



Article DFT Calculation, Hirshfeld Analysis and X-Ray Crystal Structure of Some Synthesized N-alkylated(S-alkylated)-[1,2,4]triazolo[1,5-a]quinazolines

Hatem A. Abuelizz ¹, Saied M. Soliman ², Hazem A. Ghabbour ³, Mohamed Marzouk ⁴, Mohamed M. Abdellatif ⁵ and Rashad Al-Salahi ^{1,*}

- ¹ Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia; Habuelizz@ksu.edu.sa
- ² Department of Chemistry, Faculty of Science, Alexandria University, Ibrahimia, Alexandria 21321, Egypt; saied1soliman@yahoo.com
- ³ Department of Medicinal Chemistry, Faculty of Pharmacy, Mansoura University, Mansoura 35516, Egypt; ghabbourh@yahoo.com
- ⁴ Chemistry of Tanning Materials and Leather Technology Department, Organic Chemicals Industries Division, National Research Centre, Dokki, Cairo 12622, Egypt; msmarzouk@yahoo.co.uk
- ⁵ Department of Chemistry, Graduate School of Science, Tokyo Metropolitan University, 1-1 Minami Osawa, Tokyo 192-0397, Japan; Mohamed-soliman@tmu.ac.jp
- * Correspondence: ralsalahi@ksu.edu.sa

Abstract: The present work aimed to synthesize 2-methylthio-triazoloquinazoline derivatives and study their X-ray, NMR, DFT and Hirshfeld characteristics. The cyclocondensation of dimethyl-N-cyanodithiocarbonate with 2-hydrazinobenzoic acid hydrochloride resulted in an intermediate, 2-methylthio-[1,2,4]triazolo[1,5-a]quinazolin-5-one (A), which upon treatment with phosphorus pentasulfide, transformed into the 2-methylthio-[1,2,4]triazolo[1,5-a]quinazolin-5-thione (B). Reaction of 2-methylthio-triazoloquinazolines (A&B) with alkyl halides (allyl bromide and ethyl iodide) in basic medium afforded 4-allyl-2-methylthio-[1,2,4]triazolo[1,5-a]quinazolin-5-one (1; N-alkylated) and 5-ethylthio-2-methylthio-[1,2,4]triazolo[1,5-a]quinazoline (2; S-alkylated), respectively. Their molecular and supramolecular structures were presented. Unambiguously, the molecular structures of 1 and 2 were confirmed via NMR and single-crystal X-ray diffraction. The resulting findings confirmed the structures of 1 and 2 and determined their crystalized system (monoclinic system; $P2_1/n$ space group). Hirshfeld analysis of 1 revealed the importance of the significantly short O…H (6.7%), S···S (1.2%) and C···C (2.8%); however, the short H···H (42.6%), S···H (16.3%) and C···C (4.3%) were showed in 2 by intermolecular interactions in the molecular packing. The 1,2,4-triazoloquinzolines (1&2) were anticipated to be relatively polar compounds with net dipole moments of 2.9284 and 4.2127 Debye, respectively. The molecular electrostatic potential, atomic charge distribution maps and reactivity descriptors for 1 and 2 were also determined. The calculated nuclear magnetic resonance spectra of the targets 1 and 2 were well correlated with the experimental data.

Keywords: triazoloquinazoline; cyclocondensation; thionation; alkylation; X-ray; DFT; Hirshfeld analysis

Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/).

1. Introduction

In pharmaceutical chemistry, the synthesis of new bioactive agents has recently achieved notable prominence as a result of the increasing spread of various diseases [1,2]. Nitrogen heterocycles, which are found in various natural and synthetic products, represent the most important class of biologically active substances and pharmaceutically relevant molecules. Among them, quinazolines and triazoles have attracted considerable attention in synthetic medicinal chemistry and the materials science area. Due to the significance of these pharmacophore classes as well as their roles in the construction of pharmacologically active molecules, including antimicrobial, antimalarial, anti-



Citation: Abuelizz, H.A.; Soliman, S.M.; Ghabbour, H.A.; Marzouk, M.; Abdellatif, M.M.; Al-Salahi, R. DFT Calculation, Hirshfeld Analysis and X-Ray Crystal Structure of Some Synthesized *N*-alkylated(*S*-alkylated)-[1,2,4]triazolo[1,5-a]quinazolines. *Crystals* **2021**, *11*, 1195. https:// doi.org/10.3390/cryst11101195

