Single-Crystal Investigation, Hirshfeld Surface Analysis, and DFT Study of Third-Order NLO Properties of Unsymmetrical Acyl Thiourea Derivatives

Muhammad Ashfaq,* Muhammad Nawaz Tahir, Shabbir Muhammad, Khurram Shahzad Munawar,* Akbar Ali, Georgii Bogdanov, and Saleh S. Alarfaji

ABSTRACT: In the current research work, unsymmetrical acyl thiourea derivatives, 4-((3-benzoylthioureido)methyl)cyclohexane-1-carboxylic acid (BTCC) and methyl 2-(3-benzoylthioureido)benzoate (MBTB), have been synthesized efficiently. The structures of these crystalline thioureas were unambiguously confirmed by single-crystal diffractional analysis. The crystallographic investigation showed that the molecular configuration of both compounds is stabilized by intramolecular N···O bonding. The crystal packing of BTCC is stabilized by strong N···O bonding and comparatively weak O···S, C···H, C···π, and C···O···π interactions, whereas strong N···O bonding and comparatively weak C···H···O, C···H···S, and C···H···π interactions are responsible for the crystal packing of MBTB. The noncovalent interactions that are responsible for the crystal packing are explored by the Hirshfeld surface analysis for both compounds. The void analysis is performed to find the quantitative strength of crystal packing in both compounds. Additionally, state-of-the-art applied quantum chemical techniques are used to further explore the structure–property relationship in the above-entitled molecules. The optimization of molecular geometries showed a reasonably good correlation with their respective experimental structures. Third-order nonlinear optical (NLO) polarizability calculations were performed to see the advanced functional application of entitled compounds as efficient NLO materials. The average static γ amplitudes are found to be 27.30 × 10⁻³⁶ and 102.91 × 10⁻³⁶ esu for the compounds BTCC and MBTB, respectively. The γ amplitude of MBTB is calculated to be 3.77 times larger, which is probably due to better charge-transfer characteristics in MBTB. The quantum chemical analysis in the form of 3-D plots was also performed for their frontier molecular orbitals and molecular electrostatic potentials for understanding charge-transfer characteristics. We believe that the current investigation will not only report the new BTCC and MBTB compounds but also evoke the interest of the materials science community in their potential use in NLO applications.

1. INTRODUCTION

Acylthioureas have assembled a new unique class of organic compounds because of the presence of carbonyl and thio carbonyl groups simultaneously within one molecule. These types of compounds are successful in gaining the attention of many researchers due to their worldwide employment in biological processes.¹ Acyl thiourea and its derivatives have demonstrated potential antimicrobial, antibacterial, antifungal, antiviral, and plant protection regulating activities.² They can act as inhibitors for the lipoxygenase, polo-like kinase 1, inhibitors for a polo-box domain and anti-Alzheimer’s agents.³ In addition to this, thiourea derivatives also possess anticancer activities.⁴ Acylthioureas can possess very interesting chelating behavior toward the development of coordination chemistry due to the presence of S, N, and O atoms as donor sites, together. It is obvious from the documented literature that substituted acyl thiourea ligands can behave as monodentate via a sulfur atom or bidentate using either oxygen and sulfur or oxygen and nitrogen atoms as donor sites.⁵ They can also coordinate through the keto or enol tautomeric forms depending upon the nature of the ligands themselves and the metal centers used in complexation.⁶ The crystallographic parameters and intramolecular hydrogen bonding are the most promising interactions that have an effect on the conformation of the molecules in the crystal packing.⁷ Based on the presence of intramolecular...
hydrogen bonding between N–H (thiourea) and O (amidic), a six-membered ring is formed. As a result, the ligand behaves in a monodentate manner to coordinate through the sulfur atom. On the other hand, acyl thiourea, which does not have such a kind of hydrogen bonding, tends to bind in a bidentate fashion using sulfur and acyl oxygen atoms as donor sites with metal atoms. Acylthioureas are usually termed as S-donor ligands upon coordination with soft Lewis acids like copper, silver, and gold. Acyl thiourea also exhibits thione–thiol tautomerism due to the presence of a thioamide moiety in their structure. The transition metal complexes of acyl thiourea have received increasing attention in the last few decades due to their versatility, antibacterial, antifungal, and antimalarial activities, and they also play a key role in flotation processes. Due to various promising kinds of tautomeric and binding characteristics, the single crystals and packing of unit cells make them very interesting from a coordination and bioorganic point of view. Although hundreds of derivatives of acylthioureas have been reported in the last few decades, the interest of researchers in these particular compounds is matchless. Herein, we are going to describe the synthesis and crystalline feature investigations of two novel acylthioureas, i.e., 4-((3-benzoylethioureido)methyl)cyclohexane-1-carboxylic acid (BTCC) and methyl 2-(3-benzoylethioureido)benzoate (MBTB). In addition to this, quantum chemical methods will be used to explore the potential of synthesized compounds for their third-order nonlinear optical (NLO) response properties. The NLO materials play a very significant role in modern hi-tech applications, including laser frequency modulators, optical data storage, and telecommunications.

The organic class of compounds has always been a front runner in designing new NLO materials due to the vast variety of their functional groups, better donor–acceptor molecular configurations, and ease of fabrication. As the above-mentioned two novel acylthioureas are freshly prepared, it will be interesting to explore their possibility of possessing NLO response properties. Over the last two decades, quantum chemical methods have emerged as a vibrant tool to look into the NLO structure–property relationships of huge classes of compounds, which, in fact, provide and semiquantitatively very reasonable approximate for NLO response properties. Thus, density functional methods combined with a finite field approach will be used to calculate third-order NLO polarizability of the abovementioned compounds.

