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Copper-catalysed heteroannulation with alkynes: a general and highly regio- and stereoselective method for the synthesis of (*E*)-2-(2-arylvinyl) quinazolinones

Nitya G. Kundu* and Gopeswar Chaudhuri

Department of Organic Chemistry, Indian Association for Cultivation of Science, Jadavpur, Calcutta 700 032, India

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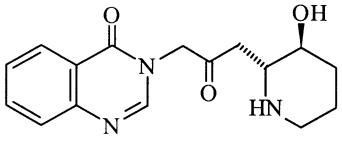
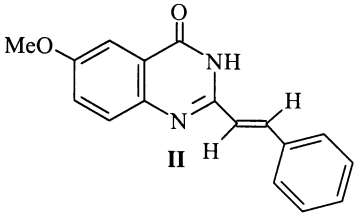
Abstract—A highly regio- and stereoselective procedure for the synthesis of 2-substituted-1,2,3,4-tetrahydroquinazolinones through a two-step procedure, e.g. (i) palladium–copper catalysed *C*-arylation of terminal alkynes and (ii) copper-catalysed cyclisation of disubstituted alkynes, is described. 2-(*N*-Alkyl-*N*-prop-2′-ynyl)amino-*N*′- *p*-tolyl benzamides **5a** and **5b** reacted with aryl iodides **2** in the presence of $(Ph_3P)_2PdCl_2$ (2.5 mol%), CuI (5 mol%), Et_3N (5 equiv.) in CH_3CN at rt for 16 h to yield the disubstituted alkynes **6**–**18** which could then be cyclised with CuI (20 mol%), K_2CO_3 (2.5 equiv.), Bu_4NBr (1 equiv.) in CH_3CN at 80°C for 16–24 h to yield 1-methyl (benzyl)-(*E*)-2-(2-arylvinyl)-3-*p*-tolyl-1,2,3,4-tetrahydroquinazolin-4-ones **19**–**31** in good yields. Only in a few cases, the benzodiazepinones **32**–**34** could be obtained in poor yield. The synthesis of novel uracil derivatives **35** and **36** is also described.

1. Introduction

The quinazoline[1] structure has been the integral part of many naturally occurring and biologically active compounds. For example, febrifugine (**I**) and isofebriguine were isolated as the active principles[2–4] of the roots of *Dichroa febrifuga* Lour (Chinese name: Chang Shan) which have been used effectively against malaria fever in China for centuries. Recently a new type of febrifugine derivative has been reported[5] which showed high activity against *P. falciparum* malaria in vitro and was equally effective against *P. berghei* in vivo as the clinically used drug chloroquine. Similarly, quinazoline containing structures have been known as tyrosine kinase inhibitors,[6] dihydrofolate reductase (DHFR) inhibitors,[7] tubulin polymerisation inhibitors[8] (**II**) and tumour necrosis factors.[9] Thus, many quinazoline containing molecules have been developed as anticonvulsants,[10] antihypertensives,[11] antidiabetics,[12] and as antitumour,[13] antimicrobial[14] and antibacterial[15] agents. In view of the importance of quinazolines and their derivatives, many classical methods for the synthesis of quinazolines and quinazolinones have been reported in the literature.[1,16]



Febrifugine **I**



II

Palladium-catalysed reactions[17] have been of immense significance in both carboannulation[18] and heteroannulation[19] processes. We have utilised palladium–copper catalysed reactions[20] of terminal alkynes for the synthesis of various benzofused heterocyclic compounds.[21] Recently, we have described[22] a highly regio- and stereoselective procedure for the synthesis of (*Z*)-3-arylidene-2,3-dihydro-5*H*-1,4-benzodioxepin-5-ones **4a** and (*Z*)-3-arylidene-2,3-dihydro-5*H*-4,1-benzoxazepin-5-ones **4b** through palladium–copper catalysed reactions of **1a** and **1b** with aryl iodides **2**, where in the final step, a copper-catalysed *exo*-dig attack by a carboxylate ion on the disubstituted alkynes **3a** and **3b** took place (Scheme 1).

In this article we describe a general palladium and copper catalysed procedure for the synthesis of

Keywords: quinazolinones; disubstituted alkynes; palladium–copper catalysis; copper-catalysed heteroannulation; terminal alkynes.

* Corresponding author. Tel.: +91-33-473-4971; fax: +91-33-473-2805; e-mail: ocbn@mahendra.iacs.res.in

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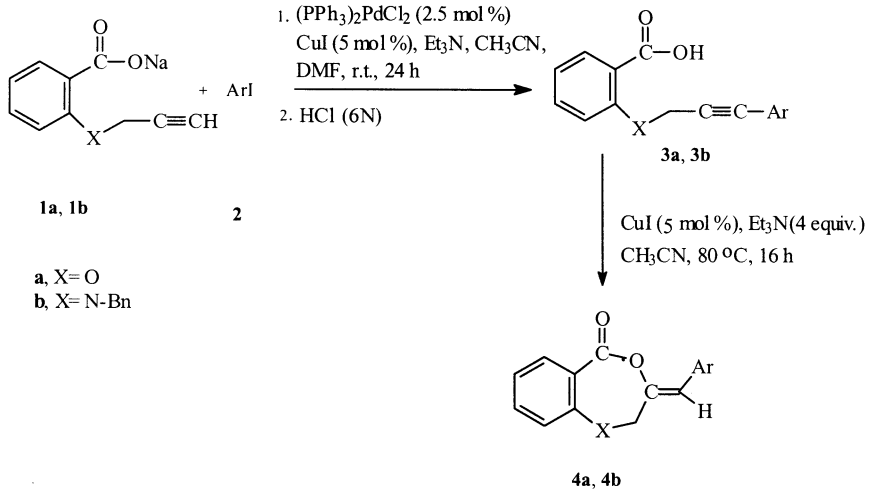


Scheme 1.

2-substituted-1,2,3,4-tetrahydroquinazolin-4-ones[23] where in contrast to the expected benzodiazepinone derivatives, the tetrahydroquinazolin-4-ones were formed predominently.

2. Results and discussion

2.1. Synthesis of disubstituted alkynes

2-(*N*-Methyl-*N*-prop-2′-ynyl)amino-*N*′-*p*-tolylbenzamide **5a** or, 2-(*N*-benzyl-*N*-prop-2′-ynyl)amino-*N*′-*p*-tolylbenzamide **5b** reacted with the aryl iodides **2** in the presence of bis(triphenylphosphine)palladium(II) chloride (2.5 mol%), cuprous iodide (5 mol%), triethylamine (5 equiv.) in acetonitrile at rt for 16 h to yield the disubstituted alkynes (**6**–**18**) in good yields. Both the palladium-catalyst and the cuprous iodide as co-catalyst were found to be essential for the *C*-arylation of the terminal alkynes. Also, triethylamine was found to be the base of choice. However, triethylamine alone could not act as the solvent since the benzamides **5a** and **5b** were found to be sparingly soluble in triethylamine. The use of CH_3CN as solvent facilitated the formation of the disubstituted alkynes. It is to be noticed that in the reaction of the benzamides **5a** or **5b** with the aryl iodides **2**, the disubstituted alkynes were the sole products. In contrast to the formation of the 1,4-benzodioxans[21g,h] under palladium–copper catalysed reaction where C-arylation and cyclisation took place in one step, in this case no cyclic products were formed in one-step under palladium–copper catalysed conditions.

