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CARDIOVASCULAR AND ANTI-INFLAMMATORY ACTIVITY OF 6-NITRO-2-AMINO-1,3 BENZOTHIAZOLE DERIVATIVES BY INCORPORATING OF 5-MTHYL-4-OXO-THIAZOLIDENE MOIETIES

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ABSTRACT:

A new series of 2-[2'-{2"-aryl-5-methyl-4-oxo-1, 3-thiazolidene}-acetyl-amino]-6-nitro-4-1,3benzothiazolets compounds **4(a–m)** has been synthesized from 6-nitro-2-amino-benzo-thiazole as the starting material. The structures of all the synthesized compounds were confirmed by chemical methodology and spectral analyses, such as FT-IR, ^{1}H-NMR, ^{13}C-NMR and mass spectroscopy. All the final synthesized compounds 5(a–m) were screened for their cardiovascular activity. The change in blood pressure (B.P.), heart rate (HR), effect on Carotid Occlusion (CO) and Nordaniline (NA) pressure responses were observed for the cardiovascular profile. The cardiovascular profile of compounds 3c, 3e, 3l, 3k, 3n,4f, 4j,4e, 4f, 4i,4h, 4k, 4l, 4m, and 4n were suggestive of peripheral site of action.

KEYWORDS: 6-Nitro-2-amino-1,3-benzothiazole, 5-methyl-4-oxo-thiazolidene, cardiovascularand Anti-inflammatory activity

INTRODUCTION

Cardiovascular drugs are a group of drugs, which have major action on the heart or blood vessels or those used primarily for cardiovascular disorders, so that they check the total output of the hearts as well as the distribution of blood to certain parts of the circulatory system. Thiazole derivatives have shown to possess wide range of biological activities such as antipsycotic2, fungicidal3, antibacterial4, antimicrobial5 antiviral6 , cyclo-oxygenes inhibition7 ,anticancer8 ,antitubercular9, insecticidal9 , antitumor10-12 antiinflammatory13-14anti-viability15 , Syk inhibitor16, antiproliferative17 and anticandidal activity18etc. ThiazoliFurther, 4-Thiazolidinone also possess a wide range of pharmacological activity viz. antitubercular19, anticonvulsant20, antiviral21, antibiotic22, anticancer23, antihypertensive24, cardiovascular Activity25 etc. Moreover, thiazole derivatives have attracted a great deal of interest due to their wide applications in the field of pharmaceuticals. The present work is the result of cardiovascular study which has been done for 6-nitro-benzothiazole, with incorporating 4-thiazolidinone moiety (Scheme 1). The compounds were studied for the elemental and spectral analysis as well as their cardiovascular profile.

EXPERIMENTAL SECTION

Melting points were taken in open capillaries and are uncorrected. The progress of the reactions was monitored by silica gel-G coated TLC plates using MeOH:CHCl3 (3:7) system. The spot was visualized by exposing the dry plate to iodine vapors. The IR spectra were recorded in KBr discs on a Shimadzu 8201 PC FTIR spectrophotometer (vmax in cm-1) and the 1H-NMR and 13C-NMR spectra were measured on a Bruker DRX-300 spectrometer in CDCl3 at 300 and 75 MHz, respectively, using TMS as an internal standard. All chemical shifts are reported on δ scales. Elemental analyses were realized on a Carlo Erba-1108 analyzer. The analytical data of all the compounds were satisfactory. For column chromatographic purification of the products, Merck silica gel 60 (230–400 mesh) was used. The reagent grade chemicals were purchased from commercial sources and further purified before use.

Preliminary cardiovascular activity tests were carried out on albino rats 100-120g of either sex (the pregnancy was excluded) for all the synthesized 6-nitrobenzothiazole-thiazolidene-4 one derivatives. The newly synthesized compounds (test drugs) were administered intravenously (from right femoral vein) by dissolving them in propylene glycol and the effect on blood pressure (B.P), heart rate (HR) and pressure responses evoked either by carotid occlusion (CO) or intravenous noradrenalin (NA) 1-2 µg/Kg injection was observed. Injection of 20mL of propylene glycol induced a mild and transient decrease of 1-2 mmHg in blood pressure without affecting the CO and NA response. The blood pressure was recorded from the left common carotid artery by means of a mercury

manometer from femoral artery on one channel of "Encardiorite" (India) polygraph using status P25 transducer. Electrocardiogram (Lead II) was recorded on one channel of "Encardiorite" (India) polygraph in all the experiments.

