Indian Journal of Chemistry
Vol. 47B, October 2008, pp. 1587-1590

Note

Synthesis and β-adrenergic blocking activity of naphthyloxypropylamines

Ramya Vattipalli[1], Prabhakar Y Shirodkar[2], Rakesh R Somani*[1] & Vilasrao J Kadam[1]

[1]Department of Medicinal Chemistry, Bharati Vidyapeeth's College of Pharmacy, C.B.D., Belapur, Navi Mumbai 400 614, India

[2]Konkan Gnyanpeeth Rahul Dharkar's College of Pharmacy and Research Institute, Dahivali, Karjat, Raigad 410 201, India

E-mail: rakeshrsomani@yahoo.com

Received 9 January 2008; accepted (revised) 22 July 2008

A series of 1-isopropylamino-3-(3'-substituted-2'-naphthyloxy)-2-propanols have been synthesized and their structures have been confirmed by spectral analysis. All the derivatives have shown β-adrenergic blocking effect when tested on perfused frog heart. Compound **4e** exhibited 100% blockade of adrenaline response.

Keywords: Synthesis, β-adrenergic blockers, aryloxypropanol-amines

β-Blocking agents as a class have always attracted lot of interest from the medical fraternity, especially after the development of cardioselective β-blockers. A lot of data has been collected to suggest the β-blockers are among the very few antiarrhythmic agents which do not exhibit any pro-arrhythmic tendencies, unlike most other classes of antiarrhythmic agents[1-3].

Adrenergic β-receptor blocking compounds are structurally of two basic types, arylethanolamines (A, **Scheme I**) or aryloxypropanolamines (B, **Scheme I**). The titled compounds are of the type B.

The β-adrenergic blocking activity of aryloxy-propanolamines demands some essential structural features which include an aromatic or heterocyclic ring, an oxypropanol unit containing the secondary alcohol in the *S* configuration, and a secondary amine bearing at least two carbon constituents[5-7].

Previous work reported[8,9] showed that the compounds containing naphthyl group as the aromatic ring exhibited good pharmacological activity and hence, prompted us to undertake the present work. All the compounds were tested for their β-adrenergic blocking activity on the perfused frog heart.

Results and Discussion

The aim of the present work was to synthesize and evaluate for pharmacological activity a series of 1-isopropylamino-3-(3'-substituted-2'-naphthyloxy)-2-propanols from the starting material 3-hydroxy-2-naphthoic acid. The starting material was reacted with various aromatic amines to get a series of anilides **2a-2l** (ref.10)**.** Epichlorhydrin was used to convert the anilides into their respective epoxides, **3a-3l** (ref**.**11, 12)**.** The titled compounds **4a-4l** were obtained by the reaction of epoxides with isopropylamine[13], thus opening the epoxide ring (**Scheme II**). The various substituents and their analytical data is described in **Table I**. All the compounds showed moderate to good pharmacological activity and compound **4e** exhibited 100% blockade of adrenaline response.

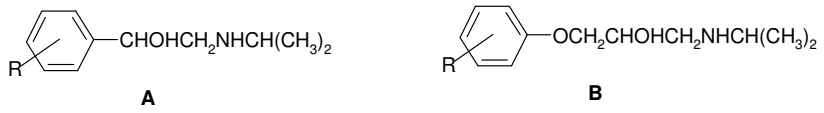
Pharmacological evaluation

Aqueous solutions of the titled compounds were used for testing pharmacological activity[9]. The activity was measured in terms of the percent (%) inhibition of the adrenaline response produced due to the administration of the titled compounds. The % inhibition was calculated by comparing the heart rate on administration of plain adrenaline solution with the reduced heart rate produced due to the presence of the compound. Propranol was used as the standard.

