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A Process for Preparation of 2-[6-substituted-[1,2,4]-triazolo[3,4-b] [1,3,4] thiadiazole-3-yl]phenol and it's Antimicrobial Activity

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ABSTRACT

A STTP promoted series of compound 2-[6-substituted-[1,2,4]-triazolo[3,4-b][1,3,4]thiadiazole-3-yl]phenol(3a-j) was synthesis by 4-Amino-5-mercapto-4H-1,2,4-triazole (1) (0.1mole) and,Various acid derivatives (2a-j) in presence of phosphorous oxychloride (100 ml) in alcoholic solvent was heated at reflux temp for 6-8 hrs. This procedure is compatible with a broad range of functional groups describe R^1 = various amide derivative afforded good yield 72-85% in suitable alcoholic solvent and excess of phosphorus oxychloride was removed under vacuum in presence of alcohol solvent. The Product STPP (3a-j) purification done by acid base treatment and recrystlaistion in alcohol to give highly pure compound ; 2-[6-substituted-[1,2,4]-triazolo[3,4-b][1,3,4]thiadiazole-3-yl]phenol (3a-j).

Keywoeds : [1,2,4]-triazolo[3,4-b][1,3,4]thiadiazole-3-yl] Phenol, Antimicrobial Evaluation

I. INTRODUCTION

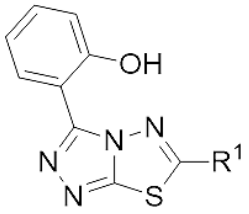
1,2,4-Triazoles and their derivatives occupy a essential position in medicinal chemistry because of their potential biological activities such as antibacterial [1], antifungal [2], antitubercular [3], anti-inflammatory[4] etc. Recently, it was reported that the [1,2,4]triazolo[3,4-b] [1,3,4]thiadiazoles and [1,2,4]triazolo[3,4-b] [1,3,4] thiadiazines possess antimicrobial activities[5]. Also, 6-substituted 3-(1-adamantyl)-1,2,4- triazolo[3,4-b] [1,3,4]thiadiazoles have been evaluated for their antiviral activity[6]. The [1,2,4]triazoles and [1,3,4] thiadiazoles are known for their broad-spectrum of biological activities[7-11] and many other uses Various acid derivatives [12-18] mentioned in on cyclization with 4-Amino-5-mercapto-4H-1,2,4-triazole (1) in presence of phosphorous oxy chloride to form triazolothiadiazole derivatives (3a-j).

II. METHODS AND MATERIAL

Measurements

All commercial chemicals and solvents used are of reagent grade and were used without further treatment unless otherwise noted. 1H NMR spectra were recorded with a Bruker Advance II 300 NMR spectrometer. Chemical shifts were recorded in parts per million (ppm) and were reported relative to the TMS. Mass spectral data were recorded on an Applied Bio system Qtrap 3200 LC-MS/MS system in ESI mode. The FT-IR spectra of the synthesized compounds were recorded on Schimadzu IRPrestige-21 in KBr. Melting points of the compounds were determined using a Veego digital melting point apparatus and are reported uncorrected. The purity of the compounds was confirmed by thin layer chromatography using Merck silica gel 60 F254 coated alumina plates.

The General Structure of Target Molecule



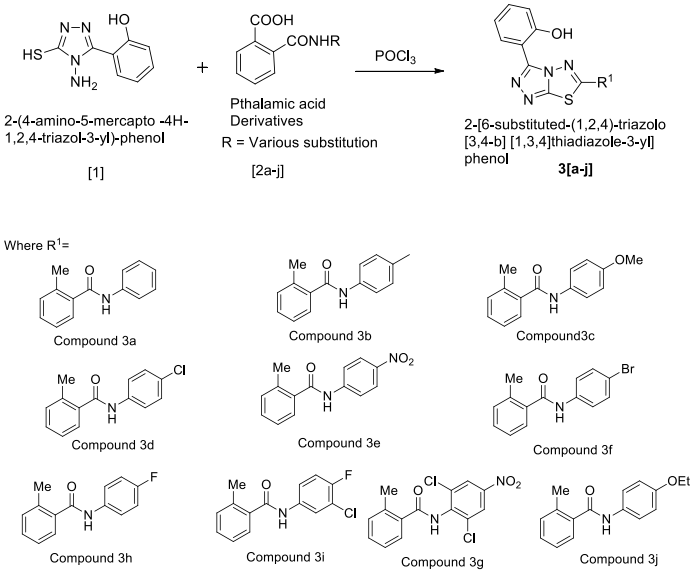
2-[6-substituted-(1,2,4)-triazolo [3,4-b] [1,3,4]thiadiazole-3-yl] phenol

