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High-yielding synthesis of 1-isoindolinone derivatives via palladium-catalysed cycloaminocarbonylation

Diána Marosvölgyi-Haskó [a], Attila Takács [a], Zsuzsanna Riedl [b], László Kollár [a,*]

[a] Department of Inorganic Chemistry, University of Pécs, H-7624 Pécs, PO Box 266, Hungary
[b] Institute of Biomolecular Chemistry, Chemical Research Center, Hungarian Academy of Sciences, H-1525 Budapest, PO Box 17, Hungary

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ABSTRACT

1-Isoindolinone derivatives were synthesised in high yields (up to 89%) by using 2-iodobenzyl bromide and 2-iodobenzylamine as bifunctional substrates in palladium-catalysed carbonylation. Depending on the *N*-nucleophiles, two types of compounds were synthesised with 2-iodobenzyl bromide: the use of primary amines, including amino acid methylesters, resulted in the formation of *N*-substituted 1-isoindolinones, while secondary amines react both with the benzyl bromide and iodoarene moieties resulting in the corresponding *ortho*-(*N*-piperidino/morpholinomethyl)-benzamides. The parent 1-isoindolinone was obtained in a facile, highly chemoselective intramolecular aminocarbonylation of 2-iodobenzylamine. The mechanistic details of the ring-closure reaction and the conditions leading to side-products are discussed as well.

1. Introduction

The treatment of schizophrenia with neuroleptic drugs has been one of the major focuses of pharmaceutical chemistry. After the introduction of chlorpromazine and a dibenzodiazepine derivative, clozapine as an atypical antipsychotic agent,[1,2] among others, *N*-substituted 1-isoindolinones were selected for further evaluation. In the seminal work of Norman et al. the synthesis of the variety of 1-isoindolinone-based derivatives were described.[3] Several methodologies, such as condensation of ω-aminoalkanols with phthalide, the reactions of 2-(bromomethyl)benzoate with primary amines and the monoreduction of phthalimide followed by alkylation were used for the synthesis of the basic 1-isoindolinone skeleton. Further synthetic approaches, such as acid-mediated intramolecular cationic cyclization involving *N*-acyliminium species,[4] rearrangement of *ortho*-phthalaldehyde with urea and thiourea analogs under the catalysis of trimethylchlorosilane,[5] the synthesis of non-racemic 1-isoindolinone targets by using γ-lactam derivatives as *N*-aciliminium ion precursors,[6] reaction of arylmagnesium reagents bearing *o*-chloromethyl group with isocyanates,[7] and via oxidative radical cyclization,[8] for the synthesis of the 1-isoindolinone bicyclic system were published.

Transition metal-catalysed carbonylation reactions, among them mainly palladium-catalysed amino and alkoxycarbonylation and carbonylative coupling reactions, are widely used in synthetic chemistry.[9,10] Unsaturated carboxamides or aryl carboxamides with various structures were synthesised using enol-triflate/iodo-alkene or aryl triflate/aryl halide type substrates in palladium-catalysed aminocarbonylation, respectively.[11] Palladium(0) and palladium(II) precatalysts were used efficiently in cyclocarbonylations as well.[12]

Transition metal catalysis was also applied for the synthesis of 1-isoindolinone derivatives. A synthetic method for obtaining bis(isoindolinones) starting from aryl chlorides in nickel(0)-catalysed reaction was described.[13] Palladium-catalysed reactions of 2-iodo-*N*-substituted benzamides,[14] that of aryl iodides in carbonylation–amination–Michael addition cascade[15] and that of 2′-bromoacetophenone with primary amines under carbon monoxide[16] proved to be highly efficient for the synthesis of the 1-isoindolinone scaffold. Isoindolinones via room temperature palladium nanoparticle-catalysed carbonylation–amination cascade were synthesised.[17] Isoindolinones and hydroisoindolinones were obtained via the reaction of primary amines with 2-bromobenzaldehyde and 2-bromocyclohex-1-enecarbaldehyde, respectively, in the presence of palladium(II) precursors.[18,19]

Although 2-iodobenzylamine may act both as an iodoarene substrate and as an *N*-nucleophile, no precedence for its use as a bifunctional substrate in carbonylation reaction has been reported.

* Corresponding author. E-mail address: kollar@ttk.pte.hu (L. Kollár).

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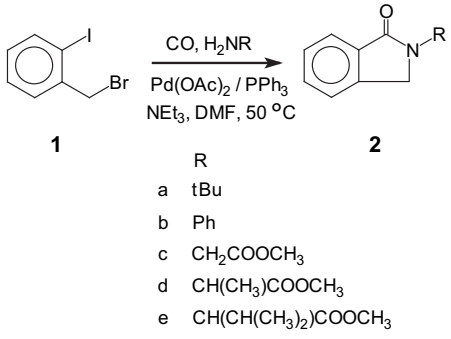
Similarly, in this paper, the highly chemoselective cycloaminocarbonylation of bifunctional 2-iodobenzyl bromide towards the variety of *N*-substituted 1-isoindolinones of pharmaceutical importance is described.

