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Synthesis and Hydrolysis Kinetic Study of Few Co-drugs of Propranolol and other Antihypertensive Drugs

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ABSTRACT

The different acyl halide analogs of propranolol were synthesized by reacting Propanolol with different acyl anhydrides in toluene medium. The derivatives were reacted with thionyl chloride to get propranolol hemi acyl chloride. Finally the co-drugs were synthesized by reacting propranolol hemi acyl chloride with different classes of antihypertensive drugs like Nifedepine (PSN,PMN,PPN), Hydrochlorthiazide (PSH, PMH, PPH) and Acetazolamide(PSA, PMA, PPA) by ester linkage. The structure of the synthesized derivative of propranolol analogs were confirmed by MP, TLC, IR and NMR data.

Key words: Propranolol, Acyl anhydrided, Antihypertensive drugs.

INTRODUCTION

A co-drug is comprised two or more covalently bound moieties, wherein each moiety is a residue of a constituent compound having a biological activity, or a prodrug form thereof, wherein said codrug is cleaved under physiological conditions to regenerate each constituent compound[1]. In present investigation the various co-drugs were made by reacting propranolol with other class of antihypertensive drugs like nifedepine, hydrochlorthiazide and acetazolamide through anhydride (Succinic, Maleic, Phthalic) bridge. The reactions were monitored by single spot TLC and the structures of the compounds were confirmed by MP, TLC, IR and NMR data (Table II and III)

EXPERIMENTAL

Melting points were recorded in open capillary tubes and are uncorrected. The IR spectra were carried out using KBr pellets at IISc, Bangalore. The NMR spectra of the compounds were carried out in Bruker spectrospin-200 NMR spectrophotometer at IISc, Bangalore.(Table II and III)

Synthesis of Propranolol hemi ester

Mixture of 1 eq of propranolol hydrochloride and 1 eq.of acyl anhydride (Succinic, Maleic, Phthalic) were refluxed in redistilled toluene for 7 hrs with occasional strring. The newly-formed products were separated as oil during the reaction.

The toluene was decanted and the product was crystallized from acetone. The product showed the single spot on TLC using methanol and n-butanol (1:1) as mobile phase.[2]

Synthesis of propranolol hemi acyl chloride

0.5g of dry propranolol hemiester was taken into a flask fitted with reflux condenser. To this 5 ml of redistilled thionyl chloride was added carefully. The reaction mixture was refluxed for 30 min. Cotton wool was placed in top of the condenser to reduce the entry of moisture. The excess thionyl chloride was distilled at 78^{0}C from the reaction mixture. The liquid was cooled and collected the solid.[2]

Synthesis of codrug of propranolol

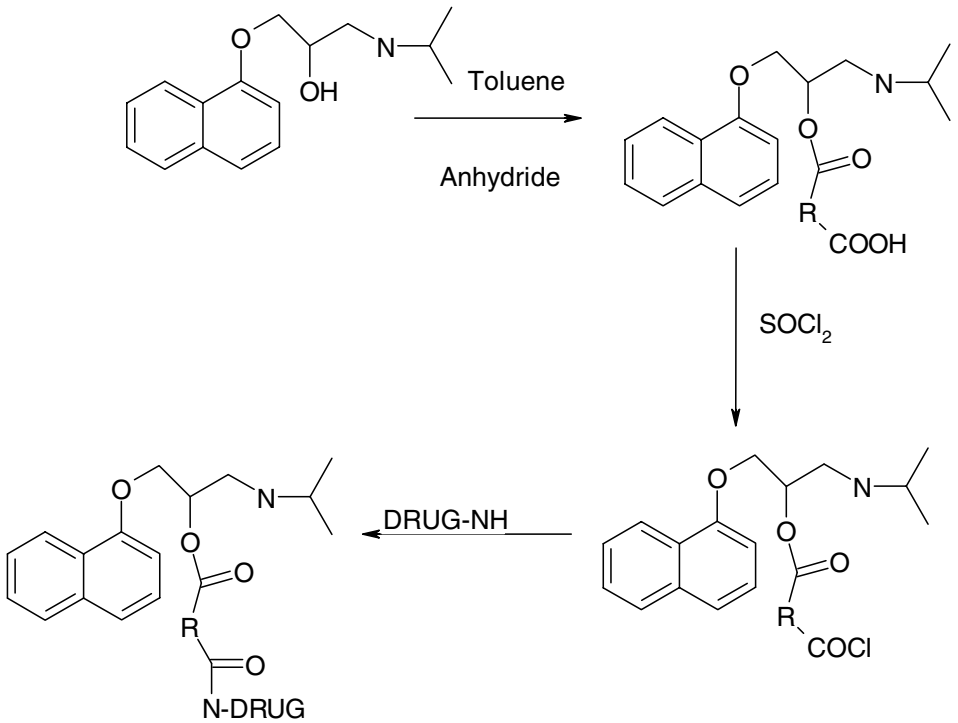
Co-drug of propranolol with nifedepine through amidation reaction

