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RESEARCH ARTICLE

Anticonvulsant Activity of Some Novel Substituted Thiazolidinone Derivatives against Maximal Electro Shock Induced Seizure

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ABSTRACT

The main objective of this study is to synthesize 2-(substituted phenyl)-3-[{4-(1-naphthyl) - 1, 3 - thiazol-2-yl} amino] -4-oxo- 1, 3) -thiazolidin-5-yl] acetic acid (**TA_1-TA_{10}**) from 1-acetyl naphthalene. The synthesized compound, characterized on the basis of satisfactory analytical and spectral (IR, H^1NMR) data, have shown moderate to good anticonvulsant activity.

KEYWORDS

Antihyperglycemic activity, 1-Acetylnaphthalene, Thiazoles, Thiazolidinones

INTRODUCTION

Thiazolidinone are important assembly of heterocyclic mixtures including sulfur and nitrogen in a five constituent ring. The nucleus is furthermore renowned as wonder nucleus because it presents out different derivatives with all distinct types of biological undertakings.[1] Publications survey reveals that 4-thiazolidinones are usually synthesized starting from thiourea[2-4], thiosemicarbazides[5] and azomethines[6]. Thiazolidinones have been synthesized and screened for possible antimicrobial undertaking[7-11] furthermore; thiazolidinones have a very wide spectrum of pharmacological properties like anti HIV[12], antipsychotic[13], anticonvulsant[14] and antitubercular[15] undertaking. The β-lactams furthermore serve as synthons for numerous biologically important categories for many biologically important categories of organic blends[16]. Due to this, the enquiry of chemistry and biological research of these blends extend to request the synthetic and medicinal organic chemists.

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MATERIALS AND METHOD

Chemicals and Reagents

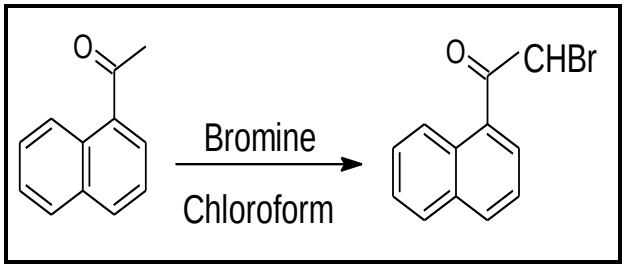
1-acetylnaphthalene, chloroform, bromine, Substituted benzaldehyde thio semicarbazones, ethanol, thiolactic acid, thioglycolic acid, dioxane, zinc chloride.

Method of Synthesis

Synthesis of 1-bromoacetyl naphthalene

1-Acetylnaphthalene (0.02 moles) was taken in 20 mL of chloroform in a 250 mL conical flask. A solution of bromine (0.04 moles) in chloroform was prepared. The bromine solution was added to flask containing 1-acetylnaphthalene solution, drop wise with stirring. The chloroform mixture was distilled on a water bath. The solid obtained was washed with petroleum ether and then recrystallized

from benzene yielding 1-bromoacetyl naphthalene.



