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Cardiovascular activity of Indole derivatives by incorporating Oxadiazole, Azetidinone and Thiazolidinone Moieties: A Review

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Abstract:
In the present review, a series of substituted Indole derivatives were studied for their cardiovascular activity. A series of Compounds by incorporating moieties, Oxadiazole, Azetidinone, Thiazolidinone at 3-position of Indole were screened for cardiovascular activity. The Indole and Oxadiazole moiety led the compounds 2a-e, Indole and Azetidinone moiety led the compounds 3a-e, 4a-e, further Indole and Azetidinone moiety led the compounds 5a-e, for the study. The change in blood pressure (BP), heart rate (HR), effect on Carotid Occlusion (CO) and Nordaniline (NA) pressor responses were observed for the cardiovascular profile. The cardiovascular profile of compounds 2c, 2d, 3a, 5b, 5c, 5d and 5e were suggestive of peripheral site of action.

Keywords: Indole derivatives, Oxadiazole, Azetidinone, Thiazolidinone, cardiovascular activity.

Introduction:

Medicinal Chemistry has an important aspect to establish a relationship between chemical structure and pharmacological activity. It has been found that half of the therapeutic agents are made up of heterocyclic compounds. Indole is an aromatic heterocyclic compound. It has a bicyclic structure consisting of six member carbon ring & nitrogen containing pyrrole ring. In last few years, it was reported that Indole has activities like- CNS-depressant[1], antiviral[2], anthelmintic[3], antibacterial[4], anticonvulsant[5], cardiovascular activity[6], antihypertensive activity[7] etc. On the other hand, other heterocyclic moieties like Ozadiazole, Azetidinone, Thiazolidinone also posses pharmacological activity (Figure 1). Oxadiazole reported antimicrobial activity[8], antifungal[9], antituberculosis[10], anticonvulsant[11], cardiovascular activity[12]. Azetidinone derivatives are reported to show a variety of antibacterial[13], antimicrobial[14], cardiovascular[15], antinflammentory[16] and antitubercular activity[17]. Further, Thiazolidinone also possess a wide range of pharmacological activity viz. antitubercular[18], anticonvulsant[19], antiviral[20], antibiotic[21], anticancer[22], antihypertensive[23], cardiovascular activity[24]etc. The present work is the result of cardiovascular study which has been done for Indole, with incorporating Oxadiazole moiety (Scheme I), with incorporating Azetidinone moiety (Scheme II & III) and with incorporating Thiazolidinone moiety (Scheme IV). The compounds were studied for the elemental analysis and the cardiovascular profile.

Experimental

Material and Methods

The melting point of the compounds was determined in open glass capillaries with the help of thermionic melting point apparatus and is uncorrected. The homogeneity of all the newly synthesized compounds was routinely checked by TLC on silica gel G plates and spots were located by using iodine chamber. Elemental analysis of all the synthesized compounds were determined by a Perkin-Elimer 2400 elemental analyzer and results were found within the ± 0.4% of theoretical values. IR spectra were recorded in KBR on a Perkin-Elmer spectrum RX-I, spectrometer. ^{1}H NMR spectra were recorded by Bruker AC-300 F instrument using $CDCl_3$/DMSO-Cl_6 as solvent and tetra methyl silane (TMS) as internal reference standard. All chemical shift values were recorded as δ (pap). Mass spectra were determined on a VG-70-S instrument.

Cardiovascular activity

Preliminary cardiovascular activity tests were carried out on albino rats 100-120g of either sex (the pregnancy was excluded) for all the synthesized indole 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 pressor responses evoked either by carotid occlusion (CO) or intravenous noradrenalin (NA) 1-2 µg/Kg injection was observed. Injection of .20 mL 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 stathus P_{25} 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 (ALD_{50}) of the promising compounds was determined in albino mice. The mice of either sex weighing between 18-25 gm were used for the study. The drugs were injected by intraperitonial (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, ALD_{50} was calculated by using method[25] (Smith, 1960).

General procedure of synthesis

General procedure of synthesis for 2-substitutedaryldenylamino-5-(3'-indolomethylene)-1, 3, 4-oxadiazoles 2(a-e).

