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RESEARCH ARTICLE

Anticonvulsant Activities of 4-benzylidene-6-(4-methyl-phenyl)-4,5-dihydropyridazin-(2H)-ones and 4-benzylidene-6-(4-chloro-phenyl)-4,5-dihydropyridazin-(*2H*)-ones

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Abstract:

Background:

Two series of 4-benzylidene-6-(4-methyl-phenyl)-4,5-dihydropyridazin-(2H)-one compounds (3a-e) and 4-benzylidene-6-(4-chloro-phenyl)-4,5-dihydropyridazin-(2H)-ones (3f-j) were synthesized and evaluated as anticonvulsant agents.

Methods:

Synthesized compounds (3a-3j) were tested against maximum electro shock (MES) and Isoniazid (INH) induced convulsion methods for anticonvulsant activities and neurotoxicity.

Results:

In MES induced convulsions, result found that the compounds 3e and 3j exhibited highest anticonvulsant activities. In INH induced convulsions, result was indicated that all the compounds exhibited good anticonvulsant activities., whereas compounds 3d and 3j showed maximum activity. Methyl derivatives were more active than chloro derivatives. Phenytoin sodium (25mg/kg) and sodium vaproate (50mg/kg) were used as reference drugs. All these synthesized pyridazinone compounds (3a-j) did not exhibit any neurotoxicity up to 100 mg/kg dose levels.

Conclusion:

All compounds showed good anticonvulsant activities against both MES and INH induced convulsion models. Many such explorations are anticipated in the near future.

Keywords: Anticonvulsant, Isoniazid, Maximum electro shock, Pyridazinones, Synthesis.

INTRODUCTION

Pyridazine and pyridazinone derivatives having various types of pharmacological activities such as antimicrobial, antitubercular, antifungal, antiviral, anti-HIV, analgesic, anti-inflammatory, antipyretic, selective COX-2 inhibitors, insecticidal, molluscicidal, insect and their larval growth regulator, anticancer, anti-asthmatic, anti-allergic, antifeedant, herbicidal, antidiabetic, anti-ulcer, caridovascular agent like PDE-inhibitors, antihypertensive, antiplatelet, ionotropic, antianginal, antiarrthmic, and neurological activity, like anti anxiety, antidepressant, anticonvulsant and other anticipated biological properties. It is also used as intermediate for drugs synthesis and agrochemicals [1 - 15].

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Epilepsy is supposed to be a condition of paroxysmal cerebral dysrhythmia. A common type of epilepsy is grand mal (Generalized tonic-clonic) and petit mal (absence seizures) epilepsy. Grand mal epilepsy: Major epilepsy (Generalized tonic-clonic) commonest last to 1-2 min and illustrated by complete loss of consciousness, followed by transient muscular rigidity (tonic phase) and ultimately falls into violent clonic convulsions followed by prolonged sleep and depression of all "CNS" function. Petit mal: It this usually momentary loss of consciousness prevails. This particular state is free of convulsions. However, occasionally blinking movements of the eyelids and jerking movements of the head or arms are observed [16 - 18]. Epilepsy management is still a major problem due to uncontrolled seizures in some types of epilepsy, drug toxicity, side effects and long period treatment even throughout a life time. Risks of tolerance developed against the presently used medicines. Various antiepileptic drugs available in the market, due to above mentioned reasons, development of new antiepileptic drugs are still necessary. The maximum electroshock (MES) induced seizures in animal represents the grand mal type of epilepsy and chemo convulsions are due to Pentylenetetrazole (PTZ), strychnine (STR), isoniazide (INH) which produced petit mal type of convulsions [16 - 20]. The drug design is based on the opinion that at least one phenyl or aryl group in close proximity to two electron donor atoms in the molecule is necessary for the activity against MES induced seizure, an alkyl group substituted close to two electron donor atoms in the molecule is necessary for the activity against chemo convulsions. Many researches indicated that the presence of at least one aryl group, one or two electron donor atoms and/or an imino (NH) group in spatial arrangement is vital for antiepileptic activity. So, syntheses of new pyridazinone compounds are tested for their anticonvulsant screening. Most of the drugs are used as antiepileptic agents today contain ureide structure such as barbiturates, benzodiazepines, oxazolidinediones, succinimides and glutarimides [21 - 25].

Thus, the present work is to concentrate on preparation of various new substituted pyridazinones and tested for their anticonvulsant activity against MES and INH-induced convulsions. The essential requirement is not only design and development of the drug molecule, but also the progress of its testing methods, mode of actions and its usefulness. New pyridazinone derivatives are designed to prepare effective drug molecule with minimum or lesser side effects.

CHEMISTRY

All compounds were synthesized according to Schemes (**1**). All chemicals were used for synthesis of pyridazinone compounds were purchased from Loba Chem, Central drug house (CDH), Merck, SD-fine and High media, India. Melting points of all the synthesized compounds were determined by open tube capillary method and were uncorrected. The purity of the compounds was checked by using thin layer chromatography (TLC) methods and plates were prepared from silica gel G and solvent system toulene, ethylacetoacetae, formic acid (4:5:1 ratio) and benzene, acetone (3:1) was used as mobile phase, the spot of synthesized compounds were visualized by using the iodine vapors and ultra-violet (UV) light. Elementary analyses were carried out on a LECO CHNS 932 analyzer for determining C,H,N atom values. The FT-IR spectra were recorded on Bio-rad FTS-135 spectrophotometer using KBr pellets; λ max values are given in cm^{-1}. The NMR spectra were recorded on Bruker Avance-II 400 NMR spectrometer using $CDCl_3$ as solvent and tetra methyl silane (TMS) was used as an internal standard and chemical shifts were given in δ (ppm) scale and the Mass spectra were recorded on JEOL-JMS-DX 303 system, prepared with direct inlet probe system.

