Cerium(IV) sulfate catalyzed simple and convenient synthesis of β-acetamidocarbonyl compounds

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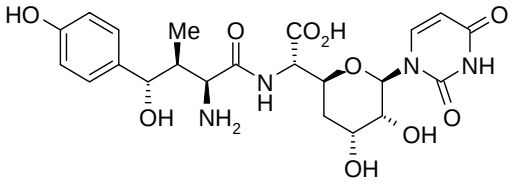
Abstract

A simple and convenient protocol for the synthesis of β-acetamido ketones has been described by one-pot three-component reaction of aromatic aldehydes and enolizable ketones or β-keto esters and acetonitrile using cerium(IV) sulfate as a catalyst. The present methodology offers several advantages such as excellent yields, non hazardous reaction condition and short reaction times.

Keywords: Cerium(IV) sulfate, β-acetamido carbonyl, one-pot three-component, aromatic aldehyde, β-keto esters

Introduction

Multi-component reactions (MCRs) are a promising and vital field of chemistry because the synthesis of complicated molecules can be achieved in a very fast, efficient, and time saving manner without the isolation of any intermediates and hence it has drawn the attraction of organic chemists to develop novel multicomponent reaction.[1] Several β-acetamido ketones/esters were synthesized as they are potential core structures for mechanism based inhibitors for various proteases. The β-acetamido esters are also useful precursors to β-aryl homoisothreonine derivatives which can be incorporated in an amino acid residue to afford the corresponding dipeptide isosteres. They could easily be converted to 1,3-amino alcohols[5] or β-amino acids, which are utilized for the synthesis of several antibiotics such as nikkomycins or neopolyoxines.[6] Thus, the synthesis of β-acetamido carbonyl compounds has attracted much attention in organic synthesis.



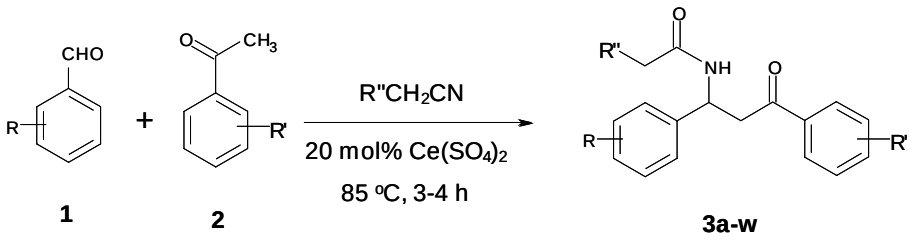
Nikkomycin B

β-Acetamido ketones were usually prepared through acylation of β-aminoketones,[7] Michael addition to α,β-unsaturated ketones,[8] or photoisomerisation of phthalimides.[9] Conventionally, this class of compounds was prepared by the Dakin-West reaction involving condensation of an α-amino acid with acetic anhydride in the presence of a base *via* an intermediate azalactone.[10] The best-known route for the synthesis of these compounds is the one-pot condensation of an aldehyde, an enolizable ketone, acetyl chloride, and acetonitrile, originally reported by Iqbal and co-workers.[11] β-Acetamido ketones have also been synthesized using Sn(II),[12] Sc(III) triflates,[13] $InCl_3$,[13] $CoCl_2$,[14] montmorillonite K-10 clay,[15] H_2SO_4/SiO_2,[16] Zirconia,[17] ZnO,[18] phosphotungstic acid,[19] sulfamic acid,[20a] Aluminium hydrogen sulfate[20b] and $CeCl_3$[21] as catalysts. Although these methods are valuable, they suffer from one or more of the following disadvantages such as hazardous reagents, high temperature, long reaction time, low yield, and tedious workup. Hence, the development of a simple and new protocol with more efficiency is still in demand.

Results and Discussion

In continuation of our interest in the application of cerium(IV) sulfate[22a, 23] in organic synthesis and on the synthesis of diversely substituted amides,[22] we herein disclose a simple and efficient one-pot synthesis of β-acetamido ketone/ester from aromatic aldehydes, enolizable ketone or β-ketoesters and acetonitrile catalysed by cerium(IV) sulfate at reflux in good yields. To the best of our knowledge for the first time, the synthesis of β-acetamido carbonyl compounds have been achieved without employing acetyl chloride.

In our initial endeavour, the reaction was studied with different mole ratios of $Ce(SO_4)_2$ and the best catalytic activity of cerium(IV) sulfate was optimized to be 20 mol% and any excess of the catalyst did not show further increases in terms of conversion and yield. According to this procedure, the reaction of substituted benzaldehydes and acetophenones with nitriles proceeded smoothly at 85 ^oC in the presence of 20 mol% of $Ce(SO_4)_2$ to afford the corresponding β-acetamido ketones in good yields (Scheme 1 and Table 1).



Scheme 1

Table 1. Synthesis of β-amido ketones from benzaldehydes and acetophenones with nitriles

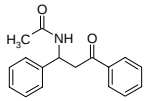
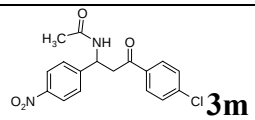
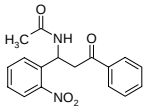
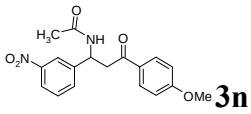
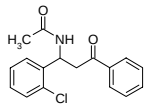
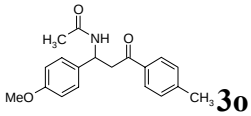
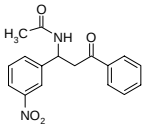
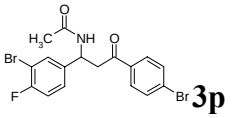
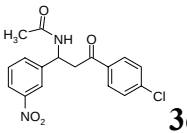
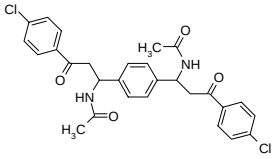
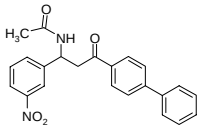
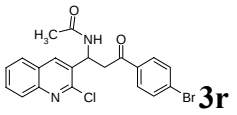
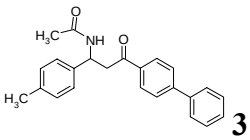
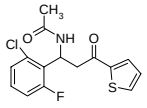
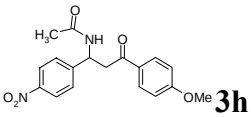
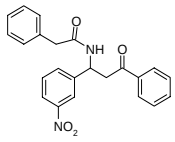
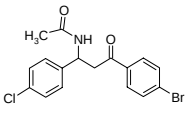
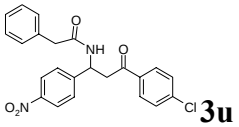
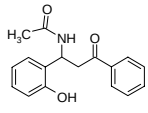
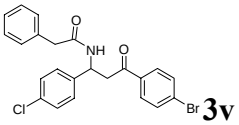
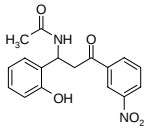
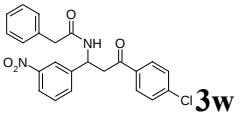
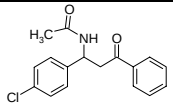
#	Product **3**[a]	Time (h)	Yield (%)[b]	#	Product **3**[a]	Time (h)	Yield (%)[b]
1	 **3a**	3.5	83	13	 **3m**	3.5	83
2	 **3b**	3.0	80	14	 **3n**	3.0	89
3.	 **3c**	3.0	80	15	 **3o**	3.5	87
4	 **3d**	3.0	85	16	 **3p**	3.0	85
5	 **3e**	3.0	87	17	 **3q**	4.5	75
6	 **3f**	3.0	85	18	 **3r**	3.0	88
7	 **3 g**	3.0	83	19	 **3s**	3.0	90
8	 **3h**	3.5	90	20	 **3t**	3.0	90
9	 **3i**	3.5	84	21	 **3u**	3.0	88
10	 **3j**	4.0	82	22	 **3v**	3.5	89
11	 **3k**	4.0	78	23	 **3w**	3.5	86

Table 1. Continued

#	Product **3**[a]	Time (h)	Yield (%)[b]	#	Product **3**[a]	Time (h)	Yield (%)[b]
12	 **3l**	3.5	80				

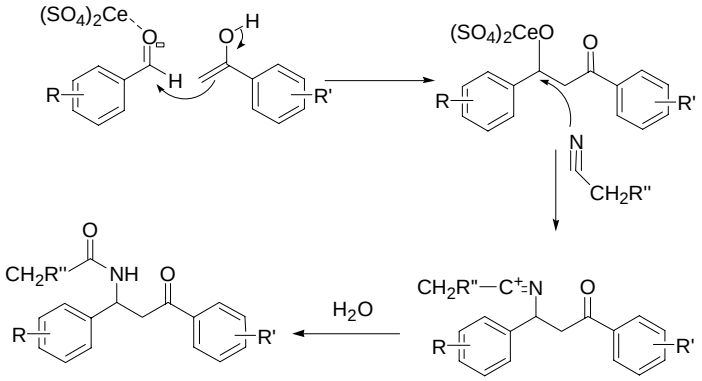
[a]All products were characterized by Mass, IR, ^{1}H NMR, ^{13}C NMR and elemental analysis.
[b]Isolated yields.