Academic Editor: Peter Baran

Received: 2 September 2021 Accepted: 28 September 2021 Published: 30 September 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations. inflammatory, antihypertensive, anticonvulsant, antidiabetic and anticancer agents as well as cholinesterase inhibitors, their synthesis has been a hot topic in organic synthesis [3,4]. Thus, the combination of both quinazoline and triazole moieties results in the synthesis of a triazoloquinazoline scaffold, which exhibits varied pharmacological activities [3]. Indeed, many triazoloquinazolines have been reported to exhibit promising antihistamine activity [5,6]. Some 1,2,4-triazoloquinazolines have been investigated as potent adrenoblockers and were found to display good hypotensive activity [7,8]. A series of 2-alkoxy-triazoloquinazolines were found to act as potent adenosine receptor antagonists [9,10]. The presence of lactam and thiolactam in triazoloquinazolines skeleton was valuable to appear in more pharmacophoric moieties associated with a diversity in biological properties. For example, S-alkylated triazoloquinazolines showed significant antimicrobial effects [11,12]; however, their N-alkylated compounds demonstrated strong antiviral activity [13,14]. Furthermore, potential antidiabetic activity was reported for triazologuinazoline, which manifested itself via its ability to inhibit α -glucosidase activity [15]. Additionally, some 1,2,4-triazoloquinazolines have been observed to possess potential antioxidant properties and promising cytotoxicity [16–21]. Hence, we focus on triazoloquinazoline chemistry, particularly studying the crystal structure of 1,2,4-triazolo[1,5-a]quinazoline derivatives [22–27]; herein, we report X-crystal structures, NMR, MS, IR, DFT and Hirshfeld studies of the synthesized triazoloquinazolines 1 and 2.

2. Materials and Methods

2.1. General Information

The IR spectrum was determined using a Perkin Elmer FT-IR Spectrum BX system. The NMR spectra were measured with a Bruker AMX 500-MHz instrument, and the data were described as ppm values relative to tetramethylsilane at 500 and 125 MHz for ¹H and ¹³C NMR, respectively, and DMSO- d_6 used as solvent. Employing a Micromass Quattro microTM triple-quadruple tandem mass spectrometer to measure ESI-MS spectra.

2.2. Synthesis of the Triazoloquinazolines 1 and 2

According to the reported detailed methodologies in our previous papers [28,29], the compounds 1 and 2 were prepared.

2.2.1. 4-Allyl-2-methylthio-[1,2,4]triazolo[1,5-a]quinazolin-5-one (1)

¹H NMR (DMSO-*d*₆): δ ppm 8.26 (br d, J = 8.0 Hz, 1H), 7.77 (br d, J = 8.0 Hz, 1H), 7.75 (br t, J = 7.5 Hz, 1H), 7.51 (br t, J = 7.50 Hz, 1H), 6.00 (m, 1H), 5.31 (br d, J = 17.50 Hz, 1H), 5.21 (br d, J = 10.50 Hz, 1H), 4.80 (d, J = 5.00 Hz, 2H), 2.65 (s, 3H, SCH₃); ¹³C NMR (DMSO-*d*₆): δ ppm 167.32, 154.43, 145.72, 138.14, 133.17, 131.33, 129.21, 127.60, 117.23, 114.90, 112.25, 45.50, 13.90 ppm; ESI-MS (*m*/*z*): 271.1 [M–H][–] (negative mode) for MW = 272.

2.2.2. 5-Ethylthio-2-methylthio-[1,2,4]triazolo[1,5-a]quinazoline (2)

¹H NMR (DMSO-*d*₆): δ ppm 8.22 (br d, J = 8.2 Hz, 2H), 8.08 (br d, J = 8.05 Hz, 1H), 7.69 (br t, J = 7.68 Hz, 1H), 4.80 (q, J = 7.20 Hz, 2H, SCH₂CH₃), 2.69 (s, 3H, SCH₃), 1.42 (t, J = 7.00 Hz, 3H, SCH₂CH₃); ¹³C NMR (DMSO-*d*₆): δ (ppm) 167.69, 164.61, 152.73, 135.95, 133.73, 126.78, 126.01, 117.50, 115.55, 24.48, 14.44, 13.97; ESI-MS (*m*/*z*): 275.3 [M−H]⁻ (negative mode) for MW = 276.

2.3. X-ray Crystallography Analysis

Crystals of 2-Methylthiotriazoloquinazolines (1&2) were formed from saturated ethanolic solution by evaporation over 2 days at room temperature. Data collection was conducted on a Bruker APEX-II D8 Venture area diffractometer equipped with graphite monochromatic Mo K α radiation at 100 (2) K. By employing Bruker SAINT SHELXT software, the cell refinement and reduction data were performed [30,31], and the solved structures were obtained by using SHELXT software. The final refinement was carried out using a fullmatrix least-squares techniques with anisotropic thermal data for non-hydrogen atoms on *F*. Triazoloquinazolines **1** and **2** comprise the crystallographic data supplementary and can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif (2 September 2021).

2.4. Hirshfeld Surface Analysis

Using Crystal Explorer 17.5 program, the topology analyses were carried out [32].

Computational Methods

Employing gaussian 09 software package, B3LYP/6-31G(d,p) method and NBO 3.1 program, all DFT calculations were carried out, the optimized obtaining structures revealed no imaginary frequencies and natural population analysis was completed, respectively [33–37]. The chemical shifts of ¹H and ¹³C NMR spectrometry were computed applying the GIAO method in DMSO- d_6 [38].

