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SYNTHESIS AND CHARACTERIZATION OF VARIOUS 3-(6-SUBSTITUTED-3-HYDROXY-2,2-DIMETHYL-3,4-DIHYDRO-2*H*-BENZOPYRAN-4-YL)-2-SUBSTITUTED-1,3-THIAZOLIDIN-4-ONES AND THEIR ANTIHYPERTENSIVE ACTIVITY

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ABSTRACT

The present work was aimed at exploring a series of novel 3-(6-substituted-3-hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-benzopyran-4-yl)-2-substituted-1,3-thiazolidin-4-ones by utilizing substituted phenols as their starting material. The methodology comprised of acylation, fries rearrangement reaction, cyclisation, reduction, epoxidation, ring opening reaction, Schiff's reaction. Substituted phenols were first acylated with acetic acid in presence of Lewis acid to substituted acetophenones which were smoothly converted to benzopyran derivatives showing excellent yields. The structures of the synthesized compounds were established through ^{1}HNMR, MASS and FT-IR Spectroscopic techniques. The synthesized compounds were screened for their *in vivo* antihypertensive activity using tail-cuff method in fructose-induced Albino Wistar rats.

KEYWORDS: Benzopyrans, Fries rearrangement reaction, Schiff's reaction, thiazolidin-4-ones, antihypertensive activity, tail-cuff method.

INTRODUCTION

Hypertension is the most common cardiovascular disease and is the major risk factor for coronary artery disease, heart failure, stroke and renal failure. Drug therapy in the management of hypertension must be individualized and adjusted based on co-existing risk factors, including the degree of blood pressure elevation, severity of disease, presence of underlying cardiovascular or other risk factors, response to therapy and tolerance to drug

induced adverse effects. Antihypertensive therapy generally is reserved for patients who fail to respond to non-drug therapies along with lifestyle modifications, such as diet including sodium restriction and adequate potassium intake regular aerobic physical activity, moderation of alcohol consumption and weight reduction.[1,2]

There is a large number of compounds available in the market to reduce the hypertension and its associated complications. The drugs presently available in the market for the treatment of hypertension are not completely ideal as some of the as some of the available compounds are known to produce toxicity and other side effects.[3]

One of the newly accepted mechanism for the treatment of hypertension is by the mechanism of opening potassium channels. They are called as ATP sensitive potassium channel openers.[4] Among the wide variety of potassium channels so far described, the ATP-sensitive potassium channels (K_{ATP}) are of particular interest because they couple cell metabolism to cell excitability. Such ionic channels are present in multiple cell types including endocrine cells,[5] skeletal and smooth muscle cells,[6,7] cardiac cells, [8] and central neurons.[9] K_{ATP} channels are involved in main physiological processes such as smooth muscle cell contractile activity, myocardial protection and neurotransmitters release.[10] Several compounds are known to activate K_{ATP} channels and have been named 'potassium channel openers'.[11] Cromakalim is an example of such compounds (Fig.1). The drug exhibits a marked myorelaxant activity resulting from the activation of smooth muscle K_{ATP} channels.[12]

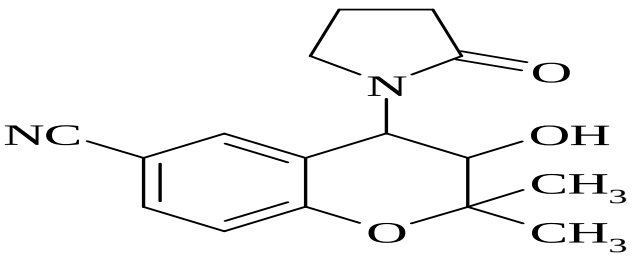


Fig.1: Chemical structure of Cromakalim

Since the discovery of cromakalim, a potent antihypertensive agent, a variety of related compounds possessing a benzopyran skeleton have been reported as K^+ channel openers.[13,14] Benzopyran and their derivatives have shown various pharmacological and biological properties.[15,16] These benzopyrans exert a hypotensive effect by relaxing peripheral vascular smooth muscle via opening the ATP-sensitive K^+ channels in the cell membrane.[17]

