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Synthesis of methyl 2-((2-(cyclohexylamino)-2-oxo-1-phenylethyl) amino)benzoate

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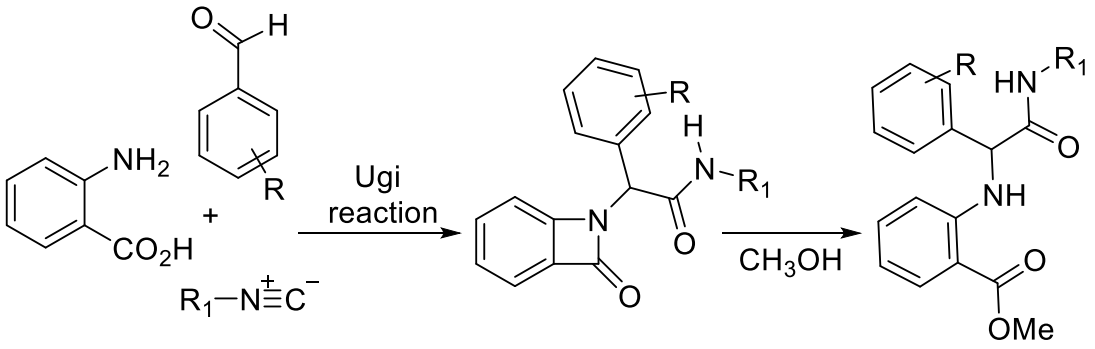
Abstract

Reaction between substituted benzaldehydes, anthranilic acid, and cyclohexyl isocyanide gave rise to pure methyl 2-((2-(cyclohexylamino)-2-oxo-1-phenylethyl) amino)benzoates, that can be useful to design new drugs.



Keywords: Anthranilic acid, isocyanide, Ugi reaction, multicomponent reactions

Introduction

The synthesis of molecules with high diversity and complexity using readily available starting materials is an interesting approach in combinatorial chemistry and drug discovery.

In this regard, combining the multicomponent reactions MCRs has been used as an efficient method for the synthesis of highly functionalized compounds.[1] (MCRs) have opened a new paradigm in terms of efficiently and naturally benign synthesis of small molecule libraries which have significant pharmaceutical importance.[2-5]

Among them, isocyanide based MCRs such as the Ugi and Passerini reactions are well known in medicinal chemistry.[6-8] Recently, a new version of the isocyanide-based Ugi three-component coupling reaction (3CC) using an aldehyde and acid has been developed as a bi-functional substrate.[9,10] Intermolecular versions of the Ugi reaction have also been reported, where two of the four functional groups are present in the same molecule. The possibility of generating heterocyclic molecules using bi-functional compounds is known as the Ugi-4-centre-3-component reaction (U-4C-3CR).[11,12]

Among the various bioactive heterocyclic molecules, N-substituted anthranilic acid derivatives have been the object of intense studies because of their biological activities and therapeutic applications.[13] Mefenamic acid and meclofenamates[14] both are *N*-phenylanthranilic acid derivatives, which have been used as anti-inflammatory agents in treatments. A considerable amount of work has been done on the structural variation of this subclass of drugs broadly known as non-steroidal anti-inflammatory drugs (NSAIDs). It has been observed that the best known NSAIDs are in form acidic. In this regard, our attention has been directed to the variation at position-2 of anthranilic acid with a view to synthesize new analogies with improved anti-inflammatory effects. Recent literatures show that substitutions at 2-position of anthranilic acid (2-amino benzoic acid) by different substituted aryl or heteroaryl moieties markedly modulate the anti-inflammatory activity.[15,16]

As part of our program is aimed at developing new isocyanide-based multi-component reactions for the synthesis of heterocycles, herein we report a new efficient synthesis of methyl 2-((2-(cyclohexylamino)-2-oxo-1-phenylethyl)amino)benzoate via Ugi reaction.

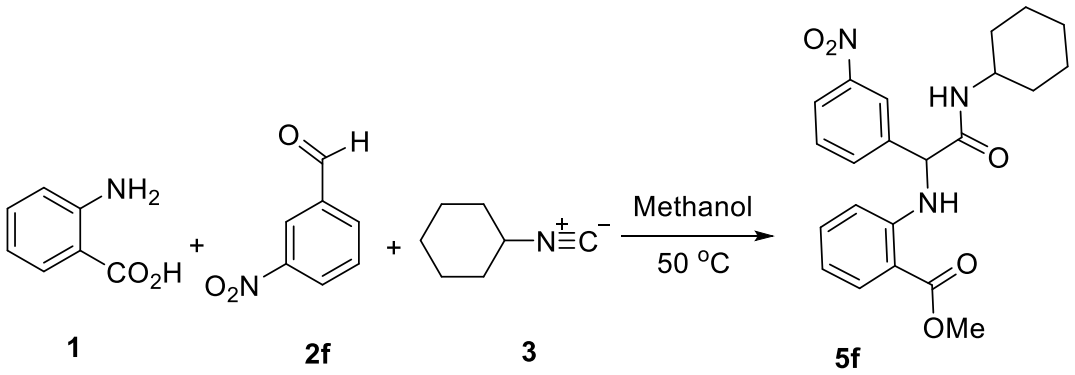
Results and Discussion

In order to achieve, we have identified methyl 2-((2-(cyclohexylamino)-2-oxo-1-phenylethyl)amino)benzoate using a Ugi-three-component reaction involving anthranilic acid, various aldehydes and isocyanides in methanol.

