**Supporting Information**

# Marbostat-100 defines a new class of potent and selective anti-inflammatory and antirheumatic histone deacetylase 6 inhibitors

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**Content:**



## Enzymatic Inhibitory Activities on HDACs 1,2,4,5,6,8 and 11 and $K_i$-values

HDAC enzyme inhibition assays were conducted by Reaction Biology Corporation (Malvern, PA, USA) using a tenpoint dose response curve with half-log serial dilutions, fluorogenic peptides at 50 µM as enzymatic substrates. Substrate for HDAC1,2,6 and 11: fluorogenic peptide from p53 residues 379-382 (RHKK(Ac)AMC). Substrate for HDAC-4 and -5: fluorogenic HDAC class II substrate (Boc-Lys(TFA)-AMC). Substrate for HDAC-8: fluorogenic peptide from p53 residues 379-382 (RHK(Ac)K(Ac)AMC) at a concentration of 100 µM. Marbostat-100 (**5a**) inhibited HDAC6 selectively, on basis of the enzymatic inhibitory study in a panel of 10 $Zn^{2+}$-dependent HDACs.

$K_i$ values were calculated from the respective $IC_{50}$ values, determined in duplicate, according to the following formula:[1]

$$K_i = IC_{50} / [1+(S/K_m)]$$

With:
$K_i$ = Inhibition constant
$IC_{50}$: Concentration of inhibitor that causes 50% of inhibition of the enzymatic reaction.
$K_m$= Michaelis constant of the substrate (S).
S = Substrate concentration.

According to the companys informations the following parameters were used:

| HDAC-subtype | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 10 | 11 |
|---|---|---|---|---|---|---|---|---|---|---|
| $K_m$ [µM] | 5.2 | 5.8 | 3.2 | 33.4 | 43.4 | 13.2 | 53.5 | 226.5 | 4.3 | 7.4 |

## Cell culture and treatment conditions

The human leukemia cell lines MV4-11, Jurkat, HEL and BV173 were seeded in 6 well dishes with a density of 200,000 cells per ml for whole cell lysates and with a density of 150.000 cells per ml in 12 well dishes for flow cytometry. After an adaption time of at least 2 h, the cells were exposed to different HDACi as described in figure legends. The human adherent cells HEK293T were cultured in 6 well dishes with 400,000 cells per dish and stimulated after an adaption time of 24 h as described. Leukemia cell lines were maintained in RPMI 1640 (Sigma) + 10 % FBS (Gibco) + 1 % Pen/Strep (Gibco) and adherent cells were maintained in DMEM (Sigma) + 10 % FBS + 1 % Pen/Strep.

## Isolation of PBMCs

Peripheral blood mononuclear cells (PBMCs) were isolated by Ficoll Histopaque®-1077 (Sigma) density gradient centrifugation from buffy coats. The samples were obtained from blood donors from the blood bank of the University Medical Center Mainz. PBMCs were washed three times with PBS + 2 mM EDTA + 0.05 % BSA and seeded at 1 x $10^6$ cells/ml in 12 well plates for flow cytometry in RPMI 1640 + 10 % FBS + 1 % Pen/Strep.

## Western blot and antibodies

Western blot was done as described in Beyer *et al.*[2]. The proteins were detected via fluorescence coupled antibodies (LI-COR) using the Odyssey® imaging system. The antibodies used for Western blot were purchased from Sigma-Aldrich (acetylated Tubulin, catalog no. T7451), Merck (acetylated histone H3, catalog no. 06-599), Enzo (HSP90 (AC88), catalog no. ADI-SPA-830), Cell Signaling (HDAC6 (D2E5), catalog no. 7558.

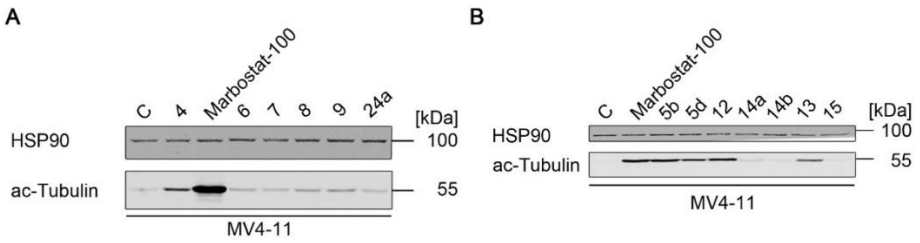



**Figure S1a: A**) and **B**) MV4-11 cells were treated for 24 h with 100 nM Marbostat-100 and compared with different compounds designed as potential new HDAC6i. The cells were analysed by Western blot. HSP90 served as loading control. The results are shown are representative from at least two independent experiments.

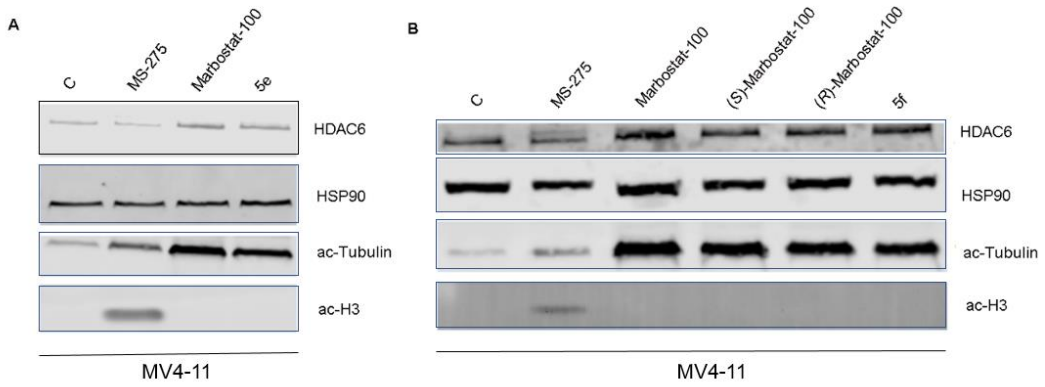



**Figure S1b: A**) and **B**) MV4-11 cells were treated for 24 h with 200 nM Marbostat-100 or MS-275 (5 µM) and compared with different compounds designed as potential new HDAC6i. The cells were analysed by Western blot. For information about the selectivity of the compounds investigated, acetylation of H3 was performed in addition to the detection of acetyl-tubulin as a marker for inhibition of HDAC6. Accumulation of hyperacetylated histone H3 shows an inhibition of class I HDACs (HDAC1,-2,-3, and -8). The slight hyperacetylation of tubulin in MS275-treated cells is a side effect of a sligt degradation of HDAC6. The results shown are representative from at least two independent experiments.

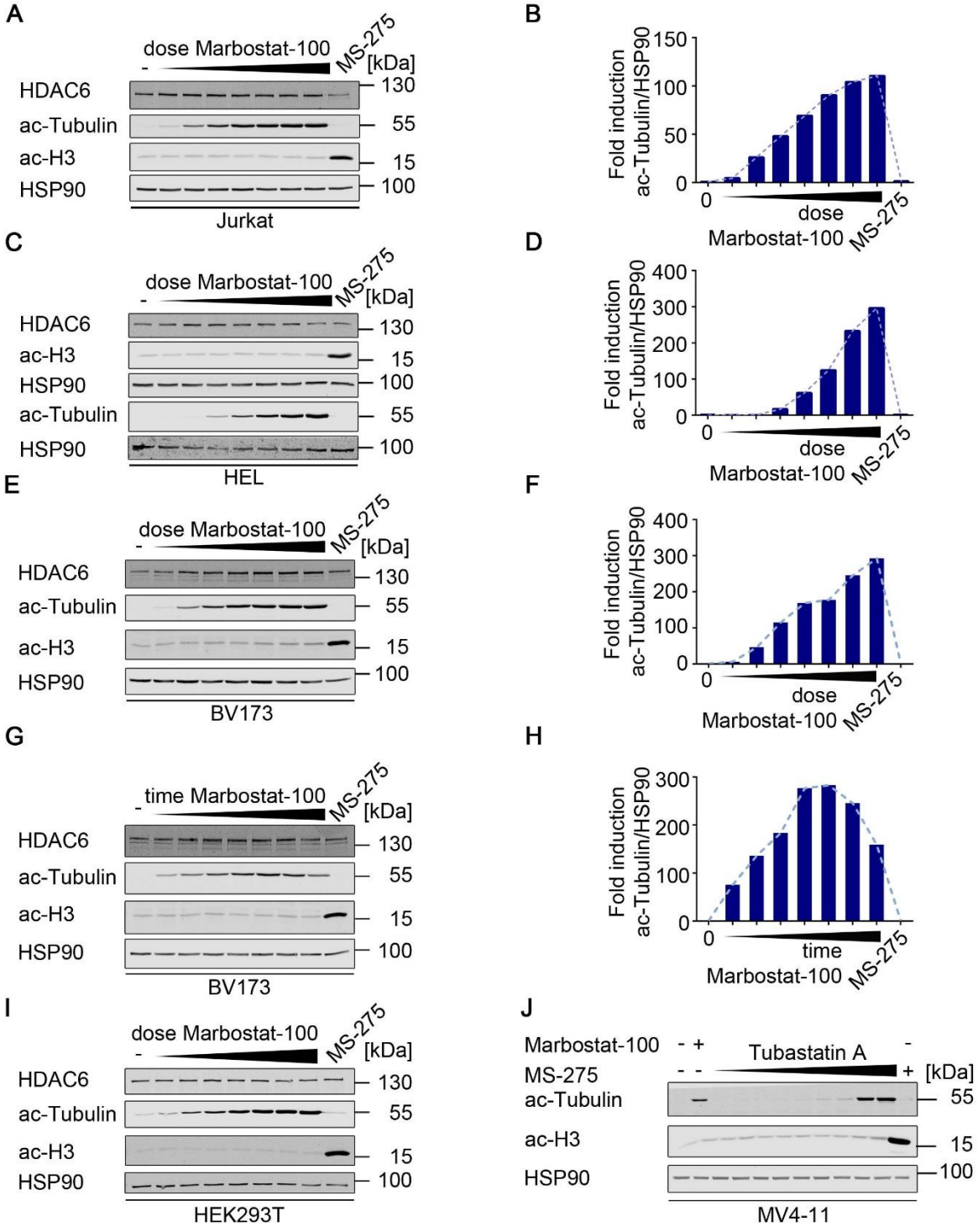
## Flow cytometry

Cell cycle distributions were determined with propidium iodide (PI; Sigma) using a flow cytometer (FACS canto II). The cells were collected on ice and permeabilized for at least 1 h in 80% EtOH at –20°C, followed by aRNase digestion step (1 µg per sample) for 1 h at room temperature. PI was added to every sample and measured on the flow cytometer immediately.
To differente between apoptosis and necrosis, we performed Annexin V/PI double staining. Cells were collected on ice and stained with Annexin V (Miltenyi) for 30 min on ice. Afterwards, PI was added and samples were measured immediately. As unstained control, an untreated cell sample was divded in half and stained with Annexin V and PI. This single stained sample was included to compensate the overlay of the dyes as well as the autofluorescence.

## Transfection

Cells were transfected with the plasmids HDAC6 FLAG (# 13823 from Addgene) and pcDNA3.1 as empty vector control. 4 µl Turbofectamin (Thermoscientific) and 2 µg plasmid were mixed in 200 µl Gibco™ Opti-MEM® I reduced serum medium and incubated for 20 min at room temperature. After the incubation time, the mixtures were added to the cells for 48 h.
Afterwards, the cells were seeded again and after an adaption time of 24 h stimulated with 500 nM Marbostat-100 for 48 h and prepared for SDS-PAGE.

**Biological effects of Marbostat-100 in different human cell lines**



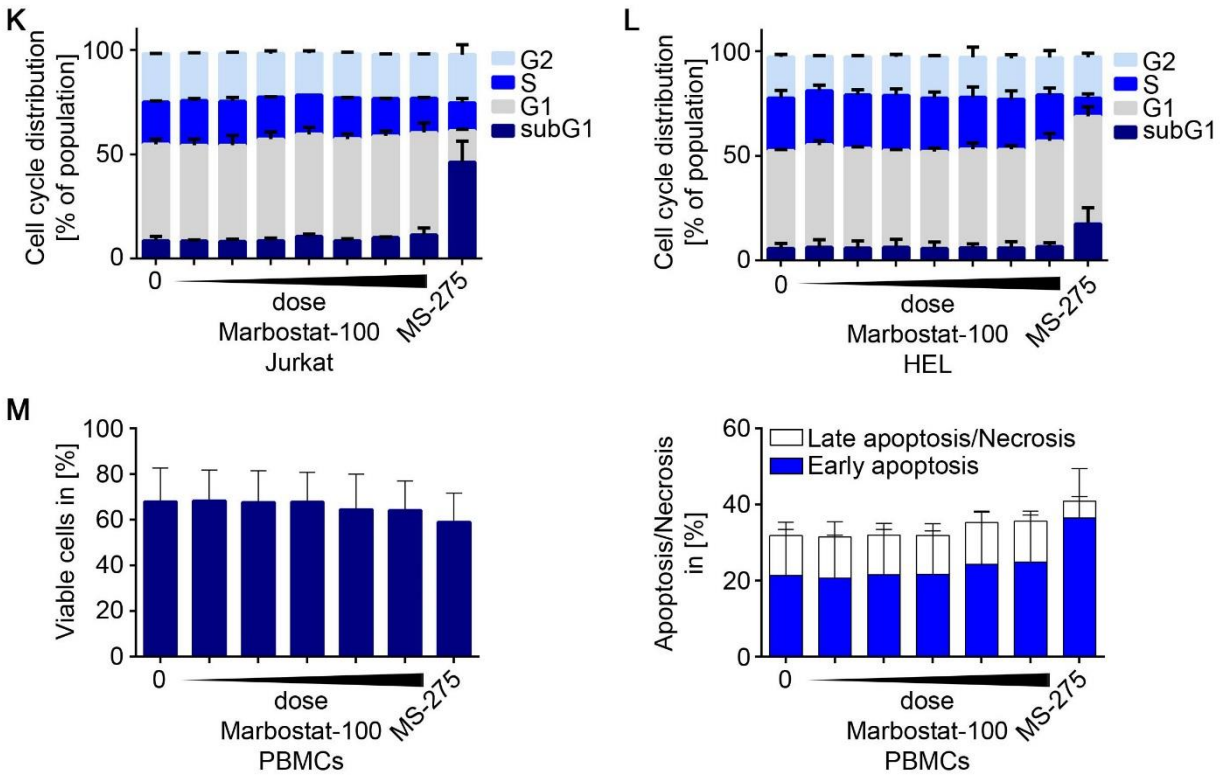



**Figure S2:** Human leukemia cell lines (a) Jurkat, (c) HEL and (e) BV173 were treated with increasing concentrations of Marbostat-100 (5, 20, 50, 100, 250, 500 and 1000 nM) or with 5 µM MS-275 for 24 h. Effects of the drugs and biological effects were determined via Western blot. HSP90 serves as loading control. Densitometric analyses of the blots was performed, to quantify the hyperacetlyation of α-Tubulin compared to HSP90 ((b) Jurkat, (d) HEL and (f) BV173). (g) BV173 cells were treated with 50 nM Marbostat-100 for different time points (10 min, 30 min, 1 h, 2 h, 16 h, 24 h and 48 h) or 5 µM MS-275 for 24 h. The hyperacetylation of α-Tubulin compared to the loading control HSP90 was evaluated by densitometry (h). HEK293T cells were treated with Marbostat-100 (5, 20, 50, 100, 250, 500 and 1000 nM) or 5 µM MS-275 for 24 h. (j) MV4-11 cells were stimulated with 50 nM Marbostat-100, different doses of the HDAC6i Tubastatin A (5 nM, 20 nM, 50 nM, 100 nM, 250 nM, 500 nM, 1 µM, 5 µM and 10 µM), or 5 µM MS-275 for 24 h. The effects were analysed by Western blot. (k) Jurkat and (l) HEL cell lines were stimulated with increasing doses of Marbostat-100 (5, 20, 50, 100, 250, 500 or 1000 nM) or 5 µM MS-275 for 24 h. The effects to cell cycle distribution were analysed by flow cytometry. (m) PBMCs were treated with Marbostat-100 (50, 100, 250, 500 and 1000 nM) or 5 µM MS-275 for 24 h and apoptosis was analysed by flow cytometry. All results are shown are representative of at least two indepent experiments.

## Induction, assessment of arthritis and scoring

Score points were assigned for inflamed toes, midfeet and ankles. Each limb was scored separately and scored as follows: 0, no swelling; 0.5, mild ankle swelling; up to 2.0, severe ankle swelling. Scores for all toes and ankles were totaled for each mouse. The maximum arthritis score amounted to 12 points per extremity (2 points for each of four toes, 2 points for midfeet and ankle) and 48 per animal.

Additionally, paw diameters were assessed using an electronic external caliper gauge (Kroeplin, Schlüchtern, Germany) totaling the paw diameters per animal, and body weights were determined. After a total of 15 days of continuous treatment, mice were killed by $CO_2$ asphyxia and the paws andseveral organs (liver, kidneys) were collected for further analysis.

For histological analysis and scoring, limbs were fixed for 24 h with a neutral buffered solution containing 3.7% formalin and subsequently decalcified in a 14% EDTA (Sigma,

Deisenhofen, Germany) solution buffered to pH 7.2. After dehydration with a neutral buffered 20% sucrose solution, decalcified paws were then embedded in Tissue Tek O.C.T compound (Sakura Finetek, Leiden, the Netherlands). 10µm thick sections were cut using a freezing microtome (Leica, Germany). For histological assessment of arthritis signs in the joints, sections were stained with 1,9- Dimethyl-Methylene blue solution (DMMB). DMMB is a cationic dye that specifically binds to sulfated glycosaminoglycans, which are highly expressed in articular cartilage. Hence, DMMB staining also allows for an estimate of cartilage quality. The two hindlimbs per mouse were scored separately in a blinded manner and the mean score was calculated for each animal. Following aspects were analyzed in this histological evaluation of mouse joints: A typical sign of arthritic joints is the invasion of immune cells into the joint cavity and adjacent tissues such as synovial tissue and muscle tissue. This invasion of cells into the joint cavity and into adjacent tissue was each separately scored with 0-4 points, higher scores describing a higher amount of invading cells. Additionally, the inflammation of the periosteum and erosion of underlying cortical bone was scored with 0-4 points, higher scores meaning higher inflammation and more erosion. Other hallmarks of arthritic joints like the erosion of articular and subchondral bone (0-4 points) and the degradation of articular cartilage (0-4 points, higher score=more cartilage degradation) were scored separately. Ultimately, score points of all five aspects were totaled per extremity, resulting in a maximum score of 20, and the mean out of two hind extremities was calculated for each animal.

**Bone parameter analysis by microCT: Scanning, reconstruction of volumes, 3D morphometry measurements**

All scans were performed on the microCT system phoenix v|tome|x s 240/180 research edition from GE Sensing & Inspection Technologies GmbH (software phoenix datos|x 2 acquisition 2.4.0). Scanning parameters for hind paws were as follows: 30 kV voltage, 230 µA current, 500 ms time, 800 images, voxel size 20 µm. Both hind paws were scanned of all mice with CIA. Additionally, both hind paws from age matched healthy mice served as control. Reconstructed volumes were processed using the respective manufacturer's software phoenix datos|x 2 reconstruction 2.4.0. The morphometric parameters were determined using the software Volume Graphics VG Studio Max 2.2.3. The morphometric parameters examined were volume fraction (BV/TV, data not shown), relative bone surface (BS/BV) as an indicator for erosions in bone. The region of interest (ROIs) for the hind paws were defined as follows: ROIs were created in the reconstructed volumes of the second, third and fourth toe. The ROIs were extended from the middle toe joint 1.0 mm distal and 2.2 mm proximal resulting in (3.20 ± 0.05) mm long areas along the bones axis. From 20 hind paws analyzed per treatment group and from 10 hind

paws in the healthy control group, outliers beyond the group mean±2.0*SD in each group were excluded in the BS/BV analysis (see also figure 6L, main part).

## Hematogram data

Whole blood was collected in EDTA coated tubes after cardiac puncture and subsequently analyzed by a full automatic counter. Hemoglobin, erythrocytes and leukocytes were determined in blood samples from the first (Marbostat-100 *versus* vehicle, Figure S3 A,B,C) and second (compound **5f** *versus* vehicle, Figure S3 D,E,F) experiment. Compared to vehicle, no significant changes in the blood parameters were detected (Mann-Whitney test was used to compare groups).

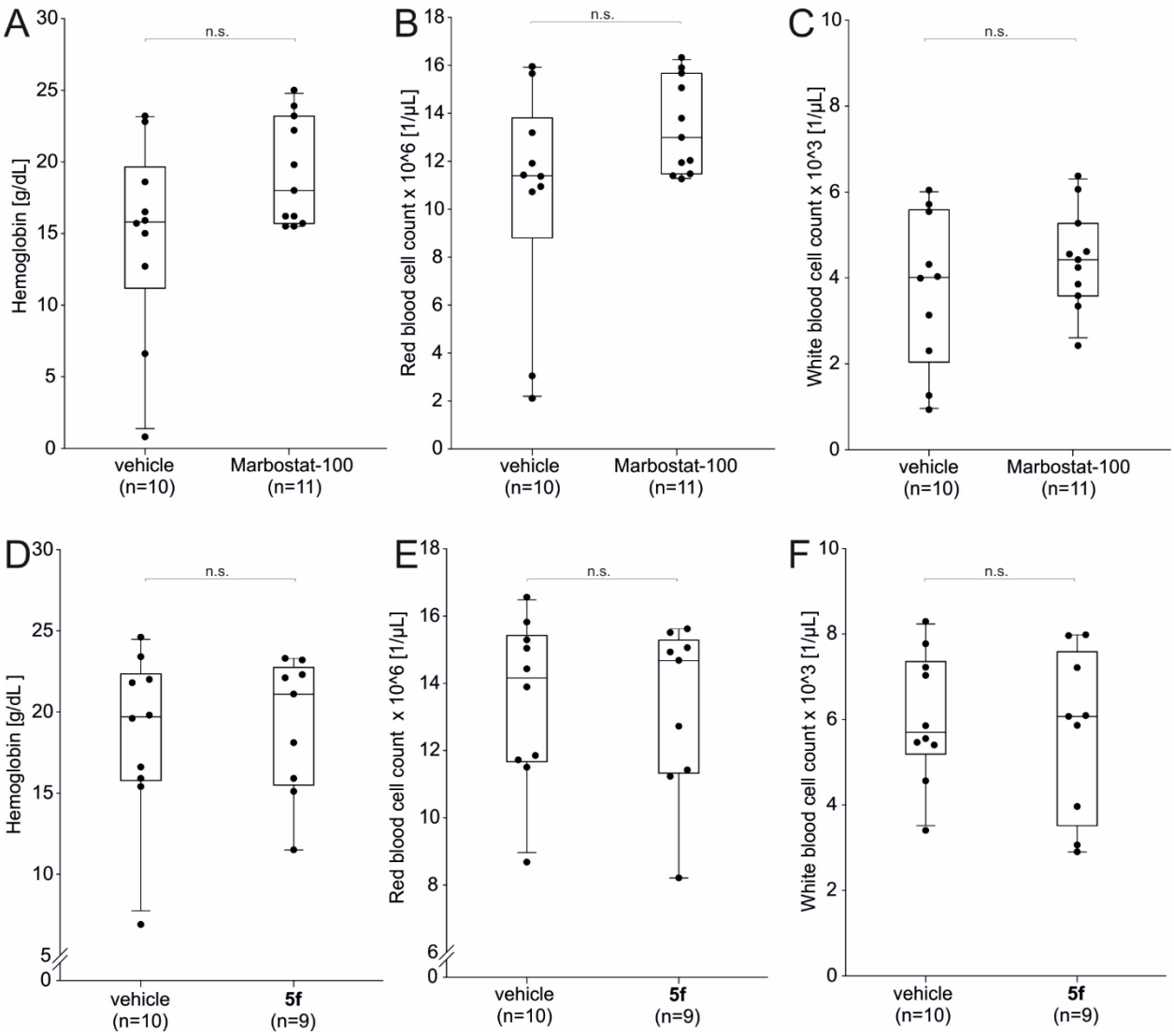
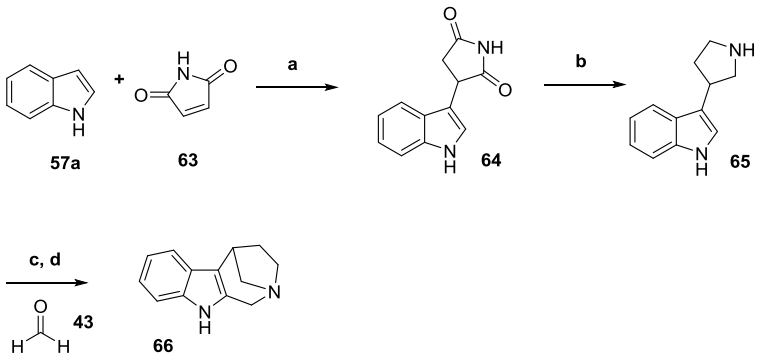



**Figure S3. Hematogram from Marbostat-100and compound 5f treatment groups in CIA.** Hemoglobin (A), red blood cell count (B), and white blood cell count (C) from the first experiment testing Marbostat-100 (30mg/kg) against vehicle treatment in CIA. Hemoglobin (D), red blood cell count (E), and white blood cell count (F) from the second experiment testing compound **5f** (42.3mg/kg) against vehicle treatment in CIA. One dot represents the value of one blood sample and mouse analyzed. See figure legend in the main part for explanation of box plots and abbreviations.

## Synthesis schemes for intermediates and non-key-compounds

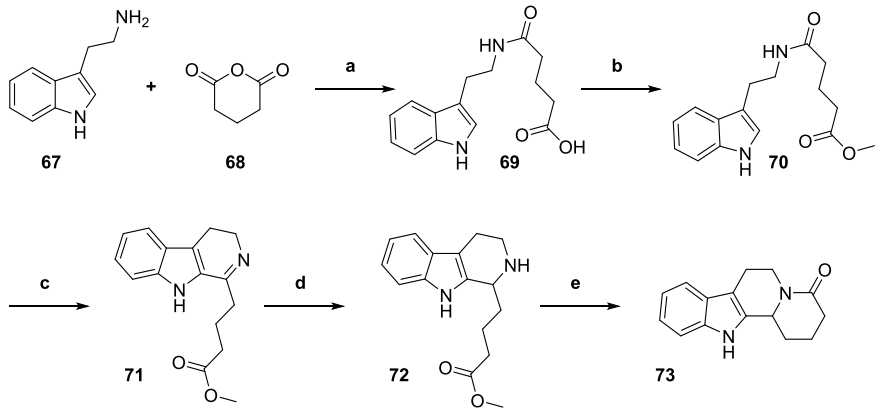
**Scheme S1.** Synthesis of methylene bridged tetrahydro-*β*-carboline (HEAD 1)[a].




[a]Reagents and conditions: (a) AcOH, Δ, 48 h.(b) THF, $LiAlH_4$, 65 °C, 16 h.(c) EtOH, TFA, formaldehyde (**43**), 60 °C, 3 h.(d) Methoxyamine hydrochloride, $H_2O$, 60 °C, 2 h.

Modified from the literature[3, 4] 1*H*-pyrrole-2,5-dione (**63**) was added to indole (**57a**) to give **64**. Reduction of **64** using $LiAlH_4$ led to the secondary amine **65**.[5, 6]The ring closure to **66** was performed with formaldehyde (**43**) by acidic catalysis.[5]

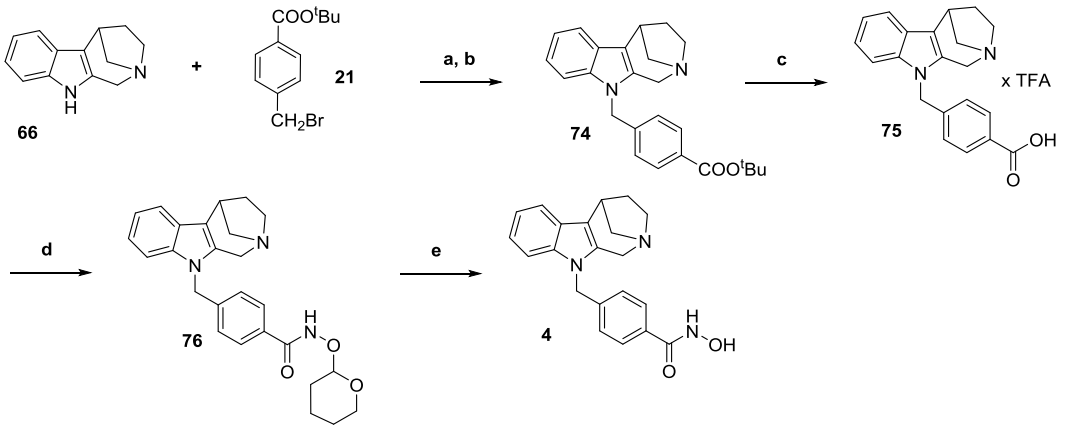
**Scheme S2.** Synthesis of head group 3, a tetrahydro-*β*-carboline angularly fused with a cyclohexanone[a].




[a]Reagents and conditions: (a) THF, glutaric anhydride **68**, rt, 20 min. (b) MeOH, $SOCl_2$, 20 °C, 3 h.(c) toluene, MeCN, $POCl_3$, reflux, 5 h.(d) MeOH, $NaBH_4$, rt, 1 h.(e) MeOH, $HCl_{aq}$, rt, 1 h.

Compound **73** (scheme S2), a tetrahydro-*β*-carboline angularly fused with a cyclohexanone which was investigated as head group, was prepared as follows: Tryptamine (**67**) was reacted with glutaric acid anhydride (**68**) and directly esterified according to Da Silva *et al.* to **70**.[7] The imine **71** was obtained by Bischler-Napieralski cyclization.[8, 9] Subsequent ring closure was achieved by sodium borohydride reduction and acidic catalyzation to afford **73**.[10]

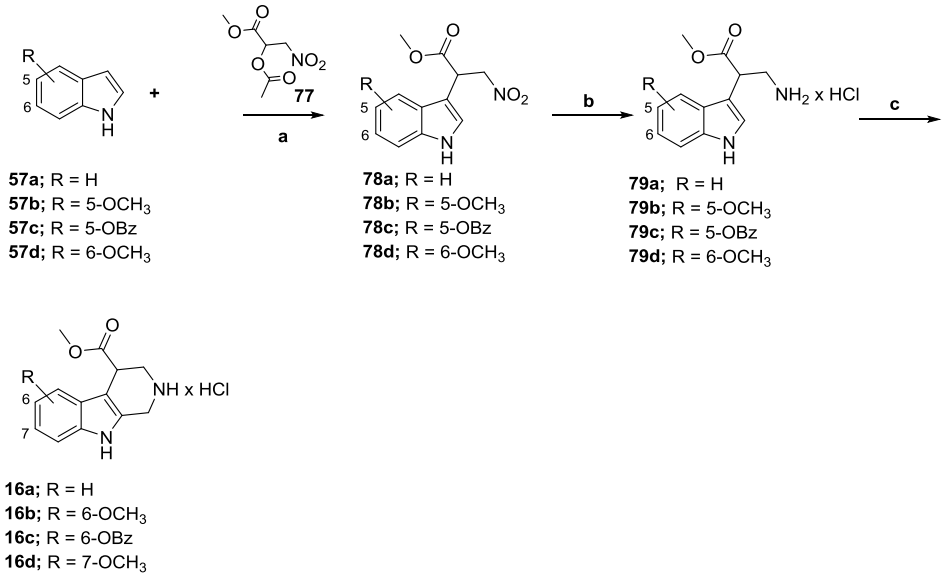
**Scheme S3.** Synthesis of compound **4**[a].




[a]Reagents and conditions: (a) DMF, NaH, 0 °C, 15 min. (b) rt, 1 h.(c) TFA, rt, 30 min. (d) DMF, BOP **25**, $NH_2OTHP$ **26**, rt, 2 - 3 h.(e) MeOH, $HCl_{aqu.}$, rt.

Compound **4**, bearing the 1,3,4,9-tetrahydro-2,4-methanopyrido[3,4-b]indolyle as a tetracylic head group 1 was available from the respective indole derivative **66**[5]as shown in scheme S3a. The general synthetic strategy to obtain methyl-2,3,4,9-tetrahydro-1*H*-pyrido [3,4-*b*] indole-4-carboxylate hydrochlorides (**16a-d**)[11] as intermediates for the synthesis of derivatives bearing head group 2 and derivatives thereof is shown in scheme S4. $Al_2O_3$ catalyzed addition of methyl 2-acetoxy-3-nitropropanoate (**71**)[12, 13] to the indoles **57a-d** according to Ballini *et al.*[14]initially leads to racemic methyl 2-(1*H*-indol-3-yl)-3-nitropropanoates (**78a-d**). Reduction with Zn/HCl and alkaline work-up gives methyl 3-amino-2-(1*H*-indol-3-yl) propanoates (**79a-d**),[11] which were purified by conversion into their hydrochlorides. Pictet-Spengler reaction of the hydrochlorides **79a-d** with formaldehyde (**43**) according to Shi *et al.*[15] leads to the formation of methyl-2,3,4,9-tetrahydro-1*H*-pyrido [3,4-*b*] indole-4-carboxylate hydrochlorides (**16a-d**).[11]

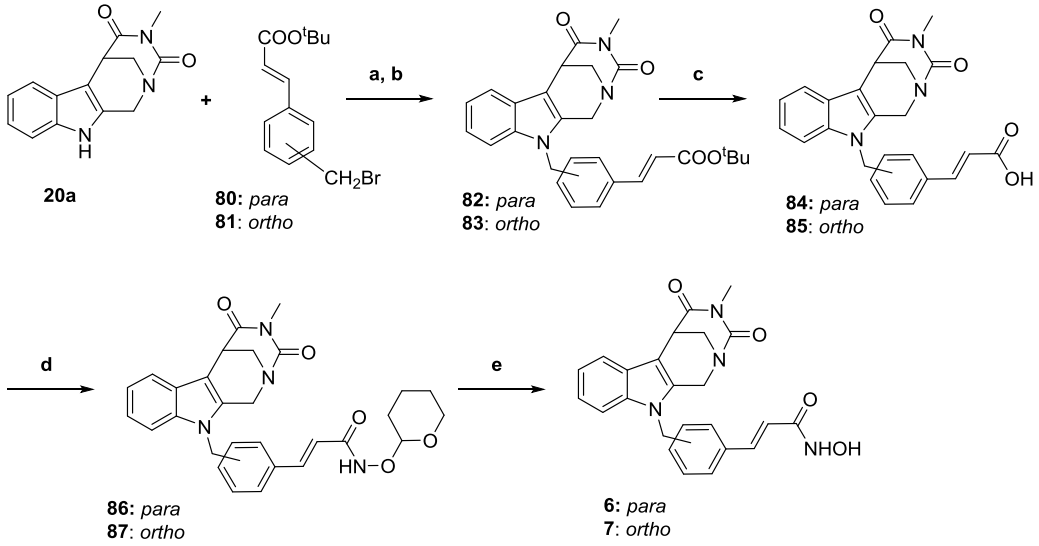
**Scheme S4.** Synthesis of **16a-d** for modification of head group 2[a].




[a]Reagents and conditions: conditions: (a) $Al_2O_3$, 2 h, 65 °C. (b) MeOH, THF, Zn, HCl. (c) MeOH, formaldehyde (**43**), 16 h, rt.

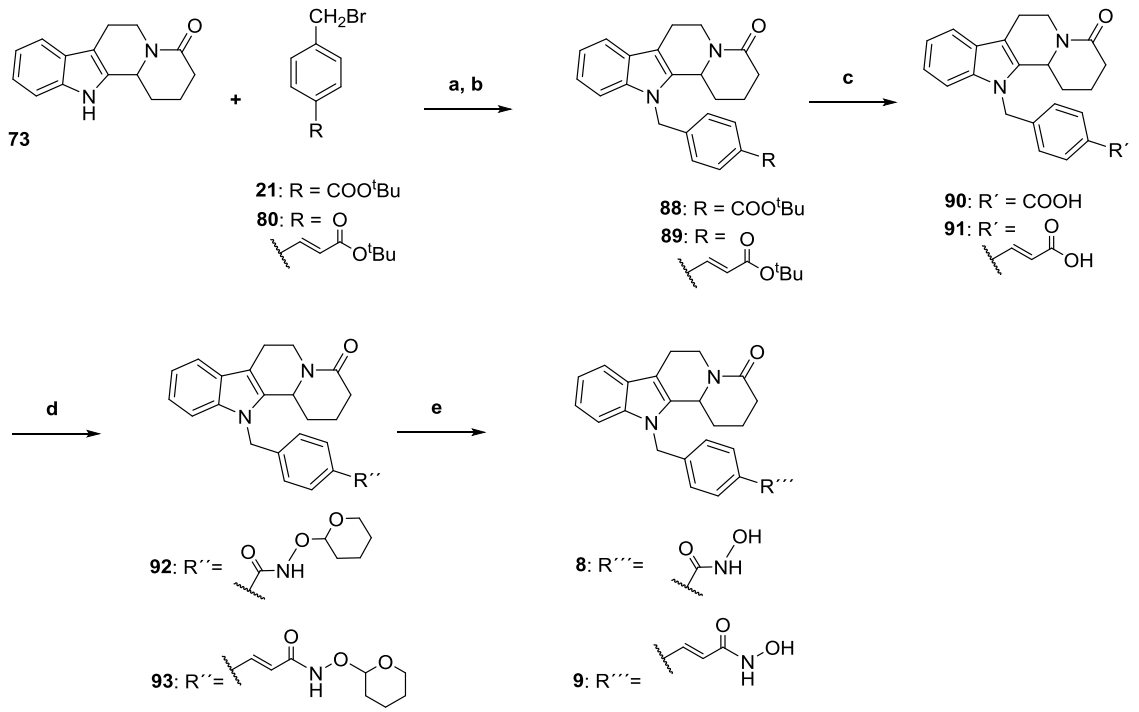
Use of bromomethylphenylacrylates **80**[16, 17] or **81**[17, 18] for alkylation of **20a** following the same reaction pathways led to the acrylic acid derivatives **6** and **7**, respectively (scheme S5).

**Scheme S5.** Synthesis of Marbostat-100 derivatives **6** and **7** with an acryl linker[a].




[a]Reagents and conditions: (a) DMF, NaH, 0 °C, 15 min. (b) rt, 1 h.(c) TFA, rt, 30 min. (d) DMF, BOP (**25**), $NH_2OTHP$ (**26**), rt, 2 - 3 h.(e) MeOH, $HCl_{aqu}$, rt.

**Scheme S6.** Synthesis of target compounds **8** and **9** with an angular fused D-ring incorporated into the head group[a].



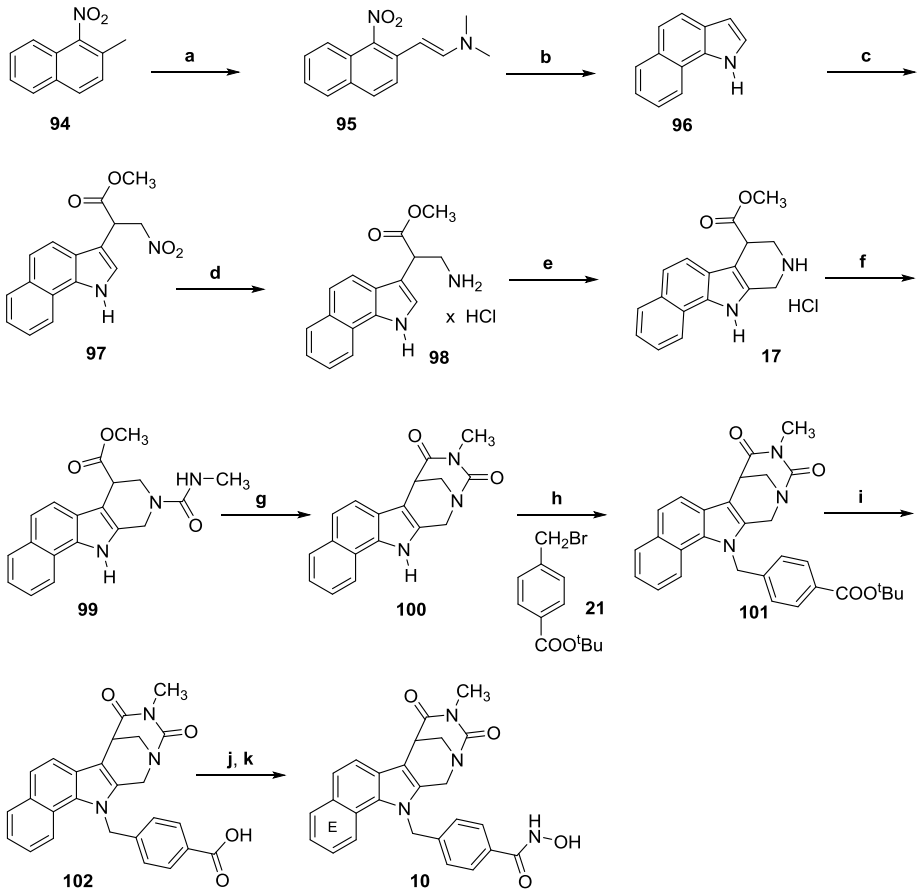

[a]Reagents and conditions: (a) DMF, NaH, 0 °C, 15 min. (b) rt, 1 h.(c) TFA, rt, 30 min. (d) DMF, BOP, $NH_2OTHP$, rt, 2 - 3 h.(e) MeOH, $HCl_{aqu}$, rt.

The target compounds **8** and **9** with an angularly fused D-ring incorporated into the head group were prepared by use of 1,2,3,6,7,12*b*-hexahydroindolo[2,3-*a*]quinolizin-4(12*H*)-one (**73**)[10] and

tert-butyl 4-(bromomethyl)benzoate (**21**) or (*E*)-tert-butyl 3-(4-(bromomethyl)phenyl)acrylate (**80**) (scheme S5), respectively.

Head group 4 with an angularly fused benzene ring as an E-ring system (scheme S7) was built up starting from 2-methyl-1-nitronaphthalene (**94**), which was transformed into (*E*)-*N*,*N*-dimethyl-2-(1-nitronaphthalen-2-yl)ethenamine (**95)** by use of DMFDMA according to Riesgo *et al.*.[19] Ring closure by reduction according to *Siu et al.*[20] led to 1*H*-benzo[*g*]indole (**96**). Using the reaction sequence described for the synthesis of Marbostat-100 - addition of methyl 2-acetoxy-3-nitropropanoate (**77**)[12, 13] according to Ballini *et al.*[14], reduction, Pictet-Spengler reaction[11], reaction with 2,5-dioxopyrrolidin-1-yl methylcarbamate and subsequent cyclization yielded **100,** which was alkylated by use of **21** and transformed to the final compound **10**in 3 steps.

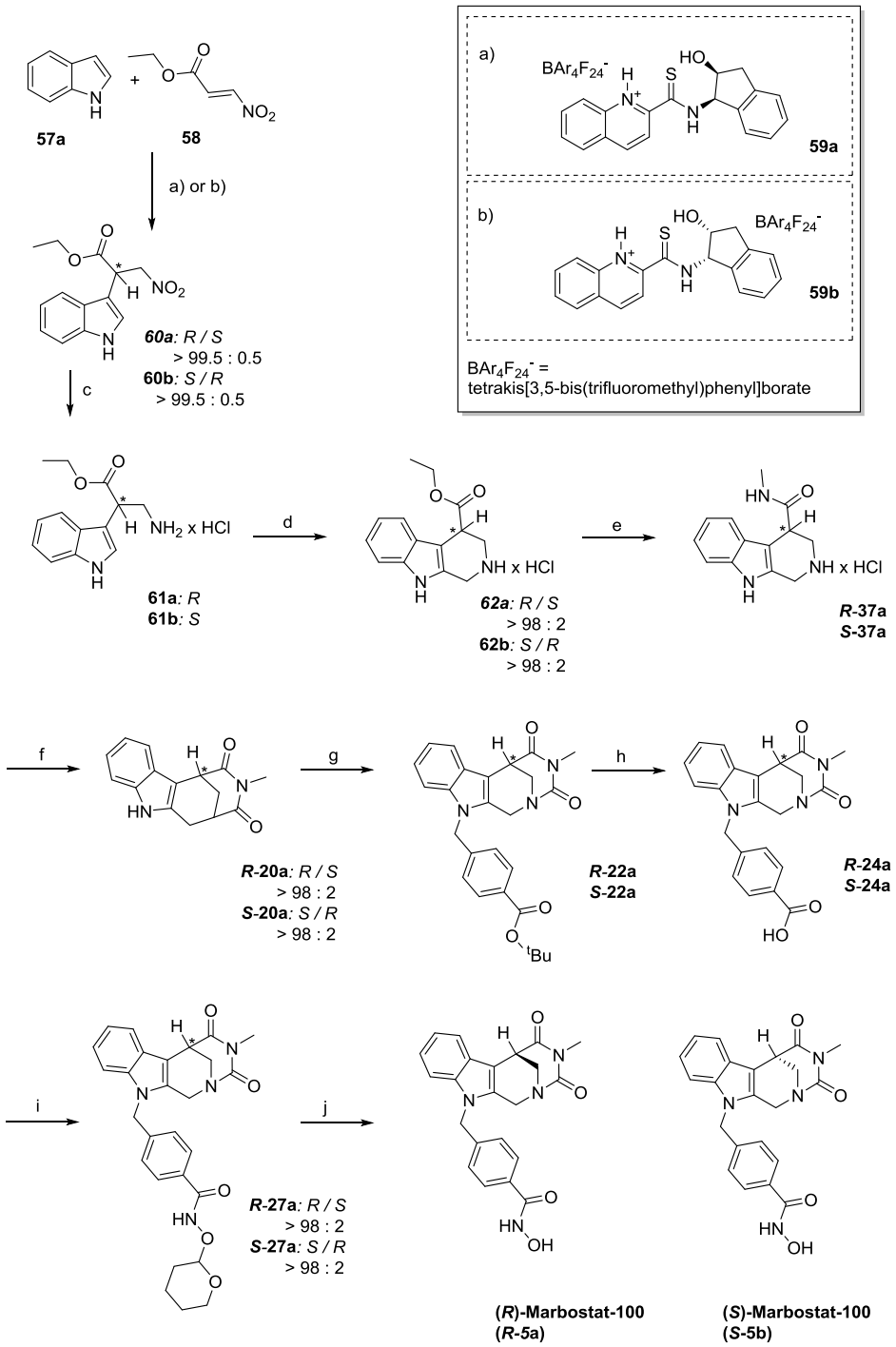
**Scheme S7.** Synthesis of target compound **10**, using head group 4 with an angularly fused benzene ring (E-ring system) incorporated into the head group[a].




[a]Reagents and conditions: (a) DMFDMA, DMF, 6 h 140 °C, 26 h 25 °C. (b) Pd/C (10 %), $H_2$, MeOH, $CH_2Cl_2$, 18 h.(c) $Al_2O_3$, **77**, 2 h, 65 °C. (d) MeOH, THF, Zn, HCl. (e) MeOH, formaldehyde (**43**), 16 h, rt. (f) MeCN, $EtN(^iProp)_2$, 2,5-dioxopyrrolidin-1-yl methylcarbamate (**18**), rt, 16 h.(g) dioxane, $Cs_2CO_3$, 110 °C, 2 h. (h) 2-butanone, $K_2CO_3$, Δ, 16 h.(i) TFA, rt, 30 min. (j) DMF, BOP, $NH_2OTHP$, rt, 2 - 3 h. (k) MeOH, $HCl_{aqu.}$, rt.

The enantioselective synthesis of *R*- and *S*-Marbostat-100 (*R*-**5a** / ***S***-**5a**) is shown in scheme S8.

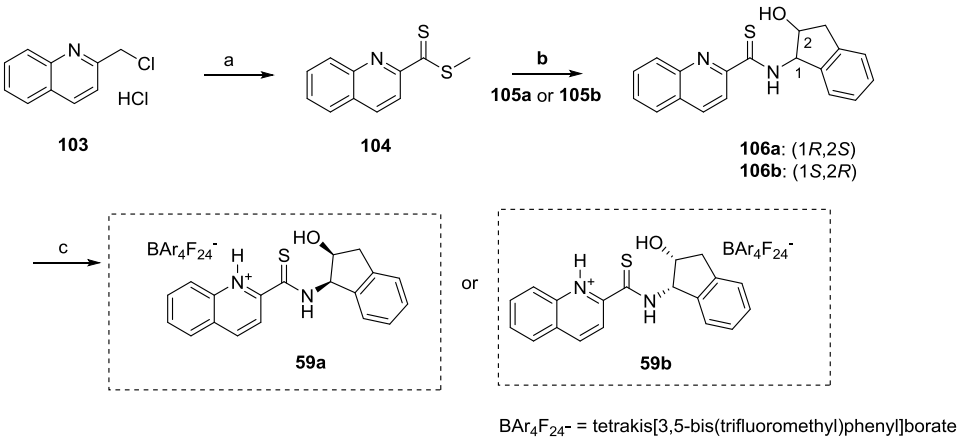
**Scheme S8:** Enantioselective synthesis of *R*- and *S*-Marbostat-100 (*R*-**5a** / *S*-**5a**)




[a]Reagents and conditions: (a) 2-(((1R,2S)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)carbamothioyl)quinolin-1-ium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (**59a**), $CHCl_3$, - 60 °C, 16 h.(b) 2-(((1S,2R)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)carbamothioyl)quinolin-1-ium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (**59b**), $CHCl_3$, -60 °C, 16 h.(c) ) MeOH, THF, Zn, HCl. (d) Formaldehyde (**43**), MeOH, rt, 24 h.(e) $CH_3NH_2$, NaCN (kat), MeOH, O °C, 5d.(f) Triphosgene, pyridine, $CH_2Cl_2$, 0 °C.(g) (**21**), $K_2CO_3$, 2-butanone, 80 °C, 10 h.(h) $CH_2Cl_2$, $CF_3COOH$, rt. (i) $NH_2OTHP$ (**26**), BOP (**25**), $(^iProp)_2NEt$, THF, rt, 2 h. (j) MeOH, $HCl_{aqu.}$, rt.

The synthesis of the respective cis-aminoindanol thiourea organocatalysts **59a** and **59b** used for the enantioselective additions of indole **57a** to (*E*)-ethyl 3-nitroacrylate (**58**) was performed following literature procedures[21] as shown in scheme S13. Reaction of 2-(chloromethyl)quinoline hydrochloride(**103**) with sulfur, followed by alkylation with iodomethane resulted in formation of methyl quinoline-2-carbodithioate (**104**), which was further reacted with (1*R*,2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-ol (**105a**), respective (1*S*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-ol (**105b**) to form the precatalysts**106a** (1*R*,2*S*) and **106b** (1*S*,2*R*). By treatment of the precatalysts with trifluoromethanesulfonic acid and sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate in $CHCl_3$ solution the active thiourea catalysts **59a** and **59b** were prepared *in situ*.

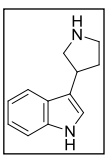
**Scheme S9:** Synthesis of 2-(((1*R*,2*S*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)carbamothioyl)quinolin-1-ium–tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (**59a**) and 2-(((1*S*,R*S*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)carbamothioyl)quinolin-1-ium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (**59b**)[a]




[a]Reagents and conditions: (a) i) S, $NEt_3$, DMSO, 3 h, ii) $CH_3I$.(b) (1*R*,2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-ol (**105a**), respective (1*S*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-ol (**105b**), $CH_2Cl_2$, 20 °C, 16 h. (c) trifluoromethanesulfonic acid, sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate, $CHCl_3$, 20 °C.

## Analytical data and preparation of intermediates

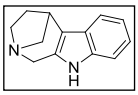
### 3-(Pyrrolidin-3-yl)-1*H*-indole (65)[5, 6, 22]



Following the literature[5, 6], indole (**57a**) (10.0 mmol) and maleimide (**63**) (30.0mmol) were dissolved in AcOH (50.0 mL) under $N_2$ and refluxed for 48h (TLC monitoring). The reaction mixture was concentrated, sat. $NaHCO_3$ solution (50.0 mL) was added

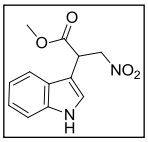
and the mixture extracted with EtOAc (3 x 50.0 mL). The combined organic layers were dried ($NaSO_4$) and concentrated under reduced pressure. The oily residue was purified bycc ($CH_2Cl_2$/ EtOAc2:1) to obtain **64**. **64** (9.0 mmol) was dissolved whilst stirring in a suspension of $LiAlH_4$ (45.0 mmol, 5 equ.) in anhydrous THF (50 mL, 0 °C, Ar). The solution was stirred at 65 °C for 16 h (TLC monitoring), cooled to rt and quenched with $Na_2SO_4$ x 10 $H_2O$ (15.0 g). Water (1.0 mL) and EtOAc (150 mL) were added and stirring was continued overnight. The suspension was filtered over Celite, the solvent was evaporated and cc ($CH_2Cl_2$ / MeOH / ammonia 3:1:0.1) and crystallization from MeCN yielded 1.10 g (5.91 mmol, 65 %) red-brown solid. mp: 103.1-104.8 °C, lit.[22]: 102.0-104.5 °C (MeCN); $^1$H NMR (300 MHz, DMSO-$d_6$): δ 10.93 (s, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.16 (s, 1H), 7.07 (m, 1H), 6.97 (m, 1H), 3.91 (bs, 1H), 3.45 – 3.23 (m, 2H), 3.13 – 2.89 (m, 2H), 2.87 – 2.73 (m, 1H), 2.33 – 2.07 (m, 1H), 1.95 – 1.73 (m, 1H). EI-MS (70 eV) *m/z* (%): 186 [$M^{+}$·] (100), 144 (92).

