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Robustness of thioamide $\{\cdots H–N–C=S\}_2$ synthon: synthesis and the effect of substituents on the formation of layered to cage-like supramolecular networks in coumarin-thiosemicarbazone hybrids

Aminah Hameed[a], Zahid Shafiq[a], Muhammad Yaqub[a], Mazhar Hussain[a], Hafiz Badaruddin Ahmad[a], Muhammad Nawaz Tahir[b] and Muhammad Moazzam Naseer[c]*

[a]*Institute of Chemical Sciences, Organic Chemistry Division, Bahauddin Zakariya University, Multan 60800, Pakistan*

[b]*Department of Physics, University of Sargodha, Sargodha, Pakistan*

[c]*Department of Chemistry, Quaid-i-Azam University, Islamabad 45320, Pakistan*

Abstract:

The applications of thioureas in crystal engineering have increased dramatically over the past few years. However, their analogs namely *N*-imino thioureas/thiosemicarbazones are largely ignored, despite of the fact that these can be more interesting with respect to crystal engineering applications due to the presence of additional *N*-imino moiety. Aiming to highlight their importance in crystal engineering/supramolecular chemistry, three structurally related coumarin-thiosemicarbazone hybrids (**3a-3c**) have been designed, synthesized and crystallographically characterized. All of the compounds showed a general preference for the adoption of the *cis, trans* conformation around the central thiourea moiety; a conformation which is ideal for the formation of a dimeric hydrogen-bonded $R_2^2(8)$ $\{\cdots H–N–C=S\}_2$ synthon as the building block. Therefore, this dimeric synthon is observed in all of the compounds, regardless of the formation of layered to cage-like three dimensional supramolecular networks depending on different substituents. The prevalence of the *cis, trans* conformation and robustness of thioamide dimer synthon in thiosemicarbazones indicates their potential use as a design element in crystal engineering.

*Corresponding author: Fax: +92 51 90642241. Tel.; +92 51 90642129; E-mail: moazzam@qau.edu.pk (M.M. Naseer), zahidshafiq25@hotmail.com (Z. Shafiq)

1. Introduction

The relationship between structure and function is the main driving force for the crystal engineers to dissect the solid state networks into supramolecular synthons so that the involved principles in their composition can be understood and the acquired knowledge may be used for the deliberate design of novel crystalline materials with desired functions.[1-22] In this context, nevertheless, highly consistent synthons with sufficiently directional non-covalent interactions are required. Among many such identified synthons so far, urea and thiourea occupy a prominent place in crystal engineering, that are capable of forming persistent hydrogen-bonded chains in a variety of environments.[23-31] It is interesting to mention here that at one stage, the potential of thioureas was underestimated relative to ureas, most probably due to the consideration of weak hydrogen-bond accepting ability of thiocarbonyl as compared to carbonyl group.[32-34] Once, it was established that the strength of any hydrogen bond depends more on donor acidity than on acceptor basicity,[35, 36] thioureas having stronger hydrogen bond donating ability,[37] emerged as equally attractive and robust supramolecular synthons in crystal engineering.[34, 38-43] In fact, a comparative study of structurally similar urea and thiourea derivatives showed the latter to have a larger dimerization constant in solution.[44]

Thiosemicarbazones or *N*-iminothioureas can be approached by the simple condensation reaction of aldehydes/ketones with thiosemicarbazides.[45-49] These are versatile molecules not only due to their broad profile in the medicinal chemistry but also due to their ligating abilities in coordination chemistry in various ways. Being thiourea analogs, however, their use in crystal engineering remains largely unexplored.[50-52] As realized from the available crystal data of this class of compounds, they are conformationally freezed due to intramolecular hydrogen bonding (a feature that is absent in thioureas) and adopt *cis-trans* conformation in most cases (Figure 1)

as compared to both the *trans-trans* and *cis-trans* geometries of thioureas depending on the substituents. Due to this preferred *cis-trans* conformation, they offer thioamide moiety for the formation of intermolecular $R_2^2(8)$ cyclic dimers $\{\cdots H–N–C=S\}_2$ *via* two complementary NH···S hydrogen bonds (Figure 1). Furthermore, the proton on nitrogen, due to the direct attachment of sp^2-hybridized imino moiety, is relatively more acidic as compared to substituted thioureas. These two features make this class of compounds more attractive than thioureas in crystal engineering.

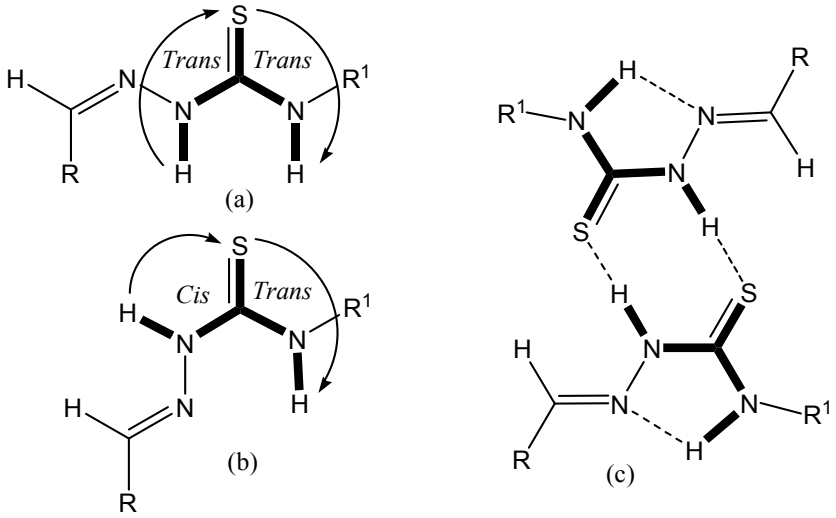


Figure 1. Thiourea moiety in thiosemicarbazones: a) *trans, trans* conformation; b) *cis, trans* conformation; c) formation of thioamide dimer $\{\cdots H–N–C=S\}_2$ synthon due to *cis, trans* conformation

Very recently, we have highlighted these features using ferrocene-based thiosemicarbazones[53] and herein as continuation of previous work and our continuous research interests in the study of non-covalent interactions,[54-57] we report the synthesis of new structurally related coumarin-thiosemicarbazone hybrid molecules **3a-3c** and using these molecules as platform, demonstrate the robustness of thioamide dimer $\{\cdots H–N–C=S\}_2$ synthon of thiosemicarbazones. The purpose of introducing freely rotatable coumarin moiety in these structures is to create a flexible environment for different possible non-covalent interactions.

