Three-component Reaction of Cycloheptanone, 6-Amino-1,3-Dimethyluracil and Aromatic Aldehydes; X-Ray Structure, and Anti-inflammatory Evaluation of the Products

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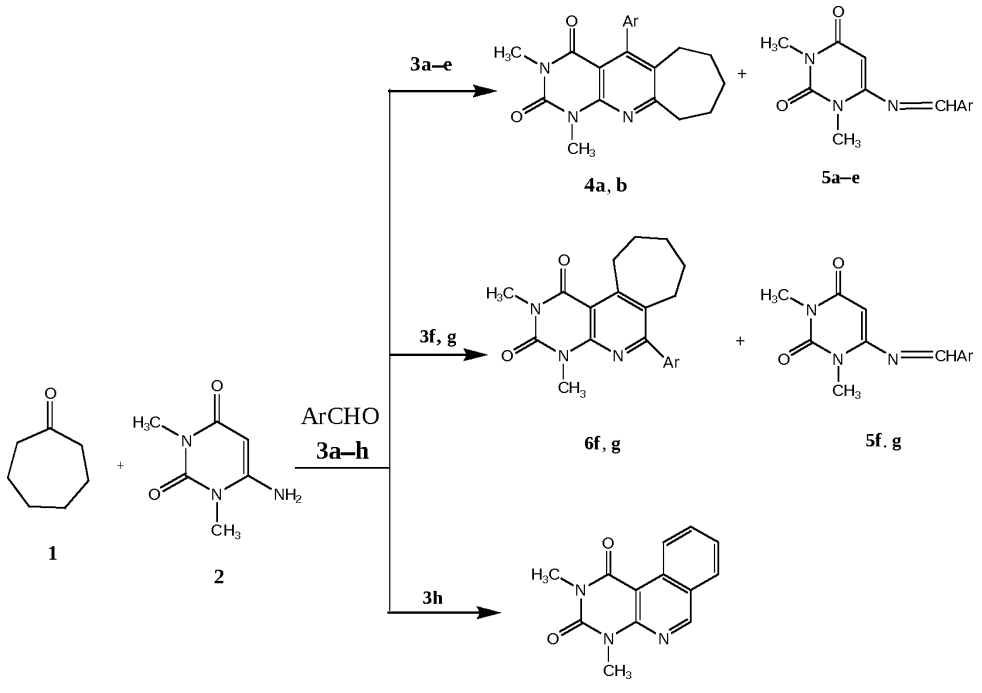
1,3-Dimethyl-5-aryl-1,6,7,8,9,10-hexahydrocyclohepta[5,6]pyrido[2,3-*d*]pyrimidine-2,4-diones **4a**, **b** (the linear regioisomers) and the Schiff bases, 6-*N*-benzylidenamino-1,3-dimethyluracil derivatives **5a**, **b**, were isolated from a three-component reaction of cycloheptanone, 6-amino-1,3-dimethyluracil, and 4-chloro- or 4-bromobenzaldehyde. Surprisingly, 1,3-dimethyl-10-aryl-1,5,6,7,8,9-hexahydrocyclohepta[4,5]pyrido-[2,3-*d*]pyrimidine-2,4-diones **6f**, **g** (the angular regioisomers which are described for the first time in the literature under the given reaction conditions) and the Schiff bases, 6-*N*-benzylidenamino-1,3-dimethyluracil derivatives **5f**, **g**, were isolated and characterized from the reaction with 4-methoxybenzaldehyde and 4-cyanobenzaldehyde. However, the three-component reaction of 6-amino-1,3-dimethyluracil, cycloheptanone, and 2-methoxybenzaldehyde afforded 1,3-dimethylbenzo[4,5]pyrido[3,2-*d*]pyrimidine-3,4-dione (**7**). Single crystal X-ray diffraction and ^{13}C NMR studies of **4a** and **6f** provided support for the established structures. Some of the new products were tested for antiinflammatory activity comparable to indomethacin.

Key words: Hexahydrocyclohepta[5,6]pyrido[2,3-*d*]pyrimidines, Hexahydrocyclo-hepta[4,5]pyrido[2,3-*d*]pyrimidines, Benzo[4,5]pyrido[3,2-*d*]pyrimidines, X-Ray Structure Determination, Antiinflammatory Action

Among the methods for the synthesis of 1,3-dimethylpyrido[2,3-*d*]pyrimidine(1*H*,3*H*)-2,4-diones [1, 2], the three component condensation reaction of 6-amino-1,3-dimethyluracil with cyclic ketones and appropriate aromatic aldehydes is a facile variant. Theoretically, this reaction can afford products with a linear structure and/or an angular structure [2, 3]. However, under the conditions of our experiments, only one regioselective product that has the linear structure was isolated and characterized as published in previous reports, and to our knowledge in no case the angular product was characterized or isolated [4 – 6]. This three-component reaction was reported also for amino-substituted heterocyclic compounds (2-aminobenzimidazole, 3-amino-5-methylthio-1,2,4-triazole, 3,5-diamino-1,2,4-triazole) with cyclic ketones and aromatic aldehydes, and under reaction conditions similar to ours, the linear structure of the products was found [7 – 9]. Also, the microwave-assisted synthesis in a one-pot reaction was reported to give the linear products [10, 11].

The interest in the synthesis of pyrido[2,3-*d*]pyrimidines is due to their versatile biological activities. They were reported as adenosine kinase inhibitors [12, 13], calcium antagonists [3], herbicide antidotes [14], antimicrobial [15] and antibacterial agents [16 – 20], antihistaminic [21], analgesic [22], antitumor [23, 24], diuretic, antiaggressive [25], antifolate [26, 27] anticonvulsant [28, 29], antileishmanial [30], antiinflammatory [31], antiviral [32, 33], antihypertensive [34, 35], and CNS depressing agents [36] and as mulluscidal agents against *Biomphalaria alexandrina* snails [37]. In our previous studies [2] we isolated only the linear pyrido[2,3-*d*]pyrimidine products from the one-pot reaction of 6-amino-1,3-dimethyluracil with equimolar amounts of cyclic ketones or cyclic 1,3-diketones and aromatic aldehydes. In the present work we report further on the reaction of 6-amino-1,3-dimethyluracil with equimolar amounts of cycloheptanone and appropriate aromatic aldehydes, and on the effort to determine the structure of the products. Also, we aim at the evaluation of the antiinflammatory activity of some of the newly prepared products.



a, Ar = 4-ClC_6H_4; **b**, Ar = 4-BrC_6H_4; **c**, Ar = 2-BrC_6H_4; **d**, Ar = C_6H_5; **e**, Ar = 1-$C_{10}H_7$; **f**, Ar = 4-$CH_3OC_6H_4$; **g**, Ar = 4-CNC_6H_4; **h**, Ar = 2-$CH_3OC_6H_4$.

