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Synthesis, Characterization and Biological Screening of New 4-Thiazolidinones having Potentially Active Tetrazole Moiety

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ABSTRACT

A series of new 4- Thiazolidinones (II) have been synthesized by the reaction of 2-Amino-4-substituted phenyl- 1-(2H)-Tetrazole(s) with substituted Phenyl isothiocynate(s) to generate N'-(4-substitutedphenyl)-N"-1-[(3'-substituted Phenyl)-6-tetrazolyl]-Thiocarbamide(s) (I). Which was further reacted with mono chloro acetic acid in presence of anhydrous sodium acetate and acetic acid to form new 4-Thiazolidinone(s) (II). The synthesized compounds have been confirmed by their elemental and spectral analysis. The synthesized 4- Thiazolidinones have been screened against *E coli* for their antibacterial activity. Some of the compounds are shown good antibacterial activity.

Key words: Tetrazole, Thiocarbamides, 4- Thiazolidinones, Antibacterial, *E. coli.*

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INTRODUCTION

4-Thiazolidinones have been synthesized and used for the treatment of Cardiac [1-2] diseases. Modifications on 2, 3, 4 and 5 positions of 4- Thiazolidinones give out anti diabetic drugs and potent aldose reductase inhibitors, which are used in the treatment of diabetic complications Like Cataracts, nephropathy neuropathy[3].4-Substituted Thiazolidinone derivatives have been synthesized and reported to show a variety of pharmacological and microbiological activities such as antibacterial[4],antifungal, analgesic etc. Significant anti parkinsonian activity against termor, rigidity, hypokinesia and catatonia has been evaluated "*in vivo*" in rats and mice in quinazoline Thiazolidinone [5]. Anticonvulsant [6] and anticancer [7] activities have been observed in many alkoxy phtalimide derivatives. Many amino-oxy compounds have been tested for their ability to inhibit the growth of the malaria parasite *Plasmodium falciparum inVitro* [8]. Heterocyclic ring attached to alkoxy phtalimide group have been synthesized [9] and tested for antimicrobial and antimalerial [10] activities.4-Thiazolidinones are also reported as anti-hyperglycemic activity [11].Tetrazole moiety exhibits a wide and growing number of applications. This nitrogen rich heterocyclic ring is used in propellants [12] and in pharmaceuticals [13-16]. The extensive use of antibiotics has led to the appearance of multi-drug resistant microbial pathogen [17]. Mudasir Rashid Bande et.al synthesized 4- Thiazolidinones and screened for microbial activities against *Escherchia coli, enterobacter acrogens, staphyloco aureus* and *salmonella typhi* by cup plate method [18].

Led by above facts , coupled with our desire of synthesizing 4- Thiazolidinones with tetrazole moiety , we report herein the synthesis of some new 4- Thiazolidinone incorporating tetrazole moiety together in order to prepare the molecules having enhanced biological activity.

MATERIALS AND METHODS

All the used chemicals are lab grade chemicals. All melting points were determined in open capillary tube using precision melting point apparatus. Thin layer chromatography was performed with fluorescent silica gel plates HF 254(Merck) plates were viewed under UV 254 and 265 nm .IR spectra's were recorded on Shimadzu FTIR 4000; Using KBr discs.1HNMR spectra were recorded on Bruker spectrophotometer at 300 MHz frequency in DMSO using TMS as a internal standard reference. Peaks are reported on δ ppm scale down Field of TMS.

Chemistry

Following the reaction scheme, eighteen compounds were synthesized, characterized and evaluated for biological screening. 2-Amino-4-substitutedPhenyl-1-(2H) - Tetrazole(s) was reacted with substituted Phenyl isothiocynate (s) to generate N'-(4-substituted phenyl)-N"-1-(3-substituted Phenyl)-6-tetrazolyl)-Thiocarbamide (s) (I). Compound (I) under goes cyclization with mono chloro acetic acid in presence of anhydrous sodium acetate and acetic acid to form title 4-Thiazolidinone(s) (II) having tetrazole moiety.

