Isovanillin derived N-(un)substituted hydroxylamines possessing ortho-allylic group: valuable precursors to bioactive N-heterocycles

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**GENERAL:**

All reactions were carried out under an inert atmosphere using dry solvents, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), using UV light detection. Visualization of the spots on TLC plates were achieved either by using UV light or by staining the plates in 2,4-di-nitro phenyl hydrazine stain, Ninhydrin stain and charring on hot plate. Flash chromatography was performed on silica gel (230-400 mesh) using distilled hexane, ethyl acetate, dichloromethane. $^1$H NMR, $^{13}$C NMR, 1D-NOE, and 2D-NOE spectra were recorded in CDCl$_3$ solution by using VARIAN 400 MHz spectrometers. Chemical shifts are reported as δ values relative to internal CDCl$_3$ δ 7.26 or TMS δ 0.0 for $^1$H NMR and CDCl$_3$ δ 77.0 for $^{13}$C NMR. $^1$H NMR data is presented as follows: chemical shift [multiplicity, coupling constant(s) J (Hz), relative integral] where multiplicity is defined as: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), m (multiplet), bs (broad singlet). FTIR spectra were recorded on Bruker (Alpha) spectrometer. Mass spectra were recorded on Micro Mass VG-7070H mass spectrometer for ESI and are given in mass units (m/z). High resolution mass spectra (HRMS) [ESI+] were obtained using either a TOF or a double focusing spectrometer.

**X-ray crystallographic studies**

X-ray data was collected at room temperature using a Bruker Smart Apex CCD diffractometer with graphite monochromated MoKα radiation (λ=0.71073Å) with ω-scan method. Preliminary lattice parameters and orientation matrices were obtained from four sets of frames. Unit cell dimensions were determined using 8485 reflections. Integration and scaling of intensity data were accomplished using SAINT program. The structures were solved by Direct Methods using SHELXS97 and refinement was carried out by full-matrix least-squares technique using SHELXL97. Anisotropic displacement parameters were included for all non-hydrogen atoms. H atoms were positioned geometrically and treated as riding on their parent C atoms, with C-H distances of 0.93--0.96 Å, and with $U_{iso}(H) = 1.2U_{eq} (C)$ or 1.5$U_{eq}$ for methyl atoms.
Crystal data for 8a: C$_{23}$H$_{31}$NO$_3$Si, $M = 397.58$, colorless block, 0.15 x 0.08 x 0.05 mm$^3$, monoclinic, space group $P2_1/c$ (No. 14), $a = 12.368(12)$, $b = 13.474(14)$, $c = 13.097(13)$ Å, $\beta = 102.866(17)^{\circ}$, $V = 2128(4)$ Å$^3$, $Z = 4$, $D_c = 1.241$ g/cm$^3$, $F_{000} = 856$, CCD Area Detector, MoK$\alpha$ radiation, $\gamma = 0.71073$ Å, $T = 294(2)$K, $2\theta_{\text{max}} = 50.0^{\circ}$, 19940 reflections collected, 3744 unique ($R_{\text{int}} = 0.0237$). Final $\text{Goof} = 1.033$, $R_I = 0.0506$, $wR_2 = 0.1381$, $R$ indices based on 3243 reflections with $I>2\sigma(I)$ (refinement on $F^2$), 259 parameters, 0 restraints, $\mu = 0.134$ mm$^{-1}$. CCDC 908038 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223 336 033; email: deposit@ccdc.cam.ac.uk].

2. Sheldrick, G. M. SHELXS97 and SHELXL97, Programs for crystal structure solution and refinement; University of Gottingen: Germany, 1997.
2-Allyl-3-(tert-butyldimethylsilyloxy)-4-methoxybenzaldehyde (1a):

To a solution of 2-allyl-3-hydroxy-4-methoxybenzaldehyde (1.92 g, 10 mmo) and imidazole (1.36 g, 20 mmol) in N,N-dimethylformamide (6 mL) tert-butyldimethylsilyl chloride (3 g, 20 mmol) was added under N₂, and the solution was stirred for overnight. The resulting mixture was diluted with saturated NH₄Cl solution (10 mL) and extracted with CH₂Cl₂ (2 x 50 mL). The combined organic layer was collected, washed with saturated aqueous sodium bicarbonate solution and water, dried over Na₂SO₄, filtered and concentrated under low vacuum to give the desired product (2.99 g, 98%). Rₛ = 0.7 (1:9 EtOAc : Hex); ¹H NMR (400 MHz, CDCl₃) δ 10.10 (s, 1H), 7.52 (d, J = 14.6 Hz, 1H), 6.87 (d, J = 14.6 Hz, 1H), 6.10-5.92 (m, 1H), 4.99 (d, J = 10.2 Hz, 1H), 4.86 (d, J = 17.2 Hz, 1H), 3.95 (s, 3H), 1.07 (s, 9H), 0.18 (s, 6H); ¹³CNMR (100 MHz, CDCl₃) δ 191.3, 154.5, 143.1, 136.8, 133.1, 128.2, 126.1, 115.3, 108.9, 54.8, 28.6, 26.1 (3C), 18.9, -3.7 (2C); Mass (ES): m/z 307.05 (M+H, 100%).

(E)-Ethyl 4-(2-(tert-butyldimethylsilyloxy)-6-formyl-3-methoxyphenyl)but-2-enoate (1b):

An oven dried round bottomed flask fitted with a rubber septum containing a stir bar was charged with 2-allyl-3-(tert-butyldimethylsilyloxy)-4-methoxybenzaldehyde (0.95 g, 3.10 mmol), ethyl acrylate (0.99 mL, 9.10 mmol), freshly distilled CH₂Cl₂ (25 mL), Grubbs-2 catalyst (0.079 g, 9.10 μmol), and CuI (0.011 g, 9.10 μmol) under an N₂ atmosphere. The rubber septum was then replaced with a reflux condenser under an N₂ atmosphere. The solution was then heated at 50 °C (oil bath temperature) for 3h. After cooling to room temperature, the reaction mixture was concentrated under vacuum and the residue was purified by using column chromatography on silica gel (eluting with 30% EtOAc/hexane) to afford the desired product as a colorless oil (1.0 g, 86%); Rₛ = 0.3 (1:9 EtOAc: Hex); IR (cm⁻¹): 3010, 2957, 2858, 2720 (CH aldehyde), 1720 (CO aldehyde), 1700 (CO ester), 1600, 1247; ¹H NMR (400 MHz, CDCl₃) δ 9.93 (s, 1H), 7.45 (d, J = 8.5 Hz, 1H), 7.15-7.05 (td, J =
15.7, 5.8 Hz, 1H), 6.90 (d, J = 8.5 Hz, 1H), 5.59 (d, J = 15.6 Hz, 1H), 4.12 (q, J = 7.2 Hz, 3H), 4.09-4.01 (m, 2H), 3.90 (s, 3H), 1.26 (t, J = 7.2 Hz, 4H), 1.03 (s, 9H), 0.20 (s, 6H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 191.3, 166.5, 154.5, 147.0, 143.6, 130.4, 128.6, 128.1, 121.6, 109.2, 60.0, 54.9, 27.6, 26.0 (3C), 18.9, 14.2, -3.7 (2C); Mass (ES): m/z 379.15 (M+H, 100%).

\((E)-2\text{-}\text{allyl-3-(\text{tert}-\text{butyldimethylsilyloxy})-4-methoxybenzaldehyde oxime (2):}\)

\[
\begin{align*}
  &\text{H}_3\text{CO} &\text{OTBS}
\end{align*}
\]

To a solution of 2-allyl-3-\((\text{tert}-\text{butyldimethylsilyloxy})\)-4-methoxybenzaldehyde (0.612 g, 2 mmol) in MeOH (5 mL) was added NH\(_2\)OH·HCl (0.207 g, 3 mmol) and NaOAc (0.246 g, 3 mmol) and the mixture was refluxed for 1.0 h. After completion of the reaction, MeOH was removed using high vacuum and the residue was treated with water. The mixture was extracted with ethyl acetate (20 mL). The organic layer was collected, dried over anhydrous Na\(_2\)SO\(_4\), filtered, and concentrated to afford the desired product as a light yellow oil (0.60 g, 88%); \(R_f = 0.75\) (1:9 EtOAc: Hex); IR (cm\(^{-1}\)): 3430, 3029, 2975, 2852, 1728 (CO, ester), 1612, 1583, 1456, 1255; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.30 (s, 1H), 7.62 (d, \(J = 14.8\) Hz, 1H), 6.90 (d, \(J = 14.8\) Hz, 1H), 6.14-5.94 (m, 1H), 5.01 (d, \(J = 10.4\) Hz, 1H), 4.92 (d, \(J = 17.2\) Hz, 1H), 3.96 (s, 3H), 1.08 (s, 9H), 0.19 (s, 6H); \(^{13}\)CNMR (100 MHz, CDCl\(_3\)) \(\delta\) 154.7, 148.1, 143.1, 136.9, 133.1, 128.3, 126.0, 115.3, 108.8, 56.7, 28.7, 26.1 (3C), 18.9, -3.5 (2C); Mass (ES): m/z 322.08 (M+H, 100%).

