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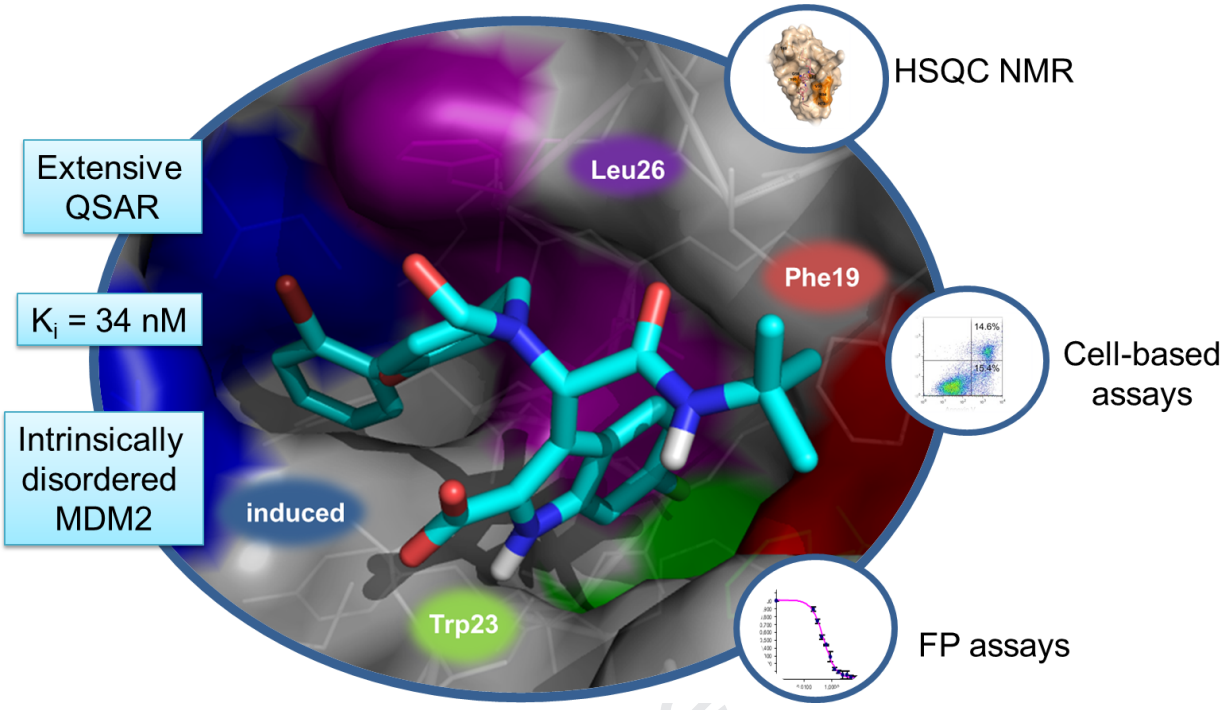

Hitting on the move: targeting intrinsically disordered protein states of the MDM2-p53 interaction

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ABSTRACT

Intrinsically disordered proteins are an emerging class of proteins without a folded structure and currently disorder-based drug targeting remains a challenge. p53 is the principal regulator of cell division and growth whereas MDM2 consists its main negative regulator. The MDM2-p53 recognition is a dynamic and multistage process that amongst other, employs the dissociation of a transient α-helical N-terminal ‘‘lid’’ segment of MDM2 from the proximity of the p53-complementary interface. Several small molecule inhibitors have been reported to inhibit the formation of the p53-MDM2 complex with the vast majority mimicking the p53 residues Phe19, Trp23 and Leu26. Recently, we have described the transit from the 3-point to 4-point pharmacophore model stabilizing this intrinsically disordered N-terminus by increasing the binding affinity by a factor of 3. Therefore, we performed a thorough SAR analysis, including chiral separation of key compound which was evaluated by FP and 2D NMR. Finally, p53-specific anti-cancer activity towards p53-wild-type cancer cells was observed for several representative compounds.

Keywords: Intrinsically disordered proteins, p53-MDM2, 4-point pharmacophore model, Ugi reaction, SAR analysis, AnchorQuery, ^{1}H-^{15}N 2D HSQC NMR, cancer

INTRODUCTION

Drug discovery remains slow, expensive and unreliable. Although immense progress in individual whole genome sequencing for personalized medicine has provided a wealth of novel drug targets, very few small molecule drugs for post-genomic identified targets are currently in development.[1–3] A major hurdle to the efficient and fast generation of novel drugs is the slow and traditional approach performed in early drug discovery and development. The rationale behind modern drug design is based on all the theoretical and experimental knowledge of the particular system under investigation. Of outmost importance is considering the dynamical nature of the proteins. Proteins are flexible entities, thus move. The determined conformations of a protein often differ in its ligand-bound and unbound forms. Protein conformational changes could open new ligand binding sites, whose exploration is a key to fully access the efficacy of a drug as well as to identify non-specific targeting with possible undesired effects.[3–7] Intrinsically disordered protein states (IDPs) are an emerging family of proteins whose most characteristic feature is that they don't present a folded structure, and thus challenge the sequence-structure-function paradigm.[8–10] This lack of stable structure, over the entire protein length or in some regions (Intrinsically Disordered Regions or IDRs), provides them a structural plasticity which is not achievable by ordered proteins that is essential to carry out their cellular function.

The tumor-suppressor protein p53 is the principal regulator of cell division and growth, as it is able to control genes that are implicated in cell-cycle control, apoptosis, angiogenesis, senescence and autophagia.[11–13] The *TP53* gene is one of the most frequently mutated genes in a multitude of human cancer.[14] Additionally, in most cases where *TP53* is intact, p53's function is impaired by its negative regulators, mouse double minute 2 and 4 homologues

(MDM2 and MDMX), due to amplification or enhanced expression of their coding genes.[11,12,14] MDM2 functions as an E3 ligase leading to p53-ubiquitilation and then proteasomal inactivation. The MDM2-p53 recognition is a dynamic and multistage process that employs the binding-induced folding of p53,[15–18] the stepwise p53 induced MDM2 binding pocket formation starting with pocking of p53-Trp23 into MDM2,[19] the rearrangement of the Leu26 subpocket of MDM2 by a twist of the Tyr100 ring from the ‘‘closed’’ to the ‘‘open’’ (anti)conformations,[15,20–23] and the dissociation of a transient α-helical N-terminal ‘‘lid’’ segment of MDM2 (residues 19–23) from the proximity of the p53-complementary interface.[24–28] Several potent small molecules are currently in clinical trials, which are direct antagonists of the p53-MDM2 interaction and which mimic the p53 hot-spot triad $Phe^{19}Trp^{23}Leu^{26}$ described with the classical three finger pharmacophore model.[29–31] In more detail, the great majority of the small molecule inhibitors of the p53-MDM2 interaction target the same “closed” Tyr100 state and are incapable of reaching the N-terminal “lid” segment, an intrinsically disordered region of MDM2 (Figure 1,A).[32–36] However some time ago,[37] we were able to discover, for the first time, an inhibitor that could bound to the “open” Tyr100 conformation leading to a four point pharmacophore interaction (Figure 1,B).[38]

A. **B.**

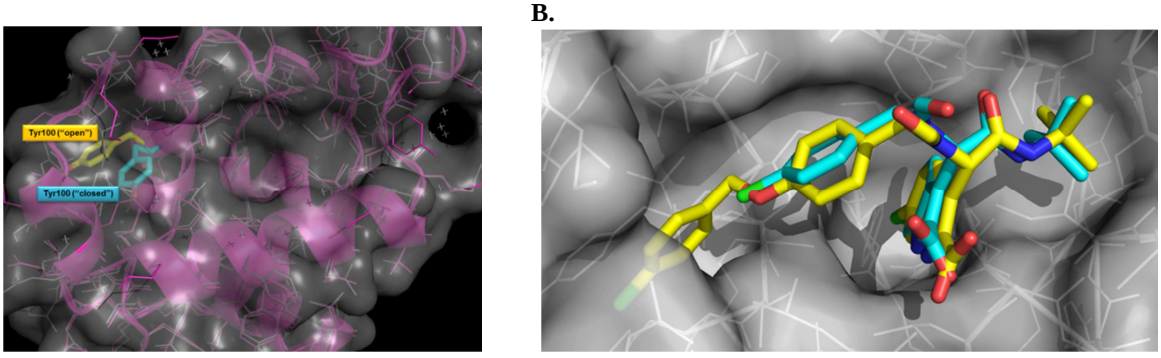


Figure 1. (A) Alignment of the two co-crystal structures demonstrating the closed (cartoon, magenta) and open lid (gray surface); (B) Alignment of the two inhibitors YH119 (PDB ID 3TJ2) and YH300 (PDB ID 4MDN).

In this way, we were able to transit from a 3-point pharmacophore model (YH119, PDB ID 3TJ2) to a 4-point (YH300, PDB ID 4MDN), increasing the binding affinity by almost three times (Figure 2,A). The co-crystal structure with the inhibitor YH300 surprisingly, but clearly, indicated that the 4-chlorobenzyl phenyl ether moiety filled the Leu26 and an induced subpocket, the *tert*-butyl group occupied the Phe19 pocket and the anchoring 6-chloroindole, by default, filled the Trp23 pocket (Figure 2,B). Herein, with all this information in hand, we performed a thorough SAR analysis (Figure 2,C), mostly focusing on the Leu26 and the newly presented induced sub cleft (4th pharmacophore) which was evaluated with two different biorthogonal assays, followed by cell-based studies using p53-wild-type and p53-deleted cells. The results were rationalized by further modeling studies.

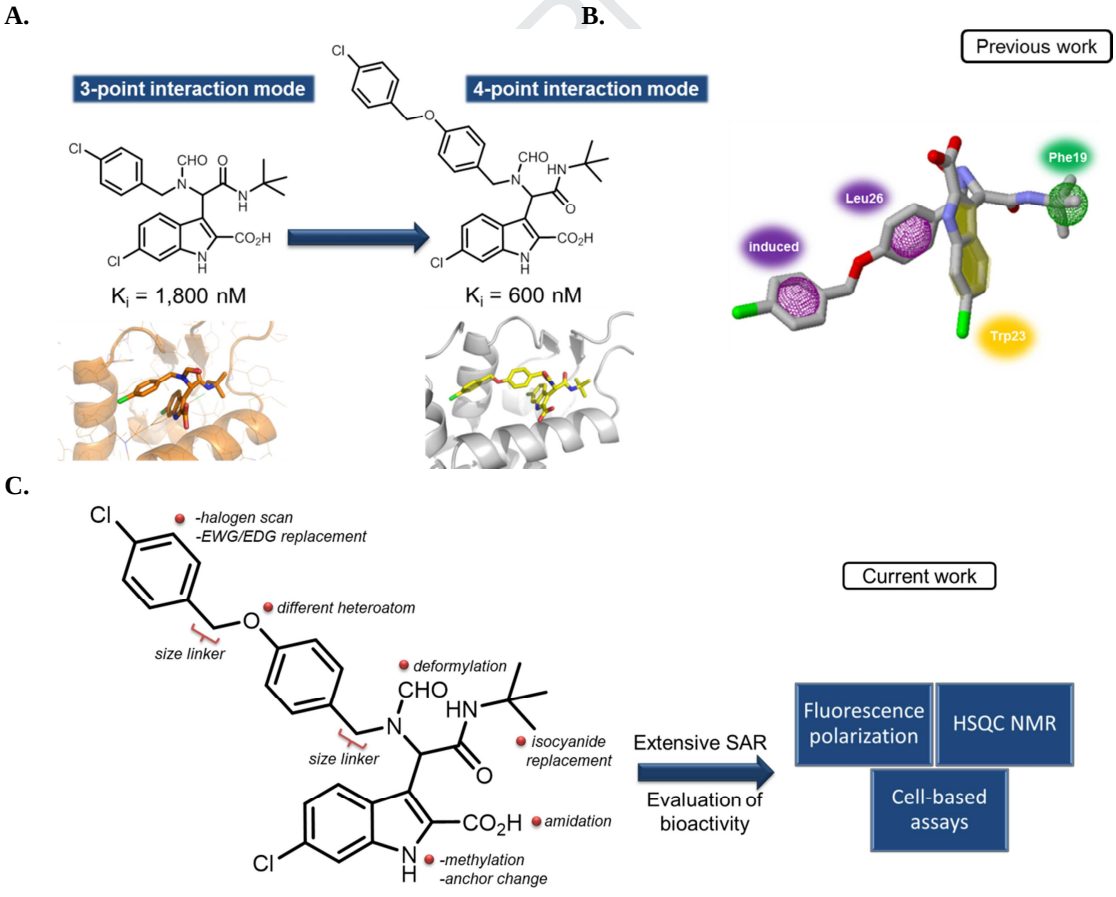


Figure 2. (A) The transition from the 3-point to 4-point interaction point with increasing binding affinity; (B) the binding mode of the YH300; (C) SAR analysis studies evaluated with two different biorthogonal assays presented in the current manuscript.

RESULTS AND DISCUSSION

Design and synthesis

In continuation of our previous work on successfully developing potent inhibitors of the p53-MDM2/X interaction, we demonstrate an effective strategy of scaffold hopping (Figure 3).[39–44] As a design tool we used our open access pharmacophore-based virtual screening web-platform AnchorQuery™ (http://anchorquery.csb.pitt.edu),[16,45] which is a specialized pharmacophore search technology that brings interactive virtual screening of novel protein-protein inhibitors to the desktop. It leverages the concept of anchors, amino acid residues that bury a large amount of solvent accessible surface area at the protein-protein interface.[16,39,43,45] Every compound in our multi-component reaction (MCR) accessible virtual library contains an anchor analog, a functional group that is a chemical mimic of a specific amino acid. AnchorQuery™ pharmacophore queries always include an anchor feature in addition to the standard hydrophobic, ionic and hydrogen bond donors. The utilization of convergent MCR chemistry allowed us for a rapid SAR analysis and discovery of potent compounds that could eventually serve as an excellent starting point for further development of pharmaceutically relevant p53-MDM2 interaction inhibitors.

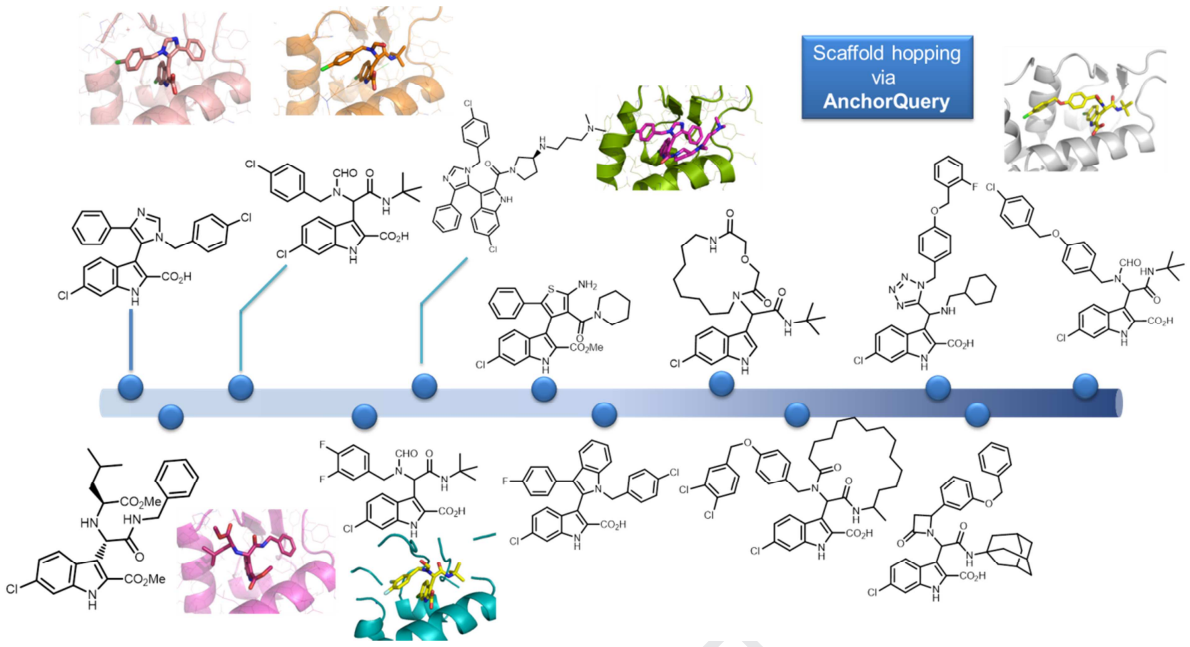
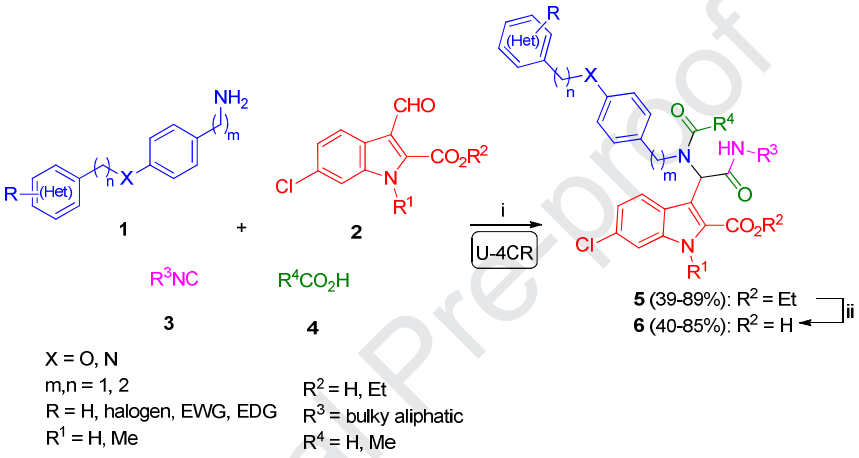


Figure 3. Potent inhibitors of p53-MDM2/X interaction discovered by our group; Scaffold hopping employing different MCR scaffolds via AnchorQuery™. The light blue color on the axis corresponds to the design and synthesis of inhibitors based on the 3-point interaction mode, whereas the dark blue on the 4-point.

We examined the possibility of a halogen bond, therefore we employed a variety of electron donating and withdrawing substituents and we utilized different heteroatoms or linkers' size. In addition, in order to verify our hypothesis and the co-crystal structure of YH300 (PDB ID 4MDN), we modified the anchoring indole moiety, we replaced the formyl with acetyl group and we deformylated our adducts to examine how the binding affinity would be affected. We also probed the Phe19 pocket by replacing the *tert*-butyl moiety with other bulky, aliphatic groups. Finally, we performed hydrolysis and amidation reactions of the ester group (Figure 2,C). Hence, an equimolar mixture of suitable substituted benzylamines **1**, the 6-chloro-indole carboxaldehyde **2**, the corresponding isocyanides **3** and carboxylic acids **4**, was stirred in MeOH at rt for 48 h yielding the Ugi-4CR adducts **5**. The importance of the carboxylate moiety was taken into account, as found in previous MDM2 binders, since -CO_2H group contributes to the formation of

several hydrogen bonds with water molecules interacting with MDM2.[37,39,46] For that reason, the hydrolysis with LiOH in water-ethanol (1:1) of the ester group was followed, affording the targeted compounds **6** (Scheme 1).

Scheme 1. Reactions and conditions of the general synthetic strategy; i) rt, 48 h, MeOH (1 M), ii) LiOH (10.0 eq), rt, 24 h, H_2O-EtOH (1:1).



Probe of Leu26 and induced pocket

The cocrystal structure of MDM2-YH300 (PDB ID 4MDN) revealed that the large 4-chlorobenzyl phenyl ether filled the enlarged Leu26 new subpocket (induced pocket, blue color, Figure 4,A). Due to the presence of several carbonyl oxygens of a series of amino acids (Gln24, Ala21, Glu23, Pro20, Ile19, His96 and Ile99) in a range of 3.5-4.0 Å from the benzyl group, we suspected the possibility of involving halogen bonding (Figure 4,B).[47] Thus, we started our structure-activity relation studies by performing an exhaustive halogen scanning around the benzyloxy ring.

A. **B.**

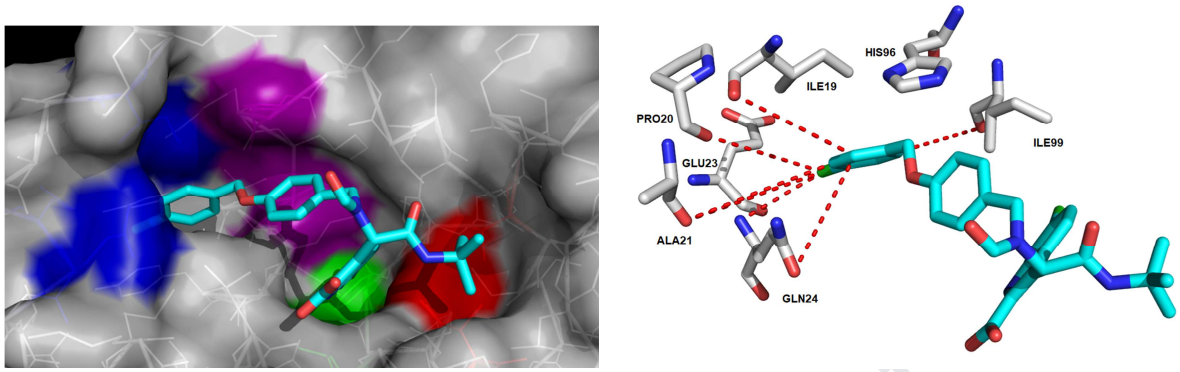
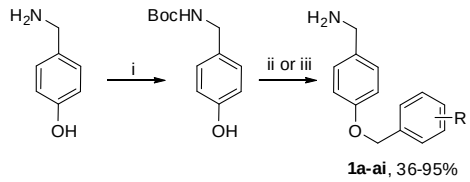


Figure 4. (A) A close-up view of the YH300 with the 4 subpockets visible; (B) Halogen bonding to **6** (red dotted lines) and surrounding carbonyl oxygens of amino acids in a 3.5-4.0 Å range.

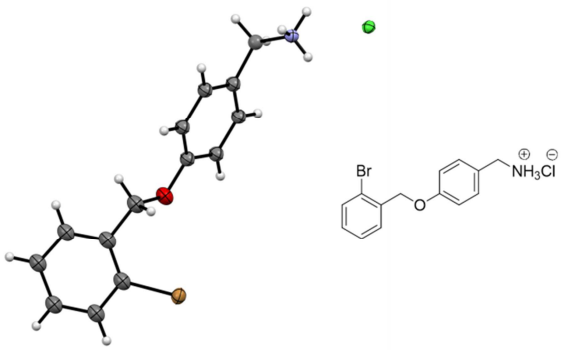
To explore this Leu26 and its induced subpocket, we utilized the elongated halogen-substituted benzylamines **1a-t** which were easily accessible either via Williamson or Mitsunobu reaction from the corresponding 4-hydroxybenzylamine (Scheme 2,A). For easier handling and purification, the corresponding elongated benzylamines were used as hydrochloric or triflic salts in the next steps (Scheme 2,A,B). The aldehyde **2** was synthesized from the 6-chloro-indole derivative using the Vilsmeier-Haack formylation reaction.[41–43]

Scheme 2. (A) *Reactions and conditions*: i) $(Boc)_2O$, $NaHCO_3$, rt, MeOH, or $(Boc)_2O$, rt, H_2O, ii) RCH_2X, K_2CO_3, reflux, MeCN or iii) RCH_2OH, DIAD or DEAD, PPh_3, 0 ^oC-rt, THF; (B) Molecular geometry observed in the crystal structures of **1m** (CCDC 1848075), showing the atom labeling scheme. Displacement ellipsoids of non-hydrogen atoms are drawn at the 30% probability level. H atoms are presented as small spheres with an arbitrary radius; (C) *Reactions and conditions*: i) NaH, rt, DMF; ii) $LiAlH_4$, reflux, THF; (D) Molecular geometry observed in the crystal structures of **1sa** (CCDC 1848076), showing the atom labeling scheme. Displacement ellipsoids of non-hydrogen atoms are drawn at the 30% probability level. H atoms are presented as small spheres with an arbitrary radius

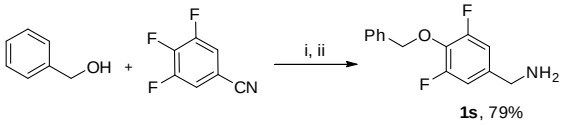
A.



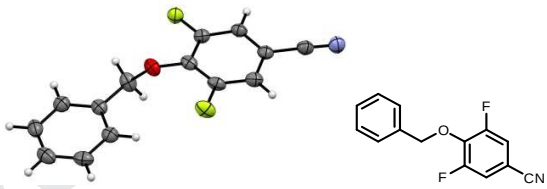
B.



C.

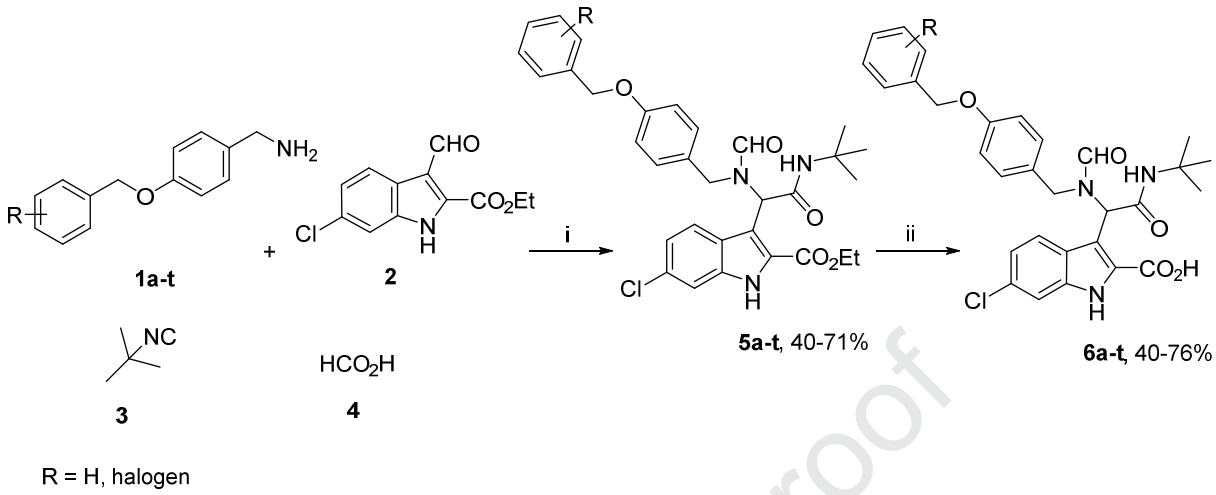


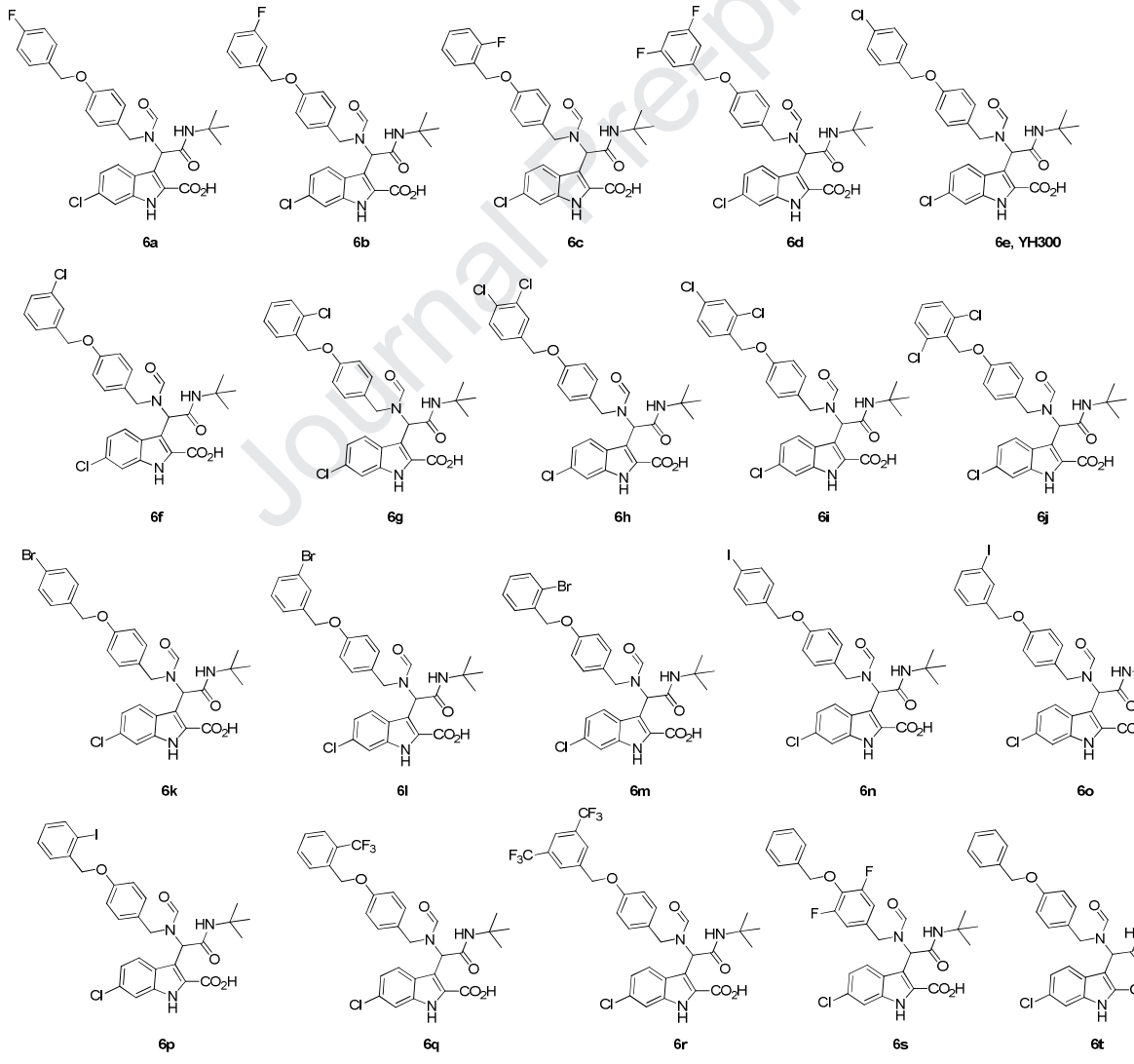
D.



Consequently, the U-4CR of the benzylamines **1a-t**, 6-chloro-indole carboxaldehyde **2**, *tert*-butyl isocyanide and formic acid afforded compounds **5a-t** which were hydrolyzed towards the acids **6a-t** (Scheme 3). We synthesized not only the corresponding *para*-substituted fluoro, bromo and iodo-based derivatives (e.g. **6a**, **6k**, **6n**) but also on all the other positions, including few disubstituted halogen compounds (e.g. **6d**, **6h**, **6j**). In addition, we enriched our SARs studies by employing -CF_3 substituted derivatives (**6r**) and suitably halogen-substituted derivatives on the phenoxy group (Leu26 pocket, Figure 4, magenta color, Scheme 2,C) as indicated by the crystal structure analysis (Figure 4,B e.g. **6s**). We also synthesized the non-halogen substituted derivative **5t** which served as a "control" compound in order to compare the binding affinities.

Scheme 3. *Reactions and conditions*: i) rt, 48 h, MeOH (1 M), ii) LiOH (10.0 eq), rt, 24 h, H_2O-EtOH (1:1)





Two complementary assays based on independent physicochemical principles, HSQC NMR and fluorescence polarization (FP) were used to exclude false positive hits. FP assay was employed to determine the inhibitory affinities (K_i) of the derivatives against MDM2/X as previously described.[48] Halogen bonding has been known for decades, but in drug design the utility of these interactions is rather a random finding than rational. The halogen bond can be formed between a halogen and any accessible Lewis base in the binding pocket, where in most of the cases the most prominent Lewis base is the backbone carbonyl oxygen of an amino acid. Side chain oxygens of serine, threonine, tyrosine, aspartate, glutamate, asparagine and glutamine and nitrogen of histidine have been also occasionally engaged in halogen bonding.

The FP results from the halogen dancing exercise (Table 1) indicate the possibility of halogen bond existence. It can be seen that the binding affinity increases from the *p*-substituted fluorine derivative to the corresponding iodine i.e. K_i = 1.02 μM, 0.60 μM, 0.39 μM and 0.32 μM, respectively (entries 1, 5, 11, 16). The same correlation applies to the *o*-substituted halogens (*o*-F<*o*-Cl<*o*-Br<*o*-I), giving even higher binding affinities (K_i = 0.74 μM, 0.36 μM, 0.07 μM and 0.05 μM, respectively (entries 3, 7, 13, 18)). Clearly, these trends show a size-dependent activity, driven by the σ-hole, relationship being in accordance with literature.[47,49]

In *m*-substituted derivatives this trend, by the exception of **6o** (entry 17, K_i = 0.43 μM), can also be identified. Thus, the affinity of *m*-F derivative (**6b**) is similar to *m*-Cl (**6f**, entries 2 and 6), which is increased by the *m*-disubstituted (**6d**, entry 4) and *m*-Br (**6l**, entry 12), i.e. K_i = 0.6 μM, 0.42 μM and 0.30 μM, respectively. Moreover, the substitution of R = H (**6t**, entry 22, K_i = 0.76 μM) by heavier halogens (Br, Cl, I) both in para, meta and ortho position enhances the halogen bond as expected and increases the affinity.

The combination of other disubstituted chloro derivatives as the meta and para substituted (**6h**, entry 8) or ortho and para substituted (**6i**, entry 9) gave increased binding affinities comparing with the corresponding para (**6e**, entry 5) and meta (**6f**, entry 6) monosubstituted derivatives, i.e K_i = 0.26 μM and 0.37 μM compared to 0.60 μM and 0.63 μM, respectively. The di-ortho substituted chloro derivative (**6j**, entry 10) found to be rather inactive (K_i = 4.7 μM).

Other halogenated ligands as the $–CF_3$ moieties were also employed (entries 19 and 20) showing affinities of 0.24 μM and 1.6 μM for the mono ortho-substituted and di meta-substituted derivative, respectively. Again, the halogenated substituent on ortho position gave the highest binding affinity similar to ortho-substituted chloro derivative. The difluoro substituted on the phenoxy group derivative (**6s**) resulted in loss of the activity (entry 21). Figure 5 shows a binding affinity plot in comparison with the σ-hole of the used halogen (see also SI, Figure S4).