Synthesis of Substituted Thiosemicarbazone

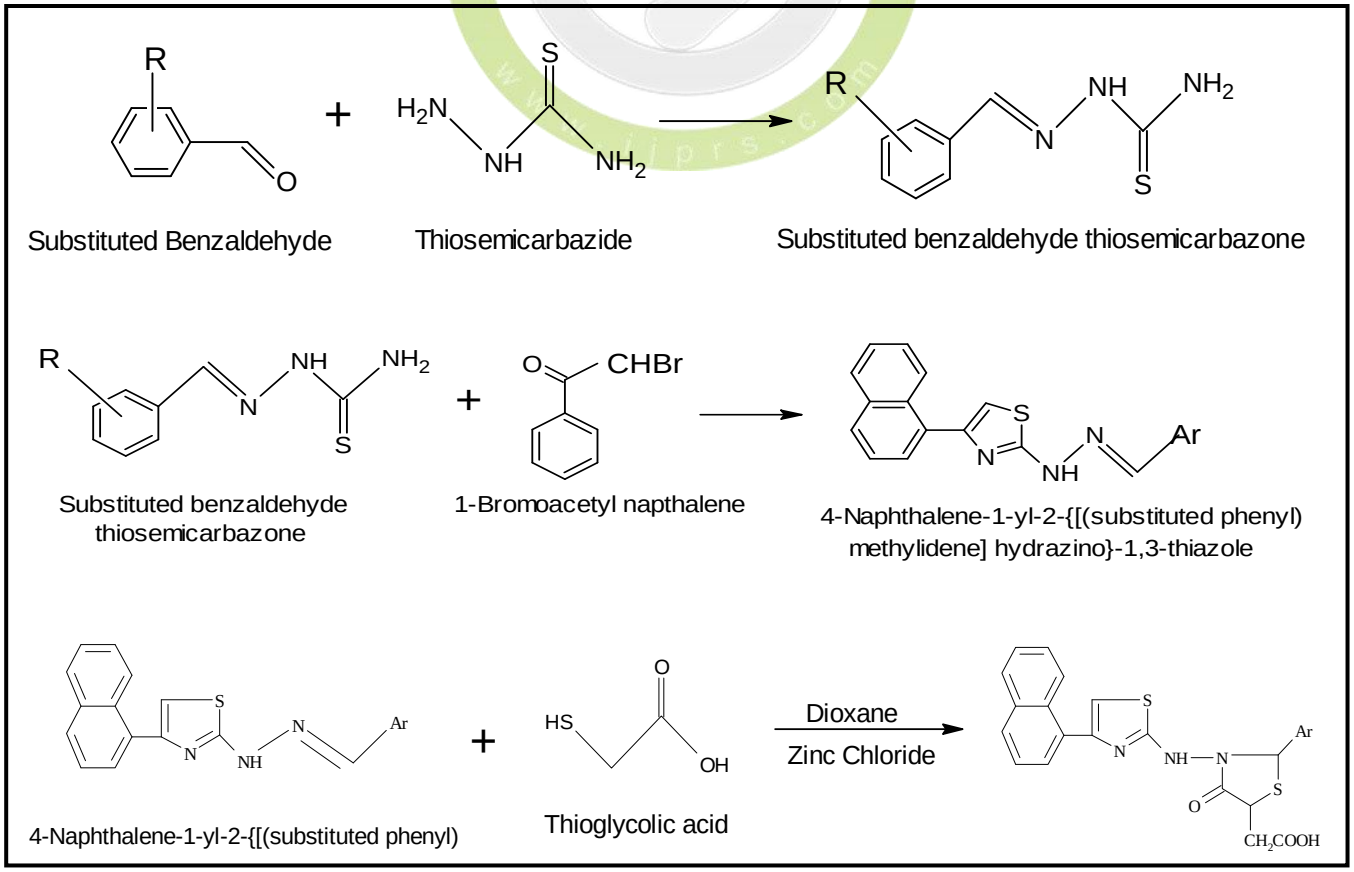
A solution of 0.05 mol. Substituted benzaldehyde in warm alcohol (300 ml) and a solution of 0.05 mol thiosemicarbazide in 300 ml water were mixed slowly. The product, which separated, was filtered off after cooling and recrystallised from ethanol. Other thiosemicarbazones were prepared in the same way.

Synthesis of 4-naphthalen-1-yl-2-{2-[(substituted phenyl) methyl idene] hydrazino}-1, 3- thiazole

Equimolar quantities (0.01mole) of 1-bromoacetylnaphthalene and substituted benzaldehyde thiosemicarbazones were dissolved in 50 mL of ethanol in a 100 mL round bottom flask. The reaction mixture was refluxed for 1-2 h. A solid was separated during refluxing which was hot filtered, dried and recrystallized from ethanol yielding 4-naphthalen-1-yl-2-{2- [(substituted phenyl) methylidene] hydrazino}- 1,3-thiazole.

Synthesis of [2-(substituted phenyl)-3-[{4-(1-naphthyl)-1, 3 -thiazol-2-yl) amino] -4-oxo- 1, 3 -thiazolidin-5-yl} acetic acid (TA_1-TA_{10})

A mixture of 4-(1-naphthyl)-2-(substituted benzylidine amino)-1, 3-thiazoles (0.01 mole) and thiomalic acid (0.015 moles) in 25 ml dioxane was taken in a 100 ml round bottom flask. To this solution a pinch of $ZnCl_2$ was added and the reaction mixture was refluxed for 6-10 hr. The mixture was then poured on crushed ice and solid so obtained was filtered, washed with water, dried and recrystallized from dioxane. The purity of compounds was established on the basis of TLC.



