European Journal of Medicinal Chemistry 45 (2010) 825–830

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Short communication

Synthesis, characterization and biological activities of some new benzo[b]thiophene derivatives

Arun M. Isloor [a,*], Balakrishna Kalluraya [b], K. Sridhar Pai [c]

[a] Department of Chemistry, National Institute of Technology-Karnataka, Surathkal, Mangalore 575 025, India
[b] Department of Chemistry, Mangalore University, Mangalagangothri, Mangalore 574 199, India
[c] Department of Pharmacology, Manipal College of Pharmaceutical Sciences, Manipal University, Manipal 576 104, India

ARTICLE INFO

Article history:
Received 9 July 2009
Received in revised form
3 October 2009
Accepted 5 November 2009
Available online 11 November 2009

Keywords:
Benzo[b]thiophene
Anti-inflammatory activity
Antibacterial & antifungal activity

ABSTRACT

Benzo[b]thiophene molecules are found to be important tools in synthetic medicinal chemistry. They are of current interest due to their wide spectrum of pharmacological properties. In view of the biological activities of benzo[b]thiophene containing molecules, in this present research work, we propose the synthesis of some new benzo[b]thiophene derivatives such as thiadiazoles, oxadiazoles, pyrazolin & diaryl pyrazoles starting from 3-chlorobenzo[b]thiophene-2-carboxyl chloride. These newly synthesized compounds were characterized by elemental analyses, I.R, NMR and Mass spectral studies. Some of the selected compounds were screened for their antibacterial, antifungal and anti-inflammatory studies. Many of the molecules were found to be potent.

1. Introduction

Sulphur containing heterocycles paved way for the active research in the pharmaceutical Chemistry. Nowadays benzothiophene derivatives in combination with other ring systems have been used extensively in Pharmaceutical applications such as antiallergic [1], analgesic [2], anti-inflammatory [3] and Ocular hypotensive activities [4]. Raloxifene a drug based on benzo[b]-thiophene has been approved by the U.S Food and Drug Administration for the prevention and treatment of osteoporosis associated with woman postmenopausal [5].

On the other hand compounds bearing 1,2,4-triazole ring are very well known to exhibit powerful antimicrobial [6], anticonvulsant [7], antidepressant [8], analgesic [9] activities. Moreover some 1,2,4-triazolo [3,4-b][1,3,4]thiadiazines are associated with diverse pharmacological activities [10–14]. Further various oxadiazole derivatives [15], pyrazolin-5-ones [16], diaryl pyrazole derivatives [17] also exhibits wide spectrum pharmacological activities.

Continuing our efforts directed [6] towards the synthesis of new heterocyclic compounds with expected biological activities, we hereby report the synthesis of some new benzo[b]thiophene derivatives and their characterization by IR, NMR & Mass spectrometry techniques. Newly synthesized compounds were also screened for their antimicrobial and anti-inflammatory activities.

2. Chemistry

In the present investigation benzo[b]thiophene moiety is used as the building block. 3-Chlorobenzo[b]thiophene-2-carboxyl chloride **2** was prepared from cinnamic acid and thionyl chloride in chlorobenzene medium using pyridine as the catalyst, following the procedure of Castle et al. [18]. Acid chloride **2** was converted into acid **3** by hydrolysis with methanolic potassium hydroxide. It was reacted with various 3-substituted-4-amino-1,2,4-triazoles to get the corresponding triazolothiadiazoles **4**. In another series, the acid chloride **2** was converted into the corresponding ester **7** by treating with methanol, further on reacting with hydrazine hydrate yielded hydrazide **8**. These hydrazides were reacted with ethyl butyrate derivatives **9** to get substituted pyrazolin-5-one **10** (Fig. 1).

Another series of pyrazoles containing benzo[b]thiophene were synthesized by reacting its hydrazide **8** and various α-bromopropenones **11**. Similarly a series of 2,5-disubstituted oxadiazoles **6** were synthesized by the cyclization of the hydrazide derivative **5** using phosphorous oxychloride. Newly synthesized compounds were characterized by IR, NMR, Mass spectral and C, H, N analyses.

3. Pharmacology

3.1. Antimicrobial studies

Antibacterial activity studies of newly synthesized compounds were carried out against four different pathogenic organisms, two

* Corresponding author. Tel.: +91 824 2474000x3206; fax: +91 8242474033.
E-mail address: isloor@yahoo.com (A.M. Isloor).

