Synthesis of New β-adrenoceptor Blocking Agent Including 1,3,4 Thiadiazole with Expected Adrenoceptor Blocking Activity

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Abstract

β-Adrenergic blocking agents, mostly comprising of β-amino alcohols, are of pharmaceutical significance and have received major attention due to their utility in the management of cardiovascular disorders including hypertension, angina pectoris, cardiac arrhythmias and other disorders related to the sympathetic nervous system. 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 with an N-substituted oxypropanolamine moiety attached to the 1, 3, 4-thiadiazole derivatives. According to this information, eight 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, Schiff base

تحضير مركبات جديدة كمثبطات لمستلمات بيتا الأدرينالية متضمنا حلقة 4,3,1- ثايادايازول ذات فعالية متوقعة كمثبطات ادرينالية

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الخلاصة

تعتبر مثبطات مستلمات بيتا الأدرينالية, والتي تتألف معظمها من الكحولات الأمينية, ذات أهمية دوائية عالية وقد حظيت باهتمام كبير نظرا لفائدتها في التدبير العلاجي لاضطرابات القلب والأوعية الدموية بما في ذلك ارتفاع ضغط الدم, الذبحة الصدرية, عدم انتظام ضربات القلب وغيرها من الاضطرابات المتعلقة بالنظام العصبي السمبثاوي. ان أكثر المركبات المتوفرة للعلاج السريري تنتمي الى صنف اريل اوكسي بروبانول امين التي تعتبر من الجيل الثاني لمثبطات مستلمات بيتا الأدرينالية . ان البحث المقدم يشتمل على تخليق مركبات فيها مجموعة اوكسي بروبانول معوضة الامين مرتبطة بمشتقات حلقة 4,3,1- ثايادايازول. اعتمادا على هذه المعلومات, فقد تم تصنيع ثمان مركبات وتشخيصها بواسطة الاشعة تحت الحمراء والتحليل الدقيق للعناصر والتي اثبتت صحة تراكيب المركبات المحضرة .

الكلمات المفتاحية: مثبطات مستلمات بيتا الادرينالية ، ا,3, 4 – ثايا دايازول ، قواعد شيف .

Introduction

β-Adrenergic receptors (β-ARs) are G protein-coupled receptors (GPCRs) that mediate physiological responses to adrenaline and noradrenaline. These receptors are the molecular targets for some of the most commonly prescribed drugs in the history of medicine. There are three receptor subtypes in this family: β1-AR is found at its highest levels in the heart and brain [(1)], β2-AR is more widely expressed in bronchial and vascular smooth muscle cells [(2)], and β3-AR is found at its highest levels in adipose tissue [(3)]. All three receptors couple primarily to Gαs to stimulate adenylyl cyclase, but can also couple to Gαi in some cells under certain conditions [(4)]. There is an additional β- adrenoceptor subtype which has been identified in cardiac tissue and is a putative, atypical subtype classified as the β_4-adrenoceptor[(5)]. Likewise, β-adrenoceptor antagonists have also been classified as β1 and β2-blockers. 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[(6)]. 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:-

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- 1-(4-methylpiperazin-1-yl)-3-(4-((5-(4-nitrobenzylthio)-1,3,4-thiadiazol-2-ylimino)methyl) phenoxy)propan-2-ol. **Compound 13**
- 1-(2,6-dimethylpiperidin-1-yl)-3-(4-((5-(4-nitrobenzylthio)-1,3,4-thiadiazol-2-ylimino)methyl) phenoxy)propan-2-ol. **Compound 14**
- 1-(4-((5-(4-nitrobenzylthio)-1,3,4-thiadiazol-2-ylimino)methyl)phenoxy)-3-(piperidin-1-yl) propan-2-ol. **Compound 15**
- 1-(4-((5-(4-nitrobenzylthio)-1,3,4-thiadiazol-2-ylimino)methyl)phenoxy)-3-(pyrrolidin-1-yl) propan-2-ol. **Compound 16**
- 1-(4-((5-(4-chlorobenzylthio)-1,3,4-thiadiazol-2-ylimino)methyl)phenoxy)-3-(4-methylpiperazin -1-yl)propan-2-ol. **Compound 17**
- 1-(4-((5-(4-chlorobenzylthio)-1,3,4-thiadiazol-2-ylimino)methyl)phenoxy)-3-(2,6-dimethyl piperidin-1-yl)propan-2-ol. **Compound 18**
- 1-(4-((5-(4-chlorobenzylthio)-1,3,4-thiadiazol-2-ylimino)methyl)phenoxy)-3-(piperidin-1-yl) propan-2-ol. **Compound 19**
- 1-(4-((5-(4-chlorobenzylthio)-1,3,4-thiadiazol-2-ylimino)methyl)phenoxy)-3-(pyrrolidin-1-yl) propan-2-ol. **Compound 20**

