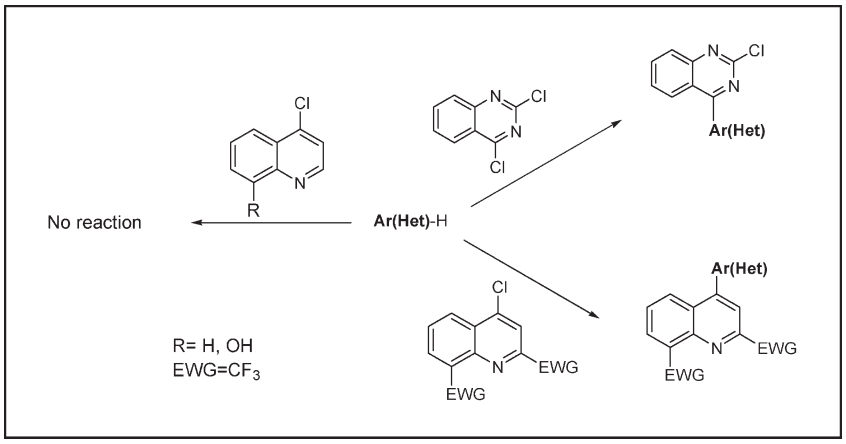
Shailesh Kumar and Devi Prasad Sahu*

Medicinal and Process Chemistry Division, Central Drug Research Institute, Lucknow 226001, India
*E-mail: dpsahuin@yahoo.com (or) dp_sahu@cdri.res.in

Received February 28, 2009
DOI 10.1002/jhet.144
Published online 14 July 2009 in Wiley InterScience (www.interscience.wiley.com).

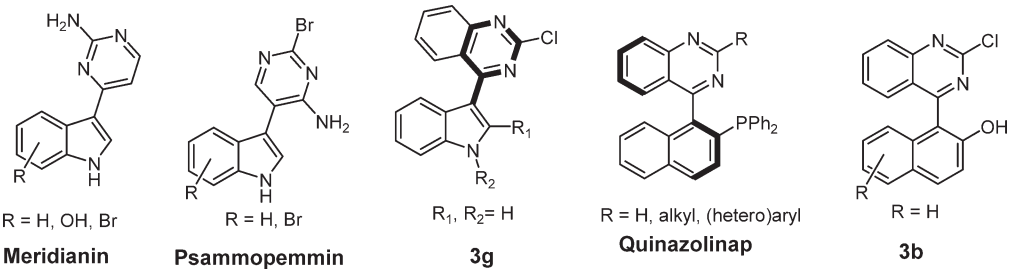


Anhydrous $AlCl_3$-mediated heteroarylation of various arenes and heteroarenes with 2,4-dichloro-quinazoline (**1**) and 4-chloroquinoline (**4**) afforded exclusively 4-aryl/heteroarylquinazolines (**3**) and 4-aryl/heteroarylquinolines (**5**), respectively. Compared with the available synthetic protocols, aluminum chloride induced C—C bond formation is direct and convenient to access bis-(hetero)aryl quinazolines and quinolines. The products were obtained in good to excellent yields by this method.

J. Heterocyclic Chem., **46**, 748 (2009).

INTRODUCTION

Biaryls and biheteroaryls are significant building blocks in a large number of natural products [1] and are also an important structural motif in a variety of biologically active compounds [2]. Pyrazinopyridine biheteroaryls have been reported as potent VEGFR-2 inhibitors [3]. The meridianins and related psammopemmin marine alkaloids containing 3-(2-aminopyrimidine)-indole motifs are potent protein kinase inhibitors [4] and possess antitumor activity [5]. The biheteroaryls have drawn a great attention in advanced materials including conductive polymers [6], liquid crystals [7], supramolecules [8], and molecular electronics [9]. Quinazolines and quinolines are of considerable interest because of their synthetic and therapeutic utility [10]. Biheteroaryls containing these scaffolds may have interesting biological and physicochemical properties. Important class of atropisomeric biaryl ligands with axial chirality, quinazolinap [11], and related ligands [12] containing nitrogen in one of the aryl rings have been used in various asymmetric reactions. These important biheteroaryls were earlier synthesized by metal-catalyzed reactions, which include palladium-catalyzed Suzuki-Miyaura cross coupling [13] between organoboronic acid and halides, nickel- or palladium-catalyzed Negishi coupling [14] of organozinc compounds with various halides, or Stille coupling [15] between stannanes and halides. These synthetic protocols require multistep reactions involving either pyrophoric organolithium reagents or toxic and expensive catalysts. Alternately, anhydrous $AlCl_3$-mediated heteroarylation of arenes [16] and heteroarenes could be a cheap, convenient, and straightforward synthetic methodology to access the bis-heteroaryls 1-(2-chloroquinazolin-4-yl)-naphthalen-2-ol (**3b**) and 2-chloro-4-(1H-indol-3-yl)quinazoline (**3g**), which are structurally similar to quinazolinap and meridianins, respectively. As a part of our ongoing program devoted to the diversity-oriented synthesis (DOS), we had reported synthesis and biological activity of some azaheterocycles and coumarine derivatives. In the continuation of our studies [17], herein we report a facile and direct synthesis of 4-aryl/heteroaryl quinazolines and 4-aryl/heteroaryl quinolines by $AlCl_3$-mediated direct C—C bond forming reactions.



RESULTS AND DISCUSSION

The heteroarylation of arenes and heteroarenes with 2,4-dichloroquinazoline [18] was explored under Friedel-Crafts reaction conditions. When one equivalent of arene/heteroarene was reacted with one equivalent of 2,4-dichloroquinazoline in the presence of 1.2 equiv of anhydrous aluminum chloride using dichloroethane as solvent, 4-(hetero)aryl-substituted-2-chloroquinazolines were formed exclusively in good to excellent yields. The results are summarized in Table 1. Alternatively, on carrying out reactions at relatively lower temperature (40–45°C) for a longer duration of time (8–10 h), similar yield of the arylated and heteroarylated products could be obtained.

