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Molecular diversity in cyclization of Ugi-products leading to the synthesis of 2,5-diketopiperazines: computational study

Vahideh Zadsirjan[1] · **Morteza Shiri**[1] · **Majid M. Heravi**[1] · **Tayebeh Hosseinnejad**[1] · **Suhas A. Shintre**[2] · **Neil A. Koorbanally**[2]

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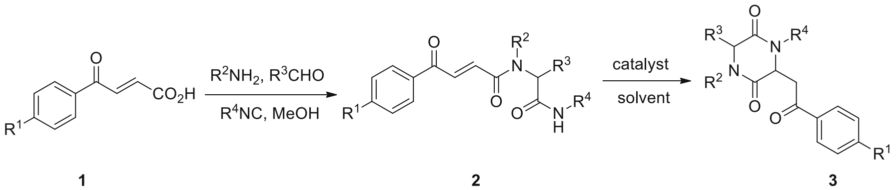
Abstract Ugi-adducts were obtained via a one-pot four-component reaction of divergent aldehydes, amines, aroylacrylic acids and isocyanide in methanol. These products were subjected to intramolecular Michael addition in the presence of K_2CO_3 in DMF at room temperature to afford a single product. Literally, the formation of two heterocyclic systems, 6-membered diones or 7-membered diones are possible, which could not be identified by conventional spectroscopic methods. The X-ray crystallographical data was obtained for one selected product, which indicated preferential formation of the corresponding 6-membered dione. In order to establish the generality of this mode of cyclization, the quantum chemistry calculations were performed. The obtained results confirmed the favorable formation of 6-membered diones in the gas and also several solution phases. All the products were screened for their antibacterial and antifungal activities.

Graphical Abstract



✉ Morteza Shiri
mshiri@alzahra.ac.ir

✉ Majid M. Heravi
mmh1331@yahoo.com

[1] Department of Chemistry, Alzahra University, Vanak, Tehran 1993893973, Iran

[2] School of Chemistry and Physics, University of KwaZulu-Natal,
Private Bag X54001, Durban 4000, South Africa

Keywords Ugi reaction · Aroylacrylic acids · Base catalysis · Intramolecular Michael addition · 2,5-Diketopiperazines · Molecular diversity · Density functional theory · Quantum theory of atoms in molecules · Polarized continuum model · Antibacterial and antifungal activities

Introduction

The 2,5-Diketopiperazines (2,5-DKPs), cyclodipeptides can be prepared by the reaction of two α-amino acids. They are found in nature, and are usually created from the degradation of polypeptides found in beverages and processed food. They are present in various bacteria, fungi, mammals and the plant kingdom. For example, 2,5-DKPs abound in the structure of numerous natural products such as okaramine N [1], dysamide B [2], FR106969 [3] and citreoindole [4] (Fig. 1). Due to the ability of 2,5-diketopiperazines to bind to a number of receptors, they can be considered as attractive scaffolds in drug discovery. In these small heterocyclic molecules, it is possible to have a number of stereocenters to create diverse structures.

Several reviews on the synthesis of natural products containing 2,5-diketopiperazines had been published as early as 1975 and 1990 [5, 6]. The improvements in the synthesis of 2,5-diketopiperazines [7–9], properties and biological activities of them have been reviewed [10–12].

In recent years, diversity-oriented synthesis gained much attention in the pharmaceutical industry. In this area, multicomponent reactions (MCRs), especially the Ugi four-component condensation reaction (Ugi 4CC) is a convenient method to form a large diversity of molecules [13–15]. The Ugi reaction was first reported by Ivar Ugi [16] in which a ketone or aldehyde, an amine, an isocyanide and a carboxylic acid were reacted to provide a bis-amide [17].

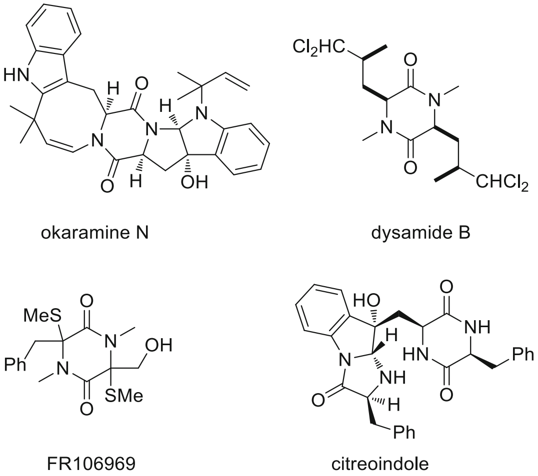


Fig. 1 Naturally occurring molecules containing the 2,5-DKP scaffold

Post-condensation modifications, including other multicomponent reactions (MCRs), can be performed to yield a variety of heterocyclic compounds. These compounds can serve as scaffolds for the synthesis of natural products, therapeutic agents, and combinatorial libraries.

Numerous procedures have been reported for post-condensational modification (PCM). This makes the Ugi condensation a popular alternative to traditional approaches for the synthesis of complex molecules. Many advantages such as high atom efficiency, convergence of reaction and the construction of high molecular complexity in a single step make the Ugi condensation a distinguished reaction.

In order to synthesize diverse molecules, starting materials with multifunctional groups such as fumaric acid derivatives have been applied as an appropriate acid source in the Ugi reaction [12]. Santra and Andreana [18] developed a sequential Ugi/Michael/aza-Michael cascade reaction for the synthesis of natural product-like fused azaspiro tricycles and azaspirotetracycles by using microwave irradiation in water without any additives. They used *o*-nitrobenzaldehydes or *o*-nitrobenyzlamines in the formation of Ugi-adducts and reported a one-pot, two-step reaction for the synthesis of regiochemically differentiated 1,2,4,5-tetrahydro-1,4-benzodiazepin-3-ones under microwave irradiation [19]. Synthesis of precursors containing thiophene via the Ugi reaction and the transformation of them into 3-oxoisoindolines in the presence of *m*-CPBA have also been developed [20]. The employing of the intramolecular Diels-alder reaction in post-Ugi modification led to the synthesis of highly diverse polycyclic compounds [21–30]. Also, recently, an efficient method was developed for the preparation of functionalized β-lactams and pyrrolidine-2,5-diones *via* sequential Ugi-4CR/cyclization reaction. Diversity-oriented synthesis, good to high yields, short reaction times and easy work-up are some advantages of this procedure [31].

Noticeably, the Ugi condensation provides a significant procedure for the synthesis of 2,5-diketopiperazines. Due to the importance of Ugi condensation for the preparation of diverse products, we wished to try the application of aroylacrylic acids as a significant acid in the Ugi reaction. Various β-aroylacrylic acids and their derivatives show biological activities [32, 33]. Significantly, aroylacrylic acids were applied in the formation of various heterocyclic products. A number of highly substituted 2,5-diketopiperazines were synthesized through a one-pot Ugi/Aza Michael reaction by using β-acyl substituted acrylic acids and *p*-toluene sulfonyl methyl isocyanide as a less hindered isocyanide to generate the corresponding Ugi-adducts, which cyclized to the 2,5-diketopiperazines in a single reaction-step without any additives [34]. The synthesis of different small molecules containing 2,5-diketopiperazines through the Ugi/Aza Michael reaction under microwave conditions was also reported [35].

In continuation of our experimental researches on the synthesis of heterocyclic compounds [36–41] via Ugi reactions [42–46], and in order to investigate computational approaches as argumentative and sound tools for explication and prediction of experimental data [47–51], in this work, we wish to report the synthesis of a series of new 2,5-diketopiperazines through the cyclization of Ugi-adducts obtained from the reaction of aroylacrylic acids, aldehydes, amines, and isocyanides under mild conditions in combination with theoretical interpretations.

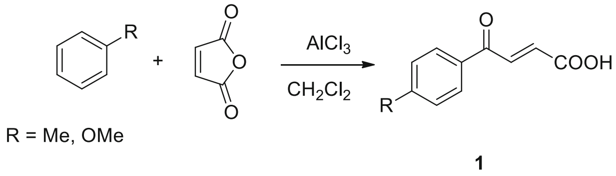
Density functional theory (DFT) [52] and the quantum theory of atoms in molecules (QTAIM) computations [53, 54] were used to present underlying theoretical reasons for the selective behavior of the intramolecular cyclization step. A reliable agreement between experimental and computational electronic interpretations was found. Moreover, polarized continuum model (PCM) [55] computations have been carried out to analyze the solvent effect on the efficiently and selectivity of the intramolecular cyclization reaction. A reliable agreement between experimental and computational interpretations was found.

Results and discussion

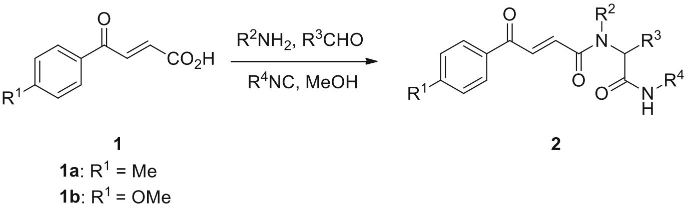
Initially, aroylacrylic acids **1** were prepared by the reaction of maleic anhydride and appropriate arenes (Scheme 1) [56]. This was followed by the synthesis of Ugi-adducts **2a-l** in good yields (84–96 %) in a one-pot reaction of 1 mmol each of aroylacrylic acids, aldehydes, amines and cyclohexylisocyanide (Scheme 2, Table 1). The reaction was conducted in methanol at room temperature in the absence of any catalyst or additives and took place within 24 h.

