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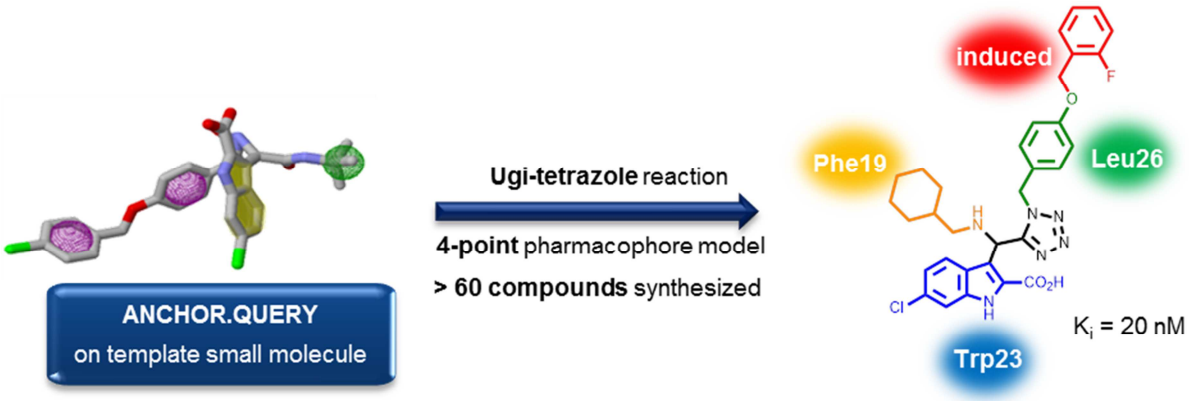

Rational design and synthesis of 1,5-disubstituted tetrazoles as potent inhibitors of the MDM2-p53 interaction

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Abstract

Using the computational pharmacophore-based ANCHOR.QUERY platform a new scaffold was discovered. Potent compounds evolved inhibiting the protein-protein interaction p53-MDM2. An extensive SAR study was performed based on our four-point pharmacophore model, yielding derivatives with affinity to MDM2 in the nanomolar range. Their binding affinity with MDM2 was evaluated using both fluorescence polarization (FP) assay and 2D-NMR-HSQC experiments.

1. Introduction

The tumor suppressor p53 protein, 'the guardian of the genome', has an overarching role in protecting the organism from cancer. From the time of its discovery in l979, it has become one of the most frequently researched proteins. Its regulation complexity, variety of roles and importance in cancer makes it one of the best known, but still not fully understood, challenging protein.

Nearly all human cancers have either mutated the p53 itself (50% all cancers) or compromised the effectiveness of the p53 pathway.[1] The latter group of tumors retains the

wild type p53 (wt-p53) but its pathway is inactivated by negative regulators, mainly the MDM2 and MDMX proteins. Therefore, a low-molecular-weight antagonist capable to disrupt the MDM2/p53 interaction can reactivate p53 and inhibit or reverse tumor formation.[2,3]

On the other hand, in tumors containing the wild type p53 blocking the interaction with MDM2/MDMX by utilizing small molecule inhibitors, should provide an efficient, non-genotoxic alternative for anticancer therapy.[2] As far as the latter strategy is concerned, in the last ten years tremendous progress has been observed[4] since the initial demonstration of the efficacy of the early inhibitor Nutlin-3.[5] This resulted in the development of many small molecule MDM2 inhibitors of different scaffolds, which several also entered into clinical evaluations.[4,6] However, the discovery of new p53/MDM2/MDMX scaffolds is still of high interest due to insufficient PKPD properties currently seen in clinical trials.[6-10]

MDM2/p53 interaction relies on the steric complementarity of the MDM2 cleft and the hydrophobic face of the p53 helix, in particular a triad of p53 amino acids: Phe19, Trp23 and Leu26, which is inserted deeply inside the binding pocket of MDM2.[11,12] Such interactions define a three-finger-pharmacophore-model which characterizes the vast majority of the currently available small-molecule MDM2 inhibitors.[13] Nevertheless, certain new approaches, as the four-finger-model, were recently proposed.[14-17]

We have previously described highly potent p53-MDM2 antagonists addressing a novel pocket formed by the often disordered *N*-terminus of MDM2.[15] The scaffold consisted of an α-aminoacylamide which can be conveniently formed in one synthetic step from commercial or easily accessible starting materials using multicomponent reaction chemistry.[18] In order to change the physicochemical properties of the previously reported compound series, in this study we used our pharmacophore-based virtual screening ANCHOR.QUERY platform to discover alternative scaffolds.[19] Among others, 1,5-disubstituted-1*H*-tetrazoles appeared as promising scaffolds. Here we report the discovery, synthesis, optimization of the targeted library of novel substituted tetrazoles based on the four-point pharmacophore model and initial SAR for this class of compounds.

2. Results and discussion

2. 1. Virtual Screening (VS)-based tetrazole scaffold discovery

The discovery of the current inhibitors was based on the recent four-point pharmacophore model experimentally shown by co-crystallization by Bista el al.[15] The main features of the model are presented in Figure 1. The structure of novel inhibitor contains the 6-chloroindole-2-carboxylic acid which was used as an 'anchor' in order to mimic the Trp23 amino acid and constrain the position of other substituents. Three additional binding sites were defined, that is Phe19, Leu26 and the induced Leu26 subpocket, enlarged by the Tyr100 'open' position. Such model was evaluated using the open access pharmacophore based virtual screening platform ANCHOR.QUERY software (http://anchorquery.csb.pitt.edu) (Figure 1A).[19]

Thus, we uploaded the receptor of PDB ID 4MDN and we deleted the crystallographic waters as Scorpion analysis declares them as less important.[15] When using our recently described α-aminoacylamide **1** with K_i of 600 nM as a template in ANCHOR.QUERY (Figure 1B), the program automatically proposes a useful pharmacophore consisting of 1 aromatic, 2 aliphatic and 1 anchor pharmacophores (Figure 1C). However, we changed the character of the initially hydrophobic site on top of Ar1 to an aromatic character. Querying this model against a virtual library of ~2 billion compounds stored in ANCHOR.QUERY resulted in a high ranking α-aminomethyl tetrazole scaffold which attracted our immediate attention due to its drug-like features and ease of synthesis (Figure 1D). The scaffold was predicted such that the Trp23 subpocket was occupied by an indole analogue, the Phe19 subpocket by an aliphatic substituent whereas the Leu26 subpocket by a substituted phenyl group (Figure 1E). Finally, the induced Leu26 subpocket was occupied by a benzyloxy group. The tetrazole residue occupied the central upper part of the pocket and served as a hub providing appropriate substitution vectors to access the three subpockets (Figure 1).

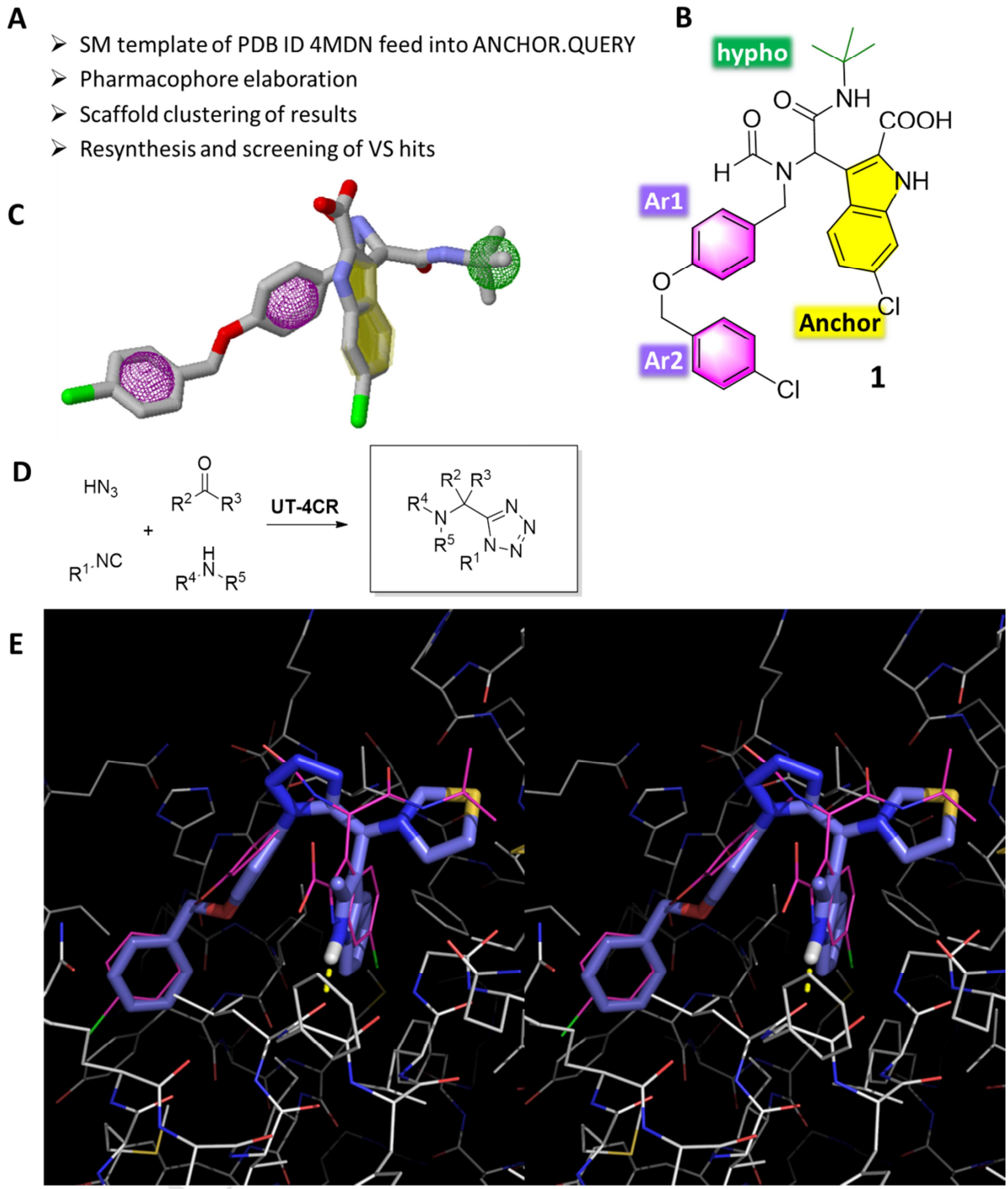
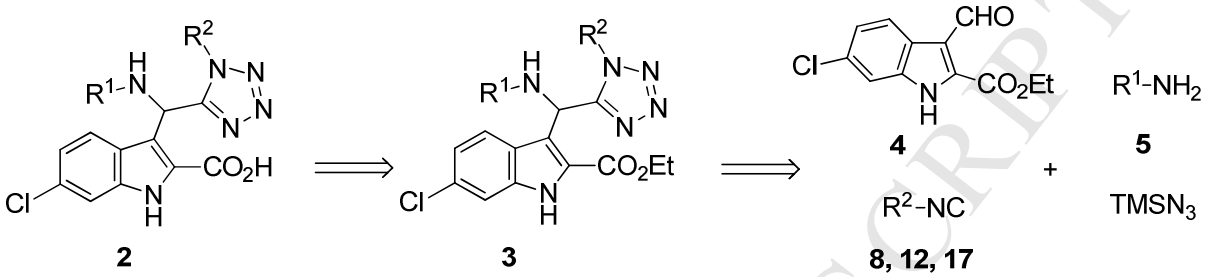


Figure 1. VS-based discovery of tetrazoles as potent p53 MDM2 antagonists. (A) Schematic of the VS method for discovering new scaffolds based on template **1** from PDB ID 4MDN; (B) 2D structure of **1** and imposed pharmacophore characters; (C) ANCHOR.QUERY derived 3D four point pharmacophore model of **1**: anchor in yellow, aromatic in pink, hydrophobe in green; (D) one-pot MCR synthesis of tetrazole scaffold; (E) stereoview of alignment of small molecule **1** (red lines) – MDM2 complex (grey lines) 4MDN with a predicted tetrazole derivative (no 9 in ranking, blue sticks), hydrogen bond to backbone Leu54 is indicated with yellow dotted line.

2.2. Synthesis of 1,5-disubstituted-1H-tetrazoles

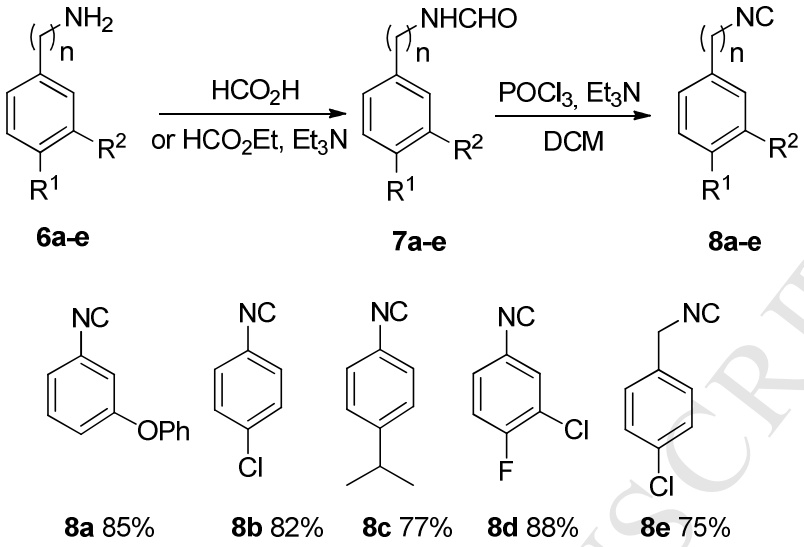
The desired scaffold **2** can be easily obtained by an Ugi-tetrazole reaction (UT-4CR) involving the anchoring 6-chloro-indole carboxaldehyde **4**, the appropriate aliphatic amines and isocyanides as well as $TMSN_3$ (Scheme 1).

Scheme 1. Retrosynthetic scheme for the tetrazole derivatives.



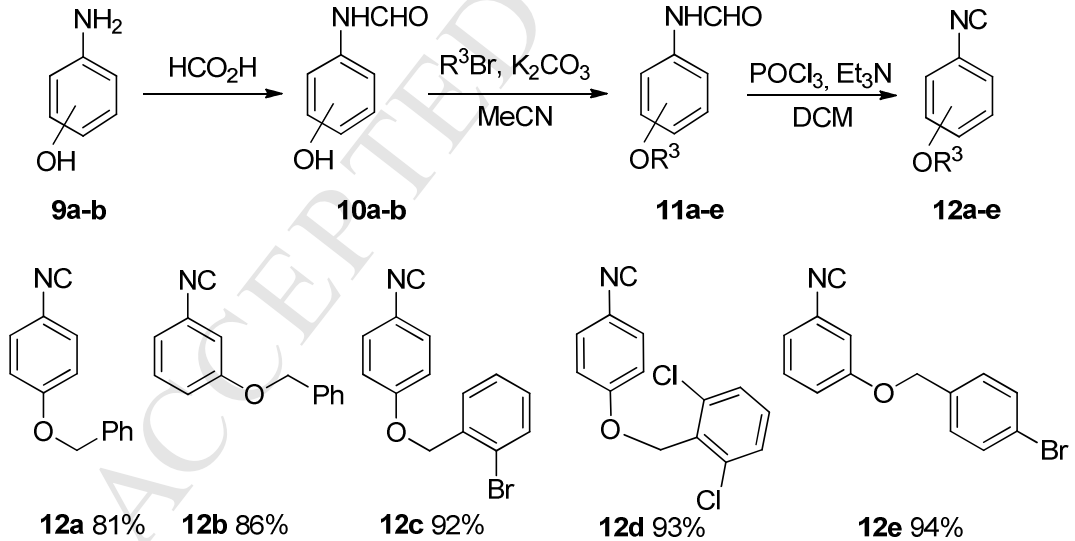
Aldehyde **4** was synthesised from 6-chloro-indole derivative using the Vilsmeier-Haack formylation reaction.[20] To explore SAR of the Phe19 pocket we used commercially available, bulky aliphatic amines. To explore Ile26 and induced pockets we probed *m*- and *p*-substituted anilines and benzylamines with different degrees of rotational flexibility. The isocyanides **8**, **12** and **17** were prepared by dehydration of the corresponding formamides (**7**, **11**, **16** respectively) with $POCl_3$.[21] In the case of isocyanides **8a-d**, the required formamides **7a-d** were prepared by refluxing of the corresponding anilines **6a-d** or 4-chlorobenzylamine **6e** with formic acid.[22] The isocyanides **12a-e** were prepared by formylation of hydroxyanilines **9a-b**,[22] followed by the Williamson ether synthesis with various benzyl halides[23] affording the formamides **11a-e** suitable for the isocyanide preparation. For the isocyanides **17a-c**, the first step was the amino group protection of 4-hydroxybenzylamine **13**.[24] Next, the Williamson ether synthesis followed by deprotection resulted in the substituted benzylamine hydrochlorides **15a-c**. Finally, the latter can be easily formylated by refluxing in ethyl formate with the presence of trimethylamine.[25] All details describing synthesis of the required precursors are shown in Schemes 2-4.

Scheme 2. A general scheme for preparation of isocyanides **8a-e**, based on anilines and 4-chlorobenzylamine.[a]



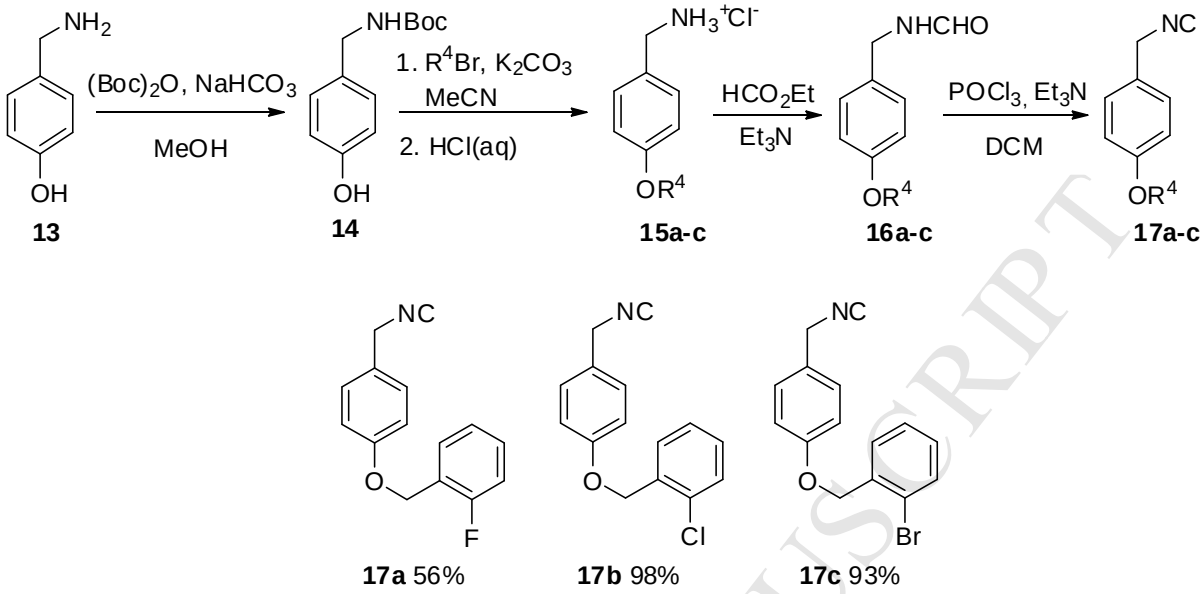
[a]*Reagents and conditions*: (a) cmpds **6a-e** (1.0 equiv.), formic acid (excess), reflux, 16 h, 80-99%; (b) cmpds **7a-e** (1.0 equiv.), $POCl_3$ (1.0 equiv.), Et_3N (4.0 equiv.), DCM 0 ºC-rt, 3 h, 75-88%.

Scheme 3. A general scheme for preparation of isocyanides **12a-e**, based on benzyloxyanilines.[a]



[a]*Reagents and conditions:* (a) cmpds **9a** or **9b** (1.0 equiv.), formic acid (excess), reflux, 16 h, 72-95%; (b) cmpds **10a** or **10b** (1.0 equiv.), benzyl bromide (1.1 equiv.), potassium carbonate (1.5 equiv.), acetonitrile, reflux, 16 h, 70-83%; (c) cmpds **11a-e** (1.0 equiv.), $POCl_3$ (1.0 equiv.), Et_3N (4.0 equiv.), DCM, 0 ºC-rt, 3 h, 81-94%.

Scheme 4. A general scheme for preparation of isocyanides **17a-c**, based on *N*-(benzyloxybenzyl) formamides.[a]



[a]*Reagents and conditions:* (a) Cmpd **13** (1.0 equiv.), Boc_2O (1.1 equiv.), $NaHCO_3$ (2.5 equiv.), methanol, rt, 16 h, 99%; (b) (i). cmpd **14** (1.0 equiv.), benzyl bromide (1.1 equiv.), potassium carbonate (1.5 equiv.), acetonitrile, reflux, 16 h, (ii). 2 M HCl in MeOH, rt, 16 h; (c) cmpds **15a-c** (1.0 equiv.), Et_3N (4.0 equiv.), ethyl formate/MeOH (4:1, excess), reflux, 16 h 82-94%; (d) cmpds **16a-c** (1.0 equiv.), $POCl_3$ (1.0 equiv.), Et_3N (4.0 equiv.), DCM, 0 ºC-rt, 3 h 56-98%.

It was possible to confirm the structure of the isocyanide **12a** by a single crystal X-ray analysis revealing a coplanarity between the two phenyl groups with the isocyanide group (Figure 2).

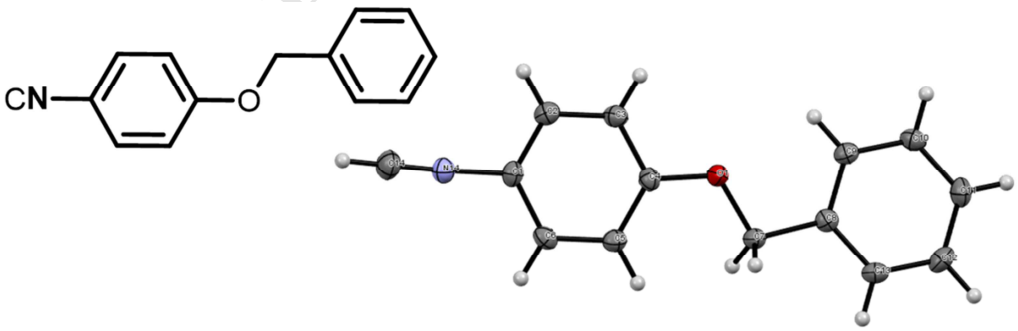
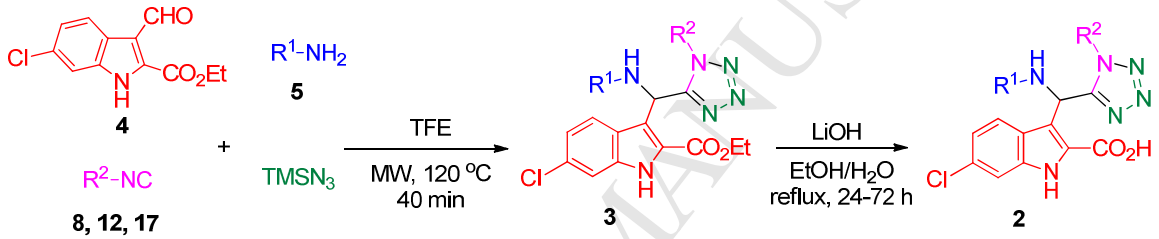


Figure 2. Molecular geometry observed in the crystal structures of **12a**, showing the atom labelling scheme. Displacement ellipsoids of non-hydrogen atoms are drawn at the 50% probability level. H atoms are presented as small spheres with an arbitrary radius.

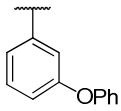
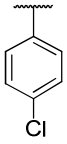
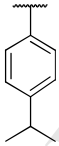
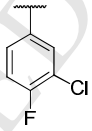
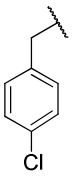
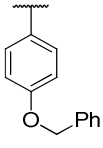
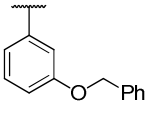
Next, we proceeded in the UT-4CR and the subsequent carboxylic acid ethyl ester hydrolysis (Scheme 5). After some optimization, the MCRs were performed under microwave irradiation at 120 °C for 40 min (we found that they also proceed after refluxing in sealed tubes for 2-3 days) yielding the tetrazole esters **3**. To the contrary, the reaction did not proceed at room temperature, even after several days of stirring with an already pre-formed Schiff base. The yields of the products did not significantly vary depending on the nature of the isocyanide or amine. It is noteworthy, that sometimes when methanol was used as a solvent, transterification occurred, whereas this was not the case when 2,2,2-trifluoroethanol (TFE) was used. The hydrolysis was performed in an ethanol/water solution (1:1) with excess of LiOH (10.0 equiv.) affording the target acids **2**. The compounds are presented in Table 1.

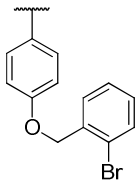
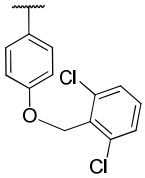
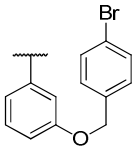
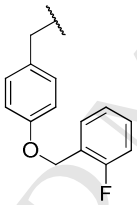
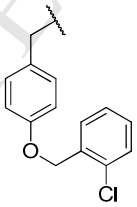
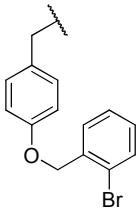
Scheme 5. The general synthetic scheme for the tetrazole derivatives.[a]



[a]*Reagents and conditions:* (a) 6-chloro-3-formyl-1*H*-indole-2-carboxylate **4** (1.0 equiv.), amine **5** (1.0 equiv.), isocyanide **8**, **12**, **17** (1.0 equiv.), $TMSN_3$ (1.0 equiv.), 2,2,2-trifluoroethanol (1 mL), 120 °C, 40 min, MW, 38-74%; (b) UT-4CR product **3** (1.0 equiv.), LiOH (10.0 equiv.), EtOH/H_2O (1:1, 4 mL), reflux, 24-72 h, 10-79%.

Table 1. Yields and activities of tetrazole-based inhibitors of p53-MDM2/X interaction.

Compound Ester/Acid	Amine (R^1)	Isocyanide (R^2)	Yield (%)		K_i [μM] for MDM2[a]	
			Ester 3	Acid 2	Ester 3	Acid 2
3.1/2.1	cyclopentyl	**8a** 	51	69	n.a.	4.38
3.2/2.2	cyclohexyl		71	65	n.a.	4.89
3.3/2.3	cycloheptyl		60	62	n.a.	10.87
3.4/2.4	cyclohexylmethyl	**8b** 	74	32	117 (46)	0.17 (44)
3.5/2.5	amyl		45	33	n.a.	0.29
3.6/2.6	cyclohexylmethyl	**8c** 	58	53	44 (55)	0.64
3.7/2.7	amyl		74	52	n.a.	0.10
3.8/2.8	cyclohexylmethyl	**8d** 	56	37	n.a.	0.52
3.9/2.9	amyl		43	55	n.a.	0.65
3.10/2.10	4-chlorobenzyl	**8e** 	44	21	n.a.	0.17
3.11/2.11	cyclohexylmethyl		47	53	n.a.	0.06
3.12/2.12	amyl		45	59	n.a.	0.08
3.13/2.13	cyclopentyl	**12a** 	40	46	n.a.	15.70
3.14/2.14	cyclohexyl		46	63	n.a.	2.47
3.15/2.15	cycloheptyl		32	67	n.a.	0.99
3.16/2.16	cyclopentyl	**12b** 	57	62	9.52 (16.17)	1.06
3.17/2.17	cyclohexyl		41	63	n.a	1.93
3.18/2.18	cycloheptyl		30	63	n.a	1.53

3.19/2.19	1-adamantyl	**12c** 	10	21	n.a.	1.64
3.20/2.20	cyclohexylmethyl		57	21	n.a.	0.23
3.21/2.21	cyclobutyl		66	67	n.a.	0.17
3.22/2.22	amyl		72	57	n.a.	0.20
3.23/2.23	cyclohexylmethyl	**12d** 	59	23	n.a.	36.57
3.24/2.24	amyl		62	53	n.a.	0.97
3.25/2.25	cyclohexylmethyl	**12e** 	48	29	n.a.	0.68
3.26/2.26	amyl		64	35	n.a.	0.86
3.27/2.27	cyclohexylmethyl	**17a** 	52	25	26.08 (6.99)	0.02
3.28/2.28	amyl		41	25	18.14	0.05 (4.29)
3.29/2.29	cyclohexylmethyl	**17b** 	52	56	n.a.	0.13
3.30/2.30	amyl		46	60	n.a.	0.03
3.31/2.31	cyclohexylmethyl	**17c** 	57	47	n.a.	0.07
3.32/2.32	4-chlorobenzyl		51	79	n.a.	0.09
3.33/2.33	amyl		52	67	n.a.	0.12

[a] data in parentheses refers to MDMX protein whenever the compound showed any 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 experimental section and supporting information).

The purity and identity of all intermediates and final compounds were confirmed by various methods (LC-MS, NMR, HRMS, elemental analysis and IR). In addition, the structure and identity of the described scaffold was confirmed by a single crystal X-ray analysis of compound **3.26** (Figure 3). The structure demonstrates that the ring planes of substituents at positions 1 and 5 are almost coplanar, being constrained by tetrazole geometry and are oriented vertically to the plane of the tetrazole ring.