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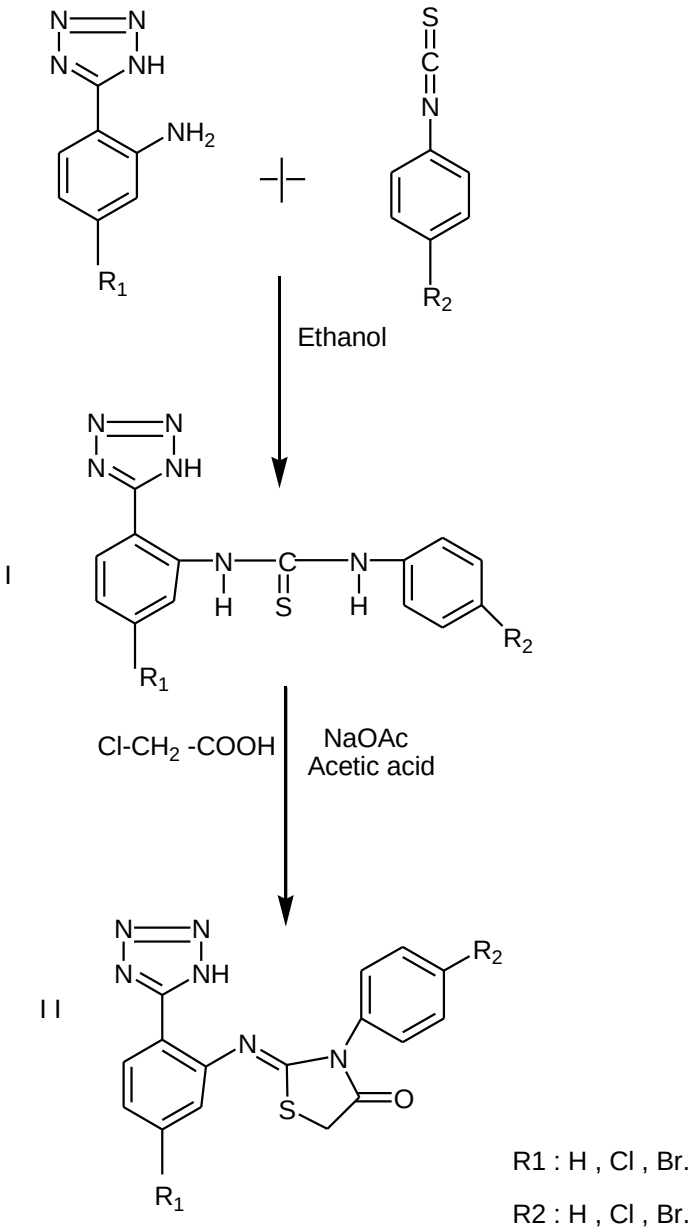
Reaction Scheme:



RESULTS AND DISCUSSION

In this study, 4-Thiazolisinones (II) were synthesized from 2-amino - 4-Substituted phenyl -1-(2H)-Tetrazole followed by respective Thiocarbamides (I) having tetrazole moiety. Synthesized 4- Thiazolidinones are screened against *E.coli* for their antibacterial activity by measuring the inhibition area. The results of antibacterial screening indicated that the good activity was shown by compound II-5, II- 6, II-8 and II-9.

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Experimental

N'-(4-bromophenyl)-N"-1-[(3'-chloro Phenyl)-6-tetrazolyl]-Thiocarbamide (s) (I):

Placed 2.0 gm (0.010moles) 2-amino - 4-Chlorophenyl-1-(2H)-Tetrazole in 100 ml RBF then added 30.0 gm ethanol. Started stirring after five minutes clear dark brown colored solution was observed, and then prepared solution of 4-Bromo phenyl isothiocynate, 2.2 gm, (0.01227moles) dissolved in 20.0 gm of ethanol. Then it was added drop wise to the reaction mass at 50 to 60°C. After complete addition, heating was raised, to reflux. Reflux is continued till the reaction completion. After completion of the reaction, the reaction mass was concentrated by distillation of ethanol (25gm) then cooled it to 10°C cream colored solid was isolated by filtration, solid washed with cold ethanol (5 gm). It was dried in drier at 50-55^{o} C for 2 hrs. Yield, MP and elemental analysis of all the synthesized compounds are recorded in Table 1.

Table No 1 : Elemental Analysis, Melting Point and Yield of Compound I-1 to I-9.