2. RESULTS AND DISCUSSION

2.1. Crystal Structure of BTCC and MBTB. In BTCC (Figure 1, Table 1), the thio carbonyl group (C9 = S1) and the carbonyl group (C10 = O3) are orientated in opposite directions with respect to each other, as evident from the torsion angles S1-C9-N2-C10 = 175.7(2)°, N1-C9-N2-C10 = −4.5(4)°, and O3-C10-N2-C9 = 40.4(2)°. Some selected bond lengths and bond angles are specified in Table S1. The O atoms of carbonylate group A (C1/O1/O2) are found to be disordered over two sets of sites with an occupancy ratio of 0.837(7) : 0.163(7) and major part B (C1/O1A/O2A) is twisted at a dihedral angle of 40.94(2)° with respect to minor part C (C1/O1B/O2B). The cyclohexane ring D (C2-C7) adopts a chair configuration with puckering amplitude Q = 0.580(3) Å, θ = 2.9(3)° and 356(6)°; the equatorial sites are occupied by (C2/C5) atoms. 1-Methylthiourea moiety E (C8/C9/N1/N2/S1) and benzaldehyde group F (C10-C16/O3) are found to be planar with respective root-mean-square (r.m.s) deviations of 0.0093 and 0.0400 Å and orientated at a dihedral angle of 5.53(2)° with respect to each other. This dihedral angle inspection inferred that moiety E and group F are almost planar. Dihedral angles B/E, B/F, C/E, and C/F are found to be 17.3(5), 18.8(5), 24.01(2), and 22.5(2)°, respectively. The molecular configuration of BTCC is stabilized by intramolecular N–H···O bonding to form an S loop. The molecules are primarily interlinked in the form of dimers through N–H···O and O–H···S bonding to form an R3(8) loop where NH attached to the carbonyl group acts as a donor and the carbonyl O atom of the carbonylate group acts as an acceptor, as shown in Figure S1 and specified in Table 2. The carbonyl O atom acts as a bifurcated acceptor as it is also involved in comparatively weak C–H···O bonding to interlinked molecules. The C11 chain is formed by N–H···O bonding and a similar C11 chain is formed by O–H···S bonding. These chains run parallel along the b crystallographic axis. Due to C–H···O bonding, the C14 chain is formed that also runs along the b crystallography axis. Crystal packing is further stabilized by weak interactions of type C−H···π and C–O···π, as shown in Figure S2 and specified in Table 2. The CH from a cyclohexane ring (C2–C7) of a molecule located in an asymmetric position is engaged in C–H···π interaction with the phenyl ring (C11–C16) of a molecule located at (x, −1 + y, z) corresponding to the H···π distance of 2.95 Å. The carbonyl group of the benzaldehyde part (C10-C16/O3) of a

![Figure 1. ORTEP diagram of BTCC drawn at a probability level of 50%. H atoms are displayed as tiny circles of arbitrary radii. Only the major parts of the disordered group are displayed for clarity.](https://doi.org/10.1021/acsomega.1c04884)
molecule is engaged in a C−O···π interaction with the phenyl ring (C11−C16) of a molecule connected by inversion symmetry corresponding to the O···π distance of 3.612 Å. The Cambridge structural database search provides two crystal structures that are most closely related to the titled compound with reference codes XUHTUR21 and EYACIQ.22 XUHTUR (N′-((2-methylphenyl)carbamothioylformamide)-cyclohexane-1,2-diamine) contains a phenyl ring substituted by a methyl group at the ortho position at one end and an unsubstituted cyclohexane ring at the other end. EYACIQ (N′-(4-methylbenzoyl)-N′-(2-oxo cyclohexyl)methylthiourea) consists of a phenyl ring substituted by a methyl group at the para position at one end and a cyclohexane ring at the other end. The asymmetric unit of XUHTUR consists of two independent molecules, whereas the asymmetric unit of BTCC contains one molecule. The crystal packing of XUHTUR is stabilized by N−H···S and N−H···O bonding. Like in EYACIQ, the thioureidomethyl moiety in BTCC is planar. The molecular configuration of XUHTUR and EYACIQ is stabilized by intramolecular N−H···O bonding, and the same intramolecular H-bonding is present in BTCC. In EYACIQ, the authors do not describe the crystal packing, whereas we have explored the crystal packing of BTCC in detail.

In MBTB (Figure 2, Table 1), there are two molecules (A and B) in the asymmetric unit that are independent. Some selected bond lengths and bond angles in molecules A and B are given in Table S1. In molecule A, methyl benzoate group A1 (C1−C8/O1/O2), N-carbamothioylformamide moiety A2 (C9/C10/N1/N2/O3/S1), and phenyl ring A3 (C11−C16) are found to be planar with respective r.m.s deviations of 0.0487, 0.0527, and 0.0055 Å. Molety A5 is twisted at dihedral angles of 43.9(9) and 39.6(1)° with respect to group A1 and ring A2. Group A3 and ring A5 are almost parallel as the

### Table 1. Experimental Details of BTCC and MBTB

| Crystal Data | BTCC | MBTB |
|--------------|------|------|
| CCDC         | 2068399 | 2068400 |
| Chemical formula | C_{17}H_{20}N_{2}O_{5}S | C_{17}H_{20}N_{2}O_{5}S |
| M          | 320.40 | 314.35 |
| Crystal system, space group | triclinic, P1 | orthorhombic, P2_12_1 |
| Temperature (K) | 296 | 296 |
| a, b, c (Å) | 5.9027 (9), 10.2604 (16), 14.2883 (3) | 8.2190 (11), 10.4446 (11), 35.069 (4) |
| α, β, γ (deg) | 108.6124 (10), 97.581 (10), 97.514 (7) | 90, 90, 90 |
| V (Å³) | 801.5 (2) | 3010.5 (6) |
| Z    | 2 | 8 |
| Density (calculated) g/cm³ | 1.328 | 1.387 |
| F(000) | 340 | 1312 |
| Radiation type | Mo Kα | Mo Kα |
| Wavelength (Å) | 0.71073 Å | 0.7073 Å |
| μ (mm⁻¹) | 0.216 | 0.229 |
| Crystal size (mm) | 0.43 × 0.34 × 0.20 | 0.40 × 0.22 × 0.18 |

