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Synthesis of 2-aryl-3-(3-disubstituted aminomethyl-2-thio-4-oxo-thiazolidin-5yl)-methylenyl-indoles as CNS active agents

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Abstract. A new series of the title compounds has been synthesised and their lethal and gross CNS activities on the brain of albinomice investigated. The intermediate 2-aryl-3-(3-thio-4-oxo-thiazolidin-5yl)-methylenyl indoles (1–3) were prepared by the 'Knoevenagel Condensation' of 2-thio-4-oxo-thiazolidine with 2-aryl-indol-3-aldehydes. The aforesaid compounds (1–3) gave fifteen new title 2-aryl-3-(3-disubstituted aminomethyl 2-thio-4-oxo-thiazolidin-5yl)-methylenyl-indoles (4–18) by the 'Mannich reaction' with different secondary amines, utilising the thio-amidic active hydrogen at position-3 of thiazolidine ring. The structures of all the newly synthesised compounds have been assigned by their elemental analysis (C, H, N) and spectral studies (IR and PMR). In their pharmacological screenings, the compounds were found to be psychotropics and relatively nontoxic except one compound. Few of the tested compounds have induced writhing and showed effect on the body temperature.

Keywords. Thiazolidinyl-methylenyl-indoles; Mannich reaction; psychotropics; CNS depressants; CNS stimulants; writhing.

1. Introduction

A large number of indole derivatives are known to effect different biological systems. Serotonin, an indole derivative, is a neurohumoral transmitter (Hertzler 1961). The investigations, regarding the activities of serotonin and its precursor, 5 HT, on the mental illness, show that serotonin is somehow related to anticonvulsants, as the serotonin level in brain is increased by various anticonvulsants (Delgado and Isaacson 1970). Further, a wide number of indole derivatives are reported to have valuable therapeutic effectiveness for the cure of convulsions (Kaesling and Willette 1964), CNS depressions (Tachikawa *et al* 1977) and MAO inhibition (Allmany *et al* 1966) along with their antidepressant (Warner Lamber Co. 1980) and CNS blocking (Pigerol *et al* 1978) properties. On the other hand, oxothiazolidin-2-thione derivatives are known to possess psychotropic properties

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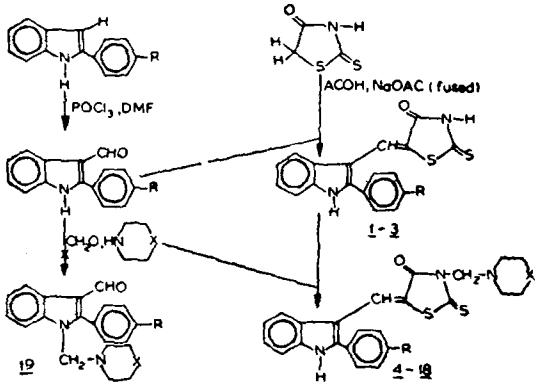
(Agarwal *et al* 1980). It is also worth mentioning that ' Hydantoin ', a well-known anticonvulsant and CNS depressant nucleus (Waser *et al* 1978), is a close structural analogue of thiazolidin-2-thione, differing only in that N–H at position-1 and oxygen of C=O at position-2 replace the sulphur atoms. Moreover, different secondary amines like morpholine, piperidine and N-substituted piperazines are also known to impart a variety of effect on the CNS disorders (Kojima *et al* 1978 ; Kubela *et al* 1978 ; Weber *et al* 1979).

The aforementioned literature reports prompted the authors to synthesise fifteen new title indole derivatives and to subject them for toxicity test and gross Central Nervous System (CNS) screening on the brain of albinomice. In this connection some 2-aryl-3-(2-thio-4-oxo-thiazolidin-5yl)-methylenyl-indoles (1–3) were synthesised by the Knoevenagel condensation between the aldehydic group of 2-aryl indol-3-aldehydes and active methylenyl group of 2-thio-4-oxo thiazolidine, using acetate ion as a mild base (a fundamental necessity for such a type of reaction). The cyclo-thio-amidic active hydrogen at position-3 was blocked by the Mannich reaction with different secondary amines in aqueous formaldehyde solution (40%) to form a methylene bridge, to furnish the title compounds (4–18).

