Michael Adducts—Source for Biologically Potent Heterocycles

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Received November 23, 2007; accepted February 13, 2008; published online February 19, 2008

A new class of pyrimidinetriones, thioxopyrimidinediones, pyrazolidinediones and isoxazolidinediones were prepared from (*E*)-1,4-diarylbut-2-ene-1,4-diones. All the new compounds synthesized were screened for antimicrobial activity.

Key words (*E*)-1,4-diarylbut-2-ene-1,4-dione; pyrimidinetrione; thioxopyrimidinedione; pyrazolidinedione; isoxazolidinedione; Michael addition

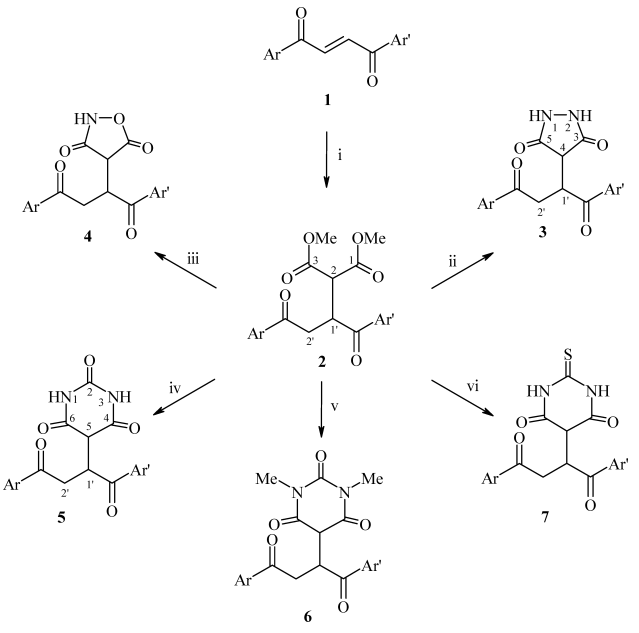
Scientific effort for the design and synthesis of novel heterocyclic compounds has been focused continuously because of their wide range utility as pharmacological agents. Barbiturates are a family of drugs that depress nerve activity in the brain producing changes in mental activity ranging from mild sedation and sleep to deep coma. Commonly they are used to treat anxiety, insomnia, seizure disorders, migraine headaches and in surgery as general anaesthetics.[1—6] In fact, methohexital is still used worldwide in hospitals as injection narcotics.[7] In addition, pyrazole and isoxazole derivatives have gained importance due to their various chemotherapeutic properties *viz.*, bacteriostatic, antidiabetic, analgesic, antiarrhythmic, anti-inflammatory, antifungal and antiviral.[8—13] Indeed celecoxib, a pyrazole derivative and valdecoxib, an isoxazole derivative are now widely used in the market as anti-inflammatory drugs.[14] Hence, it is considered worthwhile to prepare molecules having these heterocyclic moieties by exploiting the synthetic utility of activated olefins *via* Michael addition followed by condensation with different nucleophiles. It is well documented that pyrazole, isoxazole, pyrimidine and thioxopyrimidine derivatives were prepared by treating *gem* dicarboxylates with hydrazine hydrate, hydroxylamine hydrochloride, urea, *N*,*N*′-dimethylurea and thiourea.[15—20]

Chemistry

The Michael adduct, dimethyl 2-(1′,2′-diaroyl-ethyl)malonate (**2**) is prepared by the addition of dimethyl malonate to (*E*)-1,4-diarylbut-2-ene-1,4-dione (**1**). The compound **2** is used as a synthon for the synthesis of different heterocyclic rings. Cyclocondensation of **2** with hydrazine hydrate and hydroxylamine hydrochloride afforded 4-(1′,2′-diaroyl-ethyl)pyrazolidine-3,5-dione (**3**) and 4-(1′,2′-diaroyl-ethyl)-isoxazolidine-3,5-dione (**4**), respectively. Similar reaction of **2** with urea, *N*,*N*′-dimethylurea and thiourea produced 5-(1′,2′-diaroyl-ethyl)pyrimidine-2,4,6-trione (**5**), 1,3-dimethyl-5-(1′,2′-diaroyl-ethyl)pyrimidine-2,4,6-trione (**6**) and 5-(1′,2′-diaroyl-ethyl)-2-thioxopyrimidine-4,6-dione (**7**), respectively (Chart 1).

The IR spectra of **3**—**7** showed absorption bands in the region 1653—1668 (CO–N), and 1712—1732 cm^{-1} (ArCO). Apart from these, compound **4** displayed a band at 1733—1745 (CO–O) and compound **7** exhibited a band at 1490—1499 cm^{-1} (C=S). All the compounds showed an absorption band at 3310—3349 cm^{-1} (NH) except **6**. The ^{1}H-NMR spectra of **3a** and **4a** exhibited a doublet at δ 4.42, 4.45 (C_4-H), a muliplet at 4.32—4.39, 4.32—4.39 (C_1′-H) and two double doublets at 3.11 and 3.83, 3.15 and 3.86 ppm (C_2′-H). Similar type of splitting pattern is exhibited by methylene and methine protons of **5**, **6** and **7**. Thus, a doublet observed at δ 4.46, 4.44, 4.47 is assigned to C_5-H, a multiplet at δ 4.33—4.40, 4.32—4.38, 4.31—4.37 is accounted to C_1′-H and two double doublets at δ 3.12 and 3.82, 3.15 and 3.84, 3.20 and 3.88 ppm to C_2′-H of **5a**, **6a** and **7a** respectively. The structures of the compounds are further established by ^{13}C-NMR spectra.

Antimicrobial Testing The compounds **1**—**7** were tested for *in vitro* antimicrobial activity against the Gram-positive bacteria *Staphylococcus auerus*, *Bacillus subtilis*, the Gram-negative bacteria *Klebsiella pneumoniae*, *Escherichia coli* and fungi *Fusarium solani*, *Curvularia lunata* and *Aspergillus niger*. The primary screen was carried out by agar disc-diffusion method[21] using nutrient agar medium.



(i) $CH_2(COOMe)_2$ / K_2CO_3 / MEK
(ii) $NH_2NH_2.H_2O$ / NaOMe / MeOH
(iii) $NH_2OH.HCl$ / NaOMe / MeOH
(iv) NH_2CONH_2 / NaOMe / MeOH
(v) MeNHCONHMe / NaOMe / MeOH
(vi) NH_2CSNH_2 / NaOMe / MeOH

a: Ar = C_6H_5, Ar' = C_6H_5
b: Ar = *p*-$CH_3C_6H_4$, Ar' = *p*-$CH_3C_6H_4$
c: Ar = *p*-ClC_6H_4, Ar' = *p*-ClC_6H_4
d: Ar = C_6H_5, Ar' = *p*-$CH_3C_6H_4$
e: Ar = C_6H_5, Ar' = *p*-ClC_6H_4
f: Ar = *p*-$CH_3C_6H_4$, Ar' = *p*-ClC_6H_4

Chart 1

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Table 1. The *in Vitro* Antibacterial Activity of the Compounds **1**—**7**

Compound	Concentration (μg)	Zone of inhibition (mm)			
		Gram-positive bacteria		Gram-negative bacteria	
		S. aureus	*B. subtilis*	*E. coli*	*K. pneumoniae*
1a	100	—	—	—	—
	200	—	—	—	—
1b	100	—	—	—	—
	200	7	8	—	—
1c	100	13	9	9	7
	200	14	13	12	10
1d	100	8	7	—	—
	200	10	8	—	—
1e	100	9	10	9	7
	200	13	12	11	9
1f	100	10	9	7	—
	200	12	10	9	—
2a	100	8	7	—	—
	200	10	9	8	7
2b	100	9	11	—	7
	200	10	12	9	9
2c	100	14	12	11	9
	200	16	15	12	13
2d	100	11	10	9	8
	200	13	13	11	10
2e	100	12	11	10	9
	200	15	13	12	11
2f	100	10	9	8	7
	200	13	12	10	10
3a	100	20	18	17	18
	200	23	20	18	21
3b	100	19	14	12	13
	200	21	17	14	14
3c	100	33	32	20	22
	200	37	38	25	22
3d	100	18	16	13	11
	200	21	18	17	14
3e	100	25	31	21	19
	200	29	33	22	24
3f	100	21	17	16	19
	200	25	19	18	22
4a	100	17	18	12	13
	200	19	18	14	14
4b	100	15	16	13	12
	200	18	20	16	14
4c	100	34	34	18	21
	200	38	36	21	23
4d	100	17	16	11	12
	200	18	18	14	14
4e	100	19	20	16	16
	200	22	21	18	17
4f	100	16	17	17	14
	200	18	20	21	17
5a	100	12	14	9	10
	200	16	17	12	12
5b	100	13	12	—	—
	200	15	16	9	9
5c	100	14	11	7	8
	200	16	14	11	11
5d	100	11	10	—	—
	200	14	12	—	—
5e	100	14	12	8	9
	200	15	15	11	10
5f	100	12	15	9	7
	200	15	17	10	9
6a	100	—	—	—	—
	200	12	14	10	9
6b	100	—	—	—	—
	200	—	—	—	—
6c	100	9	11	—	—
	200	12	15	8	11
6d	100	—	—	—	—
	200	—	—	—	—
6e	100	10	12	9	9
	200	14	15	10	10
6f	100	—	—	—	—
	200	12	11	—	—
7a	100	14	12	10	10
	200	19	18	15	13
7b	100	12	13	9	8
	200	16	16	12	13
7c	100	29	26	20	16
	200	33	31	22	20
7d	100	12	13	7	9
	200	15	14	11	12
7e	100	19	24	16	14
	200	23	25	18	17
7f	100	15	13	11	8
	200	17	14	14	12
Chloramphenicol	100	35	38	40	42
	200	39	41	44	45

