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Synthesis, Characterization and Antimicrobial Evaluation of Some Tetrahydroquinazoline Derivatives of Benzo[b]thiophene

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ABSTRACT

In the present investigation, synthesis of 4-(1-(3-chlorobenzo[b]thiophene-2-carbonyl)-1H-indol-3-yl)-7, 7-dimethyl-3, 4, 7, 8-tetrahydroquinazoline2, 5(1H, 6H)dione **(3a-d)** is described. These unreported compounds are obtained starting from indole- 3-aldehyde and3-chloro-1benzothiophene-2-carbonylchloride **(1a-d)**. A series of compounds **(3a-d)** were prepared. The structures of the newly synthesized compounds were elucidated on the basis of IR and 1H NMR spectral data of the compounds. All the compounds have been screened for antibacterial activity against *S. aureus, E. coli*, and *P. aeruginosa* and for antifungal activity against *Candida albicans, A. niger*, and *A. clavatus* using broth dilution method and they were found to exhibit good to moderate antimicrobial activity.

Keywords: 3-chlorobenzo[b]thiophene-2-carbonyl, Synthesis, Antimicrobial activity.

INTRODUCTION

Thiophene ring fused with benzene nucleus is known as benzo[b]thiophene. It is an important pharmacophore that occurs frequently in medicinal chemistry literature. A variety of reports regarding synthetic studies of benzo[b]thiophene derivatives have been presented due to their chemical and biological interests. Benzo[b]thiophene compounds are widely used as antibacterial [1-7], antifungal [8-12], and herbicides. According to recent data, benzo[b]thiophene nucleus has attracted the attention of medicinal chemistry due to its well known anticancer activity and many substituted derivatives have recently earned great interests in chemotherapy as antitumor drugs. Beside the currently established drugs Sertaconazole, Raloxifene and Zileuten. Benzo[b]thiophene derivatives are associated with diverse biological activities viz. antiviral [13], antitumor [14-16], anti-inflammatory [17-22], antiallergy [23], antimalarial [24], antimicrobial [25-30] and analgesic. [31] Because of these widespread activities, their synthesis was continually the subject of much research and is still pursued due to new emerging methods. A novel series of benzo[b]thiophen-3-ylmethylidene derivatives was synthesized. Some compounds showed good antimicroial activity.

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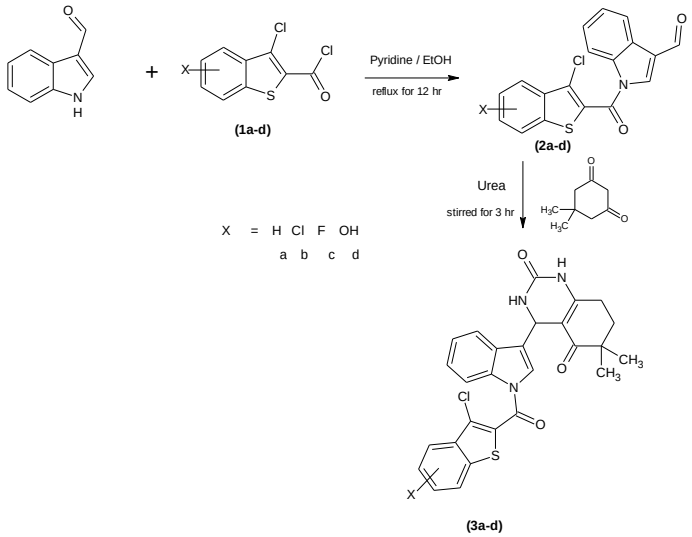
MATERIAL AND METHODS

The reagent grade chemicals were purchased from commercial sources and purified either by distillation or recrystallization before use. Purity of the compounds was checked on silica gel G TLC plates of 2 mm thickness using n-hexane and ethyl acetate as solvent system. The visualization of spot was carried out in an iodine chamber. The IR spectra of the compounds were

recorded in the 4000-450 cm^{-1} ranges using KBr discs on FTIR IR RX1 Perkin Elmer Spectrophotometers and NMR were recorded on a Bruker DRX-300 MHz spectrometer (CDCl3/DMSO) using TMS as an internal standard.

