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Pd-catalyzed one-pot stepwise synthesis of benzo[b][1,6]naphthyridines from 2-chloroquinoline-3-carbonitriles using sulphur and amines as nucleophiles

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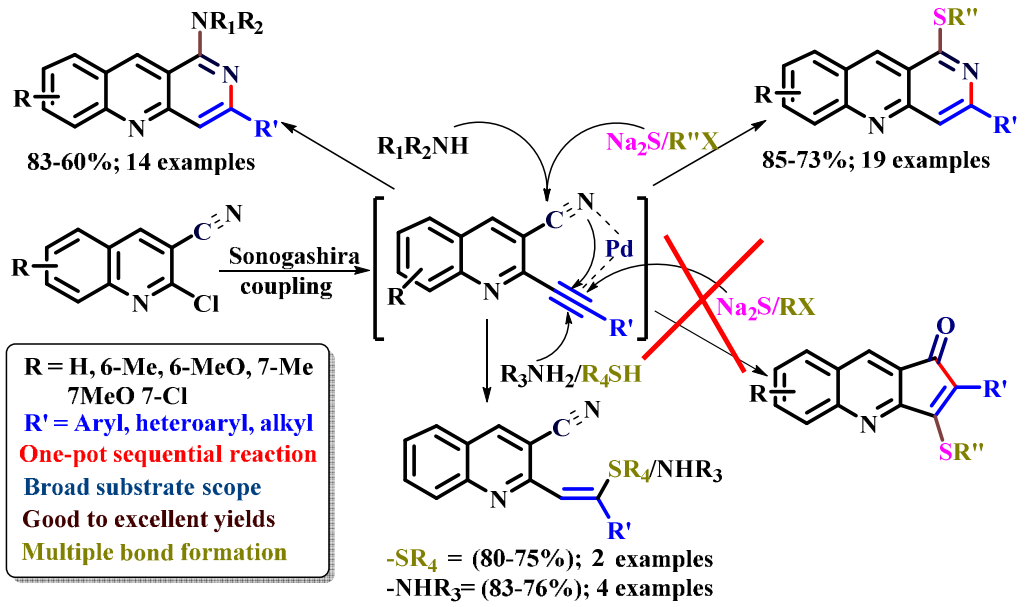


ABSTRACT: A palladium-catalyzed one-pot stepwise coupling-annulation reaction of 2-chloroqunoline-3-carbonitriles enabled the direct synthesis of sulphur-substituted benzo[b][1,6]naphthyridines via multiple bond formation. The reaction provided an unusual mode for cyclization as sodium sulphide a soft nucleophile preferred to attack on carbon of nitrile group rather than on carbon-carbon triple bond. The developed chemistry was extended with the secondary amines as nucleophile to afford nitrogen-substituted benzo[b][1,6]naphythyridines while with primary amines hydroamination products were obtained. The hydromination products were transformed to benzo[b][1,6]naphthyridones via base mediated cyclization reaction. This developed protocol features inexpensive and easily synthesizable starting materials, easy operations, high efficiency and tolerance to a broad range of substrates.

INTRODUCTION

The synthesis of polyheterocycles[1] in one-pot strategy starting from simple and unexplored precursors has garnered interest due to prevalence in various natural products as well as in functional material, photochemistry etc. Among them, nitrogen-containing heterocycles, particularly naphythyridines and their benzo/hetero-fused analogoues represent an important class of molecules. Naphythyridines are present in numerous marine alkaloids (Fig.1 a, b)[2] and exhibit wide range of distinctive biological activities such as antitumor,[3a-b] anti-inflammatory,[3c] anti-HSV (Herps Simplex Virus) properties,[4] anticancer and anti-HIV-1 (Fig. 1c),[5] adrenoceptor blocking activities[6] along with AKt1 and AKt2 inhibitor properties.[7] Besides, benzo[1,6]naphthyridines are found in synthetic drugs, such as *Benafentrine* and *Tolafentrine* (Fig. 1d) as phosphodiesterase III/IV inhibitors[8] and also exhibit luminescence properties.[9]

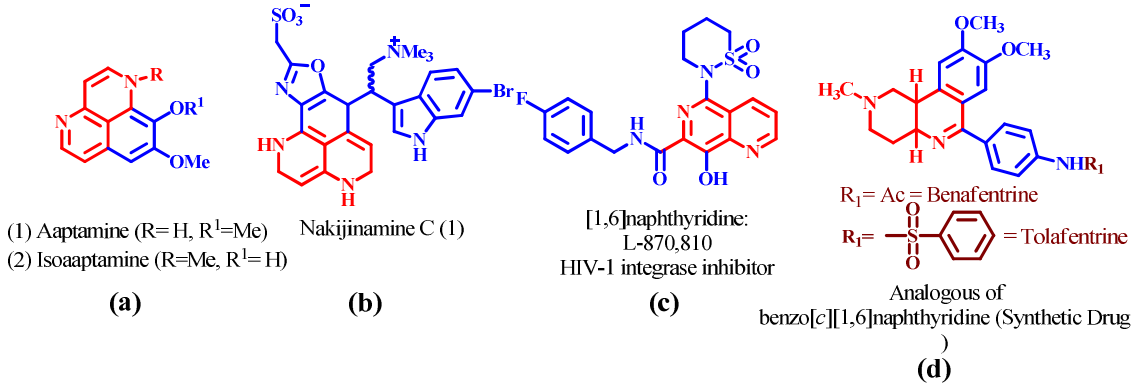


Figure 1. Significant examples of marine alkaloids (**a, b**); Biological active compound (**c**); synthetic drug (**d**) containing [1, 6]naphthyridine skeletons.

A number of synthetic strategies have been reported for [1,6]naphthyridines[10] *via* multicomponent reactions,[11] transition-metal catalyzed reactions,[12] cycloaddition reactions[13] and other approaches.[14] However, their benzo-analogues have been less explored. Coscia *et al.* have reported the first synthesis of parent compound from aniline and 1-acetyl-3-ethoxycarbonyl-4-piperidone by condensation and dehydrogenation reaction.[15] Recently, groups of Verma[16] and Langer[17] have reported silver-catalyzed tricyclic/tetetracyclic benzo[b][1,6]naphthyridines via multicomponent reactions from 2-alkynylquinoline-3-carbaldehydes respectively. We have also reported synthesis of benzo[b][1,6]naphthyridines from quinoline analogues using aqueous ammonia.[18a]

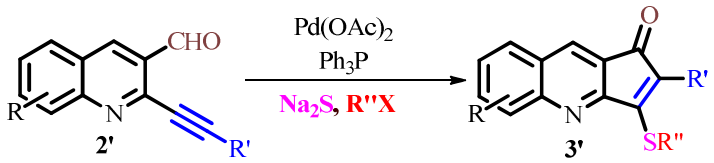
Stepwise reactions[19] in one-pot are one of the most powerful synthetic strategies in the modern era of organic chemistry for being step economy. The practical utility of "one-pot stepwise" reactions avoids the tedious purification of the intermediate along with reduces the

costs and effort for the synthesis of complex molecules.[20] Over the past few decades, transition metal-catalyzed nucleophilic cyclization reactions have achieved substantial progress. Particularly, palladium-catalyzed stepwise one-pot reactions have attracted much attention owing to activation of C-C triple bond towards a wide range of nucleophiles leading to broad range of carbo[21]-/heterocycles.[22]

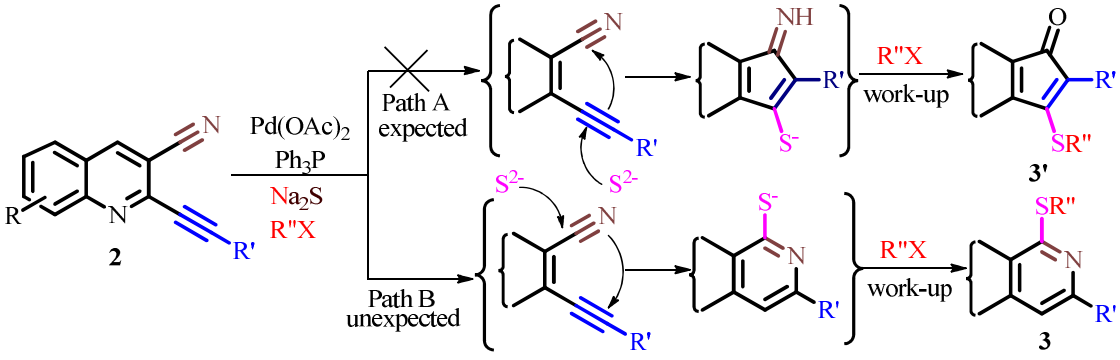
Recently, we have demonstrated sodium sulphide as an ideal nucleophilic reagent for the Pd-catalyzed cyclization of 2-alkynylquinoline-3-carbaldehydes to cyclopenta[b]quinolin-1-ones (Scheme 1A).[23] We proposed the reaction was initiated by nucleopalladation of alkynes and quenched by 1,2-addition to carbon-heteroatom for synthesis of cyclopentenone annulated quinolines. Inspired by this unusual finding and well-documentation of the fact that sulphide is a soft nucleophile and addition reaction would proceed via carbon-carbon triple bond, we further explored this nucleophilic cyclization reaction (i.e. sodium sulphide as nucleophile) towards *o*-alkynylquinolin-3-carbonitrile as cyano group has been considered as an unreactive functional group; inert to organo-palladium reagents and the nitriles are not incorporated into the molecular structure of the products.[24]

Scheme 1. Mode of attack of sulphur

(A) Previous work



(B) Present work



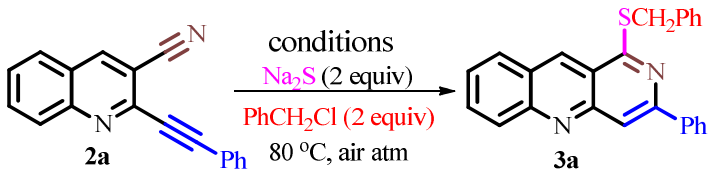
Therefore, we envisioned that 2-alkynylquinoline-3-carbonitriles **2** would undergo similar annulation reaction with sodium sulphide as a nucleophile and provide easy access to sulphur substituted cyclopenta[b]quinolin-1-ones **3'**. Thus, when 2-alkynylquinolin-3-

carbonitrile was treated under our previously reported condition, an unexpected product 1-benzylsulfanyl-3-phenyl-benzo[b][1,6]naphthyridine **3** was isolated instead of the expected product cyclopenta[b]quinolin-1-one **3'** (Scheme 1B). In continuation of our efforts in metal-catalyzed sequential one-pot reactions,[18b,23,25] we report herein palladium-catalyzed one-pot synthesis of benzo[b][1,6]naphthyridines form 2-alkynylquinolin-3-carbonitriles using sodium sulfide as nucleophile. The reaction was further extended with secondary and primary amines as nucleophilic partners to afford amino substituted benzo[b][1,6]naphthyridines and hydroamination products respectively.

RESULTS AND DISCUSSION

Initially, 2-phenylethynylquinolin-3-carbonitrile **2a** was reacted with sodium sulfide using our previous standardized reaction condition,[23] i.e. 2.5 mol% of $Pd(OAc)_2$, 5 mol% of PPh_3,2 equiv Na_2S in DMF at 80°C under an open atmosphere followed by quenching with benzyl chloride (Table 1, entry 1). The isolated product was characterized as 1-benzylsulfanyl-3-phenyl-benzo[b][1,6]naphthyridine **3a** instead of **3'** from spectral analytical data and furthermore unambiguously confirmed by single crystal X-ray analysis (Figure S1). The formation of this product revealed that the preferred attack of sulphide takes over carbonitrile rather than the alkyne in contrast to our previous observation.

