Contilisant+Belinostat hybrids, as new multi-target-directed polyfunctionalized indole derivatives able to inhibit histone deacetylase/cholinesterase/monoamine oxidase enzymes, and modulate histamine 3/sigma 1/5-HT6/dopamine 3 receptors for the treatment of cancer and neurodegenerative diseases

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Abstract: Herein we describe the design and synthesis of ***Contilisant+Belinostat*** hybrids as polyfunctionalized indole derivatives for the treatment of a broad diversity of cancers and neurodegenerative diseases, such as glioblastoma, and Alzheimer's disease (AD). The new ***Contilisant+Belinostat*** hybrids have been designed as a Multi-Target-Directed (MTD) small molecules, able to inhibit HDAC6, cholinesterase and monoamine oxidase enzymes, and modulate histamine 3, sigma 1, 5-HT6, and dopamine 3 receptors.

Contilisant*+*Belionostat hybrids has been submitted to biological evaluation in suitable *in vitro* and *vivo* glioblastoma and AD models.

Supporting information may be found in the online version of this article.

Keywords: Alzheimer's disease, Belinostat**,** cholinesterase enzymes, Contilistat, D3R, glioblastoma, Histamine 3 receptor, HDAC6, 5-HT6 receptor, inhibitors, monoamine oxidase enzymes, Sigma 1 receptor.

INTRODUCTION[1]

Histone deacetylases (HDACs) are enzymes that remove acetyl groups from lysine residues in histone and other non-histone substrates and trigger the transcription of transcriptionally silent chromatin. Eighteen HDACs have been identified and divided into four Zn-dependent groups according to phylogenetic sequence and function: class I (HDACs 1, 2, 3, and 8), class IIa (HDACs 4, 5, 7, and 9), class IIb (HDACs 6 and 10), and class IV (HDAC11). Since the epigenetic modification is considered a new promising frontier for the study and treatment of Alzheimer's disease (AD),[1] the interest in regulating histone acetylation through HDAC is rising up. The emerging role of HDAC as AD target is also supported by the evidence of the role of histone acetylation in rescuing learning and memory impairment.[1]

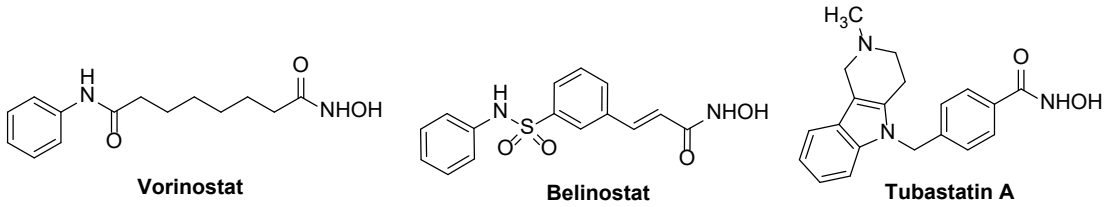


Figure 1. Structures of **Vorinostat**, **Belinostat**, and **Tubastatin** A.

Among the HDAC inhibitors (HDACis), it is worth to mention **Vorinostat** (suberoylanilide hydroxamic acid, SAHA) (Figure 1), the first HDACi approved in 2006 by the US FDA for the treatment of cutaneous T-cell lymphoma (CTCL),[2] and **Belinostat**

[1] The introduction is adapted heavily from a previous preprint by the authors, 10.26434/chemrxiv-2023-rk8bf.

(Figure 1), the first of four FDA-approved HDAC inhibitors fort the treatment of relapsed/refractory peripheral T-cell lymphoma.[3] However, Belinostat and other HDAC inhibitors have very limited therapeutic outcome for the treatment of nonhematological cancers in completed clinical trials.[4]

Among all the HDACs, particularly, it is worth noting that elevated HDAC6 activity increases tau phosphorylation interfering with its propensity to aggregate, and that HDAC6 selective inhibitor tubacin attenuates tau phosphorylation. Fan et al. demonstrated that HDAC6 inhibition ameliorates tau phosphorylation and cognitive deficits in an AD model.[5] **Tubastatin A** (Figure 1) is a highly selective HDAC6 inhibitor able to suppress the degeneration of cultivated neurons of cerebral cortex under oxidative stress conditions.[6]

AD is a neurodegenerative disease characterized by progressive deterioration of memory and learning ability due to a variety of pathological changes in the central nervous system (CNS).[7]

The literature review shows that inhibition of cholinesterases (ChEs), namely acetylcholinesterase (AChE), butyrylcholinesterase (BChE), and monoamine oxidases (MAO-A/B), in addition to modulation of monoaminergic receptors remains the focus of AD-related small molecule drug design.[8] Selective loss of cholinergic neurons leads to a decrease in acetylcholine (ACh) levels in specific brain regions that mediate cognition.[9] Therefore, the inhibition of AChE or BChE increases ACh levels at the synaptic cleft and restores cholinergic neurotransmission.[10]

On the other hand, MAOs catalyze the oxidation of amines that act as neurotransmitters, releasing H_2O_2 and consequently reactive oxygen species (ROS).[11] Thus, inhibiting MAOs imparts potent neuroprotective effects by decreasing oxidative stress, and restores impaired synaptic plasticity, memory and learning in mouse model of AD *via* control of tonic γ-aminobutyric acid levels.[12]

Histamine H3 receptors (H3Rs) are mainly expressed in the brain in the area connected with cognition and memory,[13] and since its discovery in 80-ies of the previous century they are still in the center of scientists' attention. Therapeutic utility shows that anti-H3R ligands, antagonists or inverse agonists, could be useful in the treatment of various human diseases, e.g. AD, Parkinson's disease, narcolepsy, epilepsy, pain, eating and metabolic disorders or allergy. Application in the treatment of multiple sclerosis, Tourette syndrome, depression, Huntington's disease and autism has been also suggested. Intensive works done by academic and pharmaceutical company researchers have led to

many potent and selective H3R antagonists/inverse agonists. At last, the first of them, pitolisant (Wakix®), has entered into the market as an orphan drug for narcolepsy. In the last years, H3R ligands were also designed as interacting with at least one additional biological target, such as e.g. AChE, serotonin transporter, dopamine 2 receptor (D2R), dopamine 3 receptor (D3R) or histamine H1 receptors.[14]

Sigma 1 receptor (S1R) appears to be a unique class of protein influencing and participating in a wide range of biological events, including Ca^{2+} signaling at the Endoplasmic Reticulum (ER), controlling K^+, Ca^{2+}, Cl^-, and Na^+ families of ion channels at plasma membrane and membranes, thus maintaining ER-mitochondria exchanges, and modulating transcription factors. The impact of S1R in learning and memory processes is well known, highlighting the power of S1R agonists as anti-amnesic drugs in a variety of pharmacological or pathological models, possibly due to the fact that S1R activity increases glutamatergic synapses, cholinergic synapses and the effects of trophic factors, which play a key role in memory.[15] A number of ligands have been described in the last decade showing diverse S1R/S2R affinity and antagonism/agonism profile, among them, not surprisingly, donepezil, but without clear and definitive structure-activity relationship trends.[15]

It has been demonstrated and confirmed that serotonin 5-HT6 receptor (5-HT6R) antagonists may be efficient and effective drugs for the therapy of neurodegenerative pathologies, such as AD. This is due to the fact that 5-HT6R is localized in CNS regions liable for cognition, and that 5-HT6R antagonists improve intellectual functions, as a most possibly result of the ACh liberation in cortex.[16] Not surprisingly, the administration of idalopirdine and donepezil has provided impressive clinical results, showing neuroprotective effect as a result of the combined 5-HT6R antagonist plus and AChE inhibitor activities against the toxic β amyloid-insult, and harmful radical species. To sum up, nowdays 5-HT6R is being considered as a very attractive biological target in order to design and identify new agents for AD.[17]

Similarly, D3R is another potent and confident biological target for identifying novel anti-amnesic agents. D3R is expressed in the CNS, acting in cyclin-dependent kinase 5,[18] and mammalian target of rapamycin routes,[19] promoting the liberation of ACh and glutamate.[20] Consequently, inhibition of D3R responses may enhance pro-cognitive functions.[21]

Thus, based on these investigations, combined 5-HT6R and D3R antagonists have been shown to behave as neuroprotective agents improving the animal impaired cognition

functions in *in vivo* analyses.[22] Thus, scientists designed to incorporate diverse alkyl substituents at the pyrrolidine core, a well known D3R pharmacophore, of 5-HT6R antagonist (*S*)-1-[(3-chlorophenyl)sulfonyl]-4-(pyrrolidine-3-yl-amino)-1*H*-pyrrolo[3,2-c]quinoline,[23] a therapeutic strategy that led to ligand [(*S*)-1-((3-chlorophenyl)sulfonyl)-*N*-(1-isobutylpyrrolidin-3-yl)-1*H*-pyrrolo-[3,2-*c*]quinolin-4-amine], a potent multi-target directed ligand able to modulate simultaneously D3R and 5-HT6R, showing in addition astrocyte neuroprotection against doxorubicin.[23]

RESULTS & DISCUSSION

Synthesis

In this work, we report the design and synthesis of ***Contilisant+Belinostat*** hybrids (Figure 2) as polyfunctionalized indole derivatives for the treatment of a broad diversity of cancers and neurodegenerative diseases, such as glioblastoma, and AD. The new ***Contilisant+Belinostat*** hybrids have been designed as MTD small molecules, able to inhibit HDAC6, ChEs and MAOs, and modulate H3R, S1R, 5-HT6R, and D3R, by juxtaposition of selected functional and pharmacophore groups from **Contilisant**[24,25] and **Belinostat**[3] (Figure 2). **Contilisant** is a brain-permeable neuroprotective agent that has been identified in our laboratory, that inhibits hChEs and hMAOs, modulates histamine H3 and S1 receptors, and outperformed donepezil in *in vivo* animal models of AD.[24,25]

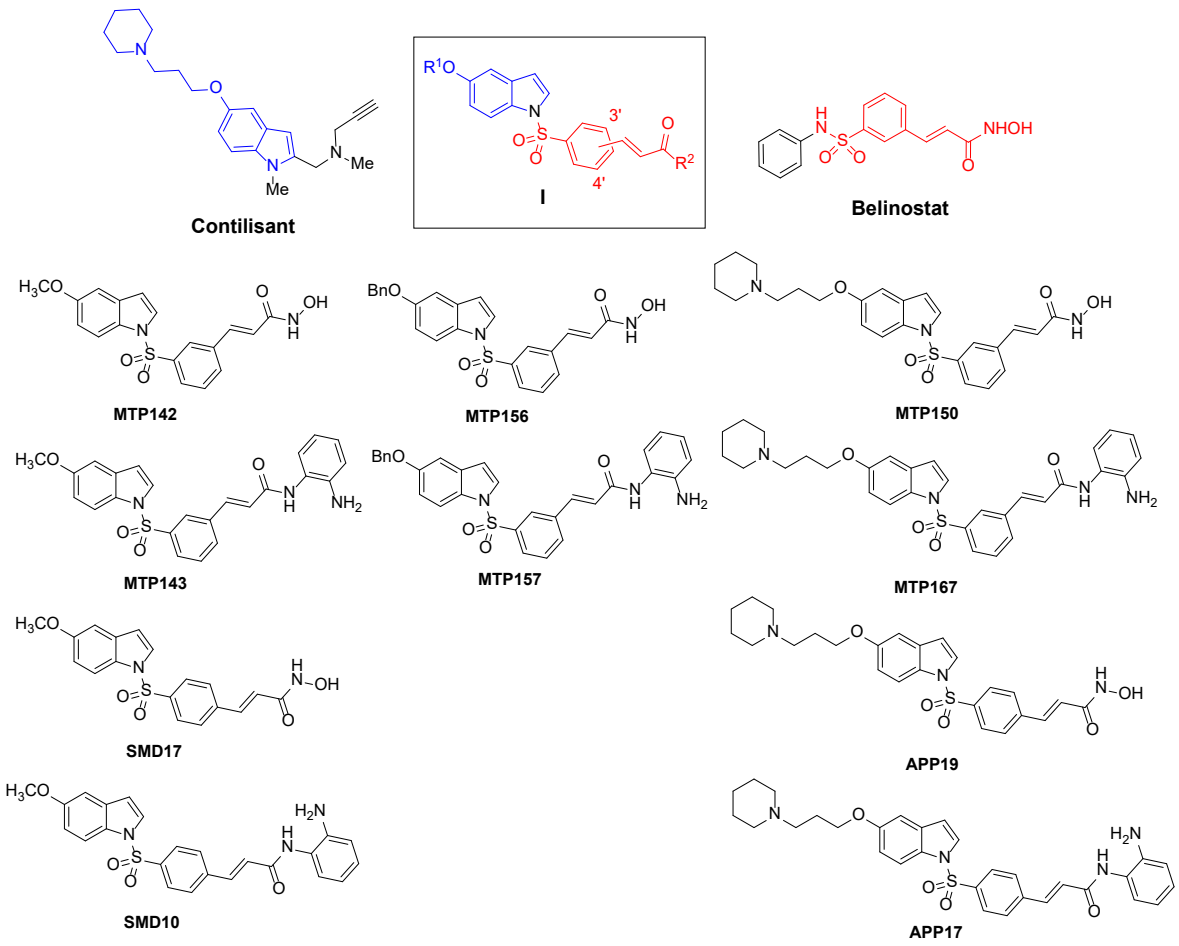
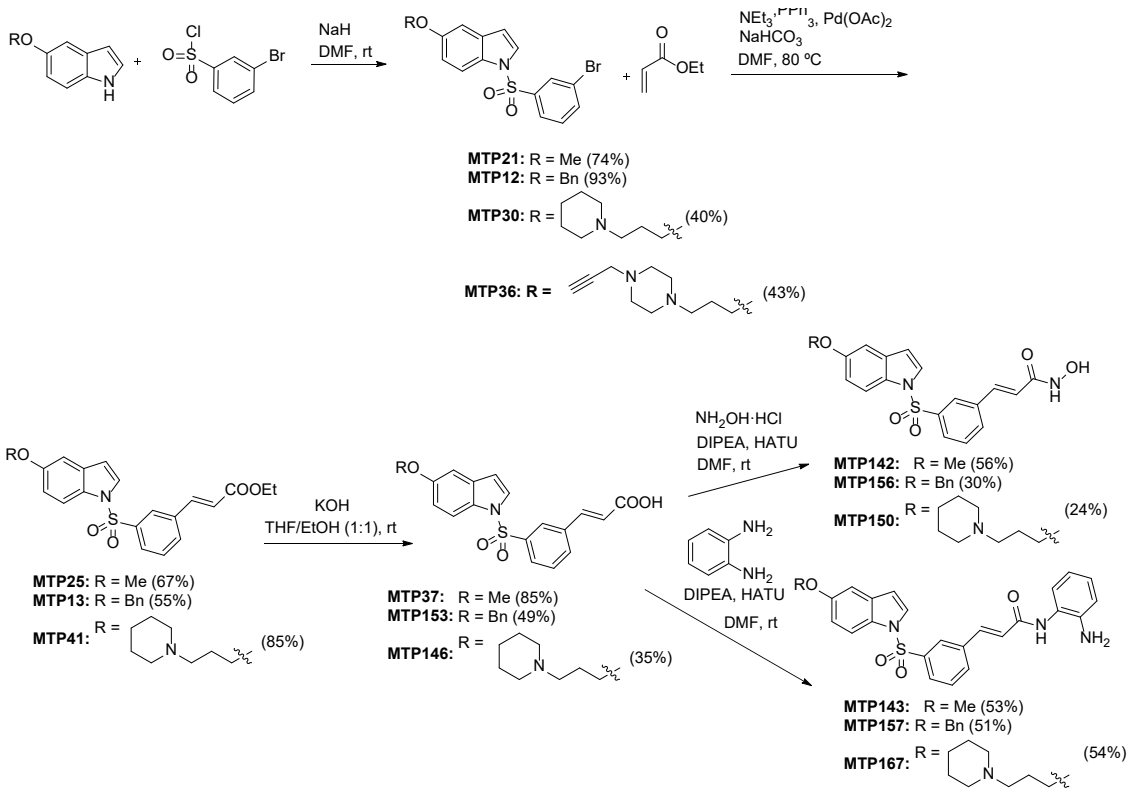