0223-5234/$ – see front matter © 2009 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2009.11.015

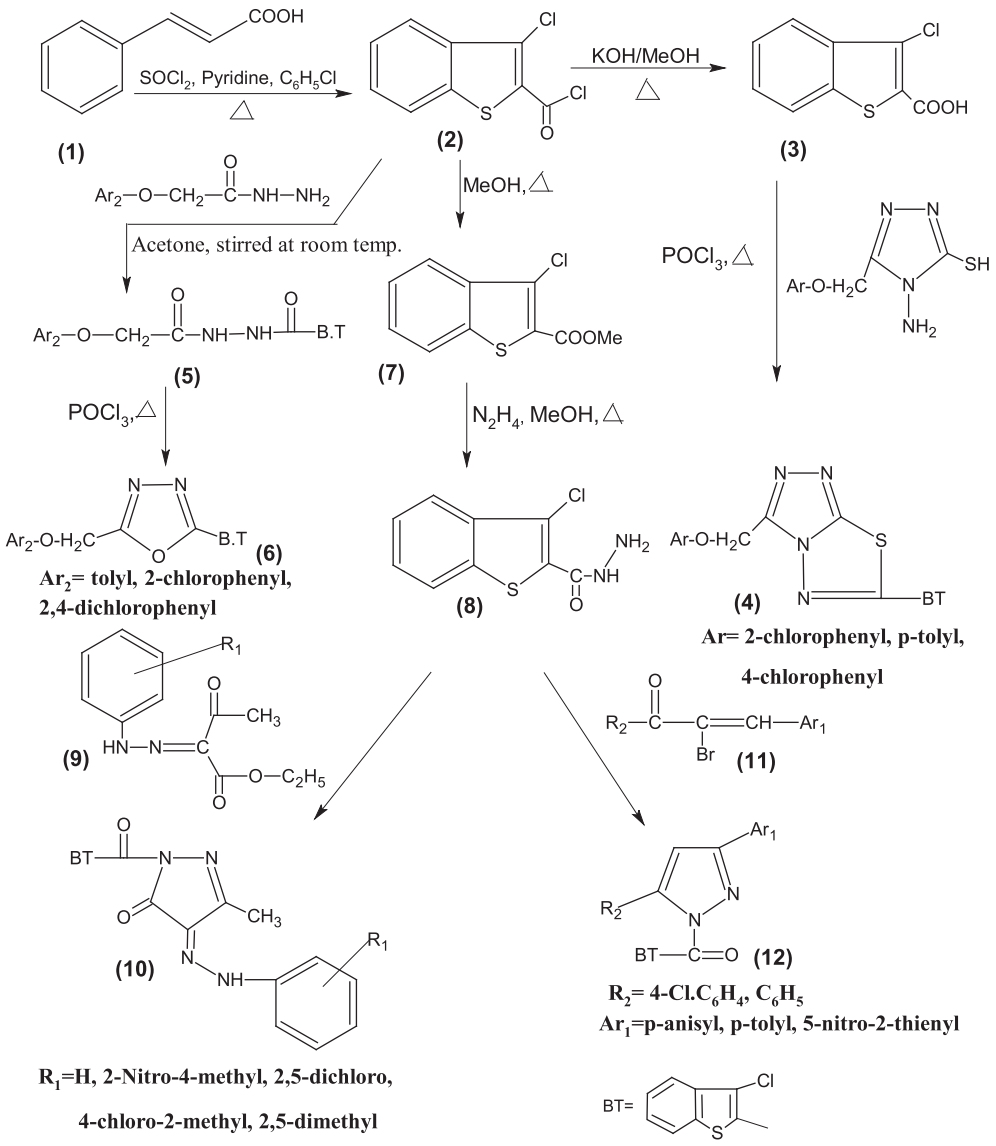

Fig. 1.

each of Gram negative & Gram positive. They are *Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa*. Antifungal activity was carried out on the fungus *Candida albicans* using the same procedure. Antimicrobial studies were assessed by Minimum Inhibitory Concentration (MIC) by serial dilution method [19].

MIC of the new synthetic compounds was determined separately for each of the organisms. For antimicrobial, the compound whose MIC has to be determined ~~is~~ was dissolved in DMF and serially diluted. A standard drop of the culture prepared for the assay is added to each of the dilutions, and incubated for 16–18 h at 37 °C. The MIC is the highest dilution of the compound, which shows clear fluid with no development of turbidity. Furacin was the standard drug for antibacterial studies, while flucanazol was used as standard for the antifungal studies.

3.2. Anti-inflammatory studies

For the anti-inflammatory studies, Rat hind paw edema method was followed using Wrister rats, which is slight modification of Winter et al. [20] method. All experiments have been approved by Institutional animal care and use Committee. The apparatus used for the measurement of the rat paw volume was that of Buttle et al. [21] modified by Singh and Ghosh [22].

In our present work, animals were divided into 5 groups of eight animals each. One group served as control, another served as a standard (Diclofenac sodium) and the rest of the groups were used for the test compounds. Rats were dosed orally with at 100 mg/kg body weight test compounds and Diclofenac sodium was suspended in 4% acacia gum solution.4% Acacia gum mucilage was used as a vehicle for the control group. Then a three hour solution of 1% carrageenan was used as an anti-inflammatory agent.

