\textbf{\textbeta{}-lactam-synthon-Interceded synthesis of isatin-imidazolidine-2-thione conjugates with structural validation using molecular dynamic simulations and cytotoxic evaluation}

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\textbf{Supplementary Information:}

\textbf{General}

Melting points were determined by open capillary using Veego Precision Digital Melting Point apparatus (MP-D) and are uncorrected. IR spectra were recorded on a Shimadzu D-8001 spectrophotometer. \textsuperscript{1}H NMR spectra were recorded in deuterochloroform with Jeol 300 (300 MHz) and BRUKER (400 MHz) spectrometers using TMS as internal standard. Chemical shift values are expressed as parts per million downfield from TMS and J values are in hertz. Splitting patterns are indicated as s: singlet, d: doublet, t: triplet, m: multiplet, dd: double doublet, ddd: doublet of a doublet of a doublet, and br: broad peak. \textsuperscript{13}C NMR spectra were recorded on Jeol 300 (75 MHz) and BRUKER (100 MHz) spectrometers in deuterochloroform using TMS as internal standard. Mass spectra were recorded on Shimadzu GCMS-QP-2000 mass spectrometer. Column chromatography was performed on a silica gel (60–120 mesh).

\textbf{General procedure for the preparation of compound 2a-c:}

To a well stirred solution of racemic 3-azido-\textbeta{}-lactam, prepared \textit{via} Staudinger reaction of 1-azadiene with azidoketene, generated from corresponding azido acetic acid and \textit{p}-toluene sulfonyl chloride in the presence of triethylamine, in dry dichloromethane was added triphenylphosphine followed by the addition of carbon disulfide and the reaction mixture was stirred for 12hrs. After completion of reaction as evidenced by TLC, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography using (5:95) EtOAc: hexane mixture resulted in the isolation of pure product.
3-Isothiocyanato-1-phenyl-4-styryl-azetidin-2-one (2a): White solid, Yield: 73%; m.p. 140-142 °C. IR (KBr) \( \tilde{\nu} \) max: 2112, 1750, 1510 cm\(^{-1}\); \(^1\)H NMR (300 MHz CDCl\(_3\)): \( \delta \) 4.92 (dd, \( J = 5.1\) Hz, 8.1 Hz, 1H, \( H_4 \)), 5.09 (d, \( J = 5.1\) Hz, 1H, \( H_3 \)), 6.24 (dd, \( J = 8.1\) Hz, 15.9 Hz, 1H, \( H_5 \)), 6.93 (d, \( J = 15.9\) Hz, 1H, \( H_6 \)), 7.10-7.45 (m, 10H, Ar-H), \(^{13}\)C (CDCl\(_3\), 75Hz): \( \delta \) 57.5, 63.4, 120.5, 123.4, 124.2, 126.4, 127.5, 127.8, 128.3, 128.8, 134.7, 140.9, 170.6; MS m/z 307(M\(^+\)); Analysis calculated for C\(_{18}\)H\(_{14}\)N\(_2\)OS: C, 70.56; H, 4.61; N, 19.30 Found: C, 70.26; H, 4.80; N, 9.14.

3-Isothiocyanato-4-styryl-1-p-tolyl-azetidin-2-one (2b): White solid, Yield: 70%; m.p. 128-130 °C. IR (KBr) \( \tilde{\nu} \) max: 2102, 1738, 1532 cm\(^{-1}\); \(^1\)H NMR (300 MHz CDCl\(_3\)): \( \delta \) 2.30 (s, 3H, CH\(_3\)), 4.91 (dd, \( J = 5.1\) Hz, 7.2 Hz, 1H, \( H_4 \)), 5.07 (d, \( J = 5.1\) Hz, 1H, \( H_3 \)), 6.21 (dd, \( J = 7.2\) Hz, 15.9 Hz, 1H, \( H_5 \)), 6.91 (d, \( J = 15.9\) Hz, 1H, \( H_6 \)), 7.06-7.47 (m, 9H, H, aromatic), \(^{13}\)C (CDCl\(_3\), 75Hz): \( \delta \) 21.7, 57.4, 63.2, 120.5, 123.1, 124.4, 126.3, 127.4, 127.9, 128.4, 129.1, 134.6, 140.7, 170.5. MS m/z 321(M\(^+\)); Analysis calculated for C\(_{18}\)H\(_{16}\)N\(_2\)OS: C, 71.22; H, 5.03; N, 8.74 Found: C, 71.16; H, 4.97; N, 8.68.

