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$AlCl_3$ 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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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

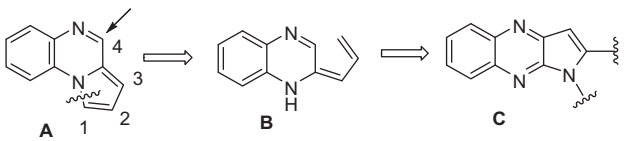

Figure 1. Design of pyrrolo[2,3-*b*]quinoxaline scaffold **C** from the regioisomeric pyrrolo[1,2-*a*]quinoxaline template **A**.

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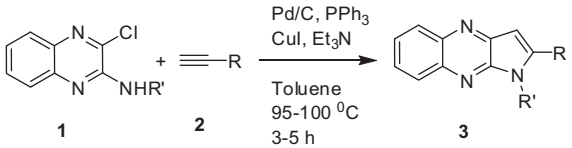
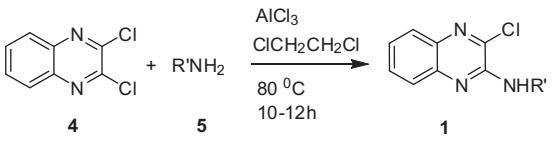
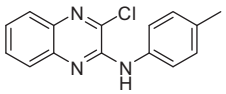
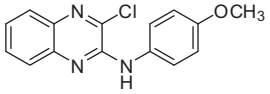
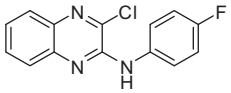
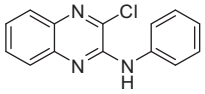
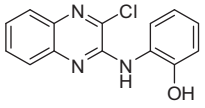


Scheme 1. Pd/C-mediated synthesis of 1,2-disubstituted pyrrolo[2,3-*b*]quinoxalines.

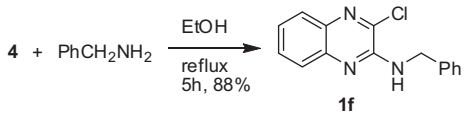
Table 1
$AlCl_3$ mediated synthesis of *N*-aryl substituted 3-chloroquinoxalin-2-amine (**1**)[a]



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]

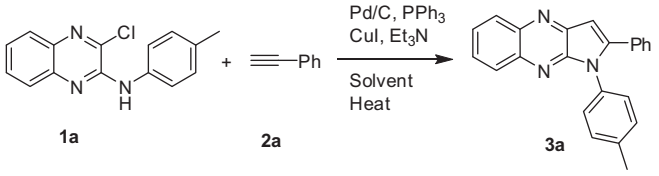
[a] All reactions were carried out using 2,3-dichloroquinoxaline (**1**, 1.0 mmol), an appropriate amine (**2**, 1.0 mmol) and $AlCl_3$ (1.1 mmol) in 1,2-dichloroethane (5 mL) at 80 °C under nitrogen.
[b] Isolated yields.
[c] Formation of a side product, for example, 3-chloro-*N*-(2-(3-chloroquinoxalin-2-yloxy)phenyl)quinoxalin-2-amine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