Acute toxicity study

The toxicity study was carried out on Charles foster mice of either sex (pregnancy was excluded). Approximate 50% lethal dose (ALD50) of the promising compounds was determined inalbino mice. The mice of either sex weighing between 18-25 gm were used for the study. The drugs were injected by intra-peritonial (i.p.) route at different dose levels in separate groups of animals. After 24 hours of drugs administration, percent mortality in each group was observed. From the data obtained, ALD50 was calculated by using method26 (Smith, 1960).

ANTIINFLAMMATORY ACTIVITY

The carageenan-induced rat paw edema method was employed for evaluating the antiinflammatory activity of the compounds at a dose 50 mg kg–1 bw in albino rats (weighing 80–110 g, each group contained 5 animal) using phenyl-butazone as the standard drug for comparison at a dose 30 mg kg-1 body weight. The rate paw edema was produced by the method of Winter et al. The percentage inhibition of inflammation was calculated by applying the Newbould formula.27

Synthesis of 2-(2-chloroacetyl)-amino-6-nitrobenzothiazole, Compound 1:

2-Amino-6-nitro-benzothiazole and chloro-acetyl chloride (1:1 mole) were dissolved in methanol. The reaction mixture was continuously stirred on a magnetic stirrer at room temperature for about 3 hours. The product was filtered and purified by column chromatography. The purified product was dried in the oven at 35–45 °C for over-night and recrystallized from ethanol to yield compound 1. Yield 73% , m. p. 142-440C. Anal.Cald for C9H6N3SO3Cl : C 40.27 %,H 2.21 %,N 15.66 % found C 40.22 %,H 2.19 %,N 15.61 % ; IR: 1363,1532(–NO2),742 (-CH2Cl),3340 (-NH-),1666, 2962 (-COCH2),3010 2856,1409,1188,1072,686 (benzothiazole); 1HNMR: 6.91-7.62 (m, 3H, Ar-H), 4.33 (s, 2H, -CH2-) 8.08 (s,1H,-NH); Mass (FAB) :272 (M+).

Synthesis of 2-hydrazino-acetylamino)-6-nitrobenzothiazole, Compound 2:

Compound 1 and hydrazine hydrate (1:1 mole) were dissolved in methanol at room temperature. The reaction mixture was continuously stirred on a magnetic stirrer at room temperature for about 5 h. The product was filtered off and purified by column chromatography. The purified product was dried in an oven at 65–70 °C for 4 hours and recrystallized from ethanol to yield compound 2. Yield 79% , m. p. 216-180C. Anal.Cald for C9H9N5SO3 : C 40.44 %,H 3.37 %,N 26.21 %, found C 40.39 %, H 3.34 %, N 26.19 %; IR: 3463,390 (-NHNH2), 1365,1529(–NO2), 3340 (-NH-),1668, 2957 (-COCH2),2996 2855,1413,1188,1069,681 (benzothiazole); 1HNMR: 8.16 (t, 1H, -NH NH2), : 5.56 (d, 2H, -NHNH2), 6.95-7.61 (m, 3H, Ar-H), 4.33 (s, 2H, -CH2-) 8.01 (s,1H,-NHCO-); Mass (FAB) :267 (M+).