1-(4-Fluoro-phenyl)-3-isothiocyanato-4-styryl-azetidin-2-one (2c): White solid, Yield: 77%; m.p. 139-141 °C. IR (KBr) \( \tilde{\nu} \) max: 2107, 1748, 1523 cm\(^{-1}\); \(^1\)H NMR (300 MHz CDCl\(_3\)): \( \delta \) 4.90 (dd, \( J = 5.1\) Hz, 8.1 Hz, 1H, \( H_4 \)), 5.05 (d, \( J = 5.1\) Hz, 1H, \( H_3 \)), 6.22 (dd, \( J = 8.1\) Hz, 15.9 Hz, 1H, \( H_5 \)), 6.89 (d, \( J = 15.9\) Hz, 1H, \( H_6 \)), 7.09-7.43 (m, 9H, H, aromatic), \(^{13}\)C (CDCl\(_3\), 75Hz): \( \delta \) 57.2, 63.0, 120.1, 123.3, 124.1, 126.2, 127.3, 127.9, 128.4, 128.7, 134.8, 140.7, 170.2. MS m/z 325(M\(^+\)); Analysis calculated for C\(_{18}\)H\(_{13}\)FN\(_2\)OS: C, 66.65; H, 4.04; N, 8.64 Found: C, 66.61; H, 3.99; N, 8.59.

**General procedure for the synthesis of isatin- imidazolidine-2-thione conjugates 3a-l:**

To a well stirred solution of sodium hydride (2.5 mmol) in dry DMF was added a solution of (1 mmol) Isatin in DMF at 0°C. The reaction resulted in the formation of a purple coloured anion and was allowed to stir at room temperature for 15 min. To this reaction mixture was added (1.0 mmol) 3-isothiocyanate-2-azetidinones 2 in dry DMF and the reaction mixture was stirred at room temperature for 1 h followed by heating at 60°C for 2 h. The progress of the reaction was monitored by using tlc and in completion was quenched by addition of ice cold water and brine in succession. The reaction mixture was extracted with ethyl acetate (2x25 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product
thus obtained on purification via column chromatography using a mixture (50:50) of ethyl acetate: hexane resulted in the isolation of desired isatin-imidazolidine-2-thione 3.

1-[Hydroxy-(1-phenyl-5-styryl-2-thioxo-imidazolidin-4-ylidene)-methyl]-1H-indole-2,3-dione (3a): White solid, Yield 54%, m.p. 187-189°C, 1H NMR (300 MHz, CDCl3): δ 4.93 (dd, J = 4.2, 7.5 Hz, 1H, H3); 6.34-6.44 (m, 1H, ArH); 6.79 (dd, J = 7.5, 16.2 Hz, 1H, H2); 6.87 (dd, J = 4.2, 16.2 Hz, 1H, H3); 7.06-7.89 (m, 13H, ArH); 9.22 (s, 1H, NH, exchangeable with D2O); 10.06 (s, 1H, OH, exchangeable with D2O); 13C NMR (CDCl3, 75Hz): δ 66.2 (C-3); 81.2 (C-4); 111.8, 118.4, 121.6, 122.0, 123.7, 125.7, 127.8, 129.5, 129.6, 130.2, 133.4, 136.7, 138.8, 144.7, 160.1 (C=O); 172.3 (C=S); 187.3 (C=O); MS m/z 453(M+), Analysis calculated for C26H19N3O3S; C, 68.86; H, 4.22; N, 9.27; Found C, 68.99; H, 4.37; N, 9.39