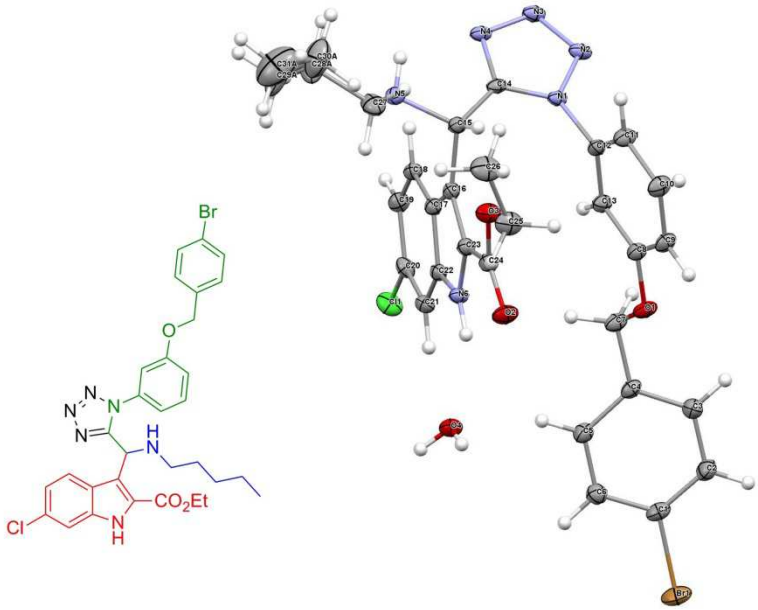


Figure 3. Crystal structure of compound **3.26** (racemic form) showing the asymmetric unit. A single water molecule has co-crystallised with the compound. Displacement ellipsoids of non-hydrogen atoms are shown at the 30% probability level. H atoms are presented as small spheres with an arbitrary radius.

2.3. Biophysical Screening and Structure-Activity Relationship Studies

Two complementary assays based on independent physicochemical principles, HSQC NMR and fluorescence polarisation (FP) were used to exclude false positive hits. Fluorescence polarization (FP) assay was employed to determine the inhibitory affinities (K_i) of tetrazole derivatives against MDM2 and MDMX as previously described.[26,27] The results are presented in Table 1.

Most of the obtained tetrazoles of a general structure of **2** are active towards MDM2, with affinity below 1 µM. Surprisingly, some of the ester precursors (**3**) were also weakly active in the tested system (**3.4**, **3.6**, **3.16**, **3.27** and **3.28**). Compound **2.27** exhibited the best affinity (20 nM), followed by compounds **2.28-2.33**. This is consistent with the design expectations

where derivatives with the elongated isocyanide moiety (based on **17a-c**) should target an additional, induced subpocket. Reducing the length of this moiety, utilizing substituted phenyl isocyanides (isocyanides: **8a-d** and **12a-12e**, tetrazoles: **2.1-2.9** and **2.13-2.26**), results in slight decrease in affinities compared to the most active compounds. The inhibitors based on the 4-chlorobenzyl isocyanide (**8e**) **2.10-2.12** exhibited better affinities than the corresponding derivatives based on 4-chlorophenyl isocyanide (**8b**) **2.4-2.5**. It seems that introducing additional flexibility at this part of the molecule is essential for tighter fit and better binding to MDM2. Noteworthy, even compounds which served as examples of the three-point pharmacophore model (**2.4-2.12**) exhibited high affinities, comparable to their four-point analogues (**2.13-2.26**).

No clear trend in affinity of compounds was observed comparing the different amine part of tested molecules. However other trends are clearly noted. Compounds having no halogen atom at the isocyanide-derived part (**2.1-2.3**, **2.13-2.18**) are generally less active compared to halogen containing derivatives. Among different halogens (e.g. F: **2.27-2.28**, Cl: **2.29-2.30**, Br: **2.31-2.33**), fluorine-substituted compounds showed best activities, with the most potent compound **2.27**, although the affinities of chlorine and bromine substituted compounds were only slightly less. Incorporation of two halogens on both ortho positions of the elongated part of the scaffold (**2.23-2.24**) significantly lowered the activity, with the worst binding compound **2.23**. A similar pattern was observed in the phenyl isocyanide-based inhibitors. Exchanging the 4-chlorophenyl (**2.4-2.5**) group for the 3-chloro-4-fluorophenyl (**2.8-2.9**) decreased the affinity. The presence of the isopropyl group lead to slightly better binding (compounds **2.6-2.7** compared to **2.4-2.5**).

Interestingly, selected compounds (**3.4**, **3.4**, **3.6**, **3.16**, **3.27**, **2.4**, **2.28**) demonstrated activity against MDMX in parallel to MDM2. Nevertheless, affinities towards MDMX were around 1000-fold lower compared to those against MDM2.

Compound **2.27** was chosen as a model for further characterization due to its high affinity towards MDM2. ^{1}H-^{15}N HSQC titration was used as a second orthogonal screening system.[28,29] Strongest ligand-induced perturbations were observed in cross peaks corresponding to residues Val88, Leu82, Gly12 and Thr49 (Figure 4). These included doubling of cross peaks (two distinct sets of resonances originating from free and ligand-bound protein); a behaviour which is characteristic for “slow” chemical exchange, for ligands characterized by K_D lower than micromolar. Perturbations in resonances of residues within the expected binding cleft advocates for the binding mode of **2.27** comparable to that

predicted in our modelling whereas the “slow” exchange compares sub-micromolar affinity of the compound.

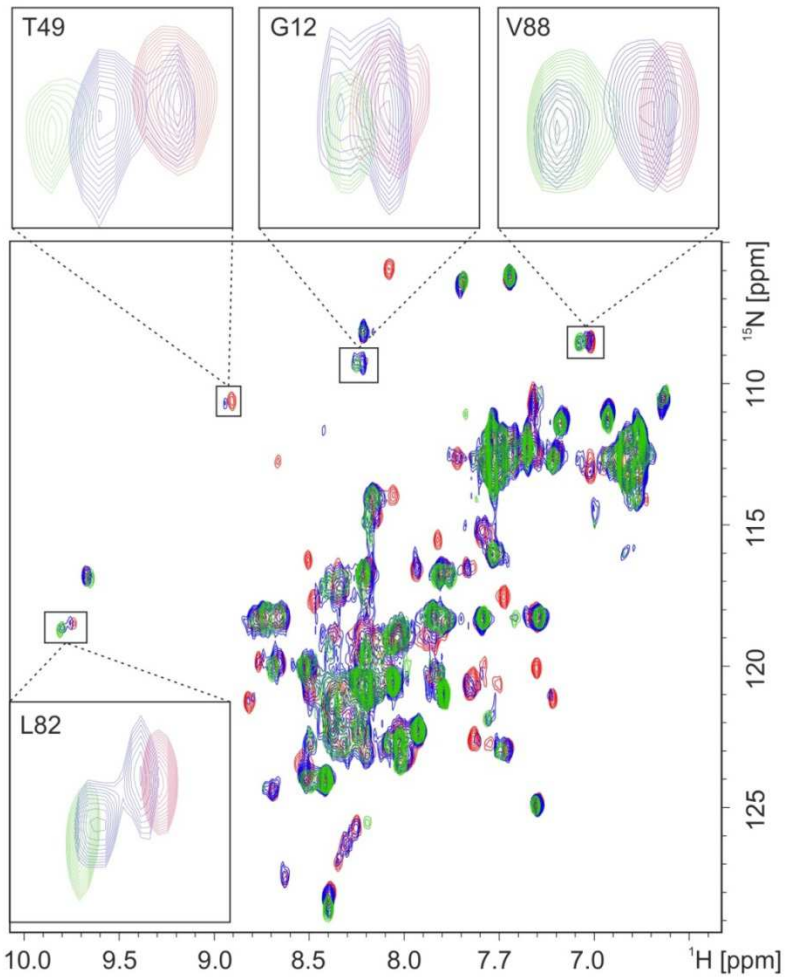


Figure 4. NMR spectra for the ^{1}H-^{15}N HSQC-based titration experiment of MDM2 with **2.27**. Red: reference MDM2 alone; blue: molar ratio protein/ligand 1:0.5; green: overtitrated MDM2 (the ratio protein/ligand 1:2). Enlarged fragments show resonance peak doubling.

3. Conclusions

A novel 1,5-disubstituted tetrazole scaffold targeting a clinically relevant p53/MDM2 interaction has been identified using our virtual screening platform approach ANCHOR.QUERY. A focused library of more than 60 compounds was synthetized using convergent 2-step multicomponent reaction chemistry. FP-monitored SAR analysis allowed for the fast optimization of the scaffold up to low nM potency. Compound (**2.27**) resulted as the most potent in the series, which inhibited the MDM2/p53 interaction with a K_i of 20 nM, improving the affinity of the templated α-aminoacylamide **1** (K_i = 600 nM). The affinity and the rough binding mode were confirmed using independent assay (2D NMR). Due to

generally satisfactory ADMET properties of tetrazoles our compounds could serve as an excellent starting point for further development of pharmaceutically relevant MDM2/p53 interaction inhibitors.

4. Experimental section

4.1. General methods

4.1.1. Virtual Screening. The receptor and small molecule **1** (derived from PDB ID 4MDN) were uploaded into ANCHOR.QUERY (http://anchorquery.csb.pitt.edu/). The pharmacophore character of the benzylic phenyl group was changed in ANCHOR.QUERY from hydrophobe to aromatic. Under the filters tab > hit reduction, the maximum hits per molecules were set to 1. The maximum total hits was set to 200 and ranking was done according to lowest molecular weight. The query yielded 134 compounds, several based on the tetrazole scaffold. The hit compounds are energy optimized and such results were further visually inspected.

4.1.2. Synthesis and analysis. All syntheses were performed using general procedures summarized in Schemes 1-5 and as described below in details. Reagents were obtained from commercial suppliers (Sigma Aldrich, ABCR, Acros and AK Scientific) and used without further purification unless otherwise noted. All microwave irradiation reactions were carried out in a Biotage Initiator™ Microwave Synthesizer.

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 δ relative to the solvent peak. Thin layer chromatography was performed on Fluka precoated silica gel plates (0.20 mm thick, particle size 25 μm). Flash chromatography was performed on a Teledyne ISCO Combiflash Rf, using RediSep Rf Normal-phase Silica Flash Columns (Silica Gel 60 Å, 230-400 mesh) and on a Reveleris® X2 Flash Chromatography, using Grace® Reveleris Silica flash cartridges (12 grams). Elemental analysis was performed on a Vario Micro Cube apparatus. Electrospray ionization mass spectra (ESI-MS) were recorded on a Waters Investigator Semi-prep 15 SFC-MS instrument or on Shimadzu LCMS-2020 apparatus. The

LC-MS measurements were performed on Shimadzu LCMS-2020 apparatus (column: KINETEX C18 5 μM, 100A, 100 x 4.6 mm; method time: 10 min; solvents gradients A: 0-10 min 80% MeCN, 20% H_2O with negative ionisation for derivatives of tetrazole-carboxylic acids; B: 0-10 min 75% MeCN, 25% MeOH with negative ionisation for amides and positive for derivatives of tetrazole-esters). Melting points were determined with a Ascon-M5 apparatus. Melting points are reported uncorrected.

4.1.3. Protein expression and purification. *N*-terminal domain of human MDM2 (residues 1-118) was cloned into pET-20 vector (Novagen) and expressed in *Escherichia coli* BL21(DE3) as described previously.[26] In brief, cells were grown at 37 °C and induced with 1 mM IPTG at OD_{600} of 0.8 and grown 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 incubating overnight at 4 °C. Ammonium sulphate 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 16/60 Superdex75 (GE Healthcare) in 50 mM phosphate buffer pH 7.4 containing 150 mM NaCl and 5 mM DTT.

N-terminal domain of human MDMX (residues 1-134) was cloned into pET-46Ek/LIC vector (Novagen). Cells were grown at 37 °C and induced with 0.5 mM IPTG at OD600 nm of 0.6. The recombinant protein expression was carried for 12 h at 20 °C. The protein was purified under native conditions using Ni-NTA Agarose (GE Healthcare). Preparation was polished by gel filtration on HiLoad 16/60 Superdex75 (GE Healthcare).

4.1.4. Fluorescence polarization binding assay. Fluorescence polarization experiments were performed as previously reported by Czarna et al.[26] using Tecan InfinitePro F200 plate reader with the 485 nm excitation and 535 nm emission filters. The fluorescence intensities, parallel and perpendicular to the plane of excitation, were measured in Corning black 96-well NBS assay plates at room temperature. Fluorescence polarization values were expressed in millipolarization units (mP). All the experiments were performed in duplicates and plates

were read 15 min after mixing of all assay components. For each assay, new protein stocks were thawed and the protein concentrations were determined using Bradford method. Assay buffer contained 50 mM NaCl, 10 mM Tris pH 8.0, 1 mM EDTA and 5% DMSO.

Competition binding assays were performed using 10 nM fluorescent P2 peptide (5'-FAM-LTFEHYWAQLTS) and protein concentration equivalent to f_0=0.8. Tested compounds, dissolved in DMSO were evaluated at serial dilutions. Nutlin 3 (Cayman Chemicals) and peptide Z (SQETFSDLWKLLPEN) served as positive controls for MDM2 and MDMX, respectively. Inhibition curves were fitted using Excel program to obtain IC_{50} and K_i values. All calculations were done according to Huang et al.[27]

4.1.5. ^{1}H-^{15}N HSQC binding assay. 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. 10% (v/v) of D_2O was added to the samples to provide lock signal. All the spectra were recorded at 300K using a Bruker Avance 600 MHz spectrometer. ^{1}H-^{15}N heteronuclear correlations were obtained using the SOFAST-HMQC pulse sequence.[i] Assignment of the amide groups of MDM2 was obtained as previously reported.[ii-iii]

4.1.6. Crystal structure determination. Single crystals of **3.26** and **12a** were obtained by slow crystallization from mixture of ethanol and water. Diffraction data were collected at 120 K on SuperNova (Rigaku Oxford Diffraction) four circle diffractometer with a microfocus Mo Kα (0.71069 Å) radiation source and a graphite monochromator equipped with a CryoJet HT cryostat system (Oxford Instruments). The crystal structure was solved using a direct method implemented in SUPERFLIP[iv] software. The crystals belonged to space group P-1 as suggested by the CrysAlisPro diffraction data processing software (Oxford Diffraction). The structure was refined by a full-matrix least squares technique using SHELXL-97.[v] Calculations were performed using WinGX (ver. 2013.2) integrated system.

All non-hydrogen atoms were refined anisotropically to ensure the convergence of the refinement process. All hydrogen atoms joined to carbon atoms were positioned with an idealized geometry, and refined using a riding model. The O- and N-bound hydrogen atoms were located from difference Fourier map and refined freely.

The disorder for the pentane moiety was modelled by splitting atoms with the highest anisotropic displacement parameters (ADPs) into two components. To ensure the convergence of the refinement some distances of disordered fragments were restrained, and the ADPs of the disordered atoms were also restrained to have similar values.

4.2. Synthetic procedures and analytical data.

*4.2.1. 6-Chloro-3-formyl-1H-indole-2-carboxylic acid ethyl ester **4***

6-Chloro-1*H*-indole-2-carboxylic acid ethyl ester (5.0 g, 22.3 mmol) and DMF (20 mL) were placed in round-bottom flask equipped with $CaCl_2$ tube. Then, $POCl_3$ (2.49 mL, 26.8 mmol) was added dropwise and reaction mixture was heated overnight (16 h) at 50 ºC. Afterwards, the reaction was cooled to rt, quenched with saturated $NaHCO_3$ solution and extracted with ethyl acetate. Organic layer was collected, washed with water and brine, dried over anhydrous $MgSO_4$ and evaporated. The crude product was washed with diethyl ether giving compound **4** as a light yellow solid in 92% (5.15 g) yield.[20]

mp: 243-244 ºC; **NMR**: **^{1}H** (600 MHz, DMSO-d_6): δ 12.90 (s, 1H), 10.58 (s, 1H), 8.22 (d, J = 8.6 Hz, 1H), 7.56 (d, J = 1.5 Hz, 1H), 7.32 (dd, J = 8.6, 1.9 Hz, 1H), 4.46 (q, J = 7.1 Hz, 2H), 1.40 (t, J = 7.1 Hz, 3H); **^{13}C** (151 MHz, DMSO-d_6): δ 187.5, 159.9, 136.1, 133.5, 130.4, 124.0, 123.9, 123.4, 118.2, 112.6, 62.0, 14.1; **IR (ATR)** [cm^{-1}]: 3154, 2992, 2908, 1726, 1639, 1571, 1532, 1433, 1300, 1221, 1195, 1100, 1163, 1030, 916, 854, 779, 698; **Elemental analysis**: Calcd for $C_{12}H_{10}ClNO_3$: C, 57.27; H, 4.01; N, 5.57, found: C, 57.51; H, 4.26; N, 5.50; **LC-MS (DAD/ESI)**: t_R = 2.97 min, Calcd for $C_{12}H_{10}ClNO_3$ (m/z): $[M-H]^-$ 250.03, $[M+2-H]^-$ 250.02, found: $[M-H]^-$ 250.05, $[M+2-H]^-$ 252.05.

*4.2.2. ^{t}Butyl 4-hydroxybenzylcarbamate **14***

4-Hydroxybenzylamine **13** (4.00 g, 32.5 mmol), $(Boc)_2O$ (7.80 g, 35.8 mmol) and $NaHCO_3$ (3.41 g, 81.2 mmol) were refluxed in methanol overnight (16 h). Afterwards, the reaction was cooled to rt and methanol was evaporated. To the resulting slurry, water and ethyl acetate were added and the aqueous phase was extracted with ethyl acetate. Organic layers were collected, washed with water and brine, dried over anhydrous $MgSO_4$ and evaporated, giving crude product as brown oil. The crude product was precipitated and washed with diethyl ether/petroleum ether (approx. 1:1) giving compound **14** as light brown solid with 99% (7.17 g) yield.[24]

mp: 87 ºC; **NMR: ^{1}H** (600 MHz, $CDCl_3$): δ 7.10 (d, J = 7.3 Hz, 2H), 6.77 (dt, J = 8.6, 2.0 Hz, 2H), 4.86 (s, 1H), 4.22 (s, 2H), 1.46 (s, 9H); **^{13}C** (151 MHz, $CDCl_3$): δ 156.3, 155.5, 130.5, 129.0, 115.6, 79.9, 44.3, 28.6; **IR (ATR)** [cm^{-1}]: 3340, 3153, 2974, 1673, 1615, 1598, 1549, 1517, 1448, 1367, 1292, 1257, 1227, 1160; **Elemental analysis**: Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27, found: C, 64.69; H, 7.50; N, 6.09; **LC-MS (DAD/ESI)**: t_R = 5.31 min, Calcd for $C_{12}H_{17}NO_3$ (m/z): $[M-H]^-$ 222.26, found: $[M-H]^-$ 222.10.

4.2.3. General synthetic procedures for formylation and analytical data

Method A

The corresponding aniline or benzylamine **6a-e** or **9a-b** and formic acid (excess, approximately 5 mL for 10 mmol of aniline) were placed together in a round-bottom flask equipped with $CaCl_2$ tube and refluxed overnight (16 h). Next, formic acid was evaporated and the resulting solid (except for compound **7c**) was washed with diethyl ether giving crude product (**7b-e** or **10a-b**; yields 72-99%).

Method B

The corresponding benzylamine hydrochloride salts **15a-c** (1.0 equiv.), Et_3N (4.0 equiv.), ethyl formate and methanol (4:1 ratio) were refluxed overnight (16 h). After the reaction was completed, the products were poured into saturated NH_4Cl solution, which was then extracted with ethyl acetate. Organic layers were collected, washed with water and brine, dried over anhydrous $MgSO_4$ and evaporated. The resulting solid was washed with diethyl ether giving crude products (**16a-c**; yields 82-94%).

*4.2.3.1. N-(3-phenoxyphenyl)formamide **7a***

To a stirred solution of 3-(phenoxy)aniline **6a** (1.0 equiv.) in ethylformate (3 mL), trimethylamine (1.0 equiv) was added. The reaction mixture was refluxed for 2 days and the resulting mixture was extracted with ethyl acetate. Organic layers were collected, washed with water and brine, dried over anhydrous $MgSO_4$ and evaporated giving the product **7a** as white solid in 80% yield.

NMR: mixture of two rotamers ^{1}**H** (600 MHz, $CDCl_3$): δ 8.58 (d, J = 10 Hz, 1H), 8.36 (s, 1H), 7.50 (d, J = 5 Hz, 2H), 7.36-7.30 (m, 4H), 7.12-6.98 (m, 12H), ; ^{13}**C** (151 MHz, $CDCl_3$): δ 162.8, 159.0, 130.1, 130.0, 123.8, 123.5, 123.0, 123.5, 122.0, 121.5, 119.8, 119.0, 118.8.

*4.2.3.2. N-(4-Chlorophenyl)formamide **7b***

Method A: 4-chloroaniline **6b** (3.3 g, 25.9 mmol). Crude product was recrystallized from $CHCl_3$ giving **7b** as light gray crystals in 90% (3.61 g) yield.

mp: 101 ºC (lit. 100-102ºC)[vi]; **NMR**: mixture of two rotamers ^{1}**H** (600 MHz, $CDCl_3$): δ (main rotamer) 10.31 (s, 1H), 8.28 (d, J = 1.8 Hz, 1H), 7.61 (dt, J = 8.9, 2.0 Hz, 2H), 7.42-7.33 (m, 2H); ^{13}**C** (151 MHz, $CDCl_3$): δ 162.5, 159.7, 137.4, 137.2, 129.2, 128.8, 127.4, 127.1, 120.7, 119.0; **IR (ATR)** [cm^{-1}]: 3258, 3193, 3122, 3061, 2896, 1686, 1668, 1608, 1543, 1490, 1398, 1312, 1255, 1172, 1088, 1012, 830, 769; **Elemental analysis**: Calcd for C_7H_6ClNO: C, 54.04; H, 3.89; N, 9.00, found: C, 54.06; H, 4.07; N, 8.98; **LC-MS (DAD/ESI)**: t_R = 2.86 min, Calcd

for C_7H_6ClNO (m/z): $[M-H]^-$ 154.01, $[M+2-H]^-$ 156.00, found: $[M-H]^-$ 154.05, $[M+2-H]^-$ 156.00.

*4.2.3.3. N-(4-Isopropylphenyl)formamide **7c***

Method A: 4-isopropylaniline **6c** (3.0 mL g, 21.9 mmol). Product **7c** was obtained as brown liquid in 99% (3.52 g) yield.[vii]

NMR: mixture of two rotamers (approx. 1:1) **^{1}H** (600 MHz, $CDCl_3$): δ 8.83 (d, J = 10.8 Hz, 1H), 8.64 (d, J = 11.4 Hz, 1H), 8.32 (d, J = 1.9 Hz, 1H), 8.04 (s, 1H), 7.47 (dt, J = 8.5, 1.9 Hz, 2H), 7.20 (dt, J = 8.5, 1.8 Hz, 2H), 7.17 (dt, J = 8.4, 1.8 Hz, 2H), 7.03 (dt, J = 8.5, 1.9 Hz, 2H), 2.93-2.82 (m, 2H), 1.22 (d, J = 6.9 Hz, 6H), 1.24 (d, J = 6.9 Hz, 6H); **^{13}C** (151 MHz, $CDCl_3$): δ 163.3, 159.5, 146.3, 145.6, 134.7, 134.5, 127.7, 120.7, 120.3, 119.2, 33.7, 33.6, 24.0; **IR (ATR)** [cm^{-1}]: 3268, 3114, 3053, 2960, 2870, 1683, 1610, 1520, 1412, 1313, 832; **LC-MS (DAD/ESI)**: t_R = 5.68 min, Calcd for $C_{10}H_{13}NO$ (m/z): $[M-H]^-$ 162.09, found: $[M-H]^-$ 162.10.

*4.2.3.4. N-(3-Chloro-4-fluorophenyl)formamide **7d***

Method A: 3-chloro-4-fluoroaniline **6d** (3.2 g, 21.8 mmol). Crude product was recrystallized from $CHCl_3$ giving compound **7d** as colorless crystals in 93% (3.52 g) yield.

mp: 96 ºC (lit. 94-95 ºC)[viii]; **NMR**: mixture of two rotamers **^{1}H** (600 MHz, DMSO-d_6): δ (main rotamer) 10.39 (s, 1H), 8.29 (d, J = 1.4 Hz, 1H), 7.90 (dd, J = 6.8, 2.6 Hz, 1H), 7.47 (ddd, J = 9.0, 4.3, 2.6 Hz, 1H), 7.38 (t, J = 9.1 Hz, 1H); **^{13}C** (151 MHz, DMSO-d_6): δ 162.8, 159.9, 154.5, 154.1, 152.9, 152.4, 135.9, 135.5, 135.5, 120.6, 119.5, 119.4, 119.3, 119.2, 119.0, 117.90, 117.85, 117.6, 117.4, 117.2, 117.0; **IR (ATR)** [cm^{-1}]: 3256, 3203, 3143, 3077, 2690, 2863, 1674, 1609, 1559, 1496, 1403, 1319, 1254, 1164, 1061, 867, 819, 754, 712; **Elemental analysis**: Calcd for C_7H_5ClFNO: C, 48.44; H, 2.90; N, 8.07, found: C, 48.63; H, 3.00; N, 8.08; **LC-MS (DAD/ESI)**: t_R = 2.80 min, Calcd for C_7H_5ClFNO (m/z): $[M-H]^-$ 172.00, $[M+2-H]^-$ 174.00, found: $[M-H]^-$ 172.00, $[M+2-H]^-$ 174.00.

*4.2.3.5. N-(4-Chlorobenzyl)formamide **7e***

Method A: 4-chlorobenzylamine **6e** (4.0 mL g, 32.9 mmol). Crude product was recrystallized from cyclohexane giving compound **7e** as colorless crystals in 86% (4.79 g) yield.

mp: 142 ºC; NMR: **^{1}H** (600 MHz, DMSO-d_6): δ 8.36 (s, 1H), 7.48-7.40 (m, 4H), 3.89 (s, 2H); **^{13}C** (151 MHz, DMSO-d_6): δ 165.5, 137.0, 132.1, 130.1, 128.3, 42.5; **IR (ATR)** [cm^{-1}]: 2892, 2783, 2708, 2635, 1624, 1574, 1497, 1442, 1370, 1342, 1153, 1100, 1010, 910, 818, 771;

Elemental analysis: Calcd for $C_7H_5ClFNO*H_2O$: C, 51.21; H, 5.37; N, 7.47, found: C, 51.17; H, 5.19; N, 7.22.

*4.2.3.6. N-(4-Hydroxyphenyl)formamide **10a***

Method A: 4-hydroxyaniline **9a** (2.0 g, 18.3 mmol). Crude product was recrystallized from $CHCl_3$/cyclohexane giving compound **10a** as light brown solid in 95% (2.39 g) yield.

mp: 137 ºC (lit. 135-137 ºC)[vi]; **NMR**: mixture of two rotamers (approx. 1:3) **^{1}H** (600 MHz, DMSO-d_6): δ (main rotamer) 9.88 (s, 1H), 9.22 (s, 1H), 8.15 (d, J = 2.0 Hz, 1H), 7.37 (dt, J = 8.8., 2.2 Hz, 2H), 6.70 (dt, J = 8.8, 2.2 Hz, 2H); **^{13}C** (151 MHz, DMSO-d_6): δ 162.6, 158.8, 154.2, 153.5, 130.0, 129.7, 120.8, 120.2, 115.8, 115.2; **IR (ATR)** [cm^{-1}]: 3305, 3094, 2979, 2883, 2798, 2677, 2611, 1657, 1558, 1507, 1400, 1379, 1252, 1170, 1107, 828; **Elemental analysis**: Calcd for $C_7H_7NO_2$: C, 61.30; H, 10.21; N, 5.14, found: C, 61.10; H, 5.43; N, 10.14; **LC-MS (DAD/ESI)**: t_R 5.16 min, Calcd for $C_7H_7NO_2$ (m/z): $[M-H]^-$ 136.13, found: $[M-H]^-$ 136.10.

*4.2.3.7. N-(3-Hydroxyphenyl)formamide **10b***

Method A: 3-hydroxyaniline **9b** (3.2 g, 21.8 mmol). Crude product was recrystallized from $CHCl_3$ giving compound **10b** as light green solid in 72% (3.64 g) yield.

mp: 112 ºC (lit. 135-137 ºC)[ix]; **NMR**: mixture of two rotamers (approx. 1:3) **^{1}H** (600 MHz, DMSO-d_6): δ (main rotamer) 10.04 (s, 1H), 9.41 (s, 1H), 8.22 (d, J = 1.9 Hz, 1H), 7.17 (t, J = 2.1 Hz, 1H), 7.07 (t, J = 8.1 Hz, 1H), 6.47 (ddd, J = 8.1, 2.3, 0.7 Hz, 1H); **^{13}C** (151 MHz, DMSO-d_6): δ 162.4, 159.5, 158.3, 157.7, 139.5, 130.2, 129.6, 110.8, 110.8, 109.9, 108.0, 106.4, 104.7; **IR (ATR)** [cm^{-1}]: 3327, 3131, 1644, 1598, 1614, 1545, 1488, 1402, 1332, 1293, 1200, 935, 783, 717; **Elemental analysis**: Calcd for $C_7H_7N_2O$: C, 61.30; H, 10.21; N, 5.14, found: C, 61.31; H, 5.14; N, 10.21; **LC-MS (DAD/ESI)**: t_R = 5.14 min, Calcd for $C_7H_7NO_2$ (m/z): $[M-H]^-$ 136.13, found: $[M-H]^-$ 136.05.

