SYNTHESIS AND BIOLOGICAL EVALUTION OF NEW NAPTH[1,2-C]PYRAZOLEBENZENESULFONYLUREAS, THIOUREAS AND THEIR CYCLIZED DERIVATIVES

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ABSTRACT: Five series of substituted p-(naphtho[l,2-c]pyrazol-2-yl)benzenesulfonylurea **3**, thioureas **4** as well as their cyclized derivatives **5-7** were prepared for evaluation as antibacterial agents. Preliminary biological testing revealed that some of these compounds possess weak antibacterial activity .

Key Words:Naphtho[1,2-c]pyrazoles,Benzenesulfonylureas,Benzenesulfonylthioureas

INTRODUCTION

A wide variety of pharmacological properties have been encountered with substituted pyrazoles. This include antiflamarory[1-3], antibacterial[4-6], antifungial[7], antidiabetic[8-10] and antiallergitic[11,12]activities. In this report many new naphtho[l,2-c]pyrazolobenzenesulfonylurea and thiourea were prepared with the hope that they may be of potential antibacterial and antifungial action.

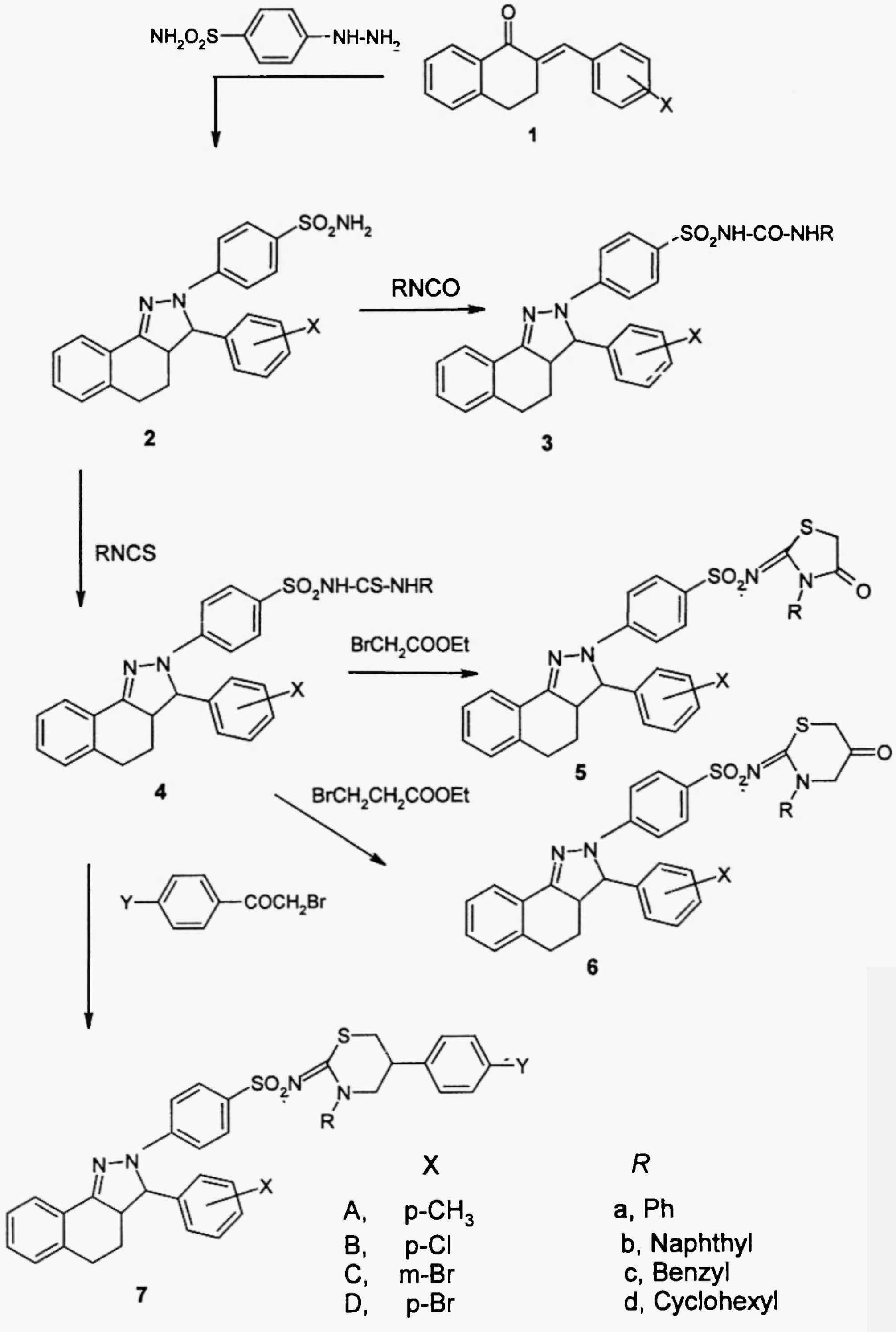
RESULTS AND DISCUSSION

Condensation of 2-arylidene-l-tetralones 1A-D with p-hydrazinobenzene sulfonamide hydrochloride afforded the corresponding naphtho[l,2-c]pyrazoline **2A-D**.

Addition of pyazolines **2** across the N=C bond of the appropriate isocyanate and isothiocyanate in dry acetone yielded the corresponding benzenesulfonylureas **3** and thioureas **4** respectively . The IR spectra of these compounds exhibited two lines at 1338-1365 cm^{-1} and 1165-1182 cm^{-1} due to SO_2N group and a urea carbonyl line at 1649-1661 cm^{-1} in the case of compounds **3** and a thiourea carbonyl absorption at 1083-1089cm^{-1} in the case of compounds **4.**

