Tetrahedron Letters 53 (2012) 6059–6066

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

$AlCl_3$ induced C–N bond formation followed by Pd/C–Cu mediated coupling–cyclization strategy: synthesis of pyrrolo[2,3-*b*]quinoxalines as anticancer agents

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ARTICLE INFO

Article history:
Received 6 July 2012
Revised 27 August 2012
Accepted 28 August 2012
Available online 1 September 2012

Keywords:
2,3-Dichloroquinoxaline
Pyrrolo[2,3-*b*]quinoxaline
$AlCl_3$
Palladium

ABSTRACT

$AlCl_3$ facilitated C–N bond forming reaction between 2,3-dichloroquinoxaline and anilines affording a convenient method for the preparation of *N*-aryl substituted 3-chloroquinoxalin-2-amines. A related *N*-benzyl derivative, however, was prepared via a conventional method. These *N*-alkyl/aryl substituted 3-chloroquinoxalin-2-amines on coupling with terminal alkynes in toluene under Pd/C–Cu catalysis afforded a range of 1,2-disubstituted pyrrolo[2,3-*b*]quinoxalines within 3–5 h in good to excellent yields. Some of the compounds synthesized showed promising anti-proliferative properties when tested in vitro against two cancer cell lines. Docking studies indicated that these molecules interact well with human Akt in silico.

While a broad spectrum of biological activities is known for quinoxaline and its derivatives[1] only limited pharmacological properties have been documented for the pyrroloquinoxaline class of compounds. These include the study of pyrrolo[1,2-*a*]quinoxalines as potent and selective 5-HT3 receptor ligands[2] and inhibitors of Akt kinase.[3] Due to their key role in tumor cell survival/proliferation and their over expression/activation in many human cancers Akt, serine/threonine protein kinase [also known as protein kinase B (PKB)] represents an attractive and potential target for therapeutic intervention. Thus, pyrrolo[1,2-*a*]quinoxaline (**A**, Fig. 1) based compounds were tested for their in vitro ability to inhibit the proliferation of the human leukemic cell lines K562, U937, and HL60, and the breast cancer cell line MCF7.[3a] Notably, three of these human cell lines (K562, U937, and MCF7) exhibited an active phosphorylated Akt form. A follow up study focusing on the SAR of new pyrrolo[1,2-*a*]quinoxalines indicated the importance of substitution at the C-4 position of the pyrroloquinoxaline ring and the need for a functionalization on the pyrrole ring.[3b] All these observations and our continuing interest on quinoxaline derivatives[4] prompted us to examine the anti cancer properties of a series of compounds based on regioisomeric pyrrolo[2,3-*b*]quinoxaline scaffold (**C**, Fig. 1). The structure **C** was reached from **A** via **B** by (i) dissecting the C–N bond of the 5-membered ring of **A** and connecting the carbon end to the C-4 to create a new pyrrole ring (ii) further functionalization of this newly created pyrrole ring. Overall our design was aimed toward the linear molecular shape of pyrroloquinoxaline as derivatives possessing this geometry, which were reported to be of potential pharmacological interest earlier.[1f] Herein we report our preliminary results on in vitro pharmacological evaluation of 1,2-disubstituted pyrrolo[2,3-*b*]quinoxalines as potential anti cancer agents.

The synthesis of pyrrolo[2,3-*b*]quinoxalines has previously been reported by the reaction of 2-alkynyl-3-trifluoroacetamidoquinoxalines with aryl and vinyl halides or triflates.[5] The methodology however required protecting and deprotecting steps to synthesize the necessary alkynylaminoquinoxalines. A more straightforward method was reported in 2010 that involved the reaction of *N*-alkyl-3-chloroquinoxaline-2-amine with terminal alkynes in the presence of $PdCl_2$–PPh_3–CuI as a catalyst system, K_2CO_3, and a surfactant, for example, lauryl sulfate in water.[6] In addition to

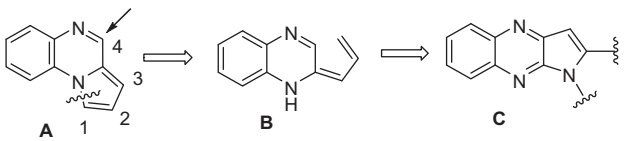

Figure 1. Design of pyrrolo[2,3-*b*]quinoxaline scaffold **C** from the regioisomeric pyrrolo[1,2-*a*]quinoxaline template **A**.

