ISSN: 0974 - 7516 Volume 7 Issue 5

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 7(5), 2011 [325-331]

Synthesis and antimicrobial activity of some new *N'*-(3-chloro-6-substituted benzo[b]thiophene-2-carbonyl)-substituted-2-oxo-2H-pyrano[2,3-*b*]quinoline-3-carbohydrazides

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[#]This work was presented at the international conference on 'Current trends in chemistry and biochemistry' held at the Departments of Chemistry and Biochemistry, Central College Campus, Bangalore University, Bangalore, during Dec 18-19, 2009 (PP-124, Page No-137)

Received: 29th January, 2011 ; Accepted: 8th February, 2011

ABSTRACT

Equimolar quantities of 3-chloro-6-substituted benzo[b]thiophene-2-carbohydrazides **(1a-b)** and diethyl malonate **(2a)** when refluxed in dry xylene for 10 hr afford ethyl 3-(2-(3-chloro-6-substitutedbenzo[b]thiophene-2-carbonyl)hydrazinyl)-3-oxopropanoate **(3a-b)**. These on further reaction with substituted-2-hydroxy-3-formyl quinolines **(4a-j)** yielded *N'*-(3-chloro-6-substitutedbenzo[b]thiophene-2-carbonyl)substituted-2-oxo-2*H*-pyrano [2,3-*b*]quinoline-3-carbohydrazides **(5a-j)**. Structures of the all the newly synthesized compounds were confirmed by elemental analysis and spectral data. All these compounds have been screened for their antibacterial activity against Gram +ve *Staphylococcus aureus* & *Bacillus subtilus and* Gram –ve *Escherichia coli* & *K. pneumonia* and antifungal activity against *Aspergillus niger* and *Candida albicans*.

KEYWORDS

Benzothiophene;
Quinolines;
Schiff bases;
Pyrano-quinoline-2-one;
Antimicrobial activity.

INTRODUCTION

Heterocycles bearing nitrogen, sulphur and oxygen atoms in their structure constitute the core structure of a number of biologically interesting compounds. Many benzothiophene derivatives reported in the literature are known to possess varied biological activities *viz*, antimicrobial activity[1], anti-inflammatory activity[2], antituberculosis activity[3], analgesic activity[4] and serotonine *N*-acetyl transferase inhibitor activity[5]. Literature survey reveals that quinoline derivatives have attracted the attention of the chemists because of their presence in many natural products associated with significant biological activities[6-11].

In view of these findings and in continuation of our research work, we hereby report the synthesis and antimicrobial activity of some ethyl 3-(2-(3-chloro-6-substituted benzo[b]thiophene-2-carbonyl)hydrazinyl)-3-oxopropanoate **(3a-b)** and *N'*-(3-chloro-6-substituted benzo[b]thiophene-2-carbonyl)substituted-2-oxo-2*H*-pyrano [2,3-*b*]quinoline-3-carbohydrazides **(5a-j)** Scheme 1.

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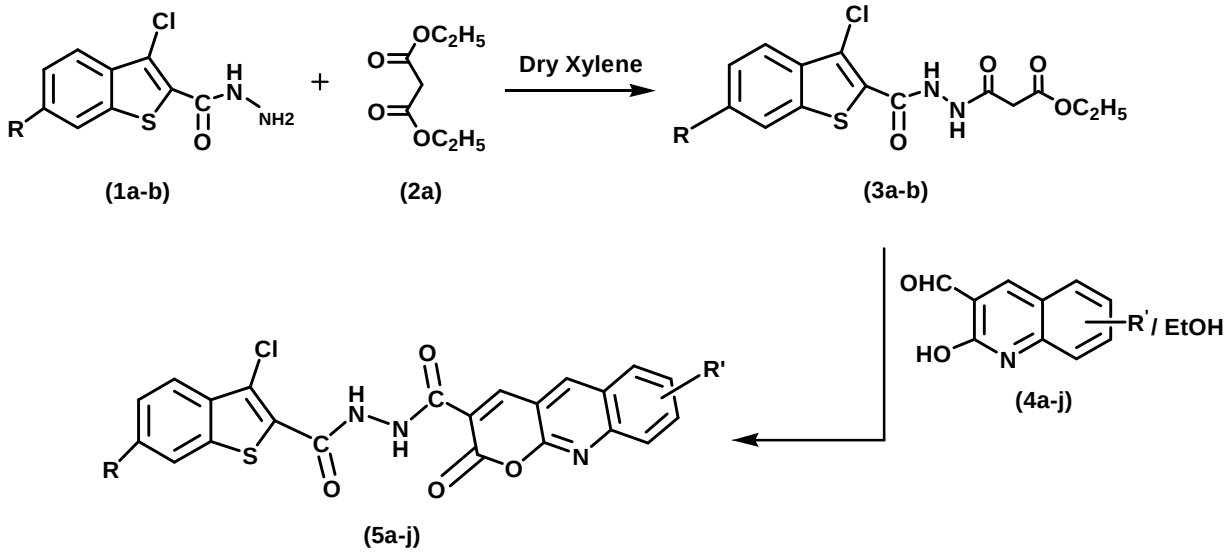
TABLE 1 : Physical and spectral data of synthesized compounds;

