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Synthesis and Evaluation of Some Substituted Indole Derivatives for Cardiovascular Activity

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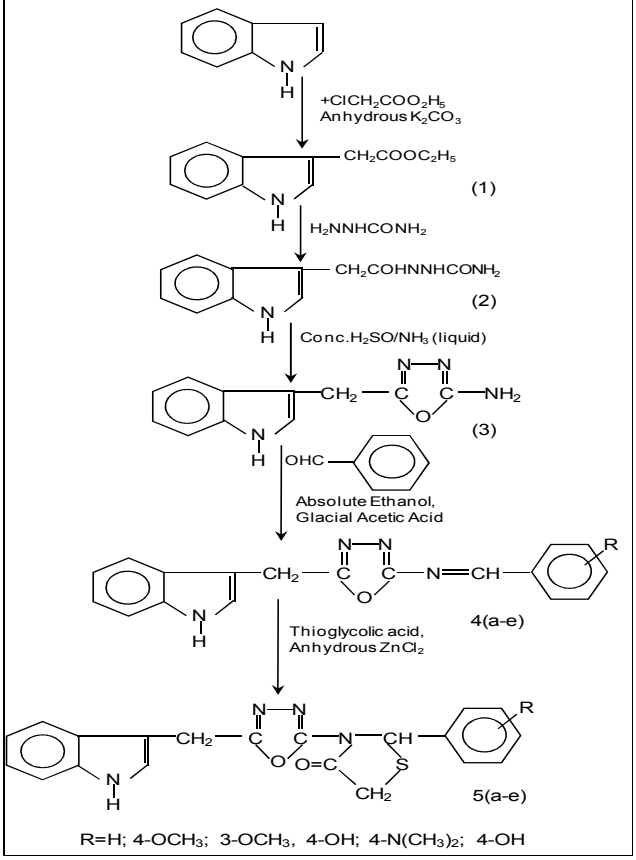
ABSTRACT
In the present study, a series of Indole containing the oxadiazole and thiazolidinones side chain at 3- position, is discussed. The synthesized Indole derivatives 4 (a-e), 5 (a-e) were evaluated for cardiovascular activities. Compound 3-[5'-(3"-indolomethylene)-1',3',4'-oxadiazol-2'-yl]-2-(p-methoxy phenyl)-4-thiazolidinone 5b, was found to be the most potent compound of the present study which showed cardiovascular activity of varying degree at dose 2.5 mg/Kg. The structures of these compounds were elucidated by IR, ^{1}H NMR, mass spectroscopy and elemental analysis.

Keywords: Indole derivatives, oxadiazole, thiazolidinone, antihypertensive, cardiovascular activity.

INTRODUCTION

The increasing complexities of day to day life have led to the increase in the incidence of cardiovascular diseases. Hypertension is the commonest cardiovascular disorder, responsible for morbidity and mortality. Different derivatives of imidazoline [1], indole [2], quinazolinone [3], oxadiazole [4], thiadiazole [5], azetidinone [6] etc have also been reported to posses promising cardiovascular activity. It has been found in the recent literature that several indole derivatives reported to possess a wide variety of biological properties e.g. CNS-depressant [7], anti-inflammatory and analgesic [8], antiviral [9], anthelmintic [10], antibacterial [11], anticonvulsant [12], cardiovascular activity [13], antihypertensive activity. [14] Substitution at 3-position of indole nucleus by different heterocyclic moieties markedly enhance the cardiovascular activity. Furthermore, oxadiazols, 4-oxo-thiazolidinones have also been reported to possess potent cardiovascular activity. In view of these observations, it was decided to synthesize new 3-[5'-(3"-indolomethyle)-1', 3', 4'-oxadiazol-2'-yl]-2-(substituted phenyl)-4-thiazolidinones by incorporating different heterocyclic nuclei like oxadiazol and thiazolidinones etc at 3-position of indole moiety (Scheme I). These compounds were screened for the elemental analysis (Table I) and for the cardiovascular activity (Table II)

SCHEME I



MATERIALS AND METHODS

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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 (ppm). Mass spectra were determined on a VG-70-S instrument.

