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SYNTHESIS AND ANTIMICROBIAL ACTIVITIES OF SOME NOVEL 3-(2-AMINOTHIAZOL)-5-(SUBSTITUTED BENZYLIDENE)THIAZOLIDINE-2, 4-DIONE DERIVATIVES

Mahendra A. Gaikwad[a*], Ramesh M. Borde [b], Rahul A. Waghmare[a], Achyut S. Munde[a]

[a]*Department of Chemistry, Milind College of Science, Nagsenvana, Chhatrapati Sambhajinagar-431001, Maharashtra, India*
[b] *Department of Chemistry, Shri Sadguru Gangageer Maharaj Science, Gautam Arts & Sanjivani Commerce College, Kopargaon, Dist- Ahmednagar-423601, Maharashtra, India*
Email: mahendragaikwad7777@gmail.com

ABSTRACT: The paper reports on synthesis of 3-(2-aminothiazol-4-yl)-5-(4-substituted benzylidene) thiazolidine-2,4-dione **(7a-h)** which was obtained by condensing substituted 5-benzylidene-3-(2-chloro acetyl)thiazolidine-2,4-dione **(6a-h)** with thiourea by Hantzsch reactions. The structure is confirmed by FT-IR, 1H NMR and GC-MS. All the synthesized compounds were evaluated for in-vitro activities against a panel of Gram-positive and Gram-negative bacteria. The entire compound exhibited excellent to moderate activity against all pathogens.

KEY WORDS: Chloroacetic acid, thiourea, 1,3-thiazolidine-2,4-dione, aldehydes, chloroacetyl chloride, Hantzsch reaction, antibacterial, antifungal activity.

INTRODUCTION

Compounds containing heterocyclic ring are of great importance due to their wide range of biological and pharmaceutical activity [i]. Thiazolidine-2,4-dione nucleus are five membered rings that have nitrogen and sulphur at position 1 and 3 respectively and carbonyl at position 2 and 4. Thiazolidinone moiety is also occurs in nature, such as actithiazic acid isolated from streptomyces strains exhibits highly specific in vitro activity against *Mycobacterium tuberculosis*[ii]. Thiazolidine-2-4-dione moiety containing antidiabetic drugs such as, Pioglitazone used to lower blood glucose levels in type-2 diabetes[iii], Thiazolidinedione derivatives exhibits diverse bioactivities such as, anti-inflammatory[iv], antioxidant[v], antimicrobial[vi], antiviral[vii], antitubuercular[viii], transpeptidase enzyme inhibitor[ix] and antiprotozoal activities[x].

Thiazole is a five membered heterocyclic moiety possessing broad spectrum for drug design and synthetic adaptability for development of new leading compounds[xi]. Thiazole derivatives has been studied by researcher in the field of medicinal chemistry for resistance of microbial strains[xii]. Wide range of thiazoles containing drugs, such as, Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID) used to pain and inflammation in rheumatic diseases and osteoarthritis[xiii], Nizatidine is a histamine H_2 receptor antagonist, used in the treatment of peptic ulcer disease and gastroesophageal reflux disease[xiv], and Talipexole is a dopamine

agonist, used for the treatment of Parkinsons disease[xv]. aminothiazole derivatives, possessing broad spectrum of biological activities, such as, anthelmintic[xvi], xanthine oxidase inhibition[xvii], antidepressant[xviii], anti-tubercular[xix], antibacterial[xx], and carbonic anhydrase[xxi].
Literature survey revealed that compounds containing more than one pharmacophore increases the biological activities. Based on the biological spectrum thiazolidine-2,4-dione ring linked with aminothiazole increases importance in medicinal, and biological field. By considering this, our interest increases to synthesize some new heterocyclic compounds with potential activity.
In the present investigation deals with, the synthesis of some new series of 3-(2-aminothiazol-4-yl)-5-(4-substituted benzylidene)thiazolidine-2,4-dione **(7a-h)** in good yields, The antibacterial and antifungal activities of the compounds **(7a-h)**, have been evaluated. The structure of newly synthesized compounds confirmed by IR, ^{1}HNMR, GC-MS data, and Elemental analysis data.

