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One-pot tandem complexity-generating reaction based on Ugi four component condensation and intramolecular cyclization

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Abstract—A novel complexity-generating reaction is described, which can be used in a high-throughput parallel solution-phase combinatorial format. The synthetic pathway features the Ugi four component reaction followed by intramolecular cyclization via C–C bond formation. Starting from readily available initial reactants, the described approach leads to generation of novel 3-oxoisoindoline-1-carboxamides with four points of diversity around the core scaffold. The scope and limitations of the involved chemistry and some chemical transformations of the synthesized compounds are discussed.

Multicomponent reactions can be carried out very efficiently in solution and are suitable for the synthesis of libraries of diverse small molecules. A classical example is the four component Ugi condensation (U-4CC) between aldehyde, amine, isonitrile and carboxylic acid, which has emerged as a powerful tool for rapid identification and optimization of lead compounds in drug discovery.[1] A Combination of the classical Ugi condensation with a postcondensation cyclization can be used for introduction of additional complexity to the generated scaffolds, and a wide number of recent studies demonstrate the usefulness of this approach for the synthesis of pharmaceutically relevant heterocyclic structures. For example, U-4CC between (*E*)-cinnamaldehyde, chloroacetic acid, primary amine and isocyanide (structures **I**–**IV**) led to chloroacetamides **V** (Scheme 1). Upon the addition of alkali into the reaction media, compounds **V** underwent cyclization into β-lactams **VI**.[2] If 4-substituted benzaldehydes or naphthaldehyde R^1–CHO were used in this reaction instead of (*E*)-cinnamaldehyde, the resulting U-4CC-adducts **VII** cyclized into 2,5-diketopiperazines **VIII**.[3,4] Of note, although the Ugi four component condensation was successfully performed by employing aliphatic aldehydes **I** as starting materials, attempts to cyclize the resulting products gave complex reaction mixtures.[3]

One of the useful modifications of this synthetic methodology is the use of 2-fluoro-5-nitrobenzoic acid as the carboxylic acid component in the Ugi coupling. When bifunctional reagents **IIIa**–**f** such as 2-aminoethanol and 2-aminophenol, or mono-Boc-substituted diamines such as hydrazine, ethylenediamine, 2-aminomethylpyrrolidone and *ortho*-phenylenediamine, are used in this condensation as amine components, the reaction leads to standard U-4CC products **9a**–**f**. The latters then can undergo intramolecular O- or N-arylation under elevated temperature in the presence of bases to give the corresponding heterocyclic products **10a**–**f**[5,6] (Scheme 1). A modified variant of this methodology is the condensation of 2-fluoro-5-nitrobenzoic acid with *N*-Boc-protected aminoaldehydes, primary amines and isonitriles. For example, after consecutive steps of condensation, deprotection of amino group and cyclization, a series of 2,4-disubstituted 5-oxo-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine-3-carboxamides were formed.[7] All the mentioned approaches lead to rare, diverse heterocyclic structures. As a rule, these approaches are compatible with high-throughput combinatorial format, and, therefore, represent valuable methods in early stages of pharmaceutical development.

