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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 Adel S.El-Azab<sup>a,b</sup>, Shyma Mary Y<sup>c</sup>, Sheena Mary Y<sup>c\*</sup>, C.Yohannan Panicker<sup>c,d</sup>, Alaa A.-M. Abdel-Aziz<sup>a,e</sup>, Menshawy A. Mohamed<sup>b,f</sup>, Stevan Armaković<sup>g</sup>, Sanja J. Armaković<sup>h</sup>, Christian Van Alsenov<sup>i</sup>

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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 wavenumbrs. From the MEP plot it is evident that the negative charge covers carbonyl group, mono substituted phenyl ring, O<sub>59</sub> 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 repesent 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-tri methoxyphenyl)propanamide as anticancer agents. Quinazolinones are associated with a wide range of biological and pharmacological activies such as analgesic [5], antiinflammatory [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 antitubercular agents. In the present work, IR and Raman spectra of the title ocmpound 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<sup>+</sup> =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 (<sup>1</sup>H and <sup>13</sup>C NMR) spectra were recorded on Bruker 500 MHz spectrometer using CDCl<sub>3</sub> as solvernt; the chemical shifts are expressed in  $\delta$  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

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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 withisothermal-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 1.3937-1.3997Å for PhI, 1.3928-1.4046Å for PhII and 1.3833-1.4090Å for PhII, which are in agreement with the reported values [39]. The bond lengths of C<sub>5</sub>-N<sub>3</sub> (1.3822Å), C<sub>33</sub>-N<sub>4</sub> (1.3857Å), C<sub>15</sub>-N<sub>4</sub> (1.4155Å), C<sub>40</sub>-N<sub>39</sub> (1.4252Å) and C<sub>37</sub>-N<sub>39</sub> (1.3780Å) are shorter than the normal C-N bond length (1.48Å) and this shows the effect of resonance in this region of the molecule [40]. The shortening of the bond length of C<sub>15</sub>-O<sub>2</sub> (1.2205Å) and C<sub>37</sub>-O<sub>38</sub> (1.2197Å) shows a double bond character. The C-O bond lengths of the title compound are C<sub>46</sub>-O<sub>54</sub> =1.3707Å, C<sub>55</sub>-O<sub>54</sub> = 1.4361Å, C<sub>47</sub>-O<sub>49</sub> = 1.3737Å, C<sub>50</sub>-O<sub>49</sub> = 1.4392Å, C<sub>45</sub>-O<sub>59</sub> = 1.3713Å and C<sub>60</sub>-O<sub>59</sub> = 1.4378Å and all the C-O bond lengths

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

In the title compound, the C-S bond lengths are 1.7846 and 1.8383Å while the reported values are in the range 1.7675-1.8641Å [43] and 1.7710-1.8110Å [44]. At C<sub>22</sub> position, the bond angles are  $C_{31}$ - $C_{22}$ - $C_{23} = 118.6^{\circ}$ ,  $C_{31}$ - $C_{22}$ - $C_{19} = 120.7^{\circ}$  and  $C_{23}$ - $C_{22}$ - $C_{19}$ = 120.7° and the reduction in the angle  $C_{31}$ - $C_{22}$ - $C_{23}$  is due to presence of adjacent methylene groups. At N<sub>4</sub> position, the bond angles  $C_{33}$ -N<sub>4</sub>- $C_{15}$  is increased by 1.0°,  $C_{33}$ - $N_4$ - $C_{16}$  is increased by 2.6° and  $C_{15}$ - $N_4$ - $C_{16}$  is decreased by 3.6° from 120° and this is due to the interaction between  $O_2$  and the methylene at  $C_{16}$  position. At  $C_{15}$  position, the bond angles, N<sub>4</sub>-C<sub>15</sub>-C<sub>14</sub> is decreased by 5.4° and C<sub>14</sub>-C<sub>15</sub>-O<sub>2</sub> is increased by 5.0° from 120° and this variation is due to the interaction between  $O_2$  and the adjacent methylene groups. Similarly at C<sub>5</sub> position, the bond angles  $C_6-C_5-C_{14} = 118.9^\circ$ ,  $N_3-C_5-C_6 = 119.1^\circ$  and  $C_{14}$ - $C_5-N_3 = 122.0^\circ$  and this asymmetry in angles is due to the interaction between the quinazoline ring and PhIII ring. Similarly at  $C_{33}$  position, the bond angles  $N_3-C_{33}-N_4 =$ 124.9° and N<sub>4</sub>-C<sub>33</sub>-S<sub>1</sub> = 115.6° and this asymmetry in angles is due to the interaction between the quinazoline ring and adjacent moieties. Similarly at N<sub>39</sub> position, the bond angles  $C_{40}$ - $N_{39}$ - $C_{37}$  = 130.1°,  $C_{40}$ - $N_{39}$ - $H_{48}$  = 117.1° and  $C_{37}$ - $N_{39}$ - $H_{48}$  = 112.6° and this asymmetry in angles is due to the interaction between the NH group and the oxygen atom  $O_{38}$ . The quinazoline moeity is planar with respect to the phenyl ring PhIII, as is evident from the torsion angles  $C_6-C_5-N_3-C_{33} = -179.6^\circ$ ,  $C_6-C_5-C_{14}-C_{15} = -179.9^\circ$ ,  $C_{12}-C_{14}-C_{15}-N_4$ = 179.1° and  $C_{12}$ - $C_{14}$ - $C_5$ - $N_3$  = 179.9° and the CH<sub>2</sub> groups at  $C_{19}$  and  $C_{16}$  are tilted from the phenyl ring PhI, as is evident from the torsion angles,  $C_{29}$ - $C_{31}$ - $C_{22}$ - $C_{19}$  = -178.5°,  $C_{31}$ - $C_{22}-C_{19}-C_{16} = 89.7^{\circ}$ ,  $C_{25}-C_{23}-C_{22}-C_{19} = 178.5^{\circ}$  and  $C_{23}-C_{22}-C_{19}-C_{16} = -88.7^{\circ}$ . The propanamide group is tilted from the phenyl ring PhII according to the torsion angles,  $C_{46}-C_{42}-C_{40}-N_{39} = -178.7^{\circ}, C_{42}-C_{40}-N_{39}-C_{37} = -60.4^{\circ}, C_{45}-C_{41}-C_{40}-N_{39} = 177.7^{\circ} \text{ and } C_{41}-C_{40}-N$  $C_{40}$ - $N_{39}$ - $C_{37}$  = 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<sup>-1</sup> for PhI, 3078-3070 cm<sup>-1</sup> for PhII and 3077-3045 cm<sup>-1</sup> for

