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Research Article

Structural Establishment and Biological Evaluation of Newly Synthesized Nitrogen Containing Hetrocyclic Compound of Pyridazinone and its Derivatives

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Abstract

Some new 6-phenyl–pyridazine-3-one were synthesized by hydrazinolysis of appropriate β-(substituted aryl) propionic acid and were converted into corresponding bis-pyridazinone (M-1 to M-6). All these synthesized compounds were characterized on the basis of spectral data and evaluated for their anticonvulsant activity.

Keywords: Pyridazine-3-One, anticonvulsant activity, synthesis

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INTRODUCTION

Pyridazinones have been reported to possess a variety of biological activities like antinociceptive[1], anticancer[2], anticonvulsant[3], antithrombotic[4], and antiinflammatory[5-6] activity. In present work we reported synthesis of some pyridazinone derivatives and their anticonvulsant activity which is not done earlier and is quite significant. Reaction between benzimidazole and succinic anhydride in presence of hydrofluoric acid produced 4-(1-H-benzo[d] imidazole-5-yl)-4-oxo-butanoic acid (MA). The product obtained from step-I reactes with hydrazine hydrate to produce 6-(1-H-benzo[d] imidazole-5-yl)-2,3,4,5-tetrahydro Pyridazin-3-one (MB). The product obtained from step-II then react with different aromatic benzaldehydes in presence of acetic anhydride gives different derivatives **(M-1** to **M-6)**

MATERIALS AND METHODS

Chemistry

Melting points were determined by open capillary tube method in liquid paraffin bath and were uncorrected. Purity of the compounds was checked on pre-coated silica- gel G plate using Toluene: Ethyl acetate: Formic acid (5:4:1) as solvent system. Infrared (IR) spectra (KBr disc) were recorded on FT-IR Perkin Elmer. ^{1}H- nuclear magnetic resonance (^{1}H-NMR) spectra were recorded in DMSO using Bruker Avance-II 400 MHz NMR spectrophotometer. The chemical shifts were expressed in terms of δ (ppm) downfield from TMS and the mass spectra were recorded on Jeol SX-102 (FAB) Mass Spectrometer

Synthetic Study

Synthesis of 4-(1-H-benzo[d] imidazole-5-yl) -4oxo-butanoic acid (MA) A mixture of benzimidazole (0.10 mol) and hydrofluoric acid (40 ml) was taken in a three neck flask and refluxed on a water bath under anhydrous condition followed by addition of succinic anhydride (0.10 mol) in small quantities with continuous stirring. Stirring and heating were continued for 4 hrs and the content after leaving overnight at room temperature were poured into ice cold hydrochloric acid (2.5% v/v) followed by steam distillation. The aqueous solution was then concentrated to a small volume by evaporating on a water bath to obtain the crude compound. It was purified by dissolving in 5% w/v sodium bicarbonate solution and filtered, filtrate on acidification with dilute hydrochloric acid yielded **MA**. It was recrystallized from aq. ethanol.

Yield: 70% ; m.p. 95-96^{0}C ; R_f 0.65. Spectroscopic analysis: IR (cm^{-1}): 3408 (Ar.NH), 1708 (C=N), 1640 (C=O); ^{1}H-NMR (DMSO, 400 MHz, δ, ppm): 12.36(1H,s), 12.05(1H,s), 8.19(1H,s), 7.52-8.00(4H,m), 6.61(1H,s).

Synthesis of 6-(1-H-benzo[d] imidazole-5-yl)-2,3,4,5-tetrahydro pyridazine-3-one (MB) alcoholic solution of MA

(0.10 mol) was refluxed for 12 hrs with hydrazine hydrate (1 ml) in ethanol (25 ml). The reaction mixture was concentrated and then poured into ice cold water to obtain compound **MB,** which was crystallized from ethanol.

Yield: 60% ; m.p. 115-116^{0}C ; R_f 0.55. Spectroscopic analysis: IR (cm^{-1}): 3416 (Ar.NH), 1667.3 (C=O), 1645.1 (C=N), 1245.7 (C-N); ^{1}H-NMR (DMSO, 400 MHz, δ, ppm): 12.36(1H,s), 8.19(1H,s), 7.70-8.06(3H,m), 7.00(1H,s), 6.49(1H,s), 5.7(1H,s).