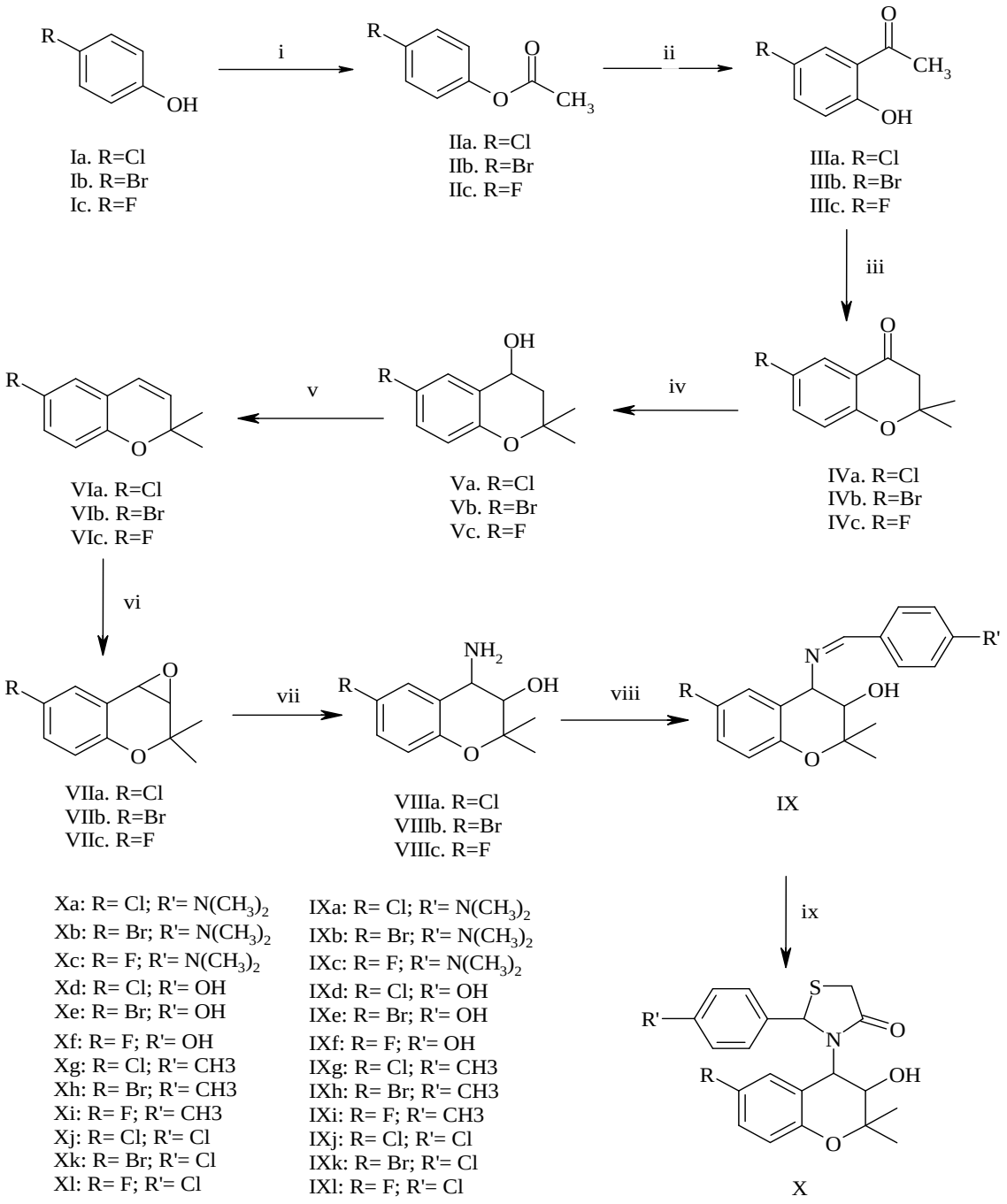
The availability of organic molecules in large numbers that modulate these channels in tissue specific manner would be useful to explore the therapeutic potential of potassium channel modulation. Medicinal chemistry research has so far concentrated on the modification of the existing molecules.[18] Our understanding of the basic mechanisms of the channel functioning is slowly progressing but further work is needed to unravel how various channels differ in structures and in their properties. This is very crucial for understanding pharmacological profile of existing potassium channel modulators.[19] There has been a rapid extension in the syntheses of molecules related to nicorandil, cromakalin, pinacidil in last few years.[20,21,22] It have taken attention of researchers, chemists and pharmacologists to synthesize new drugs which are more potent, less toxic ant at the same time better tolerated than existing drugs.[23]
In the present study, our investigations were directed toward the discovery of benzopyrans showing antihypertensive activity. We therefore synthesized a series of 3-(6-substituted-3-hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-benzopyran-4-yl)-2-substituted-1,3-thiazolidin-4-one derivatives and investigated the antihypertensive activity in rats.

