Multicomponent reactions: development, scope, and applications

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Chapter 5

N-Hydroxyimide Ugi Reaction toward α-Hydrazino-amides

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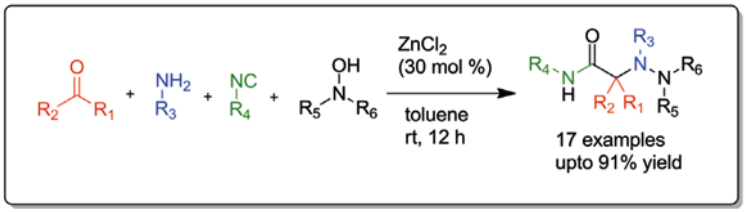


Abstract

The Ugi four-component reaction (U-4CR) with N-hydroxyimides as a novel carboxylic acid isostere has been reported. This reaction provides straightforward access to α-hydrazino-amides. A broad range of aldehydes, amines, isocyanides and *N*-hydroxyimides were employed to give products in moderate to high yields. This reaction displays N-N bond formation by cyclic imide migration in the Ugi reaction. Thus, N-hydroxyimide is added as a new acid component in the Ugi reaction and broadens the scaffold diversity.

Introduction

The Ugi reaction (U-4CR) is a widely used multicomponent reaction (MCR) for the synthesis of bis-amides and peptidomimetics.[1] This reaction has emerged as a powerful synthetic method for the organic, pharmaceutical and polymer industries.[2] However, it cannot meet the ever-increasing need for molecular complexity and diversity in organic and medicinal chemistry. An increasing demand for novel scaffolds has led to the interest in U-4CR postmodifications and single reactant replacement (SRR) by isosteres.[3] U-4CR postmodifications are useful for the synthesis of various heterocycles and peptidic scaffolds.[4] Nevertheless, isostere use in the Ugi reaction is rather limited.[5] An amine component could be replaced by secondary amines, hydroxylamines and hydrazines. As with amines, use of acid isosteres in the Ugi reaction is also limited.

In the Ugi reaction, the carboxylic acid plays several prominent structural roles, including activation of the intermediate imine, the reversible addition to the nitrilium ion and participation in the irreversible Mumm rearrangement to form the final bis-amide product. Because of carboxylic acid's substantial role in the reaction, isosteric replacement by other agents is difficult to accomplish. In 1962, Ugi reported the first acid isosteric replacements by inorganic acids, such as hydrazoic acids, cyanates, thiocyanates etc. (Figure 1).[6] To date, only a few acid isosteres have been reported. For example, our group reported the thioacetic acid as an isostere.[7] El Kaïm and co-workers reported the phenol as an acid isostere in the Ugi reaction involving Smiles rearrangement to form an N-arylamine.[8] Other Ugi-Smiles and similar strategies have been described by El Kaïm (thiophenol),[9] Charton (squaric acid),[10] and Neo (hydroxycoumarins).[11] Further, Lewis acids and CO_2 were used as acid isoteres in the U-4CR.[5]

As for the related Passerini reaction,[12] organic acid isostere replacement has remained largely unexplored for the Ugi-4CR as there are only a few examples of isostere use in the Ugi-4CR for the synthesis of peptidomimetics.[5] Therefore, finding new isosteres in U-4CR for the synthesis of diverse and complex peptidomimetic derivatives is of high interest.

We hypothesized that *N*-hydroxyimides could be used as a novel acid isostere in the U-4CR reaction, which can directly provide the α-hydrazino amides as Ugi reaction products. α-Hydrazino amides are aza analogues of β-peptides and are of interest for several reasons.[13] These foldamers exhibit the special hydrazino turn, and the hydrazidic bond is very resistant to protease.[14] Hydrazino amides are found in many natural products such as linatine, a vitamin B6 antagonist;[15a] negamycine, an antibiotic;[15b] and matlystatins, antimicrobial compounds.[15c] They also have broad applications in medicinal chemistry including use as proteasome inhibitors,[16a] antimicrobials,[16b] DNA and RNA interactors,[16c] (S)-(-)-carbidopa for the treatment of Parkinson's disease,[17] and as human leukocyte elastase (HLE) inhibitors.[18]

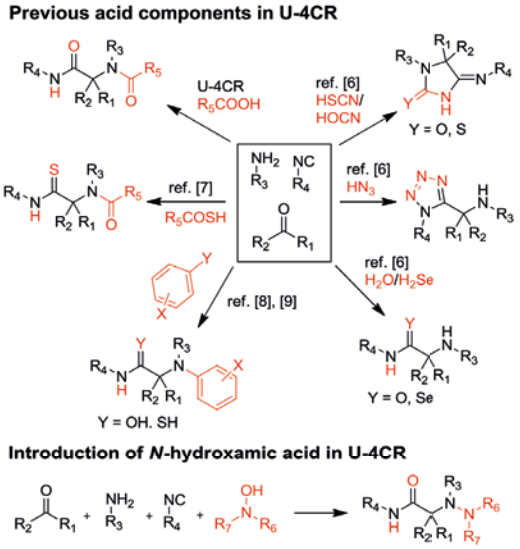


Figure 1. Previously reported and new acid isoteres in U-4CR.

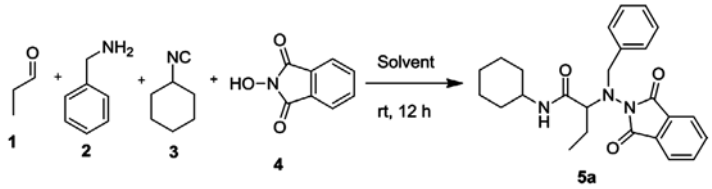
Hydrazino peptides are mainly synthesized by two methods: first, by using hydrazine derivatives[19] and, second, by coupling of an amino group with another amine typically employing oxaziridines.[14] The general use of hydrazine and oxaziridine is limited by unavailability of diverse derivatives and their highly toxic and unstable nature. Another drawback is that their synthesis is laborious. Therefore, the development of new methods for the synthesis of this important foldamer is highly desirable.

