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Synthesis, anticonvulsant activity & spectral characterization of some novel thiazolidinone derivatives

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ABSTRACT

*A series of substituted 5-ethylidene-2-(phenylimino) thiazolidin-4-ones were prepared and evaluate for their potential anticonvulsant activity by determining their ability to provide protection against convulsions induced by electroconvulsometer. The synthetic scheme involves phenylthiourea **(I)** as a starting material. Phenylthiourea on reaction with ethylchloroacetate in presence of ethanol (95%) and fused sodium acetate gives 2-(phenylimino) thiazolidin-4-one **(II)**, 2-(phenylimino) thiazolidin-4-one on further reaction with substituted benzaldehyde gives substituted 5-ethylidene-2-(phenylimino) thiazolidin-4-one **(III-VII)**. Synthesized compounds were authenticated on the basis of elemental analysis, IR and ^{1}H NMR and Mass spectral analysis.*

Keywords: Thiazole; Thiazolidinone; Synthesis; Heterocyclic; Substitution, Anticonvulsant Activity.

INTRODUCTION

Medicinal chemistry deals with the design, synthesis and production of molecules having therapeutic value. During the past few decades growth in areas like combinatorial chemistry and heterocyclic chemistry has lead to development of many privileged structure with proven utility in medicinal chemistry [1]. Thiazolidinone, a saturated form of thiazole with carbonyl group on fourth carbon, has been considered as a magic moiety (wonder nucleus) which posses almost all types of biological activities. It belongs to an important group of heterocyclic compounds containing sulfur and nitrogen in a five member ring [2]. This biologically active scaffold has encouraged our interest in synthesizing several new compounds by using several substitutions at different positions, attached to 4-thiazolidinone moieties. Our aim is to search for biologically active heterocyclic compounds containing sulfur and nitrogen, we have now synthesized a series of substituted 5-ethylidene-2-(phenylimino) thiazolidin-4-one. Substitution can be done at 2, 3

and 5 positions. The carbonyl group present is highly unreactive. Substituent at 2-, 3- and 5-positions may be varied, but the greatest difference in structure and properties is exerted by the group attached to the carbon atom in the 2-position [3]. Tetrahydro derivative of thaiazole is known as thiazolidine and the oxo derivative of thiazolidine is known as thiazolidinone.

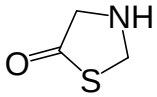


Figure 1: Thiazolidinone

The 3-unsubstituted thiazolidinone are usually solids, often melting with decomposition, but the attachment of an alkyl group to the nitrogen lowers the melting point. The thiazolidinone that do not contain aryl or higher alkyl substituents are somewhat soluble in water [4]. Thiazolidinone are known to exhibit antitubercular [5], Antibacterial [6], anticonvulsant [7], antifungal [8] and antithyroid activities [9]. Some of thiazoline derivatives were found to show interesting anti-HIV and anticancer activities [10]. Thiazolidinone, with carbonyl group at 2, 4 or 5 position have been subjected to extensive study in the recent years. Numerous reports have appeared in the literature, which highlights their chemistry and use [11]. It was observed that reaction with cyclizing reagents like α-halocarbonyl compounds such as ClCH2COCl, BrCH2COCl, BrCH2COOEt and ClCH2COCH2COOEt in boiling ethanol with fused sodium acetate have better biological profiles as thiazolidinone [12].