3[a-j]

Figure 1. Design strategy of 2-[6-substituted-[1,2,4]-triazolo[3,4-b][1,3,4]thiadiazole-3-yl]phenol

The mixture of 4-Amino-5-mercapto-4H-1,2,4-triazole (1) (0.1mole) and (0.12mole) Various acid derivatives (2a-j) in presence of phosphorous oxychloride (100 ml) was refluxed on water bath for 6 hours. Excess of phosphorus oxychloride was removed under vacuum.The progress of the reaction was monitored by TLC. The remaining reaction mixture poured in ice water. The solution was made alkali by adding KOH the deposited solid filtered and crystallized from ethanol to give 2-[6-substituted-[1,2,4]-triazolo[3,4-b][1,3,4] thiadiazole-3-yl]phenol (3a-j). This was obtained in 67-85% yield. The yields, melting points and other characterization data of these compounds are given below. The compound so obtained was dried and crystallized from ethanol.

The reaction scheme was shown below,



III. RESULTS AND DISCUSSION

RESULTS

2-[6-(N-Phenyl benzamide) -[1,2,4]-triazolo[3,4-b] [1,3,4] thiadiazole-3-yl]phenol. (Compound -3a)

Molecular Formula: $C_{22}H_{15}N_5O_2S$ Molecular Weight: 411.8 gm/mole Yield 72 (%), m.p. 205-207^oC, IR (KBr) $cm^{-1:}$ 3215 cm^{-1} (-OH gp of Ar-OH),3020-3080 cm^{-1} -CH of (Ar-C–H str), 1620-1648 cm^{-1} -C=N, 1160 cm^{-1} > C-S, 1080 cm^{-1} >C-N, 1160 cm^{-1} >C-S, 1040 cm^{-1}>N-N of triazole and Thiadiazole,1685 cm^{-1} >C=O of –CONH,3200 cm^{-1} -NH of –CONH,^{1}H NMR (400 MHz, DMSO-d_6) d(ppm): 7.3-8.8 (m, 13H, Aromatic),10.5 (s, 1H, -OH),9.5 (s, 1H, -CONH). Elemental Analysis ; %C ,%H, %N,%S Calculated: 63.92, 3.63, 16.95,7.75; Found: 55.45,6.38, 24.25,7.70.

