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Synthesis and Evaluation of Some Substituted Indole Derivatives for Cardiovascular Activity

Dr.Nallagudla Sumalatha [1],Dharavath Ramesh [2],Pulakaram Supriya [3],

ABSTRACT

This research delves into a class of indoles that have thiazolidinone and oxadiazole side chains attached to their 3-position. Evaluation of cardiovascular activity was conducted on the synthesized Indole derivatives 4 (a-e) and 5 (a-e). This compound is 3-[5'-(3"-indolomethylene)-1',3',4'-oxadiazol-2'-yl]At 2.5 mg/Kg, the most active ingredient in the current investigation, 2-(p-methoxy phenyl)-4-thiazolidinone 5b, exhibited different degrees of cardiovascular activity. Using infrared, 1H nuclear magnetic resonance, mass spectrometry, and elemental analysis, the structures of these substances were revealed.

Antihypertensive and cardiovascular effects of indole derivatives, oxadiazole, and thiazolidinone.

INTRODUCTION

Cardiovascular problems have been on the rise due to the growing complexity of daily living. When it comes to cardiovascular diseases, hypertension is by far the most frequent and deadly. There have been reports of potential cardiovascular action for several imidazoline derivatives, indole, quinazolinone, oxadiazole, thiadiazole, azetidinone, etc. Multiple indole derivatives have been reported in recent studies to have a wide range of biological effects, including central nervous system depressant [7], anti-inflammatory and analgesic [8], antiviral [9], anthelmintic [10], antibacterial [11], anticonvulsant [12], cardiovascular activity [13], and antihypertensive activity [14]. [14] The cardiovascular activity is significantly increased when various heterocyclic moieties are substituted at the 3-position of the indole nucleus. Additionally, it has been shown that oxadiazols and 4-oxo-thiazolidinones have strong effects on the cardiovascular system. The decision to produce new 3-[5'-(3"-indolomethyle) was based on these findings.One-, three-, and four-oxadiazol-2-yl]-2-(phenyl substituted)-4-thiazolidinones (Scheme I) by substituting various heterocyclic nuclei for the indole moiety at its third position. Table I shows the results of the elemental analysis, and Table II shows the results of the screening for cardiovascular activity of these compounds.

Professor[1], Associate Professor[2],Student[3],
Department of Pharmacy,
BRILLIANT GRAMMAR SCHOOL EDUCATIONAL SOCIETY'S GROUP OF INSTITUTIONS-INTEGRATED CAMPUS
Abdullapurmet (V), Hayath Nagar (M), R.R Dt. Hyderabad.

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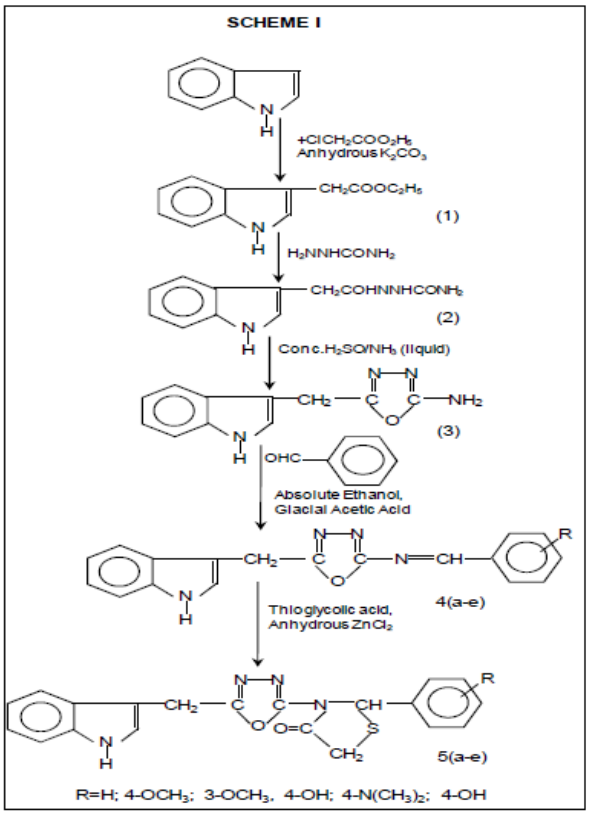
MATERIALS AND METHODS



Using a thermionic melting point equipment in open glass capillaries, the compounds' uncorrected melting points were calculated. Spots were found using an iodine chamber, and TLC was used on a regular basis to ensure that all of the freshly synthesized compounds were homogeneous on silica gel G plates. A Perkin-Elimer 2400 elemental analyzer was used to identify the elements in all the produced compounds, and the findings were within ± 0.4% of the theoretical values. A Perkin-Elmer spectrometer, the RX-I, was used to record infrared spectra in KBR. The Bruker AC-300 F instrument was used to record 1H NMR spectra. The internal reference standard was tetra methyl silane (TMS), and the solvent was CDCl3/DMSO-Cl6. A value of δ (ppm) was used to record all chemical shifts. A VG-70-S instrument was used to determine the mass spectra.