The minimal inhibitory concentration for the most active compounds **3**, **4** and **7** against the same microorganisms used in the preliminary screening was carried out using microdilution susceptibility method.[22] Chloramphenicol and ketoconazole were used as control drugs. In general, the inhibitory activity against the Gram-positive bacteria was higher than that of the Gram-negative bacteria. The observed data on the antimicrobial activity of the compounds and control drugs were given in Tables 1—3.

The compounds 4-(1′,2′-di(4-chlorobenzoyl)-ethyl)pyrazolidine-3,5-dione (**3c**), 4-(1′-(4-chlorobenzoyl)-2′-benzoyl-ethyl)pyrazolidine-3,5-dione (**3e**), 4-(1′,2′-di(4-chlorobenzoyl)-ethyl)isoxazolidine-3,5-dione (**4c**) and 5-(1′,2′-di(4-chlorobenzoyl)-ethyl)-2-thioxopyrimidine-4,6-dione (**7c**) showed excellent activity against Gram-positive bacteria (inhibitory zone $>$28 mm) and good activity against Gram-negative bacteria (inhibitory zone $>$20 mm). In fact, compounds **3c** and **4c** showed pronounced activity (38 mm) towards Gram-positive bacteria. The compounds 4-(1′,2′-dibenzoyl-ethyl)pyrazolidine-3,5-dione (**3a**), 4-(1′-(4-chlorobenzoyl)-2′-(4-methylbenzoyl)-ethyl)pyrazolidine-3,5-dione (**3f**), 4-(1′-(4-chlorobenzoyl)-2′-benzoyl-ethyl)isoxazolidine-3,5-dione (**4e**), 4-(1′-(4-chlorobenzoyl)-2′-(4-methylbenzoyl)-ethyl)isoxazolidine-3,5-dione (**4f**), 5-(1′-(4-chlorobenzoyl)-2′-benzoyl-ethyl)-2-thioxopyrimidine-4,6-dione (**7e**) displayed moderate to high activity towards Gram-positive bacteria (18—25 mm) and moderate activity towards Gram-negative bacteria (17—22 mm). On the other hand, the compounds **1**, **2**, **5** and **6** exhibited least activity against both bacteria (Table 1).

Antifungal Testing All the test compounds inhibited the spore germination of tested fungi *Fusarium solani*, *Curvularia lunata* and *Aspergillus niger*. The compounds **1** and **2** displayed least activity (7—14 mm). The compounds **3a**, **3c**, **3e**, **3f**, **4c**, **4e**, **4f**, **5c**, **6c**, **7c**, **7e** and **7f** showed high inhibitory

Table 2. The *in Vitro* Antifungal Activity of the Compounds **1**—**7**

Compound	Concentration (μg)	Zone of inhibition (mm)		
		F. solani	*C. lunata*	*A. niger*
1a	100	9	10	8
	200	11	13	12
1b	100	12	11	9
	200	14	10	11
1c	100	12	10	9
	200	14	13	12
1d	100	7	9	8
	200	10	14	10
1e	100	13	11	7
	200	14	14	9
1f	100	11	10	7
	200	13	13	8
2a	100	10	9	9
	200	14	12	11
2b	100	11	10	8
	200	13	13	10
2c	100	12	11	9
	200	14	14	10
2d	100	9	10	7
	200	13	14	9
2e	100	12	10	8
	200	14	13	10
2f	100	13	9	9
	200	14	12	11
3a	100	20	24	18
	200	34	33	32
3b	100	17	16	14
	200	22	18	18
3c	100	35	32	32
	200	39	34	35
3d	100	15	15	16
	200	18	19	18
3e	100	25	24	26
	200	30	31	28
3f	100	17	15	16
	200	32	35	30
4a	100	21	23	15
	200	24	25	19
4b	100	17	16	16
	200	20	18	19
4c	100	36	33	32
	200	38	37	34
4d	100	22	22	18
	200	24	25	22
4e	100	22	19	16
	200	32	31	33
4f	100	23	20	18
	200	34	32	33
5a	100	20	22	17
	200	25	25	20
5b	100	18	16	15
	200	20	19	17
5c	100	22	22	14
	200	32	29	30
5d	100	15	12	13
	200	19	18	18
5e	100	17	18	19
	200	22	20	22
5f	100	16	15	15
	200	20	18	16
6a	100	23	20	20
	200	26	24	22
6b	100	16	17	15
	200	19	19	16
6c	100	22	24	19
	200	30	31	29
6d	100	19	17	14
	200	21	20	17
6e	100	20	18	15
	200	23	21	19
6f	100	18	19	16
	200	20	19	17
7a	100	26	27	25
	200	22	19	17
7b	100	26	25	20
	200	25	23	22
7c	100	29	30	24
	200	33	35	30
7d	100	23	23	16
	200	24	25	20
7e	100	31	26	24
	200	34	30	28
7f	100	28	25	19
	200	30	31	32
Ketoconazole	100	38	41	36
	200	42	44	39

(28—39 mm) effect while the remaining compounds exhibited moderate inhibitory (17—25 mm) effect (Table 2).

The minimum inhibitory concentration (MIC) values were determined as the lowest concentration that completely inhibited visible growth of the microorganisms (Table 3). The structure–antimicrobial activity relationship of the synthesized compounds revealed that the compounds having pyrimidinetrione and *N*,*N*′-dimethylpyrimidinetrione moieties exhibited least activity when compared with the compounds having pyrazolidinedione, isoxazolidinedione and thioxopyrimidinedione moieties. Further, the compounds having 4-chlorophenyl substituent exhibited high activity. The maximum activity was attained with compounds **3c**, **3e** and **4c** having pyrazolidinedione and isoxazolidinedione nucleus with chloro substituent in the aryl group.

Conclusion

A variety of heterocycles, pyrimidine, pyrazole and isoxazole derivatives are developed adopting simple, elegant and well-versed methodology from (*E*)-1,4-diarylbut-2-ene-1,4-dione. The *in vitro* antimicrobial activity of the compounds revealed that the compounds, pyrazolidinediones and isoxazolidinediones having chloro substituent in the aryl group showed greater activity. Further, the Michael acceptors **1** and the Michael adducts **2** displayed lower antimicrobial activity when compared with the heterocyclic compounds **3**—**7**.

Experimental

Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. The purity of the compounds was checked by TLC (silica gel H, BDH, ethyl acetate/hexane, 1 : 3). The IR spectra were recorded on a Thermo Nicolet IR200 FT-IR spectrometer as KBr pellets and the wave numbers were given in cm^{-1}. The ^{1}H-NMR spectra were recorded in $CDCl_3$/DMSO-d_6 on a Varian EM-360 spectrometer (300 MHz). The ^{13}C-NMR spectra were recorded in $CDCl_3$/DMSO-d_6 on a Varian VXR spectrometer operating at 75.5 MHz. All chemical shifts are reported in δ (ppm) using TMS as an internal standard. The microanalyses were performed on a Perkin-Elmer 240C elemental analyzer. The starting compounds (*E*)-1,4-diarylbut-2-ene-1,4-dione (**1**) was prepared by the literature procedure.[23]

General Procedure of Synthesis of Dimethyl 2-(1′,2′-diaroylethyl)malonate (2a—f) A mixture of dimethyl malonate (15 mmol),

Table 3. The MICs of the Compounds **3c**, **3e** and **4c** against Bacteria and Fungi

Compound	Minimal inhibitory concentration MIC, μg/ml						
	S. aureus	*B. subtilis*	*E. coli*	*K. pneumoniae*	*F. solani*	*C. lunata*	*A. niger*
3c	12.5	12.5	25	50	25	25	12.5
3e	50	50	100	100	50	100	50
4c	25	25	50	50	25	25	12.5
Chloramphenicol	6.25	6.25	6.25	12.5	—	—	—
Ketoconazole	—	—	—	—	12.5	6.25	6.25

methyl ethyl ketone (5 ml) and potassium carbonate (10 mmol) was cooled to 5—10 °C. To this, compound **1** (10 mmol) was added and stirred for 3—5 h maintaining the same temperature. The contents of the flask were diluted with water and extracted with CH_2Cl_2. The organic layer was washed with water, brine and dried (anhyd. Na_2SO_4). The solvent was removed *in vacuo*. The resultant solid was recrystallized from 2-propanol.

