International Journal of ChemTech Research
CODEN(USA): IJCRGG ISSN : 0974-4290
Vol.4, No.3, pp 1212-1217, July-Sept 2012

Synthesis, characterization and antimicrobial screening of some novel 2-(1H-azol-1-yl)-N-(-2-(substituted phenyl)-4-oxothiazolidin-3-yl) acetamides

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Abstract: Some novel 4-thiazolidinone derivatives of azoles were synthesized by cyclization of intermediate Schiff bases with thioglycolic acid in presence of catalytic amount of anhydrous zinc chloride. The synthesized title compounds were characterized by IR, ^{1}H-NMR, and mass spectral analysis and screened for antimicrobial activities.
Keywords: azoles, ethybromoacetate, Schiff bases, dehydrating agent.

Introduction

Heterocyclic compounds are of great important to the medicinal chemistry being used as therapeutic agents and essential for the healthy human life.

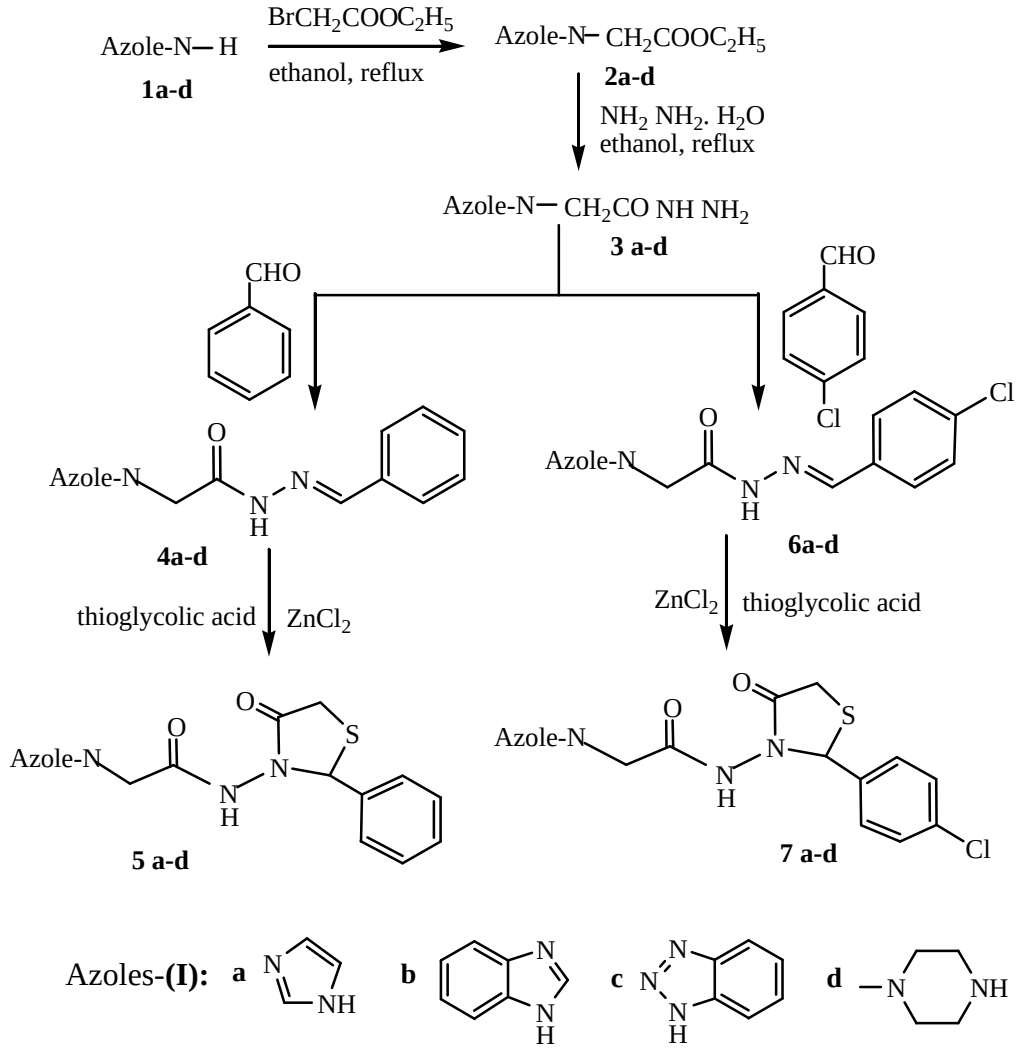
4-thiazolidinones are an important group of heterocyclic compounds associated with diverse pharmacological activities such as antibacterial[1-3], antifungal[4,5], analgesic[6], anti inflammatory[7], antitubercular[8], antimalerial[9], anti proliferative[10,11], anti histaminics[12], antithyroid[13,14], local anesthetic[15], antihelmintic[16], diural[17], and nematocidal[18]. 2-substituted thiazolidinone and analogues exhibits usually high in vitro activity against *mycobacterium tuberculosis*. It is worthwhile to note that natural products, actithiazic acid [(-) 2-(5-carboxyphenyl) thiazolidin-4-one] isolated from *Streptomyces* strain known to active against *mycobacterium tuberculosis*[19]. The activity of 1, 3-thiazolidin-4-one against *mycobacterium tuberculosis* by inhibition of dTDP-rhamnose synthesis an emerging target to combat tuberculosis disease[20].