Their ^1H NMR data are recorded in (Table 1). Cyclization of the thiourido group of compounds **4** by treatment with ethyl bromoacetate, ethyl β-bromopropionate and α-bromoacetophenones afforded the corresponding 4-oxothiazolidine **5**, 4-oxo-5,6-dihydrothiazine **6** and thiazoline7 derivatives respectively (scheme 1) . IR spectra of compounds **5** and **6** showed a cyclic carbonyl absorption at 1717-1740 cm^{-1} and two lines at 1335-1362 cm^{-1} and 1172-1180 cm^{-1} for the SO_2N group (Table 1) . The structures of the above compounds **5-7** were further supported by their ^1H NMR data which displayed signals due to aromatic and R protons, a doublet of one proton intensity at δ 5.48-5.85 and three multiplets at δ 3.45-3.82, 2.75-2.97 and 1.10-1.52 for H-3a , H-5 and H-4 respectively . In addition compounds **4,5** showed a singlet of two protons intensity at δ 3.79-4.18 for H-5' of the thiazolidinone moiety, while compounds **6** exhibited a multiplet of four protons intensity at δ 4.30-4.54 due to H-5' and H-6 of the thiazinone moiety (Table 1) . The spectral data are inadequate to show the α or β configuration of the 3- (p-substituted phenyl) groups in compounds **3-7** .

The structure of 4-oxothiazolidine derivative **5Aa** was further supported from its mass spectrum. It did not show a molecular ion peak, but we could identify some fragments that comfirmed its structure Fig 1.



