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SYNTHESIS AND ANTIMICROBIAL STUDIES OF NEW PYRIDINE DERIVATIVES

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2-(p-Acetylaminobenzenesulfonylamido)-substituted benzothiazoles were prepared from 2-amino-substituted benzothiazoles and p-acetamidobenzenesulfonyl chloride using a mixture of pyridine and Ac_2O, which formed an electrophilic N-acetyl- pyridinium complex facilitating condensation to give the desired products by removal of HCl. 2-[4-(Substituted benzothiazol-2-yl)aminosulfonylanilino]pyridine-3-carboxylic acids (synthesized from 2-chloropyridine-3-carboxylic acid and the corresponding substituted 2-(p-aminobenzenesulfonylamido)benzothiazole in 2-ethoxyethanol using Cu-powder and K_2CO_3) were then converted to acid chlorides, which on further reaction with piperazine and 4-methoxyphenylpiperazine yielded the corresponding 2-[4-(substituted benzothiazol-2-yl)amino-sulfonyl]anilino-3-(piperazinocarbonyl) pyridine and 2-[4-(substituted benzothiazol-2-yl)amino-sulfonyl]anilino-3-[(4-methoxyphenyl)piperazin-1-yl-carbonyl]pyridine. The structures of the new compounds have been established on the basis of their elemental analyses as well as IR, ^{1}H NMR, and mass-spectral data. All the compounds have been screened for antimicrobial activity and found to possess considerable antibacterial activity.

Keywords: N- and ring-substituted 2-aminobenzothiazoles, 2-chloropyridine-3-carboxylic acid, 2-ethoxyethanol, piperazine, antimicrobial activity.

The role played by organic chemistry in the pharmaceutical industry continues to be one of the main drivers in the drug discovery process. A pyridine nucleus played a central role in the development of different medical agents such as antimicrobial [1], antiviral [2], anticancer [3], antidepressants, anti-inflammatory, and analgesic [4]. 2-Aminobenzothiazole and its derivatives possess versatile activities like antibacterial [5], antifungal [6], and antitubercular [7] activities. Piperazine and its derivatives show a wide range of biological properties such as antiulcer [8], antidepressant [9], and antibacterial [10, 11].

Searching for new biologically active compounds, we have continued our previous work on 2-chloropyridine-3-carboxylic acid [12-15] with substituted benzothiazole in position 2 and piperazine in position 3 of the pyridine nucleus, encouraged by recent literature observations. The synthetic part of this work is presented in Scheme 1.

Elemental analyses, IR, ^{1}H NMR, and mass spectral studies characterized the constitution of the compounds synthesized (Tables 1-3). Thus, the IR spectra of compounds **6a,c,g,h,k** possess characteristic bands around 3435 cm^{-1} for the N–H stretching, 3130-3070 cm^{-1} (broad) for the O–H stretching, 1680 cm^{-1} for

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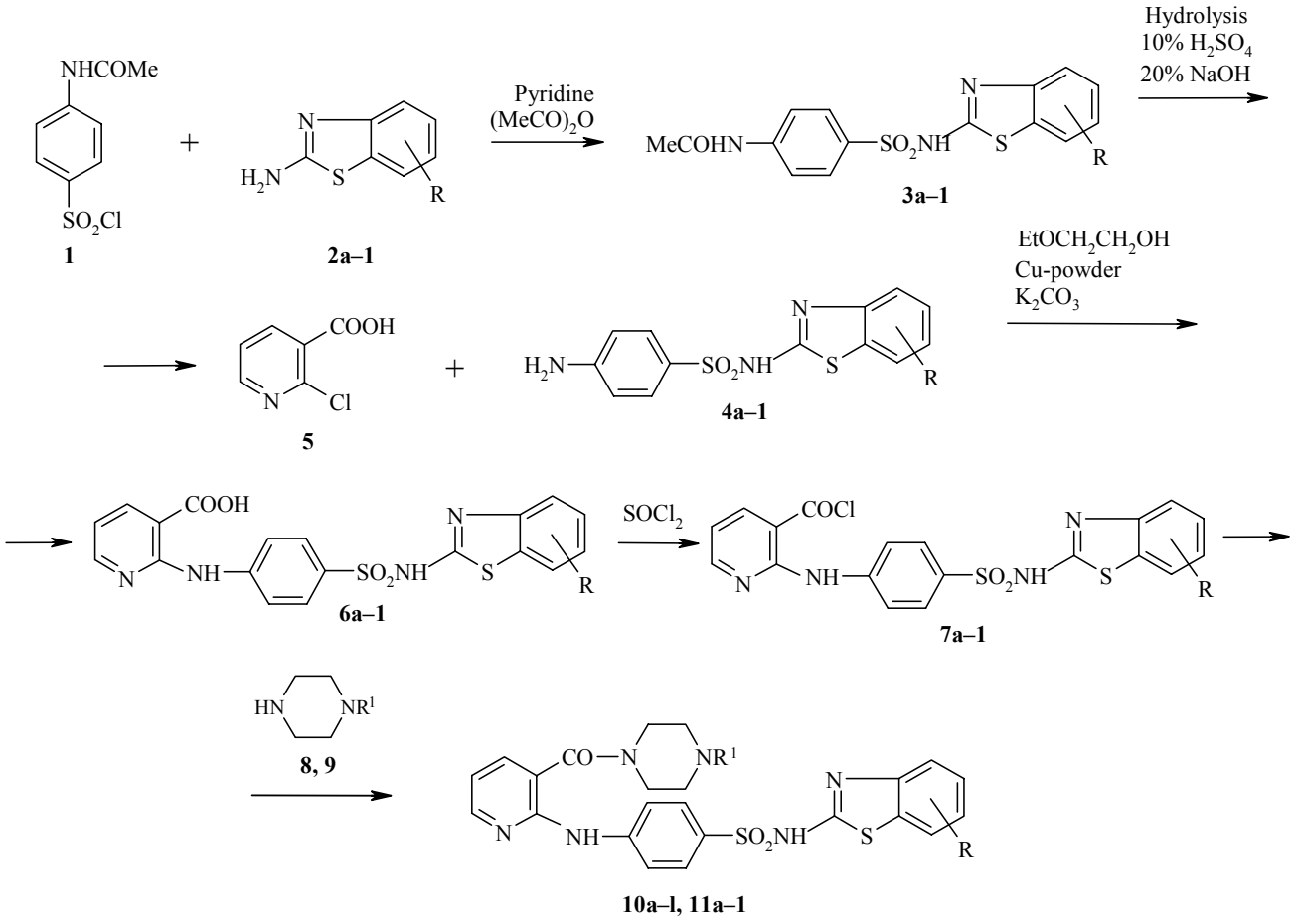
the carbonyl group, and 1450 cm^{-1} for the C–S stretching of thiazole. Their ^1H NMR spectra indicated a broad singlet around δ 13.6 ppm for COOH attached in position 3 of the pyridine ring and a sharp singlet around 8.5 ppm for the SO_2NH.

