Chemical data of synthesized compounds

**4-(2-chlorophenyl)-6-(3-nitrophenyl) pyrimidin-2-amine (5a)**: MF: $C_{15}H_{11}N_4O_2Cl$; MW: 352.5g/mol; % yield: 52%; MP: 175-178°C; IR ( $V_{max}$ $cm^{-1}$): 3371 (NH), 3000 (ArC-H), 1617 (C=N), 1570 (C=C), 754 (ArC-Cl), 1470 (ArC-$NO_2$); $^1$H NMR: $\delta$ 5.262 (s, 2H, $NH_2$), $\delta$ 6.62-7.47 (m, 8H, Ar-H), $\delta$ 7.86 (s, 1H, C5-H).

**4, 6-bis (4-methoxyphenyl) pyrimidin-2-amine (5b)**: MF: $C_{18}H_{17}N_3O_2$; MW: 307g/mol; % yield:55%; MP: 163-168°C; IR ( $V_{max}$ $cm^{-1}$): 3370 (NH), 3000 (ArC-H), (C=N), 1563 (C=C), 1174, 1239 (ArC-$OCH_3$); $^1$H NMR: $\delta$ 5.188 (s, 2H, $NH_2$), $\delta$ 6.98-7.36 (m, 8H, Ar-H), $\delta$ 8.01 (s, 1H, C5-H), 3.87 (d, 6H, $OCH_3$).

**4-[4-(dimethyamino) phenyl]-6-(2-methoxyphenyl) pyrimidin-2-amine (5c)**: MF: $C_{19}H_{20}N_4O$; MW: 320g/mol; % yield: 51%; MP: 215-218°C; IR ($V_{max}$ $cm^{-1}$): 3300(Ar-NH), 1060,1126,1243($OCH_3$), 1608,1673(C=N), 1570(C=C), 1525(CH=CH), 1357($NH_2$); $^1$H NMR: $\delta$ 5.05 (s, 2H, $NH_2$), $\delta$ 6.48-7.43 (m, 8H, Ar-H), $\delta$ 7.95 (s, 1H, C5-H), $\delta$ 3.88 (d, 3H, $OCH_3$), 2.79 (s, 6H, -$N(CH_3)_2$).

**4-(4-chlorophenyl)-6-(2-nitrophenyl) pyrimidin-2-amine (5d)**: MF: $C_{15}H_{11}N_4O_2Cl$; MW: 352.5g/mol; % yield:78%; MP:179-185°C; IR ($V_{max}$ $cm^{-1}$): 3366 (NH), 3090 (ArC-H), (C=N), 1568 (C=C), 710, 790 (ArC-Cl), 1492 (ArC-$NO_2$); $^1$H NMR: $\delta$ 5.202 (s, 2H, $NH_2$), $\delta$ 6.80-7.46 (m, 8H, Ar-H), $\delta$ 7.93 (s, 1H, C5-H).

## CONCLUSION

The overall results of the present work reflect a preliminary stage in developing of pyrimidine derivatives in targeting microbial cells. The probable mechanism of action against the microorganisms of the drug can be characterized by further studies. Moreover, to bring these molecules from laboratory to patients more scientific study should be done.


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# SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL SCREENING OF SOME NOVEL PYRIDAZINE DERIVATIVES


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## ABSTRACT

A series of 2-substituted phenyl-10H-Pyridazine (6, 1-b) quinazoline-10-one (**d-i-vii**) were synthesized. These compounds were evaluated for their anticonvulsant activity. Compound **d-iii**, and **d-v** showed 100% protection. Compound **d-i**, **d-iv**, and **d-vi** showed 66.67% protection and compound **d-vii** showed 83.33% protection. Anticonvulsant activity of these compounds was compared with phenytoin.



