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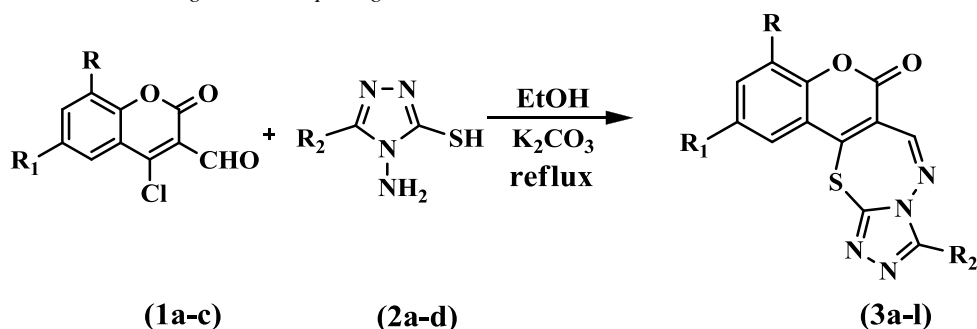
A Novel One Pot Facile Synthesis of 1,2,4-Triazolo-1,3,4-Thiadiazepino Fused Coumarins and Their Antimicrobial and Antituberculosis Activity Studies

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ABSTRACT

A novel series of [1,2,4]triazolo[3',4':2,3][1,3,4]thiadiazepino[7,6-b]coumarins (3a-l) was synthesized by the reaction of appropriate 4-chloro 3-formyl coumarins (1a-c) with various 4-amino-5-substituted-3-mercapto-1,2,4-triazoles (2a-d) in ethanol in the presence of a catalytic amount of K_2CO_3 under refluxing conditions. The structures of the synthesized compounds were established by elemental analysis and spectral data like IR, 1H -NMR, ^{13}C -APT and mass analysis. The synthesized compounds were screened for their antimicrobial and antituberculosis activity. Among all the synthesized compounds, the compounds 3a, 3e, 3j and 3k were found to be more active against tested pathogens.



Keywords: 3-mercapto-1,2,4-triazole, 1,3,4-thiadiazepines, Coumarins, Antituberculosis, Antifungal activity

INTRODUCTION

1,2,4-Triazoles, a five member heterocyclic compounds with three nitrogen atom in the ring are best known class of triazoles and these compounds have drawn a special attention due to their promising biological activities such as antimicrobial [1], anti-inflammatory [2], antiviral [3], analgesic [4] and anticancer [5]. In addition to these important biological applications, 4-amino-1,2,4-triazole-3-thiols are also of greater utility in the preparation of organic compounds by heterocyclization. The amino and mercapto groups are ready-made nucleophilic centers for the synthesis of condensed heterocyclic rings such as triazolothiadiazoles, triazolothiadiazines, triazolotetrazines and triazolothiadiazepines [6,7].

From the literature survey, it is revealed that 1,3,4-thiadiazepines are better therapeutic agents due to the presence of the $-N=C-S$ group. Various groups of researcher have reported their outstanding biological activities such as, antiviral [8], antimicrobial [9], antitumor [10], antidepressant [11], anticonvulsant [12], anti HIV [13], anti-inflammatory [14] and antifungal [15]. These compounds

are not only known for their potent biological activity but they are also known for their excellent charge generating property [16].

During past few decades, considerable reports are documented in literature for the efficiency of triazolo thiadiazepines as good therapeutic agents. They are found to possess good to excellent *in vitro* antibacterial [17], antifungal [18] and antitubercular activity [19]. Based on these compounds many potential drugs have been documented, particularly in cancer and virus research [20,21].

During our literature survey on the further fusion of triazolo thiadiazepines with other heterocycle we noticed that researcher have reported various furano fused triazolo thiadiazepines [22] benzopyrano fused triazolo thiadiazepines [23], quinolino fused triazolo thiadiazepines [24], hydrazono triazolo thiadiazepines [25], pyrazolo fused triazolo thiadiazepines [26]. All these heterocyclic fused compounds are also reported to have excellent biological activities. The survey also revealed that so far no chemists have made efforts to synthesize triazolo thiadiazepino fused coumarins and therefore in the present work it was thought worthwhile to synthesize triazolo thiadiazepino fused coumarins via simple condensation reaction and therefore herein we report synthesis of various [1,2,4]triazolo-[3',4':2,3][1,3,4]-thiadiazepino[7,6-b]coumarins.

