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An efficient protocol for the synthesis of N-fused 2,5-diketopiperazine via base catalyzed Ugi-type MCR

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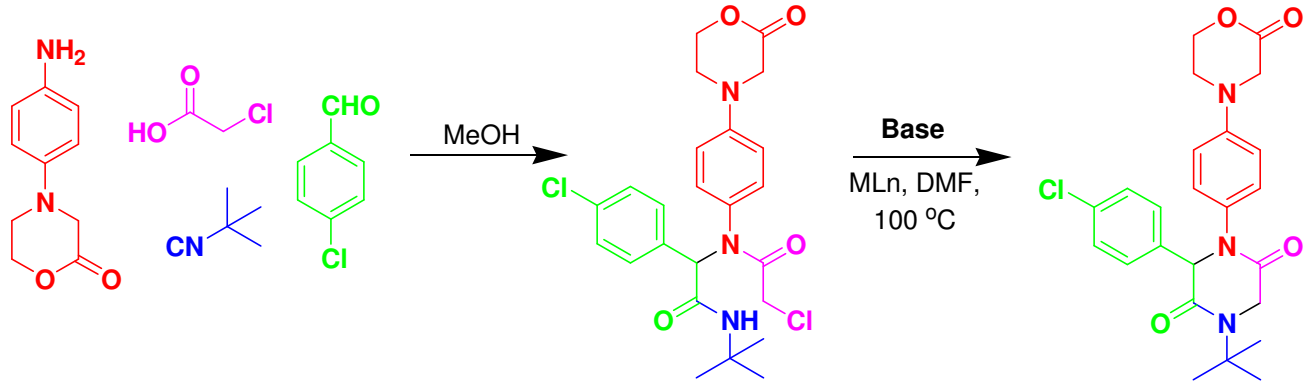
Abstract

Numerous diversity-oriented synthesis of N-fused cyclic heterocycles have been demonstrated but most of them are based on point diversity within the same library and usually include slow sequential multistep synthesis, which also hurt from low yields and/or poor originator scopes. In current context, an efficient synthesis has been developed with the use of potassium carbonate as base under catalytically free reaction conditions.



1b 2b

Keywords: Post-Ugi, four-component condensation, Cyclization, 2, 5-diketopiperazine, Ugi-Type MCR

Introduction

Multicomponent reactions (MCRs) constitute a potent synthetic tool due to their ability to build up high levels of molecular diversity in a single step- and atom-economic manner.[1-4] Since the first report by Ugi et al. in 1959[5] this reaction has been considered as one of the most versatile and robust MCRs. Ugi type reaction is not only used for biological screening in medicinal chemistry but also used for synthesis of drug molecule or drug intermediate as well.[6] The post functionalization of MCR[7-11] adducts has received considerable attention in recent years. Because of its combination with various post-transformations, typically cyclization, provides a fast and efficient entry to libraries of diverse heterocyclic scaffolds.[12]

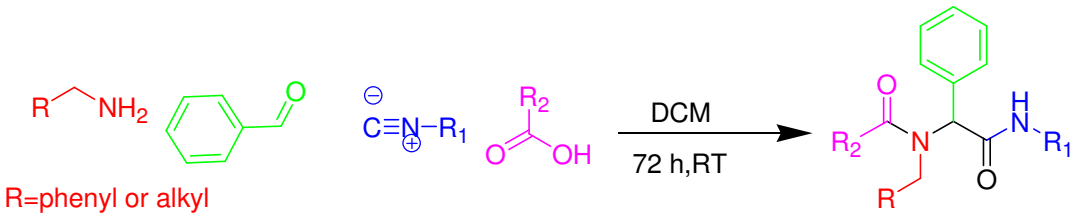


Figure 1. Typical Ugi Reaction with aromatic amine.

Isocyanide-based MCR followed by other synthetic transformations emerged as a powerful tool for creating fused multicyclic skeletons. As a part of our strategy to discover novel heterocycles by the skeletal diversity of N-rich cyclic compounds, we report our approach toward the development of efficient reaction conditions with the use of diverse N-fused cyclic heterocycles through an Ugi-type MCR.[13]

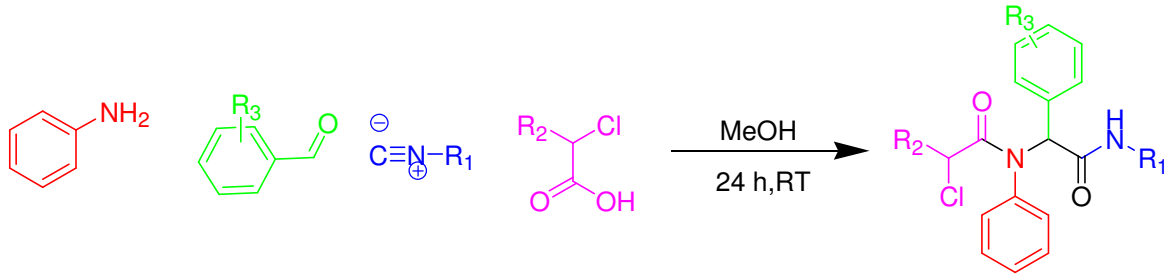


Figure 2. Our work with aromatic amine.

