Synthesis of new 2,3-disubstituted pyridines containing a 1,2,3-triazole in the side-chain via one-pot copper-catalyzed azide-alkyne cycloaddition

Meenakshi Verma, Vijay Luxami and Kamaldeep Paul*

School of Chemistry and Biochemistry, Thapar University, Patiala-147 001, India
E-mail: kpaul@thapar.edu

DOI: http://dx.doi.org/10.3998/ark.5550190.p009.175

Abstract

A series of 1,2,3-triazole-containing pyridines has been synthesized using the Cu(II) catalyzed 'click approach' from sodium azide and corresponding halides. The synthesis involves the amidation of 2-amino-3-hydroxypyridine with benzoyl chloride or cinnamic acid followed by reaction with propargyl bromide to obtain *N*-(3-(prop-2-ynyloxy)pyridin-2-yl)benzamide **5** and 3-phenyl-*N*-(3-(prop-2-ynyloxy)-pyridin-2-yl)acrylamide **10** respectively. These compounds underwent one-pot tandem copper-catalyzed azidation and CuAAC reactions to provide compounds **6a-h** and **11a-g** in moderate to good yields.

Keywords: One-pot click chemistry, pyridine, 1,2,3-triazole, benzyl halides

Introduction

Due to their chemical and biological importance, heterocyclic moieties are attractive targets in medicinal and pharmaceutical chemistry.[1-2] Among heterocyclic compounds, pyridine has proved to be the one of the most important moieties. Substituted pyridines have a major role in a wide variety of natural products, pharmaceutical drugs and various kinds of functional materials.[3-4] For the synthesis of pyridines, various methods are known in the literature. John Spencer *et al.*[5] synthesized libraries of pyridine derivatives, many of which contain a piperazine group at the 2-position. Sreekantha B. Jonnalagadda *et al.*[6] synthesized highly substituted pyridines in good yields by the use of Au loaded MgO in one-pot, multicomponent system. Haider Behbehani *et al.*[7] explored a series of 5-arylazo-2,3,6-trisubstituted pyridines from the reactions of 3-oxo-2-arylhydrazonopropanal with 3-oxo-3-phenylpropionitrile. Xie *et al.*[8] synthesized 5,6-disubstituted pyridine-2,3-dione-3-thiosemicarbazone derivatives and 5,6-disubstituted pyridine-2,3-dione *S*-benzyl-3-thiosemicarbazones via oxidation-Michael additions, condensations and nucleophilic substitutions.

Cu-promoted coupling reactions have been extensively used for the synthesis of several molecules and biomolecules.[9-11] The azidation reaction has been used as a facile method for the transformation of an aryl halide into an aryl azide. Synthetic applications of these ar-

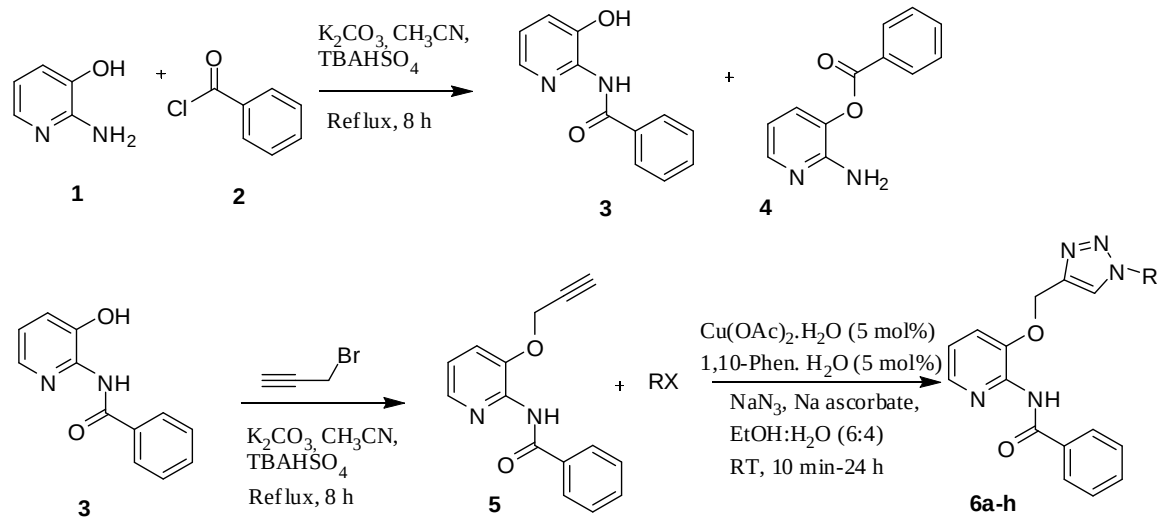
 ©ARKAT-USA, Inc.

yl/alkyl azides have become highly attractive alternatives to establish nitrogen-linked aryl/alkyl scaffolds. This high yield and regioselective reaction has found numerous applications ranging from chemistry to biology. Copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction (click chemistry) has been widely utilized for the synthesis of biologically active 1,2,3-triazole compounds. Several therapeutically active compounds containing this moiety have been reported, viz., anti-HIV agents, antimicrobials, and kinase inhibitors.[12-16] Moreover, Cu-promoted azidation and 1,3-dipolar [3 + 2] cycloaddition reactions between azides and terminal alkynes that can be carried out in one-pot synthesis are an attractive method. Herein, we demonstrate an efficient synthesis of novel 2,3-disubstituted pyridines by performing one-pot tandem copper-catalyzed azidation and CuAAC reaction.

Results and Discussion

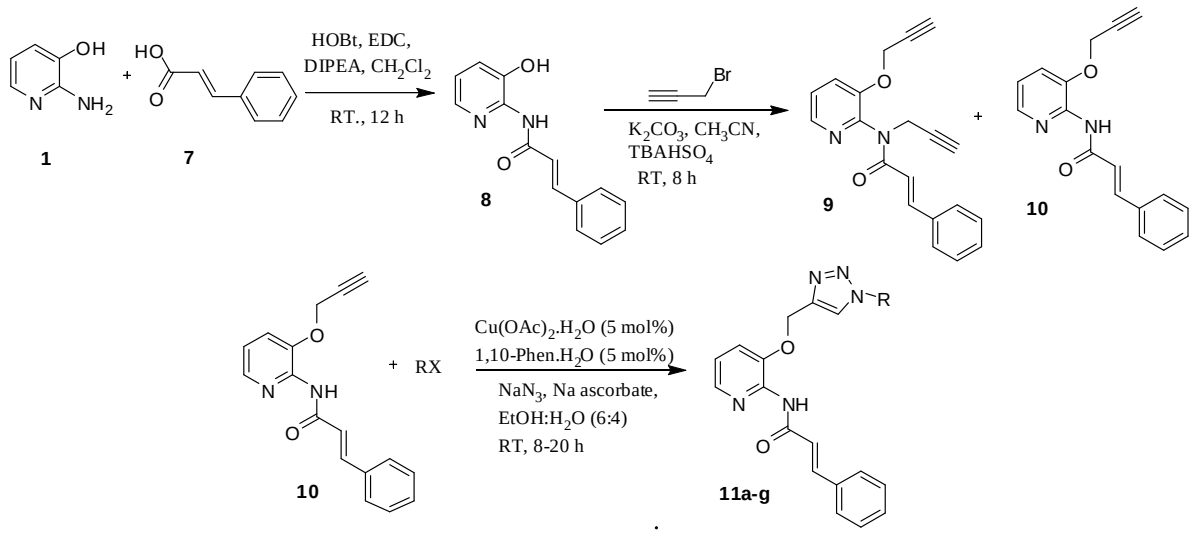
In our present work, the precursor of *N*-(3-(prop-2-ynyloxy)-pyridin-2-yl)benzamide **5** was synthesized from an easily available starting material 2-amino-3-hydroxypyridine **1** (Scheme 1). Compound **1** was reacted with benzoyl chloride **2** in the presence of potassium carbonate and acetonitrile using tetrabutylammonium hydrogen sulfate ($TBAHSO_4$) as catalyst at reflux temperature for eight hours to give of *N*-(3-hydroxy-pyridin-2-yl)benzamide **3** and benzoic acid 2-amino-pyridin-3-yl ester **4 as** white solids in 65% and 10% yields respectively. The crude **3** was > 95% pure according to ^{1}H NMR and was used in the next stage without further purification. The reaction of **3** with propargyl bromide and potassium carbonate in acetonitrile with $TBAHSO_4$ proceeded at reflux temperature for eight hours to give **5** as a brown coloured liquid in 70% yield. The final step was the synthesis of pyridine analogues containing a 1,2,3-triazole unit **6a-h** from **5** and various benzyl halides. A Cu-catalyzed click reaction was performed with **5** and benzyl chloride using sodium azide, copper(II) acetate as catalyst, sodium ascorbate as reducing agent and 1,10-phenanthroline.H_2O as ligand in EtOH:H_2O (6:4) at room temperature for 24 h to afford the crude product. Addition of cold water to the reaction mixture resulted in formation of a white precipitate. The crude product was then subjected to column chromatography to afford *N*-(3-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy)pyridin-2-yl)benzamide **6a** in 55% yield (Table 1, entry 1). Similarly, other 1,2,3-triazoles (**6b-h**, Table 1, entry 2-8) were synthesized by the reaction of compound **5** with other substituted benzyl halides and allyl bromide in moderate to good yields (55-82%). The structure of **6a** was confirmed by ^{1}H and ^{13}C NMR analysis as well as mass spectrometry. In the ^{1}H NMR spectrum, the C5-proton of the triazole ring resonated at δ 7.57, the protons of the OCH_2 group appeared as a singlet at δ 5.50 and the protons of the NCH_2 group as a singlet at δ 5.29, along with aromatic proton signals. In the ^{13}C NMR spectra, the OCH_2 carbon appeared at δ 62.7, the NCH_2 carbon appeared at δ 54.2, thje C5-carbon of the triazole was at δ 123.1, and carbonyl group of the amide at δ 164.8, along with other carbons. In EI-MS, peak appeared at m/z = 386.3 for (M^++1) ion of **6a**. Higher yields of 1,2,3-triazoles were obtained when a fluorine atom was present in the benzyl moiety.

