

N-Phenyl heteroarylamine analogues of fluazinam using the intermediate derivatization methods approach

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Abstract. Twenty-one N-phenyl heteroarylamine analogues of fluazinam 3a–3u were prepared via nucleophilic substitution reaction of 2,6-dichloro-3,5-dinitrotoluene with heteroarylamines using the intermediate derivatization method. 2,6-Dichloro-3,5-dinitrotoluene, the key intermediate, was synthesized by nitration of 2,6-dichlorotoluene. The synthesized compounds were identified by ¹H NMR, ¹³C NMR, MS and elemental analyses. Preliminary bioassays indicated that most of the compounds showed good fungicidal activity against rice blast. The activity of 3p was equal to that of fluazinam. The relationship between molecular structure and biological activity suggested that introduction of electron-withdrawing groups in the pyridine ring was important for optimizing fungicidal activity against rice blast.

Keywords. Diarylamine compounds; 2,6-Dichloro-3,5-dinitrotoluene; intermediate derivatization method; fungicides.

1. Introduction

A new approach for discovering and developing novel agrochemicals, Intermediate Derivatization Methods (IDM),^{1–3} has been reported recently and was adopted by Shenyang Research Institute of Chemical Industry (SYRICI) to obtain innovative chemical structures which in conjunction with biological screening generated patentable leads and target compounds.^{4–9} The essence of IDM is to apply simple organic chemical reactions using commercially available and inexpensive starting materials to achieve innovated structures.

One application of IDM involves the use of 2,6-dichlorotoluene as the key starting material for pesticides shown in figure 1, including herbicides dichlobenil (III),¹⁰ tembotrione (1-1)¹¹ and florasulame(1-2),¹² insecticides methoxyfenozide (1-3)¹³ and diflubenzuron (1-4),^{10,14,15} and the fungicide fluopicolide (1-5).¹⁶ 2,6-Dichlorotoluene was selected as the key starting material for these pesticides due to its suitable functionality

and its advantages of relatively low cost and wide commercial availability. We were interested in using the IDM approach with 2,6-dichlorotoluene as a starting material for the synthesis of analogues of the fluazinam, a phenylpyridinamine fungicide shown in figure 2. Fluazinam shows good control on many diseases like grey mould and downy mildew on vines; apple scab, southern blight and white mould on peanuts; tomato late blight and tuber blight on potatoes; clubroot on crucifers; rhizomania on sugar beet; white and violet root rot on fruit trees; and for controlling mites in apples as well.¹⁷ In our previous study,¹⁸ we used the IDM approach starting with 2,6-dichlorotoluene to prepare the fluazinam analogue compound A (figure 2) in which N-(3-chloro-2,6-dinitro-4-trifluoromethylphenyl) moiety of fluazinam was replaced by a N-(3-chloro-2-methyl-4,6-dinitrophenyl) group. This fluazinam analogue displayed promising control of rice blast and prompted us to explore similar analogues in order to improve its fungicidal activity. In this study, we report the synthesis of 21 new N-phenyl heteroarylamine analogues of fluazinam, prepared from key starting material 2,6-dichlorotoluene using the IDM approach, and their activity against rice blast.