MATERIALS AND METHODS

Chemicals and reagents: The chemicals and reagents used in the present project were of AR and LR grade, procured from Sigma Aldrich, SD Fine Chemicals, Sigma and Finar.

Analytical Techniques: Melting points of the synthesized compounds were determined by open capillary method and are uncorrected. Purity of the compounds were checked by thin layer chromatography using precoated TLC plates and appropriate solvent systems as mobile phase. The spots resolved were visualized using UV chamber. IR spectra were recorded on Bruker Tensor 27 Spectrophotometer. The ^{1}H NMR spectra were recorded using DMSO as solvents, chemical shifts are reported in δ values (ppm). The Mass Spectra were recorded as LC-MS on SHIMADZU.

Scheme 1: The derivatives of benzopyran was synthesized according to the following scheme.



Reagents: (i) $(CH_3CO)_2$, H_2SO_4; (ii) $AlCl_3$; (iii) acetone, pyrrolidine; (iv) $NaHB_4$, CH_3OH; (v) toluene, p-toluene sulfonic acid, $NaHCO_3$; (vi) sodium hypochlorite, disodium hydrogen phosphate; (vii) NH_3, CH_3OH; (viii) CH_3COOH, CH_3OH; (ix) 1,4-dioxane, thioglycolic acid, anhydrous $ZnCl_2$

4-Chlorophenyl Acetate (IIa). 4-Chlorophenol (50g, 0.39mol) was dissolved in acetic anhydride (37.5g, 0.4 mol). Upon addition of 1 drop of concentrated sulfuric acid, the

temperature raised to 120°C. After being cooled, the mixture was poured into a solution of sodium hydrogencarbonate (4g in 500ml of water) and extracted with diethyl ether. The organic layer was washed with a saturated hydrogen carbonate solution, dried over magnesium sulphate, and evaporated under reduced pressure. The resulting oil (57.54g, 86.74%) was used directly in the next step (Scheme 1, synthesis of **IIIa**).

5-Chloro-2-hydroxyacetophenone (IIIa). The crude ester **IIa** (10g, 0.05mol) was heated together with aluminum chloride (13.2g, 0.1mol) at 150°C for 2 h. The mixture was then poured on water and extracted with diethyl ether. The extract was dried over magnesium sulfate and evaporated under reduced pressure. The product was dissolved in methanol. The solution was treated with charcoal and filtered, and water was added to the filtrate. The resulting precipitate was collected by filtration, washed with water, and dried.

6-Chloro-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-4-one (IVa). A solution of **IIIa** (3.025g,0.017 mol), acetone (2ml, 0.03 mol) and pyrrolidine (2.25ml, 0.03 mol) in methanol (66ml) was stirred at 25°C overnight. On the next day the mixture was concentrated to red oil. Water was added, and the solution was adjusted to pH 1 with concentrated hydrochloric acid. The product was extracted with diethyl ether, and the organic layer was evaporated under reduced pressure. The residue was then dissolved in a small volume of methanol. The solution was treated with charcoal and filtered, and water was added to the filtrate. The resulting oil was extracted with diethyl ether. The organic layer was dried over magnesium sulfate, filtered, and evaporated under vacuum. The obtained oil (2.01g, 54%) was used directly in the next step (Scheme 1, synthesis of **Va**).

6-Chloro-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-4-ol (Va). Sodium borohydride (0.4g, 0.01 mol) was added to a stirred suspension of **IVa** (2g, 0.01 mol) in methanol (28 ml) at 0°C, and the mixture was maintained at this temperature for further 30 min. After the mixture was stirred for an additional 30 min at ambient temperature, concentrated hydrochloric acid was added until acid and solvent were evaporated under vacuum. Water was added to the residue, and the product was extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered and evaporated under reduced pressure. The product was recrystallized in ether/petroleum ether (1:3). The resulting precipitate was collected by filtration, washed with petroleum ether and dried (1.02g, 50.71%).

6-Chloro-2,2-dimethyl-2*H*-1-benzopyran (VIa). A solution of **Va** in toluene was added to p-toluene sulphonic acid and refluxed. After 1.5 hr checked the TLC. After 3 hr, the reaction was stopped. The reaction mixture was added to aqueous $NaHCO_3$ and extracted with ethyl acetate, crude was treated with anhydrous $MgSO_4$ and recrystallized with ethyl acetate. The yield was found to be 50%.