 ©ARKAT-USA, Inc.



Scheme 1. Synthesis of *N*-(3-(1-substituted benzyl/allyl-1*H*-[1,2,3]-triazol-4-yl)methoxy) pyridine-2-yl)-3-phenyl-acrylamide

We also reacted **1** with cinnamic acid **7** in the presence of hydroxybenzotriazole (HOBt), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC) and diisopropylethylamine (DIPEA) in dichloromethane at room temperature for 12 hours to yield *N*-(3-hydroxy-pyridin-2-yl)-3-phenyl-acrylamide **8** in 80% yield (Scheme 2). Compound **8** was then further treated with propargyl bromide in potassium carbonate and acetonitrile using $TBAHSO_4$ as catalyst at room temperature for eight hours to give 3-phenyl-*N*-prop-2-ynyl-*N*-(3-prop-2-ynyloxy-pyridin-2-yl)acrylamide **9** and 3-phenyl-*N*-(3-(prop-2-ynyloxy)-pyridin-2-yl)acrylamide **10** in 10% and 55% yields respectively. The same reaction conducted at reflux temperature gave compound **9** in 60% yield along with traces of compound **10**.

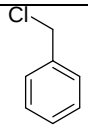
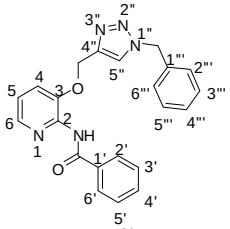
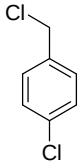
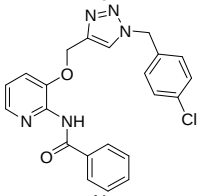
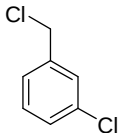
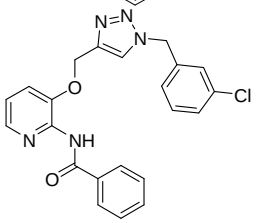
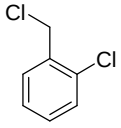
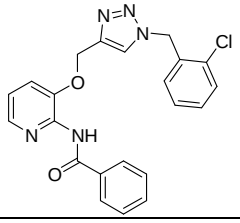


Scheme 2. Synthesis of *N*-(3-(1-substituted benzyl/allyl-1*H*-[1,2,3]-triazol-4-yl)methoxy) pyridine-2-yl)-3-phenyl-acrylamide

 ©ARKAT-USA, Inc.

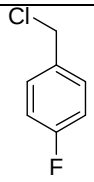
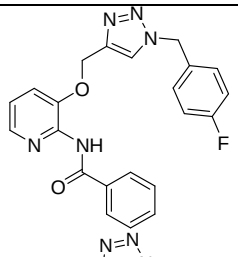
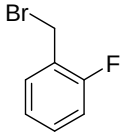
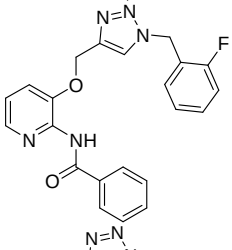
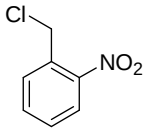
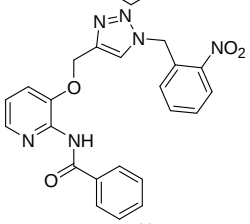
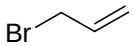
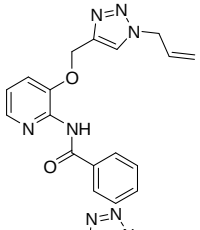
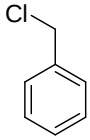
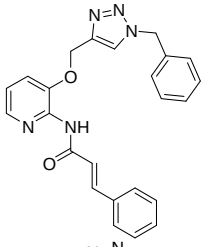
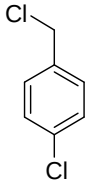
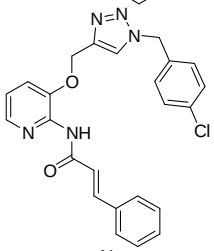
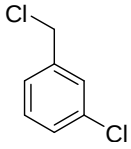
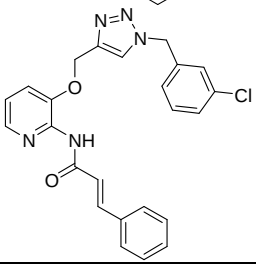
Compound **10** underwent a copper-catalyzed click reaction with benzyl chloride using sodium azide in the presence of copper(II) acetate, sodium ascorbate and 1,10-phenanthroline.H_2O in EtOH:H_2O at room temperature for 20 hours. Addition of cold water to the reaction mixture resulted in a white precipitatesof crude product which was then purified by column chromatography to give *N*-[3-(1-benzyl-1*H*-[1,2,3]triazol-4-ylmethoxy)-pyridin-2-yl]-3-phenyl-acrylamide **11a** in 50% yield (Table 1, entry 9). In the ^{1}H NMR spectrum of this compound there was a singlet at δ 7.59 for the C5-proton of the triazole ring, proton signals for the OCH_2 at δ 5.64, for the NCH_2 at δ 5.30 and signals for other protons. In the ^{13}C NMR of **11a**, the C5 carbon of the triazole ring resonated at δ 123.2, the OCH_2 carbon resonated at δ 62.4, the NCH_2 carbon at δ 54.3 and amide carbonyl group carbon resonated at δ 164.8, along with signals for the other carbons. In EI-MS, a peak appeared at *m/z* = 412.2 for (M^++1) ion of **11a**. An array of novel triazole derivatives **11a-g** was synthesized by varying the substitution on the benzyl grojup as well as allyl groups (Table 1, entry 9-15). The overall yields of compounds **6** and **11** were very good and the method is high yielding, simple, convenient and general. Structures of all newly synthesized compounds were characterized by ^{1}H and ^{13}C NMR as well as mass spectrometry (Supporting Information).