Table 1. Optimization reaction condition of annulations step (2a to 3a)[a]



Entry No.	Catalyst (mol%)	Ligand (mol%)	Solvent	Time	Yield (%)[b]
1	**$Pd(OAc)_2$ (2.5)**	**Ph_3P (5)**	**DMF**	**25 min**	**86**
2[c]	$Pd(OAc)_2$ (2.5)	Ph_3P (5)	DMF	1 h	70
3[d]	$Pd(OAc)_2$ (2.5)	Ph_3P (5)	DMF	25 min	66
4	$PdCl_2$ (2.5)	Ph_3P (5)	DMF	1h	73
5	$Pd(dba)_2$ (2.5)	Ph_3P (5)	DMF	55 min	65
6	$Pd(OAc)_2$ (2.5)	Cy_3P (5)	DMF	1 h	74
7	$Pd(OAc)_2$ (2.5)	BINAP (2.5)	DMF	1 h	55
8	$Pd(OAc)_2$ (2.5)	TMEDA (5)	DMF	1 h	74

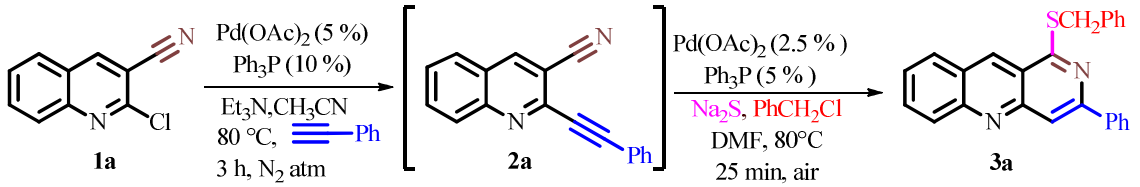
9	$Pd(OAc)_2$ (2.5)	Ph_3P (5)	MeOH	3.5 h	60
10	$Pd(OAc)_2$ (2.5)	Ph_3P (5)	THF	3 h	67
11	$Pd(OAc)_2$ (2.5)	Ph_3P (5)	Dioxane	3 h	66
12	$Pd(OAc)_2$ (2.5)	Ph_3P (5)	CH_3CN	3 h	68
13	$Pd(OAc)_2$ (2.5)	Ph_3P (5)	DMSO	1.5 h	72
14	CuI (2.5)	Ph_3P (5)	DMF	1 h	40
15	$FeCl_3$ (2.5)	Ph_3P (5)	DMF	1 h	nr[e]
16	$Ag(OTf)_3$ (2.5)	Ph_3P (5)	DMF	1 h	nr[e]
17	$RuCl_3$ (2.5)	Ph_3P (5)	DMF	1 h	nr[e]

[a]All reactions were carried out using 0.5 mmol of **2a**. [b]Isolated yield.[c] Reaction at 60 °C. [d] Reaction at 100 °C. [e] nr= no reaction with 2**a** being recovered.

Inspired by this new result, we next considered finding optimal conditions for the best yield of **3a**. The results are summarized in Table 1. Decreasing (60°C) or increasing (100°C) the reaction temperature, product yields decreased substantially (entries 2-3). The reaction with other Pd-catalysts such as $PdCl_2$ and $Pd(dba)_2$ afforded the product **3a** in low yields (entries 4-5). Similarly, monodentate ligand Cy_3P, bidentate ligand BINAP and nitrogen based ligand TMEDA (entries 6-8) were found to be less effective than PPh_3 (entry 1). Various solvents such as MeOH, THF, Dioxane, CH_3CN and DMSO (entries 9- 13) were also found to be less effective than DMF (entry 1). CuI as a catalyst afforded **3a** in 40% yield (entry 14). Other metal salts such as $FeCl_3$, $Ag(OTf)_3$ and $RuCl_3$ were totally ineffective (entries 15-17). The high yield and less time could be attributed to the better electrophilic character of the palladium complex. Thus, the combination of 0.5 mmol of **2a** with 2.5 mol% $Pd(OAc)_2$ and 5 mol% Ph_3P, 2 equiv. each of sodium sulphide and benzyl chloride in DMF at 80°C in an open atmosphere was the best reaction condition (entry 1).

As both the Sonogashira coupling and annulation steps are Pd catalyzed, thus we next examined one-pot stepwise reactions from 2-chloroquinoline-3-carbonitrile **1a** to save time, solvents and avoid the column chromatography separation of **2a**.

Scheme 2. Stepwise Sonogashira coupling and annulation



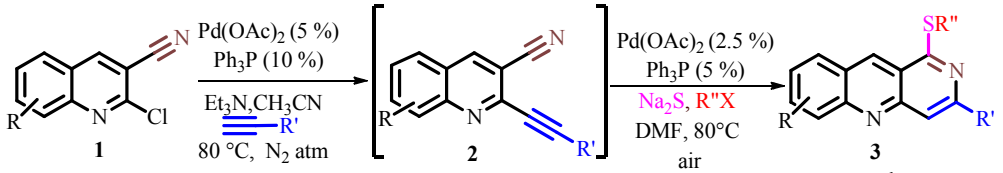
Thus, a mixture of 2-chloroquinoline-3-carbonitrile **1a** (0.5 mmol) and phenylacetylene (0.6 mmol) was treated with 5 mol % of $Pd(OAc)_2$, 10 mol % of PPh_3 and 2 equiv Et_3N in

acetonitrile at 80°C for 3 h under N_2 atm for Sonogashira coupling reaction[23]. Subsequently acetonitrile was removed under reduced pressure and DMF along with 2.5 mol % $Pd(OAc)_2$, 5 mol % Ph_3P, 2 equiv of Na_2S were added to the reaction mixture and heated at 80 °C under an open atm for 25 minutes. Quenching with 2 equiv of benzyl chloride, led to the formation of **3a** in 83% overall yield (Scheme 2). Thus, we considered the one-pot stepwise reaction as our optimized reaction condition (Scheme 2).

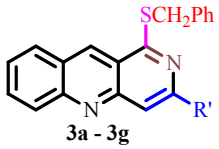
With the one-pot optimum conditions in hand, the generality of reaction with various alkynes (Table 2) was undertaken. All reactions proceeded smoothly and completed in 15-40 min. The corresponding cyclized products **3**(**b-g**) were obtained in 73-85% yields. No significant variations in the yields were found with phenylacetylene ring bearing electron donating **3**(**b-c**) or electron withdrawing groups **3d**. The cyclized products **3(e-f)** were obtained in good yields with alkyl alkynes such as oct-1-yne and pent-1-yne. Similarly, heterocyclic alkyne such as 3-ethynylthiophene afforded the cyclized product **3g** in 73% yield.

The generality of the reaction was further examined using various substituted 2-chloroquinoline-3-carbonitriles **1**(**h-k**) with phenylacetylene. All reactions proceeded smoothly and completed in 20-40 min affording the corresponding cyclized products **3**(**h-k**) in 75-78% yields (Table 2). Next, the reaction scope was explored with different alkyl halides. Similarly, the reactions proceeded smoothly and afforded the products **3**(**l-q**) in 75-82% yields (Table 2). Further, the cyclization reaction was performed with sodium sulphide followed by quenching with water. The reaction completed in 5 min and afforded the cyclized product **3r** in 78% yield. The reaction also worked well with pyridine derivative affording the cyclized product **5a** in 79%.

Table 2. Reaction scope for the synthesis of 1,3-disubstitutedbenzo[b][1,6]naphthyridines[a]

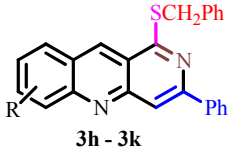


Product no., yield,[b] Time (C/A)[c]



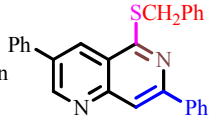
3a - 3g

3a, R' = Ph, 83%, 3 h / 25 min
3b, R' = *m*-tolyl, 84 % , 3.5 h / 35 min
3c, R' = *p*-tolyl, 85 % , 3.5 h / 35 min
3d, R' = 4F-C_6H_4, 83% , 2.5 h / 20min
3e, R' =C_3H_7, 80 % , 12h[d] / 15min
3f, R' =C_6H_{13}, 78 % , 12h[d] / 20min
3g, R' = 3-thiophene, 73 % , 3h/ 40 min

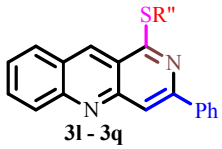


3h - 3k

3h, R = 6-Me, 78%, 3 h / 35 min
3i, R = 7-Me, 78%, 4.5 h / 35 min
3j, R = 8-Me, 76%, 5 h / 40 min
3k, R = 7-Cl, 75%, 3 h / 20min

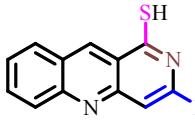


5a, 79%, 3 h/ 55 min



3l - 3q

3l, R" = Me, 83%, 3 h / 20 min
3m, R" = Et, 80%, 3 h / 25 min
3n, R" = n-pentyl, 78%, 3 h / 35 min
3o, R" = n-hexyl, 77%, 3 h / 40 min
3p, R" = Allyl, 80%, 3 h / 30 min
3q, R" = Propargyl, 75 %, 3 h / 40 min

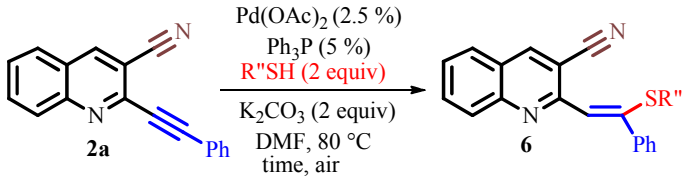


3r, 78%, 3 h/ 5 min

Conditions: [a](i) Sonogashira coupling: 5 mol % $Pd(OAc)_2$, 10 mol % Ph_3P, 2 equiv Et_3N, CH_3CN, 80 °C, N_2 atm; (ii) Annulation: 2.5 mol % $Pd(OAc)_2$, 5 mol % Ph_3P, 2 eq. each of Na_2S and R"-X, DMF, 80 °C, air. [b]Overall isolated yields over two steps. [c][C/A] means coupling time/annulation time. [d] Sonogashira coupling reaction condition for aliphatic alkynes: 5 mol % $Pd(OAc)_2$, 10 mol % Ph_3P, 15% CuI, 2 equiv Et_3N, CH_3CN, 80 °C, N_2 atm .

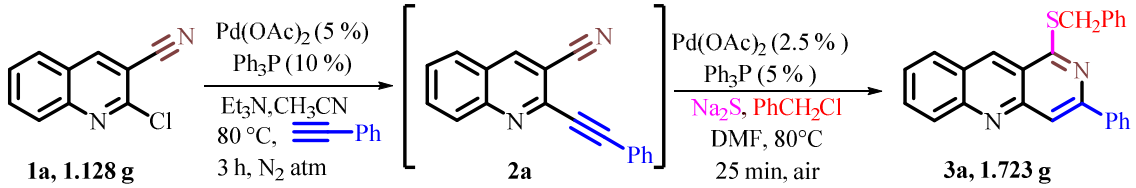
Next, we explored the reaction with other sulphur nucleophiles such as ethanethiol and thiophenol. Thus, 2-phenylethynylquinoline-3-carbonitrile **2a** was treated with ethanethiol (2 equiv) and K_2CO_3 (2 equiv) using the optimized reaction condition. The reaction completed in 1 h, surprisingly addition product across carbon-carbon triple bond **6a** was isolated rather than the anticipated cyclized product. Under similar conditions, thiophenol also afforded the addition product **6b** in 75% yield (Scheme 3).

