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SYNTHESIS AND SCREENING OF NOVEL SUBSTITUTED INDANE 2, 3- DIONE FOR ANTICONVULSANT ACTIVITY

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ABSTRACT

Indane 2, 3- dione (isatin) derivatives have shown wide range of activities like antibacterial, antifungal, anticonvulsant etc. Particularly isatin nucleus has a lactam structure which is an important part of antiepileptic drugs (AEDs).For the synthesis of various derivatives of indane 2,3 –diones , first it was treated with ethyl chloroacetate and the resultant product was then treated with hydrazine hydrate and the hydrazides thus obtained was allowed to react with different aldehydes for the corresponding hydrazones. Hydrazones were then treated with chloramine T for the required product.

KEYWORDS: Indane 2, 3-dione, Hydrazones, 1, 3, 4-oxadiazole, Anticonvulsant activity,

INTRODUCTION

Epilepsy is the second most common and frequently encountered neurological condition that imposes heavy burden on individuals, families, and also on healthcare systems. As per a recent study, 70 million people have epilepsy worldwide and nearly 90% of them are found in developing regions. 30% to 60% of patients with epilepsy have not achieved adequate control with current medication and side effects are a significant problem. So there is a need of active research to develop new drugs in this field.[1]

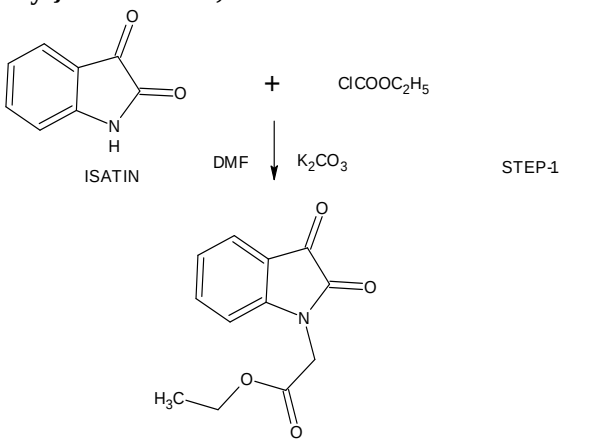
Isatin derivatives are proposed to act as selective AMPA receptor antagonists.1,3,4-oxadiazoles is an important class of heterocyclic compounds which have emerged as good anticonvulsant agents acting as benzodiazepine receptor agonists. All these factors prompted us to synthesis a hybrid molecule containing isatin and 1,3,4-oxadiazole moiety as anticonvulsant agents.[2,3]

EXPERIMENTAL METHODS

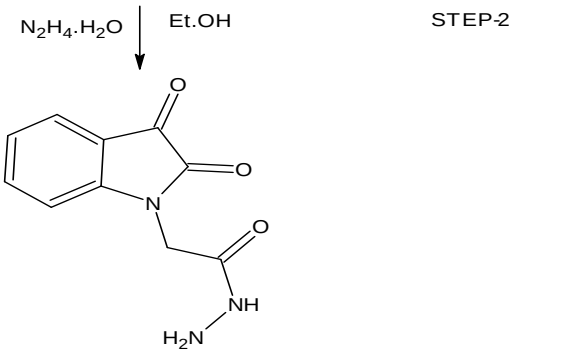
All the chemicals and reagents used were of analytical/synthetic grade. The synthesized compounds were characterized by UV Spectrophotometer, the Infrared spectra (IR), NMR and mass spectra.

Synthetic scheme

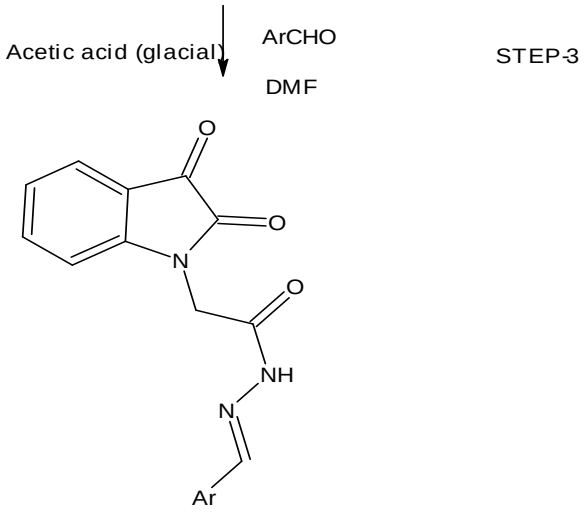
Substituted 1-{[5-(substituted)-1, 3, 4-oxadiazolyl] methyl}-1*H*-indole-2,3diones.



