
Mannich Reaction Products of 5-Arylidene-2-phenylimino-4-thiazolidinones as Anticonvulsants

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The 4-thiazolidinone is chosen as a lead molecule as its structure has the common denominator present in majority of the anticonvulsants. Molecular modifications at 2-and 5-positions are made in order to increase the lipophilicity. The dialkylaminoalkyl group (pharmacophore) present in a number of commonly used drugs, is introduced at 3-position by Mannich reaction to enhance the anticonvulsant activity and to reduce toxicity. Based on these observations, a series of twenty five 3-(dialkylaminomethyl)-5-arylidene-2-phenylimino-4-thiazolidinones have been synthesized and evaluated for anticonvulsant activity and preliminary toxicity. Some compounds have displayed significant anticonvulsant activity with out much toxicity.

A REVIEW of literature indicates that majority of anticonvulsants have a common denominator (-C-C-N-C-) in their structure. In the 4-thiazolidinone derivatives prepared, one of the =O of this denominator has been replaced by an isosteric group =NH (2-imino) (with an expectation to minimally change the biological action) and to serve as a lead for further molecular modifications to enhance the anticonvulsant activity and reduce toxicity. Substitutions at 2-and 5-positions are attempted in order to increase lipophilicity as required for anticonvulsant activity and to make ring sufficiently stable in acidic medium. Different dialkylaminoalkyl groups (pharmacophores) which are present in a number of commonly used antimalarials (chloroquine), antihistaminics (diphenhydramine), local anesthetics (procaine), narcotic analgesics (methadone) and antipsychotics (chlorpromazine), are introduced at 3-position by Mannich reaction¹ to enhance anticonvulsant activity with reduced toxicity. Since several Mannich bases of 4-thiazolidinones are already reported²⁻⁶ to have anticonvulsant activity, the present work is undertaken to replace groups at 2-and

5-positions with different substituents to arrive at possible structure activity relationship. Based on these observations, synthesis of 3-dialkylaminomethyl-5-arylidene-2-phenylimino-4-thiazolidinones (with different alkyl and aryl groups), have been carried out. The anticonvulsant activity and preliminary toxicity of all the synthesized compounds has also been evaluated.

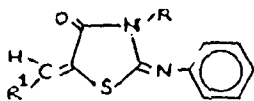
EXPERIMENTAL

5-Arylidene-2-phenylimino-4-thiazolidinones:

Compound No. 1 [5- (m-nitrobenzylidene)...], 10 [5-(p-methoxybenzylidene)...] and 20 [5-(o-nitrobenzylidene)-2-phenylimino-4-thiazolidinone] were synthesized by condensation of 2-phenylimino-4-thiazolidinone⁷ (0.1 mol) with *m*-nitrobenzaldehyde, *p*-methoxybenzaldehyde, or *o*-nitrobenzaldehyde (0.1 mol), respectively, in presence of anhydrous sodium acetate (0.2 mol) and acetic acid⁸ (80 ml). the reaction mixture was refluxed for 1-2 h. The hot mixture was poured in cold water (~ 500 ml) and kept overnight. the precipitate was filtered, washed, dried and recrystallised from acetic acid (Table 1).

