

2(3*H*)-Furanones as synthons for polyamides of 1,3-diazines and 1,3,5-triazines

Abdel-Sattar S. Hamad Elgazwy,^{*a} Hoda T. Zaky^b, Mansoura I. Mohamed,^b
and Nadia G. Kandile^b

^{a*}*Department of Chemistry, Faculty of Science, University of Ain Shams, Abbassia 11566,
Cairo, Egypt*

^b*Department of Chemistry, Faculty of Girls, University of Ain Shams, Heliopolis 11757,
Cairo, Egypt*

E-mail: aelgazwy@yahoo.com

Abstract

2(3*H*)-Furanones **3a-d** having an exocyclic double bond and an N-acetylation nucleus were converted into novel polyamides of pyrimidine derivatives *via* reaction with nitrogen nucleophiles. NMR, GC/MS and chemical evidence confirmed all proposed structures.

Keywords: 2(3*H*)-Furanones, polyamide, diazines, and triazines

Introduction

The rapid assembly of “drug-like” core templates is fundamental to the discovery phase of many medicinal chemistry programs. If the syntheses of these core templates will allow for their ready functionalization, a meaningful SAR study can be efficiently conducted. In addition to ready assembly and core functionalization, the core template should have relatively low molecular weight and $\log P$. [1,2] This will allow room for the molecule to grow as functionalization is incorporated, thus allowing the targeting of the many essential criteria of drug candidates including selectivity, potency, and efficacy. We identified compounds **5a-d**, **6a-d**, **8a-d**, and **10a-d** as attractive molecular scaffolds for our medicinal chemistry program since both platforms are relatively novel in the patent literature, compatible with our pharmacophore model and have relatively low starting molecular weights and calculated $\log P$ values. Over the past two decades, 2(3*H*)-furanones have attracted strong interest from our group [3-8], because of possible applications of the corresponding biologically active compounds [9,10]. Nitrogen heterocycles constitute an important class of natural and non-natural products many of which exhibit useful biological activity [11-14]. Isatin **1**, and a number of its derivatives, possess a reactive keto-carbonyl group that readily undergoes condensation reactions under mild conditions [15a]. It was

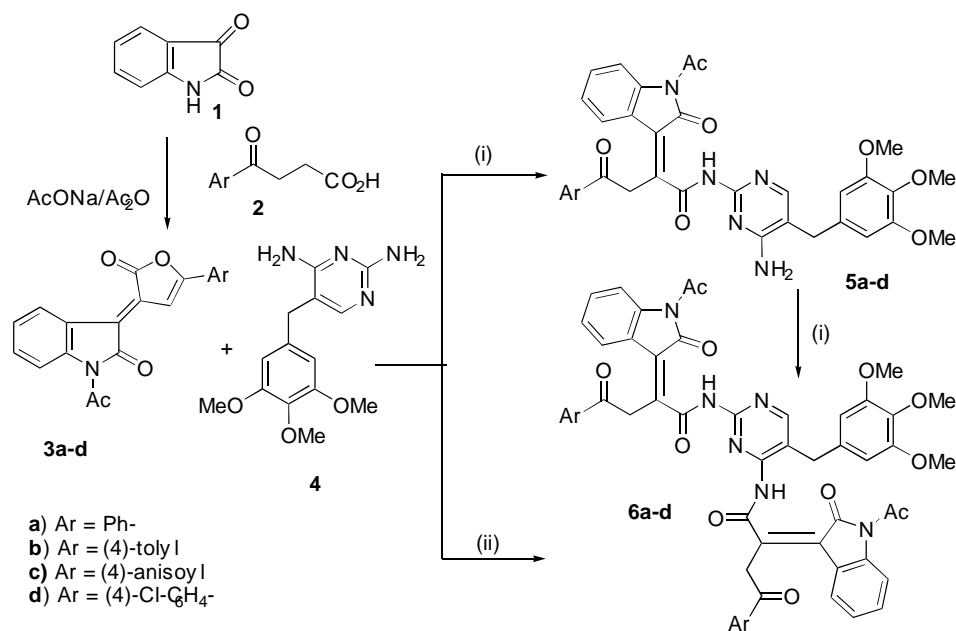
therefore speculated that isatin would be a suitable electrophilic component for the Baylis–Hillman reaction [15b] and a precursor for the synthesis of other heterocycles [16-19]. Substituted isatins are found in plants such as melosatin alkaloids obtained from the caribbean tumorigenic plant *melochia tomentosa* [20-22] as well as from fungi, 6-(3'-methylbuten-2'-yl)isatin was isolated from *streptomyces albus* [23] and 5-(3'-methylbuten-2'-yl)isatin from *chaetomium globosum* [24]. The interest in isatin derivatives stems from their pharmacological [25-26] and industrial applications [27, 28]. The present invention broadly relates to racemic compounds and their pharmaceutically acceptable salts [9], useful for treating a pathology in which reactive oxygen species and inflammatory mediators are contributing deleterious factors, such as acute or chronic inflammatory disorders, for example, asthma, rheumatoid arthritis, inflammatory bowel disease, and acute respiratory distress syndrome; neurodegenerative disorders, such as Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis, traumatic brain injury and multiple sclerosis; cardiovascular diseases, such as atherosclerosis; viral diseases, such as AIDS; skin disease, such as psoriasis; sunburn and premature aging; and eye diseases, such as glaucoma, cataract, senile macular degeneration, inflammatory eye conditions, trauma, post-traumatic eye disorders, diabetic retinopathy and eye infections.

Results and Discussion

Previously, 2(3*H*)-furanones [7] and 2(5*H*)-furanones [10] have proven to be good synthons for different, highly biological active heterocyclic compounds. Recently, 2(3*H*)-furanones **3a-d** bearing the indole nucleus were converted into amides, pyrrolones, and imidazoles [8]. Several attempts to modify the functional groups in furanones have been made; *e.g.* transformation of carbonyl groups into the corresponding C=S moieties using Lawesson's reagent [7]. As part of our previous investigation on 2-(3*H*)-furanones [3-7], the preparation of (3*E*)-1-acetyl-3(5-aryl-2-oxofuran-3(2*H*)-ylidene)-1,3-dihydro-2*H*-indol-2-ones **3a-d** was described by one of us [8]. This was consistent to the result described by Long *et al.* who studied monosubstituted 3-methyleneoxindoles and detected for most of them only the *E*-isomer [10]. We have examined the reactivity of 2(3*H*)-furanones **3a-d** towards some nitrogen nucleophiles [5,6,8].