Keywords: Ugi condensation; 3-Oxoisoindoline-1-carboxamides; Parallel synthesis; Library.
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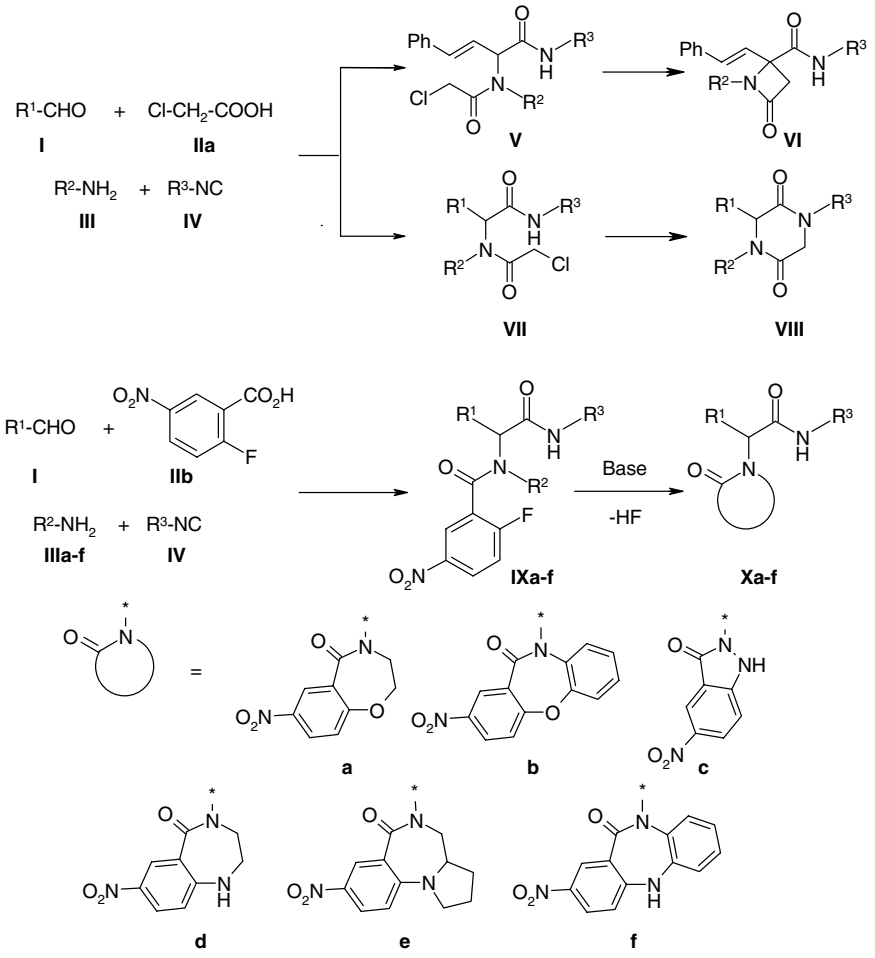


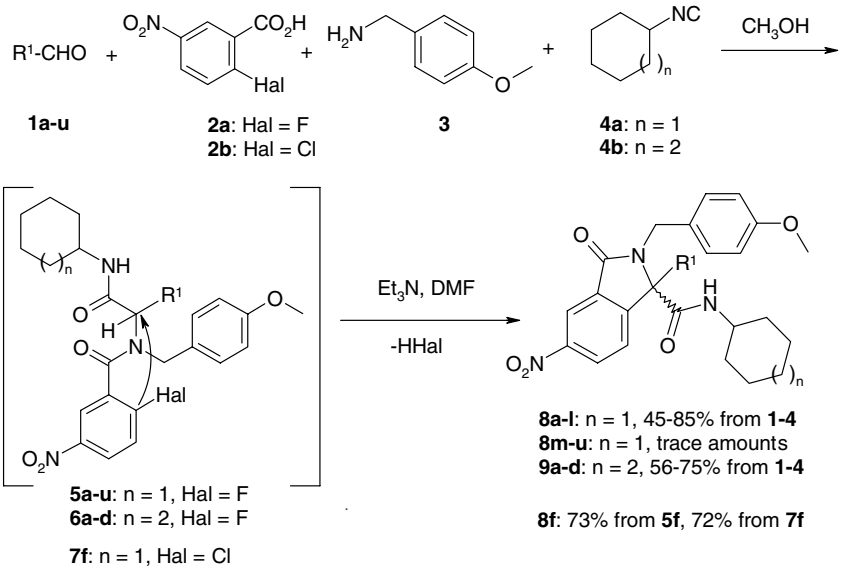
Scheme 1. U-4CC followed by postcondensation intramolecular cyclization.