6-Chloro-2,2-dimethyl-1a,7b-dihydro-2*H*-oxireno[c]-1-benzopyran (VIIa).
Sodium hypochlorite and disodium hydrogen phosphate and Jacobson's catalyst are taken in a conical flask, added 5ml of water and cooled to 0°C. To the above mixture 0.5 gm of **VIa** dissolved in methylene chloride, cooled to 0°C was added drop wise using a dropping funnel maintaining the temperature of 0°C throughout the reaction. After about 3hrs, further 1 equivalent of Sodium hypochlorite was added to the reaction mixture. After about 20hrs reaction was stopped, reaction mixture was filtered with celite and was extracted with methylene chloride. Crude mixture was finally purified by using Column Chromatography. The reaction was confirmed by TLC, IR and NMR.

4-Amino-6-chloro-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-3-ol (VIIIa). Epoxide **VIIa,** ammonia (2 mol) and methanol (20ml) was taken in a round bottom flask. The reaction mixture was kept at 50°-60°C for about 6hrs. After completion of the reaction, the reaction mixture was lkept for overnight. Next day the reaction mixture was added to ice-water, filtered and dried to obtain the compound in pure form which is used directly for the next step.

6-chloro-2,2-dimethyl-4-{[(*Z*)-phenylmethylidene]amino}-3,4-dihydro-2*H*-1-benzopyran-3-ol (IXa). A mixture of **VIIIa** (0.01 mol), substituted benzaldehyde (0.01 mol) and a drop of acetic acid was dissolved in ethanol (25ml) and heated on a steam-bath for 45-60 min or on a water-bath for 2-3 hrs. The reaction mixture was allowed to stand at room temperature for 24hrs. The product separated out was filtered, dried and recrystallized by using warm ethanol.

3-(6-Chloro-3-hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-benzopyran-4-yl)-2-phenyl-1,3-thiazolidin-4-one (Xa). To the mixture of Schiff's base (0.01mol) and thioglycolic acid (0.01mol) dissolved in 1,4-dioxane (20ml), anhydrous zinc chloride (0.004mol) was added and refluxed for 8hrs. The reaction mixture was cooled, filtered, washed with water, dried and recrystallized using ethanol.

Antihypertensive Activity (*in vivo*)

Fructose induced hypertensive rats: Seventy-two male Albino Wistar rats will be divided into groups of six animals. Control groups will be given ordinary drinking water ad libitum throughout the whole treatment course and the remaining groups will be given 10% fructose solution to drink ad libitum. Three weeks later the rats will be assigned for the activity.

Albino Wistar rats weighing 200-250gm will be used to screening for antihypertensive activity. Suspension of all the test compounds will be prepared in 1% w/v sodium carboxy methyl cellulose. Control group will receive an equal quantity of 1% w/v sodium carboxy methyl cellulose suspension. After administration of dose to animal, blood pressure will be measured by non-invasive tail cuff method using pressure meter. Measurement will be done after 1 hour and 3 hour interval .One hour after the administration of the drug the animals will be shifted to restrainers, which restricts the movement of animals. The tail will be cleaned with moist cotton to remove dirty matter and talcum powder will be sprayed on the tail to make its surface smooth. A tail cuff and a pulse transducer will be fixed around the tail. STRAT switch will be put on and the recorder records the blood pressure as SBP (systolic blood pressure), DBP (diastolic blood pressure) and MABP (mean arterial blood pressure).

RESULTS AND DISCUSSION

The scheme of synthesis for the target benzopyran analogues was given in the scheme 1. We selected different substituted phenols as starting material for the synthesis of the targeted compounds. These phenols were acetylated with acetic anhydride at room temperature. In the next step o-acetylated product undergoes Fries rearrangement in the presence of aluminium chloride to obtain the o-hydroxyacetophenone. Maintaining the temperature of this reaction at 140-150°C was very important because at high temperature the reaction get charred and for maintaining the exact temperature we used oil bath.

The compounds were confirmed by IR spectral data. The presence of broad peak at about 3400 cm^{-1} indicated the presence of –OH group and the shift of the carbonyl moiety to ortho hydroxyl moiety confirms the structure of the compound. In the next step, the hydroxyl moiety is converted to benzopyranone by the treatment with acetone under refluxing condition in the presence of piperidine as catalyst and toluene as solvent to obtain the compounds in the 4^{th} step. The formation of the compound is confirmed by IR. Here in the IR we observed the absence of broad peak at 3400 cm^{-1} for the hydroxyl group and shift of the

and shift of the carbonyl stretching vibration from 1740-1710 cm^{-1} indicated the formation of the ring.