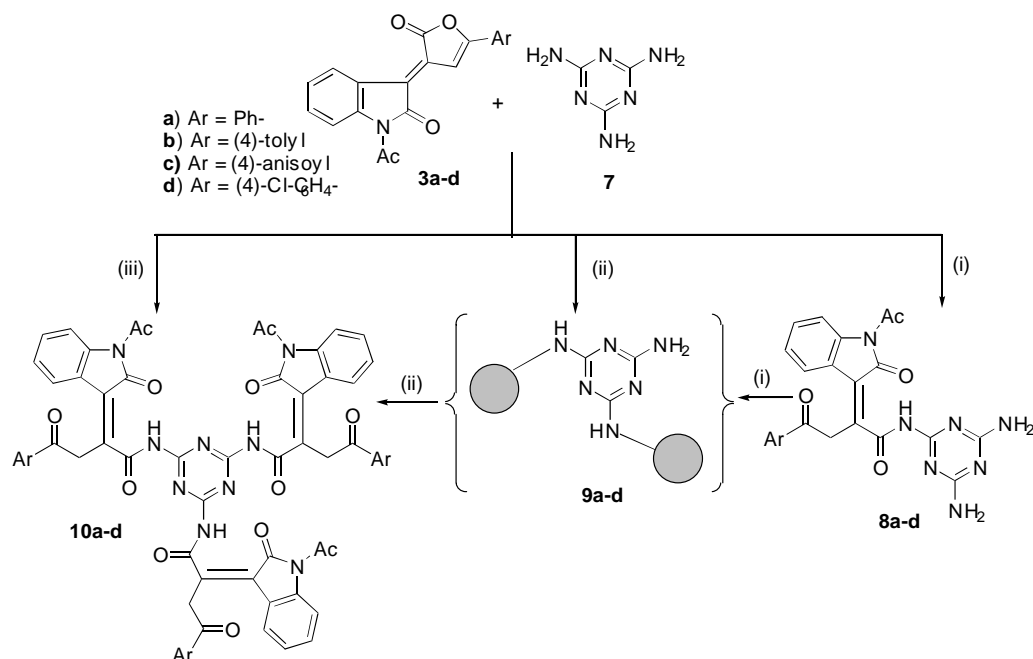
We are pleased to report herein a facile method for the synthesis of mono and diamides of biologically important pyrimidines **5a-d** and **6a-d** *via* reaction with one and two mole equivalents of 2(3*H*)-furanones **3a-d** and with one mole equivalent of trimethoprim **2** in ethanol in good to excellent yields (64-80%). There have not been reports of the synthesis of the ring systems **5a-d** and **6a-d** in the chemical literature. The reaction of 2(3*H*)-furanones **3a-d** with trimethoprim **4** in 1:1 mole ratio, refluxing in ethanol over 12 h, afforded monoamido 1,3-diazines **3a-d** in 64-80% yield (Scheme 1). In contrast, the 1,3-diazines **3a-d** were isolated in very low yield (10-15%) when the reaction took place in a non-protic solvent. However, reaction of 2(3*H*)-furanones **3a-d** with trimethoprim **4** in a 2:1 mole ratio provided the diamido 1,3-

diazines **6a-d** in 53-62% yields. The latter, **6a-d**, remain under our investigation and have anticipated biological activity.



Scheme 1. Reagent and conditions: i) Addition of 1:1 molar ratio of furanones **3a-d** into trimethoprim **4** in EtOH/refluxing for 12 hours; ii) Addition of 2:1 molar ratio of furanones **3a-d** into trimethoprim **4** in EtOH/refluxing for 12 hours.

The 2(3*H*)-furanones **3a-d** were treated neat with a molar equivalent of melamine **7** (1:1 mole ratio) and heating above the melting point over 2-3 h afforded monoamides **8a-d** in low yield (22-35%). These products **8a-d** were isolated in similar or even better yields (36-50 %) when the reaction took place in a protic solvent (EtOH) by ring opening (Scheme 1). However, when the reaction was repeated by adding two mole equivalents of **3a-d** and one mole equivalent of melamine **7** (2:1 mole ratio) the corresponding melamides **9a-d** were obtained, which were formed also by refluxing **8a-d** with one mole of **3a-d** for 6-12 hours. Since **9a-d** are the penultimate intermediates, it follows that the utility of this reaction will depend on their ease of preparation. The route described has some limitations in that it requires multiple steps as well as pure starting materials or reaction conditions that limit the ultimate utility of the reaction. Similar reaction conditions were repeated carefully by adding three mole equivalents of **3a-d** into one mole equivalent of melamine **7** (3:1 mole ratio) in refluxing ethanol to give melamides **10a-d** in 35-38 % yield. The latter were obtained also by refluxing **9a-d** with one mole equivalent of **3a-d** for 6-12 hours.



Scheme 2. Reagent and conditions: i) Addition of one molar equivalent of furanones **3a-d** into melamine **7** (1:1 molar ratio) in EtOH/refluxing for 12 hours; ii) Addition of two fold molar equivalents of furanones **3a-d** into melamine **7** (2:1 molar ratio) in EtOH/refluxing for 12 hours; iii) Addition of three fold molar equivalent of furanones **3a-d** into melamine **7** (3:1 molar ratio) in EtOH/refluxing for 12 hours.

Biological activity

Compounds **5a-d**, **6a-d**, **8a-d**, and **10a-d** remain under our investigation and show promising biological activities against Neurodegenerative disorders (Alzheimer disease), Cardiovascular diseases (atherosclerosis) and Viral diseases (AIDS). The findings from these latter studies will be published elsewhere.

Experimental Section

General Procedures. Melting points were determined on a Boetius hot-stage apparatus and are uncorrected. Chromatographic separations were performed using silica gel (Merck, 70-230 mesh). Thin-layer chromatography was carried out on Macherey-Nagel precoated silica plates (0.25 mm layer thickness). ¹H NMR and ¹³C NMR spectra were recorded with a Gemini 200 spectrometer in CDCl₃ solution unless otherwise specified (internal standard TMS). Mass spectra were taken on a VG Trio-2 and Gc/Ms-QPL000EX (EI, 70 eV) apparatus. IR spectra were recorded with a Perkin-Elmer 1430 instrument in KBr disks. M-H-W Laboratories (Phoenix Az)

and the Microanalytical center of Cairo and Ain Shams Universities performed elemental analyses.

