



**COMPARATIVE STUDY OF THE CRYSTAL STRUCTURES OF  
6-(4-BROMOPHENYL)-2-((6-METHYLBENZOFURAN-3-YL)  
METHYL) IMIDAZO [2, 1-B] [1, 3, 4] THIADIAZOLE  
(C<sub>20</sub>H<sub>14</sub>BRN<sub>3</sub>OS) AND ETHYL 2-AMINO-5-ROMOTHIAZOLE-  
4-CARBOXYLATE (C<sub>6</sub> H<sub>7</sub> BR N<sub>2</sub> O<sub>2</sub> S)**

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**ABSTRACT**

6-methyl-benzofuran-3-acetic acid has been utilized to synthesize 5- benzofuranylmethyl-2-aminothiadiazo- le with thiosemicarbazide. This illustrates the 4+1 approach for the construction of the five members heterocyclic. The core nucleus benzofuranylimidazo[2,1-*b*] [1,3,4] thiadiazoles has been synthesized by the reaction of **3** with appropriately substituted phenacyl bromides. This second approach is characteristic of the 3+2 that is double nucleophile and double electrophile approach. These crystal structured compounds may exhibit various biological and pharmacological action with various level of concentration. In future study will be concluded with in vitro and in vivo studies to investigate the potential biological property to make it commercial and to become economical compound in the industry.

**Keywords:** Methylbenzofuran, thiadiazole, bromothiazole, crystal x-ray study, Molecular Packing and hydrogen bonding.

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## INTRODUCTION

Naturally occurring and synthetic thiazole derivatives find applications as antioxidants [1], antibacterial drugs [2-4] and fungicidal treatment [5, 6]. Anti-inflammatory, analgesic and antipyretic activities are known for some thiazolyl and benzothiazolyl derivatives [7-9]. These compounds are able to block cartilage destruction during the inflammatory process and thus are a promising class of anti-inflammatory compounds [10].

The present title (I) compound 6-(4-bromophenyl)-2-((6-methylbenzofuran-3-yl)imidazo [2,1-b][1,3,4]) is one amongst a series of 2,5,6-trisubstituted thiadiazoles screened for their anti-inflammatory activity. The synthetic pathway for the preparation of the title compound is depicted in Scheme. The starting compound Ethyl-2-aminothiazole-4-carboxylate (**1**) [11] to an ice cold solution of ethyl-2-aminothiazole-4-carboxylate in glacial acetic acid a solution of bromine in acetic acid was added [12] to get the Ethyl-2-amino-5-bromothiazole-4-carboxylate. The title compound (II) was one of the series of compounds which were screened for their in vitro antitumor activity against human tumor cell lines. 2 – Aminothiazole is an important pharmacophoric moiety occurring in many sulpha drugs. The crystal structure of the compound has been determined to study the point of interest in the structure of this molecule is the orientation of the estu moiety with respect to the thiazole ring.

## MATERIALS AND METHODS

6-(4-bromophenyl)-2-((6-methylbenzofuran-3-yl) methyl) imidazo [2, 1-b] [1, 3, 4] thiadiazole (C<sub>20</sub>H<sub>14</sub>BrN<sub>3</sub>O<sub>5</sub>) and Ethyl 2-amino-5-bromothiazole-4-carboxylate (C<sub>6</sub> H<sub>7</sub> Br N<sub>2</sub> O<sub>2</sub> S) were synthesized in Department of Physics, Government College for Women, Kolar, Karnataka, India as per the designed scheme.

## EXPERIMENTAL

The present title compound (I) 6-(4-bromophenyl)-2-((6-methylbenzofuran-3-yl) methyl) imidazo [2,1-b] [1,3,4] thiadiazole is one amongst a series of 2,5,6-trisubstituted thiadiazoles screened for their anti-inflammatory activity.