PhIII rings theoretically [45]. Experimentally bands are observed at 3065, 3031 cm<sup>-1</sup> in IR and 3060, 3034 cm<sup>-1</sup> in Raman spectrum. The phenyl ring stretching modes of the title compound are assigned at 1558, 1468, 1288 cm<sup>-1</sup> (IR), 1467 cm<sup>-1</sup> (Raman), in the range 1580-1290 cm<sup>-1</sup> (DFT) for PhI with PEDs in the range 53-76%, 1572, 1368 cm<sup>-1</sup> (IR), 1573, 1543, 1460, 1363, 1250 cm<sup>-1</sup> (Raman), in the range 1571-1247 cm<sup>-1</sup> (DFT) for PhII with PEDs in the range 40-84% and 1543 cm<sup>-1</sup> (Raman), in the range 1582-1306 cm<sup>-1</sup> (DFT) for PhIII with PEDs in the range 47-81%. In the present case the PED analysis gives ring breathing modes at 1009 cm<sup>-1</sup> for PhI, 1017 cm<sup>-1</sup> for PhII and 1083 cm<sup>-1</sup> for PhIII, as expected [45, 46]. For these ring breathing modes, IR intensities are less than 10 except for the mode 1017 cm<sup>-1</sup> which has an IR intensity of 75.11. Similarly the Raman activity for the mode 1083 cm<sup>-1</sup> is very low, while the other modes, 1009 and 1017 cm<sup>-1</sup> 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<sup>-1</sup> in IR, 1027 cm<sup>-1</sup> in Raman and 1032 cm<sup>-1</sup> theoretically. For ortho substituted phenyl ring the ring breathing mode is reported at 1041 cm<sup>-1</sup> [47] and at 1086, 1011 cm<sup>-1</sup> (theoretically) [48] and at 1020 cm<sup>-1</sup> (theoretically) [49]. For the title compound, the inplane CH deformation modes are assigned at 1136 cm<sup>-1</sup> (IR), 1135, 1059 cm<sup>-1</sup> (Raman) for PhI, 1182 cm<sup>-1</sup> (IR), 1181, 1152 cm<sup>-1</sup> (Raman) for PhII and 1204, 1005 cm<sup>-1</sup> (Raman) for PhIII. The DFT calculations give these modes in the ranges 1311-1062 cm<sup>-1</sup> for PhI, 1180-1152 cm<sup>-1</sup> for PhII and 1265-1007 cm<sup>-1</sup> 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<sup>-1</sup>, 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<sup>-1</sup> (IR), 962, 892, 824 cm<sup>-1</sup> (Raman), 962, 949, 894, 827, 826 cm<sup>-1</sup> (DFT) for PhI with low IR intensities and Raman activities, 856, 857 cm<sup>-1</sup> (DFT) for PhII with IR intensities around 20 and low Raman activities and 944, 850, 750 cm<sup>-1</sup> (IR), 943, 850, 748 cm<sup>-1</sup> (Raman), 964, 946, 853, 751 cm<sup>-1</sup> (DFT) for PhIII with low IR intensities and Raman activities except for the mode at 751 cm<sup>-1</sup>. 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<sup>-1</sup> (stretching), 1500-1300, 700-600 cm<sup>-1</sup> (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<sup>-1</sup> with PED around 50%. Mary et al. [52] reported a band at 3343 cm<sup>-1</sup> in the IR spectrum, 3340 cm<sup>-1</sup> in Raman spectrum and 3433 cm<sup>-1</sup> theoretically as N-H stretching mode. For the title compound, the C-N stretching modes are assigned at 1322, 1214, 1204 cm<sup>-1</sup> in Raman and in the range 1324-965 cm<sup>-1</sup> theoretically which are in agreement with literature [45, 50, 53, 54]. The C=N stretching mode is observed at 1515 cm<sup>-1</sup> in IR and 1519 cm<sup>-1</sup> 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<sup>-1</sup> in the IR spectrum, 633 cm<sup>-1</sup> in the Ramam spectrum and at 668, 635 cm<sup>-1</sup> theoretically as expected [45].

The C=O stretching mode [45, 50, 53] is expected in the region 1750-1650 cm<sup>-1</sup> and in the present case this modes appear at 1675, 1662 cm<sup>-1</sup> in the IR spectrum, and at 1680, 1660 cm<sup>-1</sup> in the Raman spectrum. The DFT calculations give these modes at 1673 and 1663 cm<sup>-1</sup> 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<sup>-1</sup> (IR), 772, 682, 502, 471 cm<sup>-1</sup> (Raman) and at 771, 684, 495, 470 cm<sup>-1</sup> theoretically which are expected in the regions  $625 \pm 70$  and  $540 \pm 80$  cm<sup>-1</sup>, respectively [45]. The C-O-C stretching modes are expected in the range 1200-850 cm<sup>-1</sup> [45, 55]. The skeletal C-O deformation can be found in the region  $320 \pm 50$  cm<sup>-1</sup> [45]. As expected, the C-O-C vibrations are assigned at 1196, 1054, 1017, 977, 953, 910 cm<sup>-1</sup> 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<sup>-1</sup> in the IR spectrum and at 1049, 1020, 911 cm<sup>-1</sup> in the Raman spectrum.

The stretching vibrations of the CH<sub>2</sub> group and deformation modes of CH<sub>2</sub> group (scissoring, wagging, twisting and rocking modes) appears in the regions  $3000 \pm 20$ ,  $2900 \pm 25$ ,  $1450 \pm 30$ ,  $1330 \pm 35$ ,  $1245 \pm 45$ ,  $780 \pm 55$  cm<sup>-1</sup> respectively [45, 50, 53]. The CH<sub>2</sub> stretching modes are observed at 2996, 2972, 2932 cm<sup>-1</sup> (IR), 3023, 2963, 2948, 2930 cm<sup>-1</sup> (Raman) and in the range 3025-2929 cm<sup>-1</sup> theoretically. The deformation modes of CH<sub>2</sub> are assigned at 1417, 1348, 1238 cm<sup>-1</sup> in the IR spectrum, 1330, 1322, 1273, 1214, 1102 cm<sup>-1</sup> in the Raman spectrum and in the ranges 1444-1420 (scissoring),

1417-1324 (wagging), 1301-1216 (twisting), 1161-928 (rocking) cm<sup>-1</sup> theoretically as expected [45, 50, 53]. For the title compound, the CH<sub>3</sub> stretching modes are assigned at 3008, 2979, 2902 cm<sup>-1</sup> in the Raman spectrum and in the range 3015-2900 cm<sup>-1</sup> theoretically and these modes are expected in the region 2900-3050 cm<sup>-1</sup> [45]. The deformation modes of the methyl group of the title compound are assinged as 1460, 1437, 1408, 1395 cm<sup>-1</sup> in the Raman spectrum and in the ranges 1456-1399 (scissoring) and 1170-1121 cm<sup>-1</sup> (rocking) theoretically as expected [45].

