A Convenient Route to Biologically Important Quinazolines Using *N*-Arylamino-1,3-diazabuta-1,3-dienes

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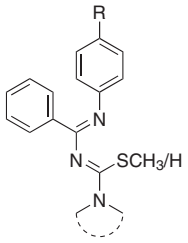
Abstract: A potential and convenient protocol for the synthesis of 4-arylquinazolines and 4-aminoquinazolines by electrocyclisation of *N*-arylamino-1,3-diazabuta-1,3-dienes is described.

Key words: quinazolines, electrocyclisation, *N*-arylamino-1,3-diazabuta-1,3-dienes, intramolecular H-bonding, amino-substituted quinazolines

Quinazoline derivatives have attracted a great deal of interest, mainly concerning their synthesis, reactions and biological properties, as this structural motif appears in a large number of pharmaceutical agents and natural products.[1,2] These compounds have shown remarkable activity as antitubercular,[3] antiviral[4] and anticancer agents[5] and are also used as DNA ligands[6] with affinity to benzodiazepines and adenosine receptors.[7] Recently a great number of fused pyrimidine derivatives became known as potential drug molecules against various types of proliferative diseases, caused by over-expression of protein kinases.[8] One of the most important compound families are quinazolines; e.g. the best inhibitor of EGFR tyrosine kinase is PD153035 [6,7-dimethoxy-4-(3′-bromophenyl)aminoquinazoline] and IRESSA™ (gefitinib, ZD1839), developed from this compound family, is currently the only approved and granted drug by the FDA for the treatment of advanced non-small-cell lung cancer (NSCLC). The growing medicinal importance of these heterocycles, especially *N*-arylaminoquinazolines, continues to provide a strong rationale for the development of synthetic methods for their preparation. Taguchi et al. have reported the synthesis of 4-arylamino-2-dialkylaminoquinazolines by reaction of dialkylcyanamides with 4-substituted phenyl isothiocyanates.[9] Recently Shi et al. have reported the preparation of 3-arylquinazolines by using $TiCl_4$/Zn system.[10] The reactions of *N*-imidoyliminophosphoranes with various aldehydes result in a variable ratio of quinazoline and dihydroquinazoline derivatives depending upon the nature of aldehydes as well as the employed reaction conditions.[11] The reaction apparently suffers from disadvantages such as longer reaction periods (25–90 h), lower yields, lack of selectivity often leading to a mixture of products and cumbersome workup procedure. We recently utilized microwave technology in the synthesis of quinazolines by the condensation of *N*-imidoyliminophosphoranes with aldehydes.[12] The methodology has been further improved and extended to the condensation of *N*-arylbenzamidines with aldehydes.[13] The quinazolines thus obtained were then tested for their antibacterial activities against a panel of susceptible and resistant Gram positive and Gram-negative organisms[14] and also as anxiolytic and GABAergic agents.[15] The reported efficient electrocyclisation of such dienes bearing phenyl and H at C-4 prompted us to explore the synthesis of some novel quinazolines through 1,3-diazabuta-1,3-dienes substituted at C-4 by secondary amino and hydrogen/thio methyl groups (Figure 1).



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N = morpholine, pyrrolidine, piperidine, *N*,*N*-diethylamine

Figure 1

Surprisingly, such dienes failed to cyclise even under stringent thermal conditions for reasons still unaccounted for. It was felt that 4-*N*-arylamino-substituted 1,3-diaza-1,3-dienes may be better contenders for the required electrocyclisation possibly because of intramolecular H-bonding between N_1–H and N_5 and the possible prototropic shift between N_1 and N_5. Also, the presence of intramolecular H-bonding in such systems should stabilize the *s-cisoid* conformation in preference to *s-trans* form, which is a prerequisite for the desired electrocyclisation. Thus in continuation of our interest in the azadiene chemistry,[16] we report herein the synthesis of novel quinazoline derivatives **3** by the thermolysis of *N*-arylamino-1,3-diazabuta-1,3-dienes **2** in refluxing toluene (6–8 h) (Scheme 1).