As a further modification of this useful synthetic strategy, in this work we developed a synthetic approach to 3-oxoisoindoline-1-carboxamides (Scheme 2). The latters represent promising synthetic targets, since many physiologically active compounds contain this heterocyclic fragment in their structures. At the first step, aromatic aldehydes **1a**–**u** and 2-fluoro-5-nitrobenzoic acid **2** were reacted with primary amine **3** and isonitrile **4a** in methanol at 50 °C for 8–10 h. In a parallel set of reactions, four arbitrary aldehydes **1a**–**d**, 2-fluoro-5-nitrobenzoic acid **2** and amine **3** were treated with isonitrile **4b** under the same conditions. R^1 aldehyde residues explored in this work are depicted in Figure 1. In both reaction sets, we observed the conversion of the initial reactants into the corresponding classical U-4CC-adducts **5a**–**u** and **6a**–**d**.

According to LCMS analysis (ELSD detection, 254 nm), in all the studied cases the reaction mixtures contained 60–100% of the condensation products **5a**–**u** and **6a**–**d**. The major side-reaction was the intermolecular cyclization. Thus, in the case of condensation with aldehydes **1f** and **1h**, the reaction mixtures contained up to 35% of structures **8f** and **8h**. Another side-reaction was the substitution of fluorine in compounds **5a**–**u** and **6a**–**d** with 4-methoxybenzylamine residue (up to 10% of the corresponding products).

Then we have found that compounds **5** and **6** can undergo intramolecular cyclization leading to the corresponding 3-oxoisoindoline-1-carboxamides **8** and **9**.[8] The possible mechanism of this reaction is the S_N2 attack of the nucleophilic carbon atom at the electron-deficient fluorine-substituted carbon atom resulting in C–C bond formation. The reaction proceeds under elevated temperatures (120 °C) in DMF media in the presence of Et_3N. The reaction was successful only in the case of compounds **5a**–**l** and **6a**–**d**: the corresponding cyclization products **8a**–**l** and **9a**–**d** were obtained in 45–85% yield (from initial **1**–**4**). At the same time, according to LCMS data, only trace amounts of **8m**–**u** were observed under the described conditions; the prolonged heating caused thermal decomposition of the reaction mixture. According to these observations, the intramolecular cyclization is possible only in the case of aromatic or heteroaromatic aldehydes R^1–CHO, such as benzaldehydes possessing the electron-withdrawing substituents or electron-deficient heteroaromatic aldehydes. Due to their electron-deficient nature, such R^1 substituents increase the acidity of the C–H bond and favour the nucleophilic substitution.

We also attempted to use 2-chloro-5-nitrobenzoic acid as the carboxylic acid component in the Ugi coupling. For instance, the reaction of aldehyde **1f**, acid **2b**, amine



Scheme 2. Synthesis of 3-oxoisoindoline-1-carboxamides via U-4CC followed by postcondensation cyclization.

