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Synthesis, Characterization of substituted 5-(methylthio)-1-(3-((1-phenyl-1H-1,2,3-triazol-4-yl) methoxy) phenyl)-1H-tetrazole

Kotturi Gangadhar[1], Radhika More[1], Panga shyam[2], Balakishan Gorre[1]
[1]*Department of Chemistry, University College of Science, Telangana University, Telangana, India-503322*
[2]*N.J. Paulbudhe College of Pharmacy, Davedi, Ahmed Nagar, Maharashtra, India-414003*
Corresponding Author: Balakishan Gorre

ABSTRACT:
We have synthesized new substituted 5-(methylthio)-1-(3-((1-phenyl-1H-1,2,3-triazol-4-yl) methoxy) phenyl)-1H-tetrazole ***7(a-l)*** *and the anti-microbial activity of these compounds* ***7(a-l)*** *was evaluated using the disc diffusion technique against three typical Gram-positive bacteria. Out of all the synthesized compounds, compounds* ***7b, 7h,*** *and* ***7i*** *have demonstrated promising activity, according to the antifungal screening; the rest of analogues have demonstrated moderate to good antifungal activity compared to standard drugs Streptomycin and Amphotericin B*

KEYWORDS: *3-isothiocyanatophenol, tetrazole, triazole. anti-microbial activity, Ribavirin, Taozodone*

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I. INTRODUCTION:

In many compounds that are biologically active, the triazole moiety is a significant structural component.[1] One of the most significant and extensively researched subfields in medical chemistry is heterocyclic organic chemistry. Triazoles have a remarkable structural motif as a result of their numerous uses in a variety of scientific fields, and they are particularly connected to the chemistry of triazoles. The 1,3-dipolar azide-alkyne cycloaddition produced by copper(I) provides an effective method to access 1,4-disubstituted 1,2,3-triazoles [2]. The mainstays of triazole synthesis are alkyne-azide click reactions that are catalyzed by copper.[3] Methods for the production of 1,4- (copper(I)-catalysed),[4] or 1,5-disubstituted (ruthenium (II)-catalysed) [5] azide-alkyne compounds 1,2,3-triazoles offer a dependable method for assembling 1,2,3-triazoles with various substituents under benign circumstances and with great regioselectivity. The 1,2,3-triazole-bearing hybrids under study have been shown to have anticancer,[10-12] antimicrobial,[13-17] anti-infective,[18-19] and antioxidant[20-22] characteristics as a result of many biological screens carried out in 2018.[6-9] Adenosine diphosphate ribosylation biology[23] was also thought to be affected by triazole-linked derivatives, which were commonly employed in peptides to simulate a trans-amide bond despite their negative effects on the activity of native peptides.[24].

Due to its numerous uses in medicines, information recording systems, photography, explosives, and rocket propellants, tetrazoles have drawn a lot of interest. [25-26] In addition to serving as precursors for a number of heterocycles [27-28] containing nitrogen, they are significant ligands for several beneficial transformations. 1- Substituted tetrazoles are among the tetrazoles that have drawn the most interest due to their broad range of applications. Unfortunately, the potential use of 1-substituted tetrazoles in medical practice is severely limited by the absence of practical procedures for preparing them. There are a great number of 5-substituted tetrazoles known, but relatively few 1-substituted tetrazoles have been reported. [29-30] The use of costly and toxic reagents, the use of high boiling solvents, low yields, lengthy reaction times, harsh reaction conditions, difficulty obtaining and preparing the starting materials, laborious work-up, and the presence of highly toxic, explosive, and volatile hydrazoic acid are just a few of the disadvantages of the previously reported methods for the synthesis of tetrazoles. [31]

Developing potent antimicrobial agents presents several challenges due to the evolving nature of microbes, their ability to develop resistance, and the complex interactions between drugs and microorganisms. We need to constantly innovate to stay ahead of the microbial adaptation and find ways to develop effective antimicrobial agents while minimizing the risk of resistance development. Overcoming the challenges in developing potent antimicrobial activity requires a combination of scientific innovation, collaborative efforts, and strategic approaches.