Initially, we examined the pattern coupling reaction of anthranilic acid (**1**) with 3-nitrobenzaldehyde (**2f**), and cyclohexylisocyanide (**3**). The reaction proceeded smoothly in MeOH at 50°C affording the corresponding methyl 2-((2-(cyclohexylamino)-1-(4-nitrophenyl)-2-oxoethyl)amino)benzoate (**5f**) in 98% yield after 12 h (Table 1).

The effect of different solvents on the reaction was also examined, and the results are summarized in Scheme 1. We found in absolute ethanol, the desired product was obtained in 90% yield while in methanol, **5f** was isolated in 98% yield (Scheme 1). When the water content in the reaction mixture was increased, the yield of the target molecule dropped, and using water as the solvent gave very low yields. According to the attack of nucleophilic solvents at the carbonyl group in the β-lactam skeleton we carried out this reaction in THF and CH_3CN as non-nucleophilic solvents under the same conditions (Scheme 1). In these solvents the desired product was not formed. On the basis of this information, **5f** was produced in higher yields using methanol

solvent much higher in comparison with that of ethanol; therefore, we chose the MeOH for this transformation because of cost and environmental concerns.

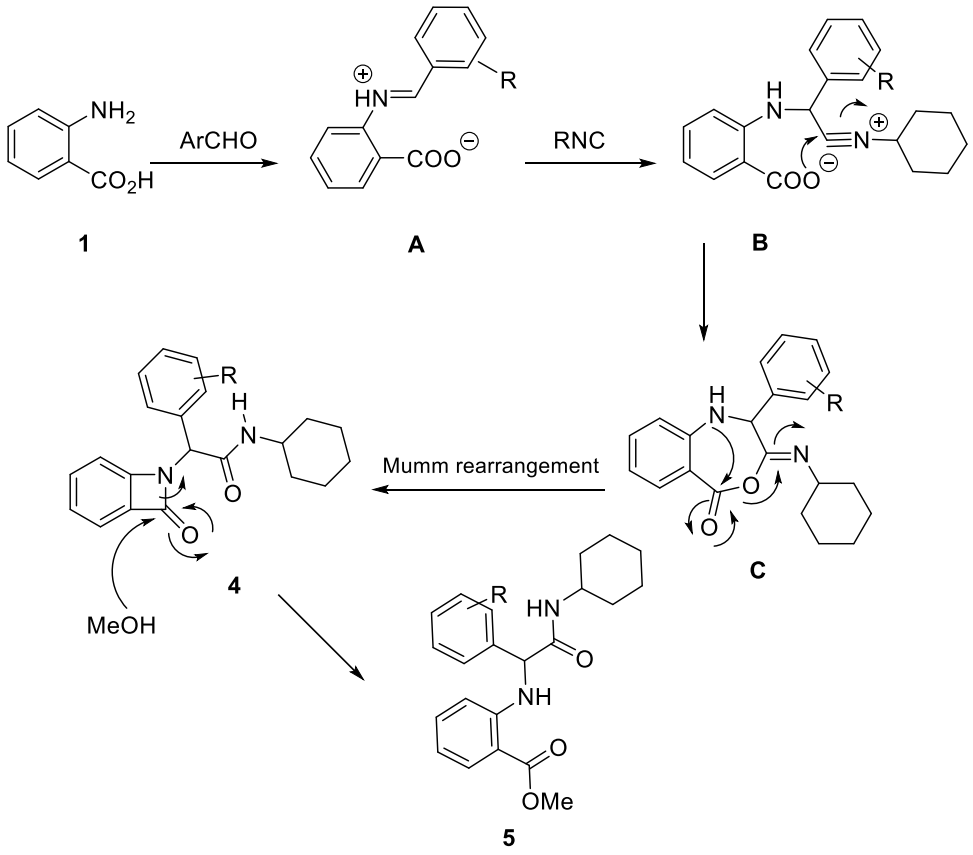


Solvent (Yield, %): MeOH (98), EtOH (90), H_2O (8), CH_3CN (n.r), THF (n.r)

Scheme 1. Synthesis of methyl 2-((2-(cyclohexylamino)-1-(3-nitrophenyl)-2-oxoethyl)amino) benzoate **5f** in various solvents.

