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C3-Functionalized Benzothiophene Sulfone Derivatives: Synthesis and Antimicrobial Evaluation

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تخليق وتفعيل مشتقات سلفون بنزوثيوفين عند الموضع *C3* وتقييم نشاطها المضاد للميكروبات

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Abstract:
This study presents a strategic synthetic approach to functionalize the traditionally unreactive C3 position of the benzothiophene core. A series of 3-chloro-N-(aryl)benzo[b]thiophene-2-carboxamides (2a–d) were synthesized in good to excellent yields (53–83%) via amidation of 3-chloro-2-chlorocarbonylbenzo[b]thiophene (1). Subsequent oxidation with hydrogen peroxide in acetic acid afforded the corresponding sulfone derivatives (3a–d), a transformation that reduced aromaticity and activated the C3 position. This activation enabled a nucleophilic aromatic substitution, where chlorine in sulfone 3b was replaced by ethylamine, isopropylamine, and diethylamine, yielding novel 3-aminobenzothiophene-1,1-dioxides (4a–c) in moderate yields (50–64%). All new compounds were fully characterized by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. The synthesized derivatives were evaluated in vitro for antimicrobial activity against Gram-positive bacteria (Staphylococcus aureus, Bacillus subtilis), Gram-negative bacteria (Escherichia coli, Pseudomonas aeruginosa), and fungal strains (Candida albicans, Crysosporium pannical, Aspergillus niger, Rhizopus oryzae). While overall activities were slight to moderate compared with standard drugs, compounds 3a and 3b displayed a promising broad-spectrum profile.These findings establish an efficient and versatile methodology for accessing C3-functionalized benzothiophenes, providing a valuable foundation for the design of new lead structures against resistant microbes.

Keywords: Benzothiophene, Sulfone, Nucleophilic Substitution, Antimicrobial Activity, C3 Functionalization.

الملخص
تهدف هذه الدراسة إلى تطوير منهجية تركيبية جديدة لتفعيل الموضع 3C في نواة البنزوثيوفين، والذي يُعرف بصعوبة تفاعله. تم تحضير سلسلة من مركبات -3كلورو-N-(أريل)بنزو[b]ثيوفين-2-كربوكساميدات (2a–d) بعوائد جيدة إلى ممتازة (53–83%) عبر تفاعل الأمدة لمركب -3كلورو-2-كلوروكربونيل بنزو[b]ثيوفين (1) بعد ذلك، أكسدت هذه الطلائع باستخدام فوق أكسيد الهيدروجين في حمض الأسيتيك لتكوين مشتقات السلفون(3a–d) ، مما أدى إلى تقليل الأروماتية وتفعيل الموضع 3C، استُغل هذا التفعيل في تفاعل إحلال إروماتي نوكليوفيلي، حيث أُزيحت ذرة الكلور في المركب 3b باستخدام إيثيل أمين، أيزوبروبيل أمين، وداي إيثيل أمين، وأُنتجت مشتقات جديدة 3-أمينو بنزوثيوفين-1,1-ديوكسيد (4a–c) بعوائد متوسطة (50–64%). وصفت جميع المركبات المحضّرة بدقة باستخدام أطياف الأشعة تحت الحمراء(IR) ، والرنين المغناطيسي النووي للبروتون (^{1}H NMR) والكربون (^{13}C NMR). كما تم تقييم فعاليتها المضادة للميكروبات في المختبر ضد بكتيريا موجبة الغرام (*المكورات العنقودية الذهبية، العصوية الرقيقة*)، وبكتيريا سالبة الغرام (*الإشريكية القولونية، الزائفة الزنجارية*)، إضافةً إلى عدة سلالات فطرية(*المبيضة البيضاء، كريزوسبوريوم، الرشاشية السوداء، الرايزوبوس*).

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أظهرت النتائج أن النشاط كان ضعيفاً إلى متوسط مقارنةً بالأدوية المرجعية، إلا أن المركبين 3a و 3b قدما نشاطاً واسع الطيف واعداً. تؤكد هذه النتائج أن المنهجية المطورة تمثل أداة فعّالة ومرنة للوصول إلى مشتقات بنزوثيوفين مفعلة عند الموضع 3C، مما يمهّد الطريق لتطوير مركبات رائدة جديدة في مواجهة الميكروبات المقاومة.

الكلمات المفتاحية: بنزوثيوفين، سلفون، إستبدال نيوكليوفيلي، النشاط المضاد للميكروبات، تفعيل الموضع C3.