Although, the anticipated thioamide dimer synthon is observed in all the structures but a significant effect of substituents/competing interactions on the geometry of thioamide dimer synthon has been realized, which dictates the formation of layered to cage-like supramolecular networks.

2. Experimental

2.1 General information

All reagents and solvents used in this study were obtained from the supplier or recrystallized/redistilled as required. Thin layer chromatography (TLC) was performed using aluminium sheets coated with silica gel 60 F_{254} (Merck). Melting points of all the synthesized compounds have been determined in open capillary tubes by using Gallenkamp apparatus (MP-D) and were uncorrected. IR spectrum in the range of 4000-400 cm^{-1} was obtained on a Thermo Nicolet-6700 FT-IR Spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker spectrometer at 300 MHz and 75 MHz in $CDCl_3$, respectively using residual solvent signals as a reference. The atom labelling scheme for the description of ^{1}H and ^{13}C NMR chemical shift values provided below is shown in Figure S1.

2.2 Synthesis of 2-[(2-oxochromen-3-yl)methoxy]benzaldehyde **1**

To a stirred mixture of salicyladehyde (5.3 ml, 50 mmol) and aqueous trimethylamine (4.4 ml, 50 mmol) in methanol (50 ml) was added methylacrylate (13.6ml, 150 mmol) dropwise. The reaction mixture was then stirred for another 24 h and the white precipitate thus appeared were filtered and washed thoroughly with methanol to give pure **1** as a white solid.

1: Yield, 78%; mp, 190℃; IR (KBr), V (cm^{-1}): 1729(C=O). ^{1}H-NMR ($CDCl_3$), $^{\delta}$ (ppm): 5.13 (s, 2H, CH_2-C_{12}-H), 7.1 (s, 1H, CH- $C_{1,3,17}$-H), 7.34 (s, 1H, CH-C_2-H), 7.4 (s, 1H, CH-C_6-H), 7.45 (s, 1H, CH_{10}-H), 7.6 (s, 1H, CH-C_{18}-H), 7.8 (s, 1H, CH-C_{16}-H), 10.5 (s, 1H, CH-C_{15}-CHO), ^{13}C

NMR ($^{\delta}$ppm) 74.4 (C_{12}-CH_2), 121.5 (C_3-phenyl), 122.3 (C5-phenyl), 125 (C1-phenyl), 126.8 (C_2-phenyl), 128.4 (C_4-phenyl), 130.9 (C_{16}-phenyl), 131.4 (C_9-phenyl), 135.6 (C18-phenyl), 161.2 (C_{14}-phenyl), 192 (C_{20}-CHO).

2.3 *Synthesis of coumarin-thiosamicarbazone hybrids* **3a-3c**

In a round bottom flask, a solution of the appropriate thiosemicarbazide **2** (1 mmol) in ethanol (10 ml) was added dropwise to a stirred solution of **1** (1 mmol) in ethanol (10 ml). *p*-Toluene sulphonic acid (TsOH) (0.1 mmol, 10 mol%) was then added as catalyst and the reaction mixture was heated to reflux for 2 h, after which, the reaction mixture was cooled to room temperature. The whitish yellow precipitates thus appeared, were filtered, washed thoroughly with cold ethanol and dried to get pure products of **3a-3c**.

3a: Yield, 90%; mp, 196℃; IR (KBr), ν (cm^{-1}): 3576, 3264, 2933(NH), 1530(C=N), 1200(C=S). ^{1}H-NMR ($CDCl_3$), $^{\delta}$ (ppm): 2.0 (s, 1H, N-NH), 4.0 (s, 1H, CS-NH), 2.35 (s, 3H, CH-C_{32}H), 6.26 (s, 1H, CH-C_{31}H), 6.27 (s, 1H, CH-C_{27}-phenyl), 6.42 (s, 1H, CH-C_{29}-phenyl), 6.9 (d, 2H, CH-$C_{16,\ 28}$-phenyl), 7.02 (d, 2H, CH-$C_{1,\ 3}$-phenyl), 7.1 (s, 1H, CH-C_2-phenyl), 7.5 (s, 1H, CH-C_{15}-phenyl), 8.1 (s, 1H, CH-C=N), ^{13}C NMR ($^{\delta}$ppm) 74.4 (C_{11}-CH_2), 121.5 (C_3-phenyl), 122.3 (C5-phenyl), 125 (C1-phenyl), 126.8 (C_2-phenyl), 128.4 (C_4-phenyl), 130.9 (C_{16}-phenyl), 131.4 (C_9-phenyl), 114.4 (C_{18}-phenyl), 116.9 (C_{14}-phenyl), 143.0 (C=N-NH), 186 (C=S), 126.2 (C_{31}-phenyl), 125.1 (C_{29}-phenyl), 123.5 (C_{27}-phenyl), 129.0 (C_{28}-phenyl), 24.3 (C_{32}-phenyl-3-CH_3).

3b: Yield, 94%; mp, 152℃; IR (KBr), ν (cm^{-1}): 3676, 3100, 2933(NH), 1531(C=N), 1176(C=S). ^{1}H-NMR ($CDCl_3$), $^{\delta}$ (ppm): 2.0 (s, 1H, N-NH), 4.0 (s, 1H, CS-NH), 3.73 (s, 3H, CH-C_{32}-OCH_3), 5.97 (s, 1H, CH-C_{31}H), 6.02 (s, 1H, CH-C_{27}-phenyl), 6.13 (s, 1H, CH-C_{29}-phenyl), 6.9 (d, 2H, CH-$C_{16,\ 28}$-phenyl), 7.02 (d, 2H, CH-$C_{1,\ 3}$-phenyl), 7.1 (s, 1H, CH-C_2-phenyl), 7.5 (s, 1H, CH-C_{15}-phenyl), 8.1 (s, 1H, CH-C=N); ^{13}C NMR ($^{\delta}$ppm) 74.4 (C_{11}-CH_2), 121.5 (C_3-phenyl),

122.3 (C5-phenyl), 125 (C1-phenyl), 126.8 (C_2-phenyl), 128.4 (C_4-phenyl), 130.9 (C_{16}-phenyl), 131.4 (C_9-phenyl), 114.4 (C18-phenyl), 116.9 (C_{14}-phenyl), 143.0 (C=N-NH), 186 (C=S), 109.7 (C_{31}-phenyl), 110.3 (C_{29}-phenyl), 118.8 (C_{27}-phenyl), 130.1 (C_{28}-phenyl), 55.9 (C_{32}-phenyl-OCH_3).

