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SYNTHESIS AND ANTIMICROBIAL STUDIES OF SUBSTITUTED BENZO (b) THIOPHENE AND THEIR DERIVATIVES

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ABSTRACT

3-Chlorobenzo (b)thiophene-2-carbonyl chloride **(1)** was prepared when cinnamic acid was refluxed for 48hr with thionyl chloride in chlorobenzene. Compound **(1)** on stirring with anthranillic acid in pyridine furnished 2-(3'-chlorobenzo (b) thiophene-2'-yl)-3, 1-benzoxazin-4-one **(2)**. Reaction of compound (2) with hydrazine hydrate in dioxane under reflux for 3hr gave 3-amino-2-(3'-chlorobenzo (b) thiophene-2'-yl) quinazol-4-one **(3)**, Compound **(2)** on refluxing with phenylhydrazine in dioxane for 3hr yielded 3-phenylamino-2-(3'-chlorobenzo (b) thiophene-2'-yl) quinazol-4-one **(4)**. Compound **(2)** was refluxed with substituted anilines in dioxane for 3hr to gave 3-substituted phenyl-2-(3'-chlorobenzo (b) thiophene-2`-yl) quinazol-4-ones **(5), (6), (7), (8)** and **(9)**. All newly synthesized compounds were characterized by IR, ^{1}H NMR and mass spectral studies. These compounds were evaluated for their antimicrobial activities.

Key words: Benzo (b) thiophene, Antimicrobiol

INTRODUCTION

A large number of studies have been carried out on benzo(b)thiophene but, there are still numerous problems to be solved. Literature survey suggests that extensive synthetic work on benzo(b)thiophene is going on in recent years. Castle et al.[1-3] have reported number of new heterocyclic systems by making use of 2-chlorobenzo (b) thiophene-2-carbonyl chloride. Many researchers have attempted to synthesise compounds with useful biological activities[4,5] by making use of benzo(b)thiophene as a basic nucleus. Different antimicrobial agents, antibacterial[7], antagonists[8], antidepressive agent[9] analgesic

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and anti-inflammatory agents[10] have been reported. In view of the above findings, we thought of synthesizing some derivatives of benzo(b)thiophenes. All the compounds synthesized in the present work were screened for their antimicrobial activity.

EXPERIMENTAL

The melting point of all synthesized compounds were determined by open capillary tubes and are uncorrected. These are expressed in degree Celsius. Purity of all the compounds was checked by TLC. The IR spectra in KBr (cm^{-1}) was taken on FTIR-8000 (Shimadzu) spectrometer at V. L. College of Pharmacy, Raichur. The ^1H NMR spectra were recorded on ACF200 Supercon-Switzerland NMR spectrophotometer and were procured from Central University, Hyderabad; Chemical shifts are expressed in δ ppm, and TMS was used as internal standard. Mass spectra were taken by using LC-MS 2010A (Shimadzu) mass spectrometer from Central University, Hyderabad.

Synthesis of 3-chlorobenzo (b) thiophene-2-carbonyl chloride (1)

A stirred mixture of cinnamic acid (74.1 g, 0.50 mol) pyridine (4.0 mL, 0.05 mol), thionyl chloride (150 mL, 0.77 mol) and chlorobenzene (300 mL) was heated at reflux for 48hr. Excess of thionyl chloride was removed under reduced pressure and the remaining material was suspended in hot n-hexane (800 mL) and then filtered. The hot filtrate was treated with charcoal, allowed to cool and then the crystalline yellow solid obtained, was filtered. The physical constants and percentage of yield and elemental analysis of **(1)** given in Table 1.

Table 1. Characterization data of Substituted benzo(b)thiophen

Comp. No.	Molecular formula	M. P. (°C)	Yield (%)	Found % (Calc.)		
				C	H	N
1	$C_9H_4OSCl_2$	150	68	46.77	1.74	-
				46.74	1.71	-
2	$C_{16}H_8O_2NSCl$	209	70	61.32	2.57	4.44
				61.34	2.56	4.47

