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Original article

The synthesis of *N*-phenoxyethyl-1-substituted-1,2,3,4-tetrahydroisoquinolines and their α_1-adrenoceptor blocking activity

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ABSTRACT

A series of phenoxyisoquinolines, *N*-phenoxyethyl-1-(2-nitrophenyl)-1,2,3,4-THIQs **3a**–**3d**, *N*-phenoxyethyl-1-benzyl-1,2,3,4-THIQ **3e**, *N*-phenoxyethyl-1-(2-aminophenyl)-1,2,3,4-THIQs **5f**–**5i**, *N*-phenoxyethyl-1-(2-phenoxyethylaminophenyl)-1,2,3,4-THIQs **5f′**–**5i′**, have been synthesized and tested in isolated rat vas deferens α-adrenoreceptors. Comparison of pA2 values for these compounds in the presence of phenylephrine confirms that α_1-adrenoceptor blocking activity of **3a**–**3d** ($-NO_2$ series) is more active than **6a**–**6c** ($-NH_2$ series) in the aortic rings isolated from SD rats. On the other hand, the electron-donating group at the 6-position of isoquinoline ring either increases or decreases the α_1-adrenoceptor blocking activity.

1. Introduction

In general, the uses of α-antagonists are limited, being restricted to selective α_1-antagonists which have been used to treat hypertension. Prazosin [1,2] was the first α_1-selective antagonist to be used for the treatment of hypertension, but it is short acting. A sympatholytic and the prototypes of β-chloroethyl amines, phenoxybenzamine [PB, *N*-benzyl-*N*-(2-chloroethyl)-*N*-(1-methyl-2-phenoxyethyl) amine hydrochloride, **1**] and WB 4101 [2,3-dihydrobenzo[1,4]dioxin-(2-ylmethyl)-[2-(2,6-dimethoxy phenoxy) ethylamine hydrochloride] have been widely used as α_1-adrenoreceptor antagonist [3,4]. They display selectivity towards α_1-adrenoreceptors with respect to α_2-adrenoreceptors [5]. However, no evidence has proved that they are able to discriminate among the α_1-adrenoreceptor subtypes [6]. Due to the lack of receptor specificity, their use is limited [7]. Labedipinediol A [2] and their derivatives, on calcium channel entry, α and β-adrenoreceptors, have been developed [8]. Phenoxyalkylamino moiety is known to be the mother structure of α-blockers and many benzylisoquinoline based alkaloids exhibited excellent antagonistic activity on Ca^{2+} channel and α-adrenoreceptor [9]. Besides, the isoquinoline backbone appears in numerous natural products and most of them contain different kinds of bioactivities [10,11]. Thus, the synthesis of isoquinolines has received much recent attention [12–17]. D'Ocon et al. [9] reported that the planarity of the isoquinoline ring decreases the affinity for α_1-adrenoreceptor, whereas the more flexible THIQ ring increases the interaction with the α_1-adrenoreceptor site. These results prompted us to design novel THIQ compounds containing phenoxyalkylamino moiety to establish a structure–activity relationship among these α_1-adrenoceptor alkylating agents.

2. Results and discussion

2.1. Chemistry

There are several approaches to synthesize isoquinolines [18–22]. We synthesized a series of *N*-phenoxyethyl-1-substituted-1,2,3,4-tetrahydroisoquinolines and their relative compounds (Chart 1) by using Bischler-Napieralski approach [18–20].

A series of 1-substituted-3,4-dihydroisoquinolines (DHIQs) [**2a**–**2e**] were synthesized by Bischier-Napieralski route (Scheme 1). The DHIQs treated with sodium boron hydride. The solvent was evaporated off and the crude products were then treated with phenoxyethylbromide in DMF over K_2CO_3 to give a series of *N*-phenoxyethyl-1-(2-nitrophenyl)-1,2,3,4-THIQs and 1-benzyl-1,2,3,4-THIQs (Scheme 2) [**3a**–**3e**]. On the other hand, a series of *N*-phenoxyethyl-1-(2-aminophenyl)-1,2,3,4-THIQs [**5f**–**5i**] and *N*-phenoxyethyl-1-(2-phenoxyethylaminophenyl)-1,2,3,4-THIQs [**5f′**–**5i′**] were prepared as outlined in Scheme 3. In this paper, we synthesize a series of molecules containing 1-(2-aminophenyl)-, 1-(2-nitrophenyl)-, and 1-benzylisoquinoline-based compounds

