

Short Note

2-[[4-(4-Bromophenyl)piperazin-1-yl]methyl]-4-(3-chlorophenyl)-5-(4-methoxyphenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione

Monika Wujec^{1,*}  and Rafał Typek^{2,*}¹ Department of Organic Chemistry, Faculty of Pharmacy, Medical University of Lublin, 20-093 Lublin, Poland² Department of Chromatography, Institute of Chemical Sciences, Faculty of Chemistry, Maria Curie-Skłodowska University in Lublin, 20-031 Lublin, Poland

* Correspondence: monika.wujec@umlub.pl (M.W.); rafal.typek@mail.umcs.pl (R.T.)

Abstract: The novel compound 2-[[4-(4-bromophenyl)piperazin-1-yl]methyl]-4-(3-chlorophenyl)-5-(4-methoxyphenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione is obtained in good yield via a three-step protocol. The product's structure is assigned by HRMS, IR, ¹H and ¹³C NMR experiments.

Keywords: 1,2,4-triazole; mannich base; NMR analysis

1. Introduction

Piperazine is a common structural motif found in agrochemicals and pharmaceuticals, in part due to its ability to positively modulate the pharmacokinetic properties of a drug substance. The incorporation of this heterocycle into biologically active compounds can be accomplished through a Mannich reaction [1]. Piperazine can be found in biologically active compounds for a variety of disease states, such as antihistamines, antiparasitic, antifungal, antibacterial, antiviral, antipsychotic, antidepressant, anti-inflammatory, anticoagulant, antitumor, and antidiabetic drugs [2–26]. Additionally, the piperazine ring is a component in potential treatments for Parkinson's and Alzheimer's disease [27–31], and known antibiotic drugs Ciprofloxacin and Ofloxacin. Moreover, they are also used as psychoactive substances used illegally for recreational purposes [32,33].

We previously described some new derivatives of 1,2,4-triazole with piperazine moiety, some of which exhibited good antibacterial activity [34].

Herein, we report on the synthesis and characterization of a novel Mannich derivative with promising antibacterial activity.

2. Results and Discussion

The title compound 2-[[4-(4-bromophenyl)piperazin-1-yl]methyl]-4-(3-chlorophenyl)-5-(4-methoxyphenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione is obtained via a four-step protocol, shown in Scheme 1. The 1,2,4-triazole derivative is prepared in the very simple and efficient procedure described previously [35]. The reaction with amine was carried out in 95% ethanol at room temperature for 24 h. The progress of the reaction was checked by TLC chromatography using the mixture CHCl₃: C₂H₅OH (10:1 *v/v*) as eluent.

The structure of the new Mannich base is assigned by HRMS, IR, ¹H, and ¹³C NMR spectra (see Supplementary Materials). The ¹H spectrum in DMSO-*d*₆ shows characteristic signals for the protons of piperazine at 2.96 and 3.16 ppm, respectively, protons of the methoxy group as a singlet at 3.75 ppm, the signal of the CH₂ group at 5.23 as a singlet, and aromatic protons in the range 6.92–7.67. There is a lack of signal characteristics for the proton NH group present in the spectrum of the initial compound. In the ¹³C NMR spectra, carbons signals were observed at expected values of chemical shift. The six aliphatic carbon were observed as four signals at 48.46, 50.14, 55.81, and 69.21 ppm. The IR spectra of



