Int J Pharm Bio Sci 2014 Oct; 5(4): (P) 552 - 560

Research Article **Medicinal chemistry**

International Journal of Pharma and Bio Sciences **ISSN 0975-6299**

SYNTHESIS OF SOME NOVEL SCHIFF BASE CONTAINING [1,2,4] TRIAZOLO RING

ANIL V PATEL , JITESH H TAILOR AND G. M. MALIK*

Department of Chemistry, Navyug Science College, Rander Road, Surat, Gujarat, 395005 India

ABSTRACT

4-amino-5-biphenyl-4-yl-4H-[1, 2, 4] triazolo-3-thiols have been prepared from biphenyl-4-carboxyclic acid (1), carbon disulphide (CS_2) and hydrazine hydrate. The resulting 4-amino-5-biphenyl-4-yl-4H-[1, 2, 4] triazolo-3-thiol was treated with substituted aromatic aldehydes to give the Schiff base. The synthesized compounds were characterized by elemental and spectral analysis (IR, ^{1}H NMR and mass spectrometry). All synthesized compounds were screened for their in vitro antimicrobial activity against bacterial strains and fungi strain and found to have significant effect against the tested microorganisms.

KEYWORDS: **Biphenyl-4-carboxyclic acid, 4-amino-5-biphenyl-4-yl-4H-[1, 2, 4] triazolo-3-thiol, hydrazine hydrate, Schiff base.**

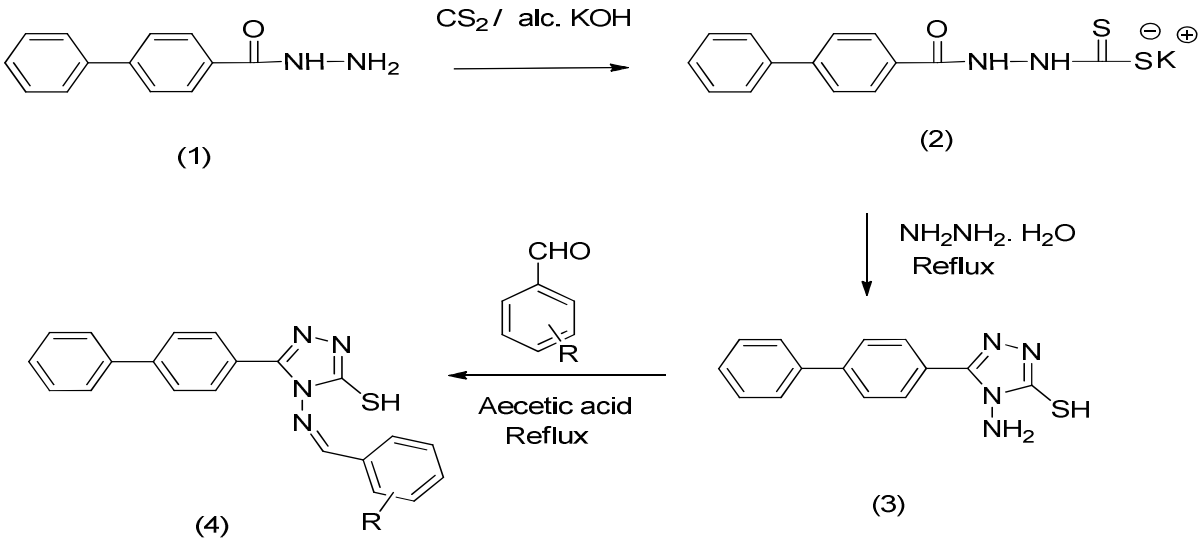
G. M. MALIK
Department of Chemistry, Navyug Science College,
Rander Road, Surat, Gujarat, 395005 India

INTRODUCTION

The triazole derivatives belong to an important group of heterocyclic compounds that have been the subject of extensive study of the recent past. Diverse biological activities such as antibacterial, antifungal, anti-inflammatory, antihypertensive and antiviral have been associated with 1, 2, 4- triazole derivatives[1-5]. 1, 2, 4-triazole nucleus shows a wide range of pharmacological activities such as antibacterial[6], antifungal[7], anti-inflammatory[8] and antioxidant[9]. 1, 2, 4-triazole proved as antibacterial, fungicidal and nematocidal agents[10]. There are so many methods for the synthesized of 1, 2, 4-triazole[11-12], one important of them is; bis-1, 2, 4-triazole were synthesized by CS_2 \ KOH and hydrazine hydrate with oxalic dihydrazide[13]. Literature survey reveals that most of the compounds having 1, 2, 4-triazole nucleus possess pharmacological[14-17], actions including antibacterial [19, 20], antituberculestic[21], anti-inflammatory, anticancer[22], antiviral, analgesic and antimigrain. 1, 2, 4- triazole derivatives constitute an important family of heterocyclic compounds. Synthesis and transformations of 1, 2, 4 triazole have received particular interest for a long period of time and accommodates wide variety of therapeutically interesting drugs. 1, 2, 4-triazole have been reported to show fungicidal and nematocidal properties.