MATERIALS AND METHODS

Melting points were determined in open capillary and are uncorrected. FT-IR spectra were recorded using Perkin-Elmer spectrometer. ^{1}H NMR spectra were recorded on Brucker Advance II 400 spectrometer in DMSO solvent by using Tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on Thermo Scientific TSQ-8000 gas chromatograph - mass spectrometer. The progress of reactions and purity of the compounds were monitored by thin layer chromatography on precoated silica plates, thickness of 0.25 mm and spots were visualized by irradiation with ultraviolet light (254 nm) or by exposed I_2.

General procedure for the synthesis of thiazolidine-2,4-dione (3):

In a 250 ml three neck flask, equimolar amount of chloroacetic acid **(1)** (0.6 mol) and thiourea **(2)** (0.6 mol) dissolved in water (60 ml). The mixture was stirred for 15 mins to obtain a white precipitate accompanied by considerable cooling. To the content of the flask then, slowly addition of conc. Hydrochloric acid (60 ml) from a dropping funnel. Then the reaction mixture was stirred and reflux for 8-10 hrs. at, 100-110 ^{o}C. on cooling, the contents of the flask solidified into a cluster of white needles. The product was filtered and washed with water to remove traces of hydrochloric acid and dried, it was recrystallization from ethanol. Yield: 90$^{\%}$, M.P: 123-125 ^{o}C.

General procedure for the Synthesis of 5-(substituted benylidene)thiazolidine-2,4-dione derivatives(5a-h):

An equimolar amount mixture of thiazolidine-2,4-dione **(3)** (0.1 mol) and substituted benzaldehyde **(4a-h)**, (0.1 mol) and sodium hydroxide (NaOH) (0.2 mol), in PEG-400 (25 ml) solvent, was heated on an oil bath at 120 ^{o}C for 2 hrs. The progress of the reaction was monitored by Thin Layer Chromatography (TLC). On completion of the reaction, the reaction mass was cooled and then poured on cold water, The result reaction mass was neutralized by using dil. HCl. The obtained solid product was filtered and washed with water, to obtained product, it was purified by recrystallization from ethyl alcohol.other compounds are prepared in same procedure **(5a-h)**.

General procedure for Synthesis of 3-(2-chloroacetyl)-5-(substituted benzylidene)thiazolidine -2,4-dione derivatives (6a-h):

An equimolar amount mixture of 5-(substituted benylidene)thiazolidine-2,4-dione **(5a-h)** (0.02 mol) in acetone (30 ml), slowly addition of chloroacetyl chloride (0.02 mol), and potassium carbonate (0.025 mol). The whole mixture reflux for 3 to 4 hrs. The progress of the reaction was monitored by Thin Layer Chromatography (TLC), solvent system (n-hexane:ethyl acetate-7:3). On completion of the reaction, the reaction mass was cooled and poured on cold water followed by neutralized with dil. HCl. The obtained solid was filtered

and washed with water. The obtained product was purified by recrystallization from ethyl alcohol. Other compounds are prepared in same procedure **(6a-h)**.

General procedure for Synthesis of 3-(2-aminothiazol-4-yl)-5-(substituted benzylidene) thiazolilidine-2,4-dione(7a-h):

An equimolar amount mixture of 3-(2-chloroacetyl)-5-(substituted benzylidene)thiazolidine-2,4-dione derivatives **(6a-h)** (0.003 mol) in ethyl alcohol (20 ml), thiourea (0.003 mol), and then, NaOH 10 mol % was added. The whole mixture reflux for 8 to 10 hrs. The progress of the reaction was monitored by Thin Layer Chromatography (TLC), solvent system (n-hexane:ethyl acetate-8:2). On completion of the reaction, the reaction mass was cooled and poured on cold water followed by neutralized with dil. HCl. The obtained solid was filtered and washed with water. The obtained product was purified by recrystallization from ethyl alcohol. Other compounds are prepared in same procedure. Other compounds are prepared in same procedure **(7a-h)**.

