Contilisant+Tubastatin A 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

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Abstract: Herein we describe the design and synthesis of **Contilisant**+**Tubastatin A** hybrids as polyfunctionalized indole derivatives for the treatment of a broad diversity of cancers, such as glioblastoma. The new **Contilisant**+**Tubastatin A** 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**+**Tubastatin A** hybrids have been submitted to biological evaluation in suitable *in vitro* and *vivo* glioblastoma models.

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

Keywords: Biological activities, cancer, glioblastoma, synthesis, Tubastatin A analogues.

INTRODUCTION

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 cancers, the interest in regulating histone acetylation through HDAC is rising up.[1]

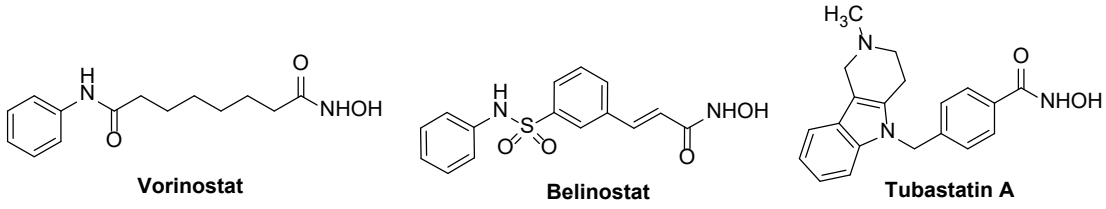


Figure 1. Structures of **Vorinostat**, **Belinostat**, and **Tubastatin** A.

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 (Figure 1), the first of four FDA-approved HDAC inhibitors for 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.[6,7]

RESULTS & DISCUSSION

Synthesis

In this work, we report the design and synthesis of **Contilisant+Tubastatin A** hybrids (Figure 2) as polyfunctionalized indole derivatives for the treatment of a broad diversity of cancers, such as glioblastoma.

The new **Contilisant+Tubastatin A** hybrids have been designed as MTD small molecules, able to inhibit HDAC6, cholinesterases (ChEs) and monoamine oxidases (MAOs), and modulate Histamine 3 receptor (H3R), Sigma 1 receptor (S1R), 5-HT6 receptor (5-HT6R), and dopamine 3 receptor (D3R), by juxtaposition of selected functional and pharmacophore groups from **Contilisant**[8,9] and **Tubastatin A**[6] (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.[8,9]

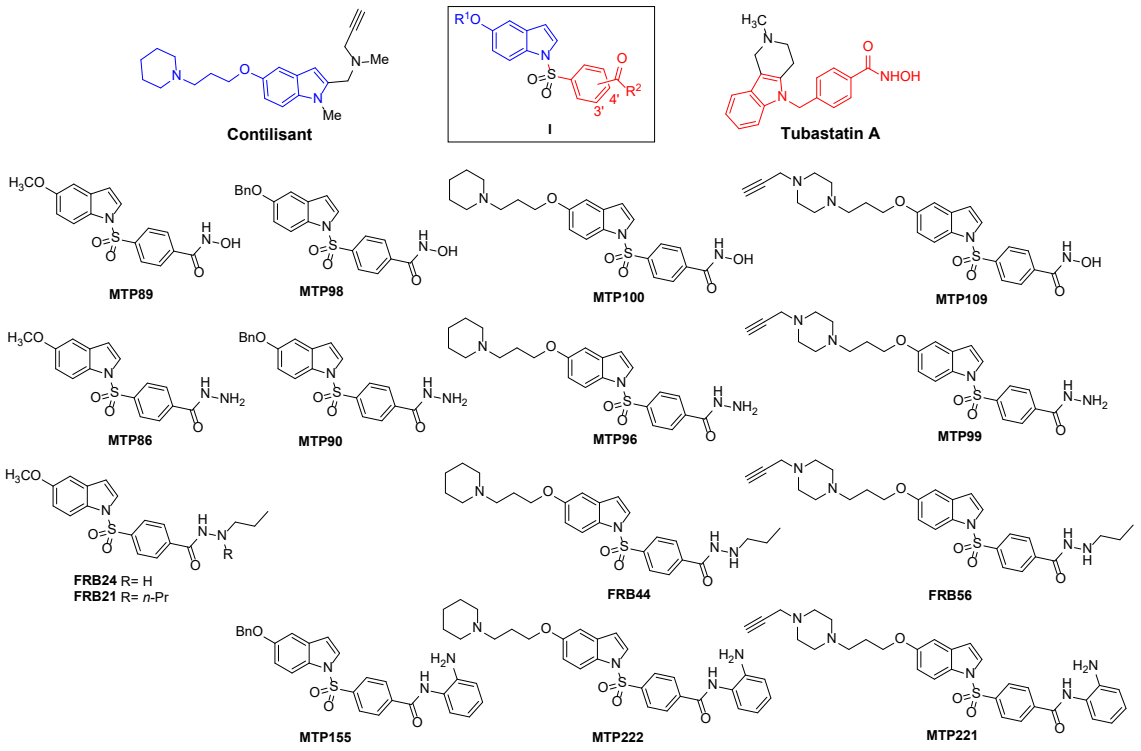
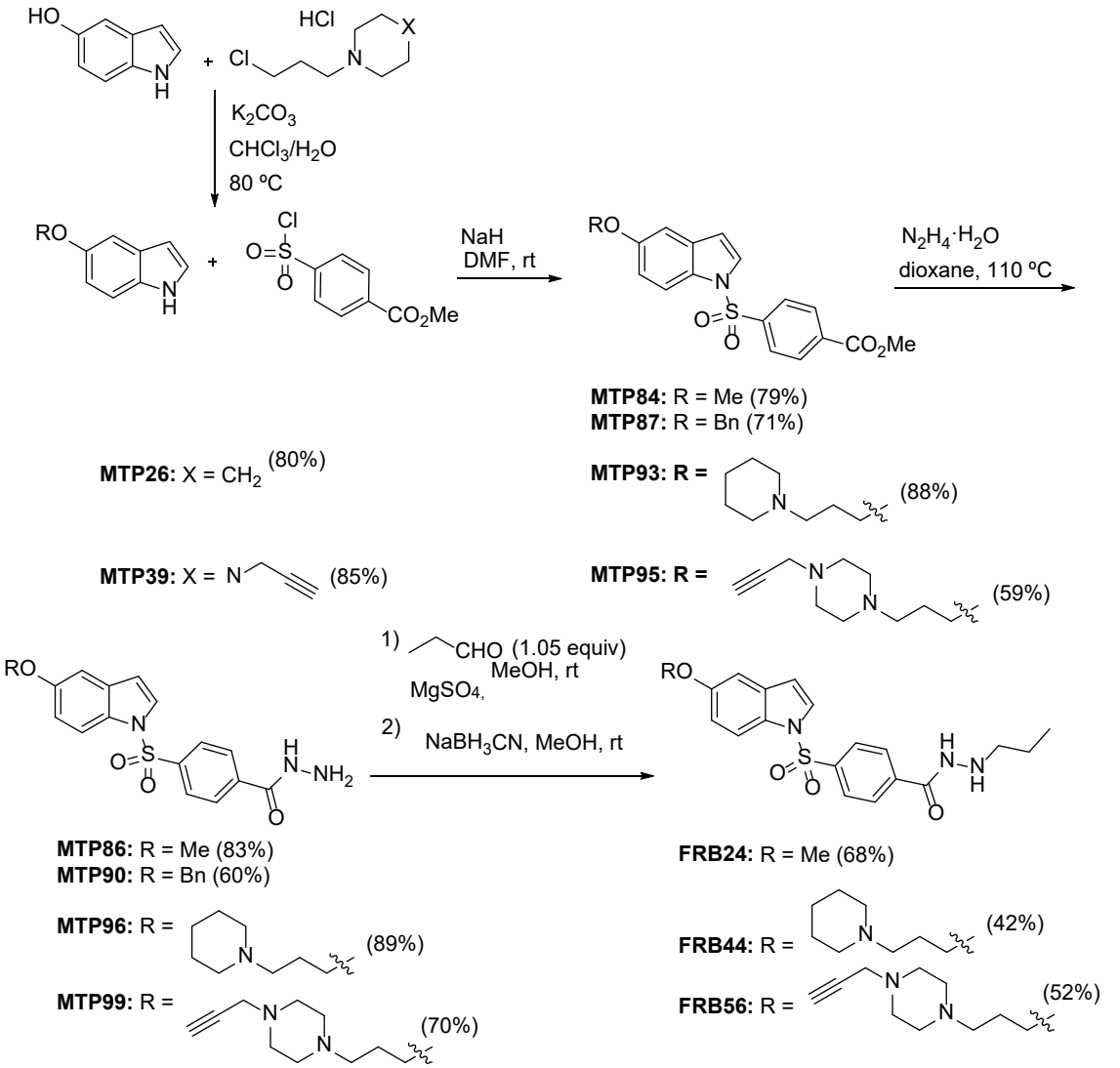


Figure 2. Structure of **Contilisant**, **Tubastatin A**, and the new fifteen **Contilisant+ Tubastatin A** hybrids (**I**).

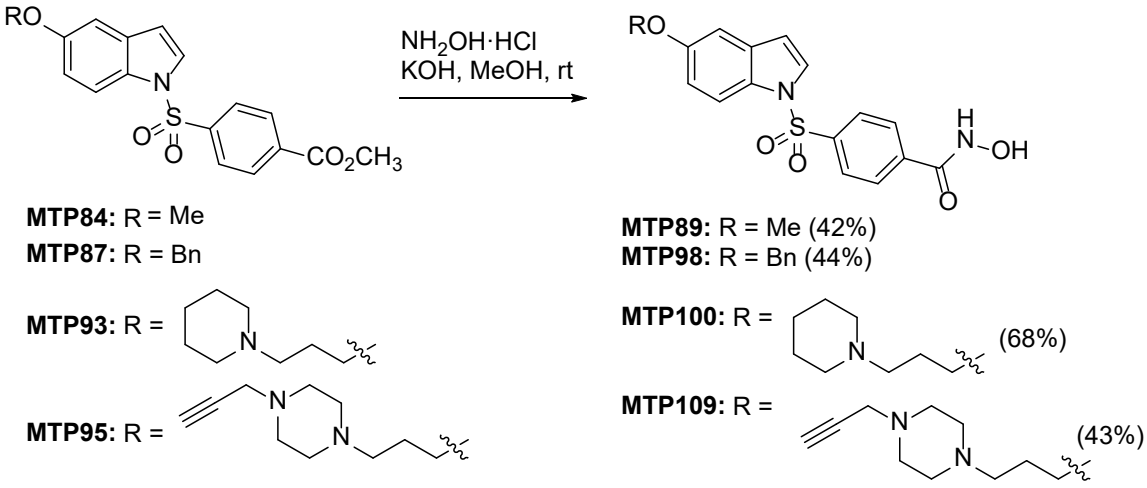
Accordingly, we have designed and prepared fifteen new compounds of type **I** where R^1 represents CH_3, Bn, piperidinepropyl, and *N*-(propargyl)pìperazinepropyl groups, and R^2 represents a $NHNH_2$, NHNH*n*-Pr, NHOH and *orto*-$NH_2(C_6H_4)NH$ groups installed in in position C4' of the *N*(1)-sulfonamide aromatic ring (Figure 2).

In Schemes 1, 2 and 3, we have shown how we have prepared the ligands bearing the $NHNH_2$/NHNH*n*-Pr, NHOH and *orto*-$NH_2(C_6H_4)NH$ groups, respectively.

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,[10] and newly prepared here 5-(3-(4-(prop-2-yn-1-yl)piperazin-1-yl)propoxy)-1*H*-indole (**MTP36**) (see **Experimental Part**), the NaH/DMF promoted reaction with commercial methyl 4-(chlorosulfonyl)benzoate gave *N*-phenylsulfonamides **MTP84**, **87**, **93** and **95**, respectively. Next, reaction of these four carboxylic esters with hydrazine hydrate in dioxane at 100 ºC afforded the corresponding hydrazides **MTP86**, **90, 96**, **99**. Reductive amination reaction with *n*-propionaldehyde in the presence of sodium cyanoborohydride gave *N*-propylhydrazides **FRB24**, **44**, and **56**, Very surprisingly, under the same experimental conditions, we were unable to obtain related *N*-propylhydrazide from the corresponding 5-OBn hydrazide **MTP90**. Note that 4-((5-methoxy-1*H*-indol-1-yl)sulfonyl)-*N*',*N*'-dipropylbenzohydrazide (**FRB21**) (Figure 2) was obtained, under the same experimental conditions, using an excess of *n*-propionaldehyde (see **Experimental Part**).

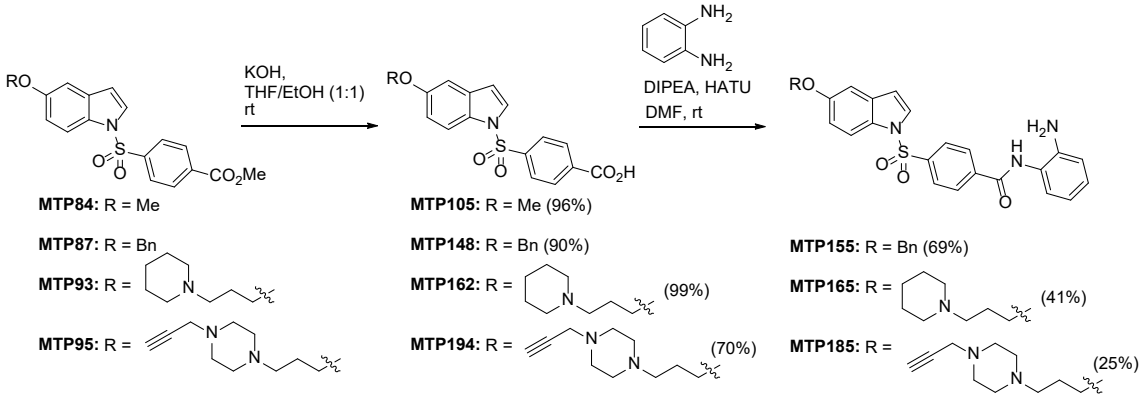


Scheme 1. Synthesis of compounds **MTP86**, **90**, **96**, **99**, and **FRB24**, **44**, **56**.



Scheme 2. Synthesis of compounds **MTP89, 98, 100, 109**.

