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Heteroaromatization with 4-Hydroxycoumarin Part II: Synthesis of Some New Pyrano[2,3-d]pyrimidines, [1,2,4]triazolo[1,5-c]pyrimidines and Pyrimido[1,6-b]-[1,2,4]triazine Derivatives.

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Abstract: A variety of novel [1,2,4]triazolo[1,5-c]pyrimidine-13-ones (**4a-f**) and (**5b-d**) could be obtained via reaction of 9-amino-7-(4'-chlorophenyl)-8,9-dihydro-8-imino-6*H*,7*H*-[1]benzopyrano[3`,4`:5,6]pyrano[2,3-d]pyrimidine-6-one (**3**) with a variety of reagents. Pyrano[2,3-d]pyrimidine-6-ones **5a**, **8a-c** and pyrimido[1,6-b][1,2,4]-triazine-3,14-dione (**6**) were also prepared. The antimicrobial activity of some of the synthesized compounds was tested.

Keywords: Pyrano[3,2-c][1]benzopyrans; Pyrano[2,3-d]pyrimidines; [1,2,4]-triazolo-[1,5-c]pyrimidines; Pyrimido[1,6-b][1,2,4]triazine; antimicrobial activities

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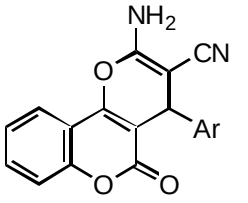
Introduction

Condensed triazoles exhibit a range of pharmacological activities such as mitotic [1], hypotensive [2], CNS stimulant [3], antinflammatory [4,5] and analgesic activities [6,7]. In connection with our investigations of novel polyfunctional heterocycles [8-11], we report here facile syntheses of the title

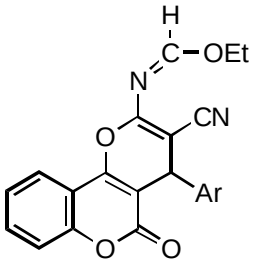
compounds using 4*H*-pyran as starting material. Such compounds could possess interesting and useful biological properties.

Results and Discussion.

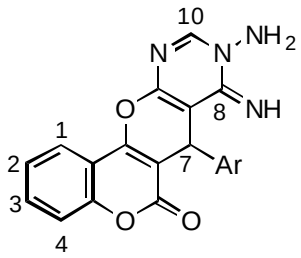
Treatment of 2-amino-4-(4'-chlorophenyl)-3-cyano-4*H*,5*H*-pyrano[3,2-*c*][1] benzopyran-5-one (**1**) [12] with triethyl orthoformate in acetic anhydride at reflux afforded 4-(4'-chlorophenyl)-3-cyano-2-ethoxymethyleneamino-4*H*,5*H*-pyrano[3,2-*c*][1]benzo-pyran-5-one (**2**) [12]. Hydrazino-lysis of the latter in ethanol at room temperature yielded 9-amino-7-(4'-chlorophenyl)-8,9-dihydro-8-imino-6*H*,7*H*-[1]benzopyrano[3`,4`:5,6]-pyrano[2,3-*d*]pyrimidine-6-one (**3**) [11] (Scheme 1).



