SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF TRIAZOLE AND FUSED TRIAZOLE DERIVATIVES

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ABSTRACT

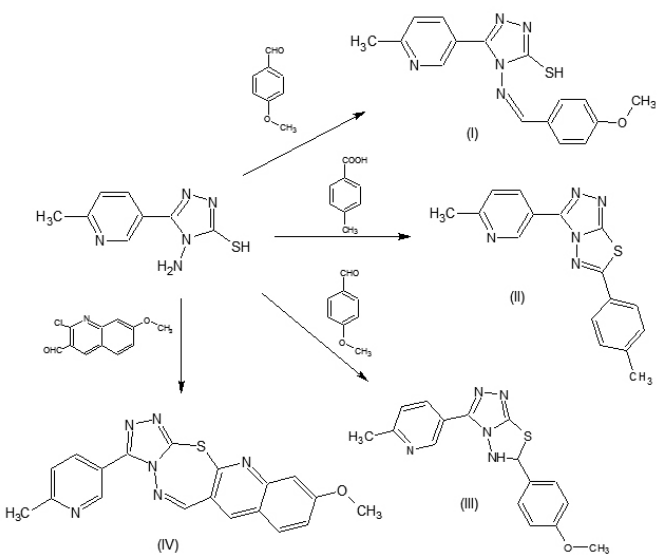
Triazole and fused heterocyclic triazole derivatives like Schiff bases, thiadiazoles, thiadiazepine, thiadiazine etc. were synthesized and characterized by IR, MS and ^{1}H NMR. The triazole derivatives were evaluated for their antibacterial activity against the gram-positive bacteria *B. megaterium* and *S. aureus*, the gram-negative bacteria *E. aerogenes* and *P. Aeruginosa* using DMSO as a solvent.

INTRODUCTION

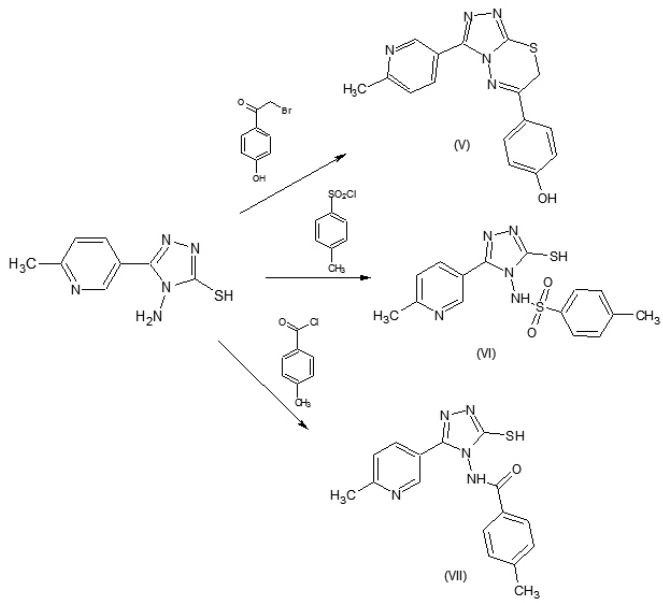
Heterocycles are in the center of research due to their versatile application[1]. The triazole ring system is of particular interest especially within the realm of medicinal chemistry because of their versatile biological activity and clinical applications[2,3]. A number of triazole derivatives are associated with good biological as well as pharmacological activities like antibacterial[4], anti-inflammatory[5], antihypertensive[6], antifungal[7], anticancer[8] and antitumor[9] activity. Fused heterocyclic triazoles also possess important clinical applications[10]. In addition to these important biological applications, 1,2,4-triazoles are also of great utility in preparative organic chemistry as well as they have useful applications in agriculture[11] and polymer[12] industries. Research in the field of pharmaceutical has its most important task in the development of new better drugs and their successful introduction into clinical practice due to bacterial resistance over old drugs and other effects. Owing such properties by triazole derivatives lead us to synthesise new derivatives and evaluate their antibacterial properties.

