ISSN 1070-4280, Russian Journal of Organic Chemistry, 2020, Vol. 56, No. 6, pp. 1077–1081. © Pleiades Publishing, Ltd., 2020.

Synthesis of 5-{[(1-Aryl-1*H*-1,2,3-triazol-4-yl)methyl]sulfanyl}-1-phenyl-1*H*-tetrazoles

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Received January 7, 2020; revised March 12, 2020; accepted March 15, 2020

Abstract—A series of novel 5-(1,2,3-triazolylmethylsulfanyl)tetrazole derivatives were synthesized by the click reaction from 1-phenyl-5-(prop-2-yn-1-ylsulfanyl)-1*H*-tetrazole and the corresponding azide. The reaction optimization results showed that higher yields are obtained using $CuSO_4$ and sodium ascorbate in DMF–water (2:1). The product structures were established on the basis of various spectral data, and their evaluation for antimicrobial activity showed moderate to good results compared to standard drugs.

Keywords: tetrazole, 1,2,3-triazole, antimicrobial activity, click reaction

DOI: 10.1134/S1070428020060172

INTRODUCTION

1,2,3-Triazoles and tetrazoles have provided a significant contribution to medicinal chemistry. Tetrazole derivatives are applicable in pharmaceutics, material science, photography, and information recording systems and are attractive as ligands in coordination chemistry [1–5]. Tetrazole derivatives possess various biological activities, including antibacterial [6], antifungal [7], antiviral [8], analgesic [9] and anti-inflammatory activities [10]. In addition, sulfanyl-substituted hetaryl compounds are present in many natural products, drugs, [11] enzymes, and structural cell proteins [12]. Drug molecules having sulfur atom in their core structure are employed to treat Alzheimer's and Parkinson's diseases, cancer, malaria, inflammations, and AIDS [13–16]. Organic sulfides display various biological activities such as antibacterial and analgesic [17–19]. Furthermore, a tetrazole fragment can be found in active pharmaceutical ingredients such as Cefamandole, Latamoxef, and Azosemide [20–22] (Fig. 1). 1,2,3-Triazoles also demonstrate a wide variety of pharmacological activities such as antimicrobial, antibacterial [23], fungicidal [24], antiallergic [25], anti-HIV [26], anticancer [27], antioxidant [28], etc. In view of the biological importance of tetrazole and 1,2,3-triazole derivatives and in continuation of our research work [29, 30], we made an attempt to combine these two important pharmacophores in a single molecule through a sulfur linkage (Scheme 1).

RESULTS AND DISCUSSION

A series of 5-{[(1-aryl-1*H*-1,2,3-triazol-4-yl)-methyl]sulfanyl)-1-phenyl-1*H*-tetrazoles **5a**–**5j** were synthesized starting from phenyl isothiocyanate (**1**) which was reacted with sodium azide to gave 1-phenyl-1*H*-tetrazole-5-thiol (**2**). The reaction of **2** with pro-

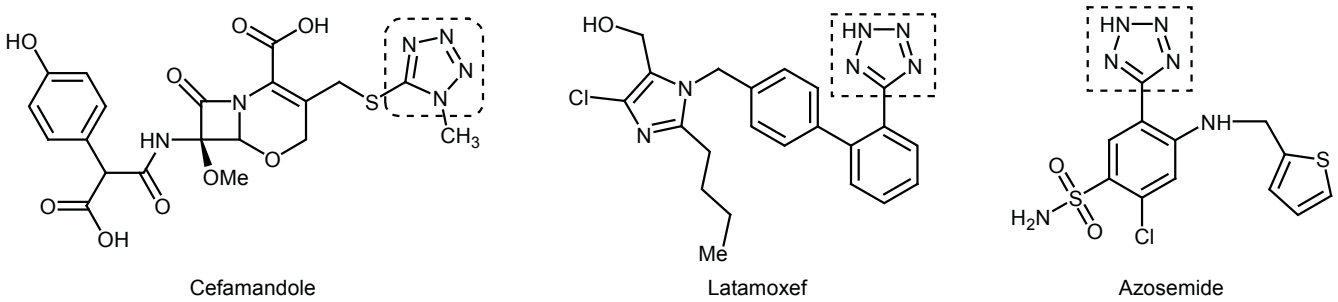
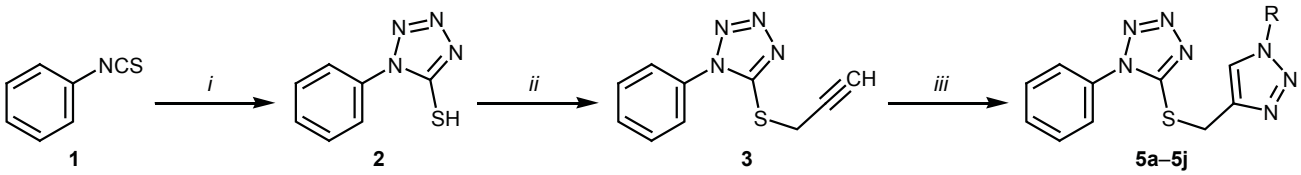


