Supplementary material

Expeditious synthesis, antibacterial activity evaluation and GQSAR studies of 3-bisoxindoles, 2-oxindolyl-2-hydroxyindan-1,3-diones and 2-oxindolyl-2-hydroxyacenaphthylen-1-ones

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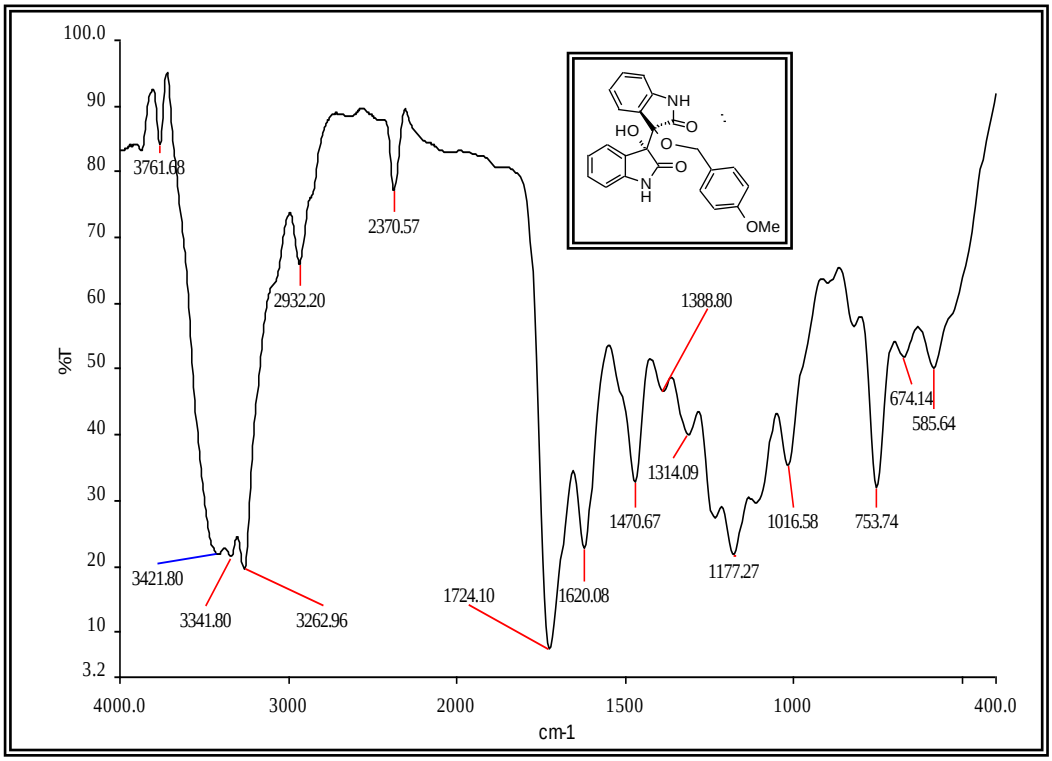

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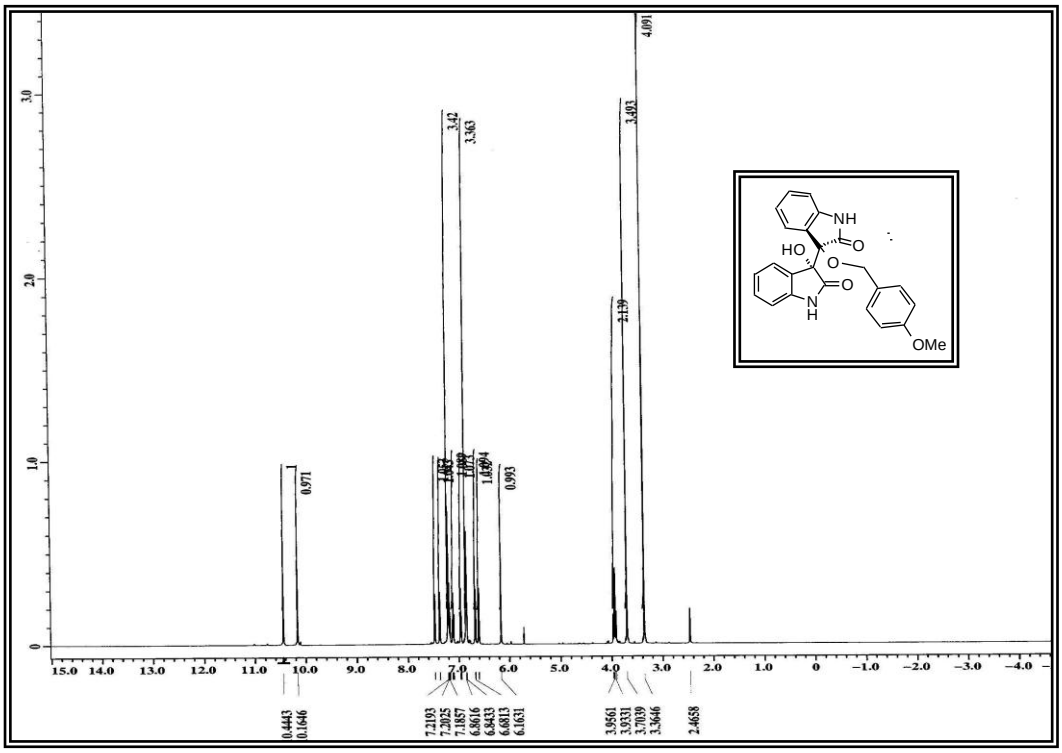

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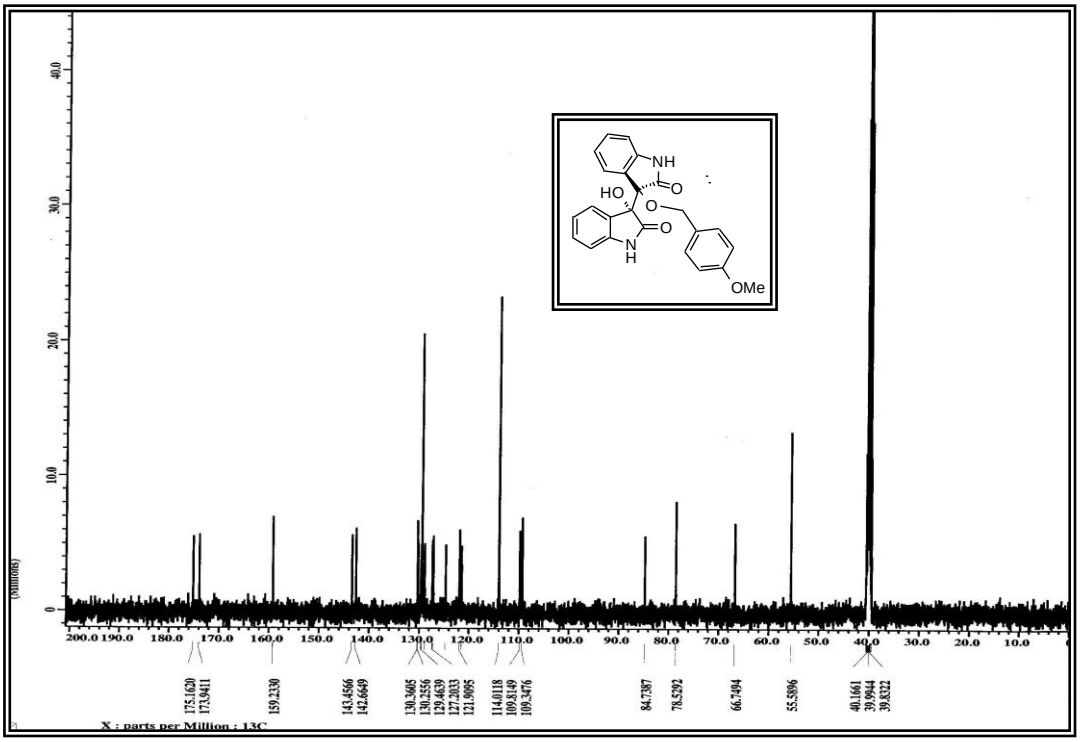