*4.2.3.8. N-4-[(2-Fluorobenzyl)oxy]benzylformamide **16a***

Method B: Hydrochloride **15a** (1.4 g, 5.2 mmol), Et_3N (2.92 mL, 21.0 mmol). Crude product was recrystallized from EtOH/H_2O giving compound **16c** as colourless solid in 82% (1.12 g) yield.

mp: 202-203 ºC; **NMR**: mixture of two rotamers **^{1}H** (600 MHz, $CDCl_3$): δ (main rotamer) 8.24 (s, 1H), 7.49 (td, J = 7.5, 1.3 Hz, 1H), 7.34-7.29 (m, 1H), 7.22 (d, J = 8.6 Hz, 2H), 7.19-7.14 (m, 1H), 7.11-7.06 (m, 1H), 6.95 (d, J = 8.6 Hz, 2H), 5.83 (s, 1H), 5.12 (s, 2H), 4.42 (d,

J = 5.5 Hz, 2H); **^{13}C** (151 MHz, $CDCl_3$): δ 161.3, 160.9, 159.6, 158.1, 130.1, 129.9, 129.8, 129.7, 129.7, 129.7, 129.3, 128.4, 124.3, 124.3, 124.0, 124.0, 111.5, 115.3, 115.3, 115.1, 63.8, 63.7, 41.7; **IR (ATR)** [cm^{-1}]: 3272, 3041, 2880, 1653, 1631, 1539, 1515, 1490, 1456, 1386, 1306, 1254, 1231, 1174, 1056, 814, 799, 784, 750; **Elemental analysis**: Calcd for $C_{15}H_{14}FNO_2$: C, 69.49; H, 5.44;, N, 5.40, found: C, 70.17; H; 5.43, N, 5.15.

*4.2.3.9. N-4-[(2-Chlorobenzyl)oxy]benzylformamide **16b***

Method B: Hydrochloride **15b** (1.2 g, 4.2 mmol), Et_3N (2.35 mL, 16.9 mmol). Crude product was recrystallized from EtOH/H_2O giving compound **16b** as colourless solid in 94% (1.09 g) yield.

mp: 111-112 ºC; **NMR**: mixture of two rotamers **^{1}H** (600 MHz, $CDCl_3$): δ (main rotamer) 8.24 (s, 1H), 7.55-7.52 (m, 1H), 7.41-7.38 (m, 1H), 7.30-7.25 (m, 2H), 7.23 (d, *J* = 8.6 Hz, 2H), 6.96 (dt, *J* = 8.5, 2.0 Hz, 2H), 5.83 (s, 1H), 5.16 (s, 2H), 4.43 (d, *J* = 5.6 Hz, 2H); **^{13}C** (151 MHz, $CDCl_3$): δ 161.0, 158.2, 134.7, 132.7, 130.3, 129.6, 129.4, 129.2, 128.9, 128.6, 127.1, 115.3, 67.3, 41.9; **IR (ATR)** [cm^{-1}]: 3281, 3023, 2874, 1648, 1515, 1443, 1382, 1351, 1305, 1254, 1219, 1181, 1126, 1045, 1036, 810, 752, 693; **Elemental analysis**: Calcd for $C_{15}H_{14}ClNO_2$: C, 65.34; H, 5.12; N, 5.08, found: C, 65.97; H, 5.22; N, 4.94; **LC-MS (DAD/ESI):** t_R = 2.81 min, Calcd for $C_{15}H_{14}ClNO_2$ (m/z): $[M-H]^-$ 274.06, $[M+2-H]^-$ 276.06, found: $[M-H]^-$ 274.05, $[M+2-H]^-$ 276.05.

*4.2.3.10. N-4-[(2-Bromobenzyl)oxy]benzylformamide **16c***

Method B: Hydrochloride **15c** (2.0 g, 6.1 mmol), Et_3N (1.71 mL, 12.2 mmol). Crude product was recrystallized from EtOH/H_2O giving compound **16c** as colourless crystals in 89% (1.74 g) yield.

mp: 120 ºC; **NMR**: mixture of two rotamers **^{1}H** (600 MHz, $CDCl_3$): δ (main rotamer) 8.25 (s, 1H), 7.59 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.33 (td, *J* = 7.6, 0.8 Hz, 1H), 7.23 (d, *J* = 8.6 Hz, 2H), 7.19 (t, *J* = 6.8 Hz, 1H), 6.95 (d, *J* = 8.6 Hz, 2H), 5.18 (s, 2H), 4.43 (d, *J* = 5.5 Hz, 2H); **^{13}C** (151 MHz, $CDCl_3$): δ 161.0, 158.2, 136.3, 132.8, 130.3, 129.4, 129.0, 128.6, 127.7, 122.5, 115.5, 115.3, 69.6, 41.9 IR (ATR) [cm^{-1}]: 3263, 3035, 2887, 1645, 1514, 1383, 1253, 1217, 1026, 752; **Elemental analysis**: Calcd for $C_{15}H_{14}BrNO_2$: C, 56.27; H, 4.41; N, 4.37, found: C, 56.54; H, 4.78; N, 4.36; **LC-MS (DAD/ESI)**: t_R = 2.84 min, Calcd for $C_{15}H_{14}BrNO_2$ (m/z): $[M-H]^-$ 318.01, $[M+2-H]^-$ 320.01, found: $[M-H]^-$ 318.05, $[M+2-H]^-$ 320.05.

4.2.4. General synthetic procedures for Williamson ethers synthesis and analytical data

Method A

The corresponding formamides **10a** or **10b** (1.0 equiv.), benzyl halide (1.1 equiv.) and K_2CO_3 (1.5 equiv.) in acetonitrile were refluxed overnight (16 h). After the reactions were completed, water was added and the resulting mixture was extracted with ethyl acetate. Organic layers were collected, washed with water and brine, dried over anhydrous $MgSO_4$ and evaporated. The resulting solid was washed with petroleum ether/diethyl ether (approx. 1:1) giving the crude product (**11c-e**; yields 71-83%).

Method B

Tert-butyl 4-hydroxybenzylcarbamate **14** (1.0 equiv.), benzyl halide (1.1 equiv.), K_2CO_3 (1.5 equiv.) and acetonitrile were refluxed overnight (16 h). After the reaction was completed, water was added and the resulting mixture was extracted with ethyl acetate. Organic layers were collected, washed with water and brine, dried over anhydrous $MgSO_4$ and evaporated giving the intermediate products as white solids. This solid was stirred overnight at rt in excess of 2 M HCl solution in MeOH (approx. 30 mL). After this, the solvent was evaporated and the resulting solid was washed with diethyl ether giving the crude product (**15a-c**; yields 82-94%).

*4.2.4.1. N-(4-benzyloxyphenyl)formamide **11a***

To a stirred solution of 4-(benzyloxy)aniline **10a** (1.0 equiv.) in ethylformate (3 mL), trimethylamine (1.0 equiv) was added. The reaction mixture was refluxed for 2 days and the resulting mixture was extracted with ethyl acetate. Organic layers were collected, washed with water and brine, dried over anhydrous $MgSO_4$ and evaporated giving the product as white solid in 70% yield.[x]

NMR: mixture of two rotamers (approx. 1:1) **^{1}H** (600 MHz, $CDCl_3$): δ 8.50 (d, J = 10.0 Hz, 1H), 8.27 (s, 1H), 7.43-7.30 (m, 12H), 7.02-6.90 (m, 6H), 5.03 (s, 4H).

*4.2.4.2. N-(3-benzyloxyphenyl)formamide **11b***

To a stirred solution of 3-(benzyloxy)aniline **10b** (1.0 equiv.) in ethylformate (3 mL), catalytic amount of *p*TsOH monohydrate was added. The reaction mixture was stirred at rt for 3 days and the resulting mixture was extracted with ethyl acetate. Organic layers were collected, washed with water and brine, dried over anhydrous $MgSO_4$ and evaporated giving the product **11b** as white solid in 80% yield.[x]

NMR: mixture of two rotamers (approx. 1:1) **^{1}H** (600 MHz, $CDCl_3$): δ 8.67 (d, J = 10.0 Hz, 1H), 8.32 (s, 1H), 7.97-7.67 (m, 22H), 5.05 (s, 2H), 5.03 (s, 2H).

*4.2.4.3. N-(4-(2-Bromobenzyloxy)phenyl)formamide **11c***

Method A: Formamide **10a** (0.9 g, 6.6 mmol), 2-bromobenzyl bromide (1.80 g, 7.1 mmol), K_2CO_3 (2.64 g, 9.8 mmol). Crude product was recrystallized from EtOH/H_2O giving compound **11c** as colourless needles in 80% (1.61 g) yield.

mp: 87 ºC; **NMR**: mixture of two rotamers (approx. 1:1) **^{1}H** (600 MHz, $CDCl_3$): δ 8.52 (d, J = 11.5 Hz, 1H), 8.33 (d, J = 1.5 Hz, 1H), 7.63 (d, J = 11.1 Hz, 1H), 7.61-7.57 (m, 2H), 7.53 (d, J = 7.7 Hz, 1H), 7.46 (dt, J = 9.1, 2.1 Hz, 2H), 7.33 (qd, J = 7.5, 1.1 Hz, 2H), 7.22-7.17 (m, 2H), 7.14 (s, 1H), 7.04 (dt, J = 8.9, 2.1 Hz, 2H), 6.98 (dt, J = 9.8, 2.3 Hz, 2H), 6.95 (dt, J = 9.0, 2.1 Hz, 2H), 5.13 (s, 2H), 5.12 (s, 2H); **^{13}C** (151 MHz, $CDCl_3$): δ 162.9, 158.9, 156.6, 155.7, 136.3, 136.0, 132.9, 132.8, 130.4, 130.0, 129.6, 129.4, 129.0, 129.0, 127.8, 127.7, 122.5, 122.5, 121.9, 121.9, 121.7, 116.1, 115.5, 69.9, 69.8; **IR (ATR)** [cm^{-1}]: 3222, 3178, 2887, 1660, 1537, 1508, 1391, 1252, 1025, 813, 759; **Elemental analysis**: Calcd for $C_{14}H_{12}BrNO_2$: C, 54.92; H, 3.95; N, 4.58, found: C, 55.06; H, 3.87; N, 4.53; **LC-MS (DAD/ESI)**: t_R = 2.89 min, Calcd for $C_{14}H_{12}BrNO_2$ (m/z): $[M-H]^-$ 304.00, $[M+2-H]^-$ 306.00, found: $[M-H]^-$ 304.05, $[M+2-H]^-$ 306.05.

*4.2.4.4. N-(4-(2,6-Dichlorobenzyloxy)phenyl)formamide **11d***

Method A: Formamide **10a** (0.6 g, 4.4 mmol), 2,6-dichlorobenzyl bromide (1.16 g, 4.8 mmol), K_2CO_3 (0.91 g, 6.6 mmol). Crude product was recrystallized from EtOH/H_2O giving compound **11d** as colourless crystals in 71% (0.92 g) yield.

mp: 132 ºC; **NMR**: mixture of two rotamers (approx. 1:1) **^{1}H** (600 MHz, $CDCl_3$): δ 8.53 (d, J = 11.4 Hz, 1H), 8.34 (d, J = 1.6 Hz, 1H), 7.70 (d, J = 11.1 Hz, 1H), 7.48 (dt, J = 8.9, 2.1 Hz, 2H), 7.39-7.35 (m, 4H), 7.28-7.22 (m, 2H), 7.19 (s, 1H), 7.09- 6.98 (m, 6H), 5.27 (s, 2H), 5.26 (s, 2H); **^{13}C** (151 MHz, $CDCl_3$): δ 162.9, 128.9, 157.0, 156.2, 137.1, 137.1, 132.3, 132.0, 130.7, 130.6, 130.2, 128.7, 128.6, 121.9, 121.8, 116.4, 115.7, 65.8, 65.8; **IR (ATR)** [cm^{-1}]: 3235, 3193, 3117, 3053, 2953, 2896, 1650, 1602, 1507, 1437, 1406, 1225, 1151, 1010, 835, 769, 704; **Elemental analysis**: Calcd for $C_{14}H_{11}Cl_2NO_2$: C, 56.78; H, 3.74; N, 4.73, found: C, 56.62; H, 4.00; N, 4.65; **LC-MS (DAD/ESI)**: t_R = 2.90 min, Calcd for $C_{14}H_{11}Cl_2NO_2$ (m/z): [M-H]- 294.01, [M+2-H]- 296.01, found: [M-H]- 294.05, [M+2-H]- 296.00.

*4.2.4.5. N-3-[(4-Bromobenzyl)oxy]phenylformamide **11e***

Method A: Formamide **10b** (1.0 g, 7.29 mmol), 4-bromobenzyl bromide (2.0 g, 8.0 mmol), K_2CO_3 (1.51 g, 10.9 mmol). Crude product was recrystallized from EtOH/H_2O giving compound **11e** as colourless solid in 83% (1.85 g) yield.

mp: 138 ºC; **NMR**: mixture of two rotamers (approx. 1:1) **^{1}H** (600 MHz, $CDCl_3$): δ 8.68 (d, J = 11.4 Hz, 1H), 8.37 (s, 1H), 7.77 (d, J = 9.8 Hz, 1H), 7.51 (tt, J = 8.9, 2.0 Hz, 4H), 7.43 (t, J = 2.2 Hz, 1H), 7.30 (dd, J = 8.3, 5.3 Hz, 4H), 7.26 (t, J = 8.3 Hz, 1H), 7.22 (t, J = 8.1 Hz, 1H), 6.98 (dd, J = 8.0, 1.3 Hz, 1H), 6.77 (dd, J = 8.3, 2.2 Hz, 1H), 6.74 (dd, J = 8.3, 2.4 Hz, 1H), 6.69 (dd, J = 7.9, 1.7 Hz, 1H), 6.67 (t, J = 2.1 Hz, 1H), 5.02 (s, 4H); **^{13}C** (151 MHz, $CDCl_3$): δ 162.3, 159.7, 159.2, 159.0, 138.2, 138.0, 135.9, 135.6, 132.0, 131.9, 130.9, 130.0, 129.3, 129.2, 122.3, 122.1, 112.4, 111.6, 111.5, 111.3, 106.9, 106.0, 69.5, 69.4; **IR (ATR)** [cm^{-1}]: 3208, 3144, 3061, 3013, 2922, 1710, 1612, 1500, 1311, 1267, 1160, 1030, 1013, 849, 808, 767; Elemental analysis: Calcd for $C_{14}H_{12}BrNO_2$: C, 54.92; H, 3.95; N, 4.58; Found: C, 54.97; H, 3.60; N, 4.45; **LC-MS (DAD/ESI)**: t_R = 2.90 min, Calcd for $C_{14}H_{12}BrNO_2$ (m/z): $[M-H]^-$ 304.00, $[M+2-H]^-$ 306.00, found: $[M-H]^-$ 304.00, $[M+2-H]^-$ 306.00.

*4.2.4.6. 4-[(2-Fluorobenzyl)oxy]benzylamine hydrochloride **15a***

Method B: Boc-protected amine **14** (2.0 g, 9.0 mmol), 2-fluorobenzyl bromide (1.19 mL, 9.9 mmol), K_2CO_3 (1.69 g, 12.2 mmol). Crude product was recrystallized from H_2O giving compound **15a** as colourless solid in 67% (1.60 g) yield.

mp: 202-203 ºC (decomposition); **NMR**: **^{1}H** (600 MHz, DMSO-d_6): δ 8.36 (s, 3H), 7.55 (t, J = 6.9 Hz, 1H), 7.49-7.39 (m, 2H), 7.29-7.21 (m, 2H), 7.06 (d, J = 8.7 Hz, 2H), 5.16 (s, 2H), 3.96 (s, 2H); **^{13}C** (151 MHz, DMSO-d_6): δ 161.2, 159.6, 158.2, 130.7, 130.7, 130.6, 130.5, 130.5, 130.4, 126.5, 124.5, 124.5, 123.7, 115.5, 115.4, 114.7, 63.6, 63.6, 41.6; **IR (ATR)** [cm^{-1}]: 3311, 3085, 2918, 1610, 1587, 1516, 14902, 1455, 1382, 1244, 1233, 1174, 1052, 832, 751.

*4.2.4.7. 4-[(2-Chlorobenzyl)oxy]benzylamine hydrochloride **15b***

Method B: Boc-protected amine **14** (2.0 g, 9.0 mmol), 2-chlorobenzyl bromide (1.01 mL, 9.9 mmol), K_2CO_3 (1.69 g, 12.2 mmol). Crude product was recrystallized from H_2O giving compound **15b** as colourless solid in 57% (1.31 g) yield.

mp: 190-191 ºC (decomposition); **NMR**: **^{1}H** (600 MHz, DMSO-d_6): δ 8.39 (s, 3H), 7.60-7.56 (m, 1H), 7.53-7.49 (m, 1H), 7.44 (d, J = 8.7 Hz, 2H), 7.42-7.36 (m, 2H), 7.06 (dt, J = 8.7, 1.8 Hz, 2H), 5.17 (s, 2H), 3.93 (s, 2H); **^{13}C** (151 MHz, DMSO-d_6): δ 158.2, 134.2, 132.7, 130.6,

130.1, 129.9, 129.4, 127.4, 126.6, 114.7, 66.9, 41.6; **IR (ATR)** [cm^{-1}]: 3303, 3073, 2920, 1608, 1513, 1448, 1380, 1295, 1250, 1175, 1048, 1037, 831, 744.

*4.2.4.8. 4-[(2-Bromobenzyl)oxy]benzylamine hydrochloride **15c***

Method B: Boc-protected amine **14** (2.50 g, 11.2 mmol), 2-bromobenzyl bromide (3.07 g, 12.2 mmol), K_2CO_3 (2.31 g, 16.8 mmol). Crude product was recrystallized from H_2O giving compound **15c** as colourless solid in 58% (2.13 g) yield.

mp: 199-200 ºC (decomposition); **NMR**: **^{1}H** (600 MHz, DMSO-d_6): δ 8.32 (s, 3H), 7.68 (dd, J = 8.0, 1.0 Hz, 1H), 7.57 (dd, J = 7.6, 1.5 Hz, 1H), 7.46-7.40 (m, 3H), 7.31 (td, J = 7.8, 1.7 Hz, 1H), 7.05 (dt, J = 8.7, 1.9 Hz, 2H), 5.14 (s, 2H), 3.94 (s, 2H); **^{13}C** (151 MHz, DMSO-d_6): δ 158.2, 135.7, 132.7, 130.6, 130.2, 127.9, 126.6, 122.9, 114.8, 69.1, 41.7; **IR (ATR)** [cm^{-1}]: 3308, 3067, 2916, 1607, 1514, 1437, 1376, 1296, 1249, 1175, 1046, 1028, 829, 743.

4.2.5.General synthetic procedures for isocyanide synthesis and analytical data

The corresponding formamide **7a-e**, **11a-e** or **16a-c** (1.0 equiv.), Et_3N (4 or 6 equiv.) and DCM were put together in a round-bottom flask and cooled to 0 ºC. Then $POCl_3$ was added dropwise and the reaction was stirred at rt for 3-4 h. After the reaction was completed, the products were poured into ice cold solution of $NaHCO_3$ and left to reach rt. The precipitated solid was filtered off and washed with DCM. The remaining water phase was extracted with DCM. Organic layers were collected, washed with water, dried over anhydrous $MgSO_4$ and evaporated. The resulting oils were purified on silica pad with copious amount of DCM, which was then collected and evaporated, giving the crude isocyanides (**8a-e**, **12a-e** or **17a-c**; yields 56-98%), which were used further without purification.

*4.2.5.1.3-Phenoxyphenyl isocyanide **8a***

Compound **7a** (0.9 g, 4.2 mmol), $POCl_3$ (0.37 mL, 3.8 mmol), Et_3N (2.75 mL, 20.0 mmol). Product **8a** was obtained as brown solid in 85% (0.7 g) yield (R_f: 0.70, petroleum ether/EtOAc 3:1)

NMR: **^{1}H** (500 MHz, $CDCl_3$): δ 7.39 (t, J = 5 Hz, 2H), 7.33 (d, J = 10 Hz, 2H), 7.19 (t, J = 10 Hz, 1H), 7.03 (d, J = 5 Hz, 2H), 6.95 (d, J = 10 Hz, 2H); **^{13}C** (125 MHz, $CDCl_3$): δ 163.6, 158.5, 155.9, 130.3, 128.2, 124.8, 120.0, 118.8.

*4.2.5.2. 4-Chlorophenyl isocyanide **8b***

Compound **7b** (3.5 g, 22.5 mmol), $POCl_3$ (2.10 mL, 22.5 mmol), Et_3N (12.55 mL, 90.0 mmol). Product **8b** was obtained as brown solid in 82% (2.80 g) yield (R_f: 0.67, petroleum ether/EtOAc 3:1).[xi]

NMR: **^{1}H** (500 MHz, $CDCl_3$): δ 7.38 (dt, J = 8.8, 2.1 Hz, 2H), 7.32 (d, J = 8.6 Hz, 2H); **^{13}C** (125 MHz, $CDCl_3$): δ 165.7, 135.6, 129.9, 127.8.

*4.2.5.3. 4-Isopropylphenyl isocyanide **8c***

Compound **7c** (2.5 g, 15.3 mmol), $POCl_3$ (1.43 mL, 15.3 mmol), Et_3N (8.55 mL, 61.3 mmol). Product **8c** was obtained as brown liquid in 77% (1.72 g) yield (R_f: 0.70, petroleum ether/EtOAc 3:1).[xii]

NMR: **^{1}H** (500 MHz, $CDCl_3$): δ 7.29 (d, J = 8.3 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 2.92 (hept, J = 7.0 Hz, 1H), 6.69 (d, J = 7.0 Hz, 6H); **^{13}C** (125 MHz, $CDCl_3$): δ 163.2 (t, J_{NC} = 5.0 Hz), 150.6, 127.5, 126.4, 34.1, 23.8.

*4.2.5.4. 4-Fluoro-3-chlorophenyl isocyanide **8d***

Compound **7d** (3.0 g, 17.3 mmol), $POCl_3$ (1.61 mL, 17.3 mmol), Et_3N (9.64 mL, 69.1 mmol). Product **8d** was obtained as dark green solid in 88% (2.37 g) yield (R_f: 0.60, petroleum ether/EtOAc 3:1).

NMR: **^{1}H** (500 MHz, $CDCl_3$): δ 7.47 (dd, J = 6.2, 2.4 Hz, 1H), 7.32-7.27 (m, 1H), 7.18 (t, J = 8.6 Hz, 1H); **^{13}C** (125 MHz, $CDCl_3$): δ 166.1, 159.3, 157.3, 128.9, 126.6, 126.5, 117.7, 117.5.

*4.2.5.5. 4-Chlorobenzyl isocyanide **8e***

Compound **7e** (2.0 g, 11.8 mmol), $POCl_3$ (1.09 mL, 11.8 mmol), Et_3N (6.58 mL, 17.2 mmol). Product **8e** was obtained as dark orange liquid in 75% (1.33 g) yield (R_f : 0.80, petroleum ether/EtOAc 3:1).[xiii]

NMR: **^{1}H** (500 MHz, $CDCl_3$): δ 7.37 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 4.62 (s, 2H); **^{13}C** (125 MHz, $CDCl_3$): δ 134.4, 130.9, 129.2, 128.1, 53.3, 45.0 (t, J_{NC} = 7.2 Hz).

*4.2.5.6. 4-(Benzyloxy)phenyl isocyanide **12a***

Compound **11a** (0.75 g, 3.3 mmol), $POCl_3$ (0.3 mL, 3.2 mmol), Et_3N (2.29 mL, 16.5 mmol). Product **12a** was obtained as brown solid in 81% (0.552 g) yield (R_f : 0.77, petroleum ether/EtOAc 3:1).

NMR: **^{1}H** (500 MHz, $CDCl_3$): δ 7.40-7.39 (m, 5 H), 7.29 (d, *J* = 10 Hz, 2H), 6.93 (d, *J* = 10 Hz, 2H), 5.06 (s, 2H); **^{13}C** (125 MHz, $CDCl_3$): δ 162.9, 159.2, 128.9, 128.5, 128.0, 127.6, 115.7, 70.5.

*4.2.5.7. 3-(Benzyloxy)phenyl isocyanide **12b***

Compound **11b** (0.310 g, 1.36 mmol), $POCl_3$ (0.13 mL, 1.4 mmol), Et_3N (0.97 mL, 6.7 mmol). Product **12b** was obtained as brown solid in 86% (0.245 g) yield (R_f : 0.76, petroleum ether/EtOAc 3:1).[xi]

NMR: **^{1}H** (500 MHz, $CDCl_3$): δ 7.41-7.39 (m, 5 H), 7.38-7.35 (m, 1H), 7.29-7.25 (m, 1H), 7.01-6.97 (m, 2H), 5.06 (s, 2H).

*4.2.5.8. 4-[(2-Bromobenzyl)oxy]phenyl isocyanide **12c***

Compound **11c** (1.50 g, 4.9 mmol), $POCl_3$ (0.46 mL, 4.9 mmol), Et_3N (2.73 mL, 19.6 mmol). Product **12c** was obtained as light yellow solid in 92% (1.30 g) yield (R_f: 0.57, petroleum ether/EtOAc 3:1).

NMR: **^{1}H** (500 MHz, $CDCl_3$): δ 7.60 (d, *J* = 8.0 Hz, 1H), 7.74 (dd, *J* = 7.7, 0.6 Hz, 1H), 7.34-7.31 (m, 3H), 7.22 (td, *J* = 7.6, 0.6 Hz, 1H), 6.96 (dt, *J* = 9.0, 1.9 Hz, 2H), 5.14 (s, 2H); **^{13}C** (125 MHz, $CDCl_3$): δ 163.0, 158.8, 135.4, 132.9, 129.7, 129.0, 128.0, 127.8, 122.5, 115.6, 69.8.

*4.2.5.9. 4-[(2,6-Dichlorobenzyl)oxy]phenyl isocyanide **12d***

Compound **11d** (0.8 g, 2.7 mmol), $POCl_3$ (0.25 mL, 2.7 mmol), Et_3N (1.51 mL, 10.8 mmol). Product **12d** was obtained as light yellow solid in 93% (0.70 g) yield (R_f: 0.63, petroleum ether/EtOAc 3:1).

NMR: **^{1}H** (500 MHz, $CDCl_3$): δ 7.38 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 8.9 Hz, 2H), 7.30-7.26 (m, 1H), 7.00 (dt, *J* = 8.7, 1.9 Hz, 2H), 5.29 (s, 2H); **^{13}C** (125 MHz, $CDCl_3$): δ 163.0, 159.2, 137.1, 131.5, 130.9, 128.7, 127.9, 115.7, 65.6.

*4.2.5.10. 3-[(4-bromobenzyl)oxy)]phenyl isocyanide **12e***

Compound **11e** (1.3 g, 4.3 mmol), $POCl_3$ (0.39 mL, 4.3 mmol), Et_3N (2.37 mL, 17.0 mmol). Product **12e** was obtained as light yellow solid in 94% (1.15 g) yield (R_f: 0.77, petroleum ether/EtOAc 3:1).

NMR: **^{1}H** (500 MHz, $CDCl_3$): δ 7.53 (d, J = 8.34 Hz, 2H), 7.32-7.27 (m, 3H), 7.01-6.97 (m, 2H), 6.95 (s, 1H), 5.01 (s, 2H); **^{13}C** (125 MHz, $CDCl_3$): δ 164.2, 159.0, 135.1, 132.0, 130.5, 129.2, 122.4, 119.4, 116.6, 112.9, 69.7.

*4.2.5.11. 4-[(2-Fluorobenzyl)oxy]benzyl isocyanide **17a***

Compound **16a** (1.0 g, 3.7 mmol), $POCl_3$ (0.35 mL, 3.7 mmol), Et_3N (3.12 mL, 23.4 mmol). Product **17a** was obtained as light yellow solid in 56% (0.50 g) yield (R_f: 0.67, petroleum ether/EtOAc 3:1).

NMR: **^{1}H** (500 MHz, $CDCl_3$): δ 7.52 (t, J = 7.3 Hz, 1H), 7.35 (q, J = 6.8 Hz, 1H), 7.29 (d, J = 8.5 Hz, 2H), 7.19 (t, J = 7.5 Hz, 1H), 7.12 (t, J = 8.8 Hz, 1H), 7.03 (d, J = 8.6 Hz, 2H), 5.16 (s, 2H), 4.58 (s, 2H); **^{13}C** (125 MHz, $CDCl_3$): δ 161.5, 158.6, 129.9, 129.9, 129.8, 129.7, 128.2, 125.1, 124.4, 124.4, 115.5, 115.4, 115.3, 63.9, 63.8, 45.1 (t, J_{NC} = 7.2 Hz).

*4.2.5.12. 4-[(2-Chlorobenzyl)oxy]benzyl isocyanide **17b***

Compound **16b** (1.0 g, 3.6 mmol), $POCl_3$ (0.34 mL, 3.6 mmol), Et_3N (2.03 mL, 14.6 mmol). Product **17b** was obtained as light yellow solid in 98% (0.92 g) yield (R_f: 0.65, petroleum ether/EtOAc 3:1).

NMR: **^{1}H** (500 MHz, $CDCl_3$): δ 7.53 (dd, J = 6.9, 2.1 Hz, 1H), 7.40 (dd, J = 7.0, 2.0 Hz, 1H), 7.30-7.35 (m, 4H), 5.17 (s, 2H), 4.56 (s, 2H); **^{13}C** (125 MHz, $CDCl_3$): δ 158.6, 134.5, 132.7, 129.5, 129.2, 128.9, 128.3, 127.1, 125.1, 115.4, 67.3, 45.1 (t, J_{NC} = 6.8 Hz).

4.2.5.13. 4-[(2-Bromobenzyl)oxy]benzyl isocyanide ***17c***

Compound **16c** (1.5 g, 4.7 mmol), $POCl_3$ (0.44 mL, 4.7 mmol), Et_3N (2.61 mL, 18.7 mmol). Product **17c** was obtained as the light yellow solid in 93% (1.32 g) yield (R_f: 0.85, petroleum ether/EtOAc 3:1).