Herein, we report the successful use of the *N*-hydroxyimides as an acid isostere in the U-4CR for a direct route to the synthesis of α-hydrazinoamides. This is the second example of cyclic imide migration to nitrogen (O→N imide transfer) in the Mumm rearrangement to form an N-N bond. This type of N-O bond breaking and N-N bond formation in a Mumm-type rearrangement has been recently reported.[20] This reaction illustrates the use of N-hydroxamic acid for N-N bond formation without phthalimidation.

Results and Discussion

We started our optimization by using propionaldehyde, benzylamine, cyclohexyl isocyanide, and N-hydroxyphthalimides (NHPI) as model reactants. Reaction in methanol did not form any desired product (Table 1, entry **1**). In polar aprotic solvents such as THF and CH_3CN, only traces of product were formed. In the polar protic solvent MeOH, the U-3CR product, α-amino-amide, was formed as a major product; in contrast, it formed only in trace amounts in solvents such as THF and toluene. This U-3CR product formation might be due to the low acidity of *N*-hydroxyimide (pKa ~7.5), which functioned only as a catalyst. This observation led us to try a nonpolar solvent and Lewis acid to activate N-hydroxyimide for the further optimization. Indeed, nonpolar solvents such as DCE and toluene allowed moderate product formation of 25% and 20%, respectively, at room temperature.

Table 1. Solvent screening.[a]

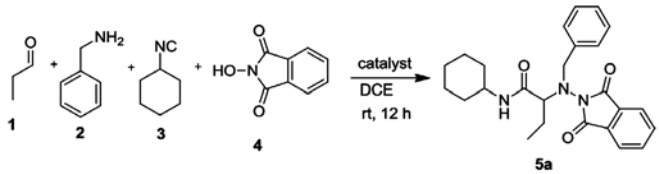


Entry	Solvent	Yield (%)[b]
1	MeOH	—
2	THF	trace
3	DCE	25
4	CH_3CN	trace
5	toluene	20

[a]The reaction was carried out with using propionaldehyde (0.5 mmol), benzylamine (0.5 mmol), cyclohexyl isocyanide (0.5 mmol) and N-hydroxyphthalimide (0.75 mmol) in 1 mL solvent. [b]Yield of isolated product **5a**.

Next, we screened various Lewis acids, (Table 2) such as $InCl_3$, I_2, $Sc(OTf)_3$ etc. (10 mol %) in DCE as a solvent. We found that $ZnCl_2$ was the best of the screened Lewis acids (Table 2, entry 3).

Table 2. Catalyst screening.[a]



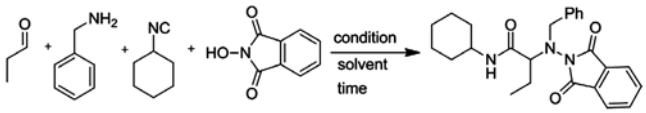
Entry	Catalyst[b]	Yield (%)[c]
1	I_2	22
2	$InCl_2$	10
3	$ZnCl_2$	22
4	$Sc(OTf)_3$	15
5	PTSA	trace
6	TBAF	trace
7	TMSCl	19
8	$AlCl_3$	17
9	$BF_3.OEt_2$	trace
10	$Zn(OTf)_2$	nd
11	ZnI_2	nd
12	$FeCl_3$	trace
13	$CeCl_2$	trace
14	$BaCl_2$	trace

Entry	Catalyst[b]	Yield (%)[c]
15	$GdCl_2$	trace
16	$AuCl_3$	trace

[a]The reaction was carried out with using propionaldehyde (0.5 mmol), benzylamine (0.5 mmol), cyclohexyl isocyanide (0.5 mmol), N-hydroxyphthalimide (0.75 mmol) and catalyst (as mentioned in table) in 1 mL DCE. [b]0.1 equivalent catalyst used [c]Yield of isolated product **5a**. nd = not determined

An increase in the temperature failed to improve the product yield (Table 3, entries **1** and **2**).

Table 3. Optimization Conditions.[a]

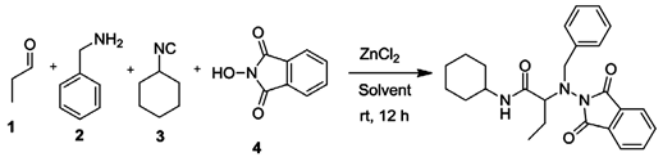


Entry	Solvent	Temp	Catalyst	Time (h)	Yield %
1[b]	THF	50 °C	I_2	12	trace
2[b]	DCE	50 °C	$ZnCl_2$	12	nd

[a]The reaction was carried out with propionaldehyde (1.0 mmol), benzylamine (1.0 mmol), cyclohexyl isocyanide (1.0 mmol) and N-hydroxyphthalimide (1.5 mmol) in 2 mL of solvent. [b]10 mol % of catalyst used. nd = not determined

In further solvent screening with $ZnCl_2$, (Table 4), we observed that toluene and xylene gave similar yields, 51% and 49%, respectively (Table 4, entries **11** and **12**). The nature of the solvent played a critical role in the success of the reaction. Next, we performed a catalyst equivalence study in toluene as solvent. An increase in the catalyst quantity to 30 mol % gave the best yield of 66% (Table 4, entry **17**). However, a further increase in the quantity of $ZnCl_2$ to 50 mol % gave a lower yield, 47% (Table 4, entry **18**). The use of sonication in this reaction did not have any effect on product yield (Table 4, entries **19** and **20**).[12a]

Table 4. Solvent and $ZnCl_2$ equivalence screening.[a]



Entry	Solvent	$ZnCl_2$ equiv	Yield (%)[b]
1	MeOH	0.1	—
2	THF	0.1	trace
3	Chloro-benzene	0.1	31
4	TFE	0.1	38
5	DCM	0.1	nd

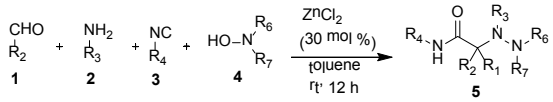
Entry	Solvent	$ZnCl_2$ equiv	Yield (%)[b]
6	$CHCl_3$	0.1	22
7	Dioxane	0.1	trace
8	Acetone	0.1	trace
19	DMSO	0.1	nd
10	CH_3CN	0.1	nd
11	toluene	0.1	51
12	xylene	0.1	49
13	DCE	0.1	22
14	DCE	0.01	25
15	DCE	0.5	40
16	DCE	1	24
17	**toluene**	**0.3**	**66**
18	toluene	0.5	47
19[c]	toluene	0.1	43
20[c]	toluene	0.3	50
19	DME	0.3	trace
20	isopropanol	0.3	trace