The structures of the quinazolines **3** were elucidated on the basis of spectral and analytical data. The detailed spectral data are given in the experimental section and only the salient features are discussed here. Thus quinazolines, **3b** for example, showed a molecular ion peak at *m*/*z* = 297. Its IR spectrum showed absorption peaks at 3460 cm^{-1} and 1568 cm^{-1} due to NH and C=N groups, respectively. Its ^1H

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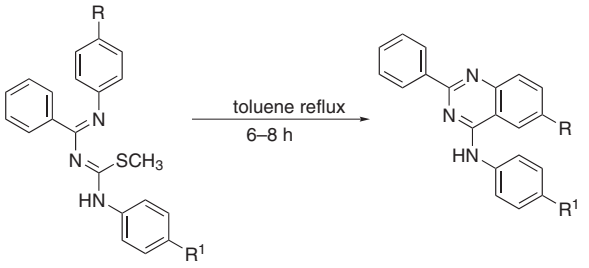
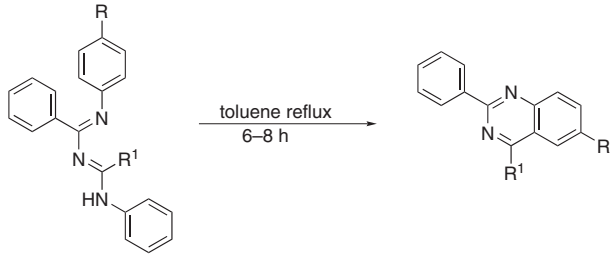


2 3

	R	R^1
a	H	H
b	CH_3	H
c	H	CH_3
d	H	OCH_3
e	H	Cl
f	CH_3	Cl

Scheme 1



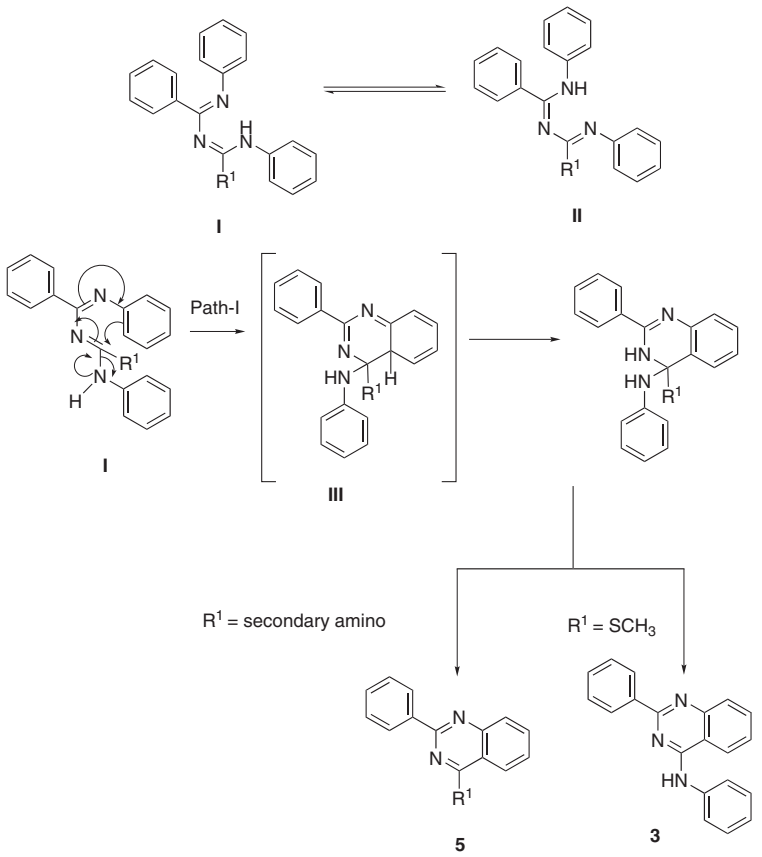
4 5

	R	R^1
a	H	pyrrolidine
b	CH_3	pyrrolidine
c	H	morpholine
d	CH_3	morpholine
e	H	piperidene
f	CH_3	piperidene