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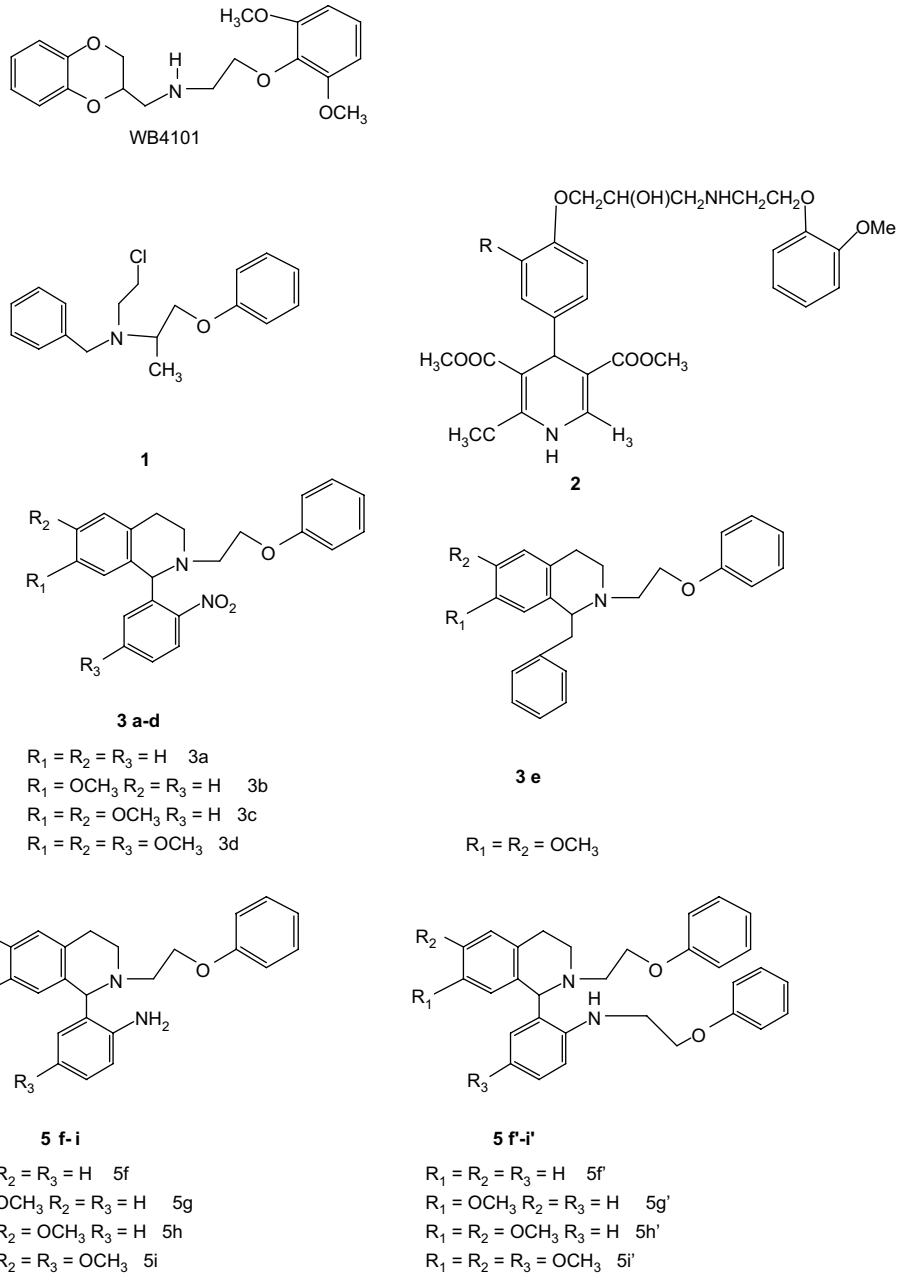
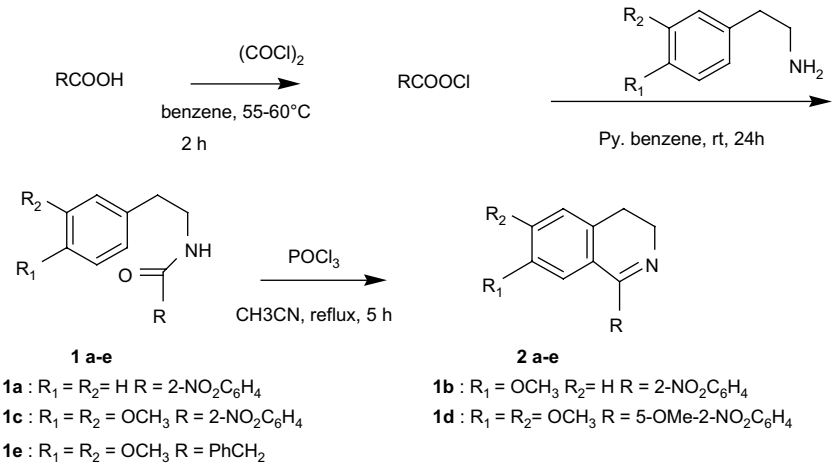


Chart 1. Phenoxybenzamine, WB 4101, Labedipinediol A and *N*-phenoxyethyl-1-substituted-1,2,3,4-tetrahydroisoquinolines and their relative compounds.

with phenoxyalkylamino moiety, and test their α-blocking activities. The structures of compounds **1**, **2**, and **4** have been determined in our previously reported literature [24,25] and compounds **3a**–**e**, **5f**–**i**, and **5f′**–**5i′** were determined on the basis of their ^{1}H NMR, ^{13}C NMR spectral data, mass spectroscopic and elemental analyses in this report.

The IR spectroscopic data of compounds **5f**–**5i** show the presence of a C–O bond absorption at 1220 cm^{-1}. The ^{1}H NMR spectroscopic data of compound **5f** show the presence of the downfield signals at δ 6.60–7.31 which suggested the presence of 13 aromatic protons and the singlet signal at δ 4.73 (1H) corresponding to the C-1 position proton (CH). These compounds having a twisted structure showed multiple signals at δ 2.78–3.21 for both methylene (CH_2) groups. ^{13}C NMR spectra indicated that these molecules contain 18 sp^2 carbons signals at δ 114–158 (δ 158.5 for Ar*C*–O, and the others for C=C), and C-1 position carbon signal present at δ 65. On the other hand, the IR spectroscopic data of compounds **5f′**–**5i′** show the presence of two C–O bond absorptions at 1250 and 1230 cm^{-1}. The ^{1}H NMR spectroscopic data of compound **5f′** show the presence of the downfield signals at δ 6.60–7.31 which suggested the presence of 18 aromatic protons. ^{13}C NMR spectra indicated that these molecules contain 22 sp^2 carbon signals at δ 114–158 (δ 158.6, 158.7 for Ar*C*–O, and the others for C=C), and C-1 position carbon signal present at δ 66. In addition, the mass spectra indicated that the molecular weights of compounds **5f**–**5i** and **5f′**–**5i′** were equal to the value of prediction. Elemental analysis confirmed the structure of the target products further.

Table 1 shows that the yields of 1-(2-aminophenyl) series are higher than 1-(2-nitrophenyl) series. It is because that amino group is the electron-releasing group, so the 1-(2-aminophenyl) series are more active than 1-(2-nitrophenyl) series in nucleophilic substitution.



Scheme 1.

2.2. Calculation of pA2 values

The pA2 values for the competitive antagonists were calculated by Schild regression analysis [23]. The ratios between the half-maximal concentrations of noradrenaline (concentration ratio, r) were calculated only when the maximal amplitude of the concentration–response curve in the presence of the competitive antagonists was similar to that obtained in its absence. Data were plotted as log antagonist concentrations (M) *vs* $\log(r-1)$. For calculation purposes the slope parameter was constrained to 1.0 when not statistically different from unity.

2.3. Structure–activity relationships

As shown in Table 2, all these compounds exhibited good antagonistic effects of α_1-adrenoceptors, except compounds **5f** and **5g′**. Concerning the relationship between structure and antagonistic effects of α_1-adrenoceptors of these compounds, the following conclusion can be made: (a) compounds **3a**–**c** bearing a nitro group ($-NO_2$) at the C-2 position of benzene ring were more potent than compounds **5f**, **5g**, **5h**, and **5i** bearing an amino group ($-NH_2$) at the C-2 position of benzene ring. (b) Compounds **3c**–**e** containing methoxy group at the C-6 position of isoquinoline ring will improve their activity. Application of Student's t test indicates that the nitro group ($-NO_2$) at the C-2 position of benzene ring and the amino group ($-NH_2$) at same position of values are statistically different ($p = 0.047$).

