Research Article

Synthesis, Characterization, and Antihypertensive Evaluation of Some Novel 2,2,8,8-Tetramethyl-2,3,7,8-tetrahydro-4,6-diamino-3,7-dihydroxy-6,7-epoxy-benzo-[1,2-b:5,4-b']dipyran Derivatives

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A series of 2,2,8,8-tetramethyl-2,3,7,8-tetrahydro-4,6-diamino-3,7-dihydroxy-6,7-epoxy-benzo-[1,2-b:5,4-b']dipyran derivatives **7a–e** and **8a–e** were synthesized from resorcinol. All the synthesized compounds were characterized by FTIR, mass spectra, and ^{1}H NMR. These compounds were evaluated for antihypertensive activity using Wister Albino Rat model. Direct antihypertensive activity was performed using the instrument BIOPAC System MP-36 Santa Barbara, California, for recording blood pressure response. Among the title compounds, compounds **7b**, **7c**, and **7d** showed potent antihypertensive activity and other compounds were also found to exert low and moderate antihypertensive activity. The relaxant potency in rat aorta and trachea was used for biological characterization of the benzopyrans. Structure-activity relationships study was investigated around position-4 of the benzopyran nucleus.

1. Introduction

Potassium specific channels are assorted group of ion channels and play a fundamental role in the modulation of cell excitability [1, 2]. Potassium channel classifications and their pharmacological activities have been reviewed extensively [3]. The term "potassium channel openers (KCOs)" was introduced to designate a group of novel synthetic molecules which are specified by cromakalim. It led to a new direction in the pharmacology of ion channels by reporting that cromakalim evoked smooth muscle relaxant effects by the opening of K^+ channels in cell membranes [4]. It has initiated major research efforts in the search for other such molecules and in the determination of the specific channel(s) involved [5]. KCO properties are demonstrated in a diverse range of synthetic chemical structures and endogenous substances [6].

Cromakalim evoked a contractile response in rabbit aorta bathed in a Ca^{2+} free solution which is related to the effects on intracellular Ca^{2+} stores [7]. These findings support those obtained from vascular smooth muscle where contractile responses to noradrenaline depend on intracellular calcium stores which are attenuated by cromakalim [8]. In contrast, the effect of cromakalim on rat pulmonary artery did not appear to involve an action on Ca^{2+} release from internal stores [9]. A variety of compounds having a benzopyran such as levocromakalim, bimakalim, and Y-27152 generally exhibit potent antihypertensive activity. Benzodipyrans have structural and chemical similarity with the cromakalim [10]. The ATP-sensitive potassium channel (K_{ATP}) openers (e.g., chromakalim) were originally developed for the treatment of hypertension due to their potent peripheral vasodilating properties [11]. To find more potent vasodilators, various benzopyran derivatives modified at position-4 were synthesized and structure-activity relationship was examined by evaluation of the extent and duration of the increase in coronary blood flow in anesthetized dogs [12]. Compounds having a 1, 6-dihydro-6-oxopyridazin-3-yl amino group at
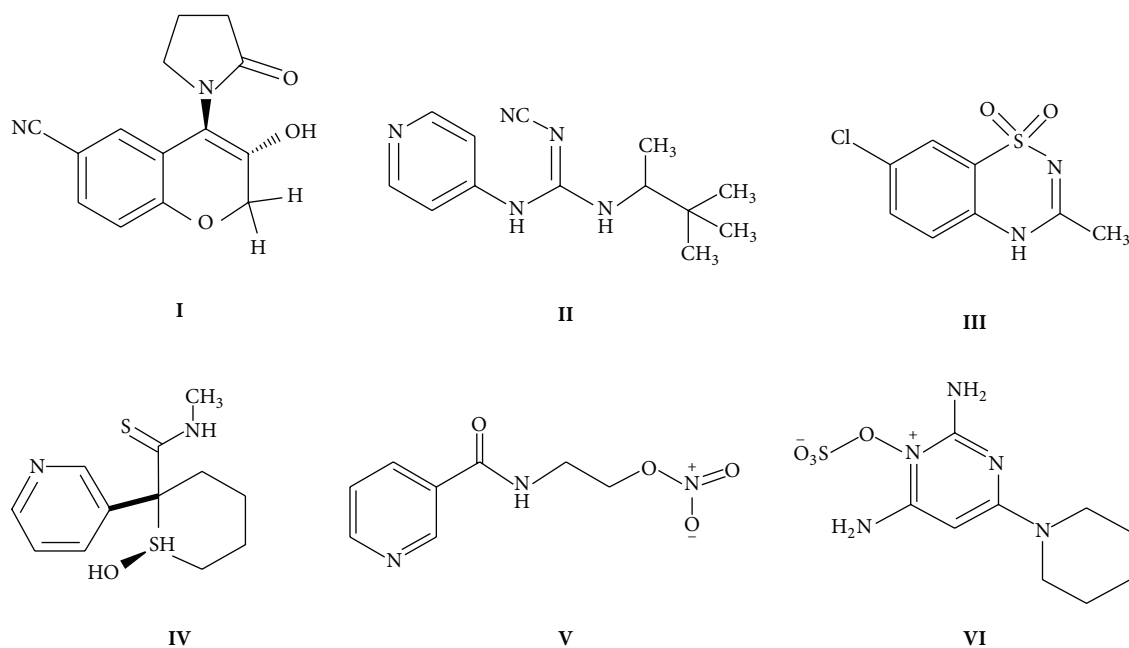
Figure 1: First generation potassium channel openers (KCOs) as antihypertensive agents.