Both aromatic aldehydes or acetophenones with activating and deactivating groups underwent smooth transformation to the corresponding β-acetamido ketones in good to excellent yields, without the formation of any side products. Several functionalities such as nitro, chloro, bromo, hydroxyl, and methoxy were compatible with this procedure. Heterocyclic aldehydes and ketones also participated in the reaction and afforded the corresponding β-acetamido ketones **3r**, **3s**. The reaction proceeded well with benzylcyanides too (Entries 20 – 23).

The structures of compounds **3a-w** were confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis. The mass spectrum of **3d** displayed the molecular ion (M+1) peak at *m/z* 313. In the IR spectrum, peaks at 3301, 1646 and 1691 cm^{-1} indicated the presence of –NH, -CO- and –C=O groups, respectively. The ^{1}H NMR spectrum of **3d** exhibited a singlet at δ 1.79 for the acetamido methyl group and a doublet at δ 8.49 (D_2O exchangeable) due to an –NH proton. In the ^{13}C NMR spectrum, the acetamido carbonyl was observed at δ 169.3 and the other carbonyl group at δ 197.1, which confirmed the incorporation of the acetamido group in the molecule. Elemental analysis was also in agreement with the proposed structure.

The experimental procedure for this reaction is remarkably simple and requires no inert atmosphere. The pure product can be easily isolated without column chromatography. After completion of the reaction, the reaction mixture was poured into crushed ice and extracted with dichloromethane. The organic layer was concentrated under reduced pressure and the crude product was stirred with a minimum amount of diethyl ether to obtain the pure product.

A plausible mechanism for the formation of β-amidoketones is shown below (Scheme 2).



Scheme 2

The scope and limitation of this methodology was further explored with cyclic ketone/ethyl methyl ketone/diketones and the corresponding products were obtained in good yields (Scheme 3 and Table 2).

Table 2. Synthesis of β-amido ketones **5**

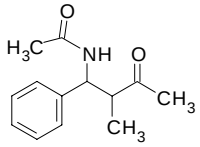
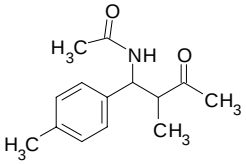
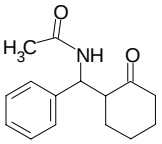
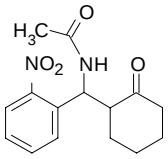
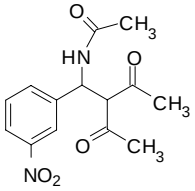
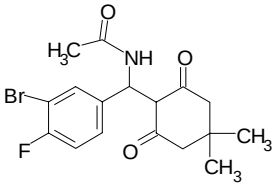
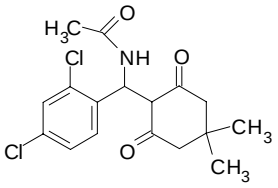
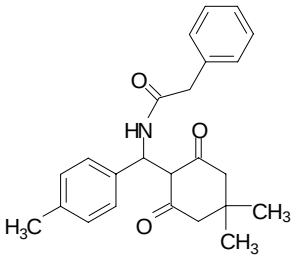
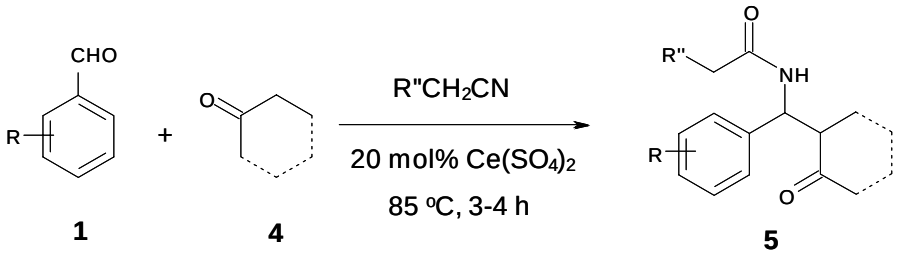
#	Product (**5**)[a]	Time (h)	Syn: anti[b]	Yield (%)[c]
1.	 **5a**	3.0	24:76	88
2.	 **5b**	3.0	30:70	88
3.	 **5c**	2.5	33:67	92
4.	 **5d**	2.5	30:70	90
5.	 **5e**	2.0	-	94
6.	 **5f**	2.0	-	95
7.	 **5g**	2.0	-	94

Table 2. Continued

#	Product (**5**)[a]	Time (h)	Syn: anti[b]	Yield (%)[c]
8.	 **5h**	2.0	-	96

[a]All products were characterized by Mass, IR, ^{1}H NMR, ^{13}C NMR and elemental analysis.
[b]Ratio of syn and anti isomers is estimated with ^{1}H NMR for methine proton (CHCO) based on coupling constants.
[c]Isolated yield of mixture of diastereomers.



Scheme 3

The structure **5e** was assigned to the product on the basis of spectral data. The IR spectrum of **5e** showed absorptions at 3349, 1651 and 1715 cm^{-1} indicating the presence of acetamido and carbonyl functionalities respectively. In the ^{1}H NMR spectrum, a singlet at δ 1.75 (acetamido methyl group) and a doublet at δ 8.55 (-NH, D_2O exchangeable) confirmed the presence of the acetamido group while the other two acetyl methyl groups appeared as singlets at δ 1.98 and 2.20, respectively. The acetamido carbonyl and the two acetyl carbonyls resonated at δ 169.4, 202.0, and 202.1 in the ^{13}C NMR spectrum. Mass spectral analysis also supported the structural assignment.

The reaction was also carried out with β-keto esters, aromatic aldehydes and nitriles. As expected, the reaction proceeded smoothly and the products were isolated in pure form without column chromatography (Scheme 4 and Table 3).

Scheme 4

Table 3. Synthesis of β-acetamido ketones **7** from β-keto esters

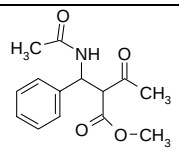
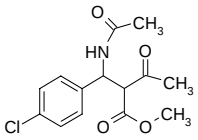
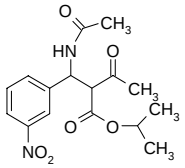
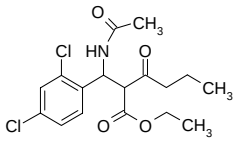
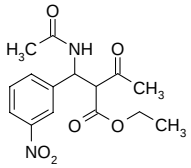
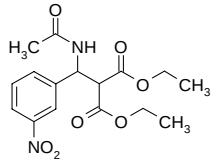
#	Product (**7**)[a]	Time (h)	Syn:anti[b]	Yield (%)[c]
1.	 **7a**	2.5	33:67	87
2.	 **7b**	2.5	28:72	86
3.	 **7c**	2.5	25:75	90
4.	 **7d**	2.5	30:70	87
5.	 **7e**	2.5	28:72	92

Table 3. Continued

#	Product (**7**)[a]	Time (h)	Syn:anti[b]	Yield (%)[c]
6.	 **7f**	2.5	-	94

[a]All products were characterized by mass, IR, ^{1}H, 13C NMR and elemental analysis. [b]Ratio of syn and anti isomers is estimated with ^{1}H NMR for methine proton (CHCO) based on coupling constants.
[c]Isolated yield of mixture of diastereomers.

Conclusions

In conclusion, we have reported an efficient procedure for the synthesis of β-acetamido ketones/esters using cerium(IV) sulphate. The major advantage of this method is the ease of work-up, i.e. the products can be isolated without column chromatography. This method also offers some other merits such as clean reactions, low loadings of catalyst, high yields of products, shorter reaction times and use of various substrates, which make it ~~a~~an useful and attractive strategy for the synthesis of β-acetamido ketones/esters.

Experimental Section

General Procedures. All substituted benzaldehydes, acetophenones, and β-keto esters were purchased from S.D. Fine Chem. Ltd. Dimedone and cerium(IV) sulphate were obtained from Aldrich. All melting points were uncorrected. IR spectra were recorded on a Perkin Elmer FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 using TMS as an internal standard at 500 MHz and 125 MHz on a JEOL spectrometer and Bruker spectrometer, respectively. Mass spectra were recorded by using an Electrospray Ionisation method with Thermo Finnegan mass spectrometer. Elemental analyses were recorded using a Thermo Finnigan FLASH EA 1112 CHN analyzer. Analytical TLC was performed on precoated plastic sheets of silica gel G/UV-254 of 0.2 mm thickness (Macherey-Nagel, Germany).