We are interested to synthesized 2,5-diketopiperazines via Post Ugi-MCR. 2,5-diketopiperazines represent privileged moieties in medicinal chemistry and are ubiquitous substructures in pharmaceuticals.[14] For example, Tadalafil (Figure 3) is potent for pulmonary arterial hypertension.[15] Retosiban & Epelsiban are oral drugs which act as an oxytocin receptor antagonist used for the treatment of preterm labour.[16, 17] Aplaviroc is a CCR5 entry inhibitor used for the treatment of HIV infection. Plinabulin (NPI-2358/KPU-2) 348 is a potent antitumor agent that is active in multidrug-resistant (MDR) tumor cell lines. Because of its biological importance, 2,5-Diketopiperazine has attracted much attention to its syntheses. However, despite much effort to its preparation, efficient methods for the synthesis of 2, 5-diketopiperazine remain to be developed.[18] We report herein a novel way to construct 2,5-diketopiperazine by using the Ugi MCR and based promoted post Ugi arylation/cyclization as key synthetic steps.

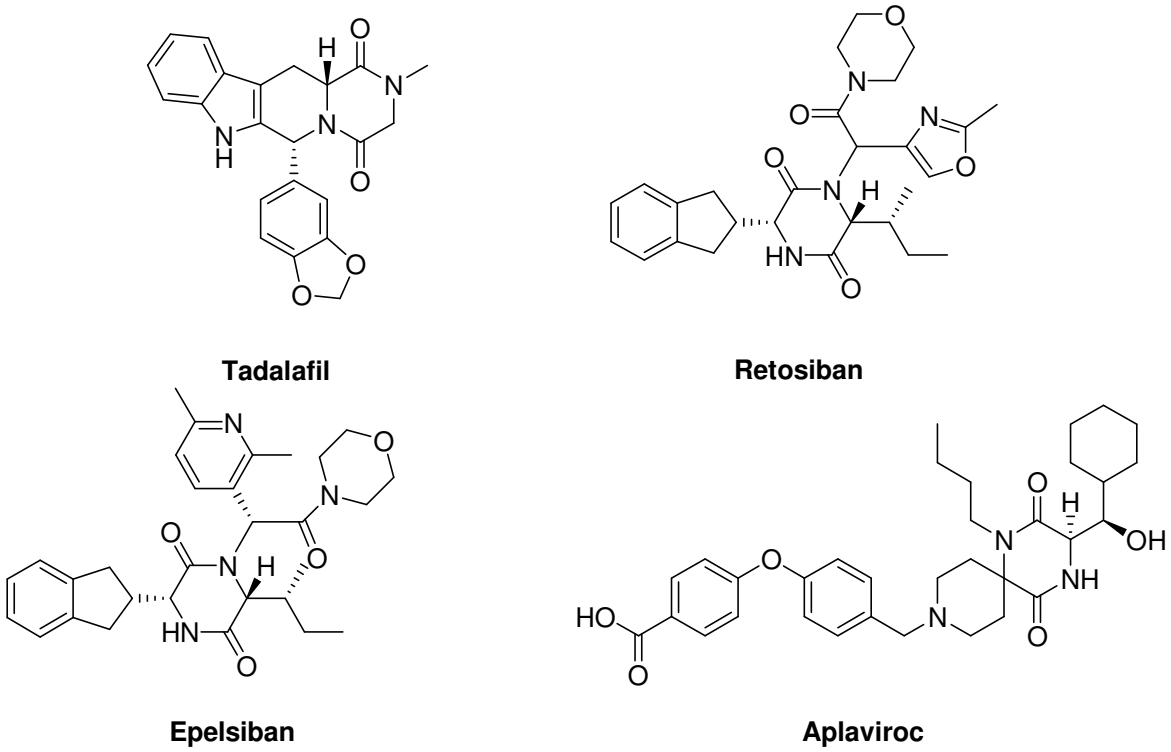
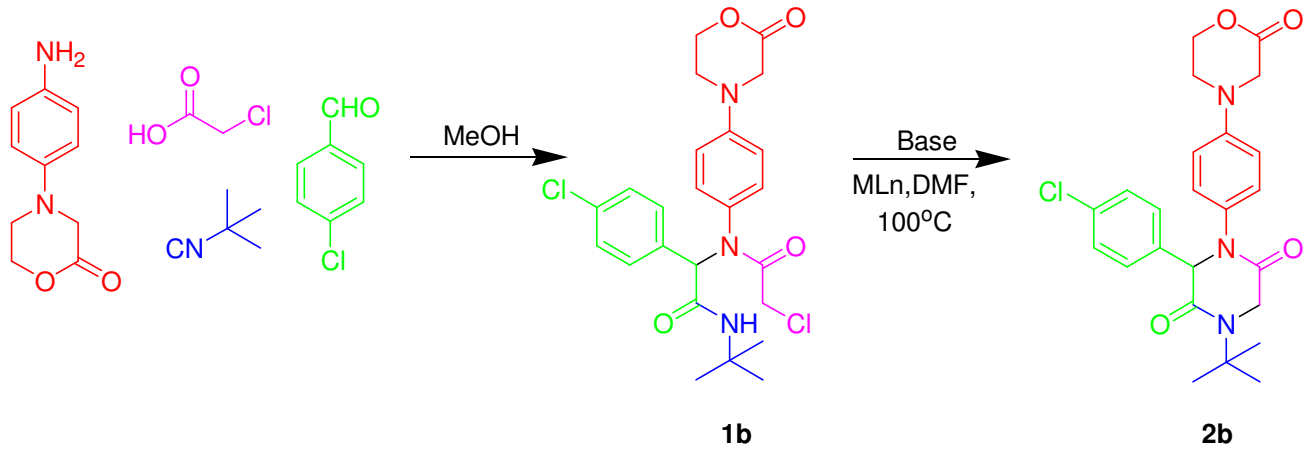


