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Parikh–Doering oxidation–dehydration–Ugi cyclization cascade in the development of lactams from formidoalkanols (3>chain length>7)

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ABSTRACT

De novo incorporation of *N*-formylated aminols as strategic substrates in legendary Ugi cyclization. Lactamization of *N*-formido alkanols is accomplished by a novel Parikh–Doering oxidation–dehydration–Ugi cyclization cascade leading to the formation of lactams up to eight carbons (ring size; n=1–4) in moderate yields using formidoaminol, substituted aniline, and aliphatic/aromatic carboxylic acid derivatives as starting materials.

1. Introduction

The essential research theme in modern organic synthesis is rapid generation of molecular complexity and diversity from simple and readily accessible starting materials. Indeed, a multi-component reaction combining three or more reactants together in a single ordered event,[1–3] offers not only great molecular complexity and diversity but also the possibility of introducing matched functionalities suitable for further transformations. A range of reactions including condensation,[4] ring-closure metathesis,[5] cycloaddition,[6] macrolactonization,[7] and intramolecular S_NAr reaction,[8] etc. have been harnessed along with an isonitrile-based multi-component reaction (MCR) for the construction of cyclic scaffolds. Ugi-MCR indeed has gained attentions of organic chemists for its potential to fulfill the above noted research theme and has been explicitly exploited to develop chemical libraries. The bifunctional substrates as starting material have been explored to architect even more complex scaffolds. Several groups have used β-amino acids in the Ugi reaction to prepare β-lactams.[9] This approach relies on acyl transfer in the Mumm's rearrangement to form the four-membered ring. Zhang et al.[10] have combined aldehydes with carboxylic acids and used the Ugi reaction to create lactams of various sizes. Short and Mjalli[11] have prepared γ-lactams from keto-acids on solid-support. None of the reported method for synthesis of such lactams, neither involved multisequential-one pot transformation nor the generation of isonitrile and aldehyde functionalities on same substrate for Ugi cyclization. These lactams possesses the carbon atom of isonitrile group within the ring thus get constructed, by the strategic exploitation of Ugi reaction are crucial and constitutes in the various biologically important scaffolds.[12,13]

2. Results and discussion

In view of above it appeared of interest to explore the scope of *N*-formido derivative of higher aminols (chain length ≤3) under Ugi reaction condition to provide cyclization. The perplexity of conditions for sequential oxidation–dehydration of *N*-formidopropanol to generate a reactive intermediate comprising aldehyde and isocyanide groups at their respective termini was sorted out by employing Parikh–Doering oxidation[14] at OH terminal and subsequent dehydration using $POCl_3$ at *N*-formyl terminal. The functional group inter-conversion from –OH to CHO and –NHCHO to –NC was confirmed by the observed IR absorption frequencies 1718 cm^{-1} and 2121 cm^{-1} for the aldehyde and isonitrile groups, respectively. These reactive pre-Ugi intermediates with four, five, six, and seven carbon atoms having –CHO and –NC were employed for 3CC-Ugi (3-component condensation Ugi) reaction using various anilines and aromatic/aliphatic carboxylic acids to yield the desired respective lactams. This novel methodology involved the utilization of Ugi condensation of *N*-formido alkanols as *dual masked substrate* to obtain γ-lactams, δ-lactams, and caprolactam

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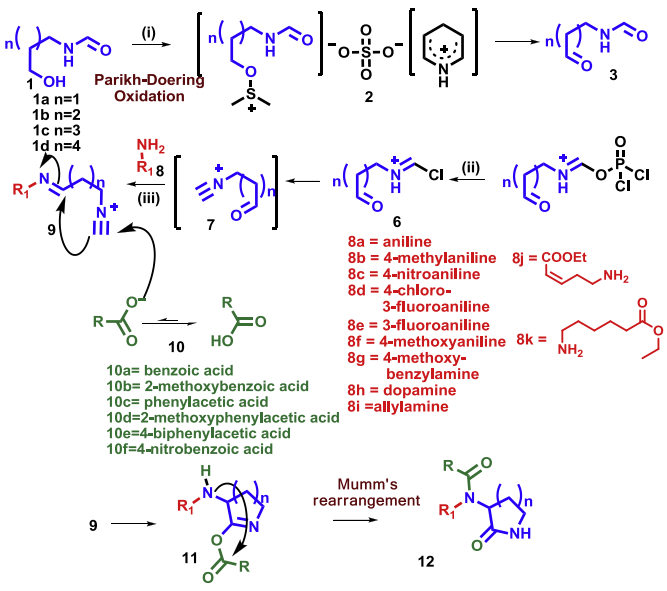
derivatives from the corresponding three, four, and five-carbon aminols through ODU (oxidation–dehydration–Ugi) cyclization cascade (Scheme 1).



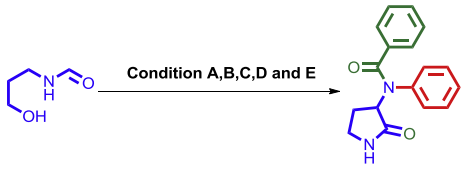
Scheme 1. Representation of Parikh–Doering oxidation–dehydration–Ugi cyclization cascade to the formation of α-amido lactams.

Optimization of the three reactions (oxidation, dehydration, and condensation), two reagents, one oxidizing agent (oxalyl chloride/DMSO) typical Swern condition[15] or Py·SO_3/DMSO/pyridine modified Swern condition[14] and other dehydrating agent ($POCl_3$/Py or TsCl/TEA) and three substrates (*N*-formidoalkanols, anilines, and carboxylic acids) was performed using simple aniline, benzoic acid, and *N*-formidopronanol. Since the Ugi reaction is either reported in neutral conditions or in the presence of acidic catalyst. So these conditions cannot be applied in the present dehydration step where the dehydrating conditions are basic in nature. Hence the ratio of the base was especially monitored in the oxidation–dehydration step and the Ugi condensation was performed in situ, with quick neutralization by 1 N hydrochloric acid solution at 0 °C relayed with addition of aniline and benzoic acid. The best results were obtained under Parikh–Doering condition. In both the cases (i.e., using TsCl or $POCl_3$ as dehydrating agent), the isolated yields were better than those obtained in the typical Swern oxidation condition as illustrated in Table 1.