**3,4,5,10-Tetrahydro-1*H*-2,5-methanoazepino[3,4-*b*]indole (66)[5]**



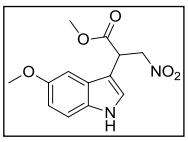
The Pictet-Spengler reaction was carried out in analogy to lit.[5].3-(Pyrrolidin-3-yl)-1*H*-indole (**65**) (3.22 mmol) was dissolved in EtOH (50.0 mL). 1.0 equ. TFA and 3 equ. of formaldehyde (**43**) (36 % in water) were added and the mixture was heated to reflux for 3 h. 2 equ. methoxyamine hydrochloride and 6.0 mL $H_2O$ were added and reflux was continued for 2 h. The mixture wasconcentrated under reduced pressure and extracted with EtOAc (3 x 50.0 mL). The organic phase was washed with sat. $NaHCO_3$ solution and dried over sodium sulfate. Crystallization from EtOH overnight afforded 0.41 g (2.10mmol,65 %) colorless crystals from EtOAc. mp: 261.8-262.6 °C, lit.[5]: 262-263 °C (EtOAc). $^1$H NMR (300 MHz, DMSO-$d_6$): δ 10.61 (s, 1H), 7.47 – 7.38 (m, 1H), 7.28 – 7.19 (m, 1H), 7.01 – 6.87 (m, 2H), 4.31 (d, *J* = 16.9 Hz, 1H), 3.64 (d, *J* = 16.9 Hz, 1H), 3.30 – 3.22 (m, 1H), 3.20 – 3.05 (m, 1H), 2.90 (d, *J* = 10.6 Hz, 1H), 2.83 – 2.65 (m, 2H), 1.98 – 1.80 (m, 2H). ESI-MS *m/z* (%): 239 [$MH^{+}$+MeCN] (100), 198 [$MH^{+}$] (40).

**Methyl 2-(1*H*-indol-3-yl)-3-nitropropanoate (78a)[14]**



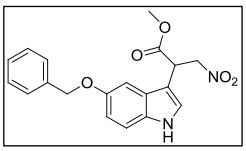
**78a** was prepared as described by Ballini *et al.*[14].$^1$H NMR (300 MHz, DMSO-$d_6$): δ 11.22 (s, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.39 (dd, *J* = 5.3, 2.7 Hz, 2H), 7.22 – 7.08 (m, 1H), 7.08 – 6.98 (m, 1H), 5.30 (dd, *J* = 14.9, 10.4 Hz, 1H), 4.95 (dd, *J* = 14.9, 5.1 Hz, 1H), 4.74 (dt, *J* = 12.0, 6.0 Hz, 1H), 3.62 (s, 3H).

**Methyl 2-(5-methoxy-1*H*-indol-3-yl)-3-nitropropanoate (78b)**



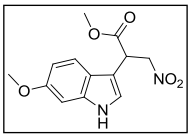
Preparation according to Ballini *et a*l..[14]Yield 4.56 g (82 %) yellow crystals. IR (KBr): 3375, 1726 $cm^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): δ 8.24 (s, 1H), 7.27 (d, *J* = 8.8 Hz, 1H), 7.08 (dd, *J* = 5.1, 2.5 Hz, 2H), 6.90 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.20 (dd, *J* = 14.2, 9.7 Hz, 1H), 4.72 (dd, *J* = 9.7, 5.0 Hz, 1H), 4.63 (dd, *J* = 14.2, 5.0 Hz, 1H), 3.87 (s, 3H), 3.74 (s, 3H). ESI-MS *m/z* (%): 218.08 [$MH^{+}$-$CH_3NO_2$] (100), 279.09 [$MH^{+}$] (99). Anal. calcd for $C_{13}H_{14}N_2O_5$: C 56.11; H 5.07; N 10.07; found: C 55.58; H 5.06; N 9.67.

**Methyl 2-(5-(benzyloxy)-1*H*-indol-3-yl)-3-nitropropanoate (78c)**[23]. was prepared according to Ballini *et a*l..[14]

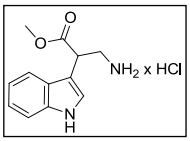


Yield 8,70 g (73 %) brown oil.$^1$H NMR (300 MHz, DMSO-$d_6$): δ 11.08 (d, *J* = 2.8 Hz, 1H), 7.52 – 7.46 (m, 2H), 7.43 – 7.23 (m, 6H), 6.84 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.26 (dd, *J* = 15.0, 10.5 Hz, 1H), 5.11 (s, 2H), 4.91 (dd, *J* = 15.1, 4.8 Hz, 1H), 4.71 (dd, *J* = 10.5, 4.8 Hz, 1H).

**Methyl 2-(6-methoxy-1*H*-indol-3-yl)-3-nitropropanoate (78d)** was prepared according to Ballini et al.[14]. Yield 5.10 g (52 %) brown oil. IR (KBr): 3424, 2924, 1733, 1627 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 10.99 (s, 1H), 7.49 (d, *J* = 8.7 Hz, 1H), 7.23 (d, *J* = 2.4 Hz, 1H), 6.88 (d, *J* = 2.2 Hz, 1H), 6.71 (dd, *J* = 8.7, 2.3 Hz, 1H), 5.26 (dd, *J* = 14.9, 10.4 Hz, 1H), 4.92 (dd, *J* = 14.9, 5.1 Hz, 1H), 4.69 (dd, *J* = 10.4, 5.0 Hz, 1H), 3.76 (s, 3H). ESI-MS *m/z* (%): 278.9 [MH$^+$] (100), [MH$^+$ + $CH_3CN$] 320.0 (70). Anal. calcd for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.07; found: C 56.16; H 5.21; N 10.04.

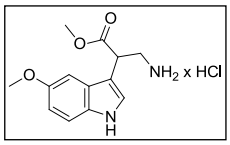


**Methyl 3-amino-2-(1*H*-indol-3-yl)propanoate hydrochloride (79a)**[11]



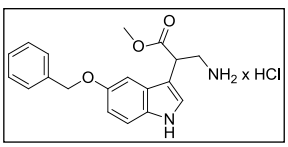
To a solution of methyl 2-(1*H*-indol-3-*yl*)-3-nitropropanoate (**78a**) (6.20 g; 25.0 mmol) in THF (155 mL) and MeOH (155 mL) were added zinc dust (31.0 g) and $CuSO_4$ (0.62 g). The solution was stirred and HCl (3N, 310 mL) was added dropwise in a rate, that the solution heated to reflux. The solution was stirred for 2 h, filtrated and then adjusted to pH 14 with $NH_3$ conc. The product was extracted with $CH_2Cl_2$ (3 x 100 mL). The combined organic layers were dried ($Na_2SO_4$) and evaporated. The residue was dissolved in THF (60 mL) and HCl (6N in dioxane) was added with stirring. The colorless product was filtered off, washed with THF and $Et_2O$ and dried. Yield 5.30 g (83 %) colorless crystals. mp: 199.5-199.7 °C. IR (KBr): 3312, 3022, 2977, 1732 cm$^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$): δ 11.28 (s, 1H), 8.20 (s, 3H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 2.5 Hz, 1H), 7.17 – 6.98 (m, 2H), 4.35 (dd, *J* = 7.9, 6.8 Hz, 1H), 3.61 (d, *J* = 7.6 Hz, 3H), 3.49 (s, 1H), 3.17 (s, 1H). ESI-MS *m/z* (%): 219 [MH$^+$] (100).

**Methyl 3-amino-2-(5-methoxy-1*H*-indol-3-yl)propanoate hydrochloride (79b)**[24]



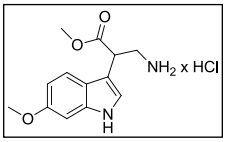
As described for **79a** from methyl 2-(5-methoxy-1*H*-indol-3-yl)-3-nitropropanoate (**78b**) (7.18 g; 25.00 mmol). Yield 5.96 g (84 %) colorless crystals. mp: 213.7-214.6 °C (THF), lit.[24]: 212-214 °C (MeOH / ETOAC). $^1$H NMR (300 MHz, DMSO-$d_6$): δ 11.12 (d, *J* = 1.9 Hz, 1H), 8.20 (s, 3H), 7.28 (t, *J* = 5.1 Hz, 1H), 7.26 (d, *J* = 2.6 Hz, 1H), 7.10 (d, *J* = 2.4 Hz, 1H), 6.77 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.33 (dd, *J* = 8.1, 6.4 Hz, 1H), 3.76 (s, 3H), 3.64 (s, 3H), 3.46 (dd, *J* = 12.7, 8.3 Hz, 1H), 3.13 (dd, *J* = 12.7, 6.3 Hz, 1H). ESI-MS *m/z* (%): 285 [MH$^+$] (100).

**Methyl 3-amino-2-(5-(benzyloxy)-1*H*-indol-3-yl)propanoate (79c)**[25]



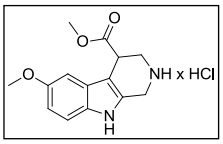
**79c** was prepared from methyl 2-(5-(benzyloxy)-1*H*-indol-3-yl)-3-nitropropanoate (**78c**) (18.58 g; 52.4 mmol) as described for **79a**. Yield 14.98 g; 79 % colorless crystals. $^1$H NMR (300 MHz, DMSO-$d_6$): δ 11.10 (d, *J* = 2.2 Hz, 1H), 8.03 (s, 3H), 7.53 – 7.23 (m, 7H), 7.17 (d, *J* = 2.3 Hz, 1H), 6.86 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.24 (dd, *J* = 8.0, 6.6 Hz, 1H), 3.61 (s, 3H), 3.46 (dd, *J* = 12.7, 8.3 Hz, 1H), 3.14 (dd, *J* = 12.7, 6.4 Hz, 1H).

**Methyl 3-amino-2-(6-methoxy-1*H*-indol-3-yl)propanoate hydrochloride (79d)**



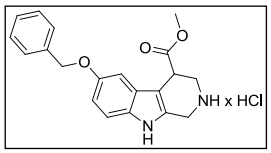
As described for **79a** from methyl 2-(6-methoxy-1*H*-indol-3-yl)-3-nitropropanoate (**78d**). Yield 3.80 g; 13.30 mmol (67 %) colorless crystals. IR (KBr): 1724, 3414 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 11.06 (d, *J* = 1.5 Hz, 1H), 8.19 (s, 3H), 7.44 (d, *J* = 8.7 Hz, 1H), 7.18 (d, *J* = 2.4 Hz, 1H), 6.89 (d, *J* = 2.2 Hz, 1H), 6.70 (dd, *J* = 8.7, 2.3 Hz, 1H), 4.30 (dd, *J* = 8.1, 6.5 Hz, 1H), 3.76 (s, 3H), 3.62 (s, 3H), 3.54 – 3.39 (m, 1H), 3.14 (s, 1H). ESI-MS *m/z* (%): 249 [$MH^+$] (100).

**Methyl 6-methoxy-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-4-carboxylate hydrochloride (16b)[26]**



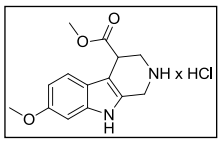
As described for **16a** from methyl 3-amino-2-(5-methoxy-1*H*-indol-3-yl)propanoate hydrochloride (**79b**). Yield 2.58 g (87 %) colorless crystals. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 11.21 (s, 1H), 10.26 (s, 1H), 9.21 (s, 1H), 7.29 (d, *J* = 8.8 Hz, 1H), 7.00 (d, *J* = 2.3 Hz, 1H), 6.77 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.39 – 4.26 (m, 2H), 4.22 (t, *J* = 4.8 Hz, 1H), 3.75 (s,, 3H), 3.72 (s, 3H), 3.66 (d, *J* = 4.6 Hz, 1H), 3.52 (dd, *J* = 12.8, 5.2 Hz, 1H).

**Methyl 6-(benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-4-carboxylate hydrochloride (16c)**



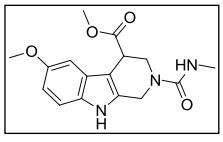
As described for **16a** from methyl 3-amino-2-(5-(benzyloxy)-1*H*-indol-3-yl)propanoate hydrochloride (**79c**). Yield 11.2 g; 30.0 mmol (77 %) colorless crystals. mp: 254.1-254.3 °C. IR (KBr): 3442, 3195, 1732 $cm^{-1}$.[1].$^1H$ NMR (300 MHz, DMSO-$d_6$): δ 11.23 (s, 1H), 9.72 (s, 2H), 7.54 – 7.24 (m, 6H), 7.08 (d, *J* = 2.4 Hz, 1H), 6.86 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.09 (s, 2H), 4.35 (d, *J* = 16.1 Hz, 1H), 4.29 (d, *J* = 15.9 Hz, 1H), 4.19 (t, *J* = 4.8 Hz, 1H), 3.68 (dd, *J* = 12.1, 3.8 Hz, 1H), 3.65 (s, 3H), 3.51 (dd, *J* = 12.9, 5.3 Hz, 1H). ESI-MS *m/z* (%): 337.15 [$MH^+$] (100). Anal. calcd for $C_{20}H_{21}ClN_2O_3$: C 64.43; H 5.86; N 7.51; found: C 65.63; H 5.84; N 7.46.

**Methyl 7-methoxy-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-4-carboxylate hydrochloride (16d)**



As described for **16a** from methyl 3-amino-2-(6-methoxy-1*H*-indol-3-yl)propanoate hydrochloride (**79d**). Yield 3.53 g; 11.90 mmol (89 %) colorless crystals. mp: 233.1 – 235.2 °C. IR (KBr): 3426, 3154, 1733 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 11.20 (s, 1H), 10.31 (s, 1H), 9.25 (s, 1H), 7.39 (d, *J* = 8.7 Hz, 1H), 6.90 (d, *J* = 2.2 Hz, 1H), 6.70 (dd, *J* = 8.7, 2.3 Hz, 1H), 4.39 – 4.24 (m, 2H), 4.21 (t, *J* = 5.0 Hz, 1H), 3.76 (s, 3H), 3.69 (s,, 3H), 3.66 (dd, *J* = 12.9, 4.9 Hz, 1H), 3.55 – 3.46 (m, 1H). ESI-MS *m/z* (%): 261 [$MH^+$] (100). Anal. calcd for $C_{14}H_{17}ClN_2O_3$: C 56.66; H 5.77; N 9.44; found: C 56.70; H 5.85; N 9.16.

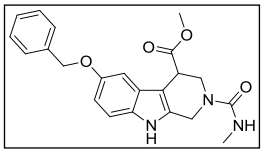
**Methyl 6-methoxy-2-(methylcarbamoyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-4-carboxylate (19b)**



As described for **19a** from methyl methyl 6-methoxy-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-4-carboxylate hydrochloride (**16b**) (0.75 g; 2.53 mol) and *N*-succinimidyl-*N*-methyl-carbamate (**18**) (0.52 g; 3.00 mol). Colorless

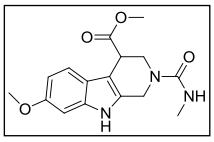
crystals 0.61 g (1.92 mmol; 76 %); mp: 233.5-234.2 °C. IR (KBr): 3345, 1730, 1634 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 10.88 (s, 1H), 7.21 (d, *J* = 8.7 Hz, 1H), 6.82 (d, *J* = 2.4 Hz, 1H), 6.69 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.63 (q, *J* = 3.9 Hz, 1H), 4.57 (d, *J* = 16.4 Hz, 1H), 4.47 (d, *J* = 16.6 Hz, 1H), 3.96 (dd, *J* = 13.1, 5.7 Hz, 1H), 3.78 – 3.67 (m, 4H), 3.65 (s, 3H), 2.60 (d, *J* = 4.2 Hz, 3H). ESI-MS m/z (%): 635 [2M+$H^+$] (100), 318 [$MH^+$] (62). Anal. calcd for ($C_{16}H_{19}N_3O_4$): C 60.56; H 6.03; N 13.24; found: C 60.66; H 6.08; N 13.32.

**Methyl 6-(benzyloxy)-2-(methylcarbamoyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-4-carboxylate (19c)**



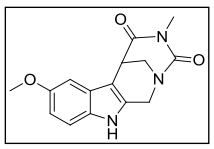
As described for **19a** from methyl 6-(benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-4-carboxylate hydrochloride (**16c**) and *N*-succinimidyl-*N*-methyl-carbamate (**18**). Colorless crystals 10.69 g (27.17 mmol; 99 %). IR (KBr): 3418, 1730, 1635, 1612, 1593 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 10.90 (s, 1H), 7.52 – 7.27 (m, 5H), 7.22 (d, *J* = 8.7 Hz, 1H), 6.91 (d, *J* = 2.4 Hz, 1H), 6.78 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.62 (d, *J* = 4.4 Hz, 1H), 5.06 (s, 2H), 4.57 (d, *J* = 16.5 Hz, 1H), 4.47 (d, *J* = 16.7 Hz, 1H), 3.96 (dd, *J* = 13.3, 5.6 Hz, 1H), 3.85 (t, *J* = 4.8 Hz, 1H), 3.69 (dd, *J* = 13.3, 4.5 Hz, 1H), 3.60 (s, 3H), 2.59 (d, *J* = 4.2 Hz, 3H). ESI-MS m/z (%): 394.17 [$MH^+$] (100). Anal. calcd for ($C_{22}H_{23}N_3O_4$): C 67.16; H 5.89; N 10.68; found: C 67.13; H 5.91; N 10.65.

**Methyl 7-methoxy-2-(methylcarbamoyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-4-carboxylate (19d)**



As described for **19a** from methyl methyl 7-methoxy-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-4-carboxylate hydrochloride (**16d**) (3.45 g; 11.63 mmol) and *N*-succinimidyl-*N*-methyl-carbamate (**18**) (2.40 g; 13.95 mmol). Colorless crystals 2.90 g (9.13 mmol; 79 %); mp: 237.0-239.2 °C. IR (KBr): 3241, 1728 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 10.86 (s, 1H), 7.20 (d, *J* = 8.6 Hz, 1H), 6.83 (d, *J* = 2.2 Hz, 1H), 6.71 – 6.46 (m, 2H), 4.54 (d, *J* = 16.0 Hz, 1H), 4.46 (d, *J* = 16.0 Hz, 1H), 3.99 – 3.80 (m, 2H), 3.74 (s, 3H), 3.74 – 3.67 (m, 1H), 3.63 (s, 3H), 2.60 (d, *J* = 4.3 Hz, 3H). ESI-MS *m/z* (%): 635 [2M+$H^+$] (100), 318 [$MH^+$] (62). Anal. calcd for $C_{16}H_{19}N_3O_4$: C 60.56; H 6.03; N 13.24; found: C 60.34; H 6.00; N 13.09.

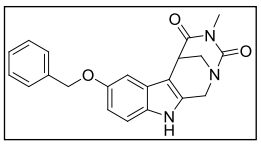
**8-Methoxy-4-methyl-6,11-dihydro-2,6-methano[1,3]diazocino[5,6-*b*]indole-3,5(1*H*,4*H*)-dione (20b)**



As described for **20a** from methyl 6-methoxy-2-(methylcarbamoyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-4-carboxylate (**19b**). Yield 0.52 g (1.82 mmol; 67 %) colorless crystals from EtOAc after cc ($SiO_2$; $CH_2Cl_2$, EtOAc; 1:1); mp: 253.0-253.6 °C. IR (KBr): 3287, 1718, 1687 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 11.02 (s, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 6.94 (d, *J* = 2.4 Hz, 1H), 6.73 (dd, *J* = 8.8, 2.5 Hz, 1H), 4.65 (s, 2H), 3.93 – 3.83 (m, 1H), 3.78 (d, *J* = 4.3 Hz, 1H), 3.76 (s, 3H), 3.42 (dd, *J* = 13.1, 2.2 Hz, 1H), 2.89 (s, 3H). $^{13}C$ NMR (75 MHz, DMSO-$d_6$): δ: 173.21 (s, 1C, quat.), 160.96 (s, 1C, quat.), 153.48 (s, 1C, quat.), 133.59 (s, 1C, quat.), 130.45 (s, 1C, quat.), 126.10 (s, 1C, quat), 112.22 (s, 1C, CH), 111.12 (s, 1C, CH), 104.50 (s, 1C, quat), 99.31 (s, 1C, CH), 55.21 (s, 1C, $OCH_3$), 49.58 (s, 1C, $CH_2$), 46.40 (s, 1C, $CH_2$), 35.96 (s, 1C, CH),

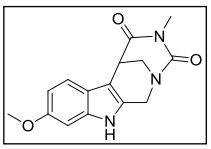
27.23 (s, 1C, $CH_3$). CI-MS ($NH_3$) *m/z* (%): 303 [M + $NH_4^+$] (100), 286 [$MH^+$] (24). Anal. calcd for $C_{15}H_{15}N_3O_3$: C 63.15; H 5.30; N 14.83; found: C 63.03; H 5.40; N 14.93.

**8-(Benzyloxy)-4-methyl-6,11-dihydro-2,6-methano[1,3]diazocino[5,6-*b*]indole-3,5(1*H*,4*H*)-dione (20c**)



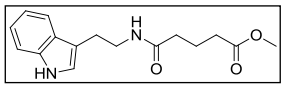
As described for **20a** from methyl 6-(benzyloxy)-2-(methylcarbamoyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-4-carboxylate (**19c**). Yield 3.87 g (10.7 mmol; 42 %); mp: 224.1-224.3 °C. IR (KBr): 3278, 1721, 1684 $cm^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$): δ 11.00 (s, 1H), 7.48 (dd, *J* = 8.1, 1.4 Hz, 2H), 7.43 – 7.28 (m, 3H), 7.24 (d, *J* = 8.8 Hz, 1H), 7.05 (d, *J* = 2.4 Hz, 1H), 6.81 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.09 (d, *J* = 12.2 Hz, 1H), 5.05 (d, *J* = 12.1 Hz, 1H), 4.63 (s, 2H), 3.88 (dd, *J* = 13.1, 1.2 Hz, 1H), 3.77 (s, 1H), 3.43 (dd, *J* = 13.1, 2.3 Hz, 1H), 2.88 (s, 3H). ESI-MS *m/z* (%): 362.15 $[MH]^+$ (100). Anal. calcd for $C_{21}H_{19}N_3O_3$: C 69.79; H 5.30; N 11.63; found: C 69.64; H 5.36; N 11.48.

**9-Methoxy-4-methyl-6,11-dihydro-2,6-methano[1,3]diazocino[5,6-*b*]indole-3,5(1*H*,4*H*)-dione (20d)**



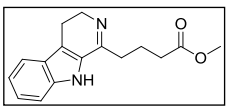
As described for **20a** from methyl 7-methoxy-2-(methylcarbamoyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-4-carboxylate (**19d**). Yield 1.52 g (5.33 mmol; 63 %) colorless crystals after silica gel chromatography ($CH_2Cl_2$, EtOAc; 1:1); mp: 223.1-225.3 °C. IR (KBr): 3306, 1724 $cm^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$): δ 10.93 (s, 1H), 7.32 (d, *J* = 8.6 Hz, 1H), 6.85 (d, *J* = 2.2 Hz, 1H), 6.68 (dd, *J* = 8.6, 2.3 Hz, 1H), 4.63 (d, *J* = 12.6 Hz, 1H), 4.58 (d, *J* = 16.8 Hz, 2H), 3.86 (d, *J* = 13.1 Hz, 1H), 3.75 (d, *J* = 3.6 Hz, 1H), 3.74 (s, 3H), 3.41 (dd, *J* = 13.1, 2.2 Hz, 1H), 2.87 (s, 3H). ESI-MS *m/z* (%): 327 [$MH^+$ + MeCN] (100), 571 [$2MH^+$] (61), 286 [$MH^+$] (14). Anal. calcd for $C_{15}H_{15}N_3O_3$: C 63.15; H 5.30; N 14.73; found: C 63.22; H 5.28; N 14.73.

**Methyl 5-((2-(1*H*-indol-3-yl)ethyl)amino)-5-oxopentanoate (70)[7]**



According to lit.[7]: tryptamine (**67**) (31.3 mmol) was dissolved in THF (100.0 mL), glutaric anhydride (**68**) (31.3 mmol in 10.0 mL THF) was added and the mixture stirred for 20 min. at rt. The solvent was evaporated and the residue dissolved in MeOH (40.0 mL). $SOCl_2$ (37.5 mmol) was added dropwise and stirring at rt was continued for 3 h. The solvent was removed and the product **70** purified by cc (EtOAc / MeOH 20:1). Yield 8.10 g (28 mmol, 89 % over 2 steps) colorless crystals; mp: 102.3-103.8 °C (EtOAc); lit.[7]: 101–102 °C;$^1$H NMR (300 MHz, $CD_3OD$): δ 7.58 – 7.52 (m, 1H), 7.34 – 7.28 (m, 1H), 7.11 – 7.03 (m, 2H), 7.03 – 6.95 (m, 1H), 3.64 (s, 3H), 3.47 (t, *J* = 7.3 Hz, 2H), 2.93 (t, *J* = 7.2 Hz, 2H), 2.28 (t, *J* = 7.4 Hz, 2H), 2.17 (t, 2H), 1.92 – 1.77 (m, 2H).

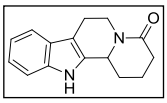
**Methyl 4-(4,9-dihydro-3*H*-pyrido[3,4-*b*]indol-1-yl)butanoate (71)[7]**



**70** (22.5 mmol) was dissolved in toluene (160.0 mL). MeCN (70.0 mL) and 3.0 equ. $POCl_3$ (66.0 mmol) were added and the mixture was refluxed for 5 h. The solvent was removed and the residue was dissolved in $CH_2Cl_2$ (400.0 mL). The solution was washed with 1 M $NaHCO_{3(aq)}$ (300.0 mL) and dried over $Na_2SO_4$. Yield 4.80 g (17.0 mmol; 80 %) red crystals from $CH_2Cl_2$; $^1$H NMR (300 MHz, $CDCl_3$): δ 9.79

(s, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 8.2 Hz, 1H), 7.31 – 7.26 (m, 1H), 7.17 – 7.13 (m, 1H), 3.88 (br t, *J* = 8.5 Hz, 2H), 3.76 (s, 3H), 2.92 – 2.84 (m, 2H), 2.68 (m, 2H), 2.51 (m, 2H), 2.09 – 1.96 (m, 2H).

**1,2,3,6,7,12*b*-Hexahydroindolo[2,3-*a*]quinolizin-4(12*H*)-one (73)[10]**

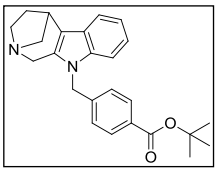


According to lit.[10]**71** (20.0 mmol) was dissolved in MeOH (100.0 mL) and $NaBH_4$ (20.0 mmol) was added. The mixture was stirred for 1 h at rt. The mixture was acidified with 10 % $HCl_{(aq)}$, stirred for 1 h and extracted with $CH_2Cl_2$ (3 × 200.0 mL). The combined organic layers were dried over sodium sulfate and purified by cc (EtOAc / MeOH 2:1). Yield 2.82 g (11.70 mmol, 58 %) crystals from $CH_2Cl_2$; $^1$H NMR (300 MHz, DMSO-$d_6$): 10.93 (s, 1H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.11 – 7.02 (m, 1H), 7.01 – 6.93 (m, 1H), 5.01 – 4.85 (m, 1H), 4.85 – 4.61 (m, 1H), 2.86 – 2.52 (m, 4H), 2.44 – 2.17 (m, 2H), 1.86 – 1.53 (m, 3H). $^1$H NMR (300 MHz, $CDCl_3$): δ 7.85 (s, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.38 – 7.31 (m, 1H), 7.23 – 7.16 (m, 1H), 7.16 – 7.08 (m, 1H), 5.24 – 5.11 (m, 1H), 4.83 – 4.74 (m, 1H), 2.94 – 2.73 (m, 3H), 2.65 – 2.33 (m, 3H), 2.05 – 1.70 (m, 3H). ESI-MS *m/z* (%): 241 [$MH^+$] (100), 481 [$2M+H^+$] (18).

**General procedure 1. Modification a (GP1a):** Under nitrogen a solutionof the carboline derivative (2.00 mmol) in DMF (10.0 mL) was cooled to 0 °C. After addition of NaH (2.20 mmol; 60 % in paraffin) the mixture was stirred for 10 min. The alkylating agent (2.20 mmol) was added and stirring at rt continued until completion of the reaction (TLC). The mixture was poured into water. The crude product was isolated by filtration or extraction of the aqueous phase with $CH_2Cl_2$ (4 x 50.0 mL). In both cases silica gel chromatography afforded the desired product.

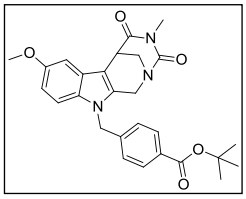
**Modification b (GP1b):** A mixtureof the *ß*-carboline derivative (2.00 mmol) in 2-butanone (40.0 mL), of the alkylating agent (2.20 mmol) and $K_2CO_3$ (20.0 mmol) was stirred at reflux overnight. The mixture was filtered off, the solvent removed under reduced pressure and the product purified by cc ($SiO_2$; $CH_2Cl_2$, EtOAc 2:1) and crystallization from $CH_2Cl_2$ by addition of light petrol.

***tert*-Butyl-4-((4,5-dihydro-1*H*-2,5-methanoazepino[3,4-*b*]indol-10(3*H*)-yl)methyl)benzoate (74)**



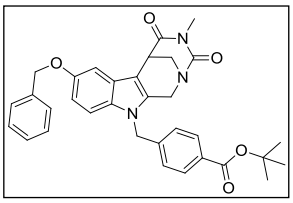
According to GP1a from 3,4,5,10-tetrahydro-1*H*-2,5-methanoazepino[3,4-*b*]indole (**66**) and *tert*-butyl 4-(bromomethyl)benzoate (**21**). Yield 0.30 g (0.80mmol, 38 %) colorless crystals after cc (EtOAc / MeOH 2:1) from EtOAc; mp: 149.3-150.1 °C. IR (KBr): 1713, 1684, 1652 $cm^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$): δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.54 – 7.47 (m, 1H), 7.33 – 7.26 (m, 1H), 7.09 (d, *J* = 8.3 Hz, 2H), 7.04 – 6.94 (m, 2H), 5.37 – 5.22 (m, 2H), 4.20 (d, *J* = 17.0 Hz, 1H), 3.67 (d, *J* = 17.0 Hz, 1H), 2.89 (d, *J* = 10.7 Hz, 1H), 2.75 – 2.66 (m, 2H), 1.98 – 1.90 (m, 2H), 1.51 (s, 9H). ESI-MS *m/z* (%): 389 [$MH^+$] (100). Anal. calcd for $C_{25}H_{28}N_2O_2$ x $^1/_4$ EtOAc): C 76.07; H 7.37; N 6.82; found: C 76.18; H 7.10; N 7.06.

***tert*-Butyl 4-((8-methoxy-4-methyl-3,5-dioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)benzoate (22b)**



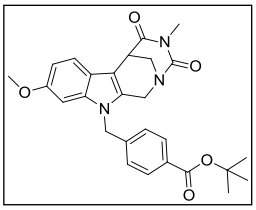
According to GP1a from 8-methoxy-4-methyl-6,11-dihydro-2,6-methano[1,3]diazocino[5,6-*b*]indole-3,5(1*H*,4*H*)-dione (**20b**) and *tert*-butyl 4-(brommethyl)benzoate (**21**)[27]. Yield 0.50 g (1.05 mmol; 45 %) colorless crystals after cc ($CH_2Cl_2$ / EtOAc 10:1). mp: 241.0-242.5 °C ($CH_2Cl_2$). IR (KBr): 2934, 1674 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.91 (d, *J* = 8.3 Hz, 2H), 7.14 (d, *J* = 2.4 Hz, 1H), 7.09 (d, *J* = 8.9 Hz, 1H), 7.03 (d, *J* = 8.3 Hz, 2H), 6.83 (dd, *J* = 8.9, 2.4 Hz, 1H), 5.29 (d, *J* = 17.0 Hz, 1H), 5.10 (d, *J* = 17.0 Hz, 1H), 4.85 (d, *J* = 16.4 Hz, 1H), 4.25 (d, *J* = 16.3 Hz, 1H), 3.94 – 3.84 (m, 5H), 3.37 – 3.28 (m, 1H), 3.07 (s, 3H), 1.57 (s, 9H). ESI-MS *m/z* (%): 476 [$MH^+$] (28), 420 [M-$C_4H_8$] (100). Anal. calcd for $C_{27}H_{29}N_3O_5$: C 68.19; H 6.15; N 8.84; found: C 67.90; H 6.11; N 8.79.

***tert*-Butyl 4-((8-(benzyloxy)-4-methyl-3,5-dioxo-3.4.5.6-tetrahydro-2.6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)benzoate(22c)**



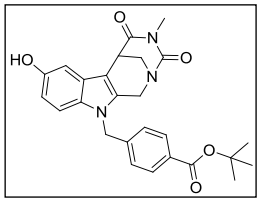
According to GP1a from 8-(benzyloxy)-4-methyl-6.11-dihydro-2,6-methano[1,3]diazocino[5,6-*b*]indole-3,5(1*H*.4*H*)-dione (**20c**) and *tert*-butyl 4-(brommethyl)benzoate **(21)**. Yield 12.4 g (22.48 mmol; 88 %) colorless crystals after chromatography over silica gel with $CH_2Cl_2$/EtOAc(9:1); mp: 238.4-239.5 °C. IR (KBr): 3442, 2966, 1698, 1682 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 7.81 (d, *J* = 8.3 Hz, 1H), 7.50 – 7.28 (m, 6H), 7.14 (d, *J* = 8.3 Hz, 2H), 7.10 (d, *J* = 2.4 Hz, 1H), 6.83 (dd, *J* = 8.9, 2.4 Hz, 1H), 5.40 (s, 2H), 5.08 (s, 2H), 4.80 (d, *J* = 16.6 Hz, 1H), 4.51 (d, *J* = 16.4 Hz, 1H), 3.89 (d, *J* = 12.8 Hz, 1H), 3.43 (dd, *J* = 13.1, 2.1 Hz, 1H), 2.90 (s, 3H), 1.51 (s, 9H). ESI-MS *m/z* (%): 496.19 [$MH^+$-$C_4H_8$] (100), 552.25 [$MH^+$] (38.95), 569.28 [M+$NH_4^+$] (31.5), 1125.48 [2M+$Na^+$] (15.21). Anal. calcd for $C_{33}H_{33}N_3O_5$: C 71.85; H 6.03; N 7.62; found: C 71.49; H 5.99; N 7.50.

**tert-Butyl 4-((9-methoxy-4-methyl-3,5-dioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)benzoate (22d)**



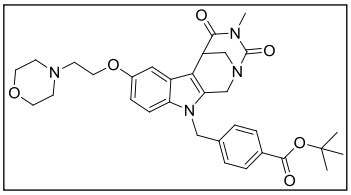
According to GP1a from 9-methoxy-4-methyl-6,11-dihydro-2,6-methano[1,3]diazocino[5,6-*b*]indole-3,5(1*H*,4*H*)-dione (**20d**) (1.40 g; 4.90 mmol) and *tert*-butyl 4-(brommethyl)benzoate (**21**)[27]. Yield 1.50 g (3.16 mmol; 64 %) colorless crystals after cc ($SiO_2$; $CH_2Cl_2$, EtOAc; 20:1) from EtOAc, mp: 210.3-213.7 °C. IR (KBr): 3452, 1729, 1704, 1683 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 8.6 Hz, 1H), 7.17 (d, *J* = 8.3 Hz, 2H), 7.01 (d, *J* = 2.1 Hz, 1H), 6.74 (dd, *J* = 8.6, 2.2 Hz, 1H), 5.44 (d, *J* = 17.3 Hz, 1H), 5.38 (d, *J* = 17.2 Hz, 1H), 4.76 (d, *J* = 16.5 Hz, 1H), 4.46 (d, *J* = 16.4 Hz, 1H), 3.86 (d, *J* = 13.2 Hz, 1H), 3.82 (s, 1H), 3.71 (s, 3H), 3.40 (dd, *J* = 13.0, 2.0 Hz, 1H), 2.88 (s, 3H), 1.51 (s, 9H). ESI-MS *m/z* (%): 476 [$MH^+$] (100). Anal. calcd for $C_{27}H_{29}N_3O_5$: C, 68.19; H, 6.15; N, 8.84; found: C 67.50; H 6.30; N 8.47.

***tert*-Butyl 4-((8-hydroxy-4-methyl-3,5-dioxo-3,4,5,6-tetrahydro-2.6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)benzoate(22e)**



*tert*-Butyl 4-((8-(benzyloxy)-4-methyl-3.5-dioxo-3.4.5.6-tetrahydro-2.6-methano[1,3]diazocino[5.6-*b*]indol-11(1*H*)-yl)methyl)benzoate **(22c)** 0.52 g (0.94 mmol) and 0.22 g PdC (10% Pd) were dissolved in tetrahydrofuran (65 ml). The mixture was stirred under hydrogen at rt until completion of the reaction was observed by TLC ($CH_2Cl_2$:MeOH (10:1)). The mixture was filtered over $Na_2SO_4$ and tetrahydrofuran was removed under reduced pressure. The product was obtained as colorless crystals. Yield 0.42 g (0.91mmol; 97%) mp: 201.2-205.1 °C. IR (KBr): 2969, 2933, 1727, 1715, 1684, 1663 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 8.89 (s, 1H), 7.81 (d, *J* = 8.3 Hz, 2H), 7.16 (t, *J* = 8.2 Hz, 3H), 6.86 (d, *J* = 2.3 Hz, 1H), 6.58 (dd, *J* = 8.8, 2.3 Hz, 1H), 5.34 (s, 2H), 4.78 (d, *J* = 16.5 Hz, 1H), 4.49 (d, *J* = 16.4 Hz, 1H), 3.86 (d, *J* = 12.9 Hz, 1H), 3.75 (s, 1H), 3.42 (dd, 1H), 2.89 (s, 3H), 1.51 (s, 9H). ESI-MS *m/z* (%): 406.14 [$MH^+$-$C_4H_8$] (100), 462.20 [$MH^+$] (16.77), 479.23 [$MNH_4$+] (39.69), 945.38 [M+$Na^+$] (4.89). Anal.calcd for $C_{26}H_{27}N_3O_5$: C 67.66; H 5.90; N 9.10; found: C 67.41; H 5.98; N 8.84.

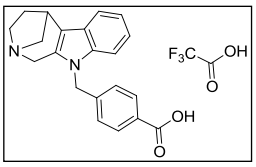
***tert*-Butyl 4-((4-methyl-8-(2-morpholinoethoxy)-3,5-dioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-b]indol-11(1*H*)-yl)methyl)benzoate (22f)**



A stirred mixture of **22e** (0.28 g, 0.61 mmol), 4-(2-chloroethyl)morpholine hydrochloride (0.15 g, 0.81 mmol) and $K_2CO_3$ (0.42 g, 3.0 mmol) in 2-butanone (30.0 mL) was heated till reflux for 4d. The mixture was cooled to rt, the solid was filtered off and the solvent removed under reduced pressure. After purification by cc ($SiO_2$; $CH_2Cl_2$, MeOH 10:1) and removal of the solvent under reduced pressure the product (0.24 g, 0.42 mmol, 68 %) was obtained as a colorless solid. mp: 204.7-208.0 °C; IR (KBr): 2857, 1714, 1687 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.3 Hz, 2H), 7.15 (d, *J* = 2.3 Hz, 1H), 7.09 (d, *J* = 9.0 Hz, 1H), 7.03 (d, *J* = 8.3 Hz, 2H), 6.83 (dd, *J* = 8.9, 2.4 Hz, 1H), 5.34 – 5.22 (m, 1H), 5.09 (d, *J* = 17.0 Hz, 1H), 4.84 (d, *J* = 16.4 Hz, 1H), 4.25 (d, *J* = 15.7 Hz, 3H), 3.89 (d, *J* = 13.3 Hz, 1H), 3.83 (d, *J* = 8.0 Hz, 5H), 3.32 (dd, *J* = 13.1, 2.1 Hz, 1H), 3.06 (s, 3H), 2.93 (s, 2H), 2.72 (s,4H), 1.56 (s, 9H). ESI-MS *m/z* (%): 575.29 [$MH^+$] (100), 1171.55 [2M$Na^+$] (0.3). Anal.calcd for $C_{32}H_{38}N_4O_6$ x 0.25 $H_2O$: C 66.36; H 6.70; N 9.67; found: C 65.98; H 6.58; N 9.43.

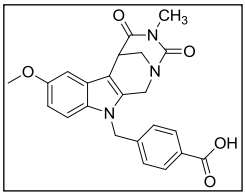
**General procedure 2.** (**GP2**): Deprotection of *tert*-butyl carbamates. A solution of the *tert*-butyl carbamate (0.50 mmol) in trifluoroacetic acid (5.0 mL) was stirred for 15 min at rt. After completion of the reaction (TLC monitoring) the mixture was poured into water. The carboxylic acid was collected by filtration und dried. If the molecule contains an amino group, the excess of trifluoroacetic acid was removed under reduced pressure and the product was obtained as its trifluoroacetic acid salt.

**4-((4,5-Dihydro-1*H*-2,5-methanoazepino[3,4-*b*]indol-10(3*H*)-yl)methyl)benzoic acid 2,2,2-trifluoroacetate (75)**



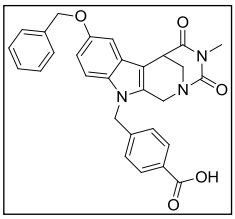
According to GP2 from *tert*-Butyl-4-((4,5-dihydro-1*H*-2,5-methanoazepino[3,4-*b*]indol-10(3*H*)-yl)methyl)benzoate (**74**). Yield 0.25 g (0.64 mmol; 97 %) red crystals; mp: 149.3-150.1 °C (decomp.). IR (KBr): 1699, 1612 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 10.90 (s, 1H), 7.88 (d, *J* = 8.2 Hz, 2H), 7.67 – 7.61 (m, 1H), 7.44 – 7.37 (m, 1H), 7.22 – 7.06 (m, 4H), 5.50 (d, *J* = 17.2 Hz, 1H), 5.34 (d, *J* = 17.2 Hz, 1H), 4.79 (d, *J* = 15.1 Hz, 1H), 4.55 (d, *J* = 15.5 Hz, 1H), 3.90 – 3.70 (m, 2H), 3.63 (d, *J* = 10.1 Hz, 1H), 3.58 – 3.45 (m, 1H), 3.43 – 3.26 (m, 1H), 2.44 – 2.26 (m, 1H), 2.26 – 2.11 (m, 1H). ESI-MS *m/z* (%): 374 [$MH^+$+ MeCN] (100), 332 [$M^+$] (51). Anal. calcd for $C_{21}H_{20}N_2O_2$x TFA x $^1/_2$ $H_2O$: C 60.66; H 4.87; N 6.15; found: C 60.48; H 4.92; N 6.18.

**4-((8-Methoxy-4-methyl-3,5-dioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)benzoic acid (24b).**



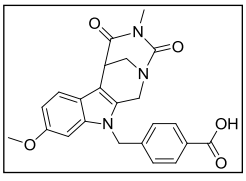
According to GP2 from *tert*-butyl 4-((8-methoxy-4-methyl-3,5-dioxo-3,4,5,6-tetrahydro-2,6-methano[1,3] diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)benzoate (**22b**) (0.30 g; 0.63 mmol). Colorless crystalls (0.26 g, 0.62 mmol; 98 %). mp: 275.0 – 275.4 °C ($H_2O$). IR (KBr): 3450, 1711, 1656 $cm^{-1}$.$^1H$ NMR (300 MHz, DMSO-$d_6$): δ 12.95 (s, 1H), 7.86 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.9 Hz, 1H), 7.13 (d, *J* = 8.2 Hz, 2H), 6.99 (d, *J* = 2.3 Hz, 1H), 6.75 (dd, *J* = 8.9, 2.4 Hz, 1H), 5.41 (s, 2H), 4.80 (d, *J* = 16.6 Hz, 1H), 4.52 (d, *J* = 16.5 Hz, 1H), 3.97 – 3.80 (m, 2H), 3.76 (s, 3H), 3.51 – 3.37 (m, 1H), 2.90 (s, 3H). ESI-MS *m/z* (%): 420 [$MH^+$] (100). Anal. calcd for $C_{23}H_{21}N_3O_5$: C 65.86; H 5.05; N 10.02; found: C 65.77; H 5.05; N 9.87.

**4-((8-(Benzyloxy)-4-methyl-3,5-dioxo-3,4,5,6-tetrahydro-2.6-methano[1,3]diazocino[5.6-*b*]indol-11(1*H*)-yl)methyl)benzoic acid (24c)**



According to GP2 from *tert*-butyl 4-((8-(benzyloxy)-4-methyl-3.5-dioxo-3,4,5,6-tetrahydro-2.6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)benzoate (**22c**). Yield 0.59 g (1.19 mmol; 88 %) colorless crystals; mp: 186.9-188.3 °C. IR (KBr): 3432, 1726, 1700 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO): δ 12.95 (s, 1H), 7.85 (d, *J* = 8.3 Hz, 2H), 7.75 (d, *J* = 7.2 Hz, 2H), 7.40 (t, *J* = 7.3 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.13 (d, *J* = 8.3 Hz, 2H), 7.01 – 6.96 (m, 2H), 6.64 (dd, *J* = 5.5, 3.0 Hz, 1H), 5.42 (s, 2H), 5.24 (d, *J* = 6.3 Hz, 2H), 4.82 (d, *J* = 16.5 Hz, 1H), 4.49 (d, *J* = 16.5 Hz, 1H), 4.14 (s, 1H), 3.86 (d, *J* = 12.6 Hz, 1H), 3.43 (dd, 1H), 2.93 (s, 3H). ESI-MS *m/z* (%): 496.19 [$MH^+$] (100). Anal.calcd for $C_{29}H_{25}N_3O_5$ x 0.33 $H_2O$: C 69.44; H 5.16; N 8.38; found: C 69.70; H 5.23; N 8.40.

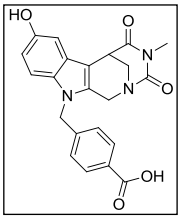
**4-((9-Methoxy-4-methyl-3,5-dioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-b]indol-11(1*H*)-yl)methyl)benzoic acid (24d)**



According to GP2 from tert-butyl 4-((9-methoxy-4-methyl-3,5-dioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-b]indol-11(1*H*)-yl)methyl)benzoate (**22d**) (1.10 g; 2.31 mmol). 0.96 g (2.29 mmol; 99 %) colorless crystals; mp: 270.3-274.2 °C. IR (KBr): 2997, 1736, 1700 cm-1.

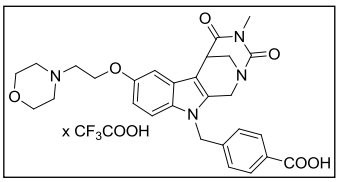
1H NMR (300 MHz, DMSO-$d_6$): δ 12.95 (s, 1H), 7.87 (d, *J* = 8.2 Hz, 2H), 7.39 (d, *J* = 8.6 Hz, 1H), 7.17 (d, *J* = 8.2 Hz, 2H), 7.02 (d, *J* = 2.0 Hz, 1H), 6.75 (dd, *J* = 8.6, 2.1 Hz, 1H), 5.45 (d, *J* = 17.3 Hz, 1H), 5.39 (d, *J* = 17.7 Hz, 1H), 4.76 (d, *J* = 16.5 Hz, 1H), 4.46 (d, *J* = 16.4 Hz, 1H), 3.86 (d, *J* = 13.5 Hz, 1H), 3.79 (d, *J* = 19.6 Hz, 1H), 3.71 (s, 3H), 3.41 (d, *J* = 11.4 Hz, 1H), 2.89 (s, 3H). ESI-MS m/z (%): 461 [$MH^+$+ $CH_3CN$] (90), 420 [MH+] (100). Anal.calcd for $C_{23}H_{21}N_3O_5$: C 65.86; H 5.05; N 10.02; found: C 65.57; H 5.25; N 9.68.

**4-((8-Hydroxy-4-methyl-3,5-dioxo-3,4,5,6-tetrahydro-2.6-methano[1,3]diazocino[5.6-*b*]indol-11(1*H*)-yl)methyl)benzoic acid (24e)**



According to GP2 from *tert*-butyl 4-((8-hydroxy-4-methyl-3,5-dioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)benzoate(**22e**). Yield 0.33 g (0.81 mmol; 75 %). The crude product was isolated by extraction of the aqueous layer with $CH_2Cl_2$ (4 x 50.0 mL) and a slightly brown solid was obtained after crystallization from EtOAc; mp: 270.5-273.4 °C.IR (KBr): 2924, 2853, 1710, 1676, 1646 $cm^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$): δ 12.91 (s, 1H), 8.90 (s, 1H), 7.85 (d, *J* = 8.2 Hz, 2H), 7.16 (dd, *J* = 14.5, 8.5 Hz, 3H), 6.86 (d, *J* = 2.2 Hz, 1H), 6.59 (dd, *J* = 8.8, 2.3 Hz, 1H), 5.35 (s, 2H), 4.78 (d, *J* = 16.5 Hz, 1H), 4.50 (d, *J* = 16.5 Hz, 1H), 3.86 (d, *J* = 12.9 Hz, 1H), 3.75 (s, 1H), 3.42 (d, *J* = 14.3 Hz, 1H), 2.89 (s, 3H). ESI-MS *m/z* (%): 406.14 [$MH^+$] (100), 833.25 [2M+$Na^+$] (3.23). Anal.calcd for $C_{22}H_{19}N_3O_5$: C 65.18; H 4.72; N 10.37, found: C 64.86; H 4.85; N 10.10.

**4-(2-((11-(4-Carboxybenzyl)-4-methyl-3,5-dioxo-1,3,4,5,6,11-hexahydro-2,6-methano[1,3]diazocino[5,6-b]indol-8-yl)oxy)ethyl)morpholin-4-ium 2,2,2-trifluoroacetate (24f)**

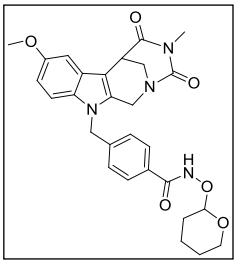


*tert*-Butyl 4-((4-methyl-8-(2-morpholinoethoxy)-3,5-dioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)benzoate (**22f**) (0.82 g, 1.43 mmol) was dissolved in $CH_2Cl_2$ (25 mL) and trifluoro acetic acid (10.0 mL) was added. The mixture was stirred at rt (2h) and the solvent and excess of trifluoro acetic acid removed under reduced pressure. Yield 0.90 g (1.42 mmol, 99 %) slightly yellow crystals; mp: 182.9-184.0 °C. IR (KBr): 3441, 1642 $cm^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): δ 12.98 (s, 1H), 9.95 (s, 1H), 7.85 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.9 Hz, 1H), 7.13 (d, *J* = 8.3 Hz, 2H), 7.10 (d, *J* = 2.4 Hz, 1H), 6.85 (dd, *J* = 8.9, 2.4 Hz, 1H), 5.43 (s, 2H), 4.82 (d, *J* = 16.6 Hz, 1H), 4.54 (d, *J* = 16.5 Hz, 1H), 4.34 (s, 2H), 3.99 (d, *J* = 11.3 Hz, 2H), 3.91 (d, *J* = 12.7 Hz, 1H), 3.83 (s, 1H), 3.71 (t, *J* = 11.9 Hz, 2H), 3.64 – 3.49 (m, 4H), 3.45 (d, *J* = 11.3 Hz, 1H), 3.23 (s, 2H), 2.90 (s, 3H). ESI-MS *m/z* (%): 519.23 [$MH^+$] (100), 1059.42 [2M$Na^+$] (0.03). Anal.calcd for $C_{30}H_{31}F_3N_4O_8$: C 56.96; H 4.94; N 8.86; found: C 56.88; H 5.05; N 8.56.

**General procedure 3.** (**GP3**): The carboxylic acid (0.50 mmol) was dissolved in DMF (5.00 mL). After addition of benzotriazol-1-yloxy-tris (dimethylamino) phosphonium hexafluorophosphate (**25**, BOP) (0.50 mmol), triethylamine (1.50 mmol) and *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (**26**) (2.00 mmol) the mixture was stirred at rt until the reaction was completed (TLC monitoring). If the product crystallized, it was filtered off anddried in vacuo. Alternatively, the mixture was extracted with $CH_2Cl_2$ (4x25.0 mL), the combined organic phases were washed with brine (25.0 mL) and dried over $Na_2SO_4$.The solvent was removed and the

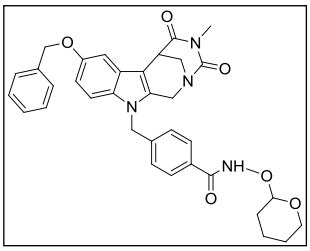
residue dried *in vacuo*. Purification by chromatography onsilica gel using ($CH_2Cl_2$, EtOAc (1:2)) or theindicatedeluent.

**4-((8-Methoxy-4-methyl-3,5-dioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy)benzamide (27b)**



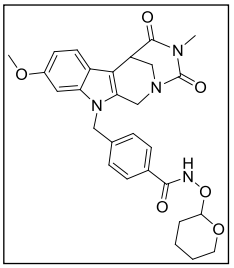
According to **GP3** from4-((8-methoxy-4-methyl-3,5-dioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-b]indol-11(1*H*)-yl)methyl)benzoic acid (**24b**) (0.26 g, 0.62 mmol). Colorless oil (0.16 g, 0.31 mmol, 50 %). IR (KBr): 2953, 1728, 1685 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ 8.88 (s, 1H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.14 (d, *J* = 2.4 Hz, 1H), 7.08 (d, *J* = 8.9 Hz, 2H), 7.04 (d, *J* = 8.2 Hz, 2H), 6.83 (dd, *J* = 8.9, 2.4 Hz, 1H), 5.29 – 5.02 (m, 3H), 4.82 (d, *J* = 16.4 Hz, 1H), 4.26 (d, *J* = 16.3 Hz, 1H), 4.00 – 3.85 (m, 5H), 3.70 – 3.57 (m, 1H), 3.32 (d, *J* = 11.0 Hz, 1H), 3.06 (s, 3H), 1.90 – 1.80 (m, 3H), 1.72 – 1.57 (m, 3H). ESI-MS *m/z* (%): 519 [$MH^+$] (11), 435 [$MH^+$ - $C_5H_8O$] (100). HRMS (ESI) *m/z*: Calcd. 519.2238, found 519.2235.

