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# Synthesis of some biologically active 2,4'-bipyridine-5--carbonitriles carrying the 4-hydroxyphenylthio moiety

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*Abstract*: A series of new 4-aryl-2'-[(4-hydroxyphenyl)thio]-6oxo-1,6-dihydro-2,4'-bipyridine-5-carbonitriles (**3a**–**k**) and 6-amino-4aryl-2'-[(4-hydroxyphenyl)thio]-2,4'-bipyridine-5-carbonitriles (**4a**–**h**) were synthesized from 4-hydroxythiophenol (**1**). The reaction of 4-hydroxythiophenol with 4-acetyl-2-chloropyridine yielded 1-{2-[(4-hydroxyphenyl)thio]pyridin-4-yl}ethanone (**2**). Further treatment of **2** with ethyl cyanoacetate in the presence of ammonium acetate with various aromatic aldehydes furnished the compounds **3a**–**k**. On the other hand, condensation of **2** with aromatic aldehydes in the presence of alcoholic malononitrile in ammonium acetate gave compounds **4a**–**h**. The structures of the newly synthesized compounds were established on the basis of their elemental analysis, as well as their IR, $^{1}$H- and $^{13}$C-NMR and mass spectral data. All the title compounds were subjected to *in vitro* antibacterial testing against two strains and antifungal screening against two fungi. Some of the compounds showed promising activity.

*Keywords:* 2,4'-bipyridine-5-carbonitriles; 3-cynopyridines; antibacterial; antifungal.

## INTRODUCTION

The pyridine skeleton is of great importance to chemists as well as to biologists as it is found in a large variety of naturally occurring compounds and also in clinically useful molecules having diverse biological activities. Its derivatives are known to possess antitubercular,[1] anti-ulcer,[2] antimicrobial,[3–6] antineoplastic,[7] antitumor,[8–12] antiviral[13] and cardiotonic[14] properties. It has been well established that the presence of biologically active thiophenols is an important structural feature of a variety of synthetic drugs.[15–21] Encouraged by the above reports, it was planned to synthesize new 2,4'-bipyridine-5-carbonitriles carrying

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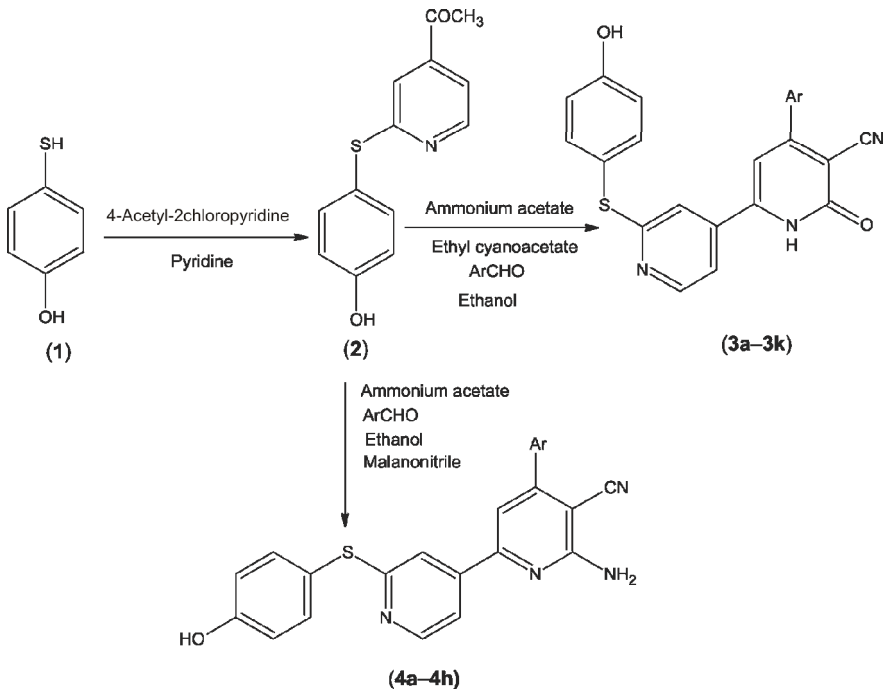
the 4-hydroxyphenylthio moiety, aiming at an investigation of new heterocycles of enhanced pharmacological activities. The present study describes the synthesis of hitherto unreported 4-aryl-2'-[(4-hydroxyphenyl)thio]-6-oxo-1,6-dihydro-2,4'--bipyridine-5-carbonitriles (**3a**–**k**) and 6-amino-4-aryl-2'-[(4-hydroxyphenyl)-thio]-2,4'-bipyridine-5-carbonitriles (**4a**–**h**) and an evaluation of their *in vitro* antibacterial and antifungal activities.

