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SYNTHESIS OF PHARMACORE MERCAPTO-1,2,4 TRIAZOLE SCHIFF'S BASE BEARING DIARYLETHER NUCLEUS AS ANTIMICROBIALS

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ABSTRACT
Mercapto-triazole among the various heterocyclic compounds has distinctive place because of its various pharmacological activities associated with it. A lot of research work has been done on various triazole derivatives to overcome with potential molecule since decades. This article focuses on the synthesis and pharmacological profile of mercapto-triazole Schiff's base comprising diarylether nucleus. A series of **(***Z***)**-5-((substituted amino aryl) methyl)-4-(3-phenoxybenzylideneamino)-4*H*-1, 2, 4-triazole-3-thiol have been synthesized and screened for their preliminary in vitro antibacterial activity against some Gram-positive, Gram-negative bacteria as well for antifungal activity and also evaluated for antimycobacterial activity against Mycobacterium tuberculosis $H_{37}Rv$ strain

KEYWORDS: Mercapto-Triazole, diarylether, Pharmacological activity.

INTRODUCTION
There is indeed for the development of new drugs as the currently available drugs are becoming futile due to the drug resistance developed by pathogens. In the last few decades the chemistry of diarylether and their fused heterocyclic derivatives have received considerable attention owing to their synthetic and effective biological importance.[1-4] As heterocyclic compounds analogues and derivatives have attracted strong interest due to their useful biological properties. There is significant advancement in the chemistry of azoles because more than hundred azole derivatives are used today as drugs. 1,2,4-triazoles and their derivatives constitute an important class of organic compounds with diverse agricultural, industrial and biological activities including anti-microbial, sedative, anti-convulsant, anti-inflammatory.[5-7] Some of the present day drugs such as Ribavirin (antiviral agent), Rizatriptan (antimigraine agent), Alprazolam (anxiolytic agent), Fluconazole and Itraconazole (antifungal agents),[8-11] are the best examples for potent molecules possessing triazole nucleus. Diarylether derivatives clubbed with heterocycles found to have diverse biological activity; anticancer, antituberculosis, antibacterial.[12-21] In continuation of our research program on the synthesis of 1,2,4-triazole compounds exhibiting biologic activity, it indeed to synthesize new antimicrobial agents, especially when the pathogenic bacteria resist toward available antibiotics is rapidly becoming a major worldwide problem. The designing of new compounds to deal with resistant bacteria has become one of the most important areas of antibacterial research today. Keeping in mind the above facts, we designed and synthesized series of some new 1,2,4-triazole-3-thione derivatives clubbed with diarylether nucleus and evaluated in vitro antibacterial and antimycobacterial activity. These modifications are carried out by using different functionalities, aliphatic chains, aromatic rings and heterocyclic ring systems, this depict in scheme.

MATERIALS AND METHOD
Chemistry protocols
All the solvents used of commercial grade and used without additional purification. Removal of all solvents was carried out under reduced pressure. Melting points were determined by the open tube capillary method and are uncorrected. The purity of the compounds was determined by TLC plates (silica gel G) using different eluent system. The IR spectra were obtained on Thermo Agilent Resolution Pro FT-IR spectrometer (KBr pellets). The ^{1}H-NMR & ^{13}C-NMR spectra were recorded on a Bruker Avance II 400 spectrometer using TMS as the internal standard in DMSO-d_6 & $CDCl_3$ SAIF, Chandigarh. The mass spectra were recorded by GCMS Agilent Resolution pro-instrument.

Biology protocols
In vitro antibacterial
All the synthesized compounds were screened against four different strains viz. two gram-positive bacteria;

Staphylococcus aureus (MTCC-96) and *Streptococcus pyogenes* (MTCC-443), two gram-negative bacteria; *Escherichia coli* (MTCC-442) and *Pseudomonas aeruginosa* (MTCC-441), and for fungi, *Candida albicans* (MTCC-227), *Aspergillus niger* (MTCC-282), and *Aspergillus clavatus* (MTCC-1323) were used. The strains were procured from Institute of Microbial Technology; Chandigarh. The MICs of the synthesized compounds was determined by the broth dilution method[22-23]

In vitro antimycobacterial

Many new methodologies have been developed recently for drug screening against mycobacteria, amongst them Microplate Alamar Blue Assay (MABA) is the most widely cited. The literature review suggested, MABA was effective with *MTB* $H_{37}Rv$, $H_{37}Ra$ and *M. avium* strain ATCC 25291, a relatively virulent isolate[24], reliable with clinical isolates of *M. tuberculosis* [25]. All the synthesized compounds were evaluated for their potency at concentration 50 µM in the initial screen.