Introduction

Benzothiophene and its derivatives constitute a significant class of heterocyclic compounds that have attracted considerable interest across various scientific disciplines, including medicinal chemistry, materials science, and agrochemistry [1, 2]. Their unique structural features, characterized by a benzene ring fused to a thiophene ring, impart a diverse range of biological activities and physicochemical properties. These compounds are known to exhibit anticancer, anti-inflammatory, antimicrobial, and antiviral activities, making them valuable scaffolds for drug discovery and development [3, 4]. The functionalization of benzothiophene derivatives, particularly at specific positions, is crucial for tailoring their properties and enhancing their utility. However, the inherent aromaticity of the thiophene ring in benzothiophene typically dictates its reactivity, favoring electrophilic substitution reactions, predominantly at the C3 position, and to a lesser extent at C2 [5, 6]. Nucleophilic substitution reactions, especially at the C3 position, are generally challenging to achieve directly due to the electron-rich nature of the aromatic system. This limitation often necessitates indirect synthetic strategies or harsh reaction conditions, which can be detrimental to sensitive functional groups [7]. To overcome these synthetic hurdles, researchers have explored various strategies to modulate the reactivity of the benzothiophene core. One effective approach involves the oxidation of the sulfur atom in the thiophene ring to form sulfoxide or sulfone derivatives. The introduction of a sulfone (SO_2) group, a potent electron-withdrawing moiety, dramatically alters the electronic distribution within the thiophene ring. This transformation leads to a significant reduction in aromaticity and an increase in the electrophilicity of adjacent carbon atoms, thereby rendering them susceptible to nucleophilic attack [8, 9]. This strategy has been successfully applied in other heterocyclic systems to facilitate otherwise difficult nucleophilic substitutions [10]. The antimicrobial potential of sulfone derivatives has also been a subject of recent reviews, suggesting that the sulfone group itself can contribute to the biological activity of the molecule [11]. This research aims to explore a synthetic pathway for novel benzothiophene derivatives by leveraging the reactivity switch induced by sulfone formation. We report the full synthesis, detailed characterization, and antimicrobial evaluation of a new series of 3-aminobenzothiophene-1,1-dioxide derivatives, providing a comprehensive and reproducible account of this work.

Material and methods

All chemicals and solvents were purchased from commercial suppliers (Sigma-Aldrich, Merck) and were used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel 60 F254 plates (Merck) and visualized under UV light (254 nm). Melting points were determined on a Stuart SMP30 melting point apparatus and are uncorrected. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer in the range of 4000-400 cm^{-1}.^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance Neo 400 MHz spectrometer at 400 MHz and 101 MHz, respectively. Chemical shifts are reported in parts per million (δ) downfield from (TMS), which was used as an internal standard. Coupling constants (*J*) are reported in Hertz (Hz). Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, m = multiplet, sept = septet, q = quartet.

Synthesis of 3-Chloro-2-chlorocarbonylbenzo[b]thiophene (1)

A mixture of cinnamic acid (12.0 g, 0.081 mol), pyridine (0.8 mL), and thionyl chloride (5 mL) was heated at 130-140 °C in an oil bath. An additional amount of thionyl chloride (17 mL) was then added dropwise over a period of 2 hours. The reaction mixture was stirred at 130-140 °C for an additional one hour. The resulting dark solution was dissolved in 600 mL of boiling hexane. The hexane solution was allowed to cool to room temperature and then placed in an ice bath. The resulting pale-yellow precipitate was collected by filtration, washed with cold hexane, and dried under vacuum to afford the title compound **1** (8.7 g, 60% yield) as pale-yellow needles. M.p. 112-113 °C (lit. [12] 114-116 °C). The product was used directly in the next step without further characterization.

General Procedure for the Synthesis of 3-Chloro-N-(aryl)benzo[b]thiophene-2-carboxamides (2a-d)

The appropriate aryl amine (4.0 mmol) was added to a stirred solution of 3-chloro-2-chlorocarbonylbenzo[b]thiophene **(1)** (0.50 g, 2.0 mmol) in dry benzene (15 mL). The reaction mixture was heated under reflux for 1-2 hours (monitored by TLC). After completion, the mixture was allowed to cool to room temperature. The resulting precipitate was collected by filtration, washed thoroughly with water (3 × 10 mL), dried, and recrystallized from the appropriate solvent (see Table 1) to afford the pure products **2a-d**.

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3-Chloro-N-phenylbenzo[b]thiophene-2-carboxamide (2a).
Obtained as a white solid. Yield: 83% (0.49 g). M.p. 166-168 °C. IR : ν 3322 (N-H), 3050 (C-H, Ar), 1641 (C=O), 1595, 1530, 1490, 1440, 1310, 750, 690 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.93 (s, 1H, NH), 7.90 (td, J = 7.6, 1.2 Hz, 1H, H-5), 7.88 (td, J = 7.6, 1.2 Hz, 1H, H-6), 7.70 (d, J = 8.0 Hz, 2H, H-2', H-6'), 7.53 (d, J = 8.0 Hz, 1H, H-7), 7.50 (d, J = 8.0 Hz, 1H, H-4), 7.40 (t, J = 8.0 Hz, 2H, H-3', H-5'), 7.20 (t, J = 7.4 Hz, 1H, H-4'). ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.7 (C=O), 138.1 (C-1'), 137.2 (C-7a), 137.0 (C-3a), 133.6 (C-3), 129.2 (C-3', C-5'), 127.7 (C-5), 125.6 (C-6), 125.1 (C-2', C-6'), 123.3 (C-4), 122.9 (C-7), 120.4 (C-4'), 118.5 (C-2).