Variations in the molecules were achieved by using *para* substituted methyl and methoxy substituted aroylacrylic acids **1a**, **b**, formaldehyde, *p*-chloro (electron withdrawing), *p*-methyl (electron donating) and *p*-dimethylaminobenzaldehdye (electron donating) and various amines such as benzylamine, *n*-butylamine and anilines, such as aniline, *p*-anisidine and *p*-toluidine.

In the final step of the reaction, the Ugi-adduct **2** was cyclized, leading to the formation of **3**. In search of the best catalyst for this reaction (*E*)-*N*-benzyl-*N*-(2-(cyclohexylamino)-2-oxoethyl)-4-oxo-4-(*p*-tolyl) was considered, but-2-enamide **2a** was chosen as the test substrate (Scheme 3). The effect of various catalysts (acids and bases) and solvents under different conditions was explored. The base catalysts



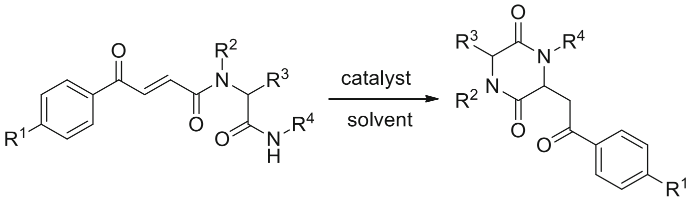
Scheme 1 Synthesis of aroylacrylic acids **1**



Scheme 2 Synthesis of Ugi-adducts **2**

Table 1 Ugi-4CC of aroylacrylic acids, amines, aldehydes and isocyanides

Entry	Product	R^1	R^2	R^3	R^4	Yield (%)
1	**2a**	Me	$C_6H_4CH_2$	H	Cyclohexyl	94
2	**2b**	OMe	$C_6H_4CH_2$	H	Cyclohexyl	92
3	**2c**	Me	$CH_3(CH_2)_3$	H	Cyclohexyl	92
4	**2d**	Me	4-MeO–C_6H_4	H	Cyclohexyl	96
5	**2e**	Me	4-Me–C_6H_4	H	Cyclohexyl	96
6	**2f**	Me	C_6H_5	H	Cyclohexyl	95
7	**2g**	Me	4-Me–C_6H_4	4-Cl–C_6H_4	Cyclohexyl	95
8	**2h**	Me	4-Me–C_6H_4	4-$(NMe_2)_2$–C_6H_4	Cyclohexyl	94
9	**2i**	OMe	4-Me–C_6H_4	4-Cl–C_6H_4	Cyclohexyl	92
10	**2j**	Me	4-Me–C_6H_4	4-Me–C_6H_4	Cyclohexyl	96
11	**2k**	Me	C_6H_5	4-Cl–C_6H_4	Cyclohexyl	90
12	**2l**	Me	$CH_3(CH_2)_3$	4-Cl–C_6H_4	Cyclohexyl	87



2 **3**

Scheme 3 Synthesis of 2,5-diketopiperazines **3**

such as Et_3N and DABCO afforded 2,5-diketopiperazine **3a** in 25 % yields. The acid catalysts, H_2SO_4 (a protic acid) and $AlCl_3$ (a Lewis acid) resulted in the formation of **3a** with slightly better yields of 50 and 40 %, respectively. Some other bases such as pyridine, sodium carbonate, sodium hydroxide, potassium hydroxide and KO*t*Bu were also examined; however, they formed a mixture of products. The best results were obtained using K_2CO_3 in dimethylformamide (DMF) at room temperature, which produced the desired product in 92 % yield from the diamide **2a** (Table 2).

Under these optimum conditions, the obtained diamides **2a–f** were efficiently converted to the desired piperazine-2,5-diones **3a–f** with high yields (Fig. 2). More complex 2,5-diketopiperazines **3g–l** were synthesized through the cyclization reaction of their corresponding diamides **2g–l** in the presence of K_2CO_3 at room temperature over 10–12 h (Fig. 2). Although the 2,5-diketopiperazines **3g–l** have two stereocentres, under these conditions, just one diastereomer selectively formed. All substrates led to the development of products **3** in good yields (73–97 %), and their structures were confirmed and characterised by IR, ^1H-NMR, ^{13}C-NMR spectroscopy and X-ray diffraction (XRD).

Table 2 Examination of different conditions in the cyclization of **2a** to **3a**[a]

Entry	Catalyst	Solvent	T (°C)	Yield (%)
1	Et_3N	DMF	r.t.	25
2	DABCO	DMF	r.t.	25
3	H_2SO_4	CH_2Cl_2	r.t.	50
4	$AlCl_3$	CH_2Cl_2	r.t.	40
5	Na_2CO_3	DMF	r.t.	NR
6	Pyridine	DMF	r.t.	NR
7	NaOH	DMF	r.t.	–[b]
8	KOH	DMF	r.t.	–[b]
9	KO*t*Bu	DMF	r.t.	–[b]
10	Cs_2CO_3	DMF	r.t.	–[b]
11	K_2CO_3	DMF	r.t.	92 %
12	K_2CO_3	MeOH	r.t.	50 %
13	K_2CO_3	CH_2Cl_2	r.t.	NR
14	K_2CO_3	CH_3CN	r.t.	NR
15	K_2CO_3	CH_3CN	Reflux	20
16	K_2CO_3	THF	Reflux	NR
17	K_2CO_3	Toluene	Reflux	NR
18	K_2CO_3	H_2O	r.t.	NR
19	K_2CO_3	H_2O	Reflux	NR

[a] **2a** (0.5 mmol), catalyst (0.5 mmol), solvent (3 ml) after 6 h

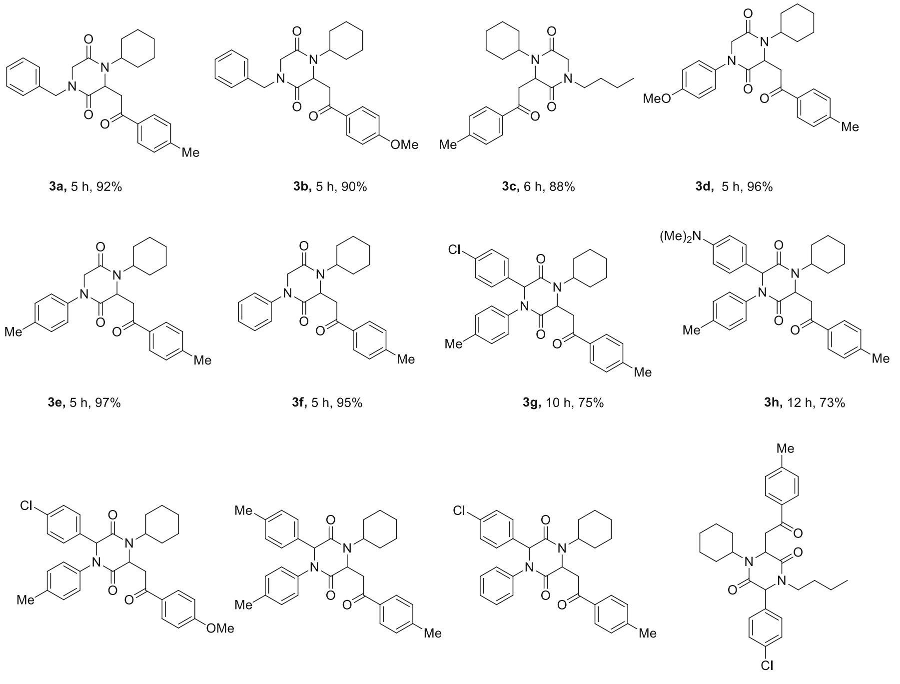
[b] Complex mixture of products

The single-crystals of compound **3f** were obtained by slow evaporation of the solvent. The molecular structure was elucidated unambiguously based on single-crystal X-ray analysis (Fig. 3). The crystallographic and refinement data are summarized in Table 3. Selected bond lengths and angles are shown in Table 4. Diffraction measurements for the crystals in oil were recorded on a Bruker Apex CCD diffractometer fitted with Mo-Kα radiation. The structure was solved with direct procedures and refined with full-matrix least-squares methods (SHELXTL-97) with anisotropic thermal parameters for all non-hydrogen atoms. Intensity data were collected at a temperature of 173 K on a Bruker APEX-CCD (D8 three-circle goniometer) (Bruker AXS) diffractometer with graphite monochromated Mo-Kαradiation ($\lambda = 0.71073$ Å).

Another significant aspect of the intramolecular cyclization step is that the cyclization of diamide Ugi-adducts resulted in selective **6-membered** piperazine-2,5-diones with high yields, while mechanistically the corresponding **7-membered** diazepane-2,5-diones can also be produced. In the following, this selective experimental behaviour will be discussed on the basis of quantum chemical computations.

