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An Insight into the Pharmacological Potency of Novel Benzothiophene Derivatives

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ABSTRACT

*A series of significant compounds containing pyrazole and pyrazolone substituted benzothiophene derivatives **2a-f** and **3a-f** have been synthesized from 2-bromobenzonitrile and methyl thioglycolate. The structure of newly synthesized compounds have been characterized by elemental analysis and spectral data. Some of the synthesized compounds have been found to exhibit better antibacterial and anti fungal activity.*

Keywords: Benzo[*b*]thiophene derivatives, Pyrazolone, Pyrazole, Antifungal, Anti-microbial.

INTRODUCTION

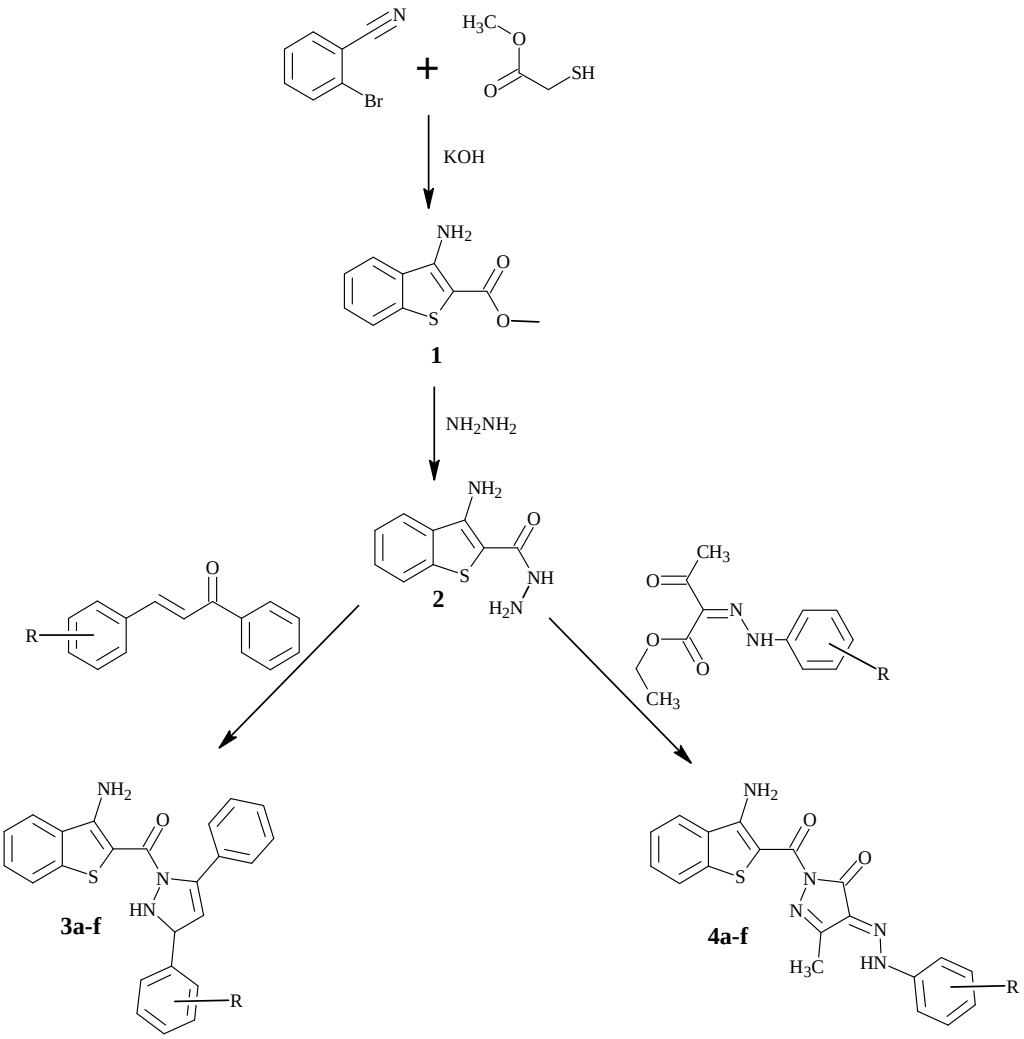
Novel benzo[*b*]thiophene derivatives are privileged structures present in many biologically active compounds. Benzo[*b*]thiophenes serve as very useful heterocyclic cores in the development of new drugs[1] and found to possess varied biological activities, *via,* estrogen receptor modulators[2], antimitotic agents [3], modulators of multidrug resistance[4], angiogenesis inhibitors[5], cognition enhancers[6], antifungal[7] and anti-inflammatory[8] etc. Pyrazolone derivatives are an important class of heterocyclic compounds that occur in many drugs and synthetic products. These compounds exhibit remarkable analgesic[9-11], antimicrobial[12-13], anti-inflammatory[14], antioxidant and antitumor activities[15-17]. Similarly, pyrazoles are five membered ring heterocyclic compounds, have some structural features with two nitrogen atoms in adjacent position. Pyrazole derivatives have showed significant biological activities such as antiproliferative[18], antiparasitic[19-20], anti-inflammatory[21], antiprotozoal[22-23] and anti-microbial[24, 25] activities. In order to synthesize active molecules of widely different composition such as combination of two heterocyclic frameworks to achieve good biological profile, it was planned to synthesize some benzothiophene derivatives containing pyrazolone and pyrazole moieties.

