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Synthesis, Structure Elucidation and Biological Studies of 2-{[5-(4-fluorophenyl)-4-phenyl-4*H*-1,2,4-triazol-3-yl]sulfanyl}-*N*-arylacetamide derivatives

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ABSTRACT: A series of ten derivatives of titled compounds was designed and synthesized using appropriate route and structures of compounds were determined by FT-IR, ^{1}H NMR and Mass spectroscopy analysis. The synthesized compounds were evaluated for their *invitro* antibacterial potential using bacterial strain *Staphylococcus aureus, Bacillus subtilis, Pseudomonas aeruginosa* and Escherichia coli where some of the compounds showed their activeness against the strain.

Keywords: Triazole; acetamide and biological evaluation.

INTRODUCTION: Heterocyclic chemistry has vast literature in the subject of organic chemistry with millions of novel molecules. In these molecules 1,2,4-triazole nucleus have generated a different class among other triazole isomers due to its biological potential like antimicrobial,[1-4] anti-inflammatory,[5-7] anti HIV,[8-9] antioxidant,[10-12] anticonvulsant,[13-15] antitumor,[16-17] antiviral,[18] antitubecular[19-20] etc. In this work we have developed series of compounds clubbed with this 1,2,4-traizole nucleus having antibacterial strength.

MATERIAL AND METHODS: In this work all the compounds were derived using laboratory and analytical grade chemicals. An open capillary method was adopted for measurement of melting points of all synthesized compounds and is uncorrected. The progress of reaction and purity of compounds were observed by using TLC plates coated by 0.25 mm silica gel (E-Merk) and spots were visualized under UV light. The IR spectral analysis was carried by using KBr and recorded on Schimadzu FT-IR spectrophotometer. Mass spectra was recorded on Agilant 100 series instrument and ^{1}H NMR analysis was carried out on Bruker AM -400 MHz instrument using DMSO as solvent and TMS as internal standard.

General Procedure for Preparation of 2-{[5-(4-fluorophenyl)-4-phenyl-4*H*-1,2,4-triazol-3-yl]sulfanyl }-*N*-arylacetamide

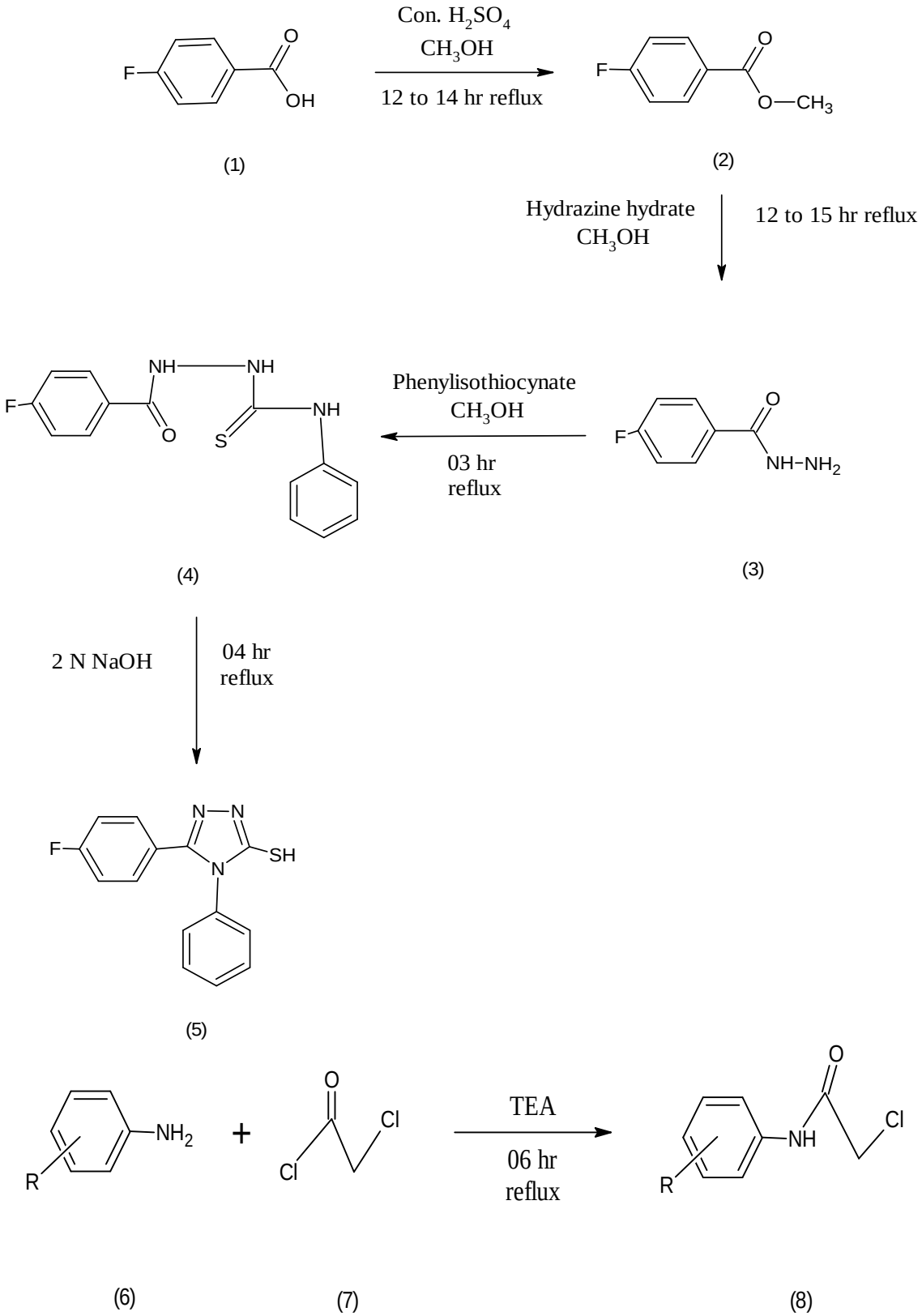
Step I: Synthesis of methyl 4-flouro benzoate (2) - In this step, 4-flouro benzoic acid (0.1 mole) in methanol (180 ml) and concentrated H_2SO_4 (6.0 ml) were refluxed for 12 to 14 hour. The resulting reaction mass was then poured into crushed ice, stirred well and separated from the reaction mass. The product was recrystallized by ethyl alcohol. The progress of reaction was monitored by TLC using toluene : acetone (8:2) as eluent.