3. Results and Discussion

3.1. Chemistry

The synthetic routes of the target compounds, namely 4-allyl-triazoloquinazolin-5-one (1) and 5-ethyl-triazoloquinazoline (2), are outlined in Scheme 1. Reaction of 2-hydrazinobenzoic HCl (1.1 mmol) with dimethyl-*N*-cyanoimidodithiocarbonate (1 mmol) in ethanolic solution (15 mL) and triethyl amine (3 mmol) yielded an intermediate (**A**). Treatment of **A** (1 mmol) with allyl bromide (1.5 mmol) in the presence of K₂CO₃ (0.5 mmol) using DMF (10 mL) as the solvent resulted in the synthesis of the target compound **1** [28]. Thionation of **A** (1 mmol) with P₂S₅ (1 mmol) in pyridine (10 mL) under reflux conditions gave 1,2,4-triazoloquinazolin-5-thione (**B**, 1 mmol), which was transformed into the target compound 5-thioethyl-triazoloquinazoline (2) upon treatment with ethyl iodide (1.5 mmol) in a basic aqueous solution (8 mL) [29]. The final products **1** and **2** were obtained as plate-like crystals after crystallization.



i : Et₃N, EtOH; ii: DMF, K₂CO₃, allyl bromide; iii: pyridine, P₂S₅, iv: ethyl iodide, NaOH

Scheme 1. Route for synthesis of the targets triazoloquinazolines (1&2).

3.2. Spectroscopic Data

Confirmation of triazoloquinazolines structures **1** and **2** was achieved by IR, NMR and MS-spectrometry. Although the chemical structures of the intermediates **A** and **B** have been previously determined [28,29] and the physiochemical properties of **1** have also been reported, we reiterated the relevant NMR data of **1** for additional explanation in this

study. The IR spectrum of 1 revealed a strong absorption band due to carbonyl group at 1679 cm⁻¹. The ¹H NMR spectra of **1** and **2** are characterized by the singlet signal of the S-methyl protons at δ 2.65 and 2.69 ppm, respectively, and their ¹³C NMR resonances were recorded at δ 13.90 and 13.97 ppm, respectively. Notably, *N*-alkylation of substrate A with an allyl moiety (Scheme 1) was proven by its four 1 H characteristic resonances at about 6.0 (m), 5.31 (br d, J = 17.5 Hz), 5.21 (br d, J = 10.5 Hz) and 4.80 (d, J = 5 Hz), which are assignable to propene moiety (CH₂CHCH₂) proton types. However, the S-alkylated product 2 confirmed by the presence of two characteristic ¹H resonances with intrinsic splitting patterns at approximately 4.80 ppm (q, J = 7.2 Hz) and 1.41 ppm (t, J = 7.0 Hz), which ascribed to $-SCH_2CH_3$ and $-SCH_2CH_3$ protons, respectively (Figure 1). Three ¹³C resonances at δ ppm 131.33, 112.25 and 45.50 were attributed to the C-12, C-13 and C-11 carbons of the allyl group in 1; whereas, two signals were detected at δ 24.48 and 14.44 ppm attributable to C11 and C12 of the ethyl group in 2 (Figure 2). In triazoloquinazolines 1 and 2, the protons of the benzofused moiety were inferred to give rise to the resonance peaks with two broad doublets and two broad triplets with Jortho values ranging between 7.5 and 8.2 Hz. Additionally, further confirmation of 1,2,4-triazoloquinazoline structures (1&2) was achieved by single X-ray analysis and electrospray ionization mass spectrometry (ESI-MS). For the molecular weight of 272 (compound 1), the ESI-MS spectrum revealed an ion band at m/z 271.1 [M–H]⁻ in the negative detection mode and showed an ion band at m/z 275.3 [M–H]⁻ for the target 2 (MW = 276). In addition to MS data, the single-crystal X-ray analysis provided an obvious confirmation of the expected structures of 1 and 2.



Figure 1. ORTEP of triazoloquinazolines **1** and **2**. At the 40% probability level for non-H atoms, the displacement ellipsoids are plotted.

Triazoloquinazoline **1** has shown promising antihistaminic effect against histamine induced bronchospasm (IC₅₀ = 0.6528 mM) in comparison with the theophylline (IC₅₀ = 0.01996 mM) [6]. Furthermore, **1** was evaluated as an α -glucosidase inhibitor in vitro assay and showed the best inhibition effect (IC₅₀ = 72.28 μ M) in regards to acarbose (IC₅₀ = 143.54 μ M) [14]. Moreover, the triazoloquinazoline **1** was also reported as an antiviral, antimicrobial and antioxidant active agent (see Introduction).



Figure 2. Three-dimensional networks viewed approximately in molecular packing of **1** and **2** (H-bonds are drawn as dashed lines).

3.3. Crystallographic Data

The refinement information and crystallographic data of triazoloquinazolines **1** and **2** ($C_{13}H_{12}N_4OS$ and $C_{12}H_{12}N_4S_2$) structures are presented in Table 1. As it can be evinced from Figure 1, the asymmetric units of **1** and **2** contain only one molecule. The length of all bonds and the angles demonstrated values in the ordinary ranges [39]. In the crystal packing (Figure 2), the molecules of compounds **1** and **2** are connected to another one via a single non-classical intermolecular hydrogen bonding interaction (Table 2).