#### 4.3. NMR spectra

The <sup>1</sup>H and <sup>13</sup>C NMR isotropic shielding are calculated with the GIAO method [56,57]. The experimental NMR values are: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  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*= 6.5Hz), 1.64 (d, 3H, *J* = 6.0 Hz). <sup>13</sup>C NMR (DMSO-d<sub>6</sub>)  $\delta$ : 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:  $\sigma_{calc}$  (TMS) calculated previously at the same theoretical level and numerical values of chemical shift  $\delta_{calc} = \sigma_{calc}(TMS) - \sigma_{calc}$  together with calculated values of  $\sigma_{calc}$  (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<sub>2</sub> group between PhI and PhIV are in the range 4.9345-3.4158, CH<sub>2</sub> group near to the sulfur atom  $S_1$  are 7.5054, 7.3882, CH<sub>2</sub> 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<sub>3</sub> groups resonate theoretically in the range 4.8518-3.6869, 4.4506-4.1358, 5.0915-3.9398 ppm for the CH<sub>3</sub> groups at C<sub>60</sub>, C<sub>50</sub> and  $C_{55}$  positions. The range of <sup>13</sup>C NMR chemical shifts of aromatic carbon atoms are normally greater than 100 ppm [58, 59] and in the present work <sup>13</sup>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<sub>2</sub> groups are 55.2783 (C<sub>19</sub>), 42.2848 (C<sub>16</sub>), 41.1976 (C<sub>34</sub>), 38.0028

 $(C_{64})$  ppm and in the CH<sub>3</sub> groups are 65.0711 ( $C_{60}$ ), 65.5945 ( $C_{50}$ ), 65.1381 ppm ( $C_{55}$ ). The carbonyl group  $C_{37}$  posses 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 ( $C_{33}$ ) and 158.3237 ( $C_{15}$ ) 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 =  $-E_{HOMO} = 7.342$  and A =  $-E_{LUMO} = 5.004$  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 ( $\chi$ ) [61], chemical hardness ( $\eta$ ) 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 ( $\mu$ ) 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, O<sub>59</sub> 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:

$$I(r) = \sum_{i} \frac{\rho_{i}(\vec{r}) |\varepsilon_{i}|}{\rho(\vec{r})}, \qquad (1)$$

where  $\rho_i(\vec{r})$  represents the electronic density of the *i*-th molecular orbital at the point  $\vec{r}$ ,  $\varepsilon_i$  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/bohr<sup>3</sup>. 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/bohr<sup>3</sup>. 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/bohr<sup>3</sup>.

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:

$$f^{+} = \frac{\left(\rho^{N+\delta}(r) - \rho^{N}(r)\right)}{\delta}, \qquad (2)$$
$$f^{-} = \frac{\left(\rho^{N-\delta}(r) - \rho^{N}(r)\right)}{\delta}, \qquad (3)$$

where N represents the number of electrons in reference state of the molecule, while  $\delta$  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<sup>th</sup> atom site as,

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

$$f_i^{+} = q_i(N+1) - q_i(N)$$
 (5)

 $f_i^{0=\frac{1}{2}}[q_i(N+1) - q_i(N-1)]$  (6)

For an electrophilic  $f_j^{-}(\mathbf{r})$ , nucleophilic or free radical attack  $f_j^{+}(\mathbf{r})$ , 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<sup>th</sup> 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 ( $\Delta f(\mathbf{r})$ ), which is defined as the difference between the nucleophilic and electrophilic Fukui function and is given by,

$$\Delta f(\mathbf{r}) = [f^{+}(\mathbf{r}) - f^{-}(\mathbf{r})]$$
(7)

For nucleophilic attack,  $\Delta f(\mathbf{r}) > 0$  and for an electrophilic attack  $\Delta f(\mathbf{r}) < 0$ . Under this situation, dual descriptors  $\Delta f(\mathbf{r})$  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 S<sub>1</sub>, C<sub>6</sub> and N<sub>3</sub> (positive value i.e.  $\Delta f(\mathbf{r}) > 0$ ). Similarly the electrophilic attack site is C<sub>5</sub>, C<sub>15</sub>, C<sub>33</sub> and C<sub>37</sub> (negative value i.e.  $\Delta f(\mathbf{r}) < 0$ ). 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  $5.465 \times 10^{-30}$  esu, which is 42.04 times that of standard NLO material urea ( $0.13 \times 10^{-30}$  esu) [74]. The reported values of hyperpolarizability of similar derivatives are  $5.05 \times 10^{-30}$  esu and  $6.00 \times 10^{-30}$  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  $-53.027 \times 10^{-37}$  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: N<sub>3</sub>-C<sub>33</sub> from S<sub>1</sub> of n<sub>2</sub>(S<sub>1</sub>) $\rightarrow \pi^*(N_3-C_{33})$ , N<sub>4</sub>-C<sub>15</sub> from O<sub>2</sub> of n<sub>2</sub>(O<sub>2</sub>) $\rightarrow \sigma^*(N_4-C_{15})$ , N<sub>4</sub>-C<sub>33</sub> from N<sub>3</sub> of n<sub>1</sub>(N<sub>3</sub>) $\rightarrow \sigma^*(N_4-C_{33})$ , N<sub>3</sub>-C<sub>33</sub> from N<sub>4</sub> of n<sub>1</sub>(N<sub>4</sub>) $\rightarrow \pi^*(N_3-C_{33})$ , C<sub>37</sub>-N<sub>39</sub> from O<sub>38</sub> of n<sub>1</sub>(O<sub>38</sub>) $\rightarrow \sigma^*(C_{37}-N_{39})$ , C<sub>37</sub>-O<sub>38</sub> from N<sub>39</sub> of n<sub>1</sub>(N<sub>39</sub>) $\rightarrow \pi^*(C_{37}-O_{38})$ , C<sub>47</sub>-C<sub>46</sub> from O<sub>49</sub> of n<sub>1</sub>(N<sub>49</sub>) $\rightarrow \sigma^*(C_{47}-C_{46})$ , C<sub>47</sub>-C<sub>46</sub> from O<sub>54</sub> of n<sub>1</sub>(O<sub>54</sub>) $\rightarrow \pi^*(C_{47}-C_{46})$  and C<sub>41</sub>-C<sub>45</sub> from O<sub>59</sub> of n<sub>2</sub>(O<sub>59</sub>) $\rightarrow \pi^*(C_{41}-C_{45})$  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, considerbale 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 tow 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  $\pi$ - $\pi$  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 (Fig. 14). The inhibitor forms a stable complex with HNE as is evident from the binding affinity -10.9 kcal/mol ( $\Delta$ G 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. Themolecular orbital calculations such as natural bond orbitals, HOMO-LUMO energy gap and mappedp moolecular 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.