Table 1. Physical data of compounds **6a–h** and **11a–g**

Entry	Compds.	RX	Product	Time	Yield (%)	mp (^{o}C)
1	**6a**			24 h	55	120 -122
2	**6b**			20 h	65	163 -164
3	**6c**			20 h	66	154 -157
4	**6d**			20 h	64	125-126

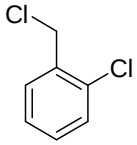
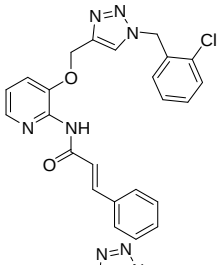
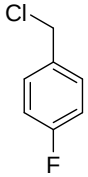
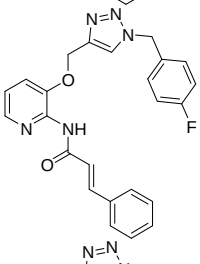
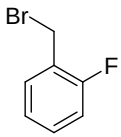
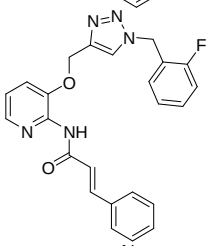
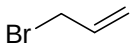
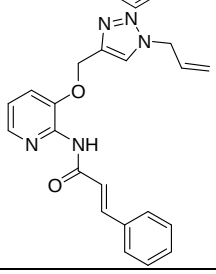
 ©ARKAT-USA, Inc.

Table 1 (continued)

Entry	Compds.	RX	Product	Time	Yield (%)	mp (°C)
5	**6e**			10 min	82	165-168
6	**6f**			15 min	78	132 -134
7	**6g**			24 h	60	119 -123
8	**6h**			18 h	55	117 -120
9	**11a**			20 h	50	125-126
10	**11b**			18 h	58	160 -162
11	**11c**			20 h	57	161 -163

©ARKAT-USA, Inc.

Table 1 (continued)

Entry	Compds.	RX	Product	Time	Yield (%)	mp (°C)
12	**11d**			18 h	56	128 -129
13	**11e**			8 h	58	169 -172
14	**11f**			8 h	55	138 -140
15	**11g**			20 h	45	120-122

Conclusions

An efficient and straightforward one pot copper catalyzed azidation and CuAAC reaction for constructing novel 1,2,3-triazole-containing pyridines has been developed. Utilizing easily available reaction materials, a small library of pyridine derivatives carrying side-chain 1,2,3-triazoles was rapidly and efficiently synthesized. Overall, we believe that the developed reaction method and novel series of pyridine substituted triazine should be considered as an important advance in medicinal and pharmaceutical chemistry.

Experimental Section

General. All chemicals and solvents were of commercial grade and used without further purification, supplied by spectrochemicals and Sigma-Aldrich. Melting points were determined in open capillaries and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Jeol ECS-

 ©ARKAT-USA, Inc.

400 MHz spectrometer at 400 MHz and 100 MHz respectively, using $CDCl_3$ as solvent. The chemical shifts are expressed in parts per million with TMS as internal reference and *J* values are given in Hz. Mass spectra were recorded on a Waters Micromass Q-Tof Micro (Milford, MA). Reactions were monitored by thin layer chromatography (TLC) with plates coated with silica gel HF-254. Column chromatography was performed with silica gel mesh size 60-120. Hexane: ethylacetate and ethyl acetate: methanol were used as solvent systems.

Synthesis of *N*-(3-hydroxypyridin-2-yl)benzamide (3) and benzoic acid 2-aminopyridin-3-yl ester (4). 2-Amino-3-hydroxy pyridine **l** (2 g, 18.17 mmol) was dissolved in acetonitrile (50 mL), K_2CO_3 (3 g, 21.75 mmol) and $TBAHSO_4$ (0.05 mmol). Benzoyl chloride **2** (3 g, 21.75 mmol) was added and the reaction mixture was heated to reflux for 8 h. The reaction mixture was neutralized with $NaHCO_3$ and extracted with chloroform, the extract dried over Na_2SO_4, filtered and concentrated to get the crude product. The crude residue was then purified by column chromatography to get pure *N*-(3-hydroxy-pyridin-2-yl)benzamide **(3)** and benzoic acid 2-amino-pyridin-3-yl ester **(4)**.

***N*-(3-hydroxypyridin-2-yl)benzamide (3).** Yield: 65%; mp 130-133 ^oC; ^1H NMR (400 MHz, $CDCl_3$): $\delta_н$ 8.62 (bs, 1H, NH), 8.34 (dd, $^2J_{(HH)}$ 4.80 Hz, $^3J_{(HH)}$ 1.48 Hz, 1H, H-6), 8.16 (dd, $^2J_{(HH)}$ 8.16 Hz, $^3J_{(HH)}$ 0.96 Hz, 2H, H-2',6'), 7.83 (d, $^3J_{(HH)}$ 7.04 Hz, 2H, H-3',5'), 7.77 (dd, $^2J_{(HH)}$ 4.8 Hz, $^3J_{(HH)}$ 8.08 Hz, 1H, H-4'), 7.60 (t, $^3J_{(HH)}$ 1.16 Hz, 1H, H-4), 7.40 (dd, $^2J_{(HH)}$ 7.32 Hz, $^3J_{(HH)}$ 5.67 Hz, 1H, H-5); MS (EI) : *m/z* 215.1 (M^++1).

Benzoic acid 2-aminopyridin-3-yl ester (4). Yield: 10%; mp 160-162 ^oC; ^1H NMR (400 MHz, $CDCl_3$): $\delta_н$ 9.87 (bs, 2H, NH_2), 8.02 (dd, $^2J_{(HH)}$ 4.56 Hz, $^3J_{(HH)}$ 1.48 Hz, 2H, H-6,2'), 7.62 (t, $^3J_{(HH)}$ 1.20 Hz, 1H, H-6'), 7.58 (t, $^3J_{(HH)}$ 7.88 Hz, 1H, H-4), 7.51 (t, $^3J_{(HH)}$ 7.88 Hz, 2H, H-3',5'), 7.41 (dd, $^2J_{(HH)}$ 8.08 Hz, $^3J_{(HH)}$ 1.48 Hz, 1H, H-5), 7.11 (dd, $^2J_{(HH)}$ 8.08 Hz, $^3J_{(HH)}$ 4.64 Hz, 1H, H-4'); MS (EI) : *m/z* 215.1 (M^++1).

Synthesis of *N*-(3-(prop-2-ynyloxy)pyridin-2-yl)benzamide (5). *N*-(3-Hydroxy-pyridin-2-yl)benzamide **3** (2 g, 10 mmol) was refluxed with propargyl bromide (1.17 g, 10 mmol) in the presence of K_2CO_3 (2 g, 15 mmol) and $TBAHSO_4$ (0.05 mmol) using acetonitrile as solvent for 8 h. Acetonitrile was removed under vacuum, $CHCl_3$ was added to it and the solution washed with water. The organic layer was dried over Na_2SO_4, filtered and concentrated to give the crude product. The crude product was purified by column chromatography to produce a sticky brown liquid of compound **5**.

***N*-(3-(prop-2-ynyloxy)pyridin-2-yl)benzamide (5).** Yield: 70%; ^1H NMR (400 MHz, $CDCl_3$): $\delta_н$ 8.72 (bs, 1H, NH), 8.16 (dd, $^2J_{(HH)}$ 4.60 Hz, $^3J_{(HH)}$ 1.36 Hz, 1H, H-6), 7.94 (d, $^3J_{(HH)}$ 7.32 Hz, 2H, H-2',6'), 7.57-7.52 (m, 1H, H-4'), 7.50-7.46 (m, 2H, H-3',5'), 7.39 (dd, $^2J_{(HH)}$ 8.24 Hz, $^3J_{(HH)}$ 1.36 Hz, 1H, H-4), 7.11 (dd, $^2J_{(HH)}$ 8.28 Hz, $^3J_{(HH)}$ 4.36 Hz, 1H, H-5), 4.80 (d, $^3J_{(HH)}$ 2.28 Hz, 2H, O-CH_2), 2.60 (t, $^3J_{(HH)}$ 2.72 Hz, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ_c 164.6 (C=O), 143.3 (C-2), 140.7 (C-3), 134.8 (C-1'), 131.9 (C-6), 128.6 (C-2',6'), 127.3 (C-4,5), 119.8 (C-3',5'), 119.6 (C-4'), 59.0 (CH), 58.9 (O-CH_2), 56.5 (C); MS (EI) : *m/z* 253.2 (M^++1); Anal. Calc. for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.75; H, 4.96; N, 11.33.