2. Results and discussion

2.1. Cycloaminocarbonylation of 2-iodobenzyl bromide in the presence of primary amines as *N*-nucleophiles

2-Iodobenzyl bromide (**1**) was reacted with various primary amines such as *tert*-butylamine (**a**), aniline (**b**), glycine methylester (**c**), alanine methylester (**d**) and valine methylester (**e**) under atmospheric carbon monoxide pressure in DMF in the presence palladium(0) catalysts generated in situ from palladium(II) acetate catalytic precursor (Scheme 1). Although efforts were made to clarify the reduction of Pd(II) precursors to Pd(0) species in various model systems,[20–23] the exact mechanism of reduction under the carbonylation conditions used in this study is still unrevealed.



Scheme 1. Cycloaminocarbonylation of 2-iodobenzyl bromide in the presence of primary amines.

Under mild reaction conditions (50 °C, 1 bar CO) various *N*-substituted 1-isoindolinone derivatives (**2a**–**e**) were obtained as exclusive products in cycloaminocarbonylation. The substrate (**1**) was fully converted to the ring-closure products in 74–79% isolated yields. Due to the highly chemoselective reaction, excellent isolated yields were obtained both with simple unfunctionalised amines (**a** and **b**) (Table 1, entries 1 and 4) and amino acid esters (**c**, **d** and **e**) (Table 1, entries 5–7). Although complete conversion can be obtained even at atmospheric carbon monoxide pressure enabling facile isolation of the target compound **2a**, the reaction time could be shortened by increasing the carbon monoxide pressure (entries 2 and 3).

The high-yielding formation of *N*-substituted 1-isoindolinones can be interpreted on the basis of a simplified reaction mechanism depicted in Fig. 1. After the benzylation of the primary amine (RNH_2) with **1**, in a similar alkylation as discussed in case of secondary amines (vide infra), the oxidative addition of the iodoaryl moiety to palladium(0) species takes place resulting in a palladium(II)–aryl intermediate (**A**). The carbon monoxide coordination brings about a terminal carbonyl complex (**B**). The insertion of the carbonyl ligand into the Pd(II)–aryl bond provides the corresponding Pd(II)-acyl complex (**C**), which react with the secondary amine moiety in intramolecular reaction in the product (**2**) forming step. The 'starting' Pd(0) complex is re-formed by the reductive elimination of HI in the presence of a base (Et_3N). Although no detailed mechanistic studies were carried out with **1** as substrate, the oxidative addition–CO insertion–reductive elimination sequence is generally

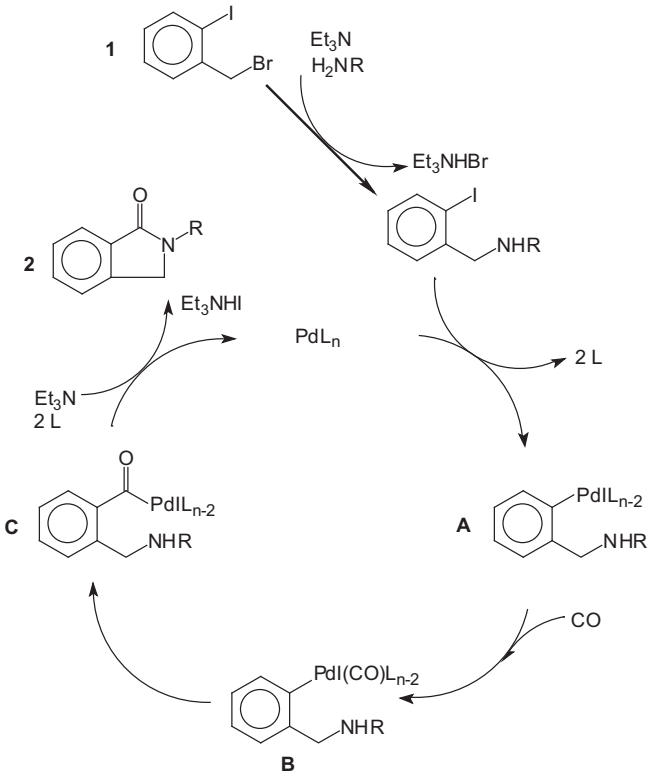


Fig. 1. The simplified reaction mechanism of cycloaminocarbonylation.