A number of derivatives of (II) were synthesised, the use of 2-aminothiazole derivatives as inhibitors of human cancer and Alzheimer's disease was studied and developed. 2-Aminothiazole-5-carboxylates are an important

class of heterocycles in organic chemistry, especially in the preparation of biologically and medicinally useful agents such as angiotensin II antagonists, DNA minor groove binding analogs of netropsin. The antitumor activity of some thiazole derivatives for example thiazole nucleoside tiazofurin, distamycin, netropsin, thia- netropsin-with binding properties to DNA and the thiazole containing antitumor agent bleomycin was reported. Ethyl 2-substituted-aminothiazole-4-carboxylate analogs were tested for their in vitro antitumor activity against human tumor cell lines.

## CRYSTALLIZATION

Compound (I) has been grown by slow evaporation technique using chloroform. Colorless block like single crystals suitable for X-ray diffraction was obtained. The density of the crystal was measured by flotation technique using potassium iodide solution. The measured density agreed with the calculated density for Z = 2. Compound (II) has been grown by slow evaporation technique using ethanol. Colorless plate like single crystals suitable for X-ray diffraction was obtained. The density of the crystal was measured by flotation technique using potassium iodide solution. The measured density agreed with the calculated density for Z = 4.

## X- RAY DATA COLLECTION

The three dimensional X-ray intensity data (I) was collected using a crystal of size 0.30 × 0.30 × 0.20 mm mounted on an CAD4 Diffractometer with Cu-K<sub>α</sub> radiation ( $\lambda = 1.54180 \text{ \AA}$ ) with temperature 293(2). The intensities of reflections 3247 were collected in the 2 $\theta$  range 3.03 to 64.94<sup>o</sup>. The data was collected using  $\omega$  and  $\phi$  scans mode with h, 0 to 7, k, -11 to 11, l, - 17 to 17. The intensities were collected for Lorentz and polarization effects. Among the 2936 unique reflections collected, 2554 observed reflections with  $I \geq 2 \sigma(I)$ . The space group  $P \bar{1}$  assigned from the systematic absences. The cell parameters refined using 536 reflections the refined cell parameters are  $a = 6.2141(17) \text{ \AA}$ ,  $b = 9.8002(11) \text{ \AA}$ ,  $c = 14.891(3) \text{ \AA}$  and  $\beta = 97.068(18)^\circ$ ,  $V = 885.7(3) \text{ \AA}^3$ . Multi-scan absorption was carried out using SADABS [13]. The calculated absorption coefficient was 4.38 mm<sup>-1</sup>.

The three dimensional intensity data was (II) collected using a crystal of size 0.2 × 0.2 × 0.1 mm mounted on an CAD4 Diffractometer with graphite monochromated Mo-K<sub>α</sub> radiation ( $\lambda = 0.71073 \text{ \AA}$ ) in fine-focused sealed tube at

temperature 292(2)K. The cell parameters were refined by least-squares method using reflections in the  $2\theta$  range 1 to  $28^\circ$ . The data was collected using  $\omega$  and  $\phi$  scans mode, with h, -11 to 10, k, -12 to 12, l, -13 to 14. The intensities were collected for Lorentz and polarisation effects. Among the 9393 reflections. 4049 independent reflections and 2730 observed reflections with  $I \geq 2 \sigma(I)$ . The space group  $P\bar{1}$  assigned from the systematic absences. The cell parameters  $a = 8.665(6) \text{ \AA}$ ,  $b = 9.903(7) \text{ \AA}$ ,  $c = 11.381(7) \text{ \AA}$  and  $\beta = 93.596(11)^\circ$ .  $V = 909.65 \text{ \AA}^3$ . Multi-scan absorption was carried out using SADABS [13]. The calculated absorption coefficient was  $4.7093 \text{ mm}^{-1}$ .

## STRUCTURE SOLUTION AND REFINEMENT

The structure was solved by direct methods using SHELXS-97 [14]. The position of all non-hydrogen atoms were revealed in the best E-map. Then refined using the program SHELXL-97 [14] by the full matrix least squares refinement. All non-hydrogen atoms treated isotropically and refined till R-value converged at  $R(F) = 0.0560$ ,  $wR(F^2) = 0.1349$ . The difference Fourier map further revealed all H-atoms. All the hydrogen atoms parameters were included in the final steps of with weight assigned to a structure factor calculations using the scheme  $w=1/[\sigma^2(F_o^2)+(0.0732P)^2+0.6587P]$  where  $P=(F_o^2+2F_c^2)/3$ . The parameters at the end of final refinement were  $R(F) = 0.0497$ ,  $wR(F^2) = 0.1290$ . The minimum and maximum electron densities from difference Fourier map are 0.698 and -0.589  $e.\text{\AA}^{-3}$  respectively.

