Tandem C-C Coupling - Intramolecular Acetylenic Schmidt Reaction under Pd/C-Cu Catalysis

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Experimental Section
**General methods:** Unless stated otherwise, reactions were performed under nitrogen atmosphere. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (60-120 mesh) using distilled petroleum ether and ethyl acetate. $^1$H NMR and $^{13}$C NMR spectra were determined in CDCl$_3$ solution on 200 & 400 and 50 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ = 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (J) are given in hertz. Infrared spectra were recorded on a FT-IR spectrometer. Melting points were determined by using melting point apparatus and are uncorrected. Thermal analysis data [Differential Scanning Calorimetry (DSC)] was generated with the help of DSC-50 detector. MS spectra were obtained on a mass spectrometer. Chromatographic purity by HPLC was determined by using area normalization method and the condition specified in each case: column, mobile phase (range used), flow rate, detection wavelength, and retention time. All the terminal alkynes used are commercially available.

**CAUTION!** Azido-containing compounds are presumed to be potentially explosive and therefore proper safety precautions should be taken before using these compounds. However, we did not encounter with any problems while using benzoyl azides in our laboratory.

**Preparation of 2-iodo benzoyl azide**$^1$ (1a):

![Chemical Structure](image)

To a mixture of 2-iodobenzoic acid (5.0 g, 20.16 mmol) and sodium azide (1.13 g, 20.16 mmol) in dry DMF (40 mL) was added POCl$_3$ (6 mL, 38.70 mmol) at 0 ºC. The reaction mixture was stirred at room temperature for 3 h. After completion of the reaction crushed ice (300 gm) was added to the reaction mixture. The white solid separated was filtered and dried under vacuum to afford the desired compound (3.6 g, 65% yield); mp 130-132 ºC; $^1$H NMR (CDCl$_3$, 200 MHz) δ 8.08-7.98 (m, 1H), 7.45 (t, J = 7.7 Hz, 1H), 7.25-7.15 (m, 2H); IR (cm$^{-1}$, KBr) 1691, 1582, 1561, 1467, 1429, 1404; $m/z$ (ES Mass), 274 (M+1,
Preparation of 2-Iodo-3-methoxy-benzoyl azide (1b):

\[
\begin{align*}
\text{O} & \quad \text{I} \\
\text{N}_3 & \quad \text{O}
\end{align*}
\]

To the stirred solution of 2-iodo-3-methoxy benzoic acid (3.5 g, 12.58 mmol) and sodium azide (0.90 gm, 13.84 mmol) in dry DMF (20 mL) was added POCl \(_3\) (3.9 g, 4 mL, 25.49 mmol) at 0 ºC. The reaction mixture was stirred at room temperature for 3 h. After completion of the reaction crushed ice (200 gm) was added to the reaction mixture. The white solid separated was filtered and dried under vacuum to afford the desired compound (2.18 g, 74 % yield); mp 102-103 ºC; \(^1\)H NMR (CDCl\(_3\), 200 MHz) \(\delta\) 7.45-7.35 (m, 2H), 7.01-6.97 (m, 1H), 3.93 (s, 3H, OMe); IR (cm\(^{-1}\), KBr) 1692, 1268, 1054; \(m/z\) (ES Mass), 304 (M\(^{+}\), 100 %), HPLC 97.7 %; Inertsil ODS 3V (150 x 4.6) mm, mobile phase A: 0.01 M KH\(_2\)PO\(_4\) (pH = 3.0 with H\(_3\)PO\(_4\)), mobile phase B: acetonitrile, gradient (T/% B) 0/30, 4/30, 16/80, 22/80, 24/30, 26/30, flow rate 1.0 mL/min, UV 210 nm, retention time 8.6 min.

Preparation of 3-substituted 2H-isoquinoline-1-ones (3):

**Typical procedure:** A mixture of 2-iodo benzoyl azide (0.3 g, 1.09 mmol), 10 % Pd/C (0.034 g, 0.033 mmol), PPh\(_3\) (0.034 g, 0.13 mmol), CuI (0.013 g, 0.065 mmol) and triethylamine (0.22 g, 0.3 mL, 2.17 mmol) in ethanol (10 mL) was stirred at 25 ºC for 30 min under nitrogen. To this mixture was added 2-methyl but-3-yn-2-ol (0.092 g, 1.09 mmol) slowly with stirring. The reaction mixture was then stirred at 80 ºC for 12h. After completion of the reaction the mixture was cooled to room temperature, diluted with EtO\(_2\)Ac (50 mL) and filtered through celite. The filtrate was collected and concentrated under vacuum. The residue was purified by column chromatography (petroleum ether-EtO\(_2\)Ac) to afford the desired product.
3-(1-Hydroxy-1-methyl-ethyl)-2H-isoquinolin-1-one (3a):