Compound [TA_1]

Preparation of 2-(4-Nitrophenyl)-3-[{4-(l naphthyl)-1,3-thiazol-2-yl}amino]-4-oxo-1,3-thiazolidin-5 -yl] acetic acid. **IR Spectra:** 3415.18 (0-H), 3247.32 (N-H), 1717.06 and 1693.88 (C=O), 1613.71 (C=N), 1542.12 (C=C), 1509.66, 1439.98 and 1040. 10. **^{1}HNMR [δ ppm]**: 2.38 (d J=12Hz, 2H, -CH2-CO-), 4.50 (t, J=6Hz, 1H, -CH-S-), 6.33 (s, 1H, -N-CH-), 7.56 (m, 9H, Ar-H), 7.92 (d, J=12Hz, 1H, Ar-H), 8.09 (d, J= I 2Hz, 1H,Ar-H), 8.24 (d, J=12Hz, 1H, Ar-H), 8.98 (s, 1H,-NH), 10.68 (s, 1H, OH).

Compound [TA_2]

Preparation of [2-(3-nitrophenyl)-3-[(4-(l-naphthyl)-1, 3-thiazol-2-yl) amino] 4-oxo-1, 3-thiazolidin-5 –yl] acetic- acid. **IR Spectra:** 3416.42 (O-H), 3247.50 (N-H), 1713.08 and, 1694.84 (C=O), 1611.16 (C=N), 1543.24 (C=C), 1515.15, 1452.66 and 1039.98. **^{1}HNMR [δ ppm]**: 2.39 (d, J=12Hz, 2H, -CH2-CO-), 4.48 (t, J=6Hz,

1H, -CH-S-), 6.58 (s, 1H, -N-CH-) 7.14 (m, 3H, Ar-H), 7.35 (s, 1H, Ar-H), 7.59-(m, 5H, Ar-H), 7.94 (d, J=12Hz. 1H. Ar-H), 8.09 (d, J=12Hz, 1H, Ar-H), 8.22 (d, J= 12 Hz, 1H, Ar-H), 8.96 (s, 1H, NH), 10.66 (s, 1H, OH).

Compound [TA_3]

Preparation of 2-(4-chlorophenyl)-3-[{4-(1 naphthyl)-1, 3-thiazol-2-yl} amino]-4-oxo-1, 3-thiazolidin-5-yl] acetic acid **IR Spectra:** 3414.68 (O-H), 3247.55 (N-H), 1712.88 and 1697.42 (C=O), 1614.20, 1551.18 (C=C), 1510.02, 1449.74 and 1040.10. **^{1}HNMR [δ ppm]**: 2.41 (d, J=12Hz, 2H, -CH2-CO-), 4.48 (t, J=6Hz, 1H, -CH-S-), 633 (s, 1H, -N-CH-), 7.17 (d, J=12Hz, 2H, Ar-H), 7.33 (m, 3H, Ar-H), 7.56 (m, 4H, Ar-H), 7.92 (d, J=12Hz, 1H, Ar-H), 8.10 (d, J=12Hz, 1H, Ar-H), 8.25 (d, J=12Hz, 1H, Ar-H), 8.98 (s, 1H, NH), 10.68 (s, 1H, OH).

Compound [TA_4]

Preparation of 2-(2, 4-dichlorophenyl)-3-[{4-(1-naphthyl)-1, 3-thiazol-2-yl)amino]-4-oxo-1,3-thiazolidin-5-yl] acetic acid**. IR Spectra:** 3415.16 (O-H), 3246.55 (N-H), 1716.04 and 1693.72 (C=O), 1613.44 (C=N), 1548.10 (C=C), 1510.16, 1445.66 and 1042.44. **^{1}HNMR [δ ppm]:** 2.40 (d, J=12Hz, 2H, -CH,-CO-), 4.52 (t, J=6Hz, 1H, -CH-S-), 6.75 (s, 1H, -N-CH-), 7.10 (d, J=12Hz, 2H, Ar-H), 7.33 (s, 1H, Ar-H), 7.43 (s, 1H, Ar-H), 7.62 (m, 4H. Ar-H), 7.95 (d, J=12Hz, 1H, Ar-H), 8.11 (d, J=1214z, 1H, Ar-H), 8.25 (d, J=12Hz, 1H, Ar-H), 8.96 (s, 1H, NH), 10.65 (s, 1H, OH).

