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Microwave Assisted Synthesis, Characterization and Pharmacological Evaluation of Pyridazinone Derivatives

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Two series of compounds (i) 2-substituted phenyl-10*H*-pyridazin (6,1-b)quinazoline-10-one (**4a-g**) and (ii) 6-substituted phenyl tetrazolo (1,5-b)pyridazine (**5a-g**) were synthesized by microwave assisted methods. These compounds were evaluated for their hypotensive and anticonvulsant activities. These drugs showed the hypotensive activity ranging from 17.8 to 27.4 % while standard drug minoxidil showed 27 % reduction in blood pressure. All these compounds showed significant anticonvulsant activity when compared with phenytoin.

Key Words: Pyridazine, Microwave, Antihypotensive.

INTRODUCTION

Pyridazinone derivatives are reported to exhibit diverse pharmacological activities such as, hypotensive[1], antihypertensive[2], antiinflamatory[3], antithrombotic[4], anticonvulsant[5], cardiotonic[6], antibacterial[7], diuretic[8] and anti-HIV activities[9]. Remarkable work have been done on pyridazinone in the last few years for their cardiovascular activity especially hypotensive activity. In continuation to the work on the pyridazine/pyridazinone ring system, some new pyridazine derivatives are synthesized and evaluated them for hypotensive activity by non-invasive method.

EXPERIMENTAL

All melting points were measured in open glass capillaries and are uncorrected. The purity of the compounds were ascertained by TLC on silica gel-G plate using the solvent systems; benzene-acetone (9:1), toluene: ethyl acetate:formic acid (5:4:1) and iodine vapour as visualizing agent. IR spectra were taken in KBr on a Bio-Rad FTIR spectrometer. ^{1}H NMR spectra were recorded on Brucker DRX-400 NMR spectrometer in $CDCl_3$ and DMSO-d_6 with TMS as internal standard. The mass

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spectra were recorded on Jeol SX102 (FAB) mass spectrometer. The elemental analysis was done on ELEMENTAR VARIO-II.

Synthesis of β-substituted aryl propionic acid: It was synthesized by Friedel Craft acylation of benzene with succinic anhydride in presence of aluminium chloride. The mixture was refluxed for 4.5 h. A solution of conc. HCl 2.5 % was then added to the mixture and the concentrated to a small volume by heating on water bath. On cooling the crystalline compound was separated out. The acid gave effervescence test with sodium bicarbonate.

Synthesis of 6-substituted phenyl-2,3,4,5-tetrahydropyridazine-3-one: The compound **2** was synthesized by condensation of carboxylic acid **1** with hydrazine hydrate in alcoholic solution. The mixture was condensed for 5.2 h. After completion of the reaction the mixture was poured into the crushed ice.

Synthesis of 3-chloro-6-substituted phenyl pyridazine: It was synthesized by reaction of compound **2** with phosphorous oxychloride. The mixture was heated at 30 ºC for 3.5 h. After completion of the reaction mixture was poured into the crushed ice and neutralized with NaOH.

Synthesis of 2-substituted phenyl-10*H*-pyridazine(6,1-b)quinazoline-10-one (4a-g): It was synthesized by condensation of compound **3** and anthranilic acid in methanol[10]. The reaction mixture was treated for 1-3 min in a microwave, then cooled and poured over crushed ice. The solid thus obtained was filtered, washed with water and recrystallized from ethanol. The physical data are given in Table-1.

2-Phenyl-10*H*-pyridazine (6,1-b) quinazoline-10-one (4a): IR (KBr): 2997, 1672, 1588, 1160, 658. ^{1}H NMR ($CDCl_3$); 6.47-7.66 (m, 11H, Ar-H). MS (m/z); 273/274 (M^+/M^++1), 261, 197, 154.

2-(4-Methylphenyl)-10*H*-pyridazine(6,1-b)quinazolin-10-one (4b): IR (KBr); 3015, 1678, 1588. ^{1}H NMR ($CDCl_3$); 2.38 (s, 3H, CH_3), 7.13-7.96 (m, 10H, Ar-H).

