Tetrahedron 64 (2008) 10162–10171

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A facile route to the synthesis of pyrimido[2,1-*b*]quinazoline core from the primary allyl amines afforded from Baylis–Hillman adducts☆

Somnath Nag, Amita Mishra, Sanjay Batra *

Medicinal and Process Chemistry Division, Central Drug Research Institute, PO Box 173, Lucknow 226001, India

ARTICLE INFO

Article history:
Received 3 July 2008
Received in revised form 14 August 2008
Accepted 14 August 2008
Available online 19 August 2008

Keywords:
Baylis–Hillman
Allyl amine
BrCN
Pyrimido[2,1-*b*]quinazoline
In
Intramolecular cyclization

ABSTRACT

A highly simplified approach for the generation of substituted pyrimido[2,1-*b*]quinazoline core from the primary allyl amines afforded from the Baylis–Hillman adducts is described. Sequential reductive alkylation of the primary allyl amine with 2-nitrobenzaldehyde, reduction of the aromatic nitro group with In, CNBr-promoted intramolecular cyclization followed by NaOMe-mediated another intramolecular cyclization furnish the title compounds.

1. Introduction

Applications of allyl amines for the syntheses of diverse compounds are widely documented.[1] The highly substituted allyl amines, in particular, serve as viable precursors to several nitrogen heterocycles including the annulated systems.[2] A variety of such amines can be readily generated from allyl acetate or allyl bromide afforded from the Baylis–Hillman adducts through nucleophilic substitution reactions (S_N2 or S_N2' type).[2a] In our program aimed at expanding the repertoire of synthetic applications of the Baylis–Hillman adducts for the generation of heterocyclic systems recently we have reported the synthesis of imidazo[1,2-*a*]pyrimdin-2-ones, pyrimido[1,2-*a*]pyrimidin-2-ones,[3] 5-benzyl-4(3*H*)-pyrimidinones, and 2-benzylidene-2,3-dihydropyrrolizin-1-ones[4] from the primary allyl amines[5] readily afforded from the Baylis–Hillman acetates. The quinazoline-fused systems are of great interest due to their importance as core units of several pharmacologically active compounds.[6] In our continuing efforts to obtain nitrogen heterocycles via Baylis–Hillman reaction assisted chemistry we envisaged the synthesis of pyrimido[2,1-*b*]quinazoline core from substituted allyl amines. This nucleus constitutes the basic unit of hypotensives, antidepressants, diuretic, and vasodilating agents.[7] There are only a few reports,[8] which include the synthesis of pyrimido-quinazoline system. Pearson and Wood unexpectedly isolated substituted pyrimido[2,1-*b*]quinazoline system by the reaction of 2-aminobenzyl alcohol with a pyrimidine derivative via an electrocyclic rearrangement of an 'Eenie–Meenie' intermediate. Earlier Kosasayama et al. have reported that 2-aminobenzophenone serves as precursor to an analogous system. More recently, Kundu et al. also isolated such tricyclic system though in low yields only. However, in no case a general approach to pyrimido[2,1-*b*]quinazoline was illustrated.

A retrosynthetic analysis, which formed the basis of our rationale for the synthesis of aforementioned nucleus is presented in Figure 1. Cleavage of the pyrimido[2,1-*b*]quinazoline nucleus, as indicated, gives the 2-amino-dihydroquinazoline, which in turn could be generated from a diamine. Such a diamine can be obtained either through a nucleophilic reaction of the primary allyl amine afforded from the Baylis–Hillman acetate of acrylonitrile with 2-nitrobenzyl bromide followed by reduction of the nitro group or via a reductive alkylation of the same amine with 2-nitrobenzaldehyde followed by the reduction of the nitro group.

Alternatively an initial addition of cyanogen bromide to the secondary allyl amine produced by the reductive alkylation of the primary allyl amine with 2-nitrobenzaldehyde would yield a substituted cyanamide. The reduction of the aromatic nitro group in this cyanamide may trigger two successive intramolecular cyclizations to directly furnish the final product. It was further reasoned that execution of similar series of reactions employing the primary allyl amines obtained from the Baylis–Hillman adducts of

☆ CDRI Communication no. 7563.

* Corresponding author. Tel.: +91 522 2621411–18x4368; fax: +91 522 2623405/938.
E-mail address: batra_san@yahoo.co.uk (S. Batra).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.08.044

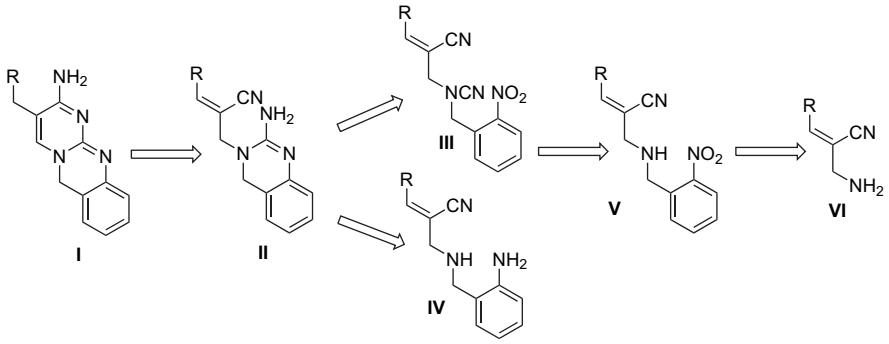
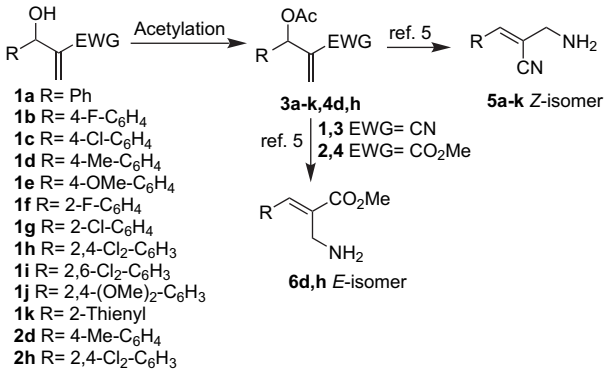


Figure 1. Retrosynthetic analysis for the preparation of pyrimido[2,1-*b*]quinazoline from the primary allyl amine afforded from the Baylis–Hillman adduct.

acrylates would result into 2*H*-pyrimido[2,1-*b*]quinazolin-2-ones. Interestingly when we conducted these studies it was observed that for reactions of substrates originating from unsubstituted 2-nitrobenzaldehyde or 5-chloro-2-nitrobenzaldehyde initial formation of diamine is essentially required. Subsequently, the cyanogen bromide-mediated reaction results in an intramolecular cyclization to yield substituted 2-aminoquinazolines, which were finally treated with a base to obtain the title compounds. On the contrary substrates originating from 3,4-dimethoxy-2-nitrobenzaldehydes and 3,4-methylenedioxy-2-nitrobenzaldehyde were first converted to the cyanamide and then subjected to chemoselective reduction to furnish the 2-amino-dihydroquinazoline in low yields, which failed to produce the title compound. These interesting results provoke us to report the details of our study in this communication.



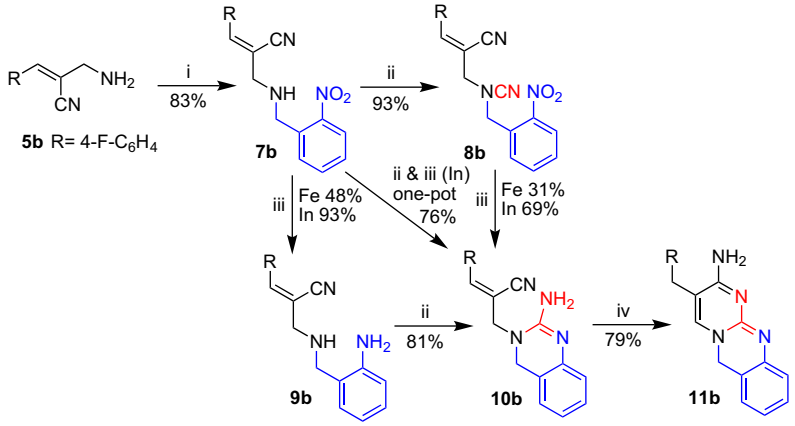
3a-k,4d,h **5a-k** *Z*-isomer

6d,h *E*-isomer

Scheme 1.

2. Results and discussion

Our synthesis commenced by generation of primary allyl amines (**5a**–**k**, **6d**,**h**) from the Baylis–Hillman acetates (**3a**–**k**, **4d**,**h**) following the earlier reported procedure[5] (Scheme 1). The stereochemistry of amines **5** was *Z* whereas **6** were obtained as *E*-isomer. Initial studies directed toward finding a general set of conditions that could be applied to a wide variety of allyl amines were carried out with compound **5b** as the model substrate. The substitution reaction of 1.2 equiv of **5b** with 1-fold of 2-nitrobenzyl bromide did not go to completion under several conditions and the best yield of the required product **7b** that was isolated was 19% only. Although literature precedence for the formation of the desired analog via use of 10 equiv of amine with 1 equiv of 2-nitrobenzyl bromide exists,[9] it was decided to follow the alternate route. Henceforth, the reductive alkylation of the **5b** with 2-nitrobenzaldehyde was performed. Accordingly the allyl amine **5b** was treated with 2-nitrobenzaldehyde in dichloromethane at room temperature to initially generate the imine that was smoothly reduced with freshly prepared sodium triacetoxyborohydride to furnish the desired secondary allyl amine **7b** in 83% yield (Scheme 2). During the optimization studies it was discovered that 1.2 equiv of amine with respect to 2-nitrobenzaldehyde provided better yields of **7b**. Thereafter compound **7b** was treated with cyanogen bromide in THF to afford the cyanamide derivative **8b** in 93% yield. It was expected that the chemoselective reduction of the aromatic nitro group may trigger cascade cyclizations to furnish the substituted-3(4*H*)-pyrimido[2,1-*b*]quinazoline. Therefore the reduction of the aromatic nitro group in **8b** was initially conducted with Fe–AcOH. Although the reaction was successful the yield of the isolated product was 31% only. A careful spectral analysis led us to establish the structure of the product as 4*H*-2-aminoquinazoline **10b**. The IR



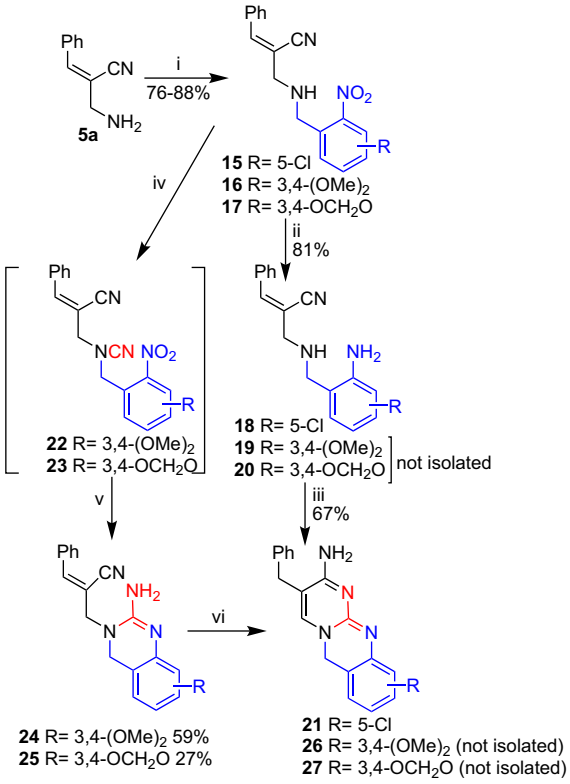
Scheme 2. Reagents and conditions: (i) (a) 2-nitrobenzaldehyde, CH_2Cl_2, rt, 3 h; (b) $NaBH(OAc)_3$, C_6H_6, 0 °C to rt, 8 h; (ii) CNBr, THF or MeOH, rt, 30 min; (iii) Fe–AcOH, 90 °C, 1 h or In–HCl, THF/H_2O (1:1, v/v), rt, 1.5 h; (iv) NaOMe, MeOH, reflux, 4 h.

spectrum characteristically displayed the signal for the nitrile group. Next the reduction of the nitro group was attempted in the presence of In–HCl under aqueous conditions. Though this reaction was completed in 1.5 h at room temperature, the product that was isolated in 69% yield had spectral characteristics similar to **10b**. At this point of optimization we investigated the one-pot procedure for the formation of **10b** from **7b**. Instead of isolating the compound **8b** after the reaction of cyanogen bromide, In was added to the reaction mixture followed by HCl. The reaction was completed in 1 h to give the product that was identical to **10b**. In light of these results, it was decided to initially generate the diamine and then carry out the reaction of cyanogen bromide, which may lead to the expected intramolecular cascade cyclization. Thus **7b** was treated with Fe–AcOH under heating at reflux. The reaction was completed within 1.5 h and the isolation and purification of the product provided the pure diamine **9b** in 48% yield.

