

Article

Synthesis of New Visnagen and Khellin Furochromone Pyrimidine Derivatives and Their Anti-Inflammatory and Analgesic Activity

Ameen Ali Abu-Hashem ^{1,†,*} and Mohamed M. Youssef ^{2,‡}

¹ Departments of Photochemistry, National Research Center, 12622 Dokki, Giza, Egypt

² Department of Chemistry, Faculty of Science, Cairo University, Giza, Egypt

[†] Current Address: Department of Chemistry, Faculty of Science, Jazan University, 2097 Jazan, Saudi Arabia.

[‡] Current Address: Department of Chemistry, Faculty of Science, Taif University, Taif, Saudi Arabia.

* Author to whom correspondence should be addressed; E-Mail: aminaliabuhashem@yahoo.com; Tel.: +966-56-351-0497, +2-012-521-1700; Fax: +966-73-245-212.

Received: 17 January 2011; in revised form: 11 February 2011 / Accepted: 17 February 2011 /

Published: 25 February 2011

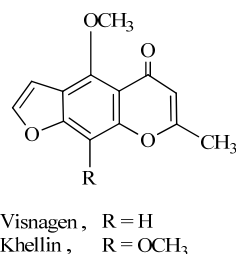
Abstract: 6-[(4-Methoxy/4,9-dimethoxy)-7-methylfurochromen-5-ylideneamino]-2-thioxo-2,3-dihydropyrimidin-4-ones **1a,b** were prepared by reaction of 6-amino-2-thiouracil with visnagen or khellin, respectively. Reaction of **1a,b** with methyl iodide afforded furochromenylideneaminomethylsulfanylpyrimidin-4-ones **2a,b**. Compounds **2a,b** were reacted with secondary aliphatic amines to give the corresponding furochromenylideneamino-2-substituted pyrimidin-4-ones **3a–d**. Reaction of **3a–d** with phosphorus oxychloride yielded 6-chlorofurochromenylidenepyrimidinamines **4a–d**, which were reacted with secondary amines to afford furochromenylideneamino-2,6-disubstituted pyrimidin-4-ones **5a–d**. In addition, reaction of **5a–d** with 3-chloropentane-2,4-dione gave 3-chloro-furochromenylpyrimidopyrimidines **6a–d**. The latter were reacted with piperazine and morpholine to give 1-(furochromenyl)-pyrimidopyrimidine-3,6,8-triylpiperazines or -3,6,8-triylmorpholines **7a–d**. The chemical structures of the newly synthesized compound were characterized by IR, ¹H-NMR, ¹³C-NMR and mass spectral analysis. These compounds were also screened for their analgesic and anti-inflammatory activities. Some of them, particularly **3–7**, exhibited promising activities.

Keywords: khellin; visnagen; furochromones; anti-inflammatory and analgesic activity

1. Introduction

Khellin and visnagen, 4,9-dimethoxy- or 4-methoxy-7-methyl-furo[3,2-*g*]chromen-5-one, respectively (Figure 1) are obtained from fruits and seeds of the plant *Ammi visnaga*. The khellin and visnagen extract has been widely employed as a herbal medicine in the treatment of angina [1]. Khellin is used as a spasmolytic agent and for kidney stone treatment [2]. Khellin and visnagen extract significantly prolongs the induction time of nucleation of calcium oxalate [3]. Khellin has been used for photochemotherapeutic treatment of vitiligo and psoriasis [4] and the photodynamic properties of khellin and visnagen in their photoreaction with DNA have been studied [5]. Recently, khellin was proved to have phototherapeutic properties that are similar to those of the psoralens, but with substantially lower phototoxic effects and DNA mutation effects. Its penetration into the hair follicles is enhanced by encapsulating it into liposomes. Subsequent activation of khellin with UV light stimulates the melanocytes in the hair follicles [6]. The fact that furochromone derivatives are known to have anti-inflammatory properties [7] and analgesic properties [8], prompted us to synthesize and investigate such properties in khellin and visnagen derivatives as typical furochromones.

Figure 1. Chemical structure of khellin and visnagen.



