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Synthesis of New B-Adrenergic Blocking Agents Having Heterocyclic Moiety with Expected Activity

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Abstract: ***β-Adrenergic antagonists (β-blockers) bind selectively to the β-drenoceptors producing a competitive and reversible antagonism of the effects of β-adrenergic stimuli on various organs. β-blockers for many years have been established as first line therapy in management of hypertension, also in treatment of heart failure, cardiac arrhythmias, glaucoma, anxiety and obesity. Most compounds available for clinical use belong to the aryloxypropanolamine series, which is considered the second generation of β-blocking agents. The present study includes the synthesis of compounds containing 1, 3, 4-thiadiazole moiety attached to amide dervatives of carboxylic acid and to propanolmine. According to this information five compounds were synthesized and characterized by IR spectra and elemental microanalysis that confirmed the structural formula of these compounds.***

Keywords: β-adrenoceptor blockers, 1, 3, 4-thiadiazole, carboxylic acid

1. Introduction

Hypertension consider as major risk factor in cardiovascular mortality [(1)] because it involves slow degenerative changes of vascular system of body leading to haemorrhag of arteries of vital organs leading to serious fatal consequences [(2)] The adrenergic receptors have been studied extensively and thoroughly by pharmacological methods. There are two major groups of receptors, designated as α and β, which are in turn subdivided into α_1, α_2, β_1, β_2, and β_3 receptors on the basis of their apparent drug sensitivity. [(3)] β-blockers can be broadly classified into (a) non-selective, those producing a competitive blockade of both β_1- andβ_2-adrenergic receptors and (b) those with much higher affinity for the β_1 than for the β_2 receptors usually calledβ_1-selective. Selectivity is, however, dose dependent and decreases or disappears when larger doses are used. Paradoxically, some β-blocker scan exert a weak agonist response (intrinsic sympathomimetic activity (ISA), and can stimulate and block the β - adrenoceptor. Several β-blockers have peripheral vasodilator activity mediated via α_1-adrenoceptor blockade (carvedilol, labetalol), β_2-adrenergic receptor agonism (celiprolol) orvia mechanisms independent of the adrenoceptor blockade. [(4)]

Most of the developed β-blockers belongs either to arylethanolamine or aryloxypropanolamine classes, where the aryloxypropanolamines are more potent β blockers than the corresponding arylethanolamines, and most of the β-blockers currently used clinically are aryloxypropanolamines [(5).] In the current study it was aimed to replace the aryl nucleus of β- adrenoceptor blocker by heterocyclic derivatives (5-amino-1, 3, 4-thiadiazole-2-thiol derivative) as an isostere in an attempt to improve β1 affinity by synthesizing the following compounds which are:

1. *N-[5- (2-Hydroxy-3-morpholin-4-yl-propyl) -[1, 3, 4]thiadiazol-2-yl]-3-phenyl-acrylamide* ***(compound (2))***
2. *N-[5- (2-Hydroxy-3-piperazin-1-yl-propyl) -[1, 3, 4]thiadiazol-2-yl]-3-phenyl-acrylamide* ***(compound (3))***
3. *N-{5-[3- (2, 6-Dimethyl-piperidin-1-yl) -2-hydroxy-propyl]-[1, 3, 4]thiadiazol-2-yl}-3-phenyl-acrylamide* ***(compound (4))***
4. *N-[5- (2-Hydroxy-3-pyrrolidin-1-yl-propyl) -[1, 3, 4]thiadiazol-2-yl]-3-phenyl-acrylamide* ***(compound (5))***
5. *N-[5- (2-Hydroxy-3-morpholin-4-yl-propyl) -[1, 3, 4]thiadiazol-2-yl]-nicotinamide* ***(compound (6))***

Thiadiazole

Is a heterocyclic five membered unsaturated ring structure composed of two nitrogen atoms and one sulfur atom. Thiadiazole is a versatile moiety that exhibits a wide variety of biological activities. It acts as “hydrogen binding domain” and “two electron donor system” with a constrained pharmacophore. [(6, 7)] Thiadiazole derivatives possess interesting biological activity probably conferred to the strong aromaticity of this ring system, which leads to great in vivo stability and generally, a lack of toxicity for higher vertebrates, including humans. When diverse functional groups that interact with biological receptors are attached to this ring, this may lead to the production of compounds possessing outstanding properties. [(7)]