Scheme 1.

Results and Discussion

The reaction of 6-amino-1,3-dimethyluracil (**2**) with equimolar amounts of cycloheptanone (**1**) and 4-chlorobenzaldehyde afforded two products, hexahydrocyclohepta[5,6]pyrido[2,3-*d*]pyrimidine-2,4-dione **4a** and the Schiff base **5a**, which were separated by column chromatography (Scheme 1). The structure of **4a** was verified by elemental analysis, spectral data and single crystal X-ray diffraction (Fig. 1). The ^{1}H NMR spectrum of **4a** showed cycloheptane protons and two types of methyl protons. In the ^{13}C NMR spectrum of **4a**, signals at δ = 148.55, 149.50, 151.52, 160.85, and 168.95 ppm are in accordance with previously reported data [38]. The mass spectrum of **4a** showed prominent molecular ion peaks at *m/z* (%) = 371 (6) $[M,Cl^{37}]^+$ and 369 (16) $[M,Cl^{35}]^+$. The identity of **5a** is also established based on the NMR data.

Similarly, two products were isolated from the reaction of cycloheptanone (**1**) with equimolar amounts of 6-amino-1,3-dimethyluracil (**2**) and 4-bromobenzaldehyde (**3b**), namely **4b** and **5b**. In the case of 2-

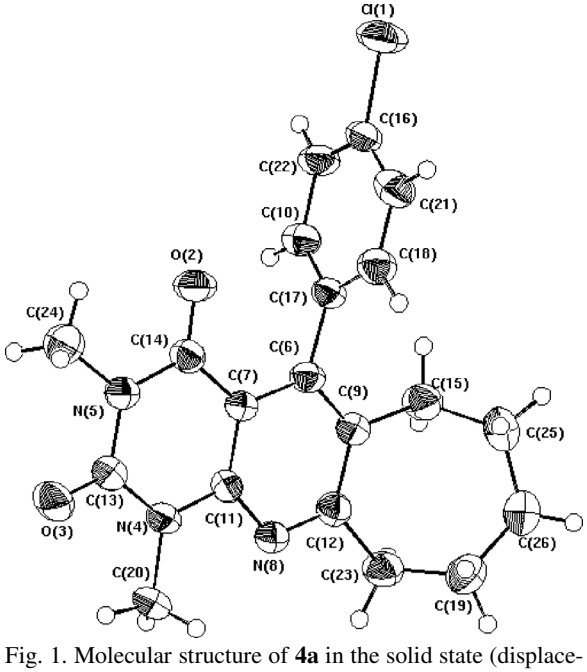


Fig. 1. Molecular structure of **4a** in the solid state (displacement ellipsoids at the 50 % probability level).

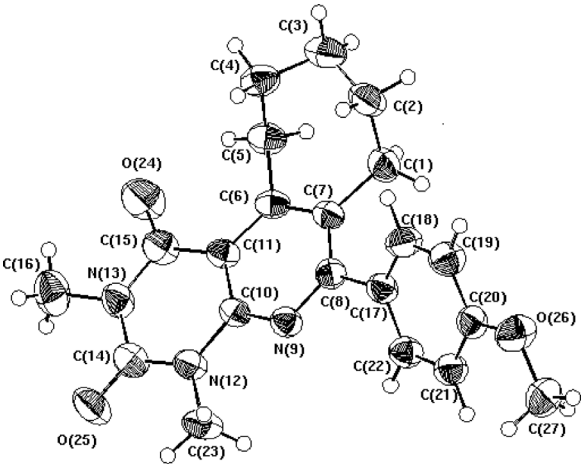


Fig. 2. Molecular structure of **6f** in the solid state (displacement ellipsoids at the 50 % probability level).

bromobenzaldehyde (**3c**), benzaldehyde (**3d**), and 1-naphthalene carbaldehyde (**3e**), only the corresponding Schiff bases **5c** – **e** were obtained, respectively, with no participation of the cyclic ketone in the reaction (Scheme 1). The structure of compounds **5c**, **d** was verified by elemental analyses, ^{1}H and ^{13}C NMR and mass spectra.