The ortho-substituted bromo (**6m**) and iodo derivatives (**6p**) have shown the strongest inhibition with K_i of 70 nM and 34 nM, respectively. It has also to be stated that the strength of halogen bonds is really dependent on the geometry of the interaction. Sometimes, stronger type of interactions or networks of synergistic interactions may displace the halogen from its favored orientation in terms of distance (between the halogen and Lewis base), σ-hole angle (between the covalent bond of the halogen and the halogen bond with the Lewis base) and the spatial orientation (torsion angle based on the bonding situation of the Lewis base).[47]

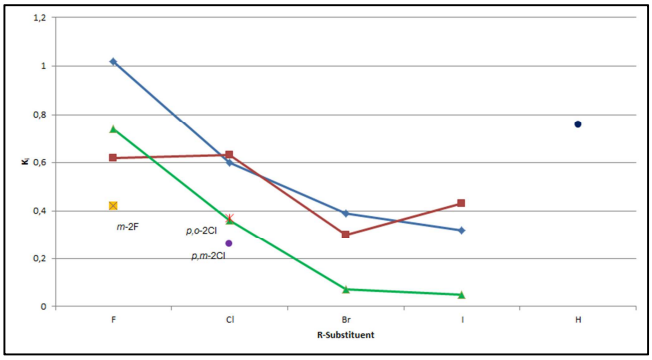
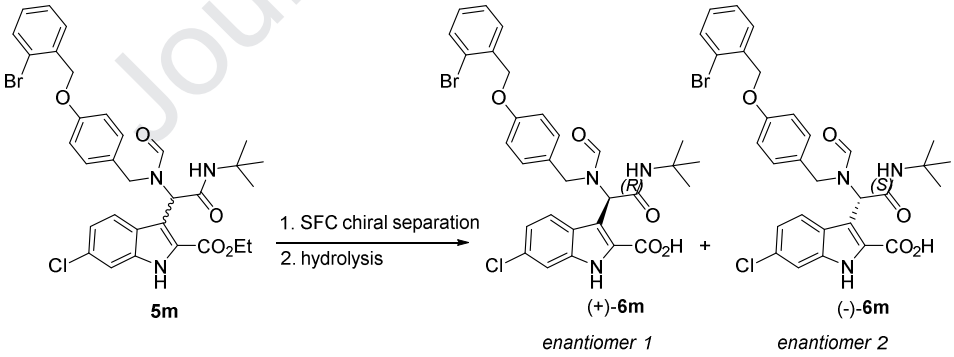


Figure 5. Binding affinity dependence on the σ-hole of the halogen; The trend of F<Cl<Br<I is observed in the para- (blue), meta- (red) and ortho-substitution (green). The blue spot depicts compound **6t** (R = H) whereas other disubstituted compounds are also depicted. Ortho-substitution with heavy halogens (Br, I) gave the best binding affinities.

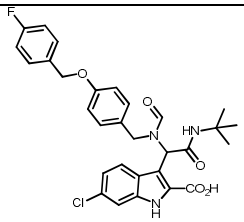
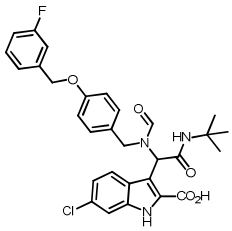
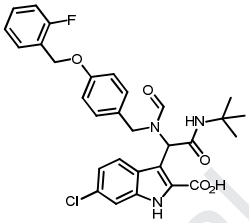
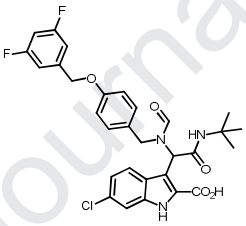
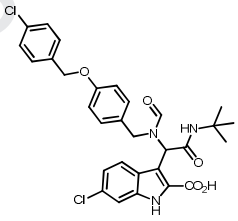
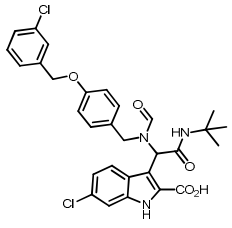
Compounds **5a-t** (ester form) were found to be rather inactive in accordance with our previous observations.[41–44] Due to both the plausible metabolic instability and the relatively higher molecular weight of the iodo compound **6p**, compound **6m** was selected to be further investigated with the two enantiomers separated. Indeed, the compound **5m** (ester form) was subjected to chiral separation providing compound (+)-**5m** (*enantiomer 1*) and (-)-**5m** (*enantiomer 2*), which were subsequently hydrolyzed to the corresponding acids.

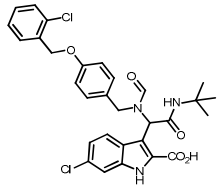
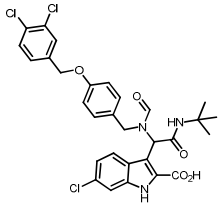
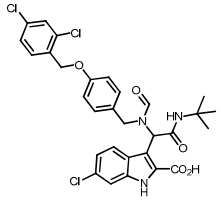
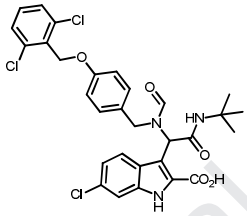
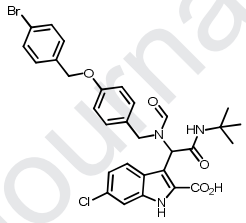
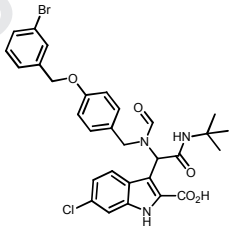
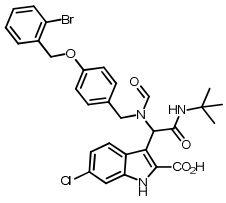
Scheme 4. *Reactions and conditions*: i) chiral separation by supercritical fluid chromatography, ii) LiOH (10.0 eq), rt, 24 h, H_2O-EtOH (1:1). Enantiomer 1 was eluted first by the chiral column and enantiomer 2 followed (see Supporting information, SI), stereochemistry is randomly assigned.

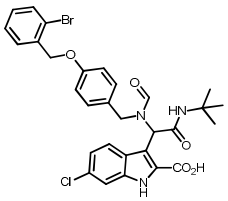
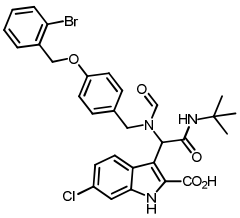
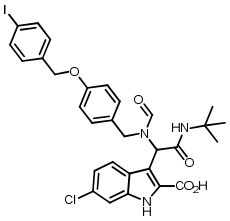
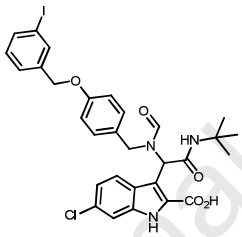
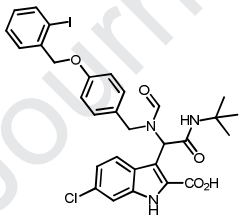
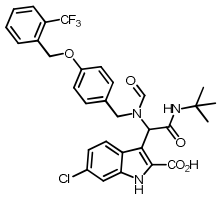
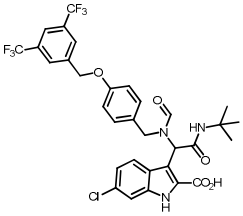


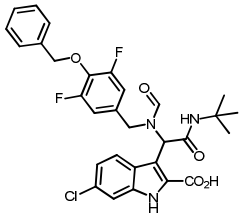
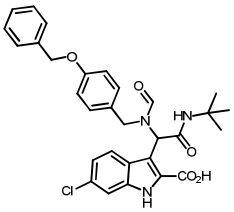
As expected, one enantiomer showed increased binding affinity comparing with the racemic mixture (K_i = 0.07 μM) when it was tested by the FP assay. The enantiomer 1 ((+)-**6m**) demonstrated a K_i of 0.140 μM and the enantiomer 2 ((-)-**6m**) a K_i of 34 nM (entries 14 and 15).

Table 1. Activities of Ugi-4CR based inhibitors of p53-MDM2/X interaction.

Entry	Code	Structure	Yield of compound 5 (%)	Yield of compound 6 (%)	K_i [μM] for MDM2[a]
1	**6a**		70	76	1.02
2	**6b**		71	68	0.62 (6.30)
3	**6c**		68	71	0.74
4	**6d**		59	68	0.42 (6.03)
5	**6e** (YH300)		49	75	0.60
6	**6f**		62	50	0.63 (6.21)

7	**6g**		69	60	0.36 (4.67)
8	**6h**		71	65	0.26 (4.73)
9	**6i**		68	59	0.37 (7.05)
10	**6j**		45	58	4.67
11	**6k**		53	67	0.39 (6.01)
12	**6l**		70	53	0.30 (3.63)
13	**6m**		70	49	0.07 (5.45)

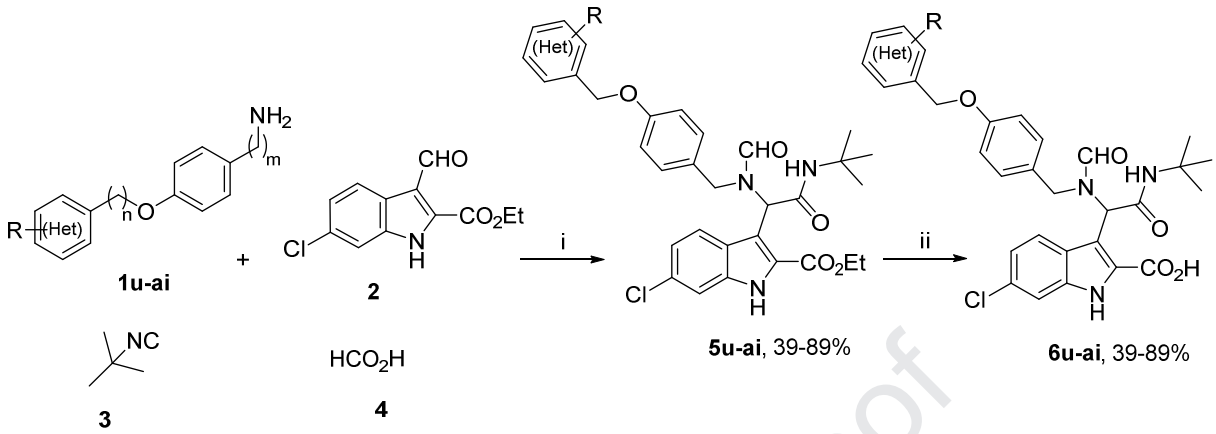
14	(+)-**6m**		-		0.14 *Enantiomer 1*
15	(-)-**6m** (DN285)		-		0.03 *Enantiomer 2*
16	**6n**		46	50	0.32 (4.74)
17	**6o**		45	40	0.43 (4.74)
18	**6p**		40	50	0.05 (6.39)
19	**6q**		65	72	0.24 (4.01)
20	**6r**		64	73	1.63

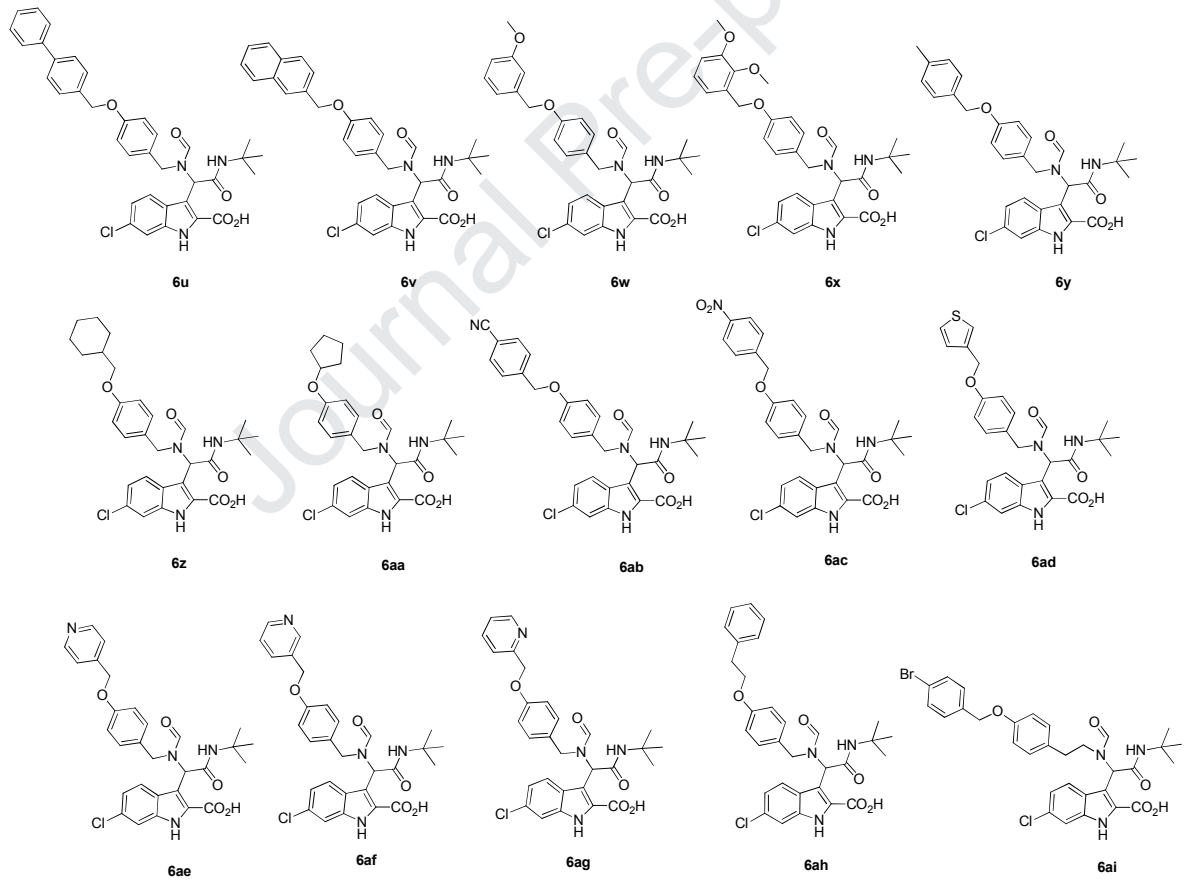
21	**6s**		65	65	11.6
22	**6t**		53	72	0.76 (5.36)

[a] Data in parentheses refers to MDMX protein whenever the compound showed any significant activity (all compounds were tested against MDM2 and MDMX). K_i values were calculated based on fluorescence polarization binding assay (see SI).

Besides the halogen scan, we synthesized derivatives with a variety of electron withdrawing and donating groups (EWG and EDG); we employed aromatic moieties as biphenyl, naphthalene, heterocycles (pyridine and thiophene derivatives), aliphatic rings (cyclohexyl, pentyl) and other donating groups as –Me or –OMe. Furthermore, we examined strong withdrawing groups as –CN or $–NO_2$. Finally, we evaluated the size of the linker by adjusting the length of the benzyl phenyl ether group (Scheme 5).

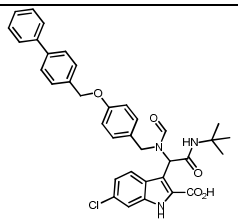
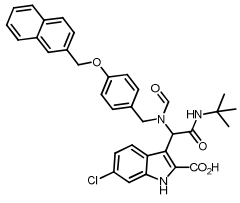
Scheme 5. *Reactions and conditions*: i) rt, 48 h, MeOH (1 M), ii) LiOH (10.0 eq), rt, 24 h, H_2O-EtOH (1:1).

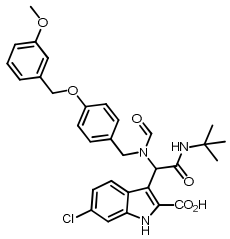
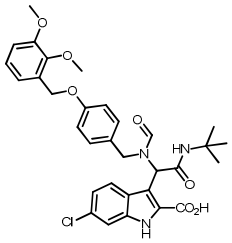
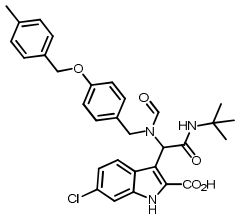
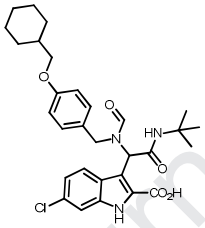
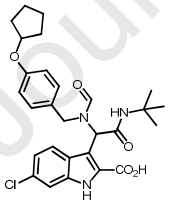
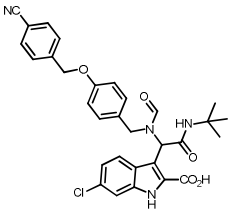
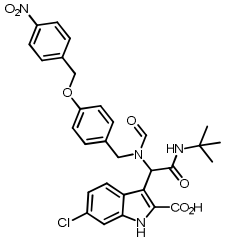


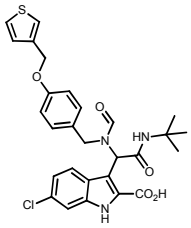
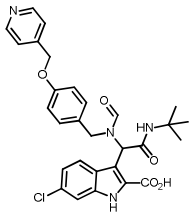
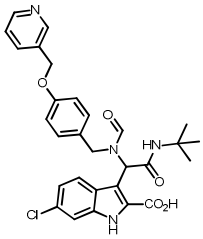
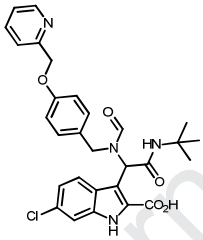
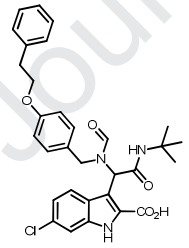
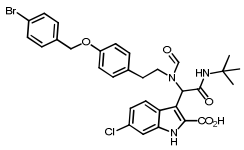


Extending towards the 4th pharmacophore point with biphenyl or naphthalene substituents (**6u,v**, entries 1 and 2, Table 2), resulted also in relatively good binders with K_i of 0.57 μM and 0.42 μM, respectively. Similar results were also obtained with EDG as 3-methoxy (**6w**, entry 3) or 2,3-dimethoxy substituents (**6x**, entry 4), giving K_i of 0.50 μM and 0.52 μM, respectively. Aliphatic substituents as cyclohexyl or cyclopentyl and strong EWG as 4-cyano or 4-nitro resulted in an actual loss of activity (entries 6-9). Replacement of the benzylic phenyl group with heterocycles as 3-thiophene (entry 10) and pyridine moieties (entries 11-13) abolished the activity or did not improve the affinity. It seems that the halogen substitution is ideal to target the fourth pharmacophore point. Next, we wanted to examine the size of the linkers; thus we added one more methylene on the benzyloxy phenyl group yielding compound **6ah** (entry 14). Indeed, the affinity was increased with a K_i of 0.26 μM compared with compound **6t** (K_i = 0.76 μM). However, this was not the case when we increased by one methylene the linker next to the phenol moiety, resulting compound **6ai** (entry 15, K_i = 4 μM) with loss of activity in comparison with compound **6k** (K_i = 0.39 μM).

Table 2. Activities of Ugi-4CR based inhibitors of p53-MDM2/X interaction.

Entry	Code	Structure	Yield of compound 5 (%)	Yield of compound 6 (%)	K_i [μM] for MDM2[a]
1	**6u**		54	55	0.57 (3.96)
2	**6v**		65	65	0.42 (5.78)

3	**6w**		70	70	0.50 (5.74)
4	**6x**		71	71	0.52
5	**6y**		39	39	0.72
6	**6z**		65	65	5.28
7	**6aa**		89	89	1.68
8	**6ab**		41	41	2.24
9	**6ac**		85	85	N/A

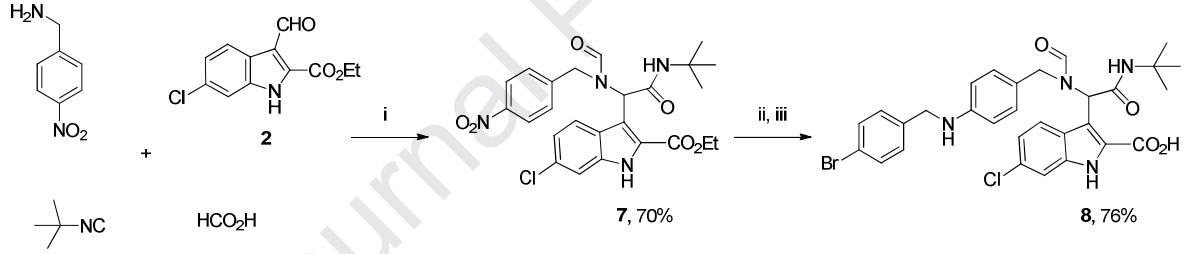
10	**6ad**		61	60	N/A *(the ester form **5ad** was found to be active, K_i = 3.68 μM)*
11	**6ae**		41	41	11.9
12	**6af**		50	50	N/A
13	**6ag**		50	50	2.54
14	**6ah**		57	49	0.26
15	**6ai**		51	55	4.23

[a] Data in parentheses refers to MDMX protein whenever the compound showed any significant activity (all compounds were tested against MDM2 and MDMX). N/A - no activity against MDM2 protein. K_i values were calculated based on fluorescence polarization binding assay (see SI).

Replacement of oxygen as heteroatom linker

In continuation of our exploration of the Leu26 and the induced subpocket, we replaced the oxygen-linker to a nitrogen (Scheme 6); A -NH in that position, as hydrogen donor, could be beneficial. We performed an U-4CR with the 4-nitrobenzylamine, followed by an *in situ* reductive amination yielding, after hydrolysis of the ester group, compound **8**. However, the replacement of the oxygen linker with the hydrogen bond donor -NH resulted in loss of activity (SI, entry 39, K_i = 1.9 μM compared with compound **6k**, K_i = 0.39 μM). Moreover, compound **8** while in solution, was found to be susceptible to degradation.

Scheme 6. *Reactions and conditions*: i) rt, 48 h, MeOH (1.0 M), ii) Zn/CH_3CO_2H, 4-bromobenzaldehyde, rt, MeOH iii) LiOH (10.0 eq), rt, 24 h, H_2O-EtOH (1:1).



Probe of Trp23 (change in anchor)

Initially, indole fragment was taken as starting point to mimic tryptophan residue, where an important hydrogen bond was observed. The starting point for our antagonist discoveries was the anchoring side chain of tryptophan embedded in a deep hydrophobic pocket formed by the residues Leu57, Phe86 and Ile99 using ANCHOR.QUERY.[37,39,50,51] Indeed, the -NH group of the 6-chloroindole group participates in a hydrogen bond with the carbonyl oxygen of Leu54 and the indole scaffold assumes an orientation almost identical to the Trp side chain in the native p53−MDM2 complex, while the chlorine atom stabilizes the interaction at the bottom of the

hydrophobic cleft. Studies by Garcia-Echeverria *et al*.[39] on a p53-derived linear octapeptide showed that a Trp23 to (6-Cl) Trp substitution gave rise to a 63-fold increase in affinity for MDM2. Accordingly, we synthesized few examples to prove our rationale (Figure 4,A, yellow color). Firstly, we synthesized a methylated on the indole –NH derivative (**9**) by using the corresponding *N*-methylated 6-chloroindole aldehyde in the Ugi reaction. Secondly, we completely switched the indole core to other chloro-substituted phenyl rings (**10**, **11**, Figure 6). The absence of the free –NH of the indole scaffold (due to the methylation), led to total loss of activity. Likewise, the replacement of the indole core with 3- or 4-chlorosubstituted phenyl groups as anchors resulted in no binding.

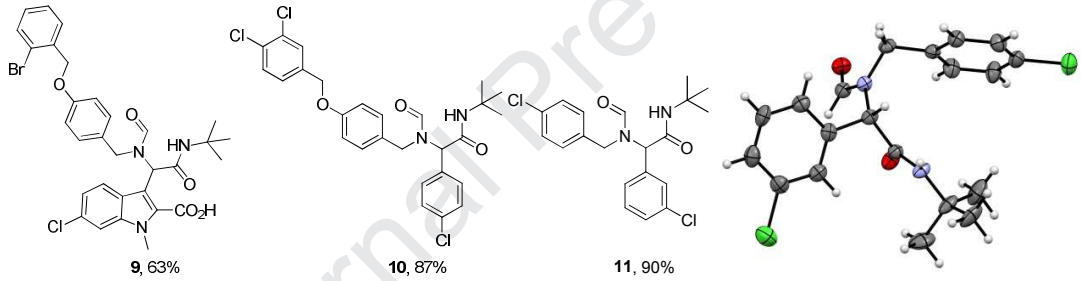


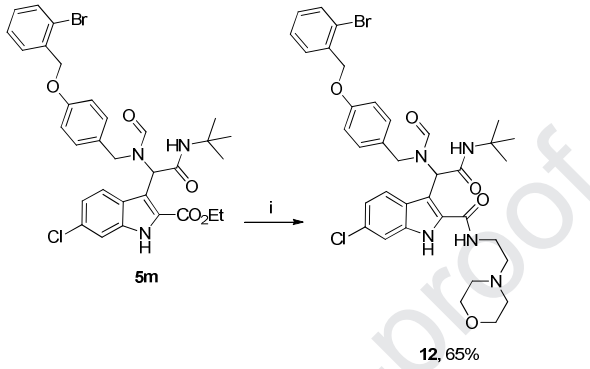
Figure 6. Probe of the subpocket Trp23; Change of the anchor with the methylated 3-indole carboxaldehyde (**9**), *p*-chlorobenazaldehyde (**10**) and *m*-chlorobenzaldehyde (**11**, CCDC 1847731).

Amidation

As it was aforementioned, the ester form of the majority of the compounds that were tested was found inactive to the contrary of the corresponding acids. To potentially improve the properties of our compounds, we also converted the ester group of the derivative **5m** into the corresponding better water soluble amide **12** with a one-step DBU-catalyzed amidation procedure (Scheme 7).[44,52] In our previous studies, amidation of the indole-2-carboxylate

offered improved water solubility.[51] However, the corresponding amidation with the morpholino moiety resulted in loss of activity (8 μM).

Scheme 7. *Reactions and conditions***:** (i) 2-Morpholinoethylamine, DBU, reflux overnight, THF.



Probe of Phe19

The cocrystal structure of YH300 revealed that the Phe19 subpocket is occupied by the *tert*-butyl group with van der Waals contacts with Ile61 and Val93 (Figure 7). By close inspection of the crystal structure, it seems that a bulky aliphatic group is necessary to address all these hydrophobic interactions (Figure 4,A, red color). Therefore, we probed this particular subpocket by employing bulky, aliphatic isocyanides as 1- and 2-adamantyl moieties and camphor (exo-endo mixture) (Figure 7). These isocyanides were prepared by the classical dehydration of the corresponding formamide using $POCl_3$.[53,54]

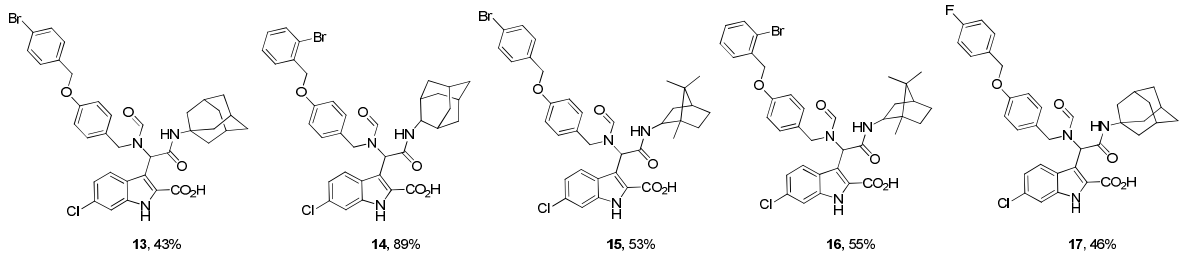
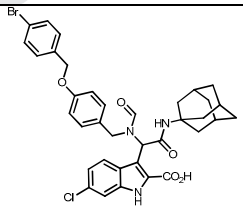
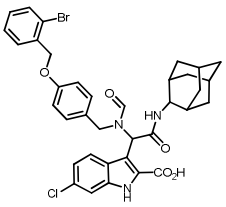
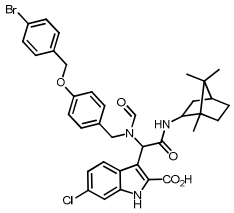
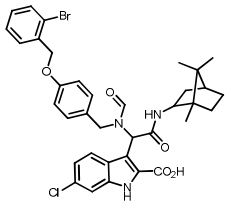
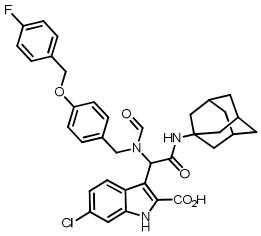


Figure 7. Probe of the subpocket Phe19; Utilization of bulky, aliphatic isocyanides.

The replacement of *tert*-butyl group with 1-adamantyl resulted almost in loss of activity (**13**, **17**, entries 1 and 5, Table 3) but the replacement with 2-adamantyl gave a binding affinity of 6 nM (**14**, entry 2) compared with compound **6m** (K_i = 70 nM). It seems that this bulky moiety stabilizes the extended hydrophobic region by the His73, Val93, and Lys94. Increased binding affinities were also achieved by employing the camphor moiety in compounds **15** (entry 3) and **16** (entry 4), giving K_i of 61 nM and 6 nM compared with compounds **6k** and **6m** respectively.

Table 3. Activities of Ugi-4CR based inhibitors of p53-MDM2/X interaction.

Entry	Code	Structure	Yield of ester (%)	Yield of acid (%)	K_i [μM] for MDM2[a]
1	**13**		40	43	3.44
2	**14** (DN389)		74	89	0.006 (1.68)

3	**15**		47	53	0.06 (1.55)
4	**16** (DN381)		51	55	0.006 (1.95)
5	**17**		44	46	N/A

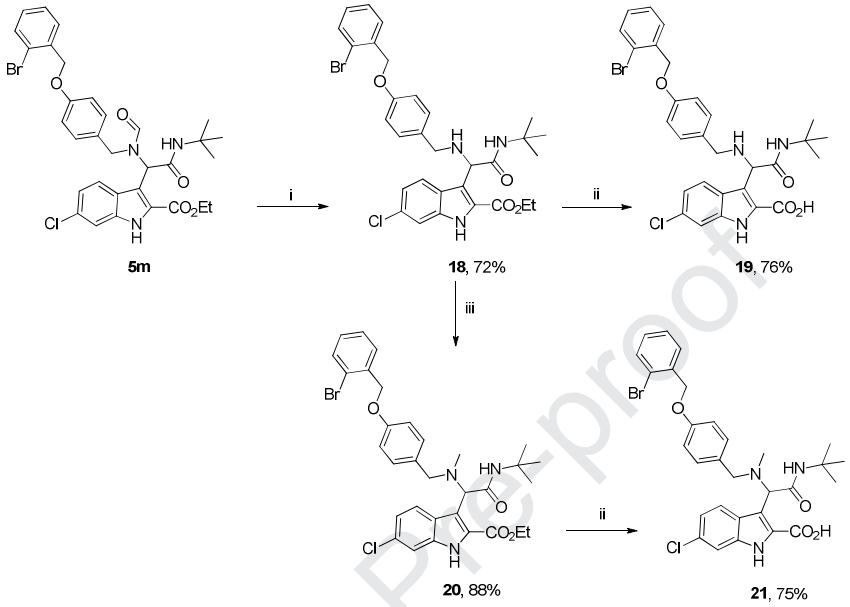
[a] Data in parentheses refers to MDMX protein whenever the compound showed any significant activity (all compounds were tested against MDM2 and MDMX). N/A - no activity against MDM2 protein. K_i values were calculated based on fluorescence polarization binding assay (see SI).

Exploitation of acid moiety/deformylation

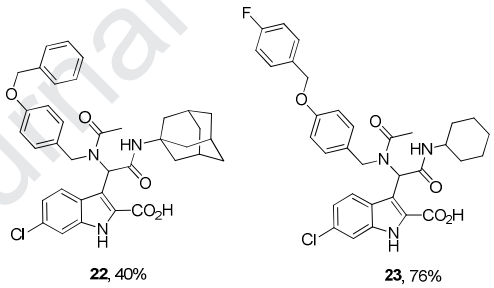
The formyl group does not participate in any sub cleft of the MDM2 and it's rather exposed to the hydrophilic part of the protein. For this reason, in order to exploit the effect of this particular group, we initially cleaved it (**18**, **19**) by treating it with HCl (5N in dioxane) and then substituted with a methyl group (**20**, **21**). We synthesized both the corresponding esters and acids (Scheme 8,A). Moreover, we exchanged the formyl to the acetyl group by simply changing the acid component in our U-4CR (**22**, **23**, Scheme 8,B).

Scheme 8. (A) *Reactions and conditions*: i) HCl (5 N in dioxane), reflux, H_2O, 1 h, ii) LiOH (10.0 eq), rt, 24 h, H_2O-EtOH (1:1), iii) MeI, K_2CO_3, THF, rt, overnight; (B) Replacement of the formyl group with acetyl

A.



B.



Deformylation, leaving a free –NH group, resulted in decrease of the affinity (K_i = 1.85 μM, SI, entry 50). In addition, replacement of the formyl group either by a methyl or acetyl group resulted in loss of activity. Although the formyl group does not seem to participate in the binding mode of the current small molecules, it is exposed to the hydrophilic surface of the pocket and stabilizes better the interaction of the small molecule and MDM2.

Miscellaneous inhibitors

Completing our SAR studies, we tried some miscellaneous ideas on using a shorter benzylamine or employing a moiety that would improve the ADMET properties, however they did not result in the increase of the affinity (**24-26**, SI, entries 54-56).

