

Microwave assisted synthesis and pharmacological evaluation of few substituted 4-thiazolidinone derivatives

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Abstract

In present investigation the synthesis of few 2-(substituted phenyl)-3-(5-substituted phenyl-4H-1, 2, 4-triazole-3-yl)-thiazolidine-4-ones and 3-(5-(4-substituted phenyl)-1, 3, 4-thiadiazole-2-yl)-2-phenylthiazolidine-4-ones is reported with the aim of achieving enhanced anticonvulsant effect. Two schemes were designed viz. first scheme for clubbed triazole-thiazolidinone derivatives and second scheme for clubbed thiadiazole-thiazolidinone derivatives. The compounds were characterized on the basis of IR, ¹H-NMR and Mass analyses. Acute toxicity study was done to determine the LD₅₀ of the compounds. Some of the compounds were evaluated for their anticonvulsant activity using PTZ induced convulsions method. The compounds DCThizd-N and NMThizd-N showed highest percentage of protection (80%) at the dose of 30mg/kg among the evaluated compounds compared to control.

Keywords: 4-Thiazolidinone, Triazole, Thiadiazole, Anticonvulsant activity.

Introduction

Epilepsy is a very common disorder, characterized by seizures, which takes various form and result from episodic neuronal discharges. Current antiepileptic drugs are effective in controlling seizures in about 70% of patients but effects such as drowsiness, ataxia, gastrointestinal disturbance, hepatotoxicity and megaloblastic anaemia and even life threatening condition often limit their use. To overcome these side effects along with maintaining the safety and effectiveness of the anticonvulsant drug there is need of research of new moiety for the treatment of the epilepsy.¹

Thiazolidinones are saturated form of thiazole with carbonyl group on forth carbon having molecular formula C₃H₅NOS and molecular mass 103.03. Thiazolidinones are also known as wonder nucleus because they possess broad spectrum of activities including some CNS activities like antipsychotic, antiparkinsonian, anticonvulsant, and FSH receptor agonist. Similarly, Thiadiazoles and Triazoles also possess various pharmacological activities including anticonvulsant activity as that of thiazolidinone. In the present investigation we propose the synthesis of few derivatives containing substituted 4- thiazolidinone ring directly attached to 3rd position of triazole and 2nd position of thiadiazole with the aim to possess more anticonvulsant potential.^{2,3}

Use of microwaves for heating of reaction mixture i. e. microwave assisted synthesis has become popular because of its advantages over the conventional heating process/method. It offers simple, fast and efficient synthesis of organic molecules. It has been observed that, this results into 90-100% yields with less byproduct. This is the reason why microwave assisted synthesis is considered as environment friendly technique. The basic difference between the microwave assisted synthesis and conventional heating is microwaves directly couple with reacting molecules leading to rapid rise in temperature (in situ

heating) while in conventional heating process, wall heat transfer occurs when a water/oil bath is applied as an energy source. Microwaves are the electromagnetic waves falling in range of 300 to 300,000 MHz of electromagnetic spectrum. The frequency for medical application and organic synthesis is 2450 MHz because it has appropriate penetration depth to interact with laboratory scale sample.^{4,5}

Materials and Methods

Materials

Laboratory reagent grade chemicals were used of makes viz. Thomas Baker, LobaChemie. Omega scientific industries' melting point apparatus was used to obtain the melting points. 60F254 Precoated silica gel plates (Merck) were used to perform TLC. The spots were visualized in UV chamber. The solvent system used for Thin-Layer Chromatography was Ethyl acetate: methanol (7:3) (Solvent system A). IR spectra of compounds were recorded on DRS on a Shimadzu 1000 FTIR spectrometer in the range of 4000-200 cm⁻¹. ¹H NMR spectra of compounds, were recorded on Bruker Advance II 400 NMR Spectrophotometer using DMSO solvent, at SAIF, Punjab University, Chandigarh. Mass spectra of compounds were recorded on WATERS, Q-TOF MICROMASS (LC-MS) at SAIF, Punjab University, Chandigarh, Punjab. All microwave reactions were carried on 'Catalyst System' CATA 2R- Scientific Microwave Synthesizer. The animals (Swiss albino mice of male sex) required for pharmacological evaluation of compounds were purchased from National Institute of Bioscience, Pune, India.