Fig. 1. Active pharmaceutical ingredients containing a tetrazole ring.

Scheme 1.



Reagents and conditions*i*: NaN_3/H_2O, reflux; *ii*: propargyl bromide, TBAB, Et_3N, CH_2Cl_2, room temp., 3 h; *iii*: ArN_3 (**4a**–**4j**), $CuSO_4 \cdot 5H_2O$, NaAsc, DMF–water, room temp., 4 h. R = Ph (**a**), 2-MeC_6H_4 (**b**), 3-MeC_6H_4 (**c**), 4-HOC_6H_4 (**d**), 4-ClC_6H_4 (**e**), 4-$O_2NC_6H_4CH_2$ (**f**), 4-MeC(O)C_6H_4 (**g**), 2-MeO-4-$O_2NC_6H_4$ (**h**), 4-MeO-2-$O_2NC_6H_4$ (**i**), cyclohexyl (**j**).

pargyl bromide afforded propargylsulfanyl derivative **3**. Finally, compound **3** was treated with various azides **1** via the click strategy to produce the corresponding 5-{[(1-aryl-1*H*-1,2,3-triazol-4-yl)methyl]sulfanyl}-1-phenyl-1*H*-tetrazoles **5a**–**5i**, as well as 5-{[(1-cyclohexyl-1*H*-1,2,3-triazol-4-yl)methyl]sulfanyl}-1-phenyl-1*H*-tetrazole **(5j)** with excellent yields. The structures of the products were established on the basis of spectral analysis data. As an example, the IR spectrum of **5a** showed characteristic peaks at 1647, 1622, and 1585 cm^{-1}, which were assigned to N=N, C=C, and C=N stretchings, respectively. In the ^1H NMR spectrum of **5a**, the 5-H proton of the newly formed triazole ring resonated at δ 8.29 ppm as a singlet, the two SCH_2 protons resonated at δ 4.77 ppm as a singlet, and the aromatic proton signals appeared in the region δ 7.44–7.72 ppm. In the ^{13}C NMR spectrum of **5a**, the following peaks were observed, δ_C, ppm: 153.7, 143.4, 136.7, 133.4, 130.2, 129.8, 129.7, 128.9, 123.6, 121.8, 120.5, 27.5. The mass spectrum of **5a** displayed $[M + H]^+$ ion peak at *m*/*z* 336.

Compounds **5a**–**5j** were evaluated for their *in vitro* antibacterial activity against four bacterial strains, Gram-positive *Staphylococcus aureus* and *Bacillus subtilis*, and Gram-negative *Pseudomonas aeruginosa* and *Escherichia coli*, by the paper disc method using norfloxacin as the standard drug. Compounds **5a**, **5d**, **5e**, and **5i** showed a good antibacterial activity against all the examined bacterial strains, and the remaining compounds showed a moderate activity (Table 1). The antifungal activity of **5a**–**5j** was tested in vitro against two fungal strains (*Sclerotium rolfsii* and *Aspergillus niger*) at a concentration of 1 mg/mL by the disc diffusion method using ketoconazole as reference drug. Compounds **5d** and **5e** proved to be more active than the other tested compounds, but the activity of all of them was lower than that of ketoconazole (Table 1).