NMR: **^{1}H** (500 MHz, $CDCl_3$): δ 7.60 (d, J = 7.9 Hz, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.34 (t, J = 7.5 Hz, 1H), 7.28 (d, J = 8.6 Hz, 2H), 7.20 (t, J = 7.1 Hz, 1H), 7.00 (d, J = 8.6 Hz, 2H), 5.14 (s, 2H), 4.57 (s, 2H); **^{13}C** (125 MHz, $CDCl_3$): δ 158.6, 136.0, 132.8, 129.5, 129.0, 128.3, 127.7, 125.2, 122.5, 115.4, 69.6, 45.2 (t, J_{NC} = 7.0 Hz).

4.2.6. General synthetic procedures for the U-T reaction and analytical data

Aldehyde **4** (1.0 mmol), amine **5** (1.0 mmol), isocyanide **8a-e**, **12a-e** or **17a-c** (1.0 mmol), $TMSN_3$ (1.0 mmol) were dissolved in 2,2,2-trifluoroethanol (1.0 mL) and placed into a microwave oven for 40 min at 120 ºC. After this time, the solvent was evaporated and the

crude mixtures were purified by flash chromatography giving the corresponding tetrazoles (**3.1**-**3.33** yields 38-74%) as yellow oils.

*4.2.6.1. Ethyl 6-chloro-3-((cyclopentylamino)(1-(3-phenoxyphenyl)-1H-tetrazol-5-yl)methyl)-1H-indole-2-carboxylate **3.1***

Aldehyde **4** (0.25 g, 1.0 mmol), pentylamine (100 μL, 1.0 mmol), isocyanide **8a** (0.2 g, 1.0 mmol), $TMSN_3$ (121 μL, 1.0 mmol). Product was purified by flash chromatography (petroleum ether/EtOAc 5:1; R_f: 0.60, petroleum ether/EtOAc 3:1) giving compound **3.1** as yellow oil in 51% (0.284 g) yield.

NMR: **^{1}H** (500 MHz, $CDCl_3$): δ 9.90 (br s, 1H), 7.81 (d, J = 10 Hz, 1H), 7.40 (t, J = 10 Hz, 2H), 7.28 (s, 1H), 7.19 (t, J = 10 Hz, 1H), 7.11 (d, J = 5 Hz, 2H), 7.04 (d, J = 10 Hz, 2H), 7.02 (d, J = 10 Hz, 1H), 6.97 (d, J = 10 Hz, 2H), 6.29 (s, 1H), 4.30-4.25 (m, 1H), 4.19-4.15 (m, 1H), 3.08 (m, 1H), 1.76-1.19 (m, 8H); **^{13}C** (125 MHz, $CDCl_3$): δ 161.0, 159.1, 155.7, 136.5, 131.7, 130.2, 128.0, 127.5, 124.8, 124.7, 124.3, 122.7, 122.0, 119.9, 118.9, 118.3, 112.1, 61.4, 57.2, 47.5, 33.4, 32.7, 30.2, 29.7, 24.2, 24.1; **LC-MS (DAD/ESI)**: t_R = 3.20 min, Calcd for $C_{30}H_{29}ClN_6O_3$ (m/z): $[M+H]^+$ 557.20, found: $[M+H]^+$ 558.17.

*4.2.6.2. Ethyl 6-chloro-3-((cyclohexylamino)(1-(3-phenoxyphenyl)-1H-tetrazol-5-yl)methyl)-1H-indole-2-carboxylate **3.2***

Aldehyde **4** (0.25 g, 1.0 mmol), hexylamine (100 μL, 1.0 mmol), isocyanide **8a** (0.2 g, 1.0 mmol), $TMSN_3$ (121 μL, 1.0 mmol). Product was purified by flash chromatography (petroleum ether/EtOAc 5:1; R_f: 0.59, petroleum ether/EtOAc 3:1) giving compound **3.2** as yellow oil in 71% (0.405 g) yield.

NMR: **^{1}H** (500 MHz, $CDCl_3$): δ 9.77 (br s, 1H), 7.81 (d, J = 10 Hz, 1H), 7.40 (t, J = 10 Hz, 2H), 7.19 (t, J = 10 Hz, 1H), 7.11 (d, J = 10 Hz, 2H), 7.04 (d, J = 3H), 6.98 (d, J = 10 Hz, 2H), 6.41 (s, 1H), 4.30-4.26 (m, 1H), 4.15-3.99 (m, 1H), 2.45 (br s, 1H), 1.94-1.11 (m, 10H); **^{13}C** (125 MHz, $CDCl_3$): δ 161.0, 159.6, 157.3, 155.7, 136.4, 131.8, 130.2, 128.1, 127.5, 124.7, 124.3, 122.7, 122.1, 119.9, 119.4, 118.4, 118.3, 112.1, 61.4, 54.2, 45.8, 33.6, 32.9, 26.0, 24.8, 24.7; **LC-MS (DAD/ESI)**: t_R = 3.15 min, Calcd for $C_{31}H_{31}ClN_6O_3$ (m/z): $[M+H]^+$ 571.21, found: $[M+H]^+$ 571.35.

*4.2.6.3. Ethyl 6-chloro-3-((cyclopecyclopentylamino)(1-(3-phenoxyphenyl)-1H-tetrazol-5-yl)methyl)-1H-indole-2-carboxylate **3.3***

Aldehyde **4** (0.25 g, 1.0 mmol), heptylamine (130 μL, 1.0 mmol), isocyanide **8a** (0.2 g, 1.0 mmol), $TMSN_3$ (121 μL, 1.0 mmol). Product was purified by flash chromatography (petroleum ether/EtOAc 5:1; R_f: 0.64, petroleum ether/EtOAc 3:1) giving compound **3.3** as yellow oil in 60% (0.351 g) yield.

NMR: **^{1}H** (500 MHz, $CDCl_3$): δ 9.55 (br s, 1H), 7.83 (d, J = 10 Hz, 1H), 7.39 (t, J = 10 Hz, 2H), 7.26 (s, 1H), 7.18 (t, J = 10 Hz, 1H), 7.13 (d, J = 10 Hz, 2H), 7.05 (d, J = 10 Hz, 2H, 7.02 (d, J = 10 Hz, 1H), 6.98 (d, J = 10 Hz, 2H), 6.36 (s, 1H), 4.30-4.24 (m, 1H), 4.17-4.10 (m, 1H), 2.65-2.60 (m, 1H), 1.86-1.36 (m, 12H); **^{13}C** (125 MHz, $CDCl_3$): δ 161.0, 159.6, 157.2, 155.6, 136.5, 131.7, 130.2, 128.0, 127.4, 124.8, 124.7, 124.3, 122.7, 121.9, 119.9, 118.8, 118.2, 112.2, 61.3, 56.0, 46.2, 35.3, 33.6, 28.5, 28.3, 24.2, 23.9, 21.1; **LC-MS (DAD/ESI)**: t_R = 3.53 min, Calcd for $C_{32}H_{33}ClN_6O_3$ (m/z): $[M]^+$ 585.10, found: $[M]^+$ 585.30.

*4.2.6.4. Ethyl 6-chloro-3-((1-(4-chlorophenyl)-1H-tetrazol-5-yl)((cyclohexylmethyl) amino)methyl -1H-indole-2-carboxylate **3.4***

Aldehyde **4** (0.25 g, 1.0 mmol), cyclohexylmethylamine (130 μL, 1.0 mmol), isocyanide **8b** (0.14 g, 1.0 mmol), $TMSN_3$ (131 μL, 1.0 mmol). Product was purified by flash chromatography (petroleum ether/EtOAc 5:1; R_f: 0.41, petroleum ether/EtOAc 3:1) giving compound **3.4** as yellow oil in 74% (0.39 g) yield. Product was recrystallized from EtOH.

mp: 126 ºC; **NMR**: **^{1}H** (500 MHz, $CDCl_3$): δ 8.97 (s, 1H), 7.76 (d, J = 8.7 Hz, 1H), 7.39 (dt, J = 8.5, 1.7 Hz, 2H), 7.30 (d, J = 1.5 Hz, 1H), 7.16 (dt, J = 8.6, 1.7 Hz, 2H), 7.07 (dd, J = 8.7, 1.7 Hz, 1H), 6.18 (s, 1H), 4.32-4.23 (m, 1H), 4.22-4.12 (m, 1H), 2.44 (dd, J = 11.2, 6.5 Hz, 1H), 2.32 (dd, J = 11.2, 6.7 Hz, 1H), 1.74-1.55 (m, 6H), 1.44-1.35 (m, 1H), 1.28 (t, J = 7.1 Hz, 3H), 1.22-1.04 (m, 3H), 0.91-0.73 (m, 2H); **^{13}C** (125 MHz, $CDCl_3$): δ 160.8, 156.8, 136.8, 136.2, 132.4, 132.3, 129.6, 127.1, 124.9, 124.3, 122.9, 122.5, 112.0, 61.5, 54.4, 49.2, 38.2, 31.5, 31.4, 26.7, 26.1, 26.1, 14.3; **IR (ATR)** [cm^{-1}]: 3163, 2915, 2847, 2107, 1712, 1534, 1492, 1429, 1299, 1227, 1186, 1093, 1015, 837; **HRMS (ESI)**: Calcd for $C_{26}H_{28}Cl_2N_6O_2$ (m/z): $[M+H]^+$ 527.1715, $[M+2+H]^+$ 529.1690, found: $[M+H]^+$ 527.1729, $[M+2+H]^+$ 529.1700; **LC-MS (DAD/ESI)**: t_R = 3.32 min, Calcd for $C_{26}H_{28}Cl_2N_6O_2Na$ (m/z): $[M]^+$ 549.15, $[M+2]^+$ 551.15, found: $[M]^+$ 549.30, $[M+2]^+$ 551.30.

*4.2.6.5. Ethyl 6-chloro-3-((1-(4-chlorophenyl)-1H-tetrazol-5-yl)(pentylamino)methyl)-1H-indole-2-carboxylate **3.5***

Aldehyde **4** (0.25 g, 1.0 mmol), amylamine (116 μL, 1.0 mmol), isocyanide **8b** (0.14 g, 1.0 mmol), $TMSN_3$ (131 μL, 1.0 mmol). Product was purified by flash chromatography (petroleum ether/EtOAc 5:1; R_f: 0.25, petroleum ether/EtOAc 3:1) giving compound **3.5** as yellow oil in 45% (0.23 g) yield. Product was recrystallized from EtOH/H_2O.

mp: 79-80 ºC; **NMR**: **^{1}H** (600 MHz, $CDCl_3$): δ 8.96 (s, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.36 (dt, *J* = 8.6, 2.0 Hz, 2H), 7.31 (dd, *J* = 1.4 Hz, 1H), 7.09 (dt, *J* = 8.7, 1.9 Hz, 2H), 7.07 (dd, *J* = 8.7, 1.8 Hz, 1H), 6.25 (s, 2H), 4.34-4.24 (m, 1H), 4.24-4.13 (m, 1H), 2.70-2.59 (m, 1H), 2.59-2.48 (m, 1H), 1.55-1.40 (m, 2H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.27-1.17 (m, 4H), 0.83 (*t*, *J* = 7.0 Hz, 3H); **^{13}C** (151 MHz, $CDCl_3$): δ 160.7, 156.6, 136.9, 136.1, 132.4, 132.2, 129.6, 127.2, 124.8, 124.2, 122.8, 122.6, 112.0, 61.6, 48.9, 47.7, 29.5, 29.4, 22.6, 14.3, 14.1; **IR (ATR)** [cm^{-1}]: 3312, 3956, 2929, 1693, 1532, 1499, 1429, 1300, 1227, 1185, 1096, 1015, 917, 838, 781; **HRMS (ESI)**: Calcd for $C_{24}H_{26}Cl_2N_6O_2$ (m/z): $[M+H]^+$ 501.1573, $[M+2+H]^+$ 503.1543, found: $[M+H]^+$ 501.1549, $[M+2+H]^+$ 503.1531; **LC-MS (DAD/ESI)**: t_R 3.25 min, Calcd for $C_{24}H_{26}Cl_2N_6O_2Na$ (m/z): $[M]^+$ 523.14 $[M+2]^+$ 525.14, found: $[M]^+$ 523.30 $[M+2]^+$ 525.30.

*4.2.6.6. Ethyl 6-chloro-3-(((cyclohexylmethyl)amino)(1-(4-isopropylphenyl)-1H-tetrazol-5-yl)methyl)-1H-indole-2-carboxylate **3.6***

Aldehyde **4** (0.25 g, 1.0 mmol), cyclohexylmethylamine (130 μL, 1.0 mmol), isocyanide **8c** (0.15 g, 1.0 mmol), $TMSN_3$ (131 μL, 1.0 mmol). Product was purified by flash chromatography (petroleum ether/EtOAc 5:1; R_f: 0.33, petroleum ether/EtOAc 3:1) giving compound **3.6** as yellow oil in 58% (0.31 g) yield. Product was recrystallized from EtOH.

mp: 120-121 ºC; **NMR**: **^{1}H** (600 MHz, $CDCl_3$): δ 8.94 (s, 1H), 7.78 (d, *J* = 6.6 Hz, 1H), 7.30 (s, 1H), 7.22 (d, *J* = 8.3 Hz, 2H), 7.07-7.02 (m, 3H), 6.16 (s, 1H), 4.24 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.11 (dq, *J* = 10.8, 7.1 Hz, 1H), 2.94 (sept, *J* = 6.9 Hz, 1H), 2.45 (dd, *J* = 10.9, 6.5 Hz, 1H), 2.36-2.29 (m, 1H), 1.72-1.57 (m, 6H), 1.46-1.35 (m, 1H), 1.26 (d, *J* = 6.9 Hz, 6H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.19-1.04 (m, 4H), 0.89-0.73 (m, 2H); **^{13}C** (151 MHz, $CDCl_3$): δ 161.1, 151.8, 136.2, 132.2, 131.5, 127.3, 125.6, 125.0, 124.4, 123.1, 122.4, 111.8, 61.5, 54.5, 49.3, 38.1, 34.1, 31.5, 31.4, 26.7, 26.1, 26.1, 24.0, 23.9, 14.3; IR (ATR) [cm^{-1}]: 3166, 2927, 2850, 1714, 1630, 1521, 1428, 1298, 1257, 1226, 1186, 1063, 917, 838; **HRMS (ESI)**: Calcd for $C_{29}H_{35}ClN_6O_2$ (m/z): $[M+H]^+$ 535.2588, $[M+2+H]^+$ 537.2559, found: $[M+H]^+$ 535.2585, $[M+2+H]^+$ 535.2559; **LC-MS (DAD/ESI)**: t_R=3.48 min, Calcd for $C_{29}H_{35}ClN_6O_2Na$ (m/z): $[M]^+$ 557.24, $[M+2]^+$ 559.24, found: $[M]^+$ 557.40, $[M+2]^+$ 559.35.

*4.2.6.7. Ethyl 6-chloro-3-((1-(4-isopropylphenyl)-1H-tetrazol-5-yl)(pentylamino) methyl)-1H-indole-2-carboxylate **3.7***

Aldehyde **4** (0.25 g, 1.0 mmol), amylamine (116 μL, 1.0 mmol), isocyanide **8c** (0.15 g, 1.0 mmol), $TMSN_3$ (131 μL, 1.0 mmol). Product was purified by flash chromatography (petroleum ether/EtOAc 5:1; R_f: 0.25, petroleum ether/EtOAc 3:1) giving compound **3.7** as yellow oil in 74% (0.38 g) yield. Product was recrystallized from $EtOH/H_2O$.

mp: 145-146 ºC; **NMR**: **^{1}H** (600 MHz, $CDCl_3$): δ 8.99 (s, 1H), 7.70 (s, 1H), 7.29 (s, 1H), 7.21 (d, *J* = 8.3 Hz, 2H), 7.04 (d, *J* = 8.5 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.21 (s, 1H), 4.24 (dq, *J* = 11.6, 7.1 Hz, 1H), 4.13 (dq, *J* = 10.7, 7.1 Hz, 1H), 2.94 (sept, *J* = 7.7 Hz, 1H), 2.68 (s, 1H), 2.59 (s, 1H), 1.60-1.46 (m, 2H), 1.30 (dd, *J* = 6.9, 2.8 Hz, 1H), 1.28-1.20 (m, 13H), 0.84 (t, *J* = 7.0 Hz, 3H); **^{13}C** (151 MHz, $CDCl_3$): δ 161.1, 151.9, 136.1, 132.3, 131.3, 127.4, 125.7, 125.0, 124.3, 122.5, 111.9, 61.6, 49.0, 47.8, 34.1, 29.4, 23.9, 22.6, 14.3, 14.1; **IR (ATR)** [cm^{-1}]: 3220, 2961, 2929, 2870, 1701, 1564, 1515, 1435, 1366, 1322, 1229, 1199, 1100, 1059, 1017, 837, 778; **HRMS (ESI)**: Calcd for $C_{27}H_{33}ClN_6O_2$ (m/z): $[M+H]^+$ 509.2432, $[M+2+H]^+$ 511.2402, found: $[M+H]^+$ 509.2419, $[M+2+H]^+$ 511.2401; **LC-MS (DAD/ESI)**: t_R = 3.47 min, Calcd for $C_{27}H_{33}ClN_6O_2Na$ (m/z): $[M]^+$ 531.22, $[M+2]^+$ 533.22, found: $[M]^+$ 531.35, $[M+2]^+$ 533.35.

*4.2.6.8. Ethyl 6-chloro-3-((1-(3-chloro-4-fluorophenyl)-1H-tetrazol-5-yl)((cyclohexyl methyl)amino)methyl)-1H-indole-2-carboxylate **3.8***

Aldehyde **4** (0.25 g, 1.0 mmol), cyclohexylmethylamine (130 μL, 1.0 mmol), isocyanide **8d** (0.16 g, 1.0 mmol), $TMSN_3$ (131 μL, 1.0 mmol). Product was purified by flash chromatography (petroleum ether/EtOAc 5:1; R_f: 0.47, petroleum ether/EtOAc 3:1) giving compound **3.8** as yellow oil in 56% (0.29 g) yield. Product was recrystallized from EtOH.

mp: 108 ºC; **NMR**: **^{1}H** (500 MHz, $CDCl_3$): δ 8.95 (s, 1H), 7.76 (d, *J* = 8.7 Hz, 1H), 7.34-7.31 (m, 2H), 7.22-7.14 (m, 2H), 7.09 (dd, *J* = 8.7, 1.4 Hz, 1H), 6.18 (s, 1H), 4.34-4.21 (m, 2H), 2.44 (dd, *J* = 11.2, 6.5 Hz, 1H), 2.33 (dd, *J* = 11.2, 6.6 Hz, 1H), 1.71-1.55 (m, 6H), 1.43-1.35 (m, 1H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.21-1.05 (m, 4H), 0.91-0.73 (m, 2H); **^{13}C** (125 MHz, $CDCl_3$): δ 160.8, 160.1, 158.4, 136.1, 132.5, 128.4, 126.1, 126.0, 125.0, 124.2, 122.7, 117.5, 117.3, 112.1, 61.9, 54.3, 49.1, 31.4, 31.3, 31.1, 26.6, 26.0, 26.0, 14.3; **IR (ATR)** [cm^{-1}]: 3084, 2922, 2835, 1706, 1498, 1426, 1298, 1261, 1226, 1185, 919, 833; **HRMS (ESI)**: Calcd for $C_{26}H_{27}Cl_2FN_6O_2$ (m/z): $[M+H]^+$ 545.1635, $[M+2+H]^+$ 547.1605, found: $[M+H]^+$ 545.1615, $[M+2+H]^+$ 547.1599; **LC-MS (DAD/ESI)**: t_R = 3.46 min, Calcd for $C_{26}H_{27}Cl_2FN_6O_2Na$ (m/z): $[M]^+$ 567.15, $[M+2]^+$ 569.14, found: $[M]^+$ 567.30, $[M+2]^+$ 569.30.

*4.2.6.9. Ethyl 6-chloro-3-((1-(3-chloro-4-fluorophenyl)-1H-tetrazol-5-yl)((pentylamino) methyl)-1H-indole-2-carboxylate **3.9***

Aldehyde **4** (0.25 g, 1.0 mmol), amylamine (116 μL, 1.0 mmol), isocyanide **8d** (0.16 g, 1.0 mmol), $TMSN_3$ (131 μL, 1.0 mmol). Product was purified by flash chromatography (petroleum ether/EtOAc 5:1; R_f: 0.30, petroleum ether/EtOAc 3:1) giving compound **3.9** as yellow oil in 43% (0.23 g) yield.

NMR: **^{1}H** (500 MHz, $CDCl_3$): δ 8.93 (s, 1H), 7.75 (d, J = 8.7 Hz, 1H), 7.33 (s, 1H), 7.29-7.26 (m, 1H), 7.18 (t, J = 8.5 Hz, 1H), 7.14-7.10 (m, 1H), 7.08 (dd, J = 8.8, 1.0 Hz, 1H), 6.24 (s, 1H), 4.36-4.20 (m, 2H), 2.62 (ddd, J = 11.0, 7.9, 6.6 Hz, 1H), 2.56-2.49 (m, 1H), 1.54-1.40 (m, 2H), 1.32 (t, J = 7.2 Hz, 3H), 1.26-1.19 (m, 4H), 0.83 (t, J = 6.8 Hz, 3H); **^{13}C** (125 MHz, $CDCl_3$): δ 160.7, 160.1, 158.1, 156.8, 136.1, 130.2, 130.2, 128.5, 128.4, 126.0, 125.9, 124.8, 124.2, 123.6, 123.2, 122.8, 122.6, 119.1, 117.4, 117.2, 112.1, 112.0, 61.7, 48.9, 47.8, 29.7, 29.5, 22.6, 14.3, 14.1; **IR (ATR)** [cm^{-1}]: 3266, 2928, 2852, 1707, 1509, 1366, 1302, 1261, 1227, 1187, 1099, 1074, 1020, 917, 817; **HRMS (ESI)**: Calcd for $C_{24}H_{25}Cl_2FN_6O_2$ (m/z): $[M+H]^+$ 519.1478, $[M+2+H]^+$ 521.1449, found: $[M+H]^+$ 519.1463, $[M+2+H]^+$ 521.1433; **LC-MS (DAD/ESI)**: t_R = 6.29 min, Calcd for $C_{24}H_{25}Cl_2FN_6O_2Na$ (m/z): $[M]^+$ 541.13, $[M+2]^+$ 543.13, found: $[M]^+$ 541.30, $[M+2]^+$ 643.30.

*4.2.6.10. Ethyl 6-chloro-3-((1-(4-chlorobenzyl)-1H-tetrazol-5-yl)((4-chlorobenzyl)amino) methyl)-1H-indole-2-carboxylate **3.10***

Aldehyde **4** (0.25 g, 1.0 mmol), 4-chlorobenzylamine (121 μL, 1.0 mmol), isocyanide **8e** (0.15 g, 1.0 mmol), $TMSN_3$ (131 μL, 1.0 mmol). Product was purified by flash chromatography (petroleum ether/EtOAc 5:1; R_f: 0.23, petroleum ether/EtOAc 3:1) giving compound **3.10** as yellow oil in 44% (0.25 g) yield. Product was then recrystallized from EtOH.

mp: 163 ºC; **NMR**: **^{1}H** (600 MHz, $CDCl_3$): δ 9.12 (s, 1H), 7.64 (d, J = 8.7 Hz, 1H), 7.25-7.21 (m, 3H), 7.14 (d, J = 8.4 Hz, 2H), 7.12 (d, J = 8.2 Hz, 2H), 7.06 (dd, J = 8.7, 1.7 Hz, 1H), 6.78 (d, J = 8.2 Hz, 2H), 6.12 (s, 1H), 5.51 (s, 2H), 4.25 (q, J = 7.1 Hz, 2H), 3.73 (d, J = 13.0 Hz, 1H), 3.63 (d, J = 13.2 Hz, 1H), 1.27 (t, J = 7.1 Hz, 3H); **^{13}C** (151 MHz, $CDCl_3$): δ 161.0, 136.0, 134.4, 132.4, 132.0, 129.9, 129.8, 129.1, 129.0, 128.8, 128.7, 128.5, 128.2, 128.1, 124.8, 124.3, 122.6, 122.4, 112.1, 111.1, 61.7, 50.0, 47.8, 47.4, 14.2; **IR (ATR)** [cm^{-1}]: 3296, 3160, 2990, 1399, 1542, 1493, 1423, 1298, 1246, 1225, 1099, 1018, 907, 892, 835, 798, 778; **HRMS (ESI)**: Calcd for $C_{27}H_{23}Cl_3N_6O_2$ (m/z): $[M+H]^+$ 569.1026, $[M+2+H]^+$ 571.0997:

Found $[M+H]^+$ 569.1038, $[M+2+H]^+$ 571.1006; **LC-MS (DAD/ESI)**: t_R = 3.08 min, Calcd for $C_{27}H_{23}Cl_3N_6O_2Na$ (m/z): $[M]^+$ 591.08, $[M+2]^+$ 591.08, found: $[M]^+$ 591.25, $[M+2]^+$ 593.25.

*4.2.6.11. Ethyl 6-chloro-3-((1-(4-chlorobenzyl)-1H-tetrazol-5-yl)((cyclohexylmethyl)amino) methyl)-1H-indole-2-carboxylate **3.11***

Aldehyde **4** (0.25 g, 1.0 mmol), cyclohexylmethylamine (130 μL, 1.0 mmol), isocyanide **8e** (0.15 g, 1.0 mmol), $TMSN_3$ (131 μL, 1.0 mmol). Product was purified by flash chromatography (petroleum ether/EtOAc 5:1; R_f: 0.12, petroleum ether/EtOAc 3:1) giving compound **3.11** as yellow oil in 47% (0.25 g) yield. Product was then recrystallized from EtOH.

mp: 95 ºC; **NMR**: **^{1}H** (600 MHz, $CDCl_3$): δ 9.08 (s, 1H), 7.68 (s, 1H), 7.23 (s, 1H), 7.18 (d, *J* = 8.3 Hz, 2H), 7.06 (dd, *J* = 8.7, 1.7 Hz, 1H), 6.91 (d, *J* = 7.6 Hz, 2H), 6.12 (s, 1H), 5.65 (d, *J* = 15.5 Hz, 1H), 5.59 (d, *J* = 15.4 Hz, 1H), 4.41-4.25 (m, 2H), 2.41-2.34 (m, 1H), 2.33-2.23 (m, 1H), 1.73-1.58 (m, 6H), 1.44-1.36 (m, 1H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.21-1.08 (m, 4H), 0.90-0.81 (m, 1H), 0.79-0.70 (m, 1H); **^{13}C** (151 MHz, $CDCl_3$): δ 161.3, 136.1, 134.6, 132.4, 129.1, 128.9, 128.5, 128.4, 124.7, 124.4, 122.6, 122.4, 112.1, 111.9, 61.7, 50.3, 49.3, 48.9, 31.6, 31.3, 26.2, 25.9, 14.4; **IR (ATR)** [cm^{-1}]: 3172, 2918, 2852, 1693, 1576, 1492, 1448, 1421, 1311, 1257, 1233, 11794, 1087, 1064, 1016, 911, 871, 821, 777; **HRMS (ESI)**: Calcd for $C_{27}H_{30}Cl_2N_6O_2$ (m/z): $[M+H]^+$ 541.1886, $[M+2+H]^+$ 543.1856, found: $[M+H]^+$ 541.1899, $[M+2+H]^+$ 543.1875; **LC-MS (DAD/ESI)**: t_R = 3.52 min, Calcd for $C_{27}H_{30}Cl_2N_6O_2Na$ (m/z): $[M]^+$ 563.17, $[M+2]^+$ 565.17, found: $[M]^+$ 563.35, $[M+2]^+$ 565.30.

*4.2.6.12. Ethyl 6-chloro-3-((1-(4-chlorobenzyl)-1H-tetrazol-5-yl)(pentylamino)methyl)-1H-indole-2-carboxylate **3.12***

Aldehyde **4** (0.25 g, 1.0 mmol), amylamine (116 μL, 1.0 mmol), isocyanide **8e** (0.15 g, 1.0 mmol), $TMSN_3$ (131 μL, 1.0 mmol). Product was purified by flash chromatography (petroleum ether/EtOAc 5:1; R_f: 0.13, petroleum ether/EtOAc 3:1) giving compound **3.12** as yellow oil in 45% (0.23 g) yield. Product was then recrystallized from $EtOH/H_2O$.

mp: 85 ºC; **NMR**: **^{1}H** (600 MHz, $CDCl_3$): δ 9.07 (s, 1H), 7.68 (d, *J* = 8.7 Hz, 1H), 7.24 (s, 1H), 7.16 (d, *J* = 8.4 Hz, 2H), 7.05 (dd, *J* = 8.7, 1.7 Hz, 1H), 6.88 (d, *J* = 7.8 Hz, 2H), 6.20 (s, 1H), 5.61 (d, *J* = 15.5 Hz, 1H), 5.55 (d, *J* = 15.5 Hz, 1H), 4.43-4.26 (m, 2H), 2.61-2.53 (m, 1H), 2.51-2.42 (m, 1H), 1.54-1.43 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.26-1.17 (m, 4H), 0.83 (t, *J* = 7.0 Hz, 3H); **^{13}C** (151 MHz, $CDCl_3$): δ 161.3, 136.1, 134.6, 132.5, 132.2, 129.0, 128.4, 124.6, 124.3, 122.6, 112.0, 61.8, 50.2, 48.8, 47.9, 29.4, 22.6, 14.4, 14.1; **IR (ATR)** [cm^{-1}]:

3223, 2954, 2928, 2862, 1699, 1542, 1493, 1428, 1368, 1374, 1301, 1246, 1227, 1096, 1015, 848, 806, 779; **HRMS (ESI)**: Calcd for $C_{25}H_{28}Cl_2N_6O_2$ (m/z): $[M+H]^+$ 515.1729, $[M+2+H]^+$ 517.1697, found: $[M+H]^+$ 515.1721, $[M+2+H]^+$ 517.1697; **LC-MS (DAD/ESI)**: t_R = 6.48 min, Calcd for $C_{25}H_{28}Cl_2N_6O_2Na$ (m/z): $[M]^+$ 537.15, $[M+2]^+$ 539.15, found: $[M]^+$ 537.30, $[M+2]^+$ 539.35.

