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Synthesis, Characterization and Anticonvulsant Activity of 2-Ketophenyl-3-(Substituted aryl)-1-Thiazolidin-4-Ones

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ABSTRACT

In the present study a series of 2-ketophenyl-3-(substituted aryl)-1-thiazolidin-4-ones were synthesized by cyclocondensation of ketoazomethines with thioglycolic acid and evaluated for their potential anticonvulsant activity by determining their ability to provide protection against convulsions induced by electroconvulsiometer. Synthesized compounds were characterized on the basis of elemental, IR, ^{1}H NMR and ^{13}C.NMR analysis. These compounds showed significant activity in MES induced convulsions in comparison to control.

Keywords: *4-thiazolidinones*, Anticonvulsant activity, Phenytoin, MES

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INTRODUCTION

The increasing diversity of heterocyclics, particularly 4-thiazolidinones derivatives [1-5] have been widely investigated for a range of pharmacological activities [6-8] such as antiviral, antihyperglycemic [9-11], antibacterial, antagonist [12], antifungal [13,14], insecticidal [15], analgesic effects and anticancer drugs. Thiazolidinone derivatives are also well known for their pronounced anticonvulsant activity [16-19]. The presence of a thiazolidine ring in penicillin and related derivatives were the first recognition of its occurrence in nature. Thiazolidine-4-one represents a prevalent scaffold in drug discovery. Thiazolidine-4-ones have many interesting activity profiles, namely COX-1inhibitors [20], antioxidant properties [21], inhibitors of the bacterial enzyme MurB, which was precursor acting during the biosynthesis of peptidoglycan, non-nucleoside inhibitors of HIV-RT [22] and anti-histamine agents [23]. The high reactivity of amino and active methylene groups next to the carbonyl of the thiazolidin ring represents useful targets for many organic reactions. Some of the transition metals complexes of 4-Thiazolidinones are essential elements for biological systems and also helps in seed germination [24] and polymer synthesis [25]. Our aim is to search for biologically active heterocyclic compounds containing sulfur and nitrogen, we have synthesized a series of 2-ketophenyl-3-(substituted aryl)-1-thiazolidin-4-ones.

MATERIAL AND METHODS

Melting points were determined in open glass capillary and were found uncorrected. Elemental analyses of samples were done on Euro EA Elemental Analyzer. Infrared spectra were recorded in KBr medium on Thermo Nicolet Nexus spectrophotometer and 300 MHz NMR spectra were recorded in dimethylsulphoxide medium on Varien C-13 spectrophotometer using TMS as internal standard. The progress of the reaction was monitored by thin layer chromatography with silica-gel MERCK 60F254 precoated Streptococcus sheets using dichloromethane/ethanol 8/2 as eluent.

General procedure for preparation of 4- thiazolidinones

Preparation of ketoazomethines (4a-f):

Phenyl glyoxal(2, 0.2 mol) and aniline (3a-f, 0.2 mol) were taken in a round bottom flask containing 200 ml of ethanol and refluxed on water bath for 8hrs. Excess of ethanol was removed from reaction mixture and cooled at room temperature. Then it was poured in ice cold water and filtered. Solid obtained were collected and recrystallized with ethanol. Similarly, other ketoazomethines of p-chloro, p-bromo, p-nitro, p-methyl and p-diethylaminoanilines were prepared.