Synthesis of 2-substituted benzylibene-hydrazino-2-(acetyl-amino)-amino- 6-nitrobenzothiazole, Compounds (3a) :

Compound 2 and benzaldehyde (1:1 mole) were dissolved in methanol and allowed to reaction. The reaction mixture was first continuously stirred on a magnetic stirrer at room temperature for about 6-7 hours and then kept on a steam bath at 90–95 °C for about 5-6 hours. The products were filtered and cooled to room temperature. The filtered products were purified by column chromatography. The purified products were dried in an oven at 70 –80 °C for 4-5 h and recrystallized from ethanol to yield compounds 3a. Yield 69% , m. p. 123-250C., Anal. Cald. for C16H13N5SO : C 54.08 %,H 3.66 %,N 19.71 %, found C 54.00%,H 3.62 %,N 19.69 %; IR: 3380, (-NH-),1563(-N=CH), 1368,1526(–NO2), 3349 (-NH-),1671, 2952 (-COCH2), 3016 2851,1416,1183,1072,689 (benzothiazole); 3010,1607 (aro. C-C-H str.); 1HNMR: 6.99-7.78 (m, 8H, Ar-H), 4.33 (s, 2H, -CH2-) 8.16 (s,1H,-NHCO-) 4.93(s, 1H,-N=CH-), 8.34 (s,1H,-NH); Mass (FAB) :355(M+).

Other compounds 3(a-j) were synthesized in the similar manner using compound 2 and various selected aromatic aldehydes. Characterization data are presented in Table-1

Synthesis of 2-[2'-{2"-aryl-4-oxo-1,3-thiazolidene}-acetyl-amino]-amino- 6-nitrobenzothiazole, compound 4a :

An appropriate compound 3a and mercapto-lactic acid(1:1mole ratio) in the presence of a pinch of anhydrous ZnCl2 were dissolved in methanol (40 ml) and allowed to react. The reaction mixture was first continuously stirred on a magnetic stirrer at 30–35°C for about4–5hours and then kept on a steam bath at 90–95 °C for about 5-6 hours. The products were filtered and cooled to room temperature. The filtered products were purified by column chromatography. The purified products were dried in an oven at 80-85 °C for 4–5 hours and recrystallized from ethanol to yield compounds 4a. Yield 54 %, m.p. 176-78 .Anal.Cald for C15H17N4S2O : C 53.66 %,H 4.80 %,N 17.51 %, found C 53.61 %,H 4.79 %,N 17.49%, IR: 2826(–CH3), 3463 (-NH-), 3380, (-NH-),1710 (>C=O, cyclic),2825(-CH3), 2986 (-NCH2S-), 3010,1607 (aro. C-C-H str.); 6.96- 7.76(m,

8H, Ar-H), 7.82 (s,1H,-NH), 1.89-1.93 (d, 3H, -CH3 , 3.68-3.70(d, 2H, -CH2S-), 8.12 (s,1H,-NHCO); Mass (FAB) :435(M+).

Other compounds 4(b-n) were synthesized in the similar manner using compounds 3(b-n) . Characterization data are presented in table no. 1.

Table 1: The analytical data of all the synthesized compounds 3(a-n) and 4(a-n)