**Key words:** 2-substituted pyridazine, anticonvulsant, pyridazinones.


## INTRODUCTION

The pyridazine ring system is a 1,2-diazine or o-diabenzene. The name pyridazine was suggested by Knorr[1], however, the first substituted pyridazines were prepared in 1886 by Fischer[2], and pyridazine itself was prepared by Tauber[3] in 1895. During last two decades numbers of pyridazine/ pyridazinones have been synthesized due to their effect on cardiovascular system pyridazine/pyridazinone derivatives were reported to exhibit lots of pharmacological activities such as anti-inflammatory[4], antibacterial[5], antithrombotic[6], antihypertensive[7], hypotensive[8], cardiotonic[9], diuretic[10] and anti-HIV[11] activities. A lot of work have been done on pyridazine/pyridazinones in the last few years for their various pharmacological activities and anticonvulsant activity[16] also. In continuation to the work on pyridazine/pyridazinone ring system, we have synthesized some new pyridazine derivatives and evaluated them for anticonvulsant activity by non-invasive methods.

## EXPERIMENTAL SECTION

**(i) Synthesis of $\alpha$-benzoyl propionic acid (a)**: After suspending anhydrous aluminium chloride (15 gm.) in dry benzene (50 ml) under anhydrous conditions, the contents were refluxed on a water bath. Succinic anhydride (10 gm) then added in small proportion through the condenser (care should be taken that after adding each lot, the second lot was added only when first lot reacted completely). After complete addition, the reaction mixture was refluxed for 6 hours. A solution of conc. Hydrochloric acid (2.5ml) in ice –cold water (7.5ml) was then added to the reaction mixture and the contents concentrated to a small volume by heating on a water bath. On cooling a crystalline compound separated out which was filtered and re-crystallized from water to give a colorless compound.

**(ii) Synthesis of 6-phenyl 2,3,4,5-tetrahydropyridazine-3-one (b)**: To a solution of $\alpha$-benzoyl propionic acid in methanol (30 ml) was added hydrazine hydrate(1ml) and sodium acetate (0.5 gm) and the contents were refluxed for 6 hours. After completion of the reaction, methanol was distilled off and residue poured into cold water. The solid which separated out, was filtered and re-crystallized from methanol.

**(iii) Synthesis of 3-chloro-6-phenylpyridazine (c)**: To a solution of 6-phenyl 2,3,4,5-tetrahydropyridazine-3-

one (1 gm) phosphorous oxy chloride (10 ml) was added. Mixture was heated for 6 hours. After completion, the reaction mixture was poured into crushed ice. The solution was neutralized with NaOH. The compound was filtered and washed with water and re-crystallized with ethanol.

**(iv) Synthesis of 2-phenyl-10H-pyridazine (6, 1-b) quinazolin-10-one (d):** The equimolar quantity of 3-chloro-6-phenylpyridazine and anthranilic acid were taken in methanol. The contents were heated for 1 hour to concentrate the mixture and poured into the crushed ice. Product was filtered and washed with water, re-crystallized with ethanol.

### Anti convulsant 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 [12]. 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 weight.

Compounds d-iii, d-v showed 100% protection while compounds d-i, d-iv, d-vi showed 66.67% protection and compound d-vii showed 83.33% protection against convulsion (Table 1).

## RESULT AND DISCUSSION

The series of compounds 2-substituted-10H-pyridazine(6,1-b)quinazoline-10-one was synthesized in the following steps, illustrated with the synthesis of compound 'd'. The $\alpha$-benzoyl propionic acid (a) was synthesized by Friedel Craft acylation of benzene with succinic acid in the presence of Lewis acid, aluminium chloride. The IR spectrum of acid showed band at 3428 and 1679 $cm^{-1}$ indicating the presence of carboxylic acid group. The $^1$H-NMR spectrum showed triplet at ä 2.59 and 3.23 for $CH_2$, $CH_2CO$ respectively. The aromatic protons appear at 7.53 to 7.95 as multiplet. The carboxylic Protons appeared at ä 12.17. The condensation of carboxylic acid with hydrazine hydrate gave 6-phenyl-2,3,4,5-tetrahydro pyridazinone (b). The compound was TLC pure. The IR spectrum showed the presence of two bands at 3206 and 1676 $cm^{-1}$ indicating the presence of amide group. The 1H-NMR spectrum showed the two triplet at ä 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 protons appeared at ä 9.50. The 3-chloro-6-phenylpyridazine (c) was synthesized by reaction of compound (b) with phosphorous oxy chloride. The compound was TLC pure and different from the starting material. The IR spectrum showed bands at 3000 and 1600 for C-H stretching and double bond. The 1H-NMR spectrum showed aromatic protons in the region of 7.31 (multiplet), 7.59 (multiplet) and 7.83 (singlet). The 2-phenyl-10H-pyridazine (6,1-b)quinazoline-10-one (d) was synthesized by condensation of compound c with anthranilic acid. The IR spectrum showed bonds at 2997$cm^{-1}$, 1672$cm^{-1}$ and 1588 $cm^{-1}$ for CH stretching, carbonyl functional group and double bond. The $^1$H-NMR spectrum showed aromatic protons at $\delta$ 6.47-7.66 as multiplet. The structure was further verified by MASS 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. A series, 2-substituted-10H-pyridazine (6,1-b) quinazoline-10-one was synthesized, which was illustrated with the synthesis of compound 'd'. All the synthesized compounds were TLC pure. These synthesized compounds were characterized by IR, 1H-NMR, and Mass Spectroscopy. The physical data of the synthesized compounds are given in Table 2.