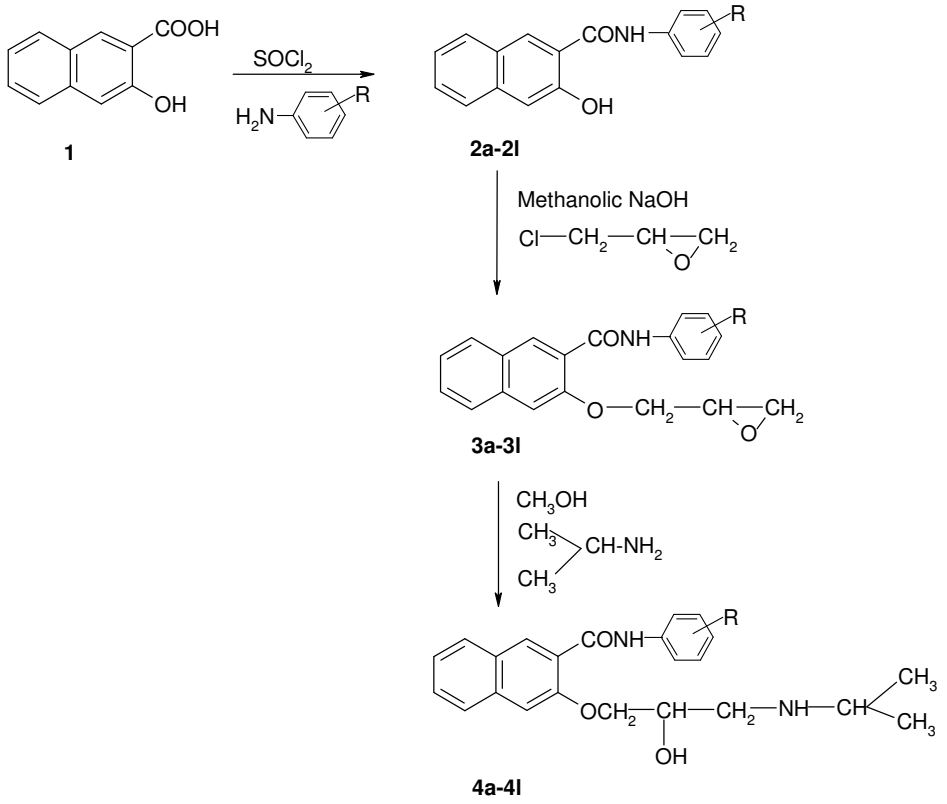
Maximum inhibitory potency was shown by the compound **4e**. This compound showed 100% inhibition of induced tachycardia at a dose of 7 µg. Presence of the same halogens (Cl and F) at any other positions gave compounds with highly varying degree of activity. Good activity was shown by compounds **4a**-**e**. However, compounds **4d** and **4f** showed the least % inhibition of tachycardia. Compounds **4i, 4j**, and **4l** which do not contain any halogens showed moderate to good activity.

Experimental Section

All the melting points were determined on a Veego VMP-D apparatus and are uncorrected. Silica gel G plates of 3 × 8 cm (Sigma-Aldrich) were used for TLC and spots were located by UV or in iodine chamber. The IR spectra were recorded in the 4000-400 cm^{-1} range using KBr discs on a FT-IR 8400 Shimadzu spectrometer. ^1H NMR spectra were



Scheme I



Scheme II

recorded on Varian Mercury (300 MHz) spectrometer in DMSO-d_6 as solvent using TMS as an internal standard and values are expressed in δ ppm. Elemental analyses performed for C, H, N were found within ±1.0% of theoretical values.

Preparation of anilides 2a-2l. 3-Hydroxy-2-naphthoic acid (10 g, 0.052 mole) was heated for 1.5 hr at 35-40°C in 60 mL of chlorobenzene containing 4.2 mL of $SOCl_2$ and 0.1 mL of DMF. When the reaction was complete, excess $SOCl_2$ was distilled off under vacuum and the solution was added dropwise over 0.5 hr at 5-10°C to a solution containing 7.5 g (0.05 mole) of the required amine and 4.1 g of anhydrous sodium acetate in 70 mL of DMF. The reaction- mixture was stirred for 3 hr at 20°C and then heated to 50°C and filtered. The product was washed with methanol and boiling water.