position-4, in addition to the two methoxymethyl groups at position-2, were found to be more potent and have an improved duration of action [13].

Myocardial preconditioning as KCOs is of great interest as myocardial protecting agents [14]. The first generation (K_{ATP}) openers **I**–**VI** (Figure 1) are potent peripheral vasodilators, but the use of these compounds for the treatment of acute myocardial ischemia is limited due to the possibility of hemodynamic alterations upon systemic administration which can result in under perfusion of the area that is already at risk [15]. It was presumed that clinical utility of these agents for the treatment of hypertension is due to their peripheral vasodilating properties, as they are widely known to open potassium channels in several tissue types. But relevant studies have shown that K_{ATP} openers have direct cardioprotective properties independent of their vasodilator effect. Therefore, tissue selective K_{ATP} openers are clearly required to explore the potential of these agents [16].

2. Experimental

2.1. General. All the reagents were purchased from Sigma-Aldrich Chemicals (Bangalore, India) and were used without further purification. All solvents were distilled and dried using dry sieves as the usual manner. TLC analysis was carried out on aluminum foil precoated with silica gel 60 F254 (Sigma-Aldrich, Bangalore dealer). Melting points were determined on a Thomas micro-hot stage apparatus and are uncorrected. FTIR spectra were determined as KBr solid discs on a Shimadzu model 470 spectrophotometer. ^{1}H NMR spectra were recorded using a Jeol Eclipse 400 MHz spectrometer using CDCl$_3$ as NMR solvent and are reported in ppm down field from the residual CDCl$_3$. ^{1}H NMR

spectrum exhibited different signals at different ppm which were assigned to the different types of protons. The synthetic route leading to the title compounds is summarized in Scheme 1.

2.2. Synthesis

2.2.1. 2,4-Diacetyl Resorcinol (2). Dry resorcinol **1** (1.0 g, 9.09 mmol) was added to a mixture of zinc chloride (2.467 g, 18.18 mmol) in dried acetic anhydride (1.89 mL, 18.18 mmol) in a round bottom flask quickly with stirring. The reaction mixture was slowly heated on wire gauze and kept at 145–150°C for 15 min. The resulting viscous reaction mixture was allowed to cool at room temperature and ice cold aqueous hydrochloride solution was added to it with constant stirring. An orange-red crystalline compound separated out, which was purified by column chromatography to obtain white color solid compound. Yield 70.58%. mp 175–177°C. IR (KBr) ν (cm^{-1}): 3414.3, 3079.8, 2926.1, 1658.6, 1588.6, 1256.7. ^{1}H NMR (CDCl$_3$, δ ppm): 12.93 (s, Ar, 2H), 8.19 (s, 1H), 6.39 (s, 1H), 2.62 (s, 6H). MS (EIMS, FAB, *m/z*): 195.4 (M + 1).