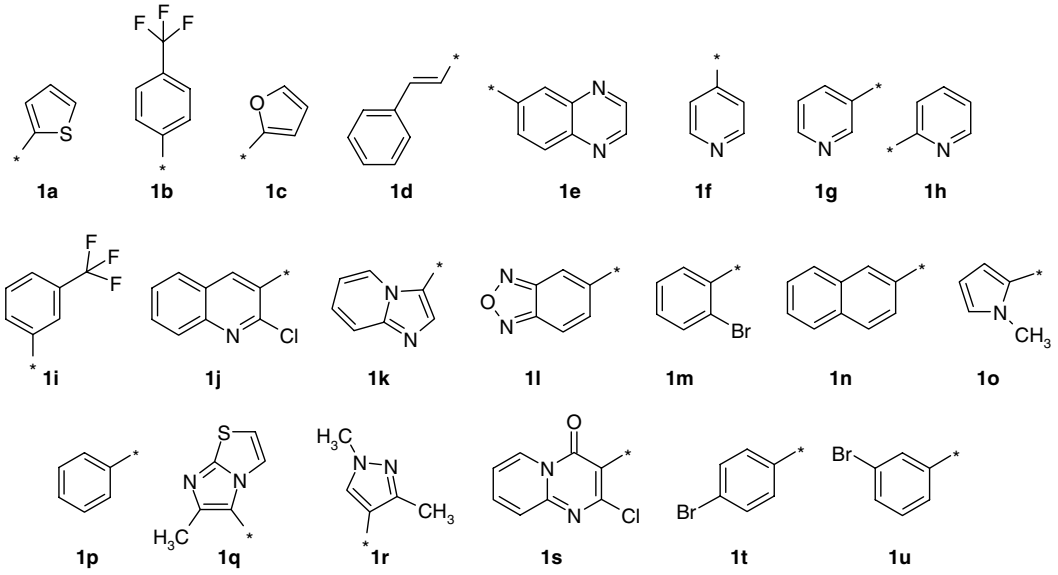


Figure 1. Aldehyde R^1 residues studied in this work.

3 and isonitrile **4a** resulted in formation of the classical U-4CC product **7f** (Scheme 2). Due to decreased electrophilicity of the chlorine-substituted carbon atom as compared to the fluorine-substituted one, the intramolecular cyclization of **7f** proceeded more slowly as compared to **5f**. Thus, according to LCMS data, almost complete conversion of compound **5f** was reached after 4 h from the initiation of the reaction, while only 80% of **7f** were converted after 24 h. However, due to decreased reactivity of chlorine-substituted compounds and, as a consequence, a reduced probability of side-reactions, the isolated yields of compound **8f** from 2-fluoro- and 2-chloro-5-nitrobenzoic acids were almost equal (73% and 72%, respectively). Therefore, both methods can be recommended for the synthesis of the final cyclization products.

Compounds **8** and **9** were obtained as racemic mixtures of enantiomers. The assignment of all structures was made on the basis of ^{1}H NMR and mass-spectroscopy data; satisfactory analytical data were obtained for all the synthesized compounds. In many cases, pure crystalline substances could be obtained, thus allowing X-ray crystallographic analysis of individual compounds. For instance, the structure of **8h** was established as *N*-cyclohexyl-1-(2-pyridyl)-2-(4-methoxybenzyl)-5-nitro-3-oxoisoindoline-1-carboxamide by single crystal X-ray analysis (Fig. 2). Single crystals of compounds suitable for X-ray analysis were grown from diethyl ether.

For introduction of additional complexity to the generated heterocyclic scaffold, we attempted to reduce the nitro group of the obtained 3-oxoisoindoline-

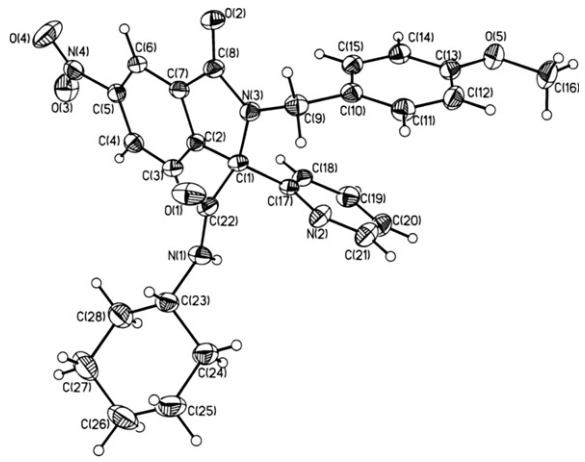


Figure 2. ORTEP plot for compound **8h**.