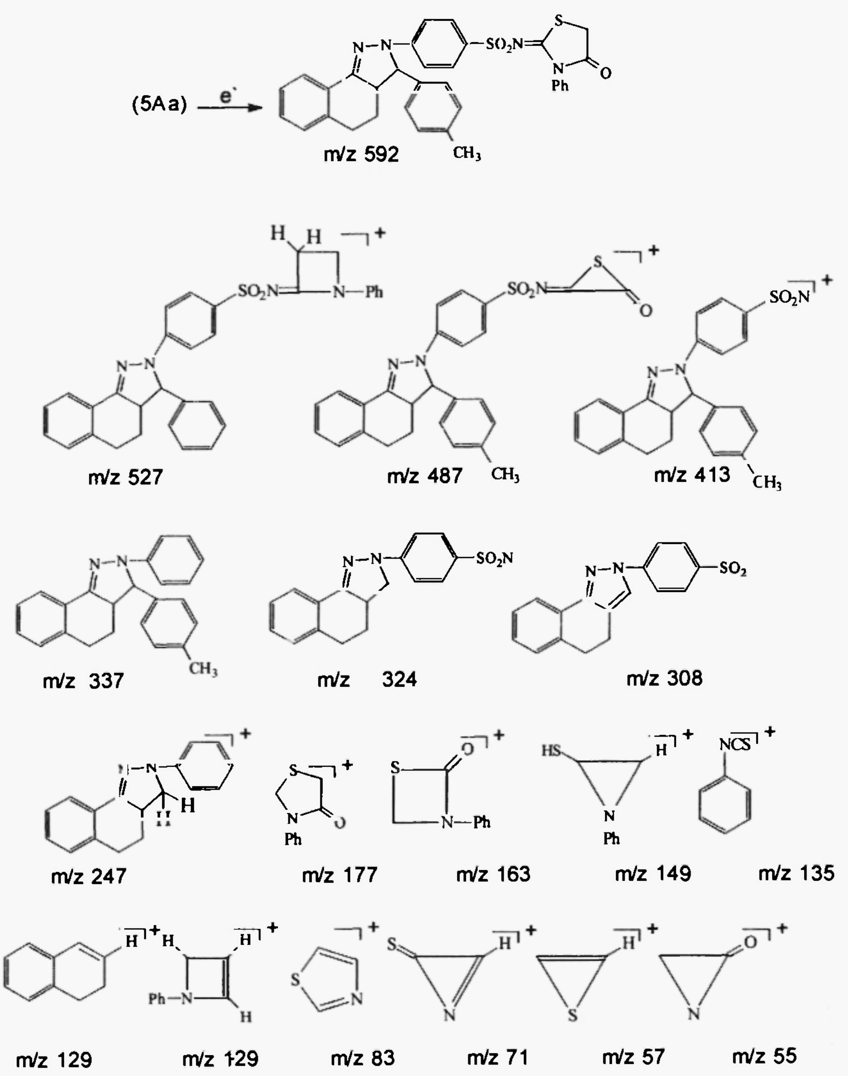
	X		R
A,	p-CH_3	a,	Ph
B,	p-Cl	b,	Naphthyl
C,	m-Br	c,	Benzyl
D,	p-Br	d,	Cyclohexyl