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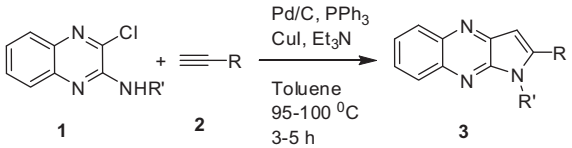
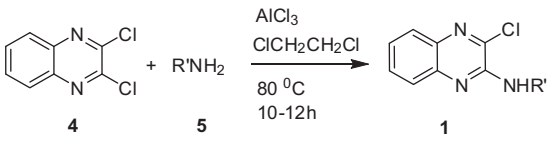
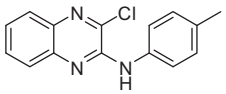
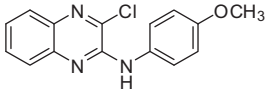
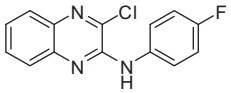
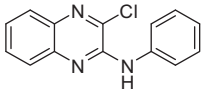
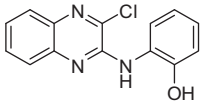
0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.08.119



Scheme 1. Pd/C-mediated synthesis of 1,2-disubstituted pyrrolo[2,3-*b*]quinoxalines.

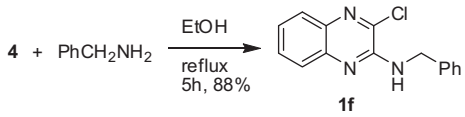
Table 1
$AlCl_3$ mediated synthesis of *N*-aryl substituted 3-chloroquinoxalin-2-amine (**1**)[a]



Entry	*N*-Aryl-3-chloroquinoxalin-2-amine (**1**)	Time (h)	Yield[b] (%)
1	 **1a**	10	75
2	 **1b**	11	72
3	 **1c**	12	70
4	 **1d**	10	72
5	 **1e**	10	55[c]

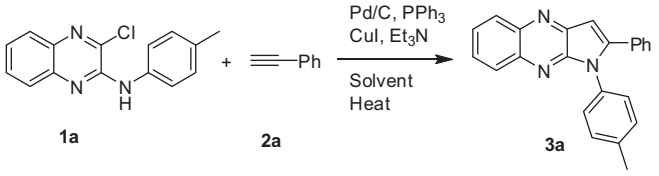
[a] All reactions were carried out using 2,3-dichloroquinoxaline (**1**, 1.0 mmol), an appropriate amine (**2**, 1.0 mmol) and $AlCl_3$ (1.1 mmol) in 1,2-dichloroethane (5 mL) at 80 °C under nitrogen.
[b] Isolated yields.
[c] Formation of a side product, for example, 3-chloro-*N*-(2-(3-chloroquinoxalin-2-yloxy)phenyl)quinoxalin-2-amine was observed.

the requirement of longer reaction time (20 h) the study was limited to the use of *N*-alkyl-3-chloroquinoxaline-2-amine only and no corresponding *N*-aryl derivatives were examined. A subsequent study on the use of propargyl bromide as an alkyne coupling partner in the presence of $(PPh_3)_2PdCl_2$, CuI, and aqueous morpholine was also limited to the use of *N*-alkyl derivatives.[7] Additionally, the alkynes employed in both the cases lacked variations. Very recently, inspired by our success of using Pd/C–CuI as a catalytic system for the efficient Sonogashira coupling[8] a Pd/C-catalyzed, multicomponent reaction of 1,2-dichloroquinoxaline with hydrazine hydrate, phenyl acetylene, and a variety of aldehydes have been reported to afford *N*-substituted pyrrolo[2,3-*b*]quinoxalines in water.[9] While the methodology appeared to be interesting the study once again was limited to the use of phenyl acetylene. It was therefore necessary to develop a more versatile, faster, and inexpensive approach for the synthesis of pyrrolo[2,3-*b*]quinoxalines. More importantly, the methodology was expected to provide us access to our targeted library of molecules based on **C** (Fig. 1). The Pd/C being an inexpensive, easily separable, and recyclable catalyst was the obvious choice[10] for the development of our required methodology. Indeed, we observed that Pd/C–Cu mediated coupling of *N*-alkyl/aryl substituted 3-chloroquinoxalin-2-amine (**1**) with terminal alkynes (**2**) in toluene afforded 1,2-disubstituted pyrrolo[2,3-*b*]quinoxalines (**3**) within 3–5 h (Scheme 1).