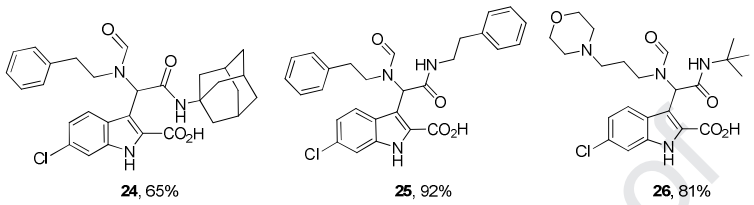


Figure 8. Miscellaneous SAR studies on elongating the scaffold without heteroatom

^{1}H-^{15}N HSQC NMR studies

We confirmed the binding properties for selected compounds using the ^{1}H-^{15}N HSQC NMR titration experiment as a second orthogonal assay to FP. The method is based on monitoring the protein amide backbone chemical shift changes.[55–57] Perturbations of cross-peak signals due to formation of the complex between an inhibitor and the target protein can be divided into three cases: fast chemical exchange presented as the cross-peak movement, an intermediate chemical exchange presented as the signal broadening and disappearing and slow chemical exchange (tight-binding) presented as signal doubling (splitting).[58,59] As expected, all tested compounds, as acids, indeed were binding to MDM2 with slow chemical exchange present at several cross-peaks (Figure 9, see also SI). Since all cross peaks in the MDM2 spectrum are assigned,[60] we can check whether the inhibitor interacts with the residues present inside the p53-binding pocket of MDM2. Analyzing the pattern of cross-peaks which undergoes slow chemical exchange plotted on to MDM2 surface it is clear that the tightest binding interaction with MDM2 amino acids was seen for the compound with the 2-bromobenzyl (**6m**, Figure 9A)

and 2,3-dichlorobenzyl (**6h**, Figure 9C) groups, which was illustrated by several residues that form the binding pocket: Leu82, Gly58 and Tyr60. Noticeably, exchanging the *tert*-butyl group of **6m** with the 2-adamantyl substituent (**14**, Figure 9B) caused the decrease of binding of several amino-acids near the binding pocket (Val93, Lys94, His73), which could be caused by lower solubility in water medium. Also, exchanging the 2-bromobenzyl group with the 2-iodobenzyl (**6p,** Figure 9D) resulted in similar changes. It is worth mentioning that the compound without any halogen atom (SI, Figure S3) showed the least tight-binding interactions which suggest that the presence of halogen atom is especially important for the binding properties. Nevertheless all the tested compounds showed at least one "split" residue within the p53-binding pocket (usually Leu82), which confirmed the excellent binding properties of our scaffold in general. Also, in all cases there are residues that lie on the other side of MDM2 and undergo slow chemical exchange. This phenomenon is caused not by direct interaction with the inhibitor but by conformational changes within the protein (Gly83, Ser92, Val88, Thr49, Leu37 etc).

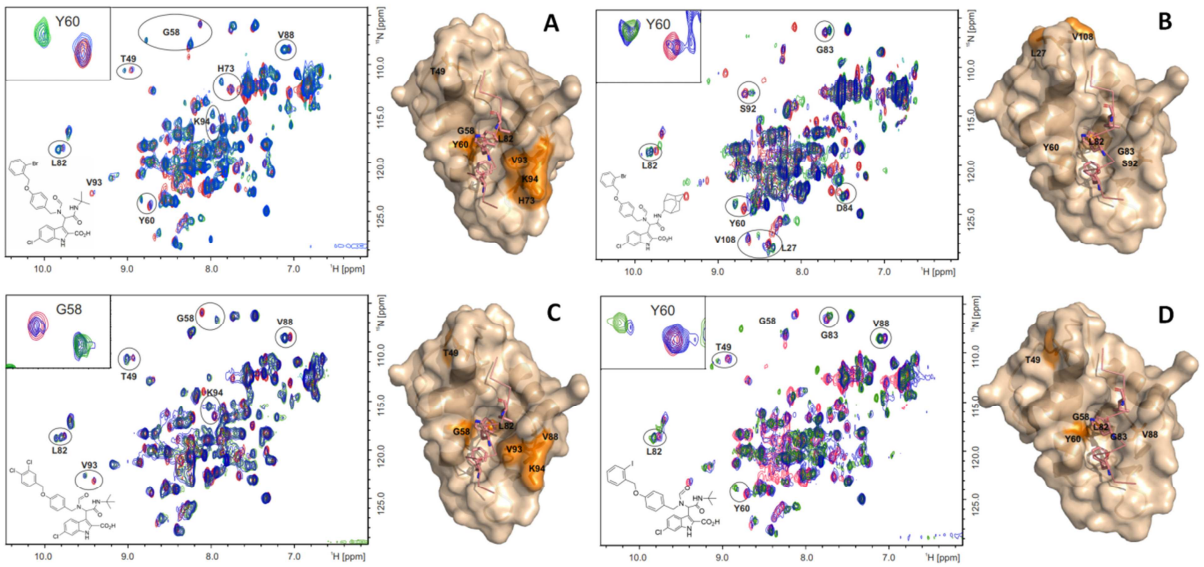


Figure 9. Titration HSQC-based experiment of the ^{15}N-labeled MDM2 with selected inhibitors. All presented inhibitors show cross-peaks splitting at 0.5-1 inhibitor/protein ratio, respectively - indicating slow chemical exchange between the free protein and the complex inhibitor-protein. Cross-peaks which undergoes splitting are marked on the MDM2 surface (PDB: Y1CR) showing an interaction of the inhibitors with the p53-binding pocket. Selected residues cross-peaks which undergo splitting were enlarged. A. **6m**: reference MDM2 - red; **6m**-MDM2 0.5:1 – blue; over titrated MDM2 – green. B. **14**: reference MDM2 - red; **14**-MDM2 0.5:1 – blue; over titrated MDM2 – green. C. **6h**: reference MDM2 - red; **6h**-MDM2 0.5:1 – blue; over titrated MDM2 – green. D. **6p**: reference MDM2 - red; **6p**-MDM2 0.5:1 – blue; over titrated MDM2 – green.

Cell-based studies

To test the biological activity of MDM2 antagonists, the compounds were subjected to cell-based assays using p53-wild-type and p53-deleted cells.[36] The specific targeting of p53 in living cells was verified by western blot analysis of the expression of MDM2 and p21 proteins, which are the products of well-known p53-regulated genes, that provide a negative-feedback regulatory loop (MDM2)[61] or execute the cell cycle arrest program upon p53 induction (p21).[62] Nutlin-3a was used in the experiment as a positive control, showing a potent induction of MDM2 and p21 in the two p53-wild-type cell lines used, i.e. SJSA-1 and U-2 OS (Figure 10,A). In the experiment, multiple molecules were examined, but only a small subgroup presented the ability to induce the expression of MDM2 and p21 (Figure 10,A). Importantly, this subgroup of the library consisted of halogen substituted derivatives as *o*-bromo compounds, proving our rationale and SAR studies. These were (-)-**6m** (DN285), **16** (DN381) and **14** (DN389), with the two latter presenting the strongest biological activities. Of note, the three active compounds presented also the highest activities in the FP assay (Table 1 and Table 3).

The anti-cancer potential of the compounds was measured by MTT cell survival assay and propidium iodide/annexin V double staining of apoptotic cells. The three compounds, (-)-**6m**, **16**

and **14**, presented selective anti-cancer activity towards p53-wild-type U-2 OS cells over the p53-deleted SAOS-2 cells (Figure 10,B). Additionally, the compounds induced apoptosis in p53-wild-type HCT 116 cells, comparable to nutlin-3a, as shown for (-)-**6m** compound (Figure 10,C and SI). Altogether, the results are consistent with *in vitro* assays and prove the p53-specific anti-cancer activity towards p53-wild-type cancer cells.

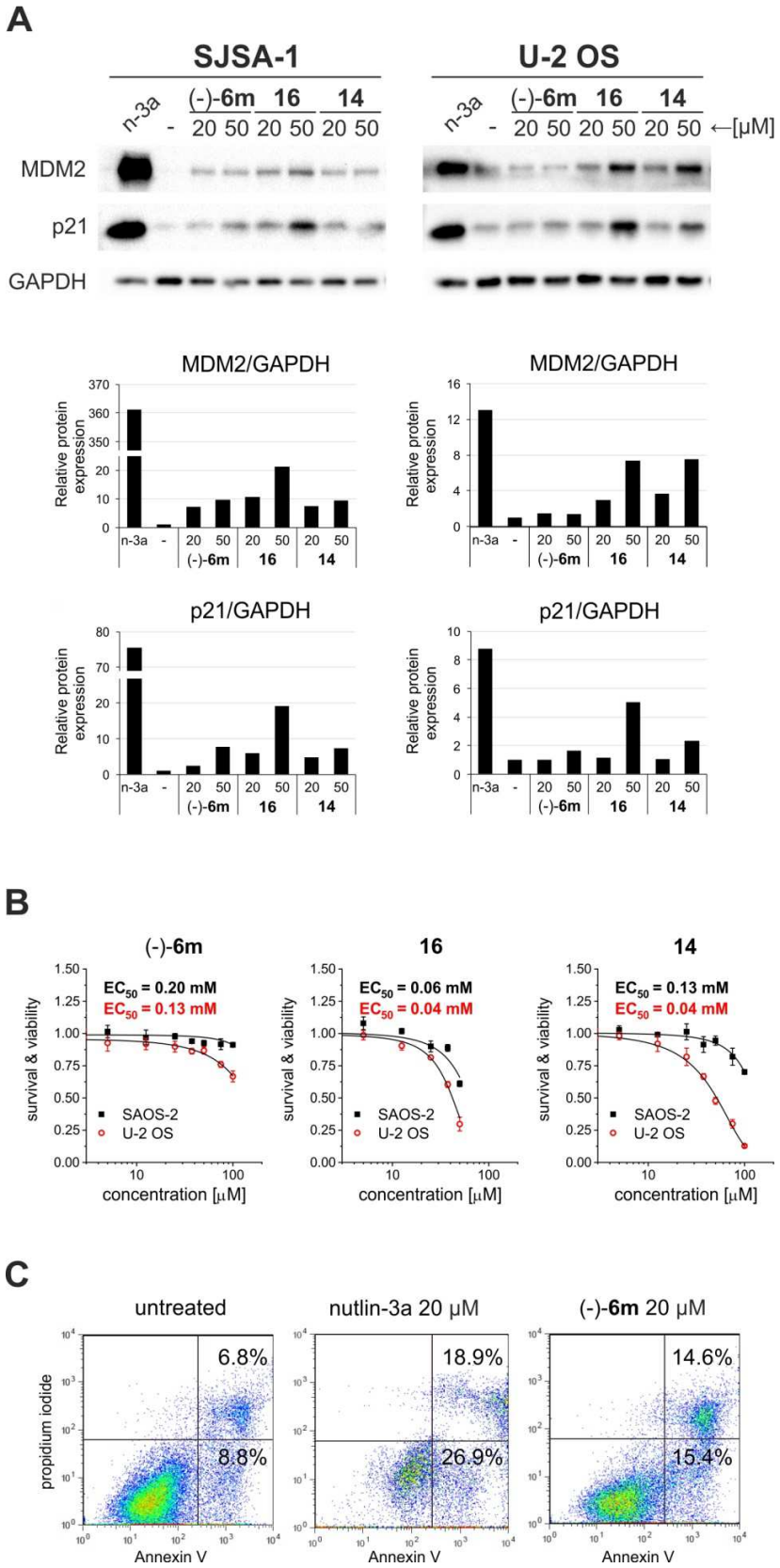

A
SJSA-1
U-2 OS
n-3a
(-)-6m
16
14
20 50 20 50 20 50
←[μM]
MDM2
p21
GAPDH
MDM2/GAPDH
p21/GAPDH
Relative protein expression
B
(-)-6m
16
14
EC50 = 0.20 mM
EC50 = 0.13 mM
EC50 = 0.06 mM
EC50 = 0.04 mM
EC50 = 0.13 mM
EC50 = 0.04 mM
survival & viability
SAOS-2
U-2 OS
concentration [μM]
C
untreated
nutlin-3a 20 μM
(-)-6m 20 μM
6.8%
8.8%
18.9%
26.9%
14.6%
15.4%
propidium iodide
Annexin V

Figure 10. The biological activity of **(-)-6m** (DN285), **16** (DN381) and **14** (DN389) compounds. (A) Western blot analysis of the expression of MDM2 and p21 in p53-wild-type SJSA-1 and U-2 OS cells following the 24 hours treatment with the indicated compounds. DMSO-treated cells served as a vehicle control (marked with "-"), and 5 µM nutlin-3a (indicated as n-3a) was used as a positive control of the treatment. The plots represent densitometry analysis of MDM2 or p21 expression, normalized to GAPDH. The protein expression was normalized to DMSO-treated control. (B) To test cell viability, MTT assay was performed. U-2 OS (p53-wild-type) and SAOS-2 (p53-deleted) cells were treated with the indicated concentrations of the compounds **(-)-6m**, **16** and **14** and cultured for 5 days. The graph shows cell viability normalized to DMSO-treated control cells. (C) The analysis of apoptosis was performed with FITC-Annexin V / propidium iodide double staining. HCT 116 cells were treated with nutlin-3a or **(-)-6m** for 72 hours followed by flow cytometry analysis of apoptosis induction. The percentages of Annexin V-positive cells, both PI-positive and PI-negative, are given on the plots.

CONCLUSIONS

Here we describe extensive SAR of a series of p53-MDM2 antagonists, performed with the use of the Ugi backbone and based on our recently described compound YH300 (**6e**). This series is able to order the otherwise disordered N-terminus (residues 19-23) of MDM2. The compounds were screened by FP and 2D NMR and were shown to be strong binders to MDM2. For the key compounds, separation of the enantiomers was performed. In addition, p53-specific anti-cancer activity towards p53-wild-type cancer cells was observed. In future, we are planning to optimize the pharmacokinetic profile of the best hits in order to proceed to a xenograft model.

EXPERIMENTAL SECTION

General procedures-materials

All the reagents and solvents were purchased from Sigma-Aldrich, AK Scientific, Fluorochem, Abcr GmbH, Acros and were used without further purification. All microwave irradiation reactions were carried out in a Biotage Initiator™ Microwave Synthesizer. Thin layer chromatography was performed on Millipore precoated silica gel plates (0.20 mm thick, particle size 25 µm). Nuclear magnetic resonance spectra were recorded on a Bruker Avance 500 or 600 spectrometers {^{1}H NMR (500 MHz; 600 MHz), ^{13}C NMR (126 MHz; 151 MHz)}. Chemical shifts for ^{1}H NMR were reported as δ values and coupling constants were in hertz (Hz). The following abbreviations were used for spin multiplicity: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, quin = quintet, dd = double of doublets, ddd = double doublet of doublets, m = multiplet. Chemical shifts for ^{13}C NMR were reported in ppm relative to the solvent peak. Flash chromatography was performed on a Reveleris® X2 Flash Chromatography, using Grace® Reveleris Silica flash cartridges (12 grams). Mass spectra were measured on a Waters Investigator Supercritical Fluid Chromatograph with a 3100 MS Detector (ESI) using a solvent system of methanol and CO_2 on a Viridis silica gel column (4.6 x 250 mm, 5 µm particle size) or Viridis 2-ethyl pyridine column (4.6 x 250 mm, 5 µm particle size). Analytical chiral SFC was performed on a Reprosil Chiral-IC column (4.6 x 250 mm, 5 µm particle size) and semi-preparative SFC was performed with stacked injector (250 µL injections) on a Reprosil Chiral-IC column (10 x 250 mm, 5 µm particle size) with 25% MeOH/CO_2 as mobile phase. High resolution mass spectra were recorded using a LTQ-Orbitrap-XL (Thermo) at a resolution of 60000@m/z400. Optical rotations were measured in MeOH on a Schmidt + Haensch polarimeter (Polartronic MH8) with a 10 cm cell (c given in g/100mL).

Protein Expression and Purification

Fragment of the N-terminal domain of human MDM2 (residues 1-118) was cloned into the pET-20 (Novagen) and expressed in E. coli strain BL21-CodonPlus(DE3)-RIL as described previously.[48] In brief, cells were cultured at 37 °C. Protein expression was induced with 1 mM IPTG at OD600 of 0.8 and cultured for additional 5 h at 37 °C. Cells were collected by centrifugation and lysed by sonication. Inclusion bodies were collected by centrifugation, washed with PBS containing 0.05% Triton-X100 and subsequently solubilized in 6 M guanidine hydrochloride in 100 mM Tris-HCl, pH 8.0, containing 1 mM EDTA and 10 mM *β*-mercaptoethanol. The protein was dialyzed against 4 M guanidine hydrochloride pH 3.5 supplemented with 10 mM *β*-mercaptoethanol. Following, the protein was refolded by dropwise addition into 10 mM Tris-HCl, pH 7.0, containing 1 mM EDTA and 10 mM *β*-mercaptoethanol and slow mixing overnight at 4 °C. Ammonium sulfate was added to the final concentration of 1.5 M and the refolded protein was recovered on Butyl Sepharose 4 Fast Flow (GE Healthcare). The protein was eluted using 100 mM Tris-HCl pH 7.2 containing 5 mM β-mercaptoethanol and further purified by gel filtration on HiLoad 16/600 Superdex75 (GE Healthcare) in 50 mM phosphate buffer pH 7.4 containing 150 mM NaCl and 5 mM DTT (FP/NMR buffer).

Fluorescence Polarization Assay

All FP measurements were performed using Tecan Infinite® 200 PRO plate reader. The assay was conducted in 50 mM NaCl, 10 mM Tris pH 8.0, 1 mM EDTA containing 5% DMSO. To determine the optimal concentration of the protein for the competition binding assay, the effective concentration of MDM2 (1-118) was each time ascertained by determining the apparent K_d towards 5'FAM-LTFEHYWAQLTS (P2, 10 nM). Competition assay was performed by

contacting serial dilutions of tested compounds with 10 nM P2 at protein concentration yielding $f_0 = 0.8$. Fluorescence polarization was determined at 485 nm excitation and 535 nm emission 15 min after mixing all assay components. All tests were performed using Corning black 96-well NBS assay plates at room temperature.

NMR Experiments

Uniform ^{15}N isotope labeling was achieved by expression of the protein in the M9 minimal media containing $^{15}NH_4Cl$ as the sole nitrogen source. Final step of purification of MDM2/X for NMR consisted of gel filtration into the NMR buffer (50 mM phosphate buffer pH 7.4 containing 150 mM NaCl, 5 mM DTT). 10% (v/v) of D_2O was added to the samples to provide lock signal. Water suppression was carried out using the WATERGATE sequence.[63] All the spectra were recorded at 300K using a Bruker Avance 600 MHz spectrometer with the Cryo-Platform. ^{1}H-^{15}N heteronuclear correlations were obtained using the fast HSQC pulse sequence.[64] Assignment of the amide groups of MDM2 was obtained after Stoll *et al.*[65]

Cell-based assays

Human osteosarcoma cell lines U-2 OS (p53-wild-type) and SAOS-2 (p53-deleted) were purchased from ECACC (Sigma Aldrich) and cultured in McCoy's 5A Medium containing L-glutamine (Lonza) and supplemented with 10% heat-inactivated fetal bovine serum (FBS, Biowest). Human osteosarcoma SJSA-1 (p53-wild-type) cell line was purchased from ATCC (LGC Standards) and cultured in RPMI-1640 Medium containing L-glutamine and supplemented with 10% heat-inactivated FBS. Human colorectal carcinoma cell line HCT 116 (p53-wild-type) was kindly provided from I. Jeremias, S. Bohlander and K. Spiekermann (Klinikum Großhadern,

Munich, Germany) and primarily purchased from DSMZ, Braunschweig, Germany. The cells were cultured in RPMI 1640 medium (PAN Biotech GmbH) containing 10% heat-inactivated FBS (GIBCO, Invitrogen; LOT 4169705K, REF 10270-106), 0.292 mg mL^{-1} L-Glutamine (GIBCO), 1 M Hepes (GIBCO), 100 units mL^{-1} penicillin (GIBCO) and 100 µg mL^{-1} streptomycin (GIBCO). The cells were cultured at 37°C and 5% CO_2 in a humidified atmosphere and tested for Mycoplasma contamination using PCR-based method.

For western blotting, the cells were seeded on 12-well transparent plates (Falcon). The next day, the cells were treated with the compounds for additional 24 hours. Protein extracts were prepared with RIPA buffer (Sigma Aldrich) supplemented with protease inhibitor cocktail (Sigma Aldrich). Western blot hybridization was performed as described before[36] using the following antibodies: rabbit monoclonal anti-p21 (1:2000, Cell Signaling, cat. no. 2947), rabbit monoclonal anti-MDM2 (1:2000, Thermo Fisher Scientific, cat. no. 700555), rabbit monoclonal anti-GAPDH antibody (1:2000, Cell Signaling, cat. no. 2118), and anti-rabbit antibody conjugated with horseradish peroxidase (1:2000, Cell Signaling, cat. no. 7074).

Cell viability was examined with MTT test, as described before.[66] In short, U-2 OS cells (500 cells per well) and SAOS-2 cells (1500 cells per well) were seeded on 96-well transparent plates (Falcon) and treated the next day with the compounds. The 1000x-concentrated compound stock solutions were first prepared in DMSO, and then added to the growth media, allowing for the constant content of DMSO between samples (0.1% DMSO). The cells were cultured for additional 5 days and thiazolyl blue tetrazolium bromide (MTT, Sigma Aldrich) was added at the final concentration of 0.5 mg/ml. The cells were incubated for 1 h at 37°C. The medium was carefully removed and formazan crystals were dissolved in isopropanol containing 40 mM HCl.

The absorbance was measured with Infinite 200 microplate reader (Tecan Group Ltd.) at 570 nm with the reference wavelength 650 nm for background subtraction.

The apoptosis analysis was performed using the FITC Annexin V Apoptosis Detection Kit I (BD Pharmigen), containing the 10X Annexin Binding Buffer, the FITC Annexin V, and the Propidium Iodide (PI) Staining solution. After the incubation with test substances for 72 h, HCT 116 were harvested and analyzed. Then 2×10^5 cells were washed twice with ice-cold PBS and resuspended with 1X binding buffer in a concentration of 1×10^6 mL^{-1}. After staining with PI and fluorescein isothiocyanate (FITC)-conjugated Annexin-V (1:20 solution) the cells were incubated for 15 min at RT and then directly analyzed by flow cytometry. Annexin V binds specifically to phosphatidylserine, a lipid that is normally on the inside of the cell membrane but in early apoptosis is exposed on the cell surface. Propidium iodide was used to assess the membrane integrity. PI and Annexin negative cells in the lower left quadrant were classified as living cells, whereas cells in the lower right quadrant, only Annexin positive cells, were in an early apoptotic state. The cells in the upper quadrants, the PI positive cells, are late apoptotic or necrotic.

Synthetic procedures and analytical data

General procedure of the Ugi four-component (U-4CR) reaction and analytical data of adducts 5a-ai, 7, 8a, 9a, 10, 11, 13a-17a, 22a-26a

To a stirred solution of the corresponding amine **1** (1.0 mmol) in MeOH (1 M), the corresponding aldehyde **2** (1.0 mmol), isocyanide **3** (1.1 mmol) and carboxylic acid **4** (1.1 mmol) were added *(If the hydrochloric or triflic salt of the amine was used, then Et_3N (0.9 mmol) was also added to the reaction mixture).* The reaction mixture was stirred at rt for 2-3 d (TLC

monitored). Afterwards, the solvent was evaporated and the mixture was purified by flash chromatography (petroleum ether/EtOAc 1:1 or EtOAc) giving the corresponding U-4CR adducts.

Ethyl 3-(1-(*N*-(4-((4-fluorobenzyl)oxy)benzyl)formamido)-2-(tert-butylamino)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (5a)

Yellow oil, 70% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.21 (s, 9H), 1.30 (s, 9H), 1.35 (s, 12H), 1.39 (s, 12H), 4.24-4.36 (m, 6H), 4.54 (dd, *J* = 10.0 Hz, 1H), 4.76 (dd, *J* = 10.0 Hz, 1H), 4.91 (s, 2H), 4.97 (s, 2H), 5.48 (s, 1H), 5.55 (s, 1H), 6.10 (s, 1H), 6.47 (d, *J* = 5.0 Hz, 2H), 6.55 (d, *J* = 10.0 Hz, 2H), 6.67 (s, 1H), 6.75 (d, *J* = 10.0 Hz, 2H), 6.97 (d, *J* = 10.0 Hz, 2H), 7.10-7.11 (m, 6H), 7.23 (s, 1H), 7.34-7.35 (m, 4H), 7.60 (d, *J* = 10.0 Hz, 2H), 7.85 (d, *J* = 5.0 Hz, 2H), 8.02 (s, 1H), 8.28 (d, *J* = 5.0 Hz, 1H), 8.41 (s, 1H), 8.48 (s, 1H), 9.10 (s, 1H), 9.46 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.6, 28.2, 28.5, 28.9, 29.1, 31.1, 46.3, 49.7, 52.1, 52.6, 57.7, 61.8, 69.5, 111.9, 112.5, 112.9, 113.9, 114.5, 115.2, 115.4, 116.4, 123.1, 125.1, 125.9, 126.4, 126.8, 127.4, 128.1, 130.2, 131.9, 132.9, 136.1, 136.2, 136.3, 157.7, 158.1, 160.9, 163.7, 164.9, 168.3. LC-MS (DAD/ESI): t_R = 3.96 min, calculated for $C_{32}H_{33}ClFN_3O_5$ (m/z): $[M+H]^+$ 594.21, found: $[M+H]^+$ 594.10.

Ethyl 3-(1-(*N*-(4-((3-fluorobenzyl)oxy)benzyl)formamido)-2-(tert-butylamino)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (5b)

Yellow oil, 71% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.20 (s, 9H), 1.30 (s, 8H), 1.34 (s, 13H), 1.39 (d, *J* = 2.9 Hz, 16H), 1.67 (s, 4H), 4.24 (s, 1H), 4.27 (d, *J* = 3.7 Hz, 1H), 4.30 – 4.43 (m, 4H), 4.55 (d, *J* = 15.9 Hz, 1H), 4.79 (d, *J* = 14.8

Hz, 1H), 4.96 (s, 2H), 5.01 (s, 2H), 5.41 (s, 1H), 5.50 (s, 1H), 6.09 (s, 1H), 6.44 (d, *J* = 8.4 Hz, 2H), 6.52 (d, *J* = 8.7 Hz, 2H), 6.67 (s, 1H), 6.71 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 8.6 Hz, 2H), 6.99 – 7.22 (m, 9H), 7.34 – 7.45 (m, 2H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.86 (d, *J* = 8.8 Hz, 1H), 8.03 (s, 2H), 8.28 (d, *J* = 12.5 Hz, 2H), 8.41 (s, 1H), 8.48 (s, 1H), 8.86 (s, 1H), 9.17 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.6, 14.6, 28.6, 28.8, 29.1, 31.2, 46.2, 49.7, 52.1, 52.7, 57.7, 61.8, 61.9, 69.1, 69.2, 111.9, 112.3, 114.2, 114.3, 114.4, 114.9, 114.9, 115.1, 122.5, 122.8, 122.8, 122.9, 123.3, 125.2, 127.3, 129.5, 130.3, 130.4, 131.9, 132.2, 136.1, 157.4, 157.8, 160.7, 160.8, 163.6, 164.7, 168.2. LC-MS (DAD/ESI): t_R = 3.66 min, calculated for $C_{32}H_{33}ClFN_3O_5$ (m/z): $[M+H]^+$ 594.21, found: $[M+H]^+$ 594.34.

Ethyl 3-(1-(*N*-(4-((2-fluorobenzyl)oxy)benzyl)formamido)-2-(tert-butylamino)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (5c)

Yellow oil, 68% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.20 (s, 9H), 1.29 (s, 7H), 1.34 (d, *J* = 2.6 Hz, 10H), 1.36 (d, *J* = 2.7 Hz, 3H), 1.38 (s, 10H), 4.22 – 4.37 (m, 6H), 4.52 (d, *J* = 16.0 Hz, 1H), 4.76 (d, *J* = 14.9 Hz, 1H), 4.95 (s, 1H), 5.01 (s, 2H), 5.60 (d, *J* = 14.8 Hz, 2H), 6.11 (s, 1H), 6.46 (d, *J* = 8.6 Hz, 2H), 6.53 (d, *J* = 8.7 Hz, 2H), 6.69 (s, 1H), 6.73 (d, *J* = 8.6 Hz, 2H), 6.96 (d, *J* = 8.6 Hz, 2H), 7.02 (tt, *J* = 7.9, 3.5 Hz, 2H), 7.11 (ddd, *J* = 8.8, 3.6, 1.7 Hz, 4H), 7.15 – 7.19 (m, 1H), 7.24 (dd, *J* = 8.9, 1.6 Hz, 2H), 7.35 (dtt, *J* = 8.2, 5.9, 2.9 Hz, 2H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 1H), 8.01 (d, *J* = 1.7 Hz, 1H), 8.26 (s, 1H), 8.28 (s, 1H), 8.41 (s, 1H), 8.47 (s, 1H), 9.62 (s, 1H), 10.01 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 28.5, 28.7, 29.0, 31.0, 46.2, 49.7, 52.0, 52.8, 57.7, 61.7, 61.7, 69.1, 69.2, 112.1, 112.5, 113.7, 114.1, 114.3, 114.4, 114.8, 115.0, 115.7, 122.3, 122.5, 122.5, 122.8, 122.8, 123.0, 125.0, 125.8, 126.4, 127.4, 129.5, 130.2, 130.3, 130.3, 131.6, 131.8, 136.2,

136.3, 157.5, 157.8, 160.9, 160.9, 163.2, 163.7, 164.8, 168.3, 168.4. LC-MS (DAD/ESI): t_R = 3.65 min, calculated for $C_{32}H_{33}ClFN_3O_5$ (m/z): $[M+H]^+$ 594.21, found: $[M+H]^+$ 594.37.

Ethyl 3-(2-(tert-butylamino)-1-(*N*-(4-((3,5-difluorobenzyl)oxy)benzyl)formamido) -2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (5d)

Yellow oil, 59% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.20 (s, 9H), 1.29 (s, 9H), 1.36 (s, 12H), 1.38 (s, 12H), 4.25-4.35 (m, 6H), 4.53 (dd, *J* = 15.0 Hz, 1H), 4.78 (dd, *J* = 15.0 Hz, 1H), 4.92 (s, 2H), 4.98 (s, 2H), 5.54 (s, 1H), 6.11 (s, 1H), 6.49 (d, *J* = 10.0 Hz, 2H), 6.53 (d, *J* = 10.0 Hz, 2H), 6.70 (s, 1H), 6.73 (d, *J* = 10.0 Hz, 2H), 6.89-6.93 (m, 5H), 7.10-7.12 (m, 2H), 7.60 (d, *J* = 10.0 Hz, 1H), 7.83 (d, *J* = 10.0 Hz, 1H), 8.01 (s, 1H), 8.28 (d, *J* = 10.0 Hz, 1H), 8.41 (s, 1H), 8.48 (s, 1H), 9.86 (s, 1H), 10.19 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.2, 14.5, 28.5, 28.7, 29.0, 30.1, 32.0, 46.3, 49.6, 51.9, 52.9, 57.7, 61.6, 68.7, 103.1, 103.3, 103.5, 109.7, 109.8, 109.9, 112.1, 112.5, 114.3, 114.7, 115.2, 122.3, 122.5, 123.0, 125.1, 124.9, 126.4, 127.4, 127.5, 129.6, 130.5, 131.8, 132.9, 136.4, 141.4, 157.3, 157.5, 160.9, 161.0, 163.2, 163.6, 164.8, 168.3. LC-MS (DAD/ESI): t_R = 3.61 min, calculated for $C_{32}H_{32}ClF_2N_3O_5$ (m/z): $[M-H]^-$ 610.20, found: $[M-H]^-$ 610.10.

Ethyl 3-(2-(tert-butylamino)-1-(*N*-(4-((4-chlorobenzyl)oxy)benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (5e, YH300)

Yellow oil, 49% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.19 (s, 9H), 1.28 (s, 6H), 1.33-1.36 (m, 6H), 4.22-4.25 (m, 1H), 4.29-4.38 (m, 4H), 4.37 (m, 1H), 4.49 (dd, *J* = 16.2 Hz, 1H), 4.76 (dd, *J* = 15.0 Hz, 1H), 4.89-5.01 (m, 3H), 5.69 (m, 1H), 6.12 (s, 1H), 6.47 (m, 1H), 6.54 (m, 1H), 6.70 (s, 1H), 6.72 (m, 2H), 6.87 (m, 1H), 6.97 (m,

2H), 7.10 (m, 2H), 7.18 (m, 1H), 7.25 (s, 1H), 7.29-7.30 (m, 2H), 7.59 (d, *J* = 9.0 Hz, 1H), 7.81 (d, *J* = 9.0 Hz, 1H), 8.38 (s, 1H), 8.47 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.3, 14.4, 28.4, 28.6, 28.9, 30.8, 41.5, 46.2, 49.5, 50.5, 51.8, 51.9, 52.8, 57.6, 61.5, 69.1, 69.2, 112.1, 112.5, 113.4, 114.3, 114.7, 115.0, 115.4, 122.1, 122.3, 122.8, 124.7, 125.5, 126.3, 127.3, 127.4, 128.7, 128.8, 129.1, 129.4, 129.9, 130.0, 131.4, 131.6, 133.7, 135.4, 135.5, 136.2, 157.4, 157.7, 157.9, 160.8, 160.9, 161.4, 163.2, 163.6, 164.8, 168.3. LC-MS (DAD/ESI): t_R = 3.96 min, calculated for $C_{32}H_{33}Cl_2N_3O_5$ (m/z): $[M+H]^+$ 610.18, found: $[M+H]^+$ 610.31.

Ethyl 3-(2-(tert-butylamino)-1-(*N*-(4-((3-chlorobenzyl)oxy)benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (5f)

Yellow oil, 62% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.20 (s, 9H), 1.29 (s, 9H), 1.33 (m, 12H), 1.37 (m, 12H), 4.23-4.34 (m, 6H), 4.53 (dd, *J* = 15.0 Hz, 1H), 4.80 (dd, *J* = 15.0 Hz, 1H), 4.91 (s, 2H), 4.97 (s, 2H), 5.71 (s, 1H), 6.47 (d, *J* = 10.0 Hz, 2H), 6.52 (d, *J* = 10.0 Hz, 2H), 6.71 (d, *J* = 10.0 Hz, 2H), 6.94 (d, *J* = 10.0 Hz, 2H), 7.10 (d, *J* = 10.0 Hz, 2H), 7.24-7.30 (m, 9H), 7.39 (d, *J* = 10.0 Hz, 2H), 7.62 (d, *J* = 10.0 Hz, 1H), 7.83 (d, *J* = 10.0 Hz, 2H), 7.99 (s, 1H), 8.27 (d, *J* = 10.0 Hz, 2H), 8.40 (s, 1H), 8.47 (s, 1H), 10.2 (s, 1H), 10.6 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.5, 28.5, 28.8, 29.0, 31.0, 46.2, 49.7, 52.0, 52.8, 57.7, 61.7, 69.1, 69.2, 111.9, 112.5, 114.4, 114.8, 122.5, 122.6, 123.0, 125.4, 127.4, 128.2, 129.5, 130.1, 130.4, 139.4, 157.7, 160.8, 163.2, 164.8, 168.3. LC-MS (DAD/ESI): t_R = 3.87 min, calculated for $C_{32}H_{33}Cl_2N_3O_5$ (m/z): $[M+H]^+$ 610.18, found: $[M+H]^+$ 610.10.