Thiadiazole ring:

Thiadiazole is a heterocyclic compound containing two nitrogen atom and one sulfur atom as part of the aromatic five-membered ring. They occur in nature in four isomeric forms as 1,2,3-thiadiazole (I); 1,2,4-thiadiazole (II); 1,2,5-thiadiazole (III) and 1,3,4-thiadiazole (IV).

1, 3, 4-thiadiazole are important because of their versatile biological actions which exhibits a wide variety of biological activities such as CNS depressants[7], hypoglycemic[8] ,antinflammatory[9], antimicrobial [10] ,antihypertensive[11], antifungal [12],anticancer[13] and antioxidant activity[14]. Among them 2,5-disubstituted 1,3,4-thiadiazoles are associated with diverse biological activity probably virtue of –N=C-S- grouping. Thiadiazole moiety acts as a "hydrogen binding domain" and "two-electron donor system". Thiadiazoles carrying mercapto, amino substituents can exists in many tautomeric forms [15] and considered as useful intermediates in organic synthesis. Moreover, these groups can react with electrophiles, for instance some alkylation or schiff base reactions that take place at S- or N-atom [16]. Schiff bases have gained great importance because of physiological and pharmacological activities associated with them. There has been considerable attention to the chemistry of schiff bases because of their wide range of applications in many fields including biological, organic, inorganic and analytical chemistry. They are used as pigments, dyes, catalysts, intermediates in organic and inorganic synthesis and polymer stabilizers [17]. Schiff bases containing heterocyclic rings are known to show cytotoxic, anticonvulsant, antimicrobial, anticancer, antifungal, antimalarial, antiviral, antidepressant and enzyme inhibitor activities [18]. Furthermore, some schiff bases are used in ion sensors and electrochemical sensors to empower detection with enhanced selectivity and sensitivity [19].

Experimental work

Chemicals and equipments

Acetic anhydride, carbon disulfide, p-chlorobenzyl chloride, p-nitrobenzyl chloride, N-methyl piprazine, piperidine, pyrrolidine, p-hydroxy benzaldehyde, thiosemicarbazide, 2,6-dimethylpiperidine. 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, and was done at AL-al Bayt University in AL-Mafraq (Jordan).

Chemical Synthesis

Synthesis of heterocyclic ring 5-amino-1,3,4-thiadiazole-2-thiol (compound 1) [20]

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, and R_f values are listed in table (1).

Synthesis of series A compounds

Synthesis of N-(5-mercapto-1,3,4-thiadiazol-2-yl)acetamide [21].(compound 2)

A mixture of (0.022 mole, 3g) of compound 1 and (0.11 mole, 10ml) of acetic

anhydride containing (0.5ml) of concentrated sulphuric acid was heated in a steam-bath for 1hr. Later the mixture was poured into (60 ml) of cold water and the mixture was boiled to decompose the excess of acetic anhydride. When cold, filter the residual insoluble acetyl derivative and wash with little of cold water and recrystalize from distilled water or aqueous ethanol. The physical appearances, percentage yield, melting point and R_f value were listed in table (1).

Table (1): The physical appearances, percentage of yield, melting points, R_f values of the intermediate and final compounds .

Compound No.	Physical appearance	%Yield	Melting point (˚C)		R_f values			
			Observed	Reported	A	B	C	D
1	Faint yellow crystal	69%	232-234	230-232	0.8	0.67	---	---
2	Pale yellow powder	93%	295-296	--------	0.76	0.41	---	---
3	Off-white powder	58.9%	252-254	--------	0.74	0.64	---	---
4	Pale yellow powder	60%	209-211	--------	0.88	0.71	---	---
5	Pale yellow powder	73.9%	168.5-170	-------	0.67	0.4	---	---
6	White powder	76%	161-163	162-164	0.93	0.49	---	---
7	Yellow powder	40%	193-196	-------	0.42	0.62	---	---
8	Bright yellow powder	41%	202-204	-------	0.53	0.71	---	---
13	Orange powder	28%	143-146	-------	---	---	0.23	0.26
14	Dark yellow powder	28.3%	99-102	-------	---	---	0.20	0.24
15	Grey yellow powder	26%	109-112	------	---	---	0.21	0.23
16	Yellow powder	33.5%	110-113	------	---	---	0.18	0.2
17	Dark yellow powder	38.7%	146-148	------	---	---	0.24	0.34
18	Yellow powder	42.6%	148-151	------	---	---	0.21	0.3
19	Grey yellow powder	43.8%	150-152	------	---	---	0.23	0.31
20	Dark yellow powder	39.6%	136-138	------	---	---	0.19	0.28