Equimolar quantity of propranolol hemi acyl chloride and nifedepine were taken in round bottom flask. 15ml Toluene and 1 ml Triethyl amine were added to the reaction mixture. The reaction mixture was refluxed for 30 min and cooled. The dark color solution was filtered and concentrated. [3]

Co-drug of propranolol with hydrochlorthiazide and acetazolamide through amidation reaction

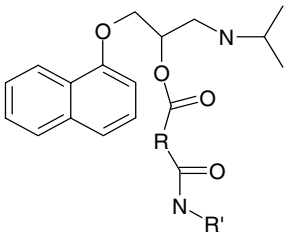
1.7mM of each hydrochlorthiazide and acetazolamide was dissolved in 10 ml of distilled water in a separate RBF. The pH of the solution was adjusted to 7 after that 8 ml of Dioxan were added slowly to the solution. The solution was kept at 8 degree C during this entire procedure

The solution containing the propranolol hemi acyl chloride was added drop wise to hydrochlorthiazide and acetazolamide solution with constant stirring. Maintained the temperature at 8 degree C throughout the reaction. The pH was maintained between 8.5 to 9.5 in both the flask by addition of a few drops of sodium hydroxide (1N). The pH of the solutions was checked frequently and maintained. The reaction was considered to be completed when the pH did not drop on the addition of the anhydride solution in both the reaction vessels. The reaction mixture was then allowed to stand at 8 degree C for an additional 20-30 min. The precipitate was obtained, collected through filtration.



Scheme of synthesis

Table-I Structure of synthesized codrug



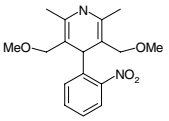
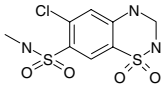
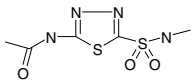
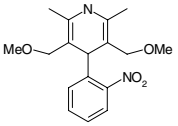
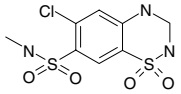
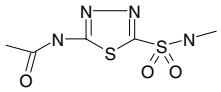
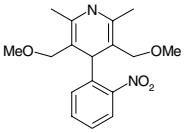
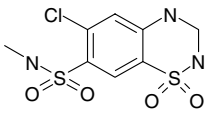
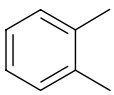
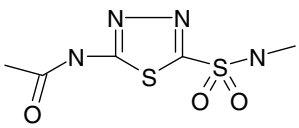
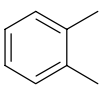
Codrug	R^1	R	Molecular formula
PSN		—CH_2CH_2—	$C_{37}H_{45}N_3O_8$
PSH		—CH_2CH_2—	$C_{27}H_{31}ClN_4O_8S_2$
PSA		—CH_2CH_2—	$C_{24}H_{29}N_5O_7S_2$
PMN		-CH=CH-	$C_{37}H_{43}N_3O_8$
PMH		-CH=CH-	$C_{31}H_{31}ClN_4O_8S_2$
PMA		-CH=CH-	$C_{24}H_{27}N_5O_7S_2$
PPN			$C_{41}H_{45}N_3O_8$
PPH			$C_{31}H_{31}ClN_4O_8S_2$
PPA			$C_{28}H_{29}N_5O_7S_2$