Scheme 3. Addition of thiols across the triple bond



	R"	Time	Yield (%)
6a	Et	1 h	80
6b	Ph	2 h	75

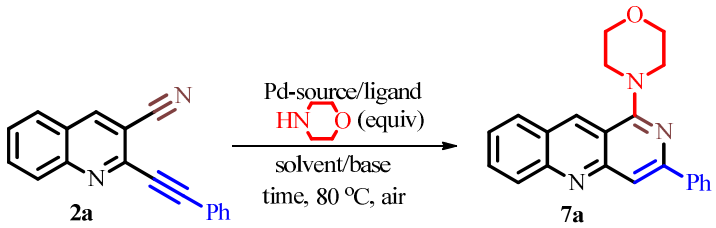
Scheme 4. Gram scale synthesis 3a.



The robustness of chemistry was examined in large-scale reactions. A large-scale experiment (**1a**, 6 mmol, 1.128 g) was carried out under the standard optimized condition. The reaction proceeded smoothly, providing the desired **3a** in 76% (1.723 g) (Scheme 4).

After establishing the reaction with sulphur nucleophiles, we became intrigued to explore the scope of chemistry with nitrogen nucleophiles such as amines (primary and secondary amines) due to their prevalence in medicinal chemistry.[26] We selected morpholine (a secondary amine) as nucleophile for the optimization of reaction conditions (Table 3).

Table 3. Optimization of the reaction conditions for synthesis of 7a[a]



Entry no.	Catalyst (mol %)	Ligand (mol %)	Solvent	Morpholine (equiv.)	Base (equiv.)	Time (h)	Yield (%)[b]
1	$Pd(OAc)_2$ (2.5)	Ph_3P (5)	CH_3CN	2	K_2CO_3 (2)	24	15
2	$Pd(OAc)_2$ (5)	Ph_3P (10)	CH_3CN	2	K_2CO_3 (2)	24	20
3	$Pd(OAc)_2$ (5)	Ph_3P (10)	CH_3CN	3	K_2CO_3 (2)	24	30
4	$Pd(OAc)_2$ (5)	Ph_3P (10)	CH_3CN	4	K_2CO_3 (2)	13	80
5	$Pd(OAc)_2$ (5)	Ph_3P (10)	CH_3CN	5	K_2CO_3 (2)	13	80
6	$Pd(OAc)_2$ (10)	Ph_3P (20)	CH_3CN	4	K_2CO_3 (2)	13	70
7	$PdCl_2$ (5)	Ph_3P (10)	CH_3CN	4	K_2CO_3 (2)	18	40
8	$Pd(dba)_2$ (5)	Ph_3P (10)	CH_3CN	4	K_2CO_3 (2)	15	60
9	$Pd(OAc)_2$ (5)	Cy_3P (10)	CH_3CN	4	K_2CO_3 (2)	20	50
10	$Pd(OAc)_2$ (5)	BINAP (10)	CH_3CN	4	K_2CO_3 (2)	15	60
11	$Pd(OAc)_2$ (5)	Ph_3P (10)	CH_3CN	4	K_3PO_4 (2)	13	75
12	$Pd(OAc)_2$	Ph_3P	CH_3CN	4	Cs_2CO_3	24	25

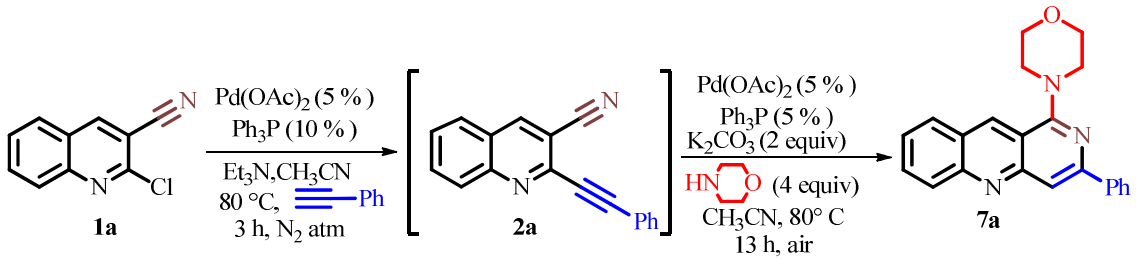
	(5)	(10)			(2)		
13	$Pd(OAc)_2$ (5)	Ph_3P (10)	DMF	4	K_2CO_3 (2)	18	40
14	$Pd(OAc)_2$ (5)	Ph_3P (10)	DMSO	4	K_2CO_3 (2)	20	35
15[c]	**$Pd(OAc)_2$ (5)**	**Ph_3P (10)**	**CH_3CN**	**4**	**K_2CO_3 (2)**	**13**	**78**

[a] All the reactions performed in 0.5 mmol scale. [b]Isolated yield. [c]One-pot sequential reaction of Sonogashira coupling and intramolecular cyclization reactions.

Initially, 2-phenylethynylquinoline-3-carbonitrile **2a** (0.5 mmol) was treated with 2.5 mol % of $Pd(OAc)_2$, 5 mol % of PPh_3 and 2 equiv morpholine along with 2 equiv K_2CO_3 in CH_3CN at 80 °C under air atomophere. The starting material was not completely consumed even after 24 h and isolated product 1-(morpholin-4-yl)-3-phenylbenzo[b][1,6]naphthyridine **7a** was obtained in 15 % yield (Table 3, entry 1). On increasing the mol % of $Pd(OAc)_2$ to 5 % and Ph_3P to 10 % , the reaction completed in 24 h with **7a** isolated in 20 % yield (entry 2). Further, using 3 equiv of morpholine under similar condition, the reaction completed in 24 h with yield increased to 30% (entry 3). However, using 4 equiv of morpholine, the reaction completed in 13 h and yield of **7a** enhanced upto 80 % (entry 4). Further, increasing the equivalency of morpholine did not improve the yield of **7a** (entry 5). On the other hand, increasing the mol% of $Pd(OAc)_2$ to 10 % and Ph_3P to 20 % along with 4 equiv morpholine and 2 equiv K_2CO_3 did not improve the yield (entry 6). Other palladium catalysts such as $PdCl_2$ and $Pd(dba)_2$ also did not improve the yield of **7a** (entries 7-8). Similarly, other ligands such as monodentate ligand Cy_3P and bidentate ligand BINAP were found to be less effective (entries 9-10) than Ph_3P (entry 4). Other inorganic bases such as K_3PO_4 and Cs_2CO_3 were also screened. K_3PO_4 was found equally effective (entry 11) as K_2CO_3 (entry 3). However, Cs_2CO_3 was found to be less effective (entry 12). Similarly, solvents such as DMF and DMSO were found to be less effective (entries 13-14) than CH_3CN (entry 3). Thus, the combination of 0.5 mmol of **2a** with 5 mol % $Pd(OAc)_2$, 10 mol % Ph_3P, 4 equiv morpholine and 2 equiv K_2CO_3 in acetonitrile at 80°C under aerobic atmosphere is an optimal reaction condition for the best yield of **7a** (entry 3). We next examined one-pot stepwise reactions from 2-chloroquinoline-3-carbonitrile **1a** *via* Sonogashira coupling and annulation reaction with a view to save time, solvents and avoid the column chromatography separation of **2a** (Table 3, entry 15). Thus, a mixture of 2-chloroquinoline-3-carbonitrile **1a** (0.5 mmol) and phenylacetylene (0.6 mmol) were treated with 5 mol % of $Pd(OAc)_2$, 10 mol % of PPh_3 and 2 equiv Et_3N in acetonitrile at 80°C for 3 h under N_2 for Sonogashira coupling and subsequently added 5 mol % $Pd(OAc)_2$, 10 mol % Ph_3P and 4 equiv morpholine along with 2

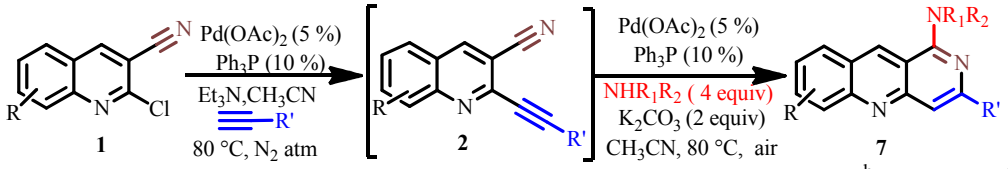
equiv K_2CO_3 in acetonitrile and heated at 80°C under aerobic atmosphere. The reaction was completed in 13 h with **7a** isolated in 78% overall yield (Scheme 5).

Scheme 5. One-pot stepwise Sonogashira coupling and annulation using morpholine

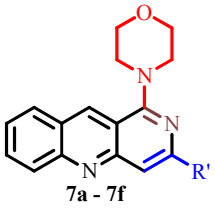


With the one-pot stepwise optimum reaction condition in hand, the scope of reaction with various alkynes was carried out. These results are summarized in Table 4. The reactions proceeded smoothly and completed in 10-15 h affording the corresponding cyclized products **7(a-e)** in 74-80 % yields (Table 4). The reaction with alkyl acetylenes such as oct-1-yne failed to provide the cyclized product **7f**, as a complex TLC was observed. The scope of the reaction was further examined with various quinoline derivatives. All the reactions proceeded smoothly and completed in 9-18 h affording the products **7(g- k)** in 65-74% yield. Various secondary amines such as piperidine, pyrolidine and dimethyl amine were also examined as nucleophiles for cyclization reaction. Cyclic secondary amines such as piperidine and pyrolidine afforded the cyclized product in good yield**7(l- m)**, however acyclic amine such as dimethylamine failed to provide the product **7n** with only coupling product 2-phenylethynylquinolin-3-carbonitrile **2a** recovered even after prolonged heating which could be due to steric effect. The reaction was also successful with pyridine analogue with the cyclized product **8a** obtained in 65% yield. The structure of cyclized product was further confirmed by the single crystal X-ray analysis of compound **7i** (Figure S2).

Table 4. Reaction scope for the synthesis of amino substituted benzo[b][1,6]naphthyridines[a]

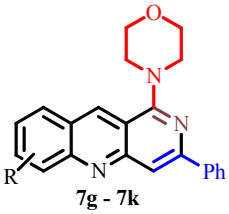


Product no., yield,[b] Time (C/A)[c]



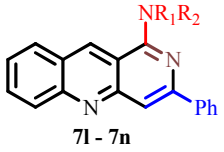
7a - 7f

7a, R' = Ph, 78%, 3 h / 13 h
7b, R' = m-tolyl, 75 % , 3.5 h / 15 h
7c, R' = p-tolyl, 74 % , 3.5 h / 15 h
7d, R' = 4MeO-C_6H_4, 80 % , 4 h / 17 h
7e, R' = 4F-C_6H_4, 83% , 2.5 h / 10 h
7f, R' =C_6H_{13}, 00 % , 12h[d] / 24 h



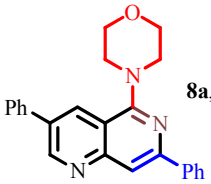
7g - 7k

7g, R = 6-Me, 74 %, 3 h / 16 h
7h, R = 7-Me, 74 %, 4.5 h / 16 h
7i, R = 6-MeO, 72 %, 5 h / 18 h
7j, R = 7-MeO, 70 %, 5 h / 18 h
7k, R = 7-Cl, 75 %, 3 h / 9 h



7l - 7n

7l, NR_1R_2 = Piperidine, 60 %, 3 h / 15 h
7m, NR_1R_2 = Pyrrolidine, 71 %, 3 h / 12 h
7n, NR_1R_2 = $(CH_3)_2NH$, 00%, 3 h / 24 h

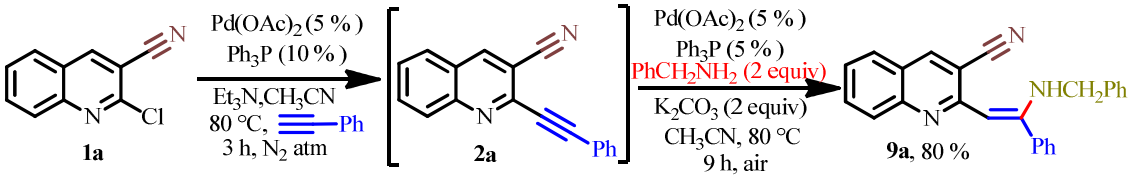


8a, 65%, 3 h/ 14 h

Conditions:[a] (i) Sonogashira coupling: 5 mol % $Pd(OAc)_2$, 10 mol % Ph_3P, 2 equiv Et_3N, CH_3CN, 80 °C, N_2 atm; (ii) Annulation: 5 mol % $Pd(OAc)_2$, 10 mol % Ph_3P, 2° amine (4 equiv), K_2CO_3 (2 equiv), CH_3CN, 80 °C, air. [b] Overall isolated yields over two steps. [c] [C/A] = coupling time/annulation time. [d]Sonogashira coupling reaction condition for aliphatic alkynes: 5 mol % $Pd(OAc)_2$, 10 mol % Ph_3P, 15% CuI, 2 equiv Et_3N, CH_3CN, 80 °C, N_2 atm .