A) Chloroform: ethylacetate: methanol (2:2:1), B) toluene: ethylacetate:formic acid(5:4:1)
C) n-Hexane: Isopropanol: Methanol (9: 0.9:0.1), D) n-Hexane: Isopropanol: Methanol (8.5: 1.2:0.3)

Synthesis of N-[5-(4-nitrobenzylthio)-1,3,4-thiadiazol-2-yl]acetamide [22]***.(Compound 3)***

To a mixture of compound (2) (1mmole ,0.175g) and p-nitrobenzyl chloride (1mmole, 0.1715g) in ethanol (15ml), KOH(1.1mmole, 66mg in 5 ml of H_2O) was added drop wise while the mixture was stirred at room temperature overnight. Then water (20 ml) was added and the separated solid was filtered off, washed with H_2O, and crystallized from ethanol: water (90:10).The physical appearances, percentage yield, melting point and R_f value were listed in table (1).

Synthesis of N-[5-{(4-chlorobenzyl)thio}-1,3,4-thiadiazolyl] acetamide.(Compound 4)

The same procedure was carried out as mentioned previously for compound (3), but starting with p-chlorobenzyl chloride (1mmole, 0.161g) which was coupled with compound (2)(1mmole, 0.175g).The physical appearances, percentage yield, melting point and R_f value were listed in table (1).

Synthesis of 5-(4-nitrobenzylthio)-1,3,4-thiadiazol-2-amine [23]***. (Compound 5)***

A mixture of (0.01mole, 3.1g) compound (3), 6ml of concentrated HCl and 40ml ethanol was refluxed in oil bath for 3hrs. After a part of ethanol had evaporated, the obtained suspension was allowed to cool slowly. The solid mass was filtered and crystallized from water. The physical appearances, percentage yield, melting point and R_f value were listed in table (1).

Synthesis of 5-[(4-chlorobenzyl)thio]-1,3,4-thiadiazol-2-amine. (Compound 6)

The same procedure was carried out as mentioned previously for compound (5) but starting with compound (4) (0.01mole, 3g). The physical appearances, percentage yield, melting point and R_f value were listed in table (1).

Synthesis of (E)-4-[{(5-(4-nitrobenzyl)thio)-1,3,4-thiadiazol-2-ylimino]methyl phenol.(compound 7)

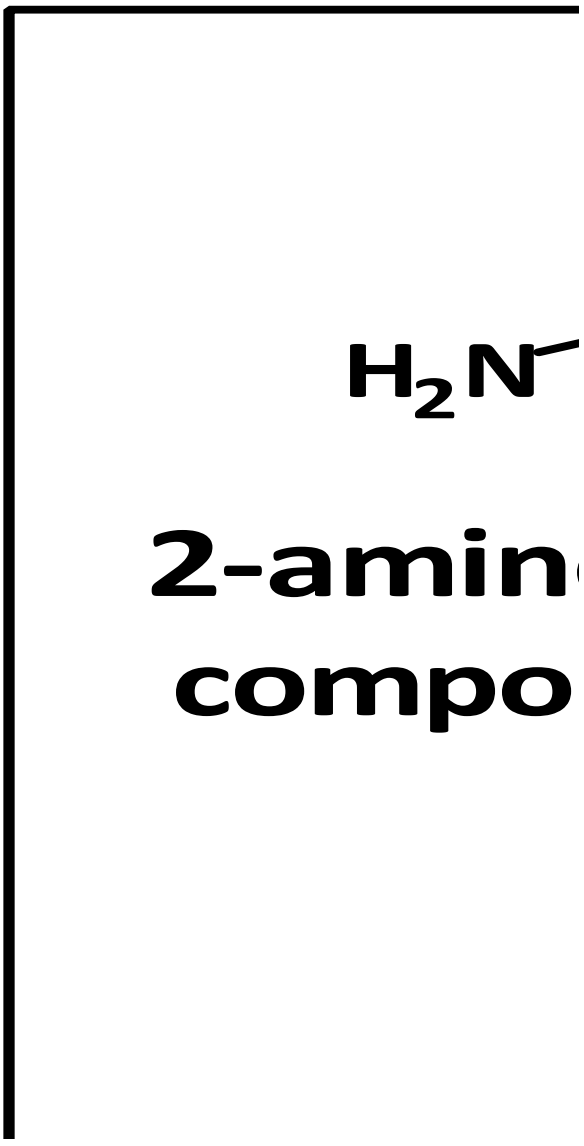
The mixture of compound (5) (0,002mole, 0.53g) and p-hydroxybenzaldehyde (0.0023mole, 0.29g) in 25ml ethanol with 2 drops of concentrated H_2SO_4 was refluxed for 6 hr. Then, the solution was concentrated and kept overnight bellow 20˚C. The solid mass separated was filtered and washed with hot water: ethanol (1:1, 20ml). Recystallization of the product from 95% ethanol was carried out. The physical appearances, percentage yield,