REACTION SCHEME



Synthesis of 1-[(3-chloro-1-benzothiophen-2-yl) carbonyl]-1H-indole-3carbaldehyde (2a)

A mixture of indole- 3-aldehyde (0.01mol) and 3-chloro-1-benzothiophene-2-carbonylchloride **(1a-d)** (0.01mol) in presence of base were dissolved in ethanol and refluxed for 12 hours at room temperature with stirring. Completion of reaction was monitored using TLC and mixture was kept overnight at room temperature. The precipitate was filtered, washed, dried and recrystallized from ethanol.

IR (KBr) cm^{-1}: 3076(C-H str., Aromatic ring), 1682(C=O str., Amide group), 687(C-S-C str., Benzo[b] thiophene ring), 752(C-Cl str.); 1H NMR (DMSO-d6) δ: 7.31-8.19(9H, m, Ar-H), 4.85(1H, s, =C-H,indol ring), 9.65(1H, s, CHO).

1-[(3, 6-dichloro-1-benzothiophen-2-yl) carbonyl]-1H-indole-3-carbaldehyde (2b)

IR (KBr) cm^{-1}: 3074(C-H str., Aromatic ring), 1680(C=O str., Amide group), 682(C-S-C str., Benzo[b] thiophene ring), 758(C-Cl str.); 1H NMR (DMSO-d6) δ: 7.31-8.21(7H, m, Ar-H), 4.75(1H, s, =C-H,indol ring), 9.74(1H, s, CHO).

1-[(3-chloro-6-fluoro-1-benzothiophen-2-yl) carbonyl]-1H-indole-3-carbaldehyde (2c)

IR (KBr) cm^{-1}: 3079(C-H str., Aromatic ring), 1687(C=O str., Amide group), 689(C-S-C str., Benzo[b] thiophene ring), 759(C-Cl str.), 1153(C-F str.); 1H NMR (DMSO-d6) δ: 7.29-8.15(7H, m, Ar-H), 4.75(1H, s, =C-H,indol ring), 9.52(1H, s, CHO).

1-[(3-chloro-6-hydroxy-1-benzothiophen-2-yl) carbonyl]-1H-indole-3-carbaldehyde (2d)

IR (KBr) cm^{-1}: 3081(C-H str., Aromatic ring), 1680(C=O str., Amide group), 681(C-S-C str., Benzo[b] thiophene ring), 753(C-Cl str.), 3384 (OH str.); 1H NMR (DMSO-d6) δ: 7.22-8.19(7H, m, Ar-H), 4.78(1H, s, =C-H,indol ring), 9.21(1H, s, CHO), 5.82(1H, s, O-H).

Synthesis of 4-(1-(3-chlorobenzo[b]thiophene-2carbonyl)-1H-indol-3-yl) 7, 7-dimethyl-3, 4, 7, 8-tetrahydroquinazoline-2, 5(1H, 6H) dione (3a)

A mixture of compound **(2a-d)** (0.01mol), 5,5-dimethylcyclohexane1, 3-dione (0.01mol) and urea (0.012mol) were taken in 100 ml RB flask, and stirred at 100-110°C for 3 hr. Then the mixture was cooled to room temperature. The solid obtained was washed with ethanol and recrystallized to afford **(3a-d).**

IR (KBr) cm^{-1}: 3080(C-H str., Aromatic ring), 2959(C-H str., -CH3 group), 3258(N-H str.,), 681(C-S-C str., Benzo[b] thiophene ring), 742 (C-Cl str.), 1690(C=O str.); 1H NMR (DMSO-d6) δ: 6.91-8.10(8H, m, Ar-H), 1.32(6H, s, Ar-CH_3), 8.56(2H, s, -NH quinazoline ring), 5.56(1H, s, =CH), 1.96(2H, t, CH_2, quinazoline ring), 1.32(2H, t, CH_2, quinazoline ring).

4-(1-(3-chlorobenzo[b]thiophene-2carbonyl)-1H-indol-3-yl) 7, 7-dimethyl-3, 4, 7, 8-tetrahydroquinazoline-2, 5(1H, 6H) dione (3b)

IR (KBr) cm^{-1}: 3056(C-H str., Aromatic ring), 2958(C-H str., -CH3 group), 3256(N-H str.,), 692(C-S-C str., Benzo[b] thiophene ring), 749 (C-Cl str.), 1686(C=O str.); 1H NMR (DMSO-d6) δ: 6.93-8.12(7H, m, Ar-H), 1.32(6H, s, Ar-CH_3), 8.61(2H, s, -NH quinazoline ring), 5.59(1H, s, =CH), 1.98(2H, t, CH_2, quinazoline ring), 1.36(2H, t, CH_2, quinazoline ring).

4-(1-(3-chlorobenzo[b]thiophene-2carbonyl)-1H-indol-3-yl) 7, 7-dimethyl-3, 4, 7, 8-tetrahydroquinazoline-2, 5(1H, 6H) dione (3c)

IR (KBr) cm^{-1}: 3057(C-H str., Aromatic ring), 2952(C-H str., -CH3 group), 3265(N-H str.,), 684(C-S-C str., Benzo[b] thiophene ring), 749 (C-Cl str.), 1686(C=O str.), 1157(C-F str.); 1H NMR (DMSO-d6) δ: 6.92-8.09(7H, m, Ar-H), 1.30(6H, s, Ar-CH_3), 8.59(2H, s, -NH quinazoline ring), 5.51(1H, s, =CH), 2.05(2H, t, CH_2, quinazoline ring), 1.39(2H, t, CH_2, quinazoline ring).

4-(1-(3-chlorobenzo[b]thiophene-2carbonyl)-1H-indol-3-yl) 7, 7-dimethyl-3, 4, 7, 8-tetrahydroquinazoline-2, 5(1H, 6H) dione (3d)

IR (KBr) cm^{-1}: 3053(C-H str., Aromatic ring), 2958(C-H str., -CH3 group), 3255(N-H str.), 687(C-S-C str., Benzo[b] thiophene ring), 769(C-Cl str.), 1680(C=O str.), 3380(OH str.); 1H NMR (DMSO-d6) δ: 6.99-8.11(7H, m, Ar-H), 1.26(6H, s, Ar-CH_3), 8.49(2H, s, -NH quinazoline ring), 5.56(1H, s, =CH), 5.79(1H, s, O-H), 1.99(2H, t, CH_2, quinazoline ring), 1.33(2H, t, CH_2, quinazoline ring).

Antimicrobial Activity

The newly synthesized compounds were screened for their antibacterial activity against gram positive bacteria *S. aureus* and gram negative *E. coli*, *Pseudomonas aeruginosa* and for antifungal activity against *Candida albicans, A. niger*, and *A. clavatus*. Antimicrobial activity was carried out by serial broth dilution method. The standard strains used for the antimicrobial activity was procured from Institute of Microbial Technology, Chandigarh. The compounds **(3a-d)** were screened for their antimicrobial activity at different concentrations of 1000, 500, 200, 100, 50µg/ml

as shown in (Table 2). The results were recorded in the form of primary and secondary screening. The synthesized compounds were diluted at 1000µg/ml concentration, as a stock solution. The drugs which were found to be active in primary screening were similarly diluted to obtain 100, 50µg/ml concentrations. 10µg/ml suspensions were further inoculated on appropriate media and growth was noted after 24 and 48 h. The lowest concentration, which showed no growth after spot subculture was considered as MIC for each drug. The highest dilution showing at least 99% inhibition is taken as (MIC). The test mixture should contain 10^8 cells/ml. The standard drug used in this study was 'Ampicillin' for evaluating antibacterial activity which showed (50, 100, and 50µg/ml) MIC against *E. coli, P. aeruginosa* and *S. aureus* respectively. For antifungal activity 'Griseofulvin' was used as a standard drug, which showed (100, 100, and 100µg/ml) MIC against *C. albicans, A. niger*, and *A. clavatus*, respectively.

RESULTS

Physical and analytical data of the synthesized compounds are given in Table 1. Table 2 describes results for antibacterial and antifungal activities. Synthesized compounds have been screened against three bacterial strains viz. *E. coli, P. aeruginosa, S. aureus* and three fungal strains viz. *C. albicans, A. niger, A. clavatus*. Compound **3c** is considered to be good active against *P. aeruginosa.* For the antifungal activity compounds **3c** is considered as good active against *A. niger* and *A. clavatus.*

DISSCUSSION

The NH proton of indol ring was replaced by various substituted 3-chlorobenzo[b]thiophene-2carbonyl **(1a-d)** in ethanol using pyridine as a catalyst afforded **(2a-d)**, were confirmed by a new band at 752 cm^{-1} of C-Cl stretching and band at 687 due to C-S-C Stretching. Final compounds **(3a-d)** were synthesized using the Biginelli reaction, a multi component coupling of an equivalent moles of 5,5dimethylcyclohexane-1,3-dione, 1-[(3-chloro-1-benzothiophen-2-yl) carbonyl]-1H-indole-3carbaldehyde **(2a-d)** and urea to furnished bicyclic compounds 4-(1-(3-chlorobenzo[b]thiophene-2-carbonyl)1H-indol-3-yl)-7,7-dimethyl-3,4,7,8-tetrahydroquinazoline-2,5(1H,6H)dione **(3a-d)**. Structures of these compounds were confirmed by the presence of N-H stretching band at 3258 cm-1. The 1H NMR spectral also confirms the structure of **(3a-d)**, exhibited a singlet at δ 8.56 for N-H of quinazoline ring and a new singlet for =C-H proton of quinazoline ring at δ 5.56.

For antibacterial activity, compound **3c** is considered to be good active against *P. aeruginosa*, while for *S. aureus* compounds **3b, 3d** and for *E. coli* compound **3c, 3d** are moderately active. For the antifungal activity compound **3c** is considered as good active against *A. niger* and *A. clavatus* while compound **3d** against *C. Albicans* and *A. niger*. The discussion and comparison of antibacterial and antifungal activities have been compared with Ampicillin and Griseofulvin respectively.

Table 1: Physical and analytical data of synthesized compounds

Compound No.	Molecular formula	Molecular weight	Melting point (°C)	Yield (%)	Found/ Calculated (%) N
2a	$C_{18}H_{10}ClNO_2S$	339.79	276	81	4.10/4.12
2b	$C_{18}H_9Cl_2NO_2S$	374.24	152	79	3.72/3.74
2c	$C_{18}H_9ClFNO_2S$	357.78	285	80	3.89/3.91
2d	$C_{18}H_{10}ClNO_3S$	355.79	162	72	3.91/3.94
3a	$C_{27}H_{22}ClN_2O_3S$	503.99	480	73	8.32/8.34
3b	$C_{27}H_{21}Cl_2N_3O_3S$	538.44	336	68	7.78/7.80
3c	$C_{27}H_{21}ClFN_3O_3S$	521.99	484	71	8.03/8.05
3d	$C_{27}H_{22}ClFN_3O_4S$	519.99	342	70	8.02/8.08

Table 2: Biological activity of synthesized compounds (4a-d)

S. No.	Antibacterial Strains			Antifungal Strains		
	Gram negative		Gram positive	*C. albicans*	*A. niger*	*A. clavatus*
	E. coli	*P. aeruginosa*	*S. Aureus*			
3a	500	250	250	500	500	250
3b	250	250	100	500	250	500
3c	100	100	250	250	100	100
3d	100	250	100	100	100	250
S.D.*	**50**	**100**	**50**	**100**	**100**	**100**

S.D= Ampicilin for antibacterial drug; S.D= Griseofulvin for antifungal drug

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