Synthesis and Evaluation of Antimicrobial Activity of Thiazolidinone Derivatives

Ravichandran Veerasamy*[,a,b], Harish Rajak[c], Krishnan Suresh Kumar[d] and Ram Kishore Agrawal[a]

[a]*Department of Pharmaceutical Sciences, Dr. H. S. Gour Vishwavidyalaya, Sagar (MP), India*

[b]*Faculty of Pharmacy, AIMST University, Semeling – 08100, Kedah, Malaysia*

[c]*SLT Institute of Pharmaceutical Sciences, Guru Ghasidas University, Bilaspur (CG), India*

[d]*Medicinal chemistry research Laboratory, KMCH College of Pharmacy, Coimbatore, India*

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Abstract: A series of 1,3-thiazolidin-4-one derivatives were prepared by the reaction of respective aromatic amine, aromatic aldehyde and thioglycolic acid in dry benzene/toluene. The newly synthesized compounds were characterized on the basis of elemental analysis, IR, ^{1}HNMR and mass spectra. The newly synthesized final compounds were evaluated for their *in-vitro* antibacterial, antifungal and anti-viral activities. Preliminary results indicated that most of the compounds demonstrated moderate to good antimicrobial activity, comparable to standard drugs. Structure–activity relationship studies revealed that the nature of the substituents at the 2nd and 3rd positions of the thiazolidinone nucleus had a significant impact on the *in-vitro* antimicrobial activity of this class of potent antimicrobial agents.

Keywords: Thiazolidinones, Antibacterial, Antifungal, Anti-viral, Schiff's reaction.

INTRODUCTION

Viral infections caused by the rapid emergence of antiviral drug resistant strains have become a serious threat to the globe and have fostered the search for new antiviral agents directed against unexplored drug targets. Various nucleoside analogues had been currently used as antiviral agent. These derivatives often inhibit viral polymerases enzyme. However, only few non-nucleoside antiviral agents are currently used in the market.

Thiazolidin-4-ones had been reported to possess a wide range of biological activities including antibacterial [1], antituberculosis [2], antitumor [3], antihistaminic [4], anti-inflammatory [5] and anticonvulsant activity [6]. Several 2,3-diaryl-1,3-thiazolidin-4-ones had proved to be highly effective against non-nucleoside HIV reverse transcriptase inhibitors (NNRTIs) [7]. Barrecca *et al*. (2002) have stated that these compounds may be considered as an ''open compound model'' [8] of previously described 1H,3H-thiazolo[3,4-a]benzimidazoles (TBZs) [9] because they contain necessary pharmacophoric elements of those HIV-1 NNRTIs, namely a benzene-fused ring, an aryl group at C-1 and the nitrogen atom of the thiazole nucleus. Structure activity relationship (SAR) studies had shown that anti-HIV activity strongly depends on the nature of substituents at C-2 and N-3 of thiazolidinone ring. It has been reported that a high antiviral activity was associated with the presence of a 2,6-dihalo-substituted phenyl ring at C-2 and pyridin-2-yl or pyrimidin-2-yl rings at N-3 [8,10].

*Address correspondence to this author at the Department of Pharmaceutical Chemistry, Faculty of Pharmacy, AIMST University, Semeling – 08100, Kedah, Malaysia; Tel: 006-04-4298000 Ext. 1029; Fax: 006-04-4298007; E- mail: phravi75@rediffmail.com

In 2002, Rao *et al.* stated the synthesis of diastereoisomers of trans- and cis-5-methyl-2,3-diaryl-1,3-thizolidin-4-ones from 2,6-dihalobenzaldehyde, heteroaromatic amine and racemic 2-mercaptopropionic acid. It was concluded that stereochemistry has not influenced the anti-HIV activity of the compounds. Surprisingly, the stereoselectivity of thiazolidin-4-ones has not yet been profoundly studied [11]. Rao *et al.* (2004) synthesized and evaluated anti-HIV activity of new 2,3-diaryl-1,3-thiazolidin-4-ones. The *in-vitro* tests results showed that few compounds were found to be effective inhibitors of HIV-1 replication at 10–40 nM concentrations with minimal cytotoxicity [12]. In 2007, Rawal *et al*. reported the anti-HIV activity of 2-aryl-3-heteroaryl-1,3-thiazolidin-4-ones and concluded that one of the synthesized compound was found highly active against HIV-1 replication and it exhibited EC_{50} at 0.26 μM with minimal toxicity in MT-4 cells as compared to 0.35 μM for thiazobenzimidazole (TBZ) [13]. In 2007 and 2009, Balzarini *et al*. reported the synthesis of series of novel thiazolidin-4-ones bearing a lipophilic adamantyl substituent at position 2 or 3 and observed that majority of the synthesized compound showed a modest anti-HIV-1 activity [14,15].