Dimethyl 2-(1′,2′-Dibenzoyl-ethyl)malonate (**2a**): White solid; yield 74%, mp 98—100 °C; IR (KBr) cm^{-1}: 1712 (C=O), 1736 (CO–O); ^{1}H-NMR (DMSO-d_6) δ: 3.45 (dd, 1H, C_2′-H, J=8.9, 14.4 Hz), 3.53 (dd, 1H, C_2′-H, J=4.2, 14.9 Hz), 3.58 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 4.02 (d, 1H, C_2-H, J=8.2 Hz), 4.20—4.27 (m, 1H, C_1′-H), 7.15—7.36 (m, 10H, Ar-H); ^{13}C-NMR (DMSO-d_6) δ: 39.4 (C-1′), 52.5 and 53.3 (OCH_3), 54.7 (C-2′), 60.7 (C-2), 167.8 and 168.6 (CO_2Me), 202.5 (Ar-CO), 205.7 (Ar′-CO), 127.8, 129.6, 130.1, 131.5, 133.7, 134.2, 135.9, 138.1 (aromatic carbons); *Anal.* Calcd for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47; Found: C, 68.50; H, 5.41.

Dimethyl 2-(1′,2′-Di(4-methylbenzoyl)-ethyl)malonate (**2b**): White solid; yield 77%, mp 148—150 °C; IR (KBr) cm^{-1}: 1727 (C=O), 1742 (CO–O); ^{1}H-NMR (DMSO-d_6) δ: 2.32 (s, 6H, Ar-CH_3, Ar′-CH_3), 3.42 (dd, 1H, C_2′-H, J=9.0, 14.3 Hz), 3.56 (dd, 1H, C_2′-H, J=4.5, 14.8 Hz), 3.59 (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3), 4.05 (d, 1H, C_2-H, J=8.4 Hz), 4.24—4.30 (m, 1H, C_1′-H), 7.21—7.72 (m, 8H, Ar-H); ^{13}C-NMR (DMSO-d_6) δ: 22.7 (Ar-CH_3, Ar′-CH_3), 39.7 (C-1′), 52.9 and 53.5 (OCH_3), 54.5 (C-2′), 60.2 (C-2), 167.2 and 168.1 (CO_2Me), 201.5 (Ar-CO), 204.1 (Ar′-CO), 128.2, 129.2, 130.4, 132.6, 133.2, 133.8, 135.4 (aromatic carbons); *Anal.* Calcd for $C_{23}H_{24}O_6$: C, 69.68; H, 6.10; Found: C, 69.63; H, 6.06.

Dimethyl 2-(1′,2′-Di(4-chlorobenzoyl)-ethyl)malonate (**2c**): Colourless crystals, yield 75%, mp 180—182 °C; IR (KBr) cm^{-1}: 1725 (C=O), 1748 (CO–O); ^{1}H-NMR (DMSO-d_6) δ: 3.40 (dd, 1H, C_2′-H, J=9.2, 14.6 Hz), 3.54 (dd, 1H, C_2′-H, J=4.4, 14.9 Hz), 3.63 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 4.07 (d, 1H, C_2-H, J=8.5 Hz), 4.28—4.35 (m, 1H, C_1′-H), 7.24—7.77 (m, 8H, Ar-H); ^{13}C-NMR (DMSO-d_6) δ: 39.3 (C-1′), 52.3 and 53.0 (OCH_3), 54.8 (C-2′), 60.5 (C-2), 168.3 and 168.9 (CO_2Me), 202.5 (Ar-CO), 204.8 (Ar′-CO), 128.7, 130.0, 130.8, 131.4, 133.1, 133.6, 134.7, 135.5 (aromatic carbons); *Anal.* Calcd for $C_{21}H_{18}Cl_2O_6$: C, 57.68; H, 4.15; Found: C, 57.71; H, 4.10.

Dimethyl 2-(1′-(4-Methylbenzoyl)-2′-benzoyl-ethyl)malonate (**2d**): White solid, yield 78%, mp 138—140 °C; IR (KBr) cm^{-1}: 1716 (C=O), 1738 (CO–O); ^{1}H-NMR (DMSO-d_6) δ: 2.35 (s, 3H, Ar′-CH_3), 3.46 (dd, 1H, C_2′-H, J=9.1, 14.6 Hz), 3.54 (dd, 1H, C_2′-H, J=4.3, 14.8 Hz), 3.60 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 4.01 (d, 1H, C_2-H, J=8.3 Hz), 4.25—4.31 (m, 1H, C_1′-H), 7.19—7.46 (m, 9H, Ar-H); ^{13}C-NMR (DMSO-d_6) δ: 22.2 (Ar′-CH_3), 39.9 (C-1′), 52.2 and 53.1 (OCH_3), 54.3 (C-2′), 60.2 (C-2), 167.5 and 168.1 (CO_2Me), 201.6 (Ar-CO), 204.1 (Ar′-CO), 129.6, 130.4, 131.3, 131.8, 133.4, 134.6, 135.3 (aromatic carbons); *Anal.* Calcd for $C_{22}H_{22}O_6$: C, 69.10; H, 5.80; Found: C, 69.14; H, 5.76.

Dimethyl 2-(1′-(4-Chlorobenzoyl)-2′-benzoyl-ethyl)malonate (**2e**): White crystals, yield 70%, mp 165—167 °C; IR (KBr) cm^{-1}: 1722 (C=O), 1736 (CO–O); ^{1}H-NMR (DMSO-d_6) δ: 3.46 (dd, 1H, C_2′-H, J=8.9, 14.5 Hz), 3.55 (dd, 1H, C_2′-H, J=4.4, 14.9 Hz), 3.62 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 4.03 (d, 1H, C_2-H, J=8.5 Hz), 4.21—4.27 (m, 1H, C_1′-H), 7.14—7.39 (m, 9H, Ar-H); ^{13}C-NMR (DMSO-d_6) δ: 39.5 (C-1′), 52.8 and 53.5 (OCH_3), 54.4 (C-2′), 60.7 (C-2), 167.6 and 168.4 (CO_2Me), 201.9 (Ar-CO), 204.7 (Ar′-CO), 128.4, 129.7, 131.8, 132.4, 134.2, 134.7, 135.7, 138.3 (aromatic carbons); *Anal.* Calcd for $C_{21}H_{19}ClO_6$: C, 62.61; H, 4.75; Found: C, 62.66; H, 4.79.

Dimethyl 2-(1′-(4-Chlorobenzoyl)-2′-(4-methylbenzoyl)-ethyl)malonate (**2f**): White solid, yield 73%, mp 174—176 °C; IR (KBr) cm^{-1}: 1726 (C=O), 1734 (CO–O); ^{1}H-NMR (DMSO-d_6) δ: 2.33 (s, 3H, Ar-CH_3), 3.49 (dd, 1H, C_2′-H, J=9.1, 14.6 Hz), 3.57 (dd, 1H, C_2′-H, J=4.3, 14.8 Hz), 3.63 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 4.01 (d, 1H, C_2-H, J=8.2 Hz), 4.22—4.30 (m, 1H, C_1′-H), 7.19—7.47 (m, 8H, Ar-H); ^{13}C-NMR (DMSO-d_6) δ: 22.9 (Ar-CH_3), 39.3 (C-1′), 52.7 and 53.3 (OCH_3), 54.9 (C-2′), 60.3 (C-2), 167.7 and 168.5 (CO_2Me), 201.6 (Ar-CO), 203.6 (Ar′-CO), 129.3, 129.8, 130.7, 131.4, 133.5, 134.3, 136.1, 137.4 (aromatic carbons); *Anal.* Calcd for $C_{22}H_{21}ClO_6$: C, 63.39; H, 5.08; Found: C, 63.34; H, 5.12.

General Procedure of Synthesis of 4-(1′,2′-Diaroyl-ethyl)pyrazolidine-3,5-dione (3a-f) The compound **2** (10 mmol), hydrazine hydrate (15 mmol), MeOH (20 ml) and 10% NaOMe (5 ml) was refluxed for 4—5 h. The solution was cooled and poured onto crushed ice containing conc. HCl. The solid obtained was filtered, dried and recrystallized from MeOH.