2.2.2. 2,2,8,8-Tetramethyl-2,3,7,8-tetrahydro-4H,6H-benzo-[1, 2-b:5,4-b′]-dipyran-4,6-dione (3). 2,4-Diacetyl resorcinol **2** (1.0 g, 5.15 mmol) was mixed with piperidine (0.875 g, 10.3 mmol) and acetone (3.0 mL) in toluene in a round bottom flask which was fixed with Dean Stark apparatus. The resulting reaction mixture was slowly heated at 120–125°C for 24 hr. After completion of reaction, the reaction mixture was distilled off to remove the solvents. It was quenched with ice cold water and extracted with chloroform. Organic layer was separated and dried over sodium sulfate and solvent
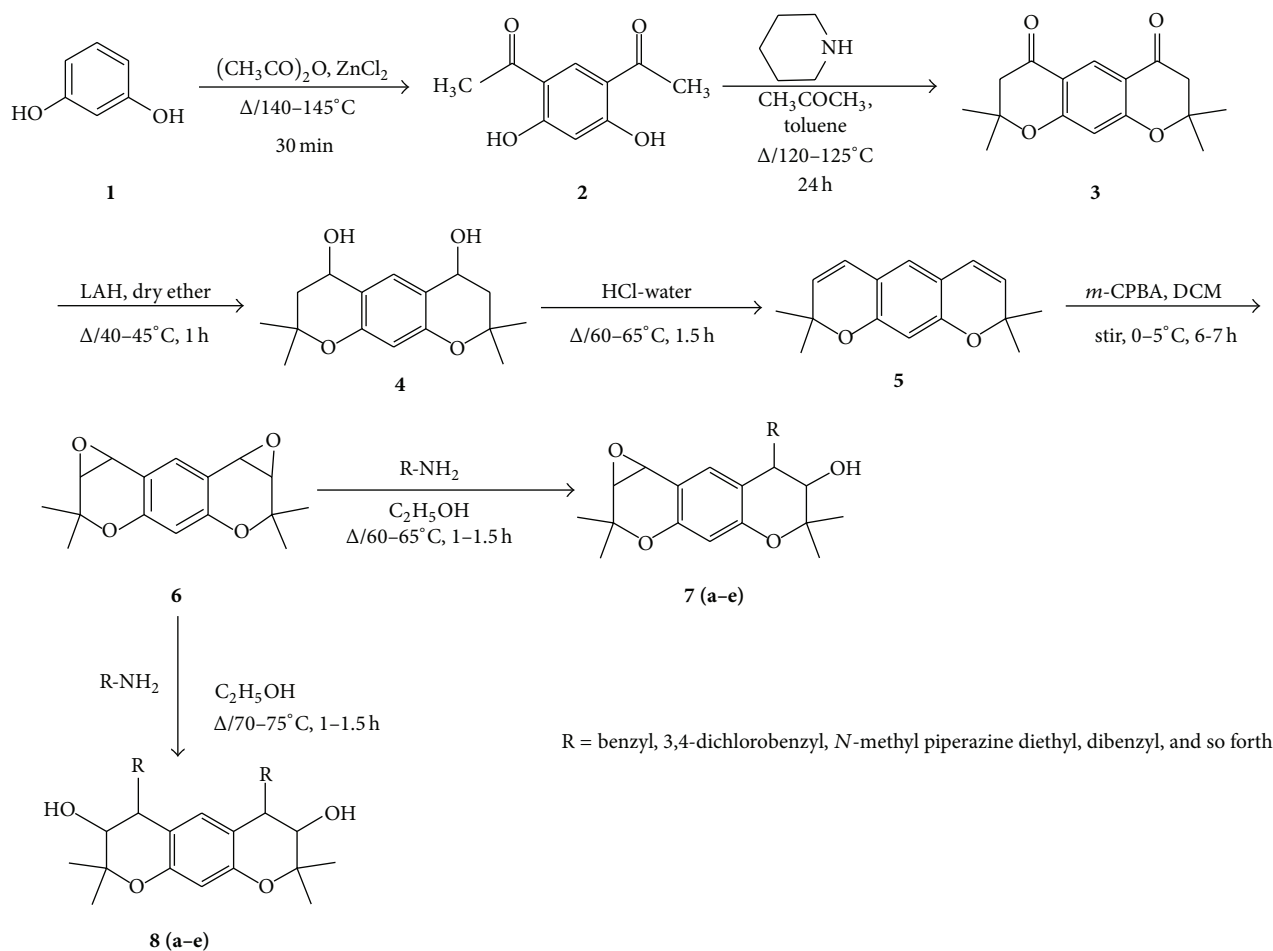
SCHEME 1: Synthesis of 2,2,8,8-tetramethyl-2,3,7,8-tetrahydro-4,6-diamino-3,7-dihydroxy-6,7-epoxy-benzo-[1,2-*b*:5,4-*b'*]dipyran derivatives **7a–e** and **8a–e** from resorcinol for antihypertensive activity.

