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Synthesis, characterization and biological activity of 4-thiazolidinone derivatives containing *1H*-pyrazolo[*3,4-b*]pyridine nucleus

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ABSTRACT

The thiazolidinone derivatives substituted at 2- and 3-position are associated with diverse biological activities. Considerable evidence has been accumulated to demonstrate the wide applications of thiazolidinone derivatives and also Pyrazolo[3,4-b]pyridine nucleus have drawn the attention of chemists due to diversified biological activities associated with it. In view of these findings, it appeared of interest to synthesize, newer thiazolidinone derivatives with better potency. The constitution of the synthesized products have been characterized by using elemental analysis (N), infrared and ^{1}H-nuclear magnetic resonance spectroscopy and further supported by mass spectroscopy. All the compounds have been evaluated for their in vitro biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity.

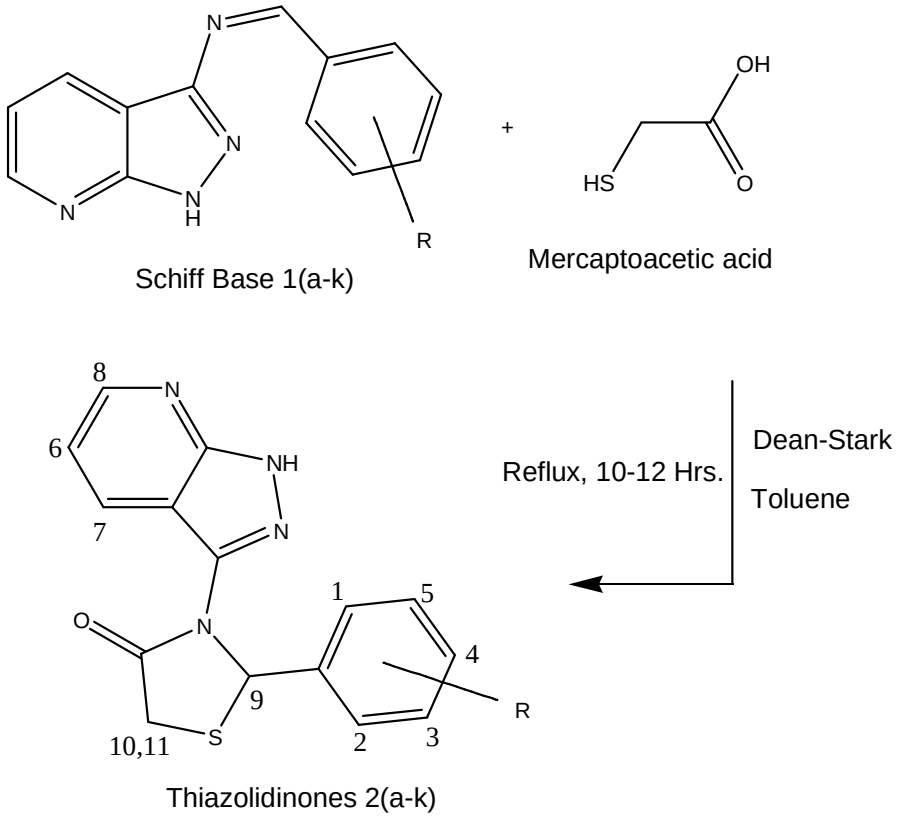
Key words: Thiazolidinones, Biological activities, ^{1}H NMR, IR