\(5-(\text{tert}-\text{butyldimethylsilyloxy})-3-(2\text{-ethoxy-2-oxoethyl})-6\text{-methoxy-3,4 dihydro isoquinoline 2-oxide (3):}\)

\[
\begin{align*}
  &\text{H}_3\text{CO} &\text{OTBS} &\text{COC}_2\text{H}_5
\end{align*}
\]

To a solution of \((E)-\text{ethyl-4-(2-(\text{tert}-\text{butyldimethylsilyloxy})-6-formyl-3-methoxyphenyl)but-2-enoate (0.758 g, 2 mmol) in MeOH (5 mL) was added NH\(_2\)OH·HCl (0.207 g, 3 mmol) and NaOAc (0.246 g, 3 mmol) and the mixture was refluxed for 1.0 h. After completion of the reaction MeOH was removed using high vacuum and the residue was treated with water (5
mL). The mixture was extracted with ethyl acetate (2x20 mL). The combined organic layer was collected, dried over anhydrous Na$_2$SO$_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (eluting with 100% EtOAc) to afford the desired product as a colorless oil (0.69 g, 88%); R$_f$ = 0.7 (8:2 EtOAc: Hex); IR (cm$^{-1}$): 3030, 2965, 2862, 1728 (CO, ester), 1610, 1587, 1468, 1247; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.67 (s, 1H), 6.75 (s, 2H), 4.50-4.60 (m, 1H), 4.24-4.11 (m, 2H), 3.82 (s, 3H), 3.35-3.05 (m, 4H), 2.55-2.65 (dd, $J = 16.3, 9.3$ Hz, 1H), 1.33 (t, $J = 7.4$ Hz, 3H), 1.03 (s, 9H), 0.17 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.2, 151.8, 142.5, 134.0, 121.5, 119.9, 119. 1, 110.1, 63.5, 60.9, 54.9, 35.6, 29.6, 27.1, 25.9 (3C), 18.7, 14.1, -3.9, -4.0; Mass (ES): m/z 394.20 (M+H, 10%), 192.17 (100%); HRMS (ESI): calcd for C$_{20}$H$_{32}$NO$_5$Si (M+H)$^+$ 394.2049 found 394.2035.

1,3-Dipolar addition of 3 with ethyl acrylate:

To a solution of 5-(tert-butyldimethylsilyloxy)-3-(2-ethoxy-2-oxoethyl)-6-methoxy-3,4 dihydroisoquinoline 2-oxide (0.393 g, 1 mmol) in ethanol (5 mL) was added ethylacrylate (0.5 g, 5 mmol) and the mixture was refluxed for 3.5 h. After completion of the reaction, solvent was removed under high vacuum and the residue was purified by column chromatography on silica gel (eluting with 10% EtOAc/hexane) to afford the desired product(s).

**Ethyl7-(tert-butyldimethylsilyloxy)-5-(2-ethoxy-2-oxoethyl)-8-methoxy-2,5,6,10b-tetrahydro-1H-isoxazolo [3,2-a] isoquinoline-1-carboxylate (4a):**

Colorless viscous oil; Yield: 50%; R$_f$ = 0.6 (2:8 EtOAc: Hex); IR (cm$^{-1}$): 3050, 2966, 2862, 1735 (CO ester), 1725 (CO ester), 1620; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.76 (s, 2H), 4.76 (d, $J = 8.9$ Hz, 1H), 4.40-4.35 (dd, $J = 9.7, 8.4$ Hz, 1H), 4.32-4.23 (m, 2H), 4.22-4.11 (m, 2H), 4.10-4.06 (dd, $J = 8.1, 6.4$ Hz, 1H), 3.77 (s, 3H), 3.44-3.33 (m, 2H), 3.17-3.12 (dd, $J = 16.7, 3.7$ Hz, 1H), 2.95-2.89 (dd, $J = 15.4, 6.5$ Hz, 1H), 2.54-2.41 (ddd, $J = 21.1, 16.0, 8.5$ Hz,
Ethyl 7-(tert-butyldimethylsilyloxy)-5-(2-ethoxy-2-oxoethyl)-8-methoxy-2,5,6,10b-tetrahydro-1H-isoxazolo [3,2-a] isoquinoline-2-carboxylate (4b):

\[
\text{\begin{center}
\begin{tikzpicture}
\node (n1) at (0,0) {\text{H}};

\end{tikzpicture}
\end{center}
}\]

Colorless viscous oil; Yield: 20%; \( R_f = 0.6 \) (2:8 EtOAc: Hex); IR (cm\(^{-1}\)): 3050, 2966, 2862, 1735 (CO ester), 1725 (CO ester), 1620; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 6.75 (t, \( J = 7.4 \) Hz, 1H), 6.69 (d, \( J = 8.4 \) Hz, 1H), 4.75 (dd, \( J = 10.0, 3.4 \) Hz, 1H), 4.63 (dd, \( J = 10.6, 7.5 \) Hz, 1H), 4.29-4.12 (m, 4H), 3.78 (s, 3H), 3.45-3.37 (m, 1H), 3.11 (dd, \( J = 16.7, 3.5 \) Hz, 1H), 2.98 (dd, \( J = 15.5, 6.75 \) Hz, 1H), 2.83-2.75 (m, 1H), 2.62-2.41 (m, 3H), 1.34-1.27 (m, 7H), 0.99 (s, 9H), 0.21 (s, 3H), 0.15 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 172.3, 171.3, 148.3, 141.7, 127.3, 124.5, 119.3, 110.3, 75.7, 63.1, 61.4, 60.5, 54.9, 53.8, 40.8, 39.5, 30.8, 26.0 (3C), 18.8, 14.2, 14.1, -3.8, -4.0; Mass (ES): m/z 494.25 (M+H, 100%); HRMS (ESI): calcd for C\(_{25}\)H\(_{40}\)NO\(_7\)Si (M+H)\(^+\) 494.2574 found 494.2595.

Ethyl 2-(5-(tert-butyldimethylsilyloxy)-6-methoxy-1,2,3,4 tetrahydroisoquinolin-3-yl) acetate (5):

To a solution of 5-(tert-butyldimethylsilyloxy)-3-(2-ethoxy-2-oxoethyl)-6-methoxy-3,4 dihydroisoquinoline 2-oxide (0.393 g, 1 mmol) in acetic acid (5 mL) was added activated zinc (0.64 g, 10 mmol) and the mixture was stirred at room temperature for 0.5 h. After completion of the reaction NaOAc·H\(_2\)O was added followed by water (2.5 mL). The mixture was extracted with ethyl acetate (2x25 mL). The combined organic layer was dried over anhydrous Na\(_2\)SO\(_4\), filtered, and concentrated. The residue was purified by column
chromatography on silica gel (eluting with 100% EtOAc) to afford the desired product as a colorless oil (0.228 g, 60%); R_f = 0.5 (8:2 EtOAc: Hex); IR (cm⁻¹): 3300, 3040, 2956, 2872, 1740 (CO ester), 1620; ¹H NMR (400 MHz, CDCl₃) δ 6.68 (d, J = 8.3 Hz, 1H), 6.59 (d, J = 8.3 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.99 (q, J = 15.4 Hz, 2H), 3.75 (s, 3H), 3.32-3.18 (m, 1H), 2.92-2.86 (dd, J = 16.7, 4.1 Hz, 1H), 2.64-2.51 (m, 2H), 2.37-2.30 (dd, J = 16.6, 10.5 Hz, 1H), 2.00 (s, 1H), 1.27 (t, J = 7.2 Hz, 3H), 0.99 (s, 9H), 0.16 (d, J = 20.0 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) 172.2, 147.8, 142.3, 128.0, 125.9, 118.2, 109.3, 103.6, 54.9, 50.4, 47.2, 40.9, 30.5, 26.1 (3C), 18.9, 14.2, -3.8, -3.9; Mass (ES): m/z 380.22 (M+H, 100%); HRMS (ESI): calcd for C₂₀H₃₄NO₄Si (M+H)⁺ 380.2257 found 380.2249.

**General procedure for the 1,3-dipolar cycloaddition**

To a solution of aldehyde (1a-b, 1.0 mmol) in ethanol (5 mL) was added aryl hydroxyl amine (6, 2 mmol) and MgSO₄ (5 mmol) under a nitrogen atmosphere. The reaction mixture was refluxed for 3-5 h (for inversion in the yields of regio isomers the reaction mixture was heated at 130 °C for 12 h). After completion of the reaction, ethanol was removed under vacuum and the residue was purified by column chromatography on silica gel to give the desired product.

(E)-N-(2-allyl-3-(tert-butyldimethylsilyloxy)-4-methoxybenzylidene)-2-cyanoaniline oxide (7e):

![N-(2-allyl-3-(tert-butyldimethylsilyloxy)-4-methoxybenzylidene)-2-cyanoaniline oxide](image)

The title compound was synthesized by using the general procedure; colorless solid; mp 176-178 °C; Yield (88%), R_f = 0.5 (2:8 EtOAc: Hex); IR (cm⁻¹): 3277, 2935, 2857, 2120 (CN), 1725, 1662, 1600, 1247; ¹H NMR (400 MHz, CDCl₃) δ  7.96 (d, J = 8.6 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.34-7.28 (m, 1H), 6.88 (t, J = 7.5 Hz, 1H), 6.84 (t, J = 6.6 Hz, 1H), 6.62 (d, J = 8.0 Hz, 1H), 6.06-5.93 (m, 2H), 5.06-5.03 (dd, J = 10.2, 1.5 Hz, 1H), 4.84-4.78 (dd, J = 17.2, 1.6 Hz, 1H), 3.82 (s, 3H), 3.69-3.51 (m, 2H), 1.04 (s, 9H), 0.19 (s, 6H); ¹³CNMR (100 MHz, CDCl₃) δ 165.0, 150.2, 147.5, 142.9, 137.4, 133.7 (2C), 129.5, 128.9, 128.5, 120.2,
119.1, 115.5, 115.2, 114.4, 109.6, 54.5, 29.7, 26.1 (3C), 18.8, -3.8, -3.82; Mass (ES): m/z 423.2 (M+H, 100%).

5-(tert-butyldimethylsilyloxy)-6-methoxy-1-phenyl-3,3a,4,8b-tetrahydro-1H-indeno[1,2-c] isoxazole (8a):

The title compound was synthesized by using the general procedure; colorless solid; m.p: 210-212 °C; Yield (36%), Rf = 0.7 (1:9 EtOAc: Hex); IR (cm⁻¹): 3050, 2967, 2847, 1620, 1575, 1465, 1280; ¹H NMR (400 MHz, CDCl₃) δ 7.34 (t, J = 7.6 Hz, 2H), 7.20 (d, J = 7.9 Hz, 2H), 7.06 (d, J = 8.1 Hz, 1H), 7.02 (dd, J = 17.3, 10.1 Hz, 1H), 6.85 (d, J = 8.2 Hz, 1H), 5.36 (d, J = 7.5 Hz, 1H), 4.18 (t, J = 7.9 Hz, 1H), 3.89-3.77 (m, 4H), 3.49-3.38 (m, 1H), 1.03 (s, 9H), 0.20 (t, J = 5.6 Hz, 6H); ¹³C NMR (100MHz, CDCl₃) δ 150.9, 150.1, 140.6, 135.1, 134.4, 128.9 (2C), 121.6, 117.6 (2C), 114.6, 111.8, 76.3, 74.1, 55.4, 46.4, 35.6, 25.9 (2C), 18.6, -4.1, -4.15; Mass (ES): m/z 398.21 (M+H, 100%), 292.13 (30%); HRMS (ESI): calcd for C₂₃H₃₂NO₅Si (M+H)⁺ 398.2151 found 398.2165.