Compounds	Ar.	Yield (%)	M.P. (^{0}C)	Molecular Formula
3b	2-ClC_6H_4	71	140-42	$C_{13}H_{15}N_4SCl$
3c	3-ClC_6H_4	68	158-60	$C_{13}H_{15}N_4SCl$
3d	4-ClC_6H_4	64	152-54	$C_{13}H_{15}N_4SCl$
3e	2-BrC_6H_4	53	172-74	$C_{13}H_{15}N_4SBr$
3f	3-BrC_6H_4	48	181-83	$C_{13}H_{15}N_4SBr$
3g	4-BrC_6H_4	61	166-68	$C_{13}H_{15}N_4SBr$
3h	2-$NO_2C_6H_4$	63	216-18	$C_{13}H_{15}N_5SO_2$
3i	3-$NO_2C_6H_4$	67	196-98	$C_{13}H_{15}N_5SO_2$
3j	4-$NO_2C_6H_4$	59	188-90	$C_{13}H_{15}N_5SO_2$
3k	2-$CH_3OC_6H_4$	48	139-41	$C_{14}H_{18}N_4SO$
3l	3-$CH_3OC_6H_4$	51	123-25	$C_{14}H_{18}N_4SO$
3m	4-$CH_3OC_6H_4$	41	129-30	$C_{14}H_{18}N_4SO$
3n	$(CH_3)_2NC_6H_4$	69	156-58	$C_{18}H_{23}N_5S_2O$
4b	2-ClC_6H_4	69	121-23	$C_{16}H_{18}N_4S_2ClO$
4c	3-ClC_6H_4	71	128-30	$C_{16}H_{18}N_4S_2ClO$
4d	4-ClC_6H_4	73	126-28	$C_{16}H_{18}N_4S_2ClO$
4e	2-BrC_6H_4	54	154-56	$C_{16}H_{18}N_4S_2BrO$
4f	3-BrC_6H_4	59	162-64	$C_{16}H_{18}N_4S_2BrO$
4g	4-BrC_6H_4	52	169-71	$C_{16}H_{18}N_4S_2BrO$
4h	2-$NO_2C_6H_4$	61	173-75	$C_{16}H_{18}N_5S_2O_3$
4i	3-$NO_2C_6H_4$	64	176-78	$C_{16}H_{18}N_5S_2O_3$
4j	4-$NO_2C_6H_4$	62	171-73	$C_{16}H_{18}N_5S_2O_3$
4k	2-$CH_3OC_6H_4$	66	149-51	$C_{19}H_{25}N_5S_2O_2$
4l	3-$CH_3OC_6H_4$	63	136-38	$C_{19}H_{25}N_5S_2O_2$
4m	4-$CH_3OC_6H_4$	70	141-43	$C_{19}H_{25}N_5S_2O_2$
4n	$(CH_3)_2NC_6H_4$	65	184-86	$C_{20}H_{29}N_6S_2O_2$

Table : 2 Cardiovascular activity of the synthesised Compounds 3(a-n) and 4 (a-n)

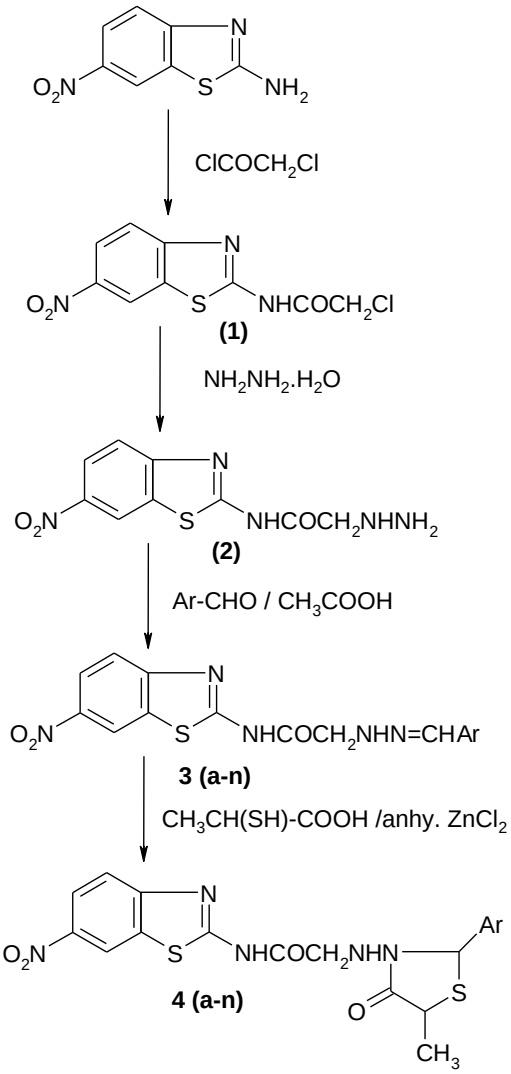
comp	Dose mg/Kg i.v.	Control Mean± SE	Change in mean blood pressure mmHg			Change in resting HR bpm	Effect on response s CO	pressure NA	ALD50 mg/Kg p.o.
			Immediate Mean± SE	Delayed Mean± SE	Duration in minutes				
3a	2.5	135.6 ± 9.93	130.8±10.77	127 ± 9.31	10.6 ± 2.96	Inhibited	potential	-	>1000
3b	2.5	143.8 ± 9.60	133.8±10.36*	132.6 ± 7.88*	22.6 ± 3.97	potential	-	-	>1000
3c	2.5	142.6 ± 6.18	126.8±5.93**	124 ± 8.78**	48.6 ± 3.97	Inhibited	Inhibited	Inhibited	>1000
3d	2.5	143.4 ± 8.56	131.8±10.32*	132.6 ± 7.88*	22.2 ± 3.91	potential	-	-	>1000