The typical Swern oxidation protocol with $POCl_3$/TEA and tosyl chloride/TEA (condition A and C, Table 1) as dehydrating agent resulted in low yields (16% and 32%, respectively) in comparison to the results obtained with modified version of classical Swern oxidation (condition B and D). The moderate yields were obtained due to the *amine exchange reaction*[16] with the salts of organic bases present in the reaction mixture. The rate of amine exchange reaction was slower in the case of anilines than aliphatic amines and therefore poor or no product was obtained with aliphatic amine. The yield of the reaction did not depend only on 3CC-Ugi step but also showed significant dependence on the ring size, which had effect on the acceleration of movement of *Mumm's rearrangement*[17] in forward direction.

The optimized methodology was employed with other anilines and carboxylic acid derivatives to obtain the desired lactams (Table 2, **12a**–**h**). This methodology was expanded to sculpate six, seven, and eight membered lactams from *N*-formidobutanol, *N*-fomidopentanol, and *N*-formidohexanols, respectively, which are described in Table 2 (**12i**–**u**) along with the yields and reaction

Table 1
Conditions used in the optimization of ODU cascade for the preparation of *N*-(2-oxopyrrolidin-3-yl)-*N*-phenylbenzamide



Condition	Oxidizing reagents	Dehydrating reagents	Yield (%)[a]
A	DMSO/$(COCl)_2$/TEA (1.5:3:6.5)	$POCl_3$/TEA (1:4)	16
B	Py·SO_3/DMSO/Py (2:1.5:2)	$POCl_3$/py (1:3.5)	68
C	DMSO/$(COCl)_2$/TEA (1.5:3:6.5)	TsCl/TEA (1:2)	32
D	Py·SO_3/DMSO/Py (2:1.5:2)	TsCl/py (1:2)	54
E	Py·SO_3/DMSO/Py (2:1.5:2)	$POCl_3$/KO^{t}Bu (1:1.5)[b,c]	62

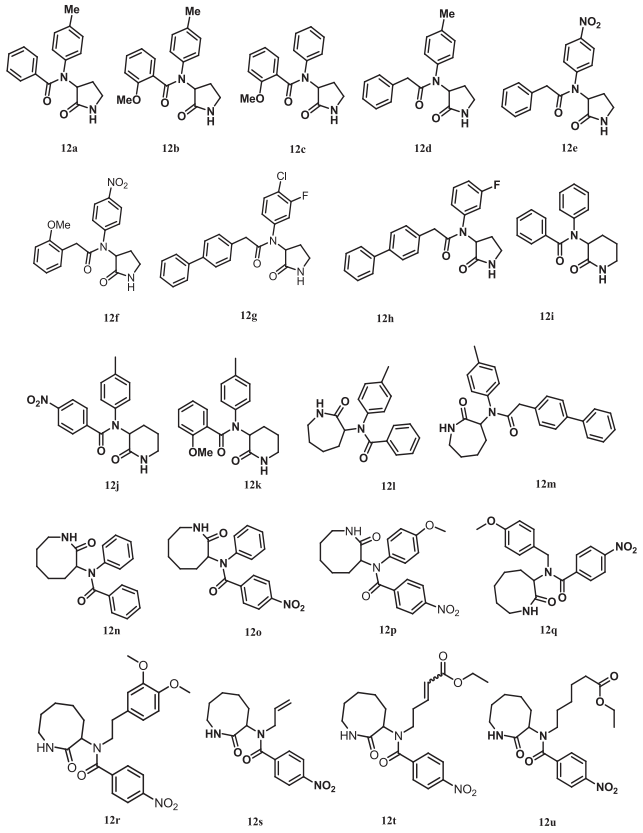
[a] Isolated yields.
[b] The condition was employed in the case of aliphatic amines (**8g**–**k**) to minimize the amine exchange reaction thus causes to the formation of desired products (**12q**–**u**).
[c] These conditions were also used in the case of arylamine but not such increase in terms of yields were obtained.

time. The observed lower yields in the case of aliphatic amine when conditions (A–D) were employed due to the amine exchange reaction which decreases the residence time of the amines required for the in situ formation of Schiff base crucial for the initiation of the cascade, when tertiary amine were employed as base in the dehydration step the similar kind of transfer reaction are found prominent even when pyridine were employed resulted in the lower yield. Keeping these fact in mind we anticipated that sodium alkoxides can be a better substitute than the tertiary amines as there would not be any scope for the amine exchange. Therefore, potassium *tert*-butoxides (KO^{t}Bu) was used followed by the addition of Phosphorus Oxychloride ($POCl_3$) resulted to the formation of isocyanoaldehydes, which was neutralized and added respective aliphatic amines and carboxylic acid in equimolar amounts gave the desired lactams (**12q**–**u**) in moderate yields. The structure of the synthesized lactams was confirmed via NMR spectroscopy. In the case of *N*-(2-oxopyrrolidin-3-yl)-*N*-*p*-tolylbenzamide (**12a**) a triplet centered at 4.67 ppm with coupling constant of 8.8 Hz for the

Table 2
Yields and time of ODU cyclization reaction cascade with various amines and carboxylic acids