*For correspondence

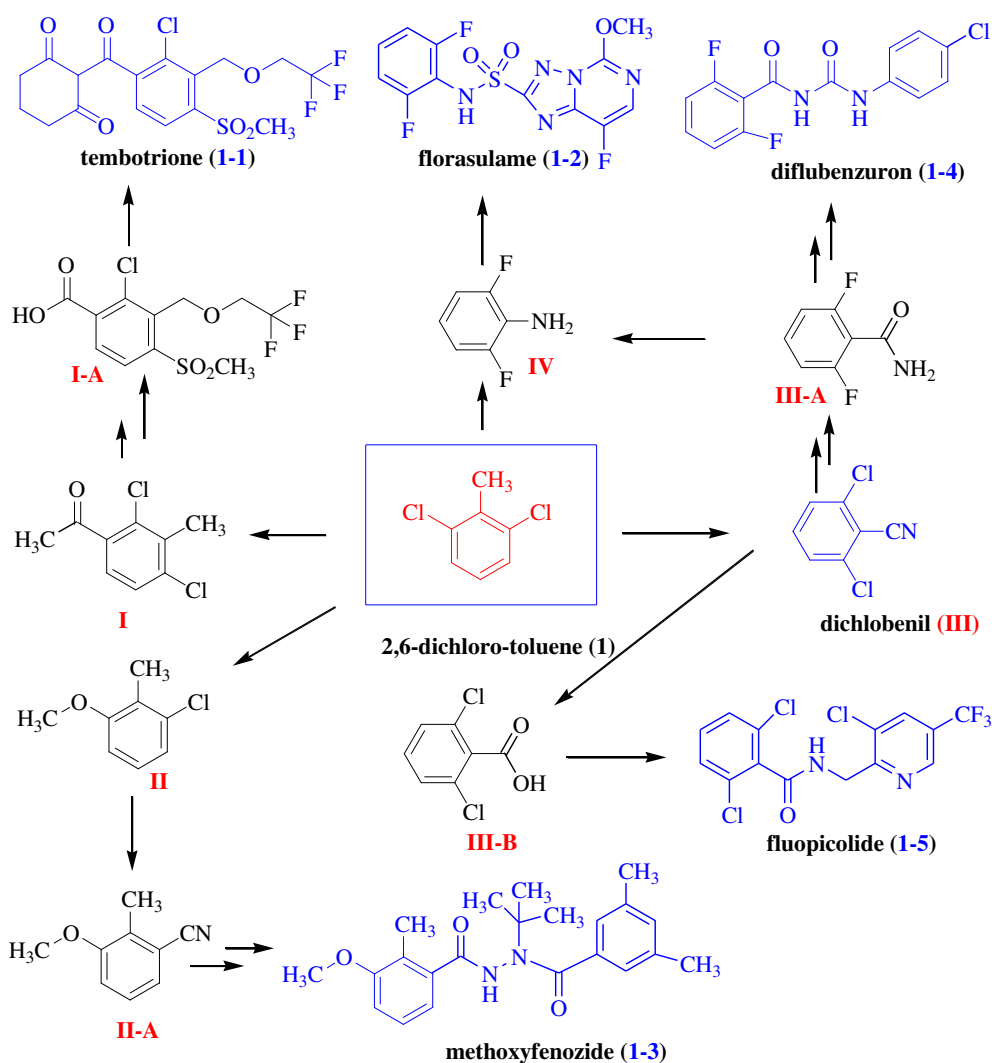


Figure 1. Pesticides synthesized from key starting material 2,6-dichlorotoluene.

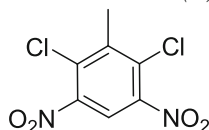
2. Experimental section

2.1 Materials

The reactions were monitored by TLC on aluminum-backed silica plate visualized by UV light. Melting points were determined on a Büchi melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on a Mercury 300 (Varian, 300 MHz) spectrometer with deuteriochloroform as the solvent and tetramethylsilane (TMS) as the internal standard. Mass

spectra were recorded using a JEOL JMS-700 mass spectrometer. Elemental analyses were determined on a Yanaco MT-3CHN elemental analyzer. All starting materials, reagents and solvents were commercially available and used without further purification.

2.2 Synthesis of key intermediate 2,6-dichloro-3,5-dinitrotoluene (2)



The synthesis sequence is outlined in scheme 1. To a mixture of 2,6-dichlorotoluene (50 mmol) and concentrated sulfuric acid (30 mL), cooled to 5°C, was added fuming nitric acid ($d = 1.52$, 10 mL) dropwise for 20 min, while being stirred continuously. The reaction mixture was stirred at room temperature for an hour and then poured into icy water. The resulting pre-

