Electronic Supplementary Information

Indion 860 catalyzed cascade reaction: A greener approach to functionalized cyclohexanones and their novel analogues

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Table of contents

Experimental ........................................................................................................................................Page 2
Chemistry........................................................................................................................................... Page 2
General methods ................................................................................................................................Page 2
General procedure for the preparation of functionalized cyclohexanones (3)...............Page 2
Preparation of tetrahydro-1H-dibenzo[b,e][1,4] diazepine(5)..............................................Page 12
Preparation of ethoxy-3-oxoprop-1-en-1-yl (7).................................................................Page 12
General procedure for the preparation of hexahydro-1H-indazoles (9)...................... Page 13
Pharmacology..............................................................................................................................Page 16
**General methods:** Unless stated otherwise, solvents and chemicals were obtained from commercial sources and were used without further purification. 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 (230-400 mesh) using hexane and ethyl acetate. $^1$H NMR and $^{13}$C NMR spectra were determined in DMSO-$d_6$ solution by using 400 or 100 MHz spectrometers, respectively. Proton chemical shifts ($\delta$) are relative to tetramethylsilane (TMS, $\delta = 0.00$) 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 using melting point B-540 apparatus and are uncorrected. MS spectra were obtained on a mass spectrometer. HRMS was determined using waters LCT premier XETOF ARE-047 apparatus. The chiral chromatographic separation was performed by using Chiral pak AD-H (250 x 4.6mm 5µm) and the mobile phase used was a mixture of ethanol, methanol and diethylamine in a ratio 800:200:1. The flow rate was 0.5 mL/min and the wavelength selected for the quantization was 254 nm.

The ion exchange resin i.e. Indion 860 was supplied by the manufacturer Ion exchange India Pvt. Ltd., India. It is a styrene divinyl benzene copolymer and appears in off white to brown opaque beads. Tertiary amine is the characteristic functional group and was supplied as free base. It can be operated at a pH range of 0 to 14 and it is resistant to both oxidizing and reducing agents.

**General procedure for the preparation of compound 3a-3r**

To a solution of $\beta$-keto ester or diketone 2 (2.2 mmol) and aldehyde 1 (1.0 mmol) in ethanol (10 ml) was added Indion 860 resin (20% w/w) and the mixture was stirred at 80 °C for 15 h. After completion of the reaction indicated by TLC the mixture was cooled to room temperature. The resin was separated by filtration and the filtrate was concentrated under low vacuum to give the crude product. The crude product was purified by recrystallization from ethanol (or by flash column chromatography on silica gel with hexanes/ethyl acetate for liquid product) to give the desired product 3.

**Diethyl 4'-bromo-5-methyl-3-oxo-1,2,3,4-tetrahydro-[1,1'-biphenyl]-2,6-dicarboxylate (3a)**
White solid; mp 150-151°C; $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 7.48 (d, $J = 8.0$ Hz, 2H), 7.27 (d, $J = 8.0$ Hz, 2H), 4.97 (s, OH), 3.97-3.79 (m, 6H), 3.29 (d, $J = 8.0$ Hz, 1H), 2.92 (d, $J = 16.0$ Hz, 1H), 2.34 (d, $J = 16.0$ Hz, 1H), 0.96 (s, 3H), 0.88 (t, $J = 8.0$ Hz, 3H), 0.87 (t, $J = 8.0$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 200.7, 173.5, 167.4, 137.3, 131.7, 129.7, 121.6, 72.9, 62.2, 61.1, 60.9, 56.7, 52.6, 44.5, 28.5, 13.9, 13.6; IR (KBr): 3433, 1736, 1598, 1364, 1174, 775 cm$^{-1}$; HRMS (ESI): calcd for C$_{19}$H$_{24}$O$_6$Br (M+H)$^+$ 427.0756, found 427.0736; MS (ESI): m/z ([M+H]$^+$): 427.1

**Diethyl 4-hydroxy-4-methyl-2-(4-nitrophenyl)-6-oxocyclohexane-1,3-dicarboxylate (3b)**

Light brown solid; mp 159-161 °C; $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 8.15 (d, $J = 8.0$ Hz, 2H), 7.62 (d, $J = 8.0$ Hz, 2H), 5.12 (s, OH), 4.06 (t, $J = 12.0$ Hz, 1H), 3.98 (d, $J = 11.0$ Hz, 1H), 3.85 (m, 4H), 3.42 (d, $J = 12.0$ Hz, 1H), 2.97 (d, $J = 13.6$ Hz, 1H), 2.38 (d, $J = 13.6$ Hz, 1H), 1.27 (s, 3H), 0.96 (t, $J = 8.0$ Hz, 3H), 0.87 (t, $J = 8.0$ Hz, 3H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz): $\delta$ 202.7, 170.1, 167.9, 148.0, 146.5, 129.9, 123.3, 72.7, 61.1, 60.2, 59.7, 55.7, 54.2, 43.9, 28.1, 13.8, 13.7; IR (KBr): 3405, 1732, 1598, 1352, 1177, 775 cm$^{-1}$; HRMS (ESI): calcd for C$_{19}$H$_{24}$NO$_8$ (M+H)$^+$ 394.1502, found 394.1508; MS (ESI): m/z ([M+H]$^+$): 394.2