3-(2-aminothiazol-4-yl)-5-benzylidenethiazolidine-2,4-dione(7a):

Creamy colour, Yield: 80 %, m.p.: 190-191 ºC. ^{1}H NMR (DMSO, 400 MHz): δ 8.11 (s, 1H, =CH), 7.48 (m, 3H, Ar-H), 7.34 (m, 2H, Ar-H), 5.20 (s, 1H, thiazole), 3.58 (brs, 2H, NH_2). IR (KBr, ν_{max}, cm^{-1}): 3276, 3176 (NH str.), 3070, 3048 (Ar-CH str.), 1710, 1668 (CO str. thiazolidine), 1602 (C-S str.), 1431, 1412 (C=C str. in Ar.), 1247 (C-N str.). Mass (GC-MS): m/z 304.08 (M+1). Elemental analysis calcd. (Found) % for $C_{13}H_9N_3O_2S_2$: C, 51.47 (51.44); H, 2.99 (2.90), N; 13.85 (13.82).

3-(2-aminothiazol-4-yl)-5-(4-chlorobenzylidene)thiazolidine-2,4-dione(7b):

Yellow colour, Yield: 85%, m.p.: 218-219 ºC. ^{1}H NMR (DMSO, 400 MHz): δ 8.10 (s, 1H, =CH), 7.45-7.32 (m, 4H, Ar-H), 5.14 (s, 1H, thiazole), 3.45 (brs, 2H, NH_2). IR (KBr, ν_{max}, cm^{-1}): 3278, 3173 (NH str.), 3073, 3058 (Ar-CH str.), 1714, 1678 (CO str. thiazolidine), 1595 (C-S str.), 1428 (C=C str. in Ar.), 1279 (C-N str.), 810 (C-Cl str.). Mass (GC-MS): m/z 337.05 (M+1). Elemental analysis calcd. (Found) % for $C_{13}H_8ClN_3O_2S_2$: C, 46.22 (46.19); H, 2.39 (2.37), N; 12.44 (12.39).

3-(2-aminothiazol-4-yl)-5-(4-hydroxybenzylidene)thiazolidine-2,4-dione(7c):

Orange colour, Yield: 90%, m.p.: 270-272 ºC. ^{1}H NMR (DMSO, 400 MHz): δ 10.44 (s, 1H, Ar-OH), 8.00 (s, 1H, =CH), 7.48 (d, 2H, Ar-H), 6.80 (d, 2H, Ar-H), 5.11 (s, 1H, thiazole), 3.38 (brs, 2H, NH_2). IR (KBr, ν_{max}, cm^{-1}): 3284 (OH str.), 3270, 3165 (NH str.), 3067, 3045 (Ar-CH str.), 1709, 1634 (CO str. thiazolidine), 1587 (C-S str.), 1423, 1410 (C=C str. in Ar.), 1278 (C-N str.). Mass (GC-MS): m/z 320.27 (M+1). Elemental analysis calcd. (Found) % for $C_{13}H_9N_3O_3S_2$: C, 48.89 (48.83); H, 2.84 (2.82), N; 13.16 (13.13).

3-(2-aminothiazol-4-yl)-5-(4-methylbenzylidene)thiazolidine-2,4-dione(7d):

Sand colour, Yield: 87%. m.p.: 180-82 ºC. ^{1}H NMR (DMSO, 400 MHz): δ 8.13 (s, 1H, =CH) 7.44 (d, 2H, Ar-H, 7.18 (d, 2H, Ar-H), 5.12 (s, 1H, thiazole), 3.29 (brs, 2H, NH_2), 2.42 (s, 3H, Ar-CH_3). IR (KBr, ν_{max}, cm^{-1}): 3074, 3050 (Ar-CH str.), 2987, 2862 (CH_3 str.), 1714, 1638 (CO str. thiazolidine), 1581 (C-S str.), 1427, 1414 (C=C str. in Ar.), 1280 (C-N str.). Mass (GC-MS): m/z 318.10 (M+1). Elemental analysis calcd. (Found) % for $C_{14}H_{11}N_3O_3S_2$: C, 52.98 (52.93); H, 3.49 (3.44), N; 13.24 (13.21).