Scheme 1



2–4, 6, 7, 10, 11 a R = H, **b** R = 4-NO_2, **c** R = 5-NO_2, **d** R = 6-NO_2, **e** R = 4-Cl, **f** R = 5-Cl, **g** R = 6-Cl, **h** R = 4-Me, **i** R = 5-Me, **j** R = 6-Me, **k** R = 4-OMe, **l** R = 6-OMe;
8, 10a-l R^1 = H; **9, 11a-l** R^1 = 4-$MeOC_6H_4$

The structures were also proved by the mass spectra, which gave molecular ion peaks at *m/z* 426, 471, 460, 440, and 456 for **6a,c,g,h,k**, respectively.

Acids **6a-l** on a treatment (*via* acid chlorides) with piperazine (**8**) or 4-(4-methoxyphenyl)piperazine (**9**) yielded compounds **10a-l** and **11a-l**, respectively. Their structures were also confirmed by spectral studies.

The absence of broad absorption bands for O–H stretching in the IR spectrum and the absence of a sharp broad singlet for COOH in the ^1H NMR spectrum confirmed the formation of new amide derivatives **10a-l** and **11a-l**. Their mass spectra contain peaks at *m/z* 494, 539, 528, 508, 524 for **10a,d,g,i,k** and at *m/z* 600, 645, 638, 615, 630 for **11a,c,g,h,l**, corresponding to their molecular ions, respectively. All the spectra showed a common peak at *m/z* 78, corresponding to the pyridinyl cation (see mass spectral fragmentation pattern in Schemes 2 and 3).

TABLE 1. Characteristics of compounds **2a–l**, **4a–l, 6a–l, 10a–l,**and **11a–l**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
1	2	3	4	5	6	7
2a	$C_7H_6N_2S$	55.95 / 55.97	4.00 / 4.03	18.61 / 18.65	147	74
2c	$C_7H_5N_3O_2S$	43.05 / 43.07	2.56 / 2.58	21.48 / 21.53	120	72
2g	$C_7H_5ClN_2O_2S$	38.79 / 38.81	2.30 / 2.33	12.95 / 12.93	198	70
2h	$C_8H_8N_2S$	58.50 / 58.51	4.89 / 4.91	17.00 / 17.06	119	71
2l	$C_8H_8N_2OS$	53.27 / 53.31	4.42 / 4.47	15.50 / 15.54	133	72
4a	$C_{13}H_{11}N_3O_2S_2$	51.10 / 51.13	3.59 / 3.63	13.75 / 13.77	210	62
4d	$C_{13}H_{10}N_4O_4S_2$	44.50 / 44.55	2.81 / 2.87	15.95 / 15.98	215	60
4g	$C_{13}H_{10}ClN_3O_2S_2$	45.94 / 45.96	2.94 / 2.97	12.34 / 12.38	204	61
4i	$C_{14}H_{13}N_3O_2S_2$	52.63 / 52.65	4.08 / 4.11	13.11 / 13.16	216	57
4k	$C_{14}H_{13}N_3O_3S_2$	50.11 / 50.14	3.86 / 3.90	12.49 / 12.53	206	57
6a	$C_{19}H_{14}N_4O_4S_2$	53.49 / 53.52	3.30 / 3.31	13.13 / 13.15	234	66
6b	$C_{19}H_{13}N_5O_6S_2$	48.35 / 48.40	2.77 / 2.78	14.81 / 14.86	245	61
6c	$C_{19}H_{13}N_5O_6S_2$	48.38 / 48.40	2.74 / 2.78	14.85 / 14.86	256	67
6d	$C_{19}H_{13}N_5O_6S_2$	48.36 / 48.40	2.75 / 2.78	14.84 / 14.86	240	59
6e	$C_{19}H_{13}ClN_4O_4S_2$	49.49 / 49.52	2.79 / 2.84	12.14 / 12.15	267	60
6f	$C_{19}H_{13}ClN_4O_4S_2$	49.47 / 49.52	2.80 / 2.84	12.11 / 12.15	228	61
6g	$C_{19}H_{13}ClN_4O_4S_2$	49.50 / 49.52	2.78 / 2.84	12.10 / 12.15	248	63
6h	$C_{20}H_{16}N_4O_4S_2$	54.50 / 54.54	3.60 / 3.65	12.68 / 12.72	267	58
6i	$C_{20}H_{16}N_4O_4S_2$	54.48 / 54.54	3.64 / 3.65	12.69 / 12.72	198	60
6j	$C_{20}H_{16}N_4O_4S_2$	54.49 / 54.54	3.59 / 3.65	12.70 / 12.72	223	64
6k	$C_{20}H_{16}N_4O_5S_2$	52.58 / 52.63	3.49 / 3.53	12.25 / 12.28	252	68
6l	$C_{20}H_{16}N_4O_5S_2$	52.60 / 52.63	3.50 / 3.53	12.24 / 12.28	272	65
10a	$C_{23}H_{22}N_6O_3S_2$	55.81 / 55.85	4.44 / 4.48	16.97 / 16.99	251	61
10b	$C_{23}H_{21}N_7O_5S_2$	51.16 / 51.20	3.88 / 3.92	18.15 / 18.17	195	53
10c	$C_{23}H_{21}N_7O_5S_2$	51.18 / 51.20	3.90 / 3.92	18.18 / 18.17	211	62
10d	$C_{23}H_{21}N_7O_5S_2$	51.17 / 51.20	3.87 / 3.92	18.16 / 18.17	239	59
10e	$C_{23}H_{21}ClN_6O_3S_2$	52.20 / 52.22	3.98 / 4.00	15.88 / 15.89	261	54
10f	$C_{23}H_{21}ClN_6O_3S_2$	52.17 / 52.22	3.96 / 4.00	15.85 / 15.89	197	55
10g	$C_{23}H_{21}ClN_6O_3S_2$	52.19 / 52.22	3.97 / 4.00	15.90 / 15.89	234	63
10h	$C_{24}H_{24}N_6O_3S_2$	56.62 / 56.67	4.75 / 4.76	16.48 / 16.52	259	64
10i	$C_{24}H_{24}N_6O_3S_2$	56.65 / 56.67	4.74 / 4.76	16.53 / 16.52	267	60
10j	$C_{24}H_{24}N_6O_3S_2$	56.66 / 56.67	4.75 / 4.76	16.49 / 16.52	270	62