melting point and R_f value were listed in table (1).

Synthesis of (E)-4-((5-(4-chlorobenzylthio)-1,3,4-thiadiazol-2-ylimino)methyl phenol.(Compound 8)

The same procedure was carried out as mentioned previously for compound (7), but starting with compound (6) (0.002mole, 0.51g) which was coupled with p-hydroxybenzaldehyde (0.0023mole, 0.29g). The physical appearances, percentage yield, melting point and R_f value were listed in table (1).

The overall reaction steps are shown in scheme (I) as shown bellow



Synthesis of series B compounds (epichlorohydrin – substituted amines)

This series include the following compounds:

- 1-chloro-3-(piperidin-1-yl)propan-2-ol (compound 9)
- 1-chloro-3-(2,6-dimethylpiperidin-1-yl)propan-2-ol (compound10)
- 1-chloro-3-(pyrrolidin-1-yl)propan-2-ol (compound11)
- 1-chloro-3-(4-methylpiprazin-1-yl)propan-2-ol (compound 12)

These compounds (9-12) were synthesized by mixing equimolar quantities of epichlorohydrin and amines including (piperidine, 2,6-dimethylpiperidine, pyrrolidine, N-methylpiprazine) in methanol at room temperature (not exceeding 25 ˚C) for (48 hrs.). The resulting chloropropanolamines table (2) (9-12) were stored in refrigerator and were used without further purifications[24].

Table (2): Synthesis of series B compounds (9-12)

Compound	Amine used	Chemical structure of series B
9	piperidine	
10	2,6-Dimethylpiperidine	
11	Pyrrolidine	
12	N-Methylpiprazine	

Synthesis of final products (Compounds (13-20))

The synthesis was accomplished by the O-alkylation of the final compound of series A (compound 7 & 8) with those of series B compounds including (9-12). As in the following procedure:

To a stirred solution of one of the series A (7, 8) compounds (0.01 mol.) in methanol containing potassium hydroxide (0.01mol.), a solution of one of series B compounds (9-12) (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, melting point and R_f value were listed in table (1), the elemental analysis results are presented in table (3), while the IR data are shown in table (4).

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. In the acetylation of compound (1), where this step includes the synthesis of amide; it was done by treatment of an amine with acetic anhydride in the presence of a few drops of sulphuric acid as catalyst. Conversion of the amino group into the acetamido group by acetylation modifies the interaction of the nitrogen lone pair with the π-electron system of the aromatic ring so that the ring is less powerfully activated toward electrophilic attack. Alkylation of compound (2) which includes the synthesis of thioether or alkyl sulphide , it was done by treatment of a thiol with a base, such as KOH, giving the corresponding thiolate ion (RS^-).Which undergoes reaction with a primary or secondary alkyl halide to give a sulfide. The reaction occurs by an S_N2 mechanism, analogous to the Williamson synthesis of ethers. Thiolate anions are among the best nucleophiles known, and product yields are usually high in these S_N2 reactions. Then the amide group of compound (3&4) is hydrolyzed (amide hydrolysis) by heating in either aqueous acid or aqueous base mediums.