1-carboxamides. Thus, we have found that the reaction of a sample compound **9h** with sodium dithionite smoothly led to isoindol-5-ylsulfamic acid **10h**.[9] The latter was converted into the corresponding amine **11h** upon treatment with aqueous HCl. Alternatively, the nitro group of compound **9h** was reduced by treatment with $SnCl_2$ in aqueous HCl. Both methods gave comparable yields of **11h**[10] (49% and 43%, respectively). Our experiments demonstrated that the amino group of compound **11h** can be readily acylated and sulfonylated upon treatment with acyl and sulfonyl chlorides, respectively, or converted into the pyrrole moiety upon the reaction with 2,5-dimethoxytetrahydrofurane (Scheme 3).[11]

In summary, in this work we have shown that 3-oxoisoindoline-1-carboxamides can be efficiently prepared by a novel modification of four component Ugi reaction followed by postcondensation intramolecular C–C bond formation. Considering the availability of initial reactants, convenient synthesis and isolation of products, and amenability to introduction of additional complexity to the synthesized heterocyclic structures, the developed route provides a new valuable entry to a wide variety of novel 3-oxoisoindoline-1-carboxamides. Compounds synthesized in this work constitute examples of conformationally rigid peptidomimetics, which are the subject of increasing interest as potential new small molecule therapeutics. Biological testing of the obtained compounds is currently in progress.

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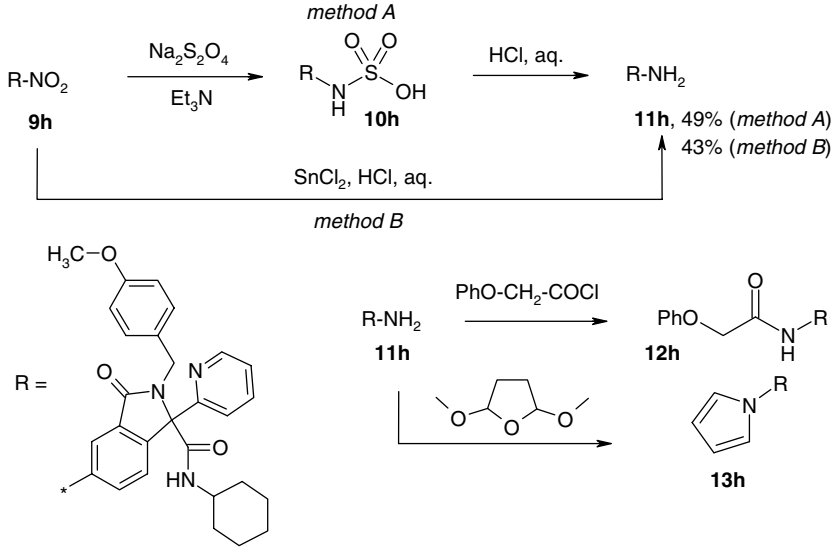
References and notes

1. (a) Ugi, I.; Lohberger, S.; Karl, R. In *Comprehensive Organic Synthesis*; Pergamon: Oxford, 1991; Vol. 2, Chapter 4.6; (b) Domling, A.; Ugi, I. *Angew. Chem.* **2000**, *39*, 3168–3210.
2. Bossio, R.; Fernandez Marcos, C.; Marcaccini, S.; Pepino, R. *Tetrahedron Lett.* **1997**, *38*, 2519–2520.
3. Marcaccini, S.; Pepino, R.; Pozo, M. C. *Tetrahedron Lett.* **2001**, *42*, 2727–2728.
4. Ilyin, A. P.; Trifilenkov, A. S.; Petrunin, V. N.; Dmitriev, D. E.; Dorogov, M. V.; Balakin, K. V.; Ivachtchenko, A. V. *Izv. Vuzov. Khim. Techn. (Russia)* **2006**, *49*, 117–123.
5. Zhu, J.; Bienayme, H. *Multicomponent Reactions*; Wiley-VCH: Weinheim, 2005; p 468.
6. Tempest, P.; Ma, V.; Kelly, M. G.; Jones, W.; Hulme, C. *Tetrahedron Lett.* **2001**, *42*, 4963–4968.
7. Tempest, P.; Pettus, L.; Gore, V.; Hulme, C. *Tetrahedron Lett.* **2003**, *44*, 1947–1950.
8. *General procedure for the preparation of 3-oxoisoindoline-1-carboxamides* **8a–l**, **9a–d**. The equimolar amounts of aldehydes **1a–l**, acid **2**, 4-methoxybenzyl amine **3** and isonitrile **4a,b** (1.0 mmol of each component) were successively dissolved in methanol (3 mL). The reaction mixture was stirred at 50 °C for 10 h. The solvent was evaporated



