

## Transition metal mediated construction of pyrrole ring on 2,3-dihydroquinolin-4(1*H*)-one: synthesis and pharmacological evaluation of novel tricyclic heteroarenes†

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Received 23rd September 2010, Accepted 3rd December 2010

DOI: 10.1039/c0ob00771d

A facile two-step method for the construction of fused pyrrole ring leading to 5-substituted 2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinolin-1-ones via C–C followed by intramolecular C–N bond forming reaction is described. *In vitro* pharmacological evaluation and molecular modelling studies of some of the compounds synthesized are presented.

The 5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline framework (**A**, Fig. 1) has attracted particular attention in the area of new drug discovery because of their various pharmacological properties.<sup>1–4</sup> The 6-oxopyrroloquinoline ring **B** (Fig. 1) on the other hand though uncommon in nature has been an integral part of a promising antiviral agent PHA-529311.<sup>5</sup> A combination of both in a single molecule therefore would provide a new template **C** for the design and identification of compounds of potential pharmacological interest. Prompted by this idea and due to our long standing interest in the area of metabolic disorder<sup>6</sup> we became interested in the synthesis and pharmacological evaluation of a library of compounds containing the heterocyclic structure **C**. Our objective was to identify novel small molecules as activators of SIRT1 that are structurally unrelated to resveratrol<sup>7</sup> which belongs to the *trans*-stilbene class. Synthetic 2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinolin-1-ones have been reported in the literature preparation

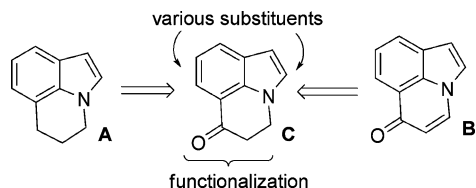


Fig. 1 Design of new template **C** as potential pharmacophore.

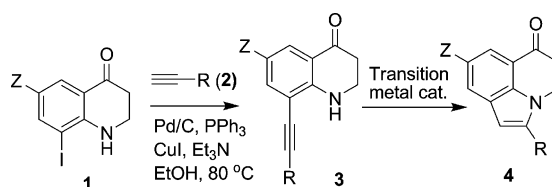
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† Electronic supplementary information (ESI) available: Experimental procedures, spectral data for all new compounds, results of docking study. See DOI: 10.1039/c0ob00771d

of which mainly involve two general strategies, for example, (i) the construction of a new six membered ring between N1 and C7 of an indole,<sup>8</sup> or (ii) the construction of a pyrrole ring onto a 2,3-dihydroquinolin-4(1*H*)-one.<sup>9</sup> Recently, derivative of **C** has been isolated as a side product during Pt-mediated cyclization of *N*-(2-alkynylphenyl)lactams.<sup>10</sup> Nevertheless, a general method for the synthesis of 5-substituted 2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinolin-1-one following the second strategy is not common in the literature. Due to our continuing interest in this strategy<sup>11</sup> we now report a new and two-step synthesis of 5-substituted 2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinolin-1-ones under transition metal catalysis (Scheme 1) along with their pharmacological evaluation as potential SIRT1 activators. The present communication addresses several challenging issues *e.g.* (i) the preparation and use of iodoarene **1** as starting material (ii) the reactivity of alkyne **3** towards transition metal-mediated intramolecular cyclization, (iii) the optimal catalyst system and (iv) SIRT1 activating potential of tricyclic compound **4**.



Scheme 1 Synthesis of 5-substituted 2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinolin-1-ones (**4**).

To this end we focused on establishing an optimized condition to obtain compound **4** *via* intramolecular C–N bond formation. The starting alkynes **3** (*Z* = Me & Cl) were prepared by using a Pd/C-mediated coupling reaction in ethanol. Thus, 6-substituted 8-iodo-2,3-dihydroquinolin-4(1*H*)-one (**1**), prepared according to a modified procedure (Scheme 2) based on a reported method,<sup>12</sup> was reacted with a number of terminal alkynes in the presence of 10%Pd/C–CuI–PPh<sub>3</sub> in EtOH using Et<sub>3</sub>N as a base (*e.g.* Sonogashira coupling) to afford the desired products **3**.<sup>13</sup> The results are summarized in Table 1.