*4.2.6.13. Ethyl 6-chloro-3-((1-(4-benzyloxyphenyl)-1H-tetrazol-5-yl)(cyclopentylamino) methyl)-1H-indole-2-carboxylate **3.13***

Aldehyde **4** (0.25 g, 1.0 mmol), pentylamine (100 µL, 1.0 mmol), isocyanide **12a** (0.2 g, 1.0 mmol), $TMSN_3$ (121 µL, 1.0 mmol). Product was purified by flash chromatography (petroleum ether/EtOAc 5:1; R_f: 0.47, petroleum ether/EtOAc 3:1) giving compound **3.13** as yellow oil in 40% (0.228 g) yield.

NMR: **^{1}H** (500 MHz, $CDCl_3$): δ 9.16 (br s, 1H), 7.83 (d, J = 10 Hz, 1H), 7.43-7.38 (m, 4H), 7.37-7.35 (m, 1H), 7.06-7.03 (m, 1H), 7.01 (d, J = 10 Hz, 2H), 6.94 (d, J = 10 Hz, 2H), 6.22 (s, 1H), 5.09 (s, 2H), 4.25-4.19 (m, 1H), 4.13-4.03 (m, 1H), 3.08-3.03 (m, 1H), 1.76-1.71 (m, 1H), 1.64-1.60 (m, 3H), 1.64-1.32 (m, 4H), 1.24 (t, J = 10 Hz, 3H); **^{13}C** (125 MHz, $CDCl_3$): δ 161.1, 160.3, 157.0, 136.3, 136.2, 132.1, 129.0, 128.6, 127.4, 126.6, 124.8, 124.5, 123.1, 122.3, 119.2, 115.4, 112.0, 70.6, 61.5, 57.3, 47.6, 33.5, 32.9, 24.3, 14.4; **LC-MS (DAD/ESI)**: t_R = 3.40 min, Calcd for $C_{31}H_{31}ClN_6O_3$ (m/z): $[M+H]^+$ 571.21, found: $[M+H]^+$ 571.29.

*4.2.6.14. Methyl 6-chloro-3-((1-(4-benzyloxyphenyl)-1H-tetrazol-5-yl)(cyclohexylamino) methyl)-1H-indole-2-carboxylate **3.14***

Aldehyde **4** (0.25 g, 1.0 mmol), hexylamine (110 µL, 1.0 mmol), isocyanide **12a** (0.2 g, 1.0 mmol), $TMSN_3$ (121 µL, 1.0 mmol). Product was purified by flash chromatography (petroleum ether/EtOAc 5:1; R_f: 0.45, petroleum ether/EtOAc 3:1) giving compound **3.14** as yellow oil in 46% (0.182 g) yield.

NMR: **^{1}H** (500 MHz, $CDCl_3$): δ 8.96 (s, 1H), 7.60 (d, J = 10 Hz, 2H), 7.45 (m, 4H), 7.14 (d, J = 10 Hz, 2H), 6.98 (d, J= 10 Hz, 2H), 6.94 (d, J = 10 Hz, 2H), 6.34 (s, 1H), 5.15 (s, 2H), 3.68 (s, 3H), 1.39 (br s, 1H), 1.93-1.10 (m, 10H); **^{13}C** (125 MHz, $CDCl_3$): δ 160.3, 140.8, 129.0, 128.6, 127.69, 127.66, 127.4, 123.2, 123.2, 122.5, 116.4, 115.4, 112.0, 70.7, 54.3, 52.1, 45.8, 33.6, 33.0, 29.9, 26.1, 25.0, 24.9; **LC-MS (DAD/ESI)**: t_R = 3.45 min, Calcd for $C_{31}H_{31}ClN_6O_3$ (m/z): $[M+H]^+$ 571.21, found: $[M+H]^+$ 571.29.

*4.2.6.15. Methyl 6-chloro-3-((1-(4-benzyloxyphenyl)-1H-tetrazol-5-yl)(cycloheptylamino) methyl)-1H-indole-2-carboxylate **3.15***

Aldehyde **4** (0.25 g, 1.0 mmol), heptylamine (130 μL, 1.0 mmol), isocyanide **12a** (0.2 g, 1.0 mmol), $TMSN_3$ (121 μL, 1.0 mmol). Product was purified by flash chromatography (petroleum ether/EtOAc 5:1; R_f: 0.45, petroleum ether/EtOAc 3:1) giving compound **3.15** as yellow oil in 32% (0.262 g) yield.

NMR: **^{1}H** (500 MHz, $CDCl_3$): δ 8.70 (br s, 1H), 7.86 (d, J = 10 Hz, 1H), 7.44-7.43 (m, 4H), 7.28 (s, 1H), 7.08 (d, J = 10 Hz, 1H), 7.01 (d, J = 10 Hz, 2H), 6.95 (d, J = 10 Hz, 2H), 6.27 (s, 1H), 5.11 (s, 2H), 3.67 (s, 3H), 1.80-1.39 (m, 12H); **^{13}C** (125 MHz, $CDCl_3$): δ 161.4, 160.3, 157.1, 136.4, 132.4, 129.0, 128.6, 127.4, 126.6, 124.4, 123.3, 115.4, 112.0, 70.6, 56.2, 52.1, 46.2, 35.4, 33.9, 28.7, 28.4; **LC-MS (DAD/ESI)**: t_R = 3.43 min, Calcd for $C_{32}H_{33}ClN_6O_3$ (m/z): $[M+H]^+$ 585.23, found: $[M+H]^+$ 585.21.

*4.2.6.16. Ethyl 6-chloro-3-((1-(3-benzyloxyphenyl)-1H-tetrazol-5-yl)(cyclopentylamino) methyl)-1H-indole-2-carboxylate **3.16***

Aldehyde **4** (0.25 g, 1.0 mmol), pentylamine (110 μL, 1.0 mmol), isocyanide **12b** (0.2 g, 1.0 mmol), $TMSN_3$ (121 μL, 1.0 mmol). Product was purified by flash chromatography (petroleum ether/EtOAc 5:1; R_f: 0.45, petroleum ether/EtOAc 3:1) giving compound **3.16** as yellow oil in 57% (0.325 g) yield.

NMR: **^{1}H** (500 MHz, $CDCl_3$): δ 8.81 (br s, 1H), 7.85 (d, J = 5 Hz, 1H), 7.45 (s, 4H), 7.37-7.29 (m, 2H), 7.09-7.08 (m, 2H), 6.76 (d, J = 10 Hz, 1H), 6.71 (s, 1H), 6.30 (s, 1H), 4.94 (q, J = 15 Hz), 4.27-4.24 (m, 1H), 4.14-4.10 (m, 1H), 3.9-3.06 (m, 1H), 1.77-1.73 (m, 8H), 1.33-1.24 (m, 4H), 1.22 (t, J = 10 Hz, 3H); **^{13}C** (125 MHz, $CDCl_3$): δ 161.0, 159.5, 156.8, 136.3, 134.7, 132.3, 130.3, 128.9, 128.6, 127.7, 124.6, 123.3, 122.6, 118.3, 117.5, 112.3, 111.9, 70.5, 61.7, 57.3, 47.7, 33.6, 33.0, 29.9, 24.4, 24.3, 14.4; **LC-MS (DAD/ESI)**: t_R = 3.55 min, Calcd for $C_{31}H_{31}ClN_6O_3Na$ (m/z): $[M]^+$ 593.21, found: $[M]^+$ 593.29.

*4.2.6.17. Ethyl 6-chloro-3-((1-(3-benzyloxyphenyl)-1H-tetrazol-5-yl)(cyclohexylamino) methyl)-1H-indole-2-carboxylate **3.17***

Aldehyde **4** (0.25 g, 1.0 mmol), hexylamine (110 μL, 1.0 mmol), isocyanide **12b** (0.2 g, 1.0 mmol), $TMSN_3$ (121 μL, 1.0 mmol). Product was purified by flash chromatography (petroleum ether/EtOAc 3:1; R_f: 0.51, petroleum ether/EtOAc 3:1) giving compound **3.17** as yellow oil in 41% (0.239 g) yield.

NMR: **^{1}H** (500 MHz, $CDCl_3$): δ 9.21 (br s, 1H), 7.83 (d, *J* = 10 Hz, 1H), 7.38-7.25 (m, 5H), 7.06 (t, *J* = 0.5 Hz, 2H), 6.78 (d, *J* = 5 Hz, 1H), 6.75 (s, 1H), 6.42 (s, 1H), 4.94 (dd, *J* = 30, 15 Hz, 2H), 4.25-4.22 (m, 1H), 4.10-4.08 (m, 1H), 2.44 (br s, 1H), 1.68-1.11 (m, 10H) ; **^{13}C** (125 MHz, $CDCl_3$): δ 161.0, 159.4, 157.1, 136.4, 136.1, 134.7, 132.1, 130.2, 128.9, 128.5, 127.6, 124.7, 124.5, 123.1, 122.3, 119.4, 118.2, 117.4, 112.3, 112.0, 70.0, 61.5, 54.3, 45.9, 33.7, 33.0, 26.1, 25.0, 24.8, 14.4; **LC-MS (DAD/ESI)**: t_R = 3.20 min, Calcd for $C_{32}H_{33}ClN_6O_3$ (m/z): $[M]^+$ 584.23, found: $[M+H]^+$ 585.20.

*4.2.6.18. Methyl 6-chloro-3-((1-(3-benzyloxyphenyl)-1H-tetrazol-5-yl)(cycloheptylamino) methyl)-1H-indole-2-carboxylate **3.18***

Aldehyde **4** (0.25 g, 1.0 mmol), heptylamine (130 µL, 1.0 mmol), isocyanide **12b** (0.2 g, 1.0 mmol), $TMSN_3$ (121 µL, 1.0 mmol). Product was purified by flash chromatography (petroleum ether/EtOAc 3:1; R_f: 0.52, petroleum ether/EtOAc 3:1) giving compound **3.18** as yellow oil in 30% (0.175 g) yield.

NMR: **^{1}H** (500 MHz, $CDCl_3$): δ 8.97 (br s, 1H), 7.85 (d, *J* = 10 Hz, 1H), 7.39-7.25 (m, 6H), 7.08 (t, *J* = 10 Hz, 2H), 6.79 (d, *J* = 10 Hz, 1H), 6.75 (s, 1H), 6.35 (s, 1H), 4.96 (dd, *J* = 30, 10 Hz, 2H), 3.68 (s, 3H), 2.61-2.57 (m, 1H), 1.83-1.16 (m, 12H) ; **^{13}C** (125 MHz, $CDCl_3$): δ 161.3. 159.5, 157.0, 136.4, 136.1, 134.7, 132.3, 131.3, 130.3, 128.9, 128.5, 127.7, 124.5, 124.5, 123.2, 122.5, 119.6, 118.3. 117.5, 116.7, 113.4, 112.3, 112.0, 108.3, 70.5, 56.3, 52.1, 46.2, 35.4, 33.9, 28.6, 28.4, 24.4, 24.2; **LC-MS (DAD/ESI)**: t_R = 3.36 min, Calcd for $C_{32}H_{33}ClN_6O_3$ (m/z): $[M+H]^+$ 585.23, found: $[M+H]^+$ 585.20.

*4.2.6.19. Ethyl 3-(((5r,7r)-adamantan-2-ylamino)(1-(4-((2-bromobenzyl)oxy)phenyl)-1H-tetrazol-5-yl)methyl)-6-chloro-1H-indole-2-carboxylate **3.19***

Aldehyde **4** (0.25 g, 1.0 mmol), adamantylamine (0.151 g, 1.0 mmol), isocyanide **12c** (0.2 g, 1.0 mmol), $TMSN_3$ (121 µL, 1.0 mmol). Product was purified by flash chromatography (petroleum ether/EtOAc 3:1; R_f: 0.62, petroleum ether/EtOAc 3:1) giving compound **3.19** as yellow oil in 10% (0.071 g) yield.

NMR: **^{1}H** (500 MHz, $CDCl_3$): δ 8.68 (br s, 1H), 7.98 (d, *J* = 5 Hz, 1H), 7.63 (d, *J* = 10 Hz, 1H), 7.54 (d, *J* = 5 Hz, 1H), 7.38 (t, *J* = 10 Hz, 1H), 7.26-7.23 (m, 2H), 7.08 (d, *J* = 10 Hz, 1H), 6.99 (s, 4H), 6.43 (s, 1H), 5.17 (s, 2H), 4.30-4.26 (m, 1H), 4.13-4.09 (m, 1H), 1.98 (br s, 3H), 1.61-1.47 (m, 13H), 1.28 (t, *J* = 10 Hz, 3H); **^{13}C** (125 MHz, $CDCl_3$): δ 160.9, 160.1, 158.9, 136.4, 135.5, 133.1, 130.0, 127.8, 127.0, 124.0, 122.4, 115.5, 111.8, 70.0, 61.6, 52.3,

43.3, 42.1, 36.6, 29.7, 14.5; **LC-MS (DAD/ESI)**: t_R = 3.79 min, Calcd for $C_{36}H_{36}BrClN_6O_3$ (m/z): $[M+H]^+$ 715.17, found: $[M+H]^+$ 715.18.

*4.2.6.20. Ethyl 3-((1-(4-((2-bromobenzyl)oxy)phenyl)-1H-tetrazol-5-yl)((cyclohexylmethyl) amino) methyl)-6-chloro-1H-indole-2-carboxylate **3.20***

Aldehyde **4** (0.25 g, 1.0 mmol), cyclohexylmethylamine (130 μL, 1.0 mmol), isocyanide **12c** (0.29 g, 1.0 mmol), $TMSN_3$ (131 μL, 1.0 mmol). Product was purified by flash chromatography (petroleum ether/EtOAc 5:1; R_f: 0.39, petroleum ether/EtOAc 3:1) giving compound **3.20** as yellow oil in 57% (0.39 g) yield. Product was recrystallized from EtOH.

mp: 90 ºC; **NMR**: **^{1}H** (500 MHz, $CDCl_3$): δ 8.87 (s, 1H), 7.79 (d, *J* = 8.7 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.29 (s, 1H), 7.24 (t, *J* = 7.9 Hz, 1H), 7.08-7.02 (m, 3H), 6.94 (d, *J* = 8.9 Hz, 2H), 6.16 (s, 1H), 5.15 (s, 2H), 4.25 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.19-4.12 (m, 1H), 2.46 (dd, *J* = 11.2, 6.5 Hz, 1H), 2.32 (dd, *J* = 11.1, 6.8 Hz, 1H), 1.73-1.56 (m, 6H), 1.41 (br s, 1H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.21-1.05 (m, 3H), 0.92-0.74 (m, 2H); **^{13}C** (151 MHz, $CDCl_3$): δ 161.0, 160.0, 136.1, 135.4, 133.0, 132.2, 129.9, 129.1, 127.9, 127.3, 125.0, 124.4, 122.6, 122.4, 115.9, 111.9, 69.9, 61.6, 58.6, 54.4, 49.3, 31.44, 31.38, 26.7, 26.0, 18.6, 14.4; **IR (ATR)** [cm^{-1}]: 3211, 2923, 2847, 1708, 1516, 1443, 1311, 1249, 1226, 1175, 1100, 1022, 834, 756; **HRMS (ESI)**: Calcd for $C_{33}H_{34}BrClN_6O_3Na$ (m/z): $[M]^+$ 699.1462, $[M+2]^+$ 701.1441, found: $[M]^+$ 699.1469, $[M+2]^+$ 701.1414; **LC-MS (DAD/ESI)**: t_R = 3.77 min, Calcd for $C_{33}H_{34}BrClN_6O_3Na$ (m/z): $[M]^+$ 699.15, $[M+2]^+$ 701.14, found: $[M]^+$ 699.35, $[M+2]^+$ 701.35.

*4.2.6.21. Ethyl 3-((1-(4-((2-bromobenzyl)oxy)phenyl)-1H-tetrazol-5-yl)(cyclobutylamino) methyl)-6-chloro-1H-indole-2-carboxylate **3.21***

Aldehyde **4** (0.25 g, 1.0 mmol), cyclobutylamine (85 μL, 1.0 mmol), isocyanide **12c** (0.29 g, 1.0 mmol), $TMSN_3$ (131 μL, 1.0 mmol). Product was purified by flash chromatography (petroleum ether/EtOAc 5:1; R_f: 0.11, petroleum ether/EtOAc 3:1) giving compound **3.21** as yellow oil in 66% (0.42 g) yield. Product was recrystallized from EtOH.

mp: 110 ºC; **NMR**: **^{1}H** (600 MHz, $CDCl_3$): δ 8.97 (s, 1H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.64-7.60 (m, 1H), 7.51 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.37 (td, *J* = 7.9, 1.6 Hz, 1H), 7.05 (dd, *J* = 8.7, 1.8 Hz, 1H), 6.97 (dt, *J*= 9.0, 2.3 Hz, 2H), 6.92 (dt, *J* = 8.9, 2.2 Hz, 2H), 4.32-4.23 (m, 1H), 4.19-4.10 (m, 1H), 3.40-3.29 (m, 1H), 2.17-2.02 (m, 1H), 1.91-1.77 (m, 2H), 1.70-1.59 (m, 2H), 1.58-1.49 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H); **^{13}C** (151 MHz, $CDCl_3$): δ 161.0, 160.0, 136.1, 135.4, 133.0, 132.3, 129.9, 129.1, 127.9, 127.4, 126.6, 124.7, 124.4, 123.1, 122.6, 122.5,

116.3, 115.4, 111.9, 69.9, 61.6, 52.5, 47.0, 30.9, 30.6, 15.1, 14.4; **IR (ATR)** [cm^{-1}]: 3111, 2926, 1520, 1451, 1437, 1382, 1258, 1212, 1177, 1092, 1058, 1026, 997, 830, 747; **HRMS (ESI)**: Calcd for $C_{30}H_{28}BrClN_6O_3Na$ (m/z): $[M]^+$ 657.0992, $[M+2]^+$ 659.0972, found: $[M]^+$ 657.1003, $[M+2]^+$ 659.0962; **LCMS (DAD/ESI)**: t_R = 3.13 min, Calcd for $C_{30}H_{28}BrClN_6O_3Na$ (m/z): $[M]^+$ 657.10, $[M+2]^+$ 659.10, found: $[M]^+$ 657.25, $[M+2]^+$ 659.30.

*4.2.6.22. Ethyl 3-((1-(4-((2-bromobenzyl)oxy)phenyl)-1H-tetrazol-5-yl)(pentylamino)methyl)-6-chloro-1H-indole-2-carboxylate **3.22***

Aldehyde **4** (0.25 g, 1.0 mmol), amylamine (116 μL, 1.0 mmol), isocyanide **12c** (0.29 g, 1.0 mmol), $TMSN_3$ (131 μL, 1.0 mmol). Product was purified by flash chromatography (petroleum ether/EtOAc 5:1; R_f: 0.18, petroleum ether/EtOAc 3:1) giving compound **3.22** as yellow oil in 72% (0.47 g) yield. Product was recrystallized from EtOH.

mp: 81 ºC; **NMR**: **^{1}H** (500 MHz, $CDCl_3$): δ 8.82 (s, 1H), 7.77 (d, *J* = 8.7 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.31 (d, *J* = 1.4 Hz, 1H), 7.23 (t, *J* = 7.8 Hz, 1H), 7.06 (dd, *J* = 8.8, 1.7 Hz, 1H), 6.99 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 6.20 (s, 1H)), 5.14 (s, 2H), 4.33-4.21 (m, 1H), 4.19-4.08 (m, 1H), 2.68-2.59 (m,1H), 2.56-2.59 (m, 1H), 1.63 (br s, 1H), 1.53-1.42 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.24-1.18 (m, 4H), 0.83 (t, *J* = 6.9 Hz, 3H); **^{13}C** (125 MHz, $CDCl_3$): δ 160.9, 159.9, 156.8, 136.1, 135.4, 133.0, 132.3, 129.9, 129.1, 127.9, 126.8 124.9, 124.3, 123.1, 122.6, 122.5, 115.3, 111.8, 69.9, 61.5, 49.0, 47.8, 29.7, 29.5, 22.6, 14.4, 14.1; **IR (ATR)** [cm^{-1}]: 3323, 2956, 2929, 2859, 1682, 1519, 1442, 1316, 1247, 1226, 1101, 1013, 835, 756; **HRMS (ESI)**: Calcd for $C_{31}H_{32}BrClN_6O_3Na$ (m/z): $[M]^+$ 673.1305, $[M+2]^+$ 675.1285, found: $[M]^+$ 673.1310, $[M+2]^+$ 675.1264; **LC-MS (DAD/ESI)**: t_R=3.44 min, Calcd for $C_{31}H_{32}BrClN_6O_3Na$ (m/z): $[M]^+$ 673.35, $[M+2]^+$ 675.13, found: $[M]^+$ 673.35, $[M+2]^+$ 675.30.

*4.2.6.23. Ethyl 6-chloro-3-(((cyclohexylmethyl)amino)(1-(4-((2,6-dichlorobenzyl)oxy)phenyl)-1H-tetrazol-5-yl)methyl)-1H-indole-2-carboxylate **3.23***

Aldehyde **4** (0.25 g, 1.0 mmol), cyclohexylmethylamine (130 μL, 1.0 mmol), isocyanide **12d** (0.28 g, 1.0 mmol), $TMSN_3$ (131 μL, 1.0 mmol). Product was purified by flash chromatography (petroleum ether/EtOAc 5:1; R_f: 0.28, petroleum ether/EtOAc 3:1) giving compound **3.23** as yellow oil in 59% (0.39 g) yield. Product was recrystallized from EtOH.

mp: 118 ºC; **NMR**: **^{1}H** (500 MHz, $CDCl_3$): δ 8.97 (s, 1H), 7.84 (d, *J* = 8.7 Hz, 1H), 7.40 (d, *J* = 7.4 Hz, 2H), 7.33-7.28 (m, 2H), 7.12-7.06 (m, 3H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.17 (s, 1H), 5.29 (s, 2H), 4.31-4.21 (m, 1H), 4.18-4.08 (m, 1H), 2.46 (dd, *J* = 11.2, 6.5 Hz, 1H), 2.32 (dd,

J = 11.2, 6.7 Hz, 1H), 1.72-1.58 (m, 6H), 1.46-1.37 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.22-1.05 (m, 3H), 0.91-0.72 (m, 2H); **^{13}C** (115 MHz, $CDCl_3$): δ 161.0, 160.3, 156.8, 137.1, 136.2, 132.2, 131.5, 131.0, 128.7, 127.3, 1269, 125.0, 124.4, 123.2, 122.4, 119.2, 115.3, 111.9, 65.6, 61.5, 54.5, 49.2, 38.2, 31.5, 31.4, 26.7, 26.1, 26.1, 14.4; **IR (ATR)** [cm^{-1}]: 3448, 3169, 2921, 2851, 1717, 1518, 1439, 1299, 1226, 116, 1093, 1015, 783; **HRMS (ESI)**: Calcd for $C_{33}H_{33}Cl_3N_6O_3Na$ (m/z): $[M]^+$ 689.1577, $[M+2]^+$ 691.1548, found: $[M]^+$ 689.1549, $[M+2]^+$ 691.1531; **LC-MS (DAD/ESI)**: t_R = 3.83 min, Calcd for $C_{33}H_{33}ClN_6O_3Na$ (m/z): $[M]^+$ 689.16, $[M+2]^+$ 691.15, found: $[M]^+$ 689.35,$[M+2]^+$ 691.35.

*4.2.6.24. Ethyl 6-chloro-3-((1-(4-((2,6-dichlorobenzyl)oxy)phenyl)-1H-tetrazol-5-yl)(pentylamino) methyl)-1H-indole-2-carboxylate **3.24***

Aldehyde **4** (0.25 g, 1.0 mmol), amylamine (116 μL, 1.0 mmol), isocyanide **12d** (0.28 g, 1.0 mmol), $TMSN_3$ (131 μLμL, 1.0 mmol). Product was purified by flash chromatography (petroleum ether/EtOAc 5:1; R_f: 0.20, petroleum ether/EtOAc 3:1) giving compound **3.24** as yellow oil in 62% (0.40 g) yield. Product was recrystallized from EtOH.

mp: 120 ºC; **NMR**: **^{1}H** (500 MHz, $CDCl_3$): δ 8.97 (s, 1H), 7.83 (d, *J* = 8.7 Hz, 1H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.33-7.38 (m, 2H), 7.07 (dd, *J* = 8.7, 1.5 Hz, 1H), 7.03 (d, *J* = 8.9 Hz, 2H), 6.98 (d, *J* = 8.9 Hz, 2H), 6.21 (s, 1H), 5.28 (s, 2H), 4.34-3.22 (m, 1H), 4.17-4.09 (m, 1H), 2.69-2.59 (m, 1H), 2.55-2.48 (m, 1H), 1.55-1.41 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.24-1.19 (m, 4H), 0.83 (t, *J* = 6.9 Hz, 3H); **^{13}C** (125 MHz, $CDCl_3$): δ 161.0, 160.3, 156.8, 137.1, 136.2, 132.2, 131.4, 131.0, 128.7, 127.4, 126.8, 124.9, 124.3, 123.1, 122.4, 119.1, 115.3, 111.9, 65.6, 61.6, 49.0, 47.8, 29.7, 29.5, 22.6, 14.3, 14.1; **IR (ATR)** [cm^{-1}]: 3314, 2959, 2938, 2856, 1704, 1517, 1438, 1302, 1247, 1227, 1094, 1012, 833, 779; **HRMS (ESI)**: Calcd for $C_{31}H_31Cl_3N_6O_3$ (m/z): $[M+H]^+$ 641.1601, $[M+2+H]^+$ 643.1572, found: $[M+H]^+$ 641.1600, $[M+2+H]^+$ 643.1580; **LC-MS (DAD/ESI)**: t_R = 3.66 min, Calcd for $C_{31}H_{31}Cl_3N_6O_3Na$ (m/z): $[M]^+$ 663.14, $[M+2]^+$ 665.14, found: $[M]^+$ 663.33, $[M+2]^+$ 665.30.

*4.2.6.25. Ethyl 3-((1-(3-((4-bromobenzyl)oxy)phenyl)-1H-tetrazol-5-yl)((cyclohexylmethyl) amino) methyl)-6-chloro-1H-indole-2-carboxylate **3.25***

Aldehyde **4** (0.25 g, 1.0 mmol), cyclohexylmethylamine (130 μL, 1.0 mmol), isocyanide **12e** (0.29 g, 1.0 mmol), $TMSN_3$ (131 μL, 1.0 mmol). Product was purified by flash chromatography (petroleum ether/EtOAc 5:1; R_f: 0.22, petroleum ether/EtOAc 3:1) giving compound **3.25** as yellow oil in 48% (0.32 g) yield. Product was recrystallized from EtOH.

mp: 169 ºC; **NMR**: **^{1}H** (500 MHz, $CDCl_3$): δ 8.97 (s, 1H), 7.76 (d, *J* = 8.7 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.34-7.26 (m, 4H), 7.08-7.01 (m, 2H), 6.81 (*J* = 7.8 Hz, 1H), 6.73 (s, 1H), 6.22 (s, 1H), 4.91 (d, *J* = 11.6 Hz, 1H), 4.83 (d, *J* = 11.6 Hz, 1H), 4.29-4.17 (m, 1H), 4.17-4.08 (m, 1H), 2.46 (dd, *J* = 11.2, 6.5 Hz, 1H), 2.32 (dd, *J* = 11.1, 6.7 Hz, 1H), 1.71-1.57 (m, 5H), 1.45-1.36 (m, 1H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.18-1.01 (m, 3H), 0.9-0.73 (m, 2H); **^{13}C** (125 MHz, $CDCl_3$): δ 160.8, 159.0, 156.5, 136.1, 134.9, 134.7, 132.0, 121.9, 130.1, 129.1, 124.9, 124.3, 123.0, 122.3, 122.3, 118.1, 117.2, 111.8, 111.7, 69.5, 61.4, 54.4, 49.2, 38.1, 31.4, 31.3, 26.5, 26.0, 15.9, 14.2; **IR (ATR)** [cm^{-1}]: 3303, 2924, 2853, 1683, 1605, 1490, 1443, 1317, 1224, 1163, 1100, 1070, 1101, 848, 799, 779, 691; **HRMS (ESI)**: Calcd for $C_{33}H_{34}BrClN_6O_3$ (m/z): $[M+H]^+$ 677.1643, $[M+2+H]^+$ 679.1622, found: $[M+H]^+$ 677.1630, $[M+2+H]^+$ 679.1603; **LC-MS (DAD/ESI)**: t_R = 3.56 min, Calcd for $C_{33}H_{34}BrClN_6O_3Na$ (m/z): $[M]^+$ 699.15, $[M+2]^+$ 701.14, found: $[M]^+$ 699.35, $[M+2]^+$ 701.30.

