**In-vivo Anticonvulsant and In-vitro Antimycobacterial Activities of 6-Aryl Pyridazine-3(2H)-One Derivatives**

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Received February 26, 2013; Revised May 12, 2013; Accepted January 06, 2014

**Abstract** Some 6-aryl-4,5-dihydropyridazin-3(2H)-one compounds (2a-f) were synthesized and evaluated for their in-vivo anticonvulsant activities against maximal electro shock (MES) and isoniazid (INH) induced seizure methods at 50mg/kg dose level. Neurotoxicity of all compounds (2a-f) was also tested at 50, 100 and 200mg/kg dose level. The in-vitro antitubercular activity was evaluated against *Mycobacterium tuberculosis* H37Rv by using the Microplate Alamar Blue Assay (MABA) method. The result showed that all compounds (2a-f) showed significant anticonvulsant activity against both MES and INH induced convulsion methods. Among all compounds (2a-f), highest activity was exhibited by compound 2e against MES and compound 2b against INH-induced convulsion methods. In both methods, phenytion sodium (25mg/kg) and sodium valproate (50mg/kg) were used as reference drugs. All compounds did not showed any neurotoxicity up to 200mg/kg dose level. In antitubercular activity, minimum inhibitor concentration of compound 2e and 2f was 12.5μg/ml and other remaining compounds (2a-d) were showed 25μg/ml when compared with reference drugs Isoniazid (3.12μg/ml), Pyrizinamide (3.12μg/ml) and Streptomycin (6.25μg/ml).

**Keywords:** anticonvulsant, antituberculosis, nephrotoxicity, pyridazinone

**Cite This Article:** Mohammad Asif, Anita Singh, and Lakshmayya, “In-vivo Anticonvulsant and In-vitro Antimycobacterial Activities of 6-Aryl Pyridazine-3(2H)-One Derivatives.” *American Journal of Pharmacological Sciences* 2, no. 1 (2014): 1-6. doi: 10.12691/ajps-2-1-1.

1. Introduction

Pyridazinones belong to an important six member heterocyclic compounds. A lot of research has been done on pyridazinone compounds, these compounds gives out almost all types of biological activities. Large numbers of pyridazinone compounds are exhibits diversified pharmacological activities. In recent years, substantial number of 6-arylpyridazi-3(2H)-one none have been reported to possess various activities like, antimicrobial, analgesic, anti-inflammatory, antiifeedant, antiadibetic, herbicidal, antiplatelet activities, anticancer effects, antitubercular, antidepressant, antithrombotic, diuretics, anti-HIV, antifungal, antipyretics, neurological disorders, cardio tonic, antihypertensive, myocardial imaging agent, anticonvulsant, anti-asthamatic, antidepressant, anxiolytic and other anticipated activities [1,2]. Some pyridazinone derivatives are used as drugs and already appeared in the clinical market, these drugs are mainly indolidan, bemoradan, primobendan, levosimendan (antihypertensive), minaprine (antidepressant), emorfazone (antiinflammatory), and azanrinone (cardiotonic) [3]. Large numbers of pyridazinone derivatives are also well known as chemical intermediates for drugs synthesis and agrochemicals.

Epilepsy is a brain disorder, in which clusters of nerve cells, or neurons in the brain and normal pattern of neuronal activity becomes disturbed causing strange sensations, emotions, and behaviors or sometimes convulsions, muscle spasms, and loss of consciousness. Anticonvulsant drugs are important for the treatment of epilepsy [4]. Once epilepsy is diagnosed, it is important to begin treatment as soon as possible because seizures can be controlled with modern medicines and surgical techniques in about 80% of patients who’s diagnosed with epilepsy [5].