4-(1′,2′-Dibenzoyl-ethyl)pyrazolidine-3,5-dione (**3a**): Yellow solid, yield 79%, mp 190—192 °C; IR (KBr) cm^{-1}: 1662 (CO–NH), 1721 (C=O), 3325 (NH); ^{1}H-NMR ($CDCl_3$) δ: 3.11 (dd, 1H, C_2′-H, J=3.3, 15.1 Hz), 3.83 (dd, 1H, C_2′-H, J=9.6, 14.9 Hz), 4.32—4.39 (m, 1H, C_1′-H), 4.42 (d, 1H, C_4-H, J=13.6 Hz), 7.06—7.94 (m, 10H, Ar-H), 9.04 (bs, 2H, NH); ^{13}C-NMR ($CDCl_3$) δ: 52.7 (C-2′), 57.4 (C-1′), 63.3 (C-4), 171.5 (C-3, C-5), 204.5 (Ar-CO), 205.8 (Ar′-CO), 129.6, 130.5, 131.1, 132.0, 133.3, 133.7, 135.3, 136.8 (aromatic carbons). *Anal.* Calcd for $C_{19}H_{16}N_2O_4$: C, 67.85; H, 4.79; N, 8.33; Found: C, 68.00; H, 4.85; N, 8.47.

4-(1′,2′-Di(4-methylbenzoyl)-ethyl)pyrazolidine-3,5-dione (**3b**): Light yellow solid, yield 72%, mp 202—204 °C; IR (KBr) cm^{-1}: 1664 (CO–NH), 1725 (C=O), 3329 (NH); ^{1}H-NMR ($CDCl_3$) δ: 2.29 (s, 6H, Ar-CH_3, Ar′-CH_3), 3.13 (dd, 1H, C_2′-H, J=3.5, 15.0 Hz), 3.80 (dd, 1H, C_2′-H, J=9.5, 15.1 Hz), 4.30—4.38 (m, 1H, C_1′-H), 4.45 (d, 1H, C_4-H, J=14.0 Hz), 7.06—7.92 (m, 8H, Ar-H), 9.10 (bs, 2H, NH); ^{13}C-NMR ($CDCl_3$) δ: 23.7 (Ar-CH_3, Ar′-CH_3), 53.5 (C-2′), 58.2 (C-1′), 62.5 (C-4), 172.3 (C-3, C-5), 203.8 (Ar-CO), 204.9 (Ar′-CO), 128.1, 129.4, 130.6, 131.9, 132.6, 134.8, 135.5 (aromatic carbons). *Anal.* Calcd for $C_{21}H_{20}N_2O_4$: C, 69.22; H, 5.53; N, 7.69; Found: C, 69.32; H, 5.50; N, 7.79.

4-(1′,2′-Di(4-chlorobenzoyl)-ethyl)pyrazolidine-3,5-dione (**3c**): Colourless crystals, yield 77%, mp 214—216 °C; IR (KBr) cm^{-1}: 1656 (CO–NH), 1724 (C=O), 3310 (NH); ^{1}H-NMR ($CDCl_3$) δ: 3.15 (dd, 1H, C_2′-H, J=3.7, 14.9 Hz), 3.79 (dd, 1H, C_2′-H, J=9.7, 15.0 Hz), 4.33—4.39 (m, 1H, C_1′-H), 4.47 (d, 1H, C_4-H, J=13.5 Hz), 7.01—7.79 (m, 8H, Ar-H), 9.44 (bs, 2H, NH); ^{13}C-NMR ($CDCl_3$) δ: 53.9 (C-2′), 58.8 (C-1′), 63.8 (C-4), 172.5 (C-3, C-5), 204.3 (Ar-CO), 205.5 (Ar′-CO), 129.5, 130.8, 131.5, 132.6, 133.4, 134.1, 135.6, 137.2 (aromatic carbons). *Anal.* Calcd for $C_{19}H_{14}Cl_2N_2O_4$: C, 56.31; H, 3.48; N, 6.91; Found: C, 56.28; H, 3.51; N, 6.86.

4-(1′-(4-Methylbenzoyl)-2′-benzoyl-ethyl)pyrazolidine-3,5-dione (**3d**): Yellow solid, yield 79%, mp 176—178 °C; IR (KBr) cm^{-1}: 1662 (CO–NH), 1727 (C=O), 3342 (NH); ^{1}H-NMR ($CDCl_3$) δ: 2.33 (s, 3H, Ar′-CH_3), 3.12 (dd, 1H, C_2′-H, J=3.4, 15.4 Hz), 3.76 (dd, 1H, C_2′-H, J=9.6, 15.2 Hz), 4.30—4.37 (m, 1H, C_1′-H), 4.40 (d, 1H, C_4-H, J=13.2 Hz), 6.98—7.40 (m, 9H, Ar-H), 9.24 (bs, 2H, NH); ^{13}C-NMR ($CDCl_3$) δ: 22.3 (Ar′-CH_3), 53.4 (C-2′), 58.5 (C-1′), 63.3 (C-4), 171.3 (C-3, C-5), 203.4 (Ar-CO), 204.5 (Ar′-CO), 128.5, 129.2, 131.4, 132.7, 133.5, 134.8, 136.9, 138.2 (aromatic carbons). *Anal.* Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00; Found: C, 68.66; H, 5.22; N, 8.18.

4-(1′-(4-Chlorobenzoyl)-2′-benzoyl-ethyl)pyrazolidine-3,5-dione (**3e**): Light yellow crystals, yield 74%, mp 182—184 °C; IR (KBr) cm^{-1}: 1668 (CO–NH), 1725 (C=O), 3333 (NH); ^{1}H-NMR ($CDCl_3$) δ: 3.19 (dd, 1H, C_2′-H, J=3.7, 15.2 Hz), 3.67 (dd, 1H, C_2′-H, J=9.8, 15.0 Hz), 4.29—4.35 (m, 1H, C_1′-H), 4.41 (d, 1H, C_4-H, J=13.4 Hz), 7.18—7.62 (m, 9H, Ar-H), 9.38 (bs, 2H, NH); ^{13}C-NMR ($CDCl_3$) δ: 53.8 (C-2′), 58.9 (C-1′), 63.7 (C-4), 171.9 (C-3, C-5), 204.7 (Ar-CO), 205.6 (Ar′-CO), 129.8, 130.6, 131.1, 132.4, 133.1, 134.7, 136.2, 136.8 (aromatic carbons). *Anal.* Calcd for $C_{19}H_{15}ClN_2O_4$: C, 61.55; H, 4.08; N, 7.56; Found: C, 61.50; H, 4.14; N, 7.65.

4-(1′-(4-Chlorobenzoyl)-2′-(4-methylbenzoyl)-ethyl)pyrazolidine-3,5-dione (**3f**): Yellow solid, yield 76%, mp 194—196 °C; IR (KBr) cm^{-1}: 1658

(CO–NH), 1721 (C=O), 3327s (NH); ^{1}H-NMR ($CDCl_3$) δ: 2.27 (s, 3H, Ar-CH_3), 3.16 (dd, 1H, C_2'-H, J=3.5, 15.2 Hz), 3.73 (dd, 1H, C_2'-H, J=9.4, 15.1 Hz), 4.32—4.38 (m, 1H, C_1'-H), 4.44 (d, 1H, C_4-H, J=13.5 Hz), 7.12—7.81 (m, 8H, Ar-H), 9.55 (bs, 2H, NH); ^{13}C-NMR ($CDCl_3$) δ: 23.8 (Ar-CH_3), 53.2 (C-2′), 58.3 (C-1′), 63.4 (C-4), 172.8 (C-3, C-5), 203.9 (Ar-CO), 205.1 (Ar′-CO), 128.8, 129.6, 130.8, 131.6, 132.7, 134.5, 135.4, 138.2 (aromatic carbons). *Anal.* Calcd for $C_{20}H_{17}ClN_2O_4$: C, 62.42; H, 4.45; N, 7.28; Found: C, 62.58; H, 4.42; N, 7.39.

General Procedure of Synthesis of 4-(1′,2′-Diaroyl-ethyl)isoxazolidine-3,5-dione (4a—f) To a solution of **2** (10 mmol) in MeOH (20 ml), hydroxylamine hydrochloride (10 mmol) and 10% NaOMe (5 ml) were added and refluxed for 6—8 h. The reaction mixture was cooled and poured onto crushed ice containing conc. HCl. The solid separated was filtered, dried and recrystallized from MeOH.

