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Fluorinated isatin derivatives. Part 1: Synthesis of new N-substituted (*S*)-5-[1-(2-methoxymethylpyrrolidinyl)sulfonyl]isatins as potent caspase-3 and -7 inhibitors

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ABSTRACT

A series of new N-substituted (*S*)-5-[1-(2-methoxymethylpyrrolidinyl)sulfonyl]isatin derivatives has been synthesized and tested as inhibitors of caspases-3 and -7, which are known to be downstream enzymes critical in the execution of apoptosis. *N*-Propyl- and *N*-butyl isatins, as well as the corresponding terminal alcohols and regioisomeric fluorobutyl derivatives were shown to be excellent inhibitors having different binding potencies for caspases-3 and -7. In contrast, the corresponding fluoroethyl and fluoropropyl compounds were about 100–1000 times less active. Fluorinated *N*-benzyl isatins as well as trifluoroalkyl and difluoroalkyl derivatives were moderate inhibitors. However, isatins bearing different alkylether groups at *N*-1 are very weak or not active as inhibitors of caspases-3 and -7.

1. Introduction

Programmed cell death, called apoptosis, is induced by either receptor-mediated mechanisms, where a specific protein binds to a receptor on the cell surface and triggers the cell death signal (death receptor pathway), or direct damage of DNA by for example, toxic substances or radiation, followed by mitochondrial induction of the cell death program (mitochondrial pathway).[1] Both mechanisms trigger a complex cell death program—apoptosis—resulting in a complete removal of the concerned cell without inflammatory response. Downstream of the initial cellular process a class of intracellular 'death enzymes', caspases (*c*ysteinyl *asp*artate-specific prote*ases*) is activated.[1–3] Apoptosis is known to be present in many human diseases such as neurodegenerative diseases, cardiovascular diseases and others. Thus, apoptosis is an important target for novel drugs.[2,4] Therapeutic inhibition of caspase-3 and -7 has been indeed shown to prevent cells from apoptosis.[5]

Since caspases have been identified as suitable biological targets for anti-apoptotic strategies, it is reasonable to synthesize compounds, which specifically bind to the active site of these enzymes with high potency. Besides peptidic inhibitors,[6–8] the low molecular weight pyrrolidinylsulfonyl isatins are known to possess caspase inhibitory activity.[9,10] Recently, the therapeutic action of isatins as caspase inhibitors has been demonstrated.[11] It has been shown that the lead structure (*S*)-5-[1-(2-methoxymethylpyrrolidinyl)sulfonyl]isatin (**1**) perfectly fits into the active site of caspase-3.[5] Recently, we and others have also succeeded in the development of new radiotracers (compounds suitable for application in Positron Emission Tomography, PET) based on the isatin lead structure.[12–15]

Here, we report our recent results on the synthesis of a group of new fluorinated and non-fluorinated 5-pyrrolidinylsulfonyl isatins as caspase inhibitors. Some of them have been proven to exhibit excellent inhibitory activity for caspases-3 and -7.

2. Results and discussion

2.1. Chemistry

Based on the results of earlier work,[5,12] we initially prepared some basic non-fluorinated *N*-alkyl isatins **2b**–**2d**, some polar variants **2f**, **2h** and **2i** and several potential precursors **2e**, **2g** and **2j** for the preparation of fluorinated analogs **2k**–**2m** in order to deter-

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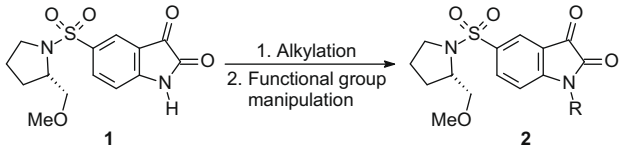
mine their inhibition activity towards caspases-3 and -7 (Scheme 1, Table 1).

Compounds **1** and **2a** have been prepared in previous work.[5,12] Compounds **2b**–**2f** and **2i** were synthesized by treatment in dry DMF of isatin **1** with the corresponding substituted alkyl bromides in presence of anhydrous K_2CO_3 giving the target N-alkylation products in 59–86% isolated yields. Subsequently, the hydroxyalkyl-isatin derivatives **2f** and **2i** were used as starting materials for further functional group manipulations. The mesylate **2g** and the tosylate **2j** were prepared by treatment of the alcohols **2f** and **2i** with mesyl- or tosyl chloride, respectively, in the presence of triethylamine. However, we failed to convert the mesylate **2g** to the terminal fluoride **2l** by nucleophilic substitution under different reaction conditions. Also, the direct treatment of the alcohol **2f** (prepared from **1** by reaction with 3-bromopropanol in presence of half an equivalent of K_2CO_3), with diethylaminosulfur trifluoride (DAST) failed to give **2l**. Instead, this reaction proceeded both at the terminal OH group and the C_3 carbonyl function to give the trifluoride **3b**. Similarly, treatment of the *N*-propyl derivative **2c** with DAST gave the 3,3-difluoro isatin **3a** (Scheme 2). Compound **2l** finally was prepared by direct base mediated alkylation of **1** with 1-bromo-3-fluoropropane.

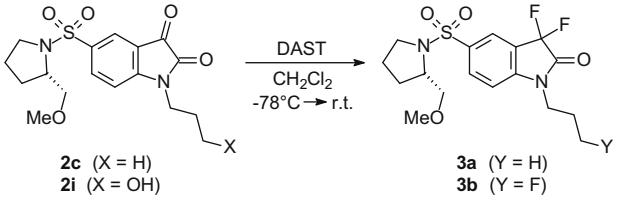


Scheme 1. Alkylation of the lead isatin derivative **1**.

Table 1
Yield and IC_{50} values of the lead compound **1** and synthesized *N*-alkyl isatin derivatives **2** and **3**–**10**

Compound	R	Yield (%)	IC_{50}[a] (nM)	
			Caspase-3	Caspase-7
1[5]	H	47	120 ± 26	170 ± 47
2a[12]	CH_3	82	2.4 ± 0.3	304 ± 73
2b	C_2H_5	59	183 ± 48	319 ± 59.8
2c	*n*-C_3H_7	65	5.3 ± 3.8	58 ± 15
2d	*n*-C_4H_9	86	29 ± 13	8.1 ± 1.1
2e	$C_2H_4CH_2Cl$	69	90 ± 36	79 ± 34
2f	$C_2H_4CH_2OH$	71	78 ± 26	52 ± 37
2g	$C_2H_4CH_2OMs$	40	230 ± 56	217 ± 70
2h	C_2H_4COOH	58	187 ± 56	129 ± 14
2i	$C_3H_6CH_2OH$	70	30 ± 4.8	11 ± 3.6
2j	$C_3H_6CH_2OTs$	61	56 ± 3	29 ± 5
2k	C_2H_4F	53	1840 ± 166	2940 ± 151
2l	$C_2H_4CH_2F$	42	5120 ± 1150	1440 ± 306
2m	$C_3H_6CH_2F$	70	41 ± 17	28 ± 6
2n	$(CH_2)_2CHFCH_3$	70	25 ± 3	6.8 ± 1.9
2o	$CH_2CF{=}CH_2$	44	499 ± 239	266 ± 96
2p	$(CH_2)_2CF{=}CF_2$	64	83 ± 7	178 ± 67
2q	$CH_2C_6H_4$-*p*-F	62	191 ± 107	44 ± 19
2r	$CH_2C_6H_4$-*p*-CF_3	38	82 ± 67	11 ± 9
2s	$CH_2C_6H_3$-3,5-$(CF_3)_2$	58	43 ± 2	135 ± 54
3a	*n*-C_3H_7	63	>100,000	>100,000
3b	$C_2H_4CH_2F$	30	6080 ± 2240	5640 ± 4350
4	$(CH_2)_3O(CH_2)_3OH$	72	60,900 ± 6660	113,000 ± 11,100
5	$[(CH_2)_3O]_2CH_2CH_2F$	45	9430 ± 2870	19,400 ± 2630
6	$(CH_2)_3O(CH_2)_3OMs$	85	>100,000	>100,000
7	$(CH_2)_3O(CH_2)_3F$	35	>100,000	>100,000
8	$CH_2CH(OH)CH_2Cl$	35	13.3 ± 8.9	123 ± 68
9a	$(CH_2)_2CF_3$	47	359 ± 210	40 ± 18
9b	$(CH_2)_3CF_3$	88	213 ± 6	100 ± 19
10	$(CH_2)_{10}CHF_2$	40	66 ± 12	111 ± 24

[a] Values are the mean of three assays.



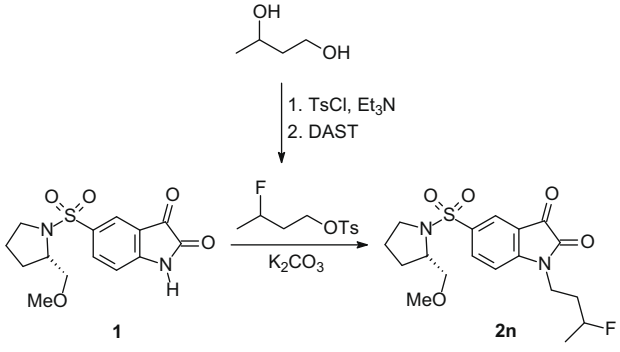
Scheme 2. Substitution of oxygen functions with DAST.

The 4-fluorobut-1-yl compound **2m** was found to be a highly active inhibitor for caspases-3 and -7 (see below). Based on this result, we were interested in the synthesis of the regioisomers **2n** bearing a secondary fluorine substituent. Thus, we first prepared the desired alkylation reagent, 3-fluorobutyltosylate from butan-1,3-diol by tosylation of the primary OH group and subsequent substitution of the secondary one with fluorine by treatment with DAST (Scheme 3).

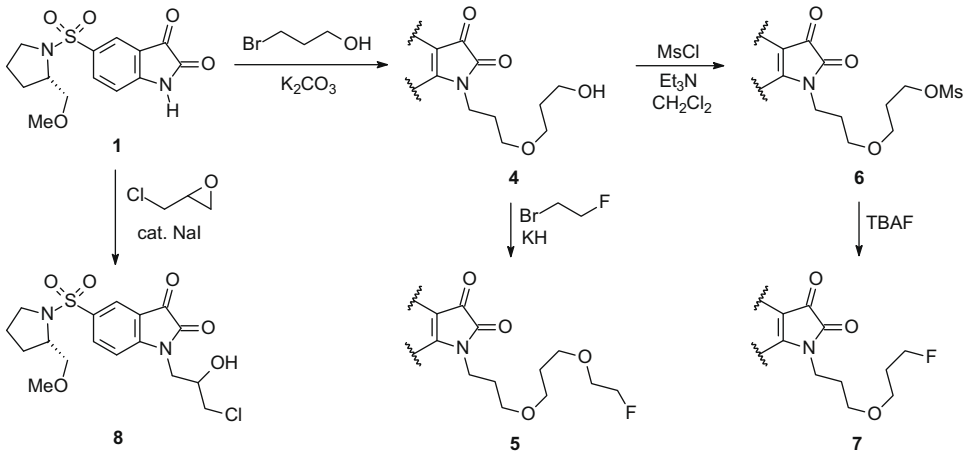
Also, *N*-alkenyl isatins bearing vinylic fluorine substituents were synthesized. Treatment of compound **1** with 2-fluoroallyltosylate[16,17] in presence of K_2CO_3 gave the corresponding *N*-allyl isatin **2o**, while the alkylation with 4-bromo-1,1,2-trifluorobut-1-ene gave **2p**, each in 64% yield. Fluorinated benzyl substituents were also introduced at the isatin nitrogen. In this way the *p*-fluoro- (**2q**), the *p*-trifluoromethyl- (**2r**) and the 3,5-bis-(trifluoromethyl)benzyl- (**2s**) isatins were synthesized from **1** by treatment with the corresponding benzylbromides in presence of NaH in dry DMF (Table 1).