Further these compounds were reduced to hydroxyl function by treating with sodium borohydrate in methanol. Sodium borohydrate is a good reducing agent and the reaction was done in room temperature properly forming the compounds in the 5^{th} step. These compounds were confirmed by the IR spectras where we observed the presence of broad peak at about 3400 cm^{-1} indicating the formation of hydroxyl group. The conversion of the hydroxyl benzopyran moiety to benzopyran was done in the next step by refluxing with toluene in the para toluene sulphonic acid as a catalyst. This reaction was done at high temperature and water molecules were removed from the reaction by using Dean Stack apparatus.

The compounds of this step was confirmed by IR spectroscopy. The absence of hydroxyl peak at about 3430 cm^{-1} confirms the formation of sixth step compounds. In the next step different epoxides were prepared by reacting with sodium hypochlorite where dichloromethane and water was used as a solvent. Because all the inorganic solvents are not dissolved in dichloromethane and should be dissolved in water.

The formation of the compounds were confirmed by IR. Then in the next step ring opening reactions were formed. In the next step Schiff's base reaction took place with different substituted benzaldehydes using acetic acid as a catalyst. The reaction was done in steam bath for 45-60 mins. The reaction was then kept at room temperature for 24 hrs to form the compounds.

The last step compounds were prepared by treating the previous step compounds with thioglycolic acid and anhy zinc as a catalyst. All the compounds were confirmed by IR, NMR and Mass Spectroscopy. Several anti-hypertensive drugs effectively prevent and reverse the increase in blood pressure induced by high fructose diets. The present study showed that after drinking a high fructose solution for 6 weeks, normal rats exhibited significant increases in blood pressure. Treatment with the synthesized compounds blocked the continued elevation of blood pressure and provoked a return to normal values.

