Synthesis of 1,2,4-triazolo[4,3-*a*][1,8]naphthyridines using chloranil under microwave irradiation

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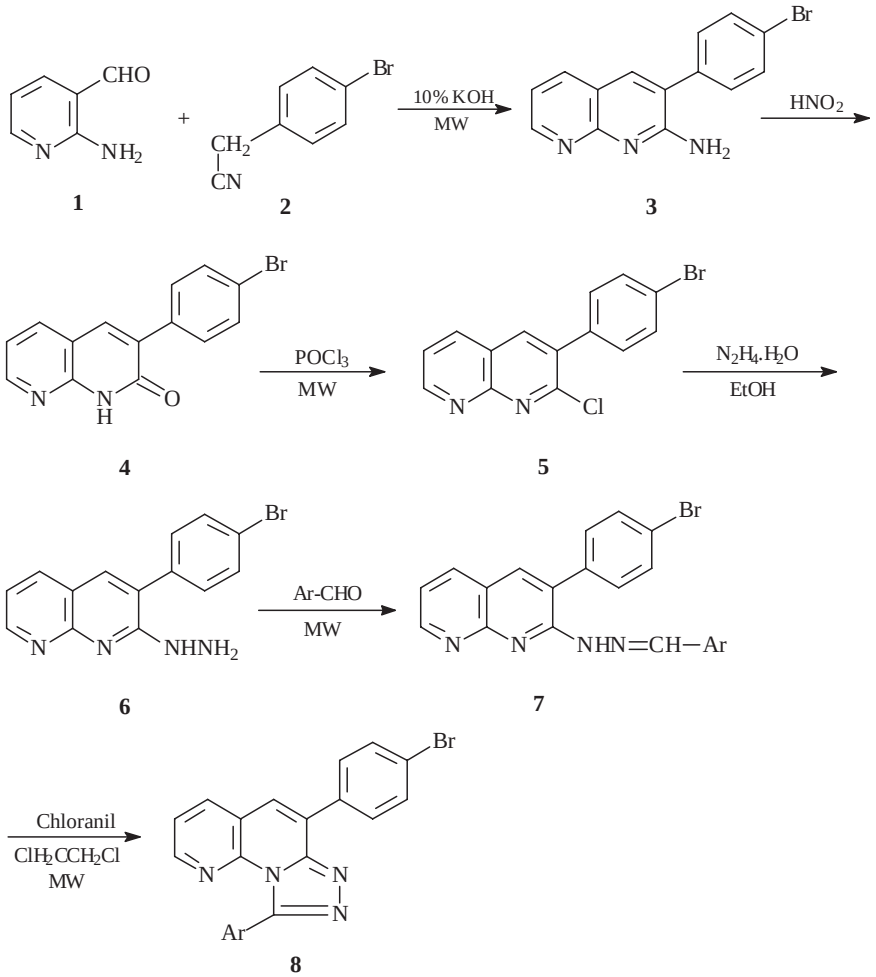
A simple and highly efficient procedure has been described for the synthesis of 1-aryl-4-[p-bromophenyl)-1,2,4-triazolo[4,3-a][1,8]naphthyridines (**8**) by the oxidation of the corresponding aryl aldehyde 3-(p-bromophenyl)-1,8-naphthyridin-2-ylhydrazones (**7**) with chloranil under microwave irradiation. The products are obtained in good yields and in a state of high purity.

Keywords: 1,2,4-triazole, 1,8-naphthyridine, chloranil, microwave irradiation

Fused 1,2,4-triazoles generate a widespread interest due to diverse pharmacological and microbiological activities.[1-3] The synthesis of a fused 1,2,4-triazole system is possible by two distinct routes either by treatment of a suitably substituted 1,2,4-triazole with appropriate reagents to give rise either to the fused 1,2,4-triazole system as such or an intermediary product which may be cyclised subsequently[4] or more conventionally by starting from a suitable α-hydrazino heterocycle and creating the triazole unit thereon. The latter method for the formation of fused 1,2,4-triazoles has been discussed in a review[5] and is the one more frequently employed for the synthesis. The wide applicability of this approach was recognised by a number of workers and a variety of fused 1,2,4-triazoles were prepared by a proper choice of conditions and reactants.[6-9] However, these methods are not very satisfactory due to drawbacks, such as low yields, expensive reagents, longer reaction time at higher reaction temperature and tedious work-up procedures. Therefore, a good and useful method for the synthesis of fused 1,2,4-triazoles is highly desirable. Further, the 1,8-naphthyridine ring system is an important pharmacophoric element in medicinal chemistry.[10-12] In recent years, microwave irradiation using commercial domestic ovens has been rapidly increased for optimisation and acceleration of organic synthesis.[13-16]