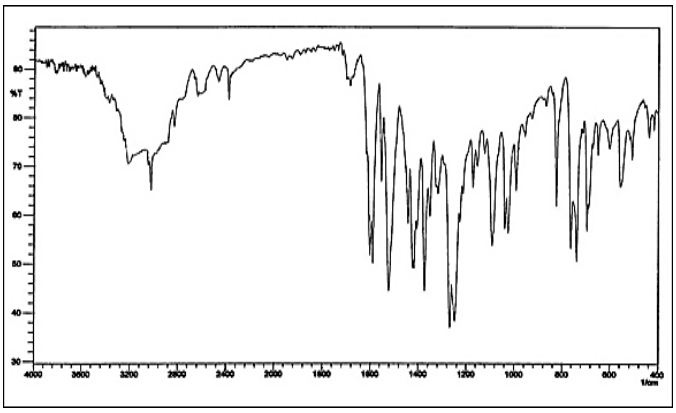


Figure 1. IR spectrum of Compound 3a

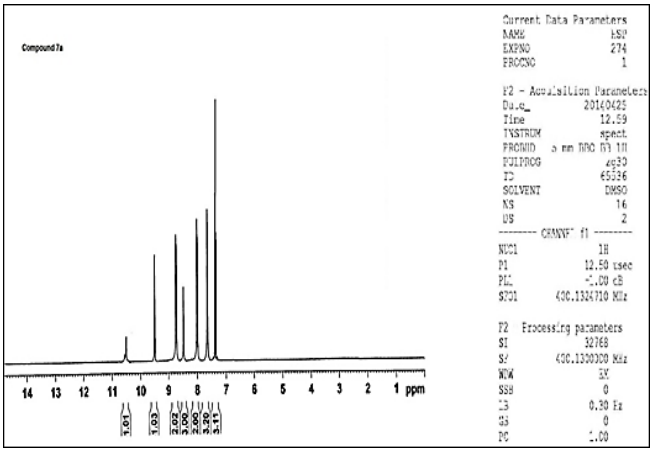


Figure 2. ^{1}HNMR spectrum of Compound 3a

[6-(N-4-methyl Phenyl benzamide)-[1,2,4]-triazolo[3,4-b][1,3,4]thiadiazole-3-yl]phenol mpound-3b)

Molecular Formula: $C_{23}H_{17}N_5O_2S$ Molecular Weight: 428.2 gm/mole Yield 80(%), m.p. 200-202^oC, IR (KBr) $cm^{-1:}$ -NH of –CONH 3250 cm^{-1}, 3200 cm^{-1} (OH gp of Ar-OH),3015-3065 cm^{-1} CH of (Ar C–H str), 2950 cm^{-1} Ar-CH_3, 1620-1648 cm^{-1} -C=N, 1160 cm^{-1} > -C-S, 1080 cm^{-1} >CH, -NH, 1160 cm^{-1} >C-S, 1040 cm^{-1}>N-N of triazole and Thiadiazole,1685 cm^{-}=Oof –CONH,3200 cm^{-1} -NH of –CONH,^{1}H NMR (400 MHz, DMSO-d_6) ^{1} (s, 1H, Ar-OH) 7.34-8.80 (m, 12H, Aromatic),10.5 (s, 1H, -OH),9.5 (s, 1H, -CONH),2.35 (s, 3H, -CH_3) Elemental Analysis ; %C ,%H, %N,%S Calculated: 64.63 3.98 16.39 7.49;