SYNTHESIS OF AROYL-PROPIONIC ACID DERIVATIVES (1A AND 1B)

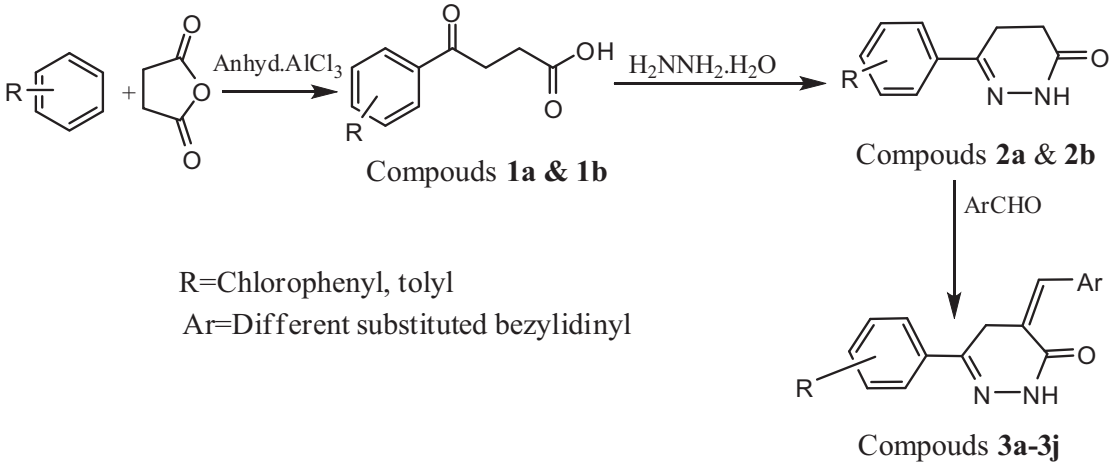
Anhydrous $AlCl_3$ (0.15 mol) was suspended in appropriate aryl hydrocarbons (50 mL) under the anhydrous condition and the reaction mixture was refluxed on a water bath. Then the succinic anhydride (0.10 mol) was added into the reaction mixture in small portions with nonstop stirring for 6 h (Scheme **1**). The reaction mixture was cooled down, left overnight and after that made acidic by adding an ice cold concentrated HCl solution (2.5% v/v). The reaction mixture was concentrated to a small volume by heating on a water bath. The precipitate was formed and separated out and collected it. The precipitated product was purified by dissolving in 5% w/v Na_2CO_3 solution and followed by extraction with ether. The acidification with dilute HCl acid gave an aroyl propionic acid (Fig. **1**) in the aqueous layer [26 - 28].

Other propionic acids were synthesized by a similar process with minor changes in temperature of reaction and nitrobenzene used as a solvent. All these compounds were re-crystallized with aqueous ethanol.

β-toloyl Propionic Acid (1a)

Molecular formula: $C_{11}H_{12}O_3$, molecular weight: 192, melting point: 122°C; 67% yield. IR: (KBr, cm^{-1}): 1658.80 (CO), 2995.62 (CH), 3412.60 (OH), 1H-NMR (DMSO-d6, δ ppm): 2.38 (s, 3H, CH_3), 2.78 (t, 2H, CH_2), 2.99 (t, 2H,

CH_2), 7.26 (t, 2H, H3',5', Ar-H), 12.15 (s,1H, COOH), MS (m/z): 193 (M^++1).



Scheme 1. Synthetic route of 6-aryl-4-benzylidene-4,5-dihydro pyridazino-3(*2H*)-ones (**3a-j**).

4-Chloro Benzoyl Propanoic Acid (1b)

Molecular formula $C_{10}H_9O_3Cl$, molecular weight 212, melting point: 122 C, yield 54. IR Spectra: 2950 cm^{-1} (CH), 3212.60 (OH), 1710 cm^{-1} (C=O).NMR Spectra: ^{1}HNMR($CDCl_3$) ppm 2.82 (2H, t, CH_2), 3.31 (2H, t, CH_2), 7.74 (CH_2, m, H-3, 5), 7.79 (2H, m, H-2, 6), MS (m/z): 112 (M^{+1}).

SYNTHESIS OF 6-ARYL-4,5-DIHYDROPYRIDAZIN-3(2H)-ONE DERIVATIVES (2A AND 2B)

To a solution of β-aroyl propionic acid (1a) (0.1 mol) in CH_3OH (30 ml), NH_2NH_2. H_2O (1ml) and CH_3COONa (0.5 g) were added and the reaction mixture was refluxed for 6 h. After completing the reaction, CH_3OH was distilled off and reaction mixture was transferred into cold water [29 - 31]. The solid product (Fig. **1**) was separated out, filters it and re-crystallized from methanol (Scheme **1**).

Other pyridazinone was synthesized by a similar process with minor alteration in temperature of reactions and solvent nitrobenzene is used.

6-(4-methylphenyl)-4,5-dihydropyridazin-3(2H)-one (2a)

Molecular formula $C_{11}H_{12}N_2O$, molecular weight 188.20, melting point: 151 C, yield: 71%, R_f value 0.70, IR: (KBr,cm^{-1}): 1658.7 (C=O), 3217.4 (NH), 1510.8 (C=N), ^{13}C NMR ($CDCl_3$) (ppm): 20.9, 27.1, 35.6, 128.2, 129.3, 128.9, 140.0, 155.6, 161.2, ^{1}H NMR ($CDCl_3$) (ppm): 2.38 (s, 3H, CH_3), 2.61 (m,2H, CH_2-CO), 2.97 (t, 2H, CH_2-aryl), 7.26 (t, 2H, Ar-H3',H5'), 7.63 (d, 2H, Ar-H2',H6'), 8.79 (s, 1H, NH), MS (m/z): 189 (M^{+1}).