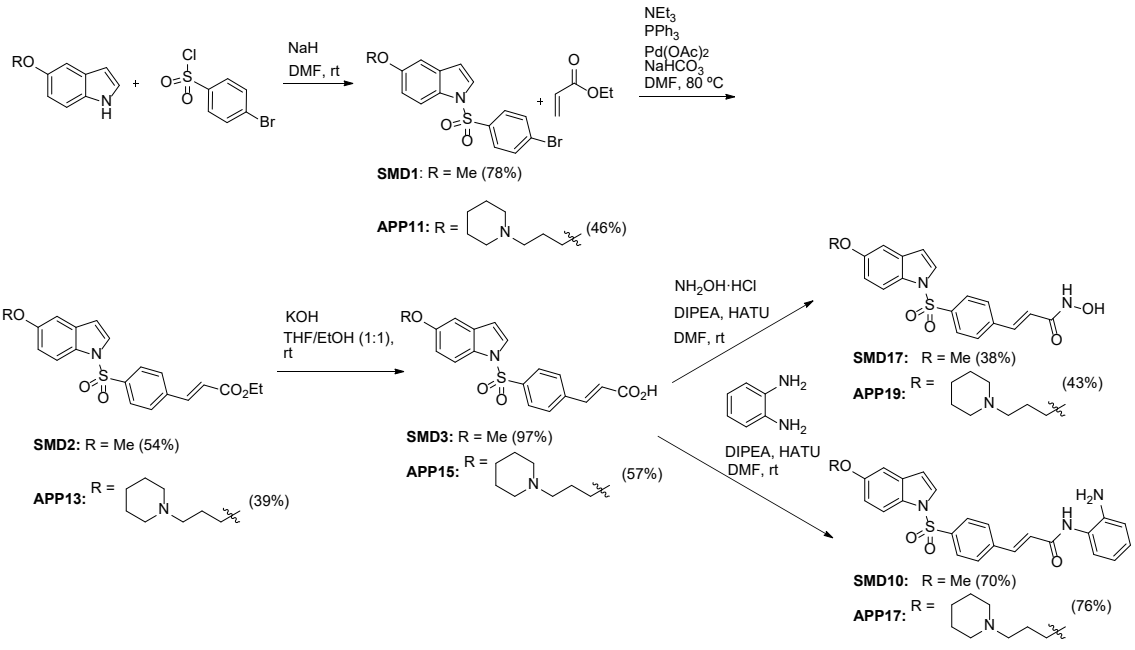
Figure 2. Structure of **Contilisant**, **Belinostat**, and the new ten ***Contilisant+Belinostat*** hybrids (**I**).

Accordingly, we have designed and prepared ten new compounds of type **I** where R^1 represents CH_3, Bn, and piperidinepropyl, and R^2 represents a NHOH and *orto*-$NH_2(C_6H_4)NH$ groups installed in an α,β-unsaturated motif located in positions C3' and C4' of the *N*(1)-sulfonamide aromatic ring (Figure 2).

In Scheme 1 we have shown how we have prepared the ligands bearing the *α,β*-unsaturated motif located in position C3' of the *N*(1)-sulfonamide aromatic ring, whereas in Scheme 2 we represent the synthesis of molecules bearing the *α,β*-unsaturated motif located in position C4' of the *N*(1)-sulfonamide aromatic ring.



Scheme 1. Synthesis of compounds **MTP142**, **156**, **150**, and **MTP143**, **157**, and **167**.



Scheme 2. Synthesis of compounds **SMD17**, **APP19**, and **SMD10**, **APP 17**.

In both approaches, identical synthetic protocols have been investigated and carried out with success to provide the desired target ligands in good overall yields from readily available precursors. So, as shown in Scheme 1, starting from commercial 5-methoxy-1*H*-indole, 5-(benzyloxy)-1*H*-indole, previously reported 5-(3-(piperidin-1-

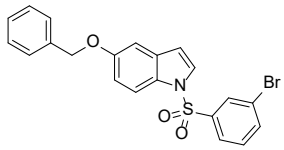
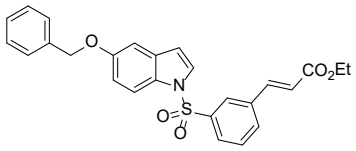
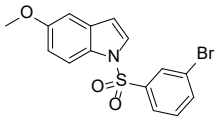
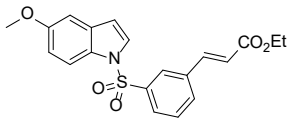
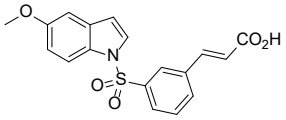
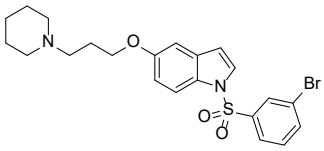
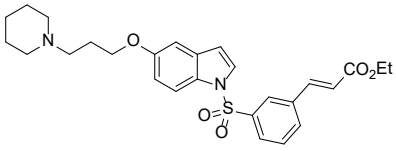
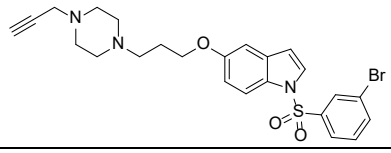
yl)propoxy)-1*H*-indole (**MTP30**),[26] and newly prepared here 5-(3-(4-(prop-2-yn-1-yl)piperazin-1-yl)propoxy)-1*H*-indole (**MTP36**) (see **Experimental Part**), the reaction with 3-bromobenzenesulfonyl chloride gave *N*-phenylsulfonamides **MTP21**, **12**, **30** and **43**, respectively. Next, Heck reaction with ethyl acrylate afforded the corresponding ethyl esters **MTP25**, **13** and **41**. Very surprisingly, Heck reaction of **MTP43** did not afford the expected coupling product. In the next step, basic hydrolysis to give acids **MTP37**, **153** and **146**, followed by amide standard coupling with commercial hydroxylamine or or 1,2-phenylenediamine provided compounds **MTP142**, **156**, **150**, and **MTP143**, **157**, and **167**, respectively. As shown in Scheme 2, similar protocols, starting from commercial 5-methoxy-1*H*-indole, 5-(benzyloxy)-1*H*-indole or previously reported 5-(3-(piperidin-1-yl)propoxy)-1*H*-indole,[26] but using 4-bromobenzenesulfonyl chloride afforded the appropriate intermediates, that after treatment with hydroxylamine or 1,2-phenylenediamine gave the final desired ligands **SMD17**, **APP19**, and **SMD10**, **APP17**, respectively.

All new compounds gave satisfactory analytical and spectroscopic data in good agreement with their structures (see **Supporting Information**).

In vitro Pharmacological Activity

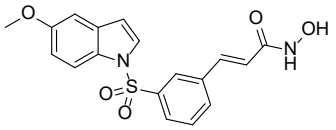
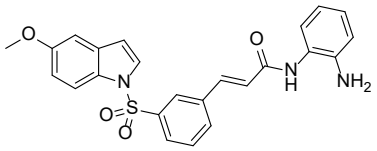
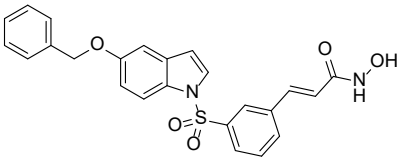
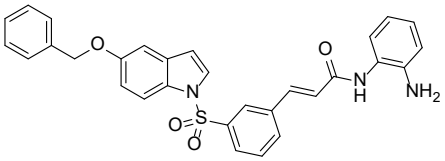
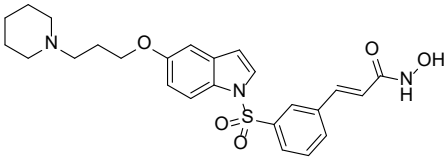
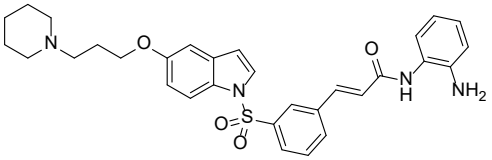
Compounds **MTP12**, **13**, **21**, **25**, **37**, **30**, **41**, **43** have been sent to Prof. Andrzej J. Bojarski (Department of Medicinal Chemistry, Maj Institute of Pharmacology Polish Academy of Sciences, Kraków, Poland) laboratory to test its ability to modulate 5-HT6R.

Prof. Andrezj Bojarski (30/07/2021)

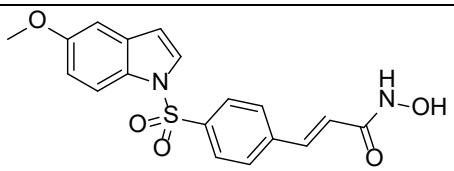
Ref.	Structure	Analysis	Solubility	Quantity
MTP12		Chemical Formula: $C_{21}H_{16}BrNO_3S$ Molecular Weight: 442,33	DMSO	30.0 mg
MTP13		Chemical Formula: $C_{26}H_{23}NO_5S$ Molecular Weight: 461,53	DMSO	24.0 mg
MTP21		Chemical Formula: $C_{15}H_{12}BrNO_3S$ Molecular Weight: 366,23	DMSO	30.0 mg
MTP25		Chemical Formula: $C_{20}H_{19}NO_5S$ Molecular Weight: 385,43	DMSO	29.0 mg
MTP37		Chemical Formula: $C_{18}H_{15}NO_5S$ Molecular Weight: 357,38	DMSO	30.0 mg
MTP30		Chemical Formula: $C_{22}H_{25}BrN_2O_3S$ Molecular Weight: 477,42	DMSO	30.0 mg
MTP41		Chemical Formula: $C_{27}H_{32}N_2O_5S$ Molecular Weight: 496,62	DMSO	30.0 mg
MTP43		Chemical Formula: $C_{24}H_{26}BrN_3O_3S$ Molecular Weight: 516,45	DMSO	30.0 mg

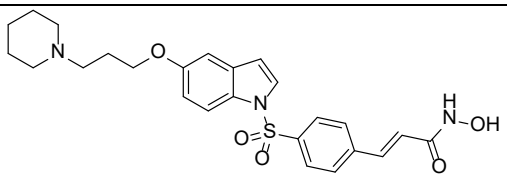
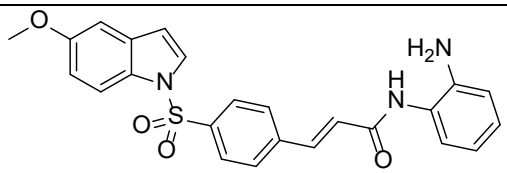
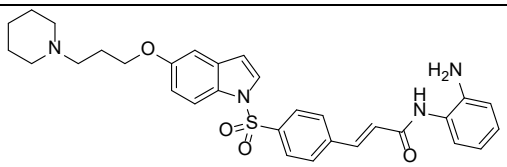
Compounds **MTP142**, **156**, **150**; **MTP143**, **157**, **167**; and **SMD17**, **APP19**; **SMD10**, **APP17** have been also sent to Dr. Finn K. Hansen (Pharmaceutical Institute, University of Bonn, Germany) in order to investigate their capacity to inhibit HDAC1 and HDAC6.

Dr. Finn K. Hansen (25/01/2022)

Ref.	Structure	Analysis	Solubility	Quantity
MTP142		Chemical Formula: $C_{18}H_{16}N_2O_5S$ Molecular Weight: 372,40	DMSO	3.8 mg
MTP143		Chemical Formula: $C_{24}H_{21}N_3O_4S$ Molecular Weight: 447,51	DMSO	4.9 mg
MTP156		Chemical Formula: $C_{24}H_{20}N_2O_5S$ Molecular Weight: 448,49	DMSO	3.2 mg
MTP157		Chemical Formula: $C_{30}H_{25}N_3O_4S$ Molecular Weight: 523,61	DMSO	3.0 mg
MTP150		Chemical Formula: $C_{25}H_{29}N_3O_5S$ Molecular Weight: 483,58	DMSO	3.6 mg
MTP167		Chemical Formula: $C_{31}H_{34}N_4O_4S$ Molecular Weight: 558,70	DMSO	5.3 mg

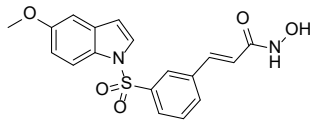
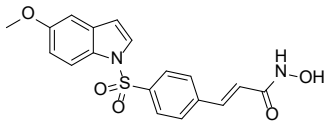
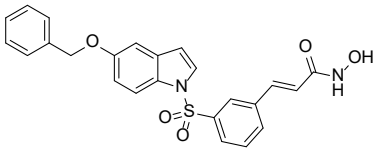
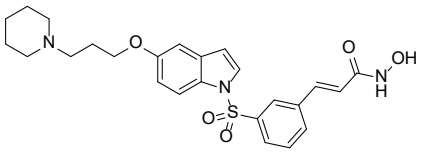
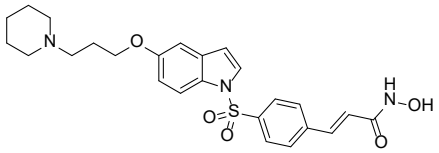
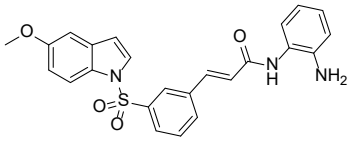
Dr. Finn K. Hansen (21/12/2022)

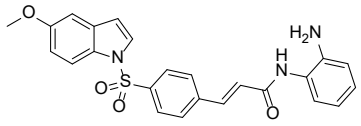
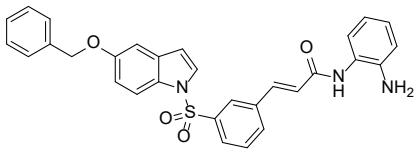
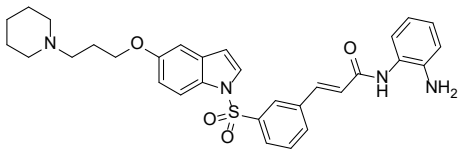
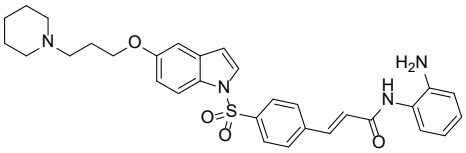
Ref.	Structure	Solub.	Weight
SMD17	 Chemical Formula: $C_{18}H_{16}N_2O_5S$ Molecular Weight: 372,3950	DMSO	5.1 mg

APP19	 Chemical Formula: $C_{25}H_{29}N_3O_5S$ Molecular Weight: 483,5830	DMSO	4.4 mg
SMD10	 Chemical Formula: $C_{24}H_{21}N_3O_4S$ Molecular Weight: 447,5090	DMSO	5.1 mg
APP17	 Chemical Formula: $C_{31}H_{34}N_4O_4S$ Molecular Weight: 558,6970	DMSO	4.1 mg

Compounds **MTP142**, **156**, **150**; **MTP143**, **157**, **167**; **SMD17**, **APP19**; **SMD10**, **APP17** have been sent to Prof. Dr. Michael Gütschow (Pharmaceutical Institute, University of Bonn, Germany) laboratory to test its ability to inhibit ChEs, and MAOs.