General procedure for 3a-d. 2-(3*H*)-Furanones (**3a-d**) were prepared following the literature method [24,27], *via* condensation of isatin **1** (1.47 gm, 0.01 mol) with 3-arylpropionic acids **2** (0.01 mole) in acetic anhydride (10 mL) and fused sodium acetate (0.03 mol) under Perkin conditions. The corresponding *E*-isomers were obtained as the sole products, with no detectable amount of the *Z*-isomers being identified by TLC and ¹H NMR. The reddish green precipitate was collected by filtration and recrystallized from acetic acid to give **3a-d**.

General procedure for 5a-d. To a suspension of **3a-d** (0.1 mol) in ethanol (30 mL), was added trimethoprim **4** (0.1 mol) and the reaction mixture was refluxed for 6-12 hours. After cooling, the reddish brown precipitate was collected by filtration and recrystallized from toluene to give **5a-d**.

2-([(2*E*)-2-(1-Acetyl-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)--4-oxo-4-phenylbutanoyl]amino)-5-(3,4,5-trimethoxybenzyl)-4-aminopyrimidine (5a**).** Brown crystals 2.07 g, 64.17 % yield, mp >300 °C; IR (KBr pellet): 3653.14-3751.9 ((s), 3429.4 (broad band) for (NH amide), 1772.2 (m), 1727.4 (v), for (C=O) of ketone 1672.6 (very sharp) for cyclic oxopyrrolone ring and N-COCH₃, 1618.5 (s), for (C=O) of amide, 1585.3 (S), 1530.4 (s), for (C=N), 1487.7 (s), 1481.0 (s), 1348.5, 760.9 (s) cm⁻¹; LRMS (EI): m/z 620 [(M⁺- 1), 0.27], 510 (0.33), 417 (0.25), 289 (10.70), 261 (9.97), 156 (9.80), 105 (20.35), 101 (15.83), 77 (100), 76 (14.44), 75 (10.07), 74 (14), 50 (55.05); GC: *t*_R = 7.611 min; column: DB-5 6 m x 0.01 mm + 1m guard column: temp. prog: 50°C/2 min./20°C/1min./325°C/10 min; ¹H NMR (CDCl₃, 200 MHz): δ 13.61 (s, 1H, CONH), 8.88 (s, 2H, Ar-NH₂), 8.10 (s, 1H, pyrimidine-H(6)), 7.87-7.12 (m, 11H, -Ar-H), 6.58 (s, 2H, pyrimidine-CH₂-Ar), 6.34 (s, 2H, -CH₂-Ar), 3.78 (s, 6H, -(OCH₃)₂), 3.65 (s, 3H, -OCH₃), 2.36 (s, 3H, COCH₃). Calcd. for C₃₄H₃₁N₅O₇ (621.639); C, 65.69; H, 5.03; N, 11.27; Found: C, 65.90; H, 5.00.; N, 11.20.

2-([(2*E*)-2-(1-Acetyl-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)-4-(4-methylphenyl)-4-oxobutanoyl]amino)-5-(3,4,5-trimethoxybenzyl)-4-aminopyrimidine (5b**).** Brown crystals 2.1 g, 66.67 % yield, mp >300 °C; IR (KBr pellet): 3468.8 (broad band) for (NH amide), 3168.6, 3107.8, 3061.0, 3022.1, 2959.9 (s), 2923.9 (v), 2856.3 (s), 1772.2 (s), 1726.2 (very sharp), for (C=O) of ketone 1672.9 (very sharp) for cyclic oxopyrrolone ring and N-COCH₃, 1618.5 (s), for (C=O) of amide, 1585.7 (S), 1566.8 (s), for (C=N), 1541.8 (s), 1463.0 (s), 1433.2 (s), 1240.6 (s), 748.3 (m) cm⁻¹; LRMS (EI): m/z 303 [(M⁺- 332), 23.20], 271 (2.22), 247 (2.99), 148 (9.20), 156 (28.71), 129 (5.21), 128 (22.73), 127 (12.07), 120 (12.20), 119 (100), 103 (5), 102 (12), 101 (24.39), 90.95 (4.32), 91 (90.24), 89 (34.59), 65 (35.92), 63 (19.90), 53 (4), 50 (11.75); GC: *t*_R = 7.339 min; column: DB-5 6 m x 0.01 mm + 1m guard column: temp. prog: 50°C/2 min./20°C/1 min/320 °C/10 min; ¹H NMR (CDCl₃, 200 MHz): δ 13.56 (s, 1H, CONH), 8.86 (s, 2H, Ar-NH₂), 8.12 (s, 1H, pyrimidine-H(6)), 8.10-7.24 (m, 10H, -Ar-H), 6.85 (s, 2H, pyrimidine-CH₂-Ar), 6.54 (s, 2H, -CH₂-Ar), 3.75 [(s, 6H, -(OCH₃)₂), 3.66 (s, 3H, -OCH₃), 2.67 (s, 3H, COCH₃), 2.40 (s, 3H, -CH₃); Calcd. for C₃₅H₃₃N₅O₇ (635.23); C, 66.13; H, 5.23; N, 11.01; Found: C, 66.70; H, 4.90; N, 11.30.