MATERIALS AND METHODS

All melting points were recorded in open capillaries and on Veergo melting point apparatus. The ^{1}H NMR spectra were recorded on a Bruker 300 MHz spectrometer at 300 MHz using TMS as an internal standard. The IR spectra were recorded on a Perkin Elmer Spectrum 100 FTIR spectrometer and the Mass spectra on a Waters Micromass Q-ft instrument. The chemicals used are of LR grade and were obtained from the local market.



Reaction scheme I



Reaction scheme II

Procedure for the synthesis of compound (I-VII)

Compound I : A mixture of 4-amino-5-(6-methylpyridin-3-yl)-4*H*-1,2,4-triazole-3-thiol(0.01M) and p-methoxy benzaldehyde (0.01M) was taken in ethanol(25 ml) and 2-3 drops of acetic acid was added and the reaction mixture was refluxed for 10 hours. The product (I) was isolated and crystallized by absolute alcohol. The resulting product dried and weighed.

Compound II : To a mixture of 4-amino-5-(6-methylpyridin-3-yl)-4*H*-1,2,4-triazole-3-thiol(0.01M) and P-toluic acid (0.01M) was added $POCl_3$ (25ml) and the reaction mixture was refluxed for 10 hours, poured on to crushed ice and the resulting solid was filtereda and washed with water. The resulting product (II) was crystallised from ethanol and then dried and weighed.

Compound III : To a mixture of 4-amino-5-(6-methylpyridin-3-yl)-4*H*-1,2,4-triazole-3-thiol(0.01M) and P-anisaldehyde(0.01M) in 50 ml dimethylformamide, 50 mg p-toluene sulphonic acid (p-TsOH) was added and the reaction mixture was refluxed for 10 hours, poured on to crushed ice and the resulting solid was filtered and washed with water. The resulting product (III) was crystallised from ethanol and then dried and weighed.

Compound IV : A mixture of 4-amino-5-(6-methylpyridin-3-yl)-4H-1,2,4-triazole-3-thiol (0.01M), 2-chloro-3-formyl-7-methoxy quinoline (0.01M) in dry DMF (20 ml) was added anhydrous K_2CO_3 (2.09 g) and refluxed at 80^{o}C for 4 hrs. It was cooled and poured onto crushed ice. The product (IV) was isolated and crystallised from ethanol and then dried and weighed.

Compound V : A mixture of 4-amino-5-(6-methylpyridin-3-yl)-4H-1,2,4-triazole-3-thiol (0.01M), p-hydroxy-phenacyl bromide (0.01M) in dry

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methanol (50 ml) was heated under reflux condition for 5 hrs, then cooled and neutralised with aqueous potassium carbonate solution. The product (V) was isolated and crystallised from ethanol and then dried and weighed.

Compound VI : A mixture of 4-amino-5-(6-methylpyridin-3-yl)-4H-1,2,4-triazole-3-thiol (0.01M) and p-toluene sulfonyl chloride (0.01M) was refluxed in dry pyridine for 4-5 hrs. Product (VI) was isolated and crystallised from ethanol and then dried and weighed.

Compound VII : A mixture of p-methylbenzoylchloride (0.01 mol) and 4-amino-5-(6-methylpyridin-3-yl)-4H-1,2,4-triazole-3-thiol (0.01 mol) was refluxed in dry pyridine for 8 hrs. Product (VII) was isolated and crystallised from ethanol and then dried and weighed.

Table 1 Characteristics and Yield of Synthesised compounds.