Ethyl 3-(2-(tert-butylamino)-1-(*N*-(4-((2-chlorobenzyl)oxy)benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (5g)

Yellow oil, 69% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.21 (s, 11H), 1.30 (s, 9H), 1.34 (s, 42H), 1.38 (s, 39H), 4.22 – 4.31 (m, 3H), 4.33 – 4.41 (m, 4H), 4.55 (d, *J* = 16.0 Hz, 1H), 4.77 (d, *J* = 14.9 Hz, 1H), 5.05 (d, *J* = 5.3 Hz, 2H), 5.11 (s, 2H), 5.48 (s, 1H), 5.55 (s, 1H), 6.09 (s, 1H), 6.47 (d, *J* = 8.6 Hz, 2H), 6.57 (d, *J* = 8.6 Hz, 2H), 6.67 (s, 1H), 6.77 (d, *J* = 8.6 Hz, 2H), 6.97 (d, *J* = 8.6 Hz, 2H), 7.14 (dd, *J* = 8.8, 1.5 Hz, 2H), 7.24 – 7.34 (m, 8H), 7.38 – 7.43 (m, 2H), 7.47 – 7.54 (m, 2H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.86 (d, *J* = 8.8 Hz, 1H), 8.03 (s, 3H), 8.28 (d, *J* = 12.4 Hz, 3H), 8.41 (s, 1H), 8.48 (s, 1H), 9.30 (s, 1H), 9.63 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.6, 14.6, 28.6, 28.8, 28.8, 29.0, 29.1, 29.9, 31.1, 46.2, 49.7, 52.0, 52.8, 57.7, 61.8, 61.8, 67.2, 67.3, 112.0, 112.4, 114.4, 114.9, 122.5, 122.7, 122.8, 123.2, 126.4, 127.1, 127.4, 128.9, 129.0, 129.2, 129.3, 129.6, 129.6, 130.4, 131.8, 132.1, 136.2, 157.9, 160.8, 160.9, 163.1, 163.6, 164.7. LC-MS (DAD/ESI): t_R = 3.65 min, calculated for $C_{32}H_{33}Cl_2N_3O_5$ (m/z): $[M+H]^+$ 610.18, found: $[M+H]^+$ 610.29.

Ethyl 3-(2-(tert-butylamino)-1-(*N*-(4-((3,4-dichlorobenzyl)oxy)benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (5h)

Yellow solid, 71% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.20 (s, 9H), 1.29 (s, 9H), 1.38 (m, 6H), 4.25-4.40 (m, 6H), 4.54 (dd, *J* = 60.0, 15.0 Hz, 1H), 4.78 (dd, *J* = 60.0, 15.0 Hz, 1H), 4.90 (s, 2H), 4.96 (s, 2H), 5.44 (s, 1H), 5.53 (s, 1H), 6.11 (s, 1H), 6.47 (d, *J* = 10.0 Hz, 2H), 6.52 (d, *J* = 10.0 Hz, 2H), 6.68 (s, 1H), 6.71 (d, *J* = 10.0 Hz, 2H), 6.95 (d, *J* = 5.0 Hz, 2H), 7.12-7.22 (m, 3H), 7.45-7.51 (m, 3H), 7.59 (d, *J* = 10.0 Hz, 1H), 7.85 (d, *J* = 10.0 Hz, 2H), 8.41 (s, 1H), 8.48 (s, 1H), 8.96 (s, 1H), 9.10 (s, 1H), 9.40 (s, 1H)); ^{13}C

NMR (126 MHz, $CDCl_3$) δ [ppm] 28.6, 29.2, 31.1, 52.3, 68.9, 109.8, 110.0, 112.1, 112.4, 114.9, 122.5, 128.9, 130.0, 131.5, 141.4, 146.7, 157.7, 161.0, 163.7, 168.5. LC-MS (DAD/ESI): t_R = 3.98 min, calculated for $C_{32}H_{32}Cl_3N_3O_5$ (m/z): $[M+H]^-$ 642.14, found: $[M-H]^-$ 642.05.

Ethyl 3-(2-(tert-butylamino)-1-(*N*-(4-((2,4-dichlorobenzyl)oxy)benzyl) formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (5i)

Yellow oil, 68% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.21 (s, 9H), 1.29 (s, 6H), 1.34 (s, 6H), 1.36 (s, 5H), 4.18 – 4.37 (m, 5H), 4.51 (d, *J* = 15.9 Hz, 1H), 4.82 (d, *J* = 15.0 Hz, 1H), 4.96 (s, 1H), 5.02 (s, 2H), 5.80 (d, *J* = 4.4 Hz, 2H), 6.14 (s, 1H), 6.52 (d, *J* = 8.7 Hz, 1H), 6.57 (d, *J* = 8.7 Hz, 1H), 6.70 – 6.77 (m, 3H), 6.99 (d, *J* = 8.6 Hz, 2H), 7.10 (ddd, *J* = 8.6, 6.1, 1.7 Hz, 2H), 7.24 (d, *J* = 8.3 Hz, 2H), 7.29 – 7.33 (m, 2H), 7.35 – 7.41 (m, 2H), 7.43 (d, *J* = 8.3 Hz, 1H), 7.63 (d, *J* = 8.8 Hz, 1H), 7.82 (d, *J* = 8.8 Hz, 1H), 7.97 (d, *J* = 2.0 Hz, 1H), 8.27 (d, *J* = 12.4 Hz, 1H), 8.41 (s, 1H), 8.48 (s, 1H), 10.38 (s, 1H), 10.71 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.2, 14.3, 14.3, 21.0, 28.4, 28.6, 28.8, 30.8, 46.4, 49.5, 51.7, 51.8, 53.0, 57.5, 60.4, 61.4, 66.6, 66.6, 112.2, 112.6, 113.4, 114.3, 114.6, 115.3, 122.0, 122.2, 122.3, 122.7, 124.7, 125.5, 126.3, 127.3, 127.3, 127.5, 129.1, 129.1, 129.4, 129.6, 129.7, 130.2, 131.3, 131.5, 133.1, 133.2, 133.3, 133.4, 134.1, 134.1, 136.3, 136.4, 157.3, 157.5, 160.8, 160.9, 161.0, 163.3, 163.6, 164.7, 168.3, 168.4. LC-MS (DAD/ESI): t_R = 3.31 min, calculated for $C_{32}H_{32}Cl_3N_3O_5$ (m/z): $[M-H]^-$ 642.14, found: $[M-H]^-$ 642.50.

Ethyl 3-(2-(tert-butylamino)-1-(*N*-(4-((2,6-dichlorobenzyl)oxy)benzyl) formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (5j)

Yellow oil, 45% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.21 (s, 9H), 1.30 (s, 8H), 1.34 (s, 5H), 1.38 (s, 10H), 6.12 (s, 1H), 6.54 (d, *J* = 8.5 Hz, 1H), 6.64 (d, *J* = 8.5 Hz, 1H), 6.69 (s, 1H), 6.85 (d, *J* = 8.5 Hz, 2H), 6.99 (d, *J* = 8.5 Hz, 1H), 7.07 (d, *J* = 8.5 Hz, 2H), 7.14 (ddd, *J* = 8.7, 4.5, 1.5 Hz, 2H), 7.26 (dt, *J* = 12.4, 7.4 Hz, 4H), 7.36 (dd, *J* = 7.9, 5.3 Hz, 3H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 8.22 – 8.32 (m, 1H), 8.43 (s, 1H), 8.49 (s, 1H), 9.31 (s, 1H), 9.67 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.3, 14.5, 14.6, 22.9, 28.5, 28.8, 29.1, 31.1, 32.1, 46.4, 49.7, 52.0, 52.1, 52.9, 57.8, 61.8, 61.8, 65.4, 65.6, 112.0, 112.4, 114.0, 114.7, 115.1, 115.4, 116.1, 122.4, 122.6, 122.7, 123.2, 125.1, 125.8, 126.3, 127.5, 128.7, 129.4, 129.8, 130.5, 130.7, 131.8, 132.0, 132.2, 136.1, 136.2, 137.1, 137.1, 158.1, 158.4, 160.9, 161.2, 163.1, 163.7, 164.8, 168.3. MS (ESI): calculated for $C_{32}H_{32}Cl_3N_3O_5$ (m/z): $[M+H]^+$ 644.14, found: $[M+H]^+$ 644.16.

Ethyl 3-(1-(*N*-(4-((4-bromobenzyl)oxy)benzyl)formamido)-2-(tert-butylamino)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (5k)

Yellow oil, 53% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.21 (s, 9H), 1.30 (s, 9H), 1.35 (s, 12H), 1.39 (s, 12H), 4.29 (dd, *J* = 10.0 Hz, 1H), 4.30-4.34 (m, 4H), 4.38 (dd, *J* = 10.0 Hz, 1H), 4.55 (dd, *J* = 10.0 Hz, 1H), 4.78 (dd, *J*= 10.0 Hz, 1H), 4.91 (s, 2H), 4.97 (s, 2H), 5.47 (s, 1H), 5.54 (s, 1H), 6.10 (s, 1H), 6.46 (d, 2H, *J*= 5Hz), 6.53 (d, *J* = 10.0 Hz, 2H), 6.67 (s, 1H), 6.73 (d, *J* = 10.0 Hz, 2H), 6.96 (d, *J* = 10.0 Hz, 2H), 7.13 (d, *J* = 10.0 Hz, 2H), 7.24 (d, *J* = 10.0 Hz, 2H), 7.28 (d, *J* = 10.0 Hz, 2H), 7.51-7.53 (m, 3H), 7.61 (d, *J* = 10.0 Hz, 2H), 7.86 (d, *J* = 5.0 Hz, 2H), 8.03 (s, 1H), 8.28 (d, *J* = 5.0 Hz, 1H), 8.41 (s, 1H), 8.48

(s, 1H), 9.10 (s, 1H), 9.46 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.6, 28.6, 28.8, 29.1, 31.1, 46.3, 49.7, 52.1, 52.8, 57.7, 61.8, 69.3, 69.4, 112.0, 112.4, 113.9, 114.5, 114.9, 116.0, 122.1, 122.5, 123.2, 125.1, 125.9, 126.4, 127.4, 129.2, 129.6, 130.3, 131.9, 132.1, 136.1, 136.2, 136.3, 157.5, 157.9, 160.9, 163.6, 164.8, 168.2, 168.3. LC-MS (DAD/ESI): t_R = 3.94 min, calculated for $C_{32}H_{33}BrClN_3O_5$ (m/z): $[M+H]^+$ 654.13, found: $[M+H]^+$ 654.15.

Ethyl 3-(1-(*N*-(4-((3-bromobenzyl)oxy)benzyl)formamido)-2-(tert-butylamino)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (5l)

Yellow oil, 70% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.21 (s, 6H), 1.29 (s, 6H), 1.34 (s, 12H), 1.38 (s, 12H), 4.24-4.39 (m, 6H), 4.53 (dd, *J* = 10.0 Hz, 1H), 4.77 (dd, *J* = 10.0 Hz, 1H), 4.94 (s, 2H), 4.98 (s, 2H), 5.47 (s, 1H), 5.55 (s, 1H), 6.10 (s, 1H),), 6.43 (d, *J* = 8.6 Hz, 2H), 6.51 (d, *J* = 8.6 Hz, 2H), 6.68 (s, 1H), 6.71 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 8.6 Hz, 2H), 7.13 (d, *J* = 8.8 Hz, 2H), 7.19 (d, *J* = 1.6 Hz, 1H), 7.36 – 7.22 (m, 6H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.58 (dd, *J* = 23.6, 10.3 Hz, 3H), 7.85 (d, *J* = 8.8 Hz, 1H), 8.05 – 7.99 (m, 1H), 8.28 (d, *J* = 12.4 Hz, 1H), 8.41 (s, 1H), 8.48 (s, 1H), 9.11 (s, 1H), 9.49 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.3, 14.6, 14.6, 22.9, 28.6, 28.8, 29.0, 29.1, 31.1, 32.1, 46.2, 49.7, 52.1, 52.7, 57.7, 61.8, 61.8, 69.0, 69.1, 112.0, 112.4, 114.4, 114.8, 122.5, 122.6, 122.7, 123.1, 125.9, 127.3, 129.5, 130.2, 130.3, 130.4, 130.4, 131.2, 136.1, 139.7, 157.7, 160.9, 163.6, 164.8, 168.3. LC-MS (DAD/ESI): t_R = 3.71 min, calculated for $C_{32}H_{33}BrClN_3O_5$ (m/z): $[M+H]^+$ 654.13, found: $[M+H]^+$ 654.30.

Ethyl 3-(1-(*N*-(4-((2-bromobenzyl)oxy)benzyl)formamido)-2-(tert-butylamino)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (5m)

Yellow oil, 70% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.21 (s, 9H), 1.30 (s, 9H), 1.34 (s, 12H), 1.38 (s, 12H), 4.29 (dd, *J* = 10.0 Hz, 1H), 4.24-4.41 (m, 5H), 4.55 (dd, *J* = 15.0 Hz, 1H), 4.65 (dd, *J*= 15.0 Hz, 1H), 5.01 (d, *J* = 5.0 Hz, 2H), 5.07 (s, 2H), 5.44 (s, 1H), 5.54 (s, 1H), 6.10 (s, 1H), 6.46 (d, *J* = 10.0 Hz, 2H), 6.56 (d, *J* = 10.0 Hz, 2H), 6.67 (s, 1H), 6.77 (d, *J* = 10.0 Hz, 2H), 6.98 (d, *J* = 5.0 Hz, 2H), 7.13 (d, *J* = 10.0 Hz, 2H), 7.19-7.21 (m, 2H), 7.28 (d, *J* = 10.0 Hz, 2H), 7.33-7.36 (m, 2H), 7.47-7.50 (m, 2H), 7.60 (d, *J* = 10.0 Hz, 2H), 7.86 (d, *J* = 10.0 Hz, 2H), 8.03 (s, 1H), 8.28 (d, *J* = 5.0 Hz, 1H), 8.42 (s, 1H), 8.49 (s, 1H), 9.10 (s, 1H), 9.40 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.3, 28.4, 28.6, 28.8, 29.1, 30.8, 46.3, 49.5, 50.4, 51.8, 52.9, 57.5, 69.4, 112.3, 112.6, 114.3, 114.6, 116.0, 122.3, 124.7, 125.5, 126.4, 127.5, 127.6, 129.0, 129.3, 132.6, 136.2, 157.4, 157.6, 161.0, 163.3, 164.7, 168.3. LC-MS (DAD/ESI): t_R = 3.89 min, calculated for $C_{32}H_{33}BrClN_3O_5$ (m/z): $[M+H]^+$ 654.13, found: $[M+H]^+$ 654.04.

Ethyl 3-(1-(*N*-(4-((4-iodobenzyl)oxy)benzyl)formamido)-2-(tert-butylamino)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (5n)

White solid, 46% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.20 (s, 10H), 1.29 (s, 10H), 1.34 (s, 6H), 1.38 (d, *J* = 2.0 Hz, 8H), 4.25 (t, *J* = 14.8 Hz, 2H), 4.35 (q, *J* = 7.1 Hz, 3H), 4.75 (s, 1H), 4.89 (s, 2H), 4.95 (s, 2H), 5.45 (s, 1H), 5.53 (s, 1H), 6.09 (s, 1H), 6.44 (d, *J* = 8.6 Hz, 2H), 6.52 (d, *J* = 8.6 Hz, 2H), 6.66 (s, 1H), 6.72 (d, *J* = 8.6 Hz, 2H), 6.95 (d, *J* = 8.6 Hz, 2H), 7.10 – 7.18 (m, 6H), 7.20 (d, *J* = 1.7 Hz, 1H), 7.22 – 7.29 (m, 2H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.72 (t, *J* = 8.0 Hz, 4H), 7.84 (d, *J* = 8.8 Hz, 1H), 8.00 – 8.05 (m, 1H),

8.28 (d, *J* = 12.4 Hz, 1H), 8.40 (s, 1H), 8.48 (s, 1H), 9.03 (s, 1H), 9.44 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.6, 14.6, 22.9, 28.6, 28.8, 29.1, 29.2, 31.1, 32.1, 46.3, 49.7, 52.1, 52.1, 52.8, 57.7, 61.8, 61.8, 69.4, 69.4, 77.0, 77.2, 77.5, 112.0, 112.4, 114.5, 114.9, 116.0, 122.5, 122.7, 122.7, 123.2, 125.1, 126.3, 127.4, 129.4, 129.4, 129.6, 130.3, 130.3, 132.1, 136.1, 136.1, 136.9, 137.9, 157.5, 157.9, 160.9, 163.6, 164.8, 168.3; LC-MS (DAD/ESI): t_R = 3.81 min, calculated for $C_{32}H_{33}ClIN_3O_5$ (m/z): $[M+H]^+$ 702.12, found: $[M+H]^+$ 702.24.

Ethyl 3-(1-(*N*-(4-((3-iodobenzyl)oxy)benzyl)formamido)-2-(tert-butylamino)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (5o)

White solid, 45% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.21 (s, 8H), 1.26 (s, 3H), 1.29 (s, 7H), 1.34 (s, 14H), 1.38 (s, 16H), 4.25 (dd, *J* = 15.5, 4.7 Hz, 2H), 4.32 – 4.41 (m, 3H), 4.54 (d, *J* = 16.0 Hz, 1H), 4.78 (d, *J* = 15.0 Hz, 1H), 4.90 (d, *J* = 3.5 Hz, 1H), 4.95 (s, 2H), 5.35 (s, 1H), 5.48 (s, 1H), 5.55 (s, 1H), 5.96 (s, 1H), 6.10 (d, *J* = 4.4 Hz, 1H), 6.43 (d, *J* = 8.5 Hz, 2H), 6.51 (d, *J* = 8.5 Hz, 2H), 6.68 (s, 1H), 6.71 (d, *J* = 8.5 Hz, 2H), 6.93 (d, *J* = 8.5 Hz, 2H), 7.14 (t, *J* = 7.8 Hz, 4H), 7.27 (d, *J* = 4.5 Hz, 2H), 7.32 – 7.39 (m, 2H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.67 (t, *J* = 7.1 Hz, 2H), 7.76 (d, *J* = 10.6 Hz, 2H), 7.85 (d, *J* = 8.7 Hz, 1H), 8.02 (s, 1H), 8.28 (d, *J* = 12.4 Hz, 1H), 8.41 (s, 1H), 8.48 (d, *J* = 5.5 Hz, 1H), 9.21 (s, 1H), 9.58 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.6, 14.6, 27.9, 28.6, 28.7, 28.8, 29.0, 29.1, 29.9, 31.1, 46.2, 49.7, 52.1, 52.7, 57.7, 61.8, 61.8, 69.0, 69.1, 112.0, 112.4, 114.4, 114.8, 122.5, 122.6, 122.7, 123.1, 126.6, 127.3, 129.5, 130.4, 130.5, 130.5, 131.8, 132.0, 136.2, 136.3, 137.2, 160.9, 163.6, 164.8, 168.3. LC-MS (DAD/ESI): t_R = 3.79 min, calculated for $C_{32}H_{33}ClIN_3O_5$ (m/z): $[M-H]^-$ 700.12, found: $[M-H]^-$ 700.31.

Ethyl 3-(1-(*N*-(4-((2-iodobenzyl)oxy)benzyl)formamido)-2-(tert-butylamino)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (5p)

White solid, 40% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.21 (s, 9H), 1.29 (s, 8H), 1.35 – 1.41 (m, 6H), 4.20 – 4.45 (m, 8H), 4.52 (d, *J* = 16.0 Hz, 1H), 4.74 (d, *J* = 14.9 Hz, 1H), 4.92 (s, 2H), 4.98 (s, 2H), 5.02 (d, *J* = 7.0 Hz, 2H), 5.50 (s, 1H), 5.59 (s, 1H), 6.12 (s, 1H), 6.47 (d, *J* = 8.3 Hz, 1H), 6.56 (d, *J* = 8.4 Hz, 1H), 6.68 (s, 1H), 6.77 (d, *J* = 8.3 Hz, 2H), 6.87 – 7.06 (m, 6H), 7.07 – 7.16 (m, 2H), 7.16 – 7.23 (m, 3H), 7.41 (ddt, *J* = 40.3, 13.1, 7.6 Hz, 5H), 7.58 (d, *J* = 8.7 Hz, 1H), 7.79 – 7.90 (m, 3H), 8.22 (s, 1H), 8.40 (s, 1H), 8.48 (s, 1H), 9.13 (s, 1H), 9.58 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.3, 14.6, 14.6, 22.9, 28.6, 28.8, 32.0, 41.8, 46.3, 49.7, 52.0, 52.1, 52.8, 57.7, 61.8, 61.8, 74.0, 74.1, 74.1, 97.4, 97.5, 112.0, 112.4, 113.8, 114.5, 115.0, 115.3, 115.5, 115.9, 122.4, 122.6, 123.1, 125.0, 125.8, 126.3, 127.4, 127.4, 128.5, 128.6, 128.6, 128.8, 128.9, 129.4, 129.6, 129.8, 130.2, 130.4, 130.4, 132.0, 136.1, 139.2, 139.5, 139.5, 157.5, 157.8, 158.1, 160.8, 161.2, 163.7, 164.9, 168.3. MS (ESI): calculated for $C_{32}H_{33}ClIN_3O_5$ (m/z): $[M+H]^+$ 702.12, found: $[M+H]^+$ 702.19.

Ethyl 3-(2-(tert-butylamino)-2-oxo-1-(*N*-(4-((2-(trifluoromethyl)benzyl)oxy) benzyl)formamido)ethyl)-6-chloro-1*H*-indole-2-carboxylate (5q)

Yellow oil, 65% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.20 (s, 10H), 1.29 (s, 7H), 1.34 (d, *J* = 1.9 Hz, 23H), 1.37 (d, *J* = 2.1 Hz, 22H), 4.21 – 4.36 (m, 6H), 4.52 (d, *J* = 15.9 Hz, 1H), 4.78 (d, *J* = 14.9 Hz, 1H), 5.14 (s, 1H), 5.19 (s, 2H), 5.74 (dd, *J* = 14.5, 5.0 Hz, 4H), 6.11 (s, 1H), 6.49 (d, *J* = 8.6 Hz, 2H), 6.56 (d, *J* = 8.7 Hz, 3H), 6.70 (s, 1H), 6.72 – 6.78 (m, 2H), 6.98 (d, *J* = 8.6 Hz, 2H), 7.10 (dt, *J* = 8.8, 1.5 Hz, 2H), 7.32 (dd, *J* = 12.1, 1.7 Hz, 2H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.57 (t, *J* = 6.8 Hz, 2H), 7.64 (dd, *J* = 16.7,

8.3 Hz, 2H), 7.69 (d, *J* = 7.9 Hz, 3H), 7.83 (d, *J* = 8.8 Hz, 1H), 8.00 (s, 2H), 8.26 (d, *J* = 12.4 Hz, 2H), 8.39 (s, 1H), 8.46 (s, 1H), 10.28 (d, *J* = 18.0 Hz, 1H), 10.62 (d, *J* = 16.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) *δ* [ppm] 14.4, 28.4, 28.7, 28.9, 30.9, 46.3, 49.6, 50.5, 51.8, 51.9, 52.9, 57.6, 61.5, 66.3, 112.2, 112.6, 113.5, 114.3, 114.7, 115.1, 115.4, 122.1, 122.3, 122.5, 122.9, 124.9, 125.7, 126.0, 126.1, 126.4, 127.5, 127.9, 127.9, 128.7, 128.9, 129.3, 129.5, 130.3, 131.6, 132.2, 135.7, 136.5, 157.4, 157.7, 160.9, 161.1, 163.3, 163.6, 164.7, 168.3, 168.4. LC-MS (DAD/ESI): t_R = 3.43 min, calculated for $C_{33}H_{33}ClF_3N_3O_5$ (m/z): $[M+H]^+$ 644.21, found: $[M+H]^+$ 644.26.

Ethyl 3-(1-(*N*-(4-((3,5-bis(trifluoromethyl)benzyl)oxy)benzyl)formamido)-2-(tert-butylamino)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (5r)

Yellow oil, 64% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* [ppm] 1.21 (s, 8H), 1.30 (s, 6H), 1.36 (d, *J* = 17.2 Hz, 20H), 4.21 – 4.41 (m, 5H), 4.55 (d, *J* = 16.0 Hz, 1H), 4.82 (d, *J* = 15.0 Hz, 1H), 5.03 (s, 1H), 5.09 (s, 2H), 5.68 (s, 2H), 6.13 (s, 1H), 6.44 (s, 1H), 6.50 – 6.65 (m, 3H), 6.68 – 6.82 (m, 3H), 7.00 (d, *J* = 7.7 Hz, 2H), 7.12 (s, 2H), 7.31 (s, 2H), 7.80 – 7.97 (m, 6H), 8.01 (s, 1H), 8.27 (d, *J* = 12.3 Hz, 1H), 8.42 (s, 1H), 8.48 (s, 1H), 10.05 (s, 1H), 10.35 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) *δ* [ppm] 14.4, 14.4, 28.5, 28.7, 29.0, 30.9, 46.3, 49.6, 51.9, 52.0, 53.0, 57.7, 61.6, 61.6, 68.6, 68.6, 112.2, 112.6, 114.3, 114.7, 115.5, 121.9, 122.3, 122.5, 122.9, 124.5, 124.9, 125.7, 126.4, 127.3, 127.3, 127.5, 127.6, 129.6, 130.8, 131.6, 131.8, 131.9, 132.2, 136.4, 139.8, 139.9, 157.2, 157.4, 160.9, 161.0, 163.3, 163.7, 164.8, 168.3, 168.4. LC-MS (DAD/ESI): t_R = 3.15 min, calculated for $C_{34}H_{32}ClF_6N_3O_5$ (m/z): $[M+H]^+$ 712.19, found: $[M+H]^+$ 712.14.

Ethyl 3-(1-(*N*-(4-(benzyloxy)-3,5-difluorobenzyl)formamido)-2-(tert-butylamino)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (5s)

Yellow solid, 65% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.30 (d, *J* = 3.7 Hz, 17H), 1.34 (s, 11H), 1.38 (s, 11H), 1.43 (td, *J* = 7.1, 1.9 Hz, 6H), 4.02 (d, *J* = 15.6 Hz, 1H), 4.22 (d, *J* = 16.6 Hz, 1H), 4.35 (dd, *J* = 10.8, 7.2 Hz, 1H), 4.37 – 4.43 (m, 2H), 4.46 (dd, *J* = 10.8, 7.1 Hz, 1H), 4.51 (d, *J* = 16.9 Hz, 1H), 4.99 (d, *J* = 15.7 Hz, 1H), 5.02 – 5.12 (m, 4H), 5.42 (d, *J* = 23.9 Hz, 2H), 5.94 (d, *J* = 8.7 Hz, 2H), 6.11 (s, 1H), 6.22 (d, *J* = 8.8 Hz, 2H), 6.68 (s, 1H), 7.17 (td, *J* = 5.0, 2.4 Hz, 3H), 7.24 (d, *J* = 1.7 Hz, 1H), 7.35 – 7.49 (m, 10H), 7.66 (d, *J* = 8.8 Hz, 1H), 7.83 (d, *J* = 8.5 Hz, 1H), 8.02 (s, 1H), 8.27 (d, *J* = 12.4 Hz, 1H), 8.37 (s, 1H), 8.45 (s, 1H), 8.70 (s, 1H), 9.01 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.4, 28.5, 28.6, 28.7, 28.9, 30.8, 45.7, 49.3, 50.6, 51.9, 52.1, 52.4, 57.0, 61.7, 61.7, 75.9, 76.0, 109.2, 109.4, 109.4, 110.6, 110.7, 110.8, 112.3, 112.6, 112.8, 114.6, 122.0, 122.3, 122.4, 122.5, 124.7, 125.5, 126.7, 127.6, 128.3, 128.4, 128.5, 128.5, 128.6, 131.8, 133.7, 136.3, 136.6, 154.3, 156.3, 160.8, 160.9, 161.1, 163.5, 163.5, 163.9, 164.6, 168.4. HRMS (ESI) m/z calculated for $C_{32}H_{32}ClF_2N_3O_5$ (m/z): $[M+H]^+$ Exact Mass: 612.1999, found: $[M+H]^+$ 612.2100.

Ethyl 3-(1-(*N*-(4-(benzyloxy)benzyl)formamido)-2-(tert-butylamino)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (5t)

Yellow oil, 53% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.19 (s, 9H), 1.28 (s, 9H), 1.32 (s, 12H), 1.35 (s, 12H), 4.21-4.31 (m, 6H), 4.50 (dd, *J* = 60.0, 15.0 Hz, 1H), 4.78 (dd, *J* = 60.0, 10.0 Hz, 1H), 4.78 (dd, *J* = 15.0 Hz, 1H), 4.99 (s, 2H), 5.01 (s, 2H), 6.45 (d, *J* = 5.0 Hz, 2H), 6.55 (d, *J* = 5.0 Hz, 2H), 6.70 (s, 1H), 6.74 (d, *J* = 10.0 Hz, 2H), 6.95 (d, *J* = 10.0 Hz, 2H), 7.08-7.10 (m, 2H), 7.25-7.33 (m, 4H), 7.34-7.37 (m, 7H), 7.62 (d,

J = 5.0 Hz, 2H), 7.82 (d, *J* = 5.0 Hz, 2H), 7.96 (s, 1H), 8.26 (d, *J* = 15.0 Hz, 1H), 8.39 (s, 1H), 8.47 (s, 1H), 10.20 (s, 1H), 10.60 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.4, 28.4, 28.7, 28.9, 30.9, 31.1, 46.2, 49.6, 51.8, 51.9, 52.9, 57.6, 61.5, 69.8, 70.0, 112.2, 112.6, 113.5, 114.4, 114.8, 115.4, 122.03, 122.2, 122.4, 122.8, 124.9, 126.4, 127.4, 128.0, 128.6, 131.6, 136.4, 137.1, 157.7, 158.0, 161.0, 163.2, 163.6, 164.7, 168.3. LC-MS (DAD/ESI): t_R = 3.82 min, calculated for $C_{32}H_{33}ClIN_3O_5$ (m/z): $[M+H]^+$ 576.22, found: $[M+H]^+$ 576.16.

Ethyl 3-(1-(*N*-(4-([1,1'-biphenyl]-4-ylmethoxy)benzyl)formamido)-2-(tert-butylamino)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (5u)

Yellow oil, 54% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.20 (s, 8H), 1.28 (s, 6H), 1.32 (s, 7H), 1.36 (s, 10H), 2.04 (d, *J* = 6.5 Hz, 2H), 4.08 – 4.17 (m, 1H), 4.19 – 4.40 (m, 5H), 4.51 (d, *J* = 15.9 Hz, 1H), 4.77 (d, *J* = 14.9 Hz, 1H), 4.99 (s, 2H), 5.04 (s, 2H), 5.54 – 5.68 (m, 2H), 6.09 – 6.14 (m, 1H), 6.42 – 6.48 (m, 2H), 6.57 (d, *J* = 8.3 Hz, 2H), 6.69 (d, *J* = 2.6 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 8.1 Hz, 2H), 7.10 (d, *J* = 8.8 Hz, 2H), 7.18 (d, *J* = 4.2 Hz, 1H), 7.23 (s, 1H), 7.34 (t, *J* = 7.3 Hz, 2H), 7.45 (dt, *J* = 14.6, 8.0 Hz, 7H), 7.56 – 7.65 (m, 8H), 7.82 (d, *J* = 8.8 Hz, 1H), 7.98 (s, 1H), 8.26 (d, *J* = 12.4 Hz, 1H), 8.41 (s, 1H), 8.48 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.3, 14.4, 14.5, 28.5, 28.7, 29.0, 30.9, 46.3, 49.7, 51.9, 52.0, 57.7, 61.6, 61.6, 69.7, 69.8, 112.1, 112.5, 113.6, 114.5, 114.9, 122.2, 122.2, 122.4, 122.4, 122.5, 123.0, 124.9, 125.7, 126.4, 127.2, 127.2, 127.4, 127.4, 127.4, 127.5, 127.6, 128.0, 128.9, 129.0, 129.5, 129.9, 130.0, 136.1, 136.2, 136.3, 140.7, 140.8, 141.1, 158.1, 160.9, 160.9, 163.6, 163.6, 164.8, 168.3, 168.4. HRMS (ESI) m/z calculated for $C_{38}H_{38}ClN_3O_5$ (m/z): $[M+H]^+$ 652.2500, found: $[M+H]^+$ 652.2513.

Ethyl 3-(2-(tert-butylamino)-1-(*N*-(4-(naphthalen-2-ylmethoxy)benzyl) formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (5v)

Yellow oil, 65% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.18 (s, 10H), 1.27 (s, 11H), 1.33 (d, *J* = 6.4 Hz, 12H), 1.37 (d, *J* = 6.3 Hz, 12H), 4.22 (dd, *J* = 21.2, 15.5 Hz, 2H), 4.26 – 4.42 (m, 4H), 4.51 (d, *J* = 16.0 Hz, 1H), 4.77 (d, *J* = 14.9 Hz, 1H), 5.09 – 5.19 (m, 4H), 5.39 (s, 1H), 5.46 (s, 1H), 5.55 (s, 1H), 6.08 (s, 1H), 6.37 (d, *J* = 8.5 Hz, 2H), 6.55 (d, *J* = 8.6 Hz, 2H), 6.64 (s, 1H), 6.71 – 6.81 (m, 3H), 6.91 (d, *J* = 8.6 Hz, 2H), 7.03 – 7.13 (m, 3H), 7.51 (qd, *J* = 6.6, 2.2 Hz, 6H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.81 (s, 1H), 7.82 – 7.92 (m, 8H), 8.00 (d, *J* = 1.6 Hz, 1H), 8.27 (d, *J* = 12.4 Hz, 1H), 8.40 (s, 1H), 8.47 (s, 1H), 8.93 (s, 1H), 9.57 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.5, 14.6, 28.5, 28.8, 28.9, 29.1, 31.1, 46.2, 49.7, 52.0, 52.0, 52.7, 57.7, 61.7, 61.7, 70.0, 70.2, 111.9, 112.4, 114.6, 115.0, 115.8, 122.3, 122.5, 122.6, 123.0, 125.0, 125.4, 125.4, 126.4, 126.4, 126.5, 126.6, 126.8, 127.2, 127.3, 127.9, 128.0, 128.0, 128.0, 128.5, 128.5, 129.4, 130.0, 130.2, 131.6, 131.9, 133.5, 134.8, 134.9, 136.0, 136.2, 157.5, 158.0, 160.8, 163.6, 164.8, 168.4. HRMS (ESI) m/z calculated for $C_{36}H_{36}ClN_3O_5$ (m/z): $[M+H]^+$ 626.2343, found: $[M+H]^+$ 626.2244.