6-(4-chlorophenyl)-4,5-dihydropyridazin-3(2H)-one (2b)

Molecular formula $C_{10}H_9ClN_2O$, molecular weight 208, yield 55%, melting point. 130 C, R_f value 0.60. IR (cm^{-1})1685(C=O), 1352 (NO_2), 3000 (CH), 3550 (NH), 2.60 (t, 2H, CH_2), 3.2 (t, 2H, CH_2), 7.53-7.68 (m, 2H, H-3'-H-5', Ar-H), 7.97 (d, 2H, H-2'-H-6', Ar-H), 8.78 (s, NH).

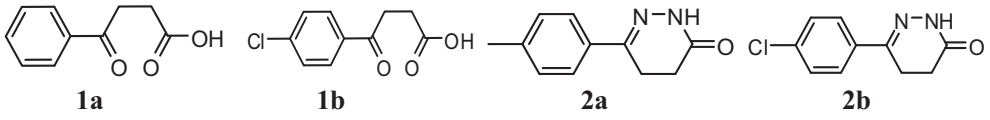


Fig. (1). Structures of aroyl-propionic acids (**1a-b**) and 6-arylpropyridazine derivatives **(2a-b).**

SYNTHESIS OF 4-BENZYLIDENE-6-(4-SUBSTITUTED-ARYL)-4,5-DIHYDROPYRIDAZIN-(2H)-ONES

The 6-(4-chlorophenyl)-4,5-dihydropyridazin-3(2H)-one or 6-(4-methylphenyl)-4,5-dihydro pyridazin-3(2H)-one (0.005 mol), appropriate aldehyde derivatives (0.005 mol) in C_2H_5OH (20 ml) and ethanolic C_2H_5ONa solution were added. Then reaction mixture was left overnight at room temperature, diluted with water and rendered acidic with concentrated HCl and filter the product. The crude product (**3a-j**) (Fig. **2**) was re-crystallized with 90% ethanol [32 - 34].

4-benzylidene-6-(4-chloro-phenyl)-4,5-dihydropyridazin-(2H)-one (3a)

Molecular formula $C_{17}H_{13}ClN_2O$, molecular weight 296, yield: 62%; melting point; 170 ºC; IR (KBr) in cm^{-1}: KBr): 3185 (NH), 2949 (Ar-CH), 2831 (C-H), 1602.56 (-C=C), 1255.3 (C-N), 1685 (C=O), 718 (C-Cl), ^{1}H-NMR ($CDCl_3$, δ, ppm): 3.9 (s, 2H, CH_2), 7.16 (s, 1H, H-4), 7.14-7.48 (m, 5H, aryl ring), 7.20 (s, 1H, CH), 7.42 and 7.73 (d, each, *p*-substituted aryl ring), 10.72 (s, 1H, NH), ^{13}C NMR ($CDCl_3$) (ppm): 28.4, 126.2, 127.7, 128.4, 129.0, 129.2, 129.3, 130.4, 134.2, 134.9, 136.1, 155.6, 160.0, MS (*m/z*): 297 (M^++1). Elemental analysis: calculated (%): C = 68.81, H = 4.42, N = 9.44; Found (%): C= 68.93, H = 4.45, N = 9.43.

4-(4-chloro-benzylidene)-6-(4-chloro-phenyl)-4,5-dihydropyridazin-(2H)-one (3b)

Molecular formula $C_{17}H_{12}Cl_2N_2O$, molecular weight 331, yield: 55%; melting point; 190 ºC; IR (cm-1, KBr): 3179 (NH), 2957 (C-H), 1688 (C=O), 726 (C-Cl), 1602.56 (C=C), 1292.07 (C-N), ^{1}H-NMR ($CDCl_3$, δ, ppm): 3.9 (s, 2H, CH_2), 7.20 (s, 1H, CH), 8.6 (1H, s, NH), 7.11 (s, 1H, H-4), 7.23 (m, 4H, H-2,3,5,6, aryl ring), 7.34 and 7.41 (d, each, *p*-substituted aryl), 10.97 (s, 1H, NH), ^{13}C NMR (CDCl3) (ppm): 28.4, 127.6, 128.8, 129.0, 129.2, 129.3, 130.4, 136.1, 133.0, 134.2, 155.6, 162.2, MS (*m/z*): 332 (M^++1). Elemental analysis: calculation (%): C= 61.65, H=3.65, N= 8.46; Found (%): C= 61.55, H= 3.67, N = 8.47.

4-(4-hydroxy-benzylidene)-6-(4-chloro-phenyl)-4,5-dihydropyridazin-(2H)-one (3c)

Molecular formula $C_{17}H_{13}ClN_2O_2$, molecular weight Molecular Weight: 312, yield: 52%, melting point; 180 ºC; IR (cm-1, KBr): 3175 (NH), 2942 (CH), 1688 (C=O), 722 (C-Cl), ^{1}H-NMR ($CDCl_3$, δ, ppm): 3.84 (s, 2H, CH_2), 6.15 (m, 1H, OH), 7.06 (m, 2H, H-2,6, benzyl ring), 7.04 (s, 1H, CH), 7.31 (s, 1H, H-4), 7.47 and 7.71 (d, each, *p*-substituted aryl), 7.49 (m, 2H, H-3,5, aryl ring), 9.41 (s, 1H, NH), ^{13}C NMR (CDCl3) (ppm): 28.4, 115.6, 127.5, 127.6, 129.0, 129.2, 129.3, 130.4, 134.2, 136.1, 156.5, 155.6, 162.0, MS (*m/z*): 313(M^++1). Elemental analysis: calculated (%): C= 65.29, H= 4.19, N= 8.96; Found (%): C= 65.39, H= 4.17, N= 8.97.