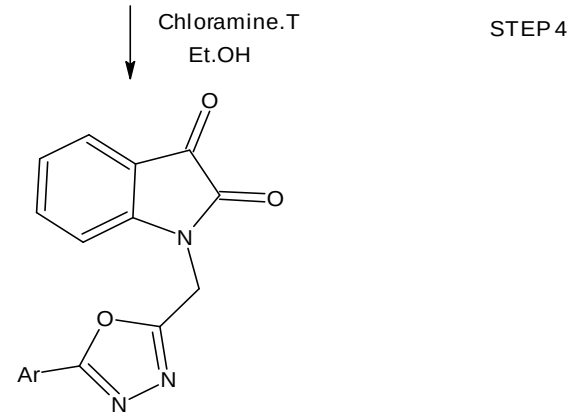
Ethyl (2, 3-dioxo-2,3-dihydro-1*h*-indol-1-yl)acetate (1)



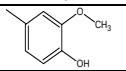
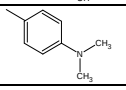
2-(2,3-dioxo-2,3-dihydro-1*H*-indol-1-yl) acetohydrazide (2)



Substituted [1-(2, 3-dioxo-2, 3-dihydro-1H-indol-1-yl)-2-oxoethyl] hydrazine (3a-3f)



1-{[5-(substituted)-1, 3, 4-oxadiazol-2-yl]methyl}-1*H*-indole-2,3dione (4a-4f)

Compd code	Ar-
4a	
4b	
4c	
4d	
4e	
4f	

Synthetic Procedures

Synthesis of ethyl (2, 3-dioxo-2,3-dihydro-1*H*-indol-1-yl)acetate(1). Isatin (0.42 g, 29 mmol) and ethyl chloroacetate (29 mmol) were mixed with DMF 10 ml in a 50 ml round bottom flask. Potassium carbonate (0.96 g, 7 mmol) was added to the mixture, the contents of the flask were refluxed for about two hours ,cooled and poured into 50 ml cold water the resultant orange red precipitate was collected washed with water dried and recrystallised from ethanol as reddish orange crystals. yield- (0.43 g, 64%). $C_{12}H_{11}NO_4$, M.Wt-233.22, m.p.-170^{0}C,R_f- (chloroform: methanol) (8:2)-0.52,UV-(λmax,nm)-299; IR(KBr): 3190 (ringN-H) 1600 (ringC=O), 748 (arylC-H). 2926 (N-CH_2), 1746 (C=O ester)

Synthesis of 2-(2,3-dioxo-2,3-dihydro-1*H*-indol-yl) acetohydrazide.(2) A mixture of ethyl (2,3-dioxo-2,3-dihydro-1*H*-indol-1-yl)acetate(**1**) (2.33 g,10 mmol) and hydrazine hydrate (0.75 ml,15 mmol) in ethanol 30 ml was refluxed on a water bath for 6 hrs. The reaction mixture was cooled and poured into ice cold water with stirring. The separated solid was filtered, washed with water and recrystallized from ethanol as cream coloured crystals. ^{154},$C_{10}H_9N_2O_3$,M.Wt-219.19,% yield (1.97g ,90%),m.p.-210^{0}C, R_f--Solvent system (toluene: chloroform:methanol) (5:3:2:)-0.40,UV-(λmax,nm)-273, IR(KBr):3300 (N-H amide), 1350 (C-N,2^0 amine), 2926 (N-CH_2), 798 (C-H aryl), 1680 (NH-CO), 1170 (N-N)

General procedure for the synthesis of substituted1-(2,3-dioxo-2,3-dihydro-1H-indol-1-yl)-2-oxoethyl]hydrazone(3a-3f) A mixture of (2a) (5 mmol) and appropriate aldehyde (5 mmol) in acetic acid (glacial) 10 ml was refluxed for 1 hr. The cooled reaction mixture was poured into ice cold water. The solid was filtered dried and recrystallized from ethanol as yellow crystalline solid.

