Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters
ELSEVIER
Bioorganic & Medicinal Chemistry Letters 14 (2004) 2797–2800

1- And 2-substituted naphthalenes: a new class of potential hypotensive agents

Vishnu K. Tandon,* Kunwar A. Singh and Gajendra K. Goswamy

Department of Chemistry, University of Lucknow, Lucknow 226007, India

Received 20 January 2004; accepted 22 March 2004

Abstract—A series of 2-substituted aminomethyloxy naphthalenes **1** and 4-(1-naphthoxy-2-substituted aminomethyl)-butanoic acids **2** were synthesized by Mannich reaction of 4-(2-naphthoxy)-butanoic acid **3** and 4-(1-naphthoxy)-butanoic acid **4** with appropriate secondary amines and *para*-formaldehyde. The newly synthesized compounds were tested for their hypotensive activity at 5 mg/kg iv dose in cats. The results indicated that the analogue 2-(N^4-phenyl-N^1-piperazino)-methyloxy naphthalene **1d** (>N = N^4-phenyl-N^1-piperazino) was the most active analogue when its hypotensive activity was compared to the reference compound propranolol.

Hypotensive drugs play an important role in decrease of blood pressure in hypertensive patients. The three main classes to which hypotensive drugs belong to are: (i) ACE inhibitors; (ii) β-adrenergic receptor antagonists; (iii) Ca^{2+} and K^+ channel blockers. During recent years a number of compounds isolated from natural sources have exhibited promising hypotensive activity.[1,2] Enalapril the hypotensive drug belongs to ACE inhibitors class of compounds.[3] Propranolol and atenolol the hypotensive drugs of choice act as β-adrenergic receptor antagonists[4] while amlodepine acts as Ca^{2+} channel blocker.[4] Bufuralol analogues have recently been found to act as potent β-blockers.[5] *cis*/*trans*-Dicyclopropylmethyl-(4,5-dimethyl-4,5-dihydro-3*H*-pyrrol-2-yl)-amine (LNP 509), an I_1 imidazoline receptor selective ligand has been found to possess marked hypotensive activity.[6]

In our efforts to discover novel molecules having hypotensive activity, we used molecular model of one of the β-adrenergic receptor antagonist propranolol[7–11] (Fig. 2) to synthesize 4-(1-napthoxy-2-substituted aminomethyl) butanoic acids **2** and corresponding analogue using 1- and 2-naphthols as starting materials.

Screening of **1a**–**f** and **2a**–**f** (Fig. 1) for hypotensive activity using propranolol as standard drug resulted in the lead compound **1d**. Compound **1d** exhibited marked hypotensive activity [fall of BP 60 mm/Hg (120′)] at a dose of 5 mg/kg iv in anaesthetized cats. We sought to investigate the structure–activity relationship (SAR) of compounds **1** and **2** in comparison with propranolol **6** (Fig. 2). Table 1 describes the hypotensive activity of **1a**–**f** and **2a**–**f**.[12]

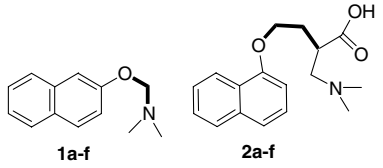
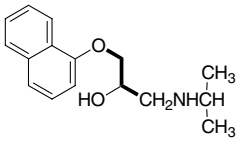


Figure 1.

In general N-phenyl-piperazino moiety caused maximum fall of blood pressure in both compounds **1** and **2**. Piperidino chain too caused significant fall of blood pressure though for lesser duration of time. Other secondary amino chains viz morpholino, piperazino, N-methyl piperazino caused almost similar effect on fall of blood pressure, which was moderate at a dose of 5 mg/kg iv. Introduction of a carbonyl group in **2a**–**f** resulted in lower fall of BP when compared to propranolol with



6

Figure 2.