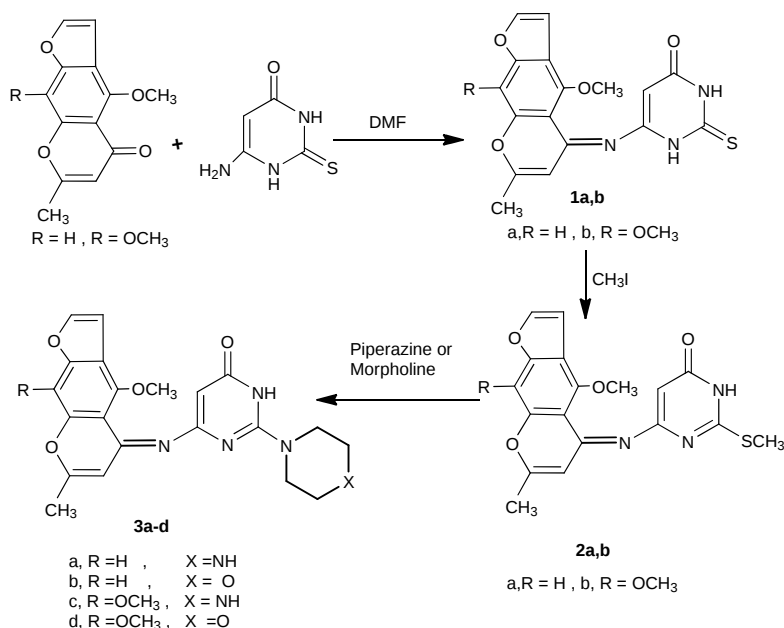
From a photobiological point of view, furochromones show valuable phototoxicity toward various kinds of microorganisms and also valuable genotoxic activity on various biological substrates [9,10]. In the present work, we planned the synthesis of various furochromenyldenylylpyrimidine derivatives representing new heterocyclic compounds. These compounds were also screened for their anti-inflammatory and analgesic activities.

2. Results and Discussion

Condensation of visnagen and khellin with 6-amino-2-thiouracil in dimethylformamide [11,12] yielded the 6-(4-methoxy/4,9-dimethoxy)-7-methylfuro[3,2-*g*]chromen-5-ylideneamino)-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-ones **1a,b**. The IR spectra of compounds **1a,b** revealed the presence of only one carbonyl band, in addition to the absence of the amino group band. The mass spectra of **1a** and **1b** showed molecular ion peaks at *m/z* 355 (96%) and 385 (90%), respectively. Compounds **1a,b** underwent alkylation at the sulphur atom upon treatment with methyl iodide in aqueous ethanolic KOH solution, to afford 6-((4-methoxy/4,9-dimethoxy)-7-methylfuro[3,2-*g*]chromen-5-ylidene-

amino)-2-methylsulfanyl-3*H*-pyrimidin-4-ones **2a,b**. The $^1\text{H-NMR}$ spectra of **2a** and **2b** showed singlets at δ 2.68 and 2.65 ppm, respectively, corresponding to a SCH_3 group. Reaction of the 2-methylsulfanyl derivatives **2a,b** with secondary aliphatic amines, namely piperazine and morpholine, in methanol [13] produced the 6-(4-methoxy/4,9-dimethoxy)-7-methylfuro[3,2-*g*]chromen-5-ylideneamino)-2-(piperazin/morpholin)-1-yl-3*H*-pyrimidin-4-ones **3a–d** (Scheme 1).

Scheme 1. Condensation of khellin and visnagen with aminothiouracil, methylation and reaction with secondary amines.