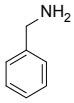
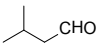
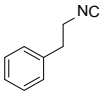
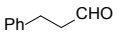
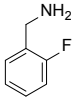
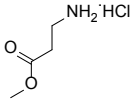
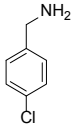
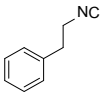
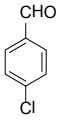
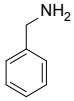
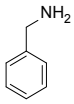
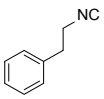
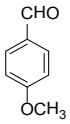
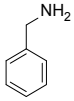
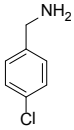
[a]The reaction was carried out with using propionaldehyde (0.5 mmol), benzylamine (0.5 mmol), cyclohexyl isocyanide (0.5 mmol), N-hydroxyphthalimide (0.75 mmol) and $ZnCl_2$ (as mentioned in table) in 1 mL solvent. [b]Yield of isolated product 5a. [c]Reaction performed in sonication nd = not determined

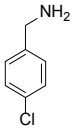
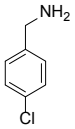
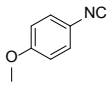
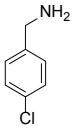
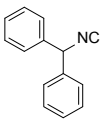
With these optimized conditions in hand, next we examined the generality of this U-4CR by using various aldehydes, amines, isocyanides and N-hydroxyimides (Table 5). Aliphatic aldehydes offered good yields, up to 78% (Table 5, entries **1**–**3**). Aromatic aldehydes are also useful substrates in this reaction (Table 5, entries **6**–**9**).

Electron-withdrawing and -donating groups in aromatic aldehydes at different positions such as ortho and para provided moderate to good yields. Amines with protected functional groups like acetal and halogens were well-tolerated in this reaction, affording moderate to good yields of the products (Table 5, entries **3**, **4**, and **6**). The acid-protected amino acid b-alanine ester gave only 18% yield (Table 5, entry **5**). Various aliphatic and aromatic isocyanides such as cyclohexyl, phenylethyl, 2-nitrobenzyl, benzyl, 4-methoxyphenyl, and b-cyanoethyl were well-suited within the developed methodology.

Table 5. Substrate Scope.[a]

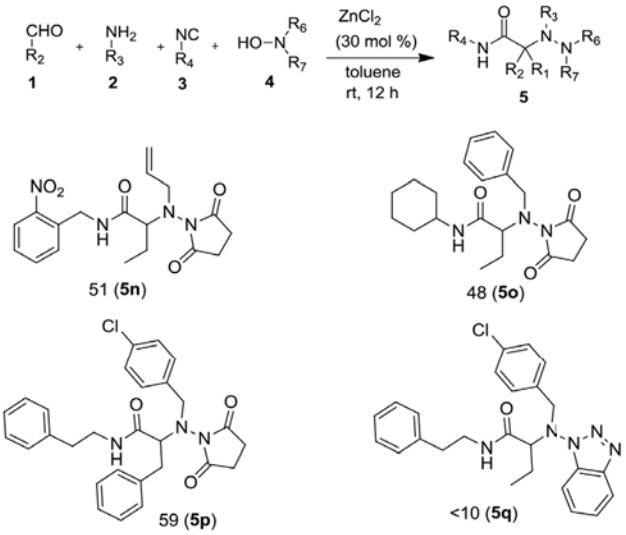


Entry	1	2	3	4	% Yield[b]
1				NHPI	66 (**5a**)
2				NHPI	74 (**5b**)
3				NHPI	78 (**5c**)
4				NHPI	58 (**5d**)
5[c]				NHPI	18 (**5e**)
6				NHPI	57 (**5f**)
7				NHPI	51 (**5g**)
8				NHPI	46 (**5h**)
9				NHPI	21 (**5i**)
10				NHPI	91 (**5j**)

Entry	1	2	3	4	% Yield[b]
11				NHPI	38 (**5k**)
12				NHPI	71 (**5l**)
13				NHPI	65 (**5m**)

[a]Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), **3** (1.0 mmol), and **4** (1.5 mmol), $ZnCl_2$ (30 mol %) in toluene (2 mL) at rt for overnight. [b]Isolated yield. [c]1.5 equivalent triethylamine used.

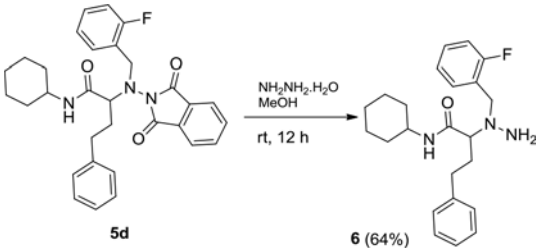
Among *N*-hydroxyimides, N-hydroxysuccinimides (NHS) also proceeded smoothly similarly to NHPI and gave 48-59% yield (Scheme 1, **5n-p**). However, the reaction with hydroxybenzotriazole (HOBt) resulted in only trace product formation (Scheme **1, 5q**).



Scheme 1. *N*-Hydroxyimides Scope.

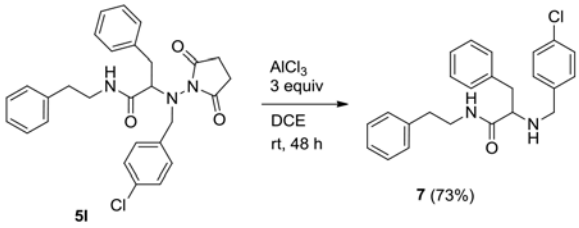
A abroad functional group tolerance in this reaction could be of interest for the postmodification condensations. Thus, among the vast number of possible post-modification reactions with this modified U-4CR, we attempted several. Hydrazines are important intermediates for the synthesis of many heterocycles and scaffolds.[19] The U-4CR product (**5d**) treatment with hydrazine hydrate

deprotects the NHPI and forms the free hydrazine derivatives **6**.[12a] We obtained free hydrazine in a good yield of 64% after overnight reaction (Scheme 2).