Table 1
Palladium-catalysed aminocarbonylation of **1** with primary and secondary amines as *N*-nucleophile[a]

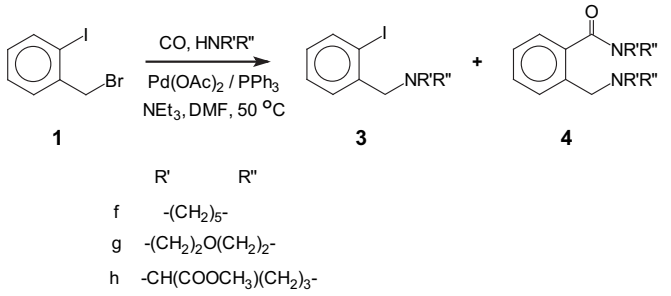
Entry	Amine	*p*(CO) [bar]	t_R[b] [h]	**1**/Amine ratio	Composition of the reaction mixture[c] [%]	Isolated yield[d] (amide) [%]
1	**a**	1	90	1/6	100 (**2a**)	89 (**2a**)
2	**a**	60	10	1/6	100 (**2a**)	74 (**2a**)
3	**a**	50	24	1/6	100 (**2a**)	77 (**2a**)
4	**b**	1	48	1/4	100 (**2b**)	85 (**2b**)
5	**c**	1	24	1/2.2	100 (**2c**)	89 (**2c**)
6	**d**	1	24	1/2.2	100 (**2d**)	82 (**2d**)
7	**e**	1	24	1/2.2	100 (**2e**)	75 (**2e**)
8	**f**	1	24	1/3	49 (**3f**); 51 (**4f**)	n.d (**3f**); n.d.[e] (**4f**)
9	**f**	1	120	1/3	100 (**4f**)	89 (**4f**)
10	**f**	60	93	1/3	100 (**4f**)	88 (**4f**)
11	**g**	1	1	1/3	80 (**3g**); 20 (**4g**)	55 (**3g**); n.d.[e] (**4g**)
12	**g**	1	24	1/3	9 (**3g**); 91 (**4g**)	n.d. (**3g**); 72 (**4g**)
13	**h**	1	120	1/2.2	57 (**3h**); 43 (**4h**)	50 (**3h**); n.d.[e] (**4h**)
14	**h**	60	24	1/2.2	100 (**4h**)	72 (**4h**)

[a] Reaction conditions: 0.025 mmol $Pd(OAc)_2$; 0.05 mmol PPh_3, 1 mmol substrate (**1**); 0.5 mL triethylamine; 10 mL DMF; temperature: 50 °C.
[b] Practically complete conversion (>99%) determined by GC–MS was obtained in all cases.
[c] Determined by GC–MS (internal standard: naphthalene).
[d] Based on the amount of the substrate (**1**) used.
[e] n.d.=not determined (i.e., the target compound was not isolated as a pure substance).

accepted in aminocarbonylation and has been proved in various model reactions.[24,25]

2.2. Aminocarbonylation of 2-iodobenzyl bromide in the presence of secondary amines as *N*-nucleophiles

2-Iodobenzyl bromide (**1**) was reacted with secondary amines, such as piperidine (**f**), morpholine (**g**) and proline methylester (**h**) under atmospheric and 60 bar carbon monoxide pressure using the same catalytic system as above (Scheme 2). Two types of compounds were isolated after work-up: tertiary amines containing 2-iodobenzyl substituent (**3f**–**h**) and 2-aminoalkyl-substituted benzamides (**4f**–**h**). Under normal conditions (1 bar CO, 50 °C) the mixture of **3** and **4** was obtained in all cases. While **1** was totally converted in all cases, the ratio of **3**/**4** depended strongly on the secondary amine used: product ratios 49/51 and 9/91 were obtained with **f** and **g**, respectively (Table 1, entry 8 and 12).



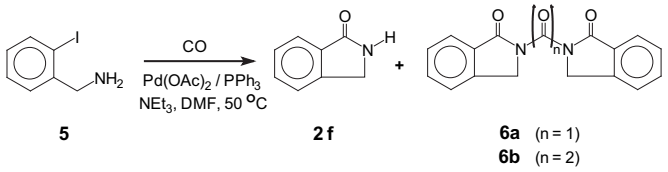
Scheme 2. Aminocarbonylation of 2-iodobenzyl bromide in the presence of secondary amines.

However, at elevated reaction times (Table 1, entry 9 and 12) the ratio of the two products was shifted towards the carbonylated product **4**. The application of high pressure has shown the same effect (entry 10 and 14).

It was proved also by GC–MS analysis that the final product **4** was obtained in the aminocarbonylation of the 2-iodobenzylamine derivatives **3**. For example, the ratio of **3g**–**4g** was varied as follows: 80/20, 60/40, 53/47 and 9/91 in 1 h, 2 h, 6 h and 24 h, respectively. It has to be noted that the alkylation towards **3g** took place in a fast reaction, i.e., no starting material (**1**) was found in the reaction mixture after 1 h.