4-(1′,2′-Dibenzoyl-ethyl)isoxazolidine-3,5-dione (**4a**): White solid, yield 80%, mp 177—179 °C; IR (KBr) cm^{-1}: 1659 (CO–NH), 1729 (C=O), 1737 (CO–O), 3335 (NH); ^{1}H-NMR ($CDCl_3$) δ: 3.15 (dd, 1H, C_2'-H, J=3.4, 15.2 Hz), 3.86 (dd, 1H, C_2'-H, J=9.4, 14.9 Hz), 4.30—4.36 (m, 1H, C_1'-H), 4.45 (d, 1H, C_4-H, J=13.6 Hz), 7.09—7.94 (m, 10H, Ar-H), 10.15 (bs, 1H, NH); ^{13}C-NMR ($CDCl_3$) δ: 52.9 (C-2′), 58.5 (C-1′), 62.6 (C-4), 172.6 (C-3), 175.2 (C-5), 204.5 (Ar-CO), 205.9 (Ar′-CO), 129.5, 130.6, 131.7, 132.1, 132.5, 134.2, 136.3, 137.8 (aromatic carbons). *Anal.* Calcd for $C_{19}H_{15}NO_5$: C, 67.65; H, 4.48; N, 4.15; Found: C, 67.71; H, 4.52; N, 4.22.

4-(1′,2′-Di(4-methylbenzoyl)-ethyl)isoxazolidine-3,5-dione (**4b**): White solid, yield 78%, mp 190—192 °C; IR (KBr) cm^{-1}: 1666 (CO–NH), 1726 (C=O), 1740 (CO–O), 3338 (NH); ^{1}H-NMR ($CDCl_3$) δ: 2.34 (s, 6H, Ar-CH_3, Ar′-CH_3), 3.13 (dd, 1H, C_2'-H, J=3.4, 15.1 Hz), 3.85 (dd, 1H, C_2'-H, J=9.7, 15.0 Hz), 4.35—4.41 (m, 1H, C_1'-H), 4.48 (d, 1H, C_4-H, J=13.3 Hz), 7.06—7.97 (m, 8H, Ar-H), 10.21 (bs, 1H, NH); ^{13}C-NMR ($CDCl_3$) δ: 22.7 (Ar-CH_3, Ar′-CH_3), 53.4 (C-2′), 58.6 (C-1′), 63.3 (C-4), 174.5 (C-3), 176.3 (C-5), 204.1 (Ar-CO), 205.2 (Ar′-CO), 129.4, 131.4, 131.8, 132.8, 134.2, 135.5, 137.1, 137.6 (aromatic carbons). *Anal.* Calcd for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24; N, 3.83; Found: C, 69.14; H, 5.21; N, 3.78.

4-(1′,2′-Di(4-chlorobenzoyl)-ethyl)isoxazolidine-3,5-dione (**4c**): Colourless crystals, yield 81%, mp 211—213 °C; IR (KBr) cm^{-1}: 1662 (CO–NH), 1730 (C=O), 1743 (CO–O), 3315 (NH); ^{1}H-NMR ($CDCl_3$) δ: 3.15 (dd, 1H, C_2'-H, J=3.6, 15.2 Hz), 3.87 (dd, 1H, C_2'-H, J=9.6, 15.1 Hz), 4.28—4.35 (m, 1H, C_1'-H), 4.45 (d, 1H, C_4-H, J=13.5 Hz), 7.00—7.18 (m, 8H, Ar-H), 10.19 (bs, 1H, NH); ^{13}C-NMR ($CDCl_3$) δ: 53.0 (C-2′), 58.8 (C-1′), 63.7 (C-4), 173.4 (C-3), 175.5 (C-5), 204.3 (Ar-CO), 205.7 (Ar′-CO), 129.1, 130.9, 131.2, 132.4, 133.3, 134.7, 135.6, 138.5 (aromatic carbons). *Anal.* Calcd for $C_{19}H_{13}Cl_2NO_5$: C, 56.18; H, 3.23; N, 3.45; Found: C, 56.10; H, 3.25; N, 3.52.

4-(1′-(4-Methylbenzoyl)-2′-benzoyl-ethyl)isoxazolidine-3,5-dione (**4d**): White solid, yield 82%, mp 165—167 °C; IR (KBr) cm^{-1}: 1664 (CO–NH), 1713 (C=O), 1735 (CO–O), 3342 (NH); ^{1}H-NMR ($CDCl_3$) δ: 2.30 (s, 3H, Ar′-CH_3), 3.18 (dd, 1H, C_2'-H, J=3.7, 14.8 Hz), 3.84 (dd, 1H, C_2'-H, J=9.3, 14.9 Hz), 4.29—4.35 (m, 1H, C_1'-H), 4.41 (d, 1H, C_4-H, J=13.6 Hz), 7.02—7.20 (m, 9H, Ar-H), 10.14 (bs, 1H, NH); ^{13}C-NMR ($CDCl_3$) δ: 23.5 (Ar′-CH_3), 53.5 (C-2′), 58.2 (C-1′), 63.1 (C-4), 173.9 (C-3), 176.1 (C-5), 204.9 (Ar-CO), 205.8 (Ar′-CO), 128.2, 129.4, 130.8, 131.9, 132.6, 133.5, 133.8, 134.8 (aromatic carbons). *Anal.* Calcd for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.99; Found: C, 68.46; H, 4.90; N, 3.95.

4-(1′-(4-Chlorobenzoyl)-2′-benzoyl-ethyl)isoxazolidine-3,5-dione (**4e**): White solid, yield 79%, mp 173—175 °C; IR (KBr) cm^{-1}: 1658 (CO–NH), 1726 (C=O), 1745 (CO–O), 3312 (NH); ^{1}H-NMR ($CDCl_3$) δ: 3.18 (dd, 1H, C_2'-H, J=3.5, 15.2 Hz), 3.83 (dd, 1H, C_2'-H, J=9.5, 15.1 Hz), 4.32—4.38 (m, 1H, C_1'-H), 4.46 (d, 1H, C_4-H, J=13.5 Hz), 7.02—7.20 (m, 9H, Ar-H), 10.17 (bs, 1H, NH); ^{13}C-NMR ($CDCl_3$) δ: 53.7 (C-2′), 58.1 (C-1′), 63.8 (C-4), 172.8 (C-3), 175.7 (C-5), 203.9 (Ar-CO), 205.1 (Ar′-CO), 128.7, 130.4, 132.3, 132.8, 133.6, 134.0, 134.5, 138.1 (aromatic carbons). *Anal.* Calcd for $C_{19}H_{14}ClNO_5$: C, 61.38; H, 3.80; N, 3.77; Found: C, 61.50; H, 3.85; N, 3.83.

4-(1′-(4-Chlorobenzoyl)-2′-(4-methylbenzoyl)-ethyl)isoxazolidine-3,5-dione (**4f**): White crystals, yield 77%, mp 180—182 °C; IR (KBr) cm^{-1}: 1661 (CO–NH), 1721 (C=O), 1734 (CO–O), 3319 (NH); ^{1}H-NMR ($CDCl_3$) δ: 2.31 (s, 3H, Ar-CH_3), 3.19 (dd, 1H, C_2'-H, J=3.6, 15.0 Hz), 3.80 (dd, 1H, C_2'-H, J=9.4, 14.8 Hz), 4.34—4.39 (m, 1H, C_1'-H), 4.47 (d, 1H, C_4-H, J=13.7 Hz), 7.02—7.20 (m, 8H, Ar-H), 10.14 (bs, 1H, NH); ^{13}C-NMR ($CDCl_3$) δ: 23.1 (Ar-CH_3), 53.5 (C-2′), 56.4 (C-1′), 63.5 (C-4), 173.8 (C-3), 176.4 (C-5), 203.4 (Ar-CO), 204.8 (Ar′-CO), 129.8, 130.7, 131.4, 132.8, 133.2, 133.9, 134.3, 137.9 (aromatic carbons). *Anal.* Calcd for $C_{20}H_{16}ClNO_5$: C, 62.26; H, 4.18; N, 3.63; Found: C, 62.30; H, 4.20; N, 3.60.

General Procedure of Synthesis of 5-(1′,2′-Diaroyl-ethyl)pyrimidine-2,4,6-trione (5a—f)/1,3-Dimethyl-5-(1′,2′-diaroyl-ethyl)pyrimidine-2,4,6-trione (6a—f) The compound **2** (10 mmol), urea/*N*,*N*′-dimethylurea (10 mmol), 10% NaOMe (5 ml) and MeOH (10 ml) was refluxed for 10—12 h. The contents were cooled and poured onto crushed ice containing conc. HCl. The separated solid was filtered, dried and recrystallized from MeOH.