Tuberculosis (TB), is an infectious disease caused by *Mycobacterium tuberculosis*. TB is the one of primary cause of mortality in the world. *Mycobacterium* is ubiquitos organism that is becoming increasingly important intracellular pathogens that establish an infection in oxygen rich macrophage of the lung. The emergence of AIDS, decline of socioeconomic standards and a reduced emphasis on TB control programs contribute to the disease’s resurgence [6]. Resistance of *M. tuberculosis* strains to anti-TB drugs is an increasing problem worldwide. In spite of severe toxicity on repeated dosing of first line drugs like, isoniazid (INH), rifampicin, streptomycin (STR), pyrizinamide (PZ) and ethambutol for chemotherapy of TB [7].

The current work described the synthesis of 6-arylpyridazin-3(2H)-one derivatives and evaluated them for anticonvulsant activity against maximum electro shock
2. Material and Methods

2.1. Chemistry

All title compounds (2a-f) were synthesized according to Scheme 1. All chemicals were used for synthesis of title compounds was purchased from Central drug house (CDH), Loba Chem, High media, SD-fine, India. Melting points of all synthesized compounds were determined by open tube capillary method and were uncorrected. Purity of the compounds were checked by thin layer chromatography (TLC) plates (silica gel G) and toulene, ethylacetatoacetate and formic acid (4:5:1 ratio) was used as mobile phase, the spot of synthesized compounds were visualized by exposing to iodine vapors and UV light. The FT-IR spectra were recorded on Bio-rad FTS-135 spectrophotometer using KBr pellets; ymax values are given in cm⁻¹. 1H NMR spectra were recorded on Bruker Spectrosin DPX 300 MHz using CDCl₃ as solvent and tetra methyl silane (TMS) was used as an internal standard and chemical shifts are given in d (ppm) scale.

![Scheme 1](image)

**Scheme 1. Protocol for the synthesis of 6aryl-4,5-dihydropyridazinones**

**2.1.1. Synthesis of β-aryl propionic acids (1a-f)**

**2.1.1.1. Synthesis of β-benzoyl propionic acid (1a)**

To a solution of β-benzoyl propionic acid (1a) (0.10mol) was then added to the reaction mixture in small portions with continuous stirring and heating were continued for 6h. The reaction mixture then was left overnight at room temperature and then added ice cold solution of conc. HCl acid (2.5% v/v) to make acidic mixture [8,9]. The mixture was concentrated to a small volume by heating on a water bath then precipitates were formed and separated by filtration. It was purified by dissolving in 5% w/v sodium bicarbonate solution, followed by extraction with ether. The aqueous layer on acidify with dil. HCl acid gave crude benzoyl-propionic acids. It was crystallized from aqueous ethanol to give a colorless compound. Melting point: 1250°C, yield 65%, Rₚ value 0.35, Molecular formula: C₉H₈O₃, molecular weight 178, melting point: 125°C; 70% yield; IR (cm⁻¹) 3133.5 (OH), 1705 (C=O); 13C NMR (CDCl₃) (ppm): 28.34, 29.27, 128.28, 129.10, 140.0, 155.6, 161.2, 1H NMR (CDCl₃) (ppm): 20.9, 27.1, 35.6, 128.2, 129.3, 128.9, 129.10, 133.66, 133.89, 174.06, 174.28, 198.96, MS (m/z): 175 (M⁺). All the remaining acids (1b-f) were synthesized by analogous procedure with minor modification in temperature of reaction and use of nitrobenzene as a solvent.