The heteroarylation proceeded well in the presence of various aryl and heteroaryl reactants. Arenes activated with electron donating groups were found to be effective for heteroarylation (entries 1–6). With 1,3,5-trimethoxybenzene as reactant, an excellent yield (85%) of the product **3e** was obtained in a short time (entry 5). Free phenolic hydroxyl groups were found to be well tolerated during the reaction and heteroarylation occurred at the ring carbon rather than oxygen (entries 1, 2, 3, and 6). With 2-hydroxynaphthalene (entry 2), a trace of 2,4-diarylquinazoline was formed along with the product **3b**. The structures of the products synthesized were established by analytical and spectroscopic data. The regioselectivity of the product **3a–d** were confirmed by NOESY experiment (Figure 1). In the ^{1}H NMR spectrum of compound **3a**, the signals at δ 3.49, 6.46, 7.01, and 7.68 were assigned for H-19, H-15, H-17, and H-4, which in ^{13}C NMR were appeared at δ 55.25, 104.00, 116.21, and 128.65, respectively.

The existence of correlations in the NOESY experiment of **3a** between the protons signals of H-19 and H-15, between the protons signals of H-19 and H-17 and the protons signals of H-15 and H-4 suggested that there is no substitution at C-15 and C-17, which is the confirmatory evidence of structure for the compound **3a**. Similarly, the connectivity in compound **3d** was confirmed from correlation between the proton signals at δ 6.61 (H-4) and δ 3.71 (H-7), between the protons signals of δ 6.67 (H-2) and δ 3.90 (H-8) and between the protons signals of δ 6.61 (H-4) and δ 3.90 (H-8) in the NOESY experiment of compound. A number of nitrogen-containing heteroarenes, e.g., pyrrole (entry 11), indoles (entries 7–10), and indolizines (entries 12–15) were used in the $AlCl_3$-induced reaction.

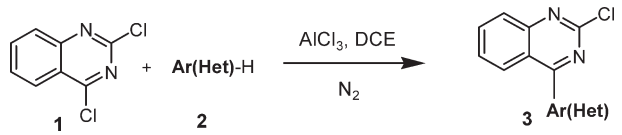
The reactivity toward indole and pyrrole derivatives (entries 7–15) were somewhat more than those of naphthyl derivatives which might be due to differences in their nucleophilicity. Similarly, with 1,3-dimethoxybenzene and *sym*-trimethoxybenzene, the arylation was completed within 2 h at 65–70°C, and the products were isolated in excellent yields (entries 4 and 5). The reaction of 2,4-dichloroquinazoline with various indolizines (fused pyrroles) (entries 12–15) were completed at 40–45°C within a few minutes. Imidazoles (entries 16 and 17), surprisingly, did not react under similar conditions. This is perhaps due to the formation of a metal-ionic complex with imidazole ($pK_a = 7.1$) resulting in a decrease of nucleophilicity. Thus, unlike pyrrole derivatives, the more basic imidazole system having an additional nitrogen atom deactivates the ring for arylation to occur.

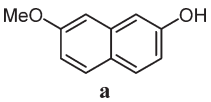
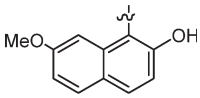
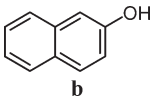
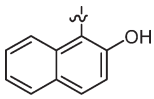
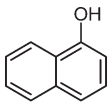
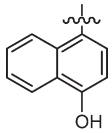
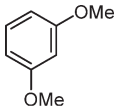
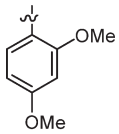
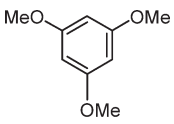
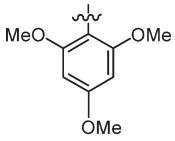
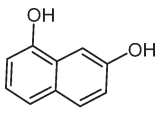
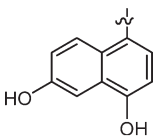
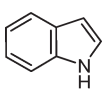
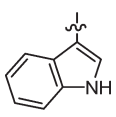
The arylation of 4-chloroquinoline derivatives with arenes and heteroarenes under similar conditions furnished 4-(hetero)aryl-substituted quinolines. The results are shown in Table 2. In the case of 4-chloro-2,8-bis(trifluoromethyl)quinoline, the reaction occurred in 72–80% yield at 60–65°C in 45–50 min for 1,3-dimethoxy-benzene and 1,3,5-trimethoxybenzene as nucleophiles. However, unsubstituted 4-chloroquinoline and 8-hydroxy quinoline failed to undergo arylation with arenes and heteroarenes.

The proposed mechanism is shown in Figure 2. The two chlorine atoms in 2,4-dichloroquinazoline are in different electronic environments, the chlorine at C-4 becomes more labile due to a greater electron withdrawing effect involving both the N atoms through mesomeric effects and hence can be easily replaced by a suitable nucleophile to give the regioselective product. A similar mechanism in the case of 4-chloro-2,8-bis(trifluoromethyl)quinoline may be invoked. Trifluoromethyl groups in the quinoline derivative make the reaction more facile by participating in decreasing the electron density at C-4 and thereby making this position more electrophilic for the nucleophilic attack.

Table 1

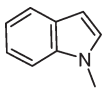
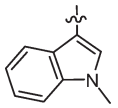
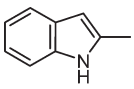
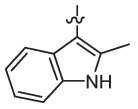
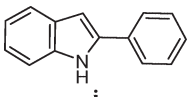
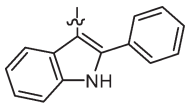
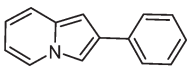
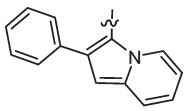
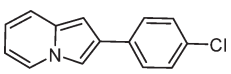
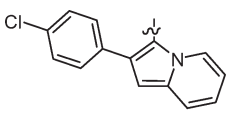
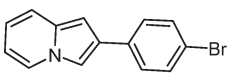
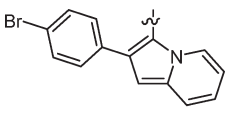
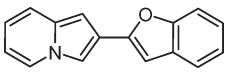
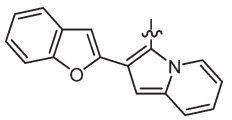
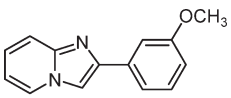
Regioselective $AlCl_3$-mediated synthesis of 4-(hetero)arylquinazolines.[a]



