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A direct access to bioactive fused N-heterocyclic acetic acid derivatives†

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A Cu-catalyzed new sequence involving the Ullmann type intermolecular C–C followed by an intramolecular C–N coupling and then intramolecular aza-Michael type addition (and oxidation) in a single pot afforded various fused N-heterocyclic acetic acid derivatives as inhibitors of PDE4.

The development of direct, simple and efficient strategies that offer ample flexibilities is of high demand in modern organic synthesis. The use of metal catalyzed domino reactions[1] has attracted considerable interest for this purpose, because of their ability to produce diverse and novel classes of compounds in a single synthetic operation.

The N-heterocyclic acetic acid framework **A** (Fig. 1) is prevalent in many bioactive compounds, including non-steroidal anti-inflammatory drugs[2] (NSAIDs) *e.g.* indomethacin, tolmetin, zomepirac *etc.* The impressive and proven anti-inflammatory activities of these drugs prompted us to explore fused N-heterocyclic acetic acids as a novel class of potential inhibitors[3] of phosphodiesterase 4 (PDE4). The development of PDE4 inhibitors[4] is beneficial, as in addition to chronic obstructive pulmonary

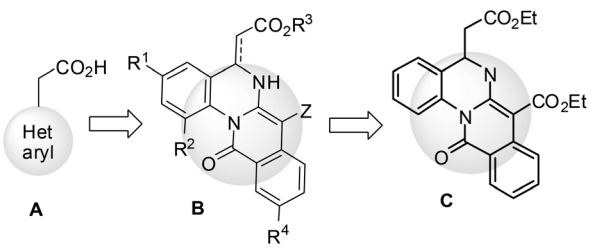

Fig. 1 Design of novel bioactive molecules **B**/**C** (as potential PDE4 inhibitors) derived from **A**.

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†Electronic supplementary information (ESI) available: Experimental procedures, spectral data for all new compounds, copies of spectra, results of *in vitro* and docking studies. See DOI: 10.1039/c3ob42535e

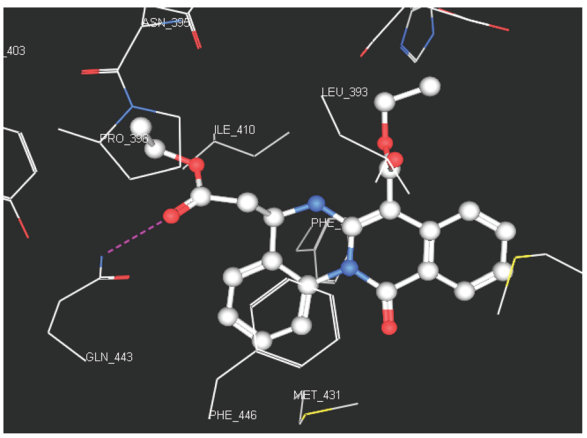
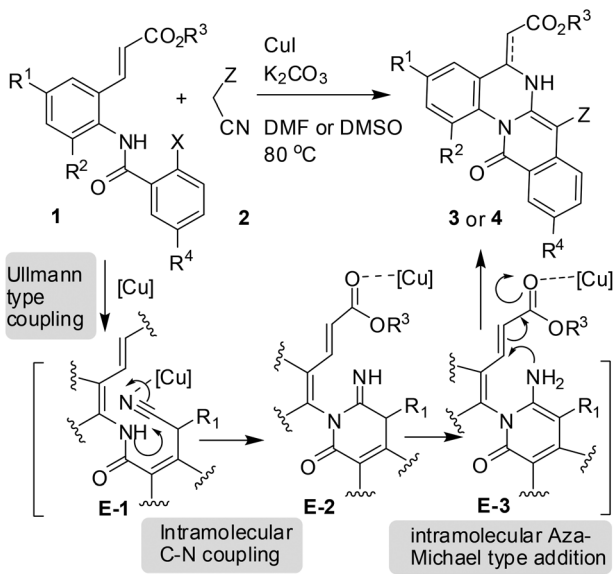
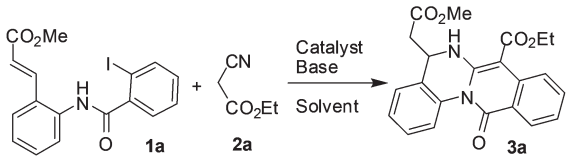


Fig. 2 Docking of **C** into the active site of PDE4B (PDB code 1XMY).



Scheme 1 Synthesis of **3** *via* Cu-catalyzed domino reactions.

