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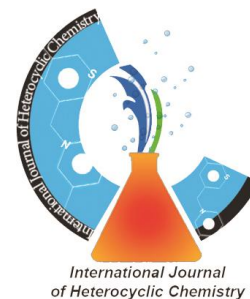
## Research article

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

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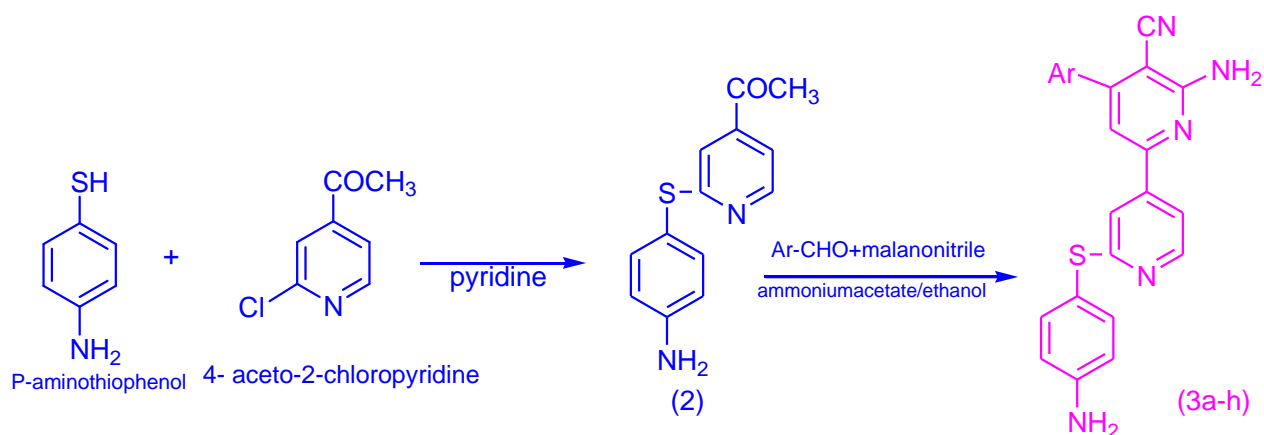
**Keywords:** 2,4'-bipyridine-5-carbonitriles, 3-cynopyridines, antibacterial, antifungal.

**Abstract:** A series of new 6-amino-4aryl-2'-[(4-Aminophenyl)thio]-2,4'-bipyridine-5-carbonitriles (**3a-h**) were synthesized from 4-aminothiophenol (**1**). The reaction of 4-aminothiophenol with 4-acetyl-2-chloropyridine yielded 1-{2-[(4-aminophenyl)thio]pyridin-4-yl}ethanone(**2**). Further treatment of **2** with aromatic aldehydes in the presence of alcoholic malanonitrile in ammonium acetate gave compounds (**3a-h**). The structures of the newly synthesized compounds were established on the basis of their elemental analysis, as well as their IR and <sup>1</sup>H-NMR 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.

### 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 clinically useful molecules having diverse biological activities. Its derivatives are known to possess antitubercular,<sup>1</sup> antiulcer,<sup>2</sup> antimicrobial<sup>3-6</sup> antineoplastic,<sup>7</sup> antitumor,<sup>8-12</sup> antiviral<sup>13</sup> and cardiotoxic<sup>14</sup> properties. It has been well established that the presence of biologically active thiophenols is an important structural feature of a variety of synthetic drugs.<sup>15-21</sup> Encouraged by the above reports, it was planned to synthesize new 4-aminophenylthio moiety, aiming at an investigation of new heterocycles of enhanced pharmacological activities. The present study describes the synthesis of 6-amino-4-aryl-2'-[(4-aminophenyl)-thio]-2,4'-bipyridine-5-carbonitriles (**3a-h**) and an evaluation of their *in vitro* antibacterial and antifungal activities.

### Scheme 1. The synthesis of the title compounds.



## EXPERIMENTAL

The melting points were determined in open capillaries and are uncorrected (melting point apparatus). The purity of the compounds was checked by thin layer chromatography (TLC) on a silica-coated aluminum sheet (silica gel 60F254) using chloroform and methanol (9:1, v/v).

The IR spectra were recorded on a simandzu 8000s -FTIR spectrometer. The  $^1\text{H}$ - NMR spectra were recorded on a Varian 300 MHz NMR spectrometer using DMSO 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) multiplet (m). The elemental analysis was carried out using a Flash EA 1112 Series, CHNSO analyzer (Thermo). The solvents and reagents were purchased from commercial vendors in the appropriate grade and were used without purification.

