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COMMUNICATION

# 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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**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.[1–4] 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.[5] 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[6] 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[7] 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 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,[8] or (ii) the construction of a pyrrole ring onto a 2,3-dihydroquinolin-4(1*H*)-one.[9] Recently, derivative of **C** has been isolated as a side product during Pt-mediated cyclization of *N*-(2-alkynylphenyl)lactams.[10] Nevertheless, a general method for the synthesis of 5-subtituted 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[11] we now report a new and two-step synthesis of 5-subtituted 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**.

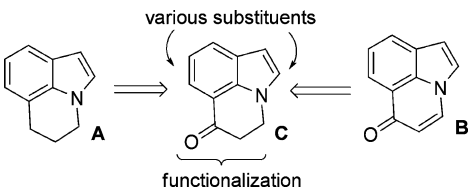
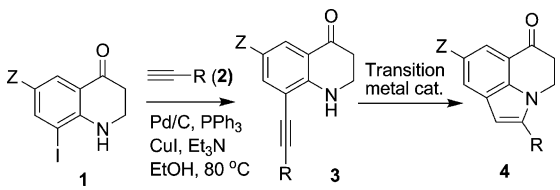



**Fig. 1** Design of new template **C** as potential pharmacophore.




**Scheme 1** Synthesis of 5-subtituted 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,[12] was reacted with a number of terminal alkynes in the presence of 10%Pd/C–CuI–$PPh_3$ in EtOH using $Et_3N$ as a base (*e.g.* Sonogashira coupling) to afford the desired products **3**.[13] 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),

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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

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

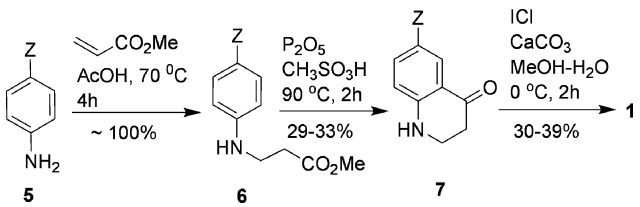
| Entry | **1**; Z = | Alkyne; R = | Time (h) | Product (**3**) | % Yield[b] |
|---|---|---|---|---|---|
| 1 | **1a**; Me | $C_6H_5$ | 4.0 | **3a** | 88 |
| 2 | **1a** | $C_6H_5Me$-*p* | 2.0 | **3b** | 70 |
| 3 | **1a** | $C_6H_4NO_2$-*m* | 6.0 | **3c** | 60 |
| 4 | **1a** | $(CH_2)_3CN$ | 10 | **3d** | 90 |
| 5 | **1a** | $(CH_2)_3Cl$ | 12 | **3e** | 90 |
| 6 | **1a** | $CMe_3$ | 12 | **3f** | 55 |
| 7 | **1a** | $(CH_2)_2OH$ | 4.0 | **3g** | 85 |
| 8 | **1b**; Cl | $C_6H_5$ | 8.0 | **3h** | 76 |

[a] All the reactions were carried out using **1** (1.0 mmol), terminal alkyne (1.5 mmol), 1 : 4 : 10 ratio of Pd/C-$PPh_3$-CuI and $Et_3N$ (2.6 mmol) in EtOH at 80 °C. [b] Isolated yield.

**Table 2** Transition metal-mediated intramolecular cyclization of **3a**[a]

| Entry | Catalyst (mmol) | Solvent | Time (h) | *T*/°C | % Yield[b] |
|---|---|---|---|---|---|
| 1 | $AgNO_3$ (0.5) | DMF | 12 | 80 | 75 |
| 2 | $AgSbF_6$ (0.5) | DMF | 10 | 80 | 80 |
| 3 | $AgSbF_6$ (0.5) | Ethylene glycol | 12 | 80 | 70 |
| 4 | $AgSbF_6$ (0.5) | DMSO | 15 | 80 | 70 |
| 5 | $PdCl_2$ (0.5) | MeCN | 3.0 | 80 | 85 |
| 6 | $PdCl_2$ (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 |

[a] All the reactions were carried out using **3a** (1.0 mmol) and catalyst in a solvent. [b] Isolated yield.

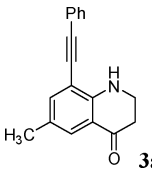
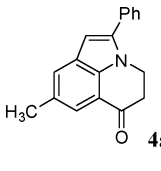
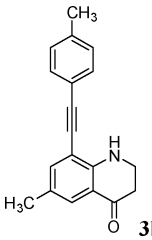
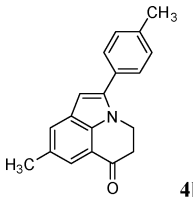
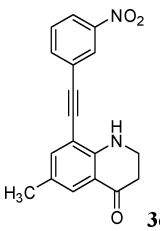
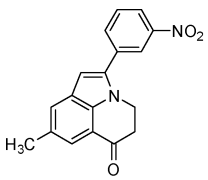
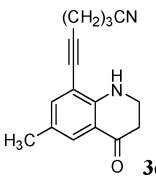
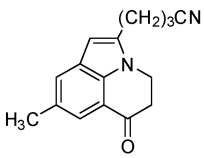
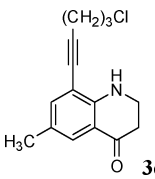
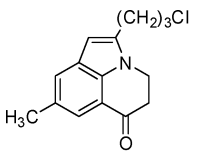
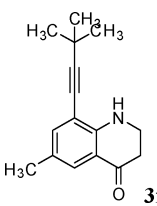
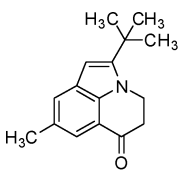
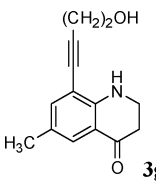
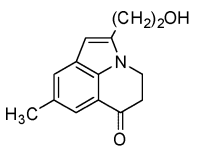
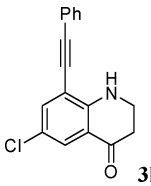
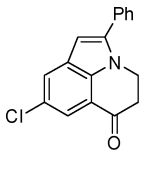