Simultaneously the reduction was also investigated with In–HCl under aqueous medium. The reduction was completed in 1.5 h to yield the pure diamine in 93% yield. The reaction of cyanogen bromide with **9b** in methanol for 30 min led to furnish the product in 81% yield, which was identified to be **10b**. Treating **10b** with sodium methoxide in methanol as disclosed earlier[10] resulted in the desired pyrimido[2,1-*b*]quinazoline **11b** in 79% yield. At this stage it occurred to us that the reaction of cyanogen bromide and sodium methoxide can be conducted in one-pot as the solvent used for both reactions was methanol. Consequently after reaction of compound **10b** with cyanogen bromide for 30 min, sodium was added to the reaction mixture at 0 °C and the stirring was continued for another 4.0 h under heating at reflux. Gratifyingly the workup and isolation gave the final product **11b** in 74% yields. To demonstrate the generality of the method, several allyl amines (**5a**–**k**) were subjected to reductive alkylation with 2-nitrobenzaldehyde followed by reduction with In–HCl to furnish the corresponding diamines (**9a**–**k**) (Scheme 3). Subsequently these diamines (**9a**–**k**) were subjected to reaction with cyanogen bromide followed by sodium methoxide-mediated intramolecular cyclization to smoothly afford the 2-amino-3-arylmethyl-6*H*-pyrimido[2,1-*b*]quinazolines (**11a**–**k**) in good yields.

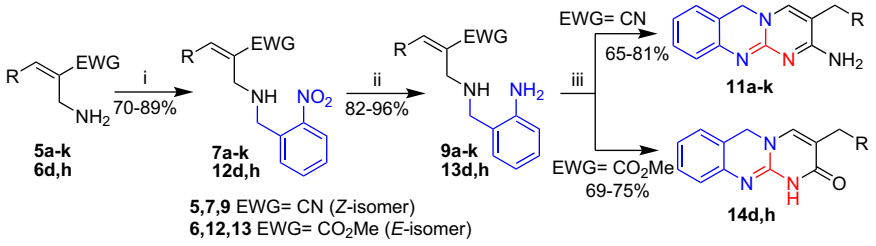
Once the objective to obtain the desired compounds from the allyl amines synthesized from the Baylis–Hillman product of acrylonitrile was accomplished we directed our attention toward the allyl amines generated from Baylis–Hillman adducts of acrylates. Therefore the allyl amines **6d**,**h**, which were synthesized from the acetates **4d**,**h** were subjected to reductive alkylation with 2-nitrobenzaldehyde to furnish the desired secondary allyl amine **12d**,**h** in good yields. Treatment of **12d**,**h** with In-HCl at room temperature furnished diamines **13d**,**h**. One-pot two-step reaction of these diamines (**13d**,**h**) with cyanogen bromide and sodium methoxide resulted in the anticipated products (**14d**,**h**) in good yields (Scheme 3).

With the intent to introduce more diversity in the products employing this strategy, it was decided to carry the reductive alkylation with substituted 2-nitrobenzaldehydes. Consequently, the



Scheme 4. Reagents and conditions: (i) (a) substituted 2-nitrobenzaldehyde, CH_2Cl_2, rt, 3 h; (b) $NaBH(OAc)_3$, C_6H_6, 0 °C to rt, 8 h; (ii) In–HCl, THF/H_2O (1:1, v/v), rt, 1.5 h; (iii) (a) CNBr, MeOH, rt, 30 min; (b) NaOMe, MeOH, rt, 1 h; (iv) CNBr, THF, rt, 30 min; (v) In–HCl, H_2O, rt, 1.5 h.

reductive alkylations of **5a** with 5-chloro-2-nitrobenzaldehyde, 3,4-dimethoxy-2-nitrobenzaldehyde, and 3,4-methylenedioxy-2-nitrobenzaldehyde were performed to obtain the corresponding products (**15**–**17**) in good yields (Scheme 4). The reduction of the nitro group in the presence of In–HCl of **15** resulted into the diamine **18** but similar reduction in **16** and **17** yielded the diamines, which were highly unstable and could not be isolated. It is likely that the electron donating character of the substitutions present on the phenyl ring made the diamines **19** and **20** unstable possibly leading to polymerization. As a result the diamine **18** was subjected to treatment with cyanogen bromide followed by reaction with sodium methoxide in one-pot. Expectedly this reaction led to the formation of **21** in 67% yield (Scheme 4). On the other hand for compounds **16** and –**17** it was decided to generate the 2-amino-3-benzyl-4*H*-quinazoline via initial formation of cyanamide followed by reduction of the nitro group in one-pot. Therefore, compounds **16** and –**17** were treated with cyanogen bromide in the presence of THF. On completion of reactions (TLC analysis), In was added to the reactions for reduction. The reactions were complete in 1.5 h and the products were isolated after the workup albeit in low yields



Scheme 3. Reagents and conditions: (i) (a) 2-nitrobenzaldehyde, CH_2Cl_2, rt, 3 h; (b) $NaB(OAc)_3$, C_6H_6, 0 °C to rt, 8 h; (ii) In–HCl, THF/H_2O (1:1, v/v), rt, 1.5 h; (iii) (a) CNBr, MeOH, rt, 30 min; (b) NaOMe, MeOH, reflux, 4 h for **9** (one-pot) and NaOMe, MeOH, rt, 1.5 h for **13** (one-pot).

only. The substrate **16** resulted in the formation of **24** whereas **17** provided **25** implying that the formation of cyanamides **22** and **23** occurred as envisaged. In order to prepare **26** and **27** from **24** and **25**, respectively, they were treated with sodium methoxide or sodium hydride as described earlier in the text. Unfortunately, under these conditions decomposition of the substrates occurred as no spot for the corresponding products were observed during the TLC analysis. These results reflected that the formation of the pyrimido[2,1-*b*]quinazoline is influenced by the nature of substituent present on the phenyl ring of the quinazoline portion.

3. Conclusions

In summary, a concise and practical approach for the synthesis of 2-amino-3-arylmethyl-6*H*-pyrimido[2,1-*b*]quinazolines and 3-arylmethyl-1,6-dihydro-2*H*-pyrimido[2,1-*b*]quinazoline-2-ones has been disclosed starting from the primary allyl amines obtained from the Baylis–Hillman adducts. This strategy is attractive as it employs commonly available cheap reagents and does not require any elaborate reaction conditions. This detailed investigation has also provided an insight into the scope and limitation of the methodology.

4. Experimental

4.1. General

Melting points are uncorrected and were determined in capillary tubes on an apparatus containing silicon oil. The spectroscopic and the analytical data were recorded at the SAIF Division of this institute. IR spectra were recorded using a Perkin–Elmer Spectrum RX I FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded either on a Bruker DPX-200 FT or Bruker Avance DRX-300 spectrometer, using TMS as an internal standard (chemical shifts in δ). The ESMS and FABMS were recorded on MICROMASS Quadro-II LCMS and JEOL SX/102/DA 6000 system, respectively. The HRMS spectra were recorded as EI-HRMS on a JEOL system or as DART-HRMS (recorded as ES+) on a JEOL-AccuTOF JMS-T100LC Mass spectrometer having DART (Direct Analysis in Real Time) source. Elemental analyses were performed on a Carlo Erba 108 or an Elementar Vario EL III microanalyzer. All yields described herein are the isolated yields after column chromatography. The ^{13}C NMR spectra of 2-fluorophenyl derivatives display extra peaks due to the C–F couplings. The ratios of the solvent systems are v/v everywhere.

4.2. General procedure for 7a–k as exemplified for 7b

To a stirred solution of allyl amine **5b** (2.00 g, 11.36 mmol) in dry CH_2Cl_2 (25 mL), 2-nitrobenzaldehyde (1.43 g, 9.47 mmol) was added and the reaction was allowed to continue at room temperature for 3 h. In another RB flask $NaBH_4$ (0.90 g, 23.68 mmol) was taken in dry benzene (30 mL) and to it glacial AcOH (4.07 mL, 71.09 mmol) dissolved in dry benzene (20 mL) was added dropwise at 0 °C. This mixture was allowed to stir at room temperature for 3 h. Thereafter to it the Schiff's base prepared above was added dropwise at 0 °C and the combined reaction mixture was continued for 8 h at room temperature. After completion the solvent was removed under vacuum and the residue was dissolved in EtOAc (50 mL) and neutralized by saturated aqueous $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with EtOAc (3×25 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated to render a residue, which after purification via silica gel column chromatography (hexanes/EtOAc, 9:1) yielded 2.44 g (83%) of **7b** as yellow solid.

4.2.1. (Z)-3-(4-Fluorophenyl)-2-{[(2-nitrobenzyl)amino]-methyl}prop-2-enenitrile (**7b**)

Mp 92–93 °C; R_f=0.26 (hexanes/EtOAc, 3:1); ν_{max} (KBr): 2211 (CN), 3431 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ=3.59 (d, 2H, J=0.5 Hz, CH_2), 4.11 (s, 2H, CH_2), 7.08–7.14 (m, 3H, ArH and =CH), 7.41–7.47 (m, 1H, ArH), 7.59–7.68 (m, 2H, ArH), 7.75–7.79 (m, 2H, ArH), 7.96 (dd, 1H, J_1=0.5 Hz, J_2=8.1 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=49.4, 53.0, 109.6, 116.0 (d, J=21.7 Hz), 118.3, 124.8, 128.3, 129.4, 130.9 (d, J=8.2 Hz), 131.2, 133.3, 134.7, 142.8, 149.1, 163.3 (d, J=250.5 Hz); mass (ES+) m/z=312.0 (M^++1). Anal. Calcd for $C_{17}H_{14}FN_3O_2$ (exact mass: 311.1070): C, 65.59; H, 4.53; N, 13.50. Found: C, 65.43; H, 4.72; N, 13.38.