Brown solid; mp 88-90 °C; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.27 (d, $J = 7.5$ Hz, 1H), 7.70 (t, $J = 7.5$ Hz, 1H), 7.47 (t, $J = 6.8$ Hz, 1H), 7.43 (d, $J = 6.8$ Hz, 1H), 6.62 (s, 1H), 1.91 (bs, OH), 1.60 (s, 6H); IR (cm$^{-1}$, KBr) 3284, 1736; m/z (CI Mass) 205 (M+1, 100%), 187 (M$^+$-18, 30%); $^{13}$C NMR (CDCl$_3$, 50 MHz) $\delta$ 161.7, 137.2, 134.9, 131.9, 129.5, 128.1, 126.4, 125.9, 99.9, 83.9, 28.2 (2C); HPLC 99.0%, Inertsil ODS 3V (150 x 4.6) mm, mobile phase A: 0.01M KH$_2$PO$_4$, mobile phase B: CH$_3$CN, gradient (T/% B): 0/30, 2/30, 12/80, 22/80, 23/30, 24/30, flow rate 1.0 mL/min, UV 230 nm, retention time 7.0 min. Elemental analysis found C, 70.74; H, 6.42; N, 6.94; C$_{12}$H$_{13}$NO$_2$ requires C, 70.92; H, 6.45; N, 6.89.

3-(3-Hydroxypropyl)-2H-isoquinolin-1-one (3b):

White solid; mp 66-68 °C; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.26 (d, $J = 8.0$ Hz, 1H), 7.68 (t, $J = 7.8$ Hz, 1H), 7.46 (t, $J = 8.0$ Hz, 1H), 7.36 (d, $J = 7.8$ Hz, 1H), 6.30 (s, 1H), 3.74 (t, $J = 6.1$ Hz, 2H), 2.66 (t, $J = 7.5$ Hz, 2H), 2.02-1.95 (m, 2H), 1.57 (bs, -OH); IR (cm$^{-1}$, KBr) 3285, 1739; m/z (CI Mass) 205 (M+1, 100%); $^{13}$C NMR (CDCl$_3$, 50 MHz) $\delta$ 162.9, 137.4, 134.7, 129.4 (2C), 127.6 (2C), 124.9, 103.3, 61.5, 29.8 (2C); HPLC 95.7%, Inertsil ODS 3V (150 x 4.6) mm, mobile phase A: 0.01M KH$_2$PO$_4$, mobile phase B: CH$_3$CN, gradient (T/% B) 0/30, 3/30, 12/80, 18/80, 20/30, 22/30, flow rate 1.5 mL/min, UV 210 nm, retention time 5.0 min; Elemental analysis found C, 71.09; H, 6.46; N, 7.00; C$_{12}$H$_{13}$NO$_2$ requires C, 70.92; H, 6.45; N, 6.89.

3-(2-Hydroxy-propyl)-2H-isoquinolin-1-one (3c):
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Light brown semi solid; \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 8.25 (d, \(J = 8.0\) Hz, 1H), 7.68 (t, \(J = 7.5\) Hz, 1H), 7.49 (t, \(J = 7.5\) Hz, 1H), 7.37 (d, \(J = 8.0\) Hz, 1H), 6.36 (s, 1H), 4.00-3.96 (m, 2H), 2.68-2.60 (m, 1H), 1.31 (d, \(J = 8.2\) Hz, 3H); IR (cm\(^{-1}\), neat) 3388, 1715; \(m/z\) (CI Mass) 205 (M\(^{+}\), 100%); \(^{13}\)C NMR (CDCl\(_3\), 50 MHz) \(\delta\) 164.3, 137.3, 134.8, 129.5, 128.4, 127.9 (2C), 125.2, 105.1, 65.6, 43.1, 23.1; HPLC 96.17%, Inertsil ODS 3V (4.6 x 250) mm, mobile phase A: 0.01M KH\(_2\)PO\(_4\), mobile phase B: CH\(_3\)CN, gradient (T/% B) 0/30, 4/30, 13/65, 16/80, 26/80, 30/30, flow rate 1.0 mL/min, UV 230 nm, retention time 7.6 min; Elemental analysis found C, 71.56; H, 6.40; N, 6.75; C\(_{12}\)H\(_{13}\)NO\(_2\) requires C, 70.92; H, 6.45; N, 6.89.