TABLE 1 (continued)

1	2	3	4	5	6	7
10k	$C_{24}H_{24}N_6O_4S_2$	54.91 54.95	4.60 4.62	16.00 16.02	218	51
10l	$C_{24}H_{24}N_6O_4S_2$	54.93 54.95	4.58 4.62	16.01 16.02	255	60
11a	$C_{30}H_{28}N_6O_4S_2$	59.96 59.98	4.68 4.70	13.97 13.99	210	55
11b	$C_{30}H_{27}N_7O_6S_2$	55.76 55.80	4.20 4.22	15.15 15.18	232	59
11c	$C_{30}H_{27}N_7O_6S_2$	55.77 55.80	4.18 4.22	15.14 15.18	194	61
11d	$C_{30}H_{27}N_7O_6S_2$	55.75 55.80	4.16 4.22	15.16 15.18	274	63
11e	$C_{30}H_{27}ClN_6O_4S_2$	56.70 56.73	4.25 4.28	13.19 13.23	225	59
11f	$C_{30}H_{27}ClN_6O_4S_2$	56.69 56.73	4.26 4.28	13.21 13.23	243	53
11g	$C_{30}H_{27}ClN_6O_4S_2$	56.71 56.73	4.27 4.28	13.18 13.23	210	60
11h	$C_{31}H_{30}N_6O_4S_2$	60.55 60.57	4.89 4.92	13.66 13.67	185	59
11i	$C_{31}H_{30}N_6O_4S_2$	60.52 60.57	4.90 4.92	13.60 13.67	277	66
11j	$C_{31}H_{30}N_6O_4S_2$	60.53 60.57	4.88 4.92	13.62 13.67	260	58
11k	$C_{31}H_{30}N_6O_5S_2$	59.00 59.03	4.78 4.80	13.30 13.32	180	60
11l	$C_{31}H_{30}N_6O_5S_2$	59.01 59.03	4.77 4.80	13.27 13.32	249	61

TABLE 2. IR spectra of compounds **2a,d,e,i,l**, **4a,d,g,i,k**, and **6a,c,g,h,k**

