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Journal of Chemical and Pharmaceutical Research, 2012, 4(12):5185-5190

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Synthesis and evaluation of some new azetidinone derivatives for antihypertensive activity

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ABSTRACT

Indol treated with ethylchloroacetate in presence of anhydrous K_2CO_3 was converted into ethyl-3-indoloacetate. This compound on refluxing with semicarbazide results into 1-(3'-indoloacetyl) semicarbazide 2. Overnight treatment of compound 2 with conc. H_2SO_4 followed by neutralization with liquid ammonia gives 2-ammino-5-(3'-indolomethylene)-1,3,4-oxadiazole 3. Mixture of compound 3 and anisaldehyde in presence of glacial acetic acid refluxed in absolute ethanol to obtain 2-(substituted arylidenylamino)-5-(3' – indolomethylene)-1,3,4-oxadiazole 4(a-e). Mixture of synthesized compounds, anhydrious $ZnCl_2$ and thioglycolic acid, refluxed in dry DMF, resulting derivatives 1-[5'-(3"- indolomethylene)-1',3',4'- oxadiazol-2'- yl-]-4-(substituted phenyl)-2-azetidinone 5(a-e).The structure of the hitherto unknown compounds have been confirmed from analytical and spectral data. The newly synthesized compounds were screened for antihypertensive activity.

Keywords: azitidinones, oxadiazole, thiazolidinone, hypertensive activity, cardiovascular activity

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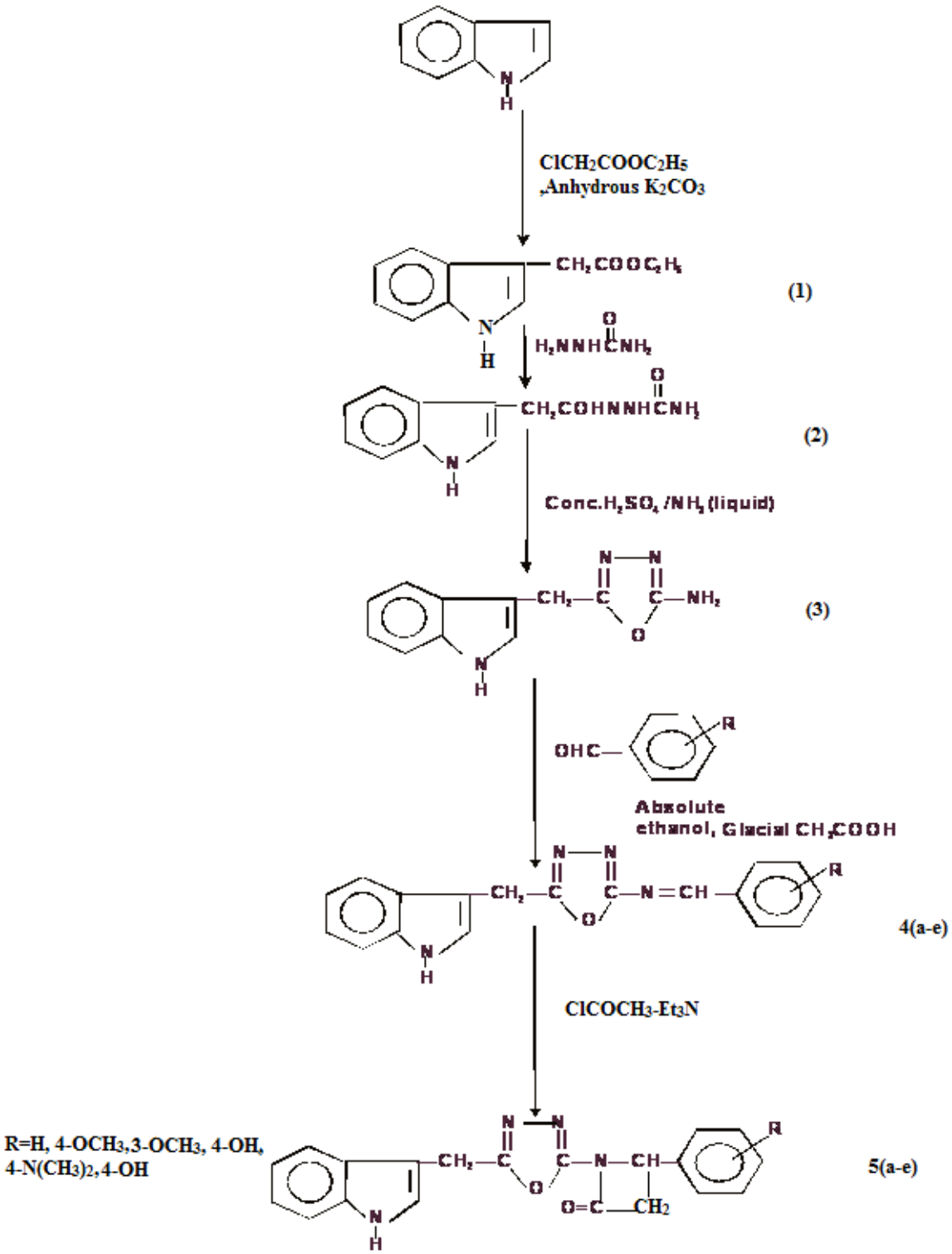
INRODUCTION

