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$AlCl_3$ induced C-arylation/cyclization in a single pot: a new route to benzofuran fused *N*-heterocycles of pharmacological interest

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ABSTRACT

A new and one-pot synthesis of benzofuran fused *N*-heterocycles has been accomplished via $AlCl_3$-mediated C–C followed by C–O bond formation between 2,3-dichloropyrazine or its derivatives and phenols. The methodology provided novel compounds as potential inhibitors of PDE4B. The single crystal X-ray data of a synthesized benzofuran derivative are presented. Scope of the methodology, in vitro pharmacological data of some of the synthesized compounds, along with docking study of an active compound are described.

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Conformational restriction of bioactive molecules offers the possibility of generating attractive structures that may provide valuable insights regarding the interaction of the precursory flexible molecule with the putative receptor or enzyme. A series of polycyclic derivatives **B** therefore were generated by introducing restrictions in the parent compounds **A** (Fig. 1).[1a]

Since this strategy has been viewed as a potential opportunity for the identification of compounds possessing increased potency, we became interested in the synthesis and pharmacological evaluation of a series of nitrogen containing heterocycles **C** possessing benzofuran moiety as a central ring (Fig. 2). We were further encouraged by the pharmacological properties of similar class of compounds, for example, **D** (Elbfluorene—ALX-270-389) as selective inhibitor of cyclin-dependent kinase 1 (CDK1/cyclin B; IC_{50} = 4.2 μM)[1b] or a benzofuro[3,2-*d*]pyrimidine derivative MP-470 (**E**) as an inhibitor of multitargeted receptor tyrosine kinase (Fig. 2).[2] Both the compounds are presently undergoing phase 1 clinical trials. In our effort[3] to identify novel inhibitors of PDE4 (phosphodiesterase 4) we were particularly interested in assessing PDE4 inhibitory properties of compounds **C** in vitro. While PDE4 inhibitory properties of benzofuran derivatives have been reported earlier[4–6] to the best of our knowledge the use of benzofuran fused *N*-heterocycle has not been explored as a potential template for the discovery of novel PDE4 inhibitors.

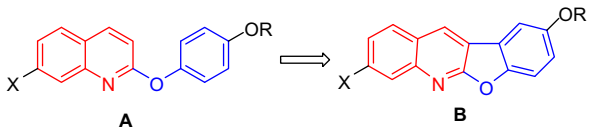

Figure 1. Design of polycyclic structure **B** via conformational restriction of ether derivative **A**.

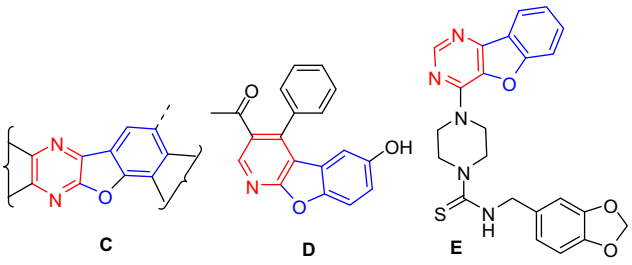

Figure 2. Benzofuran fused *N*-heterocycles: designed compound **C** and reported bioactive molecules **D** and **E**.

A number of methods have been reported for the synthesis of benzo[4,5]furo heterocycles[1,7] which include (i) construction of the heterocyclic ring on the furan ring of benzofuran moiety, (ii) intramolecular cyclization (C–C bond formation) leading to a furan

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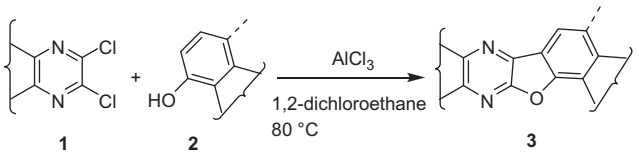
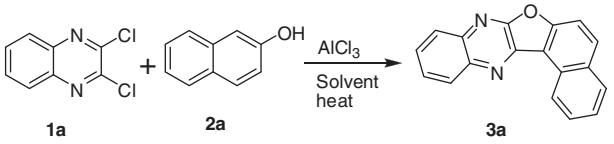