Table 1 Effect of conditions on domino reaction of **1a** with **2a**[a]



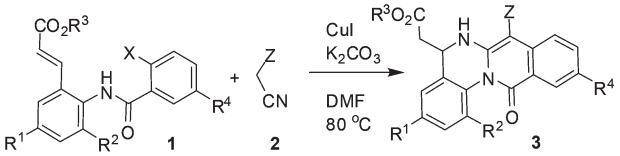
Entry	Catalyst	Base	Solvent	Yield[b] (%)
1	CuI	K_2CO_3	DMF	89
2	CuI	Na_2CO_3	DMF	79
3	CuI	Cs_2CO_3	DMF	88
4	CuI	K_2CO_3	DMSO	88
5	CuI	K_2CO_3	1,4-Dioxane	53
6	CuBr	K_2CO_3	DMF	80
7	CuCl	K_2CO_3	DMF	71
8	$Cu(OAc)_2$	K_2CO_3	DMF	78
9	$Cu(OTf)_2$	K_2CO_3	DMF	80
10	CuI	K_2CO_3	DMF	0[c]
11	—	K_2CO_3	DMF	0

[a] Reactions were carried out using **1a** (1 mmol), **2a** (1.2 mmol), catalyst (0.1 mmol) and base (3 mmol) in a solvent (2 mL) at 80 °C for 0.5 h under anhydrous conditions (no inert atmosphere). [b] Isolated yield. [c] Reaction performed at room temperature.

disease (COPD) and asthma, PDE4 has been reported as a potential therapeutic target for neurodegenerative diseases, cancer and memory loss. Most of the leading PDE4 inhibitors, including the marketed drug roflumilast (Daxas®, Nycomed), suffer from side effects including nausea and emesis.[4] It is therefore desirable to identify novel PDE4 inhibitors having fewer side effects. In our effort, initial *in silico* docking studies of a representative compound **C**, in the active site of PDE4B, aided us in the design of the target molecules **B** (Fig. 1 and 2). To obtain **B** we have developed a direct, Cu-mediated domino reaction, leading to the one-pot synthesis of **B** (or **3** and **4**, Scheme 1) under mild conditions without using any co-catalyst, ligand or additive. Herein, we report our preliminary results.

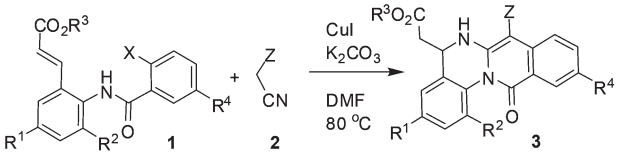
While more simple heterocyclic acid derivatives have been prepared *via* a number of efficient methods,[5] none of them appeared to be useful for the synthesis of **3** or **4**. In view of the recent success of Cu-catalyzed domino reactions[6] to construct tri- and tetracyclic ring systems, we envisioned[3f] that a Cu-mediated Ullmann type intermolecular C–C coupling of **1** with **2** (*e.g.* **E-1**), followed by an intramolecular nucleophilic addition of the amidic NH to CN, would afford the initial

Table 2 Cu-catalyzed synthesis of 2-(12-oxo-6,12-dihydro-5*H*-isoquinolino[2,3-*a*]quinazolin-5-yl)acetate (**3**)[a]



Entry	Halide (**1**) R^1, R^2, R^3, R^4, X	Nitrile (**2**) Z	Time (h)	Product (**3**) R^1, R^2, R^3, R^4, Z	Yield[b] (%)
1	H, H, Me, H, I **1a**	CO_2Et **2a**	0.5	H, H, Me, H, CO_2Et **3a**	89
2	**1a**	CO_2Me **2b**	0.5	H, H, Me, H, CO_2Me **3b**	84
3	**1a**	$PO(OEt)_2$ **2c**	2.0	H, H, Me, H, $PO(OEt)_2$ **3c**	81
4	**1a**	$CO_2{}^tBu$ **2d**	0.5	H, H, Me, H, $CO_2{}^tBu$ **3d**	81
5	H, H, Et, H, I **1b**	**2a**	0.5	H, H, Et, H, CO_2Et **3e**	87
6	**1b**	**2b**	0.5	H, H, Et, H, CO_2Me **3f**	83
7	**1b**	**2c**	1.5	H, H, Et, H, $PO(OEt)_2$ **3g**	79
8	**1b**	**2d**	0.5	H, H, Et, H, $CO_2{}^tBu$ **3h**	81
9	H, H, Me, NO_2, Cl **1c**	**2a**	1.5	H, H, Me, NO_2, CO_2Et **3i**	76
10	**1c**	**2b**	1.5	H, H, Me, NO_2, CO_2Me **3j**	73
11	**1c**	**2c**	2.5	H, H, Me, NO_2, $PO(OEt)_2$ **3k**	73
12	F, H, ^{t}Bu, H, Br **1d**	**2a**	2.0	F, H, ^{t}Bu, H, CO_2Et **3l**	80
13	**1d**	**2c**	2.5	F, H, ^{t}Bu, H, $PO(OEt)_2$ **3m**	75
14	F, H, Me, NO_2, Cl **1e**	CN **2e**	2.5	F, H, Me, NO_2, CN **3n**	68
15	Cl, H, Me, H, I **1f**	**2a**	0.5	Cl, H, Me, H, CO_2Et **3o**	85