**Scheme 2** Preparation of 8-iodo-2,3-dihydroquinolin-4(1*H*)-ones (**1**).

*e.g.* (a) $AgNO_3$ in DMF at 80 °C (entry 1, Table 2) or (b) $AgSbF_6$ in DMF at 80 °C (entries 2–4, Table 2) or (c) $PdCl_2$ 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 $PdCl_2$ in acetonitrile at 80 °C for 3 h when the desired product **4a** was isolated in 88% yield. The use of other [*e.g.* $Cu(OAc)_2$] 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 $PdCl_2$ in $CH_3CN$ (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).

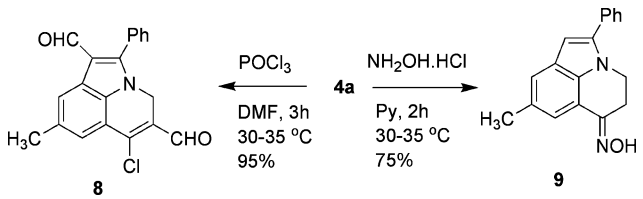
Having prepared a number of 5-subtituted 2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinolin-1-ones (**4**) we explored further structural elaboration of some of the compounds synthesized. Accordingly, compound **4a** was converted to a chloro dialdehyde **8** under

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

| Entry | Alkyne **3** | Product (**4**) | Time (h) | % Yield[b] |
|---|---|---|---|---|
| 1 |  **3a** |  **4a** | 3.0 | 88 |
| 2 |  **3b** |  **4b** | 4.0 | 70 |
| 3 |  **3c** |  **4c** | 4.0 | 60 |
| 4 |  **3d** |  **4d** | 6.0 | 90 |
| 5 |  **3e** |  **4e** | 5.0 | 90 |
| 6 |  **3f** |  **4f** | 4.0 | 65 |
| 7 |  **3g** |  **4g** | 10 | 85 |
| 8 |  **3h** |  **4h** | 4.0 | 76 |

[a] All the reactions were carried out using **3** (0.6 mmol) and $PdCl_2$ (0.028 mmol) in MeCN at 80 °C. [b] 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 σ-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.

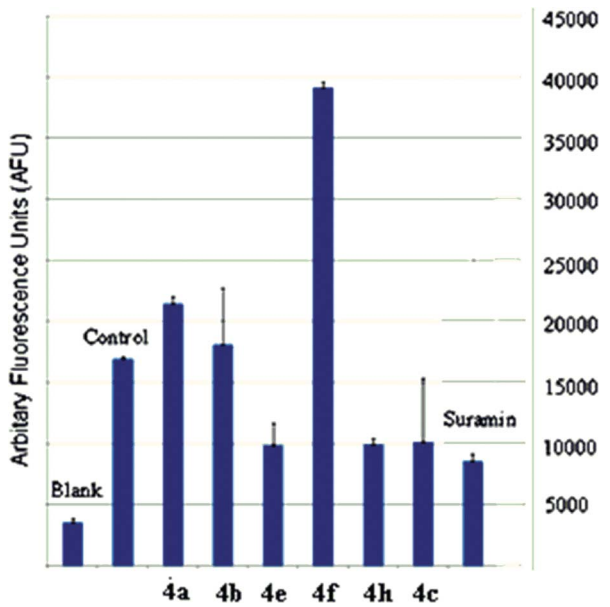



**Fig. 2** SIRT1 activation by some of the 5-subtituted 2,3-dihydro-1*H*-pyrrolo[3,2,1-ij]quinolin-1-ones *in vitro*.

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

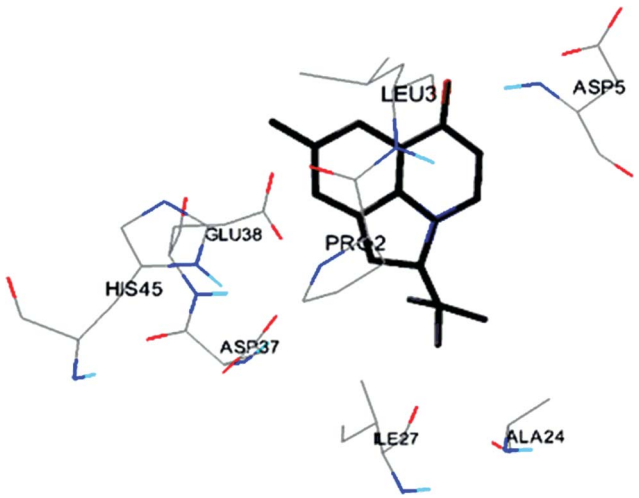



**Fig. 3** Docking of **4f** into the active site of SIRT1.

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.

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