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Design and synthesis some analogs of propranolol using essential amino acid

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ABSTRACT

Propranolol is a non-selective beta blocker mainly used in the treatment of hypertension. It was the first successful beta blocker developed. Due to its nonselective and other pharmacokinetic problem, now a days it was not been the first line choice of drug . Various analogs of propranolol were synthesized to increase the duration of action and marketability. The new analogs (IV) were synthesized by reacting epichlorohydrine (I) with alpha naphthol (II) and then the product epoxy naphthol (III) was reacted with ethyl ester of various essential amino acids (V). The synthesized compounds were characterized by various spectral analyses.

Key word: Antihypertensive, epichlorohydrine, Propranolol.

INTRODUCTION

Hypertension is a consequence of many diseases and needed long term therapy and regular intake of single or multiple medicines which may leads to a sever side effect.

Propranolol is a non-selective beta blocker mainly used in the treatment of hypertension. The aryloxypropanolamine moiety and the alcoholic hydroxyl group present in the propranolol are essential for activity[1]. The present investigation was done to improve the treatment of hypertension by synthesizing the analogs of propranolol which may enhance the duration of action and reduce the side effect. The isopropyl amine moiety of propranolol was replaced with ester of various essential amino acid.

EXPERIMENTAL

All the reactions were carried out under purified nitrogen atmosphere. Solvent were purified by standard procedure and freshly distilled before use. TLC was performed to access the reaction and purity of product. Melting points of the derivatives were recorded in Theil's Melting Point Tube and were uncorrected. IR spectra were recorded in Perkin Elmer 297 spectrophotometer in KBr pellets and only noteworthy absorption levels (reciprocal centimeter) are listed. The H^1-NMR spectra were recorded at 400 MHz on Bruker amx 400 MHz spectrophotometer in various solvent using TMS as internal standard.

Preparation of epoxy naphthol (III) [2]

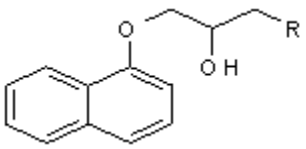
Dissolved one equivalent alpha naphthol in acetone and added ten equivalent dried potassium carbonate. The ten equivalent epichlorohydrine was added drop by drop and refluxed the mixture about 12hr. After 12 hr the product was cooled and stirred at room temperature for about 4hr.The product was filtered and the clear light brown color filtrate was taken. The liquid was distilled to remove acetone and collect the product. The pure epoxy naphthol was collected by column chromatography (mobile phase was hexane: ethyl acetate= 8: 2). The yield was found to be 70%. M.P 95°C

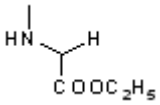
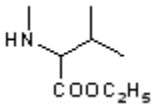
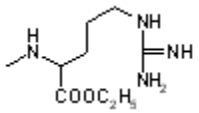
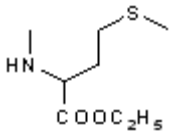
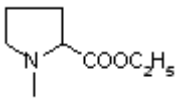
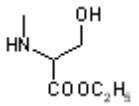
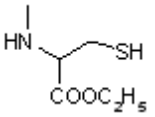
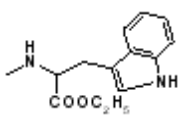
TLC:Hexane: Ethyl acetate: triethyl amine = 8: 1.5: 0.5 . Rf value 0.66.
NMR spectral data δ8.3 (1H t Ar H), δ7.8 (1H t Ar H), δ7.5 (1H t Ar H), δ7.4 (1H d Ar H0, δ7.3 (1H d Ar H) δ6.8 (1H d Ar H), δ4.4 (2H t Al H), δ4.1(2H t Al H0, δ2.9 (2 H t Al H).

