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SYNTHESIS, CHARACTERIZATION AND EVALUATION OF SOME NEW SUBSTITUTED 1,3,4-THIADIAZOLES FOR THEIR ANTIMICROBIAL ACTIVITIES

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ABSTRACT

1,2,4-Triazole substituted 1,3,4 – thiazodiazoles 2, 3 and 4 have been prepared from 4-amino-5-(4- chlorophenyl) -3-mercapto-1,2,4-Triazole1 by reaction with various reagents to synthesize a variety of novel heterocyclic system is described. The antimicrobial activity of newly synthesized have been evaluated against gram positive *Staphylococus aurens*, gram negative *Escherichia coli* and *Pseudomonas aeruginosa.* The antifungal activities were evaluated against *Aspergillus niger* and *Candida albicans* by neat samples and serial plate dilution method. The inhibitory concentration (MIC) of components 2 and 3 was found to be 1000µg/ml against *Escherichia coli* and *Pseudomonas aeruginosa* compound 3 and 4 showed activity against *Pseudomonas aeruginosa* and *Candida albicans.*

KEYWORDS: Thiadiazoles, 1,2,4-triazoles, Antimicrobial, Gram-Positive Bacteria, Gram-Negative Bacteria, Antifungal

1,3,4-Thiadiazoles hold wide variety of biological activities. A few of them which are worthy of mention are diuretic (Jain and Mishra 2004), CNS depressants (Mishra *et al.* 1990), hypoglycemic (Agarwal *et al.* 1986), antimicrobial (Zamani *et al.* 2004), anthelmintic (Husain and Kumar; 1992), antiviral (Pandey *et al.* 2003) and anticancer (Terzioglu and Gursoy; 2003) activities. Similarly, 1,2,4-triazoles are also reported to possess antimicrobial (Kidwai *et al.* 1997, Srivastava and Sen 1994, Uchil and Joshi 1999) , anticonvulsant (Kane *et al.* 1990), diuretic (Srivastava *et al.* 2002) activities. Keeping the above facts in mind, the author synthesized the compounds which contain both biolabile group in the same molecular framework to see the combined effect.

The reaction of 4-amino -5-(4-bromorophenyl)-3-mercapto -1,2,4 -triazole 1 with various reagents to afford a variety of novel heterocyclic system is described The products are characterized on the basis of elemental analyses and spectral data. The antimicrobial activity of newly synthesized compounds have been evaluated against gram-positive Staphylococcus aureus, gram-negative *Escherichia coli* and *Pseudomonas aeruginosa.* The antifungal activities were evaluated against *Aspergillus niger* and *Candida albicans* by neat samples and serial plate dilution method (Nakahara *et al.* 1977). The minimum inhibitory concentration (MIC) of compounds 2 and 3 was found to be 1000 ug / mL against *E.coli* and *P. aeruginosa*. Compound 3 and 4 showed activity against *P. aeruginosa* and *C. albicans*.

ANTIMICROBIAL ACTIVITY

The minimum inhibitory concentrations (MIC) of compounds 2 and 3 were determined by the microbroth dilution technique using Mueller - Hinton broth for bacteria, RPMI- 1640 medium for yeast strain. Serial two - fold dilutions ranging from 5000 to 4.9 µg / mL were prepared in media. Clotrimazole was used as reference powder for bacteria and yeast, respectively. The incoulum was prepared using a 4-7 hr broth culture of each bacteria and yeast strains adjusted to a turbidity equivalent to a 0.5 Mc Farland standard. The trays were covered and placed in plastic bags to prevent evaporation. The trays containing Mueller-Hinton broth were incubated at 35°C for 18-20 hr. and the trays containing RPMI-1640 medium were incubated at 35°C for 46-50 hr. The MIC was defined at the lowest concentration of compound giving complete inhibition of visible growth. The MIC of compound 2 and 3 was found to be 1000 ug / ML against E.coli and P. aeruginosa. Compounds 3 and 4 showed activity against C. albicans. The standard used was voriconazole.