Number of studies have highlighted its analgesic, antiparkinsonian[21] and known to show diverse biological activities such as CNS stimulants, anticonvulsants[22], antipsychotic, anticancer[23], and anti –HIV[24]. Thiazolidinone derivatives inhibit the biosynthesis of the peptidoglycan polymer essential for cell wall of bacteria on inactivation of MurB enzyme. MurB enzyme is a unique target for the antibacterial activity of thiazolidinone[25]. Nitro substituted 4-thiazolidinone derivatives have shown significant cytotoxic activity in lung, melanoma and renal cancers[26], exhibits substantial NA inhibition (Ic_{50}=21.3µM) and reported as first thiazolidine neuraminidase inhibitor, blocks the viral life cycle

and prove to be effective for the treatment of influenza[27]. 4-thiazolidinone derivatives are effective against intracellular T. gondii[28].Thiazolidinone derivatives also been utilized as hypolipidermic, hypochlolestermics[29], Ca antagonists, antioxidants[30], fungicides and herbicides[31].Recently an improved protocol has been reported wherein anhydrous zinc chloride is used as dehydrating agent to accelerate the intramolecular cyclization. Anhydrous zinc chloride provides mild reaction condition[32].

Experimental

All chemicals used are of analytical grade and solvents were distilled prior to use. Melting points are uncorrected. FTIR spectra were recorded on Shimadzu 8400 IR spectrometer. ^{1}H NMR spectra were recorded on 400 MHz Varian NMR Instrument model Mercury plus spectrometer and their chemical shifts are reported in δ values in ppm. Mass spectra were obtained with Waters acquity UPLC TQ Detector Mass spectrometer. The progress of reactions was monitored by TLC.
The synthetic strategy applied is given in **Scheme 1.**



Scheme 1

Results and discussion

General procedure for the synthesis of azole-1-yl acetic acid ethyl ester 2a-d:
To a solution of azole **1a-d** (0.05mol) in dry ethanol (30ml), ethylbromoacetate (0.05mol) was slowly added in presence of 06 g of anhydrous potassium carbonate. The resulting solution was refluxed for 18-20 hr. on water bath. Then the reaction mixture was cooled to room temperature and filtered. The products obtained were used in next step without further purification.

General procedure for the synthesis of azole-1-yl acetic acid hydrazides 3a-d:
To a solution of azole-1-yl acetic acid ester **2a-d** (0.05mol) in ethanol (30ml), hydrazine hydrate (0.1mol) was added with stirring. The reaction mixture was refluxed for 18-20 hr. on water bath. The products obtained were used for next step without purification.

General procedure for the synthesis of hydrazones 4a-d, 6a-d:
To azole-1-yl acetic acid hydrazide **3a-d** (0.02mol) in dry ethanol (50ml), benzaldehyde and 4-chlorobenzaldehyde (0.02mol) was added in presence of acid catalyst. The reaction mixture was refluxed for about 14-16 hr. It was cooled to room temperature and added on crushed ice. The residue obtained which was washed with cold water for two/three times and recrystallized from suitable solvent in moderate to good yields of **4a-d**, and **6a-d** respectively.