**4-((8-(Benzyloxy)-4-methyl-3,5-dioxo-3.4.5.6-tetrahydro-2.6-methano[1,3]diazocino[5.6-*b*]indol-11(1*H*)-yl)methyl)-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy)benzamide (27c)**



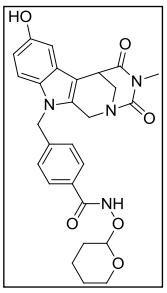
According to GP3 from 4-((8-(benzyloxy)-4-methyl-3.5-dioxo-3.4.5.6-tetrahydro-2.6-methano[1,3]diazocino[5.6-*b*]indol-11(1*H*)-yl)methyl)benzoic acid (**24c**). Yield 0.65 g (1.09 mmol; 54 %) colorless crystals after chromatography; mp: 162.1-165.4 °C. IR (KBr): 3433, 1700, 1696 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 11.60 (s, 1H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 6.8 Hz, 2H), 7.43 – 7.27 (m, 5H), 7.13 (d, *J* = 8.3 Hz, 2H), 7.10 (d, *J* = 2.4 Hz, 1H), 6.83 (dd, *J* = 8.9, 2.4 Hz, 1H), 5.37 (s, 2H), 5.14 – 5.01 (m, 2H), 4.83 (d, *J* = 16.5 Hz, 1H), 4.53 (d, *J* = 16.4 Hz, 1H), 3.93 – 3.79 (m, 2H), 3.47 (t, *J* = 13.6 Hz, 2H), 2.89 (d, *J* = 2.5 Hz, 3H), 1.85 – 1.13 (m, 9H). ESI-MS *m/z* (%): 511.20 [$MH^+$-3,4-dihydro-2*H*-pyran] (100), 595.26 [$MH^+$] (9.14), 617 [$MNa^+$] (7.96). Anal.calcd for $C_{34}H_{34}N_4O_6$: C 68.67; H 5.76; N 9.42, found: C 68.40; H 5.79; N 9.39.

**4-((9-Methoxy-4-methyl-3,5-dioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy)benzamide (27d)**



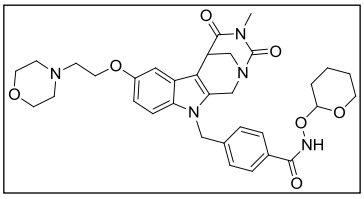
According to GP3 from 4-((9-methoxy-4-methyl-3,5-dioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)benzoic acid (**24d**) (0.55 g; 1.31 mmol).Yield 0.56 g (1.11 mmol; 77 %) colorless foam after silica gel chromatography.;mp: 105.8-108.1 °C. IR (KBr): 3440, 2950, 1730, 1683 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 11.61 (s, 1H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.38 (d, *J* = 8.6 Hz, 1H), 7.16 (d, *J* = 8.2 Hz, 2H), 7.00 (d, *J* = 2.0 Hz, 1H), 6.74 (dd, *J* = 8.6, 2.1 Hz, 1H), 5.41 (d, *J* = 17.3 Hz, 1H), 5.35 (d, *J* = 17.2 Hz, 1H), 4.96 (s, 1H), 4.78 (d, *J* = 16.5 Hz, 1H), 4.47 (d, *J* = 16.4 Hz, 1H), 4.03 (dd, *J* = 14.2, 7.1 Hz, 1H), 3.91 – 3.80 (m, 2H), 3.71 (s, 3H), 3.54 – 3.37 (m, 3H), 2.89 (s, 3H), 1.70 (s, 3H), 1.53 (s, 3H). ESI-MS *m/z* (%): 519 [$MH^+$] (100).

**4-((8-Hydroxy-4-methyl-3.5-dioxo-3.4.5.6-tetrahydro-2.6-methano[1,3]diazocino[5.6-*b*]indol-11(1*H*)-yl)methyl)-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy)benzamide (27e)**



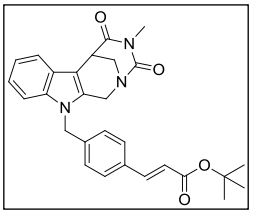
According to GP3 from 4-((8-hydroxy-4-methyl-3.5-dioxo-3.4.5.6-tetrahydro-2.6-methano[1,3]diazocino[5.6-*b*]indol-11(1*H*)-yl)methyl)benzoic acid (**24e**). Yield 0.28 g (0.55 mmol; 69 %) colorless crystals after chromatography over silica gel with EtOAc and crystallization from MeOH; mp: 213.6-214.9 °C. IR (KBr): 2954, 1718, 1667, 1618 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 11.60 (s, 1H), 8.89 (s, 1H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.15 (dd, *J* = 12.7, 8.5 Hz, 3H), 6.86 (d, *J* = 2.2 Hz, 1H), 6.58 (dd, *J* = 8.8, 2.3 Hz, 1H), 5.32 (s, 2H), 4.96 (s, 1H), 4.80 (d, *J* = 16.6 Hz, 1H), 4.51 (d, *J* = 16.4 Hz, 1H), 4.02 (s, 1H), 3.87 (d, *J* = 12.7 Hz, 1H), 3.75 (s, 1H), 3.42 (d, *J* = 11.1 Hz, 1H), 2.89 (s, 3H), 1.61 (d, *J* = 49.3 Hz, 7H). ESI-MS *m/z* (%): 421.15 [$MH^+$-3,4-dihydro-2*H*-pyran] (100), 505.21 [$MH^+$] (8.52), 527.19 [$MNa^+$] (11.79), 1031.39 [2M+$Na^+$] (12.45). Anal.calcd for $C_{27}H_{28}N_4O_6$ x 0.5 MeOH: C 63.54; H 5.81; N 10.76; found: C 63.24; H 5.83; N 10.94.

**4-((4-Methyl-8-(2-morpholinoethoxy)-3,5-dioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-b]indol-11(1*H*)-yl)methyl)-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy)benzamide (27f)**



A mixture of 4-(2-((11-(4-carboxybenzyl)-4-methyl-3,5-dioxo-1,3,4,5,6,11-hexahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-8-yl)oxy)ethyl)morpholin-4-ium 2,2,2-trifluoroacetate (**24f**) (0.63 g; 1.00 mmol), BOP (0.53 g, 1.20 mmol) diisopropylethylamine (0.52 mL, 3.00 mmol) and *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine in THF was stirred at room temperature overnight. The mixture was poured into water, extracted with ethyl acetate (3 x 50 mL), the combined organic layers dried ($Na_2SO_4$), the solvent removed and the product purified by cc ($SiO_2$, $CH_2Cl_2$, MeOH 20:1). Yield 0.66 g (1.00 mmol, 99 %) colorless foam. mp: 135.7-138.0 °C; IR (KBr): 3433, 1729, 1684 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 11.60 (s, 1H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.9 Hz, 1H), 7.12 (d, *J* = 8.3 Hz, 2H), 7.00 (d, *J* = 2.4 Hz, 1H), 6.75 (dd, *J* = 8.9, 2.4 Hz, 1H), 5.37 (s, 2H), 4.95 (s, 1H), 4.82 (d, *J* = 16.6 Hz, 1H), 4.53 (d, *J* = 16.4 Hz, 1H), 4.13 – 3.98 (m, 3H), 3.89 (d, *J* = 12.8 Hz, 1H), 3.84 (s, 1H), 3.59 (d, *J* = 4.6 Hz, 3H), 3.57 (s, 2H), 3.53 – 3.39 (m, 2H), 2.89 (s, 3H), 2.70 (t, *J* = 5.7 Hz, 2H), 2.54 (s, 2H), 1.61 (d, *J* = 49.1 Hz, 6H), 1.17 (t, *J* = 7.1 Hz, 1H); ESI-MS *m/z* (%): 618.29 [$MH^+$] (100).

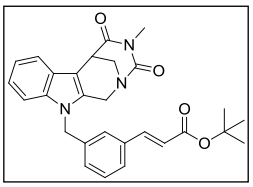
**(*E*)-*tert*-Butyl 3-(4-((4-Methyl-3,5-dioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)phenyl)acrylate (82)**



According to GP1a from 4-methyl-6,11-dihydro-2,6-methano[1,3]-diazocino[5,6-*b*]indole-3,5-(1H,4*H*)-dione (**20a**) and (*E*)-*tert*-butyl 3-(4-(bromomethyl)phenyl) acrylate (**80**)[16, 17]. Yield 1.24 g (2.63 mmol; 66 %) colorless crystals from n-Hexane; mp: 117.0-124.0 °C. IR (KBr): 2977, 1730, 1688 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 7.62 (d, *J* = 8.2 Hz, 2H), 7.57 – 7.45 (m, 2H), 7.43 (dd, *J* = 6.8, 1.7 Hz, 1H), 7.28 – 6.94 (m, 4H), 6.47 (d, *J* = 16.0 Hz, 1H), 5.38 (s, 2H), 4.86 (d, *J* = 16.6 Hz, 1H), 4.57 (d, *J* = 16.5 Hz, 1H), 3.90 (d, *J* = 12.7 Hz, 2H), 3.45 (d, *J* = 11.1 Hz, 1H), 2.89 (s, 3H), 1.46 (s, 9H). ESI-MS *m/z* (%): 489 [$MNH_4^+$] (17),

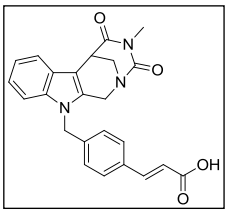
416 [$MH^+$- $C_4H_8$] (100). Anal. calcd for $C_{28}H_{29}N_3O_4$): C 71.32; H 6.20; N 8.91; found: C 71.08; H 6.17; N 8.79.

**(*E*)-*tert*-Butyl 3-(3-((4-Methyl-3,5-dioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)phenyl)acrylate (83)**



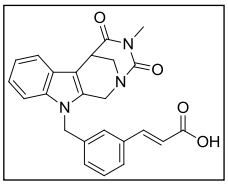
According to GP1a from 4-methyl-6,11-dihydro-2,6-methano-[1,3]diazocino[5,6-*b*]indole-3,5-(1*H*,4*H*)-dione (**20a**) (1.03 g; 2.00 mmol) and (*E*)-*tert*-butyl 3-(3-(bromomethyl)phenyl) acrylate (**81**).[17, 18] Yield 1.56 g (3.31 mmol; 83 %) colorless crystals after crystallization from n-Hexan; mp: 114.0-120.0 °C. IR (KBr): 2976, 1730, 1685 $cm^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$): δ 7.59 – 7.29 (m, 6H), 7.19 – 7.00 (m, 3H), 6.44 (d, *J* = 16.0 Hz, 1H), 5.36 (s, 2H), 4.89 (d, *J* = 16.6 Hz, 1H), 4.64 (d, *J* = 16.5 Hz, 1H), 3.97 – 3.76 (m, 2H), 3.49 (dd, *J* = 12.9, 1.9 Hz, 1H), 2.91 (s, 3H), 1.46 (s, 9H). ESI-MS *m/z* (%): 489 [$MNH_4^+$] (17), 472 [$MH^+$] (11), 416 [$MH^+$-$C_4H_8$] (100). Anal. calcd for $C_{28}H_{29}N_3O_4$: C 71.32; H 6.20; N 8.91; found: C 71.17; H 6.17; N 8.88.

**(*E*)-3-(4-((4-Methyl-3,5-dioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)phenyl)acrylic acid (84)**



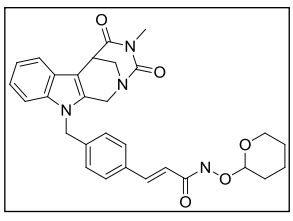
According to GP2 from (*E*)-*tert*-butyl 3-(4-((4-methyl-3,5-dioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)phenyl)acrylate (**82**). Yield 1.00 g (2.41 mmol; 99 %) colorless crystals; mp: 266.0-271.0 °C. IR (KBr): 1730, 1685 $cm^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$): δ 12.38 (s, 1H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.57 – 7.49 (m, 2H), 7.42 (dd, *J* = 6.8, 1.7 Hz, 1H), 7.16 – 7.02 (m, 4H), 6.48 (d, *J* = 16.0 Hz, 1H), 5.46 – 5.26 (m, 2H), 4.87 (d, *J* = 16.6 Hz, 1H), 4.57 (d, *J* = 16.5 Hz, 1H), 4.00 – 3.75 (m, 2H), 3.45 (d, *J* = 11.2 Hz, 2H), 2.89 (s, 3H). ESI-MS *m/z* (%): 416 [$MH^+$] (100). Anal. calcd for $C_{24}H_{21}N_3O_4$ x 1/3 $H_2O$: C 68.40; H 5.18; N 9.97; found: C 68.48; H 5.25; N 9.72.

**(*E*)-3-(3-((4-Methyl-3,5-dioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)phenyl)acrylic acid (85)**



According to GP2 from (*E*)-*tert*-butyl 3-(3-((4-methyl-3,5-dioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)phenyl)-acrylate (**83**). Yield 0.40 g (0.96 mmol; 97 %) colorless crystals; mp: 209.1-209.8 °C. IR (KBr): 1726, 1684 $cm^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$): $^1$H NMR (300 MHz, DMSO-$d_6$): δ 12.41 (s, 1H), 7.61 – 7.29 (m, 6H), 7.14-7.04 (m, 3H), 6.46 (d, *J* = 16.0 Hz, 1H), 5.35 (d, *J* = 12.7 Hz, 2H), 4.90 (d, *J* = 16.6 Hz, 1H), 4.64 (d, *J* = 16.5 Hz, 1H), 3.91 (d, *J* = 13.5 Hz, 2H), 3.49 (dd, *J* = 12.8, 1.8 Hz, 1H), 2.91 (s, 3H). ESI-MS *m/z* (%): 416 [$MH^+$] (100). Anal. calcd for $C_{24}H_{21}N_3O_4$ x 1/3 $H_2O$: C 68.40; H 5.18; N 9.97; found: C 68.54; H 5.18; N 9.75.

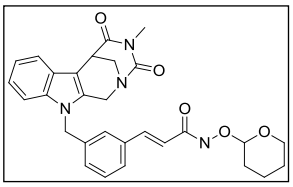
**(*E*)-3-(4-((4-Methyl-3,5-dioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)phenyl)-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy)acrylamide (86)**



According to GP3 from (*E*)-3-(4-((4-methyl-3,5-dioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)-

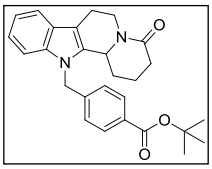
phenyl)acrylic acid (**84**) (1.21 g; 2.91 mmol). Yield 0.94 g (1.83 mmol; 63 %) colorless crystals after crystallization fromEtOAc; mp: 226.0-230.1 °C. IR (KBr): 3299, 2934, 1718, 1669 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 11.22 (s, 1H), 7.58 – 7.39 (m, 5H), 7.15 – 7.02 (m, 4H), 6.45 (d, *J* = 15.9 Hz, 1H), 5.38 (s, 2H), 4.86 (d, *J* = 16.6 Hz, 2H), 4.57 (d, *J* = 16.5 Hz, 1H), 3.90 (d, *J* = 13.1 Hz, 3H), 3.49 (dd, *J* = 18.7, 11.4 Hz, 2H), 2.89 (s, 3H), 1.68 (s, 3H), 1.52 (s, 3H). ESI-MS *m/z* (%): 515 [$MH^+$] (2), 431 [$MH^+$ - $C_5H_8O$] (100). Anal. calcd for $C_{29}H_{30}N_4O_5$ x ¼ EtOAc: C 66.90; H 6.13; N 10.89; found: C 66.67; H 5.84; N 10.80.

**(*E*)-3-(3-((4-Methyl-3,5-dioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-b]indol-11(1*H*)-yl)methyl)phenyl)-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy)acrylamide (87)**



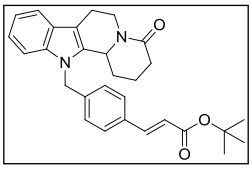
According to GP3 from (*E*)-3-(3-((4-methyl-3,5-dioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)-phenyl)acrylic acid (**85**) (1.48 g; 3.56 mmol). Yield 1.07 g (19.4 mmol; 55 %) colorlesssolid; mp: 146.0-151.8 °C. IR (KBr): 3240, 2950, 1727, 1684 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 11.24 (s, 1H), 7.55 – 7.29 (m, 6H), 7.16 – 7.02 (m, 3H), 6.45 (d, *J* = 15.9 Hz, 1H), 5.38 (s, 2H), 4.99 – 4.80 (m, 2H), 4.61 (d, *J* = 16.6 Hz, 1H), 3.91 (d, *J* = 13.7 Hz, 3H), 3.58 – 3.28 (m, 3H), 2.90 (s, 3H), 1.68 (s, 3H), 1.53 (s, 3H). ESI-MS *m/z* (%): 515 [$MH^+$] (88), 431 [$MH^+$ - $C_5H_8O$] (100). Anal. calcd for $C_{29}H_{30}N_4O_5$ x ¼ EtOAc: C 66.90; H 6.13; N 10.89; found: C 66.98; H 5.86; N 10.76.

***tert*-Butyl 4-((4-oxo-1,3,4,6,7,12*b*-hexahydroindolo[2,3-*a*]quinolizin-12(2*H*)-yl)methyl)benzoate (88)**



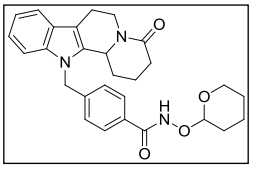
According to GP1a from 1,2,3,6,7,12*b*-hexahydroindolo[2,3-*a*]quinolizin-4(12*H*)-one (**73**) and *tert*-butyl4-(brommethyl)benzoate (**21**). Yield 1.2 g (2.79 mmol, 67 %) colorlesscrystals after chromatography (EtOAc/ $CH_2Cl_2$6:1) and crystallizationfrom MeOH / $H_2O$; mp: 145.5 -146.4 °C. IR (KBr): 1711, 1634 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.54 – 7.47 (m, 1H), 7.19 – 7.13 (m, 1H), 7.12 – 7.01 (m, 4H), 5.63 (d, *J* = 18.0 Hz, 1H), 5.46 (d, *J* = 18.3 Hz, 1H), 5.01 – 4.81 (m, 2H), 2.81 – 2.56 (m, 3H), 2.37 – 2.17 (m, 3H), 1.78 – 1.59 (m, 2H), 1.49 (s, 9H). ESI-MS *m/z* (%):472 [$MH^+$+MeCN] (100), 431 [$MH^+$] (31). Anal. calcd for $C_{27}H_{30}N_2O_3$ x $^1/_3$ $H_2O$: C 74.29; H 7,08; N 6,42; found: C 74.24; H 6.83; N 6.52.

**(*E*)-*tert*-Butyl 3-(4-((4-oxo-1,3,4,6,7,12*b*-hexahydroindolo[2,3-*a*]quinolizin-12(2*H*)-yl)methyl)phenyl)acrylate (89)**



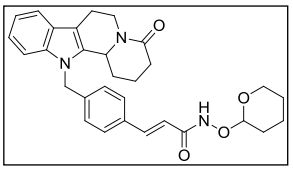
According to GP1a from 1,2,3,6,7,12*b*-hexahydroindolo[2,3-*a*]quinolizin-4(12*H*)-one (**73**) and (*E*)-*tert*-butyl 3-(4-(bromomethyl)phenyl) acrylate (**80**)[16, 17]. Yield 0.71 g (1.55mmol; 75 %) colorless crystals after chromatography ($CH_2Cl_2$ / EtOAc1:2) from EtOAc; mp: 157.7-158,8 °C. IR (KBr): 1699, 1662 $cm^{-1}$, 1635 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 7.62 (d, *J* = 8.2 Hz, 2H), 7.53 – 7.45 (m, 2H), 7.22 – 7.15 (m, 1H), 7.11 – 7.01 (m, 2H), 6.99 (d, *J* = 8.2 Hz, 2H), 6.46 (d, *J* = 16.0 Hz, 1H), 5.49 (m, 2H), 5.01 – 4.80 (m, 2H), 2.81 – 2.55 (m, 3H), 2.40 – 2.18 (m, 3H), 1.81 – 1.61 (m, 2H), 1.46 (s, 9H), 1.39 (m, 1H). ESI-MS *m/z* (%): 457 [$MH^+$] (100), 401 [M-$C_4H_8$] (26). Anal. ($C_{29}H_{32}N_2O_3$ x $^1/_6$ EtOAc): C 75.61; H 7.13; N 5.94; found: C 75.75; H 7.08; N 5.90.

**4-((4-Oxo-1,3,4,6,7,12b-hexahydroindolo[2,3-a]quinolizin-12(2*H*)-yl)methyl)-N-((tetrahydro-2*H*-pyran-2-yl)oxy)benzamide (92)**



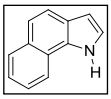
According to GP2 from *tert*-butyl 4-((4-oxo-1,3,4,6,7,12*b*-hexahydroindolo[2,3-*a*]quinolizin-12(2*H*)-yl)methyl)benzoate (**88**). The crude intermediate 4-((4-oxo-1,3,4,6,7,12*b*-hexahydroindolo[2,3-*a*]quinolizin-12(2*H*)-yl)methyl)benzoic acid (**90**) was used in the next step without further purification according to GP3. Yield over 2 steps 0.75 g (1.60mmol,80 %) colorless crystals after cc ($CH_2Cl_2$ / MeOH 30:1); mp: 219.0–219.3 °C (EtOAc). IR (KBr): 1666, 1606 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ 8.97 (s, 1H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.60 – 7.51 (m, 1H), 7.19 – 7.10 (m, 2H), 7.09 – 6.98 (m, 3H), 5.44 – 5.26 (m, 2H), 5.22 – 5.09 (m, 1H), 5.06 (s, 1H), 4.69 (d, *J* = 9.1 Hz, 1H), 4.06 – 3.91 (m, 1H), 3.72 – 3.56 (m, 1H), 2.94 – 2.64 (m, 3H), 2.55 (d, *J* = 16.5 Hz, 1H), 2.47 – 2.21 (m, 2H), 1.93 – 1.48 (m, 9H). ESI-MS *m/z* (%): 474 [$MH^+$] (100), 947 [$2MH^+$] (19). Anal. calcd for $C_{28}H_{31}N_3O_4$ x $^1/_4$ EtOAc: C 70.28; H 6.71; N 8.48; found: C 69.93; H 6.55; N 8.78.

**(*E*)-3-(4-((4-Oxo-1,3,4,6,7,12*b*-hexahydroindolo[2,3-*a*]quinolizin-12(2*H*)-yl)methyl)phenyl)-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy)acrylamide (93)**



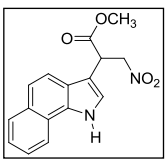
According to GP2 from (*E*)-*tert*-Butyl 3-(4-((4-oxo-1,3,4,6,7,12*b*-hexahydroindolo[2,3-*a*]quinolizin-12(2*H*)-yl)methyl)phenyl)acrylate (**89**). The crude intermediate (*E*)-3-(4-((4-Oxo-1,3,4,6,7,12*b*-hexahydroindolo[2,3-*a*]quinolizin-12(2*H*)-yl)methyl)phenyl)acrylic acid (**91**) was used in the next step without further purification according to GP3. Yield 0.16 g (0.32 mmol, 30 %) colorless oil after cc ($SiO_2$;$CH_2Cl_2$ /MeOH 20:1); IR (KBr): 2926, 1627 $cm^{-1}$.$^1H$ NMR (300 MHz, $CDCl_3$): δ 8.57 (s, 1H), δ 7.70 (d, *J* = 15.7 Hz, 1H), 7.61 – 7.52 (m, 1H), 7.45 (d, *J* = 8.1 Hz, 2H), 7.20 – 7.07 (m, 3H), 7.00 (d, *J* = 8.1 Hz, 2H), 5.44 – 5.23 (m, 2H), 5.22 – 5.10 (m, 1H), 4.99 (s, 1H), 4.69 (br d, *J* = 9.2 Hz, 1H), 4.07 – 3.87 (m, 1H), 3.73 – 3.59 (m, 1H), 2.97 – 2.64 (m, 3H), 2.63 – 2.48 (m, 1H), 2.48 – 2.25 (m, 2H), 1.91 – 1.76 (m, 4H), 1.68 – 1.58 (m, 6H), ESI-MS *m/z* (%): 500 [$MH^+$] (20), 416 [$MH^+$- $C_5H_8O$] (100).

**1*H*-benzo[*g*]indole (96)**



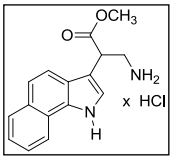
**96** was prepared in two steps from 2-methyl-1-nitronaphthalene (**94**) according to lit.[19, 20]. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 12.03 (s, 1H), 8.36 (d, *J* = 8.2 Hz, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.67 (d, *J* = 8.6 Hz, 1H), 7.57 – 7.48 (m, 1H), 7.47 – 7.35 (m, 3H), 6.59 (dd, *J* = 3.0, 1.9 Hz, 1H).

**Methyl 2-(1*H*-benzo[*g*]indol-3-yl)-3-nitropropanoate (97)**



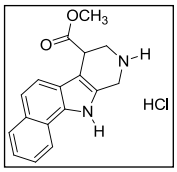
Preparation analogous to lit.[14] from 1*H*-benzo[*g*]indole (**96**). Yield 1.19 g; 4.0 mmol (33 %) beige foam after cc ($SiO_2$; $CH_2Cl_2$; mp: 48.0 – 52.0 °C. IR (KBr): 3421, 1733, 1635 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 12.18 (s, 1H), 8.34 (d, *J* = 7.4 Hz, 1H), 7.93 (d, *J* = 7.4 Hz, 1H), 7.77 (d, *J* = 8.7 Hz, 1H), 7.59 – 7.38 (m, 4H), 5.36 (dd, *J* = 15.0, 10.4 Hz, 1H), 5.01 (dd, *J* = 15.0, 5.1 Hz, 1H), 4.84 (dd, *J* = 10.4, 5.0 Hz, 1H), 3.63 (s, 3H). ESI-MS *m/z* (%): 299 [$MH^+$] (100). Anal. calcd. for $C_{16}H_{14}N_2O_4$: C 64.42; H 7.73; N 9.39; found: C 64.49; H 7.59; N 9.32.

**Methyl 3-amino-2-(1*H*-benzo[*g*]indol-3-yl)propanoate hydrochloride (98)**



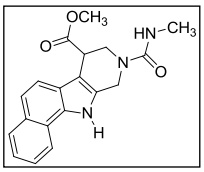
According to **79a** from methyl 2-(1*H*-benzo[*g*]indol-3-yl)-3-nitropropanoate (**97**). Yield 1.05 g; 3.45 mmol (85 %) grey foam; mp: 142.7 °C (decomp.). IR (KBr): 3423, 1718, 1631 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 12.25 (s, 1H), 8.39 (d, *J* = 8.2 Hz, 1H), 8.13 (s, 3H), 7.93 (d, *J* = 8.3 Hz, 1H), 7.70 (d, *J* = 8.7 Hz, 1H), 7.59 – 7.48 (m, 2H), 7.47 – 7.35 (m, 2H), 4.42 (dd, *J* = 8.1, 6.4 Hz, 1H), 3.64 (s, 3H), 3.57 – 3.48 (m, 1H), 3.30 – 3.14 (m, 1H). ESI-MS *m/z* (%): 269 [$MH^+$] (100). Anal. calcd. for $C_{16}H_{17}ClN_2O_2$ x 3/4 $H_2O$: C 60.47; H 5.83; N 8.82; found: C 60.62; H 6.03; N 8.80.

**Methyl 8,9,10,11-tetrahydro-7*H*-benzo[*g*]pyrido[3,4-*b*]indole-7-carboxylate hydrochloride (17)**



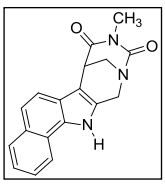
As described for **16a** from methyl 3-amino-2-(1*H*-benzo[*g*]indol-3-yl)propanoate hydrochloride (**98**). Yield 0.88 g; 2.78 mmol (80 %) beige crystals; mp: 270.0 °C (decomp). IR (KBr): 3150, 2943, 1734 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 12.44 (s, 1H), 10.19 (s, 1H), 9.22 (s, 1H), 8.31 (d, *J* = 8.2 Hz, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.68 (d, *J* = 8.7 Hz, 1H), 7.60 – 7.48 (m, 2H), 7.48 – 7.39 (m, 1H), 4.59 – 4.40 (m, 2H), 4.40 – 4.32 (m, 1H), 3.83 – 3.73 (m, 1H), 3.72 (s, 3H), 3.64 – 3.53 (m, 1H). ESI-MS *m/z* (%): 281 [$MH^+$] (100). Anal. calcd. for $C_{17}H_{17}ClN_2O_2$ x 1/6 $H_2O$: C 63.95; H 5.43; N 8.78; found: C 63.98; H 5.41; N 8.70.

**Methyl 9-(methylcarbamoyl)-8,9,10,11-tetrahydro-7*H*-benzo[*g*]pyrido[3,4-*b*]indole-7-carboxylate (99)**



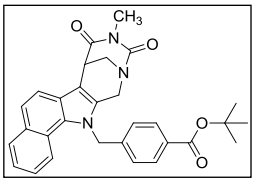
As described for **16a** from methyl 8,9,10,11-tetrahydro-7*H*-benzo[*g*]pyrido[3,4-*b*]indole-7-carboxylate hydrochloride (**17**). Yield 0.90 g; 2.67 mmol (92 %) beige crystals; mp: 266.0 °C (decomp.). IR (KBr): 3266, 1725, 1615 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 11.96 (s, 1H), 8.29 (d, *J* = 8.3 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.60 – 7.31 (m, 4H), 6.68 (q, *J* = 4.3 Hz, 1H), 4.67 (q, *J* = 16.2 Hz, 2H), 4.07 – 3.97 (m, 2H), 3.84 – 3.71 (m, 1H), 3.66 (s, 3H), 2.62 (d, *J* = 4.2 Hz, 3H). ESI-MS *m/z* (%): 338 [$MH^+$] (100). Anal. calcd. for $C_{19}H_{19}N_3O_3$ x 1/2 $H_2O$: C 65.90; H 5.78; N 12.13; found: C 65.83; H 5.50; N 12.04.

**9-Methyl-12,13-dihydro-7,11-methanobenzo[*g*][1,3]diazocino[5,6-*b*]indole-8,10(7*H*,9*H*)-dione (100)**



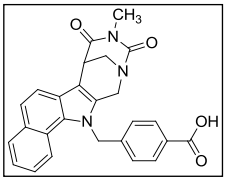
As described for **20a** frommethyl 9-(methylcarbamoyl)-8,9,10,11-tetrahydro-7*H*-benzo[*g*]pyrido[3,4-*b*]indole-7-carboxylate (**99**). Yield 0.60 g; 1.97 mmol (73 %) colorless crystals after silica gel chromatography with $CH_2Cl_2$ / EtOAc (1 : 1% ); mp: 345.5 – 347.9 °C (decomp.). IR (KBr): 3334, 1721, 1681 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 12.08 (s, 1H), 8.22 (d, *J* = 8.3 Hz, 1H), 7.92 (d, *J* = 7.5 Hz, 1H), 7.62 (d, *J* = 8.6 Hz, 1H), 7.58 – 7.46 (m, 2H), 7.44 – 7.35 (m, 1H), 4.78 (s, 2H), 3.99 – 3.88 (m, 2H), 3.56 – 3.43 (m, 1H), 2.89 (s, 3H). ESI-MS *m/z* (%): 306 [$MH^+$] (100). Anal. calcd. for $C_{18}H_{15}N_3O_2$: C 70.80; H 4.95; N 13.76; found: C 70.61; H 5.02; N 13.56.

**_tert_-Butyl 4-((9-methyl-8,10-dioxo-7,9,10,12-tetrahydro-7,11-methanobenzo[_g_][1,3]diazocino[5,6-_b_]indol-13(8_H_)-yl)methyl)benzoate (101)**



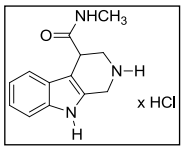
According to GP1b from 9-methyl-12,13-dihydro-7,11-methanobenzo[*g*][1,3]diazocino[5,6-*b*]indole-8,10(7*H*,9*H*)-dione (**100**) and *tert*-butyl-4-(brommethyl)benzoate (**21**). Yield 0.66 g; 1.33 mmol (95 %) colorless crystals after cc ($SiO_2$; $CH_2Cl_2$ / EtOAc, 2 : 1); mp: 239.3 – 240.9 °C. IR (KBr): 2977, 1712, 1688 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$):δ 8.13 – 8.00 (m, 1H), 7.98 – 7.88 (m, 1H), 7.80 (d, *J* = 8.3 Hz, 2H), 7.72 (d, *J* = 8.6 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 1H), 7.38 – 7.28 (m, 2H), 7.07 (d, *J* = 8.3 Hz, 2H), 5.88 (s, 2H), 4.89 (d, *J* = 16.4 Hz, 1H), 4.66 (d, *J* = 16.4 Hz, 1H), 4.04 (s, 1H), 3.97 (d, *J* = 13.2 Hz, 1H), 3.54 (d, *J* = 13.4 Hz, 1H), 2.93 (s, 3H), 1.48 (s, 9H). ESI-MS *m/z* (%): 496 [$MH^+$] (23), 440 (100). Anal. calcd. for $C_{30}H_{29}N_3O_4$ x 1/5 EtOAc: C 72.10; H 5.97; N 8.19; found: C 72.15; H 5.94; N 8.33.

**4-((9-Methyl-8,10-dioxo-7,9,10,12-tetrahydro-7,11-methanobenzo[_g_][1,3]diazocino[5,6-_b_]indol-13(8_H_)-yl)methyl)benzoic acid (102)**



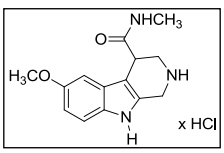
According to GP2 from *tert*-butyl 4-((9-methyl-8,10-dioxo-7,9,10,12-tetrahydro-7,11-methanobenzo[*g*][1,3]diazocino[5,6-*b*]indol-13(8*H*)-yl)methyl)benzoate (**101**). Yield 0.50 g; 1.14 mmol (91 %) beige crystals; mp: 191.0 – 194.0 °C. IR (KBr): 3443, 1729, 1682 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$):δ 12.92 (s, 1H), 8.12 – 8.03 (m, 1H), 7.97 – 7.89 (m, 1H), 7.85 (d, *J* = 8.3 Hz, 2H), 7.72 (d, *J* = 8.6 Hz, 1H), 7.60 (d, *J* = 8.6 Hz, 1H), 7.38 – 7.29 (m, 2H), 7.08 (d, *J* = 8.5 Hz, 2H), 5.89 (s, 2H), 4.90 (d, *J* = 16.5 Hz, 1H), 4.66 (d, *J* = 16.4 Hz, 1H), 4.04 (s, 1H), 3.97 (d, *J* = 13.2 Hz, 1H), 3.55 (d, *J* = 13.1 Hz, 1H), 2.92 (s, 3H). ESI-MS *m/z* (%): 440 [$MH^+$] (100). Anal. calcd. for $C_{26}H_{21}N_3O_4$ x 5/4 $H_2O$: C 67.61; H 5.09; N 9.10; found: C 67.61; H 5.07; N 8.77.

***N*-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-4-carboxamide hydrochloride (37a)**



Based on the procedure of Perez-Alvarez *et al.*[25] 1.0 g (3.75 mmol) **16a** was dissolved in 18 mL methylamine (40 % in MeOH). After three days of stirring at rt the solvent was removed *in vacuo* and the residue purified by cc ($SiO_2$, EtOAc/MeOH, 1:1). Yield 0.77 g (2.90 mmol; 77 %) colorless crystals; mp: 187 °C (decomp.). IR (KBr): 3293, 2931, 1726, 1643 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$):δ 11.29 (s, 1H), 9.57 (s, 2H), 8.76 (q, *J* = 4.5 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.15 – 6.96 (m, 2H), 4.49 – 4.24 (m, 2H), 4.06 – 3.96 (m, 1H), 3.60 – 3.39 (m, 2H), 2.66 (d, *J* = 4.4 Hz, 3H). ESI-MS *m/z* (%): 230 [$MH]^+$ (100). Anal. calcd for $C_{13}H_{16}ClN_3O$ x 0.33 $CH_3OH$: C 57.94; H 6.32; N 15.21; found: C 57.79; H 6.56; N 15.37.

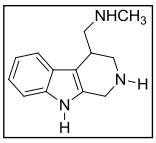
**6-Methoxy-*N*-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-4-carboxamide hydrochloride (37b)**



9.75 g (32.86 mmol) of **16b** were dissolved in 140.0 mL of methylamine (40 % in MeOH). After three days of stirring at rt (TLC: $SiO_2$, EtOAc / MeOH, 1:1). the solvent was removed *in vacuo* and the residue purified by cc. 7.65 g (25.87 mmol, 79 %) colorless powder after cc ($SiO_2$, EtOAc / MeOH, 1:1); mp: 110-112 °C. IR (KBr): 3254, 2937, 2812, 1648 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 11.14 (s, 1H), 9.57 (s, 2H), 8.86 (q, *J* = 4.5 Hz, 1H), 7.26 (d, *J* = 8.8 Hz, 1H), 7.17 (d, *J* = 2.4 Hz,

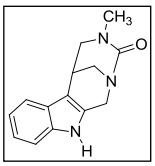
1H), 6.74 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.44 – 4.22 (m, 2H), 4.03 – 3.93 (m, 1H), 3.74 (s, 3H), 3.58 – 3.39 (m, 2H), 2.67 (d, *J* = 4.4 Hz, 3H). ESI-MS *m/z* (%): 260 $[MH]^+$ (100). ). Anal. calcd for $C_{14}H_{18}ClN_3O_2$ x 0.66 $CH_3OH$ x 1.25 $H_2O$: C 51.87; H 6.87; N 12.38; found: C 51.95; H 6.40; N 12.10.

**_N_-Methyl-1-(2,3,4,9-tetrahydro-1_H_-pyrido[3,4-_b_]indol-4-yl)methanamine (38)**



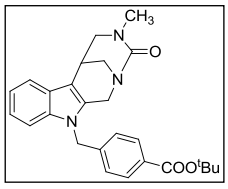
Based on Van *et al.*[26](1981) 5.0 g (21.81 mmol) of **37a** were dissolved in 200 mL of THF and cooled to 0 °C. 2.5 g (65.88 mmol) of $LiAlH_4$ were added in portions at rt followed by 3 h stirring at rt and heating to reflux for 16 h. After cooling to 0 °C 50 mL of sat. $Na_2SO_4$ solution were added dropwise and stirring at rt continued for 2 h. The salts are filtered off and washed three times with 100 mL EtOAc. The aqueous phase is separated and extracted with EtOAc (3 x 50.0 mL). After drying and removal of the solvent the residue was purified by cc. (3.16 g; 14.70 mmol; 67 %) beige foam after cc ($SiO_2$, 7N $NH_3$ in Methanol/Methanol; 1:10); mp: 157-159 °C. IR (KBr): 3390, 3315, 3045, 2931, 2857 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 10.67 (s, 1H), 7.48 – 7.41 (m, 1H), 7.25 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.02 – 6.86 (m, 2H), 3.80 (s, 2H), 3.13 – 3.02 (m, 1H), 2.91 – 2.78 (m, 3H), 2.69 (dd, *J* = 11.4, 8.3 Hz, 1H), 2.33 (s, 3H). ESI-MS *m/z* (%): 216 $[MH]^+$ (53), 156 (100). Anal. calcd for $C_{13}H_{17}N_3$ x 0.25 $H_2O$: C 71.04; H 8.03; N 19.12; found: C 70.95; H 8.01; N 19.05.

**4-Methyl-4,5,6,11-tetrahydro-2,6-methano[1,3]diazocino[5,6-_b_]indole-3(1_H_)-one (39)**



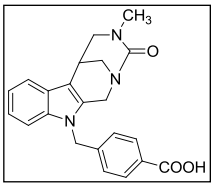
1.40 g (8.4 mmol) of CDI were added in portions to a solution of 1.51 g (7.0 mmol) of **38** in 35 mL of THF. The mixture was stirred at rt for 3 h and at reflux for 18 h. The solvent was removed under reduced pressure and the residue purified by cc. Yield 1.05 g (4.35 mmol; 62 %) colorless crystals after cc ($SiO_2$, EtOAc); mp: 223-225 °C. IR (KBr): 2909, 1639 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 10.87 (s, 1H), 7.52 – 7.43 (m, 1H), 7.33 – 7.25 (m, 1H), 7.10 – 6.92 (m, 2H), 4.50 (d, *J* = 16.3 Hz, 1H), 4.31 – 4.13 (m, 1H), 3.69 (dd, *J* = 10.9, 5.6 Hz, 1H), 3.43- 3.26 (m, 3H), 3.20 – 3.01 (m, 1H), 2.69 (s, 3H). ESI-MS *m/z* (%): 242 $[MH]^+$ (100). Anal. calcd for $C_{14}H_{15}N_3O$: C 69.69; H 6.27; N 17.41; found: C 69.22; H 6.19; N 17.55.

***tert*-Butyl 4-((4-methyl-3-oxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino-[5,6-_b_]indol-11(1_H_)-yl)methyl)benzoate (40)**



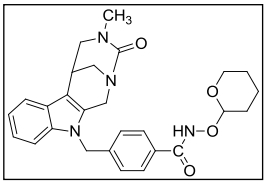
0.50 g (2:07 mmol) of **39** were dissolved in 40 mL of THF and the mixture cooled to 0 °C. After adding 92.0 mg of sodium hydride (2.30 mmol, 60 % in paraffine) the mixture was stirred for 30 min at 0 °C. A solution of 0.62 g (2.30 mmol) *tert*-butyl 4-(bromomethyl) benzoate (**21**) in 5.0 mL of DMF was added dropwise and the mixture stirred at rt for 2 h. The mixture was poured into 100 mL of water and extracted with EtOAc. After drying over $Na_2SO_4$ the solvent was removed and the residue purified by cc. Yield 0.58 g (1.34 mmol; 65 %) beige powder after cc ($SiO_2$, EtOAc/Methanol 10:1); $^1H$ NMR (300 MHz, DMSO-$d_6$):δ 7.85 – 7.76 (m, 2H), 7.59 – 7.51 (m, 1H), 7.41 – 7.33 (m, 1H), 7.20 – 7.12 (m, 2H), 7.11 – 6.97 (m, 2H), 5.48 – 5.27 (m, 2H), 4.65 (d, *J* = 16.5 Hz, 1H), 4.11 (d, *J* = 16.4 Hz, 1H), 3.72 (dd, *J* = 10.9, 5.8 Hz, 1H), 3.41 (d, *J* = 12.4 Hz, 2H), 3.33 – 3.24 (m, 1H), 3.15 (d, *J* = 10.9 Hz, 1H), 2.70 (s, 3H), 1.51 (s, 9H). Anal.calcd for $C_{26}H_{29}N_3O_3$ x 0.15 EtOAc: C 71.82; H 6.85; N 9.45; found: C 71.99; H 6.83; N 9.27.

**4-((4-Methyl-3-oxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)benzoic acid (41)**



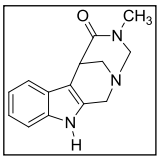
A solution of **40** (0.33 g; 0.76 mmol) in 5.0 mL of $CH_2Cl_2$ and 3.0 mL of $CF_3COOH$ was stirred at rtfor 3.5 h. The mixture was poured into 50 mL ice-water and extracted with 30 mL of $CH_2Cl_2$.The organic phase was dried and the solvent removed. The residue was digested with a small amount of $CH_2Cl_2$ and diethyl ether, the solid filtered off and dried. Yield 0.25 g (0.67mmol,88 %) light beige powder; mp: 160.5 °C (decomp.). IR (KBr): 3432, 2909, 1702 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$):δ 7.96 – 7.75 (m, 2H), 7.55 (dd, *J* = 7.1, 1.8 Hz, 1H), 7.45 – 7.32 (m, 1H), 7.22 – 6.98 (m, 4H), 5.49 – 5.27 (m, 2H), 4.65 (d, *J* = 16.5 Hz, 1H), 4.11 (d, *J* = 16.4 Hz, 1H), 3.72 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.48 – 3.23 (m, 3H), 3.15 (d, *J* = 10.9 Hz, 1H), 2.70 (s, 3H). ESI-MS *m/z* (%): 376 $[MH]^+$ (100). Anal. calcd for $C_{22}H_{21}N_3O_3$ x 0.66 $CH_2Cl_2$: C 63.08; H 5.21; N 9.74; found: C 62.97; H 5.45; N 9.44.

**4-((4-Methyl-3-oxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy)benzamide (42)**



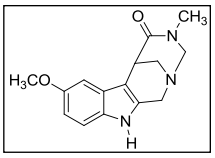
0.25 g (0.67mmol) of **41** were dissolved in 10 mL of THF. After addition ofbenzotriazol-1-yloxy-tris (dimethylamino) phosphonium hexafluorophosphate (BOP) (0.33 g,0.74mmol), O-(tetrahydro-2*H*-pyran-2-yl) hydroxylamine (0.17 g,1.40mmol) and 0.25 mL of triethylamine the mixture was stirred at rt for16 h. The mixture was poured into 50 mL water and extracted with EtOAc. After drying of the organic layer ($Na_2SO_4$) the solvent was removed and the residue purified by cc. ($SiO_2$, EtOAc / MeOH10:1). Yield 0.20 g (0.42mmol, 63 %) colorless foam; mp: 193-196 °C. IR (KBr): 3435, 2943, 1619 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$):δ 11.59 (s, 1H), 7.76 – 7.60 (m, 2H), 7.55 (dd, *J* = 6.9, 1.9 Hz, 1H), 7.45 – 7.31 (m, 1H), 7.23 – 6.94 (m, 4H), 5.49 – 5.20 (m, 2H), 4.95 (d, *J* = 2.8 Hz, 1H), 4.68 (d, *J* = 16.6 Hz, 1H), 4.22 – 3.94 (m, 2H), 3.72 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.56 – 3.23 (m, 4H), 3.15 (d, *J* = 10.8 Hz, 1H), 2.71 (s, 3H), 1.69 (d, *J* = 3.7 Hz, 3H), 1.52 (d, *J* = 7.0 Hz, 3H). ESI-MS *m/z* (%): 475 $[MH]^+$ (100), 391 (79). Anal. calcd for $C_{27}H_{30}N_4O_4$ x 0.66 $CH_3OH$: C 67.02; H 6.64; N 11.30; found: C 66.93; H 6.75; N 11.49.

**4-Methyl-3,4,6,11-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indole-5(1*H*)-one (44a)**



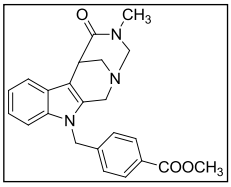
Based on the procedure of Perez-Alvarez *et al.*[25] 0.46 g (2.0 mmol) of **37a** were dissolved in 20.0 mL of MeOH. After addition of 0.6 mL formaldehyde (**43**) (36 % in water) the mixture was stirred at 70 °C for 2 h. The solvent was removed and the residue purified by cc ($SiO_2$, EtOAc / MeOH 1:1). Yield 0.43 g (1.78 mmol, 89 %) yellow solid; mp: 165 °C (decomp.). IR (KBr): 3249, 2932, 1641 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$):δ 10.92 (s, 1H), 7.45 (dd, *J* = 7.1, 1.6 Hz, 1H), 7.30 – 7.23 (m, 1H), 7.04 – 6.91 (m, 2H), 4.58 – 4.40 (m, 2H), 4.24 (dd, *J* = 12.0, 1.6 Hz, 1H), 4.06 (d, *J* = 17.8 Hz, 1H), 3.55 – 3.37 (m, 2H), 3.11 (dt, *J* = 12.9, 1.7 Hz, 1H), 2.57 (s, 3H). ESI-MS *m/z* (%): 242 $[MH]^+$ (98). Anal. calcd for $C_{14}H_{15}N_3O$ x 0.33 $CH_3OH$ x 0.75 $H_2O$: C 64.86; H 6.77; N 15.83; found: C 64.94; H 6.39; N 15.42.

**8-Methoxy-4-methyl-3,4,6,11-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indole-5(1*H*)-one (44b)**



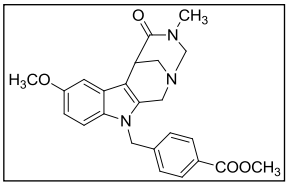
2.07 g (8.0 mmol) of **37b** were dissolved in 80 mL of MeOH. After addition of 2.4 mL formaldehyde **43** (36% in water) the mixture was stirred at 70 °C for 2 h. On evaporation of the solvent under reduced pressure a yellowish solid precipitated. The product was filtered off, washed with MeOH and dried. Yield 1.60 g (5.90 mmol, 74 %) yellow solid; mp: 268.0-268.5 °C. IR (KBr): 3188, 2935, 2871, 1622 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$):δ 10.71 (s, 1H), 7.15 (d, *J* = 8.7 Hz, 1H), 6.93 (d, *J* = 2.4 Hz, 1H), 6.64 (dd, *J* = 8.7, 2.5 Hz, 1H), 4.56 – 4.37 (m, 2H), 4.22 (dd, *J* = 11.9, 1.6 Hz, 1H), 4.03 (d, *J* = 17.8 Hz, 1H), 3.74 (s, 3H), 3.48 (dd, *J* = 13.0, 2.1 Hz, 1H), 3.38 (d, *J* = 1.9 Hz, 1H), 3.09 (dt, *J* = 13.0, 1.6 Hz, 1H), 2.57 (s, 3H). ESI-MS *m/z* (%): 272 $[MH]^+$ (100). Anal. calcd for $C_{15}H_{17}N_3O_2$ x 0.25 $CH_3OH$: C 65.57; H 6.50; N 15.04; found: C 65.60; H 6.31; N 15.10.

**Methyl 4-((4-methyl-5-oxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl) benzoate (96a)**



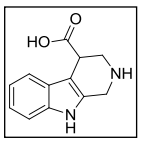
3.34 g (13.83 mmol) of **44a** were dissolved in DMF (100 mL) and cooled to 0 °C. After addition of 0.66 g (16.31 mmol) of NaH (60 % in paraffine) the mixture was stirred for 30 min at 0 °C. 4.26 g (15.71 mmol) of methyl 4-(bromomethyl)benzoate (**45**) in 20.0 mL of DMF were added dropwise and the mixture was stirred at rt for 3 h. The mixture was poured into 500 mL of water and extracted with EtOAc (3 x 200 mL). The combined organic layers were dried ($Na_2SO_4$), the solvent removed and the residue purified by cc ($SiO_2$, EtOAc / MeOH 10:1). Yield 2.96 g (7.60 mmol, 55 %) colorless foam; mp: 66.8 °C (decomp.). IR (KBr): 3422, 2952, 1718, 1652 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$):δ 7.94 – 7.83 (m, 2H), 7.58 – 7.47 (m, 1H), 7.40 – 7.29 (m, 1H), 7.22 – 7.12 (m, 2H), 7.09 – 6.97 (m, 2H), 5.52 – 5.26 (m, 2H), 4.53 (d, *J* = 12.1 Hz, 1H), 4.35 (d, *J* = 17.9 Hz, 1H), 4.23 – 4.07 (m, 2H), 3.82 (s, 3H), 3.57 – 3.44 (m, 2H), 3.11 (d, *J* = 12.6 Hz, 1H), 2.58 (s, 3H). ESI-MS *m/z* (%): 390 $[MH]^+$ (100). Anal. calcd for $C_{23}H_{23}N_3O_3$ x $H_2O$: C 67.80; H 6.18; N 10.31; found: C 67.43; H 6.07; N 9.92.

**Methyl 4-((8-methoxy-4-methyl-5-oxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)benzoate (96b)**



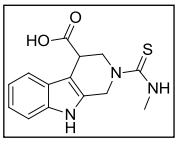
0.40 g (1.50 mmol) of **44b** were dissolved in 10 mL DMSO by heating and then cooled to rt. After addition of 66.0 mg (1.65 mmol) of NaH (60% in paraffine) the mixture was stirred for 30 min at 0 °C. 0.40 g (1.7 mmol) of methyl 4-(bromomethyl)benzoate (**45**) were added and the mixture was stirred at rt for 3 h. The mixture was poured into 120 mL of water. A yellowish solid precipitates, which was filtered off, dried and purified by cc ($SiO_2$, EtOAc / MeOH 5:1). Yield 0.32 g (0.76 mmol, 51 %) yellowish foam; mp: 82.0-85.8 °C. IR (KBr): 3416, 2943, 1720, 1648 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$):δ 7.93 – 7.83 (m, 2H), 7.23 (d, *J* = 8.8 Hz, 1H), 7.18 – 7.08 (m, 2H), 7.00 (d, *J* = 2.4 Hz, 1H), 6.68 (dd, *J* = 8.9, 2.4 Hz, 1H), 5.48 – 5.21 (m, 2H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.32 (d, *J* = 17.9 Hz, 1H), 4.21 – 4.05 (m, 2H), 3.81 (s, 3H), 3.75 (s, 3H), 3.55 – 3.42 (m, 2H), 3.10 (d, *J* = 12.9 Hz, 1H), 2.58 (s, 3H). ESI-MS *m/z* (%): 420 $[MH]^+$ (100). Anal. calcd for $C_{24}H_{25}N_3O_4$ x 0.60 EtOAc: C 67.13; H 6.36; N 8.90; found: C 66.82; H 6.27; N 9.31.

