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Reference:

El-Azab Adel S., Mary Y. Shyma, Mary Y. Sheena, Panicker C. Yohannan, Abdel-Aziz Alaa A. -M., Mohamed Menshawwy A., Armakovic Stevan, Armakovic Sanja J., Van Alsenoy Christian.- Spectroscopic and reactive properties of a newly synthesized quinazoline derivative : combined experimental, DFT, molecular dynamics and docking study

Journal of molecular structure - ISSN 0022-2860 - 1134(2017), p. 863-881

Full text (Publisher's DOI): <http://dx.doi.org/doi:10.1016/J.MOLSTRUC.2017.01.032>

To cite this reference: <http://hdl.handle.net/10067/1423830151162165141>

Accepted Manuscript

Spectroscopic and reactive properties of a newly synthesized quinazoline derivative: Combined experimental, DFT, molecular dynamics and docking study

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PII: S0022-2860(17)30032-7
DOI: 10.1016/j.molstruc.2017.01.032
Reference: MOLSTR 23337
To appear in: *Journal of Molecular Structure*
Received Date: 10 September 2016
Accepted Date: 08 January 2017

Please cite this article as: Adel S. El-Azab, Shyma Mary Y, Sheena Mary Y, C.Yohannan Panicker, Alaa A.-M. Abdel-Aziz, Menshawy A. Mohamed, Stevan Armaković, Sanja J. Armaković, Christian Van Alsenoy, Spectroscopic and reactive properties of a newly synthesized quinazoline derivative: Combined experimental, DFT, molecular dynamics and docking study, *Journal of Molecular Structure* (2017), doi: 10.1016/j.molstruc.2017.01.032

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Highlights

- IR, Raman, NMR spectra and NBO analysis were reported.
- Most reactive sites are predicted by using MEP plot
- BDEs are calculated to investigate autoxidation and degradation properties
- The compound might exhibit inhibitory activity against HNE

Spectroscopic and reactive properties of a newly synthesized quinazoline derivative:

Combined experimental, DFT, molecular dynamics and docking study

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Abstract

The molecular geometry, the normal mode wavenumbers and corresponding vibrational assignments, natural bond orbital analysis and the HOMO-LUMO analysis of 3-(4-oxo-phenethyl-3,4-dihydroquinazolin-2-ylthio)-N-(3,4,5-trimethoxyphenyl)propanamide were performed by B3LYP level of theory using the 6-311++G(d,p)(5D,7F) basis set. The experimentally obtained wavenumbers are in agreement with the theoretically predicted wavenumbers. From the MEP plot it is evident that the negative charge covers carbonyl group, mono substituted phenyl ring, O₅₉ atom and the positive region is over the

nitrogen atoms and hydrogen atoms. NLO behaviour of the title molecule was investigated by the determination of the first and second order hyperpolarizabilities. The molecular orbitals and molecular electrostatic potential map are also reported. The NMR spectra and Fukui indices are also analyzed. Molecule sites important from the aspect of reactivity have been determined by calculations of average local ionization energy (ALIE), Fukui functions and bond dissociation energies (BDE). BDE for hydrogen abstraction served us to investigate the possibility for autoxidation mechanism of the investigated molecule. Molecular dynamics (MD) simulations were used in order to investigate which atoms of the title molecule have the most pronounced interactions with water molecules. Molecular docking studies reveal that the inhibitor forms a stable complex with HNE as is evident from the binding affinity -10.9 kcal/mol and the results suggest that the compound exhibit inhibitory activity against HNE.

Keywords: DFT; IR and Raman; BDE; RDF; Quinazoline; Molecular docking.

1. Introduction

Quinazolines represent the most interesting group of heterocycles that contain pyrimidine nucleus in their structure, which exhibit various biological activities including containment of inflammatory disorders such as osteoarthritis [1], inflammatory bowel syndrome [2] and neuro-degenerative impairments [3], invoking interest in synthesis of their analogs. Al-Suwaidan et al. [4] reported the synthesis and biological evaluation of 2-substituted-3-((4-oxo-3-phenethyl-3,4-dihydroquinazolin-2-yl)thio)-N-(3,4,5-trimethoxyphenyl)propanamide as anticancer agents. Quinazolinones are associated with a wide range of biological and pharmacological activities such as analgesic [5], anti-inflammatory [6], antifungal [7, 8], antiviral [9] and antihistaminic activities [10, 11]. Olgen et al. [12] reported the antimicrobial and antiviral screening of novel indole carboxamide and propanamide derivatives. Naqvi et al. [13] reported the design, synthesis and molecular docking of substituted 3-hyrazinyl-3-oxo-propanamides as anti-tubercular agents. In the present work, IR and Raman spectra of the title compound are reported both experimentally and theoretically. The natural bonding orbital analysis, molecular electrostatic potential, first and second hyperpolarizability studies are also reported. Due to the different potential biological activity of the title compound, molecular docking of the title compound is also reported.

Emerging organic pollutants such as pharmaceutical care products represent great threat for the environment. Great attention is paid to the synthesis of new biologically active molecules which serve as the active components in new drugs. Their frequent usage has led to the fact that representatives of this class of compounds have been detected in all types of water all over the world [14]. These molecules are synthesized to be very stable, because of which conventional water purification methods are not effective [15,16], while in the same time advanced oxidation processes are seen as an alternative [14,15, 17,18]. Systematic investigation of reactive properties of newly synthesized biologically active molecules is prerequisite for the development of water purification methods. In this regard forced degradation studies very useful, but in the same time they are long and expensive procedures. DFT calculations and MD simulations present effective and inexpensive tools for optimization and rationalization of reactivity studies related to biologically active molecules [19-22].

2. Experimental details

A mixture of 2-mercapto-3-phenethylquinazolin-4(3*H*)-one (2 mmol, 564 mg) and 3-chloro-*N*-(3,4,5-trimethoxyphenyl)propanamide (2.1 mmol, 575 mg) in 15 ml acetone containing anhydrous potassium carbonate (3 mmol, 415 mg) was stirred at room temperature for 12 h. The reaction mixture was filtered, the solvent was removed under reduced pressure and the solid obtained was dried and recrystallized from ethanol. Mp: 216-218 °C, yield 93%, MS: $M^+ = 519$. The FT-IR spectrum (Fig.1) was recorded using KBr pellets on a DR/Jasco FT-IR 6300 spectrometer. The FT-Raman spectrum (Fig.2) was obtained on a Bruker RFS 100/s, Germany. For excitation of the spectrum the emission of Nd:YAG laser was used, excitation wavelength was 1064 nm, maximal power was 150 mW and measurement was carried out on solid sample. Nuclear magnetic resonance (^1H and ^{13}C NMR) spectra were recorded on Bruker 500 MHz spectrometer using CDCl_3 as solvent; the chemical shifts are expressed in δ ppm using TMS as internal standard.

3. Computational details

Calculations of the title compound were carried out using Gaussian 09 software [23] by using B3LYP/6-311++G(d,p)(5D,7F) basis set [24, 25] and the theoretically predicted wavenumbers are multiplied by a scaling factor of 0.9613 [26]. The optimized

geometrical parameters (Fig.3) are given in Table 1. The assignments of the wave numbers are done by GAUSSVIEW program [27] and the potential energy distribution (PED) is calculated with the help of GAR2PED software package [28]. Jaguar 9.0 program [29], as implemented in Schrödinger Materials Science Suite 2015-4, was used for the DFT calculations of average local ionization energy (ALIE) surfaces, Fukui functions and bond dissociation energies (BDE), while Desmond program [30-33] was used for MD simulations and calculations of radial distribution functions (RDFs). In cases of DFT calculations B3LYP exchange-correlation functional [34] was used with 6-311++G(d,p), 6-31+G(d,p) and 6-311G(d,p) basis sets, respectively, for calculations of ALIE, Fukui functions and BDEs. For MD simulations OPLS 2005 force field [35] was employed with simulation time of 10 ns and with isothermal-isobaric (NPT) ensemble class. Modeling of system was performed by placing one title compound molecule in the cubic box with ~3000 water molecule. The value of cut off radius was set to 12 Å, while temperature and pressure were set to 300 K and 1.0325 bar, respectively. Simple point charge (SPC) model [36] was used for the description of solvent. Noncovalent interactions were determined with the help of method by Johnson [37, 38], which is also implemented in Jaguar 9.0 program.

4. Results and discussion

In the following discussion, the mono, poly, ortho-substituted phenyl rings are designated as PhI, PhII and PhIII respectively and the quinazoline ring as PhIV.

4.1. Geometrical parameters

In the phenyl rings of the title compound, the C-C bond lengths lie in the range 1.3937-1.3997 Å for PhI, 1.3928-1.4046 Å for PhII and 1.3833-1.4090 Å for PhII, which are in agreement with the reported values [39]. The bond lengths of C₅-N₃ (1.3822 Å), C₃₃-N₄ (1.3857 Å), C₁₅-N₄ (1.4155 Å), C₄₀-N₃₉ (1.4252 Å) and C₃₇-N₃₉ (1.3780 Å) are shorter than the normal C-N bond length (1.48 Å) and this shows the effect of resonance in this region of the molecule [40]. The shortening of the bond length of C₁₅-O₂ (1.2205 Å) and C₃₇-O₃₈ (1.2197 Å) shows a double bond character. The C-O bond lengths of the title compound are C₄₆-O₅₄ = 1.3707 Å, C₅₅-O₅₄ = 1.4361 Å, C₄₇-O₄₉ = 1.3737 Å, C₅₀-O₄₉ = 1.4392 Å, C₄₅-O₅₉ = 1.3713 Å and C₆₀-O₅₉ = 1.4378 Å and all the C-O bond lengths

are greater than the average distance of 1.362 Å [41] which is due to hydrogen bonding in the molecule [42].

In the title compound, the C-S bond lengths are 1.7846 and 1.8383 Å while the reported values are in the range 1.7675-1.8641 Å [43] and 1.7710-1.8110 Å [44]. At C₂₂ position, the bond angles are C₃₁-C₂₂-C₂₃ = 118.6°, C₃₁-C₂₂-C₁₉ = 120.7° and C₂₃-C₂₂-C₁₉ = 120.7° and the reduction in the angle C₃₁-C₂₂-C₂₃ is due to presence of adjacent methylene groups. At N₄ position, the bond angles C₃₃-N₄-C₁₅ is increased by 1.0°, C₃₃-N₄-C₁₆ is increased by 2.6° and C₁₅-N₄-C₁₆ is decreased by 3.6° from 120° and this is due to the interaction between O₂ and the methylene at C₁₆ position. At C₁₅ position, the bond angles, N₄-C₁₅-C₁₄ is decreased by 5.4° and C₁₄-C₁₅-O₂ is increased by 5.0° from 120° and this variation is due to the interaction between O₂ and the adjacent methylene groups. Similarly at C₅ position, the bond angles C₆-C₅-C₁₄ = 118.9°, N₃-C₅-C₆ = 119.1° and C₁₄-C₅-N₃ = 122.0° and this asymmetry in angles is due to the interaction between the quinazoline ring and PhIII ring. Similarly at C₃₃ position, the bond angles N₃-C₃₃-N₄ = 124.9° and N₄-C₃₃-S₁ = 115.6° and this asymmetry in angles is due to the interaction between the quinazoline ring and adjacent moieties. Similarly at N₃₉ position, the bond angles C₄₀-N₃₉-C₃₇ = 130.1°, C₄₀-N₃₉-H₄₈ = 117.1° and C₃₇-N₃₉-H₄₈ = 112.6° and this asymmetry in angles is due to the interaction between the NH group and the oxygen atom O₃₈. The quinazoline moiety is planar with respect to the phenyl ring PhIII, as is evident from the torsion angles C₆-C₅-N₃-C₃₃ = -179.6°, C₆-C₅-C₁₄-C₁₅ = -179.9°, C₁₂-C₁₄-C₁₅-N₄ = 179.1° and C₁₂-C₁₄-C₅-N₃ = 179.9° and the CH₂ groups at C₁₉ and C₁₆ are tilted from the phenyl ring PhI, as is evident from the torsion angles, C₂₉-C₃₁-C₂₂-C₁₉ = -178.5°, C₃₁-C₂₂-C₁₉-C₁₆ = 89.7°, C₂₅-C₂₃-C₂₂-C₁₉ = 178.5° and C₂₃-C₂₂-C₁₉-C₁₆ = -88.7°. The propanamide group is tilted from the phenyl ring PhII according to the torsion angles, C₄₆-C₄₂-C₄₀-N₃₉ = -178.7°, C₄₂-C₄₀-N₃₉-C₃₇ = -60.4°, C₄₅-C₄₁-C₄₀-N₃₉ = 177.7° and C₄₁-C₄₀-N₃₉-C₃₇ = 121.6°.

4.2. IR and Raman spectra

The calculated (scaled) wave numbers, observed IR, Raman bands and assignments are given in table 2.

For the title compound, the CH stretching modes of the phenyl rings are assigned in the range 3065-3033 cm⁻¹ for PhI, 3078-3070 cm⁻¹ for PhII and 3077-3045 cm⁻¹ for

PhIII rings theoretically [45]. Experimentally bands are observed at 3065, 3031 cm^{-1} in IR and 3060, 3034 cm^{-1} in Raman spectrum. The phenyl ring stretching modes of the title compound are assigned at 1558, 1468, 1288 cm^{-1} (IR), 1467 cm^{-1} (Raman), in the range 1580-1290 cm^{-1} (DFT) for PhI with PEDs in the range 53-76%, 1572, 1368 cm^{-1} (IR), 1573, 1543, 1460, 1363, 1250 cm^{-1} (Raman), in the range 1571-1247 cm^{-1} (DFT) for PhII with PEDs in the range 40-84% and 1543 cm^{-1} (Raman), in the range 1582-1306 cm^{-1} (DFT) for PhIII with PEDs in the range 47-81%. In the present case the PED analysis gives ring breathing modes at 1009 cm^{-1} for PhI, 1017 cm^{-1} for PhII and 1083 cm^{-1} for PhIII, as expected [45, 46]. For these ring breathing modes, IR intensities are less than 10 except for the mode 1017 cm^{-1} which has an IR intensity of 75.11. Similarly the Raman activity for the mode 1083 cm^{-1} is very low, while the other modes, 1009 and 1017 cm^{-1} have a Raman activity around 18. The PEDs of all these modes are in between 40 and 52%. Raj et al. [44] reported the ring breathing mode of a poly-substituted benzene ring at 1025 cm^{-1} in IR, 1027 cm^{-1} in Raman and 1032 cm^{-1} theoretically. For ortho substituted phenyl ring the ring breathing mode is reported at 1041 cm^{-1} [47] and at 1086, 1011 cm^{-1} (theoretically) [48] and at 1020 cm^{-1} (theoretically) [49]. For the title compound, the in-plane CH deformation modes are assigned at 1136 cm^{-1} (IR), 1135, 1059 cm^{-1} (Raman) for PhI, 1182 cm^{-1} (IR), 1181, 1152 cm^{-1} (Raman) for PhII and 1204, 1005 cm^{-1} (Raman) for PhIII. The DFT calculations give these modes in the ranges 1311-1062 cm^{-1} for PhI, 1180-1152 cm^{-1} for PhII and 1265-1007 cm^{-1} for PhIII, as expected [45]. For the mono substituted ring PhI, the IR intensities and Raman activities are less than 10, except for the mode at 1176 cm^{-1} , the Raman activity is high with a value of 46.25. The PEDs of these modes lie in the range 42 to 77%. For the rings PhII and PhIII, the IR intensities are high with PEDs around 50%. The out-of-plane C-H modes are assigned at 824 cm^{-1} (IR), 962, 892, 824 cm^{-1} (Raman), 962, 949, 894, 827, 826 cm^{-1} (DFT) for PhI with low IR intensities and Raman activities, 856, 857 cm^{-1} (DFT) for PhII with IR intensities around 20 and low Raman activities and 944, 850, 750 cm^{-1} (IR), 943, 850, 748 cm^{-1} (Raman), 964, 946, 853, 751 cm^{-1} (DFT) for PhIII with low IR intensities and Raman activities except for the mode at 751 cm^{-1} . The PEDs of all the out-of-plane CH deformation modes are high.