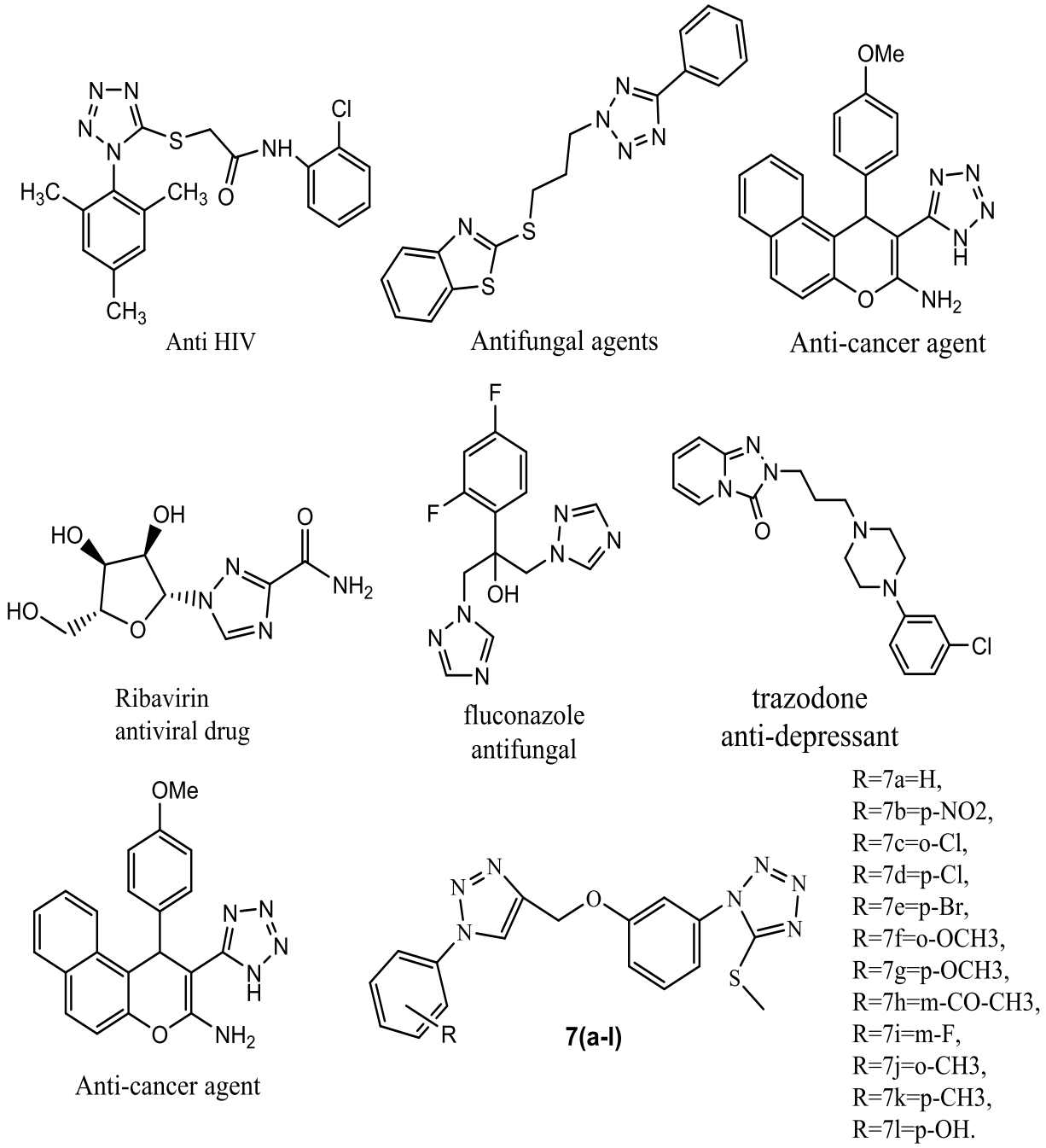
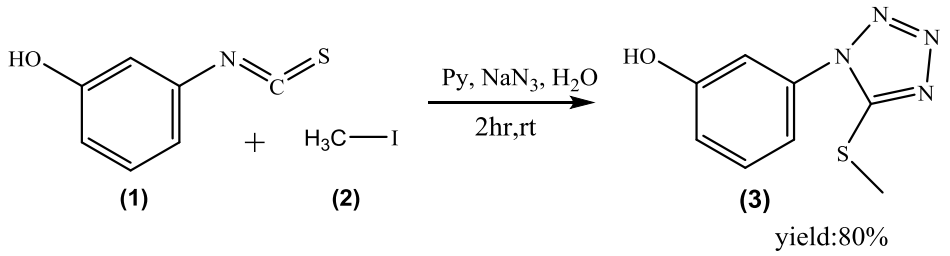