2-([(2E)-2-(1-Acetyl-2-oxo-1,2-dihydro-3H-indol-3-ylidene)-4-(4-methoxyphenyl)-4-oxobutanoyl]amino)-5-(3,4,5-trimethoxybenzyl)-4-aminopyrimidine (5c). Brown crystals 2.16 g, 70 % yield, mp >300 °C, IR (KBr pellet): 3428.4 (bm) for (NH), 1773.2(s), 1723.7 (v) for (C=O), 1670.1 (v), 1606.2 (s), 1585.4 (m) and 1509 (sv) for (C=N) cm^{-1} ; LRMS (EI): m/z 651 (M^+), 7.73), 650 (M^+-1) (7.7), 149 (17.90), 147 (9.84), 142 (9.813), 139 (8.29), 127 (9.91), 119 (14.30), 102 (10.50), 101 (9.81), 98 (10.50), 97 (15.47), 95 (19.31), 91 (19.23), 97 (8.93), 95 (20.52), 93 (23.7), 91 (20.99), 70 (23.20), 67 (34.25), 57 (100), 55 (99.45), 51 (10.50); GC: t_R = 3.219 min; column: DB-5 6 m x 0.01 mm + 1m guard column: temp. prog: 50°C/2 min./20°C/1 min./320°C / 10 min; ^1H NMR (CDCl_3 , 200 MHz): δ 13.45 (s, 1H, CONH), 8.89 (s, 2H, Ar-NH₂), 8.09 (s, 1H, pyrimidine-H(6)), 8.08-7.23 (m, 10H, -Ar-H), 6.78 (s, 2H, pyrimidine-CH₂-Ar), 6.54 (s, 2H, -CH₂-Ar), 3.79 [(s, 6H, -(OCH₃)₂], 3.77 (s, 3H, -OCH₃), 3.71 (s, 3H, -OCH₃), 2.58 (s, 3H, COCH₃); Calcd. for C₃₅H₃₃N₅O₈ (651.68); C, 64.50; H, 5.10; N, 10.74; Found: C, 64.30; H, 5.10; N, 10.50.

2-([(2E)-2-(1-Acetyl-2-oxo-1,2-dihydro-3H-indol-3-ylidene)-4-(4-chlorophenyl)-4-oxobutanoyl]amino)-5-(3,4,5-trimethoxybenzyl)-4-aminopyrimidine (5d). Brown crystals 1.60 g, 52% yield, mp >300 °C, IR (KBr pellet): 3432.6 (broad band) for (NH), 1731.2(v), 1672.3 (v) for (C=O), 1620.6 (v), 1589.6 (s), 1540.1 (m) and 1486.4 (sv), 1094.5 (v), 827.7 (sv), 752.4 (sv) cm^{-1} ; LRMS (EI): m/z 651 [(M^+-5)(6.55)], 453 (5), 384 (12), 323 (32), 232 (10), 114 (3), 113 (31.71), 112 (9.29), 111 (100), 101 (19.56), 77 (13.12), 76 (20.17), 75 (70.17), 71 (27.97), 62 (11.73), 61 (7.95), 51 (10.14); GC: t_R = 7.465 min; column: DB-5 6 m x 0.01 mm + 1m guard column: temp. prog: 50°C/2 min./20°C/1 min./325°C/10 min; ^1H NMR (CDCl_3 , 200 MHz): δ 13.62 (s, 1H, CONH), 8.91 (s, 2H, Ar-NH₂), 8.15 (s, 1H, pyrimidine-H(6)), 8.13-7.22 (m, 10H, -Ar-H), 6.81 (s, 2H, pyrimidine-CH₂-Ar), 6.54 (s, 2H, CH₂-Ar), 3.80 [(s, 6H, -(OCH₃)₂], 3.75 (s, 3H, -OCH₃), 2.76 (s, 3H, COCH₃); Calcd. for C₃₄H₃₀N₅O₇ Cl (656.09); C, 62.24; H, 4.60; N, 10.67; Cl, 5.40; Found: C, 62.50; H, 4.60; N, 11.10.; Cl, 5.20.

General procedure for 6a-d. To a suspension of **3a-d** (0.2 mol) in ethanol (30 mL), was added trimethoprim **2** (0.1 mol) and the reaction mixture was refluxed for 6-12 hours. After cooling, the reddish brown precipitate was collected by filtration and recrystallized from toluene to give **6a-d**.

2,4-Bis-[(2E)-2-(1-acetyl-2-oxo-1,2-dihydro-3H-indol-3-ylidene)-4-oxo-4-phenylbutanoyl]diamino-5-[(3,4,5-trimethoxybenzyl)]pyrimidine (6a). Reddish Brown crystals 0.17 g, 53 % yield, mp 115-117 °C; IR (KBr pellet): 3323.1, 3193.3, 2962.2, 2837.7 (bv) for (NH), 1774.0 (s), 1722.4 (s), 1662.3 (v), for (C=O) 1618.0 (s), 1618.5 (s), 1590.8 (S), 1453.1 (sv), 1425.7 (s), 1375.2(s), 1238.4 (sv), 1124.6 (sv), 1006.1 (s), 754.9 (v), 683.9 (s).; cm^{-1} ; ^1H NMR (CDCl_3 , 200 MHz): δ 12.42 (s, 1H, CONH), 10.87 (s, 1H, CONH), 9.10 (d, 1H, J = 12.4 Hz, Ar-H), 8.75 (d, 1H, J = 12.2 Hz, Ar-H), 8.09 (s, 1H, pyrimidine-H(6)), 8.01-6.77(m, 18H, -Ar-H), 6.75 (s, 2H, -CH₂), 6.56 (s, 2H, pyrimidine-CH₂-Ar), 6.44 (s, 2H, -CH₂), 3.92 (s, 3H, -(OCH₃)), 3.72 (s, 3H, -OCH₃), 3.56 (s, 3H, -OCH₃), 1.94 (s, 6H, COCH₃). Calcd. for C₅₄H₄₄N₆O₁₁ (952.98); C, 68.06; H, 4.65; N, 8.81; Found: C, 68.50; H, 4.40.; N, 9.23.