3. Conclusion

We have synthesized a series of phenoxyisoquinolines. Most of these compounds exhibited good antagonistic effects of α_1-adrenoceptors. However, the compounds bearing a nitro group ($-NO_2$) at the C-2 position of benzene ring were more potent than compounds bearing an amino group ($-NH_2$) at the C-2 position of benzene ring. Also, with electron-donating group at the C-6 position of isoquinoline ring will improve their activity.

4. Experimental section

4.1. Chemistry

All melting points were determined on a Digital MEL-TEMP melting point apparatus and are uncorrected. Infrared spectra were recorded on a Digilab FTIR spectrophotometer. The ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. High-resolution mass spectra were recorded on a double focusing magnetic sector mass spectrometer using EI at 70 eV. All reactions were monitored by analytical TLC (silica gel 60 F_{254}, Merck). The residues were purified by flash chromatography (230–400 mesh). Elemental analyses were recorded using a Heraeus CHNO-Rapid elemental analyzer.

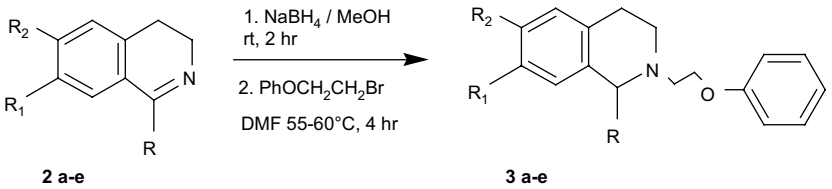
4.2. N-*Phenylethyl-2-nitrobenzamides (**1a**–**1d**)*

4.2.1. General procedure A1

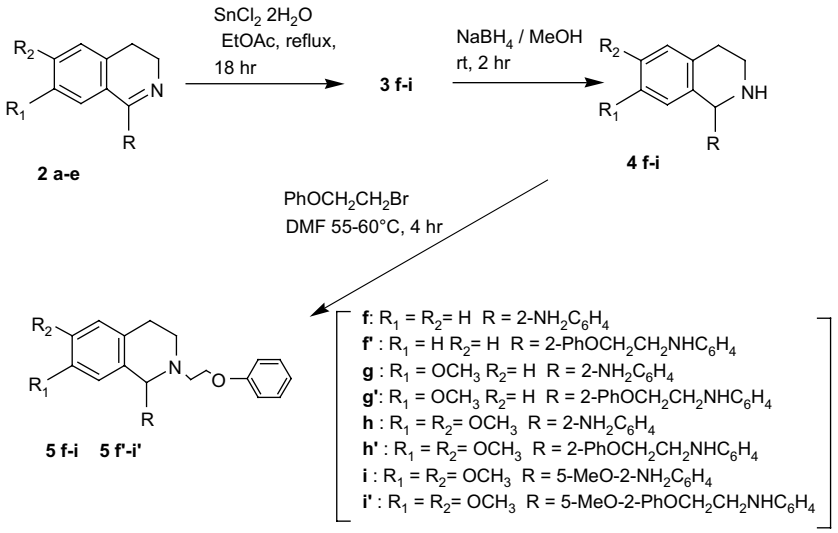
2-Nitrobenzoyl chloride (27.7 mmol) was dissolved in dry benzene (30 mL) and added dropwise to a stirred solution of phenethylamine (30 mmol) and pyridine (38 mmol) in dry benzene (80 mL). The mixture was continuously stirred at room temperature overnight and then poured into water (200 mL). Filtered the solution and the solid was washed with 1.0 N HCl (100 mL), 1.0 N NaOH (100 mL), and water (100 mL). The crude products were recrystallized from EtOAc and *n*-hexane.

4.2.2. General procedure A2

The 5-methoxy-2-nitrobenzoic acid was treated with oxalyl chloride in dry benzene. The resulting solution was stirred at 50–60 °C for 2 h. The excess oxalyl chloride was removed under reduced pressure. The resulting acid chloride was dissolved in dry benzene, and added



Scheme 2.



Scheme 3.

dropwise to a stirred solution of phenethylamine and pyridine in dry benzene. The mixture was continuously stirred at room temperature overnight and then poured into water (200 mL). Filtered the solution and the solid was washed with 1.0 N HCl (100 mL), 1.0 N NaOH (100 mL), and water (100 mL), and the crude product was recrystallized from EtOAc/*n*-hexane. The mother liquid was evaporated and the residue was recrystallized from EtOAc/*n*-hexane. The crystals were combined. Compounds **1a**–**1d** were synthesized as described before [24,25].

4.2.3. N-*(3,4-Dimethoxyphenethyl)-phenyl acetamide (**1e**)*

Phenylacetyl chloride (27.7 mmol) was dissolved in dry benzene (30 mL) and added dropwise to a stirred solution of 2,3-dimethoxyphenethylamine (30 mmol) and pyridine (38 mmol) in dry benzene (80 mL). The mixture was continuously stirred at room temperature overnight and then poured into water (200 mL). Filtered the solution and the solid was washed with 1.0 N HCl (80 mL), 1.0 N NaOH (80 mL), and water (80 mL). The crude product was recrystallized from EtOAc/*n*-hexane.

4.3. *(2-Nitrophenyl)-3,4-dihydroisoquinolines (**2a**–**2e**) [25–27]*

4.3.1. General procedure B1

$POCl_3$ (4.99 g, 32 mmol) was added dropwise to a stirred solution of **1a**–**1d** (12.9 mmol) in dry CH_3CN (80 mL), and the stirring was continued for 1 h at room temperature. The resulting mixture was refluxed for approximately 5 h. After removal of the solvent *in vacuo*, $CHCl_3$ (40 mL) and H_2O (40 mL) were added, and the aqueous phase was adjusted with aqueous 10 N NaOH to pH ~ 12. The organic layer was washed with saturated aqueous $NaHCO_3$ (3 × 100 mL), dried over anhydrous Na_2SO_4, and removal of the solvent *in vacuo*. The 1-(2-nitrophenyl)-3,4-DHIQs are precipitated on addition of *n*-hexane, followed by recrystallization of the crude product from EtOAc/*n*-hexane.

4.3.2. General procedure B2

A mixture of **1e** (12.1 mmol), $POCl_3$ (61 mmol), and dry toluene (100 mL) was refluxed for 3 h. The cooled mixture was poured into ice water (100 mL) and stirred for 2 h. The organic layer was discarded. The water layer and precipitates were then basified with 2 N NaOH (100 mL) and extracted with CH_2Cl_2 (50 mL × 3). The extracts were washed with water (100 mL), dried (Na_2SO_4), and evaporated to give product as a solid (76%). Recrystallization from *n*-hexane/acetone gave an analytical sample.