Aminols	Reactants		Product	Yield[a] (%)	Time[b] (h)
1a	**8b**	**10a**	**12a**	68	8.5
	8b	**10b**	**12b**	62	12
	8a	**10b**	**12c**	71	26
	8b	**10c**	**12d**	78	18
	8c	**10c**	**12e**	62	20.5
	8c	**10d**	**12f**	60	28
	8d	**10e**	**12g**	65	26
	8e	**10e**	**12h**	75	30
1b	**8a**	**10a**	**12i**	76	25
	8b	**10f**	**12j**	78	28
	8b	**10b**	**12k**	62	36
1c	**8b**	**10a**	**12l**	48	20
	8b	**10e**	**12m**	51	16
1d	**8a**	**10f**	**12n**	54	32
	8a	**10f**	**12o**	50	25
	8f	**10f**	**12p**	48	30
	8g	**10f**	**12q**	36	48
	8h	**10f**	**12r**	42	42
	8i	**10f**	**12s**	36	36
	8j	**10f**	**12t**	51	25
	8k	**10f**	**12u**	38	50

[a] Isolated yields.
[b] Time (in h) required for the optimum completion of the reaction as per TLC (Silica gel 60 F_{254}).



Condition B for **12a-p:** (i) Py-SO_3 (2.0 mmol), DMSO (1.5 mmol), Py (2.0 mmol), 1.5 h, 0°-10°C; (ii) $POCl_3$ (1.3 mmol), Py (3.5 mmol), 2.5h, -10°C-50°C; (iii) HCl (neutralization) at 0°C, RNH_2 (1.0mmol), RCOOH(1.0 mmol); **Condition E for 12q-u**: (i) Py-SO_3 (2.0 mmol), DMSO (1.5 mmol), Py (2.0 mmol), 1.5 h, 0°-10°C;(ii) $POCl_3$ (1.3 mmol), KO^{t}Bu (3.0 mmol), 2.5h, -30°C-60°C in MeOH; (iii) HCl (neutralization) at 0°C, RNH_2 (1.0mmol), RCOOH (1.0 mmol).

proton at α-amido center, protons at β-carbon showed a multiplet centered at 2.48 ppm, whereas the protons at δ carbon got split into a double triplet at 3.95 ppm with coupling constant of 6.6 and 1.5 Hz due to the neighboring CH and CH_2 centers. In a general observation the ODU cyclization cascade crops lower amount of medium sized lactams (seven and eight membered; **12l**–**u**) than in comparison with lower sized ring (five and six membered; **12a**–**k**), the possible explanation points at stereoelectronic preference of the nucleophile, i.e., isocyano terminal to approach nearly planar to the plane of imine (**9**) (*exo trig* cyclization), which is more preferentially possible in the case smaller ring (Baldwin Rule[18]) and decreases as the size of the ring increases. The optimized reaction conditions were not analyzed for the case of higher formidoalkanols (larger than 7-amino heptanol) and substituted derivatives of formidoalkanols but on the basis of the results thus obtained for the reported examples we can assure the similar results.

3. Conclusions

In conclusion we have found a novel method of employing aminols with carbon chain length ≥3 more for the preparation of the respective lactams with ring size n+2. Using the above mentioned method we have developed a single pot oxidation–dehydration–Ugi condensation cascade of reaction having potential of providing eight membered lactams and thus may be considered as a powerful technique for Lactamization which can be further explored for synthesizing new bioactive entities including natural product containing α-amido lactams as core.

4. Experimental

4.1. General method

Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without purification. Dichloromethane was distilled under nitrogen. Dimethylsulfoxide was used without distillation. All reactions were carried out under an atmosphere of dry nitrogen. Solutions were evaporated under reduced pressure with a rotary evaporator and the residue was purified by silica gel flash chromatography using an ethyl acetate/hexane mixture as the eluent unless specified otherwise. NMR spectra were recorded on 300 MHz spectrometers. Chemical shifts were reported in parts per million relative to the residual solvent peak (7.26 ppm for $CHCl_3$) for H spectra and (77.0 ppm for $CDCl_3$) for ^{13}C spectra. High Resolution Mass spectroscopy data in electronic impact were recorded with a resolution of 5000 RP at 5%. Electronic impact (EI) and chemical ionization (CI) mass spectroscopies were recorded on a HP5989B device. Infrared spectra were recorded on an FT IR spectrometer in neat for all compounds.

4.2. General procedure

The N-formylation of the amino was accomplished by refluxing the respective aminols in ethylformate (used as solvent and reagent) in quantitative yields.[19]

Condition A: (*Oxidation step*) In a 50 ml RB flask, flushed with nitrogen 10 ml dried DCM was taken and added freshly distilled oxalyl chloride (3.0 mmol) cooled the reaction mixture to −60 °C using liquid nitrogen/ethanol bath followed by the addition of dried DMSO (1.5 mmol) after 15–30 min of stirring. A solution of formidoalkanol (1.0 mmol) dissolved in DCM was added dropwise to the Swern reagent via syringe. After 30 min of stirring 6.5 mmol of TEA was added and allowed the reaction to attain room temperature. (*Reduction step*) The mixture obtained was again cooled to −30 °C and $POCl_3$ (1.2 mmol) was added gradually and allowed the reaction mixture to stir at 0 °C for 10–30 min and warmed up to 50 °C, after 1.0–1.5 h of stirring the reaction mixture was cautiously neutralized with the dil HCl solution (if necessary, pH=6.6). To this slightly acidic reaction mixture added amine (1.0 mmol) and RCOOH (1.0 mmol) controlled the reaction by TLC. After the optimum completion of the reaction, solvent was evaporated and purified by flash chromatography (eluent 10:90; EtOAc/hexane).