5-(tert-butyldimethylsilyloxy)-6-methoxy-1-p-tolyl-3,3a,4,8b-tetrahydro-1H-indeno[1,2-c] isoxazole (8b):

The title compound was synthesized by using the general procedure; yellow color solid; mp: 180-183 °C; Yield (32%), Rf = 0.9 (1:9 EtOAc: Hex); IR (cm⁻¹): 3030, 2953, 2868, 1609,
$^{1}$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.13 (m, 4H), 7.09-7.01 (m, 1H), 6.85 (d, J = 8.2 Hz, 1H), 5.32 (d, J = 7.5 Hz, 1H), 4.19 (t, J = 8.0 Hz, 1H), 3.87-3.78 (m, 4H), 3.48-3.36 (m, 1H), 3.25-3.15 (dd, J = 16.8, 8.5 Hz, 1H), 3.05-2.95 (dd, J = 16.8, 2.7 Hz, 1H), 2.34 (s, 3H), 1.09 (s, 9H), 0.19 (d, J = 5.1 Hz, 6H); $^{13}$CNMR (100 MHz, CDCl$_3$) $\delta$ 150.2, 148.7, 140.7, 135.2, 134.4, 131.1, 129.5, 117.7, 114.9 (2C), 111.9, 76.5, 74.2, 55.5, 46.4, 35.7, 25.9 (3C), 20.6, 18.7, -4.1, -4.0. Mass (ES): m/z 412.22 (M+H 100%); HRMS (ESI): calcd for C$_{24}$H$_{34}$NO$_3$Si (M+H)$^+$ 412.2307 found 412.2297.

4-(5-(tert-butyldimethylsilyloxy)-6-methoxy-3,3a,4,8b-tetrahydro-1H-indeno[1,2-c]isoxazol-1-yl) benzonitrile (8c):

The title compound was synthesized by using the general procedure; white color solid; mp: 210-214 °C; Yield (32%), R$_f$ = 0.9 (1:9 EtOAc: Hex); IR (cm$^{-1}$): 3050, 2967, 2847, 2220, 1615, 1565, 1477, 1269; $^{1}$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.57 (d, J = 8.9 Hz, 2H), 7.18 (d, J = 8.9 Hz, 2H), 6.98 (d, J = 8.2 Hz, 1H), 6.83 (d, J = 8.2 Hz, 1H), 5.33 (d, J = 7.6 Hz, 1H), 4.12-4.01 (m, 1H), 3.89-3.86 (dd, J = 8.3, 2.6 Hz, 1H), 3.80 (s, 3H), 3.61-3.49 (m, 1H), 3.33-3.15 (dd, J = 16.9, 8.7 Hz, 1H), 3.11-2.99 (dd, J = 16.9, 3.1 Hz, 1H), 1.07 (s, 9H), 0.18 (d, J = 6.4 Hz, 6H); $^{13}$CNMR (100 MHz, CDCl$_3$) $\delta$ 154.1, 150.4, 140.8, 134.5, 133.9 (2C), 133.4, 119.5, 117.5, 114.0 (2C), 111.9, 103.7, 75.2, 74.5, 55.4, 46.6, 35.4, 25.9 (2C), 18.6, -4.0, -4.1; Mass (ES): m/z 423.20 (M+H 80%), 307.16 (100%); HRMS (ESI): calcd for C$_{24}$H$_{31}$N$_2$O$_3$Si (M+H)$^+$ 423.2103 found 423.2093.

N-(3-(5-(tert-butyldimethylsilyloxy)-6-methoxy-3,3a,4,8b-tetrahydro-1H-indeno[1,2-c]isoxazol-1-yl) phenyl) methanesulfonamide (8d):
The title compound was synthesized by using the general procedure; yellow color solid; mp: 190-193 °C; Yield (30%), Rf = 0.2 (1:9 EtOAc: Hex); IR (cm\(^{-1}\)): 3247, 3078, 2928, 2856, 1713, 1598, 1489, 1320, 1277; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.28-7.24 (dd, \(J = 9.21, 6.90\) Hz, 1H), 7.09-6.93 (m, 3H), 6.87-6.78 (m, 2H), 6.64 (s, 1H), 5.30 (d, \(J = 7.53\) Hz, 1H), 4.13 (t, \(J = 7.96\) Hz, 1H), 3.91-3.74 (m, 5H), 3.48-3.38 (m, 1H), 3.22-3.16 (dd, \(J = 16.8, 8.6\) Hz, 1H), 3.01 (s, 3H), 1.03 (s, 10H), 0.19 (d, \(J = 8.8\) Hz, 6H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 152.4, 150.2, 140.7, 137.6, 134.5, 130.2 (2C), 117.6, 113.3, 111.8 (2C), 111.4, 106.5, 76.11, 74.2, 55.4, 46.5, 39.3, 35.4, 25.9 (2C), 18.6, -4.1; Mass (ES): m/z 513.18 (M+Na, 100%), 491.20 (M+H 90%); HRMS (ESI): calcd for C\(_{24}\)H\(_{35}\)N\(_2\)O\(_5\)SiS (M+H)\(^+\) 491.2035 found 491.2021.

**Ethyl 5-(tert-butyldimethylsilyloxy)-6-methoxy-1-phenyl-3,3a,4,8b-tetrahydro-1H-indeno[1,2-c]isoxazole-3-carboxylate (8f):**

The title compound was synthesized by using the general procedure; Colorless oil: yield (78%), Rf = 0.6 (1: 9 EtOAc: Hex); IR (cm\(^{-1}\)): 3011, 2925, 2854, 1737, 1610, 1578, 1449, 1247; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.36-7.22 (m, 4H), 7.07-6.96 (m, 1H), 6.89 (d, \(J = 8.2\) Hz, 1H), 6.78 (t, \(J = 6.6\) Hz, 1H), 5.37 (d, \(J = 7.2\) Hz, 1H), 4.31 (d, \(J = 5.9\) Hz, 1H), 4.18 (q, \(J = 7.1\) Hz, 2H), 3.79 (s, 3H), 3.74-3.63 (m, 1H), 3.15 (d, \(J = 3.8\) Hz, 2H), 1.27 (q, \(J = 7.2\), 3H), 1.05 (s, 9H), 0.19 (d, \(J = 9.5\) Hz, 6H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 170.7, 150.6, 150.5, 141.3, 134.3, 133.2, 128.6, 122.2, 117.8, 115.8 (2C), 111.7, 83.4, 75.4, 512
61.4, 55.4, 50.1, 33.2, 29.7, 25.9 (3C), 18.6, 14.0, −4.0, −4.1; Mass (ES): m/z 470.23 (M+H, 100%), 366.18 (40%); HRMS (ESI): calcd for C_{26}H_{36}NO_{5}Si (M+H)^+ 470.2362 found 470.2348.

**Compound (9a):**

The title compound was synthesized by using the general procedure; Color less oil; yield (60%), R_f = 0.5 (1:9 EtOAc: Hex); IR (cm⁻¹): 3060, 2977, 2857, 1610, 1567, 1455, 1291; ¹H NMR (400 MHz, CDCl₃) δ 7.26 (m, 3H), 7.13 (d, J = 7.6 Hz, 2H), 6.97 (d, J = 7.3 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 6.70 (d, J = 8.2 Hz, 1H), 5.12-5.03 (m, 1H), 4.59 (d, J = 4.2 Hz, 1H), 3.77 (s, 3H), 3.09 (d, J = 2.4 Hz, 1H), 2.83-2.78 (dd, J = 17.8, 1.8 Hz, 1H), 2.31 (m, 1H), 1.99 (d, J = 11.1 Hz, 2H), 1.00 (s, 9H), 0.18 (d, J = 9.6 Hz, 6H); ¹³CNMR (100 MHz, CDCl₃) δ 151.6, 149.2, 143.2, 130.4, 128.1 124.9, 121.9, 119.4, 116.2 (2C), 108.8, 73.7, 66.1, 54.5, 34.3, 32.6, 25.8 (3C), 25.3, 18.5 -3.9, -4.2.; Mass (ES): m/z 398.21 (M+H, 100%), 292.13 (30%); HRMS (ESI): calcd for C_{23}H_{32}NO_{3}Si (M+H) + 398.2151 found 398.2152.

**Compound (9b):**

The title compound was synthesized by using the general procedure; Light yellow oil; yield (68%), R_f = 0.6 (1:9 EtOAc: Hex); IR (cm⁻¹): 3025, 2978, 2856, 1580, 1495, 1268; ¹H NMR (400 MHz, CDCl₃) δ 7.15-7.01 (m, 4H), 6.86 (d, J = 8.2 Hz, 1H), 6.72 (d, J = 8.2 Hz, 1H), 5.14-5.02 (m, 1H), 4.55 (d, J = 4.2 Hz, 1H), 3.87 (s, 3H), 3.22-3.06 (m, 1H), 2.81 (d, J = 17.7 Hz, 1H), 2.38-2.23 (m, 4H), 1.98 (d, J = 11.1 Hz, 1H), 1.05 (s, 9H), 0.20 (d, J = 10.9
Hz, 6H); $^{13}$CNMR (100 MHz, CDCl$_3$) δ 149.6, 149.4, 143.5, 131.5, 130.8, 128.9 (2C), 125.2, 119.6, 116.6 (2C), 109.1, 73.9, 66.6, 54.7, 34.6, 32.6, 26.0 (3C), 20.5, 18.8, -3.7 -3.9; Mass (ES): m/z 412.23 (M+H 100%); HRMS (ESI): calcd for C$_{24}$H$_{34}$NO$_3$Si (M+H)$^+$ 412.2307 found 412.2309.