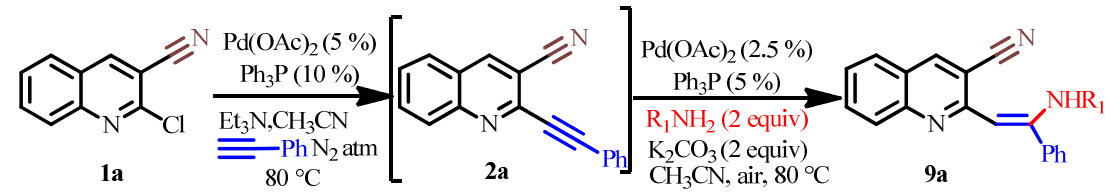
We next explored the scope of reaction with primary amines. Using the optimal stepwise reaction condition of secondary amines, the reaction was attempted with 2 equiv of benzyl amine (a primary amine). The reaction completed in 9 h, surprisingly isolating hydroamination product **9a** via addition across carbon-carbon tripe bond (Scheme 6) and no cyclization reaction occurred.

Scheme 6. One-pot stepwise Sonogashira coupling and annulation attempt using benzyl amine

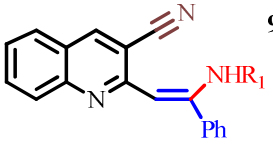


The reaction was also examined with other primary alkylamines such as *n*-butyl, *i*-propyl and cyclohexyl as nucleophiles under similar reaction condition. But in all cases only the hydroamination products **9b-d** was isolated (Table 5). The structure of hydroamination product was further confirmed by the single crystal X-ray analysis of compound **9c** (Figure S3).

Table 5. Substrate scope for the hydroamination reactions[a]



Product no., yield, Time (C/Ha)[b]



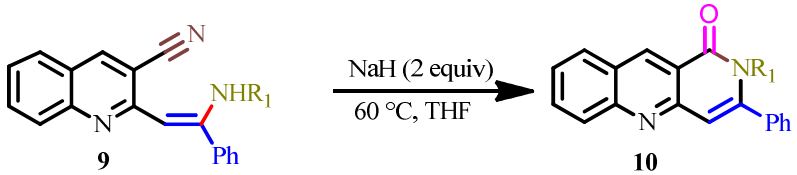
9b, R_1 = *n*-Butyl, 83 %, 3 h/ 7 h **9c**, R_1 = i-Propyl, 78 % , 3 h/ 4 h

9d, R_1 = cyclohexyl, 76 % , 3 h/ 12 h

Conditions: [a] (i) Sonogashira coupling: 5 mol % $Pd(OAc)_2$, 10 mol % Ph_3P, 2 equiv Et_3N, CH_3CN, 80 °C, N_2 atm; (ii) Hydramination: 2.5 mol % $Pd(OAc)_2$, 5 mol % Ph_3P, Primary amines (2 equiv), K_2CO_3 (2 equiv), CH_3CN, 80 °C, air. [b] [C/Ha] = coupling time/Hydro-amination time. [c] Overall isolated yields over two steps.

Next, we became interested to cyclize the hydroamination products **9** (Scheme 6). Thus, hydroamination products **9** were treated with 2 equiv sodium hydride in THF at 60^0C under aerobic condition. The reactions completed in 14-16 h affording benzo[b][1,6]naphthyridin-1(2H)-ones **10a-b** as a single product in 75-80% yields (Scheme 7).

Scheme 7. Base mediated synthesis of benzo[b][1,6]naphthyridin-1(2H)-ones



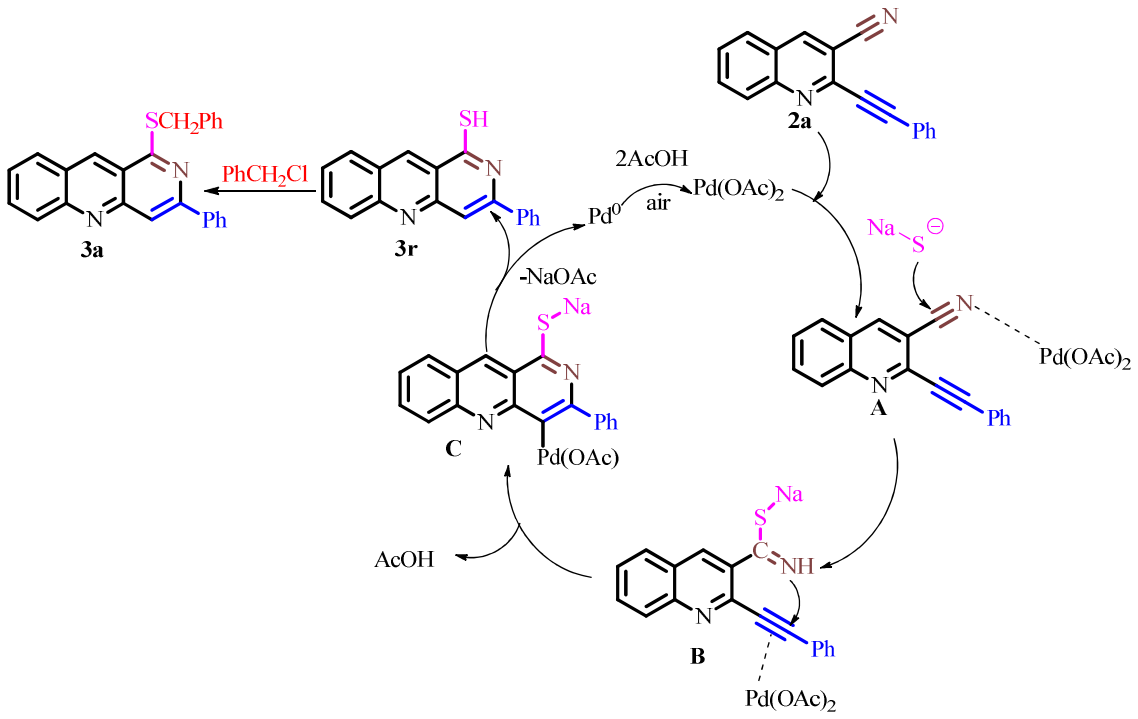
9 **10**

10a, R_1 = $PhCH_2$, 80%, 16 h

10b, R_1 = $(CH_2)_3CH_3$, 75%, 14 h

A plausible mechanism for Pd-catalyzed cyclization is illustrated in Scheme 8. In this reaction $Pd(OAc)_2$ plays dual role[22c]: (1) as a Lewis acid which forms complex **A** with the nitrogen atom of the cyano group, facilitating the nucleophilic attack of $^-$SNa ion on carbon atom of cyano group; (2) as a transition metal catalyst which forms complex **B** with π-electrons of alkyne; (3) complex **B** undergoes cyclization to give organopalladium intermediate **C** which on protonation gives **3r** and exclusion of Pd^0 which upon aerial oxidation gets converted to Pd(II). Further, quenching with benzyl chloride gives cyclized product **3a**.

Scheme 8. Proposed Mechanism for annulation process



CONCLUSIONS

In summary, we have developed palladium-catalyzed one-pot stepwise synthesis of sulphur and nitrogen appended benzo[b][1,6]naphthyridines using sodium sulphide and secondary amines as nucleophiles with 2-chloroquinoline-3-carbonitriles respectively. The protocol involved making of four new bonds (C-C, S-C, N-C and S-C bonds) for sulphur substituted and three bonds (one C-C and two N-C bonds) for nitrogen substituted benzo[b][1,6]naphthyridines all in stepwise manner. With thiols and primary amines addition products across C-C triple bond were obtained. The hydroamination products were transformed into benzo[b][1,6]naphthyridin-1(2H)-ones in good yields.

EXPERIMENTAL SECTION

General Methods

Unless otherwise stated, all reactions were performed under nitrogen atmosphere and air successively. Solvents were purified following standard literature procedures. Melting points were measured in an open capillary tube and are uncorrected. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a 300 MHz spectrometer. Multiplicities are given as: s (singlet), brs (broad singlet), d (doublet), t (triplet), dd (doublet of doublets) or m (multiplet).

The chemical shifts (δ ppm) and coupling constants (*J* Hz) are reported in the standard fashion with reference to either internal tetramethylsilane (for ^{1}H) or the central line (77.0 ppm) of $CDCl_3$ (for ^{13}C). Moisture and residual peak of $CDCl_3$ appear at δ 1.5 and 7.2 ppm respectively in ^{1}H NMR. High resolution mass spectra (HRMS) were obtained on TOF/6500 SRIES QTOF B.05.00 (B5042.0). Thin-layer chromatographies (TLC) were performed on glass plates (7.5 x 2.5 and 7.5 x 5.0 cm) coated with silica gel GF 254 and various combinations of ethyl acetate and hexane were used as eluent. Visualisation of spots was accomplished by exposure to UV light. Silica gel (60-120 mesh) was used for column chromatography (approximately 15-20 g per 1g of the crude product).

Procedure for Palladium-catalyzed synthesis of 1-Benzylsulfanyl-3-phenyl-benzo[b][1,6]naphthyridine (3a).

A mixture of 2-phenylethynylquinolin-3-carbonitrile **2a** (0.50 mmol), 2.5 mol% of $Pd(OAc)_2$, 5 mol% of PPh_3 and 2 equiv $Na_2S.9H_2O$ were added in 2 mL of DMF and reaction was heated at 80°C under aerobic atmosphere. After completion of reaction, the reaction mixture was quenched by benzyl chloride (2 equiv). The mixture was diluted with water, extracted with ethyl acetate, washed with brine solution and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography on silica gel using EtOAc/hexane to afford **3a**.

General procedure for the one-pot synthesis of 1,3-disubstituted benzo[b][1,6]naphthyridines (3).

A mixture of substituted 2-chloroquinoline-3-carbonitrile (**1a**) (0.50 mmol), alkynes (1.2 equiv), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %) and triethylamine (2 eq.) in CH_3CN (2.0 mL) were heated under N_2 at 80°C. After completion of reaction (as monitored by TLC), solvent was evaporated under reduced pressure and DMF (2.0 mL) was added followed by $Pd(OAc)_2$ (2.5 mol %), PPh_3 (5 mol %), and $Na_2S.9H_2O$ (2 equiv) respectively and heated at 80 °C under aerobic atmosphere. After completion of reaction, the reaction mixture was quenched by appropriate alkyl halides (2 equiv). The mixture was diluted with water, extracted with ethyl acetate, washed with brine solution and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography on silica gel using EtOAc/hexane to afford the products **3a-q**.