Compound [TA_5]

Preparation of [2-(2, 6-dichloroplienyl)-3-[{4-(1-naphthyl)-1, 3-Thiazol-2-yl} amino]-4-oxo-1, 3- thizolidin-5-yl] acetic acid. **IR Spectra:** 3417.04 (O-H), 3244.64 (N-H), 1712.08 and 1691.98 (C=O), 1609.50 (C=N), 1551.28 (C=C), 1510.10, 1448.62 and 1050.66. **^{1}HNMR [δ ppm]**: 2.41 (d, J=12Hz, 2H, -CH,-CO-), 4.50 (t, J=6Hz, 1H, -CH-S-), 6.85 (s, 1H, -N-CH-), 7.33 (s, 1H, Ar-H), 7.53 (m. 7H, Ar-H), 7.96 (d, J=12Hz, 1H, Ar-H), 8.13 (d, J=12Hz, 1H, Ar-H), 8.26 (d, J=12Hz, 1H, Ar-H), 8.95 (s, 1H, NH), 10.66 (s, 1H, OH).

Compound [TA_6]

Preparation of 2-(3-fluorophenyl)-3-[{4-(1 naphthyl)-1, 3-thiazol-2-yl} amino]-4-oxo-1, 3-thiazolidin-5 -yl] acetic acid. **IR Spectra:** 3417.44 (0-H), 3243.88 (N-H). 1713.98 and 1695.15 (C=O), 1610.10 (C=N), 1548.42 (C=C), 1510.04, 1447.90 and 1045.44. **^{1}HNMR [δ ppm]**: 2.38 (d, j=12Hz, 2H, -CH2-CO-), 4.48 (t, J=6Hz, 1H, -CH-S-). 6.52 (s, 1H, -N-CH-), 6.90 (m, 1H, Ar-H), 7.16 (m. 2H, Ar-H), 7.33 (s, 1H, Ar-H), 7.58 (m, 5H, Ar-H), 7.94 (d, J=12Hz, 1H, Ar-H), 8.10 (d, J=12Hz, 1H. Ar-H), 8.23 (d, J= I 2Hz, 1H, Ar-H), 8.94 (s, 1H, NH), 10.64 (s, 1H, OH).

Compound [TA_7]

Preparation of 2-(2-hydroxy-4-bromophenyl)-3-[{4-(1-naphthyl)-1, 3-thiazol-2-yl) amino] 4-oxo-1, 3-thiazolidin-5-yl] acetic acid. **IR Spectra:** 3442.96 and 3417.84 (O-H), 3248.50 (N-H), 1715.16 and 1692.38 (C=O), 1609.65 (C=N), 1540.10 (C=C), 1510.18, 1445.08 and 1040.12. **^{1}HNMR [δ ppm]:** 2.41 (d, J=12Hz, 2H, -CH2-CO-), 4.50 (t, J=6Hz, 1H, -CH-S-).

6.52 (s, 1H, -N-CH-), 7.02 (m, 3H, Ar-,H), 7-135 (s, 1H, Ar-H), 7.58 (m, 4H, Ar-H), 7.98 (d, J= I 2Hz, 1H, Ar-H), 8.10 (d, J=12Hz, 1H, Ar-H), 8.26 (d, J=12Hz, 1H, Ar-H), 8.89 (s, 1H, NH), 10.55 (s, 1H, OH), 10.95 (s, 1H, OH).