Scheme 1. One-pot **s**ynthesis of benzofuran fused *N*-heterocycles.

ring fused between the benzene and heterocyclic moiety pre-connected through an ether linkage, and (iii) intramolecular cyclization (C–O bond formation) of *o*-hydroxyaryl heteroarenes. All these approaches however require lengthy multistep synthesis or harsh reaction conditions or the use of special reagents/transition metal catalysts. While the third approach offers notable synthetic opportunities as its application in the synthesis of benzofuran fused *N*-heterocycles represented by **C** is less common.[7a,8] Recently, we have observed that derivatives of 2,3-dichloropyrazine reacted smoothly with phenols in the presence of $AlCl_3$ to give benzofuran fused *N*-heterocycles in a good yield. In this Letter we present our preliminary results of this $AlCl_3$ induced C–C followed by C–O bond formation leading to the compound **C** (or **3**, Scheme 1).

$AlCl_3$-induced C–C bond forming reaction between heteroaryl chlorides containing –C(Cl)=N– moiety and various arenes or heteroarenes has been explored by us earlier.[9] We envisaged that a similar reaction between heteroaryl chlorides containing –N=C(Cl)–C(Cl)=N– moiety using phenols may proceed one-step further, that is, intramolecular cyclization via a C–O bond forma-

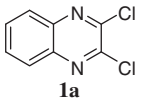
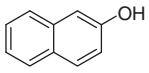
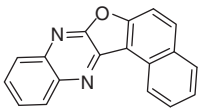
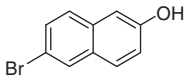
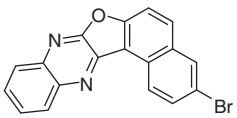
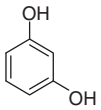
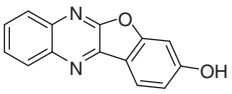
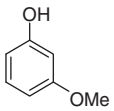
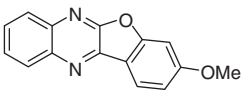
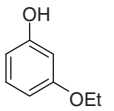
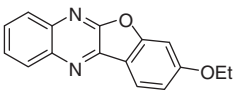
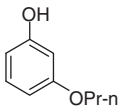
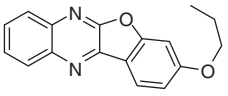
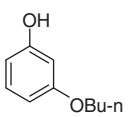
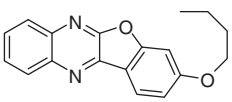
Table 1
The reaction of **1a** with **2a** under various conditions[a]



Entry	Solvent	Time[b] (h)	%Yield[c]
1	$ClCH_2CH_2Cl$	1	89
2	$ClCH_2CH_2Cl$	8	85[d]
3	CH_2Cl_2	12	62[d]
4	$CHCl_3$	12	78[d]
5	EtOAc	3	75
6	CH_3CN	4	80
7	Toluene	6	40

[a] All the reactions were carried out using compound **1a** (1.0 equiv), **2a** (1.0 equiv) and $AlCl_3$ (1.0 equiv) in a solvent (5 mL) at 80 °C followed by addition of extra quantity of $AlCl_3$ (1.0 equiv) and then stirring again at 80 °C.
[b] Total time taken to yield the product **3a**.
[c] Isolated yield.
[d] The reaction was carried out at 40–60 °C for both the step.

Table 2
Synthesis of benzofuran fused *N*-heterocycles (**3**) via $AlCl_3$-mediated C–C and C–O bond forming reaction between **1** and **2**[a]

Entry	Hetaryl chlorides (**1**)	Phenols (**2**)	Products (**3**)	Yield[b] (%)
1	 **1a**	 **2a**	 **3a**	85
2	**1a**	 **2b**	 **3b**	84
3	**1a**	 **2c**	 **3c**	80
4	**1a**	 **2d**	 **3d**	78
5	**1a**	 **2e**	 **3e**	78
6	**1a**	 **2f**	 **3f**	80
7	**1a**	 **2g**	 **3g**	75

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