

# Synthesis, Molecular Structure and Anticancer Activity of (*E*)-*N*-((2-Piperidin-1-yl)Quinolin-3-yl)methylene)Aniline Derivatives

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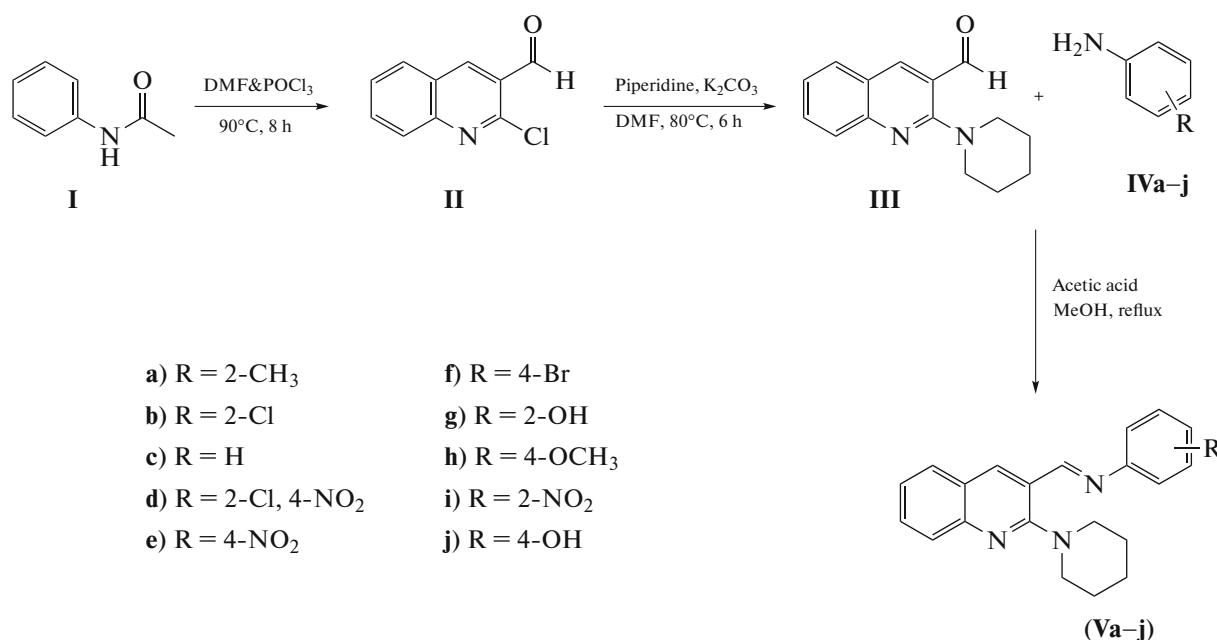
**Abstract**—A series of (*E*)-*N*-((2-(piperidin-1-yl)quinolin-3-yl)methylene)aniline derivatives have been synthesized from 2-(piperidin-1-yl)quinoline-3-carbaldehyde with substituted anilines and these were characterized on the basis of spectral data such as IR, H-NMR, mass spectrometry and X-ray single crystal diffraction analysis. The title compounds were evaluated for their in vitro anticancer activity against various human cells.

**Keywords:** 2-(piperidin-1-yl)quinoline-3-carbaldehyde, X-ray single crystal diffraction, Schiff's bases, anticancer activity

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Heterocyclic compounds play an important role in the designing new class of drug derivatives. Among them the Quinoline derivatives have displayed potent anticancer activities with targeting different active sites [1–3] and these also show a wide variety of pharmacological activities such as antibacterial [4], antimicrobial [5], antiallergenic [6], anti-inflammatory [7], antitumor [8], anti-tuberculosis [9], anti-malarial [10], anti-obesity [11], antihypertensive [12], tyrosine kinase platelet-derived growth factor receptor tyrosine kinase (PDGF-RTK) [13], and phosphodiesterase 10A (PDE10A) inhibiting agents [14]. On the other hand,

piperidine derivatives show a variety of biological activities including as antimicrobial [15], anticonvulsant [16], antidepressant (Paroxetine), and attention-deficit hyperactivity disorder (ADHD) drugs. Furthermore, Schiff bases are one of the important chemical entities in pharmaceutical fields due to a broad spectrum of biological activities including as antimicrobial [17], antitubercular [18], anticancer [19], antioxidant [20]. In the view of importance of quinolines and their derivatives, we have prompted us to take synthesized a series of (*E*)-3-(2-arylvinylyl)-2-(piperidin-1-yl)quinolines and evaluated their anticancer activity (Scheme 1).