1-[Hydroxy-(5-styryl-2-thioxo-1-p-tolyl-imidazolidin-4-ylidene)-methyl]-1H-indole-2,3-dione (3b): White solid, yield 56%, m.p. 195-197°C, 1H NMR (300 MHz, CDCl3): δ 2.29 (s, 3H, CH3); 4.76 (d, J = 7.5 Hz, 1H, H3); 6.51 (dd, J = 7.5, 15.9 Hz, 1H, H2); 6.71-6.80 (m, 2H, H1+ArH); 6.99-7.58 (m, 12H, ArH); 9.59 (s, 1H, NH, exchangeable with D2O); 10.34 (s, 1H, OH, exchangeable with D2O); 13C NMR (CDCl3, 75Hz): δ 20.4 (CH3); 63.0 (C-3); 79.5 (C-4); 86.5 (C-5); 111.9, 117.2, 121.3, 122.5, 123.4, 125.0, 126.7, 128.5, 129.4, 130.1, 133.5, 135.3, 137.8, 144.0, 163.5 (C=O); 171.1 (C=S); 187.5 (C=O); MS m/z 467(M+), Analysis calculated for C27H21N3O3S; C, 69.36; H, 4.53; N, 8.99; Found C, 69.48; H, 4.59; N, 8.86

1-[1-(4-Fluoro-phenyl)-5-styryl-2-thioxo-imidazolidin-4-ylidene]-hydroxy-methyl]-1H-indole-2,3-dione (3c): White solid, yield 52%, m.p. 191-193°C, 1H NMR (300 MHz, CDCl3): δ 4.86 (d, J = 7.9 Hz, 1H, H3); 6.30 (dd, J = 7.9, 15.6 Hz, 1H, H2); 6.77-7.73 (m, 12H, ArH); 10.26 (s, 1H, NH, exchangeable with D2O); 10.98 (s, 1H, OH, exchangeable with D2O); 13C NMR (CDCl3, 75Hz): δ 66.4 (C-3); 81.3 (C-4); 86.7 (C-5); 111.8, 118.5, 121.7, 122.0, 123.4, 125.5, 127.7, 129.4, 130.4, 133.4, 136.6, 138.9, 144.6, 162.5 (C=O); 172.5 (C=S); 186.4 (C=O) MS m/z 471(M+), Analysis calculated for C28H18FN3O3S; C, 66.23; H, 3.85; N, 8.91; Found C, 66.37; H, 3.73; N, 8.99

1-[Hydroxy-(1-phenyl-5-styryl-2-thioxo-imidazolidin-4-ylidene)-methyl]-5-methyl-1H-indole-2,3-dione (3d): White solid, yield 52%, m.p. 189-190°C, 1H NMR (300 MHz, CDCl3): δ 2.33 (s, 3H, CH3); 4.96 (d, J = 7.9 Hz, 1H, H3); 6.28 (dd, J = 7.9, 15.9 Hz, 1H, H2); 6.68 (d, J = 15.9 Hz, 1H, H1); 7.13-7.37 (m, 13H, ArH); 10.26 (s, 1H, NH, exchangeable with D2O); 10.97 (s, 1H, OH, exchangeable with D2O); 13C NMR (CDCl3, 75Hz): δ 20.5 (CH3); 63.5 (C-3); 80.5 (C-4); 86.9 (C-5); 111.8, 117.3, 118.5, 121.7, 122.0, 123.4, 125.5, 127.7, 128.4, 129.4, 129.6,
1-[Hydroxy-(5-styryl-2-thioxo-1-p-tolyl-imidazolidin-4-ylidene)-methyl]-5-methyl-1H-indole-2,3-dione (3e): Pale yellow solid, yield 58%, m.p. 198-200°C, $^1$H NMR (300 MHz, CDCl$_3$): δ 2.31 (s, 3H, CH$_3$); 2.35 (s, 3H, -CH$_3$); 4.85 (d, $J = 7.5$ Hz ,1H, H$_3$); 6.42 ( dd, $J = 7.5$, 15.9Hz, 1H, H$_2$); 6.75-6.82 (m, 2H, H$_4$-ArH); 6.91-7.52 (m, 11H, ArH); 10.23 (s, 1H, NH, exchangeable with D$_2$O); 10.92 (s, 1H, OH, exchangeable with D$_2$O); $^{13}$C NMR (CDCl$_3$, 75Hz): δ 20.6 (CH$_3$); 20.9(CH$_3$); 63.8(C-3); 80.2 (C-4); 86.8(C-5); 111.7, 112.1, 117.1, 117.5, 118.5, 120.1, 121.7, 125.9, 128.3, 128.5, 130.0, 133.8, 134.5, 135.3, 137.3, 140.0, 161.3 (C=O); 171.5(C=S); 187.6 (C=O). MS m/z 481 (M$^+$), Analysis calculated for C$_{28}$H$_{23}$N$_3$O$_3$S; C, 69.83; H, 4.81; N, 8.73; Found C, 69.94; H, 4.69; N, 8.80