Anhydrous acetone (80 ml), ethylcholoroacetate (0.01 mole), indole (0.01 mole), and 8 g of anhydrous K2CO3 were reflux-heated for 24 hours to produce ethyl-3-indoloacetate. Once cooled, the solvent was filtered and rinsed with water, and any remaining surplus was distilled out. Recrystallization from methanol yielded compound 1 from the resulting product. 1H NMR (CDCl3): 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; IR (KBr, cm-1): 3180, 3050, 2860, 1740, 1580. [M]+ at m/z 203. 1-(3'-indoloacetyl); mass spectrometry 2. semicarbazide: For 16 hours, a solution of 0.075 mole of Compound 1 and 0.075 mole of semicarbazide in 70 ml of methanol was refluxed on a steam bath. Compound 2 was obtained by distilling out the surplus solvent and then pouring the thick mixture into ice-cold water, filtering it, and then recrystallizing it from ethanol. The 1H NMR spectrum (CDCl3) shows δ9.74 (brs, 1-H); 8.30 (brs, 4-H); 7.15-6.60 (m, 5-H); and 4.25 (s, 2-H). MS: [M]+ in the 2-amino5. 5-(3'-indolomethylene)anhydrous 1,3,4-oxadiazole 3. A solution containing 0.05 mole of compound 2 and 15 ml of concentrated H2SO4 was left at room temperature overnight. The next day, it was diluted with ice cold water and neutralized with liquid ammonia. The resulting solid was filtered and recrystallized from methanol to obtain compound 3. The infrared spectra for compound 3 are 3340, 3140, 3060, 2840, 1680, 1560, and 1093 cm-1. The 1H nuclear magnetic resonance (CDCl3) peaks at δ9.10 (brs, 1-H), 7.67-7.10 (m, 5-H), 6.15 (s, 2-H), and 4.10 (s,2-H) ppm. MS: [M]+ at 214 m/z. An Overview of the Oxadiazole Derivatives Synthesis Process, parts 4a–e: The following was added: a few drops of glacial acetic acid, 80 ml of 100% ethanol, and 0.01 mole of 2-amino-5-(3'-indolomethylene)-1, 3, 4-oxadiazole 3. For 8 hours, the mixture was refluxed with anisaldehyde (0.01 mole). After removing the surplus solvent, the thick bulk was rinsed with an 8:2 combination of water and ether. Compounds were produced by recrystallizing the resulting solid using carefully chosen solvents. Parts 4a–e.

1. 1H NMR (CDCl3): δ 9.24 (brs, 1-H); 8.25 (s, 1-H); 4.32 (s, 2-H); 6.47-6.68 (m, 5-H) ppm; 4a: methanol; IR (KBr cm-1): 3135, 3040, 2850, 1682, 1560, 1070. The chemical formula for 2-(p-methoxybenzylidenylamino)-5-(3'-indolo methylene)-1,3,4-oxadiazole is 4b:(etanol/water). The infrared spectra are 3120, 3050, 2860, 1635, 1582, and 1080 cm-1. The proton nuclear magnetic resonance (CDCl3) assignments are 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. The chemical formula is 4-(p-hydroxy, m-methoxy benzyli denylamino)-5-(3'-indolomethylene)-1, 3, 4-oxadiazol, with coordination numbers 4c: (DMF). The infrared

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spectra, measured in KBr cm-1, are 3360, 3145, 2840, 1680, 1612, and 1062. The following 1H NMR spectra were recorded in CDCl3: δ 9.20 (brs, 1-H); 8.35 (s, 1-H); 4.25 (s, 2-H); 3.72 (s, 3-H); and 12.78 (ss, 1-H)... The chemical formula for 2-(p-N,N-dimethylbenzylidenylamino)-5-(3'-indolomethylene)-1, 3, 4-oxadizole is given by the following formula: 4-d: (ethanol/water); IR (KBr cm-1): 3320, 3144, 2830, 1683, 1610, 1297; 1H NMR (CDCl3): 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). [M]+ at m/z 377 in MS.

p-hydroxybenzylidenylamino-5-(3'-indolo methylene)- 1, 3, 4-oxadizole, 4e: Infrared (KBr cm-1): 3380, 3142, 2860, 1683, 1611, 1294; ethanol/water:The following 1H NMR spectra were recorded in CDCl3: δ 9.21 (brs, 1-H); 8.38 (s, 1-H); 4.28 (s, 2-H); 6.60-6.76 (m, 4-H); and 12.81 (ss, 1-H). m/z 318: [M]+ in MS.