Com-pound	ν, cm^{-1}
1	2
2a	3424, 3252 (NH_2), 1347 (C–N), 1652 (C=N), 1450 (Bt*)
2d	3455, 3228 (NH_2), 1346 (C–N), 1655 (C=N), 1450 (Bt), 1563, 1322 (NO_2, *asym*, *sym*)
2e	3428, 3212 (NH_2), 1648 (C=N), 1451 (Bt), 1337 (C–N), 752 (C–Cl)
2i	3440, 3244 (NH_2), 2966 (C–CH_3), 1638 (C=N), 1448 (Bt), 1340 (C–N)
2l	3420, 3242 (NH_2), 1648 (C=N), 1446 (Bt), 1338 (C–N), 1240 (C–OCH_3)
4a	3429, 3218 (NH_2), 1632 (C=N), 1444 (Bt), 1362 (S=O, *asym*), 1340 (C–N), 1150 (S=O, *sym*)
4d	3439, 3225 (NH_2), 1637 (C=N), 1556, (NO_2, *asym*), 1449 (Bt), 1366 (S=O, *asym*), 1344 (C–N), 1328 (NO_2, *sym*), 1148 (S=O, *sym*)
4g	3456, 3268 (NH_2), 1632 (C=N), 1445 (Bt), 1360 (S=O, *asym*), 1337 (C–N), 1135 (S=O, *sym*), 760 (C–Cl)
4i	3381, 3245 (NH_2), 2975 (C–CH_3), 1650 (C=N), 1454 (Bt), 1362 (S=O, *asym*), 1338 (C–N), 1144 (S=O, *sym*)
4k	3450, 3220 (NH_2), 1629 (C=N), 1447 (Bt), 1368 (S=O, *asym*), 1335 (C–N), 1140 (S=O, *sym*), 1255 (C–OCH_3)
6a	3430, 3228 (NH str), 3135–3076 (OH, str, br.), 1690 (C=O), 1488 (C–N, C–C ring str), 1448 (Bt), 1362 (S=O, *asym*), 1344 (C–N str), 1148 (S=O, *sym)*
6c	3430, 3235 (NH str), 3142–3030 (OH, str, br.), 1688 (C=O), 1477 (C–N, C–C ring str), 1451 (Bt), 1360 (S=O, *asym*), 1552, 1325 (NO_2, *asym*, *sym*), 1345 (C–N str), 1138 (S=O, *sym*)
6g	3424, 3236 (NH str), 3136-3044 (OH, str, br.), 1685 (C=O), 1470 (C–N, C–C ring str), 1448 (Bt), 1358 (S=O, *asym*), 1344 (C–N str), 1142 (S=O, *sym*), 756 (C–Cl)
6h	3432, 3224 (NH str), 3128–3078 (OH, str, br.), 2980 (C–CH_3), 1680 (C=O), 1472 (C–N, C–C ring str), 1450 (Bt), 1355 (S=O, *asym*), 1345 (C–N str), 1150 (S=O, *sym*)
6k	3422, 3228 (NH str), 3140–3026 (OH, str, br.), 1678 (C=O), 1475 (C–N, C–C ring str), 1450 (Bt), 1360 (S=O, *asym*), 1340 (C–N str), 1258 (C–OCH_3), 1148 (S=O, *sym*)

TABLE 2 (continued)

1	2
10a	3433, 3298 (NH str), 2926, 2842 (C–H str), 1682 (Amide-I), 1490 (C–N, C–C), 1451 (Bt), 1345 (S=O, *asym*), 1290 (C–N Ar), 1166 (S=O, *sym*), 1100 (C–N al)
10d	3428, 3308 (NH str), 2940, 2845 (C–H str), 1681 (Amide-I), 1488 (C–N, C–C), 1448 (Bt), 1350 (S=O, *asym*), 1290 (C–N Ar), 1166 (S=O, *sym*), 1102 (C–N al)
10g	3422, 3300 (NH str), 2933, 2852 (C–H str), 1680 (Amide-I), 1488 (C–N, C–C), 1451 (Bt), 1348 (S=O, *asym*), 1288 (C–N Ar), 1165 (S=O, *sym*), 1098 (C–N al)
10i	3430, 3311 (NH str), 2930, 2844 (C–H str), 1684 (Amide-I), 1492 (C–N, C–C), 1449 (Bt), 1352 (S=O, *asym*), 1282 (C–N Ar), 1169 (S=O, *sym*), 1094 (C–N al)
10k	3431, 3318 (NH str), 2942, 2851 (C–H str), 1678 (Amide-I), 1482 (C–N, C–C), 1450 (Bt), 1355 (S=O, *asym*), 1284 (C–N Ar), 1170 (S=O, *sym*), 1092 (C–N al)
11a	3418, 3315 (NH str), 2940, 2850 (C–H str), 1675 (Amide-I), 1484 (C–N, C–C), 1448 (Bt), 1350 (S=O, *asym*), 1279 (C–N Ar), 1161 (S=O, *sym*), 1099 (C–N al)
11c	3420, 3322 (NH str), 2933, 2845 (C–H str), 1678 (Amide-I), 1487 (C–N, C–C), 1450 (Bt), 1346 (S=O, *asym*), 1280 (C–N Ar), 1165 (S=O, *sym*), 1100 (C–N al)
11g	3429, 3295 (NH str), 2928, 2840 (C–H str), 1680 (Amide-I), 1486 (C–N, C–C), 1452 (Bt), 1348 (S=O, *asym*), 1286 (C–N Ar), 1164 (S=O, *sym*), 1098 (C–N al)
11h	3436, 3318 (NH str), 2922, 2838 (C–H str), 1681 (Amide-I), 1494 (C–N, C–C), 1448 (Bt), 1353 (S=O, *asym*), 1283 (C–N Ar), 1165 (S=O, *sym*), 1096 (C–N al)
11l	3427, 3310 (NH str), 2935, 2835 (C–H str), 1674 (Amide-I), 1480 (C–N, C–C), 1450 (Bt), 1351 (S=O, *asym*), 1288 (C–N Ar), 1168 (S=O, *sym*), 1100 (C–N al)

* Bt – benzothiazole.

TABLE 3. ^{1}H NMR spectra of compounds **2a,d,e,i,l, 4a,d,g,i,k,** and **6a,c,g,h,k**