3c: Yield, 95%; mp, 222℃; IR (KBr), V (cm^{-1}): 3315, 3270, 2933(NH), 1533(C=N), 1208(C=S). ^{1}H-NMR ($CDCl_3$), $^{\delta}$ (ppm): 2.0 (s, 1H, N-NH), 4.0 (s, 1H, CS-NH), 7.03 (s, 1H, CH-C_{30}H), 6.34 (s, 1H, CH-C_{27}-phenyl), 6.63 (s, 1H, CH-C_{29}-phenyl), 6.9 (d, 2H, CH-$C_{16,\ 28}$-phenyl), 7.02 (d, 2H, CH-$C_{1,\ 3}$-phenyl), 7.1 (s, 1H, CH-C_2-phenyl), 7.5 (s, 1H, CH-C_{15}-phenyl), 8.1 (s, 1H, CH-C=N), ^{13}C NMR ($^{\delta}$ppm) 74.4 (C_{11}-CH_2), 121.5 (C_3-phenyl), 122.3 (C5-phenyl), 125 (C1-phenyl), 126.8 (C_2-phenyl), 128.4 (C_4-phenyl), 130.9 (C_{16}-phenyl), 131.4 (C_9-phenyl), 114.4 (C_{18}-phenyl), 116.9 (C_{14}-phenyl), 143.0 (C=N-NH), 186 (C=S), 131.7 (C_{29}-4-Cl phenyl), 129.3 (C_{27}-phenyl), 127.3 (C_{28}-phenyl), 130.6 (C_{30}-phenyl), 136.8 (C_{31}-phenyl).

2.4 Crystallographic data collection and structural refinement

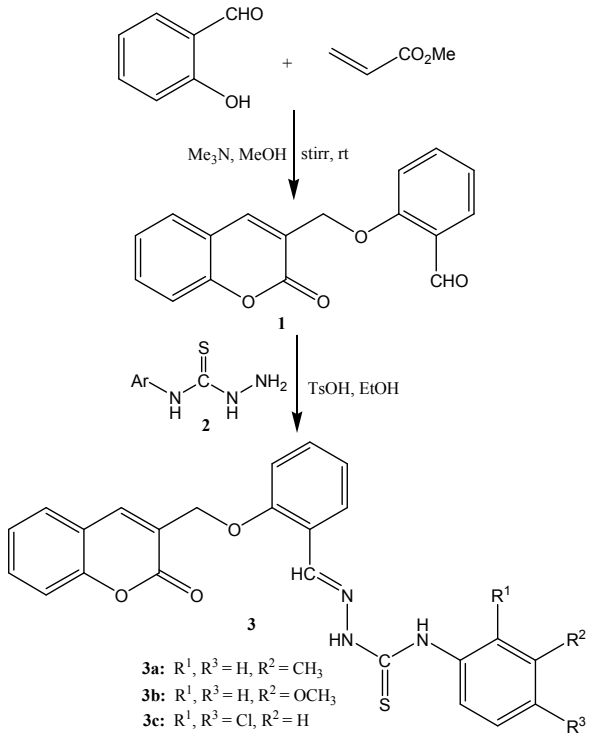
Single crystals of **3a-3c** were mounted on a thin glass fiber at room temperature and the reflection data were collected on a Bruker kappa APE XII CCD diffractometer equipped with graphite mono-chromated MoKα radiation (λ = 0.71073 Å). The data were also corrected to Lorentz and polarization effect. The structure was solved using SHELXS-97. Final refinement on F^2 was carried out by full-matrix least-squares techniques using SHELXL-97.[58] The crystal data of **3a-3c** and refinement values are summarized in Table 1.

Table 1. X-ray crystallographic data of **3a-3c**

Crystal data	**3a**	**3b**	**3c**
CCDC	1036467	1036468	1036469
Chemical formula	$C_{25}H_{21}N_3O_3S$	$C_{52}H_{46}N_6O_9S_2$	$C_{24}H_{17}Cl_2N_3O_3S$
M_r	443.51	963.06	498.36
Crystal system, space group	Triclinic, $P\bar{1}$	Monoclinic, $P2_1/c$	Monoclinic, $P2_1/c$
Temperature (K)	296	296	296
a, b, c (Å)	7.2519 (3), 11.3182 (5), 13.2908 (7)	13.2436 (6), 18.3753 (10), 19.6353 (11)	16.0381 (11), 9.7005 (7), 15.3686 (9)
α, β, γ (°)	91.507 (2), 98.145 (3), 94.768 (2)	102.698 (2)	108.349 (2)
V (Å^3)	1075.35 (9)	4661.5 (4)	2269.4 (3)
Z	2	4	4
Radiation type	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$
μ (mm^{-1})	0.18	0.18	0.41
Crystal size (mm)	0.40 × 0.30 × 0.26	0.42 × 0.28 × 0.26	0.40 × 0.30 × 0.16
Data collection			
Diffractometer	Bruker Kappa APEXII CCD diffractometer	Bruker Kappa APEXII CCD diffractometer	Bruker Kappa APEXII CCD diffractometer
Absorption correction	Multi-scan (*SADABS*; Bruker, 2005)	Multi-scan (*SADABS*; Bruker, 2005)	Multi-scan (*SADABS*; Bruker, 2005)
T_{min}, T_{max}	0.932, 0.957	0.930, 0.955	0.853, 0.935
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	16919, 4689, 3847	38623, 10150, 6744	19175, 4953, 3555
R_{int}	0.027	0.036	0.036
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0.639	0.639	0.639
Refinement			
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.036, 0.105, 1.02	0.044, 0.120, 1.01	0.039, 0.108, 1.02
No. of reflections	4689	10150	4953
No. of parameters	290	634	298
H-atom treatment	H-atom parameters constrained	H-atom parameters constrained	H-atom parameters constrained
$\Delta\rangle_{max}$, $\Delta\rangle_{min}$ (e Å^{-3})	0.22, -0.22	0.30, -0.28	0.21, -0.35