Synthesis of benzaldehyde[1-(2,3-dioxo-2,3-dihydro-1*H*-indol-1-yl)-2 oxoethyl]hydrazone(3a), $C_{17}H_{13}N_3O_3$, M. Wt 307.304, prepared by the reaction of (2a) (2.19 g,10 mmol) and benzaldehyde(1.06 g,10 mmol) as yellow crystalline solid (2.91g, 95%), m.p.218-220 ^{0}C, R_f--(toluene: chloroform: methanol) (5:3:2:)-0.48, IR (KBr):3415 (sec. NH), 1680 (NH-CO), 1350 (C-N,2^0 amine), 2926 (N-CH_2), 798 (C-H aryl), 1158 (N-N), 3415 (N-H 2^0 amine).

Synthesis of 4-chlorobenzaldehyde [1-(2,3-dioxo-2,3-dihydro-1H-indol-1-yl)-2-oxoethyl]hydrazone(3b), $C_{17}H_{12}ClN_3O_3$, M. Wt 341.304, prepared by the reaction of (2a) (2.19 g,10 mmol) and 4-chloro benzaldehyde (1.4 g,10 mmol) as yellow crystalline solid (3.97 g, 95%),m.p.230-232, R_f-- (toluene:chloroform:methanol))-0.57, IR(KBr):3415 (sec. NH), 1680 (NH-CO), 1350 (C-N,2^0 amine), 2926 (N-CH_2), 798 (C-H aryl), 1158 (N-N), 3415 (N-H 2^0 amine), 1011 (C-Cl).

Synthesis of 2,4 -dichlorobenzaldehyde [1-(2,3-dioxo-2,3-dihydro-1*H*-indol-1-yl)-2-oxoethyl]hydrazone (3c), M.Wt 376.193, $C_{17}H_{11}Cl_2N_3O_3$ prepared by the reaction of (2a) (2.19 g,10 mmol) and 2,4 -dichlorobenzaldehyde (1.75 g, 10 mmol as yellow crystalline solid(3.57 g, 95%),m.p.240, R_f--(toluene:chloroform:methanol))-0.58, IR(KBr):3415 (sec. NH), 1680 (NH-CO), 1350 (C-N,2^0 amine), 2926

($N\text{-}CH_2$), 798 (C-H aryl), 1158 (N-N), 3415 (N-H 2^0 amine) 1011 (C-Cl).

Synthesis of 4-hydroxybenzaldehyde [1-(2,3-dioxo-2,3-dihydro-1*H*-indol-1-yl)-2-oxoethyl]hydrazone(3d) $C_{17}H_{13}N_3O_4$, M.Wt 323.303, prepared by the reaction of (2a) (2.19 g, 10 mmol) and 4- hydroxybenzaldehyde (1.22 g, 10 mmol) as a yellow crystalline solid,(3.00 g, 93%) m.p. 230 ^{0}C, R_f--(toluene:chloroform:methanol) (5:3:2:)-0.58, IR(KBr):3236 (sec N-H), 1680 (NH-CO), 1350 (C-N,2^0 amine), 2926 ($N\text{-}CH_2$), 798 (C-H aryl), 1158 (N-N), 3415 (N-H 2^0 amine), 3373 (O-H), 1285 (C-O).

Synthesis of 4-hydroxy-3-methoxybenzaldehyde [1-(2,3-dioxo-2,3-dihydro-1*H*-indol-1-yl)-2-oxoethyl]hydrazine (3e) $C_{18}H_{15}N_3O_5$, M.Wt 353.329 prepared by the reaction of (2a) (2.19 g, 10 mmol) and 4-hydroxy-3-methoxybenzaldehyde (1.52 g, 10 mmol) as a yellow crystalline solid (3.21 g, 94%), m.p. 250 ^{0}C, Rf-(toluene:chloroform: methanol)(5:3:2)-0.47, IR(KBr): 3236 (sec N-H), 1680 (NH-CO), 1350 (C-N,2^0 amine), 2926 ($N\text{-}CH_2$), 798 (C-H aryl), 1158 (N-N), 3415 (N-H 2^0 amine), 1271 (C-O-C,assym), 1098 (C-O-C symm), 3373 (O-H), 1285 (C-O).