4-(4-methoxy-benzylidene)-6-(4-chloro-phenyl)-4,5-dihydropyridazin-(2H)-one (3d)

Molecular formula $C_{18}H_{15}ClN_2O_2$, molecular weight 326, Yield: 67%; melting point; 155 ºC; IR (KBr) in cm^{-1}: 3165 (NH), 3001 (CH), 1675 (C=O), 1602.57 (C=C), 1255.30 (C-N), 1166.72 (OCH_3), 717 (C-Cl), ^{1}H-NMR ($CDCl_3$, δ, ppm): 7.20 (s, 2H, CH_2), 3.70 (s, 2H, CH_2), 3.71 (s, 3H, OCH_3), 6.8 (s, 1H, H-4), 7.13 and 7.36 (d, each, *p*-substituted benzyl ring), 7.59 (m, 2H, H-3,5, phenyl ring), 7.68 (m, 2H, H-2,4, phenyl ring), 10.70 (s, 1H, NH), ^{13}C NMR (CDCl3) (ppm): 28.4, 115.6, 127.5, 127.6, 129.0, 129.2, 129.3, 130.4, 134.2, 136.1, 156.5, 155.6, 162.0, MS (*m/z*): 326(M^+). Elemental analysis: calculated (%): C= 66.16, H= 4.63, N= 8.57; Found (%): C= 66.23, H= 4.61, N= 8.55.

4-(4-hydroxy-3-methoxy-benzylidene)-6-(4-chloro-phenyl)-4,5-dihydro-pyridazin-(2H)-one (3e)

Molecular formula $C_{18}H_{15}ClN_2O_3$, molecular weight 342, yield: 48%; melting point; 201 ºC; IR (cm-1, KBr): 3173 (NH), 2951 (CH), 1680 (C=O), 713 (C-Cl), ^{1}H-NMR ($CDCl_3$, δ, ppm): 3.78 (s, 2H, CH_2), 3.72 (s, 3H, OCH_3), 6.53 (s, 1H, H-4), 7.07-7.26 (m, 3H, H-2,5,6, di-substituted aryl ring), 7.2 (s, 2H, CH_2), 7.46 and 7.71 (d, each, *p*-substituted aryl ring), 10.92 (s, 1H, NH), ^{13}C NMR (CDCl3) (ppm): 28.4, 56.3, 113.2, 116.6, 119.9, 128.5, 129.0, 129.2, 129.3, 130.4, 134.2, 136.1, 142.1, 149.1, 155.6, 162.1,162.2, MS (*m/z*): 343(M^++1). Elemental analysis: calculated (%): C = 63.07, H=4.41, N= 8.17; Found (%): C= 62.97, H= 4.39, N= 8.19.

4-benzylidene-6-(4-Methyl-phenyl)-4,5-dihydropyridazin-(2H)-one (3f)

Molecular formula $C_{18}H_{16}N_2O$, molecular weight 276, yield: 55%; melting point; 160 ºC; IR (cm-1, KBr): 3180 (NH), 2995 (CH), 1696 (C=O), ^{1}H-NMR ($CDCl_3$, δ, ppm): 3.94 (s, 3H, CH_3), 3.02 (s, 2H, CH_2), 6.86 (s, 1H, H-4),

7.02-7.43 (m, 5H, benzyl ring), 7.22 (s, 1H, CH), 7.46 and 7.79 (d, each, *p*-substituted aryl ring), 8.92 (s, 1H, NH), ^{13}C NMR (CDCl3) (ppm): 20.9, 28.4, 126.2, 127.7, 128.2, 128.4, 128.9, 129.2, 129.3, 134.2, 134.9, 140.0, 155.6, 162.2, MS (*m/z*): 277 (M^++1). Elemental analysis: calculated (%): C= 78.24, H= 5.84, N= 10.14; Found (%): C= 78.23, H= 5.87, N= 10.17.

4-(4-chloro-benzylidene)-6-(4-methyl-phenyl)-4,5-dihydropyridazin-(2H)-one (3g)

Molecular formula $C_{18}H_{15}ClN_2O$, molecular weight 310, yield: 48%; melting point; 175 ºC; IR (cm-1, KBr): 3173 (NH), 2939 (CH), 1683 (C=O), 718 (C-Cl), ^{1}H-NMR ($CDCl_3$, δ, ppm): 3.90 (s, 3H, CH_3), 2.6 (s, 2H, CH_2), 7.23 (s, 1H, CH), 7.24 (s, 1H, H-4), 7.26 and 7.56 (d, each, *p*-substituted aryl ring), 7.28-7.35 (m, 4H, H-2,3,5,6, phenyl ring), 10.69 (s, 1H, NH), 7.26-7.56 (m, H, 4-CH_3-benzyl ring), 7.28-7.35 (m, 4H, 4-chlorophenyl ring), 10.69 (s, 1H, NH), 13C NMR (CDCl3) (ppm): 20.9, 28.4, 127.6, 128.2, 128.8, 128.9, 129.2, 129.3, 133.0, 134.2, 140.0, 155.6, 162.2, MS (*m/z*): 311 (M^++1). Elemental analysis: calculated (%): C= 69.57, H=4.86, N= 9.01; Found (%): C= 69.53, H= 4.87, N= 8.99.