MATERIALS AND METHODS

Melting points were determined using Stuart SMP10 MP apparatus and are uncorrected. The purity was checked by TLC. The IR spectra (v, cm^{-1}) were obtained with a 8400 FT-IR-435 spectrometer in KBr pellets. ^{1}H-NMR spectra (δ, ppm) were recorded in DMSO-d6 solutions on a Bruker-Avance 400 MHz spectrometer using TMS as internal reference. Mass spectra were recorded on Waters Micro mass Q-Tof Micro having range of 4000 amu in quadruple and 20000 amu in ToF. Elemental analysis was performed on an ECS 4010 Elemental Combustion System. Scheme-1: Synthesis of 5-Biphenyl-4-yl-4-[(substituted benzylidene)-amino]-4H-(1,2,4)triazole-3-thiol. (4 a-j)



Synthesis of potassium salt of N'-(Biphenyl-4-carbonyl)- hydrazine carbo dithioate (2)

In a 250 ml round bottom flask, Biphenyl-4-carboxylic acid hydrazide (1) (0.01 mole) and solution of carbon disulphide (CS_2) (0.012 mole) in ethanol reacted and followed by drop wise addition of alcoholic KOH and as a base catalyst. The reaction mixture was monitored during reaction by TLC (ethyl acetate and hexane (6:4)). After completion of reaction, the mixture was diluted with dichloro methane (50 ml) solvent and separated out layer. Excess of dichloro methane was distilled out. The solid thus obtained and dried. Recrystallization from ethanol to yield white solid potassium salt of N'-(Biphenyl-4-carbonyl)- hydrazine carbo dithioate (2).

Potassium salt of N'-(Biphenyl-4-carbonyl)- hydrazine carbo dithioate (2)

Off white crystals, mp 159°C, yield 68 %; IR (KBr, cm^{-1}) : 3312 (N-H),708c (C-S), 1350 (C-N), 1210 (C=S), 1672 (C=O); ^{1}H NMR (400.1 MHz, DMSO): δ_H 4.64 (s, 1H, -NH), 6.82-7.89 (m, 9H,Ar-H), 8.4 (s, 1H, NH); Anal. Calcd for: $C_{14}H_{11}KON_2S_2$ (326.4); Found (C, 51.46; H, 3.39; K, 11.90; N, 8.52; O, 4.88; S, 19.60 %); requires (C, 51.5; H, 3.40; K, 11.98; N, 8.58; O, 4.90; S, 19.64%); MS: *m/z*: 326 (M+).

Synthesis of 4-amino-5-biphenyl-4-yl-4H-[1,2,4] triazole-3-thiol (3)

In a 250 ml round bottom flask, potassium salt of N'-(Biphenyl-4-carbonyl)-hydrazine carbodithioate (2) (0.01 mole) was refluxed with hydrazine hydrate (0.01 mole) in methanol with 5-7 hrs. The reaction mixture was monitored during reaction by TLC (ethyl acetate and hexane (6:4)). After completion of the reaction, the mixture was neutralized with diluted HCl and then poured into the crushed ice. The solid thus obtained was washed with cold water, filtered and dried. Recrystallization from ethanol to yield white solid 4-amino-5-biphenyl-4-yl-4H-(1,2,4) triazole-3-thiol (3).

4-amino-5-biphenyl-4-yl-4H-[1,2,4] triazole-3-thiol (3)

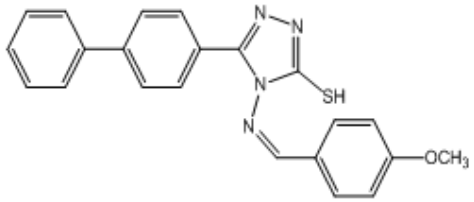
Off white crystals, mp 146°C, yield 65 %; IR (KBr, cm^{-1}) : 3298 (N-H),2410 (S-H), 1373 (C-N), 1623 (C=N),760 (C-S) ; ^{1}H NMR (400.1 MHz, DMSO): δ_H 9.32 (s, 1H, SH), 6.82-7.98 (m, 9H,Ar-H), 5.60 (s, 2H, NH_2); Anal. Calcd for: $C_{14}H_{12}N_4S$ (268.3); Found (C, 69.27; H, 4.31; N, 7.95; O, 9.02; S, 8.83 %); requires (C, 62.66; H, 4.51; N, 20.88; S, 11.95%); MS: *m/z*: 268 (M+).