1-Benzylsulfanyl-3-phenyl-benzo[b][1,6]naphthyridine(3a)

Red solid; yield: 156.8 mg, 83%; mp 169-170 °C; R_f= 0.35 (05:95 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ= 4.85 (s, 2H), 7.27-7.39 (m, 2H), 7.45-7.59 (m, 7H), 7.87 (t, *J* =7.2 Hz,

1H), 8.01 (d, *J* = 8.4 Hz, 1H), 8.19 (d, *J* = 10.8 Hz, 2H), 8.28 (d, *J* = 7.5 Hz, 2H), 9.11 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 34.5, 112.1, 119.7, 126.0, 126.3, 127.0, 127.3, 128.1, 126.7, 128.7, 129.0, 129.2, 130.7, 132.8, 134.5, 137.2, 138.2, 149.8, 150.6, 152.2, 161.5 ppm; IR (KBr, cm^{-1}): 1595, 2926; HRMS (ESI) m/e calcd for $C_{25}H_{19}N_2S$ $[M+H]^+$ 379.1263, found 379.1281.

1-Benzylsulfanyl-3-m-tolyl-benzo[b][1,6]naphthyridine (3b).

Yellow solid; yield: 164.6 mg, 84%; mp 185-186 °C; R_f = 0.35 (05:95 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ= 2.47 (s, 3H), 4.84 (s, 2H), 7.27-7.44 (m, 5H), 7.55 (t, *J* = 8.4 Hz, 3H), 7.86 (t, *J* = 7.2 Hz, 1H), 8.02 (t, *J* = 8.4 Hz, 3H), 8.16 (t, *J* = 8.7 Hz, 2H), 9.10 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6, 34.4, 113.0, 119.8, 124.1, 126.1, 127.3, 127.7, 128.6, 128.6, 128.8, 128.9, 129.0, 129.9, 132.3, 133.8, 137.4, 138.2, 138.8, 150.5, 151.5, 152.0, 161.2 ppm; IR (KBr, cm^{-1}): 1596, 2926; HRMS (ESI) m/e calcd for $C_{26}H_{21}N_2S$ $[M+H]^+$ 393.1420, found 393.1434.

1-Benzylsulfanyl-3-p-tolyl-benzo[b][1,6]naphthyridine (3c).

Yellow solid; yield: 166.6 mg, 85%; mp 140-141 °C; R_f = 0.35 (05:95 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ= 2.44 (s, 3H), 4.85 (s, 2H), 7.27-7.40 (m, 5H), 7.54 (t, *J* = 11.7 Hz, 3H), 7.86 (t, *J* = 7.5 Hz, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 8.17 (t, *J* = 8.1 Hz, 4H), 9.09 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3, 34.4, 112.3, 119.7, 126.1, 126.8, 127.3, 128.6, 129.0, 129.5, 130.7, 132.3, 133.8, 135.7, 137.4, 139.2, 150.5, 151.4, 151.9, 161.2 ppm; IR (KBr, cm^{-1}) : 1593, 2926; HRMS (ESI) m/e calcd for $C_{26}H_{21}N_2S$ $[M+H]^+$ 393.1420, found 393.1434.

1-Benzylsulfanyl-3-(4-fluoro-phenyl)-benzo[b][1,6]naphthyridine (3d).

Light yellow solid; yield: 164.3 mg, 83%; mp 159-160 °C; R_f = 0.35 (05:95 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ= 4.83 (s, 2H), 7.20 (t, *J* = 8.7 Hz, 1H), 7.28-7.36 (m, 3H), 7.51-7.60 (m, 4H), 7.87 (t, *J* = 7.8 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 8.09 (s, 1H), 8.17-8.27 (m, 3H), 9.11 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 34.5, 112.5, 115.5, 115.8, 119.7, 126.2, 127.4, 128.6, 128.7, 128.8, 129.0, 130.0, 132.4, 133.8, 134.6, 134.6, 137.2, 150.3, 150.8, 151.5, 161.6 ppm; IR (KBr, cm^{-1}): 1599, 2924; HRMS (ESI) m/e calcd for $C_{25}H_{18}FN_2S$ $[M+H]^+$ 397.1169, found 397.1184.

1-Benzylsulfanyl-3-propyl-benzo[b][1,6]naphthyridine (3e).

Red solid; yield: 137.6 mg, 80%; mp 97-98 °C; R_f = 0.35 (05:95 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ= 1.04 (t, J= 7.2 Hz, 3H), 1.88-1.95 (m, 2H), 2.94 (t, *J* = 7.5 Hz, 2H), 4.70 (s, 2H), 7.27-7.36 (m, 4H), 7.48-7.56 (m, 3H), 7.83 (t, *J* = 7.2 Hz, 1H), 7.98 (d, *J* = 8.4

Hz, 1H), 8.15 (d, *J* = 8.7 Hz, 1H), 9.06 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 22.0, 34.0, 40.2, 114.9, 119.2125.8, 125.9, 127.1, 128.4, 128.8, 128.9, 129.1, 132.1, 133.7, 150.3, 151.2, 157.5, 160.5 ppm; IR (KBr, cm^{-1}): 1603, 2956; HRMS (ESI) m/e calcd for $C_{22}H_{21}N_2S$ $[M+H]^+$ 345.1420, found 345.1426.

1-Benzylsulfanyl-3-hexyl-benzo[b][1,6]naphthyridine (3f).

Yellow liquid; yield: 150.5 mg, 78%; mp R_f = 0.35 (05:95 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ= 0.89 (t, *J* = 5.7 Hz, 3H), 1.32-1.43 (m, 6H), 1.92-1.92 (m, 2H), 2.96 (t, *J* = 7.5 Hz, 2H), 4.71 (s, 2H), 7.29-7.34 (m, 4H), 7.48-7.56 (m, 3H), 7.83 (t, *J* = 7.2 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 8.15 (d, *J* = 8.7 Hz, 1H), 9.06 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 22.6, 28.8, 28.9, 31.7, 34.0, 38.1, 114.8, 119.3, 125.8, 125.9, 127.1, 128.4, 128.8, 129.0, 129.1, 132.2, 133.9, 138.0, 150.4, 151.2, 157.8, 160.5 ppm; IR (KBr, cm^{-1}): 1621, 2945; HRMS (ESI) m/e calcd for $C_{25}H_{27}N_2S$ $[M+H]^+$ 387.1889, found 387.1906.

1-Benzylsulfanyl-3-thiophen-3-yl-benzo[b][1,6]naphthyridine (3g).

Light green solid; yield: 140.1 mg, 73%; mp 82-83 °C; R_f = 0.35 (05:95 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ= 4.04 (s, 2H), 7.32 (d, *J* = 7.8 Hz, 3H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.67-7.75 (m, 4H), 7.87 (d, *J* = 8.4 Hz, 2H), 8.03 (s, 1H), 8.06 (s, 1H), 8.86 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 42.8, 108.9, 114.5, 124.2, 125.3, 125.4, 126.1, 128.5, 128.9, 129.0, 130.8, 131.9, 135.9, 135.9, 142.6, 147.9, 150.6, 153.7, 161.6, 162.1 ppm; IR (KBr, cm^{-1}): 1590, 2926; HRMS (ESI) m/e calcd for $C_{23}H_{17}N_2S_2$ $[M+H]^+$ 385.0828, found 385.0841.

1-Benzylsulfanyl-8-methyl-3-phenyl-benzo[b][1,6]naphthyridine (3h).

Orange solid; yield 152.8 mg, 78%; mp 158-159 °C; R_f = 0.35 (05:95 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ= 2.57 (s, 3H), 4.84 (s, 2H), 7.27-7.36 (m, 4H), 7.41-7.54 (m, 4H), 7.68-7.81 (m, 3H), 8.10 (t, *J* =13.5 Hz, 2H), 8.27 (d, *J* = 7.5 Hz, 1H), 8.98 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6, 34.4, 112.3, 119.8, 121.2, 126.2, 126.9, 127.3, 128.6, 128.7, 129.0, 129.8, 133.2, 135.2, 135.6, 136.4, 137.4, 138.4, 149.3, 149.6, 151.7, 161.2 ppm; IR (KBr, cm^{-1}): 1614, 2925; HRMS (ESI) m/e calcd for $C_{26}H_{21}N_2S$ $[M+H]^+$ 393.1420, found 393.1433.

1-Benzylsulfanyl-7-methyl-3-phenyl-benzo[b][1,6]naphthyridine (3i).

Light yellow solid; yield: 152.8 mg, 78%; mp 145-146 °C; R_f = 0.35 (05:95 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ= 22.58 (s, 3H), 4.84 (s, 2H), 7.27-7.36 (m, 3H), 7.44-7.54 (m, 5H), 7.69-7.81 (m, 3H), 8.04-8.16 (m, 2H), 8.27 (d, *J* = 7.2 Hz, 1H), 8.99 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6, 34.4, 113.0, 120.0, 126.5, 126.7, 127.0, 127.4, 128.7, 128.8, 129.1, 129.2, 130.0, 133.0, 135.5, 136.4, 137.6, 138.7, 150.0, 150.5, 151.7, 161.3 ppm; IR

(KBr, cm^{-1}): 1613, 2924; HRMS (ESI) m/e calcd for $C_{26}H_{21}N_2S$ $[M+H]^+$ 393.1420, found 393.1424.

1-Benzylsulfanyl-6-methyl-3-phenyl-benzo[b][1,6]naphthyridine (3j).

Light yellow solid; yield: 148.9 mg, 76%; mp 95-98 °C; R_f= 0.35 (05:95 EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$): δ= 2.92 (s, 3H), 4.85 (s, 2H), 7.29-7.35 (m, 3H), 7.45-7.55 (m, 5H), 7.68 (t, *J* =6.3 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 8.21 (s, 1H), 8.31 (d, *J* = 6.9 Hz, 1H), 9.04 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.2, 34.4, 113.7, 119.7, 126.1, 126.9, 127.0, 127.3, 128.5, 128.6, 128.7, 128.9, 129.0, 131.6, 132.3, 133.6, 138.7, 142.8, 149.8, 151.1, 151.4, 161.0 ppm; IR (KBr, cm^{-1}): 1610, 2926; HRMS (ESI) m/e calcd for $C_{26}H_{21}N_2S$ $[M+H]^+$ 393.1420, found 393.1428.

1-Benzylsulfanyl-7-chloro-3-phenyl-benzo[b][1,6]naphthyridine (3k).

Yellow solid; yield: 154.5 mg, 75%; mp 92-93 °C; R_f= 0.35 (05:95 EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$): δ= 4.85 (s, 2H), 7.05 (s, 1H), 7.31-7.36 (m, 2H), 7.44-7.53 (m, 6H), 7.95 (d, *J* =9.0 Hz, 1H), 8.10 (d, *J* = 17.7 Hz, 2H), 8.27 (d, *J* = 7.5 Hz, 2H), 9.08 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 34.5, 112.7, 119.7, 121.4, 124.4, 127.0, 128.6, 128.8, 129.0, 129.4, 130.2, 133.9, 137.2, 138.3, 138.7, 139.5, 141.8, 148.3, 151.4, 152.4, 161.6 ppm; IR (KBr, cm^{-1}): 1610, 2926; HRMS (ESI) m/e calcd for $C_{25}H_{18}ClN_2S$ $[M+H]^+$ 413.0874, found 413.0872.

1-Methylsulfanyl-3-phenyl-benzo[b][1,6]naphthyridine (3l).