EXPERIMENTAL

All the melting points are uncorrected. All reactions were performed with commercially available reagents and they were used without further purification. Organic solvents were purified by standard methods and stored over molecular sieves. All the IR spectra (KBr disc) were recorded on Shimadzu FT-IR 8400-S spectrometer. ¹H-NMR and ¹³C APT spectra were recorded on Bruker Advance 400 spectrometer operating at 400 MHz for ¹H-NMR and 100 MHz for ¹³C-APT. The chemical shift (δ) is reported in ppm using chloroform-d as a solvent and calibrated standard solvent signal. Mass spectra were recorded on Shimadzu QP 2010 spectrometer. Elemental analysis was carried out on Perkin-Elmer 2400 C-H-N-S-O Analyzer Series-II. Column chromatography was performed with silica gel 60-120 mesh (Merck, Mumbai, India.). All the compounds were routinely checked for completion of the reaction on silica gel 60 F254 TLC plates and their spots were visualized by exposure to a UV lamp, iodine vapour or KMnO₄ reagents.

General method for the synthesis of [1,2,4]triazolo[3',4':2,3][1,3,4]thiadiazepino[7,6-b]coumarins(3a-l)

A solution of appropriate 4-amino-5-substituted-3-mercapto-1,2,4-triazoles (0.025 mol) (2a-d) in ethanol (5 ml) was taken in 100 ml round bottom flask. To this catalytical amount of K₂CO₃ (0.03 mol) was added and stirred for 30 min at room temperature. The after an appropriate 4-chloro-3-formyl coumarin (1a-c) (0.025 mol) in ethanol (15 mL) was added dropwise followed by addition of 2-3 drops of acetic acid to above well stirred solution during 10 min at room temperature. The reaction mixture was then refluxed for 10 min and further stirred at room temperature for two hrs. The solid obtained was filtered out and washed with hexane and dried. The compounds were obtained as yellowish colored solid, which were recrystallized from chloroform-hexane.

The structure of all the synthesized compounds (3a-l) were confirmed by their analytical and spectral data like IR, ¹H-NMR, ¹³C-APT, elemental analysis and representative mass spectral data given below.

3-Methyl-[1,2,4]triazolo[3',4':2,3][1,3,4]thiadiazepino[7,6-b]coumarins(3a)

Yellow solid, Yield= 85%; M.P; 198-201 Anal. Calcd. For C₁₃H₈N₄O₂S: C, 54.92; H, 2.84; N, 19.71, %. Found: C, 54.90; H, 2.80; N, 19.69 %. IR (KBr, ν_{max}, cm⁻¹); 756(C-S-C Stretching), 1714 (C=O stretching of δ-lactone of coumarin), 1586 (aromatic C=C stretching), 1476 (aromatic C=N stretching), 2852(aliphatic C-H Stretching), 3043 (aromatic C-H stretching). ¹H NMR (400MHz, CDCl₃, δ): 2.47 (3H, s, CH₃), 7.20-8.39 (5H, m, aromatic protons). ¹³C APT (100MHz, CDCl₃, δ): 20.88 (CH₃), 112.80 (C), 113.76(C), 115.83(C), 117.54 (C), 125.24(CH), 128.77(CH), 130.48(CH), 134.98(CH), 136.63(C), 138.50(CH), 155.90(C), 160.43(CO of coumarin). The mass spectrum of compound showed M⁺ peak at 284 (18%) (m/z%) along with some other fragments peaks at 257(23%), 77(12%), 57(11%), 44(100%) etc. The appearance of molecular ion peak at 284 mass unit supports the structure of compound 3a.

3,9-Dimethyl-[1,2,4]triazolo[3',4':2,3][1,3,4]thiadiazepino[7,6-b]coumarins (3b)

Yellow solid; yield=75%; mp 193-196°C; Anal. Calcd. For C₁₄H₁₀N₄O₂S: C, 56.34; H, 3.36; N, 18.78%. Found: C, 56.37; H, 3.38; N, 18.75%. IR (KBr, ν_{max}, cm⁻¹); 750(C-S-C Stretching), 1714 (C=O stretching of δ-lactone of coumarin), 1586 (aromatic C=C stretching), 1476 (aromatic C=N stretching), 2852(aliphatic C-H Stretching), 3043 (aromatic C-H stretching). ¹H NMR (400 MHz, CDCl₃, δ): 2.64 (6H, s, 2 × CH₃), 7.33-8.42 (4H, m, Ar-H). ¹³C APT (100MHz, CDCl₃, δ): 20.85 (CH₃), 23.14 (CH₃), 115.14(C), 117.85(CH), 119.40(C), 123.15(C) 124.55(CH), 128.05(C), 129.45 (CH), 131.51 (CH), 135.95(C), 138.43(C), 152.80(C), 162.61 (CO of coumarin).