4-(4-hydroxy-benzylidene)-6-(4-methyl-phenyl)-4,5-dihydropyridazin-(2H)-one (3h)

Molecular formula $C_{18}H_{16}N_2O_2$, molecular weight 292, yield: 47%; melting point; 185 ºC; IR (cm-1, KBr): 3165 (NH), 2957 (CH), 1695 (C=O), ^{1}H-NMR ($CDCl_3$, δ, ppm): 3.93 (s, 3H, CH_3), 2.82 (s, 2H, CH_2), 6.41 (s, 1H, H-4), 6.63 (m, 2H, H-2,6, phenyl ring), 6.66 (m, 2H, H-2,6, benzyl ring), 6.79 (m, 2H, H-3,5, phenyl ring), 6.81 (m, 2H, H-3,5, benzyl ring), 7.20 (s, 1H, CH), 12.25 (s, 1H, NH), ^{13}C NMR (CDCl3) (ppm): 20.9, 28.4, 115.6, 127.5, 127.6, 128.2, 128.9, 129.2, 129.3 134.2, 140.0, 155.6, 156.5, 162.0, MS (*m/z*): 293 (M^++1). Elemental analysis: calculated (%): C = 73.96, H= 5.52, N= 9.58; Found (%): C= 73.98, H= 5.51, N= 9.57.

4-(4-methoxy-benzylidene)-6-(4-methyl-phenyl)-4,5-dihydropyridazin-(2H)-one (3i)

Molecular formula $C_{19}H_{18}N_2O_2$, molecular weight 306, yield: 46%; melting point; 202 ºC; IR (cm^{-1}, KBr): 3185 (NH), 2954 (CH), 1686 (C=O), ^{1}H-NMR ($CDCl_3$, δ, ppm): 3.83 (s, 3H, CH_3), 3.04 (s, 3H, CH_2), 3.92 (s, 2H, OCH_3), 6.79 (s, 1H, H-4), 7.01 (s, 1H, CH), 7.37 and 7.82 (d, each, *p*-substituted aryl ring), 7.49 (m, 2H, H-3,5, phenyl ring), 7.72 (m, 2H, H-2,6, phenyl ring), 11.15 (s, 1H, NH), ^{13}C NMR (CDCl3) (ppm): 20.9, 28.4, 56.0, 114.0, 127.2, 128.2, 128.9, 129.2, 129.3, 134.2, 140.0, 155.6, 162.1, 162.2, MS (*m/z*): 307 (M^+). Elemental analysis: calculated (%): C= 74.49, H= 5.92, N= 9.14; Found (%): C= 74.53, H= 5.91, N= 9.13.

4-(4-hydroxy-3-methoxy-benzylidene)-6-(4-methyl-phenyl)-4,5-dihydropyridazin-(2H)-one (3j)

Molecular formula $C_{19}H_{18}N_2O_3$, molecular weight 322, yield: 51%; melting point; 175 ºC; IR (cm^{-1}, KBr): 3189 (NH), 2948 (CH), 1687 (C=O), ^{1}H-NMR ($CDCl_3$, δ, ppm):) 3.86 (s, 2H, CH_2), 3.25 (s, 3H, OCH_3), 2.39 (s, 3H, CH_3), 6.34 (s, 1H, OH), 6.82 (s, 1H, H-4), 7.04 (m, 1H, H-6, benzyl ring), 7.24 (s, 1H, CH), 7.25 (m, 2H, H-3,5, phenyl ring), 7.53 (m, 1H, H-2, benzyl ring), 7.68 (m, 2H, H-2,6, phenyl ring), 7.75 (m, 1H, H-5, benzyl ring), 10.73 (s, 1H, NH), 13C NMR (CDCl3) (ppm): 20.9, 28.4, 56.3, 113.2, 155.6, 116.6, 119.9, 128.2, 128.5, 128.9, 129.2, 129.3, 134.2, 140.0, 142.1, 149.1, 162.2,MS (*m/z*): 323 (M^++1). Elemental analysis: calculated (%): C=70.79, H= 5.63, N= 8.69; Found (%): C= 70.83, H= 5.65, N= 8.67.

BIOLOGICAL EVALUATION

The synthesized compounds were subjected to the following evaluation. All chemicals were purchased from CDH (Central drug House), Merck, Loba Chem, and S.D. Fine Chemicals, Mumbai, India and used without purification. Strychnine (STR) (Sigma Aldrich, India) and Phenytoin (Sun Pharma Ltd, India) were used in the present study.

Experimental Animals

Swiss albino rats weighing 25-30 g were maintained under controlled conditions of light (12 hr) and temperature 25±2°C in the animal house of Department of Pharmacy, GRD(PG)IMT, Dehradun, India, two weeks before the experiment for acclimatization. Animals had access to food and water *ad libitum*. All pharmacological activities were carried out as per Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) norms (Regn No: 1145/a/07/CPCSEA), after getting the approval from the Institutional Animal Ethics Committee (IAEC) of Department of Pharmacy, GRD (PG) IMT, Dehradun, India.

Neurotoxicity Screening

Minimal motor impairment was tested on mice by using the rotarod (Techno, India) test model. The mice were skilled to stay on an accelerating rotarod (diameter 3.2 cm) that rotates at 10 revolutions per min (rpm). Before skilled mice were given test compounds i.p. in doses of 25, 50 and 100 mg/kg. Neurotoxicity was signified by the incapability of the animal to keep equilibrium on the rod for at least one min. in each of the three tests [35].