In order to modify the polarity of the N-substituent, we also introduced ether functions. Thus, applying a different molar ratio of reactants, the reaction of **1** with 3-bromopropanol and K_2CO_3 (1:2:3) gave the hydroxyether **4**, which was transformed to the fluorinated dioxa derivative **5** by treatment with 1-bromo-2-fluoroethane and KH in DMF in the presence of catalytic amount of Bu_4NI. Furthermore, mesylation of **4** yielded compound **6**, which in turn was transformed to the terminal fluoride **7** by treatment with Bu_4NF in acetonitrile at elevated temperature (Scheme 4). Also, treatment of compound **1** with epichlorohydrin in presence of catalytic amounts of NaI provided the chlorohydrin **8** instead of the desired epoxide (Scheme 4).

We also were interested in the effect of trifluoromethylated and difluoromethylated *N*-alkyl groups on the inhibitory activity of isatin derivatives. Thus, the alkylation of **1** with 1-bromo-3,3,3-trifluoropropane, 1-bromo-4,4,4-trifluorobutane and 1-bromo-11,11-difluoroundecane[18] led to the target products **9a**, **9b** and **10**, respectively (Scheme 5).



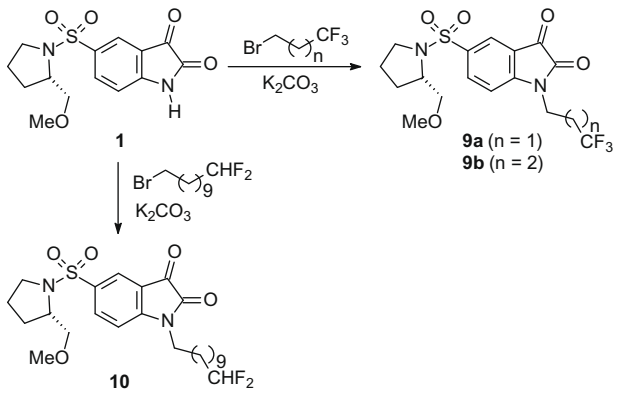
Scheme 3. Synthesis of isatin derivative **2n**.



Scheme 4. Synthesis of more polar isatin derivatives **4**–**8**.

2.2. Structure–activity relationships (SAR)

Among the simple *N*-alkyl isatins, the methyl[12] and the propyl derivatives **2a** and **2c** were shown to be excellent caspase-3 inhibitors with IC_{50} values as low as 2.4 or 5.3 nM, respectively, while the *n*-butyl isatin **2d** is an excellent caspase-7 inhibitor (IC_{50} = 8.1 nM). In contrast, the ethyl derivative **2b** was much less active against both caspases. The *N*-alkyl isatins **2e**–**2j** were moderate inhibitors of caspases-3 and -7. Surprisingly, the fluoroethyl- and fluoropropyl isatins **2k** and **2l** exhibited very weak inhibitory activity in the micromolar range, while the 4-fluorobut-1-yl-isatin **2m** is a rather potent inhibitor. The diastereomeric 3-fluorobut-1-yl derivatives **2n** are better inhibitors, particularly for caspase-7 with 3.5-fold higher inhibition potency as compared with caspase-3. Replacement of a saturated by an unsaturated fluorinated side chain led to a decrease of inhibitory activity. The 2-fluoroallyl derivative **2o** is a moderate inhibitor and the trifluoro derivative **2p** is only slightly more active. However, the fluorobenzylated compounds **2q**–**2s** are potent inhibitors. The *p*-trifluoromethyl derivative **2r** is a very active caspase-7 inhibitor (IC_{50} = 11 nM). Introduction of a trifluoromethyl group (compounds **9a** and **9b**) led to decreased inhibition potency in comparison to the simple alkyl counterparts (compounds **2c** and **2d**), however, compound **9a** shows a ninefold higher inhibition potency for caspase-7 compared with that of caspase-3. The long chain difluorinated compound **10** is a moderate inhibitor of caspases-3 and -7. All isatin derivatives bearing an alkyl ether function at the nitrogen were shown to be weakly or not active as caspase inhibitors. Isatins **3a** and **3b** bearing a difluoromethylene moiety instead of the 3-carbonyl function completely lost the activity.



Scheme 5. Synthesis of isatin derivatives **9a**, **9b** and **10**.

3. Conclusion

A series of fluorinated and non-fluorinated (*S*)-5-[1-(2-methoxymethylpyrrolidinyl) sulfonyl]isatins has been prepared as potential effector caspase inhibitors. A broad variety of N-substituents are tolerated without loss of caspase-3 and -7 inhibition potency. Among the substituted and unsubstituted alkyl chains, the butyl compounds were shown to be the most active caspase-3 and caspase-7 inhibitors. The 3-fluorobut-1-yl derivative **2n** was one of the most active caspase inhibitors and even more active than the 4-fluorobut-1-yl compound **2m**. Also terminal difluoroalkyl- and trifluoroalkyl compounds were shown to be moderate inhibitors, while compounds bearing fluorinated or non-fluorinated ether functions on *N*-1 are no inhibitors at all. Fluorinated or trifluoromethylated *N*-benzyl compounds have been shown to be moderate inhibitors of caspase-3 and caspase-7.

4. Experimental

4.1. General methods

All the chemicals, reagents and solvents for the synthesis of compounds were analytical grade and used without further purification, unless otherwise specified. ^{1}H NMR (300.13 MHz and 400.13 MHz), ^{13}C NMR (75.5 MHz and 100.63 MHz) and ^{19}F NMR (282.4 MHz) spectra were recorded in $CDCl_3$ with TMS for ^{1}H NMR, $CDCl_3$ for ^{13}C NMR and $CFCl_3$ for ^{19}F NMR as the internal standards. All chemical shift values were recorded in ppm (δ). Exact mass analyses were conducted on a Waters Quattro LC and a Bruker MicroTof apparatus. All spectroscopic and analytical investigations were performed by staff members of the Organic Chemistry Institute, University of Münster. Silica coated aluminium foils (Silica Gel 60 F_{254}) from MERCK with 0.2 mm layer thickness were used for thin layer chromatography (TLC). Column chromatography was usually performed on silica gel (60–120 mesh) using suitable solvent mixtures. 1-Bromo-3-fluoropropane was prepared from 3-bromopropanol with DAST[19] and 1-tosyloxybutan-3-ol[20] from butane-1,3-diol according to published protocols. 2-Fluoroallyl tosylate[17] and 11-bromo-1,1-difluoroundecane[18] were synthesized as described elsewhere.

4.1.1. 4-Bromobutyl pivalate

To a cooled (−20 °C) solution of 4-bromobutanol (500 mg, 3.26 mmol) in dry CH_2Cl_2 (5 mL), pivaloyl chloride (0.44 mL, 3.59 mmol) followed by triethylamine (0.55 mL, 3.92 mmol) were slowly added under argon atmosphere. The reaction mixture was initially stirred at −15 to −20 °C for 1 h and then at ambient temperature for 14–16 h. The work-up procedure was the same as mentioned in procedure C (see below). The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:19) to yield a colourless oil. Yield: 450 mg (58%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (s, 9H), 1.78–1.97 (m, 4H), 3.46 (t, 2H, $^3J_{H,H}$ = 6.5 Hz), 4.11 (t, 2H, $^3J_{H,H}$ = 6.3 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.2, 27.3, 29.4, 33.2, 38.8, 63.4, 178.5 ppm.

4.1.2. 1-Fluoro-3-tosyloxybutane

3-Tosyloxybutan-1-ol (200 mg, 0.81 mmol) was converted to 1-fluoro-3-tosyloxybutane using fresh DAST (0.21 mL, 1.63 mmol) as described in the general procedure C (see below) except that addition of DAST was carried out at 0 °C and the reaction mixture was initially stirred at the same temperature for 30 min and then at ambient temperature for 14 h followed by quenching with chilled water and not with saturated $NaHCO_3$ solution. The crude product was purified by column chromatography (ethyl acetate/cyclohexane 3:7) to yield a dense colourless oil. Yield: 170 mg (84%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (dd, 3H, $^3J_{H,H}$ = 6.2 Hz, $^3J_{H,F}$ = 23.9 Hz), 1.85–2.00 (m, 2H), 2.45 (s, 3H), 4.16 (t, 2H, $^3J_{H,H}$ = 6.0 Hz). 4.63–4.88 (m, 1H), 7.36 (d, 2H, $^3J_{H,H}$ = 8.0 Hz), 7.80 (d, 2H, $^3J_{H,H}$ = 8.3 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.9 (d, $^2J_{C,F}$ = 22.2 Hz), 21.6, 36.2 (d, $^2J_{C,F}$ = 21.1 Hz), 66.5 (d, $^3J_{C,F}$ = 4.9 Hz), 86.9 (d, $^1J_{C,F}$ = 165.9 Hz), 127.9 (2C), 130.0 (2C), 132.7, 144.9 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −177.1 (m, 1F) ppm. HRMS (ESI-MicroTof): *m*/*e* 269.0606 $(M+Na)^+$, calcd for $C_{11}H_{15}FNaO_3S$ 269.0618.

4.1.3. General procedure for the synthesis of N-1-alkylated derivatives (procedure A)

To a solution of (*S*)-5-[1-(2-methoxymethylpyrrolidinyl)sulfonyl]isatin (**1**) in dry DMF (3 mL) in a round-bottomed flask, anhydrous potassium carbonate (2.5–3.2 equiv) was added under argon atmosphere and the reaction mixture was stirred at ambient temperature for 30 min. An excess of the alkylating reagent, (2–3 equiv) was slowly added and the reaction mixture was stirred at ambient temperature for 6–48 h (depending on the type of electrophile used) followed by dilution with 20 mL of ethyl acetate and subsequent filtration after 15 min of further stirring. Removal of the solvents in vacuo yielded the crude products, which were then purified by silica gel chromatography.