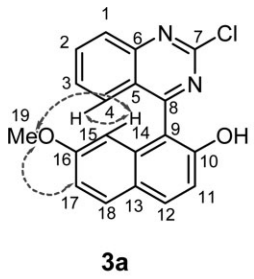
Entry	Substrate **2**; **Ar(Het)**-H	Temp. (°C)	Time	Product **3**; **Ar(Het)** =	Yield[b] (%)	m.p. (°C)
1	 **a**	75–80	3 h	 **a**	70	173–175
2	 **b**	75–80	3 h	 **b**	64	168–170
3	 **c**	75–80	3 h	 **c**	65	155–157
4	 **d**	65–70	2 h	 **d**	83	140–142
5	 **e**	65–70	1.5 h	 **e**	85	200–202
6	 **f**	75–80	3 h	 **f**	60	>250
7	 **g**	75–80	3 h	 **g**	77	175–177

(*Continued*)

Table 1
(*Continued*)

Entry	Substrate **2**; **Ar(Het)**-H	Temp. (°C)	Time	Product **3;** **Ar(Het)** =	Yield[b] (%)	m.p. (°C)
8	 **h**	75–80	2.5 h	 **h**	80	142–144
9	 **i**	75–80	2.5 h	 **i**	57	>250
10	 **j**	75–80	2.5 h	 **j**	50	260–262
11	 **k**	75–80	2.5 h	 **k**	85	107–109
12	 **l**	40–45	15 min	 **l**	80	192–194
13	 **m**	40–45	15 min	 **m**	85	218–220
14	 **n**	40–45	10 min	 **n**	85	190–192
15	 **o**	40–45	10 min	 **o**	80	146–148
16	 **p**	75–80	4 h		No reaction	
17	 **q**	75–80	4 h		No reaction	

[a] Reaction stoichiometries: **1** (1.0 equiv), **2a–2q** (1.0 equiv), $AlCl_3$ (1.2 equiv).
[b] Isolated yield.



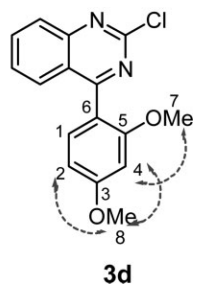


Figure 1. NOESY correlations in **3a** and **3d**.

CONCLUSIONS

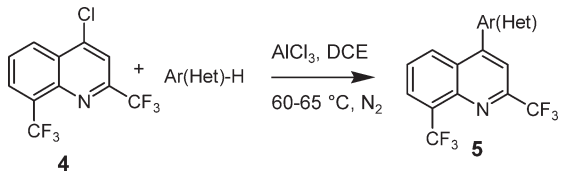
In conclusion, we have explored for the first time the scope and limitation of $AlCl_3$-mediated arylation and heteroarylation of mono and dichloroazarenes through a direct C—C bond forming reaction with arenes and heteroarenes. Suitably substituted chloroazarenes with single nitrogen atom such as 4-chloro-2,8-bis(trifluoromethyl)quinoline could be arylated regioselectively to furnish 4-arylquinolines. Similarly, arylation of 2,4-dichloroquinazoline leads to the formation 4-aryl and 4-heteroaryl quinazolines which are of biological importance. The biheteroaryls with ortho substituent are obtained in their racemic form, which after resolution could be separated into atropisomers, providing an easy route to access the P, N ligands. Surprisingly, demethylation and debromination of the product were not observed in any case in the presence of anhydrous aluminum chloride under the comparatively mild conditions.

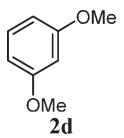
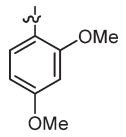
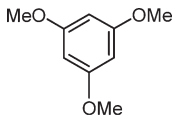
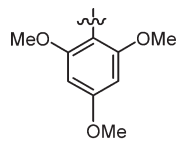
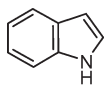
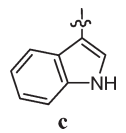
EXPERIMENTAL

General methods. All the reactions were performed under nitrogen atmosphere in oven-dried glass wares. The nucleophilic substrates **2a–q** used were either commercially available or prepared in laboratory. Aluminum chloride used was of commercial grade. A commercial grade dichloroethane stored

Table 2

$AlCl_3$-mediated synthesis of 4-(hetero)arylquinolines.[a]



Entry	Substrate **Ar(Het)-H**	Time	Product **5**; **Ar(Het)**=	Yield[b] (%)	m.p. (°C)
1	 **2d**	45 min	 **a**	80	105–107
2	 **2e**	50 min	 **b**	72	133–135
3	 **2g**	2.5 h	 **c**	68	141–143

[a] Reaction stoichiometries: **4** (1.0 equiv), **2d, 2e**, and **2g** (1.0 equiv), $AlCl_3$ (1.2 equiv).
[b] Isolated yield.

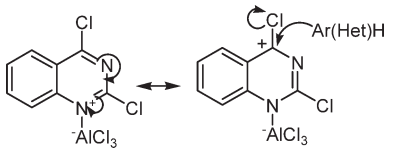


Figure 2. Proposed mechanism for the regioselective substitution in quinazoline.

over calcium chloride was used. Reaction progress was monitored by TLC aluminum sheets silica gel 60 F_{254}. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Supercon Magnet DPX-200 or DRX-300 spectrometers (operating at 200 and 300 MHz, respectively, for ^{1}H; 50 and 75 MHz, respectively, for ^{13}C) using $CDCl_3$ and DMSO-d_6 as solvent. Tetramethylsilane (δ 0.00 ppm) served as an internal standard in ^{1}H NMR and $CDCl_3$ (δ 77.23 ppm) in ^{13}C NMR. Splitting patterns are described as singlet (s), broad singlet (brs), doublet (d), triplet (t), and multiplet (m). Electrospray mass spectra (ES-MS) were recorded on a Micromass Quattro II triple quadruple mass spectrometer. High-resolution electron impact mass spectra (HREIMS) were obtained on JEOL MS route 600H instrument. Elemental analysis was performed on Vario EL-III C H N S analyzer. Column chromatography was performed over Merck silica gel (particle size: 60–120 mesh) obtained from Qualigens (India), or flash silica gel (particle size: 230–400 mesh).