### Data Collection

| | BTCC | MBTB |
|----------------|------|------|
| Diffractometer | Bruker APEXII CCD | Bruker APEXII CCD |
| Absorption correction | Multiscan (SADABS; Bruker, 2007) | Multiscan (SADABS; Bruker, 2007) |
| No. of measured, independent, and observed [I > 2σ(I)] reflections | 9207, 3449, 1967 | 18 961, 6553, 3760 |
| R_int | 0.048 | 0.060 |
| θ range for data collection (deg) | 3.001 to 26.994 | 2.270 to 26.995 |
| Index ranges | -5 ≤ h ≤ 7, -12 ≤ k ≤ 13, -17 ≤ l ≤ 18 | -10 ≤ h ≤ 9, -13 ≤ k ≤ 7, -41 ≤ l ≤ 44 |
| (sin θ/λ) max (Å⁻¹) | 0.639 | 0.639 |

### Data Refinement

| | BTCC | MBTB |
|----------------|------|------|
| R[F² > 2σ(F²)], wR[F²], S | 0.057, 0.177, 1.03 | 0.055, 0.136, 0.99 |
| No. of reflections | 3449 | 6553 |
| No. of parameters | 212 | 409 |
| No. of restraints | 14 | |
| H-atom treatment | H atoms treated by a mixture of independent and constrained refinement | H-atoms constrained |
| Δρ_{max}, Δρ_{min} (e Å⁻³) | 0.22, -0.22 | 0.20, -0.22 |

### Table 2. Hydrogen-Bond Geometry (Å, deg) for BTCC and MBTB along with C−H···π and C−O···π in BTCC and C−H···π in MBTB

| Bond | BTCC | MBTB |
|------|------|------|
| D−H···A’ | 0.86 (1) | 0.86 (1) |
| D−H···A’ | 2.32 (1) | 2.64 (6) |
| D−H···A’ | 3.088 (2) | 3.177 (14) |
| C−H···π | 0.86 | 0.86 |
| C−H···π | 2.47 | 2.47 |
| C−H···π | 3.036 (4) | 3.27 (2) |
| C−H···π | 1.96 | 2.13 |
| C−H···π | 2.631 (3) | 3.173 (4) |
| C−H···π | 166 | 146 |
| C−H···π | 134 | 157 |
| C−O···π | 0.97 | 0.93 |
| C−O···π | 2.95 | 2.13 |
| C−O···π | 3.843 (3) | 3.003 (10) |
| C−O···π | 154 | 146 |
| C−H···π | 1.2160 | 3.612 (2) |
| C−H···π | 3.646 (3) | 81.94 (17) |

**Symmetry codes:** (i) x + 1, y − 1, z; (ii) x − 1, y + 1, z; (iii) x, −1 + y, z; (iv) −x, −1 − y, −1 + z; (v) x, y − 1, z; (vi) x + 1, y + 1, z; (vii) −1/2 + x, 1/2 − y, −z. Cg1 is the centroid of the phenyl ring (C11−C16) for BTCC and MBTB.
The dihedral angle between them is found to be just 4.7(2)°. In molecule B, methyl formate group B1 (C17/C18/O4/O5) of the methyl benzoate part is disordered over two sets of sites with an occupancy ratio of 0.684(17): 0.316(17). The major part B2 (C17A/C18A/O4A/O5A) is twisted at a dihedral angle of 39.6(3)° with respect to the plane of minor part B3 (C17B/C18B/O4B/O5B). The phenyl ring B4 (C19–C24), N-carbamothioylformamide moiety B5 (C25/C26/N3/N4/O6/S2) and phenyl ring B6 (C27–C32) are found to be planar with respective r.m.s deviation of 0.0065, 0.0186, and 0.0075 Å. The dihedral angles among B4/B5, B5/B6, and B4/B6 are 52.4(1), 25.9(2), and 75.9(1)°.

To determine the difference between the molecules A and B, a molecular overlay plot is formed using Mercury software (Figure 3). In the formation of plot, molecule A is inverted and then made to overlap with molecule B. This investigation shows that the RMSD (root-mean-square deviation) and maximum deviation obtained by overlapping of molecule A on B are 1.1156 and 2.9023 Å, respectively. The configuration of molecules A and B is stabilized by N–H···O bonding. Due to intramolecular H-bonding, S(6) loops are formed. Molecules A and B are connected with each other through N–H···O, comparatively weak C–H···O and C–H···S bonding (Table 2, Figure S3). The C8 chain is formed by the combination of two intermolecular H-bonding named N4–H4A···O3 and N2–H2···O6 that run along the b crystallographic axis. The C9 zigzag chain is formed by the combination of C12–H12···O6 and N2–H2···O6 bonding that also runs along the b crystallographic axis. The molecules A and B are also interlinked by C–H···S bonding, where CH is from a minor part of disordered methyl formate group and the S atom is from the N-carbamothioylformamide moiety A2. Crystal packing is further stabilized by weak interaction of type C–H···π. CH of the phenyl ring (C27–C32) of molecule B located in an asymmetric position is engaged in a C–H···π interaction with a phenyl ring (C11–C16) of molecule A, corresponding to the H···π distance of 2.72 Å, as given in Table 2 and shown in Figure S4. The Cambridge structural database search provides two crystal structures that are most closely related to MBTB, one with reference code KUVGEO (nitrobenzene ring at one end, while an ethyl benzoate ring at the other end) and the other with reference code URATEN (3,5 dinitrobenzene ring at one end while ethyl benzoate ring at the other end). Like in MBTB, the molecular configuration of KUVGEO and URATEN is stabilized by intramolecular N–H···O bonding. In URATEN, the dihedral angle between benzene rings is 9.04(15)°, whereas in molecule A of MBTB, the dihedral angle is 7.54(3)° and in molecule B of MBTB, the dihedral angle is 75.92(1)°. The crystal packing of KUVGEO and URATEN is mainly stabilized by N–H···O bonding.

Figure 2. ORTEP diagram of MBTB drawn at a probability level of 50%. H atoms are shown by small circles of arbitrary radii. Only a major part of the disordered group is shown for clarity.

Figure 3. Molecular overlay plot of MBTB, showing the difference between two independent molecules present in the asymmetric unit, molecule A (red) and molecule B (blue).
whereas the crystal packing of MBTB is stabilized by N–H···O and C–H···S bonding.