In 1979, Fenech *et al*. had screened three 3-substituted-2-adamantyl-4-thiazolidinones activity against twelve bacterial strains. The minimum inhibitory concentrations (MIC−125 mg/mL) indicated that these compounds exhibited poor antibacterial activity [16]. Sayyed *et al.* (2006) had reported antibacterial activity of some new 2,3-diaryl-1,3-thiazolidin-4-ones as antibacterial agents [17]. Based on the above observations, we designed and synthesized a series of novel thiazolidin-4-one derivatives (**1** to **6**) bearing different aryl, heteroaryl substituent at position 2, and several substituents on the nitrogen atom in the thiazolidine ring.

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MATERIALS AND METHODS

Chemistry

Melting points of the compounds were determined using an open-ended capillary method and are uncorrected. The purity of the synthesized compounds was checked by TLC. UV/VIS spectra were taken in a Schimadzu UV/VIS 1700 spectrophotometer. FT-IR was recorded on a Jasco FT-IR spectrophotometer, ^{1}HNMR spectra were recorded at 300 MHZ on a Bruker FT-NMR spectrophotometer and mass spectra on a Varian Atlas CH-7 mass spectrophotometer at 70 ev. The elemental analysis was obtained on a Vario-EL instrument.

General Procedure for Synthesis of 1,3-Thiazolidin-4-Ones

Derivatives of 1,3-thiazolidin-4-one was synthesized with slight modification in the method reported by Rawal *et al*. (2007) [13]. The appropriate (hetero) aromatic amine (0.005 mol) and appropriate (hetero) aromatic aldehyde (0.005 mol) was stirred under reflection for 0.5 - 2.5 h in dry benzene/toluene (10 mL). Mercaptoacetic acid (0.010 mol) was added and the mixture was refluxed for further 3 - 45 h (Scheme **1**). The reaction was monitored by TLC (Mobile phase: Cyclohexane and ethyl acetate 8:2, spots were visualized by exposing them to iodine vapor). After completion of the reaction, the reaction mixture was concentrated to dryness under reduced pressure and the residue was taken up in ethyl acetate. The organic layer was successively washed with 5% aqueous citric acid, water, 5% sodium hydrogen carbonate, and then finally with brine. The organic layer was dried over sodium sulfate, filtered and solvent was removed under reduced pressure to get crude (solid or oily) product. The oily residue was solidified by treatment with a mixture of ethanol and diethyl ether. All the compounds were recrystallized from ethanol. The synthesized compounds were found highly to be soluble in DMSO, soluble in DMF, $CHCl_3$, ethanol and methanol, and sparingly soluble in water. The structures of synthesized compounds were elucidated by means of FTIR, ^{1}HNMR, FAB-MS and elemental analyses. The results of elemental analyses for N and S were found to be within ± 0.4% of the theoretical values.

2-(4-Chloro-phenyl)-3-(6-methyl-pyridin-2-yl)-thiazolidin-4-one [1]

Mixture of 6-methyl-2-aminopyridine (0.005 mol) and 4-chlorobenzaldehyde (0.005 mol) was stirred under reflux for 2 h in dry benzene (10 mL). Then mercaptoacetic acid was (0.010 mol) was added and the mixture was refluxed for further 30 h. Further treatments were the same as given under general procedure. Yield: 42%; IR (KBr, in cm^{-1}): 2964 (C-H str. for CH_3), 1683.30 (C=O str.), 1493.32 (ring C=C str.), 1355 (Ar-C-N str.), 1270 (C-O-C Str.); ^{1}HNMR ($CDCl_3$, δ in ppm): 2.55 (s, 3H, OCH_3), 3.89 (d, 1H, J = 15.7 Hz, 5-H_A), 4.15 (dd, 1H, J = 15.7 and 1.9 Hz, 5-H_B), 5.94 (s, 1H, H-2), 6.92-7.98 (m, 7H, ArH); Mass: 306 $(M+H)^+$.

