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# Structure–Activity Relationship Analysis of the Peptide Deformylase Inhibitor 5-Bromo-1*H*-indole-3-acetohydroxamic Acid

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*The lead compound 5-bromoindolyl-3-acetohydroxamic acid (**10**) was recently identified as a potent inhibitor of bacterial peptide deformylases (PDFs). The synthesis and associated activities of new variants were investigated at position 5 to optimize the fit at the S1′ subsite and at position 1 to improve both potency and antibacterial activity. A morphomimetic series, termed "reverse-indole" was synthesized. The indole derivatives remain selective in vitro inhibitors of PDF2 over PDF1. Bromide is the best group at position 5 and cannot be replaced by bulkier substituents. In this series, an N-benzyl group at position 1 in **19e** improves the potency relative to **10**. In the case of PDF1, and unlike PDF2, potency is increased as the alkyl chain becomes longer and more ramified. These data support the results of NMR footprinting experiments that were performed with $^{15}$N-labeled Ni-PDF and the corresponding 3-acetic acid derivatives. Most of the compounds have antibacterial activities toward* B. subtilis*, but are inefficient toward* E. coli *owing to active removal by the major efflux pumps. Among the reverse-indole derivatives, **23c**, which is the exact mirror image of **19e**, shows strong potency in vitro against PDF2, but little against PDF1, although this compound displays significant antibacterial activity toward an efflux-minus mutant of* E. coli*. All the compounds were assessed with major pathogenic bacteria, but most of them are inefficient antibacterial agents. The reverse-indole compounds **23a** and **23c** have potency against* S. pneumoniae *that is similar to that of actinonin.*

## Introduction

Peptide deformylase (PDF) has received special attention in the course of the search for new antibacterial agents with novel modes of action. PDF is involved in the cleavage of the N-formyl group of nascent polypeptide. This process is essential to the growth of bacteria.[1,2] Three-dimensional structures of PDF from various species have been solved either free or in complex with specific inhibitors such as actinonin. Two bacterial PDF types have been distinguished, PDF1B and PDF2, which are found in Gram-negative and Gram-positive bacteria, respectively.[3,4] Recently, PDF homologues have been identified in eukaryotic cells and classified as type-1A.[5,6] Characterization of the human form as an effective PDF was considered to be a serious issue to the validation of PDF as a good target;[7–9] however, comparison of the crystal structures of PDF1A with those of PDF1B and PDF2 revealed significant differences that were considered for the design of selective inhibitors.[10] PDF1A shows a smaller S1′ binding pocket than PDF1B or PDF2, and PDF1A shows an enlargement of the S2′ pocket relative to PDF2. Most of the inhibitors that have been described so far are peptidic or pseudopeptidic analogues of actinonin, a natural inhibitor compound.[11] Only very few nonpeptidic inhibitors, which are assumed to be less prone to degradation have been designed.[12–17] By using NMR screening, new derivatives with a 5-bromoindole scaffold were recently designed.[18] The lead compound, 2-(5-bromo-1*H*-indol-3-yl)-*N*-hydroxyacetamide (**10**) acts as a potent inhibitor of both types of bacterial PDF (i.e., PDF1B and PDF2), but is more potent against PDF2. It shows antibacterial activity toward *Bacillus subtilis* that was shown to specifically depend on the inhibition of both PDF.

Herein we describe the SAR of this hydroxamate indole series. New substituents have been introduced at position 5 or 3, and on the indole nitrogen position (1) with the aim to improve the overall properties of the series. The associated potency was determined against PDF1B from *Escherichia coli* and PDF2 from *Bacillus stearothermophilus*, and their antibacterial activity was evaluated against *E. coli* and *B. subtilis* as well as against some other pathogens.

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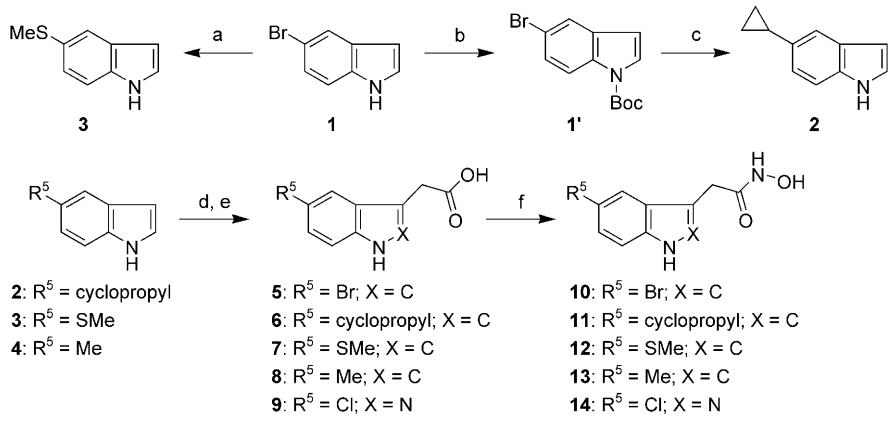
## Results and Discussion

### Chemistry

#### *Synthesis of 2-(5-substituted-1*H*-indol-3-yl)-*N*-hydroxyacetamide*

Several 5-substituted 3-acetohydroxamic acid indolyl derivatives that are shown in Scheme 1 were prepared to complete the series that was previously described.[18] Regiospecific lithiation of the potassium salt of 5-bromoindole (**1**) at position 5 with *tert*-butyllithium followed by reaction of the lithiated derivative with dimethyldisulfide afforded 5-thiomethylindole **3** in 85% yield.[19] A cyclopropyl group was introduced through a palladium-catalyzed Suzuki cross-coupling reaction of *N*-Boc-5-bromoindole **1′** with the commercially available cyclopropylboronic acid in the presence of tricyclohexylphosphine ($PCy_3$).[20] The yield was only acceptable when the indole was protected by a Boc group.[21] Deprotection with trifluoroacetic acid (TFA) in dichloromethane afforded the 5-cyclopropyl derivative **2**. 5-Cyclopropylindole **2**, 5-thiomethylindole **3**, and 5-methylindole **4** were further converted into their corresponding 3-acetic acid derivatives **6**, **7**, and **8** in two steps. Reaction of **2**, **3**, and **4** with oxalyl chloride in anhydrous diethyl ether[22] followed by treatment with a saturated aqueous solution of sodium bicarbonate afforded indole-3-glyoxalic acids, which were subsequently reduced by a Wolff–Kishner-type reaction with hydrazine hydrate in 2-methoxyethanol in the presence of sodium methoxide.[23] 5-Trifluoromethylindole was also prepared from 5-trifluoromethylaniline, but this compound was too deactivated to further react with oxalyl chloride.[24] 5-Chloro-3-indazoleacetic acid **9** was prepared from 5-chloro-2-nitrobenzaldehyde as previously described.[25]

The most efficient method to introduce the hydroxamic function is the reaction of the different acids, **5**–**9**, with *O*-(*tert*-butyldimethylsilyl)hydroxylamine in freshly distilled and anhydrous *N*,*N*-dimethylformamide (DMF) by using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI) and 1-hydroxybenzotriazole (HOBT) as coupling agents in the presence of *N*-methylmorpholine (NMM), which produced the O-silylated hydroxamic acids. The silylated derivatives were then transformed in situ into the corresponding hydroxamic acids **10**–**14** by treatment with tetra-*n*-butylammonium fluoride ($Bu_4NF$) in tetrahydrofuran (THF).




**Scheme 1.** Synthesis of 2-(5-chloro-1*H*-indazol-3-yl)-*N*-hydroxyacetamide and 2-(1*H*-indol-3-yl)-*N*-hydroxyacetamide functionalized with various substituents at position 5. Reagents and conditions: a) 1) KH, *t*BuLi, THF, −78 °C, 2) $CH_3SSCH_3$; b) 1) NaH, THF, 2) $Boc_2O$; c) 1) cyclopropyl boronic acid, $PCy_3$, $Pd(OAc)_2$, toluene, 2) TFA, $CH_2Cl_2$ (0.1:1 *v*/*v*); d) 1) oxalyl chloride, $Et_2O$, 0 °C, 20 min, 2) aq $NaHCO_3$, reflux, 30 min; e) $NH_2NH_2$, NaOMe; f) 1) HOBT, NMM/DMF, EDCI, $NH_2OSiMe_2tBu$, 2) $Bu_4NF$/THF.

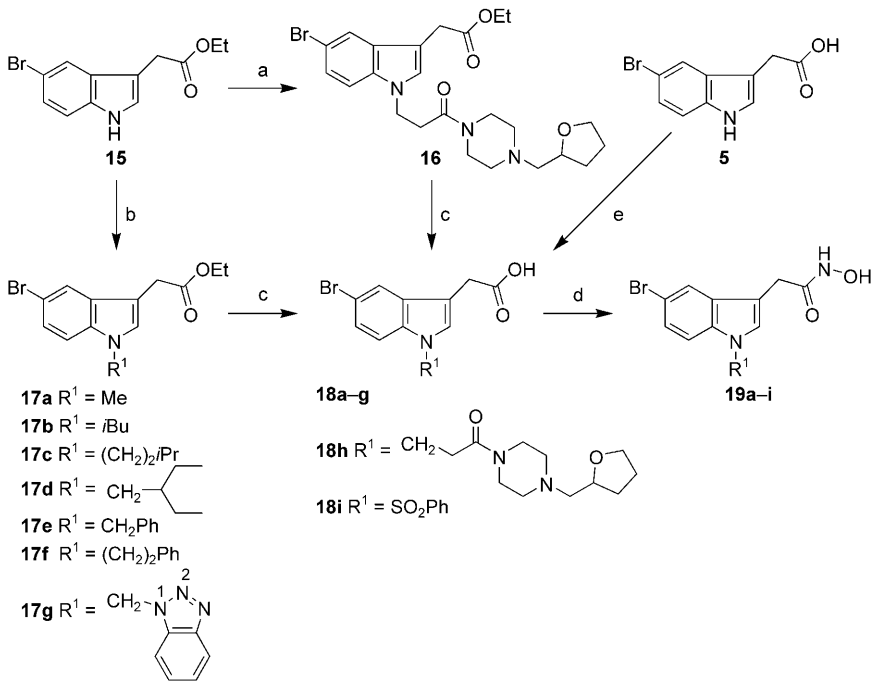
#### *Synthesis of N-substituted 5-bromoindole-3-acetohydroxamic acid*

Several N-substituted derivatives were synthesized by following the reaction pathways that are shown in Scheme 2. Compounds **17a**–**17g** were obtained from 5-bromoindole-3-acetic acid ethyl ester, **15**, which was N-alkylated with alkyl halides or benzyl bromide, phenylethyl bromide, and 1-chloromethylbenzotriazole after forming the sodium salt of **15** with sodium hydride in DMF.[26] Compound **18h** was prepared in three steps by N-alkylation of **15** with *tert*-butylacrylate in dioxane in the presence of a catalytic amount of benzyltrimethylammonium hydroxide according to a previously described procedure,[27] followed by acid hydrolysis of the *tert*-butyl ester with TFA in dichloromethane, and condensation of the acid with 1-(tetrahydro-2-furanylmethyl)piperazine in the presence of EDCI, HOBt, and NMM. Synthesis of *N*-phenylsulfonyl indole **18j** was directly achieved from 5-bromoindole-3-acetic acid by reaction of the dilithiated salt with phenylsulfonyl chloride at −78 °C.[28] At this low temperature, the alkylation is selective at the indole nitrogen atom of **5**, as was previously observed for the preparation of the *N*-benzyloxycarbonyl indole-3-acetic acid.[18] After saponification of the ethyl ester, the hydroxamic acid was prepared as mentioned above.

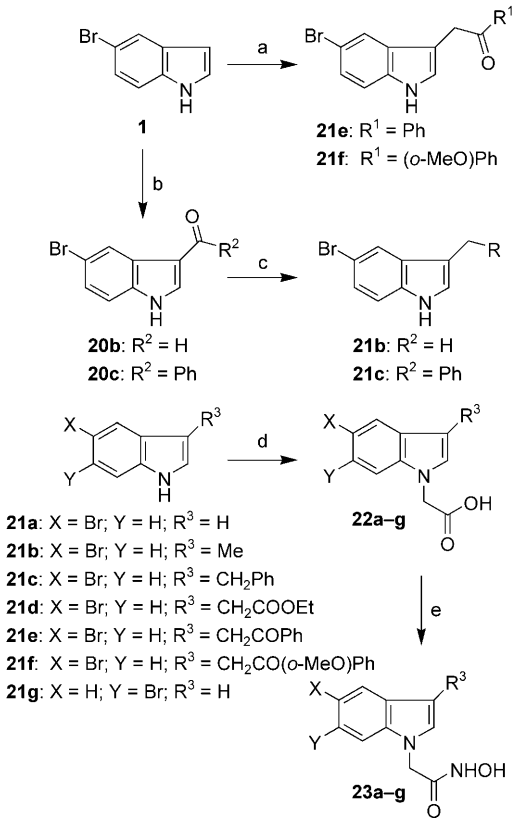
#### *Synthesis of* N*-hydroxyacetamide indole derivatives ("reverse-indole" derivatives)*

We designed and synthesized a new series of acetohydroxamic acid, which is shown in Scheme 3 in which substituents at positions 1 and 3 of the indole are reversed relative to the previous series. 5-Bromoindole **1** was first functionalized at position 3. The 3-acylindoles **20b** and **20c** were prepared by Vilsmeier–Haack reaction of **1** with phosphoryl chloride and DMF,[29] and with benzoyl chloride in dichloromethane in the presence of trimethylaluminum,[30] respectively. Further reduction with lithium aluminum hydride in THF provided 3-methyl-5-bromolindole **21b** and 3-benzyl-5-bromoindole **21c**. Reaction of the zinc salt of **1** with phenacyl bromide and 2-bromo-




**Scheme 2.** Synthesis of N-substituted 2-(indol-3-yl)-*N*-hydroxyacetamide. Reagents and conditions: a) 1) *tert*-butylacrylate, benzyltrimethylammonium hydroxide/dioxane, 2) TFA, $CH_2Cl_2$ (0.1:1 *v/v*), 3) HOBT, NMM, DMF, EDCI, 1-(tetrahydro-2-furanylmethyl)piperazine; b) 1) NaH/DMF, 0 °C, 2) $R^1X$; c) NaOH, dioxane; d) 1) HOBT, NMM, DMF, EDCI, $NH_2OSiMe_2tBu$, 2) $Bu_4NF$, THF; e) 1) LiHMDS (2 equiv), THF −78 °C, 2) $PhSO_2Cl$.




**Scheme 3.** Synthesis of reverse-indoles. Reagents and conditions: a) 1) *n*BuLi, THF, $ZnCl_2$, $Et_2O$, 10 °C, 2) $BrCH_2COR$, toluene; b) 1) $POCl_3$, DMF or $AlMe_3$, ArCOCl, 2) NaOH, dioxane; c) $LiAlH_4$, THF; d) 1) NaH, DMF, 0 °C, 2) $BrCH_2COOEt$, 3) NaOH, dioxane; e) 1) HOBT, NMM, DMF, EDCI, $NH_2OSiMe_2tBu$, 2) $Bu_4NF$, THF.

2′-methoxyacetophenone afforded selectively **21e** and **21f**, respectively. Introducing the acetohydroxamic acid at position 1 was performed in three steps. Compounds **21a–g** were N-alkylated with ethyl bromoacetate after deprotonation of the indole NH with NaH for **21a,b,c,d,g**,[26] or under milder conditions for **21e,f** by using $Cs_2CO_3$ as a base to avoid the side-reactions that are derived from deprotonation of the acetyl substituent at position 3. Basic hydrolysis of the resulting ethyl ester followed by peptide coupling of the acid with *O*-(*tert*-butyldimethylsilyl)hydroxylamine, and in situ desilylation with $Bu_4NF$ in THF promoted the formation of the *N*-hydroxyacetamide indoles **23a–g**.