Methods⁶

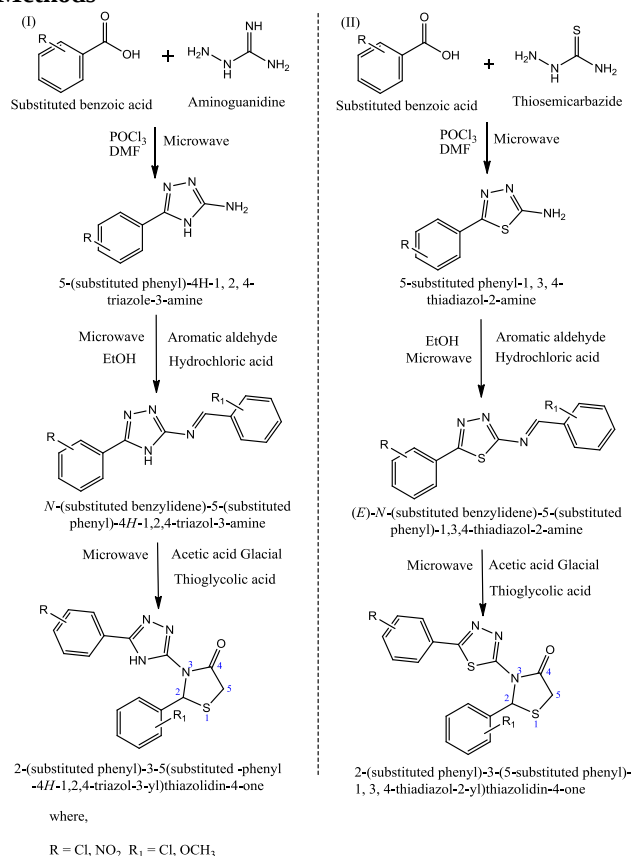


Fig. 1: Synthetic schemes for the title compounds

General procedure for synthesis of the 5-(substituted phenyl)-4H-1, 2, 4-triazole-3-amine. Aminoguanidine bicarbonate (0.03mol) was suspended in dimethyl formamide (30ml) and stir with addition of substituted benzoic acid (0.03mol). Then phosphorous oxychloride was added at 0°C. The mixture was irradiated under microwave at 350W for 6-25 minutes. Then cooled to room temperature. The solvent was evaporated and the resulting solid mass was poured into the crushed ice. The mixture was basified by the addition of 40% NaOH solution. The precipitate obtained was filtered and recrystallized from ethanol.

Similar procedure was followed for the synthesis of 5-substituted phenyl-1,3,4-thiadiazol-2-amine by replacing aminoguanidine with thiosemicarbazide. The reaction mixtures were irradiated at 350 W for time ranging between 15-25 minutes

General procedure for synthesis of the N-(substituted benzylidene)-5-(substituted phenyl)-4H-1, 2, 4-triazol-3-amine and N-(substituted benzylidene)-5-phenyl-1,3,4-thiadiazole-2-amine. To the 1 equivalent of the aromatic amines synthesized in above step, 5 equivalents of substituted benzaldehyde was added in 15-20 ml ethanol as solvent. Then 1ml concentrated hydrochloric acid was added to this reaction mixture. The reaction mixture was irradiated in microwave system and the reaction conditions for compounds 1a-6a and compounds 1b-6b is shown in

Table 1 and Table 2 respectively. The reaction mixture was poured into crushed ice to obtain the solid.

General procedure for synthesis of 2-(substituted phenyl)-3-(5-(substituted phenyl)-4H-1,2,4-triazol-3-yl)-thiazolidin-4-one and 2-(substituted phenyl)-3-(5-substituted phenyl)-1, 3, 4-thiadiazol-2-yl)-thiazolidin-4-one. To the Schiff's bases synthesized in above step, thioglycolic acid was added in equimolar proportion and the mixture was irradiated at 420 W for 20 minutes using glacial acetic acid as solvent. The mixture is cooled and mixed with sodium carbonate solution (10%). Resultant solid was collected and washed with cold water and recrystallized with ethanol.