3-(2 -pyridin-2-yl)-2-pyridin-2-yl-thiazolidin-4-one [2]

Mixture of 2-aminopyridine (0.005 mol) and pyridine-2-aldehyde (0.005 mol) was stirred under reflux for 0.5 h in dry toluene (10 mL). Then mercaptoacetic acid (0.010 mol) was added and the mixture was refluxed for further 15 h. Further treatments were the same as given under general procedure. Yield: 38%; IR (KBr, in cm^{-1}): 1685.56(C=O str.), 1438.80 (ring C=C str.), 1372 (Ar-C-N str.),; ^{1}HNMR (DMSO d6, δ in ppm): 4.10 (d, 1H, J = 15.7 Hz, 5-H_A), 4.22 (dd, 1H, J = 15.7 and 1.6 Hz, 5-H_B), 6.03 (s, 1H, H-2), 8.12-8.36 (m, 8H, ArH); Mass: 272 $(M+H)^+$.

3-(4-Chloro-phenyl)-2-pyridin-2-yl-thiazolidin-4-one [3]

Mixture of 4-chloroaniline (0.005 mol) and pyridine-2-aldehyde (0.005 mol) was stirred under reflux for 2.5 h in dry toluene (10 mL). Then mercaptoacetic acid (0.010 mol) was added and the mixture was refluxed for further 25 h. Further treatments were the same as given under general procedure. Yield: 40%; IR (KBr, in cm^{-1}): 1693.13(C=O str.), 1472.70 (ring C=C str.), 1362.86 (Ar-C-N str.); ^{1}HNMR (DMSOd6, δ in ppm): 3.80 (d, 1H, J = 15.6 Hz, 5-H_A), 4.11 (dd, 1H, J = 15.6 and 1.6 Hz, 5-H_B), 5.90 (s, 1H, H-2), 6.54-6.83 (m, 6H, ArH), 7.58-7.86 (m, 2H, ArH); Mass: 292 $(M+H)^+$.

3-(4-Chloro-phenyl)-2-(3-nitro-phenyl)-thiazolidin-4-one [4]

Mixture of 4-chloroaniline (0.005 mol) and 3-nitrobenzaldehyde (0.005 mol) was stirred under reflux for 2 h in dry toluene (10 mL). Then mercaptoacetic acid (0.010 mol) was added and the mixture was refluxed for further 35 h. Further treatments were the same as given under general procedure. Yield: 43%; IR (KBr, in cm^{-1}): 1709 (C=O str.), 1458.89 (ring C=C str.), 1362 (Ar-C-N str.); ^{1}HNMR ($CDCl_3$, δ in ppm): 3.98 (d, 1H, J = 15.3 Hz, 5-H_A), 4.18 (d, 1H, J = 15.3 Hz, 5-H_B), 6.06 (s, 1H, H-2), 7.29-7.66 (m, 6H, ArH), 7.93-8.02 (m, 2H, ArH); Mass: 336 $(M+H)^+$.

2,3-Bis-(4-chloro-phenyl)-thiazolidin-4-one [5]

Mixture of 4-chloroaniline (0.005 mol) and 4-chlorobenzaldehyde (0.005 mol) was stirred under reflux for 2 h in dry benzene (10 mL). Then mercaptoacetic acid (0.010 mol) was added and the mixture was refluxed for further 33 h. Further treatments were the same as given under general procedure. Yield: 45%; IR (KBr, in cm^{-1}): 1694.16 (C=O str.), 1490 (ring C=C str.), 1365 (Ar-C-N str.); ^{1}HNMR ($CDCl_3$, δ in ppm): 3.96 (d, 1H, J = 15.5 Hz, 5-H_A), 4.10 (d, 1H, J = 15.5 Hz, 5-H_B), 6.26 (s, 1H, H-2), 6.48-6.53 (m, 2H, ArH), 7.08-7.34 (m, 5H, ArH); Mass: 325 $(M+H)^+$.