**Diethyl 2-(4-cyanophenyl)-4-hydroxy-4-methyl-6-oxocyclohexane-1,3-dicarboxylate (3c)**
White solid; mp 176-177 °C; ¹H NMR (CDCl₃, 400 MHz): δ 7.62 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 4.12-3.98 (m, 3H), 3.88 (q, J = 8.0 Hz, 2H), 3.62 (d, J = 12.8 Hz, 1H), 3.57 (s, OH), 3.03 (d, J = 12.0 Hz, 1H), 2.74 (d, J = 13.2 Hz, 1H), 2.52 (dd, J = 3.2 Hz, 1H), 1.35 (s, 3H), 1.07 (s, J = 8.0 Hz, 3H), 0.85 (t, J = 8.0 Hz, 3H); ¹³C NMR (DMSO- d₆, 100 MHz): δ 202.8, 170.1, 167.9, 145.8, 132.1, 129.5, 118.6, 109.9, 72.6, 61.1, 60.1, 59.7, 55.7, 54.1, 44.1, 28.1, 13.8, 13.7; IR (KBr): 3430, 1710, 1598, 1352, 774 cm⁻¹; HRMS (ESI): calcd for C₂₀H₂₅NO₆ (M+H)+ 374.1604, found 374.1618; MS (ESI): m/z ([M+H]+): 374.2.

Diethyl 4-hydroxy-4-methyl-6-oxo-2-(p-tolyl)cyclohexane-1,3-dicarboxylate (3d)

White solid; mp 131-132 °C; ¹H NMR (CDCl₃, 400 MHz) δ 7.10 (q, J = 8.0 Hz, 4H), 4.08-3.97 (m, 3H), 3.91-3.82 (m, 2H), 3.70 (bs, OH), 3.63 (d, J = 12.4 Hz, 1H), 3.01 (d, J = 12.4 Hz, 1H), 2.70 (d, J = 14.4 Hz, 1H), 2.49 (d, J = 14.4 Hz, 1H), 2.29 (s, 3H), 1.33 (s, 3H), 1.06 (t, J = 8.0 Hz, 3H), 0.82 (t, J = 8.0 Hz, 3H); ¹³C NMR (DMSO- d₆, 100 MHz): δ 203.5, 170.6, 168.2, 136.9, 135.9, 128.5, 128.2, 72.5, 62.0, 59.9, 59.4, 56.3, 54.0, 43.6, 28.2, 20.6, 13.8, 13.7; IR (KBr): 3434, 1710, 1598, 1352, 774 cm⁻¹; HRMS (ESI): calcd for C₂₀H₂₇O₆ (M+H)+ 363.1808, found 363.1819; MS (ESI): m/z ([M+H]+): 363.2.

Diethyl 2-(2-formylphenyl)-4-hydroxy-4-methyl-6-oxocyclohexane-1,3-dicarboxylate (3e)
Diethyl 2-(4-chlorophenyl)-4-hydroxy-4-methyl-6-oxocyclohexane-1,3-dicarboxylate (3f)

White solid; mp 180-182 °C; $^1$H NMR (DMSO-$d_6$, 400 MHz): $\delta$ 10.4 (s, 1H), 7.39 (d, $J = 8.0$ Hz, 1H), 7.26 (m, 2H), 7.01 (d, $J = 8.0$ Hz, 1H), 5.97 (d, $J = 5.2$ Hz, 1H), 5.46 (d, $J = 5.2$ Hz, 1H), 4.94 (s, OH), 4.42 (d, $J = 11.6$ Hz, 1H), 4.18 (q, $J = 8.0$ Hz, 2H) 3.97 (q, $J = 8.0$ Hz, 2H), 3.01 (d, $J = 11.6$ Hz, 1H), 2.62 (d, $J = 15.2$ Hz, 1H), 2.44 (d, $J = 15.2$ Hz, 1H), 1.24 (t, $J = 8.0$ Hz, 6H), 1.03 (t, $J = 8.0$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 206.2, 188.0, 171.7, 170.3, 144.2, 143.0, 128.7, 127.8, 125.6, 123.9, 78.0, 72.5, 68.7, 60.8, 60.0, 55.8, 28.1, 22.5, 14.2, 13.8; IR (KBr): 3433, 1710, 1694, 1598, 1362, 775 cm$^{-1}$; HRMS (ESI): calcd for C$_{20}$H$_{25}$O$_7$ (M+H)$^+$ 377.1600, found 377.1611; MS (ESI): m/z ([M+H]$^+$): 377.2.