Figure 1: Some of the existed Compounds shows good activity and our synthesised compounds

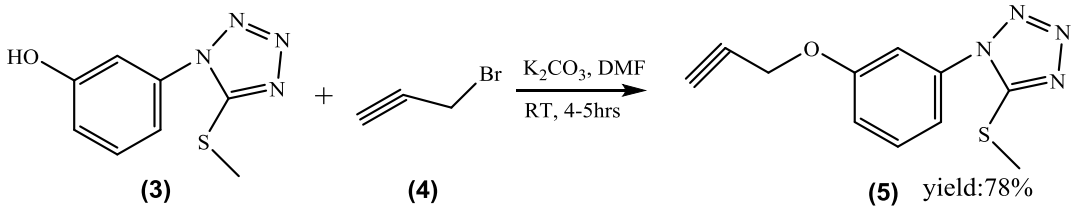
II. RESULT AND DISCUSSION:

We outline the general process for creating novel substituted Five-(methylthio)-1-(3-((1-phenyl-1H-1,2,3-triazol-4-yl) methoxy) phenyl)-1H-tetrazole **7(a-l)**. As a base constituent, we have utilized 3-isothiocyanatophenol (**1**), which is widely accessible and reasonably priced. 3. For two to three hours at room temperature, combine 1 mmol of isothiocyanato-phenol (**1**), 1.3 mmol of methyl iodide, 3 mmol of sodium azide, and 3.5 mmol of pyridine. to get phenol 3-(5-(methylthio)-1H-tetrazol-1-yl). In a yield of 80%. After compound (**3**) combines with DMF as a solvent, K2CO3 (2.5 eq) is added as a base, and propargyl bromide (PBr) is added to produce compound (**5**), which has a 78% yield. In order to create compound **7(a-l)** with an 86% yield, DMF was used as a solvent for treating compound (**5**) with aromatic substituted aizides.

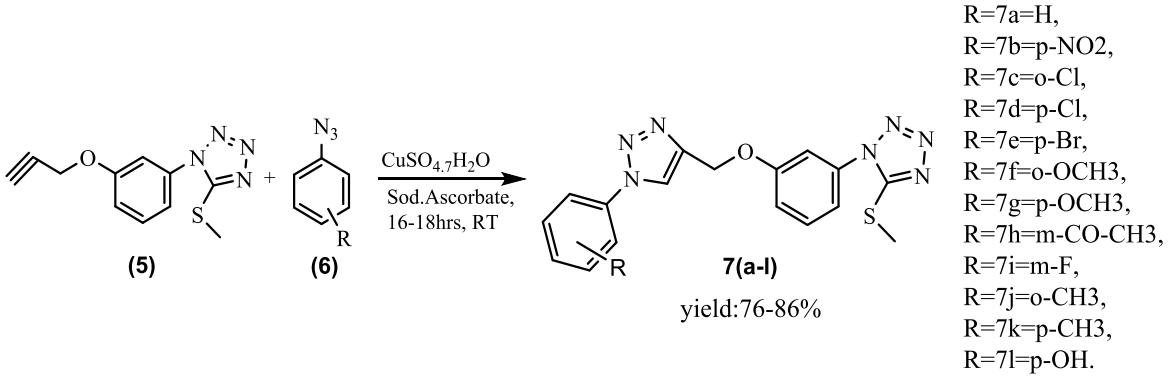
CuSO4.7H2O (2 ml) and sodium ascorbate (Na2S2O3) were then added, and the reaction mixture was stirred for 16–18 hours at room temperature. produces just 1,2,3-triazoles, which are connected to Tetrazoles analogues. This is the most popular way to make these substances. The final compound's analytical data **(7)** matched the data that had been previously reported. The total yield is 76–86%