4.4. N-*Phenoxyethyl-1-(2-nitrophenyl)-1,2,3,4-tetrahydroisoquinolines and* N-*phenoxyethyl-1-benzyl-1,2,3,4-tetrahydroisoquinolines*

4.4.1. General procedure C

To a solution of 1-(2-nitrophenyl)-1,2,3,4-tetrahydroisoquinolines or 1-benzyl-1,2,3,4-tetrahydroisoquinolines in dry methanol

Table 1
Physical properties and reaction of *N*-phenoxyethyl-1-substituted-1,2,3,4-tetrahydroisoquinolines

No.	Compounds	Temp.[a] (°C)	Time[b] (h)	Mp (°C)	Yield[c] (%)
1	**3a**	55, 60	3, 16	–	16
2	**3b**	55, 60	3, 18	109–110	27
3	**3c**	55, 60	3, 18	–	43
4	**3d**	55, 60	3, 18	–	38
5	**3e**	rt, 60	24	–	46
6	**5f**	rt, 60	24	–	36
7	**5f′**	rt, 60	24	–	38
8	**5g**	rt, 60	24	–	34
9	**5g′**	rt, 60	24	–	29
10	**5h**	rt, 60	24	–	39
11	**5h′**	rt, 60	24	142–144	43
12	**5i**	rt, 60	24	–	27
13	**5i′**	rt, 60	24	–	22

[a] Two steps from compounds **2a**–**2e** to **3a**–**3e** or **3f**–**3i** to **5f**–**5i** (**5f′**–**5i′**).
[b] Reaction time.
[c] Isolated yield.

Table 2
The pA2 of *N*-phenoxyethyl-1-substituted-1,2,3,4-tetrahydroisoquinolines

No.	Compound	R	R_1	R_2	pA2
	Prazosin				9.45 ± 0.21
1	**3a**	$2\text{-}NO_2C_6H_4$	H	H	7.94 ± 0.17
2	**3b**	$2\text{-}NO_2C_6H_4$	OCH_3	H	8.11 ± 0.11
3	**3c**	$2\text{-}NO_2C_6H_4$	OCH_3	OCH_3	9.01 ± 0.13
4	**3d**	$5\text{-OMe-}2\text{-}NO_2C_6H_4$	OCH_3	OCH_3	8.46 ± 0.09
5	**3e**	$PhCH_2$	OCH_3	OCH_3	8.23 ± 0.25
6	**5f**	$2\text{-}NH_2C_6H_4$	H	H	5.46 ± 0.11
7	**5f′**	$2\text{-}PhOCH_2CH_2NHC_6H_4$	H	H	7.71 ± 0.17
8	**5g**	$2\text{-}NH_2C_6H_4$	OCH_3	H	7.36 ± 0.23
9	**5g′**	$2\text{-}PhOCH_2CH_2NHC_6H_4$	OCH_3	H	6.72 ± 0.08
10	**5h**	$2\text{-}NH_2C_6H_4$	OCH_3	OCH_3	7.66 ± 0.20
11	**5h′**	$2\text{-}PhOCH_2CH_2NHC_6H_4$	OCH_3	OCH_3	8.33 ± 0.13
12	**5i**	$5\text{-MeO-}2\text{-}NH_2C_6H_3$	OCH_3	OCH_3	7.51 ± 0.14
13	**5i′**	$5\text{-MeO-}2\text{-}PhOCH_2CH_2NHC_6H_3$	OCH_3	OCH_3	8.34 ± 0.28

Values are shown as means ± SEM.
The antagonist potency of compounds at α_1-adrenoceptors was expressed by pA2.

$NaBH_4$ was added in portions, the mixture was continuously stirred at room temperature for approximately 2 h. After removal of the solvent *in vacuo*, CH_2Cl_2 (40 mL) and H_2O (40 mL) were added. The aqueous phase was extracted with CH_2Cl_2 (20 mL × 2), and the combined organic layers were washed with water (30 mL × 2) and dried over anhydrous $MgSO_4$. The solvent was evaporated *in vacuo* and the crude product was dissolved in DMF over K_2CO_3, and was added dropwise phenoxyethylbromide the mixture was then heated at 55 °C for 4 h. DMF was evaporated *in vacuo* and the residue partitioned between H_2O and CH_2C1_2. The organic layer was separated, dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The crude product was purified by column chromatography using silica gel (EtOAc/*n*-hexane, 2:1).

4.4.2. N-*Phenoxyethyl-1-(2-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline (**3a**)*

Yellowish liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (1H, d, J = 7.6 Hz, H-3′), 7.34–7.43 (2H, m, H-4′,6′), 7.23–7.30 (3H, m, H-5,6,8), 7.06–7.17 (1H, m, H-7), 6.92 (1H, d, J = 7.2 Hz, H-4″), 6.83–6.87 (4H, m, H-2″,3″,5″,6″), 5.39 (1H, s, H-1), 4.02 (2H, m, CH_2–O), 3.16 (1H, t, J = 6.4 Hz, H-3a), 2.84–3.00 (5H, m, H-3e, H-4, CH_2CH_2O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7 (C-1″), 151.0 (C–NO_2), 138.8 (C-1′), 135.0 (C-8a), 134.9 (C-4a), 131.9 (C-3′), 131.8 (CH-5′), 129.4 (C-3″,5″), 128.9 (CH-6′), 127.9 (CH-6), 126.6 (CH-7), 126.0 (CH-8), 123.4 (CH-5), 120.6 (C-4′), 114.4 (C-2″,6″), 66.0 (O$CH_2$$CH_2$N), 62.6 (CH-1), 52.9 ($OCH_2CH_2$N), 47.0 (C-3), 27.3 (C-4). EI-MS m/z (%) = 374 (3.5) [M^+], 373 (1.0) [$M^+ - H$], 357 (100) [$M^+ - OH$], 267 (46) [$M^+ - PhOCH_2$], 252 (12.5) [$M^+ - H - PhOCH_2CH_2$]. Anal. Calcd for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.68; H, 6.02; N, 7.56.