Experimental

General procedure

Synthesis of A (1-10): ethyl-2-(substituted-arylamino)acetate

To a solution of aromatic amine (0.1mol) in dry DMF (25 ml), anhydrous potassium carbonate (2.5mol) and ethylchloroacetate (1.25mol) were added at r.t. The resultant mixture was stirred at 80^{o}C for 15-17 h. The reaction was monitored by TLC on silica gel using mobile phase ethyl acetate: toluene (3:7 v/v). After the completion of the reaction, cooled to room temperature and poured the reaction mixture to a large amount of water with stirring. The solid separated was filtered, washed with excess of water and dried. The crude product was purified by recrystallization from methanol with good yield.

Synthesis of B (11-20): 2-(substituted-arylamino) acetohydrazide

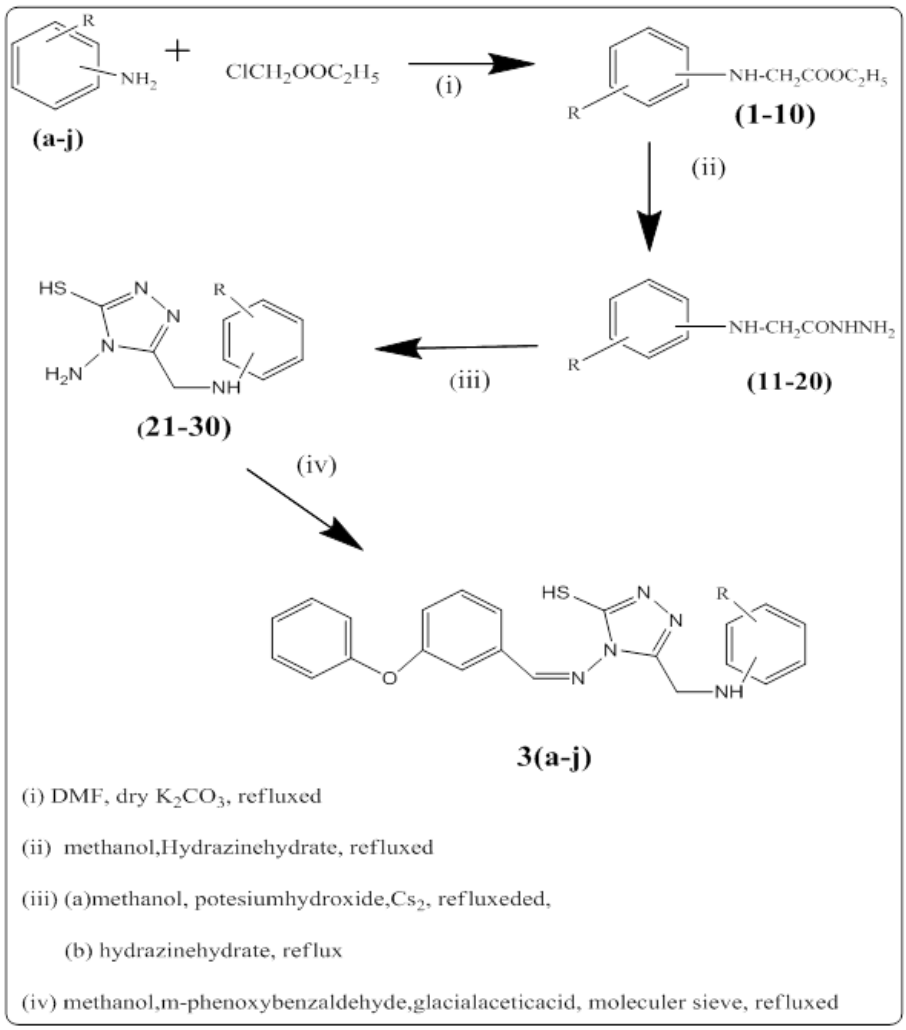
To a solution of ethyl-2-(substituted-arylamino)acetate (0.05mol) in methanol (30 ml), added hydrazine hydrate (0.1 mol) at r.t. The reaction mixture was refluxed on a water bath for 10-12 h. The reaction was monitored by TLC on silica gel using ethyl acetate: toluene (2:8 v/v). After the completion of the reaction, the solvent was evaporated under reduce pressure and the crude solid was washed with water and recrystallized from acetone to give 2-(4-chlorophenylamino) acetohydrazide with a good yield.

