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Synthesis of Different Substituted Pyridazinone Derivatives and Their Anticonvulsant Activity

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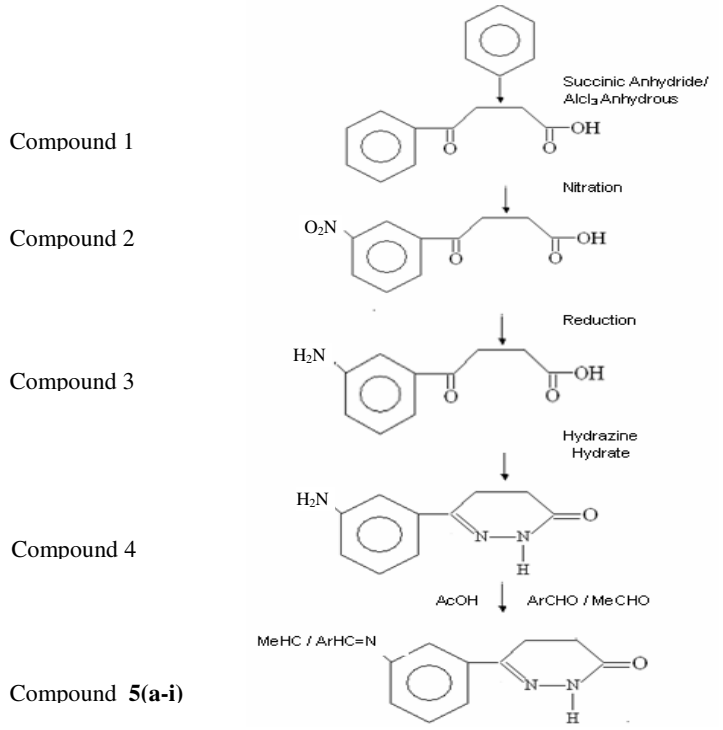
Abstract: 6-Phenyl(3'-imino-benzylidene)-2,3,4,5-tetrahydro pyridazin-3-one derivatives were synthesized from 6-(3'-aminophenyl)-2,3,4,5-tetrahydro pyridazin-3-one by reaction with different aldehydes. The respective pyridazinone was prepared by cyclization of appropriate *β*-(aminophenyl) propionic acid with hydrazine hydrate. The pyridazinone derivatives were tested for anticonvulsant activity by MES (maximal electro shock) method and found that few of them have shown significant anticonvulsant activity.

Keywords: Anticonvulsant, Cyclization, MES, Pyridazinone.

Introduction

Pyridazinone derivatives have been reported to possess wide variety of biological activities like antidiabetic[1], anticancer[2,3] anti AIDS, antihypertensive[1,4,5], antimicrobial[6], fungicidal[7], herbicidal[8], antifeedant[9], antiplatelet[10,11], analgesic, anti-inflammatory[3,12-15] and anticonvulsant[16-18] activities. In the view of above biological importance the new substituted pyridazinone derivatives were developed. The rationale behind the present study mainly was to prepare and identify the esteemed new molecule effective against the deadly convulsions. The wide range of activities of pyridazinone derivatives enacted us to proceed onto the present study. In continuation to our work on such derivatives, we now report the synthesis of nine pyridazinone derivatives (Table 1) and their anticonvulsant activity (Table 2). The pyridazinone derivatives were synthesized as shown in Scheme 1 by following sequence of reactions: (i) Friedel Craft acylation of benzene with succinic anhydride in the presence of anhydrous aluminium chloride yielded *β*-benzoyl propionic acid; (ii) nitration of *β*-benzoyl propionic acid with conc. HNO_3 and conc. H_2SO_4 that form *β*-*m*-nitrobenzoyl propionic acid; (iii) reduction of β-*m*-nitrobenzoyl propionic acid with Sn and

Conc. HCl to form β-*m*-aminobenzoyl propionic acid; (iv) cyclization of *β-m*-nitrobenzoyl propionic acid to react with hydrazine hydrate to form 6-(3'-nitrophenyl)-2,3,4,5-tetrahydro pyridazin-3-one (pyridazinone ring) and (iv) condensation of 6-(3'-nitrophenyl)-2,3,4,5-tetrahydro pyridazin-3-one with different aldehydes to form different pyridazinone derivatives.



Scheme 1. Reaction scheme

Aldehydes used were:
5a:Acetaldehyde, **5b:**4-OH benzaldyde, **5c:**Anisaldehyde, **5d:**Benzaldehyde, **5e:**Vanillin **5f:**Furfuradehyde, **5g:**2-Methoxy benzaldehyde, **5h:***p*-Dimethyl amino Benzaldehyde, **5i**: Salicylaldehyde

Experimental

Chemicals

Chemicals were procured from Central Drug House (P) Ltd.**,** India. All other chemicals & solutions used were of analytical grade.