Compound code	Molecular formula	Molecular weight (g mol^{-1})	M.P. (^{o}C)	Yield (%)	R_f[a] value
Compound I	$C_{16}H_{15}N_5OS$	325.38	222	69	0.75
Compound II	$C_{16}H_{13}N_5S$	307.37	216	76	0.63
Compound III	$C_{16}H_{15}N_5OS$	325.38	187	69	0.64
Compound IV	$C_{19}H_{14}N_6OS$	374.41	150	77	0.54
Compound V	$C_{16}H_{13}N_5OS$	323.37	278	71	0.70
Compound VI	$C_{15}H_{15}N_5O_2S_2$	361.44	181	59	0.62
Compound VII	$C_{16}H_{15}N_5OS$	325.38	188	82	0.61

[a]Solvent Systems: Acetone:Benzene(2:8)

Preparation of Plates and Microbiological Assays

The in *vitro* antibacterial activity of the synthesised compounds was tested against some clinically important bacteria by the well diffusion method using Mueller-Hinton agar No.2 as the nutrient medium. Solutions of the synthesized compounds were prepared (10 mg ml^{-1}) in dimethylformamide. The bacterial strains were activated by inoculating a loop full of the test strain in to 25 ml of nutrient broth and incubated for 24 hrs in an incubator at 37 ^{o}C. The activated strain (0.2 ml) was inoculated in Mueller Hinton agar at 45 ^{o}C. It was then poured into Petri dishes and allowed to solidify, then 0.85 cm ditch was made in the plates using a sterile cork borer and these were completely filled with the compound solution. The dishes were incubated for 24 hrs at 37 ^{o}C. The experiment was repeated three times simultaneously under the same condition for each compound and the mean value obtained for three wells was used to calculate the inhibition zone growth. The controls were maintained for each bacterial strain with the solvent, where pure solvent was inoculated into the well. The inhibition zone, formed by the compounds against the particular bacterial strain was subtracted from the control, thereby determining the antibacterial activities of the triazole derivatives.

RESULTS AND DISCUSSION

Table 1 shows the molecular formula, molecular weight, melting point, percentage yield and R_f value of all synthesised compounds. The Elemental analysis, IR, NMR and Mass spectral data are given below.

Characterization of Compound I-VII

Compound I: Elemental analysis : found (calcd): C, 58.97(59.06); H, 4.61 (4.65); N, 21.45 (21.52); IR (KBr, cm^{-1}): 3006 (Ar-C-H str.), 2933 (-C-H str.), 1606 (-C=N str.), 1508 (-C=C str.), 1029 (-C-O-C str.), 690 (-C-S str.). MS: 325[M.]; ^{1}H NMR (ppm)($CDCl_3$): 13.81 (1H, singlet, -SH), 9.72 (1H, singlet, N=CH), 7.00-9.13 (7H, multiplet, Ar-H), 3.83 (3H, singlet, Ar-OCH_3), 2.65 (3H, singlet, Ar-CH_3).

Compound II: Elemental analysis : found (calcd): C, 62.42(62.52); H, 4.23 (4.26); N, 22.72 (22.78); IR (KBr, cm^{-1}): 3005 (Ar-C-H str.), 2849 (-C-H str.), 1611 (-C=N str.), 1485 (-C=C str.), 1256 (-C-N str.), 671 (-C-S str.). MS: 307[M.]; ^{1}H NMR (ppm)($CDCl_3$): 7.03-9.13 (7H, multiplet, Ar-H), 2.68 (3H, singlet, Ar-CH_3), 2.35 (3H, singlet, Ar-CH_3).

Compound III: Elemental analysis : found (calcd): C, 58.96(59.06); H, 4.62 (4.65); N, 21.47 (21.52); IR (KBr, cm^{-1}): 3234 (N-H str.), 2933 (-C-H str.), 1602 (-C=N str.), 1513 (-C=C str.), 1014 (-C-O-C str.), 676 (-C-S str.). MS: 325[M.]; ^{1}H NMR (ppm)($CDCl_3$): 9.72 (1H, singlet, S-CH), 7.02-9.13 (7H, multiplet, Ar-H), 5.76 (1H, singlet, -NH), 3.86 (3H, singlet, Ar-OCH_3), 2.68 (3H, singlet, Ar-CH_3).