2-(4-Ethylphenyl)-10*H*-pyridazino-(6,1-b)quinazolin-10-one (4d): IR (KBr); 3060, 1680, 1590. ^{1}H NMR ($CDCl_3$); 0.858 (d, 3H, CH_3), 1.18-1.23 (m, 2H, CH_2), 6.47-6.68 (m, 10H, Ar-H).

2-(4-Chlorophenyl)-10*H*-pyridazino-(6,1-b)quinazolin-10-one (4e): IR (KBr); 3077, 1678, 1587, 1239, 915. ^{1}H NMR ($CDCl_3$); 6.47-7.99 (m, 10H, Ar-H).

2-(4-Methoxyphenyl)-10*H*-pyridazino-(6,1-b)quinazolin-10-one (4f): IR (KBr); 2964, 1677, 1613, 1237. ^{1}H NMR (DMSO-d_6); 3.8 (s, 3H, CH_3O), 6.43-7.69 (m, 10H, Ar-H).

2-(4-Biphenyl)-10*H*-pyridazino-(6,1-b)quinazolin-10-one (4g): IR (KBr); 3000, 1673, 1618. ^{1}H NMR ($CDCl_3$); 6.45-7.78 (m, 15H, Ar-H). MS (m/z); 350/352 (M^+/M^++2).

Synthesis of 6-substituted phenyl tetrazolo(1,5-b)pyridazine (5a-g): It was synthesized by the reaction of compound **3** with sodium azide in DMF[10]. The reaction mixture was treated for 1-3 min in a microwave. The mixture was cooled and poured over crushed ice. The solid thus obtained was filtered washed with water and recrystallized with methanol. The physical data are given in Table-1.

TABLE-1
ELEMENTAL AND PHYSICAL DATA OF
THE SYNTHESIZED COMPOUNDS **4a-g and 5a-g**

Compd. No.	m.f.	Elemental analysis (%): Calcd. (Found)			Physical data			
		C	H	N	m.p. (ºC)	R_f value	Yield (%)	Final reflux duration (min)
4a	$C_{17}H_{13}N_3O$	74.18 (74.62)	4.72 (4.94)	15.27 (15.87)	143.8	0.53	56	1.5
4b	$C_{18}H_{15}N_3O$	74.74 (74.26)	5.19 (4.98)	14.53 (15.01)	164.7	0.68	56	1.6
4c	$C_{19}H_{17}N_3O$	74.24 (75.16)	5.61 (5.82)	13.86 (14.02)	166.8	0.54	61	1.5
4d	$C_{19}H_{17}N_3O$	75.24 (74.98)	5.61 (5.28)	13.86 (14.08)	139.6	0.67	52	1.4
4e	$C_{17}H_{12}N_3ClO$	65.91 (66.04)	3.88 (4.10)	13.57 (13.26)	126.9	0.75	62	1.5
4f	$C_{18}H_{15}N_3O_2$	70.82 (71.16)	4.92 (5.08)	13.77 (13.28)	133.9	0.72	64	1.0
4g	$C_{23}H_{17}N_3O$	78.63 (79.04)	4.84 (4.80)	11.96 (12.12)	141.4	0.67	43	1.2
5a	$C_{10}H_7N_5$	60.91 (61.26)	3.55 (4.01)	35.53 (35.25)	165.6	0.67	55	2.0
5b	$C_{11}H_9N_5$	62.55 (63.05)	4.26 (4.82)	33.17 (33.68)	152.9	0.86	58	2.5
5c	$C_{12}H_{11}N_5$	64.01 (64.86)	4.89 (5.10)	31.11 (31.68)	188.7	0.58	56	2.3
5d	$C_{12}H_{11}N_5$	64.00 (63.98)	4.89 (4.66)	31.12 (31.58)	85.8	0.48	40	2.2
5e	$C_{10}H_6N_5Cl$	51.83 (67.02)	2.59 (2.42)	30.23 (30.62)	162.8	0.58	54	2.2
5f	$C_{11}H_9N_5O$	58.15 (58.86)	3.96 (4.26)	30.83 (29.98)	103.8	0.46	67	2.5
5g	$C_{16}H_{11}N_5$	70.33 (70.67)	4.02 (3.98)	25.64 (26.06)	93.6	0.54	40	2.0