1

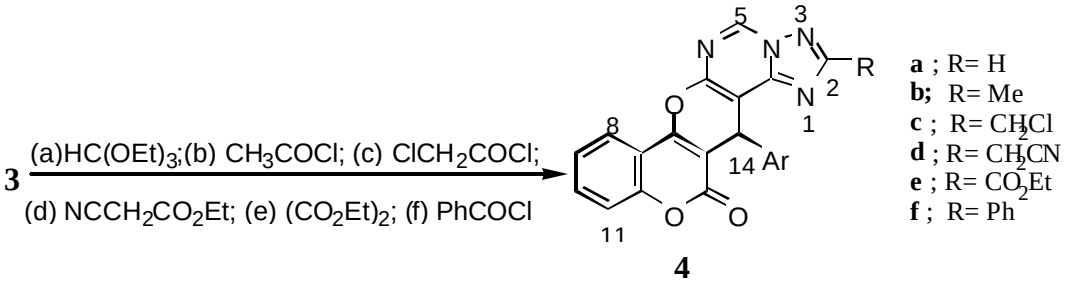


2



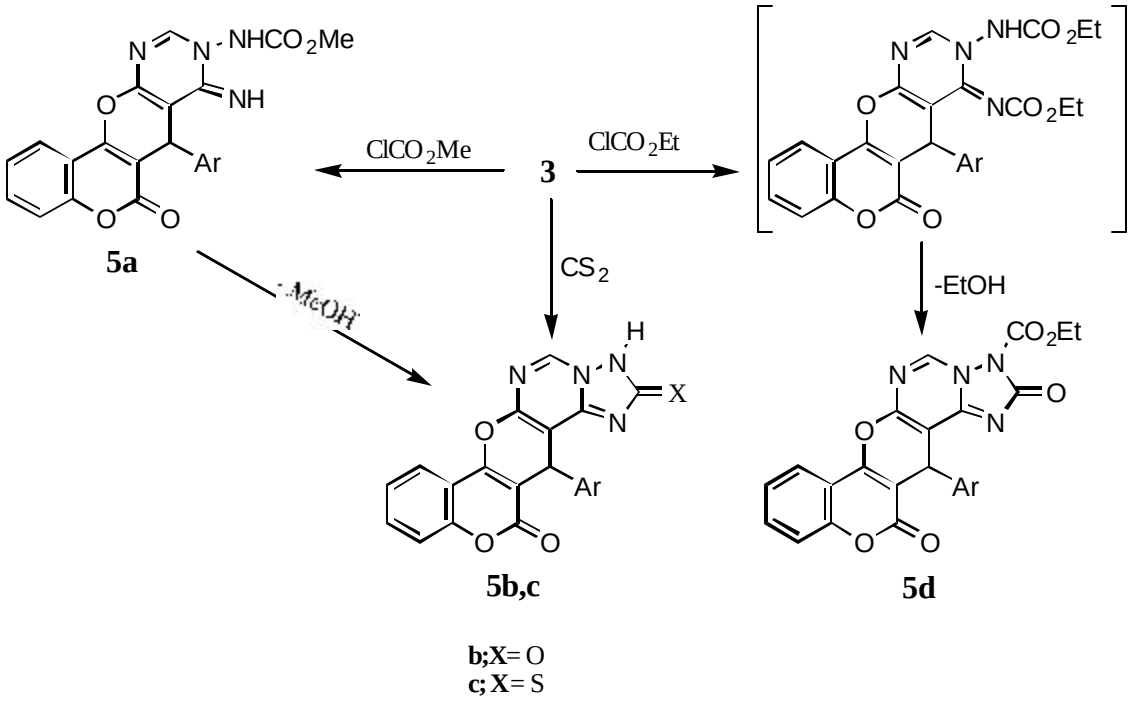
3

Ar= C_6H_4Cl-p



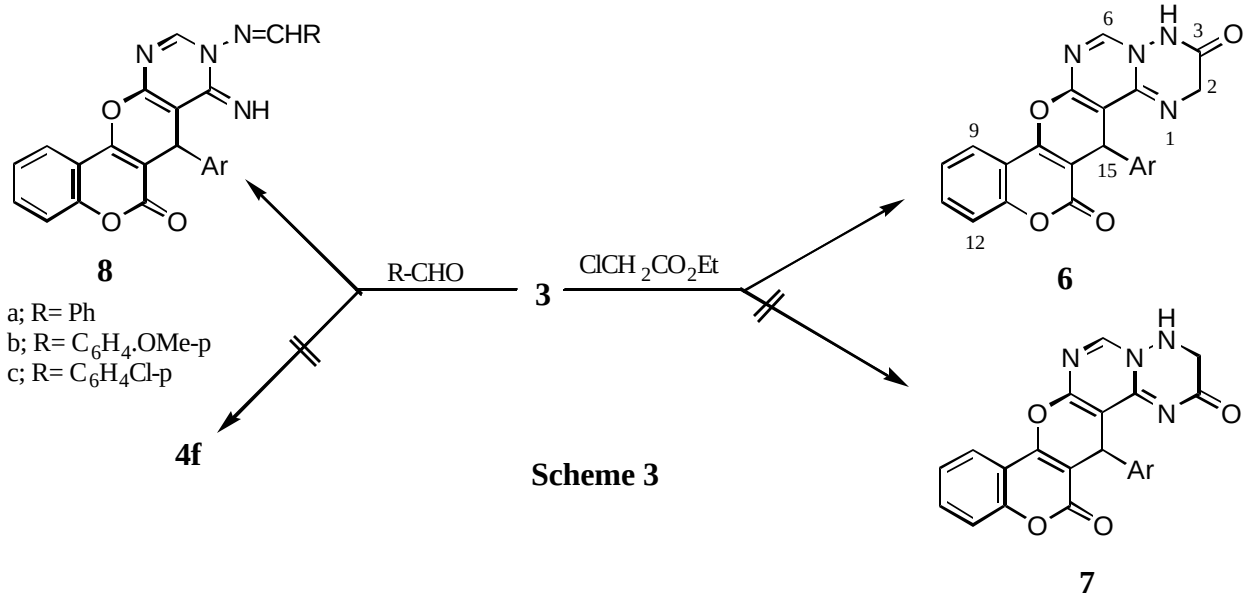
Scheme 1

Refluxing compound **3** with triethyl orthoformate afforded the [1,2,4]triazolo[1,5-*c*]pyrimidine **4a**, while with acetyl chloride or chloroacetyl chloride compounds **4b** and **4c** were formed, respectively. Reaction of **3** with ethyl cyanoacetate and diethyl oxalate afforded the heterocycles **4d** and **4e**, respectively, while with benzoyl chloride the 2-phenyl derivative **4f** was obtained (Scheme 1). Structure **4** was established by spectral data and analogy with our previous work [9,10]. When **3** was treated with methyl chloroformate for 30 min, the methoxycarbonyl derivative **5a** was formed, while heating of **3** with methyl chloroformate under reflux for 6 h afforded [1,2,4]triazolo[1,5-*c*]pyrimidine **5b** via elimination of methanol from **5a**. The structure of **5b** was supported by an independent synthesis from **5a** and ethanol under reflux for 5h. When **3** was treated with ethyl chloroformate an intermediate bis(ethoxycarbonyl) derivative was formed, which eliminated ethanol to furnish the ester **5d**. Treatment of **3** with carbon disulfide in alcoholic potassium hydroxide solution [9] gave the 2-thione derivative **5c** (Scheme 2).



Scheme 2

Interaction of **3** with ethyl chloroacetate in methanolic sodium methoxide afforded the triazin-3,14-dione derivative **6**. The alternate structure **7** was excluded on the basis of spectral data [13,14]. Based on the reaction conditions (sodium methoxide) structure **6** is thought to result from the initial formation of a sodium salt on the less basic imino nitrogen atom, which cyclizes into **6** [13], with elimination of NaCl and EtOH (Scheme 3). The IR spectrum of **6** showed a characteristic C=O absorption band at 1650 cm^{-1}, whereas if structure **7** were correct, one would expect an absorption band for the carbonyl band at a higher frequency than that observed for **6** [13,14]. The ^{1}H-NMR spectrum revealed a singlet at δ 4.95 ppm, characteristic for the methylene proton.



Scheme 3

The reaction of **3** with aromatic aldehydes gave pyrimidines **8** (Scheme 3) instead of the anticipated formation of triazolopyrimidines such as **4f** [14]. The proposed structures of **8** were also supported by the spectral data.

Antibacterial activity

Newly synthesized compounds **1**, **2**, **4c-e**, **5d** and **8e** were screened in vitro for their antimicrobial activities against Gram positive bacteria *Staphylococcus aureus* (NCTC-7447), *Bacillus cereus* (ATCC-14579) and Gram negative bacteria *Serratia marcesens* (IMRU-70) and *Proteus merabitis* (NTCC-289) using the paper disk diffusion method for the antibiotic sensitivity technique [15]. The tested compounds were dissolved in N,N-dimethylformamide (DMF) to obtain a 1 mg/mL solution.. The inhibition zones of microbial growth produced by different compounds were measured in millimeters at the end of an incubation period of 48 h at 28^{o}C. DMF alone showed no inhibition zone. An ampicillin standard (25 μg) was used as a reference to evaluate the potency of the tested compounds. The results are illustrated in Table I.