Synthesis of 2.4-(dimethylamino)benzaldehyde [1-(2,3-dioxo-2,3-dihydro-1*H*-indol-1-yl)-2-oxoethyl]hydrazine (3f) $C_{19}H_{18}N_4O_3$, M.Wt 350.371 prepared by the reaction of (2a) (2.19 g, 10 mmol) and 4-(dimethylamino) benzaldehyde (1.50 g, 10 mmol) as a yellow crystalline solid,(3.29 g, 94%), m.p. 245 ^{0}C, R_f-(toluene:chloroform:methanol)(5:3:2:)-0.46, IR(KBr): 3236 (sec N-H), 1680 (NH-CO), 1350 (C-N, 3^0 amine), 2926 ($N\text{-}CH_2$), 798 (C-H aryl), 1158 (N-N), 3415 (N-H 2^0 amine).

General procedure for the synthesis of 1-{[5-(substituted)-1,3,4-oxadiazol-2-yl]methyl}-1*H*-indole-2,3-dione (4a-4f). Hydrazone (10 mmol) was dissolved in ethanol and chloramine T (50 mmol) refluxed for 4 hours. Excess ethanol was completely removed by boiling on a water bath leaving behind a solid mass which was recrysatallized from ethanol.

Synthesis of 1-[(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]-1*H*-indole-2,3-dione(4a) $C_{17}H_{11}N_3O_3$, M.Wt 305.288 prepared by the reaction of (3a) (3.07 g, 10 mmol) and chloramineT $3H_2O$ (2.81 g, 10 mmole) as yellow crystalline solid,(2.86 g, 94%) m.p.180 ^{0}C R_f-(toluene:chloroform:methanol)(5:3:2:)-0.71, UV-(λmax, nm) -305, IR(KBr):1350 (C-N,2^0 amine), 2926 ($N\text{-}CH_2$), 798 (C-H aryl), 1158 (N-N), 1271 (C-O-C,assym), 1098 (C-O-C symm), 1596 (C=N).

Synthesis of 1-{[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]methyl}-1*H*-indole-2,3-dione (4b) $C_{17}H_{10}ClN_3O_3$, M.Wt 339.732 prepared by the reaction of (3b) (3.41 g, 10 mmol) and chloramine T $3H_2O$ (2.81 g, 10 mmol) as yellow crystalline solid,(3.18 g, 94%)m.p.190 ^{0}C. R_f-(toluene:chloroform:methanol)(5:3:2:)-0.80, UV-(λmax, nm) -310, IR(KBr):1350 (C-N,2^0 amine), 2926 ($N\text{-}CH_2$), 798 (C-H aryl), 1158 (N-N), 1271 (C-O-C,assym), 1098 (C-O-C symm), 1596 (C=N), 673 (C-Cl).

Synthesis of 1-{[5-(2,4-dichlorophenyl)-1,3,4-oxadiazol -2-yl]methyl}-1*H*-indole-2,3-dione (4c) $C_{17}H_9Cl_2N_3O_3$, M. Wt 374.177 prepared by the reaction of (3c) (3.76 g, 10 mmol) and chloramine T $3H_2O$ (2.81 g, 10 mmol) as yellow crystalline solid,(3.47 g, 93%) m.p. 205 ^{0}C, R_f- (toluene: chloroform: methanol) (5:3:2:) -0.81, UV-(λmax,nm)-317, IR(KBr): 1350 (C-N,2^0 amine), 2926 ($N\text{-}CH_2$), 798 (C-H aryl), 1158 (N-N), 1271 (C-O-C,assym), 1098 (C-O-C symm), 1596 (C=N), 673 (C-Cl).