Scheme 2

NMR spectrum exhibited the presence of *N*-arylamino group, apart from other aromatic protons and the absence of the thiomethyl group. The methodology has been further extended to the electrocyclisation of *N*-arylamino-1,3-diazabuta-1,3-dienes **4**, where R^1 is a secondary amino group. As expected, the reaction resulted in the synthesis of amino-functionalised quinazolines **5** (Scheme 2). The structures of these compounds were once again established on the basis of spectral and analytical evidences. The compound **5b** for example showed a molecular ion peak at $m/z = 289$. Its ^{1}H NMR spectrum exhibited multiplets at $\delta = 2.03$ and $\delta = 3.73$ due to four protons each of the pyrrolidine group.

Secondary amino substituted quinazoline constitute an important class of medicinal entities acting as α_1-receptor antagonists and antihypertensive agents[17] and the important members include Prazosin and Doxazosin. A plausible mechanism leading to the formation of quinazolines **3** and **5** is depicted in (Scheme 3). As reported earlier, *N*-aryl substituted 1,3-dienes exist in tautomeric forms **I** and **II**. In this mechanism, it is assumed that the electrocyclic



I II III 5 3

Scheme 3

ring closure of the stable tautomer form **I** leads initially to an intermediate **III** which undergoes aromatisation via the expected elimination of methyl mercaptan (R^1 = SCH_3) and aromatic amine (R^1 = secondary amine) leading to the desired quinazolines **3** and **5**, respectively.

Thus a convenient protocol for the synthesis of 4-*N*-aryl substituted and 4-secondary amino substituted quinazolines has been developed. The reaction depends upon the substitution pattern of imino nitrogen, the conformational preferences and only the *N*-arylamino-1,3-diazabuta-1,3-dienes underwent electrocyclisation to quinazoline derivatives.

Melting points were determined by the open capillary technique using Veego Precision Digital Melting Point apparatus (MP-D) and are uncorrected. IR spectra were recorded on a Shimadzu D-8001 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ with Bruker AC-E 200 (200 MHz) and Jeol FT NMR AL-300 (300 MHz) spectrometers using TMS as internal standard. Chemical shift values are expressed in ppm and *J* values are given in Hz. Splitting patterns are indicated as s: singlet, d: doublet, t: triplet, m: multiplet, q: quartet and br: broad peak. Mass spectra were recorded on a Shimadzu GCMS-QP-2000 mass spectrometer. Elemental analyses were performed on a Heraus CHN-O-Rapid Elemental Analyzer. 1,3-Diazabuta-1,3-dienes were prepared according to the reported procedure.[18]

Cyclisation Reactions of 1,3-Diazabuta-1,3-dienes; General Procedure

A solution of *N*-arylamino-1,3-diazabuta-1,3-diene (0.01 mol) in anhyd toluene was refluxed for 6–8 h. The progress of the reaction was monitored by TLC. On completion, the reaction mixture was concentrated and triturated with hexane. The isolated product was purified by recrystallisation with the hexane–EtOAc (10:1) mixture.

2-Phenyl-4-(*N*-phenylamino)quinazoline (3a)

Yield: 82%; mp 220–222 °C.

IR (KBr): 3460 (NH), 1595, 1568 (C=N) cm^{-1}.

^{1}H NMR (300 MHz): δ = 7.12–7.17 (m, 1 H, ArH), 7.36–7.49 (m, 7 H ArH, NH), 7.66–7.90 (m, 5 H, ArH), 8.51–8.55 (m, 2 H, ArH).

^{13}C NMR (75 MHz): δ = 113.7, 120.2, 121.2, 123.9, 125.9, 128.4, 128.5, 128.9, 129.1, 130.2, 132.8, 138.5, 138.6, 150.9, 157.2, 160.3.

Anal. Calcd for $C_{20}H_{15}N_3$: C, 80.78; H, 5.08; N, 14.13. Found: C, 80.62; H, 5.19; N, 14.19.