Synthesis of Phenyl di-[6-(1-H-benzo[d] imidazole-5-yl)-pyridazine-3-one-2yl] methane derivatives (M-1 to M-6) Compound MB (0.02 mol) was refluxed with each six different substituted benzaldehydes (0.01 mol) in the presence of acetic anhydride (10 ml) for 26 hrs (monitored with the help of TLC) and then poured into ice cold water to get compound **M-1 to M-6** which was also crystallized from ethanol.

Synthesis of Phenyl di-[6-(1-H-benzo[d] imidazole-5-yl)-pyridazine-3-one-2yl] methane (M-1) Yield: 40% ; m.p. 88-89^{0}C ; R_f 0.49. Spectroscopic analysis: IR (cm^{-1}): 3423.4 (NH, aromatic), 3079.9 (C-H, aromatic), 2944.0 (C-H, aliphatic), 1669.4 (C=O), 1620.8 (C=N); ^{1}H-NMR (DMSO, 400 MHz, δ, ppm): 12.36 (d, 2H, N-H), 8.19 (d, 2H,NH-CH), 7.67-8.06 (m, 6H, Ar-H), 7.23-7.26 (m, 5H, Ar-H), 6.91 (s, 1H, Al-H), 6.39 (d, 2H, Ar-H) 5.79 (d, 2H, Ar-H); MS (m/z): 510.0 (M$^+$).

Synthesis of p-methoxy Phenyl di-[6-(1-H-benzo[d] imidazole-5-yl)- pyridazine-3-one-2yl] methane (M-2) Yield: 72% ; m.p. 140-141^{0}C ; R_f 0.52. Spectroscopic analysis: IR (cm^{-1}): 3415.0 (NH, aromatic), 2979.0 (C-H), 1656.4 (C=H), 1625.8 (C=N), 1302.0 (C-N); ^{1}H-NMR (DMSO, 400 MHz, δ, ppm): 12.36 (d, 2H, N-H), 8.19 (d, 2H,NH-CH), 7.67-8.06 (m, 6H, Ar-H), 7.26-7.43 (m, 5H, Ar-H), 6.91 (s, 1H, Al-H), 6.39 (d, 2H, Ar-H) 5.79 (d, 2H, Ar-H), 3.83 (s, 3H, OCH_3); MS (m/z): 535.0 (M$^+$).

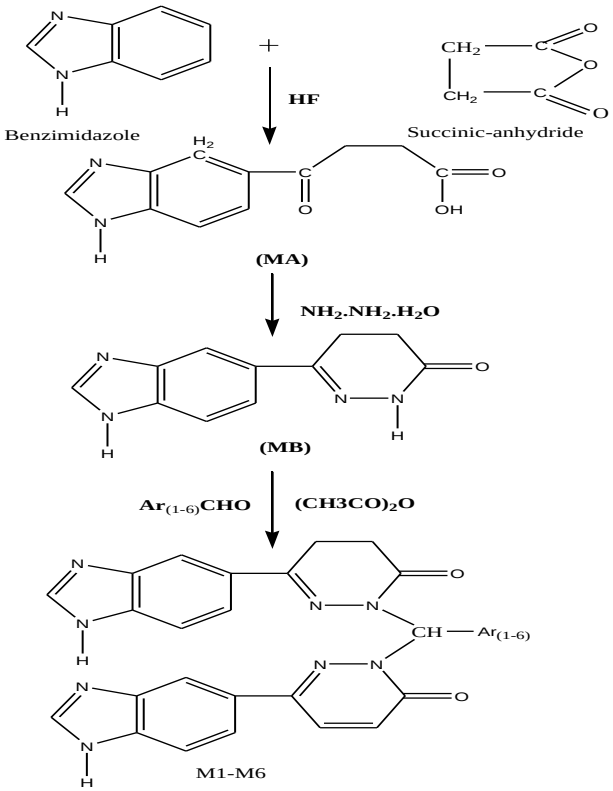
Synthesis of m- chloro Phenyl di-[6-(1-H-benzo[d] imidazole-5-yl)- pyridazine-3-one-2yl] methane (M-3) Yield: 55% ; m.p. 157-158^{0}C ; R_f 0.42. Spectroscopic analysis: IR (cm^{-1}): 3435.1 (NH, aromatic), 2963.9 (C-H), 1687.4 (C=O), 1633.9 (C=N), 1302.0 (C-N), 711.3 (C-Cl); ^{1}H-NMR (DMSO, 400 MHz, δ, ppm): 12.36 (d, 2H, N-H), 8.19 (d, 2H,NH-CH), 7.67-8.06 (m, 6H, Ar-H), 7.26-7.43 (m, 5H, Ar-H), 6.91 (s, 1H, Al-H), 6.43 (d, 2H, Ar-H) 5.79 (d, 2H, Ar-H); MS (m/z): 543.0 (M$^+$).