3-(2-Hydroxy-ethyl)-2\(H\)-isoquinolin-1-one (3d):

Brown solid; mp 50-52 °C; \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 8.25 (d, \(J = 8.0\) Hz, 1H), 8.10 (d, \(J = 7.5\) Hz, 1H), 7.69 (t, \(J = 8.0\) Hz, 1H), 7.47 (t, \(J = 7.5\) Hz, 1H), 6.30 (s, 1H), 3.75 (t, \(J = 6.2\) Hz, 2H), 2.54 (t, \(J = 6.2\) Hz, 2H); IR (cm\(^{-1}\), KBr) 3383, 1715; \(m/z\) (CI Mass) 190 (M\(^{+}\), 100%); \(^{13}\)C NMR (CDCl\(_3\), 50 MHz) \(\delta\) 163.0, 137.3, 134.8 (2C), 129.4, 127.8 (2C), 125.1, 104.8, 59.5, 36.8; HPLC 98.6%, Inertsil ODS 3V (150 x 4.6) mm, mobile phase A: 0.01M KH\(_2\)PO\(_4\), mobile phase B: CH\(_3\)CN, gradient (T/% B) 0/25, 5/25, 15/80, 22/80, 23/25, 24/25, flow rate 1.0 mL/min, UV 230 nm, retention time 7.9 min; Elemental analysis found C, 69.59; H, 5.83; N, 7.49; C\(_{11}\)H\(_{11}\)NO\(_2\) requires C, 69.83; H, 5.86; N, 7.40.

3-(4-hydroxy-butyl)-2\(H\)-isoquinolin-1-one (3e):
Colorless semi solid; \( ^1 \)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 8.25 (d, \( J = 7.8 \) Hz, 1H), 7.68 (t, \( J = 7.0 \) Hz, 1H), 7.45 (t, \( J = 7.0 \) Hz, 1H), 7.35 (d, \( J = 7.8 \) Hz, 1H), 6.27 (s, 1H), 3.70 (t, \( J = 6.4 \) Hz, 2H), 2.58 (t, \( J = 7.0 \) Hz, 2H), 1.83-1.80 (m, 2H), 1.79-1.70 (m, 2H), 1.63 (bs, D\(_2\)O exchangeable, 1H); IR (cm\(^{-1}\), neat) 3408, 1727; \( m/z \) (CI Mass) 219 (M+1, 100%); \(^{13}\)C NMR (CDCl\(_3\), 50 MHz) \( \delta \) 163.0, 137.5, 134.7, 129.5 (2C), 127.6 (2C), 125.0, 103.1, 62.4, 33.2, 29.7, 23.2; HPLC 96.28%, Inertsil ODS 3V (150 x 4.6) mm, mobile phase A: 0.01M KH\(_2\)PO\(_4\), mobile phase B: CH\(_3\)CN; gradient (T/% B) 0/30,2/30, 12/80, 20/80, 21/30, 22/30, flow rate 1.0 mL/min, UV 230 nm, retention time 7.6 min; Elemental analysis found C, 71.77; H, 6.98; N, 6.81; C\(_{13}\)H\(_{15}\)NO\(_2\) requires C, 71.87; H, 6.96; N, 6.45.

3-Hexyl-2\(H\)-isoquinolin-1-one (3f):

Brown semi solid; \( ^1 \)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 8.26 (d, \( J = 7.8 \) Hz, 1H), 7.55 (t, \( J = 7.2 \) Hz, 1H), 7.45 (t, \( J = 7.2 \) Hz, 1H), 7.35 (d, \( J = 7.8 \) Hz, 1H), 6.21 (s, 1H), 2.52 (t, \( J = 7.5 \) Hz, 2H), 1.72-1.71 (m, 2H), 1.34-1.25 (m, 5H), 0.91-0.70 (m, 4H); IR (cm\(^{-1}\), neat) 3385, 1745; \( m/z \) (CI Mass) 229 (M\(^+\), 100%); \(^{13}\)C NMR (CDCl\(_3\), 50 MHz) \( \delta \) 163.0, 137.6, 134.6, 129.5, 128.8, 127.5 (2C), 124.9, 102.8, 33.5, 31.4, 28.6, 26.8, 22.4, 13.9; HPLC 99.81%, Inertsil ODS 3V (150 x 4.6) mm; mobile phase A: 0.01M KH\(_2\)PO\(_4\), mobile phase B: CH\(_3\)CN, gradient (T/% B) 0/50, 2/50, 7/80, 18/80, 20/80, 21/30, 22/30, flow rate 1.0 mL/min, UV 228 nm, retention time 9.9 min; Elemental analysis found C, 78.76; H, 8.32; N, 6.08; C\(_{15}\)H\(_{19}\)NO requires C, 78.56; H, 8.35; N, 6.11.