2.2. Hirshfeld Surface Analysis. Noncovalent interactions interlink the molecules in a single crystal. For the elaboration of these interactions, Hirshfeld surface (HS) analysis was performed on Crystal Explorer version 17.5.25 The concept of HS merges from an attempt to divide the molecular electron density into small fragments. The Hirshfeld surface plotted over dnorm can be employed to show strong H-bonding as well as H-bonding interactions using different colors.26 This surface contains three colors, red, white, and blue. The red color stands for the interatomic contacts for which the distance between the atoms is less than the sum of van der Waals radii of atoms involved. The blue regions around the atoms indicate that the distance between the atoms is greater than the sum of the van der Waals radii of atoms involved. If the distance between the atoms is equal to the sum of van der Waals radii of the atoms involved, then a white spot is present on the HS. Figure 4a,b shows two views of the HS plotted over dnorm for BTCC. The red spots are present on the HS around the S atom, and O atoms of the carboxylate group, NH directly attached to the carbonyl group, and the CH of the phenyl ring (C11–C16). This indicates that these atoms are engaged in H-bonding interactions. Figure 4c,d shows HS plotted over dnorm for molecules A and B of MBTB, respectively. The red spots are present on the HS around the NH directly attached to the carbonyl group, and the O atom of the carbonyl group indicates that these atoms are engaged in H-bonding. Figure 4e shows HS containing both molecules of MBTB. The atoms that are involved in H-bonding interactions are shown by red spots on HS around them. The interactions that are weaker than H-bonding, like π···π stacking interactions, can also be represented by HS. For that purpose, HS is plotted over the shape index. For BTCC (Figure 4f), molecule A of MBTB (Figure 4g), molecule B of MBTB (Figure 4h), and molecules A and B of MBTB (Figure 4i), the presence of consecutive red and blue regions of the triangular shape around the aromatic rings indicate that π···π stacking interaction is present in the crystal packing. But the π···π stacking interaction is very weak in both titled compounds as the centroid-to-centroid separation ranges from 4.655(3) to 5.978(3) Å in MBTB and 4.883(2) Å in BTCC.

We can quantitate the contribution of each interatomic contact that is the main aspect of the crystal packing of single crystals. For this, 2D fingerprint plots are formed by both compounds.27 For the interatomic contact calculation, reciprocal contact of each contact is added. d_c and d_i stand for the distance from the HS to the nearest nucleus outside and inside the HS, respectively. Figure 5a shows the 2D plot for overall interactions in the crystal packing of BTCC. The contact of utmost importance in the crystal packing of BTCC is H···H because it has a 51% contribution to the crystal packing (Figure 5b). O···H and S···H contacts also have a
significant contribution to the crystal packing of 16.7% for O···H (Figure 5c) and 12.4% for S···H (Figure 5d). The contacts of minor contributors in the crystal packing are displayed in Figure 5e–f. Separate 2D plots are formed for molecule A and molecule B of MBTB to show the role of molecules A and B in the crystal packing. For both molecules A and B, H···H contact is the most important one because it has the highest contribution to the crystal packing of 33.8% for molecule A (Figure 6a) and 35.4% for molecule B (Figure 6b). The comparison of various interatomic contacts for molecules A and B is shown in Figure 6a,b. Figure 7a shows the 2D fingerprint plot for overall interactions by drawing a HS containing both molecules A and B of MBTB. Like in BTCC, the H···H contact is the most important one to the crystal packing of MBTB with a percentage contribution of 35.3% (Figure 7b). The C···H, O···H, and S···H contacts also have significant contributions to the crystal packing of MBTB of 30% for C···H (Figures 7c), 15.9% for O···H (Figure 7d), and 12.7% for S···H (Figure 7e). The contacts of a minor contributor in the crystal packing are shown in Figure 7f–k.

Figure 5. 2D fingerprint plots of BTCC for (a) overall interactions and (b–l) individual interatomic contacts.
Now, we are going to compare the crystal packing of BTCC and MBTB in terms of interatomic contacts. The molecular arrangement in the crystal structure of the compound BTCC is simple and consists of multiple planes stacked in the direction with Miller indexes of (−15 −15 55) (Figure S5). Within each plane, molecules comprise rows, where in every other row, the molecules are turned around for 180° (Figure S5A). This way, molecular packing reaches the most favorable tightness of the structure. The only strong atom−atom contact that binds planes together is S···H−H−S (Figure S5B). The molecular arrangement in the crystal structure of the compound MBTB, on the other hand, is much more complex (Figure S6). From one point of view (Figure S6A), the molecules create stacks, which have a V shape, and alternate within the structure. Due to the presence of two almost independent molecules oriented to each other, each of them creates a plane (Figure S6B). Here, the O···H−H−O and C···H−H−···C intermolecular interactions ensure the rigidity of the crystal structure. Comparing the two title derivatives of thiourea, we can see that compound BTCC has larger gaps between the molecules, which, together with intermolecular interactions analysis, potentially shows a higher possibility for the compound BTCC to bind to another molecule.

To explore how an atom located inside the HS interacts with the atoms of molecules located in the neighborhood of HS, a quantitative analysis is performed, which provides the percentage contribution of such interactions. This investigation showed that the most significant contribution is from H−ALL interaction for both compounds, where ALL represents all of the atoms of molecules located in the neighborhood of HS with which H atoms of HS interact. The percentage contribution of H−ALL interaction is found to be 68.3 and 61.7% for BTCC and MBTB, respectively, as shown in Figure S7. Other such interactions for BTCC are O−ALL, C−ALL, S−ALL, and N−ALL with respective percentage contributions of 11.2, 10.7, 8, and 1.8%. Likewise, the other such interactions for MBTB are C−ALL, O−ALL, S−ALL, and N−ALL with respective percentage contributions of 19.1, 9, 8.5, and 1.5%.