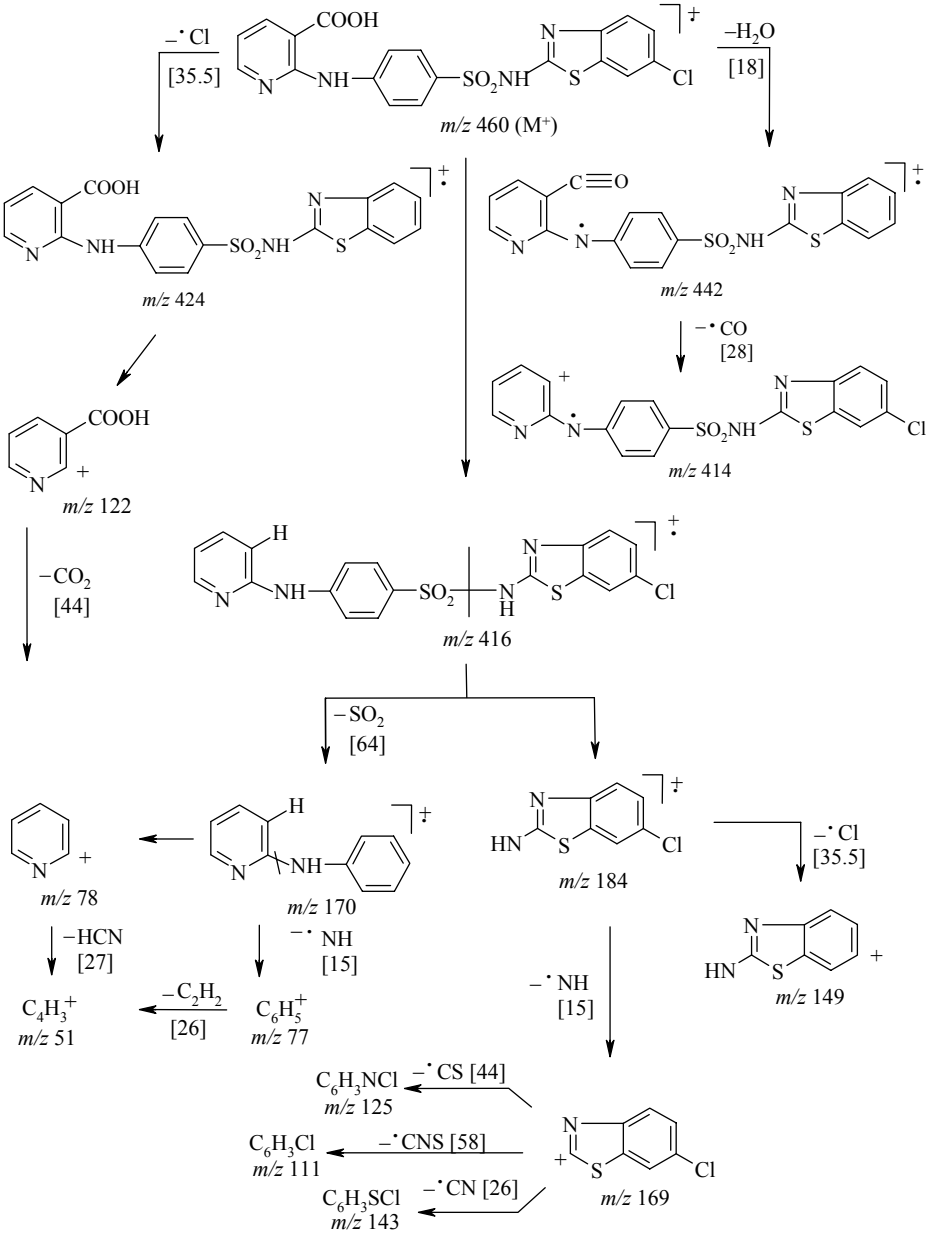
Com-pound	δ, ppm
1	2
2a	8.05-7.58 (4H, m, H Ar), 5.71 (2H, s, NH_2)
2d	8.10-7.52 (3H, m, H Ar), 5.80 (2H, s, NH_2)
2e	8.00-7.48 (3H, m, H Ar), 5.76 (2H, s, NH_2)
2i	8.08-7.50 (3H, m, H Ar), 5.78 (2H, s, NH_2), 2.35 (3H, s, CH_3)
21	8.12-7.60 (3H, m, H Ar), 5.71 (2H, s, NH_2), 3.90 (3H, s, OCH_3)
4a	8.50 (IH, s, SO_2NH), 7.947.10 (8H, m, H Ar), 5.75 (2H, s, NH_2)
4d	8.58 (IH, s, SO_2NH), 8.00-7.15 (7H, m, H Ar), 5.78 (2H, s, NH_2)
4g	8.60 (IH, s, SO_2NH), 7.967.12 (7H, m, H Ar), 5.76 (2H, s, NH_2)
4i	8.54 (IH, s, SO_2NH), 8.007.16 (7H, m, H Ar), 5.80 (2H, s, NH_2), 2.38 (3H, s, CH_3)
4k	8.52 (1H, s, SO_2NH), 7.927.00 (7H, m, H Ar), 5.74 (2H, s, NH_2), 3.80 (3H, s, OCH,)
6a	13.65 (IH, s, COOH), 10.68 (IH, s, NH), 8.50 (IH, s, SO_2NH), 8.11-7.20 (11H, m, H Py*, Ar)
6c	13.70 (IH, s, COOH), 10.74 (IH, s, NH), 8.58 (IH, s, SO_2NH), 8.15-7.14 (10H, m, H Py, Ar)
6g	13.65 (IH, s, COOH), 10.75 (IH, s, NH), 8.60 (IH, s, SO_2NH), 8.20-7.24 (10H, m, H Py, Ar)
6h	13.70 (IH, s, COOH), 10.70 (IH, s, NH), 8.58 (IH, s, SO_2NH), 8.22-7.15 (10H, m, H Py, Ar), 2.40 (3H, s, CH_3)
6k	13.77 (IH, s, COOH), 10.77 (IH, s, NH), 8.54 (IH, s, SO_2NH), 8.21-7.18 (10H, m, H Py, Ar), 3.87 (3H, s, OCH_3)
10a	10.60 (IH, s, NH), 9.25 (IH, s, NH), 8.58 (IH, s, SO_2NH), 8.20-7.38 (11H, m, H Py, Ar), 3.20-2.94 (8H, m, P)
l0d	10.58 (IH, s, NH), 9.32 (IH, s, NH), 8.60 (IH, s, SO_2NH), 8.22-7.35 (10H, m, H Py, Ar), 3.18-2.95 (8H, m, P)
10g	10.62 (IH, s, NH), 9.34 (IH, s, NH), 8.64 (IH, s, SO_2NH), 8.20-7.40 (10H, m, H Py, Ar), 3.15-2.90 (8H, m, P)
10i	10.62 (IH, s, NH), 9.35 (IH, s, NH), 8.65 (IH, s, $S0_2NH$), 8.18-7.30 (10H, m, H Py, Ar), 3.22-2.92 (8H, m, P), 2.44 (3H, s, CH_3)
10k	10.60 (IH, s, NH), 9.33 (IH, s, NH), 8.58 (IH, s, SO_2NH), 8.22-7.33 (10H, m, H Py, Ar), 3.90 (3H, s, OCH_3), 3.20–2.92 (8H, m, P)
11a	10.55 (IH, s, NH), 8.50 (IH, s, SOjNH), 8.16-7.40 (15H, m, Py, H Ar), 3.80 (3H, s, OCH_3), 3.12–2.88 (8H, m, P)