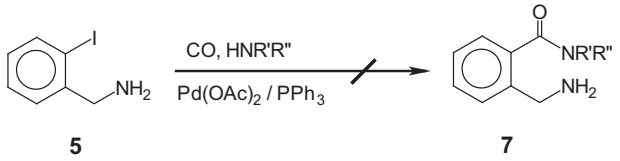
2.3. Cycloaminocarbonylation of 2-iodobenzylamine

2-Iodobenzylamine (**5**) undergoes cycloaminocarbonylation under the mild reaction conditions yielding 1-isoindolinone (**2f**) as major product (Table 2, entry 1). The explanation for its formation, based on a simplified reaction mechanism, could be summarised as follows. The in situ formed palladium(0) complexes are highly reactive towards oxidative addition of the iodoarene functionality resulting in a palladium(II)-aryl intermediate. It has to be added that the mechanism discussed above (Fig. 1) can be considered also in this case (R=H). This species is able insert carbon monoxide yielding the palladium(II)–acyl complex, which reacts with the primary amine (benzylamine) moiety of **5** providing the parent compound of the above series, 1-isoindolinone (**2f**). Although **2f** was formed as major product under all conditions used, the carbonylation products of **2f**, that is, **6a** and **6b**, were also found in the reaction mixture as minor products unless primary amines were added (entry 1, 3 and 5) (Scheme 3). In the presence of primary amines, e.g., *tert*-butylamine (**a**), the exclusive formation of **2f** can be observed (entry 2 and 4). A possible explanation for the role of the primary amine is, that instead of the carbonylation of the primary ring-closure product **6** leading to **6a** and **6b**, the usual carbonylation and double carbonylation of the amine (**a**) takes place yielding *N*,*N*′-di-*tert*-butyl-urea and *N*,*N*′-di-*tert*-butyl-glyoxylamide in a side-reaction,[26] respectively.



Scheme 3. Cycloaminocarbonylation of 2-iodobenzylamine.

It is worth noting that the application of various primary amines (**a**–**e**) even in large excess does not result in the formation of carboxamides (**7**) (Scheme 4). That is, no 2-aminomethyl benzamide derivatives, formed in aminocarbonylation of the iodoarene functionality of **5**, could be detected by GC–MS. Even highly reactive primary amines, such as *tert*-butylamine (**a**) and glicin methylester (**c**) could not compete with the aminomethyl moiety at the adjacent *ortho*-position to the iodo-substituent.



Scheme 4. An alternative way for the aminocarbonylation of 2-iodobenzylamine in the presence of amines.

3. Conclusions

It has been shown that 2-iodobenzylamine can be transformed via a palladium-catalysed intramolecular aminocarbonylation to give 1-isoindolinone, a basic skeleton of an atypical antipsychotic agent. Furthermore, the highly chemoselective cycloaminocarbonylation of bifunctional 2-iodobenzyl bromide towards *N*-substituted 1-isoindolinones of pharmaceutical importance was explored. The high-yielding, facile one-pot reaction, carried out under mild reaction

Table 2
Palladium-catalysed cycloaminocarbonylation of **5**[a]

Entry	p(CO) [bar]	t_R[b] [h]	Composition of the reaction mixture[c] [%]	Isolated yield[d] (compound) [%]
1	1	70	92 (**2f**); 8 (**6a**)	76 (**2f**); n.d.[e] (**6a**)
2	1[f]	70	100 (**2f**)	89 (**2f**)
3	40	91	93 (**2f**); 7 (**6a**)	78 (**2f**), n.d. (**6a**)
4	40[f]	71	100 (**2f**)	90 (**2f**)
5	100	72	73 (**2f**); 10 (**6a**); 17 (**6b**)	54 (**2f**); 6 (**6a**)

[a] Reaction conditions: 0.025 mmol $Pd(OAc)_2$; 0.05 mmol PPh_3, 1 mmol substrate (**5**); 0.5 mL triethylamine; 10 mL DMF, 50 °C.
[b] Practically complete conversions (>99%), determined by GC–MS, were obtained in all cases.
[c] Determined by GC–MS (internal standard: naphthalene).
[d] Based on the amount of the substrate (**5**) used.
[e] n.d.=not determined (i.e., the target compound was not isolated as a pure substance).
[f] *t*-$BuNH_2$ (3 mmol) was added.

conditions, is based on the benzylation of the primary amine by the benzyl bromide moiety, followed by ring-closing intramolecular aminocarbonylation of the iodoaromatic functionality. In this way, a widely applicable reaction for 1-isoindolinone. Synthesis, which is tolerant towards primary amine functionalities has been developed.