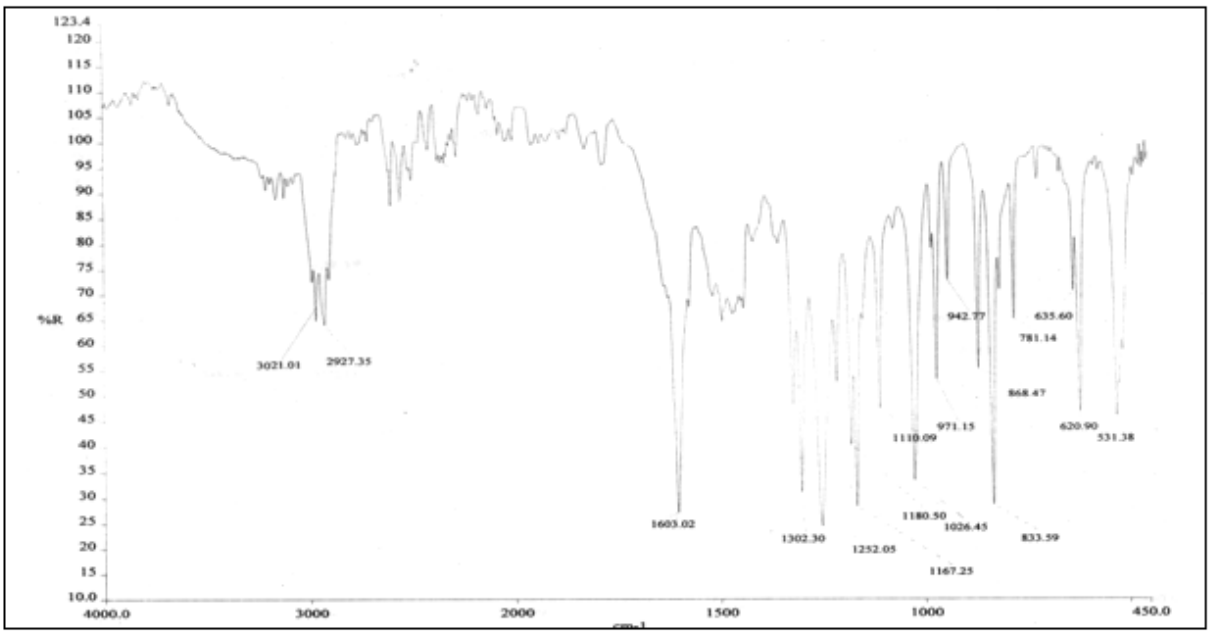
General procedure for the synthesis of 5-Biphenyl-4-yl-4-[(substituted benzylidene)-amino]-4H-[1,2,4]triazole-3-thiol (4 a-j)

4-amino-5-biphenyl-4-yl-4H-[1, 2, 4] triazole-3-thiol (11) (0.01 mole) and substituted aromatic benzaldehyde (0.01 mole) in 25 mL of glacial acetic acid was stir for 5 h at refluxed temperature. The completion of reaction was confirmed by TLC. After completion of reaction, the mixture was cooled and poured into the crushed ice. The product obtained was filtered and wash with ethanol and water, filtered and dried. The products were recrystallized from absolute methanol. It was dried to give the compounds **4 a-j** (yields.75-83%) The physical data of the synthesized compounds are shown in below.

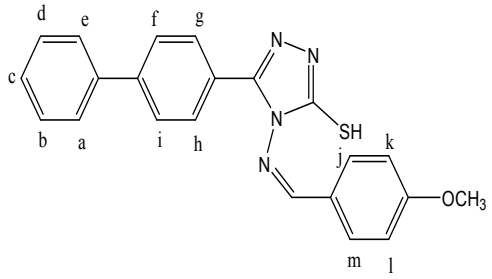
5-Biphenyl-4-yl-4-[(4-methoxybenzylidene)-amino]-4H-[1,2,4]triazole-3-thiol (4a)