4.1.4. General procedure for the synthesis of N-1-alkylated derivatives (procedure B)

5-[1-(2-Methoxymethylpyrrolidinyl)sulfonyl]isatin (**1**) was placed in a round-bottomed flask and dissolved in 50 mL of dry dimethylformamide. Under an argon-atmosphere, 1.5 equiv of sodium hydride were added. During stirring for 30 min at ambient temperature the solution turned dark red. An excess of the corresponding benzylbromides were added and the reaction mixture was stirred for further 2 or 3 h at ambient temperature. Removal of the solvent in vacuo afforded the crude products, which were purified by silica gel chromatography.

4.1.5. General procedure for the synthesis of mesylates (procedure C)

To a solution of the alcohols **2f**, **2i** and **4** and 4-dimethylaminopyridine (DMAP, 0.05 equiv) in dry CH_2Cl_2 (5 mL), fresh MsCl (1.2 equiv) followed by dry triethylamine (1.2 equiv) were added at −10 °C under argon atmosphere. The reaction mixture was then stirred at −10 to 0 °C for 1.5–2.0 h followed by dilution with excess CH_2Cl_2 (20 mL) and quenching with 0.1 N HCl solution (2 mL). The two layers were separated and the organic layer was washed with water (10 mL). The aqueous layer was again extracted with CH_2Cl_2 (10 mL) and the combined organic extracts were dried over $MgSO_4$. Filtration, followed by removal of the solvent in vacuo resulted in the crude products, which were then purified by silica gel chromatography.

4.1.6. General procedure for the synthesis of *gem*-difluoro derivatives (of isatin carbonyl moiety—procedure D)

To a solution of the starting material in dry CH_2Cl_2 (3–6 mL), fresh DAST (2.0–3.2 equiv) was added dropwise at −78 °C under argon atmosphere and the reaction mixture was initially stirred below −60 °C for 1 h and then at ambient temperature for 6–14 h. The reaction mixture was then cooled to 0 °C, diluted with an excess CH_2Cl_2 (10 mL) and then quenched with chilled saturated $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were dried over $MgSO_4$. Filtration, followed by the removal of the solvent in vacuo yielded the crude products, which were then purified by silica gel chromatography.

4.1.6.1. (*S*)-1-Ethyl-5-[1-(2-methoxymethylpyrrolidinyl)sulfonyl]isatin (2b). (*S*)-5-[1-(2-Methoxymethylpyrrolidinyl)sulfonyl]isatin (**1**) (50 mg, 0.154 mmol) was converted to **2b** using anhydrous K_2CO_3 (53 mg, 0.386 mmol) and ethyl bromide (0.022 mL, 0.308 mmol) as described in the general procedure A and stirred for 14 h. The crude product was purified by column chromatography (ethyl acetate/cyclohexane 3:2) to yield a golden yellow coloured gummy solid. Yield: 32 mg (59%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 (t, 3H, $^3J_{H,H}$ = 7.2 Hz), 1.60–1.72 (m, 2H), 1.86–1.95 (m, 2H), 3.09–3.17 (m, 1H), 3.35–3.48 (m, 2H), 3.37 (s, 3H), 3.60 (dd, 1H, $^2J_{Hb,Ha}$ = 9.4 Hz, $^3J_{Hb,H}$ = 3.8 Hz), 3.73–3.77 (m, 1H), 3.88 (q, 2H, $^3J_{H,H}$ = 7.2 Hz), 7.05 (d, 1H, $^3J_{H,H}$ = 8.2 Hz), 8.05–8.12 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.5, 24.1, 28.8, 35.5, 49.4, 59.1, 59.2, 74.9, 110.2, 117.4, 124.6, 133.7, 137.5, 153.4, 157.5, 182.2. HRMS (ESI-MicroTof): *m*/*e* 407.1244 $(M+Na+-CH_3OH)^+$, calcd for $C_{17}H_{24}N_2NaO_6S$ 407.1247.

4.1.6.2. (*S*)-5-[1-(2-Methoxymethylpyrrolidinyl)sulfonyl]-1-propylisatin (2c). (*S*)-5-[1-(2-Methoxymethylpyrrolidinyl)sulfonyl]isatin (**1**) (50 mg, 0.154 mmol) was converted to **2c** using anhydrous K_2CO_3 (53 mg, 0.386 mmol) and *n*-propyl bromide (0.028 mL, 0.308 mmol) as described in the general procedure A and stirred for 8 h. The crude product was purified by column chromatography (ethyl acetate/cyclohexane 3:2) to yield a golden yellow coloured gummy solid. Yield: 37 mg (65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04 (t, 3H, $^3J_{H,H}$ = 7.3 Hz), 1.64–1.80 (m, 4H, $^3J_{H,H}$ = 7.4 Hz), 1.89–1.95 (m, 2H), 3.11–3.15 (m, 1H), 3.35–3.48 (m, 2H), 3.37 (s, 3H), 3.60 (dd, 1H, $^2J_{Hb,Ha}$ = 9.4 Hz, $^3J_{Hb,H}$ = 3.8 Hz), 3.73–3.78 (m, 3H), 7.04 (d, 1H, $^3J_{H,H}$ = 8.3 Hz), 8.05 (d, 1H, $^4J_{H,H}$ = 1.6 Hz), 8.10 (dd, 1H, $^3J_{H,H}$ = 8.3 Hz, $^4J_{H,H}$ = 1.7 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.4, 20.7, 24.1, 28.8, 42.3, 49.4, 59.1, 59.2, 74.8, 110.4, 117.3, 124.6, 133.6, 137.5, 153.8, 157.8, 182.2 ppm. HRMS (ESI-MicroTof): *m*/*e* 421.1409 $(M+Na+CH_3OH)^+$, calcd for $C_{18}H_{26}N_2NaO_6S$ 421.1404.

4.1.6.3. (*S*)-1-Butyl-5-[1-(2-methoxymethylpyrrolidinyl)sulfonyl]isatin (2d). (*S*)-5-[1-(2-Methoxymethylpyrrolidinyl)sulfonyl]isatin (**1**) (30 mg, 0.093 mmol) was converted to **2d** using anhydrous K_2CO_3 (32 mg, 0.231 mmol) and *n*-butyl bromide (0.02 mL, 0.185 mmol) as described in the general procedure A and stirred for 6 h. The crude product was purified by column chromatography (ethyl acetate/cyclohexane 3:2) to yield a golden yellow coloured solid. Yield: 32 mg (86%). ^{1}H NMR (300 MHz,

$CDCl_3$): δ 1.00 (t, 3H, $^3J_{H,H}$ = 7.3 Hz), 1.48 (sextuplet, 2H, $^3J_{H,H}$ = 7.4 Hz), 1.65–1.76 (m, 4H), 1.89–1.95 (m, 2H), 3.10–3.18 (m, 1H), 3.35–3.47 (m, 2H), 3.37 (s, 3H), 3.60 (dd, 1H, $^2J_{Hb,Ha}$ = 9.4 Hz, $^3J_{Hb,H}$ = 3.8 Hz), 3.73–3.80 (m, 3H), 7.04 (d, 1H, $^3J_{H,H}$ = 8.3 Hz), 8.04 (d, 1H, $^4J_{H,H}$ = 1.7 Hz), 8.10 (dd, 1H, $^3J_{H,H}$ = 8.3 Hz, $^4J_{H,H}$ = 1.9 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.6, 20.1, 24.1, 28.8, 29.2, 40.5, 49.3, 59.1, 59.2, 74.8, 110.4, 117.4, 124.5, 133.7, 137.5, 153.7, 157.8, 182.2 ppm. HRMS (ESI-MicroTof): *m*/*e* 435.1558 $(M+Na+CH_3OH)^+$, calcd for $C_{19}H_{28}N_2NaO_6S$ 435.1563.

4.1.6.4. (*S*)-1-(3-Chloropropyl)-5-[1-(2-methoxymethylpyrrolidinyl)sulfonyl]isatin (2e). (*S*)-5-[1-(2-Methoxymethylpyrrolidinyl)sulfonyl]isatin (**1**) (200 mg, 0.617 mmol) was converted to **2e** using anhydrous K_2CO_3 (213 mg, 1.54 mmol) and 1-bromo-3-chloropropane (0.02 mL, 0.185 mmol) as described in the general procedure A and stirred for 6 h. The crude product was purified by column chromatography (ethyl acetate/cyclohexane 3:2) to yield a golden yellow coloured solid. Yield: 171 mg (69%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.63–1.73 (m, 2H), 1.86–1.94 (m, 2H), 2.25 (quintet, 2H, $^3J_{H,H}$ = 6.5 Hz), 3.10–3.16 (m, 1H), 3.35–3.46 (m, 2H), 3.36 (s, 3H), 3.59 (dd, 1H, $^2J_{Hb,Ha}$ = 9.4 Hz, $^3J_{Hb,H}$ = 3.9 Hz), 3.70 (t, 2H, $^3J_{H,H}$ = 6.0 Hz), 3.71–3.77 (m, 1H), 4.00 (t, 2H, $^3J_{H,H}$ = 7.0 Hz), 7.20 (d, 1H, $^3J_{H,H}$ = 8.3 Hz), 8.03 (d, 1H, $^4J_{H,H}$ = 1.8 Hz), 8.11 (dd, 1H, $^3J_{H,H}$ = 8.3 Hz, $^4J_{H,H}$ = 1.9 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.1, 28.8, 30.0, 38.2, 42.0, 49.3, 59.1, 59.2, 74.8, 110.4, 117.4, 124.6, 134.0, 137.6, 153.4, 158.0, 181.8 ppm. HRMS (ESI-MicroTof): *m*/*e* 423.0743 $(M+Na)^+$, calcd for $C_{17}H_{21}ClN_2NaO_5S$ 423.0752.

4.1.6.5. (*S*)-1-(3-Hydroxypropyl)-5-[1-(2-methoxymethylpyrrolidinyl)sulfonyl]isatin (2f). (*S*)-5-[1-(2-Methoxymethylpyrrolidinyl)sulfonyl]isatin (**1**) (800 mg, 2.47 mmol) was converted to **2f** using anhydrous K_2CO_3 (187 mg, 1.358 mmol) and 3-bromopropanol (0.65 mL, 7.40 mmol) as described in the general procedure A and stirred for 48 h. The crude product was purified by column chromatography (5% MeOH in CH_2Cl_2) to yield a golden yellow coloured solid. Yield: 675 mg (71%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.66–2.09 (m, 7H), 3.07–3.19 (m, 1H), 3.35–3.48 (m, 2H), 3.37 (s, 3H), 3.60 (dd, 1H, $^2J_{Hb,Ha}$ = 9.4 Hz, $^3J_{Hb,H}$ = 3.9 Hz), 3.70–3.83 (m, 3H, $^3J_{H,H}$ = 5.6 Hz), 3.96 (t, 2H, $^3J_{H,H}$ = 6.6 Hz), 7.17 (d, 1H, $^3J_{H,H}$ = 8.3 Hz), 8.05 (d, 1H, $^4J_{H,H}$ = 1.7 Hz), 8.11 (dd, 1H, $^3J_{H,H}$ = 8.3 Hz, $^4J_{H,H}$ = 1.9 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.1, 28.8, 29.7, 37.4, 49.3, 59.0, 59.1, 59.2, 74.8, 110.6, 117.4, 124.5, 134.0, 137.6, 153.6, 158.4, 182.0 ppm. HRMS (ESI-MicroTof): *m*/*e* 437.1358 $(M+Na)^+$, calcd for $C_{18}H_{26}N_2NaO_7S$ 437.1353.