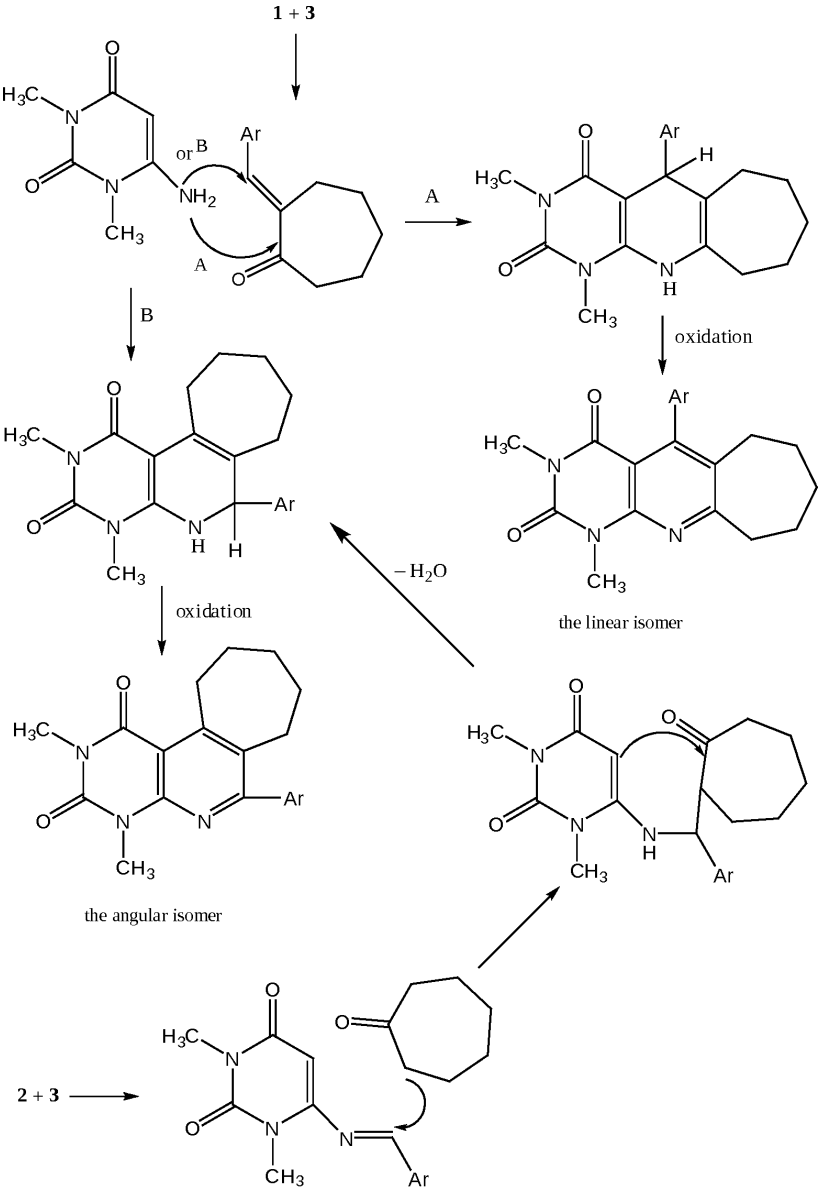
On the other hand, the reaction of cycloheptanone (**1**) with equimolar amounts of 6-amino-1,3-dimethyluracil (**2**) and 4-methoxybenzaldehyde (**3f**) afforded two products, the angular product hexahydrocyclohepta[4,5]-pyrido[2,3-*d*]pyrimidine-2,4-dione **6f** and the Schiff base **5f** (Scheme 1). Compound **6f**, which has the angular structure, is reported for the first time from such a one-pot reaction under the given reaction conditions. Compounds that have such an angular structure were prepared, however, by using other reactants such as the cyclic vinyl aldehydes and 6-aminopyrimidines [39, 40]. The structure of **6f** was verified by spectral data and elemental analysis. The ^{1}H NMR spectrum of **6f** showed ten cycloheptane and two types of methyl group protons. The ^{13}C NMR spectrum of **6f** showed signals at δ = 106.58 (C-5), 113.41 (C-6), 159.52 (C-7), 159.81 (C-8a′), 159.87 (C-4), and 162.25 (C-2) ppm. These data are different from those of **4a** and **4b**. Besides, the single crystal X-ray diffraction analysis of **6f** (Fig. 2) confirmed the proposed angular structure.

Two products were also isolated from the reaction of cycloheptanone (**1**) with equimolar amounts of 6-amino-1,3-dimethyluracil (**2**) and 4-cyanobenzaldehyde (**3g**) and were identified as hexahydrocyclohepta[4,5]-pyrido[2,3-*d*]pyrimidine-2,4-dione **6g** and the Schiff base **5g** (Scheme 1). The ^{1}H and ^{13}C NMR spectra of compound **6g** are compatible with the proposed constitution of **6f**; characteristic ^{13}C signals are found at δ = 107.86 (C-5), 112.38 (C-6), 118.45 (CN), 160.09, and 162.06 ppm (2 CO).

There are several possibilities for the mechanism of this reaction [2], one of them is based on the assumption that it proceeds initially *via* the formation of the α,β-unsaturated ketone intermediate, with a subsequent nucleophilic attack by the amino group of the uracil derivative on the carbonyl carbon of the α,β-unsaturated ketone intermediate, followed by cyclization to give the linear structure (route A) (Scheme 2). A second possibility is the nucleophilic attack by the amino group of the uracil derivative on the methylenic carbon of the α,β-unsaturated ketone intermediate, followed by cyclization to give the angular structure (route B) (Scheme 2). An alternative nucleophilic attack of the amino group of the uracil derivative on the aldehyde group to give the Schiff base, followed by the reaction with the cyclic ketone in a stepwise mechanism to give finally the angular structure (Scheme 2), can also be postulated.

Surprisingly, the three component one-pot reaction of cycloheptanone (**1**) with equimolar amounts of 6-amino-1,3-dimethyluracil (**2**) and 2-methoxybenzaldehyde (**3h**) gave only one product, 1,3-dimethylbenzo-[4,5]pyrido[3,2-*d*]pyrimidine-3,4-dione (**7**). The formation of compound **7** can be accounted for by the formation of the intermediate Schiff base which is present in the *Z*-form across the imino double bond and a subsequent electrocyclic ring closure and elimination of methanol (without participation of the cyclic ketone in the reaction), as shown in Scheme 3. It is noteworthy to mention that similar Schiff bases having *Z*-configuration and an appropriate *ortho*-group on the aryl ring were suggested to undergo such ring closure reactions [27]. The structure of **7** was verified by spectral data and elemental analysis. The ^{1}H NMR spectrum of **7** revealed the absence of methoxy, 5-CH, and cycloheptane protons. The ^{13}C NMR spectrum of **7** showed signals at δ = 39.16 (CH_3), 39.32 (CH_3), 111.05 (C-5), 124.25, 125.36, 127.15, 129.48, 133.03, 139.32, 148.50 (Ar-C + C-4a + C-10a), 148.65 (C-9), 151.25 (C-4), and 160.88 (C-2), and the mass spectrum showed the prominent molecular ion peak at *m/z* (%) = 241 (74) $[M]^+$.