Scheme 3. Chemical transformations of compound **9h**.

in vacuo, then DMF (3 mL) and Et_3N (2 mmol) were added to the residue. The resulting mixture was stirred at 120 °C for 5 h. The reaction was followed by TLC (5% MeOH in CH_2Cl_2). On completion, the reaction mixture was cooled to rt and poured into water (15 mL). The formed precipitate was filtered off and purified by recrystallization from methanol. Satisfactory analytical data were obtained for all the synthesized compounds.

For example: *N^1-Cyclohexyl-2-(4-methoxybenzyl)-5-nitro-3-oxo-1-(4-pyridyl)-1-isoindolinecarboxamide* (**8f**). Yield 73%; mp 127–129 °C; H^1 NMR, DMSO-d_6, δ ppm: 0.89–1.26 (5H, m, cyclohexyl); 1.39–1.70 (5H, m, cyclohexyl); 3.42–3.58 (1H, m, CH cyclohexyl); 3.63 (3H, s, CH_3O); 4.53, 4.77 (2H, dd, CH_2, $J = 15.9$ Hz); 6.62, 6.84 (4H, dd, *p*-MeO–phenyl, $J = 8.4$ Hz); 7.14 (2H, d, $2CH_{Py}$, $J = 4.9$ Hz); 7.85–7.98 (2H, m, $2CH_{ar}$); 8.42 (2H, d, $2CH_{Py}$, $J = 4.9$ Hz); 8.47 (1H, s, CH_{ar}); 8.52 (1H, d, CH_{ar}, $J = 8.4$ Hz); LC–MS: $M^+ = 501{,}4$.

N^1-Cyclohexyl-2-(4-methoxybenzyl)-5-nitro-3-oxo-1-(2-pyridyl)-1-isoindolinecarboxamide (**8h**). Yield 81%, mp 152–154 °C; H^1 NMR, DMSO-d_6, δ ppm: 0.93–1.25 (5H, m, cyclohexyl); 1.45–1.68 (5H, m, cyclohexyl); 3.45–3.59 (1H, m, CH cyclohexyl); 3.62 (3H, s, CH_3O); 4.55, 4.81 (2H, dd, CH_2, $J = 15.7$Hz); 6.59, 6.75 (4H, dd, *p*-MeO–phenyl, $J = 8.7$ Hz); 7.21–7.29 (2H, m, $2CH_{ar}$); 7.61–7.70 (1H, m, CH_{ar}); 7.91–8.04 (2H, m, $2CH_{ar}$); 8.38–8.45 (2H, m, $2CH_{ar}$); 8.52 (1H, d, CH_{ar}, $J = 8.5$ Hz).

N^1-Cycloheptyl-2-(4-methoxybenzyl)-5-nitro-3-oxo-1-(2-thienyl)-1-isoindolinecarboxamide (**9a**). Yield 59%, mp 98–101 °C; H^1 NMR, DMSO-d_6, δ ppm: 0.61–0.81 (2H, m, cycloheptyl); 1.12–1.58 (10H, m, cycloheptyl); 3.43–3.61 (1H, m, CH cycloheptyl); 3.79 (3H, s, CH_3O); 3.91, 5.06 (2H, dd, CH_2, $J = 15.1$ Hz); 5.74 (1H, d, CH_{ar}, $J = 7.5$ Hz);6.78–7.05 (4H, m, $4CH_{ar}$); 7.24–7.42 (3H, m, $3CH_{ar}$); 7.86 (1H, d, CH_{ar}, $J = 8.5$ Hz); 8.40 (1H, d, CH_{ar}, $J = 8.5$ Hz); 8.71 (1H, s, CH_{ar}); LC–MS: $M^+ = 520.4$.