3e	2.5	138.0 ± 8.36	93.4±9.86***	121.6 ±10.16*	76.2 ± 3.8	2 bpm	Inhibited	-	>1000
3f	2.5	135.0 ± 9.35	114.8±7.70*	122.4 ±8.68*	30.6 ± 1.94	-	Inhibited	-	>1000
3g	2.5	137 ± 10.36	104±11.61**	116.8 ±9.84*	55.3 ± 1.67	-	Inhibited	-	>1000
3h	2.5	140.6 ± 9.93	120.4± 10.66	130.6± 10.25	20.6 ±1.95	Inhibited	potential	potential	>1000
3i	2.5	139.6 ± 11.32	114.4± 10.83**	124± 11.5	40.2±11.05	-	Inhibited	-	>1000
3j	2.5	132.2 ± 6.49	120.4± 10.66	110.4± 5.77***	8.8 ±3.11	-	-	-	>1000
3k	2.5	134.8 ± 14.77	109.2± 13.08	124.6± 14.98	35 ±4.12	-	Inhibited	-	>1000
3l	2.5	135.0 ± 9.35	114.8± 7.70	122.4± 8.68*	30.6 ±1.94	-	Inhibited	-	>1000
3m	2.5	133.2 ± 6.45	90.2 ± 7.62***	123.2± 5.40**	68.2 ±2.644	-	Inhibited	potential	>1000
3n	2.5	140 ± 11.87	109.8± 8.17	121.4± 9.60	65±3.08	Inhibited	potential	-	>1000
4a	2.5	136.6 ± 7.43	-	68.0±7.21***	30.4±1.67	-	-	-	>1000
4b	2.5	139 ± 12.48	-	79.9±12.63***	14±1.00	-	-	-	>1000
4c	2.5	135 ± 5	-	92±6.41***	25.2±2.16	-	-	-	>1000
4d	2.5	137 ± 9.35	-	88±5.41***	23.2±3.18	-	-	-	>1000
4e	2.5	138.8 ± 9.75	94.6± 9.86***	114.4± 6.74**	78.4 ±2.52	potential	Inhibited	potential	>1000
4f	2.5	137.6± 7.66	145.6 ±6.50	96.8± 5.00*	59.8± 2.86	-	Inhibited	-	>1000
4g	2.5	142 ± 12.04	154 ±11.61*	72.2± 11.18***	110.8± 5.77	-	Inhibited	-	>1000
4h	2.5	144.4 ±8.90	166.2 ±9.88**	44.2 ± 8.40*	186.4±6.10	-	Inhibited	-	>1000
4i	2.5	136 ± 12.94	141 ±13.87	76.6 ± 11.18*	63.8±3.03	-	Inhibited	-	>1000
4j	2.5	137.6± 7.66	145.6 ±6.50	96.8± 5.00*	59.8± 2.86	-	Inhibited	-	>1000
4k	2.5	142.4 ± 6.34	108.7 ±6.54***	107.1± 7.88	60.8±1.09	-	Inhibited	Inhibited	>1000
4l	2.5	142.4 ± 6.34	108.7 ±6.54***	107.1± 7.88	60.8±1.09	-	Inhibited	Inhibited	>1000
4m	2.5	142.4 ± 6.34	108.7 ±6.54***	107.1± 7.88	60.8±1.09	-	Inhibited	Inhibited	>1000
4n	2.5	139 ± 9.61	79.6± 8.38***	110± 9.98**	71±2.64	-	Inhibited	Inhibited	>1000
*p>0.05: ** p > 0.001 : *** p < 0.001									