4.1.6.6. (*S*)-3-{5-[1-(2-Methoxymethylpyrrolidinyl)sulfonyl]-2,3-dioxoindolin-1-yl}propyl methanesulfonate (2g). (*S*)-1-(3-Hydroxypropyl)-5-[1-(2-methoxymethylpyrrolidinyl)-sulfonyl] isatin (**2f**) (100 mg, 0.26 mmol) was converted to **2g** using DMAP (1.5 mg, 0.013 mmol), fresh MsCl (0.024 mL, 0.31 mmol) and dry triethylamine (0.043 mL, 0.314 mmol) as described in the general procedure C and stirred for 1 h. The crude product was purified by column chromatography (1% MeOH in CH_2Cl_2) to yield a dull yellow coloured gummy solid. Yield: 48 mg (40%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.62–1.94 (m, 4H), 2.18–2.24 (m, 2H), 3.03–3.15 (m, 1H), 3.06 (s, 3H), 3.35–3.47 (m, 2H), 3.37 (s, 3H), 3.60 (dd, 1H, $^2J_{Hb,Ha}$ = 9.4 Hz, $^3J_{Hb,H}$ = 3.9 Hz), 3.73–3.78 (m, 1H), 3.97 (t, 2H, $^3J_{H,H}$ = 6.9 Hz), 4.34 (t, 2H, $^3J_{H,H}$ = 5.7 Hz), 7.11 (d, 1H, $^3J_{H,H}$ = 8.3 Hz), 8.08 (d, 1H, $^4J_{H,H}$ = 1.7 Hz), 8.14 (dd, 1H, $^3J_{H,H}$ = 8.3 Hz, $^4J_{H,H}$ = 1.9 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.1, 27.2, 28.8, 37.3, 37.6, 49.4, 59.1, 59.2, 66.9, 74.8, 110.4, 117.4, 124.8, 134.2, 137.7, 153.6, 158.7, 181.5 ppm. HRMS (ESI-MicroTof): *m*/*e* 483.0871 $(M+Na)^+$, calcd for $C_{18}H_{24}N_2NaO_8S_2$ 483.0866.

4.1.6.7. (*S*)-3-{5-[1-(2-Methoxymethylpyrrolidinyl)sulfonyl]-2,3-dioxoindolin-1-yl}propanoic acid (2h). A mixture of a saturated solution of aqueous $NaHCO_3$ (0.4 mL, 0.131 mmol) and a 1 M NaOCl solution (0.13 mL, 0.14 mmol) was added to a solution of (*S*)-1-(3-hydroxypropyl)-5-[1-(2-methoxymethylpyrrolidinyl)sulfonyl]isatin (**2f**) (50 mg, 0.13 mmol), 2 M KBr solution (0.01 mL, 0.013 mmol) and 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO, 0.0026 mmol) in CH_2Cl_2/H_2O (1:1, 2 mL) at 0 °C and the reaction mixture was stirred at the same temperature for 1.5–2 h followed by quenching with MeOH (0.5 mL), neutralization with 10% HCl and evaporation to dryness in vacuo. The crude product was then purified by column chromatography (10% MeOH in CH_2Cl_2) to yield a golden yellow coloured sticky solid. Yield: 30 mg (58%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.60–1.74 (m, 2H), 1.85–1.94 (m, 2H), 2.67 (t, 2H, $^3J_{H,H}$ = 7.4 Hz), 3.08–3.17 (m, 1H), 3.27–3.40 (m, 2H), 3.35 (s, 3H), 3.55–4.07 (m, 4H), 7.27 (m, 2H, isatinAr*H*, $CHCl_3$), 7.92–8.14 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.0, 28.7, 35.3, 39.8, 49.4, 59.1, 59.2, 74.9, 110.0, 117.4, 124.6, 133.5, 137.7, 153.3, 159.2, 170.8, 182.8 ppm. HRMS (ESI-MicroTof): *m*/*e* 419.0908 $(M+Na)^+$, calcd for $C_{17}H_{20}N_2NaO_7S$ 419.0883.

4.1.6.8. (*S*)-1-(4-Hydroxybutyl)-5-[1-(2-methoxymethylpyrrolidinyl)sulfonyl]isatin (2i). (*S*)-5-[1-(2-Methoxymethylpyrrolidinyl)sulfonyl]isatin (**1**) (320 mg, 2.47 mmol) was converted to **2i** using anhydrous K_2CO_3 (272 mg, 1.97 mmol) and 4-bromobutyl pivalate (700 mg, 2.96 mmol) as described in the general procedure A and stirred for 12 h followed by dilution with an excess water (10 mL) and complete extraction with CH_2Cl_2 (3 × 10 mL). The organic extracts were dried over $MgSO_4$, filtered and the solvent was removed completely in vacuo to afford the crude product. It was dissolved in 1,4-dioxane (10 mL) and a 4 N HCl solution (5 mL) was added. The above mixture was then heated at 80–90 °C for 8–10 h followed by complete evaporation under vacuum. The residue was purified by column chromatography (initially with ethyl acetate/toluene 9:1) to separate the non-polar impurities followed by final elution with 5% MeOH in CH_2Cl_2 to yield a golden yellow coloured sticky solid. Yield: 275 mg (70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.65–1.93 (m, 9H), 3.09–3.17 (m, 1H), 3.35–3.44 (m, 2H), 3.37 (s, 3H), 3.61 (dd, 1H, $^2J_{Hb,Ha}$ = 9.4 Hz, $^3J_{Hb,H}$ = 3.8 Hz), 3.72–3.79 (m, 3H, $^3J_{H,H}$ = 6.0 Hz), 3.85 (t, 2H, $^3J_{H,H}$ = 7.2 Hz), 7.08 (d, 1H, $^3J_{H,H}$ = 8.3 Hz), 8.05 (d, 1H, $^4J_{H,H}$ = 1.7 Hz), 8.10 (dd, 1H, $^3J_{H,H}$ = 8.3 Hz, $^4J_{H,H}$ = 1.9 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.9, 24.1, 28.8, 29.4, 40.5, 49.4, 59.1, 59.2, 62.0, 74.9, 110.5, 117.4, 124.6, 133.8, 137.5, 153.6, 157.9, 182.1 ppm. HRMS (ESI-MicroTof): *m*/*e* 419.1265 $(M+Na)^+$, calcd for $C_{18}H_{24}N_2NaO_6S$ 419.1247.

4.1.6.9. (*S*)-4-{5-[1-(2-Methoxymethylpyrrolidinyl)sulfonyl]-2,3-dioxoindolin-1-yl}butyl 4-methyl-benzenesulfonate (2j). (*S*)-1-(4-Hydroxybutyl)-5-[1-(2-methoxymethylpyrrolidinyl)-sulfonyl] isatin (**2i**) (230 mg, 0.58 mmol) was converted to **2j** using DMAP (14.0 mg, 0.116 mmol), fresh TsCl (166 mg, 0.87 mmol) and dry triethylamine (0.12 mL, 0.87 mmol) as described in the general procedure C except that the reaction mixture was initially stirred at 0 °C for 30 min and then at ambient temperature for 12 h. Also, after dilution with CH_2Cl_2, the reaction mixture was washed with water and not quenched with 0.1 N HCl solution as mentioned in the general procedure. The crude product was purified by column chromatography (ethyl acetate/toluene 7:3) to yield a light orange coloured gummy solid. Yield: 195 mg (61%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.67–1.94 (m, 8H), 2.45 (s, 3H), 3.09–3.17 (m, 1H), 3.36–3.48 (m, 2H), 3.37 (s, 3H), 3.61 (dd, 1H, $^2J_{Hb,Ha}$ = 9.4 Hz, $^3J_{Hb,H}$ = 3.8 Hz), 3.72–3.81 (m, 3H, $^3J_{H,H}$ = 6.7 Hz), 4.09 (t, 2H, $^3J_{H,H}$ = 5.6 Hz), 7.07 (d, 1H, $^3J_{H,H}$ = 8.3 Hz), 7.36 (d, 2H, $^3J_{H,H}$ = 8.0 Hz), 7.77 (d, 2H, $^3J_{H,H}$ = 8.3 Hz), 8.06 (d, 1H, $^4J_{H,H}$ = 1.8 Hz), 8.12 (dd, 1H, $^3J_{H,H}$ = 8.3 Hz, $^4J_{H,H}$ = 1.9 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.7, 23.4, 24.1, 26.2, 28.8, 39.9, 49.4, 59.1,

59.2, 69.3, 74.9, 110.5, 117.4, 124.7, 127.9 (2C), 130.0 (2C), 132.6, 133.9, 137.6, 145.1, 153.3, 157.9, 181.9 ppm. HRMS (ESI-MicroTof): *m*/*e* 573.1331 $(M+Na)^+$, calcd for $C_{25}H_{30}N_2NaO_8S_2$ 573.1336.

4.1.6.10. (*S*)-1-(2-Fluoroethyl)-5-[1-(2-methoxymethylpyrrolidinyl)sulfonyl]isatin (2k). (*S*)-5-[1-(2-Methoxymethylpyrrolidinyl)sulfonyl]isatin (**1**) (50 mg, 0.154 mmol) was converted to **2k** using anhydrous K_2CO_3 (53 mg, 0.385 mmol) and freshly distilled 1-bromo-2-fluoroethane (0.023 mL, 0.308 mmol) as described in the general procedure A and stirred for 14 h. The crude product was purified by column chromatography (ethyl acetate/cyclohexane 7:3) to yield an orange-yellow coloured solid. Yield: 31 mg (53%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.60–1.75 (m, 2H), 1.85–1.96 (m, 2H), 3.08–3.16 (m, 1H), 3.34–3.47 (m, 2H), 3.36 (s, 3H), 3.60 (dd, 1H, $^2J_{Hb,Ha}$ = 9.4 Hz, $^3J_{Hb,H}$ = 3.9 Hz), 3.71–3.78 (m, 1H), 4.11 (dt, 2H, $^3J_{H,H}$ = 4.6 Hz, $^3J_{H,F}$ = 26.9 Hz), 4.80 (dt, 2H, $^2J_{H,F}$ = 47.0 Hz, $^3J_{H,H}$ = 4.5 Hz), 7.20 (d, 1H, $^3J_{H,H}$ = 8.3 Hz), 8.05 (d, 1H, $^4J_{H,H}$ = 1.5 Hz), 8.10 (dd, 1H, $^3J_{H,H}$ = 8.3 Hz, $^4J_{H,H}$ = 1.9 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.1, 28.8, 41.4 (d, $^2J_{C,F}$ = 20.4 Hz), 49.4, 59.1, 59.2, 74.8, 81.9 (d, $^1J_{C,F}$ = 171.8 Hz), 111.3 (d, $^5J_{C,F}$ = 4.4 Hz), 117.3, 124.5, 134.0, 137.5, 153.7, 157.9, 181.5 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −220.1 (dtt, 1F, $^2J_{H,F}$ = 53.8 Hz, $^3J_{H,F}$ = 26.8 Hz, $^6J_{H,F}$ = 1.0 Hz) ppm. HRMS (ESI-MicroTof): *m*/*e* 425.1148 $(M+Na+CH_3OH)^+$, calcd for $C_{17}H_{23}FN_2NaO_6S$ 425.1153.