Ethyl 3-(2-(tert-butylamino)-1-(*N*-(4-((3-methoxybenzyl)oxy)benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (5w)

Red solid, 70% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.22 (s, 9H), 1.26 (s, 4H), 1.30 (s, 8H), 1.33 – 1.40 (m, 14H), 3.50 (s, 2H), 3.66 (s, 3H), 4.25 – 4.40 (m, 5H), 4.57 (d, *J* = 16.2 Hz, 1H), 4.78 (d, *J* = 15.0 Hz, 1H), 5.58 (s, 1H), 5.65 (s, 1H), 5.99 (s, 1H), 6.15 (s, 1H), 6.21 (d, *J* = 7.4 Hz, 1H), 6.52 (d, *J* = 7.8 Hz, 1H), 6.57 (s, 1H), 6.64 (d, *J* = 7.4 Hz, 1H), 6.69 (d, *J* = 6.7 Hz, 1H), 6.74 (s, 1H), 6.87 (t, *J* = 7.8 Hz, 1H), 7.06 (t, *J* =

7.8 Hz, 1H), 7.13 (t, *J* = 9.7 Hz, 2H), 7.27 (d, *J* = 15.7 Hz, 2H), 7.60 (d, *J* = 8.7 Hz, 1H), 7.85 (d, *J* = 8.7 Hz, 1H), 8.43 (s, 1H), 8.52 (s, 1H), 9.59 – 9.79 (m, 1H), 9.97 – 10.14 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.3, 14.4, 14.5, 22.8, 28.5, 28.7, 29.0, 29.2, 31.0, 32.0, 46.8, 50.2, 52.0, 52.0, 52.8, 55.0, 55.1, 57.8, 61.7, 61.8, 111.2, 112.1, 112.5, 113.1, 113.2, 113.5, 118.3, 120.4, 122.3, 122.4, 122.5, 123.0, 125.0, 125.8, 126.5, 127.6, 129.0, 129.5, 131.8, 136.3, 139.2, 139.3, 159.3, 159.7, 160.9, 163.3, 163.8, 164.9, 168.4. HRMS (ESI) m/z calculated for $C_{33}H_{36}ClN_3O_6$ (m/z): $[M+H]^+$ 602.2293, found: $[M+H]^+$ 602.2299.

Ethyl 3-(2-(tert-butylamino)-1-(*N*-(4-((2,3-methoxybenzyl)oxy)benzyl) formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (5x)

Yellow oil, 71% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.20 (s, 9H), 1.27 (d, *J* = 16.9 Hz, 8H), 1.35 (d, *J* = 8.1 Hz, 8H), 3.75 – 3.99 (m, 11H), 4.27 (dd, *J* = 33.0, 15.0 Hz, 6H), 4.50 (d, *J* = 15.6 Hz, 1H), 4.72 (d, *J* = 14.7 Hz, 1H), 4.92 – 5.16 (m, 4H), 5.58 (d, *J* = 33.2 Hz, 2H), 6.11 (s, 1H), 6.44 (d, *J* = 7.1 Hz, 2H), 6.56 (d, *J* = 7.3 Hz, 2H), 6.68 (s, 1H), 6.79 (d, *J* = 7.4 Hz, 2H), 6.87 – 7.22 (m, 11H), 7.57 (d, *J* = 8.3 Hz, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 8.42 (s, 1H), 8.48 (s, 1H), 9.29 (s, 1H), 9.79 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.5, 14.5, 28.5, 28.7, 31.0, 46.3, 49.7, 52.0, 52.0, 52.9, 55.9, 57.8, 61.2, 61.2, 61.7, 61.7, 65.1, 65.3, 112.0, 112.4, 112.5, 113.8, 114.6, 115.0, 121.0, 121.1, 122.3, 122.4, 122.5, 123.1, 124.3, 124.3, 125.0, 126.4, 127.4, 129.6, 129.8, 130.0, 131.0, 131.8, 136.2, 152.8, 157.9, 158.3, 160.8, 163.7, 164.9, 168.4. HRMS (ESI) m/z calculated for $C_{34}H_{38}ClN_3O_7$ (m/z): $[M+H]^+$ 636.2398, found: $[M+H]^+$ 636.2400.

Ethyl 3-(2-(tert-butylamino)-1-(*N*-(4-((4-methylbenzyl)oxy)benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (5y)

Yellow oil, 39% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]; 1.20 (s, 9H), 1.28 (s, 9H), 1.33 (s, 12H), 1.37 (s, 12H), 2.37 (s, 6H), 4.19-4.35 (m, 6H), 4.49(dd, *J* = 15.0 Hz, 1H), 4.74 (dd, *J* = 15.0 Hz, 1H), 4.92 (s, 2H), 4.98 (s, 2H), 5.52 (s, 1H), 5.61 (s, 1H), 6.10 (s, 1H), 6.42 (d, *J* = 5.0 Hz, 2H), 6.53 (d, *J* = 5.0 Hz, 2H), 6.67 (s, 1H), 6.74 (d, *J* = 5.0 Hz 2H), 6.91-7.13 (m, 5H), 7.24 (d, *J* = 10.0 Hz, 2H), 7.28 (d, *J* = 10.0 Hz, 2H), 7.57 (d, *J* = 5.0 Hz, 1H), 7.81 (d, *J* = 5.0 Hz, 1H), 7.99 (s, 1H), 8.39 (s, 1H), 8.47 (s, 1H), 9.20 (s, 1H), 9.71 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.4, 28.4, 28.6, 28.8, 28.9, 30.8, 30.9, 46.2, 50.4, 51.3, 51.8, 52.9, 57.5, 61.4, 69.9, 69.4, 112.2, 112.6, 113.4, 114.2, 115.3, 121.9, 122.2, 122.4, 122.9, 124.8, 125.6, 126.4, 127.4, 128.0, 128.6, 129.4, 129.8, 129.9, 131.2, 131.4, 136.3, 136.4, 137.0, 157.7, 158.0, 161.0, 163.1, 163.3, 163.6, 164.7, 168.3, 168.4. LC-MS (DAD/ESI): t_R = 3.71 min, calculated for $C_{33}H_{36}ClN_3O_5$ (m/z): $[M+H]^+$ 590.23, found: $[M+H]^+$ 590.16.

Ethyl 3-(2-(tert-butylamino)-1-(*N*-(4-(cyclohexylmethoxy)benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (5z)

Yellow oil, 65% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 0.99-1.03 (m, 5H), 1.19 (s, 9H), 1.29 (s, 9H), 1.34 (s, 12H), 1.36 (s, 12H), 1.68-1.85 (m, 15H), 3.61 (d, *J* = 10.0 Hz, 2H) 3.68-3.72 (m, 3H), 4.21-4.31 (m, 6H), 4.49 (d, *J* = 10.0 Hz, 1H), 4.72 (d, *J* = 10.0 Hz, 1H), 6.10 (s, 1H), 6.51 (s, 3H), 6.69 (d, *J* = 10.0 Hz, 4H), 6.83 (d, *J* = 10.0 Hz, 2H), 7.00 (d, *J* = 10.0 Hz, 2H), 7.08 (d, *J* = 10.0 Hz, 2H), 7.18 (d, *J* = 10.0 Hz, 1H), 7.35 (s, 2H), 7.61 (d, *J* = 10.0 Hz, 1H), 7.81 (d, *J* = 10.0 Hz, 1H), 7.98 (s, 1H), 8.25 (d, *J* = 10.0 Hz, 2H), 8.38 (s, 1H), 8.46 (s, 1H), 10.50 (s, 1H), 10.80 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm]

14.4, 25.8, 26.5, 28.4, 28.9, 29.9, 30.9, 37.7, 41.6, 46.3, 49.5, 50.4, 51.3, 53.1, 57.6, 61.4, 73.6, 112.3, 112.6, 114.1, 114.5, 114.7, 115.5, 122.0, 122.2, 122.5, 122.9, 124.9, 125.6, 127.4, 127.5, 129.1, 129.3, 131.5, 136.5, 158.5, 158.7, 160.9, 161.0, 161.1, 161.4, 163.3, 163.3, 164.7, 168.3. LC-MS (DAD/ESI): t_R = 3.59 min, calculated for $C_{32}H_{40}ClN_3O_5$ (m/z): $[M+H]^+$ 582.27, found: $[M+H]^+$ 582.21.

Ethyl 3-(2-(tert-butylamino)-1-(*N*-(4-(cyclopentyloxy)benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (5aa)

Yellow oil, 89% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.20 (s, 9H), 1.29 (s, 9H), 1.34 (s, 12H), 1.36 (s, 12H), 1.57-1.87 (m, 17H), 4.25-4.35 (m, 6H), 5.80 (s, 1H), 5.82 (s, 1H), 6.12 (s, 1H), 6.48 (s, 3H), 6.65 (d, *J* = 10.0 Hz, 4H), 6.70 (s, 1H), 6.79 (d, *J* = 10.0 Hz, 2H), 6.98 (d, *J* = 10.0 Hz, 2H), 7.08-7.17 (m, 3H), 7.31 (d, *J* = 10.0 Hz, 2H), 7.61 (d, *J* = 10.0 Hz, 1H), 7.81 (d, *J* = 10.0 Hz, 1H), 7.97 (s, 1H), 8.27 (d, *J* = 10.0 Hz, 1H), 8.39 (s, 1H), 8.47 (s, 1H), 10.47 (s, 1H), 10.78 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.3, 23.9, 28.4, 28.6, 28.9, 30.8, 32.7, 32.8, 41.6, 46.3, 49.6, 50.4, 51.2, 51.8, 53.1, 57.6, 61.4, 79.2, 112.2, 112.6, 115.1, 115.5, 115.7, 121.9, 122.1, 122.4, 122.8, 124.8, 125.6, 126.4, 127.4, 127.5, 129.0, 129.4, 131.2, 131.5, 136.4, 136.5, 157.2, 157.5, 160.9, 161.0, 161.4, 163.2, 164.7, 168.3, 168.7. LC-MS (DAD/ESI): t_R = 3.68 min, calculated for $C_{30}H_{36}ClN_3O_5$ (m/z): $[M+H]^+$ 554.24, found: $[M+H]^+$ 554.17.

Ethyl 3-(2-(tert-butylamino)-1-(*N*-(4-((4-cyanobenzyl)oxy)benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (5ab)

Yellow solid, 41% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.21 (s, 9H), 1.26 (t, *J* = 7.1 Hz, 4H), 1.30 (s, 7H), 1.34 – 1.41 (m, 8H), 4.22 – 4.40 (m, 5H), 4.53 (d, *J* = 16.0 Hz, 1H), 4.78 (d, *J* = 14.9 Hz, 1H), 5.00 (s, 1H), 5.06 (s, 2H), 5.51 (s, 1H), 5.57 (s, 1H), 6.11 (s, 1H), 6.47 – 6.58 (m, 3H), 6.69 (s, 1H), 6.73 (d, *J* = 8.3 Hz, 2H), 6.99 (d, *J* = 8.3 Hz, 2H), 7.08 – 7.17 (m, 2H), 7.27 (d, *J* = 10.5 Hz, 2H), 7.50 (dd, *J* = 15.3, 7.9 Hz, 3H), 7.60 (d, *J* = 8.7 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 3H), 7.84 (d, *J* = 8.7 Hz, 1H), 8.41 (s, 1H), 8.48 (s, 1H), 9.32 (d, *J* = 15.6 Hz, 1H), 9.69 (d, *J* = 17.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.4, 14.5, 14.6, 21.2, 28.5, 28.8, 29.1, 31.1, 46.3, 49.6, 52.0, 52.1, 52.8, 57.7, 60.6, 61.7, 61.8, 69.0, 69.0, 111.8, 112.0, 112.4, 114.3, 114.8, 118.8, 122.4, 122.6, 123.1, 125.0, 126.3, 127.4, 127.6, 127.6, 127.7, 129.7, 130.6, 130.6, 132.5, 142.7, 157.3, 157.6, 160.9, 163.7, 164.8, 168.3. HRMS (ESI) m/z calculated for $C_{33}H_{33}ClN_4O_5$ (m/z): $[M+H]^+$ 601.2139, found: $[M+H]^+$ 601.2144.

Ethyl 3-(2-(tert-butylamino)-1-(*N*-(4-((4-nitrobenzyl)oxy)benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (5ac)

Gray solid, 85% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.21 (s, 9H), 1.30 (s, 9H), 1.40 (t, *J* = 5.0 Hz, 6H), 4.30 (dd, *J* = 10.0 Hz, 1H), 4.32-4.38 (m, 4H), 4.37 (dd, *J* = 10.0 Hz, 1H), 4.56 (dd, *J* = 15.0 Hz, 1H), 4.81 (dd, *J* = 15.0 Hz, 1H), 5.05 (s, 2H), 5.10 (s, 2H), 6.10 (s, 1H), 6.51 (d, *J* = 5.0 Hz, 2H), 6.56 (d, *J* = 10.0 Hz, 2H), 6.68 (s, 1H), 6.74 (d, *J* = 10.0 Hz, 2H), 6.98 (d, *J* = 10.0 Hz, 2H), 7.13 (d, *J* = 10.0 Hz, 2H), 7.26 (d, *J* = 10.0 Hz, 2H), 7.28 (d, *J* = 10.0 Hz, 2H), 7.54-7.61 (m, 5H), 7.86 (d, *J* = 5.0 Hz, 2H), 8.24 (d, *J* = 10.0 Hz, 3H), 8.40 (s, 1H), 8.48 (s, 1H), 8.90 (s, 1H), 9.22 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$)

δ [ppm] 14.6, 28.6, 28.8, 46.4, 49.7, 52.2, 52.8, 57.7, 61.9, 62.0, 68.9, 111.9, 112.3, 113.9, 114.4, 114.8, 116.0, 122.7, 122.8, 123.4, 124.0, 129.7, 130.8, 136.0, 144.7, 147.8, 157.3, 157.6, 160.8, 163.7, 164.8, 168.2, 168.3. HRMS (ESI) m/z calculated for $C_{32}H_{33}ClN_4O_7$ (m/z): $[M+H]^+$ 621.2038, found: $[M+H]^+$ 621.2041.

Ethyl 3-(2-(tert-butylamino)-2-oxo-1-(*N*-(4-(thiophen-3-ylmethoxy)benzyl) formamido)ethyl)-6-chloro-1*H*-indole-2-carboxylate (5ad)

Yellow oil, 61% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.22 (s, 10H), 1.30 (s, 10H), 1.38 (dt, *J* = 7.1, 3.6 Hz, 8H), 4.12 – 4.28 (m, 3H), 4.29 – 4.40 (m, 4H), 4.52 (d, *J* = 15.8 Hz, 1H), 4.72 (d, *J* = 14.8 Hz, 1H), 5.58 (s, 1H), 5.65 (s, 1H), 6.09 (s, 1H), 6.32 – 6.39 (m, 2H), 6.40 – 6.49 (m, 2H), 6.58 – 6.65 (m, 2H), 6.69 (s, 1H), 6.77 – 6.88 (m, 2H), 7.12 (dt, *J* = 8.8, 1.6 Hz, 2H), 7.38 (dd, *J* = 8.4, 1.9 Hz, 2H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.84 (d, *J* = 8.8 Hz, 1H), 8.20 (s, 2H), 8.41 (s, 1H), 8.46 (s, 1H), 10.23 (s, 1H), 10.34 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.5, 28.5, 28.7, 46.2, 49.8, 51.9, 52.9, 57.7, 61.5, 61.6, 112.3, 112.6, 115.0, 115.4, 115.4, 122.1, 122.3, 122.6, 122.9, 125.0, 125.7, 126.6, 127.2, 127.3, 127.6, 127.9, 128.1, 128.4, 128.4, 129.4, 131.3, 131.6, 136.5, 156.2, 156.4, 161.0, 161.0, 163.7, 164.7, 168.4, 168.6. HRMS (ESI) m/z calculated for $C_{30}H_{32}ClN_3O_5S$ (m/z): $[M+H]^+$ 582.1751, found: $[M+H]^+$ 582.1755.

Ethyl 3-(2-(tert-butylamino)-2-oxo-1-(*N*-(4-(pyridin-4-ylmethoxy)benzyl) formamido)ethyl)-6-chloro-1*H*-indole-2-carboxylate (5ae)

Yellow solid, 41% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.21 (s, 9H), 1.30 (s, 9H), 1.39 (t, *J* = 10.0 Hz, 6H), 4.23-4.29 (m, 2H), 4.33-4.39 (m, 4H),

4.55-4.58 (m, 2H), 4.83 (dd, *J* = 15.0 Hz, 1H), 4.95 (s, 2H), 5.02 (s, 2H), 5.42 (s, 1H), 5.50 (s, 1H), 6.10 (s, 1H), 6.46 (d, *J* = 10.0 Hz, 2H), 6.53 (d, *J* = 10.0 Hz, 2H), 6.67 (s, 1H), 6.71 (d, *J* = 5.0 Hz, 2H), 6.93 (d, *J* = 5.0 Hz, 2H), 7.14 (d, *J* = 10.0 Hz, 2H), 7.29 (d, *J* = 10.0 Hz, 2H), 7.31-7.40 (m, 5H), 7.63(d, *J* = 10.0 Hz, 1H), 7.73 (d, *J* = 10.0 Hz, 1H), 7.87 (s, 1H), 7.89 (s, 1H), 8.36 (d, *J* = 5.0 Hz, 1H), 8.41 (s, 1H), 8.48 (s, 1H), 8.62-8.63 (m, 2H), 9.25 (br s, 1H), 9.36 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.6, 14.7, 28.6, 28.9, 41.7, 46.2, 49.7, 52.1, 52.7, 57.8, 61.9, 68.2, 68.3, 111.9, 112.2, 114.3, 114.7, 121.8, 122.3, 122.6, 123.3, 127.4, 128.7, 129.2, 129.5, 130.5, 133.7, 147.8, 150.0, 157.5, 161.3, 163.6, 164.7, 168.2, 168.3. LC-MS (DAD/ESI): t_R = 4.31 min, calculated for $C_{31}H_{33}ClN_4O_5$ (m/z): $[M+H]^+$ 577.21, found: $[M+H]^+$ 577.10.

Ethyl 3-(2-(tert-butylamino)-2-oxo-1-(*N*-(4-(pyridin-3-ylmethoxy)benzyl) formamido)ethyl)-6-chloro-1*H*-indole-2-carboxylate (5af)

Yellow oil, 50% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.23 – 1.28 (m, 15H), 1.32 (d, *J* = 13.4 Hz, 15H), 4.18 – 4.36 (m, 6H), 4.56 (d, *J* = 16.1 Hz, 1H), 4.90 (d, *J* = 15.1 Hz, 1H), 4.98 (s, 2H), 5.02 (s, 2H), 6.12 (s, 1H), 6.40 (d, *J* = 8.6 Hz, 2H), 6.48 (d, *J* = 8.6 Hz, 2H), 6.65 (d, *J* = 8.6 Hz, 2H), 6.71 (s, 1H), 6.83 (d, *J* = 8.5 Hz, 2H), 7.13 (ddd, *J* = 8.7, 3.1, 1.9 Hz, 2H), 7.20 (d, *J* = 1.3 Hz, 1H), 7.24 (d, *J* = 1.6 Hz, 1H), 7.28 (s, 1H), 7.36 (dt, *J* = 7.8, 4.7 Hz, 2H), 7.64 (d, *J* = 8.8 Hz, 1H), 7.73 (dd, *J* = 16.0, 7.8 Hz, 2H), 7.87 (d, *J* = 8.8 Hz, 1H), 8.43 (d, *J* = 8.5 Hz, 2H), 8.47 (s, 1H), 8.52 – 8.56 (m, 1H), 8.56 – 8.64 (m, 2H), 10.06 (s, 1H), 10.29 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.5, 14.5, 28.6, 28.8, 29.8, 46.1, 49.7, 52.0, 52.1, 52.5, 57.5, 60.6, 61.6, 61.7, 67.5, 67.6, 112.0, 112.4, 113.6, 114.6, 114.8, 115.5, 122.3, 122.5, 122.5, 123.0, 123.8, 123.9, 125.0, 125.8, 126.5, 127.1, 127.5, 129.1, 130.7, 130.7, 131.6, 131.8, 132.8, 132.9, 135.5, 135.6, 136.3, 148.6, 148.7, 149.1, 149.2, 157.0,

157.3, 160.9, 163.6, 164.8, 168.4, 168.5. HRMS (ESI) calculated for $C_{31}H_{33}ClN_4O_5$ (m/z): $[M+H]^+$ 577.2139, found: $[M+H]^+$ 577.2135.

Ethyl 3-(2-(tert-butylamino)-2-oxo-1-(*N*-(4-(pyridin-2-ylmethoxy)benzyl) formamido)ethyl)-6-chloro-1*H*-indole-2-carboxylate (5ag)

Yellow oil, 50% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.21 (s, 9H), 1.26 (s, 6H), 1.30 (s, 8H), 1.33 (s, 6H), 4.28 (td, *J* = 16.1, 14.2, 8.6 Hz, 6H), 4.53 (d, *J* = 16.0 Hz, 1H), 4.78 (d, *J* = 15.0 Hz, 1H), 5.06 (s, 2H), 5.12 (s, 2H), 5.69 (dd, *J* = 19.2, 4.7 Hz, 2H), 6.12 (s, 1H), 6.45 (d, *J* = 8.6 Hz, 2H), 6.56 (d, *J* = 8.6 Hz, 2H), 6.69 (s, 1H), 6.75 (d, *J* = 8.5 Hz, 2H), 6.95 (d, *J* = 8.5 Hz, 2H), 7.09 – 7.16 (m, 2H), 7.20 – 7.26 (m, 4H), 7.46 (dd, *J* = 19.4, 7.8 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.72 (td, *J* = 7.0, 6.3, 2.2 Hz, 2H), 7.85 (d, *J* = 8.8 Hz, 1H), 8.42 (s, 1H), 8.47 (s, 1H), 8.56 (d, *J* = 4.4 Hz, 2H), 9.70 (d, *J* = 18.1 Hz, 1H), 10.04 (d, *J* = 19.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.5, 14.5, 28.5, 28.8, 29.8, 30.5, 46.3, 49.7, 52.0, 52.0, 52.8, 57.7, 61.6, 61.7, 70.8, 112.0, 112.4, 114.4, 114.8, 121.6, 121.7, 122.3, 122.5, 122.9, 123.0, 123.1, 125.0, 125.8, 126.4, 127.4, 129.5, 130.3, 130.4, 136.3, 137.1, 137.1, 149.3, 157.3, 157.6, 157.8, 160.9, 163.7, 164.9, 168.4. HRMS (ESI) calculated for $C_{31}H_{33}ClN_4O_5$ (m/z): $[M+H]^+$ 577.2139, found: $[M+H]^+$ 577.2122.

Ethyl 3-(2-(tert-butylamino)-2-oxo-1-(*N*-(4-phenethoxybenzyl)formamido)ethyl)-6-chloro-1*H*-indole-2-carboxylate (5ah)

Yellow oil, 57% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.19 (s, 9H), 1.28 (s, 9H), 1.31 (s, 12H), 1.34 (s, 12H), 2.95-3.00 (m, 4H), 4.15-4.20 (m, 4H), 4.20-4.34 (m, 10H), 4.56 (d, *J* = 15.0 Hz, 1H), 5.06 (d, *J* = 15.0 Hz, 1H), 6.13 (s, 1H), 6.29

(d, *J* = 10.0 Hz, 2H), 6.44 (d, *J* = 10.0 Hz, 2H), 6.57 (d, *J* = 15.0 Hz, 2H), 6.65 (s, 1H), 6.75 (d, *J* = 10.0 Hz, 2H), 7.08-7.10 (m, 2H), 7.15-7.18 (m, 2H), 7.25-7.27 (m, 8H), 7.40 (d, *J* = 10.0 Hz 2H), 7.47 (s, 2H), 7.78 (d, *J* = 10.0 Hz, 2H), 7.85 (d, *J* = 5.0 Hz, 2H), 7.88 (s, 1H), 8.33 (s, 1H), 8.43 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.5, 28.5, 28.8, 29.1, 31.1, 35.9, 46.3, 49.7, 52.0, 53.0, 57.8, 61.7, 68.9, 112.4, 112.5, 114.2, 114.7, 122.3, 122.5, 122.7, 123.2, 125.1, 126.7, 128.7, 129.1, 129.6, 129.8, 136.3, 138.4, 158.3, 160.8, 161.0, 163.2, 163.7, 164.7, 168.3. MS (ESI) calculated for $C_{33}H_{36}ClN_3O_5$ (m/z): $[M-H]^-$ 588.23, found: $[M-H]^-$ 588.20.

Ethyl 3-(1-(*N*-(4-((4-bromobenzyl)oxy)phenethyl)formamido)-2-(tert-butylamino)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (5ai)

Yellow oil, 51% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.29 (s, 6H), 1.34 (s, 13H), 1.38 (s, 3H), 1.40 (dd, *J* = 7.2, 2.4 Hz, 2H), 1.94 (dq, *J* = 12.6, 5.2 Hz, 1H), 2.12 – 2.19 (m, 1H), 2.24 (dt, *J* = 15.2, 7.9 Hz, 1H), 2.70 (td, *J* = 12.7, 5.1 Hz, 1H), 3.27 – 3.34 (m, 1H), 3.40 – 3.48 (m, 1H), 3.53 (dd, *J* = 8.3, 5.8 Hz, 1H), 3.77 – 3.88 (m, 1H), 4.30 – 4.43 (m, 3H), 4.90 (s, 3H), 6.23 (s, 1H), 6.53 (dd, *J* = 15.5, 8.4 Hz, 3H), 6.63 – 6.71 (m, 3H), 6.81 (s, 1H), 7.14 (t, *J* = 7.8 Hz, 2H), 7.25 (dd, *J* = 9.7, 3.7 Hz, 3H), 7.36 – 7.40 (m, 1H), 7.46 (ddd, *J* = 9.2, 6.9, 1.7 Hz, 4H), 7.63 (d, *J* = 8.8 Hz, 1H), 7.86 (d, *J* = 8.8 Hz, 1H), 8.07 (s, 1H), 8.37 (s, 1H), 10.49 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.3, 14.4, 14.5, 28.7, 29.0, 31.0, 33.4, 36.5, 46.2, 48.4, 51.9, 52.2, 52.7, 57.7, 61.7, 61.9, 69.3, 112.6, 112.8, 114.7, 114.9, 115.8, 121.9, 121.9, 122.5, 123.1, 124.7, 125.6, 126.5, 129.2, 129.6, 129.7, 130.6, 131.4, 131.7, 131.9, 136.2, 136.3, 136.4, 157.0, 157.2, 161.0, 161.3, 163.5, 164.2, 168.4, 168.6. LC-MS (DAD/ESI): t_R = 3.79 min, calculated for $C_{33}H_{35}BrClN_3O_5$ (m/z): $[M+H]^+$ 668.14, found: $[M+H]^+$ 668.34.

Ethyl 3-(1-(*N*-(4-((2-bromobenzyl)oxy)benzyl)formamido)-2-(tert-butylamino)-2-oxoethyl)-6-chloro-1-methyl-1*H*-indole-2-carboxylate (9a)

Yellow oil, 63% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.23 (s, 8H), 1.29 (s, 12H), 3.67 (s, 4H), 3.81 (s, 3H), 4.39 (d, *J* = 6.0 Hz, 7H), 4.52 (s, 1H), 4.81 (d, *J* = 15.1 Hz, 1H), 4.99 (s, 3H), 5.04 (s, 2H), 5.11 (d, *J* = 7.3 Hz, 7H), 5.70 (d, *J* = 20.0 Hz, 6H), 6.00 (s, 1H), 6.36 (d, *J* = 8.5 Hz, 3H), 6.53 (d, *J* = 8.6 Hz, 3H), 6.63 (s, 2H), 6.69 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 8.6 Hz, 6H), 7.15 – 7.24 (m, 14H), 7.32 (td, *J* = 10.9, 5.4 Hz, 8H), 7.46 (s, 3H), 7.52 (d, *J* = 8.1 Hz, 3H), 7.58 (dd, *J* = 7.6, 5.4 Hz, 6H), 7.65 (s, 1H), 7.86 (d, *J* = 8.8 Hz, 1H), 7.98 – 8.02 (m, 5H), 8.20 – 8.26 (m, 8H), 8.42 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.5, 28.5, 28.7, 29.0, 30.9, 32.2, 32.7, 41.6, 45.7, 49.6, 51.9, 53.1, 57.9, 61.6, 61.7, 69.5, 110.3, 110.6, 113.9, 114.4, 115.1, 115.3, 122.2, 122.4, 122.5, 122.5, 122.8, 122.9, 124.5, 127.3, 127.7, 128.5, 129.0, 129.1, 129.1, 129.3, 129.4, 129.4, 129.5, 130.1, 130.2, 130.6, 131.5, 132.7, 132.8, 136.2, 157.5, 158.0, 160.8, 161.1, 161.3, 163.3, 163.5, 164.5, 168.4, 168.6. HRMS (ESI) calculated for $C_{33}H_{35}BrClN_3O_5$ (m/z): $[M+H]^+$ 668.1449, found: $[M+H]^+$ 668.1451.

***N*-(tert-butyl)-2-(4-chlorophenyl)-2-(*N*-(4-((3,4-dichlorobenzyl)oxy)benzyl) formamido)acetamide (10)**

White solid, 90% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.26 (s, 5H), 1.31 (s, 8H), 1.34 (s, 6H), 1.38 (s, 7H), 4.35 (d, *J* = 15.5 Hz, 1H), 4.45 (d, *J* = 14.9 Hz, 1H), 4.51 – 4.56 (m, 1H), 4.78 (s, 1H), 4.97 (s, 2H), 5.01 (s, 2H), 5.41 (s, 1H), 5.61 (s, 1H), 5.79 (s, 1H), 6.77 (d, *J* = 8.6 Hz, 2H), 6.90 (dd, *J* = 8.5, 5.2 Hz, 3H), 7.10 (d, *J* = 8.4 Hz, 1H), 7.17 (d, *J* = 8.7 Hz, 1H), 7.20 (d, *J* = 1.2 Hz, 3H), 7.22 – 7.25 (m, 2H), 7.31 (d, *J* = 8.5 Hz,

1H), 7.34 (s, 1H), 7.46 (dd, *J* = 8.2, 3.5 Hz, 2H), 7.50 – 7.55 (m, 2H), 8.22 (d, *J* = 3.4 Hz, 2H), 8.32 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) *δ* [ppm] 27.8, 28.5, 28.5, 28.6, 28.9, 30.8, 46.8, 49.9, 51.9, 60.2, 64.4, 68.6, 114.9, 115.2, 126.5, 126.5, 128.1, 128.8, 129.0, 129.1, 129.2, 129.2, 129.2, 129.3, 130.0, 130.1, 130.6, 130.8, 133.0, 134.5, 137.1, 157.8, 163.6, 163.9, 165.5, 167.8. HRMS (ESI) calculated for $C_{27}H_{27}Cl_3N_2O_3$ (m/z): $[M+H]^+$ 533.1087, found: $[M+H]^+$ 533.1089.

***N*-(tert-butyl)-2-(*N*-(4-chlorobenzyl)formamido)-2-(3-chlorophenyl)acetamide (11)**

White solid, 87% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* [ppm] 1.29 (s, 6H), 1.33 (s, 8H), 4.44 (d, *J* = 16.0 Hz, 1H), 4.53 – 4.60 (m, 2H), 4.77 (s, 1H), 5.41 (s, 1H), 5.69 (s, 1H), 5.73 (s, 1H), 6.91 (d, *J* = 8.4 Hz, 2H), 7.13 – 7.19 (m, 6H), 7.22 (dq, *J* = 4.9, 2.7 Hz, 2H), 7.25 – 7.33 (m, 3H), 8.25 (s, 1H), 8.33 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) *δ* [ppm] 47.0, 49.7, 52.2, 52.5, 59.9, 64.9, 126.8, 127.7, 128.8, 128.9, 129.0, 129.0, 129.1, 129.4, 129.9, 130.1, 130.2, 130.6, 134.9, 135.5, 136.4, 163.8, 164.1, 167.7. HRMS (ESI) calculated for $C_{20}H_{22}Cl_2N_2O_2$ (m/z): $[M+H]^+$ 393.1058, found: $[M+H]^+$ 393.1054.

Ethyl 3-(2-((3*s*,5*s*,7*s*)-adamantan-1-ylamino)-1-(*N*-(4-((4-bromobenzyl)oxy) benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (13a)

White solid, 40% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* [ppm] 0.88 (t, *J* = 6.8 Hz, 5H), 1.28 (d, *J* = 18.6 Hz, 9H), 1.38 (t, *J* = 6.7 Hz, 6H), 1.56 – 1.76 (m, 24H), 1.84 (s, 15H), 1.93 (d, *J* = 13.6 Hz, 6H), 2.02 (s, 10H), 2.11 (d, *J* = 25.4 Hz, 5H), 4.24 (t, *J* = 15.8 Hz, 2H), 4.29 – 4.42 (m, 4H), 4.53 (d, *J* = 16.0 Hz, 1H), 4.79 (d, *J* = 14.9 Hz, 1H), 4.90 (s, 2H), 4.94 (s, 2H), 5.34 (s, 1H), 5.41 (s, 1H), 5.95 (s, 1H), 6.07 (s, 1H), 6.44 (d, *J* = 8.4 Hz, 2H), 6.52 (d, *J* = 8.5 Hz, 2H), 6.66 (s, 1H), 6.72 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H),

7.14 (d, *J* = 8.6 Hz, 2H), 7.26 (q, *J* = 7.9 Hz, 5H), 7.52 (dd, *J* = 8.0, 4.1 Hz, 3H), 7.64 (d, *J* = 8.8 Hz, 1H), 7.86 (d, *J* = 8.8 Hz, 1H), 8.28 (d, *J* = 12.4 Hz, 1H), 8.40 (s, 1H), 8.46 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.3, 14.6, 14.6, 22.9, 29.2, 29.4, 29.5, 29.5, 32.1, 36.0, 36.3, 36.4, 41.3, 41.5, 42.0, 44.3, 52.8, 57.7, 61.8, 69.3, 69.4, 114.4, 114.8, 122.7, 127.4, 129.2, 129.5, 131.9, 136.2, 157.5, 157.9, 162.3, 163.6, 164.7, 168.0. HRMS (ESI) calculated for $C_{38}H_{39}BrClN_3O_5$ (m/z): $[M+H]^+$ 732.1762, found: $[M+H]^+$ 732.1766.