The N-H vibrations give rise to bands in the regions, 3500-3300 cm^{-1} (stretching), 1500-1300, 700-600 cm^{-1} (bending) [45, 50, 51] and for the title compound the DFT calculations give these modes at 3439 with a PED of 100%, 1442 and at 613 cm^{-1} with PED around 50%. Mary et al. [52] reported a band at 3343 cm^{-1} in the IR spectrum, 3340 cm^{-1} in Raman spectrum and 3433 cm^{-1} theoretically as N-H stretching mode. For the title compound, the C-N stretching modes are assigned at 1322, 1214, 1204 cm^{-1} in Raman and in the range 1324-965 cm^{-1} theoretically which are in agreement with literature [45, 50, 53, 54]. The C=N stretching mode is observed at 1515 cm^{-1} in IR and 1519 cm^{-1} theoretically with high IR intensity and PED of 43% as expected [27]. For the title compound C-S stretching modes are observed at 632 cm^{-1} in the IR spectrum, 633 cm^{-1} in the Raman spectrum and at 668, 635 cm^{-1} theoretically as expected [45].

The C=O stretching mode [45, 50, 53] is expected in the region 1750-1650 cm^{-1} and in the present case this modes appear at 1675, 1662 cm^{-1} in the IR spectrum, and at 1680, 1660 cm^{-1} in the Raman spectrum. The DFT calculations give these modes at 1673 and 1663 cm^{-1} and the IR intensities of these modes are very high and the PED contribution is 73%. For the title compound, the C=O deformation bands are observed at 773, 500 cm^{-1} (IR), 772, 682, 502, 471 cm^{-1} (Raman) and at 771, 684, 495, 470 cm^{-1} theoretically which are expected in the regions 625 ± 70 and 540 ± 80 cm^{-1} , respectively [45]. The C-O-C stretching modes are expected in the range 1200-850 cm^{-1} [45, 55]. The skeletal C-O deformation can be found in the region 320 ± 50 cm^{-1} [45]. As expected, the C-O-C vibrations are assigned at 1196, 1054, 1017, 977, 953, 910 cm^{-1} theoretically for the title compound with PEDs ranging from 42 to 78%, which are in agreement with the literature [53]. Experimentally bands are observed at 1020, 911 cm^{-1} in the IR spectrum and at 1049, 1020, 911 cm^{-1} in the Raman spectrum.

The stretching vibrations of the CH_2 group and deformation modes of CH_2 group (scissoring, wagging, twisting and rocking modes) appears in the regions 3000 ± 20 , 2900 ± 25 , 1450 ± 30 , 1330 ± 35 , 1245 ± 45 , 780 ± 55 cm^{-1} respectively [45, 50, 53]. The CH_2 stretching modes are observed at 2996, 2972, 2932 cm^{-1} (IR), 3023, 2963, 2948, 2930 cm^{-1} (Raman) and in the range 3025-2929 cm^{-1} theoretically. The deformation modes of CH_2 are assigned at 1417, 1348, 1238 cm^{-1} in the IR spectrum, 1330, 1322, 1273, 1214, 1102 cm^{-1} in the Raman spectrum and in the ranges 1444-1420 (scissoring),

1417-1324 (wagging), 1301-1216 (twisting), 1161-928 (rocking) cm^{-1} theoretically as expected [45, 50, 53]. For the title compound, the CH_3 stretching modes are assigned at 3008, 2979, 2902 cm^{-1} in the Raman spectrum and in the range 3015-2900 cm^{-1} theoretically and these modes are expected in the region 2900-3050 cm^{-1} [45]. The deformation modes of the methyl group of the title compound are assigned as 1460, 1437, 1408, 1395 cm^{-1} in the Raman spectrum and in the ranges 1456-1399 (scissoring) and 1170-1121 cm^{-1} (rocking) theoretically as expected [45].

4.3. NMR spectra

The ^1H and ^{13}C NMR isotropic shielding are calculated with the GIAO method [56,57]. The experimental NMR values are: ^1H NMR (DMSO-d_6): δ 10.39 (s, 1H), 8.18-7.30 (m, 9H), 7.03 (s, 2H), 4.72 (d, 2H, $J = 6.0$ Hz), 4.26 (d, 2H, $J = 6.5$ Hz), 3.73 (s, 6H), 3.62 (s, 3H), 3.04 (t, 2H, $J = 6.5$ Hz), 1.64 (d, 3H, $J = 6.0$ Hz). ^{13}C NMR (DMSO-d_6): δ : 17.5, 33.4, 45.5, 46.2, 55.6, 60.0, 96.8, 118.8, 125.7, 125.9, 126.4, 126.6, 128.5, 133.5, 134.5, 134.9, 137.5, 146.7, 152.6, 155.5, 160.3, 169.1.

The TMS shielding: σ_{calc} (TMS) calculated previously at the same theoretical level and numerical values of chemical shift $\delta_{\text{calc}} = \sigma_{\text{calc}}(\text{TMS}) - \sigma_{\text{calc}}$ together with calculated values of $\sigma_{\text{calc}}(\text{TMS})$, are given in Table 3. The protons of the phenyl rings resonate in the range 7.9837-7.7091 for PhI, 7.0741-6.9133 for PhII and 8.707-7.5011 ppm for PhIII theoretically. The chemical shifts of the hydrogen atoms outside the rings have the following values theoretically: CH_2 group between PhI and PhIV are in the range 4.9345-3.4158, CH_2 group near to the sulfur atom S_1 are 7.5054, 7.3882, CH_2 group near to the carbonyl group is 3.7117, 2.8111 and for the amide hydrogen the shift is 6.2513 ppm. The hydrogen atoms of the CH_3 groups resonate theoretically in the range 4.8518-3.6869, 4.4506-4.1358, 5.0915-3.9398 ppm for the CH_3 groups at C_{60} , C_{50} and C_{55} positions. The range of ^{13}C NMR chemical shifts of aromatic carbon atoms are normally greater than 100 ppm [58, 59] and in the present work ^{13}C NMR chemical shifts of entire phenyl carbon atoms are greater than 100 ppm as expected in literature. The predicted shifts lie in the range 137.5733-126.5891 for PhI, 156.7075-117.6511 PhII and 146.9364-121.7319 for PhIII rings. For the methoxy carbon atoms C_{45} , C_{46} and C_{47} the chemical shifts are high due to the presence of the oxygen atoms. The chemical shifts of carbon atoms in the CH_2 groups are 55.2783 (C_{19}), 42.2848 (C_{16}), 41.1976 (C_{34}), 38.0028

(C₆₄) ppm and in the CH₃ groups are 65.0711 (C₆₀), 65.5945 (C₅₀), 65.1381 ppm (C₅₅). The carbonyl group C₃₇ possesses a high chemical shift theoretically (164.4661 ppm) due to the presence of the oxygen atom. For the quinazoline ring carbon atoms the shifts are 161.9221 (C₃₃) and 158.3237 (C₁₅) and the high shift is due to the presence of neighboring substituent. The experimental NMR spectra are given in Figs. 4 and 5.

4.4. Frontier Molecular Orbital analysis

The ionization energy (I) and electron affinity (A) can be expressed through HOMO and LUMO orbital energies as $I = -E_{\text{HOMO}} = 7.342$ and $A = -E_{\text{LUMO}} = 5.004$ eV and the HOMO-LUMO gap = 2.338 eV. A large energy gap is associated with a hard molecule and small gap with a soft molecule [60]. The electro-negativity (χ) [61], chemical hardness (η) and electronic potential were computed using the orbital energy of the HOMO and the orbital energy of the LUMO at the DFT level. The ionization potential (μ) of the molecule is calculated using Koopman's theorem [62, 63] and is given by $\mu = -(I+A)/2$ and $\eta = (I-A)/2$ and electronegativity $\chi = (I+A)/2$. Parr et al. [64] have proposed electrophilicity index as a measure of energy lowering due to maximal electron flow between donor acceptor and $\omega = \mu^2/2\eta$. The quantum chemical descriptors are $\mu = -6.173$, $\eta = 1.169$, $\chi = 6.173$ and $\omega = 16.30$ eV. The HOMO and LUMO plots are given in Fig.6.

4.5. Molecular Electrostatic Potential (MEP)

To predict reactive sites for electrophilic and nucleophilic attack for the title compound, the MEP at the B3LYP optimized geometry was calculated (Fig.7). The different values of the electrostatic potential at the surface are represented by different colours. Potential increases in the order red < orange < yellow < green < blue. The negative (red, orange and yellow) regions of the MEP are related to electrophilic reactivity. From the MEP plot it is evident that the negative charge covers carbonyl group, mono substituted phenyl ring, O₅₉ atom and the positive region is over the nitrogen atoms and hydrogen atoms. The electrostatic potential value is largely responsible for the interaction of a substrate to its receptor binding sites since they recognize each other [65, 66].

4.6 ALIE surface, Fukui functions and indices, non-covalent interactions

Sjoberg et al. [67, 68] have introduced ALIE as quantum molecular descriptor for the investigation of reactivity of aromatic compounds. This descriptor turned out to be very useful tool when it comes to the assessment of local reactivity properties of some molecule and is defined as a sum of orbital energies weighted by the orbital densities:

$$I(r) = \sum_i \frac{\rho_i(\vec{r}) |\varepsilon_i|}{\rho(\vec{r})}, \quad (1)$$

where $\rho_i(\vec{r})$ represents the electronic density of the i -th molecular orbital at the point $\vec{r}$, ε_i represents the orbital energy and $\rho(\vec{r})$ is the total electronic density function. The values of ALIE are mapped to the electron density surface and show the molecule areas where it is the most easily to remove the electrons, i.e. the molecule parts where the electrons are least tightly bound. These areas are the ones where molecule is prone to electrophilic attacks. Representative ALIE surface of the title molecule is presented in Fig. 8.

ALIE surface presented in Fig.8 determine the near vicinity of sulfur atom S1 to have the lowest ALIE values, designated by the red color. In this case the lowest ALIE value is around 186 kcal/mol and the mentioned location of S1 is the most vulnerable to the electrophilic attacks. Molecule locations characterized by the highest ALIE values, designated by the blue color, are the methyl groups and hydrogen atom H48. In the case of mentioned molecule the highest ALIE values are having values of around 346 kcal/mol.

Using the method of Johnson et al. [37, 38] it is possible to perform the analysis of charge density between atoms that are not covalently bonded and to locate intramolecular noncovalent interactions. These noncovalent interactions could be responsible for some specific structural and reactive properties. Intramolecular noncovalent interactions of title molecule have been determined and visualized with corresponding strengths (in terms of electron density) in Fig. 9.

It can be seen in Fig. 9 that concerning the title compound molecule there are total of six intra-molecular non-covalent interactions. The strongest non-covalent interaction is the one between sulfur atom S1 and hydrogen atom H17, for which the strength has been calculated to be -0.017 electron/bohr³. On the other side the weakest non-covalent

interaction was calculated to be in the case of interaction between carbon atom C6 and hydrogen atom H42, with the corresponding strength of just 0.001 electron/bohr³. It is also interesting to mention the two non-covalent interactions involving oxygen atom O49 and the two adjacent methyl groups, with corresponding strengths of -0.011 and -0.012 electron/bohr³.

Beside MEP and ALIE surfaces it is also useful to employ the concept of Fukui functions in order to gain further insight into the local reactivity properties of the title molecule. Fukui functions show the changes of electron density after the addition or removal of charge. There are two Fukui functions, f^+ and f^- functions, and in Jaguar program they are calculated in the finite difference approximation according to the following equations:

$$f^+ = \frac{(\rho^{N+\delta}(r) - \rho^N(r))}{\delta}, \quad (2)$$

$$f^- = \frac{(\rho^{N-\delta}(r) - \rho^N(r))}{\delta}, \quad (3)$$

where N represents the number of electrons in reference state of the molecule, while δ is fraction of electron which default value is set to be 0.01 [69].

Once the Fukui function values have been obtained with Jaguar program it is possible to visualize them as iso-surfaces or to map them to the electron density surface. In this work, for the purpose of visualization, values of Fukui functions have been mapped to the electron density surface, Fig. 10. Positive color (purple in Fig. 10a) denotes areas at molecular surface where electron density increases with the addition of charge in the case of f^+ function, while negative color (red in Fig. 10b) denotes areas at molecular surface where electron density decreases with the removal of charge in case of f^- function. Results presented in Fig. 10a indicate that with the addition of charge electron density significantly increases in the near vicinity of six member ring with two nitrogen atoms and its adjacent benzene rings, indicating that this part of molecule acts as an electrophile in the case of charge addition. The location of red color in case of Fig. 10b indicates that benzene ring with three attached oxygen atoms with methyl groups presents area where electron density decreases after the removal of charge, i.e. the molecule location that acts as nucleophile with the removal of charge.

The Fukui indices are also a local reactivity descriptor that gives the preferred regions where a chemical species will change its density when the number of electrons is modified and it indicates the propensity of the electronic density to deform at a given position upon accepting or donating electrons [70-72]. Also, it is possible to define the corresponding condensed or atomic Fukui indices on the j^{th} atom site as,

$$f_j^- = q_j(N) - q_j(N-1) \quad (4)$$

$$f_j^+ = q_j(N+1) - q_j(N) \quad (5)$$

$$f_j^0 = \frac{1}{2}[q_j(N+1) - q_j(N-1)] \quad (6)$$

For an electrophilic $f_j^-(r)$, nucleophilic or free radical attack $f_j^+(r)$, on the reference molecule, respectively. In these equations, q_j is the atomic charge (evaluated from Mulliken population analysis, electrostatic derived charge, etc.) at the j^{th} atomic site is the neutral (N), anionic (N + 1) or cationic (N - 1) chemical species. Morell *et al.*, [73] have recently proposed a dual descriptor ($\Delta f(r)$), which is defined as the difference between the nucleophilic and electrophilic Fukui function and is given by,

$$\Delta f(r) = [f^+(r) - f^-(r)] \quad (7)$$

For nucleophilic attack, $\Delta f(r) > 0$ and for an electrophilic attack $\Delta f(r) < 0$. Under this situation, dual descriptors $\Delta f(r)$ provide a clear difference between nucleophilic and electrophilic attack at a particular site with their sign. From the values reported in Table 4, according to the condition for dual descriptor, nucleophilic site for in our title compound is S₁, C₆ and N₃ (positive value i.e. $\Delta f(r) > 0$). Similarly the electrophilic attack site is C₅, C₁₅, C₃₃ and C₃₇ (negative value i.e. $\Delta f(r) < 0$). The behavior of molecules as electrophiles/nucleophiles during reaction depends on the local behavior of molecules.