Compound IV: Elemental analysis : found (calcd): C, 60.88(60.95); H, 3.73 (3.77); N, 22.40 (22.45); IR (KBr, cm^{-1}): 3001 (Ar-C-H str.), 2956 (-C-H str.), 1636 (-C=N str.), 1621 (triazole -C=N str.), 1588 (-C=C str.), 1069 (-C-O-C str.), 648 (-C-S str.). MS: 374[M.]; ^{1}H NMR (ppm)($CDCl_3$): 7.90-9.42 (4H, multiplet, Ar-H), 7.45 (1H, singlet, thiadiazepine-CH), 7.26-7.34 (3H, multiplet, Ar-H) 4.0 (3H, singlet, Ar-OCH_3).

Compound V: Elemental analysis : found (calcd): C, 59.34(59.43); H, 4.03 (4.05); N, 21.60 (21.66); IR (KBr, cm^{-1}): 3417 (-OH str.), 3066 (Ar-C-H str.), 2983 (-C-H str.), 1596 (-C=N str.), 1554 (-C=C str.), 1355 (-OH ben.), 1056 (N-N str.), 671 (-C-S str.). MS: 323[M.]; ^{1}H NMR (ppm)($CDCl_3$): 9.48 (1H, singlet, -OH), 7.01-9.14 (7H, multiplet, Ar-H), 4.26 (2H, singlet, S-CH_2), 2.65 (3H, singlet, Ar-CH_3).

Compound VI: Elemental analysis : found (calcd): C, 49.76(49.84); H, 4.15 (4.18); N, 19.34 (19.38); IR (KBr, cm^{-1}): 3410 (N-H str.), 3068 (Ar-C-H str.), 2934 (-C-H str.), 1588 (-C=N str.), 1497 (-C=C str.), 1310 (-SO_2 ben.), 1041 (N-N str.). MS: 361[M.]; ^{1}H NMR (ppm)($CDCl_3$): 14.00 (1H, singlet, -SH), 9.65 (1H, singlet, N-NH), 7.18-9.13 (7H, multiplet, Ar-H), 2.63 (3H, singlet, Ar-CH_3), 2.32 (3H, singlet, Ar-CH_3).

Compound VII: Elemental analysis : found (calcd): C, 58.99(59.06); H, 4.61 (4.65); N, 21.47 (21.52); IR (KBr, cm^{-1}): 3220 (N-H str.), 3062 (-C-H str.), 1685 (Amide-C=O str.), 1605 (-C=N str.), 1578 (-NH def.), 1020 (N-N str.). MS: 325[M.]; ^{1}H NMR (ppm)($CDCl_3$): 13.86 (1H, singlet, -SH), 9.72 (1H, singlet, N-NH), 7.16-9.13 (7H, multiplet, Ar-H), 2.65 (3H, singlet, Ar-CH_3), 2.33 (3H, singlet, Ar-CH_3).

Antibacterial Activity

Table 2 Antibacterial Activity of synthesised compounds.

Compound code	Antibacterial activity Zone of inhibition (mm)			
	B.megaterium	*S. aureus*	*E.aerogenes*	*P.aeruginosa*
compound I	21	19	14	15
compound II	14	19	14	18
compound III	14	15	14	17
compound IV	20	13	17	13
compound V	14	18	21	16
compound VI	14	21	14	19
Com-pound VII	14	21	14	19

The zones of inhibition of compounds are shown in Table 2. It can be concluded from the data that all compounds are moderately active against all tested bacterial strains. Compounds I and IV are the most active against *B. megaterium*, compounds VI and VII show the highest activity against *S. aureus* and *P.aeruginosa* and compounds IV and V are the most active against *E.aerogenes.*

CONCLUSION

Seven new triazole derivatives were synthesized. All of them showed moderate activity against all bacterial strains. Compounds I and IV were the most active against *B. megaterium*, while compounds VI and VII showed the highest activity against *S. aureus* and *P.aeruginosa* and compounds IV and V were the most active against *E.aerogenes.*

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