The structure was solved by direct methods using SHELXS-97 [14]. The position of all non-hydrogen atoms were revealed in the best E-map. Then refined using the program SHELXL-97 [14] by the full matrix least squares refinement. All non-hydrogen atoms treated isotropically and refined till R-value converged at  $R(F) = 0.0391$ ,  $wR(F^2) = 0.1103$ . The difference Fourier map further revealed all H-atoms. All the hydrogen atoms parameters were included in the final steps of with weight assigned to a structure factor calculations using the scheme  $w=1/[\sigma^2(F_o^2) + (0.064P)^2 + 0.000P]$  where  $P=(F_o^2+2F_c^2)/3$ . The parameters at the end of final refinement were  $R(F) = 0.0537$ ,  $wR(F^2) = 0.1031$ . The minimum and maximum electron densities from difference Fourier map are -0.531 and 0.909  $e.\text{\AA}^{-3}$  respectively.

## RESULTS AND DISCUSSION

The crystallographic refinement data is given in Table.1. The bond lengths and bond angles for non-hydrogen atoms are listed in Table 2(Ia), 2(Ib) and 2(IIa), 2(IIb). Table (3 I) and (3 II) Dihedral angles formed by LSQ-planes. The distance and angles between the atoms involved in intermolecular hydrogen bonding are listed in Table 4 I and 4 II.

Fig 1 Scheme of the title compound I and II, Fig 2 A perspective view of plot of the molecule (ORTEP-3) with 50% probability thermal ellipsoids with atomic numbering is shown in Fig. 2 of I and II and packing of the molecules in the unit cell [15] viewed down b-axis is shown in Fig. 3. The least square planes and dihedral angles are listed in Table 3(a) and Table 3(b) respectively.

### Conformation of molecule

The molecule (I) exhibits L-shaped conformation. The P-bromo phenyl moiety and the imidazole ring are in one plane whereas the methylene bridged benzofuran moiety is oriented at right angles  $81.6^\circ$ .

The number of molecular in the unit cell is 2, the two benzofuran moieties are farther apart and two bromines are anti-two each other.

The molecule (II) is stabilized strong intermolecular O1-H11B hydrogen bonding ( $2.881 \text{ \AA}$ ) and another association through section S1 and H8 ( $2.983 \text{ \AA}$ ). Two weak C-H associations are also indicated between C4-H13 ( $2.870 \text{ \AA}$ ) or C5-H13 ( $2.772 \text{ \AA}$ ) There is C – H... $\pi$  interactions that links centrosymmetrically related molecules. The carbonyl group in the estu can be anti periplanar with respect to the C6 – C5 double bond (A) or it can be cis with respect to C4-C5 double bond. The carbonyl group is cis with respect to C4-C5 double b. and is peri- with respect to the C-Br bond and hence favors conformation-(B) and not (A). The C1-C2-C4-O1 dihedral angle ( $0.93^\circ$ ) and Br-C1-C2-C4 ( $2.06^\circ$ ) support the eclipsed arrangement.

This compound is occurred in dimer-form. The title compound (precursor monomer) is cyclic and planer and hence it is aromatic in nature due to presence of delocalized two pi electrons in thiazolidine ring and one lone pair of electrons on nitrogen (N2) atom. A significant deviation in bond length of N1-H1B is observed due to the formation of hydrogen bond in S1-H1A this is also reflected in the dimer form at N3-H3B and S2-H3A. There is a strong deviation in bond

angle of C1-S1-C3 due to presence of undelocalised lone pair of electrons which makes repulsion with bond pair electrons. This is also reflected in dimmer at C-7-S2- C8. In dimmer a bridging bond is observed at N2-N4. Another significant deviation in bond angle of H1B-N1-H1A (130°) due to repulsion between bond pair lone-pair electrons and withformation of hydrogen bond of S1-H1A. This is also reflected in dimmer at H3B-N3-H3A.