Compounds 2(a-e) were prepared by the method[26] (Singh et al., 2012). 2-amino-5-(3'-indolomethylene)-1, 3, 4-oxadiazole 1 (.01 mole) in absolute ethanol (80 mL) and a few drops of glacial acetic acid was added. Substituted aldehyde (.01 mole) and the mixture were refluxed for 8 hrs. The excess of the solvent was distilled off and the viscous mass was washed with a mixture of water and ether (8:2). The solid thus obtained was recrystallized with selected solvents to give compounds 2(a-e) (Scheme I). The elemental analysis is given in table- 1. All the synthesized compounds were evaluated for their cardiovascular profile.

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General procedure of synthesis for 1-(5'-(3"-indolomethylene)-1', 3', 4'-oxadiazol-2'-yl-)-4-(substituted phenyl)-2-azetidinones 3(a-e).

Compounds 3(a-e) were synthesized by the method[26] (Singh et al., 2012). To a stirred solution of compounds 2(a-e) (.01 mole) and triethylamine (.02 mole) in dioxane (40 mL), acetyl chloride (.02 mole) was added drop wise at 0-5 °C. The reaction mixture was stirred for about 5hrs. and the precipitated amine hydrochloride filtered off. The filtrate was concentrated under reduced pressure and poured into ice cold water. The products so obtained were recrystallized from selected solvents to give compounds 3(a-e) (Scheme II). The elemental analysis is given in table- 2. All the synthesized compounds were evaluated for their cardiovascular profile.

General procedure of synthesis for 1-(5'-(3"-indolomethylene)-1', 3', 4'-oxadiazol-2'-yl-)-4-(substitutedphenyl)-3-(aminomethylenesubstitutedphenyl)-2-azetidinones 4(a-e).

To a solution of compound 3(a-e) (0.01 mole) in ethanol (50 ml), formaldehyde (0.02 mole) and substituted aniline (0.02 mole) were added drop wise and the reaction mixture was refluxed for 4 hrs. The excess of the solvent was distilled off and the solid obtained was washed with petroleum ether (40-60°C) and recrystallized from Toluene/Pet. Ether to give compounds 4(a-e) (Scheme III). The elemental analysis is given in table- 3. All the synthesized compounds were evaluated for their cardiovascular profile.

General procedure of synthesis for 3-(5'-(3"-indolomethylene)-1', 3', 4'-oxadiazol-2'-yl-)-2-(substitutedphenyl)-4-thiazolidinones 5(a-e).

Compounds 5(a-e) were prepared by the method[27] (Singh et al., 2013). A stirred solution of compounds 2(a-e) (.01 mole) was refluxed in dry DMF (80 mL) containing a small amount of anhydrous $ZnCl_2$ and thioglycolic acid (.02 mole) for 18hrs. The reaction mixture was cooled and poured into ice cold water. The separated solid was filtered, washed and recrystallized from selected solvent to give compounds 5(a-e) (Scheme IV). The elemental analysis is given in table- 4. All the synthesized compounds were evaluated for their cardiovascular profile.

Results and discussion

In **scheme I**, all the five 2- substituted arylidenylamino-5-(3'-indolomethylene)-1, 3, 4-oxadiazoles 2(a-e), showed potent cardiovascular activity (table 5). The compound having substitution with N-N-dimethyl amino group (-$N(CH_3)_2$) at 4-position of phenyl ring (compound 2d) showed gradual and consistent blood pressure lowering activity, initial fall in blood pressure 30 mmHg followed by delayed fall of 20 mmHg which lasted for 65 minutes. In addition, this compound was also exhibited increase in heart rate (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 methoxy group (-OCH_3) at 3-position of phenyl ring and hydroxyl group (-OH) at 4-position of phenyl ring (compound-2c) 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 2a, 2b and 2e showed mild hypotensive activity (5 to 20 mmHg) of short

duration (10 to 22 minutes). Compound 2a and 2e was associated with inhibition of heart rate, potentiation of CO, without affecting NA response, while compound 2b showed potentiation of heart rate without affecting the pressor responses (CO and NA).

In **scheme II**, all the five azetidinones 3(a-e), exhibited statistically significant cardiovascular activity (table 6). Compound 3c which was substituted with methoxy group and hydroxyl group at 3rd and 4th position of phenyl ring respectively and compound 3d, which was substituted with N,N-dimethyl amino (-N(CH_3)$_2$) group at 4th position of phenyl ring, showed a fall in blood pressure 30 and 43 mmHg respectively. The hypotensive activity of these compounds (3c and 3d) was lasted for 55 and 70 minutes, respectively, with inhibition of CO and potentiation of NA responses. The most active compound among the azetidinones was 3a. Considering its potentiality, it was further studied at three graded doses (1.25, 2.5 and 5 mg/Kg i.v.). In lower doses 1.25 and 2.5 mg/Kg i.v., it showed fall in blood pressure of 25 and 45 mmHg respectively, while in higher doses it showed potent hypotensive activity (60 mmHg), which lasted for 100 minutes. In addition, compound 3a, 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 3b and 3e showed inhibition of CO response, without affecting NA response and heart rate.