Synthesis of m- nitro Phenyl di-[6-(1-H-benzo[d] imidazole-5-yl)- pyridazine-3-one-2yl] methane (M-4) Yield: 65% ; m.p. 132-133^{0}C ; R_f 0.82. Spectroscopic analysis: IR (cm^{-1}): 3428.6 (NH, aromatic), 2988.5 (C-H), 1656.7 (C=O), 1631.8 (C=N), 1513.5 (NO_2, aromatic asymmetric), 1378.5 (NO_2, aromatic symmetric); ^{1}H-NMR (DMSO, 400 MHz, δ, ppm): 12.36 (d, 2H, N-H), 8.19 (d, 2H,NH-CH), 7.54-8.49 (m, 4H, Ar-H), 7.27-7.42 (m, 5H, Ar-H), 6.91 (s, 1H, Al-H), 6.39 (d, 2H, Ar-H) 5.79 (d, 2H, Ar-H); MS (m/z): 556.0 (M$^+$).

Synthesis of o- nitro Phenyl di-[6-(1-H-benzo[d] imidazole-5-yl)- pyridazine-3-one-2yl] methane (M-5) Yield: 62% ; m.p. 140-141^{0}C ; R_f 0.56. Spectroscopic analysis: IR (cm^{-1}): 3428.6 (NH, aromatic), 2988.5 (C-H), 1656.7 (C=O), 1631.8 (C=N), 1513.5 (NO_2, aromatic asymmetric), 1378.5 (NO_2, aromatic symmetric); ^{1}H-NMR (DMSO, 400 MHz, δ, ppm): 12.36 (d, 2H, N-H), 8.19 (d, 2H,NH-CH), 7.57-8.06 (m, 10H, Ar-H), 6.91 (s, 1H, Al-H), 6.39 (d, 2H, Ar-H) 5.79 (d, 2H, Ar-H); MS (m/z): 556.0 (M$^+$).

Synthesis of o- hydroxy Phenyl di-[6-(1-H-benzo[d] imidazole-5-yl)- pyridazine-3-one-2yl] methane (M-6) Yield: 60% ; m.p. 122-123^{0}C ; R_f 0.48. Spectroscopic analysis: IR (cm^{-1}): 3422.8 (NH, aromatic), 3369.0 (O-H) 2932.0 (C-H), 1679.7 (C=O), 1620.9 (C=N), 1387.8 (C-N); ^{1}H-NMR (DMSO, 400 MHz, δ, ppm): 12.36 (d, 2H, N-H), 9.68 (d, 1H, OH), 8.19 (d, 2H, NH-CH), 7.26-8.06 (m, 11H, Ar-H), 6.91 (s, 1H, Al-CH), 6.39 (d, 2H, Ar-H) 5.79 (d, 2H, Ar-H); MS (m/z): 556.0 (M$^+$).