4.4.3. N-*Phenoxyethyl-7-methoxy-1-(2-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline (**3b**)*

White powders, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (1H, d, J = 8.0 Hz, H-3′), 7.34–7.43 (2H, *m*, H-4′,6′), 7.23–7.28 (3H, m, H-5′,3″,5″), 7.08 (1H, d, J = 7.6 Hz, H-5), 6.92 (1H, d, J = 7.2, 7.2 Hz, H-4″), 6.83–6.86 (2H, m, H-2″,6″), 6.75 (1H, d, J = 8.4, 2.4 Hz, H-6), 6.43 (1H, d, J = 2.4 Hz, H-8), 5.36 (1H, s, H-1), 4.02 (2H, m, CH_2–O), 3.92 (OCH_3), 3.10 (1H, t, J = 5.6 Hz, H-3a), 2.85–2.92 (5H, m, H-3e, H-4, CH_2CH_2O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6 (C-1″), 157.6 (C-7), 151.0 (C–NO_2), 138.6 (C-1′), 136.6 (C-8a), 131.9 (C-4a), 131.8 (C-3′), 129.8 (CH-5), 129.4 (C-3″,5″), 127.9 (CH-6′), 127.0 (CH-4′), 123.4 (CH-5′), 120.6 (CH-4″), 114.4 (C-2″,6″), 113.6 (CH-6), 113.1 (CH-8), 66.0 (O$CH_2$$CH_2$N), 62.6 (CH-1), 55.2 ($OCH_3$), 52.8 ($OCH_2CH_2$N), 46.7 (C-3), 26.0 (C-4). EI-MS m/z (%) = 404 (5.9) [M^+], 403 (1.3) [$M^+ - H$], 387 (100) [$M^+ - OH$], 297 (44) [$M^+ - PhOCH_2$], 282 (12.5) [$M^+ - H - PhOCH_2CH_2$]. Anal. Calcd for $C_{24}H_{24}N_2O_4$: C, 71.27; H, 5.98; N, 6.93. Found: C, 71.00; H, 5.99; N, 6.77.

4.4.4. N-*Phenoxyethyl-6,7-dimethoxy-1-(2-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline (**3c**)*

Yellowish liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (1H, d, J = 7.6 Hz, H-3′), 7.33–7.43 (2H, m, H-4′,6′), 7.22–7.28 (3H, m, H-3″,5″,5′), 6.92 (1H, d, J = 7.2 Hz, H-4″), 6.84–6.86 (2H, m, H-2″,6″), 6.64 (1H, s, H-5), 6.41 (1H, s, H-8), 5.33 (1H, s, H-1), 4.02–4.07 (2H, m, CH_2–O), 3.87 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 3.05 (1H, s, H-3a), 2.84–2.91 (5H, m, H-3e, H-4, CH_2CH_2O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.71 (C-6,7, C-1″), 147.16 (C–NO_2), 131.56 (C-1′), 129.73 (C-4a), 129.4 (C-8a), 128.7 (C-5′), 126.2 (C-3″,5″), 120.8 (C-6′), 115.9 (C-4′), 114.4 (C-4″), 111.2 (C-8), 110.6 (C-5), 110.5 (C-2″,6″), 66.7 (OCH_2–CH_2N), 66.2 (CH-1), 55.7 (OCH_3), 55.7 (OCH_3), 52.9 (OCH_2CH_2N), 42.8 (C-3), 29.7 (C-4). EI-MS m/z (%) = 434 (6.40) [M^+], 433 (2.04) [$M^+ - H$], 417 (100) [$M^+ - OH$]. Anal. Calcd for $C_{25}H_{28}N_2O_3$: C, 74.23; H, 6.98; N, 6.93. Found: C, 74.19; H, 6.79; N, 6.84.

4.4.5. N-*Phenoxyethyl-6,7-dimethoxy-1-(5-methoxy-2-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline (**3d**)*

Yellowish liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (1H, d, J = 8.8 Hz, H-3′), 7.22–7.27 (2H, m, H-4′,6′), 6.91 (2H, d, J = 7.2 Hz, H-3″,5″), 6.76–6.85 (3H, m, H-2″,4″,6″), 6.62 (1H, s, H-5), 6.40 (1H, s, H-8), 5.50 (1H, s, H-1), 4.01–4.07 (2H, m, CH_2O), 3.86 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 3.07 (1H, d, J = 7.2 Hz, H-3a), 2.83–2.90 (5H, m, H-3e, H-4, CH_2CH_2O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2 (C-5′), 158.6 (C–NO_2), 147.7 (C-6), 147.2 (C-7), 144.0 (C-1″), 142.3 (C-1′), 129.3 (C-4a), 127.3 (C-8a), 126.9 (C-3′), 126.3 (C-3″,5″), 120.5 (C-6′), 116.9 (C-4′), 114.3 (C-4″), 112.3 (C-2″,6″), 111.3 (C-5), 111.1 (C-8), 66.1 (OCH_2CH_2N), 61.9 (CH-1), 55.8 (OCH_3), 55.7 (OCH_3), 55.6 (OCH_3), 52.9 (OCH_2CH_2N), 46.3 (C-3), 30.9 (C-4). EI-MS m/z (%) = 464 (2.0) [M^+], 463 (91.6) [$M^+ - H$], 447 (100) [$M^+ - OH$], 357 (2.4) [$M^+ - PhOCH_2$]. Anal. Calcd for $C_{26}H_{28}N_2O_6$: C, 67.23; H, 6.08; N, 6.03. Found: C, 67.88; H, 5.97; N, 6.14.

4.4.6. N-*Phenoxyethyl-6,7-dimethoxy-1-benzyl-1,2,3,4-tetrahydroisoquinoline (**3e**)*

Yellowish liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21–7.35 (6H, m, H-1′,2′,3′,3″,5′,5″), 7.12–7.19 (1H, m, H-4′), 6.93–6.99 (1H, m, H-4″), 6.85–6.88 (2H, m, H-2″,6″), 6.58 (1H, s, H-8), 6.00 (1H, s, H-5), 3.85 (3H, s, OCH_3-7), 3.56 (3H, s, OCH_3-6), 4.06 (1H, m, H-1), 3.92–4.07 (2H, m, CH_2–O), 3.34–3.40 (1H, m, H-3a), 3.19–3.24 (1H, m, H-3e), 2.93–3.14 (4H, m, CH_2CH_2O, CH_2-Ph), 2.82–2.88 (1H, m, H-4a), 2.53–2.58 (1H, m, H-4e); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7 (*C*–OCH_2), 147.4 (*C*–OCH_3), 146.4 (*C*–OCH_3), 139.9 (C-1′), 130.8 (C-4a), 129.9 (C-8a), 129.4 (CH), 128.1 (CH), 125.9 (CH), 125.8 (CH), 120.7 (CH-4″), 114.5 (CH-2″,6″), 111.3 (CH-8), 111.1 (CH-5), 66.8 (OCH_2–CH_2N), 63.7 (CH-1), 55.7 (OCH_3), 55.5 (OCH_3), 52.2 (OCH_2–CH_2N), 44.3 (CH_2-3), 41.7 (CH_2Ph), 24.6 (CH_2-4). EI-MS m/z (%) = 403 (0.03) [M^+], 402 (0.22) [$M^+ - H$], 312 (100) [$M^+ - PhCH_2$]. Anal. Calcd for $C_{26}H_{29}NO_3$: C, 77.39; H, 7.24; N, 3.47. Found: C, 77.95; H, 7.19; N, 3.53.