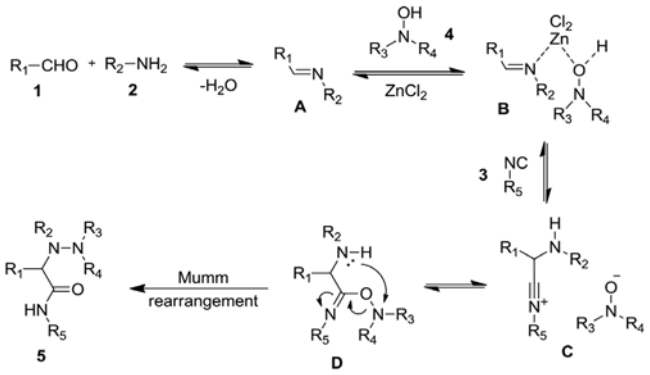
Scheme 2. Deprotection toward Hydrazine Formation

Next, we turned our attention to creating access for pharmaceutically important a-amino-amide molecules. We converted the U-4CR product (**5l**) to U-3CR product, α-amino-amides **7** in good yield (73%). This $AlCl_3$ catalyzed reaction cleave the N-N bond (Scheme 3) to form the final product.[21]



Scheme 3. Deprotection toward α-Amino Amide.

We did not carry out detailed mechanistic studies but envision the following mechanism (Scheme 4). $ZnCl_2$ activates an imine **A** to allow the nucleophilic addition of isocyanide **3** to form the nitrilium intermediate **C**. The hydroxamate nucleophilicly traps the nitrilium intermediate **C**. Finally this intermediate **D** undergoes an irreversible Mumm-like N→N migration to form the α-hydrazino-amide **5**.



Scheme 4. Anticipated mechanism for the Ugi-N-hydroxyimide reaction.

Conclusion

In conclusion, we have reported N-hydroxyimides as novel acid isosteres in the U-4CR toward the one-step synthesis of α-hydrazinoamides via N-N bond formation. This mild and general reaction requires catalytic amounts of $ZnCl_2$. This protocol uses readily available N-hydroxy imides, which replace the toxic and unstable hydrazines/oxaziridine use for the synthesis of α-hydrazinoamides. The method is applicable for a wide range of aldehydes and amines and has the potential for multiple post-modifications. Such scaffolds will be useful to fill the screening decks of the European Lead Factory (ELF).[22] Moreover, as this reaction has significant potential in peptidomimetics synthesis, studies on post-modification reactions are now in progress.

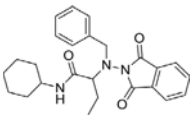
Experimental Procedures and Spectral Data of α-hydrazino-amides

General procedure for the synthesis of α-hydrazino-amides:

A mixture of amine (1 mmol), aldehyde (1 mmol), isocyanide (1 mmol), N-hydroxamic acid (1.5 mmol) and $ZnCl_2$ (0.3 equivalent) in 2 mL of toluene were stirred for overnight at room temperature. The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography using EtOAc–hexane as eluent.

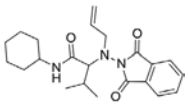
Spectral Data

2-(benzyl(1,3-dioxoisoindolin-2-yl)amino)-*N*-cyclohexylbutanamide (**5a**)



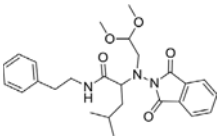
Obtained from 0.5 mmol reaction as a colorless liquid, yield: 139 mg (66%) ; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 4.9, 3.0, 2H), 7.77 (dd, *J* = 5.4, 3.1, 2H), 7.46 (d, *J* = 7.4, 2H), 7.33 (t, *J* = 7.5, 2H), 7.29 – 7.19 (m, 1H), 4.11 (d, *J* = 12.7, 1H), 3.73 (d, *J* = 12.7, 1H), 3.70 – 3.63 (m, 1H), 3.25 (s, 1H), 2.03 – 1.81 (m, 3H), 1.51 – 1.32 (m, 5H), 1.17 – 0.97 (m, 8H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.1, 153.7, 139.9, 134.3, 129.6, 128.4, 127.1, 123.5, 55.5, 55.0, 51.6, 34.2, 34.0, 26.7, 25.5, 23.4, 23.3, 10.8. MS (ESI) m/z calculated $[M+H]^+$: 420.22; found $[M+H]^+$: 420.16. HRMS (ESI) m/z calculated $[M+H]^+$: 420.22817; found $[M+H]^+$: 420.2285.

2-(allyl(1,3-dioxoisoindolin-2-yl)amino)-N-cyclohexyl-3-methylbutanamide (**5b**)



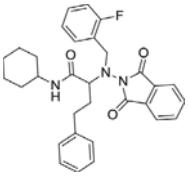
Obtained from 1 mmol reaction as a colorless solid, yield: 283 mg (74%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 5.3, 3.1, 2H), 7.77 (dd, *J* = 5.4, 3.1, 2H), 6.03 – 5.83 (m, 1H), 5.31 (dd, *J* = 17.2, 0.9, 1H), 5.13 (d, *J* = 10.3, 1H), 3.58 (dd, *J* = 14.0, 5.3, 1H), 3.45 – 3.30 (m, 2H), 3.16 (dd, *J* = 14.0, 6.1, 1H), 2.14 – 1.96 (m, 1H), 1.64 (s, 1H), 1.52 – 1.31 (m, 5H), 1.21 – 1.02 (m, 11H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.0, 153.5, 136.9, 134.3, 129.6, 123.4, 116.1, 60.2, 55.0, 50.1, 34.3, 33.8, 31.3, 25.5, 23.3, 20.2, 19.8. MS (ESI) m/z calculated $[M+H]^+$: 384.22; found $[M+H]^+$: 384.05. HRMS (ESI) m/z calculated $[M+H]^+$: 384.22817; found $[M+H]^+$: 384.2276.