Condition B: (*Oxidation step*) In a dried 25 ml RB, Py/SO_3 complex (2.1 mmol) was taken and diluted with 5 ml DCM, followed by the addition DMSO (1.5 mmol) and pyridine (2.0 mmol) after 15 min, formidoalkanols dissolved in DCM was added dropwise to the stirring mixture. (*Reduction step*) After 1.5 h, 3.5 mmol, pyridine was added to the reaction mixture followed by the addition of phosphorus oxychloride solution (1.3 mmol) after approx. 2.0 h the neutralization was accomplished and followed by the same process (as in condition A).

Condition C: (*Oxidation step*) Same as in condition A. (*Reduction step*) As the obtained mixture was not sufficiently basic therefore to the obtained reaction mixture tosyl chloride (3.0 equiv) was added three lots at −20 °C at an interval of 10 min and was allowed to stir for 2–3 h, followed by the addition of 2.0 mmol of TEA thence made the reaction mixture to reach room temperature in approximately 30–40 min. After the completion of the dehydration step the pH of the reaction mixture was maintained to ~6.5 by neutralization

with dil HCl. Then the corresponding amine and carboxylic acid was added. After the completion of the reaction, the solution was evaporated under vacuo and the crude product was purified by using flash chromatography.

Condition D: (*Oxidation step*) Same as in condition B. (*Reduction step*) Same as in condition C.

Condition E: (*Oxidation step*) Same as in condition A where potassium *tert*-butoxide (3.5 mmol) was used instead of TEA at −10 °C. (*Reduction step*) Same as in condition C.

*4.2.1. N-(2-Oxopyrrolidin-3-yl)-N-p-tolylbenzamide (**12a**).* The crude product obtained using condition A is purified using column chromatography (5% EtOAc/hexane) to give the title compound **12a** (44.0 mg, 68%) as a yellow oil; R_f (10% EtOAc/hexane) 0.44; IR (neat) cm^{-1} 3507, 3335, 1705, 1687, 1475, 1233; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05–7.62 (2H, m, ArH), 7.44 (3H, dt, *J*=4.3, 2.0, ArH), 7.19 (5H, d, *J*=7.5, ArH), 6.30 (1H, s, NH), 4.67 (1H, t, *J*=8.8, αCH), 3.95 (2H, td, *J*=6.6, 1.5,$NHCH_2$), 3.10–1.86 (5H, m, βCH_2, $ArCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.52, 170.80, 137.58, 135.48, 134.71, 130.99, 129.95, 128.57, 124.67, 47.96, 40.07, 32.29, 21.12; 875; ESI-MS (M+H) 295.1 *m*/*z* and HRMS calcd mass for $C_{18}H_{18}N_2O_2$ 294.1368 found 294.1394.

*4.2.2. 2-Methoxy-N-(2-oxopyrrolidin-3-yl)-N-p-tolylbenzamide (**12b**).* The crude product obtained using condition A is purified using column chromatography (5% EtOAc/hexane) to give the title compound **12b** (64.0 mg, 62%) as a yellow oil; R_f (10% EtOAc/hexane) 0.47; IR (neat) cm^{-1} 3510, 3323, 1711, 1683, 1468.5, 1232.6, 875; ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 (2H, dd, *J* 6.9, 1.8, ArH), 7.47 (2H, ddd, *J*=6.9, 5.9, 2.1, ArH), 7.25–6.91 (4H, m, ArH), 6.21 (1H, s, NH), 4.71 (1H, t, *J*=5.6, αCH), 3.81 (3H, s, OCH_3), 3.60–3.24 (2H, td, *J*=6.8, 4.4, $NHCH_2$), 2.92–1.86 (5H, m, $ArCH_3$, βCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.52, 167.31, 156.86, 137.58, 134.71, 132.47, 131.06, 129.95, 125.45, 124.67, 120.70, 113.66, 56.78, 47.96, 40.07, 32.29, 21.12; ESI-MS (M+H) 325.2 *m*/*z* and HRMS calcd mass for $C_{19}H_{20}N_2O_3$ 324.1473 found 324.1452.

*4.2.3. 2-Methoxy-N-(2-oxopyrrolidin-3-yl)-N-phenylbenzamide (**12c**).* The crude product obtained using condition A is purified using column chromatography (5% EtOAc/hexane) to give the title compound **12c** (44.0 mg, 71%) as a yellow oil; R_f (10% EtOAc/hexane) 0.38; IR (neat) cm^{-1} 3501, 3294, 1700, 1664,1455,1213,875; ^1H NMR (300 MHz, $CDCl_3$) δ 7.97–7.66 (1H, m, ArH), 7.66–6.89 (8H, m, ArH), 6.34 (1H, s, NH), 4.58 (1H, t, *J*=8.7, αCH), 4.33–3.68 (4H, m, NHC*H*H, OCH_3), 3.66–3.07 (1H, dt, *J*=6.6, 6.5, NHCH*H*), 2.90–1.71 (2H, m, βCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.52, 167.31, 156.86, 139.31, 132.47, 131.06, 129.01, 127.31, 126.44, 125.45, 120.70, 113.66, 56.78, 47.96, 40.07, 32.29; ESI-MS (M+H) 311.2 *m*/*z* and HRMS calcd mass for $C_{18}H_{18}N_2O_3$ 310.1317 found 310.1325.