General method for the preparation of 2,4-dichloroquinazoline 1

Step 1. A mixture of anthranilic acid (50 g, 0.36 mol) and urea (109 g, 1.82 mol) was heated [18a] in neat at 135–140°C using an air condenser for 3 h. The product mixture was poured into crushed ice (500 mL) with continuous stirring for 30 min. Quinazoline-2,4-dione thus obtained as solid was filtered, washed with water and used as such in the next step. Yield 74%; m.p. $>$ 250°C.

Step 2. A mixture of quinazoline-2,4-dione (20 g, 0.12 mol) as obtained earlier and $POCl_3$ (98 g, 0.64 mol) was refluxed in the presence of *N*,*N*-dimethylaniline (8.5 g, 0.07 mol) for 5 h [18b]. The reaction mixture was allowed to cool to room temperature and poured cautiously into crushed ice (500 mL) with continuous stirring for 20 min. The precipitate obtained was filtered, washed with water, and finally purified column chromatography using 30% ethyl acetate/hexane as eluent. Yield 73%; m.p.: 115–116°C (116–117°C) [18b].

General method for the preparation of 4-(hetero)aryl quinazolines 3a–o. To the solution of 2,4-dichloroquinazoline **1** (1 mmol, 0.198 g) in 10 mL of dichloroethane under stirring, $AlCl_3$ (1.2 mmol, 0.158 g) was added and allowed to stir for 2–5 min. Nucleophilic substrate **2a–q** (1 mmol) (Table 1) were added and allowed to stir for completion of the reaction (see Table 1 for time and temperature). Reaction was monitored by TLC using 30% of ethyl acetate-hexane mixture. The reaction mixture was cooled to room temperature and poured into crushed ice (100 mL) with continuous stirring for 15–20 min. The products were obtained either by filtration through suction pump (**3b**, **3g**) or extracted with dichloromethane (3 $\times$ 30 mL). The organic layers were combined, washed with brine, and concentrated under reduced pressure after drying over Na_2SO_4. The crude products obtained were further purified by silica gel column chromatography using ethyl acetate-hexane as eluent.

1-(2-Chloroquinazolin-4-yl)-7-methoxynaphthalen-2-ol (3a). Yield 70%; m.p.: 173–175°C; IR (potassium bromide): 3450, 1597, 1351, 1183 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.49 (s, 3H), 6.46 (d, 1H, J = 2.2 Hz), 7.01 (dd, 1H, J = 8.9, 2.3 Hz), 7.14 (d, 1H, J = 8.8 Hz), 7.44–7.49 (m, 1H), 7.68 (d, 1H, J = 8.3 Hz), 7.72 (d, 1H, J = 8.9 Hz), 7.81 (d, 1H, J = 8.9 Hz), 7.89–7.95 (m, 1H), 8.05 (d, 1H, J = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.25 (CH_3), 104.00 (CH), 113.8, 116.21 (CH), 116.44 (CH), 122.92, 124.34, 128.05 (CH), 128.25 (CH), 128.65 (CH), 130.18 (CH), 132.90 (CH), 133.98, 135.86 (CH), 153.00, 154.64, 156.70, 158.87, 170.13; ES-MS (*m*/*z*): $[M+H]^+$ 337; HRMS -EI: found: 336.0665, calculated: 336.0666. Anal. Calcd. for $C_{19}H_{13}ClN_2O_2$: C, 67.76; H, 3.89; N, 8.32. Found: C, 67.61; H, 3.78; N, 8.23.

1-(2-Chloroquinazolin-4-yl)naphthalen-2-ol (3b). Yield 64%; m.p.: 168–170°C; IR (potassium bromide): 3455, 1580 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17 (d, 1H, J = 8.3 Hz), 7.26–7.32 (m, 2H), 7.34–7.39 (m, 1H), 7.42–7.48 (m, 1H), 7.61 (d, 1H, J = 8.1 Hz), 7.85 (d, 1H, J = 7.7 Hz), 7.90–7.96 (m, 2H), 8.09 (d, 1H, J = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 115.17, 118.69, 123.48, 123.89, 124.09, 127.24, 127.80, 127.97, 128.15, 128.26, 128.44, 131.78, 133.04, 135.27, 152.50, 153.28, 157.18, 171.31; ES-MS (*m*/*z*): $[M+H]^+$ 307; HRMS-EI: found: 306.0550, calculated: 306.0560. Anal. Calcd. for $C_{18}H_{11}ClN_2O$: C, 70.48; H, 3.61; N, 9.13. Found: C, 70.16; H, 3.70; N, 8.93.

4-(2-Chloroquinazolin-4-yl)naphthalen-1-ol (3c). Yield 65%; m.p.: 155–157°C; IR (potassium bromide): 3445, 1587 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.95 (d, 1H, J = 9.1 Hz), 7.26–7.40 (m, 4H), 7.47 (d, 1H, J = 9.0 Hz), 7.66 (d, 1H, J = 6.1 Hz), 7.78–7.83 (m, 1H), 7.93 (d, 1H, J = 6.0 Hz), 8.28 (d, 1H, J = 9.0 Hz), 9.95 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ 106.27, 121.53, 122.12, 122.46, 123.50, 123.76, 125.95, 126.36, 126.45, 126.79, 128.64, 131.28, 133.72, 151.25, 154.48, 155.53, 171.47; ES-MS (*m*/*z*): $[M+H]^+$ 307; HRMS-EI: found: 306.0558, calculated: 306.0559. Anal. Calcd. for $C_{18}H_{11}ClN_2O$: C, 70.48; H, 3.61; N, 9.13. Found: C, 70.17; H, 3.66; N, 9.01.