The unit cell has 4 molecular and is stabilised by a strong inter molecular N-H...O bonds. It has an asymmetric unit existing a dimer in the solid state is clear from the unit-cell. The crystal structure is further stabilized by C-H...O, N-H...N and N-

H...O intermolecular hydrogen bonds. The crystal structure of the title compound is almost planar. The dihedral angles between bromo thiazolamine ring and ethyl formate side chain are 1.17 (1) Å and 4.04 Å in two independent molecules of asymmetric unit respectively. N3-H3A...N4 and N1- H1A...N2 intermolecular hydrogen bonds form the molecular dimer across the center of inversion in the close packing. Further these dimmers were linked by N-H...O, C-H...O hydrogen bonds by involvement of carbonyl oxygens O1 and O3. The molecules are packed in layers in ac plane.

**Table 1: Crystal data and structure refinement**

DATA	COMPOUND I	COMPOUND II
Empirical formula	C <sub>20</sub> H <sub>14</sub> Br N <sub>3</sub> O S	C <sub>6</sub> H <sub>7</sub> N <sub>2</sub> S Br O <sub>2</sub> .
a	6.2141(17) Å	8.6646(5) Å
b	9.8002(11) Å	9.9027(6) Å
c	14.891(3) Å	11.3807(7) Å
β	97.068(18)°	93.60°
Volume	885.7(3) Å <sup>3</sup>	909.65 Å <sup>3</sup>
Crystal system	Triclinic	Triclinic
Formula weight	424.31	251.097
Space group	<i>P</i> $\bar{1}$	<i>P</i> $\bar{1}$
F(000)	428	496
Radiation	Cu-K $\alpha$ ( $\lambda$ = 1.54180Å)	Mo K $\alpha$ ( $\lambda$ = 0.71073 Å)
Z	2	4
Absorption coefficient	4.381 mm <sup>-1</sup>	4.7093 mm <sup>-1</sup>
Calculated density	1.591 Mg/m <sup>3</sup>	1.8335 Mg/m <sup>3</sup>
No. Parameters	237	219
R-obs	0.0497	0.0537
wR2 (all)	0.1290	0.1031
Theta range for datacollection	3.03 to 64.94°	1.81 to 27.19°
h min, max; k min, max; l min, max	0<=h<=7, -11<=k<=11, -17<=l<=17	-10 to 10, -11 to 11, -13 to 13
Max. and min. Transmission	0.6541 and 0.5012	-0.53 and 0.97 e Å <sup>-3</sup>
Goof(S)	1.123	0.999
No. Unique reflections.	2936	2619
Temperature	293(2) K	292 K
Largest diff. peak and hole	0.6541 and 0.5012 e Å <sup>-3</sup>	0.586 and 0.225 e Å <sup>-3</sup>

**Table 2(Ia): Bond lengths [Å°]**

Atom1-atom2	Angle
C(1)-C(2)	1.371(5)
C(1)-C(6)	1.380(5)
C(1)-Br(1)	1.896(4)
C(2)-C(3)	1.383(5)
C(3)-C(4)	1.395(5)
C(4)-C(5)	1.390(5)
C(4)-C(7)	1.462(5)

C(5)-C(6)	1.384(5)
C(7)-C(8)	1.365(5)
C(7)-N(4)	1.395(4)
C(8)-N(2)	1.368(4)
C(9)-N(4)	1.308(4)
C(9)-N(2)	1.354(4)
C(9)-S(1)	1.729(3)
C(10)-N(1)	1.287(4)
C(10)-C(11)	1.499(5)