9. *N-[1-[(Cyclohexylamino)carbonyl]-2-(4-methoxybenzyl)-3-oxo-1-(2-pyridyl)-2,3-dihydro-1H-isoindol-5-yl]sulfamic acid* (**10h**). $Na_2S_2O_4$ (0.6 g, 3.5 mmol) and Et_3N (1 mL, 7 mmol) were added to a solution of **8h** (0.5 g, 1 mmol) in ethanol (5 mL). The resulting mixture was stirred at 60 °C for 2 h, and the solvent was evaporated in vacuo. The crude residue was dissolved in CH_2Cl_2 (10 mL), the solution was successively washed with water (5 mL), 2% aqueous HCl (5 mL) and with water again (5 mL). The organic layer was dried over Na_2SO_4 and kept at 0 °C overnight. The formed precipitate was filtered off, washed with CH_2Cl_2 and dried to afford 0.33 g of **10h**. Yield 60%, mp 170–172 °C; H^1 NMR, DMSO-d_6, δ ppm: 0.93–1.27 (5H, m, cyclohexyl); 1.44–1.67 (5H, m, cyclohexyl); 3.44–3.59 (1H, m, CH cyclohexyl); 3.61 (3H, s, CH_3O); 4.50, 4.75 (2H, dd, CH_2, $J = 16.2$ Hz); 6.58, 6.71 (4H, dd, *p*-MeO–Phenyl, $J = 8.5$ Hz); 7.09 (1H, d, CH_{ar}, $J = 7.8$ Hz); 7.15 (1H, d, CH_{ar}, $J = 8.3$ Hz); 7.20–7.29 (2H, m, $2CH_{ar}$); 7.51 (1H, d, CH_{ar}, $J = 8.3$ Hz); 7.59–7.67 (1H, m, CH_{ar}); 7.77 (1H, d, CH_{ar}, $J = 8.1$ Hz); 8.41 (1H, d, CH_{Py}, $J = 4.3$ Hz); NH, SO_3H in exchange. LC–MS: $M^+ = 551.5$.

10. *N-Cyclohexyl-1-(2-pyridyl)-2-(4-methoxybenzyl)-5-amino-3-oxoisoindoline-1-carboxamide* **11h**. *Method A*. Compound **10h** was suspended in 10% aqueous HCl (5 mL), and the suspension was stirred at 60 °C until complete dissolution of the solid material (approx. 2 h). The solution was cooled to rt, and then a concentrated solution of Na_2CO_3 was slowly added until pH 8 was reached. The formed precipitate was filtered off, washed with water twice and dried to afford 0.23 g of amine **11h**. *Method B*. Compound **8h** (0.5 g, 1 mmol) was suspended in a solution of $SnCl_2$ (0.8 g, 3.5 mmol) in 10% aqueous HCl (3 mL). The suspension was stirred at 70 °C until complete dissolution of the solid material (approx. 1 h). The solution was cooled to rt, and then a concentrated solution of Na_2CO_3 was slowly added until pH 8 was reached. The formed precipitate was filtered off and dried. Chloroform (10 mL) was added, and the mixture was stirred at reflux for 3 h. The solid particles were removed by filtration, and the solvent was evaporated. The crude residue was recrystallized from ether to afford 0.2 g of **11h**. Yield 49% (method A), 43% (method B); H^1 NMR, DMSO-d_6, δ ppm: 0.93–1.27 (5H, m, cyclohexyl); 1.43–1.68 (5H, m, cyclohexyl); 3.42–3.58 (1H, m, CH cyclohexyl); 3.62 (3H, s, CH_3O); 4.50, 4.73 (2H, dd, CH_2, $J = 15.8$ Hz); 6.58, 6.72 (4H, dd, *p*-MeO–phenyl, $J = 8.1$ Hz); 6.93–7.11 (3H, m, $3CH_{ar}$); 7.17–7.25 (1H, m, CH_{ar}); 7.41 (1H, d, CH_{ar}, $J = 8.0$ Hz); 7.56–7.71 (2H, m, $2CH_{ar}$); 8.41 (1H, d, CH_{Py}, $J = 3.6$ Hz); NH_2 in exchange. LC–MS: $M^+ = 471.4$.