### NMR spectroscopic screening analysis

The binding potency of some of the acetohydroxamic indole precursors was evaluated by analyzing the $\{^1H–^{15}N\}$ chemical shift perturbation of $^{15}N$-labeled *E. coli* Ni-PDF1 by complexation with these molecules. This NMR screening has previously allowed us to select the 5-bromoindole scaffold as a good candidate to develop high-affinity PDF inhibitors.[18] Some indoles that are substituted at position 5 were tested, and the following order of affinity was determined: 5-bromo is better than 5-cyclopropyl and 5-trifluoromethylindole. Introduction of an acetic acid group at position 3 led to less-efficient binding whereas introduction of a metal chelating group was expected to improve binding to the enzyme: for instance, in the bromine series, **1** is better than **5**, and in the cyclopropyl series, **2** is better than **6**. For the screening tests, the hydroxamic function appears too a strong binding group, as this results in leveling the effect of any additional substituents on the indole ring. Interestingly, in addition to the bromine at position 5, introducing substituents at positions 1 and 3 leads to more coherent results. This enables us to rank the affinity of the compounds for *E. coli* PDF1 as indicated in Figure 1. Complexation of *E. coli* PDF with the "reverse-indole" derivative **22c** induces only very little perturbation relative to the free protein spectrum. This compound appears not to be recognized by the *E. coli* enzyme. Superimposition of the 2D NMR maps that were obtained with **18d**, **18e**, and **18c**, shows that their NMR footprints (Figure 2) are very similar to that of the lead compound **10**, (the most shifted residues are: I86, E88, G89, C90, L91, G43, I44, G45, A47, and V100). Like **10** (in green in Figure 2), **18d** (in red in Figure 2) seems to bind more strongly than **18e** (in yellow Figure 2) by

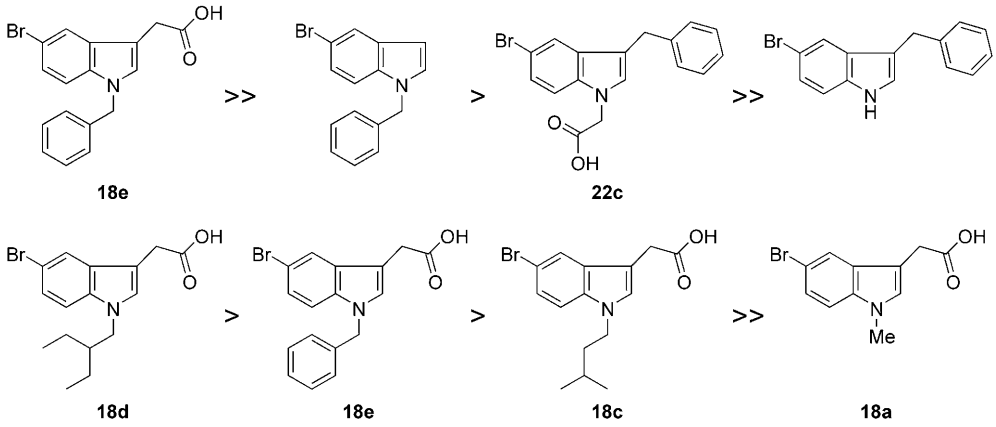



**Figure 1.** Indole derivatives assayed by NMR spectroscopy on *E. coli* $^{15}$N-labeled Ni-PDF.

inducing larger chemical shift perturbation on the same NH,[31] and modifications on other amino acid residues (Y39, E41, E42, E95 and H131, E133, M134 or H136). This NMR result with carboxylic acid derivatives suggests that the presence of a hydrophobic chain on the indole nitrogen atom is well tolerated by the active site of *E. coli* PDF.

### In vitro assessment of PDF inhibition

The potency of the hydroxamic derivatives was assessed with PDF2 from *B. stearothermophilus* (PDF2) and PDF1B from *E. coli* (PDF1B). The associated $IC_{50}$ values are listed in Table 1. Whatever the modifications of the substituents, with the exception of a cyclopropyl group at position 5 in **11**, these indole derivatives are more potent against PDF2 than PDF1B. The lead molecule, 5-bromoindole-3-acetohydroxamic acid **10** was described to tightly fit into the S1′ pocket, the bromine is located at the level of the $C_4$ methyl group of the methionine side chain.[18] Replacing bromine by chlorine or fluorine has been reported to yield inhibitors with equal potency.[18] Among the new substituents at position 5,

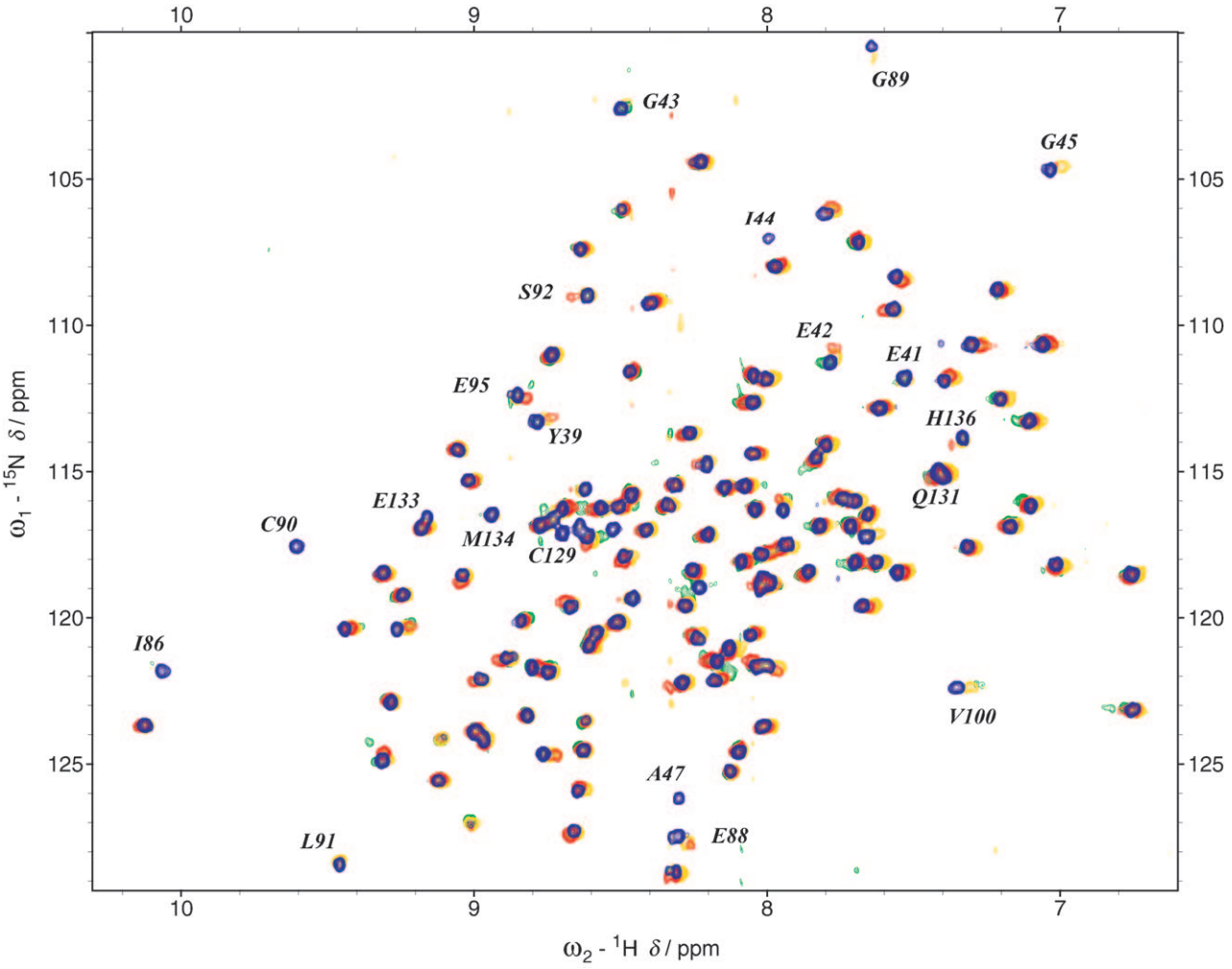



**Figure 2.** Superimposition of 2D {$^1$H–$^{15}$N} TROSY experiments of *E. coli* PDF1 with and without inhibitor: the reference spectrum of the free protein is shown in blue, the spectrum in the presence of **18d** is in red, the spectrum in the presence of **10** is in green, and the spectrum in the presence of **18e** is in yellow.

**Table 1.** Inhibitory activity of various indole derivatives against purified PDF and *B. subtilis* and *E. coli* strains.

| Compound | $IC_{50}$ [nM] PDF2[a] | PDF1B[b] | MIC [μg mL$^{-1}$] *B. subtilis* | *E. coli tolC* | *E. coli* K37[c] |
|---|---|---|---|---|---|
| actinonin | 10±2 | 10±0.5 | 1–2 | 0.125–0.25 | 32–64 |
| **10** | 11±2 | 38±2 | 4–8 | 8–16 | 32–64 |
| **11** | >800 | 127±43 | >64 | >64 | >64 |
| **12** | >1000 | >1000 | >23 | – | – |
| **13** | 45±2 | >400 | >20 | – | – |
| **14** | 9±0.5 | 120±6 | >64 | >64 | >64 |
| **19a** | 12±2 | 136±21 | 4–8 | 2–4 | >64 |
| **19b** | 31±13 | 84±10 | 2–4 | 16–32 | >64 |
| **19c** | 10±2 | 66±1 | 2–4 | 8–16 | >64 |
| **19d** | 23±8 | 49±6 | 2–4 | 16–32 | >64 |
| **19e** | 8±1 | 21±2 | 1–2 | 8–16 | >64 |
| **19f** | 360±18 | >500 | >64 | 16–32 | >64 |
| **19g** | 9±0.5 | 120±6 | >64 | >64 | >64 |
| **19h** | 655±30 | >400 | >64 | – | – |
| **19i** | 22±6 | 86±12 | 16–32 | 32–64 | >64 |
| **23a** | 397±119 | >320 | 32–64 | 32–64 | >64 |
| **23b** | >600 | >320 | 32–64 | 32–64 | >64 |
| **23c** | 24±6 | 312±97 | 8–16 | 4–8 | >64 |
| **23d** | 62±3 | >140 | 32–64 | – | – |
| **23e** | 500±25 | >500 | 32–64 | >64 | >64 |
| **23f** | 500±25 | >500 | >64 | >64 | >64 |
| **23g** | 242±47 | >320 | 32–64 | 32–64 | >64 |

[a] From *B. stearothermophilus*. [b] From *E. coli*. [c] Wild-type strain.

methyl derivative **13** is the only analogue with an $IC_{50}$ value of 45 nM for PDF2, a value that is only slightly higher than that of **10**. The performance of the various substitutions reveals that position 5 does not accept bulky substituents such as a methoxy,[18] a cyclopropyl **11**, or a thiomethyl **12**. Compound **14** with an indazole heterocycle is as efficient as **10** against PDF2.

Alkylation of the indole nitrogen atom (position 1) was expected to have only a moderate in vitro effect toward PDF1 or PDF2, as the substitution was expected to fit into the S3′ subsite or to be exposed to the solvent. Compounds with alkyl chains **19a–d**, benzyl **19e**, *N*-methylbenzotriazole **19g**, or benzylsulfonyl **19i** substituents have indeed excellent $IC_{50}$ values (i.e. <30 nM) against PDF2. The *N*-methylbenzotriazole group was chosen because a superimposition of **19g** with actinonin revealed that the N1–N2 bond of the triazole ring (see Scheme 2 for labeling) could mimic the C=O bond of the proline residue in actinonin. As a result, it could create a hydrogen bond with the NH backbone of Gly89 and Ile44 in *E. coli* that corresponds to Gly109 and Ile59 in *B. stearothermophilus*,[4,32] but **19g** proved to be a weak inhibitor of PDF1. The molecular basis of this selectivity might be explained by a molecular modeling analysis. Replacing actinonin by **19g** in the crystal structure of *B. stearothermophilus* (PDB code: 1LQY) and *E. coli* (PDB code: 1LRU) reveals differences in the interaction of **19g** with the two proteins. In *B. stearothermophilus* PDF2 (Figure 3) the benzotriazole ring is mainly exposed to the solvent and only within hydrogen-bonding distance of the peptide NH of Ile59 (N2···Ile: 3.5 Å). The situation is completely different in *E. coli* PDF1 (Figure 4). The N2 nitrogen atom of the benzotriazole is located far from Ile44 and Gly89 but the main interaction of the benzotriazole ring involves a cation–π binding with Arg97; this prevents the 5-bromoindole from fit-

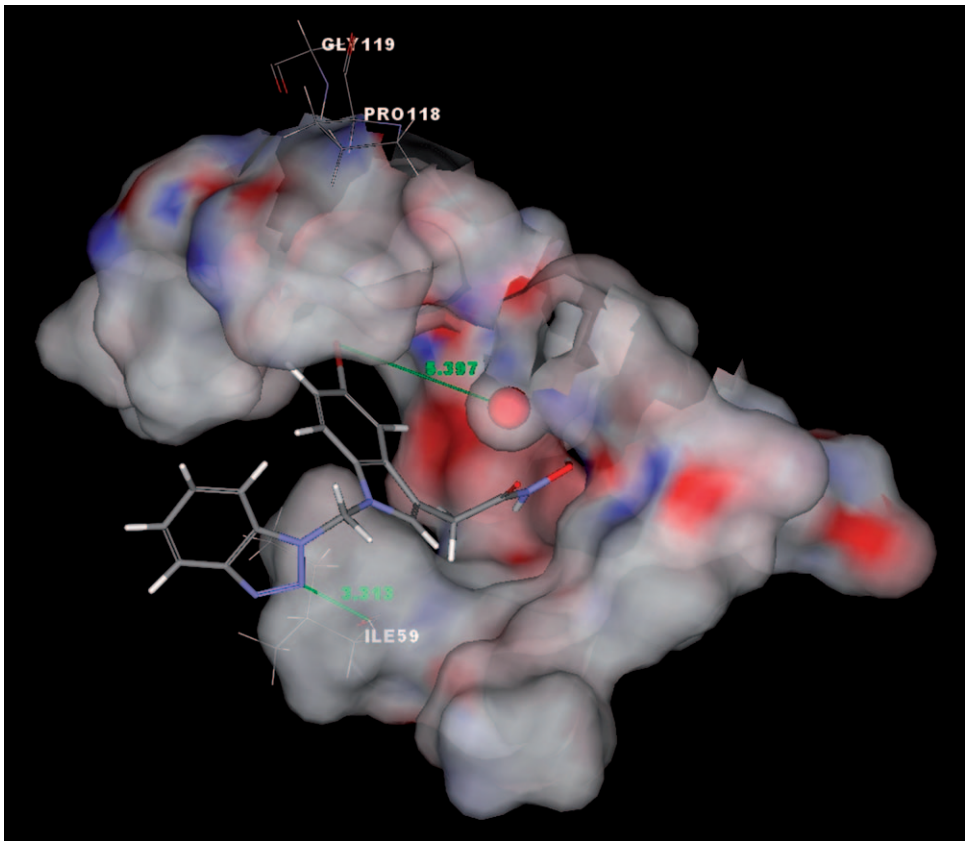



**Figure 3.** Predicted structure of **19g** in complex with *B. stearothermophilus* PDF2.

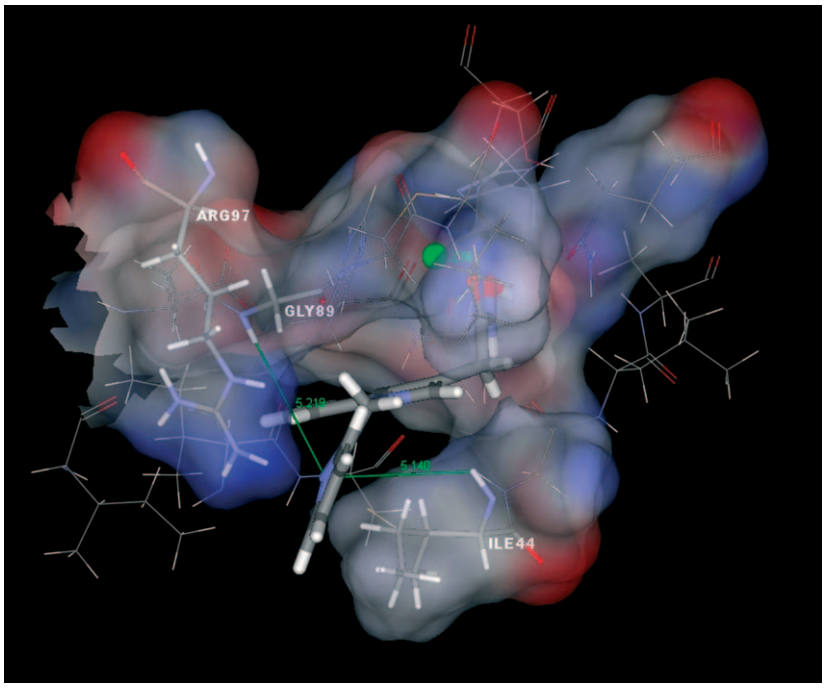



**Figure 4.** Predicted structure of **19g** in complex with *E. coli* PDF1.

ting deeply inside the S1′ pocket. The strength of this interaction[33] might explain why **19g** is a poorer inhibitor of *E. coli* PDF, and probably why alkyl chains are better tolerated. Indeed, the $IC_{50}$ values of compounds **19a–e** decrease when the chain at position 1 is more hydrophobic in keeping with their predicted binding potency that is based on that of the acid precursors that were assessed by NMR spectroscopy. Indeed, both experiments are in accordance, despite some discrepancy between the order of binding potency of the acids that was deduced from the NMR experiments (**18d** better than **18c** and **18e**) and the order of inhibitory efficacy of the related hydroxamic acids (**19e** more efficient inhibitor than **19d** or **19c**) (Table 1). Introducing a phenylethyl group (**19f**) or a (tetrahydro-2-furanylmethyl)piperazine on a propionic acid spacer (**19h**), however, resulted in a complete loss of inhibitory effect against both types of PDF. We also prepared several peptide analogues of **19h** (data not shown), but the results did not improve.