General procedure for the synthesis of β-amido ketones (3, 5, 7)
To a stirred suspension containing substituted benzaldehyde (1 mmol) and acetophenones/enolizable ketones/β-keto esters (1 mmol) in nitrile (5 mL), cerium(IV) sulphate (20 mol%) was added. The reaction mixture was stirred at 85 ^{o}C for 3–4 h. After completion of

the reaction, the reaction mixture was poured into crushed ice and extracted with dichloromethane and washed with water. The organic layer was dried over anhydrous Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure and the residue was stirred with diethyl ether (5 mL). The precipitated solid was filtered and dried to afford pure product.

***N*-(1,3-Diphenyl-3-oxopropyl)acetamide (3a).** White solid. Isolated Yield: 83%, mp: 102–104 °C (Lit.[15] 102–104 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.76 (s, 3H), 3.43 (dd, 1H, J_1 = 6.1 Hz, J_2 = 16.8 Hz), 3.77 (dd, 1H, J_1 = 5.1 Hz, J_2 = 16.8 Hz), 5.46 (m, 1H), 6.78 (d, 1H, J = 8.4 Hz), 7.20 (m, 5H), 7.46 (m, 3H), 7.93 (d, 1H, J = 8.4 Hz), 8.31 (d, 1H, J = 8.4 Hz, NH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 23.1 (q), 42.8 (t), 49.9 (d), 126.3 (d), 127.2 (d), 128.0 (d), 128.6 (d), 133.5 (s), 141.1 (s), 169.5 (s), 198.6 (s). IR (KBr, ν_{max}/cm^{-1}): 3287 (s), 1772 (s), 1659 (s), 1500 (s), 1374 (s), 1295 (m), 1188 (s), 1023 (m), 704 (s), 585 (m). Mass (ESI): 268 (M+1 ion). Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24; Found: C, 76.56; H, 6.39; N, 5.26%.

***N*-[1-(2-Nitrophenyl)-3-phenyl-3-oxopropyl]acetamide (3b).** Pale yellow solid. Isolated Yield: 80%, mp: 186–189 °C (Lit.[15] 186–188 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.72 (s, 3H), 3.41 (dd, 1H, J_1 = 3.9 Hz, J_2 = 17.5 Hz), 3.78 (dd, 1H, J_1 = 9.2 Hz, J_2 = 17.5 Hz), 5.29 (m, 1H), 7.40 (m, 3H), 7.61 (m, 2H), 7.76 (d, 1H, J = 7.7 Hz), 7.93 (d, 1H, J = 8.4 Hz), 7.99 (d, 2H, J = 7.7 Hz), 8.29 (d, 1H, J = 8.4 Hz, NH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 22.8 (q), 42.9 (t), 44.9 (d), 122.9 (d), 126.8 (d), 127.1 (d), 128.2 (d), 128.6 (d), 132.7 (d), 133.1 (d), 135.6 (s), 137.9 (s), 147.8 (s), 169.1 (s), 196.3 (s). IR (KBr, ν_{max}/cm^{-1}): 3279 (s), 3076 (m), 2938 (m), 1693 (s), 1648 (s), 1561 (s), 1512 (m), 1339 (s), 1304 (m), 1222 (s), 996 (m), 751 (s), 685. Mass (ESI): 313 (M+1 ion). Anal. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.16; N, 8.97; Found: C, 65.66; H, 5.20; N, 8.91%.

***N*-[3-(2-Chlorophenyl)-1-phenyl-3-oxopropyl]acetamide (3c).** White solid. Isolated Yield: 80%, mp: 134–136 °C(Lit.[15] 135–136 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.78 (s, 3H), 3.47 (dd, 1H, J_1 = 5.1 Hz, J_2 = 16.8 Hz), 3.53 (dd, 1H, J_1 = 5.9 Hz, J_2 = 16.8 Hz), 5.67 (m, 1H), 7.21 (m, 6H), 7.59 (d, 2H, J = 7.7 Hz)), 7.93 (d, 1H, J = 6.9 Hz), 8.21 (d, 1H, J = 7.7 Hz, NH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 24.2 (q), 42.9 (t), 49.3 (d), 120.7 (d), 123.3 (d), 126.9 (d), 127.3 (d), 127.8 (d), 128.7 (s), 133.1 (s), 135.2 (s), 169.3 (s), 198.7 (s). IR (KBr, ν_{max}/cm^{-1}): 3288 (s), 3086 (w), 2954 (w), 1690 (s), 1647 (s), 1547 (s), 1373 (m), 1202 (s), 998 (m), 758 (s), 685 (m). Mass (ESI): 302 (M+1 ion). Anal. Calcd for $C_{17}H_{16}NO_2Cl$: C, 67.66; H, 5.34; N, 4.64; Found: C, 67.99; H, 5.38; N, 4.61%.

***N*-[1-(3-Nitrophenyl)-3-phenyl-3-oxopropyl]acetamide (3d).** White solid. Isolated Yield: 85%, mp: 110–112 °C (Lit.[15] 112–115 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.79 (s, 3H), 3.43 (dd, 1H, J_1 = 5.4 Hz, J_2 = 17.6 Hz), 3.60 (dd, 1H, J_1 = 8.4 Hz, J_2 = 17.6 Hz), 5.41 (m, 1H), 7.47 (t, 2H, J = 7.7 Hz), 7.57 (m, 2H), 7.80 (d, 1H, J = 7.7 Hz), 7.92 (d, 2H, J = 7.7 Hz), 8.06 (d, 1H, J = 7.7 Hz), 8.20 (s, 1H), 8.49 (d, 1H, J = 7.7 Hz, NH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 23.0 (q), 44.5 (t), 48.9 (d), 121.7 (d), 122.3 (d), 128.4 (d), 129.0 (d), 130.2 (d), 133.8 (d), 134.1 (d), 136.8 (s), 146.0 (s), 148.3 (s), 169.3 (s), 197.1 (s). IR (KBr, ν_{max}/cm^{-1}): 3301

(s), 1691 (s), 1646 (s), 1523 (s), 1349 (s), 1294 (s), 757 (s), 686 (m). Mass (ESI): 313 (M+1 ion). Anal. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.16; N, 8.97; Found: C, 65.60; H, 5.10; N, 8.83%.

***N*-[3-(4-Chlorophenyl)-1-(3-nitrophenyl)-3-oxopropyl]acetamide (3e).** White solid. Isolated Yield: 87%, mp: 148–150 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.78 (s, 3H), 3.42 (m, 1H), 3.58 (dd, 1H, J_1 = 8.4 Hz, J_2 = 17.5 Hz), 5.40 (m, 1H), 7.53 (d, 2H, J = 8.4 Hz), 7.56 (t, 1H, J = 7.6 Hz), 7.78 (d, 1H, J = 8.4 Hz), 7.92 (d, 2H, J = 8.4 Hz), 8.06 (d, 1H, J = 7.6 Hz), 8.19 (s, 1H), 8.50 (d, 1H, J = 7.6 Hz, NH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 23.0 (q), 44.6 (t), 49.0 (d), 121.4 (d), 122.8 (d), 128.6 (d), 129.7 (d), 131.1 (d), 133.6 (d), 135.6 (s), 138.8 (s), 146.0 (s), 148.3 (s), 169.4 (s), 196.2 (s). IR (KBr, ν_{max}/cm^{-1}): 3299 (s), 1685 (s), 1645 (s), 1589 (m), 1524 (s), 1350 (m), 1093 (s), 992 (m), 813 (s), 687 (m). Mass (ESI): 347 (M+1 ion). Anal. Calcd for $C_{17}H_{15}N_2O_4Cl$: C, 58.88; H, 4.36; N, 8.08; Found: C, 59.01; H, 4.39; N, 8.12%.

***N*-[3-(Biphenyl-4-yl)-1-(3-nitrophenyl)-3-oxopropyl]acetamide (3f).** Pale Orange solid. Isolated Yield: 85%, mp: 114–118 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.80 (s, 3H), 3.48 (m, 2H), 5.46 (m, 1H)), 7.36 (t, 1H, J = 6.8 Hz), 7.44 (t, 2H, J = 7.6 Hz), 7.57 (t, 1H, J = 8.4 Hz), 7.68, (m, 4H), 7.81 (d, 1H, J = 7.6 Hz), 7.98 (m, 2H), 8.05 (d, 1H, J = 7.6 Hz), 8.22 (s, 1H), 8.55 (d, 1H, J = 7.6 Hz, NH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 23.1 (q), 44.6 (t), 49.1 (d), 121.5 (d), 122.8 (d), 126.8 (d), 128.1 (d), 129.7 (d), 129.9 (d), 130.9 (d), 133.6 (d), 134.9 (d), 135.7 (s), 139.3 (s), 145.2 (s), 146.1 (s), 148.4 (s), 169.4 (s), 196.7 (s). IR (KBr, ν_{max}/cm^{-1}): 3298 (s), 3062 (w), 1673 (s), 1603 (s), 1528 (s), 1347 (s), 1296 (m), 1102 (s), 764 (s), 690 (m). Mass (ESI): 799 (Dimer + Na ion). Anal. Calcd for $C_{23}H_{20}N_2O_4$: C, 71.12; H, 5.19; N, 7.21; Found: C, 71.29; H, 5.23; N, 7.28%.