MS: *m*/*z* = 297 [M$^+$].

6-Methyl-2-phenyl-4-(*N*-phenylamino)quinazoline (3b)

Yield: 81%; mp 218–219 °C.

IR (KBr): 3449 (NH), 1594, 1554 (C=N) cm^{-1}.

^{1}H NMR (300 MHz): δ = 2.43 (s, 3 H, CH_3), 7.25–8.20 (m, 12 H, ArH, NH), 8.65–8.69 (m, 2 H, ArH).

^{13}C NMR (75 MHz): δ = 20.8 (CH_3), 113.3, 120.5, 121.0, 124.0, 125.4, 128.3, 128.5, 129.0, 129.1, 130.4, 132.9, 138.3, 138.7, 150.4, 157.0, 160.2.

Anal. Calcd for $C_{21}H_{17}N_3$: C, 81.00; H, 5.50; N, 13.49. Found: C, 80.88; H, 5.35; N, 13.77.

MS: *m*/*z* = 311 [M$^+$].

4-(*p*-Methylamino)-2-phenylquinazoline (3c)

Yield: 82%; mp 210–211 °C.

IR (KBr): 3450 (NH), 1595, 1554 (C=N) cm^{-1}.

^{1}H NMR (300 MHz): δ = 2.38 (s, 3 H, CH_3), 7.20–8.13 (m, 12 H, ArH, NH), 8.75–8.79 (m, 2 H, ArH).

^{13}C NMR (75 MHz): δ = 21.2 (CH_3), 113.7, 120.3, 121.4, 124.1, 125.0, 128.1, 128.8, 129.0, 129.3, 130.4, 132.7, 138.2, 138.3, 150.7, 157.5, 160.1.

Anal. Calcd for $C_{21}H_{17}N_3$: C, 81.00; H, 5.50; N, 13.49. Found: C, 80.82; H, 5.42; N, 13.76.

MS: *m*/*z* = 311 [M$^+$].

4-(*p*-Methoxyphenylamino)-2-phenylquinazoline (3d)

Yield: 85%; mp 250–252 °C.

IR (KBr): 3450 (NH), 1595, 1556 (C=N) cm^{-1}.

^{1}H NMR (300 MHz): δ = 3.85 (s, 3 H, OCH_3), 3.96–6.99 (d, *J* = 8.0 Hz, 2 H, ArH), 7.40–7.48 (m, 5 H, ArH, NH), 7.71–7.82 (m, 4 H, ArH), 7.95–7.98 (d, *J* = 9.0 Hz, 1 H, ArH), 8.49–8.53 (m, 2 H, ArH).

^{13}C NMR (75 MHz): δ = 55.5 (OCH_3), 113.7, 114.1, 120.3, 123.3, 125.9, 128.3, 128.5, 129.1, 130.2, 131.6, 132.7, 138.7, 150.9, 156.4, 157.5, 160.4.

Anal. Calcd for $C_{21}H_{17}N_3O$: C, 77.04; H, 5.23; N, 12.84. Found: C, 77.16; H, 5.29; N, 12.66.

MS: *m*/*z* = 327 [M$^+$].

4-(*p*-Chlorophenylamino)-2-phenylquinazoline (3e)

Yield: 84%; mp 232–234 °C.

IR (KBr): 3501 (NH), 1593, 1563 (C=N) cm^{-1}.

^{1}H NMR (300 MHz): δ = 7.15–8.05 (m, 12 H, ArH, NH), 8.45–8.68 (m, 2 H, ArH).

^{13}C NMR (75 MHz): δ = 113.0, 120.7, 121.2, 124.0, 125.8, 128.1, 128.5, 128.8, 129.3, 130.1, 132.9, 138.0, 138.6, 150.3, 157.8, 160.2.

Anal. Calcd for $C_{20}H_{14}N_3Cl$: C, 72.40; H, 4.25; N, 12.66. Found: C, 72.20; H, 4.33; N, 12.78.

MS: *m*/*z* = 331.5 [M$^+$].

