Electronic Supplementary Information

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

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**Scheme 4.** Probable mechanism for the metal-mediated intramolecular cyclization of alkyne 3.

\[ \text{Scheme 4 image with reaction steps: } X \rightarrow Y \rightarrow 4 \]

- \( M = \text{Pd(II) or Ag(I) or Cu(I)} \)
- \( B = \text{CH}_3\text{CN, DMF} \)
Preparation of 6-substituted 8-iodo-2,3-dihydroquinolin-4(1H)-one (1)

6-Methyl-2,3-dihydroquinolin-4(1H)-one (7a): Methyl acrylate (8.0 g, 93.3 mmol) was added to a solution of 4-methylaniline (10.0 g) in acetic acid (20 mL). The mixture was heated to 70 ºC for 4.0 h. The mixture was allowed to cool to room temperature and partitioned between dichloromethane (200 mL) and H2O (100 mL). The combined organic layers were washed with brine, treated with Na2SO4, filtered and concentrated to give the crude methyl 3-(p-tolylamino)propanoate (6a) in quantitative yield. This was used in the next step without further purification.

Phosphorus pentoxide (18.0 g) in methane sulfonic acid (180.0 mL) was stirred at 130 ºC until a clear solution is obtained. The mixture was allowed to cool to room temperature for 15 min, and the compound 6a was added. The mixture was heated to 90 ºC for 12.0 h. The reaction mass was cooled to 30 ºC and poured into ice. A solution of 50% NaOH was added, until the pH was 7-8. The mixture was extracted with dichloromethane (2 x 500 mL). The combined organic layers were washed with brine, dried over anhydrous Na2SO4, filtered and concentrated. The residue was purified by column chromatography on silica gel using 10% ethyl acetate /n-hexane to afford the title compound as an off yellow solid (5.0 g, 33.3 %); mp 65 ºC; Rf 0.25 (25% E.A / n-hexane); 1H NMR (CDCl3, 400 MHz) δ 7.65 (d, J = 2.1 Hz, 1H), 7.11 (dd, J = 8.4, 2.0 Hz, 1H), 6.59 (d, J = 8.8 Hz, 1H), 4.27 (bs, 1H), 3.53 (m, 2H), 2.66 (t, J = 6.8 Hz, 1H), 2.24 (s, 3H); 13C NMR (CDCl3, 200 MHz) δ 20.1, 38.1, 42.3, 115.8, 118.3, 126.8, 126.9, 136.3, 150.1, 193.9; IR (cm⁻¹, KBr) cm⁻¹ 3370, 3020, 2920, 1660, 1245 Mass (ES) m/z 162 (M+1, 100 %); HRMS (ESI): calcd for C10H12No (M+H)+ 162.0920, found 162.0923

6-Chloro-2,3-dihydroquinolin-4(1H)-one (7b): This compound was prepared from 4-chloroaniline according to the procedure described above. This compound was isolated as yellow solid (4.5 g, 29.0 %); mp 78 ºC; Rf 0.25 (25% ethyl acetate / n-hexane); 1H NMR (CDCl3, 400 MHz) δ 7.8 (d, J = 2.1 Hz, 1H), 7.21 (dd, J = 8.2, 2.2 Hz, 1H), 6.61 (d, J = 8.5 Hz, 1H), 4.40 (bs, 1H), 3.58 (m, 2H), 2.70 (t, J = 6.8 Hz, 1H); 13C NMR (CDCl3, 200 MHz) δ 37.7, 42.1, 117.5, 120.0, 123.3, 126.9, 134.6, 135.3, 150.3, 192.5; IR (cm⁻¹, KBr) cm⁻¹ 3375, 3075, 2930, 1668, 1248 Mass (ES) m/z 182 (M+1, 100 %); HRMS (ESI): calcd for C9H9ClNo (M+H)+ 182.0402, found 182.0413
**8-Iodo-6-methyl-2,3-dihydroquinolin-4(1H)-one (1a)**

A solution of iodine monochloride (34.1 mmol) in methanol (50 mL) was added dropwise to a stirred suspension of 6-methyl-2,3-dihydro-quinolin-4(1H)-one 7a (5.0 g, 31.0 mmol) and calcium carbonate (34.1 mmol) in 4:1 methanol-water (160 mL) at 0 °C. The mixture was allowed to warm to room temperature, stirred for 2 h and filtered through a celite bed. The filtrate was extracted with dichloromethane (2 x 50 mL). The combined organic layer was washed with water, dried over anhydrous Na₂SO₄, filtered and concentrated under vacuo. The residue was purified by column chromatography on silica gel, eluting with 15% ethyl acetate / n-hexane to give the title compound as yellow solid (3.5 g, 39.3%); mp 70 -72 °C; Rₚ (25% ethylacetate-n-hexane) 0.3; ¹H NMR (CDCl₃, 400 MHz) δ 7.65 (m, 2H), 4.70 (bs, 1H), 3.60 (m, 2H), 2.67 (t, J = 6.8 Hz, 2H), 2.21 (s, 3H); ¹³C NMR (CDCl₃, 200 MHz) δ 19.7, 37.3, 42.0, 85.0, 119.5, 128.1, 128.6, 145.5, 149.0, 193.1; IR (cm⁻¹, KBr) cm⁻¹ 3378, 2917, 1666, 1241, 871; Mass (ES) m/z 288 (M+1, 100 %); HRMS (ESI): calcd for C₁₀H₁₁INO (M+H)+ 287.9885, found 287.9815