4-(1-oxo-1,2-dihydro-isoquinolin-3-yl)-butyronitrile (3g):
Brown solid; mp 54-56 °C; \( ^1H \) NMR (CDCl\(_3\), 400 MHz) \( \delta \) 8.26 (d, \( J = 7.3 \) Hz, 1H), 7.70 (t, \( J = 7.3 \) Hz, 1H), 7.49 (t, \( J = 7.8 \) Hz, 1H), 7.38 (d, \( J = 7.8 \) Hz, 1H), 6.36 (s, 1H), 2.72 (t, \( J = 7.2 \) Hz, 2H), 2.51-2.42 (m, 2H), 2.14-2.07 (m, 2H); IR (cm\(^{-1}\), KBr) 3423, 2243, 1723; \( m/z \) (CI Mass) 214 (M+1, 100%); \( ^{13}C \) NMR (CDCl\(_3\), 50 MHz) \( \delta \) 162.5, 136.9, 134.9 (2C), 129.5 (2C), 128.1, 125.3, 120.2, 104.4, 32.1, 22.6, 16.3, HPLC 98.4%, Inertsil ODS 3V (150 x 4.6) mm, mobile phase A: 0.01M KH\(_2\)PO\(_4\), mobile phase B: CH\(_3\)CN; gradient (T/% B) 0/30, 3/30, 12/80, 18/80, 20/30, 22/30, flow rate 1.0 mL/min, UV 210 nm, retention time 8.1 min; Elemental analysis found C, 73.67; H, 5.73; N, 13.05; C\(_{13}\)H\(_{12}\)N\(_2\)O requires C, 73.56; H, 5.70; N, 13.20.

3-(3-chloro-propyl)-2H-isoquinolin-1-one (3h):

\[
\begin{array}{c}
\text{NH} \\
\text{O} \\
\text{Cl}
\end{array}
\]

Ash colored solid; DSC 99.25 °C; \( ^1H \) NMR (CDCl\(_3\), 400 MHz) \( \delta \) 8.26 (d, \( J = 7.5 \) Hz, 1H), 7.68 (t, \( J = 7.5 \) Hz, 1H), 7.47 (t, \( J = 7.8 \) Hz, 1H), 7.37 (d, \( J = 7.8 \) Hz, 1H), 6.33 (s, 1H), 3.61 (t, \( J = 6.2 \) Hz, 2H), 2.73 (t, \( J = 7.3 \) Hz, 2H), 2.23-2.16 (m, 2H); IR (cm\(^{-1}\), KBr) 3423, 1723; \( m/z \) (CI Mass) 224 (M+2, 100%); HPLC 95.0%, Inertsil ODS 3V (150 x 4.6) mm, mobile phase A: 0.01M KH\(_2\)PO\(_4\), mobile phase B: CH\(_3\)CN, gradient (T/% B) 0/45, 3/45, 12/80, 20/80, 23/45, 25/45; flow rate 1.0 mL/min, UV 210 nm, retention time 8.5 min; Elemental analysis found C, 65.21; H, 5.42; N, 6.25; C\(_{12}\)H\(_{12}\)ClNO requires C, 65.02; H, 5.46; N, 6.32.