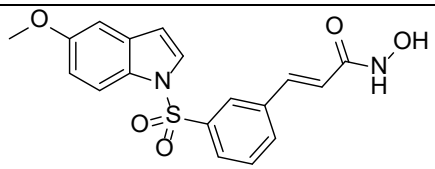
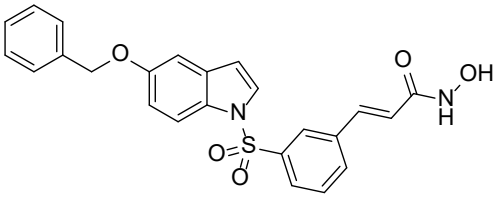
Prof. Dr. Michael Gütschow (30/09/2022)

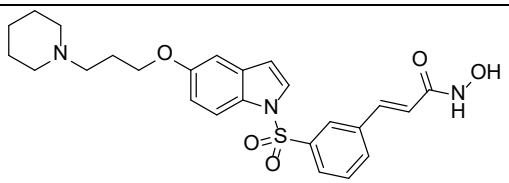
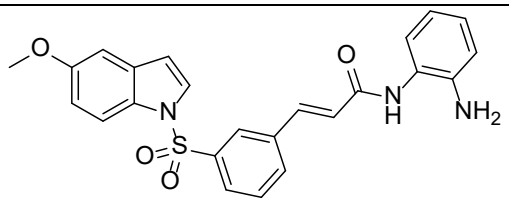
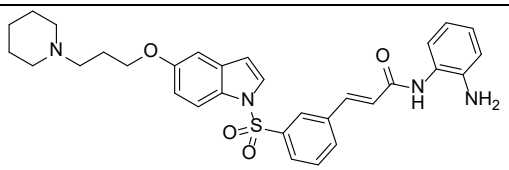
Ref.	Structure	Analysis	Solubility	Quantity
MTP142		Chemical Formula: $C_{18}H_{16}N_2O_5S$ Molecular Weight: 372,39	DMSO	12.4 mg
SMD17		Chemical Formula: $C_{18}H_{16}N_2O_5S$ Molecular Weight: 372,39	DMSO	10.3 mg
MTP156		Chemical Formula: $C_{24}H_{20}N_2O_5S$ Molecular Weight: 448,49	DMSO	10.2 mg
MTP150		Chemical Formula: $C_{25}H_{29}N_3O_5S$ Molecular Weight: 483,58	DMSO	9.0 mg
APP19		Chemical Formula: $C_{25}H_{29}N_3O_5S$ Molecular Weight: 483,58	DMSO	14.0 mg
MTP143		Chemical Formula: $C_{24}H_{21}N_3O_4S$ Molecular Weight: 447,51	DMSO	10.5 mg

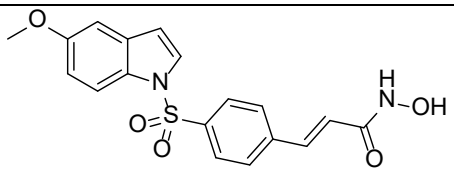
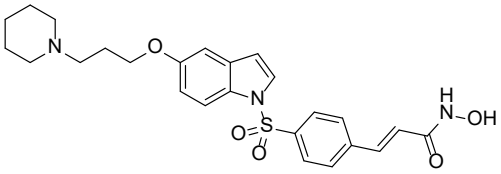
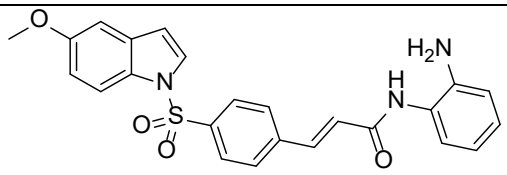
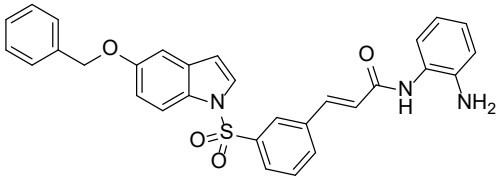
Ref.	Structure	Analysis	Solubility	Quantity
SMD10		Chemical Formula: $C_{24}H_{21}N_3O_4S$ Molecular Weight: 447,5090	DMSO	10.0 mg
MTP157		Chemical Formula: $C_{30}H_{25}N_3O_4S$ Molecular Weight: 523,6070	DMSO	11.7 mg
MTP167		Chemical Formula: $C_{31}H_{34}N_4O_4S$ Molecular Weight: 558,6970	DMSO	14.9 mg
APP17		Chemical Formula: $C_{31}H_{34}N_4O_4S$ Molecular Weight: 558,6970	DMSO	16.2 mg

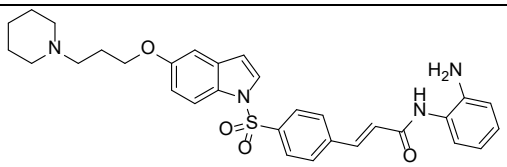
Finally, compounds **MTP142**, **MTP143**, **MTP150, MTP156, MTP157, MTP167**; and **SMD10, SMD17**, **APP17, APP19**, have been also sent to Dr. Ander Matheu (Cellular Oncology group, Biodonostia Health Research Institute, San Sebastian, Spain) in order to investigate its potential therapeutic use for glioblastoma.

Dr. Ander Matheu (02/07/2022)

Ref.	Structure	Solub.	Stock	Ander
MTP142	 Chemical Formula: $C_{18}H_{16}N_2O_5S$ Molecular Weight: 372,3950	DMSO	23.6 mg	5.5 mg
MTP156	 Chemical Formula: $C_{24}H_{20}N_2O_5S$ Molecular Weight: 448,4930	DMSO	23.5 mg	5.0 mg

MTP150	 Chemical Formula: $C_{25}H_{29}N_3O_5S$ Molecular Weight: 483,5830	DMSO	4.2 mg	5.0 mg
MTP143	 Chemical Formula: $C_{24}H_{21}N_3O_4S$ Molecular Weight: 447,5090	DMSO	53.6 mg	5.5 mg
MTP167	 Chemical Formula: $C_{31}H_{34}N_4O_4S$ Molecular Weight: 558,6970	DMSO	51.6 mg	5.7 mg

SMD17	 Chemical Formula: $C_{18}H_{16}N_2O_5S$ Molecular Weight: 372,3950	DMSO	5.4 mg
APP19	 Chemical Formula: $C_{25}H_{29}N_3O_5S$ Molecular Weight: 483,5830	DMSO	5.4 mg
SMD10	 Chemical Formula: $C_{24}H_{21}N_3O_4S$ Molecular Weight: 447,5090	DMSO	5.3 mg
MTP157	 Chemical Formula: $C_{30}H_{25}N_3O_4S$ Molecular Weight: 523,6070	DMSO	5.1 mg

APP17	 Chemical Formula: $C_{31}H_{34}N_4O_4S$ Molecular Weight: 558,6970	DMSO	5.0 mg

All these analyses are currently in advanced progress and will be reported in due course.

CONCLUSIONS

In this pre-publication, we have summarized our most advanced progresses in one of our current projects targeted to identify new MTD-indoles, such as ***Contilisant+Belinostat*** hybrids as polyfunctionalized indole derivatives, for the therapy of cancer conditions (glioblastoma) and neurodegenerative diseases (AD), based on the new and original approach consisting of the ability of these molecules to inhibit and/or modulate, simultaneously, at the least, ChEs, MAOs, HDAC6 enzymes, and H3, S1 and D3 receptors. Ten new ***Contilisant+Belinostat*** hybrids have been synthesized and are being investigated to analyze their *in vitro* and *in vivo* pharmacological activities.

MATERIALS AND METHODS

Synthesis. General Methods. Reactions were monitored by TLC using precoated silica gel aluminium plates containing a fluorescent indicator (Merck, 5539). Detection was done by UV (254 nm) followed by charring with sulfuric-acetic acid spray, 1% aqueous potassium permanganate solution or 0.5% phosphomolybdic acid in 95% EtOH. Anhydrous Na_2SO_4 was used to dry organic solutions during work-ups and the removal of solvents was carried out under vacuum with a rotary evaporator. Flash column chromatography was performed using silica gel 60 (230-400 mesh, Merck). Melting points were determined on a Kofler block and are uncorrected. IR spectra were obtained on a Perkin-Elmer Spectrum One spectrophotometer. NMR spectra were recorded in Varian System-500, Bruker Avance III HD-400, Jeol JNM-ECZ400R and Varian Inova-300 apparatus, using tetramethylsilane as internal. All the assignments for protons and carbons were in agreement with 2D COSY, HSQC, HMBC, and 1D NOESY spectra. The

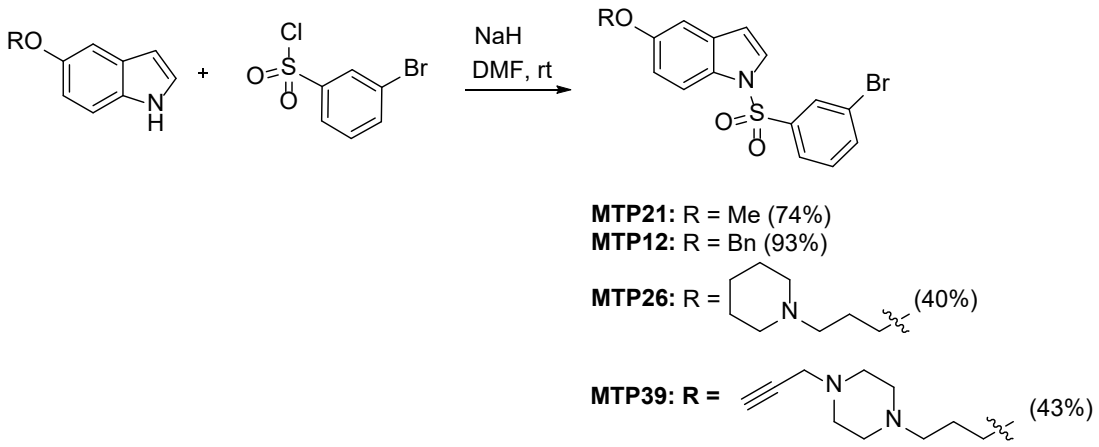
purity of compounds was checked by HPLC-MS on a HPLC Alliance e2695 apparatus, and confirmed to be $\geq$ 95%.

General Method for the Synthesis of the *N*-Sulfonamides (A). To a solution of the corresponding indole (1.0 mmol) in anhydrous DMF (6 mL), cooled at 0 °C, sodium hydride (2.0 mmol, 60% in oil) was added and the mixture was stirred for 30 min. Then, benzenesulfonyl chloride (1.1 mmol) was added and he mixture was stirred at room temperature (rt) for 24 h. After completion (TLC analysis), distilled water (20 mL) was added and the mixture was extracted with AcOEt (3 x 20 mL). The combined organic extracts were washed with water (3 x 20 mL), dried over anhydrous magnesium sulfate and evaporated. The crude product was purified using column chromatography.

General Method for the Heck Reaction (B). A mixture of the appropriate indole (1.0 mmol), ethyl acrylate (1.2 mmol), triethylamine (1.7 mmol), triphenylphosphine (0.5 mmol), palladium acetate (0.5 mmol), and sodium bicarbonate (1.0 mmol) was heated at 80 °C in DMF (2 mL) for 24 h. Then, the reaction was quenched with H_2O and extracted with CH_2Cl_2 (DCM) (3 x 30 mL). The organic layer was collected and dried over anhydrous $MgSO_4$. After the removal of $MgSO_4$ by filtration, the filtrate was concentrated *in vacuo.* The residue was purified by flash chromatography over silica gel.

General Method for Acid Synthesis (C). A mixture of the ester (1.0 equiv), 2N KOH (4.0 equiv), THF (10 mL), and ethanol (10 mL) was stirred at rt for 4 h, then it was quenched on crushed ice and made acidic with 37% HCl. Ethyl acetate (20 mL) was added, and the organic layer was separated, washed with brine (3 x 20 mL) and dried over anhydrous $MgSO_4$. After the removal of $MgSO_4$ by filtration, the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography over silica gel.

General Method for Amide Synthesis (D). *N*,*N*-Diisopropylethylamine (DIPEA) (2.5-3.5 mmol) and 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU) (1.0 mmol) were sequentially added at room temperature to a solution of the corresponding acid (1.0 mmol) in dry DMF (4 mL). The reaction was stirred for 15 min and then hydroxylamine hydrochloride or 1,2-phenylenediamine (1.0 mmol) was added. After completion (TLC analysis), the crude product was precipitated on a solution of water/brine (4:1), filtered and dried. Then, the solid was purified using column chromatography.

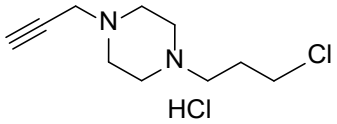


1-((3-Bromophenyl)sulfonyl)-5-methoxy-1*H*-indole (MTP21). Following the **General Method A**, the reaction of commercial 5-methoxy-1*H*-indole (500 mg, 3.40 mmol), dissolved in anhydrous DMF (48 mL), with sodium hydride (272 mg, 6.79 mmol) and 3-bromobenzenesulfonyl chloride (0.54 mL, 3.74 mmol), after purification by flash chromatography of the residue using hexane/AcOEt (10%) as eluent, gave compound **MTP21** (1.1 g, 74%) as a white solid: mp 75-77 ^{0}C; IR (cm^{-1}) ν 1373 (O=S=O), 1226 (C-O-C), 1143 (C–Br); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (t, *J* = 1.9 Hz, 1H), 7.87 (dt, *J* = 9.0, 0.7 Hz, 1H, H7), 7.77 (ddd, *J* = 7.9, 1.8, 1.0 Hz, 1H), 7.65 (ddd, *J* = 8.0, 1.9, 1.0 Hz, 1H), 7.50 (d, *J* = 3.6 Hz, 1H, H2), 7.30 (t, *J* = 8.0 Hz, 1H), 6.99 (d, *J* = 2.5 Hz, 1H, H4), 6.96 (dd, *J* = 8.9, 2.5 Hz, 1H, H6), 6.63 (dd, *J* = 3.6, 0.8 Hz, 1H, H3), 3.83 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7, 139.8, 136.8 (CH_{Ar}), 131.8, 130.7 (CH_{Ar}), 129.5 (CH_{Ar}), 129.4, 126.9 (C2), 125.2 (CH_{Ar}), 123.1, 114.3 (C7), 114.0 (C6), 110.0 (C3), 103.8 (C4), 55.6 (CH_3). HRMS (ESI): Calcd for $C_{15}H_{13}BrNO_3S^+$ [*M* + H]$^+$: 365.9794. Found: 365.9798.