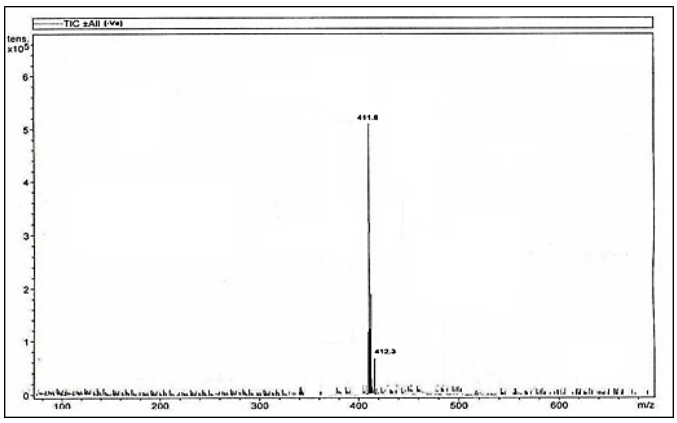


Figure 3. MASS spectrum of Compound 3a

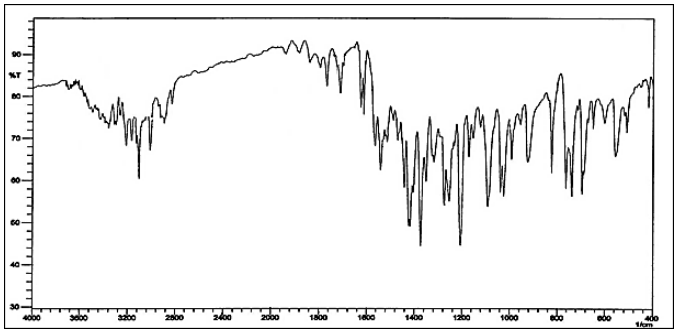


Figure 4. IR spectrum of Compound 3b

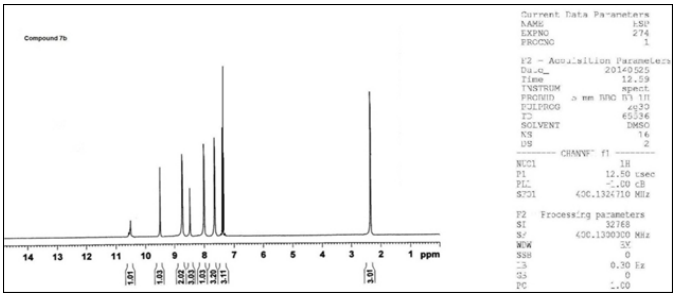


Figure 5. ^{1}H NMR spectrum of Compound 3b

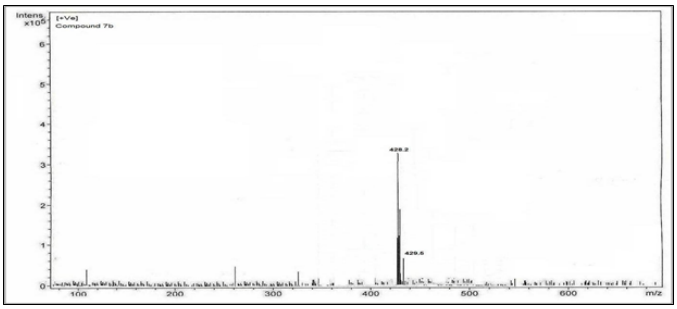


Figure 6. Mass spectrum of Compound 3b

2-[6-(N-4-methoxy Phenyl benzamide)-[1,2,4]-triazolo[3,4-b][1,3,4]thiadiazole-3-yl]phenol (Compound-3c)

Molecular Formula: $C_{23}H_{17}N_5O_3S$ Molecular Weight: 443 gm/mole Yield 74(%), m.p. 194-196^oC, IR (KBr) $cm^{-1:}$ -NH of –CONH 3250 cm^{-1}, 3200 cm^{-1} (-OH gp of Ar-OH),3015-3065 cm^{-1} -CH of (Ar C–H str), 2950 cm^{-1} Ar-OCH_3, 2820 cm^{-1} -C=N, 1160 cm^{-1} > C-S, 1080 cm^{-1} >C-N, 1160 cm^{-1} >C-S, 1040 cm^{-1}>N-N of triazole and Thiadiazole,1685 cm^{-1} 1040 cm^{-1} Ar-OCH_3>C=O of –CONH,3200 cm^{-1} -NH of –CONH,^{1}H NMR (400 MHz, DMSO-d_6) d(ppm): 7.24-8.70 (m, 12H, Aromatic),10.5 (s, 1H, -OH), 9.5(s, 1H, -CONH),3.73 (s, 3H, -OCH_3) Elemental Analysis ; %C ,%H, %N,%S Calculated: 62.30, 3.83,15.80,7.22; Found: 62.30,3.90,15.4,7.20.