3-Chloro-N-(p-tolyl)benzo[b]thiophene-2-carboxamide (2b).
Obtained as a white solid. Yield: 68% (0.43 g). M.p. 150-153 °C. IR: ν 3355 (N-H), 3030 (C-H, Ar), 2915 (C-H, CH_3), 1641 (C=O), 1590, 1520, 1495, 1445, 1305, 810 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.90 (s, 1H, NH), 7.89 (d, J = 8.0 Hz, 1H, H-7), 7.84 (d, J = 8.0 Hz, 1H, H-4), 7.56 (d, J = 8.4 Hz, 2H, H-2', H-6'), 7.53 (t, J = 7.6 Hz, 1H, H-6), 7.50 (t, J = 7.6 Hz, 1H, H-5), 7.21 (d, J = 8.4 Hz, 2H, H-3', H-5'), 2.40 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.7 (C=O), 138.2 (C-4'), 137.3 (C-7a), 136.9 (C-3a), 133.6 (C-1'), 133.6 (C-3), 129.3 (C-3', C-5'), 127.8 (C-5), 125.8 (C-6), 125.1 (C-2', C-6'), 123.4 (C-4), 122.9 (C-7), 118.5 (C-2), 21.4 (CH_3).

3-Chloro-N-(4-methoxyphenyl)benzo[b]thiophene-2-carboxamide (2c).
Obtained as a white solid. Yield: 83% (0.56 g). M.p. 195-197 °C. IR: ν 3335 (N-H), 3060 (C-H, Ar), 2930 (C-H), 1644 (C=O), 1605, 1510, 1490, 1440, 1300, 1245, 1030, 830 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.10 (s, 1H, NH), 7.82 (d, J = 8.0 Hz, 1H, H-7), 7.77 (d, J = 8.0 Hz, 1H, H-4), 7.58 (d, J = 9.0 Hz, 2H, H-2', H-6'), 7.46 (t, J = 7.6 Hz, 1H, H-5), 7.43 (t, J = 7.6 Hz, 1H, H-6), 7.24 (d, J = 9.0 Hz, 2H, H-3', H-5'), 3.85 (s, 3H, OCH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.0 (C=O), 158.0 (C-4'), 136.8 (C-7a), 136.5 (C-3a), 133.5 (C-3), 132.6 (C-1'), 128.1 (C-5), 125.8 (C-6), 125.2 (C-2', C-6'), 123.6 (C-4), 122.9 (C-7), 119.6 (C-2), 114.5 (C-3', C-5'), 55.5 (OCH_3).

3-Chloro-N-(4-nitrophenyl)benzo[b]thiophene-2-carboxamide (2d).
Obtained as a yellow solid. Yield: 54% (0.38 g). M.p. 218-221 °C. IR: ν 3378 (N-H), 3090 (C-H, Ar), 1661 (C=O), 1590, 1520, 1490, 1340 (NO_2), 1315, 1105, 855, 745 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 9.25 (s, 1H, NH), 8.28 (d, J = 9.2 Hz, 2H, H-3', H-5'), 7.94 (t, J = 7.6 Hz, 1H, H-7), 7.90 (t, J = 7.6 Hz, 1H, H-4), 7.84 (d, J = 9.2 Hz, 2H, H-2', H-6'), 7.56 (t, J = 7.6 Hz, 1H, H-5), 7.52 (t, J = 7.6 Hz, 1H, H-6). ^{13}C NMR (101 MHz, DMSO-d_6): δ 159.0 (C=O), 144.1 (C-4'), 142.9 (C-1'), 138.4 (C-7a), 136.8 (C-3a), 133.8 (C-3), 128.3 (C-5), 125.9 (C-6), 125.3 (C-2', C-6'), 123.5 (C-4), 122.99 (C-7), 119.8 (C-2), 119.4 (C-3', C-5').

General Procedure for the Synthesis of 3-Chloro-N-(aryl)benzo[b]thiophene-2-carboxamide-1,1-dioxides (3a-d)
Hydrogen peroxide (30%, 1.65 mL) was added dropwise to a stirred mixture of the appropriate carboxamide **2a-d** (1.0 mmol) in glacial acetic acid (7.5 mL) at room temperature. The reaction mixture was then heated to 60-70 °C and stirred for 3-4 hours (monitored by TLC). After completion, the mixture was poured into cold water (50 mL). The resulting precipitate was collected by filtration, washed thoroughly with water (3 × 10 mL), dried, and recrystallized from the appropriate solvent to afford the pure products **3a-d**.