4.7. Nonlinear optical studies

The calculated first hyperpolarizability of the title compound is 5.465×10^{-30} esu, which is 42.04 times that of standard NLO material urea (0.13×10^{-30} esu) [74]. The reported values of hyperpolarizability of similar derivatives are 5.05×10^{-30} esu and 6.00×10^{-30} esu [48, 49]. The average second hyperpolarizability is $\langle \gamma \rangle = (\gamma_{xxxx} + \gamma_{yyyy} + \gamma_{zzzz} + 2\gamma_{xxyy} + 2\gamma_{xxzz} + 2\gamma_{yyzz})/5$. The theoretical second order hyperpolarizability was calculated using the Gaussian09 software and is equal to -53.027×10^{-37} esu [75]. We conclude that the title compound is an attractive object for future studies of nonlinear optical properties.

4.8. Natural Bonding orbital analysis

The natural bond orbitals (NBO) calculations were performed using NBO 3.1 program [76] and the possible interactions are given in tables 5 and 6.

The intra-molecular hyper-conjugative interactions in the molecular system are: N₃-C₃₃ from S₁ of $n_2(S_1) \rightarrow \pi^*(N_3-C_{33})$, N₄-C₁₅ from O₂ of $n_2(O_2) \rightarrow \sigma^*(N_4-C_{15})$, N₄-C₃₃ from N₃ of $n_1(N_3) \rightarrow \sigma^*(N_4-C_{33})$, N₃-C₃₃ from N₄ of $n_1(N_4) \rightarrow \pi^*(N_3-C_{33})$, C₃₇-N₃₉ from O₃₈ of $n_1(O_{38}) \rightarrow \sigma^*(C_{37}-N_{39})$, C₃₇-O₃₈ from N₃₉ of $n_1(N_{39}) \rightarrow \pi^*(C_{37}-O_{38})$, C₄₇-C₄₆ from O₄₉ of $n_1(N_{49}) \rightarrow \sigma^*(C_{47}-C_{46})$, C₄₇-C₄₆ from O₅₄ of $n_1(O_{54}) \rightarrow \pi^*(C_{47}-C_{46})$ and C₄₁-C₄₅ from O₅₉ of $n_2(O_{59}) \rightarrow \pi^*(C_{41}-C_{45})$ having electron densities, 0.37197, 0.09782, 0.06033, 0.37197, 0.08000, 0.26078, 0.04620, 0.40309, 0.37757e and stabilization energies, 24.95, 30.34, 16.18, 56.09, 26.53, 59.79, 7.77, 10.14 and 9.12 KJ/mol.

The natural hybrid orbitals with high energies, considerable p-character, low occupation numbers are: $n_2(S_1)$, $n_2(O_2)$, $n_2(O_{38})$, $n_2(O_{49})$, $n_2(O_{54})$, $n_2(O_{59})$ with energies, -0.24978, -0.24517, -0.23949, -0.34379, -0.36606, -0.37165a.u and p-characters, 100, 99.99, 99.99, 94.16, 89.71, 88.97% and low occupation numbers, 1.82884, 1.85356, 1.86700, 1.92712, 1.90599, 1.90982 and the orbitals with lower energies, high occupation numbers are, $n_1(S_1)$, $n_1(O_2)$, $n_1(O_{38})$, $n_1(O_{49})$, $n_1(O_{54})$, $n_1(O_{54})$ with energies, -0.63412, -0.67228, -0.66684, -0.53312, -0.49570, -0.49287 a.u with p-characters, 31.99, 58.17, 41.88, 63.33, 68.32, 68.85% and high occupation numbers, 1.98015, 1.97619, 1.97557, 1.94413, 1.95217, and 1.95138.

Thus, a very close to pure p-type lone pair orbital participates in the electron donation to the $n_1(S_1) \rightarrow \pi^*(N_6-C_{36})$, $n_1(N_2) \rightarrow \pi^*(O_5-C_{54})$, $n_2(O_3) \rightarrow \sigma^*(N_7-C_{18})$, $n_2(O_4) \rightarrow \sigma^*(N_2-C_{36})$, $n_2(O_5) \rightarrow \sigma^*(N_2-C_{54})$, $n_1(N_6) \rightarrow \sigma^*(N_7-C_{36})$ and $n_1(N_7) \rightarrow \sigma^*(N_6-C_{36})$ interactions in the compound.

4.9 Reactive and degradation properties based on autoxidation and hydrolysis

Since forced degradation studies could be complicated and tedious procedures, DFT calculations can be readily employed for the initial assessment of degradation properties of important molecules [77-80]. Concretely, calculations of BDEs for hydrogen abstraction can be of particular interest for the initial assessment of autoxidation mechanism. If the BDE for hydrogen abstraction at some particular molecule location has the value within certain interval than it can be concluded that

autoxidation mechanism is possible. In this regard it is important to mention that allperoxy radicals have similar BDE values (87-92 kcal/mol) for which it can be approximated that are independent of the chemical surrounding [81, 82]. Study of Wright et al. [83] states that molecules are the most sensitive towards the autoxidation mechanism for the BDE values in the range between 75 and 85 kcal/mol. Similarly, according to Gryn'ova et al. [84] thermodynamic favorability of C-H bond dissociation is strongly favored for BDE values below 85 kcal/mol, disfavored for BDE values higher than 90 kcal/mol and questionable for the BDE values in the range between 85 and 90 kcal/mol [19].

In this work BDE values of hydrogen abstraction have been calculated in order to determine whether the investigated molecule is prone to autoxidation process or not. Besides, BDE values for the rest of the single acyclic bonds have also been calculated in order to determine the weakest bonds and thus to locate the possible molecule's location suitable for the start of degradation. All BDEs have been presented in the Fig. 11.

BDE values for hydrogen abstraction presented in Fig. 11 clearly indicate that the title compound molecule is not suitable for the autoxidation mechanism since all BDE values for hydrogen abstraction are significantly higher than 90 kcal/mol. This result also indicates that the investigated molecule is stable in the open air and in the presence of oxygen. On the other side the lowest BDE values for the rest of the single acyclic bonds have been calculated in the case of bonds denoted with numbers 26 and 27, indicating that degradation process could start by the detaching of methyl groups. Beside bonds 26 and 27 it is also important to mention that BDE for the bond 15 is also low and can be considered as significant. Namely, this bond is connecting two large parts of molecule and in the same time involves sulfur atom S1, which is important reactive center according to the results obtained by ALIE surfaces. Concretely, ALIE value is the lowest for precisely S1 atom.

Due to the frequent usage, biologically active molecules accumulate in water resources. In certain cases hydrolysis mechanism is very significant for the degradation of these molecules. Although it is hard to predict whether some molecule can be influenced by the hydrolysis in the extent which is suitable for degradation, it is possible to use the MD simulations and to determine which atoms of the investigated molecules

have significant interactions with water molecules by calculations of RDFs. RDF, $g(r)$, determines the probability of finding a particle in the distance r from another particle [85]. RDFs of atoms with pronounced interactions with water molecules have been presented in Fig. 12. According to the calculated RDFs presented in Fig. 12 there are four carbon atoms and four non-carbon atoms with significant interactions with water molecules. Four carbon atoms have practically the same peak distance located at somewhat more than 3.5 Å, while maximal $g(r)$ values are around 1.4, except in the case of carbon atom C37 for which the maximal $g(r)$ value is somewhat less than 1.2.

Among the non-carbon atoms, oxygen atoms O2 and O38 are very similar in terms of peak distance. Namely, maximal $g(r)$ values in cases of these two atoms are located at distance of around 2.6 Å, while there is significant difference in their maximal $g(r)$ values (around 0.8 for O2 and around 1.0 for O38). Interesting situation can be seen for oxygen atom O49, for which RDF there are three distinct solvation spheres. The influence of hydrolysis could be of certain significance because mentioned oxygen atom O49 is connected to methyl group which is characterized by very low BDE value. By all means the most significant interaction with water molecules occurs in the case of hydrogen atom H48, which maximal $g(r)$ value is located at around 1.7 Å.

4.10 Molecular docking studies

Human neutrophil elastase (HNE) has been implicated as a major contributor to tissue destruction in various disease states, including emphysema. HNE is capable of digesting the underlying elastin structure of the alveolar walls of the lung [86]. To evaluate the inhibiting activity of the title compound on HNE we have carried out molecular docking study. The 3D crystal structure of HNE was obtained from Protein Data Bank (PDB ID: 1HNE) [87] and the molecular docking simulations were performed on AutoDock-Vina software [88] as reported previously [89]. The ligand binds at the catalytic site of substrate (Fig. 13) by weak non-covalent interactions most prominent of which are H-bonding and π - π stacking interactions. Arg147 and Gly193 form hydrogen bonds with the carbonyl groups. A strong hydrogen bond is formed between NH group and Phe41 amino acid. Phe192, Phe41 and Leu143 hold the aromatic rings by π - π stacking interactions (Fig. 14). The inhibitor forms a stable complex with HNE as is evident from the binding affinity -10.9 kcal/mol (ΔG in kcal/mol) values (table 7). The

preliminary results suggest that the compound exhibit inhibitory activity against HNE. However biological tests need to be done so as to validate the computational predictions.

5. Conclusion

The spectroscopic properties of 3-((4-oxo-3-phenethyl-3,4-dihydroquinazolin-2-yl)thio)-N-(3,4,5-trimethoxyphenyl) propanamide were investigated by FT-IR and FT-Raman techniques. The geometry of the molecule was fully optimized, vibrational spectra were calculated and fundamental vibrations were assigned on the basis of potential energy distribution of the vibrational modes using GAR2PED program. The molecular orbital calculations such as natural bond orbitals, HOMO-LUMO energy gap and mapped molecular electrostatic potential surfaces were also performed. The delocalization of electron density of various constituents of the molecule has been discussed with the aid of NBO analysis. The calculated first hyperpolarizability of the title compound is 42.04 times that of standard NLO material urea and the title compound and its derivative are good objects for further studies of nonlinear optics. ALIE descriptor recognized sulfur atom S1 as significant reactive center prone to electrophilic attacks. According to the analysis of non-covalent interactions the title compound molecule is characterized by total of six such interactions, among which the strongest one is between sulfur atom S1 and hydrogen atom H17. Further analysis of local reactivity properties by Fukui functions indicated two specific parts of the title compound molecule which could possible act as electrophile (six member ring with two nitrogen atoms and adjacent benzene ring) and nucleophile (near vicinity of benzene rings to which three oxygen atoms are attached). Calculated BDE values for hydrogen abstraction indicate that the investigated molecule is not prone to autoxidation mechanism and that it is very stable in the open air. RDFs as obtained after MD simulations indicate that the most significant interactions with water molecules occurred in the case of hydrogen atom H48. Concerning the RDFs it is also meaningful to notice that oxygen atom O49, involved in the bonds with the low BDE values, also has significant interactions with water molecules which indicates that hydrolysis mechanism could be of importance in the case of the title compound molecule. Molecular docking study shows that the ligand binds at the catalytic site of substrate by weak non-covalent interactions most prominent of which are H-bonding and pi-pi stacking interactions; Arg147 and Gly193 form hydrogen bonds with the carbonyl

groups; A strong hydrogen bond is formed between NH group and Phe41 amino acid; Phe192, Phe41 and Leu143 hold the aromatic rings by pi-pi stacking interactions. The theoretically obtained geometrical parameters are in agreement with that of similar derivatives.

Acknowledgments

The authors extend their appreciation to the Deanship of Scientific Research at King Saud University for funding the work through the research group project No. RG-1435-046. The authors would like to thank the University of Antwerp for access to the University's CalcUA supercomputer cluster. Part of this work has been performed thanks to the support received from Schrödinger Inc.

References

- [1] J. Rudolph, W.P. Esler, S. O'connor, P.D. Coish, P.L. Wickens, M. Brands, D.E. Bierer, B.T. Bloomquist, G. Bondar, L. Chen, C.Y. Chuang, T.H. Claus, Z. Fathi, W. Fu, U.R. Khire, J.A. Kristie, X.G. Liu, D.B. Lowe, A.C. McClure, M. Michels, A.A.Otriz, P.D. Ramsden, R.W. Schoenleber, T.E. Shelekhin, A. Vakalopoulos, W. Tang, L. Wang, L. Yi, S.J. Gardell, J.N. Livingston, L.J. Sweet, W.H. Bullock, Quinazolinone derivatives as orally available ghrelin receptor antagonists for the treatment of diabetes and obesity, *J. Med. Chem.* 50 (2007) 5202-5216.
- [2] S. Tamaoki, Y. Yamauchi, Y. Nakano, S. Sakno, A. Asagarsu, M. Sato, Pharmacological properties of 3-amino-25,6,7,8-tetrahydro-2-{4-[4-(quinolin-2-yl)piperazin-1-yl]butyl}quinazolin-4(3H)-one (TZB-30878), a novel therapeutic agent for diarrhea-predominant irritable bowel syndrome (IBS) and its effects on an experimental IBS model, *J. Pharmacol. Exp. Ther.* 322 (2007) 1315-1323.
- [3] A. Iwashita, S. Yamazaki, K. Mihara, K. Hattori, H. Yamamoto, J. Ishida, N. Matsuoka, S. Mutoh, Neuroprotective effects of a novel poly(ADP-ribose) polymerase-1 inhibitor, 2-{3-[4-(4-chlorophenyl)-1-piperazinyl]propyl}-4(3H)-quinazolinone (FR255595), in an in vitro model of cell death and in mouse 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine model of parkinson's disease, *J. Pharmacol. Exp. Ther.* 309 (2004) 1067-1078.

- [4] I. Al-Suwaidan, A.M. Alanazi, A.A.-M. Abdel-Aziz, M.A. Mohamed, A.S. El-Azab, Design, synthesis and biological evaluation of 2-mercapto-3-phenethylquinazoline bearing anilide fragments as potential antitumor agents, molecular docking study, *Bioorg. Med. Chem. Lett.* 23 (2013) 3935-3941.
- [5] A.M. Alafeefy, A.A. Kadi, A.S. El-Azab, S.G. Abdel-Hamde, M.H. Daba, Synthesis, analgesic and anti-inflammatory evaluation of some new 3H-quinazolin-4-one derivatives, *Arch. Pharm. (Weinheim)*. 341 (2008) 377-385.
- [6] A.S. El-Azab, K.E. ElTahir, S.M. Attia, Synthesis and anticonvulsant evaluation of some novel 4(3H)-quinazolinones, *Monat. Fur. Chemie*. 142 (2011) 837-848.
- [7] A.M. Alanazi, A.A.-M. Abdel-Aziz, I.A. Al-Suwaidan, S.G. Abdel-Hamde, T.Z. Shower, A.S. El-Azab, Design, synthesis and biological evaluation of some novel substituted quinazolines as antitumor agents, *Eur. J. Med. Chem.* 79 (2014) 446-454.
- [8] M.A. Mohamed, R.R. Ayyad, T.Z. Shower, A.A.-M. Abdel-Aziz, A.S. El-Azab, Synthesis and antitumor evaluation of trimethoxyanilides based on 4(3H)-quinazolinone scaffolds, *Eur. J. Med. Chem.* 112 (2016) 106-113.
- [9] I.A. Al-Suwaidan, A.A.-M. Abdel-Aziz, T.Z. Shower, R.R. Ayyad, A.M. Alanazi, A.M. El-Morsy, M.A. Mohamed, N.I. Abdel-Aziz, M.A.-A. El-Sayed, A.S. El-Azab, Synthesis, antitumor activity and molecular docking study of some novel 3-benzyl-4(3H)quinazolinone analogues, *J. Enzy. Inhib. Med. Chem.* 31 (2016) 78-89.
- [10] A.M. Alanazi, A.A.-M. Abdel-Aziz, T.Z. Shower, R.R. Ayyad, A.M. Al-Obaid, M.H. Al-Agamy, A.R. Maarouf, A.S. El-Azab, Synthesis, antitumor and antimicrobial activity of some new 6-methyl-3-phenyl-4(3H)-quinazolinone analogues, in silico studies, *J. Enzy. Inhib. Med. Chem.* 31 (2016) 721-735.
- [11] A.M. Alanazi, I.A. Al-Suwaidan, A.A.-M. Abdel-Aziz, M.A. Mohamed, A.M. El-Morsy, A.S. El-Azab, Design, synthesis and biological evaluation of some novel substituted 2-mercapto-3-phenethyl quinazolines as antitumor agents, *Med. Chem. Res.* 22 (2013) 5566-5577.