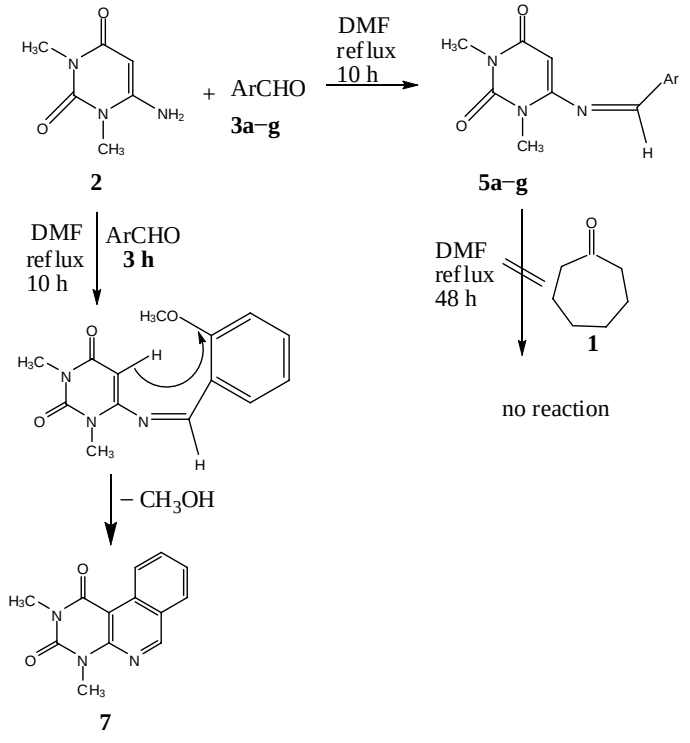
All attempts to obtain the corresponding pyridopyrimidines through the reaction of the Schiff bases **5a** – **g**



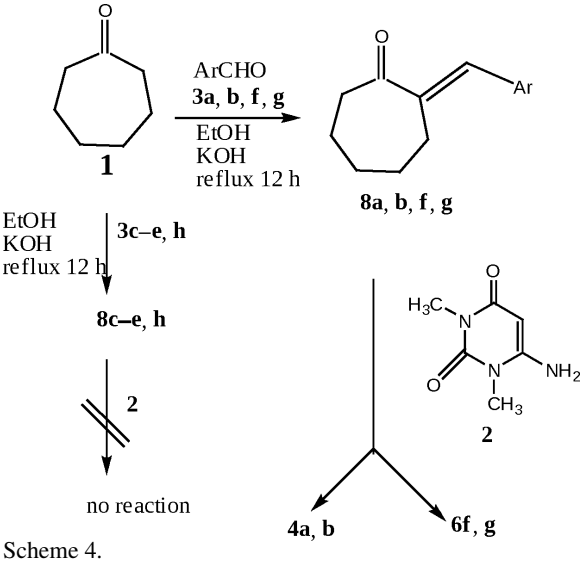
Scheme 2.

with cycloheptanone did not succeed, probably due to the presence of the aryl group of the Schiff base in the *Z*-form across the imino double bond which does not allow further reaction with cycloheptanone and subsequent ring closure as in the case of the formation of product **7**, and this result is in accordance with previous reports [27]. The reactions of 2-(arylmethylene) cycloheptanones **8a**, **b**, **f**, **g** with 6-amino-1,3-dimethyluracil gave the corresponding pyridopyrimidines **4a**, **b** and **6f**, **g**, but derivatives **8c** – **e**, **h** did not undergo any reaction when treated with compound **2** which probably suggests the presence of compounds **8c** – **e**, **h** in the *Z*-form (Scheme 4).

The molecular graphics of compounds **4a** and **6f** are shown in Figs. 1 and 2. Crystal data and details of the structure determination of compounds **4a** and **6f** are shown in Table 1. Some selected bond lengths, bond angles, and torsion angles are given in Tables 2 and 3.



Scheme 3.



Scheme 4.

Table 1. Crystal data and details of the structure determination of **4a** and **6f**.

Crystal data	Compound **4a**	Compound **6f**
Empirical formula	$C_{20}H_{21}ClN_3O_2$	$C_{21}H_{23}N_3O_2$
Formula weight	370.860	349.434
Shape/color	cube/ colorless	prismatic/ colorless
Crystal system	triclinic	triclinic
Space group	$P\bar{1}$	$P\bar{1}$
Temperature, K	298	298
Wavelength, Å	0.71073	0.71073
a, Å	9.1022 (3)	8.1147 (4)
b, Å	9.9807 (4)	9.8840 (5)
c, Å	11.4985 (5)	11.4804 (7)
α, deg	108.922 (2)	88.449 (2)
β, deg	109.622 (2)	80.566 (2)
γ, deg	94.388 (2)	87.620 (2)
Volume, Å^3	910.39 (6)	907.36 (8)
Z	2	2
Density (calculated), mg m^{-3}	1.353	1.279
θ range for data coll., deg	2.91 – 30.03	2.91 – 25.03
Index ranges *hkl*	+12, ±14, −16→13	+9, ±11, ±13
Reflections, measured	6034	4598
Reflexions, independent	5672	3558
Reflexions, observed	2277	1565
Data/parameters	2276/235	1564/244
Goodness-of-fit	1.280	1.325
R index [$I \geq 3\sigma(I)$]	0.051	0.048
*R*1/ *wR*2 indices (all data), *R*	0.128/0.105	0.118/0.121
$\Delta\rho_{fin}$ (max/min), e Å^{-3}	0.52/−0.48	0.32/−0.36

Antiinflammatory activity

The antiinflammatory activities of the tested compounds **4a**, **b**, **5a**, **c**,**d**, **e**, **6f**, **g** were evaluated according to the method of Winter *et al*. [41]. The tested compounds were compared with indomethacine as ref-

Table 2. Selected bond lengths (Å), bond angles (deg), and torsion angles (deg) for **4a**.