4-(*p*-Chlorophenylamino)-6-methyl-2-phenylquinazoline (3f)

Yield: 80%; mp 261–263 °C.

IR (KBr): 3451 (NH), 1600, 1558 (C=N) cm^{-1}.

^{1}H NMR (300 MHz): δ = 2.50 (s, 3 H, CH_3), 7.36–7.86 (m, 11 H, ArH, NH), 8.46–8.49 (m, 2 H, ArH).

^{13}C NMR (75 MHz): δ = 21.7 (CH_3), 113.5, 119.2, 122.3, 128.3, 128.4, 128.7, 128.9, 130.1, 130.9, 136.3, 137.3, 138.5, 149.3, 156.6, 159.4.

Anal. Calcd for $C_{21}H_{16}N_3Cl$: C, 72.93; H, 4.66; N, 12.15. Found: C, 72.81; H, 4.54; N, 12.40.

MS: *m*/*z* = 345.5 [M$^+$].

2-Phenyl-4-pyrrolidin-1-ylquinazoline (5a)

Yield: 82%; mp 150–151 °C.

^{1}H NMR (200 MHz): δ = 2.00–2.06 (m, 4 H, CH_2CH_2), 3.72–3.78 (m, 4 H, CH_2NCH_2), 7.50–7.58 (m, 7 H, ArH), 7.70–7.73 (m, 2 H, ArH).

^{13}C NMR (50.4 MHz): δ = 24.8 (CH_2CH_2), 46.0 (CH_2NCH_2), 117.6, 118.0, 120.2, 122.4, 125.6, 127.8, 135.8, 145.3, 158.0, 166.3.

Anal. Calcd for $C_{18}H_{17}N_3$: C, 78.52; H, 6.22; N, 15.26. Found: C, 78.35; H, 6.36; N, 15.29.

MS: *m*/*z* = 275 [M$^+$].

6-Methyl-2-phenyl-4-pyrrolidin-1-ylquinazoline (5b)
Yield: 78%; mp 140–141 °C.

^{1}H NMR (200 MHz): δ = 2.01–2.07 (m, 4 H, CH_2CH_2), 2.37 (s, 3 H, CH_3), 3.70–3.76 (m, 4 H, CH_2NCH_2), 7.50–7.58 (m, 6 H, ArH), 7.70–7.73 (m, 2 H, ArH).

^{13}C NMR (50.4 MHz): δ = 21.1 (CH_3), 24.9 (CH_2CH_2), 45.7 (CH_2NCH_2), 117.3, 118.2, 120.1, 122.5, 123.3, 125.4, 127.7, 130.2, 135.6, 145.1, 157.9, 166.6.

Anal. Calcd for $C_{19}H_{19}N_3$: C, 78.86; H, 6.62; N, 14.52. Found: C, 79.08; H, 6.60; N, 14.32.

MS: *m*/*z* = 289 [M$^+$].

4-Morpholin-4-yl-2-phenylquinazoline (5c)
Yield: 68%; mp 157–158 °C.

^{1}H NMR (200 MHz): δ = 3.83–3.89 (m, 4 H, CH_2NCH_2), 3.96–4.01 (m, 4 H, CH_2OCH_2), 7.54–7.62 (m, 7 H, ArH), 7.74–7.76 (m, 2 H, ArH).

^{13}C NMR (50.4 MHz): δ = 44.5 (CH_2NCH_2), 66.8 (CH_2OCH_2), 117.9, 126.3, 128.5, 129.5, 130.2, 131.8, 135.6, 137.5, 160.7, 168.5.

Anal. Calcd for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42. Found: C, 74.28; H, 5.64; N, 14.2.

MS: *m*/*z* = 291 [M$^+$].

6-Methyl-2-phenyl-4-morpholino-4-ylquinazoline (5d)
Yield: 71%; mp 147–148 °C.

^{1}H NMR (200 MHz): δ = 2.41 (s, 3 H, CH_3), 3.81–3.86 (m, 4 H, CH_2NCH_2), 3.98–4.02 (m, 4 H, CH_2OCH_2), 7.54–7.62 (m, 6 H, ArH), 7.74–7.76 (m, 2 H, ArH).