* Corresponding author. Fax: +91-522-2684388; e-mail: vishnutandon@yahoo.co.in

0960-894X/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.bmcl.2004.03.080

Table 1. Summary of hypotensive activity in cats of compounds **1a**–**f** and **2a**–**f**

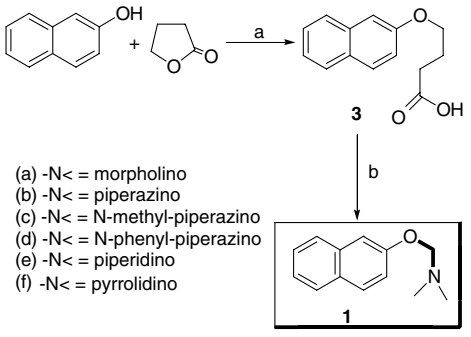
Compound	1 mg/kg iv		5 mg/kg iv	
	Fall of BP mm/Hg	% of max. effect $m \pm SE$	Fall of BP mm/Hg	% of max. effect $m \pm SE$
1a	NA	NA	50(>35)	41 ± 4
1b	NA	NA	10(2′)	7 ± 1
1c	18(2′)	21 ± 2	D	NA
1d	40(16′)	50 ± 5	60(120′)	75 ± 8
1e	20(2′)	21 ± 2	44(17′)	52 ± 5
1f	12(10′)	7 ± 1	30(16′)	19 ± 2
2a	18(2′)	17 ± 2	16(2′)	17 ± 2
2b	12(12′)	7 ± 1	25(7′)	19 ± 2
2c	18(2′)	17 ± 2	34(4′)	38 ± 4
2d	20(2′)	14 ± 2	50(7′)	40 ± 4
2e	30(16′)	19 ± 2	40(50′)	47 ± 5
2f	10(2′)	8 ± 1	20(30′)	17 ± 2
Propranolol	46(40′)	35 ± 3	50(>60′)	41 ± 4

NA: not active; figure in parentheses against fall of BP indicate duration of effect in min; D: death.

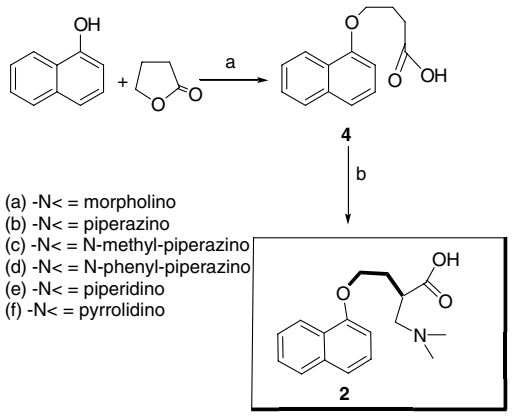
similar doses in anaesthetized cats (Table 1). However, compound **2e** having piperidino moiety in it caused considerable fall of blood pressure and can be compared with propranolol.

On comparison of SAR of **1a**–**f** with propranolol, shortening of propyl amine chain by two carbon atoms did not affect the hypotensive activity to large extent. However, a substantial enhancement of hypotensive activity was observed in **1d** when compared with propranolol or **2d**. Replacing N-phenyl-piperazine with other secondary amines resulted in decrease of hypotensive activity as observed in **2a**–**f**. Although **2e** exhibited marked hypotensive activity none of the other analogue was as potent as the lead the compound **1d**.

The synthesis of **1a**–**f** and **2a**–**f** is depicted in Schemes 1 and 2. Both 4-(2-naphthoxy)-butanoic acids **3** and 4-(1-naphthoxy)-butanoic acids **4** were first prepared by Cagniant and Charaux[13] in moderate yields from corresponding naphthol in two steps. Our improved procedure consists of one step regioselective synthesis of 4-naphthoxy-butanoic acids **3** and **4** in excellent yields. The synthetic approach to **3** involved condensation of 2-naphtol with γ-butyrolactone in presence of NaOEt and anhydrous EtOH. Compound **4** was prepared analogously to **3** from 1-naphthol according to procedure of Tandon et al.[14] The substituted butanoic acids **3** on reaction with secondary amines and *p*-formaldehyde in



Scheme 1. 2-Substituted aminomethyloxy naphthalenes **1**. Reagents and conditions: (a) NaOEt, 150 °C, dilute HCl; (b) HN<, $(CH_2O)_n$.