Pharmacological Evaluation

Acute toxicity of Synthesized Compounds

OECD guidelines (No. 425) were followed for acute toxicity studies. Acute toxicity in mice was carried out for determining median Lethal Dose (LD₅₀). Each animal was observed carefully for signs of toxicity as well as for mortality in the first 30 minutes after dosing and then occasionally for further 4 hours and daily thereafter for a period of 14 days. The number of mice dying during 48 hours was recorded.

Anticonvulsant activity

Pentylenetetrazole (PTZ) induced convulsions in mice Animals

Swiss albino mice of male sex, Weight 22-30 gm.

Animals were housed in registered animal house of MET's Institute of Pharmacy, Nashik (Registration no. 1344/ac/10/CPCSEA).

Temperature: 25±1°C,

Relative Humidity

45-55%.

All experiments were conducted according to the guidelines of Committee for Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Environments and Forests, Government of India with their procedures and protocols reviewed and approved by Institutional Animal Ethical Committee (IAEC), constituted under CPCSEA.

Preparation of doses

Pentylenetetrazole (PTZ):

Dose: 80 mg/kg, i.p.

Solvent: Distilled water.

Diazepam:

Dose: 2 mg/kg, i.p., a stock solution containing 0.2 mg/mL was prepared by dissolving it in Solvent: Distilled water.

Test compounds:

Dose I: 15 mg/kg, i.p; Dose II: 30 mg/kg, i.p

Solvent: DMSO

Procedure

The animals were then divided into Eight groups of six animals each as shown in Table 3,

Table 1: Reaction conditions for synthesis of N-(substituted phenyl)-5-(substituted phenyl)-4H-1, 2, 4-triazole-3-amine

Compound code	Ar	Ar'/R ₁	Power (watt)	Time (min)
1a	-p-Cl-C ₆ H ₅	-o-Cl-C ₆ H ₅	350	20
2a	-p-Cl-C ₆ H ₅	-p-OCH ₃ -C ₆ H ₅	420	20
3a	-p-NO ₂ -C ₆ H ₅	-p-OCH ₃ -C ₆ H ₅	420	20
4a	-p-NO ₂ -C ₆ H ₅	-o-Cl-C ₆ H ₅	350	15
5a	-p-Cl-C ₆ H ₅	-C ₆ H ₅	420	20
6a	-p-NO ₂ -C ₆ H ₅	-CH ₂ CH-CH-C ₆ H ₅	350	15

Table 2: Reaction conditions for synthesis of N-benzylidene-5-(4-substituted phenyl)-1, 3, 4-thiadiazole-2-amine

Compound code	Ar	Ar'/R ₁	Microwave	
			Power (watt)	Time (min)
1b	-p-Cl-C ₆ H ₅	-o-Cl-C ₆ H ₅	350	20
2b	-p-Cl-C ₆ H ₅	-p-OCH ₃ -C ₆ H ₅	420	20
3b	-p-Cl-C ₆ H ₅	-C ₆ H ₅	350	15
4b	-p-NO ₂ -C ₆ H ₅	-o-Cl-C ₆ H ₅	350	15
5b	-p-NO ₂ -C ₆ H ₅	-p-OCH ₃ -C ₆ H ₅	420	20
6b	-p-NO ₂ -C ₆ H ₅	-CH ₂ CH-CH-C ₆ H ₅	420	20

Table 3: Different groups of animals used for evaluation of anticonvulsant effect

Group	Compound	Dose(mg/Kg) i.p.
1	PTZ (Control)	80
2	Diazepam (Standard)	2
3	DCThizd-N	Dose-I = 15
4		Dose-II = 30
5	CMThizd-N	Dose-I = 15
6		Dose-II = 30
7	NMThizd-N	Dose-I = 15
8		Dose-II = 30

The Diazepam treated and test animals were observed following PTZ injection up to half an hour. The anticonvulsant potential of the newly synthesized compounds is evaluated on the basis of the following observations:

1. Increase in latency (onset time) to induce convulsions
 2. Percentage Protection as compared to control
- Readings of the test compounds are compared with control.