was evaporated off. The compound was purified by column chromatography over silica gel to get a white color solid product. Yield 51.85%. mp 184–186°C. IR (KBr) ν (cm^{-1}): 2973.4, 2929.7, 1703.1, 1600.9, 1234.2. ^{1}H NMR (CDCl$_3$, δ ppm): 8.46 (s, 1H), 6.38 (s, 1H), 2.69 (s, 4H), 1.45 (s, 12H). MS (EIMS, FAB, *m/z*): 275.1 (M + 1).

2.2.3. 2,2,8,8-Tetramethyl-2,3,7,8-tetrahydro-4H,6H-benzo-[1, 2-b:5,4-b']dipyran-4,6-dihydroxy (4). To a solution containing 500 mg (0.013 mol) of lithium aluminum hydride (LAH) in 25 mL ether, the corresponding chromanone **3** (1.37 g, 0.005 mole) in 30 mL of ether was added drop wise with stirring in a round bottom flask. The resulting reaction mixture was heated to reflux for an hour, allowed to cool, and then filtered. Acetone (20 mL) was added to the resulting filtrate to decompose the excess of lithium aluminum hydride and the reaction was monitored by TLC. Yield 65.43%. mp 183–185°C. IR (KBr) ν (cm^{-1}): 3281.7, 2972.2, 2361.8, 1630.1, 1254. ^{1}H NMR (CDCl$_3$, δ ppm): 8.33 (d, 3H), 6.46 (s, 2H), 2.92 (s, 2H), 1.52 (s, 4H). MS (EIMS, FAB, *m/z*): 279.7 (M + 1).

2.2.4. 2,2,8,8-Tetramethyl-2H,8H-benzo[1,2-b:5,4-b']dipyran (5). Compound **4** was refluxed with 6 M HCl (10 mL) for 10 min. Then, 50 mL water was added to it and the reaction mixture was further refluxed for 1.0 h, allowed to cool, solvent was evaporated off, and aqueous phase was extracted with methylene chloride. Organic layer was dried over sodium sulfate, concentrated, and purified by column chromatography over silica gel to get a white color solid product. Yield 83.19%. mp 195–197°C. IR (KBr) ν (cm^{-1}): 3042.7, 2977.5, 1562.7, 1212.7. ^{1}H NMR (CDCl$_3$, δ ppm): 6.61 (s, 1H), 6.27 (s, 2H), 6.25 (d, 1H, J = 9.9 Hz), 5.47 (d, 1H, J = 9.9 Hz), 1.42 (s, 12H). MS (EIMS, FAB, *m/z*): 243.5 (M + 1).

2.2.5. 2,2,8,8-Tetramethyl-2H,8H-benzo-[1,2-b:5,4-b']dipyran Oxide (6). Compound **5** (100 mg, 0.413 mmol) was dissolved in dichloromethane. *m*-Chloroperbenzoic acid (*m*-CPBA) (213 mg, 1.239 mmol) was added to resulting reaction mixture. It was allowed to stir at 0°C for 1 h. Solvent was evaporated at low temperature and excess of *m*-CPBA was decomposed by NaHCO$_3$ solution. The aqueous solution was extracted using dichloromethane and organic layer was

separated. It was concentrated and purified by column chromatography over silica gel to get a white color solid product. Yield 37.09%. mp 186–188°C. IR (KBr) ν (cm^{-1}): 3074.3, 2934.5, 1553.5, 1243.3, 1043.4. ^{1}H NMR (CDCl$_3$, δppm): 7.54 (d, 1H, J = 9.6 Hz), 6.32 (d, 1H, J = 7.8 Hz), 6.27 (s, 1H), 2.46 (s, 3H). MS (EIMS, FAB, m/z): 275.1 (M + 1).

