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Analgesic and anticonvulsant activities of 2-keto-3-(substituted aryl)-1-thiazolidin-4-ones

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ABSTRACT

Sixteen 2-keto-3-(substituted aryl)-1-thiazolidin-4-ones synthesized by cyclocondensation of ketoazomethine products of five glyoxals with primary amines have been tested for toxicity ; nine products were tested for analgesic activity and eight for anticonvulsant activity. Four non-toxic new products exhibited higher analgesic activity than reference drug morphine whereas only two compounds with high LD_{50} values found much better in anticonvulsant action than phenytoin used as reference.

Key words: 2-keto-3-(substituted aryl)-1-thiazolidin-4-ones, analgesic activity, anticonvulsant activity, toxicity, thin-layer chromatography.

INTRODUCTION

Herbs, owing to their biologically active ingredients, have high medicinal value. Development in the chemistry of natural products of medicinal plants including their isolation, identification and biological evaluation has led to the present status of synthetic drug chemistry. Like structurally specific heterocyclic drugs biological action of thiazolidin-4-ones is governed by thiazole moiety and substituted groups. These are important compounds due to their broad spectrum of biological activities[1-10]. Overviews of their synthesis, structures, properties and applications have been published. 2-Keto-3-(substituted aryl)-1-thiazolidin-4-ones have been found to exhibit manifold biological activities[11,12]. In the present communication we report synthesis and pharmacological screening for analgesic and anticonvulsant activities of new series of structurally analogous thiazolidinones in search of new effective safe drugs to cure wide spread epilepsy and chronic pains.

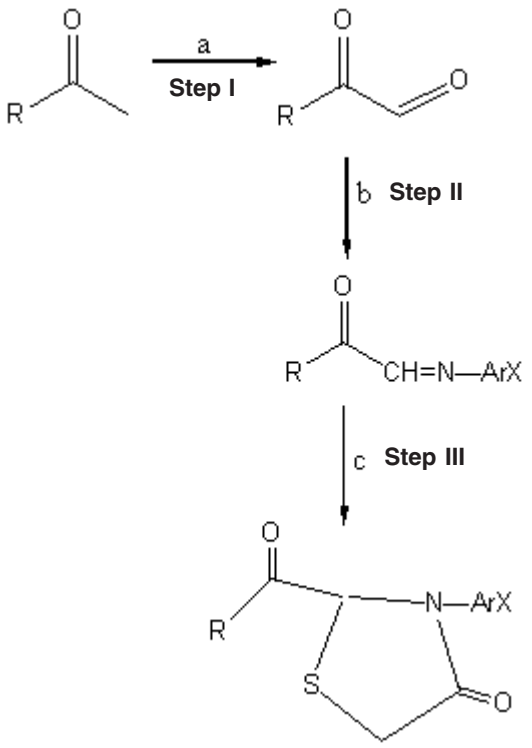
EXPERIMENTAL

Synthesis Scheme

Synthesis of 2-keto-3-(substituted aryl)-1-thiazolidin-4-ones involved three steps:

Reagent and conditions

(a) SeO_2, Methanol, rh, 2h; (b), Respective primary amines, ether/benzene, rh, 6-8h; (c) Thioglycolic acid, dry alcohol/benzene rh, 15-20h.



Step I

For the preparation of glyoxals (1 to 5) respective acetyl compound (1mole) was mixed with selenium dioxide (1mole) in methyl alcohol and refluxed for 2h; yellow reaction mixture were decanted, concentrated on water bath and poured into 2 litre water and glyoxals were extracted with ether. Products were collected after evaporation of solvent. Glyoxals gave the following analytical results : 1 %C 49.22, %H 5.31, calcd. for $C_3H_4O_2$: %C 50.00, H 5.55, N 0.0, 2 %C 61.98, %H 4.52, %N 7.38, calcd. for $C_{10}H_9O_3N$: C 62.83, H 4.71, N 7.33, 3 %C 51.83, %H 5.22, %N 0.0, calcd. for $C_4H_4O_3$: C 48.0, H 4.0, N 0.0, 4 %C 49.20, %H 3.84, %N 0.0, calcd. for $C_4H_4O_3$: C 48.0, H 4.0, N 0.0, 5 %C 68.2, %H 4.38, %N 0.0, calcd. for $C_{10}H_8O_3$: C 68.18, H 4.55, N 0.0.

Step II:

On mixing equimolar (0.5 mole) solutions of glyoxal and amine in ether or benzene ketoazomethines precipitated either immediately or obtained as residues after evaporation of the solvent were purified by crystallization from acetone or alcohol. 2e, 3f, 3j Ketoazomethines, however, were prepared by refluxing their reaction mixtures containing equimolar quanities of reactants in dry alcohol for 6-8 h followed by concentration, precipitation by benzene or ether and washing of the solids with ether and hot water successively.

Step III

2-keto-3-(substituted aryl)-1-thiazolidin-4-ones were synthesized by refluxing the mixture containing ketoazomethine (0.05 mole), thioglycolic acid (0.1 mole) and toluene-4-sulphonic acid (0.01 mole) in dry alcohol or benzene for 15-20h. Concentrated reaction mixtures on neutralization with aqueous solution of sodium bicarbonate yielded solid products except 3f, 3g, 4b and 4d which were extracted from reaction mixture with chloroform or benzene and evaporation of extracts gave solids. Insoluble water washed compounds including 1b, 2(c-e) and 5(b-d) were purified by column chromatography using their resolving solvents (Table 2) identified by thin-layer chromatography whereas water soluble and water insoluble (3h-i), 4a and 4e products were purified by crystallization from alcohol, benzene or acetone.