Cinnamic acid

Are a group of aromatic carboxylic acids appearing naturally in the plant kingdom, its appear as ester conjugates with quinic acid, known as the chlorogenic acids, but they can also form esters with other acids, sugars or lipids, or form amides with aromatic and aliphatic amines. In the last ten years, the interest of researchers on the cinnamic acid moiety has notably increased. The number of published reports having the word “cinnamic” in the title, has almost doubled, from 341in the years 1993–2003 to 633 in the period 2004–2014 according to the Scopus database (until mid-November 2014). [(8)] Cinnamic acid and cinnamate derivatives have gained attention due to

their potential protective role against oxidative damage diseases, such as coronary heart disease, stroke and cancers. ([9]) this can be understand from the fact that Free-radical-initiated peroxidation of membrane lipid which associated with a variety of chronic health problems, such as cancer, hypertension, atherosclerosis, diabetes, inflammation, ischemia, Alzheimer, Parkinsonism and aging so supplementation of antioxidants as become an attractive and promising therapeutic strategy for reducing the risk of these diseases because they are capable of trapping radicals to protect the membrane lipids from free radical chain reactions. ([10]) this can be be confirmed by Many studies have shown that individuals who consume higher proportions of fruit and vegetables, have a lower risk of cardiovascular diseases so the used of Natural and synthetic antioxidants reduce the risk of an individual developing hypercholesterolemic atherosclerosis, and decrease oxidative stress because Atherosclerosis may be a result of the oxidation of lipids, caused by the accumulation of cholesterol oxides from oxidized foods and membranes, and is the most common cause of cardiovascular diseases. [(11)] Cinnamic acid derivatives exhibit high antioxidant activity that is due to the presence of vinyl fragments. This property attracts attention to the study of these compounds as potential drugs for the treatment of pathologies related to the lipid peroxidation in cellular membranes. ([12])

Nicotinic acid

Nicotinic acid (pyridine-3-carboxylic acid), also known as niacin or vitamin B_3, is found in various plants and animals and has vital role in biological processes as production of energy, signal transduction, regulation of gene expression and synthesis of fatty acids, cholesterol and steroids. The substituted nicotinic acid is among the various heterocycles that have received most attention during last three decades as potential biomolecules [(13).]

Nicotinic acid derivatives exhibit anti-bacterial, antioxidant, anti-inflammatory and anti-carcinogenic activities. Nicotinic acid and its derivatives have good biological activities and versatile bonding modes. The structures of many of the complexes that have been reported show nicotinic acid and its derivatives acting as bridging ligands through the carboxylate group and the pyridyl N ([14).] Nicotinic acid acts as an antihyperlipidemic agent; promotes healthy skin, good digestion, and proper circulation, metabolism of carbohydrates, fats, protein and functioning of the nervous system; serves as origin for most of the commercial compounds, from anti bacterial and anticancer drugs in the biomedical industry to pesticides and herbicides in the agrochemical industry ([15])

2. Experimental Work

Chemicals and Equipments

Acetone, Chloroform, Carbon disulfide (99.5%), Dioxan, Dimethyl formamide (DMF), Epichlorhydrin 99%, Ethanol 99.9% (absolute), Ethyl acetate, Hydrochloric acid 37%, Methanol, Morpholin, piprazinee, cinnamic acid, nicotinic acid. All the solvents and materials used were of analar type and used without further purification. Infrared spectral determination was performed for all compounds in KBr disk, using FTIR at the college of pharmacy, university of Baghdad. Elemental analysis has been done using Carlo Erba elemental analyzer Euro vector was done at Ibn AL-haithum College, University of Baghdad.