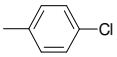
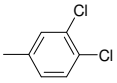
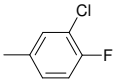
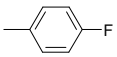
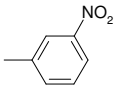
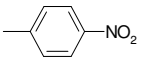
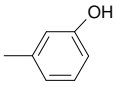
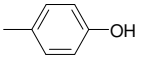
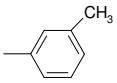
Compound **2a**: IR (KBr). 3293 and 3056 (N-H str and O-H str), 1625 (-C=O str), 1365 and 1175 (O-H bending and –C-OH str), 866, 779 and 745 cm^{-1} (C-H def).

Preparation of epoxides 3a-3l. The appropriate 3-hydroxy-2-naphthylanilide (0.005 mole) was dissolved in 10 mL 0.6*M* methanolic NaOH solution which was added over an hour into a solution of epichlorohydrin (0.1 mole) in methanol. This mixture was left overnight to yield the crude product. It was filtered, washed with water and aqueous methanol and dried.

In cases where a solid precipitate was not formed, on completion of the reaction, the excess of epichlorhydrin and methanol were removed by evaporation under vacuum. The oily residue was taken in ethyl acetate and allowed to stand overnight. The epoxide separated in the form of congealed oil in high yield. The residue so obtained was used as such for the next step.

Compound **3a**: IR (KBr): 3326 (N-H *str*), 2948 (aliphatic –CH_2 and –CH), 1658 (-C=O *str*), 1448 and

Table I – Physical and pharmacological activity data of compounds **4a-4l**

Compd	R	Molecular formula	m.p. (°C)	% Block (10 µg)
4a[†]		$C_{23}H_{25}ClN_2O_3$	146	45.79
4b		$C_{23}H_{25}ClN_2O_3$	150	31.25
4c[†]		$C_{23}H_{24}Cl_2N_2O_3$	135	42.45
4d		$C_{23}H_{24}Cl_2N_2O_3$	124-26	14.81
4e		$C_{23}H_{24}FClN_2O_3$	129-31	100[#]
4f		$C_{23}H_{25}FN_2O_3$	157	16.45
4g[†]		$C_{23}H_{25}N_3O_5$	149	40.24
4h		$C_{23}H_{25}N_3O_5$	132-34	22.25
4i		$C_{23}H_{26}N_2O_4$	152-54	17.07
4j		$C_{23}H_{26}N_2O_4$	Oil	36.98
4k		$C_{24}H_{28}N_2O_3$	135-38	16.66
4l		$C_{23}H_{27}N_3O_3$	126-28	18.75

[#] Response at 7µg [†]Ref. 14

1404 (aromatic C=C), 1338 (aromatic –OCH_2), 1251 and 1207 (epoxide C-O-C), 1077 (in plane C-H bend), 865,754 and 690 cm^{-1} (aromatics).

Preparation of titled compounds 4a-4l. 0.02 mole of the appropriate epoxide was dissolved in dry methanol and a large excess of anhydrous isopropylamine (99%) LR was added and refluxed on water-bath till the reaction was complete. At the end of the reaction, the excess isopropylamine was evaporated to dryness in vacuum. The residue obtained was extracted between 2*N* HCl and ether. The HCl layer was basified with 11 *N* NaOH. The product was filtered off and dried and recrystallised from ethyl acetate.

In cases where the product so obtained was found to be hygroscopic, they were converted into the oxalate salts. A saturated solution of oxalic acid in ethanol was added in equimolar quantities to an ethanolic solution of the compound. This solution was left overnight and the precipitated solid was filtered and dried.

Compound **4a**: IR (KBr): 3330 (O-H str and N-H str), 3055 and 2979 (aromatics and alkyl groups), 1666 (-C=O str), 1532 (aromatic C=C), 1447 [-$CH(CH_3)_2$], 1253 (C-O-C str), 1206 (sec. amine, aC-N str), 1071 (in plane C-H bend), 757 (disubstituted aromatics), 684 cm^{-1} (substituted benzene).