Crystal Data	Triazoloquinazoline 1	Triazoloquinazoline 2
Chemical formula	C ₁₃ H ₁₂ N ₄ OS	C ₁₂ H ₁₂ N ₄ S ₂
Mr	272.33	276.38
Crystal system, space group	Monoclinic, $P2_1/c$	Monoclinic, $P2_1/n$
Temperature (K)	293	293
<i>a</i> , <i>b</i> , <i>c</i> (Å)	10.3567 (12), 5.0392 (5), 25.013 (3)	9.5153 (7), 8.1162 (6), 16.1568 (12)
β (°)	104.850 (5)	102.852 (3)
V (Å ³)	1261.8 (2)	1216.50 (16)
Z	4	4
Type of radiation	Μο Κα	Μο Κα
$\mu (mm^{-1})$	0.25	0.42
Size of crystal (mm)	0.42 imes 0.21 imes 0.04	0.60 imes 0.13 imes 0.09
	Data Collection	
Diffractometer	Bruker APEX-II D8 venture diffractometer	Bruker APEX-II D8 venture diffractometer
Absorption correction	Multi-scan SADABS Bruker 2014	Multi-scan SADABS Bruker 2014
\tilde{T}_{min} , T_{max}	0.810, 0.874	0.806, 0.812
The measured, independent		
and observed	16671, 2614, 1481	27487, 2796, 1979
$[I > 2\sigma(I)]$ reflections No.		
R _{int}	0.176	0.094

Crystal Data	Triazoloquinazoline 1	Triazoloquinazoline 2
	Refinement	
$R[F^2 > 2\sigma(F^2)], wR(F^2), S$	0.064, 0.155, 1.02	0.054, 0.150, 1.03
Reflections No.	2614	2796
Parameters No.	167	165
Restraints No.	0	0
$\Delta \rho_{\text{max}} \Delta \rho_{\text{min}}$ (e Å ⁻³)	0.55, -0.50	0.57, -0.86
CCDC No.	1826859	1827320

Table 1. Cont.

Table 2.	For	triazol	loquinaz	olines	1 and 2.	
Iuvic II.	101	una de la composición de la composicinde la composición de la composición de la composición de la comp	log an laz	lonneo	I unter I	•

		Triazoloquinazoline 1		
D—H…A	D—H	H····A	D····A	D—H…A
C5—H5A…O1 ⁱ	0.9300	2.5900	3.500 (5)	164.00
	Symmetr	ry codes: (i) $-x + 2, -y - 2$	2, −z + 1.	
		Triazoloquinazoline 2		
D—H…A	D—H	$\mathbf{H}\cdots\mathbf{A}$	D····A	D—H…A
C5—H5A…S2	0.9500	2.6900	3.072 (3)	105.00
C11—H11B…N4	0.9900	2.4500	2.854 (4)	104.00

3.4. Analysis of Molecular Packing

The intermolecular interactions play an essential role for determining the stability of the studied crystals. In this regard, various intermolecular interactions in the crystal structures of both systems are analyzed quantitatively, performing Hirshfeld calculations (Figures S1 and S2). Their percentages and detected contacts are presented in Figure 3. The molecular packing of 1 is controlled by significantly short $O \cdots H$ (6.7%), $S \cdots S$ (1.2%) and C…C (2.8%) (Figure 3). In 2, the packing is controlled by short H…H (42.6%), S…H (16.3%) and C…C (4.3%) interactions. All such interactions have the characteristic features of short interactions and contribute significantly to the stability of 1 and 2 crystal structures. Notably, although the H…H (47.0%), H…C (12.97%), N…H (9.7%) and S…H (5.8%) contacts make a significant contribution to the overall molecular packing interactions in 1 (Figure 4), these contacts exhibited the characteristic features of intermolecular interactions between atoms found at longer mutual distances than the sums of the said atoms Van der Waals radii. Concerning **2**, the contact distances of the most significant H···H, S···H and C···C interactions are summarized in Table 3, and other key contacts that contributed to the molecular packing included the N···H (15.1%) and H···C (9.8%) interactions. Indeed, values for the contact distances of the most important H…H, S…H and C…C interactions were significant, which are highlighted by the corresponding red spots in the d_{norm} maps. Moreover, characteristics of short interactions were observed in the fingerprint plots (Figure 5). These interactions in 2 exhibited considerably longer interaction distances than the sum of the Van der Waals radii of the interacting atoms as well.

Table 3. Values for the short intermolecular contacts in triazoloquinazolines 1 and 2.

1	_	2	
Contact	Distance	Contact	Distance
O1 H5A	2.448	H2A H10C	2.024
S1 S1	3.448	S2 H10B	2.777
C6 C9	3.382	C1 C8	3.388



Figure 3. Intermolecular interactions summary and their % contributions to the overall molecular packing interactions of **1** and **2** crystal structures.