2-Chloro-4-(2,4-dimethoxyphenyl)quinazoline (3d). Yield 83%; m.p.: 140–142°C; IR (potassium bromide): 1611, 1209, 1161 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.71 (s, 3H), 3.90 (s, 3H), 6.61 (d, 1H, J = 2.2 Hz), 6.67 (dd, 1H, J = 8.4, 2.3 Hz), 7.41 (d, 1H, J = 8.4 Hz), 7.49–7.55 (m, 1H), 7.77 (dd, 1H, J = 8.0, 0.8 Hz), 7.85–7.90 (m, 1H), 7.99 (d, 1H, J = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.89, 56.01, 99.23, 105.64, 123.45, 127.70, 128.03, 128.65, 132.68, 135.00, 152.52, 158.66, 163.26, 171.21; FAB (*m*/*z*): 300, $[M+H]^+$ 301; HRMS-EI: found: 300.0663, calculated: 300.0666. Anal. Calcd. for $C_{16}H_{13}ClN_2O_2$: C, 63.90; H, 4.36; N, 9.31. Found: C, 63.95; H, 4.39; N, 9.29.

2-Chloro-4-(2,4,6-trimethoxyphenyl)quinazoline (3e). Yield 85%; m.p.: 200–202°C; IR (potassium bromide): 1610, 1215 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.64 (s, 6H), 3.89 (s, 3H), 6.25 (s, 2H), 7.47–7.53 (m, 1H), 7.66 (dd, 1H, J = 7.9, 0.6 Hz), 7.83–7.89 (m, 1H), 7.99 (d, 1H, J = 8.46 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.68 (OCH_3), 55.95 (OCH_3), 90.99, 106.72, 124.48, 127.59, 127.72, 134.70, 152.19, 157.22, 159.17, 163.07, 169.66. ES-MS (*m*/*z*): $[M+H]^+$ 331; HRMS-EI: found: 330.0769, calculated: 330.0771. Anal. Calcd. for $C_{17}H_{15}ClN_2O_3$: C, 61.73; H, 4.57; N, 8.47. Found: C, 61.49; H, 4.42; N, 8.15.

4-(2-Chloroquinazolin-4-yl)naphthalene-1,7-diol (3f). Yield 60%; m.p.: >250°C; IR (potassium bromide): 3452, 1585, 1352, 761 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 6.77–6.86 (m, 2H), 7.10 (d, 1H, J = 7.7 Hz), 7.27 (d, 1H, J = 9.1 Hz), 7.35 (d, 1H, J = 2.3 Hz), 7.45–7.58 (m, 2H), 7.88–7.89 (m, 2H), 9.6 (brs, 1H), 10.39 (brs, 1H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 104.43, 107.64, 119.96, 123.45, 123.63, 126.57, 127.09, 127.72, 128.12, 128.73, 135.90, 152.52, 154.39, 155.24, 156.35, 172.96, 175.22; ES-MS (*m/z*): $[M+H]^+$ 323; HRMS-EI: found: 322.0507, calculated: 322.0509. Anal. Calcd. for $C_{18}H_{11}ClN_2O_2$: C, 66.99; H, 3.44; N, 8.68. Found: C, 66.79; H, 3.41; N, 8.61.

2-Chloro-4-(1H-indol-3-yl)quinazoline (3g). Yield 77%; m.p.: 175–177°C; IR (potassium bromide): 1521, 1487, 1340 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ 7.27–7.30 (m, 2H), 7.54–7.57 (m, 1H), 7.61–7.67 (m, 1H), 7.88–7.94 (m, 1H), 7.97–8.02 (m, 2H), 8.26–8.29 (m, 1H), 8.45 (dd, 1H, J = 8.1, 0.6 Hz), 11.57 (NH); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ 111.91, 112.23, 121.12, 121.27, 121.40, 122.94, 126.03, 127.05, 127.25, 130.80, 133.98, 136.81, 152.17, 156.63, 166.35; FAB (*m/z*): 279, $[M+H]^+$ 280; HRMS-EI: found: 279.0494, calculated: 279.0485. Anal. Calcd. for $C_{16}H_{10}ClN_3$: C, 68.70; H, 3.60; N, 15.02. Found: C, 68.79; H, 3.68; N, 15.21.

2-Chloro-4-(1-methyl-1H-indol-3-yl)quinazoline (3h). Yield 80%; m.p.: 142–144°C; IR (potassium bromide): 1563, 1347, 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.93 (s, 3H), 7.28–7.36 (m, 2H), 7.38–7.43 (m, 1H), 7.55–7.61 (m, 1H), 7.78 (s, 1H), 7.84–7.89 (m, 1H), 7.97 (dd, 1H, J = 8.3, 0.7 Hz), 8.17–8.20 (m, 1H), 8.41 (dd, 1H, J = 8.6, 0.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 33.68 (CH_3), 109.96 (CH), 112.19 (C), 121.53 (C), 122.04 (CH), 122.12 (CH), 123.52 (CH), 127.00 (C), 127.29 (CH), 127.46 (CH), 128.05 (CH), 133.93 (CH), 134.33 (CH), 137.65 (C), 152.90 (C), 157.37 (C), 166.15 (C); ES-MS (*m/z*): $[M+H]^+$ 294; HRMS-EI: found: 293.0689, calcuated: 293.0719. Anal. Calcd. for $C_{17}H_{12}ClN_3$: C, 69.51; H, 4.12; N, 14.30. Found: C, 69.45; H, 4.10; N, 14.19.