Reaction Scheme



[Ar_1-C_6H_5, Ar_2-p-$C_6H_5OCH_3$, Ar_3- m-C_6H_5Cl, Ar_4-m-$C_6H_5NO_2$, Ar_5-o-$C_6H_5NO_2$, Ar_6-o-C_6H_5OH]

Anticonvulsant Activity

Animals: Male albino mice (Swiss strains) weighing between 25-35 g were used in the study. They were housed in standard laboratory condition for a week before the experiments. Animals were housed in polypropylene cage with dust free rice husk as bedding material under laboratory condition with controlled environment of temperature (25°C ± 2°C) and humidity (60% ± 10%). The animals were fasted over night. The animals were transferred to the laboratory 1 hr before starting experiment. The institutional ethical committee approved the study. Experiments were conducted between 9-14 h. Each mouse was used only once.

Maximal Electro-Shock-Induced Convulsion (MES): The anticonvulsant activity was performed by using MES method as reported (Krall et al.) on male Swiss albino mice (25-35 g). Animals were divided into different groups (control, test and standard) containing 5 animals each. The test samples (100 mg/kg) and phenytoin sodium (25 mg/kg) as a standard anticonvulsant drug were administered orally. Control animal received distilled water one hour prior to induction of convulsion. The mice were subjected to supramaximal electroshock of current intensity 60 mA, 50 Hz for 0.2 sec duration by electro-convulsometer through ear electrodes. The duration of tonic hind limb extensor phase and percentage of animal protected from convulsion have been summarised in Table 1. A complete abolition of hind limb extension was considered as 100 % protection.

Statistical Analysis

The values are expressed in mean ± SEM. The results were analysed by using ANOVA followed by student't' test. Statistical significance on comparison with control group are indicated by *mark, ***P<0.001 highly significant, **P<0.01 significant and *P<0.5 moderately significant.

RESULTS AND DISCUSSION

The pyridazinone derivatives MA, MB, M-1toM-6 were synthesized according to scheme 1 by friedel-crafts acylation of appropriate hydrocarbons with succinic anhydride in the presence of hydrofluoric acid chloride. The desired derivatives (M-1 to M-6) were produced. From the anticonvulsant screening data it has been found that M-2 and M-6 possess excellent anticonvulsant activity on the basis of extensor phase. M-1 and M-2 have hydrogen bonding property and electron withdrawing group at ortho and para position respectively, while M-4 possess meta electron withdrawing group and has minimum activity in this group. Thus we can conclude that anticonvulsant activity is increasing by substitution with orto and para directing electron withdrawing group, while decreasing with meta directing electron withdrawing group.