N'-benzylidene-2-(1H-imidazol-1-yl) acetohydrazide 4a. The solid product obtained was filtered and recrystallized from ethanol which gave yellow crystals. mp. 68-70 ^{0}C, 62% yield. IR(KBr) cm^{-1}: 3250 (NH), 3051, 1654 (C=O amide), 1629 (C=N), 752, 690. ^{1}H NMR ($CDCl_3$): δ 10.92 (s, 1H, NH), 8.67 (s, 1H, HC=N), 7.86-7.25(m, 8H, Ar-H), 4.84(s, 2H, CH_2).

N'-benzylidene-2-(1H-benzimidazol-1-yl) acetohydrazide 4b. The solid product obtained recrystallized from water- ethanol as yellow needles. mp. 60-62 ^{0}C, 74% yield. IR (KBr) cm^{-1}: 3190 (NH), 3055, 2949, 1665 (C=O amide), 1620 (C=N), 752, 686. ^{1}H NMR ($CDCl_3$): δ 10.25 (s, 1H, NH), 8.65 (s, 1H, HC=N), 7.86-783(m, 5H, benzimi-H), 7.45(s, 5H, Ar-H), 5.4(s, 2H, CH_2). LCMS (m/z, %): (M+1) 279.2 (4), 211.1(13), 210.1(18), 209.1 (100).

N'-benzylidene-2-(1H-benzotriazol-1-yl) acetohydrazide 4c. The dense solid product obtained was recrystallized from ethanol as white soft needles. mp. 208-210 ^{0}C, 78% yield. IR (KBr) cm^{-1}: 3184 (NH), 3095, 2956, 1678 (C=O amide), 1500 (C=N), 819, 744. ^{1}H NMR (DMSO-d_6): δ 11.91 (s, 1H, NH), 8.25 (s, 1H, HC=N), 8.07-7.37(m, 9H, Ar-H), 6.04(s, 2H, CH_2). LCMS (m/z, %): 281.2 (M+1, 19), 280.2 (100), 100.1 (4),

N'-benzylidene-2-(4-methylpiperazin-1-yl) acetohydrazide 4d. The solid product obtained was recrystallized from water-ethanol as white crystals. mp. 108-110 ^{0}C, 56% yield. IR (KBr) cm^{-1}: 3210 (NH), 3070, 2980, 1690 (C=O amide), 1582 (C=N), 706, 667. ^{1}H NMR ($CDCl_3$): δ 11.16 (s, 1H, NH), 8.14 (s, 1H, HC=N), 7.64-7.46(m, 5H, Ar-H), 4.64(s, 2H, CH_2), 2.24(s, 3H, N-CH_3), 2.18 (m, 8H, 4CH_2).

N'-(4-chlorobenzylidene)-2-(1H-imidazol-1-yl) acetohydrazide 6a. The solid product obtained was filtered and recrystallized from acetonitinitrile as silvery plates. mp. 47-49 ^{0}C, 58% yield. IR (KBr) cm^{-1}: 3360 (NH), 3198, 1656 (C=O amide), 1595 (C=N), 823. ^{1}H NMR ($CDCl_3$): δ 9.80 (s, 1H, NH), 8.59 (s, 1H, HC=N), 7.78-7.76(m, 3H, Ar-H Imi.), 7.47-7.29 (m, 4H, Ar-H), 5.56(s, 2H, CH_2).

N'-(4-chlorobenzylidene)-2-(1H-benzimidazol-1-yl) acetohydrazide 6b. The solid product obtained was recrystallized from water-ethanol as curdy plates. mp. 198-200 ^{0}C, 61% yield. IR (KBr) cm^{-1}: 3267 (NH), 2941, 1640 (C=O amide), 1593 (C=N), 817. ^{1}H NMR ($CDCl_3$): δ 10.39 (s, 1H, NH), 8.60 (s, 1H, HC=N), 7.83-779 (m, 5H, benzimi-H), 7.78-7.41(m, 4H, Ar-H), 5.3 (s, 2H, CH_2).