**Compound (9c):**

The title compound was synthesized by using the general procedure; Colorless oil; yield (62%), $R_f = 0.55$ (1:9 EtOAc: Hex); IR (cm$^{-1}$): 3060, 2987, 2869, 2198, 1605, 1545, 1487, 1277; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.49 (d, $J = 8.8$ Hz, 2H), 7.09 (d, $J = 8.8$ Hz, 2H), 6.76 (d, $J = 8.2$ Hz, 1H), 6.65 (d, $J = 8.3$ Hz, 1H), 5.12-5.01 (m, 1H), 4.76 (d, $J = 4.4$ Hz, 1H), 3.75 (s, 3H), 3.15-3.05 (dd, $J = 18.1$, 1.9 Hz, 1H), 2.90-2.80 (dd, $J = 18.0$, 2.2 Hz, 1H), 2.37 (td, $J = 10.7$, 5.4 Hz, 1H), 2.15 (d, $J = 8.8$ Hz, 1H), 0.99 (s, 9H), 0.17 (d, $J = 4.9$ Hz, 6H); $^{13}$CNMR (100 MHz, CDCl$_3$) δ 154.2, 149.7, 143.6, 132.8 (2C), 129.3, 124.7, 119.8, 119.6, 115.8 (2C), 108.9, 103.81, 74.3, 64.5, 54.8, 34.6, 34.6, 26.1 (3C), 18.9, -3.7, -3.8; Mass (ES): m/z 445.18 (M+Na 100%), 423.20 (M+H 80%), 307.16 (100%); HRMS (ESI): calcd for C$_{24}$H$_{31}$N$_2$O$_3$Si (M+H)$^+$ 423.2103 found 423.2085.

**Compound (9d):**

The title compound was synthesized by using the general procedure; Brown color oil; yield (65%), $R_f = 0.2$ (1:9 EtOAc: Hex); IR (cm$^{-1}$): 3233, 3063, 2954, 2854, 1713, 1595, 1479, 1310, 1257; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.17 (t, $J = 8.0$ Hz, 1H), 6.88-6.98 (dd, $J = 8.0$, 2.1 Hz, 1H), 3.71-3.61 (m, 1H), 3.18 (t, $J = 7.5$ Hz, 1H), 2.97 (tt, $J = 7.5$, 1.7 Hz, 1H), 2.86 (m, 1H), 2.38 (m, 2H), 2.23 (s, 3H), 1.98 (s, 9H), 0.15 (d, $J = 4.9$ Hz, 6H); $^{13}$CNMR (100 MHz, CDCl$_3$) δ 175.5, 150.6, 149.7, 143.6, 132.8 (2C), 129.3, 124.7, 119.8, 119.6, 115.8 (2C), 108.9, 103.81, 74.3, 64.5, 54.8, 34.6, 34.6, 26.1 (3C), 18.9, -3.7, -3.8; Mass (ES): m/z 445.18 (M+Na 100%), 423.20 (M+H 80%), 307.16 (100%); HRMS (ESI): calcd for C$_{24}$H$_{31}$N$_2$O$_3$Si (M+H)$^+$ 423.2103 found 423.2085.
6.0 Hz, 1H), 6.91-6.83 (m, 2H), 6.82-6.74 (m, 2H), 6.64 (d, J = 8.2 Hz, 1H), 5.03 (dd, J = 5.9, 2.5 Hz, 1H), 4.63 (d, J = 4.2 Hz, 1H), 3.75 (d, J = 15.5 Hz, 3H), 3.14-3.00 (m, 1H), 3.00-2.88 (m, 3H), 2.78-2.81 (dd, J = 17.9, 1.9 Hz, 1H), 2.30-2.35 (td, J = 10.7, 5.3 Hz, 1H), 0.97 (s, 9H), 0.23 (s, 6H); \(^{13}\)CNMR (100 MHz, CDCl\(_3\)) \(\delta\) 152.8, 149.6, 143.5, 137.2, 130.1, 129.7 (2C), 125.0, 120.0, 114.00, 113.4, 108.9, 106.6, 74.1, 65.8, 54.8, 39.0, 34.7, 26.1 (3C), 18.9, -3.70, -3.77; Mass (ES): m/z 513.18 (M+Na, 100%), 491.20 (M+H 90%); HRMS (ESI): calcd for C\(_{24}\)H\(_{35}\)N\(_2\)O\(_5\)SiS (M+H)\(^+\) 491.2035 found 491.2015.

Ethyl 5-(tert-butyldimethylsilyloxy)-1-(2-cyanophenylamino)-3-hydroxy-6-methoxy-1,2,3 4-tetrahydronaphthalene-2-carboxylate (10):

The title compound was synthesized by using the general procedure; white color solid; mp: 180-183 °C, Yield (58%), R\(_f\) = 0.4 (2:8 EtOAc: Hex); IR (cm\(^{-1}\)): 3311, 2934, 2856, 2140 (CN), 1729, 1620, 1600, 1489, 1247; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.99 (d, J = 7.9 Hz, 1H), 7.32 (d, J = 7.5 Hz, 1H), 6.94 (t, J = 8.1 Hz, 2H), 6.86 (d, J = 8.3 Hz, 1H), 6.76 (d, J = 7.9 Hz, 1H), 5.83 (s, 1H), 5.46 (d, J = 5.9 Hz, 1H), 4.27 (s, 1H), 4.16-4.02 (m, 2H), 3.83 (s, 3H), 3.20 (d, J = 16.3 Hz, 1H), 2.94 (d, J = 5.4 Hz, 1H), 2.45 (d, J = 6.8 Hz, 1H), 2.35 (d, J = 7.9 Hz, 1H), 1.22 (t, J = 8.4 Hz, 3H), 1.00 (s, 9H), 0.22 (s, 3H), 0.14 (s, 3H); \(^{13}\)CNMR (100 MHz, CDCl\(_3\)) \(\delta\) 170.8, 163.8, 149.9, 146.8, 142.9, 133.1, 129.0, 124.9, 124.8, 119.9, 118.5, 117.8, 115.2, 110.1, 64.6, 60.6, 54.8, 44.2, 36.4, 27.3, 25.8 (3C), 18.7, 13.9, -3.9, -4.2; Mass (ES): m/z 519.22 (M+Na, 100%), 497.24 (M+H, 80%); HRMS (ESI): calcd for C\(_{27}\)H\(_{37}\)N\(_2\)O\(_5\)Si (M+H)\(^+\) 497.2471 found 497.2459.
4-((tert-butyldimethylsilyloxy)-5-methoxy-1-(phenylamino)-2,3-dihydro-1H-inden-2-yl)-2-hydroxyacetate (11):

To a solution of (3R,3aR,8bR)-ethyl 5-((tert-butyldimethylsilyloxy)-6-methoxy-1-phenyl-3,3a,4,8b-tetrahydro-1H-indeno [1,2-c] isoxazole-3-carboxylate (8f) (0.470 g, 1.0 mmol) in MeOH (5 mL) was added 5% Pd/C (47 mg) under balloon pressure of H₂. TLC shows completion of reaction after 6h. The Pd was filtered through celite, and the filtrate was concentrated under high vacuum. The residue was purified by column chromatography with EtOAc/Hexane (2:8) as eluent to yield the desired product; yield (80%). Rf = 0.4 (2:8 EtOAc:Hex); IR (cm⁻¹): 3340, 3079, 2930, 2847, 1681, 1650, 1585; ¹H NMR (400 MHz, CDCl₃) δ 7.18 (t, J = 7.9 Hz, 2H), 6.82-6.65 (m, 5H), 5.15 (d, J = 7.3 Hz, 1H), 4.34 (d, J = 4.7 Hz, 1H), 3.96 (q, J = 10.7, 7.2 Hz, 2H), 3.77 (s, 3H), 3.63 (dd, J = 10.7, 7.1 Hz, 1H), 3.28 (bs, 1H), 3.26-2.96 (m, 2H), 1.11 (t, J = 7.1 Hz, 3H), 1.01 (s, 9H), 0.17 (d, J = 6.3 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 172.7, 150.8, 141.2, 136.6, 135.9, 132.7, 128.8 (2C), 126.7, 125.3 (2C), 118.7, 109.9 (2C), 71.1, 65.6, 55.1, 42.7, 28.2, 25.9 (3C), 18.6, 14.4, -4.1 (2C); Mass (ES): m/z 494.23 (M+Na, 100%), 379.19 (100%); HRMS (ESI): calcd for C₂₆H₃₇NO₅SiNa (M+Na)⁺ 494.2338 found 494.2341.

5-((tert-butyldimethylsilyloxy)-3-hydroxy-6-methoxy-1-phenyl-1,3a,4,8b tetrahydroindeno [1,2-b]pyrrol-2(3H)-one (12):
To a solution of (3R,3aR,8bR)-ethyl 5-(tert-butyldimethylsilyloxy)-6-methoxy-1-phenyl-3, 3a,4,8b-tetrahydro-1H-indeno [1,2-c] isoxazole-3-carboxylate (0.470 g, 1.0 mmol) in AcOH: THF:H₂O (2:1:1, 40 mL) was added Zn dust (0.4 g, 6.1 mmol) at 60 °C. The reaction mixture was stirred for 5h. After completion of the reaction the mixture was cooled to room temperature and Zn was filtered off. The filtrate was concentrated to remove THF, and neutralized with saturated NaHCO₃ solution. The reaction mixture was extracted with CH₂Cl₂ (2 x 20 mL). The combined organic layer was washed with brine (5 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography using EtOAc/Hexane (3:7) as eluent to yield a colorless solid (0.255 g, 60%); mp: 160-163 °C  Rᵣ = 0.4 (3:7 EtOAc: Hex); IR (cm⁻¹): 3450, 3088, 2965, 2874, 1700, 1630, 1565; ¹H NMR (400 MHz, CDCl₃) δ 7.40-7.33 (m, 2H), 7.26-7.20 (m, 3H), 6.46 (q, J = 8.2 Hz, 2H), 5.30 (d, J = 6.30 Hz, 1H), 4.73 (d, J = 8.3 Hz, 1H), 3.70 (s, 3H), 3.59-3.50 (m, 1H), 3.30 (s, 1H), 3.24-3.03 (m, 2H), 1.00 (s, 9H), 0.15 (d, J = 1.5 Hz, 6H); ¹³CNMR (100 MHz, CDCl₃) δ 173.3, 150.7, 141.2, 136.6, 132.8, 128.8 (2C), 126.7, 125.4 (2C), 118.7, 109.9, 71.0, 65.6, 55.1, 42.6, 28.3, 26.0 (3C), 18.6, -4.04, -4.07; Mass (ES): m/z 448.19 (M+Na, 20%), 371.23 (40%), 313.19 (100%); HRMS (ESI): calcd for C₂₄H₃₁NO₄SiNa (M+Na)⁺ 448.1920 found 448.1909.