INTRODUCTION

4-Thiazolidinones play a vital role due to their wide range of biological activities and industrial importance. 4-Thiazolidinones are always being an attraction point for researchers because of its efficiency towards various pharmacological usages. The enhanced prevalence of infectious diseases threatens world population. Although tuberculosis appeared as a curable disease for years, it is regaining importance due to the multidrug resistance[1,2]. Worldwide statistics on tuberculosis surprisingly reveals that, nearly one–third of the world's population is infected with tuberculosis, with approximately eight million new patients every year. A major issue is the increase of multi-drug resistant tuberculosis (MDRTB) giving rise to the disease expensive and incurable especially in immune deficient subjects such as AIDS patients. Hence, there is an increased demand to develop new antituberculosis agents effective against pathogens resistant to current treatment. The derivatives of 4-thiazolidinone nucleus have occupied a unique place in the field of medicinal chemistry due to wide range of biological activities like antibacterial, antitubercular, anticancer, anticonvulsant and antifungal[3]. They have interesting activity profiles mainly cox-1 inhibitors, inhibitors of bacterial enzyme, non nucleoside inhibitors of HIVRT and antihistaminic agents[4]. 4-thiazolidinones are derivatives of thiazolidinone with carbonyl group at the 4th position and formed by the attack of sulphur nucleophile on imine carbon followed by intramolecular cyclisation with elimination of water. Recent studies on molecular modification of the latter (TBZs) revealed that, dismantling of the imidazole nucleus leading to the design of new 1,3-thiazolidin-4-one derivatives, maintained the molecular requirements for enzyme inhibition[5]. A literature search revealed that, 4–thiazolidinone derivatives may exhibit antibacterial[6,7], antituberculosis[8-10], antiviral[12,5,11-16] and anticancer[17-20] properties. According to Andres et al.[6], 4-thiazolidinones

may be considered as phosphate bioisosteres and therefore inhibit the bacterial enzyme MurB which is involved in the biosynthesis of peptidoglycan layer of the cell wall[6]. In addition, some thiazolidinones were recently reported as novel inhibitors of mycobacterial rhamnose synthetic enzymes[21]. This new approach is believed to be selective as rhamnose which is not found in humans, has been shown to be essential for mycobacterial cell wall synthesis[21].

REACTION SCHEME



R = 2-OH, 3-NO_2, 4-OH, 4-$N(CH_3)_2$,4-OH-3-OCH_3 , 4-Cl, 4-NO_2, H, 4-OCH_3, 2-Cl, 4-F.

MATERIALS AND METHODS

Materials

The aromatic benzadelydes used in the preparation of Schiff base viz; a: 2- hydroxy benzaldehyde, b: 3-nitrobenzaldehyde, c: 4-hydroxybenzaldehyde, d: 4- N,N-dimethyl benzaldehyde, e: h: 4-hydroxy-3-methoxy benzaldehyde, f: 4-Cholorobenzaldelhyde, g: 4-nitro benzaldehyde, h: benzaldehyde, i: 4-methoxybenzaldehyde, j: 2-chlorobenzaldehyde, k: 4-fluorobenzaldehyde, were obtained from local dealer. All otherchemicals used where of laboratory grade.

Measurements

Melting points were determined in open capillary tubes and were uncorrected. The IR spectra were recorded in SHIMADZU FTIR 8400 Spectrophotometer; Frequency range: 4000-400 cm^{-1} (KBr disc Method) and ^1H NMR spectra in $CDCI_3$ on BRUKER Spectrometer (300 MHz) NMR spectrometer using TMS as an internal standard. Antimicrobial activity of all the compounds were studied against Gram positive bacteria (*S.pyogenus* and *s.aureus*) and Gram negative bacteria (*E.Coli* and *P.aeruginosa*).

Preparation of Schiff bases
A mixture of 1H-Pyrazolo[3,4-b]pyridine-3-amine (0.01 mol) and Aromatic benzaldehydes (0.01 mol) was taken in ethanol using catalytic amount of gla. acetic acid. The reaction mixture was refluxed for 8.0-10 hrs on water bath. The product was isolated and crystallized from absolute ethanol. Yield 80-90%.

Preparation of Thiazolidinones
The Thiazolidinone derivatives have been synthesized by the reaction of different schiffbases (0.01 mol) in Toluene (50.0 ml) and mercaptoacetic acid (0.02 mol) was added drop wise at room temperature in 15 min and stir for 30 min at room temperature then increase temperature slowly up to refluxed and maintain for 10 -12.0 hrs. Remove water by azeotropic distillation using a Dean-Stark separator. After completion of reaction, excess of toluene was distilled off and the resulting product was treated with 5% NaHCO3 solution to remove unreacted mercaptoacetic acid. The separated product was washed with water, dried and recrystallized from $CHCl_3$: Water. Yield 40-70%.