***N*-[3-(Biphenyl-4-yl)-1-(4-methylphenyl)-3-oxopropyl]acetamide (3g).** Pale orange solid. Isolated Yield: 83%, mp: 138–140 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.76 (s, 3H), 2.22 (s, 3H), 3.35 (dd, 1H, J_1 = 6.1 Hz, J_2 = 16.8 Hz), 3.46 (m, 1H), 5.33 (m, 1H), 7.07 (d, 2H, J = 7.6 Hz), 7.21 (d, 2H, J = 7.6 Hz), 7.37 (m, 1H), 7.45 (t, 2H, J = 8.4 Hz), 7.69 (d, 2H, J = 6.9 Hz), 7.77 (d, 2H, J = 8.4 Hz), 7.99 (d, 2H, J = 8.4 Hz), 8.30 (d, 1H, J = 8.4 Hz, NH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 25.6 (q), 27.8 (q), 49.8 (t), 54.0 (d), 131.5 (d), 132.2 (d), 132.7 (d), 133.6 (d), 134.3 (d), 134.8 (d), 137.2 (d), 140.6 (s), 141.1 (s), 145.1 (s), 146.0 (s), 149.8 (s), 173.6 (s), 202.0 (s). IR (KBr, ν_{max}/cm^{-1}): 3284 (s), 3056 (w), 1649 (s), 1604 (s), 1560 (m), 994 (m), 768 (s). Mass (ESI): 737 (Dimer + Na ion). Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92; Found: C, 80.99; H, 6.46; N, 3.96%.

***N*-[3-(4-Methoxyphenyl)-1-(4-nitrophenyl)-3-oxopropyl]acetamide (3h).** Brown solid. Isolated Yield: 90%, mp: 84–86 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.79 (s, 3H), 3.32 (m, 1H), 3.51 (dd, 1H, J_1 = 8.4 Hz, J_2 = 17.6 Hz), 3.80 (s, 3H), 5.40 (m, 1H), 6.99 (d, 2H, J = 9.1 Hz), 7.58 (d, 2H, J = 8.4 Hz), 7.89 (d, 2H, J = 8.4 Hz), 8.13 (d, 2H, J = 8.4 Hz), 8.44 (d, 1H, J = 7.6 Hz, NH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 23.1 (q), 44.1 (t), 49.2 (d), 56.1 (q), 114.4 (d), 123.9 (d), 128.5 (d), 129.9 (d), 130.9 (s), 146.8 (s), 151.7 (s), 163.8 (s), 169.3 (s), 195.3 (s). IR (KBr, ν_{max}/cm^{-1}): 3280 (s), 3075 (w), 1675 (s), 1600 (s), 1518 (s), 1347 (s), 1259 (s), 833 (m). Mass (ESI): 343 (M+1 ion). Anal. Calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18; Found: C, 63.27; H, 5.35; N, 8.30%.

***N*-[3-(4-Bromophenyl)-1-(4-chlorophenyl)-3-oxopropyl]acetamide (3i).** White solid. Isolated Yield: 84%, mp: 124-126 °C (Lit.[24] 125–127 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.75 (s, 3H), 3.25 (m, 1H), 3.47 (dd, 1H, J_1 = 8.4 Hz, J_2 = 16.8 Hz), 5.25 (m, 1H), 7.33 (s, 4H), 7.69 (d, 2H, J = 8.4 Hz), 7.83 (d, 2H, J = 8.4 Hz), 8.30 (d, 1H, J = 7.6 Hz, NH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 23.0 (q), 49.5 (t), 53.8 (d), 131.5 (d), 132.6 (d), 133.2 (d), 133.7 (d), 134.1 (d), 134.2 (d), 135.0 (d), 135.8 (d), 140.5 (s), 141.2 (s), 141.4 (s), 144.8 (s), 174.7 (s), 201.5 (s). IR (KBr, ν_{max}/cm^{-1}): 3296 (s), 3067 (w), 2925 (w), 1683 (s), 1648 (s), 1584 (m), 1547 (m), 1369 (m), 997 (m), 831 (s). Mass (ESI): 381 (M+1 ion). Anal. Calcd for $C_{17}H_{15}NO_2BrCl$: C, 53.64; H, 3.97; N, 3.68; Found: C, 53.77; H, 4.01; N, 3.63%.

***N*-[1-(2-Hydroxyphenyl)-3-phenyl-3-oxopropyl]acetamide (3j).** Off white solid. Isolated Yield: 82%, mp: 126–128 °C (Lit.[15] 129–130 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.81 (s, 3H), 3.51 (d, 1H, J = 7.1 Hz), 3.81 (m, 1H), 5.70 (m, 1H), 7.40 (m, 3H), 7.63 (m, 2H), 7.86 (d, 2H, J = 6.9 Hz), 8.03 (d, 2H, J = 7.7 Hz), 8.26 (d, 1H, J = 7.1 Hz, NH, D_2O exchangeable), 10.01 (br s, 1H, OH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 27.1 (q), 42.8 (t), 48.8 (d), 120.7 (d), 122.3 (d), 126.9 (d), 127.9 (d), 128.3 (d), 130.2 (s), 134.2 (s), 135.9 (s), 173.2 (s), 198.2 (s). IR (KBr, ν_{max}/cm^{-1}): 3380 (s), 3072 (w), 2978 (w), 1691 (s), 1649 (s), 1600 (m), 1506 (m), 1453 (m), 1346 (s), 1295 (s), 857 (m), 685 (m). Mass (ESI): 284 (M+1 ion). Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94; Found: C, 72.36; H, 6.10; N, 4.91%.

***N*-[1-(2-Hydroxyphenyl)-3-(3-nitrophenyl)-3-oxopropyl]acetamide (3k).** Yellow solid. Isolated Yield: 78%, mp: 128–130 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.79 (s, 3H), 3.49 (dd, 1H, J_1 = 5.4 Hz, J_2 = 17.6 Hz), 3.59 (dd, 1H, J_1 = 8.4 Hz, J_2 = 17.6 Hz), 5.44 (m, 1H), 6.88 (m, 2H), 7.45 (t, 1H, J = 8.3 Hz), 7.57 (m, 1H), 7.78 (m, 2H), 8.06 (d, 1H, J = 6.2 Hz), 8.20 (s, 1H), 8.51 (d, 1H, J = 7.7 Hz, NH, D_2O exchangeable), 11.56 (brs, 1H, OH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 23.1 (q), 46.6 (t), 48.9 (d), 117.5 (d), 121.1 (d), 129.7 (d), 131.8 (d), 133.7 (d), 134.8 (d), 135.9 (d), 137.2 (d), 146.1 (s), 148.2 (s), 148.4 (s), 160.7 (s), 169.3 (s), 202.1 (s). IR (KBr, ν_{max}/cm^{-1}): 3274 (s), 3068 (w), 1645 (s), 1529 (s), 1351 (s), 757 (m). Mass (ESI): 329 (M+1 ion). Anal. Calcd for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53; Found: C, 62.35; H, 4.94; N, 8.59%.

N-[1-(4-Chlorophenyl)-3-phenyl-3-oxopropyl]acetamide (3l). White solid. Isolated Yield: 80%, mp: 145–147 °C (Lit.[24] 147–148 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ:1.75 (s, 3H), 3.35 (dd, 1H, J_1 = 6.1 Hz, J_2 = 16.8 Hz), 3.44 (dd, 1H, J_1 = 7.7 Hz, J_2 = 16.8 Hz), 5.27 (m, 1H), 7.26 (s, 4H), 7.43 (t, 2H, J = 7.6 Hz), 7.54 (t, 1H, J = 6.9 Hz), 7.84 (d, 2H, J = 7.7 Hz), 8.48 (d, 1H, J = 7.7 Hz, NH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 23.2 (q), 44.8 (t), 48.9 (d), 128.5 (d), 128.7 (d), 129.1 (d), 129.3 (d), 131.9 (d), 133.9 (s), 137.0 (s), 142.6 (s), 169.0 (s), 197.4 (s). IR (KBr, ν_{max}/cm^{-1}): 3288 (s), 3074 (w), 1771 (m), 1687 (s), 1648 (s), 1549 (s), 1362 (s), 1292 (s), 1091 (m), 752 (m). Mass (ESI): 302 (M+1 ion). Anal. Calcd for $C_{17}H_{16}NO_2Cl$: C, 67.66; H, 5.34; N, 4.64; Found: C, 67.82; H, 5.38; N, 4.59%.