*4.2.6.26. Ethyl 3-((1-(3-((4-bromobenzyl)oxy)phenyl)-1H-tetrazol-5-yl)(pentylamino)methyl)-6-chloro-1H-indole-2-carboxylate **3.26***

Aldehyde **4** (0.25 g, 1.0 mmol), amylamine (116 µL, 1.0 mmol), isocyanide **12e** (0.29 g, 1.0 mmol), $TMSN_3$ (131 µL, 1.0 mmol). Product was purified by flash chromatography (petroleum ether/EtOAc 5:1; R_f: 0.35, petroleum ether/EtOAc 3:1) giving compound **3.26** as yellow oil in 64% (0.42 g) yield. Product was recrystallized from $EtOH/H_2O$.

mp: 130 ºC; **NMR**: **^{1}H** (600 MHz, acetone-d_6): δ 10.96 (s, 1H), 7.91 (d, *J* = 7.9 Hz, 1H), 7.60 (dt, *J* = 8.4, 1.8 Hz, 2H), 7.49 (dd, *J* = 1.9, 0.4 Hz, 1H), 7.45 (dt, *J* = 8.6, 2.1 Hz, 2H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.20 (ddd, *J* = 8.4, 2.5, 0.8 Hz, 1H), 7.07 (dd, *J* = 8.7, 1.9 Hz, 1H), 6.96 (t, *J* = 2.2 Hz, 1H) 6.93 (ddd, *J* = 7.8, 1.9, 0.9 Hz, 1H), 6.36 (s, 1H), 5.10 (d, *J* = 11.9 Hz, 1H), 5.02 (d, *J* = 11.9 Hz, 1H), 4.25 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.15 (dq, *J* = 10.8, 7.1 Hz, 1H), 2.68-2.62 (m, 1H), 2.58-2.53 (m, 1H), 1.51-1.40 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.23-1.20 (m, 4H), 0.81 (t, *J* = 7.1 Hz, 3H); **^{13}C** (151 MHz, acetone-d_6): δ 161.7, 160.0, 157.7, 137.1, 136.0, 132.5, 131.5, 131.1, 130.6, 130.5, 126.5, 125.7, 124.3, 122.3, 121.8, 119.9, 119.1, 118.1, 112.8, 70.1, 61.7, 49.6, 48.1, 23.2, 14.5, 14.3; **IR (ATR)** [cm^{-1}]: 3141, 311, 3073, 2920, 1612, 1597, 1502, 1489, 1404, 1379, 1255, 1190, 1091, 1073, 1001, 884, 799, 780, 683; **HRMS (ESI)**: Calcd for $C_{31}H_{32}BrClN_6O_3$ (m/z): $[M+H]^+$ 651.1486, $[M+2+H]^+$ 653.1466, found: $[M+H]^+$ 651.1479, $[M+2+H]^+$ 653.1439; **LC-MS (DAD/ESI)**: t_R = 3.35 min, Calcd for $C_{31}H_{32}BrClN_6O_3Na$ (m/z): $[M]^+$ 673.13, $[M+2]^+$ 675.13, found: $[M]^+$ 673.30, $[M+2]^+$ 675.30.

*4.2.6.27. Ethyl 6-chloro-3-(((cyclohexylmethyl)amino)(1-(4-((2-fluorobenzyl)oxy)benzyl)-1H-tetrazol-5-yl)methyl)-1H-indole-2-carboxylate **3.27***

Aldehyde **4** (0.25 g, 1.0 mmol), cyclohexylmethylamine (130 μL, 1.0 mmol), isocyanide **17a** (0.24 g, 1.0 mmol), $TMSN_3$ (131 μL, 1.0 mmol). Product was purified by flash chromatography (petroleum ether/EtOAc 5:1; R_f: 0.14, petroleum ether/EtOAc 3:1) giving compound **3.27** as yellow oil in 52% (0.31 g) yield. Product was recrystallized from EtOH.

mp: 157 ºC; **NMR**: **^{1}H** (600 MHz, $CDCl_3$): δ 9.34 (s, 1H), 7.62 (d, J = 8.7 Hz, 1H), 7.48 (t, J = 8.0 Hz, 1H), 7.36-7.30 (m, 1H), 7.17 (t, J = 7.5 Hz, 1H), 7.13-7.08 (m, 2H), 7.03-6.99 (m, 2H), 6.85 (d, J = 8.5 Hz, 2H), 6.05 (s, 1H), 5.69 (d, J = 15.1 Hz, 1H), 5.59 (d, J = 15.1 Hz, 1H), 5.09 (s, 2H), 4.34-4.17 (m, 2H), 2.34 (dd, J = 11.1, 6.6 Hz, 1H), 2.22 (dd, J = 11.1, 6.6 Hz, 1H), 1.73-156 (m, 5H), 1.41-1.31 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H), 1.18-1.02 (m, 4H), 0.90-0.89 (m, 2H); **^{13}C** (151 MHz, $CDCl_3$): δ 161.2, 158.7, 156.0, 136.2, 130.1, 130.0, 129.9, 129.9, 128.8, 126.5, 124.7, 124.5, 124.5, 124.4, 122.4, 122.1, 119.7, 115.7, 115,5, 115.5, 115.3, 112.0, 63.9, 63.9, 61.5, 54.6, 50.6, 49.3, 38.3, 31.6, 31.4, 26.7, 26.1, 26.1, 14.3; **IR (ATR)** [cm^{-1}]: 3217, 2931, 2850, 1700, 1612, 1513, 1447, 1314, 1225, 1179, 1095, 1004, 806, 777, 762; **HRMS (ESI)**: Calcd for $C_{34}H_{36}ClFN_6O_3$ (m/z): $[M+H]^+$ 631.2600, $[M+2+H]^+$ 633.2570, found: $[M+H]^+$ 631.2606, $[M+2+H]^+$ 633.2597; **LC-MS (DAD/ESI)**: t_R = 3.62 min, Calcd for $C_{34}H_{36}ClFN_6O_3Na$ (m/z): $[M]^+$ 653.24, $[M+2]^+$ 655.24, found $[M]^+$ 653.45, $[M+2]^+$ 655.40.

*4.2.6.28. Ethyl 6-chloro-3-((1-(4-((2-fluorobenzyl)oxy)benzyl)-1H-tetrazol-5-yl)(pentylamino) methyl)-1H-indole-2-carboxylate **3.28***

Aldehyde **4** (0.25 g, 1.0 mmol), amylamine (116 μL, 1.0 mmol), isocyanide **17a** (0.24 g, 1.0 mmol), $TMSN_3$ (131 μL, 1.0 mmol). Product was purified by flash chromatography (petroleum ether/EtOAc 5:1; R_f: 0.10, petroleum ether/EtOAc 3:1) giving compound **3.28** as yellow oil in 41% (0.25 g) yield. Product was recrystallized from EtOH.

mp: 135 ºC; **NMR**: **^{1}H** (600 MHz, $CDCl_3$): δ 9.01 (s, 1H), 7.67 (d, J = 8.7 Hz, 1H), 7.48 (td, J = 7.5, 1.5 Hz, 1H), 7.36-7.31 (m, 1H), 7.21-7.15 (m, 2H), 7.13-7.09 (m, 1H), 7.03 (dd, J = 8.7, 1.7 Hz, 1H), 6.93 (d, J = 7.8 Hz, 2H), 6.80 (d, J = 8.5 Hz, 2H), 6.17 (s, 1H), 5.57 (d, J = 15.2 Hz, 1H), 5.51 (d, J = 15.2 Hz, 1H), 5.08 (s, 2H), 4.39-4.26 (m, 2H), 2.53 (ddd, J = 11.0, 8.3, 6.2 Hz, 1H), 2.42 (ddd, J = 11.1, 8.2, 6.3 Hz, 1H), 1.50-1.39 (m, 2H), 1.32 (t, J = 7.1 Hz, 3H), 1.26-1.16 (m, 4H), 0.82 (t, J = 7.0 Hz, 3H); **^{13}C** (125 MHz, $CDCl_3$): δ 161.3, 158.6, 156.0, 136.2, 132.0, 130.1, 130.0, 129.9, 129.8, 128.7, 126.4, 124.7, 124.4, 124.4, 122.2, 119.5, 115.6, 115.5, 115.0, 112.0, 63.9, 63.9, 61.5, 50.6, 49.0, 47.9, 29.7, 29.5, 4.6, 14.3, 14.1;

IR (ATR) [cm^{-1}]: 3211, 2929, 1698, 1613, 1513, 1225, 1179, 1111, 1004, 847, 778, 759; **HRMS (ESI)**: Calcd for $C_{32}H_{34}ClFN_6O_3$ (m/z): $[M+H]^+$ 605.2443, $[M+2+H]^+$ 607.2414, found: $[M+H]^+$ 605.2456, $[M+2+H]^+$ 607.2445; **LC-MS (DAD/ESI)**: t_R = 3.37 min, Calcd for $C_{32}H_{34}ClFN_6O_3Na$ (m/z): $[M]^+$ 627.23, $[M+2]^+$ 629.22, found: $[M]^+$ 627.45, $[M+2]^+$ 629.40.

*4.2.6.29. Ethyl 6-chloro-3-((1-(4-((2-chlorobenzyl)oxy)benzyl)-1H-tetrazol-5-yl)((cyclohexylmethyl)amino)methyl)-1H-indole-2-carboxylate **3.29***

Aldehyde **4** (0.25 g, 1.0 mmol), cyclohexylmethylamine (130 μL, 1.0 mmol), isocyanide **17b** (0.26 g, 1.0 mmol), $TMSN_3$ (131 μL, 1.0 mmol). Product was purified by flash chromatography (petroleum ether/EtOAc 5:1; R_f: 0.15, petroleum ether/EtOAc 3:1) giving compound **3.29** as yellow oil in 52% (0.34 g) yield. Product was recrystallized from EtOH.

mp: 145-146 ºC; **NMR**: **^{1}H** (500 MHz, $CDCl_3$): δ 9.31 (s, 1H), 7.63 (d, J = 8.7 Hz, 1H), 7.53 (d, J = 8.3 Hz, 1H), 7.32-7.27 (m, 2H), 7.10 (s, 1H), 7.05-7.00 (m, 3H), 6.86 (d, J = 8.6 Hz, 2H), 6.07 (s, 1H), 5.69 (d, J = 15.1 Hz, 1H), 5.59 (d, J = 15.1 Hz, 1H), 5.13 (s, 2H), 4.34-4.25 (m, 1H), 4.24-4.17 (m, 1H), 2.34 (dd, J = 11.0, 6.0 Hz, 1H), 2.23 (dd, J = 11.0, 6.0 Hz, 1H),1.73-1.57 (m, 6H), 1.43-1.33 (m, 1H), 1.25 (t, J = 6.4 Hz, 3H), 1.20-1.04 (m,3H), 0.90 (m, 1H), 0.81-0.71 (m, 1H); **^{13}C** (125 MHz, $CDCl_3$): δ 161.2, 158.6, 156.0, 136.2, 134.5, 132.0, 129.6, 129.3, 128.9, 128.9, 127.1, 126.6, 124.7, 124.5, 122.4, 122.2, 119.8, 115.2, 112.0, 67.3, 61.5, 54.6, 50.6, 49.2, 38.3, 31.6, 31.4, 26.7, 26.1, 26.1, 14.3; **IR (ATR)** [cm^{-1}]: 3184, 2917, 2844, 1701, 1618, 1513, 1448, 1298, 1227, 1180, 1098, 1033, 803, 779, 754; **HRMS (ESI)**: Calcd for $C_{34}H_{36}Cl_2N_6O_3$ (m/z): $[M+H]^+$ 647.2304, $[M+2+H]^+$ 649.2275, found: $[M+H]^+$ 647,2297, $[M+2+H]^+$ 649.2282; **LC-MS (DAD/ESI)**: t_R = 3.82 min, Calcd for $C_{34}H_{36}Cl_2N_6O_3Na$ (m/z): $[M]^+$ 669.21, $[M+2]^+$ 671.21, found: $[M]^+$ 669.40, $[M+2]^+$ 67140.

*4.2.6.30. Ethyl 6-chloro-3-((1-(4-((2-chlorobenzyl)oxy)benzyl)-1H-tetrazol-5-yl)(pentylamino) methyl)-1H-indole-2-carboxylate **3.30***

Aldehyde **4** (0.25 g, 1.0 mmol), amylamine (116 μL, 1.0 mmol), isocyanide **17b** (0.26 g, 1.0 mmol), $TMSN_3$ (131 μL, 1.0 mmol). Product was purified by flash chromatography (petroleum ether/EtOAc 5:1; R_f: 0.10, petroleum ether/EtOAc 3:1) giving compound **3.30** as yellow oil in 46% (0.29 g) yield. Product was recrystallized from EtOH.

mp: 112 ºC; **NMR**: **^{1}H** (600 MHz, $CDCl_3$): δ 8.87 (s, 1H), 7.72 (d, J = 8.7 Hz, 1H), 7.54-7.59 (m, 1H), 7.44-7.40 (m, 1H), 7.33-7.27 (m, 2H), 7.23 (d, J = 1.5 Hz, 1H), 7.04 (dd, J = 8.7, 1.8 Hz, 1H), 6.93 (dt, J = 8.7, 1.8 Hz, 2H), 6.80 (dt, J = 8.7, 2.0 Hz, 2H), 6.20 (s, 1H), 5.52 (q, J = 15.2 Hz, 2H), 5.11 (s, 2H), 4.44-4.30 (m, 2H), 2.53 (ddd, J = 11.1, 8.3, 6.2 Hz, 1H), 2.42

(ddd, *J* = 11.1, 8.3, 6.3 Hz, 1H), 1.50-1.38 (m, 2H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.24-1.15 (m, 4H), 0.82 (t, *J* = 7.0 Hz, 3H); **^{13}C** (151 MHz, $CDCl_3$): *δ* 161.3, 158.6, 156.0, 136.2, 134.5, 132.8, 132.3, 129.6, 129.3, 128.9, 128.6, 127.1, 126.4, 124.6, 124.4, 122.9, 112.4, 119.9, 115.1, 111.8, 67.3, 61.7, 50.4, 48.8, 47.9, 29.7, 29.5, 22.6, 14.5, 14.1; **IR (ATR)** [cm^{-1}]: 3196, 2931, 2850, 1702, 1611, 1513, 1439, 1314, 1226, 1179, 1095, 1060, 1004, 846, 804, 778, 754; **HRMS (ESI)**: Calcd for $C_{32}H_{34}Cl_2N_6O_3$ (m/z): $[M+H]^+$ 621.2148, $[M+2+H]^+$ 623.2118, found: $[M+H]^+$ 621.2152, $[M+2+H]^+$ 623.2128; **LC-MS (DAD/ESI)**: t_R = 3.49 min, Calcd for $C_{32}H_{34}Cl_2N_6O_3Na$ (m/z): $[M]^+$ 643.20, $[M+2]^+$ 645.19, found: $[M]^+$ 643.40, $[M+2]^+$ 645.40.

*4.2.6.31. Ethyl 3-((1-(4-((2-bromobenzyl)oxy)benzyl)-1H-tetrazol-5-yl)((cyclohexylmethyl) amino) methyl)-6-chloro-1H-indole-2-carboxylate **3.31***

Aldehyde **4** (0.25 g, 1.0 mmol), cyclohexylmethylamine (130 μL, 1.0 mmol), isocyanide **17c** (0.30 g, 1.0 mmol), $TMSN_3$ (131 μL, 1.0 mmol). Product was purified by flash chromatography (petroleum ether/EtOAc 5:1; R_f: 0.18, petroleum ether/EtOAc 3:1) giving compound **3.31** as yellow oil in 57% (0.39 g) yield. Product was recrystallized from $EtOH/H_2O$.

mp: 162 ºC; **NMR**: **^{1}H** (600 MHz, $CDCl_3$): *δ* 9.09 (s, 1H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.60 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.51 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.34 (td, *J* = 7.6, 1.1 Hz, 1H), 7.20 (td, *J* = 7.9, 1.6 Hz, 1H), 7.18 (s, 1H), 7.03 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.01-6.96 (m, 2H), 6.86-6.81 (m, 2H), 6.11 (s, 1H), 5.66-5.60 (m, 1H), 5.56 (m, 1H), 5.09 (s, 2H), 4.38-4.30 (m, 1H), 4.30-4.23 (m, 1H), 2.34 (m, 1H), 2.23 (m, Hz, 1H), 1.75-1.55 (m, 6H), 1.30 (m, Hz, 3H), 1.23-1.02 (m, 3H), 0.90-0.81 (m, 1H), 0.80-0.72 (m, 1H); **^{13}C** (151 MHz, $CDCl_3$): *δ* 161.3, 158.6, 136.2, 136.1, 132.9, 132.2, 129.6, 129.0, 128.7, 127.8, 126.5, 124.6, 124.5, 122.8, 122.6, 122.3, 115.2, 111.9, 69.6, 61.6, 54.6, 50.5, 49.1, 38.2, 31.5, 31.4, 26.7, 26.1, 26.1, 14.4; **IR (ATR)** [cm^{-1}]: 3162, 2922, 2844, 1698, 1513, 1448, 1426, 1301, 1227, 1123, 1100, 1024, 817, 780, 751; **HRMS (ESI)**: Calcd for $C_{34}H_{36}BrClN_6O_3$ (m/z): $[M+H]^+$ 691.1799, $[M+2+H]^+$ 693.1779, found: $[M+H]^+$ 691.1792, $[M+2+H]^+$ 693.1773; **LC-MS (DAD/ESI)**: t_R = 3.93 min, Calcd for $C_{34}H_{36}BrClN_6O_3Na$: (m/z) $[M]^+$ 713.17, $[M+2]^+$ 715.16, found: $[M]^+$ 716.40, $[M+2]^+$ 715.40.

*4.2.6.32. Ethyl 3-((1-(4-((2-bromobenzyl)oxy)benzyl)-1H-tetrazol-5-yl)((4-chlorobenzyl) amino)methyl)-6-chloro-1H-indole-2-carboxylate **3.32***

Aldehyde 4 (0.25 g, 1.0 mmol), 4-chlorobenzylamine (121 μL, 1.0 mmol), isocyanide **17c** (0.30 g, 1.0 mmol), $TMSN_3$ (131 μL, 1.0 mmol). Product was purified by flash

chromatography (petroleum ether/EtOAc 4:1; R_f: 0.14, petroleum ether/EtOAc 3:1) giving compound **3.32** as yellow oil in 51% (0.37 g) yield.

NMR: **^{1}H** (500 MHz, $CDCl_3$): δ 9.22 (s, 1H), 7.61 (t, J = 7.9 Hz, 2H), 7.51 (d, J = 7.6 Hz, 1H), 7.34 (t, J = 7.3 Hz, 1H), 7.24-7.18 (m, 4H), 7.11 (d, J = 8.3 Hz, 2H), 7.04 (dd, J = 8.7, 1.6 Hz, 1H), 6.85 (d, J = 8.6 Hz, 2H), 6.79 (d, J = 8.7 Hz, 2H), 6.11 (s, 1H), 5.49 (s, 2H), 5.09 (s, 2H), 4.28-4.17 (m, 2H), 3.69 (d, J = 13.2 Hz, 1H), 3.61 (d, J = 13.1 Hz, 1H), 1.24 (t, J = 7.1 Hz, 3H); **^{13}C** (125 MHz, $CDCl_3$): δ 161.1, 158.5, 155.6, 137.7, 136.2, 136.0, 133.1, 132.9, 132.3, 129.9, 129.6, 129.0, 128.6, 128.6, 127.7, 126.3, 124.9, 124.5, 122.6, 122.5, 122.4, 118.9, 115.2, 112.0, 69.6, 61.7, 50.7, 50.4, 47.8, 14.3; **IR (ATR)** [cm^{-1}]: 3323, 3160, 2924, 2849, 1701, 1615, 1512, 1448, 1430, 1296, 1248, 1178, 1099, 1017, 887, 832, 803, 780, 747; **HRMS (ESI)**: Calcd for $C_{34}H_{29}BrCl_2N_6O_3$ (m/z): $[M+H]^+$ 719.0940, $[M+2+H]^+$ 721.0919, found: $[M+H]^+$ 719.0921, $[M+2+H]^+$ 721.0890; **LC-MS (DAD/ESI)**: t_R = 6.51 min, Calcd for $C_{34}H_{29}BrCl_2N_6O_3Na$ (m/z): $[M]^+$ 741.08, $[M+2]^+$ 743.07, found: $[M]^+$ 741.25, $[M+2]^+$ 743.30.

*4.2.6.33. Ethyl 3-((1-(4-((2-bromobenzyl)oxy)benzyl)-1H-tetrazol-5-yl)(pentylamino)methyl)-6-chloro-1H-indole-2-carboxylate **3.33***

Aldehyde **4** (0.25 g, 1.0 mmol), amylamine (116 µL, 1.0 mmol), isocyanide **17c** (0.30 g, 1.0 mmol), $TMSN_3$ (131 µL, 1.0 mmol). Product was purified by flash chromatography (petroleum ether/EtOAc 4:1; R_f: 0.14, petroleum ether/EtOAc 3:1) giving compound **3.33** as yellow oil in 52% (0.34 g) yield. Product was recrystallized from EtOH.

mp: 89 ºC; **NMR**: **^{1}H** (600 MHz, acetone-d_6): δ 11.03 (s, 1H), 7.95 (d, J = 8.7 Hz, 1H), 7.66 (dd, J = 8.0, 1.1 Hz, 1H), 7.60 (dd, J = 7.7, 1.5 Hz, 1H), 7.49 (dd, J = 1.9, 0.5 Hz, 1H), 7.43 (td, J = 7.5, 1.2 Hz, 1H), 7.30 (td, J = 7.7, 1.7 Hz, 1H), 7.07-7.02 (m, 3H), 6.91 (dt, J = 8.8, 2.1 Hz, 2H), 6.39 (s, 1H), 5.67 (s, 2H), 5.13 (s, 2H), 4.49-4.31 (m, 2H), 2.62-2.54 (m, 1H), 2.51-2.45 (m, 1H), 1.49-1.39 (m, 2H), 1.34 (t, J = 7.1 Hz, 3H), 1.25-1.17 (m, 4H), 0.86-0.75 (m, 3H); **^{13}C** (151 MHz, acetone-d_6): δ 162.3, 159.3, 157.0, 137.7, 137.2, 133.6, 131.6, 130.7, 130.5, 129.5, 128.7, 128.2, 126.3, 125.6, 124.4, 123.3, 121.7, 120.6, 115.7, 112.9, 70.2, 62.0, 50.7, 49.5, 48.2, 23.2, 14.6, 14.3; **IR (ATR)** [cm^{-1}]: 3196, 2953, 2929, 2856, 1702, 1613, 1513, 1437, 1304, 1229, 1178, 1026, 916, 748; **HRMS (ESI)**: Calcd for $C_{32}H_{34}BrClN_6O_3$ (m/z): $[M+H]^+$ 665.1643, $[M+2+H]^+$ 667.1622, found: $[M+H]^+$ 665.1622, $[M+2+H]^+$ 667.1606; **LC-MS (DAD/ESI)**: t_R = 3.49 min, Calcd for $C_{32}H_{34}BrClN_6O_3Na$ (m/z): $[M]^+$ 687.15, $[M+2]^+$ 689.14, found:$[M]^+$ 687.35, $[M+2]^+$ 689.35.

4.2.7. General synthetic procedures for the hydrolysis reaction and analytical data

The corresponding tetrazoles **3.1**-**3.33** (1 equiv.) and LiOH (10 equiv.) were refluxed in a mixture of EtOH/H_2O (1:1, 4 mL) for 24-72 h. After reaction was completed, it was acidified with 2 M HCl solution. The resulting mixture was extracted with ethyl acetate, washed with water and brine, dried over anhydrous $MgSO_4$ and evaporated. The resulted crude oils were precipitated and washed with diethyl ether giving the final products (**2.1**-**2.33**: yields 10-79%) as light yellow solids.

*4.2.7.1. 6-chloro-3-((cyclopentylamino)(1-(3-phenoxyphenyl)-1H-tetrazol-5-yl)methyl)-1H-indole-2-carboxylic acid **2.1***

Ester **3.1** (0.175 g, 0.30 mmol), LiOH (0.072 g, 3.0 mmol). Yield: 69% (0.109 g).

NMR: **^{1}H** (600 MHz, MeOH-d_4): δ 7.36-6.72 (m, 12H), 6.09 (br s, 1H), 3.32 (m, 1H), 1.73-1.11 (m, 8H); **^{13}C** (151 MHz, MeOH-d_4): δ 163.5, 158.5, 152.1, 135.7, 134.8, 130.1, 130.0, 127.2, 124.8, 124.4, 120.1, 119.7, 118.3, 117.9, 112.1, 105.9, 69.4, 55.3, 40.1, 40.0, 31.8, 29.6, 29.2, 22.6, 14.9; **LC-MS (DAD/ESI)**: t_R = 4.85 min, Calcd for $C_{28}H_{25}ClN_6O_3$ (m/z): $[M+2H]^+$ 530.17, found: $[M+2H]^+$ 530.15.

*4.2.7.2. 6-chloro-3-((cyclohexylamino)(1-(3-phenoxyphenyl)-1H-tetrazol-5-yl)methyl)-1H-indole-2-carboxylic acid **2.2***

Ester **3.2** (0.307 g, 0.54 mmol), LiOH (0.130 g, 5.4 mmol). Yield: 65% (0.109 g).

NMR: **^{1}H** (600 MHz, MeOH-d_4): δ 7.39-6.65 (m, 12H), 6.09 (br s, 1H), 3.52 (m, 1H), 1.82-0.74 (m, 10H); **^{13}C** (151 MHz, MeOH-d_4): δ 163.5, 157.9, 152.6134.0, 130.4, 129.9, 128.0, 125.1, 123.1, 120.7, 120.5, 118.2, 116.7, 112.8, 105.9, 69.4, 55.3, 32.8, 32.1, 29.9, 29.5, 24.9, 24.1, 22.9, 14.3; **LC-MS (DAD/ESI)**: t_R = 5.18 min, Calcd for $C_{29}H_{27}ClN_6O_3$ (m/z): $[M+H]^+$ 543.18, found: $[M+H]^+$ 543.22.

*4.2.7.3. 6-chloro-3-((cycloheptylamino)(1-(3-phenoxyphenyl)-1H-tetrazol-5-yl)methyl)-1H-indole-2-carboxylic acid **2.3***

Ester **3.3** (0.184 g, 0.32 mmol), LiOH (0.077 g, 3.2 mmol). Yield: 62% (0.110 g).

NMR: **^{1}H** (600 MHz, MeOH-d_4): δ 7.39-6.93 (m, 12H), 6.69 (br s, 1H), 3.52 (m, 1H), 2,86 (m, 1H), 1.96-0.83 (m, 12H); **^{13}C** (151 MHz, MeOH-d_4): δ 164.9, 160.0, 155.2, 134.3, 130.4, 130.3, 128.1, 127.3, 126.0, 125.0, 121.9, 120.5, 118.3, 118.0, 112.1, 57.7, 46.0, 32.5, 32.1, 29.9, 29.6, 29.1, 27.8, 24.8, 24.0, 22.9, 14.3; **LC-MS (DAD/ESI)**: t_R = 4.75 min, Calcd for $C_{29}H_{27}ClN_6O_3$ (m/z): $[M-H]^-$ 555.20, found: $[M-H]^-$ 555.13.

*4.2.7.4. 6-Chloro-3-((1-(4-chlorophenyl)-1H-tetrazol-5-yl)((cyclohexylmethyl)amino)methyl)-1H-indole-2-carboxylic acid **2.4***

Ester **3.4** (0.176 g, 0.33 mmol), LiOH (0.079 g, 3.30 mmol). Yield: 32% (0.052 g).

mp: 219 ºC; **NMR**: **^{1}H** (600 MHz, DMSO-d_6): δ 11.70 (s, 1H), 7.61-7.51 (m, 2H), 7.46 (s, 2H), 7.35 (s, 2H), 6.94 (dd, J = 8.6, 1.5 Hz, 1H), 6.16 (s, 1H)), 2.43-2.30 (m, 1H), 1.76 1.50 (m, 5H), 1.50-1.35 (m, 1H), 1.20-1.01 (m, 3H), 0.88-0.66 (m, 2H); **^{13}C** (151 MHz, DMSO-d_6): δ 135.3, 135.2, 129.7, 129.7, 129.5, 128.2, 127.6, 125.0, 119.9, 111.7, 52.6, 47.9, 36.3, 30.5, 30.5, 25.9, 25.4, 25.3; **IR (ATR)** [cm^{-1}]: 3500-2000, 3099, 2928, 2853, 1682, 1621, 1571, 1534, 1492, 1446, 1337, 1330, 1235, 1093, 1064, 1014, 832, 804; **HRMS (ESI)**: Calcd for $C_{24}H_{24}Cl_2N_6O_2$ (m/z): $[M-H]^-$ 497.1260, $[M+2-H]^-$ 499.1230, found: $[M-H]^-$ 497.1262, $[M+2-H]^-$ 499.1230; **LC-MS (DAD/ESI)**: t_R = 2.44 min, Calcd for $C_{24}H_{24}Cl_2N_6O_2$ (m/z): $[M-H]^-$ 497.13, $[M+2-H]^-$ 499.12, found: $[M-H]^-$ 497.20, $[M+2-H]^-$ 499.15.