C(10)-S(1)	1.752(3)
C(11)-C(12)	1.487(5)
C(12)-C(13)	1.333(5)
C(12)-C(20)	1.451(5)
C(13)-O(1)	1.371(5)
C(15)-C(16)	1.378(5)
C(15)-O(1)	1.381(4)
C(15)-C(20)	1.390(5)
C(16)-C(17)	1.380(6)
C(17)-C(18)	1.384(6)
C(17)-C(21)	1.505(6)
C(18)-C(19)	1.377(6)
C(19)-C(20)	1.382(5)
N(1)-N(2)	1.383(4)

C(19)-C(18)-C(17)	123.2(4)
C(18)-C(19)-C(20)	118.2(4)
(19)-C(20)-C(15)	118.0(3)
C(19)-C(20)-C(12)	136.3(3)
C(15)-C(20)-C(12)	105.7(3)
C(10)-N(1)-N(2)	108.3(3)
C(9)-N(2)-C(8)	107.4(3)
C(9)-N(2)-N(1)	117.7(3)
C(8)-N(2)-N(1)	134.9(3)
C(9)-N(4)-C(7)	103.6(3)
C(13)-O(1)-C(15)	105.3(3)
C(9)-S(1)-C(10)	88.01(16)

Table 2(IIa): Bond lengths [Å °]

Table 2(Ib): Bond lengths [Å °]

Atom1-atom2-atom3	Angle
C(2)-C(1)-C(6)	121.2(3)
C(2)-C(1)-Br(1)	118.7(3)
C(6)-C(1)-Br(1)	120.1(3)
C(1)-C(2)-C(3)	119.2(3)
C(2)-C(3)-C(4)	121.1(3)
C(5)-C(4)-C(3)	118.3(3)
C(5)-C(4)-C(7)	122.1(3)
C(3)-C(4)-C(7)	119.7(3)
C(6)-C(5)-C(4)	120.8(3)
C(1)-C(6)-C(5)	119.4(3)
C(8)-C(7)-N(4)	111.1(3)
C(8)-C(7)-C(4)	128.3(3)
N(4)-C(7)-C(4)	120.6(3)
C(7)-C(8)-N(2)	104.9(3)
N(4)-C(9)-N(2)	112.9(3)
N(4)-C(9)-S(1)	137.9(3)
N(2)-C(9)-S(1)	109.2(2)
N(1)-C(10)-C(11)	123.8(3)
N(1)-C(10)-S(1)	116.7(3)
C(11)-C(10)-S(1)	119.5(3)
C(12)-C(11)-C(10)	113.0(3)
C(13)-C(12)-C(20)	105.7(3)
C(13)-C(12)-C(11)	126.6(3)
C(20)-C(12)-C(11)	127.7(3)
C(12)-C(13)-O(1)	113.2(3)
C(12)-C(13)-H(13)	123.4
O(1)-C(13)-H(13)	123.4
C(16)-C(15)-O(1)	125.7(3)
C(16)-C(15)-C(20)	124.2(4)
O(1)-C(15)-C(20)	110.1(3)
C(15)-C(16)-C(17)	117.0(4)
C(16)-C(17)-C(18)	119.4(4)
C(16)-C(17)-C(21)	119.8(4)
C(18)-C(17)-C(21)	120.8(5)

Atom1-atom2	length
O(1) - C(4)	1.203(5)
O(2) - C(4)	1.328(5)
Br(1) - C(1)	1.862(4)
Br(2) - C(7)	1.860(4)
S(3) - C(3)	1.746(4)
S(3) - C(1)	1.725(4)
S(4) - C(7)	1.724(4)
S(4) - C(8)	1.734(4)
C(4) - C(2)	1.484(5)
C(2) - N(3)	1.386(5)
C(2) - C(1)	1.350(5)
N(3) - C(3)	1.293(5)
C(3) - N(1)	1.355(6)
N(2) - C(8)	1.345(6)
C(7) - C(9)	1.356(5)
C(8) - N(5)	1.314(5)
C(6) - C(5)	1.496(6)
O(3) - C(10)	1.330(5)
N(5) - C(9)	1.387(5)
C(10) - C(9)	1.481(5)
C(10) - O(4)	1.196(5)
C(12) - C(13)	1.499(7)