Synthesis of 1-{[5-(2-hydroxyphenyl)-1,3,4-oxadiazol-2-yl]methyl}-1*H*-indole-2,3-dione (4f) $C_{17}H_{11}N_3O_4$, M.Wt 321.287 prepared by the reaction of (3f) (3.23 g,10 mmol) and chloramine T $3H_2O$ (2.81 g, 10 mmol) as yellow crystalline solid,(3.04 g, 94%),m.p.195 ^{0}C, R_f-(toluene: chloroform: methanol) (5:3:2:)-0.80, UV-(λmax, nm)-340, IR(KBR): 1350 (C-N,2^0 amine), 2926 ($N\text{-}CH_2$), 798 (C-H aryl), 1158 (N-N), 1271 (C-O-C,assym), 1098 (C-O-C symm), 1468 (C=N), 3383 (O-H).

Synthesis of 1-{[5-(4-hydroxy-3-methoxyphenyl)-1,3,4-oxadiazol-2-yl]methyl}-1*H*-indole-2,3-dione(4j) $C_{18}H_{13}N_3O_5$, M. Wt 351.313 prepared by the reaction of (3j) (3.53 g, 10 mmol) and chloramine T $3H_2O$ (2.81 g, 10 mmol) as yellow crystalline solid,(3.29g, 94%) m.p.200 ^{0}C, R_f- (toluene: chloroform: methanol) (5:3:2:)-0.75, UV-(λmax, nm)-314. IR (KBr): 1350 (C-N, 2^0 amine), 2926 (N-CH2), 798 (C-H aryl), 1158 (N-N), 1271 (C-O-C,assym), 1098 (C-O-C symm), 1608 (C=N), 3370 (O-H). ^{1}HNMR ($CDCl_3$, 300 MHz), δ 4.4 (s, 2H, $N\text{-}CH_2$-), 7- 7.8 (m, 8H, aromatic CH), 3.5 (s,3H,OCH_3)

Synthesis of 1-({5-[4-(dimethylamino)phenyl]-1,3,4-oxadiazol-2-yl}methyl)-1*H*-indole-2,3-dione (4l) $C_{19}H_{16}N_4O_3$ M.Wt 348.355 prepared by the reaction of (3l) (3.50 g,10 mmol) and chloramine T $3H_2O$ (2.81 g, 10 mmol) as yellow crystalline solid,(3.30 g, 95%), m.p.210 ^{0}C, R_f- (toluene:chloroform:methanol)(5:3:2:)-0.72, UV-(λmax,nm)-341. IR(KBr):1365 (C-N,2^0 amine), 2926 (N-CH2), 750 (C-H aryl), 1157 (N-N), 1284 (C-O-C,assym), 1098 (C-O-C symm), 1605 (C=N). ^{1}HNMR ($CDCl_3$,300 MHz), δ 4.4 (s, 2H, $N\text{-}CH_2$-), 7- 7.8 (m, 8H, aromatic CH), 1.5(s, 3H,$N\text{-}CH_3$) , 2 (s,3H,$N\text{-}CH_3$)

Biological Activity

Synthesized compounds were randomly selected for the biological activity.

Acute Toxicity Studies[4,5]

Healthy female albino mice of weighing 20-25 g were divided into six groups of six animals each. The animals were starved overnight. The derivative as a suspension in

1% CMC was given orally in a dose of 120 mg/kg, 240 mg/kg, 480 mg/kg and 960 mg/kg and 1920mg/kg body weight. The control group was treated with vehicle only (10ml/kg body weight). After dosing the animals was closely observed for first 4 hours and intermittently for the next 24 hours to assess the morbidity and mortality. The number of deaths was noted after 24 hours. Any change in skin, eyes, mucous membrane and behavioral pattern were recorded

Anticonvulsant Activity[4,5]

Test compounds and standard drugs were administered intraperitoneally as 1% CMC suspension. After 30 minutes of drug administration, the animals were held properly. They were given electrical shock through ear electrodes of 150 mA for 0.2 sec by Electroconvulsiometer (Techno). Group 1 were treated with 1% CMC suspension and served as a control. Group 2 were treated with phenytoin (25 mg/kg) and served as a standard group III-VI were treated with 4b,4d,4e,4f(120 mg/kg) respectively 1hr before seizure induction and onset time of tonic flexion, extension, and clonic phase were noted. The convulsive score, protection index as well as reduction time of tonic extensor phase were noted and all the data (Mean ± SEM) were analyzed statistically by students" t "test.