Compound [TA_8]

Preparation of 2-(2-hydroxy-4-chlorophenyl)-3-[{4-(1-napthyl)-1, 3-thiazol-2-yl} amino] 4-oxo-1-3-thiazolidin-5-yl] acetic acid**. IR Spectra:** 3438.99 and 3414.62 (O-H), 3247.55 (N-H), 1713.224, 1695.15 (C=O), 1611.84 (C=N), 1547.50 (C=C), 1510.10, 1446-38 and 1041.02. **^{1}HNMR [δ ppm]:** 2.41 (d. J=12Hz, 2H, -CH_2-CO-)4.50(t,6Hz, 1H, -CH-S), 6.52 (s, 1H, -N-CH-), 6.98(m, 3H, Ar-H),-7.33 (s, 1H, Ar-H); 7.58 (m, 4H, Ar-H), 7.92 (d, J= 12Hz, 1H, Ar-H), 8.10 (d, J=12Hz- 1H, Ar-H), 8.26 (d, 12Hz, 1H, Ar-H), 8.92-(s,1H, NH), 10.57 (s, 1H, -OH), 10.90 (s, 1H, OH).

Compound [TA_9]

Preparation of 2-(4-dimethylaminophenyl)-3-[{4-(1-napthyl)-1, 3-thiazol-2-yl} amino] 4-oxo-1-3-thiazolidin-5-yl] acetic acid. **IR Spectra:** 3416.02 (O-H), 3239.92 (N-H), 1713.44 and 1697.60 (C=O), 1608.98 (C=N), 1544. 10 (C=C), 1510.18, 1445.48 and 1040.08. **^{1}HNMR [δ ppm]:** 2.38 (d, J=12Hz, 2H, -CH_2-CO-), 3.01 (s, 6H, CH_3), 4.50 (t, J=6Hz, 1H, -CH-S-), 6.56 (m, 3H, Ar-H, -N-CH-), 7.10 (d, J=12Hz, 2H, Ar-H), 7.32 (s, 1H, Ar-H), 7.56 (m, 4H, Ar-H), 7.95 (d, J=12Hz, 1H, Ar-H), 8.11 (d, J=12Hz, 1H, Ar-H), 8.24 (d, J=12Hz, 1H, Ar-H), 8.98 (s, 1H, NH), 10.67 (s, 1H, OH).

Compound [TA10]

Preparation of 2-(4-methoxyphenyI)-3-[{4-(1-naphthyl)-1, 3-thiazol-2-yl} amino]4-oxo-1,3-thiazolidin-5-yl] acetic acid. IR Spectra: 3417.76 (O-H), 3245.10 (N-H), 1714.86 and 1693.08 (C=O), 1609.46 (C=N), 1545.55 (C=C), 1510.10, 1443.72 and 1045.15. 1HNMR [δ ppm]: 2.38 (d, J=12Hz, 2H, -CH2,-CO-), 3.75 (s, 3H, OCH3) 4.50 (t, J=6Hz, 1H, -CH-S-), 6.53 (s, 1H, -N-CH-), 7.22 (m, 5H, Ar-H), 7.59 (m, 4H, Ar-H), 7.98 (d, J=12Hz, 1H, Ar-H), 8.13 (d, J=12Hz, 1H, Ar-H), 8.26 (d, J=12Hz, 1H, Ar-H), 8.95 (s, 1H, NH), 10.66 (s, 1H, OH).

General Procedures

Melting points were determined in open capillaries and all uncorrected. IR spectra (KBr pellet technique) were recorded using a Perkin-Elmer 237 spectrophotometer. ^{1}HNMR spectra were recorded on bruker AM 400 instrument (at 400 MHz) using tetramethylsilane (TMS) as an internal standard and DMSO-d6 as a solvent. Chemical shifts are given in parts per million(ppm). Splitting patterns are designated as follows: S-Singlet, d-doublet, t-triplet, q-quartet and m-multiplet. Mass spectra (MS) were recorded on Shimadzu GC-MS operating at 70eV. All the synthesized compounds were purified by recrystallization. The reaction were followed up and the purity of compounds was monitored on pre-coated TLC plates and visualizing the spots in ultra violet light.

RESULTS AND DISCUSSION

All the synthesized compounds were characterized on the basis of their IR, 1H NMR and elemental analysis. The study was aimed at evaluating the anticonvulsant effect of compounds on mice.