4b: Anal. Calcd for $C_{23}H_{25}ClN_2O_3$: C, 66.99; H, 6.06; N, 6.79. Found: C; 66.32; H, 7.08; N, 6.91%. **4d**: Anal Calcd for $C_{23}H_{24}Cl_2N_2O_3$: C, 61.74; H, 5.37; N, 6.26. Found: C, 61.53; H, 5.81; N, 5.95%. **4e**: Anal. Calcd for $C_{23}H_{24}FClN_2O_3$: C, 64.56; H, 4.61; N, 6.55. Found: C; 65.37; H, 4.75; N, 6.84%. **4f**: ^{1}H NMR (DMSO-d_6): δ 0.92-0.95 (s, 6H, CH_3), 2.60-2.80 (m, 3H, CH_2 and CH), 4.00 (s,1H, OH), 4.20 (m, 1H, CH), 4.30 (d, 2H, OCH_2), 5.30 (s, 1H, NH), 7.20-8.40 (Ar-H), 10.40 (s, 1H, CONH); **4g**: ^{1}H NMR (DMSO-d_6): δ 0.97-0.95 (s, 6H, CH_3), 2.70-2.90 (m, 3H, CH_2-and CH), 3.90 (s,1H, OH), 4.10 (m, 1H, CH), 4.25 (d, 2H, OCH_2), 5.47 (s, 1H, NH), 7.40-8.90 (Ar-H) , 10.80 (s, 1H, CONH); **4h**: Anal. Calcd for $C_{23}H_{25}N_3O_5$: C, 65.25; H, 5.91; N, 9.93. Found: C; 64.94; H, 6.23; N, 9.32%. **4j**: ^{1}H NMR (DMSO-d_6): 1.10 (s, 6H, CH_3), 3.00-3.20 (m, 3H, CH_2 and CH), 3.40 (s, 1H, NH), 3.40 (s,1H, OH), 4.10-4.30 (m, 3H, CH and OCH_2), 7.2-8.2 (Ar-H), 10.4 (s, 1H, CONH); Anal. Calcd for $C_{23}H_{26}N_2O_4$: C, 70.05; H, 6.56; N, 7.10. Found: C; 71.23; H, 6.74; N, 6.40%. **4k**: Anal. Calcd for $C_{24}H_{28}N_2O_3$: C, 73.47; H, 7.14; N, 7.41. Found: C; 72.36; H, 6.99; N, 7.26%. **4l**: Anal. Calcd for $C_{23}H_{27}N_3O_3$: C, 70.23; H, 6.87; N, 10.69. Found: C; 70.61; H, 7.56; N, 11.08%.

References

1 *Basic and Clinical Pharmacology*, edited by Katzung B G, 1st Edn. (Appleton and Lange, Norwolk), **2001**.

2 Micheal K P, *Drug Dev Res*, 55, **2002,** 3.

3 Kuehlkamp V, Bosch R, Mewis C S and Seipel L, *Am J Cardiovasc Drugs* , 2 (1), **2002**, 37.

4 Bramah N S, *J Cardiovas Pharmacol Therap*, 10(4), **2005**, S3- S14.

5 Powell C E & Slater T H, *J Pharmacol Expt Ther,* 122, **1958**, 480.
6 Black J W & Stephenson J S, *Lancet*, **1962**, 711.
7 Smith L H, *J Med Chem,* 20, **1977**, 705.
8 Shirodkar P Y & Jariwala D, *Indian Drugs*, 23(4),**1986**, 225.
9 Ghone A K &Shirodkar P Y, *Indian Drugs,* 29(8), **1992**, 340.
10 Kraska J &Borusczak Z, *Dyes and Pigments,* 12, **1990**, 57.
11 Crowther A F, Howe R &Smith C H, *J Med Chem,* 14, **1971**, 511.
12 Crowther A F, Howe R, Stephenson J S, Rao B S &Smith L H, *J Med Chem*, 11, **1968**, 1009.
13 Shtacher G, Rubinstein R &Somani P, *J Med Chem,* 21, **1978**, 678.
14 Shirsat V, *Studies on Cardiovascular Drugs*, M Pharm Thesis, submitted to The University of Mumbai, **1992**.