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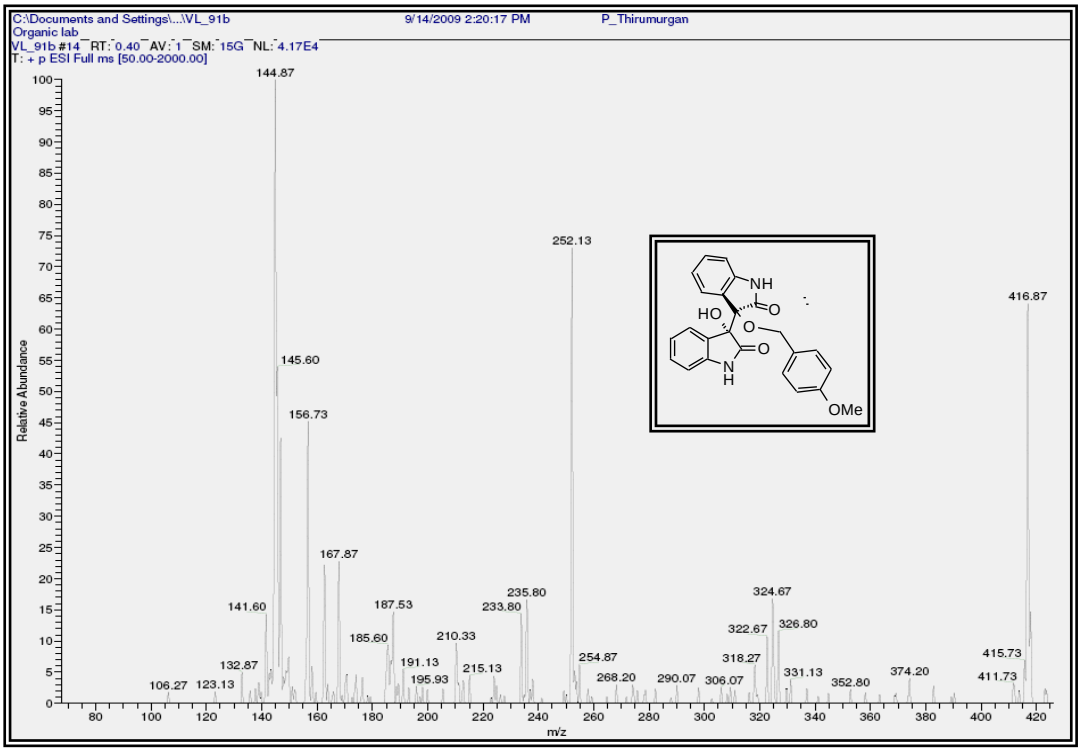

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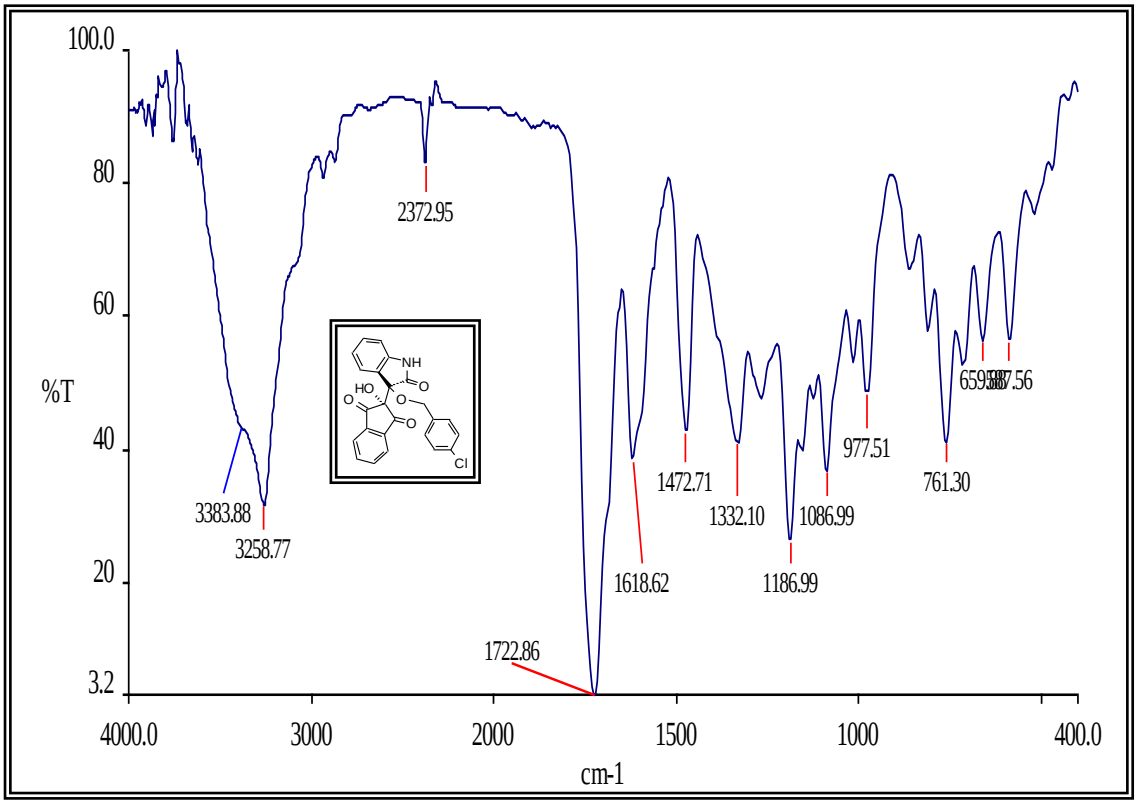
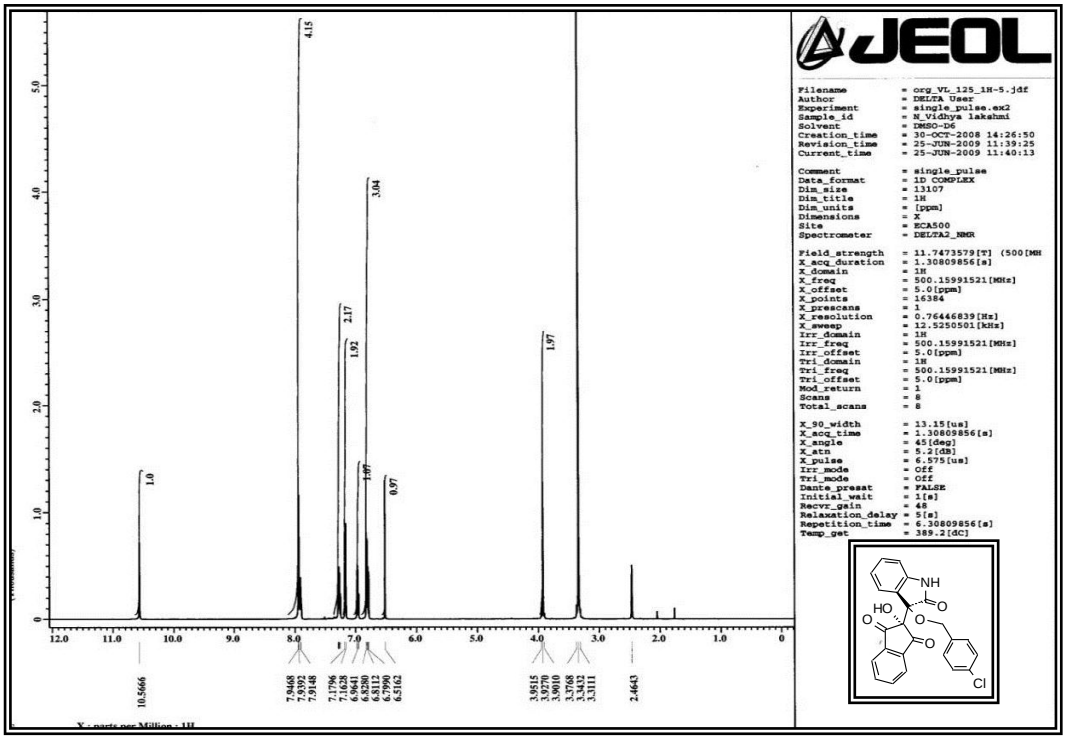