Synthesis of C (21-30): 4-amino-5-(substituted phenyl amino)-4H-1,2,4-triazole-3-thiol

A mixture of potassium hydroxide (1.0mol) in absolute ethanol (35ml), **B20** (g, 0.5mol) and carbon disulphide (1.0mol) was stirred for 12 h. To the resulting solution ether was added and the precipitated dithiocarbazinate salt was collected by filtration, washed with ether and dried under vacuum. This obtained salt was used in next step without purification. A suspension of potassium salt, hydrazine hydrate (10ml) and water (2ml) was refluxed for 6-7h. hydrogensulphide was evolved and resulted homogeneous solution, diluted with 50ml water and acidified with dilute acetic acid to yield solid product which was filtered, washed with water and recrystallized in appropriate solvent and obtained as pale yellow crystals with good yield.

Synthesis of (*Z*)-5-((substituted amino aryl) methyl)-4-(3-phenoxybenzylideneamino)-4*H*-1, 2, 4-triazole-3-thiol

To a solution of **C23** (1mol) in methanol (25 ml) added m-Phenoxybenzaldehyde (1.1. mol) and few drops of glacial acetic acid at r.t. The reaction mixture was refluxed on a water bath for 6-8 h. The reaction was monitored by TLC on silica gel using methanol: dichloromethane (2:8) as elute. The solvent was evaporated under reduce pressure and the crude was poured onto ice-water; filtered and dried. The crude solid crystallized in appropriate alcohol to give the color product (yellow) with a good yield.



Scheme.

Table-1: Properties of desired products.

Comp	Ar-substituted aminoaryl	%yield	M.P. Range (±5) °C
3a	4,6-dimethoxypyrimidin-2-amine	65	245
3b	Piperazine	58	228
3c	p-toluidine	62	202
3d	4-amino-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one	65	234
3e	4-chloroaniline	65	213
3f	5-chloro-2-methylaniline	60	225
3g	phenylmethanamine	55	210
3h	1H-1,2,3-triazole	65	200
3i	5-methylbenzo[d]thiazol-2-amine	60	203
3j	5-methylthiazol-2-amine	68	218

Spectral characterization

3a:**(Z)-5-((4,6-dimethoxypyrimidin-2-ylamino)methyl)-4-(3-phenoxybenzylideneamino)-4H-1,2,4-triazole-3-thiol**

IR (KBr); C=N (Schiff base) stretching at1655.02 cm^{-1} and N-H bands in 3065.3 cm^{-1};

^{1}HNMR (δppm): 10.23(s, 1H, SH-triazole), 8.73(s, 1H, -CH=N-), 7.1-7.6(m, 9H, Ar-H), 5.93(s, 1H, CH-pyrimidine), 4.4(s, 2H, -CH2-NH), 4.1(s, 1H, -NH), 3.76(s, 6H, $-OCH_3$);

^{13}CMR: 173.5(C_4, C_6-pyrimidine), 160.6(C_5-triazole), 158.9(C_2-pyrimidine), 157.2(Ar-C-O-C-Ar), 156.09(C=N), 151.9(C_3-triazole), 113.7-136.6(Ar-C), 75.4(C_5-pyrimidine), 57.8($-OCH_3$), 35.7($-CH_2$-NH), **MS** (EI) *m/z*: 463(M^+), 464 (M + 1).