Azetidinones, which are part of the antibiotic structure, are known to exhibit interesting biological activities. Several azetidinones derivatives have been reported to possess a wide variety of biological properties e.g. CNS-epressant[1], anti-inflammantory[2-3], analgesic[4], antibacterial[5], antimicrobial[6], anticonvulsant[7], cardiovascular activities[8], antifungal[9-10], antibiotic[11], antitubercular[12] and antitumor[13]. Substitution at 4-position of azetidinones nucleus by different aromatic moieties markedly enchance the antihypertensive activity[14]. Furthermore, oxadiazole[15], indole[16] have also been reported to possess potent antihypertensive activity. This prompted to synthesize a new series **(sheme-I)** of azetidinone by incorporating these moieties.

EXPERIMENTAL SECTION

The melting point of the compounds were determined in open glass capillaries with the help of thermonic melting point apparatus and are 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 $\pm$0.4% of theoretical values. IR spectra were recorded in KBR on a Perkin-Elmer spectrum RX-I, spectrometer.

SCHEME I


ClCH2COOC2H5
,Anhydrous K2CO3
(1)
H2NNHCNH2
(2)
Conc.H2SO4 /NH3 (liquid)
(3)
OHC—
R
Absolute
ethanol, Glacial CH3COOH
4(a-e)
ClCOCH3-Et3N
R=H, 4-OCH3,3-OCH3, 4-OH,
4-N(CH3)2,4-OH
5(a-e)

^{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 standared. All chemical shift values were recorded as δ (ppm). Mass spectra were determined on a VG-70-S instrument.

Ethyl-3-indoloacetate, 1: Indole (.01 mole), ethylcholoroacetate (.01 mole), in anhydrous acetone (80 mL) and anhydrous K_2CO_3 (8 g) were heated under reflux for 24 hours. The exess of the solvent was distilled off and after cooling, it was filtered washed with water. The compound thus obtained was recrystallized from methanol to give compound 1.

1-(3'-indoloacetyl)semicarbazide, 2: Compound 1 (.075 mole) and semicarbazide (.075 mole) in methanol (70mL) were refluxed on a steam bath for 16 hrs. 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.

2-amino-5-(3'-indolomethylene)-1,3,4-oxadiazole, 3: A mixture of compound 2 (.05 mole) and conc. H_2SO_4 (15mL) 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.

General Procedure for the Synthesis of Oxadiazole Derivatives, 4a-e: 2-amino-5-(3'-indolomethylene)-1,3,4-oxadiazole 3 (.01 mole) in absolute ethanol (80 mL) and a few drops of glacial acetic acid was added. Anisaldehyde (.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 4(a-e)