TABLE 3. Anti-inflammatory activity of compounds 4(a–n)

compound	Before carrageenan administration	Total increase in paw volume after 5 H	Inhibition, %
	means ± SEM	(means ± SEM)	
4a	0.68 ± 0.02	0.18±0.02	48.57
4b	0.64 ± 0.02	0.17 ± 0.02	51.43
4c	0.66 ± 0.02	0.16 ± 0.01	54.29
4d	0.65 ± 0.02	0.16 ± 0.02	54.29
4e	0.66 ± 0.02	0.16 ± 0.01	54.29
4f	0.67 ± 0.02	0.14 ± 0.01	60.02
4g	0.66 ± 0.02	0.15 ± 0.01	57.14
4h	0.67 ± 0.02	0.12 ± 0.02	65.71
4i	0.68 ± 0.02	0.13 ± 0.01	62.86
4j	0.65 ± 0.02	0.14 ± 0.01	60.02
4k	0.66 ± 0.02	0.15 ± 0.01	57.14
4l	0.67 ± 0.02	0.12 ± 0.02	65.71
4m	0.68 ± 0.02	0.13 ± 0.01	62.86
4n	0.65 ± 0.02	0.14 ± 0.01	60.02
Control	0.68 ± 0.02	0.35 ± 0.01	-
Standard: phynylbutazone	0.66 ± 0.03	0.10 ± 0.02	71.43

SCHEME 1



Compounds	Ar	Compounds	Ar
3a and 4a	C6H5	3h and 4h	2-$NO_2C_6H_4$
3band 4b	2-ClC_6H_4	3i and 4i	3-$NO_2C_6H_4$
3cand 4c	3-ClC_6H_4	3j and 4j	4-$NO_2C_6H_4$
3dand 4d	4-ClC_6H_4	3k and 4k	2-$CH_3OC_6H_4$
3eand 4e	2-BrC_6H_4	3l and 4l	3-$CH_3OC_6H_4$
3fand 4f	3-BrC_6H_4	3m and 4m	4-$CH_3OC_6H_4$
3gand 4g	4-BrC_6H_4	3n and 4n	4,4'-$(CH_3)_2NC_6H_4$

RESULTS AND DISCUSSION

2-Amino-6-nitro-benzothiazole on reaction with chloro-acetyl choride at room temperature afforded 2-(2-chloroacetyl-amino)- 6-nitro-benzothiazole, compound 1. The IR spectrum of compound 1 displayed absorptions at 1336 and 740 for (C–N) and (C–Cl), respectively, this clearly indicated the synthesis of compound 1.Compound 1 on reaction with hydrazine hydrate at room temperature yielded N-2-[hydrazino-2-(2-acetylamino)]- 6-nitro-benzothiazole, compound 2. The IR spectrum of compound 2 showed absorptions for NH and NH_2 at 3376 and 3439 cm–1, respectively, while the absorption for (C–Cl) in the IR spectrum of compound 1 had disappeared. The ^{1}H-NMR spectrum of 2 displayed signals at δ 8.13 and 5.51 ppm for -NH and -NH_2, respectively. Compound 2 on further reaction with several selected substituted aromatic aldehydes produced 2-substituted benzyliden-[hydrazino-2-(2-acetylamino)]-

6-nitro-benzothiazole, compounds 3(a–n). The characteristic absorption for a Schiff base (N=CH) appeared in the range 1542–1578 cm^{-1} in the IR spectra of compounds 3a–m and in the ^{1}H- and ^{13}C-NMR spectra signals appeared at δ 6.92–7.82 and δ 156.6–162.4 ppm, respectively. In the ^{1}H-NMR, the broad signal of NH_2 present in the spectrum of compound 2 had disappeared. Compounds 3a–n on treatment with mercapto-lacticacid with a pinch of anhydrous $ZnCl_2$ yielded compounds 4(a-n). In the IR spectra of compounds 4a–n,the cyclic carbonyl group of the 4-thaizolidenone ring showed a characteristic absorption in the range 1710–1732 cm^{-1} and the ^{1}H-NMR spectra of compounds 4a–j and showed two characteristic signals for (NCH_2SAr) in the range δ 3.68. All these fact collectively suggest the successful synthesis of all the above compounds.