Finally, the 5-Br "reverse-indole" series led to the finding of two new potent inhibitors of PDF2, **23c** and **23d**. Interestingly, **23c** is the reverse image of **19e**, which is the most potent inhibitor of PDF2. Nevertheless, in agreement with the NMR experiment, **23c** is less potent than **19c**. In this series, position 5 appears to be optimal for the bromine substituent because compound **23g**, which has a 6-Br substituent and is the exact reverse of **10** did not display any potent activity.

In contrast to actinonin, compound **10** was described as being selective for bacterial PDFs without any significant effect against mitochondrial PDF1A. Derivatives **19e**, **23a** and **23c** were assayed against PDF from *Arabidopsis thaliana* as a representative of PDF1A, and show, as did **10**, $IC_{50}$ values that are higher than 10 μM, whereas the $IC_{50}$ for actinonin is $20 \pm 1$ nM. This indicates that this indole series remains selective for bacterial PDFs.

### Antibacterial activities

The antibacterial activities of all these derivatives were first tested against *B. subtilis* and *E. coli* strains as representative of Gram-positive and Gram-negative bacteria, respectively. We measured minimal inhibitory concentrations (MIC). We also used an *E. coli* variant in which the *tolC* gene was deleted. This is because actinonin is known to be efficiently detoxified by the AcrAB-TolC efflux pump. The data are summarized in Table 1. All the synthesized compounds are less potent than actinonin toward the wild-type *E. coli* strain; however compounds **10**, **19a**, **19c**, **19e**, and **23c** displayed significant antibacterial activity against *E. coli tolC*. This indicates that the low antibacterial activity of our compounds is mainly due to a strong efflux by the AcrAB-TolC efflux pump of *E. coli*. Further, most indole derivatives are active against *B. subtilis*. Introducing a hydrophobic chain at the level of the indole nitrogen atom, yielded MIC values in the range of 4–8 μg mL$^{-1}$. This effect follows the direct inhibitory action of these compounds toward PDF2 enzyme quite well; the most potent inhibitor, **19e** is also the most efficient antibacterial agent with a MIC in the range of 1–2 μg mL$^{-1}$. Likewise **23c** is the only derivative of the reverse-indole series to show antibacterial activity against *B. subtilis*. As expected, no such correlation between inhibitor potency and antibacterial activity is observed in *E. coli tolC*.

Three pathogenic strains were also tested, *Staphylococcus aureus*, *Enterococcus faecalis* and *Streptococcus pneumoniae*. The MIC values for the indole series were higher than 16 μg mL$^{-1}$. The best results were obtained with the reverse-indole series, especially compounds **23a** and **23c**, which have MIC values of 4 μg mL$^{-1}$ against *S. pneumoniae* for both derivatives and 16 μg mL$^{-1}$ against *S. aureus* for **23c**. These compounds are even more potent than actinonin against *S. pneumoniae* (MIC = 8 μg mL$^{-1}$; see Table 1).

## Conclusions

In this report, we describe the synthesis of several compounds that are derived from the lead compound 5-bromoindole-3-acetohydroxamic acid. This includes N-alkylated indoles and a new series in which substitutions at positions 3 and 1 are reversed. Even if these inhibitors with an indole heterocycle are very efficiently cleared by the AcrAB-TolC efflux system and do

not inhibit the growth of *E. coli* strain, most of these molecules are selective inhibitors of PDF2 from *B. subtilis* and show a stronger antibacterial activity against *B. subtilis*. Finally, some of the synthesized compounds have antibacterial activity against some pathogens.

## Experimental Section

### Protein analysis

*E. coli* PDF (PDF1B) and *B. stearothermophilus* PDF2 (PDF2) were used as the representatives of the two bacterial PDF classes. They were purified in the presence of $NiCl_2$, to yield highly active enzymes.[34] Deformylase activity was assayed in HEPES buffer at pH 7.5 and at 37 °C by a PDF–formate dehydrogenase (FDH) coupled assay.[35] Formation of NADH was monitored either by UV spectroscopy by its absorbance at 340 nm or by its fluorescence at 465 nm ($\lambda_{ex}=340$ nm, $\lambda_{em}=465$ nm). Fo-Met-Ala-Ser (Bachem AG) was used as the substrate, and actinonin (Sigma) was used as a standard PDF inhibitor for the purpose of comparison. The reaction was started by adding purified enzyme (5–15 μL) in solution with $NiCl_2$ (2.5 μM). All inhibitors were diluted in DMSO so that the final assay buffer contained 1% of this solvent. For the determination of all $IC_{50}$ values, each inhibitor was pre-incubated with the enzyme for 7 min at 37 °C prior to the addition of the substrate. Each experiment was done in duplicate.

### Microbiology

Drug susceptibility was determined by culturing $1–4\times10^4$ CFU of bacteria. This inoculum was cultured for 18 h at 37 °C in 96-well plate that contained Mueller–Hinton broth medium (Sigma) and the drug at different concentrations. The MIC value corresponds to the lowest concentration of the drug that led to a growth of less than 10% of the control without the drug, as assessed by measurement of the optical density at 600 nm.

### NMR screening analysis

$^{15}$N-labeled *E. coli* PDF1 (residues 1–147) was expressed and purified as previously described.[36–38] All NMR samples contained 0.5 mM protein and 1 mM of the tested compound in 20 mM potassium phosphate buffer at pH 7.0 in $H_2O/^2H_2O$ (9:1). A pipetting robot that was connected to the flow-injection NMR probe was used to perform NMR experiments.[39,40] The mixture was refrigerated at 4 °C on a Gilson 242 Peltier rack before injection. Chemical shift perturbations were monitored with a 3-mm triple-resonance flow-injection probe that was equipped with *z*-gradients at 298 K by recording the {$^1$H–$^{15}$N} 2D correlation spectra via TROSY experiments.[41] Quadrature detection in the indirect dimension was achieved by sensitivity-enhanced echo/anti-echo gradient selection. Spectra were referenced to internal 3-trimethylsilylpropionic acid (TSP). 2D NMR processing was made by NMRPipe software,[42] and SPARKY software[43] was used to perform superimposition of TROSY experiments.

### Molecular modeling

Accelrys Discover Studio 2.0 software was used for dynamics and minimization experiments. Structures of actinonin in complex with *E. coli* (1LRU) and *B. stearothermophilus* (1LQY) were loaded from the Protein Data Bank (PDB). Crystallographic structures were prepared before using the CHARMM force field. The structure of **19g** was minimized and was introduced into the active site by superimposition with actinonin. The zinc or nickel center was fixed, and distance constraints were applied to the metal–oxygen bonds with the hydroxamic function (Zn–O14 2.0–2.5 Å and Zn–O16 1.7–2.0 Å). The structure was then refined iteratively by dynamics and minimization steps up to convergence.

### Chemistry

All the solvents and chemicals were purchased from SDS (Peypin, France), Acros, and Aldrich. DMF, THF, and $CH_2Cl_2$ were dried according to standard procedures and stored under argon. $^1$H NMR spectra were recorded on a Bruker ARX-250 spectrometer, and the chemical shifts were reported in ppm relative to the residual solvent ($CHCl_3$, $\delta_H=7.26$ ppm; DMSO, $\delta_H=2.50$ ppm; acetone $\delta_H=2.05$ ppm; $CH_3OH$ $\delta_H=3.31$ ppm; $D_2O$ $\delta_H=4.79$ ppm). IR spectra were obtained neat with a PerkinElmer Spectrum One FTIR spectrometer equipped with a MIRacle single-reflection horizontal ATR unit (zirconium–selenium crystal). ESI and CI mass spectra as well as HRMS and microanalyses were carried out at ICSN/CNRS, Gif-sur-Yvette (France). Experiments were performed under argon and run on a vacuum line.

**5-Bromoindole-1-carboxylic acid *tert*-butyl ester (1′)**: A solution of 5-bromo-1*H*-indole (500 mg, 2.55 mmol, 1 equiv) in THF (15 mL) was added to a suspension of NaH (67.3 mg, 2.8 mmol, 1.1 equiv) in THF (15 mL), at −78 °C under argon. After stirring for 1 h, a solution of di-*tert*-butyl dicarbonate ($Boc_2O$; 611.1 mg, 2.8 mmol, 1.1 equiv) in THF (20 mL) was added dropwise. The reaction was allowed to warm to room temperature and stirred overnight. The mixture was extracted with EtOAc and washed with brine. The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness to provide a white solid; yield: 732 mg (97%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta=1.70$ (s, 9H), 6.67 (d, $^3J=3.6$ Hz, 1H), 7.47 (dd, $^3J=8.6$ Hz, $^4J=1.2$ Hz, 1H), 7.72 (d, $^3J=3.6$ Hz, 1H), 7.81 (d, $^3J=8.6$ Hz, 1H), 8.11 ppm (d, $^4J=1.2$ Hz, 1H); $^{13}$C NMR (250 MHz, [D$_6$]DMSO): $\delta=8.8$, 72.3, 102.7, 114.4, 117.8, 124.3, 127.5, 127.7, 132.8, 138.9, 164.0 ppm; MS (ESI$^+$): *m/z* (%): 298.1 (95), 296.2 (100) $[M+H]^+$.

**5-Cyclopropylindole-1-carboxylic acid *tert*-butyl ester**: $Pd(OAc)_2$ (9.5 mg, 0.043 mmol) was added to a solution of 5-bromoindole-1-carboxylic acid *tert*-butyl ester (**1′**; 250 mg, 0.85 mmol), cyclopropyl boronic acid (94.5 mg, 1.10 mmol), $K_3PO_4$ (632 mg, 2.98 mmol) and tricyclohexylphosphine (24 mg, 0.085 mmol) in toluene (4 mL) and $H_2O$ (220 μL) under argon. The mixture was heated at 100 °C for 3 h and then cooled to room temperature. $H_2O$ (10 mL) was added, and the mixture was extracted with EtOAc (2×15 mL), the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated in vacuo. The product was isolated after column chromatography (EtOAc/cyclohexane, 2:8 *v/v*) as a colorless oil; yield: 204 mg (94%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta=$ 0.70 (m, 2H), 0.95 (m, 2H), 1.69 (s, 9H), 2.03 (m, 1H), 6.58 (d, $^3J=$ 3.6 Hz, 1H), 7.08 (dd, $^3J=8.6$ Hz, $^4J=1.6$ Hz, 1H), 7.32 (d, $^3J=3.6$ Hz, 1H), 7.63 (d, $^4J=1.6$ Hz, 1H), 8.03 ppm (d, $^3J=8.6$ Hz, 1H); $^{13}$C NMR (250 MHz, [D$_6$]DMSO): $\delta=8.8$, 17.6, 29.8, 72.2, 102.7, 109.8, 117.2, 117.8, 124.3, 127.5, 132.8, 138.8, 164.1 ppm; MS (ESI$^+$): *m/z* (%): 258.5 (100) $[M+H]^+$.

**5-Cyclopropyl-1*H*-indole (2)**: 5-Cyclopropylindole-1-carboxylic acid *tert*-butyl ester (230 mg, 0.89 mmol) was treated with TFA (0.5 mL) in $CH_2Cl_2$ (5 mL). The reaction was monitored by TLC (cyclohexane/EtOAc, 8:2 *v/v*; $R_f=0.55$). After completion of the reaction, half of solvent was evaporated, pentane was added, and the product was

collected by filtration; yield: 124 mg (89%). $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ = 0.74 (m, 2H), 0.94 (m, 2H), 2.07 (m, 1H), 6.51 (d, $^3J$ = 2.6 Hz, 1H), 7.01 (dd, $^3J$ = 8.3 Hz, $^4J$ = 1.1 Hz, 1H), 7.20 (d, $^3J$ = 2.6 Hz, 1H), 7.32 (d, $^3J$ = 8.3 Hz, 1H), 7.41 (d, $^4J$ = 1.1 Hz, 1H), 8.06 ppm (brs, 1H); $^{13}$C NMR (250 MHz, [D$_6$]DMSO): $\delta$ = 8.8, 17.6, 102.7, 109.8, 117.2, 117.8, 124.3, 127.5, 132.8, 138.8 ppm; MS (ESI): *m/z* (%): 156.3 (100) $[M-H]^-$.

**5-Methylsulfanyl-1*H*-indole (3)**: A 35% mineral oil suspension of KH (583 mg, 5.1 mmol) was washed with pentane (2×) and suspended in THF (10 mL). A solution of 5-bromoindole (1 g, 5.1 mmol) in THF (10 mL) was added to it, and after 15 min, the solution was cooled to −78 °C, and a solution of 1.6 M *t*BuLi in pentane (6.4 mL, 10.2 mmol) that had been precooled to −78 °C was added via cannula. A white precipitate immediately formed, and after 10 min a solution of dimethyldisulfide (905 μL, 10.2 mmol) in THF (3 mL) was added. The mixture was allowed to warm slowly to room temperature. The suspension was then poured into ice-cold 1 M $H_3PO_4$ (40 mL) and extracted with $Et_2O$ (2×). The $Et_2O$ extracts were combined, washed with 5% aq $NaHCO_3$, dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The product was purified by chromatography on silica gel ($CHCl_3$/cyclohexane, 1:1 *v/v*) to give a colorless oil; yield: 514 mg (62%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 2.49 (s, 3H), 6.45 (d, $^3J$ = 2.6 Hz, 1H), 7.16 (dd, $^3J$ = 8.4 Hz, $^4J$ = 1.6 Hz, 1H), 7.35 (d, *J* = 2.6 Hz, 1H), 7.41 (d, $^3J$ = 8.4 Hz, 1H), 7.62 (d, $^4J$ = 1.6 Hz, 1H), 10.28 ppm (brs, 1H); $^{13}$C NMR (250 MHz, [D$_6$]acetone): $\delta$ = 17.8, 101.2, 112.2, 116.3, 118.2, 123.8, 126.7, 128.6, 133.5 ppm; MS (ESI$^-$): *m/z* (%): 162.4 (100) $[M-H]^-$.