It is noteworthy that during the Mannich reaction, the disubstituted aminomethyl group goes at position-3 of thiazolidin nucleus not at position-1 of indole, which was confirmed by the lack of downfield band of former N–H in the IR and PMR spectra of title compounds. This is further supported by the fact that when plain 2-aryl-indole-3-aldehyde was subjected to Mannich reaction under similar conditions and with the same amines, it didn't give the desired N[1]-disubstituted aminomethyl congener. The obtained compound was identified as the starting one. The failure of reaction is presumably due to the steric hindrance by the adjacent aryl group at position-2 of indole.

The current paper deals with the synthesis and CNS activities of these compounds along with their toxicity. The synthetic route is as follows:



2. Pharmacological screening

2.1. *Determination of toxicity and gross* CNS *effects*

All the compounds (4–18) were tested for their toxicity and their action on the CNS of albinomice of either sex.

To evaluate the lethal values, the compounds were administered, at different doses as 464 and 1000 mg/kg weight of mice, intraperitoneally as a suspension of gum acacia and the approximate lethal doses in 50% of the tested animals (ALD_{50}) were determined by a standard method (Weil 1952).

For their effect on the CNS, they were finally introduced in albino mice, by the similar aforementioned procedure, at 1/5th of their ALD_{50} and changes in their spontaneous motor activity (SMA) and reaction to sound, touch and body temperature were recorded. To substantiate these gross CNS observations, mobility counts were noted, at time intervals of 1/2, 1, 2 and 3 hr after the compound's administration, using an actophotometer equipped with photocells.

3. Results and discussion

The results of the study of toxicity test and gross CNS observations are cited in table 1. All the compounds were found to be quite nontoxic except compound no. 13 (ALD_{50} : 316 mg/kg). It was observed that some of the title compounds were found to be CNS depressants while others were stimulants, as they decreased or increased the SMA and reactivity respectively. Few of the compounds induced writhing (twisting of belly) and on this basis, they may be tried as muscle relaxants. The compounds have also shown marked effect on the body temperature. Moreover, from the structure and pharmacological data of the final products, a definite structure activity relationship has been drawn, which is summarised as follows :

(i) The substitution at para position to phenyl ring, present at position-2 of indole, showed a wide role on the CNS effects of the compounds, *viz.*, the compounds without any substitution at that position were CNS depressants whereas the methyl and chloro analogues were found to be stimulant on the CNS.

(ii) From the data of mobility counts after 3 hr of the compounds injection it appears that :

(a) The N-phenyl piperazino derivatives have the highest depressant (compound 7, 46·72%) and lowest stimulant (compounds 13 and 17 respectively, 1·45 and 0·72%) effects in their groups of five. From these results it was presumed that the presence of CH_3 or Cl group at para to phenyl ring has increased the mobility counts for compounds 13 and 17, in the same trend as is observed in the remaining compounds (9–18), but due to the highly depressant nature of N–Ph piperazino group, the compounds 13 and 17, have overcome the stimulant nature of CH_3 and Cl groups and thus have the lowest stimulant nature.

(b) On the other hand, the morpholino congeners have shown the reversed activities as compared to the aforesaid findings, *viz.*, the morpholino derivatives have the lowest depressant (compound No. 4, 2·92%) and highest stimulant (Nos. 9 and 14 respectively, 28·46 and 14·59%) effects in their groups of five.

(iii) It is also worth mentioning that the compounds, which were grossly CNS depressants, have also decreased the body temperature (hypothermia by 0·3 to 0·8° C) whereas, the stimulant compounds increased the same (hyperthermia) in the range of 0·1 to 1·6° C.

Table 1. ALD_{50} and gross CNS observations of the compounds 4–18 at 1/5th of their ALD_{50}.

Compd. No.	ALD_{50} mg/kg (i.p.)	Gross CNS observations					Mobility counts					Depressant activity (%)	Stimulant activity (%)
		SMA & reactivity	Death	Writhing	Change in body temp. (°C)		0 hr	½ hr	1hr	2 hrs	3 hrs		
						C	239	181	158	146	137		
4.	681	↓	0/5	(—)	↓ 0·4	T	233	152	146	143	133	2·92	(—)
5.	681	↓	0/5	(—)	↓ 0·4		238	168	139	142	119	13·14	(—)
6.	>1000	↓	0/5	(+)	↓ 0·5		232	139	140	130	118	13·87	(—)
7.	1000	↓	0/5	(+)	↓ 0·8		206	115	143	125	73	46·72	(—)
8.	>1000	↓	0/5	(+)	↓ 0·3		206	90	135	120	111	18·98	(—)
9.	>1000	↑	0/5	(+)	↑ 0·4		265	242	202	189	176	(—)	28·46
10.	681	↑	0/5	(—)	↑ 0·1		268	169	241	176	151	(—)	10·21
11.	>1000	↑	0/5	(—)	↑ 0·9		241	184	171	156	142	(—)	3·64
12.	>1000	↑	0/5	(—)	(—)		235	170	163	148	139	(—)	1·45
13.	316	↑	0/5	(—)	(—)		263	179	161	153	149	(—)	8·75
14.	>1000	↑	0/5	(—)	1·1		252	192	177	164	157	(—)	14·59
15.	681	↑	0/5	(+)	↑ 1·6		253	188	167	151	143	(—)	4·37
16.	1000	↑	0/5	(+)	↑ 0·1		230	181	167	154	145	(—)	5·83
17.	>1000	↑	0/5	(+)	↑ 0·6		229	173	147	142	138	(—)	0·72
18.	>1000	↑	0/5	(+)	↑ 0·2		241	172	168	157	146	(—)	6·56