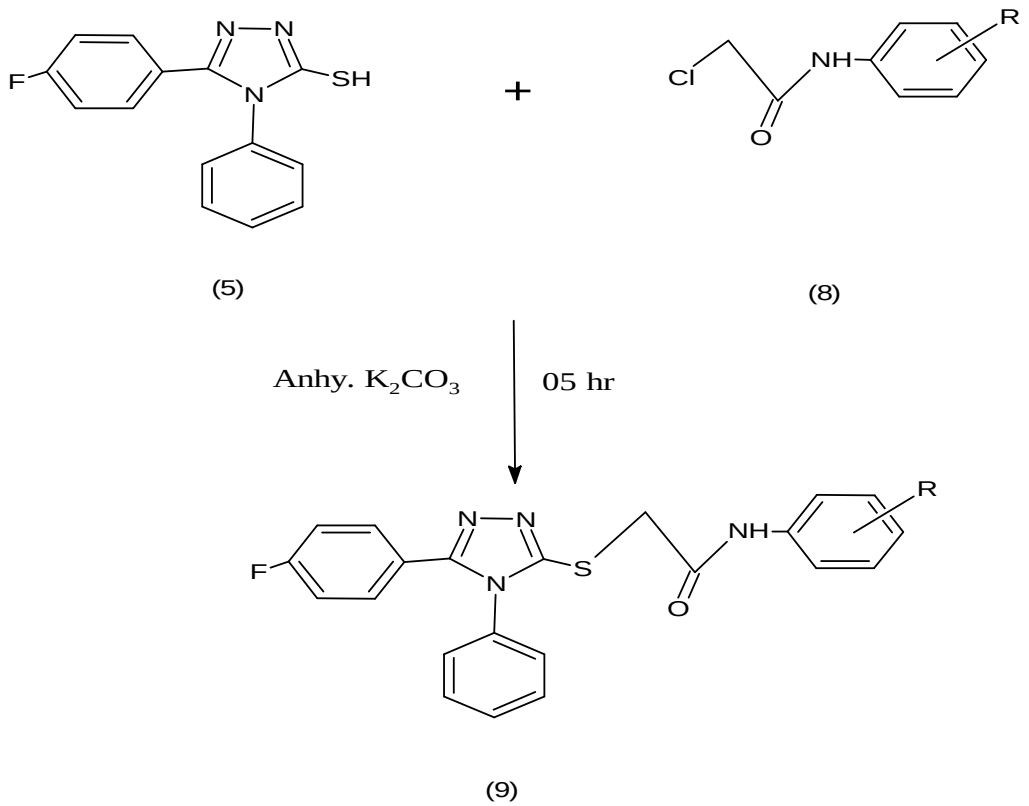
Step II: Synthesis of 4-fluorobenzohydrazide (3) - To synthesized the product 4-fluorobenzohydrazide, methyl 4-flouro benzoate (0.1 mole) and hydrazine hydrate (0.2 mole) were taken in (180 ml) methyl alcohol and refluxed for 12 to 15 hour then reaction mass was poured into crushed ice, stirred well, separated and washed by cold water. The product was recrystallized by ethyl alcohol. The progress of reaction was monitored by TLC using toluene : acetone (8:2) as eluent.

