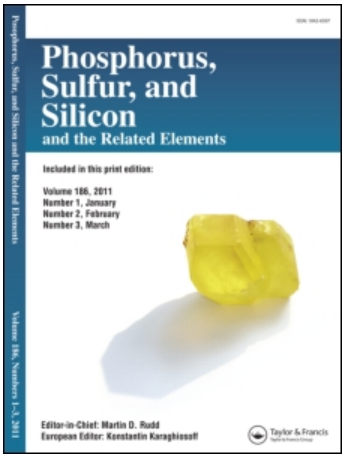

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Synthesis of Benzo[b]thiophene Substituted Carbamates, Ureas, Semicarbazides, and Pyrazoles and Their Antimicrobial and Analgesic Activity

Tholappanavara H. Suresha Kumara,[1] Kittappa M. Mahadevan,[1] Hosanagara N. Harishkumar,[1] Basavaraj Padmashali,[2] and Gadada Naganagowda[2]
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*2-Azidocarbonyl-3-chlorobenzo[b]thiophene **3** was obtained from 3-chloro-benzo[b]thiophene-2-carbonyl chloride **1** and 3-chloro-benzo[b]thiophene-2-carboxy hydrazide **2**. The compound **3** on Curtius rearrangement with various alcohols, amines, and hydrazines afforded the corresponding carbamates **4a–b**, ureas **5a–j**, and semicarbazides **6a–g**, respectively. Compound **2** was also utilized for the synthesis of pyrazoles **7a–c** by treatment with various chalcones. The structures of the newly synthesized compounds were elucidated on the basis of IR, ^{1}H NMR, and mass spectral data and have been screened for antimicrobial and analgesic activities.*

Keywords Analgesic activity; antimicrobial activity; 2-azidocarbonyl-3-chlorobenzo[b]thiophene; Curtius rearrangement

INTRODUCTION

The acyl azido group is most useful in organic synthesis, due to its ready conversion to amino groups or due to its photochemical or cycloaddition reactions or Curtius rearrangement in the presence of nucleophiles. Curtius rearrangement describes the degradation of an acyl azide into an isocyanate through a concerted mechanism.[1] Trapping the isocyanates with nucleophiles is a most widely used method for synthesizing amine derivatives. Acyl azides can be prepared from carboxylic acid derivatives such as hydrazides,[2] acyl chlorides,[3]and mixed

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anhydrides.[4,5] These acyl azides can be isolated, and Curtius rearrangement is then performed in a separate step. The literature is rich with references related to Curtius rearrangements that involve the synthesis of carbamates and ureas.[6,7]

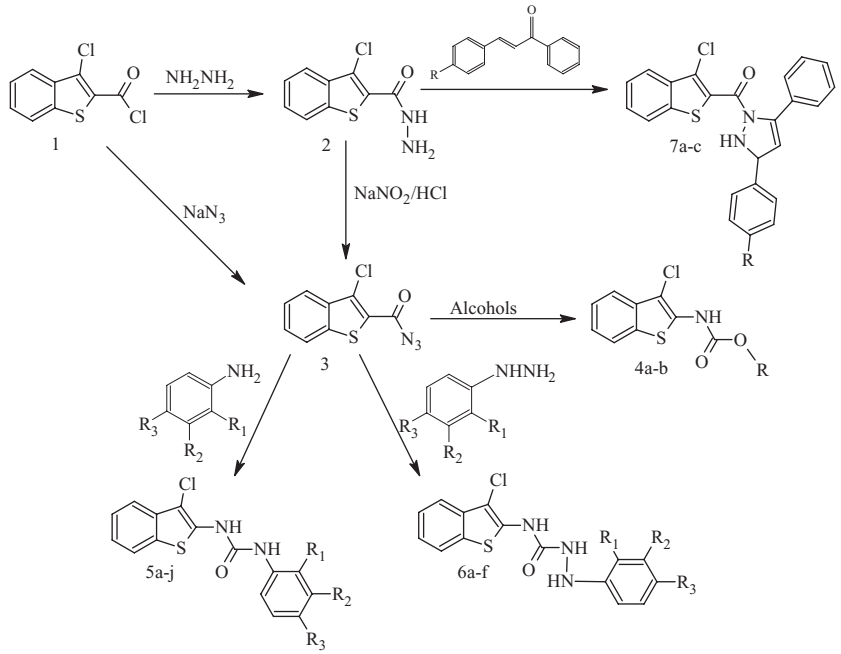
The benzo[b]thiophene derivatives have been found to exhibit analgesic activity,[8] anti-inflammatory activity,[9] serotonine N-acetyltransferase inhibitor activity,[10] antitubercular activity, and antimicrobial activity.[11] It was also thought to be of interest to synthesize some benzo[b]thiophene derivatives containing other biologically potent moieties. In view of the diverse and remarkable biological properties of several heterocyclic systems with pendant carbamates[12–13] and diphenylureas,[14–16] we thought of coupling these moieties with benzo[b]thiophene. Pyrazoles are well documented to possess antihypertensive,[17] antibacterial,[18,19] anti-inflammatory,[20,21] and anti-tumor activities,[22] and they have wide applications as pharmaceuticals and agrochemical agents.[23,24] Hence, in the third series of compounds, the synthesis of the pyrazole derivatives of benzo[b]thiophene is reported.