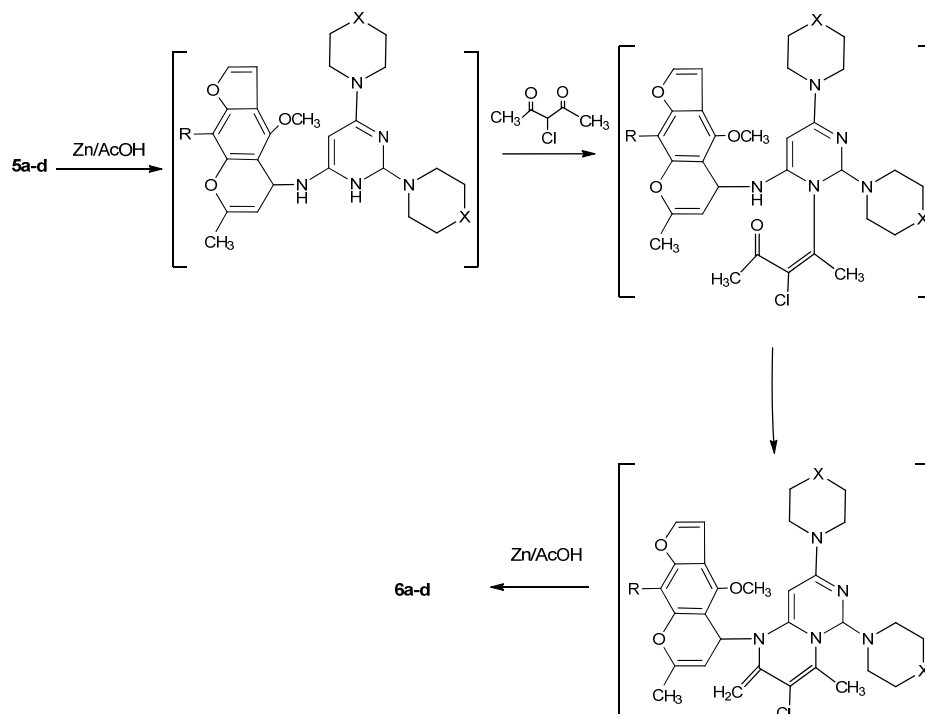


Moreover, the reaction of **3a–d** with phosphorus oxychloride in dry dioxane [14] afforded the (6-chloro-2-(piperazin/morpholin)-1-yl-pyrimidin-4-yl)-(4-methoxy/4,9-dimethoxy)-7-methylfuro[3,2-*g*]chromen-5-ylidene)amines **4a–d**. The IR spectra of **4a–d** revealed the absence of any absorption bands in the NH and carbonyl regions. Compounds **4a–d**, having an active chlorine substituent, reacted with either piperazine or morpholine in boiling methanol to produce 2,6-(dipiperazin/dimorpholin)-1-yl-pyrimidin-4-yl)-(4-methoxy/4,9-dimethoxy)-7-methylfuro[3,2-*g*]chromen-5-ylidene)amines **5a–d**. The structures of compounds **5a–d** were confirmed by their correct elemental analyses values, as well as compatible spectral data (see Experimental). Compounds **5a–d** reacted with 3-chloropentane-2,4-dione (a typical β -diketone) in acetic acid, in the presence of zinc dust, to afford the corresponding 3-chloro-1-(4-methoxy/4,9-dimethoxy)-7-methyl-5*H*-furo[3,2-*g*]chromen-5-yl)-2,4-dimethyl-6,8-dipiperazin/dimorpholin)-1-yl-1,3,4,6-tetrahydro-2*H*-pyrimido[1,6-*a*]pyrimidines **6a–d** in good yield. Formation of **6a–d** from the corresponding **5a–d** may proceed by initial reduction of compounds **5a–d**, followed by cyclocondensation of the intermediates produced with the diketone followed by a necessary final reduction step to produce **6a–d**.