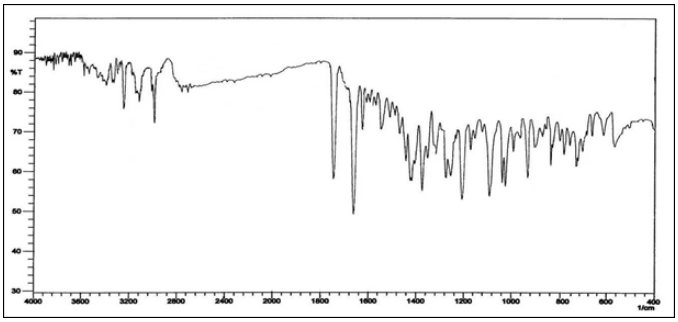


Figure 7. IR spectrum of Compound 3c

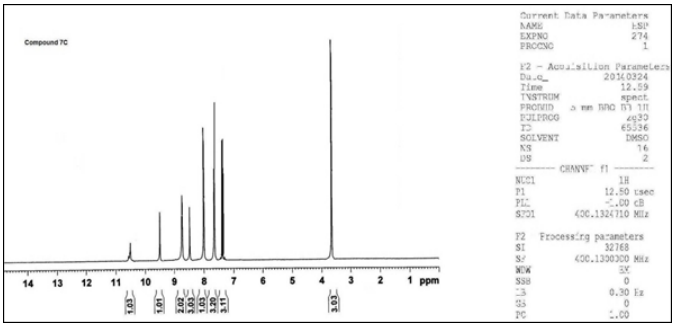


Figure 8. IR spectrum of Compound 3c

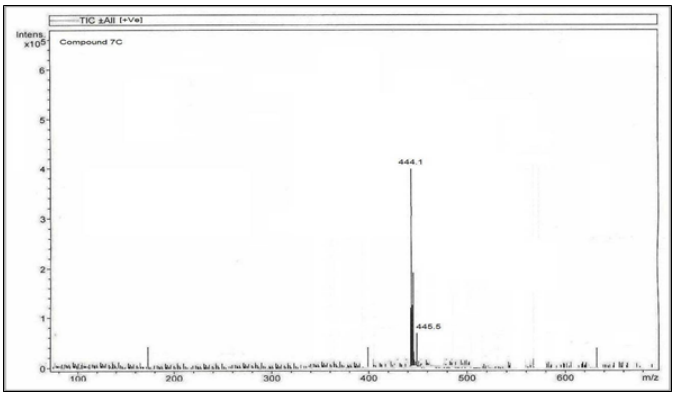


Figure 9. MASS spectrum of Compound 3c

2-[6-(N-4-chloro Phenyl benzamide)-[1,2,4]-triazolo[3,4-b][1,3,4]thiadiazole-3-yl]phenol (Compound-3d)

Molecular Formula: $C_{22}H_{14}N_5O_2SCl$ Molecular Weight: 447.5 gm/mole Yield 70(%), m.p. 202-204^oC, IR (KBr) $cm^{-1:}$ -NH of –CONH 3250 cm^{-1}, 3200 cm^{-1} (OH gp of Ar-OH),3015-3065 cm^{-1} -CH of (Ar C–H str), 2950 cm^{-1} Ar-OCH_3, 2820 cm^{-1} -C=N, 1160 cm^{-1} > C-S, 1080 cm^{-1} >C-N, 1160 cm^{-1} >C-S, 1040 cm^{-1}>N-N of triazole and Thiadiazole,1685 cm^{-1} C=O of –CONH, 3200 cm^{-1} -NH of –CONH,1090 cm^{-1} Ar-Cl ^1H NMR (400 MHz, DMSO-d_6) d(ppm): 7.20-8.75 (m, 12H, Aromatic),10.5 (s, 1H, -OH), 9.5(s, 1H, -CONH), Elemental Analysis ; %C ,%H, %N, %S, %Cl Calculated: 58.99,3.13,15.64,7.15,7.93
; Found: 59.00,3.10,15.60,7.10,8.00.

2-[6-(N-4-nitro Phenyl benzamide)-[1,2,4]-triazolo[3,4-b][1,3,4]thiadiazole-3-yl]phenol (Compound-3e)

Molecular Formula: $C_{22}H_{14}N_6O_4S$ Molecular Weight: 447.5 gm/mole Yield 70(%), m.p. 198-200^oC, IR (KBr) cm^{-1}: 3215 cm^{-1} -OH of Aromatic, 3020-3080 cm^{-1} -CH of Aromatic,1620-1648 cm^{-1} -C=N,1160 cm^{-1} C-S, 1080 cm^{-1} C-N,1040 cm^{-1} N-N of triazole and Thiadiazole,1685 cm^{-1} -C=O of –CONH, 3200 cm^{-1} -NH of -CONH 1527 cm^{-1} Ar-NO_2 , ^1H NMR (400 MHz, DMSO-d_6) d(ppm): 7.22-8.70 (m, 12H, Aromatic),10.5 (s, 1H, -OH),9.5(s,1H,-CONH),Elemental
Analysis ; %C ,%H, %N, %S, Calculated: 57.64,3.05,18.34,6.98
; Found: 57.60, 3.00, 18.30,7.00.