1 **2** **3** **4** **5** **6** **7** **8**

Scheme 1

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It has been reported for the variety of reactions such as synthesis of heterocycles[13-16] and more recently for synthesis of polymers,[17] because of advantages such as reduction in reaction time, improved energy utilisation, potential for lower processing temperature and improved product uniformity. Microwave irradiation has also been applied to organic solvents such as methanol, ethanol, *N*,*N*-dimethylformamide (DMF), 1,2-dichloroethane (DCE), *o*-dichlorobenzene, *etc*. as energy transfer media which absorb microwave energy efficiently through dipole rotation. In view of this and in continuation of our interest in microwave-assisted organic transformations on 1,8-naphthyridine derivatives,[18-21] we report here, a convenient, practical and efficient method for the synthesis of 1,2,4-triazolo[4,3-*a*][1,8]naphthyridines using chloranil under microwave irradiation.

2-Aminonicotinaldehyde (**1**) on condensation with *p*-bromophenylacetonitrile (**2**) in the presence of 10% KOH without any solvent under microwave irradiation afforded 2-amino-3-(*p*-bromophenyl)-1,8-naphthyridine (**3**), which is converted into 1,2-dihydro-3-(*p*-bromophenyl)-1,8-naphthyridin-2-one (**4**) by the reaction with HNO_2. Treatment of **4** with $POCl_3$ under microwave irradiation yielded 2-chloro-3-(*p*-bromophenyl)-1,8-naphthyridine (**5**), which on hydrazinolysis with refluxing hydrazine hydrate furnished 2-hydrazino-3-(*p*-bromophenyl)-1,8-naphthyridine (**6**).

Condensation of **6** with various aromatic aldehydes in the presence of a catalytic amount of DMF under microwave irradiation afforded the corresponding hydrazones, aryl aldehyde 3-(*p*-bromophenyl)-1,8-naphthyridin-2-ylhydrazones (**7**) in excellent yields.

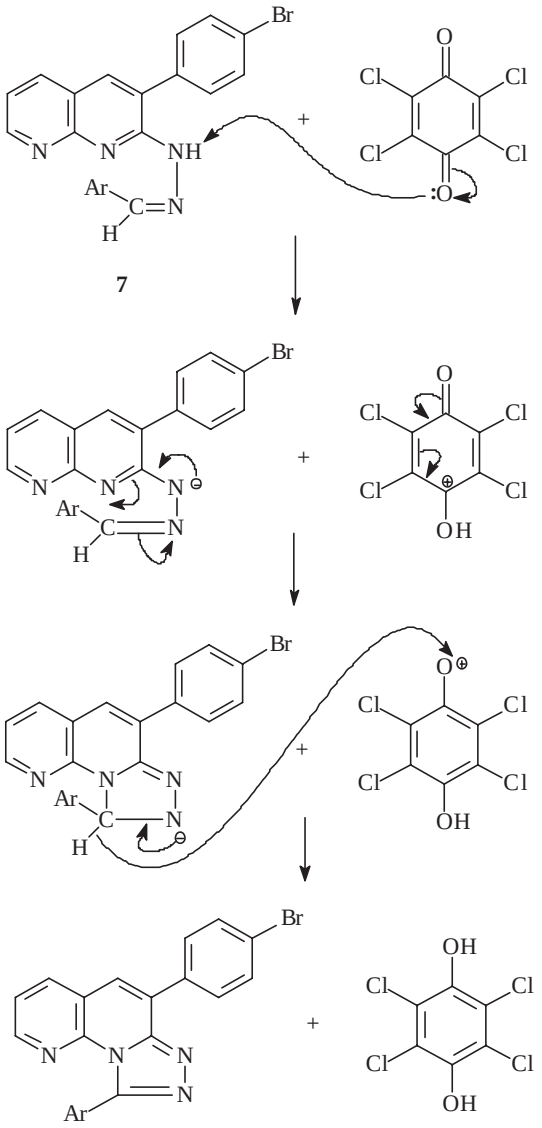
Oxidative cyclisation of **7** with chloranil in 1,2-dichloroethane under microwave irradiation furnished the respective 1-aryl-4-(*p*-bromophenyl)-1,2,4-triazolo[4,3-a][1,8] naphthyridines (**8**) (Scheme 1). The oxidative transformation is clean and efficient. The experimental procedure is very simple. The high yield transformations did not form any undesirable by-products. Furthermore, the products were obtained with a high degree of purity by this procedure and no further purification was needed. A mechanistic rationalisation of the reaction is given in Scheme 2. Interestingly, this oxidative reaction proceeds only to a minor extent (6-8% in 4.0–6.0 min) when conducted under conventional conditions in an oil-bath preheated to 110 °C (temperature measured at the end of exposure during microwave experiment) which confirms the rate augmentation during microwave heating.