5-(Benzyloxy)-1-((3-bromophenyl)sulfonyl)-1*H*-indole (MTP12). Following the **General Method A**, the reaction of commercial 5-(benzyloxy)-1*H*-indole (200 mg, 0.90 mmol), dissolved in dry DMF (13 mL), with NaH (72 mg, 1.79 mmol) and 3-bromobenzenesulfonyl chloride (0.15 mL, 0.99 mmol), after purification by flash chromatography of the residue using hexane/AcOEt (10%) as eluent, afforded compound **MTP12** (360 mg, 93%) as a white solid: mp 105-107 ºC; IR (cm^{-1}) ν 1354 (O=S=O), 1200 (C-O-C), 1180 (C–Br); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (t, *J* = 1.9 Hz, 1H), 7.80 (dd, *J* = 8.8, 0.8 Hz, 1H, H7), 7.68 (ddd, *J* = 7.9, 1.8, 1.0 Hz, 1H), 7.60 - 7.53 (m, 1H), 7.41 (d, *J* = 3.7 Hz, 1H, H2), 7.38 - 7.17 (m, 6H), 7.01 - 6.92 (m, 2H, H4 and H6), 6.53 (dd, *J* = 3.7, 0.8 Hz, 1H, H3), 4.99 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 139.8, 136.9, 136.8 (CH_{Ar}), 131.8, 130.7 (CH_{Ar}), 129.6, 129.5 (CH_{Ar}), 128.6 ($2CH_{Ar}$), 128.0

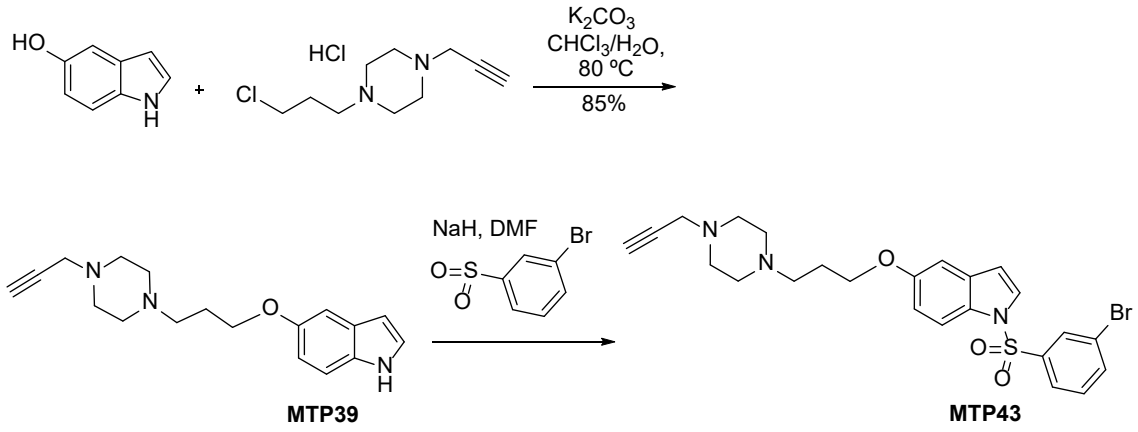
(CH_{Ar}), 127.5 (2CH_{Ar}), 126.9 (C2), 125.2 (CH_{Ar}), 123.1, 114.7 (C6), 114.4 (C7), 110.0 (C3), 105.2 (C4), 70.5 (CH_2). HRMS (ESI): Calcd for $C_{21}H_{16}BrNNaO_3S^+$ [*M* + Na]$^+$: 463.9926. Found: 463.9923.

1-((3-Bromophenyl)sulfonyl)-5-(3-(piperidin-1-yl)propoxy)-1*H*-indole (MTP30). Following the **General Method A**, the reaction of 5-(3-(piperidin-1-yl)propoxy)-1*H*-indole (**MTP26**)[26] (400 mg, 1.55 mmol), dissolved in dry DMF (22 mL), with NaH (124 mg, 3.10 mmol) and 3-bromobenzenesulfonyl chloride (0.25 mL, 1.70 mmol), after purification by flash chromatography of the residue using DCM/MeOH (5%) as eluent, provided compound **MTP30** (300 mg, 40%) as a brown oil: IR (cm^{-1}) ν 1376 (O=S=O), 1265 (C-O-C), 1181 (C–Br); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (t, *J* = 1.9 Hz, 1H), 7.76 (d, *J* = 9.0 Hz, 1H), 7.66 (dt, *J* = 8.1, 1.3 Hz, 1H), 7.54 (dt, *J* = 7.9, 1.3 Hz, 1H), 7.39 (d, *J* = 3.7 Hz, 1H), 7.19 (t, *J* = 8.0 Hz, 1H), 6.96 - 6.80 (m, 2H), 6.52 (d, *J* = 3.7 Hz, 1H), 3.93 (t, *J* = 6.2 Hz, 2H), 2.59 - 2.38 (m, 6H), 2.06 - 1.89 (m, 2H), 1.57 (q, *J* = 5.7 Hz, 4H), 1.39 (d, *J* = 6.1 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9, 139.7, 136.7 (CH_{Ar}), 131.8, 130.6 (CH_{Ar}), 129.4 (CH_{Ar}), 129.3, 126.8 (C2), 125.1 (CH_{Ar}), 123.0, 114.4 (C7), 114.2 (C6), 110.0 (C3), 104.7 (C4), 66.6 (CH_2), 55.8 (CH_2), 54.4 (2CH_2), 26.3 (CH_2), 25.3 (2CH_2), 23.9 (CH_2). HRMS (ESI): Calcd for $C_{22}H_{26}BrN_2O_3S^+$ [*M* + H]$^+$: 477.0842. Found: 477.0835.



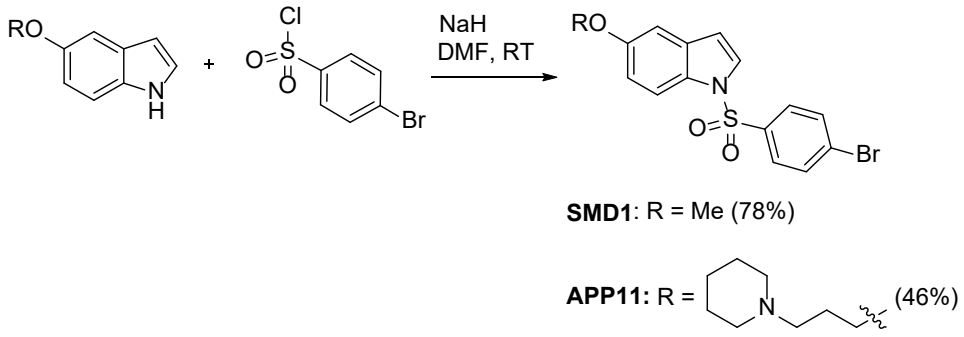
1-(3-Chloropropyl)-4-(prop-2-yn-1-yl)piperazine hydrochloride (MTP36). To a solution of piperazine (3 g, 34.88 mmol, 2.0 equiv) in anhydrous DCM (26 mL), cooled at 0 ^{0}C, di-*tert*-butyl dicarbonate (4 g, 17.44 mmol, 1.0 equiv) was added and the mixture was stirred at room temperature (rt) overnight. After complete reaction (TLC analysis), the solvent was evaporated *in vacuo* and water (10 mL) was added to the residue. The solution was filtrated and washed with water (20 mL) was added, and the mixture was extracted with diethyl ether (3 x 20 mL). Combined organic extracts were washed with water (3 x 20 mL), dried over anhydrous magnesium sulfate and evaporated to, give *tert*-butyl piperazine-1-carboxylate. To a solution of *tert*-butyl piperazine-1-carboxylate (2 g, 10.75 mmol, 1.0 equiv) in anhydrous DCM (38 mL), cooled at 0 ^{0}C, triethylamine (3mL, 20.97 mmol, 2.6 equiv) and 1-bromo-3-chloropropane (2 mL, 20.97 mmol, 10 mmol) were added. The resulting mixture was stirred at 50 ^{0}C for overnight. After complete

reaction (TLC analysis), the residue was added brine solution and extracted with DCM (3 x 20 mL). Combined organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo* gave crude *tert*-butyl 4-(3-chloropropyl)piperazine-1-carboxylatet that was used in the next step without further purification. A mixture of *tert*-butyl 4-(3-chloropropyl)piperazine-1-carboxylate (2 g, 7.63 mmol, 1.0 equiv) and hydrochloric acid in ethanol (36 mL, 28.70 mmol, 4 equiv) was dissolved in ethanol (4 mL) Then, the reaction mixture was stirred at room temperature (rt) for 16 h. After complete reaction (TLC analysis), the mixture was extracted with diethyl ether (3 x 20 mL). Combined organic extracts were dried over anhydrous magnesium sulfate and evaporated. A mixture of 1-(3-chloropropyl)piperazine hydrochloride (2 g, 8.49 mmol, 1.0 equiv), triethylamine (3 mL, 20.40 mmol, 3.0 equiv) and propargyl bromide (1 mL, 7.47 mmol, 1.1equiv) was dissolved in DCM (1 mL). Then, the reaction mixture was stirred at room temperature for 24 h. After complete reaction (TLC analysis), distilled water (20 mL) was added to and it was extracted with chloroform (3 x 20 mL). Combined organic extracts were washed with brine (15 mL), dried over anhydrous magnesium sulfate and evaporated. Product was purified by flash chromatography over silica gel, using DCM/MeOH (98:2) as eluent to give compound **MTP36** (1 g, 74%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.60 (t, *J* = 6.6 Hz, 2H), 3.30 (d, *J* = 2.4 Hz, 2H), 2.69 - 4.43 (m, 10H), 2.25 (t, *J* = 2.4 Hz, 1H), 2.00 - 1.91 (m, 2H).



1-((3-Bromophenyl)sulfonyl)-5-(3-(4-(prop-2-yn-1-yl)piperazin-1-yl)propoxy)-1*H*-indole (MTP43). Commercial 5-hydroxi-1*H*-indol (310 mg, 2.33 mmol) was dissolved in a mixture of $CHCl_3$ (6 mL) and H_2O (2 mL), and reacted with K_2CO_3 (965 mg, 6.98 mmol) and 1-(3-chloropropyl)-4-prop-2-yn-1-ylpiperazine hydrochloride (701 mg, 3.5 mmol) at 80 ^{0}C for 3 d. After purification by flash chromatography of the residue using DCM/MeOH (5%) as eluent, 5-(3-(4-(prop-2-yn-1-yl)piperazin-1-yl)propoxy)-1*H*-

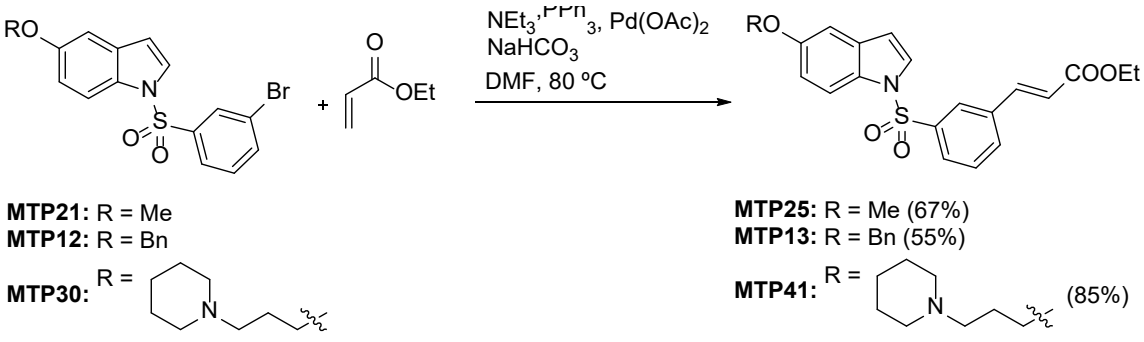
indole (**MTP39**) (590 mg, 85%) was obtained as a white solid: mp 144-146 ^{0}C; IR (cm^{-1}) ν 1265 (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (s, 1H, N*H*), 7.27 (s, 1H), 7.17 (t, *J* = 2.8 Hz, 1H), 7.09 (d, *J* = 2.4 Hz, 1H), 6.82 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.48 - 6.42 (m, 1H), 4.04 (t, *J* = 6.3 Hz, 2H), 3.29 (d, *J* = 2.5 Hz, 2H), 2.64 - 2.57 (m, 10H), 2.23 (t, *J* = 2.4 Hz, 1H), 2.16 - 1.81 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.5, 131.0, 128.3, 124.8 (C2), 112.9 (C7), 111.6 (C6), 103.6 (C3), 102.4 (C4), 78.8, 73.2 (CH), 67.0 (CH_2), 55.3 ($2CH_2$), 53.0 ($2CH_2$), 51.7 (CH_2), 46.8 (CH_2), 26.8 (CH_2); HRMS (ESI): Calcd for $C_{19}H_{23}N_3O^+$ [*M* + H]$^+$: 298.1914. Found: 298.1924; Anal. Calcd for $C_{18}H_{23}N_3O \cdot 1/5H_2O$: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.72; H, 7.65; N, 13.58. Following the **General Method A**, the reaction of compound **MTP39** (400 mg, 1.34 mmol), dissolved in dry DMF (19 mL), with NaH (108 mg, 2.70 mmol) and 3-bromobenzenesulfonyl chloride (0.2 mL, 1.48 mmol), after purification by flash chromatography of the residue using DCM/MeOH (5%) as eluent, produced compound **MTP43** (270 mg, 43%) as an oil: IR (cm^{-1}) ν 1372 (O=S=O), 1224 (C-O-C), 1180 (C–Br); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (t, *J* = 1.9 Hz, 1H), 7.85 (d, *J* = 9.0 Hz, 1H, H7), 7.75 (ddd, *J* = 8.0, 1.9, 1.0 Hz, 1H), 7.64 (ddd, *J* = 8.0, 1.9, 1.0 Hz, 1H), 7.49 (d, *J* = 3.6 Hz, 1H, H2), 7.29 (t, *J* = 8.0 Hz, 1H), 6.99 (d, *J* = 2.5 Hz, 1H, H4), 6.94 (dd, *J* = 9.0, 2.5 Hz, 1H, H6), 6.61 (dd, *J* = 3.6, 0.8 Hz, 1H, H3), 4.03 (t, *J* = 6.2 Hz, 2H), 3.33 (d, *J* = 2.5 Hz, 2H), 2.64 - 2.57 (m, 10H), 2.27 (t, *J* = 2.5 Hz, 1H), 2.02 - 1.99 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9, 139.8, 136.8 (CH_{Ar}), 131.8, 130.7 (CH_{Ar}), 129.5 (CH_{Ar}), 129.4, 126.9 (C2), 125.2 (CH_{Ar}), 123.1, 114.4 (C7), 114.3 (C6), 110.0 (C3), 104.7 (C4), 78.6, 73.4 (CH), 66.5 (CH_2), 55.1 ($2CH_2$), 52.9 ($2CH_2$), 51.4 (CH_2), 46.7 (CH_2), 26.4 (CH_2); HRMS (ESI): Calcd for $C_{24}H_{27}BrN_3O_3S^+$ [*M* + H]$^+$: 516.0951. Found: 516.0954. Anal. Calcd for $C_{24}H_{26}BrN_3O_3S \cdot H_2O$: C, 53.93; H, 5.28; N, 7.86; S, 6.00. Found: C, 53.83; H, 5.13; N, 7.82; S, 5.96.