Chemical Synthesis

Synthesis of heterocyclic ring 5-amino-1, 3, 4-thiadiazole-2-thiol (compound1) ([16])

To thiosemicarbazide (0.1 mole, 10gm) suspended in anhydrous ethanol (40 ml), anhydrous sodium carbonate (0.054 mole, 5.82 gm) was added together with carbon disulfide (0.12 mole, 10.1 gm). The reaction mixture was heated with stirring under reflux for (5 hr.). The completion of the reaction was indicated by TLC. The solvent was largely removed under reduced pressure by using rotary evaporator. The residue was dissolved in water (44 ml), and acidified with concentrated hydrochloric acid 37% (8.8 ml). The product was recrystallized from ethanol/water to give the pure compound. The physical appearances, percentage yield, melting point, are listed in table (1).

Synthesis of series A compounds:

Conventional solution method was used as coupling method between aromatic carboxylic acids and compound (1) in synthesis of intermediate compounds to afford compound A1 and A2.ECF (ethylchloroformate) used as coupling reagent for amide bond formation of aromatic carboxylic acids linked to compound (1).

Synthesis of N- (5-Mercapto-[1, 3, 4] thiadiazol-2-yl) -3-phenyl-acrylamide (Compound (A1) [(17)]

Cinnamic acid (10mmole, 1.48gm) was dissolved in THF (20 ml) containing (TEM) (10mmol, 1.012g) and was cooled in an ice bath at -10 °C. ECF (10 mmol, 1.08g) was added over aperiod of 10 min and the solution was continuously stirred for 40min.compound 1 (10 mmole, 1.33g) was dissolved in 10 ml of distilled water containing NaOH (10 mmole, 0.4 g) and cooled to 0 °C and was added at once to the above mixture which was for 3 hr at -10 °C and further 2hr at room temperature. THF was evaporated under reduced pressure and the aquous solution was acidified with diluted HCL solution (0, 1N) to pH 3.5. the resultant precipitate was washed excessively with distilled water, dried in an oven at 50 °C, washed with toluene to remove the unreacted carboxylic acid and recrystallize from thanol / toluene (2:8).

The physical appearances, percentage yield, melting point, are listed in table (1).

Synthesis of (N- (5-Mercapto-[1, 3, 4] thiadiazol-2-yl) -nicotinamide. (Compound (A2)). [(17)]

Nicotinic acid (10mmole, 1.23gm) was dissolved in THF (20 ml) containing (TEM) (10mmol, 1.012g) and was cooled in an ice bath at -10 °C. ECF (10 mmol, 1.08g) was added over a period of 10 min and the solution was continuously stirred for 40min.Compound 1 (10 mmole,

1.33g) was dissolved in 10 ml of distilled water containing NaOH (10 mmole, 0.4 g) and cooled to 0 °C and was added at once to the above mixture which was stirred for 3 hr at -10 °C and for further 2hr at room temperature. THF was evaporated under reduced pressure and the aqueous solution was acidified with diluted HCL solution (0, 1N) to pH 3.5. the resultant precipitate was collected and washed excessively with distilled water, dried in an oven at 50 °C, washed with hot water to remove the unreacted carboxylic acid and recrystallize from ethanol The physical appearances, percentage yield, melting point, are listed in table (1)

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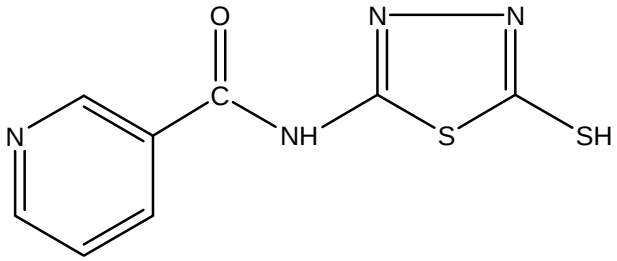


CompoundA2

Table 1: Physical parameters and yields of all the synthesized compounds

Compound	*Physical appearance*	*%Yield*	*m.p. (°C)*
1	faint Yellow crystal	69%	232-234
A1	Pale yellow	70%	267-268
A2	Yellow	58%	286-287
2	Pale yellow	72%	184-186
3	Yellow	67%	200-202
4	Pale yellow	52%	208-209
5	Yellow	59%	190-192
6	Pale yellow	30%	172-174