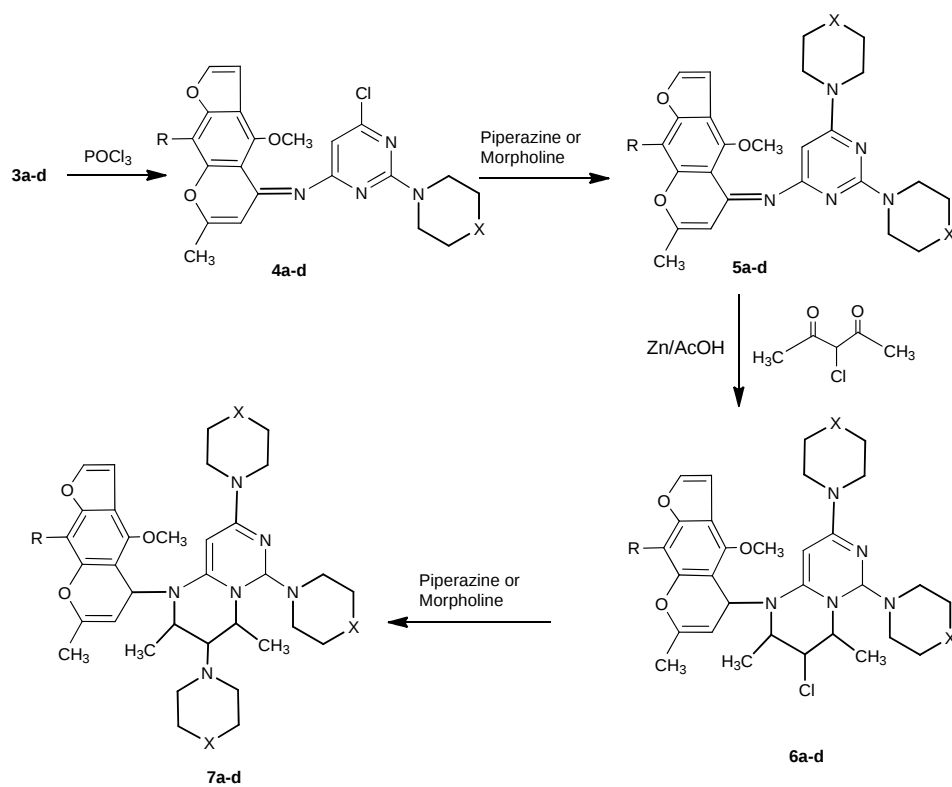
The steps of the suggested mechanism are shown in Scheme 2. The $^1\text{H-NMR}$ spectrum of **6a**, for example, showed a doublet at 1.15 ppm, a multiplet at 3.14 and a triplet at 3.92, which support the proposed reduced structure **6**. Finally, the 3-chlorofurochromenepyrimido/pyrimidines reacted with either piperazine or morpholine in boiling methanol to give the corresponding 3,6,8-tripiperazin-1-yl

or 3,6,8-trimorpholin-1-yl derivatives **7a–d** (Scheme 3). Compatible analytical and spectral data were obtained for compounds **7a–d** (see Experimental).

Scheme 2. Suggested mechanism for the formation of **6a–d** from **5a–d**.



Scheme 3. Chlorination of **3a–d**, condensation with amines and cyclocondensation with β -diketone.



a, R = H , X = NH
b, R = H , X = O
c, R = OCH₃ , X = NH

2.1. Anti-Inflammatory Activity

The anti-inflammatory activity was evaluated in rats by the carrageenan-induced paw edema test. The data (Table 1) indicated that all the tested compounds protected rats from carrageenan-induced inflammation, and that some of the tested compounds (**6a–d** and **7a–d**) are more potent than our previously reported ones [15,16]. Compounds **2–5** showed similar and higher anti-inflammatory activity than diclofenac sodium.

Table 1. Percent anti-inflammatory activity of the tested compounds (carrageenan-induced paw edema test in rats).