IR spectrum of compound 8d



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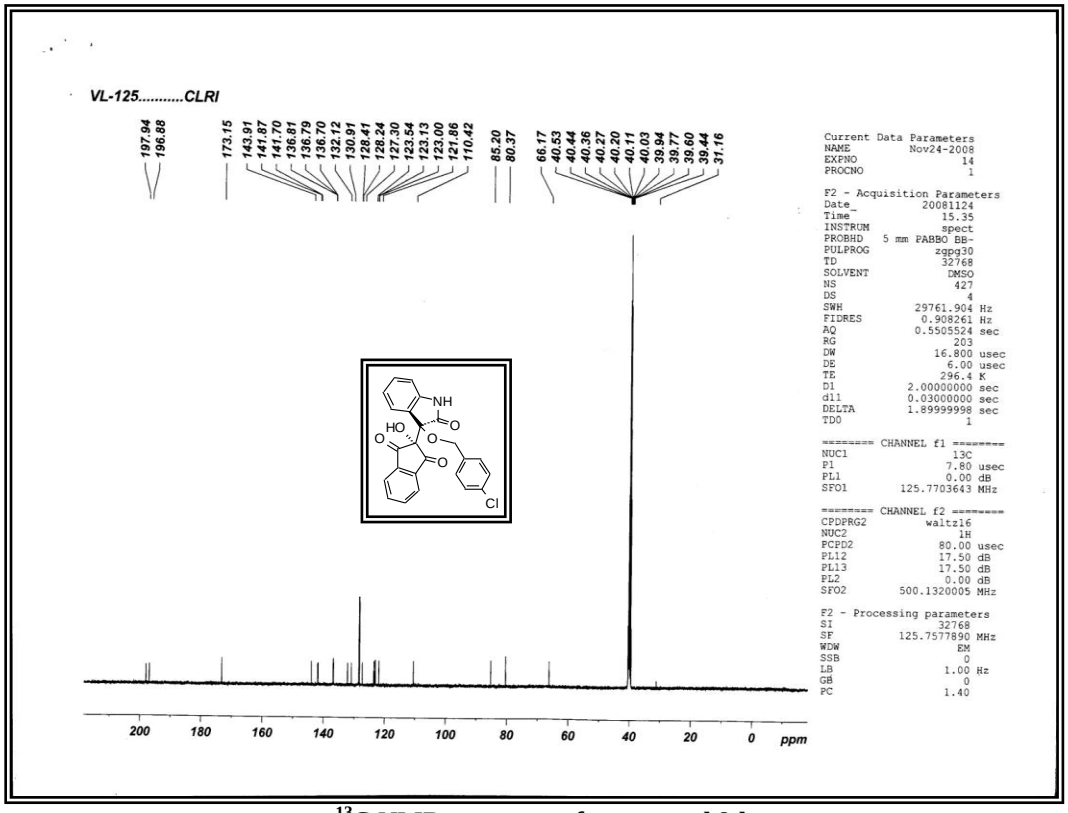

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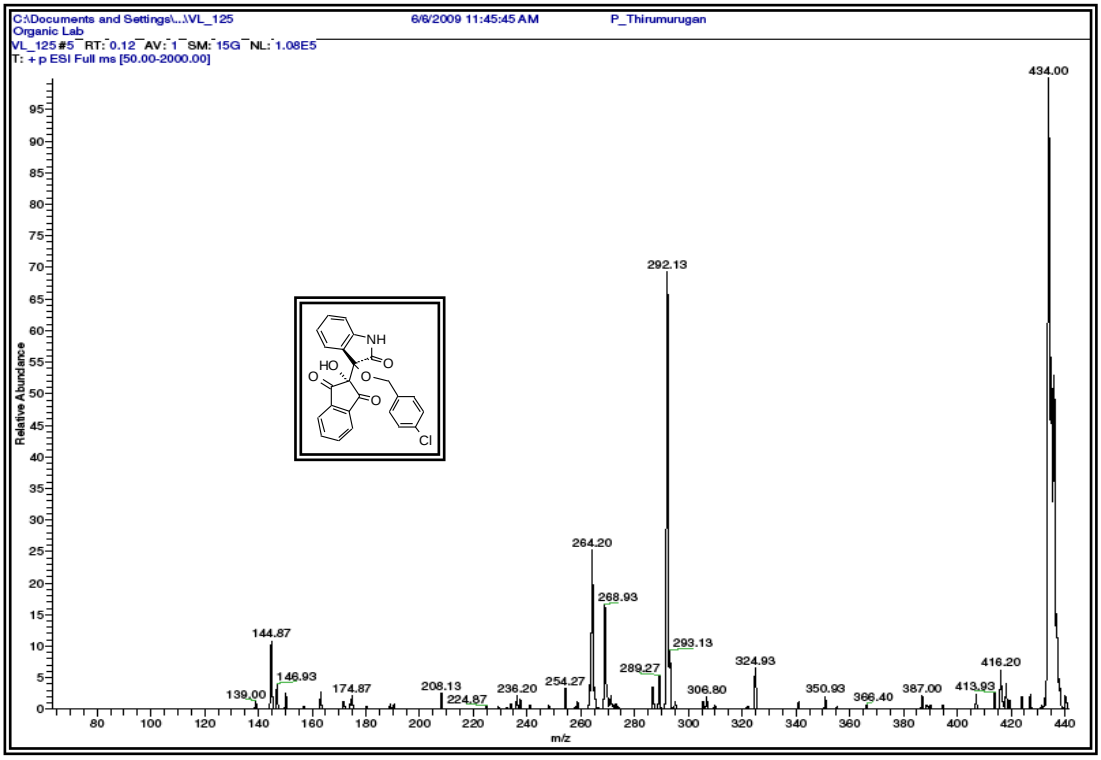

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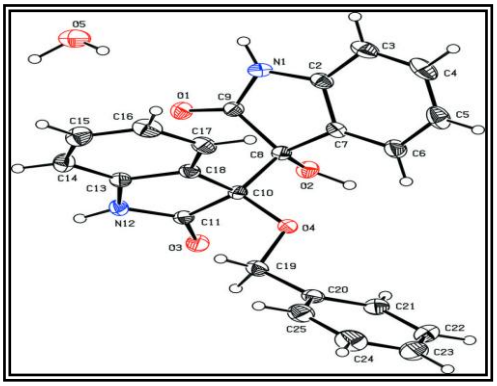

Fig. 1 ORTEP diagram of compound **6a**

The crystal has the molecular formula $C_{23}H_{18}N_2O_4 \cdot H_2O$ in which the two oxindole rings subtend a dihedral angle of 54.29 (5)°. Its molecular weight is 404.41.

Crystal data

$C_{23}H_{18}N_2O_4 \cdot H_2O$	$Z = 2$
$Mr = 404.41$	$F_{000} = 424$
Triclinic	$D_x = 1.418$ Mg m^{-3}
Hall symbol: -P 1	Mo $K\alpha$ radiation $\lambda = 0.71073$ Å
$a = 9.8243$ (3) Å	Cell parameters from 4635 reflections
$b = 9.9304$ (6) Å	$\theta = 2.1–25.0^o$
$c = 11.4460$ (5) Å	$\mu = 0.10$ mm^{-1}
$\alpha = 107.517$ (2)º	$T = 293$ K
$\beta = 114.227$ (3)º	Block, colourless
$\gamma = 93.918$ (2)º	0.28 × 0.25 × 0.20 mm
$V = 947.17$ (8) Å^3	

Data collection

Bruker Kappa APEXII area-detector diffractometer	3335 independent reflections
Radiation source: fine-focus sealed tube	3045 reflections with $I > 2\sigma(I)$
Monochromator: graphite	$R_{int} = 0.021$
$T = 293$ K	$\theta_{max} = 25.0^o$
ω and φ scans	$\theta_{min} = 2.1^o$
Absorption correction: Multi-scan (SADABS; Sheldrick, 2001)	$h = -11 \rightarrow 11$
$T_{min} = 0.972$, $T_{max} = 0.980$	$k = -11 \rightarrow 11$
16894 measured reflections	$l = -13 \rightarrow 13$

Refinement

Refinement on F^2	Hydrogen site location: inferred from neighbouring sites
Least-squares matrix: full	H atoms treated by a mixture of independent and constrained refinement
$R[F^2 > 2\sigma(F^2)] = 0.032$	$w = 1/[\sigma^2(F_o^2) + (0.038P)^2 + 0.3004P]$ where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.084$	$(\Delta/\sigma)_{max} = 0.003$
$S = 1.05$	$\Delta\rho_{max} = 0.23$ e Å^{-3}
3335 reflections	$\Delta\rho_{min} = -0.18$ e Å^{-3}
292 parameters	Extinction correction: SHELXL, $Fc^*=kFc[1+0.001xFc^2\lambda^3/\sin(2\theta)]^{-1/4}$
Primary atom site location: structure-invariant direct methods	Extinction coefficient: 0.038 (3)

Secondary atom site location: difference Fourier map

Refinement: Refinement of F^2 against ALL reflections. The weighted *R*-factor *wR* and goodness of fit *S* are based on F^2, conventional *R*-factors *R* are based on *F*, with *F* set to zero for negative F^2. The threshold expression of $F^2 > \sigma(F^2)$ is used only for calculating *R*-factors (gt) *etc*. and is not relevant to the choice of reflections for refinement. *R*-factors based on F^2 are statistically about twice as large as those based on *F*, and *R*- factors based on ALL data will be even larger.[20]

(20) P. Ramesh, S. S. Sundaresan, N. V. Lakshmi, P. T. Perumal, M. N. Ponnuswamy, *Acta Cryst.*, 2009, **E65**, o994.