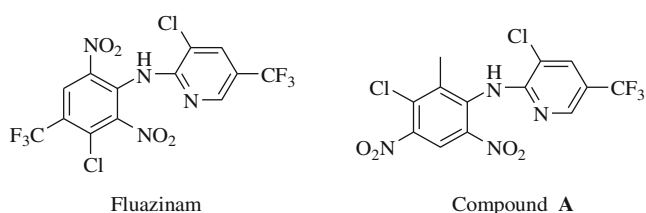
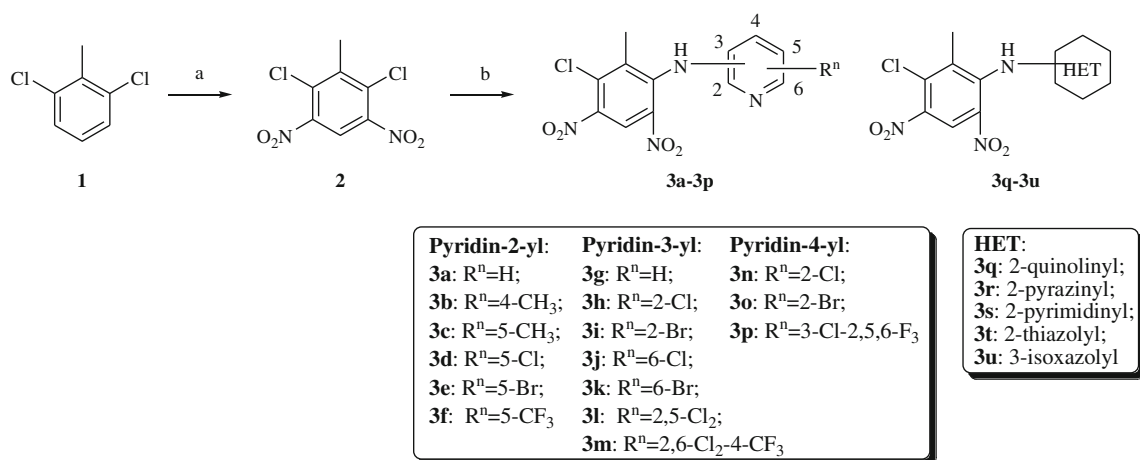


Figure 2. Structures of fluazinam and compound A



Scheme 1. Reagents and conditions: (a) fuming nitric acid in c.H₂SO₄/5 °C-room temperature; (b) heteroarylamines, NaOH in DMF, room temperature (25°C).

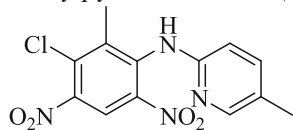
cipitate was collected by filtration, washed with water and recrystallized from ethanol giving 2,6-dichloro-3,5-dinitrotoluene as pale green needles, M.p. 131–132°C.

2.3 General synthetic procedure for N-phenyl heteroamines (3a–3u)

The synthesis sequence is outlined in scheme 1. Heteroarylamine **4** (5 mmol) was added in portions to a suspension of NaOH (10 mmol, 60%) in DMF (20 mL) at room temperature. After 30 min, a solution of 2,6-dichloro-3,5-dinitrotoluene (6 mmol) in 30 mL of THF was added and then the resulting mixture was stirred overnight. After reaction completion (TLC), the mixture was filtered. The filtrate was concentrated under reduced pressure and the residue was purified on a silica column to afford the N-phenyl heteroarylamines **3a–3u** in 60–91% yield. All these target compounds are new and are characterized as follows.

2.4 Characterization of N-phenyl heteroarylamines (3a–3u)

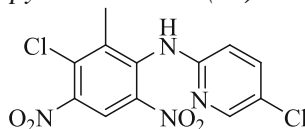
2.4a N-(3-chloro-2-methyl-4,6-dinitrophenyl)-5-methylpyridin-2-amine (3c):



Yield 70%. Orange solid. M.p.: 187–189°C; ¹H NMR (300 MHz, CDCl₃): δ (ppm) 9.04 (bs, 1H, NH), 8.62 (s, 1H, Ph-H), 8.03 (s, 1H, pyridin-6H), 7.50 (dd, 1H, *J* = 2.4, 8.4 Hz, pyridin-4H), 6.83 (d, 1H, *J* = 8.4 Hz, pyridin-3H), 2.25 (s, 3H, Ph-CH₃), 2.05