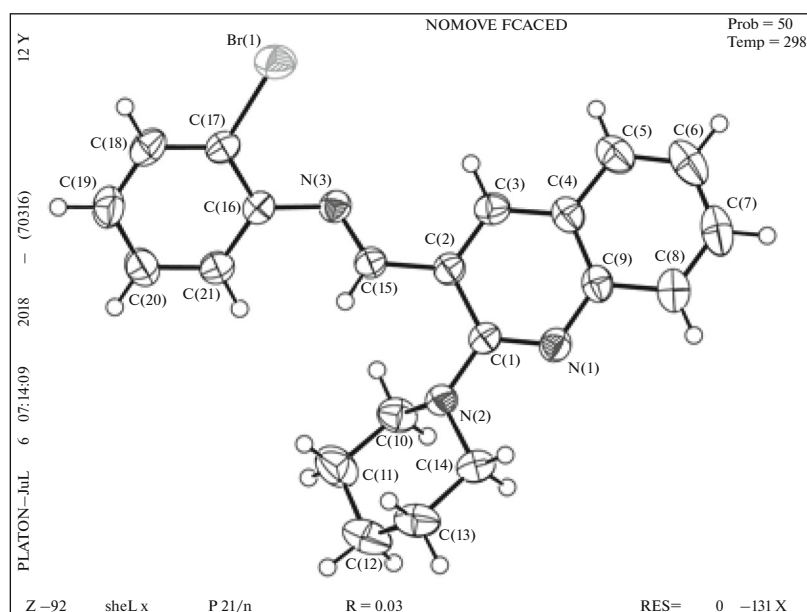


Fig. 1. ORTEP diagram of (*E*)-4-bromo-*N*-((2-(piperidin-1-yl)quinolin-3-yl)methylene)aniline (**Va**).

## EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. The purity of the compounds was checked by TLC using precoated silica gel plates 60<sub>254</sub> (Merck). IR (KBr) spectra were recorded on a Shimadzu FT-IR-8400s spectrophotometer. <sup>1</sup>H NMR spectrums were recorded on Bruker Advance II 400 MHz spectrometer using tetramethylsilane as an internal standard. Mass spectra were recorded on a GCMS-QP 1000 EX mass spectrometer.

## RESULTS AND DISCUSSION

The synthesis of (*E*)-*N*-((2-(piperidin-1-yl)quinolin-3-yl)methylene)anilines (**Va–j**) was shown in Scheme 1. The 2-chloroquinoline-3-carbaldehyde (**II**) was synthesized by the reaction of acetanilide with Vilsmeier-Haack reagent (DMF/POCl<sub>3</sub>). The compound (**II**) was reacted with piperidine in the presence of potassium carbonate to yield 2-(piperidin-1-yl)quinoline-3-carbaldehyde (**III**) intermediate. The compound (**III**) reacted with substituted aromatic amines (**IVa–j**) to afford Schiff bases (**Va–j**) in excellent yield. The structures of the compounds (**Va–j**) were established by using spectral data such as IR, <sup>1</sup>H-NMR and mass spectroscopy. In IR spectrum the compounds shows strong absorption at 1620–1628 cm<sup>-1</sup> corresponds to CH=N group. In the <sup>1</sup>H-NMR spectrum of compounds shows a singlet resonated between δ 8.7–8.9 ppm indicating the presence proton of CH=N. In the mass spectrum of all the compounds showed their *m/z* as M + H peak. The spectral analysis confirmed synthesis of titled compounds.

## Experimental Section for SXRD

X-ray reflections were collected on Bruker D8 QUEST, CCD diffractometer equipped with a graphite mono-chromator and MoK<sub>α</sub> fine-focus sealed tube (λ = 0.71073 Å). Intensities for absorption were corrected using SADABS. Structures were solved and refined using SHELXL-2018 with anisotropic displacement parameters for non-H atoms. Hydrogen atoms were experimentally located through the Fourier difference electron density maps in all crystal structures. All C–H atoms were geometrically fixed using HFIX command in SHELX-TL program of Bruker-AXS. Crystallographic cif file are available at [www.ccdc.cam.ac.uk/data](http://www.ccdc.cam.ac.uk/data) with ref no. CCDC1876405 (Fig. 1, Table 1).