3-(2-Hydroxy-ethyl)-5-methoxy-2H-isoquinolin-1-one (3i):

\[
\begin{array}{c}
\text{OCH}_3 \\
\text{OH} \\
\text{O}
\end{array}
\]

Yellow solid; mp 107-109 °C; \( ^1H \) NMR (CDCl\(_3\), 400 MHz) \( \delta \) 7.85 (d, \( J = 8.0 \) Hz, 1H), 7.41 (t, \( J = 8.2 \) Hz, 1H), 7.15 (dd, \( J = 8.0 \) & 1.0 Hz, 1H), 6.72 (s, 1H), 3.99 (t, \( J = 6.2 \) Hz,
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2H), 3.92 (s, 3H), 2.80 (t, J = 6.2 Hz, 2H), 1.25 (bs, -OH); IR (cm⁻¹, KBr) 3485, 1710; m/z (CI Mass) 221 (M+1, 100%); ¹³C NMR (CDCl₃, 50 MHz) δ 162.8, 153.9, 128.0, 127.8, 120.7 (2C), 114.4 (2C), 99.1, 59.7, 55.9, 37.1; HPLC 97.96%, Symmetry shield RP8 (250 x 4.6) mm; mobile phase A: 0.01M KH₂PO₄, mobile phase B: CH₃CN, gradient (T/% B): 0/25, 5/25, 17/80, 22/80, 24/25, 25/25, flow rate 1.0 mL/min, UV 235 nm, retention time 14.6 min; Elemental analysis found C, 65.54; H, 5.95; N, 6.55; C₁₂H₁₃NO₃ requires C, 65.74; H, 5.98; N, 6.39.

4-(5-Methoxy-1-oxo-1,2-dihydro-isoquinolin-3-yl)-butyronitrile (3j):

White solid; mp 70-72 °C; ¹H NMR (CDCl₃, 400 MHz) δ 7.85 (d, J = 8.0 Hz, 1H), 7.41 (t, J = 8.2 Hz, 1H), 7.12 (dd, J = 8.0 & 1.0 Hz, 1H), 6.72 (s, 1H), 3.91 (s, 3H), 2.74 (t, J = 7.2 Hz, 2H), 2.45-2.40 (m, 2H), 2.00 (t, J = 7.0 Hz, 2H); IR (cm⁻¹, KBr) 2930, 1722 m/z (CI Mass) 243 (M⁺, 100%); ¹³C NMR (CDCl₃, 50 MHz) δ 168.1, 153.7, 138.2, 131.4 (2C), 128.9 (2C), 119.6, 114.3, 93.0, 55.5, 32.4, 22.5, 16.5; HPLC 98.02%, Inertsil ODS 3V (150 x 4.6) mm, mobile phase A: 0.01M KH₂PO₄, mobile phase B: CH₃CN, gradient (T/% B) 0/30, 2/30, 12/80, 20/80, 24/30, 25/30, flow rate 1.0 mL/min, UV 228 nm, retention time 6.4 min; Elemental analysis found C, 69.49; H, 5.80; N, 11.45; C₁₄H₁₄N₂O₂ requires C, 69.41; H, 5.82; N, 11.56.

3-Hexyl-5-methoxy-2H-isoquinolin-1-one (3k):


White solid; mp 78-80 °C; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.84 (d, $J = 7.0$ Hz, 1H), 7.37 (t, $J = 8.0$ Hz, 1H), 7.12 (d, $J = 8.0$ Hz, 1H), 6.61 (s, 1H), 3.92 (s, 3H), 2.53 (t, $J = 8.0$ Hz, 2H), 1.74-1.70 (m, 2H), 1.39-1.29 (m, 6H), 0.90 (t, $J = 7.0$ Hz, 3H); IR (cm$^{-1}$, KBr) 2930, 1722; m/z (CI Mass) 260 (M$^+$, 100%); $^{13}$C NMR (CDCl$_3$, 50 MHz) $\delta$ 164.2, 153.6, 137.6, 127.6 (2C), 120.8, 114.2 (2C), 97.1, 55.8, 33.7, 31.5, 28.7, 26.9, 22.5, 14.0; HPLC 98.7 %, Symmetry Shield RP 8 (150 x 4.6) 5 mm, mobile phase A 0.01M KH$_2$PO$_4$, mobile phase B CH$_3$CN, gradient (T/% B) 0/50, 2/50, 8/80, 20/80, 24/50, 25/50, flow rate 1.0 mL/min, UV 210 nm, retention time 10.7 min; Elemental analysis found C, 74.29; H, 8.14; N, 5.25; C$_{16}$H$_{21}$NO$_2$ requires C, 74.10; H, 8.16; N, 5.40.