↑ Increased, ↓ = Decreased, (+) = Present, (—) = Not effected, temp. = temperature, C = Controlled, T = Treated.

4. Experimental

Melting points were determined in open capillaries using AR H_2SO_4 bath and are uncorrected. IR spectra in KBr phase were recorded on a Perkin-Elmer 157 and 177 spectrophotometers (ν_{max} in cm^{-1}) and PMR spectra in DMSO-D_6 or $CDCl_3$ on a varian A60D instrument using TMS as internal standard (chemical shift in δ ppm). Purity of the compounds was checked by TLC using silicagel-G coated (0·25 mm) plates and benzene–ethanol (100 : 5) as irrigant.

4.1. *Synthesis of 2-thio-4-oxo-thiazolidine*

It was prepared by the method of Julian and Bernard (1935).

4.2. *Synthesis of 2-aryl-indol-3-aldehydes*

The desired aldehydes have been prepared according to the method of Weisbach *et al* (1964).

4.3. *Synthesis of 2-(4-chlorophenyl)-3-(2-thio-4-oxo-thiazolidin-5yl)-methylenyl-indole* (3)

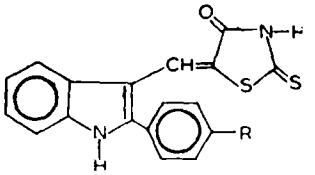
A mixture of 2-(4-chlorophenyl)-indol-3-aldehyde (0·01 mol), 2-thio-4-oxo-thiazolidine (0·01 mol) and fused sodium acetate (5 g) in glacial acetic acid (50 ml) was refluxed for 4 hr on a wire gauze with occasional shaking. Thereafter, it was cooled and poured with stirring in ice-cold water (200 ml). The condensation product obtained was filtered, washed well with water and recrystallised from dioxane, m.p. 238° C, yield 85%. Analysis : Found : C, 58·33 ; H, 3·01 ; N, 7·62, $C_{18}H_{11}ON_2S_2Cl$. Calc.: C, 58·29 ; H, 2·96 ; N, 7·55% ; IR: 3400, 3200 (N–H str for thiazolidine and indole moieties respectively), 3050, 2900 (C–H, Ar and Ali), 1690 (N–C=O), 1600 (N–H bending) and 1220 (C=S) ; PMR : 9·82 (s, 1H, N–H of thiazolidine), 8·1 (s, 1H, N–H of indole) and 7·72–7·05 (m, 9H, 8Ar-H and 1 –C=C–H). The downfield position of N–H of thiazolidine in IR and PMR was expected to be due to the presence of C=O and C=S groups adjacent to N–H.

Similarly other compounds (1, 2) of the series were prepared and are listed in table 2.

4.4. *Synthesis of 2-phenyl-3-[3-(4-phenyl piperazino) methyl-2-thio-4-oxo thiazolidin-5yl]-methylenyl-indole* (7)

To a suspension of 2-phenyl-3-(2-thio-4-oxo thiazolidin-5yl)-methylenyl-indole (0·0025 mol) in warm ethanol (20 ml), formaldehyde solution (37%, 1 ml) was added. To the resulting suspension, N-phenyl piperazine (0·0025 mol) was added with constant vigorous stirring and the solution then again heated. Thereafter the reaction mixture was kept aside for 24 hr and the product that separated out was filtered, washed with pet ether (60–80°) and recrystallised from ethylacetate, m.p .194°C, yield 90%. Analysis: Found: C, 68·19; H, 5·16; N, 10·91; $C_{29}H_{26}ON_4S_2$. Calc.: C, 68·23; H, 5·09; N, 10·98%; IR : 3200 (N–H of indole), 3050, 2900

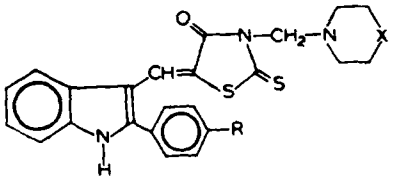
Table 2. 2-aryl-3-(2-thio-4-oxo-thiazolidin-5yl)-methylenyl indoles.