Compds	R	R	M.P ^{0}C (Yield %)	Spectral data* (IR (KBr)ν_{max} in cm^{-1}; ^{1}H NMR in δ; Mass in m/z)
3a	H	-	225 (90)	1181 (C-O-C), 1672, 1683, 1747 (C=O/C=O/C=O), 3202, 3328 (NH/NH); 1.22 (t, 3H, -CH_3), 3.36 (s, 2H, CO-CH_2-CO), 4.09 (q, 2H, -CH_2), 7.59-8.14 (m, 4H, ArH), 10.39 (s, 1H, -CONH), 10.51 (s, 1H, -CONH).
3b	OCH_3	-	220 (69)	1184 (C-O-C), 1618, 1658, 1671 (C=O/C=O/C=O), 3162, 3272 (NH/NH).
5a	H	H	248 (62)	1160 (C-O-C), 1556 (C=N), 1617, 1646, 1683 (C=O/C=O/C=O), 3187, 3272 (NH/NH); 7.21-8.75 (m, 10H, ArH), 10.12 (s, 1H, -CONH), 10.23 (s, 1H, -CONH); 450, 452 (50%, 16%), 252, 254 (40%, 13%), 174 (100%), 146 (45%).
5b	H	7-CH_3	140 (68)	1190 (C-O-C), 1584 (C=N), 1625, 1645, 1661 (C=O/C=O/C=O), 3074, 3208 (NH/NH); 2.42 (s, 3H, CH_3), 6.74-8.75 (m, 9H, ArH), 10.12 (s, 1H, -CONH), 10.23 (s, 1H, -CONH); 464, 466 (50%, 16%), 421, 423 (40%, 13%), 396, 398 (10%, 3%), 333 (40%), 202 (5%), 160 (9%).
5c	H	8-CH_3	180 (64)	1167 (C-O-C), 1591 (C=N), 1613, 1651, 1667 (C=O/C=O/C=O), 3252, 3292 (NH/NH).
5d	H	9-CH_3	189 (74)	1161 (C-O-C), 1563 (C=N), 1612, 1646, 1660 (C=O/C=O/C=O), 3039, 3207 (NH/NH).
5e	H	9-OCH_3	283 (67)	1174 (C-O-C), 1574 (C=N), 1613, 1644, 1658 (C=O/C=O /C=O), 3183, 3291 (NH/NH).
5f	OCH_3	H	295 (70)	1178 (C-O-C), 1570 (C=N), 1615, 1641, 1683 (C=O/C=O /C=O), 3229, 3293 (NH/NH).
5g	OCH_3	7-CH_3	275 (67)	1172 (C-O-C), 1567 (C=N), 1609, 1628, 1665 (C=O/C=O /C=O), 3235, 3298 (NH/NH).
5h	OCH_3	8-CH_3	218 (59)	1185 (C-O-C), 1583 (C=N), 1601, 1625, 1641 (C=O/C=O /C=O), 3198, 3282 (NH/NH).
5i	OCH_3	9-CH_3	235 (64)	1182 (C-O-C), 1583 (C=N), 1641, 1670, 1702 (C=O/C=O /C=O), 3171, 3272 (NH/NH).
5j	OCH_3	9-OCH_3	263 (65)	1181 (C-O-C), 1538 (C=N), 1579, 1625, 1655 (C=O/C=O /C=O), 3129, 3288 (NH/NH).