3-Chloro-N-phenylbenzo[b]thiophene-2-carboxamide-1,1-dioxide (3a).
Obtained as a white solid. Yield: 80% (0.29 g). M.p. 145-148 °C. IR: ν 3393 (N-H), 3060 (C-H, Ar), 1664 (C=O), 1595, 1535, 1495, 1445, 1310, 1150 (S=O), 755, 690 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H, NH), 7.87-7.76 (m, 4H, H-4, H-5, H-6, H-7), 7.63 (d, J = 8.0 Hz, 2H, H-2', H-6'), 7.36 (t, J = 8.0 Hz, 2H, H-3', H-5'), 7.19 (t, J = 7.4 Hz, 1H, H-4'). ^{13}C NMR (101 MHz, DMSO-d_6): δ 154.0 (C=O), 136.5 (C-1'), 135.5 (C-7a), 134.6 (C-3a), 133.3 (C-3), 130.3 (C-5), 129.5 (C-3', C-5'), 129.2 (C-6), 125.6 (C-2', C-6'), 124.5 (C-4), 121.5 (C-7), 120.6 (C-4'), 120.4 (C-2).

3-Chloro-N-(p-tolyl)benzo[b]thiophene-2-carboxamide-1,1-dioxide (3b).
Obtained as a white solid. Yield: 74% (0.28 g). M.p. 200-201 °C. IR: ν 3392 (N-H), 3050 (C-H, Ar), 2915 (C-H, CH_3), 1657 (C=O), 1590, 1525, 1490, 1440, 1305, 1145 (S=O), 810 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.23 (s, 1H, NH), 7.85-7.75 (m, 4H, H-4, H-5, H-6, H-7), 7.55 (d, J = 8.4 Hz, 2H, H-3', H-5'), 7.26 (d, J = 8.4 Hz, 2H, H-2', H-6'), 2.36 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6): δ 154.2 (C=O), 137.8 (C-4'), 136.8 (C-7a), 135.5 (C-3a), 133.3 (C-3), 133.3 (C-1'), 130.2 (C-5), 129.8 (C-3', C-5'), 129.1 (C-6), 125.5 (C-2', C-6'), 124.3 (C-4), 121.7 (C-7), 120.9 (C-2), 21.3 (CH_3).

3-Chloro-N-(4-methoxyphenyl)benzo[b]thiophene-2-carboxamide-1,1-dioxide (3c).
Obtained as a white solid. Yield: 47% (0.18 g). M.p. 189-190 °C. IR: ν 3336 (N-H), 3060 (C-H, Ar), 2935 (C-H), 1643 (C=O), 1600, 1515, 1495, 1445, 1300, 1245, 1140 (S=O), 1030, 830 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.91 (s, 1H, NH), 7.90 (d, J = 8.0 Hz, 1H, H-7), 7.85 (d, J = 8.0 Hz, 1H, H-4), 7.63 (d, J = 9.0 Hz, 2H, H-2', H-6'), 7.55 (t, J = 7.6 Hz, 1H, H-6), 7.51 (t, J = 7.6 Hz, 1H, H-5), 7.32 (d, J = 9.0 Hz, 2H, H-3', H-5'), 3.78 (s, 3H, OCH_3). ^{13}C NMR (101 MHz, DMSO-d_6): δ 158.8 (C=O), 156.2 (C-4'), 136.4 (C-7a), 135.9 (C-3a), 133.5 (C-3), 132.6 (C-1'), 130.1 (C-5), 129.0 (C-6), 125.7 (C-2', C-6'), 124.8 (C-4), 122.1 (C-7), 120.5 (C-2), 115.2 (C-3', C-5'), 55.8 (OCH_3).

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3-Chloro-N-(4-nitrophenyl)benzo[b]thiophene-2-carboxamide-1,1-dioxide (3d).
Obtained as a pale-yellow solid. Yield: 31% (0.12 g). M.p. 231-234 °C. IR: ν 3378 (N-H), 3095 (C-H, Ar), 1662 (C=O), 1595, 1525, 1345 (NO_2), 1305, 1145 (S=O), 1105, 855, 745 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 9.25 (s, 1H, NH), 8.28 (d, J = 9.2 Hz, 2H, H-3', H-5'), 7.98-7.82 (m, 3H, H-7, H-2', H-6'), 7.59-7.53 (m, 3H, H-4, H-5, H-6). ^{13}C NMR (101 MHz, DMSO-d_6): δ 159.0 (C=O), 144.1 (C-4'), 142.9 (C-1'), 138.4 (C-7a), 136.8 (C-3a), 134.8 (C-3), 128.3 (C-5), 125.9 (C-6), 125.3 (C-2', C-6'), 124.8 (C-4), 123.0 (C-7), 120.8 (C-2), 119.8 (C-3', C-5').