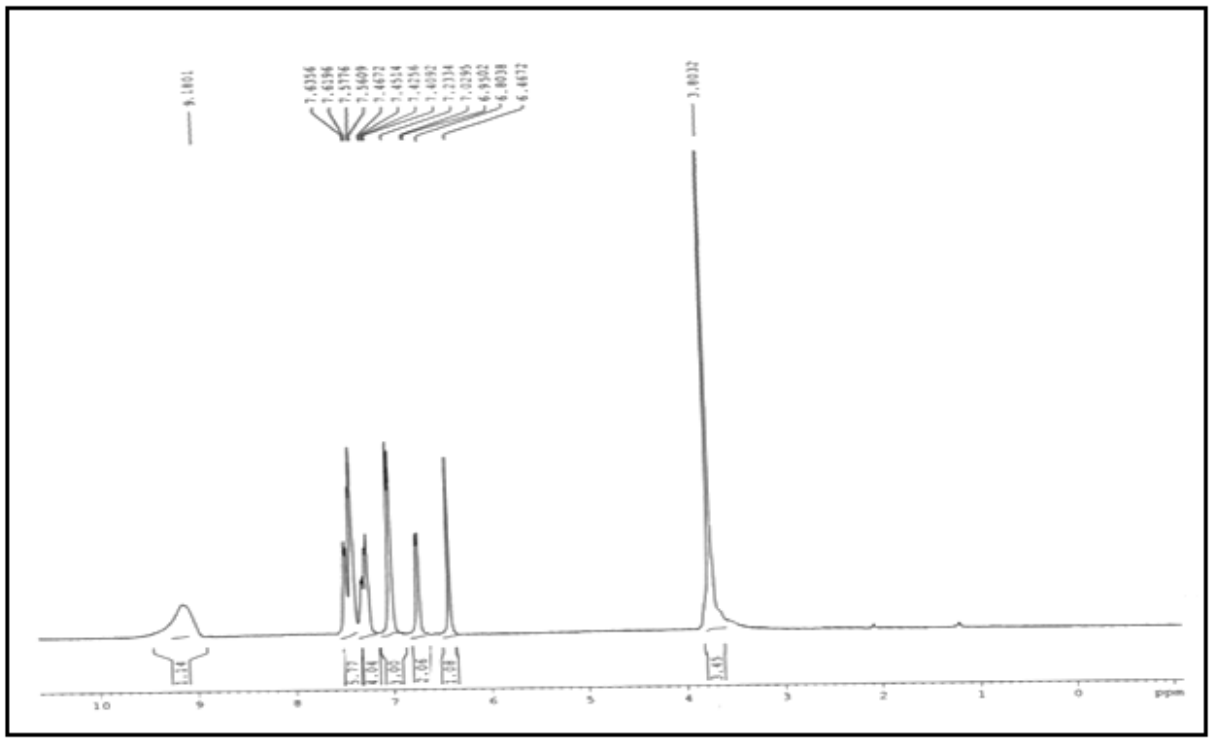
Pale yellow crystals, mp 165°C, yield 60 %; IR (KBr, cm^{-1}) 781 (C-S), 1603 (C=N), 3021 (C-H), 1252 (C-O-C); ^{1}H NMR (400.1 MHz, DMSO): δ_H 9.18 (s, 1H, SH), 6.46 (s, 1H, N=CH), 6.80-7.63 (m, 13H,Ar-H), 3.80 (s, 3H, OCH_3); Anal. Calcd for: $C_{22}H_{18}ON_4S$ (386.4); Found (C, 68.29; H, 4.63; N, 14.48; O, 4.15; S, 8.34 %); requires (C, 68.37; H, 4.69; N, 14.50; O, 4.14; S, 8.30%); MS: *m/z*: 386.2 (M+).





IR (KBr, cm^{-1}) 781 (C-S), 1603 (C=N), 3021 (C-H), 1252 (C-O-C)





^{1}H NMR (400.1 MHz, DMSO): δ_H 9.18 (s, 1H, SH), 6.46 (s, 1H, N=CH), 6.80-7.63 (m, 13H,Ar-H), 3.80 (s, 3H, OCH_3).

5-Biphenyl-4-yl-4-[(4-chlorobenzylidene)-amino]-4H-[1,2,4] triazole-3-thiol (4b)
Off white crystals, mp 154°C; yield 63 %; IR (KBr, cm^{-1}): 775 (C-S), 1620 (C=N), 3025 (C-H), 761 (C-Cl); ^1H NMR (400 MHz, DMSO): δ_H 9.32 (s, 1H, SH), 6.70 (s, 1H, N=CH), 6.85-7.86 (m, 13H, Ar-H); Anal. Calcd for: $C_{21}H_{15}N_4SCl$ (390.8); Found (C, 64.49; H, 3.85; Cl, 9.06; N, 14.31; S, 8.18 %); requires (C, 64.53; H, 3.87; Cl, 9.07 N, 14.34; S, 8.20 %); MS: m/z: 390.8 (M+).