**General Procedure I: Introduction of a glyoxalic acid at position 3**: Freshly distilled oxalyl chloride (422.7 mg, 286 μL, 3.3 mmol) in anhydrous $Et_2O$ (2 mL) was added dropwise over 10 min at 0 °C under argon to a solution of the indole derivative (3 mmol) in $Et_2O$ (12 mL). An orange precipitate formed. Sat. aq $NaHCO_3$ (6 mL) was then added with caution, and the mixture was heated at reflux for 30 min, then cooled and acidified with 10% HCl; this resulted in the precipitation of the indole-3-glyoxalic acid, which was filtered and dried.

**General Procedure II: Reduction of the glyoxalic acid to the acetic acid analogues**: Hydrazine hydrate (122.1 mg, 2.44 mmol, 5 equiv) was added to a solution of substituted indole-3-glyoxalic acid (0.49 mmol, 1 equiv) in 2-methoxyethanol (1.2 mL). The temperature of the mixture was increased to 60 °C and NaOMe (283.2 mg, 5.24 mmol, 10.7 equiv) was added portionwise. The mixture was slowly heated at 150 °C, whereby MeOH, $H_2O$, hydrazine, and part of the solvent were evaporated. The mixture was kept at 150 °C for 1 h, cooled, and poured onto crushed ice. The aqueous layer was extracted with $Et_2O$ and acidified with concentrated HCl at 0 °C. The oil that formed was extracted with $Et_2O$. The $Et_2O$ solution was washed with $H_2O$, dried over $MgSO_4$, and evaporated in vacuo.

**(5-Cyclopropyl-1*H*-indol-3-yl)oxoacetic acid**: The product was obtained from 5-cyclopropyl-1*H*-indole (**2**; 185 mg, 1.18 mmol) by following general procedure I; yield: 90 mg (33%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 0.74 (m, 2H), 1.00 (m, 2H), 2.07 (m, 1H), 7.09 (dd, $^3J$ = 8.3 Hz, $^4J$ = 1.5 Hz, 1H), 7.49 (d, $^3J$ = 8.3 Hz, 1H), 8.10 (s, 1H), 8.71 (d, $^4J$ = 1.5 Hz, 1H), 11.36 ppm (brs, 1H); $^{13}$C NMR (250 MHz, [D$_6$]acetone): $\delta$ = 8.8, 17.5, 104.2, 109.8, 117.1, 117.4, 123.1, 127.4, 132.1, 137.2, 166.3, 181.2 ppm; MS (ESI$^-$): *m/z* (%): 228.6 (100) $[M-H]^-$.

**(5-Cyclopropyl-1*H*-indol-3-yl)acetic acid (6)**: The product was obtained as an orange solid from (5-cyclopropyl-1*H*-indol-3-yl)oxoacetic acid (90 mg, 0.39 mmol) by following general procedure II; yield: 35 mg (42%). $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ = 0.73 (m, 2H), 0.96 (m, 2H), 2.05 (m, 1H), 3.83 (s, 2H), 7.00 (dd, $^3J$ = 8.6 Hz, $^4J$ = 1.5 Hz, 1H), 7.20 (s, 1H), 7.33 (d, $^3J$ = 8.6 Hz, 1H), 7.37 (d, $^4J$ = 1.5 Hz, 1H), 8.02 ppm (brs, 1H, 1H); $^{13}$C NMR (250 MHz, [D$_6$]DMSO): $\delta$ = 8.8, 17.6, 44.9, 70.2, 88.0, 107.1, 109.8, 119.2, 119.8, 123.0, 127.5, 167.0 ppm; MS (ESI$^-$): *m/z* (%): 214.2 (100) $[M-H]^-$.

**(5-Methylsulfanyl-1*H*-indol-3-yl)oxoacetic acid**: The product was obtained from 5-methylsulfanyl-1*H*-indole (**3**; 247 mg, 1.51 mmol) by following general procedure I; yield: 258 mg (75%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 2.57 (s, 3H), 2.81 (brs, 1H), 7.32 (dd, $^3J$ = 8.4 Hz, $^4J$ = 1.6 Hz, 1H), 7.58 (d, $^3J$ = 8.4 Hz, 1H), 8.32 (d, $^4J$ = 1.6 Hz, 1H), 8.76 (s, 1H), 11.45 ppm (brs, 1H); $^{13}$C NMR (250 MHz, [D$_6$]acetone): $\delta$ = 18.5, 104.2, 110.8, 118.2, 119.5, 123.1, 127.4, 129.1, 132.7, 166.3, 181.2 ppm; MS (ESI$^-$): *m/z* (%): 234.2 (100) $[M-H]^-$.

**(5-Methylsulfanyl-1*H*-indol-3-yl)acetic acid (7)**: The product was obtained as an orange solid from (5-methylsulfanyl-1*H*-indol-3-yl)oxoacetic acid (293 mg, 1.25 mmol) by following general procedure II; yield: 273 mg (98%).$^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 2.49 (s, 3H), 3.77 (s, 2H), 7.17 (dd, $^3J$ = 8.0 Hz, $^4J$ = 1.6 Hz, 1H), 7.34 (s, 1H), 7.38 (d, $^3J$ = 8.0 Hz, 1H), 7.67 (d, $^4J$ = 1.6 Hz, 1H), 10.18 ppm (brs, 1H); $^{13}$C NMR (250 MHz, [D$_6$]DMSO): $\delta$ = 19.3, 36.1, 111.3, 112.2, 118.2, 118.8, 123.2, 129.7, 132.5, 133.5, 178.2 ppm; MS (ESI$^-$): *m/z* (%): 220.4 (100) $[M-H]^-$.

**(5-Methyl-1*H*-indol-3-yl)oxoacetic acid**: The product was obtained from 5-methyl-1*H*-indole (**4**; 1 g, 7.59 mmol) by following general procedure I; yield: 863 mg (55%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 2.48 (s, 3H), 2.91 (brs, 1H), 7.17 (dd, $^3J$ = 8.5 Hz, $^4J$ = 1.6 Hz, 1H), 7.49 (d, $^3J$ = 8.5 Hz, 1H), 8.16 (s, 1H), 8.72 (d, $^4J$ = 1.6 Hz, 1H), 11.32 ppm (brs, 1H); $^{13}$C NMR (250 MHz, [D$_6$]acetone): $\delta$ = 21.4, 104.2, 110.6, 119.6, 121.3, 123.1, 127.4, 131.3, 132.7, 166.3, 181.1 ppm; MS (ESI): *m/z* (%): 202.5 (100) $[M-H]^-$.

**(5-Methyl-1*H*-indol-3-yl)acetic acid (8)**: The product was obtained as a yellow solid from (5-methyl-1*H*-indol-3-yl)oxoacetic acid (863 mg, 4.22 mmol) by following general procedure II; yield: 650 mg (81%).$^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 2.42 (s, 3H), 2.97 (brs, 1H), 3.73 (s, 2H), 6.96 (d, $^3J$ = 8.1 Hz, $^4J$ = 1.6 Hz, 1H), 7.26 (s, 1H), 7.28 (d, $^3J$ = 8.1 Hz, 1H), 7.40 (d, $^4J$ = 1.6 Hz, 1H), 9.97 ppm (brs, 1H); $^{13}$C NMR (250 MHz, [D$_6$]DMSO): $\delta$ = 28.6, 42.1, 108.6, 109.9, 116.9, 121.4, 122.8, 125.6, 126.3, 133.3, 171.1 ppm; MS (ESI): *m/z* (%): 188.6 (100) $[M-H]^-$.

**(5-Chloro-1*H*-indazol-3-yl)acetic acid (9)**: This compound was prepared from 5-chloro-2-nitrobenzaldehyde (1 g, 5.4 mmol) by following a previously described procedure;[25] yield: 768 mg (68%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 3.08 (brs, 1H), 4.04 (s, 2H), 7.37 (dd, $^3J$ = 8.8 Hz, $^4J$ = 1.4 Hz, 1H), 7.59 (d, $^3J$ = 8.8 Hz, 1H), 7.85 ppm (d, $^4J$ = 1.4 Hz, 1H); $^{13}$C NMR (250 MHz, [D$_6$]DMSO): $\delta$ = 33.2, 112.3, 120.3, 123.3, 124.6, 126.6, 139.3, 139.8, 171.9 ppm; MS (ESI): *m/z* (%): 211.0 (75), 209.1 (25) $[M-H]^-$.

**(5-Bromo-1*H*-indol-3-yl)acetic acid ethyl ester (15)**: A solution of (5-bromo-1*H*-indol-3-yl)acetic acid (1 g, 3.9 mmol) and $H_2SO_4$ (0.8 mL) was heated at reflux in EtOH (8 mL) for 24 h. The mixture was diluted with $H_2O$, extracted with $CH_2Cl_2$, and successively washed with 30% aq NaOH and brine. The organic layer was dried over $MgSO_4$, and concentrated in vacuo to give a light-brown solid; yield: 1.05 g (95%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 1.24 (t, $^3J$ = 7.4 Hz, 3H), 3.77 (s, 2H), 4.14 (q, $^3J$ = 7.4 Hz, 2H), 7.24 (dd, $^3J$ = 8.6 Hz, $^4J$ = 1.7 Hz, 1H), 7.37 (s, 1H), 7.43 (d, $^3J$ = 8.6 Hz, 1H), 7.79 (d, $^4J$ = 1.7 Hz, 1H), 10.32 ppm (brs, 1H); $^{13}$C NMR (250 MHz, $CDCl_3$): $\delta$ = 14.7, 31.7, 61.5, 113.0, 113.3, 116.9, 122.3, 122.5, 125.3,

133.1, 137.5, 171.2 ppm; MS (ESI$^-$): *m/z* (%): 282.3 (95), 280.1 (100) [*M*−H]$^-$.

**3-(5-Bromo-3-ethoxycarbonylmethylindol-1-yl)propionic acid *tert*-butyl ester**: A 40% benzyltrimethylammonium hydroxide solution in MeOH (195 μL) was added to a suspension of **15** (1.1 g, 3.9 mmol) and *tert*-butylacrylate (3.5 mL, 23.4 mmol) in dioxane (9 mL) at 25 °C. The resulting solution was heated at 50–60 °C for 30 min, then allowed to stand at 25 °C for 18 h, and then poured into $H_2O$. The mixture was extracted with EtOAc, and the combined extracts were washed with 0.1 N HCl, $H_2O$, and dried over $MgSO_4$. After evaporating the solvent, the product was purified by chromatography on silica gel (cyclohexane/EtOAc, 7:3 *v/v*); yield: 1.57 g (98%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 1.24 (t, $^3J$ = 7.2 Hz, 3H), 1.37 (s, 9H), 2.77 (t, $^3J$ = 6.8 Hz, 2H), 3.74 (s, 2H), 4.10 (q, $^3J$ = 7.2 Hz, 2H), 4.46 (t, $^3J$ = 6.8 Hz, 2H), 7.29 (d, $^4J$ = 1.6 Hz, 1H), 7.33 (d, $^3J$ = 8.7 Hz, 1H), 7.45 (s, 1H), 7.77 ppm (dd, $^3J$ = 8.7 Hz, $^4J$ = 1.6 Hz, 1H); $^{13}$C NMR (250 MHz, [D$_3$]MeCN): $\delta$ = 27.5, 32.0, 41.6, 51.2, 80.2, 106.9, 111.8, 116.8, 121.1, 121.3, 127.4, 129.3, 134.5, 171.6, 173.6 ppm; MS (ESI$^+$): *m/z* (%): 412.3 (95), 410.1 (100) [*M*+H]$^+$.

**General Procedure III: N-alkylation**: A solution of (5-bromo-1*H*-indol-3-yl)acetic acid ethyl ester (1 g, 3.6 mmol) in DMF (3 mL) was added to a suspension of NaH (134.6 mg, 5.6 mmol, 1.1 equiv) in DMF (3 mL) via cannula at 0 °C under argon. After stirring for 45 min at 0 °C, the electrophile (1.1 equiv) in DMF (3 mL) was added to the mixture. After 3 h, the reaction was diluted with $H_2O$, extracted with EtOAc, washed with 0.1 N HCl and brine. The organic layer was dried over $MgSO_4$, and concentrated in vacuo.

**(5-Bromo-1-methyl-indol-3-yl)acetic acid ethyl ester (17a)**: Reaction of **15** (200 mg, 1.02 mmol) with methyl iodide (160.4 mg, 71 μL, 1.13 mmol) provided **17a** by following general procedure III; yield: 120.4 mg (41%). $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ = 1.27 (t, $^3J$ = 7.2 Hz, 3H), 3.73 (s, 2H), 3.76 (s, 3H), 4.16 (q, $^3J$ = 7.2 Hz, 2H), 7.07 (s, 1H), 7.18 (dd, $^3J$ = 8.7 Hz, $^4J$ = 1.6 Hz, 1H), 7.33 (d, $^3J$ = 8.7 Hz, 1H), 7.76 ppm (d, $^4J$ = 1.6 Hz, 1H); $^{13}$C NMR (250 MHz, CDCl$_3$): $\delta$ = 14.7, 33.7, 41.4, 61.5, 113.0, 113.3, 116.9, 122.6, 122.9, 126.7, 135.1, 139.5, 171.2 ppm; MS (ESI): *m/z* (%): 298.3 (95), 296.1 (100) [*M*+H]$^+$.

**(5-Bromo-1-isobutylindol-3-yl)acetic acid ethyl ester (17b)**: Reaction of **15** (200 mg, 1.02 mmol) with 1-bromo-2-methylpropane (154.8 mg, 123 μL, 1.13 mmol) provided **17b** by following general procedure III; yield: 206 mg (60%). $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ = 0.95 (d, $^3J$ = 6.6 Hz, 6H), 1.27 (t, $^3J$ = 7.4 Hz, 3H), 2.16 (m, 1H), 3.73 (s, 2H), 3.87 (d, $^3J$ = 7.3 Hz, 2H), 4.19 (q, $^3J$ = 7.4 Hz, 2H), 7.05 (s, 1H), 7.18 (dd, $^3J$ = 8.8 Hz, $^4J$ = 1.4 Hz, 1H), 7.32 (d, $^3J$ = 8.8 Hz, 1H), 7.70 ppm (d, $^4J$ = 1.4 Hz, 1H); $^{13}$C NMR (250 MHz, CDCl$_3$): $\delta$ = 14.7, 21.0, 28.2, 33.7, 61.5, 66.5, 113.0, 113.3, 116.9, 122.6, 122.9, 126.7, 135.1, 139.5, 171.2 ppm; MS (ESI): *m/z* (%): 340.2 (95), 338.2 (100) [*M*+H]$^+$.

**[5-Bromo-1-(3-methylbutyl)indol-3-yl]acetic acid ethyl ester (17c)**: The product was obtained by reaction of **15** (200 mg, 1.02 mmol) with 1-bromo-3-methylbutane (170.7 mg, 143 μL, 1.13 mmol) by following general procedure III; yield: 181 mg (51%). $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ = 0.85 (t, $^3J$ = 7.1 Hz, 3H), 0.92 (d, $^3J$ = 6.4 Hz, 1H), 1.52 (m, 1H), 1.63 (m, 2H), 3.66 (s, 2H), 4.04 (t, $^3J$ = 7.1 Hz, 2H), 4.10 (q, $^3J$ = 7.3 Hz, 2H), 7.14 (m, 3H), 7.69 ppm (d, $^4J$ = 1.3 Hz, 1H); $^{13}$C NMR (250 MHz, CDCl$_3$): $\delta$ = 14.7, 23.1, 26.8, 33.8, 39.2, 53.9, 61.5, 113.1, 113.3, 116.8, 122.6, 122.9, 126.7, 135.0, 139.4, 171.2 ppm; MS (ESI$^+$): *m/z* (%): 354.2 (95), 352.2 (100) [*M*+H]$^+$.