**6-Chloro-8-iodo-2,3-dihydroquinolin-4(1H)-one (1b):** This compound was prepared according to the procedure described above and was isolated as yellow solid (2.5 g, 30%); mp 131 -133 °C; Rₚ (25% ethyl acetate/n-hexane) 0.3; ¹H NMR (CDCl₃, 400 MHz) δ 7.82 (d, J = 2.0 Hz, 1H), 7.75 (d, J = 2.4 Hz, 1H), 4.85 (bs, 1H), 3.63 (m, 2H), 2.68 (t, J = 6.8 Hz, 2H); ¹³C NMR (CDCl₃, 200 MHz) δ 36.7, 41.7, 85.0, 119.6, 123.3, 127.5, 143.4, 149.4, 191.7; IR (cm⁻¹, KBr) cm⁻¹ 3370, 2923, 1670, 1245, 873; Mass (ES) m/z 308 (M+1, 100 %); HRMS (ESI): calcd for C₉H₈ClINO (M+H)+ 307.9338, found 307.9325

**Preparation of 6-substituted-8-alkynyl-2,3-dihydroquinolin-4(1H)-one (3)**

Typical procedure: A mixture of compound 1a (300 mg, 1.04 mmol), 10% Pd/C (11.12 mg, 0.01 mmol), PPh₃ (10.91 mg, 0.04 mmol), CuI (19.8 mg, 0.10 mmol) and TEA (2.60 mmol) in ethanol (8 mL) was stirred at 25 °C for 1 h under nitrogen. The acetylenic compound 2 (1.56 mmol) was added and the mixture was stirred at 80 °C for the time mentioned in Table 1. After completion, the reaction mixture was cooled to room temperature, diluted with EtOAc (120 mL) and filtered through a celite bed. The filtrate was concentrated and the residue was purified by column chromatography on silica gel using hexane-ethyl acetate to afford the desired product.
6-Methyl-8-(phenylethynyl)-2,3-dihydroquinolin-4(1H)-one (3a)

Yield 88%; light yellow solid; mp 146-148 °C; Rf 0.45 (25% ethyl acetate / n-hexane);

$^1$H NMR (CDCl$_3$, 400 MHz) δ: 7.66 (s, 1H), 7.54-7.52 (m, 2H), 7.38-7.36 (m, 4H), 5.12 (bs, 1H), 3.67-3.63 (m, 2H), 2.71 (t, $J = 7.2$ Hz, 2H), 2.24 (s, 3H); IR (cm$^{-1}$, KBr) ν: 3567, 3343, 2919, 2343, 1667, 1511; Mass (ES): m/z 262 (M+1, 100%); $^{13}$C NMR (CDCl$_3$, 200 MHz) δ: 20.1, 37.9, 42.0, 84.3, 95.7, 109.3, 118.8, 122.7, 126.3, 128.0, 128.4, 128.6 (2C), 131.5 (2C), 138.7, 150.3, 193.4.

6-Methyl-8-(p-tolylethynyl)-2,3-dihydroquinolin-4(1H)-one (3b)

Yield 70%; yellow solid; mp 173-175 °C; Rf 0.40 (25% ethyl acetate / n-hexane); $^1$H NMR (CDCl$_3$, 400 MHz) δ: 7.65 (s, 1H), 7.41 (d, $J = 8.4$ Hz, 2H), 7.36 (d, $J = 2.0$ Hz, 1H), 7.16 (d, $J = 8.0$ Hz, 2H), 5.12 (bs, 1H), 3.67-3.63 (m, 2H), 2.70 (t, $J = 6.8$ Hz, 2H), 2.38 (s, 3H), 2.24 (s, 3H); $^{13}$C NMR (CDCl$_3$, 200 MHz) δ: 20.1, 21.5, 37.9, 42.0, 83.6, 95.9, 109.5, 118.8, 119.5, 126.3, 127.8, 129.2 (2C), 131.4 (2C), 138.6, 138.9, 150.3, 193.5; IR (cm$^{-1}$, KBr) ν: 3375, 2918, 2855, 1661; Mass (ES): m/z 276.1 (M+1, 100%).