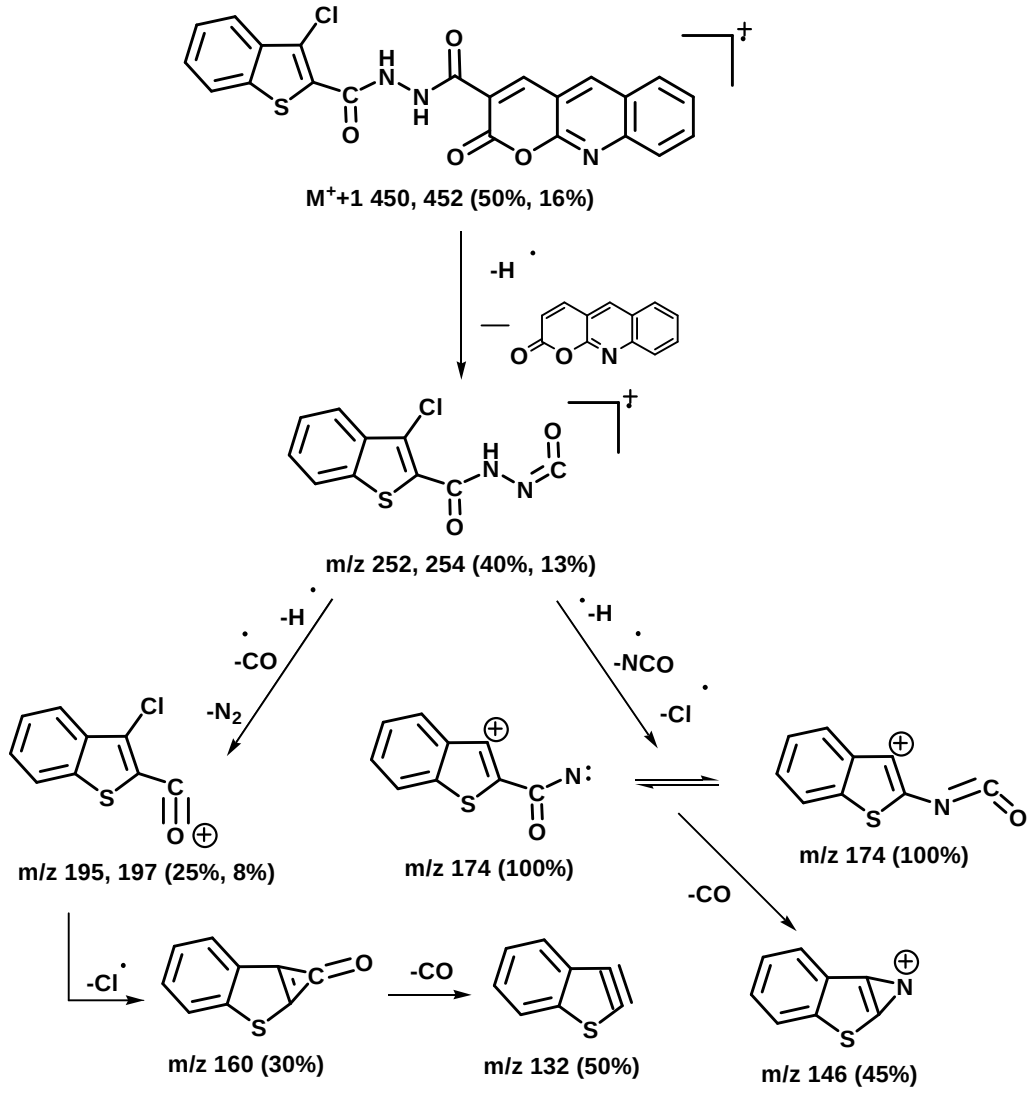
	a	b	c	d	e	f	g	h	I	j
R =	-H	-H	-H	-H	-H	-OCH_3	-OCH_3	-OCH_3	-OCH_3	-OCH_3
R'=	-H	-6-CH_3	-7-CH_3	-8-CH_3	-8-OCH_3	-H	-6-CH_3	-7-CH_3	-8-CH_3	-8-OCH_3