4.1.6.11. (*S*)-1-(3-Fluoropropyl)-5-[1-(2-methoxymethylpyrrolidinyl)sulfonyl]isatin (2l). (*S*)-5-[1-(2-Methoxymethylpyrrolidinyl)sulfonyl]isatin (**1**) (70 mg, 0.216 mmol) was converted to **2l** using anhydrous K_2CO_3 (74.5 mg, 0.540 mmol) and crude 1-bromo-3-fluoropropane (0.06 mL, 0.648 mmol) as described in the general procedure A and stirred for 36 h. The crude product was purified by column chromatography (ethyl acetate/cyclohexane 3:2) to yield an orange-yellow coloured solid. Yield: 35 mg (42%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.61–1.76 (m, 2H), 1.85–1.96 (m, 2H), 2.20 (d of quintet, 2H, $^3J_{H,H}$ = 6.7 Hz, $^3J_{H,F}$ = 27.5 Hz), 3.10–3.18 (m, 1H), 3.35–3.48 (m, 2H), 3.37 (s, 3H), 3.60 (dd, 1H, $^2J_{Hb,Ha}$ = 9.4 Hz, $^3J_{Hb,H}$ = 3.9 Hz), 3.72–3.80 (m, 1H), 3.96 (t, 2H, $^3J_{H,H}$ = 7.0 Hz), 4.60 (dt, 2H, $^2J_{H,F}$ = 47.0 Hz, $^3J_{H,H}$ = 5.4 Hz), 7.11 (d, 1H, $^3J_{H,H}$ = 8.3 Hz), 8.07 (d, 1H, $^4J_{H,H}$ = 1.7 Hz), 8.12 (dd, 1H, $^3J_{H,H}$ = 8.3 Hz, $^4J_{H,H}$ = 1.9 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.1, 28.4 (d, $^2J_{C,F}$ = 20.0 Hz), 28.8, 37.2 (d, $^3J_{C,F}$ = 4.3 Hz), 49.4, 59.1, 59.2, 74.8, 81.0 (d, $^1J_{C,F}$ = 166.1 Hz), 110.3, 117.4, 124.7, 134.0, 137.6, 153.5, 158.0, 181.8 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −221.2 (tt, 1F, $^2J_{H,F}$ = 55.1 Hz, $^3J_{H,F}$ = 27.6 Hz) ppm. HRMS (ESI-MicroTof): *m*/*e* 407.1049 $(M+Na)^+$, calcd for $C_{17}H_{21}FN_2NaO_5S$ 407.1047.

4.1.6.12. (*S*)-1-(4-Fluorobutyl)-5-[1-(2-methoxymethylpyrrolidinyl)sulfonyl]isatin (2m). (*S*)-5-[1-(2-Methoxymethylpyrrolidinyl)sulfonyl]isatin (**1**) (50 mg, 0.154 mmol) was converted to **2m** using anhydrous K_2CO_3 (53 mg, 0.385 mmol) and 1-bromo-4-fluorobutane (0.033 mL, 0.308 mmol) as described in the general procedure A and stirred for 10 h. The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:1) to yield an orange-yellow coloured solid. Yield: 43 mg (70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.64–1.95 (m, 8H), 3.11–3.17 (m, 1H), 3.35–3.47 (m, 2H), 3.37 (s, 3H), 3.60 (dd, 1H, $^2J_{Hb,Ha}$ = 9.4 Hz, $^3J_{Hb,H}$ = 3.9 Hz), 3.71–3.79 (m, 1H), 3.86 (t, 2H, $^3J_{H,H}$ = 6.9 Hz), 4.54 (dt, 2H, $^2J_{H,F}$ = 47.0 Hz, $^3J_{H,H}$ = 5.3 Hz), 7.07 (d, 1H, $^3J_{H,H}$ = 8.3 Hz), 8.05 (d, 1H, $^4J_{H,H}$ = 1.8 Hz), 8.10 (dd, 1H, $^3J_{H,H}$ = 8.3 Hz, $^4J_{H,H}$ = 1.9 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.5 (d, $^3J_{C,F}$ = 4.0 Hz), 24.1, 27.6 (d, $^2J_{C,F}$ = 20.1 Hz), 28.8, 40.2, 49.4, 59.1, 59.2, 74.8, 83.3 (d, $^1J_{C,F}$ = 165.6 Hz), 110.4, 117.4, 124.6, 133.8, 137.5, 153.4, 157.8, 182.0 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −219.4 (tt, 1F, $^2J_{H,F}$ = 53.1 Hz, $^3J_{H,F}$ = 26.6 Hz) ppm. HRMS (ESI-MicroTof): *m*/*e* 453.1460 $(M+Na+CH_3OH)^+$, calcd for $C_{19}H_{27}FN_2NaO_6S$ 453.1465.

4.1.6.13. (*S*)-1-(3-Fluorobutyl)-5-[1-(2-methoxymethylpyrrolidinyl)sulfonyl]isatin (2n). (*S*)-5-[1-(2-Methoxymethylpyrrolidinyl)sulfonyl]isatin (**1**) (35 mg, 0.108 mmol) was converted to **2n** using anhydrous K_2CO_3 (37 mg, 0.27 mmol) and 3-fluorobutyl 4-methylbenzenesulfonate (53 mg, 0.216 mmol) as described in the general procedure A and stirred for 14 h. The crude product was purified by column chromatography (ethyl acetate/toluene 3:2) to yield an orange-yellow coloured solid. Yield: 31 mg (70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.45 (dd, 3H, $^3J_{H,H}$ = 6.2 Hz, $^3J_{H,F}$ = 24.0 Hz), 1.65–1.74 (m, 2H), 1.85–2.09 (m, 4H), 3.09–3.17 (m, 1H), 3.35–3.48 (m, 2H), 3.36 (s, 3H), 3.60 (dd, 1H, $^2J_{Hb,Ha}$ = 9.4 Hz, $^3J_{Hb,H}$ = 3.8 Hz), 3.72–3.79 (m, 1H), 3.95 (t, 2H, $^3J_{H,H}$ = 7.3 Hz), 4.64–4.86 (m, 1H), 7.12 (d, 1H, $^3J_{H,H}$ = 8.3 Hz), 8.05 (d, 1H, $^4J_{H,H}$ = 1.7 Hz), 8.11 (dd, 1H, $^3J_{H,H}$ = 8.3 Hz, $^4J_{H,H}$ = 1.9 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.0 (d, $^2J_{C,F}$ = 22.3 Hz), 24.1, 28.8, 34.5 (d, $^2J_{C,F}$ = 20.8 Hz), 37.1 (d, $^3J_{C,F}$ = 4.1 Hz), 49.4, 59.1, 59.2, 74.8, 88.4 (d, $^1J_{C,F}$ = 166.0 Hz), 110.4, 117.3, 124.6, 133.8, 137.6, 153.5, 157.9, 181.9 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −175.6 (m, 1F, $^2J_{H,F}$ = 51.1 Hz, $^3J_{H,F}$ = 24.0 Hz, $^3J_{H,F}$ = 27.3 Hz). HRMS (ESI-MicroTof): *m*/*e* 421.1204 $(M+Na)^+$, calcd for $C_{18}H_{23}FN_2NaO_5S$ 421.1205.

4.1.6.14. (*S*)-1-(2-Fluoroallyl)-5-[1-(2-methoxymethylpyrrolidinyl)sulfonyl]isatin (2o). (*S*)-5-[1-(2-Methoxymethylpyrrolidinyl)sulfonyl]isatin (**1**) (100 mg, 0.3 mmol) was converted to **2o** using anhydrous K_2CO_3 (106 mg, 0.77 mmol) and 2-fluoroallyl tosylate (212 mg, 0.925 mmol) as described in the general procedure A and stirred for 14 h. The crude product was purified by column chromatography (ethyl acetate/toluene 1:1) to yield a golden yellow coloured gummy solid. Yield: 52 mg (44%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.68–1.69 (m, 2H), 1.91–1.98 (m, 2H), 3.10–3.15 (m, 1H), 3.35–3.46 (m, 2H), 3.36 (s, 3H), 3.59 (dd, 1H, $^2J_{Hb,Ha}$ = 9.4 Hz, $^3J_{Hb,H}$ = 3.7 Hz), 3.70–3.79 (m, 1H), 4.51 (d, 2H, $^3J_{H,F}$ = 13.0 Hz), 4.64–4.81 (dd, 1H, $^2J_{Ha,Hb}$ = 3.5 Hz, $^3J_{Ha,F}$ = 47.4 Hz), 4.94 (dd, 1H, $^2J_{Hb,Ha}$ = 3.6 Hz, $^3J_{Hb,F}$ = 16.0 Hz), 7.14 (d, 1H, $^3J_{H,H}$ = 7.8 Hz), 8.08–8.11 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.2, 28.8, 40.9 (d, $^2J_{C,F}$ = 33.6 Hz), 49.4, 59.1, 59.2, 74.8, 95.0 (d, $^2J_{C,F}$ = 16.9 Hz), 111.1, 117.4, 124.6, 134.3, 137.5, 152.8, 157.3, 158.1 (d, $^1J_{C,F}$ = 262.2 Hz), 181.1 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −102.4 to −102.7 (m, 1F, $^3J_{Ha,F}$ = 47.4 Hz, $^3J_{Hb,F}$ = 28.6 Hz, $^3J_{H,F}$ = 12.9 Hz) ppm. HRMS (ESI-MicroTof): *m*/*e* 437.1149 $(M+Na+CH_3OH)^+$, calcd for $C_{18}H_{23}FN_2NaO_6S$ 437.1153.