N'-(4-chlorobenzylidene)-2-(1H-benzotriazol-1-yl)acetohydrazide 6c. The solid product obtained was recrystallized from water-ethanol as yellow plates. mp. 176-179 ^{0}C, 67% yield. IR (KBr) cm^{-1}: 3200 (NH), 3095, 2978, 1647 (C=O amide), 1587 (C=N), 823. ^{1}H NMR (DMSO-d_6): δ 11.90 (s, 1H, NH), 8.72 (s, 1H, HC=N), 8.25-7.37(m, 8H, Ar-H), 5.78(s, 2H, CH_2).

N'-(4-chlorobenzylidene)-2-(4-methylpiperazin-1-yl) acetohydrazide 6d. The solid product obtained was recrystallized from ethanol as intense yellow plates. mp. 199-200 ^{0}C, 86% yield. IR (KBr) cm^{-1}: 3200 (NH), 2939, 1627 (C=O amide), 1585 (C=N), 862, 817. ^{1}H NMR (DMSO-d_6) : δ 10.21 (s, 1H, NH), 8.70 (s, 1H, HC=N), 7.89-7.55(m, 4H, Ar-H),

4.82(s, 2H, CH_2), 2.27(s, 3H, N-CH_3), 2.21 (m, 8H, 4CH_2).

General procedure for the synthesis of 2-(1H-azol-1-yl)-N-(-2-(substituted phenyl)-4-oxothiazolidin-3-yl) acetamides 5a-d, 7a-d.
The Schiff bases **4a-d** and **6a-d** (0.0025moles) were refluxed with thioglycolic acid (0.004moles) in presence of catalytic amount of anhydrous zinc chloride in dry methanol/ benzene/1,4-dioxane (30ml) for 9-10 hr. The reaction mixture was then cooled to rt., neutralized with cold dil. $NaHCO_3$ (20ml). The residue separated was filtered, recrystallized from ethanol to give **5a-d** and **7a-d** respectively.

2-(1H-imidazol-1-yl)-N-(-4-oxo-2-phenylthiazolidin-3-yl) acetamide 5a: The solid product obtained was recrystallized from water-ethanol as yellow powder in 61% yield, mp.158-160^{0}C. IR (KBr) cm^{-1}: 3203 (NH), 3074, 2947, 1697 (C=O), 1683(C=O, amide), 1622 (C=N), 1298, 752, 690. ^{1}H NMR ($CDCl_3$): δ 9.23 (s, 1H, NH), 7.82-7.14(m, 8H, Ar-H), 7.12 (s, 1H, NCHS), 5.22(s, 2H, CH_2), 4.39(s, 2H, CH_2S). Mass (m/z, %): 301.2 (M^+ -1, 3), 222.2(8), 210(15) and 209(100).

2-(1H-benzimidazol-1-yl)-N-(-4-oxo-2-phenylthiazolidin-3-yl) acetamide 5b: The solid product obtained was recrystallized from water-ethanol as yellow crystals in 67% yield, mp.174-176^{0}C. IR (KBr) cm^{-1}: 3440 (NH), 3055, 2945, 1687 (C=O), 1653(C=O, amide), 1622 (C=N), 752, 688.

2-(1H-benzotriazol-1-yl)-N-(4-oxo-2-phenylthiazolidin-3-yl) acetamide 5c: The solid product obtained was recrystallized from water-ethanol as yellow powder in 72% yield, mp.110-112^{0}C. IR (KBr) cm^{-1}: 3257 (NH), 3146, 3034, 2909, 1720 (C=O), 1689 (C=O, amide), 752, 701.

2-(4-methylpiperazin-1-yl)-N-(4-oxo-2-phenylthiazolidin-3-yl) acetamide 5d: The solid product obtained was recrystallized from water-ethanol as yellow powder in 57% yield, mp.156-158^{0}C. IR (KBr) cm^{-1}: 3219 (NH), 3049, 2932, 2867, 1708 (C=O), 1687 (C=O, amide), 754, 709.

N-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl)-2-(1H-imidazol-1-yl) acetamide 7a: The solid product obtained was recrystallized from water-ethanol as yellow crystals in 64% yield, mp.204-206^{0}C. IR (KBr) cm^{-1}: 3390 (NH), 3010, 2960, 1720 (C=O), 1680 (C=O, amide), 810. ^{1}H NMR ($CDCl_3$): δ 8.63 (s, 1H, NH), 7.79-7.51 (m, 7H, Ar-H), 5.37(s, 1H, CH), 3.82(s, 2H, CH_2), 3.12(s, 2H, CH_2).