Synthesis of series B compounds (epichlorohydrin-substituted amines):

- 1-chloro-3- (Morpholine-yl) propan-2-ol (compoundB1)
- 1-chloro-3- (piprazin-yl) propan-2-ol (compound B2)
- 1-chloro-3- (2, 6-dimethylpiperidin-yl) propan-2-ol (compoundB3)
- 1-chloro-3- (pyrrolidin-yl) propan-2-ol (compoundB4)

These compounds (B1-B4) were synthesized by mixing equimolar quantities of epichlorohydrin and amines including (morpholine, 2, 6-dimethylpiperidine, pyrrolidine, piprazine) in methanol at room temperature (not exceeding 25 °C) for (48 hrs.), the resulting chloropropanolamines (B1-B4) were stored in a refrigerator and were used without further purifications. The resulting chloropropanolamines table (2) is stored in refrigerator and is used without further purifications. [18]

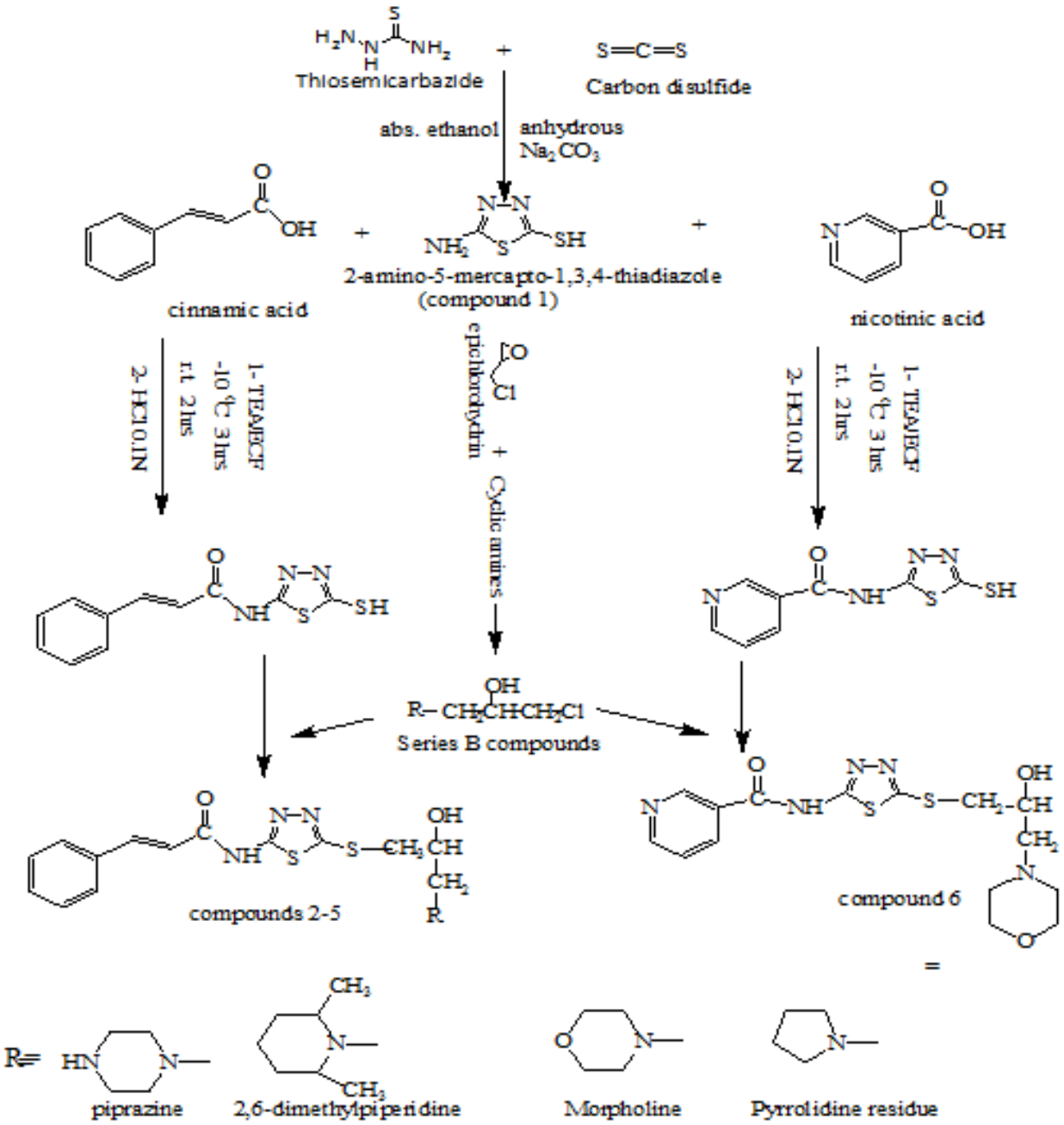
Table 2: chloropropanolamines compounds

Compound	Amine used	Chemical structure of series B
B1	Morpholine	
B2	piprazine	
B3	2, 6-Dimethylpiperidine	
B4	Pyrrolidine	

Synthesis of final products (Compounds (2-6)) [19]

The synthesis was accomplished by the S-alkylation of the final compound of compound A1 and A2 with those of series B compounds including (B1-B4). As in the following procedure: To a stirred solution of compound AI (0.01 mol.) in methanol containing potassium hydroxide (0.01mol.), a solution of one of series B compounds (B1-B4) (0.012 mol.) was added drop wise using a dropping funnel. The reaction mixture was refluxed on steam bath for (5-9 hrs.). The mixture was cooled to room temperature and the volume was then reduced under vacuum. The crude product was precipitated by gradual addition of water, collected and washed several times with water. Crystallization of all solid products was achieved using

absolute ethanol (25). The physical appearances, percentage yield and melting point were listed in table (1), the elemental analysis results are presented in table (3), while the IR data are shown in table (4). The overall reaction steps are shown in scheme (I) as shown below