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#### **Figure captions**

- Fig.1 FT-IR spectrum of 3-(4-oxo-phenethyl-3,4-dihydroquinazolin-2-ylthio)-N-(3,4,5trimethoxyphenyl) 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 <sup>1</sup>H NMR spectrum of the title compound
- Fig.5<sup>13</sup>C 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-(3,4,5trimethoxyphenyl) propanamide
- Fig.8 ALIE surface of the title molecule
- Fig.9 Visualization of intra-molecular non-covalent interactions with their corresponding strengths [electron/bohr<sup>3</sup>]
- 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, pipi stacking interactions are represented by green and violet dotted lines, respectively

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Fig.3 Optimized geometry of 3-(4-oxo-phenethyl-3,4-dihydroquinazolin-2-ylthio)-N-(3,4,5trimethoxyphenyl) propanamide



Fig.4 <sup>1</sup>H NMR spectrum of the title compound



Fig.5<sup>13</sup>C NMR spectrum of the title compound



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



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



# 186.47 ALIE [kcal/mol] 346.19

#### Fig.8 ALIE surface of the title molecule



Fig.9 Visualization of intra-molecular non-covalent interactions with their corresponding strengths [electron/bohr<sup>3</sup>]





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

Bond lengths (Å)								
S1-C33	1.7846		S1-C34	1.8383		O2-C15	1.2205	K
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		С6-Н7	1.0834		C6-C8	1.3833	
С8-Н9	1.0846		C8-C10	1.4057		С10-Н11	1.0836	7
C10-C12	1.3834		С12-Н13	1.0831		C12-C14	1.4034	
C14-C15	1.4632		C16-H17	1.09		C16-H18	1.0887	
C16-C19	1.5405		С19-Н20	1.0932		C19-H21	1.0926	
C19-C22	1.5125		C22-C23	1.3995		C22-C31	1.3997	
С23-Н24	1.0856		C23-C25	1.3937		С25-Н26	1.0845	
C25-C27	1.3941		С27-Н28	1.0842		C27-C29	1.3939	
С29-Н30	1.0844		C29-C31	1.3938		С31-Н32	1.0856	
С34-Н35	1.0891		С34-Н36	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		С41-Н43	1.0833		C41-C45	1.3928	
С42-Н44	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	
С50-Н52	1.0937		С50-Н53	1.0894		O54-C55	1.4361	
С55-Н56	1.0953		С55-Н57	1.0912		С55-Н58	1.0892	
O59-C60	1.4378		С60-Н61	1.0919		С60-Н62	1.0946	
С60-Н63	1.0892	1	С64-Н65	1.0905		С64-Н66	1.0921	
Bond angles (°	<u>')</u>							
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	С5-С6-Н7		118.4
C5-C6-C8		120.1	H7-C6-C8		121.6	С6-С8-Н9		119.6

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

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	С10-С12-Н13	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	С17-С16-Н18	108.0
C17-C16-C19	111.0	H18-C16-C19	109.8	С16-С19-Н20	109.2
С16-С19-Н21	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	С22-С23-Н24	119.4
C22-C23-C25	120.8	H24-C23-C25	119.8	С23-С25-Н26	119.8
C23-C25-C27	120.1	H26-C25-C27	120.1	С25-С27-Н28	120.2
C25-C27-C29	119.6	H28-C27-C29	120.2	С27-С29-Н30	120.1
C27-C29-C31	120.1	H30-C29-C31	119.7	C22-C31-C29	120.8
С22-С31-Н32	119.6	С29-С31-Н32	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	Н35-С34-Н36	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
С37-N39-Н48	112.6	C40-N39-H48	117.1	N39-C40-C41	119.1
N39-C40-C42	121.1	C41-C40-C42	119.8	С40-С41-Н43	120.9
C40-C41-C45	120.2	H43-C41-C45	118.8	С40-С42-Н44	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
О49-С50-Н51	110.6	О49-С50-Н52	110.4	О49-С50-Н53	106.2
Н51-С50-Н52	110.1	Н51-С50-Н53	109.8	Н52-С50-Н53	109.7
C46-O54-C55	116.2	О54-С55-Н56	110.3	О54-С55-Н57	111.2
О54-С55-Н58	105.9	Н56-С55-Н57	110.1	Н56-С55-Н58	109.4
Н57-С55-Н58	110.0	C45-O59-C60	115.7	O59-C60-H61	111.1

О59-С60-Н62	110.3	О59-С60-Н63	105.9	Н61-С60-Н62	110.1
Н61-С60-Н63	109.9	Н62-С60-Н63	109.5	C34-C64-C37	114.6
С34-С64-Н65	110.8	С34-С64-Н66	107.2	С37-С64-Н65	105.8
С37-С64-Н66	110.6	H65-C64-H66	107.7		
Dihedral angles (°)					
C34-S1-C33-N3	1.2	C34-S1-C33-N4	-178.8	C33-S1-C34-35	-62.8
С33-S1-С34-Н36	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	С14-С5-С6-Н7	-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	С5-С6-С8-Н9	-179.8	C5-C6-C8-C10	0.1
Н7-С6-С8-Н9	-0.0	H7-C6-C8-C10	179.9	С6-С8-С10-Н11	-180.0
C6-C8-C10-C12	-0.0	Н9-С8-С10-Н11	-0.1	Н9-С8-С10-С12	179.9
С8-С10-С12-Н13	180.0	C8-C10-C12-C14	-0.1	Н11-С10-С12-Н13	-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
С17-С16-С19-Н20	64.3	С17-С16-С19-Н21	-178.5	C17-C16-C19-C22	-57.2
Н18-С16-С19-Н20	-176.3	Н18-С16-С19-Н21	-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
С19-С22-С23-Н24	-1.8	C19-C22-C23-C25	178.5	С31-С22-С23-Н24	179.8
C31-C22-C23-C25	0.1	C19-C22-C31-C29	-178.5	С19-С22-С31-Н32	1.9
C23-C22-C31-C29	-0.1	С23-С22-С31-Н32	-179.7	С22-С23-С25-Н26	179.7
C22-C23-C25-C27	-0.1	H24-C23-C25-H26	0.0	H24-C23-C25-C27	-179.8