FIGURE 1 : EXTENSOR PHASE SHOWN BY DIFFERENT DERIVATIVES, STANDARD AND CONTROL DRUGS

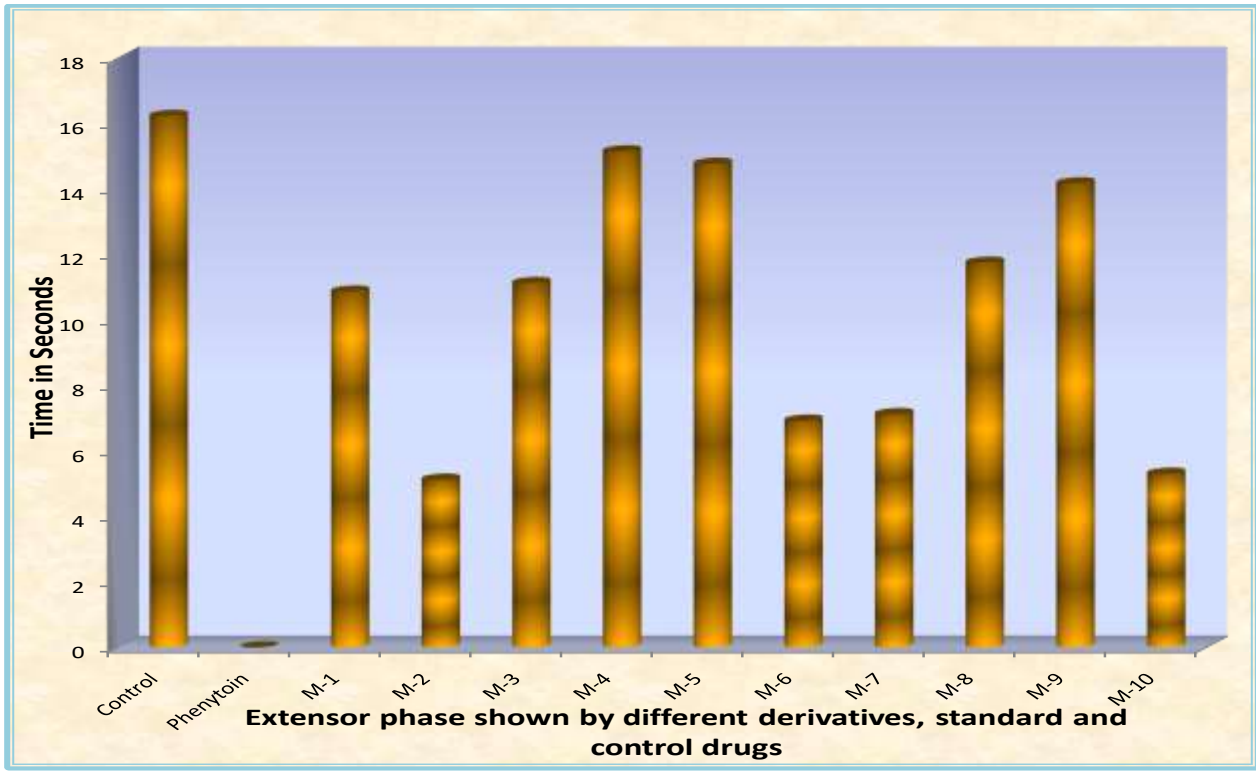


Table 1: Anticonvulsant activity of Pyridazinone derivatives

Group (n=5)	Treatment Dose (100 mg/kg)	Flexion mean + SEM (sec.)	Extensor mean +SEM (sec.)	Clonus mean +SEM (sec.)	Stupor mean +SEM (sec.)	R/ D
1.	Control	3.72 ± 1.45	16.22 ± 1.45	7.84 ± 0.74	52.6 ± 8.12	40 % R
2.	Phenytoin	1.13 ± 0.045	0.00 ± 0.00	1.67 ± 0.212	7.18 ± 0.561	100 % R
3.	M-1	2.08 ± 0.216	10.86 ± 1.32	4.08 ± 1.13	35.46 ± 4.12	60 % R
4.	M-2	2.5 ± 0.402	5.12 ± 0.625	4.12 ± 0.735	22.12 ± 2.27	80 % R
5.	M-3	2.82 ± 0.295	11.12 ± 1.18	3.86 ± 0.512	28.21 ± 8.12	60 % R
6.	M-4	2.11 ± 0.110	15.14 ± 1.28	5.12 ± 1.41	28.92 ± 7.42	40 % R
7.	M-5	2.18 ± 0.142	14.76 ± 1.42	5.49 ± 1.53	26.62 ± 7.41	40 % R
8.	M-6	1.86 ± 0.108	6.92 ± 1.32	4.12 ± 1.21	24.16 ± 4.92	80 % R

Animals were divided into eight group (1- 8) for studying anticonvulsant effect

n = Number of animals **SEM = Standard error mean** **Standard Drug = Phenytoin sodium (25mg/kg)**