N4–C11	1.382 (3)	N4–C11–N8	115.7 (2)
N4–C13	1.371 (4)	C7–C11–N8	123.6 (2)
N4–C20	1.471 (3)	N8–C12–C9	123.2 (2)
N5–C13	1.395 (3)	N8–C12–C23	115.4 (2)
N5–C14	1.386 (3)	C9–C12–C23	121.4 (2)
N5–C24	1.467 (4)	O3–C13–N4	122.6 (2)
N8–C11	1.341 (3)	C12–N8–C11–N4	179.7 (4)
N8–C12	1.340 (3)	C12–N8–C11–C7	−1.0 (3)
C11–N4–C13	122.6 (2)	C6–C9–C12–N8	2.6 (3)
C11–N4–C20	119.9 (2)	C15–C9–C12–N8	−178.4 (4)
C13–N4–C20	117.5 (2)	N4–C11–N8–C12	179.7 (4)
C13–N5–C14	125.4 (2)	C13–N4–C11–N8	−176.0 (4)
C13–N5–C24	116.9 (2)	C20–N4–C11–N8	3.3 (2)
C14–N5–C24	117.6 (2)	N8–C11–N4–C13	−176.0 (4)
C11–N8–C12	118.2 (2)	N8–C12–C9–C15	−178.4 (4)

Table 3. Selected bond lengths Å, bond angles (deg), and torsion angles (deg) for **6f**.

N12–C10	1.396 (3)	C14–N12–C10–N9	172.9 (4)
N12–C14	1.372 (3)	C10–N12–C14–O25	−179.3 (5)
N12–C23	1.460 (3)	C14–N12–C10–C11	−5.1 (3)
N9–C8	1.343 (3)	C10–N12–C14–N13	0.3 (3)
N9–C10	1.321 (3)	C23–N12–C10–N9	−0.4 (3)
N13–C14	1.387 (3)	C6–C11–C10–N9	5.3 (3)
N13–C15	1.380 (4)	C15–C11–C10–N12	4.1 (3)
N13–C16	1.470 (3)	C15–C11–C10–N9	−173.7 (5)
C10–N12–C14	122.9 (2)	C10–C11–C15–N13	1.3 (3)
C10–N12–C23	119.5 (2)	C6–C11–C15–N13	−177.7 (5)
C14–N12–C23	117.3 (2)	C17–C8–N9–C10	174.3 (4)
C14–N13–C15	126.2 (2)	N9–C10–N12–C23	−0.4 (3)
C14–N13–C16	116.3 (2)	C11–C10–N9–C8	−1.5 (3)
C15–N13–C16	117.5 (2)	N9–C10–C11–C6	5.3 (3)

Table 4. Antiinflammatory activity for the tested compounds **4a**, **b**, **5a**, **c**, **d**, **e**, **6f**, **g**[a].

	1 h		2 h		3 h		4 h	
Compd.	Edema rate (%)	Inhibition rate (%)	Edema rate (%)	Inhibition rate (%)	Edema rate (%)	Inhibition rate (%)	Edema rate (%)	Inhibition rate (%)
Cont.	84.82 ± 5.09	–	93.78 ± 5.54	–	95.58 ± 6.91	–	98.67 ± 6.03	–
4a	69.66 ± 4.21	−17.87	89.19 ± 2.64	−4.89	94.75 ± 2.28	−0.87	97.36 ± 5.13	−1.33
4b	71.07 ± 2.57	−16.21	87.81 ± 4.52	−6.37	87.85 ± 4.34	−8.09	92/67 ± 4.50	−6.08
5a	66.57 ± 4.83	−21.51	86.93 ± 5.55	−7.30	91.93 ± 3.25	−3.82	94.13 ± 6.24	−4.60
5c	85.55 ± 5.41	0.86	102.50 ± 8.67	9.30	103.68 ± 3.73	8.48	100.80 ± 5.38	2.16
5d	76.54 ± 5.56	−9.76	87.59 ± 4.93	−6.59	88.45 ± 6.32	−7.46	92.95 ± 6.77	−5.80
5e	71.08 ± 4.75	−16.19	88.68 ± 1.34	−5.43	93.49 ± 3.96	−1.71	96.54 ± 3.94	−2.15
6f	68.19 ± 5.53	−19.61	89.44 ± 4.86	−4.63	95.13 ± 4.67	−0.47	79.92 ± 3.50	−0.76
6g	79.27 ± 5.02	−6.54	86.49 ± 4.29	−7.77	83.47 ± 7.95	−12.66	91.07 ± 7.05	−7.70
7	68.68 ± 5.97	−19.03	76.03 ± 6.92	−18.93	76.88 ± 3.70	−19.56	76.86 ± 6.74	−22.10
Indo..	36.35 ± 2.30[b]	−57.15	41.38 ± 3.92[b]	−55.88	54.11 ± 4.44[b]	−43.39	61.28 ± 4.75[b]	−37.89

[a] Cont. = control; Indo. = indomethacin; [b] $P < 0.05$: statistically significant from control (Dunnett's test).

erence drug. The results are listed in Table 4. Results showed that the tested compounds have weak activities.

Experimental Section

Melting points were determined in open glass capillaries using an IA 9000 SERIES digital melting point apparatus (Electrothermal, Essex, U. K.) and are uncorrected. Microanalyses were performed for all products on an Elementar-Vario EL, Microanalytical Unit, Central Services Laboratory, National Research Centre, Cairo, Egypt. The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer (Faculty of Science, Cairo University, Cairo, Egypt) and on a Jeol EX-500 NMR spectrometer (Central Services Laboratory, National Research Centre, Cairo, Egypt). ^{1}H NMR spectra were run at 300 and 500 MHz, and ^{13}C NMR spectra were run at 75.46 and 125.76 MHz in $CDCl_3$ (δ = 7.26 ppm) or DMSO (δ = 2.50 ppm) as solvent. Chemical shifts are quoted in δ and are related to that of the solvents. Mass spectra, EI (70 eV), were recorded on a Thermo Finnigan TRACE GC 2000 GC/MS ISO 9001 instrument (Thermo Electron Corporation, Bremen, Germany), (Central Services Laboratory, National Research Centre, Cairo, Egypt). IR spectra were obtained on a Bruker-Vector 22 instrument using KBr wafers (Micro-analytical Center of Cairo University). Compounds **8a**, **d** [42], **8b**, **c** [43], **8f**, **h** [44] were prepared according to literature procedures. Yields of the products refer to samples after purification.