In this context, it was contemplated to synthesize benzo[b]thiophene substituted carbamates, ureas, semicarbazides, and pyrazoles, as shown in Scheme 1.

RESULTS AND DISCUSSION

In this article, we report the synthesis and biological properties of some carbamates **4a–b,** ureas **5a–j**, semicarbazides **6a–g** incorporated with the benzo[b]thiophene ring, using the well-known Curtius rearrangement. The starting material, 2-acylazidobenzo[b]thiophene-3-chloride **3**, was prepared by reacting 3-chlorobenzo[b]thiophene-2-carbonyl chloride[25] **1** with sodium azide in acetone medium. The acyl azide **3** can also be prepared by treating the carbonyl chloride **1** with hydrazine to get 3-chloro-benzo[b]thiophene-2-carboxy hydrazide[26] **2** followed by diazotization. The IR spectrum of **3** showed a peak at 2184 cm^{-1} due to an azido group. The ^1H NMR spectrum showed a multiplet in the aromatic region due to four protons. The formation of **3** was also proved by the mass spectrum data, which showed a molecular ion peak at 244.

The acyl azide **3**, upon refluxing with various alcohols, produced 3-chlorobenzo[b]thiophene-2-carbamates **4a–b** in good yields. The absence of an azide band at 2184 cm^{-1} and the presence of an N–H band at 3240 cm^{-1} in IR spectrum of **4a** was the evidence for the rearrangement of azide to carbamates. The ^1H NMR (300 MHz) spectrum showed



SCHEME 1 General synthetic procedure for 3-chlorobenzo[b]thiophene substituted carbamates **4a–b**, ureas **5a–j**, semicarbazides **6a–g**, and pyrazoles **7a–c**.

a multiplet in the region δ 7.27–7.74 due to four aromatic protons, a broad peak at δ 7.40 corresponding to an NH proton, a quartet at δ 4.31–4.37 corresponding to CH_2 protons, and a triplet at δ 1.36–1.58 corresponding to CH_3 protons. This was further confirmed by its mass spectrum, which showed a molecular ion peak m/z at 255, which agrees with the molecular weight of the compound. In this series, another carbamate **4b** was also prepared by using methanol, and it was also well characterized through spectral data.

The treatment of acyl azide **3** with various anilines afforded 3-chlorobenzo[b]thiophene substituted ureas **5a–j**. The IR spectra of all these compounds showed two sharp bands at 3275–3320 cm^{-1} due to N–H groups and the sharp bands at 1628 cm^{-1} due to C=O groups. The absence of the azide band at 2184 cm^{-1} also confirms the formation of compounds **5a–j**. The ^1H NMR spectrum of compound **5a** showed a multiplet in the region δ 6.80–7.70 corresponding to eight aromatic protons, a peak at δ 7.40 corresponding to two protons of two NH groups, and a singlet at δ 3.50 corresponding to CH_3protons. This was further

confirmed by its mass spectrum, which showed a molecular ion peak m/z at 317, and which agrees with the molecular weight of the compound. In this series, the other compounds **5b–j** were prepared by using various phenyl hydrazines, and they were also characterized by their spectral data.