4.2.2. (Z)-2-{[(2-Nitrobenzyl)amino]methyl}-3-phenylprop-2-enenitrile (**7a**)

Yield: 76% as a yellow solid (3.10 g from 2.10 g); mp 84–86 °C; R_f=0.20 (hexanes/EtOAc, 3:1); ν_{max} (KBr): 2205 (CN), 3460 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ=3.63 (d, 2H, J=1.1 Hz, CH_2), 4.14 (s, 2H, CH_2), 7.15 (s, 1H, =CH), 7.43–7.49 (m, 4H, ArH), 7.61–7.71 (m, 2H, ArH), 7.77–7.80 (m, 2H, ArH), 7.98 (dd, 1H, J_1=0.8 Hz, J_2=8.0 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=49.4, 53.2, 110.0, 118.4, 124.9, 128.3, 128.9, 130.4, 131.3, 133.2, 133.3, 134.9, 144.3, 149.2; mass (ES+) m/z=294.1 (M^++1). Anal. Calcd for $C_{17}H_{15}N_3O_2$ (exact mass: 293.1164): C, 69.61; H, 5.15; N, 14.33. Found: C 69.42; H, 5.51; N, 14.21.

4.2.3. (Z)-3-(4-Chlorophenyl)-2-{[(2-nitrobenzyl)amino]methyl}-prop-2-enenitrile (**7c**)

Yield: 79% as a yellow solid (2.74 g from 1.60 g); mp 80–81 °C; R_f=0.15 (hexanes/EtOAc, 4:1); ν_{max} (KBr): 2211 (CN), 3417 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ=3.62 (d, 2H, J=1.1 Hz, CH_2), 4.13 (s, 2H, CH_2), 7.10 (s, 1H, =CH), 7.40–7.49 (m, 3H, ArH), 7.61–7.73 (m, 4H, ArH), 7.98 (d, 1H, J=8.0 Hz, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ=49.9, 53.5, 111.1, 118.5, 125.3, 128.8, 129.6, 130.5, 131.7, 132.1, 133.8, 135.1, 136.7, 143.1, 149.6; mass (ES+) m/z=328.0 (M^++1). Anal. Calcd for $C_{17}H_{14}ClN_3O_2$ (exact mass: 327.0775): C, 62.30; H, 4.31; N, 12.82. Found: C, 62.53; H, 4.69; N, 12.62.

4.2.4. (Z)-3-(4-Methylphenyl)-2-{[(2-nitrobenzyl)amino]methyl}-prop-2-enenitrile (**7d**)

Yield: 74% as a yellow solid (2.20 g from 1.46 g); mp 85–87 °C; R_f=0.21 (hexanes/EtOAc, 3:1); ν_{max} (KBr): 2211 (CN), 3399 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ=2.41 (s, 3H, CH_3), 3.61 (s, 2H, CH_2), 4.13 (s, 2H, CH_2), 7.09 (s, 1H, =CH), 7.25 (d, 2H, J=8.0 Hz, ArH), 7.43–7.48 (m, 1H, ArH), 7.60–7.70 (m, 4H, ArH), 7.98 (d, 1H, J=8.1 Hz, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ=21.6, 49.5, 53.4, 108.8, 118.7, 125.0, 128.4, 129.0, 129.7, 130.7, 131.4, 133.4, 135.0, 141.0, 144.4; mass (ES+) m/z=308.0 (M^++1). Anal. Calcd for $C_{18}H_{17}N_3O_2$ (exact mass: 307.1321): C, 70.34; H, 5.58; N, 13.67. Found: C, 70.23; H, 5.69; N, 13.86.

4.2.5. (Z)-3-(4-Methoxyphenyl)-2-{[(2-nitrobenzyl)amino]-methyl}prop-2-enenitrile (**7e**)

Yield: 86% as a yellow solid (3.03 g from 1.65 g); mp 116–117 °C; R_f=0.16 (hexanes/EtOAc, 3:1); ν_{max} (KBr): 2210 (CN), 3411 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ=3.59 (s, 2H, CH_2), 3.87 (s, 3H, OCH_3), 4.12 (s, 2H, CH_2), 6.95 (d, 2H, J=8.8 Hz, ArH), 7.04 (s, 1H, =CH), 7.43–7.48 (m, 1H, ArH), 7.63 (t, 1H, J=7.5 Hz, ArH), 7.70 (d, 1H, J=7.3 Hz, ArH), 7.77 (d, 2H, J=8.8 Hz, ArH), 7.98 (d, 1H, J=8.1 Hz, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ=49.4, 53.4, 55.5, 106.9, 114.4, 119.0, 125.0, 126.1, 128.4, 130.8, 131.4, 133.4, 135.1, 144.1, 149.3, 161.4; mass (ES+) m/z=323.9 (M^++1). Anal. Calcd for $C_{18}H_{17}N_3O_3$ (exact mass: 323.1270): C, 66.86; H, 5.30; N, 13.00. Found: C, 67.13; H, 5.64; N, 12.79.

4.2.6. (Z)-3-(2-Fluorophenyl)-2-{[(2-nitrobenzyl)amino]methyl}-prop-2-enenitrile (**7f**)

Yield: 78% as a yellow solid (2.73 g from 1.70 g); mp 78–80 °C; R_f=0.33 (hexanes/EtOAc, 3:1); ν_{max} (KBr): 2211 (CN), 3375

(NH) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ=3.65 (d, 2H, J=1.3 Hz, CH_2), 4.14 (s, 2H, CH_2), 7.10–7.16 (m, 1H, ArH), 7.22–7.27 (m, 1H, ArH), 7.39–7.49 (m, 3H, ArH and =CH), 7.61–7.71 (m, 2H, ArH), 8.00 (dd, 1H, J_1=1.1 Hz, J_2=8.1 Hz, ArH), 8.10–8.15 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=49.4, 53.1, 112.6 (d, J=2.0 Hz), 115.7 (d, J=21.5 Hz), 117.9, 121.5 (d, J=11.7 Hz), 124.5 (d, J=3.6 Hz), 124.9, 128.4 (d, J=10.8 Hz), 128.5, 131.3, 132.1 (d, J=8.7 Hz), 133.3, 134.8, 135.9 (d, J=6.6 Hz), 149.2, 160.5 (d, J=250.5 Hz); mass (ES+) m/z=312.0 (M^++1). Anal. Calcd for $C_{17}H_{14}FN_3O_2$ (exact mass: 311.1070): C, 65.59; H, 4.53; N, 13.50. Found: C, 65.74; H, 4.79; N, 13.68.

4.2.7. (Z)-3-(2-Chlorophenyl)-2-{[(2-nitrobenzyl)amino]methyl}-prop-2-enenitrile (**7g**)

Yield: 76% as yellow oil (2.63 g from 1.60 g); R_f=0.27 (hexanes/EtOAc, 3:1); ν_{max} (Neat): 2217 (CN), 3369 (NH) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ=3.58 (s, 2H, CH_2), 4.07 (s, 2H, CH_2), 7.19 (s, 1H, =CH), 7.28–7.30 (m, 1H, ArH), 7.35–7.43 (m, 3H, ArH), 7.55 (t, 1H, J=7.5 Hz, ArH), 7.62 (d, 1H, J=7.3 Hz, ArH), 7.88–7.93 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=49.3, 52.7, 113.7, 117.6, 124.9, 127.2, 128.3, 129.3, 129.8, 131.2, 131.3, 133.4, 134.1, 134.8, 140.8, 149.1; mass (ES+) m/z=328.1 (M^++1). Anal. Calcd for $C_{17}H_{14}ClN_3O_2$ (exact mass: 327.0775): C, 62.30; H, 4.31; N, 12.82. Found: C, 62.42; H, 4.59; N, 12.65.

4.2.8. (Z)-3-(2,4-Dichlorophenyl)-2-{[(2-nitrobenzyl)amino]-methyl}prop-2-enenitrile (**7h**)

Yield: 82% as a yellow solid (2.74 g from 1.40 g); mp 99–101 °C; R_f=0.27 (hexanes/EtOAc, 3:1); ν_{max} (KBr): 2213 (CN), 3417 (NH) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ=3.65 (d, 2H, J=0.8 Hz, CH_2), 4.14 (s, 2H, CH_2), 7.33–7.36 (dd, 1H, J_1=2.0 Hz, J_2=8.5 Hz, ArH), 7.43 (s, 1H, =CH), 7.46–7.48 (m, 2H, ArH), 7.60–7.70 (m, 2H, ArH), 7.93 (d, 1H, J=8.5 Hz, ArH), 7.99 (d, 1H, J=8.0 Hz, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ=49.5, 52.8, 114.4, 117.5, 125.1, 127.8, 128.5, 129.9, 130.1, 130.4, 131.5, 133.5, 134.8, 135.0, 136.7, 139.6, 149.3; mass (ES+) m/z=362.0 (M^++1). Anal. Calcd for $C_{17}H_{13}Cl_2N_3O_2$ (exact mass: 361.0385): C, 56.37; H, 3.62; N, 11.60. Found: C, 56.21; H, 3.48; N, 11.73.

4.2.9. (Z)-3-(2,6-Dichlorophenyl)-2-{[(2-nitrobenzyl)amino]-methyl}prop-2-enenitrile (**7i**)

Yield: 89% as a yellow solid (2.34 g from 1.10 g); mp 89–90 °C; R_f=0.44 (hexanes/EtOAc, 7:3); ν_{max} (KBr): 2217 (CN), 3280 (NH) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ=3.69 (d, 2H, J=1.3 Hz, CH_2), 4.19 (s, 2H, CH_2), 7.16 (s, 1H, =CH), 7.26–7.31 (m, 1H, ArH), 7.39–7.50 (m, 3H, ArH), 7.61–7.67 (m, 1H, ArH), 7.72 (d, 1H, J=7.7 Hz, ArH), 8.01 (d, 1H, J=8.1 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=49.1, 51.6, 116.4, 120.4, 125.0, 128.3, 130.5, 131.3, 132.0, 133.4, 134.3, 134.7, 139.4, 149.1; mass (ES+) m/z=362.1 (M^++1). Anal. Calcd for $C_{17}H_{13}Cl_2N_3O_2$ (exact mass: 361.0385): C, 56.37; H, 3.62; N, 11.60. Found: C, 56.71; H, 3.86; N, 11.36.

4.2.10. (Z)-3-(3,4-Dimethoxyphenyl)-2-{[(2-nitrobenzyl)amino]-methyl}prop-2-enenitrile (**7j**)

Yield: 88% a white solid (2.26 g from 1.10 g); mp 78–80 °C; R_f=0.22 (hexanes/EtOAc, 3:1); ν_{max} (KBr): 2209 (CN), 3348 (NH) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ=3.60 (d, 2H, J=0.7 Hz, CH_2), 3.94 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 4.12 (s, 2H, CH_2), 6.90 (d, 1H, J=8.4 Hz, ArH), 7.04 (s, 1H, =CH), 7.23–7.26 (m, 1H, ArH), 7.43–7.48 (m, 1H, ArH), 7.59–7.71 (m, 3H, ArH), 7.98 (dd, 1H, J_1=0.9 Hz, J_2=8.1 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=49.3, 53.3, 56.0, 106.8, 110.5, 110.8, 119.0, 123.7, 124.8, 126.2, 128.3, 131.3, 133.3, 134.9, 144.2, 149.0, 149.2, 151.0; mass (ES+) m/z=354.1 (M^++1). Anal. Calcd for $C_{19}H_{19}N_3O_4$ (exact mass: 353.1376): C, 64.58; H, 5.42; N, 11.89. Found: C, 64.37; H, 5.76; N, 11.95.