*For Correspondence

Table 1
3-Dialylaminomethyl-5-Arylidene-2-phenylimino-4-Thiazolidinones



Compd. No.	R	R ¹	m p* °C	Molecular formula**	Reflux time (h)	Yield %
1.	H		291-2	C ₁₆ H ₁₁ O ₃ N ₃ S	1.0	57
2.	Dimethylaminomethyl	-"	295-7	C ₁₉ H ₁₈ O ₃ N ₄ S	2.0	73
3.	Dimethylaminomethyl	-"	297-9	C ₂₁ H ₂₂ O ₃ N ₄ S	3.5	63
4.	Di-n-propylaminomethyl	-"	298-300	C ₂₃ H ₂₆ O ₃ N ₄ S	4.5	53
5.	Di-iso-propylaminomethyl	-"	296.8	C ₂₃ H ₂₆ O ₃ N ₄ S	5.0	52
6.	Dicyclohexylaminomethyl	-"	296-8	C ₂₉ H ₃₄ O ₃ N ₄ S	3.5	46
7.	Diphenylaminomethyl	-"	293-5	C ₂₉ H ₂₂ O ₃ N ₄ S	3.0	49
8.	Piperidinomethyl	-"	215-7	C ₂₂ H ₂₂ O ₃ N ₄ S	2.0	59
9.	Morpholinomethyl	-"	268-70	C ₂₁ H ₂₀ O ₄ N ₄ S	2.5	51
10.	H		254-6	C ₁₇ H ₁₄ O ₂ N ₂ S	2	68
11.	Dimethylaminomethyl	-"	261-2	C ₂₀ H ₂₁ O ₂ N ₃ S	5	86
12.	Dimethylaminomethyl	-"	259.60	C ₂₂ H ₂₅ O ₂ N ₃ S	5	78
13.	Diethanolaminomethyl	-"	256-7	C ₂₂ H ₂₅ O ₄ N ₃ S	3.5	69
14.	Di-n-propylaminomethyl	-"	259-60	C ₂₄ H ₂₉ O ₂ N ₃ S	8.0	73
15.	Di-iso-propylaminomethyl	-"	251-2	C ₂₄ H ₂₉ O ₂ N ₃ S	5	68
16.	Dicyclohexylaminomethyl	-"	255-7	C ₃₀ H ₃₇ O ₂ N ₃ S	3.5	54
17.	Diphenylaminomethyl	-"	258-9	C ₃₀ H ₂₅ O ₂ N ₃ S	3.5	64
18.	Piperidinomethyl	-"	257-8	C ₂₃ H ₂₅ O ₂ N ₃ S	6	60
19.	Morpholinomethyl	-"	235-6	C ₂₂ H ₂₃ O ₃ N ₃ S	4.5	59
20.	H		238-40	C ₁₆ H ₁₁ O ₃ N ₃ S	1.0	64
21.	Dimethylaminomethyl	-"	233-5	C ₁₉ H ₁₈ O ₃ N ₄ S	1.0	55

Compd. No.	R	R'm p* °C	Molecular formula**	Reflux time (h)	Yield %	
22.	Diethylaminomethyl	-"	226-8	C ₂₁ H ₂₂ O ₃ N ₄ S	3.5	90
23.	Diethanolaminomethyl	-"	172-4	C ₂₁ H ₂₂ O ₅ N ₄ S	4.0	84
24.	Di-iso-propylaminomethyl	-"	220.2	C ₂₃ H ₂₆ O ₃ N ₄ S	5.0	53
25.	Di-n-butylaminomethyl	-"	214-6	C ₂₅ H ₃₀ O ₃ N ₄ S	5.0	53
26.	Diphenylaminomethyl	-"	210-2	C ₂₉ H ₂₂ O ₃ N ₄ S	3.0	42
27.	Piperidinomethyl	-"	168-9	C ₂₂ H ₂₂ O ₃ N ₄ S	2.0	82
28.	Morpholinomethyl	-"	225-7	C ₂₁ H ₂₀ O ₄ N ₄ S	2.5	93

* All the melting points are uncorrected.

** The C, H, N analysis results of all the compounds were satisfactory ($\pm 0.4\%$). IR (KBr) spectral bands of all Mannich bases showed absence of (N-H) peak at 3200 cm⁻¹ present in parent compound No. 1, 10 and 20.

3-Dialkylaminomethyl-5-arylidene-2-phenylimino-4-thiazolidinones : (Compound No.2-9, 11-19, 21-28)

To a continuously stirred solution of compound No. 1, 10 or 20 (0.005 mol) in dimethylformamide (15 ml), appropriate secondary amine (0.005 mol) was added, followed by formalin (37-40 %, 0.007 mol), dropwise¹. The resulting mixture was refluxed on an oil bath for 1-8 h and thereafter, poured on to crushed ice. The separated product was filtered, washed with water, and recrystallised from dimethylformamide.

The purity and identity of all compounds was ascertained by their mp (uncorrected), TLC (silica gel-G plates, benzene:ethylacetate:methanol : 85:14:1), IR spectra (Perkin Elmer 157 IR Spectrophotometer) and elemental analyses (reports from CDRI, Lucknow) (Table 1).