5-Biphenyl-4-yl-4-[(4-hydroxybenzylidene)-amino]-4H-[1,2,4] triazole-3-thiol (4c)
Off white crystals, mp 163°C ; yield 56 %; IR (KBr, cm^{-1}) : 3412 (O-H), 782 (C-S), 1613 (C=N), 3016 (C-H); ^1H NMR (400.1 MHz, DMSO): δ_H 9.30 (s, 1H, SH), 6.58 (s, 1H, N=CH), 6.92-7.89 (m, 13H,Ar-H), 4.92 (s, 1H, OH); Anal. Calcd for: $C_{21}H_{16}ON_4S$ (372.4); Found (C, 67.70 H, 4.32; N, 15.06; O, 4.35; S, 8.64 %); requires (C, 67.72; H, 4.33; N, 15.05; O, 4.30; S, 8.61 %); MS: m/z: 372.4 (M+).

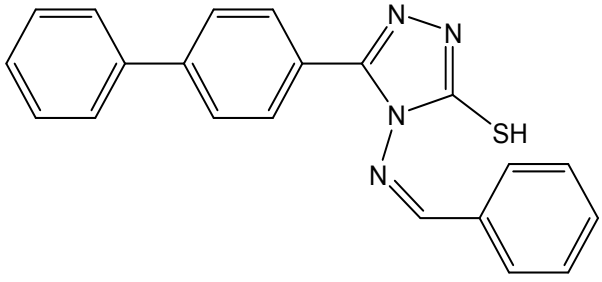
5-Biphenyl-4-yl-4-[(4-fluorobenzylidene)-amino]-4H-[1,2,4] triazole-3-thiol (4d)
Pale yellow, mp 165°C ; yield 70 %; IR (KBr, cm^{-1}): 1310 (C-F), 775 (C-S), 1626 (C=N), 3009 (C-H); ^1H NMR (400.1 MHz, DMSO): δ_H 9.29 (s, 1H, SH), 6.61 (s, 1H, N=CH), 6.89-7.95 (m, 13H,Ar-H); Elemental analysis: $C_{21}H_{15}N_4SF$ (374.4) ; Found (C, 67.35; H, 4.08; F, 5.05; N, 15.02; S, 8.53 %); requires (C, 67.36; H, 4.04; F, 5.07; N, 15.01; S, 8.56%); MS: m/z: 374.4M+).

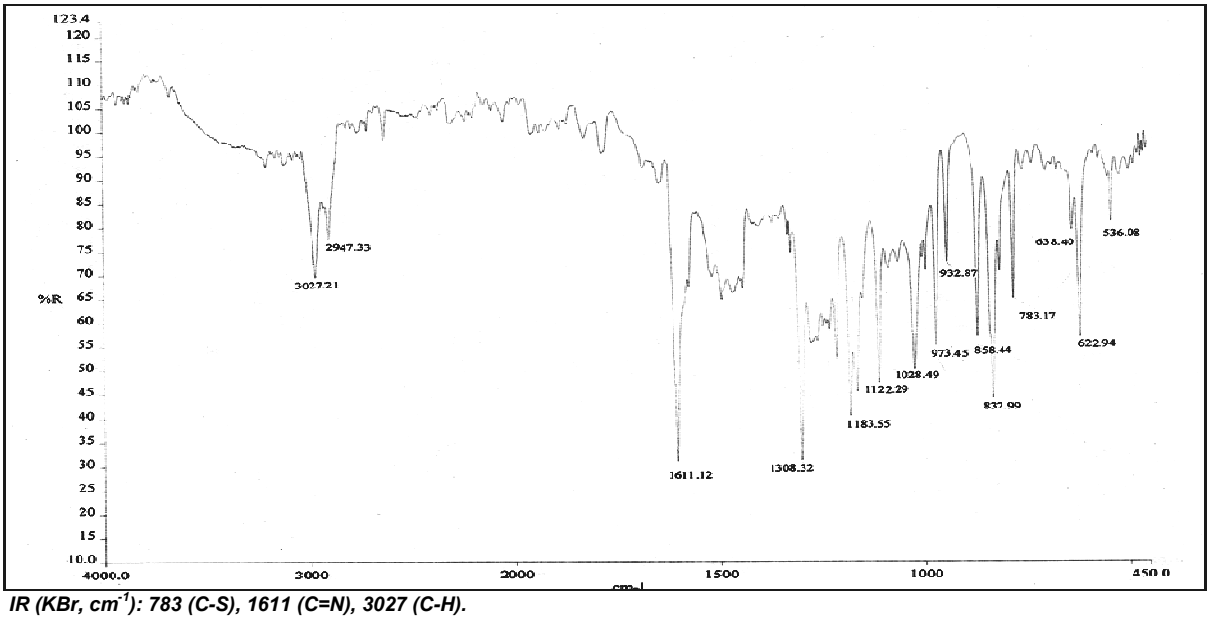
5-Biphenyl-4-yl-4-[(4-dimethylaminobenzylidene)-amino] -4H-[1,2,4] triazole-3-thiol (4e)
Off white crystals, mp 172°C ; yield 71 %; IR (KBr, cm^{-1}): 775 (C-S), 1611 (C=N), 1350 (C-N), 3018 (C-H); ^1H NMR (400.1 MHz, DMSO): δ_H 9.30 (s, 1H, SH), 6.63 (s, 1H, N=CH), 6.85-7.99 (m, 13H,Ar-H), 2.98 (s, 6H, $N(CH_3)_2$); Elemental analysis: $C_{23}H_{21}N_5S$ (399.5); Found (C, 69.10; H, 5.29; N, 17.50; S, 7.97 %); requires (C, 69.15; H, 5.30; N, 17.54; S, 8.03%); MS: m/z: 399.5 (M+).