General procedure for synthesis of 6a-h. In a round bottom flask, $Cu(OAc)_2.H_2O$ (5 mol%), 1,10-phenanthroline monohydrate (5 mol%) and sodium L-ascorbate (107 mg, 0.54 mmol) were added in EtOH:H_2O (6:4, 10 mL) and the mioxture stirred for 5 mins at room

 ©ARKAT-USA, Inc.

temperature. *N*-(3-(prop-2-ynyloxy)-pyridin-2-yl)benzamide **5** (100 mg, 0.40 mmol), sodium azide (76 mg, 1.17 mmol) and the benzyl halide (0.40 mmol) were added to the reaction mixture with stirring at room temperature. Reaction time varied from 10 min to 24 h for various benzyl halides. After completion of the reaction (monitored by TLC), ice cold water was added to the reaction mixture till the product precipitated, it was filtered off and washed with cold water. The crude product was then dried under vacuum. The crude product was purified by column chromatography using AcOEt:MeOH (98:2) as eluent to give compounds **6a-h**.

***N*-(3-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy)pyridin-2-yl)benzamide (6a).** Yield: 55%; mp 120-122 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.50 (bs, 1H, NH), 8.13 (dd, $^{2}J_{(HH)}$ 5.04 Hz, $^{3}J_{(HH)}$ 1.36 Hz, 1H, H-6), 7.89-7.87 (m, 2H, H-C2',6'), 7.57-7.53 (m, 2H, H-4',5'), 7.48-7.44 (m, 2H, H-3',5'), 7.42 (dd, $^{2}J_{(HH)}$ 8.24 Hz, $^{3}J_{(HH)}$ 1.36 Hz, 1H, H-5), 7.35 (t, $^{3}J_{(HH)}$ 2.76 Hz, 3H, H-2''',4''',6'''), 7.23-7.21 (m, 2H, H-3''',5'''), 7.09 (dd, $^{2}J_{(HH)}$ 8.24 Hz, $^{3}J_{(HH)}$ 5.04 Hz, 1H, H-4'), 5.50 (s, 2H, O-CH_2), 5.29 (s, 2H, N-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 164.8 (C=O), 144.6 (C-2), 143.2 (C-3), 142.1 (C-1',C-4''), 140.4 (C-1'''), 134.6 (C-5''), 131.9 (C-6), 129.1 (C-2',6'), 128.8 (C-4'), 128.6 (C-3',5'), 128.0 (C-2''',6'''), 127.4 (C-4), 123.1 (C-5), 120.4 (C4'''), 120.2 (3''',5'''), 62.7 (O-CH_2), 54.2 (N-CH_2); MS (EI) : *m/z* 386.3 (M^++1); Anal. Calc. for $C_{22}H_{19}N_5O_2$: C, 68.56; H, 4.97; N, 18.17. Found: C, 68.73; H, 5.23; N, 18.34.

***N*-(3-((1-(4-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)pyridin-2-yl)benzamide (6b).** Yield: 65%; mp 163-164 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.49 (bs, 1H, NH), 8.12 (d, $^{3}J_{(HH)}$ 3.20 Hz, 1H, H-6), 7.88 (d, $^{3}J_{(HH)}$ 7.32 Hz, 2H, H-2',6'), 7.58 (s, 1H, H-5''), 7.56 (d, $^{3}J_{(HH)}$ 7.32 Hz, 1H, H-4), 7.48 (t, $^{3}J_{(HH)}$ 7.32 Hz, 2H, H-3',5'), 7.41 (d, $^{3}J_{(HH)}$ 7.76 Hz, 1H, H-5), 7.30 (d, $^{3}J_{(HH)}$ 8.28 Hz, 2H, H-2''',6'''), 7.16 (d, $^{3}J_{(HH)}$ 8.72 Hz, 2H, H-3''',5'''), 7.09-7.06 (m, 1H, H-4'''), 5.46 (s, 2H, O-CH_2), 5.29 (s, 2H, N-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 164.9 (C=O), 144.8 (C-2), 143.5 (C-3), 142.0 (C-1',4''), 140.3 (C-1'''), 134.8 (C-4'''), 134.5 (C-5''), 132.6 (C2''',6'''), 131.8 (C-6), 129.9 (C-2',6'), 129.0 (C-4'), 128.7 (C-3',5'), 127.4 (C-4), 123.2 (C-5), 122.9 (C-3'''), 120.7 (C-5'''), 62.7 (O-CH_2), 53.5 (N-CH_2); MS (EI) : *m/z* 420.1 (M^++1); Anal. Calc. for $C_{22}H_{18}ClN_5O_2$: C, 62.93; H, 4.32; N, 16.68. Found: C, 62.79; H, 4.48; N, 16.59.

***N*-(3-((1-(3-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)pyridin-2-yl)benzamide (6c).** Yield: 66%; mp 154-157 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.52 (bs, 1H, NH), 8.13 (dd, $^{2}J_{(HH)}$ 5.04 Hz, $^{3}J_{(HH)}$ 1.36 Hz, 1H, H-6), 7.90 (d, $^{3}J_{(HH)}$ 6.88 Hz, 2H, H-2',6'), 7.61 (s, 1H, H-5''), 7.57-7.54 (m, 1H, H-4), 7.48 (t, $^{3}J_{(HH)}$ 7.36 Hz, 2H, H-3',5'), 7.41 (dd, $^{2}J_{(HH)}$ 8.24 Hz, $^{3}J_{(HH)}$ 1.40 Hz, 1H, H-5), 7.33-7.28 (m, 2H, H-2''',6'''), 7.22 (t, $^{3}J_{(HH)}$ 1.84 Hz, 1H, H-4'), 7.10 (dd, $^{2}J_{(HH)}$ 8.24 Hz, $^{3}J_{(HH)}$ 5.04 Hz, 2H, H-4''',5'''), 5.47 (s, 2H, O-CH_2), 5.31 (s, 2H, N-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 164.9 (C=O), 144.8 (C-2), 143.5 (C-3), 142.1 (C-1',4''), 140.7 (C-1'''), 140.3 (C-2'''), 136.1 (C-3'''), 134.9 (C-6'''), 134.6 (C-5''), 131.8 (C-6), 131.0 (C-2',6'), 129.0 (C-4'), 128.4 (C-3',5'), 127.4 (C-4), 123.0 (C-5), 121.2 (C-4'''), 120.0 (C-5'''), 62.7 (O-CH_2), 53.5 (N-CH_2); MS (EI) : *m/z* 420.1 (M^++1); Anal. Calc. for $C_{22}H_{18}ClN_5O_2$: C, 62.93; H, 4.32; N, 16.68. Found: C, 62.71; H, 4.53; N, 16.47.

***N*-(3-((1-(2-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)pyridin-2-yl)benzamide (6d).** Yield: 64%; mp 125-126 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.53 (bs, 1H, NH), 8.13 (dd, $^{2}J_{(HH)}$ 5.04 Hz, $^{3}J_{(HH)}$ 1.40 Hz, 1H, H-6), 7.90 (d, $^{3}J_{(HH)}$ 7.32 Hz, 2H, H-2',6'), 7.66 (s, 1H, H-5''), 7.57-7.54 (m, 1H, H-5), 7.48 (t, $^{3}J_{(HH)}$ 2.76 Hz, 2H, H-3',5'), 7.43-7.39 (m, 2H, H-

 ©ARKAT-USA, Inc.

4’’’,6’’’), 7.32-7.28 (m, 1H, H-3’’’), 7.25-7.21 (m, 1H, H-5’’’), 7.19 (dd, $^{2}J_{(HH)}$ 7.76 Hz, $^{3}J_{(HH)}$ 1.84 Hz, 1H, H-4), 7.09 (dd, $^{2}J_{(HH)}$ 8.24 Hz, $^{3}J_{(HH)}$ 5.04 Hz, 1H, H-4’), 5.64 (s, 2H, O-CH_2), 5.30 (s, 2H, N-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ_c 164.9 (C=O), 144.6 (C-2), 143.1 (C-3), 142.1 (C-1’,4’’), 140.5 (C-1’’’), 134.6 (C-5’’), 133.5 (C-2’’’), 131.9 (C-6), 130.5 (C-2’,6’), 130.4 (C-3’’’), 129.9 (C-4’), 128.6 (C-3’,5’), 127.6 (C-6’’’), 127.4 (C-4), 123.4 (C-5), 120.4 (C-4’’’), 120.3 (C-5’’’), 62.7 (O-CH_2), 51.5 (N-CH_2); MS (EI) : *m/z* 420.1 (M^++1); Anal. Calc. for $C_{22}H_{18}ClN_5O_2$: C, 62.93; H, 4.32; N, 16.68. Found: C, 62.59; H, 4.57; N, 16.85.