MATERIALS AND METHODS

All the melting points were determined in an open capillary and were uncorrected. IR spectra were recorded on Bruker alpha FT IR spectrophotometer, ^{1}H NMR spectra were measured on Bruker AV 400MHZ using $CDCl_3$ and DMSO as solvent. Chemical shifts are expressed in δ ppm. Mass spectra were

performed on a Joel JMS-D 300 mass spectrometer operating at 70 eV. All the reactions were followed and checked by TLC, and further purification was done by column chromatography. All the reagents used were of AR grade and they were again purified by distillation.

Scheme-1



Compounds	R	Compounds	R
3a	**OH**	**4a**	**Br**
3b	**OCH_3**	**4b**	**4-NO_2**
3c	**NO_2**	**4c**	**2-NO_2**
3d	**Cl**	**4d**	**Cl**
3e	**F**	**4e**	**OCH_3**
3f	**CH_3**	**4f**	**3-Cl, 4-F**

General procedure and spectral data of the compounds

Preparation of methyl 3-amino-1-benzothiophene-2-carboxylate 1: 2-Bromobenzonitrile (5.46g, 0.03mol) was added to stirred solution of methylthioglycolate (2.7ml, 0.03 mol) and potassium hydroxide (4.12g, 0.075mol) in DMF at 75° C for 10 h. The completion of the reaction was monitored by TLC. After

completion, the reaction mixture was cooled to room temperature and poured in to crushed ice. The pale yellow solid separated out was filtered and washed with water, dried and purified by column chromatography using ethyl acetate and n-hexane.

Preparation of 3-amino-1-benzothiophene-2-carbohydrazide 2 : To a stirred solution of methyl 3-amino-1-benzothiophene-2-carboxylate **1** (2.07g, 0.01mol) in absolute alcohol (50ml) was added hydrazine hydrate (0.3ml, 0.01mol) at room temperature. Then the reaction mixture was refluxed on a water bath for 6 h. The completion of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to room temperature and poured into crushed ice. The pale yellow solid separated was filtered, washed with water, dried and recrystallized by ethyl acetate.

3-Amino-1-benzothiophen-2-yl)[3-(2-hydroxyphenyl)-5-phenyl-2,3-dihydro-1*H*-pyrazol-1-] methanone 3a: Mixture of 1,3-diphenylprop-2-en-1-one (0.208g, 0.001mol) and catalytic amount of acetic acid in 1,4-dioxane (40ml) was stirred for 15 minutes at reflux temperature and then added 3-amino benzothiophene-2-carbohydrazide **2** (0.207g, 0.001mol). The reaction mixture was refluxed for 28 h. The completion of the reaction was monitored by TLC. After completion, the reaction mixture was cooled and poured in to crushed ice. The solid separated was filtered, washed with water, dried and purified by column chromatography using ethyl acetate and n-hexane. Similarly, the compounds **3b-f** were prepared.