2.2.6. 2,2,8,8-Tetramethyl-2,3,7,8-tetrahydro-4,6-diamino-3,7-dihydroxy-6,7-epoxy-benzo-[1,2-b:5,4-b$'$]dipyran Derivatives (7a–e) and 2,2,8,8-Tetramethyl-2,3,7,8-tetrahydro-4,6-diamino-3,7-dihydroxy-benzo-[1,2-b:5,4-b$'$]dipyran Derivatives (8a–e). Compound **6** (100 mg, 0.364 mmol) was dissolved in 30 mL ethanol in a 100 mL round bottom flask. Benzylamine (0.78 mL, 729 mmol) was added to the above reaction mixture and was allowed to reflux at 80°C for 3 h and reaction was monitored by TLC. After completion of reaction, it was distilled off to remove solvent from the reaction mixture. Then, it was quenched with ice cold water and extracted with dichloromethane. Organic layer was distilled off to get crude product. Further purification was accomplished by column chromatography. Mobile phase: ethyl acetate: hexane = 6:4.

2.3. Antihypertensive Activity

2.3.1. Toxicity Studies to Fix Up LD$_{50}$. Toxicity studies were carried out according to the OECD guidelines numbers 420 and 421 in order to fix up the dose to carry out the antihypertensive activity [17, 18]. Wister Albino Rats weighing 200–250 g were chosen and oral route is selected for the drug administration. Six groups of animals each containing three animals were initially selected as per the guidelines numbers 420 and 421. Given dose of 70 mg/kg body weight was monitored in the animal for the toxic symptoms as well as mortality [19]. The animals showed high toxicity symptoms such as increased intestinal motility, diarrhoea, tail erection, and irritation to nose, and all the animals were dead after 3.0 h. Hence, we decreased the dose to 50 mg/kg body weight and administered to the next group of animals, monitored for toxic symptoms and mortality. In this dose, animals were safe but showed fewer toxic symptoms and only few were died. Toxicity symptoms were diarrhoea, tail erection, and irritation to the nose. Once again, we decreased the dose and it was fixed to a dose of 20 mg/kg body weight to the next set of animals and observed for the toxic symptoms and mortality. All the animals were safe and no toxic symptoms were seen at this specific dose. Hence, it was concluded that 20 mg/kg body weight dose was safe and recommended dose for further antihypertensive activity [20].

2.3.2. Direct Antihypertensive Activity. Direct antihypertensive activity was carried out using the instrument BIOPAC System MP-36 Santa Barbara California for recording the blood pressure response [21]. The instrument was calibrated before carrying out the experiment and process was thoroughly practiced and understood including handling and surgically cannulating artery for monitoring blood pressure and a vein for drug administration [22, 23].

2.3.3. Preparation of Model. Male albino rats weighing 200–250 g were used for the antihypertensive activity. Rats were anesthetized using urethane hydrochloride (1.25 g/kg). Rats were prepared by shaving the neck and inguinal region using animal hair clippers. Jugular vein was surgically cannulated for the drug administration. Left carotid artery was isolated and exposed by dissection for blood pressure recording using PE-50 tubing [24]. By means of a three-way plastic stop cock and a stainless steel needle at the end of the PE tubing, arterial cannula and venous cannula were attached to a blood-pressure transducer and syringe, respectively [25, 26]. Fluid was filled in the both cannulae with heparinised saline before cannulation. Arterial cannula was connected via the BSL pressure transducer (SS13L) to the BIOPAC Systems, Inc. Criterion for antihypertensive activity was the reduction of systolic arterial pressure by about 10–20 mmHg [27].

2.3.4. Experimental Procedure. Adrenaline (5.0 μg/kg, i.v.) was administered intravenously for the sympathetic system activation to induce hypertension [28, 29]. Venous cannula was flushed with 0.2 mL of normal saline and allowed to return to preinjection level. Test compound 20 mg/kg solution was injected intravenously and allowed to equilibration in the system. Adrenaline (5.0 μg/kg, i.v.) was repeated as described previously. Blood-pressure response was observed and recorded to each procedure [30–32]. Antihypertensive activity of the benzodipyran derivatives **7a–e** and **8a–c** was summarized in Table 1.