1-((4-Bromophenyl)sulfonyl)-5-methoxy-1*H*-indole (SMD1). Following the **General Method A**, the reaction of commercial 5-methoxy-1*H*-indole (300 mg, 2.04 mmol),

dissolved in dry DMF (28.5 mL), with NaH (98 mg, 4.08 mmol) and 4-bromobenzenesulfonyl chloride (573 mg, 2.24 mmol), after purification by flash chromatography of the residue using hexane/AcOEt (10:1) as eluent, gave compound **SMD1** (585 mg, 78%) as a white solid: mp 135-137 ºC; IR (cm^{-1}) ν 1371 (O=S=O), 1150 (C-O-C), 1090 (C–Br); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dt, J = 8.8, 0.7 Hz, 1H, H7), 7.75 - 7.67 (m, 2H), 7.62 - 7.52 (m, 2H), 7.49 (d, J = 3.7 Hz, 1H, H2), 6.98 (d, J = 2.5 Hz, 1H, H4), 6.94 (dd, J = 8.8, 2.5 Hz, 1H, H6), 6.62 (dd, J = 3.7, 0.8 Hz, 1H, H3), 3.82 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6, 137.0, 132.5 ($2CH_{Ar}$), 131.9, 129.4, 129.0, 128.1 ($2CH_{Ar}$), 126.9 (C2), 114.3 (C7), 113.9 (C6), 110.0 (C3), 103.8 (C4), 55.6 (OMe). HRMS (ESI): Calcd for $C_{15}H_{12}BrNNaO_3S^+$ [M + Na]$^+$: 387.9613. Found: 387.9619.

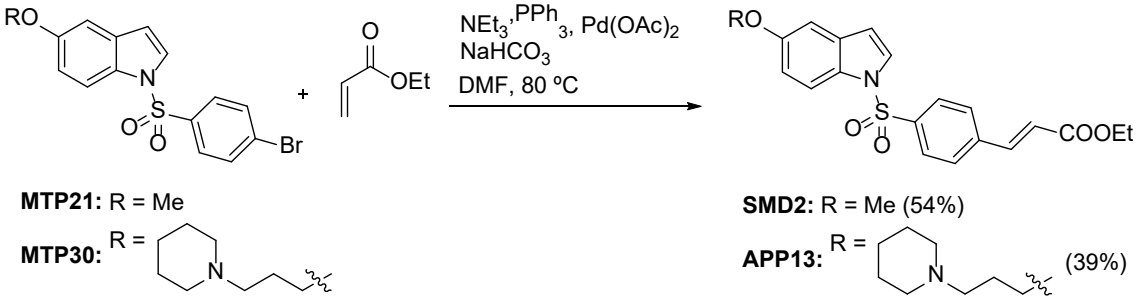
1-((4-Bromophenyl)sulfonyl)-5-(3-(piperidin-1-yl)propoxy)-1*H*-indole (APP11). Following the **General Method A**, the reaction of 5-(3-(piperidin-1-yl)propoxy)-1*H*-indole[26] (830 mg, 3.22 mmol), dissolved in dry DMF (45 mL), with NaH (154 mg, 6.43 mmol) and 4-bromobenzenesulfonyl chloride (904 mg, 3.54 mmol), after purification by flash chromatography of the residue using DCM/MeOH (2%) as eluent, afforded compound **APP11** (706 mg, 46%) as a white solid: mp 194-196 ºC: IR (cm^{-1}) ν 1396 (O=S=O), 1185 (C-O-C), 1133 (C–Br); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (dd, J = 8.9, 0.7 Hz, 1H, H7), 7.69 (d, J = 8.9 Hz, 2H), 7.55 (d, J = 8.9 Hz, 2H), 7.47 (d, J = 3.7 Hz, 1H, H2), 6.98 (d, J = 2.5 Hz, 1H, H4), 6.93 (dd, J = 8.9, 2.5 Hz, 1H, H6), 6.60 (dt, J = 3.7, 0.7 Hz, 1H, H3), 4.01 (t, J = 6.4 Hz, 2H), 2.51 - 2.35 (m, 6H), 2.12 - 1.79 (m, 2H), 1.63 - 1.55 (m, 4H), 1.47 - 1.44 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1, 137.0, 132.5 ($2CH_{Ar}$), 131.9, 129.4, 129.0, 128.1 ($2CH_{Ar}$), 126.9 (C2), 114.4 (C6), 114.3 (C7), 110.0 (C3), 104.7 (C4), 67.0 (CH_2), 56.0 (CH_2), 54.7 ($2CH_2$), 26.9 (CH_2), 26.0 ($2CH_2$), 24.4 (CH_2). HRMS (ESI): Calcd for $C_{22}H_{26}BrN_2O_3S^+$ [M + H]$^+$: 477.0842. Found: 477.0847.



Ethyl (*E*)-3-(3-((5-methoxy-1*H*-indol-1-yl)sulfonyl)phenyl)acrylate (MTP25). Following the **General Method B**, the reaction of a solution of compound **MTP21** (550 mg, 1.50 mmol) in dry DMF (3 mL) with ethyl acrylate (0.2 mL, 1.80 mmol), triethylamine (0.4 mL, 2.55 mmol), triphenylphosphine (197 mg, 0.75 mmol), palladium acetate (169 mg, 0.75 mmol), and sodium bicarbonate (126 mg, 1.5 mmol), after purification by flash chromatography of the residue using hexane/AcOEt (10%) as eluent, gave compound **MTP25** (578 mg, 67%) as a white solid: mp 95-97 ^{0}C; IR (cm^{-1}) ν 1712 (C=O), 1371 (O=S=O), 1169 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (t, *J* = 1.9 Hz, 1H), 7.89 (d, *J* = 8.9 Hz, 1H, H7), 7.82 (ddd, *J* =7.9, 1.9, 1.1 Hz, 1H), 7.67 - 7.63 (m, 1H), 7.60 (d, *J* = 16.0 Hz, 1H, C*H*=CH), 7.52 (d, *J* = 3.6 Hz, 1H, H2), 7.45 (t, *J* = 7.9 Hz, 1H), 7.01 - 6.93 (m, 2H, H4 and H6), 6.62 (dd, *J* = 3.6, 0.8 Hz, 1H, H3), 6.44 (d, *J* = 16.0 Hz, 1H, CH=C*H*), 4.28 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 156.6, 141.9 (*C*H=CH), 139.1, 135.8, 132.6 (CH_{Ar}), 131.8, 129.8 (CH_{Ar}), 129.5, 127.7 (CH_{Ar}), 127.0 (C2), 125.8 (CH_{Ar}), 121.1 (CH=*C*H), 114.3 (C7), 113.9 (C6), 109.8 (C3), 103.8 (C4), 60.9 (CH_2), 55.6 (OCH_3), 14.2 (CH_3). HRMS (ESI): Calcd for $C_{20}H_{19}NNaO_5S^+$ [*M* + Na]$^+$: 408.0876. Found: 408.0851.

Ethyl (*E*)-3-(3-((5-(benzyloxy)-1*H*-indol-1-yl)sulfonyl)phenyl)acrylate (MTP13). Following the **General Method B**, the reaction of compound **MTP12** (180 mg, 0.41 mmol), dissolved in dry DMF (0.8 mL), with ethyl acrylate (0.05 mL, 0.49 mmol), TEA (0.1 mL, 0.69 mmol), PPh_3 (53 mg, 0.20 mmol), palladium(II) acetate (46 mg, 0.20 mmol) and sodium bicarbonate (34 mg, 0.41 mmol), after purification by flash chromatography of the residue using hexane/AcOEt (3%) as eluent, provided compound **MTP13** (103 mg, 55%) as a white solid: mp 102-104 ºC; IR (cm^{-1}) ν 1643 (C=O), 1451 (O=S=O), 1114 (C-O-C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (t, *J* = 1.7 Hz, 1H), 7.90 (d, *J* = 8.9 Hz, 1H, H7), 7.83 (ddd, *J* =7.9, 1.7, 1.1 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 16.0 Hz, 1H, C*H*=CH), 7.52 (d, *J* = 3.7 Hz, 1H, H2), 7.48 - 7.30 (m, 6H), 7.80 - 7.00 (m, 2H, H4 and H6), 6.61 (dd, *J* = 3.7, 0.6 Hz, 1H), 6.44 (d, *J* = 16.0 Hz, 1H, CH=C*H*), 5.07 (s, 2H), 4.28 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.1, 155.8, 141.9 (*C*H=CH), 139.1, 136.9, 135.8, 132.6 (CH_{Ar}), 131.8, 129.9 (CH_{Ar}), 129.6, 128.6 ($2CH_{Ar}$), 128.0 (CH_{Ar}), 127.7 (CH_{Ar}), 127.4 ($2CH_{Ar}$), 127.0 (C2), 125.8 (CH_{Ar}), 121.1 (CH=*C*H), 114.6 (C7), 114.3 (C6), 109.8 (C3), 105.1 (C4), 70.5 (CH_2), 60.9 (CH_2), 14.3 (CH_3); HRMS (ESI): Calcd for $C_{26}H_{23}NNaO_5S^+$ [*M* + Na]$^+$: 484.1189. Found: 484.1188.

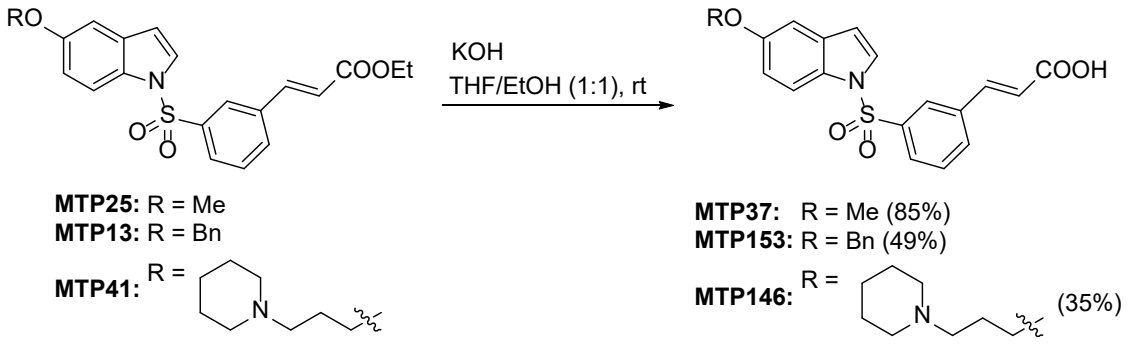
Ethyl (*E*)-3-(3-((5-(3-(Piperidin-1-yl)propoxy)-1*H*-indol-1-yl)sulfonyl)phenyl) acrylate (MTP41). Following the **General Method B**, the reaction of 1-((3-bromophenyl)sulfonyl)-5-(3-(piperidin-1-yl)propoxy)-1*H*-indole (**MTP30**) (667 mg, 1.40 mmol), dissolved in dry DMF (2.8 mL), with ethyl acrylate (0.2 mL, 1.68 mmol), TEA (0.3 mL, 2.38 mmol), PPh_3 (183 mg, 0.70 mmol), palladium(II) acetate (157 mg, 0.70 mmol) and sodium bicarbonate (117 mg, 1.40 mmol), after purification by flash chromatography of the residue using DCM/MeOH (2%) as eluent, produced compound **MTP41** (694 mg, 85%) as a brown solid: mp 95-97 ^{0}C; IR (cm^{-1}) ν 1714 (C=O), 1372 (O=S=O), 1155 (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (t, *J* = 1.8 Hz, 1H), 7.88 (dt, *J* = 9.0, 0.9 Hz, 1H, H7), 7.81 (ddd, *J* = 7.9, 1.9, 1.1 Hz, 1H), 7.65 (ddt, *J* = 7.4, 1.5, 0.9 Hz, 1H), 7.59 (d, *J* = 16.0 Hz, 1H, C*H*=CH), 7.52 (d, *J* = 3.7 Hz, 1H, H2), 7.45 (t, *J* = 7.9 Hz, 1H), 6.96 (d, *J* = 2.1 Hz, 1H, H4), 6.90 (dd, *J* = 9.0, 2.1 Hz, 1H, H6), 6.61 (dd, *J* = 3.7, 0.9 Hz, 1H, H3), 6.43 (d, *J* = 16.0 Hz, 1H, CH=C*H*), 4.28 (q, *J* = 7.1 Hz, 2H), 4.06 (t, *J* = 5.7 Hz, 2H), 3.09 - 3.00 (m, 6H), 2.44 - 2.35 (m, 2H), 2.10 - 1.95 (m, 4H), 1.78 - 1.60 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 155.6, 141.8 (*C*H=CH), 139.0, 135.8, 132.6 (CH_{Ar}), 131.8, 129.9 (CH_{Ar}), 129.6, 127.6 (CH_{Ar}), 127.0 (C2), 125.8 (CH_{Ar}), 121.1 (CH=*C*H), 114.3 (C7), 114.3 (C6), 109.8 (C3), 104.6 (C4), 66.2 (CH_2), 60.9 (CH_2), 55.7 ($2CH_2$), 54.1 ($2CH_2$), 25.5 (CH_2), 24.4 (CH_2), 23.3 (CH_2), 14.2 (CH_3); HRMS (ESI): Calcd for $C_{27}H_{33}N_2O_5S^+$ [*M* + H]$^+$: 497.2105. Found: 497.2087; Anal. Calcd for $C_{27}H_{32}N_2O_5S{\cdot}3H_2O$: C, 58.89; H, 6.96; N, 5.09; S, 5.82. Found: C, 58.98; H, 7.17; N, 5.13; S, 5.87.



