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Synthesis and analgesic activity of some new substituted aryl-4-thiazolidinones

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ABSTRACT

A new series of substituted aryl-4- thiazolidinones were prepared by cyclocondensation of ketoazomethines and thioglycolic acid. Ketoazomethines were synthesized by condensation of phenyl glyoxal (prepared by partial oxidation of acetophenone) and various Para-substituted anilines. The synthesized compounds were identified by elemental, spectral studies and screened for analgesic activity.

Key words: Synthesis, Ketoazomethines, 4-thiazolidinones, analgesic activity.

INTRODUCTION

Among biologically active heterocyclic, 4-thiazolidinones are most popular, probably owing to their high versatility in exhibiting diverse potent biological properties viz., anticonvulsant [1, 2] anti inflammatory[3-6], antiprotozoa1[7], antipyretics[8-11], anti-HIV[12], CFTR-inhibitor[13],antimicrobial[14]etc. Although plenty of thiazolidinones and their derivatives have been synthesized by condensation of schiffs bases [15-17], Haloacetanilide [18], Thiosemicarbazone [19], Thiamide [20] with thiocyanates, halo fatty acid ,aldehydes etc. In the present study we synthesize a new series of substituted aryl-4-thiazolidinones derivatives by condensing ketoazomethines (prepared by Phenyl glyoxal and p-substituted anilines) and thioglycolic acid in benzene (Scheme-1).The structures of these derivatives were assigned on the basis of elemental analysis, IR and H^1 NMR spectral data. The compounds were screened for analgesic activities.

MATERIAL AND METHODS

All the chemicals used were either E-Merck or Qualigens. 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. Column Chromatography was carried out by using silica gel (finer than 200#.)

Preparation of Phenyl Glyoxal: Phenyl Glyoxal was prepared by partial oxidation of acetophenone with selenium dioxide. Reaction mixture containing acetophenone (1, 0.2mol) and selenium dioxide (0.4mol) was taken in round bottom flask containing 300ml of ethanol and refluxed for 5 hrs. Orange yellow color reaction

mixture was decanted and concentrated over bath water and dissolved in ether to remove selenium from product.

General procedure for preparation of 4-thiazolidinones

(II) 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.

(III) preparation of 2-ketophenyl-3-substituted aryl-1-thiazolidin-4-one (6a-f)

(scheme 1) ketoazomethines (0.2mol, 4a-f) and thioglyciolic 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.

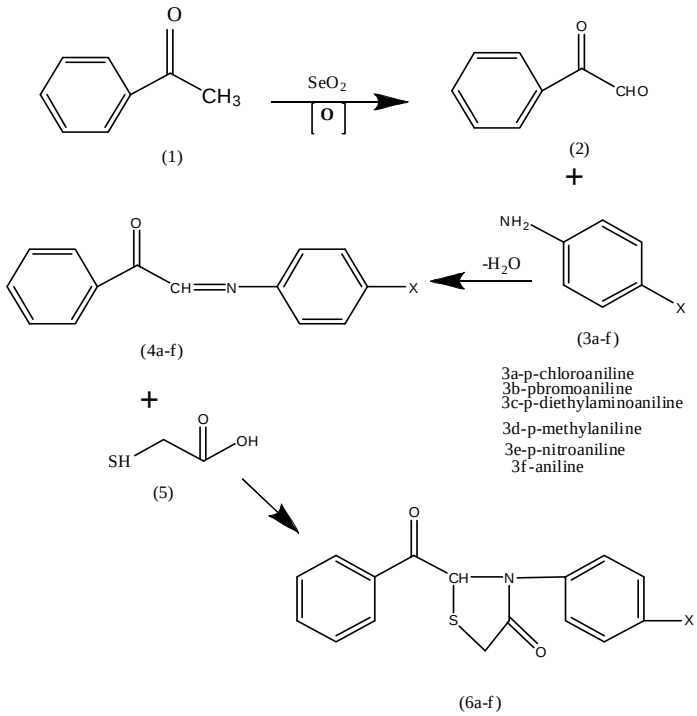
Pharmacological studies

Preparation of sample solutions

Standard solutions were prepared by dissolving known quantities of compounds in known volume of non-toxic solvent (dimethylsulphoxide).

Toxicity Study

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^{0}C) 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 50mg, 75 mg, 100mg, 200mg per kg of body weight intraperitonially whereas pair of control mice received equal volume of solvent only. 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 [21, 22] as follows



Scheme 1:

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

From probit table, Log dose values of each compound was observed and noted in

Table. 3 as LD_{50}.

Analgesic Study

For analgesic studies animals were divided into three groups.

Control group

It consisted of 6 animals treated with same volume of Vehicle (DMSO solvent) intraperitonially prior to induction to heat application.