Acid hydrolysis reaction occurs by nucleophilic addition of water to the protonated amide, followed by transfer of a proton from oxygen to nitrogen to make the nitrogen a better leaving group and for subsequent elimination. The steps are reversible with the equilibrium shifted towards the product by the protonation of the NH_2 in the final step. Reaction of compounds (5&6) with aromatic aldehyde under acidic conditions afforded the corresponding schiff bases. The mechanism of schiff base formation is a reversible, acid catalyzed process, begins with nucleophilic addition of the primary amine to a carbonyl group (aldehyde or ketone) followed by a transfer of a proton from nitrogen to oxygen to yield a neutral amino alcohol or carbinolamine. Protonation of the carbinolamine oxygen by an acid catalyst then converting the (-OH) group into a better leaving group ($–OH_2^+$), and E_1- like loss of water produces an iminium ion which after the loss of a proton from nitrogen gives the schiff base and regenerate the acid catalyst to afford series A compounds. The compounds from 2-7 & 8 were reported earlier in the literature but they were synthesized without protecting the amino or thiol groups present in compound 2 since both -SH &-NH_2 are susceptible for the reagent Cl-CH_2-C_6H_4-X, in addition the

synthesized products from 2-7&8 have different melting point and without recording their elemental analysis. This study has taken care of the susceptibility of the amino group and it was therefore protected. Furthermore, all synthesized compounds were with different melting points, in addition, the final compounds synthesized have elemental analysis which comply with the expected theoretical data. While the preparation of series B compounds was accomplished by mixing equimolar amounts of epichlorhydrin with primary or 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 actually includes the synthesis of an ether. It was done by heating an alkyl halide with the salt of an alcohol (e.g. potassium alkoxide).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-step process with pre-formation of the alkoxide salt and subsequent addition of the alkyl halide (S_N2 reaction).

Table (3): Elemental microanalysis of the final compounds (13-20)

Compound	Molecular weight	Chemical formula	% Elemental microanalysis		
			Element	calculated	Observed
13	528	$C_{24}H_{28}O_4N_6S_2$	C	54.545	54.475
			H	5.30	5.556
			N	15.90	16.368
			O	12.121	11.551
			S	12.121	12.05
14	541	$C_{26}H_{31}O_4N_5S_2$	C	57.67	58.21
			H	5.73	5.84
			N	12.939	12.5
			O	11.829	11.66
			S	11.829	11.79
15	513	$C_{24}H_{27}O_4N_5S_2$	C	56.14	56.560
			H	5.263	5.361
			N	13.645	13.184
			O	12.475	12.417
			S	12.475	12.478
16	499	$C_{23}H_{25}O_4N_5S_2$	C	55.31	55.81
			H	5.01	5.11
			N	14.02	13.61
			O	12.825	12.6
			S	12.825	12.87
17	517.5	$C_{24}H_{28}O_2N_5ClS_2$	C	55.652	57.142
			H	5.41	4.865
			N	13.526	13.50
			S	12.367	12.808
18	530.5	$C_{26}H_{31}O_2N_4ClS_2$	C	58.812	59.999
			H	5.843	5.628
			N	10.556	9.819
			S	12.064	12.015
19	502.5	$C_{24}H_{27}O_2N_4ClS_2$	C	57.313	58.361
			H	5.373	4.70
			N	11.144	11.418
			S	12.736	12.670
20	488.5	$C_{23}H_{25}O_2N_4ClS_2$	C	56.499	56.61
			H	5.117	5.335
			N	11.463	11.39
			S	13.1	13.135