*4.2.4. N-(2-Oxopyrrolidin-3-yl)-2-phenyl-N-(p-tolyl)acetamide (**12d**).* The crude product obtained using condition A is purified using column chromatography (5% EtOAc/hexane) to give the title compound **12d** (42.0 mg, 78%) as a yellow oil; R_f (10% EtOAc/hexane) 0.48; IR (neat) cm^{-1} 3507, 3325, 1715, 1681, 1469, 1240, 875; ^1H NMR (300 MHz, $CDCl_3$) δ 7.69–7.06 (8H, m, ArH), 6.90 (1H, d, *J*=7.6, ArH), 6.72 (1H, s, NH), 4.72 (1H, t, *J*=8.8, αCH), 4.24–3.49 (4H, m, OCH_3, $NHCH_2$), 2.82–1.64 (5H, m, βCH_2, $ArCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.52, 171.68, 137.70, 135.97, 134.56, 130.07, 129.40, 128.21, 124.25, 48.45, 43.12, 40.07, 32.29, 21.12; ESI-MS (M+H) 309.6 *m*/*z* and HRMS calcd mass for $C_{18}H_{20}N_2O_2$ 308.1524 found 308.1543.

*4.2.5. N-(4-Nitrophenyl)-N-(2-oxopyrrolidin-3-yl)-2-phenylacetamide (**12e**).* The crude product obtained using condition A is purified using column chromatography (5% EtOAc/hexane) to give the title compound **12e** (54.0 mg, 62%) as a yellow oil; R_f (10% EtOAc/hexane) 0.36; IR (neat) cm^{-1} 3506.2, 3333.5, 1705, 1667, 1484.2, 1239.1, 875; ^1H NMR (300 MHz, $CDCl_3$) δ 8.27 (2H, d, *J*=7.5, ArH), 7.72–6.91 (7H, m, ArH), 6.19 (1H, s, NH), 4.58 (1H, t, *J*=8.8, αCH), 4.35–3.71 (3H, m, $ArCH_2$, C*H*H), 3.63–3.02 (1H, dt, *J*=6.4, 6.5, CH*H*), 2.84–1.62 (2H, m, βCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.52, 171.68, 148.37, 143.24, 134.56, 129.40, 128.21, 125.48, 124.29, 48.45, 43.12, 40.07, 32.29; ESI-MS (M+H) 340.1 *m*/*z* and HRMS calcd mass for $C_{18}H_{17}N_3O_4$ 339.1219 found 339.1234.

*4.2.6. 2-(2-Methoxyphenyl)-N-(4-nitrophenyl)-N-(2-oxopyrrolidin-3-yl)acetamide (**12f**).* The crude product obtained using condition A is purified using column chromatography (5% EtOAc/hexane) to give the title compound **12f** (71.0 mg, 60%) as a yellow oil; R_f (10% EtOAc/hexane) 0.44; IR (neat) cm^{-1} 3507, 3325, 1705, 1687, 1634, 1468, 1234, 875; ^1H NMR (300 MHz, $CDCl_3$) δ 8.23 (1H, d, *J*=7.5, ArH), 7.56–7.20 (4H, m, ArH), 7.19–6.66 (3H, m, ArH), 6.21 (1H, s, NH), 4.65 (1H, t, *J*=8.8, αCH), 4.33–3.90 (1H, m, NHC*H*H), 3.85 (2H, s, CH_2), 3.78 (3H, s, OCH_3), 3.61–3.05 (1H, dt, *J*=6.4, 6.5, NHCH*H*), 2.75–1.72 (2H, m, βCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.52, 171.49, 153.47, 148.37, 143.24, 130.17, 129.89, 126.28, 125.48, 124.29, 123.41, 113.05, 56.78, 48.45, 40.07, 36.91, 32.29; ESI-MS (M+H) 370.1 *m*/*z* and HRMS calcd mass for $C_{19}H_{19}N_3O_5$ 369.1324 found 369.1301.

*4.2.7. 2-(Biphenyl-4-yl)-N-(4-chloro-3-fluorophenyl)-N-(2-oxopyrrolidin-3-yl) acetamide (**12g**).* The crude product obtained using condition A is purified using column chromatography (5% EtOAc/hexane) to give the title compound **12g** (72.0 mg, 65%) as a yellow oil; R_f (10% EtOAc/hexane) 0.45; IR (neat) cm^{-1} 3511, 3325, 1705, 1657, 1468.5, 1230, 875; ^1H NMR (300 MHz, $CDCl_3$) δ 7.90–7.11 (10H, m, ArH), 6.83 (2H, ddd, *J*=7.6, 5.2, 1.4, ArH), 6.22 (1H, s, NH), 4.57 (1H, t, *J*=8.8, αCH), 4.07 (1H, dt, *J*=12.4, 6.8, NHC*H*H), 3.75 (2H, s, BiphenylCH$_2$), 3.63–2.99 (1H, m, NHCH*H*), 2.82–1.56 (2H, m, βCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.52, 171.68, 169.50, 152.04, 140.41, 139.08, 138.61, 138.21, 136.82, 131.98, 131.52, 129.17, 128.91, 128.69, 128.33, 127.29, 123.76, 123.50, 122.30, 120.50, 110.30, 108.50, 48.45, 43.12, 40.07, 32.29; ESI-MS (M+H) 423.5 *m*/*z* and; HRMS calcd mass for $C_{24}H_{20}ClFN_2O_2$ 422.8792 found 422.8783.

*4.2.8. 2-(Biphenyl-4-yl)-N-(3-fluorophenyl)-N-(2-oxopyrrolidin-3-yl)-acetamide (**12h**).* The crude product obtained using condition A is purified using column chromatography (5% EtOAc/hexane) to give the title compound **12h** (84.0 mg, 75%) as a yellow oil; R_f (10% EtOAc/hexane) 0.44; IR (neat) cm^{-1} 1694, 1654, 1476, 1302, 1226, 875; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95–7.10 (10H, m, ArH), 6.82 (3H, dddd, *J*=13.5, 7.1, 3.2, 1.6, ArH), 6.12 (1H, s, NH), 4.78 (1H, t, *J*=8.8, αCH), 4.07 (1H, dd, *J*=12.4, 6.5, NHC*H*H), 3.83 (2H, s, BiphenylCH$_2$), 3.34 (1H, dt, *J*=12.4, 6.4, NHCH*H*), 2.77–1.59 (2H, m, βCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.52, 172.43, 171.68, 154.96, 140.41, 139.08, 138.61, 138.21, 136.82, 130.52, 130.05, 129.17, 128.91, 128.69, 128.33, 127.29, 124.32, 124.06, 115.35, 114.36, 113.55, 112.56, 48.45, 43.12, 40.07, 32.29; ESI-MS (M+H) 389.1 *m*/*z* and HRMS calcd mass for $C_{24}H_{21}FN_2O_2$ 388.4341 found 388.4334.