3. Results and discussion

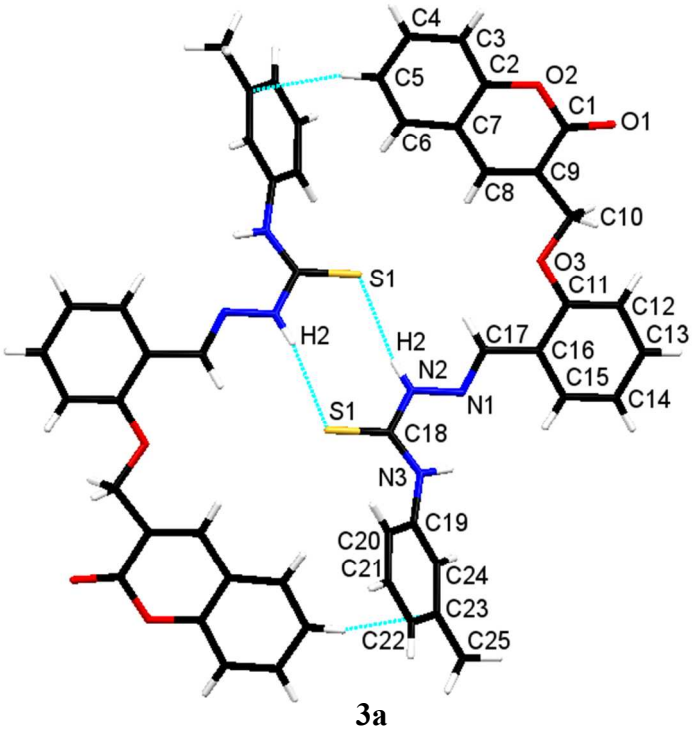
The designed coumarin-thiosemicarbazone hybrids **3a-3c** were synthesized in two steps. In the first step, coumarin derivative of salicylaldehyde **1** was prepared by the treatment of two equivalent of salicylaldehyde with one equivalent of methylacrylate through Baylis-Hillman reaction catalyzed by aqueous trimethyl amine. In the second step, **1** was then reacted with thiosemicarbazides **2** in ethanol solvent containing catalytic amount of *p*-toluene sulfonic acid to afford coumarin-thiosemicarbazone hybrids **3a-3c** in excellent yields (Scheme 1).



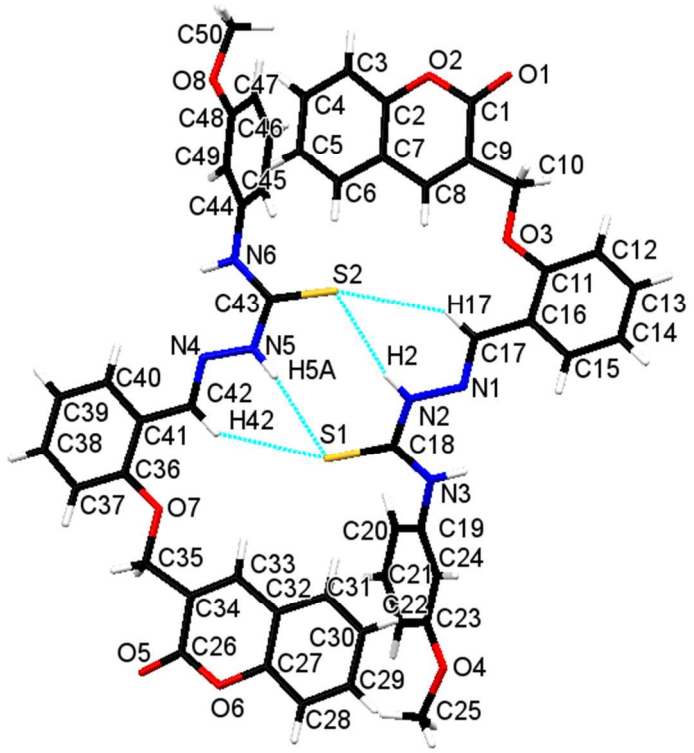
Scheme 1. Synthesis of coumarin-thiosemicarbazone hybrids **3a-3c**

Good quality single crystals of compounds **3a-3c** suitable for X-ray analysis were grown from 1,4-dioxane solvent by its slow evaporation. The molecular structures of coumarin-thiosemicarbazone hybrids **3a-3c** along with crystallographic numbering schemes are illustrated in Figure 2 and the selected geometric parameters are presented in Table 2. The central core of

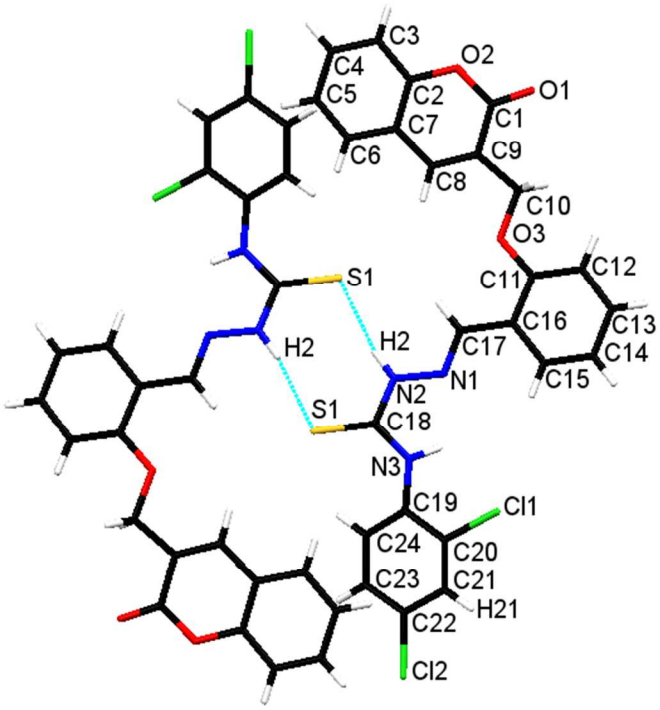
the molecules that consists of *N*-iminothiourea moiety is nearly planar in all the molecules (check torsion angles in Table 2). The reason of this planarity, nevertheless, can be credited to the significant delocalization of π-electron density over thiourea moiety, which is evidenced by the shorter N-C bond lengths [1.330(2)-1.361(2) Å] listed in Table 2, and hence the partial double bond character of N-C bonds. The slightly longer bond lengths [1.344(2)-1.361(2) Å] observed for one N-C bond, which is directly attached to the nitrogen of imino moeity (-N=C-) indicates less delocalization of nitrogen lone pair towards thiocarbonyl as compared to the other, most probably due to the attachment of sp^2-hybridized nitrogen atom. This planarity of the central core, allows the molecules to adopt different conformations highlighted in the introduction section (Figure 1). However, due to the presence of imino moiety and its apparent ability of making intramolecular hydrogen bond with the NH-protons [(N(3)-H(3A)···N(1) 2.105 Å in **3a**, 2.251 Å in **3b** (conformer A), (N(6)-H(6A)···N(4) 2.237 in **3b** (conformer B) and 2.085 Å in **3c**] provides preferably *cis, trans* conformations. It is worth noting here that this kind of intramolecular hydrogen bond can only be expected in thiosemicarbazones (thiourea analogs) of the general formula R-CH=N-NH-C(=S)-NH-R^1. There is no such internal conformational stability available in thioureas, R-NH-C(=S)-NH-R^1, resulting in both *trans, trans* and *cis, trans* conformations that are frequently observed in their structures.[39] An expected consequence of the preferred *cis, trans* conformation in thiosemicarbazones is the facile formation of a centrosymmetric thioamide $R_2^2(8)$ $\{\cdots H–N–C=S\}_2$ synthon which is observed in **3a-3c** (Figure 2).