Results and Discussion

Table 4: Physicochemical properties of 2-(substituted phenyl)-3-(5-substituted phenyl-4H-1, 2, 4-triazole-3-yl)-thiazolidine-4-one

S. No.	Comp. code	Ar	Ar'/R ₁	Melting Point (°C)	Yield (%)	Rf Value*
1	DCThizd-N	-4-Cl-C ₆ H ₅	-2-Cl-C ₆ H ₅	98-100	54	0.77
2	CMThizd-N	-4-Cl-C ₆ H ₅	-4-OCH ₃ -C ₆ H ₅	104-108	65	0.8
3	NMThizd-N	-4-NO ₂ -C ₆ H ₅	-4-OCH ₃ -C ₆ H ₅	84-86	50	0.8

*solvent system (A)

Table 5: Physicochemical properties of 3-(5-(4-substituted phenyl)-1, 3, 4-thiadiazole-2-yl)-2-phenylthiazolidine-4-one.

S. No.	Comp. code	Ar	Ar'/R ₁	Melting Point (°C)	Yield (%)	Rf Value*
1.	NMThizd-S	-4-NO ₂ -C ₆ H ₅	-4-OCH ₃ -C ₆ H ₅	84-86	50	0.8

*solvent system (A)

Table 6: Anticonvulsant effect of some synthesized 2- substituted phenyl-3-(5- substituted phenyl-1, 2, 4-triazol-2-yl)-1, 3-thiazolidine-4-one in mice using PTZ induced convulsions method

S. No	Compound Code	R	R'	Dose (mg/kg, i.p.)	Latency to Induce convulsions (Min) (Mean ±SEM)	% Protection
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1	PTZ	Pentylene-tetrazole		80 [#]	0.52±0.21	0
2	Diazepam	7-chloro-5-phenyl-2,3-dihydrobenzodiazepine-2-one		2	-	100
3	DCThizd-N (PW1)	-4-Cl-C ₆ H ₅	-2-Cl-C ₆ H ₅	15	3.06±0.22 ^{**}	80
				30	3.50±0.29 ^{**}	80
4	CMThizd-N (PW2)	-4-Cl-C ₆ H ₅	-4-OCH ₃ -C ₆ H ₅	15	2.09±0.26 ^{NS}	20
				30	2.48±0.28 [*]	60
5	NMThizd-N (PW3)	-4-NO ₂ -C ₆ H ₅	-4-OCH ₃ -C ₆ H ₅	15	2.39±0.44 [*]	60
				30	2.79±0.35 ^{**}	80

[#] Subcutaneous

N=6, in each group; *: P < 0.05; **: P < 0.01; NS: Non significant; One Way ANOVA followed by Dunnett's test.