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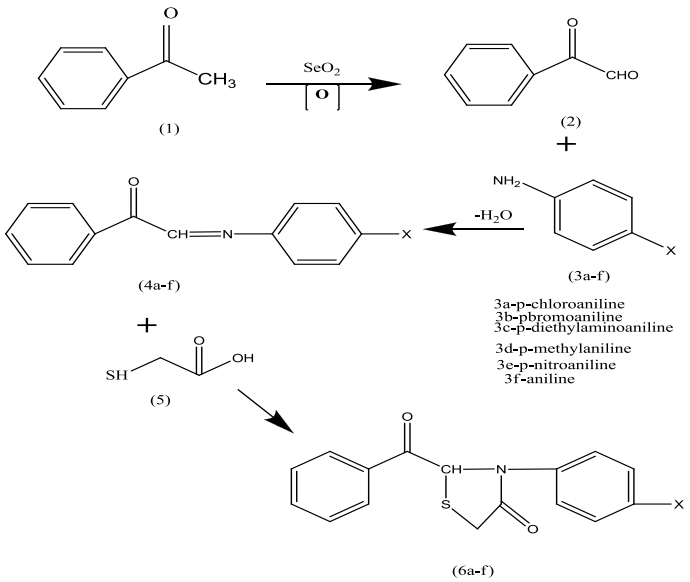

Scheme 1.

Preparation of 2-ketophenyl-3-(substituted aryl)-1-thiazolidin-4-one (6a-f) (Scheme-I)

Ketoazomethines (0.2mol, 4a-f) and thioglycolic acid (0.3mol, 5) were refluxed in dry benzene for ~ 15 hrs. The reaction mixture was concentrated to half of its volume over water bath and then neutralized with sodium bicarbonate solution. The contents were cooled and poured in ice cold water and filtered. The solid obtained was collected and purified with recrystallization. All compounds were synthesized by adopting same procedure.

RESULTS AND DISCUSSION

2-ketophenyl-3-(4-chloroaryl)-1-thiazoldin-4-one(a)

IR(KBr,cm^{-1})1648($C=O_{cyc.}$),1605($C=O_{chain}$),752(C=S),660(C-Cl),1326($C-N_{cyc.}$),3061(Ar-H)
^{1}H.NMR,($CDCl_3$,250MHz)δ(PPM)J(Hz):7.48-7.50(Ar-H,m),6.89(Ar-H,m)5.11(1H,s), 3.98(2H,s)
^{13}C.NMR,($CDCl_3$,75MHz)δ(PPM):36.27(CH_2),112.36,121.22,123.39,131.47,129.87,154.17(Ar), 172.99(C=S),200.99(C=O).

2-ketophenyl-3-(4-bromoaryl)-1-thiazoldin-4-one (b)

IR(KBr, cm−1):1651 ($C=O_{cyc}$),1609($C=O_{chain}$),763 (C=S),560(C-Br),1241($C-N_{cyc.}$),3066(Ar-H)
^{1}H.NMR,($CDCl_3$,250MHz) δ(PPM)J(Hz):7.51-7.72(Ar-H,m), 6.78(ArH,m), 5.15(1H,s), 3.82(2H,s)
^{13}C.NMR,($CDCl_3$,75MHz)δ(PPM):36.27(CH_2),112.36,121.22,123.39,131.47,129.87,154.17(Ar), 172.99(C=S),200.99(C=O).

2-ketophenyl-3-(4-diethylaminoaryl)-1-thiazoldin-4-one (c)

IR(KBr, cm^{-1}):1753 ($C=O_{cyc}$),1682($C=O_{chain}$),648 (C=S),1458(ArC-C_2H_5),3056(Ar-H),1257($C-N_{cyc}$)
^{1}H.NMR, ($CDCl_3$, 250MHz) δ(PPM) J(Hz): 7.56-7.73(Ar-H,m), 6.92(Ar-H,m),

5.21(1H,s)3.89(2H,s), 2.75(3H,m),*[13]C.NMR*, ($CDCl_3$, 75MHz) δ(PPM): 36.27(CH_2), 112.36, 121.22, 123.39, 131.47, 129.87, 154.17 (Ar), 172.99(C=S), 200.99(C=O).