3a



3b



3c

Figure 2. Dimeric pairs associated *via* the $\{\cdots H–N–C=S\}_2$ synthon in **3a-3c**

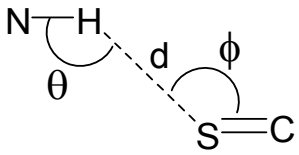
Interestingly, both compounds **3b** and **3c** crystalize in monoclinic crystal lattice with $P2_1/c$ space group as compared to **3a** which crystalizes in triclinic crystal lattice with $P\bar{1}$ space group. For **3b**, two different/independent molecules (called conformer A & conformer B) having slightly different bond lengths, bond angles and dihedral angles, present as hemi 1,4-dioxane solvate, are observed in its unit cell. However, both **3a** and **3c** have only one molecule in their crystallographic asymmetric unit cell. The unit cell parameters in all the three compounds are significantly different (Table 1), indicating the role of substituents on their crystal packing. Furthermore, the different geometries of centrosymmetric thioamide dimer $\{\cdots H–N–C=S\}_2$ synthon, also shows profound influence of substituents (see Table 3 for geometric parameters associated with this dimeric synthon operative in **3a-3c**). The sulfur atom involved in the formation of this synthon is bifurcated in case of **3b**, forming additional weak CH···S [C(17)-H(17)···S(2) 2.943 Å, C(42)-H(42)···S(1) 2.868 Å] contacts which are absent in both **3a** [C(17)-

H(9)···S(1) 3.048 Å and **3c** [C(17)-H(17)···S(1) 3.012 Å (Figure 2). Over and beyond the planner thiourea moiety in **3a-3c**, two aryl rings along with one coumarin ring are tilted to different extents depending on the substituents and available competing intermolecular interactions (see Figure S2-S4, ESI for dihedral angles of **3a-3c**).

Table 2. Selected geometric parameters; bond lengths (Å), bond angles (°) and tortion angles (°) for **1-5** derived from the X-ray crystallographic study

Compound	**3a**	**3b** (A)	**3b** (B)	**3c**
S(1)-C(18)	1.6810(13)	1.6816(18)	-	1.672(2)
S(2)-C(43)	-	-	1.6807(18)	-
N(3)-C(18)	1.3394(16)	1.330(2)	-	1.341(2)
N(6)-C(43)	-	-	1.342(2)	-
N(2)-C(18)	1.3574(17)	1.344(2)	-	1.361(2)
N(5)-C(43)	-	-	1.348(2)	-
N(2)-C(18)-S(1)	119.89(9)	118.61(19)	-	119.43(14)
N(5)-C(43)-S(2)	-	-	118.32(19)	-
N(3)-C(18)-S(1)	126.32(10)	124.7(2)	-	127.57(14)
N(6)-C(43)-S(2)	-	-	125.8(2)	-
S(1)-C(18)-N(2)-N(1)	177.93(9)	178.5(2)		172.10(14)
S(2)-C(43)-N(5)-N(4)	-	-	174.70(19)	-
S(1)-C(18)-N(3)-C(19)	-6.2(2)	-9.1(4)		-2.8(3)
S(2)-C(43)-N(6)-C(44)	-	-	-6.5(4)	-
C(24)-C(19)-N(3)-C(18)	147.84(15)	120.7(3)		31.4(3)
C(49)-C(44)-N(6)-C(43)	-	-	134.9(3)	-

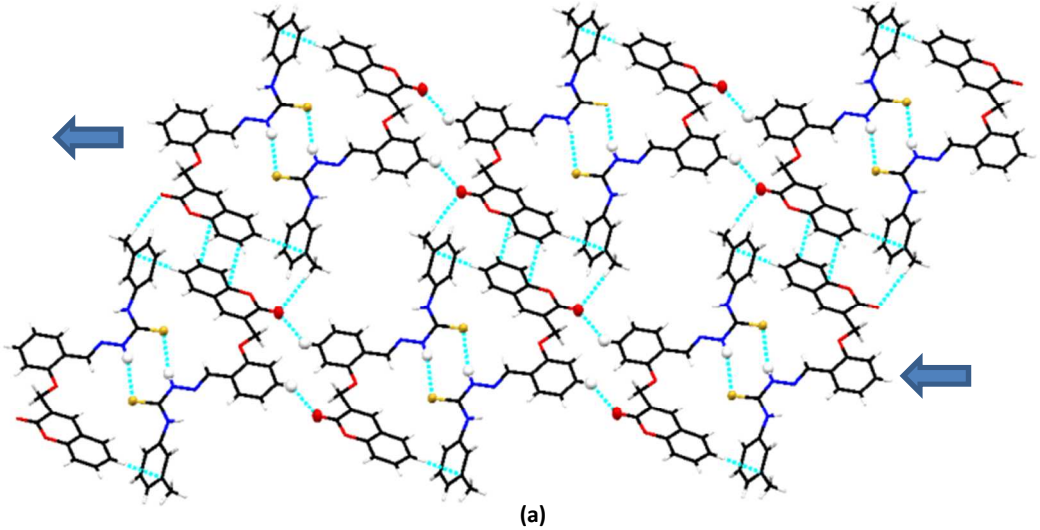
Table 3. N-H···S bond lengths and bond angles in eight-membered cyclic $R_2^2(8)$ dimeric motifs coumarin-thiosemicarbazone hybrids (**3a-3c**)



Compound	d (Å)	Θ (°)	ϕ (°)
3a	2.608	163.73	105.08
3b	2.562,	164.56,	109.43,
	2,580	154.54	110.33
3c	2.715	145.31	105.74