4. Experimental

4.1. General procedures

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Inova 400 spectrometer at 400.13 MHz and 100.62 MHz, respectively. Chemical shifts δ are reported in parts per million relative to $CHCl_3$ (7.26 and 77.00 ppm for ^{1}H and ^{13}C, respectively). Elemental analyses were measured on a 1108 Carlo Erba apparatus. Samples of the catalytic reactions were analysed with a Hewlett Packard 5830A gas chromatograph fitted with a capillary column coated with OV-1. The FT-IR spectra were taken in KBr pellets using an IMPACT 400 spectrometer (Nicolet) applying a DTGS detector in the region of 400–4000 cm^{-1}, the resolution was 4 cm^{-1}. The amount of the samples was ca. 0.5 mg.

2-Iodobenzyl bromide (**1**) and amino acid esters were purchased from Sigma–Aldrich. 2-Iodobenzylamine (**5**) was prepared according to the literature procedure[27] starting from 2-iodobenzyl bromide (**1**). In the course of the isolation and identification of **5** it was revealed, that some physical and ^{13}C NMR data (vide infra) differ from the published ones.[28] The target compounds of known structure (**2f**,[3] **2a**,[8] **2b**[5,7]) gave identical spectra with those given in the literature. However, where further analytical data for the target compounds are available, the isolated compounds with full characterization are given below.

4.2. Cycloaminocarbonylation of 2-iodobenzyl bromide (1) in the presence of primary amines under atmospheric carbon monoxide pressure

In a typical experiment $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), PPh_3 (13.1 mg, 0.05 mmol), 2-iodobenzyl bromide (297 mg,1 mmol), 6 mmol of *tert*-butylamine (0.63 mL, 6 mmol or 2.2 mmol of amino acid methylester hydrochloride) and 0.5 mL triethylamine were dissolved in DMF (10 mL) under argon in a 100 mL three-necked flask equipped with a gas inlet, reflux condenser with a balloon at the top. The atmosphere was changed to carbon monoxide. The reaction was conducted for the given reaction time upon stirring at 50 °C and analysed by GC–MS. The mixture was then concentrated and evaporated to dryness. The residue was dissolved in chloroform (20 mL) and washed with water (20 mL). The organic phase was thoroughly washed twice with 5% HCl (20 mL), saturated $NaHCO_3$ (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated to powder-like crystalline material in case of **2a**–**c** or to a waxy residue in case of **2d**,**e**. All compounds were subjected to column chromatography under the conditions indicated in Section 4.5.

4.3. Cycloaminocarbonylation of 2-iodobenzyl bromide (1) in the presence of primary amines under high carbon monoxide pressure

The above amounts of catalyst, substrate and amines were dissolved in DMF (10 mL) under argon in a 100 mL autoclave. The atmosphere was changed to carbon monoxide and the autoclave was pressurized to 60 bar with carbon monoxide. The reaction was conducted for the given reaction time upon stirring at 50 °C and analysed by GC–MS (internal standard: naphthalene). Upon cooling the autoclave was depressurized. The mixture was then concentrated and evaporated to dryness and worked-up as described in Section 4.2.

4.4. Cycloaminocarbonylation of 2-iodobenzylamine (5) under atmospheric carbon monoxide pressure

In a typical experiment $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), PPh_3 (13.1 mg, 0.05 mmol), 2-iodobenzylamine (233 mg,1 mmol or its hydrochloride (270 mg, 1 mmol)) and 0.5 mL triethylamine were dissolved in DMF (10 mL) under argon in a 100 mL three-necked flask equipped with a gas inlet, reflux condenser with a balloon at the top. The atmosphere was changed to carbon monoxide. The reaction was conducted for the given reaction time upon stirring at 50 °C and analysed by GC–MS. The mixture was then concentrated and evaporated to dryness. The residue was than directly subjected to column chromatography on silica gel and the compounds (**2f** and **6a**) were isolated under the conditions indicated in Section 4.5.

4.5. Characterization of the products

*4.5.1. N-tert-Butyl-1-isoindolinone (**2a**)*[8]. ^{1}H NMR ($CDCl_3$) δ: 7.76 (d, 7.8 Hz, 1H, Ar–H); 7.47 (t, 7.8 Hz, 1H, Ar–H); 7.36–7.43 (m, 2H, Ar–H); 4.41 (s, 2H, CH_2); 1.55 (s, 9H, *t*-Bu). ^{13}C NMR ($CDCl_3$) δ: 168.8, 140.7, 134.5, 130.8, 127.8, 123.1, 122.3, 54.3, 48.5, 28.0. IR (KBr, ν (cm^{-1})): 1677 (CON). MS (*m*/*z*/rel int.): 189(M^+)/11, 174/100, 146/14, 134/43, 116/13. Analysis calculated for $C_{12}H_{15}NO$ (189.26): C, 76.16; H, 7.99; N, 7.40. Found: C, 76.07; H, 8.23; N, 7.18. R_f (10% EtOAc/$CHCl_3$) 0.58; R_f (40% EtOAc/$CHCl_3$) 0.71. Pale yellow solid, mp 49 °C. Yield: 168 mg (89%).