4.2.11. (Z)-3-(2-Thienyl)-2-{[(2-nitrobenzyl)amino]methyl}prop-2-enenitrile (**7k**)

Yield: 71% as a white solid (2.53 g from 1.80 g); mp 83–85 °C; R_f=0.24 (hexanes/EtOAc, 3:1); ν_{max} (KBr): 2216 (CN), 3316 (NH) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ=4.98 (s, 2H, CH_2), 4.99 (s, 2H, CH_2), 7.46–7.51 (m, 2H, ArH and =CH), 7.68 (t, 2H, J=7.4 Hz, ArH), 7.75 (d, 2H, J=7.4 Hz, ArH), 8.11 (d, 2H, J=8.2 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=62.4, 125.0, 128.5, 129.8, 134.1, 136.9, 147.6; mass (ES+) m/z=300.1 (M^++1). Anal. Calcd for $C_{15}H_{13}N_3O_2S$ (exact mass: 299.0728): C, 60.18; H, 4.38; N, 14.04. Found: C, 60.31; H, 4.63; N, 13.83.

4.2.12. Methyl (E)-3-(4-methylphenyl)-2-{[(2-nitrobenzyl)-amino]methyl}prop-2-enoate (**12d**)

Yield: 70% as a white solid (2.21 g from 1.40 g); mp 87–88 °C; R_f=0.19 (hexanes/EtOAc, 3:1); ν_{max} (KBr): 1704 (CO_2Me), 3426 (NH) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ=2.39 (s, 3H, CH_3), 3.64 (s, 2H, CH_2), 3.84 (s, 3H, CO_2CH_3), 4.08 (s, 2H, CH_2), 7.19 (d, 2H, J=8.0 Hz, ArH), 7.34–7.44 (m, 3H, ArH), 7.52–7.61 (m, 2H, ArH), 7.82 (s, 1H, =CH), 7.95 (d, 1H, J=8.0 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=21.4, 45.7, 50.4, 52.0, 124.7, 127.9, 129.3, 129.4, 129.6, 131.3, 132.1, 132.9, 135.4, 139.2, 142.5, 149.3, 168.6; mass (ES+) m/z=341.1 (M^++1). Anal. Calcd for $C_{19}H_{20}N_2O_4$ (exact mass: 340.1423): C, 67.05; H, 5.92; N, 8.23. Found: C, 66.81; H, 6.18; N, 8.36.

4.2.13. Methyl (E)-3-(2,4-dichlorophenyl)-2-{[(2-nitrobenzyl)-amino]methyl}prop-2-enoate (**12h**)

Yield: 71% as yellow oil (2.78 g from 1.50 g); R_f=0.30 (hexanes/EtOAc, 3:1); ν_{max} (Neat): 1712 (CO_2Me), 3407 (NH) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ=3.48 (s, 2H, CH_2), 3.86 (s, 3H, CO_2CH_3), 4.05 (s, 2H, CH_2), 5.00 (s, 1H, NH), 7.26–7.30 (m, 2H, ArH), 7.42–7.46 (m, 2H, ArH), 7.52–7.55 (m, 2H, ArH), 7.85 (s, 1H, =CH), 7.94 (d, 1H, J=8.3 Hz, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ=46.0, 50.6, 52.5, 125.0, 125.1, 127.5, 128.4, 129.5, 130.0, 131.6, 131.9, 132.1, 133.1, 134.3, 134.9, 135.6, 138.5, 167.8; mass (ES+) m/z=395.1 (M^++1). Anal. Calcd for $C_{18}H_{16}Cl_2N_2O_4$ (exact mass: 394.0487): C, 54.70; H, 4.08; N, 7.09. Found: C, 54.52; H, 4.27; N, 7.24.

4.2.14. 3-[(5-Chloro-2-nitrobenzyl)amino]-2-(2,4-dichlorobenzyl)-prop-2-enenitrile (**15**)

Yield: 76% as a white solid (2.20 g from 1.60 g); mp 72–78 °C; R_f=0.38 (hexanes/EtOAc, 3:1); ν_{max} (KBr): 2215 (CN), 3406 (NH) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ=3.64 (d, 2H, J=1.0 Hz, CH_2), 4.15 (s, 2H, CH_2), 7.12 (s, 1H, =CH), 7.40–7.47 (m, 4H, ArH), 7.77–7.80 (m, 3H, ArH), 7.97 (d, 1H, J=8.7 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=49.0, 53.3, 109.8, 118.3, 126.5, 128.3, 128.9 (2), 130.5, 130.9, 133.1, 137.4, 140.0, 144.5, 147.1; mass (ES+) m/z=328.0 (M^++1). Anal. Calcd for $C_{17}H_{14}ClN_3O_2$ (exact mass: 327.0775): C, 62.30; H, 4.31; N, 12.82. Found: C, 62.15; H, 4.62; N, 12.97.

4.2.15. 2-Benzyl-3-[(4,5-dimethoxy-2-nitrobenzyl)amino]prop-2-enenitrile (**16**)

Yield: 83% as a white solid (1.53 g from 1.10 g); mp 92–93 °C; R_f=0.21 (hexanes/EtOAc, 7:3); ν_{max} (KBr): 2212 (CN), 3359 (NH) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ=3.63 (s, 2H, J=1.5 Hz, CH_2), 3.94 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 4.14 (s, 2H, CH_2), 7.12 (s, 1H, =CH), 7.26 (d, 1H, J=0.8 Hz, ArH), 7.41–7.44 (m, 3H, ArH), 7.63 (s, 1H, ArH), 7.74–7.78 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=49.7, 53.5, 56.4, 56.6, 108.2, 110.1, 112.3, 118.5, 128.8, 128.9, 130.5, 130.6, 133.2, 140.8, 144.4, 147.8, 153.5; mass (ES+) m/z=354.0 (M^++1). Anal. Calcd for $C_{19}H_{19}N_3O_4$ (exact mass: 353.1376): C, 64.58; H, 5.42; N, 11.89. Found: C, 64.63; H, 5.72; N, 11.56.

4.2.16. (Z)-2-({[(6-Nitro-1,3-benzodioxol-5-yl)methyl]amino}-methyl)-3-phenylprop-2-enenitrile (**17**)

Yield: 88% as a white solid (2.13 g from 1.40 g); mp 117–119 °C; R_f=0.26 (hexanes/EtOAc, 7:3); ν_{max} (KBr): 2210 (CN), 3419

(NH) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ=3.63 (d, 2H, J=1.1 Hz, CH_2), 4.08 (s, 2H, CH_2), 6.13 (s, 2H, OCH_2O), 7.14 (s, 1H, =CH), 7.17 (s, 1H, ArH), 7.43–7.47 (m, 3H, ArH), 7.55 (s, 1H, ArH), 7.77–7.80 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=49.9, 53.2, 103.0, 105.8, 109.9, 110.0, 118.4, 128.9, 130.4, 132.6, 133.2, 142.7, 144.2, 147.1, 152.2; mass (ES+) m/z=338.1 (M^++1). Anal. Calcd for $C_{18}H_{15}N_3O_4$ (exact mass: 337.1063): C, 64.09; H, 4.48; N, 12.46. Found: C, 64.32; H, 4.79; N, 12.23.

4.3. Typical procedure for synthesis of 8b from 7b

To a stirred solution of compound **7b** (1.00 g, 3.22 mmol) in MeOH (10 mL), CNBr (0.35 g, 3.30 mmol) and $NaHCO_3$ (0.27 g, 3.22 mmol) were added simultaneously and the reaction was allowed to proceed for 30 min at room temperature. Thereafter it was concentrated and the residue thus obtained was dissolved in EtOAc (40 mL), which was washed with water (40 mL). The aqueous layer was separated and extracted with EtOAc (3×30 mL). The organic layers were pooled, washed with brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo to afford a residue. The crude residue was purified through column chromatography on silica gel (hexanes/EtOAc, 7:2) to obtain **8b** (1.01 g, 93%) as a white solid.

*4.3.1. (Z)-2-Cyano-3-(4-fluorophenyl)prop-2-enyl(2-nitrobenzyl)-cyanamide (**8b**)*

Mp 103–105 °C; R_f=0.16 (hexanes/EtOAc, 3:1); ν_{max} (KBr): 2211 (CN) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ=4.06 (s, 2H, CH_2), 4.73 (s, 2H, CH_2), 7.11–7.17 (m, 3H, ArH and =CH), 7.56–7.61 (m, 1H, ArH), 7.70–7.84 (m, 4H, ArH), 8.12 (d, 1H, J=8.1 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=52.6, 56.5, 103.9 (d, J=2.2 Hz), 115.7, 116.3 (d, J=21.7 Hz), 117.2, 125.7, 128.4 (d, J=3.7 Hz) 129.4, 130.1, 131.3, 131.6 (d, J=9.0 Hz), 134.3, 146.9, 148.3, 164.3 (d, J=252.7 Hz); mass (ES+) m/z=337.2 (M^++1). Anal. Calcd for $C_{18}H_{13}FN_4O_2$ (exact mass: 336.1023): C, 64.28; H, 3.90; N, 16.66. Found: C, 64.09; H, 4.05; N, 16.73.

4.4. Typical procedure for synthesis of 10b from 8b

Method A. To a solution of compound **8b** (0.50 g, 1.49 mmol) in AcOH (15 mL), Fe powder (0.42 g, 7.50 mmol) was added and the reaction mixture was heated at 90 °C for 1 h. After completion, the mixture was cooled to ambient temperature and poured in ice cooled water and neutralized with aqueous $NaHCO_3$ and the precipitated solid was separated by filtering through a Celite bed and washed repeatedly with EtOAc. The organic layer was partitioned and washed with brine, dried over Na_2SO_4, concentrated to furnish a residue that upon column chromatography via silica gel (EtOAc/MeOH, 6:1) afforded **10b** as a white solid (0.14 g, 31%).

Method B. To a solution of compound **8b** (0.50 g, 1.49 mmol) in a mixture of THF/water (20 mL, 1:1), In powder (0.51 g, 4.47 mmol) was added followed by dropwise addition of 1 mL concd HCl. The reaction was allowed to stir at room temperature for 1.5 h, after which the THF was removed and the residue was neutralized by saturated aqueous $NaHCO_3$ solution. The mixture was filtered through a Celite bed and washed successively with EtOAc. Then organic layer was separated, washed with brine, dried (Na_2SO_4), and concentrated to provide the crude product. The crude material was purified via silica gel column chromatography (EtOAc/MeOH, 6:1) to yield 0.31 g (69%) of **10b** as a white solid.

*4.4.1. (Z)-2-{[2-Aminoquinazolin-3(4H)-yl]methyl}-3-(4-fluorophenyl)prop-2-enenitrile (**10b**)*

Mp 165–167 °C; R_f=0.32 (EtOAc/MeOH, 4:1); ν_{max} (KBr): 1658 (C=N), 2214 (CN), 3335 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ=4.45 (s, 2H, CH_2), 4.54 (s, 2H, CH_2), 6.92–6.94 (m, 2H, ArH), 7.07 (s, 1H, ArH), 7.19 (s, 1H, ArH), 7.38 (s, 2H, ArH), 7.53 (s, 1H, =CH), 7.87 (s, 2H, ArH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ=48.6, 52.3, 105.1 (d, J=2.3 Hz), 115.6, 116.8, 117.3, 118.0, 118.7, 124.9, 126.9 (d, J=4.3 Hz), 129.6, 130.3 (d, J=3.2 Hz), 132.2 (d, J=8.7 Hz), 133.6, 146.0, 153.3, 158.1 (d, J=232.4 Hz); mass (ES+) m/z=307.3 (M^++1); DART-HRMS calcd for $C_{18}H_{16}FN_4$: 307.1359, found: 307.1348.