3-(4-Chloro-phenyl)-2-(4-hydroxy-3-methoxy-phenyl)-thiazolidin-4-one [6]

Mixture of 4-chloroaniline (0.005 mol) and 4-hydroxy-3-methoxy benzaldehyde (0.005 mol) was stirred under reflux for 2 h in dry benzene (10 mL). Then mercaptoacetic acid (0.010 mol) was added and the mixture was refluxed for further 24 h. Further treatments were the same as given under general procedure. Yield: 32%; IR (KBr, in cm^{-1}): 3480 (-OH str.), 1695.12 (C=O str.), 1462.74 (ring C=C str.), 1218.65 (C-O-C str. for -C-O-CH_3); ^{1}HNMR ($CDCl_3$, δ in ppm): 3.78 (s, 3H, OCH_3), 3.86 (d, 1H, J = 15.7 Hz, 5-H_A), 4.16 (d, 1H, J = 15.7 Hz, 5-H_B), 5.12 (s, 1H, -OH), 5.94 (s, 1H, H-2), 6.82-7.06 (m, 7H, ArH); Mass: 337 $(M+H)^+$.

Antimicrobial Evaluation

In-Vitro Antibacterial Activity

Synthesized compounds were evaluated for their *in-vitro* antibacterial activity against pathogenic bacteria like *Pseudomonas aeruginosa* (National Collection of Industrial Microorganism (NCIM) No. 2200), *Staphylococcus aureus* (NCIM No. 2079), *Escherichia coli* (NCIM No. 2065) and *Bacillus subtilis* (NCIM No. 2063). The agar dilution method [18] was performed using Muller- Hinton agar (Hi-Media) medium. The medium was inoculated with the required amount of inoculum to obtain a suspension of microorganism which contains 10^6 colony forming units per milliliter (cfu/mL) and applied to plates with serially diluted compounds in DMF to be tested and incubated at 37°C overnight (approx. 20 h). The minimum inhibitory concentration (MIC) was considered to be the lowest concentration that was completely inhibited growth on agar plates. MIC values evaluated at the final concentration range of 5-100 μg/mL.

In-Vitro Antifungal Activity

The compounds were evaluated for their *in-vitro* antifungal activity against pathogenic fungi like *C. albicans* (NCIM No. 3102), *A. niger* (NCIM No. 501) and *P. notatum* (NCIM No. 742) using agar dilution method with Saburoud's dextrose agar (Hi-Media). Suspensions of each micro-organism were prepared to contain 10^5 cfu/mL and applied to agar plates which have been serially diluted with compounds to be tested in DMF. The plates were incubated at 25 °C for 72 h and MICs were determined. MIC values evaluated at the final concentration range of 5-100 μg/mL.

In-Vitro Anti-Viral Activity

Cytotoxicity and antiviral activity of all compounds were evaluated against Herpes simplex virus-1 and Herpes simplex virus-2 in HEL cell culture. Cytotoxic concentration was measured, as the concentration of compounds required to cause a microscopically detectable alteration in normal cell morphology. Cytopathogenicity was determined a concentration required to reduce virus-induced cytopathogenicity by 50 %.

Compounds were also evaluated against influenza A H3N2 and influenza B virus in Madin Darby canine kidney cells (MDCK) cultures. 50 % cytotoxic concentration was determined by measuring the cell viability with the colorimetric formazan- based MTS assay. 50 % effective concentration or concentration required to produce 50 % inhibition of virus-induced cytopathic effect was determined by measuring the visual scoring of the CPE, or by measuring the cell viability with the colorimetric formazan-based MTS assay protocol [13].