Ethyl-3-indoloacetate, 1: Indole (0.01 mole), ethylcholoroacetate (0.01 mole), in anhydrous acetone (80 ml) and anhydrous K_2CO_3 (8 g) were heated under reflux for 24 hours. The excess of the solvent was distilled off and after cooling; it was filtered and washed with water. The compound thus obtained was recrystallized from methanol to give compound 1. IR (KBr, cm^{-1}): 3180, 3050, 2860, 1740, 1580; ^{1}H NMR ($CDCl_3$): δ 9.85 (brs, 1-H), 7.69-7.00 (m, 5-H), 4.30 (s, 2-H), 3.75 (q, 2-H), 1.30 (t, 3-H) ppm. MS: $[M]^+$ at m/z 203.

1-(3'-indoloacetyl) semicarbazide, 2: Compound 1 (0.075 mole) and semicarbazide (0.075 mole) in methanol (70 ml) were refluxed on a steam bath for 16 hours. The excess of the solvent was distilled off and the viscous mass poured into ice cold water, filtered and recrystallized from ethanol to give compound 2. IR (KBr, cm^{-1}): 3350, 3160, 3040, 2853, 1720, 1560; ^{1}H NMR ($CDCl_3$): δ9.74 (brs, 1-H); 8.30 (brs, 4-H); 7.15-6.60 (m, 5-H); 4.25 (s, 2-H). MS: $[M]^+$ at m/z 232.

2-amino-5-(3'-indolomethylene)-1,3,4-oxadiazole, 3: A mixture of compound 2 (0.05 mole) and conc. H_2SO_4 (15 ml) was kept overnight at room temperature, poured into ice cold water, neutralized with liquid ammonia, and the solid thus obtained was filtered and recrystallized from methanol to get compound 3 IR (KBr, cm^{-1}): 3340, 3140, 3060, 2840, 1680, 1560, 1093; ^{1}H NMR ($CDCl_3$): δ9.10(brs, 1-H); 7.67-7.10 (m, 5-H), 6.15 (s, 2-H), 4.10 (s,2-H) ppm. MS: $[M]^+$ at m/z 214.

General Procedure for the Synthesis of Oxadiazole Derivatives, 4a-e: 2-amino-5-(3'-indolomethylene)-1, 3, 4-oxadiazole 3 (0.01 mole) in absolute ethanol (80 ml) and a few drops of glacial acetic acid was added. Anisaldehyde (0.01 mole) and the mixture were refluxed for 8 hours. 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 4a-e.

2-(benzylidenylamino)-5-(3'-indolomethylene)-1, 3, 4-oxadiazole, 4a: (methanol); IR (KBr cm^{-1}): 3135, 3040, 2850, 1682, 1560, 1070; ^{1}H NMR ($CDCl_3$): δ 9.24 (brs, 1-H); 8.25 (s, 1-H); 4.32 (s, 2-H); 6.47-6.68 (m, 5-H) ppm. MS: $[M]^+$ at m/z 302.

2-(p-methoxybenzylidenylamino)-5-(3'-indolo methylene) -1,3,4-oxadiazole, 4b:(etanol/water); IR (KBr cm^{-1}): 3120, 3050, 2860, 1635, 1582, 1080; ^{1}H NMR ($CDCl_3$): δ 9.21 (brs, 1-H); 8.40 (s, 1-H); 4.30 (s, 2-H); 3.40 (s, 3-H); 7.90-6.55 (m, 9-H) ppm. MS: $[M]^+$ at m/z 332.

2-(p- hydroxy, m-methoxy benzyli denylamino)-5-(3'-indolomethylene)-1, 3, 4-oxadiazol, 4c: (DMF); IR (KBr cm^{-1}): 3360, 3145, 2840, 1680, 1612, 1062, ^{1}H NMR ($CDCl_3$): δ 9.20 (brs, 1-H); 8.35 (s, 1-H); 4.25 (s, 2-H); 3.72 (s, 3-H); 12.78 (ss, 1-H). MS: $[M]^+$ at m/z 348.

2-(p-N,N-dimethylbenzylidenylamino)-5-(3'-indolomethylene)-1, 3, 4-oxadizole, 4d: (ethanol/ water); IR (KBr cm^{-1}): 3320,3144, 2830, 1683, 1610, 1297; ^{1}H NMR ($CDCl_3$): δ 9.23 (brs, 1-H); 8.40 (s, 1-H); 4.32 (s, 2-H); 6.63-6.78(m, 4-H); 2.15 (s, 6-H). MS: $[M]^+$ at m/z 377.