Table I- Yield and elemental analysis of compounds

Compd	R	Yield (%)	m.p.(°C)	Molecular Formula (Mol.Wt.)	Found (Calcd)% 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	50	180	$C_{20}H_{16}N_4O_2$ 344	69.74 (69.76	4.62 4.65	16.22 16.27)
5b	4-OCH_3	55	256	$C_{21}H_{18}N_4O_3$ 374	67.40 (67.37	4.84 4.81	14.95 14.97)
5c	3-OCH_3 4-OH	40	115	$C_{21}H_{18}N_4O_4$ 390	64.63 (64.61	4.58 4.61	14.38 14.35)
5d	4-$N(CH_3)_2$	45	100	$C_{22}H_{21}N_5O_2$ 387	68.23 (68.21	5.45 5.42	18.06 18.08)
5e	4-OH	35	210	$C_{20}H_{16}N_4O_3$ 360	66.70 (66.66	4.40 4.44	15.58 15.55)

General Procedure for the Synthesis of Thiazolidinone Derivatives, 5a-e: To **a** stirred solution of compounds (4a-e)(.01 mole) and triethylamine (.02 mole) in dioxane(40 mL), acetyl chloride (.02 mole) was added dropwise at 0-5 °C. The reaction mixture was stirred for about 5hr. and the precipitated amine hydrochloride filtered off. The filterate was concentrated under reduced pressure and poured into ice cold water. The products so obtained was recrystallized from selected solvents to give compounds 5(a-e).

Screening for antihypertensive activity

Preliminary anti hypertensive activity tests were carried out on albino rats 100-120g of either sex (the pregnancy was excluded) for all the synthesized azitidinone derivatives by using Dubey et.al, 1978 method[17] and Kumar et.al 1985 method[18]. 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 respons. 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.

Table 2- Anti hypertensive activity of the synthesized compounds

Compd	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	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	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		
5b	4-OCH_3	2.5	135.0±9.35	114.8±7.70*	122.4±8.68*	30.6±1.94	-	Inhibited	-	>1000
5c	3-OCH_3 4-OH	2.5	137±10.36	104±11.61**	116.8±9.84	55.3±1.67	-	Inhibited	Potentiated	>1000
5d	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
5e	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*

RESULTS AND DISCUSSION

3-[5'-(3"-indolomethylene) -1', 3', 4' – oxadiazol- 2'-yl]-2-phenyl-4-azitidinone, 5a is considered for its potentiality, it is further studied at 3 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 mm Hg), which lasted for 100 minutes. In addition, compound 5a is also found associated with either inhibition or blockade of CO, inhibition of HR (1-3 bpm) without affecting the NA response.