2.2. Synthesis of the quinazolinones

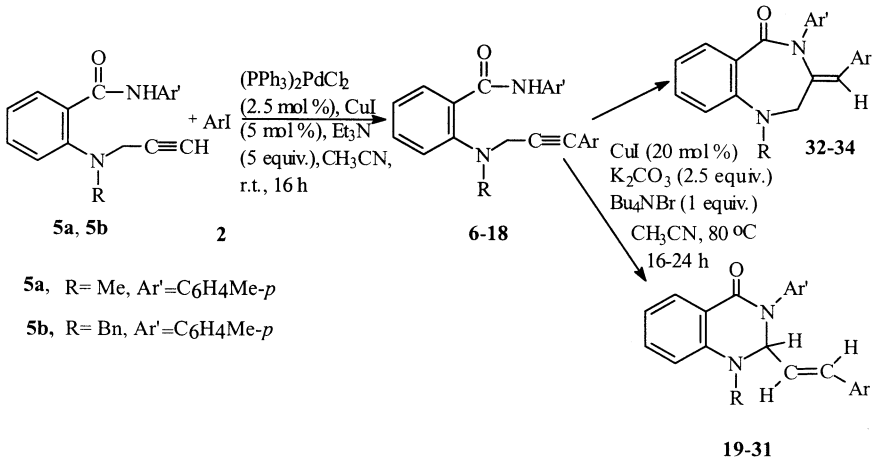
The disubstituted alkynes **6**–**18** could, however, be cyclised with cuprous iodide (20 mol%) in the presence of potassium carbonate (2.5 equiv.) and tetrabutyl ammonium bromide (1 equiv.) by heating in acetonitrile at 80°C for 16–24 h. In most cases (Table 1, entries 1–8, 11 and 13), the (*E*)-2-(arylvinyl)quinazolines **19**–**26**, **29** and **31** were formed in a highly regio- and stereoselective manner. Only in a few cases (entries 9, 10 and 12) were small amounts (7–10%) of the benzodiazepinones **32**–**34** formed (Scheme 2).

The cuprous iodide was found to be the most effective catalyst for the cyclisation process. The use of the

Table 1. Palladium–copper catalysed reactions of 2-(*N*-alkyl-*N*-prop-2′-ynyl) amino-*N*′-*p*-tolyl benzamides (**5a**, **5b**) with aryl iodides (**2**) leading to disubstituted alkynes (**6**–**18**) and their subsequent cyclisation to quinazolin-4-ones (**19**–**31**)

Entry	N–R	Aryl iodides (Ar)	Disubstituted alkynes (%)[a]	Quinazolinones (%)[b]	Benzodiazepinones (%)[b]
1	**5a** (Me)	**2a** (Ph)	**6** (84)	**19** (60)	
2	**5a** (Me)	**2b** (C_6H_4Me-*o*)	**7** (76)	**20** (67)	
3	**5a** (Me)	**2c** (C_6H_4OMe-*o*)	**8** (70)	**21** (35)	
4	**5a** (Me)	**2d** (C_6H_4OMe-*p*)	**9** (67)	**22** (31)	
5	**5a** (Me)	**2e** ($C_6H_4CO_2Me$-*o*)	**10** (90)	**23** (69)	
6	**5a** (Me)	**2f** (2-Thienyl)	**11** (75)	**24** (61)	
7	**5a** (Me)	**2g** (2,4-Dimethoxy-pyrimidin-5-yl	**12** (79)	**25** (65)	
8	**5b** (Bn)	**2b** (C_6H_4Me-*o*)	**13** (72)	**26** (63)	
9	**5b** (Bn)	**2h** (C_6H_4Me-*p*)	**14** (65)	**27** (59)	**32** (8)
10	**5b** (Bn)	**2I** (C_6H_4Cl-*m*)	**15** (67)	**28** (60)	**33** (7)
11	**5b** (Bn)	**2e** ($C_6H_4CO_2Me$-*o*)	**16** (89)	**29** (61)	
12	**5b** (Bn)	**2f** (2-Thienyl)	**17** (73)	**30** (67)	**34** (10)
13	**5b** (Bn)	**2g** (2,4-Dimethoxy-pyrimidin-5-yl)	**18** (91)	**31** (62)	

[a] Yields are based on aryl iodides.
[b] Yields are based on the corresponding disubstituted alkynes.



Scheme 2.

phase-transfer catalyst, e.g. *n*-Bu_4NBr, in the cyclisation reaction improved the yield of the quinazolinones considerably. When $Pd(OAc)_2$ was used instead of CuI, a mixture of (*E*) and (*Z*) isomers of the quinazolinones was obtained. Potassium carbonate was found to be essential for the cyclisation process. The use of triethylamine alone did not lead to any cyclisation. When NaOEt in ethanol or NaH in THF was used as the cyclising agent, a mixture of (*E*)- and (*Z*)-isomers of the quinazolinones were obtained. Again in the cyclisation process, the use of CH_3CN as a solvent led to cleaner cyclic products. The use of DMF as a solvent led to poorer yields due to formation of much coloured materials.

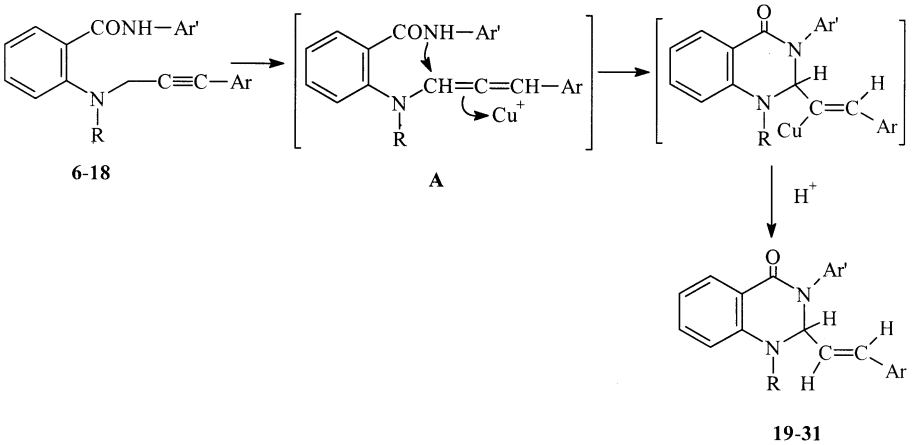
2.3. Characterisation of products

The quinazolinones **19–31** gave satisfactory analytical, IR, ^1H and ^{13}C NMR data. The absence of the –NH– peak in IR and ^1H NMR indicated the formation of the cyclic products. The identification of the cyclic products as the quinazolinones **19–31** follows from (i) the absence of a ring methylene peak for compounds **19–31** both in ^1H and ^{13}C NMR data, (ii) the presence of N_2CH as a doublet at δ 5.04–5.18 (J=6.9–8.4 Hz), (iii) the presence of =C*H*Ar as a doublet at δ 6.23–6.83 (J=15.0–15.9 Hz) and (iv) the presence of –C*H*=CAr as a double doublet at δ 6.15–6.45 (J_1=15.6–15.9 Hz and J_2=7.5–8.4 Hz). The *E*-stereochemistry around the double bond follows from the coupling constant values of 15.6–15.9 Hz for the vinylic protons.

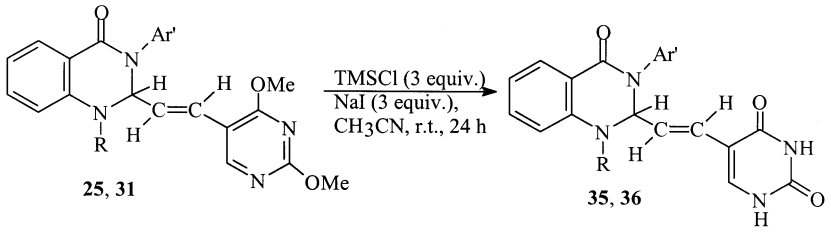
The structures of the benzodiazepinones **32–34** were established on the basis of their ^1H NMR, ^{13}C NMR and ^{13}C DEPT-135 experiments. In ^1H NMR, the presence of a vinylic proton (exocyclic=C*H*) was seen as a singlet at δ 6.23–6.62. Also, two $-CH_2$ groups were seen as two distinct singlets at δ 4.33–4.37 and 3.86–3.94, respectively. This was confirmed by ^{13}C DEPT-135 experiments where two inverted peaks were observed at δ 55.9–56.07 and 63.10–64.17 respectively. The *Z*-stereochemistry of the benzodiazepinones follows from $^3J_{CH}$ experiments—the $^3J_{CH}$ values of 3.75 and 4.25 Hz were observed for compounds **32** and **34**, respectively.[24]

2.4. Mechanism

Mechanistically, the formation of the disubstituted alkynes **6–18** is easily explained by the Sonogashira–Tohda–Hagihara coupling[20a] which involved (i) the generation of Pd^0 from $(Ph_3P)_2PdCl_2$, (ii) formation of ArPdX from ArX and Pd^0, (iii) transmetallation of the ArPdX with Cu-salt of the acetylenic compounds **5a** and **5b** and (iv) reductive elimination of Pd^0 leading to the disubstituted alkynes.[25]



Scheme 3.