Furthermore, it is also important to find out the quantitative analysis of all of the atoms located inside the HS interact with the atoms of molecules located in the neighborhood of HS. The ALL−H interaction is found to be the most significant contributor to such interactions for both compounds. In this case, ALL represents all of the atoms located inside the HS, as shown in Figure S8. The percentage contribution of ALL−H interaction is found to be 73.8 and 70% for BTCC and MBTB, respectively. Other such interactions for BTCC are ALL−O, ALL−C, ALL−S, and ALL−N with respective percentage contributions of 10.7, 9.2, 4.7, and 1.6%. Likewise, the other such interactions for MBTB are ALL−C, ALL−O, ALL−S, and ALL−N with respective percentage contributions of 15.1, 8.2, 5.4, and 1.2%.

The void analysis is one that plays a significant role when we are discussing the response of a single crystal under an applied force or stress. If voids are not large in crystal packing, then it means that this crystal has better mechanical strength as compared to a single crystal that has large voids in crystal packing. So, by keeping in view the following background knowledge, void analysis is performed on Crystal Explorer software, as shown in Figure S9. This inspection is performed by assuming that the electron density of each atom follows a spherical symmetry and then the atomic electron density of each atom is added up. The volume of void is found to be 92.21 Å³ for BTCC and 328.33 Å³ for MBTB. The % of space in crystal packing occupied by voids is found to be 11.5% for BTCC and 10.9% for MBTB. This investigation infers that the strength of crystal packing in both compounds is almost the same.

3. DETAILS OF THE APPLIED COMPUTATIONAL METHODOLOGY

The Gaussian 16 suite of programs is applied to perform all quantum chemical calculations. The visualization of molecular orbitals and electrostatic potential diagrams in 3-D plots was obtained using GaussView. For the optimization of the entitled compounds, B3LYP functional and 6-311+G(d,p) basis sets were used. The B3LYP was considered as a gateway functional for optimization purposes due to many successful combined experimental and computational investigations. The global chemical reactivity descriptors are calculated using HOMO and LUMO energies from the optimized geometries. For the purpose of brevity, all of the well-known working equations for the calculation of global chemical reactivity descriptors are provided in the Supporting Information. All theoretical calculations were performed at the same B3LYP/6-311++G(d,p) level of theory except third-order NLO polarizability. The third-order NLO polarizability was calculated using the M06-2X functional because B3LYP is reported to overestimate higher-order polarizabilities. A finite field (FF) method with a field amplitude of ±0.0003 a.u. is applied to calculate the static third-order NLO polarizability using the Coupled Perturbed Hartree–Fock/Kohn–Sham (CPHF/KS) scheme. The stability of the applied field amplitude was also tested by applying different amplitudes. From Table S2, it can be seen that the changes in average amplitudes of the BTCC compound are very small (almost negligible), so the default field amplitude applied by Gaussian is considered.
reliable here. The FF method has been widely used in recent years for its ability to provide reproducible results of higher-order polarizabilities for several classes of compounds. The method was also found to consist of other NLO calculation methods like TD-SOS, etc.

3.1. Molecular Geometries of Compounds BTCC and MBTB. The optimized geometries along with their experimental counterparts are shown in Figure 8. A thorough consideration of Figure 8 illustrations shows that, overall, there is good agreement between the main backbone skeletons of computationally optimized geometries and experimentally reported structures. Some important calculated and experimental bond lengths are compared for both the entitled compounds. For instance, in the BTCC compound, the experimental and calculated C=S bond lengths are found to be 1.671 and 1.675 Å, respectively. Similarly, the carbonyl C=O

Figure 7. 2D fingerprint plots of MBTB using HS containing both molecules A and B for (a) overall interactions and (b–k) individual interatomic contacts.
The NLO materials play a very prominent role in modern hi-tech applications, including optical data storage, laser frequency modulation, and telecommunications. The average static $\gamma$ calculated and collected in Table 3. It is obvious from Table 3 that the overall experimental geometry is reasonably well reproduced by the applied quantum chemical method. We have optimized the dimeric system with and without Grimme dispersion correction. A comparative analysis has been made in Figure S10 of the Supporting Information. The two nearest contacts of a dimer show slightly shorter distances in the optimized structure with Grimme’s dispersion correction as compared with the optimized structure without Grimme’s dispersion correction. For instance, with the Grimme’s dispersion correction optimized structure of MBTB, the distances of the O$_{40}$−N$_{42}$ and C$_{60}$−O$_{23}$ are found to be 2.868 and 3.536 Å as compared with those of 3.100 and 3.768 Å having no Grimme’s dispersion corrections (see Figure S10 of the Supporting Information).

### 3.2. Third-Order NLO Polarizability ($\gamma$)

Third-order NLO polarizability ($\gamma$), which is also known as second hyperpolarizability, is a very crucial property and is often considered as a signature for the two-photo absorption (TPA) process. The NLO materials play a very prominent role in modern hi-tech applications, including optical data storage, laser frequency modulation, and telecommunications. The static $\gamma$ amplitudes for both the entitled compounds are calculated and collected in Table 3. It is obvious from Table 3 that average static $\gamma$ values along with their individual components because individual components are often dependent on the direction of the intramolecular charge-transfer process. First, an analysis of all individual components of $\gamma$ shows that $\gamma_{xxz}$ is the largest among all components because Gaussian aligns the molecular z-axis along its dipole moment during the calculation of hyperpolarizabilities. The z-axis diagonal components are calculated to be 71.10 $\times 10^{-36}$ esu for compounds BTCC and MBTB, respectively. The larger amplitudes of diagonal components are usually an advantage over off-diagonal components where the aforementioned is easy to reproduce in an experimental setup for polar molecules. Furthermore, the average static $\gamma$ amplitudes are found to be 27.30 $\times 10^{-36}$ and 102.91 $\times 10^{-36}$ esu for the compounds BTCC and MBTB, respectively. The average $\gamma$ amplitude of compound MBTB is found to be 3.77 times larger, which might be due to better charge-transfer characteristics in MBTB, as will be discussed in the following sections. To highlight a real-time application, it is important to compare the newly designed molecules with computationally studied previous NLO molecules. Usually, urea is used as a prototype NLO molecule. We have compared the NLO amplitudes of BTCC and MBTB with urea, thiourea, and other similar derivatives by searching through the rigorous literature. As the literature about third-order NLO polarizability of thiourea derivatives is limited, we found a few examples, which are shown in Table 4. A comparative analysis