5-(1′,2′-Dibenzoyl-ethyl)pyrimidine-2,4,6-trione (**5a**): White solid, yield 72%, mp 203—205 °C; IR (KBr) cm^{-1}: 1656 (CO–NH), 1732 (C=O), 3332 (NH); ^{1}H-NMR ($CDCl_3$) δ: 3.12 (dd, 1H, C_2'-H, J=3.7, 15.1 Hz), 3.82 (dd, 1H, C_2'-H, J=9.8, 14.9 Hz), 4.33—4.40 (m, 1H, C_1'-H), 4.46 (d, 1H, C_5-H, J=13.8 Hz), 7.08—7.63 (m, 10H, Ar-H), 9.21 (bs, 2H, NH); ^{13}C-NMR ($CDCl_3$) δ: 52.2 (C-2′), 56.5 (C-1′), 64.1 (C-5), 158.5 (C-2), 164.5 (C-4, C-6), 202.3 (Ar-CO), 204.2 (Ar′-CO), 127.6, 129.4, 130.2, 132.2, 132.9, 133.7, 134.2, 135.4 (aromatic carbons). *Anal.* Calcd for $C_{20}H_{16}N_2O_5$: C, 65.93; H, 4.43; N, 7.69; Found: C, 6.00; H, 4.40; N, 7.75.

5-(1′,2′-Di(4-methylbenzoyl)-ethyl)pyrimidine-2,4,6-trione (**5b**): White solid, yield 75%, mp 213—215 °C; IR (KBr) cm^{-1}: 1663 (CO–NH), 1731 (C=O), 3344 (NH); ^{1}H-NMR ($CDCl_3$) δ: 2.31 (s, 6H, Ar-CH_3, Ar′-CH_3), 3.15 (dd, 1H, C_2'-H, J=3.9, 15.2 Hz), 3.89 (dd, 1H, C_2'-H, J=9.9, 15.1 Hz), 4.29—4.37 (m, 1H, C_1'-H), 4.42 (d, 1H, C_5-H, J=13.9 Hz), 7.03—7.74 (m, 8, Ar-H), 9.24 (bs, 2H, NH); ^{13}C-NMR ($CDCl_3$) δ: 22.1 (Ar-CH_3, Ar′-CH_3), 52.7 (C-2′), 55.9 (C-1′), 64.4 (C-5), 158.3 (C-2), 165.7 (C-4, C-6), 203.1 (Ar-CO), 205.4 (Ar′-CO), 128.8, 129.6, 131.4, 132.9, 133.1, 133.5, 134.2, 137.2 (aromatic carbons). *Anal.* Calcd for $C_{22}H_{20}N_2O_5$: C, 67.34; H, 5.14; N, 7.14; Found: C, 67.28; H, 5.12; N, 7.23.

5-(1′,2′-Di(4-chlorobenzoyl)-ethyl)pyrimidine-2,4,6-trione (**5c**): Colourless crystals, yield 68%, mp 218—220 °C; IR (KBr) cm^{-1}: 1657 (CO–NH), 1718 (C=O), 3348 (NH); ^{1}H-NMR ($CDCl_3$) δ: 3.19 (dd, 1H, C_2'-H, J=3.5, 14.9 Hz), 3.86 (dd, 1H, C_2'-H, J=9.6, 14.8 Hz), 4.30—4.36 (m, 1H, C_1'-H), 4.41 (d, 1H, C_5-H, J=13.5 Hz), 6.96—7.44 (m, 8H, Ar-H), 9.31 (bs, 2H, NH); ^{13}C-NMR ($CDCl_3$) δ: 52.5 (C-2′), 56.7 (C-1′), 64.2 (C-5), 159.2 (C-2), 164.8 (C-4, C-6), 202.5 (Ar-CO), 204.9 (Ar′-CO), 128.6, 129.2, 130.7, 132.2, 133.2, 133.8, 134.5, 138.4 (aromatic carbons). *Anal.* Calcd for $C_{20}H_{14}Cl_2N_2O_5$: C, 55.45; H, 3.26; N, 6.47; Found: C, 55.41; H, 3.30; N, 6.42.

5-(1′-(4-Methylbenzoyl)-2′-benzoyl-ethyl)pyrimidine-2,4,6-trione (**5d**): White solid, yield 69%, mp 186—188 °C; IR (KBr) cm^{-1}: 1664 (CO–NH), 1725 (C=O), 3337 (NH); ^{1}H-NMR ($CDCl_3$) δ: 2.28 (s, 3H, Ar′-CH_3), 3.14 (dd, 1H, C_2'-H, J=3.7, 15.1 Hz), 3.83 (dd, 1H, C_2'-H, J=9.7, 14.9 Hz), 4.34—4.39 (m, 1H, C_1'-H), 4.44 (d, 1H, C_5-H, J=13.7 Hz), 7.01—7.48 (m, 9H, Ar-H), 9.26 (bs, 2H, NH); ^{13}C-NMR ($CDCl_3$) δ: 23.8 (Ar′-CH_3), 53.4 (C-2′), 56.2 (C-1′), 63.8 (C-5), 159.5 (C-2), 164.3 (C-4, C-6), 201.8 (Ar-CO), 204.5 (Ar′-CO), 128.6, 129.2, 130.2, 131.2, 132.7, 133.4, 134.4, 136.3 (aromatic carbons). *Anal.* Calcd for $C_{21}H_{18}N_2O_5$: C, 66.66; H, 4.79; N, 7.40; Found: C, 66.75; H, 4.75; N, 7.50.

5-(1′-(4-Chlorobenzoyl)-2′-benzoyl-ethyl)pyrimidine-2,4,6-trione (**5e**): Colourless crystals, yield 71%, mp 195—197 °C; IR (KBr) cm^{-1}: 1656 (CO–NH), 1727 (C=O), 3324 (NH); ^{1}H-NMR ($CDCl_3$) δ: 3.10 (dd, 1H, C_2'-H, J=3.8, 15.3 Hz), 3.86 (dd, 1H, C_2'-H, J=9.6, 15.1 Hz), 4.31—4.38 (m, 1H, C_1'-H), 4.48 (d, 1H, C_5-H, J=13.6 Hz), 7.11—7.59 (m, 9H, Ar-H), 9.30 (bs, 2H, NH); ^{13}C-NMR ($CDCl_3$) δ: 52.3 (C-2′), 56.8 (C-1′), 64.4 (C-5), 158.8 (C-2), 165.7 (C-4, C-6), 202.6 (Ar-CO), 205.5 (Ar′-CO), 127.7, 128.5, 129.7, 131.7, 132.6, 133.4, 134.8, 137.9 (aromatic carbons). *Anal.* Calcd for $C_{20}H_{15}ClN_2O_5$: C, 60.23; H, 3.79; N, 7.02; Found: C, 60.32; H, 3.86; N, 7.07.

5-(1′-(4-Chlorobenzoyl)-2′-(4-methylbenzoyl)-ethyl)pyrimidine-2,4,6-trione (**5f**): White solid, yield 70%, mp 208—210 °C; IR (KBr): 1668 (CO–NH), 1730 (C=O), 3342 (NH) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 2.33 (s, 3H, Ar-CH_3), 3.11 (dd, 1H, C_2'-H, J=3.6, 14.9 Hz), 3.80 (dd, 1H, C_2'-H, J=9.8, 15.0 Hz), 4.27—4.35 (m, 1H, C_1'-H), 4.51 (d, 1H, C_5-H, J=13.9 Hz), 7.07—7.66 (m, 8H, Ar-H), 9.28 (bs, 2H, NH); ^{13}C-NMR ($CDCl_3$) δ: 23.5 (Ar-CH_3), 52.8 (C-2′), 57.5 (C-1′), 63.7 (C-5), 158.4 (C-2), 165.3 (C-4, C-6), 202.9 (Ar-CO), 204.7 (Ar′-CO), 128.7, 129.4, 130.9, 131.2, 132.7, 133.2, 134.8, 137.6 (aromatic carbons). *Anal.* Calcd for $C_{21}H_{17}ClN_2O_5$: C, 61.10; H, 4.15; N, 6.79; Found: C, 61.22; H, 4.18; N, 6.86.

1,3-Dimethyl-5-(1′,2′-dibenzoyl-ethyl)pyrimidine-2,4,6-trione (**6a**): White solid, yield 67%, mp 206—208 °C; IR (KBr) cm^{-1}: 1665 (CO–N), 1721 (C=O); ^{1}H-NMR ($CDCl_3$) δ: 2.80 (s, 6H, N-CH_3), 3.15 (dd, 1H, C_2'-H, J=3.3, 14.9 Hz), 3.84 (dd, 1H, C_2'-H, J=9.5, 14.7 Hz), 4.32—4.38 (m, 1H, C_1'-H), 4.44 (d, 1H, C_5-H, J=13.7 Hz), 7.06—7.89 (m, 10H, Ar-H); ^{13}C-NMR ($CDCl_3$) δ: 27.7 (N-CH_3), 53.6 (C-2′), 56.9 (C-1′), 64.1 (C-5), 156.4 (C-2), 167.1 (C-4, C-6), 202.5 (Ar-CO), 204.0 (Ar′-CO), 129.1, 130.3, 131.8, 132.4, 132.9, 133.6, 134.5, 135.2 (aromatic carbons). *Anal.* Calcd for $C_{22}H_{20}N_2O_5$: C, 67.34; H, 5.14; N, 7.14; Found: C, 67.44; H, 5.16; N, 7.20.