As shown in Scheme 2, the reaction of *N*-phenylsulfonamides **MTP84**, **87**, **93** and **95**, with hydroxylamine hydrochloride in basic medium gave the final desired hydroxamates **MTP89, 98, 100, 109**, respectively.



Scheme 3. Synthesis of compounds **MTP155, 165, 185**.

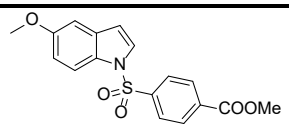
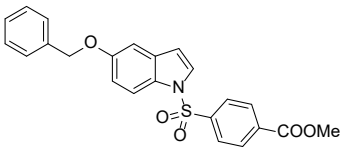
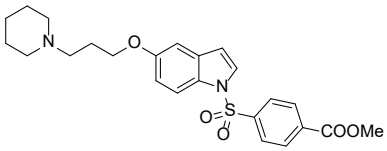
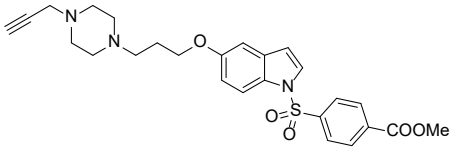
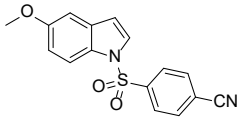
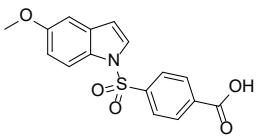
Finally, and as shown in Scheme 3, basic hydrolysis of *N*-phenylsulfonamides **MTP84**, **87**, **93** and **95** to give carboxylic acids **MTP148**, **162** and **194**, respectively, followed by reaction with 1,2-phenylenediamine, in the presence of DIPEA and HATU, gave the final desired ligands **MTP155, 165, 185**, respectively. Again, under identical experimental conditions, acid **MTP105** did not afford the expected *N*-(2-aminophenyl)-4-((5-(methoxy)-1*H*-indol-1-yl)sulfonyl)benzamide.

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

In vitro Pharmacological Activity

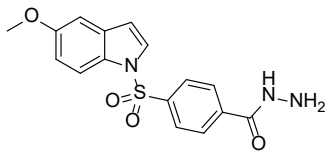
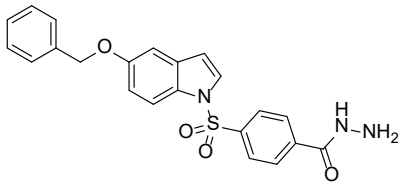
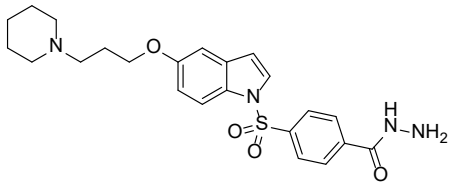
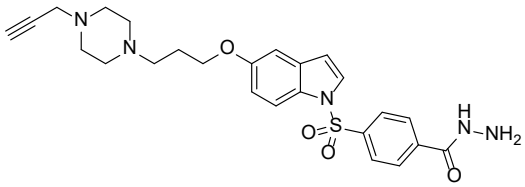
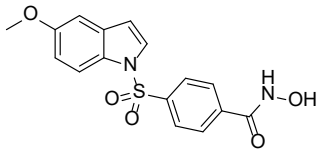
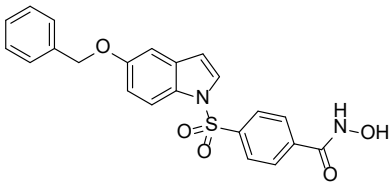
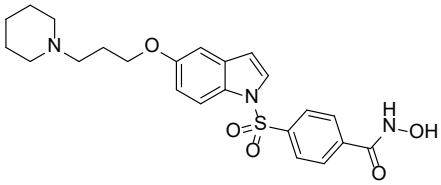
Compounds **MTP84**, **87**, **93**, **95**, **116**, **105** have been sent to Prof. Andrzej J. Bojarski (Department of Medicinal Chemistry, Maj Institute of Pharmacology Polish Academy of Sciences, Kraków, Poland) laboratory to test its ability to modulate 5-HT6R.

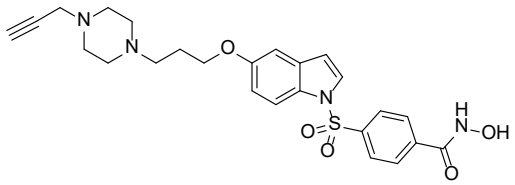
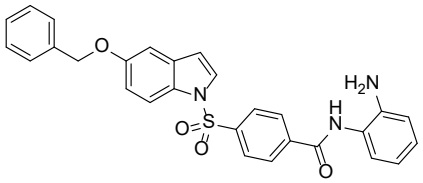
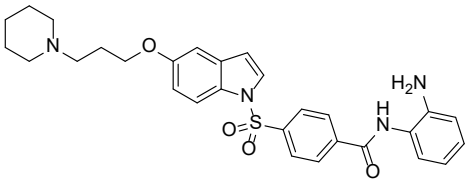
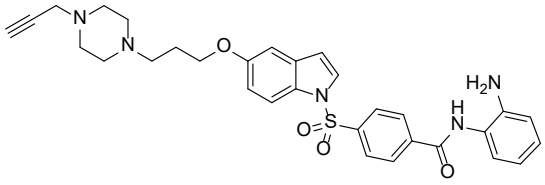
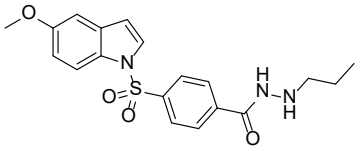
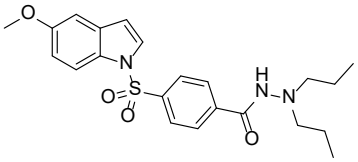
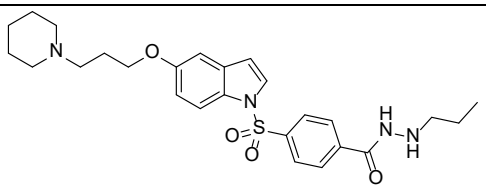
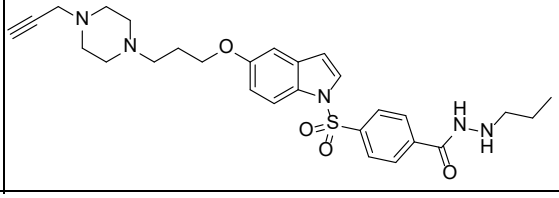
Prof. Andrezj Bojarski (30/07/2021)

Ref.	Structure	Analysis	Solubility	Quantity
MTP84		Chemical Formula: $C_{17}H_{15}NO_5S$ Molecular Weight: 345,37	DMSO	20.0 mg
MTP87		Chemical Formula: $C_{23}H_{19}NO_5S$ Molecular Weight: 421,47	DMSO	20.0 mg
MTP93		Chemical Formula: $C_{24}H_{28}N_2O_5S$ Molecular Weight: 456,56	DMSO	20.0 mg
MTP95		Chemical Formula: $C_{26}H_{29}N_3O_5S$ Molecular Weight: 495,59	DMSO	20.0 mg
MTP116		Chemical Formula: $C_{16}H_{12}N_2O_3S$ Molecular Weight: 312,34	DMSO	20.0 mg
MTP105		Chemical Formula: $C_{16}H_{13}NO_5S$ Molecular Weight: 331,34	DMSO	20.0 mg

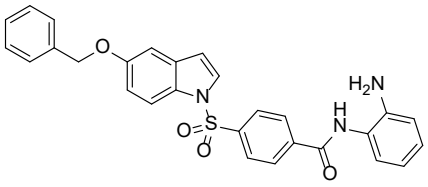
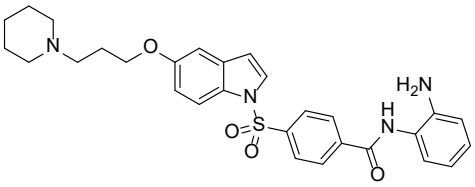
Compounds **MTP86**, **90**, **96**, **99**, **89**, **98, 100**, **109**, **155**, **165**, **195; FRB24, 21, 44, 56** have been sent to Prof. Anna Wieckowska [(Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna 9, 30-688 Krakow (Poland)] laboratory to test its ability to inhibit ChEs, and MAOs, as well as its capacity to modulate H3R and 5-HT6R.

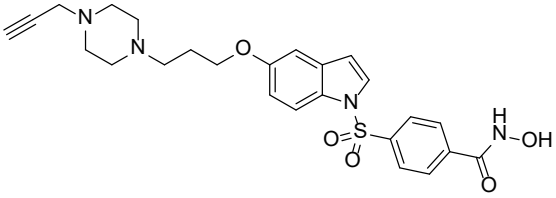
Prof. Anna Wieckowska (02/09/2022)

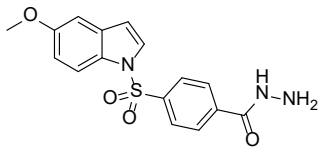
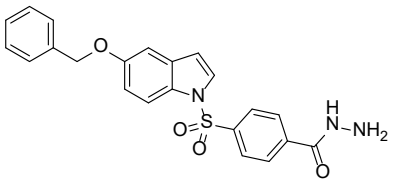
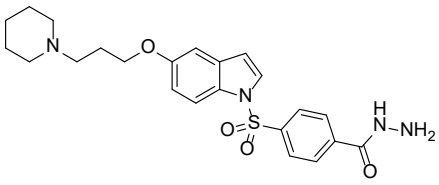
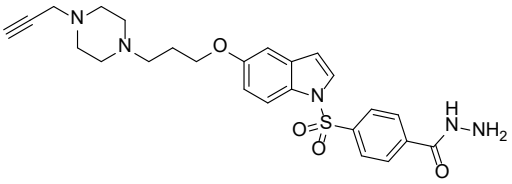
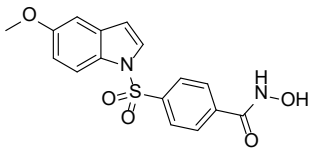
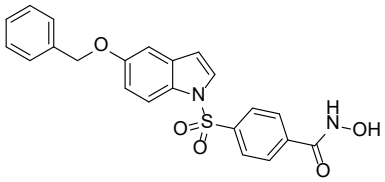
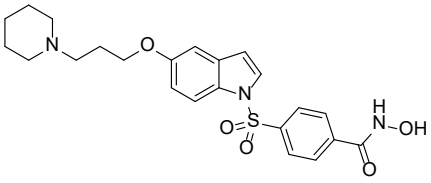
Ref.	Structure	Analysis	Solubility	Quantity
MTP86		Chemical Formula: $C_{16}H_{15}N_3O_4S$ Molecular Weight: 345,37	DMSO	17.0 mg
MTP90		Chemical Formula: $C_{22}H_{19}N_3O_4S$ Molecular Weight: 421,47	DMSO	10.2 mg
MTP96		Chemical Formula: $C_{23}H_{28}N_4O_4S$ Molecular Weight: 456,56	DMSO	12.1 mg
MTP99		Chemical Formula: $C_{25}H_{29}N_5O_4S$ Molecular Weight: 495,60	DMSO	12.5 mg
MTP89		Chemical Formula: $C_{16}H_{14}N_2O_5S$ Molecular Weight: 346,36	DMSO	12.4 mg
MTP98		Chemical Formula: $C_{22}H_{18}N_2O_5S$ Molecular Weight: 422,46	DMSO	15.5 mg
MTP100		Chemical Formula: $C_{23}H_{27}N_3O_5S$ Molecular Weight: 457,55	DMSO	11.3 mg

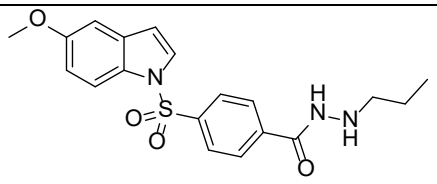
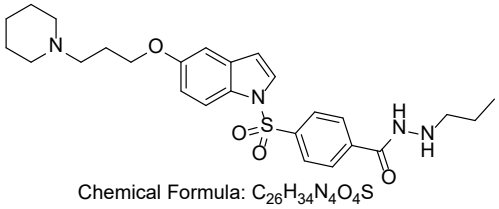
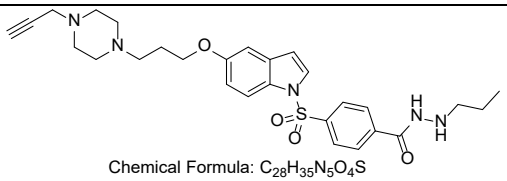
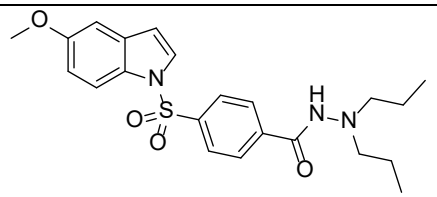
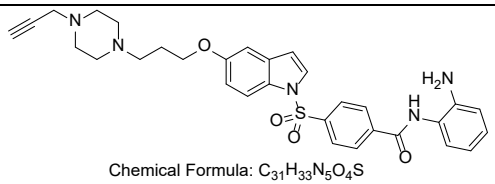
Ref.	Structure	Analysis	Solubility	Quantity
MTP109		Chemical Formula: $C_{25}H_{28}N_4O_5S$ Molecular Weight: 496,58	DMSO	15.2 mg
MTP155		Chemical Formula: $C_{28}H_{23}N_3O_4S$ Molecular Weight: 497,5690	DMSO	14.5 mg
MTP222		Chemical Formula: $C_{29}H_{32}N_4O_4S$ Molecular Weight: 532,65	DMSO	10.2 mg
MTP221		Chemical Formula: $C_{31}H_{33}N_5O_4S$ Molecular Weight: 571,69	DMSO	10.3 mg
FRB24		Chemical Formula: $C_{19}H_{21}N_3O_4S$ Molecular Weight: 387,4540	DMSO	12.7 mg
FRB21		Chemical Formula: $C_{22}H_{27}N_3O_4S$ Molecular Weight: 429,5350	DMSO	13.2 mg
FRB44		Chemical Formula: $C_{26}H_{34}N_4O_4S$ Molecular Weight: 498,6420	DMSO	10.9 mg
FRB56		Chemical Formula: $C_{28}H_{35}N_5O_4S$ Molecular Weight: 537,6790	DMSO	11.8 mg

Compounds **MTP86**, **90**, **96**, **99**, **89**, **98, 100**, **109**, **155**, **165, 195; FRB24, 21, 44, 56** 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.