4.1.6.15. (*S*)-5-[1-(2-Methoxymethylpyrrolidinyl)sulfonyl]-1-(3,4,4-trifluorobut-3-enyl)isatin (2p). (*S*)-5-[1-(2-Methoxymethylpyrrolidinyl)sulfonyl]isatin (**1**) (200 mg, 0.617 mmol) was converted to **2p** using anhydrous K_2CO_3 (210 mg, 1.54 mmol) and 4-bromo-1,1,2-trifluorobut-1-ene (0.14 mL, 1.234 mmol) as described in the general procedure A and stirred at 35–40 °C for 18 h. The crude product was purified by column chromatography (ethyl acetate/cyclohexane 7:3) to yield a deep orange coloured solid. Yield: 171 mg (64%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.64–1.71 (m, 2H), 1.89–1.94 (m, 2H), 2.71–2.81 (m, 2H), 3.13–3.19 (m, 1H), 3.36–3.47 (m, 2H), 3.36 (s, 3H), 3.59 (dd, 1H, $^2J_{Hb,Ha}$ = 9.4 Hz, $^3J_{Hb,H}$ = 3.9 Hz), 3.74–3.80 (m, 1H), 4.02 (t, 2H, $^3J_{H,H}$ = 6.7 Hz), 7.05 (d, 1H, $^3J_{H,H}$ = 8.3 Hz), 8.08 (d, 1H, $^4J_{H,H}$ = 1.7 Hz), 8.13 (dd, 1H, $^3J_{H,H}$ = 8.3 Hz, $^4J_{H,H}$ = 1.9 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.1, 24.5 (dd, $^2J_{C,F}$ = 22.0 Hz, $^3J_{C,F}$ = 2.4 Hz), 28.8, 36.9 (m, $^3J_{C,F}$ = 2.6 Hz), 49.4, 59.1, 59.2, 74.8, 109.9, 117.4, 124.8, 134.4, 137.6, 152.9, 157.7, 181.3 ppm, (signals for the two non-protonated carbons (–*C*F=*C*F$_2$) are not detectable). ^{19}F NMR (282 MHz, $CDCl_3$): δ −100.9 (dd, 1F, $^2J_{Fb,Fc}$ = 81.1 Hz, $^3J_{Fb,Fa}$ = 33.0 Hz), −121.9 (ddt, 1F, $^2J_{Fc,Fb}$ = 81.1 Hz, $^3J_{Fc,Fa}$ = 115.0 Hz, $^4J_{H,Fc}$ = 3.8 Hz), −174.6 (ddt, 1F, $^3J_{H,Fa}$ = 21.6 Hz, $^3J_{Fa,Fb}$ = 33.0 Hz, $^3J_{Fa,Fc}$ = 115.0 Hz) ppm. HRMS (ESI-MicroTof): *m*/*e* 487.1114 $(M+Na+CH_3OH)^+$, calcd for $C_{19}H_{23}F_3N_2NaO_6S$ 487.1121.

4.1.6.16. (*S*)-4-Fluorobenzyl-5-[1-(2-methoxymethylpyrrolidinyl) sulfonyl]isatin (2q). (*S*)-5-[1-(2-Methoxymethylpyrrolidinyl)sulfonyl]isatin (**1**) (324 mg, 1 mmol) was converted to **2q** using sodium hydride (60 mg, 1.5 mmol, 60% in mineral oil) and 4-fluorobenzyl bromide (0.37 mL, 567 mg, 3 mmol) as described in the general procedure B. The crude orange product was purified by silica gel chromatography (cyclohexane/ethyl acetate 1:1) and yielded **2q** as a yellow solid. Yield: 298 mg (0.69 mmol, 69%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.64–1.69 (m, 2H), 1.85–1.90 (m, 2H), 3.13–3.19 (m, 1H), 3.33 (s, 3H), 3.34–3.39 (m, 2H), 3.54 (dd, 1H, $^2J_{Hb,Ha}$ = 9.4 Hz, $^3J_{Hb,H}$ = 3.9 Hz), 3.71–3.76 (m, 1H), 4.94 (s, 2H), 6.91 (d, 1H, $^3J_{H,H}$ = 8.3 Hz), 7.03–7.09 (m, 2H), 7.31–7.36 (m, 2H), 7.98 (dd, 1H, $^3J_{H,H}$ = 8.3 Hz, $^4J_{H,H}$ = 1.9 Hz), 8.04 (d, 1H, $^4J_{H,H}$ = 1.9 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.4, 30.1, 45.0, 50.6, 60.3, 60.5, 76.1 112.3, 117.4 (d, $^2J_{C,F}$ = −22 Hz), 118.8, 125.8, 130.7, 131.0 (d, $^3J_{C,F}$ = −3 Hz), 135.7, 138.6, 154.3, 161.6 (d, $^1J_{C,F}$ = −248 Hz), 165.6, 182.9 ppm, ^{19}F NMR (282 MHz, $CDCl_3$): δ −113.1 (s, 1F) ppm. HRMS (ESI-MicroTof): *m*/*e* 487.1315 (M+Na+-CH_3OH)$^+$, calcd for $C_{22}H_{25}FN_2NaO_6S$ 487.1302.

4.1.6.17. (*S*)-4-Trifluoromethylbenzyl-5-[1-(2-methoxymethylpyrrolidinyl)sulfonyl]isatin (2r). (*S*)-5-[1-(2-Methoxymethylpyrrolidinyl)sulfonyl]isatin (**1**) (324 mg, 1 mmol) was converted to **2r** using sodium hydride (60 mg, 1.5 mmol, 60% in mineral oil) and 4-trifluorobenzyl bromide (580 mg, 3 mmol) as described in the general procedure B. The crude orange product was purified by silica gel chromatography (diisopropyl ether/acetone 9:1) and yielded **2r** as a yellow foam. Yield: 175 mg (0.38 mmol, 38%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.64–1.69 (m, 2H), 1.85–1.90 (m, 2H), 3.13–3.18 (m, 1H), 3.34 (s, 3H), 3.32–3.40 (m, 2H), 3.55 (dd, 1H, $^2J_{Hb,Ha}$ = 9.4 Hz, $^3J_{Hb,H}$ = 3.9 Hz), 3.69–3.73 (m, 1H), 5.04 (s, 2H), 6.87 (d, 1H, $^3J_{H,H}$ = 8.3 Hz), 7.46–7.50 (m, 2H), 7.63–7.66 (m, 2H), 7.98 (dd, 1H, $^3J_{H,H}$ = 8.3 Hz, $^4J_{H,H}$ = 1.9 Hz), 8.06 (d, 1H, $^4J_{H,H}$ = 1.9 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.4, 30.1, 45.3, 50.6, 60.3, 60.5, 76.1 110.9, 117.5, 124.6, 126.2, 126.3, 127.8, 130.8 (q, $^2J_{C,F}$ = −32.3 Hz), 134.4, 137.4, 137.8, 152.8, 157.8, 181.4 ppm, ^{19}F NMR (282 MHz, $CDCl_3$): δ −62.9 (s, 3F) ppm. HRMS (ESI-MicroTof): *m*/*e* 537.1272 (M+Na+CH_3OH)$^+$, calcd for $C_{23}H_{25}F_3N_2NaO_6S$ 537.1282.

4.1.6.18. (*S*)-3,5-Bis-trifluoromethylbenzyl-5-[1-(2-methoxymethylpyrrolidinyl)sulfonyl]isatin (2s). (*S*)-5-[1-(2-Methoxymethylpyrrolidinyl)sulfonyl]isatin (**1**) (324 mg, 1 mmol) was converted to **2s** using sodium hydride (60 mg, 1.5 mmol, 60% in mineral oil) and 3,5-bis-trifluorobenzyl bromide (0.27 mL, 454 g, 1.5 mmol) as described in the general procedure B. The crude orange product was purified by silica gel chromatography (cyclohexane/ethyl acetate 3:1 to 2:1) and yielded **2s** as a yellow oil. Yield: 320 g (0.58 mmol, 58%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.64–1.68 (m, 2H), 1.86–1.89 (m, 2H), 3.07–3.11 (m, 1H), 3.31 (s, 3H), 3.31–3.35 (m, 2H), 3.53 (dd, 1H, $^2J_{Hb,Ha}$ = 9.4 Hz, $^3J_{Hb,H}$ = 3.9 Hz), 3.69–3.73 (m, 1H), 5.11 (s, 2H), 6.90 (d, 1H, $^3J_{H,H}$ = 8.3 Hz), 7.82 (br s, 2H), 7.88 (br s, 1H), 8.00 (dd, 1H, $^3J_{H,H}$ = 8.3 Hz, $^4J_{H,H}$ = 1.9 Hz), 8.05 (d, 1H, $^4J_{H,H}$ = 1.9 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.5, 29.2, 44.1, 49.7, 59.4, 59.6, 75.1, 111.1, 118.0, 121.0, 122.9 (q, $^1J_{C,F}$ = −270.7 Hz), 124.8, 127.6, 132.6 (q, $^2J_{C,F}$ = −32.7 Hz), 134.6, 136.7, 137.4, 152.4, 157.9, 181.0 ppm, ^{19}F NMR (282 MHz, $CDCl_3$): δ −63.1 (s, 6F) ppm. HRMS (ESI-MicroTof): *m*/*e* 605.1137 (M+Na+-CH_3OH)$^+$, calcd for $C_{24}H_{24}F_6N_2NaO_6S$ 605.1151.

4.1.6.19. (*S*)-3,3-Difluoro-1-propyl-5-[1-(2-methoxymethylpyrrolidinyl)sulfonyl]indolin-2-one (3a). (*S*)-5-[1-(2-Methoxymethylpyrrolidinyl)sulfonyl]-1-propylisatin (**2c**) (30 mg, 0.082 mmol) was converted to **3a** using fresh DAST (0.026 mL, 0.205 mmol) as described in the general procedure D and stirred at ambient temperature for 6 h. The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:1) to yield an off-white coloured gummy solid. Yield: 20 mg (63%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01 (t, 3H, $^3J_{H,H}$ = 7.4 Hz), 1.66–1.79 (m, 4H), 1.89–2.08 (m, 2H), 3.11–3.19 (m, 1H), 3.36–3.48 (m, 2H), 3.37 (s, 3H), 3.61 (dd, 1H, $^2J_{Hb,Ha}$ = 9.4 Hz, $^3J_{Hb,H}$ = 3.9 Hz), 3.72 (t, 2H, $^3J_{H,H}$ = 7.2 Hz), 3.75–3.81 (m, 1H), 7.03 (dd, 1H, $^3J_{H,H}$ = 8.0 Hz, $^5J_{H,H}$ = 0.8 Hz), 8.00–8.03 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.2, 20.5, 24.1, 28.8, 42.2, 49.3, 59.1, 59.2, 74.9, 109.8, 111.0 (t, $^1J_{C,F}$ = 251.3 Hz), 121.0 (t, $^2J_{C,F}$ = 23.5 Hz), 124.3, 133.6, 133.7, 147.1 (t, $^3J_{C,F}$ = 6.6 Hz), 165.2 (t, $^2J_{C,F}$ = 30.2 Hz) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −112.6 (d, 2F, $^5J_{H,F}$ = 1.2 Hz) ppm. HRMS (ESI-MicroTof): *m*/*e* 411.1160 (M+Na)$^+$, calcd for $C_{17}H_{22}F_2N_2NaO_4S$ 411.1161.