4.5. Typical procedure for synthesis of 9b from 7b

Method A. To a solution of compound **7b** (0.50 g, 1.61 mmol) in AcOH (15 mL), Fe powder (0.45 g, 8.05 mmol) was added and the mixture was heated at reflux for 1 h. After completion of the reaction, the reaction mixture was cooled to room temperature and poured in ice cooled water followed by neutralization with aqueous $NaHCO_3$. The precipitated solid was separated by filtration through a Celite bed, which was repeatedly washed with EtOAc. The filtrate was partitioned in a separating funnel, the organic layer separated, washed with brine, dried (Na_2SO_4), and concentrated to obtain a residue. Purification of this residue through column chromatography on silica gel employing hexanes/EtOAc (4:1) gave 0.22 g (48%) of **9b** as a yellow solid.

Method B. To a solution of compound **7b** (0.50 g, 1.61 mmol) in a mixture of THF/water (20 mL, 1:1), In powder (0.55 g, 4.82 mmol) was added followed by dropwise addition of 1.1 mL concd HCl and the reaction was allowed to stir at room temperature for 1.5 h. On completion THF was removed from the mixture, EtOAc was added to the residue and the mixture was neutralized with saturated aqueous $NaHCO_3$. The resulting solution was filtered through a Celite bed using EtOAc. The filtrate was partitioned and the usual workup of the organic layer afforded a residue that was purified through column chromatography on silica gel. Elution with hexanes/EtOAc (4:1) yielded 0.42 g of **9b** (93%) as a yellow solid.

Method B was adopted as general procedure for the synthesis of diamines **9a–k**, **12d**,**h**, **18**.

*4.5.1. (Z)-2-{[(2-Aminobenzyl)amino]methyl}-3-(4-fluorophenyl)prop-2-enenitrile (**9b**)*

Mp 60–62 °C; R_f=0.42 (hexanes/EtOAc, 7:3); ν_{max} (KBr): 2212 (CN), 3325, 3430 (NH and NH_2) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ=3.57 (s, 2H, CH_2), 3.87 (s, 2H, CH_2), 6.67–6.71 (m, 2H, ArH), 6.97 (s, 1H, =CH), 7.02 (d, 1H, J=7.7 Hz, ArH), 7.10–7.15 (m, 3H, ArH), 7.73–7.78 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=51.5, 53.0, 109.9 (d, J=2.2 Hz) 116.0 (d, J=3.0 Hz), 116.2, 117.8, 118.3, 122.7, 128.8, 129.5 (d, J=3.0 Hz), 130.2, 130.9 (d, J=8.2 Hz), 143.1, 147.0, 163.7 (d, J=251.2 Hz); mass (ES+) m/z=282.0 (M^++1). Anal. Calcd for $C_{17}H_{16}FN_3$ (exact mass: 281.1328): C, 72.58; H, 5.73; N, 14.94. Found: C, 72.68; H, 5.96; N, 14.63.

*4.5.2. (Z)-2-{[(2-Aminobenzyl)amino]methyl}-3-phenylprop-2-enenitrile (**9a**)*

Yield: 87% as yellow oil (0.78 g from 1.00 g); R_f=0.29 (hexanes/EtOAc, 7:3); ν_{max} (Neat): 2214 (CN), 3334, 3433 (NH and NH_2) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ=3.57 (d, 2H, J=0.9 Hz, CH_2), 3.87 (s, 2H, CH_2), 6.67–6.71 (m, 2H, ArH), 7.01–7.03 (m, 2H, ArH and =CH), 7.08–7.14 (m, 1H, ArH), 7.42–7.45 (m, 3H, ArH), 7.73–7.75 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=51.4, 53.0, 110.2, 116.0, 117.8, 118.4, 122.8, 128.8, 128.9 (2), 130.2, 130.5, 133.2, 144.5, 147.0; mass (ES+) m/z=264.1 (M^++1). Anal. Calcd for $C_{17}H_{17}N_3$ (exact mass: 263.1422): C, 77.54; H, 6.51; N, 15.96. Found: C, 77.68; H, 6.86; N, 15.77.

*4.5.3. (Z)-2-{[(2-Aminobenzyl)amino]methyl}-3-(4-chlorophenyl)prop-2-enenitrile (**9c**)*

Yield: 89% as a white solid (0.58 g from 0.72 g); mp 70–72 °C; R_f=0.37 (hexanes/EtOAc, 7:3); ν_{max} (KBr): 2213 (CN), 3328, 3434 (NH and NH_2) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ=3.58 (s, 2H, CH_2), 3.88 (s, 2H, CH_2), 6.71 (t, 2H, J=6.1 Hz, ArH), 6.97 (s, 1H, =CH), 7.03

(d, 1H, J=7.2 Hz, ArH), 7.13 (t, 1H, J=7.0 Hz, ArH), 7.42 (d, 2H, J=8.4 Hz, ArH), 7.69 (d, 2H, J=8.4 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=51.5, 53.0, 111.0, 116.0, 117.8, 118.1, 122.6, 128.8, 129.2, 130.1, 130.2, 131.6, 136.4, 143.0, 146.9; mass (ES+) m/z=297.9 (M^++1). Anal. Calcd for $C_{17}H_{16}ClN_3$ (exact mass: 297.1033): C, 68.57; H, 5.42; N, 14.11. Found: C, 68.77; H, 5.79; N, 14.02.

4.5.4. (Z)-2-{[(2-Aminobenzyl)amino]methyl}-3-(4-methylphenyl)prop-2-enenitrile (**9d**)

Yield: 91% as yellow oil (0.74 g from 0.90 g); R_f=0.35 (hexanes/EtOAc, 7:3); ν_{max} (Neat): 2211 (CN), 3326, 3431 (NH and NH_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ=2.41 (s, 3H, CH_3), 3.57 (d, 2H, J=0.8 Hz, CH_2), 3.88 (s, 2H, CH_2), 6.68–6.72 (m, 2H, ArH), 6.98 (s, 1H, =CH), 7.02–7.04 (m, 1H, ArH), 7.10–7.15 (m, 1H, ArH), 7.24–7.28 (m, 2H, ArH), 7.68 (d, 2H, J=8.1 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=21.5, 51.4, 53.1, 108.8, 115.9, 117.8, 118.6, 122.8, 128.7, 128.9, 129.6, 130.2, 130.5, 141.0, 144.5, 147.0; mass (ES+) m/z=278.1 (M^++1). Anal. Calcd for $C_{18}H_{19}N_3$ (exact mass: 277.1579): C, 77.95; H, 6.90; N, 15.15. Found: C, 78.06; H, 6.72; N, 15.31.

4.5.5. (Z)-2-{[(2-Aminobenzyl)amino]methyl}-3-(4-methoxyphenyl)prop-2-enenitrile (**9e**)

Yield: 92% as yellow oil (0.75 g from 0.90 g); R_f=0.32 (hexanes/EtOAc, 7:3); ν_{max} (Neat): 2210 (CN), 3330, 3433 (NH and NH_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ=3.55 (s, 2H, CH_2), 3.86 (s, 5H, CH_2 and OCH_3), 6.67–6.71 (m, 2H, ArH), 6.93 (s, 2H, ArH), 6.96 (s, 1H, =CH), 7.02 (d, 1H, J=7.7 Hz, ArH), 7.08–7.14 (m, 1H, ArH), 7.76 (d, 2H, J=8.7 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=51.3, 53.1, 55.4, 107.0, 114.3, 115.9, 117.8, 118.9, 122.8, 126.0, 128.7, 130.2, 130.7, 144.1, 147.0, 161.3; mass (ES+) m/z=294.0 (M^++1). Anal. Calcd for $C_{18}H_{19}N_3O$ (exact mass: 293.1528): C, 73.69; H, 6.53; N, 14.32. Found: C, 73.43; H, 6.49; N, 14.52.

4.5.6. (Z)-2-{[(2-Aminobenzyl)amino]methyl}-3-(2-fluorophenyl)prop-2-enenitrile (**9f**)

Yield: 82% as yellow oil (0.52 g from 0.70 g); R_f=0.39 (hexanes/EtOAc, 7:3); ν_{max} (Neat): 2215 (CN), 3331, 3428 (NH and NH_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ=3.62 (d, 2H, J=0.9 Hz, CH_2), 3.90 (s, 2H, CH_2), 6.69–6.73 (m, 2H, ArH), 7.05 (d, 1H, J=7.7 Hz, ArH), 7.10–7.16 (m, 2H, ArH and =CH), 7.22–7.30 (m, 2H, ArH), 7.39–7.44 (m, 1H, ArH), 8.10–8.14 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ=51.9, 53.3, 113.1 (d, J=2.0 Hz), 115.9 (d, J=1.5 Hz), 118.3 (d, J=2.5 Hz), 122.0, 123.1, 125.0 (d, J=3.5 Hz), 128.9 (d, J=2.0 Hz), 129.2, 130.7, 132.5 (d, J=9.0 Hz), 136.5 (d, J=6.5 Hz), 147.4, 160.9 (d, J=250.5 Hz); mass (ES+) m/z=282.0 (M^++1). Anal. Calcd for $C_{17}H_{16}FN_3$ (exact mass: 281.1328): C, 72.58; H, 5.73; N, 14.94. Found: C, 72.32; H, 5.95; N, 14.71.

4.5.7. (Z)-2-{[(2-Aminobenzyl)amino]methyl}-3-(2-chlorophenyl)prop-2-enenitrile (**9g**)

Yield: 83% as yellow oil (0.57 g from 0.75 g); R_f=0.39 (hexanes/EtOAc, 7:3); ν_{max} (Neat): 2216 (CN), 3329, 3433 (NH and NH_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ=3.62 (d, 2H, J=1.3 Hz, CH_2), 3.90 (s, 2H, CH_2), 6.67–6.72 (m, 2H, ArH), 7.04–7.12 (m, 2H, ArH and =CH), 7.34–7.46 (m, 4H, ArH), 7.95–7.98 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=51.4, 52.6, 113.8, 116.0, 117.9, 122.7, 127.2, 128.8, 129.3, 129.8, 130.3, 131.2, 131.7, 134.1, 140.9, 146.9; mass (ES+) m/z=298.0 (M^++1). Anal. Calcd for $C_{17}H_{16}ClN_3$ (exact mass: 297.1033): C, 68.57; H, 5.42; N, 14.11. Found: C, 68.75; H, 5.31; N, 14.26.

4.5.8. (Z)-2-{[(2-Aminobenzyl)amino]methyl}-3-(2,4-dichlorophenyl)prop-2-enenitrile (**9h**)

Yield: 82% as yellow oil (0.75 g from 1.00 g); R_f=0.42 (hexanes/EtOAc, 7:3); ν_{max} (Neat): 2217 (CN), 3334, 3432 (NH and NH_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ=3.63 (d, 2H, J=1.2 Hz, CH_2), 3.91 (s, 2H, CH_2), 6.68–6.73 (m, 2H, ArH and =CH), 7.04–7.07 (m, 1H, ArH), 7.10–7.165 (m, 1H, ArH), 7.35 (dd, 2H, J_1=1.8 Hz, J_2=8.6 Hz, ArH), 7.48 (d, 1H, J=2.8 Hz, ArH), 7.91 (d, 1H, J=8.3 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=51.5, 52.6, 114.4, 116.0, 117.4, 117.9, 122.6, 127.7, 128.9, 129.7, 130.0, 130.2, 130.3, 134.8, 136.5, 139.6, 146.9; mass (ES+) m/z=331.9 (M^++1). Anal. Calcd for $C_{17}H_{15}Cl_2N_3$ (exact mass: 331.0643): C, 61.46; H, 4.55; N, 12.65. Found: C, 61.68; H, 4.83; N, 12.71.