25, **31**

35, **36**

25, R = Me, Ar' = C_6H_4Me-*p*
31, R = Bn, Ar' = C_6H_4Me-*p*

35, R = Me, Ar' = C_6H_4Me-*p*
36, R = Bn, Ar' = C_6H_4Me-*p*

Scheme 4.

In the normal cyclisation of the disubstituted alkynes, a nucleophilic attack by the amide nitrogen on the triple bond led to the benzodiazepinones **32**–**34**. However, in most of the cases, a rearrangement of **6**–**18** to the allenic intermediates A took place involving alkyne–allene rearrangement[26] in the propargyl group attached to the nitrogen atom. A subsequent nucleophilic attack by the amide nitrogen on the terminal carbon (next to the N-atom) of the allenes would result in the quinazolinones **19**–**31** (Scheme 3).

2.5. Scope

Many 2-arylvinylquinazolines have shown interesting biological properties.

Our method is amply suitable for the synthesis of such compounds. Also, the compounds **19**–**31** which are structurally similar to the existing biologically active compound **II** could demonstrate interesting biological and pharmacological properties. Of particular interest are the pyrimidine derivatives, e.g. 1-methyl-(*E*)-2-[2-(2,4-dimethoxypyrimidin-5-yl)vinyl]-3-*p*-tolyl-1,2,3,4-tetrahydroquinazolin-4-one **25** and 1-benzyl-(*E*)-2-[2-(2,4-dimethoxypyrimidin-5-yl)vinyl]-3-*p*-tolyl-1,2,3,4-tetrahydroquinazolin-4-one **31** which could be demethylated with TMSCl and NaI in CH_3CN to 1-methyl-(*E*)-2-[2-(uracil-5-yl)vinyl]-3-*p*-tolyl-1,2,3,4-tetrahydroquinazolin-4-one **35** and 1-benzyl-(*E*)-2-[2-(uracil-5-yl)vinyl]-3-*p*-tolyl-1,2,3,4-tetrahydroquinazolin-4-one **36**, respectively, novel 5-substituted uracil derivatives (Scheme 4).

Since 5-substituted uracils have shown exceedingly interesting antiviral and anticancer activities,[27] compounds **35** and **36** are of great biological curiosity.

3. Conclusion

In this paper, we have described a highly general and facile method for the synthesis of 2-substituted quinazolin-4-ones. The method involves (i) an efficient palladium–copper catalysed procedure for the synthesis of disubstituted alkynes and (ii) a highly regio- and stereoselective copper-catalysed cyclisation of the alkynes to 1,2,3,4-tetrahydroquinazolin-4-ones. The process is characterised by the easy availability of inexpensive starting materials, relatively mild reaction conditions and work-up procedures and fairly good yields of the products. We believe this is the first reported palladium–copper catalysed general procedure for the synthesis of 2-substituted quinazolinones. Also, interestingly, many quinazolines of biological importance are accessible by our synthetic procedure.

4. Experimental

4.1. General

Melting points were determined on a Reichert (285980) (Austria) melting point apparatus and are uncorrected. IR Spectra were taken on a FTIR-8300, SHIMADZU instrument. ^{1}H NMR spectra were recorded on a Varian EM-360 and a Bruker DPX-300 spectrometer for samples as indicated with tetramethylsilane as internal references. ^{13}C NMR spectra (75 MHz) were obtained on a Bruker DPX-300 spectrometer. Chemical shifts are reported in δ unit (parts per milion); *J* values given in Hz; splitting patterns are designated as follows: s, singlet; d, doublet, t, triplet, q, quartet, dd, double doublet, m, multiplet, br, broad. Analytical thin-layer chromatography (TLC) was performed on precoated 0.2 mm silica gel 60F-254 (E. Merck) and the spots were visualised with UV light. Column chromatography was done on silica gel (60–120 mesh) or neutral alumina. Elemental analyses (C,H,N) were carried out on Perkin–Elmer 240C Analyser. Propargyl alcohol, phosphorus tribromide and tetrabutyl ammonium bromide were commercially available.

Bis(triphenylphosphine)palladium(II)chloride, $Pd(OAc)_2$ and copper iodide were purchased from Aldrich Chemical Co., Milwaukee, Wisconsin, U.S.A.

The aryl iodides (**2b**–**e**, **2h**, **2i**) were prepared according to the procedures given for the synthesis of iodobenzene[28] (**2a**). 2-Iodothiophene[29] (**2f**) and 5-iodo-2,4-dimethoxypyrimidine[30] (**2g**) were synthesised according to known procedures.

4.1.1. Synthesis of 2-(*N*-methyl-*N*-prop-2′-ynyl)aminobenzoic acid. A mixture of methyl anthranilate (5 g, 33.07 mmol) and anhydrous potassium carbonate (4.56 g, 33.07 mmol) in dry DMF (20 mL) was stirred for 8 h at rt under a N_2 atmosphere. Propargyl bromide (4.72 g, 39.68 mmol) in dry DMF (10 mL) was then added slowly over 30 min. The whole mixture was heated at 80°C for 48 h with constant stirring under a N_2 atmosphere. DMF was removed from the reaction mixture under reduced pressure

and the residue was extracted with chloroform (3×50 mL) and distilled water (50 mL). The chloroform extract was washed with water (2×50 mL) and dried over anhydrous sodium sulfate. After removal of solvent, the residue was purified by column chromatography on silica gel using 1:1 chloroform–light petroleum ether (bp 60–80°C) as eluent to yield methyl 2-(*N*-prop-2′-ynyl)aminobenzoate, yield 4.43 g, (71%); mp 63–65°C; IR: ν_{max} (KBr) 3369, 3284, 1686 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 2.03 (t, J=2.0 Hz, 1H, C≡CH), 3.66 (s, 3H, $-CO_2Me$), 3.79–3.95 (dd, J=4.0 Hz, 2H, $-NCH_2$), 6.36–6.69 (m, 3H, ArH, NH), 7.09–7.42 (m, 1H, ArH), 7.66–7.89 (m, 1H, ArH). Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.4. Found: C, 69.69; H, 5.68; N, 7.29.

A mixture of methyl 2-(*N*-prop-2′-ynyl)aminobenzoate (4 g, 21.14 mmol) and anhydrous potassium carbonate (2.92 g, 21.14 mmol) in dry DMF (15 mL) was stirred for 8 h at rt under N_2 atmosphere. Methyl iodide (9 g, 63.42 mmol) was then added slowly to it under ice-cold condition over 20 min. The whole reaction mixture was heated at 60°C for 24 h under a N_2 atmosphere. The residue obtained after removal of DMF under reduced pressure was extracted with chloroform (3×40 mL) and water (50 mL). The combined chloroform layers were washed with water (2×50 mL) and dried over anhydrous sodium sulfate. After the removal of the solvent, the residue was purified by column chromatography over silica gel using 3:1 chloroform–petroleum ether as eluent. Methyl 2-(*N*-methyl-*N*-prop-2′-ynyl)aminobenzoate was obtained as a colourless oil, yield 3.1 g (72%). IR: ν_{max} (neat) 3280, 1720 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 2.13 (t, J=1.98 Hz, 1H, C≡CH), 2.82 (s, 3H, $-NCH_3$), 3.80 (s, 3H, $-CO_2Me$), 3.82 (d, J=2.0 Hz, 2H, $-NCH_2$), 6.66–7.33 (m, 3H, ArH), 7.50–7.70 (m, 1H, ArH). Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.44; N, 6.89. Found: C, 70.93; H, 6.50; N, 6.95.