EXPERIMENTAL SECTION

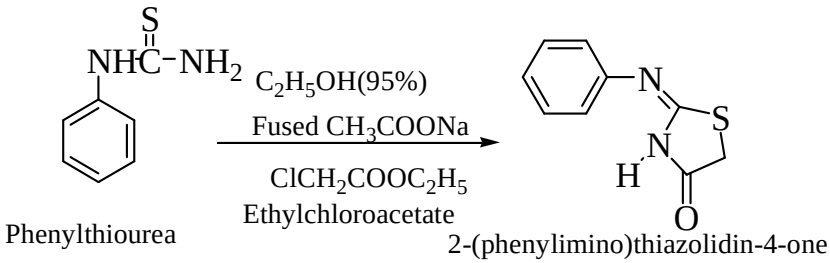
All the chemicals and reagents were obtained from Sigma (Germany) and CDH (India) and were recrystallized/ redistilled as necessary. Melting points were determined by open capillary tube method and are uncorrected. Purity of the compounds was checked on thin layer chromatography (TLC) plates precoated. With silica gel G using solvent system toluene: ethyl acetate: formic acid (5:4:1). The spots were located under iodine vapors and UV light. IR spectra were recorded using KBr on FTIR Shimadzu 8400S IR spectrophotometer (Japan). A JEOL AL300 FTNMR 300 MHz spectrometer was used to acquire ^{1}H-NMR spectra with $CDCl_3$ as solvent and TMS as internal standard. Chemical shift values are expressed in ppm. Mass spectra were obtained using Kratos-AEI MS-902S instrument. Elemental analyses were carried out with a Perkin Elmer Model 240-C apparatus (CDRI, Lucknow). The results of the elemental analysis (C, H, and N) were within ± 0.4% of the calculated amounts.

Reaction Scheme

Step 1

General Procedure for synthesis of 2-phenyliminothiazolidin-4-one (II)

Phenyl thiourea **(I)** 8g (0.04 moles) was dissolved in 16.45ml ethanol (95%). The resulting mixture was refluxed with fused sodium acetate 4.31g (0.052 moles) and ethylchloroacetate 6.46 g (5.65 mL) for 4hr. The reaction mixture was then poured in to water. Keep the reaction mixture overnight for complete precipitation. The precipitate obtained was filtered and dried at room temperature. The compound was recrystallised in ethanol (95%).



Phenylthiourea

(I)

2-(phenylimino)thiazolidin-4-one

(II)

Scheme 1: Synthesis of 2-(phenylimino) thiazolidin-4-one

Table 3: Physical property of synthesized compound (II)

Compound	R	Molecular Formula	M. Wt	R_f Value	%Yield	Reaction Time
II	H	$C_9H_8N_20S$	192.24	0.755	80.79	3-4hr

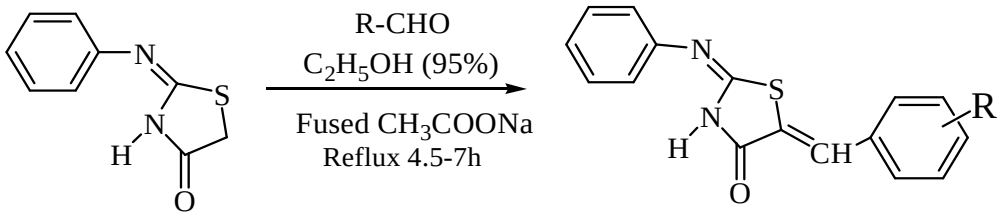
2-phenyliminothiazolidin-4-one (II)

Yield: 80.79% (solid); M.p: 175–177 °C; Rf value (T: E: F; 5:4:1): 0.755, IR (KBr): 3415, 2978, 1745, 1610 cm^{-1},^{1}H NMR (CDCl3): δ = 3.21 (s, 2H, CH2), 6.98– 7.34 (m, 5 H, phenyl), 11.82 (s, 1H, NH), MS m/z: 192 (M^+). Anal. Calcd for $C_9H_8N_2OS$: C, 55.26; N, 14.10; S, 16.60.

Step-2

General Procedure for the preparation of substituted Thiazolidinone Derivatives (III-VII)

2-phenyliminothiazolidin-4-one (II) (0.01 mole) was reacted with different aromatic aldehyde (0.01mole) with fused sodium acetate (0.01mole) in ethanol (8 ml) for 6-7 hr. The reaction mixture then cool to room temperature, poured in to ice cold water and kept overnight. The precipitate obtained was filtered and washed with water to remove unreacted aldehyde and then dried the precipitate at room temperature. The product obtained was recrystallied from dimethyl formamide.