Yellow solid; yield: 125.3 mg, 83%; mp 133-134 °C; R_f = 0.35 (05:95 EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$): δ= 2.91 (s, 3H), 7.45-7.61 (m, 4H), 7.88 (t, *J* = 7.2 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 8.18 (t, *J* = 8.7 Hz, 2H), 8.31 (d, *J* = 7.2 Hz, 2H), 9.13 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ =13.1, 112.3, 120.0, 126.1, 126.9, 127.9, 128.7, 128.8, 129.0, 129.1, 132.3, 133.7, 138.5, 150.3, 151.3, 151.7, 162.2 ppm; IR (KBr, cm^{-1}): 1604, 2926; HRMS (ESI) m/e calcd for $C_{19}H_{15}N_2S$ $[M+H]^+$ 303.0950, found 303.0960.

1-Ethylsulfanyl-3-phenyl-benzo[b][1,6]naphthyridine (3m).

Light yellow solid; yield: 126.4 mg, 80%; mp 107-108 °C; R_f= 0.35 (05:95 EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$): δ= 1.58 (t, *J* = 7.5, 3H), 3.58 (q, *J* = 7.2, 2H), 7.45-7.57 (m, 4H), 7.87 (t, *J* = 7.8 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 8.17 (t, *J* = 8.7 Hz, 2H), 8.28 (d, *J* = 7.2 Hz, 2H), 9.12 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ =14.3, 24.5, 112.4, 120.1, 126.0, 126.8, 127.8, 128.6, 128.8, 129.0, 129.0, 132.2, 133.7, 138.6, 150.4, 151.4, 151.7, 161.8 ppm; IR (KBr, cm^{-1}) : 1603, 2926; HRMS (ESI) m/e calcd for $C_{20}H_{17}N_2S$ $[M+H]^+$ 317.1107, found 317.1123.

1-Pentylsulfanyl-3-phenyl-benzo[b][1,6]naphthyridine (3n).

Light green solid; yield: 139.6 mg, 78%; mp 82-83 °C; R_f = 0.35 (05:95 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ= 0.95 (t, *J* = 7.2, 3H), 1.39-1.59 (m, 4H), 1.88-1.98 (m, 2H), 3.55 (t, *J* = 7.2, 2H), 7.42-7.59 (m, 4H), 7.86 (t, *J*= 7.2 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 8.16 (t, *J* = 8.7 Hz, 2H), 8.27 (d, *J* = 7.2 Hz, 2H), 9.12 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 22.3, 28.8, 30.1, 31.3, 112.3, 120.1, 126.0, 126.1, 126.8, 128.6, 128.8, 129.0, 129.0, 132.2, 133.8, 138.5, 150.4, 151.3, 151.7, 162.0 ppm; IR (KBr, cm^{-1}): 1597, 2926; HRMS (ESI) m/e calcd for $C_{23}H_{23}N_2S$ $[M+H]^+$ 359.1576, found 359.1584.

1-Hexylsulfanyl-3-phenyl-benzo[b][1,6]naphthyridine (3o).

Light yellow solid; yield: 143.2 mg, 77%; mp 77-78 °C; R_f = 0.35 (05:95 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ= 0.91 (t, *J* = 6.6, 3H), 1.30-1.42 (m, 4H), 1.54-1.63 (m, 2H), 1.87-1.97 (m, 2H), 3.56 (t, *J* = 7.5, 2H), 7.44-7.59 (m, 4H), 7.86 (t, *J* = 6.9 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 8.18 (t, *J* = 8.7 Hz, 2H), 8.28 (d, *J* = 7.5 Hz, 2H), 9.13 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 22.5, 28.9, 29.2, 30.2, 31.4, 112.1, 120.2, 126.1, 126.4, 126.9, 128.7, 129.0, 129.1, 130.2, 132.4, 134.1, 138.5, 150.3, 151.1, 151.9 ppm; IR (KBr, cm^{-1}): 1601, 2926; HRMS (ESI) m/e calcd for $C_{24}H_{25}N_2S$ $[M+H]^+$ 373.1733, found 373.1745.

1-Allylsulfanyl-3-phenyl-benzo[b][1,6]naphthyridine (3p).

Yellow solid; yield: 131.2 mg, 80%; mp 123-124 °C; R_f = 0.35 (05:95 EtOAc/hexane) ; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 4.25 (d, *J* = 6.6, 3H), 5.21 (d, *J* = 9.9, 1H), 5.45 (d, *J* = 17.4, 1H), 6.12-6.21 (m, 1H), 7.45-7.61 (m, 5H), 7.87 (t, *J* = 7.2 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 8.18 (t, *J* = 8.7 Hz, 1H), 8.28 (d, *J* = 7.2 Hz, 2H), 9.13 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.8, 112.7, 118.0, 119.9, 126.1, 126.8, 128.6, 128.7, 128.8, 129.0, 129.1, 132.2, 133.4, 133.7, 138.4, 150.3, 151.4, 151.6, 161.0 ppm; IR (KBr, cm^{-1}) : 1590, 2926; HRMS (ESI) m/e calcd for $C_{21}H_{17}N_2S$ $[M+H]^+$ 329.1107, found 329.1116.

3-Phenyl-1-prop-2-ynylsulfanyl-benzo[b][1,6]naphthyridine (3q).

Red solid; yield: 122.2 mg, 75%; mp 88-89 °C; R_f = 0.35 (05:95 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ= 2.57 (s, 1H), 4.35 (d, *J* = 2.1 Hz, 2H), 7.19(s, 1H), 7.43-7.62 (m, 4H), 7.88 (t, *J* = 7.2 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 8.18 (s, 1H), 8.30 (d, *J* = 7.5 Hz, 2H), 9.07 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.6, 70.8, 79.5, 113.2, 119.7, 126.2, 126.4, 127.0, 128.8, 129.0, 129.0, 129.2, 132.5, 133.6, 138.4, 143.1, 150.4, 151.9, 159.6 ppm; IR (KBr, cm^{-1}): 1612, 2926; HRMS (ESI) m/e calcd for $C_{21}H_{15}N_2S$ $[M+H]^+$ 327.0950, found 327.0954.

5-Benzylsulfanyl-3,7-diphenyl-[1,6]naphthyridine (5a).

White solid; yield: 159.5 mg, 79%; mp 179-180 °C; R_f = 0.35 (05:95 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ= 4.81 (s, 2H), 7.28-7.34 (m, 2H), 7.42-7.55 (m, 9H), , 7.70 (d, *J* = 7.2 Hz, 2H), 8.10 (s, 1H), 8.23 (d, *J* = 7.5 Hz, 2H), 8.59 (s, 1H), 9.29 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ= 34.4, 113.8, 120.9, 126.8, 127.2, 128.4, 128.4, 128.5, 128.7, 128.9, 129.0, 129.1, 129.2, 129.6, 134.2, 136.9, 137.5, 138.0, 138.4, 150.3, 152.9, 154.0, 159.7 ppm; IR (KBr, cm^{-1}): 1581, 2923; HRMS (ESI) m/e calcd for $C_{27}H_{21}N_2S$ $[M+H]^+$ 405.1420, found 405.1423.

Procedure for one-pot synthesis of *3-Phenyl-benzo[b][1,6]naphthyridine-1-thiol 3r*.

A mixture of substituted 2-chloroquinoline-3-carbonitrile (**1a**) (0.50 mmol), alkynes (1.2 equiv), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %) and triethylamine (2 eq.) in CH_3CN (2.0 mL) were heated under N_2 at 80°C. After completion of reaction (as monitored by TLC), solvent was evaporated under reduced pressure and DMF (2.0 mL) was added followed by $Pd(OAc)_2$ (2.5 mol %), PPh_3 (5 mol %), and $Na_2S.9H_2O$ (2 equiv) and heated at 80 °C under aerobic atmosphere. After completion of reaction, the reaction mixture was quenched by addition of water, extracted with ethyl acetate, washed with brine solution and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography on silica gel using EtOAc/hexane to afford the products **3r**.

3-Phenyl-benzo[b][1,6]naphthyridine-1-thiol (3r).

Red solid; yield: 112.3 mg, 78%; mp 80-81 °C; R_f = 0.35 (05:95 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ= 2.91 (s, 3H), 7.45-7.61 (m, 4H), 7.88 (t, *J* = 7.2 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 8.18 (t, *J* = 8.7 Hz, 2H), 8.31 (d, *J* = 7.2 Hz, 2H), 9.13 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ =13.1, 112.3, 120.0, 126.1, 126.9, 127.9, 128.7, 128.8, 129.0, 129.1, 132.3, 133.7, 138.5, 150.3, 151.3, 151.7, 162.2 ppm; IR (KBr, cm^{-1}): 1591, 2926; HRMS (ESI) m/e calcd for $C_{18}H_{13}N_2S$ $[M+H]^+$ 289.0794, found 289.0805.

Procedure for palladium-catalyzed synthesis of addition products 6.

To a solution 2-phenylethynylquinolin-3-carbonitrile **2a** (0.50 mmol) in DMF (2 mL) under aerobic atmosphere were added thiols (2 equiv), $Pd(OAc)_2$ (2.5 mol %), PPh_3 (5 mol %), K_2CO_3 (2 equiv) and the reaction mixture heated at 80 °C for 1-2 h. After completion of the reaction cold water was poured into the reaction mixture and extracted with ethyl acetate, dried over anhydrous sodium sulphate (Na_2SO_4), concentrated under vacuum and the residue was purified by column chromatography to afford products **6a-b**.

2-(2-ethylsulfanyl-2-phenyl-vinyl)-quinoline-3-carbonitrile (6a).

White solid; yield: 124.4 mg, 80%; mp 119-120 °C; R_f = 0.35 (05:95 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ= 1.07 (t, *J* = 7.2 Hz, 3H), 2.45 (q, *J* = 7.5 Hz, 2H), 7.09 (s, 1H), 7.39 (t, *J* = 10.8 Hz, 3H), 7.52-7.61 (m, 3H), 7.83 (q, *J* = 5.4 Hz, 2H), 8.23 (d, *J* = 8.4 Hz, 1H), 8.48 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4, 27.7, 106.3, 107.1, 121.9, 123.9, 127.3, 127.7, 128.4, 128.4, 129.2, 129.2, 132.5, 139.6, 142.2, 148.1, 152.6, 154.0 ppm; IR (KBr, cm^{-1}): 1548, 2221, 2924; HRMS (ESI) m/e calcd for $C_{20}H_{16}N_2NaS$ $[M+Na]^+$ 339.0926, found 339.0921.

2-(2-Phenyl-2-phenylsulfanyl-vinyl)-quinoline-3-carbonitrile (6b).

White solid; yield: 136.5 mg, 75 %; mp 127-128 °C; R_f = 0.35 (05:95 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.04 (s, 3H), 7.14-7.22 (m, 5H), 7.39 (d, *J* = 3.6 Hz, 2H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.82-7.89 (m, 2H), 8.28 (d, *J* = 8.1 Hz, 1H), 8.51 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 100.3, 106.3, 117.0, 122.4, 124.0, 127.2, 127.5, 127.7, 128.0, 128.2, 129.1, 129.2, 132.7, 133.3, 139.3, 142.3, 148.0, 151.3, 153.7 ppm; IR (KBr, cm^{-1}): 1582, 2222, 2956; HRMS (ESI) m/e calcd for $C_{24}H_{17}N_2S$ $[M+H]^+$ 365.1107, found 365.1104.

Procedure for Palladium-catalyzed synthesis of 7a.

A mixture of 2-phenylethynylquinolin-3-carbonitrile **2a** (0.50 mmol), $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), morpholine (2 equiv) and K_2CO_3 (2 equiv) in CH_3CN (4 mL) were stirred under aerobic condition at 80°C. After completion of the reaction (as monitored by TLC), cold water was added into the reaction mixture and extracted with ethyl acetate, dried over anhydrous sodium sulphate (Na_2SO_4), concentrated under vacuum. The residue was purified by column chromatography to afford product **7a**.