Compd. No.	Percent protection		
	1 hour	2 hours	3 hours
Visnagen	38.6 ± 1.38 *	40.2 ± 1.39 *	26.2 ± 1.29 *
Khellin	40.3 ± 1.40 *	41.5 ± 1.42 *	30.4 ± 1.32 *
1a	41.5 ± 1.35 *	40.4 ± 1.36 *	28.2 ± 1.28 *
1b	42.6 ± 1.45 *	41.5 ± 1.28 *	30.1 ± 1.30 *
2a	44.5 ± 1.28 *	43.6 ± 1.24 *	33.1 ± 1.01 *
2b	45.7 ± 1.30 *	44.8 ± 1.28 *	34.2 ± 1.02 *
3a	52.6 ± 1.10 **	50.8 ± 1.30 *	39.4 ± 1.25 *
3b	48.6 ± 1.40 *	45.6 ± 1.40 *	35.1 ± 1.04 *
3c	52.8 ± 1.12 **	52.6 ± 1.10 *	39.6 ± 1.23 *
3d	49.9 ± 1.50 **	48.8 ± 1.42 *	36.5 ± 1.20 *
4a	54.4 ± 1.23 **	53.6 ± 1.22 *	40.4 ± 1.04 *
4b	53.8 ± 1.20 **	52.6 ± 1.10 *	40.1 ± 1.02 *
4c	55.3 ± 1.25 **	54.8 ± 1.24 *	40.6 ± 1.05 *
4d	54.1 ± 1.22 **	53.2 ± 1.20 *	40.2 ± 1.03 *
5a	57.9 ± 1.39 **	58.9 ± 1.30 *	41.5 ± 1.08 *
5b	57.3 ± 1.37 **	58.8 ± 1.29 *	41.3 ± 1.06 *
5c	58.4 ± 1.40 **	59.1 ± 1.31 **	42.1 ± 1.23 *
5d	57.6 ± 1.38 **	60.0 ± 1.68 **	41.4 ± 1.07 *
6a	59.7 ± 1.45 **	59.5 ± 1.35 **	42.8 ± 1.26 *
6b	59.4 ± 1.05 **	59.1 ± 1.31 **	42.2 ± 1.24 *
6c	59.8 ± 1.52 **	59.7 ± 1.45 **	45.7 ± 1.52 *
6d	59.6 ± 1.41 **	59.2 ± 1.32 **	42.4 ± 1.25 *
7a	61.8 ± 1.88 **	61.4 ± 1.74 **	48.2 ± 1.65 *
7b	60.5 ± 1.80 **	60.2 ± 1.62 **	46.6 ± 1.60 *
7c	62.3 ± 1.92 **	61.6 ± 1.78 **	48.5 ± 1.68 *
7d	60.9 ± 1.85 **	60.4 ± 1.65 **	47.1 ± 1.63 *
Control	6.3 ± 0.26	5.6 ± 0.40	3.4 ± 0.96
Diclofenac Sodium	52.6 ± 0.96 *	60.5 ± 1.55 **	42.2 ± 1.39 *

Each value represents the mean ± S.E (n = 6). Significance levels * p < 0.5, ** p < 0.001 as compared with respective control. Dose (20 mg/kg). For the selected tested compound.

2.2. Analgesic Activity

The analgesic activity was determined by the hot-plate test (central analgesic activity) and acetic acid induced writhing assay. The results (Tables 2 and 3) revealed that all tested compounds exhibited significant activity. Most of the tested compounds have nearly the same activity as the reference drug and the remaining tested compound have good activities in central analgesic activity. Also compound **7c** exhibited activities higher than the reference.

Table 2. Central analgesic activity (Hot plate test).

Group	Reaction time (min)			
	0 min	30 min	60 min	90 min
Control	8.25 ± 0.35	8.20 ± 0.36 b	8.75 ± 0.55 b	9.80 ± 0.48 b
Visnagen	5.40 ± 0.56	6.30 ± 0.50	8.90 ± 0.60	9.80 ± 0.25 a
Khellin	5.50 ± 0.58	6.50 ± 0.40	9.01 ± 0.70	10.01 ± 0.22 a
1a	5.60 ± 0.30	6.70 ± 0.43	9.25 ± 0.55	10.10 ± 0.20a
1b	6.10 ± 0.20	7.30 ± 0.10 b	7.40 ± 0.10 a	10.20 ± 0.25 a
2a	6.20 ± 0.10	7.45 ± 0.20 b	8.10 ± 0.20 a	10.50 ± 0.30 a
2b	6.40 ± 0.20	7.55 ± 0.25 b	8.25 ± 0.30 a	10.80 ± 0.35 a
3a	7.01 ± 0.30	8.10 ± 0.40	10.55 ± 0.50 a	10.90 ± 0.60 a b
3b	6.65 ± 0.10	7.90 ± 0.20 b	8.45 ± 0.50 a	11.20 ± 0.30 a
3c	7.10 ± 0.10	8.20 ± 0.30 a	9.50 ± 0.25 a	10.55 ± 0.10 a b
3d	6.65 ± 0.10	7.90 ± 0.20 b	8.45 ± 0.50 a	11.20 ± 0.30 a
4a	7.85 ± 0.35	8.60 ± 0.40 a	10.01 ± 0.20a	11.05 ± 0.40 a b
4b	7.30 ± 0.20	8.30 ± 0.40 a	9.80 ± 0.30 a	10.80 ± 0.20 a b
4c	8.10 ± 0.20	8.80 ± 0.25 a	10.10 ± 0.25 a	11.10 ± 0.30 b
4d	7.40 ± 0.30	8.50 ± 0.30 a	9.90 ± 0.35 a	10.90 ± 0.30 a b
5a	8.75 ± 0.60	9.10 ± 0.50 a	10.70 ± 0.40 a	11.50 ± 0.40 b
5b	8.30 ± 0.30	8.90 ± 0.30 a	10.30 ± 0.20 a	11.20 ± 0.25 b
5c	8.95 ± 0.68	9.20 ± 0.60 a	10.90 ± 0.50 a	11.60 ± 0.30 b
5d	8.55 ± 0.50	9.01 ± 0.40 a	10.50 ± 0.30 a	11.40 ± 0.30 b
6a	9.30 ± 0.30	9.40 ± 0.30 a	10.40 ± 0.25 a	11.10 ± 0.30 a b
6b	9.10 ± 0.30	9.20 ± 0.40 a	10.20 ± 0.20 a	11.10 ± 0.40a b
6c	9.40 ± 0.40	9.50 ± 0.30 a	10.50 ± 0.20 a	11.20 ± 0.35 a b
6d	9.20 ± 0.20	9.30 ± 0.10 a	10.30 ± 0.30 a	11.01 ± 0.20 a b
7a	9.70 ± 0.40	9.80 ± 0.55 a	10.75 ± 0.35 a	11.44 ± 0.44 a b
7b	9.50 ± 0.20	9.60 ± 0.40 a	10.60 ± 0.25 a	11.30 ± 0.30 a b
7c	9.80 ± 0.50	9.95 ± 0.65 a	10.85 ± 0.45 a	11.98 ± 0.88 a b
7d	9.60 ± 0.30	9.70 ± 0.45 a	10.65 ± 0.30 a	11.40 ± 0.40 a b
Diclofanc sodium	6.50 ± 0.45	10.05 ± 0.15 a	11.40 ± 0.55 a	13.18 ± 0.40 a