Step III: Synthesis of 2-(4-fluorobenzoyl)-*N*-phenylhydrazinecarbothioamide (4) - The mixture of 4-flourobenzohydrazide (0.1 mole) and phenyl isothiocynate (0.1 mole) were refluxed in (120 ml)

methyl alcohol for 03 hour. The resulting mass was then poured into crushed ice, stirred well, filtered and washed by cold water. The product was recrystallized by ethyl alcohol. The progress of reaction was monitored by TLC using toluene: acetone (8:2) as eluent.

Reaction Scheme





[R = a) 4-CH_3, b) 2-NO_2, c) 4-Br, d) –H, e) 2-Cl, f) 4-$COCH_3$, g) 4-Cl, h) 4-NO_2, i) 2-Br, j) 2,4,6-Cl]

Step IV: Synthesis of 5-(4-fluorophenyl)-4-phenyl-4*H*-1,2,4-triazole-3-thiol (5) - The 5-(4-fluorophenyl)-4-phenyl-4*H*-1,2,4-triazole-3-thiol was obtained by refluxing 2-(4-fluorobenzoyl)-*N*-phenylhydrazinecarbothioa-mide (0.05 mole) in 2N NaOH (80 ml) for 04 hour. The obtained reaction mass was then poured into crushed ice, neutralized by 2N HCl. The obtained precipitates were filtered and washed by cold water. The product was recrystallized by ethyl alcohol. The progress of reaction was monitored by TLC using toluene: acetone (8:2) as eluent.

Step V: Synthesis of 2-chloro-*N*-arylacetamide (8) - The mixture of chloro acetyl chloride (0.1 mole), 2-4 drop of TEA and (0.1 mole) various aromatic amine was taken in (150 ml) toluene, the reaction mass was then refluxed for 06 hour. The resulting product was then separated from the reaction mass and washed. The product was recrystallized by ethyl alcohol. The progress of reaction was monitored by TLC using toluene : acetone (8:2) as eluent.

Step VI: 2-{[5-(4-fluorophenyl)-4-phenyl-4*H*-1,2,4-triazol-3-yl]sulfanyl}-*N*-arylacetamide (9) - The mixture of 2-chloro-*N*-arylacetamide (0.1 mole), 5-(4-fluorophenyl)-4-phenyl-4*H*-1,2,4-triazole-3-thiol (0.1 mole) and anhydrous K_2CO_3 (0.2 mole) were taken in dry acetone (70 ml) and stirred for 05 hour. The reaction mixture was then poured into crushed ice, stirred well, filtered and washed by cold water. The products were recrystallized by ethyl alcohol. The progress of reaction was monitored by TLC using toluene: acetone (8:2) as eluent.

Characterization:

9a: 2-{[5-(4-fluorophenyl)-4-phenyl-4*H*-1,2,4-triazol-3-yl]sulfanyl}-*N*-(4-methylphenyl)acetamide

Yield 69%, m.p. 192-194˚ C, FT-IR (KBr):1327 (C-F), 1481 (-C=C-), 1608 (-C=N-), 1680 (-C=O), 2927 (-CH_2-), 3286 (-NH-); ^{1}H NMR (400 MHz, DMSO-d_6) : δ 2.24 (s, 3H, -CH_3), δ 4.18 (s, 2H, -CH_2-), δ 7.10-7.12 (s. 2H, Ar-H), δ 7.19-7.23 (t, 2H, Ar-H), δ 7.37-7.46 (m, 5H, Ar-H), δ 7.55-7.56 (m, 4H, Ar-H), δ 10.29 (s, 1H, -NH-), MS : m/z 419, Anal. Calcd for $C_{23}H_{19}FN_4OS$: C-66.01, H-4.58, N-13.39, S-7.66 Anal. Found C-65.98, H-4.54, N-13.37, S-7.63%.