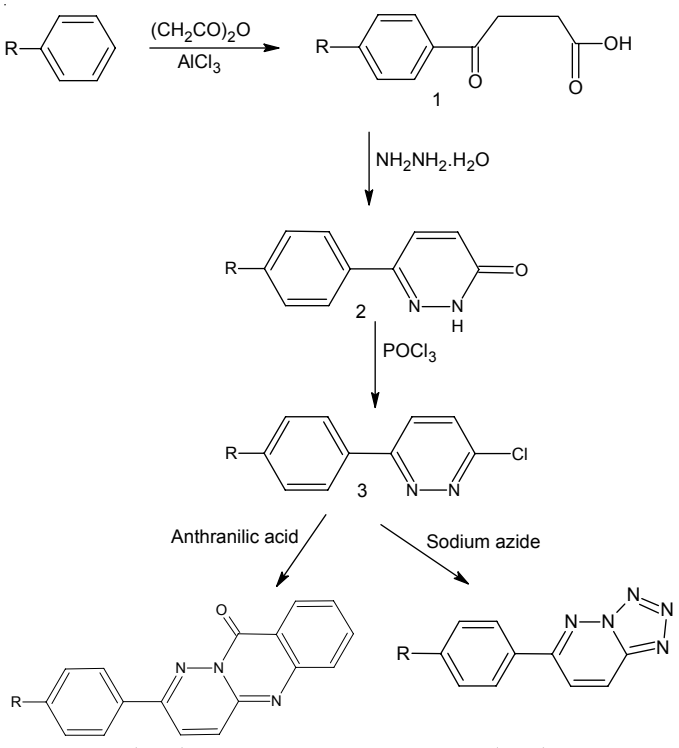
6-Phenyl tetrazolo(1,5-b)pyridazine (5a): IR (KBr); 3000, 1605. ^{1}H NMR ($CDCl_3$); 7.39-8.08 (m, 7H, Ar-H).

6-(4-Methylphenyl)tetrazolo(1,5-b)pyridazine (5b): IR (KBr); 3001, 1608.

6-(4-Ethylphenyl)tetrazolo(1,5-b)pyridazine (5d): IR (KBr); 2964, 1600.

RESULTS AND DISCUSSION

First series of compounds, 2-substituted-10*H*-pyridazin (6,1-b) quinazoline-10-one was synthesized in the following steps, illustrated with the synthesis of compound '**4**' (**Scheme-I**). The β-benzoyl propionic acid (**1**) was synthesized by Friedel craft acylation of benzene with succinic anhydride in presence of aluminium chloride. IR spectrum of acid showed bands at 3428 and 1679 cm^{-1} indicating the presence of carboxylic group. The ^1H NMR spectrum showed triplet at δ 2.59 and 3.23 for CH_2, CH_2CO, respectively. the aromatic proton appears at 7.53 to 7.95 as multiplet. The carboxylic proton appeared at δ 12.17. The condensation of carboxylic acid (**1**) with hydrazine hydrate gave 6-phenyl-2,3,4,5-tetrahydro pyridazinone (**2**). The compound was TLC pure. IR spectrum showed the presence of two bands at 3206 and 1676 cm^{-1} indicating the presence of amide group. ^1H NMR spectrum showed the two triplets at δ 2.60 and 2.96 for CH_2, CH_2O moiety, respectively. The aromatic protons appeared in the region 7.41-7.73. The aromatic proton appeared at δ 9.50. The 3-chloro-6-phenyl pyridazine (**3**) was synthesized by reaction of compound '**2**' with phosphorous oxy chloride. The compound was TLC different from the starting material. IR spectrum showed bands at 3000 and 1600 for C-H



(**4a-g**) (**5a-g**)