Compound No.	Substituent		MP	Yield	Molecular Formula	Elemental Analysis, Actual & (Theoretical)			
	R1	*R2*	*°C*	*%*		*C (%)*	*H (%)*	*N (%)*	*S (%)*
I-1	H	H	111	78	C14H12N6S	56.28 (56.75)	3.99 (4.05)	28.32 (28.37)	10.72 (10.81)
I-2	H	Cl	104	82	C14H11N6ClS	50.79 (50.83)	3.30 (3.32)	25.39 (25.41)	9.71 (9.68)
I-3	H	Br	121	81	C14H11N6BrS	44.82 (44.80)	2.88 (2.93)	22.39 (22.4)	8.49 (8.53)
I-4	Cl	H	126	68	C14H11N6ClS	50.79 (50.83)	3.31 (3.32)	25.42 (25.41)	9.67 (9.68)
I-5	Cl	Cl	132	74	C14H10N6Cl2S	45.99 (46.02)	2.70 (2.73)	23.05 (23.01)	8.72 (8.76)
I-6	Cl	Br	144	69	C14H10N6ClBrS	41.00 (41.02)	2.41 (2.44)	20.49 (20.51)	7.77 (7.81)
I-7	Br	H	133	72	C14H11N6BrS	44.84 (44.80)	2.90 (2.93)	22.41 (22.4)	8.50 (8.53)
I-8	Br	Cl	142	76	C14H10N6BrClS	41.04 (41.02)	2.39 (2.44)	20.47 (20.51)	7.79 (7.81)
I-9	Br	Br	129	69	C14H10N6Br2S	37.02 (37.00)	2.20 (2.20)	18.44 (18.50)	7.00 (7.04)

IR (cm-1): 620 (C-Cl), 1240 (C=S), 1589 (C=N), 3250 (=NH).
NMR (δ ppm): 3.35 (s, CH), 4.5(s, 2NH), 7.0-7.8(m, 8H, Aromatic Proton) and 11.2(s, NH)

4-Chloro phenyl-1-(2H)-Tetrazolyl-2-imino-[3-(4'-bromo phenyl)-4-Thiazolidinone] (II):

Placed in to 100 ml RBF, Compound (I) 1.0 gm, (0.002moles), 40 gm glacial acetic acid then stirring was started, clear solution was observed, then added 0.2 gm (0.0021moles) mono

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chloro acetic acid and anhydrous Zinc chloride 0.18 gm, (0.0021moles). The reaction mass was reflux for 8 hours then it was concentrated by vacuum distillation and left over reaction mass was poured on crushed ice. Obtained solid was filtered. Washed with cold water and recrystalised from ethanol. Yield, MP and elemental analysis of all the synthesized compounds are recorded in Table 2.

Table No 2: Elemental Analysis, Melting Point & Yield of Compound II-1 to II-9

Compound No.	Substituent		MP	Yield	Molecular Formula	Elemental Analysis, Actual &(Theoretical)				
	R1	*R2*	*°C*	*%*		*C (%)*	*H (%)*	*N (%)*	*O (%)*	*S (%)*
II-1	H	H	135	72	C16H12N6OS	57.18 (57.14)	3.54 (3.57)	24.88 (25.00)	4.78 (4.76)	9.60 (9.52)
II-2	H	Cl	158	76	C16H11N6ClOS	51.79 (51.82)	2.93 (2.96)	22.63 (22.67)	4.29 (4.31)	8.60 (8.63)
II-3	H	Br	177	88	C16H11N6BrOS	46.22 (46.26)	2.62 (2.65)	20.20 (20.24)	3.81 (3.85)	7.74 (7.71)
II-4	Cl	H	142	71	C16H11N6ClOS	51.80 (51.82)	2.91 (2.96)	22.62 (22.67)	4.33 (4.31)	8.66 (8.63)
II-5	Cl	Cl	164	74	C16H10N6Cl2OS	47.38 (47.40)	2.43 (2.46)	20.71 (20.74)	3.90 (3.95)	7.93 (7.90)
II-6	Cl	Br	155	70	C16H10N6ClBrOS	42.68 (42.71)	2.20 (2.22)	18.61 (18.68)	3.52 (3.55)	7.06 (7.11)
II-7	Br	H	162	68	C16H11N6BrOS	46.20 (46.26)	2.63 (2.65)	20.22 (20.24)	3.83 (3.85)	7.70 (7.71)
II-8	Br	Cl	167	71	C16H10N6BrClOS	42.68 (42.71)	2.20 (2.22)	18.64 (18.68)	3.52 (3.55)	7.09 (7.11)
II-9	Br	Br	182	74	C16H10N6Br2OS	38.82 (38.86)	2.00 (2.02)	16.92 (17.00)	3.20 (3.23)	6.42 (6.47)

IR (cm^{-1}): 620 (C-Cl), 704 (C-S-C), 1599 (C=N), 1772 (tert. amide =N-C-), 3250(=NH).
NMR (δ ppm): 4.1(s, 1H, CH), 4.4(d, 2H=CH2), 7.0-7.9 (m, 8H, Aromatic Protons), 9.3 (s, 1H, NH).

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