Experimental Section

General

All the chemicals required for determining the biological activities were purchased from Sigma-Aldrich (St Louis, MO, USA), Himedia (Mumbai, India) and SRL (Mumbai, India) and the five bacterial strains (*S. aureus* NCIM5021, *E. coli* NCIM 2931, *P. vulgaris* NCIM 2813, *S. typhi* NCIM 2501 and *P. aeruginosa* NCIM 5029) were purchased from National Chemical Laboratory, Pune, India. VLifemds3.5 is a software package for computer aided drug discovery (VLife Sciences Technologies Pvt. Ltd., Pune, India, http://www.vlifesciences.com) and it is used for molecular modelling. IR measurements were done as KBr pellets for solids using Perkin Elmer Spectrum RXI FT-IR. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded as DMSO-d_6 solution for all compounds with TMS as an internal standard on a JEOL instrument. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), multiplet (m), and broad (br). The mass were analyzed by using a Electrospray Ionisation Method with Thermo Finnigan Mass spectrometer. Melting points were determined in capillary tubes and are uncorrected. Elemental analyses were recorded using a Thermo Finnigan FLASH EA 1112 CHN analyzer. Analytical TLC was performed on precoated aluminium sheets of silica gel G/UV-254 of 0.2 mm thickness (Merck, Germany). To facilitate the QSAR, the observed activity (Minimum Inhibitory Concentration against the three microorganisms calculated as μg/ml) was converted to –log (μM).

Antibacterial evaluation

In vitro antibacterial activity (MIC) of the oxindole derivatives were determined by microdilution broth assay method with modifications as reported by Sarker *et al*. using resazurin as an indicator. [35] Muller hinton broth was used to grow the bacterial strains to a final inoculum size of 5 × 105 CFU/mL. The compounds were dissolved in absolute ethanol to a concentration of 10 mg/mL. [36] These serially diluted solutions were added to successive wells in a 96-well microtiter plate and incubated with the organisms for 18 h at 37 °C. Growth and sterility controls were maintained during the experiment. Compounds serially diluted with ethanol were also kept in the 96-well microtiter plates (uninoculated dilution) to determine if they precipitated out during the course of the experiments. A blank array with ethanol alone and its effect on inhibition of microorganism was also studied. Ten microliters of 0.01% resazurin solution was added and incubated for 2 h. Effect of ethanol on the growth of the microorganism was also studied. The color change was assessed visually, with the highest dilution remaining blue (inhibition of growth) indicating minimum inhibitory concentration. A change in color from blue to pink shows the growth of the organism.

Modelling studies

Twenty compounds were synthesized which have the oxindole as the common template, while the functional groups at the R^1 and R^2 positions are different. The MIC (μM) data of

oxindoles listed in **Table 4** was converted to –log(μM) for developing the QSAR. Twenty of these oxindoles were sketched using the Vlife mds 3.5 software and their minimum energy conformations were determined using MMFF force field. [37] Three hundred and seventy four descriptors relating to spatial, electronic, thermodynamic, conformational, topological, information-content, quantum mechanical and structural properties of the substituent groups in the R^1 and R^2 position for all the compounds are calculated. Several references deal in detail with these descriptors. [29,38,39] The total twenty molecules were divided into training and test sets. The former consists of fifteen molecules which are used for the development of GQSAR equation and the later consisting of five molecules (compounds **6d, 6e, 6i, 8c** and **10c**) which are selected at random are used for the validation of these models. This technique is known as an external validation. The developed GQSAR is also validated by calculating several statistical parameters such as r^2, r^2 adj, q^2, F-ratio and standard error (40). This procedure is known as internal validation method. Genetic Algorithm technique (GFA) is used to develop the best GQSAR equation relating the descriptors with the activity. GFA technique is useful when one has a large pool of descriptors, but limited data, where the challenge is to select the best set of descriptors. Other researchers have also used GFA technique effectively to develop the QSAR models. [41]

Representative procedure for preparation of compounds 6a-j:

To a refluxing dry CH_2Cl_2 solution of $Rh_2(OAc)_4$ (1 mol%), benzyl alcohol **3** (0.60 mmol) and isatin **5** (0.50 mmol) under argon atmosphere 3-diazo-1,3-dihydro-indol-2-one **1** (0.60 mmol) in dry dichloromethane was added dropwise (approximately 10 ml in 60 minutes). After the addition was completed, the reaction mixture was allowed to reflux for 30-40 minutes until the disappearance of starting materials, as determined by TLC and cooled to room temperature. The solid formed in the reaction mixture was filtered, dried and recrystallized from ethanol to obtain the pure product and appropriate isolated yield is shown in **Table 1.**

Representative procedure for the synthesis of 2-oxindolyl-2-hydroxyindan-1,3-diones (8a-e)

To a refluxing dry CH_2Cl_2 solution of $Rh_2(OAc)_4$ (1 mol%), benzyl alcohol **3** (0.60 mmol) and ninhydrin **7**(0.50 mmol) under argon atmosphere 3-diazo-1,3-dihydro-indol-2-one **1** (0.60 mmol) in dry dichloromethane was added dropwise (approximately 10 ml in 60 minutes). After the addition was completed, the reaction mixture was allowed to reflux for 10-20 minutes until the disappearance of starting materials, as determined by TLC. and was cooled in a refrigerator for about 60 minutes. The solid formed in the reaction mixture was filtered, dried and recrystallized from ethanol to obtain the pure product and appropriate isolated yield is shown in **Table 2.**

Representative procedure for the synthesis of 2-oxindolyl-2-hydroxyacenaphthylen-1-ones (10a-e)

To a refluxing dry CH_2Cl_2 solution of $Rh_2(OAc)_4$ (1 mol%), benzyl alcohol **3** (0.60 mmol) and acenaphthenequinone **9** (0.50 mmol) under argon atmosphere, 3-diazo-1,3-dihydro-indol-2-one **1** (0.60 mmol) in dry dichloromethane was added dropwise (approximately 10 ml in 60

minutes). After the addition was completed, the reaction mixture was allowed to reflux for 15-20 minutes until the disappearance of starting materials, as determined by TLC. The solid formed in the reaction mixture was filtered, dried and recrystallized from ethanol to obtain the pure product and appropriate isolated yield is shown in **Table 3.**

Spectral Data

3'-Benzyloxy-3-hydroxy-1,3,1',3'-tetrahydro-[3,3']biindolyl-2,2'-dione (Table 1, entry 1, 6a)

White solid, mp 168-170 ^{o}C, R_f 0.25 (50% EtOAc/Petroleum ether), IR (KBr): 3503, 3384, 3222, 1718, 1619, 1470, 1177, 1118, 755 cm^{-1}, ^{1}H NMR (500 MHz, DMSO-d$_6$): δ 4.02 (ABq, 2H, *J* = 24.7 Hz), 6.2 (br s, 1H, -O*H*, D$_2$O exchangeable), 6.61 (d, 1H, *J* = 8.4 Hz, -Ar-*H*), 6.67 (d, 1H, *J* = 8.4 Hz, -Ar-*H*), 6.85 (t, 1H, *J* = 7.6 Hz, -Ar-*H*), 6.95 (t, 1H, *J* = 6.9 Hz, -Ar-*H*), 7.11 (t, 1H, *J* = 7.65 Hz, -Ar-*H*), 7.18 (t, 1H, *J* = 7.65 Hz, -Ar-*H*), 7.23 (t, 1H, *J* = 6.85 Hz, -Ar-*H*), 7.27-7.33 (m, 4H, -Ar-*H*), 7.38 (d, 1H, *J* = 7.6 Hz, -Ar-*H*), 7.46 (d, 1H, *J* = 7.65 Hz, -Ar-*H*), 10.18 (br s, 1H, -N*H*, D$_2$O exchangeable), 10.47 (br s, 1H, -N*H*, D$_2$O exchangeable), ^{13}C NMR (125 MHz, DMSO-d$_6$): δ 66.9, 78.5, 84.7, 109.3, 109.8, 121.4, 124.5, 125.8, 126.4, 127.7, 127.9, 128.5, 128.6, 128.7, 128.8, 129.6, 130.2, 130.3, 138.4, 143.1, 143.4, 175.1, 176.3, MS (ESI LCQ-MS): *m/z* 387.2 [M$^+$+H$^+$]. Anal. Calcd for $C_{23}H_{18}N_2O_4$: C 71.49 H 4.70 N 7.25. Found: C 71.53 H 4.62 N 7.31.