The acyl azide **3** also underwent smooth rearrangement with various phenyl hydrazines to produce 3-chlorobenzo[b]thiophene substituted semicarbazides **6a–g**. The IR spectra of all these compounds showed two sharp bands at 3290–3320 due to CONH groups, 3335–3350 due to N-H groups, and a sharp band at 1628 cm^{-1} due to C=O groups. The absence of the azide band at 2184 cm^{-1} also confirmed the formation of compounds **6a–g**. The ^1H NMR spectrum of compound 6**a** showed a singlet at δ 8.90 corresponding to two protons of CONH, a multiplet in the region δ 7.30–7.90 due to the nine aromatic protons, and a singlet at δ 6.80 corresponding to one proton of NH. This was further confirmed by its mass spectrum, which showed molecular ion peak m/z at 318, and which agrees with the molecular weight of the compound. In this series, the other compounds **6b–g** were also prepared by using various phenyl hydrazines, and they were also characterized by their spectral data.

The intermediate 3-chloro benzo[b]thiophene-2-carboxyhydrazide **2** was utilized for the synthesis of pyrazoles **7a–c** by reacting it with various chalcones. The IR spectra of all these compounds showed 3320 (singlet) corresponds to N-H and sharp signal at 1628 cm^{-1} due to C=O. The ^1H-NMR spectrum (compound 7**a**) showed a signal at 10.0 (singlet) due to pyrazole proton, 7.20–8.0 corresponding to fifteen aromatic protons, and the signal at 6.50 corresponding to one proton of CH. This was further confirmed by its mass spectrum, which showed molecular ion peak m/z at 418, and which agrees with the molecular weight of the compound. In this series, other pyrazoles **7b–c** were prepared by using different chalcones, and they were also characterized by their spectral data.

The physical properties of the synthesized compounds are shown in Table I and have been screened for antimicrobial and analgesic activities.

ANTIBACTERIAL ACTIVITY

All the synthesized compounds were screened for their antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *S. paratyphi-A*, and *Bacillus subtilis*. The activity was carried out using the cup plate agar diffusion method.[27] The zone of inhibition was measured in

TABLE I Characterization Data of the Compounds

Sl. No	Comp	R	R_1	R_2	R_3	Nature	Yield (%)	Mp (°C)
1	3	—	—	—	—	Crystalline	85	101–105
2	4a	CH_2CH_3	—	—	—	Amorphous	40	68–71
3	4b	CH_3	—	—	—	Amorphous	38	65–68
4	5a	—	H	H	CH_3	Crystalline	96	218–220
5	5b	—	H	CH_3	H	Crystalline	92	214–218
6	5c	—	CH_3	H	H	Crystalline	90	213–216
7	5d	—	H	OCH_3	H	Crystalline	86	235–238
8	5e	—	OCH_3	H	H	Crystalline	95	229–231
9	5f	—	H	H	OCH_3	Crystalline	92	238–240
10	5g	—	H	H	Cl	Crystalline	90	221–225
11	5h	—	H	Cl	H	Crystalline	85	220–223
12	5i	—	H	H	H	Crystalline	92	206–210
13	5j	—	F	H	NO_2	Crystalline	80	245–250
14	6a	—	H	H	H	Crystalline	88	190–195
15	6b	—	H	H	CH_3	Crystalline	96	203–205
16	6c	—	H	CH_3	H	Crystalline	90	201–203
17	6d	—	CH_3	H	H	Crystalline	86	203–206
18	6e	—	H	H	Cl	Crystalline	91	207–210
19	6f	—	H	H	F	Crystalline	80	205–208
20	7a	H	—	—	—	Amorphous	65	142–145
21	7b	Cl	—	—	—	Amorphous	60	148–150
22	7c	NO_2	—	—	—	Amorphous	50	157–159

millimeters. DMF was used as a vehicle. Choramphenicol and Streptomycin were used as standard drugs for comparison. The compounds were tested at 40 μg/mL concentration. All the synthesized compounds were found to show moderate to poorly active against all bacteria. The zones of inhibition are presented in Table II.

ANALGESIC ACTIVITY

Albino mice of either sex (20–30 g) were subjected to acetic acid induced writhing to test for analgesic activity.[28] Acetic acid solution (0.6%, 10 mL/kg) was used to induce writhing in mice. The mice were divided into 13 groups, each consisting of six animals. The analgesic response was assessed by counting the number of abdominal constrictions for 20 min starting 3 min after the injection of acetic acid solution. Groups 1 to 12 received the suspension of test compounds (100 mg/kg dose), respectively, and group 13 received the standard drug suspension (Ibuprofen) at the dose of 100 mg/kg. After 1 h, acetic acid solution was administered intraperitoneally and number of abdominal constrictions was