Table I: Antibacterial activity of some compounds

Compd.	*Staphylococcus aureus* (NCTC-7447)	*Bacillus cereus* (ATCC-14579)	*Serratia marcesens* (IMRU-70)	*Proteus merabitis* (NTCC-289)
1	23	19	18	20
2	22	24	24	23
4c	23	22	23	22
4d	22	19	24	22
4e	23	22	25	23
5d	24	22	21	23
8e	18	20	24	21
Ampicillin	26	25	26	27

Antifungal activity

Newly synthesized compounds **1**, **2**, **4c-e**, **5d** and **8e** were screened for their antifungal activity against two species of fungi, *Aspergillus ochraceus Wilhelm* (AUCC-230) and *Penicillium chrysogenum Thom* (AUCC-530) using the paper disk diffusion method [16]. The tested compounds were dissolved in DMF to get a 1 mg/mL solution. The inhibition zones were measured in millimeters at the end of an incubation period of 48h at 28^{o}C. A standard of mycostatin (30 μg) was used as a reference and the results are shown in Table II.

Table II: Antifungal activity of some compounds

Compd.	*Aspergillus ochraceus Wilhelm (AUCC-230)*	*Penicillium chrysogenum Thom (AUCC-530)*
1	14	16
2	19	16
4c	19	19
4d	19	13
4e	19	20
5d	15	17
8e	19	18
Mycostatin	22	24

Experimental

General

Mps are uncorrected. Elemental analyses were carried out in the Microanalytical Laboratories of the Faculty of Science, Cairo University, and the results are given in Table III. IR spectra (KBr disks) were measured on a FT IR/5300 spectrometer. ^{1}H-NMR spectra (δ/ppm) were recorded for DMSO-d_6 solutions on Varian Gemini (200 MHz) or Varian Mercury (300 MHz) spectrometers. Mass spectra were obtained on a Shimadzu GC-MS-QP 1000 EX spectrometer.

2-Amino-4-(4'-chlorophenyl)-3-cyano-4H,5H-pyrano[3,2-c][1]benzopyran-5-one (**1**): A solution of 4-hydroxycoumarin (0.01 mol) in ethanol (30 mL) and α-cyano-*p*-chlorocinnamonitrile (0.01 mol) was heated for 30 min. to give **1** (85% yield), m.p. 261°C (lit. [12] 258-260°C).

4-(4'-Chlorophenyl)-3-cyano-2-ethoxymethyleneamino-4H,5H-pyrano[3,2-c][1]benzopyran-5-one (**2**): A mixture of **1** (3.49g, 0.01 mol), triethyl orthoformate (0.01 mol) and acetic anhydride (20 mL) was refluxed for 5 h. The solvent was removed under vacuum. The residue obtained was recrystallized from benzene to give **2** (73% yield), m.p. 236°C (lit. [12] 221-223°C).

9-Amino-7-(4'-chlorophenyl)-8,9-dihydro-8-imino-6H,7H-[1]benzopyrano[3',4':5,6]-pyrano[2,3-d]-pyrimidine-6-one (**3**): A solution of **2** (4.06 g, 0.01 mol) and hydrazine hydrate (99%, 5mL) in ethanol (50 mL) was stirred for 45 min at room temperature. The colourless solid obtained was filtered off and crystallized from benzene to give **3** (76% yield); IR: 3568, 3547 (NH_2), 3337 (NH), 1718 (δ-lactone C=O), 1653 (C=N). ^{1}H-NMR: 9.79(br, 1H, NH), 8.65 (s, 1H, H-10), 7.30-8.05 (m, 10H, arom., NH_2), 5.44 (s, 1H, H-7).

14-(4'-Chlorophenyl)-13H,14H-[1]benzopyrano[3',4':5,6]pyrano[3,2-e][1,2,4]triazolo [1,5-c]-pyrimidine-13-one (**4a**): A solution of **3** (3.91g, 0.01 mol) and triethyl orthoformate (0.01 mol) in dry

benzene (30 mL) was refluxed for 6h to give **4a** (78% yield); IR: 2940 (CH stretching), 1720 (δ-lactone C=O).