2-(phenylimino)thiazolidin-4-one

(II)

Substituted 5-ethylidene-2-(phenylimino)thiazolidin-4-one

(III-VII)

Scheme 2: Synthesis of substituted 5-ethylidene-2-(phenylimino) thiazolidin-4-ones

Table 4: Physical properties of synthesized compounds (III-VII)

Compound	R	Molecular Formula	M. Wt.	(%) yield	ReactionTime (hr)
III	2,4-dichloro	$C_{16}H_{11}ClN_2OS$	349.23	87.9	4.0-5
IV	4-Methoxy	$C_{17}H_{14}N_2O_2S$	310.37	93.75	2.5-3.0
V	4-Fluoro	$C_{16}H_{11}FN_2OS$	298.33	66.0	6-7
VI	4-chloro	$C_{16}H_{11}ClN_2OS$	314.79	76.19	2.5-4.0
VII	4-Nitro	$C_{16}H_{11}N_3O_3S$	325.34	54.5	1.0- 2.30

Spectral Data of the synthesized compounds

5-(2, 4-dichlorobenzylidene)-2-(phenylamino) thiazolidin-4-one (III)

Yield 87.9% (solid); M.p 186-188˚C, Rf value (T: E: F; 5:4:1): 0.679, IR (KBr): 3461, 3037, 2953, 1671 cm-1,^{1}H NMR (CDCl3, δ ppm) 6.99-7.20 (m, 10H, phenyl and benzylidene); 7.60 (s, 1H, C=CH); 8.2 (s, 1H, NH), MS (m/z): 347.98 (M^+), Anal. Calcd for $C_{16}H_{10}Cl_2N_2OS$: C, 55.0; N, 8.00; S, 9.10.

5-(4-methoxybenzylidene)-2-(phenylamino) thiazolidin-4-one (IV)

Yield: 93.75% (solid); M.p: 195-197˚C, Rf value (T: E: F; 5:4:1): 0.638, IR (KBr): 1638, 1332, 1220 cm^{-1}, ^{1}H NMR (CDCl3) δ ppm: 7.00-7.15 (m, 9H, phenyl and benzylidene); 7.35 (m, 1H, C=CH); 8.2 (s, 1H, NH), MS (m/z): 312.08 (M^+), Anal. Calcd for $C_{17}H_{14}N_2O_2S$: C 65.30, N 8.97, S, 10.25

5-(4-fluorobenzylidene)-2-(phenylimino) thiazolidin-4-on (V)

Yield: 66 %(solid); M.p: 272-274˚C, R_f value (T: E: F; 5:4:1): 0.681, IR (KBr): 3467, 3050, 1680, 1600, 1032 cm^{-1} , ^{1}H NMR ($CDCl_3$, δ ppm): 6.80-7.20 (m, 5H, phenyl); 7.20 (d, 2H, benzylidine); 6.90 (d, 2H, benzylidine), 7.62 (s, 1H, C=CH); 8.35 (s, 1H, NH), MS (m/z) 298.05 (M^+), Anal. Calcd for $C_{16}H_{11}FN_2OS$ (298.33): Calcd C, 64.40; N, 9.35; S, 10.73.

5-(4-chlorobenzylidene)-2-(phenylamino) thiazolidin-4-one (VI)

Yield: 76.19%, M.p: 285-287˚C; Rf value (T: E: F; 5:4:1): 0.80, IR (KBr): 1674, 1240, 1190 cm^{-1} , ^{1}H NMR ($CDCl_3$, δ ppm): 6.9-7.2 (m, 5H, phenyl); 7.20 (d, 2H, benzylidene); 7.22 (d, 2H, benzylidene); 6.70 (s, 1H, C=CH); 8.38 (s, 1H, NH), MS (m/z): 314.02 (M^+), Anal. Calcd for $C_{16}H_{11}ClN_2OS$: C, 61.02; N, 8.70; S, 10.19.