4.1.6.20. (*S*)-3,3-Difluoro-1-(3-fluoropropyl)-5-[1-(2-methoxymethylpyrrolidinyl)sulfonyl]indolin-2-one (3b). (*S*)-1-(3-Hydroxypropyl)-5-[1-(2-methoxymethylpyrrolidinyl)sulfonyl]-isatin (**2f**) (50 mg, 0.13 mmol) was converted to **3b** using fresh DAST (0.055 mL, 0.41 mmol) as described in the general procedure D and stirred at ambient temperature for 14 h. The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:1) to yield an off-white coloured gummy solid. Yield: 16 mg (30%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.65–1.72 (m, 2H), 1.89–1.95 (m, 2H), 2.06–2.19 (m, 2H), 3.11–3.17 (m, 1H), 3.36–3.47 (m, 2H), 3.37 (s, 3H), 3.60 (dd, 1H, $^2J_{Hb,Ha}$ = 9.4 Hz, $^3J_{Hb,H}$ = 3.9 Hz), 3.75–3.81 (m, 1H), 3.91 (t, 2H, $^3J_{H,H}$ = 7.0 Hz), 4.55 (dt, 2H, $^2J_{H,F}$ = 47.0 Hz, $^3J_{H,H}$ = 5.4 Hz), 7.09 (d, 1H, $^3J_{H,H}$ = 8.9 Hz), 8.02–8.04 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.1, 28.2 (d, $^2J_{C,F}$ = 20.1 Hz), 28.8, 37.2 (d, $^3J_{C,F}$ = 4.3 Hz), 49.3, 59.1, 59.2, 74.9, 80.9 (d, $^1J_{C,F}$ = 166.4 Hz), 109.8 (d, $^4J_{C,F}$ = 1.4 Hz), 110.9 (t, $^1J_{C,F}$ = 251.5 Hz), 120.9 (t, $^2J_{C,F}$ = 23.4 Hz), 124.4, 133.7, 134.0 (d, $^4J_{C,F}$ = 1.8 Hz), 146.9 (t, $^3J_{C,F}$ = 6.4 Hz), 165.3 (t, $^2J_{C,F}$ = 30.2 Hz) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −112.5 (s, 2F), −221.2 (tt, 1F, $^2J_{H,F}$ = 54.9 Hz, $^3J_{H,F}$ = 27.5 Hz) ppm. HRMS (ESI-MicroTof): *m*/*e* 429.1066 (M+Na)$^+$, calcd for $C_{17}H_{21}F_3N_2NaO_4S$ 429.1066.

4.1.6.21. (*S*)-1-[3-(3-Hydroxypropoxy)propyl]-5-[1-(2-methoxymethylpyrrolidinyl)sulfonyl]isatin (4). (*S*)-5-[1-(2-Methoxymethylpyrrolidinyl)sulfonyl]isatin (**1**) (500 mg, 1.54 mmol) was converted to **4** using anhydrous K_2CO_3 (680 mg, 4.938 mmol) and 3-bromopropanol (0.30 mL, 3.395 mmol) as described in the general procedure A and stirred for 36 h. The crude product was purified by column chromatography (4% MeOH in CH_2Cl_2) to yield a pale yellow coloured gummy solid. Yield: 490 mg (72%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.54–1.94 (m, 8H), 3.09–3.17 (m, 1H), 3.32–3.49 (m, 6H), 3.37 (s, 3H), 3.60 (dd, 1H, $^2J_{Hb,Ha}$ = 9.4 Hz, $^3J_{Hb,H}$ = 3.8 Hz), 3.70–3.83 (m, 3H, $^3J_{H,H}$ = 6.2 Hz), 3.84 (t, 2H, $^3J_{H,H}$ = 7.1 Hz), 7.01 (d, 1H, $^3J_{H,H}$ = 8.2 Hz), 8.06 (d, 1H, $^4J_{H,H}$ = 1.7 Hz), 8.10 (dd, 1H, $^3J_{H,H}$ = 8.2 Hz, $^4J_{H,H}$ = 1.9 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.1, 25.2, 28.8, 29.7, 36.0, 49.3, 58.6, 59.0, 59.1, 61.2, 61.3, 75.1, 110.6, 117.4, 124.5, 134.0, 137.6, 153.6, 158.4, 182.0 ppm. HRMS (ESI-MicroTof): *m*/*e* 463.1514 (M+Na)$^+$, calcd for $C_{20}H_{28}N_2NaO_7S$ 463.1509.

4.1.6.22. (*S*)-1-{3-[3-(2-Fluoroethoxy)propoxy]propyl}-5-[1-(2-methoxymethylpyrrolidinyl)-sulfonyl]isatin (5). To a solution of (*S*)-1-[3-(3-Hydroxypropoxy)propyl]-5-[1-(2-methoxymethylpyrrolidinyl)sulfonyl]isatin (**4**) (60 mg, 0.136 mmol) in dry DMF (2 mL) KH (20% suspension in oil) (33.0 mg, 0.163 mmol) was added under argon atmosphere at −10 °C. The reaction mixture was initially stirred at the same temperature for 30 min and at ambient temperature for 1 h and then, catalytic amount of TBAI together with freshly distilled 1-bromo-2-fluoroethane (0.02 mL, 0.273 mmol) were added. The above mixture was stirred at ambient temperature for 96 h and then quenched with water (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 15 mL), the combined organic layers were dried over $MgSO_4$, filtered and the solvent

evaporated completely in vacuo. The resulting crude product was purified by column chromatography (ethyl acetate/cyclohexane 2:3) to yield an off-white coloured gummy solid. Yield: 30 mg (45%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.63–1.96, (m, 8H), 3.09–3.18 (m, 1H), 3.32–3.59 (m, 10H), 3.37 (s, 3H), 3.60 (dd, 1H, $^2J_{Hb,Ha}$ = 9.4 Hz, $^3J_{Hb,H}$ = 3.8 Hz), 3.71–3.80 (m, 1H), 3.81 (t, 2H, $^3J_{H,H}$ = 6.8 Hz), 4.55 (dt, 2H, $^2J_{H,F}$ = 47.0 Hz, $^3J_{H,H}$ = 5.4 Hz), 7.13 (d, 1H, $^3J_{H,H}$ = 8.3 Hz), 8.07 (d, 1H, $^4J_{H,H}$ = 1.5 Hz), 8.13 (dd, 1H, $^3J_{H,H}$ = 8.3 Hz, $^4J_{H,H}$ = 1.9 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.1, 27.6, 28.8, 29.7, 36.8, 49.4, 59.1, 59.2, 61.2, 61.3, 68.0, 70.1 (d, $^2J_{C,F}$ = 20.0 Hz), 75.3, 83.0 (d, $^1J_{C,F}$ = 166.9 Hz), 110.4, 117.4, 124.6, 133.9, 137.5, 153.7, 158.5, 181 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −222.7 (tt, 1F, $^2J_{H,F}$ = 54.3 Hz, $^3J_{H,F}$ = 27.5 Hz) ppm. HRMS (ESI-MicroTof): *m*/*e* 509.1722 $(M+Na)^+$, calcd for $C_{22}H_{31}FN_2NaO_7S$ 509.1728.

4.1.6.23. (*S*)-3-{3-[5-(1-(2-Methoxymethylpyrrolidinyl)sulfonyl)-2,3-dioxoindolin-1-yl]propoxy}-propyl methanesulfonate (6). (*S*)-1-[3-(3-Hydroxypropoxy)propyl]-5-[1-(2-methoxymethylpyrrolidinyl)sulfonyl]isatin (**4**) (137 mg, 0.311 mmol) was converted to **6** using DMAP (1.9 mg, 0.015 mmol), fresh MsCl (0.029 mL, 0.37 mmol) and dry triethylamine (0.052 mL, 0.37 mmol) as described in the general procedure C and stirred for 1 h. The crude product was purified by column chromatography (1% MeOH in CH_2Cl_2) to yield an off-white coloured gummy solid. Yield: 120 mg (85%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.61–1.96 (m, 8H), 3.02–3.11 (m, 1H), 3.04 (s, 3H), 3.32–3.49 (m, 6H), 3.36 (s, 3H), 3.61 (dd, 1H, $^2J_{Hb,Ha}$ = 9.4 Hz, $^3J_{Hb,H}$ = 3.8 Hz), 3.72–3.79 (m, 1H), 3.83 (t, 2H, $^3J_{H,H}$ = 6.8 Hz), 4.20 (t, 2H, $^3J_{H,H}$ = 5.7 Hz), 7.11 (d, 1H, $^3J_{H,H}$ = 8.2 Hz), 8.07 (d, 1H, $^4J_{H,H}$ = 1.8 Hz), 8.13 (dd, 1H, $^3J_{H,H}$ = 8.2 Hz, $^4J_{H,H}$ = 1.9 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.1, 25.2, 27.2, 28.8, 36.2, 37.5, 49.3, 59.0, 59.2, 61.2, 61.3, 66.8, 75.1, 110.4, 117.4, 124.8, 134.2, 137.6, 153.6, 158.4, 182.0 ppm. HRMS (ESI-MicroTof): *m*/*e* 541.1287 $(M+Na)^+$, calcd for $C_{21}H_{30}N_2NaO_9S_2$ 541.1285.

4.1.6.24. (*S*)-1-[3-(3-Fluoropropoxy)propyl]-5-[1-(2-methoxymethylpyrrolidinyl)sulfonyl]isatin (7). To a solution of (*S*)-3-[5-{1-(2-methoxymethylpyrrolidinyl)sulfonyl}-2,3-dioxoindolin-1-yl]propyl methanesulfonate (**2g**) (200 mg, 0.386 mmol) in acetonitrile (5 mL) TBAF·3H$_2$O (245 mg, 0.772 mmol) was added under argon atmosphere. The reaction mixture was heated at 50 °C for 6 h and the solvent evaporated in vacuo. The resulting crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:1) to yield an off-white coloured gummy solid. Yield: 60 mg (35%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.60–1.96 (m, 6H), 2.11 (m, 2H, $^3J_{H,H}$ = 6.3 Hz, $^3J_{H,F}$ = 27.1 Hz), 3.10–3.19 (m, 1H), 3.32–3.58 (m, 6H), 3.39 (s, 3H), 3.66 (dd, 1H, $^2J_{Hb,Ha}$ = 9.2 Hz, $^3J_{Hb,H}$ = 3.8 Hz), 3.72–3.79 (m, 1H), 3.82 (t, 2H, $^3J_{H,H}$ = 7.0 Hz), 4.52 (dt, 2H, $^2J_{H,F}$ = 47.0 Hz, $^3J_{H,H}$ = 5.5 Hz), 7.12 (d, 1H, $^3J_{H,H}$ = 8.2 Hz), 8.06 (d, 1H, $^4J_{H,H}$ = 1.7 Hz), 8.12 (dd, 1H, $^3J_{H,H}$ = 8.2 Hz, $^4J_{H,H}$ = 1.9 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.1, 25.2, 28.4 (d, $^2J_{C,F}$ = 21.2 Hz), 28.8, 36.0, 49.3, 59.1, 59.2, 61.2 (d, $^3J_{C,F}$ = 3.8 Hz), 61.3, 74.8, 81.0 (d, $^1J_{C,F}$ = 165.9 Hz), 110.3, 117.5, 124.7, 134.0, 137.6, 153.5, 158.4, 182.0 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −221.0 (tt, 1F, $^2J_{H,F}$ = 54.3 Hz, $^3J_{H,F}$ = 27.2 Hz) ppm. HRMS (ESI-MicroTof): *m*/*e* 465.1465 $(M+Na)^+$, calcd for $C_{20}H_{27}FN_2NaO_6S$ 465.1466.