Esterification of amino acid (V)[3]

The concentrated solution of sulphuric acid was added care fully in to the suspension of amino acid (Glycine, Valine, Arginine, Methionine, Proline, Serine, Cysteine, Triptophane) (59.8 mmol) in absolute ethanol (40ml). The resulting yellow solution is heated at reflux for 5hr. cooled the solution at 0^0C and neutralized with concentrated aqueous ammonia solution. The precipitated produc was then collected by filtration, washed with cold water and

Table 1: Analytical data of different synthesized compounds



S. No.	Name of the compound	Structure (R)	Molecular formula	BP 0C	Rf value	% Yield
1	VI a		$C_{17}H_{21}NO_4$	152	0.32	40
2	VI b		$C_{20}H_{27}N0_4$	163	0.54	44
3	VI c		$C_{20}H_{20}N_4O_2$	165	0.40	45
4	VI d		$C_{20}H_{27}NO_4S$	50	0.41	155
5	VI e		$C_{20}H_{25}NO_4$	150	0.50	44
6	VI f		$C_{19}H_{23}NO_5$	140	0.60	60
7	VI g		$C_{20}H_{23}NO_4S$	170	0.60	608
8.	VI h		$C_{26}H_{28}N_2O_4$	48	0.32	137

recrystalized from aqueous ethanol. The yield was found to be about 40%. TLC was taken by taking n-butanol, glacial acetic acid and water as mobile phase and ninhydrine solution as detecting agent.

Reaction of Epoxy naphthol with ester of amino acid (VI a, b, c. d. e, f, g, h)[4,5,6]

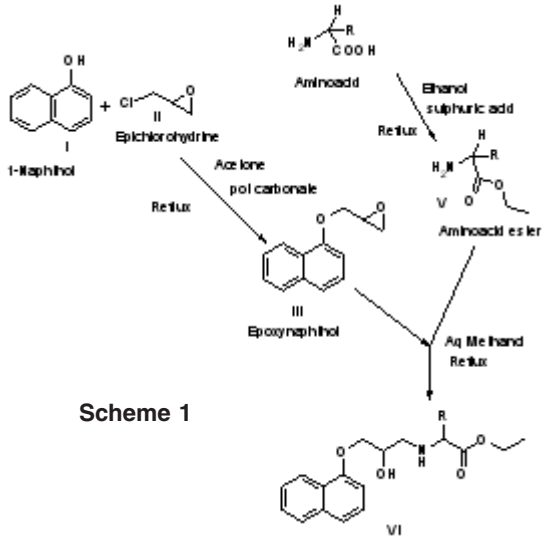
Two mmol quantity of epoxy naphthol and the ester of amino acid ware taken and 15ml of methanol were added. The mixture was heated about 50^{0}C with few drops of water. The solution was kept aside for 4hr and extracted with ethyl acetate. After that the solution was distilled under reduce pressure to remove solvent. The pure yellow liquid was obtained. The yield was found to be about50%. (Table 1).TLC solvent hexane: ethyl acetate= 9:1.

RESULTS AND DISCUSSION

Different analogs of propranolol were synthesized by reacting epichlorohydrine with alpha naphthol, and the product epoxy naphthol were reacted with ester of essential; amino acid (ethyl ester of Glycine, Valine, Arginine, Methionine, Proline, Serine, Cysteine, Triptophane).