In scheme I, synthesised compounds3a, 3b,3c, 3h, 3n showed potent cardiovascular activity (table-2). The compound having substitution with N-N-dimethyl amino group [$-N(CH3)_2$] at 4-position of phenyl ring (compound 4n) showed gradual and consistent bloodpressure lowering activity, initial fall in blood pressure 30 mmHg followed by delayed fall of 20 mmHg which lasted for 65 minutes. In addition, thiscompound was also exhibited increase in heartrate (tachycardia) 1-2 beats per minutes and was also associated with potentiating of CO response without affecting NA response, which might be suggestive of central site of action of this compound. The compound which was substituted with chloro group at 3-position of phenyl ring (compound-3c) showed mild hypotensive activity (15 mmHg) of gradual onset which lasted for about 50 minutes and was associated with inhibition of CO and NA responses and heart rate (2-3 bpm). Such a pharmacological profile is suggestive of peripheral site of action of this compound. Furthermore, compounds 3a, 3b and 3h showed mild hypotensive activity (5 to 20 mmHg) of short duration (10 to 22 minutes). Compound 3a and 3h was associated with inhibition of heart rate, potentiation of CO, without affecting NA response, while compound 3b showed potentiation of heart rate without affecting the pressor responses (CO and NA). Compound 4g which was substituted with bromogroup in 4^{th} position of phenyl ring respectively and compound 4m, which was substituted with $–NO_2$ group at 4th position of phenyl ring, showed a fall in blood pressure 30 and 43 mmHg respectively. The hypotensive activity of these compounds (4g and 3m) was lasted for 55 and 70 minutes, respectively, with inhibition of CO and potentiation of NA responses. The most active compound among the 4- thiazolidinone was 4k. Considering its potentiality, it was further studied at three graded doses (2.5 mg/Kg i.v. In addition, compound 3k, was also associated with either inhibition or blockade of CO, inhibition of HR (1-3 bpm), without affecting the NA response, which might be suggestive central site of action of these compounds. Compound 3f and 3i showed inhibition of CO response, without affecting NA response and heart rate.The compounds 4a, 4b,4c,4d and 4j elicited potent cardiovascular activity of varying degree (14-70 mmHg) and of 8 to 30 minutes duration. It is important to mention that these compounds did not show any response on pressure responses. Such a profile of pharmacological effect is indicative of direct vasodilators. The compound 4i showed biphasic response in blood pressure . There was an immediate rise in blood pressure (5 mmHg) which was followed by potent fall in blood pressure (60 mmHg).The hypotensive activity of this compound lasted for about 65 minutes, with inhibition of CO response without affecting the NA response. The compound which was substituted with chloro&bromoat 4^{th} position of phenyl ring (compound 5d & 5g) also showed biphasic response. There was an immediate mild rise in blood pressure (12 mmHg) followed by a gradual fall in blood pressure of 70 mmHg at a dose of 2.5 mg/Kg i.v. The hypotensive activity of this compound lasted for about 110 minutes. As this compound exhibited potent hypotensive activity. The results of cardiovascular activity are given in table 2. Interestingly enough both the compounds (compound 3d &3g) were associated with inhibition of CO response without affecting NA response. Such a cardiovascular profile might be suggestive of central site of action of these compounds. Compounds 4a, 4d and 4e exhibited the hypotensive activity of varying degree (35-60 mmHg) and duration (60-80 minutes). The compound 4e inhibited the CO and potentiated the heart rate and NA responses, while compound 5m and 5n inhibited both CO and NA responses. Such a cardiovascular profile is suggestive of peripheral site of action of compounds 5m and 5n.

CONCLUSION

The results of all the described activities are summarized in Tables 2 and 3. The results shown in Tables 2and 3 revealed that all the synthesized compounds 4a–N have a structure activity relationship (SAR) because the activity of the compounds varied with substitution. Based on the SAR, it can be concluded that the activity of the compounds depends on electron withdrawing nature of the substituent groups.

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