***N*-[3-(4-Chlorophenyl)-1-(4-nitrophenyl)-3-oxopropyl]acetamide (3m).** Off white solid. Isolated Yield: 83%, mp: 124–126 °C (Lit. [24] 125–127 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ:1.78 (s, 3H), 3.43 (m, 1H), 3.57 (dd, 1H, J_1 = 8.4 Hz, J_2 = 17.6 Hz), 5.39 (m, 1H), 7.53 (d, 2H,

J = 9.2 Hz), 7.59 (d, 2H, *J* = 8.4 Hz), 7.91 (m, 2H), 8.13 (d, 2H, *J* = 8.4 Hz), 8.50 (d, 1H, *J* = 7.7 Hz, NH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 23.1 (q), 27.8 (t), 48.6 (d), 124.0 (d), 128.5 (d), 128.7 (d), 129.8 (d), 131.2 (s), 135.5 (s), 146.9 (s), 151.5 (s), 170.2 (s), 196.2 (s). IR (KBr, ν_{max}/cm^{-1}): 3261 (s), 1683 (s), 1642 (s), 1590 (m), 1520 (m), 1401 (m), 1374 (s), 1298 (m), 1094 (s), 995 (m), 819 (m). Mass (ESI): 347 (M+1 ion). Anal. Calcd for $C_{17}H_{15}N_2O_4Cl$: C, 58.88; H, 4.36; N, 8.08; Found: C, 59.04; H, 4.30; N, 8.12%.

***N*-[3-(4-Methoxyphenyl)-1-(3-nitrophenyl)-3-oxopropyl]acetamide (3n).** Off white solid. Isolated Yield: 89%, mp: 130–131 °C (Lit.[25] 132 °C). ^1H NMR (500 MHz, DMSO-d_6) δ:1.75 (s, 3H), 3.46 (dd, 1H, J_1 = 3.6 Hz, J_2 = 17.6 Hz), 3.57 (dd, 1H, J_1 = 8.4 Hz, J_2 = 17.6 Hz), 3.87 (s, 3H), 5.39 (m, 1H), 7.47 (d, 1H, *J* = 8.4 Hz), 7.67 (d, 2H, *J* = 8.4 Hz), 7.73 (m, 3H), 7.83 (d, 1H, *J* = 8.4 Hz), 8.16 (s, 1H), 8.65 (d, 1H, *J* = 8.4 Hz, NH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 23.1 (q), 42.4 (t), 46.3 (d), 56.7 (q), 114.2 (d), 121.2 (d), 121.8 (d), 132.6 (d), 133.4 (d), 134.7 (d), 135.4 (s), 141.8 (s), 144.7 (s), 166.3 (s), 169.8 (s), 197.9 (s). IR (KBr, ν_{max}/cm^{-1}): 3282 (s), 3063 (w), 2974 (w), 1712 (m), 1686 (s), 1648 (m), 1531 (s), 1348 (s), 1225 (m), 1198 (s), 996 (m), 732 (s). Mass (ESI): 343 (M+1 ion). Anal. Calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18; Found: C, 63.40; H, 5.36; N, 8.12%.

***N*-[3-(4-Methoxyphenyl)-1-(4-methylphenyl)-3-oxopropyl]acetamide (3o).** Off white solid. Isolated Yield: 87%, mp: 218–220 °C. ^1H NMR (500 MHz, DMSO-d_6) δ: 1.75 (s, 3H), 2.21 (s, 3H), 3.25 (dd, 1H, J_1 = 6.1 Hz, J_2 = 16.8 Hz), 3.38 (m, 1H), 3.79 (s, 3H), 5.30 (m, 1H), 6.98 (d, 2H, *J* = 9.2 Hz), 7.06 (d, 2H, *J* = 7.6 Hz), 7.18 (d, 2H, *J* = 7.6 Hz), 7.88 (d, 2H, *J* = 8.4 Hz), 8.27 (d, 1H, *J* = 7.6 Hz, NH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 20.5 (q), 22.6 (q), 44.2 (t), 48.8 (d), 55.5 (q), 113.8 (d), 126.5 (d), 128.7 (d), 129.5 (d), 130.3 (s), 135.8 (s), 139.9 (s), 163.1 (s), 168.2 (s), 195.5 (s). IR (KBr, ν_{max}/cm^{-1}): 3286 (s), 3074 (w), 2936 (w), 1679 (s), 1644 (s), 1602 (m), 1376 (m), 1228 (m), 1196 (s), 992 (m), 787 (s). Mass (ESI): 312 (M+1 ion). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50; Found: C, 73.45; H, 6.87; N, 4.46%.

***N*-[3-(4-Bromophenyl)-1-(3-bromo-4-fluorophenyl)-3-oxopropyl]acetamide (3p).** Off white solid. Isolated Yield: 85%, mp: 178–180 °C. ^1H NMR (500 MHz, DMSO-d_6) δ: 1.72 (s, 3H), 3.54 (m, 2H), 5.23 (m, 1H), 7.24 (m, 1H), 7.42 (s, 1H), 7.64 (d, 1H, *J* = 6.1 Hz), 7.67 (d, 2H, *J* = 8.4 Hz), 7.84 (d, 2H, *J* = 7.7 Hz), 8.51 (d, 1H, *J* = 7.7 Hz, NH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 23.4 (q), 46.3 (t), 48.8 (d), 111.4 (d), 118.8 (d), 126.3 (d), 132.3 (d), 132.6 (s), 133.0 (s), 137.1 (s), 140.1 (s), 162.6 (s), 170.1 (s), 198.6 (s). IR (KBr, ν_{max}/cm^{-1}): 3278 (s), 3109 (w), 1684 (s), 1643 (s), 1549 (m), 1406 (m), 1233 (s), 1045 (m), 816 (m), 603 (s). Mass (ESI): 442 (M+1 ion). Anal. Calcd for $C_{17}H_{14}NO_2Br_2F$: C, 46.08; H, 3.18; N, 3.16; Found: C, 46.32; H, 3.19; N, 3.18%.

***N*-[1-{4-[1-Acetylamino-3-(4-chlorophenyl)-3-oxopropyl]phenyl}-3-(4-chlorophenyl)-3-oxopropyl]acetamide (3q).** White solid. Isolated Yield: 75%, mp: 168–170 °C. ^1H NMR (500 MHz, DMSO-d_6) δ: 1.73 (s, 6H), 3.41 (m, 2H), 5.28 (s, 2H), 7.26 (s, 4H), 7.54 (s, 5H), 7.93 (s, 5H), 8.33 (br s, 2H, NH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 23.1 (q), 45.1 (t), 48.1 (d), 126.4 (d), 127.7 (d), 128.7 (d), 129.7 (d), 130.0 (d), 131.1 (d), 135.7 (s), 138.7 (s),

142.0 (s), 168.9 (s), 196.8 (s). IR (KBr, ν_{max}/cm^{-1}): 3270 (s), 3068 (m), 1650 (s), 1588 (m), 1401 (m), 1371 (s), 1092 (s), 994 (m), 824 (m). Mass (ESI): 547 (M+Na ion). Anal. Calcd for $C_{28}H_{26}N_2O_4Cl_2$: C, 64.01; H, 4.99; N, 5.33; Found: C, 64.25; H, 5.03; N, 5.38%.

***N*-[3-(4-Bromophenyl)-1-(2-chloroquinolin-3-yl)-3-oxopropyl]acetamide (3r).** Reddish brown solid. Isolated Yield: 88%, mp: 238–240 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.82 (s, 3H), 3.25 (dd, 1H, J_1 = 9.1 Hz, J_2 = 16.8 Hz), 3.46 (dd, 1H, J_1 = 3.8 Hz, J_2 = 16.8 Hz), 5.40 (m, 1H), 7.13 (t, 1H, J = 6.9 Hz), 7.28 (d, 1H, J = 7.6 Hz), 7.42 (t, 1H, J = 7.6 Hz), 7.63 (d, 1H, J = 7.6 Hz), 7.68 (d, 2H, J = 8.4 Hz), 7.76 (s, 1H), 7.91 (d, 2H, J = 8.4 Hz), 8.24 (d, 1H, J = 7.6 Hz, NH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 27.9 (q), 47.4 (t), 50.6 (d), 120.1 (d), 124.2 (d), 127.1 (d), 132.5 (d), 135.1 (d), 136.9 (s), 138.7 (s), 140.1 (s), 143.1 (s), 166.4 (s), 173.9 (s), 201.7 (s). IR (KBr, ν_{max}/cm^{-1}): 3279 (s), 3070 (w), 2848 (w), 1659 (s), 1570 (m), 996 (m), 752 (m). Mass (ESI): 432 (M+1 ion). Anal. Calcd for $C_{20}H_{16}N_2O_2BrCl$: C, 55.64; H, 3.74; N, 6.49; Found: C, 55.79; H, 3.78; N, 6.42%.