3-(3-Hydroxy-propyl)-5-methoxy-2H-isoquinolin-1-one (3l):

White solid; mp 82-84 °C; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.82 (d, $J = 8.0$ Hz, 1H), 7.38 (t, $J = 8.1$ Hz, 1H), 7.13 (d, $J = 8.0$ Hz, 1H), 6.67 (s, 1H), 3.92 (s, 3H), 3.74 (t, $J = 6.2$ Hz, 2H), 2.69 (t, $J = 7.2$ Hz, 2H), 2.01-1.95 (m, 2H), 1.25 (bs, OH); IR (cm$^{-1}$, KBr) 3408, 1725; m/z (CI Mass) 235 (M$^+$+1, 100%); $^{13}$C NMR (CDCl$_3$, 50 MHz) $\delta$ 163.9, 156.8, 128.0, 127.8 (2C), 120.7, 114.3 (2C), 97.6, 61.5, 55.8, 29.9, 29.9; HPLC 98.46%, Inertsil ODS 3V (150 x 4.6) mm; mobile phase A: 0.01M KH$_2$PO$_4$; mobile phase B: ACN; gradient (T/% B): 0/30, 2/30, 12/80, 20/80, 21/30,22/30, flow rate: 1.0 mL/min, UV 210nm, retention time 6.3 min; Elemental analysis found C, 67.09; H, 6.45; N, 5.79; C$_{13}$H$_{15}$NO$_3$ requires C, 66.94; H, 6.48; N, 6.00.

3-Phenyl-2H-isoquinolin-1-one$^{2a}$ (3m):

White solid; mp 78-80 °C; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.82 (d, $J = 8.0$ Hz, 1H), 7.38 (t, $J = 8.1$ Hz, 1H), 7.13 (d, $J = 8.0$ Hz, 1H), 6.67 (s, 1H), 3.92 (s, 3H), 3.74 (t, $J = 6.2$ Hz, 2H), 2.69 (t, $J = 7.2$ Hz, 2H), 2.01-1.95 (m, 2H), 1.25 (bs, OH); IR (cm$^{-1}$, KBr) 3408, 1725; m/z (CI Mass) 235 (M$^+$+1, 100%); $^{13}$C NMR (CDCl$_3$, 50 MHz) $\delta$ 163.9, 156.8, 128.0, 127.8 (2C), 120.7, 114.3 (2C), 97.6, 61.5, 55.8, 29.9, 29.9; HPLC 98.46%, Inertsil ODS 3V (150 x 4.6) mm; mobile phase A: 0.01M KH$_2$PO$_4$; mobile phase B: ACN; gradient (T/% B): 0/30, 2/30, 12/80, 20/80, 21/30,22/30, flow rate: 1.0 mL/min, UV 210nm, retention time 6.3 min; Elemental analysis found C, 67.09; H, 6.45; N, 5.79; C$_{13}$H$_{15}$NO$_3$ requires C, 66.94; H, 6.48; N, 6.00.
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Light brown solid, mp 195 ºC (lit\textsuperscript{2a} 205 ºC); \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) δ 8.32 (d, \textit{J} = 8.3 Hz, 1H), 7.90-7.88 (m, 2H), 7.74-7.70 (m, 1H), 7.52-7.43 (m, 5H), 6.95 (s, 1H); IR (cm\textsuperscript{-1}, KBr) 2923, 1730 m/z (CI Mass) 223.0 (M\textsuperscript{+}, 100%); we were not able to prepare analytically pure 3m which was always found to be contaminated with other side products.

3-phenyl-4-phenylethynyl-2\textit{H}-isoquinolin-1-one (3mm):

\[
\begin{align*}
\text{NH} & \\
O & \\
\end{align*}
\]

White solid; mp 144-146 ºC; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) δ 8.36 (d, \textit{J} = 7.8 Hz, 1H), 8.24 (dd, \textit{J} = 7.8, 1.9 Hz, 2H), 8.12 (d, \textit{J} = 8.1 Hz, 1H), 7.88-7.84 (m, 1H), 7.59 (t, \textit{J} = 7.5 Hz, 1H), 7.54-7.48 (m, 5H), 7.39-7.37 (m, 3H); IR (cm\textsuperscript{-1}, KBr) 3057, 1745; m/z (CI Mass) 323 (M+1, 100%); \textsuperscript{13}C (CDCl\textsubscript{3}, 50 MHz): δ 161.9, 137.0, 135.1 (2C), 132.3, 131.3 (2C), 130.4, 129.5, 128.7(2C), 128.6 (2C), 128.5 (2C), 128.1 (2C), 125.3, 122.7, 119.7, 99.7, 97.5, 82.7; HPLC 97.4%, Inertsil ODS 3V (150 x 4.6) mm, mobile phase A: 0.01M KH\textsubscript{2}PO\textsubscript{4}, mobile phase B: CH\textsubscript{3}CN, gradient (T/% B) 0/65, 2/65, 6/80, 24/80, 26/65, 28/65, flow rate 1.0 mL/min, UV 210 nm, retention time 9.9 min.