**[5-Bromo-1-(2-ethylbutyl)indol-3-yl]acetic acid ethyl ester (17d)**: The product was obtained by reaction of **15** (200 mg, 1.02 mmol) with (3-bromomethyl)pentane (186.5 mg, 159 μL, 1.13 mmol) by following general procedure III; yield: 151 mg (40%). $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ = 0.89 (t, $^3J$ = 6.9 Hz, 6H), 1.30 (m, 7H), 1.82 (m, 1H), 3.72 (s, 2H), 3.94 (d, $^3J$ = 7.2 Hz 2H), 4.19 (q, $^3J$ = 7.3 Hz, 2H), 7.08 (s, 1H), 7.18 (dd, $^3J$ = 8.6 Hz, $^4J$ = 1.6 Hz, 1H), 7.28 (d, $^3J$ = 8.6 Hz, 1H), 7.65 ppm (d, $^4J$ = 1.6 Hz, 1H); $^{13}$C NMR (250 MHz, CDCl$_3$): $\delta$ = 11.8, 14.7, 25.8, 33.7, 39.7, 60.8, 61.5, 113.0, 113.3, 116.9, 122.6, 122.9, 126.7, 135.1, 139.5, 171.2 ppm; MS (ESI$^+$): *m/z* (%): 368.4 (95), 366.4 (100) [*M*+H]$^+$.

**(1-Benzyl-5-bromoindol-3-yl)acetic acid ethyl ester (17e)**: The product was obtained by reaction of **15** (200 mg, 1.02 mmol) with benzyl bromide (193.3 mg, 134 μL, 1.13 mmol) by following general procedure III; yield: 372 mg (98%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 1.24 (t, $^3J$ = 7.3 Hz, 3H), 3.78 (s, 2H), 4.14 (q, $^3J$ = 7.3 Hz, 2H), 5.45 (s, 2H), 7.36 (m, 8H), 7.79 ppm (d, $^4J$ = 1.4 Hz, 1H); $^{13}$C NMR (250 MHz, CDCl$_3$): $\delta$ = 14.7, 33.7, 61.5, 62.2, 113.0, 113.3, 116.9, 122.6, 122.9, 126.0, 126.7, 128.5, 129.8, 135.1, 137.8, 139.5, 171.2 ppm; MS (ESI$^+$): *m/z* (%): 374.6 (95), 372.3 (100) [*M*+H]$^+$.

**(5-Bromo-1-phenethylindol-3-yl)acetic acid ethyl ester (17f)**: The product was obtained by reaction of **15** (200 mg, 1.02 mmol) with (2-bromoethyl)benzene (209.1 mg, 155 μL, 1.13 mmol) by following general procedure III; yield: 89 mg (23%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 1.24 (t, $^3J$ = 7.3 Hz, 3H), 3.15 (t, $^3J$ = 7.0 Hz, 2H), 3.72 (s, 2H), 4.13 (q, $^3J$ = 7.3 Hz, 2H), 4.47 (t, $^3J$ = 7.0 Hz, 2H), 7.24 (m, 7H), 7.41 (d, $^3J$ = 8.7 Hz, 1H), 7.71 ppm (d, $^4J$ = 1.3 Hz, 1H); $^{13}$C NMR (250 MHz, CDCl$_3$): $\delta$ = 14.6, 33.8, 35.7, 58.5, 61.5, 113.0, 113.3, 116.9, 122.6, 122.9, 125.9, 126.7, 128.2, 128.8, 135.1, 139.5, 141.2, 171.2 ppm; MS (ESI$^+$): *m/z* (%): 388.3 (95), 386.1 (100) [*M*+H]$^+$.

**(1-Benzotriazol-1-ylmethyl-5-bromoindol-3-yl)acetic acid ethyl ester (17g)**: The product was obtained by reaction of **15** (200 mg, 1.02 mmol) with 1-chloromethyl-1*H*-benzotriazole (188.7 mg, 1.13 mmol) by following general procedure III; yield: 409 mg (97%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 1.24 (t, $^3J$ = 7.4 Hz, 3H), 3.76 (s, 2H), 4.12 (q, $^3J$ = 7.4 Hz, 2H), 7.22 (s, 2H), 7.41 (m, 2H), 7.58 (m, 1H), 7.80 (m, 3H), 8.01 ppm (m, 2H); $^{13}$C NMR (250 MHz, [D$_6$]DMSO): $\delta$ = 15.1, 34.0, 61.8, 79.3, 113.6, 114.2, 117.2, 123.4, 123.7, 126.9, 128.7, 128.9, 131.1, 134.8, 135.1, 139.5, 171.2 ppm; MS (ESI$^+$): *m/z* (%): 415.5 (95), 413.6 (100) [*M*+H]$^+$.

**5-Bromo-1*H*-indole-3-carbaldehyde (20b)**: POCl$_3$ (2.86 mmoL, *d* = 1.64, 267 μL) was added under argon at 0 °C to 5-bromo-1*H*-indole (**1**; 466.5 mg, 2.38 mmol) in DMF (5 mL). The mixture was stirred at room temperature overnight, 2 N aq NaOH (2 mL) was then added, and the solution was stirred for 2 h, then poured into EtOAc. After washing the organic layer with $H_2O$, drying, and evaporating to dryness, **20b** was isolated as a white solid; yield: 506 mg (95%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 7.42 (dd, $^3J$ = 8.6 Hz, $^4J$ = 1.8 Hz, 1H), 7.55 (d, $^3J$ = 8.6 Hz, 1H), 8.28 (s, 1H), 8.41 (d, $^4J$ = 1.8 Hz, 1H), 10.04 (s, 1H), 11.34 ppm (s, 1H); $^{13}$C NMR (250 MHz, [D$_6$]DMSO): $\delta$ = 114.9, 115.2, 117.8, 123.3, 126.3, 126.4, 136.1, 139.6, 185.5 ppm; IR: $\tilde{\nu}_{C=O}$ = 1688 cm$^{-1}$; MS (ESI$^-$): *m/z* (%): 224.3 (95), 222.1 (100) [*M*−H]$^-$.

**(5-Bromo-1*H*-indol-3-yl)phenylmethanone (20c)**: A 2 M solution of Me$_3$Al in toluene (7.75 mL, 15.5 mmol, 1.52 equiv) was added to a solution of 5-bromo-1*H*-indole (**1**; 2 g, 10.2 mmol, 1 equiv) in $CH_2Cl_2$ (45 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min, then acetyl chloride (1.78 mL, 15.3 mmol) in $CH_2Cl_2$ (45 mL) was added dropwise. The resulting solution was stirred at 0 °C for 2 h, and at room temperature for 24 h. $H_2O$ was added dropwise to quench the reaction, then 30% aq NaOH was added to neutralize the solution. The organic layer was washed with 1 N HCl and brine.

The product was purified by chromatography on silica ($CHCl_3$/cyclohexane, 1:9 *v/v*); yield: 2.8 g (91%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 7.56 (m, 5H), 7.78 (m, 3H), 7.86 (s, 1H), 10.33 ppm (br s, 1H); $^{13}$C NMR (250 MHz, [D$_6$]DMSO): $\delta$ = 114.7, 114.8, 115.1, 124.0, 126.1, 128.5, 128.7, 128.8, 131.6, 135.9, 137.3, 140.5, 190.2 ppm; IR: $\tilde{\nu}_{C=O}$ = 1711 cm$^{-1}$; MS (ESI$^-$): *m/z* (%): 300.1 (95), 298.1 (100) [*M*−H]$^-$.

**5-Bromo-3-methyl-1*H*-indole (21 b)**: A solution of **20 b** (1 g, 4.5 mmol) in dry THF (8.5 mL) was added dropwise with stirring and under argon to a suspension of $LiAlH_4$ (340 mg, 9 mmol) in dry THF (2.5 mL). The mixture was heated at reflux for 4 h and then kept at room temperature for 24 h. EtOAc (2 mL) was added to destroy the excess $LiAlH_4$, then $H_2O$ (3 mL) was added. The organic salts were discarded, and the solution was extracted with EtOAc. The product was purified by chromatography on silica gel (EtOAc/cyclohexane, 2:8 *v/v*); yield: 869 mg (92%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 2.30 (s, 3H), 7.17 (s, 1H), 7.21 (dd, $^3J$ = 8.7 Hz, $^4J$ = 1.5 Hz, 1H), 7.35 (d, $^3J$ = 8.7 Hz, 1H), 7.68 (d, $^4J$ = 1.5 Hz, 1H) 10.12 ppm (br s, 1H); $^{13}$C NMR (250 MHz, [D$_6$]acetone): $\delta$ = 12.1, 111.2, 112.3, 115.2, 121.9, 122.1, 122.7, 132.6, 134.3 ppm; MS (ESI$^-$): *m/z* (%): 210.2 (95), 208.1 (100) [*M*−H]$^-$.

**3-Benzyl-5-bromo-1*H*-indole (21 c)**: The compound was prepared by following the procedure that was described for the reduction of **20 b** into **21 b**; **21 c** was obtained from **20 c** (1 g, 3.5 mmol) after chromatography of the crude product on silica gel (EtOAc/cyclohexane, 25:75 *v/v*); yield: 881 mg (88%). $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ = 4.09 (s, 2H), 6.94 (s, 1H), 7.28 (m, 5H), 7.56 (m, 1H), 7.68 (s, 1H), 7.75 (m, 1H), 8.08 ppm (br s, 1H); $^{13}$C NMR (250 MHz, [D$_3$]MeCN): $\delta$ = 30.5, 111.2, 112.9, 114.3, 116.5, 117.7, 117.8, 120.8, 123.7, 124.2, 125.6, 128.0, 128.1, 135.0, 141.2 ppm; MS (ESI$^-$): *m/z* (%): 286.2 (95), 284.1 (100) [*M*−H]$^-$.

**2-(5-Bromo-1*H*-indol-3-yl)-1-phenylethanone (21 e)**: A 1.6 M solution of *n*BuLi in hexane (1.7 mL, 2.55 mmol) was added to a solution of 5-bromo-1*H*-indole (**1**; 2.55 mmol) in THF (5 mL), which was maintained below 0 °C with a NaCl/ice bath. After 15 min, a 1 M solution of $ZnCl_2$ in $Et_2O$ (2.55 mL, 2.55 mmol) was added, and the cooling bath was removed. After stirring the mixture for 24 h and evaporating the solvent under argon, a wax was obtained, which was dissolved in anhydrous toluene (5 mL). 2-Bromoacetophenone (507.6 mg, 2.55 mmol) was added to this solution, which was stirred for 24 h. The mixture was then acidified with 1 N HCl and poured into EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. The product was purified by chromatography on silica gel (EtOAc/cyclohexane, 2:8 *v/v*); yield: 690 mg (54%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 4.51 (s, 2H), 7.22 (dd, $^4J$ = 1.7 Hz, $^3J$ = 8.6 Hz, 1H), 7.36 (d, $^3J$ = 8.6 Hz, 1H), 7.40 (m, 2H), 7.53 (m, 2H), 7.63 (m, 1H), 7.82 (s, 1H), 8.16 (m, 2H), 10.35 ppm (br s, 1H); $^{13}$C NMR (250 MHz, [D$_6$]acetone): $\delta$ = 36.4, 114.3, 114.4, 122.7, 125.2, 126.9, 129.7, 129.8, 134.1, 136.3, 136.6, 138.1, 138.8, 198.2 ppm; MS (ESI$^-$): *m/z* (%): 314.4 (95), 312.1 (100) [*M*−H]$^-$.

**2-(5-Bromo-1*H*-indol-3-yl)-1-(2-methoxyphenyl)ethanone (21 f)**: The compound was prepared by following the same procedure that was used for the preparation of **21 e**, from **1** (2.55 mmol) and 2-bromo-2′-methoxyacetophenone (584.1 mg, 2.55 mmol). Compound **21 f** was obtained after chromatography over silica gel (EtOAc/cyclohexane, 2:8 *v/v*); yield: 420 mg (48%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 4.03 (s, 3H), 4.41 (s, 2H), 6.99 (m, 1H), 7.18 (m, 2H), 7.31 (s, 1H), 7.35 (d, $^3J$ = 8.6 Hz, 1H), 7.50 (d, $^3J$ = 8.3 Hz, 1H), 7.56 (dd, $^3J$ = 8.6 Hz, $^4J$ = 1.4 Hz, 1H), 7.72 (s, $^4J$ = 1.4 Hz, 1H), 10.27 ppm (br s, 1H); $^{13}$C NMR (250 MHz, [D$_6$]acetone): $\delta$ = 39.4, 57.3, 113.2, 114.1, 114.9, 117.1, 121.6, 123.5, 123.9, 124.2, 125.1, 130.4, 134.2, 134.8, 136.4, 163.0, 197.8 ppm; MS (ESI$^-$): *m/z* (%): 344.2 (95), 342.3 (100) [*M*−H]$^-$.

**(5-Bromoindol-1-yl)acetic acid ethyl ester**: The compound was obtained as a brown solid by following the general procedure III by using **21 a** (500 mg, 2.55 mmol) and bromoacetic acid ethyl ester (548.1 mg, 409 μL, 2.81 mmol); yield: 781 mg (98%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 1.24 (t, $^3J$ = 7.1 Hz, 3H), 4.14 (q, $^3J$ = 7.1 Hz, 2H), 4.99 (s, 2H), 6.49 (d, $^3J$ = 3.1 Hz, 1H), 7.28 (dd, $^4J$ = 1.6 Hz, $^3J$ = 8.7 Hz, 1H), 7.35 (m, 2H), 7.75 ppm (d, $^3J$ = 1.6 Hz, 1H); $^{13}$C NMR (250 MHz, [D$_6$]acetone): $\delta$ = 14.2, 59.8, 60.1, 103.4, 113.9, 116.9, 123.1, 124.0, 128.2, 131.1, 138.9, 171.1 ppm; MS (ESI$^+$): *m/z* (%): 284.1 (95), 282.1 (100) [*M*+H]$^+$.

**(5-Bromo-3-methylindol-1-yl)acetic acid ethyl ester**: The compound was obtained as a brown solid by following general procedure III by using **21 b** (662 mg, 3.15 mmol) and bromoacetic acid ethyl ester (578.7 mg, 384 μL, 3.46 mmol); yield: 734 mg (79%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 1.22 (t, $^3J$ = 7.0 Hz, 3H), 2.30 (s, 3H), 4.16 (q, $^3J$ = 7.0 Hz, 2H), 4.96 (s, 2H), 7.17 (s, 1H), 7.21 (dd, $^3J$ = 8.6 Hz, $^4J$ = 1.3 Hz, 1H), 7.35 (d, $^3J$ = 8.6 Hz, 1H), 7.68 ppm (d, $^4J$ = 1.3 Hz, 1H); $^{13}$C NMR (250 MHz, [D$_6$]acetone): $\delta$ = 14.3, 14.6, 59.8, 60.1, 112.7, 113.9, 116.9, 123.1, 124.0, 128.2, 131.1, 138.9, 171.1 ppm; MS (ESI$^+$): *m/z* (%): 298.3 (95), 296.1 (100) [*M*+H]$^+$.

**(3-Benzyl-5-bromoindol-1-yl)acetic acid ethyl ester**: The compound was obtained as a brown solid by following general procedure III by using **21 c** (729 mg, 2.54 mmol) and bromoacetic acid ethyl ester (468 mg, 310 μL, 2.8 mmol); yield: 842 mg (89%). $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ = 1.21 (t, $^3J$ = 7.1 Hz, 3H), 4.09 (s, 2H), 4.14 (q, $^3J$ = 7.1 Hz, 2H), 4.94 (s, 2H), 6.93 (s, 1H), 7.27 (m, 5H), 7.54 (m, 1H), 7.67 (s, 1H), 7.72 ppm (m, 1H); $^{13}$C NMR (250 MHz, [D$_3$]MeCN): $\delta$ = 13.2, 30.4, 46.9, 60.9, 111.0, 111.7, 114.4, 116.9, 121.1, 123.9, 125.6, 128.0, 128.1, 128.3, 129.2, 135.5, 140.8, 168.3 ppm; MS (ESI$^+$): *m/z* (%): 374.5 (95), 372.3 (100) [*M*+H]$^+$.