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

A mixture of 12.6 g (0.10mol) of 4-aminothiophenol (1) and 18.7 g (0.12 mol) of 4-acetyl-2-chloropyridine 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  $1/4^{\text{th}}$  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,  $\text{cm}^{-1}$ ): 3066 ( $\text{CH}_3$ ), 1700 ( $\text{C}=\text{O}$ ), 1587 (Ar);  $^1\text{H}$ -NMR ( $\text{CDCl}_3+\text{DMSO}-d_6$ ,  $\delta$  ppm): 2.45 (3H, s,  $\text{CH}_3$ ), 6.93 (2H, d,  $\text{C}_3$ -,  $\text{C}_5$ -H of aminophenylthio), 7.17 (1H, s,  $\text{C}_3$ -H of pyridine), 7.35 (2H, d,  $\text{C}_5$ -H of pyridine), 7.48 (2H, d,  $\text{C}_2$ -,  $\text{C}_6$ -H of aminophenylthio), 8.55 (1H, d,  $\text{C}_6$ -H of pyridine).

### **General procedure for the preparation of 6-amino-4-aryl-2'-[(4-aminophenyl)thio]-2,4'-bipyridine-5-carbonitriles (3a-h)**

A mixture of 1-{2-[(4-aminophenyl)thio]pyridin-4-yl}ethanone (2) (1.0 mol), an substituted aromatic aldehyde (1.0 mol), malanonitrile (1.0 mol), ammonium acetate (4.0 mol) 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.

## 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-aminophenyl)thio]pyridin-4-yl}ethanone (**2**), required for the preparation of the target compounds was obtained by the condensation 4-aminothiophenol (**1**) with 2-chloro-4-acetylpyridine in pyridine medium. The compound **2** on treatment with aromatic aldehydes in presence of alcoholic malanitrile in ammonium acetate gave 6-amino-4-aryl-2'-[(4-aminophenyl)thio]-2,4'-bipyridine-5-carbonitriles (**3a-h**). The structural elucidations of new compounds were based on their elemental analysis and spectral (IR and <sup>1</sup>H-NMR) 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-h.

Compd.	Aromatic moiety	Mole. formula	Mole. wt.	M.P. <sup>0</sup> C	Elemental analysis found (calcd.)%		
					C	H	N
3a	4-chlorophenyl	C <sub>23</sub> H <sub>16</sub> N <sub>5</sub> SCl	431.88	231	63.96(63.94)	3.73(3.70)	16.43(16.41)
3b	4-methoxyphenyl	C <sub>24</sub> H <sub>19</sub> N <sub>5</sub> SO	426.451	210	67.59(67.54)	4.48(4.47)	16.64(16.61)
3c	3,4-dimethoxyphenyl	C <sub>25</sub> H <sub>21</sub> N <sub>5</sub> SO <sub>3</sub>	456.475	206	65.78(65.74)	4.63(4.60)	15.55(15.54)
3d	4-methylphenyl	C <sub>24</sub> H <sub>19</sub> N <sub>5</sub> S	410.452	231	70.23(70.20)	4.66(4.63)	17.29(17.27)
3e	3-Hydroxy-4-methoxy phenyl	C <sub>25</sub> H <sub>16</sub> N <sub>5</sub> SO <sub>2</sub>	454.463	261	66.06(66.04)	4.21(4.20)	15.62(15.60)

3f	4-chlorophenyl	C <sub>23</sub> H <sub>16</sub> N <sub>5</sub> SCl	431.88	231	63.96(63.94)	3.73(3.70)	16.43(16.41)
3g	phenyl	C <sub>23</sub> H <sub>17</sub> N <sub>5</sub> S	396.427	208	69.68(69.65)	4.31(4.25)	17.90(17.79)
3h	4-nitrophenyl	C <sub>23</sub> H <sub>16</sub> N <sub>6</sub> SO <sub>2</sub>	441.43	251	63.58(63.54)	3.63(3.60)	19.03(19.00)

### Spectral data of synthesized compounds (3a - h):

**6-Amino-4-(4-chlorophenyl)-2'-[(4-aminophenyl)thio]-2,4'-bipyridine-5-carbonitrile (3a).** IR (KBr, cm<sup>-1</sup>): 3468 (NH<sub>2</sub>), 2216 (CN), 1579 and 1494 (C=C); <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, δ/ppm): 6.90 (2H, d, C<sub>2</sub>-, C<sub>3</sub>-H of aminophenyl thio), 7.40 (2H, d, C<sub>5</sub>-, C<sub>6</sub>-H of aminophenylthio), 7.55–7.75 (7H, d, aromatic protons of pyridines and aryl moiety), 8.50 (1H, d, C<sub>6</sub>-H of pyridine moiety), 4.00 (2H, s, amino H).

**6-Amino-4'-[(4-methoxyphenyl)-2-(4-aminophenyl)-2,4'-bipyridine-5-carbonitrile (3b).** IR (KBr, cm<sup>-1</sup>): 3420 (NH<sub>2</sub>), 2960 (CH<sub>3</sub>), 2221 (C=N), 1464 (C=C); <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, δ / ppm): 3.80 (3H, s, -OCH<sub>3</sub>), 6.85 (2H, d, C<sub>3</sub>, C<sub>5</sub>-H of aminophenylthio), 7.18 (2H, d, C<sub>3</sub>-, C<sub>5</sub>-H of aryl), 7.36 (4H, m, C<sub>2</sub>-, C<sub>6</sub>-H of aminophenylthio, C<sub>2</sub>, C<sub>6</sub>, H of aryl), 7.6 (2H, d, aromatic protons of pyridine), 7.90 (1H, s, C<sub>3</sub>, H of pyridine), 8.52 (1H, d, C<sub>6</sub>, H of pyridine moiety), 4.10 (1H, s, amino H).

**6-Amino-4-(3,4-dimethoxyphenyl)-2'-[(4-aminophenyl)thio]-2,4'-bipyridine-5-carbonitrile (3c).** IR (KBr, cm<sup>-1</sup>): 3635 (OH), 3337 (NH<sub>2</sub>), 2976 (CH<sub>3</sub>), 2217 (C=N), 1510 (C=C); <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, δ ppm): 3.6 (3H, s, -OCH<sub>3</sub>), 3.8 (3H, s, -OCH<sub>3</sub>), 6.89 (4H, m, C<sub>3</sub>-, C<sub>5</sub>-H of aminophenylthio, C<sub>2</sub>-, C<sub>5</sub>-H of 4-aryl), 7.20 (1H, d, C<sub>6</sub>-H of 4-aryl), 7.26 (3H, m, aromatic protons of pyridine), 7.42 (2H, d, C<sub>2</sub>, C<sub>6</sub>-H of aminophenylthio), 8.54 (1H, d, C<sub>6</sub>-H of pyridine), 4.03 (1H, s, amino H).

**6-Amino-4-[(4-methylphenyl)]-2,-(4'-aminophenylthio)-2,4'-bipyridine-5-carbonitrile (3d).** IR (KBr,  $\text{cm}^{-1}$ ): 3416 ( $\text{NH}_2$ ), 2919 ( $\text{CH}_3$ ), 2203 ( $\text{C}=\text{N}$ ), 1547( $\text{C}=\text{C}$ ) 2255 ( $-\text{CH}_3$ );  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ,  $\delta$  / ppm): 2.40 (3H, s,  $\text{CH}_3$ ), 6.90 (2H, d,  $\text{C}_3-$   $\text{C}_5$ -H of aminophenylthio), 7.30 (2H d,  $\text{C}_2-$ ,  $\text{C}_6$ -H of aminophenylthio), 7.42–7.70 (7H, m, aromatic protons phenyl and pyridine), 8.57 (1H, d,  $\text{C}_6$ -H of pyridine moiety).

**6-Amino-4-(3-hydroxy-4-methoxyphenyl)-2'-[(4-aminophenylthio)]-2,4'-bipyridine-5-carbonitrile (3e)** IR (KBr,  $\text{cm}^{-1}$ ): 3340 ( $\text{NH}_2$ ), 2930 ( $\text{CH}_3$ ), 2179( $\text{C}=\text{N}$ ), 1556 ( $\text{C}=\text{C}$ );  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ,  $\delta$  / ppm): 3.4 (3H, s,  $-\text{OCH}_3$ ), 6.79(2H, d,  $\text{C}_3-$ ,  $\text{C}_5$ -H of aminophenylthio), 7.35 (2H, d,  $\text{C}_2-$ ,  $\text{C}_6$ -H of aminophenylthio), 7.42 (6H, m, aromatic protons of aryl and pyridine), 8.66 (1H, d,  $\text{C}_6$ -H of pyridine moiety), 4.20 (1H, s, amino H).

**6-Amino-4-(4-chlorophenyl)-2'-[(4-aminophenylthio)]-2,4'-bipyridine-5-carbonitrile (3f).** IR (KBr,  $\text{cm}^{-1}$ ): 3410 ( $\text{NH}_2$ ), 2964 (Ar-H), 2210 ( $\text{C}=\text{N}$ ), 1570( $\text{C}=\text{C}$ ), 1486 ( $\text{C}=\text{C}$ );  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ,  $\delta$  / ppm): 6.69 (2H, d,  $\text{C}_3-$ ,  $\text{C}_5$ -H of aminophenylthio), 7.20 (2H, d,  $\text{C}_2-$ ,  $\text{C}_6$ -H of aminophenylthio), 7.40–7.80(2H, m, aromatic protons phenyl and pyridine), 8.62 (1H, d,  $\text{C}_6$ -H of pyridinemoiety).