## Anticancer Activity

The newly synthesized (*E*)-*N*-((2-(piperidin-1-yl)quinolin-3-yl)methylene)anilines (**Va–j**) were screened for their anticancer activity against four different human cancer cell lines including A-549 (Lung), A-375 (Melanoma), HT-29 (Colon4) and MCF-7 (Breast) by MTT method. The 1 × 10<sup>4</sup> cells/well were seeded in 200 mL DMEM, supplemented with 10% FBS in each well of 96-well micro culture plates and incubated for 24 h at 37°C in CO<sub>2</sub> incubator. The compound (**Va–j**) were diluted to the desired concentrations in culture medium, were added to the wells with respective vehicle control. After 48 h of incubation, 10 mL MTT (5 mg/mL) was added to each well and the plates were further incubated for 4 h. Then the supernatant from each well was carefully removed, formed crystals were dissolved in 100 mL of DMSO

and absorbance at 540 nm wavelength was recorded. The resulted values were expressed as the compound concentration ( $\mu\text{mol/L}$ ) that causes 50% inhibition of cell growth ( $\text{IC}_{50}$ ), are shown in Table 2. The *Combretastatin-A4* used as positive control. Among them, the compounds **Vc**, **Vd**, **Ve** and **Vi** were demonstrated almost near to positive control.

#### General Method for the Synthesis of Schiff's Bases (Va-j)

To a mixture of 2-(piperidin-1-yl)quinoline-3-carbaldehyde (1 mmol) (**III**) and substituted aniline (1 mmol) (**IVa-j**) in methanol, and 2-3 drops of glacial acetic acid was added to it, then the mixture was refluxed for 2–3 h. The progress of reaction monitored by TLC, after completion of the reaction the solvent evaporated under reduced pressure and cooled. The product obtained was filtered, washed with water, dried and recrystallized from methanol to afford pure crystalline products (**Va-j**).

#### Spectral Data

**(Va) (E)-2-Methyl-N-((2-(piperidin-1-yl)quinolin-3-yl)methylene)aniline:** M. p. 89–91°C; Yield: 94%; IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1251, 1502, 1577, 1612 and 1627;  $^1\text{H}$  NMR,  $\delta$ , ppm: 1.67–1.81 (m, 6H, 3CH<sub>2</sub>), 2.43 (s, 3H, CH<sub>3</sub>), 3.39–3.41 (t, 4H, CH<sub>2</sub>), 6.93–6.95 (d, 1H, Ar–H), 7.14–7.27 (m, 3H, Ar–H), 7.35–7.39 (dd, 1H, Ar–H), 7.61–7.65 (m, 1H, Ar–H), 7.80–7.87 (m, 2H, Ar–H), 8.55 (s, 1H, –Ar–H), 8.74 (s, 1H, HC=N); HRMS (ESI):  $m/z$  [M + H]<sup>+</sup> calcd for C<sub>22</sub>H<sub>24</sub>N<sub>3</sub>: 330.1970; found: 330.2012.

**(Vb) (E)-2-Chloro-N-((2-(piperidin-1-yl)quinolin-3-yl)methylene)aniline:** M. p. 117–119°C; Yield: 94%; IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1260, 1508, 1580, 1607 and 1624;  $^1\text{H}$  NMR,  $\delta$ , ppm: 1.67–1.79 (m, 6H, CH), 3.39–3.42 (t, 4H, CH<sub>2</sub>), 7.03–7.05 (dd, 1H, Ar–H), 7.15–7.19 (m, 1H, Ar–H), 7.29–7.39 (m, 2H, Ar–H), 7.46–7.48 (dd, 1H, Ar–H), 7.62–7.66 (m, 1H, Ar–H), 7.81–7.87 (m, 2H, Ar–H), 8.55 (s, 1H, –Ar–H), 8.78 (s, 1H, HC=N); HRMS (ESI):  $m/z$  [M + H]<sup>+</sup> calcd for C<sub>22</sub>H<sub>24</sub>ClN: 350.1424; found: 350.1469. HRMS (ESI):  $m/z$  [M + H]<sup>+</sup> calcd for C<sub>22</sub>H<sub>24</sub>ClN<sub>2</sub>: 350.1424; found: 350.1469.