This result provided an incentive for further study, to consider anthranilic acid and different aromatic aldehydes and isocyanide. Interestingly, substituted aromatic aldehydes with electron-withdrawing groups such as, *p*-bromo, *p*-chloro, *m*-chloro, *p*-nitro, *m*-nitro derivatives and substituted aromatic aldehydes with electron-donating groups such as *p*-methyl, *p*-methoxy each participated effectively in this reaction. In all the cases, the reactions were clean and provided the desired methyl 2-((2-(cyclohexylamino)-2-oxo-1-phenylethyl) amino)benzoate derivatives in high yields. The Ugi-adduct was purified by chromatography to result in the production of **5a-l**. All products were fully characterized and confirmed by NMR, IR and elemental analysis. The scope and generality of this process is illustrated with respect to anthranilic acid and different aromatic aldehydes (Table 1).

A plausible mechanism for this reaction is shown in scheme 2. We assume that the reaction proceeds via the initial formation of imine (**A**) which is formed *in situ* from the aromatic aldehyde and anthranilic acid. The imine intermediate is attacked by the nucleophilic isocyanide, followed by abstraction of a proton from the carboxylic acid leading to formation of nitrilium carboxylate (**B**). The subsequent attack of the carboxylate anion on the nitrilium ion generates the cyclic intermediate (**C**), which undergoes a Mumm rearrangement to give the desired lactam **4** and finally nucleophilic attack of methanol on the carbonyl group of lactam **4** affords the product **5** (Scheme 2).



Scheme 2. A plausible reaction pathway.

Table 1: Ugi three-component, four-center reaction of anthranilic acid, aryl aldehyde with cyclohexyl isocyanide

Entry	R	Mp (˚C)	Yield%*
a	2-Cl	116-118	85
b	4-Cl	190-192	92
c	3-Cl	139-140	89
d	2-NO2	182-183	98
e	3-NO2	125-127	98
f	3-F	165-167	82
g	3-Br	164-166	87
h	4-Br	184-185	90
i	4-F	199-200	93
J	H	188-190	96
k	4-CF3	71-73	85
l	4-OCH3	173-174	85

Conclusions

In conclusion, we have developed Ugi Reaction that allows the facile synthesis of methyl 2-((2-(cyclohexylamino)-2-oxo-1-phenylethyl)amino)benzoate derivatives, starting from easily accessible materials. The reactions include some important aspects like a simple operation, mild conditions, and absence of catalysts.

Experimental Section

General. All of the chemicals and solvents such as ethyl acetate and ethanol, obtained from Merck Chemical. Co. and were used without further purification. Melting points were determined on a Melt-Tem II melting point apparatus and are uncorrected. IR spectra were obtained on a Matson-1000 FT-IR spectrometer. Peaks are reported in wave numbers (cm^{-1}). All NMR spectra were recorded on a Bruker model DRX-400 AVANCE (^1H: 500 MHz) ^{13}C: 125 MHz) NMR spectrometer. Chemical shift are reported in parts per million (ppm) from tetramethylsilane (TMS) as an internal standard in DMSO-d_6 as a solvent. Element analyses (C, H, and N) were performed with a Heracus CHN-O-Rapid analyzer. Purity of the compounds was checked by thin layer chromatography (TLC) on Merck silica gel 60 F_{254} percolated sheets in n-Hexane/ethyl acetate mixture and spots were developed using iodine vapors'/ultraviolet light as visualizing agent.

General Procedure. A mixture of anthranilic acid (1 mmol), benzaldehyde (1 mmol) and cyclohexylisocyanide (1.2 mmol) in methanol (5 mL) was stirred at 50 °C for the appropriate time. The progress of the reaction was monitored by TLC. Upon completion, solvent was removed under reduced pressure and the crude product was purified by chromatography (n-hexane–ethylacetate 5:1) to afford the pure methyl 2-((2-(cyclohexylamino)-2-oxo-1-arylethyl)amino)benzoate.

Methyl 2-((1-(2-chlorophenyl)-2-(cyclohexylamino)-2-oxoethyl)amino)benzoate (5a). Yellow powder**;** Yield = 85%; M.p = 116-118 ˚C. **IR** (KBr) ($\bar{\upsilon}_{max}$, cm^{-1}): 3327 and 3300 (NH), 2953, 2853, 1684 and 1642 (C=O). ^1H NMR ($CDCl_3$, 500 MH_Z): δ 8.74 (d, 1H, *J* 5.2 Hz, NH), 7.97 (d of d, 1H, *J* 8.0, 1.6 Hz, Ar-H), 7.50-7.48 (m, 1H, Ar-H), 7.46-7.43 (m, 1H, Ar-H), 7.34-7.31 (m, 1H, Ar-H), 7.27-7.25 (m, 1H, Ar-H), 6.71-6.68 (m, 1H, Ar-H), 6.48 (d, 1H, *J* 8.4Hz, NH), 6.36 (d, 1H, *J* 8.0 Hz, Ar-H), 5.40 (d, 1H, *J* 5.2 Hz, methine), 3.92 (s, 3H, OCH_3), 3.88-3.77 (m, 1H, methine of cyclohexane), 2.01-1.02 (m, 10H) ppm. ^{13}C NMR ($CDCl_3$, 125 MH_Z): δ 168.7 and 168.6(C=O), 148.9, 136.4, 134.6, 133.4, 131.7, 129.8, 129.5, 128.4, 127.8, 116.3, 112.3, 111.6, 58.6 (CH), 51.8 (CH_3), 48.4 (CH), 32.9 (CH_2), 32.6 (CH_2), 25.4 (CH_2), 24.6 (CH_2), 24.5 (CH_2); Calcd. for ($C_{22}H_{25}ClN_2O_3$): C, 65.91; H, 6.29; N, 6.99%. Found: C, 65.80; H, 6.35; N, 6.84%.