Figure 4. Results of the Hirshfeld analysis conducted on **1**. Red, white and blue colors indicated shorter, equal and longer contact distances than the vdWs radii sum of the interacting atoms, respectively.



Figure 5. Results of the Hirshfeld analysis conducted on **2**. Red, white and blue colors indicated shorter, equal and longer contacts distances than the vdWs radii sum of the interacting atoms, respectively.

4. DFT Analysis

4.1. Geometric Parameters

The compounds **1** and **2** optimized geometries are presented in Figure 6. It can be evinced from this figure that the calculated geometric features of both structures match very well their counter parts experimentally determined, using X-ray diffraction data. The calculated and optimized bond distances are in good agreement with each other (Table S1). Good correlations were also determined to exist between the experimental and the calculated bond distances for the **1** and **2** structures (Figure 7). Indeed, the correlation coefficients values are very close to unity, and the maximum absolute errors do not exceed 0.04 Å and 3.8° for bond distances and bond angles, respectively.



Figure 6. Optimized structures (upper) and matching between the calculated and experimental structures (lower) of 1 and 2.



Figure 7. Cont.



Figure 7. Correlation between the calculated and experimental bond distances of 1 and 2.

The calculated natural atomic charges are presented (Table S2). For triazoloquinazoline 1, the O and N atoms as well as the majority C atoms are negatively charged. The atomic site with the largest negative charge is the carbonyl oxygen (O2: -0.6098 e). Hydrogen and carbon atoms attached to N, O or S atoms are all positively charged. The atom with the largest positive charge is the carbonyl carbon (C20:0.6855 e). In the case of **2**, it was found that N5 (-0.5299 e) and C18 (0.5649 e) were the most negative and positive sites, respectively. The molecular electrostatic potential maps reported in Figure 8 demonstrated these results very well. Triazoloquinazolines **1** and **2** are polar compounds characterized by values for the net dipole moments of 2.9284 and 4.2127 Debye.



Figure 8. Molecular electrostatic potential maps of **1** and **2**. Blue, turquoise, yellow and red indexed colors provide visual information on the electron density—turquoise indicates the lowest electron density, whereas red indicates the highest electron density.

4.2. Analysis of Reactivity

Investigation of the highest occupied and lowest unoccupied molecular orbitals (HOMO and LUMO) of **1** and **2** indicated beyond doubt the distribution of these molecular orbitals over the π -system of the studied molecules (Figure 9). The energies of these orbitals and the corresponding reactivity indices [40–45], such as ionization potential, electron affinity, chemical potential, hardness and electrophilicity (I, A, μ , η and ω) were calculated (Table 4). Both HOMO levels have almost the same energy in the two compounds. However, the energy of LUMO in **1** is higher than **2**. From the results, both compounds have similar ionization potentials but different electron affinities. In the case of **1**, the η value (4.3250 eV) is higher than that of **2** (3.8053 eV). In addition, the electrophilicity of **1** is lower



(1.7852 eV) than that of **2** (2.2087 eV). In Table 4, all the calculated values for I, A, ω , and the HOMO–LUMO gap for both crystals are listed.

Figure 9. Visual representations of HOMO and LUMO of 1 and 2.

able 4. The calculated feactivity indices of 1 and 2	Fable 4.	The calcula	ted reactivity	v indices	of 1 and 2
--	----------	-------------	----------------	-----------	------------

D (4	•
Parameter	1	2
НОМО	-6.0921	-6.0026
LUMO	-1.7671	-2.1973
$I = -E_{HOMO}$	6.0921	6.0026
$A = -E_{LUMO}$	1.7671	2.1973
$\eta = (I - A)/2$	4.3250	3.8053
$\mu = -(I + A)/2$	-3.9296	-4.1000
$\omega = \mu^2/2\eta$	1.7852	2.2087

5. NMR Spectra

The chemical shifts of the resonance peaks in the ¹H and ¹³C NMR spectra of triazoloquinazolines **1** and **2** were computed, and the findings are listed in Tables S3 and S4, alongside the corresponding experimental data. As it can be evinced from Figure 10, a good relation exists between the calculated and the experimentally determined chemical shifts. In particular, the correlation coefficients are 0.97 and 0.98 for both ¹H and ¹³C NMR spectral data.



Figure 10. Correlations between the calculated and experimentally determined ¹HNMR (**left**) and ¹³C (**right**) chemical shift (C.S) values for both crystals.