***N*-(3-((1-(4-Fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)pyridin-2-yl)benzamide (6e).** Yield: 82%; mp 165-168 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta_н$ 8.52 (bs, 1H, NH), 8.12 (d, $^{3}J_{(HH)}$ 4.56 Hz, 1H, H-6), 7.88 (d, $^{3}J_{(HH)}$ 6.88 Hz, 2H, H-2’,6’), 7.57 (s, 1H, H-5’’), 7.56-7.54 (m, 1H, H-4), 7.47 (t, $^{3}J_{(HH)}$ 7.32 Hz, 2H, H-3’,5’), 7.41 (dd, $^{2}J_{(HH)}$ 7.80 Hz, $^{3}J_{(HH)}$ 1.36 Hz, 1H, H-5), 7.22-7.19 (m, 2H, H-2’’’,6’’’), 7.09 (dd, $^{2}J_{(HH)}$ 8.28 Hz, $^{3}J_{(HH)}$ 5.04 Hz, 1H, H-4’), 7.03-6.98 (m, 2H, H-3’’’,5’’’), 5.46 (s, 2H, O-CH_2), 5.29 (s, 2H, N-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ_c 164.9 (C=O), 144.8 (C-2), 143.4 (C-3), 142.0 (C-4’’), 140.6 (C-1’), 140.3 (C-1’’’), 134.5 (C-5’’), 131.8 (C-6), 130.5 (C-2’,6’), 130.0 (C2’’’), 129.3 (C-4’), 128.9 (C-3’,5’), 128.3 (C-6’’’), 127.4 (C-4), 123.2 (C-5), 120.0, 119.9 (C-3’’’), 115.5, 115.3 (C-5’’’), 62.7 (O-CH_2), 53.4 (N-CH_2); MS (EI) : *m/z* 404.2 (M^++1); Anal. Calc. for $C_{22}H_{18}FN_5O_2$: C, 65.50; H, 4.50; N, 17.36. Found: C, 65.38; H, 4.33; N, 17.51.

***N*-(3-((1-(2-Fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)pyridin-2-yl)benzamide (6f).** Yield: 78%; mp 132-134 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta_н$ 8.53 (bs, 1H, NH), 8.13 (d, $^{3}J_{(HH)}$ 4.56 Hz, 1H, H-4), 7.90 (d, $^{3}J_{(HH)}$ 6.84 Hz, 2H, H-2’,6’), 7.66 (s, 1H, H-5’’), 7.57-7.53 (m, 1H, H-4), 7.48 (t, $^{3}J_{(HH)}$ 7.32 Hz, 2H, H-3’,5’), 7.42 (dd, $^{2}J_{(HH)}$ 8.24 Hz, $^{3}J_{(HH)}$ 1.36 Hz, 1H, H-5), 7.37-7.32 (m, 1H, H-6’’’), 7.24 (dd, $^{2}J_{(HH)}$ 7.80 Hz, $^{3}J_{(HH)}$ 1.84 Hz, 1H, H-4’), 7.13-7.05 (m, 3H, H-3’’’,4’’’,5’’’), 5.56 (s, 2H, O-CH_2), 5.29 (s, 2H, N-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ_c 164.8 (C=O), 144.6 (C-2), 143.2 (C-3), 142.1 (C-4’’), 140.7 (C-1’), 140.4 (C-1’’’), 134.7 (C-5’’), 131.7 (C-6), 129.9 (C-2’,6’), 128.9, 128.8 (C-2’’’), 128.4 (C-4’), 127.4 (C-3’,5’), 124.2 (C-6’’’), 123.2 (C-4), 121.0 (C-4’’’), 120.5 (C-3’’’), 119.8, 119.7 (C-5’’’), 62.7 (O-CH_2), 47.8 (N-CH_2); MS (EI) : *m/z* 404.2 (M^++1); Anal. Calc. for $C_{22}H_{18}FN_5O_2$: C, 65.50; H, 4.50; N, 17.36. Found: C, 65.33; H, 4.68; N, 17.18.

***N*-(3-((1-(2-Nitrobenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)pyridin-2-yl)benzamide (6g).** Yield: 60%; mp 119-123 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta_н$ 8.56 (bs, 1H, NH), 8.14 (dd, $^{2}J_{(HH)}$ 7.76 Hz, $^{3}J_{(HH)}$ 1.32 Hz, 2H, H-6,4’’’), 7.90 (d, $^{3}J_{(HH)}$ 7.36 Hz, 2H, H-2’,6’), 7.84 (s, 1H, H-5’’), 7.58-7.50 (m, 3H, H-4,3’,5’), 7.48 (m, 3H, H-5,4’,6’’’), 7.10-7.05 (m, 2H, H-3’’’,5’’’), 5.90 (s, 2H, O-CH_2), 5.34 (s, 2H, N-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ_c 164.8 (C=O), 147.3 (C-2’’’), 144.6 (C-2), 142.1 (C-3,4’’), 140.2 (C-1’), 140.0 (C-1’’’), 134.5 (C-5’’), 134.2 (C-3’’’), 131.8 (C-6), 131.1 (C2’,6’), 130.0 (C-2’’’), 129.8 (C-6’’’), 129.0 (C-4’), 128.3 (C-3’), 127.4 (C-5’), 125.5 (C-4), 125.2 (C-4’’’), 124.3 (C-4’’’), 120.1 (C-3’’’), 62.7 (O-CH_2), 51.0 (N-CH_2); MS (EI) : *m/z* 431.4 (M^++1); Anal. Calc. for $C_{22}H_{18}N_6O_{40}$: C, 61.39; H, 4.22; N, 19.53. Found: C, 61.47; H, 4.39; N, 19.76.

***N*-(3-((1-Allyl-1*H*-1,2,3-triazol-4-yl)methoxy)pyridin-2-yl)benzamide (6h).** Yield: 55%; mp 117-120 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta_н$ 8.58 (bs, 1H, NH), 8.13 (d, $^{3}J_{(HH)}$ 4.12 Hz, 1H, H-6), 7.92-7.90 (m, 2H, H-2’,6’), 7.65 (s, 1H, H-5’’), 7.57-7.53 (m, 1H, H-5), 7.49-7.46 (m, 2H, H-3’,5’), 7.43 (dd, $^{2}J_{(HH)}$ 7.80 Hz, $^{3}J_{(HH)}$ 1.36 Hz, 1H, H-4), 7.09 (dd, $^{2}J_{(HH)}$ 8.28 Hz,

 ©ARKAT-USA, Inc.

$^{3}J_{(HH)}$ 4.56 Hz, 1H, H-4'), 6.00-5.93 (m, 1H, allyl-CH), 5.33-5.24 (m, 4H, allyl-CH_2, O-CH_2), 4.96-4.94 (m, 2H, N-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 164.9 (C=O), 144.8 (C-2), 143.1 (C-3), 142.1 (C-4''), 134.6 (C-5''), 131.9 (C-6), 130.7 (C-2',6'), 128.6 (C-4'), 127.4 (C-3',5'), 123.0 (C-4), 120.2 (C-5), 62.7 (O-CH_2), 52.8 (N-CH_2); MS (EI) : *m/z* 336.3 (M^++1); Anal. Calc. for $C_{18}H_{17}N_5O_2$: C, 64.47; H, 5.11; N, 20.88. Found: C, 64.39; H, 5.39; N, 20.65.

Synthesis of *N*-(3-hydroxypyridin-2-yl)-3-phenylacrylamide 8. In a 100 ml round bottom flask, cinnamic acid (2.6 g, 18 mmol) was stirred in CH_2Cl_2 (50 mL) at 0 ^{o}C in the presence of HOBt (5.4 g, 40 mmol), EDC (6.2 g, 40 mmol) and DIPEA (2.5 g, 20 mmol). 2-Amino-3-hydroxy pyridine **l** (2 g, 18 mmol) was added to the above suspension and the miture stirred at room temperature for 12 h. After completion of the reaction, the reaction mixture was extracted with water. The organic layer was separated, dried over Na_2SO_4, filtered and concentrated to get crude product. Purification with column chromatography resulted in compound **8** as a yellow solid.

