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Synthesis, biological evaluation, X-ray molecular structure and molecular docking studies of RGD mimetics containing 6-amino-2,3-dihydroisoindolin-1-one fragment as ligands of integrin $\alpha_{IIb}\beta_3$

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ABSTRACT

A series of novel RGD mimetics containing phthalimidine fragment was designed and synthesized. Their antiaggregative activity determined by Born's method was shown to be due to inhibition of fibrinogen binding to $\alpha_{IIb}\beta_3$. Molecular docking of RGD mimetics to $\alpha_{IIb}\beta_3$ receptor showed the key interactions in this complex, and also some correlations have been observed between values of biological activity and docking scores. The single crystal X-ray data were obtained for five mimetics.

1. Introduction

Thrombosis is the most important pathological process underlying many cardiovascular diseases, which are responsible for elevated mortality worldwide.[1] The use of ADP and thromboxane inhibition does not preclude the formation of thrombus, because platelets can still be activated by other mechanisms. It gave a stimulus to the development of an entirely separate class of antiplatelet drugs - fibrinogen receptor (integrin $\alpha_{IIb}\beta_3$) antagonists. During the platelet activation process, the surface of the platelet transforms its shape to expose the fibrinogen receptors. These receptors bind to fibrinogen and Von Willebrand factor, resulting in clot formation and clot adherence, respectively.[2] Binding of fibrinogen to $\alpha_{IIb}\beta_3$ on platelets is responsible for securing aggregated platelets to one another. Thus, blocking these receptors prevents platelet aggregation regardless of the activation pathway.[3,4] Inhibitors of $\alpha_{IIb}\beta_3$ have proven useful in reducing the risk of periprocedural MI and urgent target vessel revascularization during catheterization and have claimed a place in therapy for these indications.[5] There exist three different $\alpha_{IIb}\beta_3$ inhibitors approved for use: abciximab (Eli Lilly & Company, Indianapolis, Indiana), eptifibatide (Schering-Plough, Kenilworth, New Jersey), and tirofiban (Medicure, Winnipeg, Canada).[6] However, the current agents have several limitations, including the need for intravenous infusion and, most important, the induction of thrombocytopenia in some patients.[7] These limitations of above mentioned drugs give evidence of need in new $\alpha_{IIb}\beta_3$ inhibitors.

Although, more frequently the design of $\alpha_{IIb}\beta_3$ antagonists is based on the mimicking of Arg–Gly–Asp (RGD) sequence, alternative approach represents the use of dodecapeptide sequence.[8,9] The main binding sites of RGD sequence are δ-guanidine of arginine and β-carboxylic group of aspartyl, and for the dodecapeptide sequence - lysine amino group and aspartyl carboxylic group, correspondingly. Similarity of these two approaches is evident.

In our recent publication, the use of phthalimidine scaffolds for designing potent integrin $\alpha_{IIb}\beta_3$ antagonists has been demon-

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strated.[10] Herein, we describe the optimization of the novel Arg surrogates for obtaining RGD mimetics active inhibitors.

This article describes the synthesis of new RGD mimetics containing phthalimidine (2,3-dihydroisoindol-1-one) fragment and study of their antiaggregative properties. We also discuss the possibility to use the residues of 4-piperidineacetic, 4-piperidine-4-yl-butyric, 4-piperidine-4-yl-benzoic, 4-piperazine-1-yl-benzoic, 1,2,3,4-tetrahydroisoquinoline-7-carboxylic, and 3-piperazine-1-yl-benzoic acids as Arg surrogates for RGD mimetics design.

2. Results and discussion

2.1. Synthesis

Description of the synthesis of 6-amino-2,3-dihydroisoindolin-1-one building blocks **5a–d** was given in a previous report (Scheme 1). The key step was the formation of the 6-amino-2,3-dihydroisoindolin-1-one building blocks **5a–d** by reduction of phthalimides **1a–d** using zinc amalgam. As a result of nitration of the compounds **2a–d**, there were obtained nitro-derivatives **3a–d** followed by their reduction by H_2/Pd(C). Regioselectivity of nitration reaction is expected. The X-ray analysis data obtained for the compound **5b** is a confirmation.

The view of molecular structure of **5b** is shown in Figure 1. The molecule has a rather flat skeleton as evidenced by the dihedral angle of 8.8° between the planes of almost coplanar nonhydrogen atoms of methylpropionate chain and phthalimide core. The geometric parameters of planar aminophthalimide core are in line with the related 3-(1-oxo-1,3-dihydroisoindol-2-yl)propionic acid,[11] but these molecules differ by the molecular shape as far as the latter one has an angular conformation.

Homologation of Boc protected piperidine-4-carboxylic acid gave the 1-Boc-4-piperidineacetic acid (**6**), by a similar method reported in the literature.[12] Initial Boc derivatives of the 4-piperidine-4-yl-butyric (**7**)[13] and 4-piperidine-4-yl-benzoic (**8**)[14] acids have been synthesized using previously published methods. Isomeric methyl esters of the 4-piperazine-4-yl-benzoic (**9a**)[15] and 3-piperazine-4-yl-benzoic (**9b**) acids were made using methyl esters of aminobenzoic acids and bis-(2-chloroethyl)amine. Boc-protection of the compounds **9a** and **9b** with Boc_2O resulted in the methyl esters **10a** and **10b**, respectively. Subsequent saponification of ester groups of compounds **10a** and **10b** yielded the target acids **11a,b** (Scheme 2).

Precursor compound **14** was prepared in three steps in contrast to our previously published route for four-steps synthesis.[16] Acylation of 2-acetyl-1,2,3,4-tetrahydroisoquinoline (**12**) with oxalyl chloride at the presence of aluminum chloride gave 1-acetyl-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid (**13**). Further

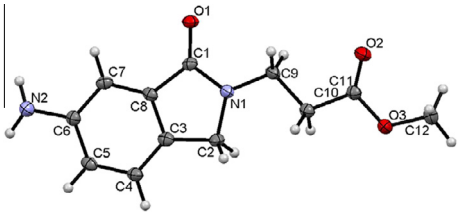
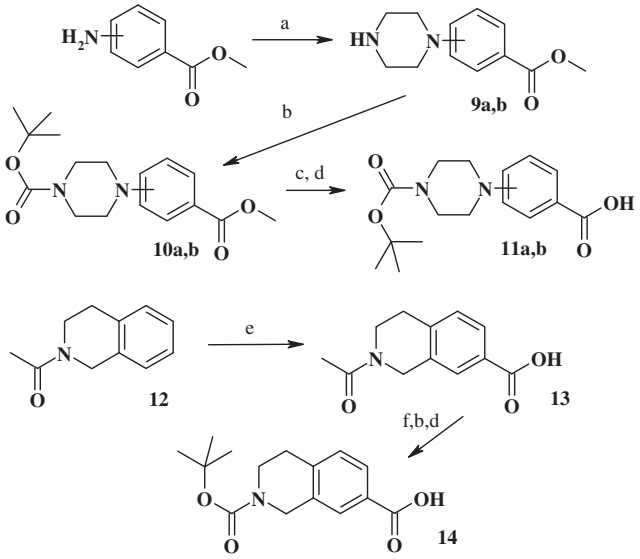


Figure 1. View of **5b**. ORTEP diagram with the numbering scheme. The thermal ellipsoids are of 50% probability level, with hydrogens as spheres of arbitrary diameter.

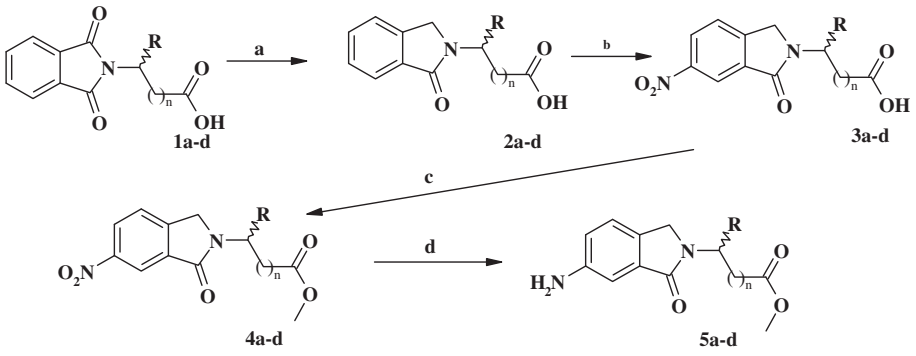


Scheme 2. Synthesis of the acids **11** and **14**. Reagents: (a) HCl*NH(CH_2CH_2Cl)$_2$, K_2CO_3, BuOH, reflux, ≈177 h; (b) Boc_2O, room temperature, overnight; (c) NaOH, H_2O 40 °C, 6 h; (d) HCl, H_2O; (e) $(COCl)_2$, $AlCl_3$; (f) NaOH, H_2O.

removal of the acetyl group and reaction with Boc_2O resulted in the acid **14** (Scheme 2). The structure of compound **14** has been confirmed by data of X-ray analysis (Fig. 2).

The molecular structure **15** is shown in Figure 2. The molecule has an angular shape with the aza-cycle of the 1,2,3,4-tetrahydroisoquinoline core being in a half-chair conformation with the N1 atom deviating at −0.574(3) Å from the mean plane of cyclic C-atoms, the rms deviation of fitted carbon atoms being 0.056 Å.

Condensation of acids **6–8**, **11a,b** and **14** with amines **5a–d** has been conducted using the HBTU or HATU (Scheme 3). Subsequent saponification of ester groups of the compounds **15a–u** and



Scheme 1. Synthesis of aminophthalimidines. Reagents: (a) Zn (Hg), HCl, reflux, 4 h; (b) HNO_3, H_2SO_4, −5 °C, 6 h; (c) MeOH (H_2SO_4), reflux, 3 h; (d) H_2/Pd (C), MeOH, room temperature, 7 h.

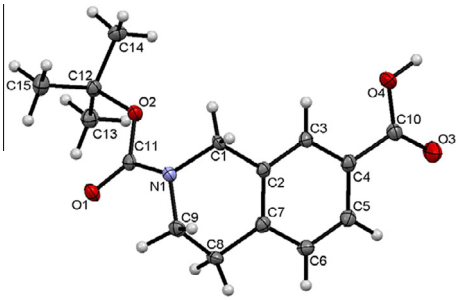


Figure 2. View of **15**. ORTEP diagram with the numbering scheme. The thermal ellipsoids are of 50% probability level, with hydrogens as spheres of arbitrary diameter.

elimination of Boc-protective groups yielded the target mimetics **17a**–**u**. Mimetics **17l**–**q** were obtained only as racemic mixtures in order to reveal potent compounds and to determinate general characteristics of structure–activity relationships.

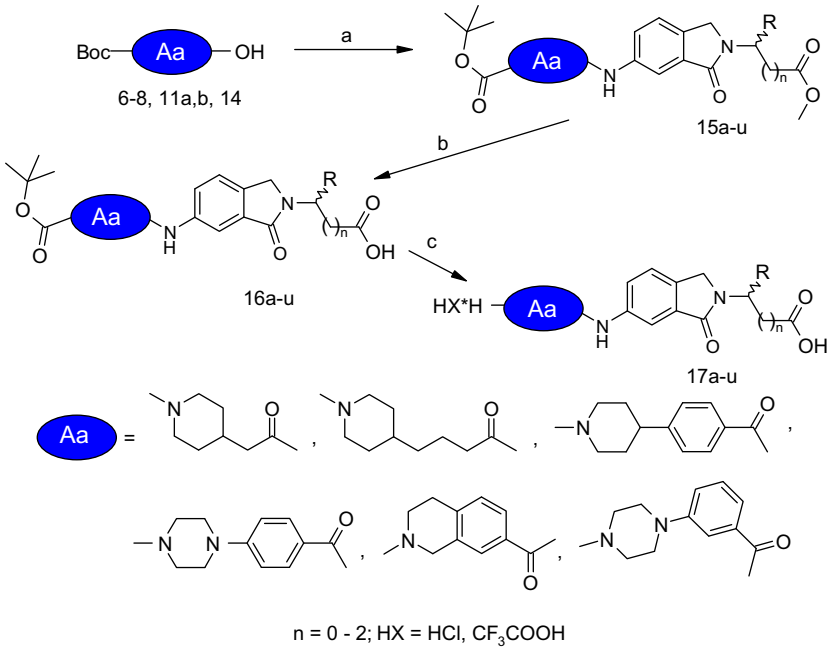
2.2. X-ray structure

Fortunately, single crystals of target compounds were grown from water, and X-ray data were obtained for five mimetics, **17c**,**h**,**i**,**j**,**t**. They were fixed in the solid crystalline state as either trifluoroacetate or chloride salt with the compositions **17c**,**h** and **17i**,**j**,**t**·H_2O. After 2 h of boiling of aqueous solutions of compounds **17c** and **17h** and then their cooling to room temperature, single crystals were grown. They were identified as the hydrates of zwitterionic forms, **17c**-TfaOH·$5H_2O$ and **17h**-TfaOH·$2H_2O$. The ORTEP drawings for the formula units are shown in Figure 3. All the mimetics molecules bear three planar fragments, the benzoyl ring, the 1-oxo-1,3-dihydroisoindolyl core with the equivalent bond lengths being similar within themselves, in the parent **5b** and in the closely related 3-(1-oxo-1,3-dihydroizoindol-2-yl)propionic acid,[11] and the amide bridge between these moieties. The amide bridge is always fixed in the *syn*-conformation with regard to the phthalimidine core and anti-conformation with regard to the benzoyl moieties as the torsion angles O2–C9–N2–C6 and C10–C9–N2–C6 indicate falling in the ranges 0.6(8)–8.7(9)° and 171.1(6)–179(1)°, respectively (Table 1). The molecules differ by mutual orientations of the above-mentioned planar molecular moieties, by the orientation of piperidine or piperazine fragment with respect to the benzoyl moieties, and carboxylic tails with respect to the indolyl core. Moreover, the different mutual arrangement (*cis*- or *trans*-) of the amide and indolyl carbonyl oxygen atoms O1 and O2 should be mentioned. The conformational flexibility and essential variation of cross-molecule distance between the distal cyclic N and carboxylic O-atoms in the wide range 16.297–21.434 Å, Table 1, indicate the possibility to fine tuning substrate-receptor interactions.

2.3. In vitro biology

Functional activity was determined by measuring the inhibition of ADP induced platelet aggregation in human platelet-rich plasma (PRP) by Born's method.[17] Mode of action for some compounds was subsequently revealed in vitro by measuring the ability of compounds to inhibit the binding of fluoresceinisothiocyanate-labeled fibrinogen (FITC-Fg)[18] to $\alpha_{IIb}\beta_3$ (in a suspension of human washed platelets).[19] Experimental data (Table 2) evidently show high affinities of the compounds **17** for $\alpha_{IIb}\beta_3$. RGDS peptide and Tirofiban were used as standard inhibitors.

We first investigated the SAR of compounds **17a**–**e**, containing a fragment of (1-oxo-1,3-dihydroisoindol-2-yl)acetic acid. These compounds showed low in vitro antiaggregative activity, except for the leader of the group, mimetic **17d** containing 4-piperazine-4-yl-benzoyl, as Arg isostere. Homologation of C-terminal template resulted in increased activity for five compounds **17f**–**j** containing the same surrogates of Arg. Here again was the leading mimetic **17i**, containing a residue of 4-piperazine-4-yl-benzoic acid. Leading indicators of antiaggregative activity of compounds containing 4-piperazine-4-yl-benzoyl, forced us to test 3-piperazine-4-yl-benzoyl derivative **17k**. It was found that the compound **17k** was five times less active than its isomer **17i**. Further increase of C-terminal



Scheme 3. Synthesis of RGD mimetics. Reagents: (a) NEt_3, HBTU, **5a**–**d**, room temperature, overnight; (b) 1 M NaOH, H_2O, MeOH, room temperature, overnight, 1 M HCl; (c) CH_2Cl_2, HCl gas, 0 °C, 1 h or CH_2Cl_2, TFA, 0 °C, 2 h.