(4-(tert-butyldimethylsilyloxy)-5-methoxy-1-(phenylamino)-2,3-dihydro-1H-inden-2-yl)methanol (13):

The title compound was synthesized by using a procedure similar to the synthesis of 11; brown viscous oil, yield (88%), Rᵣ = 0.4 (1:9 EtOAc: Hex); IR (cm⁻¹): 3373, 3088, 2915, 2854, 1600, 1494, 1443; ¹H NMR (400 MHz, CDCl₃) δ 7.27-7.22 (m, 2H), 6.89-6.80 (m, 3H), 6.73 (q, J = 8.1 Hz, 2H), 5.06 (d, J = 6.6 Hz, 1H), 3.84-3.77 (m, 4H), 3.72 (dd, J = 11.2, 4.6 Hz, 1H), 3.40-3.27 (bs, 1H), 3.05-2.86 (m, 3H), 1.02 (s, 9H), 0.19 (d, J = 12.2 Hz, 6H); ¹³CNMR (100 MHz, CDCl₃) δ 150.1, 148.0, 141.1, 137.3, 133.1, 129.4 (2C), 118.1, 116.1, 113.6 (2C), 110.8, 63.4, 61.0, 55.3, 44.5, 31.1, 25.9 (3C), 18.6, -4.0, -4.2; Mass (ES):
m/z 422.21 (M+H, 40%), 400.23 (35%), 307.17 (100%); HRMS (ESI): calcd for C$_{23}$H$_{34}$NO$_3$Si (M+H)$^+$ 400.2307 found 400.2313.

7-((tert-butyl(dimethyl)silyloxy)-8-methoxy-1-phenyl-5,5a,6,10b-tetrahydro-1H-indeno[1,2-e][1,4]oxazepin-2(3H)-one (14):

To a solution of (4-((tert-butyl(dimethyl)silyloxy)-5-methoxy-1-(phenylamino)-2,3-dihydro-1H-inden-2-yl)methanol (0.422 g, 1.0 mmol) in dry DMF (10 mL), was added ethylbromo acetate (0.2 g, 1.2 mmol) and oven dried K$_2$CO$_3$ (0.548 g, 4.0 mmol). The mixture was refluxed for 36 h. After completion of the reaction, the mixture was diluted with saturated NH$_4$Cl solution (20 mL) and extracted with CH$_2$Cl$_2$ (2x25 mL). The combined organic layer was collected, washed with 2N HCl and water, then dried over anhydrous Na$_2$SO$_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel using EtOAc/Hexane (3:7) as eluent to afford the desired product as a brown solid (0.228 g, 60%); mp: 280-282 °C; Yield (60%), R$_f$ = 0.4 (3:7 EtOAc: Hex); IR (cm$^{-1}$): 3021, 2973, 2877, 1720, 1615, 1585; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.41 (t, $J =$ 7.7 Hz, 2H), 7.34 (d, $J =$ 7.3 Hz, 2H), 7.31-7.23 (m, 1H), 6.92 (d, $J =$ 8.0 Hz, 1H), 6.75 (d, $J =$ 8.0 Hz, 1H), 5.30 (d, $J =$ 7.1 Hz, 1H), 4.34 (d, $J =$ 15.5 Hz, 1H), 4.11 (dd, $J =$ 12.6, 3.9 Hz, 1H), 3.91 (d, $J =$ 15.5 Hz, 1H), 3.79 (s, 3H), 3.72 (dd, $J =$ 12.7, 4.8 Hz, 1H), 2.94 (dd, $J =$ 20.0, 13.3 Hz, 3H), 1.00 (s, 9H), 0.20 (s, 3H), 0.13 (s, 3H); $^{13}$CNMR (100 MHz, CDCl$_3$) 172.6, 150.2, 144.5, 141.3, 134.8, 131.8, 129.2 (2C), 126.9, 126.5 (2C), 114.7, 110.5, 72.5, 71.7, 68.8, 55.2, 43.5, 32.0, 25.8 (3C), 18.5, -4.2, -4.4; Mass (ES): m/z 462.20 (M+Na, 100%), 440.22 (M+H, 10%), 289.16 (80%); HRMS (ESI): calcd for C$_{25}$H$_{33}$NO$_4$NaSi (M+Na)$^+$ 462.2076 found 462.2060.
A typical procedure for the removal of tert-butyldimethylsilyloxy group of compound 8c:

To a solution of 4-(5-(tert-butyldimethylsilyloxy)-6-methoxy-3,3a,4,8b-tetrahydro-1H-indeno[1,2-c] isoxazol-1-yl) benzonitrile (8c) (1 mmol) in dry THF (5 mL), was added tetra-butyl ammonium iodide (1.5 mmol) at 0°C. The reaction mixture was stirred at the same temperature for 0.5 h, THF was removed under high vacuum followed by extraction with DCM (2x10 mL). The combined DCM layer was collected, dried over anhydrous Na$_2$SO$_4$, filtered and concentrated. The residue was purified by using column chromatography over silica gel to give the product 4-(5-hydroxy-6-methoxy-3,3a,4,8b-tetrahydro-1H-indeno[1,2-c]isoxazol-1-yl)benzonitrile (15).

![Chemical structure of 15](image)

White color solid; mp 180 °C; Yield (88%), $R_f = 0.2$ (1:9 EtOAc: Hex); IR (cm$^{-1}$): 3430, 3256, 3060, 2973, 2868, 2205, 1555, 1486, 1276; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.58 (d, $J = 8.9$ Hz, 2H), 7.19 (d, $J = 8.9$ Hz, 2H), 6.93 (d, $J = 8.1$ Hz, 1H), 6.84 (d, $J = 8.2$ Hz, 1H), 5.67 (s, 1H), 5.35 (d, $J = 7.6$ Hz, 1H), 4.10-4.05 (m, 1H), 3.98-3.85 (m, 4H), 3.56-3.48 (m, 1H), 3.30-3.22 (m, 1H), 3.03 (dd, $J = 16.9$, 3.1 Hz, 1H); $^{13}$CNMR (100 MHz, CDCl$_3$) δ 154.0, 146.6, 141.4, 134.5 (2C), 133.4, 128.6, 119.5, 116.1, 114.0 (2C), 110.7, 103.8, 75.0, 74.6, 56.4, 46.7, 34.2, 29.7; Mass (ES): m/z 309.13 (M+H 100%).

6-methoxy-1-phenyl-3,3a,4,8b-tetrahydro-1H-indeno[1,2-c]isoxazol-5-ol (16):

![Chemical structure of 16](image)
The title compound was synthesized by following the typical procedure for synthesis of compound 15; colorless solid; mp 180 °C; Yield (90%), R_f = 0.2 (1:9 EtOAc: Hex); IR (cm⁻¹): 3360, 3040, 2957, 2832, 1620, 1565, 1445, 1290; ¹H NMR (400 MHz, CDCl₃) δ 7.34 (t, J = 7.6 Hz, 2H), 7.20 (d, J = 7.9 Hz, 2H), 7.03 (d, J = 8.1 Hz, 2H), 6.83 (d, J = 8.1 Hz, 1H), 5.65 (s, 1H), 5.35 (d, J = 7.5 Hz, 1H), 4.17 (t, J = 7.9 Hz, 1H), 3.83 (s, 3H), 3.84-3.82 (m, 1H), 3.48-3.42 (m, 1H), 3.25-3.18 (dd, J = 16.8, 8.6 Hz, 1H), 3.08-2.98 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 148.1, 145.0, 141.6, 135.1, 134.4, 128.9 (2C), 121.6, 117.6 (2C), 114.6, 111.8, 76.3, 74.1, 55.4, 46.4, 25.9; Mass (ES): m/z 284.21 (M+H, 100%).

6-Methoxy-1-p-toly-3,3a,4,8b-tetrahydro-1H-indeno [1, 2-c] isoxazol-5-ol (17):

The title compound was synthesized by following the typical procedure for synthesis of compound 15; light yellow solid; m.p: 170 °C; Yield (86%), R_f = 0.2 (1:9 EtOAc: Hex); IR (cm⁻¹): 3296, 3050, 2963, 2878, 1619, 1567, 1476, 1286; ¹H NMR (400 MHz, CDCl₃) δ 7.19-7.09 (m, J = 8.7 Hz, 4H), 6.97 (d, J = 8.2 Hz, 1H), 6.81 (d, J = 8.2 Hz, 1H), 5.30 (d, J = 7.5 Hz, 1H), 4.16 (t, J = 8.0 Hz, 1H), 3.85 (s, 3H), 3.79-3.68 (dd, J = 8.4, 2.7 Hz, 1H), 3.47-3.37 (m, 1H), 3.19 (dd, J = 16.8, 8.6 Hz, 1H), 2.99 (dd, J = 16.8, 2.6 Hz, 1H), 2.30 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 148.6, 146.4, 141.4, 135.9, 131.21, 129.5, 116.2, 114.9 (2C), 110.7, 76.3, 74.2, 56.4, 46.6, 34.4, 20.5. Mass (ES): m/z 298.13 (M+H, 100%).

