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ARTICLE

One Pot Three-Component Synthesis of Thiazolidinone Derivatives of 4-Methylthiazole-5-carbaldehyde and its Biological Evaluation

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ABSTRACT

Thiazolidin-4-one is synthesized by highly efficient three-component reaction system. Three component involved are 2-(4-phenyl substituted) -4-methylthiazole-5-carbaldehyde (**1**) with *p*-substituted aniline (**2**), in presence of *p*-toluene sulfonic acid (*p*-TsOH) as an acid catalyst in toluene as an solvent with separation of azeotropic water, followed by cyclo-condensation with mercaptoacetic acid in a single pot. A series of compounds 2-(4-methyl-2-phenylthiazol-5-yl)-3-phenylthiazolidin -4-one (**4a-h**) were synthesized and structures of these compounds were elucidated by IR, ^{1}H NMR, GC-MS. Synthesized compounds were screened for antibacterial activity against Gram-negative (*E. coli* and *P. aeruginosa*) and Gram-positive (*S. aureus* and *B. subtilis*) bacteria, antifungal activity against pathogenic fungal strains and *in vitro* anti-inflammatory activities. Some of the compounds exhibited promising antibacterial, antifungal and anti-inflammatory activities.

KEYWORDS

p-Substituted aniline, *p*-Toluene sulfonic acid, Mercaptoacetic acid, Thiazolidinone, Antimicrobial activity, Anti-inflammatory activities.

INTRODUCTION

Thiazolidin-4-one is the derivative of thiazolidine which belong to an important group of heterocyclic compounds containing S and N in a five member ring. It has been considered as a magic moiety which possesses almost all types of medicine and pharmaceutical activities. The synthesis of compounds belonging to thiazolidinone series constitutes an important research area due to their interesting diverse pharmacological activities.

Thiazoles and their derivatives have found applications in the drug development for the treatment of allergies [1], hypertension [2], inflammation [3], schizophrenia [4], bacterial infections [5], HIV infections [6], hypnotics [7] and more recently for the treatment of pain [8], as fibrinogen receptor antagonists with antithrombotic activity [9] and as new inhibitors of bacterial DNA gyrase B [10]. Thiazole nucleus is also an integral part of all the available penicillin which have revolutionized the therapy of bacterial diseases [11]. There are several thiazole containing drugs available in market such as; nizatidine is a histamine H_2-receptor antagonist that inhibits stomach

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acid production and commonly used in the treatment of peptic ulcer disease (PUD) and gastroesophageal reflux disease (GERD), niridazole as schistosomicidal, sulfathiazole as antibiotic, fanetizole as anti-inflammatory, combendazole as fungicidal. Compounds belonging to this structural class, exhibit a broad range of interesting biological properties, including hypoglycemic, antibacterial [12], anticancer [13], antitubercular [14-16], antioxidant [17], anti-inflammatory [18], COX-1 inhibitory [19], anti-HIV [20] and antihistaminic [21] activities.

Literature survey reveals that there are number of methodology available for the synthesis of thiazolidin-4-one, which include solid phase [22], microwave [23] and polymer supported [24-27] systems. The main synthetic route for synthesis of thiazolidin-4-ones involve the three-component reaction of an amine, carbonyl group compounds and mercapto carboxylic acid. A multicomponent reaction (MCRs) is a powerful tool for synthesis of five-membered heterocycles. Multicomponent reactions facilitate the synthesis of compounds of biological and pharmacological importance by introducing several steps in one pot reaction [28,29].

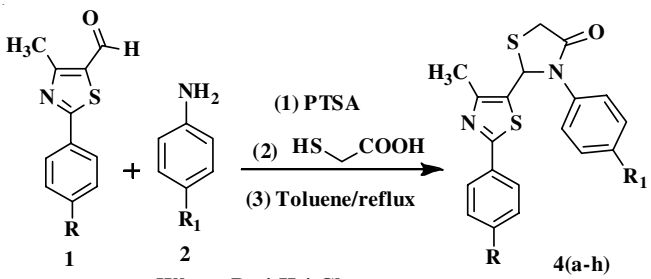
By considering the wide spectrum of biological profile of thiazole and thiazolidin-4-one and their increasing importance in pharmaceutical and biological field, and in continuation of our ongoing research on biologically active heterocycles [30,31], it was thought of interest to accommodate thiazole and thiazolidin-4-one moieties in a single molecular frame work to synthesize some new heterocyclic compounds with potential biological activity.