2-[6-(N-4-bromo Phenyl benzamide)-[1,2,4]-triazolo[3,4-b][1,3,4]thiadiazole-3-yl]phenol (Compound-3f)

Molecular Formula: $C_{22}H_{14}N_5O_2SBr$ Molecular Weight:492gm/mole Yield 70(%), m.p. 199-202^oC, IR (KBr) cm^{-1}: 3215 cm^{-1} -OH of Aromatic, 3200 cm^{-1} -NH of -CONH 3020-3080 cm^{-1} CH of Aromatic,1620-1648 cm^{-1} -C=N,1160 cm^{-1} C-S, 1080 cm^{-1} C-N, 1070 cm^{-1} Ar-Br,1040 cm^{-1} N-N of triazole and Thiadiazole,1685 cm^{-1} -C=O of –CONH, 3200 cm^{-1} -NH of -CONH 1527 cm^{-1} Ar-NO_2 , ^1H NMR (400 MHz, DMSO-d_6) d(ppm): 7.24-8.70 (m, 12H, Aromatic),10.7 (s, 1H, -OH), 9.4(s, 1H, -CONH), Elemental Analysis ; %C ,%H, %N,%S, **%Br** Calculated: 57.64,3.05,18.34,6.98, 16.26, Found: 57.60, 3.00, 18.30,7.00, 16.10.

2-[6-(N-4-nitro-2,6-di chloro Phenyl benzamide)-[1,2,4]-triazolo[3,4-b][1,3,4]thiadiazole-3-yl]phenol (Compound-3g)

Molecular Formula: $C_{22}H_{12}N_6O_4SCl_2$Molecular Weight: 527gm/mole Yield 73(%), m.p. 205-207^oC, IR (KBr) cm^{-1}: 3020-3080 cm^{-1} >CH of Aromatic,3215 cm^{-1} OH of Aromatic,1620-1648 cm^{-1} -C=N ,1160 cm^{-1} C-S,1080 cm^{-1} C-N, 1040 cm^{-1} N-N of triazole and Thiadiazole,1685 cm^{-1} -C=O of –CONH,3200 cm^{-1} -NH of –CONH,1090 cm^{-1} Ar-Cl 1527 cm^{-1} Ar-$NO_2$$^1H$ NMR (400 MHz, DMSO-d_6) d(ppm): 7.15-8.30 (m, 12H, Aromatic),10.5 (s, 1H, -OH), 9.3(s, 1H,-CONH),Elemental
Analysis %C, %H, %N, %S, %Cl

Calculated: 50.09, 2.27, 15.93, 6.07, 3.47 Found: 50.00,2.30,16.00, 6.00,13.50.

2-[6-(N-4-fluoro Phenyl benzamide)-[1,2,4]-triazolo[3,4-b][1,3,4]thiadiazole-3-yl]phenol (Compound-3h)

Molecular Formula: $C_{22}H_{14}N_5O_2SF$ Molecular Weight: 431gm/mole Yield 68(%), m.p. 210-212^oC, IR (KBr) cm^{-1}: 3020-3080 cm^{-1}, -CH of Aromatic,3215 cm^{-1},-OH of Aromatic,1620-1648 cm^{-1} -C=N,1160 cm^{-1} C-S,1080 cm^{-1}, -C-N,1040 cm^{-1} N-N of triazole and Thiadiazole,1685 cm^{-1} -C=O of –CONH, 3200 cm^{-1} -NH of –CONH, 1200 cm^{-1} Ar-F ^1H NMR (400 MHz, DMSO-d_6) d(ppm): 7.20-8.5 (m, 12H, Aromatic), 10.5 (s, 1H, -OH), 9.3(s, 1H, -CONH), Elemental Analysis ; %C ,%H, %N,%S, **%F** Calculated: 61.25,3.24,16.24,7.42 4.40 Found: 61.20, 3.20,16.20,7.40,4.40.