Scheme 2. Preparation of *N*-benzyl-3-chloroquinoxalin-2-amine (**1f**).

Table 2
Effect of reaction conditions on Pd/C-mediated coupling of **1a** with **2a**[a]



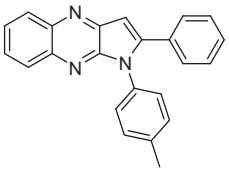
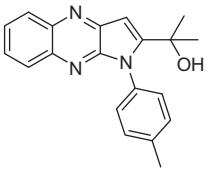
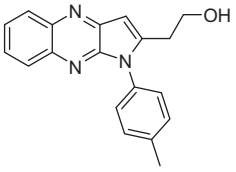
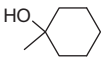
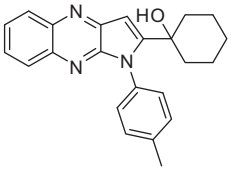
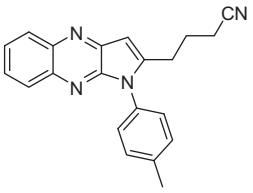
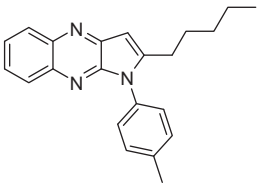
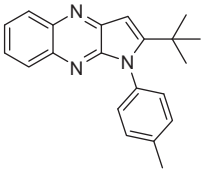
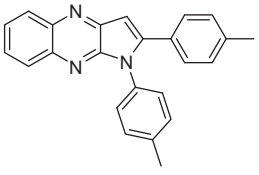
Entry	Pd-catalyst	Solvent	Time[b] (h)	Yield[c] (%)
1	10% Pd/C–PPh_3	Toluene	3	92
2	10% Pd/C–PPh_3	Toluene	6	82
3	10% Pd/C–PPh_3[d]	Toluene	3	40
4	10% Pd/C–PPh_3	Ethanol	6	60[e]
5	10% Pd/C–PPh_3	Methanol	6	60[e]
6	10% Pd/C–PPh_3	CH_3CN	6	65[e]

[a] All reactions were carried out by using **1a** (1.0 mmol), **2a** (1.8 mmol), 10% Pd/C (0.028 mmol), PPh_3 (0.15 mmol), CuI (0.052 mmol), Et_3N (2.5 mmol) in a solvent (5 mL) at 95–100 °C under N_2.
[b] After adding **2a**.
[c] Isolated yields.
[d] The reaction was carried out without the CuI.
[e] The reaction was carried out at refluxing temp.

The preparation of key starting material, for example, *N*-aryl substituted 3-chloroquinoxalin-2-amine (**1**) required for our study was an initial challenge as unlike aliphatic amines[6] the nucleophilic substitution of 2,3-dichloroquinoxaline (**4**) with aromatic amines (**5**) did not proceed well. While the reaction proceeded in the presence of a base, for example, Et_3N a mixture of products, that is, compound **1** along with the corresponding N^2,N^3-diarylquinoxaline-2,3-diamines were isolated in this case. Finally, the compound **1a–e** was prepared in acceptable yield via the reaction of **4** with **5** in the presence of $AlCl_3$ in 1,2-dichloroethane (Table 1). While, the present strategy of $AlCl_3$ mediated C–N bond forming reaction was not known earlier the methodology however did not work when an aliphatic amine was used perhaps due to its complexation with $AlCl_3$. Thus, *N*-benzyl-3-chloroquinoxalin-2-amine (**1f**) was prepared via the reaction of **4** with benzyl amine in EtOH (Scheme 2).[6] The use of 2,3-dibromoquinoxaline prepared according to the reported method[5] was also explored in our present strategy. While the reaction proceeded well when benzyl amine was used (in EtOH under refluxing condition for 5 h to give the corresponding *N*-benzyl-3-bromoquinoxalin-2-amine in 69% yield), it afforded a complex mixture of products when 4-methylaniline was used in the presence of $AlCl_3$ under the conditions presented in Table 1.