1-[(1-[4-Fluoro-phenyl]-5-styryl-2-thioxo-imidazolidin-4-ylidene]-hydroxy-methyl]-5-methyl-1H-indole-2,3-dione (3f): Pale yellow, yield 55%, m.p. 188-190°C, $^1$H NMR (300 MHz, CDCl$_3$) δ 2.30 (s, 3H, CH$_3$), 4.86 (d, $J = 8.1$ Hz, 1H, H$_3$); 6.39 (dd, $J = 8.1$, 15.9 Hz, 1H, H$_2$); 6.75-6.82 (m, 2H, Ar-H); 6.89-6.95 (m, 2H, Ar-H); 7.08 (d, $J = 8.1$ Hz, 1H, H$_8$); 7.25-7.46 (m, 8H, ArH); 7.56 (s, 1H, H$_{10}$); 9.93 (s, 1H, NH, exchangeable with D$_2$O); 10.86 (s, 1H, OH, exchangeable with D$_2$O); $^{13}$C NMR (CDCl$_3$+DMSO,75Hz): δ 20.7 (CH$_3$); 63.9 (C-3); 79.7 (C-4); 87.2 (C-5); 111.3, 112.5, 115.9, 117.7, 118.6, 119.3, 120.9, 126.9, 128.7, 128.9, 129.6, 132.9, 134.5, 135.4, 136.8, 140.7, 161.6 (C=O); 171.8 (C=S); 187.8 (C=O), MS m/z 485 (M$^+$), Analysis calculated for C$_{27}$H$_{20}$FN$_3$O$_3$S; C, 66.79; H, 4.15; N, 8.65; Found C,66.89; H, 4.27; N, 8.57

5-Fluoro-1-[hydroxy-(1-phenyl-5-styryl-2-thioxo-imidazolidin-4-ylidene)-methyl]-1H-indole-2,3-dione (3g): Pale yellow, yield 55%, m.p. 182-183°C, $^1$H NMR (300MHz, CDCl$_3$): δ 4.88 (dd, $J= 4.2$, 7.5 Hz, H$_3$); 6.34 (dd, $J= 7.5$, 15.9 Hz, H$_2$); 6.70-6.83 (m, 2H, H$_4$-ArH); 6.98-7.56 (m, 11H, ArH); 7.66 (s, 1H, H$_{10}$); 9.4 (s, 1H, NH, exchangeable with D$_2$O); 10.18 (s, 1H, OH, exchangeable with D$_2$O); $^{13}$C NMR (CDCl$_3$, 75Hz): δ 63.7 (C-3); 79.8 (C-4); 86.2 (C-5); 111.2, 112.4, 117.4, 117.6, 118.3, 119.6, 121.5, 126.7, 128.5, 128.7, 130.1, 133.5, 134.2, 135.3, 137.8, 141.3, 160.5 (C=O); 171.4 (C=S); 187.1 (C=O). MS m/z 471(M$^+$), Analysis calculated for C$_{27}$H$_{18}$FN$_3$O$_3$S; C, 66.23; H, 3.85; N, 8.91 Found C, 66.41; H, 3.91; N, 8.78

5-Fluoro-1-[hydroxy-(5-styryl-2-thioxo-1-p-tolyl-imidazolidin-4-ylidene)-methyl]-1H-indole-2,3-dione (3h): White solid, yield 56%, m.p. 192-194°C, $^1$H NMR (300 MHz, CDCl$_3$):
δ 2.25 (s, 3H, CH₃); 4.88 (d, J = 7.5 Hz, 1H, H²); 6.36 (dd, J = 7.5, 15.9 Hz, 1H, H²); 6.75-6.82 (m, 2H, H¹+ArH); 6.98-7.56 (m, 11H, ArH); 9.55 (s, 1H, NH, exchangeable with D₂O), 10.25 (s, 1H, OH, exchangeable with D₂O); ¹³C NMR (CDCl₃, 75 Hz): δ 20.4 (CH₃); 63.0 (C-3); 79.5 (C-4); 86.5 (C-5); 111.9, 112.0, 117.2, 117.3, 118.9, 119.1, 121.3, 126.7, 128.5, 128.6, 129.4, 133.5, 134.2, 135.3, 137.8, 140.0, 160.5 (C=O); 171.1 (C=S); 187.5 (C=O). MS m/z 485 (M⁺);
Analysis calculated for C₂₇H₂₀FN₃O₃S; C, 66.79; H, 4.15; N, 8.65; Found C, 66.92; H, 4.26; N, 8.58