2-((2,2-dimethoxyethyl)(1,3-dioxoisoindolin-2-yl)amino)-4-methyl-*N*-phenethylpentanamide (**5c**)



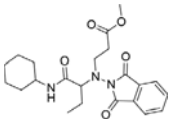
Obtained from 1 mmol reaction as a colorless liquid, yield: 364 mg (78%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 5.4, 3.1, 2H), 7.76 (dd, *J* = 5.4, 3.1, 2H), 7.08 (t, *J* = 6.6, 3H), 6.96 (d, *J* = 6.0, 2H), 4.50 (t, *J* = 5.3, 1H), 3.79 (t, *J* = 7.5, 1H), 3.63 – 3.48 (m, 2H), 3.40 (s, 6H), 3.06 (dd, *J* = 11.9, 6.0, 1H), 2.62 (t, *J* = 6.9, 2H), 2.50 (dd, *J* = 11.9, 4.8, 1H), 1.90 – 1.77 (m, 1H), 1.64 (t, *J* = 7.2, 2H), 0.95 (d, *J* = 6.6, 3H), 0.92 (d, *J* = 6.6, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.3, 157.0, 139.5, 134.3, 129.4, 128.8, 128.1, 126.0, 123.5, 103.7, 54.0, 53.2, 52.88, 49.0, 48.5, 42.1, 37.5, 24.8, 22.8, 22.7. MS (ESI) m/z calculated $[M+H]^+$: 468.24; found $[M+H]^+$: 468.10. HRMS (ESI) m/z calculated $[M+H]^+$: 468.2493; found $[M+H]^+$: 468.24969.

N-cyclohexyl-2-((1,3-dioxoisoindolin-2-yl)(2-fluorobenzyl)amino)-4-phenylbutanamide (**5d**)



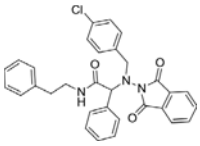
Obtained from 1 mmol reaction as a colorless liquid, yield: 298 mg (58%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 5.4, 3.1, 2H), 7.77 (dd, *J* = 5.4, 3.1, 2H), 7.56 – 7.47 (m, 1H), 7.30 – 7.21 (m, 6H), 7.18 (t, *J* = 6.8, 1H), 7.12 (t, *J* = 7.5, 1H), 7.08 – 7.01 (m, 1H), 4.11 (d, *J* = 12.9, 1H), 3.81 (d, *J* = 12.9, 1H), 3.75 (t, *J* = 7.1, 1H), 3.11 (s, 1H), 2.96 – 2.83 (m, 1H), 2.82 – 2.70 (m, 1H), 2.31 – 2.16 (m, 1H), 2.15 – 2.03 (m, 1H), 1.85 (s, 1H), 1.50 – 1.21 (m, 5H), 1.14 – 0.90 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.9, 162.3, 160.3, 153.8, 141.4, 134.3, 130.7, 130.6, 129.6, 128.8, 128.8, 128.6, 128.4, 126.0, 124.1, 124.1, 123.5, 115.4, 115.3, 55.1, 53.5, 45.3, 45.2, 35.4, 34.1, 33.9, 32.1, 25.4, 23.4. MS (ESI) m/z calculated $[M+H]^+$: 514.25; found $[M+H]^+$: 514.10. HRMS (ESI) m/z calculated $[M+H]^+$: 514.25005; found $[M+H]^+$: 514.25055.

methyl 3-((1-(cyclohexylamino)-1-oxobutan-2-yl)(1,3-dioxoisoindolin-2-yl)amino)propanoate (5e)



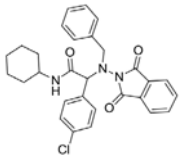
Obtained from 1 mmol reaction as a colorless liquid, yield: 74 mg (18%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 5.3, 3.1, 2H), 7.79 (dd, *J* = 5.4, 3.1, 2H), 3.73 (s, 3H), 3.69 (t, *J* = 7.5, 1H), 3.47 (brs, 1H), 3.30 – 3.21 (m, 1H), 2.84 – 2.75 (m, 1H), 2.61 (t, *J* = 6.1, 2H), 1.92 – 1.84 (m, 2H), 1.52 – 1.39 (m, 5H), 1.23 – 1.17 (m, 2H), 1.17 – 1.11 (m, 2H), 1.09 (t, *J* = 7.4, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.1, 163.9, 153.5, 134.3, 129.5, 123.4, 56.5, 55.0, 51.7, 43.2, 34.8, 34.1, 34.0, 26.6, 25.5, 23.3, 10.6. MS (ESI) m/z calculated $[M+H]^+$: 416.21; found $[M+H]^+$: 416.25. HRMS (ESI) m/z calculated $[M+H]^+$: 416.218; found $[M+H]^+$: 416.21805.

2-((4-chlorobenzyl)(1,3-dioxoisoindolin-2-yl)amino)-*N*-phenethyl-2-phenylacetamide (5f)



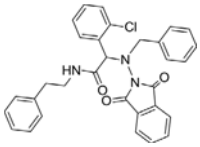
Obtained from 1 mmol reaction as a colorless solid, yield: 298 mg (57%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (brs, 2H), 7.78 (dd, *J* = 5.4, 3.0, 2H), 7.56 (d, *J* = 7.6, 2H), 7.42 – 7.34 (m, 4H), 7.33 – 7.26 (m, 3H), 7.11 – 7.02 (m, 3H), 6.85 (dd, *J* = 7.0, 1.9, 2H), 4.77 (s, 1H), 4.07 (d, *J* = 13.2, 1H), 3.84 (d, *J* = 13.2, 1H), 3.33 (t, *J* = 6.9, 2H), 2.52 (td, *J* = 6.8, 3.2, 2H), 2.15 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.3, 155.8, 139.4, 138.1, 137.2, 134.5, 132.9, 130.0, 129.4, 128.8, 128.6, 128.2, 128.2, 127.5, 126.1, 123.7, 57.9, 50.9, 49.0, 37.1. MS (ESI) m/z calculated $[M+H]^+$: 524.17; found $[M+H]^+$: 524.05. HRMS (ESI) m/z calculated $[M+H]^+$: 524.17355; found $[M+H]^+$: 524.17432.