Computational section

In the present section, we have focused on quantum chemistry assessment of the cyclization reaction of diamide Ugi-adducts to their corresponding diones based on



3a, 5 h, 92% **3b,** 5 h, 90% **3c,** 6 h, 88% **3d,** 5 h, 96%

3e, 5 h, 97% **3f,** 5 h, 95% **3g,** 10 h, 75% **3h,** 12 h, 73%

3i, 11 h, 73% **3j,** 10 h, 74% **3k,** 11 h, 80% **3l,** 12 h, 77%

Fig. 2 The structures of 2,5-diketopiperazines **3**

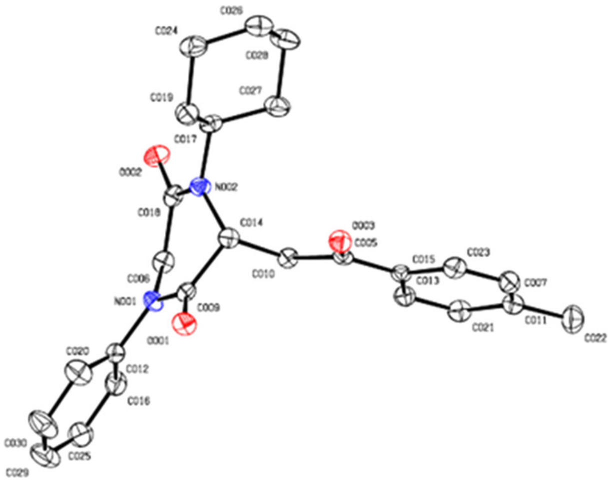


Fig. 3 ORTEP structure of **3f**

DFT [49, 53] and QTAIM [50, 51] calculations. From the experimental viewpoint, the cyclization of diamides led to the formation of the corresponding **6-membered** piperazine-2,5-diones with high affordance, while mechanistically, **7-membered**

Table 3 Crystallographical data and structure refinement of compound **3f**

Identification code	Shelx	
Empirical formula	$C_{25}H_{28}N_2O_3$	
Formula weight	404.49	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Unit cell dimensions	a = 11.3322(8) Å	$\alpha = 90°$
	b = 18.4113(14) Å	$\beta = 90°$
	c = 10.4353(8) Å	$\gamma = 90°$
Volume	2177.2(3) $Å^3$	
Z	4	
Density (calculated)	1.234 Mg/m^3	
Absorption coefficient	0.081 mm^{-1}	
F (000)	864	
Crystal size	0.51 × 0.25 × 0.23 mm^3	
Theta range for data collection	2.11°–28.32°	
Index ranges	$-14 \leq h \leq 15, -24 \leq k \leq 24, -11 \leq l \leq 8$	
Reflections collected	9902	
Independent reflections	4313 [R(int) = 0.0418]	
Completeness to theta = 28.32°	88.2 %	
Max. and min. transmission	0.9816 and 0.9598	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	4313/1/272	
Goodness-of-fit on F^2	1.091	
Final R indices [I > 2sigma(I)]	$R_1 = 0.0613$, $wR_2 = 0.1826$	
R indices (all data)	$R_1 = 0.0764$, $wR_2 = 0.1957$	
Absolute structure parameter	0(2)	
Extinction coefficient	0.0014(17)	
Largest diff. peak and hole	0.479 and −0.404 e $Å^{-3}$	

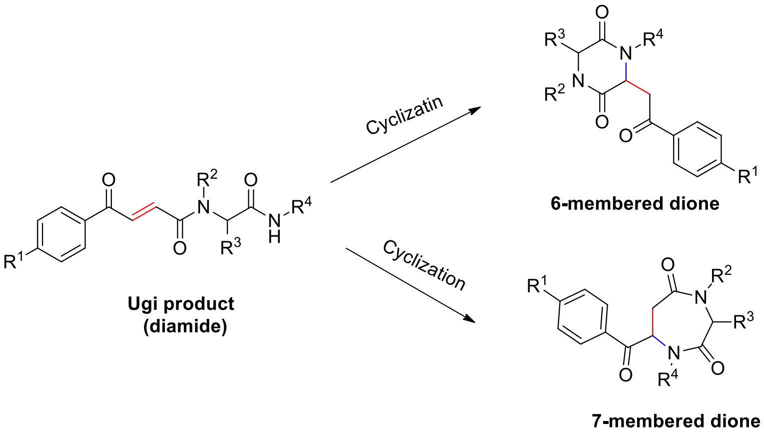
Table 4 The electronic energy of cyclization reaction of diamide Ugi-adducts to their corresponding **3f-6** membered and **3f-7** membered compounds, calculated at M08-HX/6-311+G** level of theory in the solution phase

	3f-6 membered	**3f-7** membered
DMF	−11.74	7.41
Methanol	−7.66	10.76
Acetonitrile	−2.80	16.04
Water	−2.04	16.83

diazepane-2,5-diones can also be produced. In this context, we investigated the theoretical basis to present the computational underlying interpretations for the formation of **6-membered** diones over their **7-membered** counterparts via a reliable cyclization reaction model. The two competing reactions are depicted in Scheme 4.

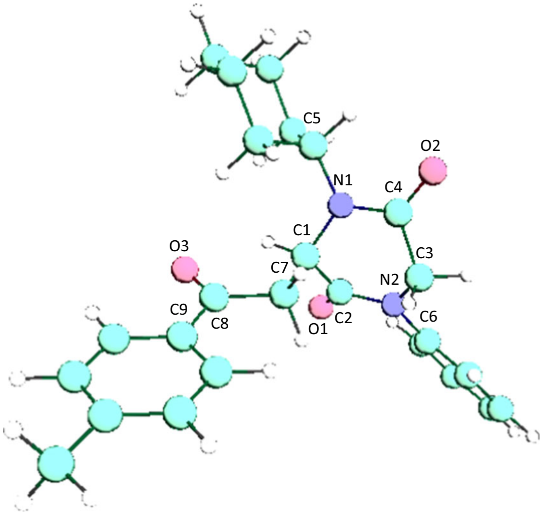
In the first step, we have examined the ability of DFT methods to predict our obtained crystallographical data of **3f** compound, known as 4-cyclohexyl-3-(2-oxo-2-(*p*-tolyl)ethyl)-1-phenylpiperazine-2,5-dione (hereafter denoted as **3f-6 membered**). In this respect, we have first determined the optimized structure of the **3f-6 membered** compound using B3LYP [52, 57] and M08-HX [58] density functional methods. It should be mentioned that the popular B3LYP functional is classified as a hybrid functional and incorporates a portion of exact exchange from Hartree-Fock theory with exchange and correlation from ab initio and semi-empirical sources, and the M08-HX functional has been introduced as a modern hybrid meta-GGA (generalized gradient approximation) exchange-correlation functional combined with a Hartree-Fock exchange contribution. Moreover, harmonic frequency analysis was applied to confirm that the calculated optimized structures correspond to minima. A comparison was then made between our calculated bond lengths and angles of the **3f-6 membered** compound, performed at B3LYP/6-31G* and M08-HX/6-31G* levels of theory with our obtained X-ray crystallographical data. All DFT computations were performed using the GAMESS suite of programs [59].

In Fig. 4, the calculated optimized geometry of the **3f-6 membered** compound obtained at the M08-HX/6-31G* level is displayed. We have also reported some of the selected bond lengths and angles of the **3f-6 membered** compound calculated at the B3LYP/6-31G* and M08-HX/6-31G* levels of theory, as well as X-ray ones in Table 4. The average absolute deviation (AAD) of X-ray experimental data of the **3f-6 membered** compound with B3LYP/6-31G* and M08-HX/6-31G* calculated bond lengths are 0.007 and 0.015 %, respectively. Moreover, the AAD of the X-ray data of the **3f-6 membered** compound with the calculated bond angles at B3LYP/6-31G* and M08-HX/6-31G* levels are 0.020 and 0.030 %, respectively. The reported results of Table 4 indicate that in overall, these computational levels have a reliable agreement with the X-ray structure of the **3f-6 membered** compound, while there is a relative superiority in using the M08-HX functional method. Thus, the rest



Scheme 4 The structures of **6-membered** and **7-membered** diones

Fig. 4 Atomic numbering and energy-minimized structure of the **3f-6 membered** compound obtained at the M08-HX/6-31G* level of theory



of the computational studies were devoted to the calculations at the M08-HX level of theory.

In the next step, in order to expound the preference in producing of piperazine-2,5-diones as **6-membered** diones with high affordance in comparison with their corresponding diazepane-2,5-diones as **7-membered** diones, we focused on topological analysis of electron density functions via the QTAIM approach [53, 54]. In this respect, the resulting M08-HX/6-311+G** wave function files for the optimized structures of **3f-6 membered** compound and its corresponding **7-membered** dione, known as 1-cyclohexyl-7-(4-methylbenzoyl)-4-phenyl-1,4-diazepane-2,5-dione (hereafter denoted as **3f-7 membered**) were applied as input parameters in the AIM2000 program [60]. Topological analysis of electron density was then performed on bond and ring critical points (BCPs and RCPs, respectively) and their associated bond paths to interpret the preference in producing a **3f-6 membered** compound with high yield in comparison with a **3f-7 membered** compound.