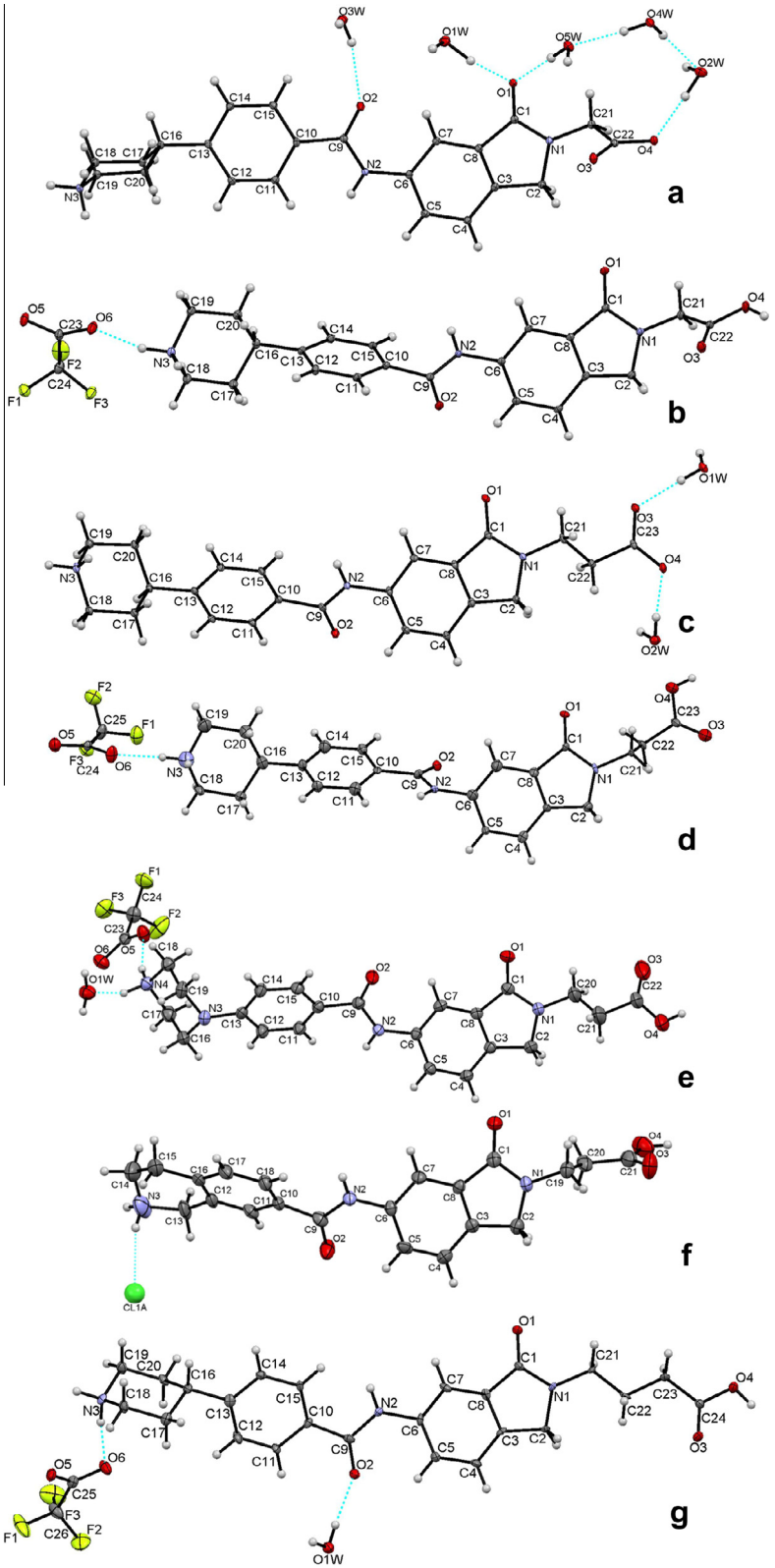


Figure 3. ORTEP diagram with the numbering scheme for **17c**-TfaOH·5H_2O (a), **17c** (b), **17h**-TfaOH·2H_2O (c), **17h** (d), **17i**·H_2O (e), **17j**·H_2O (f), and **18t**·H_2O (g). The thermal ellipsoids are of 30% probability level, with hydrogens as spheres of arbitrary diameter. Only major positions are shown for the disordered fragments.

residue length by another one carbon atom led to a decrease in aggregative properties. Surprise for us was the value of IC_{50} for compound **17r**. Mimetic **17r** was more active than the mimetic **17b**, these two compounds have the same number of atoms between the N- and C-terminals. Finally, replacing C-terminal fragment β-alanine with β-methyl-β-alanine led to compounds **17l–p**.

Table 1
Main geometrical parameters for **17** entities in studied compounds

Compounds	Geometric parameter						
	[a]ϕ_1 (°)	[b]ϕ_2 (°)	[c]ϕ_1 (°)	[d]ϕ_2 (°)	[e]ϕ_3 (°)	[f]ϕ_4(°)	[g]r (Å)
17c-TfaOH·5H_2O	−2.5(3)	176.8(2)	84.87(5)	26.51(8)	7.48(6)	79.1(2)	16.466(2) 18.377(2)
17c	4.4(6)	−174.3(3)	87.5(1)	23.7(2)	39.7(1)	59.7(3)	17.256(5) 18.718(5)
17h-TfaOH·2H_2O	−1.7(4)	175.6(3)	70.53(9)	4.9(2)	45.1(1)	10.3(3)	18.913(3) 19.6857(3)
17h	3(3)	179(1)	61.1(7)	15.3(9)	65.3(4)	9.8(9)	18.05(3) 19.10(3)
17i·H_2O	2.2(4)	−175.3(2)	56.06(8)	22.3(1)	17.3(1)	8.6(6)	16.297(4) 16.885(4)
17j·H_2O	−0.6(8)	−179.5(4)	3.8(3)	29.9(2)	30.9(2)	75.8(2)	16.803(7) 17.091(7)
17t·H_2O	−8.7(9)	171.1(6)	80.2(2)	16.6(3)	15.8(3)	15.5(1)	20.235(7) 21.434(7)

[a] Torsion angle O2–C9–N2–C6.
[b] Torsion angle C10–C9–N2–C6.
[c] Dihedral angle between the average planes through the terminal piperydine/piperazine ring and phenyl ring, C10/C11/C12/C13/C14/C15.
[d] Dihedral angle between the average planes through the phenyl ring, C10/C11/C12/C13/C14/C15 and amide bridge, C10/C9/O2/N2/C6.
[e] Dihedral angle between the average planes through the amide bridge, C10/C9/O2/N2/C6 and phthalimidine core, C1 > C8/N1/O1.
[f] Dihedral angle between the average planes through the phthalimidine core, C1 > C6/N1/O1 and carboxylic group, defined by C,O,O atoms.
[g] Cross-molecule distance between the cyclic N and carboxylic O-atoms.

Effect of CH_3 group is ambiguous. In two cases, antiaggregative activity observed for mimetics containing β-methyl-β-alanine fragment (**17o** and **17q**) was lower than for unsubstituted ones (**17i** and **17k**). As for methylated/unmethylated pairs **17m**/**18g** and **17n**/**17h**, their antiaggregative activities were nearly equal. Positive effect of methyl group was observed only for compounds **17l** and **17p** compared to their unsubstituted analogs **17f** and **17j**, correspondingly. Compound **17p** possessed the highest antiaggregative activity among all compounds synthesized in this study.

2.4. Molecular docking

Molecular docking studies have been performed in order to give a microscopic insight into experimentally observed structure–property relationship. FlexX tool from LeadIT package has been used.[20] The X-ray structure of complex of Tirofiban with headpiece of $\alpha_{IIb}\beta_3$ integrin (2VDM) has been taken from Protein Data Bank.[21] Structure of the pocket has been prepared and four water molecules have been kept in the cavity: two water molecules, coordinated with Mg^{2+} metal ion-dependent adhesive site (MIDAS) of the $\alpha_{IIb}\beta_3$ integrin, and two water molecules coordinated with Asp232 residue of the α_{IIb}-subunit. Investigated compounds have been docked in the prepared pocket. Because the interaction of ligands of $\alpha_{IIb}\beta_3$ integrin with αAsp224 and MIDAS are essential for compound binding and activity, only best poses which follow these requirements have been taken for further analysis.[21]

A reasonable correlation between affinity for $\alpha_{IIb}\beta_3$ and docking score has been observed ($R_{Spearman}$ = 0.72, Fig. 4) for a small subset of compounds for which the activity values were available. Antiaggregative activity poorly correlates with docking score ($R_{Spearman}$ = 0.35). However, exclusion of one outlier (compound **17u**) significantly improves the correlation ($R_{Spearman}$ = 0.52, Fig. 4).

Discovered correlations suggest that docking score can be used for elucidation of antiaggregative activity of the compounds. Thus, higher antiaggregative potency of **17f–j** compared to **17a–e** could be explained by the fact that the former form additional H-bonds to OH-group of Tyr190 or to water molecules connected with αAsp232, whereas the latter cannot form hydrogen bonds to OH-group of αTyr190 due to the steric reasons (Fig. 5, compounds **17e** and **17j**).

Compounds **17s**,**t** resulted from the increase of length of the Asp-mimetic part of **17g**,**h**, are too big compared to the cavity and, therefore they do not interact efficiently with the protein residues (Fig. 5, compounds **17h** and **17t**).The difference between activity of the compounds **17b** and **17r**, which have the same topological length between Asp- and Arg-mimetic parts, can be explained by different protein–ligand interaction patterns. The carboxylic acid group of **18r** is buried deeper in the receptor pocket and interacts with βAsn215 as well as with MIDAS, and carbonyl group of 2,3-dihydroisoindol-1-one moiety forms H-bond with OH-group of αTyr190. On the other hand, carboxylic acid group of **17b** interacts only with MIDAS, whereas carbonyl group of 4-piperidin-4-yl-butanoyl forms H-bond with water molecules coordinated to αAsp232 (Fig. 5, compounds **17b** and **17r**). Comparison of the docking pose of **17i** with that of **17d** shows that **17i** is characterized by bent conformation whereas **18d** adopts almost linear form. Furthermore, **17i** is characterized by higher docking score value compared to **17d** (38.6 vs 36.4).

3. Conclusion

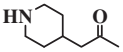
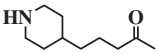
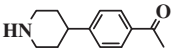
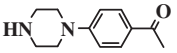
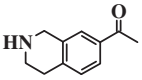
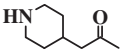
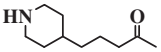
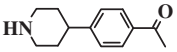
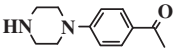
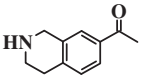
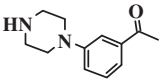
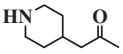
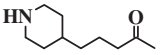
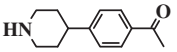
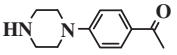
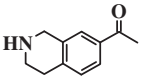
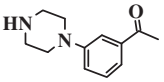
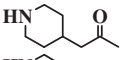
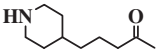
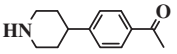
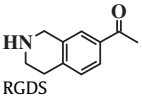
This paper is devoted to rational design of the $\alpha_{IIb}\beta_3$ integrin antagonists. It has been demonstrated that RGD mimetics containing 2,3-dihydroisoindol-1-one can be effifiiciently used as $\alpha_{IIb}\beta_3$ antagonists and platelet aggregation inhibitors through appropriate structural modulation. In particular, modification of the Arg surrogates represents an attractive way of optimizing $\alpha_{IIb}\beta_3$ integrin ligands. It can be summarized that the most preferable structural features for high antiaggregative activity are tetrahydroisoquinoline and β-methyl-β-alanine as Arg and Asp bioisosteres, respectively. Combination of these fragments within the given phthalimidine series leads to the best prospective inhibitor of platelet aggregation. The most active compounds identified display favorable biological properties which are promising for further development of antithrombotics.

4. Experiment

4.1. Chemistry

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded on Bruker AVANCE-II-400 (at 400 MHz for proton), or Bruker Avance DRX 500 (at 500 MHz for proton and 125 MHz for carbon) spectrometers with chemical shifts in ppm with the internal TMS as a standard. Electron ionization (EI) and fast-atom bombardment (FAB) mass spectra were recorded on a VG Analytical VG 70-70EQ instrument. FAB spectra were performed equipped with an argon primary atom beam, and an *m*-nitrobenzyl alcohol matrix was utilized. High-resolution mass spectra (HRMS) were recorded under FAB conditions. The purity was measured by HPLC

Table 2
Biological properties of RGD mimetics **17**, RGDS peptide and Tirofiban

Compounds	HX	Aa	*n*	*R*	IC_{50}, (PRP)[a] (μM)	IC_{50}, (FITC-Fg/$\alpha_{IIb}\beta_3$)[b] (μM)
17a	TFA		0	H	51 ± 11.0	––
17b	TFA		0	H	66.0 ± 9.0	––
17c	TFA		0	H	24.0 ± 3.0	0.27 ± 0.06
17d	TFA		0	H	3.3 ± 0.5	––
17e	HCl		0	H	120.0 ± 20.0	1.2 ± 0.1
17f	TFA		1	H	7.4 ± 1.4	––
17g	TFA		1	H	5.9 ± 0.6	0.0055 ± 0.009
17h	TFA		1	H	9.6 ± 1.9	0.0068 ± 0.0012
17i	TFA		1	H	0.54 ± 0.06	––
17j	HCl		1	H	1.1 ± 0.1	0.0065 ± 0.0005
17k	TFA		1	H	2.7 ± 0.5	––
17l	TFA		1	CH_3	2.7 ± 0.6	––
17m	HCl		1	CH_3	5.4 ± 1.0	0.35 ± 0.03
17n	HCl		1	CH_3	6.2 ± 1.2	––
17o	HCl		1	CH_3	3.74 ± 0.51	0.037 ± 0.08
17p	HCl		1	CH_3	0.086 ± 0.007	0.0065 ± 0.0012
17q	HCl		1	CH_3	62.0 ± 5.0	––
17r	TFA		2	H	1.8 ± 0.3	––
17s	TFA		2	H	51.0 ± 3.0	––
17t	TFA		2	H	410.0 ± 60.0	––
17u	HCl		2	H	330.0 ± 50.0	––
		RGDS			31.0 ± 2.0	13.0 ± 1.6
		Tirofiban			0.032 ± 0.004	0.0024 ± 0.0004

[a] Concentration required to reduce ADP-induced human platelet aggregation response by 50%. The IC_{50} values are expressed as the average of at least three determinations. The average error for the IC_{50} determinations was 15%.

[b] Concentration required to reduce binding of FITC-Fg to $\alpha_{IIb}\beta_3$ on the suspension of washed human platelets by 50%. The IC_{50} values are expressed as the average of at least three determinations. The average error for the IC_{50} determinations was 15%.

conducted on an Shumadzu system (System Controller CBM-20A, two pumps LC-8A and Photo-diode Array detector SPD-M20A) using a Hypersil GOLD 3 μm (4.6 × 150 mm) or Hypersil GOLD aQ 3 μm (4.6 × 150 mm) column. The progress of reactions was monitored by TLC (silica gel 60 F254, Merck).

The compound **11a** was prepared from 4-aminobenzoic acid methyl ester by the procedure. The method of synthesis of **11b** from 3-aminobenzoic acid methyl ester not significantly differ from the procedure for compound **11a**. The acids **7**, **8** and **14** have been synthesized using previously published method.

4.1.1. General procedure for a preparation of compound 2

24.5 g of mossy zinc was amalgamated with 1 g of metallic mercury and 1 M HCl solution (100 ml) in water. The suspension was shaken for 5 min, and then the aqueous layer was discarded. The zinc was covered with 24.5 ml of concentrated HCl and to this was added 0.0488 mol of compound **1**. The mixture was heated to boiling for 0.5 h. At this stage, it is necessary to keep the reaction temperature under control (at rapid foaming, heating was terminated and reaction mixture was shortly cooled externally). After all the compound **1** was dissolved the mixture was boiled under re-

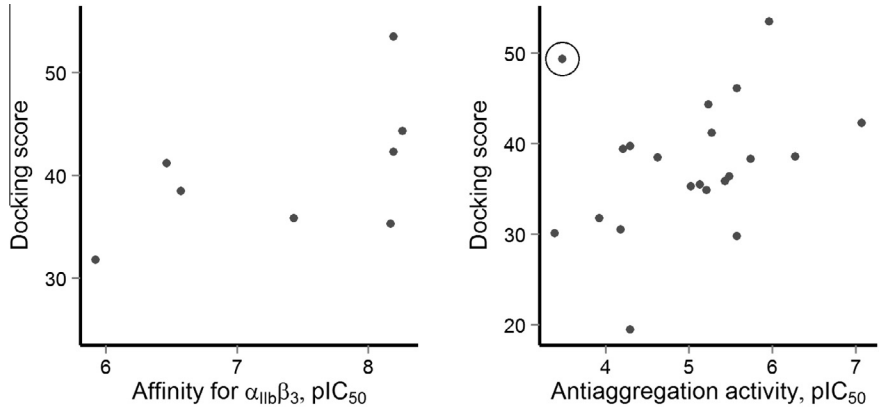


Figure 4. Plots of affinity for $\alpha_{IIb}\beta_3$ of **17c**,**e**,**g**,**h**,**j**,**m**,**o**,**p** and antiaggregative activity of **17a**–**u** against docking score.

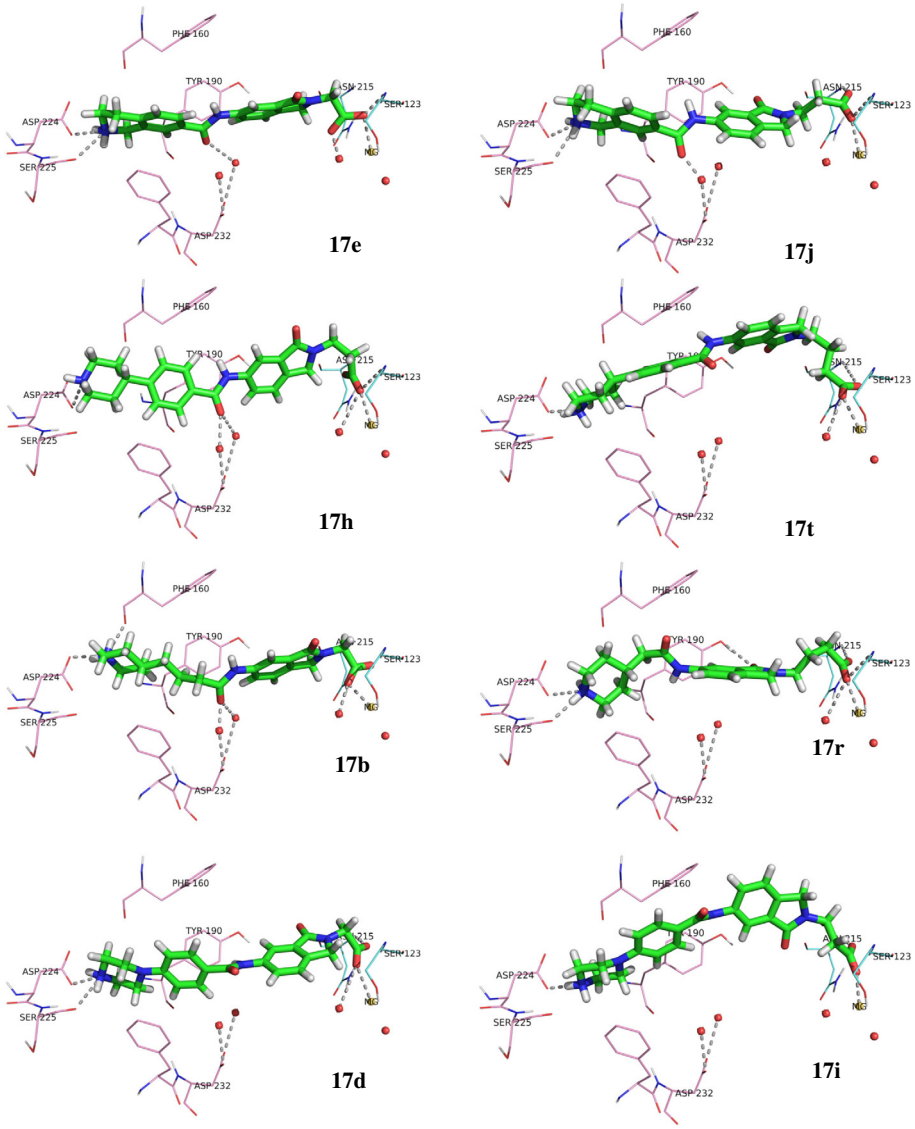


Figure 5. Docking poses and interactions of compounds **17b**,**d**,**e**,**h**–**j**,**r**,**t** inside the $\alpha_{IIb}\beta_3$ receptor cavity.

flux for 4 h. The hot solution was decanted from undissolved zinc and allowed to cool. A white crystalline solid precipitated and was collected. Recrystallization from water to give pure compound **2**.