N-(3-(5-(tert-butyldimethylsilyloxy)-6-methoxy-3,3a,4,8b-tetrahydro-1H-indeno[1,2-c] isoxazol-1-yl) phenyl) methanesulfonamide (18):
The title compound was synthesized by following the typical procedure for synthesis of compound 15; yellow solid; mp: 190-193 °C; Yield (70%), $R_f = 0.2$ (3:7 EtOAc: Hex); IR (cm$^{-1}$): 3437, 3068, 2948, 2856, 1711, 1588, 1482, 1310, 1287; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.25-7.21 (dd, $J = 9.21, 6.90$ Hz, 1H), 7.11-6.95 (m, 3H), 6.89-6.79 (m, 2H), 6.54 (s, 1H), 5.32 (d, $J = 7.5$ Hz, 1H), 4.15 (t, $J = 7.9$ Hz, 1H), 3.93-3.77 (m, 5H), 3.51-3.41 (m, 1H), 3.24-3.19 (dd, $J = 16.8, 8.6$ Hz, 1H), 3.09 (s, 3H); $^{13}$CNMR (100 MHz, CDCl$_3$) $\delta$ 153.4, 151.2, 141.2, 138.2, 135.1, 130.9 (2C), 118.5, 113.6, 112.2, 111.9 (2C), 105.7, 77.4, 75.2, 56.4, 47.5, 39.8, 36.4, 26.9; Mass (ES): m/z 377.10 (M+H 100%).

**Compound 19:**

The title compound was synthesized by following the typical procedure for synthesis of compound 15; colorless viscous oil; Yield (72%), $R_f = 0.15$ (1:9 EtOAc: Hex); IR (cm$^{-1}$): 3423, 3070, 2992, 2876, 2198, 1615, 1565, 1497, 1287; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.48 (d, $J = 8.8$ Hz, 2H), 7.09 (d, $J = 8.8$ Hz, 2H), 6.72 (d, $J = 8.1$ Hz, 1H), 6.66 (d, $J = 8.1$ Hz, 1H), 5.72 (s, 1H), 5.11-5.02 (m, 1H), 4.78 (d, $J = 4.40$ Hz, 1H), 3.84 (s, 3H), 3.11 (dd, $J = 18.0, 1.8$ Hz, 1H), 2.88 (dd, $J = 18.0, 2.2$ Hz, 1H), 2.47-2.31 (m, 1H), 2.17 (d, $J = 11.1$ Hz, 1H); $^{13}$CNMR (100 MHz, CDCl$_3$) $\delta$ 154.3, 149.7, 143.6, 140.3, 132.8 (2C), 124.7 (2C), 119.7, 119.6, 115.8, 108.9, 103.6, 74.2, 64.5, 54.8, 41.0, 24.3; Mass (ES): m/z 309.16 (M+H 100%).

**Compound (20):**
The title compound was synthesized by following the typical procedure for synthesis of compound 15; brown semi solid, Yield (80%), R_f = 0.2 (1:9 EtOAc: Hex); IR (cm⁻¹): 3345, 3050, 2967, 2875, 1620, 1566, 1465, 1298; ¹H NMR (400 MHz, CDCl₃) δ 7.24 (t, J = 7.9 Hz, 2H), 7.12 (d, J = 7.7 Hz, 2H), 6.93 (t, J = 7.3 Hz, 1H), 6.76 (d, J = 8.1 Hz, 1H), 6.67 (d, J = 8.1 Hz, 1H), 5.79 (s, 1H), 5.12-5.00 (m, 1H), 4.59 (d, J = 4.3 Hz, 1H), 3.84-3.74 (m, 3H), 3.10 (dd, J = 17.7, 2.0 Hz, 1H), 2.80 (dd, J = 17.8, 1.7 Hz, 1H), 2.32 (td, J = 10.9, 5.3 Hz, 1H), 2.04-1.96 (m, 1H); ¹³CNMR (100 MHz, CDCl₃) δ 153.6, 146.7, 141.8, 132.8, 129.3, 124.7, 119.8, 119.6, 115.9, 108.9, 103.8, 74.2, 64.5, 54.8, 48.9, 34.6, 26.1; Mass (ES): m/z 284.21 (M+H, 100%).

**Compound 21:**

The title compound was synthesized by following the typical procedure for synthesis of compound 15; colorless semi solid; Yield (90%), R_f = 0.8 (1:9 EtOAc: Hex); IR (cm⁻¹): 3346, 3053, 2987, 2867, 1590, 1505, 1286; ¹H NMR (400 MHz, CDCl₃) δ 7.07-7.01 (m, 4H), 6.77 (d, J = 8.1Hz, 1H), 6.69 (d, J = 8.1 Hz, 1H), 5.12-4.98 (m, 1H), 5.98-5.45 (m, 1H), 4.53 (d, J = 4.3 Hz, 1H), 3.82 (s, 3H), 3.10 (dd, J = 17.7, 1.8 Hz, 1H), 2.80 (dd, J = 17.7, 1.6 Hz, 1H), 2.38-2.29 (m, 1H), 2.29 (d, J = 11.0 Hz, 3H), 1.99 (d, J = 11.1 Hz, 1H); ¹³CNMR (100 MHz, CDCl₃) δ 149.6, 146.1, 144.1, 131.7, 131.2 (2C), 129.1, 119.8, 118.4, 116.7 (2C), 108.3, 73.9, 66.6, 56.1, 33.2, 33.0, 20.6; Mass (ES): m/z 298.13 (M+H 100%).

**Compound (22):**
The title compound was synthesized by following the typical procedure for synthesis of compound 15; colorless semi solid; yield (85%), Rf = 0.2 (3:7 EtOAc: Hex); IR (cm⁻¹): 3420, 3253, 3083, 2965, 2874, 1713, 1585, 1489, 1320, 1267; ¹H NMR (400 MHz, CDCl₃) δ 7.20 (t, J = 8.0 Hz, 1H), 6.97 (s, 1H), 6.90 (d, J = 8.1 Hz, 1H), 6.80-6.73 (m, 2H), 6.67 (d, J = 8.2 Hz, 1H), 5.12-5.03 (m, 1H), 4.66 (d, J = 4.3 Hz, 1H), 5.93-5.46 (m, 1H), 3.85 (s, 3H), 3.11 (dd, J = 17.9, 1.7 Hz, 1H), 2.95 (s, 3H), 2.85 (dd, J = 17.8, 1.8 Hz, 1H), 2.45-2.35 (m, 1H), 2.10 (d, J = 11.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) 152.8, 146.1, 144.0, 137.1, 130.4, 129.7 (2C), 119.5, 118.6 (2C), 113.9, 113.4, 108.6, 108.1, 74.0, 65.6, 56.0, 39.1, 33.9; Mass (ES): m/z 513.18 (M+Na, 100%), 377.20 (M+H 90%).

Ethyl-5-hydroxy-6-methoxy-1-phenyl-3,3a,4,8b-tetrahydro-1H-indeno[1,2-c]isoxazole-3-carboxylate (23):

The title compound was synthesized by following the typical procedure for synthesis of compound 15; Light yellow color oil; yield (88%), Rf = 0.2 (1:9 EtOAc: Hex); IR (cm⁻¹): 3367, 3067, 2954, 2874, 1742, 1620, 1565, 1435, 1255; ¹H NMR (400 MHz, CDCl₃) δ 7.33-7.23 (m, 4H), 7.00 (ddd, J = 8.3, 6.9, 3.6 Hz, 1H), 6.84-6.73 (m, 2H), 5.70 (s, 1H), 5.37 (d, J = 7.3 Hz, 1H), 4.33 (d, J = 5.8 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.85 (d, J = 11.8 Hz, 4H), 3.73 (ddd, J = 13.4, 6.4, 3.4 Hz, 1H), 3.23-3.08 (m, 2H), 1.25 (t, J = 7.14 Hz, 4H); ¹³C NMR(100MHz,CDCl₃)δ 170.7, 150.4, 146.2, 141.9, 134.8, 128.6 (2C), 127.4, 122.2, 116.3, 115.9 (2C), 110.5, 83.4, 75.1, 61.4, 56.3, 50.2, 32.2, 14.0; Mass (ES): m/z 355.24 (M+H, 100%).

2-(Hydroxyl methyl)-5-methoxy-1-(phenylamino)-2,3-dihydro-1H-inden-4-ol (24):

2-(Hydroxyl methyl)-5-methoxy-1-(phenylamino)-2,3-dihydro-1H-inden-4-ol (24):
The title compound was synthesized by following the typical procedure for synthesis of compound 15; yellow color viscous oil, Yield (88%), R_f = 0.3 (3:7 EtOAc: Hex); IR (cm⁻¹): 3383, 3089, 2950, 2864, 1610, 1534, 1484, 1453; ¹H NMR (400 MHz, CDCl₃) δ 7.27-7.12 (m, 2H), 6.80-6.69 (m, 5H), 5.05 (d, J = 6.8 Hz, 1H), 3.83 (s, 3H), 3.79-3.72 (m, 1H), 3.65 (dd, J = 11.2, 4.8 Hz, 1H), 3.04-2.92 (m, 2H), 2.87 (d, J = 12.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 148.0, 146.4, 141.8, 137.9, 129.4 (2C), 127.4, 118.2, 114.5, 113.7 (2C), 109.8, 63.4, 61.0, 56.3, 44.6, 29.9; Mass (ES): m/z 285.21 (M+H, 100%).