Table 1: Characterization data of 4-thiazolidinones (6a-f)

Comp.	M.F.	Colour	Yield %	M.P.(°C)	Elemental analysis (%) Cald.(found)			
					S	C	H	N
6a	$C_{16}H_{12}NO_2SCl$	Pink	67.4	223	7.62 (7.74)	60.37(60.44)	3.77(3.18)	4.40(4.76)
6b	$C_{16}H_{12}NO_2SBr$	Yellow	78.5	245	9.2(9.18)	53.35(53.39)	3.31(3.35)	3.86(3.15)
6c	$C_{20}H_{22}N_2O_2S$	Light Brown	63.6	235	8.03(7.82)	67.79(67.83)	6.21(6.35)	7.90(7.65)
6d	$C_{17}H_{15}NO_2S$	Brown	71.5	218	8.91(7.82)	68.68(68.85)	5.75(5.86)	4.71(4.23)
6e	$C_{16}H_{12}N_2O_4S$	Light Green	65.6	228	8.61(8.53)	58.53(58.74)	3.65(3.46)	8.53(8.32)
6f	$C_{16}H_{13}NO_2S$	Orange	59.5	210	8.31(8.45)	67.84(67.73)	4.59(4.13)	4.96(4.12)

2-ketophenyl-3-(4-methylaryl)-1-thiazoldin-4-one (d)

IR (KBr, cm^{-1}): 1680 ($C=O_{cyc.}$),1709($C=O_{chain}$),778 (C=S),1316($C-N_{cyc}$), 2970(Ar-H), 1407(ArC-CH_3), *[1]H.NMR*, ($CDCl_3$, 250MHz) δ(PPM) J(Hz): 7.48-7.51(ArH,m), 4.02(2H,s),4.31(2H,s), 2.75(3H,s,Ar-CH_3),5.34(1H,s), *[13]C.NMR*, ($CDCl_3$, 75MHz) δ(PPM): 36.27(CH_2), 112.36, 121.22, 123.39, 131.47, 129.87, 154.17 (Ar), 172.99(C=S), 200.99(C=O).

2-ketophenyl-3-(4-nitroaryl)-1-thiazoldin-4-one (e)

IR(KBr,cm^{-1}):1753($C=O_{cyc}$),1652($C=O_{chain}$),771(C=S),1286($C-N_{cyc.}$)3062(Ar-H) 1569,1286(ArC-NO_2), *[1]H.NMR*, ($CDCl_3$,250MHz), δ(PPM), J(HZ): 7.337.36 (ArH,m), 4.05(2H,s), 4.28(2H,s),5.52(1H,s),*[13]C.NMR*, ($CDCl_3$, 75MHz) δ(PPM): 36.27(CH_2), 112.36, 121.22, 123.39, 131.47, 129.87, 154.17 (Ar), 172.99(C=S), 200.99(C=O).

2-ketophenyl-3-aryl-1-thiazoldin-4-one (f)

IR(KBr, cm^{-1}): 1670 ($C=O_{cyc.}$),1595($C=O_{chain}$),1238,1316($C-N_{cyc.}$),3052(Ar-H),756 (C=S), *[1]H.NMR*, ($CDCl_3$, 250MHz) δ(PPM) J(Hz): 7.35-7.54(ArH,m),4.25(2H,s),5.23(1H,s), *[13]C.NMR*, ($CDCl_3$, 75MHz) δ(PPM): 36.27(CH_2), 112.36, 121.22, 123.39, 131.47, 129.87, 154.17 (Ar), 172.99(C=S), 200.99(C=O).

Toxicity Studies

Albino mice of either sex weighing approximately 25-30 gm, kept in propylene cages in groups of 5 mice per cage under controlled environmental conditions of temperature (22 ± 2^0C) and humidity (50-55%) with 12:12 hour light dark cycle and free access to food and water, were administered the sample solutions in different doses of 10mg, 50mg, 75 mg, 100mg per kg of body weight intraperitonially whereas pair of control mice received equal

volume of solvent only. All the experiments were conducted after obtaining permission from the Institutional Animal Ethics Committee (IAEC).

Mortality of each mice administered different doses was observed after 2hrs and 24hrs for each sample.LD_{50} values of drugs under study were calculated [26,27] as follows. After calculating log dose of each compound corrected factor for 0% and 100% deaths have been calculated as 5% and 95% respectively using formulae.