3-Methyl-9-Chloro-[1,2,4]triazolo[3',4':2,3][1,3,4]thiadiazepino[7,6-b]coumarins (3c)

Pale yellow solid; yield=79%; mp 200-202°C; Anal. Calcd. For C₁₃H₇N₄O₂SCl: C, 48.99; H, 2.21; N, 11.12%. Found: C, 48.96; H, 2.18; N, 11.08%. IR (KBr, ν_{max}, cm⁻¹); 752(C-S-C Stretching), 1719 (C=O stretching of δ-lactone of coumarin), 1584 (aromatic C=C stretching), 1473 (aromatic C=N stretching), 2854 (aliphatic C-H Stretching), 3041 (aromatic C-H stretching). ¹H NMR (400MHz, CDCl₃, δ): 2.35 (3H, s, CH₃), 7.33-8.38 (4H, m, Ar-H). ¹³C APT (100MHz, CDCl₃, δ): 20.95 (CH₃), 115.34(C), 117.35(CH), 119.50(C), 123.25(C), 125.55(CH), 128.69(C), 129.99(CH), 131.25(C), 134.95(C), 138.43(CH), 157.80(C), 161.81(CO of coumarin).

3-Phenyl-[1,2,4]triazolo-[3',4':2,3][1,3,4]-thiadiazepino[7,6-b]coumarins (3d)

Pale yellow solid; yield=79%; mp 212-214°C; Anal. Calcd. For C₁₈H₁₀N₄O₂S: C, 62.42; H, 2.91; N, 16.18 %. Found: C, 62.40; H, 2.89; N, 16.13%. IR (KBr, ν_{max}, cm⁻¹); 756(C-S-C Stretching), 1715 (C=O stretching of δ-lactone of coumarin), 1585 (aromatic

C=C stretching), 1476 (aromatic C=N stretching), 3045 (aromatic C-H stretching). ¹H NMR (400 MHz, CDCl₃, δ): 7.21-8.95 (10H, m, Ar-H). ¹³C APT (100 MHz, CDCl₃, δ): 114.55(C), 115.60(C), 115.65(C), 117.12(CH), 124.05(CH), 125.36(CH), 125.99(CH), 128.95(CH), 129.55(C), 130.01(CH), 133.70(CH), 141.94(C), 143.56(C), 150.88(C), 156.66(C), 161.56(CO of coumarin).

3-Phenyl-9-methyl-[1,2,4]triazolo-[3',4':2,3][1,3,4]-thiadiazepino[7,6-b]coumarins (3e)

Pale yellow solid; yield=75%; mp 230-232°C; Anal. Calcd. For C₁₉H₁₂N₄O₂S: C, 63.32; H, 3.36; N, 15.55 %. Found: C, 62.32; H, 3.35; N, 15.50%. IR (KBr, ν_{max}, cm⁻¹); 751(C-S-C Stretching), 1719 (C=O stretching of δ-lactone of coumarin), 1581 (aromatic C=C stretching), 1475 (aromatic C=N stretching), 2956 (aliphatic C-H stretching), 3041 (aromatic C-H stretching). ¹H NMR (400MHz, CDCl₃, δ): 2.34(3H, s, CH₃) 7.30-8.52 (9H, m, Ar-H). ¹³C APT (100MHz, CDCl₃, δ): 20.68(CH₃), 112.80(C), 113.70(C), 115.63(C), 117.52(CH), 118.46(C), 125.04(CH), 128.70(CH), 130.43(CH), 135.03(C), 136.33(CH), 138.90(C), 143.43(CH), 145.73(CH), 153.48(C), 155.04(C), 163.98 (CO of coumarin).