Potassium hydroxide (1.40 g, 25.08 mmol) dissolved in water (7 mL) was added dropwise to a methanolic solution (20 mL) of methyl 2-(*N*-methyl-*N*-prop-2′-ynyl)aminobenzoate (2.55 g, 12.54 mmol) with constant stirring. This was stirred at rt for 24 h. The residue obtained after the removal of methanol was neutralised with dil. HCl and worked-up with chloroform (3×40 mL) and water (50 mL). The solid residue obtained after the removal of chloroform was crystallised from petroleum ether (bp 60–80°C)–chloroform. 2-(*N*-Methyl-*N*-prop-2′-ynyl)aminobenzoic acid was obtained as a white crystalline solid, yield 2.14 g (90%); mp 107°C; IR ν_{max} (KBr) 3295, 1690 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 2.20 (t, J=2.0 Hz, 1H, C≡CH), 2.85 (s, 3H, $-NCH_3$), 3.85 (d, J=2.0 Hz, 2H, $-NCH_2$), 6.68–7.35 (m, 3H, ArH), 7.51–7.72 (m, 1H, ArH), 10.18 (s, br, 1H, $-CO_2H$). Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.80; H, 5.79; N, 7.38.

4.1.2. Synthesis of 2-(*N*-methyl-*N*-prop-2′-ynyl)amino-*N*′-*p*-tolyl benzamide 5a. 2-(*N*-Methyl-*N*-prop-2′-ynyl)aminobenzoic acid (2 g, 10.6 mmol) was dissolved in benzene (20 mL) and thionyl chloride (5 mL) and pyridine (10 drops) added. The reaction mixture was heated with stirring at 55°C for 1.5 h. The residue, obtained after removal of solvent and excess $SOCl_2$, was dissolved in benzene (15 mL) and cooled in an ice-H_2O bath. To the ice-cold solution, *p*-toluidine (1.7 g, 15.9 mmol) in benzene (15 mL) was added and the reaction mixture was stirred at rt for 16 h under N_2-atmosphere. After usual work-up and purification on silica gel, using chloroform–light petroleum ether (3:1) as eluent, 2-(*N*-methyl-*N*-prop-2′-ynyl)amino-*N*′-*p*-tolylbenzamide was obtained as a colourless oil, yield 1.8 g (61%); IR: ν_{max} (neat) 3290, 3236, 2116, 1666, 1595 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 2.3 (s, 3H, Ar–CH_3), 2.33 (t, J=2.0 Hz, 1H, C≡CH), 3.0 (s, 3H, $-NCH_3$), 3.82 (d, J=2.0 Hz, 2H, $-NCH_2$), 6.92–7.66 (m, 7H, ArH), 8.13–8.33 (m, 1H, ArH), 11.80 (s, br, 1H, –CONH). Anal. Calcd for $C_{18}H_{18}N_2O$: C, 77.66; H, 6.51; N, 10.06. Found: C, 77.72; H, 6.54; N, 10.14.

4.1.3. Synthesis of 2-(*N*-benzyl-*N*-prop-2′-ynyl)amino-*N*′-*p*-tolyl benzamide 5b. 2-(*N*-Benzyl-*N*-prop-2′-ynyl)-amino-*N*′-*p*-tolyl benzamide **5b** was synthesised from 2-(*N*-benzyl-*N*-prop-2′-ynyl)aminobenzoic acid by following the procedure used for the synthesis of compound **5a**. Yield 65%; colourless crystalline solid; mp 125°C; IR: ν_{max} (KBr) 3294, 3230, 2106, 1666, 1595 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 2.31 (s, 3H, Ar–CH_3), 2.32 (t, J=2.0 Hz, 1H, ≡CH), 3.69 (d, J=2.0 Hz, 2H, $-NCH_2$), 4.36 (s, 2H, $-NCH_2Ph$), 6.89–7.56 (m, 12H, Ar–H), 8.19–8.46 (m, 1H, ArH), 11.5 (s, br, 1H, –CONH). Anal. Calcd for $C_{24}H_{22}N_2O$: C, 81.32; H, 6.25; N, 7.90. Found: C, 81.30; H, 6.09; N, 7.71.

4.2. General procedure for the synthesis of 6–18

A mixture of aromatic iodocompounds **2**, $(Ph_3P)_2PdCl_2$ (2.5 mol%), CuI (5 mol%), Et_3N (5 equiv.) was stirred in acetonitrile at rt for 30 min under an argon atmosphere. The acetylenic compound **5a** or **5b** (1 equiv.) dissolved in acetonitrile was added slowly to it and the reaction mixture was allowed to stir at rt for a further period of 16 h. The residue obtained after removal of CH_3CN was taken up in chloroform. The $CHCl_3$ layer was washed with water, dried over anhydrous sodium sulphate and was purified by column chromatography on silica gel (60–120 mesh) using chloroform–light petroleum (3:1) as eluent to yield the disubstituted alkynes (**6–18**) in excellent yields (65–91%).

4.2.1. 2-[*N*-Methyl-*N*-(3′-phenyl-prop-2′-ynyl)amino]-*N*′-*p*-tolyl benzamide 6. Colourless sticky oil; IR: ν_{max} (neat) 3163, 2223, 1667, 1600 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 2.26 (s, 3H, $ArCH_3$), 2.92 (s, 3H, NCH_3), 3.90 (s, 2H, $-NCH_2$), 6.82–7.66 (m, 12H, ArH), 8.06–8.33 (m, 1H, ArH), 11.66 (s, 1H, –CONH). Anal. Calcd for $C_{24}H_{22}N_2O$: C, 81.32; H, 6.25; N, 7.90. Found: C, 81.20; H, 6.16; N, 7.69.

4.2.2. 2-{*N*-Methyl-*N*-[3′-(*o*-methylphenyl)prop-2′-ynyl]-amino}-*N*′-*p*-tolyl benzamide 7. Colourless sticky oil; IR: ν_{max} (neat) 3165, 2233, 1668, 1595 cm^{-1}; ^1H NMR (60MHz, CCl_4) δ 2.33 (s, 6H, 2×Ar–CH_3), 3.00 (s, 3H, $-NCH_3$), 4.03 (s, 2H, $-NCH_2$), 6.89–7.69 (m, 11H, Ar–H), 8.13–8.33 (m, 1H, ArH), 11.62 (s, br, 1H, CONH). Anal. Calcd for $C_{25}H_{24}N_2O$: C, 81.48; H, 6.56; N, 7.60. Found: C, 81.27; H, 6.40; N, 7.42.

4.2.3. 2-{*N*-Methyl-*N*-[3′-(*o*-methoxyphenyl)prop-2′-ynyl]-amino}-*N*′-*p*-tolyl benzamide 8. Colourless sticky oil; IR:

ν_{max} (neat) 3168, 2230, 1665, 1600 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 2.23 (s, 3H, Ar–CH_3), 2.95 (s, 3H, –NCH_3), 3.76 (s, 3H, OCH_3), 3.96 (s, 2H, –NCH_2), 6.73–7.89 (m, 11H, ArH), 8.03–8.62 (m, 1H, ArH), 11.61 (s, br, 1H, CONH). Anal. Calcd for $C_{25}H_{24}N_2O_2$: C, 78.09; H, 6.29; N, 7.28. Found: C, 78.05; H, 6.13; N, 7.09.

4.2.4. 2-{*N*-Methyl-*N*-[3′-(*p*-methoxyphenyl)prop-2′-ynyl]-amino}-*N*′-*p*-tolyl benzamide 9. Colourless sticky oil; IR: ν_{max} 3170, 2228, 1665, 1600 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ (s, 3H, Ar–CH_3), 2.96 (s, 3H, –NCH_3), 3.76 (s, 3H, –OCH_3), 3.98 (s, 2H, –NCH_2), 6.78–7.88 (m, 11H, ArH), 8.31–8.65 (m, 1H, ArH), 11.61 (s, br, 1H, CONH). Anal. Calcd for $C_{25}H_{24}N_2O_2$: C, 78.09; H, 6.29; N, 7.28. Found: C, 77.86; H, 6.08; N, 7.05.

4.2.5. 2-{*N*-Methyl-*N*-[3′-(*o*-methoxycarbonylphenyl)-prop-2′-ynyl]amino}-*N*′-*p*-tolyl benzamide 10. Colourless sticky oil; IR: ν_{max} (neat) 3161, 2224, 1728, 1664, 1595 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 2.26 (s, 3H, Ar–CH_3), 3.09 (s, 3H, –NCH_3), 3.82 (s, 3H, –CO_2Me), 4.03 (s, 2H, –NCH_2), 6.80–7.62 (m, 10H, ArH), 7.72–8.00 (m, 1H, ArH), 8.09–8.30 (m, 1H, ArH), 11.70 (s, br, 1H, CONH). Anal. Calcd for $C_{26}H_{24}N_2O_3$: C, 75.70; H, 5.86; N, 6.79. Found: C, 75.51; H, 5.84; N, 6.76.