2-(benzyl(1,3-dioxoisoindolin-2-yl)amino)-2-(4-chlorophenyl)-*N*-cyclohexylacetamide (5g)



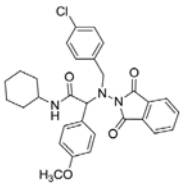
Obtained from 1 mmol reaction as a colorless liquid, yield: 256 mg (51%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 2.7, 2H), 7.84 – 7.74 (m, 2H), 7.65 (d, *J* = 8.1, 2H), 7.51 (d, *J* = 7.4, 2H), 7.41 – 7.32 (m, 4H), 7.27 (t, *J* = 7.4, 1H), 4.85 (s, 1H), 4.24 (d, *J* = 13.0, 1H), 3.99 (d, *J* = 13.0, 1H), 3.17 (s, 1H), 2.25 (s, 1H), 1.51 – 1.20 (m, 5H), 1.17 – 0.93 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.9, 152.4, 139.4, 136.6, 134.5, 133.8, 129.5, 129.0, 128.8, 128.6, 128.5, 127.3, 123.6, 56.6, 55.3, 51.6, 34.0, 33.6, 25.4, 23.4, 23.2. MS (ESI) m/z calculated $[M+H]^+$: 502.18; found $[M+H]^+$: 502.06. HRMS (ESI) m/z calculated $[M+H]^+$: 502.1892; found $[M+H]^+$: 502.1893.

2-(benzyl(1,3-dioxoisoindolin-2-yl)amino)-2-(2-chlorophenyl)-*N*-phenethylacetamide (5h)



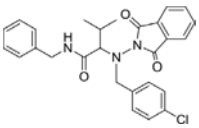
Obtained from 1 mmol reaction as a colorless liquid, yield: 240 mg (46%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 7.8, 1.2, 1H), 7.92 – 7.81 (m, 2H), 7.76 (dd, *J* = 5.4, 2.8, 2H), 7.43 (d, *J* = 7.3, 2H), 7.39 – 7.35 (m, 1H), 7.34 – 7.29 (m, 3H), 7.28 – 7.23 (m, 2H), 7.09 – 6.96 (m, 3H), 6.91 – 6.82 (m, 2H), 5.16 (s, 1H), 4.07 (d, *J* = 12.7, 1H), 3.88 (d, *J* = 12.7, 1H), 3.41 – 3.32 (m, 1H), 3.31 – 3.19 (m, 1H), 2.48 (t, *J* = 6.9, 2H), 2.09 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.3, 155.3, 139.4, 139.2, 135.5, 134.5, 133.7, 129.8, 129.6, 129.4, 128.9, 128.8, 128.4, 128.1, 127.8, 127.3, 126.0, 123.7, 55.6, 52.3, 48.9, 36.9. MS (ESI) m/z calculated $[M+H]^+$: 524.17; found $[M+H]^+$: 524.18. HRMS (ESI) m/z calculated $[M+H]^+$: 524.17355; found $[M+H]^+$: 524.17413.

2-((4-chlorobenzyl)(1,3-dioxoisoindolin-2-yl)amino)-*N*-cyclohexyl-2-(4-methoxyphenyl)acetamide (5i)



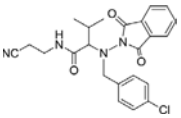
Obtained from 1 mmol reaction as a colorless liquid, yield: 112 mg (21%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 2.9, 2H), 7.79 (dd, *J* = 5.4, 3.1, 2H), 7.60 (d, *J* = 8.4, 2H), 7.46 (d, *J* = 8.1, 2H), 7.31 (d, *J* = 8.2, 2H), 6.94 (d, *J* = 8.5, 2H), 4.81 (s, 1H), 4.20 (d, *J* = 13.2, 1H), 3.97 (d, *J* = 13.2, 1H), 3.81 (s, 3H), 3.19 (s, 1H), 1.50 – 1.30 (m, 4H), 1.28 – 1.20 (m, 1H), 1.17 – 0.92 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.0, 159.3, 152.9, 138.3, 134.5, 132.8, 129.9, 129.5, 128.7, 128.5, 123.6, 114.0, 56.9, 55.3, 55.1, 50.9, 34.0, 33.5, 25.4, 23.3, 23.2. MS (ESI) m/z calculated $[M+H]^+$: 532.19; found $[M+H]^+$: 532.12. HRMS (ESI) m/z calculated $[M+H]^+$: 532.19976; found $[M+H]^+$: 532.20056.

***N*-benzyl-2-((4-chlorobenzyl)(1,3-dioxoisoindolin-2-yl)amino)-3-methylbutanamide (5j)**



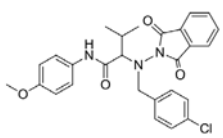
Obtained from 1 mmol reaction as a colorless liquid, yield: 432 mg (91%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 – 7.87 (m, 2H), 7.84 – 7.74 (m, 2H), 7.36 (d, *J* = 8.4, 2H), 7.33 – 7.27 (m, 2H), 7.24 – 7.14 (m, 3H), 7.02 (d, *J* = 6.9, 2H), 4.40 (q, *J* = 16.1, 2H), 4.14 (d, *J* = 13.3, 1H), 3.77 (d, *J* = 13.3, 1H), 3.43 (d, *J* = 9.0, 1H), 2.25 – 2.08 (m, 1H), 1.95 (s, 1H), 1.23 (d, *J* = 6.6, 3H), 1.13 (d, *J* = 6.7, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.9, 163.7, 157.9, 139.2, 138.5, 134.5, 134.5, 132.7, 129.8, 129.4, 128.5, 128.2, 126.6, 126.5, 123.7, 123.6, 60.2, 50.8, 50.7, 31.6, 20.1, 19.6. MS (ESI) m/z calculated $[M+H]^+$: 476.17; found $[M+H]^+$: 476.11. HRMS (ESI) m/z calculated $[M+H]^+$: 476.17355; found $[M+H]^+$: 476.17398.

2-((4-chlorobenzyl)(1,3-dioxoisoindolin-2-yl)amino)-*N*-(2-cyanoethyl)-3-methylbutanamide (5k)



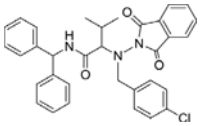
Obtained from 1 mmol reaction as a white liquid, yield: 166 mg (38%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 – 7.84 (m, 2H), 7.84 – 7.73 (m, 2H), 7.39 (d, *J* = 8.4, 2H), 7.29 (d, *J* = 8.4, 2H), 4.08 (d, *J* = 13.4, 1H), 3.77 (d, *J* = 13.4, 1H), 3.40 – 3.30 (m, 1H), 3.27 – 3.17 (m, 2H), 2.27 (t, *J* = 6.7, 2H), 2.14 – 1.99 (m, 1H), 1.87 (s, 1H), 1.16 (d, *J* = 6.6, 3H), 1.07 (d, *J* = 6.7, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.4, 163.4, 158.9, 138.2, 134.6, 132.8, 129.7, 129.1, 128.6, 123.7, 117.6, 60.6, 50.6, 43.2, 31.5, 20.0, 19.9, 19.5. MS (ESI) m/z calculated $[M+H]^+$: 439.15; found $[M+H]^+$: 439.12. HRMS (ESI) m/z calculated $[M+H]^+$: 439.15314; found $[M+H]^+$: 439.15314.