**2,3,4,9-Tetrahydro-1*H*-pyrido[3,4-*b*]indole-4-carboxylic acid (47)**



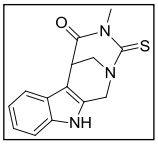
Methyl 2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-4-carboxylate hydrochloride (**16a**) (5.32 g; 20.0 mmol) was dissolved in a mixture of MeOH (40 mL), THF (40.0 mL) and water (20 mL). LiOH (1.01 g, 42.0 mmol) was added and the mixture stirred over night at rt. The solution was heated till reflux for 2 h and the organic solvents removed under reduced pressure. Water was added (30 mL) and the solution acidified untill pH = 6 with acetic acid. The precipitating colorless crystals were collected by filtration, washed with a small amount of water and dried. Yield 3.98 g (18.4 mmol, 92 %). IR (KBr): 3424, 1625, 1583, 1478 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 10.93 (s, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 7.9 Hz, 1H), 7.04-6.91 (m, 2H), 4.70 (s, 2H), 4.06 (d, *J* = 16.7 Hz, 1H), 4.00 (d, *J* = 16.7 Hz, 1H), 3.61 (d, *J* = 12.8 Hz, 1H), 3.43 – 3.26 (m, 1H), 3.00 (dd, *J* = 12.5, 3.8 Hz, 1H). ESI-MS *m/z* (%): 217.09 $[MH]^+$ (100). Anal. calcd for $C_{12}H_{12}N_2O_2$ x 1/3 $H_2O$: C 64.85; H 5.74; N 12.60; found: C 64.48; H 5.67; N 12.50.

**2-(Methylcarbamothioyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-4-carboxylic acid (48)**



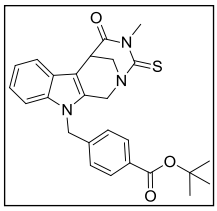
2,3,4,9-Tetrahydro-1*H*-pyrido[3,4-*b*]indole-4-carboxylic acid (**47**) (1.15 g; 5.00 mmol) was suspended in a mixture of aceton (17.5 mL) and DMSO (17.5 mL). Methylisothiocyanate (0.37 g; 5.00 mmol) was added and the mixture heated to reflux for 2 h. The resulting solution was poured onto water (200 mL), the solution acidified with diluted acetic acid and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried ($Na_2SO_4$) and the solvent removed under reduced pressure. Crystallization from EtOAc afforded 0.95 g (3.28 mmol; 66 %) beige crystals; mp: 205.3-205.8 °C.IR (KBr): 3422, 1613 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 12.61 (s, 1H), 11.08 (s, 1H), 7.98 (d, *J* = 4.2 Hz, 1H), 7.47 (d, *J* = 7.7 Hz, 1H), 7.32 (d, *J* = 7.9 Hz, 1H), 7.13 – 7.01 (m, 1H), 7.01 – 6.89 (m, 1H), 5.32 – 4.88 (m, 2H), 4.24 (dd, *J* = 13.7, 6.5 Hz, 1H), 4.14 (dd, *J* = 13.7, 4.6 Hz, 1H), 3.92 (t, *J* = 5.3 Hz, 1H), 2.95 (d, *J* = 4.0 Hz, 3H), 2.54 (s, 2H). ESI-MS *m/z* (%): 290 $[MH^+]$ (100). Anal. calcd for $C_{14}H_{15}N_3O_2S$: C 58.11; H 5.23; N 14.52; found: C 57.53; H 5.47; N 14.10.

**4-Methyl-3-thioxo-3,4,6,11-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-5(1*H*)-one (49)**



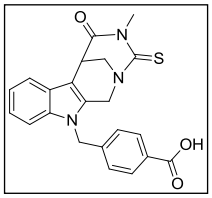
Synthesis of 4-methyl-3-thioxo-3,4,6,11-tetrahydro-2,6-methano[1,3]-diazocino[5,6-*b*]indol-5(1*H*)-one (**49**) was performed as a modification of the method described by Kumar[28] as follows: 2-(Methylcarbamothioyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-4-carboxylic acid (**48**) (1.80 g; 6.22 mmol) was disolved in MeCN (50 mL) and CDI (1.10 g; 6.78 mmol) was added. The solution was strirred for 30 min and poured into water. The precipitating product was removed by filtration, washed with water and dried. Yield 1.48 g (5.46 mmol; 88 %) colorless crystals; mp: 233.0-236.7 °C.IR (KBr): 3383, 1714 $cm^{-1}$.$^1H$ NMR (300 MHz, DMSO-$d_6$): δ 11.22 (s, 1H), 7.46 (d, *J* = 7.3 Hz, 1H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.14 – 6.89 (m, 2H), 5.40 (d, *J* = 15.8 Hz, 1H), 5.10 (d, *J* = 15.8 Hz, 1H), 4.06 (d, *J* = 12.8 Hz, 1H), 3.92 (s, 1H), 3.75 (dd, *J* = 12.7, 2.0 Hz, 1H), 3.21 (s, 3H). ESI-MS *m/z* (%): 312 $[MH^+ + MeCN]$ (40), 271 $[MH^+]$ (100). Anal. calcd for $C_{14}H_{13}N_3OS$: C 61.97; H 4.83; N 15.49; found: C 61.90; H 4.93; N 15.49.

***tert*-Butyl 4-((4-methyl-5-oxo-3-thioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)benzoate(50)**



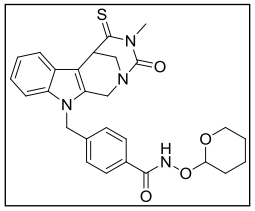
According to GP1a from 4-methyl-3-thioxo-3,4,6,11-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-5(1*H*)-one (**49**) (1.48 g; 5.45 mmol) and *tert*-butyl 4-(brommethyl)benzoate (**21**).[27] Yield 2.40 g (5.20 mmol; 95 %) colorless crystals from $CH_2Cl_2$/petrolether; mp: 186.9-188.4 °C. IR (KBr): 3440, 1729, 1697 $cm^{-1}$.$^1$H NMR (300 MHz, DMSO-$d_6$): δ 7.80 (d, *J* = 8.3 Hz, 2H), 7.57 – 7.46 (m, 1H), 7.42 – 7.34 (m, 1H), 7.20 (d, *J* = 8.3 Hz, 2H), 7.14 – 7.01 (m, 2H), 5.53 (d, *J* = 16.1 Hz, 1H), 5.42 (d, *J* = 17.6 Hz, 2H), 5.03 (d, *J* = 16.0 Hz, 1H), 4.08 (d, *J* = 12.7 Hz, 1H), 3.98 (s, 1H), 3.77 (dd, *J* = 12.8, 1.9 Hz, 1H), 3.23 (s, 3H), 1.50 (s, 9H).ESI-MS *m/z* (%): 462 [$MH^+$] (25), 406 [$MH^+$- $C_4H_8$] (100). Anal. calcd for $C_{26}H_{27}N_3O_3S$: C 67.65; H 5.90; N 9.10; found: C 67.26; H 5.87; N 8.98.

**4-((4-Methyl-5-oxo-3-thioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)benzoic acid (51)**



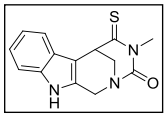
According to GP2 from *tert*-butyl 4-((4-methyl-5-oxo-3-thioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)benzoate (**50**) (2.40 g; 5.20 mmol). Yield 1.35 g (3.33 mmol; 64 %) colorless crystals; mp: 285.5-286.5 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): δ 12.94 (s, 1H), 7.84 (d, *J* = 8.2 Hz, 2H), 7.56 – 7.49 (m, 1H), 7.45 – 7.38 (m, 1H), 7.20 (d, *J* = 8.3 Hz, 2H), 7.16 – 7.04 (m, 2H), 5.52 (d, *J* = 16.1 Hz, 1H), 5.46 (s, 2H), 5.04 (d, *J* = 16.0 Hz, 1H), 4.08 (d, *J* = 12.6 Hz, 1H), 3.99 (s, 1H), 3.77 (dd, *J* = 12.8, 1.8 Hz, 1H), 3.23 (s, 3H). ESI-MS *m/z* (%): 406 [$MH^+$] (100). Anal. calcd for $C_{22}H_{19}N_3O_4$ x $^1/_3$ $H_2O$: C 64.22; H 4.82; N 10.21; S 7.79 found: C 64.33; H 4.85; N 9.88, S 7,50.

**4-((4-Methyl-3-oxo-5-thioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy)benzamide (52)**



According to GP3 from 4-((4-methyl-3-oxo-5-thioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)benzoic acid (**51**) (0.40 g; 0.99 mmol). Yellow solid after cc ($SiO_2$; $CH_2Cl_2$, EtOAc, 3:2). Yield 0.39 g (0.77 mmol, 77 %); $^1$H NMR (300 MHz, DMSO-$d_6$): δ 11.60 (s, 1H), 7.68 (t, *J* = 5.3 Hz, 3H), 7.41 (dd, *J* = 6.5, 2.1 Hz, 1H), 7.23 – 7.00 (m, 4H), 5.40 (d, *J* = 13.2 Hz, 2H), 4.93 (dd, *J* = 18.1, 3.7 Hz, 2H), 4.59 (dd, *J* = 16.6, 5.1 Hz, 1H), 4.44 (s, 1H), 4.18 – 3.77 (m, 2H), 3.49 (d, *J* = 11.0 Hz, 2H), 3.30 (s, 3H), 1.69 (s, 3H), 1.53 (s, 3H). ESI-MS *m/z* (%): 505 [$MH^+$] (100). Anal. calcd. for $C_{27}H_{28}N_4O_4S$ x ½ ETOAC: C 63.49; H 5.88; N 10.21; S 5.84; found: C 63.27; H 5.82; N 10.53; S 5.88.

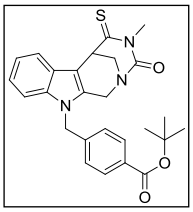
**4-Methyl-5-thioxo-4,5,6,11-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-3(1*H*)-one (53)**



A solution of **20a** (0.50 g, 1.96 mmol) and Lawesson's reagent (0.80 g, 1.96 mmol) in THF (25 mL) was refluxed for 48 h. The mixture was poured into water (80 mL) and extracted with EtOAc (3 x 30 mL). The organic layer was separated, dried ($Na_2SO_4$) and the solvent removed under reduced pressure. The residue was purified by cc ($CH_2Cl_2$/MeOH 20:1). Colorless crystals (0.50 g, 1.84 mmol, 47 %); mp: 226.6 – 227.3 °C.

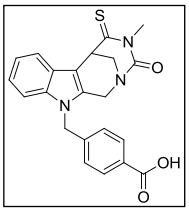
IR (KBr): 3389, 1698 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 11.16 (s, 1H), 7.62 (d, *J* = 7.3 Hz, 1H), 7.39 – 7.29 (m, 1H), 7.12 – 6.94 (m, 2H), 4.89 – 4.58 (m, 2H), 4.38 (s, 1H), 3.96 – 3.82 (m, 1H), 3.52 – 3.41 (m, 1H), 3.29 (s, 3H). ESI-MS *m/z* (%):272 [$MH^+$] (100). Anal. calcd. for $C_{14}H_{13}N_3OS$: C 61.97; H 4.83; N 15.49; S 11.82; found: C 61.98; H 4.83; N 15.50; S 11.78.

**_tert_-Butyl 4-((4-methyl-3-oxo-5-thioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)benzoate (54)**



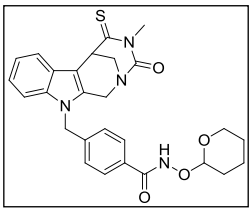
According to GP1a from 4-methyl-5-thioxo-4,5,6,11-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-3(1*H*)-one (**53**) (0.72 g; 2.76 mmol) and *tert*-butyl 4-(brommethyl)benzoate (**21**)[27]. Yellow crystals (0.52 g, 1.13 mmol, 40 %) after crystallization from petrol ether and ethyl acetae (2:1). mp: 203.6 – 205.4 4 °C. IR (KBr): 1701, 3433 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.97 – 7.84 (m, 3H), 7.24 – 7.14 (m, 3H), 7.06 (d, *J* = 8.3 Hz, 2H), 5.24 (dd, *J* = 63.0, 17.0 Hz, 2H), 4.91 (d, *J* = 16.3 Hz, 1H), 4.57 – 4.51 (m, 1H), 4.25 (dd, *J* = 16.3, 1.0 Hz, 1H), 3.91 (d, *J* = 12.7 Hz, 1H), 3.44 (s, 3H), 3.33 (dd, *J* = 13.0, 2.3 Hz, 1H), 1.57 (s, 9H). ESI-MS *m/z* (%): 462 [$MH^+$] (100). Anal. calcd. for $C_{26}H_{27}N_3O_3S$ x ¼ EtOAc: C 67.06; H 6.04; N 8.68; S 6.63; found: C 66.70; H 5.96; N 8.69; S 6.64.

**4-((4-Methyl-3-oxo-5-thioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)benzoic acid(55)**



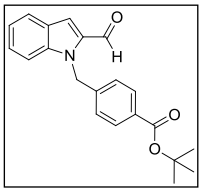
According to GP2 from *tert*-butyl 4-((4-methyl-3-oxo-5-thioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)benzoate (**54**) (0.54 g; 1.18 mmol). Pale oil (0.47 g, 1.11 mmol, 98 %) after extraction with EtOAc / water. IR (KBr): 3432, 1718 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 12.94 (s, 1H), 7.86 (d, *J* = 8.2 Hz, 2H), 7.75 – 7.63 (m, 1H), 7.49 – 7.39 (m, 1H), 7.18 (d, *J* = 8.2 Hz, 2H), 7.15 – 7.01 (m, 2H), 5.43 (d, *J* = 13.1 Hz, 2H), 4.91 (d, *J* = 16.5 Hz, 1H), 4.59 (d, *J* = 16.5 Hz, 1H), 4.44 (s, 1H), 3.90 (d, *J* = 12.8 Hz, 1H), 3.49 (dd, *J* = 13.1, 2.2 Hz, 1H), 3.30 (s, 3H). ESI-MS *m/z* (%):406 [$MH^+$] (100).

**4-((4-Methyl-3-oxo-5-thioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy)benzamide (56)**



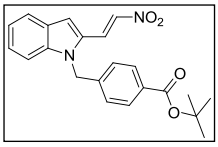
According to GP3 from 4-((4-methyl-3-oxo-5-thioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)benzoic acid (**55**) (0.40 g; 0.99 mmol). Yellow crystals 0.39 g (0.77 mmol, 77 %) after cc ($CH_2Cl_2$, EtOAc, 3:2); mp: 148.5 – 150.3 °C; IR (KBr): 1702, 1644 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 11.60 (s, 1H), 7.68 (t, *J* = 5.3 Hz, 3H), 7.41 (dd, *J* = 6.5, 2.1 Hz, 1H), 7.23 – 7.00 (m, 4H), 5.40 (d, *J* = 13.2 Hz, 2H), 4.93 (dd, *J* = 18.1, 3.7 Hz, 2H), 4.59 (dd, *J* = 16.6, 5.1 Hz, 1H), 4.44 (s, 1H), 4.18 – 3.77 (m, 2H), 3.49 (d, *J* = 11.0 Hz, 2H), 3.30 (s, 3H), 1.69 (s, 3H), 1.53 (s, 3H). ESI-MS *m/z* (%): 505 [$MH^+$] (100). Anal. calcd. for $C_{27}H_{28}N_4O_4S$ x ½ EtOAc: C 63.49; H 5.88; N 10.21; S 5.84; found: C 63.27; H 5.82; N 10.53; S 5.88.

***tert*-Butyl 4-((2-formyl-1*H*-indol-1-yl)methyl)benzoate (29)**



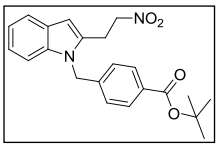
According to GP1a from 1*H*-indole-2-carbaldehyde (**28**) and *tert*-butyl 4-(bromomethyl)benzoate (**21**). Silica gel chromatography ($CH_2Cl_2$/light petrol 1:1) afforded the desired product. Yield 27.16 g (80.98 mmol, 64 %) yellow crystals after cc ($CH_2Cl_2$) from $CH_2Cl_2$/light petrol; mp:131.7-133.1 °C. IR (KBr): 1709, 1671 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ 9.90 (s, 1H), 7.92 – 7.84 (m, 2H), 7.78 (d, *J* = 8.1 Hz, 1H), 7.42 – 7.29 (m, 3H), 7.20 (ddd, *J* = 8.0, 6.6, 1.3 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 2H), 5.88 (s, 2H), 1.54 (s, 9H). HRMS (ESI-MS) m/z: calc.: 336.1594 [$MH^+$], found: 336.1603 [$MH^+$], Anal. calcd. for $C_{21}H_{21}NO_3$: C 75.20; H 6.31; N 4.18; found C 75.07; H 6.33; N 4.09.

**(*E*)-*tert*-Butyl 4-((2-(2-nitrovinyl)-1*H*-indol-1-yl)methyl)benzoate (30)**



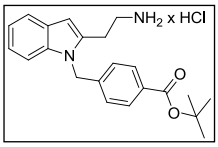
(*E*)-*tert*-butyl 4-((2-(2-nitrovinyl)-1*H*-indol-1-yl)methyl)benzoate (**30**) was prepared according to a modified lit.procedure[29]: A solution of *tert*-butyl 4-((2-formyl-1*H*-indol-1-yl)methyl)benzoate (**29**) (24.55g; 73.20 mmol) and ammonium acetate (2.82 g, 36.6 mmol) in nitromethane (250 mL) was heated at reflux for 10 h under nitrogen. After removal of half of the solvent the mixture was cooled, the crystalline precipitated product removed by filtration and crystallized from ethanol. Yield 17.50 g (46.2mmol,63 %) yellow crystals from ethanol; mp:196.3-199.5 °C. IR (KBr): 1704, 1632 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ 8.03 (d, *J* = 13.3 Hz, 1H), 7.92 (d, *J* = 8.3 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 13.4 Hz, 1H), 7.37 – 7.28 (m, 2H), 7.19 (td, *J* = 6.2, 1.8 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 5.53 (s, 2H), 1.56 (s, 9H).HRMS (ESI-MS) m/z: calcd.: 379.1652 [$MH^+$], found: 379.1657 [$MH^+$]. Anal.calcd. for $C_{22}H_{22}N_2O_4$: C 69.83; H 5.86; N 7.40, found: C 69.81; H 5.92; N 7.42.

***tert*-Butyl 4-((2-(2-nitroethyl)-1*H*-indol-1-yl)methyl)benzoate (31)**



To a solution of (*E*)-*tert*-butyl 4-((2-(2-nitrovinyl)-1*H*-indol-1-yl)methyl)benzoate (**30**) (15.0 g; 39.7 mmol) in $CHCl_3$ (750 mL) and $^i$propanol (75 mL) silica gel (75 g) and $NaBH_4$ (47.6 mmol; 1.80 g) were added and the mixture stirred over night at room temperature. Water (100 mL) was added dropwise whilst stirring, the mixture filtered over a pad of celite, the organic layer died ($Na_2SO_4$) and purified by cc ($SiO_2$; $CH_2Cl_2$). Yield 11.18 g (29.4mmol,74 %) yellow crystals from $CH_2Cl_2$; mp:150.4-152.2 °C. IR (KBr): 1704, 1555 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.94 – 7.87 (m, 2H), 7.60 (dd, *J* = 6.5, 1.7 Hz, 1H), 7.23 – 7.09 (m, 3H), 6.98 (d, *J* = 8.3 Hz, 2H), 6.41 (s, 1H), 5.40 (s, 2H), 4.63 (t, *J* = 7.3 Hz, 2H), 3.38 (t, *J* = 7.3 Hz, 2H), 1.56 (s, 9H). HRMS (ESI-MS) m/z: calcd.: 381.1809 [$MH^+$], found: 381.1814 [$MH^+$]; Anal. calcd. for $C_{22}H_{24}N_2O_4$: C 69.46; H 6.36; N 7.36; found: C 69.29; H 6.33; N 7.19.

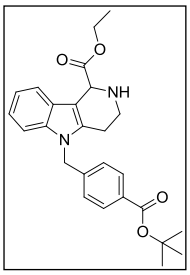
***tert*-Butyl 4-((2-(2-aminoethyl)-1*H*-indol-1-yl)methyl)benzoate hydrochloride (32)**



To a stirred solution of *tert*-butyl 4-((2-(2-nitroethyl)-1*H*-indol-1-yl)methyl)benzoate (**31**) (10.80 g; 28.4 mmol) in HOAc (108 mL) zinc dust (170 mmol; 11.13 g) was added in small portions at 20 °C. After 4 h, ice was added (250 g) and the mixture alkalized with aqueous ammonia (25 %) until pH = 14. The mixture was filtered, the aqueous layer extracted with ethyl acetate (3 x 100 mL),

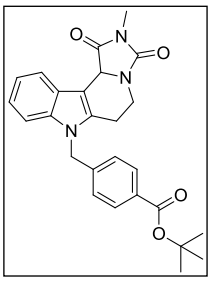
the combined organic layers dried ($Na_2SO_4$) and the solvent removed under reduced pressure. The remaining solid was dissolved in THF (10 mL), the solution cooled to 0 °C and HCl (5-6N in $^{i}$propanol) was added dropwise till pH = 2. $Et_2O$ was added whilst stirring, the precipitating hydrochloride filtered off and washed with $Et_2O$. Yield 9.60 g (24.8 mmol,84 %) colorless crystals; mp:208.9-210.2 °C. IR (KBr): 3446, 1718, 1506 $cm^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$): δ 7.86 (s, 2H), 7.82 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 6.7 Hz, 1H), 7.35 (d, *J* = 7.7 Hz, 1H), 7.10 – 6.99 (m, 4H), 6.46 (s, 1H), 5.54 (s, 2H), 3.08 (d, *J* = 7.3 Hz, 2H), 2.99 (d, *J* = 7.4 Hz, 2H), 1.51 (s, 9H). HRMS (ESI-MS) m/z: calcd.: 351.2067[$MH^+$], found: 351.2075[$MH^+$]; Anal.calcd. for $C_{22}H_{27}ClN_2O_2$: C 68.29; H 7.03; N 7.24; found: C 68.08; H 7.04; N 7.07.

**Ethyl 5-(4-(*tert*-butoxycarbonyl)benzyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-1-carboxylate (33)**



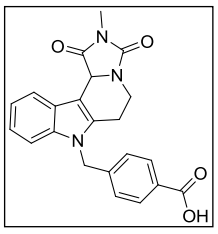
To a stirred solution of *tert*-butyl 4-((2-(2-aminoethyl)-1*H*-indol-1-yl)methyl)benzoate hydrochloride (**32**) (9.00 g; 23.3 mmol) in MeOH (200 mL) ethyl glyoxalate (5.56 mL; 50% in toluene) and silica gel (18.0 g) were added and the mixture stirred for 1 h. The solvents were removed under reduced pressure and the product purified by cc ($SiO_2$; $CH_2Cl_2$, MeOH, $NH_3$(25%), 10:1:0.1) (dry load method). Yield 9.90 g (22.8 mmol, 98%) yellow foam; IR (KBr): 3049, 2931, 1733, 1712 $cm^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.89 (d, *J* = 8.3 Hz, 2H), 7.79 – 7.72 (m, 1H), 7.21 – 7.08 (m, 3H), 7.03 (d, *J* = 8.3 Hz, 2H), 5.33 (d, *J* = 17.6 Hz, 1H), 5.26 (d, *J* = 17.4 Hz, 1H), 4.94 (s, 1H), 4.35 – 4.10 (m, 2H), 3.49 (ddd, *J* = 13.0, 9.1, 4.7 Hz, 1H), 3.24 (ddd, *J* = 12.5, 5.4, 4.0 Hz, 1H), 2.81 – 2.53 (m, 1H), 2.38 (s, 1H), 1.56 (s, 9H), 1.32 (t, *J* = 7.1 Hz, 3H). HRMS (ESI-MS) m/z: calcd.: 435.2278 [$MH^+$], found: 435.2285 [$MH^+$]; Anal.calcd.for $C_{26}H_{30}N_2O_4$ x 0.5 $H_2$0: C 70.41; H 7.04; N 6.32, found: C 70.34; H 6.79; N 6.24.

***tert*-Butyl 4-((2-methyl-1,3-dioxo-2,3,5,6-tetrahydro-1*H*-imidazo[1',5':1,2]pyrido[4,3-*b*]indol-7(11c*H*)-yl)methyl)benzoate (34)**



Ethyl 5-(4-(tert-butoxycarbonyl)benzyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-1-carboxylate (**33**) (3.00 g; 6.90 mmol) was dissolved in MeCN (15.0 mL). With stirring diisopropylethylamine (3.0 mL) was added. After addition of *N*-succinimidyl-*N*-methyl-carbamate (**18**) (1.31 g; 7.60 mmol) stirring was continued for 16 h at rt. The mixture was poured into water and the crude product was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried ($Na_2SO_4$) and evaporated. Yield 1.44 g (3.23mmol,47 %) colorless foam after cc ($CH_2Cl_2$, ethyl acetate 10:1). $^1$H NMR (300 MHz, $CDCl_3$): δ 8.12 – 8.01 (m, 1H), 7.84 (d, *J* = 8.3 Hz, 2H), 7.19 – 7.08 (m, 3H), 6.96 (d, *J* = 8.3 Hz, 2H), 5.34 (t, *J* = 1.8 Hz, 1H), 5.24 (s, 2H), 4.48 (dd, *J* = 13.7, 6.0 Hz, 1H), 3.20 – 3.05 (m, 1H), 2.97 (s, 3H), 2.88 – 2.71 (m, 1H), 2.56 (dd, *J* = 16.0, 4.7 Hz, 1H), 1.51 (s, 9H).

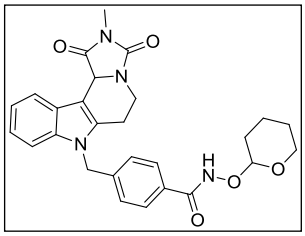
**4-((2-Methyl-1,3-dioxo-2,3,5,6-tetrahydro-1*H*-imidazo[1',5':1,2]pyrido[4,3-*b*]indol-7(11c*H*)-yl)methyl)benzoic acid (35)**



*tert*-Butyl 4-((2-methyl-1,3-dioxo-2,3,5,6-tetrahydro-1*H*-imidazo[1',5':1,2]-pyrido[4,3-*b*]indol-7(11c*H*)-yl)methyl)benzoate (**34**) (1.00 g; 2.24 mmol) was

dissolved in trifluoro acetic acid (10.0 mL) and the mixture stirred for 15 min at rt. The solution was added to water (100 mL), the precipitating product collected by filtration and dried *in vacuo*. Yield 0.83 g (2,12 mmol; 95 %). mp: 267.2-269.6 °C; IR (KBr): 1717, 1678 $cm^{-1}$;$^1$H NMR (300 MHz, DMSO-$d_6$): δ 12.91 (s, 1H), 7.94 – 7.89 (m, 1H), 7.86 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 7.1 Hz, 1H), 7.15 (d, *J* = 8.2 Hz, 2H), 7.13 – 7.05 (m, 2H), 5.52 (s, 1H), 5.46 (s, 2H), 4.33 (dd, *J* = 13.6, 4.9 Hz, 1H), 3.28 – 3.15 (m, 2H), 2.86 (s, 3H), 2.78 (s, 1H). HRMS (ESI-MS) m/z: calcd.: 390.1361 [$MH^+$], found: 390.1360 [$MH^+$]; Anal.calcd.for $C_{22}H_{19}N_3O_4$ x 0.5 $H_20$: C 66.32; H 5.06 ; N 10.55; found: C 66.01; H 5.09; N 10.19.

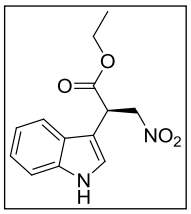
**4-((2-Methyl-1,3-dioxo-2,3,5,6-tetrahydro-1*H*-imidazo[1',5':1,2]pyrido[4,3-*b*]indol-7(11*cH*)-yl)methyl)-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy)benzamide (36)**



4-((2-Methyl-1,3-dioxo-2,3,5,6-tetrahydro-1*H*-imidazo[1',5':1,2]pyrido-[4,3-*b*]indol-7(11c*H*)-yl)methyl)benzoic acid (**35**) (0.78 g, 2.00 mmol) was dissolved in DMF (15.0 mL) and BOP (1.2 equ.), $EtN(iProp)_2$ (0.78 mL) and *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (3.0 equ.) were added. The solution was stirred over night at room temperature, poured into water and extracted with ethyl acetate (3 x 50 mL). CC ($SiO_2$, $CH_2Cl_2$, MeOH (10:1) and removal of the solvent under reduced pressure yielded the product as colorless foam; Yield 0.97 g (1.98 mmol; 98 %). mp: 184.7-186.9°C; IR (KBr): 3412, 2950, 1770, 1706 $cm^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): δ 11.58 (s, 1H), 7.91 (dd, *J* = 6.6, 2.1 Hz, 1H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 7.2 Hz, 1H), 7.16 – 7.04 (m, 4H), 5.52 (s, 1H), 5.44 (s, 2H), 4.95 (s, 1H), 4.33 (dd, *J* = 13.5, 5.1 Hz, 1H), 3.49 (d, *J* = 11.3 Hz, 1H), 3.28 – 3.14 (m, 1H), 2.87 (s, 3H), 2.76 (d, *J* = 17.0 Hz, 2H), 2.09 (s, 1H), 1.61 (d, *J* = 49.2 Hz, 6H). HRMS (ESI-MS) m/z: calcd.: 489.2132 [$MH^+$], found: 489.2133 [$MH^+$].

**Enantioselective synthesis of *R*- and *S*-Marbostat-100**

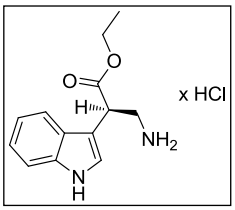
**R-Enantiomer:**
**(*R*)-Ethyl 2-(1*H*-indol-3-yl)-3-nitropropanoate (60a)**



*N*-((1*R*,2*S*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)quinoline-2-carbothioamide (**106a**) (1.375 g; 4.29 mmol), which was prepared from methyl quinoline-2-carbodithioate (**104**) and (1*R*,2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-ol (**105a**) as described for the enantiomeric (1*S*, 2*R*) derivative **105b** in the literature[21], was dissolved under Ar in dry $CHCl_3$ (80.0 mL) and $CF_3SO_3H$ (382.5 µL) was added at rt. The solution was stirred for 5 min at rt and sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (4.0 g; 4.24 mmol) was added in one portion. Stirring was continued for 10 min at rt to form the active thiourea catalysts **59a** *in situ*. The mixture was cooled to -60 °C and a solution of (*E*)-ethyl 3-nitroacrylate (**58**)[30] (2.5 g; 17.23 mmol) in $CHCl_3$ (5.0 mL) was added by a dropping funnel. A solution of indole (**57a**) (3.0 g; 25.61 mmol) in $CHCl_3$ was added and the mixture stirred at -60 °Cfor 16 h. In order to quench the reaction an aqueous NaCl-solution (5.0 mL) was added, the mixture allowed to reach rt, the organic layer was separated, washed with HCl (2M), dried ($Na_2SO_4$), the solvent removed under reduced pressure and the product purified by cc ($SiO_2$; $CH_2Cl_2$, n-hexane, EtOAc 1:5:1). Yield 2.00 g (8.62 mmol, 50 %) yellow oil. $^1$H NMR (300 MHz, DMSO-$d_6$): δ 11.21 (s, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.40 – 7.35 (m, 2H), 7.15 – 7.00 (m, 2H), 5.28 (dd, *J* = 15.0, 10.5 Hz, 1H), 4.93 (dd, *J* =

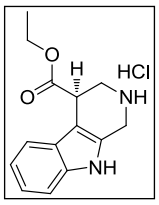
15.0, 5.0 Hz, 1H), 4.71 (dd, *J* = 10.5, 4.9 Hz, 1H), 4.18 – 3.98 (m, 2H), 1.11 (t, *J* = 7.1 Hz, 3H). The ee was determined by HPLC analysis with a Chiralcel OD-H column, hexane/2-propanol (85:15), flow rate = 0.6 mL/min,220 nm. $t_R$=105.66 min (major), 90.81 min (minor), ≥ 99%ee, $[\alpha]^{20}_{589}$ +134.093 (c 0.1; MeOH). HRMS (ESI-MS) m/z: calcd: 263.1026 [$MH^+$], found: 263.1031 [$MH^+$].

**(*R*)-Ethyl 3-amino-2-(1*H*-indol-3-yl)propanoate hydrochloride(61a)**



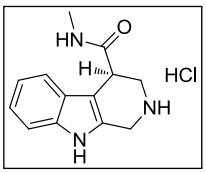

From (*R*)-ethyl 2-(1*H*-indol-3-yl)-3-nitropropanoate (**60a**) as described for **79a**. Yield1.5 g (6.46 mmol; 88%) colorless foam.IR (KBr): 3310, 3021, 2975, 1730 $cm^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$): δ 11.25 (s, 1H), 8.12 (s, 2H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 2.5 Hz, 1H), 7.17 – 6.97 (m, 2H), 4.30 (t, *J* = 7.3 Hz, 1H), 4.10 (qq, *J* = 10.8, 7.1 Hz, 2H), 3.47 (dd, *J* = 12.7, 8.1 Hz, 1H), 3.15 (dd, *J* = 12.7, 6.6 Hz, 1H), 1.12 (t, *J* = 7.1 Hz, 3H). $[\alpha]^{20}_{589}$ +86.891 (c 0.1; MeOH). HRMS (ESI-MS) m/z: calcd: 233.1285 [$MH^+$], found: 233.1289 [$MH^+$].

**(*R*)-Ethyl 2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-4-carboxylate hydrochloride (62a)**



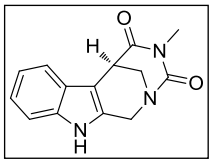

From (*R*)-ethyl 3-amino-2-(1*H*-indol-3-yl)propanoate hydrochloride (**61a**) as described for **16a** at rt for 24 h. Yield 2.3 g (9.42mmol; 55 %) colorless crystals after crystallization from diethyl ether.mp: 269.1-271.8 °C. IR (KBr): 3201, 1730 $cm^{-1}$.$^1$H NMR (300 MHz, DMSO-$d_6$):δ 11.40 (s, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.17 – 6.98 (m, 2H), 4.41 – 4.28 (m, 2H), 4.24 (t, *J* = 4.9 Hz, 1H), 4.22 – 4.07 (m, 2H), 3.68 (dd, *J* = 12.8, 4.8 Hz, 1H), 3.52 (dd, *J* = 12.8, 5.3 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H). The ee was determined by HPLC analysis with a Chiralcel OD-H column, hexane/2-propanol (85:15), flowrate=0.6 mL/min, 220 nm. $t_R$=20.66min (major), 19.32 min (minor), ≥96% ee, $[\alpha]^{20}_{589}$ +97.190 (c 0.1; MeOH). Anal.calcd for $C_{14}H_{17}ClN_2O_2$: C 59.89; H 6.10; N 9.98; found: C 59.97; H 6.28; N 9.95.

**(*R*)-*N*-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-4-carboxamide hydrochloride (*R* -37a)**



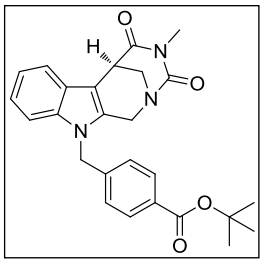

Following aprotocol for aminolysis of esters by use of cyanide as an efficient and mild catalyst[31](*R*)-ethyl 2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-4-carboxylate hydrochloride (**62a**) (0.5 g; 3.56 mmol) was dissolved in a methanolic methylamine solution (30 %, 0.6 mL) at 0 °C and a catalytic amount of NaCN (0.01 g) was added. The mixture was stirred at 0 °C for 5 d, silica gel was added and the solvent removed under reduced pressure. Purification by cc ($SiO_2$; $CH_2Cl_2$, MeOH, $NH_{3conz}$ 50:10:0.1) (dry load technique) yielded 1.39 g (6.07mmol; 77 %) colorless crystals. mp: 265.6-267.0 °C. IR (KBr): 2925, 1653 $cm^{-1}$.$^1$H NMR (300 MHz, DMSO-$d_6$): δ 10.81 (s, 1H), 7.95 (d, *J* = 4.6 Hz, 1H), 7.31 (dd, *J* = 24.2, 7.8 Hz, 2H), 7.04 – 6.87 (m, 2H), 3.95 – 3.77 (m, 2H), 3.51 (t, *J* = 4.5 Hz, 1H), 3.11 (dd, *J* = 12.9, 4.5 Hz, 1H), 2.99 (dd, *J* = 12.9, 4.9 Hz, 1H), 2.60 (d, *J* = 4.6 Hz, 3H). $[\alpha]^{20}_{589}$ +24.996 (c 0.1; MeOH)

**(6*R*)-4-Methyl-6,11-dihydro-2,6-methano[1,3]diazocino[5,6-*b*]indole-3,5(1*H*,4*H*)-dione (*R*-20a)**



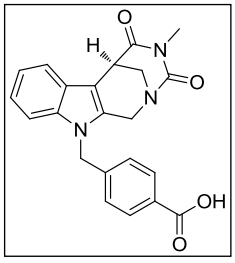
(*R*)-*N*-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-4-carboxamide hydrochloride (***R*-37a**) (0.23 g, 0.90 mmol) was dissolved under argon atmosphere in a mixture of $CH_2Cl_2$ (17.0 mL) and pyridine (1.25 mL) and cooled to 0 °C. A solution of triphosgene (216 mg) in $CH_2Cl_2$ (6.0 mL) was added dropwise and the mixture stirred at 0 °C for 3h. The mixture was diluted with $CH_2Cl_2$, the organic layer washed with HCl (1N), dried ($Na_2SO_4$) and the solvent removed under reduced pressure. Yield 0.11 g; 0.44 mmol (49 %) colorless crystals . mp: 260.8-263.0 °C. IR (KBr): 3266, 1729, 1675 $cm^{-1}$.$^1$H NMR (300 MHz, $CDCl_3$):δ 8.07 (s, 1H), 7.69 (dd, *J* = 6.5, 1.9 Hz, 1H), 7.32 (dd, *J* = 6.6, 1.9 Hz, 1H), 7.23 – 7.12 (m, 2H), 4.90 (d, *J* = 16.3 Hz, 1H), 4.57 – 4.48 (m, 1H), 3.91 (d, *J* = 13.4 Hz, 1H), 3.38 (dd, *J* = 12.8, 1.9 Hz, 1H), 3.06 (s, 3H). The ee was determined by HPLC analysis with a Chiralcel OD-H column, hexane/2-propanol (85:15), flow rate = 0.6 mL/min, 220 nm. $t_R$=37.16 min (major), 44.34 min (minor), ≥ 96%ee, $[\alpha]^{20}_{589}$ -136.190 (c 0.1; MeOH). Anal.calcd for $C_{14}H_{13}N_3O_2$: C 65.87; H 5.13; N 16,46; found: C 65.69; H 5.26; N 16.22.

***tert*-Butyl 4-(((6*R*)-4-Methyl-3,5-dioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)benzoate (*R*-22a)**



A stirred mixture of (6*R*)-4-methyl-6,11-dihydro-2,6-methano[1,3]diazocino[5,6-*b*]indole-3,5(1*H*,4*H*)-dione (***R*-20a**) (0.64 g; 2.52 mmol), tert-butyl 4-(bromomethyl)benzoate (**21**) (0.82 g, 3.0 mmol) and $K_2CO_3$ (0.42 g, 3.0 mmol) in 2-butanone (30.0 mL) was heated to 80 °C for 10 h. The mixture was cooled to rt, the solid filtered off and the solvent removed under reduced pressure. After purification by cc ($SiO_2$; $CH_2Cl_2$, EtOAc 3:1) and removal of the solvent under reduced pressure the product (0.82 g, 1.84 mmol, 73 %) was obtained as colorless crystals. mp: 96.4-97.0 °C. IR (KBr): 1712, 1688 $cm^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$):δ 7.94 – 7.89 (m, 2H), 7.76 – 7.70 (m, 1H), 7.25 – 7.16 (m, 3H), 7.06 (d, *J* = 8.3 Hz, 2H), 5.35 (d, *J* = 17.0 Hz, 1H), 5.13 (d, *J* = 17.0 Hz, 1H), 4.86 (d, *J* = 16.4 Hz, 1H), 4.27 (dd, *J* = 16.4, 1.0 Hz, 1H), 3.90 (d, *J* = 12.0 Hz, 2H), 3.33 (dd, *J* = 13.5, 2.6 Hz, 1H), 3.06 (s, 3H), 1.57 (s, 9H). $[\alpha]^{20}_{589}$ -115.591 (c 0.1; MeOH). Anal. calcd for $C_{26}H_{27}N_3O_4$: C 70.09; H 6.11; N 9,43; found: C 70.32; H 6.07; N 9.43.

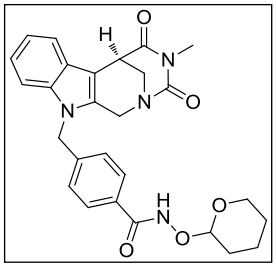
**4-(((6*R*)-4-Methyl-3,5-dioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)benzoic acid (*R*-24a)**



*tert*-Butyl 4-(((6*R*)-4-methyl-3,5-dioxo-3,4,5,6-tetrahydro-2,6-methano-[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)benzoate (***R*-22a**) (1.21 g; 2.73 mmol) was dissolved in $CH_2Cl_2$ ( 20 mL), $CF_3COOH$ was added (10 mL) and the solution stirred for 2.5 h at rt. $H_2O$ (100 mL) was added, the organic layer separated, dried ($Na_2SO_4$), the solvent removed under reduced pressure and the solid obtained crystallized from $Et_2O$. Yield 0.89 g (2.29 mmol; 84 %) colorless crystals . mp: 244.0-247.4 °C. IR (KBr): 1725, 1694 $cm^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$): δ 12.96 (s, 1H), 7.86 (d, *J* = 8.3 Hz, 2H), 7.53 (dd, *J* = 6.4, 2.2 Hz, 1H), 7.42 (dd, *J* = 6.7, 1.8 Hz, 1H), 7.16 (d, *J* = 8.3 Hz, 2H), 7.13 – 7.06 (m, 2H), 5.45 (s, 2H), 4.83 (d, *J* = 16.6 Hz, 1H), 4.55 (d, *J* = 16.5 Hz, 1H), 3.90 (d, *J* = 11.9 Hz, 2H), 3.45 (dd, *J* =

13.4, 2.5 Hz, 1H), 2.89 (s, 3H). $[\alpha]^{20}_{589}$ -141.690 (c 0.1; MeOH). Anal. calcd for $C_{22}H_{19}N_3O_4$: C 67.86; H 4.92; N 10,79; found: C 67.56; H 5.14; N 10.50.

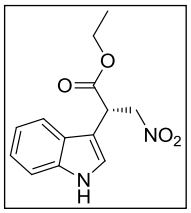
**4-(((6*R*)-4-methyl-3,5-dioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy)benzamide (*R*-27a)**



4-(((6*R*)-4-methyl-3,5-dioxo-3,4,5,6-tetrahydro-2,6-methano-[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)benzoic acid (***R*-24a**) (0.89 g; 2.28 mmol) was dissolved in THF (15.0 mL), *N*,*N*-Diisopropyl-ethylamine (0.89 mL), $NH_2OTHP$ (0.80 g; 6.84 mmol) and BOP (1.01 g; 2.28 mmol) were added and the mixture stirred at rt for 2 h. The mixture was poured into water (100 mL), extracted with ethyl acetate (3 x 20 mL), dried ($Na_2SO_4$) and the solvents removed under reduced pressure. MeOH (10 mL) was added to the remaining solid and the mixture macerated at 40 °Cfor 1 h by rotation of the flask. The methanolic solution was decanted and the solid dried in vacuo.0.47 g; 0.96 mmol (42 %) colorless foam. mp: 228.3-230.1 °C. IR (KBr): 2942; 1723, 1678 $cm^{-1}$.$^1$H NMR (400 MHz, DMSO-$d_6$):δ 11.58 (s, 1H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.55 – 7.50 (m, 1H), 7.41 (d, *J* = 7.5 Hz, 1H), 7.15 (d, *J* = 8.2 Hz, 2H), 7.14 – 7.05 (m, 2H), 5.48 – 5.36 (m, 2H), 4.96 (s, 1H), 4.86 (d, *J* = 16.6 Hz, 1H), 4.56 (d, *J* = 16.5 Hz, 1H), 4.02 (t, *J* = 7.1 Hz, 1H), 3.90 (d, *J* = 13.9 Hz, 2H), 3.55 – 3.41 (m, 2H), 2.90 (s, 3H), 1.61 (d, *J* = 68.6 Hz, 6H).). The ee was determined by HPLC analysis with a Phenomenex Lux Cellulose-2 column, MeOH/2-propanol (90:10), flowrate=0.5 mL/min, 215 nm. $t_R$ = 20-26.20 min (major), 26.20 - 32.00 min (minor), 96% ee, $[\alpha]^{20}_{589}$ -133.593 (c 0.1; $C_3H_6O$), Anal.calcd for $C_{27}H_{28}N_4O_5$: C 66.38; H 5.78; N 11,47; found: C 66.00; H 6.06; N 11.25.

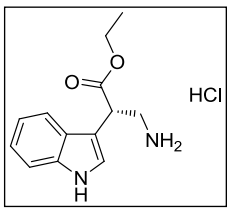
**S-Enantiomer**

**(*S*)-Ethyl 2-(1*H*-indol-3-yl)-3-nitropropanoate (60b)**



Preparation as described above for the *R*-Enantiomer **60a** by use of *N*-((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)quinoline-2-carbothioamide **106b**[21] as precatalyst. Yield 1.91 g (8.23 mmol; 48 %) yellow oil.$^1$H NMR (300 MHz, $CDCl_3$):δ 8.23 (s, 1H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.19 (ddd, *J* = 7.2, 6.5, 1.9 Hz, 2H), 5.21 (dd, *J* = 14.2, 9.7 Hz, 1H), 4.74 (dd, *J* = 9.7, 4.9 Hz, 1H), 4.64 (dd, *J* = 14.2, 4.9 Hz, 1H), 4.33 – 4.07 (m, 2H), 1.23 (dd, *J* = 8.5, 5.8 Hz, 3H). The ee was determined by HPLC analysis with a Chiralcel OD-H column, hexane/2-propanol (85:15), flowrate =0.6 mL/min, 220 nm. $t_R$=107.92 min (major), 90.81 min (minor), ≥ 99% ee, $[\alpha]^{20}_{589}$ -134.090 (c 0.1; MeOH). HRMS (ESI-MS) m/z: calcd: 263.1026 [$MH^+$], found: 263.1030 [$MH^+$].

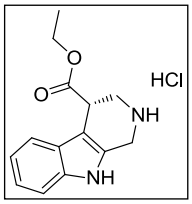
**(*S*)-Ethyl 3-amino-2-(1*H*-indol-3-yl)propanoate hydrochloride (61b)**



Preparation as described above for the *R*-Enantiomer**61a** by use of (*S*)-Ethyl 2-(1*H*-indol-3-yl)-3-nitropropanoate (**60b**). Yield 1.5 g (6.46 mmol; 88%) colorless foam. IR (KBr): 3310, 3021, 2975, 1730 $cm^{-1}$.$^1$H NMR (300 MHz, DMSO-$d_6$):δ 11.26 (s, 1H), 8.13 (s, 2H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 2.5 Hz, 1H), 7.15 – 6.99 (m, 2H), 4.30 (t, *J* = 7.3 Hz,

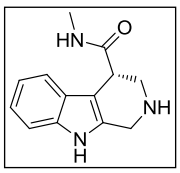
1H), 4.10 (qq, *J* = 10.8, 7.1 Hz, 2H), 3.47 (dd, *J* = 12.7, 8.1 Hz, 1H), 3.15 (dd, *J* = 12.8, 6.7 Hz, 1H), 1.12 (t, *J* = 7.1 Hz, 3H). $[\alpha]^{20}_{589}$ -86.896 (c 0.1; MeOH). HRMS (ESI-MS) m/z: calcd: 233.1285 [$MH^+$], found: 233.1288 [$MH^+$].

**(*S*)-Ethyl 2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-4-carboxylate hydrochloride (62b)**



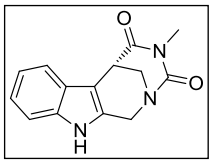

Preparation as described above for the *R*-Enantiomer **62a** by use of (*S*)-Ethyl 3-amino-2-(1*H*-indol-3-yl)propanoate hydrochloride (**61b**). Yield 2.5 g (10.24 mmol; 60 %) colorless crystals after recrystallization from diethyl ether. mp: 268.8-271.4 °C. IR (KBr): 3200, 1730 $cm^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$):δ 11.35 (s, 1H), 9.64 (s, 1H), 7.56 (d, *J* = 7.7 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.08 (ddd, *J* = 14.9, 13.9, 7.0 Hz, 2H), 4.42 – 4.28 (m, 2H), 4.23 (dd, *J* = 10.2, 4.1 Hz, 1H), 4.21 – 4.09 (m, 2H), 3.69 (dd, *J* = 12.8, 4.7 Hz, 1H), 3.52 (dd, *J* = 12.9, 5.3 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H). The ee was determined by HPLC analysis with a Chiralcel OD-H column, hexane/2-propanol (85:15), flowrate=0.6 mL/min, 220 nm. $t_R$=17.71 min (major), 19.29 min (minor), ≥ 96% ee. $[\alpha]^{20}_{589}$ -97.195 (c 0.1; MeOH). Anal.calcd for $C_{14}H_{17}ClN_2O_2$: C 59.89; H 6.10; N 9.98; found: C 59.92; H 6.16; N 9.90.

**(*S*)-*N*-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-4-carboxamide (*S*-37a)**



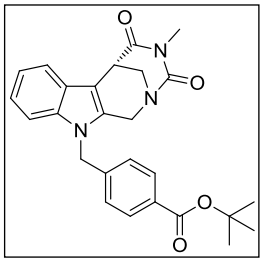

Preparation as described above for the *R*-Enantiomer ***R*-37a** by use of (*S*)-ethyl 2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-4-carboxylate hydrochloride (**62b**). Yield 0.24g (1.05mmol; 63 %) colorless foam. mp: 239.3-241.2 °C. IR (KBr): 2926, 1653 $cm^{-1}$.$^1$H NMR (300 MHz, DMSO-$d_6$):δ 10.81 (s, 1H), 7.95 (d, *J* = 4.6 Hz, 1H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 7.9 Hz, 1H), 7.04 – 6.87 (m, 2H), 3.94 – 3.78 (m, 2H), 3.51 (t, *J* = 4.5 Hz, 1H), 3.17 (s, 1H), 3.10 (dd, *J* = 12.9, 4.5 Hz, 1H), 2.98 (dd, *J* = 12.9, 4.8 Hz, 1H), 2.59 (d, *J* = 4.6 Hz, 3H). $[\alpha]^{20}_{589}$ -24.999 (c 0.1; MeOH)

**(6*S*)-4-Methyl-6,11-dihydro-2,6-methano[1,3]diazocino[5,6-*b*]indole-3,5(1*H*,4*H*)-dione (*S*-20a)**




Preparation as described above for the *R*-Enantiomer ***R*-20a** by use of(*S*)-*N*-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-4-carboxamide (***S*-37a**). Yield 0.12 g (0.47 mmol; 45 %) colorless crystals. mp: 251.4-254.0 °C. IR (KBr): 3266, 1729, 1675 $cm^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): δ 8.06 (s, 1H), 7.69 (dd, *J* = 6.6, 1.8 Hz, 1H), 7.32 (dd, *J* = 6.6, 1.8 Hz, 1H), 7.23 – 7.12 (m, 2H), 4.90 (d, *J* = 16.4 Hz, 1H), 4.58 – 4.49 (m, 1H), 3.91 (d, *J* = 13.4 Hz, 2H), 3.38 (dd, *J* = 12.8, 1.9 Hz, 1H), 3.06 (s, 3H). The ee was determined by HPLC analysis with a Chiralcel OD-H column, hexane/2-propanol (85:15), flowrate = 0.6 mL/min, 220nm. $t_R$=41.72min (major), 37.92 min (minor), ≥ 96% ee, $[\alpha]^{20}_{589}$ +136.193 (c 0.1; MeOH). Anal.calcd for $C_{14}H_{13}N_3O_2$: C 65.87; H 5.13; N 16,46; found: C 65.62; H 5.22; N 16.19.

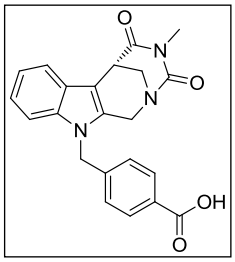
***tert*-Butyl 4-(((6*S*)-4-methyl-3,5-dioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)benzoate (*S*-22a)**




Preparation as described above for the *R*-Enantiomer ***R*-22a** by use of(6*S*)-4-methyl-6,11-dihydro-2,6-methano[1,3]diazocino[5,6-*b*]indole-3,5(1*H*,4*H*)-dione (***S*-20a**). Yield 0.71 g (1.60 mmol; 78 %) colorless crystals. mp: 96.7-97.4 °C. IR (KBr): 1711, 1688 $cm^{-1}$. $^1$H NMR

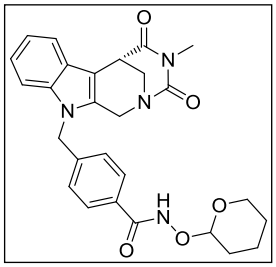
(300 MHz, $CDCl_3$):δ 7.92 (dd, 2H), 7.77 – 7.70 (m, 1H), 7.24 – 7.15 (m, 3H), 7.06 (d, *J* = 8.4 Hz, 2H), 5.35 (d, *J* = 17.0 Hz, 1H), 5.13 (d, *J* = 17.0 Hz, 1H), 4.86 (d, *J* = 16.4 Hz, 1H), 4.27 (dd, *J* = 16.4, 1.0 Hz, 1H), 3.90 (d, *J* = 11.9 Hz, 2H), 3.33 (dd, *J* = 13.5, 2.6 Hz, 1H), 3.06 (s, 3H), 1.57 (s, 9H). $[\alpha]^{20}_{589}$ +155.594 (c 0.1; MeOH). Anal.calcd for $C_{26}H_{27}N_3O_4$: C 70.09; H 6.11; N 9,43; found: C 70.26; H 5.99; N 9.42.