## RESULTS AND DISCUSSION

### *Chemistry*

The reaction sequences employed for the synthesis of the title compounds is shown in Scheme 1. The key intermediate, 1-{2-[(4-hydroxyphenyl)thio]pyridin--4-yl}ethanone (**2**), required for the preparation of the target compounds was obtained by the condensation 4-hydroxythiophenol (**1**) with 2-chloro-4-acetylpyridine in pyridine medium. The compound **2** on treatment with aromatic aldehydes in presence of ethyl cyanoacetate and ammonium acetate in ethanolic medium yielded the compounds 4-aryl-2'-[(4-hydroxyphenyl)thio]-6oxo-1,6-dihydro-2,4'--bipyridine-5-carbonitriles (**3a**–**k**). On the other hand, condensation of **2** with aromatic aldehydes in presence of alcoholic malononitrile in ammonium acetate gave 6-amino-4-aryl-2'-[(4-hydroxyphenyl)thio]-2,4'-bipyridine-5-carbonitriles (**4a**–**h**).




Scheme 1. The synthesis of the title compounds.

The structural elucidations of new compounds were based on their elemental analysis and spectral (IR, $^1$H- and $^{13}$C-NMR and mass) data. The characterization data of all the new compounds are summarized in Table I and their spectral data are given below.

TABLE I. Characterization data of compounds **3a**–**k** and **4a**–**h**

| Compd. | Aromatic moiety | Molecular formula | Yield % | M.p. °C | Elemental analysis Found (Calcd.), % | | |
|---|---|---|---|---|---|---|---|
| | | | | | C | H | N |
| **3a** | Phenyl | $C_{23}H_{15}N_3O_2S$ | 397.5 | >260 | 70.00 (69.50) | 3.91 (3.80) | 10.80 (10.57) |
| **3b** | 4-Chlorophenyl | $C_{23}H_{14}ClN_3O_2S$ | 432 | >260 | 64.00 (63.96) | 3.33 (3.27) | 10.00 (9.73) |
| **3c** | 3,4-Dimethoxyphenyl | $C_{25}H_{19}N_3O_4S$ | 457.5 | 238–240 | 65.70 (65.63) | 4.25 (4.19) | 9.20 (9.18) |
| **3d** | 3-Hydroxy-4-methoxyphenyl | $C_{24}H_{17}N_3O_4S$ | 443.5 | >260 | 65.50 (65.00) | 3.90 (3.86) | 9.52 (9.48) |
| **3e** | 4-*N*,*N*-Diethylamino-2-hydroxyphenyl | $C_{27}H_{24}N_4O_3S$ | 484.5 | >260 | 67.00 (66.92) | 5.02 (4.99) | 11.60 (11.56) |
| **3f** | 4-Methylphenyl | $C_{24}H_{17}N_3O_2S$ | 411.5 | >260 | 70.10 (70.05) | 4.18 (4.16) | 10.24 (10.21) |
| **3g** | 4-Methoxyphenyl | $C_{24}H_{17}N_3O_3S$ | 427.5 | >260 | 67.50 (67.43) | 4.00 (4.01) | 9.85 (9.83) |
| **3h** | 4-Biphenylyl | $C_{29}H_{19}N_3O_2S$ | 473.5 | >260 | 73.60 (73.55) | 4.10 (4.04) | 8.90 (8.87) |
| **3i** | 2-Amino-3-pyridyl | $C_{22}H_{15}N_5O_2S$ | 413.5 | >260 | 64.00 (63.91) | 3.70 (3.66) | 17.00 (16.94) |
| **3j** | 2,3,5-Trihydroxyphenyl | $C_{23}H_{15}N_3O_5S$ | 445.5 | >260 | 62.08 (62.02) | 3.42 (3.39) | 9.50 (9.43) |
| **3k** | 6-Methoxy-2-naphthyl | $C_{28}H_{19}N_3O_3S$ | 477.5 | 250–252 | 70.50 (70.42) | 4.00 (4.01) | 8.84 (8.80) |
| **4a** | 4-Chlorophenyl | $C_{23}H_{15}ClN_4OS$ | 431 | 230–232 | 64.14 (64.11) | 3.54 (3.51) | 13.10 (13.00) |
| **4b** | 4-Methoxyphenyl | $C_{24}H_{17}N_4O_2S$ | 426.5 | 210–12 | 67.62 (67.59) | 4.28 (4.25) | 13.20 (13.14) |
| **4c** | 3,4-Dimethoxyphenyl | $C_{25}H_{20}N_4O_3S$ | 456.5 | 205–07 | 65.80 (65.77) | 4.46 (4.42) | 12.30 (12.27) |
| **4d** | 4-Methylphenyl | $C_{24}H_{18}N_4OS$ | 410.5 | 230–32 | 70.30 (70.22) | 4.45 (4.42) | 13.70 (13.65) |
| **4e** | 3-Hydroxy-4-methoxyphenyl | $C_{24}H_{18}N_4O_3S$ | 442.5 | >260 | 65.20 (65.14) | 4.12 (4.10) | 12.70 (12.66) |
| **4f** | 4-Biphenylyl | $C_{29}H_{20}N_4OS$ | 472.5 | >260 | 73.80 (73.71) | 4.30 (4.27) | 11.90 (11.86) |
| **4g** | 2-Amino-3-pyridyl | $C_{22}H_{16}N_6OS$ | 429.5 | >260 | 64.00 (64.06) | 3.96 (3.91) | 20.40 (20.38) |
| **4h** | 2,3,5-Trihydroxyphenyl | $C_{23}H_{16}N_4O_4S$ | 444.5 | >260 | 59.80 (59.73) | 4.00 (3.92) | 12.20 (12.11) |

*2'-[(4-Hydroxyphenyl)thio]-6-oxo-4-phenyl-1,6-dihydro-2,4'-bipyridine-5-carbonitrile (**3a**)*. IR (KBr, $cm^{-1}$): 2912 (ArH), 2218 (C=N), 1640 (C=O), 1589 (C=C); $^1$H-NMR (DMSO-$d_6$, $\delta$ / ppm): 6.90 (2H, *d*, $C_3$–, $C_5$–H of hydroxyphenylthio), 7.41 (2H, *d*, $C_2$–, $C_6$–H of 4-hydroxyphenylthio), 7.60 (5H, *m*, aryl moiety), 7.70 (3H, *m*, of pyridines), 8.50 (1H, *d*, $C_6$–H of pyridine moiety), 10.00 (1H, *s*, phenolic OH), 13.00 (1H, *s*, NH of pyridine moiety). LC–MS (*m*/*z*): 398 (M, 100 %).

*4-(4-Chlorophenyl)-2'-[(4-hydroxyphenyl)thio]-6-oxo-1,6-dihydro-2,4'-bipyridine-5-carbonitrile (**3b**)*. IR (KBr, $cm^{-1}$): 2903 (ArH), 2217(C=N), 1717 (C=O), 1512 (C=C); $^1$H-NMR (DMSO-$d_6$, $\delta$ / ppm): 6.90 (2H, *d*, $C_3$–, $C_5$–H of hydroxyphenylthio), 7.40 (2H, *d*, $C_2$–, $C_6$–H of hydroxyphenylthio), 7.55–7.75 (7H, *m*, aromatic protons of pyridines and aryl moiety), 8.50 (1H, *d*, $C_6$–H of pyridine moiety), 10.00 (1H, *s*, phenolic OH), 13.00 (1H, *s*, NH of pyridine moiety); MS--FAB (*m*/*z*): 432 (M+1, 100 %), 431(M, 20 %), 415 (M–OH).

*4-(3,4-Dimethoxyphenyl)-2'-[(4-hydroxyphenyl)thio]-6oxo-1,6-dihydro-2,4'--bipyridine-5-carbonitrile (**3c**)*. IR (KBr, $cm^{-1}$): 2882 (ArH), 2206 (C=N), 1716 (C=O), 1498 (C=C); $^1$H-NMR (DMSO-$d_6$, $\delta$ / ppm): 3.80 (3H, *s*, $OCH_3$), 3.90 (3H, *s*, $OCH_3$), 6.85 (m, 4H, $C_3$–, $C_5$–H of hydroxyphenylthio, $C_2$–, $C_5$–H of aryl), 7.18 (1H, *d*, $C_6$–H of aryl), 7.36 (3H, *m*, aromatic protons of pyridines), 7.42 (2H, *d*, $C_2$–, $C_6$–H of hydroxyphenylthio), 8.54 (1H, *d*, $C_6$–H of pyridine), 10.00 (1H, *s*, phenolic OH), 13.00 (1H, *s*, NH of pyridine); MS-FAB (*m*/*z*): 458 (M+1, 100 %), 457 (M, 20 %).

*4-(3-Hydroxy-4-methoxyphenyl)-2'-[(4-hydroxyphenyl)thio]-6-oxo-1,6-dihydro-2,4'-bipyridine-5-carbonitrile (**3d**)*. IR (KBr, $cm^{-1}$): 2854 (ArH), 2220 (C=N), 1743 (C=O), 1515 (C=C); $^1$H-NMR (DMSO-$d_6$, $\delta$ / ppm): 4.0 (3H, s, $OCH_3$), 6.90 (2H, *d*, $C_3$–, $C_5$–H of hydroxyphenylthio), 7.40 (4H, *m*, $C_2$–, $C_5$–H of aryl, $C_2$–, $C_6$–H of hydroxyphenylthio), 7.42 (3H, *m*, aromatic protons of pyridine), 8.6 (1H, *d*, $C_6$–H of pyridine moiety), 10.00 (1H, *s*, phenolic OH), 13.00 (1H, *s*, NH of pyridine moiety); MS-FAB (*m*/*z*): 444 (M+1, 100 %).

*4-(4-*N,N*-Diethylamino-2-hydroxyphenyl)-2'-[(4-hydroxyphenyl)thio]-6oxo-1,6--dihydro-2,4'-bipyridine-5-carbonitrile (**3e**)*. IR (KBr, $cm^{-1}$): 2954 (ArH), 2225 (C=N), 1740 (C=O), 1510 (C=C); MS-FAB (*m*/*z*): 485 (M+1, 100 %), 484 (M, 40 %).

*2'-[(4-Hydroxyphenyl)thio]-4-(4-methylphenyl)-6-oxo-1,6-dihydro-2,4'-bipyridine-5-carbonitrile (**3f**)*. IR (KBr, $cm^{-1}$): 2913 (ArH), 2221 (C=N), 1638 (C=O), 1489 (C=C); $^1$H-NMR (DMSO-$d_6$, $\delta$ / ppm): 2.40 (3H, *s*, $CH_3$), 6.90 (2H, *d*, $C_3$–, $C_5$–H of hydroxyphenylthio), 7.35 (2H, *d*, $C_2$–, $C_6$–H of hydroxyphenylthio), 7.44–7.60 (7H, *m*, aromatic protons of phenyl and pyridine), 8.5 (1H, *d*, $C_6$–H of pyridine moiety), 9.90 (1H, *s*, phenolic OH), 12.90 (1H, *s*, NH of pyridine moiety).

*2'-[(4-Hydroxyphenyl)thio]-4-(4-methoxyphenyl)-6-oxo-1,6-dihydro-2,4'-bipyridine-5-carbonitrile (**3g**)*. IR (KBr, $cm^{-1}$): 2903 (ArH), 2217 (C=N), 1717 (C=O), 1512 (C=C); $^1$H-NMR (DMSO-$d_6$, $\delta$ / ppm): 3.85 (3H, *s*, $OCH_3$), 6.90 (2H, *d*, $C_3$–, $C_5$–H of hydroxyphenylthio), 7.10 (2H, *d*, $C_2$–, $C_6$–H of hydroxyphenylthio), 7.20 (2H, *d*, methoxyphenyl), 7.42 (2H, *d*, methoxyphenyl) 7.7 (3H, *m*, pyridine), 8.5 (1H, *d*, $C_6$–H of pyridine moiety), 12.90 (1H, *s*, phenolic OH), 13.00 (1H, *s*, NH of pyridine moiety).

*4-(4-Biphenylyl)-2'-[(4-hydroxyphenyl)thio]-6-oxo-1,6-dihydro-2,4'-bipyridine-5-carbonitrile (**3h**)*. IR (KBr, $cm^{-1}$): 2934 ($CH_3$), 2221 (C=N), 1644 (C=O), 1585 (C=C), 1489 (C=C); $^1$H-NMR (DMSO-$d_6$, $\delta$ / ppm): 6.90 (2H, *d*, $C_3$–, $C_5$–H of hydroxyphenylthio), 7.40 (2H, *d*, $C_2$–, $C_6$–H of hydroxyphenylthio), 7.45––7.90 (12H, *m*, aromatic protons biphenyl and pyridine), 8.50 (1H, *d*, $C_6$–H of pyridine moiety), 10.00 (1H, *s*, phenolic OH), 13.00 (1H, *s*, NH of pyridine moiety).

*4-(2-Amino-3-pyridyl)--2'-[(4-hydroxyphenyl)thio]-6-oxo-1,6-dihydro-2,4'-bipyridine-5-carbonitrile (**3i**)*. IR (KBr, $cm^{-1}$): 3450 ($NH_2$), 2948 (ArH), 2236 (C=N), 1675 (C=O), 1611 (C=C), 1561 (C=C); $^1$H-NMR (DMSO-$d_6$, $\delta$ / ppm): 6.90 (2H, *d*, $C_3$–, $C_5$–H of hydroxyphenylthio), 7.20 (2H, *m*, $C_2$–, $C_6$–H of hydroxyphenylthio), 7.42 (4H, *m*, protons of pyridines), 8.0 (1H, *d*, $C_6$–H of 2-amino-3-pyridyl moiety), 8.6 (1H, *d*, $C_6$–H of pyridine moiety), 10.00 (1H, *s*, phenolic OH), 13.00 (1H, *s*, NH of pyridine moiety).

*2'-[(4-Hydroxyphenyl)thio]-6-oxo-4-(2,3,5-trihydroxyphenyl)-1,6-dihydro--2,4'-bipyridine-5-carbonitrile (**3j**)*. IR (KBr, $cm^{-1}$): 2922 (ArH), 2224 (C=N), 1672 (C=O), 1589 (C=C), 1510 (C=C).

*2'-[(4-Hydroxyphenyl)thio]-4-(6-methoxy-2-naphthyl)-6-oxo-1,6-dihydro--2,4'-bipyridine-5-carbonitrile (**3k**)*. IR (KBr, $cm^{-1}$): 2936 (ArH), 2220 (C=N), 1658 (C=O), 1579 (C=C), 1488 (C=C); $^1$H-NMR (DMSO-$d_6$, $\delta$ / ppm): 3.90 (3H, *d*, $OCH_3$), 6.9–8.0 (14H, *m*, aromatic protons), 8.6 (1H, *d*, $C_6$–H of pyridine moiety), 10.00 (1H, *s*, phenolic OH), 12.90 (1H, *s*, NH of pyridine moiety).

*6-Amino-4-(4-chlorophenyl)-2'-[(4-hydroxyphenyl)thio]-2,4'-bipyridine-5-carbonitrile (**4a**)*. IR (KBr, $cm^{-1}$): 3468 ($NH_2$), 2216 (CN), 1579 and 1494 (C=C); $^1$H-NMR (DMSO-$d_6$, $\delta$ / ppm): 6.90 (2H, *d*, $C_3$–, $C_5$–H of hydroxyphenylthio), 7.40 (2H, *d*, $C_2$–, $C_6$–H of hydroxyphenylthio), 7.55–7.75 (7H, *m*, aromatic protons of pyridines and aryl moiety), 8.50 (1H, *d*, $C_6$–H of pyridine moiety), 10.00 (1H, *s*, phenolic OH); MS-FAB (*m*/*z*): 432 (M+1, 90 %), 431(M, 10 %).

*6-Amino-2'-[(4-hydroxyphenyl)thio]-4-(4-methoxyphenyl)-2,4'-bipyridine-5--carbonitrile (**4b**)*. IR (KBr, $cm^{-1}$): 3425 ($NH_2$), 2970 ($CH_3$), 2211(C=N), 1494 (C=C); $^1$H-NMR (DMSO-$d_6$, $\delta$ / ppm): 3.85 (3H, *s*, $OCH_3$), 6.85 (2H, *d*, $C_3$–, $C_5$–H of hydroxyphenylthio), 7.18 (2H, *d*, $C_3$–, $C_5$–H of aryl), 7.36 (4H, *m*, $C_2$–, $C_6$–H of hydroxyphenylthio, $C_2$–, $C_6$–H of aryl), 7.6 (2H, *d*, aromatic protons of

pyridine), 7.90 (1H, *s*, $C_3$–H of pyridine), 8.52 (1H, *d*, $C_6$–H of pyridine moiety), 10.00 (1H, *s*, phenolic OH).

*6-Amino-4-(3,4-dimethoxyphenyl)-2'-[(4-hydroxyphenyl)thio]-2,4'-bipyridine-5-carbonitrile (**4c**)*. IR (KBr, $cm^{-1}$): 3630 (OH), 3337 ($NH_2$), 2970 ($CH_3$), 2207 (C=N), 1515 (C=C); $^1$H-NMR (DMSO-$d_6$, $\delta$ / ppm): 3.8 (3H, *s*, $OCH_3$), 3.9 (3H, *s*, $OCH_3$), 6.90 (4H, *m*, $C_3$–, $C_5$–H of hydroxyphenylthio, $C_2$–, $C_5$–H of 4-aryl), 7.22 (1H, *d*, $C_6$–H of 4-aryl), 7.36 (3H, *m*, aromatic protons of pyridine), 7.42 (2H, *d*, $C_2$, $C_6$–H of hydroxyphenylthio), 8.54 (1H, *d*, $C_6$–H of pyridine), 10.00 (1H, *s*, phenolic OH); MS-FAB (*m*/*z*): 457(M, 10 %).

*6-Amino-2'-[(4-hydroxyphenyl)thio]-4-(4-methylphenyl)-2,4'-bipyridine-5-carbonitrile (**4d**)*. IR (KBr, $cm^{-1}$): 3416 ($NH_2$), 2919 ($CH_3$), 2206 (C=N), 1547 (C=C); $^1$H-NMR (DMSO-$d_6$, $\delta$ / ppm): 2.40 (3H, *s*, $CH_3$), 6.90 (2H, *d*, $C_3$–, $C_5$–H of hydroxyphenylthio), 7.30 (2H, *d*, $C_2$–, $C_6$–H of hydroxyphenylthio), 7.42––7.70 (7H, *m*, aromatic protons phenyl and pyridine), 8.60 (1H, *d*, $C_6$–H of pyridine moiety), 10.00 (1H, *s*, phenolic OH).

*6-Amino-4-(3-hydroxy-4-methoxyphenyl)-2'-[(4-hydroxyphenyl)thio]-2,4'-bipyridine-5-carbonitrile (**4e**)*. IR (KBr, $cm^{-1}$): 3349 ($NH_2$), 2935 ($CH_3$), 2199 (C=N), 1555 (C=C); $^1$H-NMR (DMSO-$d_6$, $\delta$ / ppm): 4.0 (3H, *s*, $OCH_3$), 6.90 (2H, *d*, $C_3$–, $C_5$–H of hydroxyphenylthio), 7.30 (2H, *d*, $C_2$–, $C_6$–H of hydroxyphenylthio), 7.42 (6H, *m*, aromatic protons of aryl and pyridine), 8.65 (1H, *d*, $C_6$–H of pyridine moiety), 10.00 (1H, *s*, phenolic OH); MS-FAB (*m*/*z*): 444 (M+1, 100 %).

*6-Amino-4-(4-biphenylyl)-2'-[(4-hydroxyphenyl)thio]-2,4'-bipyridine-5-carbonitrile (**4f**)*. IR (KBr, $cm^{-1}$): 3416 ($NH_2$), 2954 (ArH), 2214 (C=N), 1575 (C=C), 1490 (C=C); $^1$H-NMR (DMSO-$d_6$, $\delta$ / ppm): 6.90 (2H, *d*, $C_3$–, $C_5$–H of hydroxyphenylthio), 7.30 (2H, *d*, $C_2$–, $C_6$–H of hydroxyphenylthio), 7.42–7.90 (12H, *m*, aromatic protons biphenyl and pyridine), 8.60 (1H, *d*, $C_6$–H of pyridine moiety), 10.00 (1H, *s*, phenolic OH).

*6-Amino-4-(2-amino-3-pyridyl)-2'-[(4-hydroxyphenyl)thio]-2,4'-bipyridine--5-carbonitrile (**4g**)*. IR (KBr, $cm^{-1}$): 3449 ($NH_2$), 2934 (ArH), 2197 (C=N), 1497 (C=C); $^1$H-NMR (DMSO-$d_6$, $\delta$ / ppm): 6.90 (2H, *d*, $C_3$–, $C_5$–H of hydroxyphenylthio), 7.20 (2H, *m*, $C_2$–, $C_6$–H of hydroxyphenylthio), 7.42 (4H, *m*, protons of pyridines), 8.0 (1H, *d*, $C_6$–H of 2-amino-3-pyridyl moiety), 8.50 (1H, *d*, $C_6$–H of pyridine moiety), 10.00 (1H, *s*, phenolic OH).

*6-Amino-2'-[(4-hydroxyphenyl)thio]-4-(2,3,5-trihydroxyphenyl)-2,4'-bipyridine-5-carbonitrile (**4h**)*. IR (KBr, $cm^{-1}$): 3410 ($NH_2$), 2926 (ArH), 2210 (C=N), 1487 (C=C); $^1$H-NMR (DMSO-$d_6$, $\delta$ / ppm): 5.90 (1H, *s*, $C_4$–H of 2,3,5-trihydroxyphenyl), 6.16 (1H, *s*, $C_4$–H of 2,3,5-trihydroxyphenyl), 6.90 (2H, *d*, $C_3$–, $C_5$–H of hydroxyphenylthio), 7.20 (2H, *d*, $C_2$–, $C_6$–H of hydroxyphenylthio), 7.42 (3H, *m*, protons of pyridine), 8.50 (1H, *d*, $C_6$–H of pyridine moiety), 10.00 (1H, *s*, phenolic OH).

The formation 1-{2-[(4-hydroxyphenyl)thio]pyridin-4-yl}ethanone (**2**) was confirmed by FTIR, $^1$H-NMR, $^{13}$C-NMR and elemental analyses. The IR spectrum of **2** exhibited absorption bands at 3066, 1700 and 1587 cm$^{-1}$ due to $CH_3$, C=O and aromatic C=C stretching frequencies, respectively. Its $^1$H-NMR spectrum showed singlets at $\delta$ 2.45, 7.17 and 9.48 ppm, which are due to $CH_3$, pyridine proton and hydroxyl proton, respectively. Further, doublets at 6.93 and 7.48 ppm are due to the aromatic protons of the 4-hydroxyphenylthio group, while the doublets at 7.35 and 8.55 ppm are due to protons of the pyridine nucleus. Its $^{13}$C--NMR spectrum showed peaks at 26.07, 116.28, 116.73, 117.04, 117.40, 136.73, 142.88, 149.72, 158.67, 164.48 and 196.54 ppm, which are due to $CH_3$, $C_1$ of 4-hydroxyphenylthio, $C_3$ and $C_5$ of 4-hydroxyphenylthio, $C_3$ of pyridine, $C_5$ of pyridine, $C_2$ and $C_6$ of 4-hydroxyphenylthio, $C_4$ of pyridine, $C_6$ of pyridine, $C_4$ of 4-hydroxyphenylthio, $C_2$ of pyridine and C=O, respectively. It was observed that the peaks due to quaternary carbons disappeared on DEPT experimentation.

The build up of 2'-[(4-hydroxyphenyl)thio]-6-oxo-4-phenyl-2,4'-bipyridine--5-carbonitrile (**3a**) was established on the basis of FTIR, $^1$H-NMR, $^{13}$C-NMR, mass spectral and elemental analyses. Its IR spectrum exhibited peaks at 2920, 2218, 1640 and 1590 cm$^{-1}$ due to stretching frequencies of $CH_3$, C≡N, C=O and C=C groups, respectively. Its $^1$H-NMR spectrum exhibited two doublets at $\delta$ 6.90 and 7.41 ppm, due to the presence of the 4-hydroxyphenylthio moiety, and one multiplet for five protons at 7.60 ppm due to phenyl group at the position 4. Also, it appeared as a multiplet at 7.70 ppm, integrating for three protons, due to the pyridine rings and a doublet at 8.5 ppm due to the $C_6$–H of pyridine. The OH and pyridine –NH protons appeared at $\delta$ 10.00 and 13.00 ppm, respectively. The LC––mass spectrum displayed the molecular ion peak at *m*/*z* 398.1 (M+1, 100 %), which is in agreement with the molecular formula $C_{23}H_{15}N_3O_2S$.

The structure of 6-amino-4-chlorophenyl-2'-[(4-hydroxyphenyl)thio]-2,4'-bipyridine-5-carbonitrile (**4a**) was established on the basis of FTIR, $^1$H-NMR, mass spectral and elemental analyses. The IR spectrum exhibited peaks at 3468, 2216 and 1579 cm$^{-1}$, which are due to the presence of $NH_2$, CN and C=C groups, respectively. The $^1$H-NMR spectrum exhibited doublets at $\delta$ 6.90 and 7.40 ppm, which are due to the four protons of the 4-hydroxyphenylthio moiety. The appearance of a multiplet at 7.55–7.75 ppm is due to seven aromatic protons of the pyridines and aryl moiety. Furthermore, the appearance of a doublet at $\delta$ 8.50 ppm is due to $C_6$–H of the pyridine moiety. In addition, the proton of the hydroxyl group resonates at $\delta$ 10 ppm as a broad singlet. The FAB mass spectrum showed the molecular ion peak at *m*/*z* 431(M+1, 100 %), which is in accordance with the molecular formula $C_{23}H_{15}ClN_4OS$.

*Biological screening*

*Antibacterial activity*. All the title compounds, **3a**–**k** and **4a**–**h**, were evaluated for their *in vitro* antibacterial activity against two bacteria, *viz*., *Staphylococcus aureus* and *Escherichia coli*, using the cup plate method.[22,23] The solvent, *N*,*N*-dimethylformamide, showed no zone of inhibition. The activities were compared with the known standard drug gentamycin, used at a concentration of 1000 ppm. The results are summarized in Table II.

TABLE II. Antimicrobial activity of the title compounds

| Compound | Zone of inhibition, mm | | | |
|---|---|---|---|---|
| | Antibacterial activity | | Antifungal activity | |
| | *Staphylococcus aureus* | *Escherichia coli* | *Aspergillus niger* | *Candida albicans* |
| **3a** | 16 | 17 | 20 | 22 |
| **3b** | 18 | 15 | 18 | 14 |
| **3c** | 12 | 14 | 20 | 16 |
| **3d** | 16 | 14 | 18 | 19 |
| **3e** | 10 | 12 | 21 | 20 |
| **3f** | 20 | 21 | 16 | 19 |
| **3g** | 17 | 22 | 22 | 23 |
| **3h** | 14 | 16 | 20 | 22 |
| **3i** | 17 | 15 | 20 | 18 |
| **3j** | 13 | 12 | 15 | 14 |
| **3k** | 14 | 15 | 17 | 16 |
| **4a** | 14 | 16 | 19 | 20 |
| **4b** | 16 | 12 | 17 | 16 |
| **4c** | 17 | 15 | 16 | 18 |
| **4d** | 16 | 16 | 15 | 12 |
| **4e** | 18 | 14 | 19 | 18 |
| **4f** | 14 | 16 | 20 | 22 |
| **4g** | 15 | 17 | 21 | 18 |
| **4h** | 17 | 13 | 14 | 16 |
| Standard (flucanazole) | – | – | 25 | 24 |
| Standard (gentamycin) | 21 | 23 | – | – |

Results of antibacterial studies revealed that compounds **3f** and **3g** showed fairly good activity against both the strains, while compounds **4b**, **4e** and **4g** showed good activity against *S. aureus*, and the remaining compounds exhibited moderate activity, compared to the standard gentamycin. The enhanced antibacterial activity in the compounds is attributed to the presence of 4-methylphenyl and 4-methoxyphenyl groups at the position 4 of the pyridine ring.

*Antifungal activity*. All the title compounds, **3a**–**k** and **4a**–**h**, were screened for their *in vitro* antifungal activity against *Aspergillus niger* and *Candida albicans* using the cup plate method.[22,23] The solvent, *N*,*N*-dimethylformamide

showed no zone of inhibition. The activities were compared with the known standard drug flucanazole, used at a concentration of 1000 ppm. The results are tabulated in Table II.

The results of the antifungal screening showed that compounds **3a**, **3e**, **3g**, **3h**, **4a**, **4f** and **4h** displayed good activity against both fungal strains, which were comparable with the standard flucanazole. Compounds **3b**, **3c**, **3d**, **3k** and **4e** showed good activity against *A. niger*, while the remaining compounds exhibited moderate activity when compared to flucanazole. It was noticed that the presence of the phenyl, *N*,*N*-diethylamino-2-hydroxyphenyl, 4-methoxyphenyl, 4-chlorophenyl, 4,4'-biphenyl-1-yl and 2-amino-3-pyridyl group at position 4 of the pyridine moiety led to increased antifungal activity.

## EXPERIMENTAL

The melting points were determined in open capillaries and are uncorrected (melting point apparatus: Serwell Instruments Inc., India). The purity of the compounds was checked by thin layer chromatography (TLC) on a silica-coated aluminum sheet (silica gel $60F_{254}$) using chloroform and methanol (9:1, v/v). The IR spectra were recorded on a Nicolet Avatar 330-FTIR spectrometer. The $^1$H- and $^{13}$C-NMR spectra were recorded on a Varian 300 MHz NMR spectrometer using TMS as the internal standard. The chemical shifts ($\delta$) are reported in ppm and the signals are described as singlet (*s*), doublet (*d*), triplet (*t*), quartet (*q*), broad (*br*) and multiplet (*m*). The FAB mass spectra were recorded on a Jeol SX 102/DA-6000 spectrophotometer/data system using argon/xenon (6 KV, 10 mA) FAB gas, at 70 eV. Elemental analysis was carried out using a Flash EA 1112 Series, CHNSO analyzer (Thermo). The solvents and reagents were purchased from commercial venders in the appropriate grade and were used without purification.