14-(4'-Chlorophenyl)-2-methyl-13H,14H[1]benzpyrano[3',4':5,6]pyrano[3,2-e][1,2,4]-triazolo[1,5-c]-pyrimidine-13-one (**4b**): To a solution of **3** (3.91 g, 0.01 mol) in dry benzene (30 mL) acetyl chloride was added (0.01 mol) dropwise with stirring. The reaction mixture was boiled at reflux for 3 h and after cooling poured into ice-water (50 mL) to give **4b** (78% yield); IR 2940 (CH stretching), 1720 (δ-lactone C=O); MS: m/z 416 (M^+, 3.84%), 418 (M+2, 1.3%), (ratio 3:1), 402 (35.6), 404 (12.87), (ratio 3:1), 291 (100), 264 (8.98), 200 (1.49), 165 (3.47), 121 (2.89), 75(4.72).

2-Chloromethyl-14-(4'-chlorophenyl)-13,14H-[1]benzopyrano[3',4':5,6]pyrano-[3,2-e][1,2,4]-triazolo[1,5-c]pyrimidine-13-one (**4c**): Compound **4c** was prepared from **3** (3.91 g, 0.01 mol) and chloroacetyl chloride (0.01 mol) according to the procedure described for **4b**; (71% yield); IR: 3086 (CH stretching), 1724 (δ-lactone C=O); MS: m/z 450 (M^+, 25.1%), 452 (M+2, 15.9%), 454 (M+4, 3.32), 339 (100), 341 (35.35) (ratio 3:1), 264 (13.85), 236 (17.26), 185 (13.81), 129 (26.66), 55 (78).

14-(4'-Chloromethyl)-2-cyanomethyl-13H,14H-[1]benzopyrano[3',4':5,6]pyrano[3,2-e][1,2,4]-triazolo[1,5-c]pyrimidine-13-one (**4d**): A mixture of **3** (3.91g, 0.01 mol), ethyl cyanoacetate (0.01 mol) and absolute ethanol (20 mL) was refluxed for 6 h. On cooling, the solid obtained was crystallized from benzene to give **4d** (67% yield); IR: 3068, 2928, 2816 (CH stretching), 2262 (CN), 1724 (δ-lactone C=O); MS: m/z 441 (M^+, 16.9%), 443 (M+2, 6.04%), (ratio 3:1), 330 (63.38), 264 (7.24), 237 (4.47), 173 (2.9), 117(4), 89 (6.13).

14-(4'-Chlorophenyl)-2-ethoxycarbonyl-13H,14H-[1]benzopyrano[3',4':5,6]-pyrano[3,2-e]-[1,2,4]-triazolo[1,5-c]pyrimidine-13-one (**4e**): Prepared from **3** (3.91g, 0.01 mol) and diethyl oxalate (0.01 mol) according to the procedure described for **4d**; (78% yield); IR: 3052, 2985 (CH stretching), 1741 (ester C=O), 1724 (δ-lactone C=O); ^{1}H-NMR: 9.88 (s, 1H, H-5), 7.26-8.32 (m, 8H, arom.), 5.51 (s, 1H, H-14), 4.41 (q, 2H, CH_2, J= 6.7 Hz), 1.34 (t, 3H, CH_3, J= 6.7 Hz).

14-(4'-Chlorophenyl)-2-phenyl-13H,14H-[1]benzopyrano[3',4':5,6]pyrano[3,2-e]-[1,2,4]triazolo-[1,5-c]pyrimidine-13-one (**4f**): Prepared from **3** (3.91g, 0.01 mol) and benzoyl chloride (0.02 mol) according to the procedure described for **4a**; (67% yield); MS: m/z 478 (M^+, 33.66%), 480 (M+2, 12.71%), (ratio 3:1), 367 (100), 291 (1.2), 264 (4.02), 165 (2.37), 121(2.8), 77 (7.48).