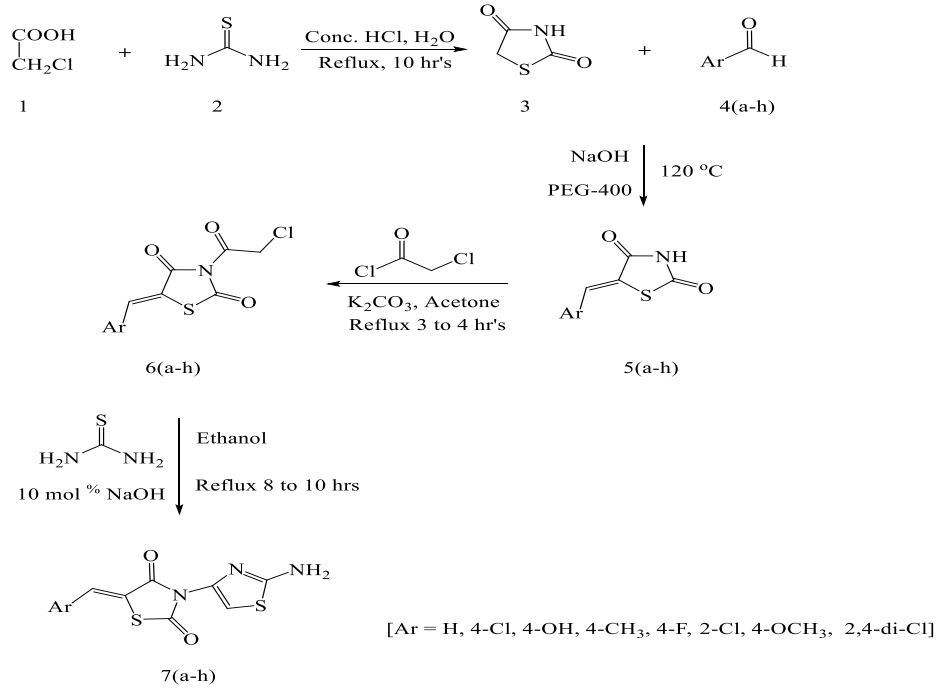
3-(2-aminothiazol-4-yl)-5-(4-fluorobenzylidene)thiazolidine-2,4-dione(7e):

Orange colour, Yield: 75%, m.p.: 250-252 ºC. ^{1}H NMR (DMSO, 400 MHz): δ 8.28 (s, 1H, =CH), 7.90 (m, 2H, Ar-H), 7.65 (m, 2H, Ar-H), 5.20 (s, 1H, thiazole), 3.68 (brs, 2H, NH_2). IR (KBr, ν_{max}, cm^{-1}): 3087, 3067 (Ar-CH str.), 1723, 1670 (CO str. thiazolidine), 1586 (C-S str.), 1479, 1454 (C=C str. in Ar.), 1283 (C-N str.). 1168 (C-F str.). Mass (GC-MS): m/z 322.44 (M+1). Elemental analysis calcd. (found) % for $C_{13}H_8FN_3O_2S_2$: C, 48.59 (48.54); H, 2.51 (2.49), N; 13.08 (13.00).

3-(2-aminothiazol-4-yl)-5-(2-chlorobenzylidene)thiazolidine-2,4-dione(7f):
Khakhi colour, Yield: 82%. m.p.: 230-231 ºC. ^{1}H NMR (DMSO, 400 MHz): δ 8.13 (s, 1H, =CH), 7.48 (m, 2H, Ar-H), 7.33 (m, 2H, Ar-H), 5.23 (s, 1H, thiazole), 3.48 (brs, 2H, NH_2). IR (KBr, ν_{max}, cm^{-1}): 3070, 3040 (Ar-CH str.), 1718, 1623 (CO str. thiazolidine), 1567 (C-S str.), 1458, 1422 (C=C str. in Ar.), 1244 (C-N str.), 814 (C-Cl str.). Mass (GC-MS): m/z 337.18 (M+1). Elemental analysis calcd. (Found) % for $C_{13}H_8ClN_3O_2S_2$: C, 46.22 (46.19); H, 2.39 (2.37), N; 12.44 (12.37).