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

Compd.	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 (9.13)	68.68 (68.65)	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)
6d	$C_{16}H_{13}NO_2S$	Orange	59.5	210	8.31 (8.45)	67.84 (67.73)	4.59 (4.13)	4.96 (4.12)

Table 2: IR, H^1 NMR Spectral data of the compounds (6a-f)

Compd.	IR (cm^{-1}) (KBr)	H^1 NMR (δ ppm)
6a	560, 700, 750,818, 1241,1324,1486, 1542, 1605,1651,3061	7.48-7.50(Ar-H,m),6.89(Ar-H,m), 5.11(1H,s),3.98(2H,s)
6b	660, 752 , 822, 1326, 1489,1549, 1609, 1648,3066	7.51-7.72(Ar-H,m), 6.78(Ar-H,m), 5.15(1H,s),3.82(2H,s)
6c	692,778,1407,1594,1680,1684, 2970,3032	7.56-7.73(Ar-H,m), 6.92(Ar-H,m), 5.21(1H,s)3.89(2H,s), 2.75(3H,m)
6d	694,756,1238,1316,1496,1543, 1595,1670,3052	7.48-7.51(Ar-H,m),4.02(2H,s),4.31(2H,s), 2.75(3H,s,Ar-CH_3),5.34(1H,s)
6e	683,771,888,1286, 1569,1652, 1713, 3045	7.33-7.36(ArH,m),4.05(2H,s), 4.28(2H,s),5.52(1H,s)
6f	648,700,748,813,1257,1458, 1515,1682,1726,3056	7.35-7.54(Ar-H,m),4.25(2H,s),5.23(1H,s)

Morphine Treated group

It consisted of 6 animals treated with 5mg/kg o body weight of morphine intraperitonially 30 minutes prior to heat application.

Sample Treated group

It consisted of 6 animals per group treated with different doses of each of the thiazolidinones intraperitonially 30 minutes prior to seizure induction. Three doses of each of thiazolidinones proposed were administered to each group of mice.

Analgesic studies were conducted on three thiazolidinones, phenyl-2-keto-3-(4-chloroaryl)-1-, phenyl-2-keto-3-(4-bromoaryl)-1-, phenyl-2-keto-3-aryl-1-thiazolidin-4-one as typical examples using Hot Plate Method[23]. Animals were individually placed on hot plate maintained at constant temperature

Table 3: Toxicity observations and LD_{50} values

Compound	Dose mg. /kg. body weight	Log dose	No. of animals survived in group of 5	Death (%)	Corrected%	Probit value body weight	LD_{50} mg./kg.
$C_{16}H_{12}NO_2SBr$	10.00	1.00	5	0	5	3.36	**123.13**
	50.00	1.70	5	0	5	3.36	
	75.00	1.87	4	20	20	3.97	
	100.00	2.00	3	40	40	4.75	
$C_{16}H_{12}NO_2SCl$	10.00	1.00	5	0	5	3.36	**112.35**
	50.00	1.70	5	0	5	3.36	
	75.00	1.87	3	40	40	4.75	
	100.00	2.00	3	40	40	4.75	
$C_{17}H_{15}NO_2S$	10.00	1.00	5	0	5	3.36	**97.46**
	50.00	1.70	5	0	5	3.36	
	75.00	1.87	4	20	20	3.97	
	100.00	2.00	2	60	60	5.25	

Table 4: Statistical data of analgesic study

Compound	Gp. of mice	Average of reaction time in (seconds)			Standard deviation		
		after 30 minutes	after 60 minutes	after 90 minutes	after 30 minutes	after 60 minutes	after 90 minutes
CONTROL	-	2.82	4.24	9.46	1.08	0.98	1.19
Morphine	-	5.05	4.78	5.83	2.24	3.14	3.36
$C_{16}H_{12}NO_2SBr$	A	3.88	3.61	4.05	2.08	2.48	2.57
	B	2.43	3.85	3.36	2.78	2.83	3.15
	C	2.84	3.52	3.19	2.84	3.21	3.16
$C_{16}H_{12}NO_2SCl$	A	3.52	4.49	3.97	1.02	3.24	4.01
	B	3.49	3.83	4.49	1.98	2.35	2.04
	C	3.96	4.87	5.07	2.15	3.24	3.45
$C_{17}H_{15}NO_2S$	A	6.22	2.11	3.99	3.56	3.24	1.58
	B	4.16	4.68	2.15	1.08	3.64	3.84
	C	3.25	4.47	4.94	1.87	2.04	2.34

(55^{0}C) and the reaction of animals, such as paw licking or jump response was taken as end point. Normally animals showed response in 6-10 seconds. A cut off period of 15 seconds was observed to avoid damage to the paws. All the three thiazolidinones selected for pharmacological studies were tested for their toxicity (Table 3). Observations on analgesic activity and the statistical data of three thiazolidinones tested are noted in Table 4.

RESULTS AND DISCUSSION

All the tested compounds have shown some analgesic activity. The compounds phenyl-2-keto-3-(4-chloroaryl)-1-, phenyl-2-keto-3-(4-bromoaryl)-1-, showed moderate analgesic activity while phenyl-2-keto-3-aryl-1-thiazolidin-4-one showed feeble activity. Therefore from the results it is evident that compounds having electronegative groups are responsible for analgesic activity.

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