3-Phenyl 9-Chloro-[1,2,4]triazolo-[3',4':2,3][1,3,4]-thiadiazepino[7,6-b]coumarins (3f)

Pale yellow solid; yield=80%; mp 215-217°C; Anal. Calcd. For C₁₈H₉N₄O₂SCl: C, 56.77; H, 2.38; N, 14.71 %. Found: C, 56.72; H, 2.35; N, 14.68 %. IR (KBr, ν_{max}, cm⁻¹); 754(C-S-C Stretching), 1719 (C=O stretching of δ-lactone of coumarin), 1582 (aromatic C=C stretching), 1476 (aromatic C=N stretching), 3043 (aromatic C-H stretching). ¹H NMR (400 MHz, CDCl₃, δ): 7.32-8.59 (9 H, m, Ar-H). ¹³C APT (100 MHz, CDCl₃, δ): 111.57(C), 113.80(C), 114.70(C), 115.63(C), 117.52 (CH), 118.90(C), 125.04(CH), 128.70(CH), 130.43(CH), 135.03(CH), 136.33(C), 138.98(CH), 143.43(CH), 153.04(C), 156.98(C), 162.48(CO of coumarin).

3-Pyridyl-[1,2,4]triazolo-[3',4':2,3][1,3,4]-thiadiazepino[7,6-b]coumarins (3g)

Pale yellow solid; yield=82%; mp 252-254°C; Anal. Calcd. For C₁₇H₉N₅O₂S: C, 58.78; H, 2.61; N, 20.16 %. Found: C, 58.72; H, 2.63; N, 20.10 %. IR (KBr, ν_{max}, cm⁻¹); 751(C-S-C Stretching), 1719 (C=O stretching of δ-lactone of coumarin), 1581 (aromatic C=C stretching), 1475 (aromatic C=N stretching), 3041 (aromatic C-H stretching). ¹H NMR (400 MHz, CDCl₃, δ): 7.22-8.88 (9 H, m, Ar-H). ¹³C-APT (100 MHz, CDCl₃, δ): 110.21(C), 113.02(C), 115.65(C), 117.76(CH), 118.29(C), 120.23(C), 125.86(CH), 125.97(C), 128.96(CH), 131.81(CH), 135.28(CH), 138.39(CH), 142.98(CH), 152.98(C), 163.81(CO of coumarin).

3-Pyridyl-9-methyl-[1,2,4]triazolo-[3',4':2,3][1,3,4]-thiadiazepino[7,6-b]coumarins (3h)

Pale yellow solid; yield=86%; mp 268-270°C; Anal. Calcd. For C₁₈H₁₁N₅O₂S: C, 59.82; H, 8.07; N, 19.38 %. Found: C, 59.75; H, 8.10; N, 19.36 %. IR (KBr, ν_{max}, cm⁻¹); 756(C-S-C Stretching), 1712 (C=O stretching of δ-lactone of coumarin), 1585 (aromatic C=C stretching), 1475 (aromatic C=N stretching), 2854 (Aliphatic C-H stretching), 3045 (aromatic C-H stretching). ¹H NMR (400 MHz, CDCl₃, δ): 2.58(3 H, s, CH₃), 7.23-8.89 (8 H, m, Ar-H). ¹³C-APT (100 MHz, CDCl₃, δ): 20.43(CH₃), 111.31(C), 112.73(C), 113.80(C), 115.57(C), 117.58(CH), 118.37(C), 125.16(C), 126.13(CH), 131.72(CH), 136.03(C), 139.89(CH), 142.37(CH), 145.13(CH), 152.43(C), 163.79(CO of coumarin).

3-Pyridyl-9-Chloro-[1,2,4]triazolo-[3',4':2,3][1,3,4]-thiadiazepino[7,6-b]coumarins (3i)

Pale yellow solid; yield=79%; mp 236-237°C; Anal. Calcd. For C₁₇H₈N₅O₂SCl: C, 53.48; H, 2.11; N, 18.34 %. Found: C, 53.45; H, 2.08; N, 18.30 %. IR (KBr, ν_{max}, cm⁻¹); 754(C-S-C Stretching), 1715 (C=O stretching of δ-lactone of coumarin), 1580 (aromatic C=C stretching), 1472 (aromatic C=N stretching), 3045 (aromatic C-H stretching). ¹H NMR (400 MHz, CDCl₃, δ): 7.21-8.58 (8 H, m, Ar-H). ¹³C-APT (100MHz, CDCl₃, δ): 111.22(C), 112.82(C), 115.65(C), 117.77(CH), 118.29(C), 120.23(C), 125.66(CH), 125.77(C), 129.16(CH), 131.81(CH), 136.18(C), 140.36(CH), 143.82(CH), 153.28(C), 163.41(CO of coumarin).