3-(2-aminothiazol-4-yl)-5-(4-methoxybenzylidene)thiazolidine-2,4-dione(7g):
Sunset colour, Yield: 84%, m.p.: 200-201 ºC. ^{1}H NMR (DMSO, 400 MHz): δ 8.00 (s, 1H, =CH), 7.38 (d, 2H, Ar-H), 6.70 (d, 2H, Ar-H), 5.10 (s, 1H, thiazole), 3.78 (s, 3H, Ar-OCH_3), 3.33 (brs, 2H, NH_2). IR (KBr, ν_{max}, cm^{-1}): 3043, 3014 (Ar-CH str.), 1712, 1613 (CO str. thiazolidine), 1534 (C-S str.), 1448, 1419 (C=C str. in Ar.), 1224 (C-N str.), 1162 (OCH_3 str.). Mass (GC-MS): m/z 334.36 (M+1). Elemental analysis calcd. (Found) % for $C_{14}H_{11}N_3O_3S_2$: C, 50.44 (50.42); H, 3.33 (3.29), N; 12.60 (12.54).

3-(2-aminothiazol-4-yl)-5-(2,4-dichlorobenzylidene)thiazolidine-2,4-dione(7h):
Brown colour, Yield: 86 %. m.p.: 195-197 ºC. ^{1}H NMR (DMSO, 400 MHz): δ 8.09 (s, 1H, =CH), 7.68 (m, 1H, Ar-H), 7.55 (m, 2H, Ar-H), 5.30 (s, 1H, thiazole), 3.53 (brs, 2H, NH_2). IR (KBr, ν_{max}, cm^{-1}): 3066, 3037 (Ar-CH str.), 1714, 1619 (CO str. thiazolidine), 1545 (C-S str.), 1468, 1444 (C=C str. in Ar.), 1233 (C-N str.), 820 (C-Cl str.). Mass (GC-MS): m/z 371.44 (M+1). Elemental analysis calcd. (Found) % for $C_{13}H_7Cl_2N_3O_2S_2$: C, 41.95 (41.93); H, 1.90 (1.88), N; 11.29 (11.26).



Scheme: 1. synthesis of 3-(2-aminothiazol-4-yl)-5-(substituted benzylidene) thiazolilidine-2,4-dione derivatives (7a-h).

BIOLOGICAL ACTIVITY

Antibacterial and antifungal activities:

The synthesized of 3-(2-aminothiazol-4-yl)-5-(substituted benzylidene)thiazolidine-2,4-dione **(7a-h)**, were screened for antibacterial activity against two Gram-positive bacteria viz., *B. licheniforims* and *B. subtilis*, and one Gram-negative bacteria viz. *E. coli* by disc diffusion assay[xxii], using Chloramphenicol (100 µg/disc) as the reference standard for comparing the result. The antibacterial activity was screened by using Nutrient agar obtained from Hi-

media. Composition (gL^{-1}): Sodium chloride-5; Beef extract- 3; Peptone- 5.0 (P^H 7.2). Newly synthesized compounds were screened for their antifungal activity against *C. albicans* by agar diffusion assay[xxiii], using Amphotericin B (100 units / disc) as the reference standard. The anifungal activity was screened by using Sabouraud Agar media and DMSO as a control solvent. The zone diameter in mm was measured by Vernier Caliper. The antibacterial and antifungal activity of the 3-(2-aminothiazol-4-yl)-5-(substituted benzylilidene)thiazolidine-2,4-dione **(7a-h)** shown in **Table-1.** Screening of the structure activity relationship study revealed that, compounds with (**7d)** electron donating p-methyl group on the phenyl rings shows significant activity against Gram-positive bacteria i.e. *B. licheniforims*. Compounds with **(7f)** electron withdrawing 2-chloro substituents on the phenyl ring increases antibacterial activity against *B. subtilis* bacterial strains, due to resonance and inductive effect. Compounds with **(7f, 7h)** chloro substituents on the phenyl ring also increases activity against Gram-negative bacteria i.e. *E. coli* compared with standard chloramphenicol. The investigation of antifungal activity data revealed that, compounds **(7c, 7d)** electron donating p-methyl, hydroxyl group on the phenyl ring shows highest zone of inhibition against *C. albicans* fungal strains, compared with standard amphotericin B drugs.