3b: **(Z)-4-(3-phenoxybenzylideneamino)-5-(piperazin-1-ylmethyl)-4H-1,2,4-triazole-3-thiol**

IR (KBr); C=N (Schiff base) stretching at1645.02 cm^{-1} and N-H bands in 3032.2cm^{-1};

^{1}HNMR (δppm): 10.35(s, 1H, SH-triazole), 8.83(s, 1H, -CH=N-), 7.1-7.6(m, 9H, Ar-H), 4.4(s, 2H, -CH2-NH), 2.76(d, 4H, -CH_2-piperazine), 2.66(d, 4H, -CH_2-piperazine), 1.86(s,1H,-NH-piperazine);
^{13}CMR: 160(C_5-triazole), 158.9(CH=N), 156.2(C-O-C, diarylether), 152.9(C_3-triazole), 113.7-136.6(Ar-C), 59.2(C_3,C_5-piperazine), 48.8(-CH_2), 44.7(C_2,C_6,-piperazine), **MS** (EI) *m/z*: 394(M^+).

3c:(Z)-4-(3-phenoxybenzylideneamino)-5-((p-tolylamino)methyl)-4H-1,2,4-triazole-3-thiol.
IR (KBr); C=N (Schiff base) stretching at1665.02 cm^{-1} and N-H bands in 3048.4 cm^{-1};
^{1}HNMR (δppm): 10.33(s, 1H, SH-triazole), 8.53(s, 1H, -CH=N-), 6.98-7.65(m, 13H, Ar-H), 4.4(s, 2H, -CH_2-NH), 4.1(s, 1H, -NH), 2.76(s, 3H, -CH_3);
^{13}CMR: 160.6(C_5-triazole), 158.2(Ar-C-O-C-Ar), 156.09(C=N), 153.9(C_3-triazole), 116.7-146.6(Ar-C), 33.7(-CH_2-NH), 25.8(-CH_3), **MS** (EI) *m/z*: 415(M^+), 416 (M + 1).

3d:(Z)-4-((5-mercapto-4-(3-phenoxybenzylideneamino)-4H-1,2,4-triazol-3-yl)methylamino)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one.
IR (KBr); C=N (Schiff base) stretching at1675.02 cm^{-1} and N-H bands in 3052.4 cm^{-1};
^{1}HNMR (δppm): 10.63(s, 1H, -SH-triazole), 8.93(s, 1H, -CH=N-), 6.98-7.85(m, 14H, Ar-H), 4.1(s, 2H, -CH_2-NH), 3.46(s, 3H, -CH_3-N-), 2.86(s, 3H, -CH_3), 2.1(s, 1H, -NH);
^{13}CMR: 165.3(C_5-pyrazolidinone),162.6(C_5-triazole),159.2(C-O-C,diarylether),154.09(CH=N), 152.9(C_3-triazole), 116.7-148.6(Ar-C), 134.2(C3-pyrazolidinone),117.8(C5-pyrazolidinone),35.7(-CH_2-NH), 26.8(-CH_3-N), 26.8(-CH_3); **MS** (EI) *m/z*: 512 (M^+).

3e:(Z)-5-((4-chlorophenylamino)methyl)-4-(3-phenoxybenzylideneamino)-4H-1,2,4-triazole-3-thiol
IR (KBr); C=N (Schiff base) stretching at1685.02 cm^{-1} and N-H bands in 3056.4 cm^{-1};
^{1}HNMR (δppm): 10.43(s, 1H, -SH-triazole), 8.93(s, 1H, -CH=N-), 7.1-7.95(m, 13H, Ar-H), 4.3(s, 2H, -CH_2-NH), 4.1 (s, 1H, -NH);
^{13}CMR: 160.6(C_5-triazole),157.2(C-O-C, diarylether),155.09(CH=N), 151.9(C_3-triazole), 116.7-149.6(Ar-C),38.7(-CH_2-NH); **MS** (EI) *m/z*: 436 (M^+),438(M^{+2}).

3f:(Z)-5-((5-chloro-2-methylphenylamino)methyl)-4-(3-phenoxybenzylideneamino)-4H-1,2,4-triazole-3-thiol.
IR (KBr); C=N (Schiff base) stretching at1645.02 cm^{-1} and N-H bands in 3030.8 cm^{-1};
^{1}HNMR (δppm): 10.53(s, 1H, SH-triazole), 8.73(s, 1H, -CH=N-), 6.98-7.85(m, 12H, Ar-H), 4.6(s, 2H, -CH_2-NH), 4.3(s, 1H, -NH), 2.46(s, 3H, -CH_3);
^{13}CMR: 162.6(C_5-triazole), 159.2(Ar-C-O-C-Ar), 155.09(C=N), 152.9(C_3-triazole), 116.7-148.6(Ar-C), 35.7(-CH_2-NH), 23.8(-CH_3), **MS** (EI) *m/z*: 450 (M^+), 452 (M + 2).