3. Result and Discussion

3.1. Chemistry. 4, 6-Diacetyl resorcinol **2** was synthesized using a mixture of zinc chloride in dried acetic anhydride from dry resorcinol **1** by constant stirring. It was kept at high temperature for 30 min and was purified through column chromatography [33, 34]. Compound **3** (2,2,8,8-tetramethyl-2,3,7,8-tetrahydro-4H,6H-benzo[1,2-b:5,4-b$'$]dipyran-4,6-dione) was synthesized from 4,6-diacetyl resorcinol using acetone and piperidine in a solution in a Dean Stark apparatus using toluene as solvent. The reaction mixture was slowly heated at 120–125°C for 24 h to get the compound **3** [35, 36]. Compound **4** (2,2,8,8-tetramethyl-2,3,7,8-tetrahydro-4H,6H-benzo[1,2-b:5,4-b$'$]dipyran-4,6-dihydroxy) was synthesized using lithium aluminum hydride (LAH) in ether; the corresponding chromanone in ether and both these solutions were added drop wise with stirring. The resulting reaction mixture was heated to reflux for 1 h [37]. This reaction mixture was taken as such for the synthesis of 2,2,8,8-tetramethyl-2H,8H-benzo[1,2-b:5,4-b$'$]dipyran **5** by adding 6 M HCl and allowed to reflux for 1.5 h. After completion of the reaction, solvent was evaporated and the remaining aqueous phase was extracted with methylene chloride [38, 39]. 2,2,8,8-Tetramethyl-2H,8H-benzo[1,2-b:5,4-b$'$]dipyran oxide **6** was synthesized from compound **5** by dissolving in dichloromethane and required quantity of m-chloroperbenzoic acid (m-CPBA) was added to it. The resulting reaction mixture was allowed to stir at 0–5°C for 6-7 h [40]. Different benzodipyran derivatives **7a–e** and **8a–e**

TABLE 1: Antihypertensive activity of the benzodipyran derivatives **7a**–**e** and **8a**–**c**.

Comp. code	Parameter	Baseline	With adrenaline	With test alone	With test + adrenaline	Inference
7a	SBP	101.2 (±0.693)	147.8 (±1.308)	140.6 (±1.121)	141.4 (±2.040)	Minimal activity
	DBP	57.9 (±0.769)	79.2 (±0.861)	83.2 (±1.240)	73.9 (±1.167)	
	MABP	77.5 (±0.480)	143.9 (±1.202)	107.2 (±1.387)	109.3 (±0.894)	
	HR	196.5 (±3.201)	291.9 (±3.158)	248.1 (±3.118)	260.2 (±3.201)	
7b	SBP	106.4 (±0.482)	160.6 (±1.198)	124.6 (±1.389)	126.0 (±1.406)	Antihypertensive
	DBP	47.8 (±0.927)	75.1 (±3.054)	53.0 (±0.107)	59.3 (±1.541)	
	MABP	72.97 (±0.890)	122.1 (±1.883)	83.44 (±0.488)	109.2 (±0.931)	
	HR	299.9 (±3.106)	326.0 (±5.431)	321.0 (±0.557)	302.4 (±3.658)	
7c	SBP	105.7 (±1.203)	148.2 (±1.055)	127.1 (±1.031)	132.4 (±2.049)	Antihypertensive
	DBP	63.1 (±1.202)	86.5 (±1.218)	62.1 (±3.983)	84.2 (±1.160)	
	MABP	68.1 (±0.399)	109.1 (±0.963)	119.8 (±1.991)	101.3 (±0.896)	
	HR	278.8 (±2.697)	302.1 (±2.616)	298.7 (±2.065)	296.4 (±3.120)	
7d	SBP	120.8 (±1.061)	162.7 (±1.211)	143.6 (±0.892)	121.7 (±0.231)	Antihypertensive
	DBP	64.2 (±0.381)	86.8 (±0.665)	84.6 (±0.820)	71.1 (±1.858)	
	MABP	98.2 (±0.485)	120.7 (±1.390)	111.7 (±1.057)	99.2 (±1.524)	
	HR	209.5 (±1.161)	267.2 (±1.108)	248.9 (±2.868)	266.8 (±2.830)	
7e	SBP	108.9 (±0.519)	135.4 (±1.328)	160.8 (±0.940)	167.0 (±3.027)	Moderately active
	DBP	61.0 (±1.291)	87.1 (±1.966)	68.2 (±1.332)	91.3 (±1.857)	
	MABP	88.9 (±1.135)	102.1 (±1.503)	106.2 (±1.887)	119.3 (±0.197)	
	HR	232.2 (±2.097)	241.0 (±3.088)	209.2 (±3.210)	216.1 (±2.118)	
8a	SBP	128.8 (±3.62)	182.7 (±2.63)	168.8 (±0.85)	198.0 (±3.43)	Minimal activity
	DBP	70.89 (±2.33)	108.4 (±2.02)	134.3 (±0.95)	143.1 (±3.93)	
	MABP	103.7 (±3.28)	139.3 (±1.532)	149.9 (±1.152)	163.9 (±0.852)	
	HR	286.4 (±5.128)	304.6 (±3.210)	338.6 (±3.308)	341.9 (±1.409)	
8b	SBP	106.8 (±2.367)	178.6 (±1.349)	179.3 (±2.101)	189.3 (±0.239)	No activity
	DBP	84.0 (±2.105)	126.2 (±0.968)	128.7 (±1.151)	148.6 (±1.059)	
	MABP	112.9 (±2.250)	146.7 (±2.152)	182.3 (±1.788)	195.6 (±1.272)	
	HR	306.3 (±3.977)	331.8 (±3.300)	34.6 (±2.312)	361.8 (±2.008)	