*4.5.2. N-Phenyl-1-isoindolinone (**2b**)*[5,7]. ^{1}H NMR ($CDCl_3$) δ: 7.92 (d, 7.8 Hz, 1H, Ar–H); 7.86 (d, 7.7 Hz, 2H, Ph-*ortho*); 7.58 (t, 7.7 Hz, 1H, Ph-*para*); 7.50 (t, 7.7 Hz, 2H, Ph-*meta*); 7.38–7.43 (m, 2H, Ar–H); 7.18 (t, 7.8 Hz, 1H, Ar–H); 4.81 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ: 167.5, 140.2, 139.5, 133.3, 132.1, 129.1 (double intensity), 128.4, 124.5, 124.1, 122.6, 119.5 (double intensity), 50.7. IR (KBr, ν (cm^{-1})): 1685 (CON); MS (*m*/*z*/rel int.): 209(M^+)/100, 180/53, 152/10. Analysis calculated for $C_{14}H_{11}NO$ (209.25): C, 80.36; H, 5.30; N, 6.69. Found: C, 80.17; H, 5.18; N, 6.44. R_f (10% EtOAc/$CHCl_3$) 0.70. Off-white solid, mp 162.5 °C. Yield: 177 mg (85%).

*4.5.3. N-(Methoxycarbonylmethyl)-1-isoindolinone (**2c**).* ^{1}H NMR ($CDCl_3$) δ: 7.81 (d, 7.8 Hz, 1H, Ar–H); 7.50 (t, 7.8 Hz, 1H, Ar–H); 7.39–7.44 (m, 2H, Ar–H); 4.48 (s, 2H, CH_2); 4.38 (s, 2H, CH_2); 3.71 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$) δ: 169.5, 168.8, 141.6, 131.8, 131.7, 128.0, 123.9, 122.8, 52.2, 50.5, 43.7. IR (KBr, ν (cm^{-1})): 1732 (COO), 1693 (CON); MS (*m*/*z*/rel int.): 205(M^+)/41, 173/3, 146/100, 136/4, 118/16. Analysis calculated for $C_{11}H_{11}NO_3$ (205.21): C, 64.38; H, 5.40; N, 6.83; Found: C, 64.17; H, 5.18; N, 6.60. R_f (40% EtOAc/$CHCl_3$) 0.50. Off-white solid, mp 114.5 °C. Yield: 182 mg (89%).

*4.5.4. N-(1-(Methoxycarbonyl)-ethyl)-1-isoindolinone (**2d**).* ^{1}H NMR ($CDCl_3$) δ: 7.84 (d, 7.8 Hz, 1H, Ar–H); 7.52 (t, 7.5 Hz, 1H, Ar–H); 7.41–7.45 (m, 2H, Ar–H); 5.20 (q, 7.0 Hz, 1H, C*H*CH_3); 4.58 (d, 17.0 Hz, 1H, CH_aH$_b$); 4.41 (d, 17.0 Hz, 1H, CH$_a$H$_b$); 3.72 (s, 3H, OCH_3); 1.59 (d, 7.0 Hz, 3H, CHCH_3). ^{13}C NMR ($CDCl_3$) δ: 172.3, 168.6, 141.7, 132.2, 131.6, 128.0, 123.9, 122.9, 52.3, 49.1, 46.8, 15.8. IR (KBr, ν (cm^{-1})): 1743 (COO), 1690 (CON); MS (*m*/*z*/rel int.): 219 (M^+)/16, 160/100, 132/15. Analysis calculated for $C_{12}H_{13}NO_3$ (219.24): C, 65.74; H, 5.98; N, 6.39. Found: C, 65.50; H, 5.78; N, 6.15. R_f (20% EtOAc/$CHCl_3$) 0.70. Yellow waxy material. Yield: 180 mg (82%).

*4.5.5. N-(1-(Methoxycarbonyl)-2-methyl-propyl)-1-isoindolinone (**2e**).* ^{1}H NMR ($CDCl_3$) δ: 7.84 (d, 7.8 Hz, 1H, Ar–H); 7.53 (t, 7.5 Hz, 1H, Ar–H); 7.41–7.46 (m, 2H, Ar–H); 4.81 (d, 10.2 Hz, 1H, NC*H*COO); 4.70 (d, 17.1 Hz, 1H, CH_aH$_b$); 4.40 (d, 17.1 Hz, 1H, CH$_a$H$_b$); 3.70 (s, 3H, OCH_3); 2.27–2.42 (m, 1H, C*H*$(CH_3)_2$); 1.04 (d, 6.6 Hz, 3H, CHCH_3); 0.92 (d, 6.6 Hz, 3H, CHCH_3). ^{13}C NMR ($CDCl_3$) δ: 171.5, 168.9, 141.7,

131.8, 131.7, 128.0, 124.0, 122.8, 59.8, 51.9, 47.2, 29.0, 19.4, 19.1. IR (KBr, ν (cm^{-1})): 1730 (COO), 1683 (CON); MS (*m*/*z*/rel int.): 247(M^+)/30, 204/36, 188/100, 134/29. Analysis calculated for $C_{14}H_{17}NO_3$ (247.29): C, 68.00; H, 6.93; N, 5.66. Found: C, 68.17; H, 6.67; N, 5.50. R_f (10% EtOAc/$CHCl_3$) 0.77. Yellow waxy material. Yield: 185 mg (75%).