**4-(((6S)-4-Methyl-3,5-dioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)benzoic acid (*S*-24a)**




Preparation as described above for the *R*-Enantiomer ***R*-24a** by use of *tert*-butyl 4-(((6*S*)-4-methyl-3,5-dioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)benzoate (***S*-33a**). Yield 0.31 g (0.80 mmol; 50 %) colorless crystals. mp: 241.8-243.7 °C. IR (KBr): 1725, 1693 $cm^{-1}$.$^1$H NMR (400 MHz, DMSO-$d_6$):δ 12.93 (s, 1H), 7.86 (d, *J* = 8.3 Hz, 2H), 7.56 – 7.50 (m, 1H), 7.42 (d, *J* = 7.3 Hz, 1H), 7.15 (t, *J* = 7.0 Hz, 2H), 7.15 – 7.04 (m, 2H), 5.45 (s, 2H), 4.83 (d, *J* = 16.6 Hz, 1H), 4.55 (d, *J* = 16.5 Hz, 1H), 3.90 (d, *J* = 12.6 Hz, 2H), 3.45 (dd, *J* = 13.6, 2.5 Hz, 1H), 2.90 (s, 3H). $[\alpha]^{20}_{589}$ +141.693 (c 0.1; MeOH). Anal.calcd for $C_{22}H_{19}N_3O_4$: C 67.86; H 4.92; N 10,79; found: C 67.54; H 4.93; N 10.48.

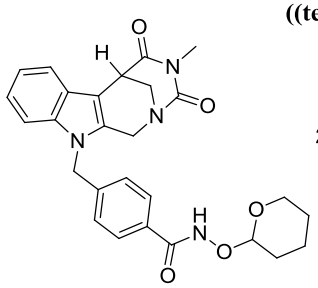
**4-(((6*S*)-4-Methyl-3,5-dioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy)benzamide (*S*-27a)**




Preparation as described above for the *R*-Enantiomer ***R*-27a** by use of 4-(((6S)-4-methyl-3,5-dioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)benzoic acid (***S*-24a**). Yield 0.22 g (0.45 mmol; 56 %) colorless foam. mp: 242.6-243.0 °C. IR (KBr): 2944, 1723, 1679 $cm^{-1}$.$^1$H NMR (300 MHz, $CDCl_3$):δ 8.86 (s, 1H), 7.72 (dd, *J* = 8.9, 5.6 Hz, 1H), 7.66 (t, *J* = 6.9 Hz, 2H), 7.19 (q, *J* = 3.4 Hz, 3H), 7.05 (d, *J* = 8.1 Hz, 2H), 5.30 (dd, *J* = 16.9, 9.4 Hz, 1H), 5.19 – 5.12 (m, 1H), 5.08 (d, *J* = 13.2 Hz, 1H), 4.83 (dd, *J* = 16.3, 8.2 Hz, 1H), 4.27 (d, *J* = 16.4 Hz, 1H), 3.99 (d, *J* = 8.8 Hz, 1H), 3.90 (d, *J* = 12.1 Hz, 2H), 3.63 (d, *J* = 11.0 Hz, 1H), 3.33 (dd, *J* = 13.4, 2.4 Hz, 1H), 3.04 (s, 3H), 1.76 (d, 6H). The ee was determined by HPLC analysis with a Phenomenex Lux Cellulose-2 column, MeOH/2-propanol (90:10), flowrate = 0.5 mL/min, 215 nm. $t_R$ = 20-26.20 min (major), 26.20- 32.00 min (minor), ≥ 96% ee, $[\alpha]^{20}_{589}$ 133.590 (c 0.1; $C_3H_6O$) Anal. calcd for $C_{27}H_{28}N_4O_5$: C 66.38; H 5.78; N 11.47; found: C 66.00; H 6.08; N 11.26.

## HPLC Chromatograms

**4-((4-Methyl-3,5-dioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy)benzamide**

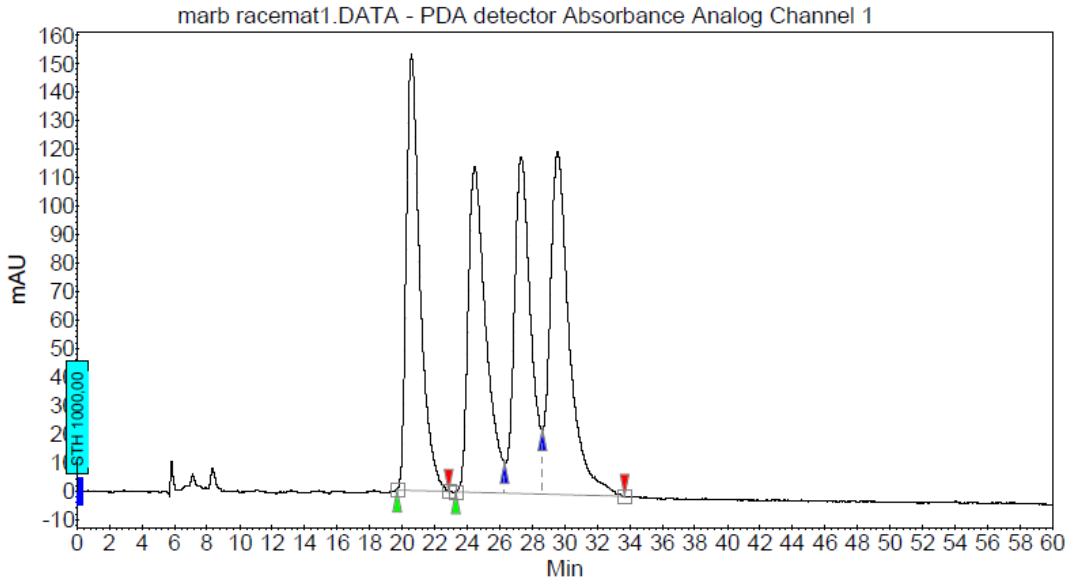


**27a**

Vail : 111
Method : Phe_Cel2_0-10-0-90_0.5
Run time : 60,00 min
Inj. vol. : 10,000 µl

λ : 215 nm

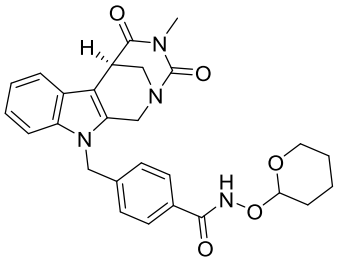
Column : Phenomenex Lux Cellulose-2,
4.6 x 250 mm, 5 µm
Eluents : A = n-Heptane
B = i-Propanol
Flow : 0.5 ml/min




### Peak Results :

| Index | Name | Time [Min] | Quantity [% Area] | Height [mAU] | Area [mAU.Min] | Area % [%] |
|---|---|---|---|---|---|---|
| 1 | UNKNOWN | 20,56 | 24,91 | 153,1 | 149,3 | 24,911 |
| 2 | UNKNOWN | 24,46 | 23,93 | 114,3 | 143,4 | 23,933 |
| 3 | UNKNOWN | 27,33 | 23,18 | 118,3 | 138,9 | 23,184 |
| 4 | UNKNOWN | 29,55 | 27,97 | 120,1 | 167,6 | 27,972 |
| | | | | | | |
| Total | | | 100,00 | 505,9 | 599,3 | 100,000 |

**4-(((6*R*)-4-Methyl-3,5-dioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy)benzamide**

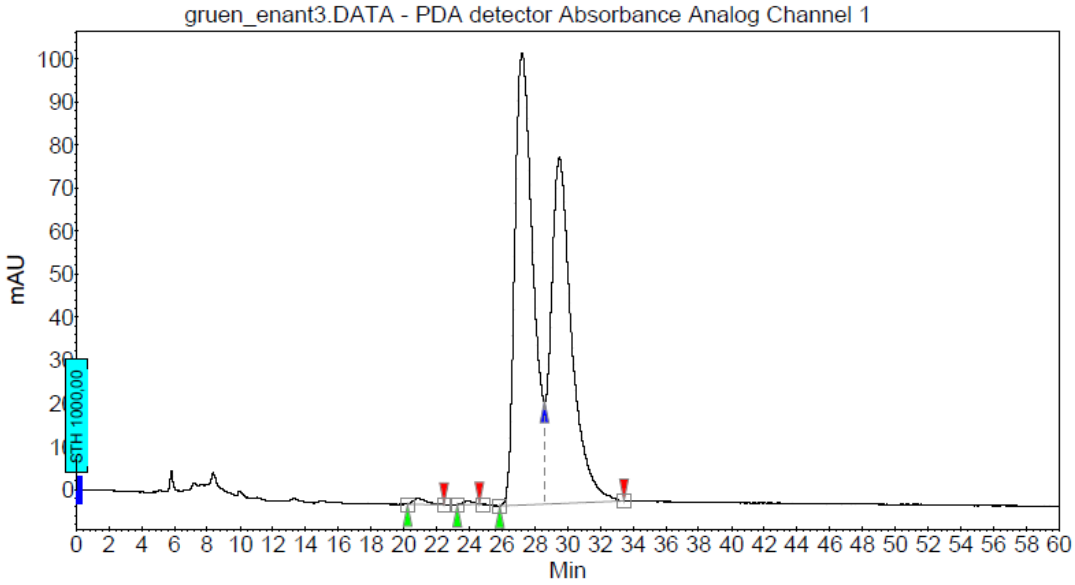


**R-27a**

Vail : 82
Method : Phe_Cel2_0-10-0-90_0.5
Run time : 60,00 min
Inj. vol. : 10,000 µl

λ : 215 nm

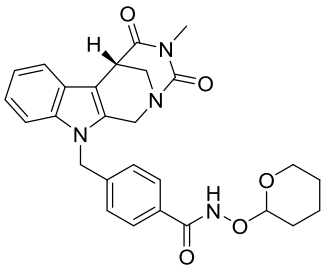
Column : Phenomenex Lux Cellulose-2,
4.6 x 250 mm, 5 µm
Eluents : A = n-Heptane
B = i-Propanol
Flow : 0.5 ml/min




## Peak Results :

| Index | Name | Time [Min] | Quantity [% Area] | Height [mAU] | Area [mAU.Min] | Area % [%] |
|---|---|---|---|---|---|---|
| 1 | UNKNOWN | 20,85 | 0,54 | 1,4 | 1,4 | 0,541 |
| 2 | UNKNOWN | 23,90 | 0,24 | 0,9 | 0,6 | 0,239 |
| 3 | UNKNOWN | 27,20 | 52,82 | 104,9 | 135,2 | 52,819 |
| 4 | UNKNOWN | 29,49 | 46,40 | 80,4 | 118,7 | 46,401 |
| | | | | | | |
| Total | | | 100,00 | 187,5 | 255,9 | 100,000 |

**4-(((6*S*)-4-Methyl-3,5-dioxo-3,4,5,6-tetrahydro-2,6-methano[1,3]diazocino[5,6-*b*]indol-11(1*H*)-yl)methyl)-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy)benzamide**

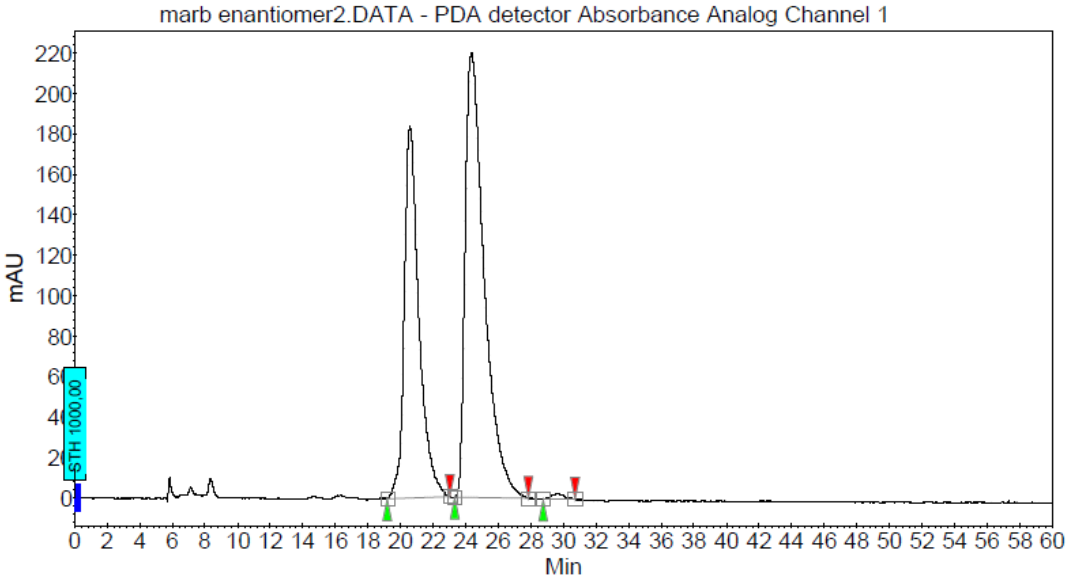


**S-27a**

Vail : 112
Method : Phe_Cel2_0-10-0-90_0.5
Run time : 60,00 min
Inj. vol. : 10,000 µl

λ : 215 nm

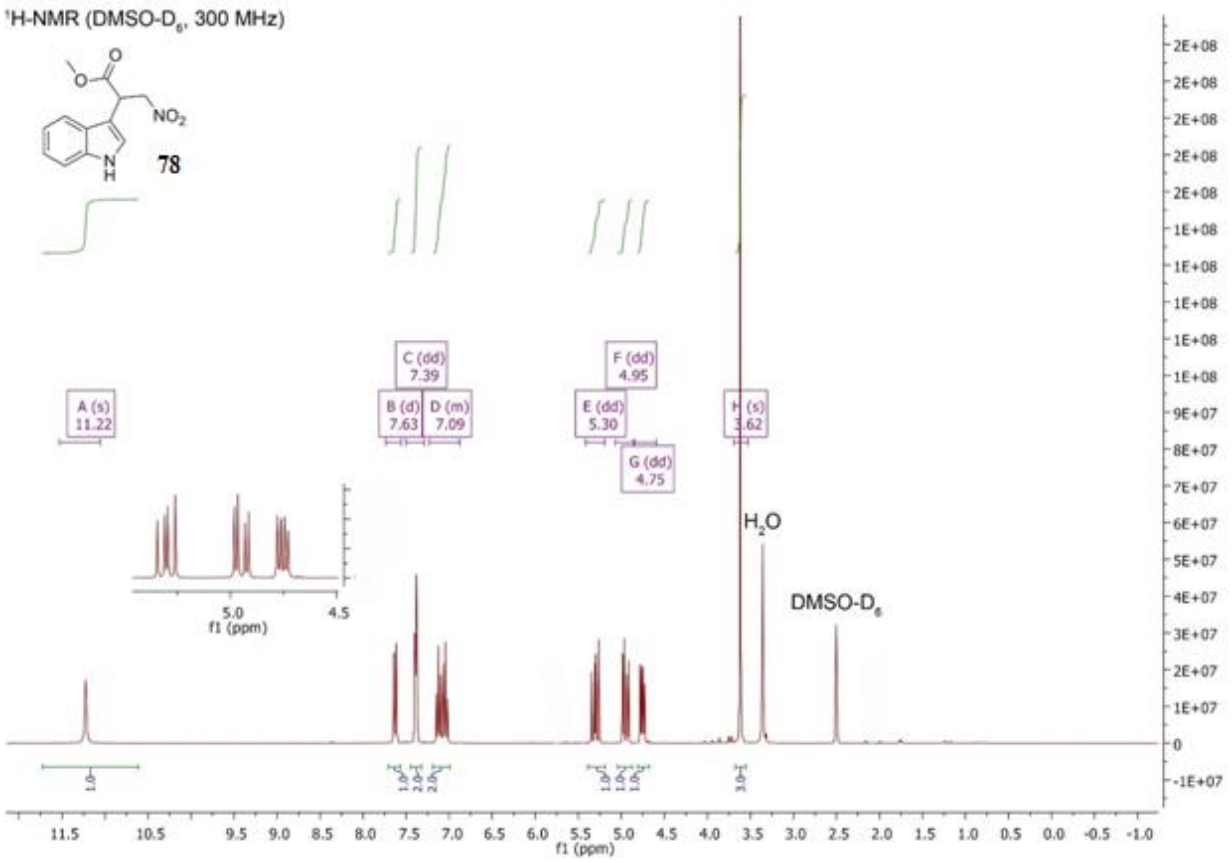
Column : Phenomenex Lux Cellulose-2,
4.6 x 250 mm, 5 µm
Eluents : A = n-Heptane
B = i-Propanol
Flow : 0.5 ml/min

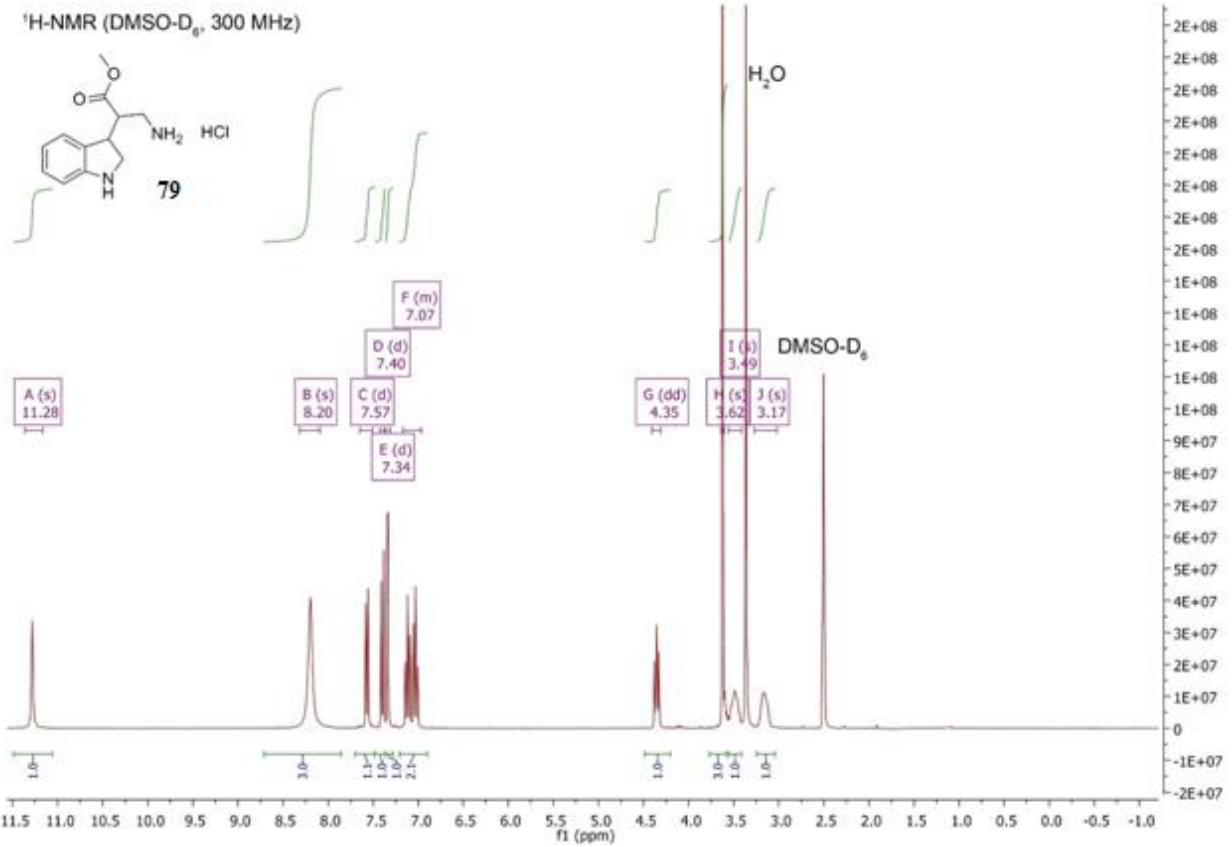


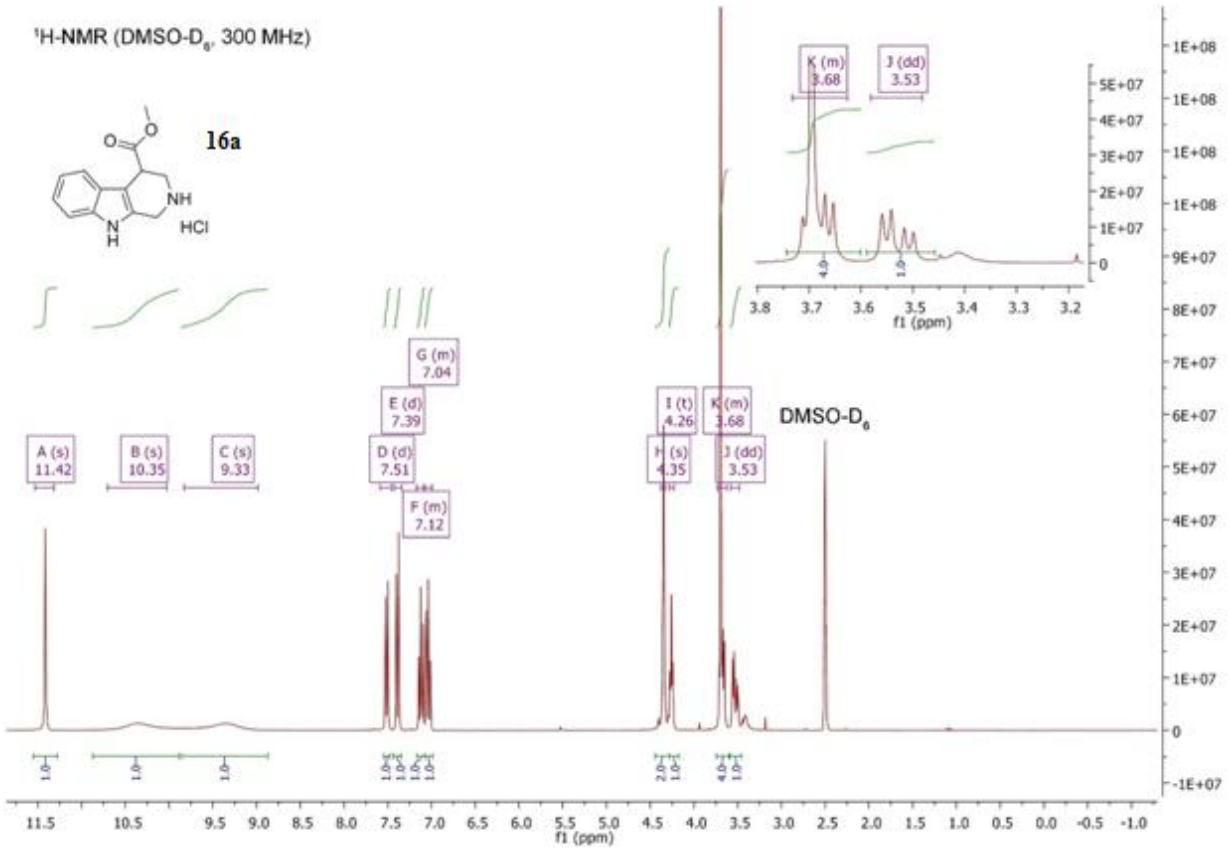

## Peak Results :

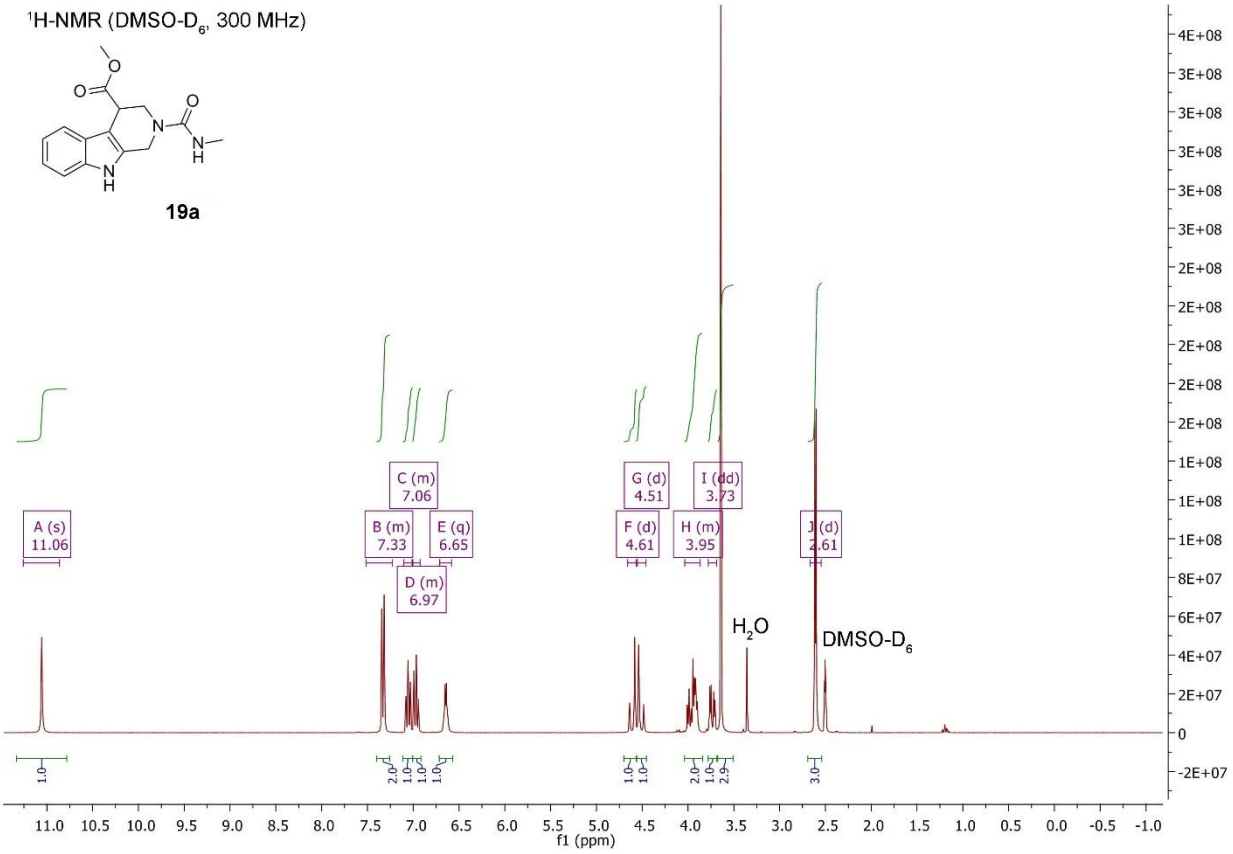
| Index | Name | Time [Min] | Quantity [% Area] | Height [mAU] | Area [mAU.Min] | Area % [%] |
|---|---|---|---|---|---|---|
| 1 | UNKNOWN | 20,57 | 39,08 | 184,2 | 192,1 | 39,079 |
| 2 | UNKNOWN | 24,36 | 60,38 | 219,9 | 296,8 | 60,381 |
| 3 | UNKNOWN | 29,57 | 0,54 | 2,7 | 2,7 | 0,540 |
| | | | | | | |
| Total | | | 100,00 | 406,8 | 491,5 | 100,000 |

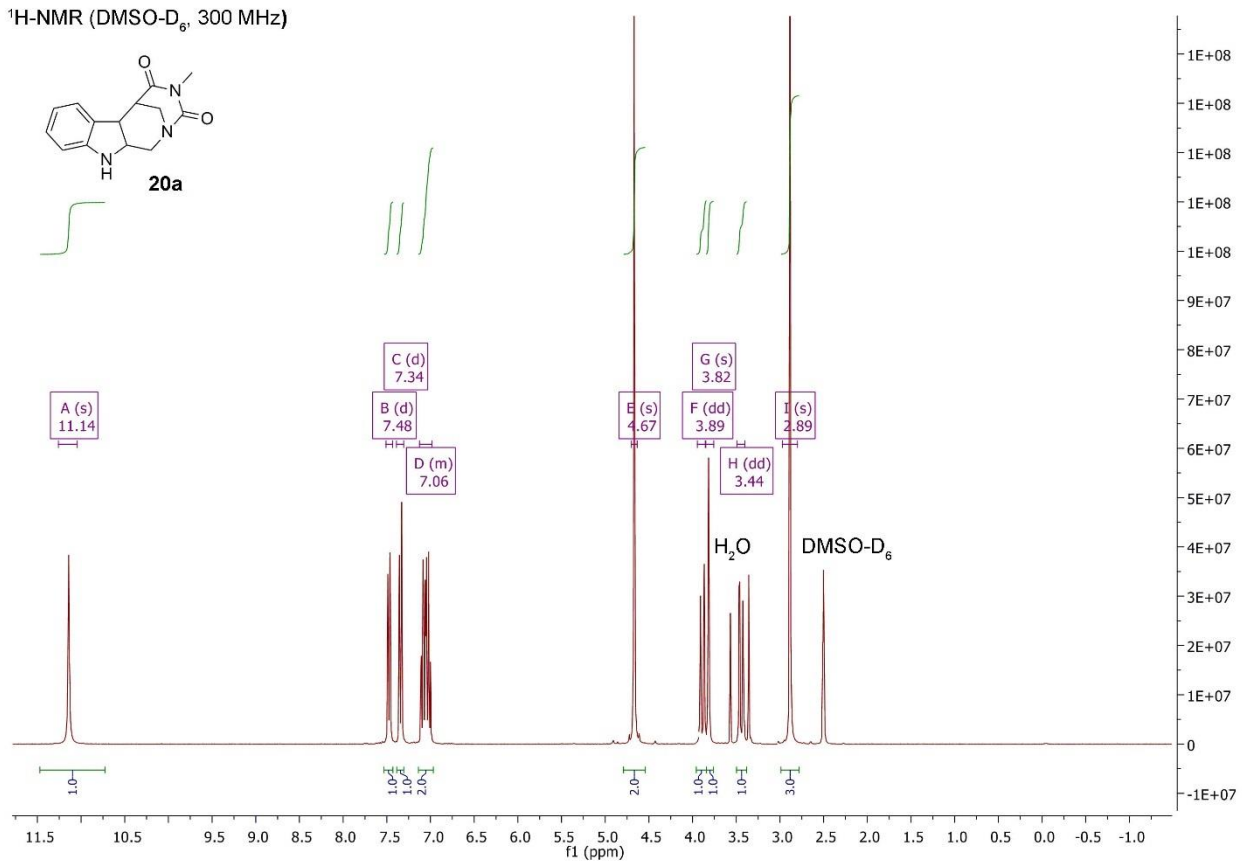
**NMR spectra of intermediates of Marbostat-100 (5a) according to the synthetic path, Marbostat-100 (5a) and final test compounds 5a-16**

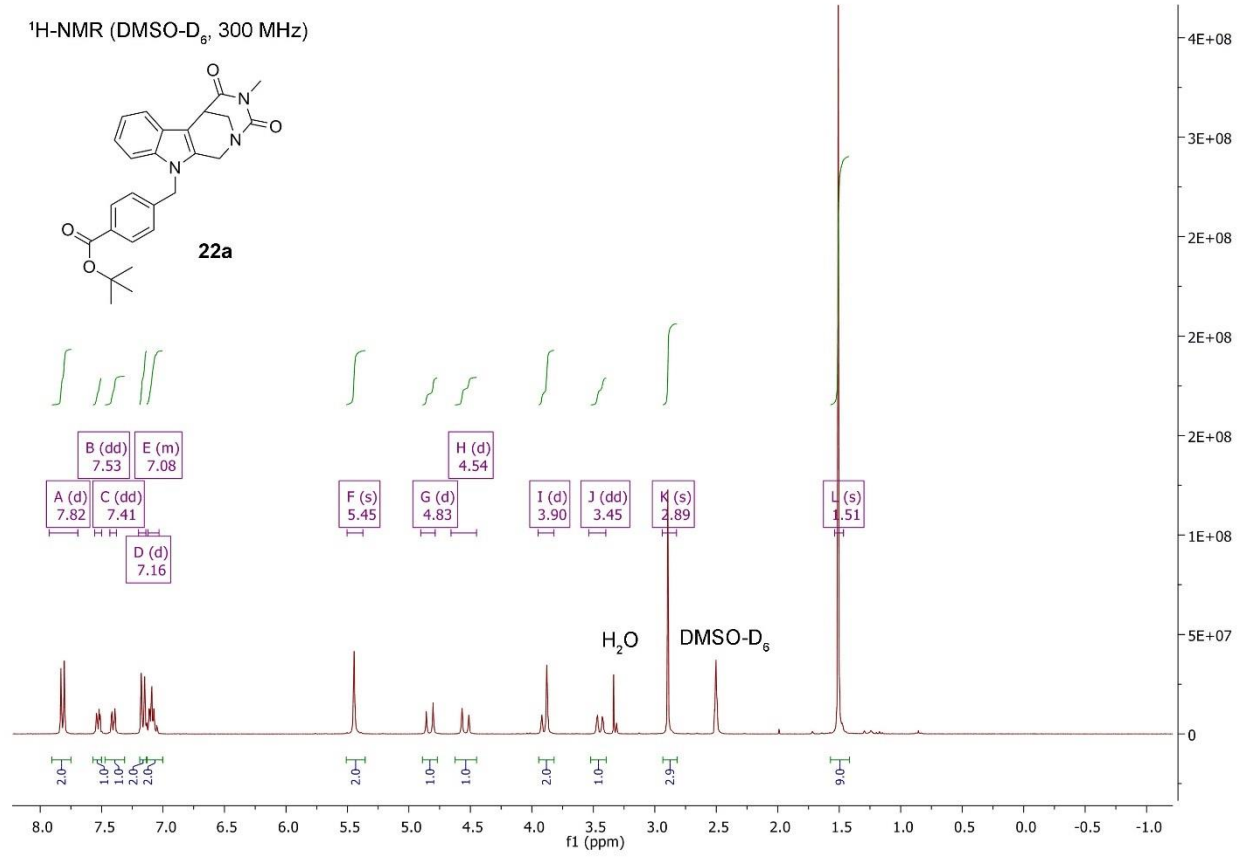


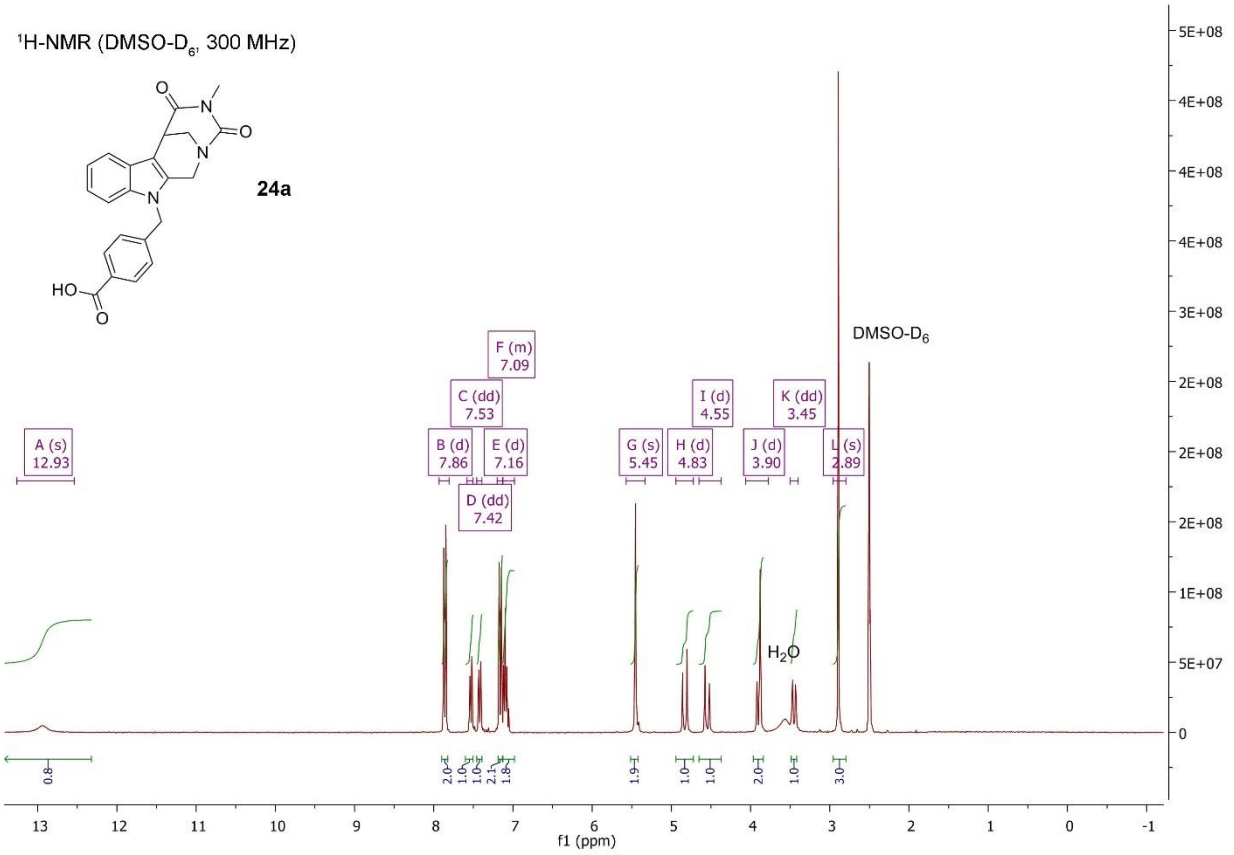



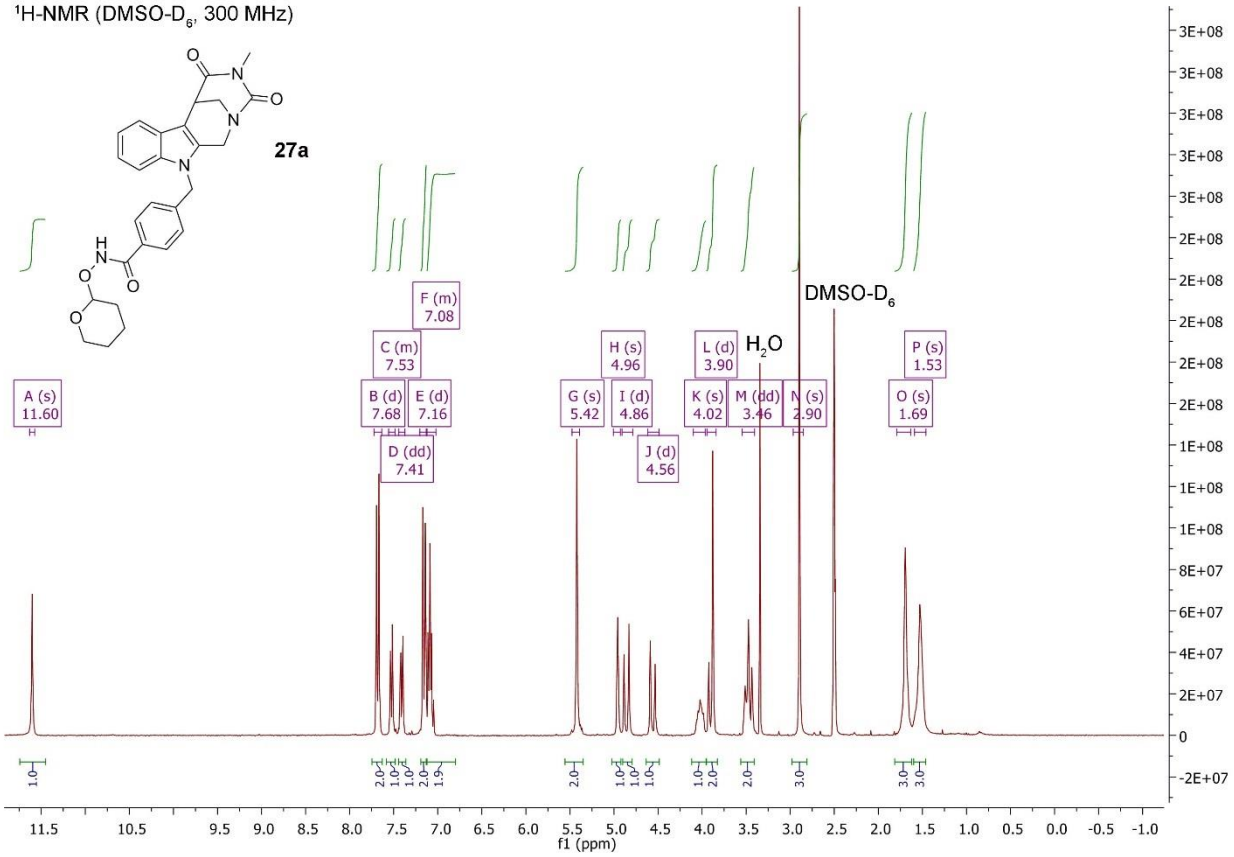

¹H-NMR (DMSO-D6, 300 MHz)
16a
NH
HCl
A (s) 11.42
B (s) 10.35
C (s) 9.33
D (d) 7.51
E (d) 7.39
F (m) 7.12
G (m) 7.04
H (s) 4.35
I (t) 4.26
J (dd) 3.53
K (m) 3.68
DMSO-D6
f1 (ppm)

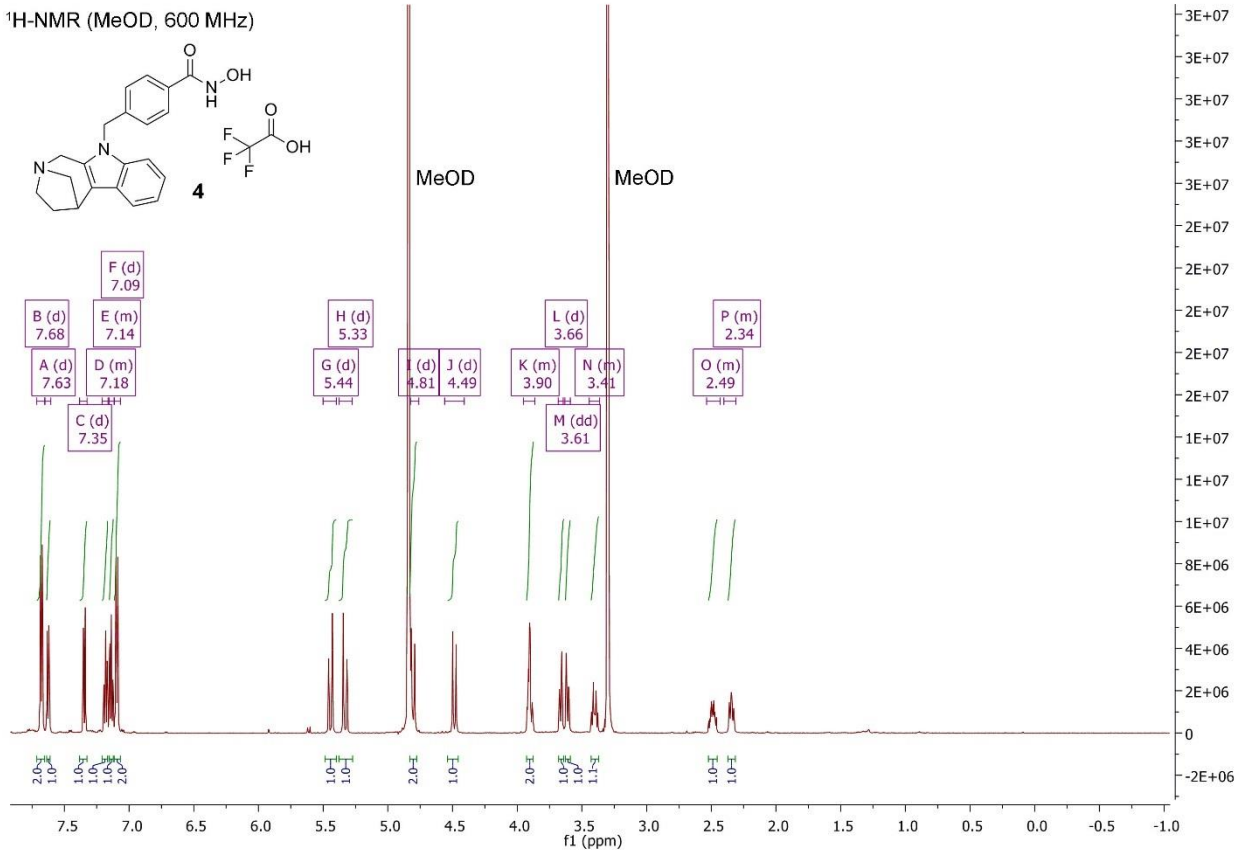

¹H-NMR (DMSO-D6, 300 MHz)
19a
A (s) 11.06
B (m) 7.33
C (m) 7.06
D (m) 6.97
E (q) 6.65
F (d) 4.61
G (d) 4.51
H (m) 3.95
I (dd) 3.73
J (d) 2.61
H2O
DMSO-D6
f1 (ppm)

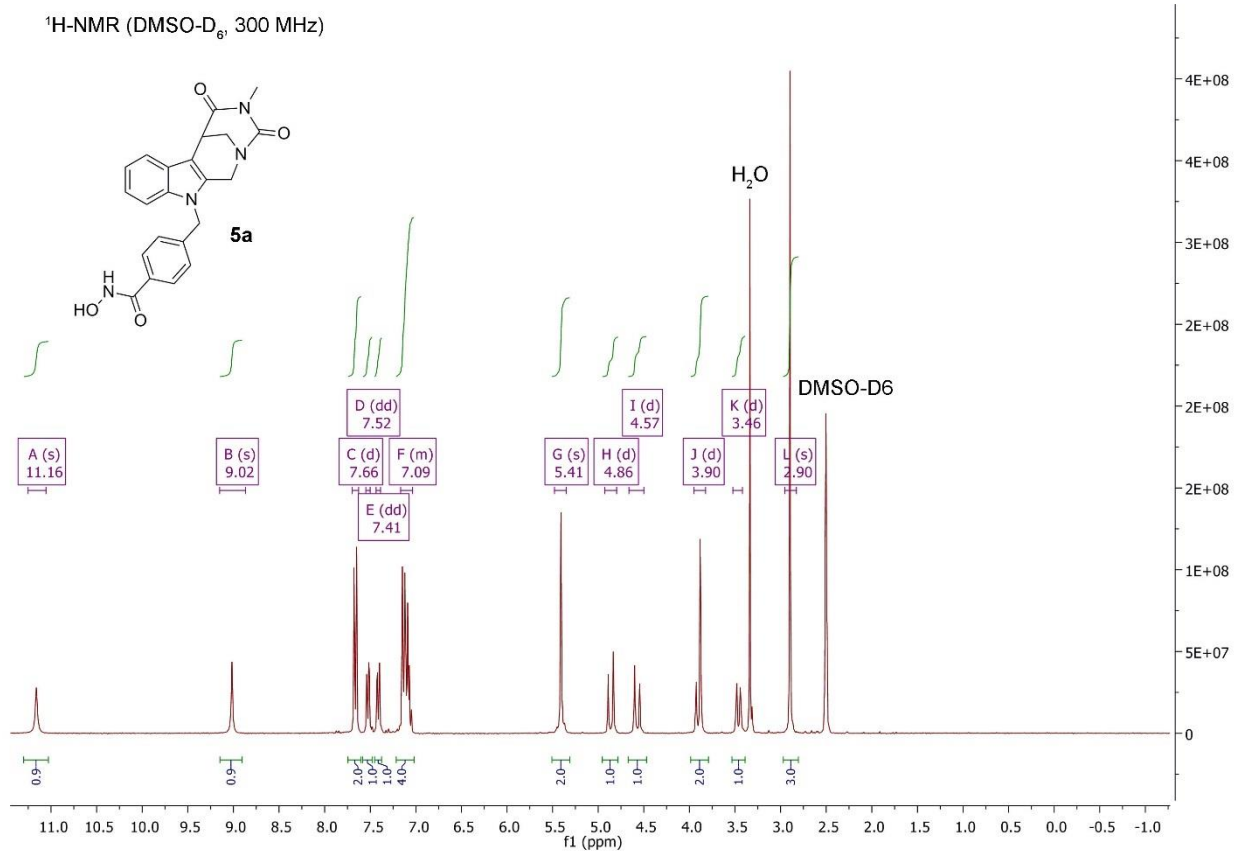

¹H-NMR (DMSO-D6, 300 MHz)
20a
A (s) 11.14
B (d) 7.48
C (d) 7.34
D (m) 7.06
E (s) 4.67
F (dd) 3.89
G (s) 3.82
H (dd) 3.44
I (s) 2.89
H2O
DMSO-D6
f1 (ppm)

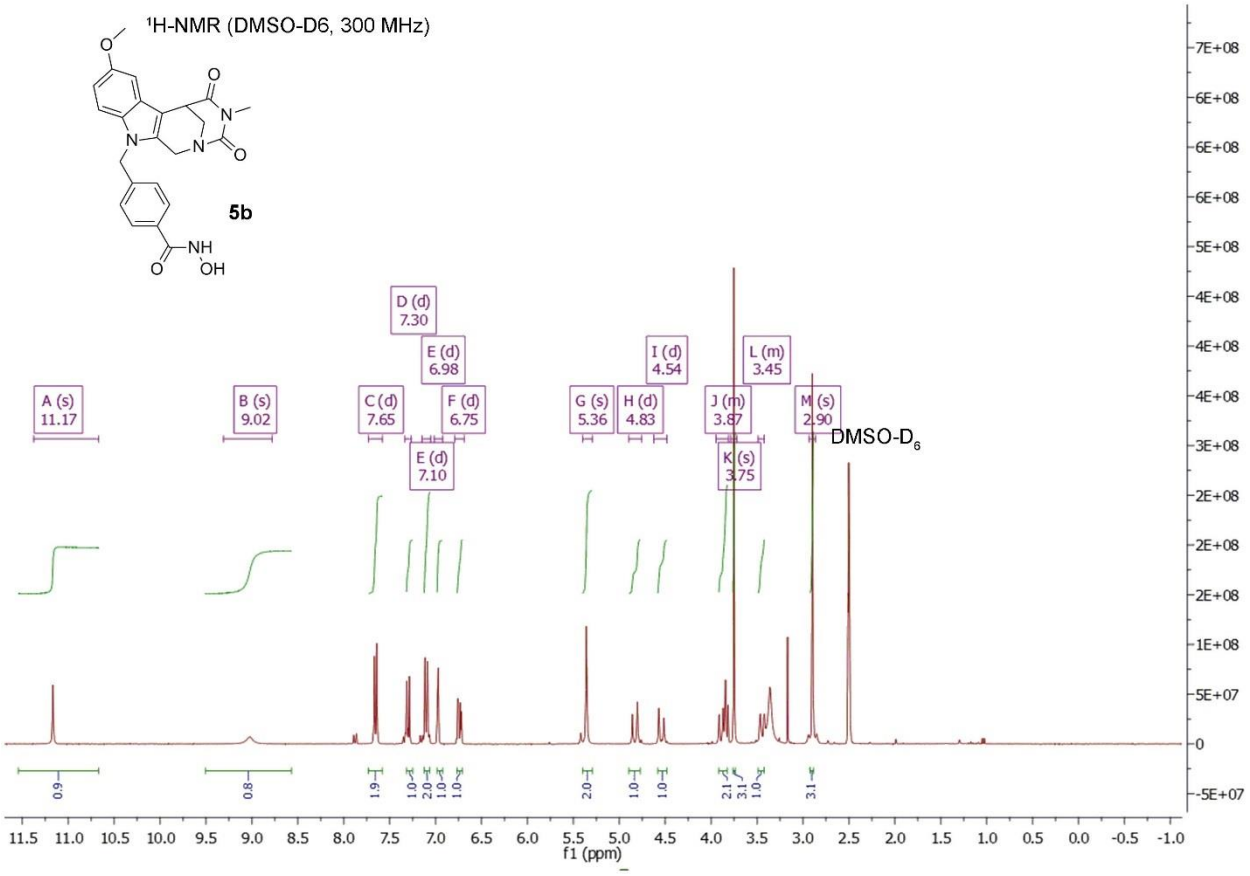

¹H-NMR (DMSO-D6, 300 MHz)
22a
A (d) 7.82
B (dd) 7.53
C (dd) 7.41
D (d) 7.16
E (m) 7.08
F (s) 5.45
G (d) 4.83
H (d) 4.54
I (d) 3.90
J (dd) 3.45
K (s) 2.89
L (s) 1.51
H2O
DMSO-D6
f1 (ppm)

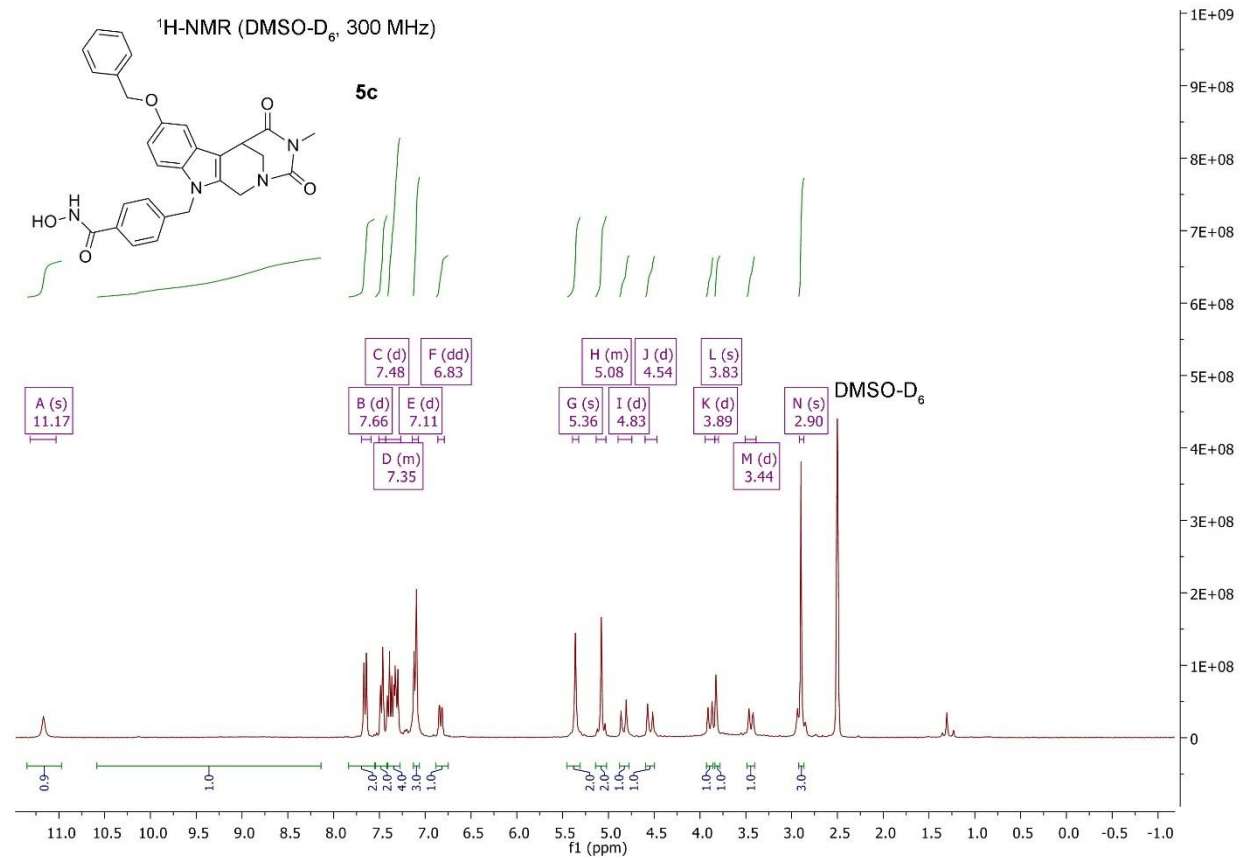

¹H-NMR (DMSO-D6, 300 MHz)
24a
A (s) 12.93
B (d) 7.86
C (dd) 7.53
D (dd) 7.42
E (d) 7.16
F (m) 7.09
G (s) 5.45
H (d) 4.83
I (d) 4.55
J (d) 3.90
K (dd) 3.45
L (s) 2.89
DMSO-D6
H2O
f1 (ppm)