2-(p-hydroxybenzylidenylamino)-5-(3'-indolo methylene)-1, 3, 4-oxadizole, 4e: (ethanol/ water); IR (KBr cm^{-1}): 3380, 3142, 2860, 1683, 1611, 1294; ^{1}H NMR ($CDCl_3$): δ 9.21 (brs, 1-H); 8.38 (s, 1-H); 4.28 (s, 2-H); 6.60-6.76(m, 4-H); 12.81 (ss, 1-H). MS: $[M]^+$ at m/z 318.

General procedure for the synthesis of thiazolidinone derivatives, 5a-e: A stirred solution of compounds (4a-e) was refluxed in dry DMF (80 ml) containing a small amount of anhydrous $ZnCl_2$ and thioglyconic acid (0.02 moles) for 18 hours. 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 (5a-e).

3-[5'-(3"-indolomethylene) -1', 3', 4' – oxadiazol- 2'-yl]- 2 -phenyl- 4 –thiazolidinone, 5a: (ethanol/ water); IR (KBr cm^{-1}): 3154, 3055, 2850, 1710, 1675, 1554, 1075; ^{1}H NMR ($CDCl_3$): δ 9.00 (brs, 1-H); 6.72 (s, 1-H); 4.25 (s, 2-H); 3.89 (s, 2-H); 6.68-6.77 (m, 5-H). MS: $[M]^+$ at m/z 376.

3-[5'-(3"-indolomethylene) -1', 3', 4' – oxadiazol- 2'-yl]-2-(p-methoxyphenyl)-4-thiazolidinone, 5b: (ethanol/ benzene); IR (KBr cm^{-1}): 3170, 3060, 2853, 1740, 1670, 1560, 1080; ^{1}H NMR ($CDCl_3$): δ 9.10 (brs, 1-H); 6.75 (s, 1-H); 4.25 (s, 2-H); 3.90 (s, 2-H); 3.45 (s, 3-H). MS: $[M]^+$ at m/z 406.

3-[5'-(3"-indolomethylene) -1', 3', 4' – oxadiazol- 2'-yl]- 2 –(p-hydroxy, m-methoxy phenyl)- 4 –thiazolidinone, 5c:(ethanol/benzene); IR (KBr cm^{-1}): 3153, 3040, 2840, 1711, 1676, 1575, 1072; ^{1}H NMR ($CDCl_3$): δ 9.10 (brs, 1-H); 6.61 (s, 1-H); 4.24 (s, 2- H); 3.83 (s, 2-H); 2.14(s, 6-H); 6.68-6.79 (m, 4-H). MS: $[M]^+$ at m/z 422.

3-[5'-(3"-indolomethylene) -1', 3', 4' – oxadiazol- 2'-yl]- 2 –(p-N, N- dimethylphenyl)- 4 –thiazolidinone, 5d: (ethanol/ water); IR (KBr cm^{-1}): 3152, 3050, 2850, 1710, 1674, 1510, 1080; ^{1}H NMR ($CDCl_3$): δ 8.89 (brs, 1-H); 6.75 (s, 1-H); 4.23 (s, 2- H); 3.85 (s, 2-H); 3.57(s, 3-H); 12.71 (ss,1-H); 3.63(s, 3-H). MS: $[M]^+$ at m/z 419.

3-[5'-(3"-indolomethylene) -1', 3', 4' – oxadiazol- 2'-yl]- 2 –(p- hydroxyphenyl)-4 –thiazolidinone, 5e: (ethanol/ water); IR (KBr cm^{-1}): 3145, 3040, 2853, 1730, 1684, 1525, 1075; ^{1}H NMR ($CDCl_3$): δ 9.10 (brs, 1-H); 6.74 (s, 1-H); 4.23 (s, 2-H); 3.90 (s, 2-H); 6.67-6.76 (m, 4-H); 12.71 (ss,1-H). MS: $[M]^+$ at m/z 392.