Scheme 1: Synthesis of Final Compounds

3. Results and Discussion

The 2- amino – 5 – mercapto -1, 3, 4 - thiadiazole was synthesized through steps of reactions starting from thiosemicarbazide with carbon disulphide in a basic medium. Then compoundA1 and A2 were synthesized by the mixed anhydride method using ECF as activating agent. The mixed anhydrides were prepared by the reaction of the carboxyl group of cinnamic acid and nicotinic acid with ECF in the presence of TEA. The resultant mixed anhydrides were allowed to react with sodium salt of 5-amino-1, 3, 4-thiadiazole-2-thiol in an aqueous solution. While the preparation of series B compounds was accomplished by mixing equimolar amounts of epichlorhydrin with secondary amines in methanol at room temperature (not exceeding 25 ˚C) for 48 hrs. In the reaction of amines and epichlorhydrin, a considerable variety of products may be obtained by varying temperature, molar ratio of reactants, reaction media, and basicity of the amine. In the synthesis of the final compounds It was done by heating an alkyl halide with the thiolate salt. The procedure is recognized as an adaptation of the williamson method for the synthesis of ethers. The reactions are therefore often run as a two steps process with pre-formation of the thiolate salt and subsequent addition of the alkyl halide (SN2 reaction).

Table 3: Elemental microanalysis of the final compounds (2-6)

Compound	*Molecular weight*	*Empirical formula*	*Elemental microanalysis %*		
			Element	*Calculated*	*Observed*
2	432.60	$C_{21}H_{28}N_4O_2S2$	C	53.18	51.152
			H	5.45	5.643
			N	13.78	14.309
			S	15.78	16.133
3	405.54	$C_{18}H_{23}N_5O_2S_2$	C	53.31	54.02
			H	5.72	5.617
			N	17.27	17.895
			S	15.81	16.512
4	432.60	$C_{21}H_{28}N_4O_2S_2$	C	58.3	57.225
			H	6.52	6.272
			N	12.95	13.163
			S	14.82	15.261
			C	55.36	55.951
	390.52	$C_{18}H_{22}N_4O_2S_2$	H	5.68	5.613
5			N	14.35	13.745
			S	16.42	15.706
6	381.47	$C_{15}H_{19}N_5\ O_3S_2$	C	47.23	47.071
			H	5.02	5.123
			N	18.36	17.751
			S	16.81	16.125