2,4-Bis-[(2E)-2-(1-Acetyl-2-oxo-1,2-dihydro-3H-indol-3-ylidene)-4-(4-methylphenyl)-4-oxobutanoyl]diamino-5-[(3,4,5-trimethoxybenzyl)]pyrimidine (6b). Reddish Brown crystals 0.18 g, 59 % yield, mp 190-192 °C; IR (KBr pellet): 3344.1 (bv), 3187.2 (bv), 2934.9 (bv), 2837.7 (bv) for (NH), 1766.2 (s), 1718.3 (s), 1662.1 (v), for (C=O) 1618.0 (s), 1618.5 (s), 1506.4 (S), 1460.2 (sv), 1423.6 (s), 1302.5 (s), 1239.0 (sv), 1125.2 (sv), 1010.6 (s), 755.2(v) cm^{-1} ; ^1H NMR (CDCl_3 , 200 MHz): δ 12.53 (s, 1H, CONH), 10.91 (s, 1H, CONH), 9.10 (d, 1H, $J = 12.2$ Hz, Ar-H), 8.70 (d, 1H, $J = 12.2$ Hz, Ar-H), 8.03 (s, 1H, pyrimidine-H(6)), 7.88-6.77(m, 16H, -Ar-H), 6.57 (s, 2H, pyrimidine-CH₂-Ar), 6.34 (s, 2H, -CH₂-Ar), 5.97 (s, 2H, -CH₂-Ar), 3.82-3.73 [(singlet with shoulder signal, 6H, -(OCH₃)₂), 3.63-3.54 (singlet with shoulder signal, 3H, -(OCH₃), 2.36 [(s, 6H, COCH₃)₂], 1.92 [(s, 6H, (CH₃)₂]. Calcd. for C₅₆H₄₈N₆O₁₁ (981.03); C, 68.56; H, 4.93; N, 8.56; Found: C, 69.00; H, 5.10; N, 8.23.

2,4-Bis-[(2E)-2-(1-Acetyl-2-oxo-1,2-dihydro-3H-indol-3-ylidene)-4-(4-methoxyphenyl)-4-oxobutanoyl]diamino-5-[(3,4,5-trimethoxybenzyl)]pyrimidine (6c). Reddish Brown crystals 0.19 g, 62 % yield, mp 110-112 °C; IR (KBr pellet): 3344.1 (bv), 3187.2 (bv), 2934.9 (bv), 2837.7 (bv) for (NH), 1766.2 (s), 1718.3 (s), 1662.1 (v), for (C=O) 1618.0 (s), 1618.5 (s), 1506.4 (S), 1460.2 (sv), 1423.6 (s), 1302.5 (s), 1239.0 (sv), 1125.2 (sv), 1010.6 (s), 755.2(v) cm^{-1} ; ^1H NMR (CDCl_3 , 200 MHz): δ 12.53 (s, 1H, CONH), 10.91 (s, 1H, CONH), 9.10 (d, 1H, $J = 12.2$ Hz, Ar-H), 8.70 (d, 1H, $J = 12.2$ Hz, Ar-H), 8.03 (s, 1H, pyrimidine-H(6)), 7.88-6.77(m, 16H, -Ar-H), 6.57 (s, 2H, pyrimidine-CH₂-Ar), 6.34 (s, 2H, -CH₂), 5.97 (s, 2H, -CH₂), 3.82-3.73 [(singlet with shoulder signal, 6H, -(OCH₃)₂), 3.63-3.54 (singlet with shoulder signal, 3H, -(OCH₃), 2.36 [(s, 6H, COCH₃)₂], 1.92 [(s, 6H, (CH₃)₂); Calcd. for C₅₆H₄₈N₆O₁₃ (1013.03); C, 66.39; H, 4.77; N, 8.29; Found: C, 66.93; H, 5.00; N, 8.79.

2,4-Bis-[(2E)-2-(1-Acetyl-2-oxo-1,2-dihydro-3H-indol-3-ylidene)-4-(4-chlorophenyl)-4-oxobutanoyl]diamino-5-[(3,4,5-trimethoxybenzyl)]pyrimidine (6d). Brown crystals 1.60 g, 52% yield, mp >300 °C, IR (KBr pellet): 3432.6 (broad band) for (NH), 1731.2(v), 1672.3 (v) for (C=O), 1620.6 (v), 1589.6 (s), 1540.1 (m) and 1486.4 (sv), 1094.5 (v), 827.7 (sv), 752.4 (sv) cm^{-1} ; LRMS (EI): m/z 651 [(M⁺-5)(6.55)], 453 (5), 384 (12), 323 (32), 232 (10), 114 (3), 113 (31.71), 112 (9.29), 111 (100), 101 (19.56), 77 (13.12), 76 (20.17), 75 (70.17), 71 (27.97), 62 (11.73), 61 (7.95), 51 (10.14); GC: $t_R = 7.465$ min; column: DB-5 6 m x 0.01 mm + 1m guard column: temp. prog: 50°C/2 min./20°C/1 min./325°C/10 min; ^1H NMR (CDCl_3 , 200 MHz): δ 12.38 (s, 1H, CONH), 10.87 (s, 1H, CONH), 9.12 (d, 1H, $J = 12.2$ Hz, Ar-H), 8.75 (d, 1H, $J = 12.2$ Hz, Ar-H), 8.33 (s, 1H, pyrimidine-H(7)), 8.12-6.77 (m, 18H, -Ar-H), 6.75 (s, 2H, -CH₂COAr), 6.56 (s, 2H, pyrimidine-CH₂-Ar), 6.44 (s, 2H, -CH₂COAr), 3.92 (s, 3H, -(OCH₃), 3.72 (s, 3H, -OCH₃), 3.56 (s, 3H, -OCH₃), 1.94 (s, 6H, COCH₃).; Calcd. for C₅₄H₄₂N₆O₁₁ Cl₂ (1021.87); C, 63.47; H, 4.14; N, 8.2; Cl, 6.93; Found: C, 63.88; H, 3.90; N, 8.56.; Cl, 6.71.

General procedure for 8a-d

To a suspension of **3a-d** (0.1 mol) in ethanol (30 mL), was added melamine **5** (0.1 mol) and the reaction mixture was refluxed for 6-12 hours. After cooling, the semi-solid precipitate was collected by filtration and titrated with pet. ether. The solid product obtained was recrystallized from ethanol to give **8a-d**.

2-[(2E)-2-(1-Acetyl-2-oxo-1,2-dihydro-3H-indol-3-ylidene)-4-oxo-4-phenylbutanoyl amino]4,6-diamino-1,3,5-triazine (8a). Deep brown crystal 455 mg, 50 % yield, mp 245-247 °C; IR (KBr pellet): 3468.4--2975.2 (bm), 3429.4 (broad band) for (NH amide), 1772.2 (m), 1727.4 (v), for (C=O) of ketone 1655.5 (very sharp) for cyclic oxopyrroline ring and N-COCH₃, 1550.6 (s), for (C=O) of amide, 1463.2 (S), 1375.2 (s), for (C=N), 1320.6 (s), 1047.8 (s) cm⁻¹; LRMS (EI): m/z 456 [(M⁺- 1), 11.74], 184 (83), 105 (100), 77 (94.74), 75 (10.07), 74 (14), 50 (55.05); GC: t_R = 7.914 min; column: DB-5 6 m x 0.01 mm + 1m guard column: temp. prog. 50°C/2min./20°C/1min./325°C/10 min; ¹H NMR (CDCl₃, 200 MHz), δ 8.94 (s, 1H, -NHCOAr), 7.85 (s, 4H, -NH₂), 7.51-7.25 (m, 9H, -Ar-H), 5.41 (s, 2H, -CH₂COAr), 2.03 (s, 3H, COCH₃); Calcd. for C₂₃H₁₉N₇O₄ (457.45); C, 60.39; H, 4.18; N, 21.43; Found: C, 60.50; H, 3.90.; N, 21.70.