Melting points of the pyridazinone derivatives were recorded in open capillary tube in liquid paraffin bath as well as in precision melting point apparatus and are uncorrected. Percentage yields were recorded accordingly (Table 1). Solvent system used throughout the experimental work for running TLC plates was toluene, ethyl acetate and formic acid (TEF) in the ratio of 5:4:1 and another solvent system also used were benzene and acetone in the ratio of 4:1. IR spectra were recorded by using KBr pellet technique on Perkin Elmer 337 IR spectrophotometer. ^{1}H NMR spectra were recorded in deuterated chloroform using tetra methyl silane (TMS) as an internal reference standard on BRUKER AVANCEII 400 NMR spectrometer.

Table 1. IR and ^{1}H NMR characteristics of the compounds

Compd No.	M.P, ^{0}C	Yield,%	Molecular formula	I.R and ^{1}H NMR spectra
1	120	70	$C_{10}H_{10}O_3$	**IR**: 3250 cm^{-1} (OH), 1720 cm^{-1} (C=O),
2	108	50	$C_{10}H_9NO_5$	3400 cm^{-1} (NH_2), 1617 cm^{-1} (C=C),
3	95	52	$C_{10}H_{11}NO_3$	**^{1}H NMR:** ($CDCL_3$) ppm 2.82(2H,
4	90	65	$C_{10}H_{11}N_3O$	t, CH_2), 3.32(2H, t, CH_2), 7.40-8.0 (m,Ar-H), 7.79(2H, m, H-2, 6).
5a	130	48	$C_{12}H_{13}N_3O$	**IR**:1360 cm^{-1} (NO_2), 1700 cm^{-1} (C=O),
5b	140	42	$C_{17}H_{25}N_3O_2$	1580 cm^{-1} (C=C) exo, 3450 cm^{-1} (NH).
5c	127	55	$C_{18}H_{17}N_3O_2$	**^{1}H NMR:**($CDCl_3$) ppm 2.8(s, 2H, CH_2),
5d	139	51	$C_{17}H_{15}N_3O$	3.1(s, 2H, CH_2), 7.2(s, H =CH), 7.40-
5e	164	62	$C_{18}H_{17}N_3O_3$	8.0(m, H, Ar-H), 8.8-9.0.0 (s, H, NH).
5f	158	53	$C_{15}H_{14}N_3O_2$	
5g	146	42	$C_{18}H_{17}N_3O_2$	
5h	157	55	$C_{19}H_{20}N_4O$	
5i	145	62	$C_{17}H_{15}N_3O_2$	

*Synthesis of benzoylpropionic acid (**1**)*

A mixture of benzene (30 mL) and anhydrous aluminium chloride (0.15 mole) was taken in three neck flask and refluxed on a water bath under anhydrous condition using calcium chloride guard tube at the top of condenser, followed by addition of succinic anhydride (0.10 mole) in small quantity with continuous stirring[1,3,13]. The stirring and heating were continued for 4 h. The reaction usually starts immediately. HCl gas was evolved and mixture becomes hot. In case of minimal and gentle reactions warmed gently. After leaving over night at room temperature the contents were poured into ice cold hydrochloric acid (2.5% v/v) followed by steam distillation. The aqueous solution was concentrated to small volume by evaporating on the water bath to obtain crude compound. It was purified by dissolving the 5% w/v of sodium bicarbonate solution followed by extraction with ether and chloroform. The aqueous layer on acidification with dilute hydrochloric acid gave **1** and was re-crystallized from aqueous ethanol.

Melting point:120 ^{0}C, yield 70%, R_f = 0.77, IR Spectra: 3250 cm^{-1} (OH),1720 cm^{-1} (C=O). NMR Spectra: ^{1}H NMR($CDCL_3$) ppm 2.82 (2H, t, CH_2), 3.32 (2H, t, CH_2), 7.74 (CH_2, m, H-3, 5), 7.79 (2H, m, H-2, 6).

*Synthesis of β-m-nitrobenzoylpropionic acid (**2**)*

To a mechanically stirred mixture of 12 mL concentrated nitric acid and 12 mL of concentrated sulphuric acid, 6 g of **1** was added in portion while keeping the mixture at 0-10 ^{0}C by efficient cooling (30-40 min.)[19-21]. The temperature was further allowed to rise to 15 ^{0}C in the course of 120 minutes and the solution was slowly stirred in ice-water. The precipitated material was washed with cold water to free from acid and re-crystallized from methanol. Lightly yellow color **2** was obtained. IR Spectra: 3091 cm^{-1} (CH), 1705 cm^{-1} (C=O), 1353 cm^{-1} (NO_2), 1617 cm^{-1} (C=C). NMR Spectra: ^{1}H NMR (DMSO) ppm 3.0 (t, 2H, CH_2), 3.36 ((t, 2H, CH_2),7.30- 8.2 (m, Ar-H), 8.82 (s, H, Ar-H).