Cont…

Comp. No.	Molecular formula	M. P. (ºC)	Yield (%)	Found % (Calc.)		
				C	H	N
3	$C_{16}H_{10}ON_3SCl$	140	82	58.72	3.01	12.80
				58.72	3.06	12.84
4	$C_{22}H_{14}ON_3SCl$	172	68	65.49	3.47	10.41
				65.51	3.47	10.42
5	$C_{22}H_{13}ON_2SCl$	190	73	68.00	3.33	7.20
				68.04	3.35	7.22
6	$C_{22}H_{15}ON_2SCl$	185	56	68.62	3.70	6.93
				68.66	3.73	6.97
7	$C_{23}H_{15}O_2N_2SCl$	195	75	66.03	3.58	6.68
				66.03	3.59	6.70
8	$C_{22}H_{12}ON_2SCl_2$	204	54	62.57	2.82	6.63
				62.56	2.84	6.64
9	$C_{22}H_{12}ON_2SClBr$	201	50	56.50	2.57	6.00
				56.53	2.57	6.00

Table 2. Antibacterial activity of substituted benzo(b)thiophen

Comp. No	Zone of inhibition (mm*)					
	Antibacterial Activity				Antifungal Activity	
	S. aureus	***B. subtilis***	***P. valgaris***	***E. coli***	***A. niger***	***C. albicans***
2	8	09	13	10	09	08
3	11	12	10	12	13	12
4	10	14	12	10	14	12
5	11	11	14	11	15	14

Cont…

Comp. No	Zone of inhibition (mm*)					
	Antibacterial Activity				Antifungal Activity	
	S. aureus	***B. subtilis***	***P. valgaris***	***E. coli***	***A. niger***	***C. albicans***
6	12	09	11	14	13	10
7	16	15	16	12	16	14
8	14	16	16	16	17	17
9	12	15	13	14	16	15

* Including diameter of the bore 6 mm.

The IR spectra of compound **(1)** displayed a strong absorption band at 1776 cm^{-1} due to carbonyl group. The ^1H NMR spectrum of compound **(1)** displayed a characteristics signal at δ 7.0 to 8.0 multiplet due to 4H of aromatic protons. Further, the structure of the compound **(1)** was established by it mass spectrum, where it gave a molecular ion peak at m/z 231, which exactly corresponds to its molecular weight.

Synthesis of 2-(3`-chlorobenzo (b) thiophene-2'-yl)-3, 1-benzoxazin-4-one (2)

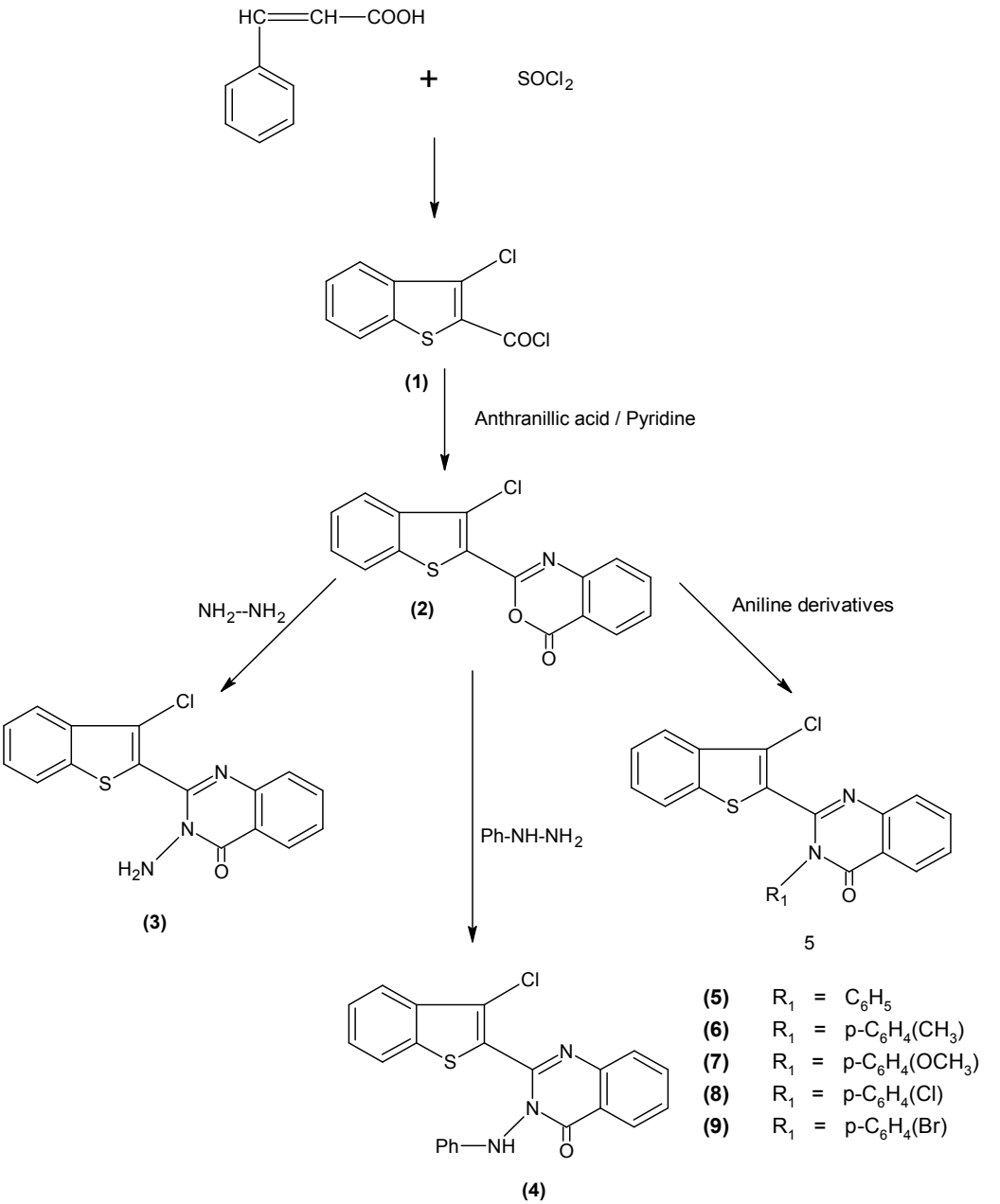
To a solution of anthranilic acid (1.38 g, 0.01 mol) dissolved in pyridine (6 mL), 3-chlorobenzo(b)thiophene-2-carbonyl chloride (2.3 g, 0.01 mol) was added and then the mixture was stirred for 0.5 hr followed by treatment with sodium bicarbonate (30 mL, 5%). The separated solid was crystallized from benzene. The physical constants and percentage of yield and elemental analysis of **(2)** are given in Table 1.

The IR spectra of compound **(2)** displayed a strong absorption band at 1778 cm^{-1} due to carbonyl group of oxazinone moiety. A band observed at 1600 cm^{-1} may be due to C=N function. The ^1H NMR spectrum of compound **(2)** displayed a characteristics signal at δ 7.2 to 8.2 multiplet due to 8H of aromatic protons. Further, the structure of the compound **(2)** was established by its mass spectrum, where it gave a molecular ion peak at m/z 313, which exactly corresponds to its molecular weight.

Synthesis of 3-amino-2-(3'-chlorobenzo (b) thiophene-2'-yl)-3, 1-quinazol-4-one (3)

A mixture of 2-(3'-chlorobenzo (b) thiophene-2'-yl)-3, 1-benzoxazin-4-one (2) (1 g, 0.003 mol) and hydrazine hydrate (0.15 mL, 0.003 mol) in dioxane was refluxed for 3hr and cooled. The separated solid was filtered and crystallized from dioxane-benzene. The

physical constants and percentage of yield and elemental analysis of **(3)** are given in Table 1.



Scheme 1

The IR spectra of compound **(3)** exhibited a broad hump in the region 3100 to 3400 cm^{-1}, which clearly shows the presence of $–NH_2$ group in the molecule. The carbonyl function of quinazoline part of the molecule showed a sharp band at 1720 cm^{-1} as pure C=O and also at 1660 cm^{-1} as enolisable C=O, respectively. One more band was observed near 1600 cm^{-1}, which may be of C=N group. The ^1H NMR spectrum of compound **(3)** displayed a characteristics signal at δ 2.0 singlets for 2H of NH_2; 7.0 to 8.0 multiplet due to 8H of aromatic protons.

Further, the structure of the compound **(3)** was established by its mass spectrum, where it gave a molecular ion peak at m/z 327, which exactly corresponds to its molecular weight. One more peak was recorded at 329 clearly tells about the presence of chlorine atom in the molecule.

Synthesis of 3-phenylamino-2-(3'-chlorobenzo (b) thiophene-2'-yl)-3, 1-quinazol-4-one (4)

A mixture of 2-(3' -chlorobenzo (b) thiophene-2'-yl)-3, 1-benzoxazin-4-one **(2)** (1 g, 0.003 mol) and phenyl hydrazine (0.34 mL, 0.003 mol) in dioxane was refluxed for 3hr and cooled. The separated solid was filtered and crystallized from benzene. The physical constants and percentage of yield and elemental analysis of **(4)** are presented in Table 1.

The IR spectra of compound **(4)** exhibited a broad hump in the region 3200 cm^{-1} due to NH function. Another sharp band was observed at 1750 cm^{-1} due to C=O group of quinazoline moiety. Two bands at 1650 and 1600 cm^{-1} were observed; may be of enolic C=O and C=N functions, respectively. The ^1H NMR spectrum of compound **(4)** displayed a characteristics signal at δ 4.0 singlet for 1H of NH; 6.6 to 8.0 multiplet due to 13H of aromatic protons. Further, the structure of the compound **(4)** was established by its mass spectrum, where it gave a molecular ion peak at m/z 403, which exactly corresponds to its molecular weight.

Synthesis of 3-phenyl-2-(3'-chlorobenzo (b) thiophene-2'-yl)-3, 1-quinazol-4-one (5)

A mixture of 2-(3'-chlorobenzo(b)thiophene-2'-yl)-3, 1-benzoxazin-4-one **(2)** (1 g, 0.003 mol) and aniline (0.29 mL, 0.003 mol) in dioxane was refluxed for 3hr and cooled. The separated solid was filtered and crystallized from alcohol.

The remaining compounds of this series **(6), (7), (8)** and **(9)** were synthesized

following the similar method by using different substituted primary aromatic amines and compound **(2)** and the products were crystallized by appropriate solvent. The physical constants and percentage of yield and elemental analysis of these compounds are presented in Table 1.

The IR spectra of compound **(8)** displayed a broad band in the region 1750 cm^{-1} due to C=O group of quinazoline moiety. The ^{1}H NMR spectrum of compound **(8)** displayed a characteristics signal at δ 7.0 to 8.0 multiplet 12H of aromatic protons. Further the structure of the compound **(8)** was established by its mass spectrum, where it gave a molecular ion peak at m/z 423, which exactly corresponds to its molecular weight.

Antibacterial activity

The *in vitro* antibacterial activity of the new compounds were determined by cup-plate method using *E. coli, P. aeruginosa, S. epidermatitis and B. Subtilis* organism at the concentration of 100 µg \ 0.1ml in DMF. Compounds **(7)**, **(8)** and **(9)** exhibited activity nearly equal to that of standard (Ampicillin) against all the organisms. Compounds 3 and 4 exhibited moderate activity against organisms.

Antifungal activity

The *in vitro* antifungal activity of the new compounds was determined by cup-plate method against *A. niger* and *C. albicans* at the concentration of 100 µg \ 0.1ml using nyatatin as a standard drug. The Zone of inhibition was recorded after 24h of incubation at $37^{0}C$. The compounds **7**, **8** and **9** were exhibited marked activity against *A. niger* and *C. Albicans*. The remaining compounds were showed moderate antifungal activity against both fungi when compared to standard drug.

RESULTS AND DISCUSSION

Benzo(b)thiophenes have been found to possess antibacterial, antifungal, and are used as antidepressive agents and nasal decongestant. 3-Chlorobenzo (b) thiophene-2-carbonyl chloride **(1)** was prepared, by treating cinnamic acid with thionyl chloride in chlorobenzene. Compound **(1)** on stirring with anthranilic acid in pyridine furnished 2-(3'-chlorobenzo (b) thiophene-2'-yl)-3, 1-benzoxazin-4-one **(2)**. Reaction of compound (2) with hydrazine hydrate in dioxane gave 3-amino-2-(3'-chlorobenzo (b) thiophene-2'-yl) quinazol-4-one **(3).** When compound **(2)** was refluxed with phenyl hydrazine in dioxane, it yielded 3-phenylamino-2-(3'-chlorobenzo (b) thiophene-2'-yl) quinazol-4-one **(4)**. Compound **(2)** on refluxing with substituted anilines in dioxane gave 3-substituted phenyl-

2-(3'-chlorobenzo (b) thiophene-2'-yl) quinazol-4-ones **(5), (6), (7), (8)** and **(9)**. All newly synthesized compounds were characterized by spectral analysis.

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