General Procedure for the Synthesis of 3-Amino-N-(4-methylphenyl)benzo[b]thiophene-2-carboxamide-1,1-dioxides (4a-c)
The appropriate amine (ethylamine, isopropyl amine, or diethyl amine; 0.5 mL, large excess) was added to a stirred solution of 3-chloro-N-(p-tolyl)benzo[b]thiophene-2-carboxamide-1,1-dioxide **(3b)** (0.10 g, 0.29 mmol) in dry benzene (10 mL). The reaction mixture was heated under reflux for 2 hours (monitored by TLC). The solvent and excess amine were then removed under reduced pressure. The resulting crude solid was triturated with water, collected by filtration, dried, and recrystallized from the appropriate solvent to afford the pure products **4a-c**.

3-(Ethylamino)-N-(p-tolyl)benzo[b]thiophene-2-carboxamide-1,1-dioxide (4a).
Obtained as a white solid. Yield: 64% (0.067 g). M.p. 193-195 °C. IR: ν 3359 (N-H, amide), 3151 (N-H, amine), 2970 (C-H, CH_2), 1611 (C=O), 1590, 1520, 1490, 1440, 1305, 1140 (S=O), 810 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 9.80 (s, 1H, NH, amide), 7.95 (d, J = 8.0 Hz, 1H, H-7), 7.90 (d, J = 8.0 Hz, 1H, H-4), 7.80 (t, J = 7.6 Hz, 1H, H-6), 7.66 (t, J = 7.6 Hz, 1H, H-5), 7.36 (d, J = 8.4 Hz, 2H, H-3', H-5'), 7.13 (d, J = 8.4 Hz, 2H, H-2', H-6'), 6.50 (t, J = 5.6 Hz, 1H, NH, amine), 2.80 (m, 2H, CH_2), 2.30 (s, 3H, Ar-CH_3), 1.40 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6): δ 162.0 (C=O), 155.1 (C-2), 140.1 (C-4'), 140.1 (C-1'), 134.6 (C-7a), 134.2 (C-3a), 133.2 (C-5), 129.5 (C-3', C-5'), 127.5 (C-6), 125.8 (C-2', C-6'), 121.9 (C-4), 121.3 (C-7), 96.5 (C-3), 40.9 (CH_2), 20.9 (Ar-CH_3), 15.6 (CH_3).

3-(Isopropylamino)-N-(p-tolyl)benzo[b]thiophene-2-carboxamide-1,1-dioxide (4b).
Obtained as a white solid. Yield: 50% (0.055 g). M.p. 210-214 °C. IR: ν 3381 (N-H, amide), 2974 (N-H, amine), 2920 (C-H), 1631 (C=O), 1595, 1525, 1495, 1445, 1310, 1145 (S=O), 810 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 9.90 (s, 1H, NH, amide), 7.94 (d, J = 8.0 Hz, 1H, H-7), 7.87 (d, J = 8.0 Hz, 1H, H-4), 7.82 (t, J = 7.6 Hz, 1H, H-6), 7.65 (t, J = 7.6 Hz, 1H, H-5), 7.35 (d, J = 8.4 Hz, 2H, H-3', H-5'), 7.10 (d, J = 8.4 Hz, 2H, H-2', H-6'), 6.45 (d, J = 8.0 Hz, 1H, NH, amine), 4.32 (sept, J = 6.4 Hz, 1H, CH), 2.30 (s, 3H, Ar-CH_3), 1.40 (d, J = 6.4 Hz, 6H, 2×CH_3). ^{13}C NMR (101 MHz, DMSO-d_6): δ 162.1 (C=O), 154.3 (C-2), 140.2 (C-4'), 140.2 (C-1'), 134.5 (C-7a), 134.2 (C-3a), 133.3 (C-5), 129.5 (C-3', C-5'), 127.2 (C-6), 126.0 (C-2', C-6'), 125.8 (C-4), 121.9 (C-7), 96.1 (C-3), 47.0 (CH), 24.2 (CH_3), 20.9 (Ar-CH_3).

3-(Diethylamino)-N-(p-tolyl)benzo[b]thiophene-2-carboxamide-1,1-dioxide (4c).
Obtained as a white solid. Yield: 58% (0.067 g). M.p. 150-152 °C. IR: ν 3335 (N-H, amide), 2960 (C-H), 1643 (C=O), 1590, 1520, 1495, 1440, 1300, 1140 (S=O), 810 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.03 (s, 1H, NH, amide), 7.82 (d, J = 8.0 Hz, 1H, H-7), 7.70 (d, J = 8.0 Hz, 1H, H-4), 7.65 (t, J = 7.6 Hz, 1H, H-6), 7.62 (t, J = 7.6 Hz, 1H, H-5), 7.48 (d, J = 8.4 Hz, 2H, H-3', H-5'), 7.13 (d, J = 8.4 Hz, 2H, H-2', H-6'), 3.60 (q, J = 7.2 Hz, 4H, 2×CH_2), 2.31 (s, 3H, Ar-CH_3), 1.20 (t, J = 7.2 Hz, 6H, 2×CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.4 (C=O), 156.8 (C-2), 140.5 (C-4'), 139.8 (C-1'), 135.1 (C-7a), 134.3 (C-3a), 133.2 (C-5), 129.5 (C-3', C-5'), 131.7 (C-6), 125.9 (C-2', C-6'), 121.4 (C-4), 120.6 (C-7), 120.6 (C-3), 46.6 (CH_2), 20.9 (Ar-CH_3), 13.2 (CH_3).