9b: 2-{[5-(4- fluorophenyl)-4-phenyl-4*H*-1,2,4-triazol-3-yl]sulfanyl}-*N*-(2-nitrophenyl)acetamide

Yield 61%, m.p. 165-167˚ C, FT-IR (KBr):1349 (C-F), 1463 (-C=C-), 1572 (-C=N), 1669 (-C=O), 2832 (-CH_2-), 3212 (-NH-); ^{1}H NMR (400 MHz, DMSO-d_6) : δ 4.29 (s, 2H, -CH_2-), δ 7.04-7.08 (s. 2H, Ar-H), δ 7.22-7.26 (t, 2H, Ar-H), δ 7.36-7.44 (m, 5H, Ar-H), δ 7.62-7.66 (m, 2H, Ar-H), δ 7.77-7.81 (m, 2H, Ar-

H), δ 10.18 (s, 1H, -NH-), MS : m/z 451, Anal. Calcd for $C_{22}H_{16}FN_5O_3S$: C-58.79, H-3.59, N-15.58, S-7.13 Anal. Found C-58.82, H-3.62, N-15.60, S-7.16 %.

9c: 2-{[5-(4- fluorophenyl)-4-phenyl-4*H*-1,2,4-triazol-3-yl]sulfanyl}-*N*-(4-bromophenyl)acetamide

Yield 71%, m.p. 172-174˚ C, FT-IR (KBr) :651 (C-Br),1349(C-F), 1452 (-C=C-), 1593 (-C=N), 1686 (-C=O), 2873 (-CH_2-), 3257 (-NH-); ^{1}H NMR (400 MHz, DMSO-d_6) : δ 4.38 (s, 2H, -CH_2-), δ 7.19-7.23 (s. 2H, Ar-H), δ 7.31-7.35 (t, 2H, Ar-H), δ 7.47-7.53 (m, 5H, Ar-H), δ 7.68-7.72 (m, 2H, Ar-H), δ 7.89-7.93 (m, 2H, Ar-H), δ 10.34 (s, 1H, -NH-), MS : m/z 485, Anal. Calcd for $C_{22}H_{16}FBrN_4OS$: C-54.67, H-3.34, N-11.59, S-6.63 Anal. Found C-54.65, H-3.31, N-11.57, S-6.60%.

9d: 2-{[5-(4-fluorophenyl)-4-phenyl-4*H*-1,2,4-triazol-3-yl]sulfanyl}-*N*-phenylacetamide

Yield 73%, m.p. 196-198 ˚ C, FT-IR (KBr): 1321(C-F), 1462 (-C=C-), 1588 (-C=N), 1680 (-C=O), 2887 (-CH_2-), 3271 (-NH-); ^{1}H NMR (400 MHz, DMSO-d_6) : δ 4.29 (s, 2H, -CH_2-), δ 7.16-7.20 (s. 2H, Ar-H), δ 7.28-7.32 (t, 2H, Ar-H), δ 7.43-7.51 (m, 5H, Ar-H), δ 7.65-7.71 (m, 3H, Ar-H), δ 7.82-7.86 (m, 2H, Ar-H), δ 10.29 (s, 1H, -NH-), MS : m/z 405, Anal. Calcd for $C_{22}H_{17}FN_4OS$: C-65.33, H-4.24, N-13.85, S-7.93 Anal. Found C-65.31, H-4.23, N-13.82, S-7.90 %.