Scheme-1: Synthesis of compound 3



Scheme-2: Synthesis of compound 5



Scheme-3: Synthesis of compound 7(a-l)

III. ANTI-MICROBIAL ACTIVITY:

Antibacterial Activity of Compounds 7 (a-l):

All the newly synthesized compounds **7(a-l)** were assayed for their antibacterial activity against three representative Gram-positive bacteria *viz*. *Bacillus Subtilis* (MTCC 441), *Bacillus Sphaericus* (MTCC 11) and *Staphylococcus Aureus* (MTCC 96), and three Gram-negative bacteria *viz*. *Pseudomonas Aeruginosa* (MTCC 741), *Klobsinella Aerogenes* (MTCC 39) and *Chromobacterium Violaceum* (MTCC 2656) by disc diffusion method. For the antibacterial assay standard inoculums ($1\text{-}2\times10^7$ c.f.u/mL 0.5 Mc Farland standards) were introduced on to the surface of sterile agar plates, and a sterile glass spreader was used for even distribution of the inoculums. The discs measuring 6.26 mm in diameter were prepared from Whatman no.1 filter paper and sterilized by dry heat at 140 ˚C for 1 h. The sterile discs previously soaked in a known concentration of the test compounds were placed in nutrient agar medium. The plates were inverted and incubated for 24 h at 37 ˚C. The mean inhibition zones were measured and compared with the standard drug Streptomycin and the results are presented in **Table 1**.

ANTIBACTERIAL ACTIVITY OF COMPOUNDS 7(a-l)

Compound	**Mean Zone Inhibition (MZI) in 100 µg/Ml**					
	B. Subtilis	***B.Sphaericus***	***S. Aureus***	***P.aeruginosa***	***K.aerogenes***	***C.violaceum***
7a	22	21	16	18	20	18
7b	**30**	**27**	**33**	**27**	**27**	**28**
7c	21	22	22	22	20	18
7d	22	19	18	20	18	22
7e	22	20	26	22	22	21
7f	21	22	18	22	26	23
7g	21	22	23	18	22	22
7h	**30**	**26**	**33**	**26**	**26**	**28**
7i	**21**	**27**	**32**	**27**	**27**	**29**
7j	22	22	23	24	22	21
7k	20	20	22	20	21	22
7l	20	22	23	22	21	22
Streptomycin	**32**	**28**	**34**	**28**	**28**	**30**
Streptomycin (50 µg/disc) was used as positive reference and compounds **7(a-l)** (50 µg/disc).[a] Values are mean (n=3)						

The Compounds **7b**, **7h,** and **7i**,exhibited potent good antibactirial activity compared to standard drug at the tested concentrations.The presence of **(7b)** 4-Nitrophenyl, **(7h)** 2-acetophenyl and **(7i)** 3-flourophenyl on triazole moiety might be the reason for the significant inhibitory activity.

Antifungal Activity of Compounds 7(a-l):

Compounds **7(a-l)** were further tested using the disc diffusion technique in dimethyl sulfoxide (DMSO) for their antifungal activity against Aspergillus fumigatus (HIC 6094), Trichophyton rubrum (IFO 9185), Trichophyton mentagrophytes (IFO 40996), and Candida albicans (ATCC 10231). The MZI values of the compounds examined are shown in Table 2. Amphotericin B was utilized as the reference medication, and the mean inhibition zone (MZI) data were obtained and compared with controls.