4.5. 1-(2-Aminophenyl)-3,4-dihydroisoquinolines

4.5.1. General procedure D [25–27]

Compounds **2a**–**2e** (1.105 g, 4.4 mmol) and $SnCl_2 \cdot 2H_2O$ (5.96 g, 26.4 mmol) in dry EtOAc (150 mL) were refluxed until completion of the reaction (30 h). To this mixture were added with stirring H_2O (20 mL) and 10 N NaOH (5 mL), and the resulting solution was carefully poured into saturated aqueous $NaHCO_3$ (100 mL). After extraction with EtOAc (3 × 50 mL), the combined organic layers were filtered, dried over $MgSO_4$ (3 h), and evaporated *in vacuo*. Pure product was obtained by recrystallization of the crude product from EtOAc/*n*-hexane.

4.6. 1-(2-Aminophenyl)-1,2,3,4-tetrahydroisoquinolines [24]

4.6.1. General procedure E

To a solution of 1-(2-aminophenyl)-3,4-dihydroisoquinolines in dry methanol (80 mL) $NaBH_4$ was added in portions, the mixture was continuously stirred at room temperature for approximately 2 h. After removal of the solvent *in vacuo*, CH_2Cl_2 (40 mL) and H_2O (40 mL) were added. The aqueous phase was extracted with CH_2Cl_2 (20 mL × 2), and the combined organic layers were washed with water (30 mL × 2) and dried over anhydrous $MgSO_4$. The solvent was evaporated *in vacuo* and the crude product was recrystallized from acetone/*n*-hexane.

4.7. N-*Phenoxyethyl-1-substituted-1,2,3,4-tetrahydroisoquinolines*

4.7.1. General procedure F

To a solution of 1,2,3,4-tetrahydro-1-substituted isoquinolines in DMF over K_2CO_3 was added phenoxyethylbromide dropwise.

This mixture was then heated at 55 °C for 4 h. DMF was evaporated *in vacuo* and the residue partitioned between H_2O and CH_2C1_2. The organic layer was separated, dried (Na_2SO_4) and evaporated *in vacuo*. The crude product was purified by column chromatography using silica gel (EtOAc/*n*-hexane, 1:5).

4.7.2. N-*Phenoxyethyl-1-(2-aminophenyl)-1,2,3,4-tetrahydroisoquinoline (**5f**)*

IR (neat, cm^{-1}) 3400, 3300 (NH_2), 3018 (aromatic CH), 2956, 2838 (aliphatic CH), 1595, 1500 (aromatic C=C), 1240 (C–O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.31, (2H, m, H-6,7), 7.11–7.18 (3H, m, H-5,8,4″), 7.03–7.08 (2H, m, H-3″,5″), 6.96 (1H, d, J = 7.2 Hz, H-6′), 6.82–6.87 (3H, m, H-4′,2″,6″), 6.72–6.75 (1H, m, H-5′), 6.60 (1H, J = 8.0, 1.2 Hz, H-3′), 4.73 (1H, s, H-1), 4.08–4.11 (2H, m, CH_2–O), 3.50 (1H, J = 5.2, 4.0 Hz, H-3a), 3.08–3.21 (2H, m, CH_2CH_2O), 2.78–2.94 (3H, m, H-3e,4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7 (C-1″), 145.9 (C–NH_2), 136.5 (C-4a), 134.5 (C-8a), 131.8 (C-1′), 129.5 (C-4′), 128.5 (C-6′), 128.3 (C-3″,5″), 127.6 (C-5), 126.3 (C-6), 126.3 (C-7), 125.9 (C-8), 120.7 (C-4″), 117.2 (C-5′), 116.7 (C-3′), 114.4 (C-2″,6″), 69.0 (O$CH_2$$CH_2$N), 65.8 (C-1), 53.1 (OCH$_2$$CH_2$N), 48.9 (C-3), 28.4 (C-4). EI-MS m/z (%) = 344 (44.3) [M^+], 343 (9.3) [$M^+ - H$], 252 (100) [$M^+ - H$–PhOCH$_2$CH$_2$]. Anal. Calcd for $C_{23}H_{24}N_2O$: C, 80.20; H, 7.02; N, 8.13. Found: C, 80.68; H, 6.92; N, 7.92.

4.7.3. N-*Phenoxyethyl-1-(2-*N*-phenoxyethylaminophenyl)-1,2,3,4-tetrahydroisoquinoline (**5f′**)*

IR (neat, cm^{-1}) 3300 (NH), 3018 (aromatic CH), 2956, 2838 (aliphatic CH), 1595, 1500 (aromatic C=C), 1250, 1230 (C–O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.34 (1H, m, H-7), 7.21–7.30 (4H, m, H-5,6,8,5′), 7.02–7.13 (2H, m, 2PhO-*p*), 6.90–6.99 (4H, m, 2PhO-*m*), 6.78–6.83 (4H, m, 2PhO-*o*), 6.70–6.75 (2H, m, H-4′,6′), 6.65 (1H, d, J = 8.0 Hz, H-3′), 4.70 (1H, s, H-1), 4.01–4.10 (2H, m, CH_2O), 3.96–4.00 (1H, m, NHCH$_2$$CH_2$O-α), 3.40–3.45 (1H, m, NHCH$_2$$CH_2$O-β), 3.31–3.38 (3H, m, H-3a, NCH_2), 3.12–3.19 (1H, m, NHCH_2-α), 3.00–3.04 (1H, m, NHCH_2-β), 2.73–2.84 (3H, m, H-3e,4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.67 (2PhO–C-1), 147.09 (C-2′), 136.93 (C-4a), 134.73 (C-8a), 131.95 (C-1′), 129.58 (CH), 129.48 (CH), 129.40 (CH), 128.71 (PhO-*m*), 128.02 (PhO-*m*), 127.25 (CH), 126.15 (CH), 126.02 (CH), 125.79 (CH), 120.77 (PhO-*p*), 120.61 (PhO-*p*), 115.92 (C-3′), 114.43 (PhO-*o*), 111.20 (NHCH$_2$$CH_2$OPh-*o*), 69.74 (O$CH_2$$CH_2$N), 66.58 (O$CH_2$$CH_2$NH), 66.21 (C-1), 53.05 (OCH$_2$$CH_2$N), 49.62 (C-3), 42.08 (NHCH_2), 28.90 (C-4). EI-MS m/z (%) = 464 (2.4) [M^+], 343 (9.3) [M^+ – PhOCH$_2$CH$_2$]. Anal. Calcd for $C_{31}H_{32}N_2O_2$: C, 80.14; H, 6.94; N, 6.93. Found: C, 80.35; H, 6.89; N, 6.84.