### Table 3. Average Third-Order Nonlinear Polarizabilities (a.u. and $10^{-36}$ esu Units) along with Their Individual Components for BTCC and MBTB at the M06-2X/6-31G* Level of Theory

|        | BTCC          | MBTB          |
|--------|---------------|---------------|
| $\gamma_{xxz}$ | 2.1945 $\times 10^4$ a.u. | 16.9326 $\times 10^4$ a.u. |
| $\gamma_{yyy}$ | 1.2379 $\times 10^4$ a.u. | 5.2303 $\times 10^4$ a.u. |
| $\gamma_{zzz}$ | 14.5152 $\times 10^4$ a.u. | 40.9299 $\times 10^4$ a.u. |
| $\gamma_{xyy}$ | 0.8733 $\times 10^4$ a.u. | 7.1102 $\times 10^4$ a.u. |
| $\gamma_{xzz}$ | 2.8846 $\times 10^4$ a.u. | 8.4681 $\times 10^4$ a.u. |
| $\gamma_{yxx}$ | 0.8200 $\times 10^4$ a.u. | 3.9560 $\times 10^4$ a.u. |
| $\gamma_{zxy}$ | 5.4208 $\times 10^4$ a.u. | 20.4327 $\times 10^4$ a.u. |

**Figure 8.** Molecular geometries for compounds BTCC and MBTB at the B3LYP/6-311++G(d,p) level of theory, where both experimental and optimized geometries are shown side-by-side.
hyyperpolarizabilities with full parameter dependence has been studied in our previous studies. For more detailed studies about the abovementioned two-level and three-level approximations, we encourage the reader to look into the works of Bredest et al. and Nakano et al., along with others. For the purpose of brevity, we can currently consider transition energy as a crucial factor owing to its cubic terms, which are involved in the denominator of the two-level and three-level approximations. The UV-visible spectra indicate that MBTB shows lower transition energy as compared to BTCC, which might have contributed more to enhancing its NLO response property as compared to BTCC.

### 3.4. Frontier Molecular Orbitals (FMOs)

The FMOs having HOMO – i and LUMO + i (where i = 0 and 1) are visualized from optimized geometry to comprehend the trend of the inter-/intra-molecular charge-transfer process inside the entitled molecules. The 3-D diagrams of these orbitals are shown in Figure 10. The evaluation of FMOs of compound BTCC shows that its HOMO and HOMO-1 are localized over the periphery of the sulfur and carbon bond, which might be composed of a lone pair of sulfur atoms in the BTCC molecule. While on the other hand, the LUMO and LUMO + 1 can be seen spreading over the pi-conjugation toward the phenyl ring, which is obvious because the other side consists of unconjugated cyclohexane carboxylic acid. Unlike the BTCC molecule, MBTB shows an intermolecular charge-transfer character owing to its dimeric structure. Such a kind of charge transfer is crucial for obtaining better NLO response properties because usually, the electric field produced by the internal charge-transfer process interacts with the field of intense laser light to cause a change in its frequency, leading to the NLO phenomenon. Furthermore, the energy values of frontier orbitals are also calculated for optimized electronic structures, and are given in Table 5 for HOMO – i and LUMO + i (where i = 0, 1, 2, and 3). The HOMO–LUMO energy gaps (ΔE_{H-L}) for compounds BTCC and MBTB are calculated to be 3.95 and 3.59 eV, respectively. The ΔE_{H-L} value of MBTB is seen to be 0.36 eV lower as compared to BTCC owing to slight destabilization (about 0.306 eV) of HOMO in MBTB.

### 3.5. Molecular Electrostatic Potential (MEP) Analysis

The tendency of nucleophilic or electrophilic attacks on the surface of a given molecule can be predicted using MEPs. The positive and negative charge distributions are used to create

Table 4. Average Third-Order Nonlinear Polarizabilities (a.u. and 10\(^{-36}\) esu Units) along with Their Individual Components for BTCC and MBTB at the M06-2X/6-31G* Level of Theory

|        | γ \(\times 10^4\) a.u. | γ \(\times 10^{-36}\) esu |
|--------|------------------------|--------------------------|
| BTCC   | 5.4208                 | 27.30  present study     |
| MBTB   | 20.4327                | 102.91 present study     |
| urea   | 0.1674                 | 0.84   present study     |
| thio尿a| 0.2109                 | 1.062 present study      |
| 4-benzyl-1-(1-ferroceny lethyl) thiosemicarbazones (1)\(^a\) | 2.1175 | 10.66  ref 45 |
| 4-(4-chlorobenzyl)-1-(1-ferrocenyl-ethy l) thiosemicarbazone (2)\(^a\) | 2.7400 | 13.80  ref 45 |
| 4-(2-bromo benzyl)-1-(1-ferrocenylethyl)thiosemicarbazone (3)\(^a\) | 2.5973 | 13.08  ref 45 |
| (Z)-N-cyclohexyl-2-((2-oxo-2H-chromen-3-yl)-methoxy)benzy ldene) hydrazin ecarbothioamide \((3a)^{a}\) | 16.1500 | 81.34  ref 47 |
| (Z)-N-(2,4-dimethylphenyl)-2-((2-oxo-2H-chromen-3-yl)-methoxy) benzylidene)hydrazin ecarbothioamide \((3b)^{a}\) | 18.610 | 93.73  ref 47 |
| 3-(4-chlorophenyl)-1-(pyridin-3-yl) prop-2-en-1-one\(^d\) | 5.1800 | 26.10  ref 46 |
| 4 Present study used M06-2X/6-31G*.      | 7M06-2X/6-311+G(d,p).   |
| 5 M06-2X/6-311+G(d,p).                   | 6M06/6-311+G(d,p).      |
| 7B3LYP/6-31G(d,p).                      | For unit conversion of γ, 1 a.u. = 0.00050367 \(\times 10^{-36}\) esu.

indicates that the γ amplitudes of BTCC and MBTB are about 26 and 102 times larger than thiourea, as calculated in the present study at the same M06-2X/6-31G* level of theory. Similarly, the γ amplitudes of BTCC and MBTB are also larger than the ferrocenylethyl-thiosemicarbazone derivatives (1, 2, and 3) studied by Jawaria et al. and Shkir et al. Furthermore, a comparison with hydrazinecarbothioamide derivatives shows that compound MBTB possesses slightly larger amplitudes than the reported derivatives. These comparable γ amplitudes indicate that the above-entitled compounds will be penitential candidates for efficient third-order NLO applications.