General procedure for the one-pot reaction of 6-amino-1,3-dimethyluracil, cycloheptanone and an aromatic aldehyde

A mixture of cycloheptanone (**1**) (1.4 g, 10 mmol), 6-amino-1,3-dimethyluracil (**2**) (1.5 g, 10 mmol) and the appropriate aromatic aldehyde (**3**) (10 mmol) was refluxed in 20 mL of *N*,*N*-dimethylformamide (DMF) for 10 h. The solvent was evaporated, and the residue was purified by crystallization or by column chromatography.

*Reaction of **1**, **2** and 4-chlorobenzaldehyde (**3a**)*

The products **4a** and **5a** were isolated by column chromatography (silica gel 60, particle size 0.06 – 0.20 mm) us-

ing ethyl acetate : petroleum ether 40 – 60 °C (1 : 10 v/v) as eluent.

*1,3-Dimethyl-5-(4-chlorophenyl)-1,6,7,8,9,10-hexahydrocyclohepta[5,6]pyrido[2,3-d]pyrimidine-2,4-dione (**4a**)*

Colorless crystals, yield 1.4 g (40 %). – M. p. 187 – 190 °C. – IR: ν = 1700, 1660 (C=O) cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.72 – 2.02 (m, 6 H, 3 CH_2), 2.41 (t, J = 5 Hz, 2 H, CH_2), 3.11 (t, J = 5 Hz, 2 H, CH_2), 3.29 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 6.97 (d, J = 10 Hz, 2 H, Ar-H), 7.40 (d, J = 10 Hz, 2H, Ar-H). – ^{13}C NMR: δ = 26.18, 27.50, 28.35 (3 CH_2), 28.91 (1-CH_3), 29.71 (3-CH_3), 31.85 (CH_2), 39.77 (CH_2), 105.95 (C-6, C-4a), 128.05 (C-1′), 132.04 (C-3′, C-5′), 133.15 (C-2′, C-6′), 137.25 (C-4′), 148.55 (C-5), 149.50 (C-8a), 151.52 (C-7′), 160.85 (C-4), 168.95 (C-2). – MS: *m/z* (%) = 371 (6) $[M,Cl^{37}]^+$, 369 (16) $[M,Cl^{35}]^+$, 340 (4), 277 (34), 275 (100), 249 (14), 247 (45), 217 (5), 190 (11), 177 (6), 165 (30), 163 (90), 128 (14), 114 (14). – $C_{20}H_{20}ClN_3O_2$ (369.83): calcd. C 64.94, H 5.45, Cl 9.58, N 11.36; found C 64.83, H 5.38, Cl 9.93, N 11.30.

*6-[N-(4-Chlorobenzylidene)amino]-1,3-dimethyluracil (**5a**)*

Colorless crystals, yield 0.7 g (30 %). – M. p. 234 – 235 °C. – IR: ν = 1699, 1668 (C=O), 1630 (C=N) cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 3.51 (s, 3H, CH_3), 3.71 (s, 3H, CH_3), 7.03 (s, 1 H, 5-CH), 7.45 (d, J = 10 Hz, 2 H, Ar-H), 7.85 (d, J = 10 Hz, 2H, Ar-H), 7.98 (s, 1 H, CH=N). – ^{13}C NMR: δ = 28.57 (CH_3), 29.68 (CH_3), 110.95 (C-5), 123.00, 126.99, 127.21, 130.30, 139.45, 139.80 (Ar-C), 149.20 (C-6), 150.18 (C=N), 151.48 (C-4), 161.10 (C-2). – $C_{13}H_{12}ClN_3O_2$ (277.70): calcd. C 56.22, H 4.35, N 15.13; found C 56.10, H 4.29, N 15.00.

*Reaction of **1**, **2** and 4-bromobenzaldehyde (**3b**)*

The products **4b** and **5b** were isolated by column chromatography (silica gel 60, particle size 0.06 – 0.20 mm) using ethyl acetate : petroleum ether 40 – 60 °C (1 : 10 v/v) as an eluent.

*1,3-Dimethyl-5-(4-bromophenyl)-1,6,7,8,9,10-hexahydrocyclohepta[5,6]pyrido[2,3-d]pyrimidine-2,4-dione (**4b**)*

Colorless crystals, yield 0.8 g (20 %). – M. p. 192 – 195 °C. – IR: ν = 1703, 1658 (C=O) cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.73 – 2.05 (m, 6 H, 3 CH_2), 2.40 (t, J = 5 Hz, 2 H, CH_2), 3.12 (t, J = 5 Hz, 2 H, CH_2), 3.29 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 6.96 (d, J = 10 Hz, 2 H, Ar-H), 7.38 (d, J = 10 Hz, 2H, Ar-H). – ^{13}C NMR: δ = 26.18, 27.49, 28.33, 28.90, 29.71 (5 CH_2), 31.85 (CH_3), 39.77 (CH_3), 105.94, 128.05, 132.05, 133.14, 137.24, 148.55, 149.49, 151.52 (Ar-C), 160.84 (C-4), 168.95 (C-2). – MS: *m/z* (%) = 414 (100) $[M]^+$, 398 (16), 384 (19), 305 (3), 207 (5), 193 (3), 167 (3). – $C_{20}H_{20}BrN_3O_2$ (414.28): calcd. C 57.98, H 4.86, Br 19.28, N 10.14; found C 57.80, H 4.75, Br 19.00, N 9.89.

*6-[N-(4-Bromobenzylidene)amino]-1,3-dimethyluracil (**5b**)*

Colorless crystals, yield 0.5 g (15 %). – M. p. 284 – 287 °C. – IR: ν = 1701, 1667 (C=O), 1630 (C=N) cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 3.50 (s, 3H, CH_3), 3.71 (s, 3H, CH_3), 7.05 (s, 1 H, 5-CH), 7.45 (d, J = 10 Hz, 2 H, Ar-H), 7.84 (d, J = 10 Hz, 2H, Ar-H), 7.98 (s, 1 H, CH=N). – ^{13}C NMR: δ = 28.56 (CH_3), 29.68 (CH_3), 110.95 (C-5), 123.01, 126.98, 127.21, 130.30, 139.43, 139.79 (Ar-C), 149.21 (C-6), 150.19 (C=N), 151.48 (C-4), 161.11 (C-2). – $C_{13}H_{12}BrN_3O_2$ (322.15): calcd. C 48.46, H 3.75, N 13.04; found C 48.14, H 3.58, N 12.88.