5-Fluoro-1-{[1-(4-fluoro-phenyl)-5-styryl-2-thioxo-imidazolidin-4-ylidene]-hydroxy-methyl}-1H-indole-2,3-dione (3i): Pale yellow solid, yield 51%, m.p. 179-181°C, ¹H NMR (300 MHz, CDCl₃): δ 4.80 (d, J = 7.9 Hz, 1H, H³); 6.42 (dd, J = 7.9, 15.6, 1H, H²); 6.79-6.97 (m, 2H, H¹+ArH); 7.05-7.71 (m, 10H, ArH); 7.72 (d, J = 3.0 Hz, 1H, ArH); 10.25 (s, 1H, NH, exchangeable with D₂O); 10.95 (s, 1H, OH, exchangeable with D₂O); ¹³C NMR (CDCl₃, 75 Hz): δ 64.3 (C-3); 80.0 (C-4); 86.9 (C-5); 111.6, 112.3, 116.5, 117.2, 118.9, 119.2, 121.3, 126.4, 128.4, 128.5, 129.5, 133.7, 134.6, 135.3, 137.3, 140.5, 161.2 (C=O); 171.7 (C=S); 187.6 (C=O). MS m/z 489 (M⁺); Analysis calculated for C₂₆H₁₇F₂N₃O₃S; C, 63.80; H, 3.50; N, 8.58 Found C, 63.93; H, 3.64; N, 8.65

5-Chloro-1-[hydroxy-(1-phenyl-5-styryl-2-thioxo-imidazolidin-4-ylidene)-methyl]-1H-indole-2,3-dione (3j): Pale yellow solid, yield 51%, m.p. 207-209°C, ¹H NMR (300 MHz, CDCl₃): δ 4.90 (d, J = 8.0 Hz, 1H, H³); 6.34 (dd, J = 8.0, 15.9 Hz, 1H, H²); 6.70-6.83 (m, 2H, H¹+ArH); 7.00-7.43 (m, 11H, ArH); 7.77 (s, 1H, ArH); 10.26 (s, 1H, NH, exchangeable with D₂O); 10.97 (s, 1H, OH, exchangeable with D₂O); ¹³C NMR (CDCl₃, 75 Hz): δ 63.6 (C-3); 79.5 (C-4); 86.7 (C-5); 111.2, 112.5, 117.2, 117.3, 118.9, 119.5, 121.6, 126.5, 128.3, 129.8, 133.5, 134.7, 135.3, 137.8, 141.1, 160.9 (C=O); 171.7 (C=S); 187.4 (C=O). MS m/z 487 (M⁺); Analysis calculated for C₂₆H₁₇ClN₃O₃S; C, 64.00 H, 3.72; N, 8.61; Found C, 64.03; H, 3.70; N, 8.63

5-Chloro-1-[hydroxy-(5-styryl-2-thioxo-1-p-tolyl-imidazolidin-4-ylidene)-methyl]-1H-indole-2,3-dione (3k): Pale yellow solid, yield 57%, m.p. 210-212°C, ¹H NMR (300 MHz, CDCl₃): δ 2.33 (s, 3H, CH₃); 4.78 (d, J = 7.5 Hz, 1H, H³); 6.51 (dd, J = 7.5 Hz, 15.9 Hz, 1H, H²), 6.75-6.82 (m, 2H, H¹+ArH); 6.87-7.51 (m, 11H, ArH); 10.24 (s, 1H, NH, exchangeable with D₂O); 10.86 (s, 1H, OH, exchangeable with D₂O); ¹³C NMR (CDCl₃, 75 Hz): δ 20.5 (CH₃); 64.2 (C-3); 80.1 (C-4); 85.9 (C-5); 111.8, 113.0, 117.3, 117.7, 118.5, 120.3, 121.6, 126.1, 128.3,
128.5, 130.1, 133.8, 134.5, 136.2, 137.3, 140.5, 161.5 (C=O); 171.5 (C=S); 187.6 (C=O); MS m/z 501(M⁺); Analysis calculated for C_{27}H_{20}ClN_{3}O_{3}S; C, 64.60; H, 4.02; N, 8.37; Found C, 64.62; H, 4.05; N, 8.39