**2.1.2. Synthesis of 6-Aryl-4,5-Dihydropyridazin-3(2H)-One Derivatives (2a-f)**

**2.1.2.1. Synthesis of 6-Phenyl-4,5-Dihydropyridazin-3(2H)-One (2a)**

To a solution of β-benzoyl propionic acid (1a) (0.1mol) in methanol (30ml), hydrazine hydrate (1ml) and sodium acetate (0.5g) were added and the mixture was refluxed for 6h. After completion of the reaction, methanol was distilled off and the content was poured into cold water. The solid that separated out was filtered and crystallized from methanol [8,9]. Melting point: 250°C, yield 72 %, Rₚ value 0.45, molecular formula C₁₀H₁₂N₂O, molecular weight 174.19, melting point: 250°C, yield: 72%, Rₚ value 0.45. 3290 (NH), 1660 (C=O); 13C NMR (CDCl₃) (ppm): 22.35, 26.41, 126.08, 128.95, 129.74, 149.9, 1167.48, 1H NMR (CDCl₃) (ppm): 2.62 (t, 2H, CH₂-C-C₆H₅), 3.3 (t, 2H, CH₂-aryl), 7.41 (m, 3H, Ar -H₃', Ar-H₅'), 12.17 (s, 1H, COOH), 1H NMR (CDCl₃) (ppm): 2.38 (s, 3H, CH₃), 2.60 (m, 2H, CH₂-aryl), 7.26 (t, 2H, Ar-H₂', Ar-H₆'), 7.63 (d, 2H, Ar-H₂', Ar-H₆'), 8.79 (s, 1H, NH), MS (m/z): 175 (M⁺).

**2.1.2.2. Synthesis of 6-(4-Methylphenyl)-4,5-Dihydropyridazin-3(2H)-One (2b)**

M.P: 151°C, yield 70%, Rₚ value 0.70, Molecular formula C₁₄H₁₂N₂O, molecular weight 188.22, melting point: 151°C; yield: 70%; Rₚ value 0.70. IR: (KBr, cm⁻¹): 1658.8(C=O), 3217.4 (NH), 1510.8 (C=N), 13C NMR (CDCl₃) (ppm): 20.9, 27.1, 35.6, 128.2, 129.3, 128.9, 140.0, 155.6, 161.2, 1H NMR (CDCl₃) (ppm): 2.38 (t, 2H, CH₂, 1H, CH₃), 2.60 (m, 2H, CH₂-aryl), 7.26 (t, 2H, Ar-H₂', Ar-H₆'), 7.63 (d, 2H, Ar-H₂', Ar-H₆'), 8.79 (s, 1H, NH), MS (m/z): 189 (M⁺).

**2.1.2.3. Synthesis of 6-(2-Naphthyl)-4,5-Dihydropyridazin-3(2H)-One (2c)**

M.P: 151°C, yield 70%, Rₚ value 0.70, Molecular formula C₁₄H₁₂N₂O, molecular weight 224.22, IR Spectra: 3091 cm⁻¹ (CH), 1705 cm⁻¹ (C=O), 1617 cm⁻¹ (C=C), 13C NMR (CDCl₃) (ppm): 27.1, 35.6, 125.9, 126.4, 128.0, 128.1, 128.5, 135.9, 133.7, 155.6, 162.2 1H NMR (CDCl₃) (ppm): 2.8 (t, 2H, CH₂-CO), 3.0 (t, 2H, CH₂-aryl), 7.30- 8.2 (m, 7H, Ar-H), 8.82 (s, 1H, NH), MS (m/z): 225 (M⁺).
2.1.2.4. Synthesis of 6-(4-Ethylphenyl)-4,5-Dihydropyridazin-3(2H)-One (2d)

M.P: 119°C, yield 70%, Rf value 0.73, Molecular formula C17H14N2O, molecular weight 202.25, melting point: 119°C, yield 70%, Rf value 0.73. IR: (KBr, cm⁻¹): 1665.8 (C=O), 3427.7 (NH), 1595.3 (C=N), 1H NMR (CDCl₃) (ppm): 2.34 (t, 2H, -CH₂-CH₃), 2.65 (m, 2H, -CH₂-CO), 3.01 (t, 2H, -CH₂-aryl), 7.26 (d, 2H, Ar-H3', Ar-H5'), 7.65 (d, 2H, Ar-H2', Ar-H6'), 8.54 (s, 1H, NH), MS (m/z): 202 (M+1).