3-Hydroxy-3'-(4-methoxy-benzyloxy)-1,3,1,3'-tetrahydro-[3,3']biindolyl-2,2'dione (Table 1, entry 2, 6b)

White solid, mp 162-164 ^{o}C, R_f 0.25 (50% EtOAc/Petroleum ether), IR (KBr): 3421, 3341, 3262, 1724, 1620, 1470, 1177, 753 cm^{-1}, ^{1}H NMR (500 MHz, DMSO-d$_6$): δ 3.7 (s, 3H), 3.94 (ABq, 2H, *J* = 19.45 Hz), 6.16 (br s, 1H, -O*H*, D$_2$O exchangeable), 6.61 (d, 1H, *J* = 7.6 Hz, -Ar-*H*), 6.67 (d, 1H, *J* = 7.65 Hz, -Ar-*H*), 6.84-6.86 (m, 3H, -Ar-*H*), 6.96 (t, 1H, *J* = 7.65 Hz, -Ar-*H*), 7.11 (t, 1H, *J* = 7.65 Hz, -Ar-*H*), 7.17-7.21 (m, 3H, -Ar-*H*), 7.37 (d, 1H, *J* = 7.65 Hz, -Ar-*H*), 7.47 (d, 1H, *J* = 6.85 Hz, -Ar-*H*), 10.16 (br s, 1H, -N*H*, D$_2$O exchangeable), 10.44 (br s, 1H, -O*H*, D$_2$O exchangeable), ^{13}C NMR (125 MHz, DMSO-d$_6$): δ 55.5, 66.7, 78.5, 84.7, 109.3, 109.7, 114, 121.4, 121.8, 125.2, 127.1, 127.3, 128.9, 129.4, 129.5, 130, 130.1, 130.2, 130.3, 142.6, 143.4, 159.2, 173.9, 175.1, MS (ESI LCQ-MS): *m/z* 416.87 [M$^+$+H$^+$]. Anal. Calcd for $C_{24}H_{20}N_2O_5$: C 69.22 H 4.84 N 6.73. Found: C 69.28 H 4.78 N 6.80.

3-Hydroxy-3'-(4-methyl-benzyloxy)-1,3,1,3'-tetrahydro-[3,3']biindolyl-2,2'dione (Table 1, entry 3, 6c)

White solid, mp 162-164 ^{o}C, R_f 0.25 (50% EtOAc/Petroleum ether), IR (KBr): 3435, 3395, 3202, 1727, 1620, 1468, 1118, 756 cm^{-1}, ^{1}H NMR (500 MHz, DMSO-d$_6$): δ 2.24 (s, 3H), 3.96 (ABq, 2H, *J* = 18.0 Hz), 6.18 (br s, 1H, -O*H*, D$_2$O exchangeable), 6.6 (d, 1H, *J* = 7.6 Hz, -Ar-*H*), 6.67 (d, 1H, *J* = 7.65 Hz, -Ar-*H*), 6.83-6.89 (m, 1H, -Ar-*H)*, 6.93-6.99 (m, 1H, -Ar-*H)*, 7.08-7.12 (m, 3H, -Ar-*H*) 7.17-7.19 (m, 3H, -Ar-*H*), 7.38 (d, 1H, *J* = 7.6 Hz, -Ar-*H*), 7.47 (t, 1H, *J* = 7.65 Hz, -Ar-*H*), 10.16 (br s, 1H, -N*H*, D$_2$O exchangeable), 10.44 (br s, 1H, -N*H*, D$_2$O exchangeable), ^{13}C NMR (125 MHz, DMSO-d$_6$): δ 21.2, 66.8, 74.5, 84.7, 109.3, 109.8, 121.8, 124.6, 125.2, 127.1, 127.3, 127.6, 127.7, 127.9, 128.4, 128.7, 128.8, 129.8, 130.2, 135.5, 137, 142.6, 173.8, 175.1, MS (ESI LCQ-MS): *m/z* 401.32 [M$^+$+H$^+$]. Anal. Calcd for

$C_{24}H_{20}N_2O_4$: C 71.99 H 5.03 N 7.0. Found: C 72.92 H 5.11 N 6.93

3'-(4-chloro-benzyloxy)-3-hydroxy-1,3,1',3'-tetrahydro-[3,3']biindolyl-2,2'-dione (Table 1, entry 4, 6d)

White solid, mp 164-166 ^oC, R_f 0.25 (50% Ethyl acetate/Petroleum ether), IR (KBr): 3444, 3397, 3198, 1725, 1620, 1470, 1119, 755 cm^{-1}, ^1H NMR (500 MHz, DMSO-d_6): δ 4.02 (ABq, 2H, *J* = 16.42 Hz), 6.23 (br s, 1H, -O*H*, D_2O exchangeable), 6.59 (d, 1H, *J* = 7.65 Hz, -Ar-*H*), 6.66 (d, 1H, *J* = 7.65 Hz, -Ar-*H*), 6.85 (t, 1H, *J* = 7.6 Hz, -Ar-*H*), 6.93 (t, 1H, *J* = 7.65 Hz, -Ar-*H*), 7.1 (t, 1H, *J* = 7.65 Hz, -Ar-*H*), 7.17 (t, 1H, *J* = 7.65 Hz, -Ar-*H*), 7.33-7.37 (m, 5H, -Ar-*H*), 7.44 (d, 1H, *J* = 7.65 Hz, -Ar-*H*) 10.18 (br s, 1H, -N*H*, D_2O exchangeable), 10.46 (br s, 1H, -N*H*, D_2O exchangeable) ^{13}C NMR (125 MHz, DMSO-d_6): δ 66.2, 78.5, 84.7, 109.3, 109.8, 112.7, 121.5, 121.9, 124.3, 125.2, 127.0, 127.2, 128.5, 128.6, 128.7, 129.6, 130.0, 130.3, 137.5, 138.8, 142.6, 173.7, 175.1, MS: *m*/*z* = 421.63 (M^++H^+), Anal. Calcd for $C_{23}H_{17}ClN_2O_4$: C 65.64 H 4.07 N 6.66. Found: C 66.72 H 4.13 N 6.61.

3'-(4-Bromo-benzyloxy)-3-hydroxy-1,3,1',3'-tetrahydro-[3,3']biindolyl-2,2'-dione (Table 1, entry 5, 6e)

White solid, mp 172-174 ^oC, R_f 0.25 (50% EtOAc/Petroleum ether), IR (KBr): 3399, 3444, 3205, 1726, 1621, 1471, 1118, 759 cm^{-1}, ^1H NMR (500 MHz, DMSO-d_6): δ 4.01 (ABq, 2H, *J* = 17.15 Hz), 6.23 (br s, 1H, -O*H*, D_2O exchangeable), 6.6 (d, 1H, *J* = 7.65 Hz, -Ar-*H*), 6.66 (d, 1H, *J* = 7.65 Hz, -Ar-*H*), 6.68 (t, 1H, *J* = 7.65 Hz, -Ar-*H*), 6.93 (t, 1H, *J* = 7.65 Hz, -Ar-*H*), 7.1 (t, 1H, *J* = 7.65 Hz, -Ar-*H*), 7.17 (t, 1H, *J* = 7.65 Hz, -Ar-*H*), 7.3 (d, 2H, *J* = 8.4 Hz, -Ar-*H*), 7.36 (d, 1H, *J* = 7.65 Hz, -Ar-*H*), 7.43 (d, 1H, *J* = 6.9 Hz, -Ar-*H*), 7.49 (d, 2H, *J* = 8.45 Hz, -Ar-*H*), 10.18 (br s, 1H, -N*H*, D_2O exchangeable), 10.47 (br s, 1H, -N*H*, D_2O exchangeable), ^{13}C NMR (125 MHz, DMSO-d_6): δ 66.2, 78.5, 84.8, 109.3, 109.8, 118.3, 120.9, 121.5, 123.2, 125.2, 126.9, 127.2, 128.7, 129.6, 129.8, 129.9, 131.4, 138.8, 142.6, 143.1, 173.7, 175.1, MS (ESI LCQ-MS): *m*/*z* 466.18 [M^++H^+]. Anal. Calcd for $C_{23}H_{17}BrN_2O_4$: C 59.37 H 3.68 N 6.02. Found: C 59.45 H 3.74 N 6.10.

3'-Benzyloxy-5-chloro-3-hydroxy-1,3,1',3'-tetrahydro-[3,3']biindolyl-2,2'-dione (Table 1, entry 7, 6f)

White solid, mp 192-194 ^oC, R_f 0.25 (50% EtOAc/Petroleum ether), IR (KBr): 3395, 3244, 1726, 1619, 1472, 1180, 1103, 756 cm^{-1}, ^1H NMR (500 MHz, DMSO-d_6): δ 4.02 (ABq, 2H, *J* = 23.87 Hz), 6.5 (br s, 1H,-O*H*, D_2O exchangeable), 6.67 (d, 1H, *J* = 7.65 Hz, -Ar-*H*), 6.73 (d, 1H, *J* = 7.65 Hz, -Ar-*H*), 6.9 (t, 1H, *J* = 7.65 Hz, -Ar-*H*), 7.22-7.31 (m, 7H, -Ar-*H*), 7.41-7.43 (m, 1H, -Ar-*H*), 7.53 (d, 1H, *J* = 6.9 Hz, -Ar-*H*), 10.29 (br s, 1H,-N*H*, D_2O exchangeable), 10.49 (br s, 1H,-N*H*, D_2O exchangeable), ^{13}C NMR (125 MHz, DMSO-d_6): δ 67.1, 78.6, 84.9, 109.9, 110.7, 122.1, 124.4, 125.5, 127.8, 127.9, 128, 128.1, 128.7, 129.3, 130.4, 131.2, 138.3, 141.6, 143.4, 173.7, 174.5, MS (ESI LCQ-MS): *m*/*z* 421.4 [M^++H^+]. Anal. Calcd for $C_{23}H_{17}ClN_2O_4$ C 65.64 H 4.07 N 6.66. Found: C 65.74 H 4.13 N 6.72.