4.1.1.1. (1-Oxo-1,3-dihydroisoindol-2-yl)acetic acid (2a). Mp = 177–179.5 °C; ^{1}H NMR δ (500 MHz, d_6-DMSO) 4.30 (s, 2H), 4.53 (s, 2H), 7.50–7.53 (m, 1H), 7.56–7.58 (m, 2H), 7.68 (d, J = 7.4 Hz, 1H), 12.93 (s, 1H); MS (EI) m/z: 191.

4.1.1.2. 3-(1-Oxo-1,3-dihydroisoindol-2-yl)propionic acid (2b). Mp = 113–116 °C; ^{1}H NMR δ (500 MHz, d_6-DMSO) 2.62 (t, J = 7.0 Hz, 2H), 3.74 (t, J = 7.0 Hz, 2H), 4.50 (s, 2H), 7.47–7.50 (m, 1H), 7.60 (d, J = 3.6 Hz, 2H), 7.68 (d, J = 7.3 Hz, 1H), 12.34 (br s, 1H); MS (EI) m/z: 205.

4.1.1.3. 3-(1-Oxo-1,3-dihydroisoindol-2-yl)butyric acid (2C). Mp = 205.5–206 °C; ^{1}H NMR δ (500 MHz, d_6-DMSO) 1.28 (d, J = 6.6 Hz, 3H), 2.64 (ddd, J = 31.4, 15.3, 7.3 Hz, 2H), 4.46 (dd, J = 28.4, 17.6 Hz, 2H), 4.62 (dt, J = 13.9, 6.6 Hz, 1H), 7.47–7.50 (m, 1H), 7.60–7.61 (m, 2H), 7.67 (d, J = 7.6 Hz, 1H), 12.26 (br s, 1H); MS (EI) m/z: 219.

4.1.1.4. 4-(1-Oxo-1,3-dihydroisoindol-2-yl)butyric acid (2d). Mp = 125–127 °C; ^{1}H NMR δ (400 MHz, d_6-DMSO) 1.8 (dt, J = 14.2, 7.2 Hz, 2H) 2.2 (t, J = 7.3 Hz, 2H) 3.5 (t, J = 7.0 Hz, 2H) 7.5 (m, J = 7.9, 7.9, 4.0 Hz, 1H) 7.6 (m, J = 3.9 Hz, 2H) 7.7 (d, J = 7.6 Hz, 1H) 12.1 (br s, 1H); MS (EI) m/z: 219.

4.1.2. General procedure for a preparation of compound 3

Compound **2** (0.0252 mol) was dissolved in concentrated H_2SO_4 (37.7 ml) at 0 °C, and to this solution was added HNO_3 (12.7 ml, d = 1.5) at −10 °C. The mixture was stirred for 6 h at −5 °C. The reaction mixture was poured onto crushed ice (200 g). A crystalline solid precipitated and was collected. The filtered product was recrystallized from methanol.

4.1.2.2. (6-Nitro-1-oxo-1,3-dihydroisoindol-2-yl)acetic acid (3a) Mp = 222–223 °C; ^{1}H NMR δ (400 MHz, DMSO-d_6) 4.33 (s, 2H), 4.68 (s, 2H), 7.91 (d, J = 8.3 Hz, 1H), 8.37 (d, J = 2.1 Hz, 1H), 8.48 (dd, J = 2.1 Hz, 8.3 Hz, 1H); MS (EI) m/z: 219.

4.1.2.3. 3-(6-Nitro-1-oxo-1,3-dihydroisoindol-2-yl)propionic acid (3b). Mp = 196.5–197 °C; ^{1}H NMR δ (400 MHz, DMSO-d_6) 2.65 (t, J = 7.0 Hz, 2H), 3.77 (t, J = 7.0 Hz, 2H), 4.67 (s, 2H), 7.90 (d, J = 8.3 Hz, 1H), 8.33 (d, J = 2.1 Hz, 1H), 8.45 (dd, J = 2.1 Hz, J = 8.3 Hz, 1H); MS (EI) m/z: 250.

4.1.2.4. 3-(6-Nitro-1-oxo-1,3-dihydroisoindol-2-yl)butyric acid (3C). Mp = 194–195 °C; ^{1}H NMR δ (500 MHz, d_6-DMSO) 1.31 (d, J = 6.8 Hz, 3H), 2.67 (ddd, J = 36.9, 15.5, 7.3 Hz, 2H), 4.58–4.68 (m, 3H), 7.90 (d, J = 8.3 Hz, 2H), 8.33 (d, J = 1.7 Hz, 1H), 8.46 (dd, J = 8.3, 1.7 Hz, 1H), 12.31 (s, 1H); MS (EI) m/z: 264.

4.1.2.5. 4-(6-Nitro-1-oxo-1,3-dihydroisoindol-2-yl)butyric acid (3d). Mp = 153–155 °C; ^{1}H NMR δ (500 MHz, d_6-DMSO) δ ppm 1.87 (dt, J = 13.8, 7.0 Hz, 2H) 2.28 (t, J = 7.0 Hz, 2H) 3.59 (t, J = 7.0 Hz, 2H) 4.65 (s, 2H) 7.90 (d, J = 8.3 Hz, 1H) 8.34 (s, 1H) 8.46 (d, J = 8.0 Hz, 1H) 12.07 (s, 1H); MS (EI) m/z: 264.

4.1.3. General procedure for a preparation of compound 4

Compound **3** (0.0169 mol) was dissolved in methanol (50 ml), and to this solution was added concentrated H_2SO_4 (0.5 ml). The reaction solution was refluxed for 3 h. The solvent was removed via evaporation in vacuo, and the residue was triturated with water. A solid precipitated and was collected. The filtered product was recrystallized from methanol.

4.1.3.1. (6-Nitro-1-oxo-1,3-dihydroisoindol-2-yl)acetic acid methyl ester (4a). Mp = 113–115 °C; ^{1}H NMR δ (400 MHz, d_6-DMSO) 3.70 (s, 3H), 4.46 (s, 2H), 4.70 (s, 2H), 7.94 (d, J = 8.3 Hz, 1H), 8.39 (d, J = 2.1 Hz, 1H), 8.50 (dd, J = 2.1 Hz, 8.3 Hz, 1H); MS (EI) m/z: 250.

4.1.3.2. 3-(6-Nitro-1-oxo-1,3-dihydroisoindol-2-yl)propionic acid methyl ester (4b). Mp = 150–152 °C; ^{1}H NMR δ (400 MHz, d_6-DMSO) 2.74 (t, J = 7.0 Hz, 2H), 3.62 (s, 3H), 3.80 (t, J = 7.0 Hz, 2H), 4.67 (s, 2H), 7.90 (d, J = 8.3 Hz, 1H), 8.33 (d, J = 2.0 Hz, 1H), 8.46 (dd, J = 8.3, 2.0 Hz, 1H); MS (EI) m/z: 264.

4.1.3.3. 3-(6-Nitro-1-oxo-1,3-dihydroisoindol-2-yl)butyric acid methyl ester (4C). Mp = 125–126 °C; ^{1}H NMR δ (500 MHz, d_6-DMSO) 1.32 (d, J = 6.8 Hz, 3H) 2.76 (ddd, J = 35.4, 15.2, 7.3 Hz, 2H) 3.57 (s, 3H) 4.59–4.67 (m, 3H) 7.91 (d, J = 8.3 Hz, 1H) 8.34 (s, 1H) 8.46 (dd, J = 8.3, 2.2 Hz, 1H); MS (EI) m/z: 278.

4.1.3.4. 4-(6-Nitro-1-oxo-1,3-dihydroisoindol-2-yl)butyric acid methyl ester (4d). Mp = 86–87 °C; ^{1}H NMR δ (500 MHz, d_6-DMSO) 1.90 (dt, J = 13.8, 6.7 Hz, 2H), 2.37 (t, J = 7.0 Hz, 2H), 3.55 (s, 3H), 3.59 (t, J = 6.7 Hz, 2H), 4.65 (s, 2H), 7.90 (d, J = 8.3 Hz, 1H), 8.34 (s, 1H), 8.46 (d, J = 8.3 Hz, 1H); MS (EI) m/z: 278.

4.1.4. General procedure for a preparation of compound 5

The nitro compound **4** (0.015 mol) dissolved in methanol (100 ml) was subjected to catalytic hydrogenation at room temperature for 7 h in the presence of 3% palladium on carbon (1 g). The filtered solution was then evaporated in vacuo to give compound **5**.

4.1.4.1. (6-Amino-1-oxo-1,3-dihydroisoindol-2-yl)acetic acid methyl ester (5a). Mp = 142–143 °C; ^{1}H NMR δ (400 MHz, d_6-DMSO) 3.68 (s, 3H), 4.32 (s, 2H), 4.34 (s, 2H), 5.38 (s, 2H), 6.83 (dd, J = 2.1 Hz, 8.1 Hz, 1H), 6.87 (d, J = 2.1 Hz, 1H), 7.23 (d, J = 8.1 Hz, 1H); MS (EI) m/z: 220.

4.1.4.2. 3-(6-Amino-1-oxo-1,3-dihydroisoindol-2-yl)propionic acid methyl ester (5b). Mp = 147–148.5 °C; ^{1}H NMR δ (400 MHz, d_6-DMSO) 2.66 (t, J = 7.1 Hz, 2H), 3.61 (s, 3H), 3.71 (t, J = 7.1 Hz, 2H), 4.28 (s, 2H), 5.30 (s, 2H), 6.79 (dd, J = 2.1 Hz, J = 8.0 Hz, 1H), 6.82 (d, J = 2.1 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H); MS (EI) m/z: 234.

4.1.4.3. 3-(6-Amino-1-oxo-1,3-dihydroisoindol-2-yl)butyric acid methyl ester (5C). Mp = 86–86.5 °C; ^{1}H NMR δ (500 MHz, d_6-DMSO) 1.25 (d, J = 6.8 Hz, 3H), 2.68 (ddd, J = 27.0, 15.1, 7.3 Hz, 2H), 3.56 (s, 3H), 4.23 (dd, J = 24.5, 16.4 Hz, 2H), 4.58 (dt, J = 13.9, 6.8 Hz, 1H), 5.30 (s, 2H), 6.79 (dd, J = 8.1, 1.5 Hz, 1H), 6.82 (s, 1H), 7.20 (d, J = 8.1 Hz, 1H); MS (EI) m/z: 248.

4.1.4.4. 4-(6-Amino-1-oxo-1,3-dihydroisoindol-2-yl)butyric acid methyl ester (5d). Mp = 97–98 °C; ^{1}H NMR δ (400 MHz, d_6-DMSO) 1.82 (dt, J = 14.2, 7.2 Hz, 2H), 2.30 (t, J = 7.2 Hz, 2H), 3.46 (t, J = 7.2 Hz, 2H), 3.52 (s, 3H), 4.23 (s, 2H), 5.28 (s, 2H), 6.76 (dd, J = 8.1, 2.1 Hz, 1H), 6.81 (d, J = 2.1 Hz, 1H), 7.17 (d, J = 8.1 Hz, 1H); MS (EI) m/z: 248.

4.1.5. 1-Boc-4-piperidineacetic acid (6)

1-Boc-piperidine-4-carboxylic acid (2.29 g, 10 mmol) was dissolved in anhydrous THF (25 ml) under argon. The solution was cooled to −15 °C, and triethylamine (1.4 ml, 10 mmol), and then isobutyl chloroformate (1.3 ml, 10 mmol), were added. The reactor was protected from light. After 30 min, an ethereal solution of diazomethane was added. The mixture was allowed to warm to room temperature for 2 h without stirring and was left overnight. The reaction solution was diluted with chloroform (final volume −200 ml). The excess of diazomethane was destroyed by addition of few drops of acetic acid, and saturated aqueous solution of $NaHCO_3$ (10 ml) was added carefully. The aqueous layer was separated, and the organic layer was washed with saturated aqueous NaCl (10 ml). The organic layer was dried over anhydrous Na_2SO_4, filtered, and the solvent was evaporated in vacuo to dryness. The crude product, the diazoketone, was used directly in the next step.

The diazoketone was dissolved in THF (40 ml), and water (10 ml) and silver oxide (0.3 g) were added, and the mixture (protected from light) was stirred for 2–3 h at 45 °C (the reaction was monitored by TLC). Silver oxide was removed by centrifugation and the supernatant was evaporated in vacuo to dryness. The residue was dissolved in chloroform (100 ml) and the solution was washed with 5% aqueous solution of NaOH (30 ml). The aqueous layer was separated and pH of aqueous solution was brought to three, and the product was extracted with chloroform. The organic layer was washed with saturated aqueous NaCl (50 ml). The organic layer was dried over anhydrous Na_2SO_4, filtered, and chloroform was evaporated to yield oily residue of **6**. After a period of few days, oil was converted into solid waxy substance.

4.1.6. 2-Acetyl-1,2,3,4-tetrahydroisoquinoline-7-carboxylic (13)

Compound **12** (2.5 g, 0.117 mol) was dissolved in anhydrous CH_2Cl_2 (50 ml). The solution was cooled to −10 °C, and with intensive stirring oxalyl chloride (5 ml, 0.117 mol) was added. $AlCl_3$ (2.85, 0.643 mol) was added in small portions to the stirred solution with temperature kept below −9 °C. The mixture was stirred for 1 h at −10 °C. Then additional $AlCl_3$ (3.81, 0.643 mol) was added, and the mixture was stirred for another 2 h at −10 °C. The reaction mixture was allowed to stand overnight at room temperature and then poured onto ice (100 g). The aqueous phase was extracted with CH_2Cl_2 (100 ml). The organic phase was dried with anhydrous Na_2SO_4, filtered, and the solvent was evaporated in vacuo. The residue was dissolved in acid, with stirring and heating (40 °C). To the warm solution, ice was added. pH of the mixture was brought to three and the product was extracted with chloroform. The chloroform phase was dried with anhydrous Na_2SO_4, filtered, and the solvent was evaporated in vacuo to dryness. The resulting **13** obtained as a solid residue was used in subsequent transformations without further purification. Cream powder, yield 53%. Mp = 183.5–184.5 °C.

4.1.7. General procedure for a preparation of compound 15

The 10 mmol of acid (**6**–**8**, **11a**,**b** or **14**) was dissolved in anhydrous acetonitryle (25 ml). The solution was cooled to −5 °C, and triethylamine (1.4 ml, 10 mmol), and then HBTU (3.79 g, 10 mmol) or HATU (3.8 g, 10 mmol), were added. The mixture was stirred for 1 h at −5 °C and then 10 mmol of amine **5** was added. The reaction mixture was allowed to stand overnight at room temperature. The residual amount of the activated ether (Bt- or At-ether of starting acid) was destroyed by addition of few drops of *N*,*N*-dimethylpropane-1,3-diamine, and the solvent was evaporated in vacuo to dryness. The residue was dissolved in 100 ml of chloroform. The solution was washed with water (40 mL), aqueous solution of 1 M HCl (40 ml) and 5% aqueous solution of $NaHCO_3$ (40 ml). The organic layer was dried over Na_2SO_4, filtered off, and the solvent was evaporated in vacuo to dryness. The resulting residue was triturated with warm hexane (20 ml), and the precipitate was collected by filtration and dried.

4.1.7.1. {6-[2-(1-Boc-piperidin-4-yl)acetylamino]-1-oxo-1,3-dihydroisoindol-2-yl}acetic acid methyl ester (15a). Mp = 193–195 °C; ^{1}H NMR δ (400 MHz, d_6-DMSO) 1.07 (ddd, J = 24.3, 12.1, 3.9 Hz, 2H), 1.38 (s, 9H), 1.65 (d, J = 11.0 Hz, 2H), 1.94 (m, J = 3.7 Hz, 1H), 2.27 (d, J = 6.8 Hz, 2H), 2.64–286 (m, 2H), 3.67 (s, 3H), 3.90 (d, J = 11.7 Hz, 2H), 4.37 (s, 2H), 4.45 (s, 2H), 7.52 (d, J = 8.1 Hz, 1H), 7.68 (dd, J = 8.3, 2.0 Hz, 1H), 8.07 (d, J = 1.2 Hz, 1H), 10.13 (s, 1H); HRMS (FAB) m/z calcd for $C_{23}H_{33}N_3O_6$ $[M+H]^+$: 446.5280, found: 446.5273.

4.1.7.2. {6-[4-(1-Boc-piperidin-4-yl)butyrylamino]-1-oxo-1,3-dihydroisoindol-2-yl}acetic acid methyl ester (15b). Mp = 149–150 °C; ^{1}H NMR δ (400 MHz, d_6-DMSO) 0.95 (ddd, J = 24.3, 12.2, 4.0 Hz, 2H), 1.24 (dd, J = 14.9, 6.6 Hz, 2H), 1.39 (s, 9H), 1.41–1.50 (m, 1H), 1.59–1.67 (m, 4H), 2.33 (t, J = 7.3 Hz, 2H), 2.60–2.75 (m, 2H), 3.69 (s, 3H), 3.92 (d, J = 11.0 Hz, 2H), 4.39 (s, 2H), 4.46 (s, 2H), 7.54 (d, J = 8.2 Hz, 1H), 7.72 (dd, J = 8.2, 1.8 Hz, 1H), 8.08 (d, J = 1.8 Hz, 1H), 10.13 (s, 1H); HRMS (FAB) m/z calcd for $C_{25}H_{36}N_3O_6$ $[M+H]^+$: 474.5822, found: 474.5826.