2-[(2E)-2-(1-Acetyl-2-oxo-1,2-dihydro-3H-indol-3-ylidene)-4-(4-methylphenyl)-4-oxobutanoyl]amino-4,6-diamino-1,3,5-triazine (8b). Reddish Brown crystals 454 mg, 48 % yield, mp 242-244 °C; IR (KBr pellet): 3340.7 (m), 3176.2 (broad band) for (NH amide), 2955.9, 2924.9 (s), 2854.8 (w), 1694.7 (vp), for (C=O) of ketone 1616.7 (s) for cyclic oxopyrroline ring and N-COCH₃, 1546.8 (s), for (C=O) of amide, 1501.7 (s), 1462.8 (m), for (C=N), 1376.2 (m), 1273.5 (s) cm⁻¹; LRMS (EI): m/z 448 [(M⁺- 23), .50], 303 (17), 259 (8), 257 (2.01), 247 (5), 156 (12), 119 (100), 117 (2.9), 101 (11.55), 100 (2.17), 91 (50.02), 90 (7.03), 89 (12.01), 70 (10.75), 65 (20), 51 (10); GC: t_R = 6.793 min; column: DB-5 6 m x 0.01 mm + 1m guard column: temp. prog. 50°C/2 min./20°C/1 min/300°C/10 min; ¹H MR (CDCl₃, 200 MHz): δ 8.90 (s, 1H, NHCO), 8.05 (s, 4H, NH₂), 7.75-6.84 (m, 8H, -Ar-H), 5.23 (s, 2H, -CH₂COAr), 2.43 (s, 3H, COCH₃), 1.79 (s, 3H, -CH₃); Calcd. for C₂₄H₂₁N₇O₄ (471.47); C, 61.14; H, 4.48; N, 20.79; Found: C, 61.50; H, 4.40; N, 21.00.

2-[(2E)-2-(1-Acetyl-2-oxo-1,2-dihydro-3H-indol-3-ylidene)-4-(4-methoxyphenyl)-4-oxobutanoyl]amino-4,6-diamino-1,3,5-triazine (8c). Reddish Brown crystals 350 mg, 36 % yield, mp 262-264 °C; IR (KBr pellet): 3344.5 (m), 3214.9 (broad band) for (NH amide), 2920.4, 2847.5 (w), 1713.3 (s), 1605.3 (vp), for (C=O), 1508.7 (s), 1501.7 (s) for (C=N), 1463.5 (m), 1376.2 (m), 1253.2 (vp), 1170.8 (m) cm⁻¹; LRMS (EI): m/z 481 [(M⁺- 6), .10.45], 305.20 (12.00), 303.00 (10.90), 270.55 (11.91), 272.30 (17.91), 240.30 (15.97), 213.05 (9.70), 195.05 (11.10), 157 (10.45), 136 (19.10), 135 (100), 134 (11.10), 132 (10.45), 120 (13.13), 107 (23.13), 103 (14.93), 101 (15.97), 92 (92.84), 87 (12.00), 77 (55.21), 70 (25.37), 84 (35.07), 63 (40.51), 51 (15.87); GC: t_R = 9.133 min; column: DB-5 6 m x 0.01 mm + 1m guard column: temp. prog. 50°C/2 min./20°C/1 min/320°C/10 min; ¹H MR (CDCl₃, 200 MHz): δ 8.89 (s, 1H, NHCO), , 8.08 (s, 4H, NH₂), 7.97-6.84 (m, 8H, -Ar-H), 5.23 (s, 2H, -CH₂COAr), 3.89 (s, 3H, OCH₃), 2.42 (s, 3H, COCH₃); Calcd. for C₂₄H₂₁N₇O₅ (487.47); C, 59.13; H, 4.34; N, 20.11; Found: C, 59.40; H, 4.30; N, 19.90.

2-[(2E)-2-(1-Acetyl-2-oxo-1,2-dihydro-3H-indol-3-ylidene)-4-(4-chlorophenyl)-4-oxobutanoyl]amino-4,6-diamino-1,3,5-triazine (8d). Deep Brown crystals 440 mg, 45 % yield, mp 244-246 °C; IR (KBr pellet): 3469.6.5 (w), 3420.7 (m), 3337.8 (s), 3137.9 (broad band) for

(NH amide), 2922.1, 2847.5 (w), 1648.7 (vp), for (C=O), 1549.4 (s), 1463.9 (s) for (C=N), 1439.0 (m), 1370.8 (m), 1317.3 (vp), 1221.0 (m) cm^{-1} ; LRMS (EI): m/z 490.50 [$(M^+ - 1)$, 17.24], 168 (42.52), 155 (21.04), 126 (100), 125 (29.44), 111 (40.23), 83 (83.22), 75 (22.90), 74 (24.14), 68 (45.90), 63 (22.90), 62 (25.29), 55 (21.94), 53 (27.50), 52 (26.44), 51 (31.03); GC: t_R = 6.727 min; column: DB-5 6 m x 0.01 mm + 1m guard column: temp. prog: 50°C/2 min./20°C/1 min/320°C/10 min; ^1H NMR (CDCl_3 , 200 MHz): δ 11.10 (s, 1H, NHCOAr), 8.88 (d, 2H, J = 7.8 Hz, Cl- C_6H_4 -), 8.07 (s, 4H, NH_2), 7.77 (t, 1H, J = 8.2 Hz, pyrimidine-H), 7.43 (m, 3H), 6.84 (d, 2H, J = 7.8 Hz, Cl- C_6H_4 -), 5.47 (s, 2H, $-\text{ArCOCH}_2$), 2.09 (s, 3H, COCH_3); Calcd. for $\text{C}_{23}\text{H}_{18}\text{N}_7\text{O}_4\text{Cl}$ (491.89); C, 56.16; H, 3.68; N, 19.93; Cl, 7.20; Found: C, 56.50; H, 3.50; N, 20.50, Cl, 7.60.