We report here a synthetic approach of these heterocycles involving three-component in one flask, with this in mind, the aim of the current paper was to achieve the synthesis of a new series of thiazolidinone derivatives by the condensation of *p*-substituted aniline with novel 4-methylthiazole-5-carbaldehyde and thioglycollic acid *via* a one pot, three-component reaction using *p*-toluene sulfonic acid (*p*-TsOH) as a catalyst in toluene solvent with azeotropic separation of water by Dean-Stark separator according to MCRs protocol to obtained derivatives of 2-(4-methyl-2-phenylthiazol-5-yl)-3-phenylthiazolidin-4-one (**4a-h**). The antibacterial and antifungal activities and *in-vitro* anti-inflammatory activity of the compounds (**4a-h**) have also been evaluated. The structure of newly synthesized compounds was confirmed by IR, ^{1}H NMR, GC-MS Mass spectrometry and elemental analysis data

EXPERIMENTAL

Melting points were determined in open capillary and are uncorrected. FT-IR spectra wererecorded using Perkin-Elmer spectrometer. ^{1}H NMR spectra were recorded on Brucker Advance II 400 spectrometer in DMSO solvent by using TMS as internal standard. Chemical shift (δ) values are reported in ppm units, relative to TMS as internal standard. Mass spectra were recorded on GC-MS Mass spectrometer. The reactions were monitored by thin layer chromatography (TLC) using silica coated plates (Merck).The products were purified by column chromatography on silica gel (100-200) by benzene:ethyl acetate solvent system.

General procedure for the synthesis of 2-(4-methyl-2-phenylthiazol-5-yl)-3-phenylthiazolidin-4-one (4a-h): To a solution of 2-(4-chlorophenyl)-4-methylthiazole-5-carbaldehyde (**1**) (0.01 mol) in a dry toluene (50 mL), aniline (**2**) (0.015 mol), (10 mol %) *p*-toluenesulfonic acid (*p*-TsOH) and mercapto acetic acid (**3**) (0.016 mol) was added. The reaction mixture was refluxed (110 ºC) for 13-15 h with azeotropic separation of water using Dean and Stark apparatus. Completion of reaction was determined by TLC analysis. Toluene was removed under vacuum to give viscous oil, which was treated with a saturated aqueous $NaHCO_3$ solution to remove any unreacted mercaptoacetic acid. The product was extracted with ethyl acetate, washed with water, brine and dried over Na_2SO_4. The solvent was removed under reduced vacuum. The crude product was purified by column chromatography using benzene:ethyl acetate (8:2) solvent system to give 2-(2-(4-chlorophenyl)-4-methylthiazol-5-yl)-3-phenylthiazolidin-4-one (**4e**) (**Scheme-I**).



Scheme-I: Synthesis of 2-(4-methyl-2-phenylthiazol-5-yl)-3-phenylthiazolidin-4-one (**4a-h**)

2-(4-Methyl-2-phenylthiazol-5-yl)-3-phenylthiazolidin-4-one (4a): Yield: 62 %. m.p.: 184-188 ºC. ^{1}H NMR (DMSO, 400 MHz): δ 7.57-7.52 (m, 5H, Ar-H), 7.28 (m, 2H, Ar-H), 7.0 (m, 3H, Ar-H), 6.35 (s, 1H, -SCH), 3.80 (AB, quartet, 2H, thiazolidinone-CH_2), 2.13 (s, 3H, thiazolic-CH_3). IR (KBr, ν_{max}, cm^{-1}): 3077, 3000 (Ar-CH *str.*), 2925 (CH_3 *str.*), 1690 (CO, cyclic), 1600 (C-S *str.*), 1580, 1441 (C=C *str.* in Ar.), 1252 (C-N *str.*). Mass (GC-MS): *m/z* 352.0 (M^+). Elemental analysis calcd. (found) % for $C_{19}H_{16}N_2OS_2$: C, 64.74 (64.70); H, 4.58 (4.56), N; 7.95 (7.90).