Table 2(IIb): Bond angles [°]

Atom1-atom2-atom3	Angle
C(3)-S(3)-C(1)	88.4(2)
C(7)-S(4)-C(8)	88.7(2)
O(1)-C(4)-O(2)	124.3(4)
O(1)-C(4)-C(2)	124.5(4)
O(2)-C(4)-C(2)	111.3(3)
C(4)-C(2)-N(3)	119.2(3)
C(4)-C(2)-C(1)	125.4(4)
N(3)-C(2)-C(1)	115.4(3)
C(2)-N(3)-C(3)	110.6(3)
S(3)-C(3)-N(3)	115.1(3)
S(3)-C(3)-N(1)	120.5(4)
N(3)-C(3)-N(1)	124.3(4)
Br(2)-C(7)-S(4)	116.7(2)
Br(2)-C(7)-C(9)	132.2(3)
S(4)-C(7)-C(9)	111.1(3)
S(4)-C(8)-N(2)	120.8(3)

S(4)-C(8)-N(5)	114.8(3)
N(2)-C(8)-N(5)	124.3(4)
Br(1)-C(1)-S(3)	117.9(2)
Br(1)-C(1)-C(2)	131.5(3)
S(3)-C(1)-C(2)	110.6(3)
C(8)-N(5)-C(9)	110.8(3)
O(3)-C(10)-C(9)	112.2(3)

O(3)-C(10)-O(4)	124.2(4)
C(9)-C(10)-O(4)	123.6(4)
C(7)-C(9)-N(5)	114.6(3)
C(7)-C(9)-C(10)	128.8(4)
N(5)-C(9)-C(10)	116.6(3)

**Table (3 I): Dihedral angles formed by LSQ-planes**

Plane	Plane	Angle (°)
1	2	81.63(0)

**Table (3 II): Dihedral angles formed by LSQ-planes**

NIL

**Table (4 I): Hydrogen bonding geometry.**

(D-H...A)	(D-H) Å	(H...A) Å	(D...A) Å	(D-H...A)°
C3-H3...N4	0.930(0)	2.520(0)	2.863(0)	102
C8-H8...N1 <sup>i</sup>	0.930(0)	2.972(1)	3.548(1)	121
C8-H8...S1 <sup>ii</sup>	0.930(0)	2.983(1)	3.670(1)	132
C11-H11B...O1 <sup>ii</sup>	0.970(0)	2.581(1)	3.542(1)	171
C16-H16...O1 <sup>iii</sup>	0.930(0)	2.762(1)	3.614(1)	153
C16-H16...π	0.930(0)	2.67(0)	3.692(0)	173

Equivalent positions:

- (i) -x+2, -y, -z+1,
- (ii) (ii) x+1, +y, +z
- (iii) (iii) -x, -y, -z+2

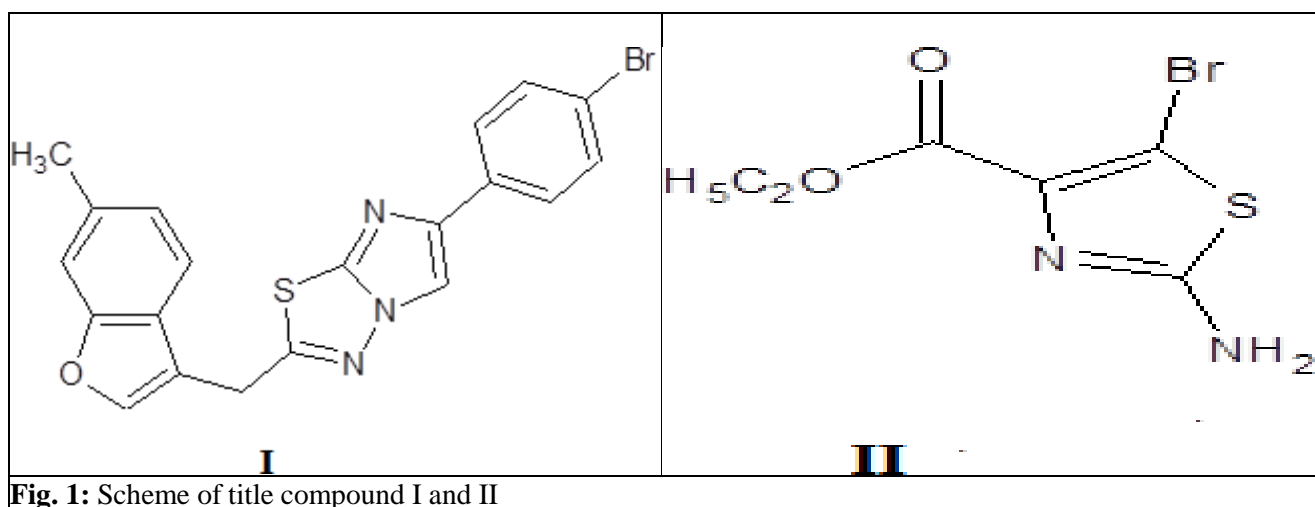
**Table (4 II): Hydrogen bonding geometry.**

(D-H...A)	(D-H) Å	(H...A) Å	(D...A) Å	(D-H...A)°
N1—H1A...N2 <sup>i</sup>	0.86(0)	2.13(2)	2.971 (5)	165
N3—H3A...N4 <sup>ii</sup>	0.86(0)	2.19(2)	3.014 (5)	162
N3—H3B...O1 <sup>iii</sup>	0.86(0)	2.31(1)	3.086 (5)	150

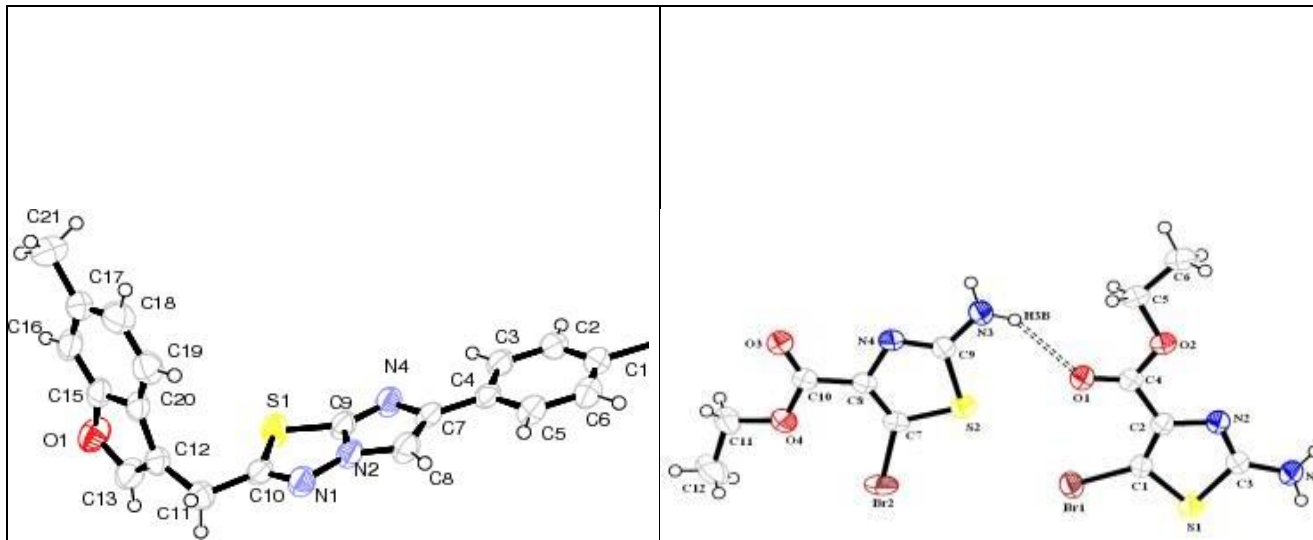
Symmetry codes: (i) -x+1, -y, -z+1

(ii) -x+1, -y+2, -z,

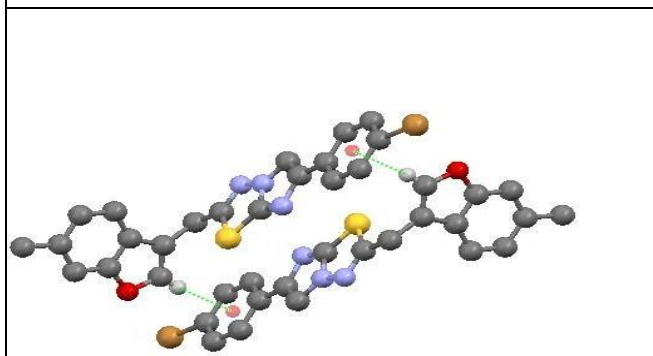
(iii) -x+2, -y+1, -z+1



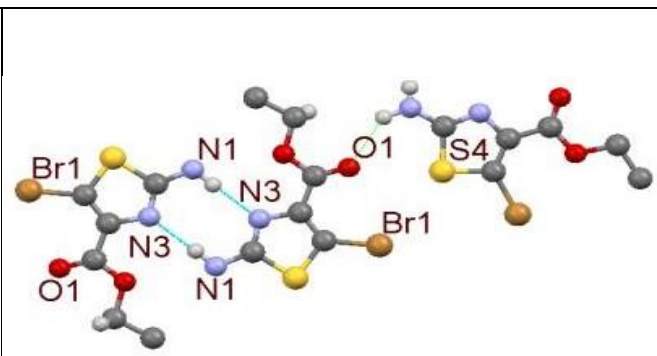
**Fig. 1:** Scheme of title compound I and II



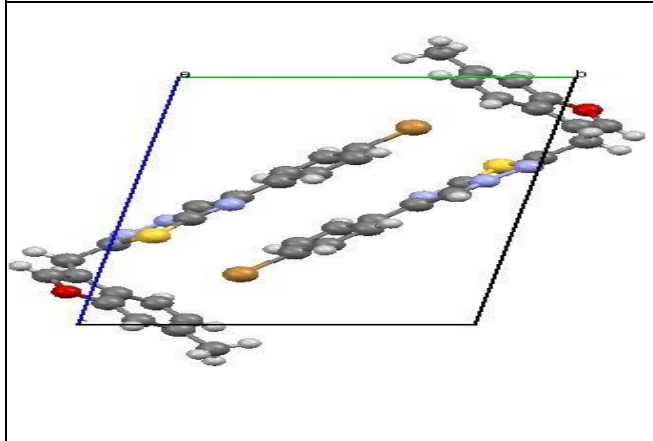