2.1.2.5. Synthesis of 6-(3,4-Dimethylphenyl)-4,5-Dihydropyridazin-3(2H)-One (2e)

M.P: 162°C, yield 50%, Rf value 0.50, Molecular formula C17H16N2O, molecular weight 202.25, melting point: 162°C, yield 50%, Rf value 0.50. IR: (KBr, cm⁻¹): 1660.6 (C=O), 3218.0 (NH), 1507.9 (C=N), 1H NMR (CDCl₃) (ppm): 2.38 (s, 3x3H, 2xCH₃), 2.63 (t, 2H, CH₂-CO), 3.01 (t, 2H, CH₂-aryl), 7.44 (d, 1H, Ar-H5'), 7.65 (d, 1H, Ar-H6'), 8.72 (s, 1H, NH), MS (m/z): 203 (M+1).

2.1.2.6. Synthesis of 6-(1,1'-Biphenyl-4-yl)-4,5-Dihydropyridazin-3(2H)-One (2f)

M.: 240°C, yield 90%, Rf value 0.72, Molecular formula C₂₀H₁₆N₂O, molecular weight 250, melting point: 240°C, yield 90%, Rf value 0.72. IR: (KBr, cm⁻¹): 3250 (NH), 1700 (C=O); 1H NMR (CDCl₃) (ppm): 2.7 (t, 2H, CH₂-aryl), 2.98 (t, 2H, CH₂-aryl), 7.41-7.9 (m, 9H, Ar-H), 8.94 (s, 1H, NH), MS (m/z): 251 (M+1).

3. Pharmacology

3.1. Experimental Animals

Swiss albino mice (Swiss, 20-30g) of either sex were used. The mice were kept at room temperature (25-30°C) on an adequate diet and allowed free access to food and water except during the short time they were removed from the cages for testing. All the experimental protocols were carried out with the permission from Institutional Animal Ethics Committee (IAEC). Animals were obtained from the Animal House, GRD (PG) IMD, Dehradun, India. The test compounds 2a-f were suspended in 0.5% carboxyl methyl cellulose (CMC) and distilled water mixture. In preliminary screening, each compound was administered through an i.p. injection at dose level (50mg/kg body mass) and the anticonvulsant activity was assessed after 0.5 h of administration.

3.2. Anticonvulsant Screening

3.2.1. Maximum electroshocks (MES) method

The anticonvulsant evaluations of the test compounds (2a-2f) were performed according by the anticonvulsant drug development protocol [10,11]. Albino mice were stimulated through corneal electrodes to 50mA current at a pulse of 60Hz applied for 0.20s. Animals were previously given the test drug i.p. Abolition of the hind limb tonic extension spasm was recorded as the anticonvulsant activity. The test compounds were suspended in 0.5% CMC in distilled water. In preliminary screening, each compound was administered through an i.p. injection at dose levels (50mg/kg) and the anticonvulsant activity was assessed after 0.5h of administration. The anticonvulsant efficacy was evaluated by the maximal electroshock-induced seizure (MES) and data are presented in Table 3.

3.2.2. Isoniazid (INH) Induced Seizures Method:

Isoniazide (INH) induced seizures test was performed on mice (25-30g). The mice were injected with test drug 50 mg/kg i.p. After 30 min, INH injection of dose 250mg/kg was given i.p. The sequence of seizure latency, seizure duration and % protection were studied. Animals exhibiting these seizures pattern were detected. The standard drug used in this model was sodium valproate (50mg/kg) [12,13].

3.2.3. Neurotoxicity Screening

Activity of the drug interfering with motor coordination was checked by the rotorod test [14] and mice were trained to stay on the rotorod before experiment. The rod was rotated by 10 rotations min⁻¹ and its diameter was 3.2cm. Normal mice could maintain equilibrium on the rotating rod for long periods of time. The test compounds 2a-f were injected i.p. at three doses of 50, 100 and 200mg/kg body mass and measure the effect of the test drugs. Neurotoxicity of compounds was indicated by the inability of the animal to maintain equilibrium on the rod for at least one minute in each of the three trials. Mice lost their balance due to their skeletal muscle relax effect of the drug.