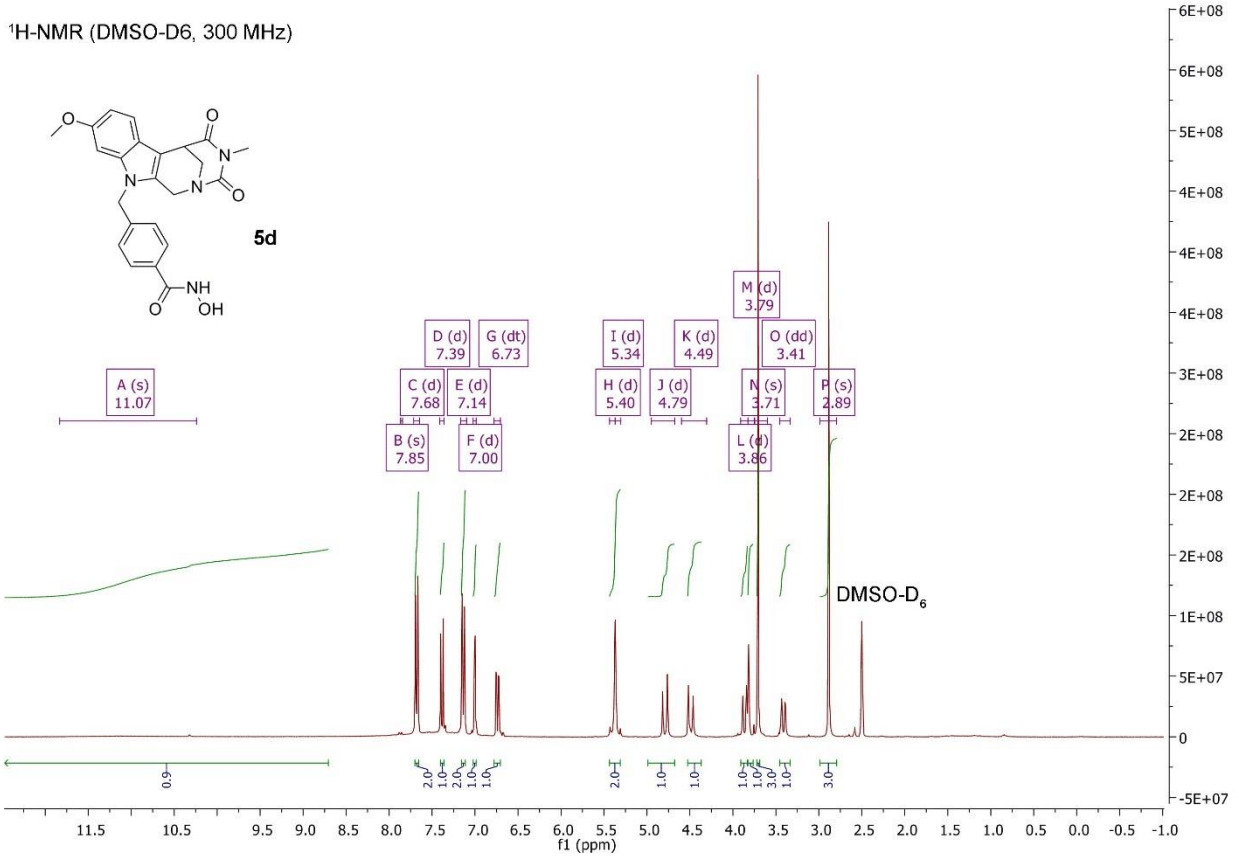

¹H-NMR (DMSO-D6, 300 MHz)
27a
A (s) 11.60
B (d) 7.68
C (m) 7.53
D (dd) 7.41
E (d) 7.16
F (m) 7.08
G (s) 5.42
H (s) 4.96
I (d) 4.86
J (d) 4.56
K (s) 4.02
L (d) 3.90
M (dd) 3.46
N (s) 2.90
O (s) 1.69
P (s) 1.53
DMSO-D6
H2O
f1 (ppm)

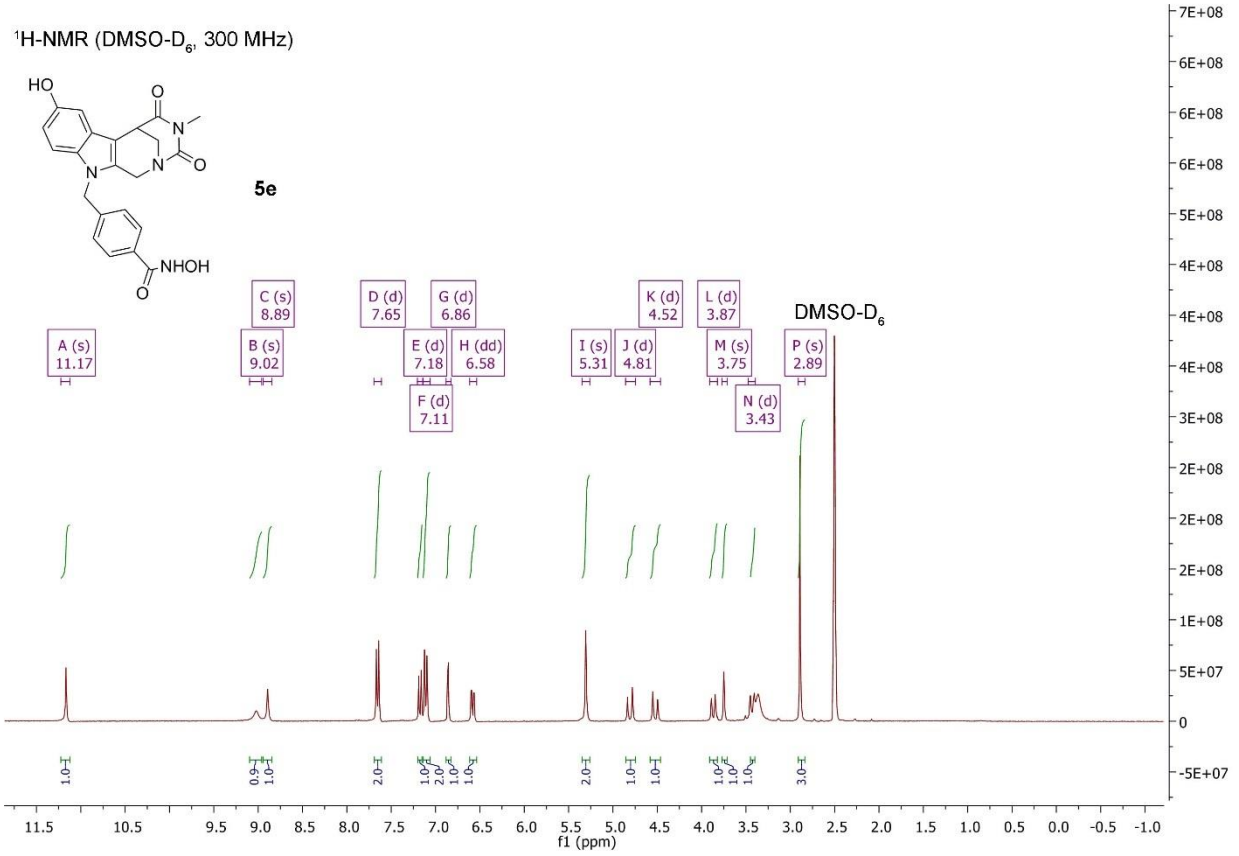

¹H-NMR (MeOD, 600 MHz)
4
MeOD
MeOD
F (d) 7.09
B (d) 7.68
E (m) 7.14
H (d) 5.33
L (d) 3.66
P (m) 2.34
A (d) 7.63
D (m) 7.18
G (d) 5.44
I (d) 4.81
J (d) 4.49
K (m) 3.90
N (m) 3.41
O (m) 2.49
C (d) 7.35
M (dd) 3.61
f1 (ppm)

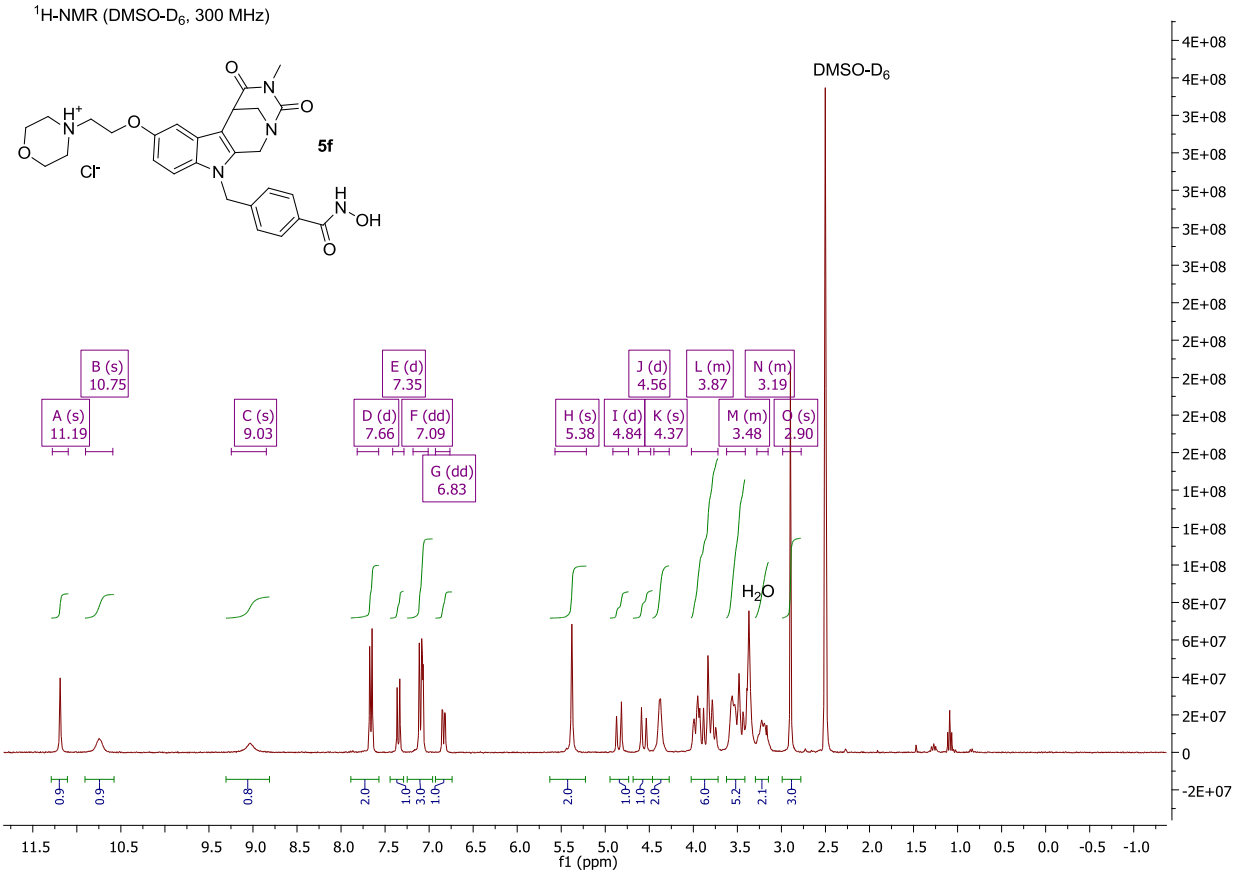

¹H-NMR (DMSO-D6, 300 MHz)
5a
H2O
DMSO-D6
D (dd) 7.52
I (d) 4.57
K (d) 3.46
A (s) 11.16
B (s) 9.02
C (d) 7.66
F (m) 7.09
G (s) 5.41
H (d) 4.86
J (d) 3.90
L (s) 2.90
E (dd) 7.41
f1 (ppm)

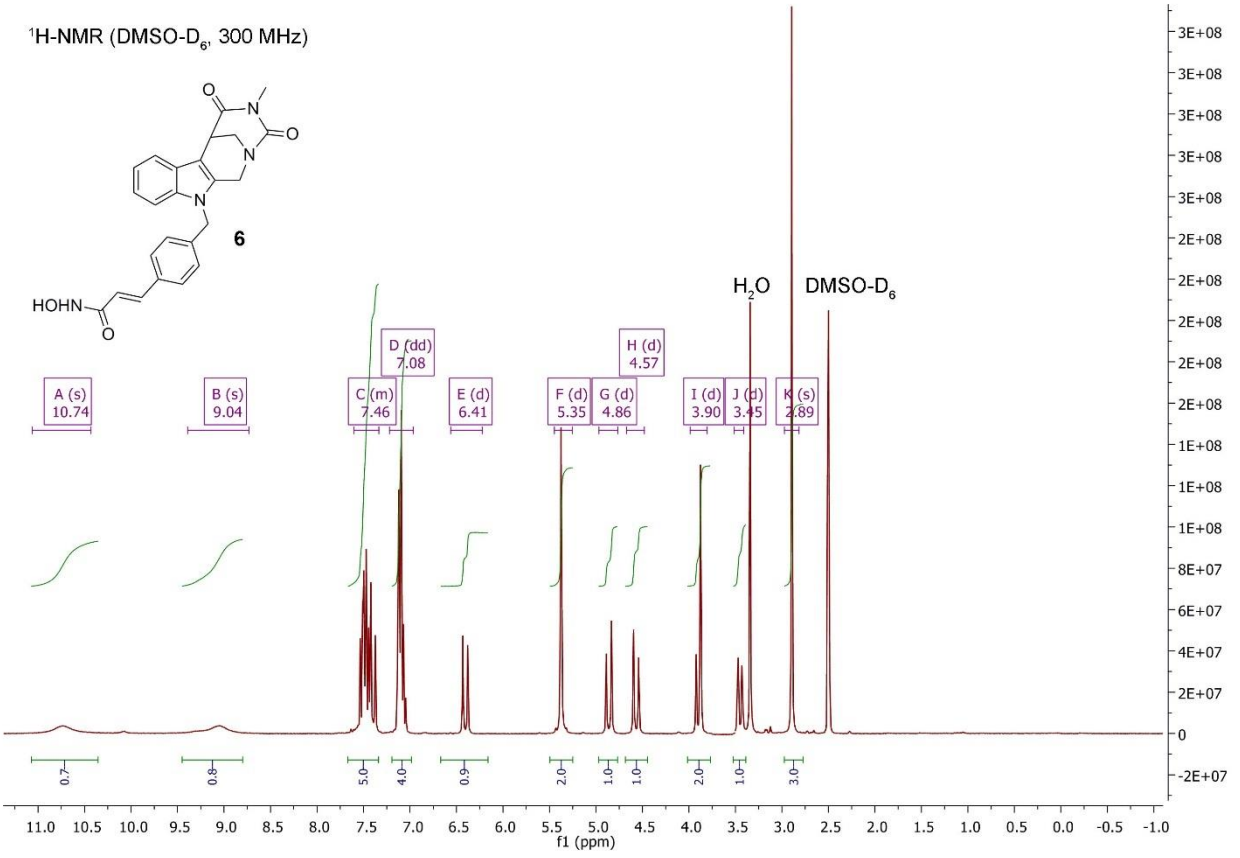

¹H-NMR (DMSO-D6, 300 MHz)
5b
A (s) 11.17
B (s) 9.02
C (d) 7.65
D (d) 7.30
E (d) 6.98
E (d) 7.10
F (d) 6.75
G (s) 5.36
H (d) 4.83
I (d) 4.54
J (m) 3.87
K (s) 3.75
L (m) 3.45
M (s) 2.90
DMSO-D6
f1 (ppm)

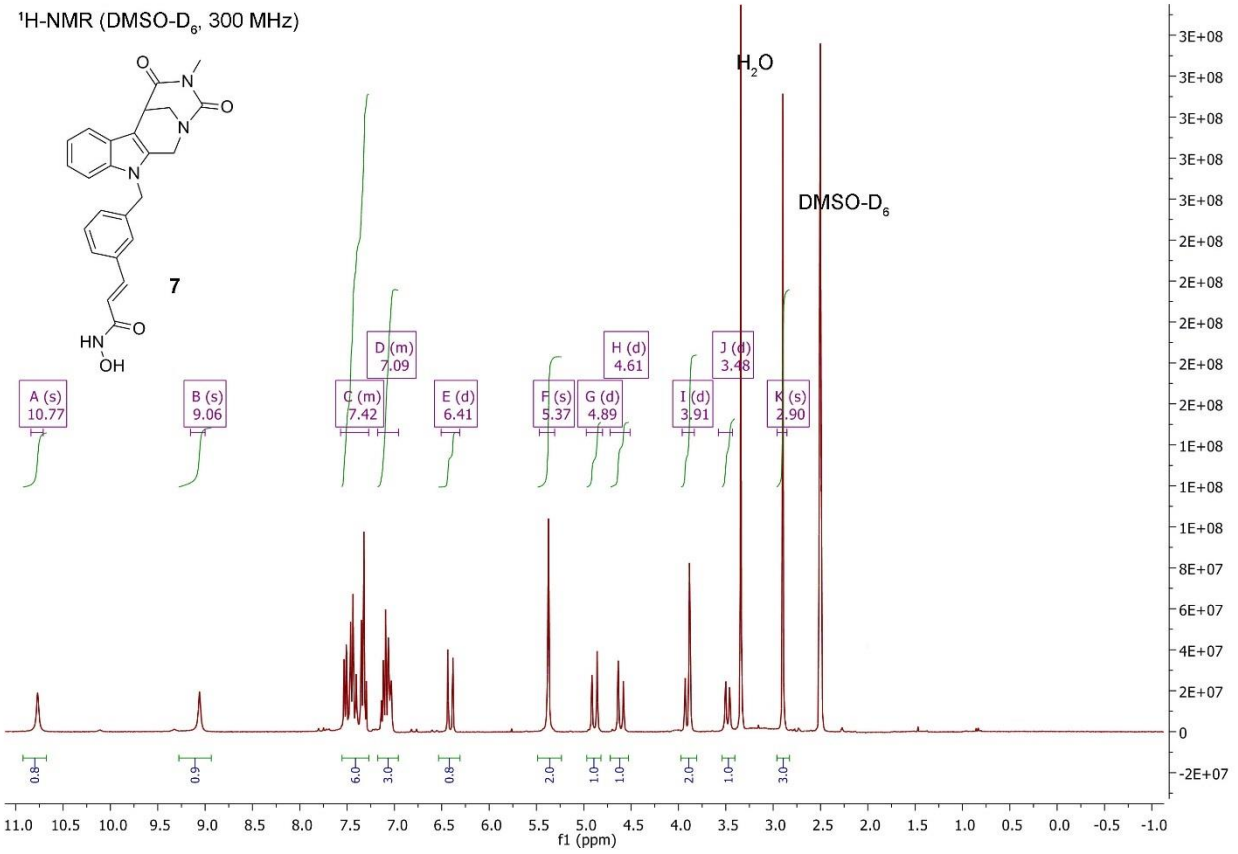

¹H-NMR (DMSO-D6, 300 MHz)
5c
A (s) 11.17
B (d) 7.66
C (d) 7.48
D (m) 7.35
E (d) 7.11
F (dd) 6.83
G (s) 5.36
H (m) 5.08
I (d) 4.83
J (d) 4.54
K (d) 3.89
L (s) 3.83
M (d) 3.44
N (s) 2.90
DMSO-D6
f1 (ppm)

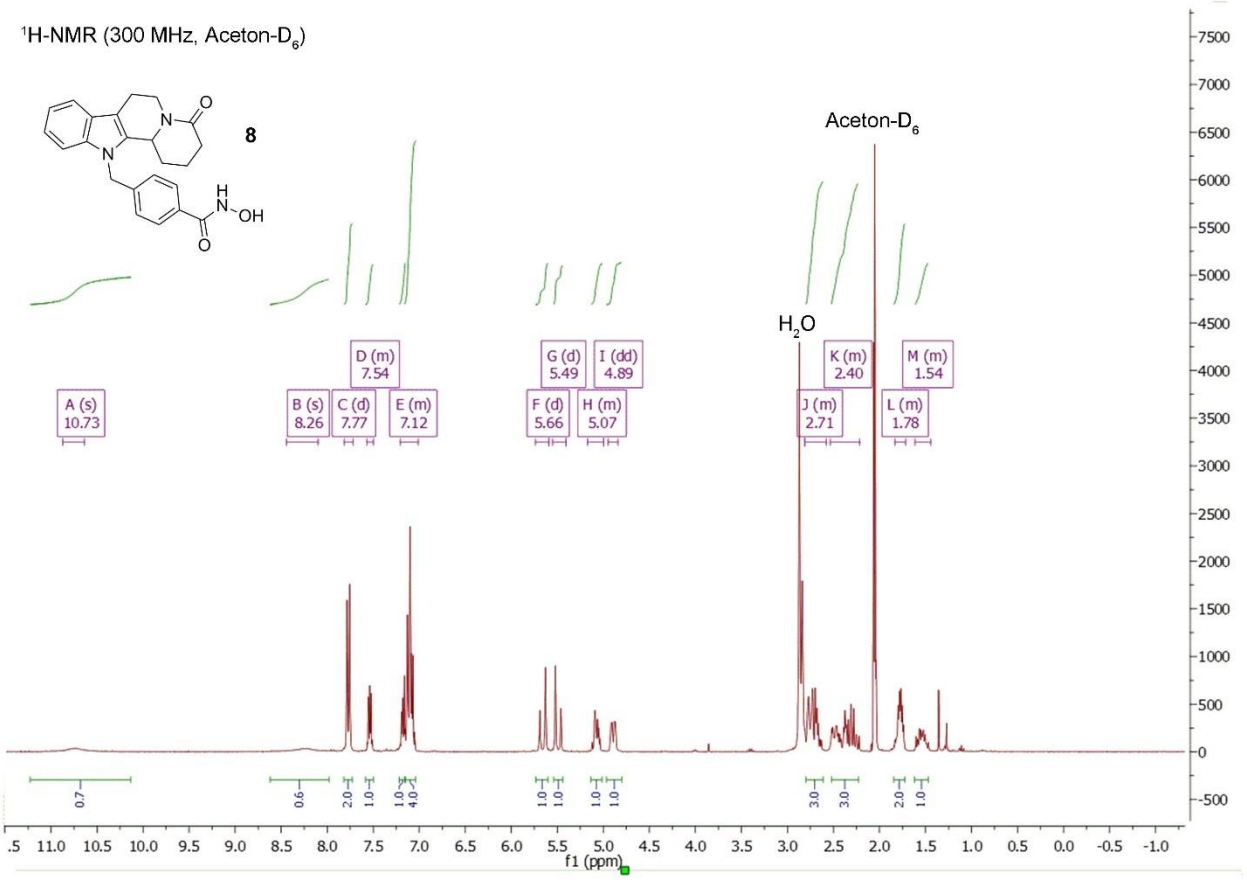

¹H-NMR (DMSO-D6, 300 MHz)
5d
A (s) 11.07
B (s) 7.85
C (d) 7.68
D (d) 7.39
E (d) 7.14
F (d) 7.00
G (dt) 6.73
H (d) 5.40
I (d) 5.34
J (d) 4.79
K (d) 4.49
L (d) 3.86
M (d) 3.79
N (s) 3.71
O (dd) 3.41
P (s) 2.89
DMSO-D6
f1 (ppm)

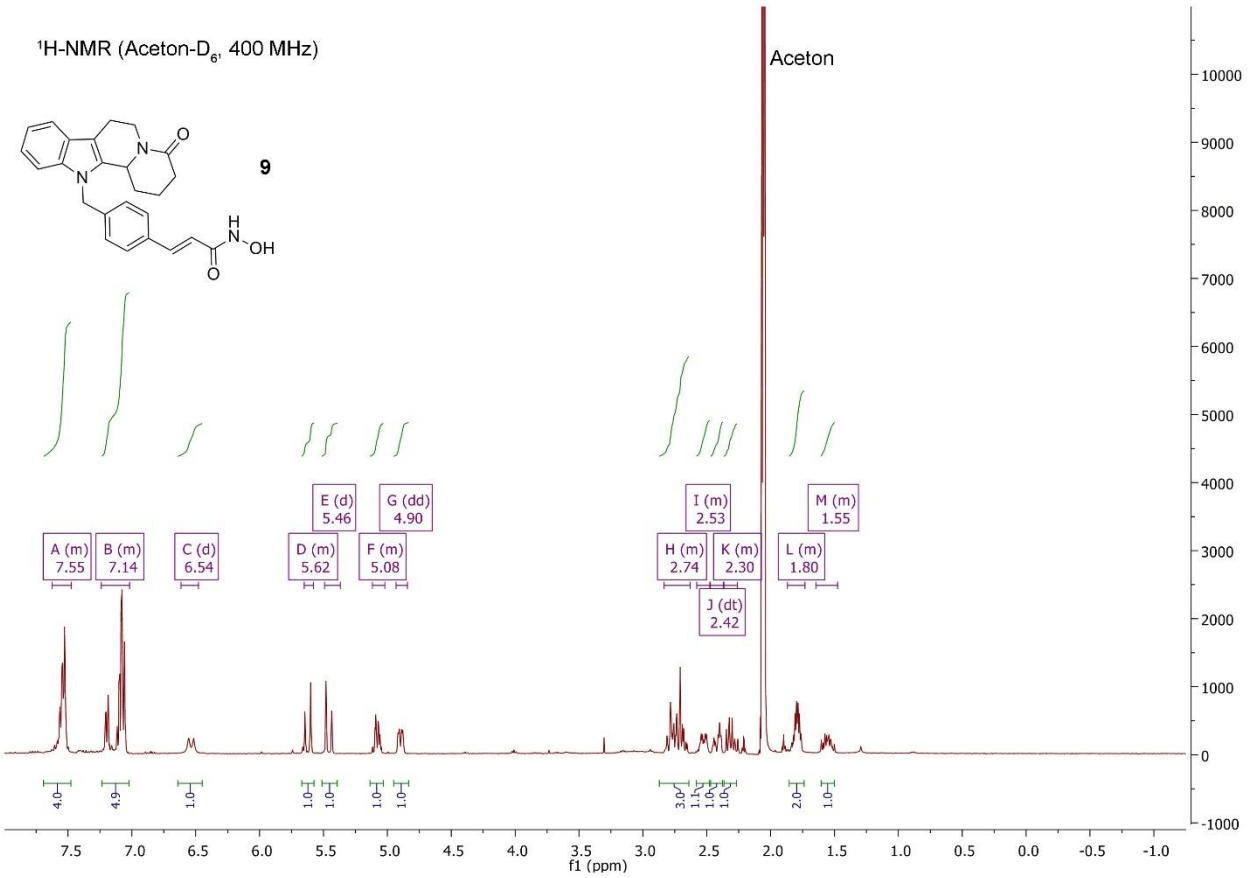

¹H-NMR (DMSO-D6, 300 MHz)
5e
A (s) 11.17
B (s) 9.02
C (s) 8.89
D (d) 7.65
E (d) 7.18
F (d) 7.11
G (d) 6.86
H (dd) 6.58
I (s) 5.31
J (d) 4.81
K (d) 4.52
L (d) 3.87
M (s) 3.75
N (d) 3.43
P (s) 2.89
DMSO-D6
f1 (ppm)

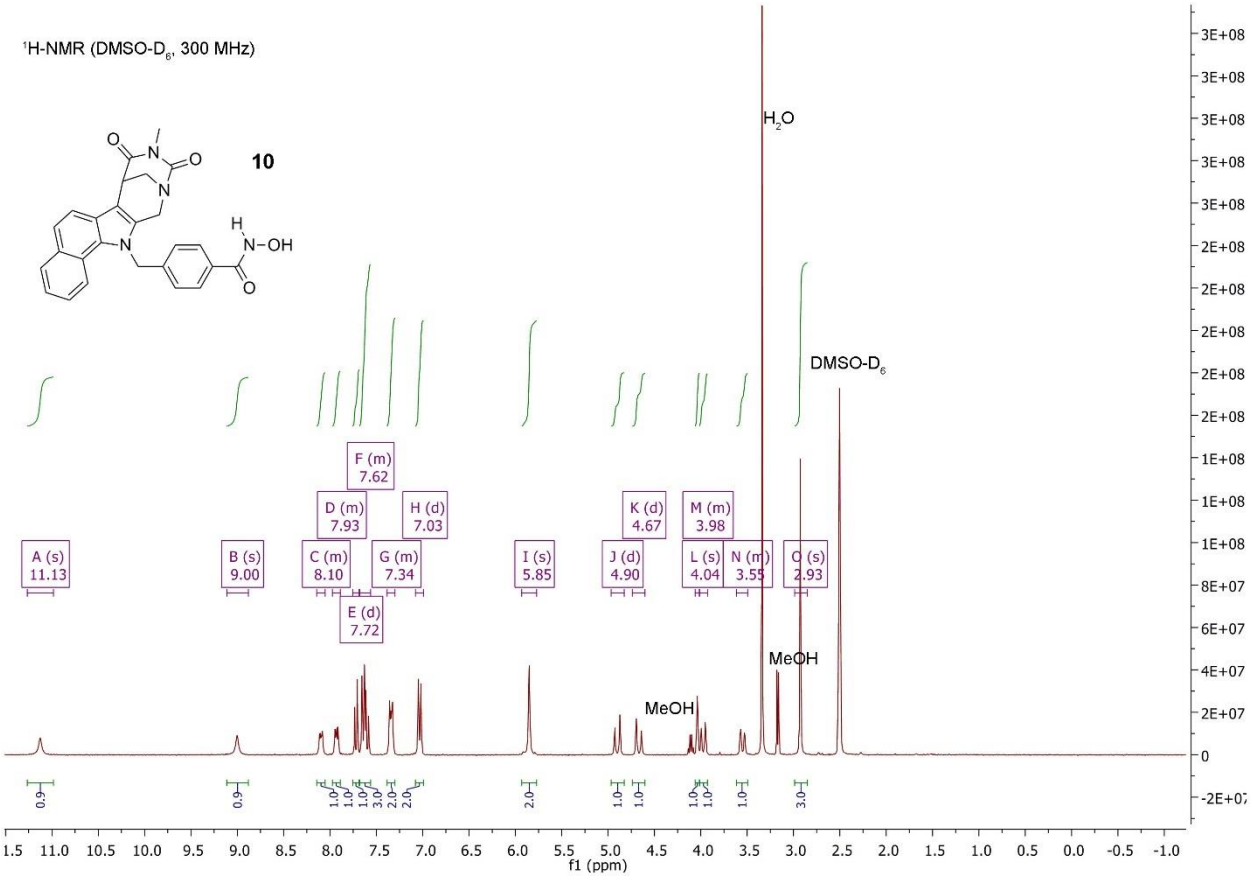

$^1$H-NMR (DMSO-D$_6$, 300 MHz)
5f
Cl$^-$
DMSO-D$_6$
A (s) 11.19
B (s) 10.75
C (s) 9.03
D (d) 7.66
E (d) 7.35
F (dd) 7.09
G (dd) 6.83
H (s) 5.38
I (d) 4.84
J (d) 4.56
K (s) 4.37
L (m) 3.87
M (m) 3.48
N (m) 3.19
O (s) 2.90
H$_2$O
f1 (ppm)

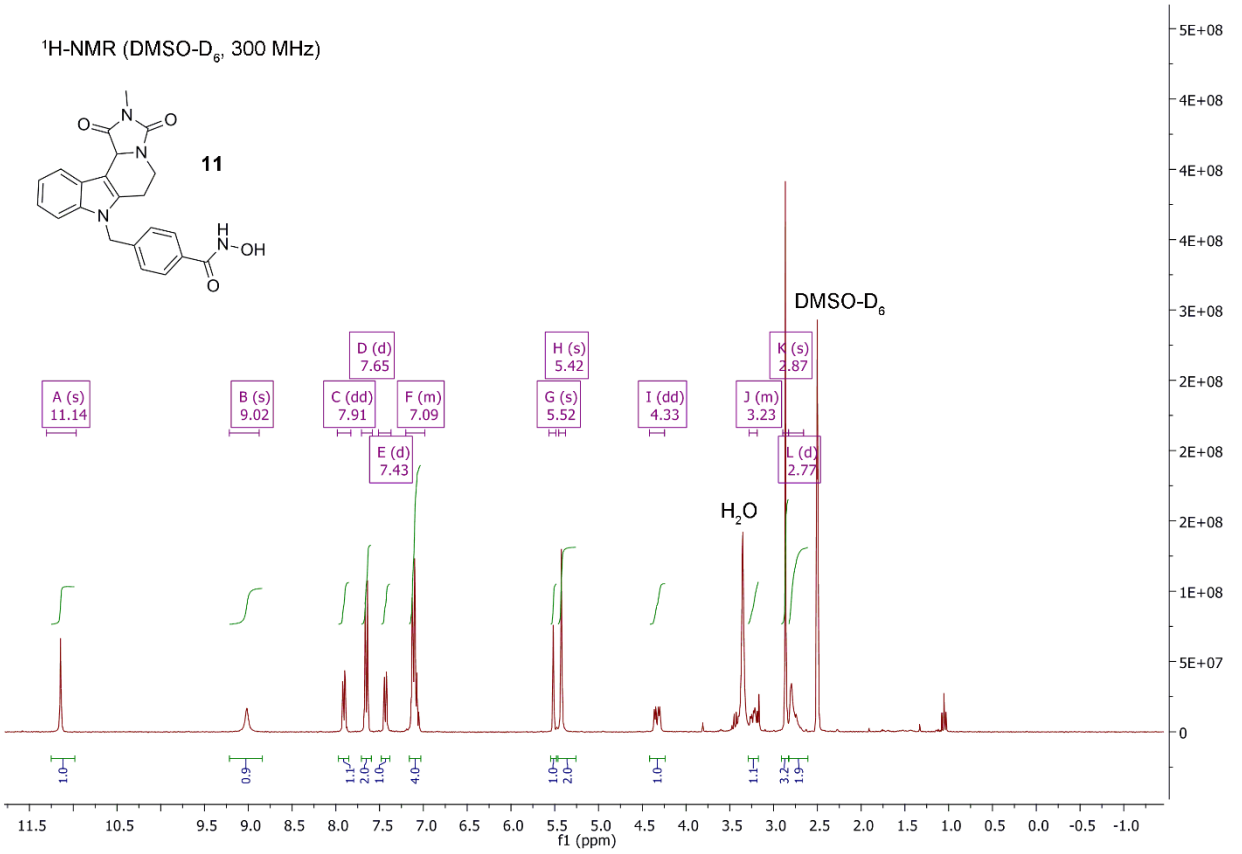

$^1$H-NMR (DMSO-D$_6$, 300 MHz)
6
HOHN
H$_2$O
DMSO-D$_6$
A (s) 10.74
B (s) 9.04
C (m) 7.46
D (dd) 7.08
E (d) 6.41
F (d) 5.35
G (d) 4.86
H (d) 4.57
I (d) 3.90
J (d) 3.45
K (s) 2.89
f1 (ppm)

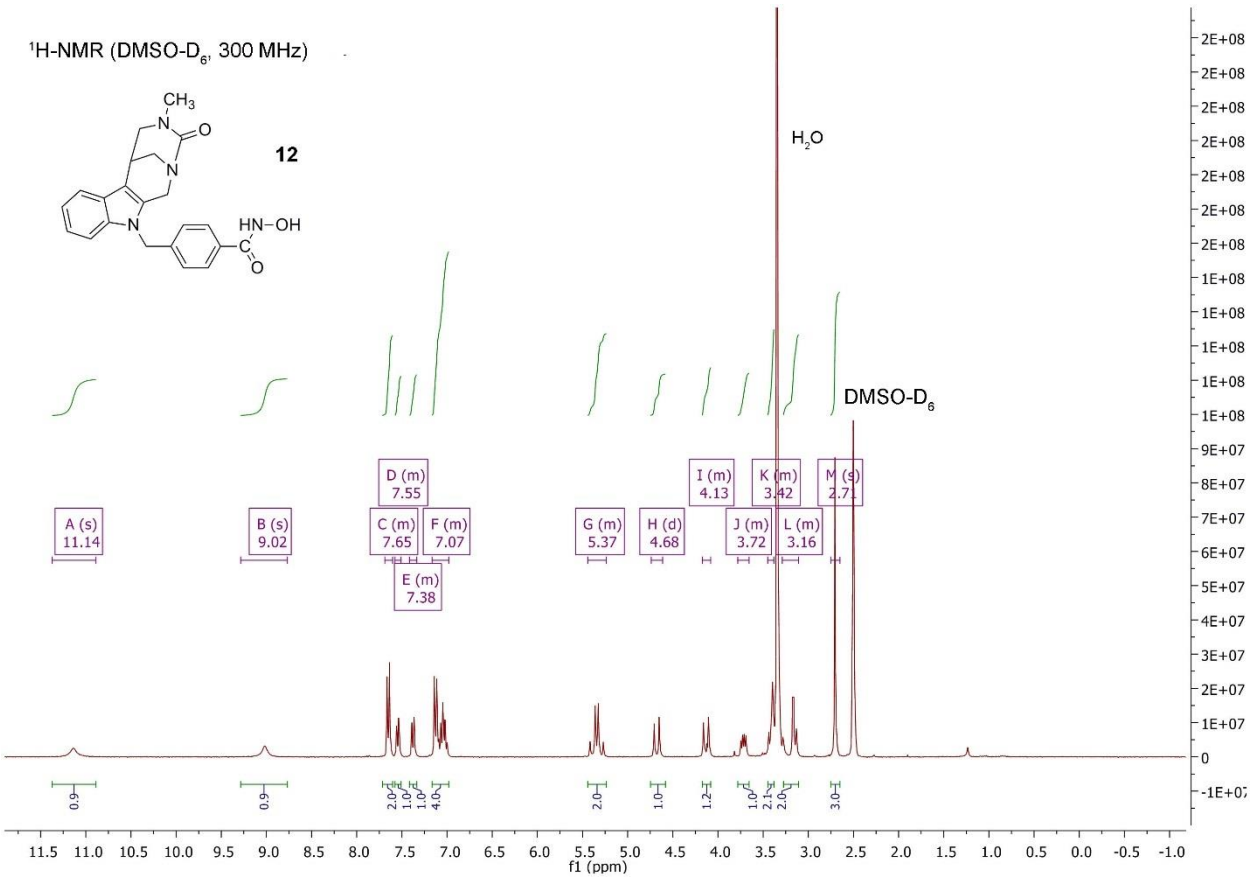

¹H-NMR (DMSO-D6, 300 MHz)
7
H2O
DMSO-D6
A (s) 10.77
B (s) 9.06
C (m) 7.42
D (m) 7.09
E (d) 6.41
F (s) 5.37
G (d) 4.89
H (d) 4.61
I (d) 3.91
J (d) 3.48
K (s) 2.90
f1 (ppm)

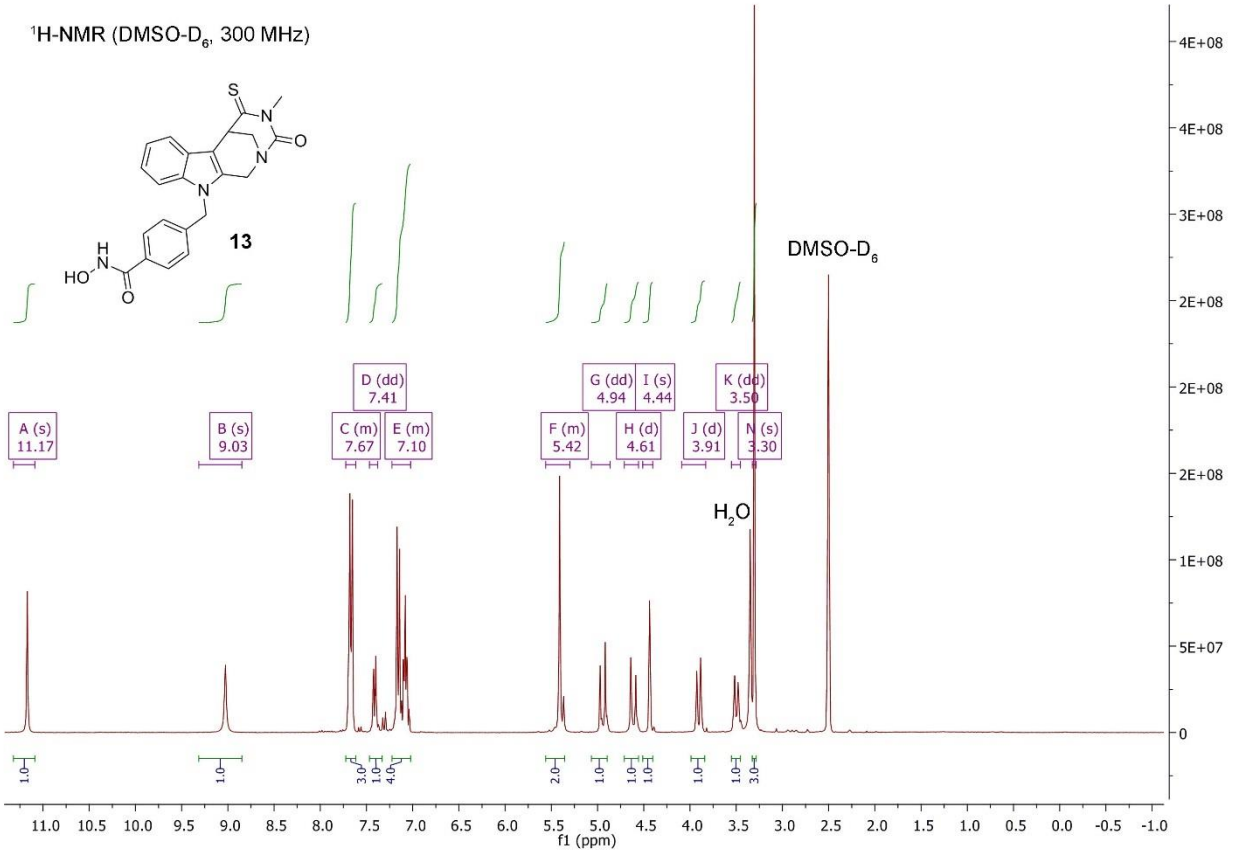

¹H-NMR (300 MHz, Aceton-D6)
8
Aceton-D6
H2O
A (s) 10.73
B (s) 8.26
C (d) 7.77
D (m) 7.54
E (m) 7.12
F (d) 5.66
G (d) 5.49
H (m) 5.07
I (dd) 4.89
J (m) 2.71
K (m) 2.40
L (m) 1.78
M (m) 1.54
f1 (ppm)

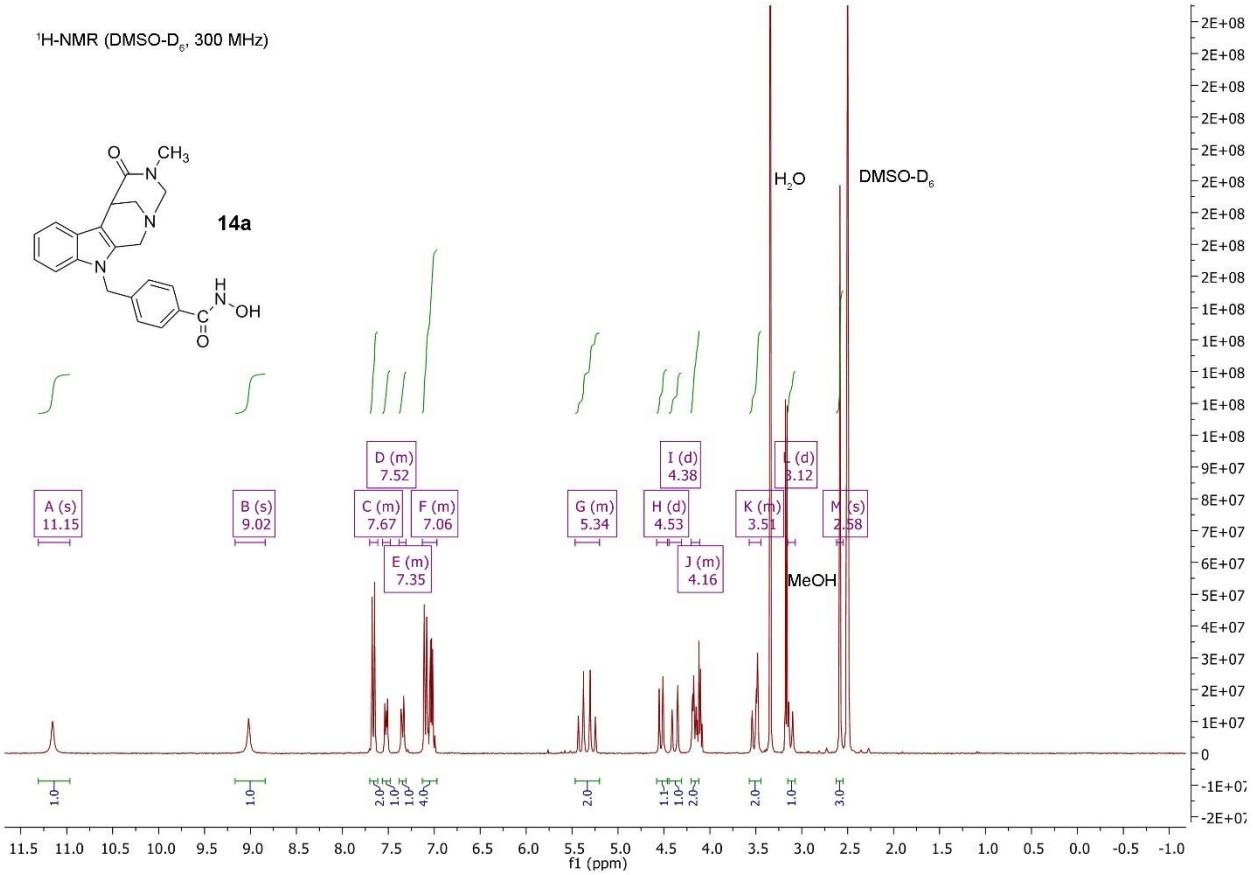

¹H-NMR (Aceton-D6, 400 MHz)
9
Aceton
A (m) 7.55
B (m) 7.14
C (d) 6.54
D (m) 5.62
E (d) 5.46
F (m) 5.08
G (dd) 4.90
H (m) 2.74
I (m) 2.53
J (dt) 2.42
K (m) 2.30
L (m) 1.80
M (m) 1.55
f1 (ppm)

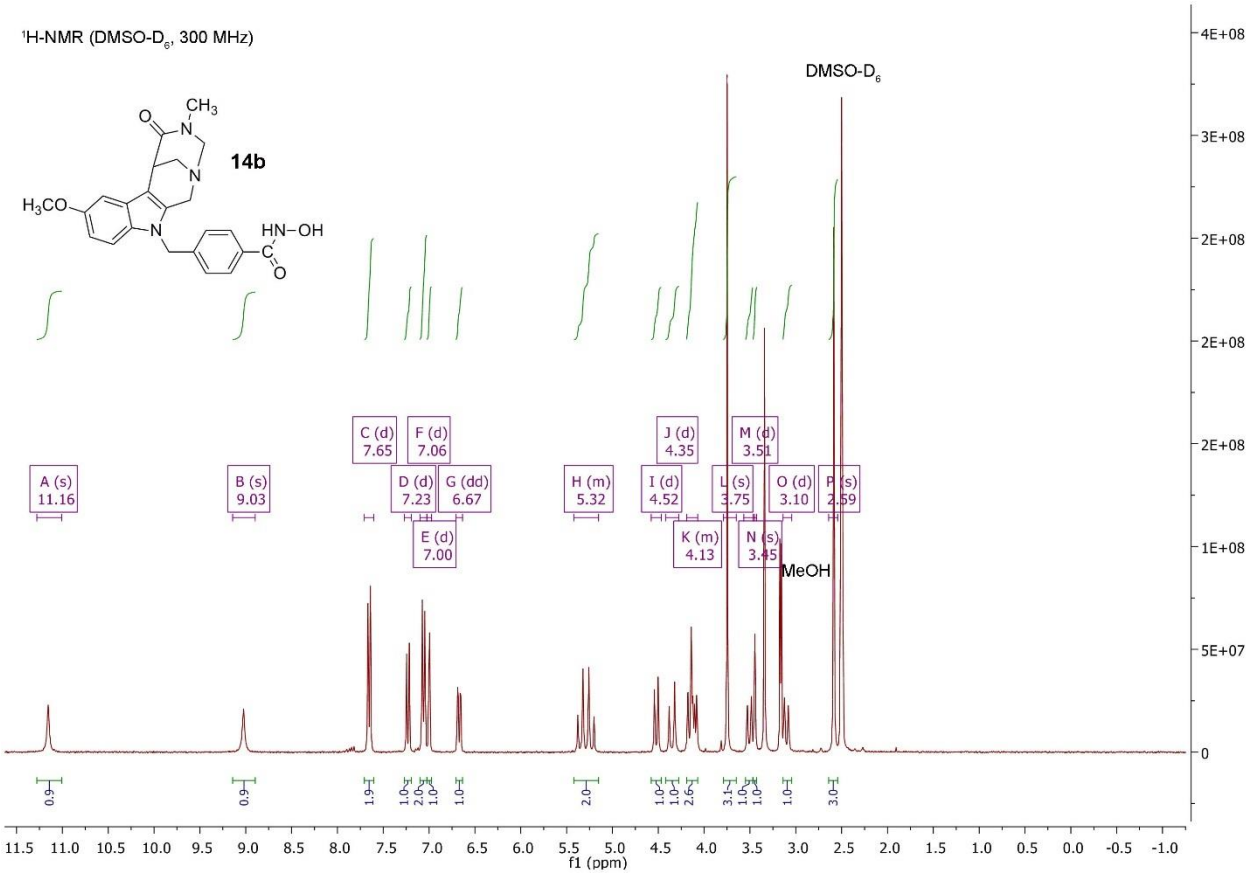

¹H-NMR (DMSO-D6, 300 MHz)
10
H2O
DMSO-D6
MeOH
MeOH
A (s) 11.13
B (s) 9.00
C (m) 8.10
D (m) 7.93
E (d) 7.72
F (m) 7.62
G (m) 7.34
H (d) 7.03
I (s) 5.85
J (d) 4.90
K (d) 4.67
L (s) 4.04
M (m) 3.98
N (m) 3.55
O (s) 2.93
f1 (ppm)

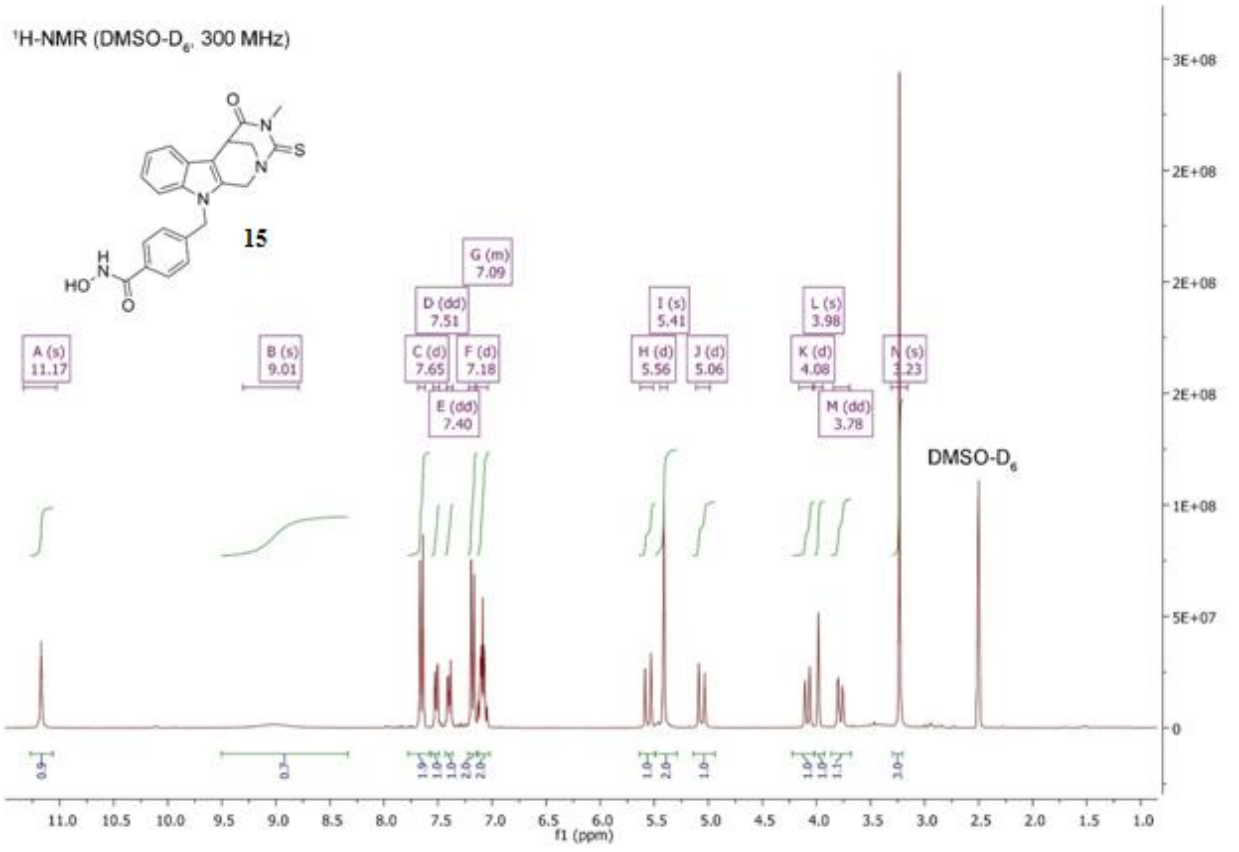

¹H-NMR (DMSO-D6, 300 MHz)
11
A (s) 11.14
B (s) 9.02
C (dd) 7.91
D (d) 7.65
E (d) 7.43
F (m) 7.09
G (s) 5.52
H (s) 5.42
I (dd) 4.33
J (m) 3.23
K (s) 2.87
L (d) 2.77
H2O
DMSO-D6
f1 (ppm)


¹H-NMR (DMSO-D6, 300 MHz)
12
A (s) 11.14
B (s) 9.02
C (m) 7.65
D (m) 7.55
E (m) 7.38
F (m) 7.07
G (m) 5.37
H (d) 4.68
I (m) 4.13
J (m) 3.72
K (m) 3.42
L (m) 3.16
M (s) 2.71
H2O
DMSO-D6
f1 (ppm)


¹H-NMR (DMSO-D6, 300 MHz)
13
DMSO-D6
H2O
A (s) 11.17
B (s) 9.03
C (m) 7.67
D (dd) 7.41
E (m) 7.10
F (m) 5.42
G (dd) 4.94
H (d) 4.61
I (s) 4.44
J (d) 3.91
K (dd) 3.50
N (s) 3.30
f1 (ppm)

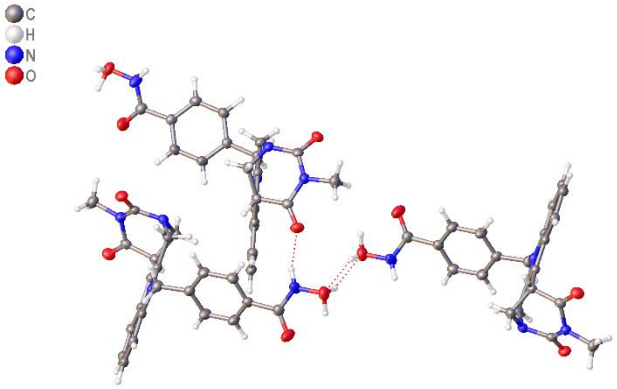

¹H-NMR (DMSO-D6, 300 MHz)
14a
H2O
DMSO-D6
MeOH
A (s) 11.15
B (s) 9.02
C (m) 7.67
D (m) 7.52
E (m) 7.35
F (m) 7.06
G (m) 5.34
H (d) 4.53
I (d) 4.38
J (m) 4.16
K (m) 3.51
L (d) 3.12
M (s) 2.58
f1 (ppm)


¹H-NMR (DMSO-D6, 300 MHz)
14b
DMSO-D6
MeOH
A (s) 11.16
B (s) 9.03
C (d) 7.65
D (d) 7.23
E (d) 7.00
F (d) 7.06
G (dd) 6.67
H (m) 5.32
I (d) 4.52
J (d) 4.35
K (m) 4.13
L (s) 3.75
M (d) 3.51
N (s) 3.45
O (d) 3.10
P (s) 2.59
f1 (ppm)


¹H-NMR (DMSO-D6, 300 MHz)
15
DMSO-D6
A (s) 11.17
B (s) 9.01
C (d) 7.65
D (dd) 7.51
E (dd) 7.40
F (d) 7.18
G (m) 7.09
H (d) 5.56
I (s) 5.41
J (d) 5.06
K (d) 4.08
L (s) 3.98
M (dd) 3.78
N (s) 3.23
f1 (ppm)

**Crystallographic data of Marbostat-100 (5a),**

Crystal Data and Experimental. For Full details see Cambridge Crystallographic Data Centre: http://www.ccdc.cam.ac.uk/ deposit@ccdc.cam.ac.uk. The data have been assigned to the following deposition number: CCDC 1518348




**Experimental.** Single colourless prism-shaped crystals of (**n126**) were obtained by recrystallization from methanol. A suitable crystal (0.31×0.23×0.07) mm³ was selected and mounted on a MiTeGen holder with inert oil on a SuperNova, Single source at offset, Atlas diffractometer. The crystal was kept at $T$ = 123(1) K during data collection. Using **Olex2** (Dolomanov et al., 2009), the structure was solved with the **ShelXT** (Sheldrick, 2015) structure solution program, using the Intrinsic Phasing solution method. The model was refined with version 2014/7 of **ShelXL** (Sheldrick, 2015) using Least Squares minimisation.