*4.2.9. N-(2-Oxopiperidin-3-yl)-N-phenylbenzamide (**12i**).* The crude product obtained using condition A is purified using column chromatography (5% EtOAc/hexane) to give the title compound **12i** (44.0 mg, 76%) as a yellow oil; R_f (10% EtOAc/hexane) 0.38; IR (neat) cm^{-1} 3507,3335,1705, 1687, 1475, 1233, 875; ^1H NMR (300 MHz, $CDCl_3$) δ 8.01–7.66 (2H, m, ArH), 7.60–6.93 (8H, m, ArH), 6.36 (1H, s, NH), 4.44 (1H, t, *J*=7.9, αCH), 3.24 (2H, t, *J*=5.2, $NHCH_2$), 2.90–1.49 (4H, m, βCH_2CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.89, 170.44, 139.31, 135.48, 130.99, 129.01, 128.57, 127.31, 126.44, 51.80, 40.81,

24.42, 23.99; ESI-MS (M+H) 295.1 *m*/*z* and HRMS calcd mass for $C_{18}H_{18}N_2O_2$ 294.1368 found 294.1394.

*4.2.10. 4-Nitro-N-(2-oxopiperidin-3-yl)-N-p-tolylbenzamide (**12j**).* The crude product obtained using condition A is purified using column chromatography (5% EtOAc/hexane) to give the title compound **12j** (97.0 mg, 78%) as a yellow oil; R_f (10% EtOAc/hexane) 0.35; IR (neat) cm^{-1} 3507, 3335, 1705, 1687, 1475, 1233, 875; ^1H NMR (300 MHz, $CDCl_3$) δ 8.33 (2H, d, *J*=7.6, ArH), 8.11 (2H, d, *J*=7.6, ArH), 7.48–6.92 (4H, m, ArH), 6.31 (1H, s, NH), 4.76–4.13 (1H, m, αCH), 3.48–3.02 (2H, m, $NHCH_2$), 2.92–1.50 (7H, m, βCH_2CH_2, $ArCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.89, 170.44, 148.54, 140.12, 137.58, 134.71, 129.95, 129.01, 124.67, 123.99, 51.80, 40.81, 24.42, 23.99, 21.12; ESI-MS (M+H) 354.2 *m*/*z* and HRMS calcd mass for $C_{19}H_{19}N_3O_4$ 353.1375 found 353.1364.

*4.2.11. 2-Methoxy-N-(2-oxopiperidin-3-yl)-N-p-tolylbenzamide (**12k**).* The crude product obtained using condition A is purified using column chromatography (5% EtOAc/hexane) to give the title compound **12k** (41.0 mg, 62%) as a dark yellow oil; R_f (15% EtOAc/hexane) 0.40; IR (neat) cm^{-1} 3527, 3313, 1687, 1641, 1374, 1232, 875; ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (1H, dd, *J*=6.8, 1.6, ArH), 7.69–6.91 (7H, m, ArH), 6.19 (1H, s, NH), 4.66–4.20 (1H, m, NCH), 3.83 (3H, s, OCH_3), 3.46–3.02 (2H, m, $NHCH_2$), 2.85–2.14 (4H, m, $ArCH_3$, NCCHH), 2.10–1.48 (3H, m, $NHCH_2CHH$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.44, 167.93, 156.86, 137.58, 134.71, 132.47, 131.06, 129.95, 125.45, 124.67, 120.70, 113.66, 56.78, 51.80, 40.81, 24.42, 23.99, 21.12; ESI-MS (M+H) 339.1 *m*/*z* and HRMS calcd mass for $C_{20}H_{22}N_2O_3$ 338.1630 found 338.1621.

*4.2.12. N-(2-Oxoazepan-3-yl)-N-p-tolylbenzamide (**12l**).* The crude product obtained using condition A is purified using column chromatography (5% EtOAc/hexane) to give the title compound **12l** (34.0 mg, 48%) as a yellow oil; R_f (10% EtOAc/hexane) 0.42; IR (neat) cm^{-1} 3537, 3325, 1667, 1455, 1235, 875; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05–7.64 (2H, m, ArH), 7.44 (3H, dt, *J*=4.2, 1.9, ArH), 7.34–7.03 (4H, m, ArH), 5.02–4.62 (1H, m, αCH), 4.47 (2H, dd, *J*=10.3, 5.0, $NHCH_2$), 3.17 (1H, dt, *J*=12.6, 5.4, βCHH), 2.87–1.93 (5H, m, $ArCH_3$, $\beta CHHCH_2$), 1.90–0.73 (4H, m, CH_2CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.89, 169.46, 137.58, 135.48, 134.71, 130.99, 129.95, 128.57, 124.67, 55.32, 42.43, 30.90, 29.87, 24.32, 21.12; ESI-MS (M+H) 323.1 *m*/*z* and HRMS calcd mass for $C_{20}H_{22}N_2O_2$ 322.1681 found 322.1643.