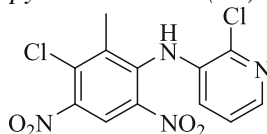
(s, 3H, pyridin-CH₃); ¹³C NMR (75 MHz, DMSO-d₆) δ 151.76, 146.32, 141.55, 140.42, 139.09, 137.04, 134.49, 129.94, 125.81, 120.64, 111.39, 17.22, 16.52; Anal. Calcd. for C₁₃H₁₁ClN₄O₄: C, 48.38; H, 3.44; N, 17.36; Found: C, 48.31; H, 3.56; N, 17.31.

2.4b 5-Chloro-N-(3-chloro-2-methyl-4,6-dinitrophenyl)pyridin-2-amine (3d):



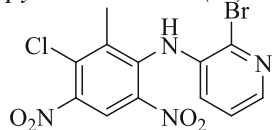
Yield 77%. Orange solid. M.p.: 168–170°C; ¹H NMR (300 MHz, CDCl₃): δ (ppm) 8.89 (bs, 1H, NH), 8.59 (s, 1H, Ph-H), 8.13 (d, 1H, *J* = 2.7 Hz, pyridin-6H), 7.63 (dd, 1H, *J* = 2.7, 8.7 Hz, pyridin-4H), 6.86 (d, 1H, *J* = 8.7 Hz, pyridin-3H), 2.25 (s, 3H, CH₃); Anal. Calcd. for C₁₂H₈Cl₂N₄O₄: C, 42.00; H, 2.35; N, 16.33; Found: C, 42.06; H, 2.46; N, 16.25.

2.4c 2-Chloro-N-(3-chloro-2-methyl-4,6-dinitrophenyl)pyridin-3-amine (3h):



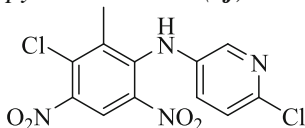
Yield 75%. Orange solid. M.p.: 136–138°C; ¹H NMR (300 MHz, CDCl₃): δ (ppm) 8.88 (bs, 1H, NH), 8.67 (s, 1H, Ph-H), 8.15 (dd, 1H, *J* = 1.5, 4.8 Hz, pyridin-6H), 7.18–7.22 (m, 1H, pyridin-5H), 6.83 (dd, 1H, *J* = 0.9, 7.8 Hz, pyridin-4H), 2.20 (s, 3H, CH₃); Anal. Calcd. for C₁₂H₈Cl₂N₄O₄: C, 42.00; H, 2.35; N, 16.33; Found: C, 42.04; H, 2.48; N, 16.26.

2.4d 2-Bromo-N-(3-chloro-2-methyl-4,6-dinitrophenyl)pyridin-3-amine (**3i**):



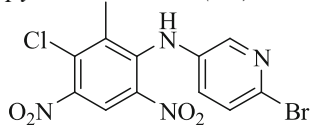
Yield 76%. Orange solid. M.p.: 140—142 °C; ¹H NMR (300 MHz, CDCl₃): δ (ppm) 8.89 (bs, 1H, NH), 8.68 (s, 1H, Ph-H), 8.13 (dd, 1H, *J* = 1.5, 4.8 Hz, pyridin-6H), 7.19–7.24 (m, 1H, pyridin-5H), 6.78 (dd, 1H, *J* = 1.5, 8.1 Hz, pyridin-4H), 2.18 (s, 3H, CH₃); Anal. Calcd. for C₁₂H₈BrClN₄O₄: C, 37.19; H, 2.08; N, 14.46; Found: C, 37.11; H, 2.14; N, 14.51.