The structure of compounds **3–8** were confirmed by their spectroscopic (IR, ^{1}H NMR and MS) and analytical data. To the best of our knowledge this is the first report on microwave-assisted chloranil mediated synthesis of 1,2, 4-triazolo[4,3-*a*][1,8]-naphthyridines.

In conclusion, we have demonstrated a convenient and highly efficient protocol for the synthesis of 1,2,4-triazolo[4,3-*a*] [1,8]naphthyridines using chloranil under microwave irradiation. The significant advantages of the procedure are operational simplicity, short reaction time, pure products and high yields. The biological screening of the compounds **8** is in progress and will be reported in further publications.

Experimental

Melting points were recorded on a Cinex melting point apparatus and are uncorrected. The purity of the compounds was checked using precoated TLC plates (Merk, 60F-254). IR spectra (KBr) (ν_{max}: cm^{-1}) were recorded on a Perkin-Elmer BX series FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer (chemical shifts in δ ppm) using TMS as internal standard. Mass spectra (EI-MS) were determined on a Finnigan MAT 8230 GC-MS spectrometer at 70 eV. Microanalyses were performed on a Perkin-Elmer 240 CHN elemental analyser. For microwave irradiation LG MG 556P (2450 MHz) domestic microwave oven was used.



Scheme 1

2-Amino-3-(p-bromophenyl)-1,8-napthyridine (**3**): A mixture of 2-aminonicotin-aldehyde (**1**) (0.01 mol), *p*-bromophenylacetonitrile (**2**) (0.01 mol) and 10% KOH (5 drops) was subjected to microwave irradiation at 400 watts intermittently at 30 s intervals for 2.5 min. On completion of reaction, as monitored by TLC, the reaction mixture was cooled and treated with chilled water. The solid that precipitated was filtered, washed with water and recrystallised from ethanol to give **3**, yield 98%, m.p. 215–216°C; IR: 3473, 3082, (NH_2), 1642 (C–NH_2), 1590 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$): δ 5.50 (s, 2H, NH_2), 7.95 (m, 2H, C_4–H, C_6–H), 8.09 (m, 1H, C_5–H), 8.86 (m, 1H, C_7–H), 7.17–7.76 (m, 4H, Ar–H); *m/z* (EI) 300 (M^+); Anal. Calcd. for $C_{14}H_{10}BrN_3$: C, 56.00; H, 3.33; N, 14.00; Found C, 56.17; H, 3.38; N, 14.08.

1,2-Dihydro-3-(p-bromophenyl)-1,8-naphthyridin-2-one (**4**) To a cold solution of **3** (0.01 mol) in 2 M HCl (25 ml) was added $NaNO_2$ solution (0.01 mol in 25 ml water) and the reaction mixture was stirred at room temperature for 0.5 h and treated with chilled water. The precipitated solid was filtered, washed with water and recrystallised from methanol to afford **4**, yield 88%, m.p. 168–170°C; IR: 3450 (NH), 1654 (C=O), 1598 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$): δ 8.23 (m, 2H, C_4–H, C_6–H), 8.74 (m, 1H, C_5–H), 9.14 (m, 1H, C_7–H), 7.21–7.96 (m, 4H, Ar–H), 11.80 (s, 1H, NH); *m/z* (EI) 301 (M^+); Anal. Calcd for $C_{14}H_9BrN_2O$: C, 55.81; H, 2.99; N, 9.30; Found C, 55.95; H, 2.96; N, 9.37.