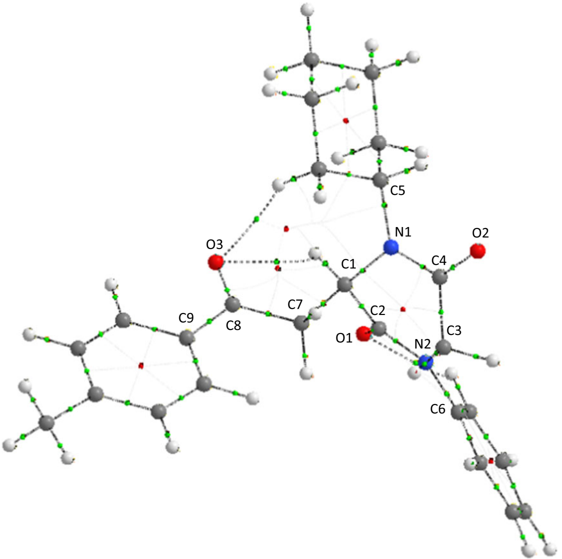
In Table 5, we report the calculated values of electron density, ρ_b, its Laplacian, $\nabla^2\rho_b$, electronic kinetic energy density, G_b, electronic potential energy density, V_b,

Table 5 The M08-HX/6-311+G** calculated values of C1–N1 and C7–N1 bond orders in **3f-6 membered** and **3f-7 membered** compounds, respectively, in the presence of solvent

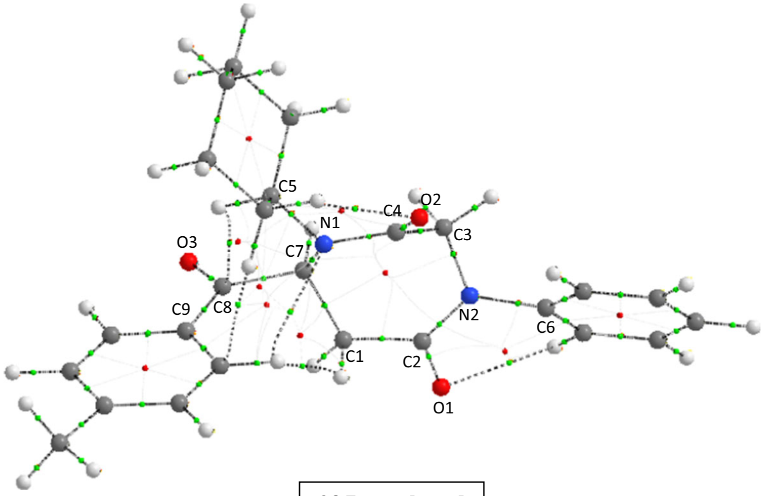
	3f-6 membered (C1–N1)	**3f-7 membered** (C7–N1)
DMF	0.787	0.735
Methanol	0.703	0.621
Acetonitrile	0.626	0.557
Water	0.597	0.539

Note that the numbering of atoms is in accordance with Fig. 5

total electronic energy density, H_b and ratio of $|V_b|/G_b$ of BCPs and RCPs that were formed via the intramolecular cyclization process in **3f-6 membered** and **3f-7 membered** compounds. In Fig. 5, we have presented the QTAIM molecular graphs of **3f-6 membered** and **3f-7 membered** compounds.



3f-6 membered



3f-7 membered

Fig. 5 Complete molecular graphs (MGs) of **3f-6 membered** and **3f-7 membered** compounds obtained by QTAIM analysis of M08-HX/6-311+G**electron density. Bond critical points *green circles*; ring critical points *red circles*; bond paths *gray lines*. (Color figure online)

It should be stated that the magnitude of $\rho(\mathrm{r})$ and its Laplacian $\nabla^2\rho(\mathrm{r})$ at BCPs are important indicators for the nature and strength of chemical bonds [61, 62]. In order to assign the stabilization of accumulation of charge at a given BCP, densities of local electronic energy, $H(\mathrm{r})$, its components (kinetic energy $G(\mathrm{r})$ and potential energy $V(\mathrm{r})$; as $H(\mathrm{r}) = G(\mathrm{r}) + V(\mathrm{r})$) and their ratio ($|V_b|/G_b$) at BCPs are used [63, 64].

A comparative survey of the reported results clearly indicate the following facts: (1) the large positive values of electron density together with the negative values of $\nabla^2\rho_b$and H_b and also $|V_b|/G_b > 2$ values on C1–N1 and C7–N1 BCPs in **3f-6 membered** and **3f-7 membered** compounds, respectively, proves the covalent character of these newly formed bonds; (2) The calculated values of electron density properties and indicators on C1–N1 BCP in the **3f-6 membered** compound (as a new formed bond via the intramolecular cyclization process), is larger and electron-richer than that of the **3f-7 membered** compound, C7–N1 BCP (with 0.254 and 0.214 electron density values for C1–N1 and C7–N1 BCPs in **3f-6 membered** and **3f-7 membered** compounds, respectively). On the other hand, at (C1–C2–N2–C3–C4–N1) RCP (that is formed through the intramolecular cyclization) in the **3f-6 membered** compound, the computed value of $\rho(\mathrm{r})$ is larger than that of the **3f-7 membered** compound, (C7–C1–C2–N2–C3–C4–N1) RCP (with 0.021 and 0.013 electron density values for the aforementioned RCPs in **3f-6 membered** and **3f-7 membered** compounds, respectively).

It is worthwhile to note that all calculated QTAIM results confirmed the more electronic tendency to produce the **3f-6 membered** compound through an intramolecular cyclization procedure and, thus, these quantum chemical issues can be mainly considered as a theoretical basis for the experimental preference in producing the **3f-6 membered** compound with high yields via the cyclization reaction.

From another viewpoint, in the next step we focused on the comparative evaluation of the effect of various chemical environments on the energetic aspects in the cyclization reaction of diamide Ugi-adducts to their corresponding diones, via PCM computations [55]. In this respect, we have determined the electronic energy of cyclization reaction at the M08-HX/6-311+G** level of theory in the presence of dimethylformamide (DMF), methanol, acetonitrile and water as solvents.

In Table 6, we have reported comparatively the M08-HX/6-311+G** calculated electronic energy changes of the cyclization reaction. The reported results of Table 6 reveal the following two facts: (1) the energetic preference in the formation of the **3f-6** membered compound through the cyclization reaction, in all solution phases (with negative values of electronic energy changes for producing **3f-6** membered compound in comparison with positive values for producing **3f-7** membered compound, and (2) the cyclization process is more favorable energetically in DMF solution than methanol, acetonitrile and water, respectively, which confirms the experimental preference trend in using DMF, methanol, acetonitrile and water as solvent.

Moreover, in order to assess the solvent effect more accurately on the cyclization reaction mode, we have concentrated on evaluation of some key bond orders in **3f-6** membered and **3f-7** membered compounds in the solution phases. In this respect, we

Table 6 The selected bond lengths and angles of the **3f-6 membered** compound, calculated at B3LYP/6-31G* and M08-HX/6-31G* levels of theory together with X-ray values

Calculated experimental dev (%)
X-ray

	M08-HX/6-31G*	B3LYP/6-31G*		M08-HX/6-31G*	B3LYP/6-31G*
Bond lengths (Å)					
N2–C6	1.42	1.43	1.43	−0.006	0.000
N2–C3	1.47	1.48	1.45	0.013	0.020
N2–C2	1.38	1.38	1.37	0.007	0.007
C1–C2	1.52	1.53	1.52	0.000	0.006
C3–C4	1.53	1.55	1.51	0.013	0.026
N1–C4	1.36	1.38	1.35	0.007	0.022
C1–N1	1.46	1.49	1.46	0.000	0.020
N1–C5	1.47	1.50	1.48	−0.006	0.013
C4–O2	1.23	1.24	1.21	0.016	0.024
C2–O1	1.23	1.24	1.21	0.016	0.024
C1–C7	1.55	1.55	1.54	0.006	0.006
C7–C8	1.51	1.52	1.52	−0.006	0.000
C8–O3	1.23	1.25	1.21	0.016	0.033
C8–C9	1.48	1.48	1.49	−0.006	−0.006
Bond angles (°)					
C1–N1–C4	119.3	117.6	123.4	−0.033	−0.047
C2-N2–C3	119.6	117.9	123.0	−0.027	−0.041
C2–C1–N1	109.0	110.3	106.4	0.024	0.036
C3–C4–N1	113.8	112.5	114.0	−0.001	−0.013
C4–C3–N2	112.5	113.8	115.2	−0.023	−0.012
C1–C2–N2	112.5	110.3	114.2	−0.014	−0.034

Two last columns contain the deviation percentages between the calculated results with crystallographic data. Note that numbering of atoms is in accordance with Fig. 4

have calculated C1–N1 and C7–N1 bond orders, that were newly formed via the intramolecular cyclization process in **3f-6** membered and **3f-7** membered compounds, respectively, at the M08-HX/6-311+G** level of theory in the presence of DMF, methanol, acetonitrile and water as solvents (presented in Table 7). The reported results of Table 7 demonstrate that both C1–N1 and C7–N1 bond orders in **3f-6** membered and **3f-7 membered** compounds have larger calculated values in DMF solution in comparison with those calculated in methanol, acetonitrile and water, which is in reliable agreement with the obtained experimental results in more efficiency for using DMF as solvent. Furthermore, comparative analysis of C1–N1 with C7–N1 bond orders calculated values in **3f-6** membered and **3f-7** membered compounds, respectively, indicates the more electronic tendency to form the **3f-6** membered compound via an intramolecular cyclization reaction in comparison with the production of the **3f-7** membered compound.

Table 7 Mathematical properties of selected critical points (CPs) in **3f-6 membered** and **3f-7 membered** compounds

	ρ_b	$\nabla^2\rho_b$	G_b	V_b	H_b	$\lvert V_b\rvert/G_b$
3f-6 membered						
BCP (C1–N1)	0.2547	−0.6434	0.1304	−0.4218	−0.2914	3.2346
RCP (C1–C2–N2–C3–C4–N1)	0.0216	0.1411	0.0295	−0.0238	0.0057	0.8067
3f-7 membered						
BCP(C7–N1)	0.2149	−0.6506	0.1175	−0.3977	−0.2802	3.3846
RCP(C7–C1–C2–N2–C3–C4–N1)	0.0138	0.0673	0.0142	−0.0115	0.0027	0.8098

The properties were obtained via QTAIM analysis on the M08-HX/6-311+G** calculated wave function of electron density. Note that numbering of atoms is in accordance with Fig. 5

Biological activity

Antibacterial and antifungal activities

In the following, the synthesized compounds were screened for their antibacterial and antifungal activity against two Gram +ve [*Staphylococcus aureus* (ATCC 25923) and methicillin resistant *S. aureus* (MRSA) (ATCC BAA-1683)] and three Gram −ve strains [*E. coli* (ATCC 25922), *Klebsiella pneumonia* (ATCC 31488) and also *Pseudomonas aeruginosa* (ATCC 27853)] as well as one fungal species [*Candida albicans* (ATCC 10231)] using the disc diffusion assay. These compounds showing a zone of inhibition >7 mm were chosen to further determine their MBC values. The results are summarized in Table 8. Ciprofloxacin and ampicillin were used as standards for the antibacterial assay, and also tioconazole was used for the antifungal assay.