TABLE II Antibacterial Activity of the Compounds

Compound	Diameter of zone of inhibition (mm)			
	Staphylococcus aureus	*Escherichia coli*	*S. Paratyphi-A*	*Bacillus subtilis*
4a	14	08	10	12
4b	13	12	15	17
5a	11	12	14	18
5b	11	13	15	15
5c	12	11	16	16
5d	12	12	12	15
5e	13	10	14	17
5f	15	12	13	17
5g	12	12	15	14
5h	13	09	10	11
5i	14	13	14	18
5j	11	10	16	17
6a	14	09	13	14
6b	14	09	17	17
6c	15	08	11	15
6d	13	13	13	17
6e	14	12	15	16
6f	15	11	16	17
7a	11	12	14	17
7b	13	10	16	15
7c	11	11	15	16
DMF	00	00	00	00
Chloramphenicol	20	14	18	22

recorded for 20 min starting 3 min after the injection of acetic acid solution. Analgesic activity was calculated as the percentage maximum possible effect (%MPE), and the results are given in Table III.

EXPERIMENTAL SECTION

Melting points were determined in an open capillary and are uncorrected. ^{1}H NMR (300 MHz) spectra were run in $CDCl_3$ and DMSO solutions. Chemical shifts are expressed in δ ppm. Mass spectra were performed on a Joel JMS-D 300 mass spectrometer operating at 70 eV. IR spectra were recorded by using JASCO FT/IR-300 E spectrometer from a KBr pelleted sample. Elemental analysis was done by a Perkin-Elmer auto analyzer at IISc Bangalore. The purity of the compounds was checked by TLC, and further purification was done by column chromatography.

TABLE III Analgesic Activity of the Compounds

Compound	Dose mg/kg	Mean number of abdominal constrictions occurred between 3 and 20 min		% MPE
		Before drug	After drug	
4a	100	40.6 ± 2.1	15.8 ± 1.43	61.1*
4b	100	52.4 ± 2.5	17.2 ± 3.61	67.3*
5a	100	26.4 ± 1.5	10.1 ± 0.89	62.1*
5b	100	24.8 ± 1.2	8.4 ± 0.92	66.1*
5c	100	40.1 ± 2.0	15.2 ± 1.40	60.1*
5d	100	23.1 ± 1.6	8.9 ± 0.79	63.4*
5e	100	26.4 ± 1.5	10.1 ± 0.89	62.1*
5f	100	24.8 ± 1.2	8.4 ± 0.92	66.1*
5g	100	39.6 ± 2.1	14.8 ± 1.43	61.7*
5h	100	40.1 ± 2.0	15.2 ± 1.40	60.1*
5i	100	28.6 ± 1.7	12.2 ± 1.21	64.1*
5j	100	40.6 ± 2.1	13.8 ± 0.43	61.3*
6a	100	52.4 ± 2.5	17.2 ± 2.61	60.3*
6b	100	26.4 ± 1.5	10.4 ± 1.89	68.3*
6c	100	24.8 ± 1.2	8.5 ± 1.92	68.5*
6d	100	34.1 ± 2.0	15.1 ± 0.40	60.1*
6e	100	23.1 ± 1.5	8.9 ± 0.82	66.4*
6f	100	26.4 ± 1.6	10.4 ± 1.3	62.2*
6g	100	23.8 ± 1.0	8.3 ± 1.2	61.7*
7a	100	33.1 ± 2.0	13.9 ± 0.60	60.1*
7b	100	28.4 ± 1.3	12.8 ± 1.20	67.4*
7c	100	22.1 ± 1.3	8.9 ± 0.79	64.0*
Ibuprofen	100	47.1 ± 2.5	11.8 ± 1.27	75.1*

Analgesic activity, $^*P < 0.001$ vs. control; student's t-test, $n = 6$.

Preparation of 3-Chlorobenzothiophene-2-carbonyl Azide (3)

Method A: To a stirred solution of 3-chloro-benzo[b]thiophene-2-carbonyl chloride **1** (2.0 g, 8.0 mmol) in anhydrous acetone (50 mL), a solution of sodium azide (0.52 g, 8.0 mmol) in water (2 mL) was added dropwise at 0°C. After the complete addition of sodium azide, the temperature of the reaction mixture was raised to 25°C, and this temperature was maintained for 30 min. to ensure the completion of the reaction. The reaction mixture was diluted with cold water (100 mL), and then the pale yellow solid obtained was filtered, washed thoroughly with cold water, and dried over phosphorous pentoxide in vacuum to get (2.08 g) 85% of the pure **3**.