***N*-[1-(2-Chloro-6-fluorophenyl)-3-(thiophen-2-yl)-3-oxopropyl]acetamide (3s).** Pale yellow solid. Isolated Yield: 90%, mp: 64–66 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.75 (s, 3H), 3.29 (dd, 1H, J_1 = 6.1 Hz, J_2 = 16.8 Hz), 3.67 (dd, 1H, J_1 = 9.2 Hz, J_2 = 16.8 Hz), 5.82 (m, 1H), 7.12 (t, 1H, J = 7.7 Hz), 7.18 (m, 3H), 7.91 (d, 1H, J = 3.9 Hz), 7.94 (d, 1H, J = 3.9 Hz), 8.39 (d, 1H, J = 6.8 Hz, NH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 22.3 (q), 54.8 (t), 67.8 (d), 114.8 (d), 124.7 (d), 126.6 (d), 127.3 (d), 128.6 (d), 129.5 (d), 133.5 (s), 134.9 (s), 143.3 (s), 159.7 (s), 168.6 (s), 189.3 (s). IR (KBr, ν_{max}/cm^{-1}): 3278 (s), 3076 (w), 2953 (w), 1693 (s), 1653 (s), 1526 (m), 1378 (m), 1293 (m), 1076 (m), 993 (m), 734 (m), 714 (m). Mass (ESI): 326 (M+1 ion). Anal. Calcd for $C_{15}H_{13}NO_2SClF$: C, 55.30; H, 4.02; N, 4.30; Found: C, 55.58; H, 4.08; N, 4.39%.

***N*-[1-(3-Nitrophenyl)-3-phenyl-3-oxopropyl]-2-phenylacetamide (3t).** White solid. Isolated Yield: 90%, mp: 126–128 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.40 (m, 2H), 3.46 (dd, 1H, J_1 = 5.4 Hz, J_2 = 17.6 Hz), 3.64 (dd, 1H, J_1 = 8.4 Hz, J_2 = 17.5 Hz), 5.45 (m, 1H), 7.14 (m, 5H), 7.48 (t, 2H, J = 7.7 Hz), 7.55 (t, 1H, J = 8.4 Hz), 7.59 (t, 1H, J = 6.9 Hz), 7.78 (d, 1H, J = 8.4 Hz), 7.93 (d, 2H, J = 7.7 Hz), 8.04 (d, 1H, J = 8.4 Hz), 8.19 (s, 1H), 8.73 (d, 1H, J = 6.9 Hz, NH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 47.5 (t), 49.3 (d), 53.9 (d), 126.4 (d), 127.1 (d), 131.5 (d), 133.2 (d), 133.9 (d), 135.0 (d), 138.6 (d), 138.8 (d), 141.3 (s), 141.6 (s), 150.6 (s), 153.0 (s), 174.9 (s), 201.9 (s). IR (KBr, ν_{max}/cm^{-1}): 3308 (s), 3063 (w), 1682 (s), 1649 (s), 1524 (s), 1350 (s), 998 (m), 694 (s). Mass (ESI): 389 (M+1 ion). Anal. Calcd for $C_{23}H_{20}N_2O_4$: C, 71.12; H, 5.19; N, 7.21; Found: C, 71.36; H, 5.23; N, 7.25%.

***N*-[3-(4-Chlorophenyl)-1-(4-nitrophenyl)-3-oxopropyl]-2-phenylacetamide (3u).** Off white solid. Isolated Yield: 88%, mp: 218–220 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.45 (m, 3H), 3.63 (dd, 1H, J_1 = 8.4 Hz, J_2 = 16.8 Hz), 5.40 (m, 1H), 7.14 (m, 4H), 7.53 (d, 2H, J = 8.4 Hz), 7.59 (d, 2H, J = 9.2 Hz), 7.91 (t, 3H, J = 8.4 Hz), 8.12 (d, 2H, J = 8.4 Hz), 8.80 (d, 1H, J = 7.7 Hz, NH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 47.7 (t), 49.3 (t), 53.6 (d), 126.5 (d), 127.1 (d), 133.9 (d), 135.0 (d), 139.0 (d), 140.3 (s), 143.5 (s), 150.6 (s), 153.0 (s), 174.0 (s), 200.1 (s). IR (KBr, ν_{max}/cm^{-1}): 3264 (s), 3082 (w), 1685 (s), 1635 (s), 1590 (s), 1348

(s), 1094 (s), 995 (m), 819 (m), 699 (s). Mass (ESI): 423 (M+1 ion). Anal. Calcd for $C_{23}H_{19}N_2O_4Cl$: C, 65.33; H, 4.53; N, 6.62; Found: C, 65.51; H, 4.58; N, 6.68%.

***N*-[3-(4-Bromophenyl)-1-(4-chlorophenyl)-3-oxopropyl]-2-phenylacetamide (3v).** Pale yellow solid. Isolated Yield: 89%, mp: 154–156 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.63 (m, 3H), 3.52 (dd, 1H, J_1 = 8.4 Hz, J_2 = 16.9 Hz), 5.30 (m, 1H), 7.13 (m, 5H), 7.47 (d, 1H, J = 8.4 Hz), 7.67 (d, 2H, J = 8.4 Hz), 7.73 (m, 1H), 7.83 (m, 3H), 8.05 (d, 1H, J = 8.4 Hz), 8.65 (d, 1H, J = 8.4 Hz, NH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 47.5 (t), 49.5 (t), 53.8 (d), 131.5 (d), 132.6 (d), 133.2 (d), 133.7 (d), 134.1 (d), 134.2 (d), 135.0 (d), 135.8 (d), 140.5 (s), 141.2 (s), 141.4 (s), 144.8 (s), 174.7 (s), 201.5 (s). IR (KBr, ν_{max}/cm^{-1}): 3325 (s), 1646 (s), 1586 (m), 1528 (m), 1330 (m), 1009 (s), 817 (m), 730 (s). Mass (ESI): 456 (M+1 ion). Anal. Calcd for $C_{23}H_{19}NO_2BrCl$: C, 60.48; H, 4.19; N, 3.07; Found: C, 60.61; H, 4.22; N, 3.11%.

***N*-[3-(4-Chlorophenyl)-1-(3-nitrophenyl)-3-oxopropyl]-2-phenylacetamide (3w).** White solid. Isolated Yield: 86%, mp: 138–142 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.46 (s, 2H), 3.62 (dd, 1H, J_1 = 9.2 Hz, J_2 = 17.6 Hz), 3.96 (m, 1H), 5.43 (m, 1H), 7.13 (m, 5H), 7.47 (d, 1H, J = 8.4 Hz), 7.67 (d, 2H, J = 8.4 Hz), 7.73 (m, 1H), 7.83 (m, 3H), 8.16 (s, 1H), 8.65 (d, 1H, J = 8.4 Hz, NH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 47.5 (t), 49.2 (t), 53.8 (d), 131.3 (d), 132.9 (d), 133.2 (d), 133.9 (d), 134.1 (d), 134.2 (d), 135.0 (d), 135.8 (d), 140.5 (s), 141.2 (s), 141.5 (s), 144.8 (s), 173.2 (s), 202.9 (s). IR (KBr, ν_{max}/cm^{-1}): 3283 (s), 3085 (w), 2925 (w), 1739 (s), 1669 (s), 1609 (m), 1524 (m), 1353 (m), 1217 (m), 1090 (s), 980 (m), 804 (m), 741 (m). Mass (ESI): 423 (M+1 ion). Anal. Calcd for $C_{23}H_{19}N_2O_4Cl$: C, 65.33; H, 4.53; N, 6.62; Found: C, 65.49; H, 4.58; N, 6.69%.

***N*-(2-Methyl-1-phenyl-3-oxobutyl)acetamide (5a).** Off white solid. Isolated Yield: 88%, mp: 124–127 °C (Lit.[15] 126–127 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.18 (d, 3H, J = 6.9 Hz), 1.81 (s, 3H), 1.96 (s, 3H), 3.10 (dd, 1H, J_1 = 6.9 Hz, J_2 = 14.8 Hz), 5.17 (m, 1H), 7.13 (d, 1H, J = 7.7 Hz), 7.42 (m, 4H), 8.16 (d, 1H, J = 7.7 Hz, NH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 16.1 (q), 23.2 (q), 30.1 (q), 51.0 (d), 55.3 (d), 126.4 (d), 127.8 (d), 128.3 (d), 141.8 (s), 169.3 (s), 213.4 (s). IR (KBr, ν_{max}/cm^{-1}): 3296 (s), 3045 (w), 2966 (w), 1712 (s), 1654 (s), 1553 (m), 1386 (m), 1307 (m), 1129 (s), 758 (m), 706 (m). Mass (ESI): 220 (M+1 ion). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39; Found: C, 71.47; H, 7.89; N, 6.42%.