9e: 2-{[5-(4-fluorophenyl)-4-phenyl-4*H*-1,2,4-triazol-3-yl]sulfanyl}-*N*-(2-chlorophenyl)acetamide

Yield 64%, m.p. 157-159 ˚ C, FT-IR (KBr):669 (C-Cl), 1353 (C-F), 1481 (-C=C-), 1582 (-C=N), 1682 (-C=O), 2875 (-CH_2-), 3253 (-NH-); ^{1}H NMR (400 MHz, DMSO-d_6) : δ 4.17 (s, 2H, -CH_2-), δ 7.03-7.07 (s. 2H, Ar-H), δ 7.19-7.25 (t, 2H, Ar-H), δ 7.37-7.46 (m, 5H, Ar-H), δ 7.56-7.62 (m, 2H, Ar-H), δ 7.76-7.80 (m, 2H, Ar-H), δ 10.22 (s, 1H, -NH-), MS : m/z 440, Anal. Calcd for $C_{22}H_{16}FClN_4OS$: C-60.20, H-3.67, N-12.77, S-7.30 Anal. Found C-60.16, H-3.66, N-12.76, S-7.26 %.

9f: 2-{[5-(4- fluorophenyl)-4-phenyl-4*H*-1,2,4-triazol-3-yl]sulfanyl}-*N*-(4-acetylphenyl)acetamide

Yield 69%, m.p. 183-185˚ C, FT-IR (KBr):1355(C-F), 1463 (-C=C-), 1591 (-C=N), 1681 (-C=O), 2876 (-CH_2-), 3253 (-NH-); ^{1}H NMR (400 MHz, DMSO-d_6) : δ 3.29 (s, 3H, -$COCH_3$) , δ 4.28 (s, 2H, -CH_2-), δ 7.09-7.13 (s. 2H, Ar-H), δ 7.25-7.27 (t, 2H, Ar-H), δ 7.39-7.47 (m, 5H, Ar-H), δ 7.60-7.64 (m, 2H, Ar-H), δ 7.78-7.82 (m, 2H, Ar-H), δ 10.43 (s, 1H, -NH-), MS : m/z 447, Anal. Calcd for $C_{24}H_{19}FN_4O_2S$: C-64.56, H-4.29, N-12.55, S-7.18 Anal. Found C-64.55, H-4.27, N-12.51, S-7.16 %.

9g: 2-{[5-(4-fluorophenyl)-4-phenyl-4*H*-1,2,4-triazol-3-yl]sulfanyl}-*N*-(4-chlorophenyl)acetamide

Yield 73%, m.p. 176-178˚ C, FT-IR (KBr): 658 (C-Cl), 1340 (C-F), 1477 (-C=C-), 1596 (-C=N), 1674 (-C=O), 2889 (-CH_2-), 3247 (-NH-); ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.22 (s, 2H, -CH_2-), δ 7.13-7.15 (s. 2H, Ar-H), δ 7.22-7.26 (t, 2H, Ar-H), δ 7.41-7.48 (m, 5H, Ar-H), δ 7.53-7.57 (m, 2H, Ar-H), δ 7.69-7.73 (m, 2H, Ar-H), δ 10.36 (s, 1H, -NH-), MS : m/z 440, Anal. Calcd for $C_{22}H_{16}FClN_4OS$: C-60.20, H-3.67, N-12.77, S-7.30 Anal. Found C-60.18, H-3.63, N-12.74, S-7.28 %.

9h: 2-{[5-(4- fluorophenyl)-4-phenyl-4*H*-1,2,4-triazol-3-yl]sulfanyl}-*N*-(4-nitrophenyl)acetamide

Yield 68%, m.p. 177-179˚ C, FT-IR (KBr):1338(C-F), 1459 (-C=C-), 1587 (-C=N), 1673 (-C=O), 2881, (-CH_2), 3269 (-NH-); ^{1}H NMR (400 MHz, DMSO-d_6) : δ 4.31 (s, 2H, -CH_2-), δ 7.14-7.18 (s. 2H, Ar-H), δ 7.29-7.33 (t, 2H, Ar-H), δ 7.43-7.49 (m, 5H, Ar-H), δ 7.71-7.75 (m, 2H, Ar-H), δ 7.85-7.89 (m, 2H, Ar-H), δ 10.43 (s, 1H, -NH-), MS : m/z 451, Anal. Calcd for $C_{22}H_{16}FN_5O_3S$: C-58.79, H-3.59, N-15.58, S-7.13 Anal. Found C-58.82, H-3.62, N-15.60, S-7.16 %.