Ref.	Structure	Analysis	Solubility	Quantity
MTP155		Chemical Formula: $C_{28}H_{23}N_3O_4S$ Molecular Weight: 497,57	DMSO	3.5 mg
MTP165		Chemical Formula: $C_{29}H_{32}N_4O_4S$ Molecular Weight: 532,66	DMSO	3.1 mg

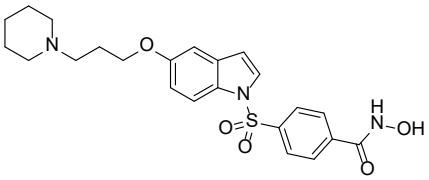
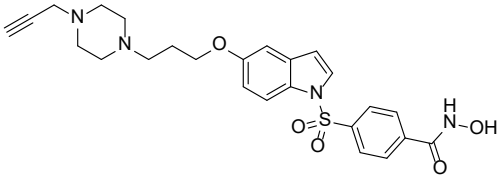
Ref.	Structure	Analysis	Solubility	Quantity
MTP109		Chemical Formula: $C_{25}H_{28}N_4O_5S$ Molecular Weight: 496,58	DMSO	3.8 mg

Ref.	Structure	Analysis	Solubility	Quantity
MTP86		Chemical Formula: $C_{16}H_{15}N_3O_4S$ Molecular Weight: 345,37	DMSO	2,8 mg
MTP90		Chemical Formula: $C_{22}H_{19}N_3O_4S$ Molecular Weight: 421,47	DMSO	2,1 mg
MTP96		Chemical Formula: $C_{23}H_{28}N_4O_4S$ Molecular Weight: 456,56	DMSO	2,9 mg
MTP99		Chemical Formula: $C_{25}H_{29}N_5O_4S$ Molecular Weight: 495,60	DMSO	3,3 mg
MTP89		Chemical Formula: $C_{16}H_{14}N_2O_5S$ Molecular Weight: 346,36	DMSO	3,0 mg
MTP98		Chemical Formula: $C_{22}H_{18}N_2O_5S$ Molecular Weight: 422,46	DMSO	3,6 mg
MTP100		Chemical Formula: $C_{23}H_{27}N_3O_5S$ Molecular Weight: 457,55	DMSO	3,5 mg

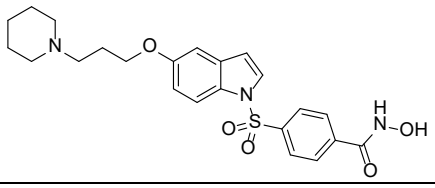
Ref.	Structure	Solub.	Stock
FRB24	 Chemical Formula: $C_{19}H_{21}N_3O_4S$ Molecular Weight: 387,4540	DMSO	4.7 mg
FRB44	 Chemical Formula: $C_{26}H_{34}N_4O_4S$ Molecular Weight: 498,6420	DMSO	4.4 mg
FRB56	 Chemical Formula: $C_{28}H_{35}N_5O_4S$ Molecular Weight: 537,6790	DMSO	4.2 mg
FRB21	 Chemical Formula: $C_{22}H_{27}N_3O_4S$ Molecular Weight: 429,5350	DMSO	4.1 mg
MTP195	 Chemical Formula: $C_{31}H_{33}N_5O_4S$ Molecular Weight: 571,6960	DMSO	5.0 mg

Compounds **MTP100**, and **MTP109** have been also sent to Dr. Mercé Pallás (Pharmacology Unit, Department of Pharmacology, Toxicology and Therapeutic Chemistry Faculty of Pharmacy and Food Sciences, University of Barcelona, Barcelona) and Dr. Ricardo Martínez Murillo (I. Cajal, CSIC, Madrid) for suitable *in vivo* tests.

Dr. Mercé Pallás (31/01/2023)

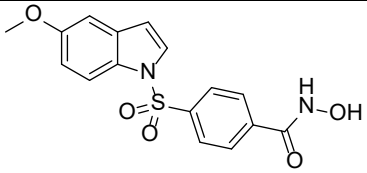
Ref.	Structure	Analysis	Solubility	Quantity
MTP100		Chemical Formula: $C_{23}H_{27}N_3O_5S$ Molecular Weight: 457,55	DMSO	20.2 mg
MTP109		Chemical Formula: $C_{25}H_{28}N_4O_5S$ Molecular Weight: 496,58	DMSO	19.8 mg

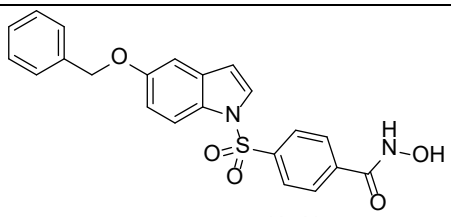
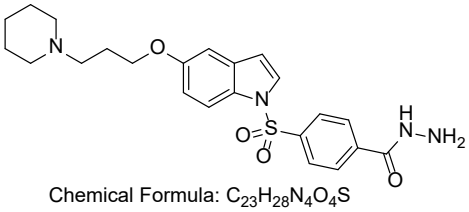
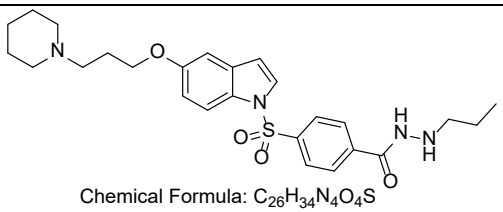
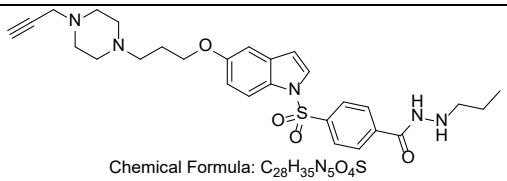
Dr. Ricardo Martínez Murillo (23-09-2022)

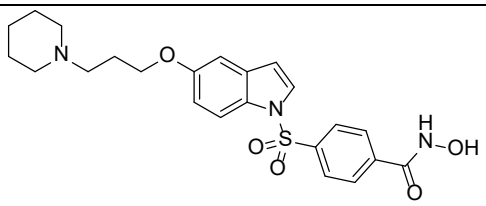
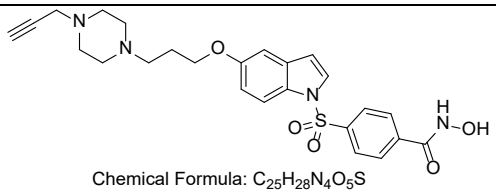
Ref.	Structure	Analysis	Solubility	Quantity
MTP100		Chemical Formula: $C_{23}H_{27}N_3O_5S$ Molecular Weight: 457,55	DMSO	40.0 mg

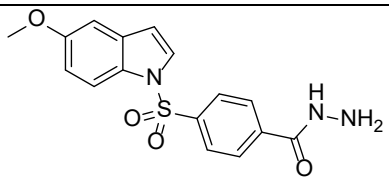
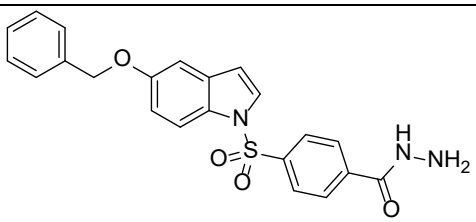
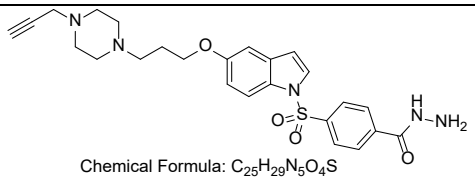
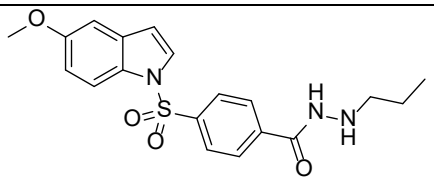
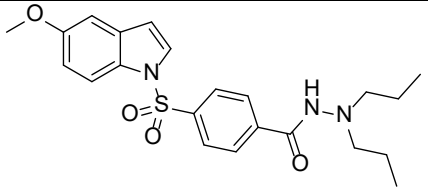
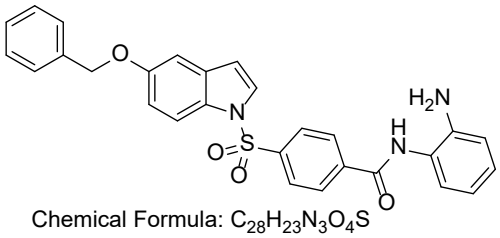
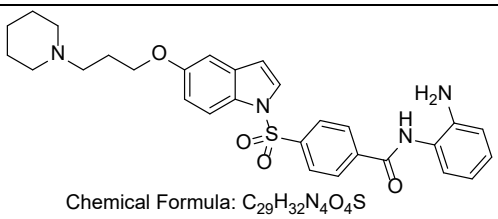
Finally, compounds **MTP86**, **90**, **96**, **99**, **89**, **98, 100**, **109**, **155**, **165, 195; FRB24, 21, 44, 56** have been also sent to Dr. Ander Matheu (Cellular Oncology group, Biodonostia Health Research Institute, San Sebastian, Spain) in order to investigate its potential therapeutic use for glioblastoma.

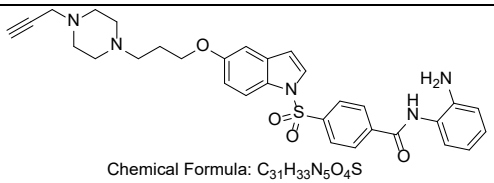
Dr. Ander Matheu (02/07/2022)

Ref.	Structure	Solub.	Stock	Ander
MTP89	 Chemical Formula: $C_{16}H_{14}N_2O_5S$ Molecular Weight: 346,3570	DMSO	16.2 mg	5.3 mg

MTP98	 Chemical Formula: $C_{22}H_{18}N_2O_5S$ Molecular Weight: 422,4550	DMSO	50.7 mg	5.2 mg
MTP96	 Chemical Formula: $C_{23}H_{28}N_4O_4S$ Molecular Weight: 456,5610	DMSO	23.7 mg	6.3 mg
FRB44	 Chemical Formula: $C_{26}H_{34}N_4O_4S$ Molecular Weight: 498,6420	DMSO	37.8 mg	5.3 mg
FRB56	 Chemical Formula: $C_{28}H_{35}N_5O_4S$ Molecular Weight: 537,6790	DMSO	3.2 mg	5.3 mg

Ref.	Structure	Solub.	Stock
MTP100	 Chemical Formula: $C_{23}H_{27}N_3O_5S$ Molecular Weight: 457,5450	DMSO	5.3 mg
MTP109	 Chemical Formula: $C_{25}H_{28}N_4O_5S$ Molecular Weight: 496,5820	DMSO	5.1 mg

MTP86	 Chemical Formula: $C_{16}H_{15}N_3O_4S$ Molecular Weight: 345,3730	DMSO	5.3 mg
MTP90	 Chemical Formula: $C_{22}H_{19}N_3O_4S$ Molecular Weight: 421,4710	DMSO	4.7 mg
MTP99	 Chemical Formula: $C_{25}H_{29}N_5O_4S$ Molecular Weight: 495,5980	DMSO	5.3 mg
FRB24	 Chemical Formula: $C_{19}H_{21}N_3O_4S$ Molecular Weight: 387,4540	DMSO	5.3 mg
FRB21	 Chemical Formula: $C_{22}H_{27}N_3O_4S$ Molecular Weight: 429,5350	DMSO	5.1 mg
MTP155	 Chemical Formula: $C_{28}H_{23}N_3O_4S$ Molecular Weight: 497,5690	DMSO	5.4 mg
MTP165	 Chemical Formula: $C_{29}H_{32}N_4O_4S$ Molecular Weight: 532,6590	DMSO	5.3 mg

MTP195	 Chemical Formula: $C_{31}H_{33}N_5O_4S$ Molecular Weight: 571,6960	DMSO	5.4 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+Tubastatin A** hybrids as polyfunctionalized indole derivatives, for the therapy of cancer conditions (glioblastoma), based on the new and original approach consisting of the ability of these molecules to inhibit and/or modulate, simultaneously, at least, ChEs, MAOs, HDAC6 enzymes, and H3, S1 and D3 receptors. Fifteen new **Contilisant+Tubastatin A** 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. ^{1}H NMR spectra were recorded with a Varian VXR-200S spectrometer, using tetramethylsilane as internal standard and ^{13}C NMR spectra were recorded with a Bruker WP-200-SY. 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 elemental analyses, conducted on a Carlo Erba EA 1108 apparatus, and confirmed to be ≥ 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, 4-chlorosulfonylbenzoate chloride (1.1 mmol) was added and the 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 Acid Synthesis (B). 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 (3 x 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 vacuum.* The residue was purified by flash chromatography over silica gel.

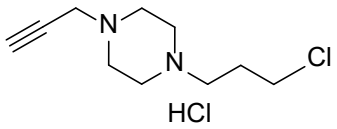
General Method for Amide Synthesis (C). *N*,*N*-Diisopropylethylamine (DIPEA) (2.5-3.5 mmol) and 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU) (1.0 mmol) were sequentially added at room temperature to a solution of the corresponding acid (1.0 mmol) in dry DMF (4 mL). The reaction was stirred for 15 min and then hydroxylamine hydrochloride or 1,2-phenylenediamine was added (1.0 mmol). 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.

General Procedure for Alkylation Reaction (D). A mixture of substituted indole (1.0 equiv), appropriate amine hydrochloride (1.5 equiv) and potassium carbonate (3 equiv) was dissolved in $CHCl_3$ (2.5 mL) and water (1.0 mL). Then, the reaction mixture was stirred at 80 °C for 3 d. After complete reaction (TLC analysis), the mixture was extracted with $CHCl_3$ (3 x 20 mL). Combined organic extracts were washed with sodium bicarbonate (15 mL), dried over anhydrous magnesium sulfate, filtered and evaporated. Product was purified using column chromatography.