3.2.4. Anti-TB Activity by Using Microplate Alamar Blue Dye (MABA) Test

The anti mycobacterial activity of synthetic compounds (2a-f) were assessed against M. tuberculosis using microplate Alamar Blue Assay (MABA). This methodology is non-toxic, uses a thermally stable reagent and shows good correlation with proportional and BACTEC radiometric method. Briefly, 200µl of sterile deionized water was added to all outer perimeter wells of sterile 96 wells plate to minimized evaporation of medium in the test wells during incubation. The 96 wells plate received 100µl of the Middle brook 7H9 broth and serial dilution of compounds was made directly on plate. The final drug concentrations 2a-f tested were 100 to 0.2µg/ml. Plates were covered and sealed with paraffilm and incubated at 37°C for five days. After this time, 25µl of freshly prepared 1:1 mixture of Almar Blue reagent and 10% tween 80 was added to the plate and incubated for 24 hrs. A blue color in the well was interpreted as no bacterial growth, and pink color was scored as growth. The MIC was defined as lowest drug concentration which prevented the color change from blue to pink [15].

4. Statistical Evaluation

All the values were reported as mean ± S. E. M. Statistical analysis was performed using one-way analysis of variance (ANOVA). If the overall p-Value was found statistically significant (p < 0.05), further comparisons among groups were made according to Tukey’s test.

5. Results and discussion
5.1. Chemistry

The 6-aryl-4,5-dihydro-pyridazinone compounds (2a–f) are described in this study, and a reaction sequence for the preparation is outlined in Scheme 1. The title compounds 2a–f were prepared by reacting appropriate aromatic hydrocarbons with succinic anhydride in presence lewis acid by conventional Friedal-Craft acylation to formed appropriate aroyl-proponic acids (1a–f). Compounds (1a–f) were react with hydrazine hydride in presence of sodium acetate and ethanolic solution (reaction time varies from 4 to 6h) to formed titled compounds 2a–f (65–90% yield value) and re-crystallized with ethanol. The purity of the compounds was checked by TLC and spectral analysis. Spectral data of Infrared spectra (IR), nuclear magnetic resonace (NMR) and mass spectra (MS) of all the synthesized compounds was in full agreement with the resonance (NMR) and mass spectra (MS) of all the compounds showed moderate anticonvulsant activities (p < 0.001) as they showed protection at the dose of 50 mg/kg. In general it was observed that the extensor phase of convulsion is used determine the anticonvulsant activity against MES method. Compound 2e was more active than the other derivatives. The order of activity was 2e > 2b > 2c > 2f > 2a > 2d. The promising nature of the compounds may be attributed to the substitutions at the pyridazinone ring.

Table 1. Anticonvulsant effect of pyridazinone compounds (2a–f) against isoniazid (INH) induced seizures

| S. No. | Groups | Seizure latency (sec) | Seizure duration (sec) | % of protection |
|-------|--------|-----------------------|------------------------|----------------|
| 1     | Control | 165.7 ± 5.64          | 64.2 ± 3.35            | 00             |
| 2     | 2a      | 2316 ± 116.3          | 13.4 ± 1.07            | 40             |
| 3     | 2b      | 2400 ± 15.81          | 03 ± 1.26              | 80             |
| 4     | 2c      | 2740 ± 102.9          | 16.8 ± 1.06            | 60             |
| 5     | 2d      | 2450 ± 76.37          | 7.3 ± 1.7              | 80             |
| 6     | 2e      | 2366 ± 101.38         | 09 ± 1.52              | 80             |
| 7     | 2f      | 2520 ± 58.31          | 25.6 ± 0.67            | 50             |
| 8     | Sod. valproate | 130.2 ± 2.15         | 7.3 ± 1.4              | 80             |
| 9     | Phenytoin sodium | 3050 ± 50.00         | 03 ± 1.00             | 100            |