Food was withdrawn overnight with adequate water before the experiment. The drug was dosed orally with the help of an oral catcher. After one hour, a subplanter injection of 0.05 ml of 1% solution of carrageenan was administered. The volume of the injected paw was measured after 3 h. The average paw swelling in a group of drug treated rats were compared with that of a group, treated with the vehicle (control group), and the % inhibition of edema was calculated using the formula

$$\%\text{Inhibition} = [1 - Vt/Vc] \times 100.$$

Where *Vt* = Edema volume in drug treated rats & *Vc* = Edema volume in control rats

4. Results and discussion

The IR spectrum of **6a** showed absorptions at 1617 cm^{-1} & 1593 cm^{-1} due to C=N & C=C bonds. The ^1H NMR spectrum of **6a**, δ, 2.29 is due to methyl group. The OCH_2 protons came into resonance as a singlet at δ, 5.40 integrating for two protons. The remaining aromatic protons of the benzo[b]thiophene and phenyl group appeared as multiplets in the region of δ, 6.96–7.99 integrating for eight protons. Characterization of the newly synthesized compounds has been given in Tables 1 and 2. Similarly NMR spectral details of other compounds have been given in Table 3.

The mass spectrum of **6b** showed molecular ion peak at *m*/*z*, 376 consistent with the molecular formula $C_{17}H_{10}Cl_2N_2O_2S$. The cluster of isotope peaks due to presence of two chlorine atoms (M + 2) and (M + 4) were observed at *m*/*z* 378 & 380. The peak at *m*/*z*, 341 is due to the loss of chlorine radical from the molecular ion.

In the IR spectrum of **4a**, the bands corresponding to the NH_2 group of the triazole and carboxyl group of the 3-chlorobenzo[b]thiophene-2-carboxylic acid were absent in the condensed product, thereby indicating the involvement of $-NH_2$ and $-CO_2H$ group in the condensation reaction. The absorption due to C=N appeared at around 1617 cm^{-1}. The ^1H NMR spectrum of **4a** showed signal due to $-OCH_2$ protons appeared at δ, 5.3 as an singlet integrating for two protons. The signals due to remaining aromatic protons of the phenyl and benzo[b]thiophene moiety overlapped with each other and appeared as multiplets in the region δ, 7.0–7.96 integrating for eight protons. The mass spectrum of **4b** showed the molecular ion peak at *m*/*z*, 412 in agreement with the assigned molecular formula $C_{19}H_{13}N_4ClS_2O$. The chlorine isotope peak was observed at *m*/*z*, 414. Similarly NMR spectra of **10b** and **10e** were recorded. Further the mass spectrum of **10b** and **10e** were recorded and which is in agreement with the proposed structures. Similarly the IR, NMR & mass spectrum of pyrazolines **12** were recorded are presented in Table 3.

5. Conclusions

In the present study we have described synthesis of various benzo[b]thiophene derivatives. These newly synthesized compounds were characterized by NMR, mass spectrometry and IR studies. Few of the selected compounds were screened for their antimicrobial (MIC – Minimum Inhibitory Concentration) and anti-inflammatory activities. The antibacterial study reveals that compounds **12c** and **12d** having 5-nitro-2-thienyl substitution exhibited maximum inhibition against *S. aureus*. Similarly compound **12d** has shown maximum inhibition against fungus *C. albicans*. Also compound **12b** with phenyl and p-anisyl has shown maximum inhibition against fungus. All remaining compounds showed significant activity as compared to the standard drugs. Antimicrobial screening details has been presented in Table 4. Benzo[b]thiophene nucleus is one of the active components present in all molecules.

Few of the selected compounds were also screened for their anti-inflammatory activity. It clearly reveals that compound **12a**

Table 1
Characterization data of new benzo[b]thiophene derivatives.