5-Chloro-1-[1-(4-fluoro-phenyl)-5-styryl-2-thioxo-imidazolidin-4-ylidene]-hydroxy-methyl]-1H-indole-2,3-dione (3l): White solid, yield 56%, m.p.207-209°C, \(^1\)H NMR (300 MHz, CDCl₃): \(\delta\) 4.77 (d, \(J = 7.5\) Hz, 1H, H\(^3\)); 6.43 (dd, \(J = 7.5\) Hz, 15.9Hz , 1H, H\(^2\)); 6.75-6.82 (m, 2H, H\(^1\)+ArH); 6.98-7.58 (m, 11H, ArH); 10.26 (s, 1H, NH, exchangeable with D₂O); 10.91 (s, 1H, OH, exchangeable with D₂O); \(^13\)C NMR (CDCl₃,75Hz): \(\delta\) 64.1(C-3), 79.9 (C-4), 85.9(C-5); 111.7, 112.5, 117.3, 117.4, 118.7, 119.2, 121.5, 125.9, 128.2, 128.67, 129.4, 133.5, 134.2, 135.3, 137.5, 140.9, 160.5 (C=O), 171.3 (C=S), 187.4 (C=O); MS m/z 505(M⁺); Analysis calculated for C_{26}H_{17}ClFN_{3}O_{3}S; C, 61.72; H, 3.39; N, 8.31; Found C, 61.85; H, 3.31; N, 8.39
Computational methods

Molecular Dynamics

Starting structures of both the enol and keto conformations of compound 3a were geometrically optimized using the Forcite module in Material Studio (MS).\textsuperscript{1} First, the Restrained Electrostatic Potential (RESP) atomic charges were developed for both structures using the General Amber Force Field (GAFF) in AMBER 9.0.\textsuperscript{2} Thereafter conformations were then soaked in the box of chloroform molecules with dimensions of 56.496 x 56.291 x 55.377 Å, using tleap module in AMBER. Each system was subsequently minimized using 1,000 steps of steepest descent, followed by conjugate gradient until their energies were lower than 0.001 kcal mol\textsuperscript{-1}Å. The equilibration step consisted of 100 picosecond where the volume of the system was kept constant, while the temperature was gradually increased until 300 K under periodic boundary conditions (PBC). Each MD simulation was performed at a constant pressure for 1 nanosecond sampling each snapshot at the interval of 1 picosecond, using AMBER 9.0 program. The analysis of both MD trajectories was further performed using the PTRAJ module of AMBER.

Pharmacology
Cytotoxic studies:
To determine IC\textsubscript{50} values, 1500 cells per well were seeded in 90 \( \mu \)L Dulbecco/Vogt Modified Eagle’s Minimal Essential Medium (DMEM) in Cellstar 96-well plates. After incubation (24 h), test samples were plated at a range of concentrations in 10 \( \mu \)L medium, with a final concentration of 0.2% DMSO and again incubated for 48 h. Observations were made and processed in the manner described for the MTT assay. MTT reagent (10 \( \mu \)L, Roche cat # 1465007) was added and the cells incubated (4 h, 37 °C). Solubilization reagent (100 \( \mu \)L) was added to each well and incubation continued (16 h, 37 °C). Upon completion of the incubation time, plates were read (595 nm) on an Anthos microplate reader 2001. A dose-response curve was analyzed by non-linear regression analysis [non-linear regression (sigmoidal dose response with variable slope)] using the GraphPad Prism 4.00 package of GraphPad software, San Diego, USA to determine the specific IC\textsubscript{50} value for the compound tested against the WHCO1 cell line.

MTT curves for tested compounds:
$^1$H NMR spectrum of 3a:

$^{13}$C NMR spectrum of 3a:
$^1$H NMR spectrum of 3e:

$^1$H NMR spectrum of 3f:
$^1$H NMR spectrum of 3h:

$^{13}$C NMR spectrum of 3h:
$^1$H-$^1$H COSY of 3h: