Research Article

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New *S*- alkyl functionalized bis-1,2,4-Triazolyles

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Abstract: New 2,2'-[(5,5'-(butane-1,4-diyl)bis(4-phenyl-4*H*-1,2,4-triazole-5,3-diyl))bis(sulfanediyl))bis(*N*-*o*-tolyl acetamide] **3a**, 2,2'-[(5,5'-(butane-1,4-diyl)bis(4-phenyl-4*H*-1,2,4-triazole-5,3-diyl))bis(sulfanediyl))bis(*N*-3-bromophenyl)acetamide) **3b** and 2,2'-[(5,5'-(butane-1,4-diyl)bis(4-phenyl-4*H*-1,2,4-triazole-5,3-diyl))bis(sulfanediyl)bis(*N*-benzylacetamide] **3c** were synthetized *via* the reaction of 5,5'-(butane-1,4-diyl)bis(4-phenyl-4*H*-1,2,4-triazole-3-thiol) **(1)** with 2-chloro-*N*-(o-tolyl)acetamides **2a,** 2-chloro-*N*-(*m*-bromophenyl)acetamide **2b** and 2-chloro-*N*-(benzy)acetamide **2c**, respectively. Target compounds were synthesized using phase transfer catalysis technique. The solid phase is potassium carbonate and the organic layer is dioxane while the catalyst is tetrabutyl ammonium bromide. Phase transfer catalysis (PTC) has the potential to enhance yields, shorten reaction times, eliminate the need for hazardous or costly reagents and solvents, and offer various additional advantages to manufacturers in the organic chemical sector. 1,2,4-Triazoles exhibit a broad spectrum of biological activities, including antifungal, antibacterial, anti-inflammatory, anticancer, antitubercular, antioxidant, antiviral, antidiabetic, analgesic and anticonvulsant properties. Therefore, the prepared compounds **3a-c** are expected to have significant biological activities. Reaction of compound **1** with alkyl halides **2a-c** proceeded at relatively low temperature and short reaction time. In addition, the synthesized products were obtained in excellent yields. The structure of the new products has been characterized by IR, NMR, and their elemental analyses.
Keywords: *Bis*-1,2,4-triazolyl-based derivatives, 2-chloro-*N*-arylacetamides, *S*-alkylation, Phase transfer catalysis.

1. Introduction

Compounds that contain triazole ring have been noted for their significant application potential across multiple fields [1-3], including agrochemistry [4-6] and material chemistry [7-9]. The distinctive structure of triazole enables the establishment of various non-covalent interactions with enzymes and receptors, leading to a diversity in biological activities, including anticancer [3], anti-HIV [10], antibacterial [11-13], and antituberculosis effects [14, 15].

Triazole derivatives, particularly 1,2,4-triazoles have been widely found in many drugs (**Fig. 1**). Notable examples include Itraconazole [16, 17], Fluconazole [18, 19], and Voriconazole [20, 21] are widely used as antifungal agents. Additionally, Ribavirin [22, 23] stands out as a broad-spectrum antiviral medication effective in treating hepatitis. Rizatriptan [24, 25] has been developed as an antimigraine drug candidate. Furthermore, Letrozole [26, 27], Anastrozole [28], and Vorozole [29, 30] are recognized as highly effective anticancer therapies.

According to the data provided above and as a further extension of our research focused on the synthesis of azoles [31-34], we studied the *S*-alkylation of compound 5,5'-(butane-1,4-diyl)bis(4-phenyl-4*H*-1,2,4-triazole-3-thiol) **(1)** under phase transfer catalysis conditions (PTC).