**Crystal Data.** $C_{22}H_{20}N_4O_4$, $M_r$ = 404.42, monoclinic, $P2_1/c$ (No. 14), a = 11.52770(15) Å, b = 10.22990(12) Å, c = 15.93783(19) Å, $\beta$ = 99.6558(12)°, $\alpha$ = $\gamma$ = 90°, $V$ = 1852.88(4) Å³, $T$ = 123(1) K, $Z$ = 4, $Z'$ = 1, $\mu$(CuK$_\alpha$) = 0.842, 55591 reflections measured, 3701 unique ($R_{int}$ = 0.0274) which were used in all calculations. The final $wR_2$ was 0.0896 (all data) and $R_1$ was 0.0333 (I > 2(I)).

| **Compound** | **Marbostat-100 (N126)** |
|---|---|
| CCDC | 1518348 |
| Formula | $C_{22}H_{20}N_4O_4$ |
| $D_{calc.}$/ g cm$^{-3}$ | 1.450 |
| $\mu$/mm$^{-1}$ | 0.842 |
| Formula Weight | 404.42 |
| Colour | colourless |
| Shape | prism |
| Size/mm³ | 0.31×0.23×0.07 |
| $T$/K | 123(1) |
| Crystal System | monoclinic |
| Space Group | $P2_1/c$ |
| $a$/Å | 11.52770(15) |
| $b$/Å | 10.22990(12) |
| $c$/Å | 15.93783(19) |
| $\alpha$/° | 90 |
| $\beta$/° | 99.6558(12) |
| $\gamma$/° | 90 |
| V/Å³ | 1852.88(4) |
| $Z$ | 4 |
| $Z'$ | 1 |
| Wavelength/Å | 1.54184 |
| Radiation type | CuK$_\alpha$ |
| $\Theta_{min}$/° | 3.890 |
| $\Theta_{max}$/° | 73.170 |
| Measured Refl. | 55591 |
| Independent Refl. | 3701 |
| Reflections Used | 3420 |
| $R_{int}$ | 0.0274 |
| Parameters | 355 |
| Restraints | 0 |
| Largest Peak | 0.236 |
| Deepest Hole | -0.263 |
| GooF | 1.039 |
| $wR_2$ (all data) | 0.0896 |
| $wR_2$ | 0.0872 |
| $R_1$ (all data) | 0.0359 |
| $R_1$ | 0.0333 |

## Structure Quality Indicators

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Reflections:** | d min (Cu) | 0.81 | I/σ | 59.2 | Rint | 2.74% | complete at 2θ=134° 100% |
| **Refinement:** | Shift | 0.000 | Max Peak | 0.2 | Min Peak | -0.3 | GooF 1.039 |

A colourless prism-shaped crystal with dimensions 0.31×0.23×0.07 mm$^3$ was mounted on a MiTeGen holder with inert oil. X-ray diffraction data were collected using a SuperNova, Single source at offset, Atlas diffractometer equipped with a Oxford Cryosystems, CryoStream 700 low-temperature device, operating at $T$ = 123(1) K.

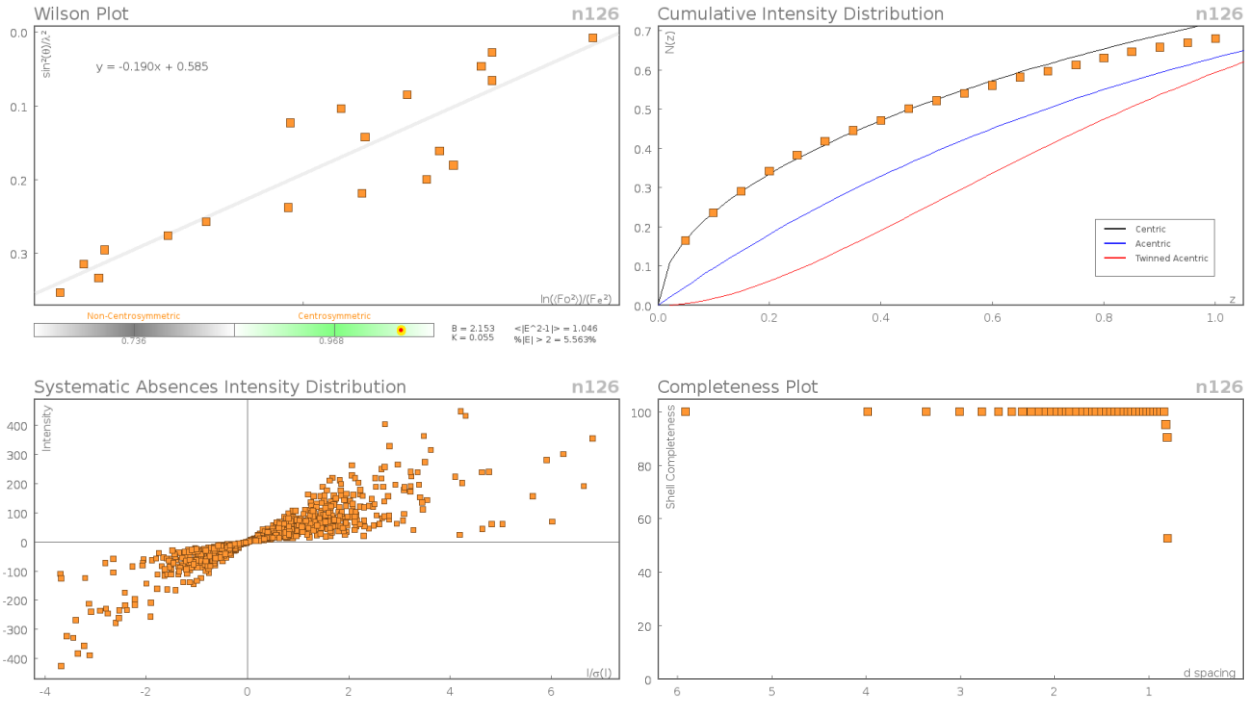
Data were measured using $\omega$ scans scans of 1.0 ° per frame for 2.5 s using CuK$_\alpha$ radiation (sealed X-ray tube, 50 kV, 0.8 mA). The total number of runs and images was based on the strategy calculation from the program **CrysAlisPro** (Agilent, V1.171.37.34, 2014). The maximum resolution achieved was $\Theta$ = 73.170. °

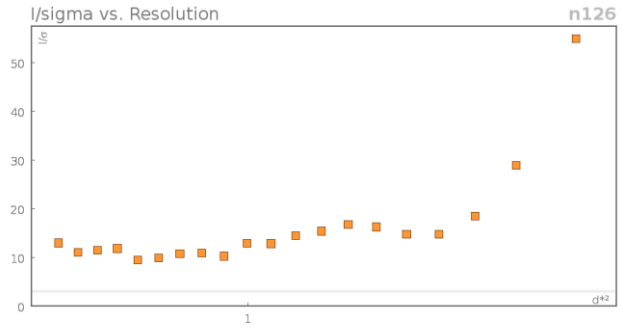
Cell parameters were retrieved using the **CrysAlisPro** (Agilent, V1.171.37.34, 2014) software and refined using **CrysAlisPro** (Agilent, V1.171.37.34, 2014) on 27788 reflections, 50 % of the observed reflections. Data reduction was performed using the **CrysAlisPro** (Agilent, V1.171.37.34, 2014) software which corrects for Lorentz polarisation. The final completeness is 100.00 out to 73.170 in $\Theta$. The absorption coefficient $\mu$ of this material is 0.842 at this wavelength ($\lambda$ = 1.54184) and the minimum and maximum transmissions are 0.85618 and 1.00000.

The structure was solved in the space group P2$_1$/c (# 14) by Intrinsic Phasing using the **ShelXT** (Sheldrick, 2015) structure solution program and refined by Least Squares using version 2014/7 of **ShelXL** (Sheldrick, 2015). All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model.

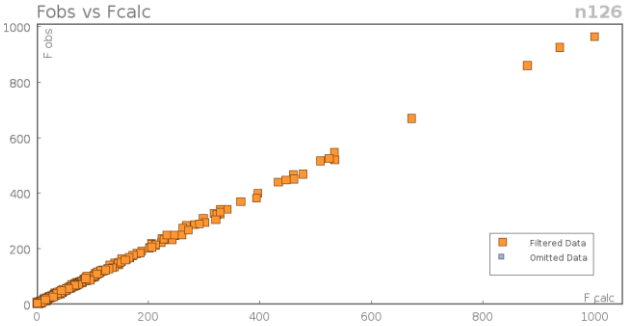
There is a single molecule in the asymmetric unit, which is represented by the reported sum formula. In other words: Z is 4 and Z' is 1.

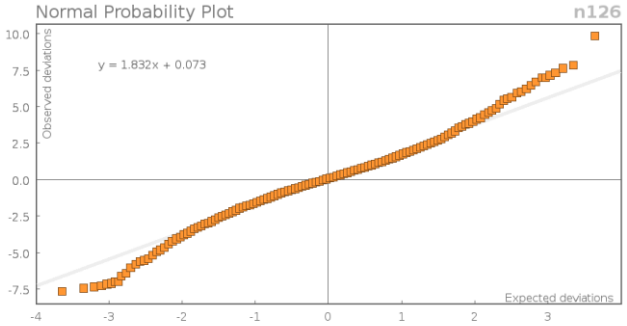
## Data Plots: Diffraction Data






## Data Plots: Refinement and Data




## Reflection Statistics

| | | | |
|---|---|---|---|
| Total reflections (after filtering) | 57597 | Unique reflections | 3701 |
| Completeness | 0.996 | Mean I/$\sigma$ | 59.18 |
| $hkl_{max}$ collected | (14, 12, 19) | $hkl_{min}$ collected | (-14, -11, -19) |
| $hkl_{max}$ used | (14, 12, 19) | $hkl_{min}$ used | (-14, 0, 0) |
| Lim $d_{max}$ collected | 100.0 | Lim $d_{min}$ collected | 0.77 |
| $d_{max}$ used | 11.36 | $d_{min}$ used | 0.81 |
| Friedel pairs | 6518 | Friedel pairs merged | 1 |
| Inconsistent equivalents | 3 | $R_{int}$ | 0.0274 |
| $R_{sigma}$ | 0.0086 | Intensity transformed | 0 |
| Omitted reflections | 0 | Omitted by user (OMIT hkl) | 0 |
| Multiplicity | (1365, 2250, 2382, 2127, 2060, 1611, 1092, 559, 285, 102, 33, 4) | Maximum multiplicity | 36 |
| Removed systematic absences | 2006 | Filtered off (Shel/OMIT) | 0 |

**Table S1**: Fractional Atomic Coordinates (×10⁴) and Equivalent Isotropic Displacement Parameters (Å²×10³) for **n126**. $U_{eq}$ is defined as 1/3 of the trace of the orthogonalised $U_{ij}$.

| Atom | x | y | z | $U_{eq}$ |
|---|---|---|---|---|
| O3 | 1607.1(8) | 55.7(8) | 400.3(6) | 32.0(2) |
| O4 | 3694.3(8) | 3607.1(9) | 1165.5(6) | 34.6(2) |
| N3 | 1425.3(9) | 853.8(9) | 1715.4(6) | 27.2(2) |
| O1 | -5700(1) | 753.2(11) | 4310.1(7) | 42.7(2) |
| N4 | 2955.8(8) | 1554.9(10) | 1002.1(6) | 26.2(2) |
| N2 | -911.4(8) | 3269.3(9) | 981.0(6) | 25.5(2) |
| C9 | -628.9(10) | 4582.5(11) | 945.8(7) | 24.9(2) |
| C20 | 3016.6(10) | 2797.5(11) | 1361.6(7) | 25.9(2) |
| C16 | 76(1) | 2610.7(11) | 1363.2(7) | 25.1(2) |
| C14 | 566.1(10) | 4736.9(11) | 1314.9(7) | 24.3(2) |
| C22 | 1953.7(10) | 765.2(11) | 1000.7(7) | 25.4(2) |
| N1 | -5015.8(10) | 903.6(12) | 3675.7(8) | 40.6(3) |
| C7 | -4031.6(10) | 1162.9(12) | 2139.7(8) | 29.2(3) |

| Atom | x | y | z | $U_{eq}$ |
|---|---|---|---|---|
| C15 | 993.4(10) | 3465.3(11) | 1572.2(7) | 24.1(2) |
| O2 | -5245.2(11) | 3074.4(10) | 3687.0(8) | 56.1(3) |
| C2 | -4096.7(10) | 2172.1(11) | 2714.9(7) | 26.3(2) |
| C5 | -2742.2(10) | 2464.5(11) | 1424.4(7) | 26.0(2) |
| C3 | -3464.5(11) | 3313.6(12) | 2650.5(8) | 32.6(3) |
| C12 | 385.8(12) | 7037.6(12) | 1040.3(8) | 31.0(3) |
| C19 | 2196.5(10) | 3022.3(11) | 2001.2(7) | 26.1(2) |
| C13 | 1072.1(11) | 5987.3(11) | 1361.9(7) | 28.2(3) |
| C10 | -1321.7(11) | 5640.1(12) | 614.7(7) | 28.8(3) |
| C6 | -3353.5(11) | 1314.2(12) | 1501.4(8) | 29.6(3) |
| C11 | -792.4(11) | 6859.3(12) | 667.7(8) | 30.7(3) |
| C4 | -2785.7(11) | 3448.7(13) | 2019.2(9) | 33.0(3) |
| C1 | -4825.7(11) | 2102.8(12) | 3405.1(8) | 30.9(3) |
| C17 | 153.9(11) | 1157.0(12) | 1504.5(8) | 28.7(3) |
| C8 | -2058.2(10) | 2672.2(13) | 701.3(8) | 28.8(3) |
| C18 | 2037.0(11) | 1699.3(12) | 2397.3(7) | 29.6(3) |
| C21 | 3686.0(12) | 1261.9(14) | 353.7(9) | 33.6(3) |

**Table S2**: Anisotropic Displacement Parameters (×$10^4$) **n126**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2} \times U_{11} + ... + 2hka^* \times b^* \times U_{12}]$

| Atom | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{23}$ | $U_{13}$ | $U_{12}$ |
|---|---|---|---|---|---|---|
| O3 | 36.1(5) | 23.7(4) | 36.9(5) | -6.1(3) | 8.4(4) | -2.1(3) |
| O4 | 31.6(4) | 27.1(4) | 46.0(5) | 1.3(4) | 9.0(4) | -6.0(4) |
| N3 | 32.1(5) | 21.0(5) | 30.1(5) | 3.9(4) | 9.4(4) | 0.4(4) |
| O1 | 49.0(6) | 43.0(6) | 41.3(6) | 7.9(4) | 22.8(5) | -0.8(5) |
| N4 | 27.6(5) | 23.4(5) | 29.0(5) | -0.9(4) | 8.3(4) | -0.1(4) |
| N2 | 25.3(5) | 24.1(5) | 29.2(5) | -0.3(4) | 10.7(4) | 0.2(4) |
| C9 | 29.9(6) | 24.3(5) | 23.0(5) | -0.3(4) | 11.8(4) | 0.8(4) |
| C20 | 25.6(5) | 22.5(6) | 28.4(5) | 2.4(4) | 1.1(4) | 0.9(4) |
| C16 | 29.6(6) | 23.2(6) | 25.1(5) | 0.7(4) | 11.6(4) | 1.3(4) |
| C14 | 29.6(6) | 23.7(6) | 21.6(5) | 0.1(4) | 9.9(4) | 1.2(4) |
| C22 | 28.9(6) | 17.2(5) | 30.6(6) | 2.5(4) | 6.2(4) | 2.7(4) |
| N1 | 39.5(6) | 36.1(6) | 52.6(7) | 16.6(5) | 26.4(5) | 11.5(5) |
| C7 | 28.2(6) | 23.9(6) | 35.8(6) | 0.1(5) | 6.5(5) | -2.8(5) |
| C15 | 29.0(6) | 21.4(5) | 23.3(5) | -0.2(4) | 8.6(4) | 0.9(4) |
| O2 | 73.6(8) | 36.4(6) | 71.8(8) | -6.6(5) | 51.1(6) | 0.0(5) |
| C2 | 23.8(5) | 24.8(6) | 31.3(6) | 2.5(5) | 7.3(4) | 2.9(4) |
| C5 | 23.2(5) | 25.4(6) | 30.1(6) | -1.3(4) | 6.7(4) | 1.4(4) |
| C3 | 37.2(7) | 25.0(6) | 39.1(7) | -7.0(5) | 16.3(5) | -1.7(5) |
| C12 | 42.4(7) | 22.4(6) | 30.9(6) | 2.1(5) | 14.2(5) | 0.1(5) |
| C19 | 31.2(6) | 22.0(6) | 24.8(5) | -1.1(4) | 3.5(5) | 0.5(4) |
| C13 | 33.8(6) | 23.8(6) | 28.5(6) | -0.5(4) | 9.4(5) | -1.2(5) |
| C10 | 31.0(6) | 31.5(6) | 25.6(5) | 1.7(5) | 10.0(5) | 5.7(5) |
| C6 | 31.8(6) | 25.2(6) | 32.6(6) | -5.5(5) | 7.2(5) | -2.0(5) |
| C11 | 40.2(7) | 27.2(6) | 27.2(6) | 5.2(5) | 13.1(5) | 9.2(5) |
| C4 | 36.6(7) | 23.7(6) | 42.4(7) | -5.2(5) | 18.0(5) | -5.5(5) |
| C1 | 29.0(6) | 30.3(6) | 34.7(6) | 2.7(5) | 9.2(5) | 1.1(5) |
| C17 | 30.9(6) | 22.8(6) | 34.7(6) | 2.8(5) | 12.6(5) | -1.8(5) |
| C8 | 27.7(6) | 29.9(6) | 30.2(6) | -4.8(5) | 8.8(5) | -2.2(5) |
| C18 | 37.5(7) | 26.4(6) | 25.4(6) | 3.8(5) | 6.6(5) | 3.2(5) |
| C21 | 30.7(6) | 37.3(7) | 35.1(7) | -4.2(5) | 12.1(5) | -0.3(5) |

**Table S3**: Bond Lengths in Å for **n126**.

| Atom | Atom | Length/Å |
|---|---|---|
| O3 | C22 | 1.2141(14) |
| O4 | C20 | 1.2149(14) |
| N3 | C22 | 1.3818(15) |
| N3 | C17 | 1.4805(15) |
| N3 | C18 | 1.4730(16) |
| O1 | N1 | 1.3913(14) |

| Atom | Atom | Length/Å |
|---|---|---|
| N4 | C20 | 1.3913(15) |
| N4 | C22 | 1.4093(15) |
| N4 | C21 | 1.4690(15) |
| N2 | C9 | 1.3857(15) |
| N2 | C16 | 1.3740(15) |
| N2 | C8 | 1.4566(15) |
| C9 | C14 | 1.4131(16) |
| C9 | C10 | 1.3948(17) |
| C20 | C19 | 1.5195(16) |
| C16 | C15 | 1.3694(16) |
| C16 | C17 | 1.5046(16) |
| C14 | C15 | 1.4265(16) |
| C14 | C13 | 1.4027(16) |
| N1 | C1 | 1.3306(17) |

| Atom | Atom | Length/Å |
|---|---|---|
| C7 | C2 | 1.3911(17) |
| C7 | C6 | 1.3917(17) |
| C15 | C19 | 1.5094(16) |
| O2 | C1 | 1.2234(16) |
| C2 | C3 | 1.3894(17) |
| C2 | C1 | 1.4937(16) |
| C5 | C6 | 1.3876(17) |
| C5 | C4 | 1.3895(17) |
| C5 | C8 | 1.5165(16) |
| C3 | C4 | 1.3813(18) |
| C12 | C13 | 1.3809(17) |
| C12 | C11 | 1.4000(19) |
| C19 | C18 | 1.5177(16) |
| C10 | C11 | 1.3848(18) |

**Table S4**: Bond Angles in ° for **n126**.

| Atom | Atom | Atom | Angle/° |
|---|---|---|---|
| C22 | N3 | C17 | 112.52(9) |
| C22 | N3 | C18 | 115.09(9) |
| C18 | N3 | C17 | 112.19(9) |
| C20 | N4 | C22 | 120.60(10) |
| C20 | N4 | C21 | 118.74(10) |
| C22 | N4 | C21 | 116.63(10) |
| C9 | N2 | C8 | 126.98(10) |
| C16 | N2 | C9 | 108.09(9) |
| C16 | N2 | C8 | 124.88(10) |
| N2 | C9 | C14 | 108.11(10) |
| N2 | C9 | C10 | 130.08(11) |
| C10 | C9 | C14 | 121.82(11) |
| O4 | C20 | N4 | 120.47(11) |
| O4 | C20 | C19 | 124.66(11) |
| N4 | C20 | C19 | 114.87(10) |
| N2 | C16 | C17 | 125.11(10) |
| C15 | C16 | N2 | 110.08(10) |
| C15 | C16 | C17 | 124.77(11) |
| C9 | C14 | C15 | 106.45(10) |
| C13 | C14 | C9 | 119.46(10) |
| C13 | C14 | C15 | 134.09(11) |
| O3 | C22 | N3 | 123.82(11) |
| O3 | C22 | N4 | 120.35(11) |
| N3 | C22 | N4 | 115.83(10) |
| C1 | N1 | O1 | 118.81(11) |
| C2 | C7 | C6 | 119.88(11) |

| Atom | Atom | Atom | Angle/° |
|---|---|---|---|
| C16 | C15 | C14 | 107.27(10) |
| C16 | C15 | C19 | 122.14(10) |
| C14 | C15 | C19 | 130.59(10) |
| C7 | C2 | C1 | 123.32(11) |
| C3 | C2 | C7 | 119.22(11) |
| C3 | C2 | C1 | 117.46(11) |
| C6 | C5 | C4 | 118.51(11) |
| C6 | C5 | C8 | 121.50(10) |
| C4 | C5 | C8 | 119.99(11) |
| C4 | C3 | C2 | 120.41(11) |
| C13 | C12 | C11 | 120.71(12) |
| C15 | C19 | C20 | 111.68(9) |
| C15 | C19 | C18 | 106.86(10) |
| C18 | C19 | C20 | 106.05(9) |
| C12 | C13 | C14 | 118.85(11) |
| C11 | C10 | C9 | 117.19(11) |
| C5 | C6 | C7 | 120.98(11) |
| C10 | C11 | C12 | 121.97(11) |
| C3 | C4 | C5 | 120.94(11) |
| N1 | C1 | C2 | 115.22(11) |
| O2 | C1 | N1 | 122.22(12) |
| O2 | C1 | C2 | 122.53(11) |
| N3 | C17 | C16 | 105.85(9) |
| N2 | C8 | C5 | 112.77(10) |
| N3 | C18 | C19 | 107.04(9) |

**Table S5**: Torsion Angles in ° for **n126**.

| Atom | Atom | Atom | Atom | Angle/° |
|---|---|---|---|---|
| O4 | C20 | C19 | C15 | 93.79(13) |
| O4 | C20 | C19 | C18 | -150.17(11) |
| O1 | N1 | C1 | O2 | -1.0(2) |
| O1 | N1 | C1 | C2 | -179.17(11) |
| N4 | C20 | C19 | C15 | -86.84(12) |
| N4 | C20 | C19 | C18 | 29.21(13) |
| N2 | C9 | C14 | C15 | 0.12(12) |

| Atom | Atom | Atom | Atom | Angle/° |
|---|---|---|---|---|
| N2 | C9 | C14 | C13 | -179.68(10) |
| N2 | C9 | C10 | C11 | -179.85(11) |
| N2 | C16 | C15 | C14 | 0.40(12) |
| N2 | C16 | C15 | C19 | -179.94(9) |
| N2 | C16 | C17 | N3 | 165.32(10) |
| C9 | N2 | C16 | C15 | -0.33(12) |
| C9 | N2 | C16 | C17 | -178.32(10) |
| C9 | N2 | C8 | C5 | -96.98(13) |
| C9 | C14 | C15 | C16 | -0.32(12) |
| C9 | C14 | C15 | C19 | -179.93(11) |
| C9 | C14 | C13 | C12 | -0.34(16) |
| C9 | C10 | C11 | C12 | -0.33(17) |
| C20 | N4 | C22 | O3 | 143.99(11) |
| C20 | N4 | C22 | N3 | -36.55(15) |
| C20 | C19 | C18 | N3 | -64.87(12) |
| C16 | N2 | C9 | C14 | 0.12(12) |
| C16 | N2 | C9 | C10 | 179.53(11) |
| C16 | N2 | C8 | C5 | 80.16(14) |
| C16 | C15 | C19 | C20 | 96.25(12) |
| C16 | C15 | C19 | C18 | -19.30(14) |
| C14 | C9 | C10 | C11 | -0.51(16) |
| C14 | C15 | C19 | C20 | -84.18(14) |
| C14 | C15 | C19 | C18 | 160.27(11) |
| C22 | N3 | C17 | C16 | -80.96(11) |
| C22 | N3 | C18 | C19 | 53.94(13) |
| C22 | N4 | C20 | O4 | -159.43(11) |
| C22 | N4 | C20 | C19 | 21.17(15) |
| C7 | C2 | C3 | C4 | 0.45(19) |
| C7 | C2 | C1 | N1 | 26.83(17) |
| C7 | C2 | C1 | O2 | -151.31(14) |
| C15 | C16 | C17 | N3 | -12.38(15) |
| C15 | C14 | C13 | C12 | 179.93(12) |
| C15 | C19 | C18 | N3 | 54.39(12) |
| C2 | C7 | C6 | C5 | -0.39(18) |
| C2 | C3 | C4 | C5 | 1.6(2) |
| C3 | C2 | C1 | N1 | -153.64(12) |
| C3 | C2 | C1 | O2 | 28.23(19) |
| C13 | C14 | C15 | C16 | 179.45(12) |
| C13 | C14 | C15 | C19 | -0.2(2) |
| C13 | C12 | C11 | C10 | 0.83(18) |
| C10 | C9 | C14 | C15 | -179.35(10) |
| C10 | C9 | C14 | C13 | 0.85(16) |
| C6 | C7 | C2 | C3 | -1.03(18) |
| C6 | C7 | C2 | C1 | 178.50(11) |
| C6 | C5 | C4 | C3 | -2.95(19) |
| C6 | C5 | C8 | N2 | -136.96(11) |
| C11 | C12 | C13 | C14 | -0.47(18) |
| C4 | C5 | C6 | C7 | 2.36(18) |
| C4 | C5 | C8 | N2 | 44.33(16) |
| C1 | C2 | C3 | C4 | -179.11(12) |
| C17 | N3 | C22 | O3 | -54.16(15) |

| Atom | Atom | Atom | Atom | Angle/° |
|---|---|---|---|---|
| C17 | N3 | C22 | N4 | 126.40(10) |
| C17 | N3 | C18 | C19 | -76.43(12) |
| C17 | C16 | C15 | C14 | 178.40(10) |
| C17 | C16 | C15 | C19 | -1.94(17) |
| C8 | N2 | C9 | C14 | 177.65(10) |
| C8 | N2 | C9 | C10 | -2.94(19) |
| C8 | N2 | C16 | C15 | -177.92(10) |
| C8 | N2 | C16 | C17 | 4.09(17) |
| C8 | C5 | C6 | C7 | -176.37(11) |
| C8 | C5 | C4 | C3 | 175.79(12) |
| C18 | N3 | C22 | O3 | 175.62(11) |
| C18 | N3 | C22 | N4 | -3.82(14) |
| C18 | N3 | C17 | C16 | 50.72(12) |
| C21 | N4 | C20 | O4 | -2.77(17) |
| C21 | N4 | C20 | C19 | 177.82(10) |
| C21 | N4 | C22 | O3 | -13.14(16) |
| C21 | N4 | C22 | N3 | 166.32(10) |

**Table S6**: Hydrogen Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for **n126**. $U_{eq}$ is defined as 1/3 of the trace of the orthogonalised $U_{ij}$.

| Atom | x | y | z | $U_{eq}$ |
|---|---|---|---|---|
| H1 | -4587(15) | 239(17) | 3608(10) | 41(4) |
| H7 | -4462(13) | 336(15) | 2164(9) | 32(4) |
| H3 | -3515(13) | 4010(16) | 3052(10) | 39(4) |
| H12 | 727(13) | 7914(16) | 1072(10) | 36(4) |
| H19 | 2579(12) | 3653(15) | 2413(9) | 28(3) |
| H13 | 1918(13) | 6105(14) | 1622(9) | 33(4) |
| H10 | -2138(13) | 5546(15) | 375(9) | 33(4) |
| H6 | -3298(14) | 591(16) | 1090(10) | 42(4) |
| H11 | -1244(14) | 7618(16) | 460(10) | 39(4) |
| H4 | -2336(14) | 4236(16) | 1987(10) | 41(4) |
| H17A | -230(13) | 889(15) | 1983(10) | 35(4) |
| H17B | -174(12) | 661(15) | 987(9) | 31(4) |
| H8A | -1963(13) | 1841(15) | 421(9) | 32(4) |
| H8B | -2517(13) | 3252(15) | 271(9) | 32(4) |
| H18A | 2803(13) | 1313(15) | 2647(9) | 31(4) |
| H18B | 1531(13) | 1762(15) | 2835(10) | 34(4) |
| H21A | 3290(14) | 1526(16) | -200(11) | 39(4) |
| H21B | 3841(14) | 323(17) | 379(10) | 42(4) |
| H21C | 4393(14) | 1739(16) | 504(10) | 39(4) |
| H1A | -5200(40) | 640(50) | 4780(30) | 83(15) |
| H1B | -5640(40) | 1690(50) | 4500(30) | 85(14) |

**Table S7**: Atomic Occupancies for all atoms that are not fully occupied in **n126**.

| Atom | Occupancy |
|---|---|
| H1A | 0.5 |
| H1B | 0.5 |

**Citations**

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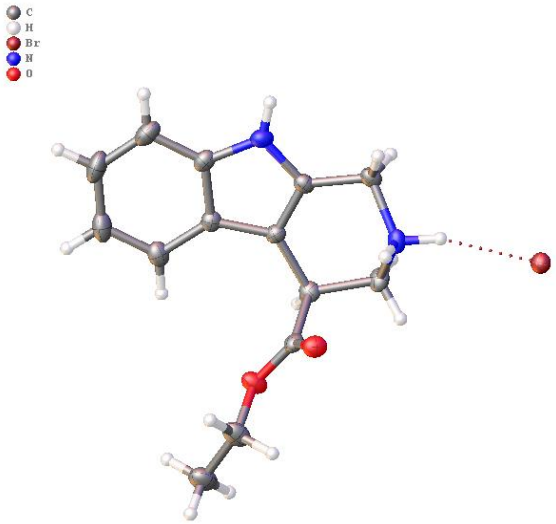
O.V. Dolomanov and L.J. Bourhis and R.J. Gildea and J.A.K. Howard and H. Puschmann, Olex2: A complete structure solution, refinement and analysis program, J. Appl. Cryst., (2009), 42, 339-341.
Sheldrick, G.M., Crystal structure refinement with ShelXL, Acta Cryst., (2015), C27, 3-8.
Sheldrick, G.M., ShelXT-Integrated space-group and crystal-structure determination, Acta Cryst., (2015), A71, 3-8

## Crystallographic data of 62b-Hydrobromide

Crystal Data and Experimental. For Full details see Cambridge Crystallographic Data Centre: http://www.ccdc.cam.ac.uk/ deposit@ccdc.cam.ac.uk. The data have been assigned to the following deposition number:1532350




**Experimental.** Single clear colourless prism-shaped crystals of (**Q014**) were obtained by recrystallization from a solution ofthe free base in MeOH/ethyl acetate (1:1) under a hydrobromide athmosphere. A Suitable crystal (0.36×0.17×0.10) $mm^3$ was selected and mounted on a MITIGEN holder oil on a GV1000, TitanS2 diffractometer. The crystal was kept at $T$ = 123.00(10) K during data collection. Using **Olex2** (Dolomanov et al., 2009), the structure was solved with the **ShelXT** (Sheldrick, 2015) structure solution program, using the Intrinsic Phasing solution method. The model was refined with version 2016/6 of **ShelXL** (Sheldrick, 2015) using Least Squares minimisation.

**Crystal Data.** $C_{14}H_{17}BrN_2O_2$, $M_r$ = 325.20, orthorhombic, $P2_12_12$ (No. 18), a = 28.07952(18) Å, b = 10.21829(6) Å, c = 5.02462(4) Å, $\alpha = \beta = \gamma = 90°$, $V$ = 1441.687(18) $Å^3$, $T$ = 123.00(10) K, $Z$ = 4, $Z'$ = 1, $\mu(CuK_\alpha)$ = 3.891, 40092 reflections measured, 2922 unique ($R_{int}$ = 0.0538) which were used in all calculations. The final $wR_2$ was 0.0703 (all data) and $R_1$ was 0.0272 (I > 2(I)).

| **Compound** | **62b x HBr (Q014)** |
|---|---|
| Formula | $C_{14}H_{17}BrN_2O_2$ |
| $D_{calc.}$/ g $cm^{-3}$ | 1.498 |
| $\mu$/$mm^{-1}$ | 3.891 |
| Formula Weight | 325.20 |
| Colour | clear colourless |
| Shape | prism |
| Size/$mm^3$ | 0.36×0.17×0.10 |
| $T$/K | 123.00(10) |
| Crystal System | orthorhombic |
| Flack Parameter | -0.025(6) |
| Hooft Parameter | -0.007(6) |
| Space Group | $P2_12_12$ |
| $a$/Å | 28.07952(18) |
| $b$/Å | 10.21829(6) |
| $c$/Å | 5.02462(4) |
| $\alpha$/° | 90 |
| $\beta$/° | 90 |
| $\gamma$/° | 90 |
| V/$Å^3$ | 1441.687(18) |
| $Z$ | 4 |
| $Z'$ | 1 |
| Wavelength/Å | 1.54184 |
| Radiation type | $CuK_\alpha$ |
| $\Theta_{min}$/° | 3.148 |
| $\Theta_{max}$/° | 73.976 |
| Measured Refl. | 40092 |
| Independent Refl. | 2922 |
| Reflections Used | 2898 |
| $R_{int}$ | 0.0538 |
| Parameters | 180 |
| Restraints | 0 |
| Largest Peak | 0.697 |
| Deepest Hole | -0.321 |
| GooF | 1.075 |
| $wR_2$ (all data) | 0.0703 |
| $wR_2$ | 0.0700 |
| $R_1$ (all data) | 0.0275 |
| $R_1$ | 0.0272 |

## Structure Quality Indicators

| | | | | |
|---|---|---|---|---|
| **Reflections:** | d min (Cu) 0.80 | I/σ 44.4 | Rint 5.38% | complete at 2θ=144° 100% |
| **Refinement:** | Shift 0.002 | Max Peak 0.7 | Min Peak -0.3 | GooF 1.075 | -0.025(6) |

A clear colourless prism-shaped crystal with dimensions 0.36×0.17×0.10 $mm^3$ was mounted on a MITIGEN holder oil.X-ray diffraction data were collected using a GV1000, TitanS2 diffractometer equipped with a Oxford Cryosystems CryoStream 700 low-temperature device, operating at $T$ = 123.00(10) K.

Data were measured using $\omega$ scans scans of 1.0 ° per frame for 1.0 s using $CuK_\alpha$ radiation (gradient vaccum rotating-anode X-ray tube). The total number of runs and images was based on the strategy calculation from the program CrysAlisPro (Agilent).The maximum resolution achieved was $\Theta$ = 73.976. °

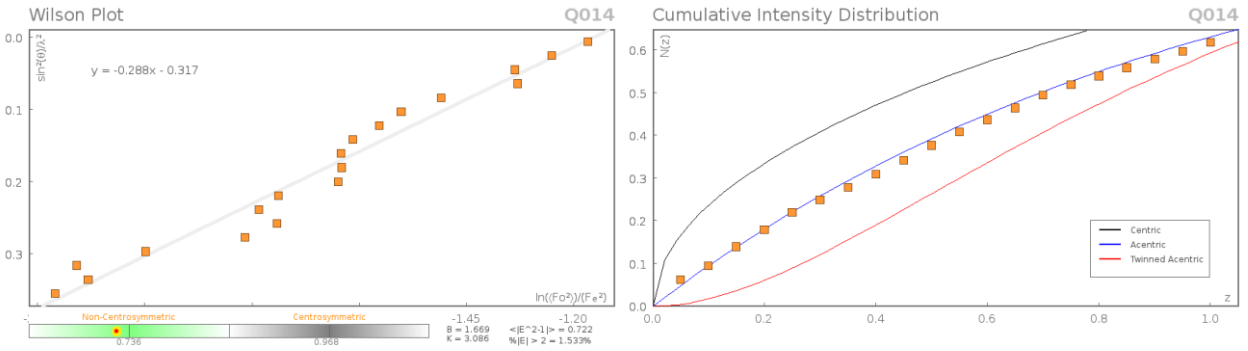
Cell parameters were retrieved using the CrysAlisPro (Agilent) software and refined using CrysAlisPro (Agilent) on 29970 reflections, 75 % of the observed reflections. Data reduction was performed using the CrysAlisPro (Agilent) software which corrects for Lorentz polarisation. The final completeness is 100.00 out to 73.976 in $\Theta$. The absorption coefficient $\mu$ of this material is 3.891 at this wavelength ($\lambda$ = 1.54184) and the minimum and maximum transmissions are 0.824 and 0.938.

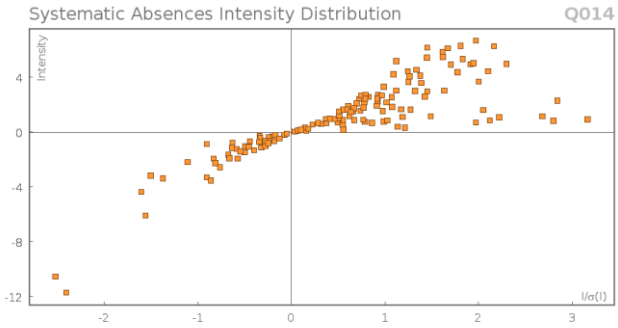
The structure was solved in the space group $P2_12_12$ (# 18) by Intrinsic Phasing using the **ShelXT** (Sheldrick, 2015) structure solution program and refined by Least Squares using version 2016/6 of **ShelXL** (Sheldrick, 2015). All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model.

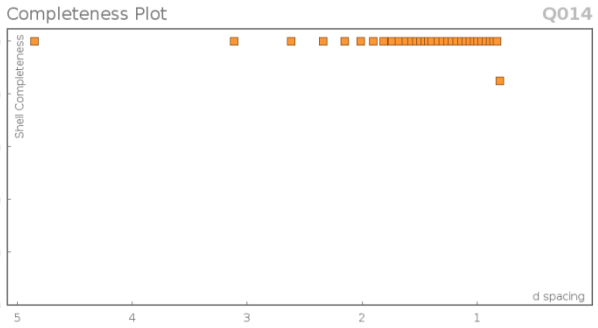
There is a single molecule in the asymmetric unit, which is represented by the reported sum formula. In other words: Z is 4 and Z' is 1.

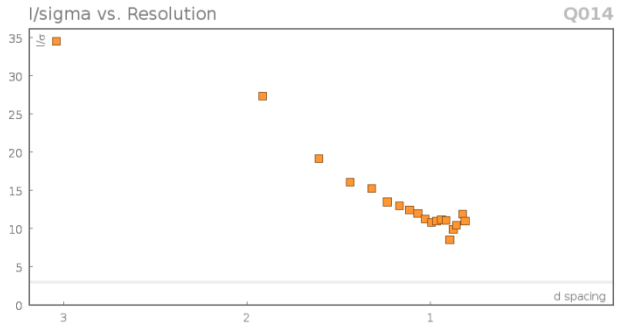
The Flack parameter was refined to -0.025(6). Determination of absolute structure using Bayesian statistics on Bijvoet differences using the Olex2 results in -0.007(6). Note: The Flack parameter is used to determine chirality of the crystal studied, the value should be near 0, a value of 1 means that the stereochemistry is wrong and the model should be inverted. A value of 0.5 means that the crystal consists of a racemic mixture of the two enantiomers.

## Data Plots: Diffraction Data

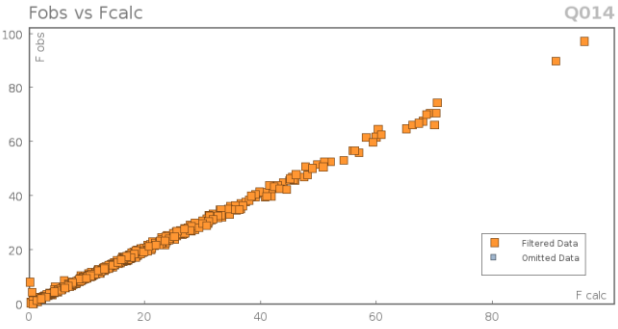


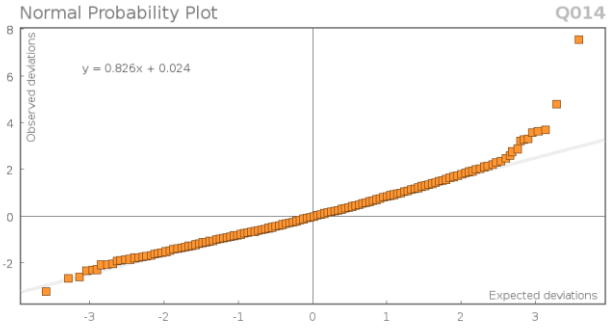



## Data Plots: Refinement and Data




## Reflection Statistics

| | | | |
|---|---|---|---|
| Total reflections (after filtering) | 40256 | Unique reflections | 2922 |
| Completeness | 0.997 | Mean $I/\sigma$ | 44.41 |
| $hkl_{max}$ collected | (35, 12, 5) | $hkl_{min}$ collected | (-34, -12, -6) |
| $hkl_{max}$ used | (34, 12, 6) | $hkl_{min}$ used | (-34, 0, 0) |
| Lim $d_{max}$ collected | 100.0 | Lim $d_{min}$ collected | 0.77 |
| $d_{max}$ used | 14.04 | $d_{min}$ used | 0.8 |
| Friedel pairs | 4974 | Friedel pairs merged | 0 |
| Inconsistent equivalents | 1 | $R_{int}$ | 0.0538 |
| $R_{sigma}$ | 0.017 | Intensity transformed | 0 |
| Omitted reflections | 0 | Omitted by user (OMIT hkl) | 0 |
| Multiplicity | (1470, 2045, 1983, 1872, 1338, 818, 633, 413, 168, 37, 4) | Maximum multiplicity | 31 |
| Removed systematic absences | 164 | Filtered off (Shel/OMIT) | 0 |

## Images of the Crystal on the Diffractometer

**Table S8**: Fractional Atomic Coordinates (×10⁴) and Equivalent Isotropic Displacement Parameters (Å²×10³) for **Q014**. $U_{eq}$ is defined as 1/3 of the trace of the orthogonalised $U_{ij}$.

| Atom | x | y | z | $U_{eq}$ |
|---|---|---|---|---|
| Br(1) | 7987.1(2) | 5771.1(3) | -1402.1(6) | 20.31(11) |
| O(1) | 6842.5(8) | 3805(2) | 6342(6) | 24.7(5) |
| O(2) | 6081.0(8) | 3373(2) | 5296(5) | 26.4(5) |
| N(2) | 6535.5(10) | 8324(3) | 7757(6) | 23.5(6) |
| N(1) | 7254.1(9) | 6154(3) | 3476(6) | 21.4(5) |
| C(4) | 6681.5(11) | 7432(3) | 5880(7) | 19.9(6) |
| C(3) | 6345.9(11) | 6486(3) | 5553(6) | 18.0(6) |
| C(2) | 6410.3(10) | 5352(3) | 3688(7) | 20.1(6) |
| C(12) | 6849.0(11) | 5576(3) | 1921(6) | 23.8(7) |
| C(6) | 5965.6(11) | 6767(3) | 7370(7) | 19.8(6) |
| C(5) | 7149.6(11) | 7498(3) | 4485(7) | 21.8(6) |
| C(7) | 6099.9(11) | 7926(3) | 8724(7) | 22.5(6) |
| C(1) | 6475.1(11) | 4095(3) | 5254(6) | 20.2(6) |
| C(11) | 5531.2(11) | 6164(3) | 8041(7) | 26.4(7) |
| C(14) | 5668.8(13) | 1381(3) | 6053(10) | 37.0(9) |
| C(10) | 5258.5(12) | 6707(4) | 10029(8) | 33.4(8) |
| C(8) | 5823.3(13) | 8476(4) | 10737(8) | 30.6(8) |
| C(13) | 6107.8(13) | 2142(3) | 6740(9) | 32.9(9) |
| C(9) | 5402.4(13) | 7855(4) | 11347(9) | 36.5(8) |

**Table S9**: Anisotropic Displacement Parameters (×10⁴) **Q014**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2} \times U_{11} + \ldots + 2hka^* \times b^* \times U_{12}]$

| Atom | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{23}$ | $U_{13}$ | $U_{12}$ |
|---|---|---|---|---|---|---|
| Br(1) | 21.71(16) | 22.53(16) | 16.69(17) | 1.06(12) | -1.10(12) | 0.53(11) |
| O(1) | 23.4(10) | 24.2(10) | 26.5(12) | 0.3(10) | -7(1) | 1.8(8) |
| O(2) | 23.2(10) | 23.2(11) | 32.9(14) | 7.5(10) | -6.8(10) | -2.2(9) |
| N(2) | 24.5(12) | 17.5(12) | 28.6(16) | -0.4(11) | -2.3(12) | 0.3(10) |
| N(1) | 19.3(11) | 29.0(14) | 16.0(13) | 5.3(12) | 0.9(11) | 2.6(9) |
| C(4) | 19.9(13) | 18.3(13) | 21.4(17) | 4.1(13) | -2.9(12) | -0.2(11) |
| C(3) | 20.2(13) | 18.2(14) | 15.5(15) | 1.2(12) | -2.4(12) | 1.8(11) |
| C(2) | 21.0(13) | 23.5(14) | 15.7(15) | 2.0(12) | -4.8(13) | -0.6(11) |
| C(12) | 24.1(14) | 32.4(17) | 14.8(16) | -1.8(13) | -1.5(12) | 1.6(12) |
| C(6) | 19.2(14) | 21.8(14) | 18.6(15) | 2.8(12) | -2.9(12) | 3.1(12) |
| C(5) | 22.1(14) | 19.8(14) | 23.3(16) | 5.1(12) | -1.7(12) | -0.6(11) |
| C(7) | 23.9(14) | 23.0(14) | 20.5(16) | 0.8(14) | -2.8(14) | 6.7(11) |
| C(1) | 21.7(14) | 20.7(14) | 18.2(15) | -4.8(13) | -0.2(11) | 0.7(12) |
| C(11) | 20.1(14) | 31.6(16) | 28(2) | 6.5(13) | -1.8(13) | 2.0(12) |
| C(14) | 36.0(18) | 24.9(16) | 50(3) | 7.2(19) | -1.1(19) | -0.4(14) |
| C(10) | 21.5(15) | 48(2) | 31(2) | 8.6(17) | 4.7(15) | 4.0(15) |
| C(8) | 35.0(17) | 30.5(17) | 26.4(19) | -4.2(15) | -2.2(15) | 12.2(14) |
| C(13) | 29.7(16) | 26.8(16) | 42(2) | 13.6(17) | -6.5(17) | 0.1(13) |
| C(9) | 31.6(16) | 50(2) | 28(2) | 1(2) | 7.0(17) | 16.6(15) |

**Table S10**: Bond Lengths in Å for **Q014**.

| Atom | Atom | Length/Å | Atom | Atom | Length/Å |
|---|---|---|---|---|---|
| O(1) | C(1) | 1.205(4) | C(3) | C(6) | 1.434(5) |
| O(2) | C(1) | 1.330(4) | C(2) | C(12) | 1.536(4) |
| O(2) | C(13) | 1.454(4) | C(2) | C(1) | 1.517(4) |
| N(2) | C(4) | 1.374(4) | C(6) | C(7) | 1.417(5) |
| N(2) | C(7) | 1.378(4) | C(6) | C(11) | 1.408(4) |
| N(1) | C(12) | 1.501(4) | C(7) | C(8) | 1.394(5) |
| N(1) | C(5) | 1.494(4) | C(11) | C(10) | 1.376(5) |
| C(4) | C(3) | 1.360(4) | C(14) | C(13) | 1.498(5) |
| C(4) | C(5) | 1.491(4) | C(10) | C(9) | 1.406(6) |
| C(3) | C(2) | 1.502(4) | C(8) | C(9) | 1.376(5) |

**Table S11**: Bond Angles in ° for **Q014**.

| Atom | Atom | Atom | Angle/° |
|---|---|---|---|
| C(1) | O(2) | C(13) | 116.4(3) |
| C(4) | N(2) | C(7) | 108.1(3) |
| C(5) | N(1) | C(12) | 112.9(2) |
| N(2) | C(4) | C(5) | 123.8(3) |
| C(3) | C(4) | N(2) | 110.3(3) |
| C(3) | C(4) | C(5) | 125.9(3) |
| C(4) | C(3) | C(2) | 122.7(3) |
| C(4) | C(3) | C(6) | 107.3(3) |
| C(6) | C(3) | C(2) | 129.9(3) |
| C(3) | C(2) | C(12) | 110.0(2) |
| C(3) | C(2) | C(1) | 110.1(3) |
| C(1) | C(2) | C(12) | 109.3(3) |
| N(1) | C(12) | C(2) | 111.5(3) |
| C(7) | C(6) | C(3) | 106.0(3) |
| C(11) | C(6) | C(3) | 135.2(3) |
| C(11) | C(6) | C(7) | 118.8(3) |
| C(4) | C(5) | N(1) | 106.9(2) |
| N(2) | C(7) | C(6) | 108.3(3) |
| N(2) | C(7) | C(8) | 129.2(3) |
| C(8) | C(7) | C(6) | 122.5(3) |
| O(1) | C(1) | O(2) | 124.6(3) |
| O(1) | C(1) | C(2) | 123.2(3) |
| O(2) | C(1) | C(2) | 112.2(3) |
| C(10) | C(11) | C(6) | 118.7(4) |
| C(11) | C(10) | C(9) | 121.2(3) |
| C(9) | C(8) | C(7) | 117.0(3) |
| O(2) | C(13) | C(14) | 106.9(3) |
| C(8) | C(9) | C(10) | 121.8(4) |

**Table S12**: Hydrogen Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for **Q014**. $U_{eq}$ is defined as 1/3 of the trace of the orthogonalised $U_{ij}$.

| Atom | x | y | z | $U_{eq}$ |
|---|---|---|---|---|
| H(2) | 6689.34 | 9011.55 | 8243.99 | 28 |
| H(1A) | 7331(14) | 5690(40) | 4800(100) | 26 |
| H(2A) | 6127.36 | 5272.15 | 2557.86 | 24 |
| H(12A) | 6948.6 | 4749.26 | 1153.46 | 29 |
| H(12B) | 6765.38 | 6161.2 | 474.77 | 29 |
| H(5A) | 7396.84 | 7780.81 | 5704.68 | 26 |
| H(5B) | 7134.32 | 8114.24 | 3018.5 | 26 |
| H(11) | 5430.63 | 5413.15 | 7158.02 | 32 |
| H(14A) | 5658.41 | 1234.74 | 4166.94 | 55 |
| H(14B) | 5392.19 | 1866.61 | 6589.7 | 55 |
| H(14C) | 5674.25 | 555.41 | 6962.98 | 55 |
| H(10) | 4973.72 | 6307.54 | 10510.97 | 40 |
| H(8) | 5918.91 | 9229.71 | 11628.04 | 37 |
| H(13A) | 6121.73 | 2301.84 | 8640.93 | 39 |
| H(13B) | 6390.34 | 1659.44 | 6218.68 | 39 |
| H(9) | 5207.84 | 8204.06 | 12666.02 | 44 |
| H(1B) | 7503(17) | 6210(50) | 2180(100) | 38(12) |

**Citations**

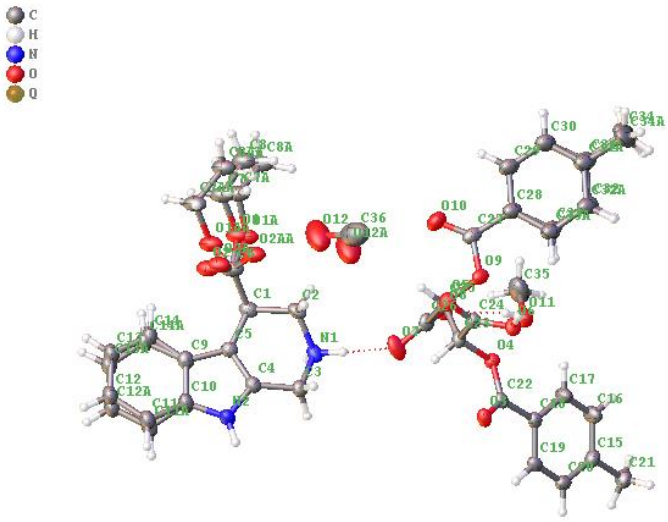

O.V. Dolomanov and L.J. Bourhis and R.J. Gildea and J.A.K. Howard and H. Puschmann, Olex2: A complete structure solution, refinement and analysis program, *J. Appl. Cryst.*, (2009), **42**, 339-341.