General

Melting points were recorded in open glass capillaries and are not corrected. IR spectra (KBr disks) were recorded using Thermo Nicolet Nexus FT-IR spectrometer. ^{1}H NMR spectra were recorded in DMSO medium using Me_4Si as an internal reference. Chemical shifts are in ppm. C,H,N analyses were carried out with Euro EA Elemental Analyser ; all the final products (III step) gave values in accordance with calculated values based on their elemental compositions and ν_{max} values (Table 1) reveal heterocyclic ring in them. ^{1}H NMR spectrum of 4c as typical example display δ 7.30, 8.30(2H, p, aromatic), 6.96(1H, thiazole), 3.95(2H,-CH_2-) which support infrared results.

For pharmacological studies standard solutions prepared in non-toxic dimethylsulphoxide (DMSO) solvent were given to each group of six mice of either sex weighing 25-30 grams interperitoneally whereas control group received equal volume of solvent as in dose solution. Different doses including 25,50,75,100,150 and 200 mg per kg of body weight of sample solutions were given to diverse groups of mice till 50% or more mortality occurs within 24 h. and LD_{50} values were calculated from plots between logdose and %probit value. Phentytoin and Morphine were used as reference drugs in anticonvulsant and analgesic studies conducted by Maximal Electro Shock[13] and Eddy's Hot Plate[14] methods respectively.

RESULTS AND DISCUSSION

The results of analgesic studies (Table 3) show that three compounds, 1b, 5b and 5c exhibit higher analgesic activity (~10 sec.) than reference drug and Analgesic action seems to be governed by electronegativity of aryl substituted group as observed in halogen substituted products (2c & 2d and 5b,5c & 5d). Among these three analgesics however, 5c could be considered best owing to its very high LD_{50} value. Although anticonvulsant results (Table 4) reveal anticonvulsant activity of all the new compounds except 3h, 4a and 4b which show lesser activity than reference drug but 3f and 4c are selective owing to complete control of seizures and high LD_{50} values (>100); 3g and 4d showing lesser activity than 3f and 4c are also effective

Table 1: Structure, melting points, yields and infrared band frequencies of compounds

R	X	Compound	% yield	M.P. (°C)	IR Peaks			
					νC=O chain	νC=	νC-N Oring	νC-S-C
1.CH_3	a : p-NO_2	1b	28.00	114	1670	1710	1590	660
2.$C_6H_5NHCOCH_2$	b : p-Cl	2c	58.60	119	1645	1710	1595	685
3.CH_3COCH_2	c : p-Br	2d	60.10	124	1660	1710	1590	645
4.CH_3CO	d : p-I	2e	29.79	238	1596	1661	1242	693
5.$C_6H_5COCH_2$	e : o-OH	3f	34.40	240	1640	1716	1594	673
	f : p-OH	3g	28.80	>290	1639	-	-	682
	g : o-CH_3	3h	35.90	260	1663	1682	1592	700
	h : p-CH_3	3i	31.60	>280	1604	1604	-	688
	i: m-OCH_3	3j	48.90	>200	1635	1678	1592	679
	j: p-COOH	4a	55.10	250	1632	-	-	672
		4b	35.50	>270	1632	-	-	655
		4c	47.20	220	1646	1682	1592	717
		4d	53.00	250	1633	1667	1581	657
		5b	58.67	194	1610	1646	1241	752
		5c	38.23	>300	1619	1727	1326	758
		5d	84.00	>320	1589	1630	1304	752

Table 2: Spot colour, resolving solvents of mixtures of ketoazomethines and thiazolidinones

Compound	Spot Colour	R_F× 100	Resolving Solvents
1b	Brown	82(94)	AcOH-Et_2O (1:2, v/v)
2c	Brown black	60(80)	AcOH-Et_2O-$CHCl_3$ (2:2:1,v/v)
2d	Brown	88(98)	AcOH-Et_2O (1:1, v/v)
2e	Brown	00(96)	EtOH
5b	Light Yellow	92(00)	$(Et)_2O$
5c	Brown	00(40)	C_6H_6
5d	Yellow	00(87)	CH_2Cl_2, PrOH-1

Values given in paranthesis are the RF values for ketoazomethines.

Table 3: Analgesic observations

Compound	LD_{50} (mg per kg of body weight)	Dose (mg per kg of body weight)	Average reaction time in a group of mice (sec)
1b	41.68	10.00	10.39
2c	55.00	10.00	7.32
2d	60.00	10.00	7.31
2e	243.00	20.00	8.21
3j	>50	20.00	7.11
4c	>100	20.00	7.53
5b	74.13	12.50	10.00
5c	243	10.00	9.80
5d	>75	10.00	6.68
Morphine	-	5.00	7.33

Table 4: Anticonvulsant observations

Compound	LD_{50} (mg per kg of body weight)	Dose (mg per kg of body weight)	Average Hind Limb Extenstion time (HLE) (sec)
3f	>100	10.00	No HLE
3g	>100	10.00	7.6
3h	>10	1.00	4.7
3i	>100	10.00	5.8
4a	>100	10.00	4.6
4b	>100	10.00	4.7
4c	>100	20.00	No HLE
4d	50	10.00	8.8
Phenytoin	-	30.00	5.2

anticonvulsants. 3f Being equally effective in lesser dose 10 mg per kg body weight than 20mg per kg body weight of 4c, could be proposed safe anticonvulsant.

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