4.2.6. 2-{*N*-Methyl-*N*-[3′-(2-thienyl)prop-2′-ynyl]amino}-*N*′-*p*-tolyl benzamide 11. Colourless sticky oil; IR: ν_{max} (neat) 3168, 2224, 1666, 1595 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 2.33 (s, 3H, Ar–CH_3), 2.95 (s, 3H, –NCH_3), 3.90 (s, 2H, –NCH_2), 6.72–7.62 (m, 10H, ArH), 8.03–8.26 (m, 1H, ArH), 11.70 (s, br, 1H, CONH). Anal. Calcd for $C_{22}H_{20}N_2OS$: C, 73.30; H, 5.59; N, 7.77. Found: C, 73.10; H, 5.43; N, 7.63.

4.2.7. 2-{*N*-Methyl-*N*-[3′-(2,4-dimethoxypyrimidin-5-yl)-prop-2′-ynyl]amino}-*N*′-*p*-tolyl benzamide 12. Light yellow sticky oil; IR: ν_{max} (neat) 3163, 2243, 1668, 1596 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 2.33 (s, 3H, Ar–CH_3), 3.00 (s, 3H, –NCH_3), 3.96 (s, 6H, –OCH_3), 4.00 (s, 2H, –NCH_2), 6.95–7.66 (m, 8H, ArH), 8.06–8.33 (m, 1H, ArH) 11.60 (s, br, 1H, CONH). Anal. Calcd for $C_{24}H_{24}N_4O_3$: C, 69.21; H, 5.80; N, 13.45. Found: C, 68.92; H, 5.66; N, 13.25.

4.2.8. 2-{*N*-Benzyl-*N*-[3′-(*o*-methylphenyl)prop-2′-ynyl]-amino}-*N*′-*p*-tolyl benzamide 13. Colourless solid; mp 138–139°C; IR: ν_{max} (KBr) 3161, 2225, 1665, 1600 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 2.30 (s, 3H, Ar–CH_3) 2.36 (s, 3H, Ar–CH_3), 3.95 (s, 2H, –NCH_2), 4.40 (s, 2H, –NCH_2Ph), 6.82–7.66 (m, 16H, ArH), 8.26–8.40 (m, 1H, ArH), 11.62 (s, br, 1H, CONH). Anal. Calcd for $C_{31}H_{28}N_2O$: C, 83.74; H, 6.34; N, 6.30. Found: C, 83.48; H, 6.17; N, 6.09.

4.2.9. 2-{*N*-Benzyl-*N*-[3′-(*p*-methylphenyl)prop-2′-ynyl]-amino}-*N*′-*p*-tolyl benzamide 14. Colourless solid; mp 146°C; IR: ν_{max} (KBr) 3160, 1660, 1595 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 2.30 (s, 3H, Ar–CH_3), 2.36 (s, 3H, Ar–CH_3), 3.90 (s, 2H, –NCH_2), 4.40 (s, 2H, –NCH_2Ph), 6.85–6.60 (m, 16H, ArH), 8.23–8.46 (m, 1H, ArH), 11.5 (s, br, 1H, –CONH). Anal. Calcd for $C_{31}H_{28}N_2O$: C, 83.74; H, 6.34; N, 6.30. Found: C, 83.57; H, 6.40; N, 6.58.

4.2.10. 2-{*N*-Benzyl-*N*-[3′-(*m*-chlorophenyl)prop-2′-ynyl]-amino}-*N*′-*p*-tolyl benzamide 15. Colourless solid; mp 141°C; IR: ν_{max} (KBr) 3165, 2227, 1659, 1593 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 2.33 (s, 3H, Ar–CH_3), 3.89 (s, 2H, –NCH_2), 4.39 (s, 2H, –NCH_2Ph), 6.92–7.66 (m, 16H, ArH), 8.26–8.42 (m, 1H, ArH), 11.66 (s, br, 1H, –CONH). Anal. Calcd for $C_{30}H_{25}N_2OCl$: C, 77.48; H, 5.41; N, 6.02. Found: C, 77.46; H, 5.64; N, 6.21.

4.2.11. 2-{*N*-Benzyl-*N*-[3′-(*o*-methoxycarbonylphenyl)-prop-2′-ynyl]amino}-*N*′-*p*-tolyl benzamide 16. Colourless solid; mp 115°C; IR: ν_{max} (KBr) 3161, 1728, 1664, 1595 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 2.29 (s, 3H, Ar–CH_3), 3.90 (s, 3H, –CO_2Me), 3.92 (s, 2H, –NCH_2), 4.50 (s, 2H, –NCH_2Ph), 6.80–7.56 (m, 15H, ArH), 7.72–8.0 (m, 1H, ArH), 8.09–8.33 (m, 1H, ArH), 11.7 (s, br, 1H, –CONH). Anal. Calcd for $C_{32}H_{28}N_2O_3$: C, 78.66; H, 5.77; N, 5.73. Found: C, 78.79; H, 5.93; N, 5.94.

4.2.12. 2-{*N*-Benzyl-*N*-[3′-(2-thienyl)prop-2′-ynyl]amino}-*N*′-*p*-tolyl benzamide 17. Colourless solid; mp 125°C; IR: ν_{max} (KBr) 3163, 2224, 1663, 1595 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 2.29 (s, 3H, Ar–CH_3), 3.89 (s, 2H, –NCH_2), 4.36 (s, 2H, –NCH_2Ph), 6.82–7.53 (m, 15H, ArH), 8.16–8.36 (m, 1H, ArH), 11.62 (s, br, 1H, –CONH). Anal. Calcd for $C_{28}H_{24}N_2OS$: C, 77.03; H, 5.54; N, 6.41. Found: C, 76.86; H, 5.46; N, 6.34.

4.2.13. 2-{*N*-Benzyl-*N*-[3′-(2,4-dimethoxypyrimidin-5-yl)prop-2′-ynyl]amino}-*N*′-*p*-tolyl benzamide 18. Light yellow solid; mp 129–131°C; IR: ν_{max} (KBr) 3165, 2228, 1664, 1597 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 2.26 (s, 3H, Ar–CH_3), 3.85 (s, 2H, –NCH_2), 3.86 (s, 3H, –OCH_3), 3.92 (s, 3H, –OCH_3), 4.33 (s, 2H, –NCH_2Ph), 6.92–7.66 (m, 13H, ArH), 8.20–8.50 (m, 1H, ArH), 11.65 (s, br, 1H, –CONH). Anal. Calcd for $C_{30}H_{28}N_4O_3$: C, 73.15; H, 5.73; N, 11.37. Found: C, 73.31; H, 5.89; N, 11.53.

4.3. General procedure for the synthesis of 19–31

A mixture of the above disubstituted alkyne **6**–**18**, CuI (20 mol%), K_2CO_3 (2.5 equiv.) and Bu_4NBr (1 equiv.) in acetonitrile was refluxed for 16–24 h under argon atmosphere. After removal of solvent under reduced pressure and after usual work-up with chloroform–water, the residue obtained after removal of chloroform was purified by column chromatography on neutral alumina using chloroform–light petroleum ether (3:1) as eluent; the quinazolinones (**19**–**31**) were obtained as predominant products (yield 60–67%).