Diethyl 2-(1,1'-biphenyl)-4-hydroxy-4-methyl-6-oxocyclohexane-1,3-dicarboxylate (3g)

White solid; mp 154-156 °C; $^1$H NMR (DMSO-$d_6$, 400 MHz): $\delta$ 7.38-7.31 (m, 4H), 4.97 (s, OH, 1H), 3.97-3.79 (m, 6H), 3.31 (d, $J = 8.0$ Hz, 1H), 2.93 (d, $J = 11.2$ Hz, 1H), 2.35 (d, $J = 11.2$ Hz, 1H), 1.24 (s, 3H), 0.96 (t, $J = 8.0$ Hz, 3H), 0.87 (t, $J = 8.0$ Hz, 3H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz): $\delta$ 203.1, 170.4, 168.1, 139.0, 131.5, 130.2, 128.0, 72.5, 61.6, 60.0, 59.6, 56.0, 54.1, 43.5, 28.2, 13.8, 13.7; IR (KBr): 3480, 2831, 1738, 1597, 1365, 1174, 1016, 776 cm$^{-1}$; HRMS (ESI): calcd for C$_{19}$H$_{24}$O$_6$Cl (M+H)$^+$ 383.1261, found 383.1266; MS (ESI): m/z ([M+H]$^+$): 383.1.
Diethyl 2-(furan-2-yl)-4-hydroxy-4-methyl-6-oxocyclohexane-1,3-dicarboxylate (3h)

Light yellow liquid; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.35 (d, $J = 14.0$ Hz, 1H), 6.30 (d, $J = 14.0$ Hz, 1H), 6.06 (d, $J = 12.4$ Hz, 1H), 5.98 (s, 1H), 4.21 (q, $J = 8.0$ Hz, 4H), 4.01 (t, $J = 8.0$ Hz, 1H), 3.86-3.81 (m, 1H), 3.68-3.62 (m, 1H), 2.83 (dd, $J = 4.8$ Hz, 1H), 2.69-2.59 (m, 1H), 2.02 (s, 3H), 1.25 (t, $J = 8.0$ Hz, 3H), 1.11 (t, $J = 8.0$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 206.6, 176.6, 170.5, 155.1, 141.7, 110.1, 106.0, 61.4, 61.2, 60.2, 56.6, 51.9, 51.0, 22.9, 22.0, 14.0, 13.9; IR (KBr): 2957, 1733, 1672, 1215, 758 cm$^{-1}$; HRMS (ESI): calcd for C$_{17}$H$_{23}$O$_7$ (M+H)$^+$ 339.1444, found 339.1447; MS (ESI): m/z ([M+H]$^+$): 321.1.

Diethyl 2-ethyl-4-hydroxy-4-methyl-6-oxocyclohexane-1,3-dicarboxylate (3i)
Diethyl 2-cyclopentyl-4-hydroxy-4-methyl-6-oxocyclohexane-1,3-dicarboxylate (3j)

Light yellow liquid; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 5.97 (s, OH), 4.21 (q, $J = 8.0$ Hz, 4H), 3.30 (t, $J = 8.0$ Hz, 1H), 2.63 (dd, $J = 5.2$ Hz, 1H), 2.34-2.28 (m, 1H), 1.99 (t, $J = 8.0$ Hz, 1H), 1.64-1.58 (m, 1H), 1.34-1.25 (m, 9H), 0.80-0.72 (m, 1H), 0.55-0.50 (m, 2H), 0.22-0.13 (m, 1H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz): $\delta$ 196.9, 171.7, 156.6, 60.7, 52.8, 50.4, 42.7, 41.6, 41.0, 22.6, 21.8, 15.0, 14.0, 4.3, 3.4, 3.0; IR (KBr): 3434, 2831, 1710, 1352, 1136, 774 cm$^{-1}$; HRMS (ESI): calcd for C$_{16}$H$_{25}$O$_6$ (M+H)$^+$ 313.1651, found 313.1650; MS (ESI): m/z ([M+H]$^+$): 313.1.

Diethyl 4-hydroxy-4-methyl-6-oxo-2-(pentan-3-yl)cyclohexane-1,3-dicarboxylate (3k)

Light yellow liquid; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 5.96 (s, OH), 4.21 (p, $J = 8.0$ Hz, 4H), 3.26 (d, $J = 11.6$ Hz, 1H), 3.13 (d, $J = 11.6$ Hz, 1H), 2.61 (q, $J = 8.0$ Hz, 1H), 2.40 (q, $J = 8.0$ Hz, 1H), 2.18-2.12 (m, 1H), 1.47 (q, $J = 8.0$ Hz, 2H), 1.38 (s, 3H), 1.17 (t, $J = 8.0$ Hz, 3H), 0.96 (t, $J = 8.0$ Hz, 3H), 0.82 (t, $J = 8.0$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 197.9, 170.8, 155.7, 60.9, 60.1, 52.2, 50.4, 39.6, 38.8, 26.2, 22.6, 20.7, 13.9, 13.9, 10.7; IR (KBr): 3391, 3019, 1728, 1664, 1215, 758 cm$^{-1}$; HRMS (ESI): calcd for C$_{15}$H$_{25}$O$_6$ (M+H)$^+$ 301.1651, found 301.1664; MS (ESI): m/z ([M+H]$^+$): 301.2.
Dimethyl 2-(4-bromophenyl)-4-hydroxy-4-methyl-6-oxocyclohexane-1,3-dicarboxylate (3l)

![Chemical Structure](image1)

Colorless liquid; $^1$H NMR (CDCl$_3$, 400 MHz) δ 6.01 (s, OH, 1H), 4.22 (q, $J = 8.0$ Hz, 4H), 3.25 (d, $J = 11.6$ Hz, 1H), 3.13 (d, $J = 11.6$ Hz, 1H), 2.58 (q, $J = 8.0$ Hz, 1H), 2.36 (q, $J = 8.0$ Hz, 1H), 2.22-2.16 (m, 1H), 1.48-1.34 (m, 5H), 1.26 (s, 3H), 1.05 (t, $J = 8.0$ Hz, 3H), 0.87 (t, $J = 8.0$ Hz, 3H), 0.78 (m, 6H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 201.9, 170.8, 155.7, 60.9, 60.1, 52.2, 50.4, 39.6, 38.8, 36.0, 23.3, 20.6, 19.7, 13.9 (2), 11.7; IR (KBr): 2926, 1717, 1215, 759 cm$^{-1}$; MS (ESI): m/z ([M+H]$^+$): 343.1.