3'-Benzyloxy-5-bromo-3-hydroxy-1,3,1',3'-tetrahydro-[3,3']biindolyl-2,2'-dione (Table 1, entry 8, 6g)

White solid, mp 190-192 ^{o}C, R_f 0.25 (50% EtOAc/Petroleum ether), IR (KBr): 3392, 3247, 1726, 1617, 1471, 1176, 1125, 761 cm^{-1}, ^{1}H NMR (500 MHz, DMSO-d$_6$): δ 4.11 (ABq, 2H, *J* = 24.1 Hz), 6.51 (br s, 1H, -O*H*, D_2O exchangeable), 6.64 (d, 1H, *J* = 7.65 Hz, -Ar-*H*), 6.74 (d, 1H, *J* = 7.65 Hz, -Ar-*H*), 7 (t, 1H, *J* = 7.65 Hz, -Ar-*H*), 7.21-7.3 (m, 7H, -Ar-*H*), 7.44-7.46 (m, 1H, -Ar-*H*), 7.55 (d, 1H, *J* = 7 Hz, -Ar-*H*), 10.3 (br s, 1H, -O*H*, D_2O exchangeable), 10.5 (br s, 1H, -O*H*, D_2O exchangeable), ^{13}C NMR (125 MHz, DMSO-d$_6$): δ 67.2, 78.6, 84.9, 109.9, 111.3, 113.3, 122.1, 124.4, 127.4, 127.7, 127.9, 128.0, 130.4, 130.6, 131.6, 132.1, 138.3, 141.9, 143.4, 173.7, 174.4 , MS (ESI LCQ-MS): *m/z* 466.12 [M^++H^+]. Anal. Calcd for $C_{23}H_{17}BrN_2O_4$: C 59.37 H 3.68 N 6.02. Found: C 59.45 H 3.75 N 6.10.

3'-Benzyloxy-3-hydroxy-5-iodo-1,3,1',3'-tetrahydro-[3,3']biindolyl-2,2'-dione (Table 1, entry 9, 6h)

White solid, mp 202-204 ^{o}C, R_f 0.25 (50% EtOAc/Petroleum ether), IR (KBr): 3368, 3240, 1718, 1615, 1470, 1178, 1119, 760 cm^{-1}, ^{1}H NMR (500 MHz, DMSO-d$_6$): δ 4.0 (ABq, 2H, J = 23.94 Hz), 6.21 (br s, 1H, -OH, D_2O exchangeable), 6.52-6.56 (m, 3H, -Ar-H), 6.74 (d, 1H, J = 7.6 Hz, -Ar-H), 6.79 (d, 1H, J = 7.65 Hz, -Ar-H), 6.84 (t, 1H, J = 7.65 Hz, -Ar-H), 7 (t, 1H, J = 7.65 Hz, -Ar-H), 7.3-7.34 (m, 2H, -Ar-H), 7.49-7.52 (m, 2H, -Ar-H), 7.74-7.76 (m, 1H, -Ar-H), 10.29 (br s, 1H, -NH, D_2O exchangeable), 10.49 (br s, 1H,-NH, D_2O exchangeable), ^{13}C NMR (125 MHz, DMSO-d$_6$): δ 67.2, 78.4, 84.9, 109.9, 111.9, 112.4, 122.1, 122.3, 124.4, 127.8, 128, 128.1, 128.6, 128.7, 130.4, 131.9, 136.3, 137.8, 138.3, 142.5, 143.4, 173.7, 174.2 , MS (ESI LCQ-MS): m/z 513.2 [M^++H^+]. Anal. Calcd for $C_{23}H_{17}IN_2O_4$: C 53.92 H 3.34 N 5.47. Found: C 53.96 H 3.41 N 5.

1-Allyl-3'-Benzyloxy-3-hydroxy-1,3,1',3'-tetrahydro-[3,3']biindolyl-2,2'-dione (Table 1, entry 9, 6i)

White solid, mp 186-188 ^{o}C, R_f 0.25 (50% EtOAc/Petroleum ether), IR (KBr): 3387, 3295, 1717, 1619, 1467, 1185, 1117, 755 cm^{-1}, ^{1}H NMR (500 MHz, DMSO-d$_6$): δ 4.05 (ABq, 2H, J = 25.0 Hz), 4.18-4.22 (m, 2H) 5.07-5.14 (m, 2H), 5.67-5.72 (m,1H), 6.37 (br s, 1H, -OH, D_2O exchangeable), 6.68 (d, 1H, J = 7.6 Hz, -Ar-H), 6.72 (d, 1H, J = 7.65 Hz, -Ar-H), 6.94-6.97 (m, 2H, -Ar-H), 7.18-7.21 (m, 2H, -Ar-H), 7.24 (t, 1H, J = 6.9 Hz, -Ar-H), 7.29-7.32 (m, 2H, -Ar-H), 7.33-7.35 (m, 2H, -Ar-H), 7.44-7.47 (m, 2H, -Ar-H), 10.50 (br s, 1H, -NH, D_2O exchangeable), ^{13}C NMR (125 MHz, DMSO-d$_6$): δ 43.4, 67.1, 78.3, 84.9, 108.9, 109.9, 117.3, 121.9, 122.2, 124.5, 125.8, 126.9, 127.5, 127.8, 127.9, 128.3, 128.6, 129.7, 130.4, 132.1, 138.4, 143.3, 143.5, 173.3, 173.8, MS (ESI LCQ-MS): m/z 427.14 [M^++H^+]. Anal. Calcd for $C_{26}H_{22}N_2O_4$: C 73.23 H 5.20 N 6.57. Found: C 73.32 H 5.14 N 6.62.

3'-Benzyloxy-3-hydroxy-1-methyl-1,3,1',3'-tetrahydro-[3,3']biindolyl-2,2'-dione (Table 1, entry 9, 6j)

White solid, mp 186-188 ^{o}C, R_f 0.25 (50% EtOAc/Petroleum ether), IR (KBr): 3322, 3297, 1718, 1694, 1469, 1198, 1108, 755 cm^{-1}, ^{1}H NMR (500 MHz, DMSO-d$_6$): δ 2.83 (s, 3H), 4.1 (ABq, 2H, J = 24.0 Hz), 6.21 (br s, 1H, -OH, D_2O exchangeable), 6.75-6.77 (m, 2H, -Ar-H), 6.82-6.85 (m, 2H, -Ar-H), 6.88 (t, 1H, J = 7.65 Hz, -Ar-H), 7.23-7.26 (m, 2H, -Ar-H), 7.28-7.31 (m, 3H, -Ar-H), 7.32-7.35 (m, 3H, -Ar-H), 10.62 (br s, 1H, -NH, D_2O exchangeable),

^{13}C NMR (125 MHz, DMSO-d_6): δ 26.2, 67.2, 78.9, 84.9, 108.7, 110.6, 122.1, 122.3, 123.7, 126.1, 126.2, 126.7, 127.8, 127.9, 128.6, 129, 130.8, 131.3, 138.3, 143.8, 144.7, 173.8, 174.4, MS (ESI LCQ-MS): m/z 401.2 [M^++H^+]. Anal. Calcd for $C_{24}H_{20}N_2O_4$: C 71.99 H 5.03 N 7.0 Found: C 71.92 H 5.12 N 7.08.

2-(3-Benzyloxy-2-oxo-2,3-dihydro-1H-indol-3-yl)-2-hydroxy-indan-1,3-dione(Table 2, entry 1, 8a)

White solid, mp 198-200 ^{o}C, R_f 0.25 (50% EtOAc/Petroleum ether), IR (KBr): 3397, 3253, 1721, 1617, 1468, 1189, 759 cm^{-1}, ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.9 (ABq, 2H, *J* = 11.45 Hz), 6.49 (br s, 1H, -O*H*, D_2O exchangeable), 6.76-6.8 (m, 3H, -Ar-*H*), 6.97 (t, 1H, *J* = 7.65 Hz, -Ar-*H*), 7.07-7.1 (m, 3H, -Ar-*H*), 7.25-7.30 (m, 2H, -Ar-*H*), 7.92-7.94 (m, 4H, -Ar-*H*), 10.57 (br s, 1H, -N*H*, D_2O exchangeable), ^{13}C NMR (125 MHz, DMSO-d_6): δ 66.8, 80.4, 85.2, 110.4, 121.8, 122.9, 123.1, 123.7, 126.5, 127.3, 127.6, 128.3, 130.9, 136.6, 136.7, 137.7, 141.8, 141.9, 143.9, 173.2, 197, 198, MS (ESI LCQ-MS): *m*/*z* 400.1 [M^++H^+]. Anal. Calcd for $C_{24}H_{17}NO_5$: C 72.17 H 4.29 N 3.51. Found: C 72.28 H 4.21 N 3.60.