2-(2-hydroxyphenyl)-3-(1H-pyrazolo[3,4-b]pyridin-3-yl)thiazolidin-4-one (2a)
Yield 56%, mp. 143 ºC, IR (KBr) cm^{-1}: 3321 (OH), 3020–3043 (CH), 1735 (C=O), 1631 (S-C=N), ^{1}H–NMR ($CDCl_3$) δ ppm: 3.38, 3.28 (d, 2H, H10, H11), 5.10 (s, 1H, OH), 5.90 (s, 1H, H9), 6.61-6.90 (m, 4H, H1,H3,H4,H5), 7.38-7.61(m, 2H, H6,H7), 8.59 (m, 1H, H8), 13.2 (s, 1H, NH); Mass (*m/z*): 312, Anal. (%) for $C_{15}H_{12}N_4O_2S$, Calcd. N, 17.94, found, 17.96.

2-(3-nitrophenyl)-3-(1H-pyrazolo[3,4-b]pyridin-3-yl)thiazolidin-4-one (2b)
Yield 50%, mp. 148-158 ºC, IR (KBr) cm^{-1}: 3030–3055 (CH), 1741 (C=O), 1639 (S-C=N), ^{1}H–NMR ($CDCl_3$) δ ppm: 3.41, 3.33 (d, 2H, H10, H11), 5.92 (s, 1H, H9), 7.36-7.43 (m, 3H, H1,H5,H6), 7.99-8.12. (m, 2H, H2,H4), 7.75(m, 1H, H7), 8.54 (m, 1H, H8), 13.4 (s, 1H, NH); Mass (*m/z*): 341, Anal. (%) for $C_{15}H_{11}N_5O_3S$, Calcd. N, 20.52, found, 20.51.

2-(4-hydroxyphenyl)-3-(1H-pyrazolo[3,4-b]pyridin-3-yl)thiazolidin-4-one (2c)
Yield 65%, mp. 151ºC, IR (KBr) cm^{-1}: 3317 (OH), 3022–3043 (CH), 1732 (C=O), 1630 (S-C=N), ^{1}H–NMR ($CDCl_3$) δ ppm: 3.36, 3.27 (d, 2H, H10, H11), 5.12 (s, 1H, OH), 5.92 (s, 1H, H9), 6.61 (m, 2H, H3,H5), 6.89(m, 2H, H1,H2), 7.40-7.61(m, 2H, H6,H7), 8.59 (m, 1H, H8), 13.7 (s, 1H, NH); Mass (*m/z*): 312, Anal. (%) for $C_{15}H_{12}N_4O_2S$, Calcd. N, 17.94, found, 17.90.

2-(4-(dimethylamino)phenyl)-3-(1H-pyrazolo[3,4-b]pyridin-3-yl)thiazolidin-4-one (2d)
Yield 60%, mp. 160ºC, IR (KBr) cm^{-1}: 3019–3032 (CH), 1729 (C=O), 1633 (S-C=N), ^{1}H–NMR ($CDCl_3$) δ ppm: 2.85 (s, 6H, N(CH3)2), 3.35, 3.24 (d, 2H, H10, H11), 5.92 (s, 1H, H9), 6.47 (m, 2H, H3,H5), 6.88(m, 2H, H1,H2), 7.38-7.72(m, 2H, H6,H7), 8.54 (m, 1H, H8), 13.6 (s, 1H, NH); Mass (*m/z*): 339, Anal. (%) for $C_{17}H_{17}N_5OS$, Calcd. N, 20.63, found, 20.65.

2-(4-hydroxy-3-methoxyphenyl)-3-(1H-pyrazolo[3,4-b]pyridin-3-yl)thiazolidin-4-one (2e)
Yield 40%, mp. 167-170ºC, IR (KBr) cm^{-1}: 3310 (OH), 3030–3055 (CH), 1740 (C=O), 1635 (S-C=N), ^{1}H–NMR ($CDCl_3$) δ ppm: 3.38, 3.28 (d, 2H, H10, H11), 3.79 (s, 1H, OCH3), 5.10 (s, 1H, OH), 5.94 (s, 1H, H9), 6.41-6.50 (m, 3H, H1,H2,H5), 7.38(m, 1H, H6), 7.75 (m, 1H, H7), 8.60 (m, 1H, H8), 13.5 (s, 1H, NH); Mass (*m/z*): 342, Anal. (%) for $C_{16}H_{14}N_4O_3S$, Calcd. N, 16.36, found, 16.37.