Having prepared the required starting materials we then chose to examine the coupling of compound **1a** with phenyl acetylene (**2a**) in the presence of 10% Pd/C–PPh_3–CuI and Et_3N in a range of

Table 3
Pd/C–Cu mediated synthesis of 1,2-disubstituted pyrrolo[2,3-*b*]quinoxalines (**3**) (Scheme 1)[a]

Entry	Chloro compound (**1**)	Alkyne; R= (**2**)	Product (**3**)	Time[b] (h)	Yield[c] (%)
1	**1a**	–Ph **2a**	 **3a**	3	92
2	**1a**	–CMe_2OH **2b**	 **3b**	3.2	82
3	**1a**	–CH_2CH_2OH **2c**	 **3c**	4	79
4	**1a**	 **2d**	 **3d**	5	75
5	**1a**	–$(CH_2)_3CN$ **2e**	 **3e**	4.2	90
6	**1a**	–$(CH_2)_4CH_3$ **2f**	 **3f**	3	92
7	**1a**	–$C(CH_3)_3$ **2g**	 **3g**	4.5	83
8	**1a**	–$C_6H_4CH_3$-*p* **2h**	 **3h**	3.5	89

(*continued on next page*)

Table 3 (*continued*)

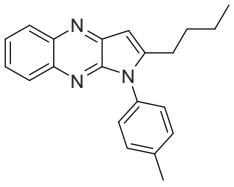
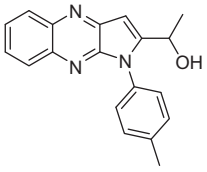
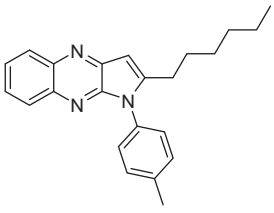
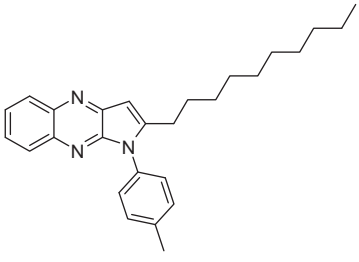
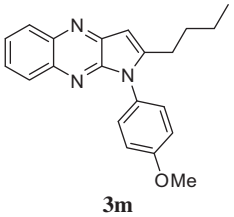
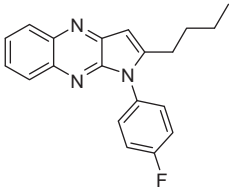
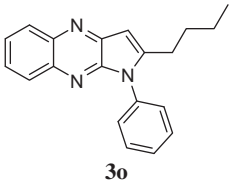
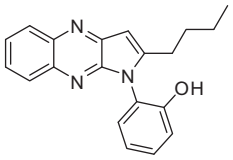
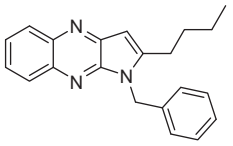
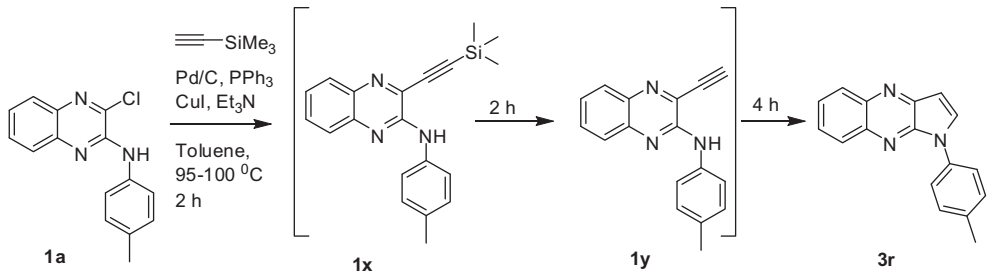
Entry	Chloro compound (**1**)	Alkyne; R= (**2**)	Product (**3**)	Time[b] (h)	Yield[c] (%)
9	**1a**	$-(CH_2)_3CH_3$ **2i**	 **3i**	3.2	84
10	**1a**	$-CH(OH)CH_3$ **2j**	 **3j**	4	90
11	**1a**	$-(CH_2)_5CH_3$ **2k**	 **3k**	3.5	85
12	**1a**	$-(CH_2)_9CH_3$ **2l**	 **3l**	3	87
13	**1b**	**2i**	 **3m**	5	82
14	**1c**	**2i**	 **3n**	4	89
15	**1d**	**2i**	 **3o**	4	78