Methyl 3-amino-1-benzothiophene-2-carboxylate 1 : Solid (crystalline); IR (KBr) (ν_{max} cm^{-1}): 3445 (NH_2), 1648 (C=O); 1H-NMR: 400 MHz: DMSO-d6: 8.03 (1H, m), 7.38-7.36 (1H, m), 7.01 (2H, bs), 6.74-6.73 (1H, m), 6.66-6.64 (1H, m), 3.86(3H, s). MS: m/z 207.

3-Amino-1-benzothiophene-2-carbohydrazide 2 : Solid (crystalline); IR (KBr) (ν_{max} cm^{-1}): 3430 (NH_2), 3340 (CONH), 1651 (C=O); 1H-NMR: 400 MHz: DMSO-d6: 8.94 (1H, bs), 8.07-8.04 (1H, m), 7.72-7.74 (1H, m), 7.32-7.24 (2H, m), 7.05 (2H, bs), 4.39(1H, bs); MS: m/z 207.

(3-Amino-1-benzothiophen-2-yl)[3-(2-hydroxyphenyl)-5-phenyl-2, 3-dihydro-1*H*-pyrazol-1-yl]methanone 3a : Solid (Amorphous); IR (KBr) (ν_{max} cm^{-1}): 3445 (NH_2), 1658 (C=O); 1H-NMR: 400 MHz: DMSO-d6; 8.53 (2H, s), 8.22-8.20 (2H, m), 7.90-7.87 (2H, m), 7.75-7.45 (5H, m), 7.08-7.05 (2H, m), 6.75-6.73 (2H, d, J=8 Hz), 5.64-5.63 (1H, m), 4.13-4.11(1H, m). MS: m/z 327.

(3-amino-1-benzothiophen-2-yl)[3-(4-methoxyphenyl)-5-phenyl-2,3-dihydro-1*H*-pyrazol-1-yl]methanone 3b : Solid (Amorphous); IR (KBr) (ν_{max} cm^{-1}): 3447 (NH_2), 1660 (C=O); 1H-NMR: 400 MHz: DMSO-d6: 8.57 (2H, s), 8.18-8.16 (2H, m), 7.80-7.77 (2H, m), 7.70-7.55 (5H, m), 7.08-7.05 (2H, d, J=8 Hz), 6.87-6.85 (2H, d, J=8 Hz), 5.94-5.93 (1H, m), 4.12-4.11(1H, m), 3.83 (3H, s). MS: m/z 399.

(3-amino-1-benzothiophen-2-yl)[3-(2-nitrophenyl)-5-phenyl-2,3-dihydro-1*H*-pyrazol-1-yl]methanone 3c: Solid (Amorphous); IR (KBr) (ν_{max} cm^{-1}): 3450 (NH_2), 1665 (C=O); 1H-NMR: 400 MHz: DMSO-d6: 8.63 (2H, s), 8.28-8.22 (2H, m), 7.99-7.81 (2H, m), 7.68-7.55 (5H, m), 7.12-7.10 (2H, m), 6.85-6.83 (2H, m), 5.68-5.63 (1H, m), 4.13-4.12(1H, m). MS: m/z 325.

(3-amino-1-benzothiophen-2-yl)[3-(4-chlorophenyl)-5-phenyl-2,3-dihydro-1*H*-pyrazol-1-yl]methanone 3d : Solid (Amorphous); IR (KBr) (ν_{max} cm^{-1}): 3442 (NH_2), 1655 (C=O); 1H-NMR: 400 MHz: DMSO-d6: 8.47 (2H, s), 8.08-8.06 (2H, m), 7.82-7.80 (2H, m), 7.70-7.40 (5H, m), 7.12-7.05 (4H, m), 5.84-5.83 (1H, m), 4.12-4.11(1H, m). MS: m/z 308.

(3-amino-1-benzothiophen-2-yl)[3-(4-fluorophenyl)-5-phenyl-2,3-dihydro-1*H*-pyrazol-1-yl]methanone 3e: Solid (Amorphous); IR (KBr) (ν_{max} cm^{-1}): 3440 (NH_2), 1652 (C=O); 1H-NMR: 400 MHz: DMSO-d6: 8.57 (2H, s), 8.12-8.10 (2H, m), 7.90-7.98 (2H, m), 7.80-7.50 (5H, m), 7.18-7.10 (4H, m), 5.79-5.73 (1H, m), 4.12-4.11(1H, m), MS: m/z 381.