5-Biphenyl-4-yl-4-[(3-methoxy,4-hydroxybenzylidene)-amino]-4H-[1,2,4] triazole-3-thiol (4f)
Off white crystals, mp 180°C ; yield 61 %; IR (KBr, cm^{-1}): 3389 (O-H), 782 (C-S), 1611 (C=N), 3015 (C-H), 1249 (C-O-C); ^1H NMR (400.1 MHz, DMSO): δ_H 9.28 (s, 1H, SH), 6.67 (s, 1H, N=CH), 6.95-8.01 (m, 12H,Ar-H), 3.73 (s, 3H, OCH_3), 5.10 (s, 1H, OH); Elemental analysis: $C_{22}H_{18}O_2N_4S$ (402.4); Found (C, 65.60; H, 4.55; N, 13.91; O,7.90; S,7.92 %); requires (C, 65.65; H, 4.51; N, 13.92; O, 7.95; S, 7.97 %); MS: m/z: 402.4 (M+).

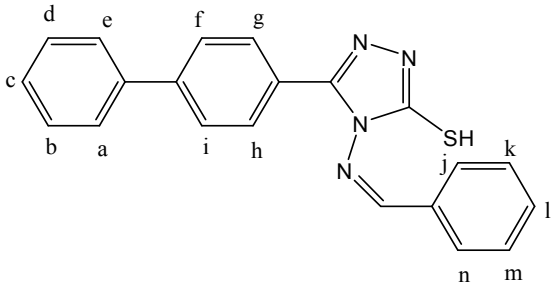
5-Biphenyl-4-yl-4- [(3, 4, 5-trimethoxybenzylidene)-amino]-4H-[1,2,4] triazole-3-thiol (4g)
Off white crystals, mp 153°C ; yield 56 %; IR (KBr, cm^{-1}): 772 (C-S), 1618 (C=N), 3011 (C-H), 1240 (C-O-C); ^1H NMR (400.1 MHz, DMSO): δ_H 9.33 (s, 1H, SH), 6.71 (s, 1H, N=CH), 6.95-8.01 (m, 11H,Ar-H), 3.82 (s, 9H, OCH_3); Elemental analysis: $C_{24}H_{22}O_3N_4S$ (446.5) ; Found (C, 64.50; H, 4.93; N, 12.53; O,10.72; S, 7.12 %); requires (C, 64.56; H, 4.97; N, 12.55; O, 10.75; S, 7.15%); MS: m/z: 446.5 (M+).