*Synthesis of β-m-aminobenzoyl propionic acid (**3**)*

0.05 mole **2** was taken in 50 mL of ethanol and was refluxed with 5.00 g of tin and 10 mL of conc. HCl for 30-40 min[20]. The reaction mixture was then poured into water treated with sodium carbonate and extracted with ether. The ethereal solution after washing with water, dried with sodium sulphate, evaporated to get **3** and crystallized from methanol.

IR Spectra: 3400 cm^{-1} (NH_2), 1700 cm^{-1} (C=O), 1617 cm^{-1} (C=C), 3090 cm^{-1} (CH).NMR Spectra: ^1H NMR ($CDCl_3$) ppm 2.8 (t, 2H, CH_2), 3.20 (t, 2H, CH_2), 7.40-8.0 (m, H, Ar-H), 8.8-9.0 (s, H, NH)(s, 2H,NH_2)

*Synthesis of 6-(3'-amino phenyl)-2,3,4,5-tetrahydro pyridazin-3-one (**4**)*

The compound **3** (0.01 mole) was refluxed for 6 h with hydrazine hydrate (0.01 mole) in methanol (10 mL.) containing sodium acetate (50 mg)[1,3]. The content was concentrated and then poured into ice cold water to get the compound **4**. It was re-crystallized from ethanol. IR Spectra: 1685 cm^{-1} (C=O), 1352 cm^{-1} (NO_2), 3100 cm^{-1} (CH), 3550 cm^{-1} (NH). ^1H NMR ($CDCl_3$) ppm 2.8 (t, 2H, CH_2), 3.2 (t, 2H, CH_2), 7.40-8.0 (m, H, Ar-H), 8.8-9.0 (s, H, NH) (s, 2H,NH_2) .

*Synthesis of 6-(3'-iminophenyl benzylidene)-2,3,4,5-tetrahydropyridazin-3-one derivatives (**5a-i**)*

A mixture of **4** (0.005 mole) and different aldehydes (0.005 mole) were taken in glacial acetic acid (20 mL) and sodium acetate (2 g.) was added in it[5,22]. The content was refluxed for 6-8 hours (monitored by TLC), cooled and then poured into ice. The solid compound (**5a-5i**) was obtained and then re-crystallized with ethanol. IR Spectra:1360 cm^{-1} (NO_2), 1700 cm^{-1} (C=O), 1580 cm^{-1} (NH). ^1H NMR Spectra: ($CDCl_3$) ppm 3.10 (s, 2H, CH_2), 7.2(s,H =CH), 7.40-8.0 (m, H, Ar-H) 8.8.0 (s, H, NH).

Structure activity relationship

The maximum activity shown by the compounds were **5h** (*p*-dimethyl amino benzaldehyde derivative) in flexion phase, **5d** (benzaldehyde derivative) in extensor phase, **5i** (salicylaldehyde derivative) in clonus phase, and **5f** (furfuraldehyde derivative) in stupor phase. The derivatives acetaldehyde, 4-OH-benzaldehyde, anisaldehyde, vanillin and 2-methoxy benzaldehyde were not produce maximum protection against convulsion in terms of recovery in comparison with others. The compounds **5h**, **5d**, **5i** and **5f** which have shown the maximum inhibition in different stages suggest that the substitution of the amino group by *p*-dimethyl amino benzaldehyde, benzaldehyde, salicylaldehyde and furfuraldehyde impart maximum efficacy *i.e.*100% recovery or 66.66% protection.

Animals

Swiss albino mice weighing 20-30 g of male sex were maintained under controlled conditions of light (12 h) and temperature 25±1 ^0C in the animal house of Department of Pharmacy, GRD (PG) Institute of Management & Technology, 214, Rajpur Road, Dehradun, Uttaranchal, India, two weeks prior to the experiment for acclimatization. Animals had access to food and water *ad libitum*. All pharmacological activities were carried out as per CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals) norms (Regn No: 1145/a/07/CPCSEA), after obtaining the approval from the Institutional Animal Ethics Committee of Department.

Results and Discussion

The compounds were characterized on the basis of IR and ^1H NMR spectral data. IR spectrum (Table 1) showed the characteristics band at 1700, 1352, 3450, and 1580 cm^{-1} authenticated the presence of C=O, NO_2, NH and C=C groups. The ^1H NMR spectrum

showed the signal in the form of multiplet near δ=2.8 for CH_2 protons at 5-position, another multiplet was observed at about δ=3.0 for CH_2 at 4 position of (**1, 2, 3, 4** & **5**) compounds. Aromatic proton also observed in the aromatic region ranging from δ=7.0-8.0. Presence of other substitutes also authenticated in the ^{1}H NMR spectra at the assigned value (Table 1).