TABLE 3 (continued)

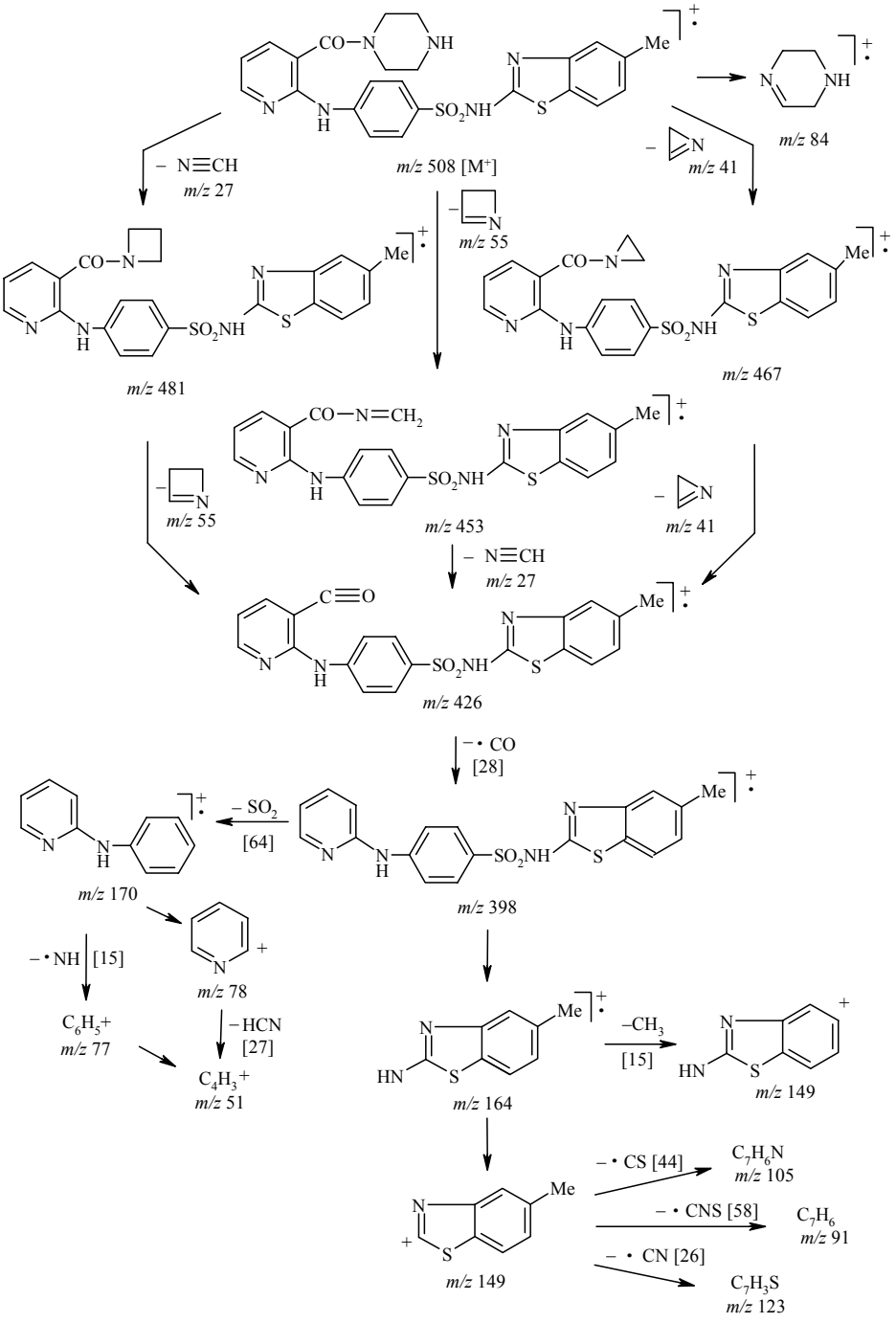
1	2
11c	10.62 (IH, s, NH), 8.54 (IH, s, SOjNH), 8.187.38 (14H, m, Py, H Ar), 3.86 (3H, s, OCH_3), 3.15-2.86 (8H, m, P)
11g	10.58 (IH, s, NH), 8.58 (IH, s, $S0_2NH$), 8.157.30 (14H, m, Py, H Ar), 3.90 (3H, s, OCH_3), 3.12-2.85 (8H, m, P)
11h	10.54 (IH, s, NH), 8.52 (IH, s, $S0_2NH$), 8.187.38 (14H, m, Py, H Ar), 3.92 (3H, s, OCH_3), 3.15-2.90 (8H, m, P), 2.48 (3H, s, CH_3)
11l	10.52 (IH, s, NH), 8.58 (IH, s, SO_2NH), 8.207.32 (14H, m, Py, H Ar), 3.94 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.142.88 (8H, m, P)

* Py – pyridine, P – piperazine.