2-Chloro-4-(2-methyl-1H-indol-3-yl)quinazoline (3i). Yield 57%; m.p.: >250°C; IR (potassium bromide): 1519, 1485, 1352 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$+DMSO-d_6): δ 2.60 (s, 3H), 7.05–7.21 (m, 2H), 7.42–7.45 (m, 2H), 7.51–7.58 (m, 1H), 7.87–8.01 (m, 2H), 8.12 (d, 1H, J = 8.3 Hz), 10.95 (brs, 1H); ^{13}C NMR (50 MHz, $CDCl_3$+DMSO-d_6): δ 13.67, 111.52, 119.62, 120.96, 122.18, 122.79, 127.26, 127.91, 128.18, 128.93, 134.88, 136.06, 139.67, 153.01, 157.41, 168.56; ES-MS (*m/z*): $[M+H]^+$ 294; HRMS-EI: found: 293.0718, calculated: 293.0719. Anal. Calcd. for $C_{17}H_{12}ClN_3$: C, 69.51; H, 4.12; N, 14.30. Found: C, 69.35; H, 4.22; N, 14.22.

2-Chloro-4-(2-phenyl-1H-indol-3-yl)quinazoline (3j). Yield 50%; m.p.: 260–262°C; IR (potassium bromide): 3223, 1598, 1345, 747 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ 7.09–7.15 (m, 1H), 7.23–7.28 (m, 4H), 7.32–7.39 (m, 3H), 7.55–7.82 (m, 2H), 7.73 (d, 1H, J = 8.2 Hz), 7.84–7.93 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ 106.57, 110.20, 117.70, 119.13, 120.14, 121.12, 125.47, 125.71, 126.32, 126.69, 126.96, 129.81, 133.24, 134.71, 138.15, 150.58, 154.79, 166.49; FAB (*m/z*): 355, $[M+H]^+$ 356. Anal. Calcd. for $C_{22}H_{14}ClN_3$: C, 74.26; H, 3.97; N, 11.81. Found: C, 74.59; H, 3.89; N, 11.75.

2-Chloro-4-(1H-pyrrol-2-yl)quinazoline (3k). Yield 85%; m.p.: 107–109°C; IR (potassium bromide): 3220, 1550 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.46–6.49 (m, 1H), 7.14–7.16 (m, 1H), 7.26–7.28 (m, 1H), 7.79–7.64 (m, 1H), 7.83–7.88 (m, 1H), 7.92 (dd, 4H, J = 8.3, 0.9 Hz), 8.53 (d, 1H, J = 8.5 Hz), 10.13 (s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 112.59, 117.33, 119.68, 123.99, 126.21, 127.85, 127.97, 128.34, 134.47, 153.26, 156.75, 159.41; ES-MS (*m/z*): $[M+H]^+$ 230; HRMS-EI: found: 229.0357, calculated: 229.0407. Anal. Calcd. for $C_{12}H_8ClN_3$: C, 62.76; H, 3.51; N, 18.30. Found: C, 62.41; H, 3.67; N, 18.54.

2-Chloro-4-(2-phenylindolizin-3-yl)quinazoline (3l). Yield 80%; m.p.: 192–194°C; IR (potassium bromide): 2366, 1598, 1350, 767 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.72–6.77 (m, 1H), 6.78 (s, 1H), 6.98–7.08 (m, 2H), 7.10–7.15 (m, 5H), 7.53–7.59 (m, 2H), 7.63–7.68 (m, 1H), 7.87 (d, 1H, J = 8.49 Hz), 8.99 (d, 1H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 101.55, 111.23, 114.25, 117.69, 119.95, 120.45, 123.43, 125.49, 125.70, 125.90, 127.24, 127.76, 133.15, 134.13, 134.22, 135.39, 151.99, 155.59, 161.36; ES-MS (*m/z*): $[M+H]^+$ 356; HRMS-EI: found: 355.0876, calculated: 355.0876. Anal. Calcd. for $C_{22}H_{14}ClN_3$: C, 74.26; H, 3.97; N, 11.81. Found: C, 73.95; H, 4.13; N, 11.49.

2-Chloro-4-[2-(4-chlorophenyl)indolizin-3-yl]quinazoline (3m). Yield 85%; m.p.: 218–220°C; IR (potassium bromide): 1597, 1349, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.69–6.74 (m, 2H), 6.96–7.13 (m, 6H), 7.51 (d, 1H, J = 8.9 Hz), 7.53 (dd, 1H, J = 8.6, 0.6 Hz), 7.66–7.71 (m, 1H), 7.87 (d, 1H J = 8.5 Hz), 8.91 (dd, 1H, J = 7.2, 0.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 102.87, 112.90, 115.55, 119.18, 121.32, 122.07, 124.86, 127.29, 127.56, 128.41, 128.91, 130.32, 133.22, 134.04, 134.21, 134.89, 136.81, 153.53, 157.09, 162.54; ES-MS (*m/z*): $[M+H]^+$ 390; HRMS-EI: found: 389.0492, calcuated: 389.0487. Anal. Calcd. for $C_{22}H_{13}Cl_2N_3$: C, 67.71; H, 3.36; N, 10.77. Found: C, 67.46; H, 3.42; N, 10.63.

4-[2-(4-Bromophenyl)indolizin-3-yl]-2-chloroquinazoline (3n). Yield 85%; m.p.: 190–192°C; IR (potassium bromide): 1597, 1348, 772cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.70–6.75 (m, 2H), 6.97–7.02 (m, 3H), 7.09–7.15 (m, 1H), 7.22–7.25 (m, 2H), 7.50–7.55 (m, 2H), 7.67–7.73 (m, 1H), 7.88 (d, 1H, J = 8.3 Hz), 8.91 (dd, 1H, J = 7.1, 0.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 102.83, 112.94, 115.55, 119.22, 121.38, 121.45, 122.08, 124.90, 127.35, 127.64, 128.42, 130.66, 131.90, 134.05, 134.72, 134.94, 136.85, 157.15, 162.58; ES-MS (*m/z*): $[M+H]^+$ 434 (Br^{78}), 436(Br^{80}); HRMS-EI: found: 432.9950, calcuated: 432.9981. Anal. Calcd. for $C_{22}H_{13}BrClN_3$: C, 60.78; H, 3.01; N, 9.67. Found: C, 60.59; H, 3.29; N, 9.43.