Control = Distilled water **R /D = Recovery/Death**

Table 2: Structure & Physiochemical data of derivatives

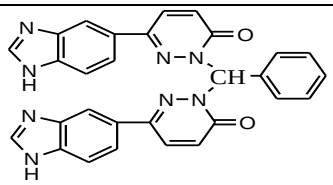
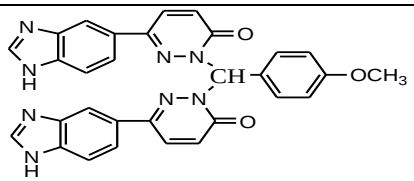
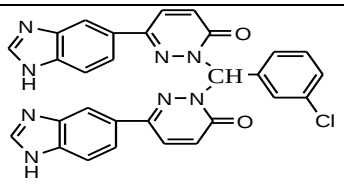
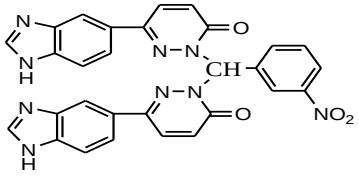
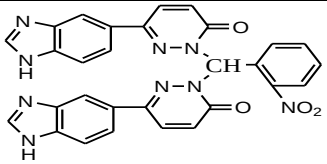
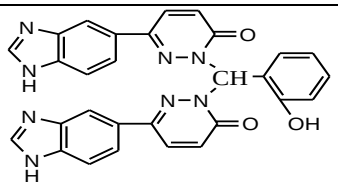
S.No.	Compound	Structure of derivatives	I.U.P.A.C Name	M.P.	Yield %	Rf value
1	M-1		Phenyl di-[6-(1-H-benzo[d] imidazole-5-yl)- pyridazine-3-one-2yl] methane	88°C	65	0.49
2	M-2		p-methoxy Phenyl di-[6-(1-H-benzo[d] imidazole-5-yl)-pyridazine-3-one-2yl] methane	140°C	72	0.52
3	M-3		m-chloro Phenyl di-[6-(1-H-benzo[d] imidazole-5-yl)-pyridazine-3-one-2yl] methane	157°C	55	0.42
4	M-4		m-nitro Phenyl di-[6-(1-H-benzo[d] imidazole-5-yl)-pyridazine-3-one-2yl] methane	132°C	65	0.82
5	M-5		o-nitro Phenyl di-[6-(1-H-benzo[d] imidazole-5-yl)- pyridazine-3-one-2yl] methane	140°C		0.56
6	M-6		o-hydroxy Phenyl di-[6-(1-H-benzo[d] imidazole-5-yl)-pyridazine-3-one-2yl] methane	122°C		0.48

Table 3: Characterization of derivatives

S.No.	Derivatives	IR (cm^{-1})	^{1}H-NMR (δ ppm)	Mass Spectral data (m/z)
1.	M-1	N-H Ar. : 3423.0, C-H Alip.: 2944.0, C=O : 1669.4, C=N : 1620.8	12.36 (2H, d) 8.19 (2H,d), 7.67-8.06 (6H, m), 6.91(1H,s), 6.39 (2H,d) 5.79 (2H,d)	510.0
2.	M-2	N-H Ar. : 3415.0 C-H : 2979.0 C=N : 1625.8 C – N : 1302.0	12.36 (2H, d) 8.19 (2H,d), 7.67-8.06 (6H, m), 6.91(1H,s), 6.39 (2H,d) 5.79 (2H,d), 3.83 (1H, s)	535.0
3.	M-3	N-H Ar. : 3435.1 C –H : 2963.9 C=O : 1687.4 C=N : 1633.9	12.36 (2H, d) 8.19 (2H,d), 7.67-8.06 (6H, m), 6.91(1H,s), 6.43 (2H, d), 5.79 (2H,d)	543.0
4.	M-4	N-H Ar. : 3428.6 C –H : 2988.5 C =O : 1656.7 C=N : 1631.8	12.36 (2H, d) 8.19 (2H,d), 7.54-8.49 (4H, m), 7.27-7.42(5H, m) 6.91(1H,s), 6.39 (2H,d) 5.79 (2H,d)	556.0
5.	M-5	N-H Ar. : 3428.6 C =O : 1662.0 C=N : 1643.2	12.36 (2H, d) 8.19 (2H,d), 7.57-8.06 (10H, m), 6.91(1H,s), 6.39 (2H,d) 5.79 (2H,d)	557.0
6.	M-6	N-H Ar. : 3428.6 O-H Ar. 3369.0 C –H : 2932.0 C =O : 1679.7 C=N : 1620.9 C-N : 1387.8	12.36 (2H, d) 9.68 (2H, s) 8.19 (2H,d), 7.26-8.06 (11H, m), 6.91(1H,s), 6.39 (2H,d) 5.79 (2H,d)	528.0

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