^{13}C NMR (50.4 MHz): δ = 21.37 (CH_3), 44.56 (CH_2NCH_2), 66.97 (CH_2OCH_2), 117.7, 126.0, 128.3, 128.5, 129.5, 129.7, 130.0, 131.3, 135.7, 137.9, 160.9, 168.7.

Anal. Calcd for $C_{19}H_{19}N_3O$: C, 74.73; H, 6.27; N, 13.76. Found: C, 74.92; H, 6.40; N, 13.44.

MS: *m*/*z* = 305 [M$^+$].

2-Phenyl-4-piperidin-1-ylquinazoline (5e)
Yield: 77%; mp 131–132 °C.

^{1}H NMR (200 MHz): δ = 1.70–1.75 (m, 6 H, $CH_2CH_2CH_2$), 3.99–4.04 (m, 4 H, CH_2NCH_2), 7.50–7.58 (m, 7 H, ArH), 7.70–7.74 (m, 2 H, ArH).

^{13}C NMR (50.4 MHz): δ = 25.1 (CH_2), 26.3 (CH_2CH_2), 44.2 (CH_2NCH_2), 117.5, 118.6, 120.8, 122.5, 125.1,130.5, 135.4, 145.5, 157.6, 166.3.

Anal. Calcd for $C_{19}H_{19}N_3$: C, 78.86; H, 6.62; N, 14.52. Found: C, 78.79; H, 6.83; N, 14.38.

MS: *m*/*z* = 289 [M$^+$].

6-Methyl-2-phenyl-4-piperidin-1-ylquinazoline (4f)
Yield: 81%; mp 137–138 °C.

^{1}H NMR (200 MHz): δ = 1.72–1.77 (m, 6 H, $CH_2CH_2CH_2$), 2.38 (s, 3 H, CH_3), 3.97–4.02 (m, 4 H, CH_2NCH_2), 7.50–7.58 (m, 6 H, ArH), 7.70–7.74 (m, 2 H, ArH).

^{13}C NMR (50.4 MHz): δ = 19.3 (CH_3), 25.2 (CH_2), 26.0 (CH_2CH_2), 44.4 (CH_2NCH_2), 117.0, 118.3, 120.4, 122.7, 123.4, 125.2, 127.9, 130.0, 135.3, 145.3, 157.7, 166.3.

Anal. Calcd for $C_{20}H_{21}N_3$: C, 79.17; H, 6.98; N, 13.85. Found: C, 79.32; H, 6.80; N, 13.88.

MS: *m*/*z* = 303 [M$^+$].

References

(1) (a) Brown, D. J. *Quinazoline: The Chemistry of Heterocyclic Compounds*, Vol 55; John Wiley and Sons: Chichester UK, **1996**, Supplement I. (b) Jones, P.; Chambers, M. *Tetrahedron* **2003**, *58*, 9973. (c) Webb, T. R.; Lvovskiy, D.; Kim, S. A.; Ji, X.; Melman, M.; Lindeu, J.; Jacobson, K. A. *Bioorg. Med. Chem.* **2003**, *11*, 77. (d) Michael, J. P. *Nat. Prod. Rep.* **2002**, 742. (e) Frère, S.; Thiéry, V.; Bailly, C.; Besson, T. *Tetrahedron* **2003**, *59*, 773.

(2) (a) Billimmoria, A. D.; Cava, M. P. *J. Org. Chem.* **1994**, *59*, 6772. (b) Blackman, A.; Hambley, T. M.; Picker, R.; Taylor, W. C.; Thirasana, N. *Tetrahedron Lett.* **1987**, *28*, 5561.

(3) Kunes, J.; Bazant, J.; Pour, M.; Waisser, K.; Slosarek, M.; Janota, J. *Farmaco* **2000**, *55*, 725.

(4) El-Sherbeny, M. A.; Gineinah, M. M.; Nasr, M. N.; El-Shafeih, F. S. *Arzneim.-Forsch.* **2003**, *53*, 206.