Table 1: IR and NMR Spectral data of synthesized compounds IIa-IXa

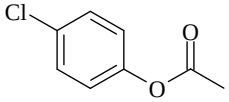
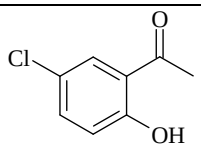
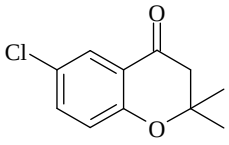
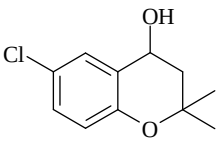
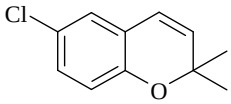
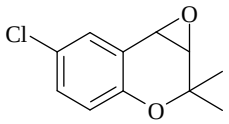
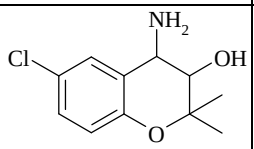
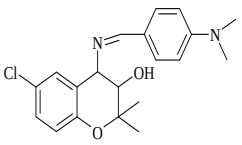
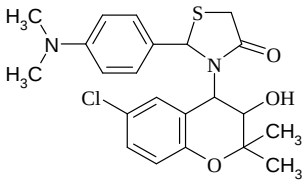
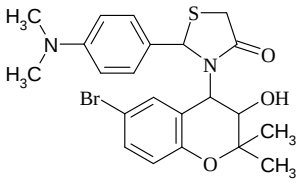
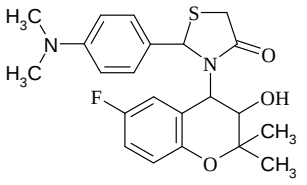
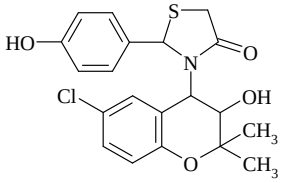
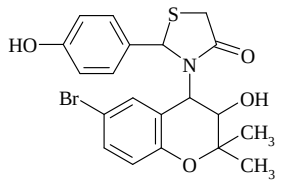
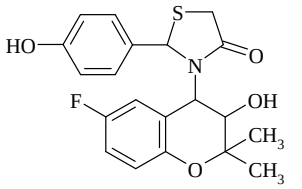
Compound No.	Structure of the compound	IR Spectral data (cm^{-1})	NMR spectral data (δ ppm)
IIa		748.41(C-Cl,st); 1236.41(C-O,st); 1750(C=O,st); 2924(-C-H,st); 1510.31(C=C)	3.317(s,3H, $COCH_3$);7.94-7.95(d,2H,ArH); 7.08-7.10 (d,1H, ArH);6.579-6.592 (d, 1H, ArH)
IIIa		3074.81(=C-H, st); 1645.43 (C=C); 1020.94(C-O, st); 3645.11(O-H, st); 746.52(C-Cl,st); 1705 (C=O, st)	7.679, 7.673(1H, d, ArH); 7.410 (1H,s,ArH);6.936, 6.913(1H,d,ArH); 2.617(3H,s, AlH)
IVa		3069.02(=C-H,st); 1604.92 (C=C); 1130.39(C-O,st); 1695.58(C=O,st); 2935.92(C-H,st,CH_3); 721.44 (C-Cl,st)	7.798,7.791(1H,s, ArH); 6.887, 6.864 (2H,d,ArH); 1.444(6H,s,AlH)
Va		3292.79(=C-H,st); 1604.92 (C=C); 2980.29(C-H, st, CH_3); 1084.09(C-O-C); 3645.09(O-H,st); 673.22(C-Cl,st)	7.806(1H,s,ArH);7.117, 7.096(1H,d,ArH); 6.724,6.702(1H,d,ArH); 1.829(1H,s,AlH);1.291 (6H,s,AlH)
VIa		2918.56(=C-H,st); 1604.92(C=C); 719.51(C-Cl,st); 1084.09(C-O-C);	7.931(1H,s,ArH); 7.114 (1H,s, ArH); 6.724,6.704 (1H,d,ArH); 1.334 (6H,s,AlH)
VIIa		2969.86(=C-H,st); 1605.84(C=C); 706.85 (C-Cl); 1265.75(cyclic ether ring)	7.389 (1H,s,ArH); 7.116 (1H,s, ArH); 6.726,6.706 (1H,d,ArH); 1.336(6H,s,AlH)
VIIIa		2975.35(=C-H,st); 3463.01(N-H, st); 1090.41(C-O, st); 706.85(C-Cl,st)	7.389 (1H,s,ArH); 7.116, 7.069 (1H,d,ArH); 6.746,6.706 (1H,d,ArH); 6.747 (1H,t,AlH); 1.347(6H,s,AlH)
IXa		3011.97(=C-H,st); 3627.30 (O-H,st); 625.44(C-Cl,st); 1663.53(C=N,st);1341.88 (C-N,st)	7.02(1H,s,ArH); 6.98, 6.66 (1H,d,ArH); 4.71(1H,d,CH); 1.48(6H,s,AlH); 2.85(6H,s,AlH); 7.44 (1H,s,ArH);

Table 2. Analytical data of synthesized compounds Xa-Xl

Compound No.	Structure of the compound	IR Spectral data (cm^{-1})	NMR Spectral data (δ ppm)	Mass Spectral data
Xa		3013.54(=C-H,st); 1667.33(C=C,st); 3489.91(O-H,st); 1297.97(C-N,st); 1687.55(C=O,st); 701.06(C-Cl,st)	7.02(1H,s,ArH); 6.98, 6.66 (1H,d,ArH); 6.47(1H,s,4H); 2.0(1H,Alc); 4.71, 4.95 (1H,CH_2.); 2.85 (6H,s,AlH); 1.48(6H,s,AlH);	M/e=432 M/e+1=433 M/e+2=434
Xb		3025.90(=C-H,st); 1611.28(C=C,st); 1275.13(C-N,st); 3648.23(O-H,st); 1699.85(C=O,st); 664.11(C-Br,st)	7.18(1H,s,ArH); 6.61, 7.14 (1H,d,ArH); 6.47(1H,s,ArH); 2.0(1H,Alc); 4.71, 4.95 (1H,CH_2.); 2.85 (6H,s,AlH); 1.48(6H,s,AlH);	M/e=477 M/e+1=478 M/e+2=479
Xc		3034.79(=C-H,st); 1322.56(C-N,st); 3600.23(O-H,st); 1698.33(C=O,st);	6.68(1H,s,ArH); 6.70, 6.72 (1H,d,ArH); 6.47(1H,s,ArH); 2.0(1H,Alc); 4.71, 4.95 (1H,CH_2.); 2.85 (6H,s,AlH); 1.48(6H,s,AlH);	M/e=416 M/e+1=417 M/e+2=418
Xd		3013.42(=C-H,st); 3041.65(=C-H,st); 3602.72(O-H,st); 1744.51(C=O,st); 1199.21(C-O,st); 758.69(C-Cl,st)	7.02(1H,s,ArH); 6.66, 6.98 (1H,d,ArH); 6.89(1H,s,ArH); 2.0(1H,Alc); 4.71, 4.95 (1H,CH_2.); 5.01(1H,ArOH); 1.48(6H,s,AlH);	M/e=405 M/e + 1=406 M/e+2=407
Xe		3015.13(=C-H,st); 3602.72(O-H,st); 1751.51(C=O,st); 1194.89(C-O,st); 694.76(C-Br,st)	7.18(1H,s,ArH); 6.61, 7.14 (1H,d,ArH); 6.89(1H,s,ArH); 2.0(1H,Alc); 4.71, 4.95 (1H,CH_2.); 5.01(1H,ArOH); 1.48(6H,s,AlH);	M/e=450 M/e + 1=451 M/e+2=452
Xf		3013.89(=C-H,st); 3059.81(=C-H,st); 3546.13(O-H,st); 1745.28(C=O,st); 1193.47(C-O,st);	6.72(1H,s,ArH); 6.68, 6.70 (1H,d, ArH); 6.61(1H,s, ArH);2.0(1H,Alc); 4.71, 4.95(1H,CH_2.) 5.01(1H,ArOH);	M/e=389 M/e + 1=390