4.3.1. 1-Methyl-(*E*)-2-(2-phenylvinyl)-3-*p*-tolyl-1,2,3,4-tetrahydroquinazolin-4-one 19. Colourless gum; IR: ν_{max} (neat) 1650, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.26 (s, 3H, Ar–CH_3), 2.85 (s, 3H, NCH_3) 5.08 (d, J=6.7 Hz, 1H, N_2CH), 6.29 (d, J=15.9 Hz, 1H, =CHPh), 6.35 (dd, J_1=6.7 Hz, J_2=15.9 Hz, 1H, HC=CPh), 6.58 (d, J=8.1 Hz, 1H, ArH), 6.83 (m, 1H, ArH), 7.09–7.22 (m, 9H, ArH), 7.30–7.36 (m, 1H, ArH), 7.98 (dd, J_1=1.5 Hz, J_2=7.6 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.53, 35.99, 81.84, 112.86, 117.70, 119.16, 123.19, 127.25, 128.90, 129.07, 129.77, 130.25, 130.42, 134.42, 134.67, 135.79, 137.41, 138.58, 147.38, 162.64; ^{13}C NMR

(75 MHz, $CDCl_3$, DEPT 135) δ 21.53, 35.99, 81.84, 112.87, 119.16, 123.19, 127.25, 127.29, 128.90, 129.07, 129.77, 130.25, 134.42, 134.67. Anal. Calcd for $C_{24}H_{22}N_2O$: C, 81.32; H, 6.25; N, 7.90. Found: C, 81.28; H, 6.21; N, 7.83.

4.3.2. 1-Methyl-(*E*)-2-[2-(*o*-tolyl)vinyl]-3-*p*-tolyl-1,2,3,4-tetrahydroquinazolin-4-one 20. Colourless gum; IR: ν_{max} (neat) 1651, 1606 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.16 (s, 3H, Ar–CH_3), 2.28 (s, 3H, Ar–CH_3), 2.88 (s, 3H, NCH_3), 5.12 (d, J=7.8 Hz, 1H, N_2CH), 6.15 (dd, J_1=7.8 Hz, J_2=15.6 Hz, 1H, *H*C=CHAr), 6.58 (d, J=15.6 Hz, 1H, =CHAr), 6.59 (d, J=8.4 Hz, 1H, ArH), 6.80–6.85 (m, 1H, ArH), 7.01–7.23 (m, 8H, ArH), 7.31–7.36 (m, 1H, ArH), 7.95–7.98 (m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.07, 21.51, 36.03, 81.78, 112.85, 117.84, 119.18, 124.69, 126.59, 127.30, 128.48, 128.70, 129.71, 130.21, 130.73, 132.80, 134.37, 135.20, 136.17, 137.40, 138.59, 147.41, 162.66; ^{13}C NMR (75 MHz, $CDCl_3$, DEPT 135) δ 19.78, 21.22, 35.74, 81.49, 112.56, 118.89, 124.40, 126.05, 126.30, 127.01, 128.41, 129.42, 129.93, 130.45, 132.51, 134.09. Anal. Calcd for $C_{25}H_{24}N_2O$: C, 81.48; H, 6.56; N, 7.60. Found: C, 81.61; H, 6.64; N, 7.76.

4.3.3. 1-Methyl-(*E*)-2-[2-(*o*-methoxyphenyl)vinyl]-3-*p*-tolyl-1,2,3,4-tetrahydroquinazolin-4-one 21. Colourless gum; IR: ν_{max} (neat) 1651, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.23 (s, 3H, Ar–CH_3), 2.85 (s, 3H, NCH_3), 3.68 (s, 3H, OCH_3), 5.07 (d, J=8.4 Hz, 1H, N_2CH), 6.33 (dd, J_1=8.4 Hz, J_2=14.7 Hz, 1H, *H*C=CHAr), 6.58 (d, J=14.7 Hz, 1H, =CHAr), 6.69–6.85 (m, 4H, ArH), 7.09–7.36 (m, 7H, ArH), 7.98 (dd, J_1=1.5 Hz, J_2=7.5 Hz, 1H, ArH). Anal. Calcd for $C_{25}H_{24}N_2O_2$: C, 78.09; H, 6.29; N, 7.28. Found: C, 77.90; H, 6.22; N, 7.12.

4.3.4. 1-Methyl-(*E*)-2-[2-(*p*-methoxyphenyl)vinyl]-3-*p*-tolyl-1,2,3,4-tetrahydroquinazolin-4-one 22. Colourless gum; IR: ν_{max} (neat) 1647, 1604 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 2.23 (s, 3H, Ar–CH_3), 2.82 (s, 3H, NCH_3), 3.67 (s, 3H, OCH_3), 5.04 (d, J=8.1 Hz, 1H, N_2CH), 6.17 (dd, J_1=8.1 Hz, J_2=15.9 Hz, 1H, *H*C=CHAr), 6.30 (d, J=15.9 Hz, 1H, =CHAr), 6.56 (d, J=8.1 Hz, 1H, ArH), 6.67–6.86 (m, 4H, ArH), 7.08–7.29 (m, 6H, ArH), 7.97 (dd, J_1=1.8 Hz, J_2=7.6 Hz, 1H, ArH). Anal. Calcd for $C_{25}H_{24}N_2O_2$: C, 78.09; H, 6.29; N, 7.28. Found: C, 77.93; H, 6.25; N, 7.22.

4.3.5. 1-Methyl-(*E*)-2-[2-(*o*-methoxycarbonylphenyl)vinyl]-3-*p*-tolyl-1,2,3,4-tetrahydroquinazolin-4-one 23. Colourless solid; mp 169°C; IR: ν_{max} (KBr) 1713, 1666, 1601 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.27 (s, 3H, Ar–CH_3), 2.91 (s, 3H, NCH_3), 3.75 (s, 3H, CO_2Me), 5.15 (d, J=8.4 Hz, 1H, N_2CH), 6.19 (dd, J_1=8.4 Hz, J_2=15.3 Hz, 1H, *H*C=CHAr), 6.59 (d, J=8.4 Hz, 1H, ArH), 6.82 (d, J=15.3 Hz, 1H, =CHAr), 7.11–7.36 (m, 9H, ArH), 7.81 (d, J=8.1 Hz, 1H, ArH), 7.97 (dd, J_1=1.5 Hz, J_2=7.8 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.51, 35.97, 52.49, 81.64, 112.81, 117.74, 119.06, 126.07, 126.09, 127.13, 128.19, 129.77, 130.19, 130.80, 131.03, 132.71, 134.18, 134.39, 137.27, 138.04, 138.67, 147.49, 162.61, 167.79; ^{13}C NMR (75 MHz, $CDCl_3$, DEPT 135) δ 21.21, 35.65, 52.21, 81.33, 112.50, 118.75, 125.74, 126.82, 127.89, 128.09, 129.46, 129.90, 130.73, 132.41, 133.89, 134.10. Anal. Calcd for $C_{26}H_{24}N_2O_3$: C, 75.70; H, 5.86; N, 6.79. Found: C, 75.61; H, 5.74; N, 6.58.

4.3.6. 1-Methyl-(*E*)-2-[2-(2-thienyl)vinyl]-3-*p*-tolyl-1,2,3,4-tetrahydroquinazolin-4-one 24. Colourless solid; mp 199°C; IR: ν_{max} (KBr) 1647, 1605 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 3H, Ar–CH_3), 2.94 (s, 3H, NCH_3), 5.13 (d, J=7.9 Hz, 1H, N_2CH), 6.18 (dd, J_1=7.9 Hz, J_2=15.6 Hz, 1H, *H*C=CHAr), 6.57 (d, J=15.6 Hz, 1H, =CHAr), 6.67 (d, J=8.1 Hz, 1H, ArH), 6.89–6.93 (m, 3H, ArH), 7.15–7.28 (m, 5H, ArH), 7.40–7.43 (m, 1H, ArH), 8.05 (dd, J_1=1.5 Hz, J_2=7.8 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.52, 36.06, 81.52, 112.91, 117.62, 119.19, 122.56, 125.78, 127.22, 127.56, 127.63, 127.90, 129.77, 130.26, 134.43, 137.42, 138.52, 140.71, 147.23, 162.63; ^{13}C NMR (75 MHz, $CDCl_3$, DEPT 135) δ 21.23, 35.77, 81.23, 112.62, 118.90, 122.27, 125.49, 126.93, 127.27, 127.35, 127.62, 129.48, 129.97, 134.14. Anal. Calcd for $C_{22}H_{20}N_2OS$: C, 73.30; H, 5.59; N, 7.77. Found: C, 73.16; H, 5.68; N, 7.97.