4.5.9. (Z)-2-{[(2-Aminobenzyl)amino]methyl}-3-(2,6-dichlorophenyl)prop-2-enenitrile (**9i**)

Yield: 86% as a white solid (0.79 g from 1.00 g); mp 98–99 °C; R_f=0.59 (hexanes/EtOAc, 7:3); ν_{max} (KBr): 2224 (CN), 3333, 3438 (NH and NH_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ=3.66 (d, 2H, J=1.1 Hz, CH_2), 3.95 (s, 2H, CH_2), 6.69–6.74 (m, 2H, ArH), 7.06–7.17 (m, 3H, ArH and =CH), 7.26–7.31 (m, 1H, ArH), 7.40–7.43 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=51.6, 51.9, 116.4, 118.3, 121.1, 123.0, 128.8, 129.3, 130.7, 130.9, 132.4, 134.7, 139.9, 147.4; mass (ES+) m/z=332.0 (M^++1). Anal. Calcd for $C_{17}H_{15}Cl_2N_3$ (exact mass: 331.0643): C, 61.46; H, 4.55; N, 12.65. Found: C, 61.86; H, 4.38; N, 12.79.

4.5.10. (Z)-2-{[(2-Aminobenzyl)amino]methyl}-3-(3,4-dimethoxyphenyl)prop-2-enenitrile (**9j**)

Yield: 88% as a white solid (0.81 g from 1.00 g); mp 125–127 °C; R_f=0.17 (hexanes/EtOAc, 7:3); ν_{max} (KBr): 2205 (CN), 3307, 3406 (NH and NH_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ=3.57 (s, 2H, CH_2), 3.88 (s, 2H, CH_2), 3.95 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 6.68–6.72 (m, 2H, ArH), 6.89–6.94 (m, 2H, ArH and =CH), 7.03 (d, 1H, J=7.7 Hz, ArH), 7.10–7.15 (m, 1H, ArH), 7.22 (dd, 1H, J_1=1.9 Hz, J_2=8.3 Hz, ArH), 7.58 (d, 1H, J=1.8 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=51.4, 53.1, 56.0, 107.1, 110.6, 111.0, 115.9, 117.7, 119.0, 122.8, 123.6, 126.2, 128.7, 130.1, 144.3, 147.0, 149.1, 151.1; mass (ES+) m/z=324.0 (M^++1). Anal. Calcd for $C_{19}H_{21}N_3O_2$ (exact mass: 323.1634): C, 70.57; H, 6.55; N, 12.99. Found: C, 70.69; H, 6.81; N, 12.82.

4.5.11. (Z)-2-{[(2-Aminobenzyl)amino]methyl}-3-(2-thienyl)prop-2-enenitrile (**9k**)

Yield: 86% as a white solid (0.74 g from 0.95 g); mp 80–82 °C; R_f=0.36 (hexanes/EtOAc, 7:3); ν_{max} (KBr): 2209 (CN), 3324, 3426 (NH and NH_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ=3.55 (d, 2H, J=0.8 Hz, CH_2), 3.88 (s, 2H, CH_2), 6.69 (dd, 2H, J_1=1.2 Hz, J_2=6.8 Hz, ArH), 7.03 (d, 1H, J=7.7 Hz, ArH), 7.11–7.14 (m, 3H, ArH and =CH), 7.50–7.53 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=51.4, 52.3, 107.0, 115.9, 117.8, 123.0, 127.7, 128.8, 129.5, 130.2, 131.5, 136.9, 137.1, 146.9; mass (ES+) m/z=270.0 (M^++1). Anal. Calcd for $C_{15}H_{15}N_3S$ (exact mass: 269.0987): C, 66.88; H, 5.61; N, 15.60. Found: C, 66.95; H, 5.86; N, 15.37.

4.5.12. Methyl (E)-2-{[(2-aminobenzyl)amino]methyl}-3-(4-methylphenyl)prop-2-enoate (**13d**)

Yield: 96% as a white solid (0.56 g from 0.64 g); mp 82–83 °C; R_f=0.40 (hexanes/EtOAc, 4:1); ν_{max} (KBr): 1703 (CO_2Me), 3363, 3438 (NH and NH_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ=2.37 (s, 3H, CH_3), 3.65 (s, 2H, CH_2), 3.83 (s, 2H, CH_2), 3.84 (s, 3H, CO_2CH_3), 6.65–6.71 (m, 2H, ArH), 6.98 (d, 1H, J=7.4 Hz, ArH), 7.11–7.15 (m, 3H, ArH), 7.30 (d, 2H, J=8.2 Hz, ArH), 7.79 (s, 1H, =CH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=21.4, 45.4, 52.1, 52.6, 115.7, 117.8, 123.8, 128.4, 129.3, 129.5, 129.6, 130.2, 132.1, 139.2, 142.0, 146.8, 168.8; mass (ES+) m/z=311.1 (M^++1). Anal. Calcd for $C_{19}H_{22}N_2O_2$ (exact mass: 310.1681): C, 73.52; H, 7.14; N, 9.03. Found: C, 73.46; H, 7.31; N, 9.19.

4.5.13. Methyl (E)-2-{[(2-aminobenzyl)amino]methyl}-3-(2,4-dichlorophenyl)prop-2-enoate (**13h**)

Yield: 95% as a yellow solid (0.49 g from 0.56 g); mp 106–108 °C; R_f=0.41 (hexanes/EtOAc, 4:1); ν_{max} (KBr): 1715 (CO_2Me), 3342,

3443 (NH and NH_2) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ=3.49 (s, 2H, CH_2), 3.77 (s, 2H, CH_2), 3.87 (s, 3H, CO_2CH_3), 6.61–6.69 (m, 2H, ArH), 6.92 (d, 1H, J=7.3 Hz, ArH), 7.05–7.13 (m, 2H, ArH), 7.26 (s, 1H, ArH), 7.42 (d, 1H, J=2.0 Hz, ArH), 7.81 (s, 1H, =CH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=45.5, 52.6, 52.7, 116.2, 118.3, 123.7, 127.5, 129.0, 129.8, 130.6, 131.7, 132.4, 132.8, 135.2, 135.7, 138.0, 147.0, 168.2; mass (ES+) m/z=365.0 (M^++1). Anal. Calcd for $C_{18}H_{18}Cl_2N_2O_2$ (exact mass: 364.0745): C, 59.19; H, 4.97; N, 7.67. Found: C, 59.43; H, 5.16; N, 7.42.

4.5.14. (Z)-2-{[(2-Amino-5-chlorobenzyl)amino]methyl}-3-phenylprop-2-enenitrile (**18**)

Yield: 81% as a white solid (0.74 g from 1.00 g); mp 73–75 °C; R_f=0.31 (hexanes/EtOAc, 7:3); ν_{max} (KBr): 2213 (CN), 3329, 3434 (NH and NH_2) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ=3.57 (d, 2H, J=1.1 Hz, CH_2), 3.84 (s, 2H, CH_2), 6.61 (d, 1H, J=8.4 Hz, ArH), 7.02 (s, 2H, ArH and =CH), 7.07 (dd, 1H, J_1=2.4 Hz, J_2=8.4 Hz, ArH), 7.43–7.47 (m, 3H, ArH), 7.75–7.78 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=51.0, 53.0, 109.9, 117.0, 118.3, 122.1, 124.1, 128.4, 128.8, 128.9, 129.8, 130.5, 133.1, 144.7, 145.6; mass (ES+) m/z=298.1 (M^++1). Anal. Calcd for $C_{17}H_{16}ClN_3$ (exact mass: 297.1033): C, 68.57; H, 5.42; N, 14.11. Found: C, 68.62; H, 5.76; N, 13.96.

4.6. Typical procedure for synthesis of 10b from 9b

To a stirred solution of compound **9b** (0.40 g, 1.42 mmol) in MeOH (15 mL), CNBr (0.15 g, 1.42 mmol) and $NaHCO_3$ (0.12 g, 1.42 mmol) were added and the reaction was allowed to continue at room temperature for 30 min. On completion, the MeOH was removed from the reaction mixture; the residue was diluted with ethyl acetate (30 mL) and washed with water (30 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2×20 mL). The organic layers were pooled, dried (Na_2SO_4), and evaporated in vacuo to afford a residue, which upon purification via column chromatography on silica gel (EtOAc/MeOH, 6:1) gave 0.35 g (81%) of **10b** as a white solid.

4.7. Typical procedure for synthesis of 11b from 10b

To a solution of NaOMe (prepared from Na (0.05 g, 2.17 mmol) in 12 mL of MeOH), compound **10b** (0.30 g, 0.98 mmol) was added and the mixture was heated at reflux for 4 h. On completion the excess MeOH was removed and to the residual mass ice cold water (20 mL) was added and the resulting mixture was extracted with EtOAc (4×15 mL). The usual workup of the combined organic layer furnished a residue, which upon purification by column chromatography on silica gel (EtOAc/MeOH, 5:1) gave 0.24 g (79%) of **11b** as a white solid.

4.8. General procedure for one-pot synthesis of 11a–k, 14d,h from 9a–k, 12d,h as exemplified for 9b

To a stirred solution of compound **9b** (0.40 g, 1.42 mmol) in dry MeOH (15 mL), CNBr (0.15 g, 1.42 mmol) was added and the reaction was allowed to stir at room temperature for 30 min. Then Na (0.10 g, 4.35 mmol) was added at 0 °C to it and the mixture was heated at reflux for 4 h. After completion MeOH was removed from the reaction mixture and the residue was diluted with EtOAC (40 mL) and water (40 mL). The aqueous layer was separated and extracted with EtOAc (4×20 mL). The organic layers were pooled and usual workup followed by purification with silica gel based column chromatography (EtOAc/MeOH, 5:1) yielded 0.32 g (74%) of **11b** as a white solid.

4.8.1. 3-(4-Fluorobenzyl)-6H-pyrimido[2,1-b]quinazolin-2-ylamine (**11b**)

Mp 202–203 °C (dec); R_f=0.15 (EtOAc/MeOH, 3:1); ν_{max} (KBr): 1684 (C=N), 3351 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ=3.61 (s, 2H, CH_2), 4.93 (s, 2H, CH_2), 6.70–6.77 (m, 2H, ArH), 6.90 (d, 1H, J=6.8 Hz, ArH), 7.03 (t, 1H, J=7.4 Hz, ArH), 7.09–7.15 (m, 3H, ArH), 7.30–7.34 (m, 2H, ArH and =CH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ=32.2, 51.7, 108.1, 115.9 (d, J=20.5 Hz), 119.7, 121.1, 122.5, 125.5, 128.8, 131.2 (d, J=8.0 Hz), 135.9 (d, J=3.0 Hz), 143.6, 146.7, 151.7, 161.8 (d, J=240.4 Hz), 162.6; mass (ES+) m/z=307.4 (M^++1). Anal. Calcd for $C_{18}H_{15}FN_4$ (exact mass: 306.1281): C, 70.57; H, 4.94; N, 18.29. Found: C, 70.37; H, 5.21; N, 18.14.