EXPERIMENTAL

All chemicals were purchased from commercial sources and were used without further purification. The solvents were dried and distilled prior to use. The ^1H and ^{13}C NMR spectra were recorded on a Bruker Biospin Avance-III spectrometer at 400 and 101 MHz, respectively, using $CDCl_3$ as solvent and tetramethyl-

Table 1. Antimicrobial activity of 5-{[(1-R-1*H*-1,2,3-triazol-4-yl)methyl]sulfanyl}-1-phenyl-1*H*-tetrazoles **5a**-**5j** (inhibition zone diameter, mm)

Compound no.	*S. aureus*	*B. subtilis*	*P. aeruginosa*	*E. coli*	*A. niger*	*S. rolfsii*
5a	19.1	14.3	22.0	15.0	8.1	9.6
5b	17.8	12.0	19.0	12.2	8.7	8.3
5c	17.0	11.7	17.8	13.0	7.9	7.4
5d	21.3	16.9	23.3	16.6	9.0	11.0
5e	22.0	18.0	22.7	17.0	7.3	12.5
5f	14.0	13.7	18.0	13.5	5.9	8.7
5g	16.7	14.0	17.7	18.1	8.1	6.0
5h	18.0	16.1	19.1	13.6	8.4	8.8
5i	20.5	12.4	20.3	11.0	7.0	8.0
5j	13.9	12.5	16.5	12.6	6.5	7.8
Norfloxacine	26.6	19.8	28.6	25.7	–	–
Ketoconazole	–	–	–	–	11.5	16.6

silane as reference. Column chromatography was conducted using silica gel (60–120 mesh, Merck). The reaction progress was monitored by TLC with silica gel 60 F254 plates, and visualization was made under UV light. The mass spectra were recorded in the ESI mode with positive ion detection.

1-Phenyl-5-(prop-2-yn-1-ylsulfanyl)-1*H*-tetrazole (3). A solution of 1-phenyl-1*H*-tetrazole-5-thiol (**2**, 1 mmol), propargyl bromide (1.2 mmol), and tetrabutylammonium bromide in a mixture of triethylamine (2 mL) and methylene chloride (5 mL) was stirred at room temperature for 3 h. After completion of the reaction (TLC), the mixture was poured into ice-cold water, and the solid product was filtered off, dried, and purified by column chromatography using ethyl acetate–hexane (8:2). Yield 87%; IR spectrum, ν, cm^{-1}: 1463 (C–S), 2120 (C≡N). ^1H NMR spectrum, δ, ppm: 2.33 t (1H, J = 2.7 Hz), 4.18 d (2H, J = 2.7 Hz),7.54–7.61 m (5H). ^{13}C NMR spectrum, δ_C, ppm: 21.8, 73.1, 76.7, 123.8, 129.9, 130.3, 133.4, 152.8. Mass spectrum: m/z 217 (I_{rel} 100%) $[M + H]^+$.

5-{[(1-Aryl-1*H*-1,2,3-triazol-4-yl)methyl]sulfanyl}-1-phenyl-1*H*-tetrazoles 5a–5j. A mixture of tetrazole **3** (1 mmol), azide **4a**–**4j** (1 mmol), $CuSO_4 \cdot 5H_2O$, and sodium ascorbate in DMF–H_2O (5 mL) was stirred at room temperature for 4 h. After completion of the reaction (TLC), the mixture was poured into ice-cold water (20 mL) and extracted with 30 mL of ethyl acetate. The extract was washed twice with a saturated solution of ammonium chloride and twice with brine, dried over Na_2SO_4, and concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel using *n*-hexane–ethyl acetate (7:3) as eluent.

1-Phenyl-5-{[(1-phenyl-1*H*-1,2,3-triazol-4-yl)-methyl]sulfanyl}-1*H*-tetrazole (5a). Yield 86%, mp 201–204°C. IR spectrum, ν, cm^{-1}: 3050 (C–H), 1595 (C=N), 1497 (C–S). ^1H NMR spectrum, δ, ppm: 4.77 s (2H, SCH_2), 7.43 t (1H, H_{arom}, J = 7.4 Hz), 7.49–7.59 m (7H, H_{arom}), 7.72 d (2H, H_{arom}, J = 7.8 Hz), 8.29 s (1H, 5-H). ^{13}C NMR spectrum, δ_C, ppm: 27.5, 55.4, 119.2, 120.5, 121.8, 123.6, 128.9, 128.9, 129.7, 129.8, 130.2, 132.5, 133.4, 136.7, 143.4, 153.7. Mass spectrum: m/z 336 (I_{rel} 100%) $[M + H]^+$.