Table 8 Antibacterial and antifungal activity of the synthesized compounds

Compound	Gram +ve bacteria		Gram −ve bacteria			Fungi
	S. aureus	*MRSA*	*E. coli*	*P. aeruginosa*	*K. pneumoniae*	*C. albicans*
2b	39.06	–	–	–	–	–
2f	19.53	–	–	–	–	–
b3	–		–	–	–	117.18
3c	–	–	78.125	–	–	–
3h		19.53	–	–	–	–
Ampicillin	19.53	625	312.5	1250	312.5	312.5
Ciprofloxacin	0.61	2.44	0.61	0.61	1.22	0.61
Tioconazole	–	–	–	–	–	39.06
DMSO	–	–	–	–	–	–

MBCs in μg mL^{-1}

Compounds, **2b** and **2f** showed MBCs of 39.06 μg mL^{-1} (for **2b**) and 19.53 μg mL^{-1} (for both **2f**) against *S. aureus*. Compound **2b** had a methoxy group on the aroylacrylic-derived portion and a benzyl group on the amine-derived portion, while compound **2f** had a *p*-methylphenyl moiety instead of the benzyl moiety on the amine-derived portion. Compound **2f** contained a *p*-methyl group on the aroylacrylic-derived portion and an unsubstituted phenyl group on the amine-derived portion. A generalization cannot be made regarding the structure of the molecules and their antibacterial activity, and; therefore, these specific groups on **2b** and **2f** must be regarded as important with regard to their antibacterial activity.

Compound **3h** (the cyclized Ugi product) with a *p*-methyl aroylacrylic moiety and an anisidine-derived amine moiety were active against MRSA in at least one order of magnitude better than ampicillin (MBCs of 19.53 μg mL^{-1} for **3h** and 625 μg mL^{-1} for ampicillin).

Compound **3c** was the only compound active against any of the Gram −ve bacterial species, being active against *E. coli* with an MBC of 78.125 μg mL^{-1}. Compound **3c** had a *p*-methyl aroylacrylic moiety with an *n*-butylamine-derived amine portion. Likewise, the cyclized Ugi compound **3b** from **2b** mentioned above was the only compound active against *C. albicans* with a MBC of 117.18 μg mL^{-1}, three times more than the standard, tioconazole. Although, some of the synthesized compounds did show antibacterial and antifungal activity, all were at least 1–2 orders of magnitude greater than that of ciprofloxacin, which was active against all the bacterial and fungal species at MBCs of 0.61 to 2.44 μg mL^{-1}.

Experimental section

Experimental procedures

Chemicals were purchased from Fluka, Merck, and Aldrich chemical companies. Melting points are uncorrected. IR spectra were recorded on a Shimadzu infrared spectrophotometer IR-435. Nuclear magnetic resonance NMR spectra were recorded on a Bruker Avance 400 MHz Spectrometer in $CDCl_3$ and referenced against tetramethylsilane (TMS). A Leco CHNS, model 932, was used for elemental analysis.

Synthesis of Ugi-adducts **2***: general procedure*

Aroylacrylic acid (0.5 mmol) and isocyanide (0.5 mmol) were added to a stirred solution of aldehyde (0.5 mmol) and amine (0.5 mmol) in MeOH (3 mL) at room temperature. This reaction was monitored by TLC after 24 h. The obtained solid was filtered and washed with Et_2O.

Cyclization of Ugi-adducts **3***: general procedure*

K_2CO_3 (1 mmol) was added into a DMF solution (2 mL) of Ugi-adduct (0.5 mmol) at room temperature. The reaction was monitored by TLC using *n*-hexanes and ethyl acetate as eluent. Upon completion of the reaction, water was added to the reaction mixture. The precipitated solid was filtered off and the collected solid recrystallized from EtOH.

Biological tests

The compounds were evaluated for their in vitro antibactericidal activity using the disc diffusion method. Two strains of *Staphylococcus aureus* (Gram +ve bacteria), *S. aureus* ATCC 25923 and *S. aureus* Rosenbach ATCC BAA-1683 (methicillin resistant *S. aureus*) (MRSA) and three Gram −ve bacteria, *Escherichia coli* ATCC 25922, *K. pneumonia* ATCC 31488 and *P. aeruginosa* ATCC 27853 were used for this study. The compounds were also evaluated for antifungal activity against *C. albicans ATCC 10231.*

The bacterial cultures were grown overnight at 37 °C in Mueller-Hinton nutrient broth and thereafter adjusted to a 0.5 McFarland standard using distilled water and lawn inoculated onto Mueller-Hinton agar (MHA) plates. A volume of 10 μL of each sample (19–24 mM, 1 mL DMSO) was inoculated onto antibiotic assay discs (6 mm diameter) and placed on the MHA plates, which were incubated overnight at 37 °C and, thereafter, the zones of inhibition were measured. Only some compounds showing a zone of inhibition >7 mm were selected for the broth dilution method to determine their MBCs.

For the broth dilution method, the microbial cultures were prepared as described previously for the disc diffusion method. The compounds, which were dissolved in dimethyl sulfoxide, were serially diluted with Mueller-Hinton Broth (MHB) (UKZN Biolab, South Africa), inoculated with bacterial cultures, and then incubated at 37 °C for 18 h. A volume of 10 μL of each dilution was spotted on MHA plates and incubated at 37 °C for 18 h to determine the MBC (μg mL^{-1}). All experiments were performed in duplicate.

Conclusion

In conclusion, a two-step synthetic method for the preparation of new 2,5-diketopiperazine derivatives was demonstrated through a convenient Ugi four-component reaction of aroylacrylic acids, diverse aromatic and aliphatic aldehydes, amines and cyclohexyl isocyanide, followed by a Michael addition under K_2CO_3 in DMF at room temperature. All products were produced in good yields, which make it a practical protocol for the library-based synthesis of 2,5-diketopiperazines. Moreover, in order to present the theoretical interpretations for the selective behaviour of the intramolecular cyclization reaction and also the solvent effect, we have assessed these experimental features via DFT, QTAIM, and PCM computational methods in the gas and solution phases, which reliably confirmed the experimental observations. Newly products were evaluated for their antibacterial and antifungal activities.

Experimental data

1. (*E*)-*N*-Benzyl-*N*-(2-(cyclohexylamino)-2-oxoethyl)-4-oxo-4-(*p*-tolyl) but-2-enamide (**2a**); M.p.: 159–163 °C; [requires: C, 74.61; H, 7.22; N, 6.69.; O, 11.47; $C_{26}H_{30}N_2O_3$ (MW = 418.53), Found, C, 74.55; H, 7.25; N, 6.81 %]; FT-IR (KBr): ν_{max} = 3292, 3086, 2933, 2854, 1658, 1637, 1553, 1495 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.92–1.89 (m, 10H), 2.43 (s, 3H), 3.65–3.79 (m, 1H), 4.03 (s, 2H), 4.79 (s, 2H), 6.84 (d, *J* = 7.5 Hz, 1H), 7.21 (d, *J* = 7.0 Hz, 1H), 7.28–7.38 (m, 5H), 7.49 (d, *J* = 14.9 Hz, 1H), 7.89–7.94 (m, 3H), 8.03 (d, *J* = 14.9 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 24.7, 25.3, 25.5, 32.9, 48.5, 51.1, 52.7, 127.0, 128.2, 129.0, 129.6, 129.8, 134.3, 135.4, 135.8, 144.9, 164.6, 166.5, 195.6 ppm.
2. 2.(*E*)-*N*-Benzyl-*N*-(2-(cyclohexylamino)-2-oxoethyl)-4-(4-methoxy-phenyl)-4-oxobut-2-enamide (**2b**); M.p.: 125–130 °C; [requires: C, 71.87; H, 6.96; N, 6.45; $C_{26}H_{30}N_2O_4$ (MW = 434.53), found: C, 72.11; H, 7.19; N, 6.56 %]; FT-IR (KBr): ν_{max} = 3295, 3076, 2933, 2852, 1645, 1596, 1553, 1512, 1436 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.92–1.99 (m, 10H), 3.67–3.77 (m, 1H), 3.88 (s, 3H), 4.03 (s, 2H), 4.79 (s, 2H), 6.40 (d, *J* = 7.5, 1H), 6.95 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.29–7.37 (m, 2H), 7.49 (d, *J* = 14.9 Hz, 1H), 7.96–8.04 (m, 3H), 8.04 (d, *J* = 14.9 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.8, 25.4, 25.6, 25.9, 32.9, 48.4, 51.0, 51.3, 55.7, 114.2, 127.2, 128.3, 128.8, 129.2, 129.9, 130.9, 131.4, 131.5, 135.9, 166.3, 164.4, 167.4, 187.6 ppm.
3. (*E*)-*N*-Butyl-*N*-(2-(cyclohexylamino)-2-oxoethyl)-4-oxo-4-(*p*-tolyl) but-2-enamide (**2c**); M.p.: 101–104 °C; [requires: C, 71.84; H, 8.39; N, 7.29; $C_{23}H_{32}N_2O_3$ (MW = 384.51), found: C, 72.15; H, 8.62; N, 7.41 %]; FT-IR (KBr): ν_{max} = 3290, 3083, 3024, 2963, 2854, 1650, 1554, 1432 cm^{-1}: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86–1.88 (m, 17H), 2.43 (s, 3H), 3.50–3.54 (m, 2H), 3.73–3.79 (m, 1H), 4.05 (s, 2H), 6.40 (d, *J* = 7.3 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.45 (d, *J* = 14.9 Hz, 1H), 7.95 (d, *J* = 8.1 Hz, 2H), 8.01 (d, *J* = 14.9 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7, 19.9, 21.8, 24.66, 24.74, 25.5, 31.3, 32.8, 48.2, 49.9, 52.2, 129.0, 129.6, 131.1, 135.3, 144.9, 165.9, 167.9, 188.8 ppm.
4. (*E*)-*N*-(2-(Cyclohexylamino)-2-oxoethyl)-*N*-(4-methoxyphenyl)-4-oxo-4-(*p*-tolyl)but-2-enamide (**2d**); M.p.: 183–186 °C; [requires: C, 71.87; H, 6.96; N, 6.45; $C_{26}H_{30}N_2O_4$ (MW = 434.53), found: C, 72.12; H, 7.17; N, 6.59 %]; FT-IR (KBr): ν_{max} = 3298, 3075, 3024, 2926, 2853, 1648, 1556, 1511, 1414 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13–1.92 (m, 10H), 2.40 (s, 3H), 3.72–3.81 (m, 1H), 3.80 (m, 3H), 4.34 (s, 2H), 6.21 (d, *J* = 7.4 Hz, 1H), 6.91 (d, *J* = 15.1 Hz, 1H), 6.93(d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.87 (d, *J* = 8.0 Hz, 2H), 7.96 (d, *J* = 15.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.9, 24.9, 25.6, 33.1, 48.5, 55.0, 55.7, 115.3, 128.6, 129.6, 132.2, 134.5, 134.8, 144.9, 159.8, 165.8, 167.4, 189.1 ppm.
5. (*E*)-*N*-(2-(Cyclohexylamino)-2-oxoethyl)-4-oxo-*N*,4-di-*p*-tolylbut-2-enamide (**2e**); M.p.: 226–229 °C; [requires: C, 74.61; H, 7.22; N, 6.69; $C_{26}H_{30}N_2O_3$