3-p-Tolyl-2\textit{H}-isoquinolin-1-one\textsuperscript{2b} (3n):

\[
\begin{align*}
\text{NH} & \\
O & \\
\end{align*}
\]

Low melting solid; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 200 MHz) δ 7.94 (d, \textit{J} = 7.52 Hz, 1H), 7.75-7.69 (m, 3H), 7.55-7.35 (m, 4H), 6.41 (s, 1H), 2.38 (s, 3H); IR (cm\textsuperscript{-1}, KBr) 2925, 1737 m/z (CI Mass) 236.9 (M\textsuperscript{+}, 100%); we were not able to prepare analytically pure 3n which was always found to be contaminated with other side products.
3-p-Tolyl-4-p-tolylethynyl-2H-isoquinolin-1-one (3nn):

White solid; mp128-130 °C; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.34 (d, $J = 8.0$ Hz, 1H), 8.16 (d, $J = 8.3$ Hz, 2H), 8.10 (d, $J = 7.8$ Hz, 1H), 7.86-7.82 (m, 1H), 7.57 (t, $J = 7.0$ Hz, 2H), 7.43 (d, $J = 7.0$ Hz, 2H), 7.30 (d, $J = 5.8$ Hz, 2H), 7.19 (d, $J = 8.0$ Hz, 2H), 2.43 (s, 3H), 2.39 (s, 3H); IR (cm$^{-1}$, neat) 3455, 1739; $m/z$ (CI Mass) 350 (M$^+$+1,100%); $^{13}$C (CDCl$_3$, 50 MHz): $\delta$ 161.0, 140.7, 138.9, 137.2 (2C), 134.9 (2C), 130.0 (2C), 129.3 (2C), 128.5 (2C), 127.8 (2C), 125.8 (2C), 125.3 (2C), 119.5, 101.0, 97.8, 82.2, 21.5, 21.5; HPLC 95.1 %, Inertsil ODS 3V (250 x 4.6) mm, mobile phase A: 0.01M KH$_2$PO$_4$, mobile phase B: ACN, gradient (T/% B): 0/30, 2/30, 12/80, 25/80, 28/30,30/30, flow rate: 1.0 mL/min, UV 230 nm, retention time 14.7 min.

3-(2-Hydroxy-2-methyl-propylidene)-2,3-dihydro-isoindol-1-one (4a):

Brown solid; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.96 (d, $J = 6.3$ Hz, 1H), 7.71 (t, $J = 7.0$ Hz, 1H), 7.68 (d, $J = 6.4$ Hz, 1H), 7.55 (t, $J = 7.0$ Hz, 1H), 6.62 (s, 1H), 1.59 (s, 3H), 1.53 (s, 3H); IR (cm$^{-1}$, KBr) 3295, 1786; $m/z$ (CI Mass) 187 (M$^+$-17, 100%); $^{13}$C NMR (CDCl$_3$, 50 MHz) $\delta$ 164.3, 134.5, 129.0 (2C), 128.1, 125.9, 125.4, 115.6, 109.6, 70.6, 30.5 (2C); HPLC 91.3%, Inertsil ODS 3V (250 x 4.6) mm, mobile phase A: 0.01M KH$_2$PO$_4$, mobile phase B: CH$_3$CN; 0/30, 3/30, 12/80, 18/80, 20/30, 22/30, flow rate 1.0 mL/min, UV 235
nm, retention time 6.3 min; Elemental analysis found C, 70.99; H, 6.41; N, 6.79; 
C\textsubscript{12}H\textsubscript{13}NO\textsubscript{2} requires C, 70.92; H, 6.45; N, 6.89.

**X-ray crystal structure of 3j:**
Single crystals suitable for X-ray diffraction of \textit{3j} C\textsubscript{14}H\textsubscript{14}N\textsubscript{2}O\textsubscript{2} were obtained by 
dissolving the compound in methanol at room temperature. The compound \textit{3j} crystallizes 
in orthorhombic crystal system (space group \textit{Pca2\textsubscript{1}}) with unit cell parameters 
a=23.78(1) Å, \textit{b}=4.560(3) Å, \textit{c}=11.134(7) Å, \textit{V}=1207(1) Å\textsuperscript{3} and \textit{Z}=4. The intensity data was 
collected on a Rigaku Mercury CCD detector with graphite monochromated Mo-K\textsubscript{\alpha} 
radiation. The crystal structure was solved by direct methods (SIR 92) and refined by 
full-matrix least squares to a final R-value of 0.073 with 1401 unique reflections. The 
ORTEP diagram is shown in Figure 1.