The effect of substituents on the molecular geometry, thioamide dimer synthon and an overall packing of **3a-3c** can be envisioned due to their different electronic and steric properties. As pointed earlier that the lone pair of electrons of nitrogens that are part of thiourea moiety delocalize towards thiocarbonyl, leaving the nitrogens slightly electron deficient with partial positive charge (Figure S5, ESI). Due to this deficiently of electrons, nitrogen, which is attached to the aryl ring containing different substituents, acts as weak electron withdrawing group, attracting the electron density mesomerically to some extent from the ring in addition to its withdrawing inductive effect. As a result, *ortho*- and *para*- positions of the ring in **3a-3c** carry partial positive charge, whereas the *meta*-position remains unaffected. Therefore, the introduction of any electron donating group at *meta*-position will not affect the thiourea moiety, but it can affect the electron density of the ring and may have some influence on the molecular packing. Keeping this in view, the methyl and methoxy groups, which are weak and strong

electron donating substituents, respectively with comparable size were introduced at this position in **3a** and **3b**. As shown in figure 3, **3a** (R^2 = CH_3) packs in layers which are composed of various 1D-chains. Each chain of the layer contains two different types of centrosymmetric dimeric motifs. The first one is the eight-membered cyclic $R_2^2(8)$ thioamide dimer [N(2)-H(2)···S(1) 2.608 Å] synthon, that is holding the two antiparallel arranged neighboring molecules; supported by CH-π interactions [C(5)-H(5)···C(23) 2.781 Å] interactions (Figure 2). The observation of CH-π contacts here may be attributed to the presence of methyl group. The second eighteen-membered cyclic $R_2^2(18)$ CH···O [C(13)-H(13)···O(1) 2.618 Å] interactions-based dimer, that is formed due to the antiparallel arrangement of coumarin and central aryl rings of two neighboring molecules, resulted in the formation of infinite 1D-chains. These chains are connected to the neighboring chains by means of CH···O [C(25)-H(13B)···O(1) 2.663 Å] and antiparallel-displaced π-π [C(2)···C(4) 3.366 Å] interactions, forming a 2D-layer (Figure 3a). Each layer of this assembly then connects to the next layer with the help of CH-π [C(10)-H(6B)···C(4) 2.645 Å, C(10)-H(6B)···C(5) 2.845 Å] and H-H[59,60] [H(6A)···H(6A) 2.282 Å, H(21)···H(25) 2.378 Å] interactions, providing an overall 3D-multilayered structure (Figure 3b & 3c).



(a)

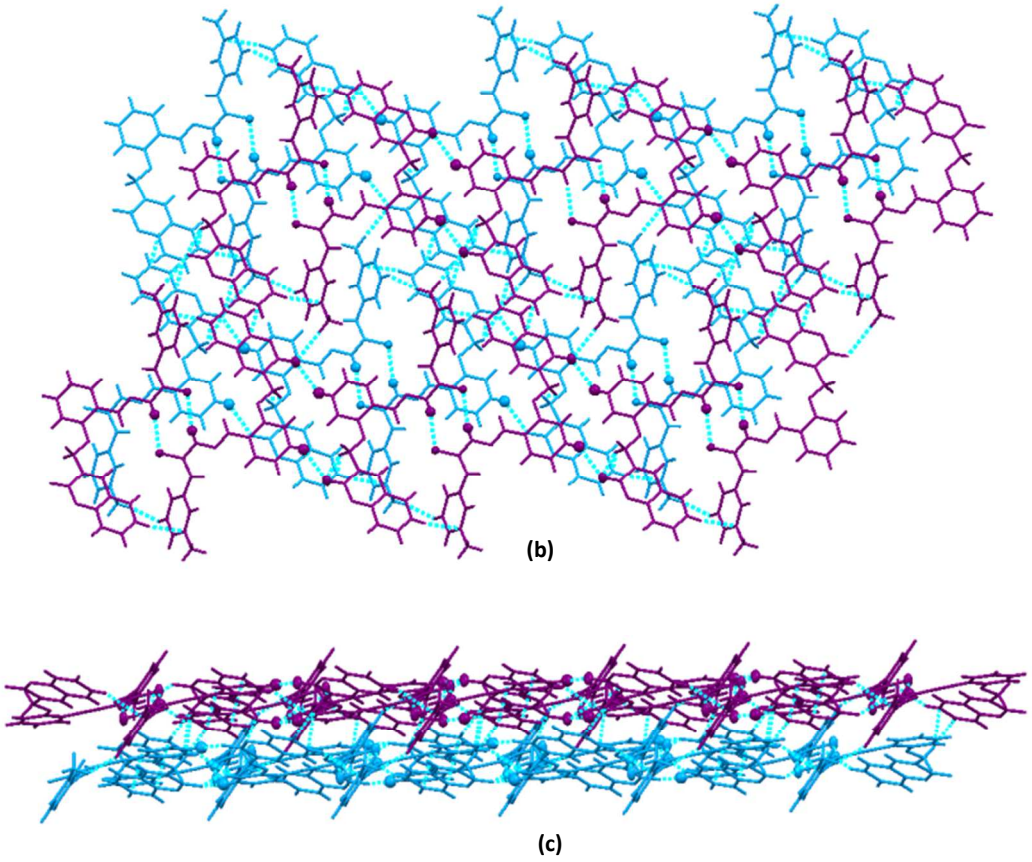
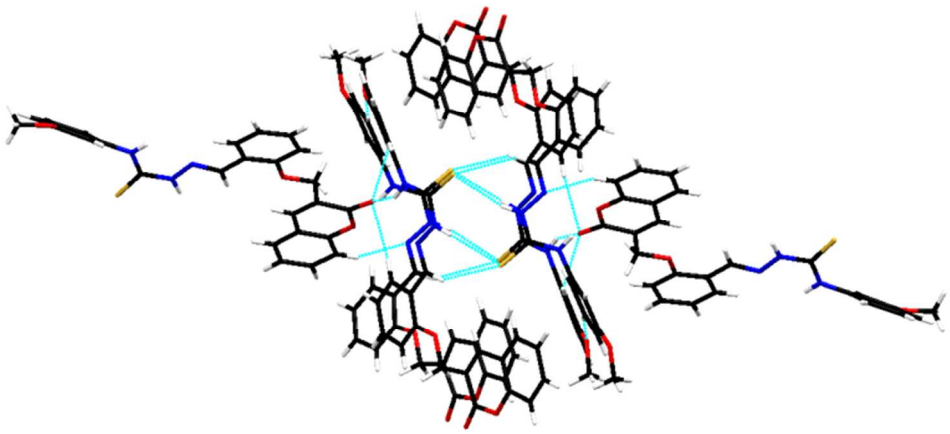