1,3-Dimethyl-5-(1′,2′-di(4-methylbenzoyl)-ethyl)pyrimidine-2,4,6-trione (**6b**): White solid, yield 71%, mp 217—219 °C; IR (KBr) cm^{-1}: 1654 (CO–N), 1714 (C=O); ^{1}H-NMR ($CDCl_3$) δ: 2.30 (s, 6H, Ar-CH_3, Ar′-CH_3), 2.85 (s, 6H, N-CH_3), 3.14 (dd, 1H, C_2′-H, J=3.5, 15.1 Hz), 3.81 (dd, 1H, C_2′-H, J=9.6, 14.9 Hz), 4.27—4.34 (m, 1H, C_1′-H), 4.39 (d, 1H, C_5-H, J=13.9 Hz), 7.10—7.85 (m, 8H, Ar-H); ^{13}C-NMR ($CDCl_3$) δ: 23.5 (Ar-CH_3, Ar′-CH_3), 27.7 (N-CH_3), 53.3 (C-2′), 56.3 (C-1′), 64.5 (C-5), 157.8 (C-2), 166.7 (C-4, C-6), 203.1 (Ar-CO), 205.5 (Ar′-CO), 129.4, 130.5, 131.3, 131.9, 132.7, 133.6, 135.2, 136.6 (aromatic carbons). *Anal.* Calcd for $C_{24}H_{24}N_2O_5$: C, 68.56; H, 5.75; N, 6.66; Found: C, 68.50; H, 5.70; N, 6.62.

1,3-Dimethyl-5-(1′,2′-di(4-chlorobenzoyl)-ethyl)pyrimidine-2,4,6-trione (**6c**): White solid, yield 68%, mp 190—192 °C; IR (KBr) cm^{-1}: 1659 (CO–N), 1720 (C=O); ^{1}H-NMR ($CDCl_3$) δ: 2.82 (s, 6H, N-CH_3), 3.18 (dd, 1H, C_2′-H, J=3.6, 14.8 Hz), 3.87 (dd, 1H, C_2′-H, J=9.9, 14.6 Hz), 4.29—4.37 (m, 1H, C_1′-H), 4.45 (d, 1H, C_5-H, J=13.6 Hz), 7.12—7.80 (m, 8H, Ar-H); ^{13}C-NMR ($CDCl_3$) δ: 27.4 (N-CH_3), 52.8 (C-2′), 56.7 (C-1′), 63.7 (C-5), 157.3 (C-2), 167.3 (C-4, C-6), 203.7 (Ar-CO), 205.1 (Ar′-CO), 128.5, 129.8, 130.1, 131.3, 132.4, 133.5, 134.2, 137.7 (aromatic carbons). *Anal.* Calcd for $C_{22}H_{18}Cl_2N_2O_5$: C, 57.28; H, 3.93; N, 6.07; Found: C, 57.40; H, 3.90; N, 6.15.

1,3-Dimethyl-5-(1′-(4-methylbenzoyl)-2′-benzoyl-ethyl)pyrimidine-2,4,6-trione (**6d**): White solid, yield 74%, mp 200—202 °C; IR (KBr) cm^{-1}: 1657 (CO–N), 1726 (C=O); ^{1}H-NMR ($CDCl_3$) δ: 2.35 (s, 3H, Ar′-CH_3), 2.84 (s, 6H, N-CH_3), 3.22 (dd, 1H, C_2′-H, J=3.3, 14.6 Hz), 3.83 (dd, 1H, C_2′-H, J=9.6, 14.7 Hz), 4.32—4.38 (m, 1H, C_1′-H), 4.46 (d, 1H, C_5-H, J=13.8 Hz), 7.07—7.71 (m, 9H, Ar-H); ^{13}C-NMR ($CDCl_3$) δ: 22.5 (Ar′-CH_3), 28.5 (N-CH_3), 52.5 (C-2′), 57.5 (C-1′), 63.5 (C-5), 156.8 (C-2), 167.8 (C-4, C-6), 204.5 (Ar-CO), 206.2 (Ar′-CO), 129.4, 130.9, 131.6, 132.5, 133.4, 134.3, 134.9, 135.7 (aromatic carbons). *Anal.* Calcd for $C_{23}H_{22}N_2O_5$: C, 67.97; H, 5.46; N, 6.89; Found: C, 68.09; H, 5.48; N, 6.82.

1,3-Dimethyl-5-(1′-(4-chlorobenzoyl)-2′-benzoyl-ethyl)pyrimidine-2,4,6-trione (**6e**): White solid, yield 69%, mp 216—218 °C; IR (KBr) cm^{-1}: 1653 (CO–N), 1718 (C=O); ^{1}H-NMR ($CDCl_3$) δ: 2.81 (s, 6H, N-CH_3), 3.17 (dd, 1H, C_2′-H, J=3.5, 14.9 Hz), 3.82 (dd, 1H, C_2′-H, J=9.4, 14.5 Hz), 4.30—4.37 (m, 1H, C_1′-H), 4.43 (d, 1H, C_5-H, J=13.5 Hz), 7.11—7.82 (m, 9H, Ar-H); ^{13}C-NMR ($CDCl_3$) δ: 27.5 (N-CH_3), 52.6 (C-2′), 56.5 (C-1′), 63.8 (C-5), 156.5 (C-2), 166.5 (C-4, C-6), 203.8 (Ar-CO), 205.3 (Ar′-CO), 129.8, 130.6, 131.1, 131.9, 132.4, 133.8, 134.5, 137.9 (aromatic carbons). *Anal.* Calcd for $C_{22}H_{19}ClN_2O_5$: C, 61.90; H, 4.49; N, 6.56; Found: C, 61.82; H, 4.54; N, 6.62.

1,3-Dimethyl-5-(1′-(4-chlorobenzoyl)-2′-(4-methylbenzoyl)-ethyl)pyrimidine-2,4,6-trione (**6f**): Colourless crystals, yield 71%, mp 210—212 °C; IR (KBr) cm^{-1}: 1655 (CO–N), 1725 (C=O); ^{1}H-NMR ($CDCl_3$) δ: 2.29 (s, 3H, Ar-CH_3), 2.86 (s, 6H, N-CH_3), 3.19 (dd, 1H, C_2′-H, J=3.7, 14.7 Hz), 3.88 (dd, 1H, C_2′-H, J=9.7, 14.8 Hz), 4.34—4.40 (m, 1H, C_1′-H), 4.48 (d, 1H, C_5-H, J=13.7 Hz), 7.09—7.79 (m, 8H, Ar-H); ^{13}C-NMR ($CDCl_3$) δ: 22.8 (Ar-CH_3), 28.1 (N-CH_3), 52.9 (C-2′), 56.8 (C-1′), 63.6 (C-5), 157.1 (C-2), 167.5 (C-4, C-6), 203.8 (Ar-CO), 205.8 (Ar′-CO), 127.2, 128.5, 129.6, 130.5, 131.7, 132.5, 133.1, 137.5 (aromatic carbons). *Anal.* Calcd for $C_{23}H_{21}ClN_2O_5$: C, 62.66; H, 4.80; N, 6.35; Found: C, 62.71; H, 4.75; N, 6.30.

General Procedure of Synthesis of 5-(1′,2′-Diaroyl-ethyl)-2-thioxopyrimidine-4,6-dione (7a—f) To an equimolar mixture (10 mmol) of **2** and thiourea, 10% NaOMe (5 ml) in MeOH (20 ml) was added and refluxed for 7—9 h. It was cooled and poured onto crushed ice containing conc. HCl. The solid separated was filtered, dried and purified by recrystallization from MeOH.

5-(1′,2′-Dibenzoyl-ethyl)-2-thioxopyrimidine-4,6-dione (**7a**): Light yellow solid, yield 73%, mp 215—217 °C; IR (KBr) cm^{-1}: 1492 (C=S), 1658 (CO–NH), 1724 (C=O), 3349 (NH); ^{1}H-NMR ($CDCl_3$) δ: 3.20 (dd, 1H, C_2′-H, J=3.8, 15.2 Hz), 3.88 (dd, 1H, C_2′-H, J=9.6, 15.0 Hz), 4.31—4.37 (m, 1H, C_1′-H), 4.47 (d, 1H, C_5-H, J=13.8 Hz), 7.12—7.78 (m, 10H, Ar-H), 9.32 (bs, 2H, NH); ^{13}C-NMR ($CDCl_3$) δ: 53.4 (C-2′), 56.2 (C-1′), 63.1 (C-5), 165.4 (C-4, C-6), 172.8 (C-2), 202.5 (Ar-CO), 204.2 (Ar′-CO), 128.2, 129.2, 130.6, 131.4, 132.0, 133.2, 134.5, 135.7 (aromatic carbons). *Anal.* Calcd for $C_{20}H_{16}N_2O_4S$: C, 63.14; H, 4.24; N, 7.36; Found: C, 63.25; H, 4.21; N, 7.45%.