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 noradrenaline (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

Table I:Yield and Elemental Analysis of Compounds

Compound	R	Yield (%)	m.p. (°C)	Molecular Formula	Mol. Wt.	Found (Calculated) %		
						C	H	N
1	-	78	44	$C_{12}H_{13}NO_2$	203	70.9 (70.93)	6.44 (6.40)	6.92 (6.89)
2	-	65	125	$C_{11}H_{12}N_4O_2$	232	56.92 (56.89)	5.20 (5.17)	24.13 (24.13)
3	-	60	185	$C_{11}H_{10}N_4O$	214	61.70 (61.68)	4.65 (4.67)	26.14 (26.16)
4a	H	55	268	$C_{18}H_{14}N_4O$	302	71.56 (71.52)	4.68 (4.63)	18.56 (18.54)
4b	4-OCH_3	58	24	$C_{19}H_{16}N_4O_2$	332	68.65 (68.67)	4.85 (4.81)	16.90 (16.86)
4c	3-OCH_3 4-OH	45	300	$C_{19}H_{16}N_4O_3$	348	65.48 (65.51)	4.63 (4.59)	16.06 (16.09)
4d	4-$N(CH_3)_2$	48	230	$C_{20}H_{19}N_5O_3$	377	69.60 (69.56)	5.54 (5.50)	20.30 (20.28)
4e	4-OH	40	200	$C_{18}H_{14}N_4O_2$	318	67.90 (67.92)	4.42 (5.50)	17.64 (20.28)
5a	H	45	220	$C_{20}H_{16}N_4O_2S$	376	63.80 (63.82)	4.27 (4.25)	14.91 (14.89)
5b	4-OCH_3	45	220	$C_{21}H_{18}N_4O_3S$	406	62.10 (62.06)	4.47 (4.43)	13.82 (13.79)
5c	3-OCH_3 4-OH	42	250	$C_{21}H_{18}N_4O$	422	59.75 (59.71)	4.24 (4.26)	13.30 (13.27)
5d	4-$N(CH_3)_2$	40	310	$C_{22}H_{21}N_5O_2S$	419	63.04 (63.00)	5.04 (5.01)	16.72 (16.70)
5e	4-OH	38	210	$C_{20}H_{16}N_4O_3S$	392	61.25 (61.22)	4.12 (4.08)	14.25 (14.28)

Table II: Cardiovascular Activity of the Synthesized Compounds

Co mpd	R	Dose (mg/ Kg i.v.)	Change in mean blood pressure mmHg			Duration in minutes Mean± SE	Change in resting HR bpm	Effect on pressor responses		ALD_{50} mg/Kg p.o.
			Control Mean± SE	Immediate Mean± SE	Delayed Mean± SE			CO	NA	
4a	H	2.5	135.6±9.93	130.8±10.77	127±9.31	10.6±2.96	Inhibited	Inhibited	-	>1000
4b	4-OCH_3	2.5	143.8±9.60	133±10.36*	132.6±7.88*	22.6±3.97	Potentiated	-	-	>1000
4c	3-OCH_3 4-OH	2.5	142±6.18	126.8±5.93**	124±8.78**	48.6±3.97	Inhibited (2-3bpm)	Inhibited	Inhibited	>1000
4d	4-$N(CH_3)_2$	2.5	140±11.87	109.8±8.17**	121.4±9.60*	65±3.08	Potentiated (1-2bpm)	Potentiated	-	>1000
4e	4-OH	2.5	140.6±9.93	120.4±10.66**	130.6±10.25	20.6±1.95	Inhibited	Potentiated	-	>1000
5a	H	2.5	138.8±9.75	94.6±9.86***	114.6±6.74**	78.4±2.52	Potentiated	Inhibited	Potentiated	>1000
		1.25	137.6±7.66	145.6±6.50*	96.8±5.00*	59.8±2.86	-	Inhibited	-	
5b	4-OCH_3	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

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 g 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 Smith (1960) method. [15]

RESULTS

3-[5'-(3"-indolomethylene) -1', 3', 4'-oxadiazol- 2'-yl]-2-(p-methoxyphenyl)-4-thiazolidinone, 5b, showed biphasic response. There was a immediate mild rise in blood pressure (12 mm Hg) followed by a gradual fall in blood pressure of 70 mm Hg at a dose of 2.5mg/Kg i.v. The cardiovascular activity of this compound lasted for about 110 minutes. This compound was associated with inhibition of CO response without affecting NA response.

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