The present study on the synthesized pyridazinone derivatives have shown significant protection against Maximal Electro Shock (MES) Induced Seizure (Table 2) as compared to diphenyl hydantoin sodium (Phenytoin sodium). It is well known fact that the drug which provide protection against seizure induced by maximal electro shock method are generally effective against toxic-clonic seizure.

Table 2. Anticonvulsant effect of different pyridazinone derivative

Group	Treatment	Flexion, sec	Extensor, sec	Clonus, sec	Stupor, sec	Recovery, %	% Inhibition
A	Control	*3.34±0.125	*15.76±01.11	*6.76±01.11	*48.90±07.65	*60	--
B	Phenytoin	1.44±0.051	0.00±0.00	1.84±0.23	7.78±0.573	100	--
C	**5a**	2.58±0.271	14.40±1.45	7.40±3.25	40.24±5.35	80	33.33
D	**5b**	2.92±0.278	12.83±1.64	9.52±2.54	29.68±3.42	80	33.33
E	**5c**	3.00±0.310	12.80±1.85	7.72±1.035	26.72±1.07	80	33.33
F	**5d**	2.77±0.281	[b]12.38±0.78	10.91±1.82	20.40±4.81	[e]100	66.66
G	**5e**	3.04±0.117	13.66±0.75	8.68±0.885	32.48±5.32	80	33.33
H	**5f**	2.88±0.346	13.06±1.03	9.62±0.668	[d]20.28±2.27	[e]100	66.66
I	**5g**	2.76±0.102	13.32±1.16	4.94±1.04	26.56±4.32	80	33.33
J	**5h**	[a]2.45±0.308	12.40±1.05	5.80±0.735	25.51±4.92	100	66.66
K	**5i**	2.82±0.152	13.86±1.08	[c]4.30±0.721	29.82±1.58	100	66.66

*Standard drug: Phenytoin sodium (25mg/kg) Control: Distilled water *Value represent mean ± S.E. [a]P< 0.05, [b]P< 0.05, [c]P< 0.02, [d]P< 0.01 and [e]P< 0.01 when compared to control (Group A)*

Anticonvulsant activity

Male albino mice (25-35 g) were used to test the drugs (synthesized pyridazinone derivatives). Maximal Electro Shock (MES) method[23,24] was used for inducing seizures (Model**:** Techno Electro Convulsometer). The MES induced convulsions in animal represent grand mal type of epilepsy. In MES, electro shock was applied through the ear pinna passing current of 60 mA for 0.2 sec. The MES convulsions were divided into five phases: (i) flexion; (ii) extensor; (iii) clonus; (iv) stupor and (v) recovery or death. The female mice were excluded because of the fact that oestrous cycle influence the seizure threshold. Suspension of test compounds was prepared in 0.5% CMC and was injected intraperitoneally at dose level 50 mg/ kg body weight, to different group of five mice each. Reduction in the extension phase was calculated in comparison to diphenyl hydantoin sodium (Phenytoin Sodium) which was used as a standard at 25 mg/kg body weight dose (Table 2). The animals were observed for all the five phases as well as the duration. The abolition of the extensor phase in drug treated group was taken as experimental criterion for anticonvulsant activity. Thereby, the compound **5d** may be assumed to bear significant anticonvulsant activity.

Statistical analysis

Significance of differences between mean values of different convulsive levels were assessed by Student's 't' test and the data were expressed as mean ± S.E. Percentage inhibition was calculated by applying the formula:

Percentage inhibition = [(mean treatment-mean control)/(mean control)]x100.

Conclusion

Aldehyde derivatives of pyridazinone ring have shown sufficient anticonvulsant activity as compared to standard drug diphenyl hydantoin sodium against MES seizure on MES induced seizure in albino mice after intraperitonially administration of 50 mg/kg body weight dose. The potency order of the test compound on the extensor phase: **5d > 5h > 5c > 5b > 5f > 5g > 5e > 5i >5a**. The compound **5h**, **5d**, **5i** and **5f** have shown maximum recovery in practice. So, the compound **5d** may be regarded as true anticonvulsant because a substance is known to possess anticonvulsant property if it reduces or abolishes the extensor phase of MES convulsions.

The essentiality of anticonvulsant drugs in the eradication of convulsion is evident. The title compounds thus may have immense potential for contribution to human benefit. Scientific exploration of further studies of more derivatives as well as on more parameters is needed to elucidate the defined role of pyridazinones at the anticonvulsive levels.

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