Comp. no.	Ar	Yield % & m.p°C	Colour & nature	Mol. formula	Analyses % found (Calcd.)		
					C	H	N
4a	o-Chlorophenyl	65 255–57	White micro crystals	$C_{18}H_{11}N_4OS_2Cl$	54.22 (54.18)	2.69 (2.75)	14.02 (14.00)
4b	p-Tolyl	50 195–96	White micro crystals	$C_{19}H_{13}N_4OS_2Cl$	55.24 (55.25)	3.14 (3.14)	13.53 (13.55)
4c	p-Chlorophenyl	87 216–18	White micro crystals	$C_{18}H_{10}N_4OS_2Cl_2$	49.85 (49.81)	2.31 (2.30)	12.90 (12.93)
Comp. No	Ar_2	Yield % & m.p°C	Color & nature	Mol. formula	Analyses % found (Calcd.)		
					C	H	N
5a	2-methylphenyl	45 152	White cotton	$C_{18}H_{15}N_2O_3SCl$	57.64 (57.68)	4.03 (4.00)	7.42 (7.47)
5b	o-Chlorophenyl	52 200–01	White cotton	$C_{17}H_{12}N_2O_3SCl_2$	51.61 (51.65)	3.01 (3.03)	7.02 (7.09)
5c	2,4-Dichlorophenyl	55 203–04	White cotton	$C_{17}H_{11}N_2O_3SCl_3$	47.50 (47.51)	2.52 (2.56)	6.51 (6.52)
6a	o-Tolyl	82 150–51	Colorless micro crystals	$C_{18}H_{13}N_2O_2SCl$	60.59 (60.56)	3.65 (3.64)	7.83 (7.85)
6b	o-Chlorophenyl–	75 158–60	Colorless micro crystals	$C_{17}H_{10}N_2O_2SCl_2$	54.11 (54.12)	2.61 (2.65)	7.38 (7.42)
6c	2,4-Dichlorophenyl–	72 174–75	Colorless micro crystals	$C_{17}H_9N_2O_2SCl_3$	49.59 (49.56)	2.14 (2.18)	6.81 (6.79)
Comp. No	R_1	Yield % & m.p°C	Color & nature	Mol. formula	Analyses % found (Calcd.)		
					C	H	N
10a	H	60 176–77	Yellow micro crystal	$C_{18}H_{13}N_4O_2SCl$	56.20 (56.25)	3.36 (3.38)	14.57 (14.58)
10b	2-Nitro-4-methyl	62 268–70	Orange micro needles	$C_{20}H_{14}N_5O_4SCl$	52.70 (52.74)	3.03 (3.07)	15.35 (15.38)
10c	2,5-Dichloro	55 213–15	Yellow cotton	$C_{19}H_{11}N_4O_2SCl_3$	48.90 (48.92)	2.39 (2.36)	12.04 (12.01)
10d	4-Chloro-2-methyl	68 192–93	Yellow micro crystal	$C_{20}H_{14}N_4O_2SCl_2$	54.08 (54.05)	3.18 (3.15)	12.58 (12.61)
10e	2,5-Dimethyl	65 171–72	Orange micro crystal	$C_{21}H_{17}N_4O_2SCl$	59.38 (59.43)	4.02 (4.00)	13.17 (13.20)
10f	4-Nitro	57 295–96	Orange micro crystal	$C_{19}H_{12}N_5O_4SCl$	51.61 (51.70)	2.73 (2.72)	15.82 (15.87)

Table 2
Characterization data of new benzo[b]thiophene derivatives.

Comp. no.	R_2	Ar_1	Yield% & m.p°C	Color & nature	Mol. formula	Analyses % found (Calcd.)		
						C	H	N
12a	p-Chlorophenyl	p-Anisyl	46 128	Pale yellow micro crystals	$C_{25}H_{16}N_2O_2SCl_2$	62.61 (62.68)	3.32 (3.34)	5.83 (5.84)
12b	Phenyl	p-Anisyl	58 201	Pale yellow micro crystal	$C_{25}H_{17}N_2O_2SCl$	67.49 (67.47)	3.81 (3.82)	6.25 (6.29)
12c	Phenyl	5-Nitro-2-Thienyl	36 118	Dark brown crystal	$C_{22}H_{12}N_3O_3S_2Cl$	56.75 (56.70)	2.63 (2.57)	9.00 (9.00)
12d	p-Chlorophenyl	5-Nitro-2-Thienyl	43 163	Golden micro needle	$C_{22}H_{11}N_3O_3S_2Cl_2$	52.80 (52.84)	2.23 (2.20)	8.41 (8.40)
12e	Phenyl	p-Tolyl	52 136	Golden micro needle	$C_{25}H_{17}N_2OSCl$	70.03 (70.01)	3.98 (3.97)	6.51 (6.54)

Table 3
Spectral characterization of benzo[b]thiophene derivatives.