4.1.7.3. {6-[4-(1-Boc-piperidin-4-yl)benzoylamino]-1-oxo-1,3-dihydroisoindol-2-yl}acetic acid methyl ester (15C). Mp = 189–191 °C; ^{1}H NMR δ (400 MHz, d_6-DMSO) 1.43 (s, 9H), 1.55 (ddd, J = 24.9, 12.4, 3.8 Hz, 2H), 1.79 (d, J = 12.7 Hz, 2H), 2.75–2.90 (m, 3H), 4.10 (d, J = 10.8 Hz, 2H), 4.29 (s, 2H), 4.50 (s, 2H), 7.44 (d, J = 7.6 Hz, 2H), 7.59 (d, J = 8.3 Hz, 1H), 7.93 (d, J = 7.3 Hz, 2H), 7.97 (d, J = 8.3 Hz, 1H), 8.22 (s, 1H), 10.41 (s, 1H); HRMS (FAB) m/z calcd for $C_{28}H_{34}N_3O_6$ $[M+H]^+$: 508.5997, found: 508.6002.

4.1.7.4. {6-[4-(4-Boc-piperazin-1-yl)benzoylamino]-1-oxo-1,3-dihydroisoindol-2-yl}acetic acid methyl ester (15d). Mp = 219–220.5 °C; ^{1}H NMR δ (500 MHz, d_6-DMSO) 1.44 (s, 9H), 3.31 (t, J = 4.6 Hz, 4H), 3.48 (t, J = 4.6 Hz, 4H), 3.70 (s, 3H), 4.41 (s, 2H), 4.50 (s, 2H), 7.05 (d, J = 8.7 Hz, 2H), 7.58 (d, J = 8.2 Hz, 1H), 7.93 (d, J = 8.7 Hz, 2H), 7.98 (dd, J = 8.2, 1.0 Hz, 1H), 8.23 (d, J = 1.0, 1H), 10.18 (s, 1H); HRMS (FAB) m/z calcd for $C_{27}H_{33}N_4O_6$ $[M+H]^+$: 509.5873, found: 509.5880.

4.1.7.5. {6-[(2-Boc-1,2,3,4-tetrahydroisoquinoline-7-carbonyl)-amino]-1-oxo-1,3-dihydroisoindol-2-yl}acetic acid methyl ester (15e). Mp = 134–137 °C; ^{1}H NMR δ (400 MHz, d_6-DMSO) 1.45 (s, 9H), 2.87 (t, J = 5.8 Hz, 2H), 3.60 (t, J = 5.8 Hz, 2H), 3.70 (s, 3H), 4.42 (s, 2H), 4.51 (s, 2H), 4.61 (s, 2H), 7.35 (d, J = 8.1 Hz, 1H), 7.61 (d, J = 8.3 Hz, 1H), 7.81 (d, J = 8.1 Hz, 1H), 7.83 (s, 1H), 8.00 (dd, J = 8.2, 1.7 Hz, 1H), 8.24 (d, J = 1.7 Hz, 1H), 10.41 (s, 1H); HRMS (FAB) m/z calcd for $C_{26}H_{30}N_3O_6$ $[M+H]^+$: 480.5455, found: 480.5447.

4.1.7.6. 3-{6-[2-(1-Boc-piperidin-4-yl)acetylamino]-1-oxo-1,3-dihydroisoindol-2-yl}propionic acid methyl ester (15f). Mp = 168–170 °C; ^{1}H NMR δ (500 MHz, d_6-DMSO) 1.09 (ddd, J = 23.9, 11.7, 3.9 Hz, 2H), 1.40 (s, 9H), 1.67 (d, J = 11.7 Hz, 2H), 1.94–1.98 (m, 1H), 2.28 (d, J = 6.7 Hz, 2H), 2.70 (t, J = 6.7 Hz, 2H), 2.74–2.80 (m, 2H), 3.61 (s, 3H), 3.76 (t, J = 6.7 Hz, 2H), 3.92 (d, J = 9.1 Hz, 2H), 4.43 (s, 5H), 7.50 (d, J = 8.3 Hz, 1H), 7.68 (d, J = 8.3 Hz, 1H), 8.04 (s, 1H), 10.12 (s, 1H); HRMS (FAB) m/z calcd for $C_{24}H_{34}N_3O_6$ $[M+H]^+$: 460.5551, found: 460.5560.

4.1.7.7. 3-{6-[4-(1-Boc-piperidin-4-yl)butyrylamino]-1-oxo-1,3-dihydroisoindol-2-yl}propionic acid methyl ester (15g). Mp = 171–172 °C; ^{1}H NMR δ (400 MHz, d_6-DMSO) 0.94 (ddd, J = 24.2, 12.2, 4.2 Hz, 2H), 1.23 (dd, J = 15.2, 6.8 Hz, 2H), 1.38 (s, 9H), 1.40–1.45 (m, 1H), 1.58–1.65 (m, 4H), 2.31 (t, J = 7.5 Hz, 2H), 2.58–2.65 (m, 2H), 2.68 (t, J = 7.0 Hz, 2H), 3.60 (s, 3H), 3.74 (t, J = 7.0 Hz, 2H), 3.91 (d, J = 12.5 Hz, 2H), 4.41 (s, 2H), 7.49 (d, J = 8.2 Hz, 1H), 7.67 (dd, J = 8.2, 1.7 Hz, 1H), 8.02 (d, J = 1.7 Hz, 1H), 10.08 (s, 1H); HRMS (FAB) m/z calcd for $C_{26}H_{38}N_3O_6$ $[M+H]^+$: 488.6093, found: 488.6087.

4.1.7.8. 3-{6-[4-(1-Boc-piperidin-4-yl)benzoylamino]-1-oxo-1,3-dihydroisoindol-2-yl}propionic acid methyl ester (15h). Mp = 199.5–200.5 °C; ^{1}H NMR δ (400 MHz, d_6-DMSO) 1.41 (s, 9H), 1.52 (ddd, J = 25.2, 12.6, 4.0 Hz, 2H), 1.77 (d, J = 12.6 Hz, 2H), 2.69 (t, J = 7.0 Hz, 2H), 2.73–2.90 (m, 3H), 3.59 (s, 3H), 3.75 (t, J = 7.0 Hz, 2H), 4.08 (d, J = 11.5 Hz, 2H), 4.44 (s, 2H), 7.41 (d, J = 8.1 Hz, 2H), 7.54 (d, J = 8.3 Hz, 1H), 7.90 (d, J = 8.1 Hz, 2H), 7.92 (dd, J = 8.3, 1.7 Hz, 1H), 8.16 (d, J = 1.7 Hz, 1H), 10.36 (s, 1H); HRMS (FAB) m/z calcd for $C_{29}H_{36}N_3O_6$ $[M+H]^+$: 522.6268, found: 522.6260.

4.1.7.9. 3-{6-[4-(4-Boc-piperazin-1-yl)benzoylamino]-1-oxo-1,3-dihydroisoindol-2-yl}propionic acid methyl ester (15i). Mp = 185–187 °C; ^{1}H NMR δ (400 MHz, d_6-DMSO) 1.43 (s, 9H), 2.71 (t, J = 6.9 Hz, 2H), 3.30 (s, 4H), 3.48 (s, 4H), 3.61 (s, 3H), 3.77 (t, J = 6.9 Hz, 2H), 4.45 (s, 2H), 7.04 (d, J = 9.0 Hz, 2H), 7.54 (d, J = 8.7 Hz, 1H), 7.91 (d, J = 9.0 Hz, 2H), 7.95 (dd, J = 8.7, 1.7 Hz, 1H), 8.18 (d, J = 1.7 Hz, 1H), 10.15 (s, 1H); HRMS (FAB) m/z calcd for $C_{28}H_{35}N_4O_6$ $[M+H]^+$: 523.6144, found: 523.6137.

4.1.7.10. 3-{6-[(2-Boc-1,2,3,4-tetrahydroisoquinoline-7-carbonyl) amino]-1-oxo-1,3-dihydroisoindol-2-yl}propionic acid methyl ester (15j). Mp = 102–103 °C; ^{1}H NMR δ (400 MHz, d_6-DMSO) 1.45 (s, 9H), 2.72 (t, J = 7.5 Hz, 2H), 2.87 (t, J = 5.9 Hz, 2H), 3.60 (t, J = 5.6 Hz, 2H), 3.62 (s, 3H), 3.78 (t, J = 7.0 Hz, 2H), 4.47 (s, 2H), 4.61 (s, 2H), 7.34 (d, J = 8.1 Hz, 1H), 7.57 (d, J = 8.1 Hz, 1H), 7.80 (d, J = 8.1 Hz, 1H), 7.82 (s, 1H), 7.95 (dd, J = 8.1, 1.5 Hz, 1H), 8.19 (d, J = 1.5 Hz, 1H), 10.37 (s, 1H); HRMS (FAB) m/z calcd for $C_{27}H_{32}N_3O_6$ $[M+H]^+$: 494.5726, found: 494.5730.

4.1.7.11. 3-{6-[3-(4-Boc-piperazin-1-yl)benzoylamino]-1-oxo-1,3-dihydroisoindol-2-yl}propionic acid methyl ester (15k). Mp = 181–183 °C; ^{1}H NMR δ (500 MHz, d_6-DMSO) 1.44 (s, 9H), 2.72 (t, J = 6.5 Hz, 2H), 3.21 (s, 4H), 3.50 (s, 4H), 3.62 (s, 3H), 3.78 (t, J = 6.1 Hz, 2H), 4.47 (s, 2H), 7.19 (d, J = 6.2 Hz, 1H), 7.38–7.44 (m, 2H), 7.50 (s, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 8.17 (m, 1H), 10.35 (s, 1H); HRMS (FAB) m/z calcd for $C_{28}H_{35}N_4O_6$ $[M+H]^+$: 523.6144, found: 523.6146.

4.1.7.12. 3-{6-[2-(1-Boc-piperidin-4-yl)acetylamino]-1-oxo-1,3-dihydroisoindol-2-yl}butyric acid methyl ester (15l). Mp = 130–132 °C; ^{1}H NMR $\boldsymbol{\delta}$ (500 MHz, $\boldsymbol{d_6}$-DMSO) 1.09 (ddd, $\boldsymbol{J}$ = 22.5, 11.7, 3.1 Hz, 2H), 1.28 (d, $\boldsymbol{J}$ = 5.7 Hz, 3H), 1.40 (s, 9H), 1.67 (d, $\boldsymbol{J}$ = 11.7 Hz, 2H), 1.91–2.00 (m, 1H), 2.27 (d, $\boldsymbol{J}$ = 6.2 Hz, 2H), 2.65–2.82 (m, 4H), 3.56 (s, 3H), 3.93 (d, $\boldsymbol{J}$ = 8.3 Hz, 2H), 4.38 (dd, $\boldsymbol{J}$ = 22.8, 17.1 Hz, 2H), 4.60 (m, 1H), 7.51 (d, $\boldsymbol{J}$ = 8.1 Hz, 1H), 7.69 (d, $\boldsymbol{J}$ = 8.1 Hz, 1H), 8.03 (s, 1H), 10.10 (s, 1H); HRMS (FAB) $\boldsymbol{m/z}$ calcd for $\boldsymbol{C_{25}H_{36}N_3O_6}$ $[M+H]^+$: 474.5822, found: 474.5823.

4.1.7.13. 3-{6-[4-(1-Boc-piperidin-4-yl)butyrylamino]-1-oxo-1,3-dihydroisoindol-2-yl}butyric acid methyl ester (15m). Mp = 133–134 °C; ^{1}H NMR $\boldsymbol{\delta}$ (500 MHz, $\boldsymbol{d_6}$-DMSO) 0.95 (ddd, $\boldsymbol{J}$ = 24.0, 12.2, 3.9 Hz, 2H), 1.22–1.25 (m, 2H), 1.28 (d, $\boldsymbol{J}$ = 6.6 Hz, 3H), 1.39 (s, 9H), 1.61–1.66 (m, 4H), 2.32 (t, $\boldsymbol{J}$ = 7.3 Hz, 2H), 2.65–2.77 (m, 4H), 3.56 (s, 3H), 3.92 (d, $\boldsymbol{J}$ = 9.3 Hz, 2H), 4.38 (dd, $\boldsymbol{J}$ = 24.0, 17.1 Hz, 2H), 4.61 (td, $\boldsymbol{J}$ = 13.7, 6.8 Hz, 1H), 7.50 (d, $\boldsymbol{J}$ = 8.3 Hz, 1H), 7.69 (d, $\boldsymbol{J}$ = 8.3 Hz, 1H), 8.02 (s, 1H), 10.07 (s, 1H); HRMS (FAB) $\boldsymbol{m/z}$ calcd for $\boldsymbol{C_{27}H_{40}N_3O_6}$ $[M+H]^+$: 502.6364, found: 502.6367.

4.1.7.14. 3-{6-[4-(1-Boc-piperidin-4-yl)benzoylamino]-1-oxo-1,3-dihydroisoindol-2-yl}butyric acid methyl ester (15n). ^{1}H NMR $\boldsymbol{\delta}$ (500 MHz, $\boldsymbol{d_6}$-DMSO) 1.30 (d, $\boldsymbol{J}$ = 6.8 Hz, 3H), 1.43 (s, 9H), 1.55 (ddd, $\boldsymbol{J}$ = 24.5, 11.7, 2.9 Hz, 2H), 1.79 (d, $\boldsymbol{J}$ = 11.7 Hz, 2H), 2.68–2.85 (m, 5H), 3.57 (s, 3H), 4.11 (d, $\boldsymbol{J}$ = 7.6 Hz, 2H), 4.42 (dd, $\boldsymbol{J}$ = 24.0, 17.6 Hz, 2H), 4.63 (dt, $\boldsymbol{J}$ = 13.9, 6.7 Hz, 1H), 7.43 (d, $\boldsymbol{J}$ = 8.1 Hz, 2H), 7.57 (d, $\boldsymbol{J}$ = 8.1 Hz, 1H), 7.92–7.96 (m, 3H), 8.18 (s, 1H), 10.38 (s, 1H); HRMS (FAB) $\boldsymbol{m/z}$ calcd for $\boldsymbol{C_{30}H_{38}N_3O_6}$ $[M+H]^+$: 536.6539, found: 536.6535

4.1.7.15. 3-{6-[4-(1-Boc-piperazin-4-yl)benzoylamino]-1-oxo-1,3-dihydroisoindol-2-yl}butyric acid methyl ester (15o). Mp = 95–97 °C (decomposes); ^{1}H NMR $\boldsymbol{\delta}$ (500 MHz, $\boldsymbol{d_6}$-DMSO) 1.29 (d, $\boldsymbol{J}$ = 6.8 Hz, 3H), 1.44 (s, 9H), 2.68–2.78 (m, 2H), 3.30 (t, $\boldsymbol{J}$ = 4.0 Hz, 4H), 3.48 (t, $\boldsymbol{J}$ = 4.0 Hz, 4H), 3.57 (s, 3H), 4.41 (dd, $\boldsymbol{J}$ = 24.2, 17.4 Hz, 2H), 4.63 (td, $\boldsymbol{J}$ = 13.9, 6.5 Hz, 1H), 7.05 (d, $\boldsymbol{J}$ = 9.0 Hz, 2H), 7.55 (d, $\boldsymbol{J}$ = 8.2 Hz, 1H), 7.92 (d, $\boldsymbol{J}$ = 9.0 Hz, 2H), 7.95 (dd, $\boldsymbol{J}$ = 8.2, 1.8 Hz, 1H), 8.17 (d, $\boldsymbol{J}$ = 1.8 Hz, 1H), 10.15 (s, 1H); HRMS (FAB) $\boldsymbol{m/z}$ calcd for $\boldsymbol{C_{29}H_{37}N_4O_6}$ $[M+H]^+$: 537.6414, found: 537.66417.

4.1.7.16. 3-{6-[(2-Boc-1,2,3,4-tetrahydroisoquinoline-7-carbonyl)-amino]-1-oxo-1,3-dihydroisoindol-2-yl}butyric acid methyl ester (15p). ^{1}H NMR δ (400 MHz, d_6-DMSO + CCl_4) 1.29 (d, J = 6.6 Hz, 3H), 1.45 (s, 9H), 2.67–2.77 (m, 2H), 2.86 (t, J = 5.0 Hz, 2H), 3.57 (s, 3H), 3.58–3.60 (m, 2H), 4.40 (dd, J = 22.0, 17.4 Hz, 2H), 4.59–4.66 (m, 3H), 7.33 (d, J = 7.5 Hz, 1H), 7.57 (d, J = 8.3 Hz, 1H), 7.79–7.82 (m, 2H), 7.95 (d, J = 7.9 Hz, 1H), 8.18 (s, 1H), 10.36 (s, 1H); HRMS (FAB) m/z calcd for $C_{28}H_{34}N_3O_6$ $[M+H]^+$: 508.5997, found: 508.5995.

4.1.7.17. 3-{6-[3-(4-Boc-piperazin-1-yl)benzoylamino]-1-oxo-1,3-dihydroisoindol-2-yl}butyric acid methyl ester (15q). Mp = 142–143.5 °C; ^{1}H NMR $\boldsymbol{\delta}$ (400 MHz, $\boldsymbol{d_6}$-DMSO) 1.30 (d, $\boldsymbol{J}$ = 6.7 Hz, 3H), 1.44 (s, 9H), 2.68–2.79 (m, 2H), 3.24 (s, 4H), 3.53 (s, 4H), 3.57 (s, 3H), 4.43 (dd, $\boldsymbol{J}$ = 24.4, 17.1 Hz, 2H), 4.63 (m, 1H), 7.25 (d, $\boldsymbol{J}$ = 7.8 Hz, 1H), 7.41 (t, $\boldsymbol{J}$ = 7.8 Hz, 1H), 7.47 (d, $\boldsymbol{J}$ = 7.5 Hz, 1H), 7.58 (d, $\boldsymbol{J}$ = 7.0 Hz, 2H), 7.98 (d, $\boldsymbol{J}$ = 8.0 Hz, 1H), 8.17 (s, 1H), 10.40 (s, 1H); HRMS (FAB) $\boldsymbol{m/z}$ calcd for $\boldsymbol{C_{29}H_{37}N_4O_6}$ $[M+H]^+$: 537.6414, found: 537.66416.