5-(4-nitrobenzylidene)-2-(phenylamino) thiazolidin-4-one (VII)

Yield: 54.5%, M.p: 320-322, Rf value (T: E: F; 5:4:1): 0.730, IR (KBr): 1510, 1674, 1335 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ: 6.90-7.32 (m, 5H, phenyl; 7.60 (s, 1H, C=CH); 7.52 (m, 2H, 4-nitrobenzylidene); 8.14 (m, 2H, 4-nitrobenzylidene); 8.2 (s, 1H, NH), MS m/z: 325.04 (M^+). Anal. Calcd for $C_{16}H_{11}N_3O_3S$: C, 59.07; N, 12.90; S, 9.80

Biological Evaluation

Albino mice of either sex, average weight between 25-30 g were used for determining anticonvulsant activity. The animals were kept on food and water *ad libitum* except during the experiments. They were housed in a room at 25 ± 2 ºC, and 50 ± 5% relative humidity. Animals were obtained from Animal House Facility, Meerut Institute of Engineering and Technology, Meerut. All the test compounds and reference drug were administered orally, suspended in 1% carboxymethyl cellulose (CMC) suspension.

Anticonvulsant activity

The synthesized compounds were evaluated for their anticonvulsant activity using maximal electroshock seizure method. The animals were randomly allocated into 3 groups of 6 animals each and were fasted for 24hr before the experiment with free access to water. Control group received only 1% carboxymethyl cellulose suspension. Standard drug phenytoin was administered orally at a dose of 30 mg/kg. The test compounds were administered orally at an equimolar oral dose of 30mg/kg phenytoin. Both the test compounds and standard drug were administered orally as suspension in carboxymethyl cellulose in water (1% w/v). Supramaximal electroshock of current intensity 50mA at a frequency of 60 Hz was given for duration of 0.2 sec of the administration of test and standard drug. 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). For statistical analysis we use sigma stat 2.03 version. (Systat Software, Inc. Point. CA, USA).

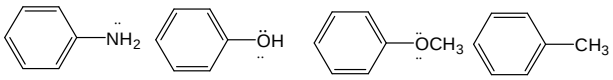
RESULTS AND DISCUSSION

It was observed that substitution in 5-ethylidene-2-(phenylimino)thiazolidin-4-one ring by elecrophilic group (electron withdrawing groups) e.g. Nitro groups usually takes longer reaction time as compared to Nucleophilic groups (electrons donating groups) like methoxy or substitution by methyl group. As presence of nitro substituted benzaldehye deactivates the ring and thus increase the rate of reaction time duration while substitution by methoxy (an electron donating group) causes activation of ring towards eletrophilc substitution and thus time duration of the reaction decreases. Within the compounds of nitro substituted series of compound, shows lesser reaction time duration as in case of nitro group para position is most active as compared to ortho and meta position. In case of methoxy substituted derivatives Para position is most active but trisubstituted like 3, 4, 5 trimethoxy takes longer time because of the hinderence provided by the bulky groups. For chloro substituted derivatives maximum effect is observed at ortho and para postions.

Comparison of reaction time for substitution by different electrophilic and nucleophilic groups

The reaction generally takes place in acidic medium in presence of ethanol (95%) and fused sodium acetate reaction of intermediates (1) with different benzaldehyde and cyclising reagents like ClCH2COCl, BrCH2COCl, BrCH2COOEt and ClCH2COCH2COOEt in boiling absolute ethanol containing anhydrous sodium acetate afforded the substituted 4- thiazolidinones derivatives. The reaction involves cyclization and complete anhydrous condition is maintained thought the reaction. Substitution by electron withdrawing groups takes longer reaction time duration as comparison to nucleophilic groups. In case of electophilic substitution at Meta position takes place easily as comparison to para position which takes longer time duration. Below are given some examples of activating and deactivating groups.

Activating Substituent's



Deactivating Substituent's

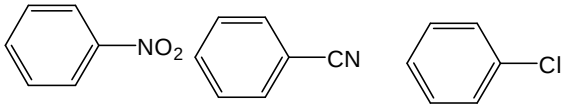


Table 1: Reaction and % of product obtained at different substituted position

Compound	Reaction	% Ortho-Product	% Meta-Product	% Para-Product
–O–CH_3	Nitration	30–40	0–2	60–70
–O–CH_3	F-C Acylation	5–10	0–5	90–95
–NO_2	Nitration	5–8	90–95	0–5
–CH_3	Nitration	55–65	1–5	35–45
–CH_3	Sulfonation	30–35	5–10	60–65
–CH_3	F-C Acylation	10–15	2–8	85–90
–Br	Nitration	35–45	0–4	55–65
–Cl	Chlorination	40–45	5–10	50–60