Antimicrobial Assay
The *in vitro* antimicrobial activity of the synthesized compounds was evaluated using the agar well diffusion method [13]. Briefly, Mueller-Hinton Agar (MHA) (HiMedia) was used for antibacterial screening against *Staphylococcus aureus* (ATCC 25923), *Bacillus subtilis* (ATCC 6633), *Escherichia coli* (ATCC 25922), and *Pseudomonas aeruginosa* (ATCC 27853). Sabouraud Dextrose Agar (SDA) (HiMedia) was used for antifungal screening against *Candida albicans* (ATCC 10231), *Aspergillus niger* (ATCC 16404), *Rhizopus oryzae* (NCMR 2574), and *Crysosporium pannical* (MTCC 2878). The test organisms were subcultured in nutrient broth for bacteria and SDB for fungi at 37 °C and 28 °C, respectively, for 24 h. The turbidity of the microbial suspensions was adjusted to 0.5 McFarland standard (~1.5×10^8 CFU/mL). 100 µL of each microbial suspension was spread evenly onto the surface of the respective agar plates. Wells (6 mm in diameter) were punched into the agar using a sterile cork borer. 100 µL of each test compound (100 µg/mL in DMF) was added to a well. Standard antibiotic solutions (Ampicillin and Streptomycin at 100 µg/mL for bacteria; Griseofulvin at 100 µg/mL for fungi) and a DMF control were included in each plate. The plates were incubated at 37 °C for 24 h (bacteria) and at 28 °C for 48-72 h (fungi). The antimicrobial activity was assessed by measuring the diameter of the zones of inhibition (including the well diameter) in millimeters (mm). All tests were performed in triplicate, and the mean values are reported.

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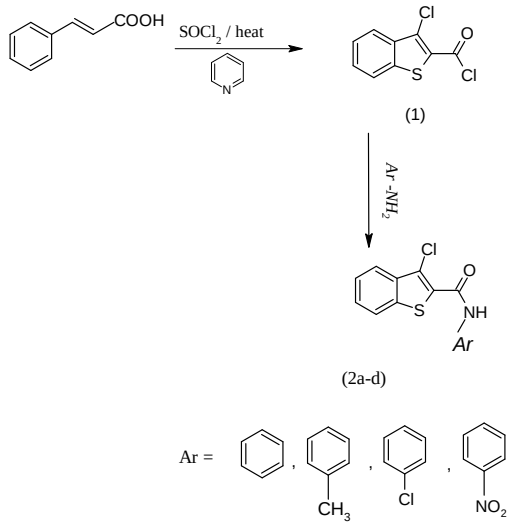
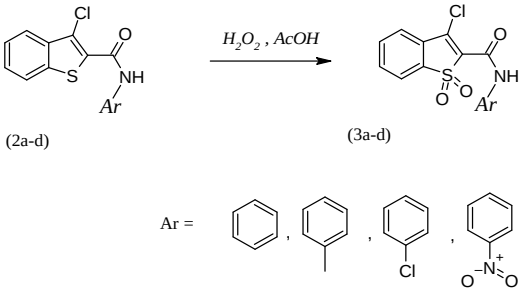
Results and discussion

Chemistry

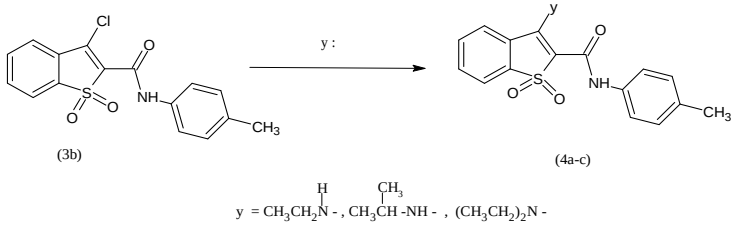
The synthetic strategy for the target compounds is outlined in Schemes 1, 2, and 3.



Scheme 1: Synthetic pathway for target compounds(2a-d).



Scheme 2: Synthetic pathway for target compounds(3a-3d).



Scheme 3: Synthetic pathway for target compounds(4a-c).

Synthesis of 3-Chloro-N-(aryl)benzo[b]thiophene-2-carboxamides (2a-d)

The key intermediate, 3-chloro-2-chlorocarbonylbenzo[b]thiophene **(1)**, was synthesized from cinnamic acid according to a modified literature procedure [12]. Amidation of acid chloride **1** with various aromatic amines (aniline, p-toluidine, p-anisidine, p-nitroaniline) in benzene afforded the target carboxamides **2a-d** in good to excellent yields (53-83%) (Table 1). The reaction proceeded smoothly, and the products were easily isolated by filtration and purified by recrystallization.