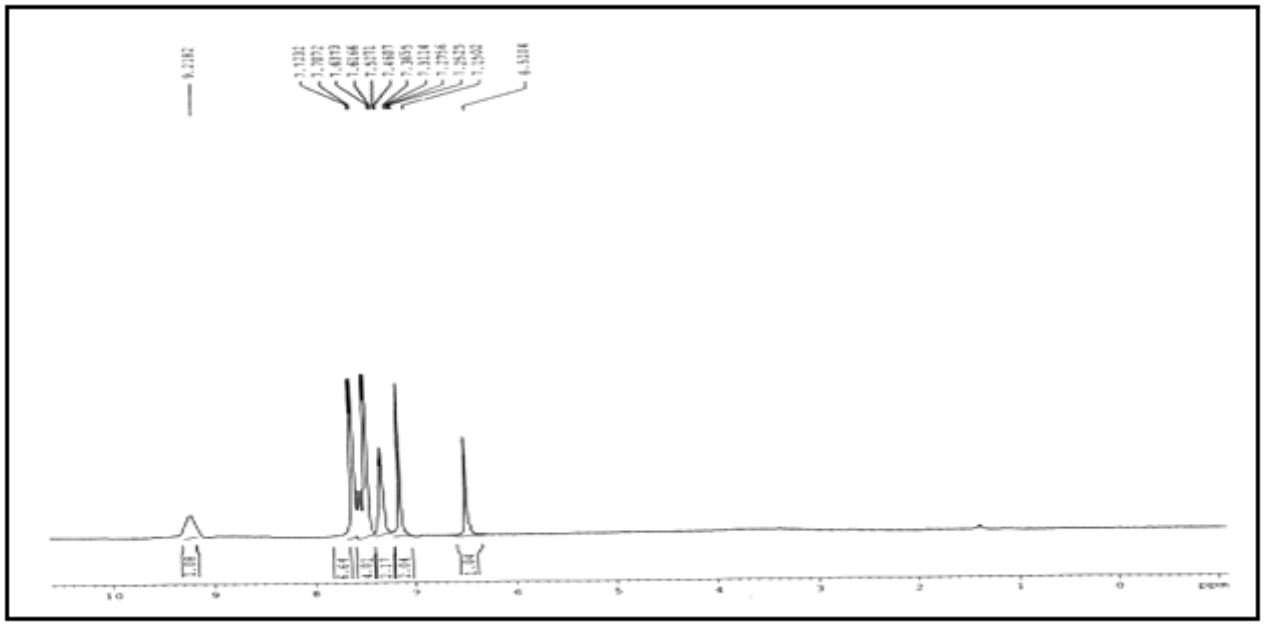
5-Biphenyl-4-yl-4-[(benzylidene)-amino]-4H-[1,2,4] triazole-3-thiol (4h)
Off white crystals, mp 157°C; yield 59 %; IR (KBr, cm^{-1}): 783 (C-S), 1611 (C=N), 3027 (C-H); ^1H NMR (400.1 MHz, DMSO): δ_H 9.21 (s, 1H, SH), 6.51 (s, 1H, N=CH), 7.15-7.72 (m, 14H, Ar-H); Anal. Calcd for: $C_{21}H_{16}N_4S$ (356.4); Found (C, 70.71; H, 4.50; N, 15.69; S, 9.08 %); requires (C, 70.76; H, 4.52; N, 15.73; S, 9.0%); m/z: 356.4 (M+).





IR (KBr, cm^{-1}): 783 (C-S), 1611 (C=N), 3027 (C-H).





^{1}H NMR (400.1 MHz, DMSO): δ_H 9.21 (s, 1H, SH), 6.51 (s, 1H, N=CH), 7.15-7.72 (m, 14H, Ar-H).

5-Biphenyl-4-yl-4-[(2-chlorobenzylidene)-amino]-4H-[1,2,4] triazole-3-thiol (4i)

Off white crystals, mp 189°C ; yield 62 %; IR (KBr, cm^{-1}): 771 (C-S), 1614 (C=N), 3018 (C-H), 760 (C-Cl); ^{1}H NMR (400.1 MHz, DMSO): δ_H 9.30 (s, 1H, SH), 6.55 (s, 1H, N=CH), 7.10-7.92 (m, 13H,Ar-H); Anal. Calcd for: $C_{21}H_{15}N_4SCl$ (390.8); Found (C, 64.50; H, 3.85; N, 14.31; Cl, 9.01; S, 8.15 %); requires (C, 64.53; H, 3.87; N, 14.34; Cl, 9.07; S, 8.20%); MS: m/z: 390.8 (M+).

5-Biphenyl-4-yl-4-[(3-nitrobenzylidene)-amino]-4H-[1,2,4] triazole-3-thiol (4j)

Pale yellow crystals, mp 192°C; yield 50 %; IR (KBr, cm^{-1}): 765 (C-S), 1610(C=N), 3012(C-H), 1530 (NO_2); ^1H NMR (400.1 MHz, DMSO): δ_H 9.40 (s, 1H, SH), 6.72 (s, 1H, N=CH), 7.16-8.30 (m, 13H, Ar-H); Anal. Calcd for: $C_{20}H_{17}N_5O_2S$ (391.4); Found (C, 61.32; H, 4.36; N, 17.42; O, 8.10; S, 8.23 %); requires (C, 61.37; H, 4.38; N, 17.45; O, 8.17; S, 8.19%); MS: m/z: 391.4 (M+).