2-Hydroxy-2-[(3-(4-methoxy-benzyloxy-2-oxo-2,3-dihydro-1H-indol-3-yl]-indan-1,3-dione (Table 2, entry 2, 8b)

White solid, mp 186-188 ^{o}C, R_f 0.25 (50% EtOAc/Petroleum ether), IR (KBr): 3441, 3215, 1723, 1613, 1486, 1254, 1183, 757 cm^{-1}, ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.64 (s, 3H), 3.83 (ABq, 2H, *J* = 11.45 Hz), 6.5 (br s, 1H, -O*H*, D_2O exchangeable), 6.66 (d, 2H, *J* = 8.4 Hz, -Ar-*H*), 6.72-6.75 (m, 2H, -Ar-*H*), 6.78 (d, 1H, *J* = 7.65 Hz, -Ar-*H*), 6.96 (t, 1H, *J* = 7.65 Hz, -Ar-*H*), 7.24-7.3 (m, 2H, -Ar-*H*), 7.89-7.94 (m, 4H, -Ar-*H*), 10.52 (br s, 1H, -N*H*, D_2O exchangeable), ^{13}C NMR (125 MHz, DMSO-d_6): δ 55.5, 66.7, 80.4, 85.2, 110.4, 113.7, 121.8, 122.9, 123.1, 123.9, 127.3, 128.2, 129.6, 130.8, 136.6, 137.7, 138.9, 141.7, 141.8, 141.9, 143.9, 158.9, 173.3, 197.1, 198, MS (ESI LCQ-MS): *m*/*z* 430.2 [M^++H^+]. Anal. Calcd for $C_{25}H_{19}NO_6$: C 69.92 H 4.46 N 3.26. Found: C 69.98 H 4.35 N 3.32.

2-Hydroxy-2-[(3-(4-methyl-benzyloxy-2-oxo-2,3-dihydro-1H-indol-3-yl]-indan-1,3-dione (Table 2, entry 1, 8c)

White solid, mp 188-190 ^{o}C, R_f 0.25 (50% EtOAc/Petroleum ether), IR (KBr): 3406, 3259, 1721, 1618, 1470, 1186, 757 cm^{-1}, ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.16 (s, 3H), 3.84 (q, 2H, *J* = 11.45 Hz), 6.47 (br s, 1H, -O*H*, D_2O exchangeable), 6.64 (d, 2H, *J* = 7.65 Hz, -Ar-*H*), 6.79 (d, 1H, *J* = 7.65 Hz, -Ar-*H*), 6.89 (d, 2H, *J* = 7.65 Hz, -Ar-*H*), 6.96 (t, 1H, *J* = 7.65 Hz, -Ar-*H*), 7.24-7.28 (m, 2H, -Ar-*H*), 7.89-7.93 (m, 4H, -Ar-*H*), 10.54 (br s, 1H, -N*H*, D_2O exchangeable), ^{13}C NMR (125 MHz, DMSO-d_6): δ 21.1, 66.8, 80.4, 85.2, 110.4, 121.8, 122.9, 123.1, 123.7, 124.4, 126.5, 127.3,128.8, 130.8, 134.7, 136.6, 136.7, 137.7, 141.8, 141.9, 144, 173.2, 197, 198.1, MS (ESI LCQ-MS): *m*/*z* 414.23 [M^++H^+]. Anal. Calcd for $C_{25}H_{19}ClNO_5$: C 72.63 H 4.63 N 3.39. Found: C 72.72 H 4.55 N 3.45.

2-[3-(4-Chlorobenzyloxy)-2-oxo-2,3-dihydro-1H-indol-3-yl]-2-hydroxy-indan-1,3-dione (Table 2, entry 4, 8d)

White solid, mp 194-196 ^{o}C, R_f 0.25 (50% EtOAc/Petroleum ether), IR (KBr): 3377, 3258, 1722, 1618, 1472, 1186, 761 cm^{-1}, ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.9 (ABq, 2H, *J* = 11.45 Hz), 6.51 (br s, 1H, -O*H*, D_2O exchangeable), 6.78-6.82 (m, 3H, -Ar-*H*), 6.96 (t, 1H, *J*

= 7.6 Hz, -Ar-*H*), 7.17 (d, 2H, *J* = 8.4 Hz, -Ar-*H*), 7.25-7.28 (m, 2H, -Ar-*H*), 7.9-7.94 (m, 4H, -Ar-*H*), 10.56 (br s, 1H, -N*H*, D_2O exchangeable), ^{13}C NMR (125 MHz, DMSO-d_6):): δ 66.2, 80.4, 85.2, 110.4, 121.9, 123.0, 123.1, 123.5, 127.3, 128.2, 128.4, 130.9, 132.1, 136.7, 136.8, 136.8, 141.7, 141.9, 143.9, 173.2, 196.9, 197.9, MS (ESI LCQ-MS): *m*/*z* 434.6 [M^++H^+]. Anal. Calcd for $C_{24}H_{16}ClNO_5$: C 66.44 H 3.72 N 3.23. Found: C 66.48 H 3.78 N 3.18.

2-[3-(4-Bromo-benzyloxy)-2-oxo-2,3-dihydro-1H-indol-3-yl]-2-hydroxy-indan-1,3-dione(Table 2, entry 1, 8e)

White solid, mp 196-198 ^oC, R_f 0.25 (50% EtOAc/Petroleum ether), IR (KBr): 3421, 3253, 1723, 1620, 1474, 1186, 754 cm^{-1}, ^1H NMR (500 MHz, DMSO-d_6): δ 3.88 (ABq, 2H, *J* = 11.45 Hz), 6.51 (br s, 1H, -O*H*, D_2O exchangeable), 6.75 (d, 2H, *J* = 8.4 Hz, -Ar-*H*), 6.79 (d, 1H, *J* = 7.6 Hz, -Ar-*H*), 6.96 (t, 1H, *J* = 7.65 Hz, -Ar-*H*), 7.24-7.3 (m, 4H, -Ar-*H*), 7.91-7.94 (m, 4H, -Ar-*H*), 10.5 (br s, 1H, -N*H*, D_2O exchangeable), ^{13}C NMR (125 MHz, DMSO-d_6): δ 66.2, 80,4, 85.2, 110.4, 120.6, 121.9, 123, 123.1, 123.5, 127.3, 128.7, 130.9, 131.2, 136.7, 136.8, 137.2, 141.7, 141.9, 143.9, 173.1, 196.9, 197.9, MS (ESI LCQ-MS): *m*/*z* 479 [M^++H^+]. Anal. Calcd for $C_{24}H_{16}BrNO_5$: C 60.27 H 3.37 N 2.93. Found: C 60.35 H 3.42 N 2.98.

3-Benzyloxy-3-(1-hydroxy-2-oxo-acenaphthen-1-yl)-1,3-dihydro-indol-2-one (Table 3, entry 1, 10a)

White solid, mp 194-196 ^oC, R_f 0.25 (50% EtOAc/Petroleum ether), IR (KBr): 3397, 3290, 2367, 1719, 1614, 1466, 1190, 1113, 774, 750 cm^{-1}, ^1H NMR (500 MHz, DMSO-d_6): δ 4.1 (ABq, 2H, *J* = 16.7 Hz), 6.55 (br s, 1H, -O*H*, D_2O exchangeable), 6.70-6.72 (m, 2H, -Ar-*H*), 6.89 (t, 1H, *J* = 6.5 Hz, -Ar-*H*), 7.25-7.28 (m, 2H, -Ar-*H*), 7.3-7.33 (m, 3H, -Ar-*H*), 7.35-7.37 (m, 2H, -Ar-*H*), 7.47 (t, 1H, *J* = 7.6 Hz, -Ar-*H*), 7.71 (t, 1H, *J* = 6.9 Hz, -Ar-*H*), 7.77 (d, 1H, *J* = 6.85 Hz, -Ar-*H*), 7.94 (d, 1H, *J* = 8.4 Hz, -Ar-*H*), 8.16 (d, 1H, *J* = 8.4 Hz, -Ar-*H*), 10.39 (br s, 1H, -N*H*, D_2O exchangeable), ^{13}C NMR (125 MHz, DMSO-d_6): δ 67.3, 81.7, 85.3, 110.6, 121.1, 122.2, 124.3, 126.3, 127.1, 127.7,127.8, 127.9, 128.6, 128.8, 128.9, 129.8, 130.3, 131.2, 131.7, 132.4, 137.1, 138.4, 141.3, 143.8, 174.6, 201.2, MS (ESI LCQ-MS): *m*/*z* 422.2 [M^++H^+]. Anal. Calcd for $C_{27}H_{19}NO_4$: C 76.95 H 4.54 N 3.32. Found: C 76.86 H 4.66 N 3.41.