3-Thiophenyl-[1,2,4]triazolo-[3',4':2,3][1,3,4]-thiadiazepino[7,6-b]coumarins (3j)

Pale yellow solid; yield=84%; mp 211-214°C; Anal. Calcd. For C₁₆H₈N₄O₂S₂: C, 54.53; H, 2.29; N, 15.90 %. Found: C, 54.50; H, 2.25; N, 15.86 %. IR (KBr, ν_{max}, cm⁻¹); 754(C-S-C Stretching), 1712 (C=O stretching of δ-lactone of coumarin), 1584 (aromatic C=C stretching), 1475 (aromatic C=N stretching), 3045 (aromatic C-H stretching). ¹H NMR (400 MHz, CDCl₃, δ): 7.06-8.34 (8 H, m, Ar-H). ¹³C-APT (100 MHz, CDCl₃, δ): 101.43(CH), 109.89(CH), 112.72(C), 113.80(C), 115.54(C), 117.50(CH), 118.37(C), 125.06(CH), 126.03(C), 129.11(CH), 131.73(CH), 136.52(C), 139.08(CH), 153.49(C), 163.99(CO of coumarin).

3-Thiophenyl-9-methyl-[1,2,4]triazolo-[3',4':2,3][1,3,4]-thiadiazepino[7,6-b]coumarins (3k)

Yellow solid; yield=75%; mp 225-227°C; Anal. Calcd. For C₁₇H₁₀N₄O₂S₂: C, 55.72; H, 2.75; N, 15.29 %. Found: C, 55.70; H, 2.74; N, 15.27 %. IR (KBr, ν_{max}, cm⁻¹); 754(C-S-C Stretching), 1715 (C=O stretching of δ-lactone of coumarin), 1580 (aromatic C=C stretching), 1472 (aromatic C=N stretching), 2854 (aliphatic C-H stretching) 3045 (aromatic C-H stretching). ¹H NMR (400 MHz, CDCl₃, δ): 2.34(3H, s, CH₃), 7.06-8.33 (7 H, m, Ar-H). ¹³C-APT (100 MHz, CDCl₃, δ): 23.32(CH₃), 101.32(CH), 109.92(C), 112.74(C), 115.28(C), 115.57(C), 118.39(C), 119.23(CH), 124.89(CH), 129.10(CH), 131.72(CH), 132.05(C), 137.58(CH), 138.42(CH), 142.38(C), 153.48(C), 163.31(CO of coumarin).

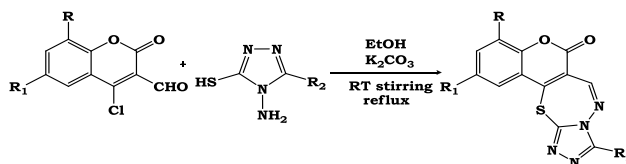
3-Thiophenyl-9-Chloro-[1,2,4]triazolo-[3',4':2,3][1,3,4]-thiadiazepino[7,6-b]coumarins (3l)

Yellow solid; yield=90%; mp 226-229°C; Anal. Calcd. For C₁₆H₇N₄O₂S₂Cl: C, 49.68; H, 1.82; N, 14.40 %. Found: C, 49.65; H, 1.84; N, 14.36 %. IR (KBr, ν_{max}, cm⁻¹); 756(C-S-C Stretching), 1718 (C=O stretching of δ-lactone of coumarin), 1585 (aromatic C=C stretching), 1475 (aromatic C=N stretching), 3041 (aromatic C-H stretching). ¹H NMR (400 MHz, CDCl₃, δ): 7.08-8.36 (7 H, m, Ar-H). ¹³C-APT (100MHz, CDCl₃, δ): 101.43(CH), 109.89(CH), 112.72(C), 113.80(C), 115.54(C), 117.50(CH), 118.37(C), 125.06(CH), 126.03(C), 129.11(CH), 131.73(CH), 136.52(C), 139.08(CH), 143.37(C), 155.52(C), 163.49(CO of coumarin).