4.3.7. 1-Methyl-(*E*)-2-[2-(2,4-dimethoxypyrimidin-5-yl)-vinyl]-3-*p*-tolyl-1,2,3,4-tetrahydroquinazolin-4-one 25. Colourless solid; mp 70°C; IR: ν_{max} (KBr) 1651, 1595 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H, Ar–CH_3), 2.94 (s, 3H, NCH_3), 3.95 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 5.12 (d, J=7.5 Hz, 1H, N_2CH), 6.34 (d, J=15.9 Hz, 1H, =CHAr), 6.45 (dd, J_1=7.5 Hz, J_2=15.9 Hz, 1H, *H*C=CHAr), 6.67 (d, J=8.1 Hz, 1H, ArH), 6.89–6.94 (m, 1H, ArH), 7.18–7.27 (m, 4H, ArH), 7.40–7.45 (m, 1H, ArH), 8.04 (dd, J_1=1.5 Hz, J_2=7.8 Hz, 1H, ArH), 8.13 (s, 1H, ArH). Anal. Calcd for $C_{24}H_{24}N_4O_3$: C, 69.21; H, 5.80; N, 13.45. Found: C, 69.48; H, 5.83; N, 13.52.

4.3.8. 1-Benzyl-(*E*)-2-[2-(*o*-tolyl)vinyl]-3-*p*-tolyl-1,2,3,4-tetrahydroquinazolin-4-one 26. Colourless gum; IR: ν_{max} (neat) 1655, 1603 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.15 (s, 3H, Ar–CH_3), 2.28 (s, 3H, Ar–CH_3), 4.26 (d, J=15.1 Hz, 1H, NCHPh), 4.77 (d, J=15.1 Hz, 1H, NCHPh), 5.20 (d, J=7.5 Hz, 1H, N_2CH), 6.21 (dd, J_1=7.5 Hz, J_2=15.6 Hz, 1H, *H*C=CHAr), 6.52 (d, J=15.6 Hz, 1H, =CHAr), 6.79–6.94 (m, 2H, ArH), 7.08–7.45 (m, 14H, ArH), 8.08 (dd, J_1=1.5 Hz, J_2=7.5 Hz, 1H, ArH). Anal. Calcd for $C_{31}H_{28}N_2O$:C, 83.74; H, 6.34; N, 6.30. Found: C, 83.80; H, 6.51; N, 6.42.

4.3.9. 1-Benzyl-(*E*)-2-[2-(*p*-tolyl)vinyl]-3-*p*-tolyl-1,2,3,4-tetrahydroquinazolin-4-one 27. Colourless gum; IR: ν_{max} (neat) 1651, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 3H, Ar–CH_3), 2.31 (s, 3H, Ar–CH_3), 4.23 (d, J=15.4 Hz, 1H, NCHPh), 4.73 (d, J=15.4 Hz, 1H, NCHPh), 5.15 (d, J=7.2 Hz, 1H, N_2CH), 6.26 (d, J=15.7 Hz, 1H, =CHAr), 6.35 (dd, J_1=7.2 Hz, J_2=15.7 Hz, 1H, *H*C=CHAr), 6.78 (d, J=8.1 Hz, 1H, ArH), 6.91–7.25 (m, 9H, ArH), 7.28–7.44 (m, 6H, ArH), 8.09 (dd, J_1=1.5 Hz, J_2=7.8 Hz, 1H, ArH). Anal. Calcd for $C_{31}H_{28}N_2O$: C, 83.74; H, 6.34; N, 6.30. Found: C, 83.77; H, 6.41; N, 6.36.

4.3.10. 1-Benzyl-(*E*)-2-[2-(*m*-chlorophenyl)vinyl]-3-*p*-tolyl-1,2,3,4-tetrahydroquinazolin-4-one 28. Colourless gum; IR: ν_{max} (neat) 1654, 1603 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3H, Ar–CH_3), 4.24 (d,

J=15.3 Hz, 1H, NCHPh), 4.75 (d, J=15.3 Hz, 1H, NCHPh), 5.18 (d, J=7.3 Hz, 1H, N_2CH), 6.23 (d, J=15.9 Hz, 1H, =CHAr), 6.37 (dd, J_1=7.3 Hz, J_2=15.9 Hz, 1H, *H*C=CHAr), 6.81 (d, J=8.4 Hz, 1H, ArH), 6.95–7.25 (m, 10H, ArH), 7.33–7.40 (m, 5H, ArH), 8.08 (dd, J_1=1.5 Hz, J_2=7.8 Hz, 1H, ArH). Anal. Calcd for $C_{30}H_{25}N_2OCl$: C, 77.48; H, 5.41; N, 6.02. Found: C, 77.34; H, 5.37; N, 5.86.

4.3.11. 1-Benzyl-(*E*)-2-[2-(*o*-methoxycarbonylphenyl)vinyl]-3-*p*-tolyl-1,2,3,4-tetrahydroquinazolin-4-one 29. Colourless gum; IR: ν_{max} (neat) 1717, 1655,1605 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.23 (s, 3H, Ar–CH_3), 3.74 (s, 3H, –CO_2Me), 4.25 (d, J=15.4 Hz, 1H, NCHPh), 4.68 (d, J=15.4 Hz, 1H, NCHPh), 5.15 (d, J=8.1 Hz, 1H, N_2CH), 6.18 (dd, J_1=8.1 Hz, J_2=15.1 Hz, 1H, *H*C=CHAr), 6.70 (d, J=8.4 Hz, 1H, ArH), 6.83 (d, J=15.1 Hz, 1H, =CHAr), 7.04–7.12 (m, 5H, ArH), 7.15–7.42 (m, 9H, ArH), 7.78 (d, J=8.1 Hz, 1H, ArH), 8.01 (dd, J_1=1.5 Hz, J_2=7.8 Hz, 1H, ArH). Anal. Calcd for $C_{32}H_{28}N_2O_3$: C, 78.66; H, 5.77; N, 5.73. Found: C, 78.45; H, 5.61; N, 5.63.

4.3.12. 1-Benzyl-(*E*)-2-[2-(2-thienyl)vinyl]-3-*p*-tolyl-1,2,3,4-tetrahydroquinazolin-4-one 30. Colourless solid; mp 117–118°C; IR: ν_{max} (KBr) 1657, 1601 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.31 (s, 3H, Ar–CH_3), 4.25 (d, J=15.3 Hz, 1H, NCHPh), 4.75 (d, J=15.3 Hz, 1H, NCHPh), 5.15 (d, J=7.5 Hz, 1H, N_2CH), 6.16 (dd, J_1=7.5 Hz, J_2=15.6 Hz, 1H, *H*C=CHA r), 6.44 (d, J=15.6 Hz, 1H, =CHAr), 6.8 (d, J=8.4 Hz, 1H, ArH), 6.90–6.97 (m, 3H, ArH), 7.13–7.15 (m, 5H, ArH), 7.24–7.42 (m, 6H, ArH), 8.09 (d, J=7.8 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.49, 52.98, 78.39, 114.32, 118.71, 119.82, 122.97 125.70, 127.13, 127.20, 127.57, 127.88, 128.01, 128.31, 129.37, 129.91, 130.25, 134.29, 137.09, 137.33, 138.40, 140.84, 146.83, 162.69; ^{13}C NMR(75 MHz, $CDCl_3$, DEPT 135) δ 21.20, 52.70 (inverted), 78.11, 114.03, 119.53, 122.68, 125.41, 126.84, 126.91, 127.28, 127.60, 127.72, 128.02, 129.09, 129.63, 129.97, 134.00. Anal. Calcd for $C_{28}H_{24}N_2OS$: C, 77.03; H, 5.54; N, 6.41. Found: C, 77.07; H, 5.50; N, 6.65.