2-[6-(N-4-fluoro-3-chloro Phenyl benzamide)-[1,2,4]-triazolo[3,4-b][1,3,4]thiadiazole-3-yl] phenol(Compound-3i)

Molecular Formula: $C_{22}H_{13}N_5O_2SFCl$ Molecular Weight: 465.5 gm/mole Yield 67(%), m.p. 208-210^oC, IR (KBr) cm^{-1}: 3020-3080 cm^{-1} CH of Aromatic,3215 cm^{-1} -OH of Aromatic,1620-1648 cm^{-1} -C=N,1160 cm^{-1} -C-S,1080 cm^{-1}C-N,1040 cm^{-1} -N-N of triazole and Thiadiazole,1685 cm^{-1} -C=O of –CONH,3200 cm^{-1} -NH of –CONH,1200 cm^{-1} Ar-F 1090 cm^{-1} Ar-Cl. ^1H NMR (400 MHz, DMSO-d_6) d(ppm): 7.2-8.6 (m, 12H, Aromatic),10.4 (s, 1H, -OH), 9.2(s, 1H, -CONH), Elemental Analysis ; %C ,%H, %N,%S, **%F, %Cl** Calculated: 56.71, 2.79,15.03, 6.87,4.08,7.62 Found: 56.70,2.80,15.00,6.80,4.00,7.60.

2-[6-(N-4-ethoxy Phenyl benzamide)-[1,2,4]-triazolo[3,4-b][1,3,4]thiadiazole-3-yl]phenol (Compound-3j)

Molecular Formula: $C_{24}H_{19}N_5O_3S$ Molecular Weight: 457gm/mole Yield 68(%), m.p. 199-202^oC, IR (KBr) cm^{-1}: 3220 cm^{-1} -OH of Aromatic, 3020-3080 cm^{-1} -CH of Aromatic, 2950 cm^{-1} -C-H of –OCH_2CH_3,1620-1650 cm^{-1} -C=N, 1170 cm^{-1} -C-S, 1080 cm^{-1}-C-N,1040 cm^{-1} N-N of triazole and Thiadiazole,1690 cm^{-1} -C=O of –CONH, 3210 cm^{-1} -NH of –CONH, 1230, 1050 cm^{-1}Ar-OCH_2. ^1H NMR (400 MHz, DMSO-d_6) d(ppm): 7.2-8.6 (m, 12H, Aromatic),10.4 (s, 1H, -OH), 9.3(s, 1H, -CONH), 1.6(t, 3H, -CH_3),4.0 (m, 2H,-O-CH_2-)Elemental analysis; %C , %H, %N, %S, Calculated: 63.92, 3.63, 16.95, 7.75Found: 55.45, 6.38, 24.25, 7.70.

DISCUSSION

Compound 2-(4-amino-5-mercapto-4H-1,2,4-triazol-3-yl)-phenol [A] and various phthalamic acid derivatives [B] have been already prepared. The primary amino and mercapto functional group of compound [C] condensed with acid functional group presence in phthalamic acid derivatives [2a-j] to form various 2-[6-substituted-(1,2,4)-triazolo [3,4-b][1,3,4]thiadiazole-3-yl] phenol [3a-j]. The reaction conventionally used bases such as piperidine, Et_3N, K_2CO_3, NaOH and K_3PO_4 proved less effective. The control experiment confirmed that in the absence of the base reaction occurred. The reaction is also complete in microwave radiation technique in 15-20minutres.Compound 1a-j reaction complies is show in TLC result.

The Compound 3 a-j is conforming by 1H NMR Spectra. Compounds (3a-j) show singlet around 10.5 δ ppm for –OH proton and singlet around 9.5 δ ppm for 1H proton of –CONH linkage. The analytical and IR, NMR and MASS spectral data for all the compounds (3a-j) are shown.

