCl+H]^+$): 344.22202, found: 344.22145.

4.1.10. *N*-(3,4-Dimethoxyphenethyl)-1-(2,4,6-trimethylphenoxy)-propan-2-amine hydrochloride 18

Similar procedures. 0.36 g (48%) from 2,4,6-trimethylphenoxyacetone (0.36 g, 0.19 mmol) and 2-(3,4-dimethoxyphenyl)ethylamine (0.34 g, 0.19 mmol). Mp 181–182 °C; IR (KBr, cm^{-1}) ν 3423, 2959, 1595, 1514, 1259, 1213, 1028; ^1H NMR (DMSO-d_6, 500 MHz) δ 1.43 (d, 3H, J = 6.70 Hz, CHCH_3), 2.19, 2.22(3s, 9H, 3 × ArCH_3), 2.94–2.99 (m, 2H, ArCH_2), 3.26 (br s, 2H, NCH_2), 3.63 (br s, 1H, CHN), 3.73, 3.76 (2s, 6H, 2 × ArOCH_3), 3.90–3.93 (m, 2H, OCH_2), 6.79–6.93 (m, 5H, ArH), 9.06 (d, 2H, J = 37.35 Hz, NH_2^+) and HRMS calcd for $C_{22}H_{31}NO_3{\cdot}HCl$ ($[M-HCl+H]^+$): 358.23767, found: 358.23562.

4.1.11. *N*-(4-Hydroxy-3-methoxyphenethyl)-1-(2,6-methyl-4-cyanophenyl)propan-2-amine hydrochloride 19

Similar procedures. 0.32 g (43%) from 3,5-dimethyl-4-(2-oxo-propoxy) benzonitrile (0.39 g, 0.19 mmol) and 2-(4-hydroxy-3-methoxyphenyl)ethylamine (0.32 g, 0.19 mmol). Mp 207–209 °C; IR (KBr, cm^{-1}) ν 3418, 2964, 1576, 1523, 1261, 1207, 1023; ^1H NMR (DMSO-d_6, 500 MHz) δ 1.44 (d, 3H, J = 6.70 Hz, CHCH_3), 2.19, 2.21(2s, 6H, 2 × ArCH_3), 2.99 (br s, 2H, ArCH_2), 3.31 (br s, 2H, NCH_2), 3.64 (br s, 1H, CHN), 3.73 (s, 3H, ArOCH_3), 3.91–3.97 (m, 2H, OCH_2), 6.79–7.11 (m, 5H, ArH), 7.95(s, 1H, OH), 9.06 (br s, 2H, NH_2^+) and HRMS calcd for $C_{21}H_{26}N_2O_3{\cdot}HCl$ ($[M-HCl+H]^+$): 355.20217, found: 355.20193.

4.2. Determination of pA_2 value of each compound

The blocking activity (pA_2) of each compound was measured by using the methods similar to those described previously.[20–23] Specifically, a male Sprague–Dawley rat (300–350 g) was killed by cervical dislocation and its anococcygeus smooth muscles were isolated. The tissues were transferred to Krebs' physiological solution that was aerated with 5% CO_2/95% O_2 at 37 °C. The solution (pH 7.4) was composed of 118.1 mM NaCl, 4.7 mM KCl, 2.5 mM $CaCl_2$, 1.16 mM $MgSO_4$, 1.0 mM NaH_2PO_4, 25 mM $NaHCO_3$, and 11.1 mM glucose. Then anococcygeus smooth muscles were transferred and suspended in a 20-mL organ chamber containing Krebs solution at 37 °C. The solution was aerated with 5% CO_2/95% O_2. The muscle preparations were set at a resting tension of 1.0 g and allowed to equilibrate for 1 h in the Krebs' solution. During this period, the smooth muscles were replenished with Krebs' solution every 20 min. After equilibration, cocaine hydrochloride, hydrocortisone and propranolol were added to the final concentrations of 30, 30, and 1 μmol L^{-1}, respectively. After 20 min, concentration–response curves with phenylephrine were obtained by adding phenylephrine to the bath in the cumulative final concentrations of 3, 10, 30 μmol L^{-1}. Each tissue was tested four times. The first concentration–response curve was the basic one, and the other three with phenylephrine were repeated by adding tested compound or Tamsulosin or DDPH, respectively. The pA_2 values of each compound, Tamsulosin and DDPH, were calculated according to Schild's graphical method,[24] and listed in Table 1.

4.3. Measurement of the antihypertensive activity of each compound

The antihypertensive activity of each compound was measured by using the methods similar to those described previously.[16] Experiments were conducted on normal male Sprague–Dawley rats of 250–350 g. The rats were anesthetized with intraperitoneal injection of urethane (1.0 g kg^{-1}), the common carotid arteries were cannulated, and the femoral vein was cannulated for intravenous injection of drugs. And the arterial blood pressure was measured with a pressure transducer, signal was amplified and band pass filtered by an alternating current amplifier. systolic pressure (SAP), diastolic pressure (DAP), mean arterial blood pressure, mean arterial pressure (MAP), and heart rate were recorded using an automatic sampling data acquisition system, displayed and stored on a computer through an analog-to-digital interface (A/D card) for subsequent off-line analysis. Because of the poor water-solubility, saline buffer containing less than 5% DMSO was used dissolve the compounds to be tested and the final concentration was 2.0 mg mL^{-1}. After blood pressure and heart rate were stabilized, drugs (5.0 mg kg^{-1}) were administered to observe the effect on the blood pressure of rats (Table 2).

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