General Procedure for Hydroxamic Acid Synthesis (E). $NH_2OH{\cdot}HCl$ (25.0 equiv) suspended in MeOH (3 mL) was mixed with KOH (25.0 equiv) in MeOH (10 mL), and the mixture was cooled to 0 ˚C in an ice bath. Then the mixture was then filtered into a solution of the substituted indole (1.0 equiv) in MeOH (34 mL) at 0 ˚C. Next, KOH (4.0 equiv) dissolved in MeOH (3 mL) was added dropwise for 5 min with stirring, and the reaction mixture was then stirred for an additional 24 h at room temperature (rt). After complete reaction (TLC analysis), the residue was concentrated *in vacuum* and purified by flash chromatography over silica gel.

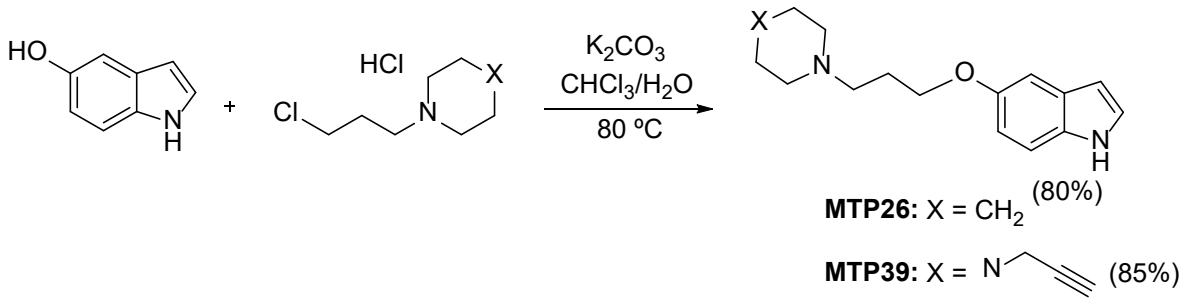
General Procedure for *N*-Propyl-hydrazide Synthesis (F). The substituted hydrazide (1.0 equiv.) was dissolved in 50 mL of methanol. Then propionaldehyde (1.05-1.6 equiv.) was added followed by $MgSO_4$ (6.9 equiv.). Four hours later, $MgSO_4$ was filtered off and the residue was concentrated in vacuum. After, to the solution of crude in MeOH was added $NaBH_3CN$ (2 equiv) and HCl/MeOH(1:1) for adjusting the mixture to pH 3-4. The reaction was stirred at room temperature for 12 h, the volatile was removed under vacuum and the crude was purified using column chromatography.

General Procedure for Hydrazide Synthesis (G). To a solution of hydrazine monohydrate (5.0 equiv) in dioxane (5 mL), substituted indole (1.0 equiv) was added. The resulting mixture was stirred at 110 ^{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, filtered and concentrated in vacuum. Product was purified using column chromatography.



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 vacuum* and water (10 mL) was added to the residue. The solution was filtrated and washed with water (20 mL) 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, filtered and evaporated to give the

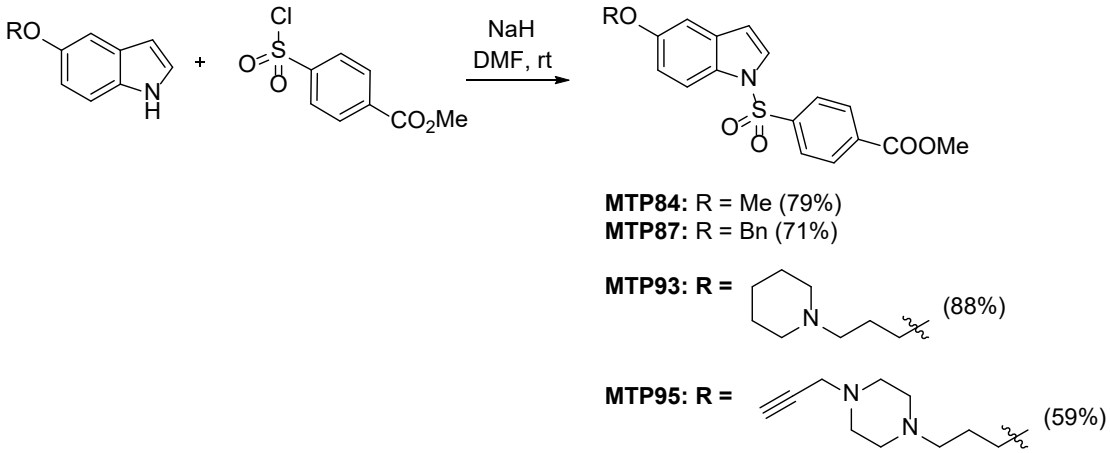
expected product that was submitted to the next step without further purification. To a solution of ***tert*-butyl piperazine-1-carboxylate** (2 g, 10.75 mmol, 1.0 equiv) in anhydrous DCM (38 mL), cooled at 0 ^{0}C, triethylamine (3mL, 20.97 mmol, 2.6 equiv) and 1-bromo-3-chloropropane (2 mL, 20.97 mmol, 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, filtered and concentrated *in vacuum* to give the expected product that was submitted to 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, filtered and evaporated to give the expected product that was submitted to the next step without further purification. 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, 1.1 equiv) 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 and it was extracted with chloroform (3 x 20 mL). Combined organic extracts were washed with brine (15 mL), dried over anhydrous magnesium sulfate, filtered 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).



5-(3-(Piperidin-1-yl)propoxy)-1*H*-indole (MTP26).[10] Following the **General Procedure D**, the reaction of commercial 1*H*-indol-5-ol (1 g, 7.51 mmol), dissolved in a

mixture of $CHCl_3$ (19 mL) and H_2O (7.5 mL), with K_2CO_3 (3 g, 22.53 mmol) and 1-(3-chloropropyl)piperidine hydrochloride (2.23 g, 11.27 mmol), after flash chromatography of the residue using DCM/MeOH (5%) as eluent, gave compound **MTP26** (1550 mg, 80%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (s, 1H, N*H*), 7.27 (d, *J* = 8.8 Hz, 1H, H7), 7.18 (t, *J* = 2.8 Hz, 1H, H2), 7.11 (d, *J* = 2.4 Hz, 1H, H4), 6.86 (dd, *J* = 8.8, 2.5 Hz, 1H, H6), 6.47 (s, 1H, H3), 4.05 (t, *J* = 6.4 Hz, 2H), 2.58 - 2.44 (m, 6H), 2.09 - 1.97 (m, 2H), 1.67 - 1.60 (m, 4H), 2.50 - 1.42 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 153.5, 131.0, 128.3, 124.8 (C2), 112.9 (C6), 111.6 (C7), 103.6 (C3), 102.3 (C4), 67.4 (CH_2), 56.2 (CH_2), 54.6 ($2CH_2$), 27.0 (CH_2), 26.0 ($2CH_2$), 24.4 (CH_2). HRMS (ESI): Calcd for $C_{16}H_{23}N_2O^+$ $[M + H]^+$: 259.1805. Found: 259.1500.

5-(3-(4-(Prop-2-yn-1-yl)piperazin-1-yl)propoxy)-1*H*-indole (MTP39). Following the **General Procedure D**, the reaction of commercial 5-hydroxi-1*H*-indol (310 mg, 2.33 mmol), dissolved in a mixture of $CHCl_3$ (6 mL) and H_2O (2 mL), 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), after flash chromatography of the residue using DCM/MeOH (5%) as eluent, gave compound **MTP39** (590 mg, 85%) 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.



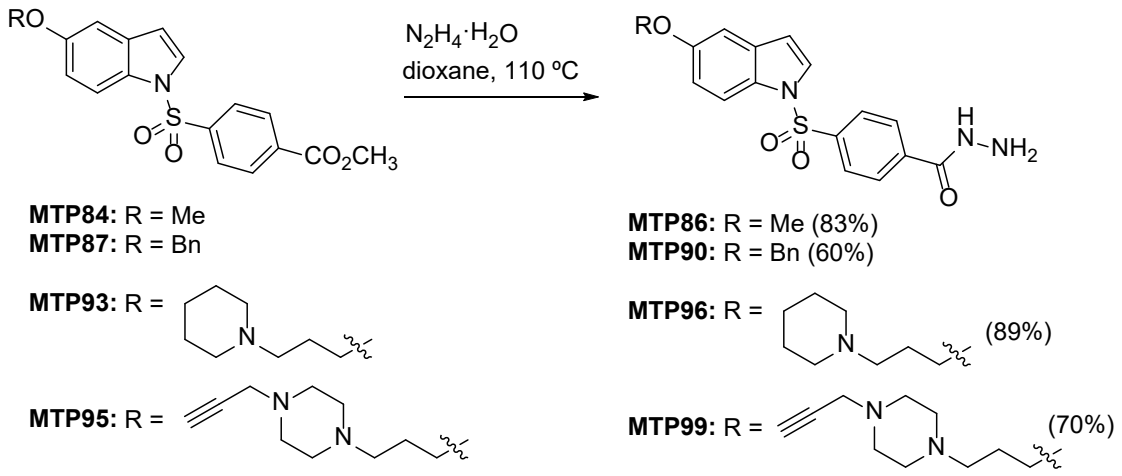
Methyl 4-((5-methoxy-1*H*-indol-1-yl)sulfonyl)benzoate (MTP84). Following the **General Method A**, the reaction of commercial 5-methoxy-1*H*-indole (400 mg, 2.72 mmol), dissolved in dry DMF (38 mL), with NaH (217 mg, 5.44 mmol) and methyl 4-chlorosulfonylbenzoate (702 mg, 3.00 mmol), after purification by flash chromatography of the residue using hexane/AcOEt (12:1) as eluent, afforded compound **MTP84** (740 mg, 79%) as a white solid: mp 106-108 ^{0}C; IR (cm^{-1}) ν 1639 (C=O), 1282 (O=S=O), 1142 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.6 Hz, 2H), 7.91 - 7.87 (m, 3H), 7.51 (d, *J* = 3.7 Hz, 1H, H2), 6.97 (d, *J* = 2.5 Hz, 1H, H4), 6.94 (dd, *J* = 9.0, 2.5 Hz, 1H, H6), 6.62 (dd, *J* = 3.7, 0.8 Hz, 1H, H3), 3.91 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2, 156.7, 141.7, 134.7, 131.9, 130.3 ($2CH_{Ar}$), 129.5, 127.0 (C2), 126.7 ($2CH_{Ar}$), 114.4 (C7), 114.0 (C6), 110.1 (C3), 103.9 (C4), 55.6 (CH_3), 52.7 (CH_3); HRMS (ESI): Calcd for $C_{17}H_{16}NO_5S^+$ [*M* + H]$^+$: 346.0744. Found: 346.0729; Anal. Calcd for $C_{17}H_{15}NO_5S$: C, 59.12; H, 4.38; N, 4.06; S, 9.28. Found: C, 59.44; H, 4.58; N, 4.13; S, 9.00.

Methyl 4-((5-(benzyloxy)-1*H*-indol-1-yl)sulfonyl)benzoate (MTP87). Following the **General Method A**, the reaction of 5-(benzyloxy)-1*H*-indole (400 mg, 1.79 mmol), dissolved in dry DMF (25 mL), with NaH (143 mg, 3.58 mmol) and methyl 4-chlorosulfonylbenzoate (462 mg, 1.97 mmol), after purification by flash chromatography of the residue using hexane/AcOEt (12:1) as eluent, provided compound **MTP87** (535 mg, 71%) as a white solid: mp 113-115 ^{0}C; IR (cm^{-1}) ν 1731 (C=O), 1375 (O=S=O), 113 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.08 (d, *J* = 8.6 Hz, 2H), 7.92 - 7.88 (m, 3H), 7.51 (d, *J* = 3.7 Hz, 1H, H2), 7.45 - 7.33 (m, 5H), 7.05 - 7.01 (m, 2H, H4 and H6), 6.61 (dd, *J* = 3.7, 0.8 Hz, 1H, H3), 5.07 (s, 2H), 3.91 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2, 155.9, 141.7, 136.9, 134.7, 131.8, 130.4 ($2CH_{Ar}$), 129.6, 128.6 ($2CH_{Ar}$), 128.0 (CH_{Ar}), 127.4 ($2CH_{Ar}$), 127.0 (C2), 126.7 ($2CH_{Ar}$), 114.7 (C7), 114.4 (C6), 110.1 (C3), 105.2 (C4), 70.5 (CH_2), 52.7 (CH_3); HRMS (ESI): Calcd for $C_{23}H_{20}NO_5S^+$ [*M* + H]$^+$: 422.1057. Found: 422.1048; Anal. Calcd for $C_{23}H_{19}NO_5S$: C, 65.55; H, 4.54; N, 3.32; S, 7.61. Found: C, 65.67; H, 4.83; N, 3.33; S, 7.49.

Methyl 4-((5-(3-(piperidin-1-yl)propoxy)-1*H*-indol-1-yl)sulfonyl)benzoate (MTP93). Following the **General Method A**, the reaction of 5-(3-(piperidin-1-yl)propoxy)-1*H*-indole (**MTP26**) (450 mg, 1.74 mmol), dissolved in dry DMF (24 mL), with. NaH (139 mg, 3.48 mmol) and methyl 4-chlorosulfonylbenzoate (450 mg, 1.92 mmol), after flash chromatography of the residue using DCM/MeOH(2%) as eluent, produced compound

MTP93 (700 mg, 88%) as a white solid: mp 100-102 ºC; IR (cm^{-1}) ν 1731 (C=O), 1266 (O=S=O), 1156 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.6 Hz, 2H), 7.89 (d, *J* = 8.6 Hz, 2H), 7.86 (d, *J* = 9.0 Hz, 1H, H7), 7.49 (d, *J* = 3.6 Hz, 1H, H2), 6.96 (d, *J* = 2.5 Hz, 1H, H4), 6.91 (dd, *J* = 9.0, 2.5 Hz, 1H, H6), 6.60 (dd, *J* = 3.6, 0.7 Hz, 1H, H3), 4.01 (t, *J* = 6.2 Hz, 2H), 3.90 (s, 3H), 2.66 - 2.50 (m, 6H), 2.10 - 2.02 (m, 2H), 1.71 - 1.65 (m, 4H), 1.51 - 1.47 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2, 155.9, 141.6, 134.7, 131.8, 130.3 ($2CH_{Ar}$), 129.4, 126.9 (C2), 126.7 ($2CH_{Ar}$), 114.4 (C7), 114.3 (C6), 110.1 (C3), 104.7 (C4), 66.6 (CH_2), 55.9 (CH_2), 54.4 ($2CH_2$), 52.7 (CH_3), 26.2 (CH_2), 25.3 ($2CH_2$), 23.9 (CH_2); HRMS (ESI): Calcd for $C_{24}H_{29}N_2O_5S^+$ [*M* + H]$^+$: 457.1792. Found: 457.1793; Anal. Calcd for $C_{24}H_{28}N_2O_5S{\cdot}7/2H_2O$: C, 55.48; H, 5.99; N, 5.39; S, 6.17. Found: C, 55.81; H, 5.63; N, 5.45; S, 6.54.