Dimethyl 2-(4-cyanophenyl)-4-hydroxy-4-methyl-6-oxocyclohexane-1,3-dicarboxylate (3m)

![Chemical Structure](image2)

White solid; mp 191-193 °C; $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 7.50 (d, $J = 8.0$ Hz, 2H), 7.26 (d, $J = 8.0$ Hz, 2H), 5.03 (s, OH), 3.99 (d, $J = 12.4$ Hz, 1H), 3.86 (t, $J = 12.4$ Hz, 1H), 3.44 (s, 3H), 3.42 (d, $J = 12.4$ Hz, 1H), 3.36 (s, 3H), 2.94 (d, $J = 13.6$ Hz, 1H), 2.35 (d, $J = 13.6$ Hz, 1H), 1.23 (s, 3H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz): δ 203.1, 170.8, 168.6, 139.7, 131.1, 130.3, 120.1, 72.6, 62.5, 56.1, 54.0, 51.5, 51.0, 43.4, 28.2; IR (KBr): 3506, 1736, 1598, 1364, 1161, 775 cm$^{-1}$; HRMS (ESI): calcd for C$_{17}$H$_{20}$O$_6$Br (M+H)$^+$ 399.0443, found 399.0440; MS (ESI): m/z ([M+H]$^+$): 399.1
White solid; mp 186-187 °C; $^1$H NMR (DMSO-$d_6$, 400 MHz): $\delta$ 7.80 (d, $J = 8.0$ Hz, 2H), 7.51 (d, $J = 8.0$ Hz, 2H), 5.12 (s, OH), 4.07 (d, $J = 12.0$ Hz, 1H), 3.96 (t, $J = 12.0$ Hz, 1H), 3.43 (s, 6H), 3.39 (d, $J = 12.0$ Hz, 1H), 2.95 (d, $J = 13.6$ Hz, 1H), 2.37 (d, $J = 13.6$ Hz, 1H), 1.24 (s, 3H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz): $\delta$ 202.8, 170.6, 168.5, 146.0, 132.2, 129.3, 118.6, 110.0, 72.7, 61.1, 55.8, 54.1, 51.5, 51.1, 44.0, 28.2; IR (KBr): 3427, 1712, 1597, 1362, 775 cm$^{-1}$; HRMS (ESI): calcd for C$_{18}$H$_{20}$NO$_6$ (M+H)$^+$ 346.1291, found 346.1292; MS (ESI): m/z ([M+H]$^+$): 346.2.

1,1'-(2-(4-bromophenyl)-4-hydroxy-4-methyl-6-oxocyclohexane-1,3-diyldiethanone (3n)

White solid; mp 167-169 °C; $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 7.46 (d, $J = 8.0$ Hz, 2H), 7.30 (d, $J = 8.0$ Hz, 2H), 5.25 (s, OH), 4.10 (d, $J = 12.0$ Hz, 1H), 3.96 (t, $J = 12.0$ Hz, 1H), 3.29 (d, $J = 12.0$ Hz, 1H), 2.92 (d, $J = 13.6$ Hz, 1H), 2.34 (d, $J = 13.6$ Hz, 1H), 1.92 (s, 6H), 1.18 (s, 3H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz): $\delta$ 209.2, 205.8, 204.8, 139.5, 131.3, 130.5, 120.1, 72.5, 67.2, 63.6, 55.2, 42.8, 30.9, 30.5, 28.0; IR (KBr): 3409, 2832, 1696, 1590, 1363, 776 cm$^{-1}$; HRMS (ESI): calcd for C$_{17}$H$_{20}$O$_4$Br (M+H)$^+$ 367.0545, found 367.0554; MS (ESI): m/z ([M+H]$^+$): 367.1

4-(2,6-diacetyl-3-hydroxy-3-methyl-5-oxocyclohexyl)benzonitrile (3o)
Light yellow solid; mp 144-146 °C; $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 7.76 (d, $J = 8.0$ Hz, 2H), 7.56 (d, $J = 8.0$ Hz, 2H), 5.30 (s, OH, 1H), 4.21 (d, $J = 12.0$ Hz, 1H), 4.09-4.02 (m, 1H), 3.36 (d, $J = 12.0$ Hz, 1H), 2.94 (d, $J = 13.6$ Hz, 1H), 2.37 (d, $J = 13.6$ Hz, 1H), 1.94 (s, 6H), 1.21 (s, 3H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz): $\delta$ 208.7, 205.5, 204.7, 145.9, 132.3, 129.5, 118.5, 109.9, 72.6, 66.8, 63.4, 55.2, 43.3, 31.1, 30.7, 28.0; IR (KBr): 3409, 2831, 1702, 1594, 1362, 775 cm$^{-1}$; HRMS (ESI): calcd for C$_{18}$H$_{20}$NO$_4$ (M+H)$^+$ 314.1392, found 314.1385; MS (ESI): m/z ([M+H$^+$]): 314.