RESULTS AND DISCUSSION

Chemistry

In the present work, various [1,2,4]triazolo-[3',4':2,3][1,3,4]-thiadiazepino[7,6-b]coumarins (3a-l) have been synthesized by reacting various 4-chloro-3-formyl coumarins (1a-c) with appropriate 4-amino-5-substituted-3-mercapto-1,2,4-triazoles (2a-d) in ethanol in the presence of catalytic amount of K_2CO_3 under reflux condition (Scheme 1). 4-Chloro-3-formyl coumarins (1a-c) and 4-amino-5-substituted-3-mercapto-1,2,4-triazole (2a-d) were prepared by reported methods [27-31].



Comp. No.	R	R ₁	R ₂	Comp No.	R	R ₁	R ₂
3a	H	H	CH ₃	3g	H	H	4-Pyridyl
3b	H	CH ₃	CH ₃	3h	H	CH ₃	4-Pyridyl
3c	H	Cl	CH ₃	3i	H	Cl	4-Pyridyl
3d	H	H	Phenyl	3j	H	H	2-Thiophenyl
3e	H	CH ₃	Phenyl	3k	H	CH ₃	2-Thiophenyl
3f	H	Cl	Phenyl	3l	H	Cl	2-Thiophenyl

Scheme 1: Synthesis method under reflux condition

BIOLOGICAL RESULTS

Antimicrobial activity

The newly synthesized target compounds (3a-l) were evaluated for their *in vitro* antibacterial activity against two Gram positive bacteria *Staphylococcus aureus* (MTCC 96) and *Bacillus subtilis* (MTCC 441) and two Gram negative bacteria *Escherichia coli* (MTCC 443) and *Salmonella typhi* (MTCC 98). They were also evaluated for their *in vitro* antifungal activity against *Candida albicans* (MTCC 227) and *Aspergillus niger* (MTCC 282) as fungal strains. Broth dilution method was used for the determination of the antibacterial and antifungal activity as recommended by NCCLS [32]. Ampicillin, Chloramphenicol and Norfloxacin were used as standard antibacterial drugs, whereas Griseofulvin and Nystatin were used as standard antifungal drugs. The synthesized compounds (3a-l) were screened for their antibacterial and antifungal activity at the concentration of 1000, 500 and 250 $\mu\text{g/mL}$ for the primary screening. The synthesized compounds showing activity against microbes in the primary screening were further screened in a second set of dilution at concentrations of 200, 100, 62.5, 50 and 25 $\mu\text{g/mL}$. The suspensions of 10 μL from each well were further incubated and growth was noted at 37°C after 24 h for bacteria and 48 h for fungi. The lowest concentration which showed no visible growth (turbidity) after spot subculture was considered as the Minimum Inhibitory Concentration (MIC) for each compound. The investigation of the data summarized in Table 1 reveals that many compounds were found to be active against Gram-positive bacteria while some of the compounds were found to be active against Gram-negative bacterial and fungal species as compared to that of the standard antimicrobial drugs.

Antimicrobial evaluation

The compounds (3a-l) were screened for their *in vitro* antibacterial and antifungal evaluation against various bacterial and fungal pathogens by broth dilution method. Ampicillin, Chloramphenicol, Norfloxacin, Griseofulvin and Nystatin were used as standard drugs. The values of MIC are summarized in Table 1.

Table 1: *In vitro* Antimicrobial activity of compounds (3a-l)

	Minimum Inhibitory Concentration (MIC, $\mu\text{g/mL}^{-1}$)					
	Gram +ve bacteria		Gram -ve bacteria		Fungi	
	<i>B.s.</i> MTCC441	<i>S.a.</i> MTCC98	<i>E.c.</i> MTCC443	<i>S.t.</i> MTCC98	<i>A.n.</i> MTCC282	<i>C.a.</i> MTCC227
3a	250	200	62.5	100	500	>1000
3b	200	100	125	200	1000	500
3c	500	200	100	125	1000	500