TABLE 1: Continued.

Comp. code	Parameter	Baseline	With adrenaline	With test alone	With test + adrenaline	Inference
8c	SBP	89.82 (±1.363)	121.1 (±2.015)	143.3 (±1.38)	147.5 (±1.843)	Minimal activity
	DBP	67.1 (±0.379)	89.5 (±0.895)	102.8 (±3.516)	123.3 (±2.331)	
	MABP	88.0 (±3.837)	135.5 (±1.293)	142.8 (±2.870)	150.2 (±0.922)	
	HR	269.8 (±3.897)	302.1 (±4.430)	348.5 (±3.772)	356.9 (±1.573)	

SBP: systolic blood pressure, DBP: diastolic blood pressure, MABP: mean arterial blood pressure, and HR: heart rate. Values are expressed in mean ± S.E.M. Number of readings: 03.

TABLE 2: Physical and spectral analysis of 2,2,8,8-tetramethyl-2,3,7,8-tetrahydro-4,6-diamino-3,7-dihydroxy-6,7-epoxy-benzo-[1,2-b:5,4-b'] dipyran derivatives **7a**–**e**.
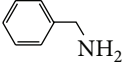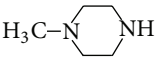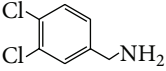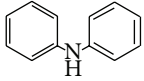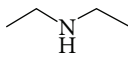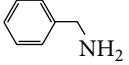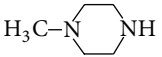
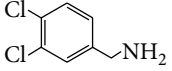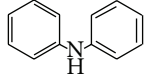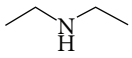| Comp. code	R	Molecular formula	R_f	FTIR (cm^{-1})	^{1}H NMR (ppm)	Mass (M + 1)
7a	(benzyl-NH$_2$)	$C_{27}H_{23}O_4N$	3.1	3352.7 (O–H str), 2934.2 (Ali C–H str), 1138.8 (C–N str), 1615 (C=C str)	δ7.16 (m, 12H), δ2.15 (s, 4H), δ1.30 (s, 12H)	382.5
7b	H$_3$C–N piperazine NH	$C_{21}H_{30}O_4N_2$	3.3	3317.8 (O–H str), 2924.4 (Ali C–H str), 1094.4 (C–N str), 1229.8 (C–O str), 1611.1 (C=C str)	δ5.37 (d, 1H), δ2.15 (s, 6H), δ1.26 (s, 12H)	374.0
7c	Cl, Cl-phenyl-NH$_2$	$C_{23}H_{25}Cl_2O_4N$	2.7	3395.5 (O–H str), 2927.9 (Ali C–H str), 1256.6 (C–O str), 1655.1 (C=C str), 1094.6 (C–N)	δ7.41 (s, 1H), δ6.37 (s, 1H), δ4.03 (d, 4H), δ1.50 (s, 4H), δ1.43 (s, 12H)	451.1
7d	diphenyl-N-H	$C_{28}H_{29}O_4N$	3.3	3266.4 (O–H str), 2940.8 (Ali C–H str), 1251.6 (C–O str), 1650.8 (C=C str), 1029.1 (C–N)	δ7.43 (m, 22H), δ2.29 (s, 6H), δ1.20 (s, 12H)	444.0
7e	diethyl-N-H	$C_{20}H_{29}O_4N$	4.2	3427 (O–H str), 3020.7 (Ali C–H str), 1216.4 (C–O str), 1562.7 (C=C str), 1041.1 (C–N)	δ3.47 (m, 4H), δ2.29 (s, 4H), δ1.20 (s, 12H)	348.2