Anticonvulsant Activity : Pentylene tetrazole seizures in albino mice of either sex (each weighing 20-25 g) were used to study the anticonvulsant activity⁹ of all compounds (in Tween 80, 0.25% w/v). The test compound (50 mg/kg and 100 mg/kg) was injected (i.p.) to a group of 10 animals. After 1 h of a administration, the mice were injected (s.c.) with pentylenetetrazole (90 mg/kg). The mice observed

for 60 min for seizures. An episode of clonic spasm that persisted for a minimum of 5 sec was considered as threshold convulsions. Animals devoid of threshold convulsions during 60 min were considered protected. The number of animals protected in each group was recorded and represented as percent protection. The animals were then observed for the next 24 h and percent mortality was recorded (Table 2).

Toxicity Studies : The approximate LD₅₀ (ALD₅₀) of all the compounds (in Tween 80, 0.25% w/v) were determined in albino mice of either sex, (each weighing 20-25 g), using the method described by Smith¹⁰. The test compounds were administered in single doses (100, 200 and 400 mg/kg, i.p.) to each animal. If no death occurred within 1-2 h, additional mice were given doses of test compounds (0.8, 1.6 and 3.2 g/kg i.p.), each. If the three doses first mentioned were lethal then doses of test compounds (12.5, 25, and 50 mg/kg, i.p.) were administered. When lethal range was reached, the largest non-fatal and smallest fatal doses were given to two or more additional mice and the approximate LD₅₀ was recorded (Table 2).

RESULTS AND DISCUSSION

It has been observed that some of the Mannich derivatives, some what surprisingly, have almost same

Table 2 : Anticonvulsant Activity and Approximate Toxicity

Compd. No.	% Protection*		% Mortality**		ALD ₅₀ g/kg
	50 mg/kg	100 mg/kg	50 mg/kg	100 mg/kg	
1.	20	30	20	60	0.8
2.	20	40	10	20	1.6
3.	40	60	00	10	1.6
4.	40	70	00	10	1.6
5.	50	80	00	10	1.6
6.	20	30	00	20	1.6
7.	20	40	00	20	1.6
8.	20	40	00	20	1.6
9.	20	30	00	10	1.6
10.	10	30	00	40	1.6
11.	50	60	00	20	0.8
12.	20	30	00	10	1.6
13.	40	60	00	10	1.6
14.	20	40	00	20	1.6
15.	10	20	00	10	1.6
16.	50	80	00	00	1.6
17.	10	20	00	10	1.6
18.	10	30	00	10	1.6
19.	10	20	00	10	1.6
20.	20	30	20	40	0.8
21.	50	80	00	00	3.2
22.	40	60	00	00	3.2
23.	20	30	00	10	3.2
24.	60	100	00	00	3.2
25.	60	100	00	00	3.2
26.	40	60	00	10	3.2
27.	40	60	00	10	3.2
28.	60	100	00	00	3.2

* Ten animals were used in a group, against pentylene tetrazole seizures.

** Animals were observed for 24 h.

melting points (table 1) as the corresponding parent compounds. Though, no attempts have been made to arrive at the E/Z configuration at 5-position, the compounds are likely to take E configuration in view of their facing lesser steric hindrance.

The anticonvulsant activity exhibited by Mannich bases of these substituted 4-thiazolidinones at doses of 50 mg/kg and 100 mg/kg against pentylene tetrazole-induced seizures and the mortality due to toxic effect of pentylene tetrazole during 24 h are shown in Table 2. All of them afforded protection ranging from 10-50% at the dose level of 50 mg/kg, and 20-100% at the dose level of 100 mg/kg. Compounds 24, 25 and 28 showed maximum protection, (100 %) indicating a need for further exploration. Compounds 5, 16 and 21 exhibited 80% protection while compound 3, 4, 11, 13, 26 and 27 exhibited only moderate degree of protection. However, compounds 6, 9, 12, 15, 17, 18, 19 and 23 exhibited lowest anticonvulsant activity. Dialkylaminomethyl substitution at 3-position appeared to increase the anticonvulsant activity in some compounds, specially those derived from compound 20. Though, even after considering the results of earlier work¹⁻⁶ in the 4-thiazolidinone series of compounds, no clear SAR could be deduced, the approximate toxicity of all Mannich bases in this series appeared to be reduced in comparison with the respective parent compounds 1, 10 and 20.

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