(MW = 418.53), found: C, 74.52; H, 7.43; N, 7.05 %]; FT-IR (KBr): ν_{max} = 3300, 3078, 3034, 2926, 2851, 1652, 1605, 1553, 1510, 1443 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13–1.93 (m, 10H), 2.37 (s, 3H), 2.41 (s, 3H), 3.74–3.80 (m, 1H), 4.36 (s, 2H), 6.21 (d, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 15.0 Hz, 1H), 7.12 (d, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 7.5 Hz, 2H), 7.87 (d, *J* = 7.5 Hz, 2H), 7.97 (d, *J* = 15.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 21.9, 24.9, 25.4, 33.1, 48.5, 54.9, 127.4, 129.6, 130.9, 132.2, 134.5, 134.8, 138.9, 139.0, 144.9, 165.7, 167.4, 189.1 ppm.

6. (*E*)-*N*-(2-(Cyclohexylamino)-2-oxoethyl)-4-oxo-*N*-phenyl-4-(*p*-tolyl) but-2-enamide (**2f**); M.p.: 185–187 °C; [requires : C, 74.23; H, 6.98; N, 6.93; $C_{25}H_{28}N_2O_3$ (MW = 404.50), found: C, 74.49; H, 7.19; N, 7.25 %]; FT-IR (KBr): ν_{max} = 3292, 3085, 2930, 2854, 1647, 1600, 1552, 1494, 1494, 1450 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14–2.1 (m, 10H), 2.42 (s, 3H), 3.77–3.81 (m, 1H), 4.38 (s, 2H), 6.18 (d, *J* = 7.4 Hz, 1H), 6.91 (d, *J* = 15.0 Hz, 1H), 7.26–7.45 (m, 7H), 7.87 (d, *J* = 8.3 Hz, 2H), 7.99 (d, *J* = 15.0 Hz, 1H) ppm; ^{13}CNMR (100 MHz, $CDCl_3$): δ = 21.9, 25.1, 25.6, 33.1, 48.5, 55.7, 127.7, 128.9, 129.1, 130.2, 132.1, 135.1, 141.6, 144.8, 165.6, 167.3, 189.1 ppm.
7. (*E*)-*N*-(1-(4-Chlorophenyl)-2-(cyclohexylamino)-2-oxoethyl)-4-oxo-*N*,4-di-*p*-tolylbut-2-enamide (**2g**); M.p.: 209–212 °C; [requires: C, 72.65; H, 6.29; N, 5.29; $C_{32}H_{33}ClN_2O_3$ (MW = 529.07), found: C, 72.19; H, 6.41; N, 5.48 %]; FT-IR (KBr): ν_{max} = 3266, 3078, 3032, 2931, 2854, 1648, 1493, 1447 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05–1.98 (m, 10H), 2.30 (s, 3H), 2.40 (s, 3H), 3.79–3.88 (m, 1H), 5.73 (d, *J* = 8.1 Hz, 1H), 6.02 (s, 1H), 6.76 (d, *J* = 15.0 Hz, 1H), 7.02 (d, *J* = 8.2 Hz, 2H), 7.13 (d, *J* = 8.3 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 7.84 (d, *J* = 8.2 Hz, 2H), 7.94 (d, *J* = 15.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3, 21.9, 24.9, 25.6, 33.0, 48.9, 65.4, 73.6, 128.8, 129.1, 129.6, 130.1, 132.9, 133.0, 134.7, 136.1, 138.9, 144.8, 165.9, 168.1, 189.2 ppm.
8. (*E*)-*N*-(2-(Cyclohexylamino)-1-(4-(dimethylamino) phenyl)-2-oxoethyl)-4-oxo-*N*,4-di-*p*-tolylbut-2-enamide (**2h**); M.p.: 131–135 °C; [requires: C, 75.95; H, 7.31; N, 7.81; $C_{34}H_{39}N_3O_3$ (MW = 537.69), found: C, 76.15; H, 7.45; N, 8.02 %]; FT-IR (KBr): ν_{max} = 3284, 3082, 3033, 2927, 2850, 1649, 1447 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ = 1.01–1.95 (m, 10H), 2.29 (s, 3H), 2.39 (s, 3H), 2.92 (s, 6H), 3.81–3.84 (m, 1H), 5.59 (d, *J* = 7. 0 Hz, 1H), 5.98 (s, 1H), 6.57 (d, *J* = 8.0 Hz, 2H), 6.76 (d, *J* = 15.0 Hz, 1H), 6.99–7.02 (m, 6H), 7.23 (d, *J* = 8.0, 2H), 7.84 (d, *J* = 8 Hz, 2H), 7.92 (d, *J* = 15.0 Hz, 1H) ppm; ^{13}CNMR (100 MHz, $CDCl_3$): δ = 21.3, 21.9, 24.9, 25.7, 33.1, 48.9, 65.8, 129.8, 130.2, 131.5, 133.6, 134.1, 134.6, 136.7, 138.3, 144.6, 165.4, 168.8, 189.5 ppm.
9. (*E*)-*N*-(1-(4-Chlorophenyl)-2-(cyclohexylamino)-2-oxoethyl)-4-(4-methoxyphenyl)-4-oxo-*N*-(*p*-tolyl)but-2-enamide (**2i**); M.p.: 207–210 °C; [requires: C, 70.51; H, 6.10; N, 5.14; $C_{32}H_{33}ClN_2O_4$ (MW = 545.07), found: C, 70.63; H, 6.23; N, 5.26 %]; FT-IR (KBr): ν_{max} = 3271, 3073, 3033, 2929, 2852, 1650, 1493 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01–1.98 (m, 10H),

2.29 (s, 3H), 3.7–3.8 (m, 1H), 3.86 (s, 3H), 5.78 (d, $J = 8.0$ Hz, 1H), 6.02 (s, 1H), 6.74 (d, $J = 15.0$ Hz, 1H), 6.91 (d, $J = 8.0$ Hz, 2H), 7.02 (d, $J = 8.0$ Hz, 2H), 7.13 (d, $J = 8.5$ Hz, 3H), 7.19 (d, $J = 8.5$ Hz, 3H), 7.92 (d, $J = 8.0$ Hz, 2H), 7.95 (d, $J = 15.0$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.3$, 24.85, 24.93, 25.6, 33.0, 48.9, 55.7, 65.3, 114.1, 128.8, 130.1, 131.4, 131.8, 132.6, 133.0, 134.7, 134.8, 136.1, 138.9, 164.2, 165.8, 167.9, 187.9 ppm.