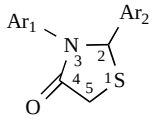
RESULTS AND DISCUSSION

The synthetic approach for the title compounds was shown in Scheme **1**. Some 1,3-thiazolidin-4ones was synthesized as per the methods reported by Rao *et al*. (2007) [13], with slight modification in the process. When aromatic primary amines react with aldehyde in the presence of organic solvent, give Schiff's base, by loosing a molecule of water (Two hydrogen atoms from primary amine and one oxygen atom from aldehyde). Schiff's base is further refluxed with thioglycolic acid in presence of suitable organic solvent, it undergoes cyclocondensation (Scheme **1**) and gives 1,3-thiazolidin-4-one derivatives (Table **1**) by losing a water molecule. The purity of the compounds was ascertained by TLC. The structures of synthesized intermediates were confirmed by IR spectra and final compounds were characterized by means of FTIR, ^{1}HNMR, FAB-MS and elemental analysis.

The IR spectrum of 1,3-thiazolidin-4-one derivatives showed absorption band at ~1695 (C=O str.), absence of absorption band at 3400-3300 (N-H str. for -NH_2), and absence of absorption band at 2830-2695 (C=H str. for -CHO) and ~1640 (N-H bend for -NH_2) confirming the formation of designed compounds. Proton NMR signals for –OCH_3, CH_3 and CH_2 protons appeared at their respective positions. The proton NMR signals at ~3.90 ppm (d, 1H) and ~4.10 ppm (d, 1H) confirmed methene protons at 5th position of 1,3-thiazolidin-4-ones. The results of elemental analyses for N and S were within ±0.4 % of the theoretical values.

Interpretation of antibacterial, antifungal and anti-viral screening data revealed that all the tested compounds **1** to **6** showed moderate to good inhibition on the growth of tested organisms (Table **2**). The compounds **1, 3** and **5** exhibited good activity comparable against all the bacterial strains. The good activity of such compound may be attributed due to the

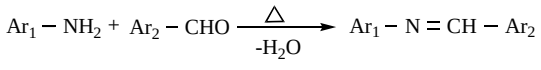
Table 1. Structure and Physical Constant of the Synthesized Compounds



Comp. Code	Ar_1	Ar_2	Molecular formula	Mol. weight	Melting point (°C)	Yield (%)
1	6-methylpyridin-2-yl	4-chlorophenyl	$C_{15}H_{13}ClN_2OS$	304.8	156-158	42
2	pyridin-2-yl	pyridin-2-yl	$C_{14}H_{13}N_3OS$	271	168-170	38
3	4-chlorophenyl	pyridin-2-yl	$C_{14}H_{11}ClN_2OS$	290.7	146-148	40
4	4-chlorophenyl	3-nitrophenyl	$C_{15}H_{11}ClN_2O_3S$	334.7	202-204	43
5	4-chlorophenyl	4-chlorophenyl	$C_{15}H_{11}Cl_2NOS$	324.2	159-161	45
6	4-chlorophenyl	4-hydroxy-3-methoxy phenyl	$C_{16}H_{14}ClNO_3S$	335.8	134-136	32

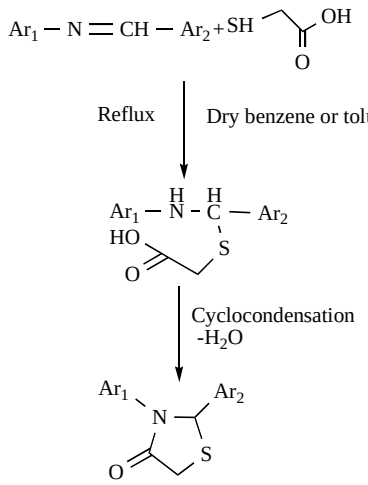
presence of 4-chlorinophenyl group at position 3 of 1,3-thiazolidin-4-ones, 4-chlorophenyl and pyridine-2-yl groups attached to position 2 of the 1,3-thiazolidin-4-ones. Introduction of mono methoxy phenyl group and mono nitrophenyl groups at position 2 of 1,3-thiazolidin-4-ones were found to reduce activity. Inclusion of 4-chlorophenyl group at position 2 and 3 of 1,3-thiazolidin-4-ones showed increase in activity against most of the strains. The compounds **2** and **4** exhibited moderate activity in comparison to the standard against all the bacterial strains.

Step-1: Schiff's base formation.



Schiff's base formation

Step-2: Cyclo-condensation of Schiff's base with thioglycolic acid.



Where Ar_1 and Ar_2 is aromatic or heterocyclic ring.