6-Methyl-8-((3-nitrophenyl)ethynyl)-2,3-dihydroquinolin-4(1H)-one (3c)
Yield 60%; light red solid; mp 151-158 °C; R_f (20% ethyl acetate/ n-hexane) 0.45; ^1H NMR (CDCl₃, 400 MHz ) δ: 8.19 (dd, J = 8.4, 1.2 Hz, 1H) 7.75-7.47 (m, 4H), 7.4 (d, J = 2.0 Hz, 1H), 5.87 (bs, 1H), 3.77-3.72 (m, 2H), 2.72 (t, J = 6.8 Hz, 2H), 2.17 (s, 3H); ^13C NMR (CDCl₃, 200 MHz): 20.5, 37.7, 41.6, 91.8, 93.6, 107.9, 118.7, 125.1, 125.8, 128.5, 129.5, 133.0, 133.4, 134.3, 138.9, 148.3, 151.6, 193.4; IR (cm⁻¹, KBr) ν : 3397, 2922, 2184, 1682, 1549; Mass (ES) m/z: 307.2 (M+1, 100 %).

6-(6-Methyl-4-oxo-1,2,3,4-tetrahydroquinolin-8-yl)hex-5-ynenitrile (3d)

Yield 90%; yellow solid; mp 85-88 °C; R_f 0.3 (40% ethyl acetate/ n-hexane); ^1H NMR (CDCl₃, 400 MHz) δ: 7.62 (d, J = 1.6 Hz, 1H), 7.25 (d, J = 1.6 Hz, 1H), 5.04 (bs, 1H), 3.63-3.59 (m, 2H), 2.71-2.55 (m, 6H), 2.21 (s, 3H), 2.02-1.97(m, 2H); ^13C NMR (CDCl₃, 200 MHz) δ : 16.3, 18.7, 20.0, 24.4, 29.6, 37.8, 41.9, 93.3, 109.2, 118.7, 119.0, 126.2, 127.6, 138.8, 150.4, 193.4; IR (cm⁻¹, KBr) ν : 3363, 2924, 2859, 1677; Mass (ES) m/z : 253.2 (M+1, 100 %); HRMS (ESI): calcd for C₁₆H₁₆N₂O (M+H) 253.1341, found 253.1351
Yield 90%; brown low melting solid; Rf 0.3 (40% ethyl acetate/ n-hexane); $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$: 7.61 (d, $J = 2.0$ Hz, 1H), 7.24 (d, $J = 2.4$ Hz, 1H), 5.03 (bs, 1H), 3.74-3.59 (m, 4H), 2.71-2.63 (m, 4H), 2.20 (s, 3H), 2.12-2.0 (m, 2H); $^{13}$C NMR (CDCl$_3$, 200 MHz) $\delta$: 17.0, 20.0, 31.2 (2C), 37.9, 41.9, 43.6, 94.5, 109.6, 118.7, 126.2, 127.4, 138.6, 150.4, 193.5; IR (cm$^{-1}$, KBr) v: 3354, 2957, 2923, 1672; Mass (E/Z) m/z: 262.2 (M+1, 100 %); HRMS (ESI): calcd for C$_{15}$H$_{17}$ClNO (M+H) 262.0999, found 262.1008

8-(3,3-Dimethylbut-1-yn-1-yl)-6-methyl-2,3-dihydroquinolin-4(1H)-one (3f)

Yield 55%; light yellow solid; mp 120-123 ºC; Rf 0.35 (25% ethyl acetate hexane); $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$: 7.58 (d, $J = 1.2$ Hz, 1H), 7.24 (d, $J = 1.5$ Hz, 1H), 5.3 (bs, 1H), 3.63-3.59 (m, 2H), 2.67 (t, $J = 6.8$ Hz, 2H), 2.21 (s, 3H), 1.35 (s, 9H); $^{13}$C NMR (CDCl$_3$, 200 MHz) $\delta$: 20.0, 28.6, 31.1, 37.9, 42.1, 74.0, 105.3, 110.0, 118.0, 126.1, 126.9, 138.5, 150.1, 193.6; IR (cm$^{-1}$, KBr) v: 3360, 3051, 2968, 2215, 1669; Mass (ES) m/z: 242.20 (M+1, 100 %).

8-(4-Hydroxybut-1-yn-1-yl)-6-methyl-2,3-dihydroquinolin-4(1H)-one (3g)
Yield 85%; yellow solid, mp 110-113 °C; Rf 0.20 (50% ethyl acetate/ n-hexane); $^1$H NMR (CDCl$_3$, 400 MHz ) δ: 7.61 (s, 1H), 7.26 (s, 1H), 5.13 (bs, 1H), 3.84 (t, $J$ = 6.0 Hz, 2H), 3.59 (t, $J$ = 6.8 Hz, 2H), 2.74 (t, $J$ = 6.4 Hz, 2H), 2.67 (t, $J$ = 6.8 Hz, 2H), 2.20 (s, 3H); $^{13}$C NMR (CDCl$_3$, 200 MHz) δ: 19.9, 23.8, 37.7, 41.7, 60.9, 93.5, 109.6, 118.3, 126.0, 127.2, 138.6 (2C), 150.4, 193.8; IR (cm$^{-1}$, KBr); 3340, 2924, 1646, 1052; Mass (ES) m/z: 230.1 (M+1, 100 %).