4-(2-Benzofuran-2-yl-indolizin-3-yl)-2-chloroquinazoline (3o). Yield 80%; m.p.: 146–148°C; IR (potassium bromide): 1596, 1350 1172, 765 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.49 (s, 1H), 6.67–6.71 (m, 1H), 6.94–6.99 (m, 1H), 7.02–7.12 (m, 4H), 7.17–7.22 (m, 1H), 7.36–7.39 (m, 1H), 7.52 (d, 1H, J = 8.9 Hz), 7.72–7.79 (m, 2H), 7.99 (d, 1H, J = 8.3 Hz), 8.68 (d, 1H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 99.79, 103.04, 109.49, 111.60, 113.77, 117.96, 119.38, 120.36, 121.16, 121.49, 122.17, 122.87, 123.14, 126.27, 126.35, 127.39, 133.58, 135.01, 149.88, 151.95, 153.21, 155.61, 161.43; ES-MS (*m/z*): $[M+H]^+$ 396; HRMS-EI: found: 395.0831, calculated: 395.0825. Anal. Calcd. for $C_{24}H_{14}ClN_3O$: C, 72.82; H, 3.56; N, 10.62. Found: C, 72.53; H, 3.70; N, 10.45.

General method for the preparation of 4-(hetero)aryl quinolines 5a-c. 4-Chloro-2,8-bis(trifluoromethyl)quinoline **4** (1 mmol, 0.299 g) was added in 10 mL of dichloroethane. Under stirring, to it was added $AlCl_3$ (1.2 mmol, 0.158 g) and

allowed to stirred for 2–5 min. Nucleophilic substrates **2d**, **2e**, and **2g** (1 mmol) (Table 2) were added and allowed to stirred at 60–65°C. The reaction mixture was cooled to room temperature and poured into ice-cold water (100 mL) with continuous stirring for 15–20 min. The products were obtained by extracting with dichloromethane (3 × 30 mL). The organic layers were combined, washed with brine and concentrated under reduced pressure after drying over Na_2SO_4. The crude products obtained further purified by silica gel column chromatography using ethyl acetate-hexane mixture.

4-(2,4-Dimethoxyphenyl)-2,8-bis-trifluoromethylquinoline (5a). Yield 80%; m.p.: 105–107°C; IR (potassium bromide): 1610, 1200, 1150 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.69 (s, 3H), 3.91 (s, 3H), 6.64–6.69 (m, 2H), 7.19 (d, 1H, $J = 8.5$ Hz), 7.54–7.62 (m, 1H), 7.72 (s, 1H), 7.92 (d, 1H, $J = 8.4$ Hz), 8.13 (d, 1H, $J = 7.1$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.70, 55.81, 99.23, 105.28, 118.33, 119.23, 126.61, 128.90, 128.97, 129.12, 131.21, 132.05, 144.16, 147.99, 148.45, 148.86, 157.97, 162.40; ES-MS (*m/z*): $[M+H]^+$ 402; HRMS-EI: found: 401.0848, calcuated: 401.0850. Anal. Calcd. for $C_{19}H_{13}F_6NO_2$: C, 56.87; H, 3.27; N, 3.49. Found: C, 57.02; H, 3.56; N, 3.24.

4-(2,4,6-Trimethoxyphenyl)-2,8-bis-trifluoromethylquinoline (5b). Yield 72%; m.p.: 133–135°C; IR (potassium bromide): 1613, 1194, 1143 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.64 (s, 6H), 3.89 (s, 3H), 6.24 (s, 2H), 7.10 (d, 1H, $J = 8.2$ Hz), 7.23 (s, 1H), 7.53–7.62 (m, 1H), 7.89 (d, 1H, $J = 8.3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.67, 55.98, 91.10, 106.70, 118.36, 119.21, 126.58, 128.87, 128.89, 130.99, 132.01, 144.12, 147.95, 148.39, 148.84, 159.10, 168.90; ES-MS (*m/z*): $[M+H]^+$ 432; HRMS-EI: found: 431.0955, calcuated: 431.0955. Anal. Calcd. for $C_{20}H_{15}F_6NO_3$: C, 55.69; H, 3.51; N, 3.25. Found: C, 55.51; H, 3.58; N, 2.97.

4-(1H-Indol-3-yl)-2,8-bis-trifluoromethylquinoline (5c). Yield 66%; m.p.: 145–147°C; IR (potassium bromide): 1611, 1522, 1403, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.21–7.27 (m, 2H), 7.52–7.58 (m, 2H), 8.01–8.13 (m, 1H), 8.26 (m, 1H), 8.27–8.29 (m, 1H), 8.39 (s, 1H), 11.53 (brs, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 111.89, 112.30, 118.21, 119.03, 120.99, 121.19, 121.31, 123.01, 126.11, 127.25, 128.63, 128.96, 130.99, 131.93, 136.71, 145.62, 147.89, 148.36, 148.67; ES-MS (*m/z*): $[M+H]^+$ 381; HRMS-EI: found: 380.0739, calculated: 380.0746. Anal. Calcd. for $C_{19}H_{10}F_6N_2$: C, 60.01; H, 2.65; N, 7.37. Found: C, 59.73; H, 2.55; N, 7.26.

Acknowledgments. S.K is thankful to the University Grants Commission, New Delhi, for the financial support and the Sophisticated Analytical Instrument Facility, CDRI, Lucknow, for providing spectroscopic data.

REFERENCES AND NOTES

[1] Bringmann, G.; Ochse, M.; Schupp, O.; Tasler, S. Progress in the Chemistry of Organic Natural Products; Springer: Wien, 2001; p 82.

[2] (a) Horton, D. A.; Bourne, G. T.; Smythe, M. L. Chem Rev 2003, 103, 893; (b) Wang, G. T.; Wang, S.; Gentles, R.; Sowin, T.; Leitza, S.; Reilly, E. B.; von Geldern, T. W. Bioorg Med Chem Lett 2005, 15, 195.

[3] Kuo, G.-H.; Prouty, C.; Wang, A.; Emanuel, S.; DeAngelis, A., Zhang, Y., Song, F. J Med Chem 2005, 48, 4892.