ANTIFUNGAL ACTIVITY OF COMPONDS 7(a-l)

Compound	**Mean zone inhibition (MZI)[a] in 100 µg/mL**			
	C. albicans	***A. fumigatus***	***T. rubrum***	***T. mentagrophytes***
7a	22	21	22	23
7b	**30**	**31**	**30**	**26**
7c	26	25	25	23
7d	21	22	23	24
7e	27	28	27	25
7f	20	22	21	22
7g	21	22	23	20
7h	**29**	**31**	**31**	**25**
7i	**30**	**30**	**30**	**27**
7j	18	19	18	17
7k	22	20	18	18
7l	22	24	24	24
Amphotericin B	**30**	**32**	**32**	**28**
Amphotericin B (100 µg/disc) was used as positive reference and compounds **7(a-l)** (100 µg/disc).				

When compared to the conventional medication at the studied concentrations, Compounds **7b, 7h,** and **7i** showed strong, positive antifungal action. Possible explanations for the strong inhibitory effect include the presence of (**7b**) 4-Nitrophenyl, (**7h**) 2-acetophenyl, and (**7i)** 3-flourophenyl on the triazole moiety.

IV. EXPERIMETAL SECTION:

All of the solvents and reagents were purchased from commercial vendors, and they were all utilized without further purification. The analytical thin-layer chromatography (TLC) was carried out on aluminium plates with MERCK precoated silica gel 60-F254 (0.5 mm). UV light was used to make the dots on TLC plates visible. Tetra methyl silane (TMS) was used as the internal standard to create a solution of the samples in DMSO, which allowed for the recording of

1H and 13C NMR spectra on a Bruker 400 MHz apparatus. Parts per million (ppm) downfield chemical changes for ^{1}H and ^{13}C are recorded from tetra methyl silane. The terms s (singlet), d (doublet), t (triplet), and m (multiplet) are used to characterize spin multiplicities. Column chromatography was carried out using silica gel (60-120) as needed. When anhydrous conditions are necessary, the reactions are conducted using newly distilled liquids under nitrogen positive pressure. Every solvent evaporation process used a rotary evaporator with lowered pressure and temperatures below 45˚C. The electrothermal digital melting point instrument IA9100 was used to determine the melting points, which are not adjusted. The experimental section's list of chemicals' names was derived from Chem Bio Draw Ultra, Version 12.0.

3-(5-(methylthio)-1H-tetrazol-1-yl) phenol. (3)

3-Isothiocyanato-phenol (1) (1 mmol), Methyl Iodide (1.3 mmol), Sodium azide, water (7 mL, 30 mL), and pyridine (3.5 mmol) should be added to a clean RB flask and let to sit at room temperature for two to three hours. After the reaction is complete, separate the organic phase. To get the product, (**3**) wash with the product (2x20 mL) and dry over anhydrous sodium sulfate.3-(5-(methylthio)-1H-tetrazol-1-yl) phenol (**3**) (Yield 80%).

^{1}HNMR (400 MHz, dmso) δ 9.46 (s,1H),7.19 (t, 1H, 4.0 Hz),7.24 (d, 1H, 8 Hz) 6.97 (d,1H, 7.5 Hz), 6.79 (s, 1H,), 2.45 (s, 3H), IR: υ_{max} : 3460, 1670, 1562,996, 813, 615 cm^{-1}, ESI-MS: *m/z* 208.04 $[M+H]^{+}$; HRMS: cacld. for $C_8H_8N_4OS$, 208.24, found: 208.04 Elemental Analysis: C, 46.14; H, 3.87; N, 26.91; O, 7.68; S, 15.40., ^{13}C NMR (DMSO, 400 MHz) : 158.5, 155.1, 143, 129.9, 122.2, 115.9, 109.9, 14.8

5-(methylthio)-1-(3-(prop-2-yn-1-yloxy) phenyl)-1H-tetrazole (5):

The reaction mixture should be stirred for approximately 4-5 hours at room temperature. Set up a clean, dry 50 ml single neck RBF, charged compound-3, and DMF as a solvent. Add K2CO3 (2.5 eq) as a base and Propargyl Bromide (PBr) (4) 1.2 eq as a reactant. Verify the TLC (20% EtOAc) to see if the starting material (SM) was finished before quinching with ice and extracting the liquid with DCM. The organic layer is distilled, forming a liquid. (**5**) (Yield 78%).