2.4e 6-Chloro-N-(3-chloro-2-methyl-4,6-dinitrophenyl)pyridin-3-amine (**3j**):



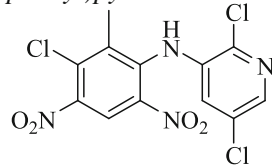
Yield 75%. Orange solid. M.p.: 108–110 °C; ¹H NMR (300 MHz, CDCl₃): δ (ppm) 9.07 (bs, 1H, NH), 8.71 (s, 1H, Ph-H), 8.05 (d, 1H, *J* = 2.7 Hz, pyridin-2H), 7.32 (d, 1H, *J* = 8.4 Hz, pyridin-5H), 7.15 (dd, 1H, *J* = 2.7, 8.4 Hz, pyridin-4H), 2.18 (s, 3H, CH₃); Anal. Calcd. for C₁₂H₈Cl₂N₄O₄: C, 42.00; H, 2.35; N, 16.33; Found: C, 41.93; H, 2.46; N, 16.24.

2.4f 6-Bromo-N-(3-chloro-2-methyl-4,6-dinitrophenyl)pyridin-3-amine (**3k**):



Yield 75%. Orange solid. M.p.: 108–110 °C; ¹H NMR (300 MHz, CDCl₃): δ (ppm) 9.03 (bs, 1H, NH), 8.71 (s, 1H, Ph-H), 8.04 (d, 1H, *J* = 3.0 Hz, pyridin-2H), 7.46 (d, 1H, *J* = 8.4 Hz, pyridin-5H), 7.04 (dd, 1H, *J* = 3.0, 8.4 Hz, pyridin-4H), 2.18 (s, 3H, CH₃); Anal. Calcd. for C₁₂H₈BrClN₄O₄: C, 37.19; H, 2.08; N, 14.46; Found: C, 37.14; H, 2.03; N, 14.57.

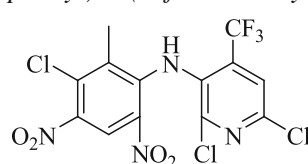
2.4g 2,5-Dichloro-N-(3-chloro-2-methyl-4,6-dinitrophenyl)pyridin-3-amine (**3l**):



Yield 78%. Orange solid. M.p.: 141–143 °C; ¹H NMR (300 MHz, CDCl₃): δ (ppm) 8.74 (bs, 1H, NH), 8.65

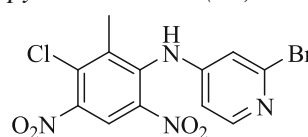
(s, 1H, Ph-H), 8.07 (d, 1H, *J* = 2.1 Hz, pyridin-6H), 6.72 (d, 1H, *J* = 2.1 Hz, pyridin-4H), 2.26 (s, 3H, CH₃). Anal. Calcd. for C₁₂H₇Cl₃N₄O₄: C, 38.17; H, 1.87; N, 14.84; Found: C, 38.25; H, 1.75; N 14.79.

2.4h 2,6-Dichloro-N-(3-chloro-2-methyl-4,6-dinitrophenyl)-4-(trifluoromethyl)pyridin-3-amine (**3m**):



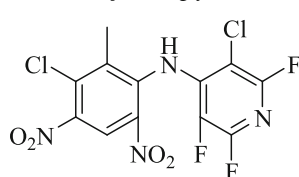
Yield 60%. Yellow solid. M.p.: 130–132 °C; ¹H NMR (300 MHz, CDCl₃): δ (ppm) 9.59 (bs, 1H, NH), 8.74 (s, 1H, Ph-H), 7.67 (s, 1H, pyridin-H), 2.00 (s, 3H, CH₃). Anal. Calcd. for C₁₃H₆Cl₃F₃N₄O₄: C, 35.04; H, 1.36; N, 12.57; Found: C, 34.99; H, 1.44; N 12.52.

2.4i 2-Bromo-N-(3-chloro-2-methyl-4,6-dinitrophenyl)pyridin-4-amine (**3o**):



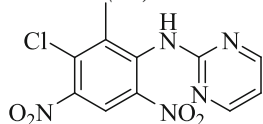
Yield 79%. Orange solid. M.p.: 170–172 °C; ¹H NMR (300 MHz, CDCl₃): δ (ppm) 8.68 (s, 1H, pyridin-2H), 8.61 (bs, 1H, NH), 8.59 (s, 1H, Ph-H), 8.30 (d, 1H, *J* = 5.4 Hz, pyridin-6H), 6.26 (d, 1H, *J* = 5.4 Hz, pyridin-5H), 2.30 (s, 3H, CH₃); Anal. Calcd. for C₁₂H₈BrClN₄O₄: C, 37.19; H, 2.08; N, 14.46; Found: C, 37.14; H, 2.10; N, 14.50.