Scheme 1

RESULTS AND DISCUSSION

The starting compounds 3-chloro-6-substituted benzo[b]thiophene-2-carbohydrazides[12-14] **(1a-b)** (0.001mol) when refluxed with diethylmalonate **(2)** for 10 hr in dry xylene (10 ml) gave ethyl 3-(2-(3-chloro-6-substitutedbenzo[b]thiophene-2-carbonyl)hydrazinyl)-3-oxo propanoate **(3a-b)**. Compound **(3a)** in its IR spectrum showed absorption bands at 1181, 1672, 1683, 1747, 3202 and 3328 cm^{-1} due to C-O-C, C=O/C=O/C=O and NH/NH functions respectively. Compound **(3a)** in its ^1H NMR spectrum displayed quatrate at δ4.09 and a triplet at δ1.22 due to the methylene and methyl protons of ethyl ester group. A singlet observed at δ3.36 due two protons of $COCH_2CO$. A multiplet observed in the range δ7.59-8.14 is due to four aromatic protons and two distinct singlets observed at δ10.39 and δ10.51 were due to two NH protons of two -CONH functions respectively.

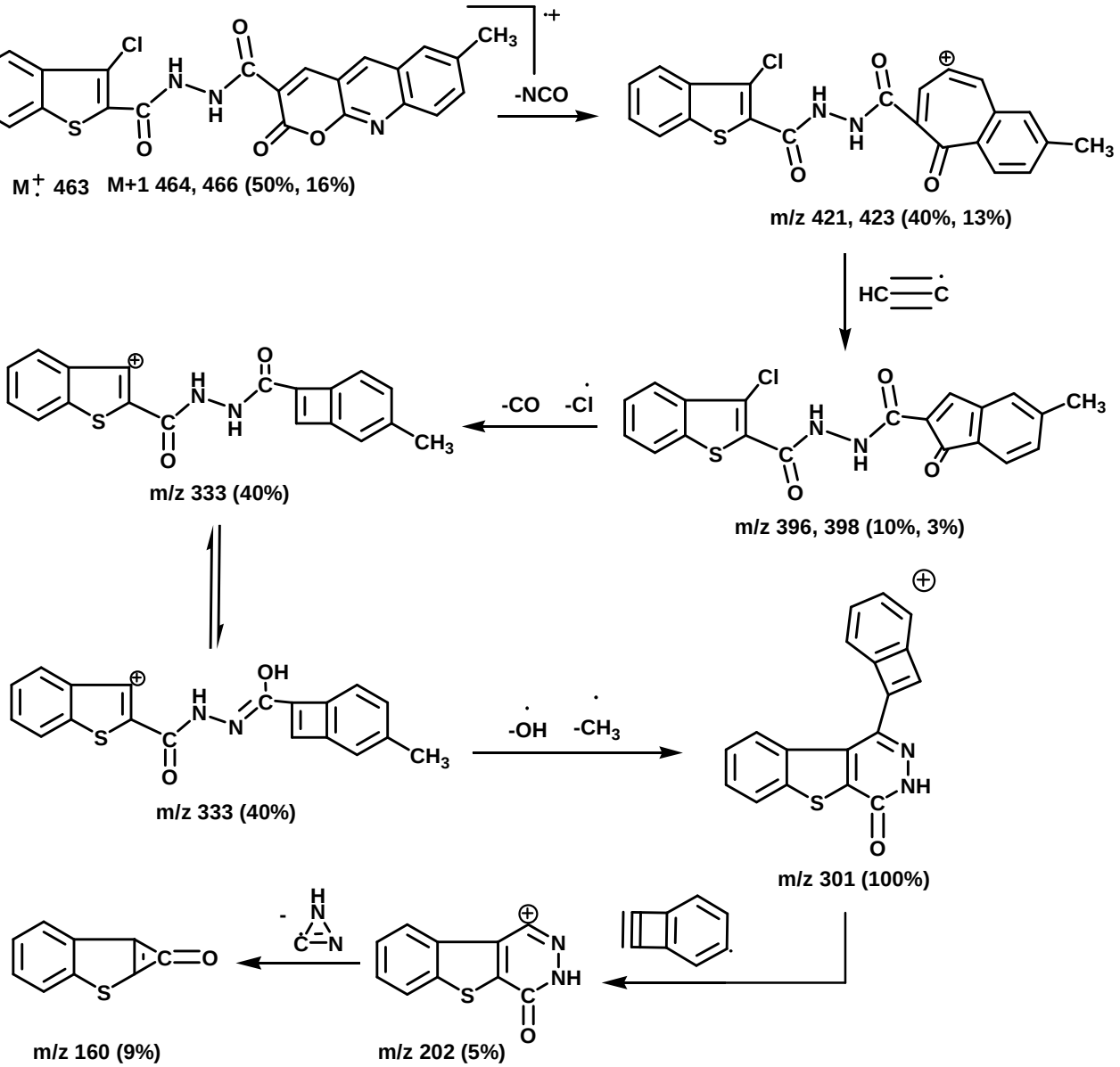
Compound **(3a-b)** on reaction with substituted-2-hydroxy-3-formyl-quinolines[15-16] **(4a-j)** in presence of catalytic amount of piperdine in ethanol under reflux conditions for 5 h afforded *N'*-(3-chloro-6-substitutedbenzo[b]thiophene-2-carbonyl)substituted-2-oxo-2*H*-pyrano[2,3-*b*] quinoline-3-carbohydrazides **(5a-j)** in a good yield. Compound **(5a)** in its IR spectrum showed absorption bands at 1160, 1556, 1617, 1646, 1683, 3187 and 3272 cm^{-1} due to C-O-C, C=N, C=O/C=O/C=O and NH/NH functions respectively. Two singlets and multiplet observed at δ10.12, δ10.23 and δ7.21-8.75 in the ^1H NMR spectrum of compound