Sheldrick, G.M., Crystal structure refinement with ShelXL, *Acta Cryst.*, (2015), **C27**, 3-8.

Sheldrick, G.M., ShelXT-Integrated space-group and crystal-structure determination, *Acta Cryst.*, (2015), **A71**, 3-8.

## Crystallographic data of 62a crystallized with (-)-di-*p*-toluolyl-L-tartaric acid

Crystal Data and Experimental. For Full details see Cambridge Crystallographic Data Centre: http://www.ccdc.cam.ac.uk/ deposit@ccdc.cam.ac.uk. The data have been assigned to the following deposition number:[1532351]




**Experimental.** Single crystals of (**mC-gauss**) were obtained by recrystallization from MeOH. A suitable crystal was selected and mounted on a MITIGEN holder oil on a diffractometer. The crystal was kept at $T$ = 293(2) K during data collection. The structure was solved, using the Unknown solution method. The model was refined with ShelXL-2014/7 (Sheldrick, 2014) using Least Squares minimisation.

**Crystal Data.** $C_{35.995}H_{37.99}N_2O_{11.995}$, $M_r$ = 690.53, monoclinic, C2 (No. 5), a = 33.0094(4) Å, b = 7.65881(11) Å, c = 14.20813(16) Å, $\beta$ = 91.1146(11)°, $\alpha$ = $\gamma$ = 90°, $V$ = 3591.31(8) Å$^3$, $T$ = 293(2) K, $Z$ = 4, $Z'$ = 1, $\mu$(Cu$K_\alpha$) = 0.808, 36890 reflections measured, 6807 unique ($R_{int}$ = 0.0338) which were used in all calculations. The final $wR_2$ was 0.1113 (all data) and $R_1$ was 0.0405 (I > 2(I)).

| **Compound** | **62a (mC-gauss)** |
|---|---|
| Formula | $C_{35.995}H_{37.99}N_2O_{11.995}$ |
| $D_{calc.}$/ g cm$^{-3}$ | 1.277 |
| $\mu$/mm$^{-1}$ | 0.808 |
| Formula Weight | 690.53 |
| $T$/K | 293(2) |
| Crystal System | monoclinic |
| Flack Parameter | -0.08(5) |
| Hooft Parameter | -0.05(4) |
| Space Group | C2 |
| $a$/Å | 33.0094(4) |
| $b$/Å | 7.65881(11) |
| $c$/Å | 14.20813(16) |
| $\alpha$/° | 90 |
| $\beta$/° | 91.1146(11) |
| $\gamma$/° | 90 |
| V/Å$^3$ | 3591.31(8) |
| $Z$ | 4 |
| $Z'$ | 1 |
| $\Theta_{min}$/° | 4.067 |
| $\Theta_{max}$/° | 73.534 |
| Measured Refl. | 36890 |
| Independent Refl. | 6807 |
| Reflections Used | 6620 |
| $R_{int}$ | 0.0338 |
| Parameters | 617 |
| Restraints | 458 |
| Largest Peak | 0.576 |
| Deepest Hole | -0.311 |
| GooF | 1.023 |
| $wR_2$ (all data) | 0.1113 |
| $wR_2$ | 0.1102 |
| $R_1$ (all data) | 0.0415 |
| $R_1$ | 0.0405 |

## Structure Quality Indicators

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Reflections:** | d min (Cu) | 0.80 | I/σ | 30.4 | Rint | 3.38% | complete at 2θ=134° 94% |
| **Refinement:** | Shift | 0.000 | Max Peak | 0.6 | Min Peak | -0.3 | GooF 1.023 | -0.08(5) |

A crystal with dimensions was mounted on a MITIGEN holder oil. Data were collected using a diffractometer equipped with a low-temperature apparatus operating at $T$ = 293(2) K.

Data were measured using scans of 1.0° per frame for 3.0 s using CuK$_\alpha$ radiation. The total number of runs and images was based on the strategy calculation from the program. The actually achieved resolution was $\Theta$ = 73.534.

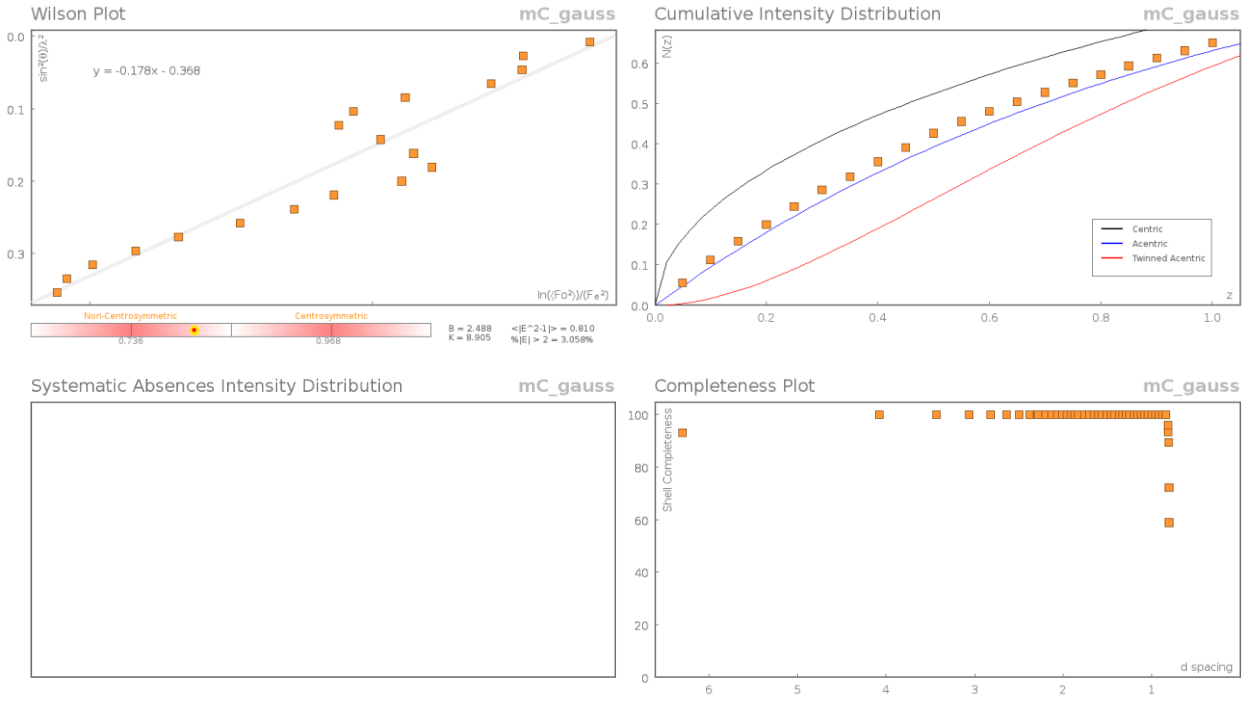
Data reduction was performed using software which corrects for Lorentz polarisation. The final completeness is 99.90 out to 73.534 in $\Theta$. The absorption coefficient ($\mu$) of this material is 0.808.

The structure was solved in the space group C2 (# 5) by Unknown using the structure solution program and refined by Least Squares using ShelXL-2014/7 (Sheldrick, 2014). All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model.

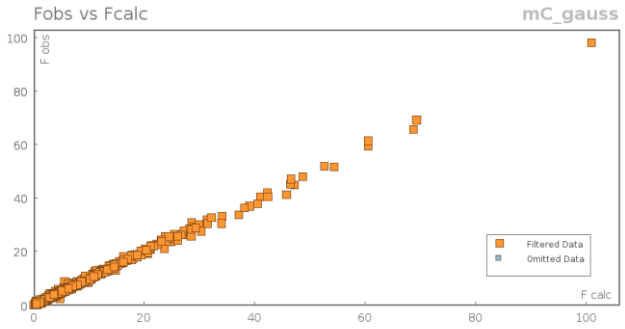
There is a single molecule in the asymmetric unit, which is represented by the reported sum formula. In other words: Z is 4 and Z' is 1.

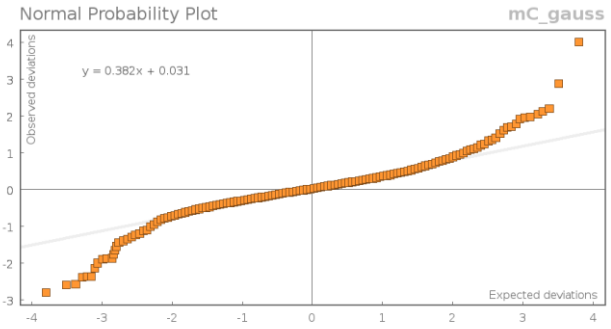
The Flack parameter was refined to -0.08(5). Determination of absolute structure using Bayesian statistics on Bijvoet differences using the Olex2 results in -0.05(4). Note: The Flack parameter is used to determine chirality of the crystal studied, the value should be near 0, a value of 1 means that the stereochemistry is wrong and the model should be inverted. A value of 0.5 means that the crystal consists of a racemic mixture of the two enantiomers.

## Data Plots: Diffraction Data



## Data Plots: Refinement and Data




## Reflection Statistics

| | | | |
|---|---|---|---|
| Total reflections (after filtering) | 36890 | Unique reflections | 6807 |
| Completeness | 0.941 | Mean I/$\sigma$ | 30.44 |
| hklsub>max</sub> collected | (40, 8, 17) | hklsub>min</sub> collected | (-40, -9, -17) |
| $hkl_{max}$ used | (40, 8, 17) | $hkl_{min}$ used | (-40, -9, 0) |
| Lim $d_{max}$ collected | 100.0 | Lim $d_{min}$ collected | 0.77 |
| $d_{max}$ used | 10.87 | $d_{min}$ used | 0.8 |
| Friedel pairs | 5259 | Friedel pairs merged | 0 |
| Inconsistent equivalents | 0 | $R_{int}$ | 0.0338 |
| $R_{sigma}$ | 0.02 | Intensity transformed | 0 |
| Omitted reflections | 0 | Omitted by user (OMIT hkl) | 0 |
| Multiplicity | (3004, 2659, 2410, 1595, 1019, 569, 375, 217, 106, 56, 28, 20, 2) | Maximum multiplicity | 18 |
| Removed systematic absences | 0 | Filtered off (Shel/OMIT) | 0 |

## Images of the Crystal on the Diffractometer

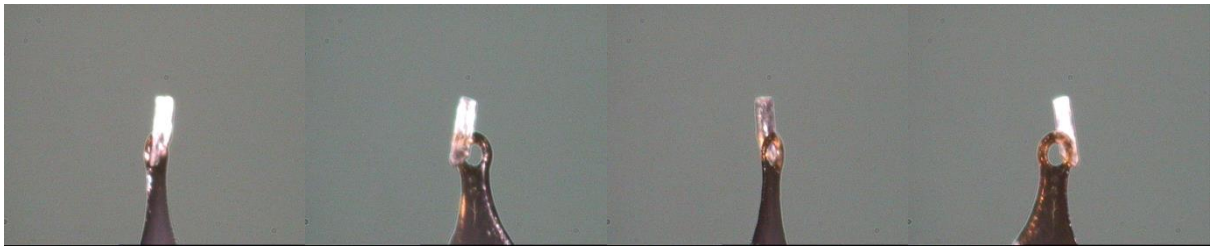


**Table S13**: Fractional Atomic Coordinates (×$10^4$) and Equivalent Isotropic Displacement Parameters (Å$^2$×$10^3$) for **mC_gauss**. $U_{eq}$ is defined as 1/3 of the trace of the orthogonalised $U_{ij}$.

| Atom | x | y | z | $U_{eq}$ |
|---|---|---|---|---|
| O4 | 5800.9(5) | 3056(2) | 5642.3(11) | 22.2(3) |
| O3 | 5475.8(5) | 1711(3) | 4441.1(13) | 27.1(4) |
| O9 | 5894.5(5) | 3507(2) | 7523.8(12) | 26.8(4) |
| O5 | 5198.4(6) | 325(3) | 7109.2(13) | 29.5(4) |
| O8 | 5782.0(6) | 6780(3) | 6913.3(13) | 29.0(4) |
| O6 | 5765.6(5) | -166(2) | 6308.0(13) | 28.1(4) |
| O10 | 5659.3(7) | 4494(3) | 8896.6(14) | 43.0(5) |
| O11 | 6586.3(6) | 6845(4) | 6450.8(15) | 43.3(5) |
| O7 | 5166.5(6) | 6196(3) | 6305.6(18) | 43.8(5) |
| N2 | 3506.3(7) | 8198(4) | 5458.6(16) | 32.3(5) |
| N1 | 4539.8(6) | 8385(3) | 6503.9(15) | 26.7(4) |
| C22 | 5767.4(7) | 2517(3) | 4748.5(17) | 22.4(5) |
| O2 | 3560(2) | 7667(10) | 8775(5) | 39.0(7) |
| O1 | 4076(2) | 9178(13) | 9371(6) | 39.0(6) |

| Atom | x | y | z | $U_{eq}$ |
|---|---|---|---|---|
| C18 | 6118.5(7) | 3080(3) | 4191.2(17) | 23.9(5) |
| C4 | 3835.2(7) | 8211(4) | 6065.7(17) | 25.4(5) |
| C19 | 6060.8(7) | 3405(4) | 3232.2(17) | 25.3(5) |
| C24 | 5468.7(7) | 797(3) | 6594.9(17) | 23.9(5) |
| C26 | 5483.7(8) | 5796(3) | 6738.8(19) | 27.2(5) |
| C3 | 4246.2(7) | 7648(4) | 5798.3(18) | 26.9(5) |
| C10 | 3179.7(8) | 8829(4) | 5930(2) | 36.4(6) |
| C20 | 6374.5(8) | 4068(4) | 2713.4(17) | 28.4(5) |
| C5 | 3726.6(8) | 8836(4) | 6924.0(17) | 25.9(5) |
| C2 | 4417.5(8) | 8082(4) | 7495.7(18) | 30.6(6) |
| C27 | 5931.7(9) | 3874(4) | 8446.2(18) | 30.4(5) |
| C15 | 6753.6(8) | 4380(4) | 3125.2(19) | 30.0(6) |
| C25 | 5511.3(8) | 3900(3) | 7074.1(18) | 26.4(5) |
| C16 | 6806.7(8) | 4022(5) | 4080(2) | 39.7(7) |
| C17 | 6493.5(8) | 3405(5) | 4614.5(18) | 34.5(6) |
| C23 | 5469.0(7) | 2668(3) | 6247.6(17) | 23.5(5) |
| C9 | 3304.3(8) | 9263(4) | 6856(2) | 30.6(6) |
| C28 | 6339.0(9) | 3409(4) | 8827.3(17) | 36.5(5) |
| C14 | 3049(4) | 9870(30) | 7529(14) | 37.3(11) |
| C1 | 4026.7(8) | 9081(4) | 7716.7(17) | 28.9(5) |
| C6 | 3879.2(10) | 8440(5) | 8664.7(19) | 38.6(5) |
| C29 | 6406.2(9) | 3513(5) | 9794.9(18) | 41.1(5) |
| C21 | 7098.0(9) | 5108(5) | 2562(2) | 38.2(7) |
| C31 | 7118(2) | 2670(12) | 9637(4) | 40.5(6) |
| C13 | 2642(3) | 10063(17) | 7298(7) | 38(1) |
| C33 | 6674.4(15) | 3039(10) | 8284(4) | 37.7(6) |
| C11 | 2754(4) | 8847(16) | 5713(9) | 39.0(11) |
| C30 | 6782.2(9) | 3067(5) | 10177(2) | 42.7(5) |
| C32 | 7057.4(19) | 2680(9) | 8666(5) | 39.2(6) |
| C12 | 2494(3) | 9555(15) | 6389(7) | 38.8(10) |
| C35 | 6717.8(12) | 8174(7) | 7071(3) | 68.2(12) |
| C34 | 7520(20) | 2250(70) | 10080(40) | 70(5) |
| C7 | 3950(3) | 8693(12) | 10313(5) | 39.9(7) |
| C36 | 4655.8(15) | 2947(9) | 8941(3) | 82.2(16) |
| C8A | 4454(4) | 9104(14) | 10836(6) | 40.8(7) |
| C31A | 7066(3) | 2410(16) | 9588(6) | 40.6(6) |
| C33A | 6619(2) | 2691(12) | 8224(5) | 37.8(6) |
| C32A | 6987(2) | 2207(11) | 8630(6) | 39.1(6) |
| C34A | 7510(30) | 2050(90) | 9980(60) | 70(5) |
| O12A | 4724(2) | 4625(11) | 8658(5) | 97(2) |
| O2A | 3637(3) | 7328(12) | 8808(6) | 39.1(7) |
| O1A | 4154(3) | 9072(17) | 9305(7) | 39.0(7) |
| C7A | 4097(4) | 8522(15) | 10278(6) | 39.9(7) |
| C8 | 4293(3) | 9222(11) | 10963(5) | 40.9(7) |
| O1AA | 3816(7) | 9490(30) | 9293(12) | 39.3(6) |
| C7AA | 3679(9) | 8920(40) | 10229(17) | 39.7(7) |
| O2AA | 3958(6) | 6710(30) | 8898(11) | 39.1(7) |
| C8AA | 4051(10) | 9010(40) | 10902(18) | 40.3(7) |
| O12 | 4455(3) | 4740(15) | 9050(7) | 97(2) |
| C14A | 2997(3) | 10000(20) | 7428(11) | 37.2(10) |
| C13A | 2610(2) | 10227(13) | 7055(5) | 38.1(10) |
| C12A | 2513(2) | 9828(12) | 6131(5) | 38.8(10) |
| C11A | 2794(3) | 9171(12) | 5547(7) | 38.9(10) |

**Table S14**: Anisotropic Displacement Parameters (×$10^4$) **mC_gauss**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2} \times U_{11} + ... + 2hka^* \times b^* \times U_{12}]$

| Atom | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{23}$ | $U_{13}$ | $U_{12}$ |
|---|---|---|---|---|---|---|
| O4 | 24.4(8) | 16.0(9) | 26.3(8) | 0.1(6) | 2.2(6) | -3.1(6) |
| O3 | 22.5(8) | 21.3(9) | 37.5(9) | -7.1(8) | -2.7(7) | -0.6(7) |

| Atom | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{23}$ | $U_{13}$ | $U_{12}$ |
|---|---|---|---|---|---|---|
| O9 | 36.5(9) | 18.4(9) | 25.7(8) | -0.6(7) | 3.2(7) | 3.4(7) |
| O5 | 30.7(9) | 21(1) | 37.0(9) | 2.4(8) | 6.0(7) | -5.5(7) |
| O8 | 34.2(9) | 16.1(9) | 36.7(9) | 1.1(7) | 0.0(7) | 0.0(7) |
| O6 | 31.2(9) | 15.6(9) | 37.6(9) | 3.1(7) | 5.1(7) | 2.2(7) |
| O10 | 46.4(12) | 48.4(15) | 34.5(10) | -8.3(10) | 9.2(9) | 4(1) |
| O11 | 34.5(10) | 54.7(15) | 40.8(11) | 2.3(11) | 1.2(8) | 5.7(10) |
| O7 | 37.9(11) | 21.0(11) | 71.9(15) | -4.9(10) | -13.2(10) | 7.0(8) |
| N2 | 29.2(10) | 37.7(14) | 29.8(10) | -5.7(10) | -5.9(8) | 5.8(10) |
| N1 | 23.2(9) | 19.2(11) | 37.7(11) | 7.1(9) | -1.4(8) | -2.7(8) |
| C22 | 22.2(11) | 14.7(11) | 30.1(11) | -1.3(9) | -2.7(9) | 4.0(9) |
| O2 | 47.5(15) | 41.3(14) | 28.2(9) | 5(1) | -3.7(10) | -14.3(12) |
| O1 | 48.1(15) | 42.3(12) | 26.4(9) | 3.8(8) | -5.7(11) | -14.3(13) |
| C18 | 24.5(11) | 19.0(13) | 28.1(11) | -2.9(10) | -0.5(9) | 0.9(9) |
| C4 | 25.6(11) | 20.7(13) | 29.9(11) | 0.8(10) | -2.5(9) | -2(1) |
| C19 | 27.1(11) | 21.0(13) | 27.8(11) | -5.2(10) | -5.2(9) | 2.5(10) |
| C24 | 24.9(11) | 19.2(13) | 27.8(11) | -1.8(9) | 0.7(9) | -2.0(9) |
| C26 | 29.7(12) | 16.4(13) | 35.5(13) | -4.3(10) | 2.4(10) | 1.8(10) |
| C3 | 26.7(12) | 21.4(13) | 32.6(12) | 1.6(10) | 0.5(9) | 1.3(10) |
| C10 | 28.8(13) | 39.3(18) | 40.8(14) | -6.3(13) | -5.1(11) | 6.3(12) |
| C20 | 34.8(13) | 26.6(14) | 23.9(11) | -1.5(10) | -0.2(9) | 4.3(11) |
| C5 | 28.6(12) | 21.9(13) | 27.2(11) | 1.8(10) | -1.6(9) | -3.4(10) |
| C2 | 31.8(12) | 27.8(15) | 31.9(12) | 9.6(11) | -8.2(10) | -5.0(11) |
| C27 | 44.8(14) | 19.2(13) | 27.4(11) | -0.1(10) | 8.1(10) | -2.0(11) |
| C15 | 30.0(13) | 27.5(15) | 32.7(13) | 0.3(10) | 6.3(10) | 1.2(10) |
| C25 | 29.2(11) | 16.6(13) | 33.5(12) | 0.1(10) | 6.6(9) | 0.9(9) |
| C16 | 25.3(13) | 58(2) | 36.0(14) | 6.9(14) | -4.9(10) | -7.9(13) |
| C17 | 27.1(12) | 49.0(19) | 27.0(11) | 5.0(12) | -4.7(9) | -4.2(12) |
| C23 | 21.4(11) | 16.6(12) | 32.5(12) | 0.6(10) | 4.0(9) | -1.7(9) |
| C9 | 29.8(12) | 23.8(14) | 38.3(14) | -2.3(11) | 0(1) | 0.4(10) |
| C28 | 50.7(10) | 32.1(11) | 26.9(8) | -1.9(8) | 1.3(8) | 7.7(9) |
| C14 | 28.5(14) | 41(2) | 42(3) | -4(2) | -1.5(14) | 6.3(13) |
| C1 | 33.4(13) | 22.6(13) | 30.3(12) | 3(1) | -4.1(10) | -7.8(11) |
| C6 | 47.7(13) | 40.7(12) | 27.2(8) | 3.4(8) | -4.7(9) | -14.1(11) |
| C29 | 54.1(11) | 39.2(12) | 29.8(9) | -5.5(9) | 1.5(8) | 6.7(10) |
| C21 | 32.4(14) | 42.9(19) | 39.5(14) | 5.3(13) | 8.7(11) | 1.3(12) |
| C31 | 54.4(12) | 36.3(14) | 30.8(9) | -2.5(10) | -3.1(10) | 11(1) |
| C13 | 29.0(12) | 42(2) | 42(3) | -3(2) | -1.9(13) | 7.0(11) |
| C33 | 51.6(12) | 33.7(13) | 27.8(9) | -2.2(10) | -0.9(9) | 10.5(10) |
| C11 | 29.1(13) | 44(2) | 43(3) | -1(2) | -3.4(14) | 6.2(13) |
| C30 | 56.7(11) | 40.2(12) | 31.0(9) | -3.6(9) | -2.0(8) | 9.7(10) |
| C32 | 52.9(12) | 34.9(14) | 29.9(9) | -2.3(10) | -1.7(9) | 11.4(10) |
| C12 | 29.0(12) | 44(2) | 43(3) | -1(2) | -2.3(13) | 6.8(11) |
| C35 | 43.6(19) | 87(3) | 74(2) | -22(2) | -16.4(17) | 7(2) |
| C34 | 81(4) | 80(10) | 48(11) | -7(8) | -15(6) | 49(7) |
| C7 | 48.8(15) | 43.5(12) | 27.2(9) | 4.0(9) | -5.4(11) | -13.9(13) |
| C36 | 70(3) | 115(5) | 61(2) | 2(3) | 3(2) | -23(3) |
| C8A | 49.1(17) | 45.0(13) | 28.0(11) | 3.7(10) | -5.3(13) | -14.0(15) |
| C31A | 54.3(12) | 36.4(14) | 31(1) | -2.5(10) | -2.9(10) | 11.2(11) |
| C33A | 51.7(12) | 33.7(13) | 28.0(9) | -2(1) | -0.9(10) | 10.6(10) |
| C32A | 52.8(12) | 34.8(14) | 29.7(9) | -2.4(10) | -1.8(9) | 11.2(10) |
| C34A | 81(4) | 80(10) | 48(11) | -8(8) | -16(7) | 49(7) |
| O12A | 72(3) | 110(5) | 110(4) | 53(4) | 14(3) | 23(3) |
| O2A | 47.8(15) | 41.2(14) | 28.2(9) | 4.9(10) | -3.8(11) | -14.8(12) |
| O1A | 48.3(15) | 42.2(12) | 26.4(9) | 4.0(9) | -5.6(11) | -14.2(13) |
| C7A | 48.6(15) | 43.5(12) | 27.2(9) | 4.1(9) | -5.3(11) | -13.9(13) |
| C8 | 49.3(17) | 44.9(13) | 28.1(11) | 3.7(10) | -5.3(13) | -13.3(15) |
| O1AA | 48.2(15) | 42.2(12) | 27.2(8) | 4.1(8) | -4.8(10) | -14.1(12) |
| C7AA | 48.6(16) | 43.2(13) | 27.1(10) | 4(1) | -5.2(12) | -13.9(14) |
| O2AA | 47.9(16) | 41.1(15) | 28.1(11) | 4.5(11) | -3.8(12) | -14.4(13) |
| C8AA | 48.9(16) | 44.1(13) | 27.6(11) | 3.9(10) | -5.3(13) | -13.8(14) |
| O12 | 73(3) | 112(5) | 108(4) | 54(4) | 16(3) | 22(3) |

| Atom | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{23}$ | $U_{13}$ | $U_{12}$ |
|---|---|---|---|---|---|---|
| C14A | 28.6(14) | 41(2) | 42(3) | -4(2) | -1.3(14) | 6.4(13) |
| C13A | 28.9(12) | 43(2) | 43(3) | -3.0(19) | -1.8(13) | 7.2(11) |
| C12A | 28.9(12) | 44(2) | 43(3) | -1.6(19) | -2.8(13) | 6.7(11) |
| C11A | 29.0(13) | 45(2) | 43(3) | -1(2) | -3.1(13) | 6.1(13) |

**Table S15**: Bond Lengths in Å for **mC_gauss**.

| Atom | Atom | Length/Å |
|---|---|---|
| O4 | C22 | 1.338(3) |
| O4 | C23 | 1.437(3) |
| O3 | C22 | 1.217(3) |
| O9 | C27 | 1.344(3) |
| O9 | C25 | 1.438(3) |
| O5 | C24 | 1.219(3) |
| O8 | C26 | 1.261(3) |
| O6 | C24 | 1.299(3) |
| O10 | C27 | 1.211(4) |
| O11 | C35 | 1.409(5) |
| O7 | C26 | 1.243(3) |
| N2 | C10 | 1.368(4) |
| N2 | C4 | 1.373(3) |
| N1 | C2 | 1.492(3) |
| N1 | C3 | 1.492(3) |
| C22 | C18 | 1.480(3) |
| O2 | C6 | 1.223(8) |
| O1 | C6 | 1.312(10) |
| O1 | C7 | 1.457(9) |
| C18 | C17 | 1.388(3) |
| C18 | C19 | 1.395(3) |
| C4 | C5 | 1.365(4) |
| C4 | C3 | 1.480(3) |
| C19 | C20 | 1.380(4) |
| C24 | C23 | 1.515(4) |
| C26 | C25 | 1.531(4) |
| C10 | C11A | 1.398(11) |
| C10 | C9 | 1.412(4) |
| C10 | C11 | 1.431(13) |
| C20 | C15 | 1.392(4) |
| C5 | C9 | 1.433(4) |
| C5 | C1 | 1.497(3) |
| C2 | C1 | 1.538(4) |
| C27 | C28 | 1.483(4) |
| C15 | C16 | 1.391(4) |
| C15 | C21 | 1.510(4) |
| C25 | C23 | 1.511(4) |
| C16 | C17 | 1.378(4) |
| C9 | C14 | 1.368(18) |
| C9 | C14A | 1.427(13) |
| C28 | C33A | 1.386(5) |
| C28 | C29 | 1.391(3) |
| C28 | C33 | 1.391(4) |
| C14 | C13 | 1.383(11) |
| C1 | C6 | 1.522(4) |
| C6 | O2A | 1.188(10) |
| C6 | O1AA | 1.22(2) |
| C6 | O1A | 1.362(11) |
| C6 | O2AA | 1.39(2) |
| C29 | C30 | 1.388(3) |
| C31 | C32 | 1.391(4) |
| C31 | C30 | 1.394(5) |
| C31 | C34 | 1.48(7) |
| C13 | C12 | 1.427(11) |
| C33 | C32 | 1.394(4) |
| C11 | C12 | 1.409(12) |
| C30 | C31A | 1.364(11) |
| C7 | C8 | 1.504(9) |
| C36 | O12A | 1.367(10) |
| C36 | O12 | 1.533(12) |
| C8A | C7A | 1.476(11) |
| C31A | C32A | 1.390(5) |
| C31A | C34A | 1.57(9) |
| C33A | C32A | 1.386(5) |
| O1A | C7A | 1.462(11) |
| O1AA | C7AA | 1.48(3) |
| C7AA | C8AA | 1.54(4) |
| C14A | C13A | 1.387(9) |
| C13A | C12A | 1.379(9) |
| C12A | C11A | 1.355(9) |

**Table S16**: Bond Angles in ° for **mC_gauss**.

| Atom | Atom | Atom | Angle/° |
|---|---|---|---|
| C22 | O4 | C23 | 117.03(18) |
| C27 | O9 | C25 | 116.9(2) |
| C10 | N2 | C4 | 108.1(2) |
| C2 | N1 | C3 | 113.07(19) |
| O3 | C22 | O4 | 123.2(2) |
| O3 | C22 | C18 | 125.3(2) |
| O4 | C22 | C18 | 111.5(2) |
| C6 | O1 | C7 | 116.6(6) |
| C17 | C18 | C19 | 119.7(2) |
| C17 | C18 | C22 | 121.4(2) |
| C19 | C18 | C22 | 118.8(2) |
| C5 | C4 | N2 | 110.2(2) |
| C5 | C4 | C3 | 126.1(2) |
| N2 | C4 | C3 | 123.7(2) |
| C20 | C19 | C18 | 119.9(2) |
| O5 | C24 | O6 | 125.8(2) |
| O5 | C24 | C23 | 118.7(2) |
| O6 | C24 | C23 | 115.5(2) |
| O7 | C26 | O8 | 126.7(3) |
| O7 | C26 | C25 | 115.6(2) |
| O8 | C26 | C25 | 117.7(2) |
| C4 | C3 | N1 | 107.7(2) |

| Atom | Atom | Atom | Angle/° |
|---|---|---|---|
| N2 | C10 | C11A | 126.6(4) |
| N2 | C10 | C9 | 108.8(2) |
| C11A | C10 | C9 | 124.4(5) |
| N2 | C10 | C11 | 132.6(6) |
| C9 | C10 | C11 | 117.7(5) |
| C19 | C20 | C15 | 121.1(2) |
| C4 | C5 | C9 | 107.0(2) |
| C4 | C5 | C1 | 122.3(2) |
| C9 | C5 | C1 | 130.6(2) |
| N1 | C2 | C1 | 111.0(2) |
| O10 | C27 | O9 | 122.9(3) |
| O10 | C27 | C28 | 125.3(2) |
| O9 | C27 | C28 | 111.8(2) |
| C16 | C15 | C20 | 118.1(2) |
| C16 | C15 | C21 | 120.5(3) |
| C20 | C15 | C21 | 121.4(2) |
| O9 | C25 | C23 | 106.4(2) |
| O9 | C25 | C26 | 112.5(2) |
| C23 | C25 | C26 | 110.3(2) |
| C17 | C16 | C15 | 121.6(2) |
| C16 | C17 | C18 | 119.7(2) |
| O4 | C23 | C25 | 106.02(19) |
| O4 | C23 | C24 | 113.33(19) |
| C25 | C23 | C24 | 109.8(2) |
| C14 | C9 | C10 | 124.0(6) |
| C10 | C9 | C14A | 115.3(5) |
| C14 | C9 | C5 | 130.0(6) |
| C10 | C9 | C5 | 105.9(2) |
| C14A | C9 | C5 | 138.8(5) |
| C33A | C28 | C29 | 122.6(4) |
| C29 | C28 | C33 | 116.6(4) |
| C33A | C28 | C27 | 118.7(4) |
| C29 | C28 | C27 | 118.2(2) |
| C33 | C28 | C27 | 124.9(3) |
| C9 | C14 | C13 | 118.7(11) |
| C5 | C1 | C6 | 114.0(2) |
| C5 | C1 | C2 | 109.2(2) |
| C6 | C1 | C2 | 107.7(2) |
| O2 | C6 | O1 | 121.7(5) |
| O2A | C6 | O1A | 125.6(7) |
| O1AA | C6 | O2AA | 119.1(12) |
| O2A | C6 | C1 | 127.7(5) |
| O1AA | C6 | C1 | 119.8(9) |
| O2 | C6 | C1 | 124.1(4) |
| O1 | C6 | C1 | 112.1(4) |
| O1A | C6 | C1 | 104.8(5) |
| O2AA | C6 | C1 | 117.2(8) |
| C30 | C29 | C28 | 119.8(3) |
| C32 | C31 | C30 | 116.4(6) |
| C32 | C31 | C34 | 122(2) |
| C30 | C31 | C34 | 121(2) |
| C14 | C13 | C12 | 120.0(9) |
| C28 | C33 | C32 | 123.4(5) |
| C12 | C11 | C10 | 117.8(9) |
| C31A | C30 | C29 | 118.0(5) |
| C29 | C30 | C31 | 123.6(4) |
| C31 | C32 | C33 | 120.0(6) |
| C11 | C12 | C13 | 121.2(8) |
| O1 | C7 | C8 | 105.7(6) |
| C30 | C31A | C32A | 121.6(8) |
| C30 | C31A | C34A | 119(3) |
| C32A | C31A | C34A | 119(3) |
| C28 | C33A | C32A | 116.0(6) |
| C33A | C32A | C31A | 121.6(8) |
| C6 | O1A | C7A | 115.6(7) |
| O1A | C7A | C8A | 107.6(7) |
| C6 | O1AA | C7AA | 122(2) |
| O1AA | C7AA | C8AA | 107(2) |
| C13A | C14A | C9 | 119.5(9) |
| C12A | C13A | C14A | 122.1(7) |
| C11A | C12A | C13A | 121.1(6) |
| C12A | C11A | C10 | 117.5(7) |

**Table S17**: Torsion Angles in ° for **mC_gauss**.

| Atom | Atom | Atom | Atom | Angle/° |
|---|---|---|---|---|
| C23 | O4 | C22 | O3 | -0.9(3) |
| C23 | O4 | C22 | C18 | 177.0(2) |
| O3 | C22 | C18 | C17 | -156.3(3) |
| O4 | C22 | C18 | C17 | 25.9(3) |
| O3 | C22 | C18 | C19 | 28.3(4) |
| O4 | C22 | C18 | C19 | -149.5(2) |
| C10 | N2 | C4 | C5 | 0.2(3) |
| C10 | N2 | C4 | C3 | -178.8(3) |
| C17 | C18 | C19 | C20 | -0.8(4) |
| C22 | C18 | C19 | C20 | 174.7(2) |
| C5 | C4 | C3 | N1 | -17.4(4) |
| N2 | C4 | C3 | N1 | 161.4(2) |
| C2 | N1 | C3 | C4 | 48.3(3) |
| C4 | N2 | C10 | C11A | 174.2(5) |
| C4 | N2 | C10 | C9 | 0.4(4) |
| C4 | N2 | C10 | C11 | -168.1(7) |
| C18 | C19 | C20 | C15 | 1.7(4) |
| N2 | C4 | C5 | C9 | -0.6(3) |

| Atom | Atom | Atom | Atom | Angle/° |
|---|---|---|---|---|
| C3 | C4 | C5 | C9 | 178.3(3) |
| N2 | C4 | C5 | C1 | -177.0(2) |
| C3 | C4 | C5 | C1 | 1.9(4) |
| C3 | N1 | C2 | C1 | -65.8(3) |
| C25 | O9 | C27 | O10 | 0.5(4) |
| C25 | O9 | C27 | C28 | 179.9(2) |
| C19 | C20 | C15 | C16 | -0.7(4) |
| C19 | C20 | C15 | C21 | -179.9(3) |
| C27 | O9 | C25 | C23 | -153.6(2) |
| C27 | O9 | C25 | C26 | 85.5(3) |
| O7 | C26 | C25 | O9 | 176.8(2) |
| O8 | C26 | C25 | O9 | -2.2(3) |
| O7 | C26 | C25 | C23 | 58.2(3) |
| O8 | C26 | C25 | C23 | -120.8(2) |
| C20 | C15 | C16 | C17 | -1.2(5) |
| C21 | C15 | C16 | C17 | 178.1(3) |
| C15 | C16 | C17 | C18 | 2.0(5) |
| C19 | C18 | C17 | C16 | -1.0(5) |
| C22 | C18 | C17 | C16 | -176.4(3) |
| C22 | O4 | C23 | C25 | -161.1(2) |
| C22 | O4 | C23 | C24 | 78.5(3) |
| O9 | C25 | C23 | O4 | -61.3(2) |
| C26 | C25 | C23 | O4 | 61.0(3) |
| O9 | C25 | C23 | C24 | 61.4(2) |
| C26 | C25 | C23 | C24 | -176.24(19) |
| O5 | C24 | C23 | O4 | -179.5(2) |
| O6 | C24 | C23 | O4 | 0.6(3) |
| O5 | C24 | C23 | C25 | 62.1(3) |
| O6 | C24 | C23 | C25 | -117.7(2) |
| N2 | C10 | C9 | C14 | -177.3(11) |
| C11 | C10 | C9 | C14 | -6.9(11) |
| N2 | C10 | C9 | C14A | 178.0(8) |
| C11A | C10 | C9 | C14A | 4.0(8) |
| N2 | C10 | C9 | C5 | -0.7(4) |
| C11A | C10 | C9 | C5 | -174.7(5) |
| C11 | C10 | C9 | C5 | 169.7(6) |
| C4 | C5 | C9 | C14 | 177.1(12) |
| C1 | C5 | C9 | C14 | -6.8(13) |
| C4 | C5 | C9 | C10 | 0.8(3) |
| C1 | C5 | C9 | C10 | 176.8(3) |
| C4 | C5 | C9 | C14A | -177.4(11) |
| C1 | C5 | C9 | C14A | -1.3(12) |
| O10 | C27 | C28 | C33A | 179.4(5) |
| O9 | C27 | C28 | C33A | 0.0(6) |
| O10 | C27 | C28 | C29 | 7.2(5) |
| O9 | C27 | C28 | C29 | -172.2(3) |
| O10 | C27 | C28 | C33 | -166.1(5) |
| O9 | C27 | C28 | C33 | 14.5(6) |
| C10 | C9 | C14 | C13 | 0.4(19) |
| C5 | C9 | C14 | C13 | -175.4(7) |
| C4 | C5 | C1 | C6 | -135.9(3) |
| C9 | C5 | C1 | C6 | 48.6(4) |
| C4 | C5 | C1 | C2 | -15.3(4) |
| C9 | C5 | C1 | C2 | 169.1(3) |
| N1 | C2 | C1 | C5 | 45.1(3) |
| N1 | C2 | C1 | C6 | 169.4(2) |
| C7 | O1 | C6 | O2 | 14.1(11) |
| C7 | O1 | C6 | C1 | 178.3(6) |
| C5 | C1 | C6 | O2A | 26.7(8) |
| C2 | C1 | C6 | O2A | -94.7(7) |

| Atom | Atom | Atom | Atom | Angle/° |
|---|---|---|---|---|
| C5 | C1 | C6 | O1AA | -113.1(12) |
| C2 | C1 | C6 | O1AA | 125.5(12) |
| C5 | C1 | C6 | O2 | 5.5(6) |
| C2 | C1 | C6 | O2 | -115.9(6) |
| C5 | C1 | C6 | O1 | -158.2(5) |
| C2 | C1 | C6 | O1 | 80.4(6) |
| C5 | C1 | C6 | O1A | -168.7(6) |
| C2 | C1 | C6 | O1A | 69.9(6) |
| C5 | C1 | C6 | O2AA | 89.4(9) |
| C2 | C1 | C6 | O2AA | -32.0(9) |
| C33A | C28 | C29 | C30 | 7.3(7) |
| C33 | C28 | C29 | C30 | -7.0(6) |
| C27 | C28 | C29 | C30 | 179.2(3) |
| C9 | C14 | C13 | C12 | 3.1(19) |
| C29 | C28 | C33 | C32 | 3.8(8) |
| C27 | C28 | C33 | C32 | 177.2(5) |
| N2 | C10 | C11 | C12 | 177.3(6) |
| C9 | C10 | C11 | C12 | 9.7(10) |
| C28 | C29 | C30 | C31A | -4.9(8) |
| C28 | C29 | C30 | C31 | 6.5(7) |
| C32 | C31 | C30 | C29 | -2.1(10) |
| C34 | C31 | C30 | C29 | 178(2) |
| C30 | C31 | C32 | C33 | -1.3(11) |
| C34 | C31 | C32 | C33 | 178(2) |
| C28 | C33 | C32 | C31 | 0.4(11) |
| C10 | C11 | C12 | C13 | -6.7(13) |
| C14 | C13 | C12 | C11 | 0.2(15) |
| C6 | O1 | C7 | C8 | 162.3(7) |
| C29 | C30 | C31A | C32A | 0.8(12) |
| C29 | C30 | C31A | C34A | 175(3) |
| C29 | C28 | C33A | C32A | -5.2(10) |
| C27 | C28 | C33A | C32A | -177.0(6) |
| C28 | C33A | C32A | C31A | 1.0(13) |
| C30 | C31A | C32A | C33A | 1.1(15) |
| C34A | C31A | C32A | C33A | -173(3) |
| O2A | C6 | O1A | C7A | -10.6(14) |
| C1 | C6 | O1A | C7A | -175.6(7) |
| C6 | O1A | C7A | C8A | 171.5(9) |
| O2AA | C6 | O1AA | C7AA | -22(3) |
| C1 | C6 | O1AA | C7AA | -179.0(17) |
| C6 | O1AA | C7AA | C8AA | 103(3) |
| C10 | C9 | C14A | C13A | 0.3(14) |
| C5 | C9 | C14A | C13A | 178.3(5) |
| C9 | C14A | C13A | C12A | -2.6(15) |
| C14A | C13A | C12A | C11A | 0.7(12) |
| C13A | C12A | C11A | C10 | 3.3(11) |
| N2 | C10 | C11A | C12A | -178.7(5) |
| C9 | C10 | C11A | C12A | -5.8(9) |

**Table S18**: Hydrogen Fractional Atomic Coordinates (×10⁴) and Equivalent Isotropic Displacement Parameters (Å²×10³) for **mC_gauss**. $U_{eq}$ is defined as 1/3 of the trace of the orthogonalised $U_{ij}$.

| Atom | x | y | z | $U_{eq}$ |
|---|---|---|---|---|
| H6 | 5740 | -1160 | 6514 | 42 |
| H11B | 6368 | 6459 | 6625 | 65 |
| H2 | 3506 | 7854 | 4882 | 39 |
| H1A | 4782 | 7905 | 6418 | 32 |
| H1B | 4563 | 9528 | 6407 | 32 |
| H19 | 5811 | 3175 | 2943 | 30 |

| Atom | x | y | z | $U_{eq}$ |
|---|---|---|---|---|
| H3A | 4307 | 8073 | 5174 | 32 |
| H3B | 4263 | 6384 | 5795 | 32 |
| H20 | 6332 | 4311 | 2078 | 34 |
| H2A | 4633 | 8462 | 7921 | 37 |
| H2B | 4375 | 6843 | 7595 | 37 |
| H25 | 5293 | 3671 | 7516 | 32 |
| H16 | 7059 | 4202 | 4364 | 48 |
| H17 | 6533 | 3209 | 5256 | 41 |
| H23 | 5213 | 2906 | 5911 | 28 |
| H14 | 3146 | 10142 | 8130 | 45 |
| H1 | 4091 | 10327 | 7769 | 35 |
| H29 | 6200 | 3880 | 10185 | 49 |
| H21A | 7258 | 4165 | 2325 | 57 |
| H21B | 7264 | 5841 | 2958 | 57 |
| H21C | 6991 | 5781 | 2045 | 57 |
| H13 | 2466 | 10525 | 7735 | 46 |
| H33 | 6641 | 3032 | 7632 | 45 |
| H11 | 2653 | 8406 | 5146 | 47 |
| H30 | 6812 | 3032 | 10829 | 51 |
| H30A | 6839 | 3212 | 10816 | 51 |
| H32 | 7272 | 2447 | 8271 | 47 |
| H12 | 2220 | 9694 | 6239 | 47 |
| H35A | 6977 | 8598 | 6880 | 102 |
| H35B | 6740 | 7715 | 7698 | 102 |
| H35C | 6525 | 9114 | 7056 | 102 |
| H34A | 7623 | 3263 | 10393 | 105 |
| H34B | 7700 | 1869 | 9609 | 105 |
| H34C | 7482 | 1328 | 10535 | 105 |
| H7A | 3903 | 7445 | 10351 | 48 |
| H7B | 3703 | 9299 | 10475 | 48 |
| H8AA | 4692 | 8536 | 10608 | 61 |
| H8AB | 4418 | 8808 | 11485 | 61 |
| H8AC | 4483 | 10346 | 10776 | 61 |
| H33A | 6563 | 2542 | 7585 | 45 |
| H32A | 7186 | 1736 | 8252 | 47 |
| H34D | 7538 | 2575 | 10590 | 105 |
| H34E | 7699 | 2530 | 9560 | 105 |
| H34F | 7547 | 809 | 10033 | 105 |
| H7AA | 4071 | 7262 | 10311 | 48 |
| H7AB | 3852 | 9042 | 10523 | 48 |
| H8A | 4365 | 10416 | 10844 | 61 |
| H8B | 4523 | 8487 | 10856 | 61 |
| H8C | 4211 | 9102 | 11604 | 61 |
| H7AC | 3574 | 7742 | 10198 | 48 |
| H7AD | 3467 | 9690 | 10448 | 48 |
| H8AD | 4282 | 8510 | 10599 | 60 |
| H8AE | 3996 | 8362 | 11465 | 60 |
| H8AF | 4107 | 10202 | 11062 | 60 |
| H14A | 3057 | 10323 | 8047 | 45 |
| H13A | 2409 | 10664 | 7440 | 46 |
| H12A | 2250 | 10013 | 5906 | 47 |
| H11A | 2734 | 8956 | 4916 | 47 |

**Table S19**: Atomic Occupancies for all atoms that are not fully occupied in **mC_gauss**.

| Atom | Occupancy | Atom | Occupancy | Atom | Occupancy | Atom | Occupancy |
|---|---|---|---|---|---|---|---|
| O2 | 0.487(11) | C31 | 0.559(6) | H33 | 0.559(6) | H30A | 0.441(6) |
| O1 | 0.487(11) | C13 | 0.441(6) | C11 | 0.441(6) | C32 | 0.559(6) |
| C14 | 0.441(6) | H13 | 0.441(6) | H11 | 0.441(6) | H32 | 0.559(6) |
| H14 | 0.441(6) | C33 | 0.559(6) | H30 | 0.559(6) | C12 | 0.441(6) |

| Atom | Occupancy |
|---|---|
| H12 | 0.441(6) |
| C34 | 0.559(6) |
| H34A | 0.559(6) |
| H34B | 0.559(6) |
| H34C | 0.559(6) |
| C7 | 0.487(11) |
| H7A | 0.487(11) |
| H7B | 0.487(11) |
| C8A | 0.398(11) |
| H8AA | 0.398(11) |
| H8AB | 0.398(11) |
| H8AC | 0.398(11) |
| C31A | 0.441(6) |
| C33A | 0.441(6) |
| H33A | 0.441(6) |
| C32A | 0.441(6) |
| H32A | 0.441(6) |
| C34A | 0.441(6) |
| H34D | 0.441(6) |
| H34E | 0.441(6) |
| H34F | 0.441(6) |
| O12A | 0.559(6) |
| O2A | 0.398(11) |
| O1A | 0.398(11) |
| C7A | 0.398(11) |
| H7AA | 0.398(11) |
| H7AB | 0.398(11) |
| C8 | 0.487(11) |
| H8A | 0.487(11) |
| H8B | 0.487(11) |
| H8C | 0.487(11) |
| O1AA | 0.113(3) |
| C7AA | 0.113(3) |
| H7AC | 0.113(3) |
| H7AD | 0.113(3) |
| O2AA | 0.113(3) |
| C8AA | 0.113(3) |
| H8AD | 0.113(3) |
| H8AE | 0.113(3) |
| H8AF | 0.113(3) |
| O12 | 0.441(6) |
| C14A | 0.559(6) |
| H14A | 0.559(6) |
| C13A | 0.559(6) |
| H13A | 0.559(6) |
| C12A | 0.559(6) |
| H12A | 0.559(6) |
| C11A | 0.559(6) |
| H11A | 0.559(6) |

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