General procedure for one-pot synthesis of 1,3-disubstituted benzo[b][1,6]naphthyridines (7) from secondary amines.

A mixture of substituted 2-chloroquinoline-3-carbonitrile (**1**) (0.50 mmol), alkynes (1.2 equiv), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %) and triethylamine (2 equiv.) in CH_3CN (2 mL) were heated under N_2 at 80°C. After completion of reaction (as monitored by TLC), subsequently added $Pd(OAc)_2$ (5 mol %), Ph_3P (10 mol %) and morpholine (4 equiv) along with K_2CO_3 (2 equiv) in acetonitrile and heated at 80°C under aerobic atmosphere. After completion of reaction, the reaction mixture was diluted with water, extracted with ethyl acetate, washed with brine solution and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography on silica gel using EtOAc/hexane to afford the products **7a-m**.

1-Morpholin-4-yl-3-phenylbenzo[b][1,6]naphthyridine (7a).

Yellow solid; yield: 132.9 mg, 78%; mp 120-121 °C; R_f = 0.30 (05:95 EtOAc/hexane): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.69 (t, *J* = 4.5 Hz, 4H), 4.06 (t, *J* = 4.8 Hz, 4H), 7.42-7.58 (m, 4H), 7.85 (t, *J* = 7.8 Hz, 1H), 8.03 (t, *J* = 8.4 Hz, 2H), 8.18-8.27 (m, 3H), 8.95 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.9, 66.9, 111.3, 114.7, 125.8, 125.9, 126.9, 128.7, 128.8, 129.0, 129.0, 132.2, 135.0, 138.9, 151.0, 151.3, 153.2, 161.3 ppm; IR (KBr, cm^{-1}): 1600, 2850, 2919, 2955; HRMS (ESI) m/e calcd for $C_{22}H_{20}N_3O$ $[M+H]^+$ 342.1601, found 342.1604.

1-Morpholin-4-yl-3-m-tolylbenzo[b][1,6]naphthyridine (7b).

Light green solid; yield: 133.1 mg, 75%; mp 135-136 °C; R_f = 0.25 (05:95 EtOAc/hexane): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.43 (s, 3H), 3.68 (t, *J* = 3.0 Hz, 4H), 4.05 (t, *J* = 3.3 Hz, 4H), 7.30 (t, *J* = 8.1 Hz, 2H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.83 (t, *J* = 7.8 Hz, 1H), 8.00 (t, *J* = 8.4 Hz, 2H), 8.15 (t, *J* = 7.8 Hz, 3H), 8.92 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2, 51.8, 66.7, 110.4, 110.5, 114.4, 125.5, 126.7, 128.8, 129.3, 131.9, 134.7, 134.8, 136.0, 138.9, 150.8, 151.2, 153.0, 161.0 ppm; IR (KBr, cm^{-1}): 1605, 2932, 2958; HRMS (ESI) m/e calcd for $C_{23}H_{22}N_3O$ $[M+H]^+$ 356.1757, found 356.1748.

1-Morpholin-4-yl-3-p-tolylbenzo[b][1,6]naphthyridine (7c).

Light yellow solid; yield: 131.3 mg, 74%; mp 112-113 °C; R_f = 0.25 (05:95 EtOAc/hexane): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.47 (s, 3H), 3.68 (t, *J* = 4.2Hz, 4H), 4.06 (t, *J* = 4.5 Hz, 4H), 7.31 (t, *J* = 8.1 Hz, 2H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.85 (t, *J* = 7.8 Hz, 1H), 8.00 (t, *J* = 10.8 Hz, 2H), 8.16 (t, *J* = 8.4 Hz, 3H), 8.94 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2, 51.9, 66.8, 110.7, 114.5, 125.6, 125.7, 126.8 128.7, 128.9, 129.4, 132.0, 134.8, 136.1, 139.0, 151.0, 151.3, 153.2, 161.2 ppm; IR (KBr, cm^{-1}): 1595, 2933; HRMS (ESI) m/e calcd for $C_{23}H_{22}N_3O$ $[M+H]^+$ 356.1757, found 356.1758.

3-(4-Methoxy-phenyl)-1-morpholin-4-yl-benzo[b][1,6]naphthyridine (7d).

Light green solid; yield: 148.4 mg, 80%; mp 145-146 °C; R_f = 0.20 (05:95 EtOAc/hexane): ^{1}H NMR (300 MHz, $CDCl_3$); δ = 3.68 (t, *J* = 4.5Hz, 4H), 3.89 (s, 3H), 4.05 (t, *J* = 4.8 Hz, 4H), 7.03 (d, *J* = 8.7 Hz, 2H), 7.54 (t, *J* = 8.1 Hz, 1H), 7.84 (t, *J* = 8.1 Hz, 1H), 8.00 (t, *J* = 10.8 Hz, 2H), 8.20 (t, *J* = 8.4 Hz, 3H), 8.93 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.9, 55.2, 66.8, 109.8, 114.0, 114.3, 125.5, 125.6, 128.2, 128.6, 128.9, 131.4, 131.9, 132.1, 134.8, 150.9, 153.2, 160.4, 161.1 ppm; IR (KBr, cm^{-1}): 1522, 2922, 2957; HRMS (ESI) m/e calcd for $C_{23}H_{22}N_3O_2$ $[M+H]^+$ 372.1707, found 372.1707.

3-(4-Fluoro-phenyl)-1-morpholin-4-yl-benzo[b][1,6]naphthyridine (7e).

Yellow solid; yield: 148.9 mg, 83%; mp 151-152 °C; R_f = 0.25 (05:95 EtOAc/hexane): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.68 (t, *J* = 4.5 Hz, 4H), 4.05 (t, *J* = 4.2 Hz, 4H), 7.18 (t, *J* = 8.7 Hz, 2H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.85 (t, *J* =7.8 Hz, 1H), 8.01 (d, *J* = 8.1 Hz, 2H), 8.16-8.25 (m, 3H), 8.94 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.9, 66.8, 110.8, 111.0, 114.5, 115.4, 115.7, 125.9, 128.5, 128.7, 128.8, 128.9, 129.0, 132.2, 134.9, 135.0, 150.3, 151.0, 153.1, 161.3, 161.8, 165.1 ppm; IR (KBr, cm^{-1}): 1595, 2942, 2959; HRMS (ESI) m/e calcd for $C_{22}H_{19}FN_3O$ $[M+H]^+$ 360.1507, found 360.1503.

8-Methyl-1-morpholin-4-yl-3-phenylbenzo[b][1,6]naphthyridine (7g).

Yellow solid; yield: 131.3 mg, 74%; mp 128-129 °C; R_f = 0.35 (05:95 EtOAc/hexane): ^{1}H NMR (300 MHz, $CDCl_3$); δ = 2.58 (s, 3H), 3.66 (t, *J* = 4.2 Hz, 4H), 4.04 (t, *J* = 4.2 Hz, 4H), 7.39-7.52 (m, 3H), 7.68 (d, *J* = 8.7 Hz, 1H), 7.76 (s, 1H), 8.06 (d, *J* =11.7 Hz, 2H), 8.24 (d, *J* = 7.5 Hz, 2H), 8.83 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5, 51.8, 66.8, 111.2, 111.4, 114.6, 125.8, 126.6, 126.7, 128.5, 128.7, 133.5, 134.7, 135.5, 138.9, 149.8, 150.5, 152.4, 161.0 ppm; IR (KBr, cm^{-1}):1598, 2914, 2956; HRMS (ESI) m/e calcd for $C_{23}H_{22}N_3O$ $[M+H]^+$ 356.1757, found 356.1748.

7-Methyl-1-morpholin-4-yl-3-phenylbenzo[b][1,6]naphthyridine (7h).

Light yellow solid; yield: 131.3 mg, 74%; mp 118-119 °C; R_f = 0.35 (05:95 EtOAc/hexane): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.62 (s, 3H), 3.67 (t, *J* = 4.5 Hz, 4H), 4.05 (t, *J* = 4.2 Hz, 4H), 7.37-7.53 (m, 4H), 7.91 (t, *J* = 8.4 Hz, 2H), 8.04 (s, 1H), 8.25 (d, *J* = 7.2 Hz, 2H), 8.88 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.3, 51.9, 66.8, 111.3, 114.2, 124.2, 126.8, 127.1, 128.5, 128.8, 134.3, 138.9, 142.8, 151.0, 151.2, 153.1, 161.2 ppm; IR (KBr, cm^{-1}): 1602, 2908, 2962; HRMS (ESI) m/e calcd for $C_{23}H_{22}N_3O$ $[M+H]^+$ 356.1757,found 356.1749.

8-Methoxy-1-morpholin-4-yl-3-phenylbenzo[b][1,6]naphthyridine (7i).

Light green solid; yield: 133.5 mg, 72%; mp 141-142 °C; R_f = 0.35 (05:95 EtOAc/hexane): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.66 (t, *J* = 4.2 Hz, 4H), 4.00 (s, 3H), 4.07 (t, *J* = 4.5 Hz, 4H), 7.19 (d, *J* = 2.4 Hz, 1H), 7.41-7.55 (m, 4H), 8.07 (d, *J* = 10.2 Hz, 2H), 8.24 (d, *J* = 7.5 Hz, 2H), 8.80 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.9, 66.9, 104.1, 111.7, 115.0, 126.8, 127.0, 128.6, 130.4, 132.3, 132.4, 139.0, 148.1, 150.2, 151.6, 157.2, 160.9 ppm; IR (KBr, cm^{-1}): 1603, 2922, 2945; HRMS (ESI) m/e calcd for $C_{23}H_{22}N_3O_2$ $[M+H]^+$ 372.1707, found 372.1700.

7-Methoxy-1-morpholin-4-yl-3-phenylbenzo[b][1,6]naphthyridine (7j).

Light green solid; yield: 124.2 mg, 70%; mp 141-142 °C; R_f = 0.25 (05:95 EtOAc/hexane): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.59 (t, *J* = 3.6 Hz, 4H), 3.92 (s, 3H), 3.99 (t, *J* = 4.2 Hz, 4H), 7.10 (d, *J* = 1.8 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.40-7.48 (m, 3H), 8.00 (d, *J* = 11.4 Hz, 2H), 8.16 (d, *J* = 7.8 Hz, 2H), 8.72 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.9, 55.6, 66.9, 104.1, 111.6, 114.9, 126.7, 126.9, 127.0, 128.6, 128.7130.3, 132.4, 139.0, 148.1, 150.1, 151.5, 157.1, 160.8 ppm; IR (KBr, cm^{-1}): 1603, 2922, 2945; HRMS (ESI) m/e calcd for $C_{23}H_{22}N_3O_2$ $[M+H]^+$ 372.1707, found 372.1703.

7-Chloro-1-morpholin-4-yl-3-phenylbenzo[b][1,6]naphthyridine (7k).

Red solid; yield: 121.8 mg, 65%; mp 95-96 °C; R_f = 0.35 (05:95 EtOAc/hexane): ^{1}H NMR (300 MHz, $CDCl_3$): δ= 3.69 (t, *J* = 3.9 Hz, 4H), 4.05 (t, *J* = 4.5 Hz, 4H), 7.41-7.54 (m, 4H), 7.95 (d, *J* = 8.7 Hz, 1H), 8.05 (s, 1H), 8.23 (t, *J* = 9.0 Hz, 3H), 8.93 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.9, 66.8, 110.8, 114.6, 124.1, 127.0, 128.3, 128.7, 129.2, 130.2, 135.2, 138.5, 138.6, 150.8, 152.0, 153.7, 161.2 ppm; IR (KBr, cm^{-1}): 1600, 1628, 2924, 2955; HRMS (ESI) m/e calcd for $C_{22}H_{19}ClN_3O$ $[M+H]^+$ 376.1211, found 376.1210.