- [12] S. Olgen, N. Altanlar, E. Karatayli, M. Bozdayi, Antimicrobial and antiviral screening of novel indole carboxamide and propanamide derivatives, *Z. Naturforsch.* 63 (2008) 189-195.
- [13] A. Naqvi, R. Malasoni, A. Srivastava, R.R. Pandey, A.K. Dwivedi, Design, synthesis and molecular docking of substituted 3-hydrazinyl-3-oxo-propanamides as anti-tubercular agents, *Bioorg. Med. Chem. Lett.* 24 (2014) 5181-5184.
- [14] B. Abramović, S. Kler, D. Šojić, M. Laušević, T. Radović, D. Vione, Photocatalytic degradation of metoprolol tartrate in suspensions of two TiO₂-based photocatalysts with different surface area. Identification of intermediates and proposal of degradation pathways, *J. Hazard. Mater.* 198 (2011) 123-132.
- [15] S.J. Armaković, S. Armaković, N.L. Finčur, F. Šibul, D. Vione, J.P. Šetrajčić, B. Abramović, Influence of electron acceptors on the kinetics of metoprolol photocatalytic degradation in TiO₂ suspension. A combined experimental and theoretical study, *RSC Advances* 5 (2015) 54589-54604.
- [16] M. Blessy, R.D. Patel, P.N. Prajapati, Y. Agrawal, Development of forced degradation and stability indicating studies of drugs—A review, *J. Pharm. Anal.* 4 (2014) 159-165.
- [17] J. Molnar, J. Agbaba, B. Dalmacija, M. Klačnjak, M. Watson, M. Kragulj, Effects of ozonation and catalytic ozonation on the removal of natural organic matter from groundwater. *J. Environmental Engineering* 138 (2011) 804-808.
- [18] J.J. Molnar, J.R. Agbaba, B.D. Dalmacija, M.T. Klačnjak, M.B. Dalmacija, M.M. Kragulj, A comparative study of the effects of ozonation and TiO₂-catalyzed ozonation on the selected chlorine disinfection by-product precursor content and structure, *Sci. Total Environ.*, 425 (2012) 169-175.
- [19] P. Lienard, J. Gavartin, G. Boccardi, M. Meunier, Predicting drug substances autoxidation, *Pharm. Res.*, 32 (2015) 300-310.
- [20] G.L. de Souza, L. M.de Oliveira, R.G. Vicari, A. Brown, A DFT investigation on the structural and antioxidant properties of new isolated interglycosidic O-(1→3) linkage flavonols, *J. Mol. Modeling*, 22 (2016) 1-9.

- [21] Z. Sroka, B. Żbikowska, J. Hładyszowski, The antiradical activity of some selected flavones and flavonols, Experimental and quantum mechanical study, *J. Mol. Modeling*, 21 (2015) 1-11.
- [22] H. Djeradi, A. Rahmouni, A.C heriti, Antioxidant activity of flavonoids: a QSAR modeling using Fukui indices descriptors, *J. Mol. Modeling*, 20 (2014) 1-9.
- [23] Gaussian 09, Revision D.01, M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G.A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H.P. Hratchian, A.F. Izmaylov, J. Bloino, G. Zheng, J.L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J.A. Montgomery, Jr., J.E. Peralta, F. Ogliaro, M. Bearpark, J.J. Heyd, E. Brothers, K.N. Kudin, V.N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J.C. Burant, S.S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J.M. Millam, M. Klene, J.E. Knox, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, R.L. Martin, K. Morokuma, V.G. Zakrzewski, G.A. Voth, P. Salvador, J.J. Dannenberg, S. Dapprich, A.D. Daniels, O. Farkas, J.B. Foresman, J.V. Ortiz, J. Cioslowski, D.J. Fox, Gaussian, Inc., Wallingford CT, 2013.
- [24] A. Irfan, R. Jin, A.G. Al-Sehemi, A.M. Asiri, Quantum chemical study of the donor bridge acceptor triphenylamine based sensitizers, *Spectrochim. Acta* 110 (2013) 60-66.
- [25] A. Irfan, A.G. Al-Sehemi, M.S. Al-Assiri, The effect of donors acceptors on the charge transfer properties and tuning of emitting color for thiophene, pyrimidine and oligoacene based compounds, *J. Fluorine Chem.* 157 (2014) 52-57.
- [26] J.B. Foresman, in: E. Frisch (Ed.), *Exploring Chemistry with Electronic Structure Methods: A Guide to Using Gaussian*, Gaussian Inc., Pittsburg, PA, 1996.
- [27] R. Dennington, T. Keith, J. Millam, *GaussView, Version 5*, Semichem Inc., Shawnee Mission KS, 2009.

- [28] J.M.L. Martin, C. Van Alsenoy, GAR2PED, A Program to Obtain a Potential Energy Distribution from A Gaussian Archive Record, University of Antwerp, Belgium, 2007.
- [29] N. Chipanina, L. Oznobikhina, T. Aksamentova, A. Romanov, A.Y. Rulev, Intramolecular hydrogen bond in the push–pull CF₃-aminoenones: DFT and FTIR study, NBO analysis, Tetrahedron 70 (2014) 1207-1213.
- [30] D. Shivakumar, J. Williams, Y. Wu, W. Damm, J. Shelley, W. Sherman, Prediction of absolute solvation free energies using molecular dynamics free energy perturbation and the OPLS force field, J. Chem. Theory Comput. 6 (2010) 1509-1519.
- [31] Z. Guo, U. Mohanty, J. Noehre, T.K. Sawyer, W. Sherma, G. Krilov, Probing the α -Helical Structural Stability of Stapled p53 Peptides: Molecular Dynamics Simulations and Analysis, Chem. Biol. Drug Design, 75 (2010) 348-359.
- [32] K.J. Bowers, E. Chow, H. Xu, R.O. Dror, M.P. Eastwood, B.A. Gregersen, J.L. Klepeis, I. Kolossvary, M.A. Moraes, F.D. Sacerdoti, Scalable algorithms for molecular dynamics simulations on commodity clusters. In: SC 2006 Conference, Proceedings of the ACM/IEEE, IEEE, 2006, pp. 43-43.
- [33] Schrödinger Release 2015-4: Desmond Molecular Dynamics System, version 4.4, D.E. Shaw Research, New York, NY, 2015. Maestro-Desmond Interoperability Tools, version 4.4, Schrödinger, New York, NY, 2015., 2015.
- [34] A.D. Becke, Density-functional thermochemistry. III. The role of exact exchange, J. Chem. Phys., 98 (1993) 5648-5652.
- [35] J.L. Banks, H.S. Beard, Y. Cao, A.E. Cho, W. Damm, R. Farid, A.K. Felts, T.A. Halgren, D.T. Mainz, J.R. Maple, Integrated modeling program, applied chemical theory (IMPACT), J. Comput. Chem., 26 (2005) 1752-1780.
- [36] H.J. Berendsen, J.P. Postma, W.F. van Gunsteren, J. Hermans, Interaction models for water in relation to protein hydration. In: Intermolecular forces, Springer, 1981, pp. 331-342.
- [37] A. Otero-de-la-Roza, E.R. Johnson, J. Contreras-García, Revealing non-covalent interactions in solids: NCI plots revisited. Phys. Chem. Chem. Phys., 14 (2012) 12165-12172.

- [38] E.R. Johnson, S. Keinan, P. Mori-Sanchez, J. Contreras-Garcia, A.J. Cohen, W. Yang, Revealing non-covalent interactions, *J. Am. Chem. Soc.*, 132 (2010) 6498-6506.
- [39] Y.S. Mary, P.J. Jojo, C. Van Alsenoy, M. Kaur, M.S. Siddegowda, H.S. Yathirajan, H.I.S. Nogueira, S.M.A. Cruz, Vibrational spectroscopic studies (FT-IR, FT-Raman, SERS) and quantum chemical calculations of cyclobenzaprinium salicylate, *Spectrochim. Acta* 120 (2014) 340-350.
- [40] R.T. Ulahannan, C.Y. Panicker, H.T. Varghese, R. Musiol, J. Jampilek, C. Van Alsenoy, J.A. War, A.A. Al-Saadi, Vibrational spectroscopic and molecular docking study of (2E)-N-(4-chloro-2-oxo-1,2-dihydroquinolin-2-yl)-3-phenylprop-2-enamide, *Spectrochim. Acta* 151 (2015) 335-349.
- [41] F.H. Allen, O. Kennard, D.G. Watson, L. Brammer, A.G. Orpen, R. Taylors, Tables of bond lengths determined by X-ray and neutron diffraction, Part 1. Bond lengths in organic compounds, *J. Chem. Soc. Perkin Trans. 2* (1987) S1-S19.
- [42] Y.S. Mary, C.Y. Panicker, T.S. Yamuna, M.S. Siddegowda, H.S. Yathirajan, A.A. Al-Saadi, C. Van Alsenoy, Theoretical investigations on the molecular structure, vibrational spectral, HOMO-LUMO and NBO analysis of 9-[3-(dimethylamino)propyl]-2-trifluoro-methyl-9H-thioxanthen-9-ol, *Spectrochim. Acta* 132 (2014) 491-501.
- [43] Y.S. Mary, K. Raju, I. Yildiz, O. Temiz-Arpaci, H.I.S. Nogueira, C.M. Granadeiro, C. Van Alsenoy, FT-IR, FT-Raman, SERS and computational study of 5-ethylsulphonyl-2-(o-chlorobenzyl)benzoxazole, *Spectrochim. Acta* 96 (2012) 617-625.
- [44] A. Raj, Y.S. Mary, C.Y. Panicker, H.T. Varghese, K. Raju, IR, Raman, SERS and computational study of 2-(benzylsulfanyl)-3,5-dinitrobenzoic acid, *Spectrochim. Acta* 113 (2013) 28-36.
- [45] N.P.G. Roeges, A guide to the complete interpretation of IR spectra of Organic Compounds, Wiley, New York 1994.
- [46] G. Varsanyi, Assignments of Vibrational Spectra of Seven Hundred Benzene Derivatives, Wiley, New York 1974.

- [47] A. Chandran, H.T. Varghese, C.Y. Panicker, C. VanAlsenoy, G. Rajendran, FT-IR and computational study of (E)-N-carbamimidoyl-4-((2-formyl benzylidene)amino)benzene sulfonamide, *J. Mol. Struct.* 1001 (2011) 29-35.
- [48] C.Y. Panicker, H.T. Varghese, K.R. Ambujakshan, S. Mathew, S. Ganguli, A.K. Nanda, V. Van Alsenoy, Y.S. Mary, Ab initio and density functional theory studies on vibrational spectra of 3-[[4-methoxyphenyl] methylene]amino}-2-phenylquinazolin-4-(3H)-one, *Eur. J. Chem.* 1 (2010) 37-43.
- [49] C.Y. Panicker, H.T. Varghese, K.R. Ambujakshan, S. Mathew, S. Ganguli, A.K. Nanda, C. Van Alsenoy, Y.S. Mary, Vibrational spectra and computational study of 3-amino-2-phenyl quinazolin-4(3H)-one, *J. Mol. Struct.* 963(2010) 137-144.
- [50] N.B. Colthup, L.H. Daly, S.E. Wiberly, *Introduction to IR and Raman spectroscopy*, Academic Press, New York 1990.
- [51] L.J. Bellamy, *The IR spectra of Complex Molecules*, John Wiley and Sons, New York, 1975.
- [52] Y.S. Mary, C.Y. Panicker, H.T. Varghese, K. Raju, T.E. Bolelli, I. Yildiz, M.C. Granadeiro, H.I.S. Nogueira, Vibrational spectroscopic studies and computational study of 4-fluoro-N-(2'-hydroxy-4'-nitrophenyl)phenylacetamide, *J. Mol. Struct.* 994 (2011) 223-231.
- [53] R.M. Silverstein, F.X. Webster, *Spectrometric Identification of Organic Compounds*, 6th ed., John Wiley Asia, 2003.
- [54] H.T. Varghese, C.Y. Panicker, D. Philip, P. Pazdera, Vibrational spectroscopic studies and ab initio calculations of 2-cyanophenylisocyanid dichloride, *Spectrochim. Acta* 67 (2007) 1055-1059.
- [55] B. Smith, *Infrared Spectral Interpretation, A Systematic approach*, CRC Press, Washington DC, 1999.
- [56] Z. Zhengyu, F. Aiping, D. Dongmei Studies on density functional theory for the electron transfer reaction mechanism between $M-C_6H_6$ and $M^+-C_6H_6$ complexes in the gas phase, *J. Quantum Chem.* 78 (2000) 186-194.
- [57] A.D. Becke, Density functional exchange energy approximation with correct asymptotic behavior, *Phys. Rev.* 38A (1988) 3098-3100.
- [58] S. Ahmad, S. Mathew, P.K. Verma, Laser Raman and FT-infrared spectra of 3,5-

- dinitrobenzoic acid, *Indian J. Pure Appl. Phys.* 30 (1992) 764-765.
- [59] Z. D. Liu, Y. Qu, M.Y. Tan, H. Zhu, 5-bromosalicylic acid, *Acta Cryst. E*60 (2004) o1310-o1311.
- [60] D.A. Prystupa, A. Anderson, B.H. Torrie, Raman and infrared study of solid benzyl alcohol, *J. Raman Spectrosc.* 25 (1994) 175-182.
- [61] S. Bavafa, Ab initio and DFT studies on tautomerization of nitrosamine in reaction of the nitrosamine isomers-H₂O₂, *Asian J. Chem.* 22 (2010) 5237-5243.
- [62] T.A. Koopmans, Über die zuordnung von wellenfunktionen und eigenwerten zu den einzelnen elektronen eines atoms, *Physica I* (1934) 104-113.
- [63] J. Zevallos, A. Toro-Labbe, A theoretical analysis of the Kohn-Sham and Hartree-Fock orbitals and their use in the determination of electronic properties, *J. Chilean Chem. Soc.* 48 (2003) 39-47.
- [64] R.G. Parr, L.V. Szentpaly, S.J. Liu, Electrophilicity index, *J. Am. Chem. Soc.* 121 (1999) 1922-1924.
- [65] F.J. Luque, J.M. Lopez, M. Orozco, Perspective on electrostatic interactions of a solute with a continuum, a direct utilization of ab initio molecular potentials for the prevision of solvent effects, *Theor. Chem. Acc.* 103 (2000) 343-345.
- [66] H. Kobinyi, G. Folkers, Y.C. Martin, 3D QSAR in Drug Design, *Recent Advances*, vol. 3, Kluwer Academic Publishers, 1998.
- [67] J.S. Murray, J.M. Seminario, P. Politzer, P. Sjöberg, Average local ionization energies computed on the surfaces of some strained molecules. *Int. J. Quantum Chem.*, 38 (1990) 645-653.
- [68] P. Politzer, F. Abu-Awwad, J.S. Murray, Comparison of density functional and Hartree-Fock average local ionization energies on molecular surfaces, *Int. J. Quantum Chem.*, 69 (1998) 607-613.
- [69] A. Michalak, F. De Proft, P. Geerlings, R. Nalewajski, Fukui functions from the relaxed Kohn-Sham orbitals, *J. Phys. Chem. A* 103 (1999) 762-771.
- [70] R.G. Parr, W. Yang, *Functional Theory of Atoms and Molecules*, Oxford University Press, New York, 1989.