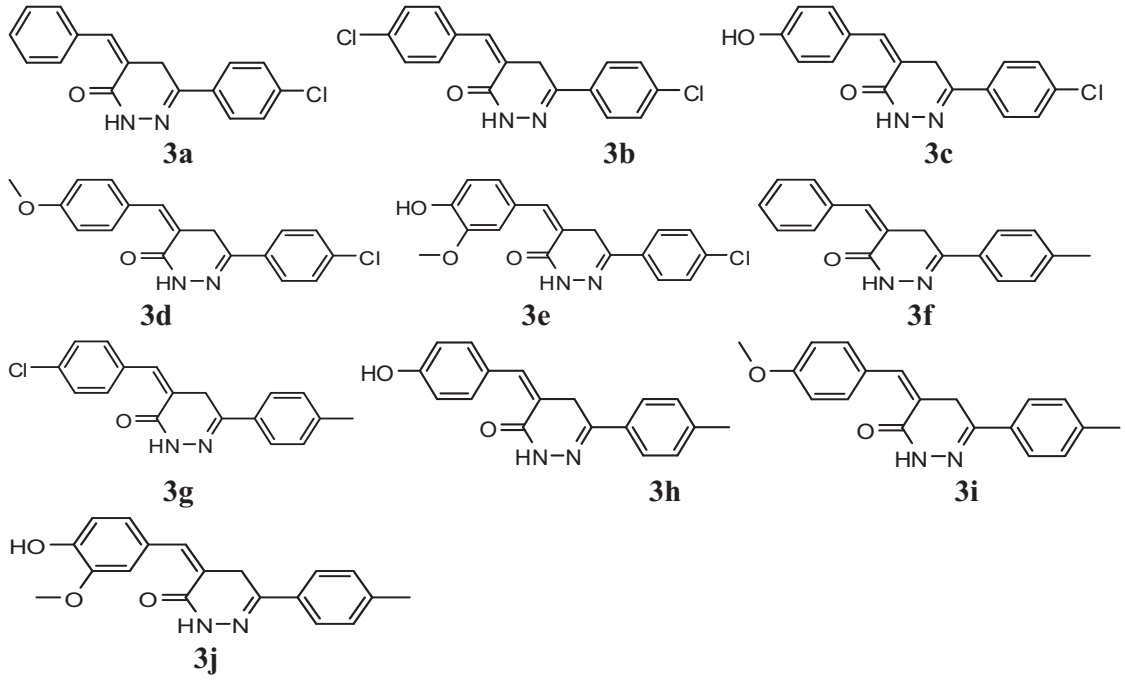


Fig. (2). Structures of 4-benzylidene-6-(4-substituted-/3-nitro-phenyl)-4,5-dihydro pyridazin-(2H)-ones (**3a-j**).

Anticonvulsant Activities

Male albino mice were used to test the synthesized pyridazinone derivatives. Maximal Electro Shock (MES) and Isoniazid (INH) induced seizure methods were used [35 - 37].

Maximal Electro Shock (MES)-induced Convulsion Method

The MES method (Model: Techno Electro Convulso-meter) was used for inducing seizures. The MES induced seizures in mice correspond to grand-mal type of epilepsy. In MES, electro shock was applied to the ear pinna by passing 50 mA current for 0.2 sec. The MES seizures were divided into five stages (a) flexion (b) extensor (c) clonus (d) stupor and (e) recovery or death. Suspension of test compounds were formed in 0.5% carboxyl methyl cellulose (CMC) and were given intraperitoneally (i.p.) at dose level 25 mg/Kg body weight to different groups of mice and each group having five mice. Reduction in the extension phase was calculated and compared to phenytoin sodium, which was used as a standard at 25mg/Kg body weight dose. The animals were examined for all the five stages. The abolition of the extensor phase in drug treated groups was taken as the experimental standard for anticonvulsant activity.

Isoniazid (INH) Induced Seizures Method

Isoniazide (INH) induced seizures method was carried out on mice (25-30 g). The mice were injected with test drugs 50 mg/kg i.p. After 30 min, INH injection of dose 250 mg/kg was given i.p. The series of seizure latency, seizure time and percentage protection were studied. Animals displaying these seizure patterns were detected. The reference drugs used in this model was phenytoin sodium (25mg/kg) and sodium valproate (100mg/kg).

Statistical Evaluation

All the values were determined as mean ± S.E.M. Statistical analysis was obtained by using one-way analysis of variance (ANOVA). If the overall p-Value was found statistically significant ($p < 0.05$), further comparisons between

groups were arranged according to Tukey's test.

RESULTS

Chemistry

All synthesized pyridazinone compounds were characterized by spectral analysis *via* IR, NMR, mass spectra and elemental analysis data. The IR spectrum exhibited the peak at 1700, 3450, and 1580 cm^{-1} validated the occurrence of C=O, NH and C=C groups. The ^{1}HNMR spectrum proved the signal in the triplet near δ=2.8 for CH_2 protons at 5-positions, another triplet is viewed at about δ=3.0 for CH_2 at 4 positions. Aromatic protons were detected in the region from δ=7.0-8.0, mass of compounds determined by mass spectroscopy. Elementary analyses gave satisfactory results and the values were found to be in range of ±0.4% theoretical value for the element analyzed or calculated (C,H,N). The presences of substitutes were determined in the IR, and ^{1}HNMR spectra according to the assigned value. In the ^{1}HNMR the signals of the respective protons of the prepared 3(*2H*)-pyridazinone compounds were verified on the basis of their chemical shifts and multiplicities. The other compounds are also identified in a similar manner. Elemental analyses gave satisfactory results.

Neurotoxicity

All the synthesized pyridazinone compounds (**3a-j**) did not exhibit any neurotoxicity up to 100 mg/kg dose levels. Neurotoxicity of compounds was pointed out by the lack of ability of the animal to retain equilibrium on the rod for at least one minute in each of the three trials.