2.4j 3-Chloro-N-(3-chloro-2-methyl-4,6-dinitrophenyl)-2,5,6-trifluoropyridin-4-amine (**3p**):



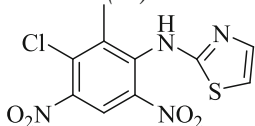
Yield 91%. Yellow Oil; ¹H NMR (300 MHz, CDCl₃): δ (ppm) 8.54 (s, 1H, Ph-H), 8.44 (bs, 1H, NH), 2.33 (s, 3H, CH₃); ¹³C NMR (75 MHz, DMSO) δ 146.23, 144.69, 142.74, 142.65, 140.19, 140.16, 135.46, 129.84, 119.35, 100.08 (d, *J* = 4.65 Hz), 99.51, 16.35; Anal. Calcd. for C₁₂H₅Cl₂F₃N₄O₄: C, 36.30; H, 1.27; N, 14.11; Found: C, 36.38; H, 1.22; N, 14.15; LC-MS (*m/z* %): 394.9 [M-H][−].

2.4k *N*-(3-chloro-2-methyl-4,6-dinitrophenyl)pyrimidin-2-amine (**3s**):



Yield 83%. Yellow solid. M.p.: 108–110°C; ^1H NMR (300 MHz, CDCl_3): δ (ppm) 8.67 (bs, 1H, NH), 8.49 (s, 1H, Ph-H), 8.44 (d, 2H, $J = 4.8$ Hz, pyrimidin-4,6-2H), 6.89–6.93 (m, 1H, pyrimidin-5H), 2.43 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO) δ 159.50, 158.29, 144.00, 142.93, 137.54, 135.59, 129.87, 119.94, 114.02, 16.57; Anal. Calcd. for $\text{C}_{11}\text{H}_8\text{ClN}_5\text{O}_4$: C, 42.66; H, 2.60; N, 22.62; Found: C, 42.62; H, 2.56; N, 22.67.

2.4l *N*-(3-chloro-2-methyl-4,6-dinitrophenyl)thiazol-2-amine (**3t**):



Yield 71%. Orange solid. M.p.: 151–153°C; ^1H NMR (300 MHz, CDCl_3): δ (ppm) 9.34 (bs, 1H, NH), 8.60 (s, 1H, Ph-H), 7.28 (d, 1H, $J = 3.6$ Hz, thiazol-4-H), 6.93 (d, 1H, $J = 3.6$ Hz, thiazol-5H), 2.31 (s, 3H, CH_3); Anal. Calcd. for $\text{C}_{10}\text{H}_7\text{ClN}_4\text{O}_4\text{S}$: C, 38.16; H, 2.24; N, 17.80; Found: C, 38.19; H, 2.30; N, 17.68.

2.5 Fungicidal assays

The *in vitro* biological activities were evaluated using a previously reported procedure¹⁸ with the aid of High Throughput Screening. A testing solution was obtained by dissolving each *N*-phenyl heteroarylamine compound in various solvents at the desired concentration, ranging from 0.1–25 mg/L. The solvents were selected from acetone, methanol or DMF according to the different solubility of each compound. The testing solution and pathogen suspensions were added into the cells of a 96-well culture plate, which then was placed in the constant temperature chamber. After 24 h pathogen germination or growth was assessed and the fungicidal activity of the compound was evaluated relative to pathogen germination or growth in the control treatment. The level of fungicidal activity was reported in the range 0 (no control) to 100% (complete control).