4.1.7.18. 4-{6-[2-(1-Boc-piperidin-4-yl)acetylamino]-1-oxo-1,3-dihydroisoindol-2-yl}butyric acid methyl ester (15r). Mp = 159–160 °C; ^{1}H NMR $\boldsymbol{\delta}$ (500 MHz, $\boldsymbol{d_6}$-DMSO) 1.06–1.12 (m, 2H), 1.40 (s, 9H), 1.67 (d, $\boldsymbol{J}$ = 11.7 Hz, 2H), 1.87 (t, $\boldsymbol{J}$ = 6.8, 2H), 1.92–1.99 (m, 1H), 2.28 (d, $\boldsymbol{J}$ = 6.5, 2H), 2.34 (t, $\boldsymbol{J}$ = 6.8, 2H), 2.65–2.80 (m, 2H), 3.52–3.56 (m, 5H), 3.92 (d, $\boldsymbol{J}$ = 8.6 Hz, 2H), 4.40 (s, 2H), 7.50 (d, $\boldsymbol{J}$ = 7.9 Hz, 1H), 7.68 (d, $\boldsymbol{J}$ = 7.9 Hz, 1H), 8.03 (s, 1H), 10.09 (s, 1H); HRMS (FAB) $\boldsymbol{m/z}$ calcd for $\boldsymbol{C_{25}H_{36}N_3O_6}$ $[M+H]^+$: 474.5822, found: 474.5819.

4.1.7.19. 4-{6-[4-(1-Boc-piperidin-4-yl)butyrylamino]-1-oxo-1,3-dihydroisoindol-2-yl}butyric acid methyl ester (15s). Mp = 151–153 °C; ^{1}H NMR δ (400 MHz, d_6-DMSO) 0.94 (ddd, J = 24.4, 12.2, 4.0 Hz, 2H), 1.23 (dd, J = 15.7, 7.3 Hz, 2H), 1.38 (s, 9H), 1.41–1.43 (m, 1H), 1.60–1.66 (m, 4H), 1.86 (dt, J = 14.2, 7.1 Hz, 2H), 2.32 (m, J = 7.1 Hz, 4H), 2.59–2.73 (m, 2H), 3.52 (t, J = 7.1 Hz, 2H), 3.53 (s, 3H), 3.91 (d, J = 11.7 Hz, 2H), 4.39 (s, 2H), 7.49 (d, J = 8.1 Hz, 1H), 7.68 (dd, J = 8.1, 1.6 Hz, 1H), 8.2 (d, J = 1.6 Hz, 1H), 10.07 (s, 1H); HRMS (FAB) m/z calcd for $C_{27}H_{40}N_3O_6$ $[M+H]^+$: 502.6364, found: 502.6363.

4.1.7.20. 4-{6-[4-(1-Boc-piperidin-4-yl)benzoylamino]-1-oxo-1,3-dihydroisoindol-2-yl}butyric acid methyl ester (15t). Mp = 166–167 °C; ^{1}H NMR $\boldsymbol{\delta}$ (400 MHz, $\boldsymbol{d_6}$-DMSO) 1.4 (s, 9H) 1.5 (ddd, $\boldsymbol{J}$ = 22.3, 12.0, 2.4 Hz, 2H) 1.8 (d, $\boldsymbol{J}$ = 12.2 Hz, 2H) 1.9 (dt, $\boldsymbol{J}$ = 13.4, 6.6 Hz, 2H) 2.3 (t, $\boldsymbol{J}$ = 6.6 Hz, 2H) 2.8 (m, 3H) 3.5 (m, 5H) 4.1 (d, $\boldsymbol{J}$ = 9.0 Hz, 2H) 4.4 (s, 2H) 7.4 (d, $\boldsymbol{J}$ = 7.3 Hz, 2H) 7.5 (d, $\boldsymbol{J}$ = 8.1 Hz, 1H) 7.9 (m, $\boldsymbol{J}$ = 6.7, 6.7 Hz, 3H) 8.2 (s, 1H) 10.4 (s, 1H); HRMS (FAB) $\boldsymbol{m/z}$ calcd for $\boldsymbol{C_{30}H_{38}N_3O_6}$ $[M+H]^+$: 536.6539, found: 536.6537.

4.1.7.21. 4-{6-[(2-Boc-1,2,3,4-tetrahydroisoquinoline-7-carbonyl)-amino]-1-oxo-1,3-dihydroisoindol-2-yl}butyric acid methyl ester (15u). Mp = 142–145 °C; ^{1}H NMR δ (400 MHz, d_6-DMSO) 1.44 (s, 9H), 1.88 (dt, J = 13.8, 6.6 Hz, 4H), 2.35 (t, J = 7.1 Hz, 2H), 2.86 (t, J = 4.9, 2H), 3.54 (s, 3H), 3.59 (t, J = 4.9, 4H), 4.44 (s, 2H), 4.60 (s, 2H), 7.33 (d, J = 7.6 Hz, 1H), 7.56 (d, J = 8.1 Hz, 2H), 7.78–7.81 (m, 2H), 7.94 (d, J = 8.1 Hz, 1H), 8.18 (s, 1H), 10.37 (s, 1H); HRMS (FAB) m/z calcd for $C_{28}H_{34}N_3O_6$ $[M+H]^+$: 508.5997, found: 508.5995.

4.1.8. General procedure for a preparation of compound 16

The compound **15** (10 mmol) was dissolved in methanol (25 ml), and to this solution was added 1 M NaOH aqueous solu-

tion (5 ml). The reaction mixture was left at room temperature overnight. Then chloroform (50 ml) was added, and pH of the mixture was brought to three with intensive stirring. When the product was not soluble in chloroform layer, an suspension was formed, the product was filtered off. The precipitate was washed (on the filter) with water, chloroform and ether, and dried in air. Thus obtained product **16** was not need to be further purified. When the reaction product was soluble in chloroform, the chloroform phase was collected and washed with water (20 ml). The chloroform phase was dried with anhydrous Na_2SO_4, filtered, and the solvent was evaporated in vacuo to dryness. The resulting residue was triturated with ether (20 ml) and the precipitate was collected by filtration and dried in air.

4.1.8.1. {6-[2-(1-Boc-piperidin-4-yl)acetylamino]-1-oxo-1,3-dihydroisoindol-2-yl}acetic acid (16a). Mp = 198–201 °C; ^{1}H NMR δ (400 MHz, d_6-DMSO) 1.07 (ddd, J = 23.6, 11.9, 3.2 Hz, 2H), 1.38 (s, 9H), 1.65 (d, J = 12.2 Hz, 2H), 1.91–197 (m, 1H), 2.26 (d, J = 6.8 Hz, 2H), 2.65–2.80 (m, 2H), 3.91 (d, J = 11.0 Hz, 2H), 4.25 (s, 2H), 4.44 (s, 2H), 7.51 (d, J = 8.3 Hz, 1H), 7.68 (d, J = 7.8 Hz, 1H), 8.06 (s, 1H), 10.13 (s, 1H), 12.86 (br s, 1H); HRMS (FAB) m/z calcd for $C_{22}H_{30}N_3O_6$ $[M+H]^+$: 432.5009, found: 432.5005.

4.1.8.2. {6-[4-(1-Boc-piperidin-4-yl)butyrylamino]-1-oxo-1,3-dihydroisoindol-2-yl}acetic acid (16b). Mp = 165.5–167 °C; ^{1}H NMR δ (400 MHz, d_6-DMSO) 0.95 (ddd, J = 24.3, 12.3, 4.0 Hz, 2H), 1.22–1.27 (m, 2H), 1.39 (s, 9H), 1.42–1.45 (m, 1H), 1.59–168 (m, 4H), 2.33 (t, J = 7.5 Hz, 2H), 2.60–2.75 (m, 2H), 3.93 (d, J = 11.2 Hz, 2H), 4.27 (s, 2H), 4.46 (s, 2H), 7.53 (d, J = 8.1 Hz, 1H), 7.71 (dd, J = 8.3, 1.7 Hz, 1H), 8.08 (d, J = 1.5 Hz, 1H), 10.12 (s, 1H), 12.96 (br s, 1H); HRMS (FAB) m/z calcd for $C_{24}H_{32}N_3O_6$ $[M+H]^+$: 460.5551, found: 460.5559.

4.1.8.3. {6-[4-(1-Boc-piperidin-4-yl)benzoylamino]-1-oxo-1,3-dihydroisoindol-2-yl}acetic acid (16C). Mp = 223–225 °C; ^{1}H NMR δ (400 MHz, d_6-DMSO) 1.43 (s, 9H), 1.53 (ddd, J = 24.9, 12.4, 3.8 Hz, 2H), 1.79 (d, J = 12.7 Hz, 2H), 2.77–2.85 (m, 3H), 4.11 (d, J = 10.8 Hz, 2H), 4.30 (s, 2H), 4.50 (s, 2H), 7.44 (d, J = 7.6 Hz, 2H), 7.59 (d, J = 8.3 Hz, 1H), 7.93 (d, J = 7.3 Hz, 2H), 7.97 (d, J = 8.3 Hz, 1H), 8.27 (s, 1H), 10.41 (s, 1H); HRMS (FAB) m/z calcd for $C_{27}H_{32}N_3O_6$ $[M+H]^+$: 494.5726, found: 494.5721.

4.1.8.4. {6-[4-(4-Boc-piperazin-1-yl)benzoylamino]-1-oxo-1,3-dihydroisoindol-2-yl}acetic acid (16d). Mp = 215–216.5 °C (decomposes); ^{1}H NMR δ (500 MHz, d_6-DMSO) 1.44 (s, 9H), 3.31 (s, 4H), 3.48 (s, 4H), 4.29 (s, 2H), 4.49 (s, 2H), 7.05 (d, J = 8.3 Hz, 2H), 7.56 (d, J = 8.3 Hz, 1H), 7.93 (d, J = 8.3 Hz, 2H), 7.98 (d, J = 8.3 Hz, 1H), 8.23 (s, 1H), 10.17 (s, 1H), 12.97 (br s, 1H); HRMS (FAB) m/z calcd for $C_{26}H_{31}N_4O_6$ $[M+H]^+$: 495.5602, found: 495.5610.

4.1.8.5. {6-[(2-Boc-1,2,3,4-tetrahydroisoquinoline-7-carbonyl)amino]-1-oxo-1,3-dihydroisoindol-2-yl}acetic acid (16e). Mp = 218–220 °C (decomposes); ^{1}H NMR δ (400 MHz, d_6-DMSO) 1.45 (s, 9H), 2.87 (t, J = 5.7 Hz, 2H), 3.60 (t, J = 5.7 Hz, 2H), 4.29 (s, 2H), 4.50 (s, 2H), 4.61 (s, 2H), 7.35 (d, J = 8.1 Hz, 1H), 7.60 (d, J = 8.3 Hz, 1H), 7.81 (d, J = 8.1 Hz, 1H), 7.83 (s, 1H), 7.98 (dd, J = 8.3, 2.0 Hz, 1H), 8.23 (d, J = 1.7 Hz, 1H), 10.41 (s, 1H), 12.96 (br s, 1H); HRMS (FAB) m/z calcd for $C_{25}H_{28}N_3O_6$ $[M+H]^+$: 466.5184, found: 466.5187.

4.1.8.6. 3-{6-[2-(1-Boc-piperidin-4-yl)acetylamino]-1-oxo-1,3-dihydroisoindol-2-yl}propionic acid (16f). Mp = 193–194 °C; ^{1}H NMR δ (400 MHz, d_6-DMSO) 1.08 (ddd, J = 24.6, 12.4, 3.3 Hz, 2H), 1.40 (s, 9H), 1.66 (d, J = 11.5 Hz, 2H), 1.90–2.01 (m, 1H), 2.28 (d, J = 7.1 Hz, 2H), 2.60 (t, J = 7.0 Hz, 2H), 2.66–2.82 (m, 2H), 3.72 (t, J = 7.1 Hz, 2H), 3.92 (d, J = 11.7 Hz, 2H), 4.43 (s, 2H), 7.51 (d, J = 8.1 Hz, 1H), 7.67 (dd, J = 8.1, 1.2 Hz, 1H), 8.04 (d, J = 1.2 Hz, 1H), 10.11 (s, 1H), 12.36 (br s, 1H); HRMS (FAB) m/z calcd for $C_{23}H_{32}N_3O_6$ $[M+H]^+$: 446.5280, found: 546.5274.

4.1.8.7. 3-{6-[4-(1-Boc-piperidin-4-yl)butyrylamino]-1-oxo-1,3-dihydroisoindol-2-yl}propionic acid (16g). Mp = 176.5–177.5 °C; ^{1}H NMR δ (400 MHz, d_6-DMSO) 0.93 (ddd, J = 23.0, 10.5, 3.2 Hz, 2H), 1.22 (dd, J = 14.2, 6.9 Hz, 2H), 1.36 (s, 9H), 1.49–1.46 (m, 1H), 1.57–1.64 (m, 4H), 2.30 (t, J = 7.3 Hz, 2H), 2.58 (t, J = 6.9 Hz, 2H), 2.62–2.76 (m, 2H), 3.69 (t, J = 6.9 Hz, 2H), 3.90 (d, J = 10.5 Hz, 2H), 4.41 (s, 2H), 7.48 (d, J = 8.1 Hz, 1H), 7.66 (dd, J = 8.1, 1.5 Hz, 1H), 8.01 (d, J = 1.5 Hz, 1H), 10.10 (s, 1H), 12.34 (br s, 1H); HRMS (FAB) m/z calcd for $C_{25}H_{36}N_3O_6$ $[M+H]^+$: 474.5822, found: 508.5828.

4.1.8.8. 3-{6-[4-(1-Boc-piperidin-4-yl)benzoylamino]-1-oxo-1,3-dihydroisoindol-2-yl}propionic acid (16h). Mp = 195–196 °C; ^{1}H NMR δ (400 MHz, d_6-DMSO) 1.41 (s, 9H), 1.52 (ddd, J = 25.1, 12.6, 3.9 Hz, 2H), 1.77 (d, J = 12.5 Hz, 2H), 2.60 (t, J = 7.1 Hz, 2H), 2.74–2.85 (m, 3H), 3.72 (t, J = 7.0 Hz, 2H), 4.08 (d, J = 10.3 Hz, 2H), 4.45 (s, 2H), 7.41 (d, J = 8.3 Hz, 2H), 7.54 (d, J = 8.1 Hz, 1H), 7.90 (d, J = 8.3 Hz, 2H), 7.92 (dd, J = 8.1, 1.7 Hz, 1H), 8.17 (d, J = 1.7 Hz, 1H), 10.37 (s, 1H), 12.37 (br s, 1H); HRMS (FAB) m/z calcd for $C_{28}H_{34}N_3O_6$ $[M+H]^+$: 508.5997, found: 508.6002.

4.1.8.9. 3-{6-[4-(4-Boc-piperazin-1-yl)benzoylamino]-1-oxo-1,3-dihydroisoindol-2-yl}propionic acid (16i). Mp >300 °C (decomposes); ^{1}H NMR δ (400 MHz, d_6-DMSO) 1.43 (s, 9H), 2.62 (t, J = 6.0 Hz, 2H), 3.30 (s, 4H), 3.48 (s, 4H), 3.74 (t, J = 6.0 Hz, 2H), 4.46 (s, 2H), 7.04 (d, J = 7.9 Hz, 2H), 7.54 (d, J = 7.5 Hz, 1H), 7.91–7.95 (m, 2H), 8.18 (s, 1H), 10.15 (s, 1H), 12.35 (br s, 1H); HRMS (FAB) m/z calcd for $C_{27}H_{33}N_4O_6$ $[M+H]^+$: 509.5873, found: 509.5870.

4.1.8.10. 3-{6-[(2-Boc-1,2,3,4-tetrahydroisoquinoline-7-carbonyl)amino]-1-oxo-1,3-dihydroisoindol-2-yl}propionic acid (16j) Mp = 118–120 °C (decomposes); ^{1}H NMR δ (400 MHz, d_6-DMSO) 1.45 (s, 9H), 2.63 (t, J = 7.1 Hz, 2H), 2.87 (t, J = 5.7 Hz, 2H), 3.60 (t, J = 5.5 Hz, 2H), 3.75 (t, J = 7.0 Hz, 2H), 4.48 (s, 2H), 4.61 (s, 2H), 7.34 (d, J = 8.1 Hz, 1H), 7.57 (d, J = 8.3 Hz, 1H), 7.80 (d, J = 8.1 Hz, 1H), 7.83 (s, 1H), 7.95 (dd, J = 8.2, 1.6 Hz, 1H), 8.19 (d, J = 1.6 Hz, 1H), 10.38 (s, 1H), 12.35 (br s, 1H); HRMS (FAB) m/z calcd for $C_{26}H_{30}N_3O_6$ $[M+H]^+$: 480.5455, found: 480.5457.

4.1.8.11. 3-{6-[3-(4-Boc-piperazin-1-yl)benzoylamino]-1-oxo-1,3-dihydroisoindol-2-yl}propionic acid (16k). Mp = 196–196.5 °C; ^{1}H NMR δ (500 MHz, d_6-DMSO) 1.43 (s, 9H), 2.53–2.54 (m, 2H), 3.21 (t, J = 6.4 Hz, 4H), 3.49 (t, J = 6.4 Hz, 4H), 3.72 (t, J = 6.8 Hz, 2H), 4.48 (s, 2H), 7.18 (d, J = 7.6 Hz, 1H), 7.38 (t, J = 7.8 Hz, 1H), 7.44 (d, J = 7.3 Hz, 1H), 7.53–7.56 (m, 2H), 7.98 (d, J = 8.1 Hz, 1H), 8.19 (s, 1H), 10.49 (s, 1H); HRMS (FAB) m/z calcd for $C_{27}H_{33}N_4O_6$ $[M+H]^+$: 509.5873, found: 509.5879.

4.1.8.12. 3-{6-[2-(1-Boc-piperidin-4-yl)acetylamino]-1-oxo-1,3-dihydroisoindol-2-yl}butyric acid (16l). Mp = 197–199 °C; ^{1}H NMR δ (500 MHz, d_6-DMSO) 1.09 (ddd, J = 23.6, 11.9, 3.1 Hz, 2H), 1.27 (d, J = 6.5 Hz, 3H), 1.40 (s, 9H), 1.67 (d, J = 12.2 Hz, 2H), 1.91–2.02 (m, 1H), 2.28 (d, J = 7.3 Hz, 2H), 2.62 (ddd, J = 31.5, 15.2, 7.3 Hz, 2H), 2.69–2.80 (m, 2H), 3.92 (d, J = 9.1 Hz, 2H), 4.39 (dd, J = 27.5, 17.4 Hz, 2H), 4.60 (td, J = 13.1, 6.0 Hz, 1H), 7.51 (d, J = 8.3 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 8.02 (s, 1H), 10.09 (s, 1H), 12.26 (s, 1H); HRMS (FAB) m/z calcd for $C_{24}H_{34}N_3O_6$ $[M+H]^+$: 460.5551, found: 450.5555.