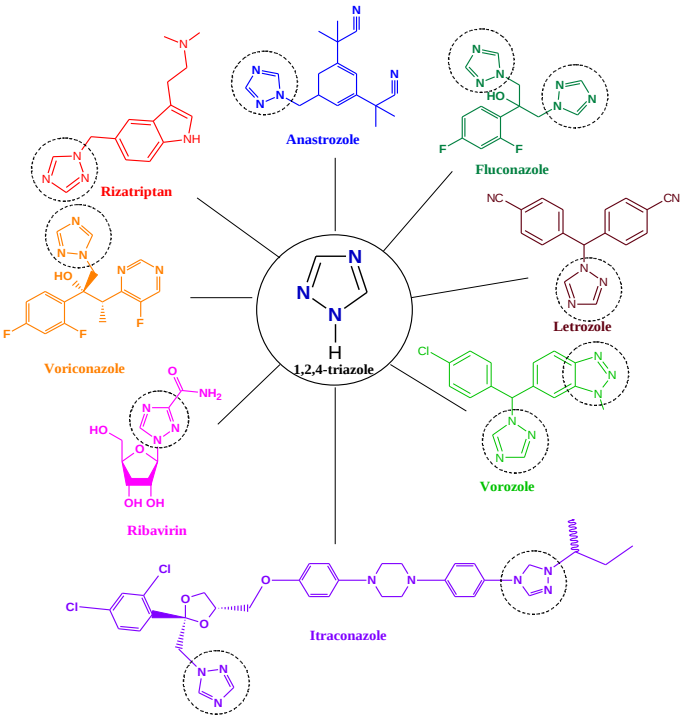


Fig. 1. Examples of drugs containing of 1,2,4-triazole ring

2. Materials and methods

All melting points were measured using a Melt-Temp-II apparatus and are reported without correction. Infrared spectra were obtained with a Nicolet 710 Fourier Transform (FT) instrument utilizing potassium bromide discs. Proton NMR (^{1}H NMR) spectra was recorded at frequency of 400 MHz, on a Bruker Bio spin AG-400 spectrometer, employing DMSO-d6 as the solvent and TMS as the reference. Elemental analyses were

performed at Cairo University "Microanalytical Center".

Synthesis of compounds 3a-c (General procedures):
A mixture of compound **1** (1 mmol, 0.4 g), anhydrous potassium carbonate (3 g), catalytic amount (0.003 g) of tetrabutylammonium bromide (TBAB) and dioxane (20 mL) was stirred for 1 h at 60 ℃. The appropriate halo compound **2a-c** (2 mmol) was added and the reaction mixture further stirred for 3 h at 80 ℃ until the reaction was completed (TLC). Carbonate layer was separated by filtration, dried and treated with water. The target product filtered off, washed with water, dried and crystallized from DMF to give **3a-c.**

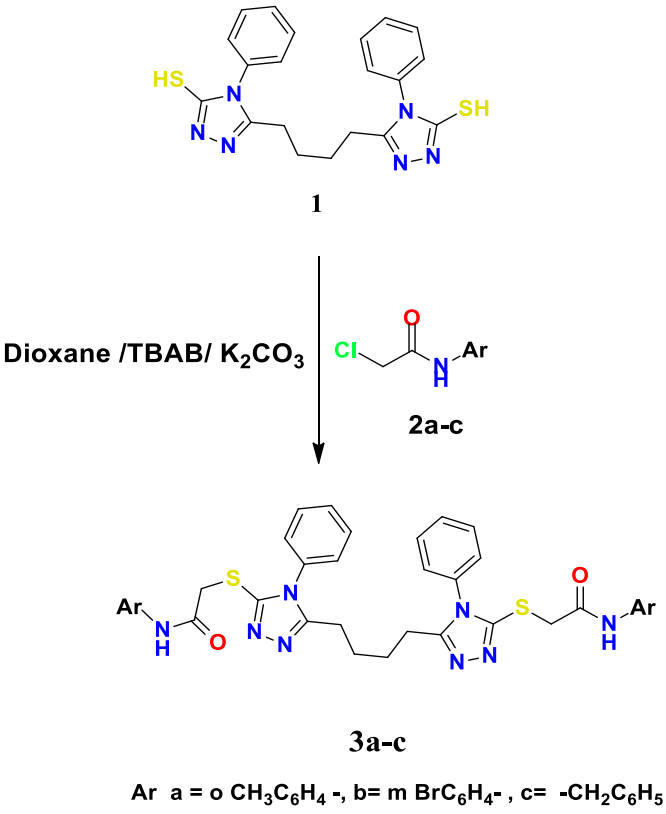
2,2'-[(5,5'-(butane-1,4-diyl)bis(4-phenyl-4*H*-1,2,4-triazole-5,3-diyl))bis(sulfanediyl))bis(*N*-(*o*-tolyl] acetamide (3a):
Melting point 210 °C; yield (0.63g, 90%); IR (ATR) ν_{max}: 3231 (NH), 1691 (C=O); ^{1}HNMR δ (ppm) 9.70 (s, 2H, 2NH), 7.58-7.08 (m, 18H, CH_{arom}), 4.10 (s, 4H, 2S-CH_2), 2.46 (t, 4H, 2CH_2), 2.18 (s, 6H, 2CH_3), 1.45 (t, 4H, 2CH_2). Anal. Calcd $C_{38}H_{38}N_8O_2S_2$ (702.89): C, 64.93; H, 5.45; N, 15.94; S, 9.12. Found: C, 64.84; H, 5.42; N, 15.98; S, 9.07.