5-(1′,2′-Di(4-methylbenzoyl)-ethyl)-2-thioxopyrimidine-4,6-dione (**7b**): Yellow solid, yield 76%, mp 220—222 °C; IR (KBr) cm^{-1}: 1499 (C=S), 1666 (CO–NH), 1728 (C=O), 3332 (NH); ^{1}H-NMR ($CDCl_3$) δ: 2.33 (s, 6H, Ar-CH_3, Ar′-CH_3), 3.15 (dd, 1H, C_2′-H, J=3.7, 14.9 Hz), 3.86 (dd, 1H, C_2′-H, J=9.9, 14.7 Hz), 4.27—4.35 (m, 1H, C_1′-H), 4.40 (d, 1H, C_5-H, J=13.5 Hz), 7.05—7.72 (m, 8H, Ar-H), 9.30 (bs, 2H, NH); ^{13}C-NMR ($CDCl_3$) δ: 23.7 (Ar-CH_3, Ar′-CH_3), 52.5 (C-2′), 56.7 (C-1′), 63.4 (C-5), 164.7 (C-4, C-6), 172.5 (C-2), 202.1 (Ar-CO), 204.8 (Ar′-CO), 128.9, 129.5, 131.2, 132.1, 132.6, 133.9, 134.5, 136.0 (aromatic carbons). *Anal.* Calcd for $C_{22}H_{20}N_2O_4S$: C, 64.69; H, 4.94; N, 6.86; Found: C, 64.61; H, 4.96; N, 6.80.

5-(1′,2′-Di(4-chlorobenzoyl)-ethyl)-2-thioxopyrimidine-4,6-dione (**7c**): Colourless crystals, yield 78%, mp 226—228 °C; IR (KBr) cm^{-1}: 1495 (C=S), 1657 (CO–NH), 1717 (C=O), 3339 (NH); ^{1}H-NMR ($CDCl_3$) δ: 3.20 (dd, 1H, C_2′-H, J=3.5, 14.7 Hz), 3.85 (dd, 1H, C_2′-H, J=9.7, 14.9 Hz), 4.34—4.41 (m, 1H, C_1′-H), 4.48 (d, 1H, C_5-H, J=13.7 Hz), 7.00—7.69 (m, 8H, Ar-H), 9.27 (bs, 2H, NH); ^{13}C-NMR ($CDCl_3$) δ: 52.3 (C-2′), 56.5 (C-1′), 63.3 (C-5), 165.1 (C-4, C-6), 173.4 (C-2), 203.2 (Ar-CO), 205.1 (Ar′-CO), 129.4, 130.3, 131.4, 132.1, 132.9, 134.7, 135.2, 138.5 (aromatic carbons). *Anal.* Calcd for $C_{20}H_{14}Cl_2N_2O_4S$: C, 53.46; H, 3.14; N, 6.23; Found: C, 53.53; H, 3.19; N, 6.13.

5-(1′-(4-Methylbenzoyl)-2′-benzoyl-ethyl)-2-thioxopyrimidine-4,6-dione (**7d**): Light yellow solid, yield 74%, mp 195—197 °C; IR (KBr) cm^{-1}: 14972 (C=S), 1664 (CO–NH), 1726 (C=O), 3343 (NH); ^{1}H-NMR ($CDCl_3$) δ: 2.30 (s, 3H, Ar′-CH_3), 3.17 (dd, 1H, C_2′-H, J=3.6, 15.1 Hz), 3.82 (dd, 1H, C_2′-H, J=9.5, 15.0 Hz), 4.32—4.39 (m, 1H, C_1′-H), 4.44 (d, 1H, C_5-H, J=13.4 Hz), 7.09—7.76 (m, 9H, Ar-H), 9.25 (bs, 2H, NH); ^{13}C-NMR ($CDCl_3$) δ (ppm): 23.2 (Ar′-CH_3), 52.9 (C-2′), 56.7 (C-1′), 63.9 (C-5), 165.5 (C-4, C-6), 172.2 (C-2), 202.7 (Ar-CO), 204.7 (Ar′-CO), 128.2, 129.0, 130.5, 131.4, 132.3, 133.4, 134.2, 135.9 (aromatic carbons). *Anal.* Calcd for $C_{21}H_{18}N_2O_4S$: C, 63.94; H, 4.60; N, 7.10; Found: C, 63.90; H, 4.66; N, 7.21.

5-(1′-(4-Chlorobenzoyl)-2′-benzoyl-ethyl)-2-thioxopyrimidine-4,6-dione (**7e**): White crystals, yield 76%, mp 203—205 °C; IR (KBr) cm^{-1}: 1490 (C=S), 1660 (CO–NH), 1722 (C=O), 3335 (NH); ^{1}H-NMR ($CDCl_3$) δ: 3.19 (dd, 1H, C_2′-H, J=3.8, 15.2 Hz), 3.88 (dd, 1H, C_2′-H, J=9.7, 14.8 Hz), 4.33—4.39 (m, 1H, C_1′-H), 4.46 (d, 1H, C_5-H, J=13.7 Hz), 7.01—7.69 (m, 9H, Ar-H), 9.29 (bs, 2H, NH); ^{13}C-NMR ($CDCl_3$) δ: 53.2 (C-2′), 56.5 (C-1′), 63.1 (C-5), 164.9 (C-4, C-6), 173.5 (C-2), 202.3 (Ar-CO), 204.4 (Ar′-CO), 128.4, 129.6, 130.1, 131.3, 131.9, 132.4, 133.7, 137.6 (aromatic carbons). *Anal.* Calcd for $C_{20}H_{15}ClN_2O_4S$: C, 57.90; H, 3.64; N, 6.75; Found: C, 57.99; H, 3.60; N, 6.71.

5-(1′-(4-Chlorobenzoyl)-2′-(4-methylbenzoyl)-ethyl)-2-thioxopyrimidine-4,6-dione (**7f**): White solid, yield 72%, mp 217—219 °C; IR (KBr) cm^{-1}: 1496 (C=S), 1663 (CO–NH), 1732 (C=O), 3349 (NH); ^{1}H-NMR ($CDCl_3$) δ: 2.28 (s, 3H, Ar-CH_3), 3.14 (dd, 1H, C_2′-H, J=3.5, 14.8 Hz), 3.85 (dd, 1H, C_2′-H, J=9.8, 15.1 Hz), 4.29—4.36 (m, 1H, C_1′-H), 4.43 (d, 1H, C_5-H, J=13.5 Hz), 7.10—7.71 (m, 8H, Ar-H), 9.31 (bs, 2H, NH); ^{13}C-NMR ($CDCl_3$) δ: 23.4 (Ar-CH_3), 52.7 (C-2′), 56.8 (C-1′), 64.3 (C-5), 164.5 (C-4, C-6), 172.7 (C-2), 203.0 (Ar-CO), 205.4 (Ar′-CO), 129.5, 129.8, 130.3, 131.1, 132.2, 133.6, 135.4, 138.3 (aromatic carbons). *Anal.* Calcd for $C_{21}H_{17}ClN_2O_4S$: C, 58.81; H, 4.00; N, 6.53; Found: C, 58.87; H, 3.98; N, 6.60.

Antimicrobial Testing The compounds **1**—**7** were dissolved in DMSO at different concentrations of 100, 200, 800 μg/ml.

Antibacterial and Antifungal Assays Preliminary antimicrobial activities of these compounds were tested by agar disc-diffusion method. Sterile filter paper discs (6 mm diameter) moistened with the test compound solution in DMSO of specific concentration 100 μg and 200 μg/disc were carefully placed on the agar culture plates that had been previously inoculated separately with the microorganisms. The plates were incubated at 37 °C and the diameter of the growth inhibition zones were measured after 24 h in case of bacteria and after 48 h in case of fungi.

The MICs of the compounds assays were carried out using microdilution susceptibility method. Chloramphenicol was used as reference antibacterial agent. Ketoconazole was used as reference antifungal agent. The test compounds, chloramphenicol and ketoconazole were dissolved in DMSO at concentration of 800 μg/ml. The two-fold dilution of the solution was prepared (400, 200, 100, 50, 25, 12.5, 6.25 μg/ml). The microorganism suspensions were inoculated to the corresponding wells. The plates were incubated at 36 °C for 24 and 48 h for bacteria and fungi, respectively. The minimum inhibitory concentrations of the compounds were recorded as the lowest concentration of each chemical compounds in the tubes with no turbidity (*i.e.* no growth) of inoculated bacteria/fungi.

Acknowledgements One of the authors Dr. A. Padmaja is thankful to UGC, New Delhi, India for financial assistance under minor research project.

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