(3-amino-1-benzothiophen-2-yl)[3-(4-methylphenyl)-5-phenyl-2,3-dihydro-1*H*-pyrazol-1-yl]methanone 3f: Solid (Amorphous); IR (KBr) (ν_{max} cm^{-1}): 3449 (NH_2), 1663 (C=O); 1H-NMR: 400 MHz: DMSO-d6: 8.47 (2H, s), 8.04-8.04 (2H, m), 7.80-7.78 (2H, m), 7.72-7.50 (5H, m), 7.00-7.6.85 (4H, m), 5.69-5.53 (1H, m), 4.14-4.12(1H, m), 2.18 (s3H, s). MS: m/z 355.

A**(4*E*)-2-[(3-amino-1-benzothiophen-2-yl)carbonyl]-4-[2-(4-bromophenyl)hydrazinylidene]-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one 4a:** Mixture of 3-amino-benzothiophene-2-carbohydrazide (0.207g, 0.001mol) and ethyl-(2Z)-3-oxo-2-(2-phenylhydrazinylidene) butanoate (0.234g, 0.001mol) in glacial acetic acid (20ml) were refluxed in an oil bath for 10-12hours. The reaction was monitored by TLC. After completion, the reaction mixture was cooled and poured in to crushed ice. The solid separated out was filtered, washed with water, dried and recrystalised by ethyl alcohol to get compound **4a**. The same procedure was used to synthesize compounds **4b-f**.

(4*E*)-2-[(3-amino-1-benzothiophen-2-yl)carbonyl]-4-[2-(4-bromophenyl)hydrazinylidene]-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one 4a: Solid (Amorphous); IR (KBr) (ν_{max} cm^{-1}): 3429 (NH_2), 1667 (C=O); 1H-NMR: 400 MHz: DMSO-d6: 11.22 (1H, s), 8.67 (2H, s), 8.26-8.24 (1H, d, J=8 Hz), 8.18-8.16 (1H, d, J=8 Hz), 7.62-7.60 (2H, m), 7.52-7.50 (2H, d, J=7.6 Hz), 6.95-6.93 (2H, J=7.6 Hz), 2.15 (3H, s). MS: m/z 382.

(4*E*)-2-[(3-amino-1-benzothiophen-2-yl)carbonyl]-5-methyl-4-[2-4(-nitrophenyl) hydrazinylidene]-2,4-dihydro-3*H*-pyrazol-3-one 4b: Solid (Amorphous); IR (KBr) (ν_{max} cm^{-1}): 3424(NH_2), 1658 (C=O); 1H-NMR: 400 MHz: DMSO-d6:10.5 (1H, s), 8.9 (2H, s), 8.10-8.00 (4H, m), 7.58-7.56 (2H, m), 7.20-7.18 (2H, J=7.2 Hz), 2.17 (3H, s). MS: m/z 450.

(4*E*)-2-[(3-amino-1-benzothiophen-2-yl)carbonyl]-5-methyl-4-[2-(2-nitrophenyl) hydrazinylidene]-2, 4-dihydro-3*H*-pyrazol-3-one 4c: Solid (Amorphous); IR (KBr) (ν_{max} cm^{-1}): 3426 (NH_2), 1659 (C=O); 1H-NMR: 400 MHz: DMSO-d6: 10.61 (1H, s), 8.97 (2H, s), 8.13-8.09 (3H, m), 7.58-7.40 (4H, m), 7.04-7.02 (1H, J=6.8 Hz), 2.16 (3H, s). MS: m/z 351.

(4*E*)-2-[(3-amino-1-benzothiophen-2-yl)carbonyl]-4-[2-(4-chlorophenyl)hydrazinylidene]-5-methyl-2, 4-dihydro-3*H*-pyrazol-3-one 4d :Solid (Amorphous); IR (KBr) (ν_{max} cm^{-1}): 3423 (NH_2), 1662 (C=O); 1H-NMR: 400 MHz: DMSO-d6: 10.93 (1H, s), 8.37 (2H, s), 8.16-8.14 (1H, d, J=8 Hz), 8.02-8.00 (1H, d, J=8 Hz), 7.62-7.60 (2H, m), 7.34-7.32 (2H, d, J=7.6 Hz), 7.04-7.02 (2H, J=7.6 Hz), 2.14 (3H, s). MS: m/z 383.