Method B: 3-Chlorobenzo[b]thiophene-2-carboxyhydrazide **2** (10 g, 44.0 mmol) was suspended in 1,4-dioxane (60 mL) and acetic acid (60 mL) and cooled to 0°C. An ice cold solution of sodium nitrite (4.85 g,

71.0 mmol) in water (18 mL) was introduced into it in small portions with vigorous stirring. Meanwhile the temperature of the reaction mixture was maintained below 5°C, then it was allowed to stay at room temperature for 30 min. The pale yellow solid that was obtained was filtered, washed thoroughly with cold water, and dried over phosphorous pentoxide in vacuum to obtain (9 g) 85% of pure **3**.

3-Chlorobenzothiophene-2-carbonyl Azide (3)

IR (KBr) ν (cm^{-1}): 2184 (N_3), 1712 (C=O), 1572 (N=N), 781 (C-S-C), 752 (C-Cl); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.20-7.90 (4H, m, ArH); MS (M^+): 244. Calcd. (%) for ($C_9H_4ClN_3OS$): C, 45.48; N, 17.68; S, 13.38; H, 4.20. Found: C, 45.25; N, 17.35; S, 13.11; H, 4.01.

Preparation of Ethyl-3-chloro-1-benzothien-2-ylcarbamate (4)

A suspension of 3-chlorobenzothiophene-2-carbonyl azide **3** (2 g, 8.2 mmol) in absolute ethanol (15 mL) was refluxed on steam bath for 3 h. The reaction mixture was concentrated under reduced pressure, and then it was diluted with cold water with stirring. The product that separated was filtered, washed with water, dried, and purified from column chromatography by using petroleum ether, and ethyl acetate (0.5:9.5) was used as an elutent to get pure **4a**. Similarly, the compound **4b** was prepared.

Ethyl-3-chloro-1-benzothien-2-ylcarbamate (4a)

IR (KBr) ν (cm^{-1}): 3240 (N-H), 1712 (C=O), 781 (C-S-C), 752 (C-Cl); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.27–7.74 (4H, m, ArH), 7.40 (1H, b, NH), 4.31–4.37 (2H, q, CH_2), 1.36–1.58 (3H, t, CH_3); MS (M^+): 255, 210. Calcd. (%) for $C_{10}H_8ClNO_2S$: C, 49.69; H, 3.34; N, 5.80; S, 13.27. Found: C, 49.35; S, 13.27; N, 5.80; H, 3.18.

Methyl-3-chloro-1-benzothien-2-ylcarbamate (4b)

IR (KBr) ν (cm^{-1}): 3240 (N-H), 1712 (C=O), 781(C-S-C), 752 (C-Cl); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.27–7.74, (4H, m, ArH), 7.40 (1H, broad, NH), 3.60 (3H, s, OCH_3); MS (M^+): 242. Calcd. (%) for $C_{10}H_8ClNO_2S$: C, 60.64; S, 13.27; N, 5.89; H, 3.34. Found: C, 60.36; S, 13.27; N, 5.52; H, 3.34.

Preparation of N-(3-Chloro-1-benzothien-2-yl)-N′-(4-methylphenyl) Urea (5)

A suspension of 3-chlorobenzothiophene-2-carbonyl azide **3** (2 g, 8.2 mmol) and p-toludine (0.878 g, 8.2 mmol) in anhydrous toluene

(15 mL) was heated under gentle reflux (110°C) in an oil bath for 4 h. The crystalline product that separated on cooling was filtered and washed with toluene and petroleum ether. The analytical sample was obtained by crystallization from chloroform. Similarly, the compounds **5b–j** were prepared.

N-(3-Chloro-1-benzothien-2-yl)-N′-(4-methylphenyl)urea (5a)

IR (KBr) ν (cm^{-1}): 3300 (N-H), 1628 (C=O), 781 (C-S-C), 752 (C-Cl); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.40 (2H, s, NH), 6.80–7.70 (8H, m, Ar H), 3.50 (3H, s, CH_3); MS (M^+): 317, 302. Calcd. (%) for $C_{16}H_{13}ClN_2OS$: C, 60.66; S, 10.12; N, 8.84; H, 4.14. Found: C, 60.26 S, 10.01; N, 8.57; H, 3.86.