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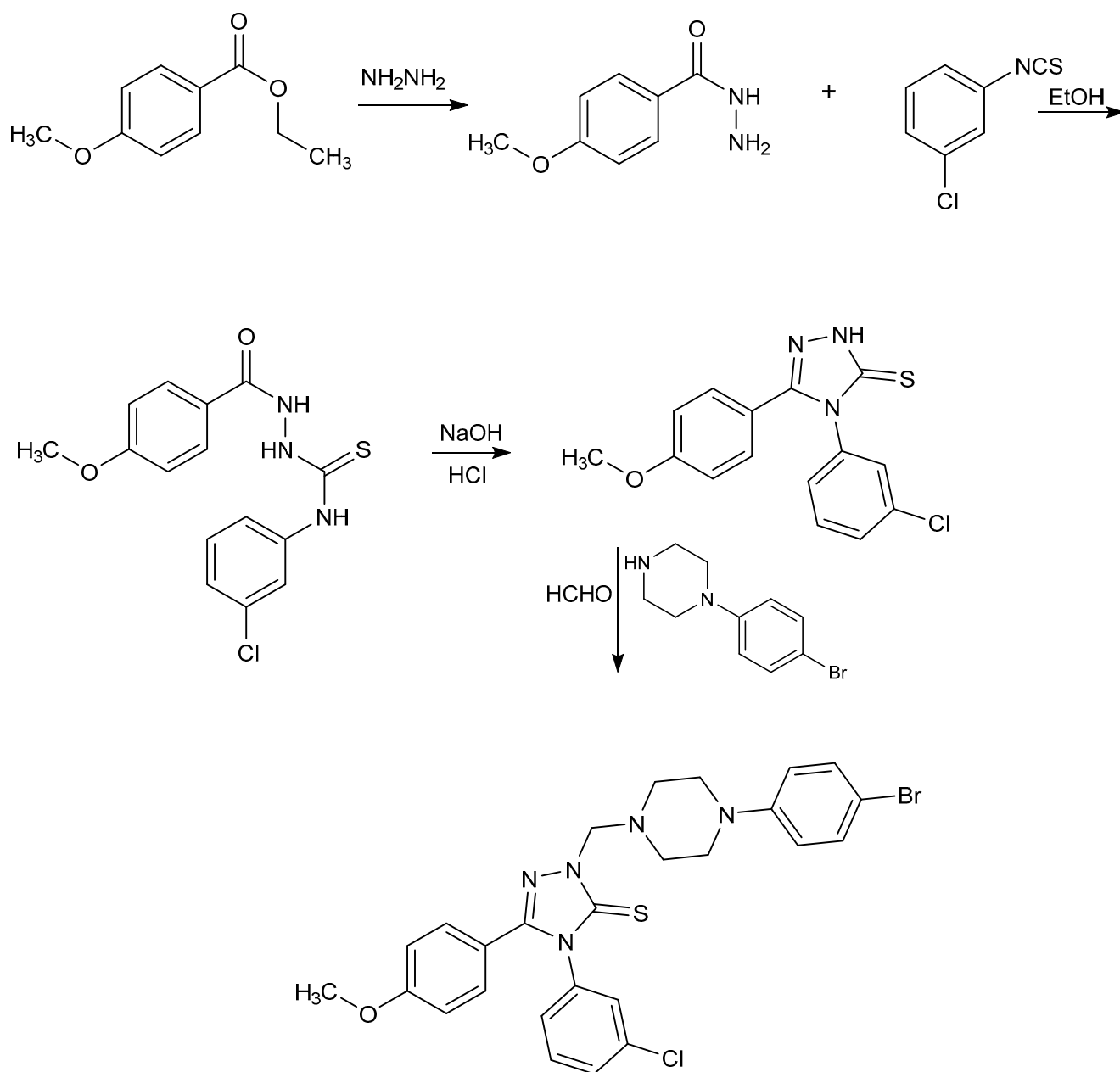
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products show a characteristic band for CH aliphatic and aromatic stretch at 2883 cm^{-1} , 2831 cm^{-1} , and 3040 cm^{-1} , respectively.



Scheme 1. Synthesis of 2-[[4-(4-bromophenyl)piperazin-1-yl]methyl]-4-(3-chlorophenyl)-5-(4-methoxyphenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione.

3. Materials and Methods

3.1. General

All reagents were purchased from Merck (Darmstadt, Germany) and were used without any further purification. Solvents (ethanol, dry ethanol, diethyl ether, chloroform) were used as purchased (POCH Gliwice, Poland). Merck silica gel (TLC-cards with fluorescent indicator 254 nm) was used for TLC chromatography. The NMR spectra were recorded on a Bruker Avance 600 spectrometer (Rheinstetten, Germany) in $\text{DMSO-}d_6$; the chemical shifts were quoted in ppm in δ -values and the coupling constants were calculated in Hz. The spectra were processed with the Topspin 3.6.2 program. The IR spectra were measured on a Spectrometer FT-IR Nicolett 8700 (Thermo Scientific, Waltham, MA, USA).

The chromatographic measurements were performed using LC/MS system consisting of UHPLC chromatograph (UltiMate 3000, Dionex, Sunnyvale, CA, USA) connect with the linear trap quadrupole-Orbitrap mass spectrometer (LTQ-Orbitrap Velos from Thermo Fisher Scientific, San Jose, CA, USA) equipped with ESI source. In all analyses a Gemini C18 column (4.6 × 100 mm, 3 μm) (Phenomenex, Torrance, CA, USA) was used for chromatographic separation.