2,2'-((5,5'-(butane-1,4-diyl)bis(4-phenyl-4*H*-1,2,4-triazole-5,3-diyl))bis(sulfanediyl))bis(*N*-(3-bromo)acetamide) (3b):
Melting point 240 °C; yield (0.76g, 92%); IR (ATR) ν_{max}: 3242 (NH), 1665 (C=O); ^{1}HNMR δ (ppm) 10.56 (s, 2H, 2NH), 7.91-7.24 (m, 18H, CH_{arom}), 4.09 (s, 4H, 2S-CH_2), 2.44 (t, 4H, 2CH_2), 1.45 (t, 4H, 2CH_2). Anal. Calcd $C_{36}H_{32}Br_2N_8O_2S_2$ (832.6): C, 51.93; H, 3.87; N, 13.46; S, 7.70. Found: C, 51.94; H, 3.85; N, 13.47; S, 7.71.

2,2'-((5,5'-(butane-1,4-diyl)bis(4-phenyl-4*H*-1,2,4-triazole-5,3-diyl))bis(sulfanediyl))bis(*N*-(3-bromophenyl)acetamide) (3c):
Melting point 220 °C; yield (0.64g, 91%); IR (ATR) ν_{max}: 3165 (NH), 1673 (C=O); ^{1}HNMR δ (ppm) 8.70 (s, 2H, 2NH), 7.58-7.22 (m, 20H, CH_{arom}), 4.27 (s, 4H, 2S-CH_2), 3.92 (s, 4H, 2N-CH_2), 2.44 (t, 4H, 2CH_2), 1.45 (t, 4H, 2CH_2). Anal. Calcd $C_{38}H_{38}N_8O_2S_2$ (702.89): C, 64.93; H, 5.45; N, 15.94; S, 9.12. Found: C, 64.95; H, 5.46; N, 15.96; S, 9.13.

3. Results and Discussion:

5,5'-(butane-1,4-diyl)bis(4-phenyl-4*H*-1,2,4-triazole-3-thiol) **(1)** was prepared according to a reported method [35]. Compound **(1)** was reacted with 2-chloro-*N*-(*o*-tolyl)acetamide **2a**, 2-chloro-*N*-(*m*-bromophenyl)acetamide **2b** or 2-chloro-*N*-(benzyl)acetamide **2c** using solid-liquid phase transfer catalysis (PTC) conditions [dioxane / K_2CO_3 / TBAB] to yield the relevant derivatives: 2,2'-((5,5'-(butane-1,4-diyl)bis(4-phenyl-4*H*-1,2,4-triazole-5,3-diyl))bis(sulfanediyl))bis(*N*-(*o*-tolyl)acetamide) **3a**, 2,2'-((5,5'-(butane-1,4-diyl)bis(4-phenyl-4*H*-1,2,4-triazole-5,3-diyl))bis(sulfanediyl))bis(*N*-(*m*-bromophenyl)acetamide) **3b** or 2,2'-((5,5'-(butane-1,4-diyl)bis(4-phenyl-4*H*-1,2,4-triazole-5,3-diyl))bis(sulfanediyl))bis(*N*-(benzyl)acetamide) **3c**, respectively (**Scheme 1**). The infrared (IR) spectrum of compound **3a** displayed new absorption bands corresponding to the NH and C=O functional groups at 3231 and 1691 cm^{-1}, respectively. Its proton NMR spectrum exhibited the following signals (δ): 9.70 (s, 2H, 2NH), 7.58-7.08 (m, 18H, CH_{arm}), 4.10 (s, 4H, 2S-CH_2), 2.46 (t, 4H, 2CH_2), 2.18 (s, 6H, 2CH_3), 1.45 (t, 4H, 2CH_2).