(4*E*)-2-[(3-amino-1-benzothiophen-2-yl)carbonyl]-4-[2-(4-methoxyphenyl)hydrazinylidene]-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one 4e; Solid (Amorphous); IR (KBr) (ν_{max} cm^{-1}): 3422 (NH_2), 1669 (C=O); 1H-NMR: 400 MHz: DMSO-d6: 10.63 (1H, s), 8.17 (2H, s), 8.10-8.02 (2H, m), 7.70-7.55 (4H, m), 7.08-7.05 (2H, d, J=8 Hz), 3.82 (3H, s), 2.16 (3H, s). MS: m/z 381.

(4*E*)-2-[(3-amino-1-benzothiophen-2-yl)carbonyl]-4-[2-(3-chloro-4-fluorophenyl) hydrazinylidene]-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one 4f; Solid (Amorphous); IR (KBr) (ν_{max} cm^{-1}): 3425 (NH_2), 1668 (C=O); 1H-NMR: 400 MHz: DMSO-d6: 10.83 (1H, s), 8.94 (2H, s), 8.13-8.10 (2H, m), 7.58-7.40 (1H, m), 6.89-6.88 (1H, m), 6.53-6.51 (1H, m). 2.16 (3H, s). MS: m/z 385.

RESULTS AND DISCUSSION

Methyl-3-amino-1-benzothiophene-2-carboxylate (**1)** was synthesized by the treatment of 2-bromobenzonitrile with methylthioglycolate in the presence of KOH and DMF as a solvent. To this added hydrazine hydrate to give 3-amino-1-benzothiophene-2-corbohydrazide (**2)**. Novel series of (3-amino-1-benzothiophen-2-yl)(3, 5-diphenyl-2, 3-dihydro-1*H*-pyrazol-1-yl)methanones **(3a-f)** were prepared by refluxing compound **2** with different 1,3-diphenylprop-2-en-1-one. In confirmation, **3a** exhibited NH_2 bands stretching at 3445, carbonyl group absorption band at 1658 cm^{-1} respectively in its IR spectrum. ^1H NMR spectra showed peak at δ 6.75-6.73 for two protons of NH_2 group and δ 5.64-5.63 for one proton of OH group. Preparation of (4E)-2-[(3-amino-1-benzothiophen-2-yl)carbonyl]-5-methyl-4-(2-phenylhydrazinylidene)-2,4-dihydro-3H-pyrazol-3-ones (**4a-f)** was done by refluxing ethyl (2Z)-3-oxo-2-(2-phenylhydrazinylidene)butanoate with compound **2.** In confirmation **4a** exhibited NH_2 stretching bands at 3429, carbonyl group absorption band at 1667 cm^{-1} respectively in its IR spectrum.`^1H NMR spectra showed a peak at δ 2.15 for three protons of CH_3 group and a peak at δ 6.95-6.93 for two protons of NH_2 group.