Methyl 4-((5-(3-(4-(prop-2-yn-1-yl)piperazin-1-yl)propoxy)-1*H*-indol-1-yl)sulfonyl) benzoate (MTP95). Following the **General Method A**, the reaction of 5-(3-(4-(prop-2-yn-1-yl)piperazin-1-yl)propoxy)-1*H*-indole (**MTP39**) (400 mg, 1.34 mmol), dissolved in dry DMF (19 mL), with NaH (108 mg, 2.69 mmol) and methyl 4-chlorosulfonylbenzoate (347 mg, 1.48 mmol), after purification by flash chromatography of the residue using DCM/MeOH (4%) as eluent, gave compound **MTP95** (390 mg, 59%) as a white solid: mp 93-95 ^{0}C; IR (cm^{-1}) ν 1651 (C=O), 1266 (O=S=O), 1155 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.6 Hz, 2H), 7.90 (d, *J* = 8.6 Hz, 2H), 7.86 (d, *J* = 9.0 Hz, 1H, H7), 7.50 (d, *J* = 3.7 Hz, 1H, H2), 6.97 (d, *J* = 2.5 Hz, 1H, H4), 6.93 (dd, *J* = 9.0, 2.5 Hz, 1H, H6), 6.60 (dd, *J* = 3.7, 0.8 Hz, 1H, H3), 4.01 (t, *J* = 6.3 Hz, 2H), 3.90 (s, 3H), 3.31 (d, *J* = 2.5 Hz, 2H), 2.69 - 2.46 (m, 10H), 2.26 (t, *J* = 2.5 Hz, 1H), 2.01 - 1.97 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2, 156.0, 141.6, 134.7, 131.8, 130.3 ($2CH_{Ar}$), 129.4, 126.9 (C2), 126.7 ($2CH_{Ar}$), 114.4 (C7), 114.3 (C6), 110.1 (C3), 104.7 (C4), 78.7, 73.2 (CH), 66.6 (CH_2), 55.1 ($2CH_2$), 53.0 (CH_3), 52.7 ($2CH_2$), 51.7 (CH_2), 46.8 (CH_2), 26.7 (CH_2); HRMS (ESI): Calcd for $C_{26}H_{30}N_3O_5S^+$ [*M* + H]$^+$: 496.1901. Found: 496.1887; Anal. Calcd for $C_{26}H_{29}N_3O_5S$: C, 63.01; H, 5.90; N, 8.48; S, 6.47. Found: C, 63.05; H, 5.99; N, 8.57; S, 6.00.



4-((5-Methoxy-1*H*-indol-1-yl)sulfonyl)benzohydrazide (MTP86). Following the **General Procedure G**, the reaction of methyl 4-((5-methoxy-1*H*-indol-1-yl)sulfonyl)benzoate (**MTP84**) (100 mg, 0.29 mmol), dissolved in dioxane (1.5 mL), with $N_2H_4 \cdot H_2O$ (0.07 mL, 1.45 mmol), after purification by flash chromatography of the residue using DCM/MeOH (3%) as eluent, afforded compound **MTP86** (83 mg, 83%) as a brown solid: mp 74-76 ^{0}C; IR (cm^{-1}) ν 3435 (N-H), 1643 (C=O), 1376 (O=S=O), 1152 (C-O-C); ^{1}H NMR (400 MHz, CD_3OD) δ 7.87 (d, *J* = 8.2 Hz, 2H), 7.80 (d, *J* = 9.0 Hz, 1H, H7), 7.74 (d, *J* = 8.2 Hz, 2H), 7.52 (d, *J* = 3.7 Hz, 1H, H2), 6.95 (d, *J* = 2.5 Hz, 1H, H4), 6.85 (dd, *J* = 9.0, 2.5 Hz, 1H, H6), 6.60 (d, *J* = 3.7 Hz, 1H, H3), 3.69 (s, 3H) (signal for "N*H*" and "NH_2" were not detected); ^{13}C NMR (101 MHz, CD_3OD) δ 167.6, 158.2, 141.4, 139.4, 133.5, 130.7, 129.1 ($2CH_{Ar}$), 128.4 (C2), 128.0 ($2CH_{Ar}$), 115.4 (C7), 114.8 (C6), 111.2 (C3), 104.9 (C4), 56.0 (CH_3); HRMS (ESI): Calcd for $C_{16}H_{16}N_3O_4S^+$ [*M* + H]$^+$: 346.0856. Found: 346.0843; Anal. Calcd for $C_{16}H_{15}N_3O_4S \cdot 1/2H_2O$: C, 54.23; H, 5.00; N, 11.86; S, 8.99. Found: C, 54.85; H, 5.62; N, 11.52; S, 8.95.

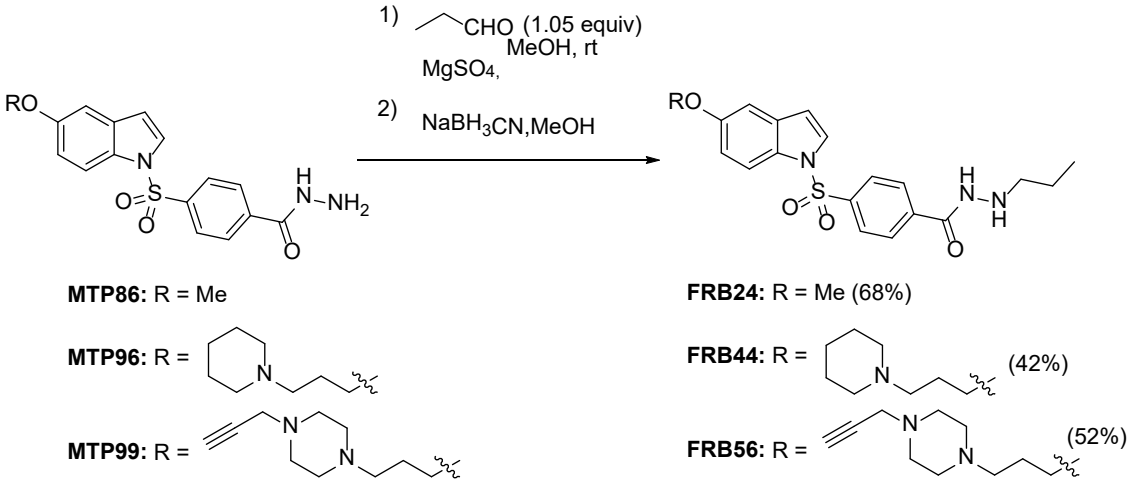
4-((5-(Benzyloxy)-1*H*-indol-1-yl)sulfonyl)benzohydrazide (MTP90). Following the **General Procedure G**, the reaction of methyl 4-((5-(benzyloxy)-1*H*-indol-1-yl)sulfonyl)benzoate (**MTP87**) (100 mg, 0.24 mmol), dissolved in dioxane (1.2 mL), with $N_2H_4 \cdot H_2O$ (0.06 mL, 1.19 mmol), after purification by flash chromatography of the residue using DCM/MeOH (3%) as eluent, provided compound **MTP90** (60 mg, 60%) as a white solid: mp 220-222 ^{0}C; IR (cm^{-1}) ν 3419 (N-H), 1645 (C=O), 1365 (O=S=O), 1156 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H, N*H*), 8.02 (d, *J* = 8.6 Hz, 2H), 7.91 (d, *J* = 8.6 Hz, 2H), 7.84 (d, *J* = 9.0 Hz, 1H, H7), 7.78 (d, *J* = 3.7 Hz, 1H, H2), 7.45 - 7.41 (m, 2H), 7.40 - 7.36 (m, 2H), 7.33 - 7.29 (m, 1H), 7.20 (d, *J* = 2.5 Hz, 1H, H4), 7.03 (dd, *J* = 9.0, 2.5 Hz, 1H, H6), 6.78 (dd, *J* = 3.7, 0.8 Hz, 1H, H3), 5.08 (s, 2H),

4.56 (s, 2H, N*H*$_2$); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 164.1, 155.3, 138.8, 138.7, 137.1, 131.7, 128.8 (CH$_{Ar}$), 128.5 (3CH$_{Ar}$), 128.3 (CH$_{Ar}$), 127.8 (CH$_{Ar}$), 127.8, 127.7 (3CH$_{Ar}$), 126.9 (CH$_{Ar}$), 114.4 (C6), 114.0 (C7), 110.2 (C3), 105.3 (C4), 69.6 (CH$_2$); HRMS (ESI): Calcd for $C_{22}H_{19}N_3NaO_4S^+$ [*M* + Na]$^+$: 444.0988. Found: 444.0996; Anal. Calcd for $C_{22}H_{19}N_3O_4S\cdot H_2O$: C, 60.13; H, 4.82; N, 9.56; S, 7.29. Found: C, 60.15; H, 4.54; N, 9.33; S, 7.12.

4-((5-(3-(Piperidin-1-yl)propoxy)-1*H*-indol-1-yl)sulfonyl)benzohydrazide (MTP96). Following the **General Procedure G**, the reaction of methyl 4-((5-(3-(piperidin-1-yl)propoxy)-1*H*-indol-1-yl)sulfonyl)benzoate (**MTP93**) (90 mg, 0.20 mmol), dissolved in dioxane (1 mL), with $N_2H_4\cdot H_2O$ (0.05 mL, 099 mmol), after purification by flash chromatography of the residue using DCM/MeOH (6%) as eluent, provided compound **MTP96** (80 mg, 89%) as a brown solid: mp 133-135 ^{0}C; IR (cm^{-1}) ν 3429 (N-H), 1641 (C=O), 1418 (O=S=O), 1265 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.5 Hz, 2H), 7.85 (d, *J* = 9.0 Hz, 1H, H7), 7.74 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 3.6 Hz, 1H, H2), 6.96 (d, *J* = 2.5 Hz, 1H, H4), 6.92 (dd, *J* = 9.0, 2.4 Hz, 1H, H6), 6.59 (dd, *J* = 3.6, 0.8 Hz, 1H, H3), 4.00 (t, *J* = 6.3 Hz, 2H), 2.54 - 2.33 (m, 6H), 2.04 - 1.91 (m, 2H), 1.62 - 1.57 (m, 4H), 1.50 - 1.41 (m, 2H) (signal for "N*H*" and "N*H*$_2$" were not detected); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, 156.1, 140.8, 137.5, 131.9, 129.4, 127.8 (2CH$_{Ar}$), 127.1 (2CH$_{Ar}$), 126.9 (C2), 114.5 (C7), 114.3 (C6), 110.2 (C3), 104.7 (C4), 66.9 (CH$_2$), 55.9 (CH$_2$), 54.5 (2CH$_2$), 26.7 (CH$_2$), 25.8 (2CH$_2$), 24.3 (CH$_2$); HRMS (ESI): Calcd for $C_{23}H_{28}N_4O_4S$ [*M* + H]$^+$: 457.1904. Found: 457.1904; Anal. Calcd for $C_{23}H_{28}N_4O_4S\cdot H_2O$: C, 58.21; H, 6.37; N, 10.99; S, 6.76. Found: C, 58.17; H, 6.33; N, 10.62; S, 6.42.

4-((5-(3-(4-(Prop-2-yn-1-yl)piperazin-1-yl)propoxy)-1*H*-indol-1-yl) sulfonyl) benzohydrazide (MTP99). Following the **General Procedure G**, the reaction of methyl 4-((5-(3-(4-(prop-2-yn-1-yl)piperazin-1-yl)propoxy)-1*H*-indol-1-yl)sulfonyl)benzoate (**MTP95**) (100 mg, 0.20 mmol), dissolved in dioxane (1 mL), with $N_2H_4\cdot H_2O$ (0.05 mL, 1.01 mmol), after purification by flash chromatography of the residue using DCM/MeOH (5%) as eluent, produced compound **MTP99** (69 mg, 70%) as an orange solid: mp 150-152 ^{0}C; IR (cm^{-1}) ν 3303 (N-H), 1672 (C=O), 1376 (O=S=O), 1155 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H, N*H*), 7.85 - 7.82 (m, 3H), 7.72 (d, *J* = 8.7 Hz, 2H), 7.46 (d, *J* = 3.7 Hz, 1H, H2), 6.95 (d, *J* = 2.5 Hz, 1H, H4), 6.90 (dd, *J* = 9.0, 2.5 Hz, 1H, H6), 6.58 (d, *J* = 3.7 Hz, 1H, H3), 3.98 (t, *J* = 6.3 Hz, 2H), 3.27 (d, *J* = 2.5 Hz, 2H), 2.66 - 2.44 (m, 10H), 2.25 (t, *J* = 2.5 Hz, 1H), 2.08 - 1.79 (m, 2H); (signal for "N*H*$_2$" were not

detected); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 155.9, 140.5, 137.4, 131.8, 129.3, 127.8 ($2CH_{Ar}$), 126.9 ($2CH_{Ar}$), 126.9 (CH_{Ar}), 114.4 (C7), 114.3 (C6), 110.1 (C3), 104.7 (C4), 78.6, 73.3 (CH), 66.6 (CH_2), 55.0 ($2CH_2$), 52.9 ($2CH_2$), 51.6 (CH_2), 46.7 (CH_2), 26.5 (CH_2); HRMS (ESI): Calcd for $C_{25}H_{29}N_5O_4S^+$ [*M* + H]$^+$: 496.2013. Found: 496.2012; Anal. Calcd for $C_{25}H_{29}N_5O_4S \cdot 2H_2O$: C, 56.48; H, 5.99; N, 12.99; S, 5.90. Found: C, 56.41; H, 5.95; N, 12.72; S, 5.80.