Methyl 2-((1-(4-chlorophenyl)-2-(cyclohexylamino)-2-oxoethyl)amino)benzoate (5b). Light yellow powder; Yield = 92%; M.p = 190-192 ˚C. IR (KBr) ($\bar{\upsilon}_{max}$, cm^{-1}): 3296 and 3079 (NH), 2934, 2854, 1686 and 1652 (C=O) 1259. ^1H NMR ($CDCl_3$, 500 MH_Z): δ 8.41 (d, 1H, *J* 3.60 Hz, NH), 8.00 (d of d, 1H, J 8.0, 1.6 Hz, Ar-H), 7.46-7.38 (m, 5H, Ar-H), 6.81-6.77 (m, 1H, Ar-H), 6.63 (d, 1H, *J* 8.4Hz, NH), 6.47 (d, 1H, *J* 8.0 Hz, Ar-H), 4.80 (d, 1H, J 3.60 Hz, methine), 3.90 (s, 3H, OCH_3), 3.86-3.77 (m, 1H, methine of cyclohexane), 1.91-1.01 (m, 10H) ppm. ^{13}C NMR ($CDCl_3$, 125 MH_Z): δ 169.5 and 168.9 (C=O), 149.3, 136.7, 134.8, 134.3, 131.7, 129.3, 128.5, 117.1, 112.5, 111.0, 63.0 (CH), 51.8(CH_3), 48.2(CH), 32.9 (CH_2), 32.8 (CH_2), 25.3 (CH_2), 24.8 (CH_2), 24.7 (CH_2); Calcd. for ($C_{22}H_{25}ClN_2O_3$): C, 65.91; H, 6.29; N, 6.99%. Found: C, 65.84; H, 6.38; N, 7.09%.

Methyl 2-((1-(3-chlorophenyl)-2-(cyclohexylamino)-2-oxoethyl)amino)benzoate (5c). Light yellow powder; Yield = 89%; M.p = 139-140˚C**.** IR (KBr) ($\bar{\upsilon}_{max}$, cm^{-1}): 3319 and 3310 (NH), 2933, 2855, 1687 and 1650 (C=O). ^1H

NMR ($CDCl_3$, 500 MH_Z): δ 8.44 (d, 1H, *J* 3.60 Hz, NH), 8.00 (d of d, 1H, *J* 8.0, 1.6 Hz, Ar-H), 7.50 (s, 1H, Ar-H), 7.43-7.34 (m, 4H, Ar-H), 6.81-6.77 (m, 1H, Ar-H), 6.62 (d, 1H, *J* 8.4Hz, NH), 6.46 (d, 1H, *J* 8.0 Hz, Ar-H), 4.83 (d, 1H, *J* 4.50 Hz, methine), 3.91 (s, 3H, OCH_3), 3.88-3.77 (m, 1H, methine of cyclohexane), 1.93-1.01 (m, 10H) ppm. ^{13}C NMR ($CDCl_3$, 125 MH_Z): δ 169.3 and 168.8(C=O), 149.2, 140.2, 134.9, 134.8, 131.7, 130.4, 128.7, 127.5, 125.2, 117.1, 112.5, 111.8, 63.1 (CH), 51.8 (CH_3), 48.3 (CH), 32.9 (CH_2), 32.7 (CH_2), 25.3 (CH_2), 24.8 (CH_2), 24.7 (CH_2); Calcd. for ($C_{22}H_{25}ClN_2O_3$): C, 65.91; H, 6.29; N, 6.99%. Found: C, 65.98; H, 6.18; N, 6.86%.