[4] (a) Gompel, M.; Leost, M.; Bal de Kier Joffé, E.; Puricelli, L.; Franco, L. H.; Palermo, J.; Meijer, L. Bioorg Med Chem Lett 2004, 14, 1703; (b) Butler, M. S.; Capon, R. J.; Lu, C. C. Aust J Chem 1992, 45, 1871.

[5] Radwan, M. A. A.; El-Sherbiny, M. Bioorg Med Chem 2007, 14, 1206.

[6] (a) Yamamoto, T.; Maruyama, T.; Zhou, Z.; Ito, T.; Fukuda, T.; Yoneda, Y.; Begum, F.; lkeda, T.; Sasaki, S.; Takezoe, H.; Fukada, A.; Kubota, K. J Am Chem Soc 1994, 116, 4832; (b) Schulz, E.; Fahmi, K.; Lemaire, M. Acros Org Acta 1995, 1, 10; (c) Zhu, S. S.; Swager, T. M. Adv Mater 1996, 8, 497; (d) Papillon, J.; Schulz, E.; Gelinas, S.; Lessard, J.; Lemaire, M. Synth Met 1998, 96, 155.

[7] Manka, J. T.; Guo, F.; Huang, J.; Yin, H.; Farrar, J. M.; Sienkowska, M.; Benin, V.; Kaszynski, P. J Org Chem 2003, 68, 9574.

[8] Lehn, J. M., Ed. Supramolecular Chemistry, 1st ed.; VCH: Weinheim, Germany, 1995; p 55.

[9] (a) Monk, P. S. M., Ed. The Viologens; Wiley: Canada, 1999; p 32; (b) Stoddart, J. F. J Am Chem Soc 2000, 122, 164; (c) Balzani, V.; Credi, A.; Raymo, F. M.; Stoddart, J. F. Angew Chem Int Ed 2000, 39, 3348; (d) Stoddart, J. F. Acc Chem Res 2001, 34, 410; (e) Benniston, A. C.; Harriman, A.; Li, P.; Rostron, J. P. Tetrahedron Lett 2005, 46, 7291; (f) Branowska, D.; Rykowski, A.; Wysocki, W. Tetrahedron Lett 2005, 46, 6223; (g) Coe, B. J.; Harris, J. A.; Brunschwig, B. S.; Garin, J.; Orduna, J. J Am Chem Soc 2005, 127, 3284; (h) Dichtel, W. R.; Miljanic, O. S.; Spruell, J. M.; Heath, J. R.; Stoddart, J. F. J Am Chem Soc 2006, 128, 10388; (i) Badjic, J. D.; Ronconi, C. M.; Stoddart, J. F.; Balzani, V.; Silvi, S.; Credi, A. J Am Chem Soc 2006, 128, 1489.

[10] (a) Connolly, D. J.; Cusack, D.; O'sullivan, T. P.; Guiry, P. J. Tetrahedron 2005, 61, 10153; (b) Mhaske, S. B.; Argade, N. P. Tetrahedron 2006, 62, 9787; (c) Fekner, T.; Bunz, H. M.; Guiry, P. J. Org Lett 2006, 8, 5109; (d) Xu, G. F.; Song, B. A.; Bhadury, P. S.; Yang, S.; Zhang, P. Q.; Jin, L. H.; Xue, W.; Hu, D. Y.; Lu, P. Bioorg Med Chem 2007, 15, 3768; (e) Sunduru, N.; Agarwal, A.; Katiyar, S. B.; Nishi, N.; Goyal, N.; Gupta, S.; Chauhan, P. M. S. Bioorg Med Chem 2006, 14, 7706.

[11] (a) Flanagan, S. P.; Goddard, R.; Guiry, P. J. Tetrahedron 2005, 61, 9808; (b) Connolly, D. J.; Lacey, P. M.; McCarthy, M.; Saunders, C. P.; Carroll, A.-M.; Goddard, R.; Guiry, P. J. J Org Chem 2004, 69, 6572; (c) McCarthy, M.; Hooper, M. W.; Guiry, P. J. Chem Commun 2000, 14, 1333; (d) McCarthy, M.; Guiry, P. J. Polyhedron 2000, 19, 541; (e) Lacey, P. M.; McDonnell, C. M.; Guiry, P. J. Tetrahedron Lett 2000, 41, 2475; (f) McCarthy, M.; Goddard, R.; Guiry, P. J. Tetrahedron: Asymmetry 1999, 10, 2797.

[12] Alcock, N. W.; Brown, J. M.; Hulmes, D. I. Tetrahedron: Asymmetry 1993, 4, 743.

[13] (a) Liu, W. J.; Xie, Y. X.; Liang, Y.; Li, J. H. Synthesis 2006, 860; (b) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. J Am Chem Soc 2006, 128, 4101 (Suzuki-Miyaura cross coupling).

[14] Lützen, A.; Hapke, M. Eur J Org Chem 2002, 2292 (Negishi coupling).

[15] Mee, S. P. H.; Lee, V.; Baldwin, J. E. Angew Chem 2004, 116, 1152 (Stille coupling).

[16] (a) Knopfel, T. F.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. Angew Chem Int Ed 2004, 43, 5971; (b) Pal, M.; Batchu, V. R.; Parasuraman, K.; Yeleswarapu, K. R. J Org Chem 2003, 68, 6806.

[17] (a) Dwivedi, A. P.; Kumar, S.; Varshney, V.; Singh, A. B.; Srivastava, A. K.; Sahu, D. P. Bioorg Med Chem Lett 2008, 18, 2301; (b) Kumar, S.; Sahu, D. P. ARKIVOC 2008, 15, 88; (c) Bhat, B. A.; Sahu, D. P. Synth Commun 2004, 34, 2169.

[18] (a) Khalifa, M.; Osman, A. N.; Ibrahim, M. G.; Ossman, A. R. E.; Ismail, M. A. Pharmazie 1982, 37, 115; (b) Curd, F. H. S.; Landquist, J. K.; Rose, F. L. J Chem Soc 1947, 775, and references therein.