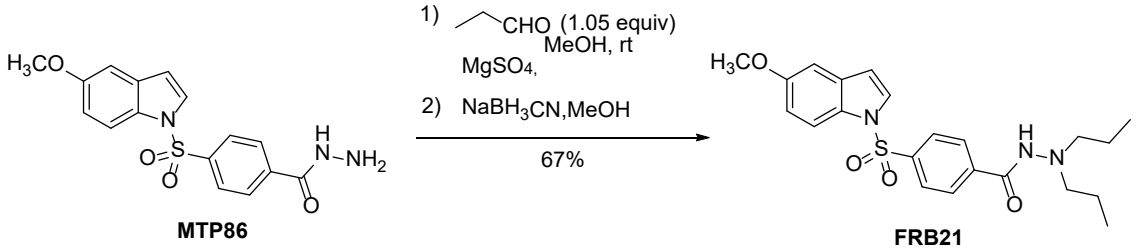


4-((5-Methoxy-1*H*-indol-1-yl)sulfonyl)-*N*'-propylbenzohydrazide (FRB24). Following the **General Procedure F**, the reaction of 4-((5-methoxy-1*H*-indol-1-yl)sulfonyl)benzohydrazide (**MTP86**) (100 mg, 0.29 mmol), dissolved in MeOH (13.5 mL), with propanal (22 µL, 0.30 mmol), $MgSO_4$ (240 mg) and $NaBH_3CN$ (36 mg, 0.58 mmol), after flash chromatography of the residue using DCM/MeOH (0.5%) as eluent, gave compound **FRB24** (76 mg, 68%) as a white solid: mp 103-5 ºC; IR (cm^{-1}) ν 3318 (N-H), 1651 (C=O), 1373 (O=S=O), 1139 C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (t, *J* = 8.6 Hz, 3H), 7.75 (d, *J* = 8.6 Hz, 1H), 7.49 (d, *J* = 3.6 Hz, 1H), 6.97 (d, *J* = 2.5 Hz, 1H), 6.93 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.62 (d, *J* = 3.7 Hz, 1H), 3.81 (s, 3H), 2.86 (t, *J* = 7.3 Hz, 2H), 1.57 - 1.48 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H) (signal for "N*H*" were not detected) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 156.7, 140.5, 137.5, 131.9, 129.4, 127.8 ($2CH_{Ar}$), 127.0 ($2CH_{Ar}$), 126.9 (CH_{Ar}), 114.3 (C7), 114.0 (C6), 110.2 (C3), 103.8 (C4), 55.6 (CH_3), 53.9 (CH_2), 21.0 (CH_2), 11.4 (CH_3); HRMS (ESI): Calcd for $C_{19}H_{22}N_3O_4S^+$ [*M* + H]$^+$: 388.1326. Found: 388.1322.

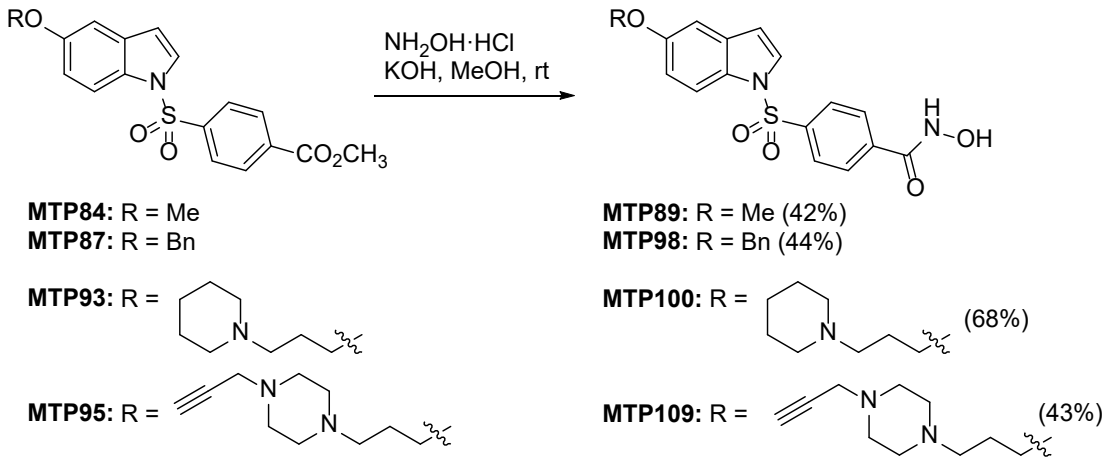
4-((5-(3-(Piperidin-1-yl)propoxy)-1*H*-indol-1-yl)sulfonyl)-*N*'-propylbenzo hydrazide (FRB44). Following the **General Procedure F**, the reaction of 4-((5-(3-(piperidin-1-yl)propoxy)-1*H*-indol-1-yl)sulfonyl)benzohydrazide (**MTP96**) (132 mg,

0.29 mmol), dissolved in MeOH (8.7 mL), with propanal (22 µL, 0.30 mmol), $MgSO_4$ (240 mg) and $NaBH_3CN$ (36 mg, 0.58 mmol), after purification by flash chromatography of the residue using DCM/MeOH/NH_4OH (97:1.7:0.3) as eluent, afforded compound **FRB44** (61 mg, 42%) as a white solid: mp 105-107 ^{0}C; IR (cm^{-1}) ν 3277 (N-H), 1655 (C=O), 1376 (O=S=O), 1181 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 - 7.80 (m, 3H), 7.73 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 3.0 Hz, 1H, H2), 6.95 (d, *J* = 2.5 Hz, 1H, H4), 6.92 (dd, *J* = 9.0, 2.4 Hz, 1H, H6), 6.58 (d, *J* = 4.0 Hz, 1H, H3), 3.98 (t, *J* = 6.3 Hz, 2H), 2.83 (t, *J* = 7.3 Hz, 2H) 2.49 - 2.36 (m, 6H), 2.01 - 1.90 (m, 2H), 1.59 - 1.54 (m, 4H), 1.53 - 1.45 (m, 2H), 1.45 - 1.40 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H) (signal for "N*H*" were not detected); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 156.2, 140.8, 137.9, 132.0, 129.5, 127.9 ($2CH_{Ar}$), 127.2 ($2CH_{Ar}$), 127.1 (C2), 114.6 (C7), 114.5 (C6), 110.3 (C3), 104.9 (C4), 67.1 (CH_2), 56.1 (CH_2), 54.8 ($2CH_2$), 54.1 (CH2), 26.9 (CH_2), 26.1 ($2CH_2$), 24.5 (CH_2), 21.3 (CH_2), 11.6 (CH_3); HRMS (ESI): Calcd for $C_{26}H_{35}N_4O_4S^+$ [*M* + H]$^+$: 499.2374. Found: 499.2369.

4-((5-(3-(4-(Prop-2-yn-1-yl)piperazin-1-yl)propoxy)-1*H*-indol-1-yl)sulfonyl)-*N*'-propylbenzohydrazide (FRB56). Following the **General Procedure F**, the reaction of 4-((5-(3-(4-(prop-2-yn-1-yl)piperazin-1-yl)propoxy)-1*H*-indol-1-yl)sulfonyl) hydrazide (**MTP99**) (126 mg, 0.25 mmol), dissolved in MeOH (7.5 mL), with propanal (19 µL, 0.27 mmol), $MgSO_4$ (212 mg) and $NaBH_3CN$ (32 mg, 0.51 mmol), after flash chromatography of the residue using DCM/MeOH (4%) as eluent, provided compound **FRB56** (70 mg, 52%) as a white solid: mp 107-109 ^{0}C; IR (cm^{-1}) ν 3288 (N-H), 1651 (C=O), 1373 (O=S=O), 1153 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (t, *J* = 8.5 Hz, 2H), 7.85 (s, 1H, H7), 7.75 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 3.7 Hz, 1H, H2), 6.97 (d, *J* = 2.5 Hz, 1H, H4), 6.93 (dd, *J* = 9.0, 2.5 Hz, 1H, H6), 6.60 (d, *J* = 3.7 Hz, 1H, H3), 4.01 (t, *J* = 6.3 Hz, 2H), 3.30 (d, *J* = 2.5 Hz, 2H), 2.86 (t, *J* = 7.3 Hz, 2H), 2.66 - 2.50 (m, 10H), 2.25 (t, *J* = 2.5 Hz, 1H), 2.01 - 1.93 (m, 2H), 1.58 - 1.47 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H) (signal for "N*H*" were not detected); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 156.0, 140.7, 137.7, 131.9, 129.4, 127.7 ($2CH_{Ar}$), 127.0 ($2CH_{Ar}$), 126.9 (CH_{Ar}), 114.4 (C7), 114.3 (C6), 110.2 (C3), 104.7 (C4), 78.8, 73.2 (CH), 66.7 (CH_2), 55.0 ($2CH_2$), 53.98 (CH_2), 53.0 ($2CH_2$), 51.2 (CH_2), 46.8 (CH_2), 26.7 (CH_2), 21.2 (CH_2), 11.5 (CH_3); HRMS (ESI): Calcd for $C_{28}H_{36}N_5O_4S^+$ [*M* + H]$^+$: 538.2483. Found: 538.2479.



4-((5-Methoxy-1*H*-indol-1-yl)sulfonyl)-*N*',*N*'-dipropylbenzohydrazide (FRB21). Following the **General Procedure F**, the reaction of 4-((5-methoxy-1*H*-indol-1-yl)sulfonyl)benzohydrazide (**MTP86**) (150 mg, 0.43 mmol), dissolved in MeOH (13 mL), with propanal (0.05 mL, 1.60 mmol), $MgSO_4$ (357 mg) and $NaBH_3CN$ (54 mg, 0.86 mmol), after purification by flash chromatography of the residue using DCM/MeOH (3%) as eluent, provided compound **FRB21** (126 mg, 67%) as a white solid: mp 142-144 ºC; IR (cm^{-1}) ν 3228 (N-H), 1650 (C=O), 1367 (O=S=O), 1137 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (t, *J* = 8.6 Hz, 3H), 7.72 (d, *J* = 8.6 Hz, 1H), 7.48 (d, *J* = 3.6 Hz, 1H), 6.96 (d, *J* = 2.5 Hz, 1H), 6.92 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.61 (d, *J* = 3.7, 1H), 3.80 (s, 3H), 2.73 (t, *J* = 7.3 Hz, 4H), 1.54 - 1.49 (m, 4H), 0.90 (t, *J* = 7.4 Hz, 6H) (signal for "N*H*" were not detected); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.0, 156.8, 140.5, 139.1, 132.1, 129.9, 129.7, 128.0 ($2CH_{Ar}$), 127.2 ($2CH_{Ar}$), 114.6 (C7), 114.2 (C6), 110.4 (C3), 104.0 (C4), 60.3 (CH_3), 56.8 ($2CH_2$), 20.4 ($2CH_2$), 11.8 ($2CH_3$); HRMS (ESI): Calcd for $C_{22}H_{28}N_3O_4S^+$ [*M* + H]$^+$: 430.1795. Found: 430.1791.



***N*-Hydroxy-4-((5-methoxy-1*H*-indol-1-yl)sulfonyl)benzamide (MTP89).** Following the **General Procedure E,** the reaction of methyl 4-((5-methoxy-1*H*-indol-1-yl)sulfonyl)benzoate (**MTP84**) (80 mg, 0.23 mmol), dissolved in MeOH (12 mL), with KOH (377 mg, 6.72 mmol) and NH_2OH·HCl (402 mg, 5.79 mmol), after purification by flash chromatography of the residue using DCM/MeOH/NH_4OH (88:10.8:1.2) as eluent,

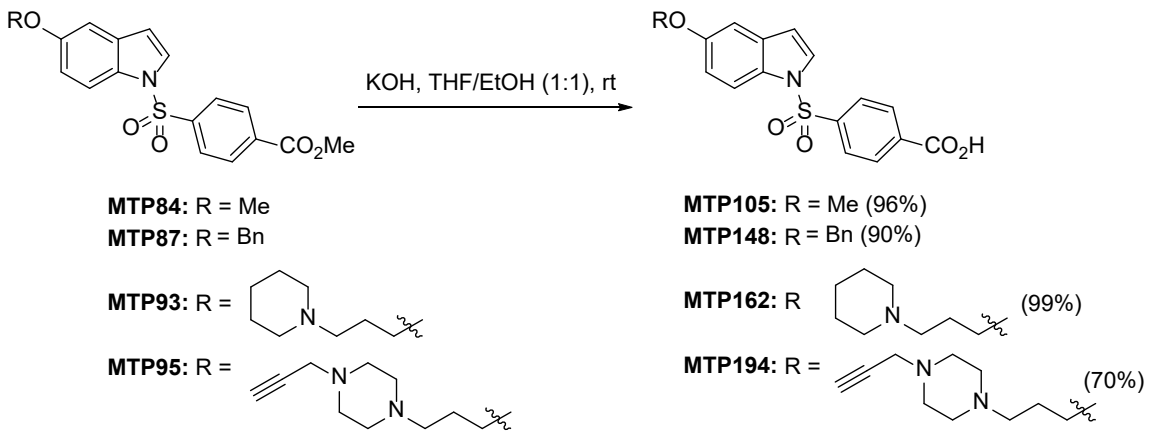
produced compound **MTP89** (34 mg, 42%) as a white solid: mp 195-197 ^{0}C; IR (cm^{-1}) ν 3585 (N-H), 3055 (O-H), 1651 (C=O), 1423 (O=S=O), 1155 (C-O-C); ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.01 (d, *J* = 8.6 Hz, 2H), 7.85 (d, *J* = 8.6 Hz, 2H), 7.83 (dd, *J* = 9.0, 0.7 Hz, 1H), 7.76 (d, *J* = 3.6 Hz, 1H), 7.11 (d, *J* = 2.6 Hz, 1H), 6.95 (dd, *J* = 9.0, 2.6 Hz, 1H), 6.79 (dd, *J* = 3.7, 0.7 Hz, 1H), 3.74 (s, 3H) (signal for "N*H*" and "O*H*" were not detected); ^{13}C NMR (126 MHz, DMSO-d$_6$) δ 162.4, 156.2, 138.8, 138.2, 131.7, 128.7, 128.2 (C2), 127.7 (2CH$_{Ar}$), 126.9 (2CH$_{Ar}$), 114.0 (C7), 113.8 (C6), 110.2 (C3), 104.1 (C4), 55.4 (CH$_3$); HRMS (ESI): Calcd for $C_{16}H_{15}N_2O_5S^+$ [*M* + H]$^+$: 347.0696. Found: 347.0688.