6-Chloro-8-(phenylethynyl) 2,3-dihydroquinolin-4(1H)-one (3h);

Yield 76%; yellow solid, mp 163-165 °C; Rf 0.4 (25% ethyl acetate / n-hexane); $^1$H NMR (CDCl$_3$, 400 MHz ) δ: 7.79 (s, 1H), 7.54-7.38 (m, 6H), 5.25 (bs, 1H), 3.69-3.66 (m, 2H), 2.72 (t, $J$ = 7.2 Hz, 2H); $^{13}$C NMR (CDCl$_3$, 200 MHz) δ: 37.4, 41.6, 82.8, 97.0, 111.1, 119.4, 122.0, 122.2, 127.4, 128.5 (2C), 129.0, 131.6 (2C), 137.0, 150.4, 192.0; IR (cm$^{-1}$, KBr) ν : 3565, 3345, 2924, 1670; Mass (ES): m/z 282 (M+1, 100 %) ; HRMS (ESI): calcd for C$_{17}$H$_{13}$ClNO (M+H) 282.0686, found 282.0698

Preparation of 5,8-disubstituted 2,3-dihydro-1H-pyrrolo[3,2,1-ij]quinolin-1-one (4)

Typical procedure for the preparation of 4a

Using AgNO$_3$: To a clear solution of 3a (100.0 mg, 0.382 mmol) in dry DMF (10 mL) was added AgNO$_3$ (32.5 mg, 0.191 mmol) at room temperature under N$_2$ condition. The reaction mixture was heated at 80 °C for 12 h. After completion, the reaction mixture was cooled to room temperature and the solvent was concentrated
under vacuum. The crude residue was purified by flash silica gel chromatography (n-hexane/EtOAc) to yield the desired product (75 mg).

**Using AgSbF$_6$:** To a clear solution of 3a (100.0 mg, 0.382 mmol) in dry DMF (10 mL) was added AgSbF$_6$ (65.8 mg, 0.191 mmol) at room temperature under N$_2$ condition. The reaction mixture was heated at 80 °C for 10 h. After completion, the reaction mixture was cooled to room temperature and the solvent was concentrated under vacuum. The crude residue was purified by flash silica gel chromatography (n-hexane/EtOAc) to yield the desired product (80 mg).

**Using CuI:** To a clear solution of 3a (100.0 mg, 0.382 mmol) in dry DMF (10 mL) was added CuI (36.47 mg, 0.191 mmol) at room temperature under N$_2$ condition. The reaction mixture was heated at 100 °C for 12 h. After completion, the reaction mixture was cooled to room temperature and the solvent was concentrated under vacuum. The crude residue was purified by flash silica gel chromatography (n-hexane/EtOAc) to yield the desired product (75 mg).

**Using PdCl$_2$:** To a clear solution of 3a (150.0 mg, 0.574 mmol) in CH$_3$CN (15 mL) was added PdCl$_2$ (5.0 mg, 0.028 mmol) at room temperature. The reaction mixture was heated at 70-80 °C for the time mentioned in Table 3. After completion, the reaction mixture was cooled to room temperature and the solvent was concentrated under vacuum. The crude residue was purified by flash silica gel chromatography (hexane/EtOAc) to yield the desired product.

**8-Methyl-5-phenyl-2,3-dihydro-1H-pyrrolo[3,2,1-ij]quinolin-1-one (4a)**

![8-Methyl-5-phenyl-2,3-dihydro-1H-pyrrolo[3,2,1-ij]quinolin-1-one (4a)](image)

Yield 88%; white solid, mp 127-130 °C; R$_f$ 0.50 (25% ethyl acetate / n-hexane); $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$: 7.63-7.42 (m, 6H), 7.37 (s, 1H), 6.58 (s, 1H), 4.44 (t, $J$ = 6.8 Hz, 2H), 3.04 (t, $J$ = 7.2 Hz, 2H), 2.4 (s, 3H); $^{13}$C NMR (CDCl$_3$, 200 MHz) $\delta$: 21.5, 38.2, 42.8, 102.2, 117.6, 119.5, 126.7, 128.1, 128.2 (2C), 128.6 (2C), 128.8, 129.9, 131.7, 139.8, 141.9, 192.9; IR (cm$^{-1}$, KBr) ν: 2917, 1682, 747; Mass (ES):
m/z 262 (M+1, 100 %); HRMS (ESI): calcd for C_{18}H_{16}NO (M+H) 262.1232, found 262.1235

8-Methyl-5-p-tolyl-2,3-dihydro-1\textit{H}-pyrrolo[3,2,1-\textit{ij}]quinolin-1-one (4b)

![Chemical structure of 8-Methyl-5-p-tolyl-2,3-dihydro-1\textit{H}-pyrrolo[3,2,1-\textit{ij}]quinolin-1-one (4b)]

Yield 70%; yellow solid; mp 118-121 ºC; R\textsubscript{f} 0.45 (25% ethyl acetate / n-hexane); \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \textdelta: 7.62-7.43 (m, 4H), 7.30-7.25 (m, 2H), 6.54 (s, 1H), 4.39 (t, J = 7.2 Hz, 2H), 3.06 (t, J = 6.8 Hz, 2H), 2.49 (s, 3H), 2.42 (s, 3H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 200 MHz) \textdelta: 22.7, 29.7, 38.3, 42.8, 101.8, 117.6, 119.3, 126.6, 128.2, 128.5 (2C), 128.8, 129.4 (2C), 129.9, 138.3, 139.8, 142.1, 192.9; IR (cm\textsuperscript{-1}, KBr) \nu: 3360, 3051, 2967, 2856, 1669; Mass (ES): m/z 276.2 (M+1, 100 %); HRMS (ESI): calcd for C_{19}H_{18}NO (M+H) 276.1388, found 276.1400