Scheme 2. 4-(1-Napthoxy-2-substituted aminomethyl)-butanoic acids. Reagents and conditions: (a) NaOEt, 150 °C, dilute HCl; (b) HN<, $(CH_2O)_n$.

absolute EtOH underwent Mannich reaction resulting in the formation of 2-substituted aminomethyloxy naphthalenes **1a**–**f**[15] (Scheme 1, Table 2). The substituted butanoic acids **4** on reaction with secondary amines and *para*-formaldehyde under similar reaction conditions, resulted in the formation of corresponding 4-(1-naphthoxy-2-substituted aminomethyl)-butanoic acids **2a**–**f** in good yield[16] (Scheme 2, Table 3).

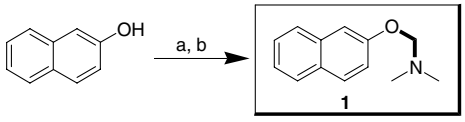
We envisaged the formation of 4-(2-napthoxy-2-substituted aminomethyl)-butanoic acids **5**[17] by Mannich reaction of 4-(2-naphthoxy)-butanoic acid **3** with secondary amines and *para*-formaldehyde. The formation of 2-substituted aminomethyloxy naphthalenes **1** may be explained by conversion of acid **3** into 2-naphthol and

Table 2. Synthetic data for compounds **1a**–**f**

Compounds	–N<	Mp (°C)	% Yield
1a	Morpholino	116	92
1b	Piperazino	94	90
1c	N-methyl-piperazino	141	89
1d	N-phenyl-piperazino	158	90
1e	Piperidino	149	92
1f	Pyrrolidino	128	76

Table 3. Synthetic data for compounds **2a–f**

Compounds	–N<	Mp (°C)	% Yield
2a	Morpholino	178	85
2b	Piperazino	119	84
2c	N-methyl-piperazino	188	90
2d	N-phenyl-piperazino	192	84
2e	Piperidino	171	82
2f	Pyrrolidino	168	87



(a) -N< = morpholino (d) -N< = N-phenyl-piperazino
(b) -N< = piperazino (e) -N< = piperidino
(c) -N< = N-methyl-piperazino (f) -N< = pyrrolidino

Scheme 3. 2-Substituted aminomethyloxy naphthalenes **1**. Reagents and conditions: (a) NaOEt, 150 °C, dilute HCl; (b) HN<, $(CH_2O)_n$.

further reaction of 2-naphthol with *para*-formaldehyde and secondary amines.

2-Substituted aminomethyloxy naphthalenes **1** have alternatively been synthesized by reaction of 2-naphthol with *p*-formaldehyde and secondary amines in support of mechanism of formation of these compounds from **3** by Mannich reaction[18] (Scheme 3).

In conclusion we have synthesized 2-substituted naphthalenes as hypotensive agents. Compound **1d** having better hypotensive profile than propranolol is being further investigated for drug development.

Acknowledgements

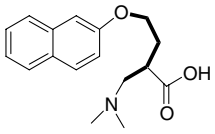
The authors are thankful to the regional sophisticated instrumentation centre, CDRI, Lucknow for elemental analysis, spectral data and pharmacological activity. This work was supported by a research grant from University Grants Commission of India.