10. (*E*)-*N*-(2-(Cyclohexylamino)-2-oxo-1-(*p*-tolyl)ethyl)-4-oxo-*N*,4-di-*p*-tolylbut-2-enamide (**2j**); M.p.: 188–190 °C; [requires: C, 77.92; H, 7.13; N, 5.51; $C_{33}H_{36}N_2O_3$ (MW = 508.65), found: C, 78.12; H, 7.19; N, 5.63 %]; FT-IR (KBr): $\nu_{max} = 3273$, 3063, 2926, 2852, 1646, 1555, 1511, 1450 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.99$–1.96 (m, 10H), 2.29 (s, 6H), 2.40 (s, 3H), 3.83–3.86 (m, 1H), 5.61 (d, $J = 7.8$ Hz, 1H), 5.99 (s, 1H), 6.77 (d, $J = 15.1$ Hz, 1H), 6.99–7.71 (m, 8H), 7.23 (d, $J = 8.0$ Hz, 2H), 7.84 (d, $J = 8.0$ Hz, 2H), 7.93 (d, $J = 15.0$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.2$, 21.9, 24.9, 25.6, 33.0, 48.9, 66.2, 129.1, 129.4, 129.5, 129.9, 130.1, 130.5, 133.4, 136.7, 138.5, 144.7, 165.5, 168.4, 189.4 ppm.
11. (*E*)-*N*-(1-(4-Chlorophenyl)-2-(cyclohexylamino)-2-oxoethyl)-4-oxo-*N*-phenyl-4-(*p*-tolyl)but-2-enamide (**2k**); M.p.: 168–172 °C; [requires: C, 72.29; H, 6.07; N, 5.44; $C_{31}H_{31}ClN_2O_3$ (MW = 515.04), found: C, 72.51; H, 6.23; N, 5.71 %]; FT-IR (KBr): $\nu_{max} = 3271$, 3069, 3034, 2932, 2852, 1650, 1492, 1650, 1492, 1450 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.04$–2.02 (m, 10H), 2.43 (s, 3H), 3.83–3.92 (m, 1H), 5.79 (d, $J = 8.0$ Hz, 1H), 6.07 (s, 1H), 6.77 (d, $J = 15.0$ Hz, 1H), 7.15 (d, $J = 8.0$ Hz, 3H), 7.21 (d, $J = 8.0$ Hz, 3H), 7.27–7.30 (m, 5H), 7.86 (d, $J = 8.1$ Hz, 2H), 7.97 (d, $J = 15.0$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.9$, 24.9, 25.6, 33.0, 49.0, 65.4, 128.3, 128.9, 129.1, 129.4, 129.6, 130.4, 132.9, 134.5, 134.8, 138.8, 144.8, 165.5, 167.9, 189.2 ppm.
12. (*E*)-*N*-Butyl-*N*-(1-(4-chlorophenyl)-2-(cyclohexylamino)-2-oxo-ethyl)-4-oxo-4-(*p*-tolyl)but-2-enamide (**2l**); M.p.: 156–159 °C; [requires: C, 70.36; H, 7.13; N, 5.66; $C_{29}H_{35}ClN_2O_3$ (MW = 494.05), found: C, 70.52; H, 7.21; N, 5.74 %]; FT-IR (KBr): $\nu_{max} = 3279$, 3086, 3035, 2930, 2851, 1648, 1489, 1449, 1416 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): $\delta = 0.76$–1.93 (m, 17H), 2.43(s, 3H), 3.41–3.47 (m, 2H), 3.80–3.82 (m, 1H), 5.89 (s, 1H), 5.95 (d, $J = 7.6$ Hz, 1H), 7.30 (d, $J = 8.0$ Hz, 2H), 7.33–7.39 (m, 4H), 7.42 (d, $J = 14.8$ Hz, 1H), 7.94 (d, $J = 8.0$ Hz, 2H), 8.02 (d, $J = 14.8$, 1H) ppm; ^{13}CNMR (100 MHz, $CDCl_3$): $\delta = 13.6$, 20.1, 21.9, 24.8, 25.6, 32.8, 32.9, 47.1, 48.8, 62.5, 128.7, 129.2, 129.7, 130.8, 132.1, 133.8, 135.5, 145.0, 166.1, 168.1, 189.1 ppm.
13. 4-Benzyl-1-cyclohexyl-3-(2-oxo-2-(*p*-tolyl) ethyl)piperazine-2,5-dione (**3a**); M.p.: 142–145 °C; [requires: C, 74.61; H, 7.22; N, 6.69; O, 11.47, $C_{26}H_{30}N_2O_3$ (MW = 418.53), found: C, 74.52; H, 7.43; N, 6.82 %]; FT-IR (KBr): $\nu_{max} = 3067$, 3032, 2961, 2854, 1647, 1474 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.06$–1.89 (m, 10H), 2.43 (s, 3H), 3.60–3.64 (m, 2H), 3.74–3.83 (m, 1H), 4.27 (d, $J = 17.0$ Hz, 1H), 4.46 (s, 2H), 4.49–4.52 (t, $J = 4.2$ Hz, 1H), 4.57 (d, $J = 17.0$ Hz, 1H), 7.22–7.32 (m, 7H), 7.80 (d, $J = 8.2$ Hz, 2H) ppm; ^{13}CNMR (100 MHz, $CDCl_3$): $\delta = 21.9$, 25.5, 26.1,

26.3, 29.7, 30.8, 41.1, 49.6, 50.3, 55.1, 56.9, 128.1, 128.3, 128.6, 129.7, 129.9, 134.0, 135.4, 144.8, 164.7, 166.8, 195.6 ppm.

14. 1-Benzyl-4-cyclohexyl-3-(2-(4-methoxyphenyl)-2-oxoethyl)-piperazine-2,5-dione (**3b**); M.p.: 143–146 °C; [requires: C, 71.87; H, 6.96; N, 6.45; $C_{26}H_{30}N_2O_4$ (MW = 434.53), found: C, 72.15; H, 6.71; N, 6.62 %]; FT-IR (KBr): $\nu_{max} = 3075, 3036, 3005, 2931, 2856, 1667, 1465$, cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 1.06$–1.84 (m, 10H), 3.54–3.57 (m, 2H), 3.69–3.74 (m, 2H), 3.74 (m, 2H), 3.84 (s, 3H), 4.22 (d, $J = 17.0$ Hz, 1H), 4.46 (t, $J = 3.9$ Hz, 1H), 4.52 (d, $J = 17.0$ Hz, 1H), 6.9 (d, $J = 8.8$ Hz, 2H), 7.2 (m, 2H), 7.27 (d, $J = 7.4$ Hz, 2H), 7.86 (d, $J = 8.8$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 25.35$, 25.98, 29.6, 30.6, 31.4, 36.5, 40.7, 49.4, 50.2, 55.0, 55.5, 56.9, 113.98, 127.9, 128.4, 128.8, 129.4, 130.4, 135.3, 162.6, 164.0, 164.5, 166.8, 194.4 ppm.
15. 1-Butyl-4-cyclohexyl-3-(2-oxo-2-(*p*-tolyl) ethyl) piperazine-2,5-dione (**3c**); M.p.: 111–115 °C; [requires: C, 71.84; H, 8.39; N, 7.29; $C_{23}H_{32}N_2O_3$ (MW = 384.51), found: C, 72.11; H, 8.48; N, 7.52 %]; FT-IR (KBr): $\nu_{max} = 3028, 2930, 2856, 1663, 1452\ cm^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.88$–1.82 (m, 17H), 2.40 (s, 3H), 3.21–3.27 (m, 2H), 3.42–3.46 (m, 2H), 3.74–3.79 (m, 1H), 3.83 (d, $J = 16.8$ Hz, 1H), 4.38–4.39 (t, $J = 4.8$ Hz, 1H), 4.43 (d, $J = 16.8$ Hz, 1H), 7.25 (d, $J = 7.9$ Hz, 2H), 7.79 (d, $J = 7.9$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.9$, 20.1, 21.8, 25.5, 26.1, 28.5, 29.7, 30.7, 41.0, 46.1, 50.9, 55.2, 57.1, 128.2, 129.6, 134.0, 144.7, 164.8, 166.4, 195.7 ppm.
16. 1-Cyclohexyl-4-(4-methoxyphenyl)-3-(2-oxo-2-(*p*-tolyl)ethyl) piperazine-2,5-dione (**3d**); M.p.: 159–162 °C; [requires: C, 71.87; H, 6.96; N, 6.45; $C_{26}H_{30}N_2O_4$ (MW = 434.53), found: C, 72.01; H, 7.15; N, 6.55 %]; FT-IR (KBr): $\nu_{max} = 3062, 3012, 2934, 2853, 1603, 1449\ cm^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.13$–1.91 (m, 10H), 2.39 (s, 3H), 3.69–3.72 (m, 1H), 3.75 (s, 2H), 3.80 (s, 3H), 4.08 (d, $J = 16.7$, 1H), 4.49 (t, $J = 3.9$ Hz, 1H), 4.81 (d, $J = 16.7$ Hz, 1H), 6.89 (d, $J = 8.0$ Hz, 2H), 7.15 (d, $J = 8.4$ Hz, 2H), 7.25 (d, $J = 8.0$ Hz, 2H), 7.86 (d, $J = 8.4$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.9$, 24.9, 25.6, 26.2, 29.8, 33.1, 41.3, 48.5, 54.3, 55.1, 55.6, 57.3, 115.3, 126.9, 128.3, 129.1, 133.2, 134.8, 144.9, 159.7, 164.7, 165.9, 167.4, 189.1, 195.9 ppm.
17. 4-Cyclohexyl-3-(2-oxo-2-(*p*-tolyl)ethyl)-1-(*p*-tolyl) piperazine-2,5-dione (**3e**); M.p.: 181–185 °C; [requires: C, 74.61; H, 7.22; N, 6.69; $C_{26}H_{30}N_2O_3$ (MW = 418.53), found: C, 74.82; H, 7.41; N, 6.85 %]; FT-IR (KBr): $\nu_{max} = 3030, 2930, 285, 1665, 1448\ cm^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.089$–1.92 (m, 10H), 2.34 (s, 3H), 2.42 (s, 3H), 3.69–3.72 (m, 2H), 3.83–3.84 (m, 1H), 4.11 (d, $J = 16.6$ Hz, 1H), 4.53 (t, $J = 4.0$ Hz, 1H), 4.85(d, $J = 16.6$ Hz, 1H), 7.15 (d, $J = 8.4$ Hz, 2H), 7.19 (d, $J = 8.4$ Hz, 2H), 7.27 (d, $J = 8.4$ Hz, 2H), 7.83 (d, $J = 8.4$ Hz, 2H) ppm; ^{13}CNMR (100 MHz, $CDCl_3$): $\delta = 21.2$, 21.8, 25.5, 26.2, 29.8, 30.9, 41.3, 53.9, 55.63, 57.2, 125.4, 128.3, 130.0, 133.9, 137.7, 144.8, 164.7, 166.9, 195.9 ppm.
18. 4-Cyclohexyl-3-(2-oxo-2-(*p*-tolyl)ethyl)-1-phenyl piperazine-2,5-dione (**3f**); M.p.: 167–170 °C; [requires: C, 74.23; H, 6.98; N, 6.93; $C_{25}H_{28}N_2O_3$