Methyl N-[7-(4'-chlorophenyl)-8-imino-6-oxo-6H,7H-[1]benzopyrano[3',4':5,6]pyrano- [2,3-d]-pyrimidyl-9]carbamate (**5a**): Prepared from **3** (3.91g, 0.01 mol) and methyl chloroformate (0.01 mol) according to the procedure described for **4a** (reaction time: 30 min.), to give **5a** (71% yield): IR: 3500-2421 centered at 3067 (NH, CH stretching), 1737 (C=O), 1720 (δ-lactone C=O); ^{1}H-NMR: 9.43 (br, 1H, C=NH), 8.92 (s, 1H, H-10), 7.37-8.01 (m, 8H, arom.), 6.88 (br, 1H, NHCO), 5.51(s, 1H, H-7), 3.58 (s, 3H, CH_3); MS: m/z 450 (M^+, 0%), 377 (46.0), 266 (100%), 239 (41.8), 121 (54.8), 92 (24.1).

14-(4'-Chlorophenyl)-2,3-dihydro-2H,13H,14H-[1]benzopyrano[3',4':5,6]pyrano[3,2-e][1,2,4]-triazolo[1,5-c]pyrimidine-2,13-dione (**5b**): Prepared in 60% yield from **3** (3.91g, 0.01 mol) and methyl chloroformate (0.01 mol) according to the procedure described for **4a**; IR: 3422 (NH), 3069, 2853 (CH stretching), 1713 (δ-lactone C=O), 1653 (C=O); ^{1}H-NMR: 12.58 (br, 1H, NH), 8.65 (s, 1H, H-5), 7.30-8.06 (m, 8H, arom.), 5.45 (s, 1H, H-14); MS: m/z 418 (M^+, 4.9%), 401 (3.7), 291 (100%), 239 (3.4), 186 (1.0), 121 (11.0), 92 (6.5), 75 (12.7).

14-(4'-Chlorophenyl)-2,3-dihydro-13-oxo-2H-13H,14H-[1]benzopyrano[3',4':5,6]-pyrano[3,2-e]-[1,2,4]triazolo[1,5-c]pyrimidine-2-thione (**5c**): A mixture of **3** (3.91g, 0.01 mol), ethanol (30 mL), KOH (0.3 g) and carbon disulfide (3 mL) was refluxed for 15 h. After removal of the ethanol, water was added and the alkaline solution was acidified with acetic acid to give the thione **5c** (55% yield); IR: 3398 (NH), 1714 (δ-lactone C=O), 1041 (C=S); MS: m/z 434 (M^+, 1%), 324 (3.3), 266 (100), 212 (3.51), 174 (3.53), 144 (1.07), 104 (1.69), 76 (5.48).

Ethyl 14-(4'-chlorophenyl)-2,13-dioxo-2,3-dihydro-2H-13H,14H-[1]benzopyrano-[3',4':5,6]-pyrano[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine-3-carboxylate (**5d**): Prepared in 45% yield from **3** (3.91g, 0.01 mol) and ethyl chloroformate (0.01 mol) according to the procedure described for **4a**; IR: 3068, 2991 (CH stretching), 1747 (ester C=O), 1736 (δ-lactone C=O), 1714 (C=O); ^{1}H-NMR: 9.03 (s, 1H, H-5), 7.30-8.39 (m, 8H, arom.), 4.84 (s, 1H, H-14), 4.04 (q, 2H, CH_2, J= 7 Hz), 1.18 (t, 3H, CH_3, J= 7 Hz).

15-(4'-Chlorophenyl)-3,4-dihydro-2H,-14H,15H-[1]benzopyrano[3',4':5,6]pyrano[2,3-d]pyrimido-[1,6-b][1,2,4]triazine-3,14-dione (**6**): A mixture of **3** (3.91g, 0.01 mol), ethyl chloroacetate (0.01 mol), methanol (30 mL) and sodium metal (0.023 g, 0.01 mol) was refluxed for 6 h. The reaction mixture was cooled, then poured into cold water to give **6** (64% yield); IR: 3468 (NH), 1726 (δ-lactone C=O), 1650 (C=O); ^{1}H-NMR: 9.78 (s, 1H, H-6), 7.36-8.17 (m, 9H, arom.+ NH), 5.47 (s, 1H, H-15), 4.95 (s, 2H, CH_2).