- [71] P.W. Ayers, R.G. Parr, Variational principles for describing chemical reactions, the Fukui functions and chemical hardness revisited, *J. Am. Chem. Soc.* 122 (2000) 2010-2018.
- [72] R.G. Parr, W. Yang, Density functional approach to the frontier electron theory of chemical reactivity, *J. Am. Chem. Soc.* 106 (1984) 4049-4050.
- [73] C. Morell, A. Grand, A. T. Labbe, New dual descriptor for chemical reactivity, *J. Phys. Chem. A* 109 (2005) 205-212.
- [74] C. Adant, M. Dupuis, J.L. Bredas, Ab initio study of the nonlinear optical properties of urea, electron correlation and dispersion effects, *Int. J. Quantum. Chem.* 56 (1995) 497-507.
- [75] C. Hatting, O. Christiansen, P. Jorgensen, Frequency dependent second hyperpolarizabilities using coupled cluster cubic response theory, *Chem. Phys. Lett.* 282 (1998) 139-146.
- [76] E.D. Glendening, A.E. Reed, J.E. Carpenter, F. Weinhold, NBO Version 3.1, Gaussian Inc., Pittsburgh, PA, 2003.
- [77] X. Ren, Y. Sun, X. Fu, L. Zhu, Z. Cui, DFT comparison of the OH-initiated degradation mechanisms for five chlorophenoxy herbicides, *J. Mol. Modeling*, 19 (2013) 2249-2263.
- [78] L-l. Ai, J-y. Liu, Mechanism of OH-initiated atmospheric oxidation of E/Z- $\text{CF}_3\text{CF}=\text{CFCF}_3$: a quantum mechanical study. *Journal of molecular modeling* 20 (2014) 1-10.
- [79] W. Sang-aroon, V. Amornkitbamrung, V. Ruangpornvisuti, A density functional theory study on peptide bond cleavage at aspartic residues: direct vs cyclic intermediate hydrolysis, *J. Mol. Model.*, 19 (2013) 5501-5513.
- [80] J. Kieffer, É. Brémond, P. Lienard, G. Boccardi, In silico assessment of drug substances chemical stability, *J. Mol. Struct. THEOCHEM* 954 (2010) 75-79.
- [81] T. Andersson, A. Broo, E. Evertsson, Prediction of Drug Candidates' Sensitivity Toward Autoxidation: Computational Estimation of C-H Dissociation Energies of Carbon-Centered Radicals, *J. Pharm. Sci.* 103 (2014) 1949-1955.
- [82] Y-R. Luo, Handbook of bond dissociation energies in organic compounds, CRC press, 2002.

- [83] J.S. Wright, H. Shadnia, L.L. Chepelev, Stability of carbon-centered radicals: Effect of functional groups on the energetics of addition of molecular oxygen, *J. Comput. Chem.* 30 (2009) 1016-1026.
- [84] G. Gryn'ova, J.L. Hodgson, M.L. Coote, Revising the mechanism of polymer autooxidation, *Org. Biomol. Chem.*, 9 (2011) 480-490.
- [85] R.V. Vaz, J.R. Gomes, C.M. Silva, Molecular dynamics simulation of diffusion coefficients and structural properties of ketones in supercritical CO₂ at infinite dilution, *J. Supercritic. Fluids* 107 (2016) 630-638.
- [86] A. Janoff, Elastase in tissue injury, *Annu. Rev. Med.* 36 (1985) 207-216.
- [87] M.A. Navia, B.M. McKeever, J.P. Springer, T.Y. Lin, H.R. Williams, E.M. Fluder, C.P. Dorn, K. Hoogsteen, Structure of human neutrophil elastase in complex with a peptide chloromethyl keton inhibitor at 1.84-Å resolution, *Proc. Natl. Acad. Sci. USA*, 86 (1989) 7-11.
- [88] O. Trott, A.J. Olson, AutoDock Vina, improving the speed and accuracy of docking with a new scoring function, efficient optimization and multithreading, *J. Comp. Chem.* 31 (2010) 455-461.
- [89] AS.El-Azab, YS.Mary, CY.Panicker, AAM.Abdel-Aziz, MA.El-Sherbeny, C.Van Alsenoy, DFT and experimental (FT-IR and FT-Raman) investigation of vibrational spectroscopy and molecular docking studies of 2-(4-oxo-3-phenethyl-3,4-dihydroquinazolin-2-ylthio)-N-(3,4,5-trimethoxyphenyl)acetamide, *J. Mol. Struct.* 1113 (2016) 133-145.

Figure captions

- Fig.1 FT-IR spectrum of 3-(4-oxo-phenethyl-3,4-dihydroquinazolin-2-ylthio)-N-(3,4,5-trimethoxyphenyl) propanamide
- Fig.2 FT-Raman spectrum of 3-(4-oxo-phenethyl-3,4-dihydroquinazolin-2-ylthio)-N-(3,4,5-trimethoxyphenyl) propanamide
- Fig.3 Optimized geometry of 3-(4-oxo-phenethyl-3,4-dihydroquinazolin-2-ylthio)-N-(3,4,5-trimethoxyphenyl) propanamide
- Fig.4 ¹H NMR spectrum of the title compound
- Fig.5 ¹³C NMR spectrum of the title compound

Fig.6 HOMO-LUMO plots of 3-(4-oxo-phenethyl-3,4-dihydroquinazolin-2-ylthio)-N-(3,4,5-trimethoxyphenyl) propanamide

Fig.7 MEP plot of 3-(4-oxo-phenethyl-3,4-dihydroquinazolin-2-ylthio)-N-(3,4,5-trimethoxyphenyl) propanamide

Fig.8 ALIE surface of the title molecule

Fig.9 Visualization of intra-molecular non-covalent interactions with their corresponding strengths [electron/bohr³]

Fig.10 Fukui functions a) f^+ and b) f^- of the title molecule

Fig.11 BDEs of all single acyclic bonds of the title molecule

Fig.12 Significant RDFs for the interactions with water molecules: a) carbon atoms and b) non-carbon atoms

Fig.13 The ligand and the co-crystallized inhibitor embedded into the catalytic site of HNE

Fig. 14 The docked confirmation of ligand binds at the catalytic site of HNE. H-bond, pi-pi stacking interactions are represented by green and violet dotted lines, respectively

**Fig.1 FT-IR spectrum of
3-(4-oxo-phenethyl-3,4-dihydroquinazolin-2-ylthio)-N-(3,4,5-
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Fig.4 ¹H NMR spectrum of the title compound

Fig.5 ^{13}C NMR spectrum of the title compound

LUMO

HOMO

Fig.6 HOMO-LUMO plots of 3-(4-oxo-phenethyl-3,4-dihydroquinazolin-2-ylthio)-N-(3,4,5-trimethoxyphenyl) propanamide

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186.47 ALIE [kcal/mol] 346.19

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Table 1. Optimized geometrical parameters of 3-(4-oxo-phenethyl-3,4-dihydroquinazolin-2-ylthio)-N-(3,4,5-trimethoxyphenyl) propanamide

Bond lengths (Å)

S1-C33	1.7846	S1-C34	1.8383	O2-C15	1.2205
N3-C5	1.3822	N3-C33	1.2914	N4-C15	1.4155
N4-C16	1.4765	N4-C33	1.3857	C5-C6	1.4084
C5-C14	1.4090	C6-H7	1.0834	C6-C8	1.3833
C8-H9	1.0846	C8-C10	1.4057	C10-H11	1.0836
C10-C12	1.3834	C12-H13	1.0831	C12-C14	1.4034
C14-C15	1.4632	C16-H17	1.09	C16-H18	1.0887
C16-C19	1.5405	C19-H20	1.0932	C19-H21	1.0926
C19-C22	1.5125	C22-C23	1.3995	C22-C31	1.3997
C23-H24	1.0856	C23-C25	1.3937	C25-H26	1.0845
C25-C27	1.3941	C27-H28	1.0842	C27-C29	1.3939
C29-H30	1.0844	C29-C31	1.3938	C31-H32	1.0856
C34-H35	1.0891	C34-H36	1.0876	C34-C64	1.5352
C37-O38	1.2197	C37-N39	1.3780	C37-C64	1.5271
N39-C40	1.4252	N39-H48	1.0123	C40-C41	1.3964
C40-C42	1.3949	C41-H43	1.0833	C41-C45	1.3928
C42-H44	1.0824	C42-C46	1.3948	C45-C47	1.4046
C45-O59	1.3713	C46-C47	1.4037	C46-O54	1.3707
C47-O49	1.3737	O49-C50	1.4392	C50-H51	1.093
C50-H52	1.0937	C50-H53	1.0894	O54-C55	1.4361
C55-H56	1.0953	C55-H57	1.0912	C55-H58	1.0892
O59-C60	1.4378	C60-H61	1.0919	C60-H62	1.0946
C60-H63	1.0892	C64-H65	1.0905	C64-H66	1.0921

Bond angles (°)

C33-S1-C34	100.0	C5-N3-C33	118.3	C15-N4-C16	116.4
C15-N4-C33	121.0	C16-N4-C33	122.6	N3-C5-C6	119.1
N3-C5-C14	122.0	C6-C5-C14	118.9	C5-C6-H7	118.4
C5-C6-C8	120.1	H7-C6-C8	121.6	C6-C8-H9	119.6

C6-C8-C10	120.8	H9-C8-C10	119.6	C8-C10-H11	120.0
C8-C10-C12	119.8	H11-C10-C12	120.2	C10-C12-H13	121.6
C10-C12-C14	120.0	H13-C12-C14	118.4	C5-C14-C12	120.5
C5-C14-C15	119.2	C12-C14-C15	120.3	O2-C15-N4	120.4
O2-C15-C14	125.0	N4-C15-C14	114.6	N4-C16-C17	108.5
N4-C16-H18	106.5	N4-C16-C19	112.7	C17-C16-H18	108.0
C17-C16-C19	111.0	H18-C16-C19	109.8	C16-C19-H20	109.2
C16-C19-H21	108.3	C16-C19-C22	111.3	H20-C19-H21	107.8
H20-C19-C22	109.9	H21-C19-C22	110.2	C19-C22-C23	120.7
C19-C22-C31	120.7	C23-C22-C31	118.6	C22-C23-H24	119.4
C22-C23-C25	120.8	H24-C23-C25	119.8	C23-C25-H26	119.8
C23-C25-C27	120.1	H26-C25-C27	120.1	C25-C27-H28	120.2
C25-C27-C29	119.6	H28-C27-C29	120.2	C27-C29-H30	120.1
C27-C29-C31	120.1	H30-C29-C31	119.7	C22-C31-C29	120.8
C22-C31-H32	119.6	C29-C31-H32	119.6	S1-C33-N3	119.5
S1-C33-N4	115.6	N3-C33-N4	124.9	S1-C34-H35	108.0
S1-C34-H36	108.0	S1-C34-C64	110.0	H35-C34-H36	108.1
H35-C34-C64	110.3	H36-C34-C64	112.3	O38-C37-N39	120.2
O38-C37-C64	121.2	N39-C37-C64	118.6	C37-N39-C40	130.1
C37-N39-H48	112.6	C40-N39-H48	117.1	N39-C40-C41	119.1
N39-C40-C42	121.1	C41-C40-C42	119.8	C40-C41-H43	120.9
C40-C41-C45	120.2	H43-C41-C45	118.8	C40-C42-H44	121.3
C40-C42-C46	120.2	H44-C42-C46	118.4	C41-C45-C47	120.4
C41-C45-O59	118.8	C47-C45-O59	120.8	C42-C46-C47	120.3
C42-C46-O54	118.3	C47-C46-O54	121.2	C45-C47-C46	119.0
C45-C47-O49	120.7	C46-C47-O49	120.2	C47-O49-C50	114.4
O49-C50-H51	110.6	O49-C50-H52	110.4	O49-C50-H53	106.2
H51-C50-H52	110.1	H51-C50-H53	109.8	H52-C50-H53	109.7
C46-O54-C55	116.2	O54-C55-H56	110.3	O54-C55-H57	111.2
O54-C55-H58	105.9	H56-C55-H57	110.1	H56-C55-H58	109.4
H57-C55-H58	110.0	C45-O59-C60	115.7	O59-C60-H61	111.1

O59-C60-H62	110.3	O59-C60-H63	105.9	H61-C60-H62	110.1
H61-C60-H63	109.9	H62-C60-H63	109.5	C34-C64-C37	114.6
C34-C64-H65	110.8	C34-C64-H66	107.2	C37-C64-H65	105.8
C37-C64-H66	110.6	H65-C64-H66	107.7		
<u>Dihedral angles (°)</u>					
C34-S1-C33-N3	1.2	C34-S1-C33-N4	-178.8	C33-S1-C34-35	-62.8
C33-S1-C34-H36	53.9	C33-S1-C34-C64	176.8	C33-N3-C5-C6	-179.6
C33-N3-C5-C14	0.4	C5-N3-C33-S1	-180.0	C5-N3-C33-N4	0.1
C16-N4-C15-O2	-0.2	C16-N4-C15-C14	179.8	C33-N4-C15-O2	-178.4
C33-N4-C15-C14	1.6	C15-N4-C16-C17	150.0	C15-N4-C16-H18	33.9
C15-N4-C16-C19	-86.6	C33-N4-C16-C17	-31.8	C33-N4-C16-H18	-147.9
C33-N4-C16-C19	91.6	C15-N4-C33-S1	178.9	C15-N4-C33-N3	-1.2
C16-N4-C33-S1	0.8	C16-N4-C33-N3	-179.3	N3-C5-C6-H7	0.2
N3-C5-C6-C8	179.9	C14-C5-C6-H7	-179.8	C14-C5-C6-C8	-0.1
N3-C5-C14-C12	179.9	N3-C5-C14-C15	0.1	C6-C5-C14-C12	-0.1
C6-C5-C14-C15	-179.9	C5-C6-C8-H9	-179.8	C5-C6-C8-C10	0.1
H7-C6-C8-H9	-0.0	H7-C6-C8-C10	179.9	C6-C8-C10-H11	-180.0
C6-C8-C10-C12	-0.0	H9-C8-C10-H11	-0.1	H9-C8-C10-C12	179.9
C8-C10-C12-H13	180.0	C8-C10-C12-C14	-0.1	H11-C10-C12-H13	-0.0
H11-C10-C12-C14	179.9	C10-C12-C14-C5	0.2	C10-C12-C14-C15	179.9
H13-C12-C14-C5	-179.9	H13-C12-C14-C15	-0.2	C5-C14-C15-O2	178.9
C5-C14-C15-N4	-1.1	C12-C14-C15-O2	-0.9	C12-C14-C15-N4	179.1
N4-C16-C19-H20	-57.7	N4-C16-C19-H21	59.5	N4-C16-C19-C22	-179.2
C17-C16-C19-H20	64.3	C17-C16-C19-H21	-178.5	C17-C16-C19-C22	-57.2
H18-C16-C19-H20	-176.3	H18-C16-C19-H21	-59.1	H18-C16-C19-C22	62.2
C16-C19-C22-C23	-88.7	C16-C19-C22-C31	89.7	H20-C19-C22-C23	150.2
H20-C19-C22-C31	-31.4	H21-C19-C22-C23	31.5	H21-C19-C22-C31	-150.1
C19-C22-C23-H24	-1.8	C19-C22-C23-C25	178.5	C31-C22-C23-H24	179.8
C31-C22-C23-C25	0.1	C19-C22-C31-C29	-178.5	C19-C22-C31-H32	1.9
C23-C22-C31-C29	-0.1	C23-C22-C31-H32	-179.7	C22-C23-C25-H26	179.7
C22-C23-C25-C27	-0.1	H24-C23-C25-H26	0.0	H24-C23-C25-C27	-179.8