Ethyl (*E*)-3-(4-((5-Methoxy-1*H*-indol-1-yl)sulfonyl)phenyl)acrylate (SMD2). Following the **General Method B**, the reaction of compound **SMD1** (580 mg, 1.58 mmol), dissolved in dry DMF (0.9 mL), with ethyl acrylate (0.2 mL, 1.90 mmol), TEA (0.4 mL, 2.69 mmol), PPh_3 (208 mg, 0.79 mmol), palladium(II) acetate (178 mg, 0.79 mmol) and sodium bicarbonate (133 mg, 1.58 mmol), after purification by flash chromatography of the residue using hexane/AcOEt (10:1) as eluent, gave compound

SMD2 (330 mg, 54%) as a yellow solid: mp 115-7 ^{0}C; IR (cm^{-1}): ν 1717 (C=O), 1312 (O=S=O), 1107 (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (dt, J = 8.9, 0.8 Hz, 1H, H7), 7.89 - 7.80 (m, 2H), 7.64 - 7.40 (m, 4H), 6.99 - 6.98 (m, 1H, H4), 6.94 (dd, J = 8.9, 2.5 Hz, 1H, H6), 6.61 (dd, J = 3.6, 0.8 Hz, 1H, H3), 6.44 (d, J = 16.0 Hz, 1H, CH=C*H*), 4.26 (q, J = 7.1 Hz, 2H), 3.82 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 156.6, 141.8 (*C*H=CH), 139.6, 138.8, 131.8, 129.5, 128.5 ($2CH_{Ar}$), 127.2 ($2CH_{Ar}$), 127.0 (C2), 122.1 (CH=*C*H), 114.4 (C6), 113.9 (C4), 109.8 (C3), 103.7 (C7), 60.9 (CH_2), 55.6 (OCH_3), 14.2 (CH_3); HRMS (ESI): Calcd for $C_{20}H_{19}NNaO_5S^+$ [M + Na]$^+$: 408.0876. Found: 408.0884.

Ethyl (*E*)-3-(4-((5-(3-(Piperidin-1-yl)propoxy)-1*H*-indol-1-yl)sulfonyl)phenyl)acrylate (APP13). Following the **General Method B**, the reaction of compound **APP11** (1 g, 2.25 mmol), dissolved in dry DMF (15 mL), with ethyl acrylate (0.3 mL, 2.70 mmol), TEA (0.53 mL, 3.82 mmol), PPh_3 (294 mg, 1.12 mmol), palladium(II) acetate (251 mg, 1.12 mmol) and sodium bicarbonate (189 mg, 2.25 mmol), after, purification by flash chromatography of the residue using DCM/MeOH (2%) as eluent, afforded compound **APP13** (439 mg, 39%) as a brown oil: IR (cm^{-1}): ν 1713 (C=O), 1371 (O=S=O), 1154 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 9.0 Hz, 1H, H7), 7.84 (d, J = 8.6 Hz, 2H), 7.58 (d, J = 16.0 Hz, 1H, C*H*=CH), 7.53 (d, J = 8.6 Hz, 2H), 7.50 (d, J = 3.7 Hz, 1H, H2), 6.97 (d, J = 2.5 Hz, 1H, H4), 6.92 (dd, J = 9.0, 2.5 Hz, 1H, H6), 6.60 (dd, J = 3.7, 0.8 Hz, 1H, H3), 6.44 (d, J = 16.0 Hz, 1H, CH=C*H*), 4.26 (q, J = 7.1 Hz, 2H), 4.01 (t, J = 6.2 Hz, 2H), 2.67 - 2.46 (m, 6H), 2.12 - 2.00 (m, 2H), 1.69 (q, J = 5.8 Hz, 4H), 1.54 - 1.45 (m, 2H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 155.8, 141.8 (*C*H=CH), 139.6, 138.8, 131.8, 129.5, 128.4 ($2CH_{Ar}$), 127.2 ($2CH_{Ar}$), 127.0 (C2), 122.1 (CH=*C*H), 114.3 (C6), 114.3 (C4), 109.8 (C3), 104.6 (C7), 66.6 (CH_2), 60.9 (CH_2), 55.9 (CH_2), 54.3 ($2CH_2$), 26.2 (CH_2), 25.5 ($2CH_2$), 23.9 (CH_2), 14.2 (CH_3); HRMS (ESI): Calcd for $C_{27}H_{33}N_2O_5S^+$ [M + H]$^+$: 497.2105. Found: 497.2111.

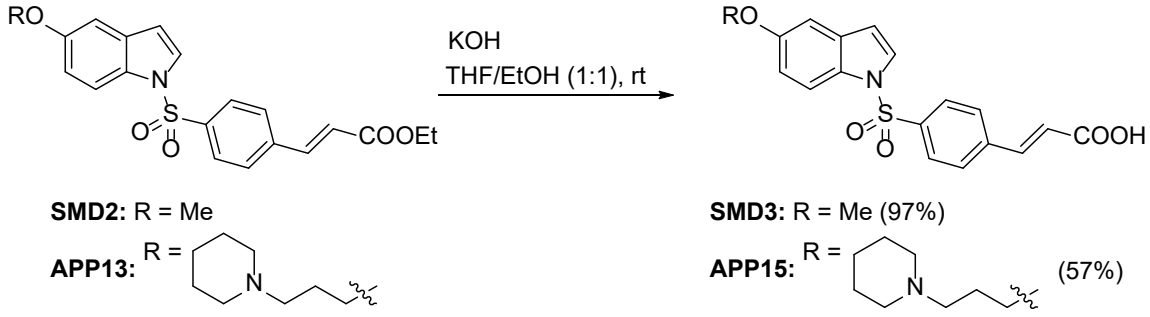


(*E*)-3-(3-((5-Methoxy-1*H*-indol-1-yl)sulfonyl)phenyl)acrylic acid (MTP37). Following the **General Method C**, the reaction of compound **MTP25** (100 mg, 0.26 mmol), dissolved in a mixture of THF/EtOH (1:1) (1 mL) with KOH (0.5 mL, 1.04 mmol), after purification by flash chromatography of the residue using DCM/MeOH (5%) as eluent, provided compound **MTP37** (75 mg, 85%) as a brown solid: mp 167-169 ^{0}C; IR (cm^{-1}) ν 3054 (COO-H), 1692 (C=O), 1422 (O=S=O), 1265 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.25 (s, 1H), 8.00 (d, *J* = 7.8 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 9.0 Hz, 1H, H7), 7.81 (d, *J* = 3.7 Hz, 1H, H2), 7.64 - 7.57 (m, 2H), 7.10 (d, *J* = 2.5 Hz, 1H), 6.94 (dd, *J* = 9.0, 2.5 Hz, 1H, H6), 6.77 (d, *J* = 3.7 Hz, 1H, H3), 6.66 (d, *J* = 16.1 Hz, 1H, CH=C*H*), 3.74 (s, 3H) (the COO*H* signal could not be assigned); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 167.2, 156.2, 141.5 (*C*H=CH), 137.8, 136.0, 133.5 (CH$_{Ar}$), 131.7, 130.4 (CH$_{Ar}$), 128.7, 127.9 (C2), 127.7 (CH$_{Ar}$), 126.2 (CH$_{Ar}$), 122.3 (CH=*C*H), 114.1 (C7), 113.7 (C6), 110.1 (C3), 104.1 (C4), 55.4 (OCH$_3$); HRMS (ESI): Calcd for C$_{18}$H$_{15}$NNaO$_5$S$^+$ [*M* + Na]$^+$: 380.0563. Found: 380.0561.

(*E*)-3-(3-((5-(Benzyloxy)-1*H*-indol-1-yl)sulfonyl)phenyl)acrylic acid (MTP153). Following the **General Method C**, the reaction of compound **MTP13** (1.1 g, 2.38 mmol), dissolved in a mixture of THF/EtOH (1:1) (10 mL), with KOH (4.5 mL, 9.53 mmol), after purification by flash chromatography of the residue using DCM/MeOH (5%) as eluent, produced compound **MTP153** (503 mg, 49%) as a brown solid: mp 166-168 ^{0}C; IR (cm^{-1}) ν 2976 (COO-H), 1694 (C=O), 1369 (O=S=O), 1155 (C-O-C); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.99 (t, *J* = 1.8 Hz, 1H), 7.91 (dt, *J* = 8.8, 1.0 Hz, 1H, H7), 7.87 (ddd, *J* = 8.0, 1.8, 1.0 Hz, 1H), 7.73 - 7.68 (m, 2H), 7.53 (d, *J* = 3.7 Hz, 1H), 7.48 (t, *J* = 8.0 Hz, 1H), 7.46 - 7.30 (m, 5H), 7.07 - 7.02 (m, 2H, H4 and H6), 6.62 (dd, *J* = 3.7, 1.0 Hz, 1H), 6.46 (d, *J* = 16.0 Hz, 1H, CH=C*H*), 5.07 (s, 2H) (the COO*H* signal could not be assigned); ^{13}C NMR (101 MHz, CDCl$_3$) δ 170.6, 155.8, 144.3 (*C*H=CH), 139.2, 136.9, 135.4 (CH$_{Ar}$), 132.8 (CH$_{Ar}$), 131.8 (CH$_{Ar}$), 130.0 (CH$_{Ar}$), 129.6, 128.6 (2CH$_{Ar}$), 128.2, 128.0 (CH$_{Ar}$),

127.5 ($2CH_{Ar}$), 127.0, 126.1 (C2), 120.0 (CH=*C*H), 114.7 (C6), 114.4 (C7), 109.9 (C3), 105.2 (C4), 70.5 (CH_2); HRMS (ESI): Calcd for $C_{24}H_{19}NNaO_5S^+$ [*M* + Na]$^+$: 456.0876. Found: 456.0881.

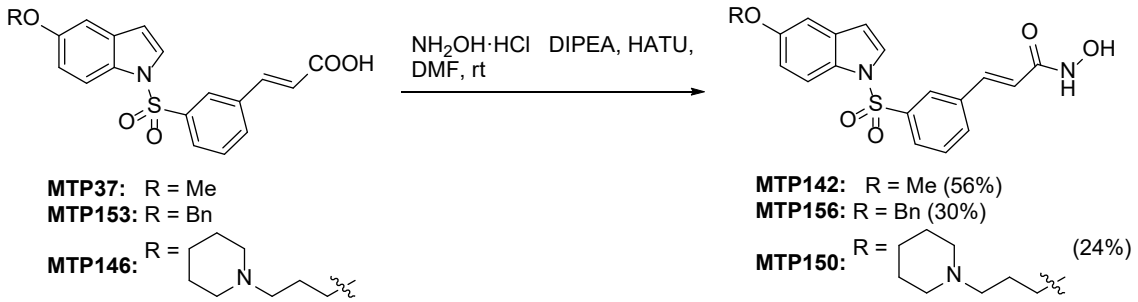
(*E*)-3-(3-((5-(3-(Piperidin-1-yl)propoxy)-1*H*-indol-1-yl)sulfonyl)phenyl)acrylic acid (MTP146). Following the **General Method C**, the reaction of compound **MTP41** (450 mg, 0.91 mmol), dissolved in a mixture of THF/EtOH (1:1) (3.6 mL), with KOH (1.7 mL, 3.62 mmol), after purification by flash chromatography of the residue using DCM/MeOH/NH_4OH (80:18:2) as eluent, gave compound **MTP146** (150 mg, 35%) as a white solid: mp 168-170 ^{0}C; IR (cm^{-1}) ν 2929 (COO-H), 1641 (C=O), 1366 (O=S=O), 1141 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.99 (d, *J* = 7.6 Hz, 1H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.87 (d, *J* = 9.0 Hz, 1H, H7), 7.80 (d, *J* = 3.7 Hz, 1H, H2), 7.65 - 7.50 (m, 2H), 7.10 (t, *J* = 2.1 Hz, 1H, H4), 6.93 (dd, *J* = 9.0, 2.1 Hz, 1H, H6), 6.76 (dd, *J* = 3.7, 1.5 Hz, 1H, H3), 6.65 (d, *J* = 16.1 Hz, 1H, CH=C*H*), 3.98 (td, *J* = 6.2, 1.7 Hz, 2H), 2.62 - 2.57 (m, 6H), 1.97 - 1.87 (m, 2H), 1.62 - 1.45 (m, 4H), 1.48 - 1.32 (m, 2H) (the COO*H* signal could not be assigned); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 155.3, 138.6, 137.8 (*C*H=CH), 137.3, 132.3 (CH_{Ar}), 131.8, 129.8, 129.6 (CH_{Ar}), 127,6 (CH_{Ar}) 127.2 (C2), 126.5 (CH=*C*H), 125.3 (CH_{Ar}), 114.4 (C7), 113.8 (C6), 109.6 (C3), 105.2 (C4), 65.8 (CH_2), 54.8 (CH_2), 53.0 ($2CH_2$), 24.1 (CH_2), 23.0 ($2CH_2$), 22.5 (CH_2); HRMS (ESI): Calcd for $C_{25}H_{29}N_2O_5S^+$ [*M* + H]$^+$: 469.1792. Found: 469.1792.



(*E*)-3-(4-((5-Methoxy-1*H*-indol-1-yl)sulfonyl)phenyl)acrylic acid (SMD3). Following the **General Method C**, the reaction of compound **SMD2** (255 mg, 0.66 mmol), dissolved in a mixture of THF/EtOH (1:1) (2.6 mL), with KOH (1.2 mL, 2.65 mmol), after purification by flash chromatography of the residue using DCM/MeOH (5%) as eluent, afforded compound **SMD3** (230 mg, 97%) as a brown solid: mp 226-228 ^{0}C; IR (cm^{-1}): ν 2971 (COO–H), 1694 (C=O), 1372 (O=S=O), 1150 (C-O-C); ^{1}H NMR (300 MHz, DMSO-d_6) *δ* 12.62 (s, 1H, COOH), 7.97 - 7.79 (m, 5H), 7.77 (d, *J* = 3.7 Hz, 1H, H2), 7.63 - 7.50 (m, 1H), 7.11 - 7.09 (m, 1H, H4), 6.94 (dd, *J* = 8.9, 2.6 Hz, 1H, H6), 6.78 (d,

J = 3.7 Hz, 1H, H3), 6.63 (d, *J* = 16.1 Hz, 1H, CH=C*H*), 3.74 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 167.0 (COOH), 156.2, 141.4 (*C*H=CH), 140.0, 137.4, 131.7, 129.2 (2CH$_{Ar}$), 128.7, 127.8 (C2), 127.1 (2CH$_{Ar}$), 123.3 (CH=*C*H), 114.0 (C7), 113.7 (C6), 110.1 (C3), 104.0 (C4), 55.4 (OCH$_3$); HRMS (ESI): Calcd for $C_{18}H_{15}NNaO_5S^+$ [*M* + Na]$^+$: 380.0563. Found: 380.0574.