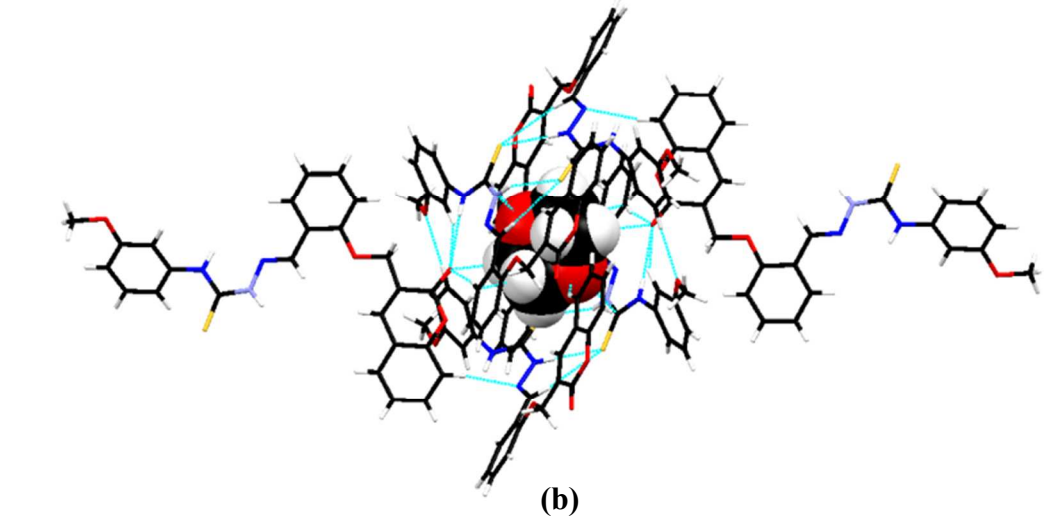
Figure 3. Packing of **3a:** a) two consecutive chains of a layer viewed along *b*-axis, arrows indicate the direction of 1D-chain; (b) two consecutive layers (shown in different colors for clarity) viewed along *b*-axis, and (c) along *c*-axis

The change of substituent from methyl (**3a**) to methoxy (**3b**) altered the packing from layered to cage-like network having a distorted 1,4-dioxane molecule in the cage cavity (Figure 4). It is important to mention here that methoxy group is not only a stronger electron donor than methyl, but is also a good hydrogen bond acceptor and can participate in hydrogen bonding through its electronegative oxygen atom.[56] Each cage of the 3D-network structure in **3b** consists of six molecules (three molecules of each conformer as it exists in the form of two conformers in the solid state). The conformer A and conformer B which are arranged antiparallel to each other interact by means of eight-membered cyclic $R_2^2(8)$ thioamide synthon [N(2)-H(2)···S(2) 2.562

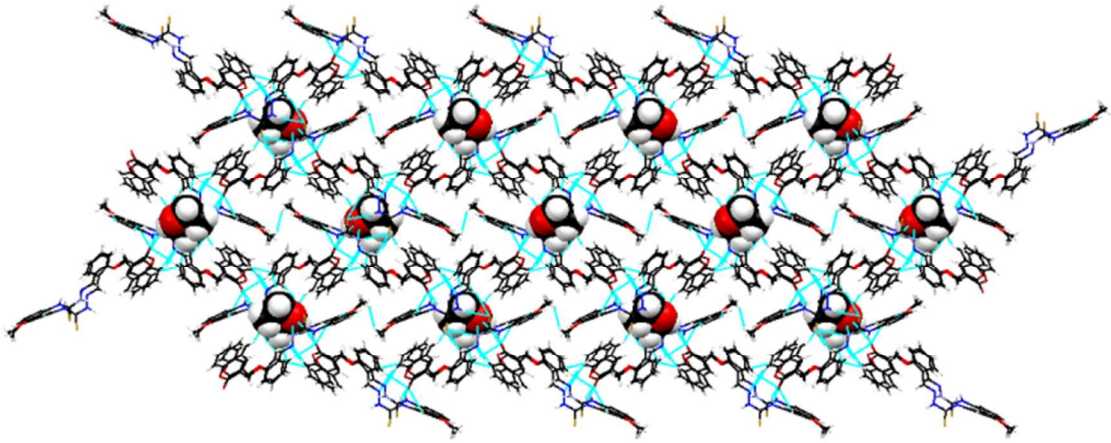
Å, N(5)-H(5A)···S(1) 2.580 Å]. The sulfur atoms here are actually bifurcated, forming weak hydrogen bond with azomethine hydrogens [C(17)-H(17)···S(2) 2.942 Å, C(42)-H(42)···S(1) 2.870 Å] (Figure 2). These paired conformers of **3b**, held together by thioamide synthon, serve as top and bottom bases of the cage (Figure 4a). Both of these bases are connected with each other by means of two CH···O [C(21)-H(21)···O(8) 2.406 Å] hydrogen bonds; formed between hydrogen of *N*-(3-methoxyphenyl) moiety of conformer A and oxygen of *N*-(3-methoxyphenyl) moiety of conformer B. Furthermore, two molecules of conformer B are acting as two pillar molecules of this assembly *via,* i) CH···N [C(28)-H(28)···N(1) 2.707 Å] interactions and ii) a trifurcated hydrogen bond, between carbonyl oxygen of its coumarin ring, and slightly acidic hydrogen at 2-position of *N*-(3-methoxyphenyl) moiety [C(49)-H(49)···O(5) 2.619 Å], thiourea hydrogen [N(6)-H(6A)···O(5) 2.547 Å] present in *trans* conformation and the hydrogen of central aryl ring (*ortho* to the semicarbazone moiety) [C(40)-H(40)···O(5) 2.625 Å] (Figure 4a). This self-assembled cage-like structure, which represent the basic supramolecular entity of the 3D-network structure, trap a molecule of 1,4-dioxane, mainly through CH···O, CH···π and lone pair-π interactions (Figure 4b).[56,61]



(a)



(b)