Scheme 1

Table 1: Spectral Data of compounds 3-7

Compound No.	R	X	Y	^{1}HNMR^a					Others	IR (KBr, cm^{-1})	
				H-3 (d,1H)	H-3a (m, 1H)	H-4 (m, 2H)	H-5 (m, 2H)	ArH & NH (m)		CO or CS	NH
3Aa	Ph	*p*-CH$_3$		5.53	3.80	1.97	2.96	7.00-8.42	2.30 (s,3H, CH$_3$); 8.8 (s, NH)	1649	3351
3Ab	Naphthyl	*p*-CH$_3$		5.60	3.72	1.70	2.86	7.01-8.34	2.22 (s,3H, CH$_3$); 8.6 (s, NH)	1652	3352
3Ba	Ph	*p*-Cl		5.20	3.68	1.75	2.90	6.75-8.28	8.75 (s, NH)	1658	3349
3Bb	Naphthyl	*p*-Cl		5.62	3.72	1.79	2.86	6.90-8.40	8.68 (s, NH)	1656	3338
3Bd	Cyclohexyl	*p*-Cl		5.82	3.65	1.73	2.84	6.88-8.30	1.45 (2m, 11H,cyclohexyl); 8.85 (s, NH)	1660	3326
3Ca	Ph	*m*-Br		5.18	3.58	1.72	2.90	6.75-8.28	8.78 (s, NH)	1661	3350
3Cb	Naphthyl	*m*-Br		5.50	3.62	1.85	2.85	6.89-8.38	8.65 (s, NH)	1658	3346
3Cd	Cyclohexyl	*m*-Br		5.78	3.68	1.75	2.98	6.82-8.30	1.50 (2m, 11H,cyclohexyl); 8.72 (s, NH)	1660	3340
4Aa	Ph	*p*-CH$_3$		5.69	3.74	1.83	3.01	6.85-8.26	2.19 (s,3H, CH$_3$); 8.66 (s, NH)	1089	3335
4Ac	Benzyl	*p*-CH$_3$		5.70	3.72	1.78	2.43	6.80-8.25	2.25 (s, 3H, CH$_3$); 4.92 (d, 2H C$\underline{H}_2$Ph); 8.62 (s, NH)	1085	3343
4Ba	Ph	*p*-Cl		5.73	3.89	1.85	3.09	6.82-8.30	8.80 (s, NH); 9.20 (s, NH)	1087	3328
4Bc	Benzyl	*p*-Cl		5.59	3.85	2.02	3.08	6.99-8.48	4.75 9[illegible] (d, 2H C$\underline{H}_2$Ph); 9.82 (s, NH); 9.95 (s, NH)	1083	3444
4Ca	Ph	*m*-Br		5.79	3.89	1.83	3.01	6.82-8.32	8.78 (s, NH); 8.99 (s, NH)	1086	3401
4Cc	Benzyl	*m*-Br		5.78	3.90	1.90	3.10	6.70-8.35	4.7[illegible] (d, 2H C$\underline{H}_2$Ph); 8.82 (s, NH); 8.90 (s, NH)	1085	3343
5Aa	Ph	*p*-CH$_3$		5.60	3.50	1.20	2.87	6.95-8.18	2.30 (s, 3H, C$\underline{H}_3$); 4.12 (s, 2H, H-5')	1736	
5Ac	Benzyl	*p*-CH$_3$		5.48	3.55	1.10	2.88	6.90-8.30	2.31 (s, 3H, C$\underline{H}_3$); 3.74 (s, 2H, H-5') 4.86 (d, 2H C$\underline{H}_2$Ph)	1740	
5Ba	Ph	*p*-Cl		5.54	3.82	1.30	2.41	7.01-8.07	4.05 (s, 2H, H-5')	1739	
5Bc	Benzyl	*p*-Cl		5.79	3.62	1.28	2.92	6.82-8.25	4.12 (s, 2H, H-5'); 4.81 (d, 2H C$\underline{H}_2$Ph)	1738	
5Ca	Ph	*m*-Br		5.85	3.75	1.52	2.80	6.89-8.23	4.18 (s, 2H, H-5')	1736	
5Cc	Benzyl	*m*-Br		5.75	3.65	1.29	2.97	7.00-8.20	4.08 (s, 2H, H-5'); 4.87 (d, 2H C$\underline{H}_2$Ph)	1738	
6Aa	Ph	*p*-CH$_3$		5.58	3.72	1.10	2.85	7.00-8.25	2.25 (s, 3H, C$\underline{H}_3$); 4.30 (m, 4H, H-5' & H-6')	1733	
6Ac	Benzyl	*p*-CH$_3$		5.59	3.80	1.20	2.86	6.97-8.20	2.29 (s, 3H, C$\underline{H}_3$); 4.32 (m, 4H, H-5' & H-6'); 4.79 (s, 2H C$\underline{H}_2$Ph)	1717	
6Ba	Ph	*p*-Cl		5.73	3.75	1.31	2.90	6.85-8.20	4.32 (m, 4H, H-5' & H-6');	1737	
6Bc	Benzyl	*p*-Cl		5.50	3.68	1.30	2.92	6.90-8.23	4.59 (m, 4H, H-5' & H-6'); 4.83 (s, 2H C$\underline{H}_2$Ph)	1735	
6Ca	Ph	*m*-Br		5.78	3.82	1.20	2.85	6.85-8.20	4.45 (m, 4H, H-5' & H-6');	1720	
6Cc	Benzyl	*m*-Br		5.85	3.45	1.28	2.88	7.00-8.25	4.54 (m, 4H, H-5' & H-6'); 4.83 (s, 2H C$\underline{H}_2$Ph)	1730	
7Ac	Benzyl	*p*-CH$_3$	Br	5.72	3.68	1.30	2.75	6.90-8.25	2.20 (s, 3H, C$\underline{H}_3$); 4.38 (s, 2H C$\underline{H}_2$Ph)		
7Bc	Benzyl	*p*-Cl	Br	5.70	3.53	1.25	2.80	6.93-8.25	4.47 (s, 2H C$\underline{H}_2$Ph)		
7Ca	Ph	*m*-Br	Br	5.70	3.69	1.31	2.82	6.90-8.10			

a solutions in mixture of CDCl$_3$ and DMSO-d6; δ in ppm


(5Aa)
e·
m/z 592
m/z 527
m/z 487
m/z 413
m/z 337
m/z 324
m/z 308
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m/z 177
m/z 163
m/z 149
m/z 135
m/z 129
m/z 129
m/z 83
m/z 71
m/z 57
m/z 55