Antimicrobial Screening

The anti-bacterial activity of the synthesized compounds was tested against two gram positive bacteria (*Staphylococcus aureus* ATCC 9144*, B. substilis* ATCC 6051) and two gram negative bacteria (*Escherichia coli* ATCC 25922 and *Klebsiella pneumoniae* ATCC 11298) using nutrient agar medium (Hi-Media Laboratories, India). The antifungal activities of the compounds were tested against *Candida albicans ATCC* 90028 using sabouraud dextrose agar medium (Hi-Media Laboratories, India).

Paper disc diffusion technique

The sterilized medium was inoculated (1mL/100 mL of medium) with the suspension (10^5cfu mL^{-1}) of the micro-organism (matched to McFarland barium sulphate standard) and poured into a a petridish to give a depth of 3-4 mm. The paper impregnated with the test compounds (100 µg/ disc) was placed on the solidified medium. The plates were pre-incubated for 1 hr at room temperature and incubated at 37°C for 24 and 48 hrs for anti-bacterial and anti-fungal activities, respectively. Ampicillin (100 µg/disc) and Flucanazole (100 µg/disc) were used as standard for anti-bacterial and anti-fungal activities, respectively [23]. The observed zone of inhibition is presented in Table-1.

Table 1
Antimicrobial activity data of synthesized compounds (4a-4j)

Compounds	Antimicrobial activity (in mm)				Antifungal activity (in mm)
	Gram positive		Gram negative		
	B. substilis	*S . aureus*	*E. coli*	*K. pneumonia*	*Candida albicans.*
4a	15	14	10	08	06
4b	08	06	10	11	12
4c	07	10	14	15	08
4d	14	13	09	06	14
4e	11	09	06	07	05
4f	10	08	10	05	07
4g	13	12	07	05	10
4h	06	05	08	10	07
4i	09	07	11	09	14
4j	10	08	12	13	06
Ampicillin	28	26	22	20	-
Flucanazole	-	-	-	-	19

RESULTS

The structure of all the synthrsized compounds was confirmed by IR, ^1H NMR and elemental analysis. The IR spectra of compounds (A_1-A_{13}) showed the C-S stretching group at 800-760 cm^{-1} in all the compounds. The C=N group is observed as a strong and sharp band at 1660-1600 cm^{-1} in these compounds and C-O-C stretching at 1252 cm^{-1} respectively. The C-H (aliphatic and aromatic), C=C stretching vibrations are observing at their usual positions. Further, ^1H NMR spectra exhibited multiplets in the region at δ 7.15-7.72 ppm for 13 aromatic protons (9 aromatic protons of diphenyl ring and 4 aromatic protons of benzene ring) (**4a**). Three proton of the $–OCH_3$ group is observed at δ 3.80 ppm as a singlet (**4a**). One protons present in CH=N of compounds (**4a**) is found to resonate as singlet at δ 6.46 ppm. The proton of the -SH group is observed at δ 9.18 ppm as a singlet (**4a**). The antibacterial activity (zone of inhibition) of the synthesized

compounds was performed against *Bacillus subtilis* (gram positive), *Staphylococcus aureus* (gram positive) *and Escherichia coli* (gram negative), *Klebsiella pneumoniae* (gram negative) by an agar cup plate method using standard ampicillin drug. For antifungal activity the standard used was flucanazole. (Table 1) The results given in Table 1 indicated that most of the compounds tested, exhibited considerable activities against one bacterial species, Compounds 4a and 4d exhibited a moderate activity against *Bacillus subtilis* and *Staphylococcus aureus*. Compounds 4c and 4j exhibited a moderate activity against *Escherichia coli* and *Klebsiella pneumoniae.* All the screened compounds were less active against *B. substilis.* As far as the anti-fungal activity concerned, compounds 4b, 4d, 4i showed moderate activity against *Candida albicans*. The other compounds tested showed less activity against the fungal species.

CONCLUSION

The title compounds 4a, 4d exhibited good activity against Bacillus substilis, and Staphylococcus aureus and 4c, 4j exhibited good activity against Escherichia coli and Klebsiella pneumoniae. The compounds 4b, 4d, 4i gave good antifungal activity against Candida albicans It can be concluded that 5-Biphenyl- 4-yl -4- [(substituted benzylidene) - amino]- 4H- [1, 2, 4] triazolo - 3- thiol synthesized from 4-amino-5-biphenyl- 4- yl- 4H- [1, 2, 4] triazole-3-thiol certainly holds great promise towards good active leads in medicinal chemistry.

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