Synthesis of thiazolidinone derivatives, 5a-e: A general process An 18-hour reflux was carried out in a stirred solution of compounds (4a-e) in 80 ml of dry DMF with a trace quantity of anhydrous ZnCl2 and thioglyconic acid (0.02 miles). Before being added to the ice-cold water, the reaction mixture was chilled. Compounds (5ae) were obtained by filtering, washing, and recrystallizing the isolated solid from a solvent of choice.

the oxadiazol-2-yl-3-[5'-(3"-indolomethylene)-1', 3', 4']1. 1H NMR (CDCl3): 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); 5-a: 2-phenyl-4-thiazolidinone, 5a: (ethanol/water); IR (KBr cm-1): 3154, 3055, 2850, 1710, 1675, 1554, 1075. Three-[5'-(3"-indolomethylene)]-MS: [M]+ at m/z 376. 2'-yl oxadiazol-1,3, and 4'-yl]2- (p-methoxyphenyl)-4-thiazolidinone, 5b: (ethanol/benzene); nuclear magnetic resonance (KBr cm-1), 1H NMR (CDCl3): 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). m/z 406: [M]+, 3-[5'-(3"-indolomethylene] 2'-yl oxadiazol-1,3, and 4'-yl]2- (p-hydroxy, m-methoxy phenyl)- 4-thiazolidinone, 5c:(ethanol/benzene); infrared spectroscopy (KBr cm-1), 1353, 3040, 2840, 1711, 1676, 1575, and 1072; one-dimensional nuclear magnetic resonance (CDCl3), 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). Three-[5'-(3"-indolomethylene) -1', 3', 4' - oxadiazol-2'-yl] is detected by mass spectrometry at m/z 422.the second one is 2-(p-nitrophenyl)- 4-thiazolidinone, labeled as 5d: (ethanol/water); infrared spectroscopy (KBr cm-1): 3152, 3050, 2850, 1710, 1674, 1510, 1080; one-dimensional nuclear magnetic resonance (CDCl3): δ 8.89 (s, 1-H); 6.75 (s, 2-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). 3-[5'-(3"-indolomethylene) -1', 3', 4' - oxadiazol-2'-yl] is detected by mass spectrometry at [M]+ at m/z 419.This compound is a 2-(p-hydroxyphenyl)-4-thiazolidinone with the molecular formula 5e: (ethanol/water); 1H NMR (CDCl3): 3145, 3040, 2853, 1730, 1684, 1525, and 1075. 9.10 (brass, 1-H); 6.74 (single, 1-H); 4.23 (solid, 2-H); 3.90 (single, 2-H); 6.67-6.76 (multiple, 4-H); 12.71 (single, 1-H). m/z 392: MS: [M]+.

CARDIOVASCULAR ACTIVITY

All of the produced indole derivatives were first evaluated for cardiovascular function in albino rats weighing 100-120g, excluding pregnant animals. In order to investigate the effects on blood pressure (B.P.), heart rate (HR), and pressor responses induced by either carotid occlusion (CO) or intravenous noradrenaline (NA), the newly synthesized compounds were dissolved in propylene glycol and then delivered intravenously (from the right femoral vein).

The injection was found to be 1-2 µg/kg. Without influencing the CO and NA response, injecting.20 mL of propylene glycol caused a small and temporary drop in blood pressure of 1-2 mmHg. Using a status P25 transducer, a mercury manometer was inserted into the left common carotid artery from the femoral artery on one channel of the "Encardiorite" (India) polygraph to record the patient's blood pressure. Throughout all of the trials, an electrocardiogram (Lead II) was captured on a single channel of the "Encardiorite" (India) polygraph.