С23-С25-С27-Н28	179.8	C23-C25-C27-C29	0.0	H26-C25-C27-H28	0.0
H26-C25-C27-C29	-179.7	С25-С27-С29-Н30	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
С27-С29-С31-Н32	179.7	H30-C29-C31-C22	-179.8	Н30-С29-С31-Н32	-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	Н35-С34-С64-Н65	-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
С64-С37-N39-Н48	171.4	O38-C37-C64-C34	109.8	O38-C37-C64-H65	-12.6
О38-С37-С64-Н66	-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	С47-О49-С50-Н51	-60.5
С47-О49-С50-Н52	61.6	С47-О49-С50-Н53	-179.6	С46-О54-С55-Н56	-62.0
С46-О54-С55-Н57	60.4	С46-О54-С55-Н58	179.8	С45-О59-С60-Н61	-60.5
С45-О59-С60-Н62	61.8	С45-О59-С60-Н63	-179.9		
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propar	namide				
<u>B3LYP/6-311++G(d,p) (5D, 7F)</u>			IR	Raman	Assignments <sup>a</sup>
<u>v(cm<sup>-1</sup></u>	)IR <sub>I</sub>	<u>R</u> A	υ(cm <sup>-1</sup>	$\upsilon(cm^{-1})$	_
3439	35.93	121.24	3325	-	υNH(100)
3978	0.90	61.26	-	-	υCHII(99)
3077	9.89	229.80	-	-	vCHIII(93)
3070	0.54	58.48	-	-	υCHII(99)
3069	8.59	98.48	-	-	vCHIII(98)
3065	19.88	364.07	3065	-	vCHI(94)
3060	9.01	141.92	-	3060	vCHIII(99)
3054	23.91	47.79	-	-	vCHI(99)
3045	6.92	92.28	-	-	vCHI(99)
3045	4.36	73.16	-	-	vCHIII(98)
3035	0.94	99.69	-	3034	vCHI(99)
3033	6.12	16.04	3031	3034	vCHI(99)
3025	2.65	41.08		3023	υCH <sub>2</sub> (96)
3015	5.18	12.36	_	-	υCH <sub>2</sub> (95)
3015	15.83	125.17	-	-	υCH <sub>3</sub> (95)
3014	21.44	94.70	-	-	vCH <sub>3</sub> (93)
3011	21.57	122.05	-	3008	υCH <sub>3</sub> (100)
2994	7.99	62.70	2996	-	υCH <sub>2</sub> (94)
2976	31.05	59.19	-	2979	υCH <sub>3</sub> (98)
2975	19.45	41.71	-	-	υCH <sub>3</sub> (97)
2973	18.48	31.83	-	-	υCH <sub>3</sub> (97)
2972	9.02	39.51	2972	-	υCH <sub>2</sub> (98)
2969	4.26	132.95	-	-	υCH <sub>2</sub> (96)
2964	7.11	62.80	-	2963	υCH <sub>2</sub> (99)
2950	8.44	117.43	-	2948	υCH <sub>2</sub> (98)

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

2929	12.59	109.55	2932	2930	υCH <sub>2</sub> (98)
2906	49.88	195.28	-	-	υCH <sub>3</sub> (99)
2904	55.41	126.35	-	2902	υCH <sub>3</sub> (98)
2900	54.43	109.93	-	-	υCH <sub>3</sub> (100)
1673	502.20	27.59	1675	1680	υC=O(73)
1663	387.95	42.19	1662	1660	υC=O(73)
1582	46.33	72.81	-	-	υPhIII(62), δCHIII(20)
1580	7.56	63.20	-	-	υPhI(56), δCHI(24)
1571	114.08	75.94	1572	1573	υPhII(57), δCHII(23)
1560	0.91	10.30	1558	-	υPhI(68), δCHI(18)
1546	114.25	17.46	-	-	vPhII(49), vPhIII(14)
1545	110.90	9.14	-	1543	vPhIII(49), vPhII(40)
1519	469.39	279.74	1515		υC=N(43), υPhIII(12)
1468	17.76	1.49	1468	1467	δCHI(21), υPhI(64)
1456	177.60	5.51	-	1460	δCH <sub>3</sub> (45), υPhII(40)
1451	8.15	7.37	-	-	δCH <sub>3</sub> (81)
1449	16.99	12.05	-	-	δCH <sub>3</sub> (72)
1446	2.22	8.68	-	-	δCH <sub>3</sub> (88)
1444	23.68	9.81	-	-	δCH <sub>2</sub> (76)
1442	113.45	31.27	-	-	δNH(44), υPhIII(47)
1436	15.33	15.72	-	1437	δCH <sub>3</sub> (43), δNH(12)
1433	19.81	8.36	-	-	δCH <sub>3</sub> (72)
1431	6.92	7.75	-	-	δCHIII(19), δCH <sub>2</sub> (20),
					vPhIII(48)
1429	21.21	6.89	-	-	δCH <sub>3</sub> (83)
1429	4.90	9.54	-	-	δCH <sub>3</sub> (80)
1428	28.52	63.08	-	-	δCH <sub>2</sub> (61)
1426	0.53	7.41	-	-	δCHI(13), vPhI(53)
1421	7.31	9.47	-	-	δCH <sub>3</sub> (40), δCH <sub>2</sub> (40)
1420	21.34	9.60	-	-	δCH <sub>2</sub> (82)
1417	39.75	9.29	1417	-	δCH <sub>2</sub> (92)