4.3.13. 1-Benzyl-(*E*)-2-[2-(2,4-dimethoxypyrimidin-5-yl)vinyl]-3-*p*-tolyl-1,2,3,4-tetrahydroquinazolin-4-one 31. Colourless solid; mp 70°C; IR: ν_{max} (KBr) 1659, 1595 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.25 (s, 3H, Ar–CH_3), 3.95 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3) 4.27 (d, J=15.3 Hz, 1H, NCHPh), 4.75 (d, J=15.3 Hz, 1H, NCHPh), 5.17 (d, J=7.5 Hz, 1H, N_2CH), 6.23 (d, J=15.9 Hz, 1H, =CHAr), 6.44 (dd, J_1=7.5 Hz, J_2=15.9 Hz, 1H, *H*C=CHAr), 6.81 (d, J=8.1 Hz, 1H, ArH), 6.91–6.96 (m, 1H, ArH), 7.14–7.17 (m, 4H, ArH), 7.22–7.44 (m, 6H, ArH), 8.08–8.11 (m, 2H, ArH); ^{13}C NMR (300 MHz, $CDCl_3$) δ 21.48, 53.07, 54.53, 55.34, 78.99, 111.54, 114.28, 118.72, 119.76, 125.19, 125.36, 127.15, 128.05, 128.30, 129.34, 129.87, 130.23, 134.26, 137.10, 137.32, 138.44, 146.87, 157.29, 162.71, 164.89, 168.61; ^{13}C NMR (75 MHz, $CDCl_3$, DEPT 135) δ 21.20, 52.75 (inverted), 54.26, 55.06, 78.71, 113.97, 119.47, 124.91, 125.05, 126.87, 127.76, 128.01, 129.06, 129.58, 129.95, 133.98, 157.01. Anal. Calcd for $C_{30}H_{28}N_4O_3$: C, 73.15; H, 5.73; N, 11.37. Found: C, 73.05; H, 5.70; N, 11.33.

4.3.14. 1-Benzyl-(*Z*)-3-[(*p*-tolyl)methylidene]-4-*p*-tolyl-1,2,3,4-tetrahydro-5*H*-benzodiazepin-5-one 32. Colourless gum; IR: ν_{max} (neat) 1652, 1598 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.25 (s, 3H, Ar–CH_3), 2.27 (s, 3H, Ar–CH_3), 3.88 (s, 2H, –CH_2), 4.35 (s, 2H, –CH_2), 6.27 (s, 1H, =CH), 6.92–7.06 (m, 6H, ArH), 7.21–7.36 (m, 10H, ArH), 7.66 (dd, J_1=1.8 Hz, J_2=7.6 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.81, 21.19, 55.87, 63.96, ($^3J_{CH}$=3.75 Hz), 118.64, 122.64, 122.78, 127.21, 127.94, 128.43, 128.76, 129.25, 129.33, 129.44, 130.55, 131.68, 131.71, 132.17, 135.03, 135.22, 136.51, 137.74, 138.54, 147.64, 169.23; ^{13}C NMR (75 MHz, $CDCl_3$, DEPT 135) δ 21.02, 21.40, 56.07 (inverted), 64.17 (inverted), 118.85, 122.85, 122.99, 127.42, 128.15, 128.64, 128.97, 129.46, 129.54, 129.64, 131.91. Anal. Calcd for $C_{31}H_{28}N_2O$: C, 83.74; H, 6.34; N, 6.30. Found: C, 83.90; H, 6.36; N, 6.33.

4.3.15. 1-Benzyl-(*Z*)-3-[(*m*-chlorophenyl)methylidene]-4-*p*-tolyl-1,2,3,4-tetrahydro-5*H*-benzodiazepin-5-one 33. Colourless gum; IR: ν_{max} (neat) 1655, 1601 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.25 (s, 3H, Ar–CH_3), 3.94 (s, 2H, –CH_2), 4.37 (s, 2H, –CH_2), 6.23 (s, 1H, =CH), 6.99–7.06 (m, 4H, ArH), 7.14–7.39 (m, 12H, ArH), 7.71 (m, 1H, ArH). Anal. Calcd for $C_{30}H_{25}N_2OCl$: C, 77.48; H, 5.41; N, 6.02. Found: C, 77.28; H, 5.31; N, 5.90.

4.3.16. 1-Benzyl-(*Z*)-3-[(2-thienyl)methylidene]-4-*p*-tolyl-1,2,3,4-tetrahydro-5*H*-benzodiazepin-5-one 34. Colourless gum; IR: ν_{max} (neat) 1658, 1649, 1596 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.28 (s, 3H, $ArCH_3$), 3.86 (s, 2H, –CH_2), 4.33 (s, 2H, –CH_2), 6.62 (s, 1H, =CH), 6.89–6.99 (m, 4H, ArH), 7.06–7.32 (m, 10H, ArH), 7.53–7.62 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.81, 55.74, 62.89 ($^3J_{CH}$=4.25 Hz), 118.63, 121.82, 122.69, 126.43, 126.67, 127.18, 127.85, 128.39, 128.42, 129.27, 129.37, 129.52, 131.68, 132.24, 133.38, 134.77, 135.62, 135.94, 137.60, 147.43, 169.11; ^{13}C NMR (75 MHz, $CDCl_3$, DEPT 135) δ 21.02, 55.95 (inverted), 63.10 (inverted), 118.84, 122.02, 122.90, 126.64, 126.88, 127.39, 128.06, 128.63, 129.48, 129.58, 129.73, 131.90. Anal. Calcd for $C_{28}H_{24}N_2OS$: C, 77.03; H, 5.54; N, 6.41. Found: C, 76.87; H, 5.44; N, 6.38.

4.3.17. Synthesis of 1-methyl-(*E*)-2-[2-(uracil-5-yl)vinyl]-3-*p*-tolyl 1,2,3,4-tetrahydroquinazolin-4-one 35. To a magnetically stirred solution of compound **25** (100 mg, 0.24 mmol) in dry acetonitrile (7 mL) under an argon atmosphere were added anhydrous sodium iodide (108 mg, 0.72 mmol) and trimethylchlorosilane (80 mg, 0.72 mmol). The resulting mixture was stirred at rt for 24 h. The solvent was removed under reduced pressure and the residue was washed with a few drops of aqueous sodium metabisulfite solution and then with cold water, filtered and dried to yield compound **35** as light yellow powder solid (65 mg; 70%); mp>200°C; IR: ν_{max} (KBr) 3030, 2925, 1715, 1680, 1595 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$+DMSO-d_6) δ 2.31 (s, 3H, $ArCH_3$), 2.92 (s, 3H, NCH_3), 5.08 (d, J=9.0 Hz, 1H, N_2CH), 6.11 (d, J=15.0 Hz, 1H, =CH), 6.63 (dd, J_1=9.0 Hz, J_2=15.0 Hz, 1H, HC=), 6.85–6.90 (m, 1H, ArH), 7.13–7.16 (m, 3H, ArH), 7.39–7.52 (m, 4H, ArH), 7.96 (d, J=6.0 Hz, 1H, =CH), 10.39 (s, 1H, –NH), 10.87 (s, 1H, –NH). Anal. Calcd for $C_{22}H_{20}N_4O_3$: C, 68.02; H, 5.19; N, 14.42. Found: C, 68.27; H, 5.06; N, 14.31.

Similar reaction condition was used for the synthesis of *1-benzyl-(E)-2-[2-(uracil-5-yl)vinyl]-3-p-tolyl-1,2,3,4-tetrahydroquinazolin-4-one* **36** from **31**.

Compound **36**: (72%); light yellow powder solid; mp>200°C; IR: ν_{max} (KBr) 3032, 2920, 1713, 1674, 1584 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$+DMSO-d_6) δ 2.25 (s, 3H, $ArCH_3$), 4.15 (d, J=15.0 Hz, 1H, NCHPh), 4.64 (d, J=15.0 Hz, 1H, NCHPh), 5.03 (d, J=6.0 Hz, 1H, N_2CH), 5.90 (d, J=15.5 Hz, 1H, =CH), 6.60 (dd, J_1=6.0 Hz, J_2=15.5 Hz, 1H, HC=), 6.67 (d, J=8.4 Hz, 1H, ArH), 6.82 (m, 1H, ArH), 7.02–7.07 (m, 4H, ArH), 7.14–7.46 (m, 7H, ArH), 7.94 (d, J=6.0 Hz, 1H, ArH), 10.08 (s, 1H, –NH), 10.77 (d, J=3.0 Hz, 1H, –NH). Anal. Calcd for $C_{28}H_{24}N_4O_3$: C, 72.39; H, 5.20; N, 12.06. Found: C, 72.22; H, 5.10; N, 11.97.

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