3.2. Synthesis of 2-[[4-(4-Bromophenyl)piperazin-1-yl]methyl]-4-(3-chlorophenyl)-5-(4-methoxyphenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione

3.2.1. Synthesis of 4-Methoxybenzhydrazide [35]

Ethyl 4-methoxybenzoate (1 mmol, 0.18 g) was dissolved in 5 mL of 96% ethanol and hydrazine hydrate (100%) (2 mL) was added. The mixture was refluxed for 3 h. After the completion of the reaction by TLC (toluene:ethyl acetate = 7:3 *v/v*), the solution was cooled and the precipitate was filtered off and dried. 4-Methoxybenzhydrazide was obtained with 85% yield (0.14 g).

3.2.2. Synthesis of 4-(3-Chlorophenyl)-1-(4-methoxyphenyl)thiosemicarbazide [35]

In the next step, hydrazide (1 mmol, 0.17 g) and 3-chlorophenyl isothiocyanate (1 mmol, 0.13 mL) was refluxed for 2 h in anhydrous ethanol (5 mL). Then, the solution was cooled to room temperature. The solid product was filtered off, washed with hot water and diethyl ether, dried, and crystallized from 96% ethanol.

3.2.3. Synthesis of 4-(3-Chlorophenyl)-5-(4-methoxyphenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione [35]

The obtained thiosemicarbazide derivative (0.31 g, yield 90%) was refluxed with 2% NaOH solution for 4 h. Next, the solution was cooled and acidified (6N HCl). The solid product was filtered and crystallized from 96% ethanol. 4-(3-Chlorophenyl)-(4-methoxyphenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione was obtained as a white solid to yield 0.22 g (70%). M.p. 261–262 °C.

3.2.4. Synthesis of 2-[[4-(4-Bromophenyl)piperazin-1-yl]methyl]-4-(3-chlorophenyl)-5-(4-methoxyphenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione

A total of 1 mmol (0.32 g) of the 4-(3-chlorophenyl)-5-(4-methoxyphenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione was dissolved in 10 mL anhydrous ethanol and then 4-(4-bromophenyl)piperazine (1 mmol, 0.24 g) and a formaldehyde solution (aq. 37%, 5 drops) were added. The mixture was stirred at room temperature for 1 h. The appearance of the product was observed. However, the complete reaction of the substrates took place after 24 h at room temperature. The progress of the reaction was checked by TLC chromatography (eluent chloroform:96% ethanol, 10:1 *v/v*). The precipitate was filtered off, dried, and crystallized from 96% ethanol.

Yield: 81%, 0.46 g. White crystals, m.p.: 226–227 °C. ¹H NMR (600 MHz (*d*₆)DMSO): 2.95–2.97 (m, 4H, 2CH₂ piperazine), 3.15–3.17 (m, 4H, 2CH₂ piperazine), 3.75 (s, 3H, CH₃), 5.25 (s, 2H, N-CH₂), 6.90 (d, 2H, ArH, *J* = 9.1 Hz), 6.95 (d, 2H, ArH, *J* = 8.9 Hz), 7.29 (d, 2H, ArH, *J* = 8.9 Hz), 7.34 (d, 2H, ArH, *J* = 9.1 Hz), 7.37–7.38 (m, 1H, ArH), 7.53 (t, 1H, ArH, *J* = 8.0 Hz), 7.58–7.60 (m, 1H, ArH), 7.67 (t, 1H, ArH, *J* = 2.0 Hz). ¹³C NMR (600 MHz, (*d*₆)DMSO): 48.46, 50.14, 55.81, 69.21, 110.56, 114.60, 117.73, 117.96, 128.31, 129.61, 130.16, 130.55, 131.39, 131.94, 133.77, 136.96, 149.36, 150.69, 161.33, 169.72. IR (KBr, cm⁻¹): 3040 (CH_{arom.}), 2883, 2831 (CH_{aliph.}), 1326 (C=S). HRMS (ESI), *m/z*: calcd for C₂₆H₂₅BrClN₅OS. Theoretical mass [M + H]⁺ 570.07300, Experimental mass [M + H]⁺ 570.07309.

4. Conclusions

2-[[4-(4-bromophenyl)piperazin-1-yl]methyl]-4-(3-chlorophenyl)-5-(4-methoxyphenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione is obtained in good yield by aminomethylation reac-

tion of 4-(3-chlorophenyl)-5-(4-methoxyphenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione with 4-(4-bromophenyl)piperazine and formaldehyde. The product is purified by crystallization from 96% ethanol and characterized by ^1H NMR, ^{13}C NMR, IR, and HRMS spectra.

Supplementary Materials: The following are available online: ^1H , ^{13}C NMR, and IR spectra.

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