C23-C25-C27-H28	179.8	C23-C25-C27-C29	0.0	H26-C25-C27-H28	0.0
H26-C25-C27-C29	-179.7	C25-C27-C29-H30	179.8	C25-C27-C29-C31	-0.0
H28-C27-C29-H30	0.0	H28-C27-C29-C31	-179.8	C27-C29-C31-C22	0.0
C27-C29-C31-H32	179.7	H30-C29-C31-C22	-179.8	H30-C29-C31-H32	-0.1
S1-C34-C64-C37	-60.4	S1-C34-C64-H65	59.3	S1-C34-C64-H66	176.5
H35-C34-C64-C37	-179.4	H35-C34-C64-H65	-59.7	H35-C34-C64-H66	57.5
H36-C34-C64-C37	60.0	H36-C34-C64-H65	179.6	H36-C34-C64-H66	-63.2
O38-C37-N39-C40	178.5	O38-C37-N39-H48	-6.8	C64-C37-N39-C40	-3.3
C64-C37-N39-H48	171.4	O38-C37-C64-C34	109.8	O38-C37-C64-H65	-12.6
O38-C37-C64-H66	-128.9	N39-C37-C64-C34	-68.4	N39-C37-C64-H65	169.3
N39-C37-C64-H66	52.9	C37-N39-C40-C41	121.6	C37-N39-C40-C42	-60.4
H48-N39-C40-C41	-52.9	H48-N39-C40-C42	125.1	N39-C40-C41-H43	-2.6
N39-C40-C41-C45	177.7	C42-C40-C41-H43	179.4	C42-C40-C41-C45	-0.3
N39-C40-C42-H44	-1.4	N39-C40-C42-C46	-178.7	C41-C40-C42-H44	176.6
C41-C40-C42-C46	-0.7	C40-C41-C45-C47	0.2	C40-C41-C45-O59	-176.7
H43-C41-C45-C47	-179.5	H43-C41-C45-O59	3.6	C40-C42-C46-C47	1.8
C40-C42-C46-O54	176.4	H44-C42-C46-C47	-175.6	H44-C42-C46-O54	-1.0
C41-C45-C47-C46	0.9	C41-C45-C47-O49	-179.5	O59-C45-C47-C46	177.7
O59-C45-C47-O49	-2.6	C41-C45-O59-C60	-111.8	C47-C45-O59-C60	71.3
C42-C46-C47-C45	-1.9	C42-C46-C47-O49	178.5	O54-C46-C47-C45	-176.3
O54-C46-C47-O49	4.0	C42-C46-O54-C55	116.6	C47-C46-O54-C55	-68.9
C45-C47-O49-C50	82.6	C46-C47-O49-C50	-97.7	C47-O49-C50-H51	-60.5
C47-O49-C50-H52	61.6	C47-O49-C50-H53	-179.6	C46-O54-C55-H56	-62.0
C46-O54-C55-H57	60.4	C46-O54-C55-H58	179.8	C45-O59-C60-H61	-60.5
C45-O59-C60-H62	61.8	C45-O59-C60-H63	-179.9		

Table 2. Calculated (scaled) wavenumbers, observed IR, Raman bands and assignments of 3-(4-oxo-phenethyl-3,4-dihydroquinazolin-2-ylthio)-N-(3,4,5-trimethoxyphenyl) propanamide

B3LYP/6-311++G(d,p) (5D, 7F)			IR	Raman	Assignments ^a
$\nu(\text{cm}^{-1})$	IR_I	R_A	$\nu(\text{cm}^{-1})$	$\nu(\text{cm}^{-1})$	-
3439	35.93	121.24	3325	-	$\nu\text{NH}(100)$
3978	0.90	61.26	-	-	$\nu\text{CHII}(99)$
3077	9.89	229.80	-	-	$\nu\text{CHIII}(93)$
3070	0.54	58.48	-	-	$\nu\text{CHII}(99)$
3069	8.59	98.48	-	-	$\nu\text{CHIII}(98)$
3065	19.88	364.07	3065	-	$\nu\text{CHI}(94)$
3060	9.01	141.92	-	3060	$\nu\text{CHIII}(99)$
3054	23.91	47.79	-	-	$\nu\text{CHI}(99)$
3045	6.92	92.28	-	-	$\nu\text{CHI}(99)$
3045	4.36	73.16	-	-	$\nu\text{CHIII}(98)$
3035	0.94	99.69	-	3034	$\nu\text{CHI}(99)$
3033	6.12	16.04	3031	3034	$\nu\text{CHI}(99)$
3025	2.65	41.08	-	3023	$\nu\text{CH}_2(96)$
3015	5.18	12.36	-	-	$\nu\text{CH}_2(95)$
3015	15.83	125.17	-	-	$\nu\text{CH}_3(95)$
3014	21.44	94.70	-	-	$\nu\text{CH}_3(93)$
3011	21.57	122.05	-	3008	$\nu\text{CH}_3(100)$
2994	7.99	62.70	2996	-	$\nu\text{CH}_2(94)$
2976	31.05	59.19	-	2979	$\nu\text{CH}_3(98)$
2975	19.45	41.71	-	-	$\nu\text{CH}_3(97)$
2973	18.48	31.83	-	-	$\nu\text{CH}_3(97)$
2972	9.02	39.51	2972	-	$\nu\text{CH}_2(98)$
2969	4.26	132.95	-	-	$\nu\text{CH}_2(96)$
2964	7.11	62.80	-	2963	$\nu\text{CH}_2(99)$
2950	8.44	117.43	-	2948	$\nu\text{CH}_2(98)$

2929	12.59	109.55	2932	2930	$\nu\text{CH}_2(98)$
2906	49.88	195.28	-	-	$\nu\text{CH}_3(99)$
2904	55.41	126.35	-	2902	$\nu\text{CH}_3(98)$
2900	54.43	109.93	-	-	$\nu\text{CH}_3(100)$
1673	502.20	27.59	1675	1680	$\nu\text{C}=\text{O}(73)$
1663	387.95	42.19	1662	1660	$\nu\text{C}=\text{O}(73)$
1582	46.33	72.81	-	-	$\nu\text{PhIII}(62)$, $\delta\text{CHIII}(20)$
1580	7.56	63.20	-	-	$\nu\text{PhI}(56)$, $\delta\text{CHI}(24)$
1571	114.08	75.94	1572	1573	$\nu\text{PhII}(57)$, $\delta\text{CHII}(23)$
1560	0.91	10.30	1558	-	$\nu\text{PhI}(68)$, $\delta\text{CHI}(18)$
1546	114.25	17.46	-	-	$\nu\text{PhII}(49)$, $\nu\text{PhIII}(14)$
1545	110.90	9.14	-	1543	$\nu\text{PhIII}(49)$, $\nu\text{PhII}(40)$
1519	469.39	279.74	1515	-	$\nu\text{C}=\text{N}(43)$, $\nu\text{PhIII}(12)$
1468	17.76	1.49	1468	1467	$\delta\text{CHI}(21)$, $\nu\text{PhI}(64)$
1456	177.60	5.51	-	1460	$\delta\text{CH}_3(45)$, $\nu\text{PhII}(40)$
1451	8.15	7.37	-	-	$\delta\text{CH}_3(81)$
1449	16.99	12.05	-	-	$\delta\text{CH}_3(72)$
1446	2.22	8.68	-	-	$\delta\text{CH}_3(88)$
1444	23.68	9.81	-	-	$\delta\text{CH}_2(76)$
1442	113.45	31.27	-	-	$\delta\text{NH}(44)$, $\nu\text{PhIII}(47)$
1436	15.33	15.72	-	1437	$\delta\text{CH}_3(43)$, $\delta\text{NH}(12)$
1433	19.81	8.36	-	-	$\delta\text{CH}_3(72)$
1431	6.92	7.75	-	-	$\delta\text{CHIII}(19)$, $\delta\text{CH}_2(20)$, $\nu\text{PhIII}(48)$
1429	21.21	6.89	-	-	$\delta\text{CH}_3(83)$
1429	4.90	9.54	-	-	$\delta\text{CH}_3(80)$
1428	28.52	63.08	-	-	$\delta\text{CH}_2(61)$
1426	0.53	7.41	-	-	$\delta\text{CHI}(13)$, $\nu\text{PhI}(53)$
1421	7.31	9.47	-	-	$\delta\text{CH}_3(40)$, $\delta\text{CH}_2(40)$
1420	21.34	9.60	-	-	$\delta\text{CH}_2(82)$
1417	39.75	9.29	1417	-	$\delta\text{CH}_2(92)$

1408	16.13	15.95	-	1408	$\delta\text{CH}_3(68)$, $\delta\text{NH}(19)$
1399	24.75	6.13	-	1395	$\delta\text{CH}_3(62)$, $\nu\text{PhII}(12)$
1364	56.27	28.05	1368	1363	$\nu\text{PhII}(53)$, $\delta\text{NH}(21)$
1352	20.98	33.04	1348	-	$\delta\text{CH}_2(72)$
1325	56.31	47.64	-	1330	$\delta\text{CH}_2(48)$, $\nu\text{CN}(12)$
1324	117.63	25.06	-	1322	$\nu\text{CN}(48)$, $\delta\text{CH}_2(40)$
1311	5.67	8.92	-	-	$\delta\text{CHI}(77)$
1306	34.20	127.11	-	-	$\nu\text{PhIII}(81)$
1301	7.73	19.74	-	1303	$\delta\text{CH}_2(59)$, $\nu\text{PhII}(22)$
1293	131.43	19.42	-	-	$\delta\text{CH}_2(44)$, $\nu\text{CO}(19)$, $\nu\text{PhII}(16)$
1290	1.64	1.55	1288	-	$\nu\text{PhI}(76)$, $\delta\text{CH}_2(15)$
1271	3.94	17.40	-	1273	$\delta\text{CH}_2(76)$
1265	25.01	18.61	-	-	$\nu\text{CN}(45)$, $\delta\text{CHIII}(40)$
1257	17.06	29.13	-	-	$\delta\text{CH}_2(52)$, $\nu\text{CN}(10)$
1247	18.83	3.08	-	1250	$\nu\text{PhII}(84)$
1241	169.83	36.19	1238	-	$\nu\text{CN}(11)$, $\delta\text{CH}_2(46)$
1216	10.61	78.40	-	1214	$\delta\text{CH}_2(40)$, $\nu\text{CN}(43)$
1206	18.50	2.24	-	1204	$\delta\text{CHIII}(41)$, $\nu\text{CN}(43)$
1196	104.15	8.45	-	-	$\nu\text{CO}(47)$, $\delta\text{PhII}(16)$, $\delta\text{CH}_3(11)$
1180	57.63	1.41	1182	1181	$\delta\text{CHII}(50)$, $\nu\text{CO}(12)$
1176	0.04	46.25	-	-	$\nu\text{CC}(38)$, $\nu\text{PhI}(12)$, $\delta\text{CHI}(42)$
1170	16.22	2.36	-	-	$\delta\text{CH}_3(74)$, $\nu\text{PhI}(12)$
1164	20.77	3.15	-	-	$\delta\text{CH}_3(59)$, $\nu\text{PhI}(20)$
1161	13.11	2.77	-	-	$\delta\text{CH}_2(69)$, $\nu\text{PhI}(10)$
1158	0.13	3.80	-	-	$\delta\text{CHI}(77)$, $\nu\text{PhI}(15)$
1152	36.91	2.25	-	1152	$\delta\text{CH}_3(54)$, $\delta\text{CHII}(40)$
1150	14.77	2.82	-	-	$\delta\text{CHIII}(28)$, $\nu\text{CN}(45)$
1136	0.69	4.53	1136	1135	$\delta\text{CHI}(76)$, $\nu\text{PhI}(16)$
1125	51.16	6.92	-	-	$\nu\text{CN}(43)$, $\delta\text{CH}_2(12)$,

					$\delta\text{CH}_3(11)$, $\nu\text{CO}(12)$
1124	51.12	7.55	-	-	$\delta\text{CHIII}(52)$, $\nu\text{CN}(10)$
1123	0.45	0.24	-	-	$\delta\text{CH}_3(89)$
1122	20.09	3.05	-	-	$\delta\text{CH}_3(81)$
1121	5.75	3.74	-	-	$\delta\text{CH}_3(93)$
1110	100.57	16.49	-	-	$\nu\text{CN}(43)$, $\delta\text{CH}_2(44)$
1103	79.42	6.72	-	1102	$\delta\text{CH}_2(61)$, $\delta\text{CHIII}(17)$
1083	2.46	1.97	1080	1085	$\delta\text{CHIII}(27)$, $\nu\text{PhIII}(51)$
1062	8.67	0.80	-	1059	$\nu\text{PhI}(26)$, $\delta\text{CHI}(55)$
1054	189.12	5.88	-	1049	$\nu\text{CO}(68)$, $\delta\text{CHI}(20)$
1017	75.11	17.33	1020	1020	$\nu\text{CO}(42)$, $\nu\text{PhII}(40)$
1009	7.15	18.68	-	-	$\nu\text{PhI}(52)$, $\delta\text{PhI}(12)$, $\delta\text{CHI}(12)$
1007	10.19	35.43	-	1005	$\nu\text{PhIII}(17)$, $\delta\text{CHIII}(53)$
998	14.74	1.55	-	-	$\nu\text{CC}(21)$, $\delta\text{CH}_2(52)$
992	26.94	1.35	-	-	$\nu\text{CC}(28)$, $\delta\text{CH}_2(52)$
991	7.57	43.68	-	-	$\nu\text{CC}(63)$, $\delta\text{CH}_2(14)$
978	0.04	48.31	-	-	$\delta\text{PhI}(64)$, $\nu\text{PhI}(36)$
977	97.16	13.12	-	-	$\nu\text{CO}(78)$, $\delta\text{PhII}(10)$
965	7.72	2.29	-	-	$\nu\text{CN}(47)$, $\delta\text{C}=\text{O}(10)$
964	0.07	0.18	-	-	$\gamma\text{CHIII}(87)$, $\tau\text{PhIII}(11)$
962	1.28	1.98	-	962	$\gamma\text{CHI}(67)$, $\tau\text{PhI}(11)$
953	26.72	2.03	-	-	$\nu\text{CO}(49)$, $\nu\text{PhII}(15)$
949	0.04	0.02	-	-	$\gamma\text{CHI}(92)$
946	1.47	0.12	944	943	$\gamma\text{CHIII}(87)$
928	14.18	4.87	-	-	$\delta\text{CH}_2(48)$, $\nu\text{CC}(20)$
910	6.11	4.38	911	911	$\nu\text{CO}(67)$, $\delta\text{CH}_2(15)$
897	3.93	1.24	-	-	$\delta\text{CH}_2(69)$, $\gamma\text{C}=\text{O}(12)$
894	1.25	4.52	-	892	$\gamma\text{CHI}(77)$, $\tau\text{PhI}(10)$
869	8.38	6.44	872	-	$\delta\text{PhIII}(31)$, $\delta\text{PhIV}(12)$, $\nu\text{CN}(12)$
857	20.77	0.73	-	-	$\gamma\text{CHII}(63)$, $\tau\text{PhII}(17)$