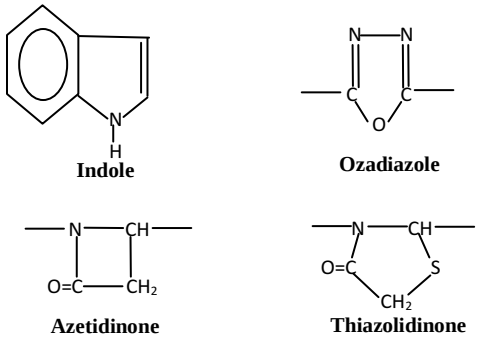
In **scheme III** the compounds 4(a-e), elicited potent cardiovascular activity of varying degree (14-70 mmHg) and of 8 to 30 minutes duration (table 7). It is important to mention that these compounds did not show any response on pressor responses. Such a profile of pharmacological effect is indicative of direct vasodilators.

Furthermore, in **scheme IV** the compound 5c showed biphasic response in blood pressure (Table 8). 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 methoxy group (-OCH_3) at 4th position of phenyl ring (compound 5b) 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, it was further studied in details at three graded doses (1.25, 2.5 and 5.0 mg/Kg i.v.). The results of cardiovascular activity are given in table 8. Interestingly enough both the compounds (5b and 5c) 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 5a, 5d and 5e exhibited the hypotensive activity of varying degree (35-60 mmHg) and duration (60-80 minutes). The compound 5a inhibited the CO and potentiated the heart rate and NA responses, while compound 5d and 5e inhibited both CO and NA responses. Such a cardiovascular profile is suggestive of peripheral site of action of compounds 5d and 5e.

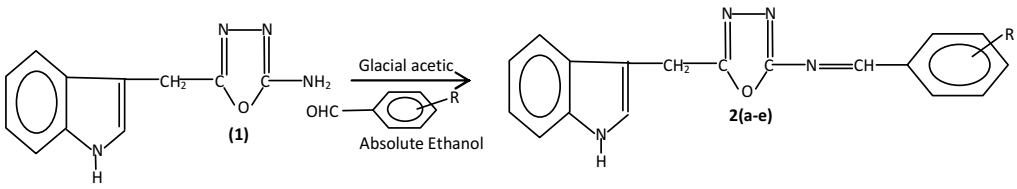
Conclusion

The review showed the cardiovascular profile of Indole derivatives by incorporating moieties, Oxadiazole, Azetidinone and Thiazolidinone. The data reported suggests the therapeutic potential of the compounds, 2-(p- hydroxy, m-methoxybenzylidenylamino)-5-(3'-indolomethylene)-1, 3, 4-oxadiazol (2c), 2-(p-N,N-dimethylbenzylidenylamino)-5-(3'-indolomethylene)-1, 3, 4-oxadizole (2d), 1-(5'-(3"-Indolomethylene)-1',3',4'-oxadiazol-2'-yl-)-4-phenyl-2-azetidinone (3a), 3-(5'-(3"-indolomethylene) -1', 3', 4' – oxadiazol-2'-yl)-2-(p-methoxyphenyl)-4-thiazolidinone (5b), 3-(5'-(3"-indolomethylene) -1', 3', 4' – oxadiazol-2'-yl)-2–(p-hydroxy, m-methoxy phenyl)- 4 –thiazolidinone (5c), 3-(5'-(3"-indolomethylene)-1', 3', 4'–oxadiazol-2'-yl)-2–(p-N, N- dimethylphenyl)- 4–thiazolidinone (5d), 3-(5'-(3"-indolomethylene) -1', 3', 4' – oxadiazol- 2'-yl)-2–(p- hydroxyphenyl)-4 –thiazolidinone (5e), as source for the development of novel cardiovascular agents. Therefore, these substances should attract the interest of researchers and pharmaceutical companies for clinical studies and other applications in the therapy of cardiovascular diseases.