2-(4-Methyl-2-phenylthiazol-5-yl)-3-*p*-tolylthiazolidin-4-one (4b): Yield: 70 %. m.p.: 100-104 ºC. ^{1}H NMR (DMSO, 400 MHz): δ 7.96 (m, 2H, Ar-H), 7.85 (m, 3H, Ar-H), 7.37 (d, 2H, Ar-H), 6.92 (d, 2H, Ar-H), 6.30 (s, 1H, -SCH), 3.82 (AB, quartet, 2H, thiazolidinone-CH_2), 2.88 (s, 3H, thiazolic-CH_3), 2.05 (s, 3H, CH_3). IR (KBr, ν_{max}, cm^{-1}): 3080, 3040 (Ar-CH *str.*), 2920 (CH_3 *str.*), 1694 (CO, cyclic), 1604 (C-S *str.*), 1571, 1461 (C=C *str.* in Ar.), 1261(C-N *str.*). Mass (GC-MS): *m/z* 366.10 (M^+). Elemental analysis calcd. (found) % for $C_{20}H_{18}N_2OS_2$: C, 65.54 (65.50); H, 4.95 (4.89), N; 7.64 (7.62).

3-(4-Methoxyphenyl)-2-(4-methyl-2-phenylthiazol-5-yl)thiazolidin-4-one (4c): Yield: 60 %. m.p.: 130-134 ºC. ^{1}H NMR (DMSO, 400 MHz): δ 7.90 (m, 2H, Ar-H), 7.38 (m, 3H, Ar-H), 6.92 (d, 2H, Ar-H), 6.88 (d, 2H, Ar-H), 6.28 (s, 1H, -SCH), 3.95 (AB, quartet, 2H, thiazolidinone-CH_2), 3.70 (s, 3H, -OCH_3), 2.14 (s, 3H, thiazolic-CH_3). IR (KBr, ν_{max}, cm^{-1}): 3061, 3028 (Ar-CH *str.*), 2964, 2845 (CH_3 *str.*), 1692 (CO, cyclic), 1605 (C-S *str.*), 1524, 1450 (C=C *str.* in Ar.), 1252 (C-N *str.*), 1160

(-OCH_3 *str.*). Mass (GC-MS): *m/z* 382.10 (M^+). Elemental analysis calcd. (found) % for $C_{20}H_{18}N_2O_2S_2$: C, 62.80 (62.78); H, 4.74 (4.70), N; 7.32 (7.33).

3-(4-Fluorophenyl)-2-(4-methyl-2-phenylthiazol-5-yl)-thiazolidin-4-one (4d): Yield: 58 %. m.p.: 128-134 ºC. ^{1}H NMR (DMSO, 400 MHz): δ 8.01 (m, 2H, Ar-H), 7.85 (m, 3H, Ar-H), 7.30-720 (m, 4H, Ar-H), 6.39 (s, 1H, -SCH), 3.90 (AB, quartet, 2H , thiazolidinone-CH_2), 2.20 (s, 3H, thiazolic-CH_3). IR (KBr, ν_{max}, cm^{-1}): 3071, 3008 (Ar-CH *str.*), 2984, 2865 (CH_3 *str.*), 1696 (CO, cyclic), 1606 (C-S *str.*), 1516, 1440 (C=C *str.* in Ar.), 1249 (C-N *str.*), 1171 (C-F *str.*). Mass (GC-MS): *m/z* 370.0 (M^+). Elemental analysis calcd. (found) % for $C_{19}H_{15}N_2OS_2F$: C, 61.60 (61.54); H, 4.08 (4.00), N; 7.56 (7.57).

