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Short Note

6-Amino-7-((4-methoxybenzyl)thio)quinazolin-4(3*H*)-one

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Abstract: The titular compound, 6-amino-7-((4-methoxybenzyl)thio)quinazolin-4(3*H*)-one, was prepared from 7-fluoro-6-nitroquinazolin-4(3*H*)-one via a nucleophilic aromatic substitution reaction followed by a reduction of the nitro group. Characterization of the target compound via ^{1}H NMR, ^{13}C NMR, and HRMS confirmed its structure.

Keywords: heterocycles; quinazoline; quinazolin-4(3*H*)-one; nucleophilic aromatic substitution; reduction

1. Introduction

Quinazolinone derivatives are frequently encountered in medicinal chemistry as their biological activity can be significantly altered by their substituents [1–4]. Examples of approved drugs based on the quinazolin-4-one scaffolds are shown in Figure 1. These include the anticancer drugs idelalisib (Figure 1a), used for the treatment of chronic lymphocytic leukemia [5–8], and raltitrexed (Figure 1b), which has been available in Europe and Canada since 1998 for the treatment of colorectal cancer [9–11], as well as the antihypertensive drug quinethazone (Figure 1c) [12,13].

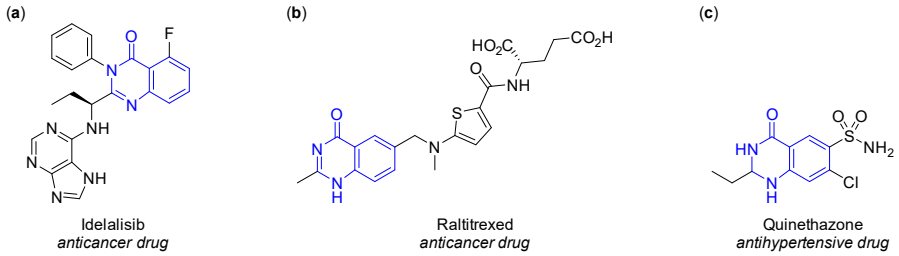


Figure 1. Examples of currently available drugs based on quinazolin-4-one scaffolds: (**a**) Idelalisib; (**b**) Raltitrexed; and (**c**) Quinethazone.

Sulfur-substituted quinazolinones have proven to be inhibitors of the eukaryotic initiation factor that is overexpressed in individuals suffering from various types of cancer, such as breast, prostate, and colon cancer [14]. Additionally, quinazolinone with sulfur substituents have shown potential in the treatment of neurodegenerative diseases [15].

2. Results and Discussion

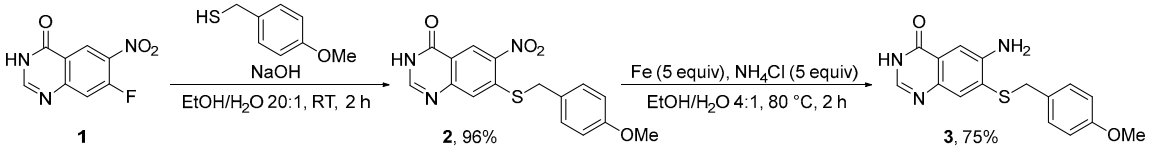
In an effort to extend our previous work to include biologically relevant scaffolds, we prepared the titular compound, 6-amino-7-((4-methoxybenzyl)thio)quinazolin-4(3*H*)-one (**3**), using a procedure previously developed by our group [16]. As shown in Scheme 1, commercially available 7-fluoro-6-nitroquinazolin-4(3*H*)-one (**1**) was treated with (4-m ethoxyphenyl)methanethiol, which, upon addition of sodium hydroxide, yielded7-((4-methoxybenzyl)thio)-6-nitroquinazolin-4(3*H*)-one (**2**). This reaction proceeded with 100% conversion, as determined by LCMS, and nitro compound **2** was isolated in a 96% yield. Characterization via ^{1}H NMR (Supporting Information, Figure S1) and ^{13}C NMR

Citation: Thapa, S.; Bolliger, J.L. 6-Amino-7-((4-methoxybenzyl)thio) quinazolin-4(3*H*)-one. *Molbank* **2024**, *2024*, M1942. https://doi.org/10.3390/M1942

Academic Editor: Oleg A. Rakitin

Received: 6 December 2024
Revised: 16 December 2024
Accepted: 17 December 2024
Published: 19 December 2024

(Supporting Information, Figure S2) confirmed both the structure of this intermediate as well as its purity. A subsequent reduction of the nitro group afforded compound **3** (the titular compound) in a 75% isolated yield. Although the reaction proceeded cleanly, some of the product was lost due to its poor solubility during the necessary step of filtration through celite to remove the residual iron.



Scheme 1. Reaction conditions for the two-step synthesis of 6-amino-7-((4-methoxybenzyl)thio)quinazolin-4(3*H*)-one (**3**).

The structure of the target molecule **3** was confirmed via ^{1}H NMR (Supporting Information, Figure S3) and ^{13}C NMR (Supporting Information, Figure S4). HRMS confirmed its expected atomic composition.

3. Materials and Methods

3.1. General Information and Analyses

Reagents and solvents were purchased from Fisher Scientific or TCI Chemicals and used as supplied. DMSO-d_6 was dried over molecular sieves.