1408	16.13	15.95	-	1408	δCH <sub>3</sub> (68), δNH(19)
1399	24.75	6.13	-	1395	δCH <sub>3</sub> (62), υPhII(12)
1364	56.27	28.05	1368	1363	υPhII(53), δNH(21)
1352	20.98	33.04	1348	-	δCH <sub>2</sub> (72)
1325	56.31	47.64	-	1330	δCH <sub>2</sub> (48), υCN(12)
1324	117.63	25.06	-	1322	υCN(48), δCH <sub>2</sub> (40)
1311	5.67	8.92	-	-	δCHI(77)
1306	34.20	127.11	-	-	vPhIII(81)
1301	7.73	19.74	-	1303	δCH <sub>2</sub> (59), υPhII(22)
1293	131.43	19.42	-	-	δCH <sub>2</sub> (44), υCO(19),
					vPhII(16)
1290	1.64	1.55	1288	-	υPhI(76), δCH <sub>2</sub> (15)
1271	3.94	17.40	-	1273	δCH <sub>2</sub> (76)
1265	25.01	18.61	-	-	υCN(45), δCHIII(40)
1257	17.06	29.13	-	-	δCH <sub>2</sub> (52), υCN(10)
1247	18.83	3.08	-	1250	vPhII(84)
1241	169.83	36.19	1238	-	υCN(11), δCH <sub>2</sub> (46)
1216	10.61	78.40	-	1214	δCH <sub>2</sub> (40), υCN(43)
1206	18.50	2.24	-	1204	δCHIII(41), υCN(43)
1196	104.15	8.45	-	-	υCO(47), δPhII(16),
					δCH <sub>3</sub> (11)
1180	57.63	1.41	1182	1181	δCHII(50), υCO(12)
1176	0.04	46.25	-	-	υCC(38), υPhI(12), δCHI(42)
1170	16.22	2.36	-	-	δCH <sub>3</sub> (74), υPhI(12)
1164	20.77	3.15	-	-	δCH <sub>3</sub> (59), υPhI(20)
1161	13.11	2.77	-	-	δCH <sub>2</sub> (69), υPhI(10)
1158	0.13	3.80	-	-	δCHI(77), υPhI(15)
1152	36.91	2.25	-	1152	δCH <sub>3</sub> (54), δCHII(40)
1150	14.77	2.82	-	-	δCHIII(28), υCN(45)
1136	0.69	4.53	1136	1135	δCHI(76), υPhI(16)
1125	51.16	6.92	-	-	υCN(43), δCH <sub>2</sub> (12),

					δCH <sub>3</sub> (11), υCO(12)
1124	51.12	7.55	-	-	δCHIII(52), υCN(10)
1123	0.45	0.24	-	-	δCH <sub>3</sub> (89)
1122	20.09	3.05	-	-	δCH <sub>3</sub> (81)
1121	5.75	3.74	-	-	δCH <sub>3</sub> (93)
1110	100.57	16.49	-	-	υCN(43), δCH <sub>2</sub> (44)
1103	79.42	6.72	-	1102	δCH <sub>2</sub> (61), δCHIII(17)
1083	2.46	1.97	1080	1085	δCHIII(27), vPhIII(51)
1062	8.67	0.80	-	1059	υPhI(26), δCHI(55)
1054	189.12	5.88	-	1049	υCO(68), δCHI(20)
1017	75.11	17.33	1020	1020	vCO(42), vPhII(40)
1009	7.15	18.68	-	-	υPhI(52), δPhI(12), δCHI(12)
1007	10.19	35.43	-	1005	υPhIII(17), δCHIII(53)
998	14.74	1.55	-	-	υCC(21), δCH <sub>2</sub> (52)
992	26.94	1.35	-	-	υCC(28), δCH <sub>2</sub> (52)
991	7.57	43.68	-	-	υCC(63), δCH <sub>2</sub> (14)
978	0.04	48.31	-	-	δPhI(64), υPhI(36)
977	97.16	13.12	-	-	υCO(78), δPhII(10)
965	7.72	2.29	-	-	υCN(47), δC=O(10)
964	0.07	0.18	-	-	γCHIII(87), τPhIII(11)
962	1.28	1.98	-	962	γCHI(67), τPhI(11)
953	26.72	2.03	-	-	vCO(49), vPhII(15)
949	0.04	0.02	-	-	γCHI(92)
946	1.47	0.12	944	943	γCHIII(87)
928	14.18	4.87	-	-	δCH <sub>2</sub> (48), υCC(20)
910	6.11	4.38	911	911	υCO(67), δCH <sub>2</sub> (15)
897	3.93	1.24	-	-	δCH <sub>2</sub> (69), γC=O(12)
894	1.25	4.52	-	892	γCHI(77), τPhI(10)
869	8.38	6.44	872	-	δPhIII(31), δPhIV(12),
					υCN(12)
857	20.77	0.73	-	-	γCHII(63), τPhII(17)

856	15.13	0.25	-	-	γCHII(64), τPhII(18)
853	1.88	0.02	850	850	γCHIII(81), τPhIII(10)
827	6.06	1.79	-	-	γCHI(45), δPhIII(10)
826	3.89	1.18	824	824	γCHI(62)
800	5.22	25.96	-	-	υCC(17), δPhI(49)
788	15.13	12.08	-	790	δPhII(41), υCO(17)
771	1.00	0.96	773	772	γC=O(38), τPhIV(21),
					τPhIII(13), γCHIII(10)
770	6.61	1.09	-	-	τPhII(38), γCO(46)
751	56.89	1.03	750	748	γCHIII(58), τPhIII(18),
					τPhIV(13)
741	8.83	3.93	-	-	δCH <sub>2</sub> (36), τPhI(14),
					γCHI(10)
734	17.73	1.39	-	-	τPhI(19), γCHI(20),
					δCH <sub>2</sub> (21)
725	10.17	3.07	723	728	υCC(21), δCH <sub>2</sub> (13),
					τPhII(12), δCN(19)
694	10.14	5.53	696	696	δPhIII(43), γCHI(24)
686	28.08	0.92		-	τPhI(47), γCHI(22)
684	30.30	10.33	-	682	τPhI(22), γC=O(46),
					τPhIII(10)
678	14.44	5.85	-	-	τPhIII(38), γC=O(30),
					γCHIII(14)
668	4.38	1.92	-	-	υCS(49), γC=O(15),
					τPhII(10)
652	2.20	3.87	655	653	υCS(18), δCO(18), γCO(12),
					τPhII(10)
644	13.28	4.87	-	-	υCS(19), γCN(17), τPhII(15),
					δCO(15)
635	1.04	1.33	632	633	υCS(46), τPhIV(32)
616	7.74	2.11	-	618	γCN(18), τPhII(37), γCO(19)