2-(2-(4-Chlorophenyl)-4-methylthiazol-5-yl)-3-phenyl-thiazolidin-4-one (4e): Yield: 72 %. m.p.:108-112 ºC. ^{1}H NMR (DMSO, 400 MHz): δ 7.49 (m, 2H, Ar-H), 7.45 (m, 3H, Ar-H), 7.20 (d, 2H, Ar-H), 6.99 (d, 2H, Ar-H), 6.35 (s, 1H, -SCH), 3.90 (AB, quartet, 2H, thiazolidin one-CH_2), 2.15 (s, 3H, thiazolic-CH_3). IR (KBr, ν_{max}, cm^{-1}): 3074, 3038 (Ar-CH *str.*), 2974, 2855 (CH_3 *str.*), 1694 (CO, cyclic), 1606 (C-S *str.*), 1560, 1480 (C=C *str.* in Ar.), 1255 (C-N *str.*), 870 (C-Cl *str.*). Mass (GC-MS): *m/z* 386.0 (M^+). Elemental analysis calcd. (found) % for $C_{19}H_{15}N_2OS_2Cl$: C, 58.98; H, 3.91, N; 7.24; found: C, 58.90; H, 3.84; N, 7.20%.

2-(2-(4-Chlorophenyl)-4-methylthiazol-5-yl)-3-*p*-tolyl-thiazolidin-4-one (4f): Yield: 76 %. m.p.138-145 ºC. ^{1}H NMR (DMSO, 400 MHz): δ 8.20 (d, 2H, Ar-H), 7.75 (d, 2H, Ar-H), 7.34 (d, 2H, Ar-H), 6.97 (d, 2H, Ar-H), 6.28 (s, 1H, -SCH), 3.88 (AB, quartet, 2H, thiazolidinone-CH_2), 2.27 (s, 3H, thiazolic-CH_3), 2.09 (s, 3H, CH_3). IR (KBr, ν_{max}, cm^{-1}): 3048, 3006 (Ar-CH *str.*), 2948, 2903 (CH_3 *str.*), 1692 (CO, cyclic), 1603 (C-S *str.*), 1548, 1427 (C=C *str.* in Ar.), 1248 (C-N *str.*), 856 (C-Cl *str.*). Mass (GC-MS): *m/z* 400.0(M^+). Elemental analysis calcd. (found) % for $C_{20}H_{17}N_2OS_2Cl$: C, 59.91 (59.88); H, 4.27 (4.24), N; 6.99 (6.97).

2-(2-(4-Chlorophenyl)-4-methylthiazol-5-yl)-3-(4-methoxyphenyl)thiazolidin-4-one (4g): Yield: 60 %. m.p.: 106-110 ºC. ^{1}H NMR (DMSO, 400 MHz): δ 7.81 (d, 2H, Ar-H), 7.45 (d, 2H, Ar-H), 7.10 (d, 2H, Ar-H), 6.90 (d, 2H, Ar-H), 6.27 (s, 1H, -SCH), 3.98 (AB, quartet, 2H, thiazolidinone-CH_2), 3.80 (s, 3H, -OCH_3), 2.17 (s, 3H, thiazolic-CH_3). IR (KBr, ν_{max}, cm^{-1}): 3078, 3026 (Ar-CH *str.*), 2988, 2853 (CH_3 *str.*), 1693 (CO, cyclic), 1604 (C-S *str.*), 1540, 1454 (C=C *str.* in Ar), 1255 (C-N *str.*), 1170 (-OCH_3 *str.*), 868 (C-Cl *str.*). Mass (GC-MS): *m/z* 416.10 (M^+). Elemental analysis calcd. (found) % for $C_{20}H_{17}N_2O_2S_2Cl$: C, 57.61 (57.60); H, 4.11 (4.09), N; 6.72 (6.67).