Table 2: NMR and IR data of synthesized compounds

S. NO	Compound	NMR Data	IR Data
1	VI a	δ8.3(d 1HArH), δ7.8(d1HArH), δ7.6(t3HArH), δ7.4(d1HArH), δ7.05(1H OH), δ7.9(d 1HArH), δ4.4(t 2HAlH), δ4.2(m5HAlH), δ4(1H NH), δ3.4(m 1HAlH), δ3.2(d 2HAlH),	3432cm^{-1}(OH st), 3035 cm^{-1}(stArH), 2969 cm^{-1}(stAlH), 1622 cm^{-1}(st CO Ester), 1582 cm^{-1}(st NH), 1345 cm^{-1}(st CN)
2	VI b	δ8.3(d2HArh), δ8.1(t1HArH), δ7.9(t2HArH), δ7.8(d2HArH), δ5.6(1HOH), δ3.9(2HAlH), δ2.6(1HNH), δ1.6(6HAlH)	3601 cm^{-1}(st OH), 3301 cm^{-1}(st Ar H), 2786.6 cm^{-1}(st AlH), 1679.7(st CO Ester) 1578.5 cm^{-1} (st NH), 1364.8 cm^{-1}(st CN)
3	VI c	δ 8.3(d 1HArH), δ7.6(d 1HArH), δ7.5(t 3HArH), δ7.35(d 1HArH), δ7.1(1H OH), δ6.8(d 1HArH), δ4.4(m1HAlH), δ4.2(d 6HAlH), δ3.4(m 5HAlH), δ3.2(d 4HAlH), ä2(m 1HAlH), δ1.8(1HAlH&NH)	3661 cm^{-1}(st OH), 3301 cm^{-1}(st Ar H), 2766 cm^{-1}(st AlH), 1666.7(st CO Ester) 1576 cm^{-1} (st NH), 1400.2 cm^{-1}(st CN)
4	VI d	δ8.3(d 1HArH), δ7.9(d 1HArH), δ7.55(t 2HArH), δ7(d 1HArH), δ7(t 1HArH), δ7.05(1H OH), δ6.7(d 1HArH), δ4.5(d 2HAlH), δ4.2(6HAlH), δ4(t 1HAlH), δ3.4(m 1HAlH), ä 3.2(d 2HAlH), δ2.8(t 1HAlH), δ2.2(1H NH)	3669 cm^{-1}(st OH), 3113 cm^{-1}(st Ar H), 2886.2 cm^{-1}(st AlH), 1681(st CO Ester) 1537 cm^{-1} (st NH), 1425.4 cm^{-1}(st CN)
5	VI e	δ 8.3(d 1HArH), δ 7.9(d 1HArH), δ7.6(t 3HArH), δ7.4(d 1HArH), δ7.25(1H OH), δ6.8(d 1HArH),δ4.5(m 7HAlH), δ4.2(d 4HAlH), δ3.4(m 1HAlH,1H NH), δ3.3(m 5HAlH)	3650.2 cm^{-1}(st OH), 3300 cm^{-1}(st Ar H), 2886.1 cm^{-1}(st AlH), 1685.7(st CO Ester) 1559.4 cm^{-1} (st NH), 1365 cm^{-1}(st CN
6	VI f	δ8.4-7.8(7HArH), δ6(HOH), δ5.9(HOH), δ4.2(2HAlH), δ4.3(t1HAlH) δ2.3-2.2(5HAlH), δ2(1HNH).	3569 cm^{-1}(st OH), 3269 cm^{-1}(st Ar H), 2834.9 cm^{-1}(st AlH), 1605.3 3(st CO Ester) 1555.7 cm^{-1} (st NH), 1400.9 cm^{-1}(st CN
7	VI g	δ 8.3(d 1HArH), δ7.7(d 1HArH), δ7.5(t 3HArH), δ7.3(1HArH), δ6.7(d 1HArH), δ4.4(t 4HAlH), δ4.1(mH NH), δ3.35(m 1554.9 cm^{-1} (st NH), 1424.9	3425.3 cm^{-1}(st OH), 3073 cm^{-1}(st Ar H), 2863.9 cm^{-1}(st AlH), δ615.3(st CO Ester) 3HAlH), t3.1(d6HAlH),cm^{-1}(st CN)
8	VI h	δ 7.9-7.3(7HArH), δ7.2-7.3(5HArH), δ7(1HArNH), δ5.4(1H OH), δ3.4-3(8HAlH), δ 2.4(1HAlNH)	3630 cm^{-1}(st OH), 3301 cm^{-1}(st Ar H), 2785 cm^{-1}(st AlH), 1686(st CO Ester) 1551 cm^{-1} (st NH), 1365 cm^{-1}(st CN)



Scheme 1

The structure of the synthesized compounds were confirm by TLC[7, 8], MP, IR[9, 10] and NMR[11] data which were tabulated (Table 2). The further investigation will be carried out to for pharmacological screening and pharmacokinetics study.

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