TABLE 3: Physical and spectral analysis of 2,2,8,8-tetramethyl-2,3,7,8-tetrahydro-4,6-diamino-3,7-dihydroxy-benzo[1,2-b:5,4-b'] dipyran **8a**–**e**.

Comp. code	R	Molecular formula	R_f	FTIR (cm^{-1})	^{1}H NMR (ppm)	Mass (M + 1)
8a	(benzyl-NH$_2$)	$C_{30}H_{36}O_4N_2$	2.8	3352.7 (O–H str), 2934.2 (Ali C–H str), 1138.8 (C–N str), 1615 (C=C str)	δ7.16 (m, 12H), δ2.15 (s, 4H), δ1.30 (s, 12H)	489.1
8b	H$_3$C–N piperazine NH	$C_{26}H_{42}O_4N_4$	2.7	3317.8 (O–H str), 2924.4 (Ali C–H str), 1094.4 (C–N str), 1229.8 (C–O str), 1611.1 (C=C str)	δ5.37 (d, 1H), δ2.15 (s, 6H), δ1.26 (s, 12H)	475.4
8c	Cl, Cl-phenyl-NH$_2$	$C_{30}H_{32}Cl_4O_4N_2$	2.3	3395.5 (O–H str), 2927.9 (Ali C–H str), 1256.6 (C–O str), 1655.1 (C=C str), 1094.6 (C–N)	δ7.41 (s, 1H), δ6.37 (s, 1H), δ4.03 (d, 4H), δ1.50 (s, 4H), δ1.43 (s, 12H)	625.0
8d	diphenyl-N-H	$C_{40}H_{40}O_4N_2$	2.7	3266.4 (O–H str), 2940.8 (Ali C–H str), 1251.6 (C–O str), 1650.8 (C=C str), 1029.1 (C–N)	δ7.43 (m, 22H), δ2.29 (s, 6H), δ1.20 (s, 12H)	613.6
8e	diethyl-N-H	$C_{23}H_{37}O_4N_2$	3.6	3427 (O–H str), 3020.7 (Ali C–H str), 1216.4 (C–O str), 1562.7 (C=C str), 1041.1 (C–N)	δ3.47 (m, 4H), δ2.29 (s, 4H), δ1.20 (s, 12H)	421.1

were synthesized from different amines such as diethylamine, 3,4-dichlorobenzylamine, dibenzylamine, benzylamine, and *N*-methyl piperazine. These derivatives were synthesized by the ring opening of epoxide and were identified by different spectroscopic techniques [41]. The synthesized compounds were screened for antihypertensive activity and some of these compounds showed significant antihypertensive activity. Physical and spectral analysis of 2,2,8,8-tetramethyl-2,3,7,8-tetrahydro-4,6-diamino-3,7-dihydroxy-6,7-epoxy-benzo-[1, 2-*b*:5,4-*b'*]dipyran derivatives **7a**–**e** are summarized in Table 2. Physical and spectral analysis of 2,2,8,8-tetramethyl-2,3,7,8-tetrahydro-4,6-diamino-3,7-dihydroxy-6,7-epoxy-benzo-[1,2-*b*:5,4-*b'*]dipyran derivatives **8a**–**e** are summarized in Table 3.

4. Conclusion

The present study describes the synthesis and evaluation of the antihypertensive activity of novel 2,2,8,8-tetramethyl-2,3, 7,8-tetrahydro-4,6-diamino-3,7-dihydroxy-6,7-epoxy-benzo-[1,2-b:5,4-*b'*]dipyran derivatives **7a**–**e** and **8a**–**e**. Compounds **7b**, **7c**, and **7d** showed potent antihypertensive activity and can constitute lead compounds. Compounds **7a**, **8a**, and **8c** showed minimal antihypertensive activity while other compounds showed moderate antihypertensive activity.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

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