EXPERIMENTAL SECTION

All melting points were taken in open capillary tubes and are uncorrected. The completion and purity of the synthesized compound were checked by TLC Silica gel-G was used for TLC. IR spectra were recorded on Perkin-Elmer-710 spectrophotometer in nujol and ' H NMR spectra were recorded on Perkin - Elmer R - 32 at 300 MHz.

4-Amino-5-(4-Chlorophenyl) -3-mercapto-1,2,4 -triazole 1. This compound has been prepared according to the method of Hoggrath et.al. m.p. 169°C) (Lit.m.p. 169°C)

5 -(4-brobophenyl) -2-(2,4 -dichlorophenoxy methyl) -1, 2, 4 -triazole-[3, 4-b]- 1 ,3,4-thiadiazole 2

A mixture of 1 (1.12g. 0.005 mole) and 2, 4-dichlorophenoxy acetic acid (1.1g. 0.005 mole) was taken in dichloromethane (10ml). The desired amount of DCC in CH_2 Cl_2 was added into it and strirred. After stirring this mixture was poured into water, solid mass were obtained which was filtered, washed, dried and crystallized from aq .ethanol .m.p. 1950 yield 69 %

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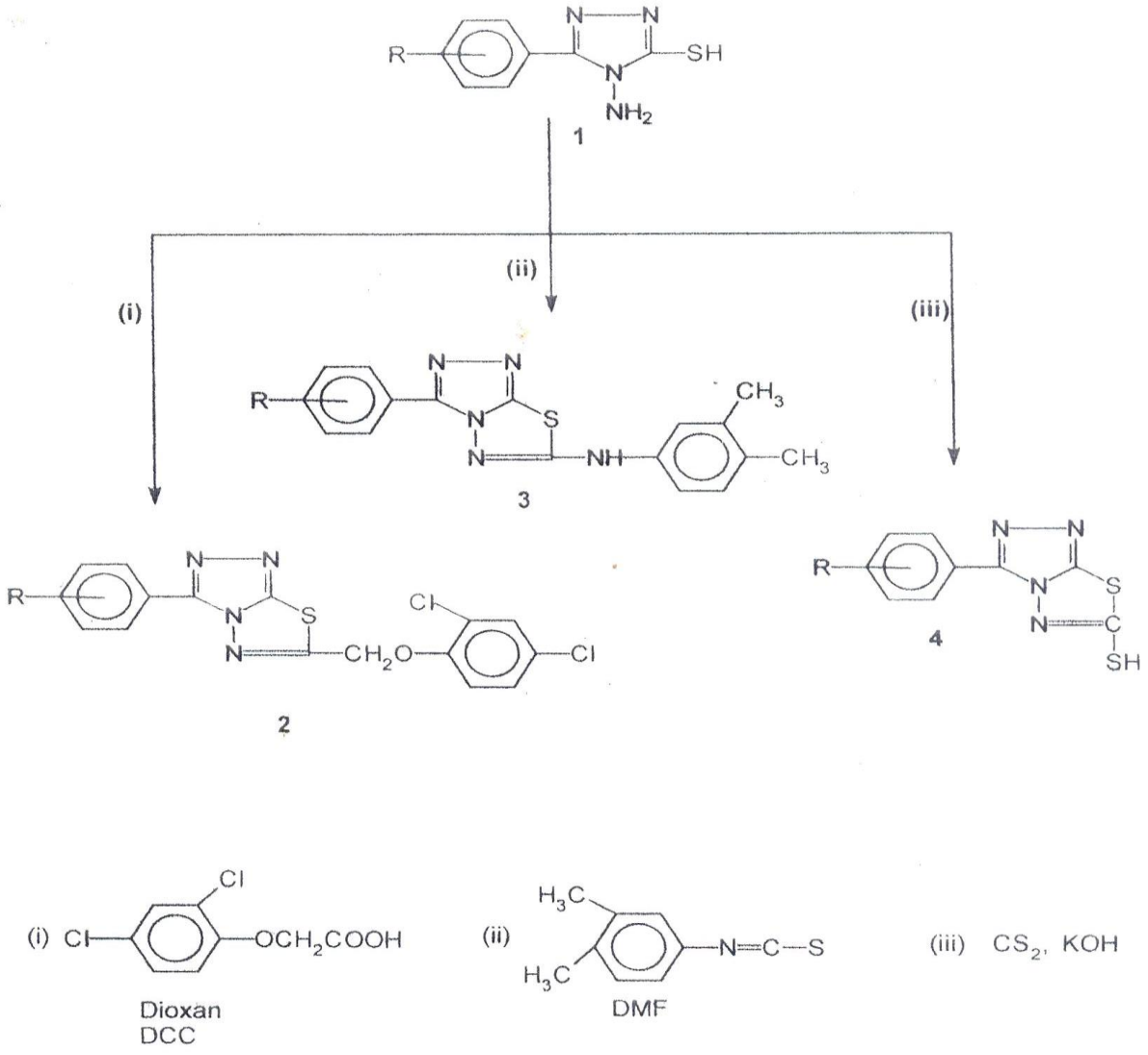
(Found:C, 46.45; H, 2.05 N. 13.42 . C_1 $8H_2$ N, SCI_2 O requires C, 46.65; H, 2.08; N , 13.65 % , IR (KBr) : 1350 (C-N), 1530, 1490, 1460 (C = C aromatic), 1580 (C = N), Cm¹, ¹HNMR (DMSO - d) . S 4.3(s , 2H , OCH_2) , 6.8-8.0 (m , 7H , Ar - H).