Preparation of Mueller Hinton agar/ sabouraud's agar:

(Composition of agar media)

The medium was prepared by dissolving the specified quantity of the dehydrated medium (Hi-media) in purified water and was dispensed in 20

ml volumes into test tubes. The test tubes were closed with cotton plugs and sterilized by autoclaving at 121^0C (15 ibs/square inch) for 15 minutes. The contents of the tubes were poured aseptically into sterile Petri plates (90 mm diameter) and allowed to solidify.

Four different bacterial cultures viz., a staphylococcus aureus, Escherichia coli, pseudomonas aeruginosa and bacterial Subtillis and one of the fungal culture, Candida albicans were used as test organisms for evaluation of antibacterial and antifungal activity. Mueller Hinton agar medium was used to inoculate bacterial cultures and Sabouraud's dextrose agar medium was used for fungal culrures.

Each Petri plate containing Mueller Hinton agar medium was inoculated with one of the bacterial cultures by spreading a suitably diluted suspension of the organism (10^6 cells/ml) with a sterile cotton swab. One filter paper disk impregnated with the solution of the test compound was placed at three places of the plate at equal distance. Filter paper disk containing the standard drug (Ampicillin 10 µg) was placed at two places of the same plate.

All the plates were kept in the refrigerator for 1 hour to allow the diffusion of the sample into the surrounding agar medium. Then the plates were incubated at 37^0C for 24 hours. Diameter of the zones of inhibition wherever produced was measured and the average diameter for each sample was calculated. The diameters obtained for the standard antibiotic was also measured and the average diameter was compared with that produced by the test compounds.

Composition of Mueller Hinton agar medium		**Composition of Sabouraud's dextrose agar medium**	
Beef Extract	300 ml	Dextrose	40 g
Casein hydro lysate	17.5 g	Peptone	10 g
Starch	1.5 g	Agar	15 g
Agar	17 g	Distilled water	1000 ml
Distilled water	1000 ml	pH	5.6$\pm$0.2
pH	7.3 $\pm$0.2		

Similar procedure was carried out for the evaluation of antifungal activity using sabouraoud's dextrode agar medium and griseofulvin 25 µg disk as standard drug. Antifungal activity was tested against candida albicans. The plates were incubated at 27^0c for 48 hours.

Table 1 : Data of Antimicrobial activity of Novel triazolothiadiazole derivatives [3a-j]

Compound Number	**Diameter of Zone of Inhibition (In mm)**				
	B. Subtilis	**S.aureus**	**E.Coli**	**P.aeruginosa**	**C.albicans**
3a	12	17	12	15	15
3b	15	20	08	08	05
3c	13	13	14	12	10
3d	12	14	12	12	08
3e	11	15	15	06	11
3f	10	11	15	12	09

3g	09	12	12	05	11
3h	11	10	11	09	11
3i	12	15	16	08	12
3j	10	11	14	13	10
Ampicillin	16	20	17	19	12
Griseofulvin	15	18	18	17	14

IV. CONCLUSION

The object of invention is the process easy and 72-85% yield observed in alcoholic solvent. We have elaborated a synthesis of 2-[6-substituted-[1,2,4]-triazolo[3,4-b] [1,3,4] thiadiazole-3-yl]phenol reaction of 1.4-Amino-5-mercapto-4H-1,2,4-triazole (1) *(0.1mole) and* Various acid derivatives (2a-j) *in presence of phosphorous oxychloride (100 ml) in alcoholic solvent was refluxed temp* monitored in TLC Plate. This present method is efficient and operationally simple, affording the desired products with good yields. The purification method is developing by simple acid base salt purification technique. This protocol also features a broad substrate scope and excellent functional-group tolerance and show potential capabilities to construct complex molecules in synthetic and pharmaceutical chemistry. The Cyclization reaction Compound [3a-j] is observed in microwave radiation method also. The Compound [3a-j] is under observation of antimicrobial activity. The good antimicrobial activity observe in **compound 3e, 3f ,3i Microbial activity as compared to the standard drugs Ampicillin and Griseofulvin.**

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