2-(1H-benzimidazol-1-yl)-N-(-2-(4-chlorophenyl)-4-oxothiazolidin-3-yl) acetamide 7b: The solid product obtained was recrystallized from water-ethanol as brown powder in 65% yield, mp.126-128^{0}C. IR (KBr) cm^{-1}: 3169 (NH), 2924, 1730 (C=O), 1668 (C=O, amide), 829. ^{1}H NMR ($CDCl_3$): δ 8.69 (s, 1H, NH), 7.32-7.18 (m, 9H, Ar-H), 5.25(s, 1H, CH), 3.31(s, 2H, CH_2), 3.05(s, 2H, CH_2). Mass (m/z, %): 387.0(M^++1, 11), 319(60), 269(13), 195(100), 119(47).

2-(1H-benzotriazol-1-yl)-N-(-2-(4-chlorophenyl)-4-oxothiazolidin-3-yl) acetamide 7c: The solid product obtained was recrystallized from ethanol as curdy powder in 59% yield, mp.196-199^{0}C. IR (KBr) cm^{-1}: 3309 (NH), 2918, 1685 (C=O), 1653 (C=O, amide), 777.

N-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl)-2-(4-methylpiperazin-1-yl) acetamide 7d: The solid product obtained was recrystallized from water-ethanol as yellow plates in 82% yield, m. p.130-131^{0}C. IR (KBr) cm^{-1}: 3203 (NH), 3041, 2929, 2890, 1703 (C=O), 1654 (C=O, amide), 819. ^{1}H NMR ($CDCl_3$): δ 8.62 (s, 1H, NH), 7.78-7.42 (dd, 4H, Ar-H), 5.78(s, 1H, CH), 5.24(s, 2H, CH_2), 4.39(s, 2H, CH_2), 2.23(s, 3H, N-CH_3), 1.96(s, 8H, 4CH_2).

Antimicrobial activity

The synthesized 4-thiazolidinone **5a-d** and **7a-d** derivatives were screened for their in vitro antimicrobial activities against *Escherichia coli*, *Staphylococcus aureus*, *Candida albicans* and *Aspergillus niger* by Disc diffusion method (Well method, Disc size 6mm, Hi media) using nutrient agar, Potato dextrose agar. The compounds were tested at the concentration of 100µg/ml in DMF. The results were compared with respective standard Streptomycin and Amphotericin-B. The zones of inhibition were measured in mm and the data is presented in Table 1.

All the compounds were found inactive against bacterial and fungal strains except one, **7b** which showed some activity against *A. niger*, given in Table 1.

Table 1. Results of antimicrobial activity of the compounds 5a-d, 7a-d

Compound No.	Antimicrobial activity*			
	E. coli	***S. aureus***	***C. albicans***	***A. niger***
5a	_	_	_	_
5b	_	_	_	_
5c	_	_	_	_
5d	_	_	_	_
7a	_	_	_	_
7b	_	_	_	7.75
7c	_	_	_	_
7d	_	_	_	_
Chloramphenicol	16.91	18.79	**NA**	**NA**
Amphotericin-B	**NA**	**NA**	14.23	15.34

Diameter in mm calculated by digital Vernier Caliper. * Zone of inhibition in mm.
'_' means no zone of inhibition. NA- Not applicable.

Conclusions

In summary an efficient, concise approach for the synthesis of 4-thiazolidinone derivatives is reported through cyclocondensation of Schiff bases with thioglycolic acid in presence of anhydrous zinc chloride.

The antimicrobial study of 4-thiazolidinone derivatives revealed that the compounds are poor in antimicrobial activity against the four test organisms examined compare with respective standards.

Acknowledgement

The authors are thankful to Principal Z. B. Patil College, Dhule, Head UDCT, North Maharashtra University, Jalgaon for providing the infrastructural facility and Director, Wockhardt Pharmaceutical, Aurangabad for providing ^{1}H NMR and Mass spectral analysis.

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