Scheme 2



Scheme 3



The structure-activity relationship study of different pyridine derivatives revealed that the substitution of pyridine in position 3 has a marked influence on antimicrobial activity. This concept inspired us to synthesize compounds **10a-l** and **11a-l**, which were screened for antibacterial and antifungal activity against Gram-positive bacteria *Pseudomonas sp.* and *B. subtilis* and Gram-negative *Ceretium* and *E. coli* and against fungi *C. albicans* using a cup-plate method with DMF as a solvent [16]. The activity of compounds at 100 and 200 μg/ml concentrations was compared with *penicillin G*, *ampicillin*, *amoxicillin*, and *amphotericin B* as standard drugs. Table 5 summarizes the *in vitro* activity of new pyridine derivatives.

TABLE 4. MS data of compounds **6a,c,g,h,k, 10a-l, and 11a-l**

Com-pound	*m/z*
6a	426 [M^+], 408, 382, 380, 170, 150, 135, 122, 109, 91, 78, 77, 51
6c	471 [M^+], 453, 427, 426, 425, 195, 180, 170, 154, 149, 136, 122, 78, 77, 51
6g	460 [M^+], 442, 424, 416, 414, 184, 170, 169, 149, 143, 125, 122, 111, 78, 77, 51
6h	440 [M^+], 426, 422, 396, 394, 170, 164, 149, 123, 122, 105, 91, 78, 77, 51
6k	456 [M^+], 438, 426, 412, 410, 180, 170, 165, 149, 139, 122, 121, 107, 78, 77, 51
10a	494 [M^+], 467, 453, 439, 412, 384, 170, 150, 135, 109, 91, 84, 78, 77, 55, 51, 41, 27
10d	539 [M^+], 512, 498, 484, 457, 429, 195, 180, 170, 154, 149, 136, 122, 84, 78, 77, 55, 51, 41, 27
10g	528 [M^+], 501, 487, 473, 446, 418, 184, 170, 169, 150, 143, 125, 111, 84, 78, 77, 55, 51, 41, 27
10i	508 [M^+], 481, 467, 453, 426, 398, 170, 164, 149, 123, 105, 91, 84, 78, 77, 55, 51, 41, 27
10k	524 [M^+], 497, 483, 469, 442, 414, 180, 170, 165, 149, 139, 121, 107, 84, 78, 77, 55, 51, 41, 27
11a	600 [M^+], 494, 467, 453, 439, 412, 384, 192, 170, 150, 135, 109, 108, 91, 78, 77, 55, 51, 41, 27
11c	645 [M^+], 539, 512, 498, 484, 457, 429, 195, 192, 180, 170, 154, 149, 136, 122, 108, 78, 77, 55, 51, 41, 27
11g	638 [M^+], 528, 501, 487, 473, 446, 418, 192, 184, 170, 169, 150, 143, 125, 111, 108, 78, 77, 55, 51, 41, 27
11h	615 [M^+], 508, 481, 467, 453, 426, 398, 192, 170, 164, 149, 123, 108, 105, 91, 78, 77, 55, 51, 41, 27
11l	630 [M^+], 524, 497, 483, 469, 442, 414, 192, 180, 170, 165, 149, 139, 121, 108, 107, 78, 77, 55, 51, 41, 27

Compounds **10f,i,j,k**, **11c,e,k** displayed good activity against *Pseudomonas sp*; **10b,c,f,h,j,l, 11d,f,h –** against *B. subtilis*; **10a,h,i,j**, **11e,f,l –** against *E. coli*; **10e,g,k**, **11c,h,l –** against *Ceretium* when compared to *penicillin G* and a*moxicillin*. Compounds **10f,j,l**, **11e,h,k** showed good activity against *Pseudomonas sp*; **10c,f,h,i,l**, **11f,h –** against *B. subtilis*; **10a,g,h,j,l**, **11c,e,f –** against *E. coli*, and **10e,k**, **11d,h,k,l –** against *Ceretium* at a higher concentration. Compounds **10f,j**, **11e,h,k** were active against *Pseudomonas sp*; **10c,l**, **11f,h –** against *B. subtilis*; **10e,k**, **11h,l –** against *Ceretium*; and **10h,j**, **11f –** against *E. coli* in both the dilutions. All the compounds synthesized were sensitive against Gram-positive and Gram-negative bacteria.

Compounds **10g,j** and **11g,l** displayed good antifungal activity against *C. albicans*. Compounds **10g,j,l** and **11a,d,g,l** showed a satisfactory antifungal activity at a higher concentration, while others were moderate to less active.

Comparing these results with those of standard antibacterial and antifungal drugs, we concluded that most of the compound show moderate activity in the above tests. Compounds **10c,f,j,l** and **11c,f,h,l** against Gram-positive bacteria **10b,g,h,l** and **11c,f,j,l** against Gram-negative bacteria exhibited a higher value of antibacterial activity as compared with other substituted derivatives. The compounds with unsubstituted or chloro-substituted benzothiazole nucleus caused a good inhibition of *C. albicans* in both dilutions.

EXPERIMENTAL

Melting points were taken in open capillaries and are uncorrected. IR spectra were recorded on a Perkin-Elmer-843 spectrometer using KBr pellets. ^{1}H NMR spectra were scanned on a Bruker DPX-200 FT-NMR spectrometer using TMS as an internal standard and DMSO-d_6 as a solvent. The FAB mass spectra were recorded on a JEOL SX 102/DA-6000 mass spectrometer using argon/xenon as the FAB gas. The samples were routinely purified by crystallization from ethanol–benzene, 1:3.

TABLE 5. Antimicrobial data of compounds **10** and **11**

Compound	Activity (inhibition zone, mm), 100 and 200 μg/ml									
	Antibacterial								Antifungal	
	Gram-positive				Gram-negative					
	Pseudomonas sp.		*B. subtilis*		*Ceretium*		*E. coli*		*C. albicans*	
10a	4	6	7	8	2	5	8	12	2	8
10b	3	5	8	9	7	8	7	11	2	2
10c	2	8	10	16	1	2	3	4	1	1
10d	7	11	3	5	2	4	2	5	—	1
10e	—	5	2	6	10	15	2	11	5	9
10f	8	13	8	12	7	10	—	3	—	—
10g	4	12	—	5	8	11	7	13	6	11
10h	—	3	8	15	3	7	9	15	2	9
10i	9	10	7	13	3	6	8	10	1	8
10j	10	15	9	11	—	—	10	17	6	10
10k	8	9	3	7	9	17	—	4	5	9
10l	5	12	9	17	7	11	7	12	4	11
11a	2	5	3	6	3	5	8	11	5	10
11b	3	3	3	5	1	6	3	4	1	9
11c	8	11	7	8	8	10	7	13	—	1
11d	2	5	8	11	7	12	—	4	5	10
11e	8	12	—	—	3	4	8	12	1	2
11f	3	7	8	15	2	4	10	16	—	1
11g	—	1	7	10	—	3	3	7	6	11
11h	7	13	10	13	10	15	3	5	5	9
11i	2	4	2	3	3	4	—	3	1	1
11j	7	10	3	3	2	4	7	8	5	8
11k	8	12	—	1	7	12	1	3	2	8
11l	7	8	7	11	8	13	8	10	6	10
Penicillin G	12	21	14	25	13	22	14	25		
Ampicillin	15	28	17	30	18	31	18	30		
Amoxicillin	13	24	16	29	15	27	16	28		
Amphotericin B									8	18

2-Amino-6-chlorobenzothiazole (2g) [5]. To glacial AcOH (20 ml) precooled to 5°C, ammonium thiocyanate (0.08 mol) and *p*-chloroaniline (0.01 mol) were added. The mixture was placed into a freezing mixture of ice and salt, mechanically stirred, while 1.6 ml of bromine in 6 ml of glacial AcOH was added from a dropping funnel at such a rate that the temperature did not rise beyond 0°C. After all the bromine was added (105 min), the solution was stirred at 0°C for an additional 2 h and at room temperature for 10 h. Then it was allowed to stand overnight during which period an orange precipitate settled at the bottom, water (6 ml) was added quickly and the slurry was heated at 85°C on a steam bath and filtered off while hot. The orange residue was placed into the reaction flask and treated with 10 ml of glacial AcOH, heated again to 85°C and filtered off while hot. The combined filtrate was cooled and adjusted to pH 6 with concentrated ammonia solution. The dark-yellow precipitate formed was collected. Recrystallization from benzene (twice) after treatment with charcoal gave colorless plates of chlorobenzothiazole **2g**. Other compounds were prepared using the same method.

2-(*p*-Acetylaminobenzenesulfonylamino)-6-chlorobenzothiazole (3g) [6, 17]. Compound **2g** was taken in a mixture of pyridine (4 ml) and Ac_2O (20 ml). To the solution formed, *p*-acetylaminobenzenesulfonyl chloride (**1**) [18] (2.5 g, 0.01 mol) was added and the reaction mixture was kept on a water bath for 5 h, then filtered off and poured onto acidic crushed ice. The solid product **3g** obtained was recrystallized from ethanol.

2-[4-(6-Chlorobenzothiazol-2-yl)aminosulfonylanilino]pyridine-3-carboxylic Acid (6g) [19]. A mixture of 2-chloropyridine-3-carboxylic acid (**5**) (0.015 mol), 4-(*p*-aminobenzenesulfonylamino)-6-chloro-benzothiazole (**4g**) [20] (0.015 mol), anhydrous K_2CO_3 (0.01 mol), and copper powder (0.01 g) was refluxed in 2-ethoxyethanol (25 ml) under stirring in an oil bath at 140°C for 5 h. The cooled mixture was diluted with water, the precipitate formed was filtered off, and the resulting solution was acidified to pH 5 with diluted HCl, while product **6g** was precipitated. The latter was recrystallized from absolute alcohol. Similarly, other compounds can be prepared by using the same method.

2-[4-(6-Chlorobenzothiazol-2-yl)aminosulfonyl]anilino-3-(piperazinocarbonyl)pyridine (10g) (Tables 2, 4) [21]. 2-[4-(6-Chlorobenzothiazol-2-yl)aminosulfonyl]anilinopyridine-3-carbonyl chloride (**7g**) prepared from acid **6g** by the method reported [22] was dissolved in pyridine (10 ml) and the solution was cooled in an ice bath. To the stirred solution, fresh dried pyridine (5 ml) and piperazine (**8**) (0.01 mol) were successively added in small portions. The mixture was warmed at 70°C for 1.5 h. After the reaction was completed the solvent was removed by vacuum distillation. Crude product **10g** was recrystallized from EtOH–benzene, 1:3. Similarly, compounds **10a-f, h-l** were prepared. 2-[(4-Substituted benzothiazol-2-yl)-2-aminosulfonyl]anilino-3-[4-(4-methoxyphenyl)piperazin-1-ylcarbonyl]pyridines **11a–l** were prepared by the same procedure using 4-(4-methoxyphenyl)piperazine (**9**).

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