3. Results and discussion

3.1 Chemistry

The preparation of target compounds **3a–3u** illustrated in scheme 1, was accomplished by adopting known

methods.^{18–20} The intermediate 2,6-dichloro-3,5-dinitrotoluene (**2**) was prepared from 2,6-dichlorotoluene (**1**) and fuming nitric acid, then reacted with heteroaryl amines (**4**) to afford target compounds (**3**) in 60–91% yields. The 21 *N*-phenyl heteroarylamine compounds are listed in table 1.

3.2 Structure-activity relationship (SAR) based on results of *in vitro* fungicide assay

The compounds were screened for fungicidal activity against rice blast (RB), a major pathogen of rice. As shown in table 2, all *N*-phenyl heteroarylamine compounds, except **3c**, displayed significant fungicidal activity against RB. Compounds **3m** and **3p** were particularly effective, providing 80% and 100% control respectively, at the lowest concentration, 0.1 mg/L and were much improved over that of compound **A** (80% at 25 mg/L) and equal to that of fluazinam. Based on the data presented in table 2, a structure-activity relationship emerged.

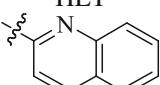




3.2a Compounds of the 2-pyridinyl type (**3a – 3f**):

When electron-donating group such as methyl group was introduced at the 5-position of the pyridine ring in the 2-pyridinyl to form **3c**, fungicidal activity reduced compared to the unsubstituted pyridine compound **3a** (50% vs. 100% control at 25 mg/L). When the methyl group was introduced at the 4-position of the pyridine ring giving **3b**, fungicidal activity remained the same as the unsubstituted pyridine compound **3a** (80% control at 8.3 mg/L). This result suggests that the introduction of methyl at 4-position would not improve fungicidal activity in this series of *N*-phenylpyridinamines. However, when the 5-position was substituted with an electron-withdrawing group (chlorine, bromine or trifluoromethyl), the fungicidal activity of compounds **3d**, **3e** and **3f** was improved over the unsubstituted pyridine compound **3a** (100%, 100%, 100% vs. 80% at 8.3 mg/L). These results imply that an electron-withdrawing group at the 5-position of the pyridine ring improves fungicidal activity.

3.2b Compounds of the 3-pyridinyl type (**3g – 3m**):

Introducing a chlorine atom at the 2- or 6-position of pyridine ring in the 3-pyridinyl type of compounds to form **3h** and **3j**, fungicidal activity was improved compared with the unsubstituted pyridine compound **3g** (80%, 80% vs 0% at 2.8 mg/L). Similarly, introducing bromine at the 2- or 6-position to form **3i** and **3k** also improved fungicidal activity compared to the unsubstituted pyridine compound **3g** (100%, 80% vs 0% at 2.8 mg/L). When hydrogen atoms at the 2- and

Table 1. Chemical structures, physical properties of compounds synthesized.

Compd.	Position of -NH- ^a	R ⁿ	M.p. (°C)	Yield (%)
3a	2	H	111-113	73
3b	2	4-CH ₃	150-152	68
3c	2	5-CH ₃	187-189	70
3d	2	5-Cl	168-170	77
3e	2	5-Br	175-177	79
3f	2	5-CF ₃	142-144	65
3g	3	H	146-148	78
3h	3	2-Cl	136-138	75
3i	3	2-Br	140-142	76
3j	3	6-Cl	108-110	75
3k	3	6-Br	156-158	78
3l	3	2,5-Cl ₂	141-143	78
3m	3	2,6-Cl ₂ -4-CF ₃	130-132	60
3n	4	2-Cl	166-168	80
3o	4	2-Br	170-172	79
3p	4	3-Cl-2,5,6-F ₃	oil	91
Compd.	HET		M.p. (°C)	Yield (%)
3q			175-177	80
3r			108-110	74
3s			178-180	83
3t			151-153	71
3u			137-139	69

^ameans that “-NH-” is attached to pyridinyl ring.