The intramolecular cyclization of alkyne **3a** was examined using a number of catalysts under various reaction conditions (Table 2),

**Table 1** Pd/C-mediated synthesis of 8-alkynyl-2,3-dihydroquinolin-4(1*H*)-one (**3**)<sup>a</sup>

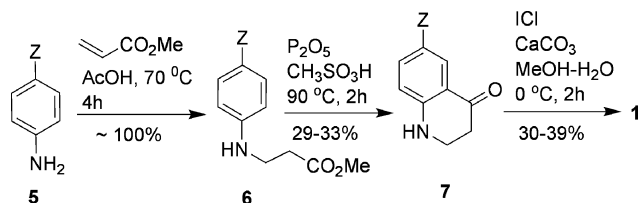
Entry	<b>1</b> ; Z =	Alkyne; R =	Time (h)	Product ( <b>3</b> )	% Yield <sup>b</sup>
1	<b>1a</b> ; Me	C <sub>6</sub> H <sub>5</sub>	4.0	<b>3a</b>	88
2	<b>1a</b>	C <sub>6</sub> H <sub>3</sub> Me- <i>p</i>	2.0	<b>3b</b>	70
3	<b>1a</b>	C <sub>6</sub> H <sub>4</sub> NO <sub>2</sub> - <i>m</i>	6.0	<b>3c</b>	60
4	<b>1a</b>	(CH <sub>2</sub> ) <sub>3</sub> CN	10	<b>3d</b>	90
5	<b>1a</b>	(CH <sub>2</sub> ) <sub>3</sub> Cl	12	<b>3e</b>	90
6	<b>1a</b>	CMe <sub>3</sub>	12	<b>3f</b>	55
7	<b>1a</b>	(CH <sub>2</sub> ) <sub>2</sub> OH	4.0	<b>3g</b>	85
8	<b>1b</b> ; Cl	C <sub>6</sub> H <sub>5</sub>	8.0	<b>3h</b>	76

<sup>a</sup> All the reactions were carried out using **1** (1.0 mmol), terminal alkyne (1.5 mmol), 1 : 4 : 10 ratio of Pd/C-PPh<sub>3</sub>-CuI and Et<sub>3</sub>N (2.6 mmol) in EtOH at 80 °C. <sup>b</sup> Isolated yield.

**Table 2** Transition metal-mediated intramolecular cyclization of **3a**<sup>a</sup>

Entry	Catalyst (mmol)	Solvent	Time (h)	T/°C	% Yield <sup>b</sup>
1	AgNO <sub>3</sub> (0.5)	DMF	12	80	75
2	AgSbF <sub>6</sub> (0.5)	DMF	10	80	80
3	AgSbF <sub>6</sub> (0.5)	Ethylene glycol	12	80	70
4	AgSbF <sub>6</sub> (0.5)	DMSO	15	80	70
5	PdCl <sub>2</sub> (0.5)	MeCN	3.0	80	85
6	PdCl <sub>2</sub> (0.05)	MeCN	3.0	80	88
7	CuI (0.5)	DMF	12	100	75
8	CuI (1.0)	DMF	12	100	75
9	No cat.	MeCN	12	100	11

<sup>a</sup> All the reactions were carried out using **3a** (1.0 mmol) and catalyst in a solvent. <sup>b</sup> Isolated yield.

**Scheme 2** Preparation of 8-iodo-2,3-dihydroquinolin-4(1*H*)-ones (**1**).

*e.g.* (a) AgNO<sub>3</sub> in DMF at 80 °C (entry 1, Table 2) or (b) AgSbF<sub>6</sub> in DMF at 80 °C (entries 2–4, Table 2) or (c) PdCl<sub>2</sub> in acetonitrile at 80 °C (entry 5 & 6, Table 2) or (d) CuI in DMF at 100 °C (entries 7 & 8, Table 2). However, the best results were obtained by using 0.05 equiv of PdCl<sub>2</sub> in acetonitrile at 80 °C for 3 h when the desired product **4a** was isolated in 88% yield. The use of other [*e.g.* Cu(OAc)<sub>2</sub>] or no catalyst (entry 9, Table 1) was also examined but afforded lower yield of product. To assess the generality of Pd-mediated intramolecular C–N bond forming reaction we then treated other alkynes, *i.e.* **3b–h** with PdCl<sub>2</sub> in CH<sub>3</sub>CN (Table 3). All the 8-arylethynyl-2,3-dihydroquinolin-4(1*H*)-one (**3a–c** & **3h**) provided the desired products (**4a–c** & **4h**) in moderate to good yields (entries 1–3 & 8, Table 3) whereas the 8-alkylethynyl derivatives (**3d–g**) afforded the corresponding products (**4d–g**) in good yields (entries 4–7, Table 3).

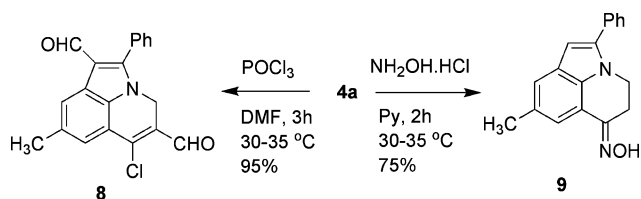
Having prepared a number of 5-substituted 2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinolin-1-ones (**4**) we explored further structural elaboration of some of the compounds synthesized. Accordingly, compound **4a** was converted to a chloro dialdehyde **8** under

**Table 3** Synthesis of 5-substituted 2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinolin-1-ones (**4**) under Pd-catalysis<sup>a</sup>

Entry	Alkyne <b>3</b>	Product ( <b>4</b> )	Time (h)	% Yield <sup>b</sup>
1			3.0	88
2			4.0	70
3			4.0	60
4			6.0	90
5			5.0	90
6			4.0	65
7			10	85
8			4.0	76

<sup>a</sup> All the reactions were carried out using **3** (0.6 mmol) and PdCl<sub>2</sub> (0.028 mmol) in MeCN at 80 °C. <sup>b</sup> Isolated yield.