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Table 1. Physical data for compounds **2a-d**.

Compound	Ar-	Yield (%)	m.p. (°C)	Recrystallization Solvent
2a	C_6H_5-	83	166-168	Ethanol
2b	4-CH_3-C_6H_4-	68	150-153	Ethanol
2c	4-CH_3O-C_6H_4-	83	195-197	Ethanol
2d	4-NO_2-C_6H_4-	54	218-221	Benzene

The formation of the amide bond was confirmed by IR spectroscopy, which showed characteristic N-H stretching vibrations in the range of 3322–3377 cm^{-1} and carbonyl (C=O) stretches between 1640–1660 cm^{-1}. The ^1H NMR spectra displayed a distinctive downfield singlet between δ 8.90–9.25 ppm, integrating for one proton, which was assigned to the amide N-H proton. The aromatic regions showed complex multiplet patterns consistent with the proposed structures. The ^{13}C NMR spectra provided further confirmation, showing the characteristic signal for the amide carbonyl carbon in the range of δ 158.7–159.0 ppm. The carbon atoms of the benzothiophene core and the aryl ring were observed in their expected regions. The combined spectroscopic data unequivocally confirmed the successful synthesis and structural integrity of carboxamides 2a-d.

Synthesis of Sulfone Derivatives (3a-d)

Oxidation of the benzothiophene carboximides 2a-d to their corresponding sulfones (3a-d) was achieved using 30% H_2O_2 in glacial acetic acid at 60-70 °C (Table 2). The reaction efficiency varied with the electronic nature of the aryl substituent on the amide nitrogen. Electron-donating groups (e.g., in 3a and 3b) generally afforded better yields (74-80%), while the strong electron-withdrawing nitro group in 3d resulted in a lower yield (31%), potentially due to decreased electron density on the sulfur atom or instability of the product under the reaction conditions.

Table 2. Physical data for sulfone derivatives **3a-d**.

Compound	Ar-	Yield (%)	m.p. (°C)	Recrystallization Solvent
3a	C_6H_5-	80	145-148	Ethanol
3b	4-CH_3-C_6H_4-	74	200-201	Ethanol
3c	4-CH_3O-C_6H_4-	47	189-190	Benzene
3d	4-NO_2-C_6H_4-	31	231-234	Ethanol

The successful formation of the sulfone group was confirmed spectroscopically. The IR spectra retained the amide N-H and C=O stretches, with the latter shifting slightly to higher wavenumbers (1657–1664 cm^{-1}) due to the enhanced electron-withdrawing effect of the sulfone group. The most notable changes were observed in the NMR spectra. In the ^1H NMR spectra, the protons on the benzothiophene ring (H-4, H-5, H-6, H-7) experienced significant downfield shifts compared to their positions in the precursors 2a-d. For example, the H-4 signal in 2b was observed as a doublet at δ 7.84, which shifted downfield and became part of a multiplet centered around δ 7.80 in 3b. This is a classic signature of reduced aromaticity and the deshielding effect of the sulfone group. The ^{13}C NMR spectra provided even more compelling evidence. The carbon signals for the thiophene ring experienced substantial downfield shifts. Notably, the amide carbonyl carbon shifted downfield from ~δ 158.7 in 2b to ~δ 154.2 in 3b. These spectroscopic changes collectively and unequivocally confirm the formation of the benzothiophene-1,1-dioxide structure.

Nucleophilic Substitution: Synthesis of 3-Amino Derivatives (4a-c)

The key innovation of this work was the nucleophilic aromatic substitution at the C3 position of the sulfone-activated intermediate. The chlorine atom in compound 3b was successfully displaced by reacting it with an excess of ethylamine, isopropyl amine, or diethyl amine in benzene under reflux conditions, affording the novel 3-aminobenzothiophene-1,1-dioxide derivatives 4a-c in moderate yields (50-64%) (Table 3). This reaction demonstrates the powerful activating effect of the sulfone group, which renders the C3 position sufficiently electrophilic for attack by neutral amines under relatively mild conditions.

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Table 3. Physical data for 3-amino derivatives **4a-c**.

Compound	R-	Yield (%)	m.p. (°C)	Recrystallization Solvent
4a	CH_3CH_2NH-	64	193-195	Hexane
4b	$(CH_3)_2CHNH$-	50	210-214	Hexane/$CHCl_3$
4c	$(CH_3CH_2)_2N$-	58	150-152	Hexane