9i: 2-{[5-(4- fluorophenyl)-4-phenyl-4*H*-1,2,4-triazol-3-yl]sulfanyl}-*N*-(2-bromophenyl)acetamide

Yield 66%, m.p. 154-156˚ C, FT-IR (KBr): 682 (C-Br),1373(C-F), 1461 (-C=C-), 1601 (-C=N), 1681 (-C=O), 2857, (-CH_2-), 3263 (-NH-); ^{1}H NMR (400 MHz, DMSO-d_6) : δ 4.32 (s, 2H, -CH_2-), δ 7.15-7.19 (s. 2H, Ar-H), δ 7.29-7.33 (t, 2H, Ar-H), δ 7.41-7.49 (m, 5H, Ar-H), δ 7.57-7.63 (m, 2H, Ar-H), δ 7.78-7.82 (m, 2H, Ar-H), δ 10.29 (s, 1H, -NH-), MS : m/z 485, Anal. Calcd for $C_{22}H_{16}FBrN_4OS$: C-54.67, H-3.34, N-11.59, S-6.63 Anal. Found C-54.63, H-3.32, N-11.56, S-6.59%.

9j: 2-{[5-(4-fluorophenyl)-4-phenyl-4*H*-1,2,4-triazol-3-yl]sulfanyl}-*N*-(2,4,6-trichlorophenyl)acetamide

Yield 67%, m.p. 186-188˚ C, FT-IR (KBr): 673 (C-Cl), 1348 (C-F), 1487 (-C=C-), 1579 (-C=N), 1693 (-C=O), 2867, (-CH_2-), 3247 (-NH-); ^{1}H NMR (400 MHz, DMSO-d_6) : δ 4.26 (s, 2H, -CH_2-), δ 7.12-7.16 (s. 2H, Ar-H), δ 7.29-7.33 (t, 2H, Ar-H), δ 7.51-7.59 (m, 5H, Ar-H), δ 7.65-7.67 (d, 1H, Ar-H), δ 7.73-7.75 (m, 1H, Ar-H), δ 10.37 (s, 1H, -NH-), MS : m/z 509, Anal. Calcd for $C_{22}H_{14}FCl_3N_4OS$: C-52.04, H-2.78, N-11.03, S-6.31 Anal. Found C-52.01, H-2.74, N-10.99, S-6.29 %.

Biological Evaluation: In the antibacterial examination of synthesized compounds a convenient disc dif-

fusion technique was selected among different methods in which *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and Escherichia coli were selected as bacterial strain, DMSO was selected as solvent and nutrient agar as culture media. The study was carried out at different concentration and measurement of zone of inhibition was done after 24 hour of incubation at 37 ^{o}C. In this study an effective streptomycin drug was selected as standard antibacterial agent and obtained results are mentioned in the following table. The antibacterial evaluation of synthesized compounds reveals that compounds 9a, 9c, 9g and 9j possess high antibacterial potential against all bacterial strength compared with used antibacterial agent while other compounds possess poor antibacterial strength and 9b and 9h were found to be inactive against different bacterial strain.

Table I: Antibacterial screening of synthesized compounds.

Comp. Code	Gram Positive Bacteria				Gram Negative Bacteria			
	Staphylococcus aureus		*Bacillus subtilis*		*Staphylococcus aureus*		*Bacillus subtilis*	
	Zone of Inhibition (mm)	MIC (µg/ml)	Zone of Inhibition (mm)	MIC (µg/ml)	Zone of Inhibition (mm)	MIC (µg/ml)	Zone of Inhibition (mm)	MIC (µg/ml)
9a	7	25	7	25	8	12.5	9	>12.5
9b	19	12.5	--	--	18	100	16	25
9c	7	12.5	8	12.5	7	25	10	50
9d	17	12.5	18	12.5	18	12.5	14	25
9e	13	12.5	14	12.5	19	12.5	16	12.5
9f	16	12.5	15	12.5	18	12.5	9	12.5
9g	8	12.5	9	12.5	8	25	7	12.5
9h	18	25	--	12.5	18	50	--	12.5
9i	13	25	15	12.5	17	50	10	12.5
9j	10	12	11	100	8	50	10	50
Standard antibacterial agent	12	>12.5	13	>12.5	16	>12.5	13	>12.5

CONCLUSION: The structures of all synthesized compounds were well supported by spectroscopy analysis data. In the antibacterial study the derivatives were subjected for their antibacterial evaluation where some of the compounds found to have excellent antibacterial potential.

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