Ethyl 3-(2-((1*r*,3*r*,5*r*,7*r*)-adamantan-2-ylamino)-1-(*N*-(4-((2-bromobenzyl)oxy) benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (14a)

White solid, 74% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.32 (q, *J* = 7.0 Hz, 7H), 1.63 (t, *J* = 11.5 Hz, 12H), 1.70 – 1.94 (m, 48H), 3.61 (d, *J* = 8.8 Hz, 1H), 4.03 (d, *J* = 7.5 Hz, 1H), 4.11 (q, *J* = 7.2 Hz, 5H), 4.19 – 4.39 (m, 7H), 4.51 (d, *J* = 15.8 Hz, 1H), 4.81 (d, *J* = 14.9 Hz, 1H), 5.00 (s, 1H), 5.04 (s, 2H), 5.08 (s, 1H), 6.21 (s, 2H), 6.24 (d, *J* = 7.8 Hz, 1H), 6.28 (d, *J* = 7.8 Hz, 1H), 6.56 – 6.64 (m, 5H), 6.71 – 6.78 (m, 3H), 6.91 (d, *J* = 8.5 Hz, 1H), 6.96 (d, *J* = 8.5 Hz, 2H), 7.08 (d, *J* = 8.8 Hz, 2H), 7.14 – 7.22 (m, 3H), 7.28 – 7.36 (m, 4H), 7.49 (q, *J* = 9.0, 8.3 Hz, 2H), 7.55 – 7.59 (m, 3H), 7.74 (d, *J* = 8.8 Hz, 1H), 8.13 (s, 2H), 8.41 (s, 1H), 8.51 (s, 1H), 10.36 (s, 1H), 10.64 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.2, 14.3, 14.3, 21.1, 26.8, 27.0, 27.0, 27.1, 27.1, 27.2, 31.2, 31.5, 31.6, 31.7, 31.7, 31.9, 33.9, 36.9, 37.0, 37.0, 37.1, 37.1, 37.2, 37.3, 37.3, 37.4, 37.5, 41.5, 46.1, 49.7, 52.4, 52.8, 54.1, 54.1, 56.5, 57.1, 60.5, 61.5, 69.4, 69.5, 112.3, 112.6, 114.4, 114.7, 115.0, 115.2, 122.1, 122.2, 122.4, 122.6, 124.7, 125.5, 126.3, 127.3, 127.6, 127.7, 128.9, 128.9, 129.0, 129.1, 129.3, 129.4, 129.4, 129.8, 131.5, 131.6, 132.6, 132.7, 136.2, 136.2, 136.3, 136.4, 157.6, 157.7, 160.9, 161.0, 161.0,

161.5, 163.7, 164.4, 164.6, 168.3, 168.3. HRMS (ESI) calculated for $C_{38}H_{39}BrClN_3O_5$ (m/z): $[M+H]^+$ 732.1762, found: $[M+H]^+$ 732.1761.

Ethyl 3-(1-(*N*-(4-((4-bromobenzyl)oxy)benzyl)formamido)-2-oxo-2-(((1*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)amino)ethyl)-6-chloro-1*H*-indole-2-carboxylate (15a)

Yellow solid, 47% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 0.51 – 0.64 (m, 4H), 0.74 – 0.99 (m, 23H), 1.05 – 1.47 (m, 16H), 1.49 – 1.85 (m, 13H), 3.91 (ddd, *J* = 33.1, 13.9, 6.9 Hz, 2H), 4.08 – 4.15 (m, 1H), 4.24 (dt, *J* = 31.6, 16.0 Hz, 6H), 4.84 – 5.02 (m, 4H), 5.80 (t, *J* = 9.1 Hz, 1H), 5.90 (t, *J* = 9.5 Hz, 1H), 6.09 – 6.23 (m, 2H), 6.56 – 6.66 (m, 3H), 6.71 (dt, *J* = 20.3, 11.0 Hz, 3H), 6.88 – 7.00 (m, 2H), 7.04 – 7.11 (m, 2H), 7.24 (d, *J* = 8.0 Hz, 4H), 7.32 (d, *J* = 13.2 Hz, 2H), 7.47 (d, *J* = 7.6 Hz, 4H), 7.59 (t, *J* = 8.6 Hz, 1H), 8.09 (s, 1H), 8.36 – 8.48 (m, 1H), 8.52 (dd, *J* = 10.8, 5.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 11.4, 11.6, 11.7, 11.8, 11.8, 12.4, 13.0, 13.6, 13.7, 13.8, 14.2, 14.2, 14.3, 15.8, 18.4, 18.5, 18.5, 19.7, 19.8, 19.8, 20.0, 20.0, 20.1, 20.1, 20.2, 20.3, 26.9, 27.0, 27.4, 27.9, 28.1, 28.2, 35.8, 35.9, 35.9, 36.0, 36.1, 37.2, 38.7, 38.9, 44.6, 44.6, 44.7, 44.8, 44.8, 45.6, 46.1, 46.9, 48.1, 48.4, 48.4, 48.6, 49.3, 49.4, 49.5, 49.7, 52.6, 52.9, 54.6, 54.7, 55.5, 56.9, 57.1, 57.2, 57.2, 57.4, 57.8, 60.4, 61.4, 69.2, 112.2, 112.6, 114.4, 114.5, 114.7, 121.7, 122.2, 122.4, 122.6, 124.3, 124.5, 125.2, 126.2, 126.3, 127.2, 127.7, 127.8, 128.9, 129.1, 129.2, 129.3, 129.5, 131.3, 131.6, 136.0, 136.1, 136.1, 136.3, 136.5, 157.6, 157.6, 157.8, 160.8, 160.9, 161.1, 161.8, 163.5, 164.1, 164.3, 164.7, 167.8, 168.0, 168.2, 169.2. HRMS (ESI) calculated for $C_{38}H_{41}BrClN_3O_5$ (m/z): $[M+H]^+$ 734.1918, found: $[M+H]^+$ 734.1920.

Ethyl 3-(1-(*N*-(4-((2-bromobenzyl)oxy)benzyl)formamido)-2-oxo-2-(((1*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)amino)ethyl)-6-chloro-1*H*-indole-2-carboxylate (16a)

Yellow oil, 51% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 0.51 (s, 2H), 0.53 (s, 1H), 0.59 (d, *J* = 5.9 Hz, 2H), 0.64 (s, 2H), 0.68 (s, 1H), 0.73 (s, 3H), 0.76 (d, *J* = 6.5 Hz, 3H), 0.79 – 0.82 (m, 3H), 0.83 – 0.87 (m, 6H), 0.91 (s, 2H), 1.14 (ddq, *J* = 16.3, 8.7, 4.3 Hz, 3H), 1.19 – 1.32 (m, 5H), 1.36 (dd, *J* = 12.6, 6.4 Hz, 7H), 1.45 – 1.90 (m, 15H), 3.81 – 4.02 (m, 2H), 4.27 – 4.39 (m, 6H), 4.56 (d, *J* = 15.9 Hz, 1H), 5.02 (t, *J* = 4.3 Hz, 2H), 5.06 (d, *J* = 7.4 Hz, 3H), 5.61 (d, *J* = 8.6 Hz, 1H), 5.75 (dd, *J* = 33.0, 8.7 Hz, 1H), 5.84 (d, *J* = 8.9 Hz, 1H), 6.12 (d, *J* = 11.8 Hz, 1H), 6.52 – 6.68 (m, 5H), 6.68 – 6.78 (m, 3H), 6.86 (d, *J* = 7.6 Hz, 1H), 6.91 – 6.95 (m, 1H), 7.11 (t, *J* = 7.6 Hz, 2H), 7.20 (t, *J* = 7.7 Hz, 3H), 7.23 – 7.26 (m, 3H), 7.35 (q, *J* = 7.3 Hz, 2H), 7.49 (dd, *J* = 13.7, 7.7 Hz, 2H), 7.60 (d, *J* = 7.9 Hz, 3H), 7.80 (d, *J* = 8.8 Hz, 1H), 8.40 – 8.46 (m, 1H), 8.53 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 11.7, 11.9, 12.0, 12.1, 12.2, 14.5, 20.2, 20.3, 27.1, 27.2, 36.0, 36.1, 36.1, 38.8, 39.0, 39.1, 39.2, 44.9, 45.0, 45.6, 46.1, 47.2, 49.8, 50.0, 52.7, 53.2, 57.0, 57.2, 57.3, 57.5, 57.6, 61.9, 69.5, 69.6, 69.6, 111.9, 112.3, 114.5, 114.7, 114.7, 114.9, 122.6, 122.9, 123.0, 127.6, 127.7, 127.8, 129.1, 129.1, 129.3, 129.5, 129.5, 129.6, 129.8, 132.3, 132.9, 136.1, 160.8, 164.5, 168.0. HRMS (ESI) calculated for $C_{38}H_{41}BrClN_3O_5$ (m/z): $[M+H]^+$ 734.1918, found: $[M+H]^+$ 734.1921.

Ethyl 3-(2-((3*s*,5*s*,7*s*)-adamantan-1-ylamino)-1-(*N*-(4-((4-fluorobenzyl)oxy) benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (17a)

White solid, 44% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 0.88 (t, *J* = 6.8 Hz, 2H), 1.28 (d, *J* = 11.7 Hz, 4H), 1.40 (dt, *J* = 7.0, 3.6 Hz, 6H), 1.66 (d, *J* = 24.4 Hz, 19H), 1.85 (d, *J* = 12.2 Hz, 9H), 1.96 (d, *J* = 13.6 Hz, 6H), 2.03 (s, 8H), 4.24 (dd, *J* =

15.4, 9.8 Hz, 2H), 4.29 – 4.44 (m, 4H), 4.54 (d, *J* = 16.0 Hz, 1H), 4.80 (d, *J* = 14.9 Hz, 1H), 4.91 (s, 2H), 4.95 (s, 2H), 5.26 (s, 1H), 5.36 (s, 1H), 6.07 (s, 1H), 6.44 (d, *J* = 8.3 Hz, 2H), 6.54 (d, *J* = 8.4 Hz, 2H), 6.65 (s, 1H), 6.73 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 8.3 Hz, 2H), 7.09 (dt, *J* = 12.5, 6.3 Hz, 3H), 7.16 (d, *J* = 8.7 Hz, 2H), 7.22 (s, 1H), 7.27 (d, *J* = 10.8 Hz, 2H), 7.37 (q, *J* = 7.4 Hz, 3H), 7.65 (d, *J* = 8.8 Hz, 1H), 7.88 (d, *J* = 8.8 Hz, 1H), 8.40 (s, 1H), 8.47 (s, 1H), 8.75 (s, 1H), 9.06 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.3, 14.6, 14.7, 22.9, 29.5, 29.5, 29.6, 32.1, 36.1, 36.4, 36.4, 41.3, 41.5, 42.1, 44.4, 46.2, 49.7, 52.7, 52.8, 57.7, 61.9, 61.9, 69.4, 69.6, 111.8, 112.2, 114.4, 114.8, 115.6, 115.8, 122.6, 122.8, 123.0, 123.4, 126.3, 127.3, 129.4, 129.5, 129.5, 129.5, 130.2, 130.3, 158.1, 160.8, 163.6, 164.7. HRMS (ESI) calculated for $C_{38}H_{39}ClFN_3O_5$ (m/z): $[M+H]^+$ 672.2652, found: $[M+H]^+$ 672.2653.

Ethyl 3-(2-((3*s*,5*s*,7*s*)-adamantan-1-ylamino)-1-(*N*-(4-(benzyloxy)benzyl) acetamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (22a)

White solid, 40% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 0.88 (t, *J* = 6.8 Hz, 2H), 1.28 (d, *J* = 18.5 Hz, 5H), 1.41 (t, *J* = 6.8 Hz, 6H), 1.65 (d, *J* = 23.7 Hz, 15H), 1.84 (s, 2H), 1.89 – 2.16 (m, 21H), 2.19 (s, 4H), 2.40 (s, 2H), 4.28 – 4.41 (m, 4H), 4.45 (q, *J* = 8.6, 6.9 Hz, 1H), 4.68 (d, *J* = 17.5 Hz, 1H), 4.95 (s, 5H), 5.24 (s, 1H), 5.57 (s, 1H), 6.33 (s, 2H), 6.48 (d, *J* = 7.9 Hz, 4H), 6.55 (d, *J* = 8.1 Hz, 2H), 6.85 (s, 1H), 7.13 (q, *J* = 13.3 Hz, 3H), 7.30 – 7.45 (m, 8H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 8.66 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.3, 14.6, 14.8, 22.4, 22.5, 22.9, 23.1, 29.6, 32.1, 36.1, 36.5, 41.6, 44.4, 44.6, 50.4, 52.7, 54.7, 61.8, 66.5, 70.0, 77.2, 100.4, 111.8, 112.0, 114.5, 122.5, 126.3, 126.5, 127.7, 127.9, 128.2, 128.4, 128.8, 129.0, 132.0, 135.9, 136.1, 140.1, 169.0. HRMS (ESI) calculated for $C_{39}H_{42}ClN_3O_5$ (m/z): $[M+H]^+$ 668.2813, found: $[M+H]^+$ 668.2811.

Ethyl 6-chloro-3-(2-(cyclohexylamino)-1-(*N*-(4-((4-fluorobenzyl)oxy)benzyl) acetamido)-2-oxoethyl)-1*H*-indole-2-carboxylate (23a)

White solid, 76% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 0.89 (d, *J* = 7.5 Hz, 1H), 0.96 – 1.22 (m, 6H), 1.23 – 1.45 (m, 12H), 1.48 – 1.98 (m, 12H), 2.04 (s, 1H), 2.16 (s, 3H), 2.42 (s, 2H), 3.88 (dd, *J* = 38.6, 8.2 Hz, 2H), 4.04 (d, *J* = 15.1 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 1H), 4.24 – 4.54 (m, 4H), 4.61 – 4.75 (m, 1H), 4.88 (s, 3H), 5.58 (d, *J* = 7.7 Hz, 1H), 6.03 (d, *J* = 7.7 Hz, 1H), 6.46 (s, 2H), 6.52 (d, *J* = 7.6 Hz, 1H), 6.59 (d, *J* = 4.9 Hz, 4H), 6.95 (s, 1H), 7.07 (dt, *J* = 14.9, 8.3 Hz, 4H), 7.23 (s, 1H), 7.30 – 7.39 (m, 3H), 7.82 (d, *J* = 8.7 Hz, 1H), 9.50 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.3, 14.5, 22.3, 24.9, 25.0, 25.6, 33.0, 33.1, 49.0, 50.1, 54.5, 60.6, 61.7, 69.4, 112.1, 114.3, 114.5, 115.5, 115.7, 122.4, 122.9, 126.5, 129.4, 129.4, 131.6, 136.1, 157.3, 160.6, 161.0, 161.6, 163.6, 169.0, 172.0. HRMS (ESI) calculated for $C_{35}H_{37}ClFN_3O_5$ (m/z): $[M+H]^+$ 634.2406, found: $[M+H]^+$ 634.2410.

Ethyl 3-(2-((1*R*,3*s*)-adamantan-1-ylamino)-2-oxo-1-(*N*-phenethylformamido) ethyl)-6-chloro-1*H*-indole-2-carboxylate (24a)

White solid, 65% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 0.88 (t, *J* = 6.8 Hz, 3H), 1.28 (d, *J* = 11.6 Hz, 5H), 1.37 (t, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H), 1.64 (d, *J* = 15.1 Hz, 13H), 1.85 (s, 2H), 1.97 (d, *J* = 13.0 Hz, 11H), 2.01 – 2.11 (m, 7H), 2.14 (s, 1H), 2.17 – 2.26 (m, 1H), 2.30 (s, 1H), 2.71 – 2.81 (m, 1H), 3.26 – 3.34 (m, 1H), 3.47 (d, *J* = 7.7 Hz, 1H), 3.56 (s, 1H), 3.79 – 3.89 (m, 1H), 4.33 – 4.48 (m, 3H), 5.40 (s, 1H), 5.50 (s, 1H), 6.20 (s, 1H), 6.63 (dd, *J* = 21.6, 4.6 Hz, 3H), 6.78 (s, 1H), 7.10 (d, *J* = 4.4 Hz, 4H), 7.18 (t, *J* = 7.8 Hz, 1H), 7.36 (s, 1H), 7.65 (d, *J* = 8.7 Hz, 1H), 7.90 (d, *J* = 8.8 Hz, 1H), 8.09 (s, 1H), 8.38 (s, 1H), 9.79 (d, *J* = 19.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.3, 14.5,

14.6, 22.9, 29.2, 29.5, 29.5, 29.6, 32.1, 34.4, 36.0, 36.3, 36.4, 37.6, 41.5, 41.6, 42.0, 44.4, 46.1, 48.2, 52.8, 53.0, 57.8, 61.9, 62.2, 112.6, 116.2, 122.8, 123.4, 124.9, 126.3, 126.6, 128.4, 128.6, 128.7, 128.7, 132.2, 136.2, 138.8, 140.3, 160.9, 163.5, 164.3, 168.2. HRMS (ESI) calculated for $C_{32}H_{36}ClN_3O_4$ (m/z): $[M+H]^+$ 562.2394, found: $[M+H]^+$ 562.2395.

Ethyl 6-chloro-3-(2-oxo-2-(phenethylamino)-1-(*N*-phenethylformamido)ethyl)-1*H*-indole-2-carboxylate (25a)

White solid, 92% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.26 (t, *J* = 7.0 Hz, 2H), 1.36 (dt, *J* = 21.9, 7.1 Hz, 5H), 1.88 (td, *J* = 12.2, 5.3 Hz, 1H), 2.04 (s, 1H), 2.26 (ddd, *J* = 29.2, 13.1, 5.7 Hz, 1H), 2.79 (dddt, *J* = 45.7, 24.2, 11.7, 5.7 Hz, 6H), 3.11 – 3.24 (m, 1H), 3.37 – 3.79 (m, 7H), 4.34 (dq, *J* = 18.1, 10.6, 8.8 Hz, 3H), 5.91 (s, 1H), 6.24 (d, *J* = 13.3 Hz, 2H), 6.56 – 6.69 (m, 3H), 6.82 (s, 1H), 7.01 (d, *J* = 6.9 Hz, 1H), 7.04 – 7.23 (m, 14H), 7.22 – 7.34 (m, 4H), 7.36 (s, 1H), 7.69 (d, *J* = 8.8 Hz, 1H), 8.03 (s, 1H), 8.34 (s, 1H), 9.98 (d, *J* = 36.2 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.4, 14.4, 14.5, 34.1, 35.4, 35.6, 35.6, 37.3, 39.4, 41.2, 41.3, 46.1, 48.2, 52.4, 57.4, 61.8, 62.1, 112.6, 122.3, 122.8, 124.8, 125.7, 126.4, 126.6, 126.7, 126.8, 126.9, 128.4, 128.7, 128.7, 128.7, 128.8, 128.8, 128.9, 128.9, 129.0, 132.0, 136.2, 137.9, 138.4, 138.5, 138.7, 160.9, 163.6, 164.2, 169.5. HRMS (ESI) calculated for $C_{30}H_{30}ClN_3O_4$ (m/z): $[M+H]^+$ 532.1925, found: $[M+H]^+$ 532.1926.

Ethyl 3-(2-(tert-butylamino)-1-(*N*-(3-morpholinopropyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (26a)

Yellow oil, 81% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 11.32 (s, 7H), 1.37 (d, *J* = 3.3 Hz, 11H), 1.39 – 1.45 (m, 6H), 2.03 – 2.13 (m, 11H), 2.17

(d, *J* = 15.4 Hz, 3H), 3.22 (s, 1H), 3.36 (d, *J* = 20.2 Hz, 2H), 3.52 (d, *J* = 15.9 Hz, 8H), 3.65 (s, 1H), 3.73 (s, 1H), 4.31 – 4.50 (m, 4H), 5.56 (s, 1H), 5.63 (s, 1H), 6.17 (s, 1H), 6.72 (s, 1H), 7.12 – 7.16 (m, 2H), 7.27 – 7.31 (m, 1H), 7.64 (d, *J* = 8.8 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 1H), 8.31 (s, 1H), 8.33 (s, 1H), 9.90 (s, 1H), 10.03 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.6, 24.8, 27.3, 28.8, 42.7, 44.5, 52.1, 52.4, 52.9, 53.5, 53.5, 55.4, 56.5, 57.7, 61.9, 62.1, 66.9, 67.0, 112.2, 112.4, 114.6, 116.0, 122.5, 122.6, 122.7, 123.2, 124.8, 125.6, 126.4, 127.3, 132.1, 132.2, 136.1, 136.2, 160.9, 161.2, 163.8, 164.3, 168.5, 168.7. HRMS (ESI) calculated for $C_{25}H_{35}ClN_4O_5$ (m/z): $[M+H]^+$ 507.2296, found: $[M+H]^+$ 507.2298.

Procedure of the deformylation reaction and analytical data of compound 18

To a stirred solution of the corresponding formylated U-4CR adduct **5m** (0.3 mmol) in water, HCl in dioxane (4 N, 5 ml) was added. The reaction mixture was refluxed overnight. Afterwards, the solvent was removed and the residue was washed with NaOH 2 M. The resulting oil was dried affording the desired compound ethyl 3-(1-((4-((2-bromobenzyl)oxy)benzyl)amino)-2-(tert-butylamino)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (**18**) as yellow oil, 72% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.33 (t, *J* = 7.0 Hz, 3H), 1.40 (d, *J* = 4.7 Hz, 9H), 3.69 (d, *J* = 21.7 Hz, 2H), 4.27 (d, *J* = 6.7 Hz, 2H), 5.11 (s, 3H), 6.91 (d, *J* = 7.3 Hz, 2H), 7.00 (d, *J* = 8.6 Hz, 1H), 7.18 (d, *J* = 8.5 Hz, 3H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.53 (d, *J* = 7.7 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.5, 29.0, 29.5, 46.3, 51.1, 52.1, 58.0, 61.3, 69.8, 112.4, 115.1, 121.5, 121.7, 122.2, 122.5, 125.2, 125.4, 127.7, 128.4, 128.6, 129.1, 129.4, 129.7, 131.5, 132.8, 132.8, 136.6, 136.6, 158.0, 161.6, 171.4. HRMS (ESI) calculated for $C_{31}H_{33}BrClN_3O_4$ (m/z): $[M+H]^+$ 626.1343, found: $[M+H]^+$ 626.1336.

General procedure the methylation reaction and analytical data of compound 20

To a stirred solution of the corresponding deformylated U-4CR adduct **18** (0.2 mmol) in THF, MeI (0.32 mmol) and K_2CO_3 (0.22 mmol) were added. The reaction mixture was stirred at rt overnight. It was quenched with water and extracted with DCM. Organic layer was collected, washed with water and brine, dried over anhydrous $MgSO_4$ and evaporated affording the desired compound ethyl 3-(1-((4-((2-bromobenzyl)oxy)benzyl)(methyl)amino)-2-(tert-butylamino)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (**20**) as yellow oil, 88% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.39 (d, J = 6.5 Hz, 3H), 1.46 (d, J = 5.0 Hz, 8H), 2.08 (s, 3H), 3.51 (s, 2H), 4.35 (s, 2H), 5.12 (s, 2H), 6.94 (d, J = 8.1 Hz, 2H), 7.02 (d, J = 7.1 Hz, 2H), 7.16 – 7.25 (m, 4H), 7.33 (t, J = 7.3 Hz, 2H), 7.56 (dd, J = 18.3, 7.7 Hz, 3H), 7.59 – 7.74 (m, 2H), 7.84 (dd, J = 20.4, 10.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.5, 25.8, 29.0, 29.5, 30.5, 39.6, 51.1, 59.7, 61.3, 65.3, 68.2, 69.7, 112.3, 115.0, 115.1, 121.4, 122.5, 125.7, 127.8, 128.3, 129.1, 129.4, 130.0, 131.9, 132.8, 136.5, 157.8, 161.7. HRMS (ESI) calculated for $C_{32}H_{35}BrClN_3O_4$ (m/z): $[M+H]^+$ 640.1499, found: $[M+H]^+$ 640.1501.

Procedure of the amidation reaction and analytical data of compound 12

To a stirred solution of the corresponding U-4CR adduct **5m** (0.5 mmol) in THF, DBU (1.0 mmol) and 2-morpholinoethanamine (10.0 mmol) were added. The reaction mixture was refluxed for 24 h. It was quenched with water and extracted with DCM. Organic layer was collected, washed with water and brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the product was purified by flash chromatography (EtOAc, DCM-MeOH 5:1) giving the desired product 3-(1-(*N*-(4-((2-bromobenzyl)oxy)benzyl)formamido)-2-(tert-butylamino)-2-oxoethyl)-6-chloro-*N*-(2-

morpholinoethyl)-1*H*-indole-2-carboxamide (**12**) as yellow solid, 65% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.20 (s, 3H), 1.26 (s, 9H), 2.39 – 2.57 (m, 9H), 2.60 (dt, *J* = 12.3, 6.2 Hz, 1H), 3.30 – 3.40 (m, 1H), 3.42 – 3.61 (m, 3H), 3.59 – 3.75 (m, 7H), 4.42 (d, *J* = 15.5 Hz, 1H), 4.72 (d, *J* = 15.5 Hz, 1H), 4.99 (s, 2H), 5.07 (s, 1H), 5.69 (s, 1H), 6.46 (s, 1H), 6.59 (d, *J* = 8.5 Hz, 2H), 6.67 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.3 Hz, 1H), 7.08 (p, *J* = 7.5 Hz, 2H), 7.17 (t, *J* = 7.7 Hz, 1H), 7.31 (q, *J* = 7.6 Hz, 3H), 7.37 – 7.53 (m, 3H), 7.57 (t, *J* = 8.7 Hz, 1H), 7.62 (d, *J* = 8.7 Hz, 1H), 8.35 (s, 1H), 10.21 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 28.5, 28.7, 36.5, 37.0, 46.5, 50.1, 52.3, 52.5, 53.6, 53.9, 57.1, 57.4, 58.0, 66.8, 67.1, 67.2, 69.6, 69.7, 108.2, 112.3, 112.5, 114.8, 115.2, 121.2, 122.0, 122.2, 122.5, 125.1, 125.6, 127.8, 128.4, 129.0, 129.1, 129.4, 129.5, 129.6, 130.1, 130.8, 131.9, 132.9, 135.8, 135.9, 136.2, 157.9, 158.2, 161.2, 164.7, 164.8, 167.7. HRMS (ESI) calculated for $C_{36}H_{41}BrClN_5O_5$ (m/z): $[M+H]^+$ 738.1980, found: $[M+H]^+$ 738.1981.

Procedure and analytical data of the ethyl 3-(2-(tert-butylamino)-1-(*N*-(4-nitrobenzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (7)

To a stirred solution of 4-nitrobenzylamine (1.0 mmol) in MeOH (1 M), the 3-indolecarboxaldehyde **2** (1.0 mmol), ^{t}BuNC (1.1 mmol) and formic acid (1.1 mmol) were added. The reaction mixture was stirred at rt for 2 d (TLC monitored). Afterwards, the solvent was evaporated and the mixture was purified by flash chromatography (petroleum ether/EtOAc 1:1 or EtOAc) giving the desired product **7** as yellow solid, 70% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.30 (s, 9H), 1.36 (s, 5H), 1.39 (s, 5H), 1.41 (dd, *J* = 7.3, 2.0 Hz, 3H), 4.27 (d, *J* = 16.1 Hz, 1H), 4.36 (dd, *J* = 13.0, 6.3 Hz, 2H), 5.19 (d, *J* = 16.0 Hz, 1H), 5.65 (d, *J* = 7.8 Hz, 1H), 6.20 (s, 1H), 6.66 (d, *J* = 8.2 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 7.13 – 7.19 (m, 1H), 7.34 (d, *J* = 7.0

Hz, 1H), 7.72 (t, *J* = 8.1 Hz, 1H), 7.78 (d, *J* = 7.4 Hz, 1H), 8.26 (d, *J* = 12.3 Hz, 1H), 8.48 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.5, 14.6, 28.6, 28.7, 28.8, 28.9, 29.1, 30.9, 31.1, 50.6, 52.1, 52.3, 56.9, 61.9, 112.4, 112.6, 114.8, 122.1, 122.3, 122.7, 122.7, 122.9, 123.0, 124.7, 125.5, 126.3, 126.5, 126.7, 127.5, 127.6, 132.1, 136.3, 145.5, 145.6, 146.6, 146.8, 160.9, 163.3, 163.5, 163.6, 164.5, 164.6, 168.1, 168.2. HRMS (ESI) calculated for $C_{25}H_{27}ClN_4O_6$ (m/z): $[M+H]^+$ 515.1619, found: $[M+H]^+$ 515.1619.

General procedure of the reductive amination

To a stirred solution of the U-4CR adduct **7** (1.0 mmol) in MeOH, the corresponding benzaldehyde (1.2 mmol), zinc (4 mmol) and acetic acid (7.0 mmol) were added. The reaction mixture was stirred at rt for 2 h. It was quenched with water and extracted with EtOAc. Organic layer was collected, washed with water and brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the product was purified by flash chromatography (petroleum ether-EtOAc, 2:1) giving the desired products Ethyl 3-(2-(tert-butylamino)-1-(*N*-(4-((4-bromobenzyl)amino)benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylate (**8a**); Yellow solid, 65% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 11.30 (s, 9H), 1.38 (t, *J* = 10.0 Hz, 6H), 4.19 (dd, *J* =15.0 Hz, 1H), 4.29-4.33 (m, 4H), 4.41 (dd, 1H, *J* = 15.0 Hz), 4.67 (dd, *J* =15.0 Hz, 1H), 5.17 (d, *J* = 15.0 Hz, 1H), 5.69 (s, 1H), 5.73 (s, 1H), 6.19 (s, 1H), 6.54 (d, *J* = 10.0 Hz, 2H), 6.76 (d, *J* = 10.0 Hz, 2H), 6.77 (s, 1H), 7.14-7.16 (m, 2H), 7.24 (d, *J* = 10.0 Hz, 2H), 7.29 (d, *J* = 10.0 Hz 2H), 7.54 (d, *J* = 5.0 Hz, 1H), 7.56 (d, *J* = 5.0 Hz, 1H), 7.69 (s, 1H), 7.71 (d, *J* = 10.0 Hz, 2H), 7.86 (d, *J* = 10.0 Hz, 1H), 8.19 (d, *J* = 5.0 Hz, 2H), 8.20 (d, *J* = 5.0 Hz, 2H), 8.45 (s, 1H), 8.48 (s, 1H), 10.14 (br s, 1H), 10.34 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.6, 28.7, 28.8, 46.0, 49.8, 52.2, 61.3, 112.7,

114.8, 120.9, 122.2, 122.8, 125.2, 125.6, 126.4, 126.8, 129.4, 130.6, 134.1, 136.4, 140.3, 147.2, 160.8, 163.7, 164.7, 168.3. LC-MS (DAD/ESI): t_R = 3.94 min, calculated for $C_{32}H_{34}BrClN_4O_4$ (m/z): $[M-H]^-$ 651.15, found: $[M-H]^-$ 651.10.

General procedure the hydrolysis and analytical data of adducts 6a-ai, 8, 9, 13-17, 19, 21, 22-26

To a stirred solution of the corresponding compound **5** (1.0 equiv.) in EtOH-water (1:1), LiOH (10.0 equiv.) was added and the reaction mixture stirred at rt for 3 days. Afterwards, pH was adjusted to approximately 6 with the addition of 1 N HCl and then the reaction mixture extracted with DCM. The organic layer was separated, washed with water, dried over anhydrous $MgSO_4$ and evaporated, affording the corresponding compounds **6**.

3-(2-(tert-butylamino)-1-(*N*-(4-((4-fluorobenzyl)oxy)benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylic acid (6a)

White solid, 76% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.15 (s, 9H), 1.26 (s, 9H), 1.33 (s, 9H), 1.37 (s, 9H), 4.28-5.00 (m, 8H), 5.28 (s, 1H), 5.74 (s, 1H), 6.22 (s, 2H), 6.63 (s, 1H), 6.91-7.18 (m, 10H), 7.46 (s, 2H), 8.02 (s, 1H), 8.25 (d, J = 10.0 Hz, 1H), 8.53 (s, 1H), 9.75 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 28.5, 29.1, 31.0, 112.1, 112.4, 114.3, 114.4, 115.6, 121.4, 121.5, 121.6, 124.8, 127.5, 129.5, 130.0, 131.5, 136.0, 136.1, 136.2, 157.3, 161.0, 161.1, 161.7, 163.6, 168.5; LC-MS (DAD/ESI): t_R = 5.03 min, calculated for $C_{30}H_{29}ClFN_3O_5$ (m/z): $[M-H]^-$ 564.18, found: $[M-H]^-$ 564.11.

3-(2-(tert-butylamino)-1-(*N*-(4-((3-fluorobenzyl)oxy)benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylic acid (6b)

White solid, 68% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.20 (s, 9H), 4.35 (d, J = 15.2 Hz, 1H), 4.85 (d, J = 14.9 Hz, 1H), 5.01 (d, J = 21.6 Hz, 3H), 5.73 (s, 1H), 6.23 (s, 1H), 6.61 (s, 2H), 6.75 (d, J = 8.1 Hz, 3H), 6.95 (d, J = 8.1 Hz, 3H), 7.08 (t, J = 9.3 Hz, 3H), 7.17 (t, J = 7.4 Hz, 2H), 7.32 (d, J = 6.6 Hz, 2H), 7.45 (dd, J = 17.3, 9.9 Hz, 3H), 7.63 (d, J = 8.6 Hz, 1H), 8.45 (s, 1H), 10.80 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm]; LC-MS (DAD/ESI): t_R = 4.07 min, calculated for $C_{30}H_{29}ClFN_3O_5$ (m/z): $[M+H]^+$ 566.18, found: $[M-H]^-$ 564.33.