Figure 1 Indole with oxadiazole, azetidinone & thiazolidinone

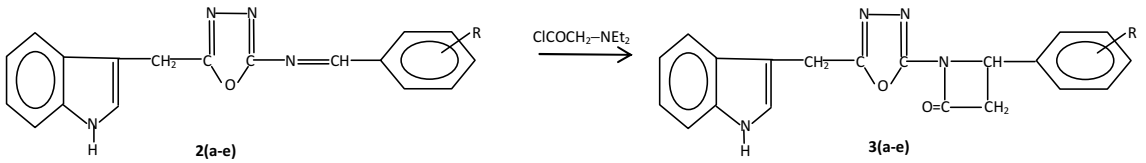


Scheme I General procedure of synthesis for 2-substitutedaryldenylamino-5-(3'-indolomethylene)-1,3,4-oxadiazoles 2(a-e)



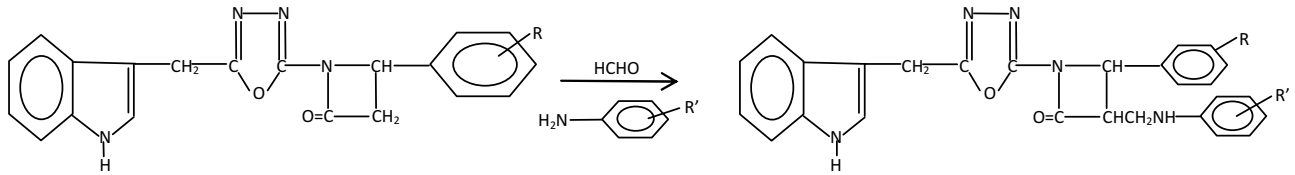
R	Compd.	Compound Name
H	2a	2-(benzylidenylamino)-5-(3'-indolomethylene)-1, 3, 4-oxadiazole
4-OCH_3	2b	2-(p-methoxybenzylidenylamino)-5-(3'-indolomethylene) -1, 3, 4-oxadiazole
3-OCH_3, 4-OH	2c	2-(p- hydroxy, m-methoxybenzylidenylamino)-5-(3'-indolomethylene)-1, 3, 4-oxadiazol
4-$N(CH_3)_2$	2d	2-(p-N,N-dimethylbenzylidenylamino)-5-(3'-indolomethylene)-1, 3, 4-oxadizole
4-OH	2e	2-(p-hydroxybenzylidenylamino)-5-(3'-indolomethylene)-1, 3, 4-oxadizole

Scheme II General procedure of synthesis for 1-[5'-(3"-indolomethylene)-1',3',4'-oxadiazol-2'-yl-]-4-(substitutedphenyl)-2-azetidinones 3(a-e)



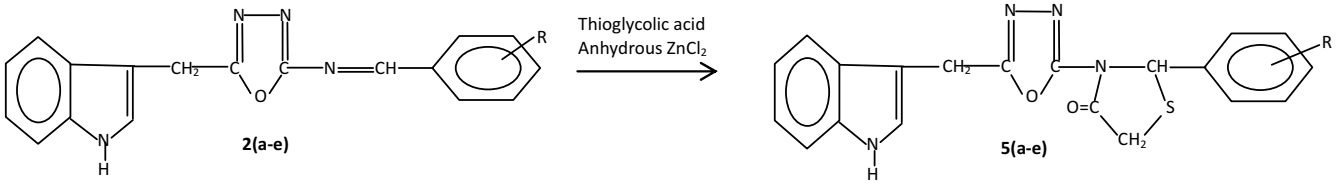
R	Compd.	Compound Name
H	3a	1-[5'-(3"-Indolomethylene)-1',3',4'-oxadiazol-2'-yl-]-4-phenyl-2-azetidinone
4-OCH_3	3b	1-[5'-(3"-Indolomethylene)-1',3',4'-oxadiazol-2'-yl-]-4-(p-methoxy phenyl)-2-azetidinone
3-OCH_3, 4-OH	3c	1-[5'-(3"-Indolomethylene)-1',3',4'-oxadiazol-2'-yl-]-4-(m-methoxy,p-hydroxy phenyl)-2-azetidinone
4-$N(CH_3)_2$	3d	1-[5'-(3"-Indolomethylene)-1',3',4'-oxadiazol-2'-yl-]-4-(p-N,N-dimethyl phenyl)-2-azetidinone
4-OH	3e	1-[5'-(3"-Indolomethylene)-1',3',4'-oxadiazol-2'-yl-]-4-(p-hydroxyphenyl)-2-azetidinone