9-Arylmethylideneamino-7-(4'-chlorophenyl)-8,9-dihydro-8-imino-6H,7H-[1]benzopyrano-[3',4':5,6]pyrano[2,3-d]pyrimidine-6-ones (**8a-c**): A mixture of **3** (3.91g, 0.01 mol), benzaldehyde, p-anisaldehyde or p-chlorobenzaldehyde (0.01 mol), piperidine (0.5 mL) and dioxane (30 mL) was refluxed for 16 h to give **8a-c** (77-85% yield after workup); **8a:** IR: 3231 (NH), 3067, 3026 (CH stretching) 1713 (δ-lactone C=O); ^{1}H-NMR: 11.30 (br, 1H, C=NH), 8.48 (s, 1H, H-10), 8.24 (s, 1H, N=CH), 7.27-7.98 (m, 13H, arom.), 6.06 (s, 1H, H-7); **8b**: IR: 3279 (NH), 2909, 2833 (CH stretching), 1707 (δ-lactone C=O); ^{1}H-NMR: 11.14 (br, 1H, C=NH), 8.45 (s, 1H, H-10), 8.16 (s, 1H, N=CH), 7.01-7.98 (m, 12H, arom.), 6.27 (s, 1H, H-7), 3.81 (s, 3H, OCH_3); **8c**: IR: 3284 (NH), 1721 (δ-lactone C=O); ^{1}H-NMR: 11.33 (br, 1H, C=NH), 8.48 (s,1H, H-10), 8.21(s, 1H, N=CH), 7.27-7.96 (m, 12H, arom.), 5.95 (s, 1H, H-7); MS: m/z 514 (M^+, 7.38%), 516 (M+2, 4.22), 5.18 (M+4, 0.73), 403 (6.79), 292 (1.53), 266 (37.09), 185 (11.63), 121 (31.24), 55 (100).

Table III: Characterization data for newly synthesized compounds

Compd. No.	M.P. (T/°C)[a]	Molecular formula (Molecular weight)	Elemental analyses Found (Required) %	
			C	H
3	250[c]	$C_{20}H_{13}ClN_4O_3$ (392.80)	61.1 (61.15)	3.3 (3.31)
4a	282	$C_{21}H_{11}ClN_4O_3$ (402.80)	62.5 (62.61)	2.7 (2.73)
4b	279	$C_{22}H_{13}ClN_4O_3$ (416.82)	63.3 (63.39)	3.0 (3.12)
4c	310	$C_{22}H_{12}Cl_2N_4O_3$ (451.27)	58.5 (58.54)	2.6 (2.66)
4d	307	$C_{23}H_{12}ClN_5O_3$ (441.83)	62.4 (62.52)	2.6 (2.71)
4e	292[b]	$C_{24}H_{15}ClN_4O_5$ (474.86)	60.6 (60.70)	3.1 (3.16)
4f	298[b]	$C_{27}H_{15}ClN_4O_3$ (478.90)	67.6 (67.71)	3.1 (3.13)
5a	248[b]	$C_{22}H_{15}ClN_4O_5$ (418.84)	58.4 (58.67)	3.1 (3.33)
5b	285	$C_{21}H_{11}ClN_4O_4$ (418.80)	60.1 (60.29)	2.4 (2.63)
5c	275	$C_{21}H_{11}ClN_4O_3S$ (434.86)	57.9 (57.99)	2.5 (2.53)
5d	286[b]	$C_{24}H_{15}ClN_4O_6$ (490.86)	58.6 (58.72)	3.0 (3.05)
6	289	$C_{22}H_{13}ClN_4O_4$ (432.82)	60.9 (61.04)	2.9 (3.00)
8a	316	$C_{27}H_{17}ClN_4O_3$ (480.91)	67.3 (67.43))	3.4 (3.53)
8b	290	$C_{28}H_{19}ClN_4O_4$ (510.94)	65.7 (65.82)	3.6 (3.72)
8c	345	$C_{27}H_{16}Cl_2N_4O_3$ (515.36)	62.8 (62.92)	3.0 (3.10)

[a]From DMF-ethanol unless indicated otherwise. [b]From dioxane. [c]From benzene

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Sample Availability: Samples are available from the authors.