5- (4 -bromophenyl) -2 (3 , 4 - dimethyl phenyl) - amino1 , 2 , 4 - triazolo- [3 ,4-b] -1, 3, 4-thiadiazole 3

A mixture of 1 (1.12g., 0.005mole) and 3, 4 - dimethylphenyl isothiocyanate (0.7 ml, 0.005 mole) was refluxed in DMF for 14 hours. After refluxing, this mixture was poured into water. The compound thus precipitated was filtered, washed with water, dried and crystallized from aq. ethanol, m.p. 145°C, yield 50% (Found : C, 57.41' , H. 4.35 ', N. 1985 C , H_1 N SBr requires C. 57.61 ; H. 4.40 ' , N. 20.00 % ; IR (KBr) : 1540 , 1500 , 1460 , (C = C , Ar H) , 1600 (C = N), 2960 (C = H) , 3300 (N - H) ; ¹HNMR (DMSO - d S 2.1 (s , 6H , CH3) , 6.2-7.8 (m , 7H , Ar H) , S 9.7 (s , 1H , NH).

3-(4 - bromoophenyl) -6 -mercapto - 1,2,4 - triazolo- [3,4 - b) -1,3,4 - thiadiazole4

A mixture of 1 (1.12 g, 0.005 mole) and Carbon disulphide (4ml, 0.005 mole) in methanol (15.0 ml) and KOH (0.3g., 0.005 mole) was added in this mixture and refluxed for 6 hours. It was poured into water and neutralised by HCI. The solid thus obtained was filtered, washed with water, dried and crystallized from aq. ethanol, p.m. 132 ° C , yield 77 % (Found : C, 39.95; H, 1.68; N , 20.65. C_2 H_2 N_2 S_2 Brrequires C,40.22 ; H , 1.70 ; N , 20.85 %) ; IR (KBr) : 1530 , 1490 , 1450 (C = C,Ar-H) ,1580 (C = N) , 2550 (S - H) ; 1HNMR (DMSO - d6) : 6.8-7.6 (m, 4H, aromatic), signal for-SH could not be observed.



SCHEME I

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