Table 3 (*continued*)

Entry	Chloro compound (**1**)	Alkyne; R= (**2**)	Product (**3**)	Time[b] (h)	Yield[c] (%)
16	**1e**	**2i**	 **3p**	5	74
17	**1f**	**2i**	 **3q**	5	62

[a] All reactions were carried out by using **1** (1.0 mmol), **2** (1.8 mmol), 10% Pd/C (0.028 mmol), PPh_3 (0.15 mmol), CuI (0.052 mmol), Et_3N (2.5 mmol) in toluene (5 mL) at 95–100 °C under N_2.
[b] After adding **2**.
[c] Isolated yields.



Scheme 3. Coupling of **1a** with trimethylsilyl acetylene under Pd/C–Cu catalysis.

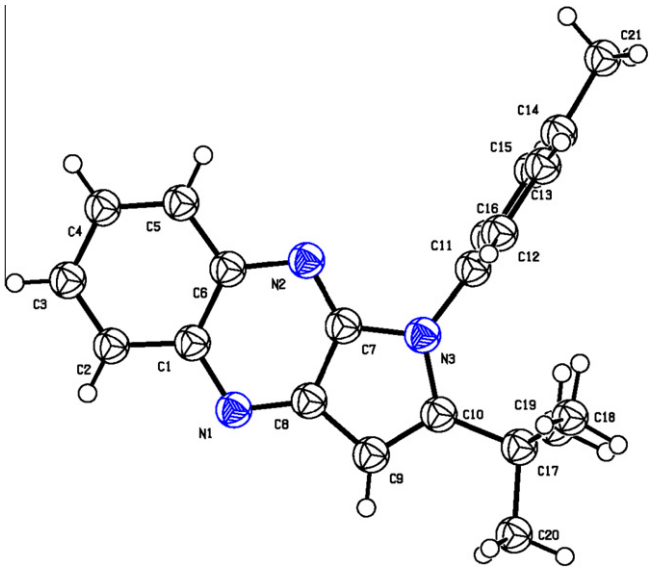
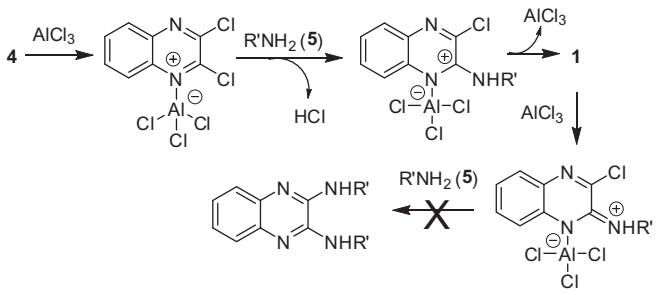


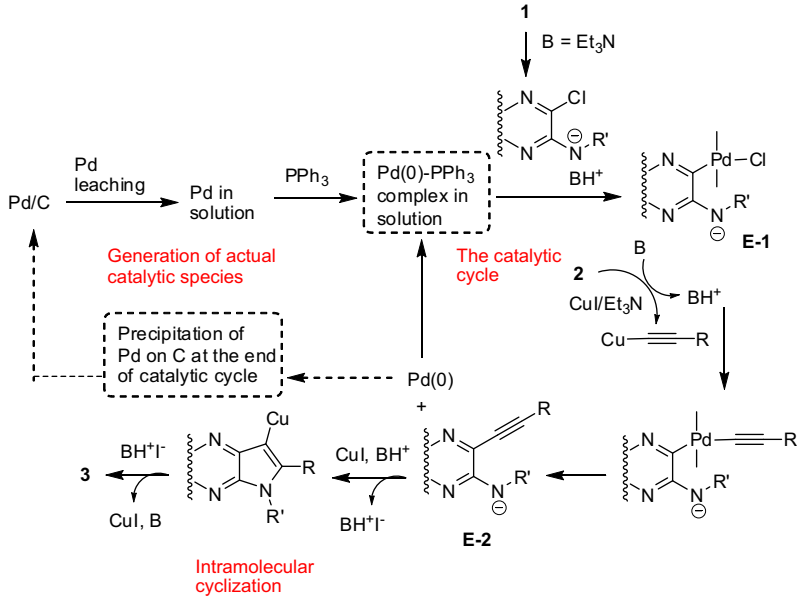
Figure 2. ORTEP representation of the compound **3g** (thermal ellipsoids are drawn at 50% probability level).