The structures of 4a-c were confirmed by comprehensive spectroscopic analysis. The IR spectra showed the appearance of new absorption bands: a broad N-H stretch around 3151 cm^{-1} for the primary amine in 4a, and characteristic aliphatic C-H stretches for the alkyl chains in all compounds. The ^1H NMR spectra clearly indicated the success of the substitution: the multiplet pattern for H-4, which was coupled to the C3-Cl in 3b, was replaced by a simplified doublet for H-4 in 4a-c due to coupling with the now-present amine proton or changed environment. New signals corresponding to the alkyl chains of the amines appeared between δ 1.20–4.32 ppm. The amide N-H proton was significantly shifted downfield (δ 9.80–10.03 ppm), likely due to the strengthened intramolecular hydrogen bond between the amide N-H and the sulfone oxygen atoms, now possible due to the coplanar arrangement enforced by the new amine group. The ^{13}C NMR spectra provided definitive proof: the carbon signal for C3 experienced a significant upfield shift from ~δ 120.1 ppm in 3b to ~δ 96.5 ppm in 4a and 4b, consistent with the replacement of chlorine with a nitrogen atom. For the tertiary amine 4c, the C3 signal was observed at δ 120.6 ppm. All other carbon signals were in agreement with the proposed structures.

Antimicrobial Activity Study

The synthesized compounds (3a-d, 4a-c) were evaluated for their *in vitro* antibacterial and antifungal activities against a panel of microorganisms using the agar well diffusion method [13]. The results, expressed as zones of inhibition (mm), are summarized in Tables 4 and 5, with ampicillin, streptomycin, and griseofulvin used as standard drugs. Dimethylformamide (DMF) was used as a solvent control and showed no activity.

Table 4. Antibacterial activity (Zone of Inhibition in mm).

Compound	S. aureus	B. subtilis	E. coli	P. aeruginosa
3a	11	14	14	13
3b	14	12	12	15
3c	11	16	15	14
3d	12	13	15	13
4a	13	11	10	14
4b	14	11	13	14
4c	10	14	13	13
Ampicillin	23	24	18	23
Streptomycin	24	22	25	21
DMF Control	0	0	0	0

Table 5. Antifungal activity (Zone of Inhibition in mm).

Compound	C. albicans	C. pannical	A. niger	R. oryzae
3a	14	14	13	14
3b	14	12	15	12
3c	13	16	14	15
3d	12	12	13	12
4a	13	11	14	10
4b	14	11	14	13
4c	15	14	13	13
Griseofulvin	24	25	23	22
DMF Control	0	0	0	0

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The oxidation of the thiophene ring to the sulfone generally modulated the biological activity, though the effect was dependent on the aryl substituent. For instance, sulfone 3a showed improved activity against *S. aureus* (11→14 mm) and *P. aeruginosa* (13→15 mm) compared to its precursor 2a. Conversely, sulfone 3b displayed a different spectrum, being more active against *E. coli* (12→15 mm) than its non-oxidized counterpart 2b. This suggests that the introduction of the strongly electron-withdrawing sulfone group significantly alters the molecule's electronic distribution, lipophilicity, and potential for hydrogen bonding, which can profoundly affect its interaction with microbial targets and its ability to penetrate cell membranes [14]. The nature of the substituent on the aryl ring attached to the amide nitrogen influenced the potency. The *p*-tolyl substituted compounds (3b, and subsequently 4a-c) often showed more consistent, broad-spectrum activity across multiple bacterial and fungal strains. This could be due to a balanced electronic and lipophilic profile offered by the methyl group. The *p*-nitrophenyl substituted derivative (3d), despite its strong electron-withdrawing nature, showed variable and generally lower activity, suggesting that extreme electronic properties might not be optimal for broad-spectrum activity or may adversely affect cell penetration. The nucleophilic substitution of the C3-chloro group in the activated sulfone 3b with various amines to yield 4a-c represents a key innovation. The resulting 3-amino derivatives exhibited moderate but broad-spectrum activity. The ethylamine derivative (4a) and the diethylamine derivative (4c) showed comparable or slightly improved activity in some cases compared to the chloro precursor (3b), particularly against fungal strains like *C. albicans* and *A. niger*. The bulkier isopropyl amine derivative (4b) showed slightly diminished activity against some organisms, possibly due to steric hindrance affecting its ability to bind efficiently to the target site. The notably good activity of 4c against *C. albicans* (15 mm) may be attributed to increased lipophilicity enhancing fungal cell membrane penetration. While the observed activities are lower than those of the standard drugs, they are significant and provide a clear and valuable starting point for a medicinal chemistry program.

Conclusion

We have successfully demonstrated a versatile and efficient synthetic route for the functionalization of the C3 position of the benzothiophene core. The key strategic element was the oxidation of benzothiophene carboxamides to their corresponding sulfone derivatives, which activated the ring for nucleophilic substitution. This methodology enabled the synthesis of novel 3-aminobenzothiophene-1,1-dioxide derivatives, a class of compounds that are otherwise difficult to access. All new compounds were fully characterized by spectroscopic methods. The antimicrobial evaluation revealed that several derivatives exhibited promising, broad-spectrum activity against a range of bacteria and fungi. Although the observed activities were not as high as those of the standard drugs, this research establishes a solid foundation for the future design, synthesis, and evaluation of more potent benzothiophene-based antimicrobial agents.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no conflict of interest.

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