*4.5.6. 2-(1-Piperidylmethyl)-N,N-(pentan-1,5-diyl)benzamide (**4f**).* ^{1}H NMR ($CDCl_3$) δ: 7.40 (d, 7.8 Hz, 1H, Ar–H); 7.15–7.28 (m, 2H, Ar–H); 7.12 (d, 7.8 Hz, 1H, Ar–H); 3.93–4.00 (m, 1H, NCH_aH$_b$); 3.63–3.69 (m, 1H, NCH_aH$_b$); 3.35–3.42 (m, 1H, NCH$_a$$H_b$); 3.20 (br s, 2H, Ar–$CH_2$); 3.02–3.11 (m, 1H, NCH$_a$$H_b$); 2.35 (br s, 4H, N($CH_2$)$_2$); 1.35–1.73 (m, 12H, 2×(CH_2)$_3$). ^{13}C NMR ($CDCl_3$) δ: 170.0, 137.0, 136.5, 129.9, 128.3, 126.7, 125.8, 60.8, 54.7 (double intensity), 48.2, 42.4, 26.3, 26.0 (double intensity), 25.7, 24.6, 24.3. IR (KBr, ν (cm^{-1})): 1635 (CON). MS (*m*/*z*/rel int.): 286(M^+)/3. 202/30, 188/11, 172/28, 84/100. Analysis calculated for $C_{18}H_{26}N_2O$ (286.42): C, 75.48; H, 9.15; N, 9.78. Found: C, 75.23; H, 9.43; N, 9.55. R_f (6% EtOH/$CHCl_3$) 0.63. Orange waxy material. Yield: 255 mg (89%).

*4.5.7. 2-(N-Morpholylmethyl)-iodobenzene (**3g**).* ^{1}H NMR ($CDCl_3$) δ: 7.81 (d, 7.8 Hz, 1H, Ar–H); 7.40 (d, 7.8 Hz, 1H, Ar–H); 7.31 (t, 7.8 Hz, 1H, Ar–H); 6.94 (t, 7.8 Hz, 1H, Ar–H); 3.67–3.73 (m, 4H, O(CH_2)$_2$); 3.50 (s, 2H, Ar–CH_2); 2.46–2.52 (m, 4H, N(CH_2)$_2$). ^{13}C NMR ($CDCl_3$) δ: 138.7, 138.1, 128.9, 127.3, 126.5, 99.2, 65.6 (double intensity), 65.3, 52.0 (double intensity). IR (KBr, ν (cm^{-1})): 1014 (C-I); MS (*m*/*z*/rel int.): 303(M^+)/86, 272/10, 217/100, 176/8, 146/62. Analysis calculated for $C_{11}H_{14}NOI$ (303.14): C, 43.58; H, 4.65; N, 4.62. Found: C, 43.39; H, 4.77; N, 4.40. R_f (40% EtOAc/$CHCl_3$) 0.73. Brown waxy material. Yield: 167 mg (55%).

*4.5.8. 2-(N-Morpholylmethyl)-N,N-(3′-oxapentan-1,5-diyl)benzamide (**4g**).* ^{1}H NMR (CDCl3) δ: 7.31 (d, 7.8 Hz, 1H, Ar–H); 7.18–7.28 (m, 2H, Ar–H); 7.11 (d, 7.8 Hz, 1H, Ar–H); 3.48–3.79 (m, 12H, NCH_2+2×O(CH_2)$_2$+Ar–CH_2); 3.10–3.24 (m, 2H, NCH_2); 2.35 (m, 4H, N(CH_2)$_2$). ^{13}C NMR ($CDCl_3$) δ: 168.8, 134.3, 128.9, 127.3, 127.0, 125.8, 124.9, 65.5 (double intensity), 65.3, 65.2, 59.1, 52.0 (double intensity), 46.0, 40.5. IR (KBr, ν (cm^{-1})): 1635 (CON); MS (*m*/*z*/rel int.): 290(M^+)/5, 204/80, 203/90, 190/35, 174/70, 145/61, 119/82, 86/100. Analysis calculated for $C_{16}H_{22}N_2O_3$ (290.36): C, 66.18; H, 7.64; N, 9.65. Found: C, 66.01; H, 7.86; N, 9.44. R_f (6% EtOH/$CHCl_3$) 0.55. Dark brown waxy material. Yield: 209 mg (72%).