11. *N^1-Cyclohexyl-2-(4-methoxybenzyl)-3-oxo-5-[(2-phenoxyacetyl)amino]-1-(2-pyridyl)-1-isoindolinecarboxamide* (**12h**). Phenoxyacetyl chloride (61.4 g, 0.36 mmol) was added to a solution of amine **11h** (0.15 g, 0.3 mmol) in 1.4-dioxane (3 mL) freshly distilled over Na. The mixture was stirred at 80 °C for 5 h, then poured into 10% solution of Na_2CO_3 (10 mL). The resulting suspension was stirred at rt for 2 h. The formed precipitate was filtered off, washed with water twice and dried to give 181 g of **12h**. Yield 85%; mp 123–125 °C; H^1 NMR, DMSO-d_6, δ ppm: 0.92–1.29 (5H, m, cyclohexyl); 1.44–1.68 (5H, m, cyclohexyl); 3.43–3.60 (1H, m, CH cyclohexyl); 3.62 (3H, s, CH_3O); 4.50 (H, d, *CH*(CH_2), $J = 15.3$ Hz); 4.69–4.82 (3H, m, *CH* (CH_2), CH_2); 6.58, 6.74 (4H, dd, *p*-MeO–phenyl, $J = 8.2$ Hz); 6.93–7.13 (4H, m, $4CH_{ar}$); 7.16–7.39 (3H, m, $3CH_{ar}$); 7.55–7.67 (2H, m, $2CH_{ar}$); 7.74–7.85 (2H, m, $2CH_{ar}$); 8.14 (1H, s, CH_{ar}); 8.42 (1H, d, CH_{Py}, $J = 4.2$ Hz); LC–MS: $M^+ = 603.5$.

N^1-Cyclohexyl-2-(4-methoxybenzyl)-3-oxo-1-(2-pyridyl)-5-(1H-pyrrol-1-yl)-1-isoindolinecarboxamide (**13h**). 2,5-Dimethoxytetrahydrofuran (64.8 mL, 0.50 mmol) was added to a solution of amine **11h** (0.20 g, 0.42 mmol) in acetic acid (2 mL). The mixture was stirred at 70 °C for 0.5 h, then poured into water (10 mL). The formed precipitate was filtered off, washed with water, dried and recrystallized from hexane to afford 0.10 g of **13h**. Yield 45%; mp 123–125 °C; H^1 NMR, DMSO-d_6, δ ppm: H^1 NMR, DMSO-d_6, δ ppm: 0.95–1.31 (5H, m, cyclohexyl); 1.46–1.69 (5H, m, cyclohexyl); 3.49–3.59 (1H, m, CH cyclohexyl); 3.62 (3H, s, CH_3O); 4.54, 4.80 (2H, dd, CH_2, $J = 15.9$ Hz); 6.30 (2H, s, 2CH pyrrol); 6.59, 6.75 (4H, dd, *p*-MeO–phenyl, $J = 8.3$ Hz); 7.13 (1H, d, CH_{ar}, $J = 8.3$ Hz); 7.19–7.28 (1H, m, CH_{Py}); 7.52 (2H, s, 2CH pyrrol); 7.58–7.68 (1H, m, CH_{Py}); 7.76 (1H, d, CH_{ar}, $J = 8.2$ Hz); 7.81–7.93 (2H, m, $2CH_{ar}$); 8.44 (1H, d, CH_{Py}, $J = 4.5$ Hz); LC–MS: $M^+ = 521.3$.