2-Chloro-3-(p-bromophenyl)-1,8-naphthyridine (**5**): A mixture of **4** (0.01 mol) and $POCl_3$ (15 ml) was exposed to microwave irradiation at 200 watts intermittently at 30 s intervals for 2.0 min.

After completion of the reaction as indicated by TLC, the reaction mixture was cooled and poured onto a mixture of crushed ice and $NaHCO_3$. The separated solid was filtered, washed with water and recrystallised from ethanol to furnish **5**, yield 92%, m.p. 195–196°C; IR: 1589 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 8.22 (m, 2H, C_4–H, C_5–H), 8.14 (m, 1H, C_6–H), 9.15 (m, 1H, C_7–H), 7.25–7.67 (m, 4H, Ar–H); *m/z* (EI) 319 (M^+); Anal. Calcd for $C_{14}H_8BrClN_2$: C, 52.58; H, 2.50; N, 8.76; Found C, 52.74; H, 2.55; N, 8.83.

2-Hydrazino-3-(p-bromophenyl)-1,8-naphthyridine (**6**): A mixture of **5** (0.01 mol) and hydrazine hydrate (0.015 mol) in ethanol (25 ml) was refluxed on a water-bath for 4 h. The reaction mixture was cooled, the solid that separated with filtered, washed with water and recrystallised from ethanol to give **6**, yield 90%, m.p. 106–108°C; IR: 3430, 3196 (–$NHNH_2$), 1618 (C–$NHNH_2$), 1592 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 2.45 (brs, 2H, NH_2), 7.69 (m, 2H, C_4–H, C_6–H), 8.02 (m, 1H, C_5–H), 8.33 (m, 1H, C_7–H), 7.02–7.51 (m, 4H, Ar–H), 8.85 (s, 1H, NH); *m/z* (EI) 315 (M^+); Anal. Calcd for $C_{14}H_{11}BrN_4$: C, 53.33; H, 3.49; N, 17.78; Found C, 53.51; H, 3.45; N, 17.87.

General procedure for the synthesis of aryl aldehyde 3-(p-bromophenyl)-1,8-naphthyridin-2-ylhydrazones (**7**): A mixture of **6** (0.01 mol), aromatic aldehyde (0.01 mol) and DMF (5 drops) was exposed to microwave at 200 watts intermittently at 30 s intervals for the specified time (Table 1). On completion of the reaction, as monitored by TLC, the reaction mixture was cooled and digested with cold water. The precipitate thus obtained was filtered, washed with water and recrystallised from ethanol to give **7**.

7a: IR: 3349 (NH), 1624 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 7.82 (m, 2H, C_4–H, C_5–H), 7.70 (m, 1H, C_6–H), 8.32 (m, 1H, C_7–H), 6.99–7.59 (m, 9H, Ar–H), 8.48 (s, 1H, N=CH), 10.27 (s, 1H, NH); *m/z* (EI) 403 (M^+).

7b: IR: 3345 (NH), 1623 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 2.39 (s, 3H, CH_3), 7.73 (m, 2H, C_4–H, C_5–H), 7.59 (m, 1H, C_6–H), 8.34 (m, 1H, C_7–H), 7.00–7.42 (m, 8H, Ar–H), 8.44 (s, 1H, N=CH), 10.25 (s, 1H, NH); *m/z* (EI) 417 (M^+).

7c: IR: 3350 (NH), 1624 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 3.83 (s, 3H, OCH_3), 7.86 (m, 2H, C_4–H, C_5–H), 7.70 (m, 1H, C_6–H), 8.37 (m, 1H, C_7–H), 7.05–7.50 (m, 8H, Ar–H), 8.48 (s, 1H, N=CH), 10.28 (s, 1H, NH); *m/z* (EI) 433 (M^+).

7d: IR: 3355 (NH), 1622 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 7.80 (m, 2H, C_4–H, C_5–H), 7.63 (m, 1H, C_6–H), 8.33 (m, 1H, C_7–H), 7.04–7.51 (m, 8H, Ar–H), 8.42 (s, 1H, N=CH), 10.27 (s, 1H, NH); *m/z* (EI) 437 (M^+).