*4.2.7.5. 6-Chloro-3-((1-(4-chlorophenyl)-1H-tetrazol-5-yl)(pentylamino)methyl)-1H-indole-2-carboxylic acid **2.5***

Ester **3.5** (0.190 g, 0.38 mmol), LiOH (0.091 g, 3.80 mmol). Yield: 33% (0.060 g).

mp: 171-172 ºC; **NMR**: **^{1}H** (600 MHz, DMSO-d_6): δ 11.78 (s, 1H), 7.47 (d, J = 8.6 Hz, 2H), 7.35-7.30 (m, 3H), 7.21 (s, 1H), 6.92 (dd, J = 8.6, 1.3 Hz, 1H), 6.20 (s, 1H), 2.80-2.70 (m, 1H), 2.66-2.60 (m, 1H), 1.58-1.42 (m, 2H), 1.25-1.11 (m, 4H), 0.80 (t, J = 6.9 Hz, 3H); **^{13}C** (151 MHz, DMSO-d_6): δ 162.7, 135.5, 135.1, 131.6, 129.5, 128.4, 127.7, 124.8, 120.1, 117.1, 47.4, 45.6, 28.3, 26.8, 21.7, 13.7; **IR (ATR)** [cm^{-1}]: 3500-2000, 3411, 3098, 2959, 2871, 1682, 1617, 1533, 1492, 1435, 1375, 11330, 1235, 1093, 1066, 1014, 833, 802; **HRMS (ESI)**: Calcd for $C_{22}H_{22}Cl_2N_6O_2$ (m/z): $[M+H]^+$ 473.1260, $[M+2+H]^+$ 476.1230, found: $[M+H]^+$ 473.1246, $[M+2+H]^+$ 475.1223; **LC-MS (DAD/ESI)**: t_R = 4.45 min, Calcd for $C_{22}H_{22}Cl_2N_6O_2$ (m/z): $[M-H]^-$ 471.11, $[M+2-H]^-$ 473.11, found: $[M-H]^-$ 471.25, $[M+2-H]^-$ 473.11.

*4.2.7.6. 6-Chloro-3-(((cyclohexylmethyl)amino)(1-(4-isopropylphenyl)-1H-tetrazol-5-yl)methyl)-1H-indole-2-carboxylic acid **2.6***

Ester **3.6** (0.310 g, 0.58 mmol), LiOH (0.139 g, 5.80 mmol). Yield: 53% (0.135 g).

mp: 215-216 ºC; **NMR**: **^{1}H** (600 MHz, DMSO-d_6): δ 11.55 (s, 1H), 7.37- 7.18 (m, 5H), 1.17-7.04 (m, 1H), 6.83 (d, J = 8.2 Hz, 1H), 6.15 (s, 1H), 2.92 (sept, J = 6.9 Hz, 1H), 2.63-2.54 (m, 1H), 2.45-2.37 (m, 1H), 1.79-1.48 (m, 6H), 1.20 (d, J = 6.9 Hz, 6H), 1.16-1.04 (m, 3H),

0.86-0.72 (m, 2H); **^{13}C** (151 MHz, DMSO-d_6): δ 163.1, 162.4, 151.0, 134.9, 127.6, 127.3, 125.6, 125.2, 119.2, 115.0, 111.6, 48.0, 33.2, 30.5, 30.5, 28.8, 25.9, 25.4, 25.3, 25.1, 23.7, 23.6; **IR (ATR)** [cm^{-1}]: 3200-2500, 3169, 2963, 2926, 2853, 1599, 1528, 1431, 1379, 1333, 1275, 1060, 823, 792; **HRMS (ESI)**: Calcd for $C_{27}H_{31}ClN_6O_2$ (m/z): $[M-H]^-$ 505.2119, $[M+2-H]^-$ 507.2089, found: $[M-H]^-$ 505.2117, $[M+2-H]^-$ 507.2097; **LC-MS (DAD/ESI)**: t_R = 2.68 min, Calcd for $C_{27}H_{31}ClN_6O_2$ (m/z): $[M-H]^-$ 505.21, $[M+2-H]^-$ 507.21, found: $[M-H]^-$ 505.30, $[M+2-H]^-$ 507.30.

*4.2.7.7. 6-Chloro-3-((1-(4-isopropylphenyl)-1H-tetrazol-5-yl)(pentylamino)methyl)-1H-indole-2-carboxylic acid **2.7***

Ester **3.7** (0.170 g, 0.33 mmol), LiOH (0.079 g, 3.30 mmol). Yield: 52% (0.139 g).

mp: 191 ºC; **NMR**: **^{1}H** (600 MHz, DMSO-d_6): δ 11.87 (s, 1H), 7.31 (d, J = 1.1 Hz, 1H), 7.20 (d, J = 8.3 Hz, 2H), 7.11 (d, J = 7.6 Hz, 2H), 7.03 (s, 1H), 6.90 (s, 1H), 6.41 (s, 1H), 2.95-2.84 (m, 1H), 2.82-2.71 (m, 1H), 1.69-1.54 (m, 2H), 1.25-1.20 (m, 4H), 1.18 (d, J = 6.9 Hz, 6H), 0.82 (t, J = 7.0 Hz, 3H); **^{13}C** (151 MHz, DMSO-d_6): δ 162.4, 151.3, 135.1, 135.1, 130.2, 127.2, 125.4, 120.9, 120.5, 111.8, 47.6, 45.7, 33.2, 30.7, 28.2, 26.0, 23.5, 21.7, 13.7; **IR (ATR)** [cm^{-1}]: 3200-2000, 3169, 2962, 2871, 1693, 1595, 1572, 1528, 1465, 1429, 1389, 1334, 1208, 1115, 1087, 1059, 846, 820, 792; **HRMS (ESI)**: Calcd for $C_{25}H_{29}ClN_6O_2$ (m/z): $[M-H]^-$ 479.1962, $[M+2-H]^-$ 481.1933, found: $[M-H]^-$ 479.1962, $[M+2-H]^-$ 481.1933; **LC-MS (DAD/ESI)**: t_R = 2.55 min, Calcd for $C_{25}H_{29}ClN_6O_2$ (m/z): $[M-H]^-$ 479.20, $[M+2-H]^-$ 481.19, found: $[M-H]^-$ 479.30, $[M+2- H]^-$ 481.30.

*4.2.7.8. 6-Chloro-3-((1-(3-chloro-4-fluorophenyl)-1H-tetrazol-5-yl)((cyclohexylmethyl) amino) methyl)-1H-indole-2-carboxylic acid **2.8***

Ester **3.8** (0.205 g, 0.38 mmol), LiOH (0.091 g, 3.80 mmol). Yield: 37% (0.073 g).

mp: 170 ºC; **NMR**: **^{1}H** (600 MHz, DMSO-d_6): δ 11.80 (s, 1H), 7.68 (d, J = 4.1 Hz, 1H), 7.49-7.40 (m, 2H), 7.36-7.31 (m, 2H), 6.96 (dd, J = 8.6, 1.7 Hz, 1H), 6.15 (s, 1H), 2.66 2.55 (m, 1H), 2.45-2.35 (m, 1H), 1.72-1.49 (m, 6H), 1.21-1.00 (m, 3H), 0.88-0.71 (m, 2H); **^{13}C** (151 MHz, DMSO-d_6): δ 162.6, 159.0, 157.4, 135.2, 129.9, 128.8, 128.5, 127.3, 127.2, 124.9, 120.5, 120.4, 120.1, 117.7, 111.7, 52.4, 47.8, 36.0, 30.7, 30.4, 25.9, 25.4, 25.3; **IR (ATR)** [cm^{-1}]: 3500-2000, 3070, 2928, 2854, 1682, 1615, 1533, 1499, 1435, 1375, 1329, 1262, 1226, 1065, 895, 803; **HRMS (ESI)**: Calcd for $C_{27}H_{23}Cl_2FN_6O_2$ (m/z): $[M-H]^-$ 515.1165, $[M+2-H]^-$ 517.1136, found: $[M-H]^-$ 515.1161, $[M+2-H]^-$ 517.1136; **LC-MS (DAD/ESI)**: t_R = 2.42 min,

Calcd for $C_{24}H_{23}Cl_2N_6O_2$ (m/z): $[M-H]^-$ 515.12, $[M+2-H]^-$ 517.11, found: $[M-H]^-$ 515.20, $[M+2-H]^-$ 517.15.

*4.2.7.9. 6-Chloro-3-((1-(3-chloro-4-fluorophenyl)-1H-tetrazol-5-yl)(pentylamino)methyl)-1H-indole-2-carboxylic acid **2.9***

Ester **3.9** (0.174 g, 0.34 mmol), LiOH (0.082 g, 3.40 mmol). Yield: 55% (0.092 g).

mp: 154 ºC; **NMR**: **^{1}H** (600 MHz, DMSO-d_6): δ 11.86 (s, 1H), 7.63 (d, J = 4.2 Hz, 1H), 7.43-7.38 (m, 1H), 7.36-7.30 (m, 2H), 7.28-7.23 (m, 1H), 6.96 (d, J = 8.1 Hz, 1H), 6.34 (s, 1H), 2.87-2.74 (m, 1H), 2.74-2.62 (m, 1H), 1.67-1.45 (m, 2H), 1.26-1.14 (m, 4H), 0.81 (t, J = 6.9 Hz, 3H); **^{13}C** (151 MHz, DMSO-d_6): δ 163.5, 159.0, 157.3, 135.1, 129.5, 128.7, 128.5, 127.2, 127.2, 124.7, 121.2, 120.5, 120.3, 120.3, 117.6, 117.5, 111.7, 47.4, 45.6, 28.3, 26.5, 21.7; **IR (ATR)** [cm^{-1}]: 3500-2000, 3436, 3076, 2959, 2934, 2871, 1615, 1533, 1498, 1435, 1376, 1329, 1263, 1229, 1065, 803; **HRMS (ESI)**: Calcd for $C_{22}H_{21}Cl_2FN_6O_2$ (m/z): $[M-H]^-$ 489.1009, $[M+2-H]^-$ 491.0979, found: $[M-H]^-$ 489.1015, $[M+2-H]^-$ 491.0984; **LC-MS (DAD/ESI)**: t_R = 4.44 min, Calcd for $C_{22}H_{21}Cl_2FN_6O_2$ (m/z): $[M-H]^-$ 489.10, $[M+2-H]^-$ 491.10, found: $[M-H]^-$ 489.20, $[M+2-H]^-$ 491.20.

*4.2.7.10. 6-Chloro-3-((1-(4-chlorobenzyl)-1H-tetrazol-5-yl)((4-chlorobenzyl)amino)methyl)-1H-indole-2-carboxylic acid **2.10***

Ester **3.10** (0.207 g, 0.36 mmol), LiOH (0.087 g, 3.60 mmol). Yield: 21% (0.041 g).

mp: 170 ºC; **NMR**: **^{1}H** (600 MHz, DMSO-d_6): δ 11.89 (s, 1H), 7.76 (s, 1H), 7.39 (d, J = 1.8 Hz, 1H), 7.31 (d, J = 8.4 Hz, 2H), 7.28 (dt, J = 8.4, 1.8 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 7.03 (dd, J = 8.7, 1.9 Hz, 1H), 6.92 (d, J = 8.4 Hz, 2H), 6.24 (s, 1H), 5.67 (d, J = 15.8 Hz, 1H), 5.59 (d, J = 15.8 Hz, 1H), 3.70 (d, J = 13.8 Hz, 1H), 3.64 (d, J = 13.8 Hz, 1H); **^{13}C** (151 MHz, DMSO-d_6): δ 162.9, 155.6, 137.7, 136.1, 133.3, 132.8, 131.6, 130.1, 129.1, 129.0, 128.9, 128.6, 128.5, 128.2, 128.1, 124.5, 122.8, 120.3, 111.9, 49.3, 49.2, 46.7; **IR (ATR)** [cm^{-1}]: 3500-2500, 2408, 2175, 3035, 1599, 1537, 1493, 1431, 1412, 1376, 1330, 1231, 1092, 1065, 1015, 907, 799; **HRMS (ESI)**: Calcd for $C_{25}H_{19}Cl_3N_6O_2$ (m/z): $[M-H]^-$ 539.0557, $[M+2-H]^-$ 541.0527, found: $[M-H]^-$ 539.0563, $[M+2-H]^-$ 541.0528; **LC-MS (DAD/ESI)**: t_R = 3.98 min, Calcd for $C_{25}H_{19}Cl_3N_6O_2$ (m/z): $[M-H]^-$ 539.06, $[M+2-H]^-$ 541.05, found: $[M-H]^-$ 539.15, $[M+2-H]^-$ 541.15.

*4.2.7.11. 6-chloro-3-((1-(4-chlorobenzyl)-1H-tetrazol-5-yl)((cyclohexylmethyl)amino)methyl)-1H-indole-2-carboxylic acid **2.11***

Ester **3.11** (0.218 g, 0.40 mmol), LiOH (0.096 g, 4.40 mmol). Yield: 53% (0.108 g).

mp: 174 ºC; **NMR**: **^{1}H** (600 MHz, DMSO-d_6): δ 11.89 (s, 1H), 7.35 (d, *J* = 1.8 Hz, 1H), 7.31-7.28 (m, 1H), 7.26 (d, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 8.7 Hz, 1H), 6.96 (dd, *J* = 8.7, 1.8 Hz, 1H), 6.93 (d, *J* = 7.9 Hz, 2H), 6.38 (s, 1H), 5.75 (d, *J* = 15.8 Hz, 1H), 3.56 (d, *J* = 15.8 Hz, 1H), 2.60-2.53 (m, 1H), 2.47-2.40 (m, 1H), 1.70-1.53 (m, 6H), 1.19-1.04 (m, 3H), 0.88-0.76 (m, 2H); **^{13}C** (151 MHz, DMSO-d_6): δ 163.0, 135.3, 132.8, 132.7, 130.3, 130.3, 128.8, 128.4, 127.3, 124.5, 122.9, 120.4, 115.4, 111.9, 69.6, 52.4, 49.5, 47.5, 30.7, 30.5, 30.4, 25.8, 25.3, 25.2; **IR (ATR)** [cm^{-1}]: 3500-2200, 3175, 2928, 2854, 1645, 1600, 1573, 1493, 1435, 1331, 1228, 1091, 1064, 1016, 899, 804; **HRMS (ESI)**: Calcd for $C_{25}H_{26}Cl_2N_6O_2$ (m/z): $[M-H]^-$ 511.1416, $[M+2-H]^-$ 516.1387, found: $[M-H]^-$ 511.1420, $[M+2-H]^-$ 513.1409; **LC-MS (DAD/ESI)**: t_R = 4.62 min, Calcd for $C_{25}H_{26}Cl_2N_6O_2$ (m/z): $[M-H]^-$ 511.14, $[M+2-H]^-$ 513.14, found: $[M-H]^-$ 511.25, $[M+2-H]^-$ 513.20.

*4.2.7.12. 6-Chloro-3-((1-(4-chlorobenzyl)-1H-tetrazol-5-yl)(pentylamino)methyl)-1H-indole-2-carboxylic acid **2.12***

Ester **3.12** (0.180 g, 0.35 mmol), LiOH (0.084 g, 3.50 mmol). Yield: 59% (0.100 g).

mp: 196 ºC; **NMR**: **^{1}H** (600 MHz, DMSO-d_6): δ 11.81 (s, 1H), 7.36 (s, 1H), 7.34 (d, *J* = 1.8 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 6.95 (dd, *J* = 8.7, 1.9 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 6.44 (s, 1H), 5.75 (d, *J* = 15.8 Hz, 1H), 5.65 (d, *J* = 15.6 Hz, 1H), 2.75-2.67 (m, 1H), 2.65-2.57 (m, 1H), 1.59-1.44 (m, 2H), 1.26-1.14 (m, 4H), 0.8 (t, *J* = 7.0 Hz, 3H); **^{13}C** (151 MHz, DMSO-d_6): δ 163.1, 135.2, 133.0, 132.8, 128.8, 128.4, 128.3, 124.6, 121.0, 120.3, 111.9, 49.4, 47.0, 45.8, 28.4, 26.8, 21.8, 13.7; **IR (ATR)** [cm^{-1}]: 3444, 3000-2000, 3039, 2964, 2935, 2861, 1636, 1567, 1545, 1449, 1422, 1370, 1331, 1279, 1249, 1097, 1016, 802, 782; **HRMS (ESI)**: Calcd for $C_{23}H_{24}Cl_2N_6O_2$ (m/z): $[M-H]^-$ 485.1260, $[M+2-H]^-$ 487.1230, found: $[M-H]^-$ 485.1255, $[M+2-H]^-$ 487.1230; **LC-MS (DAD/ESI)**: t_R = 2.34 min, Calcd for $C_{23}H_{24}Cl_2N_6O_2$ (m/z): $[M-H]^-$ 485.13, $[M+2- H]^-$ 487.12, found: $[M-H]^-$ 485.20, $[M+2-H]^-$ 487.20.

*4.2.7.13. 6-chloro-3-((1-(4-benzyloxyphenyl)-1H-tetrazol-5-yl)(cyclopentylamino)methyl)-1H-indole-2-carboxylic acid **2.13***

Ester **3.13** (0.08 g, 0.14 mmol), LiOH (0.034 g, 1.4 mmol). Yield: 46% (0.035 g).

NMR: **^{1}H** (600 MHz, MeOH-d_4): δ 7.47-7.33 (m, 8H), 7.12-7.11 (m, 2H), 6.80-6.73 (m, 2H), 6.15 (br s, 1H), 5.01 (s, 2H), 3.36-3.33 (m, 1H), 1.72-0.88 (m, 8H); **^{13}C** (151 MHz, DMSO-d_6): δ 164.4, 160.4, 155.2, 136.0, 128.7, 128.3, 127.8, 127.5, 127.0, 125.6, 121.2, 118.8,

115.4, 115.3, 112.2, 70.3, 56.7, 47.1, 30.8, 24.0, 23.8, 14.5; **LC-MS (DAD/ESI)**: t_R = 5.05 min, Calcd for $C_{29}H_{27}ClN_6O_3$ (m/z): $[M]^+$ 542.18, found: $[M]^+$ 542.17.

*4.2.7.14. 6-chloro-3-((1-(4-benzyloxyphenyl)-1H-tetrazol-5-yl)(cyclohexylamino)methyl)-1H-indole-2-carboxylic acid **2.14***

Ester **3.14** (0.09 g, 0.14 mmol), LiOH (0.040 g, 1.4 mmol). Yield: 63% (0.049 g).

NMR: **^{1}H** (600 MHz, MeOH-d_4): δ 7.40-7.20 (m, 6H), 7.07-6.69 (m, 6H), 6.15 (br s, 1H), 4.96 (s, 2H), 2.70-2.72 (m, 1H), 1.29-0.84 (m, 10H); **^{13}C** (151 MHz, DMSO-d_6): δ 164.4, 160.4, 155.2, 137.0, 136.1, 128.9, 128.8, 128.6, 128.2, 127.9, 127.7, 117.0, 116.2, 115.6, 70.7, 56.7, 47.1, 30.8, 29.9, 24.0, 23.8, 14.5; **LC-MS (DAD/ESI)**: t_R = 5.52 min, Calcd for $C_{30}H_{29}ClN_6O_3$ (m/z): $[M-H]^-$ 555.20, found: $[M-H]^-$ 555.13.

*4.2.7.15. 6-chloro-3-((1-(4-benzyloxyphenyl)-1H-tetrazol-5-yl)(cycloheptylamino)methyl)-1H-indole-2-carboxylic acid **2.15***

Ester **3.15** (0.03 g, 0.05 mmol), LiOH (0.012 g, 0.5 mmol). Yield: 67% (0.020 g).

NMR: **^{1}H** (600 MHz, MeOH-d_4): δ 7.73-7.32 (m, 8H), 7.11-7.03 (m, 2H), 6.79-6.72 (m, 2H), 6.37 (br s, 1H), 4.92 (s, 2H), 2.98 (br s, 1H), 2.00-0.84 (m, 12H); **^{13}C** (151 MHz, DMSO-d_6): δ 164.5, 160.7, 155.4, 137.0, 136.2, 129.0, 128.8, 128.9, 128.6, 127.9, 127.8, 122.0, 115.6, 70.6, 56.4, 47.3, 30.7, 29.9, 27.8, 23.9, 14.5; **LC-MS (DAD/ESI)**: t_R = 5.52 min, Calcd for $C_{32}H_{33}ClN_6O_3$ (m/z): $[M]^+$ 584.23, found: $[M]^+$ 584.31.

*4.2.7.16. 6-chloro-3-((1-(3-benzyloxyphenyl)-1H-tetrazol-5-yl)(cyclopentylamino)methyl)-1H-indole-2-carboxylic acid **2.16***

Ester **3.16** (0.02 g, 0.04 mmol), LiOH (0.010 g, 0.4 mmol). Yield: 62% (0.020 g).

NMR: **^{1}H** (600 MHz, DMSO-d_6): δ 11.8 (br s, 1H), 7.46-7.35 (m, 9H), 7.15 (d, J = 5 Hz, 1H), 7.04 (s, 1H), 6.06 (d, J = 5 Hz, 1H), 6.90 (d, J = 15 Hz, 1H), 6.09 (s, 1H), 5.00 (dd, J = 15, 10 Hz, 2H), 3.11 (s, 1H), 1.88-1.39 (m, 8H); **^{13}C** (151 MHz, DMSO-d_6): δ 158.8, 157.5, 136.3, 135.1, 133.8, 130.5, 128.5, 128.1, 127.9, 125.0, 120.2, 118.2, 117.4, 112.4, 111.7, 69.7, 56.3, 46.4, 23.4; **LC-MS (DAD/ESI)**: t_R = 4.75 min, Calcd for $C_{29}H_{27}ClN_6O_3$ (m/z): $[M+H]^+$ 543.18, found: $[M+H]^+$ 543.18.

*4.2.7.17. 6-chloro-3-((1-(3-benzyloxyphenyl)-1H-tetrazol-5-yl)(cyclohexylamino)methyl)-1H-indole-2-carboxylic acid **2.17***

Ester **3.17** (0.143 g, 0.25 mmol), LiOH (0.059g, 2.50 mmol). Yield: 63% (0.088 g).

NMR: **^{1}H** (600 MHz, MeOH-d_4): δ 7.38 (s, 6H), 7.12 (t, J = 10 Hz, 1H), 7.01 (d, J = 10 Hz, 1H), 6.95 (d, J = 10 Hz, 1H), 6.88 (d, J = 10 Hz, 1H), 6.86 (s, 1H), 6.62 (d, J = 5 Hz, 1H), 6.48 (s, 1H), 4.82 (dd, J = 15, 10 Hz, 2H), 2.31-1.17 (m, 10H); **^{13}C** (151 MHz, MeOH-d_4): δ 163.5, 158.5, 152.1, 135.7, 134.8, 132.9, 129.8, 129.3, 127.7, 127.3, 126.8, 124.1, 121.1, 119.0, 117.0, 116.6, 111.6, 111.0, 105.9, 69.4, 55.3, 45.5, 29.0, 28.4, 24.1, 23.8; **LC-MS (DAD/ESI)**: t_R = 5.03 min, Calcd for $C_{30}H_{29}ClN_6O_3$ (m/z): $[M-H]^-$ 555.20, found: $[M-H]^-$ 555.03.

*4.2.7.18. 6-chloro-3-((1-(3-benzyloxyphenyl)-1H-tetrazol-5-yl)(cycloheptylamino)methyl)-1H-indole-2-carboxylic acid **2.18***

Ester **3.18** (0.020 g, 0.03 mmol), LiOH (0.008 g, 2.50 mmol). Yield: 63% (0.010 g).

NMR: **^{1}H** (600 MHz, MeOH-d_4): δ 7.42-7.31 (m, 12H), 6.68 (s, 1H), 5.02 (br s, 2H), 2.09-0.84 (m, 13H); **^{13}C** (151 MHz, MeOH-d_4): δ 163.2, 158.1, 152.3, 135.9, 134.8, 132.9, 128.9, 128.5, 127.8, 127.7, 126.8, 124.1, 121.1, 119.0, 117.0, 116.6, 111.6, 111.0, 108.2, 70.6, 55.3, 45.5, 29.9, 28.4, 24.1, 23.8; **LC-MS (DAD/ESI)**: t_R = 5.01 min, Calcd for $C_{31}H_{31}ClN_6O_3$ (m/z): $[M-H]^-$ 569.21, found: $[M-H]^-$ 569.03.

*4.2.7.19. 3-(((5r,7r)-adamantan-2-ylamino)(1-(4-((2-bromobenzyl)oxy)phenyl)-1H-tetrazol-5-yl)methyl)-6-chloro-1H-indole-2-carboxylic acid **2.19***

Ester **3.19** (0.052 g, 0.07 mmol), LiOH (0.017 g, 0.7 mmol). Yield: 21% (0.010 g).

NMR: **^{1}H** (600 MHz, DMSO-d_6): δ 6.87 (d, J = 10 Hz, 1H), 6.78 (d, J = 10 Hz, 1H), 6.64-6.49 (m, 6H), 6.39-6.16 (m, 3H), 4.39 (s, 2H), 1.08-0.62 (m, 12H); **^{13}C** (151 MHz, DMSO-d_6): δ 159.9, 132.8, 130.4, 128.0, 122.9, 120.3, 115.7, 111.9, 69.7, 35.3, 28.6; **LC-MS (DAD/ESI)**: t_R = 5.29 min, Calcd for $C_{34}H_{32}BrClN_6O_3$ (m/z): $[M+H]^+$ 687.14, found: $[M+H]^+$ 687.24.

*4.2.7.20. 3-((1-(4-((2-Bromobenzyl)oxy)phenyl)-1H-tetrazol-5-yl)((cyclohexylmethyl)amino) methyl)-6-chloro-1H-indole-2-carboxylic acid **2.20***

Ester **3.20** (0.221 g, 0.33 mmol), LiOH (0.080 g, 3.30 mmol). Yield: 21% (0.045 g).

mp: 208 ºC; **NMR**: **^{1}H** (600 MHz, DMSO-d_6): δ 11.65 (s, 1H), 7.72 (dd, J = 8.0, 0.8 Hz, 1H), 7.62 (dd, J = 7.5, 1.2 Hz, 1H), 7.47 (td, J = 7.5, 0.9 Hz, 1H), 7.45-7.39 (m, 1H), 7.38-7.33 (m, 3H), 7.11 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.6 Hz, 1H), 6.14 (s, 1H), 5.17 (s, 2H), 2.41-2.33 (m, 1H), 1.78-1.39 (m, 6H), 1.09-1.01 (m, 3H), 0.84-0.67 (m, 2H); **^{13}C** (151 MHz,

DMSO-d_6): δ 165.4, 160.8, 136.8, 136.4, 134.2, 131.9, 129.5, 128.7, 124.4, 121.1, 116.8, 113.0, 71.1, 49.3, 32.01, 31.96, 27.4, 26.8, 26.8; **IR (ATR)** [cm^{-1}]: 3500-2000, 3171, 2924, 2851, 1682, 1644, 1607, 1570, 1511, 1441, 1379, 1333, 1240, 1170, 1109, 1063, 1025, 793, 752; **HRMS (ESI)**: Calcd for $C_{31}H_{30}BrClN_6O_3$ (m/z): $[M-H]^-$ 647.1173, $[M+2-H]^-$ 649.1153, found: $[M-H]^-$ 647.1185, $[M+2-H]^-$ 649.1176; **LC-MS (DAD/ESI)**: t_R = 3.44 min, Calcd for $C_{31}H_{30}BrClN_6O_3$ (m/z): $[M-H]^-$ 647.12, $[M+2- H]^-$ 649.12, found: $[M-H]^-$ 647.20, $[M+2-H]^-$ 649.25.

*4.2.7.21. 3-((1-(4-((2-bromobenzyl)oxy)phenyl)-1H-tetrazol-5-yl)(cyclobutylamino)methyl)-6-chloro-1H-indole-2-carboxylic acid **2.21***

Ester **3.21** (0.250 g, 0.39 mmol), LiOH (0.094 g, 3.90 mmol). Yield: 67% (0.159 g).

mp: 147 ºC; **IR (ATR)** [cm^{-1}]: 3500-300, 3427, 3296, 3202, 1662, 1600, 1544, 1512, 1438, 1357, 1241, 1176; **NMR**: **^{1}H** (600 MHz, DMSO-d_6): δ 8.50 (br s, 1H), 7.68 (d, *J* = 10 Hz, 2H), 7.64 (d, *J* = 10 Hz, 2H), 7.58-7.07 (m, 4H), 6.90 (d, *J* = 10 Hz, 2H), 6.78 (d, *J* = 10 Hz, 1H), 5.78 (s, 1H), 5.14 (s, 2H), 2.10-1.60 (m, 7H); **^{13}C** (151 MHz, DMSO-d_6): δ 162.0, 159.6, 156.2, 152.7, 136.2, 135.3, 134.3, 132.7, 130.3, 130.0, 128.0, 127.9. 127.0, 122.8, 122.7, 119.3, 115.3, 114.9, 112.1, 69.6, 69.3, 50.6, 45.6, 14.5; **HRMS (ESI)**: Calcd for $C_{28}H_{24}BrClN_6O_3$ (m/z) $[M-H]^-$ 605.0704 $[M+2-H]^-$ 607.0683, found $[M-H]^-$ 605.0723 $[M+2-H]^-$ 607.0704.

*4.2.7.22. 3-((1-(4-((2-Bromobenzyl)oxy)phenyl)-1H-tetrazol-5-yl)(pentylamino)methyl)-6-chloro-1H-indole-2-carboxylic acid **2.22***

Ester **3.22** (0.372 g, 0.57 mmol), LiOH (0.137 g, 5.70 mmol). Yield: 57% (0.202 g).

mp: 183 ºC; **NMR**: **^{1}H** (600 MHz, DMSO-d_6): δ 12.31 (s, 1H), 7.70 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.57 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.47 (td, *J* = 7.5, 1.1 Hz, 1H), 7.42 (d, *J* = 1.8 Hz, 1H), 7.38 (d, *J* = 8.8 Hz, 1H), 7.34 (td, *J* = 7.8, 1.7 Hz, 1H), 7.16-7.10 (m, 3H), 7.01-6.94 (m, 2H), 5.17-5.08 (m, 2H), 3.12-3.02 (m, 1H), 3.02-2.92 (m, 1H), 1.83- 1.68 (m, 2H), 1.33-1.18 (m, 4H), 0.84 (t, *J* = 7.0 Hz, 3H); **^{13}C** (151 MHz, DMSO-d_6): δ 161.7, 159.6, 152.3, 136.1, 135.2, 132.7, 130.3, 130.2, 129.7, 128.7, 128.0, 126.7, 125.3, 122.8, 121.9, 121.4, 115.2, 112.3, 69.6, 47.5, 46.2, 28.1, 24.8, 21.6, 13.7; **IR (ATR)** [cm^{-1}]: 3500-2500, 2957, 2871, 1698, 1539, 1521, 1429, 1400, 1346, 1309, 1253, 1212, 1174, 1025, 835, 753, 727; **HRMS (ESI)**: Calcd for $C_{29}H_{28}BrClN_6O_3$ (m/z): $[M-H]^-$ 621.1017, $[M+2-H]^-$ 623.0996, found: $[M-H]^-$ 621.0121, $[M+2-H]^-$ 623.1003; **LC-MS (DAD/ESI)**: t_R = 2.73 min, Calcd for $C_{29}H_{28}BrClN_6O_3$ (m/z): $[M-H]^-$ 621.10, $[M+2- H]^-$ 623.10, found: $[M-H]^-$ 621.20, $[M+2-H]^-$ 623.15.