2-((4-chlorobenzyl)(1,3-dioxoisoindolin-2-yl)amino)-*N*-(4-methoxyphenyl)-3-methylbutanamide (5l)



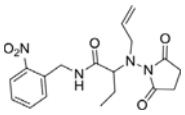
Obtained from 1 mmol reaction as a white liquid, yield: 348 mg (71%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (brs, 2H), 7.80 – 7.68 (m, 2H), 7.36 (d, *J* = 8.4, 2H), 7.31 – 7.19 (m, 2H), 6.78 – 6.68 (m, 2H), 6.64 – 6.53 (m, 2H), 4.14 (d, *J* = 12.7, 1H), 3.72 (s, 3H), 3.61 (d, *J* = 12.7, 1H), 3.24 (d, *J* = 9.2, 1H), 2.13 – 1.97 (m, 1H), 1.69 (s, 1H), 1.16 (d, *J* = 6.8, 3H), 1.09 (d, *J* = 6.6, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.0, 158.2, 156.3, 138.6, 137.8, 134.5, 132.6, 129.8, 129.2, 128.4, 123.7, 121.3, 114.2, 61.7, 55.4, 51.1, 31.7, 20.1, 20.0. MS (ESI) m/z calculated $[M+H]^+$: 492.16; found $[M+H]^+$: 492.05. HRMS (ESI) m/z calculated $[M+H]^+$: 492.16846; found $[M+H]^+$: 492.16888.

N-benzhydryl-2-((4-chlorobenzyl)(1,3-dioxoisoindolin-2-yl)amino)-3-methylbutanamide (**5m**)



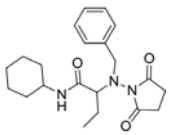
Obtained from 1 mmol reaction as a white liquid, yield: 358 mg (65%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 – 7.87 (m, 2H), 7.84 – 7.71 (m, 2H), 7.23 – 7.18 (m, 2H), 7.18 – 7.14 (m, 2H), 7.13 – 7.04 (m, 6H), 7.02 – 6.98 (m, 2H), 6.97 – 6.93 (m, 2H), 5.46 (s, 1H), 3.89 (d, *J* = 13.5, 1H), 3.49 – 3.36 (m, 2H), 2.10 – 1.95 (m, 1H), 1.80 (s, 1H), 1.10 (d, *J* = 6.6, 3H), 0.81 (d, *J* = 6.8, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.1, 163.9, 158.1, 143.8, 143.8, 138.5, 134.7, 134.7, 132.5, 129.6, 129.6, 128.4, 128.4, 128.3, 126.9, 126.9, 126.8, 126.7, 123.8, 123.7, 64.7, 60.8, 50.5, 31.6, 20.1, 19.5. MS (ESI) m/z calculated $[M+H]^+$: 552.20; found $[M+H]^+$: 552.15. HRMS (ESI) m/z calculated $[M+H]^+$: 552.20485; found $[M+H]^+$: 552.20514.

2-(allyl(2,5-dioxopyrrolidin-1-yl)amino)-*N*-(2-nitrobenzyl)butanamide (**5n**)



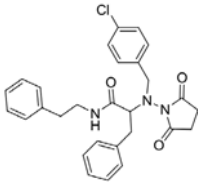
Obtained from 1 mmol reaction as a colorless liquid, yield: 191 mg (51%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 – 7.94 (m, 1H), 7.60 (td, *J* = 7.6, 1.0, 1H), 7.48 – 7.37 (m, 2H), 5.98 – 5.81 (m, 1H), 5.22 (dd, *J* = 17.2, 1.5, 1H), 5.12 (dd, *J* = 10.2, 1.2, 1H), 4.92 (s, 2H), 3.80 (t, *J* = 7.4, 1H), 3.62 – 3.48 (m, 1H), 3.26 (dd, *J* = 13.8, 6.7, 1H), 2.83 (brd, *J* = 8.3, 4H), 1.89 (p, *J* = 7.3, 2H), 1.07 (t, *J* = 7.5, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 158.8, 148.2, 136.3, 134.8, 133.3, 129.4, 127.8, 124.7, 117.0, 55.8, 50.2, 48.7, 26.6, 25.7, 10.5. MS (ESI) m/z calculated $[M+H]^+$: 375.16; found $[M+H]^+$: 375.17. HRMS (ESI) m/z calculated $[M+H]^+$: 375.1663; found $[M+H]^+$: 375.16647.

2-(benzyl(2,5-dioxopyrrolidin-1-yl)amino)-*N*-cyclohexylbutanamide (**5o**)



Obtained from 1 mmol reaction as a colorless liquid, yield: 178 mg (48%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.2, 2H), 7.31 (t, *J* = 7.5, 2H), 7.24 (t, *J* = 7.3, 1H), 4.04 (d, *J* = 12.7, 1H), 3.68 (d, *J* = 12.7, 1H), 3.66 – 3.60 (m, 1H), 3.24 (brs, 1H), 2.78 (s, 4H), 1.91 – 1.74 (m, 3H), 1.66 – 1.58 (m, 2H), 1.55 – 1.43 (m, 3H), 1.27 – 1.17 (m, 5H), 1.04 (t, *J* = 7.5, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 153.3, 139.9, 128.4, 127.0, 55.5, 55.1, 51.5, 34.5, 34.2, 26.6, 25.7, 25.6, 23.8, 23.7, 10.7. MS (ESI) m/z calculated $[M+H]^+$: 372.22; found $[M+H]^+$: 372.21. HRMS (ESI) m/z calculated $[M+H]^+$: 372.22817; found $[M+H]^+$: 372.22847.