Figure 3. Biological active compound with 2, 5-diketopiperazine.

Results and Discussion

Initially, the syntheses of Ugi MCR product **1a–f** were achieved by the condensation of aromatic 4-(4-aminophenyl) morpholin-3-one, aldehydes, chloroacetic acid and isocyanides under catalytically free reaction condition in methanol.

A small library of N-fused 2,5-dikitopiperazine have been synthesized with the use of optimized reaction conditions. In order to develop a better reaction conditions, a set of experiments were carried out by varying base, catalyst and solvent with the use of **1b** as the model substrate for intramolecular cyclization reaction (Scheme 1).



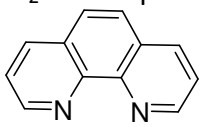
Scheme 1

CuI and $Pd(OAc)_2$ with ligand tested as shown in Table 1 but both catalyst led to a poor yield of **2b** and tedious work up procedure (entries 1-5). However, under catalytically free condition with the use of base was found more effective (table 1, entry 6) for this reaction. Subsequently, the effect of base was further investigated; K_2CO_3 was found as the most efficient base to push the reaction forward among the several bases used (Table 2). The effect of solvent was also investigated, and DMF was found to be the best solvent at 100^{o}C (Table 3). Further, the optimized conditions equally applied for the synthesis of a wide variety of N-fused cyclic heterocycles **2a–f** starting from IMCRs **1a–f** (Table 4).Excellent yields were observed for IMCRs **1a–f** (Table 4).

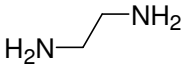
Table 1. Survey of the Reaction Condition for Post Ugi cyclization Reaction[α]

Entry	Catalyst	Ligand	Base	[β] Yield(%)
1	CuI	1,10 Phenanthroline	Cs_2CO_3	22
2	CuI	Ethylenediamine	Cs_2CO_3	25
3	CuI	D-Proline	Cs_2CO_3	Trace
4	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	30
5	$Pd(OAc)_2$	SPhos	Cs_2CO_3	46
[γ]**6**	-	-	Cs_2CO_3	75

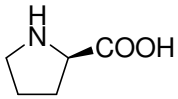
[α]Reaction conditions: substrate **1b** (1 mmol), catalyst (10 mol %), Ligand (10 mol %), base (2 mmol), solvent (2 mL) under N_2 atmosphere, reaction temperature (100 ^{o}C), reaction time (overnight), [β] Isolated yield. [γ] No addition of catalyst and no N_2 atmosphere required.



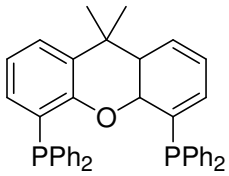
1,10 Phenanthroline



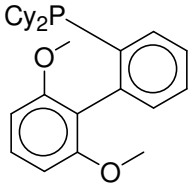
Ethylenediamine



D-Proline



Xantphos



SPhos

Figure 4. Ligand used in the model substrate.