4-((5-(Benzyloxy)-1*H*-indol-1-yl)sulfonyl)-*N*-hydroxybenzamide (MTP98). Following the **General Procedure E**, the reaction of methyl 4-((5-(benzyloxy)-1*H*-indol-1-yl)sulfonyl)benzoate (**MTP87**) (150 mg, 0.36 mmol), dissolved in MeOH (18.2 mL), with KOH (280 mg, 4.98 mmol) and NH$_2$OH·HCl (247 mg, 3.56 mmol), after purification by flash chromatography of the residue using DCM/MeOH/NH$_4$OH (88:10.8:1.2) as eluent, gave compound **MTP98** (66 mg, 44%) as a white solid: mp 174-176 ^{0}C; IR (cm^{-1}) ν 3419 (N-H), 3055 (O-H), 1635 (C=O), 1372 (O=S=O), 1155 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 11.36 (s, 1H, N*H* or O*H*), 9.24 (s, 1H, N*H* or O*H*), 8.02 (d, *J* = 8.2 Hz, 2H), 7.87 - 7.83 (m, 3H), 7.77 (d, *J* = 3.7 Hz, 1H, H2), 7.46 - 7.41 (m, 2H), 7.41 - 7.35 (m, 2H), 7.35 - 7.29 (m, 1H), 7.20 (d, *J* = 2.5 Hz, 1H, H4), 7.03 (dd, *J* = 9.1, 2.5 Hz, 1H, H6), 6.78 (d, *J* = 3.7 Hz, 1H, H3), 5.08 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 162.5, 155.3, 138.8, 138.2, 137.1, 131.6, 128.8, 128.4 (3CH$_{Ar}$), 128.3 (CH$_{Ar}$), 127.8 (CH$_{Ar}$), 127.7 (3CH$_{Ar}$), 126.9 (2CH$_{Ar}$), 114.4 (C6), 114.0 (C7), 110.2 (C3), 105.3 (C4), 69.6 (CH$_2$); HRMS (ESI): Calcd for $C_{22}H_{19}N_2O_5S^+$ [*M* + H]$^+$: 423.1009. Found: 423.1011.

***N*-Hydroxy-4-((5-(3-(piperidin-1-yl)propoxy)-1*H*-indol-1-yl)sulfonyl)benzamide (MTP100).** Following the **General Procedure E**, the reaction of methyl 4-((5-(3-(piperidin-1-yl)propoxy)-1*H*-indol-1-yl)sulfonyl)benzoate (**MTP93**) (150 mg, 0.33 mmol), dissolved in MeOH (17 mL), with KOH (535 mg, 9.53 mmol) and NH$_2$OH·HCl (571 mg, 8.21 mmol), after purification by flash chromatography of the residue using DCM/MeOH/NH$_4$OH (90:10:1) as eluent, afforded compound **MTP100** (103 mg, 68%) as a white solid: mp 135-137 ^{0}C; IR (cm^{-1}) ν 3505 (N-H), 3059 (O-H), 1713 (C=O), 1363 (O=S=O), 1223 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.99 (d, *J* = 8.5 Hz, 2H), 7.89 (d, *J* = 8.5 Hz, 2H), 7.81 (d, *J* = 9.0 Hz, 1H, H7), 7.75 (d, *J* = 3.6 Hz, 1H, H2), 7.10 (d, *J*

= 2.6 Hz, 1H, H4), 6.93 (dd, *J* = 9.0, 2.6 Hz, 1H, H6), 6.77 (d, *J* = 3.6 Hz, 1H, H3), 3.97 (t, *J* = 6.3 Hz, 2H), 2.61 - 2.47 (m, 6H), 1.94 - 1.91 (m, 2H), 1.56 - 1.52 (m, 4H), 1.41 - 1.39 (m, 2H) (signal for "N*H*" and "O*H*" were not detected); ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.2, 155.5, 138.7, 138.3, 131.7, 129.9, 128.7 (CH_{Ar}), 128.3 (CH_{Ar}), 127.7 (C2), 126.8 ($2CH_{Ar}$), 114.2 (C6), 114.0 (C7), 110.3 (C3), 104.9 (C4), 66.1 (CH_2), 54.7 (CH_2), 53.5 ($2CH_2$), 25.5 (CH_2), 24.7 ($2CH_2$), 23.4 (CH_2); HRMS (ESI): Calcd for $C_{23}H_{28}N_3O_5S^+$ [*M* + H]$^+$: 458.1750. Found: 458.1744.

***N*-Hydroxy-4-((5-(3-(4-(prop-2-yn-1-yl)piperazin-1-yl)propoxy)-1*H*-indol-1-yl) sulfonyl)benzamide (MTP109).** Following the **General Procedure E**, the reaction of methyl 4-((5-(3-(4-(prop-2-yn-1-yl)piperazin-1-yl)propoxy)-1*H*-indol-1-yl)sulfonyl)benzoate (**MTP95**) (100 mg, 0.20 mmol), dissolved in MeOH (10.3 mL), with KOH (328 mg, 5.85 mmol) and $NH_2OH{\cdot}HCl$ (351 mg, 5.04 mmol), after flash chromatography of the residue using DCM/MeOH/NH_4OH (90:10:1) as eluent, provided compound **MTP109** (43 mg, 43%) as a white solid: mp 138-140 ^{0}C; IR (cm^{-1}) ν 3303 (N-H), 3055 (O-H), 1615 (C=O), 1373 (O=S=O), 1155 (C-O-C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.00 (d, *J* = 8.2 Hz, 2H), 7.85 (d, *J* = 8.2 Hz, 2H), 7.83 (d, *J* = 9.0 Hz, 1H, H7), 7.75 (d, *J* = 3.6 Hz, 1H, H2), 7.11 (d, *J* = 2.5 Hz, 1H, H4), 6.94 (dd, *J* = 9.0, 2.5 Hz, 1H, H6), 6.77 (d, *J* = 3.6 Hz, 1H, H3), 3.97 (t, *J* = 6.3 Hz, 2H), 3.23 (d, *J* = 2.5 Hz, 2H), 3.12 (d, *J* = 3.0 Hz, 1H), 2.47 - 2.36 (m, 10H), 1.86 - 1.81 (m, 2H) (signal for "N*H*" and "O*H*" were not detected); ^{13}C NMR (101 MHz, DMSO-d_6) δ 132.3, 155.6, 138.8, 138.2, 131.7, 128.6, 128.2 ($2CH_{Ar}$), 127.6 (C2), 126.8 ($2CH_{Ar}$), 114.2 (C6), 114.0 (C7), 110.2 (C3), 104.8 (C4), 79.5, 75.6 (CH), 66.2 (CH_2), 54.4 ($2CH_2$), 52.6 ($2CH_2$), 51.2 (CH_2), 46.0 (CH_2), 26.3 (CH_2); HRMS (ESI): Calcd for $C_{25}H_{29}N_4O_5S^+$ [*M* + H]$^+$: 497.1853. Found: 497.1850.



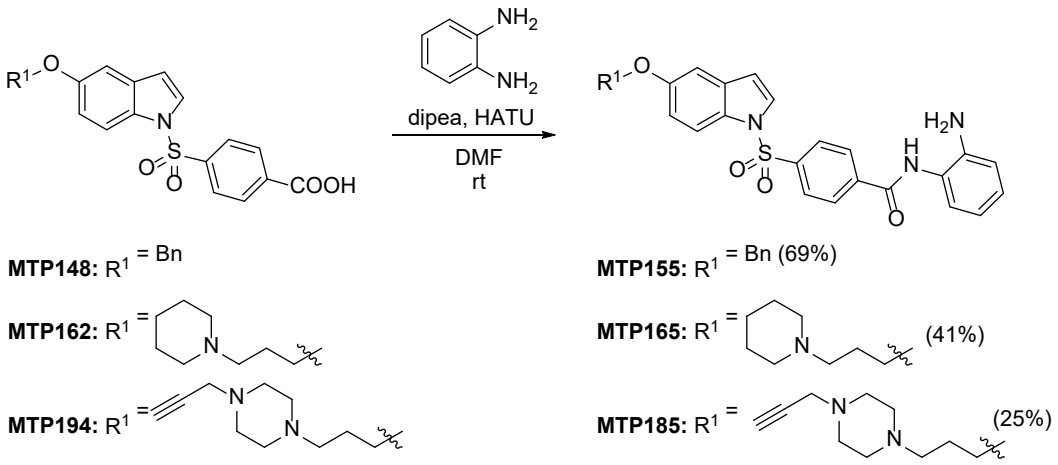
4-((5-Methoxy-1*H*-indol-1-yl)sulfonyl)benzoic acid (MTP105). Following the **General Method B**, the reaction of methyl 4-((5-methoxy-1*H*-indol-1-yl)sulfonyl)benzoate (**MTP84**) (500 mg, 1.45 mmol), dissolved in a mixture of THF/EtOH (1:1) (6 mL), with KOH (2.8 mL, 5.79 mmol), after purification by flash chromatography of the residue using DCM/MeOH(5%) as eluent, provided compound **MTP105** (460 mg, 96%) as a brown solid: mp >200 ^{0}C; IR (cm^{-1}) ν 3393 (COO-H), 1698 (C=O), 1374 (O=S=O), 1140 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.05 - 8.04 (m, 4H), 7.81 (d, *J* = 9.0 Hz, 1H, H7), 7.76 (d, *J* = 3.7 Hz, 1H, H2), 7.12 (d, *J* = 2.6 Hz, 1H, H4), 6.95 (dd, *J* = 9.0, 2.6 Hz, 1H, H6), 6.80 (d, *J* = 3.7 Hz, 1H, H3), 3.74 (s, 3H) (signal for "CO_2H" was not detected); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 165.7, 156.3, 140.3, 136.0, 131.7, 130.5 (2CH_{Ar}), 128.7, 127.7 (C2), 127.0 (2CH_{Ar}), 114.0 (C7), 113.8 (C6), 110.4 (C3), 104.1 (C4), 55.4 (CH_3); HRMS (ESI): Calcd for $C_{16}H_{14}NO_5S^+$ [*M* + H]$^+$: 332.0587. Found: 332.0588.

4-((5-(Benzyloxy)-1*H*-indol-1-yl)sulfonyl)benzoic (MTP148). Following the **General Method B**, the reaction of methyl 4-((5-(benzyloxy)-1*H*-indol-1-yl)sulfonyl)benzoate (**MTP87**) (770 mg,'lg 1.83 mmol), dissolved in a mixture of THF/EtOH (1:1) (7.4 mL), with KOH (3.4 mL, 7.31 mmol), after purification by flash chromatography of the residue using DCM/MeOH/NH_4OH (95:4.5:0.5) as eluent, produced compound **MTP148** (670 mg, 90%) as a brown solid: mp >200 ^{0}C; IR (cm^{-1}) ν 3393 (COO-H), 1688 (C=O), 1373 (O=S=O), 1143 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.07 - 7.97 (m, 4H), 7.82 (d, *J* = 9.0 Hz, 1H, H7), 7.76 (d, *J* = 3.7 Hz, 1H, H2), 7.46 - 7.28 (m, 5H), 7.20 (d, *J* = 2.5, 1H, H4), 7.03 (dd, *J* = 9.0, 2.5 Hz, 1H, H6), 6.79 (dd, *J* = 3.7, 0.8 Hz, 1H, H3), 5.08 (s, 2H) (signal for "CO_2H" was not detected); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 166.0, 155.3, 139.7, 137.1, 131.6, 130.4 (2CH_{Ar}), 128.8 (2 C), 128.4 (2CH_{Ar}), 127.8 (C2), 127.7 (CH_{Ar}), 127.7 (2CH_{Ar}), 126.8 (2CH_{Ar}), 114.4 (C6), 114.0 (C7), 110.2 (C3), 105.3 (C4), 69.6 (CH_2); HRMS (ESI): Calcd for $C_{22}H_{17}NNaO_5S^+$ [*M* + H]$^+$: 430.0720. Found: 430.0719.

4-((5-(3-(Piperidin-1-yl)propoxy)-1*H*-indol-1-yl)sulfonyl)benzoic acid (MTP162). Following the **General Method B**, the reaction of methyl 4-((5-(3-(piperidin-1-yl)propoxy)-1*H*-indol-1-yl)sulfonyl)benzoate (**MTP93**) (250 mg, 0.50 mmol), dissolved in a mixture of THF/EtOH (1:1) (2 mL), with KOH (0.9 mL, 2.0.2 mmol), after purification by flash chromatography of the residue using DCM/MeOH/NH_4OH (80:18:2) as eluent, gave compound **MTP162** (220 mg, 99%) as a white solid: mp 185-

190 ^{0}C; IR (cm^{-1}) ν 3080 (COO-H), 1608 (C=O), 1365 (O=S=O), 1179 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.99 (d, *J* = 8.6 Hz, 2H), 7.93 (d, *J* = 8.6 Hz, 2H), 7.79 (d, *J* = 9.0 Hz, 1H, H7), 7.74 (d, *J* = 3.7 Hz, 1H, H2), 7.08 (d, *J* = 2.5 Hz, 1H, H4), 6.92 (dd, *J* = 9.0, 2.5 Hz, 1H, H6), 6.74 (d, *J* = 3.7 Hz, 1H, H3), 3.97 (t, *J* = 6.3 Hz, 2H), 2.77 - 2.62 (m, 6H), 2.00 - 1.93 (m, 2H), 1.62 - 1.43 (m, 4H), 1.43 (s, 2H) (signal for "CO_2H" was not detected); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 166.4, 155.4, 131.6, 130.0 (2CH$_{Ar}$), 129.0, 128.7, 127.7 (C2), 126.4 (2CH$_{Ar}$), 125.7, 114.1 (C6), 114.0 (C7), 110.0 (C3), 104.8 (C4), 66.0 (CH$_2$), 54.5 (CH$_2$), 53.4 (2CH$_2$), 25.3 (CH$_2$), 24.5 (2CH$_2$), 23.2 (CH$_2$); HRMS (ESI): Calcd for $C_{23}H_{27}N_2O_5S^+$ [*M* + H]$^+$: 443.1635. Found: 443.1634.