3g: (Z)-5-((benzylamino)methyl)-4-(3-phenoxybenzylideneamino)-4H-1,2,4-triazole-3-thiol
IR (KBr); C=N (Schiff base) stretching at1635.02 cm^{-1} and N-H bands in 3120.4 cm^{-1};
^{1}HNMR (δppm): 10.63(s, 1H, SH-triazole), 8.43(s, 1H, -CH=N-), 6.98-7.85(m, 14H, Ar-H), 3.87(s, 2H, -CH_2-NH), 3.67(s, 2H, -CH2-Ar), 2.1(s, 1H, -NH);
^{13}CMR: 160.5(C_5-triazole), 157.2(Ar-C-O-C-Ar), 154.09(C=N), 151.8(C_3-triazole), 116.7-143.6(Ar-C), 57.7(-CH_2-Ar), 43.8(-CH_2-NH), **MS** (EI) *m/z*: 416 (M^+).

3h: (Z)-5-((1H-1,2,3-triazol-1-yl)methyl)-4-(3-phenoxybenzylideneamino)-4H-1,2,4-triazole-3-thiol.
IR (KBr); C=N (Schiff base) stretching at1665.02 cm^{-1} and N-H bands in 3035.6 cm^{-1};
^{1}HNMR (δppm): 10.63(s, 1H, SH-triazole), 8.43(s, 1H, -CH=N-),7.6-7.8(q, 2H, triazole,) 6.98-7.45(m, 9H, Ar-H), 4.87(s, 2H, -CH_2-NH);
^{13}CMR: 160.5(C_5-triazole), 157.2(Ar-C-O-C-Ar), 154.09(C=N), 151.8(C_3-triazole),136.4(C_5,1,2,3triazole), 124.6(C_4, 1,2,3triazole), 116.7-128.6(Ar-C), 46.8(-CH_2-NH); **MS** (EI) *m/z*: 377(M^+).

3i:(Z)-5-((5-methylbenzo[d]thiazol-2-ylamino)methyl)-4-(3-phenoxybenzylideneamino)-4H-1,2,4-triazole-3-thiol.
IR (KBr); C=N (Schiff base) stretching at1645.02 cm^{-1} and N-H bands in 3050.8 cm^{-1};
^{1}HNMR (δppm): 10.33(s, 1H, SH-triazole), 8.23(s, 1H, -CH=N-), 6.98-7.95(m, 13H, Ar-H), 4.47(s, 2H, -CH_2-NH), 4.1(s,1H, -NH-), 2.43(s, 3H, -CH_3);
^{13}CMR:175.3(C_2-benzothiazole), 162.5(C_5-triazole), 158.2(C-O-C, diarylether), 155.09(CH=N), 116.7-153.6(Ar-C), 39.8(-CH_2-NH), 23.4(-CH3); **MS** (EI) *m/z*: 473(M^+).

3j:(Z)-5-((5-methylthiazol-2-ylamino)methyl)-4-(3-phenoxybenzylideneamino)-4H-1,2,4-triazole-3-thiol
IR (KBr); C=N (Schiff base) stretching at1655.02 cm^{-1} and N-H bands in 3050.4 cm^{-1};
^{1}HNMR (δppm): 10.23(s, 1H, SH-triazole), 8.23(s, 1H, -CH=N-), 7.11-7.65(m, 12H, Ar-H), 6.4(s, 1H,-CH-thiazole), 4.3(s, 2H, -CH_2-NH), 4.1(s, 1H, -NH), 2.36(s, 3H, -CH_3)
^{13}CMR: 165.2(C2-thiazole), 160.6(C_5-triazole), 158.2(Ar-C-O-C-Ar), 154.09(C=N), 152.9(C_3-triazole), 138.6(C4-triazole), 123.8(C5-triazole), 116.7-148.6(Ar-C), 32.7(-CH_2-NH), 20.8(-CH_3);**MS** (EI) *m/z*: 423 (M^+), 424 (M + 1).