4.8.2. 3-Benzyl-6H-pyrimido[2,1-b]quinazolin-2-ylamine (**11a**)

Yield: 78% as a white solid (0.51 g from 0.60 g); mp 205–208 °C; R_f=0.36 (EtOAc/MeOH, 3:1); ν_{max} (KBr): 1671 (C=N), 3338 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ=3.75 (s, 2H, CH_2), 5.12 (s, 2H, CH_2), 6.92–7.00 (m, 2H, ArH), 7.09 (d, 1H, J=7.3 Hz, ArH), 7.16–7.26 (m, 2H, ArH), 7.31–7.35 (m, 4H, ArH), 7.47 (s, 1H, =CH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ=32.5, 51.1, 111.4, 117.6, 118.1, 123.0, 126.0, 127.1, 129.0, 129.2, 138.5, 138.7, 143.5, 150.2, 163.1; mass (ES+) m/z=289.4 (M^++1); HR-EIMS calcd for $C_{18}H_{16}N_4$: 288.1375, found: 288.1386.

4.8.3. 3-(4-Chlorobenzyl)-6H-pyrimido[2,1-b]quinazolin-2-ylamine (**11c**)

Yield: 72% as a white solid (0.31 g from 0.40 g); mp 225 °C (dec); R_f=0.35 (EtOAc/MeOH, 4:1); ν_{max} (KBr): 1641 (C=N), 3433 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ=3.70 (s, 2H, CH_2), 5.06 (s, 2H, CH_2), 6.90 (d, 2H, J=7.6 Hz, ArH), 7.03 (d, 1H, J=7.0 Hz, ArH), 7.13 (t, 1H, J=7.5 Hz, ArH), 7.31–7.41 (m, 5H, ArH and=CH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ=31.6, 50.9, 112.1, 116.4, 116.8, 123.9, 126.3, 128.8, 129.2, 131.0, 131.7, 135.4, 136.8, 143.7, 149.6, 163.1; mass (ES+) m/z=323.4 (M^++1). Anal. Calcd for $C_{18}H_{15}ClN_4$ (exact mass: 322.0985): C, 66.98; H, 4.68; N, 17.36. Found: C, 67.09; H, 4.92; N, 17.11.

4.8.4. 3-(4-Methylbenzyl)-6H-pyrimido[2,1-b]quinazolin-2-ylamine (**11d**)

Yield: 69% as a white solid (0.36 g from 0.48 g); mp 211–214 °C; R_f=0.22 (EtOAc/MeOH, 4:1); ν_{max} (KBr): 1672 (C=N), 3429 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ=2.27 (s, 3H, CH_3), 3.70 (s, 2H, CH_2), 5.13 (s, 2H, CH_2), 6.94–7.01 (m, 2H, ArH), 7.11 (t, 3H, J=7.7 Hz, ArH), 7.17–7.21 (m, 3H, ArH), 7.46 (s, 1H, =CH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ=24.7, 32.0, 51.0, 112.2, 117.2, 123.3, 126.1, 129.1, 129.5, 134.9, 136.1, 143.2, 149.9, 163.1; mass (ES+) m/z=303.4 (M^++1). Anal. Calcd for $C_{19}H_{18}N_4$ (exact mass: 302.1531): C, 75.47; H, 6.00; N, 18.53. Found: C, 75.76; H, 6.12; N, 18.61.

4.8.5. 3-(4-Methoxybenzyl)-6H-pyrimido[2,1-b]quinazolin-2-ylamine (**11e**)

Yield: 65% as a white solid (0.35 g from 0.50 g); mp 226–229 °C; R_f=0.18 (EtOAc/MeOH, 4:1); ν_{max} (KBr): 1676 (C=N), 3434 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ=3.66 (s, 2H, CH_2), 3.73 (s, 3H, OCH_3), 5.11 (s, 2H, CH_2), 6.88 (d, 2H, J=8.5 Hz, ArH), 6.96 (t, 2H, J=7.0 Hz, ArH), 7.07 (d, 1H, J=7.2 Hz, ArH), 7.16 (d, 1H, J=7.3 Hz, ArH), 7.23 (d, 2H, J=8.5 Hz, ArH), 7.39 (s, 1H, =CH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ=31.6, 51.0, 55.5, 112.3, 114.4, 117.3, 117.4, 123.2, 126.1, 129.0, 129.7, 130.2, 143.1, 149.9, 158.5, 163.0; mass (ES+) m/z=319.3 (M^++1). Anal. Calcd for $C_{19}H_{18}N_4O$ (exact mass: 318.1481): C, 71.68; H, 5.70; N, 17.60. Found: C, 71.76; H, 6.08; N, 17.69.

4.8.6. 3-(2-Fluorobenzyl)-6H-pyrimido[2,1-b]quinazolin-2-ylamine (**11f**)

Yield: 79% as a white solid (0.34 g from 0.40 g); mp 213 °C (dec); R_f=0.31 (EtOAc/MeOH, 3:1); ν_{max} (KBr): 1674 (C=N), 3442 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ=3.73 (s, 2H, CH_2), 5.04

(s, 2H, CH_2), 6.91 (t, 2H, J=6.8 Hz, ArH), 7.01 (d, 1H, J=7.3 Hz, ArH), 7.11–7.31 (m, 6H, ArH and =CH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ=26.4, 51.2, 109.7, 115.8, 116.1, 117.7, 118.2, 123.1, 125.1 (d, J=14.8 Hz), 126.1, 129.1, 129.5 (d, J=7.9 Hz), 131.1 (d, J=3.9 Hz), 138.6, 143.5, 150.4, 161.4 (d, J=268.8 Hz); mass (ES+) m/z=307.4 (M^++1); DART-HRMS calcd for $C_{18}H_{16}FN_4$: 307.1359, found: 307.1365.

4.8.7. 3-(2-Chlorobenzyl)-6H-pyrimido[2,1-b]quinazolin-2-ylamine (**11g**)

Yield: 81% as a white solid (0.31 g from 0.35 g); mp 245–248 °C; R_f=0.27 (EtOAc/MeOH, 3:1); ν_{max} (KBr): 1661 (C=N), 3396 (NH_2) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ=3.80 (s, 2H, CH_2), 5.07 (s, 2H, CH_2), 6.91–7.06 (m, 3H, ArH), 7.17–7.20 (m, 2H, ArH), 7.25–7.35 (m, 3H, ArH and =CH), 7.49–7.52 (m, 1H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ=31.0, 51.1, 109.7, 117.6, 117.9, 123.2, 126.1, 128.0, 129.1, 129.3, 130.1, 131.1, 134.1, 135.5, 138.2, 143.3, 150.3, 163.2; mass (ES+) m/z=323.4 (M^++1). Anal. Calcd for $C_{18}H_{15}ClN_4$ (exact mass: 322.0985): C, 66.98; H, 4.68; N, 17.36. Found: C, 66.83; H, 4.96; N, 17.15.

4.8.8. 3-(2,4-Dichlorobenzyl)-6H-pyrimido[2,1-b]quinazolin-2-amine (**11h**)

Yield: 76% as a white solid (0.41 g from 0.50 g); mp 220–223 °C; R_f=0.39 (EtOAc/MeOH, 4:1); ν_{max} (KBr): 1670 (C=N), 3359 (NH_2) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ=3.87 (s, 2H, CH_2), 5.16 (s, 2H, CH_2), 7.00–7.14 (m, 3H, ArH), 7.24–7.29 (m, 2H, ArH and =CH), 7.39 (d, 1H, J=8.3 Hz, ArH), 7.52 (dd, 1H, J_1=1.8 Hz, J_2=8.3 Hz, ArH), 7.76 (d, 1H, J=1.9 Hz, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ=30.6, 51.1, 109.3, 117.6, 118.0, 123.2, 126.0, 128.1, 129.1, 129.5, 132.4, 132.8, 134.7, 135.1, 143.4, 150.3, 163.1; mass (ES+) m/z=357.4 (M^++1); DART-HRMS calcd for $C_{18}H_{15}Cl_2N_4$: 357.0674, found: 357.0652.

4.8.9. 3-(2,6-Dichlorobenzyl)-6H-pyrimido[2,1-b]quinazolin-2-ylamine (**11i**)

Yield: 73% as a white solid (0.35 g from 0.45 g); mp >250 °C; R_f=0.42 (EtOAc/MeOH, 4:1); ν_{max} (KBr): 1668 (C=N), 3404 (NH_2) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ=3.93 (s, 2H, CH_2), 5.09 (s, 2H, CH_2), 6.72 (s, 1H, ArH), 6.97–7.06 (m, 3H, ArH), 7.20–7.25 (m, 1H, ArH), 7.43–7.48 (m, 1H, ArH), 7.58 (s, 1H, =CH), 7.61 (s, 1H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ=29.4, 50.9, 109.8, 116.4, 117.1, 123.9, 126.1, 129.1, 129.4, 130.8, 132.0, 135.6, 135.8, 140.4, 149.8, 163.0; mass (ES+) m/z=357.4 (M^++1); DART-HRMS calcd for $C_{18}H_{15}Cl_2N_4$: 357.0674, found: 357.0665.

4.8.10. 3-(3,4-Dimethoxybenzyl)-6H-pyrimido[2,1-b]quinazolin-2-ylamine (**11j**)

Yield: 64% as a white solid (0.41 g from 0.60 g); mp >250 °C; R_f=0.20 (EtOAc/MeOH, 3:1); ν_{max} (KBr): 1664 (C=N), 3408 (NH_2) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ=3.72–3.73(m, 8H, CH_2 and 2×OCH_3), 5.00 (s, 2H, CH_2), 6.81–6.97 (m, 6H, ArH), 7.07 (d, 1H, J=6.0 Hz, ArH), 7.18 (s, 1H, =CH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ=32.3, 51.2, 56.0, 108.9, 112.4, 113.3, 118.9, 120.9, 121.1, 121.4, 125.3, 128.4, 131.2, 142.8, 144.8, 147.9, 149.2, 151.3, 162.5; mass (ES+) m/z=349.3 (M^++1); HR-EIMS calcd for $C_{20}H_{20}N_4O_2$: 348.1586, found: 348.1589.

4.8.11. 3-(2-Thienylmethyl)-6H-pyrimido[2,1-b]quinazolin-2-ylamine (**11k**)

Yield: 75% as a white solid (0.33 g from 0.40 g); mp 190–191 °C (dec); R_f=0.28 (EtOAc/MeOH, 3:1); ν_{max} (KBr): 1668 (C=N), 3443 (NH_2) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ=3.93 (s, 2H, CH_2), 5.06 (s, 2H, CH_2), 6.86–6.91 (m, 2H, ArH), 6.95–7.04 (m, 3H, ArH), 7.13 (t, 1H, J=7.1 Hz, ArH), 7.37 (dd, 1H, J_1=1.4 Hz, J_2=4.6 Hz, ArH), 7.45 (s, 1H, =CH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ=27.1, 51.0, 111.5, 117.3, 117.5, 123.3, 125.3, 126.1, 126.6, 127.5, 129.0, 140.9, 143.4, 150.0, 162.8; mass (ES+) m/z=295.3 (M^++1); DART-HRMS calcd for $C_{16}H_{15}N_4S$: 295.1017, found: 295.0999.