Corrected factor for 0% deaths = 100(0.25/n)
Corrected factor for 100% deaths = 100(1-0.25/n)

Where n= number of animals in each group. After each value of corrected percent probit, probit percentage has been determined. Log dose values of each compound was observed and noted in Table. 3 as LD_{50}.

Anticonvulsant Activity

The synthesized compounds were evaluated for their anticonvulsant activity using maximal electroshock seizure method. MES seizures were induced by electroconvulsiometer. Maximal seizures were elicited by 60 Hz alternating current of 150 mA intensity for 0.2 sec using corneal electrodes. The animals were randomly allocated into 3 groups of 6 animals each and the animals were allowed to acclimatize to laboratory conditions 48 hrs before the start of the experiment. The animals were fasted for 24hrs before the experiment with free access to water. Control group received same volume of Vehicle (DMSO solvent).Standard drug phenytoin was administered orally at a dose of 25 mg/kg. The test compounds were administered orally at an equimolar oral dose of 30mg/kg phenytoin. The anticonvulsant activity was assessed after 30 min. of administration. The abolition of hind limb tonic extensor spasm was recorded as a measure of anticonvulsant activity.

Statistical Analysis

Statistical analysis of the anticonvulsant activity of the synthesized compounds on animals was evaluated using a one-way analysis of variance (ANOVA). In all the cases, post-hoc comparisons of the means of individual groups were performed using Tukey test. Differences with $P<0.001$ between experimental groups at each point were considered statistically significant. All values were expressed as mean ± SEM (standard error of mean).

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Table 3: Toxicity observations of 4-thiazolidinones

Compound	Dose mg. /kg. body weight	Log dose	No. of animals survived in group of 5	Death(%)	Corrected%	Probit value	LD_{50} mg./kg. body weight
6a $C_{16}H_{12}NO_2SCl$	10 50 75 100	1.00 1.70 1.87 2.00	5 5 4 3	0 0 20 40	5 5 20 40	3.36 3.36 3.97 4.75	123.13
6b $C_{16}H_{12}NO_2SBr$	10 50 75 100	1.00 1.70 1.87 2.00	5 5 3 3	0 0 40 40	5 5 40 40	3.36 3.36 4.75 4.75	112.35
6c $C_{20}H_{22}N_2O_2S$	10 50 75 100	1.00 1.70 1.87 2.00	5 5 4 2	0 0 20 60	5 5 20 60	3.36 3.36 3.97 5.25	97.46
6d $C_{17}H_{15}NO_2S$	10 50 75 100	1.00 1.70 1.87 2.00	5 4 3 2	0 20 40 60	5 20 40 60	3.36 3.97 4.75 5.25	103.54
6e $C_{16}H_{12}N_2O_4S$	10 50 75 100	1.00 1.70 1.87 2.00	5 5 4 4	0 0 20 20	5 5 20 20	3.36 3.36 3.97 3.97	128.34
6f $C_{16}H_{13}NO_2S$	10 50 75 100	1.00 1.70 1.87 2.00	4 4 3 3	20 20 40 40	20 20 40 40	3.97 3.97 4.75 4.75	109.76

Table 4. Extensor Phase Data of Compounds

S.No.	Compound	Dose (mg/kg)	Hind Limb Extensor (Mean ± S.E.M)
1	Control	25	86.00±0.40
2	Phenytoin	25	13.25±0.25
3	6a	25	11.5±0.76
4	6b	25	26±0.73
5	6c	25	7.9±0.61
6	6d	25	10.16 ± 0.60
7	6e	25	13.16 ± 0.60
8	6f	25	6.5±0.34

CONCLUSION

The synthesized compounds were evaluated by IR, NMR and ^{13}C.NMR techniques. The pharmacological data indicated that among all the compounds being screened, compounds 6b,6c and 6d showed significant antiepileptic activity ($P<0.001$) and compound 6a and 6e show the less significant activity ($P<0.01$) when compared to control group.

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