4-(2,6-dibenzoyl-3-hydroxy-3-methyl-5-oxocyclohexyl)benzonitrile (3p)

White solid; mp 294-295 °C; $^1$H NMR (DMSO-$d_6$, 400 MHz): $\delta$ 7.78 (d, $J = 8.0$ Hz, 2H), 7.69 (d, $J = 8.0$ Hz, 2H), 7.60 (t, $J = 8.0$ Hz, 2H), 7.55 (d, $J = 8.0$ Hz, 4H), 7.48 (t, $J = 8.0$ Hz, 2H), 7.40 (t, $J = 8.0$ Hz, 1H), 7.28 (t, $J = 8.0$ Hz, 1H), 6.0 (s, OH, 1H), 5.56 (d, $J = 11.6$ Hz, 1H), 4.40 (t, $J = 11.6$ Hz, 1H), 4.03 (d, $J = 11.6$ Hz, 1H), 3.79 (d, $J = 13.2$ Hz, 1H), 3.24 (d, $J = 13.2$ Hz, 1H), 1.39 (s, 3H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz): $\delta$ 207.3, 205.3, 196.5, 146.2, 144.5, 136.9, 133.5, 132.2, 129.4, 128.7, 128.2, 127.8, 127.2, 124.8, 118.4, 109.7, 77.1, 63.4, 61.3, 54.7, 44.5, 31.4; IR (KBr): 3412, 2831, 1709, 1587, 1363, 775 cm$^{-1}$; HRMS (ESI): calcd for C$_{28}$H$_{24}$NO$_4$ (M+H)$^+$ 438.1705, found 438.1699; MS (ESI): m/z ([M+H$^+$]): 438.2.
(4-hydroxy-4-methyl-2-(4-nitrophenyl)-6-oxocyclohexane-1,3-diy)bis(phenylmethanone)
(3q)

White solid; mp 253-255 °C; \textsuperscript{1}H NMR (DMSO-\textit{d}_{6}, 400 MHz): \(\delta\), 8.08 (d, \(J = 8.0\) Hz, 2H), 7.79 (d, \(J = 8.0\) Hz, 2H), 7.69 (d, \(J = 8.0\) Hz, 2H), 7.61 (d, \(J = 8.0\) Hz, 1H), 7.57 (t, \(J = 8.0\) Hz, 2H), 7.48 (t, \(J = 8.0\) Hz, 2H), 7.41 (t, \(J = 8.0\) Hz, 2H), 7.39 (t, \(J = 8.0\) Hz, 1H), 7.36 (s, 1H), 7.41 (t, \(J = 8.0\) Hz, 1H), 7.35 (s, 1H); \textsuperscript{13}C NMR (DMSO-\textit{d}_{6}, 100 MHz): \(\delta\) 207.2, 205.2, 196.5, 148.4, 146.3, 144.5, 136.9, 133.5, 129.7, 128.7, 128.2, 127.8, 127.2, 124.8, 123.4, 77.1, 63.5, 61.3, 54.7, 44.2, 31.4; IR (KBr): 3362, 2832, 1598, 1363, 775 cm\textsuperscript{-1}; HRMS (ESI): calcd for C_{27}H_{24}NO_{6} (M+H\textsuperscript{+}) 458.1604, found 458.1617; MS (ESI): m/z ([M+H\textsuperscript{+}]): 458.3.

4-(2,6-bis(ethoxycarbonyl)-3-hydroxy-3-methyl-5-oxocyclohexyl)benzoic acid (3r)

White colored solid; mp 174-176 °C; \textsuperscript{1}H NMR (DMSO-\textit{d}_{6}, 400 MHz) \(\delta\) 12.9 (bs, COOH), 7.83 (d, \(J = 8.0\) Hz, 2H), 7.42 (d, \(J = 8.0\) Hz, 2H), 5.02 (s, OH), 4.16-3.77 (m, 6H), 2.98 (d, \(J = 13.6\) Hz, 1H), 2.42 (d, \(J = 11.6\) Hz, 1H), 2.33 (d, \(J = 13.6\) Hz, 1H), 1.25 (s, 3H), 0.94 (t, \(J = 8.0\) Hz, 3H), 0.83 (t, \(J = 8.0\) Hz, 3H); HRMS (ESI): calcd for C_{20}H_{25}O_{8} (M+H\textsuperscript{+}) 393.1549, found 393.1530.
Preparation of (Z)-ethyl 1-(4-cyanophenyl)-3-methyl-11-oxo-2,10,11,11a-tetrahydro-1H-dibenzo[b,e][1,4]diazepine-2-carboxylate (5)