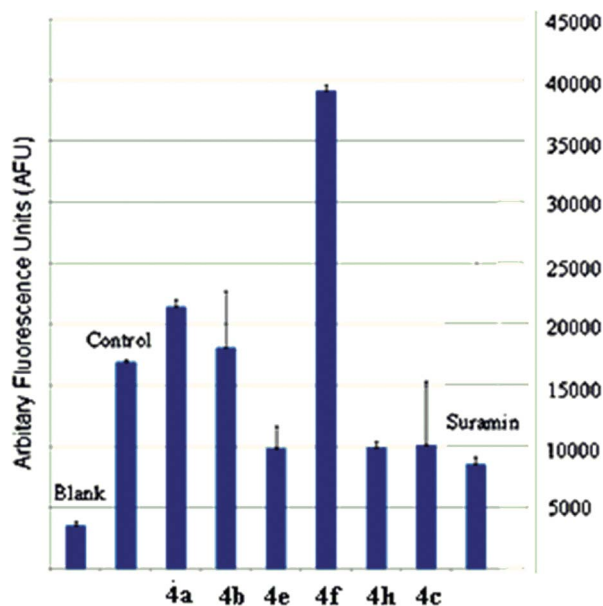
Vilsmeier-Haack conditions and a simple oxime **9** in good yields (Scheme 3).



**Scheme 3** Structural elaboration of compound **4a**.

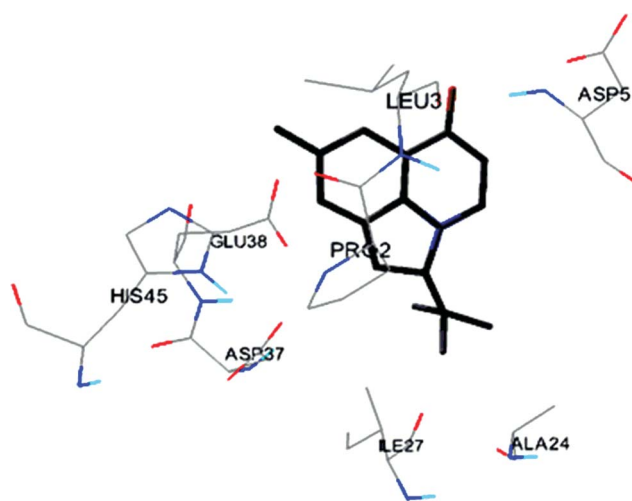
Mechanistically, the intramolecular cyclization of **3** seemed to proceed *via* initial activation of the triple bond of **3** *via* coordination to the M-salt (M = Pd, Ag and Cu) to form the  $\sigma$ -complex **X** (Scheme 4, see ESI†). Nucleophilic attack of the tetrahydroquinoline moiety to the M-coordinated triple bond through its nitrogen in an *endo* dig fashion provides the M-vinyl species **Y**. This on subsequent protonation *in situ* regenerates the catalyst producing the expected product **4**.

The *in vitro* activity of some of the compounds synthesized on SIRT1 was determined by using SIRT1 fluorescence activity assay kit. Compounds **4a**, **4b**, **4e**, **4f**, **4h** and **4c** along with suramin, a known inhibitor of SIRT1 were tested in this assay (Fig. 2). At the concentration of 10  $\mu$ M compound **4f** showed significant activation whereas **4a** and **4b** showed moderate to low activation of SIRT1 in compared to the inhibitory effect of suramin. A molecular docking simulation study to understand the interaction of **4f** with the protein *i.e.* homology model of hSIRT1 (144–217 amino acid residues) indicated that eight amino acid residues played key roles with the binding energy of  $-6.09$  Kcal/mol (Fig. 3, see ESI†). Since activation of SIRT1 could serve as a novel approach to treat type II diabetes and other metabolic disorders hence compounds **4a**, **4b** and **4f** may have pharmaceutical value.



**Fig. 2** SIRT1 activation by some of the 5-substituted 2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinolin-1-ones *in vitro*.

In summary, we have developed a simple method to give 5-substituted 2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinolin-1-ones that



**Fig. 3** Docking of **4f** into the active site of SIRT1.

were not easily accessible *via* earlier methods. This general method proceeds *via* Pd-mediated C–C bond forming reaction followed by C–N bond to afford an array of compounds of potential pharmacological significance.

The authors thank Dr Vilas Dahanukar, Dr Dipak Kalita and the analytical group of DRL. M.P. thanks DST, new Delhi, India for financial support (Grant NO. SR/S1/OC-53/2009).

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