Table 2. Selection of base

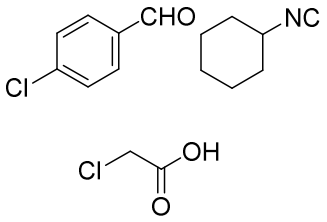
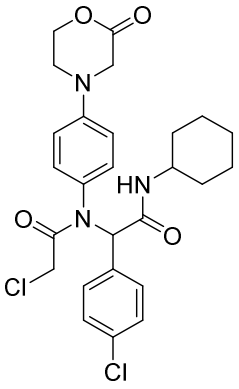
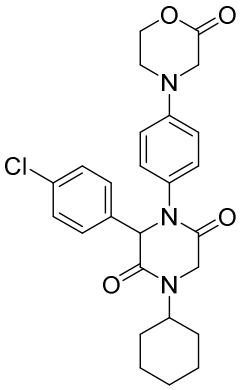
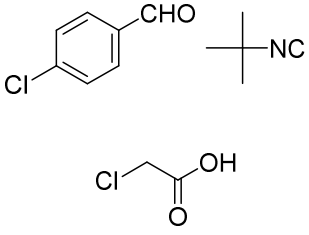
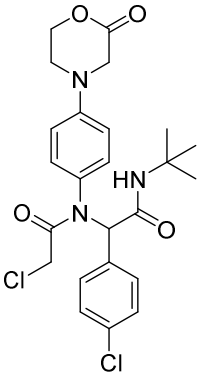
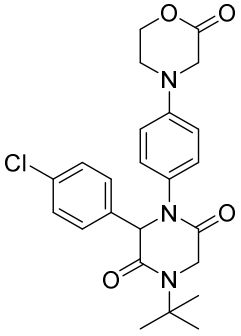
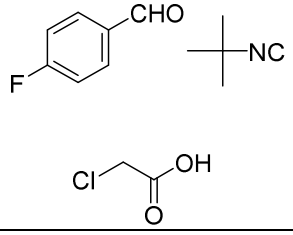
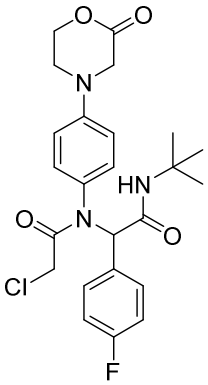
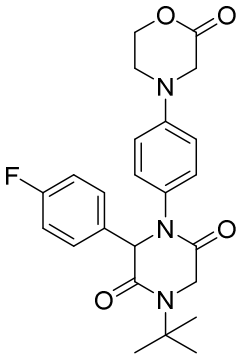
Entry	Base	Yield (%)[ζ]
1	Cs_2CO_3	75
2	K_2CO_3	80
3	Na_2CO_3	Trace
4	K_3PO_4	35
5	NaOH	-
6	K_2CO_3	45[£]

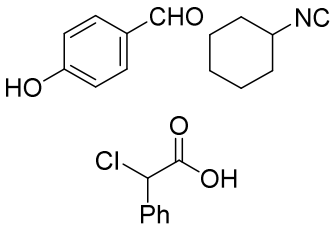
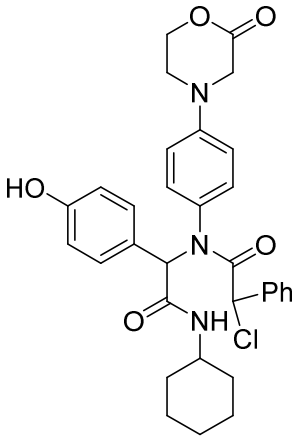
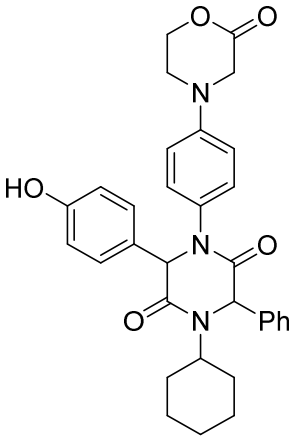
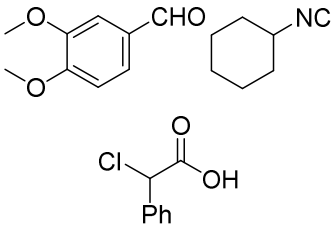
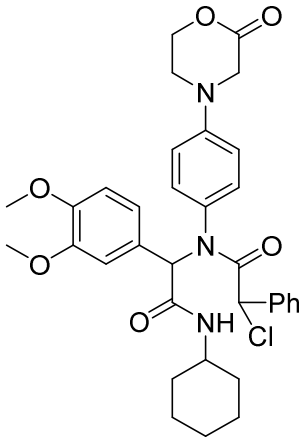
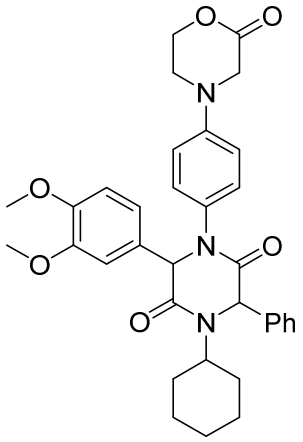
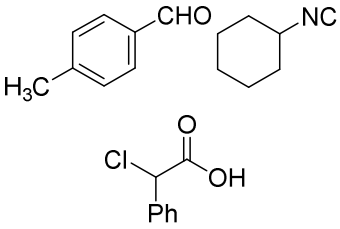
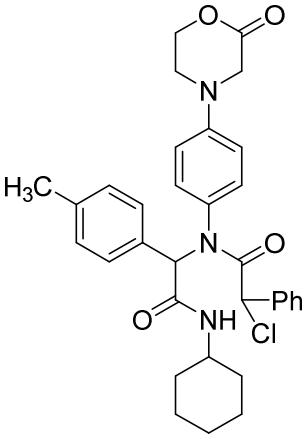
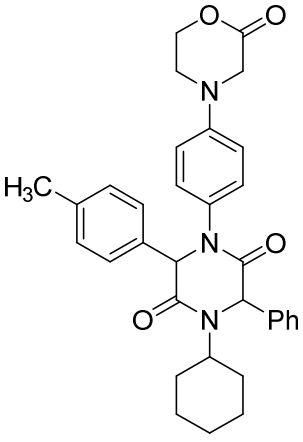
Reaction condition: substrate **1b** (1 mmol), base (2 mmol), DMF (2 mL) reaction temperature (100^{o}C), **ζ** isolated yield, **£** base (1mmol)