***N*-(3-hydroxypyridin-2-yl)-3-phenylacrylamide (8).** Yield: 80%; mp 145-147 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.90 (bs, 1H, OH), 10.20 (bs, 1H, NH), 7.94 (d, $^{3}J_{(HH)}$ 4.12 Hz, 1H, H-6), 7.88 (d, $J_{(HH)}$ 15.12 Hz, 1H, H-5), 7.52-7.50 (m, 2H, H-2',6'), 7.44-7.38 (m, 4H, CH, H-4,3',5'), 7.19 (dd, $^{2}J_{(HH)}$ 7.80 Hz, $^{3}J_{(HH)}$ 4.56 Hz, 1H, H-4'), 6.75 (d, $^{3}J_{(HH)}$ 15.60 Hz, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.3 (C=O), 145.4 (C-2), 145.1 (C-3), 140.5 (C-1'), 138.2 (CH), 133.9 (CH), 131.0 (C-6), 130.3 (C-2'), 129.3 (C-6'), 128.6 (C-4'), 128.4 (C-3'), 128.0 (C-5'), 118.5 (C-4), 117.4 (C-5). MS (EI) : *m/z* 241.1 (M^++1).

Synthesis of 3-phenyl-*N*-prop-2-ynyl-*N*-(3-(prop-2-ynyloxy)pyridin-2-yl)acrylamide (9) and 3-phenyl-*N*-(3-(prop-2-ynyloxy)pyridin-2-yl)acrylamide (10). *N*-(3-Hydroxy-pyridin-2-yl)-3-phenyl-acrylamide **8** (2 g, 10 mmol) was treated with propargyl bromide (1.17 g, 10 mmol) in the presence of K_2CO_3 (2 g, 15 mmol) and $TBAHSO_4$ (0.05 mmol) using acetonitrile as solvent. When the reaction was carried out at room temperature for 8 h, the resulting compounds were obtained as yellow solids of 3-phenyl-*N*-(3-(prop-2-ynyloxy)-pyridin-2-yl)acrylamide (**10**) and 3-phenyl-*N*-prop-2-ynyl-*N*-(3-(prop-2-ynyloxy)-pyridin-2-yl)acrylamide **(9)** in 55% and 10% yields respectively. Acetonitrile was removed under vacuum, extracted with $CHCl_3$ and water, the organic layer separated and dried over Na_2SO_4 to get the crude product. Column chromatography was required in order to get the corresponding compounds **9** and **10**. When this reaction was carried out at reflux temperature for 8 h, it resulted in formation of yellowish liquid of 3-phenyl-*N*-prop-2-ynyl-*N*-(3-(prop-2-ynyloxy)-pyridin-2-yl)acrylamide **(9)** in 60% yield with traces of compound **10**.

3-Phenyl-*N*-prop-2-ynyl-*N*-(3-(prop-2-ynyloxy)-pyridin-2-yl)acrylamide (9). Yield: 60%; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.72 (dd, $^{2}J_{(HH)}$ 4.60 Hz, $^{3}J_{(HH)}$ 1.40 Hz, 1H, H-6), 7.74 (d, $^{3}J_{(HH)}$ 15.12 Hz, 1H, H-5), 7.53 (dd, $^{2}J_{(HH)}$ 8.24 Hz, $^{3}J_{(HH)}$ 1.36 Hz, 1H, H-2'), 7.38 (dd, $^{2}J_{(HH)}$ 8.24 Hz, $^{3}J_{(HH)}$ 4.56 Hz, 1H, H-6'), 7.34 (dd, $^{2}J_{(HH)}$ 5.96 Hz, $^{3}J_{(HH)}$ 2.20 Hz, 2H, H-4,4'), 7.28 (d, $^{3}J_{(HH)}$ 2.28 Hz, 3H, CH,H-3',5'), 6.23 (d, $^{3}J_{(HH)}$ 15.12 Hz, 1H, CH), 4.74 (d, $^{3}J_{(HH)}$ 2.15 Hz, 2H, O-CH_2), 4.71 (d, $^{3}J_{(HH)}$ 2.28 Hz, 2H, N-CH_2), 2.40 (t, $^{3}J_{(HH)}$ 2.30 Hz, 1H, CH), 2.14 (d, $^{3}J_{(HH)}$ 2.72 Hz, 1H, CH). MS (EI) : *m/z* 317.1 (M^++1); Anal. Calc. for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86. Found: C, 75.67; H, 4.99; N, 8.93.

3-Phenyl-*N*-(3-(prop-2-ynyloxy)pyridin-2-yl)acrylamide (10). Yield: 55%; mp 129-131 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.10 (d, $^{3}J_{(HH)}$ 4.56 Hz, 2H, NH, H-6), 7.85 (d, $^{3}J_{(HH)}$

 ©ARKAT-USA, Inc.

16.04 Hz, 1H, H-5), 7.60-7.57 (m, 2H, H-2',6'), 7.41-7.34 (m, 4H, CH,H-4,3',5'), 7.32 (dd, $^{2}J_{(HH)}$ 8.24 Hz, $^{3}J_{(HH)}$ 1.36 Hz, 1H, H-4'), 7.05 (dd, $^{2}J_{(HH)}$ 8.24 Hz, $^{3}J_{(HH)}$ 5.04 Hz, 1H, CH), 4.79 (d, $^{3}J_{(HH)}$ 2.28 Hz, 2H, O-CH_2), 2.60 (t, $^{3}J_{(HH)}$ 2.30 Hz, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ_c 164.8 (C=O), 143.3 (C-2), 142.3 (C-3), 142.2 (C-1'), 140.1 (CH), 134.8 (CH), 129.8 (C-6), 128.7 (C-2',6'), 128.1 (C-4'), 120.6 (C-3',5'), 119.2 (C-4), 119.1 (C-5), 56.3 (O-CH_2); MS (EI) : *m/z* 279.3 (M^++1); Anal. Calc. for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.60; H, 5.32; N, 10.29.

General procedure for synthesis of 11a-g. In a round bottom flask, $Cu(OAc)_2.H_2O$ (5 mol%), 1,10-phenanthroline monohydrate (5 mol%) and sodium L-ascorbate (107 mg, 0.47 mmol) were added in EtOH:H_2O (6:4, 10 mL) and the mixture stirred for 5 mins at room temperature. Compound **10** (100 mg, 0.35 mmol), sodium azide (76 mg, 1.02 mmol) and the corresponding benzyl halide (0.40 mmol) were added to the reaction mixture and it was stirred at room temperature. Reaction time varied from 8 to 20 h for various benzyl halides. After completion of reaction (monitored by TLC), ice cold water was added to reaction mixture till the product precipitated out. It was filtered off and washed with cold water. The crude product was purified by column chromatography using AcOEt:MeOH (98:2) as eluent to get compound **11a-g**.

***N*-[3-(1-Benzyl-1*H*-[1,2,3]triazol-4-ylmethoxy)pyridin-2-yl]-3-phenyl-acrylamide (11a).** Yield: 50%; mp 125-126 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.11 (bs, 1H, NH), 8.06 (dd, $^{2}J_{(HH)}$ 4.56 Hz, $^{3}J_{(HH)}$ 0.92 Hz, 1H, H-6), 7.82 (d, $^{3}J_{(HH)}$ 15.6 Hz, 1H, H-5), 7.59-7.57 (m, 3H, H-5'',2',6'), 7.41-7.37 (m, 4H, CH,H-3',4',5'), 7.36-7.32 (m, 4H, H-2''',3''',5''',6'''), 7.31-7.27 (m, 2H, H-4,4'''), 7.03 (dd, $^{2}J_{(HH)}$ 8.28 Hz, $^{3}J_{(HH)}$ 5.04 Hz, 1H, CH), 5.54 (s, 2H, N-CH_2), 5.26 (s, 2H, N-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ_c 164.8 (C=O), 143.2 (C-2), 143.0 (C-3), 142.1 (C-1,4''), 139.9 (C-1'''), 134.9 (C-5''), 134.0 (CH), 129.9 (CH), 129.2 (C-6), 128.9 (C-2',6'), 128.7 (C-4'), 128.1 (C-3',5'), 127.9 (C-2''',6'''), 127.1 (C-4), 123.2 (C-5), 120.6 (C-4'''), 119.5 (C-3''',5'''), 62.4 (O-CH_2), 54.3 (N-CH_2); MS (EI) : *m/z* 412.2 (M^++1); Anal. Calc. for $C_{24}H_{21}N_5O_2$: C, 70.06; H, 5.14; N, 17.02. Found: C, 70.27; H, 4.82; N, 17.37.