4.1.8.13. 3-{6-[4-(1-Boc-piperidin-4-yl)butyrylamino]-1-oxo-1,3-dihydroisoindol-2-yl}butyric acid (16m). Mp = 139–140.5 °C; ^{1}H NMR δ (500 MHz, d_6-DMSO) 0.95 (ddd, J = 24.5, 12.2, 3.7 Hz, 2H), 1.20–1.25 (m, 5H), 1.39 (s, 9H), 1.42–1.44 (m, 1H), 1.59–1.65 (m, 4H), 2.32 (t, J = 7.1 Hz, 2H), 2.62–2.69 (m, 2H), 3.92 (d, J = 8.1 Hz, 2H), 4.36 (s, 2H), 4.59 (m, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.69 (d, J = 7.8 Hz, 1H), 8.03 (s, 1H), 10.23 (s, 1H); HRMS (FAB) m/z calcd for $C_{26}H_{38}N_3O_6$ $[M+H]^+$: 488.6093, found: 488.6089.

4.1.8.14. 3-{6-[4-(1-Boc-piperidin-4-yl)benzoylamino]-1-oxo-1,3-dihydroisoindol-2-yl}butyric acid (16n). Mp = 175–176 °C; ^{1}H NMR δ (500 MHz, d_6-DMSO) 1.25 (d, J = 6.4 Hz, 3H), 1.43 (s, 9H), 1.54 (ddd, J = 24.8, 12.2, 3.5 Hz, 2H), 1.79 (d, J = 12.2 Hz, 2H), 2.74–2.89 (m, 3H), 4.10 (d, J = 6.4 Hz, 2H), 4.41 (s, 2H), 4.62 (dt, J = 13.5, 6.5 Hz, 1H), 7.42 (d, J = 7.8 Hz, 2H), 7.55 (d, J = 8.3 Hz, 1H), 7.93–7.96 (m, 3H), 8.18(s, 1H), 10.43 (s, 1H); HRMS (FAB) m/z calcd for $C_{29}H_{36}N_3O_6$ $[M+H]^+$: 522.6268, found: 522.6270.

4.1.8.15. 3-{6-[4-(4-Boc-piperazin-1-yl)benzoylamino]-1-oxo-1,3-dihydroisoindol-2-yl}butyric acid (16o). Mp = 155.5–156 °C; ^{1}H NMR δ (500 MHz, d_6-DMSO) 1.29 (d, J = 6.6 Hz, 3H), 1.44 (s, 9H), 2.64 (ddd, J = 32.3, 15.3, 7.5 Hz, 2H), 3.30 (s, 4H), 3.48 (s, 4H), 4.41 (dd, J = 27.1, 17.1 Hz, 2H), 4.62 (td, J = 13.8, 7.0 Hz, 1H), 7.04 (d, J = 8.8 Hz, 2H), 7.55 (d, J = 8.1 Hz, 1H), 7.93 (d, J = 8.1 Hz, 2H), 7.95 (d, J = 8.8 Hz, 1H), 8.18 (s, 1H), 10.16 (s, 1H), 12.27 (br s, 1H); HRMS (FAB) m/z calcd for $C_{28}H_{35}N_4O_6$ $[M+H]^+$: 523.6144, found: 523.6139.

4.1.8.16. 3-{6-[(2-Boc-1,2,3,4-tetrahydroisoquinoline-7-carbonyl)-amino]-1-oxo-1,3-dihydroisoindol-2-yl}-butyric acid (16p). Mp = 153–154 °C; ^{1}H NMR δ (500 MHz, d_6-DMSO) 1.29 (d, J = 6.6 Hz, 3H), 1.45 (s, 9H), 2.64 (ddd, J = 32.8, 15.2, 7.5 Hz, 2H), 2.87 (t, J = 5.2 Hz, 2H), 3.60 (t, J = 5.2 Hz, 2H), 4.43 (dd, J = 27.1, 17.4 Hz, 2H), 4.55–4.64 (m, 3H), 7.34 (d, J = 7.8 Hz, 1H), 7.57 (d, J = 8.3 Hz, 1H), 7.80 (d, J = 8.8 Hz, 1H), 7.83 (s, 1H), 7.95 (dd, J = 8.1, 1.5 Hz, 2H), 8.18 (s, 1H) 10.36 (s, 1H), 12.30 (br s, 1H); HRMS (FAB) m/z calcd for $C_{27}H_{32}N_3O_6$ $[M+H]^+$: 494.5726, found: 493.5723.

4.1.8.17. 3-{6-[3-(4-Boc-piperazin-1-yl)benzoylamino]-1-oxo-1,3-dihydroisoindol-2-yl}butyric acid (16q). Mp >300 °C; ^{1}H NMR δ (500 MHz, d_6-DMSO) 1.29 (d, J = 3.9 Hz, 3H), 1.44 (s, 9H), 2.65 (ddd, J = 33.2, 18.0, 6.4 Hz, 2H), 3.22 (s, 4H), 3.51 (s, 4H), 4.43 (dd, J = 26.2, 16.1 Hz, 2H), 4.62 (td, J = 14.1, 6.2 Hz, 1H), 7.20 (d, J = 4.4 Hz, 1H), 7.38–7.43 (m, 2H), 7.51 (s, 1H), 7.58 (d, J = 6.5 Hz, 1H), 7.95 (d, J = 7.0 Hz, 1H), 8.16 (s, 1H), 10.35 (s, 1H), 12.30 (br s, 1H); HRMS (FAB) m/z calcd for $C_{28}H_{35}N_4O_6$ $[M+H]^+$: 523.6144, found: 523.6139.

4.1.8.18. 4-{6-[2-(1-Boc-piperidin-4-yl)acetylamino]-1-oxo-1,3-dihydroisoindol-2-yl}butyric acid (16r). Mp = 191.5–192 °C; ^{1}H NMR δ (500 MHz, d_6-DMSO) 1.06–1.13 (m, 2H), 1.40 (s, 9H), 1.67 (d, J = 12.2 Hz, 2H), 1.84 (t, J = 7.2, 2H), 1.94–1.99 (m, 1H), 2.25–2.28 (m, 4H), 2.67–2.79 (m, 2H), 3.54 (t, J = 7.2 Hz, 2H), 3.93 (d, J = 10.1 Hz, 2H), 4.41 (s, 2H), 7.50 (d, J = 7.0 Hz, 1H), 7.68 (d, J = 7.0 Hz, 1H), 8.03 (s, 1H), 10.09 (s, 1H), 12.07 (s, 1H); HRMS (FAB) m/z calcd for $C_{24}H_{34}N_3O_6$ $[M+H]^+$: 460.5551, found: 459.5559.

4.1.8.19. 4-{6-[4-(1-Boc-piperidin-4-yl)butyrylamino]-1-oxo-1,3-dihydroisoindol-2-yl}butyric acid (16s). Mp = 190–191 °C; ^{1}H NMR δ (400 MHz, d_6-DMSO) 0.94 (ddd, J = 24.4, 12.3, 3.9 Hz, 2H), 1.20–1.26 (m, 2H), 1.38 (s, 9H), 1.42–1.44 (m, 1H), 1.60–1.65 (m, 4H), 1.82 (dt, J = 14.2, 7.1 Hz, 2H), 2.24 (t, J = 7.2 Hz, 2H), 2.31 (t, J = 7.3 Hz, 2H), 2.63–2.72 (m, 2H), 3.51 (t, J = 7.0 Hz, 2H), 3.91 (d, J = 10.3 Hz, 2H), 4.40 (s, 2H), 7.49 (d, J = 8.3 Hz, 1H), 7.68 (dd, J = 8.1, 1.5 Hz, 1H), 8.02 (s, 1H), 10.08 (s, 1H), 12.09 (br s, 1H); HRMS (FAB) m/z calcd for $C_{26}H_{37}N_3O_6$ $[M+H]^+$: 488.6093, found: 488.6090.

4.1.8.20. 4-{6-[4-(1-Boc-piperidin-4-yl)benzoylamino]-1-oxo-1,3-dihydroisoindol-2-yl}butyric acid (16t). Mp = 197–197.5 °C; ^{1}H NMR δ (400 MHz, d_6-DMSO) 1.42 (s, 9H), 1.53 (ddd, J = 25.1, 12.8, 3.9 Hz, 2H), 1.78 (d, J = 13.7 Hz, 2H), 1.84 (dt, J = 14.2, 6.8 Hz, 2H), 2.25 (t, J = 7.2 Hz, 2H), 2.75–2.85 (m, 3H), 3.54 (t, J = 6.8 Hz, 2H), 4.09 (d, J = 9.8 Hz, 2H), 4.44 (s, 2H), 7.42 (d, J = 8.1 Hz, 2H), 7.55 (d, J = 8.3 Hz, 1H), 7.91–7.94 (m, 3H), 8.17 (s, 1H), 10.38 (s, 1H); HRMS (FAB) m/z calcd for $C_{29}H_{36}N_3O_6$ $[M+H]^+$: 522.6268, found: 522.6261.

4.1.8.21. 4-{6-[(2-Boc-1,2,3,4-tetrahydroisoquinoline-7-carbonyl)-amino]-1-oxo-1,3-dihydroisoindol-2-yl}butyric acid (16u). Mp = 90–93 °C; ^{1}H NMR δ (400 MHz, d_6-DMSO) 1.44 (s, 9H), 1.84 (dt, J = 13.9, 7.1 Hz, 2H), 2.26 (t, J = 7.0 Hz, 2H), 2.86 (t, J = 5.1 Hz, 2H), 3.54 (t, J = 6.7 Hz, 2H), 3.59 (t, J = 4.6 Hz, 2H), 4.45 (s, 2H), 4.60 (s, 2H), 7.33 (d, J = 7.6 Hz, 1H), 7.56 (d, J = 8.1 Hz, 2H), 7.78–7.82 (m, 2H), 7.94 (d, J = 8.1 Hz, 1H), 8.18 (s, 1H), 10.37 (s, 1H), 12.14 (br s, 1H); HRMS (FAB) m/z calcd for $C_{27}H_{32}N_3O_6$ $[M+H]^+$: 494.5726, found: 494.5721.

4.1.9. General procedures for a preparation of compound 17

Method A. This method was used when the compound **16** was not soluble in anhydrous CH_2Cl_2. The compound **16** (10 mmol) was suspended in anhydrous CH_2Cl_2, and trifluoroacetic acid (1 ml) was added. The precipitate was dissolved in a short time, and the reaction solution was kept for 2 h, protected from moisture. After the solvent was evaporated in vacuo to dryness, the residue was dried in vacuo (2 mmHg) for 2 h at 40 °C.

Method B. This method was used for the compound **16** soluble in anhydrous CH_2Cl_2. The compound **16** (10 mmol) was dissolved in anhydrous CH_2Cl_2, and the stream of dry HCl was passed through the solution for 1 h. The solvent was evaporated, and the solid residue was dried in vacuo (2 mm Hg) for 2 h at 40 °C.

4.1.9.1. [1-Oxo-6-(2-piperidinium-4-yl-acetylamino)-1,3-dihydroisoindol-2-yl]acetic acid trifluoroacetate (17a). Mp = 236–239 °C; ^{1}H NMR δ (500 MHz, d_6-DMSO) 1.41 (ddd, J = 22.6, 10.6, 2.6 Hz, 2H), 1.85 (d, J = 13.8 Hz, 2H), 2.05–2.13 (m, 1H), 2.33 (d, J = 6.7 Hz, 2H), 2.91 (dd, J = 22.8, 11.6 Hz, 2H), 3.27 (d, J = 11.9 Hz, 2H), 4.28 (s, 2H), 4.46 (s, 2H), 7.54 (d, J = 8.2 Hz, 1H), 7.69 (d, J = 8.2 Hz, 1H), 8.10 (s, 1H), 8.37 (d, J = 8.7 Hz, 1H), 8.65 (d, J = 8.7 Hz, 1H), 10.23 (s, 1H); ^{13}C NMR δ (125 MHz, d_6-DMSO) 28.64 (2C), 31.17 (1C), 43.05 (1C), 43.58 (2C), 43.95 (1C), 50.41 (1C), 113.61 (1C), 116.75 (1C, $\boldsymbol{C}F_3CO_2^-$), 123.10 (1C), 124.17 (s, 1C), 132.64 (1C), 137.06 (1C), 139.42 (1C), 158.81 (1C, $CF_3\boldsymbol{C}O_2^-$), 168.15 (1C), 170.37 (1C), 170.98 (1C); HRMS (FAB) m/z calcd for $C_{17}H_{22}N_3O_4$ $[M+H]^+$: 332.3826, found: 332.3825.

4.1.9.2. [1-Oxo-6-(4-piperidinium-4-yl-butyrylamino)-1,3-dihydroisoindol-2-yl]acetic acid trifluoroacetate (17b). Mp = 114–115 °C; ^{1}H NMR δ (400 MHz, d_6-DMSO) 0.75–0.85 (m, 4H), 1.02–1.11 (m, 1H), 1.16 (dt, J = 14.9, 7.5 Hz, 2H), 1.35 (d, J = 13.4 Hz, 2H), 1.88 (t, J = 7.2 Hz, 2H), 2.37 (dd, J = 32.5, 11.9 Hz, 1H), 2.80 (d, J = 12.2 Hz, 2H), 3.81 (s, 2H), 3.99 (s, 2H), 7.06 (d, J = 8.3 Hz, 1H), 7.24 (dd, J = 8.2, 1.1 Hz, 1H), 7.64 (s, 1H), 7.86 (d, J = 8.1 Hz, 1H), 8.17 (d, J = 8.1 Hz, 1H), 9.71 (s, 1H); HRMS (FAB) m/z calcd for $C_{19}H_{26}N_3O_4$ $[M+H]^+$: 360.4368, found: 360.4374.

4.1.9.3. [1-Oxo-6-(4-piperidinium-4-yl-benzoylamino)-1,3-dihydroisoindol-2-yl]acetic acid trifluoroacetate (17C). Mp >300 °C; ^{1}H NMR δ (400 MHz, d_6-DMSO) 1.84 (ddd, J = 26.7, 12.5, 2.9 Hz, 2H), 1.99 (d, J = 13.2 Hz, 2H), 2.93–2.98 (m, 1H), 3.04 (dd, J = 23.5, 12.2 Hz, 2H), 3.41 (d, J = 11.7 Hz, 2H), 4.30 (s, 2H), 4.50

(s, 2H), 7.41 (d, *J* = 8.3 Hz, 2H), 7.60 (d, *J* = 8.3 Hz, 1H), 7.95–7.99 (m, 3H), 8.23 (d, *J* = 1.5 Hz, 1H), 8.42 (dd, *J* = 21.3, 10.8 Hz, 1H), 8.69 (d, *J* = 11.7 Hz, 1H), 10.44 (s, 1H); ^{13}C NMR δ (125 MHz, d_6-DMSO) 29.67 (2C), 39.25 (1C), 43.98 (1C), 44.05 (2C), 50.46 (1C), 114.75 (1C), 116.89 (1C, $CF_3CO_2^-$), 124.08 (1C), 124.22 (1C), 127.06 (2C), 128.58 (2C), 132.60 (1C), 133.56 (1C), 137.50 (1C), 139.58 (1C), 148.86 (1C), 158.77 (1C, $CF_3CO_2^-$), 165.95 (1C), 168.18 (1C), 170.99 (1C); HRMS (FAB) *m*/*z* calcd for $C_{22}H_{24}N_3O_4$ $[M+H]^+$: 394.4543, found: 394.4545.

4.1.9.4. [1-Oxo-6-(4-piperazinium-1-yl-benzoylamino)-1,3-dihydroisoindol-2-yl]acetic acid trifluoroacetate (17d). Mp = 241–242 °C; ^{1}H NMR δ (500 MHz, d_6-DMSO) 3.27 (s, 4H) 3.54 (s, 4H) 4.30 (s, 2H) 4.49 (s, 2H) 7.11 (d, *J* = 8.3 Hz, 2H) 7.58 (d, *J* = 8.1 Hz, 1H) 7.96–7.99 (m, 3H) 8.23 (s, 1H) 8.96 (s, 2H) 10.23 (s, 1H); ^{13}C NMR δ (125 MHz, d_6-DMSO) 42.98 (2C), 43.97 (1C), 44.90 (2C), 50.45 (1C), 114.70 (1C), 114.73 (2C), 116.67 (1C, $CF_3CO_2^-$), 123.97 (1C), 124.19 (1C), 125.11 (1C), 129.70 (2C), 132.55 (1C), 137.15 (1C), 139.84 (1C), 152.63 (1C), 158.75 (1C, $CF_3CO_2^-$), 165.47 (1C), 168.23 (1C), 171.01 (1C); HRMS (FAB) ***m*/*z*** calcd for $C_{21}H_{23}N_4O_4$ $[M+H]^+$: 395.4419, found: 366.4422.

4.1.9.5. {1-Oxo-6-[(1,2,3,4-tetrahydroisoquinolinium-7-carbonyl)amino]-1,3-dihydroisoindol-2-yl}acetic acid chloride (17e). Mp = 297.5–298 °C (decomposes); ^{1}H NMR δ (400 MHz, d_6-DMSO) 3.11 (t, *J* = 6.0 Hz, 2H), 3.40 (dd, *J* = 10.5, 6.3 Hz, 2H), 4.30 (s, 2H), 4.35 (t, *J* = 4.0 Hz, 2H), 4.50 (s, 2H), 7.40 (d, *J* = 8.3 Hz, 1H), 7.60 (d, *J* = 8.3 Hz, 1H), 7.90–7.92 (m, 2H), 8.01 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.26 (d, *J* = 1.7 Hz, 1H), 9.76 (s, 2H), 10.59 (s, 1H); HRMS (FAB) *m*/*z* calcd for $C_{20}H_{20}N_3O_4$ $[M+H]^+$: 366.4001, found: 366.3997.