6. Conclusions

Triazoloquinazolines **1** and **2** were synthesized and confirmed by NMR and X-ray diffractometry. The crystal structures of **1** and **2**, as determined by X-ray diffractometry, were characterized by bond lengths and angles that were in the normal ranges; moreover, molecules of **1** and **2** were observed to be included in a non-classical intermolecular hydrogen bonding interaction. The molecules **1** and **2** were anticipated to be polar, with net dipole moments of 2.9284 and 4.2127 Debye. The practical data were correlated with theoretical DFT calculations (employing the B3LYP/6-311++G(d,p) basis set). The supramolecular structures of the investigated compounds were studied performing Hirshfeld calculations. The calculated geometric features of the studied compounds were appeared to be in good agreement with those experimentally identified by X-ray. Moreover, good agreement was detected between the calculated and the experimental NMR data. Different electronic and reactivity descriptors of **1** and **2** were calculated and discussed.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/ 10.3390/cryst11101195/s1, Figure S1: Hirshfeld analysis of 2, Figure S2: Hirshfeld analysis of 1, Table S1: The calculated bond distances of 1 and 2, Table S2: Natural charge populations at the different atomic sites of the studied compounds, Table S3: The calculated and experimental chemical shifts (ppm) for 1 (according to Figure 6), Table S4: The calculated and experimental chemical shifts (ppm) for 2 (according to Figure 6).

Author Contributions: H.A.A.: conceptualization, writing—original draft, investigation, methodology and data curation; S.M.S.: conceptualization, writing—original draft, software, data curation and validation; H.A.G.: conceptualization, software and validation; M.M.: writing—reviewing; M.M.A.: writing—reviewing; R.A.-S.: conceptualization, writing—original draft, investigation, methodology, data curation and supervision. All authors have read and agreed to the published version of the manuscript. **Funding:** The authors extend their appreciation to the Researchers Supporting Project, King Saud University, Riyadh, Saudi Arabia for funding this work through grant no. RSP-2021/353.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Acknowledgments: The authors extend their appreciation to the Researchers Supporting Project, King Saud University, Riyadh, Saudi Arabia for funding this work through grant no. RSP-2021/353.

Conflicts of 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.