ANTICONVULSANT ACTIVITIES

Anticonvulsant Activity Against MES-induced Convulsions

Anticonvulsant activities (ACAs) of aryl-4,5-dihydropyridazinones against maximal electro shock (MES) were found significant ACA when compared with the control group. Two series of 6-(4-Cl-Phenyl)-4-arylidene-4,5-dihydropyridazin-3(*2H*)-one (**3a-e**), 6-(4-CH_3-Phenyl)-4-arylidene-4,5-dihydropyridazin-3(*2H*)-one derivatives (**3f-j**) were evaluated as anticonvulsant agents against MES-induced convulsion method. Result found that the compounds **3e** and **3j** exhibited highest ACA, these compounds having 6-methyl phenyl, 6-chloro-phenyl pyridazinone derivatives and act by reducing extensor phase. Methyl derivatives were more active than chloro derivatives (Table **1**). For ACAs PHT sod. (25mg/kg) and sod. valproate (VPA) (50mg/kg) was used as reference drugs. Results indicated that synthesized pyridazinone compounds have moderate to good anticonvulsant activity.

Table 1. ACA of 6-(4-Chloro/4-methyl/3-nitro-Phenyl)-4-arylidene-4,5-dihydro pyridazin-3(*2H*)-ones (3a-m) against MES-induced convulsions.

S. No.	Groups	Flexion (sec)	Extensor (sec)	Clonus (sec)	Stupor (sec)	Recovery (%)
1	Control	3.34 ± 0.125	15.76±01.11	6.76 ± 01.11	48.90±07.65	60
2	PHT Sod	1.44 ± 0.051[a]	0.00 ±0.00[a]	1.84 ±0.23	7.78 ±0.58[a]	100
3	Sod VPA	3.24±0.82	5.36±0.68	7.59±1.24	46.43±2.43	80
4	Compd**3a**	2.0±0.12[aγ]	6.26±1.45[aγ]	3.62±1.12[aγ]	20.20±3.50[aγ]	80
5	Compd**3b**	2.11±0.09[aγ]	7.21±1.63[aγ]	4.24±1.42[bγ]	18.32±3.48[aγ]	80
6	Compd**3c**	2.21±0.40[aγ]	6.63±1.72[aγ]	3.88±1.64[aγ]	18.50±2.34[aγ]	100
7	Compd**3d**	1.92±0.28[aγ]	6.24±0.54[aγ]	4.12±2.12[bγ]	16.64±1.90[aγ]	100
8	Compd**3e**	1.84±0.36[aγ]	6.10±1.16[aγ]	3.92±2.14[aγ]	15.40±3.20[aγ]	100
9	Compd**3f**	2.22±0.28[aγ]	7.86±0.76[aγ]	4.21±1.66[bγ]	22.40±4.45[aγ]	80
10	Compd**3g**	2.41±0.12[aγ]	9.66±1.02[aγ]	3.98±2.26[aγ]	20.50±3.60[aγ]	80
11	Compd**3h**	2.32±0.34[aγ]	8.26±0.82[aγ]	4.43±2.0[bγ]	21.33±4.82[aγ]	80
12	Compd**3i**	2.36±0.16[aγ]	8.84±0.68[aγ]	4.82±2.86[bγ]	19.34±2.86[aγ]	80
13	Compd**3j**	2.10±0.76[aγ]	7.64±0.922[aγ]	4.64±3.23[bγ]	22.56±3.94[aγ]	80

Control group: 0.5% CMC in distilled water; Standard drug: PHT sodium (25mg/kg); Test compounds: (50 mg/kg); n= 5, no. of animals in a group; [a]P< 0.001, [b]P< 0.01, when compared to control group and γ< 0.001, when compare with standard group.

Anticonvulsant Activity Against INH-induced Convulsions

Several 6-aryl-4,5-dihydropyridazinones were screened for their *in-vivo* ACA against isoniazid (INH, anti-TB drug) induced convulsion. Two series of 6-(4-Cl-Phenyl)-4-arylidene-4,5-dihydro pyridazin-3(*2H*)-one (**3a-e**), 6-(4-CH_3-Phenyl)-4-arylidene-4,5-dihydro-pyridazin-3(*2H*)-one derivatives (**3f-j**), were evaluated as anticonvulsant against INH-induced convulsion method. The result indicated that all the compounds exhibited ACA. Compounds **3d** and **3j** showed maximum activity in 4-methyl-phenyl and chloro-phenyl compounds. Methyl derivatives were more active than chloro derivatives (Table **2**). For ACAs PHT sodium (25mg/kg) and sodium vaproate (VPA) (50mg/kg) were used as reference drugs.

Table 2. Anticonvulsant activity of 6-(p-Chloro/p-methyl/m-nitro-phenyl)-4-arylidene-4,5-dihydropyridazin-3(2H)-one compounds (3a-m) against isoniazid (INH) induced method.