(5) Khalil, A. A.; Abdel-Hamid, S. G.; Al-Obaid, A. M.; El-Subbag, H. I. *Arch. Pharm. (Weinheim, Ger.)* **2003**, *336*, 95.

(6) Malecki, N.; Caroto, P.; Rigo, B.; Goossens, J. F.; Houssin, R.; Bailly, C.; Henichart, J. P. *Bioorg. Med. Chem.* **2004**, *12*, 641.

(7) Bertelli, L.; Biagi, G.; Giorgi, I.; Livi, O.; Manera, C.; Scartoni, V.; Lucacchini, A.; Giannaccini, G.; Barili, P. L. *Eur. J. Med. Chem.* **2000**, *35*, 333.

(8) (a) Orfi, L.; Waczek, F.; Pato, J.; Varga, I.; Hegymegi-Barakonyi, B.; Houghten, R. A.; Keri, G. *Curr. Med. Chem.* **2004**, *11*, 2549. (b) Fry, D. W.; Kraker, A. J.; McMichael, A.; Ambroso, L. A.; Nelson, J. M.; Leopold, W. R.; Connors, R. W.; Bridges, A. J. *Science* **1994**, *265*, 1093.

(9) Oishi, A.; Yasumoto, M.; Goto, M.; Tsuchiya, T.; Shibuya, I.; Taguchi, Y. *Heterocycles* **1994**, *38*, 2073.

(10) Shi, D.; Wang, J.; Shi, C.; Rong, L.; Zhuang, Q.; Hu, H. *Synlett* **2004**, 1098.

(11) (a) Rossi, E.; Stradi, R.; Visentin, P. *Tetrahedron* **1990**, *46*, 3581. (b) Rossi, E.; Stradi, R.; Clenantano, G.; Strada, A. *Tetrahedron Lett.* **1990**, *31*, 903.

(12) Kumar, V.; Sharma, A. K.; Mahajan, M. P. *Synth. Commun.* **2004**, *34*, 49.

(13) Kumar, V.; Mohan, C.; Gupta, M.; Mahajan, M. P. *Tetrahedron* **2004**, *61*, 3533.

(14) Bedi, P. M.; Kumar, V.; Mahajan, M. P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5211.

(15) Goel, R. K.; Kumar, V.; Mahajan, M. P. *Bioorg. Med. Chem. Lett.,* in press.

(16) (a) Jayakumar, S.; Ishar, M. P. S.; Mahajan, M. P. *Tetrahedron* **2002**, *58*, 379. (b) Mazumdar, S. N.; Ibnusaud, I.; Mahajan, M. P. *Tetrahedron Lett.* **1987**, *28*, 2641. (c) Mazumdar, S. N.; Mahajan, M. P. *Tetrahedron* **1991**, *47*, 1473. (d) Mazumdar, S. N.; Mukherjee, S.; Sharma, A. K.; Sengupta, D.; Mahajan, M. P. *Tetrahedron* **1994**, *50*, 7579. (e) Mukherjee, S.; Mazumdar, S. N.; Sharma, A. K.; Mahajan, M. P. *Heterocycles* **1998**, *47*, 933. (f) Dey, P. D.; Sharma, A. K.; Bharatam, P. V.; Mahajan, M. P. *Tetrahedron* **1997**, *53*, 13829.

(17) Dey, S.; Ramachandra, M.; Pastan, I.; Gottesman, M. M.; Ambudkar, S. V. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 10594.

(18) (a) Sharma, A. K.; Mahajan, M. P. *Tetrahedron Lett.* **1986**, *27*, 5875. (b) Mazumdar, S. N.; Mahajan, M. P. *Synthesis* **1990**, 417. (c) Dey, P. D.; Sharma, A. K.; Bhartam, P. V.; Mahajan, M. P. *Tetrahedron* **1997**, *53*, 13829. (d) Dey, P. D.; Sharma, A. K.; Rai, S. N.; Mahajan, M. P. *Tetrahedron* **1995**, *51*, 7459.