Table 3. Screening of Solvent

Entry	Solvent	Conversion (%)
1	DMSO	56
2	DMF	80
3	THF	63
4	1,4 dioxane	52
5	toluene	34

Table 4. Two-step synthesis of 2,5 diketopiperazine

Entry	Starting Material	Ugi-MCR Product	Post-Ugi Product	Yield (%)
1		 **1a**	 **2a**	71
2		 **1b**	 **2b**	80
3				75

		1-c	**2-c**	
Entry	Starting Material	Ugi-MCR Product	Post-Ugi Product	Yield (%)
4		 **1-d**	 **2-d**	77
5		 **1-e**	 **2-e**	76
6		 **1f**	 **2f**	83

Conclusions

An efficient synthesis of novel functionalized N-fused 2,5-diketopiperazines has been reported. Considering the availability of starting material, the simple reaction procedure, simple workup and robust nature, this chemical process provides a very straightforward route to construct various highly functionalized N-fused 2,5-diketopiperazines.

Experimental Section

General. All reagents and solvents were purchased from commercial sources and used without purification. NMR spectra were recorded with 400 MHz spectrometers for ^{1}H NMR and 100 MHz for ^{13}C NMR in deuterated solvents with TMS as internal reference (chemical shifts δ in ppm, coupling constant J in Hz). Multiplicities are reported as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad singlet (br, s). Melting points were determined in open capillary tubes on an electrically heated block and are uncorrected. The reaction progress was routinely monitored by thin-layer chromatography (TLC) on precoated silica gel plates. Column chromatography was performed over silica gel (230−400 flash). All compounds were characterized by TLC, ^{1}H NMR and ^{13}C NMR and MS.

General Procedure for the Synthesis of IMCR Products 1a-f. A mixture of aromatic amine (1 mmol) and aromatic aldehyde (1 mmol) stirred at room temperature in methanol (3 mL) for 5 to 10 min afforded Schiff base which further undergoes the reaction with chloroacetic acid (1 mmol) and isocyanide (1 mmol) at room temperature to gives **1a-f** in affordable yields. After stirring at room temperature for 24 h, the solid was filtered out to obtain crude products then wash with 1-2 mL chilled methanol for purification which is ready to use for the next step.

A post Ugi cyclisation of **1a-f** were carried out by use of efficient reaction conditions by utilizing dry K_2CO_3 (2 mmol), as a base and DMF (2 mL) solvent respectively under room temperature with portion wise addition of **1a-f** for 10 min which further heated at 100 ^{o}C for 2−4 hrs. The reaction is monitored by TLC, after completion of reaction the resulting mixture was cooled to room temperature and poured on crushed ice. Collect solid and the residue was purified by flash column chromatography on silica gel by using hexane: EtOAc (95:5) as a eluent to afford the corresponding products **2a-f** in 71-80% yields.