**General Procedure IV: [5-Bromo-3-(2-oxo-2-phenylethyl)indol-1-yl]acetic acid ethyl ester**: A solution of **21 e** (561 mg, 1.79 mmol) in DMF (2 mL) was added to a suspension of $Cs_2CO_3$ (642 mg, 1.97 mmol) in DMF (2 mL) via cannula at 0 °C under argon. After stirring for 45 min at 0 °C, bromoacetic acid ethyl ester (329 mg, 1.97 mmol) was added. The reaction was monitored by TLC. The mixture was then diluted with $H_2O$, extracted with EtOAc, and washed with 0.1 N HCl and brine. The organic layer was dried over $MgSO_4$, concentrated under vacuum, and the crude product was purified by chromatography over silica gel ($CH_2Cl_2$); yield: 703 mg (98%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 1.19 (t, $^3J$ = 7.2 Hz, 3H), 4.03 (s, 2H), 4.11 (q, $^3J$ = 7.2 Hz, 2H), 5.04 (s, 2H), 7.35 (m, 6H), 8.00 (s, 1H), 8.11 ppm (d, $^3J$ = 7.4 Hz, 2H); $^{13}$C NMR (250 MHz, [D$_3$]MeCN): $\delta$ = 13.2, 39.8, 60.1, 61.0, 111.1, 113.2, 117.7, 121.2, 124.2, 127.7, 128.6, 129.2, 129.6, 132.8, 135.5, 136.0, 168.0, 198.3 ppm; MS (ESI$^+$): *m/z* (%): 402.3 (95), 400.3 (100) [*M*+H]$^+$.

**{5-Bromo-3-[2-(2-methoxyphenyl)-2-oxoethyl]indol-1-yl}acetic acid ethyl ester**: The compound was obtained from **21 f** (420 mg, 1.22 mmol) by following general procedure IV; yield: 504 mg (96%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 1.17 (t, $^3J$ = 7.1 Hz, 3H), 4.05 (m, 5H), 4.12 (q, $^3J$ = 7.1 Hz, 2H), 5.02 (s, 2H), 7.34 (m, 5H), 8.01 (s, 1H), 8.11 ppm (d, $^3J$ = 7.4 Hz, 2H); $^{13}$C NMR (250 MHz, [D$_6$]acetone): $\delta$ = 14.2, 39.1, 56.8, 59.7, 60.1, 112.5, 113.9, 114.4, 116.5, 120.9, 123.1, 123.6, 124.0, 128.2, 131.1, 134.4, 134.6, 139.9, 164.2, 171.1, 197.6 ppm; MS (ESI$^+$): *m/z* (%): 432.6 (95), 430.3 (100) [*M*+H]$^+$.

**(6-Bromoindol-1-yl)acetic acid ethyl ester**: The compound was obtained as a brown solid by following the general procedure III,

by the reaction of **21g** (100 mg, 0.51 mmol) with bromoacetic acid ethyl ester (109 mg, 82 μL, 0.56 mmol); yield: 135 mg (94%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 1.28 (t, $^3J$ = 7.1 Hz, 3H), 4.21 (q, $^3J$ = 7.1 Hz, 2H), 4.98 (s, 2H), 6.45 (d, $^3J$ = 2.8 Hz, 1H), 7.15 (d, $^3J$ = 8.3 Hz, 1H), 7.36 (d, $^3J$ = 2.8 Hz, 1H), 7.53 (d, $^3J$ = 8.3 Hz, 1H), 7.66 ppm (s, 1H); $^{13}$C NMR (250 MHz, [D$_6$]acetone): $\delta$ = 14.2, 59.9, 60.2, 103.4, 114.6, 115.2, 123.1, 125.5, 127.3, 128.2, 142.4, 171.1 ppm; MS (ESI$^+$): *m/z* (%): 284.1 (95), 282.1 (100) [*M*+H]$^+$.

**General Procedure V: Saponification of the ethyl esters**: The corresponding ester (1.17 mmol) was dissolved in a mixture of dioxane/aq 5% NaOH (1:1 *v/v*; 40 mL). After stirring the solution for 1 h at room temperature, half of the solvent was evaporated. Acidification of the aqueous phase with 1 N HCl at 0 °C resulted in precipitation of the acid, which was collected by filtration.

**(5-Bromo-1-methylindol-3-yl)acetic acid (18a)**: A beige solid of **18a** was obtained from **17a** (200 mg, 0.95 mmol) by following general procedure V; yield: 145 mg (84%). $^1$H NMR (250 MHz, D$_2$O): $\delta$ = 3.44 (s, 2H), 3.58 (s, 3H), 6.98 (d, $^3J$ = 6.1 Hz, 1H), 7.18 (d, $^3J$ = 9.7 Hz, 1H), 7.61 ppm (m, 2H); $^{13}$C NMR (250 MHz, [D$_6$]DMSO): $\delta$ = 38.8, 42.4, 113.4, 114.7, 117.8, 123.6, 124.0, 126.9, 135.5, 140.5, 177.2 ppm; MS (ESI$^-$): *m/z* (%): 268.2 (95), 266.1 (100) [*M*−H]$^-$.

**(5-Bromo-1-isobutylindol-3-yl)acetic acid (18b)**: A beige solid of **18b** was obtained from **17b** (145 mg, 0.43 mmol) by following general procedure V; yield: 110 mg (82%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 0.93 (d, $^3J$ = 6.6 Hz, 6H), 2.23 (m, 1H), 2.83 (br s, 1H), 3.76 (s, 2H), 3.97 (d, $^3J$ = 12.1 Hz, 2H), 7.26 (d, $^3J$ = 7.2 Hz, $^4J$ = 1.6 Hz, 1H), 7.32 (s, 1H), 7.41 (d, $^3J$ = 7.2 Hz, 1H), 7.78 ppm (d, $^4J$ = 1.6 Hz, 1H); $^{13}$C NMR (250 MHz, [D$_6$]DMSO): $\delta$ = 22.1, 28.4, 38.8, 66.4, 113.4, 114.8, 117.7, 123.7, 124.2, 126.8, 135.5, 140.5, 177.2 ppm; MS (ESI$^-$): *m/z* (%): 324.7 (95), 322.5 (100) [*M*−H]$^-$.

**[5-Bromo-1-(3-methylbutyl)indol-3-yl]acetic acid (18c)**: A beige solid of **18c** was obtained from **17c** (116 mg, 0.33 mmol) by following general procedure V; yield: 76 mg (71%). $^1$H NMR (250 MHz, CD$_3$OD): $\delta$ = 0.95 (d, $^3J$ = 6.4 Hz, 6H), 1.68 (m, 3H), 3.49 (s, 2H), 4.14 (t, $^3J$ = 7.0 Hz, 2H), 7.16 (dd, $^3J$ = 8.7 Hz, $^4J$ = 1.8 Hz, 1H), 7.20 (s, 1H) 7.28 (d, $^3J$ = 8.7 Hz, 1H), 7.81 ppm (d, $^4J$ = 1.8 Hz, 1H); $^{13}$C NMR (250 MHz, [D$_6$]DMSO): $\delta$ = 22.5, 27.4, 37.8, 39.2, 55.4, 113.4, 114.7, 117.3, 123.7, 124.2, 126.6, 135.5, 140.6, 177.1 ppm; MS (ESI$^-$): *m/z* (%): 324.7 (95), 322.5 (100) [*M*−H]$^-$.

**[5-Bromo-1-(2-ethylbutyl)indol-3-yl]acetic acid (18d)**: A beige solid of **18d** was obtained by starting from **17d** (110 mg, 0.30 mmol) by following general procedure V; yield: 78 mg (77%). $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ = 0.92 (t, $^3J$ = 6.8 Hz, 6H), 1.31 (m, 4H), 1.82 (m, 1H), 3.76 (s, 2H), 3.96 (d, $^3J$ = 7.3 Hz, 2H), 7.09 (s, 1H), 7.19 (dd, $^3J$ = 8.5 Hz, $^4J$ = 1.5 Hz, 1H), 7.30 (d, $^3J$ = 8.5 Hz, 1H), 7.74 ppm (d, $^4J$ = 1.5 Hz, 1H); $^{13}$C NMR (250 MHz, [D$_6$]DMSO): $\delta$ = 12.8, 26.2, 36.5, 39.9, 61.8, 113.7, 114.5, 117.1, 123.9, 124.1, 128.5, 135.9, 140.1, 178.2 ppm; MS (ESI$^-$): *m/z* (%):338.2 (95), 336.3 (100) [*M*−H]$^-$.

**(1-Benzyl-5-bromoindol-3-yl)acetic acid (18e)**: A beige solid of **18e** was obtained from **17e** (324 mg, 0.87 mmol) by following general procedure V; yield: 245 mg (82%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 2.88 (br s, 1H), 3.78 (s, 2H), 5.45 (s, 2H), 7.30 (m, 8H), 7.81 ppm (s, 1H) ppm; $^{13}$C NMR (250 MHz, [D$_6$]acetone): $\delta$ = 44.6, 61.5, 108.3, 108.4, 112.1, 113.5, 118.6, 121.5, 121.8, 122.6, 124.4, 125.7, 129.8, 135.6, 172.5 ppm; IR: $\tilde{\nu}_{C=O}$ = 1702 cm$^{-1}$; MS (ESI$^-$): *m/z* (%): 344.1 (95), 342.3 (100) [*M*−H]$^-$.

**(5-Bromo-1-phenethylindol-3-yl)acetic acid (18f)**: A beige solid of **18f** was obtained from **17f** (89 mg, 0.23 mmol) by following general procedure V; yield: 31 mg (39%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 2.86 (br s, 1H), 3.15 (t, $^3J$ = 7.1 Hz, 2H), 3.61 (s, 2H), 4.45 (t, $^3J$ = 7.1 Hz, 2H), 7.23 (m, 7H), 7.41 (d, $^3J$ = 8.7 Hz, 1H), 7.78 ppm (s, 1H); $^{13}$C NMR (250 MHz, [D$_6$]DMSO): $\delta$ = 37.2, 37.5, 59.3, 113.1, 114.5, 118.6, 123.5, 124.4, 126.7, 128.8, 130.0, 131.2, 135.6, 140.1, 141.2, 177.5 ppm; MS (ESI$^-$): *m/z* (%): 358.8 (95), 356.3 (100) [*M*−H]$^-$.

**(1-Benzotriazol-1-ylmethyl-5-bromo-1*H*-indol-3-yl)acetic acid (18g)**: A beige solid of **18g** was obtained from **17g** (90 mg, 0.218 mmol) by following general procedure V; yield: 66 mg (79%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 3.54 (s, 2H), 7.04 (s, 2H), 7.50 (m, 6H), 7.92 ppm (m, 2H); $^{13}$C NMR (250 MHz, [D$_3$]MeCN): $\delta$ = 51.2, 68.9, 112.8, 113.0, 116.1, 116.3, 119.7, 121.3, 126.2, 127.4, 127.5, 128.4, 129.1, 133.4, 146.1, 147.5, 191.6 ppm; MS (ESI$^-$): *m/z* (%): 385.2 (95), 383.0 (100) [*M*−H]$^-$.

**(1-Benzenesulfonyl-5-bromoindol-3-yl)acetic acid (18i)**: A 1 M solution of LiHMDS was added dropwise to a solution of **5** (300 mg, 1.18 mmol) in THF (2.6 mL, 2.2 equiv) at −78 °C. After 30 min at 0 °C, phenylsulfonyl chloride (251 mg, 181 μL, 1.42 mmol, 1.2 equiv) was added dropwise, and the mixture stirred at −78 °C for 1 h. After the addition of H$_2$O (10 mL), the lithium salt of the acid was quenched with 0.1 N HCl. The mixture was extracted with $CH_2Cl_2$ (2×), and the organic layer was dried over MgSO$_4$. Evaporation of the solvent gave a white solid; yield: 465 mg (98%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 2.87 (br s, 1H), 3.82 (s, 2H), 7.61 (m, 5H), 7.83 (s, 1H), 7.97 (m, 1H), 8.17 ppm (d, $^3J$ = 7.6 Hz, 1H); $^{13}$C NMR (250 MHz, [D$_6$]DMSO): $\delta$ = 36.2, 113.1, 114.8, 117.1, 124.0, 124.3, 125.1, 127.6, 130.2, 134.5, 135.9, 137.1, 139.9, 177.4 ppm; MS (ESI$^-$): *m/z* (%): 394.5 (95), 392.4 (100) [*M*−H]$^-$.

**(5-Bromoindol-1-yl)acetic acid (22a)**: A beige solid of **22a** was obtained from (5-bromoindol-1-yl)acetic acid ethyl ester (105 mg, 0.37 mmol) by following general procedure V; yield: 95 mg (78%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 2.88 (br s, 1H), 5.14 (s, 2H), 6.51 (d, $^3J$ = 3.3 Hz, 1H), 7.33 (m, 3H), 7.81 ppm (d, $^4J$ = 1.6 Hz, 1H); $^{13}$C NMR (250 MHz, [D$_6$]acetone): $\delta$ = 48.3, 102.4, 112.8, 113.6, 124.2, 125.3, 128.3, 132.1, 136.9, 170.7 ppm; IR: $\tilde{\nu}_{C=O}$ = 1727 cm$^{-1}$; MS (ESI$^-$): *m/z* (%): 254.6 (95), 252.1 (100) [*M*−H]$^-$.

**(5-Bromo-3-methylindol-1-yl)acetic acid (22b)**: A beige solid of **22b** was obtained from (5-bromo-3-methylindol-1-yl)acetic acid ethyl ester (734 mg, 2.49 mmol) by following general procedure V; yield: 505 mg (76%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 2.29 (s, 3H), 5.01 (s, 2H), 5.26 (br s, 1H), 7.14 (s, 1H), 7.30 (m, 2H), 7.63 ppm (s, 1H); $^{13}$C NMR (250 MHz, [D$_6$]acetone): $\delta$ = 15.5, 62.9, 113.2, 114.3, 117.6, 124.2, 124.9, 127.3, 134.7, 139.9, 177.6 ppm; MS (ESI$^-$): *m/z* (%): 268.5 (95), 266.2 (100) [*M*−H]$^-$.

**(3-Benzyl-5-bromoindol-1-yl)acetic acid (22c)**: A beige solid of **22c** was obtained from (3-benzyl-5-bromoindol-1-yl)acetic acid ethyl ester (947 mg, 2.54 mmol) by following general procedure V; yield: 622 mg (71%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 3.54 (br s, 1H), 4.10 (s, 2H), 5.01 (s, 2H), 7.27 (m, 8H), 7.62 ppm (s, 1H); $^{13}$C NMR (250 MHz, [D$_6$]DMSO): $\delta$ = 30.8, 47.5, 111.7, 112.4, 113.9, 121.3, 124.0, 125.2, 126.2, 128.6, 128.8, 129.0, 129.5, 129.6, 135.9, 141.5, 170.7 ppm; MS (ESI$^-$): *m/z* (%): 344.2 (95), 342.0 (100) [*M*−H]$^-$.

**(5-Bromo-3-ethoxycarbonylmethylindol-1-yl)-acetic acid (22d)**: A beige solid of **22d** was obtained by deprotection of (5-bromo-3-ethoxycarbonylmethylindol-1-yl)acetic acid *tert*-butyl ester (348 mg, 0.88 mmol) by treatment with a solution of TFA (0.5 mL) in $CH_2Cl_2$ (5 mL). The reaction was monitored by TLC (cyclohexane/EtOAc, 8:2 *v/v*). After completion of the reaction, half of the solvent was evaporated. Addition of pentane led to precipitation of the carboxylic acid, which was further collected by filtration; yield: 211 mg

(70%). $^1$H NMR (250 MHz, $CD_3OD$): $\delta = 1.26$ (t, $^3J = 7.1$ Hz, 3H), 3.70 (s, 2H), 4.15 (q, $^3J = 7.1$ Hz, 2H), 4.78 (s, 2H), 7.04 (s, 1H), 7.11 (d, $^3J = 8.7$ Hz, 1H), 7.27 (dd, $^3J = 8.7$ Hz, $^4J = 1.7$ Hz, 1H), 7.71 ppm (d, $^4J = 1.7$ Hz, 1H); $^{13}$C NMR (250 MHz, [D$_6$]acetone): $\delta = 14.6$, 34.0, 60.3, 62.4, 113.2, 114.3, 117.5, 124.2, 124.8, 127.2, 135.2, 139.8, 172.1, 177.4 ppm; MS (ESI$^-$): *m/z* (%): 340.1 (95), 338.2 (100) $[M-H]^-$.