4-((5-(3-(4-(Prop-2-yn-1-yl)piperazin-1-yl)propoxy)-1*H*-indol-1-yl)sulfonyl)benzoic acid (MTP194). Following the **General Method B**, the reaction of methyl 4-((5-(3-(4-(prop-2-yn-1-yl)piperazin-1-yl)propoxy)-1*H*-indol-1-yl)sulfonyl)benzoate (**MTP95**) (480 mg, 0.97 mmol), dissolved in a mixture of THF/EtOH (1:1) (4 mL), with KOH (1.8 mL, 3.87 mmol), after purification by flash chromatography of the residue using DCM/MeOH/NH$_4$OH (80:18:2) as eluent, afforded compound **MTP194** (328 mg, 70%) as a white solid: mp 181-183 ^{0}C; IR (cm^{-1}) ν 3294 (COO-H), 1611 (C=O), 1367 (O=S=O), 1155 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.03 (d, *J* = 8.6 Hz, 2H), 7.99 (d, *J* = 8.6 Hz, 2H), 7.80 (d, *J* = 9.0 Hz, 1H, H7), 7.75 (d, *J* = 3.6 Hz, 1H, H2), 7.10 (d, *J* = 2.5 Hz, 1H, H4), 6.93 (dd, *J* = 9.0, 2.5 Hz, 1H, H6), 6.77 (d, *J* = 3.6 Hz, 1H, H3), 3.97 (t, *J* = 6.3 Hz, 2H), 3.24 (d, *J* = 2.5 Hz, 2H), 3.14 (t, *J* = 2.5 Hz, 1H), 2.52 - 2.41 (m, 10H), 1.90 - 1.84 (m, 2H) (signal for "CO_2H" was not detected); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 166.0, 155.6, 139.6, 137.8, 131.7, 130.3 (2CH$_{Ar}$), 128.7, 127.7 (C2), 126.8 (2CH$_{Ar}$), 114.2 (C6), 114.0 (C7), 110.3 (C3), 104.8 (C4), 79.3, 75.8 (CH), 66.1 (CH$_2$), 54.2 (CH$_2$), 52.4 (2CH$_2$), 50.7 (2CH$_2$), 45.9 (CH$_2$), 25.9 (CH$_2$); HRMS (ESI): Calcd for $C_{25}H_{28}N_3O_5S^+$ [*M* + H]$^+$: 482.1744. Found: 482.1742.



***N*-(2-Aminophenyl)-4-((5-(benzyloxy)-1*H*-indol-1-yl)sulfonyl)benzamide (MTP155)**. Following the **General Method C**, the reaction of 4-((5-(benzyloxy)-1*H*-indol-1-yl)sulfonyl)benzoic (**MTP148**) (100 mg, 0.25 mmol), dissolved in dry DMF (1 mL), with DIPEA (0.11 mL, 0.61 mmol, 2.5 equiv), HATU (93 mg, 0.25 mmol) and 1,2-phenylenediamine (27 mg, 0.25 mmol), after purification by flash chromatography of the residue using DCM/MeOH (0.5%) as eluent, provided compound **MTP155** (84 mg, 69%) as a yellow solid: mp 85-87 ^{0}C; IR (cm^{-1}) ν 3364 (N-H), 1607 (C=O), 1371 (O=S=O), 1142 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.76 (s, 1H, N*H*), 8.08 - 8.06 (m, 3H), 7.96 (d, J = 8.3 Hz, 1H), 7.90 - 7.86 (m, 1H, H7), 7.77 (d, J = 3.7 Hz, 1H, H2), 7.44 - 7.42 (m, 2H), 7.39 - 7.36 (m, 2H), 7.35 - 7.28 (m, 1H), 7.20 (dd, J = 6.1, 2.5 Hz, 1H, H4), 7.09 (dd, J = 7.9, 1.5 Hz, 1H), 7.04 (dd, J = 9.0, 2.5 Hz, 1H, H6), 6.95 (td, J = 7.6, 1.6 Hz, 1H), 6.79 (d, J = 3.7 Hz, 1H, H3), 6.73 (dd, J = 8.0, 1.5 Hz, 1H), 6.55 (td, J = 7.5, 1.5 Hz, 1H), 5.09 (s, 2H), 5.08 (s, 2H, N*H*$_2$).; ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 163.9, 155.3, 143.3, 140.1, 138.8, 137.1, 131.7, 129.9 (CH$_{Ar}$), 129.1 (CH$_{Ar}$), 128.8, 128.4 (3CH$_{Ar}$), 127.8 (C2), 127.7 (3CH$_{Ar}$), 126.8 (CH$_{Ar}$), 126.6 (CH$_{Ar}$), 126.2 (CH$_{Ar}$), 122.4, 115.9 (CH$_{Ar}$), 115.8 (CH$_{Ar}$), 114.4 (C6), 114.1 (C7), 110.2 (C3), 105.3 (C4), 69.6 (CH$_2$); HRMS (ESI): Calcd for $C_{28}H_{24}N_3O_4S^+$ [M + H]$^+$: 498.1482. Found: 498.1485.

***N*-(2-Aminophenyl)-4-((5-(3-(piperidin-1-yl)propoxy)-1*H*-indol-1-yl)sulfonyl) benzamide (MTP165).** Following the **General Method C**, the reaction of 4-((5-(3-(piperidin-1-yl)propoxy)-1*H*-indol-1-yl)sulfonyl)benzoic acid (**MTP162**) (200 mg, 0.45 mmol), dissolved in dry DMF (1.8 mL), with DIPEA (0.2 mL, 1.13 mmol, 2.5 equiv), HATU (172 mg, 0.45 mmol) and 1,2-phenylenediamine (49 mg, 0.45 mmol), after purification by flash chromatography of the residue using DCM/MeOH (4%) as eluent, provided compound **MTP165** (98 mg, 41%) as a yellow solid: mp 80-82 ^{0}C; IR (cm^{-1}) ν 3233 (N-H), 1622 (C=O), 1370 (O=S=O), 1141 (C-O-C); ^{1}H NMR (400 MHz, CDCl$_3$) δ

8.11 (s, 1H, N*H*), 7.94 - 7.75 (m, 5H), 7.50 (d, *J* = 3.6 Hz, 1H, H2), 7.29 - 7.28 (m, 1H), 7.07 (td, *J* = 7.6, 1.5 Hz, 1H), 6.97 (d, *J* = 2.4 Hz, 1H, H4), 6.93 (dd, *J* = 9.0, 2.4 Hz, 1H, H6), 6.80 - 6.79 (m, 2H), 6.61 (dd, *J* = 3.7, 0.8 Hz, 1H, H3), 4.01 (t, *J* = 6.2 Hz, 2H), 3.76 (s, 2H, NH_2), 2.66 - 2.45 (m, 6H), 2.10 - 1.97 (m, 2H), 1.69 - 1.65 (m, 4H), 1.51 - 1.44 (m, 2H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.9, 155.9, 140.6, 140.4, 139.0, 131.9, 129.5, 128.2 ($2CH_{Ar}$), 127.5 (CH_{Ar}), 127.0 ($2CH_{Ar}$), 127.0 (C2), 125.1, 124.1, 119.9 (CH_{Ar}), 118.5 (CH_{Ar}), 114.4 (C6), 114.4 (C7), 110.2 (C3), 104.8 (C4), 66.6 (CH_2), 55.8 (CH_2), 54.4 ($2CH_2$), 26.1 (CH_2), 25.2 ($2CH_2$), 23.9 (CH_2); HRMS (ESI): Calcd for $C_{29}H_{33}N_4O_4S^+$ [*M* + H]$^+$: 533.2217. Found: 533.2210.

***N*-(2-Aminophenyl)-4-((5-(3-(4-(prop-2-yn-1-yl)piperazin-1-yl)propoxy)-1*H*-indol-1-yl)sulfonyl)benzamide (MTP185).** Following the **General Method C**, the reaction of 4-((5-(3-(4-(prop-2-yn-1-yl)piperazin-1-yl)propoxy)-1*H*-indol-1-yl)sulfonyl) benzoic acid **(MTP194)** (280 mg, 0.58 mmol), dissolved in dry DMF (2.3 mL), with DIPEA (0.3 mL, 1.45 mmol, 2.5 equiv), HATU (221 mg, 0.58 mmol) and 1,2-phenylenediamine (63 mg, 0.58 mmol), after purification by flash chromatography of the residue using DCM/MeOH (2%) as eluent, produced compound **MTP185** (65 mg, 25%) as a yellow solid**:** mp 77-79 ^{0}C; IR (cm^{-1}) ν 3287 (N-H), 1621 (C=O), 1371 (O=S=O), 1140 (C-O-C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 - 7.84 (m, 5H), 7.51 (d, *J* = 3.7 Hz, 1H, H2), 7.31 (d, *J* = 7.8 Hz, 1H), 7.09 (td, *J* = 7.6, 1.5 Hz, 1H), 6.98 (d, *J* = 2.4 Hz, 1H, H4), 6.94 (dd, *J* = 9.0, 2.5 Hz, 1H, H6), 6.87 - 6.76 (m, 2H), 6.62 (dd, *J* = 3.7, 0.8 Hz, 1H, H3), 4.02 (t, *J* = 6.3 Hz, 2H), 3.30 (d, *J* = 2.4 Hz, 2H), 2.70 - 2.40 (m, 10H), 2.25 (t, *J* = 2.4 Hz, 1H), 2.03 - 1.92 (m, 2H);. ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.8, 156.1, 140.7, 140.2, 139.0, 131.9, 129.4 (CH_{Ar}), 128.1 ($2CH_{Ar}$), 127.5, 127.1 ($2CH_{Ar}$), 127.0 (C2), 124.9 (CH_{Ar}), 124.2, 120.1 (CH_{Ar}), 118.7 (CH_{Ar}), 114.5 (C6), 114.4 (C7), 110.2 (C3), 104.8 (C4), 78.8, 73.2 (CH), 66.7 (CH_2), 55.1 (CH_2), 53.0 ($2CH_2$), 51.8 ($2CH_2$), 46.8 (CH_2), 26.7 (CH_2); HRMS (ESI): Calcd for $C_{31}H_{34}N_5O_4S^+$ [*M* + H]$^+$: 572.2326. Found: 572.2320.

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REFERENCES

(1) Hwang, J. Y.; Aromolaran, K. A.; Zukin, R.-S. The emerging field of epigenetics in neurodegeneration and neuroprotection. *Nat. Rev. Neurosci*. **2017**, *18*, 347-361.
(2) Marks, P. A. Discovery and development of SAHA as an anticancer agent. *Oncogene* **2007**, *26*, 1351.
(3) Poole, R.M. Belinostat: First global approval. *Drugs* **2014**, *74*, 1543.
(4) Mottamal, M.; Zheng, S.; Huang, T. L.; Wang, G. Histone deacetylase inhibitors in clinical studies as templates for new anticancer agents. *Molecules* **2015**, *20*, 3898-3941.
(5) Zhang, L.; Zhang, J.; Jiang, Q.; Zhang, L.; Song, W. Zinc binding groups for histone deacetylase inhibitors. *J. Enzyme Inhib. Med. Chem.* **2018**, *33*, 714-721.
(6) Butler, K.V.; Kalin, J.; Brochier, C.; Vistoli, G.; Langley, B.; Kozikowski, A. P. Rational design and simple chemistry yield a superior, neuroprotective HDAC6 inhibitor, tubastatin A. *J. Am. Chem. Soc.* **2010**, *132*, 10842-6.
(7) The introduction is adapted heavily from a previous preprint by the authors: (a) Marco-Contelles J, Diez-Iriepa D, Toledano-Pinedo M, Porro A, Almendros P, Rodríguez-Fernández MM, Samadi A, Iriepa I, López-Muñoz F, Artetxe-Zurutuza A, Matheu, A. Contilistat, a new polyfunctionalized histone deacetylase inhibitor, showing potential capacity to inhibit cholinesterase/monoamine oxidase enzymes, and modulate histamine 3, sigma 1, 5-HT6 and dopamine 3 receptors for the treatment of cancer and neurodegenerative diseases. ChemRxiv. Cambridge: Cambridge Open Engage; 2023. This content is a preprint and has not been peer-reviewed. ChemRxiv (2023), 1-16. doi: 10.26434/chemrxiv-2023-rk8bf; (b) Toledano-Pinedo M, Porro A, Macaulet S, Almendros P, Iriepa I, Rodríguez-Fernández MM, López-Muñoz F, Artetxe-Zurutuza A, Matheu A, Marco-Contelles J. 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. ChemRxiv. Cambridge: Cambridge Open Engage; 2023. This content is a preprint and has not been peer-reviewed. ChemRxiv (2023), 1-35. doi: 10.26434/chemrxiv-2023-m4qs6.
(8) Bautista-Aguilera, Ó. M.; Hagenow, S.; Palomino-Antolín, A.; Farré-Alins, V.; Ismaili, L.; Joffrin, P.-L.; Schwed, J. S.; Jimeno, M. L.; Soukup, O.; Janockova, J.; Kalinowsky, L.; Proschak, E.; Iriepa, I.; Moraleda, I.; Romero, A.; López-Muñoz, F.; Chioua, M.; Egea, J.; Ramsay, R. R.; Marco-Contelles, J.; Stark, H. Tripotent-directed indoles for Alzheimer's disease therapy combining cholinesterase and monoamine oxidase inhibition with H3R antagonism profile. *Angew. Chem. Int. Ed*. **2017**, *56*, 12765-12769.
(9) Bautista-Aguilera, Ó. M.; Budni, J.; Mina, F.; Behenck Medeiros, E.; Deuther-Conrad, W.; Entrena, J. M.; Moraleda, I.; Iriepa, I.; López-MuñoZ. F.; Marco-Contelles, J. Contilisant, a tetratarget small molecule for Alzheimer's disease therapy combining cholinesterase, monoamine oxidase inhibition and H3R antagonism with sigma 1R agonism profile. Marco-Contelles, J. *J. Med. Chem.* **2018**, *61*, 6937-6943.

(10) Nyantakyi, S. A.; Li, M.; Gopal. P.; Zimmerman, M.; Dartois, V.; Gengenbacher, M.; Dick, T.; Go, M.-L. Indolyl azaspiroketal Mannich bases are potent antimycobacterial agents with selective membrane permeabilizing effects and in vivo activity. *J. Med. Chem.* **2018**, *61*, 5733-5750.