4.1.9.6. 3-[1-Oxo-6-(2-piperidinium-4-yl-acetylamino)-1,3-dihydroisoindol-2-yl]propionic acid trifluoroacetate (17f). Mp = 112–114 °C; ^{1}H NMR δ (500 MHz, d_6-DMSO) 1.40 (dd, *J* = 24.9, 13.2 Hz, 2H) 1.85 (d, *J* = 15.1 Hz, 2H) 2.03–2.14 (m, 1H), 2.33 (d, *J* = 7.0 Hz, 2H), 2.61 (t, *J* = 6.8 Hz, 2H), 2.91 (dd, *J* = 22.8, 11.5 Hz, 2H), 3.27 (d, *J* = 11.9 Hz, 2H), 3.73 (t, *J* = 6.8 Hz, 2H), 4.44 (s, 2H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 8.05 (s, 1H), 8.30 (d, *J* = 10.1 Hz, 1H), 8.59 (d, *J* = 7.0 Hz, 1H), 10.19 (s, 1H); ^{13}C NMR δ (125 MHz, d_6-DMSO) 28.65 (2C), 31.16 (1C), 33.36 (1C), 38.60 (1C), 43.04 (1C), 43.59 (2C), 49.97 (1C), 113.42 (1C), 116.58 (1C, $CF_3CO_2^-$), 122.76 (1C), 124.02 (1C), 133.25 (1C), 136.85 (1C), 139.34 (1C), 158.74 (1C, $CF_3CO_2^-$), 167.64 (1C), 170.31 (1C), 173.26 (1C); HRMS (FAB) ***m*/*z*** calcd for $C_{18}H_{24}N_3O_4$ $[M+H]^+$: 346.4097, found: 374.4690.

4.1.9.7. 3-[1-Oxo-6-(4-piperidinium-4-yl-butyrylamino)-1,3-dihydroisoindol-2-yl]propionic acid trifluoroacetate (17g). Mp = 196–197 °C; ^{1}H NMR δ (400 MHz, d_6-DMSO) 1.20–1.30 (m, 4H), 1.49–1.55 (m, 1H), 1.58–165 (m, 2H), 1.81 (d, *J* = 12.9 Hz, 2H), 2.34 (t, *J* = 6.6 Hz, 2H), 2.60 (t, *J* = 6.9 Hz, 2H), 2.83 (dd, *J* = 20.8, 10.0 Hz, 2H), 3.26 (d, *J* = 11.2 Hz, 2H), 3.72 (t, *J* = 6.9 Hz, 2H), 4.43 (s, 2H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.67 (d, *J* = 7.5 Hz, 1H), 8.05 (s, 1H), 8.32 (s, 1H), 8.64 (s, 1H), 10.14 (s, 1H); HRMS (FAB) ***m*/*z*** calcd for $C_{20}H_{28}N_3O_4$ $[M+H]^+$: 374.4639, found: 374.4643.

4.1.9.8. 3-[1-Oxo-6-(4-piperidinium-4-yl-benzoylamino)-1,3-dihydroisoindol-2-yl]propionic acid trifluoroacetate (17h). Mp = 243–244 °C (decomposes); ^{1}H NMR δ (400 MHz, d_6-DMSO) 1.85 (dd, *J* = 23.7, 11.5 Hz, 2H), 1.99 (d, *J* = 13.2 Hz, 2H), 2.63 (t, *J* = 7.0 Hz, 2H), 2.93–3.09 (m, 3H), 3.42 (d, *J* = 11.7 Hz, 2H), 3.75 (t, *J* = 7.0 Hz, 2H), 4.48 (s, 2H), 7.41 (d, *J* = 8.1 Hz, 2H), 7.57 (d, *J* = 8.3 Hz, 1H), 7.94 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.97 (d, *J* = 8.1 Hz, 2H), 8.20 (d, *J* = 1.5 Hz, 1H), 8.57 (s, 1H), 8.77 (t, *J* = 12.7, 2H), 10.43 (s, 1H); HRMS (FAB) ***m*/*z*** calcd for $C_{23}H_{26}N_3O_4$ $[M+H]^+$: 408.4814, found: 408.4816.

4.1.9.9. 3-[1-Oxo-6-(4-piperazinium-1-yl-benzoylamino)-1,3-dihydroisoindol-2-yl]propionic acid trifluoroacetate (17i). Mp = 212–214 °C; ^{1}H NMR δ (400 MHz, d_6-DMSO + CCl_4) 2.62 (t, *J* = 6.6 Hz, 2H), 3.27 (s, 4H), 3.53 (s, 4H), 3.74 (t, *J* = 6.6 Hz, 2H), 4.46 (s, 2H), 7.10 (d, *J* = 8.7 Hz, 2H), 7.55 (d, *J* = 8.3 Hz, 1H), 7.93–7.99 (m, 3H), 8.19 (s, 1H), 9.02 (s, 2H), 10.21 (s, 1H); ^{13}C NMR δ (125 MHz, d_6-DMSO) 33.39 (1C), 38.61 (1C), 42.98 (2C), 44.89 (2C), 50.01 (1C), 114.50 (1C), 114.72 (2C), 116.68 (1C, $CF_3CO_2^-$), 123.83 (1C), 123.86 (1C), 129.69 (2C), 133.15 (1C), 136.94 (1C), 139.76 (1C), 152.61 (1C), 158.57 (1C, $CF_3CO_2^-$), 165.44 (1C), 167.74 (1C), 173.29 (1C); HRMS (FAB) ***m*/*z*** calcd for $C_{22}H_{25}N_4O_4$ $[M+H]^+$: 409.4689, found: 409.4696.

4.1.9.10. 3-{1-Oxo-6-[(1,2,3,4-tetrahydroisoquinolinium-7-carbonyl)amino]-1,3-dihydroisoindol-2-yl}-propionic acid chloride (17j). Mp = 276–277.5 °C; ^{1}H NMR δ (400 MHz, d_6-DMSO) 2.63 (t, *J* = 7.0 Hz, 2H), 3.10 (t, *J* = 5.9 Hz, 2H), 3.40 (dd, *J* = 6.5, 4.4 Hz, 2H), 3.74 (t, *J* = 7.0 Hz, 2H), 4.35 (s, 2H), 4.48 (s, 2H), 7.40 (d, *J* = 8.6 Hz, 1H), 7.56 (d, *J* = 8.3 Hz, 1H), 7.89–7.92 (m, 2H), 7.97 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.21 (d, *J* = 1.2 Hz, 1H), 9.67 (s, 2H), 10.54 (s, 1H); HRMS (FAB) *m*/*z* calcd for $C_{21}H_{22}N_3O_4$ $[M+H]^+$: 380.4272, found: 380.4281.

4.1.9.11. 3-[1-Oxo-6-(3-piperazinium-1-yl-benzoylamino)-1,3-dihydroisoindol-2-yl]propionic acid trifluoroacetate (17k). Mp = 102–103 °C; ^{1}H NMR δ (500 MHz, d_6-DMSO) 2.63 (t, *J* = = 7.1 Hz, 2H), 3.29 (s, 4H), 3.46 (t, *J* = 4.8 Hz, 4H), 3.75 (t, *J* = 6.8 Hz, 2H), 4.48 (s, 2H), 7.24 (d, *J* = 8.3 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.52 (s, 1H), 7.58 (d, *J* = 8.1 Hz, 1H), 7.94 (d, *J* = 7.8 Hz, 1H), 8.17 (s, 1H), 8.88 (s, 2H), 10.39 (s, 1H); ^{13}C NMR δ (125 MHz, d_6-DMSO) 33.39 (1C), 38.62 (1C), 43.17 (2C), 45.93 (2C), 50.04 (1C), 114.69 (1C), 115.37 (1C), 116.09 (1C, $CF_3CO_2^-$), 119.66 (1C), 119.78 (1C), 123.93 (1C), 124.01 (1C), 129.72 (1C), 133.21 (1C), 136.18 (1C), 137.34 (1C), 139.44 (1C), 150.46 (1C), 158.76 (1C, $CF_3CO_2^-$), 166.30 (1C), 167.67 (1C), 173.28 (1C); HRMS (FAB) ***m*/*z*** calcd for $C_{22}H_{25}N_4O_4$ $[M+H]^+$: 409.4689, found: 409.4687.

4.1.9.12. 3-[1-Oxo-6-(2-piperidinium-4-yl-acetylamino)-1,3-dihydroisoindol-2-yl]butyric acid trifluoroacetate (17l). Glassy substance; ^{1}H NMR δ (500 MHz, d_6-DMSO) 1.27 (d, *J* = 6.7 Hz, 3H), 1.37–1.44 (m, 2H), 1.85 (d, *J* = 13.5 Hz, 2H), 2.05–2.12 (m, 1H), 2.33 (d, *J* = 6.7 Hz, 2H), 2.62 (ddd, *J* = 30.8, 15.3, 7.4 Hz, 2H), 2.92 (dd, *J* = 22.8, 11.9 Hz, 2H), 3.27 (d, *J* = 11.9 Hz, 2H), 4.39 (dd, *J* = 27.8, 17.1 Hz, 2H), 4.59 (dt, *J* = 14.4, 7.5 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 8.04 (s, 1H), 8.35 (d, *J* = 7.3 Hz, 1H), 8.62 (d, *J* = 7.0 Hz, 1H), 10.20 (s, 1H); HRMS (FAB) *m*/*z* calcd for $C_{19}H_{26}N_3O_4$ $[M+H]^+$: 360.4368, found: 360.4660.

4.1.9.13. 3-[1-Oxo-6-(4-piperidinium-4-yl-butyrylamino)-1,3-dihydroisoindol-2-yl]butyric acid chloride (17m). Mp = 231–234 °C; ^{1}H NMR δ (500 MHz, d_6-DMSO) 1.21–1.29 (m, 5H), 1.32 (dd, *J* = 23.1, 11.4 Hz, 2H), 1.49–1.56 (m, 1H), 1.61 (t, *J* = 6.6 Hz, 2H), 1.79 (d, *J* = 13.5 Hz, 2H), 2.36 (t, *J* = 5.8 Hz, 2H), 2.61 (ddd, *J* = 31.1, 15.1, 7.8 Hz, 2H), 2.80 (dd, *J* = 21.2, 10.5 Hz, 2H), 3.21 (d, *J* = 11.2 Hz, 2H), 4.37 (dd, *J* = 26.7, 17.7 Hz, 2H), 4.59 (dd, *J* = 12.8, 6.4 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.74 (d, *J* = 7.0 Hz, 1H), 8.07 (s, 1H), 8.82 (d, *J* = 7.6 Hz, 1H), 9.09 (d, *J* = 7.6 Hz, 1H), 10.36 (s, 1H); ^{13}C NMR δ (125 MHz, d_6-DMSO) 18.51 (1C), 22.02 (1C), 28.30 (2C), 32.86 (1C), 35.06 (1C), 36.33 (1C), 43.15 (2C), 44.43 (1C), 45.58 (1C), 112.87 (1C), 122.25 (1C), 123.48 (1C), 133.02 (1C), 136.05 (1C), 139.27 (1C), 166.82 (1C), 171.47 (1C), 172.25 (1C); HRMS (FAB) ***m*/*z*** calcd for $C_{21}H_{30}N_3O_4$ $[M+H]^+$: 388.4910, found: 388.4872.

4.1.9.14. 3-[1-Oxo-6-(4-piperidinium-4-yl-benzoylamino)-1,3-dihydroisoindol-2-yl]butyric acid chloride (17n). Mp = 200–202 °C; ^{1}H NMR δ (500 MHz, d_6-DMSO) 1.28 (d, J = 6.7 Hz, 3H), 1.94–2.02 (m, 4H), 2.64 (ddd, J = 31.4, 15.2, 7.4 Hz, 2H), 2.94–3.04 (m, 3H), 3.36 (d, J = 10.6 Hz, 2H), 4.43 (dd, J = 27.8, 17.4 Hz, 2H), 4.61 (td, J = 14.0, 7.0 Hz, 1H), 7.40 (d, J = 7.8 Hz, 2H), 7.56 (d, J = 8.0 Hz, 1H), 7.97–8.01 (m, 3H), 8.20 (s, 1H), 9.23–9.27 (m, 1H), 9.32–9.34 (m, J = 9.6 Hz, 1H), 10.50 (s, 1H); HRMS (FAB) m/z calcd for $C_{24}H_{28}N_3O_4$ $[M+H]^+$: 422.5085, found: 422.5091.

4.1.9.15. 3-[1-Oxo-6-(4-piperazinium-4-yl-benzoylamino)-1,3-dihydroisoindol-2-yl]butyric acid chloride (17o). Mp = 258–258.5 °C (decomposes); ^{1}H NMR δ (500 MHz, d_6-DMSO) 1.28 (d, J = 6.8 Hz, 3H), 2.64 (ddd, J = 31.2, 15.3, 7.1 Hz, 2H), 3.21 (s, 4H), 3.57 (t, J = 4.3, 4H), 4.41 (dd, J = 27.9, 17.6 Hz, 2H), 4.61 (td, J = 13.6, 6.5 Hz, 1H), 7.10 (d, J = 8.3 Hz, 2H), 7.55 (d, J = 8.3 Hz, 2H), 7.97 (m, J = 8.1 Hz, 3H), 8.19 (s, 1H), 9.51 (s, 2H), 10.26 (s, 1H); ^{13}C NMR δ (125 MHz, d_6-DMSO) 18.99 (1C), 42.74 (2C), 44.76 (2C), 44.88 (1C), 46.06 (1C), 114.53 (2C), 114.69 (1C), 123.83 (1C), 123.85 (1C), 125.03 (1C), 129.73 (2C), 133.42 (1C), 136.84 (1C), 139.80 (1C), 152.63 (1C), 165.45 (1C), 167.25 (1C), 172.71 (1C); HRMS (FAB) m/z calcd for $C_{23}H_{27}N_4O_4$ $[M+H]^+$: 423.4960, found: 423.4953.

4.1.9.16. 3-{1-Oxo-6-[(1,2,3,4-tetrahydroisoquinolinium-7-carbonyl)amino]-1,3-dihydroisoindol-2-yl}butyric acid chloride (17p). Hygroscopic substance; ^{1}H NMR δ (500 MHz, d_6-DMSO) 1.29 (d, J = 6.6 Hz, 3H), 2.64 (ddd, J = 30.8, 15.2, 7.1 Hz, 2H), 3.09 (t, J = 6.0 Hz, 2H), 3.45 (d, J = 5.1 Hz, 2H), 4.39–4.48 (m, 4H), 4.62 (td, J = 14.2, 7.3 Hz, 1H), 7.42 (d, J = 8.1 Hz, 1H), 7.59 (d, Jv8.6 Hz, 1H), 7.88–7.95 (m, 3H), 8.18 (s, 1H), 9.17 (s, 2H), 10.46 (s, 1H); HRMS (FAB) m/z calcd for $C_{22}H_{24}N_3O_4$ $[M+H]^+$: 394.4543, found: 394.4546.

4.1.9.17. 3-[1-Oxo-6-(3-piperazinium-4-yl-benzoylamino)-1,3-dihydroisoindol-2-yl]butyric acid chloride (17q). Mp = 232–233 °C; ^{1}H NMR δ (500 MHz, d_6-DMSO) 1.28 (d, J = 5.4 Hz, 3H), 2.64 (ddd, J = 30.6, 14.8, 7.8 Hz, 2H), 3.24 (s, 4H), 3.52 (s, 4H), 4.42 (dd, J = 26.5, 17.4 Hz, 2H), 4.59–4.65 (m, 1H), 7.23 (d, J = 7.5 Hz, 1H), 7.41 (t, J = 6.7 Hz, 1H), 7.50 (d, J = 6.5 Hz, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.60 (s, 1H), 7.99 (d, J = 7.3 Hz, 1H), 8.20 (s, 1H) 9.53 (s, 2H), 10.52 (s, 1H); ^{13}C NMR δ (125 MHz, d_6-DMSO) 18.99 (1C), 38.72 (1C), 42.92 (2C), 44.90 (1C), 45.81 (2C), 46.10 (1C), 114.80 (1C), 115.49 (1C), 119.75 (1C), 123.91 (1C), 124.12 (1C), 129.69 (1C), 133.43 (1C), 136.08 (1C), 137.24 (1C), 139.49 (1C), 150.42 (1C), 166.28 (1C), 167.20 (1C), 172.70 (1C); HRMS (FAB) m/z calcd for $C_{23}H_{27}N_4O_4$ $[M+H]^+$: 423.4960, found: 423.4967.

4.1.9.18. 4-[1-Oxo-6-(2-piperidinium-4-yl-acetylamino)-1,3-dihydroisoindol-2-yl]butyric acid trifluoroacetate (17r). Mp = 184–185 °C; ^{1}H NMR δ (500 MHz, d_6-DMSO) 1.37–1.45 (m, 2H), 1.80–1.87 (m, 4H), 2.05–2.12 (m, 1H), 2.25 (t, J = 6.9 Hz, 2H), 2.33 (d, J = 6.7 Hz, 2H), 2.91 (dd, J = 23.0, 11.2 Hz, 2H), 3.28 (d, J = 11.2 Hz, 2H), 3.53 (t, J = 6.9 Hz, 2H), 4.41 (s, 2H), 7.51 (d, J = 7.8 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 8.05 (s, 1H), 8.33–8.38 (m, 1H), 8.61–8.66 (m, 1H), 10.20 (s, 1H); ^{13}C NMR δ (125 MHz, d_6-DMSO) 23.72 (1C), 28.65 (2C), 31.17 (1C), 31.47 (1C), 41.66 (1C), 43.05 (1C), 43.58 (2C), 49.58 (1C), 113.49 (1C), 116.17 (1C, $CF_3CO_2^-$), 122.68 (1C), 124.02 (1C), 133.34 (1C), 136.83 (1C), 139.33 (1C), 158.56 (1C, $CF_3CO_2^-$), 167.76 (1C), 170.31 (1C), 174.42 (1C); HRMS (FAB) m/z calcd for $C_{19}H_{26}N_3O_4$ $[M+H]^+$: 360.4368, found: 360.4372.