4.7.4. 7-*Methoxy*-N-*phenoxyethyl-1-(2-aminophenyl)-1,2,3,4-tetrahydroisoquinoline (**5g**)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23–7.29 (H, m, PhO-*m*), 7.09 (1H, ddd, J = 8.0, 2.0, 2.0 Hz, H-5′), 7.04 (1H, d, J = 8.4 Hz, H-3′), 6.92–6.97 (2H, m, H-4′, PhO-*p*), 6.83–6.85 (2H, m, PhO-*o*), 6.71–6.74 (1H, m, H-6′), 6.68 (1H, d, J = 7.6, 2.8 Hz, H-6), 6.59 (1H, dd, J = 8.0, 1.2 Hz, H-5), 6.35 (1H, d, J = 2.8 Hz, H-8), 4.71 (1H, s, H-1), 4.09 (2H, t, J = 6.4 Hz, H–CH_2–O), 3.63 (3H, s, OCH_3), 3.35–3.40 (1H, m, H–H-3a), 3.13–3.19 (1H, m, H–CH_2CH_2O), 2.96–2.99 (1H, m, H–CH_2CH_2O), 2.78–2.86 (3H, m, H–H-3e,4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6 (C-1″), 157.7 (C-7), 145.9 (C-NH_2), 137.3 (C-4a), 131.4 (C-8a), 129.4 (C-1′), 129.2 (C-4′), 128.5 (C-6′), 126.6 (C-3″,5″), 126.2 (C-5), 120.7 (C-6), 117.4 (C-4″), 116.8 (C-3′), 114.3 (C-5′), 112.7 (C-2″,6″), 112.6 (C-8), 68.7 (O$CH_2$$CH_2$N), 65.7 (C-1), 55.0 ($OCH_3$), 52.9 (OCH$_2$$CH_2$N), 48.8 (C-3), 27.0 (C-4). EI-MS m/z (%) = 374 (2.5) [M^+], 253 (100) [M^+ – PhOCH$_2$CH$_2$]. Anal. Calcd for $C_{24}H_{26}N_2O_2$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.39; H, 6.96; N, 7.57.

4.7.5. 7-*Methoxy*-N-*phenoxyethyl-1-(2-*N*-phenoxyethylaminophenyl)-1,2,3,4-tetrahydroisoquinoline (**5g′**)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–7.33 (5H, m, H-6′, 2PhO-*m*), 7.11–7.16 (2H, m, H-3′,4′), 7.05 (1H, ddd, J = 7.2, 7.2, 2.4 Hz, H-5′), 6.92–6.96 (2H, m, 2PhO-*p*), 6.81–6.83 (4H, m, 2PhO-*o*), 6.71 (1H, dd, J = 8.4, 2.8 Hz, H-6), 6.65 (1H, d, J = 2.8 Hz, H-5), 6.55 (1H, d, J = 8.4 Hz, H-8), 6.27 (1H, s, H-5), 4.68 (1H, s, H-1), 4.08 (2H, m), 3.76 (3H, s, OCH_3), 3.54–3.57 (1H, m, H–), 3.40–3.43 (1H, m, H–), 3.04–3.19 (2H, m, H–), 2.75–2.92 (4H, m, H–); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6 (C-7), 151.7 (NCH$_2$CH$_2$OPh–C1), 139.6 (C–NH_2), 136.2 (C-4a), 134.4 (C-8a), 129.4 (C-1′), 129.3 (CH), 128.7 (CH), 128.3 (CH), 128.0 (CH), 127.6 (CH), 126.4 (OPh-*m*), 126.0 (OPh-*m*), 120.7 (NCH$_2$CH$_2$OPh-*p*), 118.2 (NHCH$_2$CH$_2$ OPh-*p*), 117.6 (OPh-*o*), 114.4 (OPh-*o*), 114.3 (C-6), 113.0 (C-8), 68.8 (O$CH_2$$CH_2$N), 65.7 (C-1), 55.6 ($OCH_3$), 53.0 (O$CH_2$$CH_2$NH), 48.6 (C-3), 40.8 (OCH$_2$$CH_2$N), 35.4 (OCH$_2$$CH_2$NH), 28.1 (C-4). EI-MS m/z (%) = 494 (12.9) [M^+], 373 (100) [M^+ – PhOCH$_2$CH$_2$]. Anal. Calcd for $C_{32}H_{34}N_2O_3$: C, 77.70; H, 6.93; N, 5.66. Found: C, 77.34; H, 7.01; N, 5.54.

4.7.6. 6,7-*Dimethoxy*-N-*phenoxyethyl-1-(2-aminophenyl)-1,2,3,4-tetrahydroisoquinoline (**5h**)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.30 (2H, m, H-3″,5″), 7.10 (1H, ddd, J = 8.4, 7.6, 1.6 Hz, H-4″), 6.92–6.97 (2H, m, H-2″,6″), 6.83–6.87 (2H, m, H-4′,6′), 6.67–6.71 (1H, m, H-5′), 6.60 (1H, s, H-8), 6.60–6.62 (1H, m, H-3′), 6.29 (1H, s, H-5), 4.73 (1H, s), 4.08–4.13 (2H, m), 3.85 (3H, OCH_3), 3.62 (3H, OCH_3), 3.29–3.39 (1H, m), 3.08–3.20 (1H, m), 2.77–2.97 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.63, 158.56, 147.90, 147.68, 147.33, 146.05, 145.26, 133.48, 131.48, 131.00, 129.48, 129.43, 128.73, 128.41, 127.91, 126.95, 126.70, 126.50, 120.84, 120.75, 118.10, 117.27, 116.74, 114.69, 114.38, 110.91, 110.76, 110.66, 108.85, 68.00, 67.30, 65.76, 65.62, 55.83, 55.72, 55.69, 52.83, 52.76, 48.16, 47.63, 29.65, 27.12, 26.74, EI-MS m/z (%) = 404 (3.0) [M^+], 283 (100) [M^+ – PhOCH$_2$CH$_2$]. Anal. Calcd for $C_{25}H_{28}N_2O_3$: C, 74.23; H, 6.98; N, 6.93. Found: C, 74.39; H, 6.86; N, 7.06.