References

- Al-Salahi, R.; Gamal-Eldeen, A.M.; Alanazi, A.; Al-Omar, M.; Marzouk, M.; Fouda, M.G. Cytotoxic and anti-inflammatory active methylsulfanyltriazoloq uinazolines. *J. Pure Appl. Microbiol.* 2013, 7, 189–198.
- Abuelizz, H.A.; Al-Salahi, R.; Al-Asri, J.; Mortier, J.; Marzouk, M.; Ezzeldin, E.; Ali, A.A.; Khalil, M.G.; Wolber, G.; Ghabbour, H.A. Synthesis, crystallographic characterization, molecular docking and biological activity of isoquinoline derivatives. *Chem. Cent. J.* 2017, 11, 103. [CrossRef]
- 3. Abuelizz, H.A.; Al-Salahi, R. An overview of triazoloquinazolines: Pharmacological significance and recent developments. *Bioorg. Chem.* **2021**, *115*, 105263. [CrossRef]
- 4. Al-Salahi, R.; Marzouk, M. Some 2-aminobenzo[de]isoquinolin1,3-diones as antimicrobial agents. *Asian J. Chem.* 2014, 26, 8163–8165. [CrossRef]
- Alagarsamy, V.; Rupeshkumar, M.; Kavitha, K.; Meena, S.; Shankar, D.; Siddiqui, A.A.; Rajesh, R. Synthesis and pharmacological investigation of novel 4-(2-methylphenyl)-1-substituted-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-ones as new class of *H*(1)-antihistaminic agents. *Eur. J. Med. Chem.* 2008, 43, 2331–2337. [CrossRef]
- Al-Salahi, R.; Marzouk, M.; El-Eraky, W.I.; Saleh, O.S. Antihistamine Activity of a new set 1,2,4-triazolo[1,5-a]quinazolines. *Asian J. Chem.* 2014, 26, 8625–8627.
- Alagarsamy, V.; Pathak, U.S. Synthesis and antihypertensive activity of novel 3-benzyl-2-substituted-3H-[1,2,4]triazolo[5,1b]quinazolin-9-ones. *Bioorg. Med. Chem.* 2007, 15, 3457–3462. [CrossRef]
- 8. Al-Salahi, R.; Tahir, K.E.; Alswaidan, I.; Lolak, N.; Hamidaddin, M.; Marzouk, M. Biological effects of a new set 1,2,4-triazolo[1,5a]quinazolines on heart rate and blood pressure. *Chem. Cent. J.* **2014**, *8*, 3. [CrossRef]
- Francis, J.E.; Cash, W.D.; Psychoyos, S.; Ghai, G.; Wenk, P.; Friedmann, R.C.; Atkins, C.; Warren, V.; Furness, P.; Hyun, J.L.; et al. Structure–activity profile of a series of novel triazoloquinazoline adenosine antagonists. *J. Med. Chem.* 1988, *31*, 1014–1020. [CrossRef]
- Al-Salahi, R.; Geffken, D.; Koellner, M. A new series of 2-Alkoxy(aralkoxy)-[1,2,4]triazolo[1,5-a]quinazolin-5-ones as Adenosine receptor antagonists. *Chem. Pharm. Bull.* 2011, 59, 730–733. [CrossRef] [PubMed]
- 11. Al-Salahi, R.; Marzouk, M.; Awad, G.; Al-Omar, M.; Ezzeldin, E. Antimicrobial activity of newly synthesized methylsulfanyltriazoloquinazoline derivatives. *J. Pharm. Pharmacol.* **2013**, *65*, 790–797. [CrossRef]
- 12. Al-Salahi, R.; Alswiadan, I.; Alomer, M.; Marzouk, M. Synthesis and antimicrobial of new 2-Phenoxy-4H-[1,2,4]triazolo[1,5-a]quinazoline derivatives. *Life Sci. J.* 2013, *10*, 2018–2028.
- 13. Al-Salahi, R.; Alswiadan, I.; Alomer, M.; Marzouk, M. Antiviral activity of 2-Phenoxy-4H-[1,2,4]triazolo[1,5-a]quinazoline derivatives. *Life Sci. J.* 2013, *10*, 2164–2169.
- 14. Al-Salahi, R.; Alswiadan, I.; Marzouk, M.; Alsenousy, W.; Abd Elgalil, A. Antiviral activities of some methylsulfanyltriazoloquinazolines. *Res. Chem. Intermed.* 2015, 41, 151–161. [CrossRef]
- Abuelizz, H.A.; Anouar, E.H.; Ahmad, R.; Azman, N.I.I.N.; Marzouk, M.; Al-Salahi, R. Triazoloquinazolines as a new class of potent α-glucosidase inhibitors: In vitro evaluation and docking study. *PLoS ONE* 2019, *14*, e0220379. [CrossRef]
- Al-Salahi, R.; Anouar, E.H.; Marzouk, M.; Taie, H.A.; Abuelizz, H.A. Screening and evaluation of antioxidant activity of some 1,2,4-triazolo[1,5-a]quinazoline derivatives. *Future Med. Chem.* 2018, 10, 379–390. [CrossRef] [PubMed]
- Sompalle, R.; Roopan, S.M.; Al-Dhabi, N.A.; Suthindhiran, K.; Sarkar, G.; Arasu, M.V. 1,2,4-triazoloquinazoline-thiones: Nonconventional synthetic approach, study of solvatochromism and antioxidant assessment. *J. Photochem. Photobiol. B Biol.* 2016, 162, 232–239. [CrossRef] [PubMed]
- 18. Al-Salahi, R.; Marzouk, M.; Ashour, A.E.; Alswaidan, I. Synthesis and antitumor activity of 1,2,4-triazolo[1,5-*a*]quinazolines. *Asian J. Chem.* **2014**, *26*, 2173–2176. [CrossRef]
- Al-Salahi, R.; Ashour, A.E.; Marzouk, M.; Ashok, K. In Vitro Cytotoxicity Evaluation of a New Series of Benzo[g][1,2,4]triazolo[1,5α]quinazolines. *Lat. Am. J. Pharm.* 2015, 34, 1926–1930.
- Al-Salahi, R.; Elsayed, E.A.; El Dib, R.A.; Wadaan, M.; Ezzeldin, E.; Marzouk, M. Synthesis, Characterization and Cytotoxicity Evaluation of 5-Hydrazono-[1,2,4]triazolo[1,5-a]quinazolines (Part I). Lat. Amer. J. Pharm. 2016, 35, 58–65.
- Almehizia, A.A.; Abuelizz, H.A.; Taie, H.A.A.; Anouar, E.A.; Marzouk, M.; Al-Salahi, R. Investigation the antioxidant activity of benzo[g]triazoloquinazolines correlated with a DFT study. *Saudi Pharm. J.* 2019, 27, 133–137. [CrossRef] [PubMed]