5-({[1-(4-Methylphenyl)-1*H*-1,2,3-triazol-4-yl]-methyl}sulfanyl)-1-phenyl-1*H*-tetrazole (5b). Yield 90%, mp 214-217°C. IR spectrum, ν, cm^{-1}: 3051 (C–H), 1595 (C=N), 1498 (C–S). ^1H NMR spectrum, δ_C, ppm: 2.19 s (3H, CH_3), 4.79 s (2H, SCH_2), 7.29–7.44 m (4H, H_{arom}), 7.56 m (5H, H_{arom}), 8.02 s (1H, 5-H). ^{13}C NMR spectrum, δ_C, ppm: 17.8, 27.6, 123.7, 125.1, 125.9, 126.8, 129.8, 130.2, 131.5, 133.4, 136.2, 142.4, 153.7. Mass spectrum: m/z 350 (I_{rel} 100%) $[M + H]^+$.

5-({[1-(3-Methylphenyl)-1*H*-1,2,3-triazol-4-yl]-methyl}sulfanyl)-1-phenyl-1*H*-tetrazole (5c). Yield 84%, mp 199–202°C. IR spectrum, ν, cm^{-1}: 3055 (C–H), 1592 (C=N), 1493 (C–S). ^1H NMR spectrum, δ, ppm: 2.44 s (3H, CH_3), 4.78 d (2H, SCH_2, J = 8.1 Hz), 7.24 d (1H, H_{arom}, J = 7.6 Hz), 7.39 t (1H, H_{arom}, J = 7.8 Hz), 7.45 s (1H, H_{arom}), 7.47–7.58 m (6H, H_{arom}), 8.26 s (1H, 5-H). ^{13}C NMR spectrum, δ_C, ppm: 21.3, 27.5, 117.6, 121.1, 121.8, 123.6, 128.3, 129.0, 129.5, 129.6, 129.8, 130.2, 133.4, 136.7, 140.0, 143.3, 153.8. Mass spectrum: m/z 350 (I_{rel} 100%) $[M + H]^+$.

4-(4-{[(1-Phenyl-1*H*-tetrazol-5-yl)sulfanyl]-methyl}-1*H*-1,2,3-triazol-1-yl)phenol (5d). Yield 94%, mp 193–196°C. IR spectrum, ν, cm^{-1}: 3052 (C–H), 1592 (C=N), 1495 (C–S). ^1H NMR spectrum, δ, ppm: 4.75 s (2H, SCH_2), 5.70 s (1H, OH), 6.97 d (2H, H_{arom}, J = 8.4 Hz), 7.24 d (2H, H_{arom}), 7.55 m (5H, H_{arom}), 8.17 s (1H, 5-H). ^{13}C NMR spectrum, δ_C, ppm: 29.7, 116.4, 122.4, 123.7, 129.8, 130.2, 130.3, 133.4, 136.7, 140.5, 141.8, 152.4. Mass spectrum: m/z (I_{rel} 100%) $[M + H]^+$.

5-{[1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)-methyl]sulfanyl}-1-phenyl-1*H*-tetrazole (5e). Yield 85%, mp 162–165°C. IR spectrum, ν, cm^{-1}: 3050 (C–H), 1592 (C=N), 1497 (C–S). ^1H NMR spectrum, δ, ppm: 4.76 s (2H, SCH_2), 7.47–7.52 d (2H, H_{arom}), 7.53–7.99 m (5H, H_{arom}) 7.66–7.70 d (2H, H_{arom}), 8.28 s (1H, 5-H). ^{13}C NMR spectrum, δ_C, ppm: 27.4, 121.7, 123.6, 129.9, 130.3, 133.3, 134.7, 135.2, 143.7, 146.8, 153.7. Mass spectrum: m/z 370 (I_{rel} 100%) $[M + H]^+$.

5-({[1-(4-Nitrobenzyl)-1*H*-1,2,3-triazol-4-yl]-methyl}sulfanyl)-1-phenyl-1*H*-tetrazole (5f). Yield 90%, mp 159–162°C. IR spectrum, ν, cm^{-1}: 3050 (C–H), 1592 (C=N), 1496 (C–S). ^1H NMR spectrum, δ, ppm: 4.67 s (2H, SCH_2), 5.61 s (2H, NCH_2), 7.40–7.42 d (2H, H_{arom}), 7.50–7.60 m (5H, H_{arom}), 7.89 s (1H, 5-H), 8.23–8.25 d (2H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 27.4, 53.1, 121.5, 123.6, 124.3, 128.6, 129.9, 130.3, 133.3, 141.4, 148.0, 153.7. Mass spectrum: m/z 395 (I_{rel} %) $[M + H]^+$.