**[5-Bromo-3-(2-oxo-2-phenylethyl)indol-1-yl]acetic acid (22e)**: A beige solid of **22e** was obtained by starting from [5-bromo-3-(2-oxo-2-phenylethyl)indol-1-yl]-acetic acid ethyl ester (703 mg, 1.76 mmol) by following general procedure V; yield: 370 mg (57%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta = 2.82$ (br s, 1H), 3.61 (s, 2H), 5.03 (s, 2H), 7.45 (m, 6H), 8.06 ppm (m, 3H); $^{13}$C NMR (250 MHz, [D$_6$]DMSO): $\delta = 39.8$, 62.6, 113.3, 113.8, 117.9, 123.8, 124.5, 126.9, 129.2, 129.6, 133.8, 135.1, 138.2, 177.4, 197.8 ppm; MS (ESI$^-$): *m/z* (%): 372.3 (95), 370.5 (100) $[M-H]^-$.

**{5-Bromo-3-[2-(2-methoxyphenyl)-2-oxoethyl]indol-1-yl}acetic acid (22f)**: A beige solid of **22f** was obtained by following general procedure V by starting from {5-bromo-3-[2-(2-methoxyphenyl)-2-oxoethyl]indol-1-yl}acetic acid ethyl ester (540 mg, 1.26 mmol) by following general procedure V; yield: 303 mg (60%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta = 2.88$ (br s, 1H), 3.62 (s, 2H), 4.07 (s, 3H), 5.03 (s, 2H), 7.46 (m, 5H), 8.02 ppm (m, 3H); $^{13}$C NMR (250 MHz, [D$_6$]DMSO): $\delta = 39.7$, 57.1, 62.5, 113.2, 113.9, 116.1, 122.6, 123.8, 123.9, 124.1, 124.7, 127.5, 130.7, 134.4, 134.9, 140.4, 163.3, 177.5, 197.4 ppm; MS (ESI$^-$): *m/z* (%): 402.0 (95), 400.1 (100) $[M-H]^-$.

**(6-Bromoindol-1-yl)acetic acid 22g**: A beige solid of **22g** was obtained by starting from (6-bromoindol-1-yl)acetic acid ethyl ester (220 mg, 0.78 mmol) by following general procedure V; yield: 165 mg (83%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta = 2.84$ (br s, 1H), 5.12 (s, 2H), 6.53 (d, $^3J = 2.9$ Hz, 1H), 7.19 (d, $^3J = 8.2$ Hz, 1H), 7.36 (d, $^3J = 2.9$ Hz, 1H), 7.52 (d, $^3J = 8.2$ Hz, 1H), 7.58 ppm (s, 1H); $^{13}$C NMR (250 MHz, [D$_6$]acetone): $\delta = 48.2$, 103.0, 113.9, 115.8, 123.3, 123.6, 129.0, 131.5, 139.0, 170.5 ppm; MS (ESI$^-$): *m/z* (%): 254.6 (95), 252.1 (100) $[M-H]^-$.

**(5-Bromo-3-ethoxycarbonylmethylindol-1-yl)acetic acid *tert*-butyl ester**: Brown solid of (5-bromo-3-ethoxycarbonylmethylindol-1-yl)acetic acid *tert*-butyl ester was obtained by following general procedure III by reaction of **21d** (200 mg, 0.71 mmol) with bromoacetic acid *tert*-butyl ester (152 mg, 114 μL, 0.78 mmol); yield: 337 mg (91%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta = 1.24$ (t, $^3J = 7.1$ Hz, 3H), 1.45 (s, 9H), 3.76 (s, 2H), 4.14 (q, $^3J = 7.1$ Hz, 2H), 4.96 (s, 2H), 7.31 (m, 3H), 7.67 ppm (s, 1H); $^{13}$C NMR (250 MHz, [D$_6$]acetone): $\delta = 15.2$, 30.1, 34.0, 60.3, 60.9, 74.2, 113.6, 114.8, 117.5, 123.4, 124.3, 127.6, 135.3, 140.3, 172.2, 172.6 ppm; MS (ESI$^+$): *m/z* (%): 398.1 (95), 396.5 (100) $[M+H]^+$.

**3-(5-Bromo-3-ethoxycarbonylmethylindol-1-yl)propionic acid**: 3-(5-Bromo-3-ethoxycarbonylmethylindol-1-yl)propionic acid was obtained by deprotection of 3-(5-Bromo-3-ethoxycarbonylmethylindol-1-yl)propionic acid *tert*-butyl ester (1.57 g, 3.8 mmol) by treatment with a solution of TFA (2 mL) in $CH_2Cl_2$ (20 mL). The reaction was monitored by TLC (cyclohexane/EtOAc, 7:3 *v/v*). After completion of the reaction and evaporation half of solvent, adding pentane led to precipitation of the carboxylic acid which was collected by filtration; yield: 223 mg (60%). $^1$H NMR (250 MHz, $CDCl_3$): $\delta =$ 1.28 (t, $^3J = 7.4$ Hz, 3H), 2.86 (t, $^3J = 6.9$ Hz, 2H), 3.73 (s, 2H), 4.19 (q, $^3J = 7.4$ Hz, 2H), 4.41 (t, $^3J = 6.9$ Hz, 2H), 7.15 (s, 1H), 7.20 (d, 1H, $^4J = 1.4$ Hz), 7.33 (d, $^3J = 8.7$ Hz, 1H), 7.74 ppm (dd, $^3J = 8.7$ Hz, $^4J =$ 1.4 Hz, 1H); $^{13}$C NMR (250 MHz, [D$_6$]DMSO): $\delta = 15.1$, 35.2, 37.7, 52.1, 60.2, 113.1, 114.3, 116.9, 123.4, 124.2, 127.5, 135.3, 140.4, 173.3, 177.6 ppm; MS (ESI$^-$): *m/z* (%): 354.2 (95), 352.3 (100) $[M-H]^-$.

**(5-Bromo-1-{3-oxo-3-[4-(tetrahydrofuran-2-ylmethyl)piperazin-1-yl]-propyl}indol-3-yl)acetic acid ethyl ester (16)**: Brown solid of **16** was obtained by following the general procedure VI, which is described below, by starting from 3-(5-bromo-3-ethoxycarbonylmethylindol-1-yl)-propionic acid (109.4 mg, 0.31 mmol) with 1-(tetrahydrofuran-2-ylmethyl)piperazine (58.1 mg, 57 μL, 0.34 mmol); yield: 115 mg (74%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta = 1.29$ (t, $^3J = 7.1$ Hz, 3H), 1.82 (m, 4H), 2.56 (m, 8H), 3.37 (m, 6H), 3.81 (m, 3H), 4.15 (m, 4H), 7.12 (s, 1H), 7.23 (d, $^4J = 1.6$ Hz, 1H), 7.44 (d, $^3J =$ 8.6 Hz, 1H), 7.73 ppm (dd, $^3J = 8.6$ Hz, $^4J = 1.6$ Hz, 1H).

**(5-Bromo-1-{3-oxo-3-[4-(tetrahydrofuran-2-ylmethyl)piperazin-1-yl]propyl}indol-3-yl)acetic acid (18h)**: White solid of **18h** was obtained upon saponification of (5-bromo-1-{3-oxo-3-[4-(tetrahydrofuran-2-ylmethyl)piperazin-1-yl]propyl}indol-3-yl)acetic acid ethyl ester (**16**; 85 mg, 0.17 mmol) by following general procedure V; yield: 37 mg (46%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta = 1.80$ (m, 4H), 2.55 (m, 8H), 3.35 (m, 6H), 3.79 (m, 3H), 4.13 (t, $^3J = 6.8$ Hz, 2H), 7.18 (m, 2H), 7.43 (d, $^3J = 8.7$ Hz, 1H), 7.74 ppm (dd, $^3J =$ 8.7 Hz, $^4J = 1.6$ Hz, 1H).

**General Procedure VI: Peptide coupling**: EDCI·HCl (98%; 210.8 mg, 1.1 mmol) was added to a solution of the acid (1 mmol), *O*-dimethyl-*tert*-butylsilylhydroxylamine (147.3 mg, 1 mmol), HOBt (135.1 mg, 1 mmol), and NMM (101.1 mg, 109.9 μL, 1 mmol) in DMF (40 mL) at 0 °C. After 1 h at 0 °C, the solution was stirred overnight at room temperature. A 1 M solution of $Bu_4NF$ (1.2 mL) was injected, and the mixture was stirred for 2 h. The product was extracted with EtOAc, washed with sat. aq $NaHCO_3$, then acidified with 0.1 N HCl and washed with brine. The organic layer was dried over $MgSO_4$, and concentrated in vacuo, and the product was isolated as a precipitate or as an oil. This oil was dissolved in a mixture of acetone/cyclohexane (3:7 *v/v*). Slow evaporation of acetone allowed the product to precipitate. This purification procedure was repeated twice to get pure products. The presence of the hydroxamic acids was checked by a very simple test. Addition of a solution of $FeCl_3$ (1 mg in 5 mL $CH_2Cl_2$) to the hydroxamate in acetone led to the formation of an $Fe^{III}$–hydroxamate complex. Upon complexation, the color of the solution turned dark-blue.[44]

**2-(5-Cyclopropyl-1*H*-indol-3-yl)-*N*-hydroxyacetamide (11)**: A brown solid of **11** was obtained from (5-cyclopropyl-1*H*-indol-3-yl)-acetic acid (**6**; 75 mg, 0.35 mmol) by following general procedure VI; yield: 12 mg (15%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta = 0.81$ (m, 2H), 0.98 (m, 2H), 2.12 (m, 1H), 3.61 (s, 2H), 6.98 (dd, $^3J = 8.2$ Hz, $^4J = 1.6$ Hz, 1H), 7.23 (s, 1H), 7.32 (d, $^3J = 8.2$ Hz, 1H), 7.38 (d, $^4J =$ 1.6 Hz, 1H), 10.23 ppm (br s, 1H); $^{13}$C NMR (250 MHz, [D$_6$]acetone): $\delta = 8.8$, 17.7, 31.3, 111.7, 113.8, 118.2, 119.1, 123.0, 132.6, 134.2, 138.6, 167.6 ppm; HRMS (ESI): *m/z*: calcd for $C_{13}H_{14}N_2O_2$: 229.0977 $[M-H]^-$; found: 229.1007.

***N*-Hydroxy-2-(5-methylsulfanyl-1*H*-indol-3-yl)acetamide (12)**: A brown solid of **12** was obtained from 5-methylsulfanyl-1*H*-indol-3-yl)acetic acid (**7**; 420 mg, 1.9 mmol) by following general procedure VI; yield: 197 mg (44%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta = 2.49$ (s, 3H), 3.66 (s, 2H), 7.16 (dd, $^3J = 8.4$ Hz, $^4J = 1.6$ Hz, 1H), 7.35 (m, 2H), 7.65 (d, $^4J = 1.6$ Hz, 1H), 7.91 (br s, 1H), 10.21 ppm (br s, 1H); $^{13}$C NMR (250 MHz, [D$_6$]acetone): $\delta = 19.6$, 30.8, 112.2, 113.2, 119.2, 120.0, 123.6, 129.7, 132.6, 134.0, 167.7 ppm; HRMS (ESI)$^-$: *m/z*: calcd for $C_{11}H_{12}N_2O_2S$: 235.0541 $[M-H]^-$; found: 235.0553.

***N*-Hydroxy-2-(5-methyl-1*H*-indol-3-yl)acetamide (13)**: Yellow crystals of **13** were obtained from (5-methyl-1*H*-indol-3-yl)acetic acid

(**8**; 538 mg, 2.83 mmol) by following general procedure VI; yield: 301 mg (52%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 2.41 (s, 3H), 3.57 (s, 2H), 6.94 (dd, $^3J$ = 8.2 Hz, $^4J$ = 1.6 Hz, 1H), 7.22 (s, 1H), 7.28 (d, $^3J$ = 8.2 Hz, 1H), 7.41 (d, $^4J$ = 1.6 Hz, 1H), 7.92 (brs, 1H), 9.95 ppm (brs, 1H); $^{13}$C NMR (250 MHz, [D$_6$]acetone): $\delta$ = 22.5, 30.7, 111.8, 113.1, 121.2, 122.3, 123.6, 132.2, 132.6, 134.7, 167.8 ppm; elemental analysis calcd (%) for $C_{11}H_{12}N_2O_2$ (204.2): C 64.69, H 5.92, N 13.72, O 15.67; found C 64.66, H 5.81, N 13.86, O 15.73.

**2-(5-Chloro-1*H*-indazol-3-yl)-*N*-hydroxyacetamide (14)**: A beige solid of **14** was obtained from (5-chloro-1*H*-indazol-3-yl)acetic acid **9** (70 mg, 0.33 mmol) by following general procedure VI; yield: 65 mg (88%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 3.11 (brs, 1H), 3.98 (s, 2H), 7.35 (dd, $^3J$ = 8.7 Hz, $^4J$ = 1.4 Hz, 1H), 7.61 (d, $^3J$ = 8.7 Hz, 1H), 7.86 ppm (d, $^4J$ = 1.4 Hz, 1H); $^{13}$C NMR (250 MHz, [D$_6$]DMSO): $\delta$ = 41.8, 112.2, 120.2, 123.1, 124.5, 126.6, 133.2, 139.8, 167.8 ppm; HRMS (ESI$^+$): *m/z*: calcd for $C_9H_8ClN_3O_2$: 248.0203 [*M*+Na$^+$]; found: 248.0192.

**2-(5-Bromo-1-methylindol-3-yl)-*N*-hydroxyacetamide (19a)**: A brown solid of **19a** was obtained from (5-bromo-1-methylindol-3-yl)acetic acid (**18a**; 150.8 mg, 0.56 mmol) by following general procedure VI; yield: 62 mg (73%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 3.56 (s, 2H), 3.82 (s, 3H), 7.29 (m, 3H), 7.82 (d, $^3J$ = 9.9 Hz, 1H), 10.07 (brs, 1H) ppm; $^{13}$C NMR (250 MHz, [D$_6$]DMSO): $\delta$ = 32.8, 42.6, 108.0, 112.2, 114.4, 121.7, 123.8, 128.9, 130.3, 135.6, 167.6 ppm; IR: $\tilde{\nu}$ = 1628 (s), 3196 (m), 3348 (m) cm$^{-1}$; HRMS (ESI$^-$) *m/z*: calcd for $C_{11}H_{11}BrN_2O_2$: $^{79}$Br: 280.9926 [*M*−H]$^-$ 282.9905 [*M*−H]$^-$; found: $^{79}$Br: 280.9918, $^{81}$Br: 283.0000.

**2-(5-Bromo-1-isobutylindol-3-yl)-*N*-hydroxyacetamide (19b)**: An orange solid of **19b** was obtained from (5-bromo-1-isobutylindol-3-yl)acetic acid (**18b**; 109.7 mg, 0.35 mmol) by following general procedure VI; yield: 95 mg (84%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 0.92 (d, $^3J$ = 2.3 Hz, 6H), 2.16 (m, 1H) 3.57 (s, 2H), 4.00 (d, $^3J$ = 7.3 Hz, 2H), 7.26 (m, 2H), 7.41 (d, $^3J$ = 8.3 Hz, 1H), 7.81 (s, 1H), 10.01 ppm (brs, 1H); $^{13}$C NMR (250 MHz, [D$_6$]DMSO): $\delta$ = 20.2, 29.6, 31.3, 53.1, 108.0, 111.6, 112.4, 112.5, 121.7, 123.7, 123.8, 129.5, 129.6.129.7, 135.3 ppm; HRMS (ESI$^+$): *m/z*: calcd for $C_{14}H_{17}BrN_2O_2$: $^{79}$Br: 347.0371, [*M*+Na$^+$] $^{81}$Br: 349.0351 [*M*+Na$^+$]; found: $^{79}$Br: 347.0360, $^{81}$Br: 349.0324.