Comp. no.	IR (KBr) υ (cm^{-1})	^1H NMR δ (ppm) ($CDCl_3$, 400 MHz)	MS *m/z*
4a	1617 (C═N), 1556 (C═C), 3055 (Ar-H), 1028 (C–S str)	4.76(s,2H, OCH_2) 6.81–7.28 (m, 4H, Ar) 7.66–8.06 (m, Ar-H & BT-H) 4H, BT)	*m/z* 398 (M^+), 168 (due to 3-chloro-1-benzothiophene), 230 (due to triazolothiadiazole ring)
4b	1618 (C═N), 1560 (C═C), 3052 (Ar-H), 1015 (C–S str)	2.27(s, 3H, $–CH_3$ tolyl), 4.75 (s, 2H, $–OCH_2$), 6.73–7.00(m, 4H Ar-H), 7.66–8.06 (m, 4H of BT ring)	*m/z* 412 (M^+), 168 (due to 3-chloro-1-benzothiophene), 246 (due to triazolothiadiazole)
4c	1619 (C═N), 1550 (C═C), 3052 (Ar-H), 1032 (C–S str)	4.78(s,2H, OCH_2) 6.83–7.35(m, 4H, Ar) 7.69–8.10 (m, Ar-H & BT-H) 4H, BT)	*m/z* 398 (M^+), 168 (due to 3-chloro-1-benzothiophene), 230 (due to triazolothiadiazole ring)
5a	1680 (C═O), 1545 (C═C), 1018 (C–S) str, 3048 (Ar-H)	4.82 (S, 2H, OCH_2), 2.42 (s, 3H, CH_3), 7.52–8.12 (m, Ar-H & BT-H) 4H, BT)	*m/z* 374 (M^+), 168 (due to 3-chloro-1-benzothiophene), 206 (due to the cleaved hydrazine part)
5b	1675 (C═O), 1542 (C═C), 1025 (C–S) str, 3045 (Ar-H)	4.75 (S, 2H, OCH_2), 7.48–8.10 (m, Ar-H & BT-H) 4H, BT)	*m/z* 394 (M^+), 168 (due to 3-chloro-1-benzothiophene), 226 (due to cleaved hydrazine part)
5c	1672 (C═O), 1535 (C═C), 1028 (C–S) str, 3042 (Ar-H)	4.78 (S, 2H, OCH_2), 7.50–8.28 (m, Ar-H & BT-H) 4H, BT)	*m/z* 428 (M^+), 168 (due to 3-chloro-1-benzothiophene), 226 (due to cleaved hydrazine part)
6a	1617 (C═N), 1593 (C═C), 3060 (Ar-H), 1018 (C–S str)	4.97(s, 2H, $–OCH_2$), 6.73–7.01(m, 4H Ar-H), 7.44–7.97(m, 4H of BT ring)	*m/z* 356 (M^+), 168 (due to 3-chloro-1-benzothiophene), 249 (due to oxadiazole)
6b	1615 (C═N), 1588 (C═C), 3055 (Ar-H), 1020 (C–S str)	4.98(s 2H $–OCH_2$), 6.92–7.28(m, 4H Ar-H), 7.44–7.94(m, 4H of BT ring)	*m/z* 376 (M^+), 168 (due to 3-chloro-1-benzothiophene), 249 (due to 2-(3-chloro-1-benzothien-2-yl)- 1,3,4-oxadiazole cation)
6c	1618 (C═N), 1590 (C═C), 3058 (Ar-H), 1015 (C–S str)	4.97(s, 2H, $–OCH_2$), 6.73–7.01(m, 3H Ar-H), 7.44–7.97(m, 4H of BT ring)	*m/z* 410 (M^+), 168 (due to 3-chloro-1-benzothiophene), 249 (due to 2-(3-chloro-1-benzothien-2-yl)- 1,3,4-oxadiazole cation)
10a	1617 (C═N), 1580 (C═C), 1674 (C═O)	2.43 (s, 3H, CH_3), 7.41–8.31 (m, 9H, Ar-H & BT-H), 14.0 (s, 1H, NH)	*m/z* 384 ((M^+), 168 (due to 3-chloro-1-benzothiophene), 218 (due to (4*E*)-1-(hydroxymethyl)-1*H*-pyrazole-4, 5-dione 4-(phenylhydrazone))
10b	1620 (C═N), 1582 (C═C), 1670(C═O)	2.45 (s, 3H, CH_3), 2.5 (s, 3H, CH_3), 7.35–8.2 (m, 7H, Ar-H & BT-H), 14.2 (s, 1H, NH)	*m/z* 455 (M^+), 168 (due to 3-chloro-1-benzothiophene), 277 (due to (4*E*)-1-(hydroxymethyl)-1*H*-pyrazole-4, 5-dione 4-[(4-methyl-2-nitrophenyl)hydrazone])
10c	1612 (C═N), 1582 (C═C), 1668(C═O)	2.48 (s, 3H, CH_3), 7.48–8.40 (m, 7H, Ar-H & BT-H), 13.6 (s, 1H, NH)	*m/z* 464 (M^+), 168 (due to 3-chloro-1-benzothiophene), 287 (due to (4*E*)-1-(hydroxymethyl)-1*H*-pyrazole-4, 5-dione 4-[(2,4-dichlorophenyl)hydrazone])
10d	16 118 (C═N), 1585 (C═C), 1665(C═O)	2.32 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 7.40–8.51 (m, 7H, Ar-H & BT-H), 13.68 (s, 1H, NH)	*m/z* 444 (M^+), 168 (due to 3-chloro-1-benzothiophene)
10e	1618 (C═N), 1580 (C═C), 1680 (C═O)	δ, 2.37 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 6.96–8.01 (m, 7H, Ar-H & BT-H), 13.64 (s, 1H, NH)	*m/z* 424 (M^+), 168 (due to 3-chloro-1-benzothiophene), 246 (due to (4*E*)-1-(hydroxymethyl)-1*H*-pyrazole-4, 5-dione 4-[(2,5-dimethylphenyl)hydrazone])
10f	1618 (C═N), 1582 (C═C), 1668 (C═O)	2.45 (s, 3H, CH_3), 7.45–8.38 (m, 8H, Ar-H & BT-H), 13.2 (s, 1H, NH)	*m/z* 433 (M^+), 168 (due to 3-chloro-1-benzothiophene), 263 (due to (4*E*)-1-(hydroxymethyl)-1*H*-pyrazole-4, 5-dione 4-[(4-nitrophenyl)hydrazone])
12a	1645 (C═O), 1590 (C═N), 3065 (Ar-H), 1017 (C–S str)	4.12(s, 2H, $–OCH_3$), 7.25–8.18 (m, 12H, Ar-H), 6.74 (s, pyrazole ring H), 7.44–7.87(m, 4H of BT ring)	*m/z*, 478 (M^+), 168 (due to 3-chloro-1-benzothiophene), 312 (due to 5-(4-chlorophenyl)-3-(4-methoxyphenyl)- 1*H*-pyrazole-1-carbaldehyde)
12b	1650 (C═O), 1594 (C═N), 3068 (Ar-H), 1025 (C–S str)	4.10 (s, 3H, $–OCH_3$), 7.42–7.65(m, 13H, Ar-H), 6.77 (s, pyrazole ring H),7.42–7.88 (m, 4H of BT ring)	*m/z*, 444 (M^+), 168 (due to 3-chloro-1-benzothiophene), 312 (due to 5-(4-chlorophenyl)-3-(4-methoxyphenyl)- 1*H*-pyrazole-1-carbaldehyde)
12c	1645 (C═O), 1598 (C═N), 3065 (Ar-H), 1022 (C–S str)	7.35–8.38 (m, 9H, Ar-H), 6.58 (s, pyrazole ring H), 7.40–7.80 (m, 4H of BT ring)	*m/z*, 465 (M^+), 168 (due to 3-chloro-1-benzothiophene), 299 (due to 3-(5-nitrothien-2-yl)-5-phenyl-1*H*-pyrazole- 1-carbaldehyde)
12d	1648 (C═O), 1590 (C═N), 3060 (Ar-H), 1022 (C–S str)	7.36–8.42 (m, 8H, Ar-H), 6.58 (s, pyrazole ring H), 7.40–7.83 (m, 4H of BT ring)	*m/z*, 500 (M^+), 168 (due to 3-chloro-1-benzothiophene), 333 (due to 5-(4-chlorophenyl)-3-(5-nitrothien-2-yl)- 1*H*-pyrazole-1-carbaldehyde)
12e	1642 (C═O), 1590 (C═N), 3070 (Ar-H), 1022 (C–S str)	2.36 (s, 2H, $–CH_3$), 7.19–7.92 (m, 13H, Ar-H), 6.76 (s, pyrazole ring H), 7.42–7.88 (m, 4H of BT ring)	*m/z*, 428 (M^+),168 (due to 3-chloro-1-benzothiophene), 262 (due to 3-(4-methylphenyl)-5-phenyl-1*H*-pyrazole- 1-carbaldehyde),77 (due to phenyl ring)