*4.5.9. 2-(2′-(Methoxycarbonyl)pyrrolidin-1-yl-methyl)-iodobenzene (**3h**).* ^{1}H NMR ($CDCl_3$) δ: 7.80 (d, 7.8 Hz, 1H, Ar–H); 7.47 (d, 7.8 Hz, 1H, Ar–H); 7.31 (t, 7.8 Hz, 1H, Ar–H); 6.92 (t, 7.8 Hz, 1H, Ar–H); 3.92 (d, 13.9 Hz, 1H, Ar–CH_aH$_b$); 3.72 (d, 13.9 Hz, 1H, Ar–CH$_a$$H_b$); 3.63 (s, 3H, OCH_3); 3.40–3.46 (m, 1H, CHCOO); 3.01–3.08 (m, 1H, NCH_aH$_b$); 2.48–2.55 (m, 1H, NCH$_a$$H_b$); 1.75–2.20 (m, 4H, ($CH_2$)$_2$). ^{13}C NMR ($CDCl_3$) δ: 173.0, 139.6, 137.8, 128.9, 127.2, 126.6, 98.5, 63.8, 60.8, 51.6, 50.2, 27.9, 21.9. IR (KBr, ν (cm^{-1})): 1733 (COO), 1639 (CON). MS (*m*/*z*/rel int.): 345(M^+)/2, 286/100, 217/59, 158/3, 90/12. Analysis calculated for $C_{13}H_{16}NO_2I$ (345.18): C, 45.24; H, 4.67; N, 4.06. Found: C, 45.03; H, 4.43; N, 3.86. R_f (20% EtOAc/$CHCl_3$) 0.76. Dark brown waxy material. Yield: 172 mg (50%).

*4.5.10. 2-(2′-(Methoxycarbonyl)pyrrolidin-1-yl-methyl)-N,N-(1′-(methoxycarbonyl)-butan-1,4-diyl)benzamide (**4h**).* ^{1}H NMR ($CDCl_3$) δ: 7.45 (d, 7.8 Hz, 1H, Ar–H); 7.18–7.30 (m, 2H, Ar–H); 7.12 (d, 7.8 Hz, 1H, Ar–H); 3.75 (s, 3H, OCH_3); 3.70 (s, 3H, OCH_3); 3.20–3.70 (m, 8H, Ar–CH_2+2×CHCOO+2×NCH_2); 1.75–2.40 (m, 8H, 2x (CH_2)$_2$). ^{13}C NMR ($CDCl_3$) δ: 174.2, 172.8, 169.6, 137.0, 132.1, 128.8, 128.5, 127.0, 126.1, 65.4, 58.5, 58.2, 55.5, 52.2, 49.1, 47.7, 29.6, 29.1, 24.9, 24.7. IR (KBr, ν (cm^{-1})): 1743 (COO), 1636 (CON). MS (*m*/*z*/rel int.): 374(M^+)/3, 315/80, 245/100, 215/27, 166/48. Analysis calculated for $C_{20}H_{26}N_2O_5$ (374.44): C, 64.16; H, 7.00; N, 7.48. Found: C, 64.01; H, 7.23; N, 7.25. R_f (4% EtOH/$CHCl_3$) 0.40. Pale yellow waxy material. Yield: 269 mg (72%).

*4.5.11. 2-Iodobenzylamine (**5**)*[28]. White crystals, mp 63–65 °C. ^{13}C NMR ($CDCl_3$) δ: 145.0, 139.3, 128.5 (2C), 128.3, 98.9, 51.3.

*4.5.12. 1,2-Bis(1-oxo-1,3-dihydro-isoindol-2-yl)-methanone (**6a**).* ^{1}H NMR ($CDCl_3$) δ: 7.92 (d, 7.8 Hz, 1H, Ar–H); 7.65 (t, 7.8 Hz, 1H, Ar–H); 7.48–7.55 (m, 2H, Ar–H); 5.02 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ: 171.0, 166.4, 141.4, 133.8, 130.9, 128.6, 125.4, 123.2, 49.0. IR (KBr, ν (cm^{-1})): 1682 (NC(O)N). MS (*m*/*z*/rel int.): 292(M^+)/60, 160/100, 132/36, 116/35, 104/36, 77/40. Analysis calculated for $C_{17}H_{12}N_2O_3$ (292.29): C, 69.86; H, 4.14; N, 9.58. Found: C, 69.70; H, 4.41; N, 9.25. R_f (10% EtOAc/$CHCl_3$) 0.61. Brown waxy material. Yield: 18 mg (6%).

*4.5.13. 1,2-Bis(1-oxo-1,3-dihydro-isoindol-2-yl)-ethan-1,2-dione (**6b**).* MS (*m*/*z*/rel int.): 320(M^+)/10, 292/7, 207/3, 160/100, 116/27, 77/25.

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Supplementary data

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