7e: IR: 3352 (NH), 1624 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 7.72 (m, 2H, C_4–H, C_5–H), 7.57 (m, 1H, C_6–H), 8.36 (m, 1H, C_7–H), 7.01–7.47 (m, 8H, Ar–H), 8.41 (s, 1H, N=CH), 10.23 (s, 1H, NH); *m/z* (EI) 437 (M^+).

7f: IR: 3364 (NH), 1625 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 8.21 (m, 2H, C_4–H, C_5–H), 7.73 (m, 1H, C_6–H), 8.41 (m, 1H, C_7–H), 7.08–7.62 (m, 8H, Ar–H), 8.52 (s, 1H, N=CH), 10.27 (s, 1H, NH); *m/z* (EI) 448 (M^+).

7g: IR: 3372 (NH), 1623 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 8.18 (m, 2H, C_4–H, C_5–H), 7.80 (m, 1H, C_6–H), 8.43 (m, 1H, C_7–H), 7.02–7.47 (m, 8H, Ar–H), 8.57 (s, 1H, N=CH), 10.29 (s, 1H, NH); *m/z* (EI) 448 (M^+).

7h: IR: 3360 (NH), 1624 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 6.02 (s, 2H, O–CH_2–O), 7.82 (m, 2H, C_4–H, C_5–H), 7.63 (m, 1H, C_6–H), 8.38 (m, 1H, C_7–H), 7.02–7.45 (m, 7H, Ar–H), 8.48 (s, 1H, N=CH), 10.26 (s, 1H, NH); *m/z* (EI) 447 (M^+).

General procedure for the synthesis of 1-aryl-4-(p-bromophenyl)-1,2,4-triazolo[4,3-a][1,8]naphthyridines (**8**): To a solution of **7** (0.01 mol) in 1,2-dichloroethane (20 ml), chloranil (0.01 mol) was added. The reaction mixture was subjected to microwave irradiation at 200 watts intermittently at 30 s intervals for the specified time (Table 1). After complete conversion as indicated by TLC, the reaction mixture was cooled, the insoluble portion (which is 2,3,5,6-tetrachloro-1, 4-dihydroquinone) was filtered, washed with 10% NaOH (30 ml). The organic layer was washed with water (2 × 20 ml) free of alkali, dried over anhyd. Na_2SO_4 and the solvent (1,2-dichloroethane) was distilled off to obtain a residue, which was recrystallised from methanol to afford **8**.

8a: IR: 1610 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 8.12 (m, 2H, C_5–H, C_7–H), 8.27 (m, 1H, C_6–H), 8.46 (m, 1H, C_8–H), 7.45–7.89 (m, 9H, Ar–H); *m/z* (EI) 401 (M^+).

8b: IR: 1612 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 2.43 (s, 3H, CH_3), 8.04 (m, 2H, C_5–H, C_7–H), 8.24 (m, 1H, C_6–H), 8.48 (m, 1H, C_8–H), 7.30–7.82 (m, 8H, Ar–H); *m/z* (EI) 415 (M^+).

Table 1 Physical and analytical data of aryl aldehyde 3–(*p*-bromophenyl)-1,8-naphthyridin-2-ylhydrazones (**7**) and 1-aryl-4-(*p*-bromophenyl)-1,2,4-triazolo[4,3-*a*][1,8]-naphthyridines (**8**)