^{1}HNMR (400 MHz, dmso) δ 7.35 (d,1H),7.38 (t, 1H,),6.94 (d, 1H,) 6.93 (s,1H,), 4.68 (s, 2H,), 3.37 (s, 1H), 2.45(s, 3H), IR: υ_{max} : 3300, 2870, 2180, 1500.12, 1562, 997, 785, 581 cm^{-1}, ESI-MS: *m/z* 246.06 $[M+H]^{+}$; HRMS: cacld. for $C_{11}H_{10}N_4OS$,246.29, found: 246.06, Elemental Analysis: C, 53.64; H, 4.09; N, 22.75; O, 6.50; S, 13.02, ^{13}C NMR (DMSO, 400 MHz) : 160.6, 155.1, 142.6, 129.5, 121.5, 114.3, 178.7, 76.4, 14.8.

5-(methylthio)-1-(3-((1-phenyl-1H-1,2,3-triazol-4-yl) methoxy) phenyl)-1H-tetrazole (7a-l):

Set up a 50 ml single neck RBF that is dry and clean. Add 2 ml of CuSO4.7H2O, charged compound-5, and DMF as a solvent. If you notice a color shift, add two milliliters of sodium ascorbate (Na2S2O3). once a solid look is seen, add various substituted aromatic azides (1.2 eq), and let the reaction mixture sit at room temperature for 16–18 hours. Once the starting material (SM) was finished, check the TLC (50% EtOAc in pet ether), quinch with ice, filter with reaction filtrate, and wash with PET ether solid is created substituted 5-(methylthio)-1-(3-((1-phenyl-1H-1,2,3-triazol-4-yl) methoxy) phenyl)-1H-tetrazole **(7 a-l)** (Yield 76-86%).

^{1}HNMR (400 MHz, dmso) δ 9.01 (s,1H), 7.92 (s, 1H), 7.12-7.61 (m, 9H), 5.36 (s,2H,) 1.61 (s, 3H). IR: υ_{max}: 3098.35, 3067.44, 2997.65, 2671.12, 2949.04, 2870.84, 1600.23, 1562.20, 12360.49, 1233.55, 1114.94, 1088.37, 1044.35, 846.66, 720.85, 615.97 cm^{-1}, ESI-MS: *m/z* 365 $[M+H]^{+}$; HRMS: cacld. for $C_{17}H_{15}N_7OS$, 365.42, found: 365, Elemental Analysis: Elemental Analysis: C, 55.88; H, 4.14; N, 26.83; O, 4.38; S, 8.77, ^{13}C NMR (DMSO, 400 MHz): 154.4, 148.7, 132.7, 120.8, 41.6, 39.5, 38.0, 27.6

V. CONCLUSION

In conclusion, we have synthesized a variety of novel derivatives of 5-(methylthio)-1-(3-((1-phenyl-1H-1,2,3-triazol-4-yl) methoxy) phenyl)-1H-tetrazole (**7a-l**) and characterized by IR, ^{13}C NMR, ESI-MS, and 1H NMR and also evaluation of their anti-microbial activity (Anti-bacterial, anti-fungal activity). Some of the compounds ***7b, 7h, and 7i*** exhibits promising antimicrobial activity, the presence of **(7b)** 4-Nitrophenyl, **(7h)** 2-acetophenyl and **(7i)** 3-flourophenyl on triazole moiety might be the reason for the significant inhibitory activity.

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