3-(2-(tert-butylamino)-1-(*N*-(4-((2-fluorobenzyl)oxy)benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylic acid (6c)

White solid, 71% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.19 (s, 10H), 1.27 (s, 6H), 4.33 (d, J = 15.2 Hz, 1H), 4.80 (d, J = 14.9 Hz, 1H), 5.02 (d, J = 21.6 Hz, 3H), 5.73 (s, 1H), 6.20 (s, 1H), 6.60 (s, 2H), 6.73 (d, J = 8.1 Hz, 3H), 6.95 (d, J = 8.1 Hz, 3H), 7.08 (t, J = 9.3 Hz, 3H), 7.17 (t, J = 7.4 Hz, 2H), 7.32 (d, J = 6.6 Hz, 2H), 7.45 (dd, J = 17.3, 9.9 Hz, 3H), 7.63 (d, J = 8.6 Hz, 1H), 8.45 (s, 1H), 10.80 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 28.3, 28.5, 30.8, 46.0, 49.4, 51.5, 52.8, 57.1, 63.6, 63.6, 112.1, 112.4, 114.2, 114.3, 115.1, 115.3, 121.6, 122.2, 124.2, 124.2, 124.9, 127.5, 129.1, 129.2, 129.6, 129.7, 129.7, 130.1, 157.4, 164.5. HRMS (ESI) calculated for $C_{30}H_{29}ClFN_3O_5$ (m/z): $[M+H]^+$ 565.1780, found: $[M+H]^+$ 565.1783.

3-(2-(tert-butylamino)-1-(*N*-(4-((3,5-difluorobenzyl)oxy)benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylic acid (6d)

White solid, 68% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.18 (s, 9H), 1.34 (s, 9H), 1.38 (m, 6H), 4.37-4.87 (m, 15H), 5.29 (s, 1H), 5.70 (s, 2H), 6.30-6.32 (m, 4H), 6.51-7.20 (m, 15H), 7.72 (s, 2H,), 8.03 (s, 1H), 8.25 (d, 2H, *J* = 15Hz), 8.52 (s, 1H), 9.62 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 28.6, 28.8, 46.3, 49.7, 52.1, 52.8, 57.7, 61.8, 68.4, 68.7, 111.9, 112.3, 114.4, 114.9, 122.5, 122.7, 123.2, 125.01, 126.6, 129.3, 130.6, 132.1, 136.1, 137.6, 157.3, 157.6, 160.8, 163.7, 164.8, 168.3. LC-MS (DAD/ESI): t_R = 4.80 min, calculated for $C_{30}H_{28}ClF_2N_3O_5$ (m/z): $[M-H]^-$ 582.17, found: $[M-H]^-$ 582.03.

3-(2-(Tert-butylamino)-1-(*N*-(4-((4-chlorobenzyl)oxy)benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylic acid (6e)

White solid, 75% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.15 (s, 9H), 4.34-4.37 (m, 2H), 5.02 (s, 2H), 6.52 (s, 1H), 6.59 (s, 1H), 6.80-6.82 (m, 2H), 7.00-7.02 (m, 1H), 7.08-7.09 (m, 2H), 7.37-7.43 (m, 6H), 7.72 (m, 1H), 8.36 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 27.4, 27.5, 46.8, 50.8, 56.7, 68.5, 111.5, 113.9, 114.1, 114.2, 120.2, 121.4, 125.1, 126.9, 128.1, 128.2, 128.7, 128.9, 129.1, 129.4, 133.1, 135.3, 136.3, 157.8, 165.3, 169.9; LC-MS (DAD/ESI): t_R = 5.08 min, calculated for $C_{30}H_{29}Cl_2N_3O_5$ (m/z): $[M-H]^-$ 580.15, found: $[M-H]^-$ 580.11.

3-(2-(Tert-butylamino)-1-(*N*-(4-((3-chlorobenzyl)oxy)benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylic acid (6f)

White solid, 50% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.21 (s, 9H), 1.27 (s, 9H), 1.35 (s, 9H), 1.38 (s, 9H), 4.23-4.78 (m, 4H), 4.83 (s, 2H), 4.87 (s, 2H), 5.67 (s, 1H), 6.22 (s, 1H), 6.53 (d, 2H, *J*= 10Hz), 6.56 (d, 2H, *J*= 10Hz), 6.67 (d, 2H, *J*= 10Hz), 6.79 (s, 1H), 6.90 (s, 1H), 7.06 (d, 2H, *J*= 10Hz), 7.20-7.35 (m, 7H), 7.60 (d, 1H, *J*= 5Hz), 7.79 (dd, 1H, *J*= 10Hz), 8.03 (s, 1H), 8.25 (d, 1H, *J*= 10Hz), 8.35 (s, 1H), 8.54 (s, 1H), 9.35 (br s, 1H), 9.63 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 28.7, 28.8, 29.2, 31.0, 46.1, 52.3, 57.2, 69.5, 112.1, 112.4, 114.4, 115.0, 122.6, 125.5, 127.5, 128.3, 129.5, 130.1, 131.5, 136.0, 136.2, 157.3, 161.1, 163.8, 164.7, 168.7. HRMS (ESI) calculated for $C_{30}H_{29}Cl_2N_3O_5$ (m/z): $[M+H]^+$ 582.1484, found: $[M+H]^+$ 582.1484.

3-(2-(Tert-butylamino)-1-(*N*-(4-((2-chlorobenzyl)oxy)benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylic acid (6g)

White solid, 60% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.19 (s, 9H), 1.28 (s, 9H), 1.33 (s, 9H), 1.38 (s, 9H), 4.23-4.78 (m, 4H), 4.83 (s, 2H), 4.87 (s, 2H), 5.67 (s, 1H), 6.22 (s, 1H), 6.55 (d, 2H, *J*= 10Hz), 6.58 (d, 2H, *J*= 10Hz), 6.67 (d, 2H, *J*= 10Hz), 6.79 (s, 1H), 6.90 (s, 1H), 7.06 (d, 2H, *J*= 10Hz), 7.20-7.35 (m, 7H), 7.60 (d, 1H, *J*= 5Hz), 7.79 (dd, 1H, *J*= 10Hz), 8.05 (s, 1H), 8.27 (d, 1H, *J*= 10Hz), 8.39 (s, 1H), 8.51 (s, 1H), 9.31 (br s, 1H), 9.65 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 28.7, 31.0, 46.1, 52.3, 57.2, 69.5, 112.1, 112.4, 113.4, 115.0, 122.6, 125.5, 127.5, 128.3, 129.5, 130.1, 131.5, 136.0, 136.2, 157.3, 160.1, 164.8, 165.7, 168.7; ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm]; LC-MS

(DAD/ESI): t_R = 4.21 min, calculated for $C_{30}H_{29}Cl_2N_3O_5$ (m/z): $[M+H]^+$ 582.15, found: $[M+H]^+$ 582.32.

3-(2-(tert-butylamino)-1-(*N*-(4-((3,4-dichlorobenzyl)oxy)benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylic acid (6h)

White solid, 65% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.15 (s, 9H), 4.28-4.41 (m, 2H), 4.77 (s, 2H), 5.82 (s, 1H), 6.31 (s, 1H), 6.53 (s, 1H), 6.59 (s, 1H), 6.89-7.05 (m, 4H), 7.20-7.65 (m, 4H), 8.23-8.29 (m, 1H), 8.54 (s, 1H), 10.10 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm]; 28.6, 28.8, 29.9, 46.8, 52.3, 56.7, 68.8, 111.5, 113.9, 115.1, 122.3, 126.7, 129.3, 130.8, 132.2, 136.3, 137.5, 157.9, 165.3, 169.9. LC-MS (DAD/ESI): t_R = 5.44 min, calculated for $C_{30}H_{28}Cl_3N_3O_5$ (m/z): $[M-H]^-$ 614.11, found: $[M+H]^+$ 614.05.

3-(2-(tert-butylamino)-1-(*N*-(4-((2,4-dichlorobenzyl)oxy)benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylic acid (6i)

White solid, 59% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.19 (s, 9H), 1.27 (s, 3H), 1.33 (s, 1H), 1.35 (s, 1H), 4.26 – 4.33 (m, 2H), 4.88 (d, J = 15.0 Hz, 1H), 4.99 (s, 1H), 5.03 (s, 2H), 6.16 (d, J = 6.2 Hz, 1H), 6.29 (s, 1H), 6.60 (s, 1H), 6.67 – 6.74 (m, 2H), 6.94 (d, J = 8.5 Hz, 2H), 7.01 – 7.07 (m, 1H), 7.27 – 7.33 (m, 1H), 7.42 (t, J = 2.2 Hz, 2H), 7.68 (d, J = 8.8 Hz, 1H), 8.38 (s, 1H), 11.44 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 27.9, 28.1, 28.3, 30.2, 39.1, 39.2, 39.4, 39.6, 39.7, 45.8, 48.8, 50.9, 56.4, 66.0, 112.0, 113.7, 114.2, 120.7, 120.9, 121.7, 124.3, 126.8, 126.9, 127.0, 128.5, 128.7, 129.3, 129.3, 129.8, 129.9, 130.0, 132.6, 132.9, 133.4, 135.9, 156.5, 162.4, 164.0, 168.1. HRMS (ESI) calculated for $C_{30}H_{28}Cl_3N_3O_5$ (m/z): $[M+H]^+$ 616.1095, found: $[M+H]^+$ 616.1090.

3-(2-(tert-butylamino)-1-(*N*-(4-((2,6-dichlorobenzyl)oxy)benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylic acid (6j)

White solid, 58% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.20 (s, 9H), 1.28 (s, 5H), 1.34 (s, 4H), 1.38 (s, 4H), 4.35 (t, *J* = 15.4 Hz, 1H), 4.80 (d, *J* = 14.9 Hz, 1H), 5.17 (d, *J* = 23.8 Hz, 3H), 5.62 (d, *J* = 10.6 Hz, 1H), 6.20 (s, 1H), 6.66 (s, 1H), 6.80 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 7.8 Hz, 2H), 7.10 (d, *J* = 7.2 Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 1H), 7.30 – 7.40 (m, 3H), 7.43 (s, 1H), 7.63 (d, *J* = 8.6 Hz, 1H), 8.47 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 28.5, 28.7, 29.0, 31.0, 46.2, 51.8, 57.4, 65.3, 65.5, 112.2, 112.5, 114.7, 114.8, 115.1, 122.1, 122.5, 122.9, 125.1, 127.4, 127.7, 128.6, 129.5, 130.4, 130.6, 131.3, 132.2, 136.3, 137.0, 158.0, 160.7, 163.0, 163.7, 164.8, 168.4. HRMS (ESI) calculated for $C_{30}H_{28}Cl_3N_3O_5$ (m/z): $[M+H]^+$ 616.1095, found: $[M+H]^+$ 616.1094.

3-(2-(Tert-butylamino)-1-(*N*-(4-((4-bromobenzyl)oxy)benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylic acid (6k)

White solid, 67% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.19 (s, 9H), 1.26 (s, 9H), 1.33 (s, 9H), 1.36 (s, 9H), 4.26-4.70 (m, 8H), 4.83 (s, 2H), 4.86 (s, 2H), 6.51 (s, 3H), 6.62 (s, 1H), 6.63 (s, 1H), 6.76 (s, 1H), 6.84 (s, 1H), 6.85 (s, 1H), 7.09 (d, 2H, *J*= 10 Hz), 7.16-7.21 (m, 6H), 7.46 (d, 2H, *J*= 10 Hz), 7.54 (dd, 1H, *J*= 10 Hz), 7.74 (dd, 1H, *J*= 10 Hz), 8.02 (s, 1H), 8.24 (d, 1H, *J*= 15 Hz), 8.34 (s, 1H), 8.53 (s, 1H), 9.22 (br s, 1H), 9.60 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 28.3, 28.5, 28.7, 30.7, 46.1, 51.5, 57.2, 69.0, 112.1, 112.4, 114.3, 114.4, 121.4, 121.5, 121.6, 124.8, 127.5, 128.9, 130.0, 131.5, 136.0, 136.1, 136.2, 157.3, 160.8, 163.0, 164.7, 168.5. LC-MS (DAD/ESI): t_R = 5.06 min, calculated for $C_{30}H_{29}BrClN_3O_5$ (m/z): $[M-H]^-$ 624.10, found: $[M-H]^-$ 624.11.

3-(1-(*N*-(4-((3-bromobenzyl)oxy)benzyl)formamido)-2-(tert-butylamino)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylic acid (6l)

White solid, 53% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.19 (s, 9H), 1.27 (s, 4H), 1.34 (s, 2H), 4.30 (dd, *J* = 15.5, 7.7 Hz, 1H), 4.82 (d, *J* = 15.0 Hz, 1H), 4.95 (s, 2H), 5.32 (s, 1H), 5.75 (d, *J* = 7.1 Hz, 2H), 6.18 (s, 1H), 6.58 (s, 2H), 6.69 (d, *J* = 8.5 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 7.04 – 7.11 (m, 2H), 7.25 (t, *J* = 7.8 Hz, 2H), 7.29 – 7.38 (m, 2H), 7.39 – 7.46 (m, 2H), 7.55 (d, *J* = 7.3 Hz, 1H), 7.63 (d, *J* = 8.8 Hz, 1H), 8.45 (s, 1H), 10.76 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 28.4, 28.6, 28.7, 46.1, 49.5, 51.6, 52.9, 57.2, 69.0, 112.1, 112.5, 114.3, 114.4, 114.8, 121.6, 121.9, 122.3, 122.7, 124.9, 125.8, 127.5, 129.2, 130.1, 130.2, 130.9, 136.3, 139.5, 157.4, 162.9, 163.6, 164.7, 168.4. HRMS (ESI) calculated for $C_{30}H_{29}BrClN_3O_5$ (m/z): $[M+H]^+$ 626.0975, found: $[M+H]^+$ 626.0978.

3-(1-(*N*-(4-((2-bromobenzyl)oxy)benzyl)formamido)-2-(tert-butylamino)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylic acid (6m)

White solid, 49% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.16 (s, 9H), 1.33 (s, 9H), 1.37 (s, 9H), 1.36 (s, 9H), 4.31-4.71 (m, 6H), 4.63-4.71 (s, 6H), 5.08 (s, 1H), 5.35 (s, 2H), 5.78-5.97 (m, 3H), 6.32-6.43 (m, 2H), 6.62-6.80 (m, 9H), 6.92-7.52 (m, 15H), 8.02 (s, 1H), 8.25 (d, 1H, *J*= 10Hz), 8.54 (s, 1H), 9.86 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 28.6, 29.2, 31.1, 46.1, 50.8, 57.2, 69.8, 112.1, 112.4, 115.1, 115.6, 122.7, 127.5, 129.2, 129.5, 132.9, 136.6, 158.0, 161.0, 163.6, 168.5. LC-MS (DAD/ESI): t_R = 5.07 min, calculated for $C_{30}H_{29}BrClN_3O_5$ (m/z): $[M-H]^-$ 624.10, found: $[M-H]^-$ 624.04.

3-(2-(tert-butylamino)-1-(*N*-(4-((4-iodobenzyl)oxy)benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylic acid (6n)

White solid, 50% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.09 – 1.19 (m, 14H), 1.21 – 1.28 (m, 13H), 1.28 – 1.36 (m, 12H), 4.32 (dd, *J* = 15.2, 7.8 Hz, 3H), 4.75 – 4.98 (m, 6H), 5.84 (d, *J* = 28.3 Hz, 2H), 6.11 – 6.23 (m, 1H), 6.43 – 6.63 (m, 3H), 6.70 (d, *J* = 8.3 Hz, 3H), 6.82 – 6.98 (m, 3H), 6.99 – 7.20 (m, 4H), 7.39 (dt, *J* = 30.4, 6.2 Hz, 5H), 7.52 – 7.68 (m, 3H), 7.76 (d, *J* = 6.2 Hz, 2H), 8.24 – 8.47 (m, 2H), 11.06 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 28.3, 28.5, 28.7, 30.7, 39.6, 39.8, 40.0, 40.1, 40.3, 46.0, 49.3, 51.4, 52.8, 57.0, 69.1, 93.2, 112.4, 114.2, 114.3, 114.7, 121.4, 121.6, 122.2, 122.5, 124.7, 127.4, 129.1, 130.0, 130.7, 136.3, 136.7, 137.4, 157.3, 162.7, 163.3, 164.4, 168.3. HRMS (ESI) calculated for $C_{30}H_{29}ClIN_3O_5$ (m/z): $[M+H]^+$ 674.0840, found: $[M+H]^+$ 674.0844.

3-(2-(tert-butylamino)-1-(*N*-(4-((3-iodobenzyl)oxy)benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylic acid (6o)

White solid, 40% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.11 – 1.21 (m, 14H), 1.21 – 1.29 (m, 13H), 1.29 – 1.38 (m, 12H), 4.30 (dd, *J* = 15.2, 7.8 Hz, 3H), 4.74 – 4.97 (m, 6H), 5.82 (d, *J* = 28.3 Hz, 2H), 6.10 – 6.22 (m, 1H), 6.43 – 6.63 (m, 3H), 6.70 (d, *J* = 8.3 Hz, 3H), 6.82 – 6.98 (m, 3H), 6.99 – 7.20 (m, 4H), 7.39 (dt, *J* = 30.4, 6.2 Hz, 5H), 7.52 – 7.68 (m, 3H), 7.76 (d, *J* = 6.2 Hz, 2H), 8.24 – 8.47 (m, 2H), 11.06 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 28.2, 28.4, 28.5, 28.7, 29.4, 30.6, 39.5, 39.7, 39.8, 40.0, 40.2, 46.0, 49.3, 51.4, 52.7, 57.0, 68.7, 112.1, 112.4, 114.1, 114.2, 114.6, 121.5, 122.1, 122.5, 124.7, 126.3, 127.2, 127.3, 129.0, 130.0, 130.1, 135.9, 136.2, 136.7, 139.3, 157.2, 162.7, 163.3, 164.4,

168.3. HRMS (ESI) calculated for $C_{30}H_{29}ClIN_3O_5$ (m/z): $[M+H]^+$ 674.0840, found: $[M+H]^+$ 674.0843.

3-(2-(tert-butylamino)-1-(*N*-(4-((2-iodobenzyl)oxy)benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylic acid (6p)

White solid, 50% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.19 (s, 9H), 4.33 (d, *J* = 13.5 Hz, 1H), 4.40 (d, *J* = 5.5 Hz, 1H), 4.54 (d, *J* = 15.5 Hz, 1H), 4.81 (d, *J* = 13.6 Hz, 1H), 4.92 (d, *J* = 22.9 Hz, 3H), 5.03 (s, 1H), 5.74 (s, 1H), 6.21 (s, 1H), 6.61 (s, 2H), 6.67 – 6.78 (m, 2H), 6.95 (s, 3H), 6.99 – 7.15 (m, 3H), 7.25 (d, *J* = 8.2 Hz, 1H), 7.47 (dd, *J* = 27.4, 10.6 Hz, 3H), 7.62 (d, *J* = 8.1 Hz, 1H), 7.86 (d, *J* = 6.6 Hz, 1H), 8.46 (s, 1H), 10.85 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 28.4, 28.5, 30.9, 41.3, 46.1, 51.5, 57.2, 73.8, 73.9, 97.2, 112.4, 114.4, 115.0, 121.7, 122.2, 124.9, 128.3, 128.7, 129.1, 129.2, 129.5, 130.2, 130.8, 139.0, 139.2, 157.3, 161.2, 164.6, 168.4, 206.9. HRMS (ESI) calculated for $C_{30}H_{29}ClIN_3O_5$ (m/z): $[M+H]^+$ 674.0840, found: $[M+H]^+$ 674.0841.

3-(2-(tert-butylamino)-2-oxo-1-(*N*-(4-((2-(trifluoromethyl)benzyl)oxy)benzyl) formamido)ethyl)-6-chloro-1*H*-indole-2-carboxylic acid (6q)

White solid, 72% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.18 (s, 10H), 1.26 (s, 5H), 1.35 (d, *J* = 15.6 Hz, 5H), 2.17 (s, 1H), 4.33 (d, *J* = 13.8 Hz, 2H), 4.53 (d, *J* = 13.3 Hz, 1H), 4.80 (d, *J* = 14.1 Hz, 2H), 5.15 (d, *J* = 18.9 Hz, 3H), 5.80 (s, 1H), 6.22 (s, 1H), 6.67 (d, *J* = 51.5 Hz, 4H), 7.01 (d, *J* = 44.7 Hz, 4H), 7.39 (dd, *J* = 30.5, 12.7 Hz, 4H), 7.50 – 7.83 (m, 7H), 8.46 (s, 1H), 10.85 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 28.5, 28.7, 29.0, 31.0, 46.2, 49.7, 52.0, 52.8, 57.7, 61.7, 61.7, 69.1, 69.2, 112.1, 112.5, 113.7, 114.1,

114.3, 114.4, 114.8, 115.0, 115.7, 122.3, 122.5, 122.5, 122.8, 122.8, 123.0, 125.0, 125.8, 126.4, 127.4, 129.5, 130.2, 130.3, 130.3, 131.6, 131.8, 136.2, 136.3, 157.5, 157.8, 160.9, 160.9, 163.2, 163.7, 164.8, 168.3, 168.4.; HRMS (ESI) calculated for $C_{31}H_{29}ClF_3N_3O_5$ (m/z): $[M+H]^+$ 616.1748, found: $[M+H]^+$ 616.1748.

3-(1-(*N*-(4-((3,5-bis(trifluoromethyl)benzyl)oxy)benzyl)formamido)-2-(tert-butylamino)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylic acid (6r)

White solid, 73% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.33 (s, 9H), 1.36 (s, 10H), 4.33 (d, *J* = 13.2 Hz, 2H), 4.84 (s, 3H), 5.04 (s, 5H), 5.92 (s, 2H), 6.21 (s, 3H), 6.55 – 6.80 (m, 6H), 6.91 – 7.12 (m, 6H), 7.40 (s, 3H), 7.58 – 7.68 (m, 2H), 7.85 (d, *J* = 27.2 Hz, 8H), 8.00 (s, 2H), 8.26 (d, *J* = 12.3 Hz, 1H), 8.48 (s, 2H), 10.77 (s, 1H), 11.02 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 28.3, 28.4, 28.7, 30.7, 39.7, 39.8, 40.0, 46.1, 51.4, 57.2, 68.3, 112.4, 112.4, 114.2, 121.5, 122.0, 124.2, 124.8, 127.1, 129.2, 130.6, 131.4, 139.8, 141.4, 147.8, 156.9, 159.7, 160.8, 161.4, 163.0, 164.8, 168.5. HRMS (ESI) calculated for $C_{32}H_{28}ClF_6N_3O_5$ (m/z): $[M+H]^+$ 682.1622, found: $[M-H]^-$ 682.1623.

3-(1-(*N*-(4-(benzyloxy)-3,5-difluorobenzyl)formamido)-2-(tert-butylamino)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylic acid (6s)

Yellow solid, 65% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.13 (s, 11H), 1.31 (ddd, *J* = 26.5, 17.0, 8.9 Hz, 7H), 1.38 – 1.44 (m, 3H), 3.76 (s, 1H), 4.23 (d, *J* = 19.2 Hz, 2H), 4.60 (s, 1H), 5.00 (s, 3H), 5.15 (d, *J* = 18.8 Hz, 2H), 6.77 – 6.95 (m, 4H), 6.96 – 7.15 (m, 6H), 7.21 – 7.38 (m, 16H), 7.42 (t, *J* = 8.5 Hz, 4H), 9.82 (d, *J* = 17.4 Hz, 1H), 11.23 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 28.4, 28.7, 28.8, 28.9, 52.6, 64.0, 76.0,

109.1, 110.3, 110.5, 112.1, 113.3, 114.5, 119.4, 121.7, 122.6, 123.5, 126.2, 128.1, 128.3, 128.4, 128.5, 128.6, 128.7, 128.8, 128.8, 131.1, 135.8, 136.3, 137.5, 155.0, 157.0, 166.7. HRMS (ESI) calculated for $C_{30}H_{28}ClF_2N_3O_5$ (m/z): $[M+H]^+$ 584.1686, found: $[M+H]^+$ 584.1688.

3-(1-(*N*-(4-(benzyloxy)benzyl)formamido)-2-(tert-butylamino)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylic acid (6t)

White solid, 72% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.16 (s, 9H), 1.33 (s, 9H), 1.36 (s, 9H), 4.30-5.03 (m, 8H), 5.42-6.26 (m, 6H), 6.53 (s, 1H), 6.66 (s, 1H), 6.91-7.32 (m, 24H), 7.56 (s, 2H), 8.01 (s, 1H), 8.24 (d, 2H, *J*= 10Hz), 8.54 (s, 1H), 9.54 (br s, 1H), 9.78 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 28.6, 29.2, 31.0, 46.6, 52.2, 58.2, 70.3, 112.6, 115.1, 122.4, 125.4, 127.6, 128.1, 128.8, 129.6, 137.4, 161.1, 163.7, 168.9. LC-MS (DAD/ESI): t_R = 5.04 min, calculated for $C_{30}H_{30}ClN_3O_5$ (m/z): $[M-H]^-$ 546.19, found: $[M+H]^+$ 546.10.

3-(1-(*N*-(4-([1,1'-biphenyl]-4-ylmethoxy)benzyl)formamido)-2-(tert-butylamino)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylic acid (6u)

White solid, 55% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.15 (s, 7H), 1.25 (s, 3H), 4.37 (t, *J* = 16.9 Hz, 1H), 5.00 (s, 2H), 6.53 (d, *J* = 29.5 Hz, 2H), 6.75 (s, 2H), 6.93 – 7.09 (m, 3H), 7.30 – 7.38 (m, 2H), 7.38 – 7.47 (m, 5H), 7.59 (d, *J* = 7.3 Hz, 5H), 7.71 (d, *J* = 9.1 Hz, 1H), 8.37 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 28.9, 29.0, 52.5, 58.6, 70.7, 112.7, 113.2, 115.5, 115.7, 121.9, 122.1, 123.1, 123.3, 126.7, 128.1, 128.2, 128.5, 128.7, 129.1, 130.0, 130.5, 130.7, 130.8, 131.2, 137.0, 137.8, 137.9, 142.1, 142.1, 159.2,

159.4, 167.0, 171.2, 171.5. HRMS (ESI) calculated for $C_{36}H_{34}ClN_3O_5$ (m/z): $[M+H]^+$ 624.2187, found: $[M+H]^+$ 624.2188.

3-(2-(tert-butylamino)-1-(*N*-(4-(naphthalen-2-ylmethoxy)benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylic acid (6v)

Yellow oil, 65% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.17 (s, 9H), 1.25 (s, 5H), 1.33 (s, 3H), 1.36 (s, 2H), 4.29 (t, *J* = 15.5 Hz, 2H), 4.52 (d, *J* = 15.9 Hz, 1H), 4.82 (d, *J* = 15.0 Hz, 2H), 5.12 (d, *J* = 17.6 Hz, 4H), 5.81 (s, 2H), 6.19 (s, 1H), 6.56 – 6.71 (m, 2H), 6.75 (d, *J* = 8.2 Hz, 3H), 6.93 (d, *J* = 8.2 Hz, 2H), 7.05 (td, *J* = 8.2, 7.6, 1.9 Hz, 2H), 7.30 – 7.50 (m, 5H), 7.50 (d, *J* = 6.6 Hz, 1H), 7.63 (d, *J* = 8.7 Hz, 1H), 7.70 – 7.97 (m, 6H), 8.44 (s, 1H), 10.85 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 28.3, 28.5, 28.6, 28.8, 30.8, 39.7, 39.9, 40.1, 46.0, 49.5, 51.5, 52.8, 57.1, 69.9, 112.0, 112.4, 114.3, 114.4, 121.4, 121.6, 122.2, 124.8, 125.1, 126.0, 126.0, 126.2, 126.3, 127.4, 127.6, 127.8, 128.2, 129.1, 129.9, 130.7, 132.9, 133.1, 134.5, 136.2, 157.6, 163.5, 164.6, 168.4. HRMS (ESI) calculated for $C_{34}H_{32}ClN_3O_5$ (m/z): $[M+H]^+$ 598.2030, found: $[M+H]^+$ 598.2031.

3-(2-(tert-butylamino)-1-(*N*-(4-((3-methoxybenzyl)oxy)benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylic acid (6w)

Red solid, 70% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.20 (s, 8H), 1.27 (s, 3H), 3.83 (s, 3H), 4.29 (d, *J* = 14.9 Hz, 1H), 4.82 (d, *J* = 15.0 Hz, 1H), 4.96 (d, *J* = 14.3 Hz, 2H), 5.71 (d, *J* = 19.6 Hz, 1H), 6.17 (s, 1H), 6.56 (t, *J* = 6.3 Hz, 1H), 6.71 (t, *J* = 10.5 Hz, 2H), 6.92 (ddd, *J* = 33.7, 18.9, 7.6 Hz, 4H), 7.07 (t, *J* = 7.3 Hz, 1H), 7.25 – 7.34 (m, 1H), 7.39 (d, *J* = 11.0 Hz, 1H), 7.63 (d, *J* = 8.7 Hz, 1H), 8.44 (s, 1H), 10.79 (s, 1H); ^{13}C NMR

(126 MHz, $CDCl_3$) δ [ppm] 28.4, 28.6, 39.8, 40.0, 40.2, 46.0, 51.6, 55.2, 57.1, 69.6, 112.4, 112.9, 113.1, 114.2, 114.4, 119.4, 121.8, 122.3, 124.9, 127.3, 129.1, 129.6, 129.9, 136.3, 138.7, 157.5, 164.6, 168.4. HRMS (ESI) calculated for $C_{31}H_{32}ClN_3O_6$ (m/z): $[M+H]^+$ 578.1980, found: $[M+H]^+$ 578.1984.

3-(2-(tert-butylamino)-1-(*N*-(4-((2,3-methoxybenzyl)oxy)benzyl) formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylic acid (6x)

Yellow oil, 71% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.19 (s, 5H), 1.27 (d, J = 11.2 Hz, 3H), 1.35 (t, J = 10.2 Hz, 1H), 3.84 (d, J = 7.8 Hz, 3H), 3.87 (s, 3H), 4.94 – 5.08 (m, 2H), 6.26 (s, 1H), 6.48 – 6.63 (m, 1H), 6.74 (s, 1H), 6.83 (s, 1H), 6.88 – 7.23 (m, 6H), 7.57 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 28.5, 28.7, 29.0, 30.9, 42.6, 46.4, 52.2, 55.9, 61.3, 65.2, 65.3, 88.9, 90.1, 106.9, 112.4, 112.4, 114.8, 115.0, 121.1, 121.2, 122.3, 122.4, 124.4, 127.8, 129.4, 129.5, 131.0, 131.7, 136.2, 151.9, 152.8, 160.6. HRMS (ESI) calculated for $C_{32}H_{34}ClN_3O_7$ (m/z): $[M+H]^+$ 608.2085, found: $[M+H]^+$ 608.2088.

3-(2-(tert-butylamino)-1-(*N*-(4-((4-methylbenzyl)oxy)benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylic acid (6y)

Yellow oil, 39% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.18 (s, 9H), 1.35 (s, 9H), 1.38 (s, 9H), 1.36 (s, 9H), 2.35 (s, 6H), 4.39-4.72 (m, 4H), 4.86 (s, 2H), 4.87 (s, 2H), 4.94 (s, 1H), 4.99 (s, 1H), 5.35 (s, 2H), 5.78-5.97 (m, 3H), 6.26 (s, 1H), 6.51-7.26 (m, 15H), 7.54 (s, 1H), 7.72 (s, 1H), 8.02 (s, 1H), 8.25 (d, 1H, J = 10 Hz), 8.51 (s, 1H), 9.33 (br s, 1H), 9.72 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 28.6, 28.7, 29.2, 29.9, 31.0, 46.1, 52.2, 57.2, 70.3, 112.1, 112.4, 115.0, 122.3, 127.8, 128.8, 129.5, 134.1, 138.0, 158.0,

161.0, 163.7, 168.5. LC-MS (DAD/ESI): t_R = 5.07 min, calculated for $C_{31}H_{32}ClN_3O_5$ (m/z): [M-H]$^-$ 560.20, found: [M-H]$^-$ 560.14.

3-(2-(tert-butylamino)-1-(*N*-(4-(cyclohexylmethoxy)benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylic acid (6z)

Yellow oil, 65% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 0.96-1.00 (m, 3H), 1.19 (s, 9H), 1.26 (s, 9H), 1.67-1.80 (m, 10H), 3.54-3.63 (m, 3H), 4.29-4.57 (m, 3H), 5.77 (s, 1H), 6.03 (s, 1H), 6.25 (s, 1H), 6.54 (s, 1H), 6.64 (s, 3H), 6.83 (s, 1H), 6.98 (s, 2H), 7.06 (d, 2H, *J* = 10 Hz), 7.12 (s, 2H), 7.48 (s, 1H), 7.67 (d, 2H, *J* = 5 Hz) 8.29 (s, 1H), 8.54 (s, 1H), 9.64 (br s, 1H), 9.88 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 28.6, 29.9, 37.7, 52.3, 74.0, 112.7, 115.0, 115.2, 122.4, 125.4, 129.8, 131.7, 136.3, 159.2, 169.1. LC-MS (DAD/ESI): t_R = 4.97 min, calculated for $C_{30}H_{36}ClN_3O_5$ (m/z): [M-H]$^-$ 552.23, found: [M-H]$^-$ 552.15.