General procedure for 10a-d

To a suspension of **3a-d** (0.3 mol) in ethanol (30 mL), was added melamine **7** (0.1 mol) and the reaction mixture was refluxed for 6-12 hours. After cooling, the semi-solid precipitate was collected by filtration and triturated with pet. ether. The solid product obtained was recrystallized from ethanol to give **10a-d**.

2,4,6-Tri{[(2E)-2-(1-acetyl-2-oxo-1,2-dihydro-3H-indol-3-ylidene)-4-oxo-4-phenylbutanoyl]amino-1,3,5-triazine (10a)}. Brown crystal 1.20 gm, 35 % yield, mp 105-107 °C; IR (KBr pellet): 33343.4-3157.2 (broad band) for (NH amide), 1704.0 (bs), 1619.8 (m), for (C=O) of ketone 1542.8 (w) for cyclic oxopyrroline ring and N- COCH_3 , 1448.1 (s), for (C=O) of amide, 1371.8 (S), 1340.6 (s), for (C=N), 1278.1 (s), 1241.4.8 (s), 1174.6, 1101.4, 1017.5, 914.8, 887.9, 756.6 (v), 685.9 cm^{-1} ; ^1H NMR (CDCl_3 , 200 MHz δ 12.53 (s, 1H, ArCONH), 10.92 (s, 2H, ArCONH), 8.71 (d, 1H, J = 7.7 Hz, Ar-H_7), 8.20-7.85 (m, 26H, Ar-H), 6.55 (s, 2H, PhCH_2), 6.43 [s, 4H, 2(PhCH_2 -)], 2.08 (s, 3H, COCH_3), 2.04 (s, 3H, COCH_3), 1.91-1.90 (s, 3H, COCH_3); Calcd. for $\text{C}_{63}\text{H}_{45}\text{N}_9\text{O}_{12}$ (1119.10); C, 67.61; H, 3.96; N, 11.26; Found: C, 68.03; H, 3.82; N, 11.72.

2,4,6-Tri{[(2E)-2-(1-acetyl-2-oxo-1,2-dihydro-3H-indol-3-ylidene)-4-(4-methylphenyl)-4-oxobutanoyl]amino-1,3,5-triazine (10b)}. Dark brown crystal 1.30 gm, 37% yield, mp; (decomp. 142 °C) 170-172 °C; IR (KBr pellet): 3469.3 (w), 3418.7 (m), 3335.4 (bb), 3132.7, (broad band) for (NH amide), 1717.1 (bs), 1690.2 (m), for (C=O) of ketone 1658.0.8 (w) for cyclic oxopyrroline ring and N- COCH_3 , 1619.9 (s), for (C=O) of amide, 1580.7, 1546.9, 1466.5, 1435.5, 1373.7 (S), 1339.3 (s), for (C=N), 1301.2 (s), 1239.2 (s), 1181.1, 1017.9, 815.7, 754.1 cm^{-1} ; ^1H NMR (CDCl_3 , 200 MHz δ 12.51 (s, 1H, ArCONH), 10.91 (s, 2H, ArCONH), 9.08 (d, 4H, J = 7.7 Hz, CH_3 - C_6H_4 -), 8.72 (d, 1H, J = 9.6 Hz, Ar-H_7), 8.04-6.90 (m, 19H, Ar-H), 6.54 (s, 2H, ArCOCH_2 -), 6.04 [s, 4H, 2(ArCOCH_2 -)], 2.49 (s, 3H, $-\text{CH}_3$), 2.40-2.37 (s, 6H, 2- CH_3), 1.92 [(s, 9H, 3($-\text{COCH}_3$)]); Calcd. for $\text{C}_{66}\text{H}_{51}\text{N}_9\text{O}_{12}$ (1162.19); C, 68.21; H, 4.42; N, 10.84; Found: C, 68.67; H, 4.09; N, 11.20.

2,4,6-Tri{[(2E)-2-(1-acetyl-2-oxo-1,2-dihydro-3H-indol-3-ylidene)-4-(4-methoxyphenyl)-4-oxobutanoyl]amino-1,3,5-triazine (10c)}. Black crystal 1.40 gm, 38.6% yield, mp. 103-105 °C; IR (KBr pellet): 3339.8 (bb), 3131.2 (broad band) for (NH amide), 1768.1 (bs), 1691.3 (m), for

(C=O) of ketone 1603.3 (w) for cyclic oxopyrroline ring and N-COCH₃, 1506.1 (s), for (C=O) of amide, 1463.4, for (C=N), 1261.8 (s), 1239.9, 1170.4 (s), 1102.3, 1020.6, 828.8, 759.6 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz δ 10.86 (s, 2H, ArCONH), 9.51-9.25 (bs, 1H, ArCONH) 8.68 (d, 4H, *J* = 7.62 Hz, CH₃O-C₆H₄-), 7.96-7.83 (m, 8H, Ar-H), 7.37-6.85 (m, 15H, Ar-H), 6.55 (s, 2H, (-CH₂-)), 6.40 (s, 4H, 2(-CH₂-)), 3.93 (s, 3H, -O CH₃), 3.86 (s, 3H, -O CH₃), 3.78 (s, 3H, -O CH₃), 2.04 (s, 3H, COCH₃), 2.02 (s, 3H, COCH₃), 1.92 (s, 3H, COCH₃); Calcd. for C₆₆H₅₁N₉O₁₂ (1210.14); C, 65.51; H, 4.22; N, 10.42; Found: C, 66.00; H, 3.99; N, 10.00.