Table 3: NMR and IR Data Of Synthesized codrug

Codrug	NMR Data	IR Data
PSN	δ 7.7(d,2H ArH), δ7.67(d,2H ArH), δ7.52(d,2H ArH), d7.45(t,1H ArH), δ7.3(t,2H ArH), δ7.25(t,2H ArH), δ5.6(1H NH), δ3.5(s,6H OCH_3), δ3.1(m,2H AlH), δ2.8(s,4H AlH), δ2.51(s,6H AlH), δ2.3(6H AlH), δ1.4(t,4H AlH), δ1.25(d,4H AlH).	3331.04 cm^{-1}(2^0 NH str), 3099.68.01cm^{-1} (C-H aromatic), 2953.19cm^{-1} (C-H aliphatic str),1683.81 cm^{-1}(Amide C=O str), 1646.66(ester C=O) 1529.56 cm^{-1}(C=C str aromatic),1101.27 cm^{-1}(-O- str).
PSH	1.2d (CH_3,d,6H), 2.5d (CH_2, δ, 4H), 3.4d(CH_2, t, 2H), 6δ(CONH, s, 1H), 7-8.5δ(aromatic H, m, 11H)8.6δ(ring NH, s, 1H), 8.9δ(ring NH, s,1H),	3275.88 cm^{-1}(2^0 NH str), 3361 cm^{-1}(ring NH str) 2926cm^{-1},(C-H aliphatic str) 3223cm^{-1} (C-H aromatic),1679 cm^{-1} (C=O str), 1456.90 cm^{-1}(C=C str aromatic), 1367.82 cm^{-1}(SO_2 str).
PSA	1.3δ (CH_3,d,6H), 3.2d (CH_2, d, 4H), 6.3δ(CONH, s, 1H), 8.6δ(ring NH, s, 1H), 8.9δ(ring NH, s, 1H), 3.5δ(CH_2, d 2H), 7-8.5δ (aromatic H,m,7H).	3289.68cm^{-1}(2^0 NH str), 2926cm^{-1} (C-H aliphatic str) 3223.3cm^{-1} (C-H aromatic),1679cm^{-1}(C=O str),1456.90 cm^{-1}(C=C str aromatic), 1367.82 cm^{-1}(SO_2 str).
PMN	δ7.68-7.66(m,5H ArH), δ7.51-7.26(m,6H ArH), δ5.71(1H NH), δ3.83(6H CH_2), δ3.58(6H OCH_3), δ3.11(7H AlH), δ2.67(6H AlH), δ2.34(5H AlH).	3330.80 cm^{-1}(2^0 NH str), 3100.87cm^{-1} (C-H aromatic), 2953.20cm^{-1} (C-H aliphatic str) ,1683.67 cm^{-1}(Amide C=O str),1647.07 (ester C=O) 1529.16 cm^{-1}(C=C str aromatic), 1101.73 cm^{-1}(-O- str).
PMH	1.3δ (CH_3,d,6H), 2.4δ (CH_2, d, 4H), 4δ(CH, d, 2H), 6.2δ(CONH, s, 1H), 7.6δ(ring NH, s, 1H), 7.7δ(ring NH, s,1H),7.8-8.5δ(aromatic H, m, 11H)	3329 cm^{-1}(2^0 NH str), 2953.03cm^{-1} (C-H aliphatic str) ,1683.38 cm^{-1}(Amide C=O str),1647.58(ester C=O) 1529.23 cm^{-1}(C=C str aromatic), 1104.784cm^{-1}(-O- str).
PMA	1.3δ (CH_3,d,6H), 3.2δ (CH_2, d, 4H), 6.3δ(CONH, s, 1H), 8.6δ(ring NH, s, 1H), 8.9δ(ring NH, s,1H), 3.5δ(CH_2, d 2H), 7-8.5δ (aromatic H,m,7H).	3289.67cm^{-1}(2^0 NH str), 2965.27cm^{-1} (C-H aliphatic str) 3221.35cm^{-1} (C-H aromatic),1679.25cm^{-1}(C=O str),1455.95 cm^{-1}(C=C str aromatic), 1367.85 cm^{-1}(SO_2 str).
PPN	δ7.69(d,2H ArH), δ7.67(d,2H ArH), δ7.52(d,2H ArH), δ7.50(d,2H ArH), δ7.47-7.45(7H ArH), δ5.72(1H NH), δ3.59(s,6H AlH), δ3.13-3.08(m,1H AlH), δ2.69-2.65(4H AlH), δ2.53(12H AlH), δ1.42-1.38(5H AlH), δ1.25(1H AlH).	3331.42 cm^{-1}(2^0 NH str), 3078.01cm^{-1} (C-H aromatic), 2953.35cm^{-1} (C-H aliphatic str) ,1680.44 cm^{-1}(Amide C=O str),1647.38 (ester C=O) 1529.64 cm^{-1}(C=C str aromatic), 1101.11 cm^{-1}(-O- str).
PPH	1.3δ (CH_3,d,6H), 3.2δ (CH_2, d, 4H), 6.3 3301.9 cm^{-1}(2^0 NH str), 2785cm^{-1} (C-H s, 1H), 8.6δ(ring NH, s, 1H), 8.9δ(ring NH, s,	AlH), δ1.42-1.38(5H AlH), δ1.25(1H AlH). (CONH, aliphatic str). 3082.3cm^{-1} (C-H aromatic), 3.5d(CH_2, d 2H), 7-8.5d(aromatic H, m,11H) 1686 cm^{-1} (C=Ostr), 1420.40 cm^{-1} (C=C str aromatic), 1365.8 cm^{-1}(SO_2 str).
PPA	1.3δ (CH_3,d,6H), 3.5δ (CH_2, t, 2H), 6.3δ(CONH, s, 1H), 8.9δ(ring NH, s,1H), 4.2δ(CH_2, t, 2H), 9.5δ(aromatic H, m, 7H).	3277.1cm^{-1}(2^0 NH str), 2926cm^{-1} (C-H 8-aliphatic) 3104.1cm^{-1} (C-H aromatic), 1763cm^{-1}(C=O str),1458 cm^{-1}(C=C str aromatic),1336 cm^{-1}(SO_2 str).