2-Methoxy-5-(phenylamino)-5,6,7,8-tetrahydronaphthalene-1,7-diol (25):

![Chemical structure](image)

The title compound was synthesized by following the typical procedure for synthesis of compound 15; yellow color viscous oil, Yield (88%), R_f = 0.3 (3:7 EtOAc: Hex); IR (cm⁻¹): 3383, 3089, 2950, 2864, 1610, 1534, 1484, 1453; ¹H NMR (400 MHz, CDCl₃) δ 7.25-7.15 (m, 2H), 6.95 (d, J = 8.5 Hz, 1H), 6.77-6.68 (m, 4H), 6.16-6.15 (m, 1H), 6.13-5.50 (m, 1H), 4.66 (t, J = 5.9 Hz, 1H), 4.33-4.19 (m, 1H), 3.85 (s, 3H), 3.03 (dd, J = 17.1, 4.9 Hz, 1H), 2.83 (dd, J = 17.1, 6.4 Hz, 1H), 2.28-2.20 (m, 1H), 2.06-1.95 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 147.0, 145.4, 143.1, 131.0, 129.4 (2C), 121.0, 118.9, 117.9, 113.6 (2C), 108.9, 65.9, 56.1, 36.4, 32.4; Mass (ES): m/z 285.21 (M+H, 100%).

3-(2-Ethoxy-2-oxoethyl)-5-hydroxy-6-methoxy-3,4-dihydroisoquinoline-2-oxide (26):

![Chemical structure](image)

The title compound was synthesized by following the typical procedure for synthesis of compound 15; colorless oil (88%); R_f = 0.4 (8:2 EtOAc: Hex); IR (cm⁻¹): 3326, 3060, 2985, 2872, 1720 (CO, ester), 1621, 1575, 1474, 1257; ¹H NMR (400 MHz, CDCl₃) δ 7.66 (s, 1H), 6.75 (s, 1H), 6.70 (s, 1H), 6.12-5.99 (m, 1H), 4.53-4.48 (m, 1H), 4.22-4.15 (m, 2H), 3.92 (s,
5H), 3.20-3.13 (m, 3H), 3.12-3.06 (m, 1H), 2.65-2.56 (m, 1H), 1.28 (d, J = 7.1 Hz, 4H);
$^{13}$C NMR (100 MHz, CDCl$_3$) δ 173.8, 152.0, 142.5, 135.1, 121.3, 119.9, 109.8, 63.5, 60.9,
55.0, 35.8, 27.1, 14.1; Mass (ES): m/z 280.20 (M+H, 100%).

7-Hydroxy-8-methoxy-1-phenyl-5,5a,6,10b-tetrahydro-1H-indeno[1,2-e][1,4]oxazepin-2(3H)-one (27):

![Chemical Structure](image_url)

The title compound was synthesized by following the typical procedure for synthesis of compound 15; Brown solid (90%); mp: 250 °C; Yield (90%), R$_f$ = 0.2 (3:7 EtOAc: Hex); IR (cm$^{-1}$): 3345, 3051, 2983, 2867, 1710, 1625, 1575; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.42 (t, J = 7.7 Hz, 2H), 7.35 (d, J = 7.6 Hz, 2H), 7.27 (dd, J = 12.8, 4.8 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 5.82 (s, 1H), 5.29 (d, J = 6.9 Hz, 1H), 4.33 (d, J = 15.7 Hz, 1H), 3.93 (d, J = 15.7 Hz, 1H), 3.89 (d, J = 18.5 Hz, 3H), 3.79 (dd, J = 12.6, 3.3 Hz, 1H), 3.08-2.89 (m, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) 172.3,
146.4, 144.9, 141.9, 136.0, 129.3 (2C), 127.0 (2C), 126.6 (2C), 112.9, 109.4, 72.7, 72.1, 68.8,
56.2, 43.8, 31.2; Mass (ES): m/z 326.20.

3,5-Dihydroxy-6-methoxy-1-phenyl-1,3a,4,8b-tetrahydroindeno[1,2-b]pyrrol-2(3H)-one (28):

![Chemical Structure](image_url)

The title compound was synthesized by following the typical procedure for synthesis of compound 15; Colorless solid (80%); mp: 168 °C R$_f$ = 0.25 (3:7 EtOAc: Hex); IR (cm$^{-1}$):
EVALUATION OF TEST COMPOUNDS FOR CAPSAICIN LIKE ACTIVITY IN ZEBRAFISH MODEL OF ANXIETY

The compounds synthesised were inspired from Capsaicin and hence were assessed to evaluate their Capsaicin like activity. Capsaicin is known to show anxiogenic activity in various animal models [2] and therefore, was expected to show the same in zebrafish model of anxiety. We used the adult zebrafish model of light/dark box anxiety test to assess the activity [1]. This method was used as it is simple and does not require invasive procedures or euthanasia [1]. We first tested the hypothesis that Capsaicin administration results in anxiogenic behaviour in adult zebrafish. Thereafter, test compounds were tested in this model to identify the most potent anxiogenic compounds.

Graphical Abstract: The figure shows the evaluation of anxiety like behaviours in the adult zebrafish using light/dark box paradigm. Normal fish move across freely in both light and dark environments, however, when anxious their movements and higher in the dark environment as compared to light.

Materials and Methods:

Wild type Zebrafish (Danio rerio) were maintained as per the procedure mentioned by us earlier [3]. The studies on anxiety assessment using the light/dark box paradigm were conducted based on a parameters of percentage time spent in light, duration of erratic movement and number of erratic movement from the published protocol [1].
administration was carried out by a procedure reported earlier [4]. Clonidine, an anxiolytic agent was used as a positive control to ascertain the validity of the experiments. Evaluation was conducted in three parts: (a) screening of Capsaicin for assessment of its anxiogenic activity in adult zebrafish, (b) screening of test compounds at single dose to identify the most potent anxiogenic agent, and, (c) multi-dose studies on the most potent agent to verify anxiogenic activity.

Statistical analysis:

Statistical analysis was performed using graph pad prism software. Data were represented using Mean and Standard Error of the Mean (± SEM). Data was analysed using analysis of variance (ANOVA) followed by Tukey’s multiple comparative test. Statistical significance was set at the p<0.05 level.

Results:

Capsaicin when tested in the adult zebrafish model of anxiety using the dark light box paradigm showed clear anxiogenic behaviour, which was evident from the fact that the percentage time spent in light box was significantly lower in the Capsaicin treated fish as compared to control at 10 µg/kg dose and the effect was dose dependent (Fig 1 A). The erratic movement (number and duration) were also observed and they increased in a dose dependent manner in Capsaicin treated fish (Fig 1 B & 1 C). This concludes that Capsaicin shows anxiogenic effect in adult zebrafish that is similar to the effect seen in other mammalian species. Screening of test compound in a single dose screening was performed and screening suggested that compound -15 was the most potent anxiogenic compound (Fig 2). Multi-dose evaluation of Compound-15 confirmed the anxiogenic activity as the fish administered with this compound showed significant reduction in the percentage time spent in the light as compared to control fish (Fig 3 A). The erratic movement (number and duration) were also observed and there is dose-dependent increase in Compound -15 group (Fig 3 B & 3 C). This verifies that Compound -15 has anxiogenic activity which is an activity similar to Capsaicin.
Figure 1: Multi-dose evaluation of capsaicin and 15 in the adult zebrafish model of anxiety for A. Percentage time spent in light, B. Duration of erratic movements, and C. Number of erratic movements using the light/dark box paradigm. D. Structure of 15
Figure 2: Screening of compounds for anxiolytic activity. Effect of compounds was assessed at 10 mg/kg) in the light/dark box paradigm to evaluate the parameter of percentage time spent in light. Compound-15 was found to have maximum effect in this study.

References:


2. Manna SS, Umathe SN. Transient receptor potential vanilloid 1 channels modulate the anxiolytic effect of diazepam. Brain Res. 2011; 1425: 75-82.


$^1$H & $^{13}$C NMR SPECTRA

2-Allyl-3-(tert-butyldimethylsilyloxy)-4-methoxybenzaldehyde (1a):

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$CNMR (100 MHz, CDCl$_3$)
(E)-Ethyl 4-(2-(tert-butyldimethylsilyloxy)-6-formyl-3-methoxyphenyl) but-2-enoate (1b):
(E)-2-allyl-3-(tert-butyldimethylsilyloxy)-4-methoxybenzaldehyde oxime (2):

\[
\begin{array}{c}
\text{H}_3\text{CO} \\
\text{OTBS}
\end{array}
\]

\[
\begin{array}{c}
\text{1}^1\text{H NMR (400 MHz, CDCl}_3)\end{array}
\]

\[
\begin{array}{c}
\text{1}^3\text{C NMR (100 MHz, CDCl}_3)\end{array}
\]
5-(tert-butyl(dimethyl)silyloxy)-3-(2-ethoxy-2-oxoethyl)-6-methoxy-3,4 dihydro isoquinoline 2-oxide (3):

\[ \text{H NMR (400 MHz, CDCl}_3\text{)} \]

\[ \text{C NMR (100 MHz, CDCl}_3\text{)} \]
Ethyl 7-(tert-butyldimethylsilyloxy)-5-(2-ethoxy-2-oxoethyl)-8-methoxy-2, 5, 6, 10b-tetrahydro-1H-isoxazolo[3, 2-a] isoquinoline-1-carboxylate (4a):

**$^1$H NMR (400 MHz, CDCl$_3$)**

- 1H NMR data is shown with peaks at various ppm values.