N-(3-Chloro-1-benzothien-2-yl)-N′-(3-methylphenyl)urea (5b)

IR (KBr) ν (cm^{-1}): 3310 (N-H), 1628 (C=O), 781 (C-S-C), 752 (C-Cl); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.40 (2H, s, NH), 6.80–7.70 (8H, m, Ar H), 3.50 (3H, s, CH_3); MS (M^+): 317, 302. Calcd. (%) for $C_{16}H_{13}ClN_2OS$: C, 60.66; S, 10.12; N, 8.84; H, 4.14. Found: C, 60.30; S, 10.00; N, 8.56; H, 3.98.

N-(3-Chloro-1-benzothien-2-yl)-N′-(2-methylphenyl)urea (5c)

IR (KBr) ν (cm^{-1}): 3290 (N-H), 1628 (C=O), 781 (C-S-C), 752 (C-Cl); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 6.70–7.70 (8H, m, Ar H), 7.40 (2H, s, NH), 3.50 (3H, s, CH_3); MS (M^+): 317, 302; Calcd. (%) for $C_{16}H_{13}ClN_2OS$: C, 60.66; S, 10.12; N, 8.84; H, 4.14. Found: C, 60.34; S, 10.01; N, 8.54; H, 3.77.

N-(3-Chloro-1-benzothien-2-yl)-N′-(3-methoxyphenyl)urea (5d)

IR (KBr) ν (cm^{-1}): 3315 (N-H), 1628 (C=O), 781 (C-S-C), 752 (C-Cl)): ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 6.70–7.70 (8H, m, Ar H), 7.40 (2H, s, NH), 3.80 (3H, s, OCH_3); MS (M^+): 333, 332, 302. Calcd. (%) for $C_{16}H_{13}ClN_2O_2S$: C, 57.74; S, 9.64; N, 8.42; H, 3.94. Found: C, 57.55; S, 9.43; N, 8.17; H, 3.69.

N-(3-Chloro-1-benzothien-2-yl)-N′-(2-methoxyphenyl)urea (5e)

IR (KBr) ν (cm^{-1}): 3320 (N-H), 1628 (C=O), 781 (C-S-C), 752 (C-Cl)); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 6.70–7.70 (8H, m, Ar H), 7.40 (2H, s, NH), 3.80 (3H, s, OCH_3); MS (M^+): 333, 332, 302. Calcd. (%) for $C_{16}H_{13}ClN_2O_2S$: C, 57.74; S, 9.64; N, 8.42; H, 3.94. Found: C, 52.55; S, 9.45; N, 8.22; H, 3.67.

N-(3-Chloro-1-benzothien-2-yl)-N′-(4-methoxyphenyl)urea (5f)

IR (KBr) ν (cm^{-1}): 3280 (N-H), 1628 (C=O), 781 (C-S-C), 752 (C-Cl); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 6.70–7.70 (8H, m, Ar H), 7.40 (2H, s, NH), 3.80 (3H, s, OCH_3); MS (M^+): 333, 332, 302. Calcd. (%) for $C_{16}H_{13}ClN_2O_2S$: C, 57.74; S, 9.64; N, 8.42; H, 3.94. Found: C, 57.58; S, 9.40; N, 8.16; H, 3.65.

N-(3-Chloro-1-benzothien-2-yl)-N′-(4-chlorophenyl)urea (5g)

IR (KBr) ν (cm^{-1}): 3275 (N-H), 1628 (C=O), 781 (C-S-C), 752 (C-Cl); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 6.80–7.70 (8H, m, Ar H), 7.40 (2H, s, NH); MS (M^+): 338, 301, 302. Calcd. (%) for $C_{15}H_{10}Cl_2N_2OS$: C, 53.42; S, 9.51, N, 8.31; H, 2.99. Found: C, 53.12; S, 9.29, N, 8.01; H, 2.77.

N-(3-Chloro-1-benzothien-2-yl)-N′-(3-chlorophenyl)urea (5h)

IR (KBr) ν (cm^{-1}): 3320 (N-H), 1628 (C=O), 781 (C-S-C), 752 (C-Cl); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 6.80–7.70 (8H, m, Ar H), 7.40 (2H, s, NH); MS (M^+): 338, 301. Calcd. (%) for $C_{15}H_{10}Cl_2N_2OS$: C, 53.42; S, 9.51, N, 8.31; H, 2.99. Found: C, 53.12; S, 9.27, N, 8.01; H, 2.75.

N-(3-Chloro-1-benzothien-2-yl)-N′-phenylurea (5i)

IR (KBr) ν (cm^{-1}): 3300 (N-H), 1628 (C=O), 781 (C-S-C), 752 (C-Cl); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 6.80–7.70 (8H, m, Ar H), 7.40 (2H, s, NH); MS (M^+): 303, 211. Calcd. (%) for $C_{15}H_{11}ClN_2OS$: C, 59.50; S, 10.59; N, 9.25; H, 3.66. Found: C, 59.22; S, 10.37; N, 9.03; H, 3.55.

N-(3-Chloro-1-benzothien-2-yl)-N′-(2-fluoro-4-nitrophenyl)urea (5j)

IR (KBr) ν (cm^{-1}): 3310 (N-H), 1628 (C=O), 781 (C-S-C), 752 (C-Cl); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.20–9.40 (2H, s, NH), 7.20–8.20 (7H, m, Ar H); MS (M^+): 366, 348. Calcd. (%) for $C_{15}H_9ClFN_3O_3S$: C, 49.26; N, 11.49; S, 8.77; H, 2.48. Found: C, 49.00; N, 11.19; S, 8.68; H, 2.32.

Preparation of N-(3-Chloro-1-benzothien-2-yl)-2-phenylhydrazinecarboxamide (6)

A suspension of 3-chlorobenzothiophene-2-carbonyl azide **3** (2 g, 8.2 mmol) and phenyl hydrazine (0.88 g, 8.2 mmol) in anhydrous toluene (15 mL) was refluxed on an oil bath for about 6 h. Then reaction mixture was cooled to room temperature, and the solid that

separated was filtered, washed with toluene, and then with petroleum ether. It was recrystallized by methanol to get pure **6a**. Similarly, the compounds **6b–f** were prepared.

N-(3-Chloro-1-benzothien-2-yl)-2-phenylhydrazinecarboxamide (6a)

IR (KBr) ν (cm^{-1}): 3290 (CON-H), 3330 (N-H), 1628 (C=O), 781 (C-S-C), 752 (C-Cl); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.90 (2H, s, CONH), 7.30–7.90 (9H, m, Ar H), 6.80 (1H,s, NH); MS (M^+): 318, 282, 178. Calcd. (%) for $C_{15}H_{12}Cl\ N_3OS$: C, 56.69; N, 13.22; S, 10.09; H, 3.81, Found: C, 56.22; N, 13.11; S, 9.88; H, 3.66.

N-(3-Chloro-1-benzothien-2-yl)-2-(4-methylphenyl)-hydrazinecarboxamide (6b)

IR (KBr) ν (cm^{-1}): 3310 (CON-H), 3340 (N-H), 1628 (C=O), 781 (C-S-C), 752 (C-Cl); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.90 (2H, s, CONH), 7.30–7.90 (8H, m, Ar H), 6.80 (1H,s, NH), 3.40 (3H, s, CH_3); MS (M^+): 332, 317. Calcd. (%) for $C_{16}H_{14}ClN_3OS$: C, 57.91; N, 12.66; S, 9.66; H, 4.25. Found: C, 57.41, N, 12.32; S, 9.66; H, 4.25.

N-(3-Chloro-1-benzothien-2-yl)-2-(3-methylphenyl)-hydrazinecarboxamide (6c)

IR (KBr) ν (cm^{-1}): 3300 (CON-H), 3335 (N-H), 1628(C=O), 781(C-S-C), 752(C-Cl); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.80 (2H, s, CONH), 7.20–7.90 (8H, m, Ar H), 6.90 (1H,s, NH), 3.5(3H, s, CH_3); MS (M^+): 332, 318. Calcd. (%) for $C_{16}H_{14}ClN_3OS$: C, 57.91; N, 12.66; S, 9.66; H, 4.25. Found: C, 57.39, N, 12.33; S, 9.66; H, 4.27.

N-(3-Chloro-1-benzothien-2-yl)-2-(2-methylphenyl)-hydrazinecarboxamide (6d)

IR (KBr) ν (cm^{-1}): 3315 (CON-H), 3350 (N-H), 1628(C=O), 781 (C-S-C), 752 (C-Cl);); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.90 (2H, s, CONH), 7.30–7.90 (8H, m, Ar H), 6.80 (1H,s, NH), 3.60 (3H, s, CH_3); MS (M^+): 332, 318. Calcd. (%) for $C_{16}H_{14}ClN_3OS$: C, 57.91; N, 12.66; S, 9.66; H, 4.25. Found: C, 57.40, N, 12.31; S, 9.65; H, 4.24.

N-(3-Chloro-1-benzothien-2-yl)-2-(4-chlorophenyl)-hydrazine Carboxamide (6e)

IR (KBr) ν (cm^{-1}): 3290 (CON-H), 3345 (N-H), 1628 (C=O), 781 (C-S-C), 752 (C-Cl); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.0 (2H, s, CONH), 7.40–8.0 (8H, m, Ar H), 6.90 (1H, s, NH); MS (M^+): 353, 316. Calcd.

(%) for $C_{15}H_{11}C_{l2}N_3OS$: C, 51.15; N, 11.93; S, 9.10; H, 3.15. Found: C, 51.01; N, 11.52; 9.01; H, 2.89.

N-(3-Chloro-1-benzothien-2-yl)-2-(4-flurophenyl)hydrazine Carboxamide (6f)

IR (KBr) ν (cm^{-1}): 3320 (CON-H), 3330 (N-H), 1628 (C=O), 781 (C-S-C), 752 (C-Cl); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.0 (2H, s, CONH), 7.30–8.0 (8H, m, Ar H), 6.80 (1H, s, NH); MS (M^+): 337, 318; Calcd. (%) for $C_{15}H_{11}ClFN_3OS$: C, 53.65; N, 12.51; S, 9.55; H, 3.30. found: C, 53.32; N ,12.25; S, 9.33; H, 3.19.

Preparation of 1-[(3-Chloro-1-benzothien-2-yl)carbonyl]-3,5-diphenyl-2,3-dihydro-1H-pyrazole (7)

A hot mixture of 1,3-diphenylprop-2-en-1-one (2.08 g, 10 mmol) and a catalytic amount of acetic acid in 1,4-dioxane (40 mL) was stirred for 15 min, and then powdered 3-chloro benzo[b]thiophene-2-carboxyhydrazide **2** (2.265 g, 10 mmol) was added. Then the reaction mixture was refluxed for about 26 h at reflux temperature, and the completion of the reaction was monitored through TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and poured into 200 g crushed ice taken in 500 mL beaker with stirring for about 10 min. The solid that separated was filtered and washed thoroughly with water, dried, and purified through column chromatography by using ethyl acetate and petroleum ether (1:9) as an elutent to get pure sample of **7a**. Similarly, the compounds **7b–c** were prepared.

1-[(3-Chloro-1-benzothien-2-yl)carbonyl]-3,5-diphenyl-2,3-dihydro-1H-pyrazole (7a)

IR (KBr) ν (cm^{-1}): 3320 (N-H), 1628 (C=O), 781 (C-S-C), 752 (C-Cl); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 10.0 (1H, s, NH), 7.20–8.0 (15H, m, Ar H), 6.50 (1H, d, CH); MS (M^+): 418, 417, 340. Calcd. (%) for $C_{24}H_{17}ClN_2OS$: C. 69.14,; N, 6.72; S, 7.69; H, 4.11. Found: C, 69.01; N, 6.36; S, 7.55; H, 4.01.

2-[(3-Chloro-1-benzothien-2-yl)carbonyl]-5-(4-chlorophenyl)-3-phenyl-2,3-dihydro-1H-pyrazole (7b)

IR (KBr) ν (cm^{-1}): 3320 (N-H), 1628 (C=O), 781 (C-S-C), 752 (C-Cl); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 10.20 (1H, s, NH), 7.20–8.0 (14H, m, Ar H), 6.50 (1H, d, CH); MS (M^+): 453, 417. Calcd. (%) for $C_{24}H_{16}C_{l2}N_2OS$: C, 63.86; N, 6.21; S, 7.10; H, 3.57. Found: C, 63.42; N, 6.03; S, 6.90; H, 3.23.

1-[(3-Chloro-1-benzothien-2-yl)carbonyl]-3-(4-nitrophenyl)-5-phenyl-2,3-dihydro-1H-pyrazole (7c)

IR (KBr) ν (cm^{-1}): 3320 (N-H), 1628 (C=O), 1349 (N=O), 781 (C-S-C), 752 (C-Cl); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 10.10 (1H, s, NH), 7.10–8.0 (14H, m, Ar H), 6.60 (1H, d, CH); MS (M^+): 463, 417. Calcd. (%) for $C_{24}H_{16}ClN_3O_3S$: C, 62.40; N, 9.10; S, 6.94; H, 3.49. Found: C, 62.22; N, 8.77; S, 6.74; H, 3.19.

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