Scheme 2

(5a) are due to two protons of two CONH functions and ten aromatic protons respectively. Mass spectrum of compound **(5a)** has displayed M+1 peak at 450, 452 (50%, 16%). This ion on simultaneous expulsion of hydrogen radical and 2*H*-pyrano[2,3-*b*]quinolin-2-one molecule gave fragment ion at m/z 252, 254 (40%, 13%) this fragmented ion underwent fragmentation in two routes, one by simultaneous expulsion of hydrogen, -NCO and Cl radicals gave fragment ion peak at m/z 174 (100%) which is also a base peak. This on expulsion of -CO molecule gave a fragment ion recorded at m/z 146 (45%). In the second route, simultaneous expulsion of hydrogen radical, -CO and N_2 molecules gave a fragment ion at m/z 195, 197 (25%, 8%), which on sequential expulsion of Cl radical and -CO molecule gave a fragment ion peaks recorded at m/z 160 (30%) and m/z 132 (50%) respectively. These spectral data clearly support the structure of compound **(5a)**. The IR, ^{1}H NMR and mass spectral fragmentation data of compound **(5a)** are in consistency with its structure and prove the formation of compound **(5a)** by the reaction of **(3a)** with **(4a)**

Compound **(5b)** in its IR spectrum showed absorption bands at 1190, 1584, 1625, 1645, 1661, 3074 and 3208 cm^{-1} were due to C-O-C, C=N, C=O/C=O/C=O and NH/NH functions respectively.



Scheme 3

Two singlets observed in its ^{1}H NMR spectrum at δ10.12, δ10.23 and multiplet observed in the region δ6.74-8.75 in the ^{1}H NMR spectrum of compound **(5b)** are due to two protons on nitrogen of two CONH functions and nine aromatic protons respectively. A singlet observed at δ2.42 is due to protons of a methyl group. The mass spectrum of compound **(5b)** has displayed M+1 peak at 464, 466 (10%, 3%). This on fragmentation by the expulsion of hydrogen and -NCO radicals gave a peak recorded at m/z 421, 423 (50%, 16%). This on further loss of acetyl radical gave a peak at m/z 396, 398 (10%, 3%). This on simultaneous loss of -Cl radical and -CO molecule gave a fragment ion peak recorded at m/z 333 (40%). This on further loss of –OH and methyl radicals gave fragment ion peak at m/z 301 (100%) which is also a base peak. This on sequential expulsion of $-C_8H_3$ and HCN_2 radicals gave a fragment ion peak recorded at m/z 202 (5%) and m/z 160 (9%). The IR, ^{1}H NMR and mass spectral fragmentation data of compound **(5b)** are in consistency with its structure and prove the formation of compound **(5b)** from compound **(3a)** on reaction with 6-methyl-2-hydroxy-3-formylquinoline.