Methyl 2-((2-(cyclohexylamino)-1-(2-nitrophenyl)-2-oxoethyl)amino)benzoate (5d). Dark Yellow powder; Yield = 98%; M.p = 182-183 ˚C. IR (KBr) ($\bar{\upsilon}_{max}$, cm^{-1}): 3413 and 3315 (NH), 2940, 2856, 1685 and 1606 (C=O) 1511, 1351, 1264. ^1H NMR ($CDCl_3$, 400 MH_Z): δ 9.09 (d, 1H, *J* 6.4Hz, NH), 8.01 (d of d, 1H, *J* 8.0, 1.2 Hz, Ar-H), 7.95 (d of d, 1H, *J* 8.0, 1.2 Hz, Ar-H), 7.74 (d of d, 1H, *J* 8.0, 1.2 Hz, Ar-H), 7.63-7.60 (m, 1H, Ar-H), 7.49-7.45 (m, 1H, Ar-H), 7.27-7.24 (m, 1H, Ar-H), 6.70-6.65 (m, 2 H, Ar-H), 6.37 (d, 1H, *J* 8.4Hz, NH), 5.77 (d, 1H, *J* 6.4Hz, methine), 3.93 (s, 3H, OCH_3), 3.88-3.77 (m, 1H, methine of cyclohexane), 2.00-1.06 (m, 10H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.6 and 167.7(C=O), 149.0, 148.3, 134.7, 134.6, 134.2, 131.9, 129.4, 128.9, 124.9, 116.4, 111.8, 111.6, 56.2 (CH), 51.8 (CH_3), 48.6 (CH), 32.8 (CH_2), 32.5 (CH_2), 25.4 (CH_2), 24.6 (CH_2), 24.5 (CH_2); Calcd. for ($C_{22}H_{25}N_3O_5$): C, 64.22; H, 6.12; N, 10.21%. Found: C, 64.12; H, 6.19; N, 10.33%**.**

Methyl 2-((2-(cyclohexylamino)-1-(3-nitrophenyl)-2-oxoethyl)amino)benzoate (5e). Yellow powder; Yield = 98%; M.p = 125-127 ˚C. IR (KBr) ($\bar{\upsilon}_{max}$, cm^{-1}): 3282 and 3130 (NH), 2938, 2852, 1685 and 1647 (C=O) 1512, 1357, 1263. ^1H NMR ($CDCl_3$, 400 MH_Z): δ 8.56 (d, 1H, *J* 4.0 Hz, NH), 8.41-8.40 (m, 1H, Ar-H), 8.22 (d of d, 1H, *J* 8.2, 1.6 Hz, Ar-H), 8.00 (d of d, 1H, *J* 8.4, 1.2 Hz, Ar-H), 7.86 (d, 1H, *J* 7.6 Hz, Ar-H), 7.56 (t, 1H, *J* 7.6 Hz, Ar-H), 7.42-7.33 (m, 1H, Ar-H), 6.80 (t, 1H, *J* 7.6 Hz, Ar-H), 6.67 (d, 1H, *J* 8.4Hz, NH), 6.62 (d, 1H, *J* 8.4Hz, Ar-H), 5.01 (d, 1H, *J* 4.0 Hz, methine), 3.90 (s, 3H, OCH_3), 3.88-3.77 (m, 1H, methine of cyclohexane), 1.94-1.03 (m, 10H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.9 and 168.7(C=O), 148.9, 148.5, 140.3, 134.8, 133.3, 131.7, 130.1, 123.4, 122.3, 117.5, 112.4, 112.0, 62.8 (CH), 51.9 (CH_3), 48.5 (CH), 32.9 (CH_2), 32.7 (CH_2), 25.3 (CH_2), 24.7 (CH_2), 24.6 (CH_2); Calcd. for ($C_{22}H_{25}N_3O_5$): C, 64.22; H, 6.12; N, 10.21%. Found: C, 64.28; H, 6.23; N, 10.29%**.**

Methyl 2-((2-(cyclohexylamino)-1-(3-fluorophenyl)-2-oxoethyl)amino)benzoate (5f). White powder; Yield = 82%; M.p = 165-167 ˚C. IR (KBr) ($\bar{\upsilon}_{max}$, cm^{-1}): 3317 and 3311 (NH), 2933, 2856, 1686 and 1650 (C=O). ^1H NMR ($CDCl_3$, 400 MH_Z): δ 8.46 (d, 1H, *J* 3.6 Hz, NH), 7.99 (d of d, 1H, *J* 8.4, 1.2 Hz, Ar-H), 7.43-7.37 (m, 2H, Ar-H), 7.31 (s, 1H, Ar-H), 7.22 (d of t, 1H, *J* 9.6, 2.0 Hz, Ar-H), 7.09-7.04 (m, 1H, Ar-H), 6.81-6.77 (m, 1H, Ar-H), 6.63 (d, 1H, *J* 8.4Hz, Ar-H), 6.46 (d, 1H, *J* 8.4Hz, NH), 4.85 (d, 1H, *J* 3.6 Hz, methine), 3.91 (s, 3H, OCH_3), 3.88-3.77 (m, 1H, methine of cyclohexane), 1.93-1.00 (m, 10H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.4 and 168.9(C=O), 164.0 (C-F), 161.8, 149.3, 140.6, 134.8, 131.7, 130.7,122.8, 117.1, 115.5, 114.3, 112.5, 111.8, 63.2 (CH), 51.8 (CH_3), 48.3 (CH), 32.9 (CH_2), 32.7 (CH_2), 25.3 (CH_2), 24.8 (CH_2), 24.7 (CH_2); Calcd. for ($C_{22}H_{25}FN_2O_3$): C, 68.73; H, 6.55; N, 7.29%. Found: C, 68.85; H, 6.49; N, 7.37%.