*4.2.13. 2-(Biphenyl-4-yl)-N-(2-oxoazepan-3-yl)-N-p-tolylacetamide (**12m**).* The crude product obtained using condition A is purified using column chromatography (5% EtOAc/hexane) to give the title compound **12m** (46.0 mg, 51%) as a yellow oil; R_f (10% EtOAc/hexane) 0.48; IR (neat) cm^{-1} 3507, 3335, 1705, 1687, 1475, 1233, 875; ^1H NMR (300 MHz, $CDCl_3$) δ 7.94–7.08 (11H, m, ArH), 6.93 (2H, d, *J*=7.6, ArH), 4.63–4.26 (2H, m, NH, αCH), 3.92 (2H, s, $BiphenylCH_2$), 3.19 (2H, t, *J*=4.6, $NHCH_2$), 2.93–2.17 (4H, m, $ArCH_3$, βCHH), 2.15–0.95 (5H, m, βCHH, CH_2CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) precluded due to lesser concentration; ESI-MS (M+H) 413.2 *m*/*z* and HRMS calcd mass for $C_{27}H_{28}N_2O_2$ 412.2151 found 412.2134.

*4.2.14. N-(2-Oxoazocan-3-yl)-N-phenylbenzamide (**12n**).* The crude product obtained using condition A is purified using column chromatography (5% EtOAc/hexane) to give the title compound **12n** (38.0 mg, 54%) as a yellow oil; R_f (10% EtOAc/hexane) 0.40; IR (neat) cm^{-1} 3507, 3335, 1705, 1687, 1475, 1233, 875; ^1H NMR (300 MHz, $CDCl_3$) δ 8.17–7.67 (2H, m, ArH), 7.64–6.78 (8H, m, ArH), 6.29 (1H, s, NH), 4.44 (1H, t, *J*=4.1, αCH), 3.80 (1H, dt, *J*=12.5, 4.7, NHCHH), 3.21 (1H, dt, *J*=12.5, 4.6, NHCHH), 2.56–1.14 (8H, m, $4CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.53, 170.89, 139.31, 135.48, 130.99, 129.01, 129.01, 128.57, 128.57, 127.31, 126.44, 49.72, 41.51, 30.75, 28.64, 26.32, 25.80; HRMS calcd mass for $C_{20}H_{22}N_2O_2$ 322.1681 found 322.1673.

*4.2.15. 4-Nitro-N-(2-oxoazocan-3-yl)-N-phenylbenzamide (**12o**).* The crude product obtained using condition A is purified using column chromatography (5% EtOAc/hexane) to give the title compound **12o** (56.0 mg, 50%) as a yellow oil; R_f (10% EtOAc/hexane) 0.30; IR (neat) cm^{-1} 3507, 3335, 1687, 1648, 14,735, 1236, 873; ^1H NMR (300 MHz, $CDCl_3$) δ 8.45–8.24 (2H, m, ArH), 8.24–8.04 (2H, m, ArH), 7.70–6.66 (5H, m, ArH), 6.17 (1H, s, NH), 4.44 (1H, t, *J*=4.6, αCH), 3.45 (2H, dd, *J*=7.9, 3.9, $NHCH_2$), 2.54–1.25 (8H, m, $4CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.53, 170.89, 148.54, 140.12, 139.31, 129.01, 127.31, 126.44, 123.99, 49.72, 41.51, 30.75, 28.64, 26.32, 25.80; ESI-MS (M+H) 368.6 *m*/*z* and HRMS calcd mass for $C_{20}H_{21}N_3O_4$ 367.1532 found 367.1524.

*4.2.16. N-(4-Methoxyphenyl)-4-nitro-N-(2-oxoazocan-3-yl)benzamide (**12p**).* The crude product obtained using condition A is purified using column chromatography (5% EtOAc/hexane) to give the title compound **12p** (43.0 mg, 48%) as a yellow oil; R_f (10% EtOAc/hexane) 0.32; IR (neat) cm^{-1} 3507, 3335, 1705, 1687, 1475, 1233, 875; ^1H NMR (300 MHz, $CDCl_3$) δ 8.34 (2H, d, *J*=7.6, ArH), 8.12 (2H, d, *J*=7.6, ArH), 7.29 (2H, t, *J*=3.7, ArH), 6.95 (2H, d, *J*=7.5,ArH), 6.33 (1H, s, NH), 4.44 (1H, t, *J*=4.6, αCH), 3.81 (3H, s, OCH_3), 3.46 (2H, t, *J*=6.0, $NHCH_2$), 2.64–1.17 (8H, m, $4CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.53, 170.89, 156.85, 148.54, 140.12, 132.19, 129.01, 127.40, 123.99, 114.97, 56.03, 49.72, 41.51, 30.75, 28.64, 26.32, 25.80; ESI-MS (M+H) 398.4 *m*/*z* and HRMS calcd mass for $C_{21}H_{23}N_3O_5$ 397.1637 found 397.1652.

*4.2.17. N-(4-Methoxybenzyl)-4-nitro-N-(2-oxoazocan-3-yl)benzamide (**12q**).* The crude product obtained using condition A is purified using column chromatography (8% EtOAc/hexane) to give the title compound **12q** (35.0 mg, 36%) as a yellow oil; R_f (10% EtOAc/hexane) 0.34; IR (neat) cm^{-1} 1677, 1653, 1474, 1234, 875; ^1H NMR (300 MHz, $CDCl_3$) δ 8.38 (2H, d, *J*=7.6, ArH), 8.14 (2H, d, *J*=7.6, ArH), 7.51–7.11 (2H, m, ArH), 6.92 (2H, d, *J*=7.6, ArH), 6.03 (1H, s, NH), 4.64–4.21 (3H, m, αCH, $AnisylCH_2$), 4.07–3.46 (4H, m, NHCHH, OCH_3), 3.18 (1H, dt, *J*=12.5, 4.6, NHCHH), 2.61–1.28 (8H, m, $4CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.62, 170.61, 159.85, 146.84, 141.05, 129.13, 128.11, 127.36, 123.84, 113.80, 56.03, 52.92, 47.89, 41.51, 29.96, 28.64, 26.32, 25.80; ESI-MS (M+H) 412.1 *m*/*z* and HRMS calcd mass for $C_{22}H_{25}N_3O_5$ 411.1794 found 411.1773.