Table 2 *(Contd.)*



Entry	Halide (**1**) R^1, R^2, R^3, R^4, X	Nitrile (**2**) Z	Time (h)	Product (**3**) R^1, R^2, R^3, R^4, Z	Yield[b] (%)
16	**1f**	**2b**	0.5	Cl, H, Me, H, CO_2Me **3p**	81
17	**1f**	**2c**	1.5	Cl, H, Me, H, $PO(OEt)_2$ **3q**	78
18	**1f**	**2d**	1.0	Cl, H, Me, H, $CO_2{}^tBu$ **3r**	77
19	**1f**	**2e**	1.0	Cl, H, Me, H, CN **3s**	72
20	Me, H, Et, H, I **1g**	**2a**	0.5	Me, H, Et, H, CO_2Et **3t**	87
21	**1g**	**2b**	0.5	Me, H, Et, H, CO_2Me **3u**	84
22	**1g**	**2c**	2.0	Me, H, Et, H, $PO(OEt)_2$ **3v**	82
23	Me, Me, Me, H, I **1h**	**2a**	0.5	Me, Me, Me, H, CO_2Et **3w**	86
24	**1h**	**2b**	0.5	Me, Me, Me, H, CO_2Me **3x**	81
25	**1h**	**2c**	1.5	Me, Me, Me, H, $PO(OEt)_2$ **3y**	78

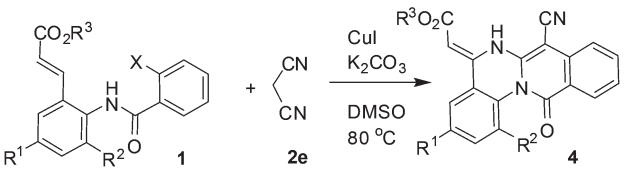
[a] All the reactions were carried out using **1** (1 mmol), **2** (1.2 mmol), CuI (0.1 mmol) and K_2CO_3 (3 mmol) in DMF (2 mL) at 80 °C under anhydrous conditions (no inert atmosphere). [b] Isolated yield.

6-membered ring *in situ* (**E-3** *via* **E-2**, Scheme 1). A subsequent intramolecular aza-Michael type addition[7] of **E-3** would furnish **3** (or **4** after aerial oxidation).[8]

The required starting material, **1**, was prepared *via* an amide bond formation between a 2-haloaryl carboxylic acid chloride and 3-(2-aminoaryl)acrylate ester, produced *via* a Heck reaction (see the ESI†). Initially, the coupling of iodo compound **1a** with ethyl cyanoacetate (**2a**) was examined (Table 1) using a range of bases (*e.g.* K_2CO_3, Na_2CO_3 and Cs_2CO_3), solvents (*e.g.* DMSO, DMF and 1,4-dioxane) and catalysts [*e.g.* CuI, CuBr, CuCl, $Cu(OAc)_2$ and $Cu(OTf)_2$]. While good results were obtained in several cases (entries 1, 3, 4, 6 and 9), the combination of CuI and K_2CO_3 in DMF (entry 1, Table 1) was chosen for further studies. All these reactions were performed at 80 °C. The reaction did not proceed at room temperature or in the absence of a catalyst (entries 10 and 11, Table 1).

To expand the scope of the present Cu-catalyzed domino reaction, compound **3** was prepared with a variety of substitution patterns (Table 2). The reaction proceeded well with various substituents on **1** including F, Cl, Me, Et, ^{t}Bu, or NO_2, irrespective of X being either I, or Br, or Cl. The use of various nitriles (**2a–e**) was also successful. Notably, the reaction of **1** with malononitrile **2e** in DMSO for a longer period afforded the compound **4** containing an exocyclic double bond with a *Z*-stereochemistry (Table 3). Moreover, the formation of the *Z*-isomer was found to be exclusive and was supported by a

Table 3 Cu-catalyzed synthesis of (*Z*)-alkyl 2-(7-cyano-12-oxo-6,12-dihydro-5*H*-isoquinolino[2,3-*a*]quinazolin-5-ylidene)acetate (**4**)[a]