Table 2. Anticonvulsant effect of pyridazinone derivatives against MES induced seizures

| Group (n=5) | Flexion (sec) | Extensor (sec) | Clonus (sec) | Stupor (sec) | Recovery time (sec) |
|------------|---------------|---------------|--------------|-------------|---------------------|
| Control (0.5% CMC) | 6.84 ± 0.10 | 16.17 ± 0.50 | 16.48 ± 0.29 | 29.3 ± 1.66 | 225.9 ± 9.61 |
| 2a | 6.08 ± 0.10 | 12.44 ± 0.43 | 14.23 ± 0.52 | 21 ± 1.01 | 192 ± 12.03 |
| 2b | 5.1 ± 0.20 | 11.5 ± 0.54 | 11.75 ± 0.70 | 20.58 ± 1.45 | 191.2 ± 6.64 |
| 2c | 4.98 ± 0.17 | 11.66 ± 0.57 | 11.34 ± 0.53 | 21.3 ± 1.23 | 173.2 ± 6.74 |
| 2d | 4.3 ± 0.14 | 12.55 ± 0.37 | 9.68 ± 0.66 | 20.47 ± 1.69 | 139 ± 4.54 |
| 2e | 3.9 ± 1.70a | 10.82 ± 0.73c | 9.62 ± 0.60c | 21.02 ± 1.83b | 196.5 ± 7.26 |
| 2f | 3.98 ± 0.16a | 11.80 ± 0.81c | 7.82 ± 0.74c | 24.04 ± 1.39 | 190.4 ± 11.02 |
| Phenytoin sodium | 3.12 ± 0.20b | 3.83 ± 0.56c | 6.76 ± 0.51c | 14.42 ± 0.82c | 111.5 ± 4.37c |
| Sodium Valproate | 3.24 ± 0.82 | 5.36 ± 0.68 | 7.59 ± 1.24 | 46.43 ± 2.43 | 128.58 ± 3.68 |

In INH induced seizure, all compounds 2a–f were found to be significantly active (p < 0.001) as they showed protection at the dose of 50 mg/kg. In general it was observed that the latency period of convulsion is used determine the anticonvulsant activity against INH method. Compound 2b was more active than the other derivatives. The order of activity was 2b > 2d > 2e > 2a > 2c > 2f. This may be because of the fact that the naphthyl substituted derivatives are better fitted into the receptor site. MES method is used determine activity of compounds against the generalized or tonic clonic seizures while chemo-convulsive (INH) method are used to determine the activity of compounds absence or petit mal seizures [16,17].

In the MES and INH convulsion investigation, most of the compounds showed moderate anticonvulsant activities and weak anti-TB activities. The result indicating further investigations of structural features required for anticonvulsant activity and probably the pharmacokinetic profile of these drugs. In conclusion, the pyridazinone derivatives can be regarded as a newer class of anticonvulsants.

5.2. Anticonvulsant Activity

All the titled compounds (2a–f) were screened for their anticonvulsant activity by using two most adopted seizure models; the MES and INH-induced seizure test. Interestingly, all the compounds were found to be active in consultant stimuli. The results of the screening data are shown in Table 1 and Table 2. In the MES investigation, all compounds 2a–f were found to be significantly active (p < 0.001) as they showed protection at the dose of 50 mg/kg. In general it was observed that the extensor phase of convulsion is used determine the anticonvulsant activity against MES method. Compound 2e was more active than the other derivatives. The order of activity was 2e > 2b > 2c > 2f > 2a > 2d. The promising nature of the compounds may be attributed to the substitutions at the pyridazinone ring.

5.3. Neurotoxicity Screening

All the compounds (2a–f) did not showed neurotoxicity up to 200mg/kg dose level. Neurotoxicity of compounds was indicated by the inability of the animal to maintain equilibrium on the rod for at least one minute in each of the three trials.

5.4. Antitubercular Activity

All the final synthesized compounds (2a–2f) were evaluated for antitubercular activity. The MIC values were
calculated by established procedures. All the synthesized compounds screened at 100-0.2μg/mL. Compound 2e and 2f emerged as more active (12.5μg/mL) than other analogue (25μg/mL) in this series against M. tuberculosis H37 Rv comparable with those of standard isoniazid (3.12μg/mL), pyrazinamide (3.12μg/mL) and streptomycin (6.25μg/mL) shown in Table 3. The results indicate that the pyridazidine with naphthyl (2e) and biphenyl (2f) showed comparable activity with the reference drugs. Considering the pharmacological results, it can be concluded that: compounds having aryl ring at position 6 possesses significant anticonvulsant activity against MES and INH induced convulsion. Compound 2e and 2f were most active among all the compounds 2a-f against MES and INH induced convulsion respectively. Compounds 2e and 2f were more active against M. tuberculosis than other 2a-d. All compounds 2a-f were found to be less potent anticonvulsant as compared to reference drug in all models and all compounds were also showed weak anti-TB activity.