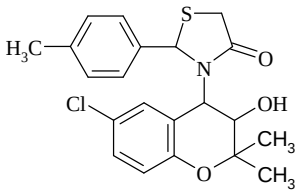
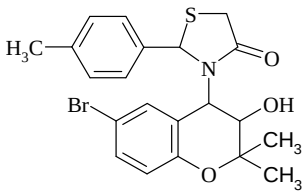
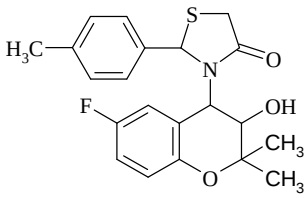
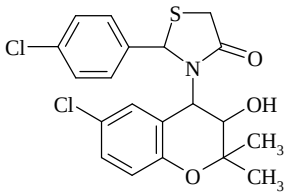
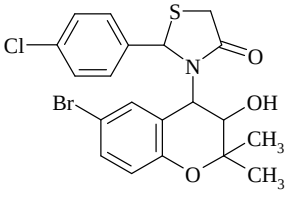
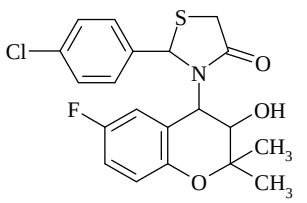
			1.48(6H,s,AlH);	
Xg		3015(=C-H,st); 1506.10(C-C,st); 2976.57(C-H,st); 1296.26(C-N,st); 3324.35(O-H,st); 1789.33(C=O,st); 705.36(C-Cl,st)	7.36(1H,s,ArH); 7.29, 6.85 (1H,d, ArH); 7.15,7.11(1H, s,ArH);2.57(1H,Alc) ; 4.71,4.95 (1H, CH_2.);3.59(1H,CH_2) ;2.21(1H,s,AlH); 1.36(6H,s,AlH);	M/e=403 M/e+1=404 M/e+2=405
Xh		3015.84(=C-H,st); 1590.85(C-C,st); 2931.18(C-H,st); 1278.36(C-N,st); 3664.86(O-H,st); 1795.75(C=O,st); 710.57(C-Br,st)	7.45(1H,s,ArH); 6.84(1H,s,ArH); 7.10(1H,s,ArH); 2.57(1H,Alc); 4.71,4.95(1H,CH_2.); 3.59(1H,CH_2); 2.21 (1H,s, AlH); 1.35 (6H,s,AlH);	M/e=448 M/e+1=449 M/e+2=450
Xi		3015.72(=C-H,st); 1572.61(C-C,st); 2933.77(C-H,st); 1284.74(C-N,st); 3596.11(O-H,st); 1748.45(C=O,st);	7.28(1H,s,ArH); 6.97,6.92(1H,d, ArH); 7.15(1H,s, ArH);2.57(1H, Alc); 4.71,4.95 (1H,CH_2.);3.59(1H, CH_2);2.21(1H,s, AlH);1.36(6H,s, AlH);	M/e=403 M/e+1=404 M/e+2=405
Xj		3011.66(=C-H,st); 1594.97(C=C, st); 1701.43 (C=O,st); 3636.33 (O-H,st); 1344.32(C-N,st); 716.08(C-Cl,st)	7.37(1H,s,ArH); 7.10(1H,s,ArH); 5.68(1H,CH_2); 2.57(1H,Alc); 4.71, 4.90(1H,CH_2.); 3.65(1H,CH_2); 1.36(6H,s,AlH);	M/e=423 M/e + 1=424 M/e+2=425
Xk		3014.29(=C-H,st); 3072.66 (=C-H,st); 1632.63(C=C, st); 1756.16 (C=O,st); 3636.12 (O-H,st); 1343.32(C-N,st); 646.25(C-Br,st); 700.91(C-Cl,st)	7.45(1H,s,ArH); 7.32(1H,s,ArH); 5.66(1H,CH_2); 2.57(1H,Alc); 4.71, 4.90(1H,CH_2.); 3.65(1H,CH_2); 1.35(6H,s,AlH);	M/e=423 M/e + 1=424 M/e+2=425
Xl		3021.64(=C-H,st); 1638.43(C=C, st); 1785.58 (C=O,st); 3613.58(O-H, st); 1284.18(C-N,st); 709.21(C-Cl,st);	7.28(1H,s,ArH); 6.97,6.93(1H,d, ArH); 7.10(1H,s, ArH);5.67(1H,CH_2); 2.57(1H,Alc); 4.71, 4.90(1H,CH_2.); 3.65(1H,CH_2); 1.36(6H,s,AlH);	M/e=468 M/e + 1=469 M/e+2=470