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[12] (Maximal Electroshock Seizure) method[17]. 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) dose after 1 hour recorded in the Table 1. Phenytoin was used as the reference drug showed 100% inhibition at a dose of 25 mg/kg animal body weight.

Compounds d-iii and d-v showed 100% protection while compound d-vii showed 83.33% protection and compounds d-I, d-iv and d-vi showed 66.67% protection against convulsion and compound d-ii showed minimum protection towards convulsion as compared to phenytoin.



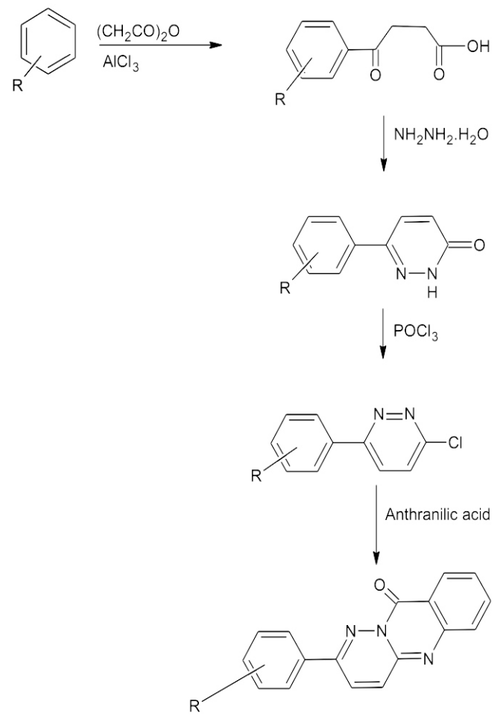
Table 1: Anticonvulsant Activity

| S. No. | Compound No. | R | Anticonvulsant Activity MES (60 min) % Protection |
|---|---|---|---|
| 1 | d-i | H | 66.67 |
| 2 | d-ii | $CH_3$ | 33.33 |
| 3 | d-iii | 3,4-$CH_3$ | 100 |
| 4 | d-iv | $C_2H_5$ | 66.67 |
| 5 | d-v | p-Cl | 100 |
| 6 | d-vi | p-$OCH_3$ | 66.67 |
| 7 | d-vii | $C_6H_5$ | 83.33 |
| 8 | Standard | Phenytoin | 100 |

Table 2: Physical data of compound d i-vii

| S.No | Compound | R | M.P ($^0$C) | Yield (%) |
|---|---|---|---|---|
| 1 | d-i | H | 140-42 | 59 |
| 2 | d-ii | $CH_3$ | 139-41 | 51 |
| 3 | d-iii | 3,4-$CH_3$ | 158-61 | 63 |
| 4 | d-iv | $C_2H_5$ | 133-32 | 53 |
| 5 | d-v | Cl | 119-21 | 55 |
| 6 | d-vi | $OCH_3$ | 126-27 | 65 |
| 7 | d-vii | $C_6H_5$ | 138-40 | 41 |

## REACTION SCHEME

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