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SYNTHESIS AND ANTIHYPERTENSIVE ACTIVITY OF VARIOUS 1-SUBSTITUTED-9-SUBSTITUTED-5,5-DIMETHYL-1,3,4,4A,5,10*b*-HEXAHYDRO-2*H*-CHROMENO[4,3-*b*]PYRIDIN-2-ONE

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ABSTRACT

The present work was aimed at exploring a series of novel 1-substituted-9-substituted-5,5-dimethyl-1,3,4,4a,5,10b-hexahydro-2*H*-chromeno[4,3-*b*]pyridin-2-one by utilizing substituted phenols as their starting material. The methodology comprised of acylation, fries rearrangement reaction, cyclisation, reduction, epoxidation, ring opening reaction and N-alkylation. Substituted phenols were first acylated with acetic acid in presence of Lewis acid to substituted acetophenones which were smoothly converted to benzopyran derivatives by N-alkylation of amines by alkyl halides occurs in aqueous media under microwave irradiation. 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, N-alkylation, antihypertensive activity, tail-cuff method.

INTRODUCTION

The discipline of medicinal chemistry is devoted to the discovery and development new agents for treating diseases.[1] The treatment and therapy of cardiovascular disease have undergone dramatic changes since 1950s. Data show that since 1968 and continuing through the 1990s, there has been a noticeable decline in mortality from cardiovascular disease.[2] 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.[3] A series of benzopyrans and their analogues were synthesized and evaluated on potassium channel opening and hypotensive activities.[4-8] The rigid spirocyclic ring fusion holds the nitrogen in an optimum orientation relative to the benzopyran ring.[9-17] ATP-sensitive potassium channels (K_{ATP} channels) are present in multiple cell types including endocrine cells, skeletal and smooth muscle cells, cardiac cells and central neurons. K_{ATP} channels are involved in main physiological processes such as hormone secretion, smooth muscle cell contractile activity, myocardial protection and neurotransmitters release. Several compounds are known to activate K_{ATP} channels and have been named "potassium channel openers" (PCOs). Potassium channel openers are known to be able to relax vascular smooth muscles and have therefore been used for the treatment of hypertension. It has now been found that benzopyran derivatives are useful as potassium channel activators which surprisingly are active on the pancreatic endocrine tissue as inhibitors of insulin secretion.[18-27] There has been a rapid extension in the synthesis of molecules related to nicorandil, cromakalin, pinacidil in last few years.[28,29] It have taken attention of researchers, chemists and pharmacologists to synthesize new drugs which are more potent, less toxic and at the same time better tolerated than existing drugs.[30]