(*E*)-3-(4-((5-(3-(Piperidin-1-yl)propoxy)-1*H*-indol-1-yl)sulfonyl)phenyl)acrylic acid (APP15). Following the **General Method C**, the reaction of compound **APP13** (1 g, 2.01 mmol), dissolved in a mixture of THF/EtOH (1:1) (8 mL), with KOH (3.7 mL, 8.10 mmol), after purification by flash chromatography of the residue using DCM/MeOH/NH$_4$OH (98:1.8:0.2) as eluent, provided compound **APP15** (533 mg, 57%) as a brown solid: mp 73-75 ^{0}C; IR (cm^{-1}): ν 3381 (COO–H), 1638 (C=O), 1364 (O=S=O), 1141 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.92 (d, *J* = 8.9 Hz, 2H), 7.85 (d, *J* = 8.9 Hz, 2H), 7.82 (d, *J* = 9.0 Hz, 1H, H7), 7.76 (d, *J* = 3.7 Hz, 1H, H2), 7.54 (d, *J* = 16.1 Hz, 1H, C*H*=CH), 7.11 (d, *J* = 2.5 Hz, 1H, H4), 6.94 (dd, *J* = 9.0, 2.5 Hz, 1H, H6), 6.76 (d, *J* = 3.7 Hz, 1H, H3), 6.63 (d, *J* = 16.1 Hz, 1H, CH=C*H*), 3.99 (t, *J* = 6.3 Hz, 2H), 2.66 - 2.53 (m, 6H), 1.95 - 1.92 (m, 2H), 1.57 - 1.53 (m, 4H), 1.43 - 1.40 (m, 2H) (the COO*H* signal could not be assigned); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 167.6 (COOH), 155.9, 141.5 (*C*H=CH), 140.6, 137.8, 132.2, 129.6 (2CH$_{Ar}$), 129.2, 128.2 (C2), 127.5 (2CH$_{Ar}$), 124.3 (CH=*C*H), 114.6 (C6), 114.5 (C7), 110.6 (C3), 105.3 (C4), 66.5 (CH$_2$), 55.0 (CH$_2$), 53.9 (2CH$_2$), 25.8 (CH$_2$), 25.0 (2CH$_2$), 23.7 (CH$_2$); HRMS (ESI): Calcd for $C_{25}H_{29}N_2O_5S^+$ [*M* + H]$^+$: 469.1792. Found: 469.1797.



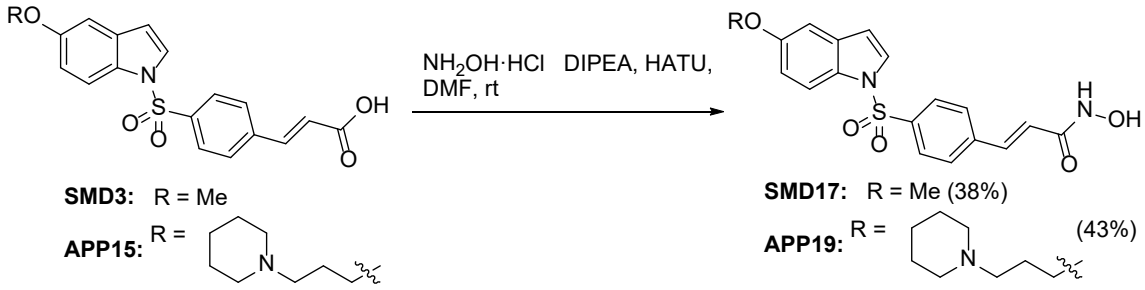
(*E*)-*N*-Hydroxy-3-(3-((5-methoxy-1*H*-indol-1-yl)sulfonyl)phenyl)acrylamide (MTP142). Following the **General Method D**, the reaction of compound **MTP37** (170 mg, 0.48 mmol), dissolved in dry DMF (1.9 mL), with DIPEA (0.3 mL, 1.67 mmol, 3.5 equiv), HATU (181 mg, 0.48 mmol) and NH$_2$OH·HCl (33 mg, 0.48 mmol), after purification by flash chromatography of the residue using DCM/MeOH/NH$_4$OH

(95:4.5:0.5) as eluent, produced compound **MTP142** (100 mg, 56%) as a white solid: mp 95-97 ^{0}C; IR (cm^{-1}) ν 3403 (O-H), 2953 (N-H), 1611 (C=O), 1245 (O=S=O), 1171 (C-O-C); ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.82 (s, 1H, N*H* or O*H*), 9.14 (s, 1H, N*H* or O*H*), 8.14 (d, *J* = 1.9 Hz, 1H), 7.92 - 7.81 (m, 3H), 7.77 (d, *J* = 3.7 Hz, 1H, H2), 7.59 (t, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 15.9 Hz, 1H, C*H*=CH), 7.11 (d, *J* = 2.6 Hz, 1H, H4), 6.95 (dd, *J* = 9.0, 2.6 Hz, 1H, H6), 6.78 (d, *J* = 3.7 Hz, 1H, H3), 6.55 (d, *J* = 15.9 Hz, 1H, CH=C*H*), 3.74 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d$_6$) δ 162.0, 156.2, 137.7, 136.5, 136.1 (*C*H=CH), 132.8 (CH$_{Ar}$), 131.7, 130.5 (CH$_{Ar}$), 128.7, 127.7 (C2), 126.9 (CH$_{Ar}$), 125.3 (CH$_{Ar}$), 122.0 (CH=*C*H), 114.0 (C7), 113.7 (C6), 110.0 (C3), 104.0 (C4), 55.4 (OCH$_3$); HRMS (ESI): Calcd for $C_{18}H_{16}N_2NaO_5S^+$ [*M* + Na]$^+$: 395.0672. Found: 395.0676.

(*E*)-3-(3-((5-(Benzyloxy)-1*H*-indol-1-yl)sulfonyl)phenyl)-*N*-hydroxyacrylamide (MTP156). Following the **General Method D**, the reaction of compound **MTP153** (180 mg, 0.42 mmol), dissolved in dry DMF (1.7 mL), with DIPEA (0.14 mL, 1.48 mmol, 3.5 equiv), HATU (158 mg, 0.42 mmol) and NH$_2$OH·HCl (29 mg, 0.42 mmol), after purification by flash chromatography of the residue using DCM/MeOH/NH$_4$OH (96:3.6:0.4) as eluent, gave compound **MTP156** (54 mg, 30%) as a white solid: mp 75-77 ^{0}C; IR (cm^{-1}) ν 3142 (O-H), 2919 (N-H), 1614 (C=O), 1369 (O=S=O), 1139 (C-O-C); ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.14 (t, *J* = 1.8 Hz, 1H), 7.89 (ddd, *J* = 7.8, 1.9, 0.9 Hz, 1H), 7.87 - 7.83 (m, 2H), 7.78 (d, *J* = 3.7 Hz, 1H, H2), 7.59 (t, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 15.9 Hz, 1H, C*H*=CH), 7.46 - 7.40 (m, 2H), 7.41 - 7.34 (m, 2H), 7.35 - 7.28 (m, 1H), 7.20 (d, *J* = 2.5 Hz, 1H, H4), 7.03 (dd, *J* = 9.0, 2.5 Hz, 1H, H6), 6.77 (dd, *J* = 3.7, 0.9 Hz, 1H, H3), 6.56 (d, *J* = 15.9 Hz, 1H, CH=C*H*), 5.08 (s, 2H) (the CON*H*O*H* signal could not be assigned); ^{13}C NMR (126 MHz, DMSO-d$_6$) δ 161.9, 155.2, 137.7, 137.1, 136.5, 136.0 (*C*H=CH), 132.8 (CH$_{Ar}$), 131.6, 130.5 (CH$_{Ar}$), 128.8, 128.4 (2CH$_{Ar}$), 127.8 (C2), 127.8, 127.7 (2CH$_{Ar}$), 126.9 (CH$_{Ar}$), 125.3 (CH$_{Ar}$), 122.1 (CH=*C*H), 114.3 (C6), 114.0 (C7), 110.0 (C3), 105.2 (C4), 69.6 (CH$_2$); HRMS (ESI): Calcd for $C_{24}H_{21}N_2O_5S^+$ [*M* + H]$^+$: 449.1166. Found: 449.1167.

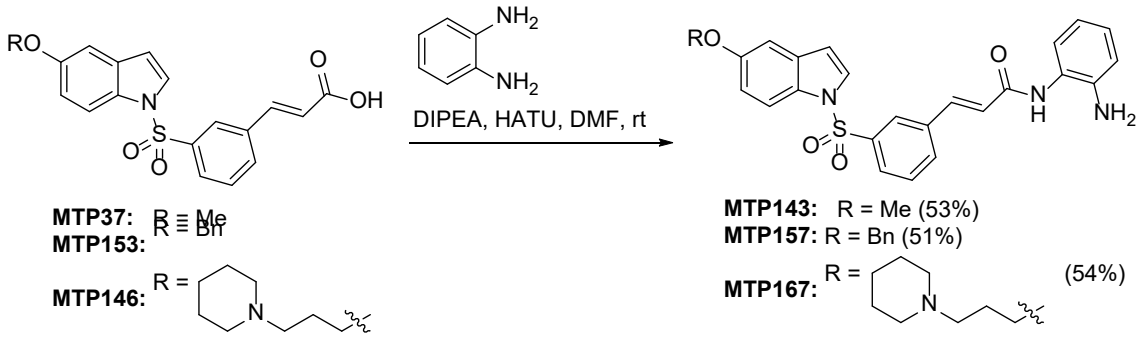
(*E*)-*N*-Hydroxy-3-(3-((5-(3-(piperidin-1-yl)propoxy)-1*H*-indol-1-yl)sulfonyl) phenyl)acrylamide (MTP150). Following the **General Method D**, the reaction of compound **MTP146** (287 mg, 0.61 mmol), dissolved in dry DMF (2.5 mL), with DIPEA (0.37 mL, 2.15 mmol, 3.5 equiv), HATU (233 mg, 0.61 mmol) and NH$_2$OH·HCl (43 mg, 0.61 mmol), after purification by flash chromatography of the residue using

DCM/MeOH/NH_4OH (90:9:1) as eluent, afforded compound **MTP150** (70 mg, 24%) as white solid: mp 108-110 ^{0}C; IR (cm^{-1}): ν 3145 (O-H), 2931 (N-H), 1611 (C=O), 1369 (O=S=O), 1141 (C-O-C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.13 (t, J = 1.9 Hz, 2H), 7.89 - 7.81 (m, 3H), 7.76 (d, J = 3.7 Hz, 1H, H2), 7.59 (t, J = 7.9 Hz, 1H), 7.48 (d, J = 15.9 Hz, 1H, C*H*=CH), 7.10 (d, J = 2.5 Hz, 1H, H4), 6.94 (dd, J = 9.0, 2.5 Hz, 1H, H6), 6.76 (d, J = 3.7 Hz, 1H, H3), 6.55 (d, J = 15.9 Hz, 1H, CH=C*H*), 3.97 (t, J = 6.3 Hz, 2H), 2.47 - 2.29 (m, 6H), 1.89 - 1.83 (m, 2H), 1.51 - 1.47 (m, 4H), 1.38 - 1.36 (m, 2H) (the CON*H*O*H* signal could not be assigned); ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.9, 155.5, 137.7, 136.5, 136.0 (*C*H=CH), 132.8 (CH_{Ar}), 131.7, 130.5 (CH_{Ar}), 128.6, 127.7 (C2), 126.9 (CH_{Ar}), 125.3 (CH_{Ar}), 122.1 (CH=*C*H), 114.2 (C6), 114.0 (C7), 110.1 (C3), 104.8 (C4), 66.2 (CH_2), 55.0 (CH_2), 53.9 ($2CH_2$), 26.1 (CH_2), 25.4 ($2CH_2$), 23.9 (CH_2); HRMS (ESI): Calcd for $C_{25}H_{30}N_3O_5S^+$ [M + H]$^+$: 484.1901. Found: 484.1902.



(*E*)-*N*-Hydroxy-3-(4-((5-methoxy-1*H*-indol-1-yl)sulfonyl)phenyl)acrylamide (SMD17). Following the **General Method D**, the reaction of compound **SMD3** (250 mg, 0.70 mmol), dissolved in dry DMF (2.80 mL), with DIPEA (0.4 mL, 2.45 mmol, 3.5 equiv), HATU (266 mg, 0.70 mmol) and NH_2OH·HCl (49 mg, 0.70 mmol), after purification by flash chromatography of the residue using DCM/MeOH/NH_4OH (98:1.8:0.2) as eluent, provided compound **SMD17** (100 mg, 38%) as a yellow solid: mp 135-137 ^{0}C; IR (cm^{-1}): ν 3123 (O–H), 2989 (N–H), 1614 (C=O), 1376 (O=S=O), 1141 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (d, J = 8.6 Hz, 2H), 7.82 (d, J = 9.0 Hz, 1H, H7), 7.75 (d, J = 3.6 Hz, 1H, H2), 7.72 (d, J = 8.6 Hz, 2H), 7.43 (d, J = 15.9 Hz, 1H, C*H*=CH), 7.11 (d, J = 2.5 Hz, 1H, H4), 6.94 (dd, J = 9.0, 2.6 Hz, 1H, H6), 6.78 (dd, J = 3.6, 0.8 Hz, 1H, H3), 6.53 (d, J = 15.9 Hz, 1H, CH=C*H*), 3.74 (s, 3H) (the CON*H*O*H* signal could not be assigned); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.8, 156.2, 140.7 (*C*H=CH), 136.8, 136.0, 131.7, 128.7, 128.5 ($2CH_{Ar}$), 127.7 (C2), 127.3 ($2CH_{Ar}$), 123.2 (CH=*C*H), 114.0 (C7), 113.7 (C6), 110.1 (C3), 104.0 (C4), 55.0 (OCH_3); HRMS (ESI): Calcd for $C_{18}H_{16}N_2NaO_5S^+$ [M + Na]$^+$: 395.0672. Found: 395.0678.

(*E*)-*N*-Hydroxy-3-(4-((5-(3-(piperidin-1-yl)propoxy)-1*H*-indol-1-yl)sulfonyl)phenyl) acrylamide (APP19). Following the **General Method D**, the reaction of compound **APP15** (200 mg, 0.43 mmol), dissolved in dry DMF (1.72 mL), with DIPEA (0.26 mL, 1.50 mmol, 3.5 equiv), HATU (162 mg, 0.43 mmol) and $NH_2OH{\cdot}HCl$ (30 mg, 0.43 mmol), after purification by flash chromatography of the residue using DCM/MeOH/NH_4OH (98:1.8:0.2) as eluent, produced compound **APP19** (89 mg, 43%) as a yellow solid: mp 95-97 ^{0}C; IR (cm^{-1}): ν 3175 (O–H), 2925 (N–H), 1613 (C=O), 1369 (O=S=O), 1143 (C-O-C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.93 (d, J = 8.4 Hz, 2H), 7.81 (d, J = 9.0 Hz, 1H, H7), 7.75 - 7.71 (m, 3H), 7.43 (d, J = 15.8 Hz, 1H, C*H*=CH), 7.10 (d, J = 2.3 Hz, 1H, H4), 6.93 (dd, J = 9.0, 2.5 Hz, 1H, H6), 6.76 (d, J = 3.7 Hz, 1H, H3), 6.53 (d, J = 15.8 Hz, 1H, CH=C*H*), 3.97 (t, J = 6.3 Hz, 2H), 2.37 - 2.34 (m, 6H), 1.85 - 1.82 (m, 2H), 1.50 - 1.44 (m, 4H), 1.38 - 1.36 (m, 2H) (the CON*H*O*H* signal could not be assigned); ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.2, 156.1, 141.2, 137.3 (*C*H=CH), 136.5, 132.2, 129.2, 129.0 ($2CH_{Ar}$), 128.2 (C2), 127.8 ($2CH_{Ar}$), 123.7 (CH=*C*H), 114.7 (C6), 114.5 (C7), 110.6 (C3), 105.3 (C4), 66.8 (CH_2), 55.6 (CH_2), 54.5 ($2CH_2$), 26.7 (CH_2), 26.0 ($2CH_2$), 24.5 (CH_2); HRMS (ESI): Calcd for $C_{25}H_{30}N_3O_5S^+$ [*M* + H]$^+$: 484.1901. Found: 484.1900.