2-Chloro-*N*-(1-(4-chlorophenyl)-2-(cyclohexylamino)-2-oxoethyl)-*N*-(4-(2-oxomorpholino)phenyl) acetamide (1a). Yield 69%, mp. 156- 158 ^{o}C;^{1}H NMR (400 MHz, DMSO) δ 8.17 (s, 1H), 7.35 (dd, *J* 31.3, 7.5 Hz, 4H), 6.85 (d, *J* 7.5 Hz, 2H), 6.71 (d, *J* 7.5 Hz, 2H), 5.82 (s, 1H), 4.59 – 4.26 (m, 6H), 3.84 (t, *J* 4.4 Hz, 1H), 3.71 (dt, *J* 15.0, 5.9 Hz, 2H), 1.93 (dt, *J* 7.5, 5.9 Hz, 2H), 1.69 (dd, *J* 11.6, 5.7 Hz, 1H), 1.62 – 1.34 (m, 7H). ^{13}C NMR (100 MHz, Common NMR Solvents) δ 172.1, 169.9, 165.4, 149.1, 135.1, 131.6, 131.4, 130.7, 129.6, 128.5, 122.2, 62.2, 59.0, 50.8, 49.5, 47.1, 43.9, 25.9, 24.7.Anal. (%) for $C_{26}H_{29}Cl_2N_3O_4$, Calcd. C, 60.24; H, 5.64; Cl, 13.68; N, 8.11; Found: C, 60.77; H, 4.10; N, 9.05.

***N*-(*tert*-Butyl)-2-(2-chloro-*N*-(4-(2-oxomorpholino)phenyl)acetamido)-2-(4-chlorophenyl) acetamide (1b).** Yield 82%;mp.178-180 ^{o}C, ^{1}H NMR (400 MHz, DMSO) δ H NMR (400 MHz, DMSO) δ 7.35 (ddd, *J* 48.7, 29.1, 8.8 Hz, 1H), 5.44 (s, 1H), 4.48 – 4.10 (m, 1H), 3.99 – 3.86 (m,1H), 3.75 – 3.57 (m, 1H), 1.38 (s, 1H). 13 C NMR (101 MHz, DMSO) δ 165.9, 164.2, 164.0, 140.0, 136.5, 136.3 Anal.(%):$C_{24}H_{27}Cl_2N_3O_4$,Calcd., C, 58.54; H, 5.53; Cl, 14.40; N, 8.53;Found: C, 58.04; H, 5.23; Cl, 14.70

***N*-(*tert*-butyl)-2-(2-Chloro-*N*-(4-(2-oxomorpholino)phenyl)acetamido)-2-(4-fluorophenyl)acetamide (1c).** Yield 87%;mp.143-145^{o}C,^{1}H NMR (400 MHz, DMSO) δ 7.54 – 7.31 (m, 1H), 7.21 (dd, *J* 21.4, 8.8 Hz, 1H), 5.42 (s, 1H), 4.41 (d, J 17.8 Hz,1H), 4.28 – 4.09 (m, 1H), 4.00 – 3.88 (m, 1H), 3.80 – 3.54 (m, 1H), 1.38 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ 165.9, 164.2, 163.8, 138.8,135.3, 135.2, 131.6, 127.6, 126.5, 125.6, 124.4, 67.4, 65.3, 61.5, 56.2, 46.3, 45.4, 26.3, 26.2 Anal.(%): $C_{24}H_{27}ClFN_3O_4$,Calcd.,C, 60.57; H, 5.72; Cl, 7.45; F, 3.99; N, 8.83.Found: C, 60.97; H, 5.72; Cl, 7.45; F, 3.99

2-Chloro-*N*-(2-(cyclohexylamino)-1-(4-hydroxyphenyl)-2-oxoethyl)-*N*-(4-(2-oxomorpholino)phenyl)-2-phenylacetamide (1d). Yield 79%;mp.153-156 ^{o}C,^{1}H NMR (400 MHz, DMSO) δ 8.41 (s, 1H), 7.41 – 7.12 (m, 7H),

7.07 (dd, *J* 13.3, 7.4 Hz, 4H), 6.78 (d, *J* 7.6 Hz, 2H), 5.82 (s, 1H), 5.77 (s, 1H), 4.56 (s, 2H), 3.82 – 3.41 (m, 5H), 1.85 – 1.49 (m, 5H), 1.41 – 1.19 (m, 5H). ^{13}C NMR (100 MHz,) δ 172.1, 167.8, 166.5, 154.8, 139.7, 137.0, 134.5, 130.4, 130.3, 130.0, 128.4, 128.2, 127.8, 125.4, 116.6, 66.4, 66.0, 62.3, 60.8, 50.8, 41.2, 25.9, 24.7. Anal.(%): $C_{32}H_{34}ClN_3O_5$,Calcd.C, 66.72; H, 5.95; Cl, 6.15; N, 7.29.Found: C, 66.32; H, 5.95; Cl, 6.37; N, 7.54.