4.1.9.19. 4-[1-Oxo-6-(4-piperidinium-4-yl-butyrylamino)-1,3-dihydroisoindol-2-yl]butyric acid trifluoroacetate (17s). Mp = 200–202 °C; ^{1}H NMR δ (400 MHz, d_6-DMSO) 1.20–1.28 (m, 4H), 1.48–1.55 (m, 1H), 1.6 (dt, J = 15.0, 7.3 Hz, 2H), 1.78–1.86 (m, 4H), 2.24 (t, J = 7.2 Hz, 2H), 2.33 (t, J = 7.1 Hz, 2H), 2.83 (dd, J = 21.7, 10.9 Hz, 2H), 3.25 (d, J = 12.2 Hz, 2H), 3.51 (t, J = 6.8 Hz, 2H), 4.40 (s, 2H), 7.49 (d, J = 8.1 Hz, 1H), 7.66 (d, J = 8.1 Hz, 1H), 8.04 (s, 1H), 8.27 (s, 1H), 8.68 (s, 1H), 10.13 (s, 1H); ^{13}C NMR δ (125 MHz, d_6-DMSO) 22.41 (1C), 23.74 (1C), 28.87 (2C), 31.50 (1C), 33.30 (1C),35.49 (1C), 36.81 (1C), 41.69 (1C), 43.80 (2C), 49.59 (1C), 113.38 (1C), 116.44 (1C, $CF_3CO_2^-$), 122.61 (1C), 123.96 (1C), 133.34 (1C), 136.61 (1C), 139.57 (1C), 157.75 (1C, $CF_3CO_2^-$), 167.81 (1C), 171.78 (1C), 174.39 (1C); HRMS (FAB) m/z calcd for $C_{21}H_{30}N_3O_4$ $[M+H]^+$: 388.4910, found: 388.4904.

4.1.9.20. 4-[1-Oxo-6-(4-piperidinium-4-yl-benzoylamino)-1,3-dihydroisoindol-2-yl]butyric acid trifluoroacetate (17t). Mp = 280–281 °C; ^{1}H NMR δ (400 MHz, d_6-DMSO) 1.79–1.90 (m, 4H), 2.00 (d, J = 12.7 Hz, 2H), 2.26 (t, J = 6.6 Hz, 2H), 2.93–3.08 (m, 3H), 3.40–3.43 (m, 2H), 3.54 (t, J = 6.5 Hz, 2H), 4.45 (s, 2H), 7.40 (d, J = 7.6 Hz, 2H), 7.56 (d, J = 7.6 Hz, 2H), 7.92–7.97 (m, 3H), 8.18 (s, 1H), 8.52 (s, 1H), 8.77 (s, 1H), 10.43 (s, 1H); ^{13}C NMR δ (125 MHz, d_6-DMSO) 23.76 (1C), 29.67 (2C), 31.53 (1C), 39.25 (1C), 41.72 (1C), 44.05 (2C), 49.66 (1C), 114.65 (1C), 116.72 (1C, $CF_3CO_2^-$), 123.83 (1C), 123.93 (1C), 127.05 (2C), 128.57 (2C), 133.31 (1C), 133.58 (1C), 137.27 (1C), 139.48 (1C), 148.85 (1C), 158.77 (1C, $CF_3CCO_2^-$), 165.91 (1C), 167.81 (1C), 174.41 (1C); HRMS (FAB) m/z calcd for $C_{24}H_{28}N_3O_4$ $[M+H]^+$: 422.5085, found: 422.5088.

4.1.9.21. 4-{1-Oxo-6-[(1,2,3,4-tetrahydroisoquinolinium-7-carbonyl)amino]-1,3-dihydroisoindol-2-yl}butyric acid chloride (17u). Hygroscopic substance; ^{1}H NMR δ (400 MHz, d_6-DMSO) 1.86 (dt, J = 13.7, 6.7 Hz, 2H), 2.27 (t, J = 6.7 Hz, 2H), 3.09 (t, J = 5.2 Hz, 2H), 3.43–3.49 (m, 2H), 3.55 (t, J = 6.7 Hz, 2H), 4.40 (s, 2H), 4.46 (s, 2H), 7.42 (d, J = 7.8 Hz, 1H), 7.58 (d, J = 8.3 Hz, 1H), 7.88 (s, 1H), 7.90–7.96 (m, 2H), 8.19 (s, 1H), 9.21 (s, 2H), 10.46 (s, 1H); HRMS (FAB) m/z calcd for $C_{22}H_{24}N_3O_4$ $[M+H]^+$: 394.4543, found: 394.4540.

4.2. X-ray diffraction

The X-ray data for **5b**, **14**, **17c**–TfaOH·5H_2O, **17h**-TfaOH·2H_2O, and **17t**·H_2O were collected utilizing MoKα radiation at Nonius kappa CCD diffractometer at 100 K, and at Xcalibur Oxford Diffraction CCD diffractometer at room temperature for **17c**, **17h**, **17i**·H_2O, and **17j**·H_2O. Final unit cell dimensions were obtained and refined on an entire data set. All calculations to solve the structures and to refine the models were carried out with the programs SHELXS97 and SHELXL97.[22] In all structures nonhydrogen nondisordered atoms have been refined with anisotropic displacement parameters. In **17c** the Tfa anion is disordered over two positions with the occupancies 0.876(3) and 0.124(4). The F atoms in the minor component were refined in isotropic approximation. In **17i**·H_2O the fluorine atoms in the Tfa anion are disordered over three positions with the occupancies 0.756(12), 0.156(10) and 0.088(7). The minor components were refined in isotropic approximation. The X-ray data for **17j**·H_2O obtained from the poor-diffracting crystal revealed the disordering of chloride anion and water molecule. For both of these disordered species five close proximal positions with different occupancies have been found and refined in isotropic approximation with the combined occupancies of unity, both for Cl anion and H_2O. In all structures the C-bound H atoms were placed in cal-

culated positions and were treated in a riding model approximation with $U_{iso}(H) = 1.2\ U_{eq}(C)$, the O- and N-bound H-atoms were found from difference Fourier maps and refined with isotropic displacement parameters $U_{iso}(H) = 1.5\ U_{eq}(O)$, $U_{iso}(H) = 1.2\ U_{eq}(N)$. The Figures were produced using Mercury.[23] CCDC 912329–912337 contain the crystallographic data for studied compounds. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

4.2.1. Crystal data and structure refinement parameters for 5b

Empirical formula: $C_{12}H_{14}N_2O_3$ formula weight: 234.25. Crystal system: monoclinic. Space group: $P2_1/n$. Unit cell dimensions: $a = 5.9940(3)$, $b = 8.1340(5)$, $c = 22.2920(13)$, $\beta = 96.223(2)^\circ$, $V = 1080.45(11)$ Å^3. Index ranges: $-7 \leqslant h \leqslant 7$, $-10 \leqslant k \leqslant 9$, $-23 \leqslant l \leqslant 28$. Range for data collection from 1.84° to 26.99°, $Z = 4$. $D_{calc} = 1.440$ mg/m^3. $F(000) = 496$. Reflections collected 6247. Independent reflections 2360 [R(int) = 0.0429]. Data/restraints/parameters 2360:0:163. Refinement method: Full matrix least squares on F^2. Goodness-of-fit on F^2: 1.006. Final R indices [$I > 2(I)$]: $R_1 = 0.0493$, $wR_2 = 0.1350$. R indices (all data): $R_1 = 0.0666$, $wR_2 = 0.1464$. Largest diff. peak and hole: 0.285 and −0.286 e Å^{-3}.

4.2.2. Crystal data and structure refinement parameters for 14

Empirical formula: $C_{15}H_{19}NO_4$ formula weight: 277.31. Crystal system: monoclinic. Space group: $P2_1/c$. Unit cell dimensions: $a = 11.9373(9)$, $b = 10.3546(8)$, $c = 11.5307(9)$, $\beta = 102.543(4)^\circ$, $V = 1391.25(19)$ Å^3. Index ranges: $-15 \leqslant h \leqslant 15$, $-12 \leqslant k \leqslant 13$, $-14 \leqslant l \leqslant 14$. Range for data collection from 2.63° to 27.00°, $Z = 4$. $D_{calc} = 1.324$ mg/m^3. $F(000) = 592$. Reflections collected 5573. Independent reflections 3015 [R(int) = 0.0541]. Data/restraints/parameters 3015:0:188. Refinement method: Full matrix least squares on F^2. Goodness-of-fit on F^2: 1.006. Final R indices [$I > 2(I)$]: $R_1 = 0.0633$, $wR_2 = 0.1400$. R indices (all data): $R_1 = 0.0910$, $wR_2 = 0.1546$. Largest diff. peak and hole: 0.248 and −0.309 e Å^{-3}.

4.2.3. Crystal data and structure refinement parameters for [1-oxo-6-(4-piperidinium-4-yl-benzoylamino)-1,3-dihydroisoindol-2-yl]acetate pentahydrate (17c-TfaOH·5H$_2$O)

Empirical formula: $C_{22}H_{33}N_3O_9$ formula weight: 483.51. Crystal system: monoclinic. Space group: $P2_1/n$. Unit cell dimensions: $a = 12.8160(3)$, $b = 11.1350(3)$, $c = 17.1290(5)$ Å, $\beta = 108.7240(8)^\circ$, $V = 2315.04(11)$ Å^3. Index ranges: $-16 \leqslant h \leqslant 16$, $-13 \leqslant k \leqslant 13$, $-21 \leqslant l \leqslant 21$. Range for data collection from 2.40° to 26.50°, $Z = 4$. $D_{calc} = 1.387$ mg/m^3. $F(000) = 1032$. Reflections collected 18213. Independent reflections 4793 [R(int) = 0.0500]. Data/restraints/parameters 4793:0:346. Refinement method: Full matrix least squares on F^2. Goodness-of-fit on F^2: 1.003. Final R indices [$I > 2(I)$]: $R_1 = 0.0474$, $wR_2 = 0.1117$. R indices (all data): $R_1 = 0.0596$, $wR_2 = 0.1185$. Largest diff. peak and hole: 0.364 and −0.366 e Å^{-3}.

4.2.4. Crystal data and structure refinement parameters for 17c

Empirical formula: $C_{24}H_{24}F_3N_3O_6$ formula weight: 507.46. Crystal system: triclinic. Space group: P-1. Unit cell dimensions: $a = 7.2240(8)$, $b = 9.8920(9)$, $c = 17.329(2)$, $\alpha = 97.142(7)$, $\beta = 93.852(4)$, $\gamma = 97.901(7)$, $V = 1212.6(2)$ Å^3. Index ranges: $-8 \leqslant h \leqslant 8$, $-11 \leqslant k \leqslant 8$, $-20 \leqslant l \leqslant 20$. Range for data collection from 2.10° to 25.00°, $Z = 2$. $D_{calc} = 1.390$ mg/m^3. $F(000) = 528$. Reflections collected 6908. Independent reflections 4135 [R(int) = 0.0374]. Data/restraints/parameters 4135:16:360. Refinement method: Full matrix least squares on F^2. Goodness-of-fit on F^2: 1.001. Final R indices [$I > 2(I)$]: $R_1 = 0.0781$, $wR_2 = 0.1818$. R indices (all data): $R_1 = 0.0972$, $wR_2 = 0.1918$. Largest diff. peak and hole: 0.639 and −0.459 e Å^{-3}.

4.2.5. Crystal data and structure refinement parameters for 17h

Empirical formula: $C_{25}H_{26}F_3N_3O_6$ formula weight: 521.49. Crystal system: monoclinic. Space group: $P2_1/c$. Unit cell dimensions: $a = 13.675(4)$, $b = 6.202(8)$, $c = 30.779(17)$ Å, $\beta = 115.42(3)^\circ$, $V = 2358(3)$ Å^3. Index ranges: $-14 \leqslant h \leqslant 14$, $-6 \leqslant k \leqslant 6$, $-32 \leqslant l \leqslant 31$. Range for data collection from 1.65° to 22.06°, $Z = 4$. $D_{calc} = 1.469$ mg/m^3. $F(000) = 1088$. Reflections collected 4516. Independent reflections 2242 [R(int) = 0.1700]. Data/restraints/parameters 2242:228:316. Refinement method: Full matrix least squares on F^2. Goodness-of-fit on F^2: 1.133. Final R indices [$I > 2(I)$]: $R_1 = 0.2046$, $wR_2 = 0.3531$. R indices (all data): $R_1 = 0.2967$, $wR_2 = 0.3908$. Largest diff. peak and hole: 0.516 and −0.414 e Å^{-3}.

4.2.6. Crystal data and structure refinement parameters for 3-[1-oxo-6-(4-piperidinium-4-yl-benzoylamino)-1,3-dihydroisoindol-2-yl]propionate dihydrate (17h-TfaOH·2H$_2$O)

Empirical formula: $C_{23}H_{29}N_3O_6$ formula weight: 443.49. Crystal system: triclinic. Space group: P-1. Unit cell dimensions: $a = 7.8610(4)$, $b = 10.0294(4)$, $c = 15.0560(5)$ Å, $\alpha = 96.388(2)$, $\beta = 99.306(2)$, $\gamma = 111.4031(18)^\circ$, $V = 1071.73(8)$ Å^3. Index ranges: $-9 \leqslant h \leqslant 9$, $-12 \leqslant k \leqslant 12$, $-18 \leqslant l \leqslant 18$. Range for data collection from 2.22° to 25.49°, $Z = 2$. $D_{calc} = 1.374$ mg/m^3. $F(000) = 472$. Reflections collected 7408. Independent reflections 3961 [R(int) = 0.0525]. Data/restraints/parameters 3961:0:310. Refinement method: Full matrix least squares on F^2. Goodness-of-fit on F^2: 1.007. Final R indices [$I > 2(I)$]: $R_1 = 0.0696$, $wR_2 = 0.1778$. R indices (all data): $R_1 = 0.0923$, $wR_2 = 0.1913$. Largest diff. peak and hole: 0.400 and −0.284 e Å^{-3}.

4.2.7. Crystal data and structure refinement parameters for 3-[1-oxo-6-(4-piperazinium-1-yl-benzoylamino)-1,3-dihydroisoindol-2-yl]propionic acid trifluoroacetate hydrate (17i·H$_2$O)

Empirical formula: $C_{24}H_{27}F_3N_4O_7$ formula weight: 540.50. Crystal system: triclinic. Space group: P-1. Unit cell dimensions: $a = 8.9199(5)$, $b = 11.8606(9)$, $c = 12.0078(7)$ Å, $\alpha = 92.329(5)$, $\beta = 93.603(5)$, $\gamma = 106.407(6)^\circ$, $V = 1213.97(13)$ Å^3. Index ranges: $-6 \leqslant h \leqslant 10$, $-14 \leqslant k \leqslant 13$, $-14 \leqslant l \leqslant 14$. Range for data collection from 3.02° to 25.05°, $Z = 2$. $D_{calc} = 1.479$ mg/m^3. $F(000) = 564$. Reflections collected 7655. Independent reflections 4295 [R(int) = 0.0251]. Data/restraints/parameters 4295:109:383. Refinement method: Full matrix least squares on F^2. Goodness-of-fit on F^2: 1.004. Final R indices [$I > 2(I)$]: $R_1 = 0.0507$, $wR_2 = 0.1147$. R indices (all data): $R_1 = 0.0923$, $wR_2 = 0.1241$. Largest diff. peak and hole: 0.495 and −0.278 e Å^{-3}.

4.2.8. Crystal data and structure refinement parameters for 3-{1-oxo-6-[(1,2,3,4-tetrahydroisoquinolinium-7-carbonyl)amino]-1,3-dihydroisoindol-2-yl}propionic acid chloride hydrate (17j·H$_2$O)

Empirical formula: $C_{21}H_{22}ClN_3O_5$ formula weight: 431.87. Crystal system: monoclinic. Space group: $C2/c$. Unit cell dimensions: $a = 46.068(7)$, $b = 5.0936(7)$, $c = 18.848(3)$ Å, $\beta = 109.607(13)^\circ$, $V = 4166.3(11)$ Å^3. Index ranges: $-54 \leqslant h \leqslant 54$, $-6 \leqslant k \leqslant 5$, $-22 \leqslant l \leqslant 18$. Range for data collection from 2.98° to 25.05°, $Z = 8$. $D_{calc} = 1.377$ mg/m^3. $F(000) = 1808$. Reflections collected 6442. Independent reflections 3648 [R(int) = 0.0647]. Data/restraints/parameters 3648:2:290. Refinement method: Full matrix least squares on F^2. Goodness-of-fit on F^2: 1.004. Final R indices [$I > 2(I)$]: $R_1 = 0.0500$, $wR_2 = 0.0917$. R indices (all data): $R_1 = 0.2115$, $wR_2 = 0.1289$. Largest diff. peak and hole: 0.209 and −0.279 e Å^{-3}.

4.2.9. Crystal data and structure refinement parameters for 4-[1-oxo-6-(4-piperidinium-4-yl-benzoylamino)-1,3-dihydroisoindol-2-yl]butyric acid trifluoroacetate hydrate (17t·H_2O)

Empirical formula: $C_{26}H_{30}F_3N_3O_7$ formula weight: 553.53. Crystal system: triclinic. Space group: *P*-1. Unit cell dimensions: $a = 7.1440(6)$, $b = 9.3970(6)$, $c = 20.6680(16)$ Å, $\alpha = 84.549(5)$, $\beta = 88.466(5)$, $\gamma = 69.296(5)°$, $V = 1291.98(17)$ Å^3. Index ranges: $-7 \leqslant h \leqslant 7$, $-10 \leqslant k \leqslant 10$, $-22 \leqslant l \leqslant 22$. Range for data collection from 1.98° to 22.50°, $Z = 2$. $D_{calc} = 1.423$ mg/m^3. $F(000) = 580$. Reflections collected 5446. Independent reflections 3288 [R(int) = 0.0838]. Data/restraints/parameters 3288:1:362. Refinement method: Full matrix least squares on F^2. Goodness-of-fit on F^2: 1.011. Final R indices [$I > 2(I)$]: $R_1 = 0.0887$, $wR_2 = 0.1985$. R indices (all data): $R_1 = 0.1432$, $wR_2 = 0.2232$. Largest diff. peak and hole: 0.345 and −0.342 e Å^{-3}.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2013.05.019. These data include MOL files and InChiKeys of the most important compounds described in this article.

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