Scheme III General procedure of synthesis for 1-[5'-(3"-indolomethylene)-1',3',4'-oxadiazol-2'-yl-]-4-(substitutedphenyl)-3-(aminomethylenesubstitutedphenyl)-2-azetidinones 4(a-e)



R	R'	Compd.	Compound Name
H	H	4a	1-[5'-(3"-Indolomethylene)-1',3',4'-oxadiazol-2'-yl-]-4-phenyl-3-(aminomethylenephenyl)-2-azetidinones
4-OCH_3	o-Cl	4b	1-[5'-(3"-Indolomethylene)-1',3',4'-oxadiazol-2'-yl-]-4-(p-methoxyphenyl)-3-(aminomethylene-o-chloroaniline)-2-azetidinones
3-OCH_3, 4-OH	H	4c	1-[5'-(3"-Indolomethylene)-1',3',4'-oxadiazol-2'-yl-]-4-(p-hydroxy,m-methoxyphenyl)-3-(aminomethylenephenyl)-2-azetidinones
4-$N(CH_3)_2$	o-Cl	4d	1-[5'-(3"-Indolomethylene)-1',3',4'-oxadiazol-2'-yl-]-4-(m-N,N-dimethylphenyl)-3-(aminomethylene --o-chloroaniline)-2-azetidinones
4-OH	m-Cl	4e	1-[5'-(3"-Indolomethylene)-1',3',4'-oxadiazol-2'-yl-]-4-(p-hydroxyphenyl)-3-(aminomethylene-m-chloroaniline)-2-azetidinones

Scheme IV General procedure of synthesis for 3-[5'-(3"-indolomethylene)-1',3',4'-oxadiazol-2'-yl-]-2-(substitutedphenyl)-4-thiazolidinones 5(a-e)



R	Compd.	Compound Name
H	5a	3-[5'-(3"-indolomethylene) -1', 3', 4' – oxadiazol-2'-yl]- 2-phenyl- 4 –thiazolidinone
4-OCH_3	5b	3-[5'-(3"-indolomethylene) -1', 3', 4' – oxadiazol-2'-yl]-2-(p-methoxyphenyl)-4-thiazolidinone
3-OCH_3, 4-OH	5c	3-[5'-(3"-indolomethylene) -1', 3', 4' – oxadiazol-2'-yl]-2–(p-hydroxy, m-methoxy phenyl)- 4 –thiazolidinone
4-$N(CH_3)_2$	5d	3-[5'-(3"-indolomethylene) -1', 3', 4'– oxadiazol-2'-yl]-2–(p-N, N- dimethylphenyl)- 4–thiazolidinone
4-OH	5e	3-[5'-(3"-indolomethylene) -1', 3', 4' – oxadiazol- 2'-yl]-2–(p- hydroxyphenyl)-4 –thiazolidinone

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Table 1- Yield and Elemental Analysis of Compounds 2(a-e)

Comp.	R	Yield (%)	m.p. (°C)	Recrystallisation solvent	Molecular Formula (Mol.Wt.)	Found (Calcd)% C	H	N
2a	H	55	268	Methanol	$C_{18}H_{14}N_4O$ (302)	71.56(71.52)	4.68(4.63)	18.56(18.54)
2b	4-OCH_3	58	240	Ethanol/water	$C_{19}H_{16}N_4O_2$ (322)	68.65(68.67)	4.85(4.81)	16.90(16.86)
2c	3-OCH_3, 4-OH	45	300	DMF	$C_{19}H_{16}N_4O_3$ (348)	65.48(65.51)	4.63(4.59)	16.06(16.09)
2d	4-$N(CH_3)_2$	48	230	Ethanol/water	$C_{20}H_{19}N_5O$ (345)	69.60(69.56)	5.54(5.50)	20.30(20.28)
2e	4-OH	40	200	Ethanol/water	$C_{18}H_{14}N_4O_2$ (318)	67.90(67.92)	4.42(5.50)	17.64(20.28)

Table 2- Yield and Elemental Analysis of Compounds 3(a-e)