Biology

Table-2: ***In vitro antibacterial activity.***

Code	Antibacterial activity(MIC)				Antifungal activity(MIC)		
	Gram negative		Gram positive				
	E.coli	*P.aeruginosa*	*S.aureus*	*S.pynogenus*	*C.abicans*	*A.niger*	*A.clavatvs*
	MTC 442	MTC 441	MTCC 96	MTC 443	MTCC 227	MTCC 282	MTCC 1323
	Microgram/ml				Microgram/ml		
3a	125	125	250	125	1000	1000	1000
3b	200	100	250	200	1000	1000	1000
3c	100	62.5	200	100	250	500	500
3d	62.5	100	250	250	500	1000	1000
3e	125	200	100	100	1000	1000	1000
3f	200	250	62.5	125	500	1000	1000
3g	250	200	100	100	>1000	>1000	>1000
3h	100	500	125	62.5	>1000	>1000	>1000
3i	200	200	200	500	1000	500	500
3j	250	100	200	200	>1000	1000	1000
Gentamycin	0.05	1	0.25	0.5	-	-	-
Ampicillin	100	100	250	100	-	-	-
Chloramphenicol	50	50	50	50			
Ciprofloxacin	25	25	50	50			
Norfloxacin	10	10	10	10			
Nystatin	-	-	-	-	100	100	100
Greseofulvin	-	-	-	-	500	100	100

Table-3: In vitro antimycobacterial activity.

sample Id	%Inh at Conc. 50 µg/ml
3a	34
3b	25
3c	23
3d	73
3e	9
3f	23
3g	23
3h	65
3i	10
3j	98
Rifampicin	100
Isoniazid	100

RESULT AND DISCUSSION

Chemistry

The IR spectrum of intermediate 25 displayed stretching bands at 3389.7-3286.6 cm^{-1} due to NH/NH_2. ^1H NMR spectrum of this sample displayed a singlet at δ 10.03 and δ 5.9 which were accounted for SH and NH_2 respectively. ^{13}C NMR spectrum of 25 showed signals at δ 166.2 and δ 152.6 due to C=S of triazole and C_5 carbon of triazole, respectively. IR spectra of hydrazones **3e** obtained from triazole-thione (25) showed C=N (Schiff base) stretching at1685.02 cm^{-1} and N-H bands in 3056.4 cm^{-1} region. ^1H NMR and ^{13}C NMR data were also in agreement with the formation of hydrazones, ^{1}HNMR spectra of **3i** showed singlets at δ10.43, δ 8.83, δ 4.2 and δ 4.02 attributed to –SH, –N=CH and-CH2, –NH protons respectively and singlet at δ 2.4 of CH3-benzothaizole. While CS and N=CH carbon of compounds in hydrazine structures was observed at δ 158.09 and δ 153.09 successively in their ^{13}C. The mass spectrum of **3i** showed a molecular ion peak at m/z 472.

Biology

The minimum inhibitory concentrations (MIC: 100 µM, 250 µM) of **3(a-j)** were screened against different strains. Results revealed (Table-2) that some of the newly synthesized some compounds with MIC: 100µM, 250µM comparable to the reference drugs Ampicilin, Chloramphenicol. Compounds **3c,3h** showed promising inhibition against *E-coli* while **3b,3d,3j** show activity against *P.aeruginosA* .Compound **3a**,**2b,3d**, and **3c,3e,3g** show potency against *S.pynogenus* and *S.aureus* respectively. Remaining compounds displayed moderate to least activity against both bacteria. Alternatively, new synthesized derivatives were tested as potential antifungal agents. Compounds **3d,3f** exhibited potency with (MIC; 500µM) against *C. albicans*, similar to that of reference drug Greseofulvin.

In vitro antimycobacterial activity

From preliminary examination results displayed in (Table-3) of the antimycobacterial activity of **3(a-j**) compound **3j** found to be an active (99 % inhibition at 50µM) against *M. tuberculosis.* Whereas compound **3d** showed encouraging activity with 73 % and **3h** 65%inhibition at 50µM while rest of the compound are not active in preliminary examination.

CONCLUSION

The synthesised new series of diarylether enclosed with mercapto-1,2,4 triazole core exhibited promising to moderate in vitro antibacterial activity against the both

pathogens strain. The present work reveals that comp **3j** is potent motif for antimycobacterial activity. The present study leads to further research in the area of anti tuberculosis to construct diarylether analogues clubbed with heterocycles.

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