### 3.3. UV–Visible Spectra and Origin of Hyperpolarizability

The theoretically calculated UV-visible absorption spectra of BTCC and MBTB at the M06-2X/6-31G* level of theory are shown in Figure 9, while complete details about transition energies, oscillator strengths, and transition dipole moments from ground to crucial excited states are shown in Table S3 of the Supporting Information. A careful analysis of Figure 9 shows that BTCC shows two peaks at about 261 and 218 nm, where 218 nm is the wavelength with the highest absorption value. On the other hand, MBTB shows the only maximum absorption peak at about 294 nm. It is clear from the spectra that both compounds possess the maximum absorption value in the UV region, with good potential as UV sensors. It is well-documented in our and others’ previous studies that hyperpolarizabilities can be correlated with the spectroscopic parameters using so-called two-level and three-level models. According to these models, a molecule with lower transition energy, higher oscillator strength, or higher transition dipole moments and larger ground to excited state dipole moment changes possesses better NLO response properties, at least for the diagonal component of hyperpolarizability. The origin of

Figure 9. Theoretically calculated UV-visible spectra of BTCC and MBTB at the M06-2X/6-31G* level of theory.
compounds to understand their chemical and biological activities. The GCRD values consist of ionization potential (IP), electron affinity (EA), electronegativity (\(\epsilon\)), chemical potential (\(\mu\)), global hardness (\(\eta\)), global softness (\(\sigma\)), and electrophilicity index (\(\omega\)) (Table 6). Both title derivatives of thiourea have high ionization potential, global hardness, and nucleophilicity index values. Global hardness represents the resistance to the change in electron distribution in a group of nuclei and electrons. In both compounds, BTCC and MBTB, we can see that being strong nucleophiles, they do not favor the change in the electron distribution. Chemical potential values for both title compounds are very low, representing low escape tendency of electrons. Overall, DFT analysis suggests that both titles of thiourea are strong nucleophiles with high electron mobility within the molecular orbitals.

4. CONCLUSIONS AND PROSPECTIVES

Two novel crystalline unsymmetrical acyl thiourea derivatives, 4-((3-benzoylthiourea)ido)methyl)cyclohexane-1-carboxylic acid (BTCC) and methyl 2-((3-benzoylthiourea)azo)benzoate (MBTB), were synthesized efficiently. The SC-XRD analysis recognized the presence of noncovalent interactive forces, mainly hydrogen bonding, responsible for crystal packing and stability. The Hirshfeld surfaces analysis demonstrated the relative percentage contributions of intermolecular interactions that are S···H/\(\mu\)/\(\sigma\)/\(\eta\)/\(\omega\)/O, O···H/\(\mu\)/\(\sigma\)/\(\eta\)/\(\omega\)/O, and H···H with 12.4, 16.7, and 51%, respectively, in the case of BTCC, while S···H/\(\mu\)/\(\sigma\)/\(\eta\)/\(\omega\)/O, O···H/\(\mu\)/\(\sigma\)/\(\eta\)/\(\omega\)/O, and C···H/\(\mu\)/\(\sigma\)/\(\eta\)/\(\omega\)/C with 12.1%, 11.6%, 17.3%, and 16.9% and 33.8%, 35.4%, 29.1%, and 29.4%, respectively (for molecules A and B), in the case of MBTB. The molecular geometries were successfully optimized and compared with their experimental counterparts using quantum chemical methods. The quantum chemical analysis illustrated the charge-transfer characteristics in the entitled molecules as visualized by their frontier molecular orbitals and MEPs. The third-order NLO polarizability amplitudes are calculated to see NLO response properties, which are found to be 27.30 × 10⁻⁶⁶ and 102.91 × 10⁻³⁶ esu for compounds BTCC and MBTB, respectively. The optical spectra for both compounds were successfully calculated theoretically and explained in terms of the NLO structure—property relationship. A comparative analysis indicates that the \(\gamma\) amplitudes of BTCC and MBTB are about 26 and 102 times larger than thiourea, as calculated in the present study at the same M06-2X/6-31G* level of theory. These nonzero \(\gamma\) amplitudes show their significant potential for possible NLO applications in the future.

5. EXPERIMENTAL SECTION

5.1. Synthetic Procedure. The literature-reported strategy was followed for the synthesis of BTCC and MBTB. Accordingly, a solution of ammonium thiocyanate in anhydrous acetone (20 mL) was heated up to the boiling point, followed by the drop-wise addition of benzyl chloride. To this solution, the preheated 4-(aminomethyl)cyclohexane-1-carboxylic acid (in the case of compound BTCC) and methyl 2-aminobenzoate (in the case of MBTB) was added and stirred for 30 min and then poured in cold water. The precipitates of the expected products were filtered, dried, and recrystallized in ethanol (Scheme 1). 