Table 3: Antihypertensive activity

Treatment	BP	SBP	DBP	Mean BP	Heart Rate
Control	93.26±1.23	102±1.62	73.2±1.31	102.12±2.2	296.5±1.16
Fructose	141.2±2.25	138.3±2.18	118.2±1.19	120.21±1.32	325.3±1.61
FRT+Xa	102±2.77***	120±1.89*	90±2.78***	99.23±2.21***	306.4±1.89*
FRT+Xb	104±1.72***	126±2.25*	95±1.80***	97±1.43***	305.21±1.72*
FRT+Xc	101±2.43***	123±1.98*	91.4±1.31***	96±2.45***	307.2±2.75*
FRT+Xd	100±2.71***	121±2.83*	96±1.23***	95.24±2.54***	311±2.12*
FRT+Xe	101±1.52***	119±2.23*	98.5±1.64***	99.56±1.78***	308.2±1.66*
FRT+Xf	97.4±2.36***	124.6±1.72*	87±2.48***	100±1.25***	313.4±1.23*
FRT+Xg	100±1.66***	120±1.32*	95±1.26***	97.21±1.39***	307.6±1.68*
FRT+Xh	100±1.36***	123±2.56*	88.2±2.64***	95.29±1.23***	311.2±1.70*
FRT+Xi	102.52±2.84***	122±1.69*	96.23±2.34***	98.41±2.12***	309±2.25*
FRT+Xj	98.2±2.68***	125±1.65*	89±1.20***	99±1.26***	305.2±1.89*
FRT+Xk	103±2.51***	122±2.36*	92.45±1.62***	96.36±1.39***	302±1.64*
FRT+Xl	101.3±1.62***	120±2.31*	97±2.12***	98±2.36***	309.3±2.23*
Frt+ Std	98.12±1.62***	121.2±1.36*	86.4±1.8***	96.12±2.1***	308.42±1.68*

Values are expressed as Mean ±SEM, n=6, analyzed in graph pad prism version 5.04 by one way ANOVA followed by Tukey's multiple comparison test.

Where * represents significant at $P \leq 0.05$,**represents highly significant at $P \leq 0.01$,

*** represents very significant at $P \leq 0.001$.

CONCLUSION

The high prevalence of hypertension worldwide has contributed to the present pandemic of cardiovascular disease. During the past century, such disease has changed from a minor cause of death and disability to one major contributors to the global burden of disease. Cardiovascular diseases are now responsible for 30% of all deaths worldwide. Benzopyran analogues are proven to have antihypertensive activity. So, further research should be done on this class of compounds which may result in the development of more effective, potent, long acting compounds with minimal side effects compare to the compounds available in the market at present for the treatment of hypertension and its related complications and help in solving the global issue of hypertension.

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