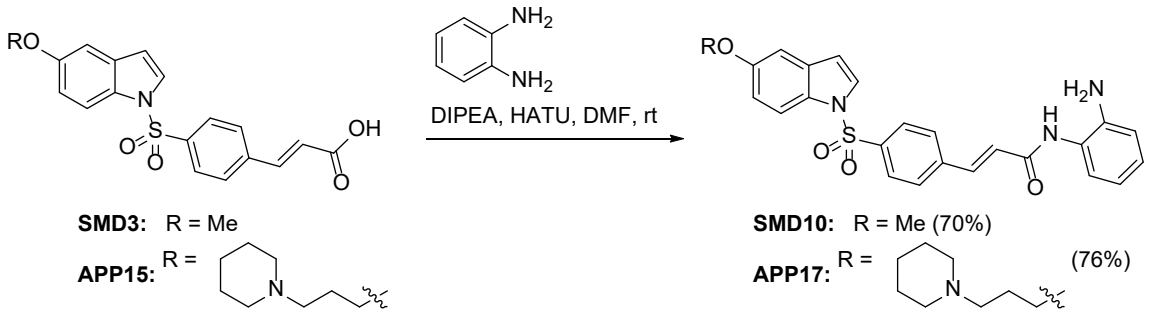
(*E*)-*N*-(2-Aminophenyl)-3-(3-((5-methoxy-1*H*-indol-1-yl)sulfonyl)phenyl) acrylamide (MTP143). Following the **General Method D**, the reaction of compound **MTP37** (150 mg, 0.42 mmol), dissolved in dry DMF (1.68 mL), with DIPEA (0.2 mL, 1.05 mmol, 2.5 equiv), HATU (160 mg, 0.42 mmol) and 1,2-phenylenediamine (45 mg, 0.42 mmol, after purification by flash chromatography of the residue using DCM/MeOH/NH_4OH (97:2.7:0.3) as eluent, produced compound **MTP143** (100 mg, 53%) as a yellow solid: mp 164-166 ^{0}C; IR (cm^{-1}): ν 3227 (N–H), 1660 (C=O), 1361 (O=S=O), 1140 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.44 (s, 1H, CON*H*), 8.21 (t, J = 1.8 Hz, 1H), 7.92 - 7.89 (m, 2H), 7.86 (d, J = 9.0 Hz, 1H, H7), 7.78 (d, J = 3.7 Hz,

1H, H2), 7.63 (t, *J* = 7.8 Hz, 1H), 7.58 (d, *J* = 15.8 Hz, 1H, C*H*=CH), 7.34 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.12 (d, *J* = 2.5 Hz, 1H, H4), 7.00 (d, *J* = 15.8 Hz, 1H, CH=C*H*), 6.98 - 6.89 (m, 2H), 6.80 (dd, *J* = 3.7, 0.7 Hz, 1H, H3), 6.75 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.58 (td, *J* = 7.5, 1.5 Hz, 1H), 4.96 (s, 2H, $CONHC_6H_4NH_2$), 3.74 (s, 3H,OCH_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.9, 156.2, 141.6, 137.8, 137.2 (*C*H=CH), 136.6, 133.1 (CH_{Ar}), 131.7, 130.6 (CH_{Ar}), 128.7 (CH_{Ar}), 128.7, 127.7 (C2), 127.0 (CH_{Ar}), 126.0 (CH_{Ar}), 125.2 (CH=*C*H), 124.7 (CH_{Ar}), 123.2, 116.3 (CH_{Ar}), 116.0 (CH_{Ar}), 114.0 (C7), 113.8 (C6), 110.1 (C3), 104.1 (C4), 55.4 (OCH_3); HRMS (ESI): Calcd for $C_{24}H_{22}N_3O_4S^+$ $[M + H]^+$: 448.1326. Found: 448.1323.

(*E*)-*N*-(2-Aminophenyl)-3-(3-((5-(benzyloxy)-1*H*-indol-1-yl)sulfonyl)phenyl) acrylamide (MTP157). Following the **General Method D**, the reaction of compound **MTP153** (120 mg, 0.28 mmol), dissolved in dry DMF (1.12 mL), with DIPEA (0.12 mL, 0.69 mmol, 2.5 equiv), HATU (105 mg, 0.28 mmol) and 1,2-phenylenediamine (30 mg, 0.28 mmol), after purification by flash chromatography of the residue using DCM/MeOH/NH_4OH (98:1.8:0.2) as eluent, afforded compound **MTP157** (74 mg, 51%) as a yellow solid: mp 148-150 ^{0}C; IR (cm^{-1}): ν 3216 (N–H), 1613 (C=O), 1356 (O=S=O), 1153 (C-O-C); ^1H NMR (400 MHz, DMSO-d_6) δ 9.43 (s, 1H, CON*H*), 8.21 (d, *J* = 1.8 Hz, 1H), 7.95 - 7.87 (m, 2H), 7.87 (d, *J* = 9.0 Hz, 1H, H7), 7.78 (d, *J* = 3.7 Hz, 1H, H2), 7.64 (t, *J* = 7.9 Hz, 1H), 7.59 (d, *J* = 15.9 Hz, 1H, C*H*=CH), 7.47 - 7.28 (m, 6H), 7.21 (d, *J* = 2.5 Hz, 1H, H4), 7.05 (dd, *J* = 9.0, 2.5 Hz, 1H, H6), 7.00 (d, *J* = 15.9 Hz, 1H, CH=C*H*), 6.93 (td, *J* = 7.7, 1.5 Hz, 1H), 6.79 (dd, *J* = 3.7, 0.7 Hz, 1H, H3), 6.75 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.58 (td, *J* = 7.5, 1.5 Hz, 1H), 5.09 (s, 2H), 4.96 (s, 2H, $CONHC_6H_4NH_2$); ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.9, 155.3, 141.6, 137.8, 137.2 (*C*H=CH), 137.1, 136.6, 133.1 (CH_{Ar}), 131.6, 130.6 (CH_{Ar}), 128.8, 128.4 ($2CH_{Ar}$), 127.8 (C2), 127.7 ($3CH_{Ar}$), 127.0 (CH_{Ar}), 126.0 (CH_{Ar}), 125.3 (CH=*C*H), 125.2 (CH_{Ar}), 124.7 (CH_{Ar}), 123.2, 116.3 (CH_{Ar}), 116.0 (CH_{Ar}), 114.4 (C6), 114.0 (C7), 110.0 (C3), 105.3 (C4), 69.6 (CH_2); HRMS (ESI): Calcd for $C_{30}H_{26}N_3O_4S^+$ $[M + H]^+$: 524.1639. Found: 524.1638.

(*E*)-*N*-(2-Aminophenyl)-3-(3-((5-(3-(piperidin-1-yl)propoxy)-1*H*-indol-1-yl) sulfonyl)phenyl)acrylamide (MTP167). Following the **General Method D**, the reaction of compound **MTP146** (166 mg, 0.35 mmol), dissolved in dry DMF (1.42 mL), with DIPEA (0.15 mL, 0.89 mmol, 2.5 equiv), HATU (135 mg, 0.35 mmol) and 1,2-phenylenediamine (38 mg, 0.35 mmol), after purification by flash chromatography of the residue using DCM/MeOH/NH_4OH (97:2.7:0.3) as eluent, gave compound **MTP167**

(107 mg, 54%) as a yellow solid: mp 89-91 ^{0}C; IR (cm^{-1}): ν 2936 (N–H), 1620 (C=O), 1371 (O=S=O), 1153 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.44 (s, 1H, CON*H*), 8.20 (s, 1H), 7.93 - 7.89 (m, 2H), 7.85 (d, *J* = 8.8 Hz, 1H, H7), 7.77 (d, *J* = 3.6 Hz, 1H, H2), 7.68 - 7.52 (m, 2H), 7.34 (d, *J* = 8.1 Hz 1H), 7.11 - 7.10 (m, 1H, H4), 7.00 (d, *J* = 15.8 Hz, 1H, CH=C*H*), 6.96 - 6.89 (m, 2H), 6.80 - 6.74 (m, 2H), 6.58 (t, *J* = 7.2 Hz, 1H), 4.96 (s, 2H, CONHC$_6$H$_4$N*H*$_2$), 3.98 (t, *J* = 6.3 Hz, 2H), 3.30 - 3.20 (m, 6H), 1.94 - 1.83 (m, 2H), 1.54 - 1.48 (m, 4H), 1.43 - 1.34 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 162.9, 155.5, 141.6, 137.8, 137.2 (*C*H=CH), 136.6, 133.1 (CH$_{Ar}$), 131.7, 130.6 (CH$_{Ar}$), 128.7, 127.7 (C2), 127.0 (CH$_{Ar}$), 126.0 (CH$_{Ar}$), 125.3 (CH$_{Ar}$), 125.2 (CH=*C*H), 124.7 (CH$_{Ar}$), 123.2, 116.3 (CH$_{Ar}$), 116.0 (CH$_{Ar}$), 114.2 (C6), 114.0 (C7), 110.1 (C3), 104.8 (C4), 66.1 (CH$_2$), 54.8 (CH$_2$), 53.7 (2CH$_2$), 25.7 (CH$_2$), 25.0 (2CH$_2$), 23.6 (CH$_2$); HRMS (ESI): Calcd for $C_{31}H_{35}N_4O_4S^+$ [*M* + H]$^+$: 559.2374. Found: 559.2372.



(*E*)-*N*-(2-Aminophenyl)-3-(4-((5-methoxy-1*H*-indol-1-yl)sulfonyl)phenyl) acrylamide (SMD10). Following the **General Method D**, the reaction of compound **SMD3** (190 mg, 0.53 mmol), dissolved in dry DMF (2.12 mL), with DIPEA (0.2 mL, 1.06 mmol, 2.5 equiv), HATU (202 mg, 0.53 mmol) and 1,2-phenylenediamine (58 mg, 0.53 mmol), after purification by flash chromatography of the residue using DCM/MeOH (2%) as eluent, compound **SMD10** (167 mg, 70%) as a yellow solid: mp 94-96 ^{0}C; IR (cm^{-1}): ν 3257 (N–H), 1619 (C=O), 1371 (O=S=O), 1173 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.48 (s, 1H, CON*H*), 7.99 (d, *J* = 8.3 Hz, 2H), 7.84 (d, *J* = 9.0 Hz, 1H, H7), 7.82 - 7.72 (m, 3H), 7.53 (d, *J* = 15.8 Hz, 1H, C*H*=CH), 7.32 (d, *J* = 7.1 Hz, 1H), 7.12 (d, *J* = 2.5 Hz, 1H, H4), 7.01 - 6.88 (m, 3H), 6.79 (d, *J* = 3.7 Hz, 1H, H3), 6.74 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.56 (t, *J* = 7.5 Hz, 1H), 4.94 (s, 2H, CONHC$_6$H$_4$N*H*$_2$), 3.75 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 162.8, 156.2, 141.6, 140.7, 137.2 (*C*H=CH), 136.9, 131.7, 128.7, 128.6 (2CH$_{Ar}$), 127.7 (C2), 127.4 (2CH$_{Ar}$), 126.4 (CH$_{Ar}$), 126.0 (CH=*C*H), 124.8 (CH$_{Ar}$), 123.2, 116.3 (CH$_{Ar}$), 116.0 (CH$_{Ar}$), 114.0 (C7), 113.7 (C6), 110.0 (C3), 104.0

(C4), 55.4 (OCH_3); HRMS (ESI): Calcd for $C_{24}H_{22}N_3O_4S^+$ [*M* + H]$^+$: 448.1326. Found: 448.1334.

(*E*)-*N*-(2-Aminophenyl)-3-(4-((5-(3-(piperidin-1-yl)propoxy)-1*H*-indol-1-yl) sulfonyl)phenyl)acrylamide (APP17). Following the **General Method D**, the reaction of compound **APP15** (200 mg, 0.43 mmol), dissolved in dry DMF (1.7 mL), with DIPEA (0.19 mL, 1.07 mmol, 2.5 equiv), HATU (168 mg, 0.43 mmol) and 1,2-phenylenediamine (46 mg, 0.43 mmol), after purification by flash chromatography of the residue using DCM/MeOH (2%) as eluent, afforded compound **APP17** (181 mg, 76%) as a yellow solid: mp 100-102 ^{0}C; IR (cm^{-1}): ν 2931 (N–H), 1619 (C=O), 1455 (O=S=O), 1152 (C-O-C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.50 (s, 1H, CON*H*), 7.98 (d, *J* = 8.6 Hz, 2H), 7.83 (d, *J* = 9.0 Hz, 1H, H7), 7.78 - 7.76 (m, 3H), 7.53 (d, *J* = 15.8 Hz, 1H, C*H*=CH), 7.32 (dd, *J* = 8.0, 1.5 Hz 1H), 7.12 (d, *J* = 2.5 Hz, 1H, H4), 6.99 (d, *J* = 15.8 Hz, 1H, CH=C*H*), 6.95 - 6.87 (m, 2H), 6.78 (dd, *J* = 3.7, 0.8 Hz, 1H, H3), 6.74 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.56 (td, *J* = 7.6, 1.5 Hz, 1H), 4.95 (s, 2H, $CONHC_6H_4NH_2$), 3.99 (t, *J* = 6.1 Hz, 2H), 2.36 - 2.35 (m, 6H), 1.90 - 1.89 (m, 2H), 1.54 - 1.50 (m, 4H), 1.38 - 1.34 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.2, 155.9, 142.1, 141.2, 137.6 (*C*H=CH), 137.4, 132.1, 129.2 (C2), 129.0 ($2CH_{Ar}$), 128.2, 127.8 ($2CH_{Ar}$), 126.8 (CH=*C*H), 126.5 (CH_{Ar}), 125.2 (CH_{Ar}), 123.6, 116.7 (CH_{Ar}), 116.5 (CH_{Ar}), 114.6 (C7), 114.5 (C6), 110.5 (C3), 105.3 (C4), 66.5 (CH_2), 55.2 (CH_2), 54.1 ($2CH_2$), 26.1 (CH_2), 25.3 ($2CH_2$), 23.9 (CH_2); HRMS (ESI): Calcd for $C_{31}H_{35}N_4O_4S^+$ [*M* + H]$^+$: 559.2374. Found: 559.2381.

CONFLICT OF INTERESTS

MTP, APP, PA, II, FLM, AM, AAZ and JMC have submitted a patent ("Histone deacetylase derivatives for the treatment of cancer", EP23382368.1).

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