***N*-[2-Methyl-1-(4-methylphenyl)-3-oxobutyl]acetamide (5b).** White solid. Isolated Yield: 88%, mp: 132–133 °C (Lit.[15] 133–134 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.16 (d, 3H, J = 6.9 Hz), 1.76 (s, 3H), 1.93 (s, 3H), 2.41 (s, 3H), 3.10 (dd, 1H, J_1 = 6.9 Hz, J_2 = 14.1 Hz), 5.13 (m, 1H), 6.96 (d, 2H, J = 7.7 Hz), 7.08 (d, 2H, J = 7.7 Hz), 8.13 (d, 1H, J = 6.9 Hz, NH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 15.2 (q), 21.6 (q), 23.4 (q), 30.1 (q), 51.6 (d), 55.4 (d), 126.7 (d), 126.9 (d), 130.1 (d), 137.1 (s), 138.0 (s), 169.9 (s), 187.0 (s). IR (KBr, ν_{max}/cm^{-1}): 3297 (s), 3076 (w), 2933 (w), 1707 (s), 1654 (s), 1552 (m), 1450 (m), 1427 (m), 1386 (m), 1308 (m), 1135 (s), 735 (s). Mass (ESI): 234 (M+1 ion). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00; Found: C, 72.36; H, 8.17; N, 5.95%.

***N*-[(2-Oxocyclohexyl)-phenyl-methyl]acetamide (5c).** Pale brown solid. Isolated Yield: 92%, mp: 218–221 °C (Lit.[15] 221–222 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.79 (s, 3H), 2.24 (m,

4H), 2.46 (d, 2H, *J* = 5.4 Hz), 2.54 (m, 2H), 2.93 (m, 1H), 5.68 (m, 1H), 6.30 (m, 1H), 7.43 (m, 4H), 8.48 (d, 1H, *J* = 8.4 Hz, NH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 19.6 (q), 26.4 (t), 42.1 (t), 47.9 (d), 59.6 (d), 126.1 (d), 128.6 (d), 141.1 (s), 168.6 (s), 211.4 (s). IR (KBr, ν_{max}/cm^{-1}): 3272 (s), 3036 (w), 2948 (w), 1698 (s), 1646 (s), 1551 (m), 1367 (m), 1222 (s), 698 (m). Mass (ESI): 246 (M+1 ion). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71; Found: C, 73.69; H, 7.76; N, 5.73%.

***N*-[(2-Nitrophenyl)-(2-oxocyclohexyl)-methyl]acetamide (5d).** Pale yellow solid. Isolated Yield: 90%, mp: 138–140 °C (Lit.[15] 139–140 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.73 (s, 3H), 2. 53 (m, 8H), 3.63 (dd, 1H, J_1 = 5.9 Hz, J_2 = 14.0 Hz), 5.63 (m, 1H), 7.61 (d, 1H, *J* = 7.7 Hz), 7.83 (m, 3H), 8.16 (d, 1H, *J* = 7.7 Hz, NH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 19.9 (q), 26.2 (t), 41.9 (t), 48.1 (d), 60.1 (d), 126.2 (d), 128.9 (d), 133.1 (d), 134.6 (s), 162.3 (s), 168.4 (s), 211.7 (s). IR (KBr, ν_{max}/cm^{-1}): 3421 (s), 2932 (w), 1671 (s), 1606 (m), 1580 (m), 1520 (m), 1340 (m), 1271 (m), 1121 (s), 971 (m), 734 (s). Mass (ESI): 291 (M+1 ion). Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.25; N, 9.65; Found: C, 62.32; H, 6.29; N, 9.59%.

***N*-[2-Acetyl-1-(3-nitrophenyl)-3-oxobutyl]acetamide (5e).** Off white solid. Isolated Yield: 94%, mp: 158–160 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.75 (s, 3H), 1.98 (s, 3H), 2.20 (s, 3H), 4.61 (d, 1H, *J* = 10.7Hz), 5.56 (t, 1H, *J* = 9.9Hz), 7.55 (t, 1H, *J* = 8.4Hz), 7.73 (d, 1H, *J* = 7.6Hz), 8.05 (d, 1H, *J* = 7.6Hz), 8.19 (s, 1H), 8.55 (d, 1H, *J* = 8.4Hz, NH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 23.0 (q), 30.7 (q), 31.1 (q), 51.6 (d), 71.5 (d), 122.5 (d), 122.9 (d), 130.0 (d), 134.8 (d), 143.4 (s), 148.3 (s), 169.4 (s), 202.0 (s), 202.1 (s). IR (KBr, ν_{max}/cm^{-1}): 3349 (s), 3067 (w), 2988 (w), 1715 (s), 1651 (s), 1532 (s), 1350 (s), 1289 (m), 1234 (m), 1107 (s) 699 (m), 600 (m). Mass (ESI): 293 (M+1 ion). Anal. Calcd for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.52; N, 9.58; Found: C, 57.74; H, 5.55; N, 9.61%.

***N*-[(3-Bromo-4-fluorophenyl)-(4,4-dimethyl-2,6-dioxocyclohexyl)-methyl]acetamide (5f).** Off white solid. Isolated Yield: 95%, mp: 166–168 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ:0.92 (s, 6H), 1.88 (s, 3H), 2.23 (br s, 4H), 3.52 (d, 1H, *J* = 6.1 Hz), 6.18 (d, 1H, *J* = 8.4 Hz), 7.14 (s, 1H), 7.18 (d, 1H, *J* = 8.4 Hz), 7.38 (d, 1H, *J* = 6.1 Hz), 7.96 (d, 1H, *J* = 9.2 Hz, NH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 15.3 (q), 18.3 (q), 26.2 (s), 42.3 (t), 51.3 (d), 72.6 (d), 108.1 (d), 116.3 (d), 124.6 (d), 133.1 (s), 143.6 (s), 165.9 (s), 170.2 (s), 208.2 (s). IR (KBr, ν_{max}/cm^{-1}): 3372 (s), 2957 (w), 2876 (w), 1692 (s), 1650 (s), 1602 (m), 1537 (m), 1382 (m), 1251 (m), 1199 (s), 890 (m), 680 (m), 594 (m). Mass (ESI): 384 (M+1 ion). Anal. Calcd for $C_{17}H_{19}NO_3BrF$: C, 53.14; H, 4.98; N, 3.65; Found: C, 53.32; H, 5.01; N, 3.60%.

***N*-[(2,4-Dichlorophenyl)-(4,4-dimethyl-2,6-dioxocyclohexyl)-methyl]acetamide (5g).** Off white solid. Isolated Yield: 94%, mp: 156–158 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.93 (s, 6H), 1.84 (s, 3H), 2.16 (br s, 2H), 3.34 (br s, 3H), 6.10 (d, 1H, *J* = 7.6Hz), 7.27 (d, 1H, *J* = 8.4Hz), 7.36 (s, 1H), 7.46 (d, 1H, *J* = 8.4Hz), 8.00 (d, 1H, *J* = 7.6Hz, NH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 15.3 (q), 18.3 (q), 22.9, 27.9, 31.9, 44.6, 45.7, 125.7 (d), 127.1 (d), 129.2 (d), 131.3 (s), 132.2 (s), 140.3 (s), 169.1 (s), 208.3 (s). IR (KBr, ν_{max}/cm^{-1}): 3380 (s), 2952 (w), 1631 (s), 1509 (m), 1380 (m), 1078 (m), 860 (m). Mass (ESI): 356 (M+1 ion). Anal. Calcd for $C_{17}H_{19}NO_3Cl_2$: C, 57.32; H, 5.38; N, 3.93; Found: C, 57.39; H, 5.41; N, 3.98%.

***N*-[(4,4-Dimethyl-2,6-dioxocyclohexyl)-(4-methylphenyl)-methyl]-phenylacetamide (5h).** White solid. Isolated Yield: 96%, mp: 137–140 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.88 (s, 6H), 2.14 (s, 3H), 2.20 (br s, 4H), 3.51 (br s, 2H), 4.20 (m, 1H), 6.16 (d, 1H, *J* = 9.2 Hz), 6.96 (br s, 4H), 7.18 (m, 5H), 7.96 (d, 1H, *J* = 9.2 Hz, NH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 21.1 (q), 28.3 (t), 32.3 (t), 43.1 (d), 45.6 (d), 46.7 (d), 114.3 (d), 125.4 (d), 126.8 (d), 128.2 (d), 129.4 (d), 130.3 (d), 135.4 (s), 136.1 (s), 140.3 (s), 169.9 (s), 208.4 (s). IR (KBr, ν_{max}/cm^{-1}): 3363 (s), 2958 (w), 1726 (s), 1617 (s), 1515 (m), 1381 (m), 1260 (m), 1197 (s), 1072 (m), 701 (m), 593 (m). Mass (ESI): 378 (M+1 ion). Anal. Calcd for $C_{24}H_{27}NO_3$: C, 76.36; H, 7.21; N, 3.71; Found: C, 76.60; H, 7.28; N, 3.68%.