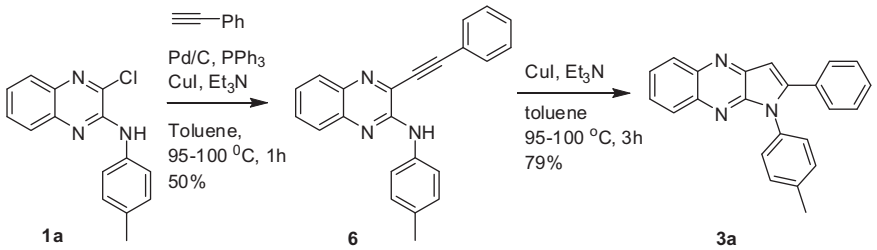
Scheme 4. Proposed mechanism for the $AlCl_3$ induced C–N bond forming reaction between **4** and **5** leading to the 3-chloroquinoxaline derivative **1**.

solvents (Table 2). We observed that the reaction proceeded smoothly in toluene at 95–100 °C affording the desired compound **3a** as the only product (Table 2, entry 1). The reaction was carried out for 3 h and a longer reaction time did not improve the product yield (Table 2, entry 2). The absence of CuI decreased the product yield significantly (Table 2, entry 3) indicating the need of CuI for the reaction to proceed smoothly. The use of other solvents, for example, EtOH, MeOH, and CH_3CN was also examined and found to be less effective in terms of product yield (Table 2, entries 4, 5, and 6). Thus a combination of Pd/C–PPh_3–CuI and Et_3N in toluene was found to be optimum for the present coupling–cyclization reaction.

Having established the optimized reaction conditions we then examined the generality and scope of the present synthesis of pyrrolo[2,3-*b*]quinoxaline. Thus, compounds **1a–f** were treated with a variety of terminal alkynes under the conditions of entry 1 of Table 2 and the results are summarized in Table 3. Both aromatic (Table 3, entries 1 and 8) and aliphatic alkynes (Table 3, entries 2–7 and 9–17) participated well in this reaction affording the desired products in good yields. Various groups such as primary, secondary, and



Scheme 5. Proposed mechanism for the synthesis of 1,2-disubstituted pyrrolo[2,3-*b*]quinoxalines (**3**) under the catalysis of Pd/C–CuI–PPh_3.



Scheme 6. Cu-mediated cyclization of compound **6**.

tertiary alcohol, CN, ^{t}Bu etc present in the terminal alkynes (**2**) employed were well tolerated. Similarly, both *N*-aryl and *N*-alkyl substituted 3-chloroquinoxaline-2-amines participated well in the present reaction. The reactions were completed within 3–5 h. Notably, the coupling of **1a** with trimethylsilyl acetylene under the reaction conditions employed provided 1-*p*-tolyl-1*H*-pyrrolo[2,3-*b*]quinoxaline (**3r**) via a stepwise formation of intermediate **1x** followed by **1y** (Scheme 3). Both the intermediates were isolated and well characterized. This observation helped in proposing a probable mechanism for the present coupling–cyclization under Pd/C–Cu catalysis. All the 1,2-disubstituted pyrrolo[2,3-*b*]quinoxalines synthesized were characterized by spectral (NMR, IR, and MS) data and this was supported by the molecular structure of a representative compound **3g** being confirmed unambiguously by single crystal X-ray diffraction study (Fig. 2).[11] Interestingly, the *N*-aryl group of **3g** was found to be in a perpendicular plane to that of the core pyrrolo[2,3-*b*]quinoxaline ring.