2-(4-chlorophenyl)-3-(1H-pyrazolo[3,4-b]pyridin-3-yl)thiazolidin-4-one (2f)
Yield 68%, mp. 134-146ºC, IR (KBr) cm^{-1}: 3022–3043 (CH), 1738 (C=O), 1630 (S-C=N), ^{1}H–NMR ($CDCl_3$) δ ppm: 3.32, 3.24 (d, 2H, H10, H11), 5.89 (s, 1H, H9), 7.00-7.19 (m, 4H, H1,H2,H3,H5), 7.40 (m, 1H, H6), 7.81 (m, 1H, H7), 8.60 (m, 1H, H8), 13.7 (s, 1H, NH); Mass (*m/z*): 330, Anal. (%) for $C_{15}H_{11}ClN_4OS$, Calcd. N, 16.94, found, 16.94.

2-(4-nitrophenyl)-3-(1H-pyrazolo[3,4-b]pyridin-3-yl)thiazolidin-4-one (2g)
Yield 52%, mp. 256ºC, IR (KBr) cm^{-1}: 3027–3053 (CH), 1728 (C=O), 1640 (S-C=N), ^{1}H–NMR ($CDCl_3$) δ ppm: 3.33, 3.21 (d, 2H, H10, H11), 5.90 (s, 1H, H9), 7.32-7.38 (m, 3H, H1,H2,H6), 7.70 (m, 1H, H7), 8.10 (m, 2H, H3,H5), 8.58 (m, 1H, H8), 13.60 (s, 1H, NH); Mass (*m/z*): 341, Anal. (%) for $C_{15}H_{11}N_5O_3S$, Calcd. N, 20.52, found, 20.54.

2-phenyl-3-(1H-pyrazolo[3,4-b]pyridin-3-yl)thiazolidin-4-one (2h)
Yield 67%, mp. 146-151 ºC, IR (KBr) cm^{-1}: 3033–3051 (CH), 1730 (C=O), 1631 (S-C=N), ^{1}H–NMR ($CDCl_3$) δ ppm: 3.38, 3.28 (d, 2H, H10, H11), 5.94 (s, 1H, H9), 7.00-7.14 (m, 5H, H1-H5), 7.39 (m, 1H, H6), 7.72 (m, 1H, H7), 8.59 (m, 1H, H8), 13.7 (s, 1H, NH); Mass (*m/z*): 296, Anal. (%) for $C_{15}H_{12}N_4OS$, Calcd. N, 18.91, found, 18.93.

2-(4-methoxyphenyl)-3-(1H-pyrazolo[3,4-b]pyridin-3-yl)thiazolidin-4-one (2i)
Yield 70%, mp. 135-137ºC, IR (KBr) cm^{-1}: 3020–3040 (CH), 1730 (C=O), 1631 (S-C=N), ^{1}H–NMR ($CDCl_3$) δ ppm: 3.33, 3.24 (d, 2H, H10, H11), 3.77 (s, 1H, OCH3), 5.90 (s, 1H, H9), 6.65 (m, 2H, H3,H5), 6.94(m, 2H, H1,H2), 7.40-7.45(m, 2H, H6,H7), 8.61 (m, 1H, H8), 13.7 (s, 1H, NH); Mass (*m/z*): 326, Anal. (%) for $C_{16}H_{14}N_4O_2S$, Calcd. N, 17.17, found, 17.19.

2-(2-chlorophenyl)-3-(1H-pyrazolo[3,4-b]pyridin-3-yl)thiazolidin-4-one (2j)
Yield 68%, mp. 132ºC, IR (KBr) cm^{-1}: 3021–3041 (CH), 1734 (C=O), 1632 (S-C=N), ^{1}H–NMR ($CDCl_3$) δ ppm: 3.33, 3.24 (d, 2H, H10, H11), 5.90 (s, 1H, H9), 7.00-7.11 (m, 4H, H1,H3,H4,H5), 7.38 (m, 1H, H6), 7.65 (m, 1H, H7), 8.52 (m, 1H, H8), 13.7 (s, 1H, NH); Mass (*m/z*): 330, Anal. (%) for $C_{15}H_{11}ClN_4OS$, Calcd. N, 16.94, found, 16.98.