***N*-{3-[1-(4-Chloro-benzyl)-1*H*-[1,2,3]triazol-4-ylmethoxy]-pyridin-2-yl}-3-phenyl-acrylamide (11b).** Yield: 58%; mp 160-162 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.07 (bs, 1H, NH), 8.06 (dd, $^{2}J_{(HH)}$ 4.80 Hz, $^{3}J_{(HH)}$ 1.60 Hz, 1H, H-6), 7.82 (d, $^{3}J_{(HH)}$ 15.56 Hz, 1H, H-5), 7.60-7.59 (m, 2H, H-2',6'), 7.57 (s, 1H, H-5''), 7.41-7.39 (m, 2H, CH, H-4'), 7.38 (d, $^{3}J_{(HH)}$ 1.36 Hz, 2H, H-5',6'), 7.37-7.34 (m, 2H, H-2''',6''''), 7.33 (t, $^{3}J_{(HH)}$ 2.28 Hz, 1H, H-4), 7.23-7.21 (m, 2H, H-3''',5'''), 7.04 (dd, $^{2}J_{(HH)}$ 8.24 Hz, $^{3}J_{(HH)}$ 5.04 Hz, 1H, CH), 5.51 (s, 2H, O-CH_2), 5.26 (s, 2H, N-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ_c 164.8 (C=O), 143.3 (C-2), 143.2 (C-3), 142.1 (C-1',4''), 140.0 (C-1'''), 135.0 (C-4'''), 134.9 (C-5''), 134.1 (CH), 132.5 (C-2''',6'''), 130.0 (CH), 129.9 (C-2',6'), 129.5 (C-4'), 129.4 (C-3'), 128.8 (C-5'), 128.1 (C-4), 123.1 (C-5), 120.5 (C-3'''), 119.5 (C-5'''), 62.4 (O-CH_2), 53.6 (N-CH_2); MS (EI) : *m/z* 446.3 (M^++1); Anal. Calc. for $C_{24}H_{20}ClN_5O_2$: C, 64.65; H, 4.52; N, 15.71. Found: C, 64.37; H, 4.73; N, 15.82.

***N*-{3-[1-(3-Chloro-benzyl)-1*H*-[1,2,3]triazol-4-ylmethoxy]pyridin-2-yl}-3-phenyl-acrylamide (11c).** Yield: 57%; mp 161-163 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.30 (bs, 1H, NH), 8.06 (dd, $^{2}J_{(HH)}$ 5.04 Hz, $^{3}J_{(HH)}$ 0.92 Hz, 1H, H-6), 7.82 (d, $^{3}J_{(HH)}$ 16.04 Hz, 1H, H-5), 7.66 (s, 1H, H-5''), 7.59-7.56 (m, 2H, H-2',6'), 7.40-7.39 (m, 2H, CH, H-4'), 7.38 (d, $^{3}J_{(HH)}$

 ©ARKAT-USA, Inc.

1.84 Hz, 3H, H-4,5',6'), 7.32-7.30 (m, 2H, H-2''',6'''), 7.28 (s, 1H, H-2'''), 7.15 (d, $^{3}J_{(HH)}$ 6.88 Hz, 1H, H-4'''), 7.06 (dd, $^{2}J_{(HH)}$ 7.80 Hz, $^{3}J_{(HH)}$ 5.04 Hz, 1H, CH), 5.51 (s, 2H, O-CH_2), 5.29 (s, 2H, N-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 164.8 (C=O), 145.9 (C-2), 143.6 (C-3), 143.4 (C-1',4''), 143.3 (C-1'''), 142.2 (C-2'''), 139.8 (C-3'''), 136.0 (C-6'''), 135.0 (CH), 134.8 (C-5''), 130.4 (CH), 129.9 (C-6), 129.1 (C-2',6'), 128.8 (C-4'), 128.7 (C-3'), 128.2 (C-5'), 128.1 (C-4), 123.3 (C-5), 120.5 (C-4'''), 119.8 (C-5'''), 62.5 (O-CH_2), 53.6 (N-CH_2); MS (EI) : *m/z* 446.3 (M^++1); Anal. Calc. for $C_{24}H_{20}ClN_5O_2$: C, 64.65; H, 4.52; N, 15.71. Found: C, 64.23; H, 4.29; N, 15.90.

***N*-{3-[1-(2-Chloro-benzyl)-1*H*-[1,2,3]triazol-4-ylmethoxy]pyridin-2-yl}-3-phenyl-acrylamide (11d).** Yield: 56%; mp 128-129 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.09 (bs, 1H, NH), 8.07 (dd, $^{2}J_{(HH)}$ 5.04 Hz, $^{3}J_{(HH)}$ 0.92 Hz, 1H, H-6), 7.59 (dd, $^{2}J_{(HH)}$ 7.80 Hz, $^{3}J_{(HH)}$ 1.36 Hz, 1H, H-5), 7.43 (s, 1H, H-5''), 7.41-7.39 (m, 2H, H-2',6'), 7.38 (d, $^{3}J_{(HH)}$ 1.36 Hz, 2H, H-3',5'), 7.33 (dd, $^{2}J_{(HH)}$ 6.88 Hz, $^{3}J_{(HH)}$ 2.28 Hz, 1H, CH), 7.29-7.27 (m, 2H, H-4,4'), 7.26 (d, $^{3}J_{(HH)}$ 1.36 Hz, 1H, H-3'''), 7.25-7.23 (m, 2H, H-5''',6'''), 7.16-7.11 (m, 1H, H-4'''), 7.04 (dd, $^{2}J_{(HH)}$ 7.80 Hz, $^{3}J_{(HH)}$ 5.04 Hz, 1H, CH), 5.68 (s, 2H, O-CH_2), 5.27 (s, 2H, N-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 164.8 (C=O), 144.5 (C-2), 143.2 (C-3), 142.9 (C-1',4''), 140.0 (C-1'''), 135.1 (CH), 134.9 (C-5''), 133.2 (C-2'''), 131.9 (CH), 130.5 (C-6), 130.4 (C-2',6'), 130.0 (C-3'''), 129.8 (C-4'), 129.2 (C-3'), 128.7 (C-5'), 128.1 (C-6'''), 127.6 (C-4), 123.5 (C-5), 120.6 (C-4'''), 119.5 (C-5'''), 62.4 (O-CH_2), 51.6 (N-CH_2); MS (EI) : *m/z* 446.3 (M^++1); Anal. Calc. for $C_{24}H_{20}ClN_5O_2$: C, 64.65; H, 4.52; N, 15.71. Found: C, 64.73; H, 4.17; N, 15.33.

***N*-{3-[1-(4-Fluoro-benzyl)-1*H*-[1,2,3]triazol-4-ylmethoxy]-pyridin-2-yl}-3-phenyl-crylamide (11e).** Yield: 58%; mp 169-172 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.20 (bs, 1H, NH), 8.05 (d, $^{3}J_{(HH)}$ 4.56 Hz, 1H, H-6), 7.81 (d, $^{3}J_{(HH)}$ 15.56 Hz, 1H, H-5), 7.62 (s, 1H, H-5''), 7.58-7.56 (m, 2H, H-2',6'), 7.39 (d, $^{3}J_{(HH)}$ 1.84 Hz, 2H, H-3',5'), 7.38-7.36 (m, 2H, CH, H-4), 7.29-7.27 (m, 3H, H-2''',6'''), 7.07 (d, $^{3}J_{(HH)}$ 8.68 Hz, 2H, H-3''',5'''), 7.06 (d, $^{3}J_{(HH)}$ 2.28 Hz, 1H, CH), 5.50 (s, 2H, O-CH_2), 5.26 (s, 2H, N-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 164.1 (C=O), 143.4 (C-2), 143.2 (C-3), 142.1 (C-4''), 139.8 (C-1'), 135.3 (CH), 134.8 (C-5''), 130.1 (CH), 130.0 (C-6), 129.9 (C-2'), 129.8 (C-6'), 128.7 (C-2'''), 128.1 (C-4'), 126.5 (C-3',5'), 123.1 (C-6'''), 120.6 (C-4), 119.6 (C-5), 116.3 (C-3'''), 114.0 (C-5'''), 62.5 (O-CH_2), 53.5 (N-CH_2); MS (EI) : *m/z* 430.2 (M^++1); Anal. Calc. for $C_{24}H_{20}FN_5O_2$: C, 67.12; H, 4.69; N, 16.31. Found: C, 66.83; H, 4.53; N, 16.43.