These biological activities of pyridazidine compounds were evaluated because well known antitubercular drug isoniazid (INH) induced convulsion [6] so we search for the development of a molecule which having both antiepileptic and anticonvulsant activities. Maximum electro induced convulsion (MES) and isoniazid (INH) is act as ionic channel inhibitor (mainly Na+ channel inhibitor) and γ-amino butyric acid (GABA) antagonist, so all title compound could inhibited both ionic channel and GABA concentration in the brain.

Literature revealed that various pyridazidine derivatives are active against epilepsy and M. tuberculosis, in both activities these molecules were different [18]. Some other compounds having different moieties (other than pyridazinones), same molecule were showed both these activities [19,20]. Aryl-pyridazidine derivatives were showed significant anticonvulsant activity but weak antitubercular activity and structure of all pyridazinone compounds having aromatic or substituted aromatic groups at 6-position and carbonyl hydrazide group in cyclic pyridazidine ring. But isoniazid produce convulsion and antitubercular activity and structure of isoniazid compounds having aromatic group (pyridinyl) at 4-position and free carbonyl hydrazide group (Figure 1). These structures similarities indicates that cyclic carbonyl hydrazide is necessary for anticonvulsant activities while open carbonyl hydrazide group necessary for antitubercular and convulsion induction.

![Figure 1. Structure similarities of Aryl Pyridazinones and antitubercular drug isoniazid](image)

Many investigations indicated that the presence of at least one aryl group, one or two electron donor atoms and/or an NH group in a special spatial arrangement is necessary for anticonvulsant activity [21,22,23]. The pyridazidine ring system agrees with this salient feature. In order to explore the activity associated with the presence of an amide moiety, cyclic or not, is present in most anticonvulsants. The most common structural feature of clinically active drugs against epilepsy appeared to be a N-hetero atomic system. It has been proposed that for activity, a compound should have a large hydrophobic group in the close proximity to at least two electron donor atoms. Compounds with an electron withdrawing substituent on the phenyl ring exhibited appreciable anticonvulsant activity. Substituting the hydrogen (from -NH in pyridazine nucleus) with methyl and acetyl group enhanced the lipophilicity of the compounds [24,25]. The lipophilic drugs must pass through blood brain barrier (BBB) and reach to its receptors in the central nervous system.

### 6. Conclusion

Most of the compounds have displayed considerable anticonvulsant activity in both MES and INH induced seizure models. These compounds also showed less antitubercular activity than reference drugs. These pyridazidine derivatives were more effective against convulsions rather than tuberculosis. Therefore pyridazidine derivatives could be a good starting point to develop new molecules in the development of new antiepileptic as well as antitubercular drugs in future.

| Table 3. Anti-tubercular activity of synthetic compounds (2a-f) |
|---------------------------------------------------------------|
| Compounds | MIC (μg/ml) |
| 2a          | 25          |
| 2b          | 25          |
| 2c          | 25          |
| 2d          | 25          |
| 2e          | 12.5        |
| 2f          | 12.5        |
| STR         | 6.25        |
| INH         | 3.125       |
| PZ          | 3.125       |

Isoniazid (INH), Streptomycin (STR) and pyrazinamide (PZ) are used as reference drugs.

### Acknowledgments

Authors are grateful to the Chairman, GRD(PG) IMT, Dehradun, India for performing synthesis and biological evaluation of synthesized compounds and Department of Microbiology, Maratha Mandal’s M.G.H. Institute of Dental Sciences and research Centre, Belgaum, India for antitubercular activity.

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