Scheme 1. Scheme for the synthesis of 1,3-thiazolidin-4-one compounds.

Compounds **1** showed good activity against *E. coli*, while compounds **3** and **5** showed good activity against *S. aureus* and *E. coli*. The compounds **1, 3, 4** and **5** also showed comparatively good activity against all fungal strains. The structures of these compounds was found to contain 4-chlorophenyl groups attached to position 2 of the 1,3-thiazolidin-4-ones. The results confirm that the antibacterial activity is strongly dependent on the nature of the substituents at C-2 and N-3 of the thiazolidinone ring [17]. The compounds **2** and **6** did not exhibit moderate activity against any fungal strains used for the study. These results indicated that 4-chloro substitution at 2nd position of 1,3-thiazolidin-4-ones gave an enhanced biological effect against all the tested bacterial and fungal strains.

Title compounds were tested against various virus like Herpes simplex virus-1 (KOS), Herpes simplex virus-2 (G), Influenza A H3N2 subtype, Influenza B (Table **3**) and evaluated their cytotoxic concentration. None of the synthesized compounds showed antiviral activity against the tested virus except compounds **1** and **5.** Compound **1** exhibited antiviral activity against Herpes simplex virus-1 and Herpes simplex virus-2 at the concentration of 25 to 29 μg/mL, where as cytotoxicity was found to be >100 μg/mL. Compound **5** showed moderate anti-viral activity against Herpes simplex virus-1 and Herpes simplex virus-2 at the concentration of 77 to 90 μg/mL, where as cytotoxicity was found to be >100 μg/mL.

CONCLUSION

The above findings reports the successful synthesis, antibacterial, antifungal and anti-viral activity of new 1,3-thiazolidin-4-ones carrying biologically active groups at C-2 (position 2) and N (position 3). Their antimicrobial screening studies revealed that all the tested compounds showed moderate to good antibacterial and antifungal activities against the tested pathogenic strains. It was observed that only few of the synthesized compounds exhibited antiviral activity. It can be concluded that a combination of two different heterocyclic systems namely 1,3-thiazolidin-4-one and pyridinyl or phenyl ring (substituted) shown promising antimicrobial and anti-viral activity and hence they are ideally suited for further modifications to obtain more efficacious antimicrobial compounds, in near future. The properties of this new class of antibacterial substances deserve further investigation in order to clarify the mode of action at molecular level, responsible for the activity observed.

Table 2. Antibacterial and Anti-Fungal Activity of the Compounds (MIC's in μg/mL[a])

Comp. Code	*E. coli*	*P. aeruginosa*	*B. subtilis*	*S. aureus*	*P. notatum*	*C. albicans*	*A. niger*
1	14	25	30	44	42	60	90
2	23	36	39	NA	NA	NA	90
3	16	14	22	28	42	53	88
4	35	28	38	52	48	67	75
5	08	10	24	22	20	15	18
6	50	62	36	61	NA	65	NA
Cip	5	5	10	15	-	-	-
Flu	-	-	-	-	15	10	15

[a]MIC- Minimum inhibitory concentration, Cip – Ciprofloxacin, Flu - Fluconazole.

Table 3. Anti-Viral Activity of the Synthesized Compounds

Comp. Code	Herpes simplex virus-1		Herpes simplex virus-2	Influenza A H3N2 subtype		Influenza B
	(in μg/mL)			(in μg/mL)		
	CC_{50}	EC_{50}	EC_{50}	CC_{50}	EC_{50}	EC_{50}
1	>100	25 ± 0.88	29 ± 1.22	>100	>100	>100
2	NA	NA	NA	NA	NA	NA
3	≥100	>100	>100	NA	NA	NA
4	NA	NA	NA	NA	NA	NA
5	>100	77 ± 1.80	90 ± 2.20	NA	NA	NA
6	>100	>100	>100	>100	>100	>100
Ganciclovir	>100	0.05 ± 0.018	0.05 ± 0.027	-	-	-
Ribavirin	-	-	-	>100	8 ± 0.40	6 ± 0.134

Where NA is not available; EC_{50} is 50 % effective concentration; CC_{50} is 50 % cytotoxic concentration.

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