2-Chloro-*N*-(2-(cyclohexylamino)-1-(3,4-dimethoxyphenyl)-2-oxoethyl)-*N*-(4-(2-oxomorpholino)phenyl)-2-phenylacetamide (1e). Yield 75%;mp.165-168 ^{o}C, ^{1}H NMR (400 MHz, DMSO) δ 7.44 – 7.14 (m, 9H), 7.09 – 6.97 (m, 2H), 6.89 (dd, *J* 8.1, 4.4 Hz, 2H), 5.82 (s, 1H), 5.77 (s, 1H), 4.56 (s, 2H), 3.84 – 3.58 (m, 11H), 1.64 (tdd, *J* 6.5, 4.8, 2.0 Hz, 5H), 1.45 – 1.17 (m, 5H);^{13}C NMR (100 MHz) δ 172.1, 167.8, 166.5, 150.0, 147.9, 139.7, 137.0, 134.5, 130.4, 130.0, 128.4, 128.2, 127.8, 123.9, 115.4, 112.6, 66.4, 66.0, 63.1, 60.8, 56.7, 50.8, 41.2, 25.9, 24.7; Anal(%):$C_{34}H_{38}ClN_3O_6$;Calcd.,C, 65.85; H, 6.18; Cl, 5.72; N, 6.78;Found: C, 65.98; H, 6.07; Cl, 5.40; N, 6.97;

2-Chloro-*N*-(2-(cyclohexylamino)-2-oxo-1-(*p*-tolyl)ethyl)-*N*-(4-(2-oxomorpholino)phenyl)-2-phenylacetamide (1f): Yield 72%;mp.169-172^{o}C, ^{1}H NMR (400 MHz, DMSO) δ 10.18 (s, 1H), 7.38 – 6.95 (m, 13H), 5.82 (s, 1H), 5.77 (s, 1H), 4.56 (s, 2H), 3.81 – 3.49 (m, 5H), 2.34 (s, 3H), 1.76 – 1.43 (m, 5H), 1.36 – 1.12 (m, 5H);^{13}C NMR (100 MHz) δ 172.1, 167.8, 166.5, 139.7, 137.0, 134.9, 134.6, 134.5, 130.4, 130.4, 130.2, 130.0, 128.4, 128.2, 127.8, 66.4, 66.0, 62.3, 60.8, 50.8, 41.2, 25.9, 24.7, 21.1; Anal(%): $C_{33}H_{36}ClN_3O_4$;Caled C, 69.04; H, 6.32; Cl, 6.17; N, 7.32; O, 11.15;Found; Caled C, 69.84; H, 6.12; Cl, 6.12; N, 7.02.

3-(4-Chlorophenyl)-1-cyclohexyl-4-(4-(2-oxomorpholino)phenyl)piperazine-2,5-dione (2a). Yield 71%; mp.152-155 ^{o}C, ^{1}H NMR (400 MHz, DMSO) δ 8.08 (d, *J* 7.7 Hz, 1H), 7.07 (d, *J* 8.4 Hz, 2H), 6.03 (s, 1H), 4.17 (s, 2H), 4.03 – 3.86 (m, 4H), 3.65 (dd, *J* 7.7, 4.6 Hz, 3H), 1.64 (ddd, *J* 43.8, 24.2, 14.0 Hz, 5H), 1.32 – 0.90 (m, 5H); Anal(%):$C_{26}H_{28}ClN_3O_4$;Caled: C, 64.79; H, 5.86; Cl, 7.36; N, 8.72;Found:C, 64.38; H, 5.97; Cl, 7.14; N, 8.56 MS(EI)m/z=481

1-(*tert*-Butyl)-3-(4-chlorophenyl)-4-(4-(2-oxomorpholino)phenyl)piperazine-2,5-dione (2b). Yield 80%; mp.165-169 ^{o}C, ^{1}H NMR (400 MHz, DMSO) δ 7.45 – 7.34 (m, 6H), 7.26 (d, *J* 8.8 Hz, 2H), 5.44 (s, 1H), 4.39 (d, *J* 17.7 Hz, 1H), 4.21 (d, *J* 27.9 Hz, 3H), 3.93 (s, 2H), 3.76 – 3.58 (m, 2H), 1.43 (d, *J* 42.1 Hz, 10H). ^{13}C NMR (100MHz, DMSO) δ 165.9, 164.2, 164.0, 140.0, 136.5, 136.3, 132.8, 128.9, 128.7, 126.7, 125.5, 67.6, 66.6, 63.3, 57.4, 48.6, 46.9, 27.0; Anal. (%):$C_{24}H_{26}ClN_3O_4$; Calcd: C, 63.22; H, 5.75; Cl, 7.78; N, 9.22; Found: C, 63.67; H, 5.32; Cl, 7.35; N, 9.54; MS (EI)m/z=456.81[M^+]

1-(*tert*-Butyl)-3-(4-fluorophenyl)-4-(4-(2-oxomorpholino)phenyl)piperazine-2,5-dione (2c). Yield 75%; mp.149-152 ^{o}C, ^{1}H NMR (400 MHz, DMSO) δ 7.45 – 7.30 (m, 4H), 7.28 – 7.11 (m, 4H), 5.42 (s, 1H), 4.41 (d, *J* 17.8 Hz, 1H), 4.27 – 4.12 (m, 3H), 4.03 – 3.88 (m, 2H), 3.76 – 3.62 (m, 2H), 1.38 (s, 9H). Anal(%):$C_{24}H_{26}FN_3O_4$;Calcd: C, 65.59; H, 5.96; F, 4.32; N, 9.56;Found; C, 65.87; H, 5.67; F, 4.67; N, 9.12; MS(EI)m/z=440[M^+]