4.2.7.23. 6-Chloro-3-(((cyclohexylmethyl)amino)(1-(4-((2,6-dichlorobenzyl)oxy)phenyl)-1H-tetrazol-5-yl)methyl)-1H-indole-2-carboxylic acid ***2.23***

Ester **3.23** (0.323 g, 0.48 mmol), LiOH (0.115 g, 4.80 mmol). Yield: 23% (0.069 g).

mp: 227 ºC; **NMR**: **^{1}H** (600 MHz, DMSO-d_6): δ 11.80 (s, 1H), 7.61 (d, J = 8.1 Hz, 2H), 7.54-7.49 (m, 1H), 7.38-7.33 (m, 2H), 7.16 (dt, J = 8.9, 2.0 Hz, 2H), 6.88 (d, J = 8.4 Hz, 1H), 6.06 (s, 1H), 5.32-26 (m, 2H), 2.67-2.57 (m, 1H), 2.48-2.42 (m, 1H), 1.73-1.54 (m, 6H), 1.30-1.03 (m, 3H), 0.88-0.74 (m, 2H); **^{13}C** (151 MHz, DMSO-d_6): δ 167.9, 162.7, 159.8, 154.8, 136.1, 135.1, 131.9, 131.2, 128.9, 128.3, 127.6, 126.1, 124.9, 120.0, 115.3, 111.7, 65.4, 52.2, 47.7, 35.8, 30.43, 30.37, 25.8, 25.3, 25.2; **IR (ATR)** [cm^{-1}]: 3200-2200, 3170, 2921, 2851, 1591, 1518, 1438, 1378, 1333, 1247, 1200, 1021, 841, 794, 785, 768; **HRMS (ESI)**: Calcd for $C_{31}H_{29}Cl_3N_6O_3$ (m/z): $[M-H]^-$ 637.1128, $[M+2-H]^-$ 639.1259, found: $[M-H]^-$ 637.1302, $[M+2-H]^-$ 639.1274; **LC-MS (DAD/ESI)**: t_R = 3.04 min, Calcd for $C_{31}H_{29}Cl_3N_6O_3$ (m/z): $[M-H]^-$ 637.13, $[M+2-H]^-$ 639.13, found: $[M-H]^-$ 637.25, $[M+2-H]^-$ 639.20.

4.2.7.24. 6-Chloro-3-((1-(4-((2,6-dichlorobenzyl)oxy)phenyl)-1H-tetrazol-5-yl)(pentylamino) methyl)-1H-indole-2-carboxylic acid ***2.24***

Ester **3.24** (0.152 g, 0.24 mmol), LiOH (0.057 g, 2.40 mmol). Yield: 53% (0.147 g).

mp: 191 ºC; **NMR**: **^{1}H** (600 MHz, DMSO-d_6): δ 11.77 (s, 1H), 7.62 (d, J =8.3 Hz, 2H), 7.40 (d, J = 8.3 Hz, 2H), 7.36 (t, J = 8.1 Hz, 1H), 7.31 (d, J = 1.2 Hz, 1H), 7.12 (dd, J = 8.3, 1.9 Hz, 1H), 6.96 (s, 1H), 6.92 (d, J = 7.2 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 6.15 (s, 1H), 5.01 (d, J = 11.9 Hz, 1H), 4.90 (d, J = 11.9 Hz, 1H), 2.80-2.69 (m, 1H), 2.67-2.60 (m, 1H), 1.66-1.44 (m, 2H), 1.24-1.13 (m, 4H), 0.79 (t, J = 6.7 Hz, 3H); **^{13}C** (151 MHz, DMSO-d_6): δ 162.8, 158.6, 135.8, 134.9, 133.7, 131.4, 130.5, 129.9, 128.5, 128.1, 125.0, 121.2, 120.0, 118.3, 117.4, 112.3, 111.6, 68.8, 47.4, 45.6, 28.3, 21.7, 13.7; **IR (ATR)** [cm^{-1}]: 3500-2000, 3402, 3078, 2958, 2871, 1683, 1606, 1565, 1517, 1438, 1381, 1304, 1248, 1093, 1001, 834, 770; **HRMS (ESI)**: Calcd for $C_{29}H_{27}Cl_3N_6O_3$ (m/z): $[M-H]^-$ 611.1132, $[M+2-H]^-$ 613.1102, found: $[M-H]^-$ 613.1126, $[M+2-H]^-$ 613.1103; **LC-MS (DAD/ESI)**: t_R = 2.78 min, Calcd for $C_{29}H_{27}Cl_3N_6O_3$ (m/z): $[M-H]^-$ 611.11, $[M+2-H]^-$ 613.11, found: $[M-H]^-$ 611.20, $[M+2-H]^-$ 613.20.

4.2.7.25. 3-((1-(3-((4-Bromobenzyl)oxy)phenyl)-1H-tetrazol-5-yl)((cyclohexylmethyl)amino) methyl)-6-chloro-1H-indole-2-carboxylic acid ***2.25***

Ester **3.25** (0.282 g, 0.42 mmol), LiOH (0.100 g, 4.20 mmol). Yield: 29% (0.078 g).

mp: 210-211 ºC; **NMR**: **^{1}H** (600 MHz, DMSO-d_6): δ 11.80 (s, 1H), 7.63 (dt, *J*= 8.4, 1.8 Hz, 2H), 7.44-7.37 (m, 3H), 7.33 (d, *J* = 1.8 Hz, 1H), 7.15 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.11 (s, 1H), 6.99 (s, 1H), 6.95 (d, *J* = 7.7 Hz, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 6.08 (s, 1H), 5.02 (d, *J* = 11.9 Hz, 1H), 4.92 (d, *J* = 11.9 Hz, 1H), 2.67-2.56 (m, 1H), 2.47-2.40 (m, 1H), 1.74-1.51 (m, 6H), 1.19-1.02 (m, 3H), 0.88-0.72 (m, 2H); **^{13}C** (151 MHz, DMSO-d_6): δ 162.6, 158.6, 135.8, 135.1, 133.8, 131.4, 130.5, 129.9, 128.3, 124.9, 121.2, 120.1, 118.3, 117.3, 112.3, 111.6, 68.9, 52.4, 47.9, 35.9, 30.5, 30.4, 25.8, 25.3, 25.2; **IR (ATR)** [cm^{-1}]: 3500-2000, 3170, 2926, 2853, 1682, 1607, 1532, 1489, 1447, 1337, 1330, 1231, 1158, 1070, 1011, 804; **HRMS (ESI)**: Calcd for $C_{31}H_{30}BrClN_6O_3$ (m/z): $[M-H]^-$ 647.1173, $[M+2-H]^-$ 349.1153, found: $[M-H]^-$ 647.1178, $[M+2-H]^-$ 649.1151; **LCMS (DAD/ESI)**: t_R = 3.11 min, Calcd for $C_{31}H_{30}BrClN_6O_3$ (m/z): $[M-H]^-$ 647.12, $[M+2-H]^-$ 649.12, found: $[M-H]^-$ 647.25, $[M+2-H]^-$ 649.20.

*4.2.7.26. 3-((1-(3-((4-bromobenzyl)oxy)phenyl)-1H-tetrazol-5-yl)(pentylamino)methyl)-6-chloro-1H-indole-2-carboxylic acid **2.26***

Ester **3.26** (0.384 g, 0.59 mmol), LiOH (0.142 g, 5.90 mmol). Yield: 35% (0.127 g).

mp: 197 ºC; **NMR**: **^{1}H** (600 MHz, DMSO-d_6): δ 11.76 (s, 1H), 7.62 (dt, *J* = 8.4, 1.7 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.36 (t, *J* = 8.1 Hz, 1H), 7.31 (d, *J* = 1.8 Hz, 1H), 7.11 (dd, *J* = 8.4 1.9 Hz, 1H), 7.08-6.99 (m, 1H), 6.92 (d, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 8.5 Hz, 1H), 6.15 (s, 1H), 5.01 (d, *J* = 11.9 Hz, 1H), 4.90 (d, *J* = 11.9 Hz, 1H), 2.80-2.69 (m, 1H), 2.67-2.59 (m, 1H), 1.67-1.44 (m, 3H), 1.25-1.13 (m, 4H), 0.79 (t, *J* = 7.0 Hz, 3H); **^{13}C** (151 MHz, DMSO-d_6): δ 162.8, 158.6, 154.7, 135.8, 134.9, 133.7, 131.4, 130.5, 129.9, 128.5, 128.1, 125.0, 121.2, 120.0, 118.3, 117.4, 112.3, 111.6, 68.8, 47.5, 45.6, 28.3, 26.8, 21.7, 13.7; **IR (ATR)** [cm^{-1}]: 3200-2000, 3170, 2957, 2929, 2859, 1605, 1526, 1490, 1466, 1428, 1410, 1389, 1334, 1280, 1259, 1225, 1194, 1012, 896, 790, 687; **HRMS (ESI)**: Calcd for $C_{29}H_{28}BrClN_6O_3$ (m/z): $[M-H]^-$ 621.1017, $[M+2-H]^-$ 623.0996, found: $[M-H]^-$ 621.1017, $[M+2-H]^-$ 623.0999; **LC-MS (DAD/ESI)**: t_R = 2.87 min, Calcd for $C_{29}H_{28}BrClN_6O_3$ (m/z): $[M-H]^-$ 621.10, $[M+2-H]^-$ 623.10, found: $[M-H]^-$ 621.20, $[M+2-H]^-$ 623.20.

*4.2.7.27. 6-Chloro-3-(((cyclohexylmethyl)amino)(1-(4-((2-fluorobenzyl)oxy)benzyl)-1H-tetrazol-5-yl)methyl)-1H-indole-2-carboxylic acid **2.27***

Ester **3.27** (0.268 g, 0.42 mmol), LiOH (0.100 g, 4.20 mmol). Yield: 25% (0.063 g).

mp: 189 ºC; **NMR**: **^{1}H** (600 MHz, DMSO-d_6): δ 11.85 (s, 1H), 7.54 (td, *J* = 7.6, 1.6 Hz, 1H), 7.45-7.39 (m, 1H) 7.38 (d, *J* = 1.8 Hz, 1H), 7.31 (s, 1H), 7.28-7.19 (m, 2H), 7.03 (d, *J* = 8.6 Hz, 2H), 6.97-6.89 (m, 3H), 6.29 (s, 1H), 5.68 (d, *J* = 15.3 Hz, 1H), 5.63 (d, *J* = 15.3 Hz,

1H), 5.10 (s, 2H), 2.43-2.37 (m, 1H), 1.76-1.56 (m, 5H), 1.55-1.46 (m, 1H), 1.20-1.03 (m, 3H), 0.92-0.75 (m, 2H); **^{13}C** (151 MHz, DMSO-d_6): δ 150.0, 148.1, 146.5, 145.0, 122.2, 117.6, 117.5, 117.4, 117.3, 116.0, 115.4, 113.5, 111.5, 111.5, 110.6, 110.5, 107.1, 102.4, 102.3, 101.7, 98.8, 50.5, 50.5, 39.4, 36.6, 34.3, 23.0, 17.4, 17.4, 12.8, 12.2, 12.2; **IR (ATR)** [cm^{-1}]: 3500-2200, 3418, 3213, 2928, 2853, 1614, 1588, 1513, 1493, 1455, 1377, 1331, 1233, 1176, 1103, 1064, 1013, 801, 758; **HRMS (ESI)**: Calcd for $C_{32}H_{32}ClFN_6O_3$ (m/z): $[M-H]^-$ 601.2130, $[M+2-H]^-$ 603.2101, found: $[M-H]^-$ 601.2138, $[M+2-H]^-$ 603.2124; **LC-MS (DAD/ESI)**: t_R = 2.50 min, Calcd for $C_{32}H_{32}ClFN_6O_3$ (m/z): $[M-H]^-$ 601.21, $[M+2-H]^-$ 603.21, found; $[M-H]^-$ 601.35, $[M+2-H]^-$ 603.30.

*4.2.7.28. 6-Chloro-3-((1-(4-((2-fluorobenzyl)oxy)benzyl)-1H-tetrazol-5-yl)(pentylamino) methyl)-1H-indole-2-carboxylic acid **2.28***

Ester **3.28** (0.156 g, 0.26 mmol), LiOH (0.062 g, 2.60 mmol). Yield: 25% (0.038 g).

mp: 168 ºC; **NMR**: **^{1}H** (600 MHz, DMSO-d_6): δ 11.87 (s, 1H), 7.54 (td, J = 7.6, 1.6 Hz, 1H), 7.46-7.39 (m, 1H), 7.37 (d, J = 1.9 Hz, 1H), 7.30-7.21 (m, 3H), 6.99 (d, J = 8.6 Hz, 2H), 6.93 (dd, J = 8.7, 1.8 Hz, 1H), 6.90 (s, J = 8.7 Hz, 2H), 6.43 (s, 1H), 5.67 (d, J = 15.3 Hz, 1H), 5.60 (d, J = 15.3 Hz, 1H), 5.09 (s, 2H), 2.78-2.67 (m, 1H), 2.67-2.55 (m, 1H), 1.62-1.44 (m, 2H), 1.29-1.13 (m, 4H), 0.81 (t, J = 6.9 Hz, 3H); **^{13}C** (151 MHz, DMSO-d_6): δ 163.2, 161.4, 159.4, 158.1, 153.7, 135.2, 130.7, 130.7, 130.5, 130.5, 129.1, 128.3, 126.5, 124.6, 124.6, 124.6, 123.7, 123.6, 121.0, 120.2, 115.5, 115.4, 114.7, 111.9, 63.6, 63.6, 49.7, 46.9, 45.8, 28.4, 26.8, 21.8, 13.8; **IR (ATR)** [cm^{-1}]: 3449, 3200-2200, 2956, 2870, 1618, 1588, 1547, 1514, 1455, 1422, 1367, 1331, 1246, 1176, 1020, 804, 783, 755; **HRMS (ESI)**: Calcd for $C_{30}H_{30}ClFN_6O_3$ (m/z): $[M-H]^-$ 575.1974, $[M+2-H]^-$ 577.1944, found: $[M-H]^-$ 575.1970, $[M+2-H]^-$ 577.1960; **LC-MS (DAD/ESI)**: t_R = 2.56 min, Calcd for $C_{30}H_{30}ClFN_6O_3$ (m/z): $[M-H]^-$ 575.20, $[M+2-H]^-$ 577.19, found:$[M-H]^-$ 575.30, $[M+2-H]^-$ 577.25.

*4.2.7.29. 6-Chloro-3-((1-(4-((2-chlorobenzyl)oxy)benzyl)-1H-tetrazol-5-yl) ((cyclohexylmethyl)amino)methyl)-1H-indole-2-carboxylic acid **2.29***

Ester **3.29** (0.285 g, 0.44 mmol), LiOH (0.105 g, 4.40 mmol). Yield: 56% (0.151 g).

mp: 193 ºC; **NMR**: **^{1}H** (600 MHz, DMSO-d_6): δ 11.87 (s, 1H), 7.59-7.56 (m, 1H), 7.53-7.50 (m, 1H), 7.41 (m, 3H), 7.31 (s, 1H), 7.04 (d, J = 8.6 Hz, 2H), 6.94 (dd, J = 8.8, 1.8 Hz, 1H), 6.92 (d, J = 8.7 Hz, 1H), 6.30 (s, 1H), 5.69 (d, J = 15.3 Hz, 1H), 5.64 (d, J = 15.4 Hz, 1H), 5.11 (s, 2H), 2.57-2.51 (m, 1H), 2.43-2.38 (m, 1H), 1.76-1.43 (m, 6H), 1.19-0.99 (m, 3H), 0.91-0.74 (m, 2H); **^{13}C** (151 MHz, DMSO-d_6): δ 163.1, 158.0, 135.3, 134.1, 132.6, 130.1,

130.0, 129.4, 129.1, 128.5, 127.4, 126.6, 124.6, 120.2, 114.8, 111.9, 67.0, 52.5, 49.7, 47.4, 36.1, 30.5, 30.5, 28.5, 25.3, 25.2; **IR (ATR)** [cm^{-1}]: 3500-2500, 2408, 314, 2928, 2853, 1613, 1513, 1443, 1376, 1331, 1245, 1178, 1061, 1033, 801, 751; **HRMS (ESI)**: Calcd for $C_{32}H_{32}Cl_2N_6O_3$ (m/z): $[M-H]^-$ 617.1835, $[M+2-H]^-$ 619.1805, found: $[M-H]^-$ 617.1824, $[M+2-H]^-$ 619.1799; **LC-MS (DAD/ESI)**: t_R = 2.60 min, Calcd for $C_{32}H_{32}Cl_2N_6O_3$ (m/z): $[M-H]^-$ 617.18, $[M+2-H]^-$ 619.30, found: $[M-H]^-$ 617.30, $[M+2-H]^-$ 619.30.

4.2.7.30. 6-Chloro-3-((1-(4-((2-chlorobenzyl)oxy)benzyl)-1H-tetrazol-5-yl)(pentylamino) methyl)-1H-indole-2-carboxylic acid ***2.30***

Ester **3.30** (0.240 g, 0.39 mmol), LiOH (0.094 g, 3.90 mmol). Yield: 60% (0.140 g).

mp: 183-184 ºC; **NMR**: **^{1}H** (600 MHz, DMSO-d_6): δ 11.85 (s, 1H), 7.59-7.56 (m, 1H), 7.53-7.50 (m, 1H), 7.42-7.36 (m, 3H), 7.25 (s, 1H), 7.00 (d, *J* = 8.6 Hz, 2H), 6.93 (dd, *J* = 8.7, 1.8 Hz, 1H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.41 (s, 1H), 5.68 (d, *J* = 15.3 Hz, 1H), 5.60 (d, *J* = 15.3 Hz, 1H), 5.11 (s, 2H), 2.76-2.67 (m, 1H), 2.66-2.58 (m, 1H), 1.60-1.43 (m, 2H), 1.28-1.12 (m, 4H), 0.81 (t, *J* = 7.0 Hz, 3H); **^{13}C** (151 MHz, DMSO-d_6): δ 163.1, 158.1, 135.2, 134.1, 132.6, 130.1, 129.9, 129.4, 129.1, 128.3, 127.4, 126.5, 124.6, 120.2, 114.7, 111.9, 67.0, 49.7, 46.9, 45.8, 28.4, 26.8, 21.7, 13.7; **IR (ATR)** [cm^{-1}]: 3500-2500, 2290, 2193, 2957, 2871, 1613, 1539, 1513, 1441, 1376, 1331, 1245, 1178, 1060, 1033, 802, 752; **HRMS (ESI)**: Calcd for $C_{30}H_{30}Cl_2N_6O_3$ (m/z): $[M-H]^-$ 591.1678, $[M+2-H]^-$ 593.1649, found: $[M-H]^-$ 591.1689, $[M+2-H]^-$ 593.1663; **LC-MS (DAD/ESI)**: t_R = 2.60 min, Calcd for $C_{30}H_{30}Cl_2N_6O_3$ (m/z): $[M-H]^-$ 591.17, $[M+2-H]^-$ 593.16, found: $[M-H]^-$ 691.25, $[M+2-H]^-$ 593.25.

4.2.7.31. 3-((1-(4-((2-Bromobenzyl)oxy)benzyl)-1H-tetrazol-5-yl)((cyclohexylmethyl)amino) methyl)-6-chloro-1H-indole-2-carboxylic acid ***2.31***

Ester **3.31** (0.291 g, 0.42 mmol), LiOH (0.101 g, 4.20 mmol). Yield: 47% (0.132 g).

mp: 185 ºC; **NMR**: **^{1}H** (600 MHz, DMSO-d_6): δ 12.21 (s, 1H), 7.68 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.55 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.43 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.39 (d, *J* = 1.8 Hz, 1H), 1.31 (td, *J* = 7.8, 1.7 Hz, 1H), 7.19 (s, 1H), 6.99 (dd, *J* = 8.8, 1.8 Hz, 1H), 6.87 (s, 2H), 6.76 (s, 2H), 5.56 (d, *J* = 15.4 Hz, 1H), 5.44 (d, *J* = 14.6 Hz, 1H), 5.07-5.00 (m, 2H), 2.74 (s, 1H), 2.68 (s, 1H), 1.79-1.55 (m, 6H), 1.33-1.07 (m, 3H), 0.93-0.77 (m, 2H); **^{13}C** (151 MHz, DMSO-d_6): δ 162.6, 157.7, 135.6, 132.5, 130.0, 130.0, 129.0, 128.6, 127.8, 125.6, 123.8, 122.6, 121.4, 120.7, 114.3, 112.0, 58.9, 52.3, 49.9, 47.5, 39.9, 30.1, 25.5, 25.0; **IR (ATR)** [cm^{-1}]: 3500-2200, 2928, 2852, 1688, 1613, 1544, 1513, 1437, 1378, 1246, 1178, 1025, 803, 749; HRMS (ESI): Calcd for $C_{32}H_{32}BrClN_6O_3$ (m/z): $[M-H]^-$ 661.1330, $[M+2-H]^-$ 663.1309,

found: $[M-H]^-$ 661.1328, $[M+2-H]^-$ 663.1319; **LC-MS (DAD/ESI)**: t_R = 2.85 min, Calcd for $C_{32}H_{32}BrClN_6O_3$ (m/z): $[M-H]^-$ 661.13, $[M+2-H]^-$ 663.13, found: $[M-H]^-$ 661.30, $[M+2-H]^-$ 663.25.

*4.2.7.32. 3-((1-(4-((2-Bromobenzyl)oxy)benzyl)-1H-tetrazol-5-yl)((4-chlorobenzyl)amino) methyl)-6-chloro-1H-indole-2-carboxylic acid **2.32***

Ester **3.32** (0.297 g, 0.41 mmol), LiOH (0.098 g, 4.10 mmol). Yield: 79% (0.225 g).

mp: 194 ºC; **NMR**: **^{1}H** (600 MHz, DMSO-d_6): δ 11.94 (s, 1H), 7.69 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.66 (s, 1H), 7.57 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.45-7.40 (m, 2H), 7.35-7.30 (m, 3H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.01 (dd, *J* = 8.7, 1.9 Hz, 1H), 6.94 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.23 (s, 1H), 5.60 (d, *J* = 15.3 Hz, 1H), 5.50 (d, *J* = 15.3 Hz, 1H), 5.10 (s, 2H), 3.73 (d, *J* = 13.8 Hz, 1H), 3.65 (d, *J* = 13.8 Hz, 1H); **^{13}C** (151 MHz, DMSO-d_6): δ 163.3, 158.5, 155.6, 136.6, 136.2, 133.1, 132.2, 130.7, 129.6, 129.5, 128.6, 128.4, 127.3, 124.9, 123.3, 123.2, 120.8, 115.3, 112.4, 69.6, 50.0, 49.7, 46.9, 31.2; IR (ATR) [cm^{-1}]: 3500-2200, 3405, 3063, 1612, 1513, 1436, 1377, 1330, 1245, 1178, 1016, 799, 749; **HRMS (ESI)**: Calcd for $C_{32}H_{25}BrCl_2N_6O_3$ (m/z): $[M-H]^-$ 689.0470, $[M+2-H]^-$ 691.0450, found: $[M-H]^-$ 689.0461, $[M+2-H]^-$ 691.0447; **LC-MS (DAD/ESI)**: t_R = 2.56 min, Calcd for $C_{32}H_{25}BrClN_6O_3$ (m/z): $[M-H]^-$ 689.05, $[M+2-H]^-$ 691.04, found: $[M-H]^-$ 689.20, $[M+2-H]^-$ 691.20.

*4.2.7.33. 3-((1-(4-((2-Bromobenzyl)oxy)benzyl)-1H-tetrazol-5-yl)(pentylamino)methyl)-6-chloro-1H-indole-2-carboxylic acid **2.33***

Ester **3.33** (0.340 g, 0.51 mmol), LiOH (0.122 g, 5.10 mmol). Yield: 67% (0.202 g).

mp: 173 ºC; **NMR**: **^{1}H** (600 MHz, DMSO-d_6): δ 12.03 (s, 1H), 7.68 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.56 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.43 (td, *J* = 7.5, 1.1 Hz, 1H), 7.38 (d, *J* = 1.9 Hz, 1H), 7.31 (td, *J* = 7.8, 1.7 Hz, 1H), 7.22 (s, 1H), 6.96 (dd, *J* = 8.7, 1.8 Hz, 1H), 6.89 (s, 2H), 6.81 (d, *J* = 8.0 Hz, 2H), 6.62 (s, 1H), 5.62 (d, *J* = 15.4 Hz, 1H), 5.51 (d, *J* = 15.2 Hz, 1H), 5.06, (s, 2H), 2.80 (s, 1H), 2.72 (s, 1H), 1.65-1.50 (m, 2H), 1.26-1.17 (m, 4H), 3.07 (t, *J* = 7.0 Hz, 3H); **^{13}C** (151 MHz, DMSO-d_6): δ 162.9, 158.0, 135.7, 135.5, 132.7, 130.17, 130.15, 128.8, 127.9, 126.1, 124.2, 122.8, 121.2, 120.6, 114.6, 112.0, 69.1, 49.9, 47.0, 45.9, 30.7, 28.3, 21.7, 13.7; **IR (ATR)** [cm^{-1}]: 3500-2500, 2957, 2870, 1699, 1613, 1513, 1438, 1378, 1331, 1245, 1178, 1025, 802, 749; **HRMS (ESI)**: Calcd for $C_{30}H_{30}BrClN_6O_3$ (m/z): $[M-H]^-$ 635.1173, $[M+2-H]^-$ 637.1153, found: $[M-H]^-$ 635.1183, $[M+2-H]^-$ 637.1163; **LC-MS (DAD/ESI)**: t_R = 2.59 min, Calcd for $C_{30}H_{30}BrClN_6O_3$ (m/z): $[M-H]^-$ 635.12, $[M+2-H]^-$ 637.12, found: $[M-H]^-$ 635.30, $[M+2-H]^-$ 637.25.

ACCESSION CODES

Crystallographic data for structures presented in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication: CCDC 1449789 (**3.26**) and CCDC 1491066 (**12a**). Copy of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

SUPPORTING INFORMATION

Supplementary data associated with this article can be found in the online version, at……and consists of FP data, details of the small molecules crystallographic experiment and structure determination, exemplary copies of spectra of final compounds and supplementary references (i-xiii)

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NOTES

The authors declare no competing financial interest.

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Figure 1. VS-based discovery of tetrazoles as potent p53 MDM2 antagonists. (A) Schematic of the VS method for discovering new scaffolds based on template **1** from PDB ID 4MDN; (B) 2D structure of **1** and imposed pharmacophore characters; (C) ANCHOR.QUERY derived 3D four point pharmacophore model of **1**: anchor in yellow, aromatic in pink, hydrophobe in green; (D) one-pot MCR synthesis of tetrazole scaffold; (E) stereoview of alignment of small molecule **1** (red lines) – MDM2 complex (grey lines) 4MDN with a predicted tetrazole derivative (no 9 in ranking, blue sticks), hydrogen bond to backbone Leu54 is indicated with yellow dotted line.

Scheme 1. Retrosynthetic scheme for the tetrazole derivatives.

Scheme 2. A general scheme for preparation of isocyanides 8a-e, based on anilines and 4-chlorobenzylamine.

Scheme 3. A general scheme for preparation of isocyanides **12a-e**, based on benzyloxyanilines.

Scheme 4. A general scheme for preparation of isocyanides **17a-c**, based on *N*-(benzyloxybenzyl) formamides.

Figure 2. Molecular geometry observed in the crystal structures of **12a**, showing the atom labelling scheme. Displacement ellipsoids of non-hydrogen atoms are drawn at the 50% probability level. H atoms are presented as small spheres with an arbitrary radius.

Scheme 5. The general synthetic scheme for the tetrazole derivatives.

Table 2. Yields and activities of tetrazole-based inhibitors of p53-MDM2/X interaction.

Figure 3. Crystal structure of compound **3.26** (racemic form) showing the asymmetric unit. A single water molecule has co-crystallised with the compound. Displacement ellipsoids of non-hydrogen atoms are shown at the 30% probability level. H atoms are presented as small spheres with an arbitrary radius.

Figure 4. NMR spectra for the ^{1}H-^{15}N HSQC-based titration experiment of MDM2 with **2.27**. Red: reference MDM2 alone; blue: molar ratio protein/ligand 1:0.5; green: overtitrated MDM2 (the ratio protein/ligand 1:2). Enlarged fragments show resonance peak doubling.

Highlights

- VS-based discovery of novel 1,5-disubstituted tetrazoles as MDM2 antagonists.
- >60 compounds were synthesized using a 2-step MCR chemistry.
- FP-monitored SAR analysis allowed for the fast optimization up to low nM potency.
- Compound **2.27** inhibited the MDM2/p53 interaction with a K_i of 20 nM.
- The affinity and the rough binding mode were also confirmed using 2D NMR.

Graphical abstract