Fig. (1)

EXPERIMENTAL SECTION

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were obtained on a Magna FT 550 spectrophotometer using potassium bromide pellets . ^{1}H NMR spectra were obtained on a Varian EM 390 (90 MHz) spectrophotometer in the solvents as indicated . Chemical shifts are reported in ppm from TMS as internal standard and are given in δ unites. MS were obtained on a Kratos MS 30 . Elemental analyses were performed by Microanalysis unit. King Abdulaziz University, Jeddah,

Pyrazolobenzenesulfonylurea derivatives 3 (Table 2).

General method

A mixture of **2**[13] (10 mmol) and anhydrous potassium carbonate (20 mmol) in dry acetone (25 ml) was stirred and refluxed with the appropriate isocyanate (11 mmol) for 18 h . Acetone was removed under reduced pressure, and the solid residue was dissolved in water. The crude product was isolated by acidification with hydrochloric acid (2M) and purified by recrystallization from ethanol in needles.

Pyrazolobenzenesulfonylthiourea derivatives 4 (Table 2).

General method

A mixture of **2** (10 mmol) and anhydrous potassium carbonate (20 mmol) in dry acetone (25 ml) was stirred and refluxed for 1 h . At this temperature a solution of the appropriate isothiocyanate (15 mmol) in dry acetone (5 mL) was added dropwise . After the mixture was stirred and refluxed for 10 h, acetone was removed under reduced pressure, the solid mass was dissolved in water and acidified with HCl (2 M). The crude product was purified by recrystallization from methanol in needles .

3-Substituted-2-[p-(3-aryl-3,3a,4,5-tetrahydro[1,2-c]pyrazol-2-yl)benzene-sulfonylimino]-4-oxothiazolidines 5 (Table 2).

A solution of the appropriate thiourea derivative (10 mmol) in absolute ethanol (20 ml) was refluxed with ethyl bromoacetate (11 mmol) and sodium acetate (20 mmol) for 2 h . The reaction mixture was then cooled and poured into ice cold water and the product that separated was recrystallized from an ethanol-benzene mixture (3:1) as needles .

3-Substituted-2-[p-(3-aryl-3,3a,4,5-tetrahydro[1,2-c]pyrazol-2-yl)benzene-sulfonylimino)-4-oxo-5,6-dihydro-1,3-thiazines 6 (Table 2).

A solution of 4 (10 mmol) in absolute ethanol (20 ml) was refluxed with ethyl β-bromopropionate (10 mmol) and sodium acetate (20 mmol) for 2 h. The reaction mixture was then cooled and poured into water ; the precipitated thiazine was recrystallized from an ethanol-benzene mixture (3:1) as needles .

3-Substituted-5-aryl-4-phenyl-2-[p-(3-aryl-3,3a,4,5-tetrahydro[1,2-c]pyrazol-2-yl)- benzene sulfonyl imino]1,3-thiazolines 7(Table 2)

A solution of the corresponding thiourea derivative **4** (10 mmol) in absolute ethanol (20 mL) was refluxed with appropriate α-bromoacetophenone (11 mmol) for 3 h . The product that separated during heating was allowed to cool, filtered and recrystallized from ethanol as yellow needles.