5.2. Chemicals and Instrumentation. For the best efficient synthesis of title compounds, reagents and solvents of the best possible quality are obtained from eminent chemical

Table 5. Calculated Energy Values (in eV) for HOMO \(- i\) and LUMO \(+ i\) where \(i = 0, 1, 2, 3\) Molecular Orbitals for the Compounds BTCC and MBTB

|       | BTCC                  | MBTB                  |
|-------|-----------------------|-----------------------|
| LUMO + 3 | −0.4539               | −1.5415               |
| LUMO + 2 | −0.6618               | −1.6629               |
| LUMO + 1 | −1.1026               | −1.9649               |
| LUMO   | −2.1421               | −2.1924               |
| \(\Delta E_{H-L}\) | 3.9473               | 3.5903               |
| HOMO   | −6.0894               | −5.7827               |
| HOMO − 1 | −6.3520               | −6.0341               |
| HOMO − 2 | −7.6450               | −6.0796               |
| HOMO − 3 | −7.7161               | −6.2494               |

MEP plots for optimized geometries of the compounds BTCC and MBTB (see Figure 11). For both compounds, BTCC and MBTB, the positive and negative maxima range from \(-5.692 e^{-2}\) to \(+5.692 e^{-2}\) and \(-6.098 e^{-2}\) to \(+6.098 e^{-2}\), respectively. An overview of Figure 11 shows that sulfur and oxygen atoms possess more negative potentials, which are favorable regions for the attraction of nucleophilic species. The positive maxima are not visible on the MEP surface of both entitled molecules. Overall, neutral green regions are dominant in both the molecules originating from carbon atom skeletons.
companies like Acros Organics, Sigma-Aldrich, etc. A Bruker Kappa APEXII CCD X-ray diffractometer is employed for data collection, which has an X-ray tube that generates Mo Kα radiation. A single crystal of suitable size is mounted on the goniometer head, and Bruker Apex-II software is employed for data collection. The mechanism for collecting data is ω-scan and integration of data is performed using SAINT software. The raw data are solved by employing a direct method in SHELXS97 software, whereas data refinement is performed using SHELXL 2018/3 software. All non-H atoms are refined by assigning anisotropic displacement parameters, whereas H atoms are located on ideal sites and refined as riding atoms with relative isotropic displacement parameters. For a graphical illustration of SC-XRD results, Mercury 4.0, PLATON, and ORTEP-3 are employed.

### ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c04884.

Packaging diagram of BTCC, only selected H atoms are shown for clarity (Figure S1); graphical representation of C−H⋯π and C−O⋯π interaction in BTCC, only selected H atoms are shown for clarity, distances are measured in Å, and Cg1 is the centroid of the phenyl ring (C11−C16) (Figure S2); packing diagram of MBTB, only selected H atoms are shown for clarity (Figure S3); graphical representation of C−H⋯π interaction in MBTB that connect molecules of opposite type with each other, only selected H atoms and a major part of the disordered group are shown for clarity (Figure S4); molecular arrangement in the BTCC: (A) within the parallel planes and (B) parallel planes (Figure S5); molecular arrangement in the MBTB: (A) stacking of the molecular layers and (B) perpendicular arrangement of molecular layers (Figure S6); percentage contribution of interaction of an atom inside HS with the atoms of molecules present in the neighborhood of the HS for BTCC and for MBTB, respectively (Figure S7); percentage contribution of interaction of all of the atoms in HS with the atoms of molecules present in the neighborhood of HS for both compounds (Figure S8); graphical representation of void analysis along a crystallographic axis for compounds BTCC (A) and MBTB (B) (Figure S9).

#### Table 6. Calculated GCRD Parameters for BTCC and MBTB

| reactivity parameters | BTCC  | MBTB  |
|-----------------------|-------|-------|
| IP                    | 7.8699| 6.8885|
| EA                    | 0.0904| 0.0850|
| γ                     | 3.9801| 3.7867|
| µ                     | −3.9801| −3.7867|
| η                     | 7.7795| 6.2035|
| σ                     | 0.01285| 0.01612|
| ω                     | 1.0182| 1.1557|
| N                     | 3.3443| 3.6382|

### Scheme 1. Synthesis of Novel Unsymmetrical Acyl Thiourea Derivatives BTCC and MBTB

![Scheme 1](image_url)

Figure 11. Molecular electrostatic potential drawn over total density surfaces for compound BTCC (left) and for compound MBTB (right). The isovalue for total surface density is ±0.002 a. u.

![Figure 11](image_url)
MBTB (B) (Figure S9); optimized dimeric system (MBTB) with Grimme’s dispersion correction (DC) and without Grimme’s DC (Figure S10); selected bond lengths (Å) and bond angles (°) for BTCC and MBTB (Table S1); average third-order nonlinear polarizabilities ($\gamma \times 10^{-36}$ esu) for BTCC under different field amplitudes at the M06-2X/6-31G* level of theory (Table S2); and change in the dipole moment between ground and excited states ($\Delta \mu$), oscillator strength ($f$), transition energies ($E^0$), and % configuration interaction of crucial transitions at the TD-M06-2X/6-31G* level of theory (Table S3) (PDF)

Benzoyltrenpub (CIF)

methanithioureapub (CIF)

■ AUTHOR INFORMATION

Corresponding Authors
Muhammad Ashfaq – Department of Physics, University of Sargodha, Sargodha 40100, Pakistan; Email: muhammadashfaq1400@gmail.com

Khurram Shahzad Munawar – Department of Chemistry, University of Sargodha, Sargodha 40100, Pakistan; orcid.org/0000-0001-9055-2519; Email: khurramchemist@gmail.com

Authors
Muhammad Nawaz Tahir – Department of Physics, University of Sargodha, Sargodha 40100, Pakistan
Shabbir Muhammad – Department of Physics, College of Science, King Khalid University, Abha 61413, Saudi Arabia; orcid.org/0000-0003-4908-3313

Akbar Ali – Department of Chemistry, Government College University Faisalabad, Faisalabad 38000, Pakistan; orcid.org/0000-0002-2914-0934

Georgii Bogdanov – Department of Chemical and Biomolecular Engineering, University of California Irvine, Irvine, California 92697, United States

Saleh S. Alarfaji – Department of Chemistry, College of Science, King Khalid University, Abha 61413, Saudi Arabia; orcid.org/0000-0001-7297-7185

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.1c04884

Notes
The authors declare no competing financial interest.

©Department of Chemistry, University of Mianwali, Mianwali 42200, Pakistan.

Department of Physics, University of Mianwali, Mianwali 42200, Pakistan.

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