Table 4
Antibacterial and antifungal activity data of newly synthesized benzo [b] thiophene derivatives.

Comp. no.	Antibacterial activity data in MIC (μg/ml)				Antifungal activity data in MIC (μg/ml)
	S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*	*C. albicans*
4a	6	6	6	6	6
4b	6	6	6	6	6
6b	6	6	6	6	6
6c	6	6	6	6	6
10a	6	6	6	6	6
10b	6	6	6	6	6
10c	12.5	6	6	6	6
10d	6	6	6	6	6
12a	6	6	6	6	6
12b	6	6	6	6	3
12c	3	6	3	6	6
12d	3	6	6	6	3
Furacin (Std)	12.5	12.5	6	12.5	Flucanazol (Std) 6
DMF (Control)	–	–	–	–	–

having p-chlorophenyl and p-anisyl substitution has showed the inhibition almost similar to that of the standard drug. Similarly compounds **10b** and **12b** showed significant activities. Remaining compounds showed moderate anti-inflammatory activity. Anti-inflammatory results are presented in Table 5.

6. Experimental protocols

Melting points were determined by open capillary method and were uncorrected. The IR spectra (in KBr pellets) were recorded using Shimadzu FT-IR 157 spectrophotometer in the range 4000–400 cm^{-1}. ^1H NMR spectra were recorded on a Perkin–Elmer EM 300 MHz spectrometer using TMS as internal standard. The mass spectra were recorded on a JEOL JMS-D 300 spectrometer operating at 70 eV. The TLC was performed on alumina silica gel 60 F_{254} (Merck). All the compounds gave C, H and N analysis within ±0.5% of the theoretical values.