3-Phenyl-1-piperidin-1-yl-benzo[b][1,6]naphthyridine (7l).

Light red solid; yield: 101.7 mg, 60%; mp 80-81 °C; R_f = 0.40 (05:95 EtOAc/hexane): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.75-1.82 (m, 2H), 1.89-196 (m, 4H), 3.65 (t, *J* = 4.8 Hz, 4H), 7.41-7.55 (m, 4H), 7.83 (t, *J* = 7.8 Hz, 1H), 8.00 (d, *J* = 6.9 Hz, 2H), 8.16 (d, *J* = 8.7 Hz, 1H), 8.26 (d, *J* = 7.2 Hz, 2H), 8.93 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.9, 26.1, 52.7, 110.0, 115.1, 125.5, 125.8, 126.9, 127.0, 128.3, 128.6, 128.9, 132.1, 135.7, 139.2, 150.5, 151.7, 153.2, 162.3 ppm; IR (KBr, cm^{-1}): 1640, 2852, 2937; HRMS (ESI) m/e calcd for $C_{23}H_{22}N_3$ $[M+H]^+$ 340.1808, found 340.1815.

3-Phenyl-1-pyrrolidin-1-yl-benzo[b][1,6]naphthyridine (7m).

Light red solid; yield: 115.3 mg, 71%; mp 105-106 °C; R_f = 0.40 (05:95 EtOAc/hexane): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.12 (t, *J* = 3.0 Hz, 4H), 4.10 (t, *J* = 6.3 Hz, 4H), 7.40-7.50 (m, 4H), 7.81 (t, *J* = 7.5 Hz, 2H), 7.93 (d, *J* = 8.4 Hz, 1H), 8.14 (d, *J* = 8.7 Hz, 1H), 8.27 (d, *J* = 7.2 Hz, 2H), 9.11 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.8, 51.4, 106.4, 104.5, 124.6, 125.0, 126.8, 128.1, 128.4, 128.7, 129.0, 131.7, 135.7, 139.5, 150.1, 152.1, 154.0, 156.8 ppm; IR (KBr, cm^{-1}): 1582, 1610, 2932; HRMS (ESI) m/e calcd for $C_{22}H_{20}N_3$ $[M+H]^+$ 326.1652, found 326.1654.

5-Morpholin-4-yl-3,7-diphenyl-[1,6]naphthyridine (8a).

Green solid; yield: 119.2 mg, 65%; mp 101-102 °C; R_f = 0.30 (05:95 EtOAc/hexane): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.53 (t, *J* = 3.9 Hz, 4H), 3.94 (t, *J* = 4.2 Hz, 4H), 7.36-7.51 (m, 6H), 7.62 (d, *J* = 7.2 Hz, 2H), 7.96 (s, 1H), 8.14 (d, *J* = 7.5 Hz, 2H), 8.41 (s, 1H), 9.17 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.9, 66.8, 112.1, 115.3, 126.8, 127.2, 128.3, 128.7, 129.0, 129.3, 130.7, 133.5, 137.4, 138.8, 152.0, 152.9, 153.1, 160.8 ppm; IR (KBr, cm^{-1}): 1601, 2912, 2960; HRMS (ESI) m/e calcd for $C_{24}H_{22}N_3O$ $[M+H]^+$ 368.1757, found 368.1756.

General procedure for palladium-catalyzed hydroamination reaction.

A mixture of substituted 2-chloroquinoline-3-carbonitrile (**1a**) (0.50 mmol), alkynes (1.2 equiv), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %) and triethylamine (2 equiv) in CH_3CN (2 mL) were heated under N_2 at 80°C. After completion of reaction (as monitored by TLC) subsequently added $Pd(OAc)_2$ (5 mol %), Ph_3P (10 mol %), different alkyl amines (2 equiv) along with K_2CO_3 (2 equiv) in acetonitrile and heated at 80°C under aerobic atmosphere. After final completion of reaction, the reaction mixture was diluted with water, extracted with ethyl acetate, washed with brine solution and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography on silica gel using EtOAc/hexane to afford pure products **9a-d**.

2-(2-Benzylamino-2-phenylvinyl)-quinoline-3-carbonitrile (9a).

Yellow solid; yield: 144.4 mg, 80%; mp 110-111 °C; R_f = 0.40 (05:95 EtOAc/hexane): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.46 (d, *J* = 5.1 Hz, 2H), 5.70 (s, 1H), 7.28-7.37 (m, 4H), 7.41-7.49 (m, 5H), 7.58-7.64 (m, 4H), 8.27 (s, 1H), 11.26 (bs, D_2O exchangeable, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 48.9, 92.9, 104.9, 117.5, 122.4, 124.7, 126.8, 127.1, 127.7, 128.1, 128.4, 128.6, 129.0, 132.2, 136.5, 139.4, 142.2, 142.3, 147.8, 157.2, 159.8 ppm; IR (KBr, cm^{-1}):1582, 2216, 2968; HRMS (ESI) m/e calcd for $C_{25}H_{20}N_3$ $[M+H]^+$ 362.1652, found 362.1658.

2-(2-Butylamino-2-phenylvinyl)-quinoline-3-carbonitrile (9b).

Yellow solid; yield: 135.7 mg, 83%; mp 95-96 °C; R_f = 0.30 (05:95 EtOAc/hexane): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.2 Hz, 3H), 1.37-1.56 (m, 4H), 3.19 (t, *J* = 6.3 Hz, 2H), 5.52 (s, 1H), 7.18-7.40 (m, 6H), 7.54-7.69 (m, 3H), 8.17 (s, 1H), 10.83 (bs, D_2O exchangeable, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 19.9, 33.0, 44.5, 92.0, 104.9, 117.6, 122.4, 124.5, 126.8, 127.9, 128.1, 128.3, 128.8, 132.2, 136.9, 142.2, 148.1, 157.4,

160.2 ppm; IR (KBr, cm^{-1}): 1582, 2223, 2926; HRMS (ESI) m/e calcd for $C_{22}H_{22}N_3$ $[M+H]^+$ 328.1808, found 328.1820.

-(2-Isopropylamino-2-phenylvinyl)-quinoline-3-carbonitrile (9c).

Yellow solid; yield: 122.0 mg, 78%; mp 105-106 °C; R_f = 0.35 (05:95 EtOAc/hexane): ^1H NMR (300 MHz, $CDCl_3$): δ = 1.24 (s, 6H), 3.36 (s, 1H), 5.57 (s, 1H), 7.36-7.50 (m, 6H), 7.62-7.77 (m, 3H), 8.24 (s, 1H), 10.85 (bs, D_2O exchangeable, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.6, 46.1, 92.6, 104.9, 117.6, 122.4, 124.6, 126.9, 127.8, 128.0, 128.3, 128.8, 132.2, 137.3, 142.3, 148.0, 157.3, 159.4 ppm; IR (KBr, cm^{-1}): 1580, 2228, 2956; HRMS (ESI) m/e calcd for $C_{21}H_{20}N_3$ $[M+H]^+$ 314.1652, found 314.1661.

2-(2-Cyclohexylamino-2-phenylvinyl)-quinoline-3-carbonitrile (9d).

Yellow solid; yield: 134.1 mg, 76%; mp 113-114 °C; R_f = 0.30 (05:95 EtOAc/hexane): ^1H NMR (300 MHz, $CDCl_3$): δ = 1.28-1.55 (m, 4H), 1.72-1.82 (m, 4H), 3.39 (d, *J* = 9.3 2H), 5.57 (s, 1H), 7.35 (t, *J* = 7.2 Hz, 1H), 7.41-7.48 (m, 4H), 7.61-7.71 (m, 3H), 7.77 (d, *J* = 8.4 Hz, 3H), 8.24 (s, 1H), 11.04 (bs, D_2O exchangeable, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.9, 25.5, 34.3, 52.1, 92.5, 104.9, 117.6, 122.3, 124.5, 126.7, 127.8, 128.3, 128.8, 132.2, 137.2, 142.2, 148.0, 157.3, 159.3 ppm; IR (KBr, cm^{-1}):1596, 2213, 2932; HRMS (ESI) m/e calcd for $C_{24}H_{23}NaN_3$ $[M+Na]^+$ 376.1784, found 376.1790.

General procedure for synthesis of *N*-alkyl-3-phenyl-2*H*-benzo[*b*][1,6]naphthyridin-1-ones 10.

To a solution of compound **9a/9b** (0.20 mmol) in THF was added sodium hydride (2 equiv) and heated at 60^0C under aerobic condition. After completion of the reactions, cold water was added into the reaction mixture and extracted with ethyl acetate. The organic layer was washed with water, brine and dried over anhydrous sodium sulphate (Na_2SO_4). The solvent was evaporated under vacuum to give crude product, which was purified by column chromatography on silica gel using EtOAc and hexane as eluent to afford pure products **10a-b**.

N-benzyl-3-phenyl-2H-benzo[b][1,6]naphthyridin-1-one (10a).

Green solid; yield: 57.9 mg, 80%; mp 121-122 °C; R_f = 0.25 (05:95 EtOAc/hexane): ^1H NMR (300 MHz, $CDCl_3$): δ = 5.26 (s, 2H), 6.81 (s, 1H), 6.92 (d, *J* = 3.3 Hz, 2H), 7.17 (d, *J* = 2.1 Hz, 3H), 7.27 (d, *J* = 7.2 Hz, 2H), 7.34-7.43 (m, 3H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.85 (t, *J* = 7.5 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 8.13 (d, *J* = 8.4Hz, 1H), 9.34 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 48.5, 110.4, 119.7, 126.2, 126.6, 126.8, 127.1, 128.3, 128.4, 128.7, 128.8, 129.2, 129.4, 132.4, 135.4, 137.2, 138.9, 148.2, 151.2, 151.7, 163.7 ppm; IR (KBr,

cm^{-1}): 1659, 2923, 3056; HRMS (ESI) m/e calcd for $C_{25}H_{19}N_2O$ $[M+H]^+$ 363.1492, found 363.1496.

N-butyl-3-phenyl-2H-benzo[b][1,6]naphthyridin-1-one (10b).

Light green solid; yield: 49.2 mg, 75%; mp 90-91 °C; R_f = 0.25 (05:95 EtOAc/hexane): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.74 (t, *J* = 7.2 Hz, 3H), 1.12-1.19 (m, 4H), 3.97 (t, *J* = 8.1 Hz, 2H), 6.77 (s, 1H), 7.49-7.59 (m, 6H), 7.84 (t, *J* = 8.1 Hz, 1H), 8.04 (t, *J* = 8.1 Hz, 1H), 8.12 (d, *J* = 8.7 Hz, 1H), 9.30 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.4, 19.8, 30.7, 45.2, 109.5, 109.5, 119.8, 126.0, 126.6, 128.5, 128.7, 129.1, 129.4, 132.2, 135.7, 138.5, 148.1, 151.1, 151.6, 163.3 ppm; IR (KBr, cm^{-1}): 1661, 2913, 3012; HRMS (ESI) m/e calcd for $C_{22}H_{21}N_2O$ $[M+H]^+$ 329.1648 found 329.1646.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:.

Crystal structure and data of compounds **3a, 7i** and **9c**.

^{1}H and ^{13}C NMR spectra's of all the new compounds.

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Notes

The authors declare no competing financial interest. This work is a part of doctoral thesis submitted by Ritush Kumar at Department of Chemistry, Banaras Hindu University, Varanasi, India.

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