**(Vc) (E)-N-((2-(Piperidin-1-yl)quinolin-3-yl)methylene)aniline:** M. p. 94–96°C; Yield: 90%; IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1269, 1506, 1585, 1612 and 1625;  $^1\text{H}$  NMR,  $\delta$ , ppm: 1.66–1.81 (m, 6H, 3CH<sub>2</sub>), 3.37–3.40 (t, 4H, 2N–CH<sub>2</sub>), 7.07–7.10 (dd, 2H, Ar–H), 7.16–7.19 (m, 2H, Ar–H), 7.28–7.33 (m, 2H, Ar–H), 7.66–7.69 (m, 1H, Ar–H), 7.77–7.85 (m, 3H, Ar–H), 8.64 (s, 1H, CH<sub>2</sub>–CO), 8.77 (s, 1H, CH=N); HRMS (ESI):  $m/z$  [M + H]<sup>+</sup> calcd for C<sub>21</sub>H<sub>22</sub>N<sub>3</sub>: 316.1814; found: 316.1856.

**(Vd) (E)-2-chloro-4-nitro-N-((2-(piperidin-1-yl)quinolin-3-yl)methylene)aniline:** 106–108°C; Yield: 89%; IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1255, 1505, 1591, 1608 and

1624;  $^1\text{H}$  NMR,  $\delta$ , ppm: 1.68–1.77 (m, 6H, 3CH<sub>2</sub>), 3.39–3.42 (t, 4H, CH<sub>2</sub>), 7.10–7.12 (d, 1H, Ar–H), 7.38–7.42 (dd, 1H, Ar–H), 7.66–7.70 (m, 2H, Ar–H), 7.82–7.88 (dd, 2H, Ar–H), 8.19–8.22 (dd, 1H, Ar–H), 8.38–8.39 (d, 1H, Ar–H), 8.54 (s, 1H, –Ar–H), 8.79 (s, 1H, HC=N); HRMS (ESI):  $m/z$  [M+H]<sup>+</sup> calcd for C<sub>21</sub>H<sub>20</sub>ClN<sub>4</sub>O<sub>2</sub>: 395.1275; found: 395.1303.

**(Ve) (E)-4-Nitro-N-((2-(piperidin-1-yl)quinolin-3-yl)methylene)aniline:** 121–123°C; Yield: 92%; IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1269, 1506, 1585, 1612 and 1625;  $^1\text{H}$  NMR,  $\delta$ , ppm: 1.69–1.80 (m, 6H, 3CH<sub>2</sub>), 3.38–3.40 (t, 4H, CH<sub>2</sub>), 7.29–7.31 (d, 2H, Ar–H), 7.37–7.41 (dd, 1H, Ar–H), 7.65–7.69 (m, 1H, Ar–H), 7.80–7.88 (dd, 2H, Ar–H), 8.30–8.33 (d, 2H, Ar–H), 8.62 (s, 1H, –Ar–H), 8.75 (s, 1H, HC=N); HRMS (ESI):  $m/z$  [M + H]<sup>+</sup> calcd for C<sub>21</sub>H<sub>21</sub>N<sub>4</sub>O<sub>2</sub>: 361.1665; found: 361.1711.

**(Vf) (E)-4-Bromo-N-((2-(piperidin-1-yl)quinolin-3-yl)methylene)aniline:** 1105–107°C; Yield: 95%; IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1263, 1500, 1590, 1607 and 1621;  $^1\text{H}$  NMR,  $\delta$ , ppm: 1.66–1.80 (m, 6H, 3CH<sub>2</sub>), 3.39–3.42 (t, 3H, CH<sub>2</sub>), 7.00–7.03 (dd, 1H, Ar–H), 7.08–7.11 (m, 1H, Ar–H), 7.34–7.39 (m, 2H, Ar–H), 7.62–7.67 (m, 2H, Ar–H), 7.81–7.87 (dd, 2H, Ar–H), 8.51 (s, 1H, Ar–H), 8.79 (s, 1H, HC=N); HRMS (ESI):  $m/z$  [M + H]<sup>+</sup> calcd for C<sub>22</sub>H<sub>24</sub>BrN<sub>3</sub>: 395.0997; found: 395.1311.