613	5.10	11.32	-	-	γNH(45), δPhI(12),
					δC=O(10)
611	1.02	2.05	-	609	δPhI(69)
594	18.10	4.12	600	592	τPhII(27), γCN(13)
585	2.85	3.67	-	-	δPhIII(48), δCS(16)
578	3.96	1.28	-	-	δPhI(38), δPhIII(18)
541	10.06	11.31	-	540	γCO(14), δCO(29), δPhII(14)
525	31.59	18.58	525	525	δPhIV(32), γNH(10),
					τCN(10)
519	89.29	6.52	-	-	τCN(33), γNH(21)
516	11.95	0.50	-	-	τPhIII(53), τPhIV(13)
495	2.85	1.84	500	502	δPhII(37), δC=O(43),
					δCN(10)
493	9.33	0.72	-	-	τPhI(53), γCC(25)
470	4.47	1.27	-	471	δC=O(46), δCN(17),
					δPhII(16)
455	4.90	2.45	456	454	δPhIV(38), δPhI(32)
433	5.77	1.22	-	-	δCN(17), δCO(12), γCO(15)
428	2.32	1.85	425	426	τPhIII(61), τPhIV(15)
399	0.06	0.11	-	402	τPhI(81)
397	5.60	2.69	-	-	δCH <sub>2</sub> (19), δCS(25),
					δPhIV(15)
390	3.76	1.86	-	391	δCN(42), δC=O(17),
					τPhI(10)
363	5.32	0.83	-	365	δPhII(29), γCO(12), δCO(22)
343	2.21	1.59	-	342	τPhII(21), δCO(24), δCN(15)
336	1.56	5.12	-	-	γCN(23), δCH <sub>2</sub> (21),
					τPhI(12), τPhIII(10)
331	1.63	0.28	-	-	δCC(45), τPhIII(24)
327	1.19	1.27	-	325	τPhII(36), δCO(36)
303	1.43	8.69	-	305	δCH <sub>2</sub> (30), δCS(20)

295	3.55	0.97	-	-	δCN(20), τPhII(18), δCO(13)
287	2.99	0.24	-	- `	δCO(42), τPhII(16), δCN(10)
285	0.90	4.45	-	283	τPhII(18), δCO(18),
					δCN(16), δCH <sub>2</sub> (14)
278	0.46	1.15	-	-	τPhIII(39), τPhIV(26),
					γCS(12)
273	0.22	3.19	-	- `	δCS(21), δCH <sub>2</sub> (34)
250	3.39	1.67	-	250	τPhI(17), δCS(24), δCH <sub>2</sub> (11)
242	11.23	2.45	-	-	τPhII(23), δCO(30), γCO(11)
230	3.01	2.27	-	231	τPhI(26), γCN(10), δCS(16)
188	5.92	1.91	-	-	τPhII(23), δCO(24), γCO(12)
186	1.39	5.10	-	183	τCH <sub>2</sub> (12), γCO(11),
					δCH <sub>2</sub> (20), δCN(10)
167	0.05	0.13	-	168	τCH <sub>3</sub> (82)
152	0.01	0.71	-	-	$\tau$ PhIV(53), $\tau$ PhIII(19)
150	0.44	0.83	-	-	τCH <sub>3</sub> (62), δCO(10)
147	0.43	0.80	-	-	τCH <sub>3</sub> (62), τCH <sub>3</sub> (11)
133	2.71	0.72	-	-	γCO(43), τCH <sub>3</sub> (17)
130	2.35	0.93		-	γCN(30), τPhIV(39)
100	3.57	0.76	-	-	τCO(22), δCS(23), γCN(15)
93	0.49	0.55	-	-	τPhIV(34), τPhIII(10),
					τCH2(10), τCS(10)
85	5.27	1.87	-	-	τCO(35), δCO(20), τPhII(10)
84	0.89	4.63	-	-	γCC(24), δCH <sub>2</sub> (23),
					$\tau PhIV(11)$
80	0.29	1.43	-	-	τCH <sub>2</sub> (41), τCC(11)
77	0.57	0.85	-	-	τCO(39), τPhII(20)
73	2.37	1.75	-	-	τCO(53), τPhII(10)
65	3.68	2.35	-	-	τCO(27), γNH(21), τCN(25)
55	1.81	1.80	-	-	τC=O(27), τCN(24),
					γNH(11)

10	0.00	0.64			
46	0.29	0.64	-	-	$\tau CO(30), \tau CS(18), \tau C=O(20)$
41	1.92	1.00	-	-	τCO(69), τPhIV(14)
34	0.74	0.80	-	-	τPhIV(22), τCC(15),
					γCN(16), δCH <sub>2</sub> (19)
29	0.07	4.47	-	-	τCC(70), τCH <sub>2</sub> (13)
25	0.04	3.39	-	-	τCN(40), τCH <sub>2</sub> (22)
17	0.25	1.32	-	-	τCN(35), τCH <sub>2</sub> (26)
12	0.34	1.46	-	-	τCN(28), τCH <sub>2</sub> (32)
9	0.18	1.54	-	-	τCH <sub>2</sub> (51), τCS(15)
5	0.35	1.42	-	-	τCH <sub>2</sub> (41), τC=O(36)

<sup>a</sup>υ-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 13C NMR isotropic chemical shifts (with respect to TMS, all values are in ppm)

Atom	σ <sub>TMS</sub> B3LY	$P/6-311++G(d,p)(5D,7F)\sigma_{calc}$	$\delta_{calc}(\sigma_{TMS} - \sigma_{calc})$
7H	32.7711	25.27	7.5011
9Н	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
36Н	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
<b>6</b> 1H	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
<u>64C</u>	196.852	158.8492	38.0028

Tal	ble	4

# Values of the Fukui function considering Mulliken charges

Atom	<u>f</u>	f	$-\nabla f_k$
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>	0.019121	0.019501	0.00038

## Table 5

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

Donor(i)	Туре	ED/e	Acceptor(j)	Туре	ED/e	E(2) <sup>a</sup>	E(j)-E(i) <sup>b</sup>	F(i,j) <sup>c</sup>
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	$\pi^*$	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	$\pi^*$	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	$\sigma^*$	0.02461	2.73	1.23	0.052
-	-	-	C5-C14	$\sigma^*$	0.03896	2.41	1.24	0.049
-	-	-	C10-C12	$\sigma^*$	0.01387	2.03	1.28	0.046

			ACCEPTED	MA	NUSCRIPT			
-	-	-	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
-	- 5	7-	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

			ACCEPTE	D MAN	NUSCRIPT			
LPS1	σ	1.98015	N3-C33	σ*	0.01654	3.28	1.22	0.056
-	π	1.82884	N3-C33	$\pi^*$	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
-	- 5	-	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