Discussion on Characterization of Synthesized Compounds

1. The IR spectra of the title compounds showed C-N- str at 1349cm⁻¹, -C=N- str at 1638-1697 cm⁻¹, -C-S-C- str at 530-689cm⁻¹, -N-H str at 3100-3300cm⁻¹,
2. The ¹H NMR spectrum of 2-(4-chloro phenyl)-3-(5-(4-chloro phenyl)-4H-1, 2, 4-triazole-3-yl)-thiazolidine-4-one, DCThizd-N showed (Ar-Ha) and (Ar-Hb) multiplet at δ 7.33-7.35, (thiazolidinone-Hd) singlet at δ 3.77, (thiazolidinone-He) singlet at δ 5.26 and multiplet for (Ar-Hf), (Ar-Hg), (Ar-Hh) and (Ar-Hi) at δ 6.86-6.88.
3. The ¹H NMR spectrum of 2-(4-methoxy phenyl)-3-(5-(4-chloro phenyl)-4H-1, 2, 4-triazole-3-yl)-thiazolidine-4-one, CMThizd-N showed (Ar-Ha) doublet at δ 7.65, (Ar-Hb) doublet at δ 7.93, (thiazolidinone-Hd) singlet at δ 3.46, (thiazolidinone-He) singlet at δ 5.14, (Ar-Hf) doublet at δ 7.28, (Ar-Hg) doublet at δ 7.95, (4-OCH₃-Hh) singlet at δ 3.77.
4. The ¹H NMR spectrum of 2-(4-methoxy phenyl)-3-(5-(4-nitro phenyl)-4H-1, 2, 4-triazole-3-yl)-thiazolidine-4-one, NMThizd-N showed (Ar-Ha) doublet at δ 8.12, (Ar-Hb) doublet at δ 7.34, (thiazolidinone-Hd) singlet at δ 3.36, (thiazolidinone-He) singlet at δ 5.25, (Ar-Hf) doublet at δ 7.32, (Ar-Hg) doublet at δ 6.89 and (4-OCH₃-Hh) singlet at δ 3.77.
5. The mass spectrum of the compound NMThizd-S 2-(4-methoxyphenyl)-3-(5-(4-nitrophenyl)-1, 3, 4-thiadiazol-2-yl) thiazolidin-4-one showed molecular ion peak at m/e 397. The mass analysis was done by Liquid Chromatography-Mass Spectrometry (LC-MS). The fragment peaks were observed at m/e 382, 366, 351, 320, 232, 218, 187, 142, 102.

Discussion on Pharmacological Evaluation⁷

The analysis of structural features revealed that substitution of chlorophenyl substituted triazole to the nitrogen of the thiazolidinone ring and chlorophenyl substitution at second position of the thiazolidinone ring enhances the anticonvulsant potential of the synthesized compounds.

The chemically induced model of evaluation for anticonvulsant potential was adopted as it is better and feasible alternative at laboratory conditions. Their potential to increase the latency to induce convulsions and increase in percent protection as compared to control (PTZ) was evaluated as shown in **Table 6**. The graphical comparison of

the latency to induce convulsion in minutes at both the dosages selected for the test compounds along with the control (PTZ, 80 mg/Kg) is shown in Fig. 2.

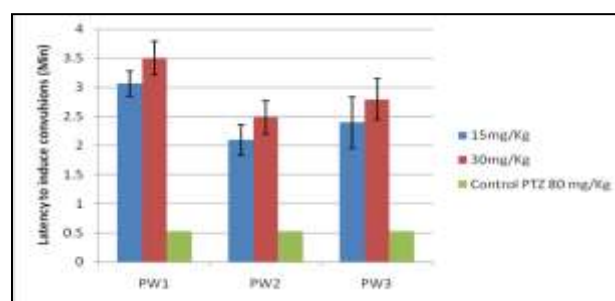


Fig. 2: Comparison of latency to induce convulsions of 2-substituted phenyl-3-(5- substituted phenyl-1, 2, 4-triazol-2-yl)-1, 3-thiazolidine-4-one in mice using PTZ induced convulsions.

It is revealed that compounds DCThizd-N showed greater increase in the latency at the dose of 30 mg/Kg. The latency was increased up 3.5 minutes for all three compounds which is a good sign for the compounds to be carried forward for clinical studies.

Conclusion

On the basis of the present investigation following conclusions are outlined:

1. The compound DCThizd-N shows highest latency as 3.50 minutes at the dose of 30mg/kg.
2. The pharmacological evaluation of the compounds showed increase in latency (onset time) to induce convulsions and increase in percent protection compared to control.
3. The compounds DCThizd-N and NMThizd-N showed highest percentage of protection (80%) at the dose of 30mg/kg among the evaluated compounds compared to control.
4. The analysis of structural features revealed that substitution of chlorophenyl substituted triazole to the nitrogen of the thiazolidinone ring and chlorophenyl substitution at second position of the thiazolidinone ring showed enhanced the anticonvulsant potential among the synthesized compound.

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Conflict of Interest: None.

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