Scheme 1: Preparation of compounds **3a-c**.

The mechanism for compounds **3a-c** synthesis consists of two consecutive catalytic steps. The first step begins with the proton removal from both thiol groups of compound **1**, which takes place on the solid potassium carbonate (K_2CO_3) surface. The resulting anion then migrates as an ion pair alongside the catalytic cation into the dioxane layer (organic phase), where the second step, associated with the substitution reaction, occurs (**Fig. 2**).

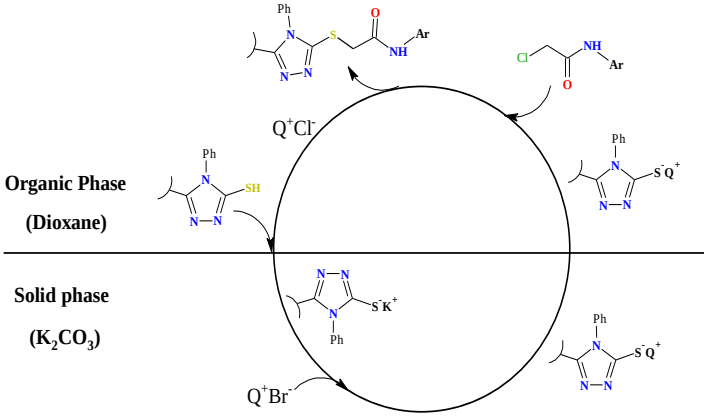


Fig. 2. Reaction mechanism of synthesis of **3a-c** under phase transfer catalysis conditions.

4. Conclusion

It was found that 5,5'-(butane-1,4-diyl)bis(4-phenyl-4*H*-1,2,4-triazole-3-thiol) **(1)** is good precursor for the synthesis of biologically important heterocyclic *S*-alkylated derivatives. This compound shows significant chemical reactivity towards active alkylated reagents; 2-chloro-*N*-arylacetamides **2a-c**, where new *S*- alkylated 1,2,4-triazole derivatives were synthesized, and chemical structures of new compounds were confirmed by elemental and spectral analysis.

CRediT authorship contribution statement:

Conceptualization, Ahmed Khodairy, Hanan Salah, Abdelraheem M. Ahmed and Marium Abo User; methodology, Ahmed Khodairy, Hanan Salah, Abdelraheem M. Ahmed and Marium Abo User; software, Ahmed Khodairy, Hanan Salah, Abdelraheem M. Ahmed and Marium Abo User; validation, Ahmed Khodairy, Hanan Salah, Abdelraheem M. Ahmed and Marium Abo User; formal analysis, Ahmed Khodairy, Hanan Salah, Abdelraheem M. Ahmed and Marium Abo User; investigation, Ahmed Khodairy, Hanan Salah, Abdelraheem M. Ahmed and Marium Abo User; resources, Ahmed Khodairy, Hanan Salah, Abdelraheem M. Ahmed and Marium Abo User; data curation, Marium Abo User; writing—original draft preparation, Marium Abo User; writing—review and editing, Ahmed Khodairy, Hanan Salah and Abdelraheem M. Ahmed; supervision, Ahmed Khodairy, Hanan Salah and Abdelraheem M. Ahmed; project administration, Ahmed Khodairy. All authors have read and agreed to the published version of the manuscript.

Data availability statement

The data used to support the findings of this study are available from the corresponding author upon request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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