*Reaction of **1**, **2** and 2-bromobenzaldehyde (**3c**)*

*6-[N-(2-Bromobenzylidene)amino]-1,3-dimethyluracil (**5c**)*

Colorless crystals (from dioxane), yield 0.9 g (22 %). – M. p. 205 – 207 °C. – IR: ν = 1700, 1658 (C=O), 1625 (C=N) cm^{-1}. – ^1H NMR ([D_6]DMSO): δ = 3.29 (s, 3H, CH_3), 3.59 (s, 3H, CH_3), 7.55 (s, 1 H, 5-CH), 7.85 – 7.87 (m, 3 H, Ar-H), 8.14 (d, J = 10 Hz, 1H, Ar-H), 9.03 (s, 1 H, CH=N). – ^{13}C NMR: δ = 28.01 (CH_3), 28.12 (CH_3), 110.0 (C-5), 124.19, 125.42, 127.17, 129.27, 133.09, 139.33 (Ar-C), 148.27 (C-6), 148.70 (C=N), 150.98 (C-4), 160.61 (C-2). – MS: *m/z* (%) = 321 (100) $[M]^+$, 293 (14), 290 (17), 241 (16), 209 (29), 207 (37), 129 (12), 114 (15). – $C_{13}H_{12}BrN_3O_2$ (322.15): calcd. C 48.46, H 3.75, N 13.04; found C 48.24, H 3.65, N 12.89.

*Reaction of **1**, **2** and benzaldehyde (**3d**)*

*6-[N-(Benzylidene)amino]-1,3-dimethyluracil (**5d**)*

Colorless crystals (from ethyl acetate), yield 0.8 g (33 %). – M. p. 327 – 330 °C. – IR: ν = 1699, 1668 (C=O), 1630 (C=N) cm^{-1}. – ^1H NMR ([D_6]DMSO): δ = 3.29 (s, 3H, CH_3), 3.34 (s, 3H, CH_3), 5.74 (s, 1 H, 5-CH), 7.07 – 7.89 (m, 5 H, Ar-H), 7.94 (s, 1 H, CH=N). – ^{13}C NMR: δ = 29.83 (CH_3), 39.16 (CH_3), 86.07 (C-5), 124.69, 126.45, 127.52, 139.56 (Ar-C + C-6), 150.41 (C=N), 154.17 (C-4), 162.66 (C-2). – MS: *m/z* (%) = 242 (100) $[M–H]^+$, 228 (2), 185 (17), 143 (5), 127 (5), 102 (7). – $C_{13}H_{13}N_3O_2$ (243.25): calcd. C 64.18, H 5.38, N 17.29; found C 63.96, H 5.23, N 17.07.

*Reaction of **1**, **2** and 1-naphthaldehyde (**3e**)*

*6-[N-(1-Naphthylmethylidene)amino]-1,3-dimethyluracil (**5e**)*

Colorless crystals (from dioxane), yield 1.0 g (33 %). – M. p. 266 – 269 °C. – IR: ν = 1689, 1656 (C=O), 1618

(C=N) cm^{-1}. – MS: *m/z* (%) = 291 (100) $[M]^+$, 263 (22), 205 (3), 191 (4), 179 (25), 164 (6), 150 (7). – $C_{17}H_{13}N_3O_2$ (291.29): calcd. C 70.09, H 4.49, N 14.42; found C 69.87, H 4.35, N 14.15.

*Reaction of **1**, **2** and 4-methoxybenzaldehyde (**3f**)*

The products **6f** and **5f** were isolated by using column chromatography (silica gel 60, particle size 0.06 – 0.20 mm) using ethyl acetate : petroleum ether 40 – 60 °C (1 : 10 v/v) as an eluent.

*1,3-Dimethyl-10-(4-methoxyphenyl)-1,5,6,7,8,9-hexahydrocyclohepta[4,5]pyrido[2,3-d]pyrimidine-2,4-dione (**6f**)*

Colorless crystals, yield 1.0 g (30 %). – M. p. 194 – 196 °C. – IR: ν = 1700, 1658 (C=O) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 1.57 – 2.18 (m, 8 H, 4 CH_2), 2.85 (t, J = 5 Hz, 2 H, CH_2), 3.36 (s, 3H, NCH_3), 3.59 (s, 3H, NCH_3), 3.77 (s, 3H, OCH_3), 6.90 (d, J = 10 Hz, 2 H, Ar-H), 7.39 (d, J = 10 Hz, 2H, Ar-H). – ^{13}C NMR: δ = 25.70, 27.44, 28.38, 28.87, 29.36 (5 CH_2), 29.85 (CH_3), 31.85 (CH_3), 55.23 (OCH_3), 106.58 (C-5), 113.41 (C-6), 130.58, 132.45, 132.98, 148.73, 151.22 (Ar-C), 159.52 (C-7), 159.81 (C-8a), 159.87 (C-4), 162.25 (C-2). – MS: *m/z* (%) = 365 (100) $[M]^+$, 350 (75), 336 (80), 322 (65), 293 (15), 279 (30), 252 (20), 222 (23), 208 (20), 192 (15), 167 (15). – $C_{21}H_{23}N_3O_3$ (365.41): calcd. C 69.02, H 6.34, N 11.49; found C 68.82, H 6.19, N 11.34.

*6-[N-(4-Methoxybenzylidene)amino]-1,3-dimethyluracil (**5f**)*

Colorless crystals, yield 0.7 g (25 %). – M. p. 261 – 263 °C. – IR: ν = 1698, 1659 (C=O), 1624 (C=N) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 3.46 (s, 3H, NCH_3), 3.77 (s, 3H, NCH_3), 3.92 (s, 3H, OCH_3), 7.07 (d, J = 10 Hz, 2 H, Ar-H), 7.22 (s, 1 H, 5-CH), 7.71 (d, J = 10 Hz, 2H, Ar-H), 7.78 (s, 1 H, CH=N). – ^{13}C NMR: δ = 28.43 (CH_3), 29.60 (CH_3), 55.76 (OCH_3), 106.00 (C-5), 108.48, 119.41, 119.96, 130.37, 139.25, 148.98 (Ar-C), 151.68 (C-6), 152.09 (C=N), 161.49 (C-4), 163.95 (C-2). – MS: *m/z* (%) = 273 (51) $[M]^+$, 272 (69), 271 (66), 243 (98), 228 (26), 213 (32), 199 (46), 186 (55), 171 (62), 159 (100), 144 (70), 129 (60), 116 (79), 102 (60), 89 (6), 77 (52). – $C_{14}H_{15}N_3O_3$ (273.28): calcd. C 61.52, H 5.32, N 15.37; found C 61.21, H 5.18, N 15.20.