***N*-{3-[1-(2-Fluoro-benzyl)-1*H*-[1,2,3]triazol-4-ylmethoxy]pyridin-2-yl}-3-phenyl-acrylamide (11f).** Yield: 55%; mp 138-140 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.16 (bs, 1H, NH), 8.05 (s, 1H, H-6), 7.81 (d, $^{3}J_{(HH)}$ 15.60 Hz, 1H, H-5), 7.70 (s, 1H, H-5''), 7.58 (d, $^{3}J_{(HH)}$ 2.40 Hz, 1H, H-2'), 7.37-7.28 (m, 7H, CH, H-4,3',4',5',6',3''',), 7.16-7.07 (m, 4H, CH, H-4''',5''',6'''), 5.60 (s, 2H, O-CH_2), 5.26 (s, 2H, N-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 161.7 (C=O), 144.5 (C-2), 143.1 (C-3), 143.0 (C-4''), 140.3 (C-1',1'''), 135.6 (CH), 134.9 (C-5''), 131.1 (CH), 131.0 (C-6), 130.6 (C-2',6'), 129.9 (C-2'''), 128.7 (C-4'), 128.1 (C-3'), 124.9 (C-5'), 123.4 (C-6'''), 121.5 (C-4), 121.3 (C-4'''), 119.5 (C-3'''), 115.7 (C-5'''), 62.4 (O-CH_2), 47.9 (N-CH_2); MS (EI) : *m/z* 430.2 (M^++1); Anal. Calc. for $C_{24}H_{20}FN_5O_2$: C, 67.12; H, 4.69; N, 16.31. Found: C, 67.43; H, 4.53; N, 16.56.

 ©ARKAT-USA, Inc.

***N*-[3-(1-Allyl-1*H*-[1,2,3]triazol-4-ylmethoxy)pyridin-2-yl]-3-phenyl-acrylamide (11g).** Yield: 45%; mp 120-122 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.45 (bs, 1H, NH), 8.29 (dd, $^{2}J_{(HH)}$ 7.76 Hz, $^{3}J_{(HH)}$ 1.80 Hz, 1H, H-6), 8.12 (s, 1H, H-5), 8.07-8.03 (m, 1H, H-2'), 7.82 (s, 1H, H-5''), 7.81-7.77 (m, 3H, H-3',5',6'), 7.68 (dd, $^{2}J_{(HH)}$ 8.28 Hz, $^{3}J_{(HH)}$ 4.60 Hz, 1H, H-4'), 7.60-7.57 (m, 1H, CH), 7.42-7.37 (m, 2H, CH, H-4), 6.10-5.87 (m, 1H, allyl-CH), 5.57-5.42 (m, 1H, allyl-CH), 5.37-5.31 (m, 3H, allyl-CH, O-CH_2), 5.01-4.91 (m, 2H, N-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 161.9 (C=O), 144.6 (C-2), 143.3 (C-3), 143.1 (C-4''), 140.0 (CH), 135.0 (C-5''), 131.2 (CH), 130.8 (C-6), 130.0 (C-2',6'), 128.8 (C-4'), 128.3 (C-3',5'), 123.6 (C-4), 120.8 (C-5), 62.6 (O-CH_2), 48.0 (N-CH_2); MS (EI) : *m/z* 362.2 (M^++1); Anal. Calc. for $C_{20}H_{19}N_5O_2$: C, 66.47; H, 5.30; N, 19.38. Found: C, 66.14; H, 5.11; N, 19.52.

Supporting Information

Supporting information (Experimental details, ^{1}H and ^{13}C NMR spectra for the compounds **3-5**, **6a-h**, **8-10** and **11a–g**), associated with this article can be found, in the online version.

Acknowledgements

We thank Department of Science and Technology, New Delhi (SR/FT/CS-40/2010) for the research grant. We also thank SAI Labs, Thapar University, Patiala for recording NMR spectra and Punjab University, Chandigarh for recording mass spectra.

References

1. Dadiboyena, S.; Nefzi, A. *Eur. J. Med. Chem*. **2011**, *46*, 5258. http://dx.doi.org/10.1016/j.ejmech.2011.09.016
2. Pitt, W. R.; Parry, D. M.; Perry, B. G. Groom, C. R. *J. Med. Chem*. **2009**, *52*, 2952. http://dx.doi.org/10.1021/jm801513z
3. Mohan, D. C.; Sarang, N. B.; Adimurthy, S. *Tetrahedron Lett*. **2013**, *54*, 6077. http://dx.doi.org/10.1016/j.tetlet.2013.08.112
4. Fesenko, A. A.; Shutalev, A. D. *Tetrahedron Lett*. **2012**, *53*, 6261. http://dx.doi.org/10.1016/j.tetlet.2012.09.022
5. Spencer, J.; Patel, H.; Callear, S. K.; Coles, S. J.; Deadman, J. J. *Tetrahedron Lett*. **2011**, *52*, 5905. http://dx.doi.org/10.1016/j.tetlet.2011.07.147
6. Pagadala, R.; Maddila, S.; Moodley, V.; van Zyl, W. E.; Jonnalagadda, S. B. *Tetrahedron Lett*. **2014**, *55*, 4006. http://dx.doi.org/10.1016/j.tetlet.2014.05.089
7. Behbehani, H.; Ibrahim, H. M. *Tetrahedron*, **2013**, *69*, 10535. http://dx.doi.org/10.1016/j.tet.2013.10.061

 ©ARKAT-USA, Inc.

8. Xie, W.; Xie, S.; Zhou, Y.; Tang, X.; Liu, J.; Yang, W.; Qiu. M. *Eur. J. Med. Chem.* **2014**, *81*, 22. http://dx.doi.org/10.1016/j.ejmech.2014.05.001
9. Berg, R.; Straub, B. F. *Beilstein J. Org. Chem.* **2013,** *9*, 2715. http://dx.doi.org/10.3762/bjoc.9.308
10. Hein, J. E.; Fokin, V. V. *Chem. Soc. Rev.*, **2010**, *39*, 1302. http://dx.doi.org/10.1039/b904091a
11. Meldal, M.; Tornøe, C. W. *Chem. Rev*. **2008**, *108*, 2952. http://dx.doi.org/10.1021/cr0783479
12. Ferreira, S. B.; Sodero, A. C. R.; Cardoso, M. F. C.; Lima, E. S.; Kaiser, C. R.; Silva, F. P.; Ferreira, V. F. *J. Med. Chem*. **2010**, *53*, 2364. http://dx.doi.org/10.1021/jm901265h
13. Yuldasheva, K.; Dzhuraev, A. D.; Makhsumov, A. G.; Amanov, N. *Pharm. Chem. J.* **1991**, *25*, 728. http://dx.doi.org/10.1007/BF00768987
14. Cho, J. H.; Bernard, D. L.; Sidwell, R. W.; Kern, E. R.; Chu, C. K. *J. Med. Chem.* **2006**, *49*, 1140. http://dx.doi.org/10.1021/jm0509750
15. Giffin, M. J.; Heaslet, H.; Brik, A.; Lin, Y.-C.; Cauvi, G.; Wong, C.-H.; McRee, D. E.; Elder, J. H.; Stout, C. D.; Torbett, B. E. *J. Med. Chem.* **2008**, *51*, 6263. http://dx.doi.org/10.1021/jm800149m
16. Reck, F.; Zhou, F.; Girardot, M.; Kern, G.; Eyermann, C. J.; Hales, N. J.; Ramsay, R. R.; Gravestock, M. B. *J. Med. Chem*. **2005**, *48*, 499. http://dx.doi.org/10.1021/jm0400810

 ©ARKAT-USA, Inc.