Anticonvulsant Activity

Anticonvulsant activity of [2-(substituted phenyl)-3-[{4-(1-naphthyl)-1, 3-thiazo1-2- yl} amino] -4-oxo- 1, 3 -thiazolidin-5 -yl] acetic acid (**TA_1-TA_{10}**) revealed that compounds **TA_7** (Ar = 4-bromo-2-hydroxyphenyl) and **TA_8** (Ar = 4-chloro-2- hydroxyl phenyl) showed highest anticonvulsant activity with respect to phenytoin but it was only 40% of the activity shown by phenytoin. All other compounds exhibited mild anticonvulsant activity.

CONCLUSION

From the above result it has been concluded that [2-(substituted phenyl)-3-[{4-(1-naphthyl) - 1,3 -thiazol-2-yl} amino] -4-oxo- 1,3) -thiazolidin-5-yl] acetic acid (**TA_1-TA_{10}**) may be used as lead compounds for anticonvulsant activity and may further be evaluated for toxicological profile.

Pharmacological Studies

Table 1: Anticonvulsant activity of [2-(substituted phenyl)-3-[{4-(1-naphthyl)-1, 3-thiazol-2-yl} amino]-4-oxo-1, 3-thiazolidin-5-yl] acetic acid (TA_1-TA_{10})

Compound	% Protection (Dose=25 mgkg-1)		
	0.5 Hr	1.5 Hr	2 Hr
Phenytoin	81.47 ± 1.22	100 ± 0.00	100.00 ± 0.00
TA_1	15.23 ± 0.171	22.11 ± 0.129*	31.70 ± 0.211**
TA_2	16.88 ± 0.365**	26.02 ± 0.252**	35.35 ± 0.300**
TA_3	20.19 ± 0.223	32.87 ± 0.85	35.14 ± 0.931
TA_4	13.57 ± 0.226	32.33 ± 0.92*	39.26 ± 0.502*
TA_5	20.19 ± 0.365	35.75 ± 0.65**	38.21 ± 0.501***
TA_6	18.21 ± 0.211**	32.87 ± 0.208**	38.22 ± 0.641**
TA_7	19.21 ± 0.297**	36.30 ± 0.465***	40.00 ± 0.611*
TA_8	21.05 ± 0.37***	29.45 ± 0.465***	40.00 ± 0.681**
TA_9	16.49 ± 0.154	30.03 ± 0.30*	39.28 ± 0.360***
TA_{10}	21.88 ± 0.600	44.04 ± 0.833	51.43 ± 1.167

* p<0.05, ** p<0.01, *** p<0.001

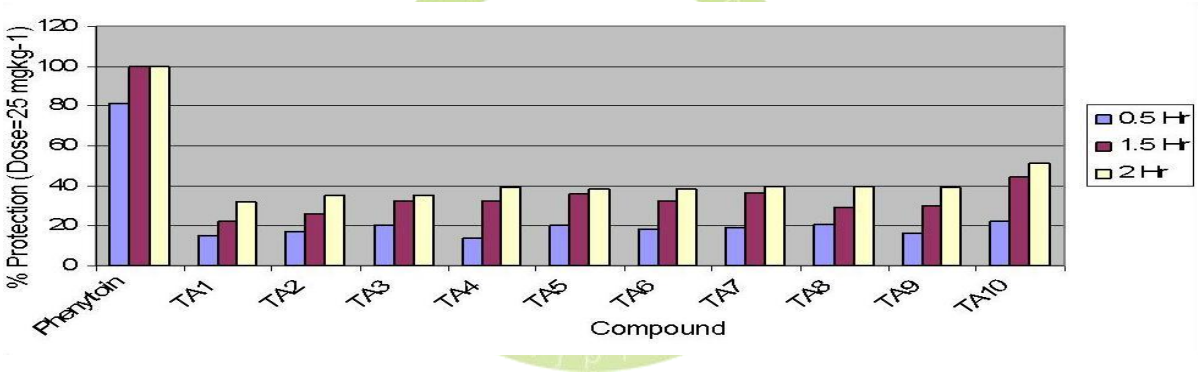


Figure: 1. Anticonvulsant activity of [2-(substituted phenyl)-3-[{4-(1-naphthyl)-1, 3-thiazol-2-yl} amino]-4-oxo-1, 3-thiazolidin-5-yl] acetic acid (TA_1-TA_{10})

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