(MW = 404.50), found: C, 74.65; H, 7.23; N, 7.18 %]; FT-IR (KBr): ν_{max} = 3032, 2933, 2856, 1665, 1493 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12–1.92 (m, 10H), 2.41 (s, 3H), 3.65–3.77 (m, 2H), 3.83–3.86 (m, 1H), 4.14 (d, *J* = 16.6 Hz, 1H), 4.54 (t, *J* = 3.8 Hz, 1H), 4.89 (d, *J* = 16.6 Hz, 1H), 7.26 (s, 1H), 7.29 (d, *J* = 7.8, 4H), 7.40 (t, *J* = 7.8, 2H), 7.83 (d, *J* = 8.1 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 25.6, 26.2, 29.4, 30.8, 41.3, 53.9, 55.3, 57.3, 125.6, 127.6, 128.3, 129.5, 129.7, 133.9, 140.3, 144.6, 164.6, 166.9, 195.9 ppm.

19. 3-(4-Chlorophenyl)-1-cyclohexyl-6-(2-oxo-2-(*p*-tolyl)ethyl)-4-(*p*-tolyl)piperazine-2,5-dione (**3g**); M.p.: 232–235 °C; [requires: C, 72.65; H, 6.29; N, 5.29; $C_{32}H_{33}ClN_2O_3$ (MW = 529.07), found: C, 72.75; H, 6.48; N, 5.45 %]; FT-IR (KBr): ν_{max} = 3033, 2927, 2860, 1677, 1605, 1513, 1485, 1430 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ = 1.07–1.80 (m, 10H), 2.24 (s, 3H), 2.43 (s, 3H), 3.47–3.53 (m, 1H), 3.78–3.90 (m, 2H), 4.60 (t, *J* = 3.7 Hz, 1H), 5.72 (s, 1H), 6.95 (d, *J* = 8.2 Hz, 2H), 7.03 (d, *J* = 8.2 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.85 (d, *J* = 8.0, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 21.9, 25.5, 26.3, 30.2, 40.9, 56.2, 59.1, 67.3, 127.2, 128.2, 128.9, 129.65, 129.90, 129.92, 134.0, 136.9, 137.6, 144.8, 166.1, 167.5, 196.4 ppm.
20. 1-Cyclohexyl-3-(4-(dimethylamino)phenyl)-6-(2-oxo-2-(*p*-tolyl) ethyl)-4-(*p*-tolyl) piperazine-2,5-dione (**3h**); M.p.: 153–159 °C; [requires: C, 75.95; H, 7.31; N, 7.81; $C_{34}H_{39}N_3O_3$ (MW = 537.69), found: C, 76.22; H, 7.51; N, 8.02 %]; FT-IR (KBr): ν_{max} = 3029, 2926, 2860, 2799, 1675, 1477 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06–2.20 (m, 10H), 2.23 (s, 3H), 2.42 (s, 3H), 2.91 (s, 6H), 3.42–3.52 (m, 1H), 3.82–3.87 (m, 2H), 4.63 (t, *J* = 3.7 Hz, 1H), 5.54 (s, 1H), 6.96 (d, *J* = 8.2 Hz, 2H), 7.02 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 8.2 Hz, 2H), 7.26–7.29 (m, 4H), 7.86 (d, *J* = 8.1 Hz, 2H) ppm; ^{13}CNMR (100 MHz, $CDCl_3$): δ = 21.2, 21.8, 25.6, 26.4, 30.1, 40.9, 56.2, 59.1, 67.5, 127.3, 128.2, 129.1, 129.6, 129.8, 134.2, 137.2, 144.6, 167.3, 196.3 ppm.
21. 3-(4-Chlorophenyl)-1-cyclohexyl-6-(2-(4-methoxyphenyl)-2-oxoethyl)-4-(*p*-tolyl) piperazine-2,5-dione (**3i**); M.p.: 241–245 °C; [requires: C, 70.51; H, 6.10; N, 5.14; $C_{32}H_{33}ClN_2O_4$ (MW = 545.07), found: C, 70.21; H, 6.33; N, 5.24 %]; FT-IR (KBr): ν_{max} = 3010, 2928, 2587, 1675, 1489, 1434 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.08–1.80 (m, 10H), 2.23 (s, 3H), 3.46–3.52 (m, 2H), 3.79–3.82 (m, 1H), 3.88 (s, 3H), 4.59 (t, *J* = 3.7 Hz, 1H), 5.71 (s, 1H), 6.94–6.97 (m, 4H), 7.02 (d, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 7.94 (d, *J* = 8.5 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 25.5, 26.2, 26.3, 30.2, 40.6, 55.7, 56.3, 59.1, 67.3, 114.1, 127.2, 128.9, 129.5, 129.9, 130.4, 134.0, 137.0, 137.2, 137.6, 164.1, 166.1, 167.6, 195.2 ppm.
22. 1-Cyclohexyl-3-(2-oxo-2-(*p*-tolyl)ethyl)-4,6-di-*p*-tolylpiperazine-2,5-dione (**3j**); M.p.: 223–226 °C; [requires: C, 77.92; H, 7.13; N, 5.51 $C_{33}H_{36}N_2O_3$ (MW = 508.65), found: C, 78.20; H, 7.41; N, 5.71 %]; FT-IR (KBr): ν_{max} = 3029, 2924, 2860, 1678, 1606, 1513, 1432 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04–2.04 (m, 10H), 2.20 (s, 3H), 2.24 (s, 3H), 2.40 (s, 3H), 3.43–3.49 (m, 1H), 3.76–3.86 (m, 2H), 4.59 (t, *J* = 3.1 Hz, 1H), 5.60 (s,

1H), 6.93 (d, $J = 8.0$ Hz, 2H), 6.98 (d, $J = 8.0$ Hz, 2H), 7.02 (d, $J = 8.0$ Hz, 2H), 7.10 (d, $J = 8.0$ Hz, 2H), 7.24 (d, $J = 8.0$ Hz, 2H), 7.83 (d, $J = 8.0$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.1$, 21.7, 25.4, 26.2, 30.0, 40.8, 56.1, 58.9, 67.6, 127.1, 128.1, 128.2, 129.3, 129.5, 129.6, 133.9, 135.5, 137.16, 137.7, 144.5, 166.5, 167.2, 198.2 ppm.

23. 3-(4-Chlorophenyl)-4-cyclohexyl-6-(2-oxo-2-(*p*-tolyl)ethyl)-1-phenylpiperazine-2,5-dione (**3k**); M.p.: 222–225 °C; [requires: C, 72.29; H, 6.07; N, 5.44; $C_{31}H_{31}ClN_2O_3$ (MW = 515.04), found: C, 72.49; H, 6.21; N, 5.62 %]; FT-IR (KBr): $\nu_{max} = 3020$, 2925, 2858, 1672, 1595, 1438 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.03$–2.01 (m, 10H), 2.39 (s, 3H), 3.42–3.48 (m, 1H), 3.79–3.80 (m, 2H), 4.54 (t, $J = 3.3$ Hz, 1H), 5.67 (s, 1H), 6.93 (d, $J = 8.6$ Hz, 2H), 7.13 (d, $J = 8.1$ Hz, 2H), 7.21 (d, $J = 8.1$ Hz, 3H), 7.25(d, $J = 8.1$ Hz, 2H), 7.32 (d, $J = 8.6$ Hz, 2H), 7.81 (d, $J = 8.1$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.9$, 25.5, 26.3, 29.9, 30.2, 40.9, 56.2, 59.3, 67.1, 121.7, 128.3, 129.1, 129.3, 129.7, 129.9, 132.5, 134.3, 136.7, 138.7, 145.1, 165.7, 167.6, 196.5 ppm.
24. 1-Butyl-3-(4-chlorophenyl)-4-cyclohexyl-6-(2-oxo-2-(*p*-tolyl) ethyl) piperazine-2,5-dione (**3l**); M.p. 156–159 °C; [requires: C, 70.36; H, 7.13; N, 5.66 $C_{29}H_{35}ClN_2O_3$ (MW = 495.05), found: C, 70.46; H, 7.25; N, 6.1 %]; FT-IR (KBr): $\nu_{max} = 3034$, 2933, 2857, 1752, 1658, 1572, 1491, 1407 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.76$–1.92 (m, 17H), 2.38 (s, 3H), 2.45–2.48(m, 2H), 3.38–3.42 (m, 1H), 3.69–3.76 (m, 4H), 4.4 (t, $J = 3.3$ Hz, 1H), 5.3 (s, 1H), 7.23–7.42 (m, 4H), 7.79 (d, $J = 8.0$, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.8$, 20.2, 25.4, 26.1, 26.3, 27.7, 30.0, 40.6, 44.6, 55.7, 58.9, 63.95, 128.2, 129.2, 129.4, 129.6, 144.8, 166.1, 167.5, 196.4 ppm.

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