856	15.13	0.25	-	-	γ CHII(64), τ PhII(18)
853	1.88	0.02	850	850	γ CHIII(81), τ PhIII(10)
827	6.06	1.79	-	-	γ CHI(45), δ PhIII(10)
826	3.89	1.18	824	824	γ CHI(62)
800	5.22	25.96	-	-	ν CC(17), δ PhI(49)
788	15.13	12.08	-	790	δ PhII(41), ν CO(17)
771	1.00	0.96	773	772	γ C=O(38), τ PhIV(21), τ PhIII(13), γ CHIII(10)
770	6.61	1.09	-	-	τ PhII(38), γ CO(46)
751	56.89	1.03	750	748	γ CHIII(58), τ PhIII(18), τ PhIV(13)
741	8.83	3.93	-	-	δ CH ₂ (36), τ PhI(14), γ CHI(10)
734	17.73	1.39	-	-	τ PhI(19), γ CHI(20), δ CH ₂ (21)
725	10.17	3.07	723	728	ν CC(21), δ CH ₂ (13), τ PhII(12), δ CN(19)
694	10.14	5.53	696	696	δ PhIII(43), γ CHI(24)
686	28.08	0.92	-	-	τ PhI(47), γ CHI(22)
684	30.30	10.33	-	682	τ PhI(22), γ C=O(46), τ PhIII(10)
678	14.44	5.85	-	-	τ PhIII(38), γ C=O(30), γ CHIII(14)
668	4.38	1.92	-	-	ν CS(49), γ C=O(15), τ PhII(10)
652	2.20	3.87	655	653	ν CS(18), δ CO(18), γ CO(12), τ PhII(10)
644	13.28	4.87	-	-	ν CS(19), γ CN(17), τ PhII(15), δ CO(15)
635	1.04	1.33	632	633	ν CS(46), τ PhIV(32)
616	7.74	2.11	-	618	γ CN(18), τ PhII(37), γ CO(19)

613	5.10	11.32	-	-	γ NH(45), δ PhI(12), δ C=O(10)
611	1.02	2.05	-	609	δ PhI(69)
594	18.10	4.12	600	592	τ PhII(27), γ CN(13)
585	2.85	3.67	-	-	δ PhIII(48), δ CS(16)
578	3.96	1.28	-	-	δ PhI(38), δ PhIII(18)
541	10.06	11.31	-	540	γ CO(14), δ CO(29), δ PhII(14)
525	31.59	18.58	525	525	δ PhIV(32), γ NH(10), τ CN(10)
519	89.29	6.52	-	-	τ CN(33), γ NH(21)
516	11.95	0.50	-	-	τ PhIII(53), τ PhIV(13)
495	2.85	1.84	500	502	δ PhII(37), δ C=O(43), δ CN(10)
493	9.33	0.72	-	-	τ PhI(53), γ CC(25)
470	4.47	1.27	-	471	δ C=O(46), δ CN(17), δ PhII(16)
455	4.90	2.45	456	454	δ PhIV(38), δ PhI(32)
433	5.77	1.22	-	-	δ CN(17), δ CO(12), γ CO(15)
428	2.32	1.85	425	426	τ PhIII(61), τ PhIV(15)
399	0.06	0.11	-	402	τ PhI(81)
397	5.60	2.69	-	-	δ CH ₂ (19), δ CS(25), δ PhIV(15)
390	3.76	1.86	-	391	δ CN(42), δ C=O(17), τ PhI(10)
363	5.32	0.83	-	365	δ PhII(29), γ CO(12), δ CO(22)
343	2.21	1.59	-	342	τ PhII(21), δ CO(24), δ CN(15)
336	1.56	5.12	-	-	γ CN(23), δ CH ₂ (21), τ PhI(12), τ PhIII(10)
331	1.63	0.28	-	-	δ CC(45), τ PhIII(24)
327	1.19	1.27	-	325	τ PhII(36), δ CO(36)
303	1.43	8.69	-	305	δ CH ₂ (30), δ CS(20)

295	3.55	0.97	-	-	$\delta\text{CN}(20)$, $\tau\text{PhII}(18)$, $\delta\text{CO}(13)$
287	2.99	0.24	-	-	$\delta\text{CO}(42)$, $\tau\text{PhII}(16)$, $\delta\text{CN}(10)$
285	0.90	4.45	-	283	$\tau\text{PhII}(18)$, $\delta\text{CO}(18)$, $\delta\text{CN}(16)$, $\delta\text{CH}_2(14)$
278	0.46	1.15	-	-	$\tau\text{PhIII}(39)$, $\tau\text{PhIV}(26)$, $\gamma\text{CS}(12)$
273	0.22	3.19	-	-	$\delta\text{CS}(21)$, $\delta\text{CH}_2(34)$
250	3.39	1.67	-	250	$\tau\text{PhI}(17)$, $\delta\text{CS}(24)$, $\delta\text{CH}_2(11)$
242	11.23	2.45	-	-	$\tau\text{PhII}(23)$, $\delta\text{CO}(30)$, $\gamma\text{CO}(11)$
230	3.01	2.27	-	231	$\tau\text{PhI}(26)$, $\gamma\text{CN}(10)$, $\delta\text{CS}(16)$
188	5.92	1.91	-	-	$\tau\text{PhII}(23)$, $\delta\text{CO}(24)$, $\gamma\text{CO}(12)$
186	1.39	5.10	-	183	$\tau\text{CH}_2(12)$, $\gamma\text{CO}(11)$, $\delta\text{CH}_2(20)$, $\delta\text{CN}(10)$
167	0.05	0.13	-	168	$\tau\text{CH}_3(82)$
152	0.01	0.71	-	-	$\tau\text{PhIV}(53)$, $\tau\text{PhIII}(19)$
150	0.44	0.83	-	-	$\tau\text{CH}_3(62)$, $\delta\text{CO}(10)$
147	0.43	0.80	-	-	$\tau\text{CH}_3(62)$, $\tau\text{CH}_3(11)$
133	2.71	0.72	-	-	$\gamma\text{CO}(43)$, $\tau\text{CH}_3(17)$
130	2.35	0.93	-	-	$\gamma\text{CN}(30)$, $\tau\text{PhIV}(39)$
100	3.57	0.76	-	-	$\tau\text{CO}(22)$, $\delta\text{CS}(23)$, $\gamma\text{CN}(15)$
93	0.49	0.55	-	-	$\tau\text{PhIV}(34)$, $\tau\text{PhIII}(10)$, $\tau\text{CH}_2(10)$, $\tau\text{CS}(10)$
85	5.27	1.87	-	-	$\tau\text{CO}(35)$, $\delta\text{CO}(20)$, $\tau\text{PhII}(10)$
84	0.89	4.63	-	-	$\gamma\text{CC}(24)$, $\delta\text{CH}_2(23)$, $\tau\text{PhIV}(11)$
80	0.29	1.43	-	-	$\tau\text{CH}_2(41)$, $\tau\text{CC}(11)$
77	0.57	0.85	-	-	$\tau\text{CO}(39)$, $\tau\text{PhII}(20)$
73	2.37	1.75	-	-	$\tau\text{CO}(53)$, $\tau\text{PhII}(10)$
65	3.68	2.35	-	-	$\tau\text{CO}(27)$, $\gamma\text{NH}(21)$, $\tau\text{CN}(25)$
55	1.81	1.80	-	-	$\tau\text{C}=\text{O}(27)$, $\tau\text{CN}(24)$, $\gamma\text{NH}(11)$

46	0.29	0.64	-	-	τ CO(30), τ CS(18), τ C=O(20)
41	1.92	1.00	-	-	τ CO(69), τ PhIV(14)
34	0.74	0.80	-	-	τ PhIV(22), τ CC(15), γ CN(16), δ CH ₂ (19)
29	0.07	4.47	-	-	τ CC(70), τ CH ₂ (13)
25	0.04	3.39	-	-	τ CN(40), τ CH ₂ (22)
17	0.25	1.32	-	-	τ CN(35), τ CH ₂ (26)
12	0.34	1.46	-	-	τ CN(28), τ CH ₂ (32)
9	0.18	1.54	-	-	τ CH ₂ (51), τ CS(15)
5	0.35	1.42	-	-	τ CH ₂ (41), τ C=O(36)

^a ν -stretching; δ -in-plane deformation; γ -out-of-plane deformation; τ -torsion; potential energy distribution (%) is given in brackets in the assignment column; PhI-mono substituted phenyl ring; PhII-poly substituted phenyl ring; PhIII-ortho-substituted phenyl ring; PhIV-Quinazoline ring.

Table 3

The predicted ^1H and ^{13}C NMR isotropic chemical shifts (with respect to TMS, all values are in ppm)

Atom	σ_{TMS}	B3LYP/6-311++G(d,p)(5D,7F) σ_{calc}	$\delta_{\text{calc}}(\sigma_{\text{TMS}} - \sigma_{\text{calc}})$
7H	32.7711	25.27	7.5011
9H	32.7711	24.8909	7.8802
11H	32.7711	25.1059	7.6652
13H	32.7711	24.0641	8.707
17H	32.7711	28.9029	3.8682
18H	32.7711	27.8366	4.9345
20H	32.7711	29.3553	3.4158
21H	32.7711	29.2512	3.5199
24H	32.7711	24.8691	7.902
26H	32.7711	24.9829	7.7882
28H	32.7711	25.062	7.7091
30H	32.7711	24.9295	7.8416
32H	32.7711	24.7874	7.9837
35H	32.7711	29.3829	3.3882
36H	32.7711	29.2657	3.5054
43H	32.7711	25.8578	6.9133
44H	32.7711	25.697	7.0741
48H	32.7711	26.5198	6.2513
51H	32.7711	28.3205	4.4506
52H	32.7711	28.6353	4.1358
53H	32.7711	28.4249	4.3462
56H	32.7711	28.8313	3.9398
57H	32.7711	27.6796	5.0915
58H	32.7711	28.4061	4.365
61H	32.7711	27.9193	4.8518
62H	32.7711	29.0842	3.6869
63H	32.7711	28.6214	4.1497

65H	32.7711	29.96	2.8111
66H	32.7711	29.0594	3.7117
5C	196.852	49.9156	146.9364
6C	196.852	70.7236	126.1284
8C	196.852	64.0103	132.8417
10C	196.852	72.2696	124.5824
12C	196.852	67.1836	129.6684
14C	196.852	75.1201	121.7319
15C	196.852	38.5283	158.3237
16C	196.852	141.5737	55.2783
19C	196.852	154.5672	42.2848
22C	196.852	59.2787	137.5733
23C	196.852	67.4344	129.4176
25C	196.852	68.5341	128.3179
27C	196.852	70.2629	126.5891
29C	196.852	68.1668	128.6852
31C	196.852	67.2496	129.6024
33C	196.852	34.9299	161.9221
34C	196.852	155.6544	41.1976
37C	196.852	32.3859	164.4661
40C	196.852	61.5729	135.2791
41C	196.852	79.2009	117.6511
42C	196.852	78.616	118.236
45C	196.852	40.1445	156.7075
46C	196.852	40.626	156.226
47C	196.852	48.3367	148.5153
50C	196.852	131.2575	65.5945
55C	196.852	131.7139	65.1381
60C	196.852	131.7809	65.0711
64C	196.852	158.8492	38.0028

Table 4

Values of the Fukui function considering Mulliken charges

Atom	f_j^-	f_j^+	∇f_k
S1	0.049496	0.094676	0.04518
O2	0.053204	0.050081	-0.003123
N3	0.002604	0.040258	0.037654
N4	0.003685	0.00925	0.005565
C5	0.028039	0.008109	-0.01993
C6	0.004757	0.022197	0.01744
H7	0.038773	0.036361	-0.002412
C8	0.034635	0.004609	-0.030026
H9	0.057709	0.043505	-0.014204
C10	0.005965	0.024966	0.019001
H11	0.053636	0.051409	-0.002227
C12	0.019488	0.015776	-0.003712
H13	0.046079	0.038659	-0.00742
C14	0.016345	0.012175	-0.00417
C15	0.046013	0.021743	-0.02427
C16	-0.014385	-0.015098	-0.000713
H17	0.020964	0.015816	-0.005148
H18	0.021722	0.023344	0.001622
C19	-0.007184	-0.009855	-0.002671
H20	0.003814	0.006464	0.00265
H21	0.008549	0.015603	0.007054
C22	0.005927	0.008375	0.002448
C23	0.002312	0.007203	0.004891
H24	0.006531	0.01592	0.009389
C25	0.002432	0.004828	0.002396
H26	0.023296	0.030151	0.006855
C27	0.008859	0.01335	0.004491
H28	0.027079	0.035284	0.008205
C29	0.002447	0.005317	0.00287
H30	0.019561	0.026993	0.007432

C31	0.003392	0.007496	0.004104
H32	-0.002855	0.004456	0.007311
C33	0.025446	0.007563	-0.017883
C34	-0.014477	-0.020399	-0.005922
H35	0.019535	0.022571	0.003036
H36	-0.004634	0.002917	0.007551
C37	0.01746	-0.000735	-0.018195
O38	0.034736	0.029555	-0.005181
N39	-0.004853	0.013034	0.017887
C40	0.022621	0.002325	-0.020296
C41	0.011431	0.005115	-0.006316
C42	0.008234	0.007912	-0.000322
H43	0.023478	0.015187	-0.008291
H44	0.033442	0.027185	-0.006257
C45	0.009232	0.00889	-0.000342
C46	0.014228	0.012041	-0.002187
C47	0.038568	0.026422	-0.012146
H48	0.027234	0.020781	-0.006453
O49	0.005145	0.013126	0.007981
C50	-0.017589	-0.015852	0.001737
H51	0.012598	0.011047	-0.001551
H52	0.017742	0.016449	-0.001293
H53	0.026666	0.02273	-0.003936
O54	0.010639	0.014087	0.003448
C55	-0.012331	-0.010775	0.001556
H56	0.005733	0.003501	-0.002232
H57	0.007151	0.005862	-0.001289
H58	0.026963	0.024492	-0.002471
O59	0.010983	0.015946	0.004963
C60	-0.006827	-0.00548	0.001347
H61	0.010251	0.009891	-0.00036
H62	-0.009873	-0.011672	-0.001799
H63	0.02394	0.022265	-0.001675

C64	-0.010582	-0.007417	0.003165
H65	0.025699	0.022516	-0.003183
<u>H66</u>	<u>0.019121</u>	<u>0.019501</u>	<u>0.00038</u>

Table 5

Second-order perturbation theory analysis of Fock matrix in NBO basis corresponding to the intramolecular bonds of the title compound.