Comp.	R	Yield (%)	m.p. (°C)	Recrystallisation solvent	Molecular Formula (Mol.Wt.)	Found (Calcd)% C	H	N
3a	H	50	180	Methanol	$C_{20}H_{16}N_4O_2$ (344)	69.74(69.76)	4.62(4.65)	16.22(16.27)
3b	4-OCH_3	55	256	Benzene	$C_{21}H_{18}N_4O_3$ (374)	67.40(67.37)	4.84(4.81)	14.95(14.97)
3c	3-OCH_3, 4-OH	40	115	Methanol	$C_{21}H_{18}N_4O_4$ (390)	64.63(64.61)	4.58(4.61)	14.38(14.35)
3d	4-$N(CH_3)_2$	45	100	Methanol	$C_{22}H_{21}N_5O_2$ (387)	68.23(68.21)	5.45(5.42)	18.06(18.08)
3e	4-OH	35	210	Methanol	$C_{20}H_{16}N_4O_3$ (360)	66.70(66.66)	4.40(4.44)	15.58(15.55)

Table 3- Yield and Elemental Analysis of Compounds 4(a-e)

Comp.	R	R'	Yield (%)	m.p. (°C)	Recrystallisation solvent	Molecular Formula (Mol.Wt.)	Found (Calcd)% C	H	N
4a	H	H	33	270	DMF	$C_{27}H_{23}N_5O_2$ (449)	72.18(71.16)	5.14(5.12)	15.63(15.59)
4b	4-OCH_3	o-Cl	30	280	Toluene	$C_{28}H_{24}N_5O_3Cl$ (514)	65.40(65.43)	4.63(4.67)	13.61(13.63)
4c	3-OCH_3,4-OH	H	32	120	DMF	$C_{28}H_{25}N_5O_4$ (495)	67.87(67.90)	5.05(5.09)	14.14(14.18)
4d	4-$N(CH_3)_2$	o-Cl	32	180	Ethanol	$C_{29}H_{27}N_6O_2Cl$ (527)	66.13(66.09)	5.14(5.12)	15.92(15.95)
4e	4-OH	m-Cl	30	250	DMF	$C_{27}H_{22}N_5O_3Cl$ (500)	64.82(64.86)	4.44(4.40)	14.05(14.01)

Table 4- Yield and Elemental Analysis of Compounds 5(a-e)

Comp.	R	Yield (%)	m.p (°C)	Recrystallisation solvent	Molecular Formula (Mol.Wt.)	Found (Calcd)% C	H	N
5a	H	45	220	Ethanol/water	$C_{20}H_{16}N_4O_2S$ (376)	63.80(63.82)	4.27(4.25)	14.91(14.89)
5b	4-OCH_3	50	200	Ethanol/benzene	$C_{21}H_{18}N_4O_3S$ (406)	62.10(62.06)	4.47(4.43)	13.82(13.79)
5c	3-OCH_3,4-OH	42	250	Ethanol/benzene	$C_{21}H_{18}N_4O_4S$ (422)	59.75(59.71)	4.24(4.26)	13.30(13.27)
5d	4-$N(CH_3)_2$	40	310	Ethanol/water	$C_{22}H_{21}N_5O_2S$ (419)	63.04(63.00)	5.04(5.01)	16.72(16.70)
5e	4-OH	38	210	Ethanol/water	$C_{20}H_{16}N_4O_3S$ (392)	61.25(61.22)	4.12(4.08)	14.25(14.28)

Table 5- Cardiovascular Activity of the Synthesized Compounds 2(a-e)

Comp.	R	Dose mg/Kg i.v.	Change in mean blood pressure mmHg: Control Mean± SE	Immediate Mean± SE	Delayed Mean± SE	Duration in minutes Mean± SE	Change in resting HR bpm	Effect on pressor responses: CO	NA	ALD50 mg/Kg p.o.
2a	H	2.5	135.6±9.93	130.8±10.77	127±9.31	10.6±2.96	Inhibited	Potentiated	—	>1000
2b	4-OCH_3	2.5	143.8±9.60	133±10.36*	132.6±7.88*	22.6±3.97	Potentiated	—	—	>1000
2c	3-OCH_3 4-OH	2.5	142±6.18	126.8±5.93**	124±8.78**	48.6±3.97 (2-3bpm)	Inhibited	Inhibited	Inhibited	>1000
2d	4-$N(CH_3)_2$	2.5	140±11.87	109.8±8.17**	121.4±9.60*	65±3.08 (1-2bpm)	Potentiated	Potentiated	—	>1000
2e	4-OH	2.5	140.6±9.93	120.4±10.66**	130.6±10.25	20.6±1.95	Inhibited	Potentiated	—	>1000