Mechanistically, the amination of 2,3-dichloroquinoxaline (**4**) seems to proceed through the complexation of $AlCl_3$ with one of the ring nitrogens[12a] of **4** followed by nucleophilic attack by the amine **5** and finally release of $AlCl_3$ affording the desired product **1** (Scheme 4). A second nucleophilic attack on **1** was disfavored perhaps due to the preferential complexation of $AlCl_3$ with the N-1 (aided by the adjacent NHR′ group) over N-4 of **1**. Notably, unlike phenols the aromatic amines did not participate in the C–C bond forming reactions[12b–f] under the conditions employed due to the higher nucleophilicity of $-NH_2$ group over phenolic –OH moiety. Nevertheless, based on the outcome of Scheme 3 a probable mechanism for the Pd/C–Cu mediated coupling–cyclization step is presented in Scheme 5. The reaction proceeds through the generation of an active Pd(0) species from the minor portion of the bound palladium (Pd/C) via a Pd leaching process into the solution.[10] The leached Pd then interacts with phosphine ligands to give a dissolved Pd(0)–PPh_3 complex which actually catalyzes the C–C bond forming reaction in solution. Once generated the active Pd(0) species undergoes oxidative addition with **1** to give the organo-Pd(II) species **E-1**. The species **E-1** then facilitates the stepwise formation of C–C bond via (i) trans organometallation with copper acetylide generated in situ from CuI and the terminal alkyne (**2**) followed by (ii) reductive elimination of Pd(0) (which is re-precipitated on the surface of the charcoal) to afford the internal alkyne **E-2**. The alkyne **E-2** thus formed subsequently undergoes Cu-mediated intramolecular ring closure[13] to give the desired product **3**. This was further supported by the fact that the compound **6** (obtained via Pd/C–Cu mediated reaction of **1a** with phenyl acetylene for 1 h) underwent intramolecular cyclization when treated with CuI in the presence of Et_3N to give the corresponding pyrrolo[2,3-*b*]quinoxaline derivative **3a** (Scheme 6).

Having prepared a variety of 1,2-disubstituted pyrrolo[2,3-*b*]quinoxalines we aimed for structural elaboration of a representative compound, for example, **3g**. Thus, 3-bromo-2-*tert*-butyl-1-*p*-tolyl-1*H*-pyrrolo[2,3-*b*]quinoxaline **7** prepared via bromination of **3g** by using *N*-bromo succinamide (see Supplementary data) was amenable for further derivatization through transition metal mediated various C–C and C–N bond forming reactions such as Sonogashira, Heck, Suzuki or Buchwald reactions.

Table 4
The % inhibition of growth of cancer cell lines by compound **3**[a]

Compounds	K-562 (leukemia)			MDA-MB-231 (breast)		
	100 μM	10 μM	1 μM	100 μM	10 μM	1 μM
3b	37.8	29.2	23.1	57.5	55.0	43.8
3c	32.3	27.1	27.8	75.0	55.8	43.5
3d	54.9	50.4	46.6	70.1	60.2	45.7
3e	58.7	49.0	43.4	61.3	50.2	48.6
3f	40.2	29.9	27.0	54.6	49.5	42.5
3g	42.5	39.5	35.6	49.5	45.3	38.1
3j	38.8	28.7	26.6	52.6	47.7	37.1

[a] Data presented are the average of three experiments.

Some of the compounds[14] (**3**) synthesized were tested in vitro for their anti-proliferative properties against leukemia (K-562) and breast (MD-AMB-231) cancer cell lines in a MTT assay. Harmine, a member of beta-carboline family of compounds showed cytotoxicity against HL60 and K562 cell lines[15] was used as a reference compound in this assay.[16] The results of active molecules identified by this assay are presented in Table 4. While **3d** and **3e** showed good activity against leukemia cells (Table 4), most of the compounds, for example, **3b**, **3c**, **3d**, **3e,** and **3f** were found to be effective against breast cancer and **3e** being the best among them (Table 4). The compound **3e** showed significant anti-proliferative properties at all the concentrations tested and maintained the same at low concentrations. Notably, IC_{50} value of Harmine was found to be 45 and 54 μM when tested against K-562 and MDA-MB 231 cell lines in our MTT assay. The compound **3e** therefore appeared to be a promising and potential anticancer agent of further interest. These findings also suggest that pyrrolo[2,3-*b*]quinoxaline framework could be a new template for the design and identification of small molecules that could be useful for the potential treatment of leukemia or breast cancer.