![ORTEP diagram](image)

**Figure 1.** ORTEP drawn at 50 % probability displacement ellipsoids for non-hydrogen 
atoms.

**In vitro anticancer activity:** we evaluated some of the compounds synthesized for in 
vitro anticancer activity. Selected compounds were initially tested on a panel of cancer
cell lines e.g. HT-29 (colon), NCI-H460 (lung) and LoVo (colon) using the NCI standard protocol for screening anticancer molecules. Based on promising GI\textsubscript{50} values (the concentration that causes 50% inhibition of cancer cell growth against a cell line is expressed as GI\textsubscript{50}) obtained for all these compounds we selected compound 3f for further in vitro studies. The results are summarized in Table 1. Additionally, the respective average LC\textsubscript{50} values (LC\textsubscript{50} or Lethal Concentration 50 is the concentration of a compound that kills 50% of cells treated) are also shown in Table 1. Thus compound 3f showed consistent anticancer activity with GI\textsubscript{50} values below 20 \(\mu\)M against SW620 (colon), LoVo (colon), 786-O (renal), PC-3 (prostrate), MDA-MB-453 (breast) etc with an average LC\textsubscript{50} of 70-100. The present study thus indicates that compound 3f could be a new and potential candidate for the development of novel anticancer agent.

**Table 1. In vitro anti cancer activities of compound 3f**

<table>
<thead>
<tr>
<th>ENTRY</th>
<th>CELL PANEL</th>
<th>CELL LINE</th>
<th>GI 50 (mM)</th>
<th>LC 50 (mM)</th>
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<tbody>
<tr>
<td>1.</td>
<td>COLON</td>
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<tr>
<td>2.</td>
<td>COLON</td>
<td>LoVo</td>
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<td>70</td>
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<td>A549</td>
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<td>8.</td>
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<td>9.</td>
<td>RENAL</td>
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<td>Jurkat E6</td>
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<td>BREAST</td>
<td>MDA-MB-453</td>
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<td>BREAST</td>
<td>MCF-7</td>
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<tr>
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<td>OSTEOSARCOMA</td>
<td>KHOS/NP</td>
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</table>

**Protocol for In Vitro Cell growth assay:** Anticancer activity of selected compounds has been tested in the cell lines as indicated above by using Sulphorhodamine B (SRB)
Supplementary Material (ESI) for Chemical Communications

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assay. Cells were maintained in RPMI 1640 with 10% FBS (Fetal Bovine Serum) and Penicillin (50 μg/mL), Streptomycin (100 μg/mL). Cells were seeded in a 96-well cell culture plates at a concentration of 10000 cells per well and incubated at 37 °C in CO2 incubator. Twenty-four hours later cells were treated with different concentrations (100, 10, 1, 0.1 & 0.01 μM) of compound dissolved in DMSO and incubated for 48 h. Cells were fixed by adding ice-cold 50% trichloroacetic acid (TCA) and incubating for 1 h at 4 °C. The plates were washed with distilled water, air-dried and stained with SRB solution (0.4% wt/vol in 1% acetic acid) for 30 minutes at room temperature. Unbound SRB was removed by washing thoroughly with 1% acetic acid and the plates were air-dried. The bound SRB stain was solubilized with 10 mM Tris buffer, and the optical densities were read on a spectrophotometric plate reader at 515 nm. At the time of drug addition separate reference plate for cell growth at time 0 h (the time at which drugs were added) was also terminated as described above. From the optical densities the percentage growths were calculated using the following formulae, If \( T \) is greater than or equal to \( T_0 \), percentage growth = 100 x \( \frac{(T-T_0)/(C-T_0)}{T_0} \) and if \( T \) is less than \( T_0 \), percentage growth = 100 x \( \frac{(T-T_0)/T_0)}{T_0} \), Where \( T \) is optical density of test, \( C \) is the optical density of control and \( T_0 \) is the optical density at time zero. From the percentage growths a dose response curve was generated and \( GI_{50} \) values were interpolated from the growth curves.

References