Table 4: Characteristic IR absorption of the final compounds

Compound	*Band (cm^{-1})*	*Interpretation*
2	3421	OH Stretching of thiopropanolamine side chain and N-H stretching vibration of the amides
	3051	CH Stretching of aromatic ring.
	2931, 2848	CH asymmetrical and symmetrical stretching vibration of CH3 &CH2.
	1629	C=O stretching vibration of amide
	1560 and 1496	C=N stretching vibration of thiadiazole (skeletal vibration)
	1342	C=S stretching vibration
	1329 and 1058	Vibrations involve interaction between C=S and C-N stretching
	1176, 1053.56	Aromatic CH in-plane bending.
	999.13, 916	Aromatic CH out of plane bending.
3	3414.12	OH Stretching of thiopropanolamine side chain N-H stretching vibration of the amides.
	3026.41	CH Stretching of aromatic ring.
	2931.90, 2841.24	CH asymmetrical and symmetrical stretching vibration of CH3 &CH2.
	1629.9	C=O stretching vibration of amide
	1550	C=N stretching vibration of thiadiazole (skeletal vibration)
	1342.5	C=S stretching vibration
	1294, 1251	Vibrations involve interaction between C=S and C-N stretching
	1170.83, 1058	Aromatic CH in-plane bending.
	993, 862	Aromatic CH out of plane bending.
4	3423	OH Stretching of thiopropanolamine side chain and N-H stretching vibration of the amides
	3149	CH Stretching of aromatic ring.
	2926, 2841	CH asymmetrical and symmetrical stretching vibration of CH3 &CH2.
	1631	C=O stretching vibration of amide
	1444	C=N stretching vibration of thiadiazole (skeletal vibration)
	1344.38	C=S stretching vibration
	1294	Vibrations involve interaction between C=S and C-N stretching
	1172.72, 1087	Aromatic CH in-plane bending. Aromatic CH out of plane bending.

	977, 862	
5	3429 3041 2962, 2885 1630 1441 1350 1286 1180 984, 858	OH Stretching of thiopropanolamine side chain and N-H stretching vibration of the amides CH Stretching of aromatic ring. CH asymmetrical and symmetrical stretching vibration of CH3 &CH2. C=O stretching vibration of amide C=N stretching vibration of thiadiazole (skeletal vibration) C=S stretching vibration Vibrations involve interaction between C=S and C-N stretching Aromatic CH in-plane bending. Aromatic CH out of plane bending.
6	3421 3030 2935, 2856 1666 1444 1358 1308 1221 1063, 1018	OH Stretching of thiopropanolamine side chain and N-H stretching vibration of the amides CH Stretching of aromatic ring. CH asymmetrical and symmetrical stretching vibration of CH3 &CH2. C=O stretching vibration of amide C=N stretching vibration of thiadiazole (skeletal vibration) C=S stretching vibration Vibrations involve interaction between C=S and C-N stretching Aromatic CH in-plane bending. Aromatic CH out of plane bending.

4. Conclusion

The synthesis of the proposed compounds was successfully achieved by applying the reported procedures and their chemical structures were characterized and confirmed by spectral and elemental analyses. The following points were attempted to improve the β1 selectivity and may improve the pharmacokinetic properties of these β- adrenoceptor blockers.

1. Replacement of the aryl nucleus of β- adrenoceptor blocker by a heterocyclic ring (5-amino-1, 3, 4 thiadiazole-2-thiol) as an isostere in an attempt to improve β1 affinity.
2. Introduction of amide group in the proposed β-adrenoceptor antagonist in an attempt to increase affinity to β1-adrenoceptor.
3. Using different derivatives of amines at thiolpropanolamine side chain to improve cardiac β1 selectivity and affinity.
4. Incorporating natural carboxylic acid group in the series a compounds may improve the pharmacokinetic properties of these β- adrenoceptor blockers.

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