Methyl 2-((1-(3-bromophenyl)-2-(cyclohexylamino)-2-oxoethyl)amino)benzoate (5g). Light yellow powder; Yield = 87%; M.p = 165-167 ˚C. IR (KBr) ($\bar{\upsilon}_{max}$, cm^{-1}): 3320 and 3329 (NH), 2924, 2851, 1690 and 1651 (C=O). ^1H NMR ($CDCl_3$, 400 MH_Z): δ 8.41 (d, 1H, *J* 4.0 Hz, NH), 7.97 (d of d, 1H, *J* 8.0, 1.5Hz, Ar-H), 7.63 (t, 1H, *J* 1.5Hz, Ar-H), 7.48-7.46 (m, 1H, Ar-H), 7.42-7.40 (m, 1H, Ar-H), 7.39-7.36 (m, 1H, Ar-H), 7.28-7.25 (m, 1H, Ar-H), 6.77-6.74 (m, 1H, Ar-H), 6.59 (d, 1H, *J* 8.0 Hz, Ar-H), 6.43 (d, 1H, *J* 8.4Hz, NH), 4.80 (d, 1H, *J* 3.6 Hz, methine), 3.88 (s, 3H, OCH_3), 3.84-3.76 (m, 1H, methine of cyclohexane), 1.90-0.96 (m, 10H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.2 and 168.8(C=O), 149.2, 134.7, 131.7, 131.6, 130.6, 130.4, 125.6, 123.1, 117.1, 112.5, 111.9, 63.1 (CH), 51.8 (CH_3), 48.3 (CH), 32.9 (CH_2), 32.7 (CH_2), 25.3 (CH_2), 24.7 (CH_2), 24.6 (CH_2); for ($C_{22}H_{25}BrN_2O_3$): C, 59.33; H, 5.66; N, 6.29%. Found: C, 59.45; H, 5.51; N, 6.13%.

Methyl 2-((1-(4-bromophenyl)-2-(cyclohexylamino)-2-oxoethyl)amino)benzoate (5h). White powder; Yield = 90%; M.p = 184-185 ˚C. IR (KBr) ($\bar{\upsilon}_{max}$, cm^{-1}): 3221 and 3222 (NH), 2934, 2855, 1668 and 1660 (C=O), 1374. ^1H

NMR (DMSO, 500 MH_Z): *δ* 8.71 (d, 1H, *J* 6.5Hz, NH), 8.28 (d, 1H, *J* 7.5Hz, Ar-H), 7.81-7.80 (m, 1H, Ar-H), 7.54 (d, 2 H, *J* 8.5Hz, Ar-H), 7.41 (d, 2 H, *J* 8.5Hz, Ar-H), 7.30-7.26 (m, 1H, Ar-H), 6.60-6.57 (m, 1H, Ar-H), 6.37 (d, 1H, *J* 8.5Hz, NH), 5.16 (d, 1H, *J* 6.5Hz, methine), 3.82 (s, 3H, OCH_3), 3.51-3.45 (m, 1H, methine of cyclohexane), 1.79-1.04 (m, 10H) ppm. ^{13}C NMR (125, MHz, DMSO) δ 168.7 and 168.3(C=O), 148.8, 139.2, 135.1, 131.9, 131.7, 129.1, 121.2, 116.3, 115.7, 112.6, 110.6, 109.9, 59.1 (CH), 52.1 (CH_3), 48.2 (CH), 32.6 (CH_2), 32.4 (CH_2), 25.5 (CH_2), 24.80 (CH_2), 24.67 (CH_2); for ($C_{22}H_{25}BrN_2O_3$): C, 59.33; H, 5.66; N, 6.29%. Found: C, 59.39; H, 5.73; N, 6.35%.