**(Vg) (E)-2-(((2-(Piperidin-1-yl)quinolin-3-yl)methylene)amino)phenol:** 125–127°C; Yield: 92%; IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1258, 1501, 1581, 1611 and 1625;  $^1\text{H}$  NMR,  $\delta$ , ppm: 1.66–1.82 (m, 6H, 3CH<sub>2</sub>), 3.36–3.39 (t, 4H, CH<sub>2</sub>), 6.92–6.96 (m, 1H, Ar–H), 7.04–7.07 (dd, 1H, Ar–H), 7.21–7.23 (m, 1H, Ar–H), 7.34–7.40 (m, 3H, Ar–H), 7.62–7.66 (m, 1H, Ar–H), 7.79–7.87 (dd, 2H, Ar–H), 8.70 (s, 1H, Ar–H), 8.89 (s, 1H, HC=N); HRMS (ESI):  $m/z$  [M + H]<sup>+</sup> calcd for C<sub>21</sub>H<sub>22</sub>N<sub>3</sub>O: 332.1763; found: 332.1806.

**(Vh) (E)-4-Methoxy-N-((2-(piperidin-1-yl)quinolin-3-yl)methylene)aniline:** 113–115°C; Yield: 94%; IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1253, 1502, 1583, 1610 and 1624;  $^1\text{H}$  NMR,  $\delta$ , ppm: 1.67–1.80 (m, 6H, 3CH<sub>2</sub>), 3.37–3.39 (t, 4H, CH<sub>2</sub>), 3.85 (s, 3H, OCH<sub>3</sub>), 6.96–6.99 (d, 2H, Ar–H), 7.28–7.37 (m, 3H, Ar–H), 7.59–7.63 (m, 1H, Ar–H), 7.77–7.86 (dd, 2H, Ar–H), 8.66 (s, 1H, Ar–H), 8.70 (s, 1H, HC=N); HRMS (ESI):  $m/z$  [M+H]<sup>+</sup> calcd for C<sub>22</sub>H<sub>24</sub>N<sub>3</sub>O: 346.1919; found: 346.1965.

**(Vi) (E)-2-Nitro-N-((2-(piperidin-1-yl)quinolin-3-yl)methylene)aniline:** 102–104°C; Yield: 92%; IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1250, 1511, 1592, 1602 and 1629;  $^1\text{H}$  NMR,  $\delta$ , ppm: 1.69–1.81 (m, 6H, 3CH<sub>2</sub>), 3.39–3.42 (t, 4H, 2N–CH<sub>2</sub>), 7.21–7.25 (m, 2H, Ar–H), 7.35–7.38 (dd, 1H, Ar–H), 7.66–7.70 (m, 1H, Ar–H), 7.78–7.91 (m, 2H, Ar–H), 8.17–8.19 (m, 1H, Ar–H), 8.66 (s, 1H, –Ar–H), 8.78 (s, 1H, HC=N); HRMS

(ESI):  $m/z$   $[M+H]^+$  calcd for  $C_{21}H_{21}N_4O_2$ : 361.1665; found: 361.1711.

**(Vj) (E)-4-(((2-(Piperidin-1-yl)quinolin-3-yl)methylene)amino)phenol:** 131–133°C; Yield: 94%; IR spectrum,  $\nu$ ,  $cm^{-1}$ : 1269, 1506, 1585, 1612 and 1625;  $^1H$  NMR,  $\delta$ , ppm: 1.66–1.81 (m, 6H, 3CH<sub>2</sub>), 3.37–3.40 (t, 4H, 2N–CH<sub>2</sub>), 3.83 (s, 1H, OH), 6.87–6.91 (dd, 2H, Ar–H), 7.19–7.30 (m, 2H,  $J = 16.4$  Hz, Ar–H), 7.34–7.42 (m, 2H, Ar–H), 7.60–7.64 (m, 1H, Ar–H), 7.78–7.91 (m, 3H, Ar–H), 8.65 (s, 1H, CH<sub>2</sub>–CO), 8.70 (s, 1H, CH=N); HRMS (ESI):  $m/z$   $[M+H]^+$  calcd for  $C_{21}H_{22}N_3O$ : 332.1763; found: 332.1806.

## CONCLUSIONS

In conclusion, a novel series of (*E*)-*N*-((2-(piperidin-1-yl)quinolin-3-yl)methylene)anilines have been successfully synthesized and characterized with different analytical data. The compounds anticancer evaluation resulted that the compounds **Vc**, **Vd**, **Ve** and **Vi** were demonstrated almost near to positive control.

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