4.7.7. 6,7-*Dimethoxy*-N-*phenoxyethyl-1-(2-*N*-phenoxyethylaminophenyl)-1,2,3,4-tetrahydroisoquinoline (**5h′**)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–7.27 (5H, m, H-5′, 2PhO-*m*), 7.03 (1H, d, J = 6.4 Hz, H-4′), 6.90–6.96 (2H, m, 2PhO-*p*), 6.78–6.83 (4H, m, 2PhO-*o*), 6.69 (2H, dd, J = 7.2, 7.2 Hz, H-3′,6′), 6.49 (1H, s, H-8), 6.27 (1H, s, H-5), 4.64 (1H, s), 3.85–4.07 (3H, m), 3.81 (3H, s), 3.80 (1H, m), 3.60 (3H, s), 3.32–3.42 (3H, m), 3.12–3.19 (1H, m), 2.65–2.91 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6 (C-6,7), 150.9 (NCH$_2$CH$_2$OPh–C1), 147.4 (NHCH$_2$CH$_2$OPh–C1), 145.9 (C-2′), 138.8 (C-4a), 131.8 (C-8a), 131.6 (C-1′), 129.3 (C-4′), 127.9 (OPh-*m*), 127.1 (OPh-*m*), 125.9 (C-6′), 123.3 (C-6′), 121.9 (C-3′), 120.6 (NCH$_2$CH$_2$OPh-*p*), 120.1 (NHCH$_2$CH$_2$OPh-*p*), 114.4 (C-8), 111.5 (C-5), 111.2 (2OPh-*o*), 66.1 (O$CH_2$$CH_2$N), 61.9 (O$CH_2$$CH_2$NH), 55.8 (C-7), 55.8 (C-6), 52.7 (C-1), 47.8 (C-3), 46.2 (2CH_2N), 29.7 (C-4). EI-MS m/z (%) = 524 (0.3) [M^+], 403 (100) [M^+ – PhOCH$_2$CH$_2$]. Anal. Calcd for $C_{33}H_{36}N_2O_4$: C, 75.55; H, 6.92; N, 5.34. Found: C, 75.26; H, 7.04; N, 5.23.

4.7.8. 6,7-*Dimethoxy*-N-*phenoxyethyl-1-(5-methoxy-2-aminophenyl)-1,2,3,4-tetrahydroisoquinoline (**5i**)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.32 (2H, m, H-3″,5″), 6.93–6.97 (2H, m, H-2″,6″), 6.91 (1H, dd, J = 2.8, 0.8 Hz, H-4″), 6.84–6.87 (2H, m, H-4′,6′), 6.69 (1H, dd, J = 8.8, 2.8 Hz, H-3′), 6.60 (1H, s, H-8), 6.56 (1H, d, J = 8.8 Hz, H-4′), 6.33 (1H, s, H-5), 4.66 (1H, s), 4.08–4.10 (2H, m, CH_2O), 3.85 (3H, OCH_3), 3.73 (3H, OCH_3), 3.67 (3H, OCH_3), 3.29–3.34 (1H, m, H-3a), 3.10–3.17 (1H, m, H-3e), 2.77–2.90 (4H, m, CH_2CH_2O, H-4). EI-MS m/z (%) = 434 (0.5) [M^+], 313 (100) [M^+ – PhOCH$_2$CH$_2$]. Anal. Calcd for $C_{26}H_{30}N_2O_4$: C, 71.85; H, 6.96; N, 6.45. Found: C, 71.57; H, 6.87; N, 6.66.

*4.7.9. 6,7-Dimethoxy-N-phenoxyethyl-1-(5-methoxy-2-N-phenoxyethylaminophenyl)-1,2,3,4-tetrahydroisoquinoline (**5i′**)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–7.32 (4H, m, 2PhO-*m*), 6.89–6.98 (2H, m, 2PhO-*p*), 6.78–6.83 (5H, m, H-4′, 2PhO-*o*), 6.67 (1H, s, H-6′), 6.62 (1H, d, $J = 8.8$ Hz, H-3′), 6.50 (1H, s, H-8), 6.31 (1H, s, H-5), 4.63 (1H, s, H-1), 3.95–4.13 (3H, m, H–), 3.83–3.86 (1H, m, H–), 3.81 (3H, s, OCH_3), 3.76 (1H, s, OCH_3), 3.62 (3H, s, OCH_3), 3.29–3.44 (3H, m, H–), 3.10–3.13 (1H, m, H–), 2.66–2.86 (4H, m, H–); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7 (C-7), 158.6 (C-6), 151.0 (C-4′), 147.5 ($NHCH_2CH_2OPh$–C1), 147.1 (NCH_2CH_2OPh–C1), 141.6 (C-2′), 129.4 (C-4a), 129.4 (C-8a), 128.4 (C-1′), 126.8 (C-3′), 120.7 (OPh-*m*), 120.6 (OPh-*m*), 118.7 (C-6′), 114.5 (C-3′), 114.4 (NCH_2CH_2OPh-*p*), 112.7 ($NHCH_2CH_2OPh$-*p*), 112.4 (C-8), 110.6 (C-5), 110.5 (2OPh-*o*), 69.0 (OCH_2CH_2N), 66.7 (OCH_2CH_2NH), 66.2 (OCH_2CH_2N), 61.5 (OCH_2CH_2NH), 55.8 (C-7), 55.7 (C-6), 55.7 (C-5′), 52.8 (C-1), 43.7 (C-3), 29.65 (C-4). EI-MS *m*/*z* (%) = 554 (0.3) [M^+], 433 (100) [$M^+ - PhOCH_2CH_2$]. Anal. Calcd for $C_{34}H_{38}N_2O_5$: C, 73.62; H, 6.91; N, 5.50. Found: C, 73.32; H, 6.95; N, 5.62.

4.8. α_1-Adrenoceptor blocking activity

Vascular α_1-adrenoceptor blocking activity was evaluated in the Wistar rat aorta preparation. Isolated rat aorta preparations were mounted in a 10 mL organ bath and suspended in Krebs solution (pH 7.4, of the following composition (mM): NaCl, 118.4; KCl, 4.7; $CaCl_2$, 2.52; $MgSO_4$, 1.2; KH_2PO_4, 1.2; $NaHCO_3$, 25.0; glucose, 11.1. $MgSO_4$ concentration was reduced to 0.6 mM) at 37 °C under a resting tension of 1.0 g. *N*-Phenoxyethyl-1-substituted-1,2,3,4-tetrahydroisoquinolines were added to the bath medium after a control concentration–response curve to norepinephrine (10^{-8}–10^{-6} M) had been obtained. The tissue was exposed to *N*-phenoxyethyl-1-substituted-1,2,3,4-tetrahydroisoquinolines for 30 min before rechallenging with norepinephrine. Inhibitions were expressed as percentages of the maximum contraction obtained by the challenge of the tissues with norepinephrine. pA2 values were obtained from the formula $pA2 = [\log(DR - 1) - \log$ molar concentration antagonist] and the slope values were calculated from individual Schild plot by regression analysis. Each value was the mean ± SEM of six to eight experimental results.

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