		ļ	CCEPTED	MAN	USCRIPT			
-	π	1.90982	C41-C45	$\sigma^*$	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

<sup>a</sup>E(2) means energy of hyper-conjugative interactions (stabilization energy in kJ/mol)

<sup>b</sup>Energy difference (a.u) between donor and acceptor i and j NBO orbitals

 ${}^{c}F(i,j)$  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 <sup>a</sup>	EDA%	EDB%	NBO	s%	p%
σS1-C33	1.97562	45.26	54.74	0.6727(sp <sup>5.06</sup> )S+	16.38	83.62
-	-0.65218	-	-	0.7399(sp <sup>2.43</sup> )C	29.10	70.90
σO2-C15	1.99419	64.90	35.10	0.8056(sp <sup>1.39</sup> )O+	41.78	58.22
-	-1.06199	-	-	0.5925(sp <sup>2.05</sup> )C	32.71	67.29
πO2-C15	1.98350	69.77	30.23	0.8353(sp <sup>1.00</sup> )O+	0.00	100.0
-	-0.36441	-	-	0.5498(sp <sup>1.00</sup> )C	0.00	100.0
σN4-C15	1.98125	64.433	35.57	0.8027(sp <sup>2.01</sup> )N+	33.18	66.82
-	-0.79247	-	-	0.5964(sp <sup>2.46</sup> )C	28.82	71.18
σN4-C33	1.98739	62.57	37.43	0.7910(sp1.88)N+	34.69	65.31
-	-0.84365	-	-	0.6118(sp <sup>1.98</sup> )C	33.55	66.45
σC5-C14	1.97303	49.32	50.68	0.7022(sp <sup>1.82</sup> )C+	35.47	64.53
-	-0.69758	-	-	0.7119(sp <sup>1.95</sup> )C	33.84	66.16
σC14-C15	1.97503	51.68	48.32	0.7189(sp <sup>2.26</sup> )C+	30.69	69.31
-	-0.67705	-	-	0.6951(sp <sup>1.61</sup> )C	38.35	61.65
σC16-C19	1.97251	50.44	49.56	0.7102(sp <sup>2.51</sup> )C+	28.48	71.52
-	-0.59523	-	-	0.7040(sp <sup>2.93</sup> )C	25.41	74.59
πC37-O38	1.98677	30.95	69.05	0.5563(sp <sup>99.99</sup> )C+	0.06	99.94
-	-0.36097	- //	-	0.8310(sp <sup>99.99</sup> )O	0.12	99.88
σC37-N39	1.98909	36.81	63.19	0.6067(sp <sup>2.23</sup> )C+	30.90	69.10
-	-0.82221	$\sim$	-	0.7949(sp <sup>1.69</sup> )N	37.18	62.82
σC40-C41	1.97187	50.67	49.33	0.7118(sp <sup>1.76</sup> )C+	36.19	63.81
-	-0.70911	-	-	0.7024(sp <sup>1.83</sup> )C	35.21	64.79
σC40-C42	1.97208	50.59	49.41	0.7118(sp <sup>1.74</sup> )C+	36.48	63.52
-	-0.71162	-	-	0.7029(sp <sup>1.84</sup> )C	35.26	64.74
σC41-C45	1.97359	50.01	49.99	0.7072(sp1.88)C+	34.74	65.26
- 5	-0.71135	-	-	0.7071(sp <sup>1.64</sup> )C	37.91	62.09
πC41-C45	1.67222	51.83	48.17	0.7199(sp <sup>1.00</sup> )C+	0.00	100.0
-	-0.26477	-	-	0.6941(sp <sup>99.99</sup> )C	0.01	99.99
σC42-C46	1.97320	50.06	49.94	0.7075(sp1.88)C+	34.69	65.31
-	-0.71023	-	-	0.7067(sp <sup>1.65</sup> )C	37.75	62.25
σC45-C47	1.97727	49.89	50.11	0.7063(sp <sup>1.73</sup> )C+	36.64	63.36

		ACCEPTE	D MANUSC	CRIPT		
-	-0.71715	-	-	0.7079(sp <sup>1.68</sup> )C	37.32	62.68
σC46-C47	1.97682	49.89	50.11	0.7063(sp <sup>1.72</sup> )C+	36.74	63.26
-	-0.71742	-	-	0.7079(sp <sup>1.68</sup> )C	37.26	62.74
n1S1	1.98015	-	-	sp <sup>0.47</sup>	68.01	31.99
-	-0.63412	-	-	-	-	-
n2S1	1.82884	-	-	sp <sup>1.00</sup>	0.00	100.0
-	-0.24978	-	-	-	-	-
n1O2	1.97619	-	-	sp <sup>0.72</sup>	58.17	41.83
-	-0.67228	-	-	-	-	-
n2O2	1.85356	-	-	sp <sup>99.99</sup>	0.01	99.99
-	-0.24517	-	-	-	-	-
n1N3	1.89180	-	-	sp <sup>2.65</sup>	27.36	72.64
-	-0.33826	-	-		-	-
n1N4	1.59160	-	-	sp <sup>99.99</sup>	0.02	99.98
-	-0.26515	-	-		-	-
n1O38	1.97557	-	- 5	sp <sup>0.72</sup>	58.12	41.88
-	-0.66684	-	-	-	-	-
n2O38	1.86700	-	-	${ m sp}^{1.00}$	0.01	99.99
-	-0.23949	-		-	-	-
n1N39	1.71037	-		sp <sup>99.99</sup>	0.09	99.91
-	-0.25583	-	-	-	-	-
n1O49	1.94413	-	-	sp <sup>1.72</sup>	36.67	63.33
-	-0.53312		-	-	-	-
n2O49	1.92712	$\overline{}$	-	sp <sup>16.10</sup>	5.84	94.16
-	-0.34379		-	-	-	-
n1O54	1.95217	-	-	sp <sup>2.15</sup>	31.68	68.32
-	-0.49570	-	-	-	-	-
n2O54	1.90599	-	-	sp <sup>8.71</sup>	10.29	89.71
-	-0.36606	-	-	-	-	-
n1O59	1.95138	-	-	sp <sup>2.21</sup>	31.15	68.85
-	-0.49278	-	-	-	-	-
n2O59	1.90982	-	-	sp <sup>8.06</sup>	11.03	88.97
-	-0.37165	-	-	-	-	_

<sup>a</sup> 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)	nity (kcal/mol) Distance from best mode (Å)		
-	-	RMSD 1.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	

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