To a solution of β-keto ester 2a (2.2 mmol) and aldehyde 1c (1.0 mmol) in ethanol (10 ml) was added Indion 860 resin (20%w/w) and the mixture was stirred at 80 °C for 15 h to ensure the completion of the reaction, which was monitored using TLC. The reaction mass was cooled to room temperature and to this was added 1,2-phenylene diamine 4 (1.0 mmol) followed by P₂O₅ (0.1 mmol). Again the reaction mass was heated to reflux for 12 h. After completion of the reaction confirmed by TLC the resin was filtered and the filtrate was concentrated under vacuum to give the crude product. The crude product was purified by recrystallization from ethanol to give the desired product 5 as a light green solid; mp 238-240 °C; ¹H NMR (CDCl₃, 400 MHz): δ 8.71 (d, J = 8.0 Hz, 1H), 8.69 (s, NH), 5.54 (q, J = 8.0 Hz, 4H), 7.33 (t, J = 8.0 Hz, 1H), 7.21-7.15 (m, 2H), 5.89 (s, 1H), 4.80 (t, J = 8.0 Hz, 1H), 4.08 (q, J = 8.0 Hz, 2H), 3.72 (dd, J = 8.0 Hz, 1H), 3.36 (dd, J = 8.0 Hz, 1H), 2.46 (s, 3H), 1.16 (t, J = 8.0 Hz, 3H); ¹³C NMR (DMSO-d₆, 100 MHz): δ 172.0, 157.6, 149.6, 148.4, 142.6, 131.8, 131.6, 128.5, 127.6, 125.9, 120.5, 119.0, 116.4, 112.3, 110.0, 108.3, 86.1, 59.6, 35.5, 21.1, 13.9; IR (KBr): 3428, 2832, 1595, 1362, 775 cm⁻¹; HRMS (ESI): calcd for C₂₄H₂₂N₃O₃ (M+H)⁺ 400.1661, found 400.1665; MS (ESI): m/z ([M+H]⁺): 400.2

Preparation of compound (E)-Diethyl 2-(4-(3-ethoxy-3-oxoprop-1-en-1-yl)phenyl)-4-hydroxy-4-methyl-6-oxocyclohexane-1,3-dicarboxylate (7)
To a solution of β-keto ester 2a (2.2 mmol) and aldehyde 1c (1.0 mmol) in ethanol (10 ml) was added Indion 860 resin (20%w/w) and the mixture was stirred at 80 °C for 15 h to ensure the completion of the reaction, which was monitored using TLC. The reaction mass was cooled to cool room temperature and to this was added Et₃N (3.0 mmol) and CuI (0.02 mmol) followed by (PPh₃)₂PdCl₂ (0.02 mmol). The reaction mass was stirred at room temp for 30 min. To this was added ethyl acrylate 6 (1.1 mmol) and the mixture was stirred at 80 °C for 4 h. After completion of the reaction, the resin and other catalyst were separated by filtration and the filtrate was concentrated under low vacuum to give the crude product. The crude product was purified by recrystallization from ethanol to afford pure product 7 as a light brown solid; mp 158-160 °C; ¹H NMR (CDCl₃, 400 MHz): δ 7.56 (d, J = 16.0 Hz, 1H), 7.41 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 6.34 (d, J = 16.0 Hz, 1H), 4.19 (q, J = 8.0 Hz, 2H), 4.00-3.90 (m, 3H), 3.83-3.77 (m, 2H), 3.58 (d, J = 12.0 Hz, 2H), 2.96 (d, J = 12.0 Hz, 1H), 2.66 (d, J = 14.0 Hz, 1H), 2.43 (d, J = 14.0 Hz, 1H), 1.28 (s, 3H), 1.26 (t, J = 8.0 Hz, 3H), 0.98 (t, J = 8.0 Hz, 3H), 0.73 (t, J = 8.0 Hz, 3H); ¹³C NMR (DMSO-d₆, 100 MHz): δ 203.2, 170.4, 168.1, 166.1, 143.9, 142.5, 132.7, 131.5, 131.4, 128.7, 128.1, 117.9, 72.6, 61.5, 60.0, 59.9, 59.5, 56.0, 54.1, 43.9, 28.2, 14.1, 13.8, 13.7; IR (KBr): 3496, 2982, 1708, 1640, 1375, 1179, 824 cm⁻¹; HRMS (ESI): calcd for C₂₄H₃₁O₈ (M+H)+ 447.2019, found 447.2011; MS (ESI): m/z ([M+H]+): 447.2.

**General procedure for the preparation of compound 9a-9e**

To a solution of β-keto ester 2 (2.2 mmol) and aldehyde 1 (1.0 mmol) in ethanol (10 ml) was added Indion 860 resin (20%w/w) and the mixture was stirred at 80 °C for 15 h to ensure the completion of the reaction, which was monitored using TLC. The reaction mass was cooled to room temperature and hydrazine hydrate 8 (1.0 mmol) was added. The mixture was stirred for another 12 h at 80 °C. After completion of the reaction (confirmed by TLC) the resin was
separated by filtration. The filtrate was concentrated under low vacuum to give the crude product that was purified by recrystallization from ethanol to afford the pure product 9a-9d.