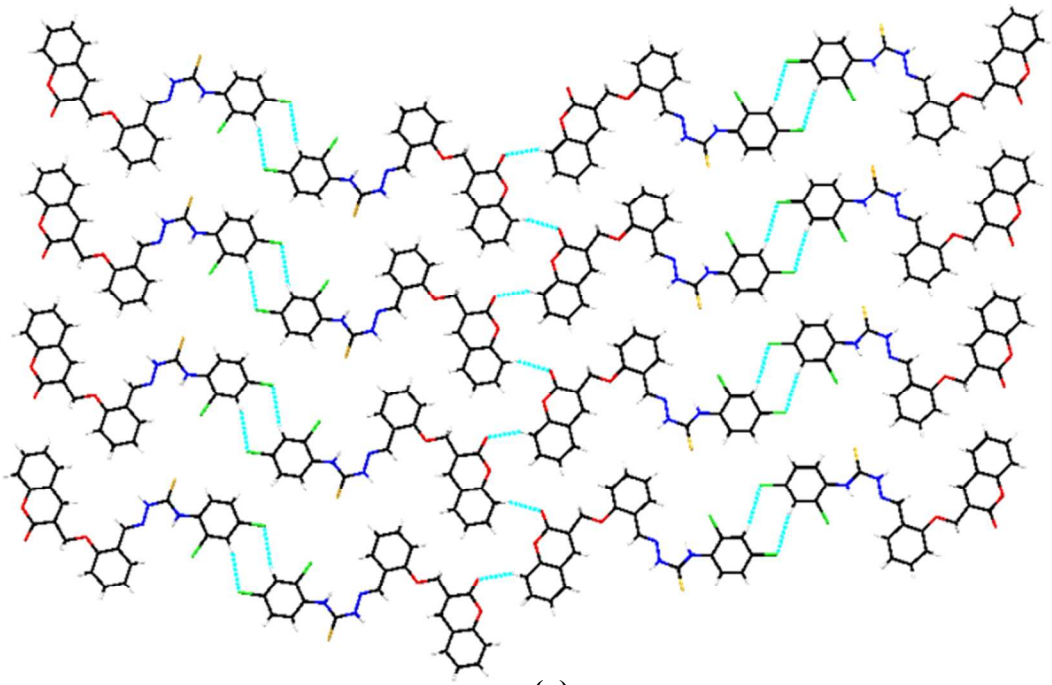


(c)

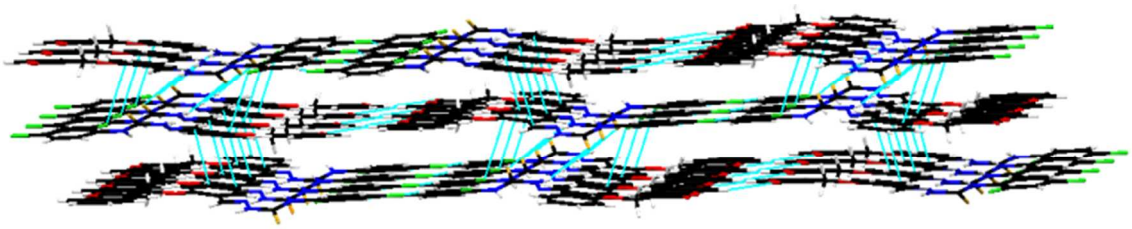
Figure 4. Packing of **3b:** (a) cage like supramolecular entity of the network, viewed along *a*-axis, solvent molecules are omitted for clarity; (b) cage like supramolecular entity of the network containing a distorted molecule of 1,4-dioxane, viewed along *c*-axis; (c) a 3D-cage like network of **3b** having 1,4-dioxane molecules encapsulated in the cage cavity

To further analyze the robustness of thioamide synthon of thiosemicarbazones in the presence of relatively strong competing hydrogen bonding interactions, two chloro substituents were introduced at 2- and 4-positions in **3c**.[62] In this case, a multi-layered assembly based on 1D zig-zag chains is obtained (Figure 5). As expected, a new centrosymmetric dimer $R_2^2(8)$ {···H–C=C-

Cl}$_2$ synthon is observed in addition to the thioamide dimer synthon. As shown in figure 5a, the 1D zig-zag chains are formed by the connection of various molecules of **3c** in head to head and tail to tail fashion through centrosymmtric CH···Cl based eight-membered [C(21)-H(21)···Cl(2) 2.908 Å] cyclic dimer synthons and CH···O [C(3)-H(3)···O(1) 2.498 Å] interactions between two coumarin rings. Each chain of the layer is then connected to its neighboring chain by means of another CH···O [C(3)-H(3)···O(1) 2.498 Å] interactions developed between two coumarin moieties (Figure 5a). Interestingly, eight-membered cyclic $R_2^2(8)$ thioamide [N(2)-H(2)···S(1) 2.715 Å] dimer synthon is slightly bent in this case, but serve as the key role in connecting different layers of this assembly along with Cl···π [Cl(1)···C(11) 3.444 Å] and π···π [C(17)···C(13) 3.277 Å] interactions, providing a multi-layered structure of **3c** (Figure 5b)**.**



(a)



(b)

Figure 5. Packing of **3c:** (a) four consecutive 1D-chains of a layer viewed along *c*-axis ; (b) three consecutive layers of a multilayered structure viewed along *b*-axis

As it is well-established that the linear bonds ($150° < \Theta < 180°$) are structurally more significant due to the dipole-monopole and dipole dipole contribution to the electrostatic energy which is a maximum at $\Theta = 180°$ and zero at $\Theta = 90°$.[36] On careful analysis of the data provided in Table 2, it can be anticipated that although packing of both **3a** and **3b** are greatly affected by the nature of two substituents, but in both of these compounds thioamide dimer synthon is the key supramolecular moiety. However, in **3c**, $\{\cdots H–C=C\text{-}Cl\}_2$ synthon is more linear (C-H···Cl, 166.39°) and appears to be dominant supramolecular moiety than relatively bent thioamide dimer synthon (145°). This also shows the powerful electron withdrawing inductive nature of two chloro-substituents, making the neighboring C-H a good H-bond donor, in addition to their own H-bond accepting abilities.[62] The prevalence of *cis-trans* conformation and in turn the formation of thioamide dimer synthon and its presence in different geometries in **3a-3c** demonstrates the flexible nature of thioamide dimer $\{\cdots H–N–C=S\}_2$ synthon of thiosemicarbazones and suggest its potential utility in the solid-state design.

4. Conclusions

In summary, we have synthesized and crystallographically characterized three new structurally similar coumarin-thiosemicarbazone hybrid molecules **3a-3c** in order to see the effect of substituents on molecular self-assembly and thioamide dimer synthon and for highlighting the

significance of thiosemicarbazones (*N*-iminothioureas) in crystal engineering in comparison to thioureas. All the compounds showed *cis, trans* conformation, providing thioamide moiety for the formation of self-complementary hydrogen bonded thioamide $\mathbf{R_2^2(8)}$ $\{\cdots$H–N–C=S$\}_2$ synthon. A significant influence of substituents on the geometry of this synthon is observed, leading to the formation of layered to cage-like network structures, which can be attributed to their different electronic contributions to the aryl ring. On the basis of the observed solid state structural features, it can be concluded that the compounds of general formula R-CH=N-NH-C(=S)-NH-R^1, being thiourea analogs, are more attractive in crystal engineering than thioureas and should get more attention from crystal engineering community. The presence of *N*-imino moiety in these compounds is not only making the neighboring NH-protons better H-bond donor, but also playing a key role in the stabilization of *cis, trans* conformation around thiourea moiety by intramolecular hydrogen bonding, providing a robust thioamide$\{\ldots$H–N–C=S$\}_2$ synthon. The prevalence of this dimer synthon in different environments advocates its robustness and the potential of this class of compounds as the design element in crystal engineering.

Acknowledgments

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