Table (4): Characteristic IR absorption of the final compounds

Compound	Band(cm^{-1})	Interpretation
13	3296.35 3107.32 2966.52,2947.23,2839.22 1681.93 1633.71-1598.99 1575.84 1508.33, 1342.46 1240.23, 1049.28 1178.51, 1014.56 894.97, 858.32	OH Stretching of oxypropanolamine side chain. CH Stretching of aromatic ring. CH asymmetrical and symmetrical stretching vibration of CH_3 &CH_2. C=N Stretching of side chain (Schiff base). C=N Stretching of heterocyclic ring Aromatic C=C stretching Asymmetrical & symmetrical N-O stretching respectively. Asymmetrical & symmetrical C-O stretching of ether. Aromatic CH in-plane bending. Aromatic CH out of plane bending.
14	3286.70 3076.46 2931.80, 2868.15,2854.65 1687.71 1598.99 1573.91 1517.98, 1344.38 1247.94, 1053.13 1192.01 858.32, 800.46	OH Stretching of oxypropanolamine side chain. CH Stretching of aromatic ring. CH asymmetrical and symmetrical stretching vibration of CH_3 &CH_2. C=N Stretching of side chain (Schiff base). C=N Stretching of heterocyclic ring Aromatic C=C stretching Asymmetrical & symmetrical N-O stretching respectively. Asymmetrical & symmetrical C-O stretching of ether. Aromatic CH in-plane bending. Aromatic CH out of plane bending.
15	3302.13 3109.25 2929.87, 2854.65 1685.79 1597.06 1571.99 1508.33, 1344.38 1236.37, 1055.06 1188.15, 1014.56 858.32, 800.46	OH Stretching of oxypropanolamine side chain. CH Stretching of aromatic ring. CH asymmetrical and symmetrical stretching vibration of CH_2. C=N Stretching of side chain (Schiff base) C=N Stretching of heterocyclic ring. Aromatic C=C stretching Asymmetrical & symmetrical N-O stretching respectively. Asymmetrical & symmetrical C-O stretching of ether Aromatic CH in-plane bending. Aromatic CH out of plane bending.
16	3284.77 3076.46 2962.66 1676.14 1598.99 1571.99 1514.12, 1344.38 1244.09, 1051.20 1190.08, 1014.56 893.04, 858.32	OH Stretching of oxypropanolamine side chain. CH Stretching of aromatic ring. CH asymmetrical stretching vibration of CH_2. C=N Stretching of side chain (Schiff base). C=N Stretching of heterocyclic ring. Aromatic C=C stretching Asymmetrical & symmetrical N-O stretching respectively. Asymmetrical & symmetrical C-O stretching of ether Aromatic CH in-plane bending. Aromatic CH out of plane bending
17	3311.78 3101.54 2937.59, 2827.64 1681.93 1600.92 1577.77-1500.62 1238.30, 1060.85 1296.16, 1014.56 1091.71 893.04, 879.54	OH Stretching of oxypropanolamine side chain. CH Stretching of aromatic ring. CH asymmetrical and symmetrical stretching vibration of CH_3 &CH_2. C=N Stretching of side chain (Schiff base). C=N Stretching of heterocyclic ring. Aromatic C=C stretching Asymmetrical & symmetrical C-O stretching of ether. Aromatic CH in-plane bending. Aromatic C-Cl stretching. Aromatic CH out of plane bending.

Table (4): Characteristic IR absorption of the final compounds

18	3317.56 3091.89 2968.45, 2935.66 1681.93 1600.92 1575.84-1500.62 1238.30, 1062.78 1091.71 1296.16, 1016.49 839.03, 736.81	OH Stretching of oxypropanolamine side chain. CH Stretching of aromatic ring. CH asymmetrical stretching vibration of CH_3 & CH_2. C=N Stretching of side chain (Schiff base). C=N Stretching of heterocyclic ring. Aromatic C=C stretching. Asymmetrical & symmetrical C-O-C stretching of ether. Aromatic C-Cl stretching. Aromatic CH in-plane bending. Aromatic CH out of plane bending.
19	3311.78 3095.75 2968.45, 2850.79 1681.93 1602.85 1575.84-1500.62 1238.30, 1064.71 1296.16, 1016.49 1091.71 879.54,738.74	OH Stretching of oxypropanolamine side chain. CH Stretching of aromatic ring. CH asymmetrical and symmetrical stretching vibration of CH_2. C=N Stretching of side chain (Schiff base). C=N Stretching of heterocyclic ring. Aromatic C=C stretching. Asymmetrical & symmetrical C-O stretching of ether. Aromatic CH in-plane bending. Aromatic C-Cl stretching. Aromatic CH out of plane bending
20	3315.63 3093.82 2968.45, 2850.79 1681.93 1602.85 1575.84-1500.62 1240.23, 1064.71 1296.16, 1016.49 1091.71 879.54, 839.03,	OH Stretching of oxypropanolamine side chain. CH Stretching of aromatic ring. CH asymmetrical and symmetrical stretching vibration of CH_2. C=N Stretching of side chain (Schiff base). C=N Stretching of heterocyclic ring. Aromatic C=C stretching. Asymmetrical & symmetrical C-O stretching of ether. Aromatic CH in-plane bending. Aromatic C-Cl stretching. Aromatic CH out of plane bending

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 imine group in the proposed β-adrenoceptor antagonist in an attempt to increase affinity to β_1-adrenoceptor.
3. Using different derivatives of amines at oxypropanolamine side chain to improve cardiac β_1 selectivity and affinity.
4. Incorporating alkyl or arylalkyl group in the series A compounds may improve the pharmacokinetic properties of these β-adrenoceptor blockers.

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