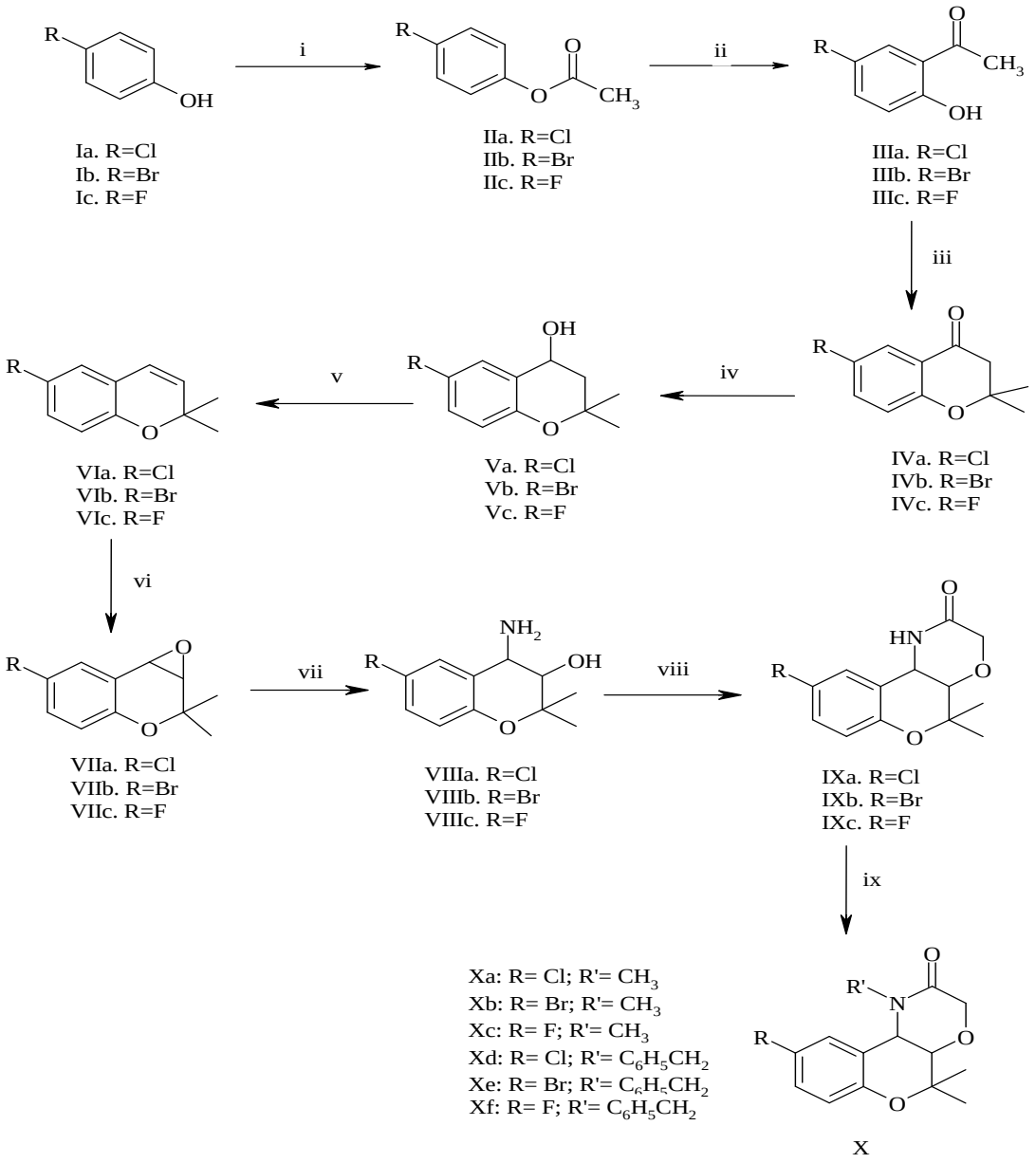
In view of these observations and the ever increasing importance of these biologically active heterocycles in pharmaceutical field, we therefore synthesized a series of novel 1-substituted-9-substituted-5,5-dimethyl-1,3,4,4a,5,10*b*-hexahydro-2*H*-chromeno[4,3-*b*]pyridin-2-one and investigated the antihypertensive activity in rats to use in the treatment of hypertension.

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) $HCONH_2$, $ClCH_2COCl$, triethylamine; (ix) benzyl chloride, methyl iodide, NaOH in water.

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.

9-chloro-5,5-dimethyl-1,4a,5,10b-tetrahydrochromeno[3,4-*b*][1,4]oxazin-2(3*H*)-one(IXa). Compound **VIIIa** (3g) was taken in a 100ml flask with 5ml $HCONH_2$, equivalent amount $ClCH_2COCl$ and 0.3ml trimethylamine as catalyzer. The mixture was refluxed at 150°C for 90min. the obtained product was filtered and rinsed with ethanol and dried at room temperature.