ANTIMICROBIAL ACTIVITY

The results showed that the compounds **(3a)**, **(3b)**, **(5e)** and **(5f)** showed good activity and compounds **(5b)**, **(5h)** and **(5j)** exhibited moderate activity against *S. aureus* when compared to that of standard drug Gentamycin at the same concentration as that of test drugs. Compounds **(3a)**, **(5e)**, **(5f)**, **(5h)** and **(5j)** showed good activity and compounds **(5b)**, **(5d)** and **(5i)** exhibited moderate activity when compared to that of standard drug Gentamycin at the same concentration as that of test drugs against *B. subtilus*. Compounds **(3a)**, **(3b)**, **(5b)**, **(5e)**, **(5h)** and **(5j)** showed good activity and compounds **(5d)**, **(5f)** and **(5i)** exhibited moderate activity against *E. coli* when compared to that of standard drug Gentamycin at the same concentration as that of test drugs. Compounds **(3a)**, **(3b)**, **(5d)**, **(5e)** and **(5h)** showed good activity and compounds **(5a)**, **(5b)**, **(5f)**, **(5g)** and **(5j)** exhibited moderate activity against *K. pneumonia* when compared to that of standard drug Gentamycin at the same concentration as that of test drugs.

Compounds **(5e)**, **(5h)** and **(5j)** showed good activity and compounds **(3a)**, **(3b)**, **(5c)**, **(5f)** and **(5g)**

TABLE 2 : Anti-microbial activity of the synthesized compounds.

Compounds	Conc-^{n} (µg/disc) in DMF	Zone of inhibition in mm*					
		Antibacterial activity				Antifungal activity	
		Gram-positive		Gram-negative			
		S.aureus	*B.subtilus*	*E.coli*	*K.pneumoniae*	*A.niger*	*C.albicans*
3a	100	18	14	16	19	20	19
3b	100	17	11	18	21	18	15
5a	100	11	10	12	14	15	19
5b	100	15	13	16	18	17	15
5c	100	11	09	11	15	19	17
5d	100	13	12	13	20	17	14
5e	100	20	16	18	22	26	20
5f	100	17	14	14	19	20	16
5g	100	14	11	12	17	18	19
5h	100	16	15	16	20	23	16
5i	100	12	10	15	16	15	17
5j	100	15	16	17	19	21	22
Gentamycin	100	25	20	22	28	-	-
Fluconazole	100	-	-	-	-	30	28
Control (DMF)	-	-	-	-	-	-	-

***Diameter of well (bore size) - 6 mm,**

TABLE 3 : Elemental analysis for compounds (3a-b) and (5a-j)

Compound	Mol. Form.	Mol. wt.	C in % Found (Calcd.)	H in % Found (Calcd.)	N in % Found (Calcd.)
3a	$C_{14}H_{13}N_2O_4SCl$	340	49.21 (49.41)	3.77 (3.82)	8.05 (8.23)
3b	$C_{15}H_{15}N_2O_5SCl$	370	48.32 (48.64)	3.97 (4.05)	7.40 (7.56)
5a	$C_{22}H_{12}N_3O_4SCl$	449	58.57 (58.79)	2.57 (2.67)	9.21 (9.35)
5b	$C_{23}H_{14}N_3O_4SCl$	463	59.46 (59.61)	2.95 (3.02)	8.88 (9.07)
5c	$C_{23}H_{14}N_3O_4SCl$	463	59.42 (59.61)	2.90 (3.02)	8.90 (9.07)
5d	$C_{23}H_{14}N_3O_4SCl$	463	59.40 (59.61)	2.97 (3.02)	8.93 (9.07)
5e	$C_{23}H_{14}N_3O_5SCl$	479	57.45 (57.62)	2.81 (2.92)	8.56 (8.76)
5f	$C_{14}H_{13}N_2O_5SCl$	479	57.44 (57.62)	2.85 (2.92)	8.60 (8.76)
5g	$C_{24}H_{16}N_3O_5SCl$	493	58.22 (58.41)	3.12 (3.24)	8.32 (8.51)
5h	$C_{24}H_{16}N_3O_5SCl$	493	58.19 (58.41)	3.15 (3.24)	8.36 (8.51)
5i	$C_{24}H_{16}N_3O_5SCl$	493	58.22 (58.41)	3.14 (3.24)	8.31 (8.51)
5j	$C_{24}H_{16}N_3O_6SCl$	509	56.37 (56.58)	3.06 (3.14)	8.11 (8.25)