Table 1: Physical and Analytical data of the compounds

Comp. no	Molecular Formula	Melting Point	Yield (%)	Elemental analysis (Cald./Found) %			
				C	H	N	S
1	$C_{10}H_9NO_2S$	138-139	85	57.95 (57.81)	4.38 (4.35)	6.75 (6.71)	15.47 (15.35)
2	$C_9H_9N_3OS$	178-179	75	52.16 (52.13)	4.34 (4.30)	20.27 (20.24)	15.47 (15.43)
3a	$C_{16}H_{10}ClN_3OS$	153-154	72	58.62 (58.55)	3.07 (3.04)	12.82 (12.79)	9.78 (9.75)
3b	$C_{16}H_9N_5O_6S$	145-146	68	48.12 (48.05)	2.27 (2.24)	17.54 (17.51)	8.02 (7.59)
3c	$C_{16}H_{11}N_3OS_2$	170-171	77	59.05 (59.02)	3.41 (3.32)	12.91 (12.87)	19.70 (18.62)
3d	$C_{16}H_{12}N_4OS$	166-167	72	62.32 (62.29)	3.92 (3.85)	18.17 (18.11)	10.40 (10.36)
3e	$C_{20}H_{19}N_3O_3S$	162-163	67	62.98 (62.93)	5.02 (4.99)	11.01 (10.55)	8.40 (8.37)
3f	$C_{18}H_{14}FN_3O_2S$	157-158	73	60.83 (60.80)	3.97 (3.94)	11.82 (11.71)	9.02 (8.85)
4a	$C_{18}H_{14}N_4O_4S$	149-150	76	56.54 (56.51)	3.69 (3.55)	14.65 (14.58)	8.38 (8.32)
4b	$C_{23}H_{19}ClN_4O_2S$	174-175	70	58.47 (58.35)	4.01 (3.89)	15.50 (15.45)	7.1 (6.95)
4c	$C_{19}H_{17}N_3O_2S$	167-168	81	64.93 (61.85)	4.87 (4.81)	11.96 (11.93)	9.12 (9.09)
4d	$C_{19}H_{17}N_3O_4S$	158-159	76	59.15 (59.11)	4.47 (4.40)	10.96 (10.93)	8.36 (8.31)
4e	$C_{20}H_{19}N_3O_3S$	160-161	74	62.98 (62.91)	5.02 (4.95)	11.01 (10.57)	8.40 (8.37)
4f	$C_{19}H_{16}ClFN_3O_2S$	179-180	67	59.14 (59.11)	4.18 (4.15)	10.89 (10.83)	8.31 (8.25)

Antibacterial Activity: Some selected compounds were screened for their antibacterial activity against *Staphylococcus aureus, Escherichia coli, Salmonella paratyphi-A* and *Bacillus subtilis* and the activity was carried out using the cup-plate agar diffusion method [26]**.** The zone of inhibition was measured in millimeters. DMF was used as a vehicle. Choramphenicol used as standard drugs for antibacterial activity. The compounds were tested at 40µg/mL concentration. The tested compounds were found to show moderate activity against all bacteria. The zones of inhibition are presented in table 2.

Table 2: Antibacterial activity of the compounds

Compound	Diameter of zone of inhibition (in mm)			
	Staphylococcus aureus	***Escherichia coli***	***Salmonella paratyphi-A***	***Bacillus subtilis***
1	14	08	10	12
2	13	11	15	17
3a	17	12	14	18
3c	19	13	15	15
3e	18	12	16	16
3f	16	12	15	21

4a	15	10	14	17
4c	14	15	15	19
4e	17	12	12	18
4f	16	15	17	11
DMF	00	00	00	00
Chloramphenicols	20	14	18	22

Antifungal Activity: Some selected compounds were screened for their antifungal activity against four species of fungi *Aspergillus Niger*, *Aspergillus fumigates*, *Candida albicans* and *Pencillium notatums*. The activity was carried out using the cup-plate agar diffusion method[27]**.** The zone of inhibition was measured in millimeters. DMF was used as a vehicle. Fluconazole was used as standard drug for antifungal activity. The compounds were tested at 40µg mL^{-1} concentration. The tested compounds were found to show moderate activity against all fungi. The zones of inhibition are presented in Table 3.

Table 3: Antifungal activity data of compounds

Compound	**Diameter of zone of inhibition (in mm)**			
	Aspergillus niger	***Pencillium notatum***	***Aspergillus fumigatus***	***Candiada albicans***
1	15	17	13	16
2	17	19	15	18
3a	20	21	19	14
3c	20	19	22	16
3e	21	20	23	15
3f	19	17	20	16
4a	12	18	18	14
4c	22	20	17	15
4e	15	18	19	13
4f	23	21	16	18
DMF	00	00	00	00
Fluconazole	25	25	25	19

APPLICATIONS

Amino-benzo[*b*]thiophene derivatives displayed potential antibacterial and antifungal activities.

CONCLUSIONS

In the present investigation, we have synthesized some novel benzo[*b*]thiophene derivatives carrying pyrazolone and pyrazole compounds with better yields. Advantage of this method is that reactions were found clean and had operational simplicity.

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