**$^{13}$C NMR (100 MHz, CDCl$_3$)**

- $^{13}$C NMR data is shown with peaks at various ppm values.
$^1$H- $^1$H COSY NMR of Compound 4a

Expansion of $^1$H- $^1$H COSY NMR of Compound 4a
Expansion of 1D NOE of Compound 4a

Ethyl7-(tert-butyldimethylsilyloxy)-5-(2-ethoxy-2-oxoethyl)-8-methoxy-2, 5, 6, 10b-tetrahydro-1H-isoxolo [3, 2-a] isoxazoline-2-carboxylate (4b):

\[ \text{Ethyl7-(tert-butyldimethylsilyloxy)-5-(2-ethoxy-2-oxoethyl)-8-methoxy-2, 5, 6, 10b-tetrahydro-1H-isoxolo [3, 2-a] isoxazoline-2-carboxylate (4b):} \]
$^1$H- $^1$H COSY NMR of Compound 4b
Expansion of $^1$H-$^1$H COSY NMR of Compound 4b

Expansion of 1D NOE of Compound 4b

Ethyl2-(5-(tert-butyldimethylsilyloxy)-6-methoxy-1, 2, 3, 4 tetrahydroisoquinolin-3-yl) acetate (5):
$^{1}H$ NMR (400 MHz, CDCl$_3$)

$^{13}C$ NMR (100 MHz, CDCl$_3$)

$(E)$-N-(2-allyl-3-(tert-butyldimethylsilyloxy)-4-methoxybenzylidene)-2-cyanoaniline oxide (7e):
5-\((\text{tert-butyldimethylsilyloxy})\)-6-methoxy-1-phenyl-3, 3a, 4, 8b-tetrahydro-1\(H\)-inden [1, 2-c] isoxazole (8a):
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H- $^1$H COSY NMR of Compound 8a

Expansion of $^1$H- $^1$H COSY NMR of Compound 8a
5-(*tert*-butyldimethylsilyloxy)-6-methoxy-1-p-tolyl-3,3a,4,8b-tetrahydro-1H-indeno[1,2-c] isoxazole (8b):

\[
\text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3\text{)}
\]

\[
\text{\textsuperscript{13}C NMR (100 MHz, CDCl}_3\text{)}
\]
4-(5-(tert-butyldimethylsilyloxy)-6-methoxy-3,3a,4,8b-tetrahydro-1H-indeno [1,2-c] isoxazol-1-yl) benzonitrile (8c):

$\begin{align*}
\text{1}^1\text{H NMR (400 MHz, CDCl}_3\text{)} \\
\text{1}^3\text{C NMR (100 MHz, CDCl}_3\text{)}
\end{align*}$
$N$-(3-($\text{tert}$-butyldimethylsilyloxy)-6-methoxy-3a,4,8b-tetrahydro-1$H$-indenol[1,2-$c$]isoxazol-1-yl) phenyl) methanesulfonamide (8d):

\[\text{\includegraphics{image.png}}\]

$^{1}$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
Ethy5-(tert-butyldimethylsilyloxy)-6-methoxy-1-phenyl-3,3a,4,8b-tetrahydro-1H-indeno[1,2-c]isoxazole-3-carboxylate (8f):

\[ \text{1H NMR (400 MHz, CDCl}_3\text{)} \]

\[ \text{13C NMR (100 MHz, CDCl}_3\text{)} \]
2D NOESY of Compound 8f

-ve noe between $H_a$ and $H_b$
Compound 9a:

\[ \text{\H NMR (400 MHz, CDCl}_3) \]

\[ \text{\C NMR (100 MHz, CDCl}_3) \]

\[ \text{\H NMR (400 MHz, CDCl}_3) \]

\[ \text{\C NMR (100 MHz, CDCl}_3) \]
$^1$H- $^1$H COSY NMR of Compound 9a

Expansion of $^1$H- $^1$H COSY NMR of Compound 9a

$H_a$: 5.12 ppm $H_c$: 3.09 ppm
$H_b$: 4.59 ppm $H_d$: 2.31 ppm
Compound (9b):

\[ \text{H NMR (400 MHz, CDCl}_3\text{)} \]

\[ \text{C NMR (100 MHz, CDCl}_3\text{)} \]

\[ ^1\text{H NMR (400 MHz, CDCl}_3\text{)} \]

\[ ^{13}\text{C NMR (100 MHz, CDCl}_3\text{)} \]
Compound (9c):

\[ \text{H NMR (400 MHz, CDCl}_3\text{)} \]

\[ \text{^13 C NMR (100 MHz, CDCl}_3\text{)} \]

S51
Compound (9d):

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
Ethyl 5-(tert-butyldimethylsilyloxy)-1-(2-cyanophenylamino)-3-hydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylate (10):
Expansion of 2D NOESY of Compound 10

$H_a$: 5.48 ppm, $H_b$: 3.25 ppm
$H_c$: 2.95 ppm, $H_d$: 2.48 ppm
4-(tert-butyldimethylsilyloxy)-5-methoxy-1-(phenylamino)-2, 3-dihydro-1H-inden-2-yl)-2-hydroxyacetate (11):

\[
\begin{align*}
\text{H NMR (400 MHz, CDCl}_3&) & \\
\text{C NMR (100 MHz, CDCl}_3&) & \\
\end{align*}
\]
5-(tert-butyldimethylsilyloxy)-3-hydroxy-6-methoxy-1-phenyl-1,3a,4,8b-tetrahydroindeno[1,2-b]pyrrol-2(3H)-one (12):

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
(4-(tert-butyldimethylsilyloxy)-5-methoxy-1-(phenylamino)-2,3-dihydro-1H-inden-2-yl) methanol (13):

![NMR spectra](image)

**1H NMR (400 MHz, CDCl₃)**

**13C NMR (100 MHz, CDCl₃)**
7-((tert-butyldimethylsilyloxy)-8-methoxy-1-phenyl-5,5a,6,10b-tetrahydro-1H-indeno[1,2-e][1,4]oxazepin-2(3H)-one (14):

**H NMR (400 MHz, CDCl₃)**

| ppm (f1) | 112.97 | 152.20 | 144.23 | 141.53 | 134.81 | 131.79 | 129.17 | 126.96 | 125.64 | 114.75 | 110.90 | 77.73 | 75.68 | 72.17 | 71.16 | 70.25 | 68.86 | 66.21 | 58.21 | 43.47 | 33.05 | 25.78 | 18.96 | 4.21 |

**C NMR (100 MHz, CDCl₃)**

| ppm (f1) |
| 150 | 148 | 146 | 144 | 142 | 140 | 138 | 136 | 134 | 132 | 130 | 128 | 126 | 124 | 122 | 120 | 118 | 116 | 114 | 112 | 110 | 108 | 106 | 104 | 102 | 100 | 98 | 96 | 94 | 92 | 90 | 88 | 86 | 84 | 82 | 80 | 78 | 76 | 74 | 72 | 70 | 68 | 66 | 64 | 62 | 60 | 58 | 56 | 54 | 52 | 50 | 48 | 46 | 44 | 42 | 40 | 38 | 36 | 34 | 32 | 30 | 28 | 26 | 24 | 22 | 20 | 18 | 16 | 14 | 12 | 10 | 8 | 6 | 4 | 2 | 0 |
4-(5-Hydroxy-6-methoxy-3,3a,4,8b-tetrahydro-1H-indeno [1, 2-c] isoxazol-1-yl) benzonitrile (15):
6-Methoxy-1-phenyl-3,3a,4,8b-tetrahydro-1H-indeno[1,2-c]isoxazol-5-ol (16):

**1H NMR (400 MHz, CDCl₃)**

**13C NMR (100 MHz, CDCl₃)**
6-Methoxy-1-<i>p</i>-tolyl-3,3a,4,8b-tetrahydro-1<i>H</i>-indenolo[1,2-<i>c</i>]isoxazol-5-ol (17):

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)**
**Compound 19**

- **H NMR (400 MHz, CDCl₃)**
- **C NMR (100 MHz, CDCl₃)**

![H NMR Spectrum of Compound 19](image1)

**1H NMR (400 MHz, CDCl₃)**

- 1H NMR data for Compound 19 is shown with peaks at various chemical shifts.

![13C NMR Spectrum of Compound 19](image2)

**13C NMR (100 MHz, CDCl₃)**

- 13C NMR data for Compound 19 is shown with peaks at various chemical shifts.

The spectra demonstrate the structural analysis of Compound 19 through NMR spectroscopy, providing insights into its molecular components and functional groups.
Compound 20:

\[
\begin{align*}
\text{H NMR (400 MHz, CDCl}_3\text{)} \\
\text{13C NMR (100 MHz, CDCl}_3\text{)}
\end{align*}
\]

\[
\begin{align*}
\text{1H NMR (400 MHz, CDCl}_3\text{)} \\
\text{13C NMR (100 MHz, CDCl}_3\text{)}
\end{align*}
\]

Compound 21:
Compound (22):

\[
\begin{align*}
\text{H NMR (400 MHz, CDCl}_3)\text{)}
\end{align*}
\]

\[
\begin{align*}
\text{\textsuperscript{13}C NMR (100 MHz, CDCl}_3)\text{)}
\end{align*}
\]
S65

$^{1}H$ NMR (400 MHz, CDCl$_3$)

$^{13}C$ NMR (100 MHz, CDCl$_3$)
Ethyl 5-hydroxy-6-methoxy-1-phenyl-3a,4,8b-tetrahydro-1H-indeno[1,2-c]isoxazole-3-carboxylate (23):

\[
\text{H NMR (400 MHz, CDCl}_3\text{)}
\]

\[
\text{C NMR (100 MHz, CDCl}_3\text{)}
\]
2-(Hydroxyl methyl)-5-methoxy-1-(phenyl amino)-2,3-dihydro-1H-inden-4-ol (24):
2-methoxy-5-(phenylamino)-5,6,7,8-tetrahydronaphthalene-1,7-diol (25):

\[
\begin{align*}
\text{H NMR (400 MHz, CDCl}_3)\text{)} \\
\text{\textsuperscript{13}C NMR (100 MHz, CDCl}_3)\text{)}
\end{align*}
\]
3-(2-ethoxy-2-oxoethyl)-5-hydroxy-6-methoxy-3,4-dihydroisoquinoline 2-oxide (26):
7-hydroxy-8-methoxy-1-phenyl-5,5a,6,10b-tetrahydro-1\textit{H}-indeno[1,2-\textit{e}] [1,4]oxazepin-2(3\textit{H})-one (27):

\begin{center}
\includegraphics[width=0.5\textwidth]{structure.png}
\end{center}

\textbf{\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3})}

\begin{center}
\includegraphics[width=\textwidth]{hnmr.png}
\end{center}

\textbf{\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3})}

\begin{center}
\includegraphics[width=\textwidth]{cnmr.png}
\end{center}
3,5-dihydroxy-6-methoxy-1-phenyl-1,3a,4,8b-tetrahydroindeno[1,2-b]pyrrol-2(3H)-one (28):

\[ \text{H NMR (400 MHz, CDCl}_3) \]

\[ \text{C NMR (100 MHz, CDCl}_3) \]