**6-Amino-4-(aryl)-2'-[(4-aminophenylthio)]-2,4'-bipyridine-5-carbonitrile (4g).** IR (KBr,  $\text{cm}^{-1}$ ): 3440 ( $\text{NH}_2$ ), 2934 (ArH), 2197 ( $\text{C}=\text{N}$ ), 1487 ( $\text{C}=\text{C}$ );  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ,  $\delta$  / ppm): 6.86 (2H, d,  $\text{C}_3-$ ,  $\text{C}_5$ -H of aminophenylthio), 7.22 (2H, m,  $\text{C}_2-$ ,  $\text{C}_6$ -H of aminophenylthio), 7.44 (4H, m, protons of pyridines), 4.21 (1H, s, amino H).

**6-Amino-2'-[(4-aminophenylthio)]-4-(4-nitrophenyl)-2,4'-bipyridine-5-carbonitrile (4h).** IR (KBr,  $\text{cm}^{-1}$ ): 3410 ( $\text{NH}_2$ ), 2926 (Ar-H), 2210 ( $\text{C}=\text{N}$ ), 1632( $\text{N}=\text{O}$ ), 1487 ( $\text{C}=\text{C}$ );  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ,  $\delta$  / ppm): 6.90 (2H, d,  $\text{C}_3-$ ,  $\text{C}_5$ -H of aminophenylthio), 7.20 (2H, d,  $\text{C}_2-$ ,  $\text{C}_6$ -H of

aminophenylthio), 7.42 (3H, m, of pyridine), 8.50 (1H, d, C<sub>6</sub>-H of pyridine moiety), 4.14 (1H, s, amino H).

The formation 1-{2-[(4-aminophenyl)thio]pyridin-4-yl}ethanone (**2**) was confirmed by FT-IR, <sup>1</sup>H-NMR, and elemental analyses. The IR spectrum of **2** exhibited absorption bands at 3066, 1700 and 1587 cm<sup>-1</sup> due to CH<sub>3</sub>, C=O and aromatic C=C stretching frequencies, respectively. Its <sup>1</sup>H-NMR spectrum showed singlets at δ 2.45 and 7.17 which are due to CH<sub>3</sub>, pyridine proton respectively. Further, doublets at 6.93 and 7.48 ppm are due to the aromatic protons of the 4-aminophenylthio group, while the doublets at 7.35 and 8.55 ppm are due to protons of the pyridine nucleus.

The structure of 6-amino-4-chlorophenyl-2'-[(4-aminophenyl)thio]-2,4'-bipyridine-5-carbonitrile (**3a**) was established on the basis of FT-IR, <sup>1</sup>H-NMR, and elemental analyses. The IR spectrum exhibited peaks at 3468, 2216 and 1579 cm<sup>-1</sup>, which are due to the presence of NH<sub>2</sub>, CN and C=C groups, respectively.

The <sup>1</sup>H-NMR spectrum exhibited doublets at δ 6.90 and 7.40 ppm, which are due to the four protons of the 4-aminophenylthio 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 δ 8.50 ppm is due to C<sub>6</sub>-H of the pyridine moiety.

### Biological screening

Antibacterial activity, All the title compounds, **3a–h**, were evaluated for their in vitro antibacterial activity against two bacteria, viz., *Staphylococcus aureus* and *Escherichia coli*, using the filter paper disc diffusion method.<sup>22,23</sup> 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

Compounds	Antibacterial activity		Antifungal activity	
	<i>S.aureus</i>	<i>E.coli</i>	<i>A. niger</i>	<i>C.albicans</i>
<b>3a</b>	13	15	20	21
<b>3b</b>	16	12	17	17
<b>3c</b>	17	16	16	19
<b>3d</b>	16	17	16	13
<b>3e</b>	19	15	20	19
<b>3f</b>	13	17	21	23
<b>3g</b>	15	18	22	18
<b>3h</b>	18	12	15	15
<b>standard</b>	<b>21</b>	<b>23</b>	<b>25</b>	<b>24</b>

Compounds Zone of inhibition, m m

Results of antibacterial studies revealed that compounds fairly good activity against both the strains, while compounds 3b, 3e and 3g 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–h, were screened for their in vitro antifungal activity against *Aspergillus niger* and *Candida albicans* using the filter paper disc diffusion method.<sup>22,23</sup>

The solvent, N,N-dimethylformamide showed no zone of inhibition. The activities were compared with the known standard drug fluconazole, used at a concentration of 1000 ppm. The



results are tabulated in Table II. The results of the antifungal screening showed that compounds 3a, 3f and 3h displayed good activity against both fungal strains, which were comparable with the standard fluconazole. Compounds 3e showed good activity against *A. niger*, while the remaining compounds exhibited moderate activity when compared to fluconazole.

## CONCLUSIONS

The successful syntheses of heterocyclic title compounds and an evaluation of the antimicrobial activity of the new pyridines containing the 4-aminophenylthio 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.

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