References and notes

1. Botta, B.; Caringnani, M.; Volpe, A. R.; Botta, M.; Corelli, F.; Delle Monache, G. *Curr. Med. Chem.* **2003**, *10*, 1845.
2. Walker, A. F.; Marakis, G.; Morris, A. P.; Robinson, P. A. *Phytother. Res.* **2002**, *16*, 48.
3. Gryglas, P. *Pol. Arch. Med. Wewn.* **2001**, *105*, 109.
4. Mettimano, M.; Pichetti, F.; Fazzari, L.; Migneco, A.; Specchia, L.; Spica, V. R.; Savi, L. *Int. J. Clin. Pract.* **2000**, *54*, 424.
5. Hwang, S. K.; Juhasz, A.; Yoon, S. H.; Bodor, N. *J. Med. Chem.* **2000**, *43*, 1525.
6. Schann, S.; Bruban, V.; Pompermayer, K.; Feldman, J.; Pfeiffer, B.; Renard, P.; Scalbert, E.; Bousquet, P.; Ehrhardt, J. D. *J. Med. Chem.* **2001**, *44*, 1588.
7. Rastogi, S. N.; Anand, N.; Prasad, C. R. *J. Med. Chem.* **1972**, *15*, 286.
8. Rastogi, S. N.; Anand, N.; Gupta, P. P.; Sharma, J. N. *J. Med. Chem.* **1973**, *16*, 797.
9. Gupta, R. C.; Mukerji, S.; Chatterjee, S. K.; Rasotgi, S. N.; Anand, N.; Dube, M. P.; Sur, R. N.; Mukerji, K. C.; Srimal, R. C. *Arzneim. Forsch.* **1978**, *28*, 241.
10. Crowther, A. F.; Smith, L. H. *J. Med. Chem.* **1968**, *11*, 1009.
11. Hoffman, B. B.; Lefkowitz, R. J. In *The Pharmacological Basis of Therapeutics*, 9th ed.; Goodman, Gilman, Eds.; McGraw-Hill: USA, 1996; pp 232–233.
12. The hypotensive activity was carried out in the pharmacology division of Central Drug Research Institute, Lucknow, India **Pharmacology**: Cats (2.5–4.0 kg) were anaesthetized with pentobarbitone sodium (35.0 mg/kg ip) and their blood pressure (BP) was recorded from a carotidartery. The arterial vase was cannulated with a polyethylene catheter, filled with sodium citrate (5%) as anticoagulant and connected to a Hg-manometer. The trachea was intubated and respiration was recorded through a *Marey's tambour*. BP and respiration were recorded on a *kymograph*. The left femoral vein was cannulated with a polyethylene tube for injection of drugs and test compound. Contractions of the nictitating membrane due to electrical stimulation of preganglionic sympathetic nerve (50 Hz, 1 ms, 5–10 V for 5–101 s) were recorded through a system of pulleys and frontal wending lever on the kymograp. Responses of intravenous adrenaline (2–4 μg), acetylcholine (1–2 μg), histamine (1–2 μg) and isoprenaline (0.1 μg) on the BP were recorded before and after the administration of 1 and 5 mg/kg iv dose of the test compound. SE was calculated on the basis of three to four experiments carried out for each of the compounds reported in Table 1.
13. Cagniant, P.; Charaux, C. *Bull. Soc. Chim.* **1966**, *10*, 3249.
14. (a) Tandon, V. K.; Chandra, A.; Khanna, J. M.; Anand, N. *Tetrahedron* **1990**, *46*, 2871; (b) Tandon, V. K.; Chhor, R. B.; Goswamy, G. K. *Ind. J. Chem.* **1998**, *37B*, 1027.
15. General procedure for the preparation of 2-substituted aminomethyloxy naphthalenes **1**: A mixture of 4-(2-naphthoxy) butanoic acid **3** (2.30 g, 10 mmol), 2°-amine (10 mmol) and *para*-formaldehyde (0.45 g, 15 mmol) in anhydrous ethanol (20 mL) containing two to three drops of concentrated HCl was refluxed for 3 h. The mixture was cooled and additional quantities of 2°-amine (10 mmol) and *para*-formaldehyde (0.45 g, 15 mmol) were added and the mixture refluxed further for 2 h. Solvent ethanol was distilled off in vacuo and the residue was dissolved in water (20 mL) and extracted with diethylether (3×30 mL). NaOH (20 mL) and the product thus separated was extracted with diethylether (3×30 mL). The ether portion washed with brine, dried over $MgSO_4$, filtered and the filtrate concentrated to distill off solvent ether. Compounds **1(a–f)** were obtained as solids and were crystallized with ethanol, for example, 2-(N^4-phenyl-N^1 piperazino)-methyloxy naphthalene (**1d**) yield 90%; mp 158 °C; IR 2835, 1605 and 1575 cm^{-1}; ^1H NMR: δ 2.24 (m, 4H, $-N(CH_2)_2$), 3.09 (m, 4H, $Ph-N(CH_2)_2$), 4.07 (s, 2H, OCH_2), 6.75–7.80 (m, 12H, phenyl and naphth-H); ^{13}C NMR: δ 51.7, 57.9, 85.1, 105.8, 113.1, 118.0, 118.8, 123.7, 126.4, 126.8, 127.7, 129.4, 129.5, 134.6, 144.5, 157.7; MS: m/z 318 [M^+]. Anal. Calcd for $C_{21}H_{22}N_2O$ (318): C 79.24, H 6.91, N 8.80. Found C 79.20, H 7.0, N 8.84.
16. General procedure for the preparation of 4-(1-naphthoxy-2 substituted aminomethyl)-butanoic acids **2**: A mixture of 4-(1-napthoxy)-butanoic acid **4** (2.30 g, 10 mmol), 2°-amine and *para*-formaldehyde (0.45 g, 15 mmol) in anhydrous EtOH (20 mL) containing two to three drops of