Chemical Compound Yield and Element Analysis (Table I)

Compound	R	Yield (%)	m.p. (°C)	Molecular Formula	Mol. Wt.	Found (Calculated) %		
						C	H	N
1	-	78	44	$C_{23}H_{20}NO_2$	269	70.9 (70.93)	6.44 (6.40)	6.92 (6.89)
2	-	65	125	$C_{23}H_{20}N_4O_2$	252	56.92 (56.89)	5.20 (5.17)	34.13 (24.13)
3	-	60	185	$C_{23}H_{20}N_4O$	214	61.70 (61.88)	4.65 (4.67)	26.14 (26.16)
4a	H	55	268	$C_{24}H_{22}N_4O$	302	71.56 (71.52)	4.68 (4.65)	18.56 (18.54)
4b	4-OCH_3	58	24	$C_{25}H_{24}N_4O_2$	332	68.65 (68.67)	4.85 (4.81)	16.90 (16.88)
4c	3-OCH_3 4-OH	45	300	$C_{25}H_{24}N_4O_3$	348	65.48 (65.51)	4.63 (4.59)	16.06 (16.08)
4d	4-$N(CH_3)_2$	48	230	$C_{26}H_{27}N_5O$	577	69.60 (69.56)	5.54 (5.50)	20.50 (20.20)
4e	4-OH	40	200	$C_{24}H_{22}N_4O_2$	318	67.90 (67.92)	4.42 (5.50)	17.64 (20.20)
5a	H	45	220	$C_{26}H_{24}N_4O_2S$	376	63.80 (63.82)	4.27 (4.25)	14.91 (14.89)
5b	4-OCH_3	45	220	$C_{27}H_{26}N_4O_3S$	406	62.10 (62.06)	4.47 (4.45)	13.82 (13.79)
5c	3-OCH_3 4-OH	42	250	$C_{26}H_{24}N_4O$	422	58.75 (58.71)	4.24 (4.26)	13.30 (13.27)
5d	4-$N(CH_3)_2$	40	310	$C_{27}H_{27}N_5O_2S$	419	63.04 (63.00)	5.04 (5.01)	16.72 (16.70)
5e	4-OH	38	210	$C_{26}H_{24}N_4O_3S$	392	61.25 (61.22)	4.12 (4.08)	14.25 (14.28)

Section II: Synthesized Compounds' Effects on the Heart and Blood Vessels

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Compd	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	155.6±9.93	130.8±10.77	127±9.31	10.6±2.96	Inhibited	Inhibited	-	>1000
4b	4-OCH_3	2.5	143.8±9.68	125±10.36*	122.6±7.88*	22.6±3.97	Potentiated	-	-	>1000
4c	3-OCH_3 4-OH	2.5	142±9.38	126.8±9.93**	124±8.78**	48.6±3.97	Inhibited (2-3bpm) Potentiated (1-2bpm)	Inhibited	Inhibited	>1000
4d	4-$N(CH_3)_2$	2.5	140±11.87	108.8±8.17**	121.4±9.69*	65±3.08	Potentiated	Potentiated	-	>1000
4e	4-OH	2.5	148.6±9.93	120.4±10.66**	130.6±10.25	20.6±3.95	Inhibited	Potentiated	-	>1000
5a	H	2.5	150.8±9.75	94.6±8.89***	114.6±6.74**	78.4±2.72	Inhibited	Potentiated	Potentiated	>1000
		1.25	157.6±7.66	145.4±6.50*	96.8±5.88*	59.8±2.86	-	Inhibited	-	
5b	4-OCH_3	2.5	143±12.04	154±11.61*	72.2±11.18***	110.8±5.77	-	Inhibited	-	>2000
		5.0	144.4±8.98	106.2±9.88**	44.2±8.48***	186.4±6.10	-	Inhibited	-	
5c	3-OCH_3 4-OH	2.5	136±12.94	142±13.87	76.6±11.38*	65.8±3.03	-	Inhibited	-	>1000
5d	4-$N(CH_3)_2$	2.5	139±9.61	78.6±8.38***	110±9.88**	71±2.64	-	Inhibited	Inhibited	>1000
5e	4-OH	2.5	142.4±8.24	108.7±9.04***	107.1±7.88	60.8±1.09	-	Inhibited	Inhibited	>1000

ACUTE TOXICITY STUDY

Charles foster mice of both sexes (excluding pregnant ones) were used in the toxicity investigation. Albino mice were used to calculate the approximate 50% fatal dose (ALD50) of the substances that showed promise. The research included male and female mice weighing 18-25 g. Different groups of animals were given varying doses of the medications by intraperitoneal (i.p.) injection. The percentage of death in each group was measured after 24 hours after medication delivery. The ALD50 was determined using the data collected by using the Smith (1960) technique. [15]

RESULTS

The toxicity research was conducted using male and female Charles foster mice, excluding pregnant ones. To determine the potential 50% lethal dose (ALD50) of the compounds, albino mice were used. Mice ranging in weight from 18 to 25 grams were used for the study. Intraperitoneal (i.p.) injections of the drugs were administered to several groups of animals at different dosages. The mortality rate in each category was assessed one day after the administration of the drug. The data was acquired using the Smith (1960) approach in order to calculate the ALD50. [15]

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