Table No. 1: Antibacterial and Antifungal Screening of Compounds (7a-h).

Zone of inhibition in mm					
Compounds		Antibacterial activity			Antifungal activity
		B. licheniforims	*B. subtilis*	*E. coli*	*C. albicans*
7a	H	8.1	-	9.6	-
7b	4-Cl	-	8.2	9.3	7.8
7c	4-OH	7.9	-	8.8	16.2
7d	4-CH_3	11.1	9.0	9.6	16.8
7e	4-F	8.5	8.7	9.3	9.9
7f	2-Cl	-	11.3	10.0	8.1
7g	4-OCH_3	8.3	8.0	8.8	8.3
7h	2,4-di-Cl	-	-	9.4	7.5
Chloramphenicol		17.0	19.0	27.1	NA
Amphotericin B		NA	NA	NA	10.11
- no zone of inhibition, NA: Not applicable					

RESULTS AND DISCUSSION

Literature survey reveals that, synthesis of 3-(2-aminothiazol-4-yl)-5-(substituted benzylidene)thiazolilidine-2,4-dione **(7a-h)** was not reported. Hence, it was thought to synthesis these compounds. In the present investigation, condensation reactions of chloroacetic acid **(1)** and thiourea **(2)** in the presence of conc. hydrochloric acid in water to yield thiazolidine-2,4-dione **(3)**, in good yields, which further reacts with substituted aldehydes **(4a-h)** in the presence of sodium hydroxide in PEG-400 as a green solvent to afford substituted 5-arylidene-2,4-thiazolidine-2,4-dione **(5a-h)** with good yield, which further reacts with chloroacetyl chloride in the presence of weak base potassium carbonate in acetone solvent, to afford substituted 5-benzylidene-3-(2-chloroacetyl)thiazolidine-2,4-dione **(6a-h)**, which further condensation with thiourea in the presence of sodium hydroxide in ethanol solvent by Hantzsch reactions of 2-aminothiazoles synthesis, to afford a new series of 3-(2-aminothiazol-4-yl)-5-(4-substituted benzylidene) thiazolidine-2,4-dione **(7a-h)**.

The IR spectrum of compounds **(7b)** shows strong absorption bands at, 3278, 3173 cm^{-1}, asymmetrical, symmetrical stretching for NH_2 functional group, 1714, 1618 cm^{-1} cyclic CO functional group of thiazolidinone, 1595 cm^{-1} for (C-S) and 1279 cm^{-1} for (C-N) stretching frequency, for the confirmation of synthesis of thiazolidinone ring. ^{1}HNMR spectrum of compounds **(7b)**, showed that, singlet at δ 8.10 for =CH, for confirmation of arylidene, singlet at δ 8.10 for thiazole ring and broad singlet at δ 3.45 for NH_2 functional group. The mass spectrum shows molecular ion peak at *m/z*- 337.05 (M+1). This spectral analysis shows that, the confirmation of synthesis of thiazolidine-2,4-dione derivatives.

CONCLUSION

In this study, we have reported the synthesis of a new series of 3-(2-aminothiazol-4-yl)-5-(4-substituted benzylidene) thiazolidine-2,4-dione **(7a-h)** derivatives. The structures of compounds containing more than one heterocyclic ring, i.e. thiazolidine-2,4-dione bearing 2-aminothiazoles, supported by spectral data (IR, ^{1}HNMR and Mass) analysis and evaluated their antibacterial and antifungal activities. The compounds with the electron donating (methyl) group on 4-position of phenyl ring and electron withdrawing (chloro) group on 2-position of phenyl rings, increases antibacterial activities against standard chloramphenicol drugs. The compounds with electron donating (hydroxyl, methyl) group on 4-position of phenyl ring, increases antifungal activities against standard amphotericin B drugs. All the synthesised compounds shows excellent to moderate activity against all pathogens and are promising lead molecules for further optimization using modelling technique.

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CONFLICT OF INTEREST: The author(s) declare that there is no conflict of interests regarding the publication of this article.

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