Table 2: Physical and Analytical Data of Compounds 3-7

Compound No.	R	X	Y	Yield %	M.P °C	Molecular Formula	Calculated % / Found %			
							C	H	N	S
3Aa	Ph	*p*-CH$_3$		80	129	$C_{31}H_{28}N_4O_3S$	69.38 69.4	5.12 5.22	10.63 10.45	6.00 5.77
3Ab	Naphthyl	*p*-CH$_3$		82	233	$C_{35}H_{30}N_4O_3S$	71.41 71.67	5.23 5.21	9.42 9.56	5.65 5.46
3Ad	Cyclohexyl	*p*-CH$_3$		77	151	$C_{31}H_{34}N_4O_3S$	68.34 68.63	6.41 6.27	10.14 10.33	6.12 5.90
3Ba	Ph	*p*-Cl		78	157	$C_{30}H_{25}ClN_4O_3S$	64.38 64.69	4.67 4.49	9.93 10.06	5.96 5.75
3Bb	Naphthyl	*p*-Cl		77	239	$C_{34}H_{27}ClN_4O_3S$	67.43 67.27	4.53 4.45	9.00 9.23	5.23 5.28
3Bd	Cyclohexyl	*p*-Cl		78	202	$C_{30}H_{31}ClN_4O_3S$	63.87 64.00	5.62 5.51	10.10 9.96	5.81 5.69
3Ca	Ph	*m*-Br		76	152	$C_{30}H_{25}BrN_4O_3S$	59.97 59.90	4.45 4.16	9.01 9.23	5.26 5.32
3Cb	Naphthyl	*m*-Br		84	236	$C_{34}H_{27}BrN_4O_3S$	62.65 62.67	4.31 4.15	8.82 8.60	4.86 4.92
3Cd	Cyclohexyl	*m*-Br		73	245	$C_{30}H_{31}BrN_4O_3S$	59.64 59.31	4.96 5.11	9.31 9.22	5.00 5.27
4Aa	Ph	*p*-CH$_3$		78	188	$C_{31}H_{28}N_4O_2S_2$	67.63 67.39	4.96 5.07	10.21 10.15	11. 11.59
4Ac	Benzyl	*p*-CH$_3$		85	171	$C_{32}H_{30}N_4O_2S_2$	67.54 67.85	5.63 5.30	9.76 9.89	11.31 11.31
4Ba	Ph	*p*-Cl		84	220	$C_{30}H_{25}ClN_4O_2S_2$	63.00 62.88	4.13 4.37	9.56 9.78	11.52 11.18
4Bc	Benzyl	*p*-Cl		82	201	$C_{31}H_{27}ClN_4O_2S_2$	63.15 63.43	4.32 4.60	9.86 9.55	11.16 10.91
4Ca	Ph	*m*-Br		74	165	$C_{30}H_{25}BrN_4O_2S_2$	58.61 58.35	3.96 4.05	9.12 9.08	10.57 10.37
4Cc	Benzyl	*m*-Br		78	170	$C_{31}H_{27}BrN_4O_2S_2$	58.62 58.95	4.18 4.28	9.00 8.88	10.40 10.14
5Ac	Benzyl	*p*-CH$_3$		69	100	$C_{34}H_{30}N_4O_3S_2$	66.83 67.33	4.76 4.95	9.08 9.24	10.35 10.56
5Ba	Ph	*p*-Cl		62	230	$C_{32}H_{25}ClN_4O_3S_2$	62.42 62.69	4.12 4.08	9.06 9.14	10.13 10.45
5Bc	Benzyl	*p*-Cl		67	142	$C_{33}H_{27}ClN_4O_3S_2$	63.02 63.21	4.13 4.31	8.68 8.94	10.00 10.21
5Ca	Ph	*m*-Br		69	248	$C_{32}H_{25}BrN_4O_3S_2$	58.76 58.45	3.62 3.80	8.26 8.52	9.53 9.74
5Cc	Benzyl	*m*-Br		63	166	$C_{33}H_{27}BrN_4O_3S_2$	58.96 59.02	4.12 4.02	8.16 8.34	9.71 9.54
6Aa	Ph	*p*-CH$_3$		67	107	$C_{34}H_{30}N_4O_2S_2$	67.73 67.33	4.72 4.95	9.06 9.24	10.32 10.56
6Ac	Benzyl	*p*-CH$_3$		56.3	161	$C_{35}H_{32}N_4O_2S_2$	66.02 67.74	5.20 5.16	8.84 9.30	10.21 10.32
6Ba	Ph	*p*-Cl		64	145	$C_{33}H_{27}ClN_4O_3S_2$	63.55 63.21	4.41 4.31	8.62 8.94	10.00 10.21
6Bc	Benzyl	*p*-Cl		73	174	$C_{34}H_{29}ClN_4O_3S_2$	63.56 63.70	4.27 4.53	8.63 8.74	10.06 9.99
6Ca	Ph	*m*-Br		63	149	$C_{33}H_{27}BrN_4O_3S_2$	58.95 59.01	3.98 4.02	8.64 8.35	9.32 9.54
6Cc	Benzyl	*m*-Br		62.5	215	$C_{34}H_{29}BrN_4O_3S_2$	59.82 59.56	4.15 4.23	7.99 8.18	9.62 9.34
7Aa	Ph	*p*-CH$_3$	OCH$_3$	65	88	$C_{40}H_{34}N_4O_2S_2$	70.16 70.38	4.72 4.99	8.11 8.21	9.42 9.38
7Ac	Benzyl	*p*-CH$_3$	Br	66	98	$C_{40}H_{33}N_4O_2S_2$	63.87 64.43	4.21 4.43	7.40 7.52	8.30 8.59
7Ba	Ph	*p*-Cl	H	61	133	$C_{38}H_{29}ClN_4O_2S_2$	66.88 67.81	4.21 4.31	8.21 8.33	9.20 9.52
7Bc	Benzyl	*p*-Cl	Br	81	159	$C_{39}H_{30}BrClN_4O_2S_2$	60.98 61.14	7.19 7.31	3.96 4.18	8.06 8.36
7Ca	Ph	*m*-Br	Br	53	150	$C_{38}H_{28}BrN_4O_2S_2$	57.33 57.29	3.29 3.52	6.99 7.03	7.89 8.04
7Cc	Benzyl	*m*-Br	H	65	142	$C_{39}H_{31}BrN_4O_2S_2$	63.95 64.02	4.03 4.24	7.38 7.66	8.49 8.75