1-[4-(4-{[(1-Phenyl-1*H*-tetrazol-5-yl)sulfanyl]-methyl}-1*H*-1.2.3-triazol-1-yl)phenyl]ethanone (5g). Yield 85%, mp 188–191°C. IR spectrum. ν. cm^{-1}: 3053

(C–H), 1596 (C=N), 1496 (C–S). ^{1}H NMR spectrum, δ, ppm: 2.66 s (3H, CH_3), 4.77 s (2H, SCH_2), 7.53–7.61 m (4H, H_{arom}), 7.83–7.90 m (5H, H_{arom}), 7.89 s (1H, 5-H). ^{13}C NMR, δ_C, ppm: 26.7, 29.7, 120.1, 122.8, 123.6, 125.5, 129.9, 128.9, 130.8, 133.3, 136.9, 139.8, 153.7, 196.6. Mass spectrum: *m*/*z* 398 (I_{rel} 100%) $[M + H]^+$.

5-({[1-(2-Methoxy-4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl]methyl}sulfanyl)-1-phenyl-1*H*-tetrazole (5h). Yield 88%, mp 205–208°C. IR spectrum, ν, cm^{-1}: 3053 (C–H), 1597 (C=N), 1495 (C–S). ^{1}H NMR spectrum, δ, ppm: 4.06 s (3H, OCH_3), 4.78 s (2H, SCH_2), 7.42–7.55 m (5H, H_{arom}), 8.12–7.93 m (2H, H_{arom}, 5-H), 8.28 s (1H, H_{arom}), 8.58–8.60 m (1H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 27.4, 56.9, 107.8, 116.6, 123.6, 125.0, 125.9, 129.2, 129.8, 130.3, 130.7, 133.3, 148.1, 150.6, 153.5. Mass spectrum: *m*/*z* 411 (I_{rel} 100%) $[M + H]^+$.

5-({[1-(4-Methoxy-2-nitrophenyl)-1*H*-1,2,3-triazol-4-yl]methyl}sulfanyl)-1-phenyl-1*H*-tetrazole (5i). Yield 83%, mp 218–221°C. IR spectrum, ν, cm^{-1}: 3056 (C–H), 1592 (C=N), 1496 (C–S). ^{1}H NMR spectrum, δ, ppm: 4.05 s (3H, OCH_3), 5.36 s (2H, CH_2), 7.38 d (1H, H_{arom}, J = 2.1 Hz), 7.41–7.55 m (5H, H_{arom}), 7.65 d (1H, H_{arom}, J = 8.8 Hz,), 7.98 d (1H, H_{arom}, J = 2.2 Hz,), 8.03 s (1H, 5-H), 8.38 s (1H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 27.4, 56.9, 107.8, 116.6, 123.6, 125.0, 125.8, 129.8, 130.7, 133.3, 140.5, 148.1, 150.6, 153.5. Mass spectrum: *m*/*z* 411 (I_{rel} 100%) $[M + H]^+$.

5-{[(1-Cyclohexyl-1*H*-1,2,3-triazol-4-yl)methyl]-sulfanyl}-1-phenyl-1*H*-tetrazole (5j). Yield 86%, mp 220–223°C. IR spectrum, ν, cm^{-1}: 3052 (C–H), 1594 (C=N), 1497 (C–S). ^{1}H NMR spectrum, δ, ppm: 1.30–1.23 m (2H, CH_2), 1.43 d.d (2H, CH_2, J = 26.0, 12.8 Hz,), 1.72 d.d (2H, CH_2, J = 20.0, 7.8 Hz),1.91 d (2H, CH_2, J = 13.5 Hz), 2.16 d (2H, CH_2, J = 10.7 Hz,), 4.68 s (2H, SCH_2), 7.61–7.47 m (5H, H_{arom}), 7.80 s (1H, 5-H). ^{13}C NMR spectrum, δ_C, ppm: 25.0, 27.7, 29.6, 33.4, 60.3, 121.3, 123.6, 129.1, 129.8, 130.2, 133.4, 153.9. Mass spectrum: *m*/*z* 342 (I_{rel} 100%) $[M + H]^+$.

ACKNOWLEDGMENTS

The authors thank Head of the Department of Chemistry, Osmania University, for providing laboratory facilities and also the director, Central Facilities for Research and Development (CFRD), Osmania University, Hyderabad, India for providing spectral data.

FUNDING

K. Thotla thanks the Council of Scientific and Industrial Research (CSIR, New Delhi, India) for financial support in the form of fellowship.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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