8-Methyl-5-(3-nitrophenyl)-2,3-dihydro-1\textit{H}-pyrrolo[3,2,1-\textit{ij}]quinolin-1-one (4c)

![Chemical structure of 8-Methyl-5-(3-nitrophenyl)-2,3-dihydro-1\textit{H}-pyrrolo[3,2,1-\textit{ij}]quinolin-1-one (4c)]

Yield 60%; light red solid; mp 161-163 ºC; R, 0.5 (20% ethyl acetate/ n-hexane); \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz ) \textdelta: 8.36 (d, J = 1.6 Hz, 1H) 8.02 (d, J = 8.8, 2H), 7.73 (d, J = 9.2, 1H) 7.44-7.40 (m, 1H), 7.24(m, 2H), 3.77-3.71 (m, 2H), 2.75 (t, J = 7.2 Hz, 2H), 2.33 (s, 3H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 200 MHz): 20.2, 36.9, 40.6, 115.8, 118.6, 120.4, 121.5, 124.7, 127.9, 131.3 (2C), 135.6, 140.4, 152.6, 157.1, 161.2, 181.9, 192.6; IR (cm\textsuperscript{-1}, KBr) \nu: 3284, 2956, 2853, 1663, 1568; Mass (ES) m/z: 307.2 (M+1, 100 %); HRMS (ESI): calcd for C_{19}H_{18}N_{2}O_{3} (M+H) 307.1082, found 307.1091
4-(8-Methyl-1-oxo-2,3-dihydro-1\textit{H}-pyrrolo[3,2,1-\textit{i}]quinolin-5-yl)butanenitrile (4d)

\[
\begin{array}{c}
\text{CH}_3\\
\text{N}\\
\text{O}\\
\end{array}
\]

Yield 90%; brown solid, mp 95-97 °C; R_f 0.35 (50% ethyl acetate/n-hexane); \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \(\delta\) 7.54 (s, 1H), 7.50 (s, 1H), 7.28 (s, 1H), 4.30 (t, \(J = 6.8\) Hz, 2H), 3.05 (t, \(J = 6.8\) Hz, 2H), 2.93 (t, \(J = 7.2\) Hz, 2H), 2.50-2.46 (m, 5H), 2.09 (t, \(J = 7.2\) Hz, 2H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 200 MHz) \(\delta\): 16.5, 21.4, 24.3, 24.8, 29.6, 37.9, 41.3, 100.3, 117.0, 118.8, 126.3, 127.7, 129.7, 138.8, 139.0, 192.5; IR (cm\textsuperscript{-1}, KBr) \(\nu\) : 3102, 3026, 2924, 2246, 1669; Mass (ES m/z) : 253.2 (M+1, 100 %); HRMS (ESI) : calcd for C\textsubscript{16}H\textsubscript{16}N\textsubscript{2}O (M+H) 253.1341, found 253.1330.

5-(3-Chloropropyl)-8-methyl-2,3-dihydro-1\textit{H}-pyrrolo[3,2,1-\textit{ij}]quinolin-1-one (4e)

\[
\begin{array}{c}
\text{CH}_3\\
\text{N}\\
\text{O}\\
\end{array}
\]

Yield 90%; brown low melting solid; 79-82 °C; R_f 0.35 (40% ethyl acetate/n-hexane); \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz ) \(\delta\) 7.53 (s, 1H), 7.48 (s, 1H), 6.27 (s, 1H), 4.31 (t, \(J = 6.8\) Hz, 2H), 3.63 (t, \(J = 6.4\) Hz, 2H), 3.08-2.93 (m, 4H), 2.46 (s, 3H), 2.23-2.17 (m, 2H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 200 MHz) \(\delta\): 21.5, 23.3, 31.4, 37.9, 41.4, 44.0, 99.9, 117.0, 118.5, 126.2, 127.9, 129.5, 138.8, 140.2, 192.7; IR (cm\textsuperscript{-1}, KBr) \(\nu\) : 3326, 3026, 2924, 2246, 1669; Mass (ES m/z) : 262.1 (M+1, 100 %); HRMS (ESI): calcd for C\textsubscript{16}H\textsubscript{17}ClNO (M+H) 262.0999, found 262.1004.