*Procedure for the preparation of 1-{2-[(4-hydroxyphenyl)thio]pyridin-4-yl}ethanone (**2**)*

A mixture of 12.6 g (0.10 mol) of 4-hydroxythiophenol (**1**) and 18.7 g (0.12 mol) of 2-chloro-4-acetylpyridine in 10 mL pyridine was heated under reflux for 8 h. After the reaction, the pyridine was evaporated under reduced pressure and the reaction mixture was diluted with water. The product was extracted with ethyl acetate and the extract was concentrated to 1/4$^{th}$ of the volume. The resulting solution was left overnight at room temperature. Solid product was collected by filtration, and finally recrystallized from ethyl acetate.

IR (KBr, cm$^{-1}$): 3066 ($CH_3$), 1700 (C=O), 1587 (Ar); $^1$H-NMR ($CDCl_3$+DMSO-$d_6$, $\delta$ / ppm): 2.45 (3H, *s*, $CH_3$), 6.93 (2H, *d*, $C_3$–, $C_5$–H of hydroxyphenylthio, $J$ = 8.72 Hz), 7.17 (1H, *s*, $C_3$–H of pyridine), 7.35 (2H, *d*, $C_5$–H of pyridine), 7.48 (2H, *d*, $C_2$–, $C_6$–H of hydroxylphenylthio), 8.55 (1H, *d*, $C_6$–H of pyridine), 9.48 (1H, *s*, OH of phenyl); $^{13}$C-NMR ($CDCl_3$+ + DMSO-$d_6$, $\delta$ / ppm): 26.07 ($CH_3$), 116.28 ($C_1$ of 4-hydroxyphenylthio), 116.73 ($C_3$ and $C_5$ of 4-hydroxyphenylthio), 117.04 ($C_3$ of pyridine), 117.4 ($C_5$ of pyridine), 136.73 ($C_2$ and $C_6$ of 4-hydroxyphenylthio), 142.88 ($C_4$ of pyridine), 149.72 ($C_6$ of pyridine), 158.67 ($C_4$ of 4-hydroxyphenylthio), 164.48 ($C_2$ of pyridine), 196.54 (carbonyl).

*General procedure for the preparation of 4-aryl- -2'-[(4-hydroxyphenyl)thio]-6-oxo-1,6- -dihydro-2,4'-bipyridine-5-carbonitriles (**3a**–**k**)*

A mixture of 1-{2-[(4-hydroxyphenyl)thio]pyridin-4-yl}ethanone (**2**) (1.0 mmol), an aromatic aldehyde (1.0 mmol), ethyl cyanoacetate (1.0 mmol), ammonium acetate (4.0 mmol) and 5.0 mL ethanol was heated at reflux for 10 h. The reaction mixture was left overnight and the separated solids were filtered and recrystallized from ethanol.

*General procedure for the preparation of 6-amino-4-aryl-2'-[(4-hydroxyphenyl)thio]-2,4'--bipyridine-5-carbonitriles (**4a**–**h**)*

A mixture of 1-{2-[(4-hydroxyphenyl)thio]pyridin-4-yl}ethanone (**2**) (1.0 mmol), an aromatic aldehyde (1.0 mmol), malononitrile (1.0 mmol), ammonium acetate (4.0 mmol) and 10 mL of ethanol was heated at reflux for 6 h. The reaction mixture was left overnight and the separated solids were filtered and recrystallized from ethanol.

## CONCLUSIONS

The successful syntheses of two series of heterocyclic title compounds and an evaluation of the antimicrobial activity of the new pyridines containing the 4-hydroxyphenylthio group were reported. From the results of the antimicrobial screening, it can be concluded that compound **3g** was found to be active against both bacteria and fungi. The activity is due to the presence of 4-methoxyphenyl group in the structure.

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## ИЗВОД

## СИНТЕЗА НЕКИХ БИОЛОШКИ АКТИВНИХ 2,4'-БИПИРИДИН-5-КАРБОНИТРИЛА КОЈИ САДРЖЕ 4-ХИДРОКСИФЕНИЛТИО ГРУПУ

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Серија нових 4-арил-2'-[(4-хидроксифенил)тио]-6-оксо-1,6-дихидро-2,4'-бипиридин-5--карбонитрила (**3a**–**k**) и 6-амино-4-арил-2'-[(4-хидроксифенил)тио]-2,4'-бипиридин-5-карбонитрила (**4a**–**h**) синтетизована је из 4-хидрокситиофенола (**1**). У реакцији 4-хидрокситиофенола са 4-ацетил-2-хлоропиридином добијен је 1-{2-[(4-хидроксифенил)тио]пиридин-4-ил}-етанон (**2**). Третирањем једињења **2** са етил-цијаноацетатом у присуству амонијум-ацетата са различитим ароматичним алдехидима добијена су једињења **3a**–**k**. С друге стране, једињење **2** кондензацијом са ароматичним алдехидима у присуству алкохолног раствора малононитрила у амонијум-ацетату наградило је једињења **4a**–**h**. Структуре нових једињења утврђене се на основу елементалне анализе, IR, $^1$H и $^{13}$C-NMR и MS спектралних података. Антибактеријска активност насловљених једињења, као и антифунгална активност тестирана је *in vitro* на два соја, односно два типа гљивица. Нека једињења показују охрабрујућу активност.

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