**Ethyl 4-(4-bromophenyl)-6-hydroxy-6-methyl-3-oxo-2,3,4,5,6,7-hexahydro-1H-indazole-5-carboxylate (9a)**

![Chemical Structure of 9a](image)

White solid; mp 303-304 °C; \(^1H\) NMR (DMSO-\(d_6\), 400 MHz): \(\delta\) 11.1 (bs, NH), 9.05 (bs, NH), 7.39 (d, \(J = 8.4\) Hz, 2H), 7.04 (d, \(J = 8.4\) Hz, 2H), 4.50 (s, OH), 4.03 (d, \(J = 10.4\) Hz, 1H), 3.96-3.88 (m, 2H), 2.76 (d, \(J = 15.6\) Hz, 1H), 2.56-2.50 (m, 2H), 1.23 (s, 3H), 0.99 (t, \(J = 8.4\) Hz, 3H); \(^13C\) NMR (DMSO-\(d_6\), 100 MHz): \(\delta\) 172.0, 158.0, 142.4, 138.9, 130.6, 130.5, 119.0, 99.0, 69.9, 59.5, 59.3, 38.8, 38.3, 36.5, 28.3, 14.0; IR (KBr): 3280, 1741, 1516, 1260, 806 cm\(^{-1}\); HRMS (ESI): calcd for C\(_{17}H_{20}N_2O_4Br\) (M+H\(^+\)) 395.0606, found 395.0598; MS (ESI): m/z ([M+H]\(^+\)): 395.0.

**Ethyl 6-hydroxy-6-methyl-4-(4-nitrophenyl)-3-oxo-3,3a,4,5,6,7-hexahydro-2H-indazole-5-carboxylate (9b)**

![Chemical Structure of 9b](image)

White solid; mp 293-294 °C; \(^1H\) NMR (DMSO-\(d_6\), 400 MHz): \(\delta\) 10.9 (bs, NH), 9.4 (bs, NH), 8.11 (d, \(J = 8.0\) Hz, 2H), 7.37 (d, \(J = 8.0\) Hz, 2H), 4.60 (s, OH), 4.21 (d, \(J = 10.8\) Hz, 1H), 3.96-3.84 (m, 2H), 2.82 (d, \(J = 16.0\) Hz, 1H), 2.63 (d, \(J = 10.8\) Hz, 1H), 2.55 (d, \(J = 16.0\) Hz, 1H), 1.25 (s, 3H), 0.97 (t, \(J = 8.0\) Hz, 3H); \(^13C\) NMR (DMSO-\(d_6\), 100 MHz): \(\delta\) 171.6, 157.9, 151.5,
146.0, 138.9, 129.6, 123.0, 98.6, 69.9, 59.6, 58.8, 36.5, 28.2, 14.0; IR (KBr): 3501, 1597, 1347, 1180, 775 cm⁻¹; HRMS (ESI): calcd for C₁₇H₂₀N₃O₆ (M+H)⁺ 362.1352, found 362.1356; MS (ESI): m/z ([M+H]+): 362.2.

**Ethyl 4-(4-cyanophenyl)-6-hydroxy-6-methyl-3-oxo-2,3,4,5,6,7-hexahydro-1H-indazole-5-carboxylate (9c)**

![Chemical Structure](image)

White solid; mp 292-293 °C; ¹H NMR (DMSO-d₆, 400 MHz): δ 11.2 (bs, NH), 9.1 (bs, NH), 7.69 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 4.56 (s, OH), 4.13 (d, J = 10.8 Hz, 1H), 3.94-3.87 (m, 2H), 2.79 (d, J = 16.0 Hz, 1H), 2.60 (d, J = 10.8 Hz, 1H), 2.58 (d, J = 16.0 Hz, 1H), 1.24 (s, 3H), 0.96 (t, J = 8.0 Hz, 3H); ¹³C NMR (DMSO-d₆, 100 MHz): δ 171.7, 157.8, 149.1, 138.9, 131.7, 129.4, 119.0, 108.8, 98.6, 69.9, 59.5, 58.8, 36.5, 28.2, 13.9; IR (KBr): 3440, 1598, 1363, 775 cm⁻¹; HRMS (ESI): calcd for C₁₈H₂₀N₄O₄ (M+H)+ 342.1454, found 342.1448; MS (ESI): m/z ([M+H]+): 342.2.

**Ethyl 4-(4-cyanophenyl)-6-hydroxy-6-methyl-3-oxo-2,3,4,5,6,7-hexahydro-1H-indazole-5-carboxylate (9d)**

![Chemical Structure](image)

White solid; mp 244-245 °C; ¹H NMR (DMSO-d₆, 400 MHz): δ 10.9 (bs, NH), 7.71 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 8.0 Hz, 2H), 7.36 (p, J = 8.0 Hz, 4H), 7.14 (t, J = 8.0 Hz, 1H), 4.84 (s, OH), 4.09 (d, J = 10.8 Hz, 1H), 3.94 (q, J = 8.0 Hz, 2H), 3.42 (d, J = 8.0 Hz, 1H), 2.94 (d, J = 16.8 Hz, 1H), 2.73 (d, J = 10.8 Hz, 1H), 1.29 (s, 3H), 0.99 (t, J = 8.0 Hz, 3H); ¹³C NMR...
(DMSO-$d_6$, 100 MHz): $\delta$ 171.4, 161.5, 149.9, 148.1, 137.5, 131.8, 129.5, 128.8, 124.2, 119.0, 118.0, 109.0, 103.6, 69.6, 58.4, 45.7, 37.0, 28.0, 14.0; IR (KBr): 3504, 2224, 1707, 1626, 1178, 758 cm$^{-1}$; HRMS (ESI): calcd for C$_{24}$H$_{24}$N$_3$O$_4$ (M+H)$^+$ 418.1767, found 418.1752; MS (ESI): m/z ([M+H$^+$]): 418.2