exhibited moderate activity when compared to that of standard drug Fluconazole at the same concentration as that of test drugs against *A. Niger*. Compounds **(3a)**, **(5e)** and **(5j)** showed good activity and compounds **(5a)**, **(5c)**, **(5g)** and **(5i)** exhibited moderate activity when compared to that of standard drug Fluconazole at the same concentration as that of test drugs against *C. albicans*. Rest of the compounds showed less activity against all the microorganisms tested. Under these conditions control DMF did not show any antibacterial and antifungal activity.

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded in KBr on Perkin-Elmer FT-IR (spectrum one, 1000 series); ^{1}H NMR spectra on a Bruker AMX (400 MHz) spectrophotometer using d_6-DMSO as solvent using TMS as an internal standard (chemical shifts in δ) and mass spectra on a Mass spectrophotometer Shimadzu LCMS-2010A instrument. Compounds were checked for their purity by TLC on silica gel G plates and spots were located by iodine vapours.

Synthesis of ethyl 3-(2-(3-chloro-6-substituted-benzo[b]thiophene-2-carbonyl)hydrazinyl) -3-oxopropanoate (3a-b)

A mixture of diethylmalonate (0.001mol) and the 3-chloro-6-substituted benzo[b]thiophene-2-carbohydrazides **(1a-b)** (0.001 mol) was refluxed for 10 hr in dry xylene (10 ml). White solid separated out after cooling was filtered, washed with ethanol, dried and recrystallized from dioxane to furnish **(3a-b)** in good yield.

Synthesis of *N'*-(3-chloro-6-substituted benzo-[b]thiophene-2-carbonyl)substituted-2-oxo-2*H*-pyrano[2,3-*b*]quinoline-3-carbohydrazide (5a-j)

A mixture of compounds ethyl 3-(2-(3-chloro-6-substitutedbenzo[b]thiophene-2-carbonyl)hydrazinyl)-3-oxopropanoate **(3a-b)** (0.001 mol) and various substituted-2-hydroxy-3-formyl-quinolines (0.001 mol) in ethanol (10 ml) was refluxed for 5 hr in presence of catalytic amount of piperdine. Excess of ethanol was removed by distillation. Residue obtained was filtered, washed with little amount of ethanol, dried and recrystallized from dioxane to afford *N'*-(3-chloro-6-substitutedbenzo[b]thiophene-2-carbonyl)substituted-2-oxo-2*H*-pyrano[2,3-*b*] quinoline-3-carbohydrazide **(5a-j)** in good yield.

ANTIMICROBIAL ACTIVITY

Antimicrobial activities of synthesized compounds have been tested for their antibacterial activity against Gram +ve *S.aureus* & *B.substilus* and Gram –ve *E.coli* & *K. pneumonia* antifungal activity against *A.niger* & *C.albicans* by cup-plate method[17-19]. Gentamycin and Fluconazole were used as standards for antibacterial and antifungal activities respectively. The compounds were tested at the concentration of 100 μg/ml in DMF

for both antibacterial and antifungal activity. The zone of inhibition after 24 hr of incubation at 37 ºC, in case of antibacterial activity and 72 hr in case of antifungal activity was compared with that of standards. The results are tabulated in the TABLE 2.

ACKNOWLEDGEMENT

The authors are thankful to the Directors, IISc., Bangalore for spectral data. Authors are also thankful to Chairman, Department of studies and Research in Chemistry, Gulbarga University, Gulbarga -585106 for providing laboratory facilities.

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