Table 3. Spectral Data of Synthesized Compounds

Compd	IR, cm^{-1}(KBr)	1H NMR. δ(ppm)
1	3180(NH of indole), 3050(aromatic C-H), 2860(CH_2), 1740(C=O),1580(C=C of aromatic ring).	δ9.85(brs, 1H, NH of indole), 7.69-7.00 (m,5H,Ar-),4.30(s,2H,CH_2), 3.75(q,2H,$COOCH_2CH_3$),1.30(t,3H, $COOCH_2CH_3$)
2	3350(NHNH), 3160(NH of indole), 3040 (aromatic C-H), 2853(CH_2), 1720(C=O), 1560(C=C of aromatic ring).	δ9.74 (brs, 1H, NH of indole), 7.15-6.60 (m,5H,Ar-H),4.25(s,2H,CH_2), 8.30(brs,4H,$NHNHCONH_2$)
3	3340(NH_2),3140(NH of indole), 3060 (aromatic C-H),2840(CH_2), 1680(C=N), 1560(C=C of aromatic ring),1093(C-O-C)	δ9.10(brs, 1H, NH of indole), 7.67-7.10 (m,5H,Ar-H),6.15(s,2H,NH_2), 4.10(s,2H,CH_2)
4a	3125(NH of indole), 3040(aromatic C-H), 2865(CH_2), 1085(C-O-C), 1630(C=N), 1580(C=C of aromatic ring)	δ9.10(brs,1H, NH of indole), 8.35(s, 1H, N=CH-Ar), 7.92-6.60(m, 9H, Ar-H), 4.35(s,2H,CH_2), 6.35-6.50(m,5H)
4b	3120(NH of indole), 3050(aromatic C-H), 2860(CH_2), 1080(C-O-C), 1635(C=N), 1580(C=C of aromatic ring), 3140(OCH_3)	δ9.21(brs,1H, NH of indole), 8.40(s, 1H, N=CH-Ar), 7.90-6.55(m, 9H, Ar-H), 4.30(s,2H,CH_2), 3.40(s,3H,Ar-OCH_3),
4c	3133(NH of indole), 3044(aromatic C-H), 2855(CH_2), 1070(C-O-C), 1633(C=N), 1575(C=C of aromatic ring), 3150(OCH_3), 3440(-OH)	δ9.15(brs,1H, NH of indole), 8.27(s, 1H, N=CH-Ar), 7.85-6.70(m, 9H, Ar-H), 4.28(s,2H,CH_2), 3.35(s,3H,Ar-OCH_3), 6.47(s,1H)
4d	3130(NH of indole), 3045(aromatic C-H), 2855(CH_2), 1067(C-O-C), 1638(C=N), 1578(C=C of aromatic ring), 3160($N(CH_3)_2$)	δ9.21(brs,1H, NH of indole), 8.40(s, 1H, N=CH-Ar), 7.90-6.55(m, 9H, Ar-H), 4.30(s,2H,CH_2), 2.21(s,6H)
4e	3128(NH of indole), 3042(aromatic C-H), 2860(CH_2), 1080(C-O-C), 1640(C=N), 1570(C=C of aromatic ring), 3430(-OH)	δ9.17(brs,1H, NH of indole), 8.32(s, 1H, N=CH-Ar), 7.85-6.78(m, 9H, Ar-H), 4.25(s,2H,CH_2), 12.81(ss,1H)
5a	3180(NH of indole), 3050(aromatic C-H), 2860(CH_2), 1760(>C=O of β-lactam ring), 1640(C=N), 1580(C=C of aromatic ring)	δ9.18(brs,1H, NH of indole), 7.88-6.95(m,9H,Ar-H), 6.75(t,1H,CH-C_6H_5) 5.30(d,2H, CH_2 of azetidinone ring) 4.22(s,2H,CH_2),6.47-6.68(m,5H)
5b	3170(NH of indole), 3060(aromatic C-H), 2855(CH_2), 1760(>C=O of β-lactam ring), 1630(C=N), 1570(C=C of aromatic ring), 3145(OCH_3)	δ9.12(brs,1H, NH of indole), 7.80-6.90(m,9H,Ar-H), 6.65(t,1H,CH-C_6H_5) 5.20(d,2H, CH_2 of azetidinone ring), 4.25(s,2H,CH_2), 3.39(s,3H,Ar-OCH_3)
5c	3180(NH of indole), 3055(aromatic C-H), 2860(CH_2), 1750(>C=O of β-lactam ring), 1640(C=N), 1590(C=C of aromatic ring), 3145(OCH_3), 3420(-OH)	δ9.20(brs,1H, NH of indole), 7.78-6.85(m,9H,Ar-H), δ6.85(t,1H,CH-C_6H_5) 5.13(d,2H, CH_2 of azetidinone ring), 4.33(s,2H,CH_2), 3.48(s,3H,Ar-OCH_3) 6.72(s,1H)
5d	3165(NH of indole), 3060(aromatic C-H), 2865(CH_2), 1755(>C=O of β-lactam ring), 1645(C=N), 1585(C=C of aromatic ring), 3153($N(CH_3)_2$)	δ9.18(brs,1H, NH of indole), 7.90-6.60(m,9H,Ar-H), 6.55(t,1H,CH-C_6H_5) 5.17(d,2H, CH_2 of azetidinone ring), 4.15(s,2H,CH_2),2.23(s,6H)
5e	3180(NH of indole), 3055(aromatic C-H),	δ9.23(brs,1H, NH of indole), 7.75-

2855(CH_2)**,** 1750(>C=O of β-lactam ring),	6.90(m,9H,Ar-H), 6.45(t,1H,CH-C_6H_5)
1640(C=N), 1590(C=C of aromatic ring),	5.35(d,2H, CH_2 of azetidinone ring),
3421(-OH)	4.35(s,2H,CH_2), 12.81(ss,1H)

Acknowledgment
Authors are thankful to Late Dr. A K Rajput **,** Medicinal Chemistry Division, Department of Pharmacology, Lala Lajpat Rai Memorial Medical College, Meerut 250 004, India for his guidance in the research work.

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