***2*-(Acetylamino-phenyl-methyl)-3-oxobutyric acid methyl ester (7a).** White solid. Isolated Yield: 87%, mp: 128–130 °C (Lit.[11] 129–131 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.86 (s, 3H), 2.32 (s, 3H), 3.93 (s, 3H), 4.13 (dd, 1H, J_1 = 6.1 Hz, J_2 = 14.0 Hz), 5.37 (m, 1H), 7.37 (m, 5H), 8.31 (d, 1H, *J* = 8.4 Hz, NH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 22.6 (q), 30.1 (q), 51.6 (d), 63.5 (d), 65.2 (t), 126.7 (d), 126.9 (d), 128.6 (d), 137.1 (s), 166.2 (s), 169.9 (s), 191.3 (s). IR (KBr, ν_{max}/cm^{-1}): 3300 (s), 3078 (w), 2963 (w), 1718 (s), 1682 (s), 1644 (s), 1095 (s), 736 (s). Mass (ESI): 264 (M+1 ion). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32; Found: C, 63.71; H, 6.56; N, 5.34%.

2-[Acetylamino-(4-chlorophenyl)-methyl]-3-oxobutyric acid methyl ester (7b). Off white solid. Isolated Yield: 86%, mp: 130–132 °C (Lit.[11] 130–132 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.70 (s, 3H), 2.20 (s, 3H), 3.41 (s, 3H), 4.07 (d, 1H, J_1 = 11.5 Hz), 5.39 (t, 1H, *J* = 9.2 Hz), 7.31 (m, 4H), 8.43 (d, 1H, *J* = 8.4 Hz, NH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 23.1 (q), 30.3 (q), 53.5 (d), 63.8 (d), 64.5 (q), 128.6 (d), 129.9 (d), 132.6 (s), 139.7 (s), 167.7 (s), 169.1 (s), 201.4 (s). IR (KBr, ν_{max}/cm^{-1}): 3326 (s), 2959 (w), 1719 (s), 1652 (s), 1539 (m), 1370 (m), 1284 (m), 1227 (m), 1163 (s), 1092 (m), 842 (m), 593 (m). Mass (ESI): 298 (M+1 ion). Anal. Calcd for $C_{14}H_{16}NO_4Cl$: C, 56.48; H, 5.42; N, 4.70; Found: C, 56.63; H, 5.45; N, 4.73%.

2-[Acetylamino-(3-nitrophenyl)-methyl]-3-oxobutyric acid isopropyl ester (7c). Off white solid. Isolated Yield: 90%, mp: 118–120 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.81 (d, 3H, *J* = 6.9 Hz), 0.95 (d, 3H, *J* = 6.1 Hz), 1.74 (s, 3H), 2.20 (s, 3H), 4.14 (d, 1H, *J* = 11.5 Hz), 4.62 (hep, 1H, *J* = 6.1 Hz), 5.45 (t, 1H, *J* = 9.2 Hz), 7.55 (m, 1H), 7.73 (d, 1H, *J* = 7.6 Hz), 8.09 (d, 1H, *J* = 7.7 Hz), 8.16 (s, 1H), 8.56 (d, 1H, *J* = 8.4 Hz, NH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 21.2 (q), 22.9 (q), 29.9 (q), 50.7 (d), 64.4 (d), 69.4 (d), 122.6 (d), 123.1 (d), 130.3 (d), 143.2 (s), 148.2 (s), 166.1 (s), 166.8 (s), 169.2 (s), 200.6 (s). IR (KBr, ν_{max}/cm^{-1}): 3286 (s), 3065 (m), 1725 (s), 1652 (s), 1519 (s), 1360 (s), 1275 (m), 1175 (s), 1143 (m), 810 (m), 740 (s), 701 (m). Mass (ESI): 337 (M+1 ion). Anal. Calcd for $C_{16}H_{20}N_2O_6$: C, 57.14; H, 5.99; N, 8.33; Found: C, 57.35; H, 6.04; N, 8.39%.

2-[Acetylamino-(2,4-dichlorophenyl)-methyl]-3-oxohexanoic acid ethyl ester (7d). Yellow solid. Isolated Yield: 87%, mp: 212–214 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.60 (t, 3H, *J* = 7.7 Hz), 1.08 (t, 3H, *J* = 6.9 Hz), 1.26 (m, 1H), 1.42 (m, 1H), 1.70 (s, 2H), 1.75 (s, 3H), 3.80 (m, 2H), 4.20 (dd, 1H, J_1 = 10.7 Hz, J_2 = 26.0 Hz), 5.78 (t, 1H, *J* = 8.4 Hz), 7.39 (m, 3H), 8.35 (d,

1H, *J* = 8.4 Hz, NH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 18.2 (q), 18.4 (q), 21.4 (t), 27.6 (q), 48.9 (t), 53.1 (d), 66.3 (d), 67.2 (t), 132.6 (d), 134.03 (d), 135.8 (d), 137.9 (s), 138.8 (s), 142.2 (s), 171.3 (s), 172.1 (s), 207.5 (s). IR (KBr, ν_{max}/cm^{-1}): 3299 (s), 2965 (w), 1743 (s), 1654 (s), 1535 (m), 1373 (m), 1301 (m), 1178 (s), 1099 (m), 830 (m). Mass (ESI): 374 (M+1 ion). Anal. Calcd for $C_{17}H_{21}NO_4Cl_2$: C, 54.56; H, 5.66; N, 3.74; Found: C, 54.67; H, 5.70; N, 3.69%.

2-[Acetylamino-(3-nitrophenyl)-methyl]-3-oxobutyric acid ethyl ester (7e). White solid. Isolated Yield: 92%, mp: 106–108 °C. ^1H NMR (500 MHz, DMSO-d_6) δ: 0.87 (t, 3H, *J* = 6.9 Hz), 1.74 (s, 3H), 2.24 (s, 3H), 3.84 (q, 2H, *J* = 6.9 Hz), 4.18 (d, 1H, *J* = 11.5 Hz), 5.47 (t, 1H, *J* = 10.3 Hz)), 7.56 (m, 3H), 8.18 (s, 1H), 8.56 (d, 1H, *J* = 8.4 Hz, NH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 18.8 (q), 21.3 (q), 22.4 (q), 54.6 (d), 59.8 (d), 66.4 (t), 121.6 (d), 122.1 (d), 129.6 (d), 134.6 (d), 144.8 (s), 148.6 (s), 170.6 (s), 172.6 (s), 202.4 (s). IR (KBr, ν_{max}/cm^{-1}): 3314 (s), 3064 (w), 1733 (s), 1647 (s), 1536 (s), 1353 (s), 1300 (m), 1150 (s), 1112 (m), 737 (s), 692 (m). Mass (ESI): 323 (M+1 ion). Anal. Calcd for $C_{15}H_{18}N_2O_6$: C, 55.90; H, 5.63; N, 8.69; Found: C, 56.08; H, 5.69; N, 8.78%.

2-[Acetylamino-(3-nitrophenyl)-methyl]malonic acid diethyl ester (7f). Off white solid. Isolated Yield: 94%, mp: 76–80 °C. ^1H NMR (500 MHz, DMSO-d_6) δ: 0.88 (t, 3H, *J* = 6.9 Hz), 1.10 (t, 3H, *J* = 6.9 Hz), 1.77 (s, 3H), 3.86 (q, 2H, *J* = 6.9 Hz), 4.02 (d, 1H, *J* = 10.7 Hz), 4.08 (m, 2H), 5.49 (t, 1H, *J* = 10.0 Hz), 7.59 (t, 1H, *J* = 8.4 Hz), 7.76 (d, 1H, *J* = 7.7 Hz), 8.09 (d, 1H, *J* = 8.4 Hz), 8.20 (s, 1H), 8.62 (d, 1H, *J* = 8.4 Hz, NH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 14.0 (q), 14.3 (q), 23.5 (q), 51.8 (d), 57.0 (d), 61.8 (t), 61.9 (t), 121.2 (d), 123.5 (d), 130.5 (d), 134.9 (d), 142.7 (s), 148.3 (s), 166.5 (s), 166.7 (s), 169.1 (s). IR (KBr, ν_{max}/cm^{-1}): 3313 (s), 3072 (w), 2991 (w), 1722 (s), 1644 (s), 1528 (s), 1353 (s), 1179 (s), 1036 (m), 692 (m). Mass (ESI): 353 (M+1 ion). Anal. Calcd for $C_{16}H_{20}N_2O_7$: C, 54.54; H, 5.72; N, 7.95; Found: C, 54.68; H, 5.76; N, 7.89%.

Acknowledgements

One of the authors N.P.S. thanks the Council of Scientific and Industrial Research, New Delhi, India for the research fellowship.

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