Table 2. Extensor Phase Data of Compounds

S. No.	Compound	Dose (mg/kg)	Hind Limb Extensor (Mean ± S.E.M)
1.	Control	30	89.00 ± 0.40
2.	Standard	30	15.25 ± 0.25
3.	III	30	12.5±0.76*
4.	IV	30	23±0.73***
5.	V	30	7.5 ± 0.61***
6.	VI	30	11.16 ± 0.60***
7.	VII	30	14.16 ± 0.60

Table 2: Anticonvulsant activity of synthesized compounds.Values are Mean ± SEM of six animals in each group. The pharmacological data indicated that among all the compounds being screened, compounds IV, V and VI showed significant antiepileptic activity (P<0.001) and compound III and VII show the less significant activity (P<0.01)

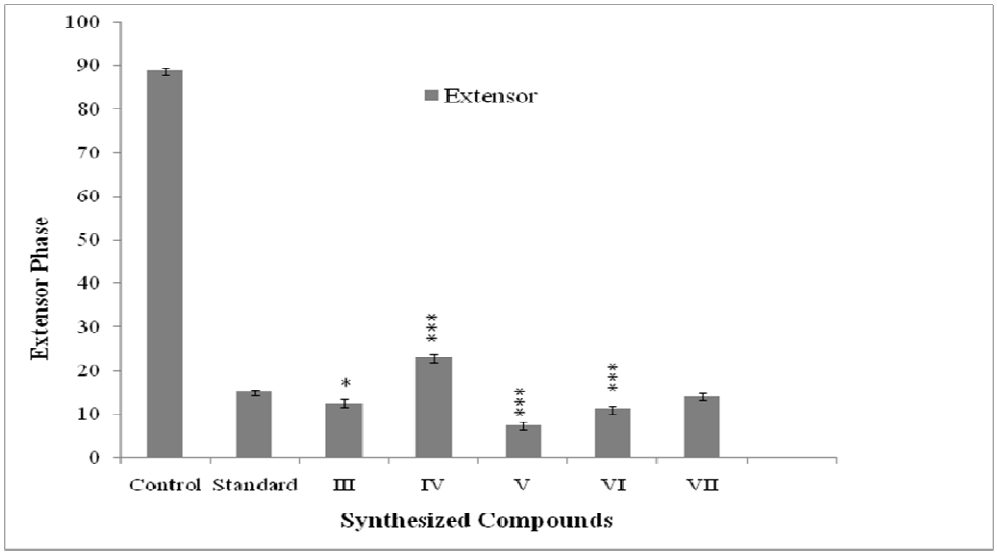


Figure 2: Anticonvulsant Activity of Synthesized Compounds at the Dose of (30 mg/kg) in albino mice.
*All the Values were expressed as Mean ±S.E.M and * **p≤ 0.001 indicates the level of stastical significance as compared with standard.*

CONCLUSION

The structures of the synthesized compounds were confirmed by IR spectra, mass spectra, ^{1}H NMR spectral analysis and elemental analysis. The IR spectra of (III-VII) exhibited some characteristic band due to =C-H str. (3100-3000cm^{-1}), C=C str. (1635-1495 cm^{-1}), C-H bending (900-860 cm^{-1}), C-H bending (substituted aryl (840-800 cm^{-1}), C-S-C str. (700-600cm^{-1}), C=N (ring) (1650-1580 cm^{-1}). Stretching vibration band, C=O (1674 cm^{-1}, 4-thiazolidinone moiety). In the ^{1}H NMR spectrums the signal appears between δ 5.1- 6.1 indicates the thiazolidinone. Among the synthesized compounds 5-(4-methoxybenzylidene)-2-(phenylamino) thiazolidin-4-one **(IV)**, 5-(4-fluorobenzylidene)-2-(phenylimino) thiazolidin-4-on **(V)**, 5-(4-chlorobenzylidene)-2-(phenylamino) thiazolidin-4-one **(VI)** showed excellent anticonvulsant activity.

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