2-(2-(4-Chlorophenyl)-4-methylthiazol-5-yl)-3-(4-fluorophenyl)thiazolidin-4-one (4h): Yield: 62 %. m.p. 92-96 ºC. ^{1}H NMR (DMSO, 400 MHz): δ 8.14 (d, 2H, Ar-H), 8.01 (d, 2H, Ar-H), 7.19-7.10 (m, 4H, Ar-H), 6.38 (s, 1H, -SCH), 3.94 (AB, quartet, 2H, thiazolidinone-CH_2), 2.19 (s, 3H, thiazolic-CH_3). IR (KBr, ν_{max}, cm^{-1}): 3080, 3016 (Ar-CH *str.*), 2990, 2880 (CH_3 *str.*), 1695 (CO, cyclic), 1604 (C-S *str.*), 1520, 1490 (C=C *str.* in Ar.), 1257 (C-N *str.*), 1174 (C-F *str.*), 886 (C-Cl *str.*). Mass (GC-MS): *m/z* 404.0 (M^+). Elemental analysis calcd. (found) % for $C_{19}H_{14}N_2OS_2ClF$: C, 56.36 (56.33); H, 3.49 (3.47), N; 6.92 (6.89).

Biological activity

Antibacterial and antifungal activities: The synthesized 2-(4-methyl-2-phenylthiazol-5-yl)-3-phenylthiazolidin-4-one (**4a-h**), were screened for antibacterial activity against two Gram-positive bacteria *viz.*, *Bacillus subtilis* and *Staphylococcus aureus* two Gram-negative bacteria *viz.*, *Escherichia coli* and *Pseudomonas aeruginosa* by using the disc diffusion method [32]. Ciprofloxacin was used as reference standard for comparing the results and DMSO as a control solvent. Newly synthesized compounds were screened for their antifungal activity against *Aspergillus niger*, *Aspergillus flavus*, *Penicillium chrysogenum*, *Fusarium moneliforme*, by standard agar disc diffusion method [33], using Griseofulvin as reference standard and DMSO as control solvent.

***in vitro* Anti-inflammatory activity:** The synthesized compounds are screened for anti-inflammatory activity by using inhibition of albumin denaturation technique, which was studied according to Gellias & Rao [34] and Ishizaka [35] with slight modification. The ibuprofen was used as standard drugs.

RESULTS AND DISCUSSION

In the present study a series of compounds (**4a-h**) were synthesized and evaluated for antibacterial, antifungal and anti-inflammatory activity. The compounds **4a-h** were synthesized in moderate to good yield and their structures were characterized by spectral data. The IR spectrum of compound **4b** showed a characteristic absorption bands appeared at 1694 cm^{-1} for cyclic CO functional group for thiazolidinone ring and 1604 cm^{-1} for (C-S *str.*), 1261 cm^{-1} for (C-N *str.*) confirmed the cyclic structure of thiazolidinone. ^{1}H NMR spectrum of compound **4b** exhibits quartet at δ 3.82 for thiazolidinone-CH_2 functional group and singlet at δ 6.30 for SCH functional group of thiazolidinone ring. The mass spectrum showed molecular ion peak at *m/z* 366.10(M^+). It is a confirmatory for the synthesis of thiazolidinone derivatives.

Biological activities: Investigation of the structure activity relationship study revealed that compounds **4e**, **4f**, **4g** and **4h** shows good activity against both *E. coli* and *S. aureus* bacteria. Compound **4d** shows good activity against *E. coli* and B. *subtilis* bacteria. Compounds **4a**, **4b** and **4c** showed moderate activity against both Gram-negative and Gram-positive bacteria. It was observed that 4-chlorophenyl group at 2-position of thiazole ring shows enhanced antibacterial activity as compared to phenyl group at 2-position of thiazole ring as compared standard by zone of inhibition data (Table-1). The investigation of antifungal activity data revealed that almost all the synthesized compounds exhibited greater antifungal activity in all four strains of fungi, compounds **4b**, **4d**, **4f** and **4h** show inhibitory effect against four fungal steins and compounds **4a**, **4c**, **4e** and **4g** show moderate inhibitory effect against *Aspergillus niger* and *Aspergillus flavus* (Table-1). Similarly most of the compounds are active against *Fusarium moneliforme*. It is also found that substitutents 4-F and 4-CH_3 attached to a phenyl ring of thiazolidinone group shows enhanced antifungal activity.