*4.2.18. N-(3,4-Dimethoxyphenethyl)-4-nitro-N-(2-oxoazocan-3yl) benzamide (**12r**).* The crude product obtained using condition E is purified using column chromatography (7% EtOAc/hexane) to give the title compound **12r** (47.0 mg, 42%) as a yellow oil; R_f (14% EtOAc/hexane) 0.37; IR (neat) cm^{-1} 3507, 3347, 1715, 1689, 1468, 1243, 875; ^1H NMR (300 MHz, $CDCl_3$) δ 8.36 (2H, d, *J*=7.6, ArH), 8.09 (2H, d, *J*=7.6, ArH), 6.89 (3H, s, ArH), 5.98 (1H, s, NH), 5.07–4.61 (1H, m, αCH), 4.44 (1H, t, *J*=7.4, NCHH), 4.13–3.76 (7H, m, NCHH, 2–OCH_3), 3.74–3.41 (1H, m, NHCHH), 3.29–2.75 (3H, m, NHCHH, $ArCH_2$), 2.58–1.09 (8H, m, $4CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.62, 170.82, 148.92, 148.78, 146.84, 141.05, 133.21, 128.11, 123.84, 122.38, 113.11, 112.80, 56.78, 51.44, 42.97, 41.51, 35.14, 29.96, 28.64, 26.32, 25.80; ESI-MS (M+H) 456.1 *m*/*z* and HRMS calcd mass for $C_{24}H_{29}N_3O_6$ 455.2056 found 455.2044.

*4.2.19. N-Allyl-4-nitro-N-(2-oxoazocan-3-yl)benzamide (**12s**).* The crude product obtained using condition E is purified using column chromatography (5% EtOAc/hexane) to give the title compound

12s (40.0 mg, 36%) as a yellow oil; R_f (10% EtOAc/hexane) 0.28; IR (neat) cm^{-1}3517, 3405, 2224, 1687, 1654, 1468, 1233, 1103, 875; ^1H NMR (300 MHz, $CDCl_3$) δ 8.33 (2H, d, J=7.5, ArH), 7.99 (2H, d, J=7.5,ArH), 6.27–5.44 (2H, m, CH, NH), 5.19 (1H, d, J=2.2, CH_2), 5.07–4.83 (1H, m, αCH), 4.46 (2H, dd, J=9.5, 6.7,NCH_2), 3.97 (1H, d, J=5.9, NHCH*H*), 3.87–3.46 (1H, m, βC*H*H), 3.20 (1H, dt, J=12.5, 5.4, NHCH*H*), 2.57–0.87 (8H, m, $4CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.62, 171.63, 146.84, 141.05, 133.56, 128.11, 123.84, 118.87, 52.08, 46.77, 41.51, 29.96, 28.64, 26.32, 25.80; ESI-MS (M+H) 295.1 m/z and HRMS calcd mass for $C_{17}H_{21}N_3O_4$ 331.1532 found 331.1524.

*4.2.20. Ethyl-5-(4-nitro-N-(2-oxoazocan-3-yl)benzamido)pent-2-enoate (**12t**).* The crude product obtained using condition E is purified using column chromatography (5% EtOAc/hexane) to give the title compound **12t** (27.0 mg, 51%) as a yellow oil; R_f (10% EtOAc/hexane) 0.30; ^1H NMR (300 MHz, $CDCl_3$) δ 8.37 (2H, d, J=7.6, ArH), 8.10 (2H, d, J=7.6, ArH), 7.19–5.79 (3H, m, CHCH, NH), 4.68–4.02 (4H, m, αCH, NHC*H*H), 3.23 (3H, dddd, J=16.8, 12.5, 10.8, 6.1, NHCH*H*, NCH_2), 2.47 (2H, dd, J=13.7, 7.2), 2.23–1.12 (11H, m, $4CH_2$,CH_3). Due lesser concentration of the compound ^{13}C NMR was percluded; ESI-MS (M+H) 418.2 m/z and HRMS calcd mass for $C_{21}H_{27}N_3O_6$ 417.1899 found 417.1874.

*4.2.21. Ethyl-6-(4-nitro-N-(2-oxoazocan-3-yl)benzamido)hexanoate (**12u**).* The crude product obtained using condition E is purified using column chromatography (5% EtOAc/hexane) to give the title compound **12u** (44.0 mg, 38%) as a yellow oil; R_f (10% EtOAc/hexane) 0.33; IR (neat) cm^{-1} 3507, 3335, 1735, 1687, 1636, 1465, 1232, 874; ^1H NMR (300 MHz, $CDCl_3$) δ 8.32 (2H, d, J=7.6, ArH), 8.02 (2H, d, J=7.6, ArH), 5.46 (1H, s, NH), 4.29 (3H, dt, J=11.8, 6.6, NHC*H*H, NCH_2), 3.99–3.47 (2H, m), 3.46–2.93 (2H, m, CH_2), 2.35 (2H, t, J=5.2, CH_2), 2.23–0.95 (16H, m, $8CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.62, 174.11, 170.82, 146.84, 141.05, 128.11, 123.84, 61.17, 51.44, 43.03, 41.51, 34.02, 29.96, 28.62, 26.52, 26.32, 25.80, 25.33, 14.69 ESI-MS (M+H) 434.5 m/z and HRMS calcd mass for $C_{22}H_{31}N_3O_6$ 433.2212 found 433.2236.

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Supplementary data

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