3-(2-(tert-butylamino)-1-(*N*-(4-(cyclopentyloxy)benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylic acid (6aa)

Yellow oil, 89% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.19 (s, 9H), 1.34 (s, 9H), 1.38 (m, 6H), 1.57-1.81 (m, 14H), 4.39-4.62 (m, 5H), 5.27 (s, 1H), 5.72 (s, 2H), 6.18 (s, 2H), 6.50 (s, 1H), 6.62 (s, 3H), 6.84-7.09 (m, 5H), 7.55 (s, 1H,), 7.71 (s, 1H), 8.03 (s, 1H), 8.27 (d, 2H, *J* = 15 Hz), 8.54 (s, 1H), 9.55 (br s, 1H), 9.72 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 24.2, 28.6, 29.2, 31.1, 33.0, 52.2, 79.6, 115.9, 122.4, 129.7, 137.6, 160.8, 163.4, 168.3. LC-MS (DAD/ESI): t_R = 5.07 min, calculated for $C_{28}H_{32}ClN_3O_5$ (m/z): [M-H]$^-$ 524.20, found: [M-H]$^-$ 524.11.

3-(2-(tert-butylamino)-1-(*N*-(4-((4-cyanobenzyl)oxy)benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylic acid (6ab)

Yellow solid, 41% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 0.99 – 1.32 (m, 9H), 1.38 (s, 1H), 1.47 (s, 1H), 1.59 (s, 1H), 4.08 – 4.54 (m, 2H), 4.82 – 5.27 (m, 3H), 6.10 – 6.20 (m, 1H), 6.31 – 7.14 (m, 8H), 7.37 – 7.73 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 28.5, 28.6, 28.9, 29.0, 29.8, 30.9, 39.7, 39.9, 40.1, 40.2, 40.4, 46.3, 51.8, 57.5, 68.9, 111.6, 112.5, 114.5, 118.8, 122.0, 122.4, 125.1, 127.6, 129.4, 130.5, 132.4, 136.2, 142.5, 142.7, 157.3, 168.6. HRMS (ESI) calculated for $C_{31}H_{29}ClN_4O_5$ (m/z): $[M+H]^+$ 573.1826, found: $[M+H]^+$ 573.1822.

3-(2-(tert-butylamino)-1-(*N*-(4-((4-nitrobenzyl)oxy)benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylic acid (6ac)

Gray solid, 85% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.27 (d, J = 11.0 Hz, 15H), 1.34 (s, 3H), 1.37 (s, 4H), 3.83 (dq, J = 10.2, 7.1 Hz, 1H), 4.39 (d, J = 16.1 Hz, 1H), 5.11 (d, J = 16.1 Hz, 1H), 5.79 (s, 1H), 6.28 (s, 1H), 6.72 – 6.81 (m, 1H), 6.91 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.7 Hz, 1H), 7.37 (d, J = 10.9 Hz, 2H), 7.68 (dd, J = 8.4, 5.3 Hz, 2H), 7.78 – 7.83 (m, 2H), 8.02 (s, 1H), 8.09 (d, J = 8.1 Hz, 1H), 8.22 (dd, J = 8.6, 3.5 Hz, 1H), 8.25 – 8.33 (m, 2H), 8.40 (dd, J = 13.2, 4.3 Hz, 1H), 8.47 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 28.5, 28.6, 28.8, 29.6, 30.8, 31.8, 39.7, 39.9, 40.0, 40.2, 40.4, 46.0, 49.6, 51.8, 56.7, 64.2, 112.6, 121.8, 122.1, 122.6, 123.3, 123.5, 123.5, 124.2, 124.5, 126.3, 127.2, 127.5, 128.9, 130.5, 130.8, 131.0, 136.2, 145.5, 146.4, 160.7, 161.5, 164.4, 168.5. HRMS (ESI) calculated for $C_{30}H_{29}ClN_4O_7$ (m/z): $[M+H]^+$ 593.1725, found: $[M+H]^+$ 593.1721.

3-(2-(tert-butylamino)-2-oxo-1-(*N*-(4-(pyridin-4-ylmethoxy)benzyl) formamido)ethyl)-6-chloro-1*H*-indole-2-carboxylic acid (6ae)

Yellow solid, 41% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.19 (s, 9H), 4.26-4.38 (m, 2H), 4.54 (d, *J* = 15.0 Hz, 1H), 5.00 (s, 2H), 5.95 (s, 1H), 6.18 (s, 1H), 6.57-6.60 (m, 2H), 6.69 (d, *J* = 10.0 Hz, 1H), 6.93 (d, *J* = 5.0 Hz, 2H), 7.06 (d, *J* = 5.0 Hz, 2H), 7.39-7.47 (m, 5H), 7.65 (d, *J* = 10.0 Hz, 2H), 7.79-7.85 (m, 1H), 8.42 (s, 1H), 9.99 (br s, 1H), 11.20 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 28.2, 28.3, 45.9, 51.3, 56.8, 67.8, 112.0, 112.3, 113.9, 114.0, 121.4, 122.0, 122.3, 123.2, 127.1, 127.3, 128.9, 130.2, 130.4, 130.6, 136.2, 156.7, 164.3, 168.3. LC-MS (DAD/ESI): t_R = 5.03 min, calculated for $C_{29}H_{29}ClN_4O_5$ (m/z): $[M+H]^+$ 547.18, found: $[M+H]^+$ 547.06.

3-(2-(tert-butylamino)-2-oxo-1-(*N*-(4-(pyridin-3-ylmethoxy)benzyl) formamido)ethyl)-6-chloro-1*H*-indole-2-carboxylic acid (6af)

Yellow oil, 50% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.21 (s, 9H), 4.28-4.38 (m, 2H), 4.55 (d, *J* = 15.0 Hz, 1H), 5.01 (s, 2H), 5.98 (s, 1H), 6.19 (s, 1H), 6.57-6.65 (m, 2H), 6.70 (d, *J* = 10.0 Hz, 1H), 6.95 (d, *J* = 5.0 Hz, 2H), 7.09 (d, *J* = 5.0 Hz, 2H), 7.41-7.49 (m, 5H), 7.67 (d, *J* = 10.0 Hz, 2H), 7.81-7.87 (m, 1H), 8.44 (s, 1H), 9.00 (br s, 1H), 11.22 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 28.4, 28.5, 45.7, 51.6, 56.9, 67.7, 112.4, 112.7, 113.0, 114.1, 121.5, 122.3, 122.4, 123.2, 127.4, 127.5, 128.9, 130.4, 130.6, 130.8, 136.7, 156.8, 164.4, 168.8. HRMS (ESI) calculated for $C_{29}H_{29}ClN_4O_5$ (m/z): $[M+H]^+$ 549.1826, found: $[M+H]^+$ 549.1830.

3-(2-(tert-butylamino)-2-oxo-1-(*N*-(4-(pyridin-2-ylmethoxy)benzyl) formamido)ethyl)-6-chloro-1*H*-indole-2-carboxylic acid (6ag)

Yellow oil, 50% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.12 – 1.43 (m, 10H), 4.31 (s, 1H), 4.79 (s, 1H), 4.86 – 5.18 (m, 2H), 6.45 – 6.80 (m, 2H), 6.90 (s, 1H), 7.05 (s, 1H), 7.23 (s, 1H), 7.67 (d, J = 44.2 Hz, 1H), 8.56 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 28.4, 28.6, 29.4, 29.6, 31.9, 70.5, 112.4, 112.4, 114.4, 121.5, 121.7, 122.3, 122.7, 125.1, 129.2, 129.2, 130.3, 130.4, 132.2, 137.0, 147.9, 149.0, 149.2, 155.2, 157.0, 157.3, 165.0, 168.6. LC-MS (DAD/ESI): t_R = 4.80 min, calculated for $C_{29}H_{29}ClN_4O_5$ (m/z): $[M+H]^+$ 549.18, found: $[M+H]^+$ 549.34.

3-(2-(tert-butylamino)-2-oxo-1-(*N*-(4-phenethoxybenzyl)formamido)ethyl)-6-chloro-1*H*-indole-2-carboxylic acid (6ah)

White solid, 49% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.16 (s, 9H), 1.33 (s, 9H), 1.37 (s, 9H), 2.97-3.07 (m, 10H), 3.97-4.44 (m, 16H), 5.72-5.80 (m, 2H), 6.59-6.61 (m, 8H), 6.91-7.25 (m, 20H), 7.53 (s, 2H), 7.70 (s, 1H), 8.01 (s, 1H), 8.22-8.27 (m, 2H), 8.53 (s, 2H), 9.54 (br s, 1H), 9.86 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 28.6, 28.8, 29.2, 29.9, 31.0, 35.9, 46.6, 52.2, 58.2, 69.1, 112.7, 114.9, 122.4, 126.7, 128.7, 129.2, 138.5, 158.4, 163.7, 168.9. LC-MS (DAD/ESI): t_R = 4.53 min, calculated for $C_{31}H_{32}ClN_3O_5$ (m/z): $[M-H]^-$ 560.20, found: $[M-H]^-$ 560.08.

3-(1-(*N*-(4-((4-bromobenzyl)oxy)phenethyl)formamido)-2-(tert-butylamino)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylic acid (6ai)

White solid, 55% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.28 (d, *J* = 10.4 Hz, 15H), 1.90 (s, 1H), 2.09 – 2.37 (m, 1H), 2.59 (s, 1H), 2.70 (s, 1H), 3.32 (s, 2H), 3.75 (s, 1H), 4.93 (s, 3H), 5.96 (s, 1H), 6.30 (s, 1H), 6.59 (d, *J* = 7.4 Hz, 3H), 6.68 (d, *J* = 7.8 Hz, 3H), 7.09 (d, *J* = 8.3 Hz, 1H), 7.29 (d, *J* = 7.2 Hz, 3H), 7.43 – 7.53 (m, 3H), 7.57 (s, 2H), 7.66 (d, *J* = 8.4 Hz, 1H), 8.32 (s, 1H), 11.44 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 28.3, 28.4, 33.0, 36.2, 39.6, 39.8, 39.9, 45.9, 48.2, 51.5, 57.1, 68.8, 112.4, 112.6, 114.2, 114.5, 114.7, 121.4, 121.5, 122.1, 122.6, 124.5, 127.3, 128.9, 129.3, 129.5, 130.6, 131.3, 131.4, 136.1, 136.3, 156.5, 162.8, 163.8, 168.6. HRMS (ESI) calculated for $C_{31}H_{31}BrClN_3O_5$ (m/z): $[M+H]^+$ 640.1136, found: $[M+H]^+$ 640.1138.

3-(2-(tert-butylamino)-1-(*N*-(4-((4-bromobenzyl)amino)benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylic acid (8)

White solid, 76% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.17 – 1.35 (m, 14H), 3.48 (d, *J* = 6.7 Hz, 1H), 4.39 (s, 1H), 4.67 (s, 1H), 5.07 (dq, *J* = 28.4, 15.8 Hz, 1H), 5.87 (s, 1H), 6.27 (s, 1H), 6.73 (d, *J* = 50.6 Hz, 1H), 6.94 (d, *J* = 28.1 Hz, 2H), 7.10 (d, *J* = 6.8 Hz, 1H), 7.41 (d, *J* = 33.2 Hz, 2H), 7.73 (dd, *J* = 28.3, 7.0 Hz, 2H), 7.79 – 7.92 (m, 2H), 8.48 (s, 1H), 10.92 – 11.14 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 15.2, 28.5, 28.6, 39.7, 39.8, 40.0, 40.2, 40.3, 46.0, 46.3, 51.7, 51.7, 51.8, 56.8, 56.9, 65.7, 112.6, 112.6, 121.2, 121.2, 121.7, 121.8, 121.9, 122.0, 122.4, 122.5, 124.6, 124.7, 125.1, 125.9, 127.2, 127.3, 127.4, 127.7, 130.8, 130.9, 131.3, 136.3, 162.8, 164.4, 168.5. HRMS (ESI) calculated for $C_{30}H_{30}BrClN_3O_5$ (m/z): $[M+H]^+$ 625.1139, found: $[M+H]^+$ 625.1140.

3-(1-(*N*-(4-((2-bromobenzyl)oxy)benzyl)formamido)-2-(tert-butylamino)-2-oxoethyl)-6-chloro-1-methyl-1*H*-indole-2-carboxylic acid (9)

Yellow oil, 63% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.21 (s, 19H), 1.28 (s, 12H), 3.69 (s, 4H), 3.84 (s, 6H), 4.22 – 4.34 (m, 3H), 4.54 (d, *J* = 15.9 Hz, 1H), 4.87 (d, *J* = 15.0 Hz, 2H), 5.00 (t, *J* = 17.0 Hz, 9H), 5.99 (s, 2H), 6.12 (s, 2H), 6.20 (s, 2H), 6.50 (d, *J* = 7.3 Hz, 3H), 6.55 (d, *J* = 7.6 Hz, 3H), 6.66 (d, *J* = 7.9 Hz, 4H), 6.82 (d, *J* = 7.7 Hz, 5H), 6.92 (d, *J* = 6.7 Hz, 1H), 7.11 (d, *J* = 8.7 Hz, 4H), 7.20 (dd, *J* = 15.0, 7.3 Hz, 6H), 7.28 – 7.35 (m, 5H), 7.47 (t, *J* = 8.2 Hz, 4H), 7.57 (d, *J* = 7.9 Hz, 4H), 7.67 (d, *J* = 8.7 Hz, 2H), 7.81 (d, *J* = 8.7 Hz, 1H), 8.29 (s, 1H), 8.43 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 28.4, 28.5, 28.8, 29.6, 30.7, 32.3, 39.7, 39.9, 40.0, 45.8, 49.6, 51.6, 57.7, 69.3, 110.0, 110.3, 113.8, 114.1, 115.1, 121.7, 122.3, 122.4, 127.4, 127.5, 128.9, 129.0, 129.3, 130.0, 132.5, 136.1, 157.2, 164.8, 168.7. HRMS (ESI) calculated for $C_{31}H_{31}BrClN_3O_5$ (m/z): $[M+H]^+$ 640.1136, found: $[M+H]^+$ 640.1139.

3-(2-((3*s*,5*s*,7*s*)-adamantan-1-ylamino)-1-(*N*-(4-((4-bromobenzyl)oxy) benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylic acid (13)

White solid, 43% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.62 (s, 9H), 1.83 (s, 7H), 1.92 (s, 3H), 2.02 (s, 5H), 4.28 (dd, *J* = 15.2, 8.7 Hz, 2H), 4.83 (d, *J* = 15.0 Hz, 1H), 4.91 (d, *J* = 14.3 Hz, 3H), 5.52 (s, 1H), 6.17 (s, 1H), 6.57 (s, 2H), 6.68 (d, *J* = 8.0 Hz, 2H), 6.91 (d, *J* = 8.0 Hz, 2H), 7.09 (t, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 7.1 Hz, 2H), 7.35 (s, 1H), 7.41 (s, 1H), 7.50 (d, *J* = 7.8 Hz, 2H), 7.65 (d, *J* = 8.7 Hz, 1H), 8.44 (s, 1H), 10.67 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 29.3, 29.4, 35.8, 36.2, 36.3, 39.9, 40.0, 40.2, 41.1, 41.3, 41.8, 44.1, 46.1, 52.4, 57.2, 69.2, 112.5, 114.3, 114.4, 114.9, 121.8, 122.0, 122.4, 124.9, 127.3,

127.5, 129.0, 129.2, 130.2, 131.0, 131.7, 136.2, 136.3, 157.5, 162.9, 164.7, 168.1. HRMS (ESI) calculated for $C_{36}H_{35}BrClN_3O_5$ (m/z): $[M+H]^+$ 704.1449, found: $[M+H]^+$ 704.1449.

3-(2-((1*r*,3*r*,5*r*,7*r*)-adamantan-2-ylamino)-1-(*N*-(4-((2-bromobenzyl)oxy) benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylic acid (14)

White solid, 89% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.21 – 1.37 (m, 3H), 1.60 (d, *J* = 12.1 Hz, 6H), 1.69 – 1.96 (m, 20H), 3.99 (s, 1H), 4.08 (dd, *J* = 22.0, 7.3 Hz, 1H), 4.34 (dd, *J* = 36.4, 15.5 Hz, 1H), 4.83 (d, *J* = 14.4 Hz, 1H), 4.98 (d, *J* = 8.2 Hz, 2H), 6.37 (s, 1H), 6.49 (s, 1H), 6.63 (d, *J* = 8.4 Hz, 1H), 6.70 (d, *J* = 6.4 Hz, 2H), 6.87 – 7.07 (m, 4H), 7.14 – 7.28 (m, 2H), 7.32 (q, *J* = 9.5, 7.5 Hz, 1H), 7.36 – 7.43 (m, 1H), 7.42 – 7.50 (m, 1H), 7.55 (q, *J* = 8.0 Hz, 2H), 8.13 (d, *J* = 9.8 Hz, 1H), 8.51 (s, 1H), 10.99 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 26.6, 26.8, 26.9, 27.0, 31.0, 31.3, 31.5, 31.7, 33.7, 36.8, 36.9, 37.0, 37.1, 37.3, 39.6, 39.8, 46.1, 52.2, 54.0, 56.4, 56.9, 69.3, 112.2, 112.4, 114.3, 114.9, 121.7, 121.8, 122.2, 124.7, 125.4, 127.4, 127.9, 128.8, 128.9, 129.2, 129.6, 129.7, 130.6, 132.4, 136.1, 136.2, 157.3, 161.0, 163.8, 164.5, 164.9, 168.5, 168.6. HRMS (ESI) calculated for $C_{36}H_{35}BrClN_3O_5$ (m/z): $[M+H]^+$ 704.1449, found: $[M+H]^+$ 704.1451.

3-(1-(*N*-(4-((4-bromobenzyl)oxy)benzyl)formamido)-2-oxo-2-(((1*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)amino)ethyl)-6-chloro-1*H*-indole-2-carboxylic acid (15)

Yellow solid, 53% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 0.39 – 0.67 (m, 6H), 0.66 – 0.88 (m, 7H), 0.86 – 1.05 (m, 3H), 1.04 – 1.43 (m, 4H), 1.43 – 1.83 (m, 5H), 2.58 (s, 1H), 3.85 (s, 1H), 4.17 – 4.44 (m, 2H), 4.93 (t, *J* = 10.2 Hz, 3H), 5.85 (dd, *J* = 34.1, 8.3 Hz, 1H), 6.21 (s, 1H), 6.67 (ddd, *J* = 29.1, 14.0, 6.9 Hz, 4H), 6.93 (dd, *J* = 37.1, 8.2

Hz, 2H), 7.05 (s, 1H), 7.28 (s, 3H), 7.34 – 7.48 (m, 2H), 7.50 (d, *J* = 8.0 Hz, 3H), 7.55 – 7.64 (m, 1H), 7.78 (s, 1H), 8.51 (d, *J* = 9.7 Hz, 1H), 10.97 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 11.3, 11.7, 13.5, 18.4, 19.7, 19.8, 20.0, 20.0, 26.8, 26.9, 28.0, 35.7, 35.9, 38.5, 38.6, 38.9, 39.7, 39.8, 40.0, 40.2, 40.3, 44.6, 44.6, 45.5, 45.9, 46.8, 48.4, 54.2, 56.9, 57.1, 69.1, 112.4, 114.3, 114.3, 114.4, 121.6, 121.8, 122.0, 122.6, 127.7, 127.9, 128.9, 128.9, 129.3, 129.6, 131.5, 136.1, 157.5, 164.2, 168.2. HRMS (ESI) calculated for $C_{36}H_{37}BrClN_3O_5$ (m/z): $[M+H]^+$ 706.1605, found: $[M+H]^+$ 706.1611.

3-(1-(*N*-(4-((2-bromobenzyl)oxy)benzyl)formamido)-2-oxo-2-(((1*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)amino)ethyl)-6-chloro-1*H*-indole-2-carboxylic acid (16)

Yellow oil, 55% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 0.79 – 0.97 (m, 19H), 1.10 – 1.20 (m, 3H), 1.27 (dt, *J* = 12.9, 5.4 Hz, 2H), 1.55 (dddt, *J* = 35.2, 18.2, 9.3, 4.4 Hz, 6H), 1.64 – 1.80 (m, 5H), 1.83 (dd, *J* = 13.2, 9.2 Hz, 2H), 3.96 (td, *J* = 9.1, 5.2 Hz, 1H), 4.30 (s, 1H), 4.47 (s, 1H), 4.95 (s, 2H), 5.91 (d, *J* = 8.5 Hz, 1H), 6.15 – 6.24 (m, 1H), 6.54 – 6.81 (m, 3H), 7.00 (d, *J* = 29.3 Hz, 3H), 7.16 (s, 3H), 7.28 (s, 2H), 7.44 (s, 2H), 7.54 (s, 2H), 7.95 (d, *J* = 11.7 Hz, 1H), 8.11 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 11.9, 12.6, 13.2, 13.8, 18.7, 19.9, 20.0, 20.2, 20.3, 20.4, 20.5, 27.0, 27.1, 27.6, 28.0, 28.2, 28.4, 29.8, 36.0, 36.2, 37.5, 39.0, 39.1, 44.7, 45.0, 47.2, 48.6, 48.9, 52.8, 55.7, 58.2, 60.7, 69.6, 114.9, 122.5, 127.7, 129.1, 129.4, 132.7, 136.1, 161.3, 162.1, 165.2. HRMS (ESI) calculated for $C_{36}H_{37}BrClN_3O_5$ (m/z): $[M+H]^+$ 706.1605, found: $[M+H]^+$ 706.1612.

3-(2-((3*s*,5*s*,7*s*)-adamantan-1-ylamino)-1-(*N*-(4-((4-fluorobenzyl)oxy) benzyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylic acid (17)

White solid, 46% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 0.88 (t, *J* = 6.4 Hz, 2H), 1.26 (s, 10H), 1.55 – 2.16 (m, 41H), 3.45 (s, 2H), 4.29 (t, *J* = 15.8 Hz, 2H), 4.53 (d, *J* = 15.9 Hz, 1H), 4.81 (d, *J* = 15.0 Hz, 1H), 4.90 (d, *J* = 16.0 Hz, 3H), 5.51 (s, 1H), 5.60 (s, 1H), 6.18 (s, 1H), 6.57 (s, 2H), 6.69 (d, *J* = 8.1 Hz, 2H), 6.76 (s, 1H), 6.91 (d, *J* = 8.0 Hz, 2H), 7.07 (t, *J* = 8.4 Hz, 3H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 9.0 Hz, 4H), 7.65 (d, *J* = 8.7 Hz, 1H), 8.26 (d, *J* = 12.4 Hz, 1H), 8.45 (s, 1H), 10.31 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 28.8, 29.3, 29.4, 29.4, 29.7, 35.7, 35.9, 36.0, 36.1, 36.2, 36.3, 39.7, 39.8, 40.0, 40.2, 40.3, 41.0, 41.2, 41.3, 41.3, 41.8, 44.1, 46.2, 52.5, 52.5, 57.3, 57.4, 69.3, 69.4, 112.1, 112.3, 112.4, 113.3, 114.4, 114.6, 115.0, 115.4, 115.5, 122.1, 122.2, 122.4, 122.6, 125.0, 125.7, 127.4, 129.2, 129.3, 129.4, 129.9, 130.0, 131.0, 131.2, 132.8, 136.1, 136.2, 157.5, 157.7, 161.5, 162.4, 163.0, 163.5, 164.9, 165.0, 168.2, 168.2. HRMS (ESI) calculated for $C_{36}H_{35}ClFN_3O_5$ (m/z): $[M+H]^+$ 644.2249, found: $[M+H]^+$ 644.2251.

3-(1-((4-((2-bromobenzyl)oxy)benzyl)amino)-2-(tert-butylamino)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylic acid (19)

White solid, 76% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.24 (s, 9H), 2.60 (s, 3H), 3.68 (dddd, *J* = 38.5, 26.7, 11.5, 6.0 Hz, 4H), 4.33 (s, 34H), 5.12 (s, 2H), 6.95 (d, *J* = 5.7 Hz, 2H), 7.03 (s, 1H), 7.09 (d, *J* = 7.3 Hz, 1H), 7.23 (d, *J* = 6.7 Hz, 1H), 7.30 – 7.44 (m, 3H), 7.48 (s, 2H), 7.53 (d, *J* = 6.2 Hz, 1H), 7.60 (d, *J* = 7.1 Hz, 2H), 7.84 (d, *J* = 7.2 Hz, 1H), 9.61 (s, 1H), 9.93 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 22.1, 22.3, 24.8, 24.9, 25.4, 32.8, 39.5, 39.7, 39.8, 40.0, 40.2, 40.3, 40.5, 46.5, 48.7, 50.0, 54.7, 57.7, 69.2,

112.1, 112.4, 114.0, 114.4, 114.9, 115.3, 115.4, 121.7, 121.9, 122.6, 125.0, 125.6, 126.5, 127.8, 128.2, 129.2, 130.5, 130.8, 131.6, 132.8, 136.1, 156.9, 157.1, 161.3, 162.4, 163.3, 169.1, 172.5. HRMS (ESI) calculated for $C_{29}H_{29}BrClN_3O_5$ (m/z): $[M+H]^+$ 598.1030, found: $[M+H]^+$ 598.1030.

3-(1-((4-((2-bromobenzyl)oxy)benzyl)(methyl)amino)-2-(tert-butylamino)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylic acid (21)

White solid, 75% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.07 – 1.17 (m, 1H), 1.35 (s, 2H), 1.42 (s, 3H), 2.69 (s, 1H), 3.47 (s, 1H), 4.02 (s, 1H), 4.92 – 5.09 (m, 1H), 6.77 (d, *J* = 6.8 Hz, 1H), 6.82 – 7.06 (m, 2H), 7.17 (dt, *J* = 14.4, 6.6 Hz, 1H), 7.26 – 7.37 (m, 2H), 7.46 (dt, *J* = 13.8, 7.6 Hz, 1H), 7.56 (t, *J* = 7.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 15.4, 28.6, 29.0, 29.6, 29.9, 51.5, 64.6, 69.5, 69.6, 112.4, 112.8, 115.3, 115.8, 120.7, 121.0, 122.0, 122.5, 127.7, 127.8, 129.0, 129.1, 129.4, 129.5, 129.7, 131.8, 132.8, 132.9, 136.0, 159.2, 179.3. HRMS (ESI) calculated for $C_{30}H_{31}BrClN_3O_5$ (m/z): $[M+H]^+$ 612.1186, found: $[M+H]^+$ 612.1188.

3-(2-((3*s*,5*s*,7*s*)-adamantan-1-ylamino)-1-(*N*-(4-(benzyloxy)benzyl) acetamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylic acid (22)

White solid, 40% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.20 (t, *J* = 6.9 Hz, 1H), 1.40 (d, *J* = 5.9 Hz, 5H), 1.64 (d, *J* = 16.3 Hz, 12H), 1.95 (s, 12H), 2.05 (d, *J* = 21.3 Hz, 6H), 2.16 (d, *J* = 11.6 Hz, 4H), 2.37 (s, 2H), 2.58 (s, 1H), 3.48 (q, *J* = 6.9 Hz, 1H), 3.88 (d, *J* = 15.5 Hz, 1H), 4.37 (d, *J* = 16.3 Hz, 3H), 4.45 (dd, *J* = 18.0, 11.2 Hz, 2H), 4.66 (d, *J* = 17.4 Hz, 1H), 4.93 (s, 5H), 5.43 (s, 1H), 5.77 (s, 1H), 6.34 (s, 1H), 6.38 (d, *J* = 6.9 Hz, 1H), 6.50 (d, *J* = 6.8 Hz, 1H), 6.58 (s, 4H), 6.86 (s, 1H), 7.08 (d, *J* = 8.5 Hz, 1H), 7.14 (d,

J = 8.5 Hz, 1H), 7.35 (d, *J* = 29.1 Hz, 12H), 7.69 (d, *J* = 8.5 Hz, 1H), 7.86 (d, *J* = 8.5 Hz, 1H), 10.33 (s, 1H), 10.50 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 29.2, 36.2, 39.6, 39.8, 40.0, 40.1, 40.3, 41.2, 49.8, 52.2, 52.5, 54.6, 61.2, 69.7, 100.8, 112.1, 112.3, 113.8, 113.9, 114.1, 114.1, 114.3, 121.8, 122.6, 125.4, 126.1, 127.2, 127.3, 127.4, 127.5, 127.8, 128.1, 128.4, 130.5, 130.8, 131.0, 136.1, 136.3, 136.9, 157.1, 161.0, 168.6, 168.9, 171.4, 182.3, 186.4. HRMS (ESI) calculated for $C_{37}H_{38}ClN_3O_5$ (m/z): $[M+H]^+$ 640.2500, found: $[M+H]^+$ 640.2512.

6-chloro-3-(2-(cyclohexylamino)-1-(*N*-(4-((4-fluorobenzyl)oxy)benzyl) acetamido)-2-oxoethyl)-1*H*-indole-2-carboxylic acid (23)

White solid, 76% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 0.90 – 1.27 (m, 10H), 1.59 (dt, *J* = 29.1, 16.4 Hz, 8H), 1.71 – 2.02 (m, 6H), 2.18 (d, *J* = 69.9 Hz, 4H), 2.38 (s, 3H), 3.82 (d, *J* = 36.3 Hz, 2H), 4.09 (d, *J* = 15.6 Hz, 1H), 4.50 (d, *J* = 17.9 Hz, 1H), 4.64 (d, *J* = 17.7 Hz, 1H), 4.77 (d, *J* = 15.8 Hz, 1H), 4.88 (s, 4H), 5.82 (s, 1H), 6.04 (d, *J* = 8.1 Hz, 1H), 6.46 – 6.68 (m, 7H), 6.72 (d, *J* = 8.1 Hz, 2H), 7.07 (q, *J* = 11.2, 8.3 Hz, 6H), 7.35 (d, *J* = 6.7 Hz, 5H), 7.51 (d, *J* = 8.9 Hz, 2H), 7.81 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 22.1, 22.3, 24.8, 24.9, 25.4, 32.8, 39.5, 39.7, 39.8, 40.0, 40.2, 40.3, 46.5, 48.7, 50.1, 54.7, 57.7, 69.2, 108.2, 112.1, 112.4, 114.0, 114.4, 114.9, 115.3, 115.4, 121.7, 121.9, 122.6, 125.0, 125.6, 126.5, 127.3, 127.8, 128.2, 129.2, 129.3, 130.6, 130.8, 131.7, 132.8, 136.1, 156.9, 157.1, 161.4, 162.5, 162.7, 163.3, 169.0, 169.1, 172.5. HRMS (ESI) calculated for $C_{33}H_{33}ClFN_3O_5$ (m/z): $[M+H]^+$ 606.2093, found: $[M+H]^+$ 606.2094.

3-(2-((1*R*,3*s*)-adamantan-1-ylamino)-2-oxo-1-(*N*-phenethylformamido) ethyl)-6-chloro-1*H*-indole-2-carboxylic acid (24)

White solid, 65% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.63 (s, 3H), 1.99 (d, *J* = 47.8 Hz, 6H), 2.69 (d, *J* = 88.4 Hz, 1H), 3.45 (d, *J* = 102.5 Hz, 1H), 5.62 (s, 1H), 6.65 (s, 1H), 7.10 (d, *J* = 27.1 Hz, 2H), 7.44 – 7.78 (m, 1H), ; ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 22.0, 29.3, 29.4, 29.9, 34.2, 36.2, 36.3, 39.7, 39.9, 40.2, 41.3, 51.5, 52.4, 52.6, 57.6, 62.8, 112.7, 112.9, 115.0, 120.9, 122.0, 122.1, 122.6, 124.7, 126.0, 127.5, 127.6, 128.1, 128.4, 128.6, 131.2, 136.3, 138.1, 138.8, 163.1, 164.4, 164.6, 168.1, 168.4, 179.6. HRMS (ESI) calculated for $C_{30}H_{32}ClN_3O_4$ (m/z): $[M+H]^+$ 534.2081, found: $[M+H]^+$ 534.2088.

6-chloro-3-(2-oxo-2-(phenethylamino)-1-(*N*-phenethylformamido)ethyl)-1*H*-indole-2-carboxylic acid (25)

White solid, 92% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 2.71 – 2.87 (m, 3H), 2.91 (t, *J* = 7.2 Hz, 1H), 3.40 (s, 2H), 3.44 – 3.59 (m, 3H), 3.46 – 3.75 (m, 4H), 4.31 (s, 1H), 5.01 (s, 1H), 6.87 – 7.61 (m, 19H), 8.00 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 14.6, 15.3, 35.6, 36.5, 39.7, 39.9, 40.0, 40.2, 40.4, 40.6, 41.1, 41.5, 65.8, 68.3, 111.1, 121.9, 122.9, 124.6, 126.2, 126.3, 126.5, 127.3, 128.2, 128.5, 128.6, 128.6, 128.8, 128.8, 128.9, 132.3, 138.8, 139.5, 158.6. HRMS (ESI) calculated for $C_{28}H_{26}ClN_3O_4$ (m/z): $[M+H]^+$ 504.1612, found: $[M+H]^+$ 504.1612.

3-(2-(tert-butylamino)-1-(*N*-(3-morpholinopropyl)formamido)-2-oxoethyl)-6-chloro-1*H*-indole-2-carboxylic acid (26)

Yellow oil, 81% yield; *mixture of rotamers observed (~1:1)*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 1.28 (s, 12H), 1.98 (d, J = 71.8 Hz, 2H), 3.04 (s, 4H), 3.50 (s, 3H), 4.01 (s, 7H), 4.31 (s, 9H), 5.35 (s, 1H), 6.18 (s, 1H), 6.69 (s, 1H), 7.07 (d, J = 8.1 Hz, 1H), 7.56 (s, 1H), 7.69 (d, J = 8.1 Hz, 1H), 8.14 (s, 1H), 11.61 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 22.0, 28.3, 28.3, 39.4, 39.5, 39.7, 39.9, 40.0, 40.8, 51.5, 51.5, 55.3, 57.2, 63.3, 112.6, 113.5, 121.7, 124.4, 130.5, 136.2, 168.6. HRMS (ESI) calculated for $C_{23}H_{31}ClN_4O_5$ (m/z): $[M+H]^+$ 479.1983, found: $[M+H]^+$ 479.1987.

ASSOCIATED CONTENT

Supporting Information

Details on synthetic procedures, analytical data of starting materials, enantiomeric separation, X-ray structure determination, FP and NMR (PDF)

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Highlights

- Transit from the 3-point to 4-point pharmacophore model in the p53 binding site
- Stabilization of the intrinsically disordered *N*-terminus of the MDM2 protein
- >100 compounds were synthesized using a 2-step MCR chemistry.
- Extensive FP and 2D NMR-monitored SAR studies, revealing a halogen bond effect
- p53-specific anti-cancer activity towards p53-wild-type cancer cells was observed.