5-\textit{tert}-Butyl-8-methyl-2,3-dihydro-1\textit{H}-pyrrolo[3,2,1-\textit{ij}]quinolin-1-one (4f)
Yield 65%; light yellow solid; mp 96-98 °C; R\textsubscript{f} 0.35 (25% ethyl acetate / n-hexane); \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \(\delta\) 7.52 (s, 1H), 7.49 (s, 1H), 6.27 (s, 1H), 4.51 (t, \(J = 6.8\) Hz, 2H), 3.03 (t, \(J = 6.8\) Hz, 2H), 1.46 (s, 3H), 1.38 (s, 9H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 200 MHz) \(\delta\): 21.3, 29.9, 32.4, 38.5, 44.8, 98.6, 117.4, 118.6, 126.4, 127.7, 129.3, 140.0, 150.8, 192.9; IR (cm\textsuperscript{-1}, KBr) \(\nu\) : 2966, 2872, 1683; Mass (ES) m/z : 242.20 (M+1, 100 %); HRMS (ESI): calcd for C\textsubscript{16}H\textsubscript{20}NO (M+H) 242.1545, found 242.1557.

5-(2-Hydroxyethyl)-8-methyl-2,3-dihydro-1\textsubscript{H}-pyrrolo[3,2,1-\textit{i}]quinolin-1-one (4g)

Yield 85%; yellow solid, mp 91-93 °C; R\textsubscript{f} 0.25 (50% ethyl acetate hexane); \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \(\delta\) 7.91 (s, 1H), 7.82 (s, 1H), 3.74 (t, \(J = 6.0\) Hz, 2H), 3.64-3.61 (m, 2H), 3.09 (t, \(J = 6.8\) Hz, 2H), 2.67 (t, \(J = 7.2\) Hz, 2H), 2.27 (s, 3H); IR (cm\textsuperscript{-1}, KBr); 3343, 2921, 1668; Mass (ES) m/z: 230.1 (M+1, 100 %); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 200 MHz) \(\delta\): 20.1, 27.3, 36.9 , 40.3, 62.0, 119.2, 120.3, 123.6, 134.3, 138.5 (2C), 151.4, 193.1; IR (cm\textsuperscript{-1}, KBr); 3343, 2921, 1668; Mass (ES) m/z: 230.1 (M+1, 100 %); HRMS (ESI): calcd for C\textsubscript{14}H\textsubscript{16}NO\textsubscript{2} (M+H) 230.1180, found 230.1169.

8-Chloro-5-phenyl-2,3-dihydro-1\textsubscript{H}-pyrrolo[3,2,1-\textit{i}]quinolin-1-one (4h)

Yield 76%; white solid, mp 127-130 °C; R\textsubscript{f} 0.45 (25% ethyl acetate / n-hexane); \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \(\delta\) 7.78 (d, \(J = 1.6\) Hz, 1H), 7.68 (d, \(J = 2.0\) Hz, 1H), 7.56 –
7.45 (m, 6H), 6.61 (s, 1H), 4.43 (t, $J = 6.8$ Hz, 2H), 3.08 (t, $J = 6.8$ Hz, 2H), 2.4 (s, 3H); $^{13}$C NMR (CDCl$_3$, 200 MHz) δ: 38.0, 42.7, 102.2, 118.4, 125.7, 126.7, 128.7(3C), 128.9 (3C), 129.0, 131.0, 139.4, 143.3, 191.7 ; IR (cm$^{-1}$, KBr) ν: 2925, 2854, 1672; Mass (ES) : m/z 282.3 (M+1, 100 %); HRMS (ESI): calcd for C$_{17}$H$_{13}$ClNO (M+H) 282.0686, found 282.0698.

Preparation of 6-chloro-8-methyl-2-phenyl-4$H$-pyrrolo[3,2,1-$ij$]quinoline-1,5-dicarbaldehyde (8)

![Chemical Structure](image)

To a cooled (0 ºC) solution of 4a (148 mg) in dry DMF (1.0 mL) was added POCl$_3$ (1.25 mL) dropwise and the temperature was raised to 25 ºC. The reaction mixture was stirred for 3 h and then poured into ice water (100 mL). The yellow solid separated was filtered, triturated with n-hexane, filtered and dried to give the pure product (180.4 mg, 95%); mp 276 -279 ºC; R$_f$ 0.45 (15% ethyl acetate/n-hexane); $^1$H NMR (CDCl$_3$, 400 MHz) δ 10.29 (s,1H), 9.77 (s,1H), 8.17 (s, 1H), 7.44-759 (m, 6H), 5.0 (s, 2H), 2.52 (s, 3H); $^{13}$C NMR (DMSO-$d_6$, 200 MHz) δ 29.0, 45.0, 116.2, 116.6, 122.3, 123.2, 124.9, 127.2, 127.6 (2C), 129.2 (2C), 130.0 (2C), 130.3, 134.0, 144.5, 149.5, 186.4, 186.3; IR (cm$^{-1}$, KBr) cm$^{-1}$ 3434, 2919, 1655, 1577, 1417; Mass (ES) m/z 336 (M+1, 100 %); HRMS (ESI): calcd for C$_{20}$H$_{15}$ClNO$_2$ (M+H)$^+$ 336.0801, found 336.0855.