Prompted by the reported Akt kinase inhibitory properties of pyrrolo[1,2-*a*]quinoxaline class of compounds[3] we decided to assess the Akt kinase inhibitory potential of compounds **3d** and **3e** in silico. Thus, these molecules were docked in human Akt (PDB 3MVH). The interactions of compound **3d** with Akt kinase protein were mainly contributed by (i) H-bond between OH of **3d** and the asn 279 and (ii) Pi-cation interaction of benzene ring of **3d** with lys179 (see Supplementary Fig. 1). Similarly, (i) a H-bond between the nitrile of **3e** with asp 439 and (ii) Pi-cation interaction of the benzene ring of **3e** with arg4 was observed in the other case (see Supplementary Fig. 2). The compound **3d** showed a dock score of −4.18 whereas that of compound **3e** was −5.46. The major contributing factor for these scores was lipophilic energy. While both the molecules filled the active site partially however this partial filling of active site gave good lipophilic scores. Thus, both the compounds showed good interactions with human Akt in silico. The observed anticancer properties of these molecules therefore could be due to their potential Akt kinase inhibitory properties.

In conclusion, *N*-aryl substituted 3-chloroquinoxalin-2-amines were elegantly prepared via $AlCl_3$ induced C–N bond forming reaction between 2,3-dichloroquinoxaline and aromatic amines affording a new method for the preparation of this class of compounds. A related *N*-benzyl derivative however was prepared via a conventional method as the $AlCl_3$ induced method did not work in this case. These *N*-alkyl/aryl substituted 3-chloroquinoxalin-2-amines on coupling with terminal alkynes in toluene under Pd/C–Cu catalysis afforded a range of 1,2-disubstituted pyrrolo[2,3-*b*]quinoxalines within 3–5 h in good to excellent yields. A probable mechanism of the C–N bond forming reaction and the coupling–cyclization process has been presented. The single crystal X-ray diffraction study of a representative compound indicated that the *N*-aryl group was in a perpendicular plane to that of the core pyrrolo[2,3-*b*]quinoxaline ring. Some of the compounds synthesized showed promising anti-proliferative properties when tested in vitro against two cancer cell lines. Docking studies indicated that these molecules interact well with human Akt in silico. Overall, our effort has led to the identification of pyrrolo[2,3-*b*]quinoxaline based small molecules that could be useful for the potential treatment of leukemia or breast cancer.

Acknowledgments

The authors thank Professor J. Iqbal for encouragement and support. M.P. thanks the DST, New Delhi, India for financial support (Grant No. SR/S1/OC-53/2009). K.S. thanks the UGC, New Delhi, India for a Dr. D.S. Kothari Post doctoral fellowship [No. F.4–2/2006(BSR)/13–24/2010(BSR)]. B. Prasad thanks the CSIR, New Delhi, India for a Senior Research Fellowship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.119.

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11. *Crystal data of* ***3g***: Molecular formula = $C_{21}H_{21}N_3$, formula weight = 315.41, crystal system = triclinic, space group = P-1, a = 9.017 (15) Å, b = 9.324 (16) Å, c = 10.768 (18) Å, V = 821.4 (2) Å^3, T = 296 K, Z = 2, D_c = 1.283 Mg m^{-3}, μ(Mo-Kα) = 0.08 mm^{-1}, 10844 reflections measured, 3582 independent reflections, 2881 observed reflections [$I > 2.0\ \sigma$ (I)], R1_obs = 0.028, goodness of fit = 1.03. Crystallographic data (excluding structure factors) for **3g** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 876150.
12. (a) This was further supported by the fact that 2-chloro-3-*p*-chloroanilino quinoxaline was obtained by refluxing an aqueous suspension of 2,3-dichloroquinoxaline and *p*-chloroaniline in the presence of very dilute hydrochloric acid, see: Haworth, R. D.; Robinson, S. *J. Chem. Soc.* **1948**, 777. The reaction seems to proceed through the protonation of one of the ring

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