4.8.12. 3-(4-Methylbenzyl)-1,6-dihydro-2H-pyrimido-[2,1-b]quinazolin-2-one (**14d**)

The residue afforded after the workup of the organic layer was crystallized using EtOAc/MeOH mixture to furnish the analytically pure product. Yield: 69% as a white solid (0.27 g from 0.40 g); mp >250 °C; R_f=0.81 (EtOAc/MeOH, 4:1); ν_{max} (KBr): 1616 (C=N), 1671 (NHCO), 3447 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ=2.25 (s, 3H, CH_3), 3.50 (s, 2H, CH_2), 4.99 (s, 2H, CH_2), 6.98 (d, 2H, J=6.9 Hz, ArH), 7.07 (d, 2H, J=7.7 Hz, ArH), 7.13–7.22 (m, 5H, ArH and =CH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ=25.7, 33.1, 49.8, 115.0, 116.8, 121.1, 122.7, 126.3, 129.0, 129.1, 129.2, 135.3, 135.9, 137.2, 138.9, 150.2, 169.8; mass (ES+) m/z=304.3 (M^++1). Anal. Calcd for $C_{19}H_{17}N_3O$ (exact mass: 303.1372): C, 75.23; H, 5.65; N, 13.85. Found: C, 75.43; H, 5.92; N, 13.63.

4.8.13. 3-(2,4-Dichlorobenzyl)-1,6-dihydro-2H-pyrimido-[2,1-b]quinazolin-2-one (**14h**)

The residue afforded after the workup of the organic layer was crystallized using EtOAc/MeOH mixture to furnish the analytically pure product. Yield: 75% as a white solid (0.37 g from 0.50 g); mp >250 °C; R_f=0.84 (EtOAc/MeOH, 4:1); ν_{max} (KBr): 1628 (C=N), 1703 (NHCO), 3306 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ=3.63 (s, 2H, CH_2), 5.01 (s, 2H, CH_2), 6.96–7.01 (m, 2H, ArH), 7.13–7.25 (m, 3H, ArH), 7.35 (s, 2H, ArH), 7.59 (s, 1H, =CH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ=31.3, 50.3, 114.1, 115.4, 117.3, 118.9, 123.3, 126.7, 128.0, 129.4, 132.5, 133.1, 136.1, 136.8, 140.0, 150.9, 175.3; mass (ES+) m/z=358.2 (M^++1). HR-EIMS calcd for $C_{18}H_{13}Cl_2N_3O$: 357.0436, found: 357.0407.

4.8.14. 3-Benzyl-8-chloro-6H-pyrimido[2,1-b]quinazolin-2-ylamine (**21**)

Yield: 67% as a white solid (0.41 g from 0.56 g); R_f=0.25 (EtOAc/MeOH, 3:1); mp >250 °C; ν_{max} (KBr): 1664 (C=N), 3407 (NH_2) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ=3.83 (s, 2H, CH_2), 5.24 (s, 2H, CH_2), 7.15 (d, 1H, J=9.2 Hz, ArH), 7.32–7.36 (m, 5H, ArH), 7.76 (s, 1H, =CH), 8.17 (s, 1H, ArH), 8.64 (s, 1H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ=32.3, 50.7, 103.9, 113.4, 117.4, 118.9, 126.5, 127.3, 127.8, 129.1, 129.3, 133.6, 137.8, 143.8, 149.3, 163.4; mass (ES+) m/z=323.4 (M^++1). HR-EIMS calcd for $C_{18}H_{15}ClN_4$: 322.0985, found: 322.0964.

4.9. General procedure for preparation of 24 and 25 as exemplified for 24

To a stirred solution of compound **16** (0.80 g, 2.27 mmol) in THF (10 mL) was added CNBr (0.24 g, 2.27 mmol) and the reaction was allowed to continue for 30 min at room temperature. Thereafter water (10 mL) and In powder (0.78 g, 6.84 mmol) were added to the flask followed by dropwise addition of concd HCl (1.6 mL). Reaction was further continued for 1.5 h after which it was concentrated, taken in EtOAc (50 mL), and neutralized with saturated aqueous $NaHCO_3$. The reaction mass was filtered through a Celite bed with EtOAc. The filtrate was washed with brine and the usual workup of the separated organic layer yielded a residue that was purified through silica gel column chromatography (EtOAc/MeOH, 6:1) to furnish 0.47 g (59%) of **24** as a white solid.

4.9.1. (Z)-2-{[2-Amino-6,7-dimethoxyquinazolin-3(4H)-yl]methyl}-3-phenylprop-2-enenitrile (**24**)

Mp 210–212 °C; R_f=0.45 (EtOAc/MeOH, 9:1); ν_{max} (KBr): 1655 (C=N), 2206 (CN), 3314 (NH_2) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ=3.71 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 4.57 (s, 2H, CH_2), 4.58 (s, 2H, CH_2), 6.67 (s, 1H, ArH), 6.84 (s, 1H, ArH), 7.52–7.55 (m, 3H, ArH), 7.62 (s, 1H, =CH), 7.79–7.82 (m, 2H, ArH), 8.02 (br s, 2H, NH_2); ^{13}C

NMR (DMSO-d_6, 75 MHz) δ=47.6, 51.5, 55.9, 56.1, 99.8, 104.4, 108.9, 109.7, 117.2, 125.8, 128.9, 129.1, 131.1, 132.8, 145.7, 147.1, 148.9, 151.9; mass (ES+) m/z=349.2 (M^++1). Anal. Calcd for $C_{20}H_{20}N_4O_2$ (exact mass: 348.1586): C, 68.95; H, 5.79; N, 16.08. Found: C, 68.82; H, 5.98; N, 15.83.

*4.9.2. (Z)-2-{[6-Amino[1,3]dioxolo[4,5-g]quinazolin-7(8H)-yl]methyl}-3-phenylprop-2-enenitrile (**25**)*

Yield: 27% as a white solid (0.08 g from 0.30 g); mp 220 °C (dec); R_f=0.42 (EtOAc/MeOH, 9:1); ν_{max} (KBr): 2215 (CN), 3409 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ=4.52 (s, 2H, CH_2), 4.64 (s, 2H, CH_2), 6.01 (s, 2H, OCH_2O), 6.63 (s, 1H, ArH), 6.82 (s, 1H, ArH), 7.50–7.53 (m, 3H, ArH), 7.66 (s, 1H, =CH), 7.78–7.80 (m, 2H, ArH), 8.38 (br s, 2H, NH_2); ^{13}C NMR (DMSO-d_6, 75 MHz) δ=48.1, 51.8, 97.3, 102.0, 104.9, 106.4, 110.7, 127.5, 129.3, 129.5, 131.4, 133.2, 144.3, 147.1, 147.7, 152.6; mass (ES+) m/z=333.2 (M^++1). Anal. Calcd for $C_{19}H_{16}N_4O_2$ (exact mass: 332.1273): C, 68.66; H, 4.85; N, 16.86. Found: C, 68.95; H, 4.99; N, 16.74.

Acknowledgements

Two of the authors (S.N. and A.M.) gratefully acknowledge the financial support from UGC and CSIR, New Delhi in the form of fellowship. This work was supported by a grant (SR/S1/OC-16/2006) from DST, New Delhi.

Supplementary data

^1H NMR and ^{13}C NMR spectra of several new compounds have been included. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.08.044.

References and notes

1. Only a few references: (a) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689–1708; (b) Cheikh, R.; Chaabouni, R.; Laurent, A.; Mison, P.; Nafti, A. *Synthesis* **1983**, 685–700; (c) Weston, M. H.; Nakajima, K.; Back, T. G. *J. Org. Chem.* **2008**, *73*, 4630–4637; (d) Chen, G.; Sasaki, M.; Yudin, A. K. *Tetrahedron Lett.* **2006**, *47*, 255–259; Groaz, E.; Banti, D.; North, M. *Tetrahedron Lett.* **2007**, *48*, 1927–1930; (e) Bennasar, M. L.; Zulaica, E.; Sole, D.; Alonso, S. *Tetrahedron* **2007**, *63*, 861–866; (f) Fukimoto, Y.; Kinashi, F.; Kawahara, T.; Chatani, N. *Org. Lett.* **2006**, *8*, 4641–4643; (g) Fernandez, I.; Munoz, L. *Tetrahedron: Asymmetry* **2006**, *17*, 2548–2557; (h) Gomez-Montano, G.; Gonzalez-Zamora, E.; Potier, P.; Zhu, J. *Tetrahedron* **2002**, *58*, 6351–6358; (i) Gamez-Montano, G.; Gonzalez-Nishi, T.; Moreisawa, Y. *Heterocycles* **1989**, *29*, 1835–1842.
2. (a) Singh, V.; Batra, S. *Tetrahedron* **2008**, *64*, 4511–4574 and references cited therein; (b) Krishna, P. R.; Reddy, P. S. *J. Comb. Chem.* **2008**, *10*, 426–435; (c) Akritopoulou-Zanze, I.; Whitehead, A.; Waters, J. E.; Henry, R. F.; Djuric, S. W. *Org. Lett.* **2007**, *9*, 1299–1302; (d) Chandrasekhar, B.; Madhan, A.; Venkateswara Rao, B. *Tetrahedron* **2007**, *63*, 8746–8751; (e) Panayides, J.-L.; Panagiotopoulos, H.; Davids, H.; Fernandes, M. A.; de Koning, C. B.; van Otterlo, W. A. L. *Tetrahedron* **2007**, *63*, 4737–4747; (f) Gracias, V.; Gasiecki, A. F.; Djuric, S. W. *Org. Lett.* **2005**, *7*, 3183–3186; (g) Xiang, Z.; Luo, T.; Lu, K.; Cui, J.; Shi, X.; Fathi, R.; Chen, J.; Yang, Z. *Org. Lett.* **2004**, *6*, 3155–3158.
3. Pathak, R.; Batra, S. *Tetrahedron* **2007**, *63*, 9448–9455.
4. Nag, S.; Madapa, S.; Batra, S. *Synthesis* **2008**, 101–109.
5. Pathak, R.; Singh, V.; Nag, S.; Kanojiya, S.; Batra, S. *Synthesis* **2006**, 813–816.
6. (a) Varano, F.; Catarzi, D.; Colotta, V.; Lenzi, O.; Filacchioni, G.; Gallib, A.; Costaglib, C. *Bioorg. Med. Chem.* **2008**, *16*, 2617–2626; (b) Varano, F.; Catarzi, D.; Colotta, V.; Calabri, F. R.; Lenzi, O.; Filacchioni, G.; Galli, A.; Costagli, C.; Deflorianc, F.; Moroc, S. *Bioorg. Med. Chem.* **2005**, *13*, 5536–5549; (c) Jantova, S.; Stankovsky, S.; Spirkova, K. *Biol. Brat.* **2004**, *59*, 741–752; (d) Ibrahim, S. S.; Abdel-Halim, A. M.; Gabr, Y.; El-Edfawy, S.; Abdel-Rahman, R. M. *J. Chem. Res., Synop.* **1997**, 154–155; *J. Chem. Res., Miniprint* **1997**, 1041–1063.
7. (a) Yamamoto, M.; Marooka, S.; Koshiba, M.; Inaba, S.; Yamamoto, K. U.S. Patent 4,179,560, 1979 (CA: 91:P211436p); (b) Yamamoto, M.; Koshiba, M.; Aono, S. Japanese Patent 78141296, 1979 (CA: 90:P168640r).
8. (a) Pearson, S. E.; Wood, R. *Tetrahedron Lett.* **2002**, *43*, 1303–1306; (b) Kosasayama, A.; Higashi, K.; Ishikawa, F. *Chem. Pharm. Bull.* **1979**, *27*, 880–892; (c) Grover, R. K.; Kesarwani, A. P.; Srivastava, G. K.; Kundu, B.; Roy, R. *Tetrahedron* **2005**, *61*, 5011–5018.
9. Mills, A. D.; Nazer, M. Z.; Haddadin, M. J.; Kurth, M. J. *J. Org. Chem.* **2006**, *71*, 2687–2689.
10. Nag, S.; Mishra, A.; Batra, S. *Eur. J. Org. Chem.* **2008**, 4334–4343.