The completion of reactions were confirmed by taking TLC using ethyl acetate : n-hexane (9:1) mobile phase and melting point was checked.[4]

Table 2: Analytical data of synthesized compound

Codrug	MP °C	Rf value of TLC	% yield
PSN	265	0.69	50
PSH	286	0.79	65
PSA	280	0.61	65
PMN	268	0.52	46
PMH	282	0.49	56
PMA	275	0.65	70
PPN	260	0.52	50
PPH	273	0.45	75
PPA	258	0.59	55

RESULTS AND DISCUSSION

Hydrolysis at pH 7.4

Twelve co-drugs ((PSN, PSH, PSA, PMN, PMH, PMA, PPN, PPH, and PPA) were synthesized out of which three derivatives, i.e., PSH, PMH, PPH have shown hydrolysis half life 30, 32 and 34 min for hydrochlorthiazide and 5.4, 5.3 and 2.2 hr for propranolol hemiester at 37^{0}C.

The compound PSA, PMA and PPA has shown hydrolysis half life 38, 32 and min for acetazolamide and 5.4, 5.2 and 3.0 hr for propranolol hemi ester at 37^{0}C.

Table 4: Hydrolysis half life of codrugs of Propranolol and Hydrochlorthiazide

Codrug	pH 1.2	pH 7.4	
		Propranolol hemi ester	Hydrochlorthiazide
PSH	No hydrolysis	5.2 hr	30 min
PMH	No hydrolysis	5.3 hr	32 min
PPH	No hydrolysis	2.2 hr	34 min

Table 5: Hydrolysis half life of codrugs of Propranolol and Acetazolamide

Codrug	pH 1.2	pH 7.4	
		Propranolol hemi ester	Hydrochlorthiazide
PSA	No hydrolysis	5.4 hr	38 min
PMA	No hydrolysis	5.2 hr	32 min
PPA	No hydrolysis	3.0 hr	40 min

Table 6: Hydrolysis half life of codrugs of Propranolol and Nifedepine

Codrug	pH 1.2	pH 7.4	
		Propranolol hemi ester	Hydrochlorthiazide
PSN	No hydrolysis	5.1	33
PMN	No hydrolysis	5.3	36
PPN	No hydrolysis	5.2	30

Similarly the compound PSN, PMN and PPN has shown hydrolysis half life 33, 36 and 30 min for nifedepine and 5.1, 5.3 and 5.2 hr for propranolol hemi ester at 37^{0}C.

All the derivatives mentioned above has shown the hydrolysis at pH-7.4 and the rate of chemical hydrolysis were significant. Table IV, V and VI [5,6]

Hydrolysis at pH 1.2

None of the synthesized codrugs were hydrolyzed at pH 1.2 at 37^{0}C (Table VI, V and VI.)

The above hydrolytic study indicates that none of the derivatives is hydrolyzed at gastric pH pass) or metabolized in the blood circulation and activated inside the body and may enhance the duration of action also. The hydrolysis kinetics of the synthesized product has shown the clear idea of release profile of synthesized drug and may prove to modify ADME, duration of action, provide controlled drug release upon hydrolysis in tissue, and finally improve bioavailability.

Further more the synthesized derivatives may also improve the formulation related difficulties. So the synthesized co-drugs may prove to be a good class of stable, long acting, low dose and cost effective antihypertensive drug.

CONCLUSION

Since the synthesized analogs have been made by combining with two different antihypertensive drugs with ester linkage by different anhydride, they may act as new class of co-drug which are metabolized slowly by liver enzyme (first

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