R = a-H, b-CH_3, c-3,4CH_3, d-C_2H_5, e-Cl, f-OCH_3, g-C_6H_5

Scheme-I

stretching and double bond. ^{1}H NMR spectrum showed aromatic protons in the region of 7.31 (multiplet), 7.59 (multiplet) and 7.83 (singlet). The 2-phenyl-10*H*-pyridazin(6,1-b)quinazoline-10-one (**4**) was synthesized by condensation of compound '**3**' with anthranilic acid. This step was a microwave assisted synthesis. The IR spectrum showed bonds at 2997, 1672 and 1588 cm^{-1} for CH stretching, carbonyl functional group and double bond. The ^{1}H NMR spectrum showed aromatic protons at δ 6.47-7.66 as multiplet. The structure was further verified by spectrum. It showed the peak at 273/274-(M^+/M+1) in accordance with formula $C_{17}H_{11}N_3O$. It showed the fragments *i.e.* peak at 261,197.

The other series *i.e.* 6-substituted phenyl tetrazolo(1,5-b)pyridazine (**5**) was synthesized by the reaction of compound '**3**' with sodium azide (**Scheme-I**). The IR spectrum showed the peak at 3010 and 1605 for CH stretching and double bond. The ^{1}H NMR spectrum showed the aromatic protons as multiplet in the aromatic region at δ 7.39-8.08.

The final compounds were screened for their hypotensive and anticonvulsant activities. The hypotensive activity was measured by Tail & Cuff method while anticonvulsant activity was measured by MES method.

Hypotensive activity: The final compounds were evaluated for hypotensive activity in normotensive rats non-invasively by Tail Cuff method[1]. The activity was compared with standard 'Minoxidil'. The per cent reduction in blood pressure by the test compounds was recorded at a dose of 50 mg/kg animal body weight. Compounds **4d**, **4f** and **4g** showed promising hypotensive activity, more than the standard drug 'minoxidil'. Rest of the compound showed moderate activity (Table-2).

TABLE-2
PER CENT REDUCTION IN BLOOD PRESSURE

Compound	1 h		3 h	
	SBP	MABP	SBP	MABP
4a	10.8	12.0	14.2	12.8
4b	14.5	12.6	17.8	15.4
5b	5.8	6.1	5.8	5.9
4d	20.0	16.1	21.8	17.9
4e	16.4	16.0	19.8	17.2
5e	11.6	8.6	14.2	14.8
4f	21.8	19.5	27.4	23.5
5f	10.8	7.4	12.6	8.4
4g	19.2	15.4	23.6	20.6
5g	13.2	13.6	17.0	17.6
Minoxidil	17.8	16.5	27.0	25.9

Anticonvulsant activity: All the final compounds were evaluated for anticonvulsant activity on albino mice at a dose of 25-30 mg/kg animal body weight by MES (maximal electroshock seizure) method[5]. The activity was compared with standard 'phenytoin'. The percent protection produced by the test compounds at

equivalent to phenytoin 28-33 mg/kg animal body weight. Standard drug showed 100 % inhibition at a dose of 25 mg/kg animal body weights.

Compounds **4c**, **4e** and **5g** showed 100 % protection while compounds **5c**, **4g** showed 83.33 % and compounds **4a**, **5a**, **4d**, **5e**, **4f** and **5f** showed 66.67 %, protection against convulsion (Table-3).

TABLE-3
ANTICONVULSANT ACTIVITY

Compound No.	R	Anticonvulsant activity maximal electroshock seizure (60 min) % protection
4a	H	66.67*
4b	CH_3	33.33
4c	3,4-CH_3	100***
4d	C_2H_5	66.67*
4e	*p*-Cl	100***
4f	*p*-OCH_3	66.67*
4g	C_6H_5	83.33**
5a	H	66.67*
5b	CH_3	50.0
5c	3,4-CH_3	83.33**
5d	C_2H_5	50.0
5e	*p*-Cl	66.67*
5f	*p*-OCH_3	66.67*
5g	C_6H_5	100***
Phenytoin	–	100***

*p < 0.1, **p < 0.01, ***p < 0.001.

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