concentrated HCl was refluxed for 3 h. The general procedure adopted for compounds **1** was followed for synthesis of **2(a–f)**. The products **2(a–f)** were crystallized from EtOH, for example, 4-(1-naphthoxy)-2-[methyl-(N^4-phenyl-N^1-piperazino)]-butanoic acid (**2d**) yield 84%; mp 192 °C; IR 3400 (OH) and 1712 (C=O) cm^{-1}; ^1H NMR: δ 1.86–2.38 (m, 4H, $2 \times CH_2$), 2.66 (m, 1H, CH), 4.02 (t, 2H, $J = 7.05$ Hz, $-OCH_2$), 6.74–8.48 (m, 13H, Ar–H and COOH); ^{13}C NMR: δ 27.8, 40.7, 53.1, 55.4, 57.9, 69.6, 103.6, 113.0, 118.0, 120.1, 121.9, 125.0, 125.5, 125.7, 126.2, 127.3, 129.4, 134.0, 144.5, 155.3, 179.5; MS: m/z 404 [M^+]. Anal. Calcd for $C_{25}H_{28}N_2O_3$ (404): C 74.25, H 6.93, N 6.93. Found C 74.02, H 6.86, N 7.01.

17. Proposed structure of **5**.



5

18. An alternative procedure for the preparation of 2-substituted aminomethyloxy naphthalenes **1**: 2-Naphthol (1.44 g, 10 mmol) was added to NaOEt (prepared from 0.25 g Na and 5 mL anhydrous EtOH). After the temperature of the solution dropped to 25 °C (room temperature); a mixture of 2°-amine (10 mmol) and *para*-formaldehyde (0.45 g, 15 mmol) in anhydrous ethanol (20 mL) containing two to three drops of concentrated HCl was refluxed for 3 h. The mixture was cooled and additional quantities of 2°-amine (10 mmol) and *para*-formaldehyde (0.45 g, 15 mmol) were added and the mixture refluxed further for 2 h. Solvent ethanol was distilled off in vacuo and the residue was dissolved in water (20 mL) and extracted with diethylether (3×30 mL). NaOH (20 mL) and the product thus separated was extracted with diethylether (3×30 mL). The ether portion washed with brine, dried over $MgSO_4$, filtered and the filtrate concentrated to distill off solvent ether. Compound **1a–f** were obtained as solids in 75–90% yields. The analytical data of **1a–f** were identical to those obtained by general procedure reported for synthesis of **1** in Ref. 15.