*6.1. General procedure for the preparation of 3-(substituted)-6-[3-chlorobenzo[b]thiophenyl 1,2,4-triazolo [3,4-b] thiadiazoles (**4**)*

3-Substituted-4-amino-5-mercapto-1,2,4-triazole (0.005 mol), the acid **3** (0.005 mol) and phosphorous oxychloride (15 ml) were taken in a round bottomed flask and the mixture was heated on a water bath for 4 h. The contents were cooled and poured into crushed ice. The solid obtained was filtered, dried and washed with sodium bicarbonate solution to remove excess of acid. The insoluble substance is dried and recrystallized from ethanol–dioxan mixture. The yield, melting point and other characterization data of the newly synthesized compounds are given in Table 1.

Table 5
Anti-inflammatory activity data of newly synthesized benzo [b] thiophene derivatives.

Comp. no.	% Inhibition
4a	41.85
4b	43.50
6a	33.74
6b	38.22
10a	48.60
10b	50.25
12a	51.25
12b	50.80
Standard (Diclofenac sodium)	51.88

*6.2. General procedure for the preparation of (N^1-aroyloxyacetyl)-N^2-(3-chlorobenzo[b]thiophene-2carboxyl) hydrazine (**5**)*

The acid chloride **2** (0.001 mol) and suitable aryloxyacethydrazide (0.001 mol) were taken in acetone (80 ml), the mixture was stirred for 4–6 h and allowed to stand for further 2 h. Then the acetone was removed to one fourth of its volume. The residue was filtered, washed with cold ethanol and dried. The compounds were recrystallized from ethanol–dioxan mixture. The physical constants and characterization data are given in Table 1.

*6.3. General procedure for the preparation of 2-[3-chloro-2benzo[b]thiophenyl]-5-aryloxymethyl-1,3,4-oxadiazole (**6**)*

The hydrazide **5** (0.001 mol) was taken in phosphorous oxychloride (20 ml) and heated on a water bath for 6–8 h. The contents were cooled and poured into crushed ice. The solid obtained was filtered, washed with water and dried. These newly synthesized compounds were recrystallized from ethanol–dioxan mixture. The yield, physical constants and other characterization data are given in Table 1.

*6.4. General procedure for the preparation of 3-chlorobenzo[b]thiophene-2-methyl carboxylate (**7**)*

The acid chloride **2** (10 g, 0.043 mol) was refluxed with 250 ml of methanol for 6 h. The excess of solvent was removed to get the sweet smelling ester **7**. It was recrystallized with ethanol. Yield was found to be 9 g (81%) and melting point was found to be 67–68 °C [23].

*6.5. General procedure for the preparation of 3-chlorobenzo[b]thiophene-2-carboxylhydrazine (**8**)*

The ester **7** (4.6 g, 0.02 mol) is dissolved in 25 ml methanol and hydrazine hydrate (1.5 g, 0.03 mol) was added to it. The solution was refluxed for 4 h. After confirming the formation of the product by TLC, excess of solvent was removed under reduced pressure and the contents were poured into ice-cold water. The solid separated was filtered, dried and recrystallized from ethanol to yield the hydrazide **8**.Yield was found to be 3.5 g (77%). The melting point is 182 °C [24].

*6.6. General procedure for the preparation of ethyl-2-aryl hydrazono-3-oxobutyrate (**9**)*

Appropriate amine (0.01 mol) was dissolved in 10 ml dilute hydrochloric acid and cooled to 0 °C in an ice bath. A cold aqueous solution of sodium nitrite (0.02 mol) was added. The diazonium salt solution was filtered into 50 ml cold ethanol containing ethyl-acetoacetate (0.01 mol) and sodium acetate (0.15 mol). The resulting yellow solid was filtered, washed with water, dried and recrystallized from methanol.

*6.7. General method for the preparation of N^1-(3-chlorobenzo[b]thiophene-2-carbonyl)-3-methyl-4-9 substituted phenylhydrazono pyrazolin-5-one (**10**)*

A mixture of hydrazide **8** (0.01 mol) and ethyl-2-arylhydrazono-3-oxo butyrate **9** (0.01 mol) in 30 ml ethanol was refluxed for 14 h. Solid product started separating after few hours. The product was filtered hot and recrystallized from ethanol–dioxan mixture. The characterization data are given in Table 1.