Ethyl 4-(4-cyanophenyl)-6-hydroxy-2-(2-hydroxyethyl)-6-methyl-3-oxo-2,3,4,5,6,7-hexahydro-1H-indazole-5-carboxylate (9e)

![Chemical Structure](image)

White solid; mp 259-260 °C; $^1$H NMR (DMSO-$d_6$, 400 MHz): $\delta$ 10.5 (bs, NH), 7.69 (d, $J = 8.4$ Hz, 2H), 7.28 (d, $J = 8.4$ Hz, 2H), 4.93 (bs, OH), 4.62 (bs, OH), 4.12-4.05 (m, 1H), 3.94 (p, $J = 8.4$ Hz, 2H), 3.79-3.62 (m, 2H), 3.60-3.53 (m, 2H), 2.69 (d, $J = 18.8$ Hz, 1H), 2.59 (d, $J = 11.2$ Hz, 1H), 2.53 (d, $J = 18.8$ Hz, 1H), 1.23 (s, 3H), 0.97 (t, $J = 8.4$ Hz, 3H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz): $\delta$ 171.7, 148.8, 146.0, 131.8, 129.5, 119.1, 108.9, 69.7, 59.6, 59.4, 58.7, 46.8, 37.5, 28.2, 14.0; IR (KBr): 3392, 2223, 1731, 1570, 1159, 707 cm$^{-1}$; HRMS (ESI): calcd for C$_{20}$H$_{24}$N$_3$O$_5$ (M+H)$^+$ 386.1716, found 386.1711; MS (ESI): m/z ([M+H$^+$]): 386.1

Pharmacology

PDE4B protein production and purification

PDE4B cDNA was sub-cloned into pFAST Bac HTB vector (Invitrogen) and transformed into DH10Bac (Invitrogen) competent cells. Recombinant bacmids were tested for integration by PCR analysis. Sf9 cells were transfected with bacmid using Lipofectamine 2000 (Invitrogen) according to manufacturer’s instructions. Subsequently, P3 viral titer was amplified, cells were infected and 48 h post infection cells were lysed in lysis buffer (50 mM Tris-HCl pH 8.5, 10 mM 2-Mercaptoethanol, 1 % protease inhibitor cocktail (Roche), 1 % NP40). Recombinant Histagged PDE4B protein was purified as previously described elsewhere (Wang et al., 1997). Briefly, lysate was centrifuged at 10,000 rpm for 10 min at 4°C and supernatant was collected.
Supernatant was mixed with Ni-NTA resin (GE Life Sciences) in a ratio of 4:1 (v/v) and equilibrated with binding buffer (20 mM Tris-HCl pH 8.0, 500 mM-KCl, 5 mM imidazole, 10 mM 2-mercaptoethanol and 10 % glycerol) in a ratio of 2:1 (v/v) and mixed gently on rotary shaker for 1 hour at 4°C. After incubation, lysate-Ni-NTA mixture was centrifuged at 4,500 rpm for 5 min at 4°C and the supernatant was collected as the flow-through fraction. Resin was washed twice with wash buffer (20 mM Tris-HCl pH 8.5, 1 M KCl, 10 mM 2-Mercaptoethanol and 10% glycerol). Protein was eluted sequentially twice using elution buffers (Buffer I: 20 mM Tris-HCl pH 8.5, 100 mM KCl, 250 mM imidazole, 10 mM 2-mercaptoethanol, 10% glycerol, Buffer II: 20 mM Tris-HCl pH 8.5, 100 mM KCl, 500 mM imidazole, 10 mM 2-mercaptoethanol, 10% glycerol). Eluates were collected in four fractions and analyzed by SDS-PAGE. Eluates containing PDE4B protein were pooled and stored at -80°C in 50% glycerol until further use.

**PDE4B enzymatic assay**

The inhibition of PDE4B enzyme was measured using PDElight HTS cAMP phosphodiesterase assay kit (Lonza) according to manufacturer’s recommendations. Briefly, 10 ng of PDE4B enzyme was pre-incubated either with DMSO (vehicle control) or compound for 15 min before incubation with the substrate cAMP (5 µM) for 1 h. The reaction was halted with stop solution followed by incubation with detection reagent for 10 minutes in dark. Luminescence values (RLUs) were measured by a Multilabel plate reader (Perklin Elmer 1420 Multilabel counter). The percentage of inhibition was calculated using the following formula:

\[
\text{% inhibition} = \left( \frac{RLU \text{ of vehicle control} - RLU \text{ of inhibitor}}{RLU \text{ of vehicle control}} \right) \times 100
\]

**Reference:**