5-position of pyridine ring were simultaneously substituted with chlorine atoms (**3l**), its activity was further enhanced compared with that of compounds **3h**, **3i**, **3j** and **3k** (50% vs. 0% control at 0.9 mg/L). Astonishingly, the trisubstituted pyridine compound **3m** which possesses electron-withdrawing groups 2,6-Cl₂-4-CF₃ provided greatly improved fungicidal activity compared to the unsubstituted pyridine compound **3g** (80% vs. no control at 0.1 mg/L), this result suggests that the strong electron-withdrawing CF₃ on 4-position of pyridine ring plays an important role in enhancing fungicidal activity in combination with 2,6-Cl₂. It is not difficult to draw the conclusion that the adjacent, and particularly para positions of nitrogen atom in pyridine ring has a significant effect on fungicidal activity.

3.2c Compounds of the 4-pyridinyl type (3n – 3p): Introducing a chlorine or bromine atom at the 2-position of the pyridine ring forming **3n** and **3o** gave 80%

control at 8.3 mg/L and 80% control at 2.8 mg/L, respectively. In this case, the bromine compound showed superior activity compared with the corresponding compound containing chlorine. The tetrasubstituted pyridine compound **3p** which includes electron-withdrawing atoms 3-Cl-2,5,6-F₃ displayed the highest fungicidal activity of all tested *N*-phenyl heteroarylamines compounds (100% control at 0.1 mg/L), which may be due to strong electronegativity of fluorine and/or multiple substituents.

3.2d Other nitrogen heterocyclic analogues (3q – 3u): Replacing the 2-pyridinyl ring of **3a** with the 3-isoxazolyl ring forming **3u** reduced fungicidal activity (50% control at 8.3 mg/L). When the 2-pyridinyl ring of **3a** was replaced with a 2-pyrazinyl or 2-pyrimidinyl ring forming compounds **3r** and **3s**, fungicidal activity was maintained (80% control at 8.3 mg/L). When the 2-pyridinyl ring of **3a** was replaced with a 2-quinolinyl

Table 2. Fungicidal activity of *N*-phenyl heteroarylamine against RB.

Compd.	Fungicidal activity against RB (% control at given concentration mg/L)					
	25	8.3	2.8	0.9	0.3	0.1
3a	100	80	0	/ ^b	/	/
3b	100	80	0	/	/	/
3c	50	/	/	/	/	/
3d	100	100	50	0	/	/
3e	100	100	50	0	/	/
3f	100	100	50	0	/	/
3g	100	50	0	/	/	/
3h	100	100	80	0	/	/
3i	100	100	100	0	/	/
3j	100	100	80	0	/	/
3k	100	100	80	0	/	/
3l	100	80	80	50	/	/
3m	100	100	100	100	100	80
3n	100	80	0	/	/	/
3o	100	100	80	0	/	/
3p	100	100	100	100	100	100
3q	100	100	80	0	/	/
3r	100	80	0	/	/	/
3s	100	80	0	/	/	/
3t	100	100	100	0	/	/
3u	100	50	0	/	/	/
Compound A	80	0	/	/	/	/
Fluazinam	100	100	100	100	100	100

^bstands for no data.

ring forming **3q**, fungicidal activity increased (80% control at 2.8 mg/L). When the 2-pyridinyl ring of **3a** was replaced with a 2-thiazolyl ring forming **3t**, fungicidal activity increased further (100% control at 2.8 mg/L). These results suggest that further structure optimization is possible outside the pyridinyl type analogues, as shown by good activity found with the quinolinyl and thiazolyl analogues.

4. Conclusions

Twenty one *N*-phenyl heteroarylamine compounds were synthesized via the intermediate derivatization method. Overall, introduction of electron-withdrawing groups to any position of pyridine ring was important to optimize fungicidal activity against rice blast. Activity was generally greater in 3- and 4-pyridinyl type analogues compared with the 2-pyridinyl type compounds and was improved when the number of electron-withdrawing substituents increased. Analogues of the non-pyridinyl type also showed promising fungicidal activity, particularly the quinolinyl and thiazolyl analogues. Further synthesis and structure optimization studies are in progress.

Supplementary Information

The electronic supporting information, the spectral data for compounds **3a**, **3b**, **3e**, **3f**, **3g**, **3n**, **3q**, **3r** and **3u**, can be seen in www.ias.ac.in/chemsci.

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