*6.8. General procedure for the preparation of 1-(3-chlorobenzo[b]thiophene-3carbonyl)-3,5-diaryl pyrazoles (**12**)*

α-Bromopropenone **11** (0.005 mol) were prepared according to literature procedure [25] was dissolved in 15 mL ethanol and 3-chlorobenzo[b]thiophene hydrazide **8** (0.005 mol) was added to it. The resulting mixture was refluxed on a water bath for 18–20 h. The excess of ethanol was removed by distilling under reduced pressure. On cooling the reaction mixture, the separated solid was collected by filtration and recrystallized from suitable solvent. The characterization data of compounds prepared by this procedure are given in Tables 1 and 2.

Acknowledgements

The authors are thankful to the RSIC, CDRI Lucknow and Director Punjab University, Chandigarh for providing micro analysis, NMR and mass spectral data. AMI is thankful to Director NITK Surathkal, India for providing research facilities and Board of Research in Nucler Sciences, Government of India for 'Young Scientsit' award.

References

[1] D.T. Connor, W.A. Cetenko, M.D. Mullican, R.J. Sorenson, P.C. Unangst, R.J. Weikert, R.L. Adolphson, J.A. Kennedy, D.O. Thueson, C.D. Wright, M.C. Conroy, J. Med. Chem. 35 (1992) 958.
[2] W.W. Wardakhani, O.M.E. Abdel-Salem, G.A. Elmegeed, Acta Pharm. 58 (2008) 1–14.
[3] A.A.R. Mohamed, M.A. Shehab, S.M. El-Shenawy, Monatsh. Chem. 140 (2009) 445–450.
[4] S.L. Graham, K.L. Shepard, P.S. Anderson, J.J. Baldwin, D.B. Best, M.E. Christy, M.B. Freedman, P. Gautheron, C.N. Habecker, J. Med. Chem. 32 (1989) 2548–2554.
[5] (a) C.D. Jones, M.G. Jevnikar, A.J. Pike, M.K. Peters, L.J. Black, A.R. Thompson, J.F. Falcone, J.A. Clements, J. Med. Chem. 27 (1984) 1057–1066;
(b) V.C. Jordan, J. Med. Chem. 46 (2003) 883–908;
(c) V.C. Jordan, J. Med. Chem. 46 (2003) 1081–1111.
[6] A.M. Isloor, B. Kalluraya, P. Shetty, Eur. J. Med. Chem. 44 (2009) 3784–3787.
[7] M.I. Hussain, M.J. Amir, Indian Chem. Soc. 63 (1986) 317–320.
[8] S.H.L. Chiu, S.E.W. Huskey, Drug Metab. Dispos. 26 (1998) 838–847.
[9] T.G. Zitouni, Z.A. Kaplancikli, K. Erol, F.S. Kilic, II Farmaco 54 (1999) 218–223.
[10] B.S. Holla, B. Kalluraya, Indian J. Chem., Sect. B 27 (1988) 683–685.
[11] A.R. Prasad, T. Ramalingam, A.B. Rao, P.W. Diwan, P.B. Sattur, Eur. J. Med. Chem. 24 (1989) 199–201.
[12] M.A. El-Dawy, A.M.M.E. Omar, A.I. Hazzaa, J. Pharm. Sci. 72 (1983) 45–50.
[13] S. Giri, H. Singh, L.D.S. Yadav, R.K. Khare, J. Indian Chem. Soc. 55 (1978) 168–171.
[14] M.K. Mody, A.R. Prasad, T. Ramalingham, P.B. Suttur, J. Indian Chem. Soc. 59 (1982) 769–770.
[15] F.A. Omar, N.M. Mahfouz, M.A. Rahman, Eur. J. Med. Chem. 31 (1996) 819–825.
[16] A.M.Soad El-Hawash, El-Sayed A.M. Badawey, M.Ibrahim El-Ashmawey, Eur. J. Med. Chem. 41 (2006) 155–165.
[17] A.M. Isloor, B. Kalluraya, M. Rao, J. Saudi Chem. Soc. 4 (2000) 265–270.
[18] S.L. Castle, P.J. Buckhaults, L.J. Baldwin, J.D. Mckenny, J. Heterocycl. Chem. 24 (1987) 1103–1108.
[19] J.G. Collee, J.P. Duguid, A.G. Fraser, B.P. Marmion (Eds.), Mackie and Mc. Cartney Practical Medicinal Microbiology, Thirteenth ed. (1989), p. 87.
[20] C.A. Winter, A. Risley, G.W. Nuss, Proc. Soc. Exp. Biol. Med. 111 (1962) 544–547.
[21] G.A.H. Buttle, P.F. D'Arcy, E.M. Howard, D.N. Kellett, Nature 179 (1957) 629.
[22] H. Singh, M.N. Ghosh, J. Pharm, Pharmacology 20 (1968) 316–317.
[23] W.O. Aboul, M.A.E. El-Metwalli, Arch. Pharm. 9 (1992) 325–603.
[24] A.M. Isloor. Ph.D thesis submitted to Mangalore University; 2001.
[25] K. Sridhar. Ph.D thesis submitted to Mangalore University; 1991.