2-((4-chlorobenzyl)(2,5-dioxopyrrolidin-1-yl)amino)-*N*-phenethyl-3-phenylpropanamide (**5p**)



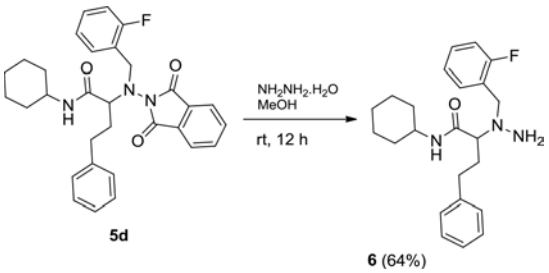
Obtained from 1 mmol reaction as a colorless liquid, yield: 288 mg (59%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 7.2, 2H), 7.32 – 7.25 (m, 4H), 7.24 – 7.18 (m, 4H), 7.17 – 7.10 (m, 2H), 6.93 (d, *J* = 7.2, 2H), 3.92 (d, *J* = 13.0, 1H), 3.77 (dd, *J* = 9.3, 5.7, 1H), 3.57 (d, *J* = 13.0, 1H), 3.11 – 2.96 (m, 3H), 2.85 – 2.72 (m, 1H), 2.71 – 2.61 (m, 2H), 2.61 – 2.49 (m, 2H), 2.37 – 2.22 (m, 2H), 1.86 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4, 154.7, 139.7, 138.1, 136.9, 132.8, 129.8, 129.7, 129.2, 129.1, 128.9, 128.8, 128.8, 128.7, 128.5, 128.5, 128.1, 126.9, 126.5, 126.0, 56.3, 50.5, 48.2, 39.6, 36.8, 25.6. MS (ESI) m/z calculated $[M+H]^+$: 490.18; found $[M+H]^+$: 490.22. HRMS (ESI) m/z calculated $[M+H]^+$: 490.1892; found $[M+H]^+$: 490.18924.

Experimental Procedures and Spectral Data for post-modifications

Experimental procedure for the synthesis of *N*-cyclohexyl-2-(1-(2-fluorobenzyl)hydrazinyl)-4-phenylbutanamide (**6**)

To a solution of **5d** (80 mg, 0.16 mmol) in 1 mL of methanol was added 64 ml of hydrazine hydrate (98%). This mixture was stirred at room temperature over 12 h, at the end of which the solvent was removed. Dissolved the residue in 10 ml of CH_2Cl_2 and washed it with 3% $NaHCO_3$ aqueous solution (4 ml × 5). The organic layer was dried over anhydrous MgSO4, and solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography using EtOAc-hexane as eluent to afford 39 mg of 6 as white solid.

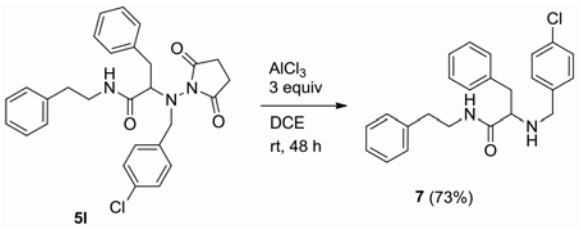
(Procedure as per ref: A. L. Chandgude, A. Dömling, *Org. Lett.* **2016**, 18, 6396−6399.)



N-cyclohexyl-2-(1-(2-fluorobenzyl)hydrazinyl)-4-phenylbutanamide (**6**)

Obtained as a white solid, yield: 39 mg (64%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.23 (m, 4H), 7.22 – 7.13 (m, 4H), 7.09 (td, *J* = 7.5, 1.0, 1H), 7.07 – 7.01 (m, 1H), 3.86 – 3.73 (m, 2H), 3.61 (d, *J* = 12.8, 1H), 3.21 – 3.07 (m, 1H), 2.67 (t, *J* = 8.0, 2H), 2.15 – 2.00 (m, 1H), 1.98 – 1.78 (m, 3H), 1.78 – 1.67 (m, 2H), 1.66 – 1.46 (m, 2H), 1.45 – 1.31 (m, 2H), 1.28 – 1.12 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6, 162.4, 160.4, 141.2, 130.7, 130.6, 129.3, 129.3, 128.5, 128.4, 126.5, 126.3, 126.1, 124.2, 124.2, 115.6, 115.4, 62.3, 47.5, 46.9, 46.9, 35.6, 33.3, 33.0, 32.4, 25.6, 24.9. MS (ESI) m/z calculated $[M+H]^+$: 384.24; found $[M+H]^+$: 384.31.

Experimental procedure for the synthesis of 2-((4-chlorobenzyl)amino)-*N*-phenethyl-3-phenylpropanamide (**7**)



To a solution of **5l** (100 mg, 0.2 mmol) in 2 mL of 1,2-dichloroethane was added $AlCl_3$ (3 equiv). This mixture was stirred at room temperature over 48 h, at the end of which the reaction was quenched

with 10% NaOH under ice cooling, and the aqueous layer was extracted with DCM. The organic layer was dried over anhydrous MgSO4, and solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography using EtOAc–hexane as eluent to afford 57 mg of **10** as white solid.
(Procedure as per ref: Y. Kikugawa, Y. Aoki, T. Sakamoto, *J. Org. Chem.* **2001**, 66, 8612-8615.)

2-((4-chlorobenzyl)amino)-*N*-phenethyl-3-phenylpropanamide (7)
Obtained as a white solid, yield: 57 mg (73%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.17 (m, 8H), 7.17 – 7.07 (m, 6H), 6.79 (d, *J* = 8.3, 2H), 3.63 – 3.44 (m, 3H), 3.34 (d, *J* = 13.6, 1H), 3.26 (dd, *J* = 9.5, 4.2, 1H), 3.17 (dd, *J* = 13.9, 4.1, 1H), 2.87 – 2.72 (m, 2H), 2.64 (dd, *J* = 13.8, 9.5, 1H), 1.66 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2, 138.8, 137.6, 137.4, 132.8, 129.2, 129.1, 129.0, 128.9, 128.9, 128.8, 128.8, 128.7, 128.6, 128.5, 127.0, 126.5, 63.1, 51.7, 39.9, 39.3, 35.6. MS (ESI) m/z calculated $[M+H]^+$: 393.17; found $[M+H]^+$: 393.00.

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