Preparation of 8-methyl-2-phenyl-4$H$-pyrrolo[3,2,1-$ij$]quinolin-6(5H)-one oxime (9)

![Chemical Structure](image)

To a solution of 4a (150 mg) in pyridine (6 mL) was added NH$_2$OH.HCl (4.59 mmol, 321.7 mg) at room temperature and the mixture was stirred for 2 h. The solvent was removed to give a gummy mass, which was poured into ice water (10 mL). The solid
was precipitated and filtered. The crud product was triturated with n-hexane, filtered and dried to get the title compound as yellow solid (119.0 mg, 75%); mp 229-232 ºC; Rf 0.40 (15% E.A / n-hexane); ¹H NMR (DMSO-d₆, 400 MHz) δ 11.28 (s, 1H), 7.62 (d, J = 7.2 Hz, 2H), 7.53-7.35 (m, 5H), 6.54 (s, 1H), 4.17 (t, J = 6.8 Hz, 2H), 3.13 (t, J = 6.4 Hz, 2H), 2.41 (s, 3H); ¹³C NMR (DMSO-d₆, 200 MHz) δ: 21.5, 22.5, 42.8, 100.9, 115.3, 116.5, 120.3, 126.9, 127.8, 128.3 (2C), 128.7(2C), 128.8, 131.7, 134.9, 140.7, 147.5 ; IR (cm⁻¹, KBr) 3232, 2922, 2922, 1603, 956; Mass (ES) : m/z 277 (M+1, 100 %); HRMS (ESI): calcd for C₁₈H₁₇N₂O (M+H) 277.1341, found 277.1350.

In Vitro assay for measuring SIRT1 activation

The activity of small molecules on Sirt1 was determined using SIRT1 fluorescence activity assay kit from Cyclex Inc. according to manufacturer’s protocol. Briefly, bacterially purified hSIRT1 enzyme was incubated with the fluorophore labeled substrate peptide (25 uM) and cofactor, NAD⁺ (25 uM) in presence or absence of 10 µM compounds (suramin, an inhibitor of Sirt1 along with compounds 4a, 4b, 4e, 4f and 4c) for 15 min at 37 ºC. Then 50 uL of stock solution was added and incubated for 45 min at room temperature. Fluorescence was read at Ex: 360 nm and Em: 450 nm. Blank consists of all components of the reaction mixture except enzyme. The difference between the blank and control reading gives the enzyme activity. Blank value is subtracted from all the sample readings. The compound control contains all the components of reaction mixture including the compound but no enzyme. So the reading obtained in the compound control indicates the autofluorescence of the compound and this is also subtracted from the reading. Finally a graph is plotted against the samples on X-axis and absorbance value after subtracting blank and autofluorescence values from the sample. Absorbance/Fluorescence is directly proportional to the enzyme activity.

Docking studies: Materials and Methods

Homology Model of hSIRT1 (144-217)

The three dimensional model of hSIRT1 (uniprot code: Q96EB6, 144-217 amino acid residues) was developed by threading method using PRIME homology modeling program (Schrödinger L.L.C., USA). The multi step Schrödinger's Protein preparation tool (PPrep) has been used for final preparation of receptor model. Hydrogen’s were
added to the model automatically via the Maestro interface. Prep neutralizes side chains and residues which are not involving in salt bridges. This step is then followed by restrained minimization using the OPLS 2005 force field to RMSD of 0.3Å.

**Docking Procedure:** The synthesized compounds were sketched by using chemdraw and converted them to their 3D representation. All the compounds and protein (homology model of hSIRT1) were prepared for docking (i.e. adding hydrogen’s, gasteiger charge addition, and energy minimization) by using Chimera program. Autodock 4.0 program was used for docking.

**Results and discussion:** The best model of activator domain of hSIRT1 was developed and validated. The receptor grid was generated with co ordinates X: 43.804; Y: 47.333; Z: 29.948. The best 5 poses and corresponding scores have been evaluated by autodock 4.0 program. The best score and interacting amino acid residues are shown in the following tables.

### Binding Energy:

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<th>Ligand</th>
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<tr>
<td>4b</td>
<td>-5.57</td>
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<td>4f</td>
<td>-6.09</td>
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### Interacting amino acids:

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<th>4f</th>
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<tr>
<td>-</td>
<td>-</td>
<td>Glu38</td>
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</table>
**Fig. 1.** Docking of compounds 4a, 4b and 4f into the active site of SIRT1

**References**


3. Michel F, Sanner. Python: A programming language for software integration
Copies of spectra
Mass Analysis Report

User Spectra

Fragmentor Voltage | Collision Energy | Ionization Mode
--- | --- | ---
100 | d | ESI

+ Scan (0.133 min) 100112030.d Subtract (1)

- 262.20
- 284.20

19
Mass Analysis Report

Sample Name
Position
User Name
IRM Calibration Status
Comment

Fragmentor Voltage  Collision Energy  Ionization Mode
125  0  El

+ Scan (0.133 min) 100122006.d Subtract (1)

Counts (%) vs. Mass-to-Charge (m/z)