Entry	Halide (**1**) R_1, R_2, R_3, X	Time/h	Product (**4**) R_1, R_2, R_3	Yield[b] (%)
1	H, H, Me, I **1a**	4.0	H, H, Me **4a**	72
2	H, H, Et, I **1b**	4.0	H, H, Et **4b**	71
3	F, H, ^{t}Bu, Br **1d**	5.0	F, H, ^{t}Bu **4c**	49
4	F, H, Me, I **1i**	6.0	F, H, Me **4d**	56
5	Cl, H, Me, I **1f**	5.0	Cl, H, Me **4e**	48
6	Me, H, Et, I **1g**	4.0	Me, H, Et **4f**	65
7	Me, Me, Me, I **1h**	4.0	Me, Me, Me **4g**	73
8	Me, Me, Et, I **1j**	6.0	Me, Me, Et **4h**	72

[a] Reactions were carried out using **1** (1 mmol), **2e** (1.2 mmol), CuI (0.1 mmol) and K_2CO_3 (3 mmol) in DMSO (2 mL) at 80 °C under anhydrous conditions (no inert atmosphere). [b] Isolated yield.

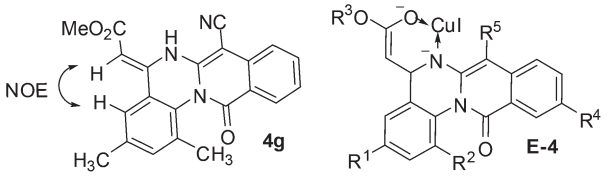
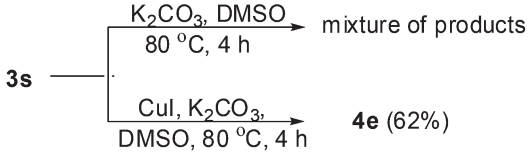


Fig. 3 (A) NOE study of **4g** and (B) complexation of **3** with Cu-catalyst.



Scheme 2 Role of CuI in the generation of compound **4**.

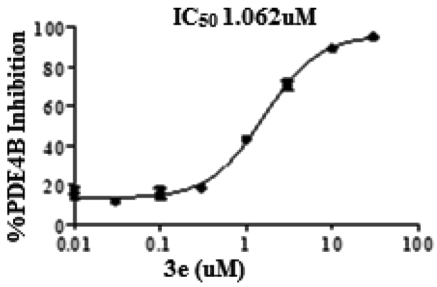


Fig. 4 Dose dependent inhibition of PDE4B by compound **3e**.

NOE study of **4g** (Fig. 3A). Mechanistically, the *Z*-isomer of **4** seemed to have been formed *in situ via* the generation of **3** (Scheme 1) and then a Cu-complex **E-4** (Fig. 3B) which on aerial oxidation afforded the olefin **4**. To gain further evidence, **3s** was treated with K_2CO_3 and CuI + K_2CO_3, separately, whereby a mixture of products was obtained in the first case and the desired **4e** (62% yield) in the second case (Scheme 2).

Several of the synthesized compounds showed promising inhibition of PDE4B [*e.g.* **3b** (71%), **3e** (93%), **3f** (86%), **3i** (66%), **3j** (66%), **3k** (78%), **3o** (62%), **3p** (62%), **3t** (83%), **3u** (93%), **3w** (71%) and **3x** (88%)] when tested *in vitro*[9] at 30 μM (see the ESI†). This result was further supported by the results of the docking of **3e** (Fig. 2) and **3u** (see the ESI†) into the PDE4B protein (Glide score −23.05 and −22.05 *vs*. rolipram's −24.61). The ester carbonyl group participated in H-bonding with the Gln443 of the Q pocket in the case of **3e** and the His234 of the metal binding pocket in case of **3u**, respectively. Additionally, both **3e** and **3u** showed a common Ar–Ar interaction with the Phe446 of PDE4B (see the ESI†). The compound **3e** showed a dose dependent inhibition of PDE4B with an IC_{50} (the half maximal inhibitory concentration) ~ 1.06 μM comparable to rolipram's IC_{50} ~ 1.0 μM (Fig. 4).

In conclusion, a robust, mild and ligand/additive-free Cu-mediated domino reaction has been developed, that allows a rapid access to novel, fused N-heterocyclic acetic acid derivatives. The reaction proceeds *via* a Cu-catalyzed domino reaction involving (i) an Ullmann type intermolecular C–C followed by (ii) an intramolecular C–N coupling and then (iii) an intramolecular aza-Michael type addition (and subsequent aerial oxidation). Several of these compounds showed promising PDE4B inhibition *in vitro* and seem to have potential for related medical applications. Overall, the one-pot methodology, presented here, may find wide use in constructing a diversity based library of small molecules for chemical and medicinal applications.

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