**2-[5-Bromo-1-(3-methylbutyl)indol-3-yl]-*N*-hydroxyacetamide (19c)**: An orange solid of **19c** was obtained from [5-bromo-1-(3-methylbutyl)indol-3-yl]-acetic acid (**18c**; 75.8 mg, 0.24 mmol) by following general procedure VI; yield: 66 mg (81%).$^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 0.98 (d, $^3J$ = 6.2 Hz, 6H), 1.65 (m, 3H), 3.57 (s, 2H), 4.22 (t, $^3J$ = 7.4 Hz, 2H), 7.26 (d, $^3J$ = 8.6 Hz, 1H), 7.30 (s, 1H), 7.40 (d, $^3J$ = 8.6 Hz, 1H), 7.81 (s, 1H), 10.06 (brs, 1H) ppm; $^{13}$C NMR (250 MHz, [D$_6$]DMSO): $\delta$ = 22.6, 25.5, 41.3, 44.1, 65.4, 65.8, 66.0, 90.0, 108.2, 112.0, 121.8, 121.9, 123.7, 167.5 ppm; HRMS (ESI$^+$): *m/z*: calcd for $C_{15}H_{19}BrN_2O_2$: $^{81}$Br: 363.0507 [*M*+Na$^+$] $^{79}$Br: 361.0528; found: $^{79}$Br: 361.0535, $^{81}$Br: 363.0532.

**2-[5-Bromo-1-(2-ethylbutyl)indol-3-yl]-*N*-hydroxyacetamide (19d)**: A brown crystals of **19d** were obtained from [5-bromo-1-(2-ethyl-butyl)indol-3-yl]acetic acid (**18d**; 78.4 mg, 0.23 mmol) by following general procedure VI; yield: 75 mg (93%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 0.92 (t, 6H), 1.31 (m, 4H), 1.84 (m, 1H), 3.57 (s, 2H), 4.07 (d, $^3J$ = 7.1 Hz, 2H), 7.33 (m, 3H), 7.78 (s, 1H), 10.12 ppm (brs, 1H); $^{13}$C NMR (250 MHz, [D$_6$]DMSO): $\delta$ = 13.6, 26.4, 30.7, 40.5, 61.6, 113.4, 114.3, 117.5, 124.0, 124.5, 127.9, 135.4, 144.0, 167.9 ppm; HRMS (ESI$^+$): *m/z*: calcd for $C_{16}H_{21}BrN_2O_2$: $^{79}$Br: 353.0865 [*M*+Na]$^+$, $^{81}$Br: 355.0844 [*M*+Na]$^+$; found: $^{79}$Br: 353.0873, $^{81}$Br: 355.0857.

**2-(1-Benzyl-5-bromoindol-3-yl)-*N*-hydroxyacetamide (19e)**: An orange powder of **19e** was obtained from (1-benzyl-5-bromoindol-3-yl)acetic acid (**18e**; 239.1 mg, 0.69 mmol) by following general procedure VI; yield: 235 mg (95%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 3.59 (s, 2H), 5.42 (s, 2H), 7.29 (m, 8H), 7.80 (s, 1H), 10.12 (brs, 1H) ppm; $^{13}$C NMR (250 MHz, [D$_6$]DMSO): $\delta$ = 30.2, 49.9, 109.3, 112.4, 113.0, 122.4, 124.6, 127.5, 127.9, 128.3, 129.2, 129.4, 129.9, 130.4, 135.5, 138.8, 168.0 ppm; HRMS (ESI$^+$, *m/z*) calcd for $C_{17}H_{15}BrN_2O_2$: $^{79}$Br: 381.0215 [*M*+Na]$^+$, $^{81}$Br: 383.0194 [*M*+Na]$^+$; found: $^{79}$Br: 381.0214, $^{81}$Br: 383.0193.

**2-(5-Bromo-1-phenethylindol-3-yl)-*N*-hydroxyacetamide (19f)**: A brown powder of **19f** was obtained from (5-bromo-1-phenethylindol-3-yl)acetic acid (**18f**; 28.3 mg, 0.079 mmol) by following general procedure VI; yield: 13 mg (44%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 3.15 (t, 2H, $^3J$ = 6.7 Hz), 3.56 (s, 2H), 4.44 (t, 2H, $^3J$ = 6.7 Hz), 7.23 (m, 7H), 7.41 (d, $^3J$ = 8.6 Hz, 1H), 7.81 (s, 1H) ppm. $^{13}$C NMR (250 MHz, [D$_6$]acetone): $\delta$ = 30.6, 32.3, 34.5, 56.7, 113.3, 113.9, 117.2, 123.6, 124.3, 126.6, 127.2, 129.0, 129.7, 135.0, 139.7, 140.1, 167.6 ppm. HRMS (ESI$^+$) *m/z*: calcd for $C_{18}H_{17}BrN_2O_2$: $^{79}$Br: 395.03571 [*M*+Na$^+$], $^{81}$Br: 397.035 [*M*+Na$^+$]; found: $^{79}$Br: 395.0371, $^{81}$Br: 397.0349.

**2-(1-Benzotriazol-1-ylmethyl-5-bromoindol-3-yl)-*N*-hydroxyacetamide (19g)**: A beige powder of **19g** was obtained from (1-benzotriazol-1-yl-methyl-5-bromo-1*H*-indol-3-yl)acetic acid (**18g**; 40 mg, 0.10 mmol) by following general procedure VI; yield: 15 mg (37%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 3.45 (s, 2H), 7.26 (d, $^4J$ = 1.6 Hz, 1H), 7.41 (m, 2H), 7.62 (dd, $^3J$ = 7.6 Hz, 2H), 7.78 (s, 1H), 7.85 (m, 2H), 8.03 (d, $^3J$ = 8.3 Hz, 1H), 8.13 (dd, $^3J$ = 8.3 Hz, $^4J$ = 1.6 Hz, 1H), 8.70 (brs,1H), 10.57 ppm (brs, 1H) ppm; $^{13}$C NMR (500 MHz, [D$_6$]DMSO): $\delta$ = 30.9, 58.3, 112.2, 112.5, 114.4, 114.6, 121.3, 123.7, 126.4, 126.6, 130.1, 130.4, 131.9, 133.9, 136.3, 147.1, 168.7 ppm. HRMS (ESI$^+$) *m/z*: calcd for $C_{17}H_{14}BrN_4O_2$: $^{79}$Br: 422.0229 [*M*+Na]$^+$, $^{81}$Br: 424.0208 [*M*+Na]$^+$; found: $^{79}$Br: 422.0208, $^{81}$Br: 424.0260.

**2-(5-Bromo-1-{3-oxo-3-[4-(tetrahydrofuran-2-ylmethyl)piperazin-1-yl]propyl}indol-3-yl)-*N*-hydroxyacetamide (19h)**: A brown powder of **19h** was obtained from (5-bromo-1-{3-oxo-3-[4-(tetrahydrofuran-2-ylmethyl)piperazin-1-yl]propyl}indol-3-yl)acetic acid (**18h**; 50 mg, 0.11 mmol) by following general procedure VI; yield: 15 mg (28%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 1.81 (m, 4H), 2.56 (m, 8H), 3.38 (m, 6H), 3.82 (m, 3H), 4.16 (t, $^3J$ = 6.8 Hz, 2H), 7.18 (m, 2H), 7.48 (d, $^3J$ = 8.6 Hz, 1H), 7.76 (dd, $^3J$ = 8.6 Hz, $^4J$ = 1.6 Hz, 1H) 10.41 ppm (brs, 1H); HRMS (ESI): *m/z*: calcd for $C_{22}H_{29}{}^{79}BrN_4O_4$: 493.1450 [*M*+H] $^+$; found: 493.1473.

**2-(1-Benzenesulfonyl-5-bromoindol-3-yl)-*N*-hydroxyacetamide (19i)**: A yellow powder of **19i** was obtained from (1-benzenesulfonyl-5-bromoindol-3-yl)acetic acid (**18i**; 28 mg, 0.072 mmol) by following general procedure VI; yield: 23 mg (78%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 3.61 (s, 2H), 7.79 (m, 8H), 8.01 (d, $^3J$ = 6.5 Hz, 1H) 10.43 ppm (brs, 1H); $^{13}$C NMR (250 MHz, [D$_6$]DMSO): $\delta$ = 32.3, 95.1, 103.5, 107.3, 109.3, 114.9, 117.2, 120.6, 125.4, 127.0, 127.3, 129.8, 130.3, 173.3 ppm. HRMS (ESI): *m/z*: calcd for $C_{16}H_{13}{}^{79}BrN_2O_4S$: 430.9677 [*M*+H]$^+$; found: 430.9696.

**2-(5-Bromoindol-1-yl)-*N*-hydroxyacetamide (23a)**: A brown powder of **23a** was obtained from (5-bromoindol-1-yl)acetic acid (**22a**; 2 g, 7.87 mmol) by following general procedure VI; yield: 1.82 g (86%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta$ = 5.02 (s, 2H), 6.54 (d, $^3J$ = 3.2 Hz, 1H), 7.24 (m, 3H), 7.79 (d, $^4J$ = 1.6 Hz, 1H), 10.34 ppm (brs, 1H); $^{13}$C NMR (250 MHz, [D$_6$]acetone): $\delta$ = 57.3, 103.1, 114.1, 117.1, 123.6, 124.5, 128.4, 131.1, 139.0, 167.7 ppm; HRMS (ESI): *m/z*: calcd for $C_{10}H_9BrN_2O_2$: $^{79}$Br: 266.9769 [*M*−H]$^-$ $^{81}$Br: 268.9749 [*M*−H]$^-$; found: $^{79}$Br: 266.9785, $^{81}$Br: 268.9767.

**2-(5-Bromo-3-methylindol-1-yl)-*N*-hydroxyacetamide (23 b)**: A green oil of **23 b** was obtained from (5-bromo-3-methylindol-1-yl)-acetic acid (**22 b**; 748 mg, 2.8 mmol) by following general procedure VI; yield: 450 mg (57%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta =$ 2.29 (s, 3H), 5.01 (s, 2H), 7.06 (s, 1H), 7.21 (m, 2H), 7.68 ppm (s, 1H); $^{13}$C NMR (250 MHz, [D$_6$]acetone): $\delta =$ 15.3, 58.2, 113.1, 114.2, 117.2, 123.2, 124.4, 127.2, 134.9, 140.0, 167.8 ppm; HRMS (ESI): *m/z*: calcd for $C_{11}H_{11}BrN_2O_2$: $^{79}$Br: 280.9926 $[M+Na]^+$; $^{81}$Br: 282.9905 $[M+Na]^+$; found: $^{79}$Br: 280.9942, $^{81}$Br: 282.9975.

**2-(3-Benzyl-5-bromoindol-1-yl)-*N*-hydroxyacetamide (23 c)**: Red crystals of **23 c** were obtained from (3-benzyl-5-bromoindol-1-yl)-acetic acid (**22 c**; 542 mg, 1.57 mmol) by following general procedure VI; yield: 361 mg (64%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta =$ 4.10 (s, 2H), 4.83 (s, 2H), 7.15 (m, 8H), 7.62 (s, 1H), 10.23 ppm (br s, 1H); $^{13}$C NMR (500 MHz, [D$_6$]DMSO): $\delta =$ 29.9, 45.9, 110.8, 113.1, 120.4, 122.9, 123.2, 125.4, 127.6, 127.6, 127.7, 127.8, 128.0, 128.7, 134.8, 140.5, 163.5 ppm; HRMS (ESI): *m/z*: calcd for $C_{17}H_{15}BrN_2O_2$: $^{79}$Br: 359.0395 $[M+Na]^+$, $^{81}$Br: 361.0375 $[M+Na]^+$; found: $^{79}$Br: 359.0389, $^{81}$Br: 361.0372

**(5-Bromo-1-hydroxycarbamoylmethylindol-3-yl)acetic acid ethyl ester (23 d)**: A beige powder of **23 d** was obtained from (5-bromo-3-ethoxycarbonylmethylindol-1-yl)acetic acid (**22 d**; (90.6 mg, 0.27 mmol) by following general procedure VI; yield: 86 mg (91%). $^1$H NMR (250 MHz, $CDCl_3$): $\delta =$ 1.29 (t, 3H $^3J =$ 7.1 Hz), 3.73 (s, 2H), 4.19 (q, $^3J =$ 7.1 Hz, 2H), 4.81 (s, 2H), 7.01 (s, 1H), 7.11 (d, $^3J =$ 8.5 Hz, 1H), 7.33 (dd, $^4J =$ 1.6 Hz, $^3J =$ 8.5 Hz, 1H), 7.75 ppm (d, $^4J =$ 1.6 Hz, 1H); $^{13}$C NMR (250 MHz, [D$_6$]acetone): $\delta =$ 12.8, 31.9, 55.2, 58.4, 111.2, 112.3, 115.2, 122.1, 122.6, 125.3, 133.0, 137.9, 165.2, 170.8 ppm; HRMS (ESI$^+$): *m/z*: calcd for $C_{14}H_{15}{}^{79}BrN_2O_4$: 377.0113 $[M+Na]^+$; found: 377.0069.

**2-[5-Bromo-3-(2-oxo-2-phenylethyl)indol-1-yl]-*N*-hydroxyacetamide (23 e)**: Brown powder of **23 e** was obtained from [5-bromo-3-(2-oxo-2-phenylethyl)indol-1-yl]acetic acid (**22 e**; (37 mg, 0.09 mmol) by following general procedure VI; yield: 33 mg (86%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta =$ 2.82 (br s, 1H), 3.61 (s, 2H), 5.14 (s, 2H), 7.45 (m, 6H), 8.06 ppm (m, 3H); $^{13}$C NMR (250 MHz, [D$_6$]acetone): $\delta =$ 39.7, 57.4, 113.3, 113.7, 117.2, 123.6, 124.6, 127.1, 129.3, 129.7, 133.8, 135.1, 138.2, 140.0, 167.6, 197.6 ppm; HRMS (ESI): *m/z*: calcd for $C_{18}H_{15}{}^{79}BrN_2O_3$: 385.0188 $[M-H]^-$; found: 385.0176.

**2-{5-Bromo-3-[2-(2-methoxyphenyl)-2-oxoethyl]indol-1-yl}-*N*-hydroxyacetamide (23 f)**: Brown powder of **23 f** was obtained from {5-bromo-3-[2-(2-methoxyphenyl)-2-oxo-ethyl]indol-1-yl}acetic acid (**22 f**; 133 mg, 0.33 mmol) by following general procedure VI; yield: 42 mg (31%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta =$ 2.88 (br s, 1H), 3.62 (s, 2H), 4.07 (s, 3H), 5.13 (s, 2H), 7.48 (m, 5H), 8.02 ppm (m, 3H); $^{13}$C NMR (250 MHz, [D$_6$]acetone): $\delta =$ 39.6, 57.2, 57.6, 113.3, 114.1, 115.1, 117.1, 121.5, 123.8, 124.3, 124.7, 127.3, 130.5, 134.3, 134.9, 140.5, 163.2, 167.7, 197.3 ppm; HRMS (ESI): *m/z*: calcd for $C_{19}H_{17}BrN_2O_4$: $^{79}$Br: 415.0293 $[M-H]^-$, $^{81}$Br: 417.0273 $[M-H]^-$; found: $^{79}$Br: 415.0290, $^{81}$Br: 417.0277.

**2-(6-Bromoindol-1-yl)-*N*-hydroxyacetamide (23 g)**: An orange oil of **23 g** was obtained from (6-bromoindol-1-yl)acetic acid (**22 g**; (165 mg, 0.65 mmol) by following general procedure VI; yield: 143 mg (82%). $^1$H NMR (250 MHz, [D$_6$]acetone): $\delta =$ 5.04 (s, 2H), 6.50 (d, $^4J =$ 3.2 Hz, 1H), 7.27 (m, 2H), 7.56 (d, $^3J =$ 8.6 Hz, 1H), 7.58 ppm (s, 1H); $^{13}$C NMR (250 MHz, [D$_6$]acetone): $\delta =$ 57.2, 103.1, 115.1, 115.8, 123.4, 125.9, 127.7, 128.5, 142.2, 167.7 ppm; HRMS (ESI): *m/z*: calcd for $C_{10}H_9BrN_2O_2$: $^{79}$Br: 266.9769 $[M-H]^-$, $^{81}$Br: 268.9749 $[M-H]^-$; found: $^{79}$Br: 266.9765, $^{81}$Br: 268.9741.

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