S. No.	Groups	Onset of convulsion (sec)	No. of convulsion	Recovery (%)
1	Compd **3a**	36.2±6.27 $^{\gamma a}$	2.5±0.22	80
2	Compd **3b**	47±4.50 $^{\gamma c}$	2.8±0.25	80
3	Compd **3c**	48.6±3.87$^{\gamma c}$	2.5±0.24	60
4	Compd **3d**	34.6±3.24$^{\gamma}$	2.4±0.36	100
5	Compd **3e**	35.2±6.98$^{\gamma}$	2.6±0.35	100
6	Compd **3f**	42.6±2.62 $^{\gamma c}$	2.0±0.32	80
7	Compd **3g**	46.8±2.06$^{\gamma c}$	2.4±0.34	80
8	Compd **3h**	48±1.82 $^{\gamma c}$	2.4±0.26	80
9	Compd **3i**	47.6±4.24 $^{\gamma c}$	2.2±0.24	60
10	Compd **3j**	48.2±4.18 $^{\gamma c}$	2.6±0.18	100
11	Sod. VPA	130.2 ± 2.15	1.4±0.22	100
12	PHT sod.	0.00	0.00	100
13	Control	26.16±.094	3.2±0.20	00

Standard drug: PHT sodium (25mg/kg) and Sodium VPA (100mg/kg), Tested drugs: (50mg/kg), Control group: INH-250mg/kg+0.5 % CMC in distilled water; n=5 (No. of animals in each group); *Value represents mean ± S.E.M. $^{c}P< 0.001$ when compared to control group $^{\gamma}P< 0.001$ when compared to standard drug sodium VPA.

Synthesized compounds have been evaluated for anticonvulsant activities by MES and INH induced convulsion methods. Results indicated that these compounds were shown good ACAs.

DISCUSSION

The nitrogen containing heterocyclic compounds is becoming more popular as an area of research because of their diverse biological activities. Pyridazine compounds have diverse biological activities. They are inexpensive and easily synthesized. Different substitutions on the pyridazine ring may cause noticeable differentiation in the biological activities. Due to these characteristics different substituents are being synthesized and evaluated for various biological activities in the search of improved therapeutic molecules. At present, much concentration has been focused on the pyridazine moiety attached with other heterocyclic ring, which has a valuable structure for molecular investigation and for the development of biological active molecules with diverse biological activities [38 - 43].

Possible Mechanisms

The discovery and development of a new chemical entity for the treatment of epilepsy rely on the use of experimental animal models. Currently there are two *in vivo* models that are commonly used by most AEDs discovery schemes. The models are MES and chemo convulsion induced seizure models. The MES and INH seizure models represent the two animal seizure models. To promote investigate the effects of the ACA in some other animal experiment models and estimation of neurotransmitters to consider about the exact possible mechanism of these compounds. PHT is inhibited sodium ion channel. There is some evidence that VPA enhances the action of GABA by a postsynaptic action. It also has effects on sodium channels, weaker than those of PHT [44].

Structural Feature of Pyridazinones as Anticonvulsant Activities

The anticonvulsant activities of pyridazinone compounds are known, there is a need for the advance of a molecule which have antiepileptic actions. Compounds active against MES-induced convulsions are working as ionic channel

inhibitor (primarily Na+ channel inhibitor). Compounds active against INH-induced convulsions are acting as GABA antagonist. Results revealed that all compounds inhibited both ionic channel and GABA concentrations in the brain. Literature exposed that different pyridazinone analogs are active against epilepsy were exhibited significant anticonvulsant action [45, 46].

CONCLUSION

In this study, various substituted 3(*2H*)-pyridazinone compounds were synthesized, characterized and evaluated as anticonvulsant against various convulsion models.

- Substituted 3(*2H*)-pyridazinone compounds, 4-benzylidene-6-(4-substituted)-4,5-dihydro pyridazin-(2*H*)-one (**3a-j**) were synthesized.
- All the synthesized 3(*2H*)-pyridazinone compounds were characterized by spectral analysis, such as IR, NMR, mass spectra, and elemental analysis.
- All the synthesized 3(*2H*)-pyridazinone compounds did not exhibit any neurotoxicity up to 100 mg/kg dose levels.
- All the synthesized 3(*2H*)-pyridazinone compounds were evaluated against MES and INH induced convulsions at 50 mg/kg dose level. In MES activity, all compounds (**3a-e**) and (**3f-j**), compounds **3e** and **3j** were exhibited highest anticonvulsant activity. In isoniazid (INH) induced convulsion, all compound**s (3a-j**) exhibited appreciable activity. Compounds **3d** and **3j** showed maximum activity. Methyl derivatives were more active than chloro- derivatives. Methyl derivatives were more active than chloro and nitro derivatives. Phenytoin sodium (25mg/kg) and sodium vaproate (50mg/kg) were used as reference drugs.
- Result indicated that all these synthesized compounds were active as anticonvulsant these compounds were found active against MES, INH induced convulsion models.
- The MES method is sensitive to sodium (Na^+) channel inhibitors (phenytoin), which compounds may inhibit voltage-gated ion channels (particularly Na^+ channels). The INH (a GABA synthesis inhibitor) was sensitive to modulate γ-amino butyric acid (GABA), compounds may inhibit the GABA concentration in the brain.

The pyridazine moiety constitutes an important class of drug for new drugs research and developments. A variation in the substitution of the pyridazinone ring often causes a marked difference in the biological activities due to different characteristics of the substituent. The conclusion is based on the observation, regarding the synthesis of new pyridazinone compounds with the hope to obtain more potent drugs because easily functionalized different structural alterations were carried out in pyridazinone ring containing molecules. These structural modifications give outcome of some fruitful biological actions [47, 48].

Directions for Future Research

Many synthetic heterocyclic compounds have different biological activities. Pyridazine ring is an essential structural feature of various pharmacologically active compounds. Pyridazine also holds considerable interest in the synthesis of various organic intermediates as well as physiologically active agents. Pyridazinone compounds could be a suitable moiety to develop new lead antiepileptic agents with a minimum or without side effects as well as resistance. These findings encourage the synthesis of some pyridazinone derivatives and evaluate them for anticonvulsant activities. These pyridazinone derivatives are more efficient against seizures. The new pyridazine derivatives may be a promising agent as anticonvulsant in the future. Several synthetic strategies were reported for the synthesis of pyridazinone compounds. These structural alterations will result in some useful biological activities.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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