3-(1-Hydroxy-2-oxo-acenaphthen-1-yl)-3-(4-methoxy-benzyloxy)-1,3-dihydro-indol-2-one (Table 3, entry 2, 10b)

White solid, mp 190-192 ^oC, R_f 0.25 (50% EtOAc/Petroleum ether), IR (KBr): 3416, 3265, 1726, 1613, 1468, 1252, 776, 753 cm^{-1}, ^1H NMR (500 MHz, DMSO-d_6): δ 3.70 (s, 3H). 4.06 (ABq, 2H, *J* = 10.9 Hz), 6.50 (br s, 1H, -O*H*, D_2O exchangeable), 6.71-6.75 (m, 3H, -Ar-*H*), 6.86-6.89 (m, 3H, -Ar-*H*), 7.24-7.28 (m, 3H, -Ar-*H*), 7.48 (t, 1H, *J* = 7.65 Hz, -Ar-*H*), 7.70 (t, 1H, *J* = 6.85 Hz, -Ar-*H*), 7.76 (d, 1H, *J* = 6.9 Hz, -Ar-*H*), 7.94 (d, 1H, *J* = 8.4 Hz, -Ar-*H*), 8.15 (d, 1H, *J* = 7.65 Hz, -Ar-*H*), 10.40 (br s, 1H, -N*H*, D_2O exchangeable), ^{13}C NMR (125 MHz, DMSO-d_6): δ 55.6, 67.1, 81.8, 85.6, 110.5, 113.9, 121.1, 122.2, 122.4, 124.4, 126.3, 126.9, 128.8, 128.9, 129.0, 129.5, 130.3, 131.1, 131.7, 132.4, 132.8, 137.1, 141.3, 143.8, 159.3, 174.6, 201.2, MS (ESI LCQ-MS): *m*/*z* 452.15 [M^++H^+]. Anal. Calcd for $C_{28}H_{21}NO_5$: C

74.49 H 4.69 N 3.10. Found: C 74.41 H 4.58 N 3.18.

3-(1-Hydroxy-2-oxo-acenaphthen-1-yl)-3-(4-methoxy-benzyloxy)-1,3-dihydro-indol-2-one (Table 3, entry 3, 10c)

White solid, mp 194-196 ^{o}C, R_f 0.25 (50% EtOAc/Petroleum ether), IR (KBr): 3393, 3295, 1717, 1619, 1467, 1185, 1117, 789, 755 cm^{-1}, ^{1}H NMR (500 MHz, DMSO-d$_6$): δ 2.05 (s, 3H). 4.08 (ABq, 2H, *J* = 15.8 Hz), 6.50 (br s, 1H, -O*H*, D$_2$O exchangeable), 6.70-6.74 (m, 2H, -Ar-*H*), 6.85 (t, 1H, *J* = 7.65 Hz, -Ar-*H*), 7.1-7.14 (m, 3H, -Ar-*H*), 7.21-7.25 (m, 3H, -Ar-*H*), 7.48 (t, 1H, *J* = 7.65Hz, -Ar-*H*), 7.70 (t, 1H, *J* = 7.65 Hz, -Ar-*H*), 7.75 (d, 1H, *J* = 6.9 Hz, -Ar-*H*), 7.94 (d, 1H, *J* = 8.4 Hz, -Ar-*H*), 8.16 (d, 1H, *J* = 8.4 Hz, -Ar-*H*), 10.40 (br s, 1H, -N*H*, D$_2$O exchangeable), ^{13}C NMR (125 MHz, DMSO-d$_6$): δ 21.3, 67.2, 81.8, 85.5, 110.5, 121.1, 121.8, 122.2, 123.4, 124.3, 126.3, 126.9, 127.8, 128.7, 128.9, 129.0, 129.1, 130.3, 131.1, 131.7, 132.3, 132.8, 135.3, 137.1, 141.3, 143.7, 174.6, 201.2, MS (ESI LCQ-MS): *m*/*z* 436.23 [M$^+$+H$^+$]. Anal. Calcd for $C_{28}H_{21}NO_4$: C 77.23 H 4.86 N 3.22. Found: C 77.31 H 4.75 N 3.18.

3-(4-Chloro-benzyloxy)-3-(1-hydroxy-2-oxo-acenaphthen-1-yl)-1,3-dihydro-indol-2-one (Table 3, entry 4, 10d)

White solid, mp 214-216 ^{o}C, R_f 0.25 (50% EtOAc/Petroleum ether), IR (KBr): 3387, 3296, 1720, 1613, 1471, 1186, 1114, 772, 757 cm^{-1}, ^{1}H NMR (500 MHz, DMSO-d$_6$): δ 4.14 (ABq, 2H, *J* = 16.6 Hz), 6.59 (br s, 1H, -O*H*, D$_2$O exchangeable), 6.65-6.7 (m, 2H, -Ar-*H*), 6.91 (t, 1H, *J* = 7.65 Hz, -Ar-*H*), 7.28 (t, 1H, *J* = 7.6 Hz, -Ar-*H*), 7.35-7.40 (m, 5H, -Ar-*H*), 7.46 (t, 1H, *J* = 8.4 Hz) 7.71 (t, 1H, *J* = 6.9 Hz, -Ar-*H*), 7.78 (d, 1H, *J* = 6.9 Hz, -Ar-*H*), 7.93 (d, 1H, *J* = 8.4 Hz, -Ar-*H*), 8.15 (d, 1H, *J* = 8.4 Hz, -Ar-*H*), 10.36 (br s, 1H, -N*H*, D$_2$O exchangeable), ^{13}C NMR (125 MHz, DMSO-d$_6$): δ 66.6, 81.6, 85.6, 110.6, 121.1, 121.8, 122.2, 122.3, 124.2, 126.4, 127.2, 128.5, 128.8, 128.9, 129.0, 129.6, 130.4, 131.2, 131.7, 132.4, 137.1, 137.5, 141.2, 143.8, 174.4, 201.2, MS (ESI LCQ-MS): *m*/*z* 456.65 [M$^+$+H$^+$]. Anal. Calcd for $C_{27}H_{18}ClNO_4$: C 71.13 H 3.98 N 3.07. Found: C 71.22 H 3.83 N 3.14.

3-(4-Bromo-benzyloxy)-3-(1-hydroxy-2-oxo-acenaphthen-1-yl)-1,3-dihydro-indol-2-one (Table 3, entry 5, 10e)

White solid, mp 208-210 ^{o}C, R_f 0.25 (50% EtOAc/Petroleum ether), IR (KBr; cm^{-1}): 3387, 3292, 1720, 1618, 1469, 1185, 1116, 785, 752 cm^{-1}, ^{1}H NMR (500 MHz, DMSO-d$_6$): δ 4.12 (ABq, 2H, *J* = 17.2 Hz), 6.59 (br s, 1H, -O*H*, D$_2$O exchangeable), 6.71 (d, 1H, *J* = 8.45 Hz, -Ar-*H*), 6.91 (t, 1H, *J* = 7.65 Hz, -Ar-*H*), 7.27 (t, 1H, *J* = 7.65 Hz, -Ar-*H*), 7.33-7.35 (m, 2H, -Ar-*H*), 7.46 (t, 1H, *J* = 7.65 Hz, -Ar-*H*), 7.49-7.53 (m, 3H, -Ar-*H*) 7.71 (t, 1H, *J* = 7.65 Hz, -Ar-*H*), 7.78 (d, 1H, *J* = 6.85 Hz, -Ar-*H*), 7.88 (t, 1H, *J* = 7.65 Hz, -Ar-*H*), 7.93 (d, 1H, *J* = 8.4 Hz, -Ar-*H*), 8.16 (d, 1H, *J* = 8.4 Hz, -Ar-*H*), 10.36 (br s, 1H, -N*H*, D$_2$O exchangeable), ^{13}C NMR (125 MHz, DMSO-d$_6$): δ 66.7, 81.6, 85.9, 110.6, 120.9, 121.1, 121.2, 122.2, 122.3, 124.2, 126.3, 127.2, 128.8, 128.9, 129.0, 129.9, 130.4, 131.2, 131.4, 131.7, 132.4, 137.1, 137.9, 141.2, 143.8, 174.4, 201.2, MS (ESI LCQ-MS): *m*/*z* 501 [M$^+$+H$^+$]. Anal. Calcd for $C_{27}H_{18}BrlNO_4$: C 64.81 H 3.63 N 2.80. Found: C 64.87 H 3.73 N 2.72.