1-Cyclohexyl-3-(4-hydroxyphenyl)-4-(4-(2-oxomorpholino)phenyl)-6-phenylpiperazine-2,5-dione (2d). Yield 77%; mp.145-147^{o}C; ^{1}H NMR (400 MHz, DMSO) δ 10.01 (s, 1H), 7.93-7.95 (m, 2H), 7.70 (d, 1H),7.23-7.38 (m, 8H), 7.08-7.10 (d, 2H), 6.07 (s, 1H), 4.16 (s, 2H), 3.91-3.94(m, 2H), 3.64-3.65(m, 2H), 3.36-3.43(m, 2H), 1.64-1.1.69 (m, 5H), 1.19-1.23 (m, 5H); ^{13}C NMR (100MHz, DMSO) δ192.1, 169.0,168.0, 165.8, 140.8, 136.9, 134.8,134.5, 134.0, 133.4, 132.3, 132.0,131.7, 131.1, 131.0, 129.3,128.4, 127.9, 126.8, 124.6, 67.6, 63.3, 62.6, 52.5, 48.4, 47.8,40.0, 39.8, 39.6, 39.4, 39.2, 39.0,38.8, 32.1, 25.1, 24.5,24.3; Anal(%): $C_{32}H_{33}N_3O_5$;Calcd: C, 71.22; H, 6.16; N, 7.79;Found; C, 71.86; H, 6.32; N, 7.12; MS (EI) *m/z* 540.06[M^+].

1-Cyclohexyl-3-(3,4-dimethoxyphenyl)-4-(4-(2-oxomorpholino)phenyl)-6-phenylpiperazine-2,5-dione (2e). Yield 76%; mp.178-181 ^{o}C ^{1}H NMR (400 MHz, DMSO) δ 7.80-7-88 (m, 2H), 7.13-7.43 (m, 6H), 6.95-6.96 (d, 5H), 6.05 (s, 1H), 4.15 (s, 2H), 3.90-3.93(m, 2H), 3.63-3.64(d, 3H), 3.34-3.41(m, 1H),2.18 (s, 3H), 1.50-1.72 (m, 5H), 0.93-1.20 (m, 5H); ^{13}C NMR (100 MHz, DMSO) δ 170.6,168.3, 166.4, 152.9, 141.3, 138.0, 134.1, 133.6, 131.6, 129.7, 129.1, 128.3, 126.8,125.4, 107.6, 77.3, 77.0, 76.7,68.5, 64.5, 64.0, 60.8, 56.1, 49.3, 48.8,40.1, 32.8,25.4,

24.8, 24.7 ; Anal(%): $C_{34}H_{37}N_3O_6$;Calcd: C, 69.96; H, 6.39; N, 7.20; C, 71.22; H, 6.16; N, 7.79;Found:C, 69.16; H, 6.54; N, 7.78MS (EI) *m/z* 537.6[M^+].

1-Cyclohexyl-4-(4-(2-oxomorpholino)phenyl)-6-phenyl-3-(p-tolyl)piperazine-2,5-dione (2f). Yield 83%; mp.142-144 ^oC; ^1H NMR (400 MHz, DMSO) δ 8.00(s, 1h), 7.17-7-28 (m, 7H), 6.91-6.93 (d, 2H), 6.58-6.60 (d, 3H), 5.99 (s, 1H), 4.79 (s, 1H), 4.29(m, 2H), 3.69-4.01(m, 6H), 3.53(s, 2H),2.21 (s, 2H), 1.58-1.64 (m, 2H), 1.55-1.56 (m, 3H), 1.27-1.33 (m, 2H), 1.00-1.10 (m, 3H); ^{13}C NMR (100MHz, DMSO) δ170.7, 169.0, 167.0, 157.1, 140.8, 138,3, 134.1, 133.6, 131.7, 131.6,131.3, 129.1, 128.3, 126.9, 125.5, 125.2, 115.5, 77.4, 77.2, 77.0, 76.7, 68.3, 64.7,63.9, 49.4, 48.8, 40.1, 32.7, 25.4, 24.8, 24.7;Anal.(%): $C_{33}H_{35}N_3O_4$;Calcd: C, 73.72; H, 6.56; N, 7.82; C, 73.22; H, 6.45; N, 7.97 MS (EI) *m/z* 585.02[M^{++}].

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Supplementary Material

Copies of mass ^1H NMR and ^{13}C NMR spectra, are available on the online version of the text.

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