Donor(i)	Type	ED/e	Acceptor(j)	Type	ED/e	E(2) ^a	E(j)-E(i) ^b	F(i,j) ^c
S1-C33	σ	1.97562	N3-C5	σ^*	0.02465	4.56	1.13	0.064
-	-	-	N4-C15	σ^*	0.09782	3.58	1.05	0.056
-	-	-	C34-C64	σ^*	0.01395	1.00	1.01	0.028
O2-C15	σ	1.99419	O2-C15	π^*	0.32185	1.73	1.38	0.044
-	-	-	N4-C16	σ^*	0.02990	2.12	1.22	0.045
-	-	-	N4-C33	σ^*	0.06033	1.57	1.32	0.041
-	-	-	C5-C6	σ^*	0.02461	2.52	1.45	0.054
-	π	1.98350	N3-C33	π^*	0.37197	7.21	0.36	0.077
N4-C15	σ	1.98125	S1-C33	σ^*	0.05380	3.02	0.97	0.049
-	-	-	N4-C16	σ^*	0.02990	1.11	1.11	0.031
-	-	-	N4-C33	σ^*	0.06033	2.07	1.22	0.045
-	-	-	C12-C14	σ^*	0.02097	1.87	1.36	0.045
N4-C33	σ	1.98739	O2-C15	σ^*	0.00857	2.10	1.44	0.049
-	-	-	N3-C33	σ^*	0.01654	1.29	1.25	0.037
-	-	-	N4-C16	σ^*	0.02990	1.62	1.17	0.039
-	-	-	N3-C33	σ^*	0.01654	2.57	1.28	0.051
-	-	-	C5-C14	σ^*	0.03896	3.56	1.25	0.060
-	-	-	C6-C8	σ^*	0.01354	2.38	1.28	0.050
-	-	-	C14-C15	σ^*	0.06034	2.88	1.16	0.052
C5-C14	σ	1.97303	O2-C15	σ^*	0.00857	2.73	1.30	0.053
-	-	-	N3-C5	σ^*	0.02465	1.29	1.18	0.035
-	-	-	C5-C6	σ^*	0.02461	3.37	1.26	0.058
-	-	-	C12-C14	σ^*	0.02097	4.01	1.27	0.064
-	-	-	C14-C15	σ^*	0.06034	1.72	1.17	0.040
C14-C15	σ	1.97503	O2-C15	σ^*	0.00857	1.47	1.28	0.039
-	-	-	N4-C16	σ^*	0.02990	3.10	1.00	0.050
-	-	-	C5-C6	σ^*	0.02461	2.73	1.23	0.052
-	-	-	C5-C14	σ^*	0.03896	2.41	1.24	0.049
-	-	-	C10-C12	σ^*	0.01387	2.03	1.28	0.046

-	-	-	C12-C14	σ^*	0.02097	2.26	1.25	0.047
C16-C19	σ	1.97251	C22-C31	π^*	0.34809	2.45	0.65	0.039
C37-O38	π	1.98677	C34-C64	σ^*	0.01395	1.74	0.72	0.032
C37-N39	σ	1.98909	N39-C40	σ^*	0.03190	1.66	1.23	0.041
C40-C41	σ	1.97187	C37-N39	σ^*	0.08000	1.83	1.17	0.042
-	-	-	N39-C40	σ^*	0.03190	1.00	1.12	0.030
-	-	-	C40-C42	σ^*	0.02572	3.78	1.28	0.062
-	-	-	C41-C45	σ^*	0.02528	2.46	1.28	0.050
-	-	-	C45-O59	σ^*	0.02538	3.84	1.07	0.057
C40-C42	σ	1.97208	N39-C40	σ^*	0.03190	1.06	1.12	0.031
-	-	-	C40-C41	σ^*	0.02490	3.79	1.28	0.062
-	-	-	C42-C46	σ^*	0.02507	2.54	1.28	0.051
-	-	-	C46-O54	σ^*	0.02508	3.68	1.08	0.056
C41-C45	σ	1.97359	N39-C40	σ^*	0.03190	4.07	1.12	0.060
-	-	-	C40-C41	σ^*	0.02490	2.83	1.28	0.054
-	-	-	C45-C47	σ^*	0.04731	3.22	1.26	0.057
-	-	-	C47-O49	σ^*	0.02317	3.66	1.07	0.056
-	-	-	O59-C60	σ^*	0.00935	1.45	0.99	0.034
-	π	1.67222	C40-C42	π^*	0.40047	21.83	0.29	0.072
-	-	-	C46-C47	π^*	0.40309	18.09	0.28	0.065
-	-	-	O59-C60	σ^*	0.00935	1.72	0.54	0.030
C42-C46	σ	1.97320	N39-C40	σ^*	0.03190	4.25	1.12	0.062
-	-	-	C40-C42	σ^*	0.02572	2.91	1.28	0.054
-	-	-	C46-C47	π^*	0.40309	3.21	1.26	0.057
-	-	-	C47-O49	σ^*	0.02317	3.65	1.07	0.056
-	-	-	O54-C55	σ^*	0.00917	1.53	0.99	0.035
C45-C47	σ	1.97727	C41-C45	σ^*	0.02528	3.23	1.29	0.058
-	-	-	C46-C47	σ^*	0.04620	3.03	1.26	0.056
-	-	-	C46-O54	σ^*	0.02508	3.59	1.08	0.056
C46-C47	σ	1.97682	C42-C46	σ^*	0.02507	3.21	1.28	0.057
-	-	-	C45-C47	σ^*	0.04731	3.00	1.26	0.055
-	-	-	C45-O59	σ^*	0.02538	3.54	1.08	0.055
-	-	-	O49-C50	σ^*	0.00992	1.17	0.99	0.030

LPS1	σ	1.98015	N3-C33	σ^*	0.01654	3.28	1.22	0.056
-	π	1.82884	N3-C33	π^*	0.37197	24.95	0.25	0.074
LPO2	σ	1.97619	N4-C15	σ^*	0.09782	1.55	1.07	0.037
-	-	-	C14-C15	σ^*	0.06034	2.77	1.15	0.051
-	π	1.85356	N4-C15	σ^*	0.09782	30.34	0.65	0.127
-	-	-	C14-C15	σ^*	0.06034	18.01	0.72	0.104
LPN3	σ	1.89180	S1-C33	σ^*	0.05380	3.41	0.51	0.038
-	-	-	N4-C33	σ^*	0.06033	16.18	0.76	0.100
-	-	-	C5-C6	σ^*	0.02461	1.52	0.90	0.034
-	-	-	C5-C14	σ^*	0.03896	9.20	0.90	0.083
LPN4	σ	1.59160	O2-C15	π^*	0.32185	49.92	0.28	0.108
-	-	-	N3-C33	π^*	0.37197	56.09	0.26	0.109
-	-	-	C16-C19	σ^*	0.02344	5.87	0.63	0.061
LPO38	σ	1.97557	C37-N39	σ^*	0.08000	1.62	1.13	0.039
-	-	-	C37-C64	σ^*	0.06478	2.17	1.04	0.043
-	-	-	C37-N39	σ^*	0.08000	26.53	0.70	0.123
-	-	-	C37-C64	σ^*	0.06478	20.49	0.61	0.102
LPN39	σ	1.71037	C37-O38	π^*	0.26078	59.79	0.28	0.116
-	-	-	C40-C41	σ^*	0.02490	4.67	0.82	0.059
-	-	-	C40-C42	σ^*	0.02572	4.71	0.82	0.060
-	-	-	C40-C42	π^*	0.40047	10.32	0.28	0.049
LPO49	-	1.94413	C45-C47	σ^*	0.04731	3.99	1.08	0.059
-	-	-	C46-C47	π^*	0.40309	4.41	0.55	0.048
-	-	-	C45-C47	σ^*	0.04731	4.21	0.89	0.055
-	-	-	C46-C47	σ^*	0.04620	7.77	0.89	0.075
-	-	-	C46-C47	π^*	0.40309	3.07	0.36	0.033
LPO54	σ	1.95217	C46-C47	σ^*	0.04620	7.06	1.04	0.077
-	-	-	C46-C47	π^*	0.40309	1.97	0.51	0.031
-	π	1.90599	C42-C46	σ^*	0.02507	4.70	0.93	0.060
-	-	-	C46-C47	σ^*	0.04620	1.79	0.91	0.037
-	-	-	C46-C47	π^*	0.40309	10.14	0.38	0.061
LPO59	σ	1.95138	C41-C45	π^*	0.37757	2.20	0.52	0.033
-	-	-	C45-C47	σ^*	0.04731	6.82	1.04	0.075

-	π	1.90982	C41-C45	σ^*	0.02528	5.06	0.94	0.063
-	-	-	C41-C45	π^*	0.37757	9.12	0.39	0.058
-	-	-	C45-C47	σ^*	0.04731	1.95	0.92	0.038

^aE(2) means energy of hyper-conjugative interactions (stabilization energy in kJ/mol)

^bEnergy difference (a.u) between donor and acceptor i and j NBO orbitals

^cF(i,j) is the Fock matrix elements (a.u) between i and j NBO orbitals

Table 6

NBO results showing the formation of Lewis and non-Lewis orbitals.

Bond(A-B)	ED/e ^a	EDA%	EDB%	NBO	s%	p%
σ S1-C33	1.97562	45.26	54.74	0.6727(sp ^{5.06})S+	16.38	83.62
-	-0.65218	-	-	0.7399(sp ^{2.43})C	29.10	70.90
σ O2-C15	1.99419	64.90	35.10	0.8056(sp ^{1.39})O+	41.78	58.22
-	-1.06199	-	-	0.5925(sp ^{2.05})C	32.71	67.29
π O2-C15	1.98350	69.77	30.23	0.8353(sp ^{1.00})O+	0.00	100.0
-	-0.36441	-	-	0.5498(sp ^{1.00})C	0.00	100.0
σ N4-C15	1.98125	64.433	35.57	0.8027(sp ^{2.01})N+	33.18	66.82
-	-0.79247	-	-	0.5964(sp ^{2.46})C	28.82	71.18
σ N4-C33	1.98739	62.57	37.43	0.7910(sp ^{1.88})N+	34.69	65.31
-	-0.84365	-	-	0.6118(sp ^{1.98})C	33.55	66.45
σ C5-C14	1.97303	49.32	50.68	0.7022(sp ^{1.82})C+	35.47	64.53
-	-0.69758	-	-	0.7119(sp ^{1.95})C	33.84	66.16
σ C14-C15	1.97503	51.68	48.32	0.7189(sp ^{2.26})C+	30.69	69.31
-	-0.67705	-	-	0.6951(sp ^{1.61})C	38.35	61.65
σ C16-C19	1.97251	50.44	49.56	0.7102(sp ^{2.51})C+	28.48	71.52
-	-0.59523	-	-	0.7040(sp ^{2.93})C	25.41	74.59
π C37-O38	1.98677	30.95	69.05	0.5563(sp ^{99.99})C+	0.06	99.94
-	-0.36097	-	-	0.8310(sp ^{99.99})O	0.12	99.88
σ C37-N39	1.98909	36.81	63.19	0.6067(sp ^{2.23})C+	30.90	69.10
-	-0.82221	-	-	0.7949(sp ^{1.69})N	37.18	62.82
σ C40-C41	1.97187	50.67	49.33	0.7118(sp ^{1.76})C+	36.19	63.81
-	-0.70911	-	-	0.7024(sp ^{1.83})C	35.21	64.79
σ C40-C42	1.97208	50.59	49.41	0.7118(sp ^{1.74})C+	36.48	63.52
-	-0.71162	-	-	0.7029(sp ^{1.84})C	35.26	64.74
σ C41-C45	1.97359	50.01	49.99	0.7072(sp ^{1.88})C+	34.74	65.26
-	-0.71135	-	-	0.7071(sp ^{1.64})C	37.91	62.09
π C41-C45	1.67222	51.83	48.17	0.7199(sp ^{1.00})C+	0.00	100.0
-	-0.26477	-	-	0.6941(sp ^{99.99})C	0.01	99.99
σ C42-C46	1.97320	50.06	49.94	0.7075(sp ^{1.88})C+	34.69	65.31
-	-0.71023	-	-	0.7067(sp ^{1.65})C	37.75	62.25
σ C45-C47	1.97727	49.89	50.11	0.7063(sp ^{1.73})C+	36.64	63.36

-	-0.71715	-	-	0.7079(sp ^{1.68})C	37.32	62.68
σC46-C47	1.97682	49.89	50.11	0.7063(sp ^{1.72})C+	36.74	63.26
-	-0.71742	-	-	0.7079(sp ^{1.68})C	37.26	62.74
n1S1	1.98015	-	-	sp ^{0.47}	68.01	31.99
-	-0.63412	-	-	-	-	-
n2S1	1.82884	-	-	sp ^{1.00}	0.00	100.0
-	-0.24978	-	-	-	-	-
n1O2	1.97619	-	-	sp ^{0.72}	58.17	41.83
-	-0.67228	-	-	-	-	-
n2O2	1.85356	-	-	sp ^{99.99}	0.01	99.99
-	-0.24517	-	-	-	-	-
n1N3	1.89180	-	-	sp ^{2.65}	27.36	72.64
-	-0.33826	-	-	-	-	-
n1N4	1.59160	-	-	sp ^{99.99}	0.02	99.98
-	-0.26515	-	-	-	-	-
n1O38	1.97557	-	-	sp ^{0.72}	58.12	41.88
-	-0.66684	-	-	-	-	-
n2O38	1.86700	-	-	sp ^{1.00}	0.01	99.99
-	-0.23949	-	-	-	-	-
n1N39	1.71037	-	-	sp ^{99.99}	0.09	99.91
-	-0.25583	-	-	-	-	-
n1O49	1.94413	-	-	sp ^{1.72}	36.67	63.33
-	-0.53312	-	-	-	-	-
n2O49	1.92712	-	-	sp ^{16.10}	5.84	94.16
-	-0.34379	-	-	-	-	-
n1O54	1.95217	-	-	sp ^{2.15}	31.68	68.32
-	-0.49570	-	-	-	-	-
n2O54	1.90599	-	-	sp ^{8.71}	10.29	89.71
-	-0.36606	-	-	-	-	-
n1O59	1.95138	-	-	sp ^{2.21}	31.15	68.85
-	-0.49278	-	-	-	-	-
n2O59	1.90982	-	-	sp ^{8.06}	11.03	88.97
-	-0.37165	-	-	-	-	-

^a ED/e is expressed in a.u.

Table 7. The binding affinity values of different poses of the title compound predicted by Autodock Vina.

Mode	Affinity (kcal/mol)	Distance from best mode (Å)	
		RMSD l.b.	RMSD u.b.
-	-		
1	-10.9	0.000	0.000
2	-10.6	1.026	1.185
3	-9.8	1.384	1.414
4	-9.7	0.682	0.531
5	-9.7	1.338	1.303
6	-9.7	1.351	1.657
7	-9.2	1.390	2.975
8	-8.6	4.450	3.224
9	-8.5	4.404	4.738