Methyl 2-((2-(cyclohexylamino)-1-(4-fluorophenyl)-2-oxoethyl)amino)benzoate (5i). White powder; Yield = 93%; M.p = 199-200 ˚C. IR (KBr) ($\bar{\upsilon}_{max}$, cm^{-1}): 3223 and 3218 (NH), 2931, 2856, 1686 and 1650 (C=O) 1239. ^{1}H NMR (DMSO, 500 MH_Z): *δ* 8.69 (d, 1H, *J* 6.5Hz, NH), 8.25 (d, 1H, *J* 8.0 Hz, Ar-H), 7.81-7.79 (m, 1H, Ar-H), 7.50-7.49 (m, 2 H, Ar-H), 7.30-7.27 (m, 1H, Ar-H), 7.15 (t, 2 H, *J* 9.0 Hz, Ar-H) 6.59-6.56 (m, 1H, Ar-H), 6.40 (d, 1H, *J* 8.5Hz, NH), 5.17 (d, 1H, *J* 6.5Hz, methine), 3.82 (s, 3H, OCH_3), 3.52-3.45 (m, 1H, methine of cyclohexane), 1.78-1.04 (m, 10H) ppm. ^{13}C NMR (125, MHz, DMSO) δ 169.1 and 168.3(C=O), 148.9 (C-F), 135.9, 135.1, 131.7, 128.9, 117.7, 115.9, 115.7, 115.6, 112.6, 110.9, 110.4, 58.9 (CH), 52.0 (CH_3), 48.1 (CH), 32.6 (CH_2), 32.4 (CH_2), 25.5 (CH_2), 24.8 (CH_2), 24.6 (CH_2); for ($C_{22}H_{25}FN_2O_3$): C, 68.73; H, 6.55; N, 7.29%. Found: C, 68.79; H, 6.61; N, 7.17%.

Methyl 2-((2-(cyclohexylamino)-2-oxo-1-phenylethyl)amino)benzoate (5J). White powder; Yield = 96%; M.p = 188-190 ˚C. IR (KBr) ($\bar{\upsilon}_{max}$, cm^{-1}): 3318 and 3309 (NH), 2933, 2854, 1686 and 1648 (C=O), 1257. ^{1}H NMR (DMSO, 500 MH_Z): *δ* 8.70 (d, 1H, *J* 6.5Hz, NH), 8.25 (d, 1H, *J* 7.9 Hz, Ar-H), 7.81 (d, 1H, *J* 7.9 Hz, Ar-H), 7.47 (d, 2H, *J* 7.7 Hz, Ar-H), 7.38-7.16 (m, 3H, Ar-H), 7.58 (d, 2H, *J* 7.6 Hz, Ar-H), 6.43 (d, 1H, *J* 8.5Hz, NH), 5.16 (d, 1H, *J* 6.5Hz, methine), 3.83 (s, 3H, OCH_3), 3.54-3.44 (m, 1H, methine of cyclohexane), 1.80-1.04 (m, 10H) ppm. ^{13}C NMR (125, MHz, DMSO) δ 169.2 and 168.8 (C=O), 149.2, 134.7, 131.7, 131.6, 130.6, 130.4, 125.6, 123.1, 117.1, 112.5, 111.9, 63.1 (CH), 51.8 (CH_3), 48.3 (CH), 32.9 (CH_2), 32.7 (CH_2), 25.3 (CH_2) , 24.7 (CH_2), 24.6 (CH_2); for ($C_{22}H_{26}N_2O_3$): C, 72.11; H, 7.15; N, 7.64%. Found: C, 72.24; H, 7.03; N, 7.75%.

Methyl 2-((2-(cyclohexylamino)-2-oxo-1-(4(trifluoromethyl)phenyl)ethyl)amino) benzoate (5k). White powder; Yield = 85%; M.p = 71-73 ˚C. IR (KBr) ($\bar{\upsilon}_{max}$, cm^{-1}): 3309 and 3299 (NH), 2934, 2865, 1687 and 1652 (C=O) 1325. ^{1}H NMR (DMSO, 500 MH_Z): *δ* 8.79 (d, 1H, *J* 6.9 Hz, NH), 8.38 (d, 1H, *J* 7.8 Hz, Ar-H), 7.85-7.80 (m, 1H, Ar-H), 7.74-7.68 (m, 4H, Ar-H), 7.28 (t, 1H, *J* 7.8 Hz, Ar-H), 6.59 (t, 1H, *J* 7.6 Hz, Ar-H), 6.38 (d, 1H, *J* 8.5Hz), 5.31 (d, 1H, *J* 6.9 Hz, methine), 3.84 (s, 3H, OCH_3), 3.50-3.48 (m, 1H, methine of cyclohexane), 1.80-1.04 (m, 10H) ppm. ^{13}C NMR (125, MHz, DMSO) δ 168.4 and 168.3(C=O), 148.7, 144.5, 135.2, 131.7, 127.7, 125.9, 125.7, 123.5, 116.0, 112.5, 110.7, 59.3 (CH), 52.1 (CH_3), 48.2 (CH), 32.6 (CH_2), 32.3 (CH_2), 25.5 (CH_2), 24.7 (CH_2), 24.6 (CH_2); for ($C_{23}H_{25}F_3N_2O_3$): C, 63.59; H, 5.80; N, 6.45%. Found: 63.68; H, 5.71; N, 6.57%.