Sl. No.	R	m.p. (°C)	Molecular formula[a]	Yield (%)	% Nitrogen (Calcd.)	% Nitrogen (Found)
1.	H	>250	$C_{18}H_{12}ON_2S_2$	90	8·33	9·39
2.	CH_3	245	$C_{19}H_{14}ON_2S_2$	85	8·00	7·92
3.	Cl	238	$C_{18}H_{11}ON_2S_2Cl$	85	7·55	7·62

[a] All the compounds recrystallised from dioxane, gave correct analysis for C and H too.

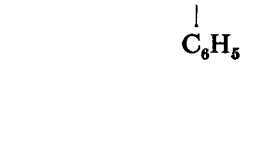
Table 3. 2-aryl-3-(3-disubstituted aminomethyl-2-thio-4-oxo-thiazolidin-5yl)-methylenyl-indoles.



Sl. No.	R	X	m.p. (°C)	Molecular formula[a]	Yield (%)	% Nitrogen (calcd.)	% Nitrogen (found)
4.	H	[O]	204	$C_{23}H_{21}O_3N_3S_2$	90	9·65	9·52
5.	H	CH_2	232	$C_{24}H_{23}ON_3S_2$	87	9·69	9·61
6.	H	N-CH_3	219	$C_{24}H_{24}ON_4S_2$	85	12·50	12·43
7.	H	N-C_6H_5	194	$C_{29}H_{26}ON_4S_2$	90	10·98	10·91
8.	H	N-$C_6H_4CH_3$ (4)	200	$C_{30}H_{28}ON_4S_2$	93	10·68	10·66
9.	CH_3	[O]	174	$C_{24}H_{23}O_3N_3S_2$	85	9·35	9·30
10.	CH_3	CH_2	188	$C_{25}H_{25}ON_3S_2$	83	9·39	9·19
11.	CH_3	N-CH_3	194	$C_{25}H_{26}ON_4S_2$	90	12·12	11·98
12.	CH_3	N-C_6H_5	194	$C_{30}H_{28}ON_4S_2$	85	10·68	10·46
13.	CH_3	N-$C_6H_4CH_3$ (4)	148	$C_{31}H_{30}ON_4S_2$	90	10·40	10·51
14.	Cl	[O]	271	$C_{23}H_{20}O_3N_3S_2Cl$	79	8·94	9·01
15.	Cl	CH_2	270	$C_{24}H_{22}ON_3S_2Cl$	80	8·98	8·76
16.	Cl	N-CH_3	180	$C_{24}H_{23}ON_4S_2Cl$	82	11·60	11·91
17.	Cl	N-C_6H_5	262	$C_{29}H_{25}ON_4S_2Cl$	85	10·28	10·05
18.	Cl	N-$C_6H_4CH_3$ (4)	260	$C_{30}H_{27}ON_4S_2Cl$	90	10·02	10·32

[a] All the compounds, recrystallised from ethyl acetate, gave correct analysis for C and H too.

(C-H Ar and Ali), 1690 (N-C=O), 1590 (N-H bending) and 1220 (C=S) ; PMR : 8·02 (s, 1H, N-H of indole), 7·7-6·7 (m, 15H, 14 Ar-H and 1-C=C-H), 5·02 (s, 2H, N-CH_2-N), 3·09 (t, J = 2·9Hz, 4H, -CH_2-N-CH_2) and 2·92 (*t*, J = 2·9Hz, 4H, -CH_2-N-CH_2).



The other compounds of the series were prepared in a similar manner. Their results are listed in table 3.

4.5. *Attempted preparation of* N^1*-(4-phenyl piperazino) methyl-2-phenyl-indol-3-aldehyde* (19)

A mixture of 2-phenyl-indol-3-aldehyde (0·0025 mol) and 4-phenyl piperazine (0·0025 mol) in ethanol (20 ml) containing aqueus formaldehyde solution (1 ml) was heated on the water bath for 10 min. The reaction was kept aside for 24 hr. Thereafter, it was concentrated to get the solid product, which was analysed by TLC and identified (m.p., m.m.p.) as the starting one.

Acknowledgement

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