RESULTS AND DISCUSSION

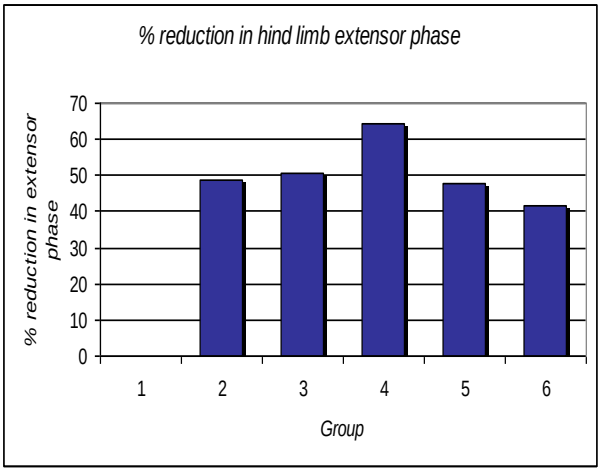
Anticonvulsant activity data of synthesized 1-{[5-(substituted)- 1,3,4- oxadiazol-2-yl] methyl}-1*H*-indole-2,3- dione

Table 1:

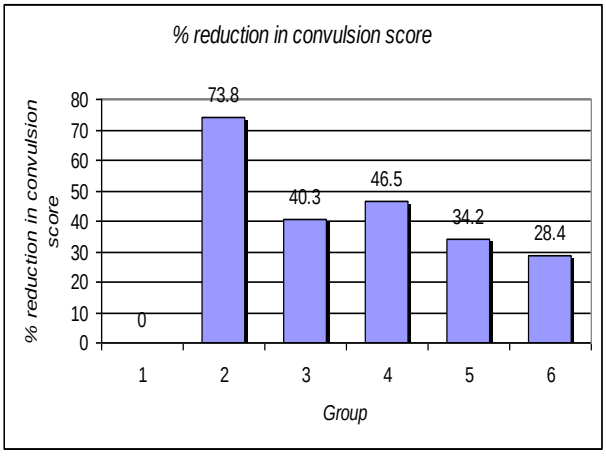
Group	Treatment	Extensor. (Mean±SEM)	Flexion (Mean±SEM)	% Redn.in hind limb extensor. phase	Convulsion score	% Redn. In convulsion score
Group1	Control	18 ± 0.3161* **	2.16 ± 0.2458* **	0	26	0
Group2	Phenytoin 25mg/Kg	9.2 ± 0.3741* **	2.4 ± 0.4901* **	48.8	17.2	73.8
Group3	4b 120mg/Kg	9 ± 0.3163* **	3.5 ± 0.6322* **	50.6	15.5	40.3
Group4	4d 120mg/Kg	6.4 ± 0.2454* **	2.5 ± 0.200* **	64.2	14.4	46.5
Group5	4e 120mg/Kg	9.4± 0.3746* **	2.3 ± 0.400* **	47.7	16.8	34.2
Group6	4f 120mg/Kg	10.6 ± 2457* *	2 ± 0.4476**	41.4	18.6	28.4

Values are mean±SEM (n=6) *** All the values are found to be highly significant when compared with control
* = significant.

% Reduction in Hind Limb Extensor Phase



Effect on % Reduction of Conzvulsion Score



Among them p-hydroxy derivative exhibited the best convulsive score reduction than corresponding p-chloro derivative. Both had comparable Log P values and perhaps the presence of electron donating substituent may be the possible reason for increased activity of the former derivative. The reduction in hind limb extensor phase is significant about 64% for p-hydroxy derivative,

50% for p-chloro derivative compared to 48.8% for phenytoin. 4e showed 47.7% reduction in hind limb extension comparable with phenytoin. 4f showed less activity among the test compounds.

CONCLUSION

The results of our study are promising and encouraging and we sincerely hope that these studies will stimulate further research in this direction and will result in the development of more effective and less toxic AEDs in near future.

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