1-Benzyl-9-chloro-5,5-dimethyl-1,3,4,4a,5,10b-hexahydro-2*H*-chromeno[4,3-*b*]pyridin-2-one (Xd). Benzyl chloride (1mmol), IXa (1mmol) and NaOH (1mmol) in water were placed in a round-bottom flask equipped with a condenser and a magnetic stirrer. The flask was placed in a Microwave Synthesis System, and subjected to MW irradiation at 80°-100°C (power 250 Watt) for 25 minutes. After completion of the reaction (monitored by TLC), the product was extracted into ethyl acetate. Solvent was removed under reduced pressure. Then the column chromatography was performed. The synthesized compounds were confirmed by IR, NMR and Mass.

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.

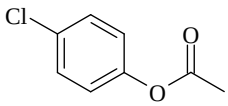
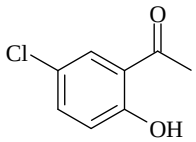
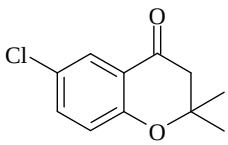
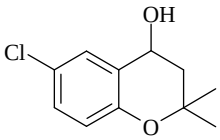
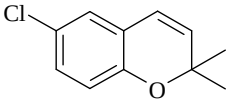
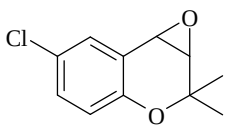
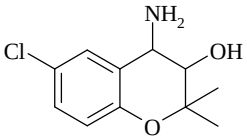
Albino Wistar rats weighing 200-250gm will be used to screening for antihypertensive activity. Suspension of all the test compounds will be prepared in 1% w/v sodium carboxy methyl cellulose. Control group will receive an equal quantity of 1% w/v sodium carboxy methyl cellulose suspension. After administration 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. For the synthesis of desired benzopyran analogues, substituted phenols are used as the starting material and the procedure followed for the synthesis of these benzopyrans are developed in the laboratory with the help of the available literature. All the compounds were confirmed by IR, NMR and Mass Spectroscopy.

Benzopyran analogues have been evaluated worldwide by the researchers for their antihypertensive activity. 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. Results of antihypertensive activity revealed that benzopyran analogues have antihypertensive properties in which some compounds show good antihypertensive activity and others with moderate or no activity.

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);1.34(6H,s,AlH)

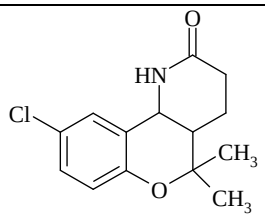
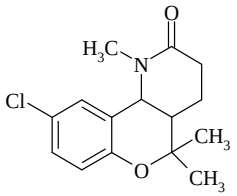
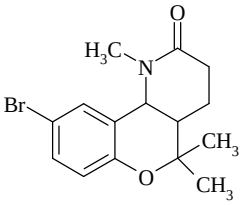
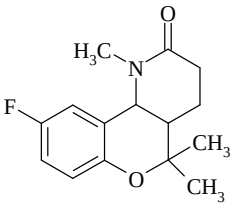
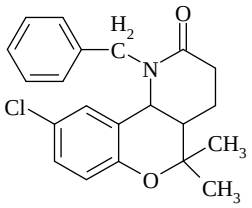
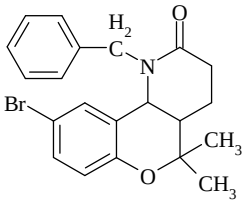
IXa		3015.90(C-H, st); 3472.32(N-H, st); 1729.31(C=O, st); 1199.99(C-N, st); 787.39(C-Cl, st)	1.42(6H,s,AlH);6.42(1H,s, NH);7.23(1H,s,ArH); 6.83 (1H,d,ArH);