Methyl 2-((2-(cyclohexylamino)-1-(4-methoxyphenyl)-2-oxoethyl)amino)benzoate (5l). White powder; Yield = 82%; M.p = 173-175 ˚C. IR (KBr) ($\bar{\upsilon}_{max}$, cm^{-1}): 3341 and 3326 (NH), 2934, 2834, 1681 and 1648 (C=O) 1250. ^{1}H NMR (DMSO, 500 MH_Z): *δ* 8.64 (d, 1H, *J* 6.8 Hz, NH), 8.19 (d, 1H, *J* 7.9 Hz, Ar-H), 7.80 (d of d, 1H, *J* 8.0, 1.7 Hz, Ar-H), 7.38-7.36 (m, 2 H, Ar-H), 7.30-7.26 (m, 1H, Ar-H), 6.89 (d, 2 H, *J* 8.7 Hz), 6.56 (t, 1H, *J* 7.6 Hz, Ar-H), 6.43 (d, 1H, *J* 8.5Hz), 5.07 (d, 1H, *J* 6.8 Hz, methine), 3.82 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.49-3.41 (m, 1H, methine of cyclohexane), 1.78-1.02 (m, 10H) ppm. ^{13}C NMR (125, MHz, DMSO) δ 169.5 and 168.3(C=O), 159.1, 145.9, 136.9, 135.0, 131.6, 128.1, 115.4, 114.3, 112.6, 109.9, 59.1 (CH), 55.4 (CH_3), 52.0 (CH_3), 48.1 (CH), 32.7 (CH_2), 32.4 (CH_2), 25.5 (CH_2), 24.8 (CH_2), 24.7 (CH_2); for ($C_{23}H_{28}N_2O_4$): C, 69.68; H, 7.12; N, 7.07%. Found: 69.74; H, 7.03; N, 7.16%.

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Supplementary Material

The experimental procedures and IR, ^{1}H NMR and ^{13}C NMR spectra associated with this article are available as supplementary data.

References

1. Domling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112*, 3083-3135. https://pubs.acs.org/doi/abs/10.1021/cr100233r
2. Biggs-Houck, J . E.; Younai, A.; Shaw, J . T. *Curr. Opin. Chem. Biol*, **2010**, *14*, 371-382. https://doi.org/10.1016/j.cbpa.2010.03.003
3. Rotstein, B. H.; Zaretsky, S., Rai, V.; Yudin, A. K. *Chem. Rev*. **2014**, *114*, 8323-8359. https://pubs.acs.org/doi/abs/10.1021/cr400615v
4. Domling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112*, 3083-3135. https://pubs.acs.org/doi/abs/10.1021/cr100233r
5. Ganem, B. *Acc. Chem. Res*. **2009**, *42*, 463-472. https://pubs.acs.org/doi/abs/10.1021/ar800214s
6. Ugi, I. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 810-819. https://doi.org/10.1002/anie.198208101
7. Riva, R.; Banfi, L.; Basso, A. *Org. React*. **2005**, *1*, 327-414. https://doi.org/10.1002/0471264180.or065.01
8. Toure, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439-4486. https://pubs.acs.org/doi/abs/10.1021/cr800296p
9. Ilyn, A. P.; Loseva, M. V.; Vvedensky, V. Y.; Putsykina, E. B.; Tkachenko, S. E.; Kravchenko, D. V.; Ivachtchenko, A. V. *J . Org. Chem.* **2006**, *71*, 2811-2819. https://pubs.acs.org/doi/abs/10.1021/ J o052640w
10. Rasouli, M. A.; Mahdavi, M.; Ranjbar, P. R..; Saeedi, M.; Shafiee, A.; Foroumadi, A. *Tetrahedron Lett.* **2012**, *53*, 7088-7092. https://doi.org/10.1016/ J .tetlet.2012.10.075
11. Ugi, I.; Steinbrückner, C. *Chem. Ber*. **1961**, *94*, 2802-2814. https://doi.org/10.1002/cber.19610941032
    Kehagia, K.;Ugi, I. K. *Tetrahedron* **1995**, 51, 9523-9530. https://doi.org/10.1016/0040-4020(95)00542-G
12. Sharma, S.; Srivastava, V. K.; Kumar, A. *Eur. J . Med. Chem*. **2002**, 37, 689-697. https://doi.org/10.1016/S0223-5234(02)01340-5
13. Peretz, A.; Degani, N.; Nachman, R.; Uziyel, Y.; Gibor, G.; Shabat, D.; Attali, B. *Mol. Pharmacol.* **2005**, *67*, 1053-1066.

https://doi.org/10.1124/mol.104.007112

14. Verma, M.; Sinha, J. N.; Gujrati, V. R.; Bhalla, T. N.; Bhargava, K. P.; Shanker, K. *Pharmacol. Res. Commun*. **1981**, *13*, 967-979.
https://doi.org/10.1016/S0031-6989(81)80068-9
15. Goel, B.; Ram, T.; Tyagi, R.; Bansal, E.; Kumar, A.; Mukherjee, D.; Sinha, J . N. *Eur.* ***J .*** *Med. Chem.*, **1999**, *34*, 265-269.
https://doi.org/10.1016/S0223-5234(99)80060-9