4.1.6.25. (*S*)-1-(3-Chloro-2-hydroxypropyl)-5-[1-(2-methoxymethylpyrrolidinyl)sulfonyl]isatin (8). To a round-bottomed flask, (*S*)-5-[1-(2-methoxymethylpyrrolidinyl)sulfonyl]isatin (**1**) (100 mg, 0.308 mmol) and sodium hydride (7.4 mg, 0.308 mmol) were suspended in epichlorohydrin (0.75 mL, 9.0 mmol) under argon atmosphere and the reaction mixture was stirred at ambient temperature for 48 h. At this stage a catalytic amount of sodium iodide was added and stirred for additional 48 h. The golden brown reaction mixture was concentrated in vacuo and the resulting crude product was purified by column chromatography (ethyl acetate/cyclohexane 4:1) to yield a yellow-orange coloured solid. Yield: 45 mg (35%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.61–1.71 (m, 2H), 1.82–1.93 (m, 2H), 3.08–3.16 (m, 1H), 3.31–3.47 (m, 2H), 3.35 (s, 3H), 3.57 (dd, 1H, $^2J_{Hb,Ha}$ = 9.4 Hz, $^3J_{Hb,H}$ = 3.9 Hz), 3.60–3.76 (m, 3H), 3.90 (dd, 1H, $^2J_{Ha,Hb}$ = 14.6 Hz, $^3J_{Ha,Hc}$ = 7.3 Hz), 4.01 (dd, 1H, $^2J_{Hb,Ha}$ = 14.6 Hz, $^3J_{Hb,Hc}$ = 3.6 Hz), 4.23–4.29 (m, 1H), 7.26 (d, 1H, $^3J_{H,H}$ = 8.4 Hz), 7.96 (d, 1H, $^4J_{H,H}$ = 1.9 Hz), 8.02 (dd, 1H, $^3J_{H,H}$ = 8.4 Hz, $^4J_{H,H}$ = 1.9 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.2, 28.9, 44.5, 47.2, 49.4, 59.1, 59.3, 69.8, 74.9, 111.9, 117.4, 124.3, 134.0, 137.4, 154.1, 158.7, 181.7 ppm. HRMS (ESI-MicroTof): *m*/*e* 439.0700 $(M+Na)^+$, calcd for $C_{17}H_{21}ClN_2NaO_6S$ 439.0701.

4.1.6.26. (*S*)-5-[1-(2-Methoxymethylpyrrolidinyl)sulfonyl]-1-(3,3,3-trifluoropropyl)isatin (9a). (*S*)-5-[1-(2-Methoxymethylpyrrolidinyl)sulfonyl]isatin (**1**) (35 mg, 0.108 mmol) was converted to **9a** using anhydrous K_2CO_3 (37 mg, 0.27 mmol) and 3,3,3-trifluoro-1-iodopropane (0.025 mL, 0.216 mmol) as described in the general procedure A and stirred for 14 h. The crude product was purified by column chromatography (ethyl acetate/toluene 1:1) to yield a golden orange coloured solid. Yield: 21 mg (47%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.66–1.72 (m, 2H), 1.89–1.94 (m, 2H), 2.64 (tq, 2H, $^3J_{H,H}$ = 7.1 Hz, $^3J_{H,F}$ = 17.3 Hz), 3.12–3.18 (m, 1H), 3.36–3.47 (m, 2H), 3.36 (s, 3H), 3.58 (dd, 1H, $^2J_{Hb,Ha}$ = 9.4 Hz, $^3J_{Hb,H}$ = 3.9 Hz), 3.72–3.79 (m, 1H), 4.05 (t, 2H, $^3J_{H,H}$ = 7.0 Hz), 7.05 (d, 1H, $^3J_{H,H}$ = 8.3 Hz), 8.08 (d, 1H, $^4J_{H,H}$ = 1.7 Hz), 8.14 (dd, 1H, $^3J_{H,H}$ = 8.3 Hz, $^4J_{H,H}$ = 1.9 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.1, 28.9, 31.9 (q, $^2J_{C,F}$ = 29.3 Hz), 34.3 (q, $^3J_{C,F}$ = 3.8 Hz), 49.4, 59.1, 59.3, 74.8, 110.1, 117.5, 124.9, 125.5 (q, $^1J_{C,F}$ = 276.9 Hz), 134.6, 137.6, 152.5, 157.7, 181.1 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −65.5 (t, 3F, $^3J_{H,F}$ = 10.1 Hz) ppm. HRMS (ESI-MicroTof): *m*/*e* 475.1114 $(M+Na+CH_3OH)^+$, calcd for $C_{18}H_{23}F_3N_2NaO_6S$ 475.1121.

4.1.6.27. (*S*)-5-[1-(2-Methoxymethylpyrrolidinyl)sulfonyl]-1-(4,4,4-trifluorobutyl)isatin (9b). (*S*)-5-[1-(2-Methoxymethylpyrrolidinyl)sulfonyl]isatin (**1**) (30 mg, 0.092 mmol) was converted to **9b** using anhydrous K_2CO_3 (32 mg, 0.23 mmol) and 4,4,4-trifluoro-1-iodobutane (44 mg, 0.185 mmol) as described in the general procedure A and stirred for 4 h. The crude product was purified by column chromatography (ethyl acetate/toluene 1:1) to yield a golden orange coloured solid. Yield: 35 mg (88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.65–1.75 (m, 2H), 1.86–1.95 (m, 2H), 2.02 (quintet, 2H, $^3J_{H,H}$ = 7.7 Hz), 2.17–2.31 (m, 2H), 3.11–3.17 (m, 1H), 3.36–3.47 (m, 2H), 3.37 (s, 3H), 3.59 (dd, 1H, $^2J_{Hb,Ha}$ = 9.4 Hz, $^3J_{Hb,H}$ = 3.9 Hz), 3.72–3.79 (m, 1H), 3.88 (t, 2H, $^3J_{H,H}$ = 7.3 Hz), 7.03 (d, 1H, $^3J_{H,H}$ = 8.3 Hz), 8.08 (d, 1H, $^4J_{H,H}$ = 1.6 Hz), 8.13 (dd, 1H, $^3J_{H,H}$ = 8.2 Hz, $^4J_{H,H}$ = 1.5 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.3 (q, $^3J_{C,F}$ = 2.8 Hz), 24.1, 28.9, 31.3 (q, $^2J_{C,F}$ = 29.6 Hz), 39.5, 49.4, 59.1, 59.2, 74.8, 110.1, 117.5, 124.9, 126.6 (q, $^1J_{C,F}$ = 276.5 Hz), 134.3, 137.7, 153.0, 157.8, 181.5 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −66.0 (t, 3F, $^3J_{H,F}$ = 10.5 Hz) ppm. HRMS (ESI-MicroTof): *m*/*e* 489.1272 $(M+Na+CH_3OH)^+$, calcd for $C_{19}H_{25}F_3N_2NaO_6S$ 489.1278.

4.1.6.28. (*S*)-1-(11,11-Difluoroundecyl)-5-[1-(2-methoxymethylpyrrolidinyl)sulfonyl]isatin (10). (*S*)-5-[1-(2-Methoxymethylpyrrolidinyl)sulfonyl]isatin (**1**) (35 mg, 0.108 mmol) was converted to **10** using anhydrous K_2CO_3 (37 mg, 0.27 mmol) and 11-bromo-1,1-difluoroundecane (58.5 mg, 0.216 mmol) as described in the general procedure A and stirred for 24 h. The crude product was purified by column chromatography (ethyl acetate/toluene 3:7) to yield an orange-yellow coloured solid. Yield: 22 mg (40%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.41–1.94 (m, 22H), 3.09–3.17 (m, 1H), 3.35–3.49 (m, 2H), 3.37 (s, 3H), 3.61 (dd, 1H, $^2J_{Hb,Ha}$ = 9.4 Hz, $^3J_{Hb,H}$ = 3.9 Hz), 3.78 (m, 3H, $^3J_{H,H}$ = 7.2 Hz), 5.91 (tt, 1H, $^2J_{H,F}$ = 57.0 Hz, $^3J_{H,H}$ = 4.5 Hz), 7.02 (d, 1H, $^3J_{H,H}$ = 8.3 Hz), 8.06 (d, 1H, $^4J_{H,H}$ = 1.7 Hz), 8.11 (dd, 1H, $^3J_{H,H}$ = 8.3 Hz, $^4J_{H,H}$ = 1.9 Hz) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 22.1 (t, $^3J_{C,F}$ = 5.4 Hz), 24.1, 26.8, 27.2, 28.8, 29.0, 29.2, 29.3, 29.4, 34.1, 34.2 (t, $^2J_{C,F}$ = 22.6 Hz), 40.7, 49.4, 59.1, 59.2, 74.8, 110.4, 117.4, 119.1 (t, $^1J_{C,F}$ = 238.8 Hz), 124.6, 133.7, 137.5, 153.7, 157.8, 182.2 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −115.7 (dt, 2F, $^2J_{H,F}$ = 57.1 Hz, $^3J_{H,F}$ = 17.7 Hz) ppm. HRMS (ESI-MicroTof): *m*/*e* 537.2239 $(M+Na)^+$, calcd for $C_{25}H_{36}F_2N_2NaO_5S$ 537.2205.

4.1.7. In vitro enzyme inhibition assays (Table 1)

The inhibition potencies of target compounds **1–10** were assayed for recombinant human caspases-3 and -7 (Alexis® Biochemicals (Switzerland)) using their peptide-specific substrate (Alexis® Biochemicals (Switzerland)) Ac-DEVD-AMC (Ac-Asp-Glu-Val-Asp-AMC, caspase-3) as already described.[10,11] The enzymatic activity of the caspases was determined by measuring the accumulation of the cleaved fluorogenic product AMC (7-amino-4-methylcoumarin). Reaction rates showing inhibitory activity of the compounds **1–10** were measured with a Fusion™ universal microplate analyzer (PerkinElmer) at excitation and emission wavelengths of 360 and 460 nm, respectively. All assays were performed at a volume of 200 µl at 37 °C in reaction buffer.[9,17] Buffers contained the compounds **1–10** in DMSO in single doses (end concentrations 500 µM, 50 µM, 5 µM, 500 nM, 50 nM, 5 nM, 500 pM, 50 pM or 5 pM). Recombinant caspases were diluted into the appropriate buffer to a concentration of 0.5 units per assay (=500 pmol substrate conversion after 60 min). After 10 min incubation time the peptide substrates (end concentration 10 µM) were added and reacted for further 10 min. The IC_{50} values were determined by non-linear regression analysis using the XMGRACE program (Linux software).

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