Compd	Ar	Reaction time /min	Yield/% [m.p.]	Mol. formula	Microanalysis calculated [found] %		
					C	H	N
7a	C_6H_5	1.5	94 [220–222]	$C_{21}H_{15}BrN_4$	62.53 [62.67]	3.72 [3.76]	13.90 [13.97]
7b	*p*-$CH_3C_6H_4$	1.5	98 [179–180]	$C_{22}H_{17}BrN_4$	63.31 [63.47]	4.08 [4.03]	13.43 [13.48]
7c	*p*-$CH_3OC_6H_4$	2.0	95 [186–188]	$C_{22}H_{17}BrN_4O$	60.97 [60.82]	3.93 [3.96]	12.93 [12.98]
7d	*o*-ClC_6H_4	2.0	94 [174–176]	$C_{21}H_{14}BrClN_4$	57.60 [57.75]	3.20 [3.25]	12.80 [12.88]
7e	*p*-ClC_6H_4	1.5	96 [190–192]	$C_{21}H_{14}BrClN_4$	57.60 [57.74]	3.20 [3.26]	12.80 [12.87]
7f	*m*-$NO_2C_6H_4$	1.0	92 [215–217]	$C_{21}H_{14}BrN_5O_2$	56.25 [56.39]	3.13 [3.18]	15.63 [15.68]
7g	*p*-$NO_2C_6H_4$	1.0	94 [230–232]	$C_{21}H_{14}BrN_5O_2$	56.25 [56.40]	3.13 [3.17]	5.63 [15.69]
7h	3,4-(O-CH_2-O)C_6H_3	1.5	96 [182–183]	$C_{22}H_{15}BrN_4O_2$	59.06 [59.22]	3.36 [3.40]	12.53 [12.60]
8a	C_6H_5	4.5	90 [>300]	$C_{21}H_{13}BrN_4$	62.84 [62.98]	3.24 [3.29]	13.97 [13.91]
8b	*p*-$CH_3C_6H_4$	4.0	94 [>300]	$C_{22}H_{15}N_4Br$	63.61 [63.77]	3.61 [3.65]	13.49 [13.56]
8c	*p*-$CH_3OC_6H_4$	5.5	89 [>300]	$C_{22}H_{15}BrN_4O$	61.25 [61.40]	3.48 [3.43]	12.99 [12.91]
8d	*o*-ClC_6H_4	4.5	88 [>300]	$C_{21}H_{12}BrClN_4$	57.86 [57.99]	2.76 [2.72]	12.86 [12.92]
8e	*p*-ClC_6H_4	4.0	92 [>300]	$C_{21}H_{12}BrClN_4$	57.86 [57.98]	2.76 [2.71]	12.86 [12.93]
8f	*m*-$NO_2C_6H_4$	5.5	87 [>300]	$C_{21}H_{12}BrN_5O_2$	56.50 [56.68]	2.69 [2.63]	15.70 [15.78]
8g	*p*-$NO_2C_6H_4$	6.0	88 [>300]	$C_{21}H_{12}BrN_5O_2$	56.50 [56.67]	2.69 [2.64]	15.70 [15.77]
8h	3,4-(O-CH_2-O)C_6H_3	5.0	90 [>300]	$C_{22}H_{13}BrN_4O_2$	59.33 [59.49]	2.92 [2.96]	12.58 [12.67]

8c: IR: 1608 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 3.86 (s, 3H, OCH_3), 8.10 (m, 2H, C_5–H, C_7–H), 8.26 (m, 1H, C_6–H), 8.52 (m, 1H, C_8–H), 7.40–7.86 (m, 8H, Ar–H); *m/z* (EI) 431 (M^+).

8d: IR: 1612 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 8.05 (m, 2H, C_5–H, C_7–H), 8.26 (m, 1H, C_6–H), 8.45 (m, 1H, C_8–H), 7.38–7.82 (m, 8H, Ar–H); *m/z* (EI) 435 (M^+).

8e: IR: 1610 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 8.10 (m, 2H, C_5–H, C_7–H), 8.34 (m, 1H, C_6–H), 8.49 (m, 1H, C_8–H), 7.42–7.87 (m, 8H, Ar–H); *m/z* (EI) 435 (M^+).

8f: IR: 1614 cm^{-1} (C=N); ^1H NMR ($CDCl_3$ + DMSO–d_6): δ 8.09 (m, 2H, C_5–H, C_7–H), 8.30 (m, 1H, C_6–H), 8.45 (m, 1H, C_8–H), 7.45–7.81 (m, 8H, Ar–H); *m/z* (EI) 446 (M^+).

8g: IR: 1612 cm^{-1} (C=N); ^1H NMR ($CDCl_3$ + DMSO–d_6): δ 8.11 (m, 2H, C_5–H, C_7–H), 8.25 (m, 1H, C_6–H), 8.48 (m, 1H, C_8–H), 7.37–7.73 (m, 8H, Ar–H); *m/z* (EI) 446 (M^+).

8h: IR: 1609 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 6.05 (s, 2H, O–CH_2–O), 8.07 (m, 2H, C_5–H, C_7–H), 8.25 (m, 1H, C_6–H), 8.44 (m, 1H, C_8–H), 7.43–7.91 (m, 7H, Ar–H); *m/z* (EI) 445 (M^+).

The authors are thankful to the Directors, IICT, Hyderabad and IIT, Chennai for providing spectral and analytical data.

Received 11 February 2005; accepted 22 April 2005
Paper 05/3066

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