3d	500	250	100	250	500	500
3e	100	100	62.5	200	>1000	1000
3f	500	500	125	250	>1000	250
3g	125	125	250	250	1000	500
3h	250	250	500	250	>1000	>1000
3i	500	500	250	500	>1000	>1000
3j	100	100	62.5	200	500	500
3k	100	62.5	200	100	500	1000
3l	200	500	250	250	1000	1000
Ampicillin	250	250	100	100	-	-
Chloramphenicol	50	50	50	50	-	-
Norflaxacin	100	10	10	10	-	-
Griseofulvin	-	-	-	-	100	500
Nystatin	-	-	-	-	100	100

Review of the antimicrobial activities of synthesized compounds (3a-l) in Table 1 indicated that compounds 3e, 3j and 3k (MIC=100 µg/mL) exhibited excellent activity toward Gram-positive bacteria *Bacillus subtilis* as compared to Ampicillin (MIC=250 µg/mL) and showed equipotent activity to Norfloxacin (MIC=100 µg/mL). Against Gram-positive bacteria *Bacillus subtilis*, compound 3g (MIC=125 µg/mL) showed activity higher than that of Ampicillin (MIC=250 µg/mL). Compounds 3b and 3l (MIC=200 µg/mL) displayed better activity than Ampicillin (MIC=250, µg/mL) toward Gram-positive bacteria *Bacillus subtilis*. Compounds 3a and 3h (MIC=250 µg/mL) showed results equivalent to that of Ampicillin (MIC=250 µg/mL) toward Gram-positive bacteria *Bacillus subtilis*. Compounds 3b, 3e and 3j (MIC=100 µg/mL) were found to be more effective against Gram-positive bacteria *Staphylococcus aureus* than Ampicillin (MIC=250 µg/mL). Against Gram-positive bacteria *Staphylococcus aureus*, compounds 3g (MIC=125 µg/mL) showed activity higher than that of Ampicillin (MIC=250 µg/mL). Compounds 3a and 3c (MIC=200 µg/mL) showed good activity against Gram-positive bacteria *Staphylococcus aureus* as compared to Ampicillin (MIC=250 µg/mL). Against Gram-positive bacteria *Staphylococcus aureus*, compounds 3d and 3h (MIC=250 µg/mL) showed equipotent activity to that of Ampicillin (MIC=250 µg/mL).

Moreover, Against Gram-negative bacteria *Escherichia coli*, compounds 3c and 3d (MIC=100 µg/mL) showed activity comparable to Ampicillin (MIC=100 µg/mL). Against Gram-negative bacteria *Salmonella typhi*, compounds 3a, 3e and 3j (MIC=62.5 µg/mL) showed excellent activity as compared to Ampicillin (MIC=100 µg/mL). Whereas compounds 3a and 3k (MIC=100 µg/mL) showed equipotent to Ampicillin (MIC=100 µg/mL) toward Gram-negative bacteria *Salmonella typhi*.

Furthermore, against *Candida albicans* fungal pathogen, however compound 3f (MIC=250 µg/mL) showed better inhibition action as compare to the standard drug Griseofulvin (MIC=500 µg/mL). Whereas compounds 3b, 3c, 3d, 3g and 3j (MIC=500 µg/mL) showed activity comparable to Griseofulvin (MIC=500 µg/mL) against fungal pathogen *Candida albicans*.

Anti-tuberculosis activity

The *in vitro* antitubercular activity of all the synthesized compounds were determined by using Lowenstein-jensen medium (Conventional method against Mycobacterium tuberculosis H37Rv strain as described by Rattan [33]). The results of the activity data are presented in Table 2 in the form of % inhibition, relative to that of standard drugs isoniazide and rifampicin. Upon study of the activity data it was observed that compound 3d and 3h showed good activity in comparison with isoniazid.

Table 2: Antitubercular activity data of compounds (3a-l)

Comp. No.	% Inhibition	Comp. No.	% Inhibition
3a	59	3g	45
3b	72	3h	90
3c	89	3i	54
3d	91	3j	36
3e	55	3k	54
3f	32	3l	85
Isoniazide=0.20 µg/ml; 99% inhibition			

CONCLUSION

Present study described successful hybridization strategy of three bioactive moieties, coumarin, triazole and thiazepines in a single scaffold. The target compounds were synthesized in good yield by adopting simple condensation reaction. Majority of the compounds were found to be active against Gram positive and gram negative bacteria. Antimicrobial screening results revealed that

compounds 3a, 3e, 3j and 3k were found to be the most proficient members of the series and antitubercular activity data revealed that compound 3d and 3h showed good activity in comparison with isoniazide.

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