* $p > 0.05$; ** $p < 0.01$; *** $p < 0.001$

Table 6- Cardiovascular Activity of the Synthesized Compounds 3(a-e)

Comp.	R	Dose mg/ Kg i.v.	Change in mean blood pressure mmHg: Control Mean± SE	Immediate Mean± SE	Delayed Mean± SE	Duration in minutes Mean± SE	Change in resting HR bpm	Effect on pressor responses: CO	NA	ALD50 mg/Kg p.o.
3a	H	1.25	134.8±14.77	109.2±13.08*	124.6±14.98	35±4.12	⇒ 1 bpm	Inhibited	—	
		2.5	138.0±8.36	93.4±9.86***	121.6±10.16*	76.2±3.8	⇒ 2 bpm	Inhibited	—	>2000
		5.0	141.0±10.67	79.8±12.18***	110.6±9.98**	100±1.41	⇒ 2-3 bpm	Inhibited		
3b	4-OCH_3	2.5	135.0±9.35	114.8±7.70*	122.4±8.68*	30.6±1.94	—	Inhibited	—	>1000
3c	3-OCH_3 4-OH	2.5	137±10.36	104±11.61**	116.8±9.84	55.3±1.67	—	Inhibited	Potentiated	>1000
3d	4-$N(CH_3)_2$	2.5	133.2±6.45	90.2±7.62***	123.2±5.40**	68.2±2.64	—	Inhibited	Potentiated	>1000
3e	4-OH	2.5	139.6±11.32	114.4±10.83**	124±11.05	40.2±11.05	—	Inhibited	—	>1000

* p > 0.05; ** p < 0.01; *** p < 0.001, ⇒ inhibited

Table 7- Cardiovascular Activity of the Synthesized Compounds 4(a-e)

Comp.	R	R'	Dose mg/ Kg i.v.	Change in mean blood pressure mmHg: Control Mean± SE	Immediate Mean± SE	Delayed Mean± SE	Duration in minutes Mean± SE	Change in resting HR bpm	Effect on pressor responses: CO	NA	ALD50 mg/Kg p.o.
4a	H	H	2.5	136.6±7.43	—	68.0±7.21***	30.4±1.67	—	—	—	>1000
4b	4-OCH_3	O-Cl	2.5	139±12.48	—	79.9±12.63***	14±1.00	—	—	—	>1000
4c	3-OCH_3 4-OH	H	2.5	135±5.00	—	92±6..41***	25.2±2.16	—	—	—	>1000
4d	4-$N(CH_3)_2$	O-Cl	2.5	138.8±11.81	—	79.8±12.87***	20±1.60	—	—	—	>1000
4e	4-OH	m-Cl	2.5	132.2±6.49	—	110.4±5.77***	8.8±3.11	—	—	—	>1000

* p > 0.05; ** p < 0.01; *** p < 0.001

Table 8- Cardiovascular Activity of the Synthesized Compounds 5(a-e)

Comp.	R	Dose mg/ Kg i.v.	Change in mean blood pressure mmHg: Control Mean± SE	Immediate Mean± SE	Delayed Mean± SE	Duration in minutes Mean± SE	Change in resting HR bpm	Effect on pressor responses: CO	NA	ALD50 mg/Kg p.o.
5a	H	2.5	138.8±9.75	94.6±9.86***	114.6±6.74**	78.4±252	Potentiated	Inhibited	Potentiated	>1000
5b	4-OCH_3	1.25	137.6±7.66	145.6±6.50*	96.8±5.00*	59.8±2.86	—	Inhibited	—	
		2.5	142±12.04	154±11.61*	72.2±11.18***	110.8±5.77	—	Inhibited	—	>2000
		5.0	144.4±8.90	166.2±9.88**	44.2±8.40***	186.4±6.10	—	Inhibited	—	
5c	3-OCH_3 4-OH	2.5	136±12.94	141±13.87	76.6±11.18*	63.8±3.03	—	Inhibited	—	>1000
5d	4-$N(CH_3)_2$	2.5	139±9.61	79.6±8.38***	110±9.98**	71±2.64	—	Inhibited	Inhibited	>1000
5e	4-OH	2.5	142.4±6.34	108.7±654***	107.1±7.88	60.8±1.09	—	Inhibited	Inhibited	>1000

* p > 0.05; ** p > 0.001; *** p < 0.001

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