Anti-inflammatory activity data (Table-2) of compounds **4a-h** revealed that compound **4b** and **4d** have excellent anti-inflammatory activity. Whereas, compounds **4c**, **4f** and **4h** showed very good anti-inflammatory activity compared to that

TABLE-1
ANTIBACTERIAL AND ANTIFUNGAL SCREENING OF COMPOUNDS (**4a-h**)

Compounds	Antibacterial activity				Antifungal activity			
	E. coli	*P. aeruginosa*	*S. aureus*	*B. subtilis*	*A. niger*	*A. flavus*	*P. chrysogenum*	*F. moneliforme*
4a	15	12	14	15	RG	RG	+ve	RG
4b	14	09	10	13	–ve	–ve	RG	–ve
4c	11	11	09	10	RG	RG	+ve	–ve
4d	17	14	15	23	–ve	–ve	–ve	RG
4e	19	10	16	12	RG	RG	–ve	+ve
4f	18	11	17	18	–ve	RG	–ve	–ve
4g	17	08	15	17	RG	–ve	RG	+ve
4h	22	15	16	19	–ve	–ve	RG	–ve
DMSO	–ve	–ve	–ve	–ve	–ve	–ve	–ve	–ve
Ciprofloxacin	27	24	22	30	–	–	–	–
Griseofulvin	–	–	–	–	+ve	+ve	+ve	+ve

–ve: No activity; +ve: Growth antifungal activity absent; RG: Reduced growth

TABLE-2
ANTI-INFLAMMATORY ACTIVITY OF
SYNTHESIZED COMPOUNDS (**4a-h**)

Compounds	Mean absorbance value ± SEM	Inhibition of denaturation (%)
Control	0.195 ± 0.04	–
Ibuprofen	0.372 ± 0.02	90.76
4a	0.317 ± 0.03	62.56
4b	0.350 ± 0.01	79.49
4c	0.324 ± 0.07	66.15
4d	0.361 ± 0.02	85.12
4e	0.313 ± 0.01	60.51
4f	0.318 ± 0.03	63.07
4g	0.300 ± 0.04	53.84
4h	0.325 ± 0.05	66.66

of standard drug ibuprofen. Compounds **4a**, **4e** and **4g** showed moderate activity. Compounds **4b** and **4d** having phenyl group at 2-position of thiazole nucleus and phenyl group of thiazolidinone ring containing 4-methyl and 4-fluoro substituents enhanced anti-inflammatory activity.

Conclusion

In this study we have reported an effective and convenient synthesis of a new series of 2-(4-methyl-2-phenylthiazol-5-yl)-3-phenylthiazolidin-4-one (**4a-h**) derivatives. The structures of these new heterocyclic compounds bearing both thiazole and thiazolidinone ring arrangements were supported by spectral (IR, ^{1}H and mass) analysis and evaluated for their antibacterial, antifungal and anti-inflammatory activities. The results proved that several synthesized derivatives exhibited significant antibacterial, antifungal and anti-inflammatory activities. It was observed that 4-chlorophenyl group at 2-position of thiazole ring shows enhanced antibacterial activity as compared to phenyl group at 2-position of thiazole ring. Compounds with 4-fluoro, 4-methyl substituents attached to a phenyl ring of thiazolidinone group shows enhanced antifungal activity. The results of anti-inflammatory studies revealed that compounds having phenyl group at 2-position of thiazole nucleus and phenyl group of thiazolidinone ring having 4-methyl and 4-fluoro substituents enhanced anti-inflammatory activity. Thus, the significant antibacterial, antifungal and anti-inflammatory profiles of some derivatives offer them as promising lead molecules for further optimization using molecular modelling techniques.

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