Melting points were determined using a MEL-TEMP apparatus (Cambridge, MA, USA) and are uncorrected. ^{1}H NMR and ^{13}C{^{1}H} NMR spectra were recorded using a 400 MHz Bruker Avance III spectrometer with a 5 mm liquid-state Smart Probe at 298 K. Chemical shifts (δ_H, δ_C) are expressed in parts per million (ppm) and reported relative to the resonance of the residual protons of the DMSO-d_6 (δ_H = 2.50 ppm) or in ^{13}C{^{1}H} NMR spectra relative to the resonance of the deuterated solvent DMSO-d_6 (δ_C = 39.52 ppm). High-Resolution Mass Spectrometry (HRMS) data were obtained using an LTQ Orbitrap XL (Thermo Fisher Scientific) in FT Orbitrap Mode at a resolution of 100,000.

3.2. Synthesis of 7-((4-Methoxybenzyl)thio)-6-nitroquinazolin-4(3H)-one

A 500 mL round-bottomed flask equipped with a stir bar was loaded with 5.228 g of 7-fluoro-6-nitroquinazolin-4(3*H*)-one (25.00 mmol, 1.00 equiv) and 200 mL of ethanol and placed under an atmosphere of argon. A total of 3.518 ml of (4-methoxyphenyl)methanethiol (3.894 g, 25.25 mmol, 1.01 equiv) was added with a syringe, followed by a dropwise addition of 1.050 g of NaOH (26.25 mmol, 1.05 equiv) dissolved in 10 mL of H_2O. The reaction mixture was stirred for 2 h at room temperature, after which the solid was filtered off and washed with H_2O, ethanol, and finally diethyl ether, yielding the product as a yellow powder in 96% yield (8.251 g, 24.03 mmol), m.p. 264–265 °C.

^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ = 12.62 (s, 1H), 8.79 (s, 1H), 8.27 (s, 1H), 7.79 (s, 1H), 7.41 (d, J = 8.6 Hz, 2H), 6.93 (d, J = 8.6 Hz, 2H), 4.43 (s, 2H), 3.74 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6, 298 K): δ = 159.8, 158.8, 151.5, 149.7, 143.0, 142.6, 130.5, 126.6, 124.8, 124.7, 118.7, 114.1, 55.1, 35.8. HRMS (ESI) m/z calculated for $[M + H]^+$ = $[C_{16}H_{14}N_3O_4S]^+$ 344.0700; observed, 344.0698 (0.6 ppm).

3.3. Synthesis of 6-Amino-7-((4-methoxybenzyl)thio)quinazolin-4(3H)-one

A 250 mL round-bottomed flask equipped with a stir bar was loaded with 8.321 g of 7-((4-methoxybenzyl)thio)-6-nitroquinazolin-4(3*H*)-one (23.48 mmol, 1 equiv), 6.285 g of NH_4Cl (117.5 mmol, 5.0 equiv), and 150 mL of EtOH/H_2O (4:1). The reaction flask was placed into an oil bath set to 80 °C, and 6.562 g of iron power (117.5 mmol, 5.0 equiv) was added while stirring. Then, the reaction flask was fitted with a reflux condenser, and the reaction was stirred under argon at 80 °C until TLC indicated a complete reduction after 2 h of reacting. Due to the poor solubility of the product in ethanol, filtration through celite was performed with hot ethanol. After concentration of the filtrate, brine was added, and

the reaction mixture was extracted three times with THF and then three times with ethyl acetate. The combined extracts were dried over $MgSO_4$ and evaporated. Recrystallization from acetone yielded the pure product as a pale-orange solid in 75% yield (5.483 g, 17.50 mmol), m.p. 259–260 °C.

^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ = 11.80 (s, 1H), 7.76 (d, J = 3.3 Hz, 1H), 7.41 (s, 1H), 7.32 − 7.27 (m, 3H), 6.86 (d, J = 8.6 Hz, 2H), 5.53 (s, 2H), 4.22 (s, 2H), 3.72 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6, 298 K): δ = 160.4, 158.4, 145.6, 141.1, 139.9, 130.1, 128.8, 128.6, 127.2, 121.7, 113.8, 106.7, 55.0, 35.5. HRMS (ESI) m/z calculated for $[M + H]^+$ = $[C_{16}H_{16}N_3O_2S]^+$ 314.0958; observed, 314.0958 (0 ppm).

4. Conclusions

In conclusion, we successfully extended a procedure previously developed by our group to the biologically active quinazolinone scaffold as demonstrated with the two-step synthesis of the titular compound, 6-amino-7-((4-methoxybenzyl)thio)quinazolin-4(3*H*)-one (**3**) from 7-fluoro-6-nitroquinazolin-4(3*H*)-one (**1**).

Supplementary Materials: The following supporting information are available online: Figure S1: ^{1}H NMR spectrum of **2**; Figure S2: ^{13}C NMR spectrum of **2**; Figure S3: ^{1}H NMR spectrum of **3**; Figure S4: ^{13}C NMR spectrum of **3**; Figure S5: HRMS of **3**.

Author Contributions: Conceptualization, J.L.B.; methodology, J.L.B.; validation, J.L.B.; investigation, J.L.B. and S.T.; resources, J.L.B.; data curation, J.L.B.; writing—original draft preparation, J.L.B.; writing—review and editing, J.L.B. and S.T.; supervision, J.L.B.; project administration, J.L.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: The original contributions presented in this study are included in the article/Supplementary Materials. Further inquiries can be directed to the corresponding author.

Acknowledgments: We are grateful to the staff of the NMR facility at Oklahoma State University for maintaining the NMR instrumentation and the staff of the Proteomics/Mass Spectrometry Core Facility for their assistance in measuring HRMS.

Conflicts of Interest: The authors declare no conflicts of interest.

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