**Fig. 2:** ORTEP diagram of the title molecule with 50% probability displacement ellipsoids with-H atoms of I and II



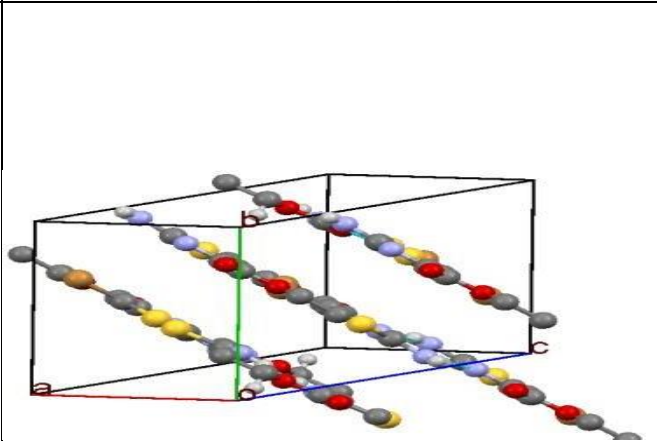
**Fig. 3.I:** Packing of the molecules showing C-H...O and C-H...Cl hydrogen bonding.



**Fig. 3.II:** Packing of the molecules showing C-H...O and C-H...Cl hydrogen bonding.



**Fig. 4.I:** Packing diagram viewed down b-axis and molecules oriented as parallel layers along c-axis.



**Fig. 4.II:** Packing diagram viewed down b-axis.

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