Table 2: Analytical data of synthesized compounds Xa-Xf

Compound No.	Structure of the compound	IR Spectral data (cm^{-1})	NMR spectral data (δ ppm)	Mass Spectral data
Xa		3013.38(=C-H, st); 2852.59(C-H, st CH_3-N); 1595.49 (C-C, st); 1079.09 (C-N, st); 1672.58 (C=O, st); 711.42 (C-Cl,st)	1.39(6H,s,AlH); 2.96(3H,s,AlH); 7.31(1H,s,ArH); 6.83(1H,d,ArH);	M/z=279 M/z+1=280 M/z+2=281
Xb		3010.03(=C-H, st); 2800.74(C-H, st CH_3-N); 1438.27 (C-C, st); 1085.29 (C-N, st); 1795.86 (C=O, st); 638.52 (C-Br, st)	1.39(6H,s,AlH); 2.96(3H,s,AlH); 7.40(1H,s,ArH); 6.82(1H,d,ArH);	M/z=324 M/z+1=325 M/z+2=326
Xc		3033.16(=C-H, st); 2744.74(C-H, st CH_3-N); 1598.50 (C-C, st); 1017.55 (C-N, st); 1728.67 (C=O, st)	1.39(6H,s,AlH); 2.96(3H,s,AlH); 7.23(1H,s,ArH); 6.92(1H,d,ArH);	M/z=263 M/z+1=264
Xd		3015.00(=C-H, st); 1455.55(C-C, st); 1700.98(C=O, st); 1135.32(C-O-C, st); 2792.82(C-H, st CH_2-N); 744.30 (C-Cl,st)	1.37(6H,s,AlH); 5.71(2H,d,AlH); 6.87(1H,d,ArH); 7.40(1H,s,ArH); 7.30(1H,s,ArH)	M/z=355 M/z+1=356 M/z+2=357
Xe		3028.72(=C-H, st); 1497.93(C-C, st); 1415.98(C-C, st); 1720.45(C=O, st); 2825.51(C-H, st CH_2-N); 667.18(C-Br, st)	1.36(6H,s,AlH); 5.71(2H,d,AlH); 6.86(1H,d,ArH); 7.49(1H,s,ArH); 7.26(1H,s,ArH)	M/z=400 M/z+1=401 M/z+2=402

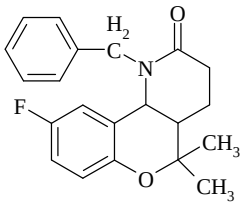
Xf		3030.42(=C-H, st); 1442.24(C-C, st); 1597.83(C-C, st); 1720.45(C=O, st); 2742.74(C-H, st CH_2-N);	1.37(6H,s,AlH); 5.72(2H,d,AlH); 6.95(1H,d,ArH); 7.32(1H,s,ArH); 7.26(1H,s,ArH)	M/z + 1=340 M/z + 2=341

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	119.7±2.31***	124.9±1.89**	107.3±1.25*	103.25±1.38**	302.3±1.67**
FRT+Xb	130.8±2.31**	126.7±1.56**	106.6±1.25**	101.78±1.90**	313.4±1.45**
FRT+Xc	133.8±1.85*	133.8±2.22*	112.7±1.50*	113.45±1.47*	313.9±1.50*
FRT+Xd	112.7±1.62***	123.7±1.36**	108.8±1.8*	106.27±2.1**	305.4±1.68**
FRT+Xe	131.2±2.57*	130.5±1.98*	109.4±2.56*	102.41±2.49**	316.3±2.36**
FRT+Xf	132.6±2.50*	136.6±1.01*	114.1±1.24*	114.21±1.50*	312.5±2.54*
FRT+Std	98.12±1.62***	121.2±1.36**	96.4±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 ≤ 0.05,**represents highly significant at P≤0.01,

*** represents very significant at P≤0.001.

CONCLUSION

Hypertension is an important worldwide public health challenge because of its high frequency and concomitant risks of cardiovascular disease. It has been identified as the leading risk factor for mortality, and is ranked third as a cause of disability-adjusted life-years. The prevalence of hypertension in various regions of the world has been widely reported. Analysis indicates that more than a quarter of the world's adult population, totaling nearly one billion had hypertension in 2000, and this proportion will increase to 29% by 2025. Substituted benzopyrans have proven to have antihypertensive activity. Further research should be done on this class of compounds for more effective, potent and long acting compounds with minimum side effects for the treatment of hypertension and it related complications.

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