- Al-Salahi, R.; Marzouk, M.; Abbas, M.; Ng, S.W. 2-Methylsulfonyl-1,2,4-triazolo[1,5-a]quinazolin-5 (4H)-one. Acta Crystallogr. 2012, E68, o1806. [CrossRef] [PubMed]
- Al-Salahi, R.; Marzouk, M.; Al-Omar, M.; Amr, A.E.; Ng, S.W.; Tiekink, E.R.T. 2-Methylsulfanyl-1,2,4-triazolo[1,5-a]quinazoline-5(4H)-thione. *Acta Crystallogr.* 2013, *E69*, o434. [CrossRef] [PubMed]
- 24. Al-Salahi, R.; Nabih, L.; Al-Omar, M.; Ng, S.W. 2-Phenoxy-1,2,4-triazolo[1,5-*a*] quinazolin-5(4H)-one. *Acta Crystallogr.* 2012, *E68*, o1808. [CrossRef] [PubMed]
- 25. Al-Salahi, R.; Al-Omar, M.; Marzouk, M.; Ng, S.W.; Tiekink, E.R.T. 5-chloro-2-methylsulfonyl-1,2,4-triazolo[1,5-*a*]quinazoline. *Acta Crystallogr.* **2012**, *E68*, o1809. [CrossRef]
- Al-Salahi, R.; Geffken, D.; Bari, A. 2-benzyloxy-1,2,4-triazolo[1,5-a] quinazolin-5(4H)-one. Acta Crystallogr. 2011, E67, o1861. [CrossRef]
- 27. Al-Salahi, R.; Geffken, D. Synthesis of Novel 2-methylsulfanyl-4*H*-[1,2,4]triazolo[1,5-*a*]quinazolin-5-one and derivatives. *Synth. Commun.* **2011**, *41*, 3512–3523. [CrossRef]
- Al-Salahi, R.; Geffken, D. Synthesis and reactivity of [1,2,4]triazolo-annelated quinazolines. *Molecules* 2010, 15, 7016–7034. [CrossRef]
- 29. Sheldrick, G.M. SHELXT-integrated space-group and crystal-structure determination. *Acta Crystallogr. A Found. Adv.* 2015, 71, 3–8. [CrossRef]
- 30. Allen, F.H.; Kennard, O.; Watson, D.G.; Brammer, L.; Orpen, A.G.; Taylor, R. Tables of bond Lengths determined by X-ray and neutron diffraction. Part 1. Bond lengths in organic compounds. *J. Chem. Soc. Perkin Trans.* **1987**, *II*, S1–S19. [CrossRef]
- 31. Turner, M.J.; McKinnon, J.J.; Wolff, S.K.; Grimwood, D.J.; Spackman, P.R.; Jayatilaka, D.; Spackman, M.A. Crystal Explorer. University of Western Australia. 2017. Available online: http://hirshfeldsurface.net (accessed on 2 September 2021).
- 32. Frisch, M.J.; Trucks, G.W.; Schlegel, H.B.; Scuseria, G.E.; Robb, M.A.; Cheeseman, J.R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G.A.; et al. *Fox, GAUSSIAN 09. Revision A02*; Gaussian Inc.: Wallingford, CT, USA, 2009.
- 33. Dennington, R., II; Keith, T.; Millam, J. Gauss View; Version 4.1; Semichem Inc.: Shawnee Mission, KS, USA, 2007.
- 34. Reed, A.E.; Curtiss, L.A.F.; Weinhold, F. Intermolecular interactions from a natural bond orbital, donor-acceptor viewpoint. *Chem. Rev.* **1988**, *88*, 899–926. [CrossRef]
- Marten, B.; Kim, K.; Cortis, C.; Friesner, R.A.; Murphy, R.B.; Ringnalda, M.N.; Sitkoff, D.; Honig, B. New model for calculation of solvation free energies: correction of self-consistent reaction field continuum dielectric theory for short-range hydrogen-bonding effects. J. Phys. Chem. 1996, 100, 11775–11788. [CrossRef]
- Tannor, D.J.; Marten, B.; Murphy, R.; Friesner, R.A.; Sitkoff, D.; Nicholls, A.; Ringnalda, M.; Goddard, W.A.; Honig, B. Accurate first principles calculation of molecular charge distributions and solvation energies from ab initio quantum mechanics and continuum dielectric theory. J. Am. Chem. Soc. 1994, 116, 11875–11882. [CrossRef]
- Cheeseman, J.R.; Trucks, G.W.; Keith, T.A.; Frisch, M.J. A Comparison of Models for Calculating Nuclear Magnetic Resonance Shielding Tensors. J. Chem. Phys. 1996, 104, 5497–5509. [CrossRef]
- 38. Sheldrick, G.M. A short history of SHELX. Acta Crystallogr. 2008, A64, 112–122. [CrossRef] [PubMed]
- 39. Foresman, J.B.; Frisch, A.E. Exploring Chemistry with Electronic Structure Methods, 2nd ed.; Gaussian: Pittsburgh, PA, USA, 1996.
- 40. Chang, R. Chemistry, 7th ed.; McGraw-Hill: New York, NY, USA, 2001.
- 41. Kosar, B.; Albayrak, C. Spectroscopic investigations and quantum chemical computational study of (E)-4-methoxy-2-[(p-tolylimino)methyl]phenol. *Spectrochim. Acta* 2011, 78, 160–167. [CrossRef] [PubMed]
- 42. Koopmans, T. About the assignment of wave functions and eigenvalues to the individual electrons of an atom. *Physica* **1934**, *1*, 104–113. [CrossRef]
- 43. Parr, R.G.; Yang, W. Density-Functional Theory of Atoms and Molecules; Oxford University Press: New York, NY, USA, 1989.
- 44. Parr, G.; Von Szentpály, L.; Liu, S.B. Electrophilicity Index. J. Am. Chem. Soc. 1999, 121, 1922–1924. [CrossRef]
- 45. Singh, R.N.; Kumar, A.; Tiwari, R.K.; Rawat, P.; Gupta, V.P. A combined experimental and quantum chemical (DFT and AIM) study on molecular structure, spectroscopic properties, NBO and multiple interaction analysis in a novel ethyl 4-[2-(carbamoyl)hydrazinylidene]-3,5-dimethyl-1H-pyrrole-2-carboxylate and its dimer. *J. Mol. Struct.* **2013**, 1035, 427–440. [CrossRef]