*Reaction of **1**, **2** and 4-cyanobenzaldehyde (**3g**)*

The products **6g** and **5g** were isolated by column chromatography (silica gel 60, particle size 0.06 – 0.20 mm) using ethyl acetate : petroleum ether 40 – 60 °C (1 : 10 v/v) as an eluent.

*1,3-Dimethyl-10-(4-cyanophenyl)-1,5,6,7,8,9-hexahydrocyclohepta[4,5]pyrido[2,3-d]pyrimidine-2,4-dione (**6g**)*

Colorless crystals, yield 1.2 g (35 %). – M. p. 258 – 261 °C. – IR: ν = 2220 (C≡N), 1700, 1660 (C=O), 1628 (C=N) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 1.59 – 1.87 (m, 6 H, 3 CH_2), 2.87 (t, J = 4.8 Hz, 2 H, CH_2), 3.48 (s, 3H, CH_3), 3.68 (s, 3H, CH_3), 3.80 (t, J = 4.8 Hz, 2 H, CH_2), 7.60 (d, J = 8.1 Hz, 2 H, Ar-H), 7.77 (d, J = 8.1 Hz, 2H, Ar-H). – ^{13}C NMR: δ = 25.36, 27.41, 28.57, 29.01, 29.31 (5 CH_2), 29.87, 31.07 (2 CH_3), 107.86 (C-5), 112.38 (C-6), 118.45 (CN), 125.95, 129.73, 132.08, 133.19, 144.60, 149.13, 151.15, 157.98 (Ar-C), 160.09, and 162.06 (2 CO). – $C_{21}H_{20}N_4O_2$ (360.41): calcd. C 69.97, H 5.59, N 15.54; found C 69.77, H 5.48, N 15.30.

*6-[N-(4-Cyanobenzylidene)amino]-1,3-dimethyluracil (**5g**)*

Colorless crystals, yield 0.8 g (35 %). – M. p. 287 – 290 °C. – IR: ν = 2225 (C≡N), 1703, 1665 (C=O), 1625 (C=N) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 3.71 (s, 3H, CH_3), 4.10 (s, 3H, CH_3), 7.63 (s, 1 H, 5-CH), 8.05 (d, J = 8.0 Hz, 2 H, Ar-H), 8.22 (d, J = 8.0 Hz, 2H, Ar-H), 8.48 (s, 1 H, CH=N). – MS: *m/z* (%) = 267 (100) $[M–H]^+$, 252 (4), 247 (14), 210 (79), 195 (22), 126 (14), 112 (10). – $C_{14}H_{12}N_4O_2$ (268.27): calcd. C 62.67, H 4.51, N 20.88; found C 62.47, H 4.45, N 22.65.

*Reaction of **1**, **2** and 2-methoxybenzaldehyde (**3h**)*

1,3-Dimethylbenzo[4,5]pyrido[3,2-d]pyrimidine-3,4-dione

Colorless crystals (from dioxane), yield 0.8 g (35 %). – M. p. 225 – 227 °C. – IR: ν = 1710, 1669 (C=O) cm^{-1}. – ^{1}H NMR ([D_6]DMSO): δ = 3.31 (s, 3H, CH_3), 3.63 (s, 3H, CH_3), 7.55 – 8.16 (m, 4 H, Ar-H), 9.04 (s, 1 H, CH=N). – ^{13}C NMR: δ = 39.16 (CH_3), 39.32 (CH_3), 111.05 (C-5), 124.25, 125.36, 127.15, 129.48, 133.03, 139.32, 148.50 (Ar-C + C-4a + C-10a), 148.65 (C-9), 151.25 (C-4), 160.88 (C-2). – MS: *m/z* (%) = 241 (74) $[M]^+$, 212 (26), 185 (33), 156 (17), 129 (100), 102 (38), 76 (13). – $C_{13}H_{11}N_3O_2$ (241.24): calcd. C 64.71, H 4.59, N 17.41; found C 64.35, H 4.48, N 17.41.

Antiinflammatory activity

The antiinflammatory testing was performed according to the method of Winter *et al.* [41]. For this purpose 55 rats (female) weighing 150 – 180 g were used. Edema was induced in the left hind paw of all rats by subcutaneous (s. c.) injection of 0.1 mL of 1 % (w/v) carrageenin in distilled water into their footpads.

Rats were divided into 11 groups of 5 rats each. The first group was kept as control, and was given the respective volume of the solvent (few drops of DMSO). Animals of the second to tenth groups were orally administered the tested

compounds **4a**, **b**, **5a**, **c**, **d**, **e**, **6f**, **g**, **7** in doses of 50 mg kg^{-1}, 1 h before carrageenin injection. The last group was administered indomethacin (Indocid®) in a dose of 10 mg kg^{-1} b. wt., orally as a standard reference. The paw volume of each rat was measured using a plethysmometer before carrageenin injection and then hourly for 4 h post administration of the plant extracts.

The edema rate and inhibition rate of each group were calculated as follows:

$$\text{Edema rate } E\ (\%) = (V_t - V_o/V_o) \times 100,$$

$$\text{Inhibition rate } I\ (\%) = (E_c - E_t/E_c) \times 100,$$

where V_o represents the volume before carrageenin injection (mL). V_t represents the volume at t hours after carrageenin injection (mL). E_c represents the edema rate of the control group. E_t represents the edema rate of the treated group, and data are expressed as mean ± S. E. M.

CCDC 686153 (**4a**) and 686154 (**6f**) contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request /cif.

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