BIOLOGICAL TESTING

Compounds **1-7** were screened for their antibacterial and antifungal activity following agar-diffusion method[14], using Gram-positive bacteria Staphylococcus aureus and Gram-negative bacteria *Escherichia coli* . The antifungal testing was carried out against *Candida albicans* . A standard sterilised filter paper disc (5 mm dia) impregnated with the solution of compound in ethanol (0.1 ml^{-1}) was placed on agar plate seeded with the test organism . The plates were incubated for 24h at 37°c and the zone of inhibition of bacterial growth around the disc was measured. Their activity was compared with that displayed by some known antibiotics taken as standard at the same concentration of solvent.

ANTIMICROBIAL ACTIVITY

Antimicrobial testing of compounds[1-7] was carried out . From the screening results, it was evident that, on the whole, compounds **1A-D, 2B, 2D, 3Aa, 3Ab, 3Bd**, and **4Aa** showed weak activity against different strains of bacteria. Although these compounds (zone of inhibition7-11 mm) showed activity comparable to that of penicillin G (8 mm), and Bacitracin (0 mm), they are much less active than other antibiotics used (zone of inhibition 19-26 mm) (Table 3) However all compounds are not significantly active towards *Candida albicans* .

Table 3: Biological Activity

Type of organism	**Compound No. (I-Z) [a]**	**Antibiotics (I-Z)**
S. Coccus (Gram-positive)	1A(8mm), 1B(8mm), 1c(10mm) 1D(8mm),2B(9mm),2D(10mm) 3Aa(7mm),3Bd(7mm),4Aa(9mm)	Erythromycin (19mm), Carbenicilin (20mm), Amoxycilin (16mm), Gentamicin (24mm), Penicilin G (8mm), Bacitiracin (0.0mm),
E. Coli (Gram-negative)	1A(7mm),1B(11mm),1C(10mm), 1D(11mm),2B(8mm),3Aa(8mm), 3Ab(7mm), 4Aa(10mm)	Erythromycin (20mm), Carbenicilin (26mm), Amoxycilin (21mm), Gentamicin (22mm), Penicilin G (8mm), Bacitiracin (0.0mm),

[a] The other tested compounds were inactive against all tested organisms; I.Z = inhibition zone in mm

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