2-(4-fluorophenyl)-3-(1H-pyrazolo[3,4-b]pyridin-3-yl)thiazolidin-4-one (2k)
Yield 54%, mp. 154-163ºC, IR (KBr) cm^{-1}: 3025–3043 (CH), 1740 (C=O), 1630 (S-C=N), ^{1}H–NMR ($CDCl_3$) δ ppm: 3.30, 3.24 (d, 2H, H10, H11), 5.90 (s, 1H, H9), 6.85 (m, 2H, H3,H5), 7.04 (m, 2H, H1,H2), 7.40 (m, 1H, H6), 7.78 (m, 1H, H7), 8.59 (m, 1H, H8), 13.7 (s, 1H, NH); Mass (*m/z*): 314, Anal. (%) for $C_{15}H_{11}FN_4OS$, Calcd. N, 17.82, found, 17.85.

RESULTS AND DISCUSSION

Antibacterial activity

The minimum inhibitory concentrations (MICs) of the tested compounds are shown in Table 1. The different compounds 2(a-k) were tested for *in vitro* against two gram positive (*S. aureus* MTCC 96, *S. pyogenus* MTCC 443) and two gram negative (*E. coli* MTCC 442, *P. aeruginosa* MTCC 441) bacteria. From the screening data, most of the compounds possessed very good antibacterial activity (MBC, 50-250 µg/ml) against gram positive *S. aureus*, some of them possessed excellent activity compared to ampicillin. Compound 2e, 2h and 2i showed MBC value in the range between 62.5-100 µg/ml while ampicillin has standard MBC value of 100 µg/ml against gram negative *E. coli* which indicates that this compounds have excellent activity, while other Compound 2b, 2c, 2e, 2f and 2j possessed MBC value in the range of 200-250 µg/ml against gram negative *E. coli* while 2g and 2j exhibited very good activity against *P. aeruginosa*.

Antifungal activity

The minimum inhibitory concentrations (MICs) of the synthesized compounds are shown in Table 1. For *in vitro* antifungal activity, three fungal species *C, albicans* MTCC 227, *A. niger* MTCC 282 and *A. clavatus* MTCC 1323 were used and compared with standard drug griseofulvin. Most of the compounds possessed very good antifungal activity against *C. albicans*; their MFC values were in the range between 100-500 µg/ml. Compounds **2c, 2g** and **2k** possessed very good activity of 500 µg/ml which is similar to griseofulvin (500 µg/ml) against *C. albicans* whereas remaining compounds possessed moderate to poor activity against *A. niger* and *A. clavatus* compared with griseofulvin.

Table 1: Biological Evaluation of 4-Thiazolidinone Derivatives

Sr. No.	Code	Antibacterial Activity				Antifungal activity		
		Minimal bactericidal concentration µg/ml				Minimal fungicidal concentration µg/ml		
		Gram +*ve* Bacteria		Gram –*ve* Bacteria				
		S.aureus	*S.pyogenus*	*E.coli*	*P.aeruginosa*	*C.albicans*	*A.niger*	*A.clavatus*
1	2a	500	200	1000	250	>1000	500	1000
2	2b	500	250	200	500	>1000	500	500
3	2c	200	1000	200	1000	500	500	200
4	2d	1000	1000	500	250	1000	250	500
5	2e	100	500	250	500	1000	500	200
6	2f	250	100	250	250	250	1000	250
7	2g	500	200	100	200	500	>1000	1000
8	2h	62.5	100	1000	250	>1000	500	500
9	2i	100	100	500	250	>1000	250	500
10	2j	1000	1000	62.5	100	250	>1000	>1000
11	2k	500	500	500	250	500	500	1000

MINIMAL INHIBITION CONCENTRATION

Standard Drugs	*E.coli*	*P.aeruginosa*	*S.aureus*	*S.pyogenus*
	(microgramme/ml)			
Gentamycin	0.05	1	0.25	0.5
Ampicillin	100	100	250	100
Chloramphenicol	50	50	50	50
Ciprofloxacin	25	25	50	50
Norfloxacin	10	10	10	10

MINIMAL FUNGICIDAL CONCENTRATION

Standard Drugs	*C.Albicans*	*A.Niger*	*A.Clavatus*
	(microgramme/ml)		
Nystatin	100	100	100
Greseofulvin	500	100	100

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