276.10
298.10
573.30
A433-CM083-41 in CDCl3
TDC-104

AR.No:12031/63
Analyst:Srikanth A
Date:2nd March 2010

Supplementary Material (ESI) for Organic & Biomolecular Chemistry

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Mass Analysis Report

User Spectra

Fragmentor Voltage | Collision Energy | Ionization Mode
100 | 0 | ESI

* Scan (0.118 min) 100302030.d Subtract (1)

Counts (%) vs. Mass-to-Charge (m/z)

- 188.10
- 251.20
- 307.20
- 635.30
Mass Analysis Report

Sample Name: A439/C0053/37
Position: Val 56
User Name: [Redacted]
IRM Calibration Status: Success
Comment: [Redacted]

Fragmentor Voltage: 70
Collision Energy: 3
Ionization Mode: ESI

+ Scan (0.125 min) 100222006.d Subtract (1)

Counts (%) vs. Mass-to-Charge (m/z)

- 253.20
- 300.20
- 346.20
- 391.20
- 527.30

125 150 175 200 225 250 275 300 325 350 375 400 425 450 475 500 525 55
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Mass Analysis Report

Sample Name: A39/CnosJ39
Position: Val 44
User Name: 
IRM Calibration Status: Success
Comment: 

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[Graph showing mass spectra with peaks at 130.20, 242.20, and 264.20]
Mass Analysis Report

Sample Name: A/39/Cmcs3/26
Position: Vial 46
User Name: 
IRM Calibration Status: Success
Comment: 

Fragmentor Voltage | Collision Energy | Ionization Mode
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+ Scan (0.118 min) 100127016.d Subtract (1)

230.10
279.10
393.20
481.30
530.30
579.20

Counts (%) vs. Mass-to-Charge (m/z)
Mass Analysis Report

Sample Name: A431CM5350
Position: Vial 17
User Name: [Redacted]
IRM Calibration Status: Success
Comment: [Redacted]

User Spectra

Fragmenter Voltage | Collision Energy | Ionization Mode
--- | --- | ---
100 | 0 | ESI

+ Scan (0.243 min) 100423017.d Subtract (1)

Counts (%) vs. Mass-to-Charge (m/z)

 Counts (%): 0.0 0.2 0.4 0.6 0.8 1.0

Mass-to-Charge (m/z): 30 125 150 175 200 225 250 275 300 325 350 375 400 425 450 525 55

Masses: 130.20, 149.00, 206.10, 251.20, 316.30, 391.30, 413.30, 450.40

Mass: 282.10
Mass Analysis Report

Sample Name: M39/Cmax3/25
Position: Vial 1
User Name: Success
IRM Calibration Status: Success
Comment:

Fragmentor Voltage: 125
Collision Energy: 0
Ionization Mode: ESI

+ Scan (0.140 min) 100125001.d Subtract (1)

Counts (%) vs. Mass-to-Charge (m/z)

- 262.10
- 220.10
- 284.10
- 439.20

Counts x10^2
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Mass Analysis Report

Sample Name: A439/Cm-3/29
Position: Vial 4
User Name: 
IRM Calibration Status: Success
Comment: 

Fragmentor Voltage: 110
Collision Energy: 0
Ionization Mode: ESI

Scan (0.130 min) 100127037.d Subtract (1)

Counts (%) vs. Mass-to-Charge (m/z)

- 149.10
- 276.20
- 391.30
- 573.30
- 663.50
Mass Analysis Report

Sample Name: A138/CM033/45
Position: Val 64
User Name: [Redacted]
IRM Calibration Status: Success
Comment: [Redacted]

+ Scan (0.118 min) 100308024.d Subtract (1)

307.20

391.40

Counts (%): Mass-to-Charge (m/z)
# Mass Analysis Report

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**Position**: Vial 38  
**User Name**: [blank]  
**IRM Calibration Status**: SUCCESS  
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Counts (%) vs. Mass-to-Charge (m/z)
Mass Analysis Report

Sample Name: 4f
Position: Vial 47
User Name: A439/Cmos3/48
IRM Calibration Status: Success

User Spectra

Fragmentor Voltage: 110
Collision Energy: 0
Ionization Mode: ESI

+ Scan (0.118 min) 100317021.d Subtract (1)

Counts (%) vs. Mass-to-Charge (m/z)

- 242.20
- 264.10
- 505.30
Supplementary Material (ESI) for Organic & Biomolecular Chemistry

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Mass Analysis Report

Sample Name: 4g

Position: 1

User Name: 1

IRM Calibration Status: SUCCESS

Comment: 4g

User Spectra

Fragmentor Voltage | Collision Energy | Ionization Mode
--- | --- | ---
+ Scan (0.133 min) 100201033.d Subtract (1)

Counts (%) vs. Mass-to-Charge (m/z)

- 230.10
- 248.10
- 279.10
- 408.30

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Mass Analysis Report

Sample Name: 4h
Position: Val 61
User Name: 439/CMOS3/51
IRM Calibration Status: Success
Comment:

Fragmentor Voltage | Collision Energy | Ionization Mode
100 | 0 | ESI

Scan (0.287 min) 100525011.d Subtract (1)
282.30

149.10 186.30 391.50

Counts (%) vs. Mass-to-Charge (m/z)