2,4,6-Tri-[(2*E*)-2-(1-acetyl-2-oxo-1,2-dihydro-3H-indol-3-ylidene)-4-(4-chlorophenyl)-4-oxobutanoyl]amino-1,3,5-triazine (10d). Brown crystal 1.30 gm, 35% yield, mp. 137-139 °C; IR (KBr pellet): 3342.7 (bb), 3134.26 (broad band) for (NH amide), 1679.0 (bs), 1623.3 (m), for (C=O) of ketone 1585.8 (w) for cyclic oxopyrroline ring and N-COCH₃, 1544.0 (s), for (C=O) of amide, 1466.2, for (C=N), 1340.3 (s), 1239.9, 1190.9 (s), 1092.7, 1011.8, 826.5, 754.7 (s) cm⁻¹; ¹H NMR (CDCl₃, 200 MHz δ 12.54 (s, 1H, ArCONH), 10.93 (s, 1H, ArCONH), 9.49 (s, 1H, ArCONH), 9.08 (d, 1H, *J* = 9.2 Hz, Ar-H₇), 8.71-6.92 (m, 23H, Ar-H), 6.59 (s, 2H, -CH₂-), 6.39 (s, 4H, 2(-CH₂-)), 2.01 (s, 3H, COCH₃), 1.91 (s, 3H, COCH₃), 1.90 (s, 3H, COCH₃); Calcd. for C₆₃H₄₂N₉O₁₂Cl₃ (1223.44); C, 61.85; H, 3.46; N, 10.30; Cl, 8.69; Found: C, 62.10; H, 3.23; N, 10.63; Cl, 9.00.

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References and Footnotes

1. Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. *J. Adv. Drug Delivery Rev.* **1997**, *23*, 3.
2. Teague, S. J.; Davis, A. M.; Leeson, P. D.; Oprea, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 3743.
3. Hamad, A-S. S.; Hashem, A. I. *J. Heterocycl. Chem.* **2002**, *39*, 1.
4. Hamad, A-S. S.; Hashem, A. I. *Molecules* **2000**, *5*, 895.
5. Hamad, A-S. S.; Hashem, A. I. *Acta. Chim. Solv.* **2001**, *48*, 431.
6. (a) Hamad, A-S. S.; Derbala H. A.; Elsayed W. A.; Hashem, A. I. *Acta. Chim. Solv.* **2001**, *48*, 417. (b) Hashem, A. I. *J. Prakt. Chem.* **1977**, *319*, 689.
7. (a) Hamad, A-S. S.; Hashem, A. I.; El-Kafrawy, A. F.; Saad, M. M. *Phosphorus, Sulfur and Silicon.* **2000**, *159*, 157. (b) Hashem, A. I.; Senning, A. *Adv. Heterocycl. Chem.* **1999**, *73*, 275. (c) Gammill, R. B.; Wilson, C. A.; Bryson, T. A. *Synth. Commun.* **1975**, *5*, 245.
8. Hamad Elgazwy, A-S. S.; Zaky, H. T.; Mohamed, M. I.; Kandile, N. G. *Heteroatom Chem.* **2003**, *14*, 434.

9. Appere, G.; Erdelmeier, I; Banissi, C.; Moutet, M.; Hopper, A. U.S. Patent, 6,265,436, 2001.
10. a) Long, D. R.; Richards, C. G.; Ross, M. S. F. *J. Heterocycl. Chem.* **1978**, *15*, 633.; b) Chiaccho, U.; Piperno, A.; Rescifina, A.; Romeo, G.; Uccella, N. *Tetrahedron* **1998**, *54*, 5695.; c) Hoye, T. R.; Hanson, P. R. *Tetrahedron Lett.* **1993**, *34*, 5043.
11. Flitsch, W. *Comprehensive Heterocyclic Chemistry*, Katritzky, A. R.; Rees, C. W. Pergamon: Oxford, 1984; Vol. 3, pp 443.
12. Swinbourne, J. F.; Hunt, H. J.; Klinkert, G. *Adv. Heterocycl. Chem.* **1987**, *23*, 103.
13. Flitsch, W. *Comprehensive Heterocyclic Chemistry*, Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Chapter. 8.01, pp 1-24.
14. Gonzalez, F. B. *Comprehensive Heterocyclic Chemistry*, Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Chapter 8.36, pp 967-1022.
15. (a) Da Silva, F. S. M.; Garden, S. J.; Pinto, A. C. *J. Braz. Chem. Soc* **2001**, *12*, 273. (b) Garden, S. J.; Skakl, J. M. S. *Tetrahedron Lett.* **2002**, *43*, 1969.
16. Sumpter, W. C. *Chem. Rev.* **1954**, *34*, 407.
17. Propp, F. D. *Adv. Heterocyclic. Chem.* **1975**, *18*, 1.
18. Shvekhgeimer, M. G. A. *Chem. Heterocycl. Cpd (Engl. Trans.)* **1996**, *32*, 249.
19. Da Silva, F. S. M.; Garden, S. J.; Pinto, A. C. <http://preprint.chemweb.com/orgchem/> (**2000**).
20. Kapodia, G. J.; Shukla, Y. N.; Choudhury, B. K.; Basak, S. P.; Fales, H. M.; Sokoloski, E. A. *J. Chem. Soc., Chem. Commun.* **1977**, 535.
21. Kapodia, G. J.; Shukla, Y. N.; Basak, S. P.; Sokoloski, E. A.; Fales, H. M. *Tetrahedron* **1980**, *36*, 2441.
22. Kapodia, G. J.; Shukla, Y. N. *Planta Med.* **1993**, *59*, 568.
23. (a) Grafe, U.; Radics, L. *J. Antibiotics* **1986**, *39*, 162. (b) Grafe, U.; Schade, W.; Fleck, W. Ger East 1986, DD 241, 749 24 Dec.; *Chem. Abstr.* **1986**, *107*, 216174k.
24. Breinholt, J.; Demuth, H.; Heide, M.; Jensen, G. W.; Moller, I. L.; Nielsen, R. I.; Olsen, C. E.; Rosendahl, C. N. *Acta . Chem. Scand.* **1996**, *50*, 443.
25. Glover, V.; Bhattacharya, S. K.; Sandler, M. *Indian J. Exp. Biol.*, **1991**, *29*, 1.
26. Sridhar, S. K.; Pandeya, S. N.; Stables, J. P.; Ramesh, A. *Eur. J. Pharm. Sci.* **2002**, *16*, 129.
27. Mudler, N. Swiss 1976, 580 673 15.; *Chem. Abstr.* **1976**, *86*, 6388e.
28. Kubo, R. JP 328156, 1991, pp 1.