Values represent the mean ± S.E. of six animals for each groups. a. $P < 0.05$: Statistically significant from Control. (Dunnett's test). b. $P < 0.05$: Statistically significant from ASA. (Dunnett's test).

* Significant at $P < 0.0$.

Table 3. Percent analgesic activity (peripheral, writhing test).

Compd. No.	Percent protection			
	30 min	1 hours	2 hour	3 hours
Visnagen	39.20 ± 1.20 *	44 ± 1.10 *	48.1 ± 1.70	32.20 ± 1.25 *
Khellin	40.7 ± 1.65 *	46 ± 1.35 *	49.4 ± 1.70	33.9 ± 1.10 *
1a	42.6 ± 1.40 *	52 ± 1.25 *	50.4 ± 1.60	35.8 ± 1.39 *
1b	45.0 ± 1.90 *	53 ± 1.40 *	55.6 ± 1.38	36.3 ± 1.20 *
2a	46.5 ± 1.50 *	50 ± 1.10 **	52.2 ± 1.30	37.5 ± 1.30 *
2b	48.2 ± 1.55 *	52 ± 1.20 *	54.3 ± 1.25	38.7 ± 1.40 *
3a	54.6 ± 1.40 *	58 ± 1.25 *	62.6 ± 1.20 *	46.4 ± 1.10 *
3b	50.3 ± 1.35 *	54 ± 1.10 *	56.4 ± 1.35	40.5 ± 1.35 *
3c	55.8 ± 1.50 *	59 ± 1.20 *	63.6 ± 1.30 *	47.3 ± 1.30 *
3d	52.6 ± 1.35 *	56 ± 1.05 *	58.6 ± 1.35	42.1 ± 1.40 *
4a	60.4 ± 1.40 **	63 ± 1.50 **	67.7 ± 1.70 **	48.4 ± 1.55 *
4b	58.5 ± 1.20 *	60 ± 1.30 *	65.4 ± 1.55 *	46.5 ± 1.35 *
4c	61.5 ± 1.50 **	64 ± 1.55 **	68.8 ± 1.80 **	49.5 ± 1.60 *
4d	59.6 ± 1.30 *	62 ± 1.40 *	66.1 ± 1.60 *	47.3 ± 1.50 *
5a	66.50 ± 1.20 **	68 ± 1.55 **	70.6 ± 1.30 **	54.5 ± 1.10 *
5b	62.50 ± 1.40 **	65 ± 1.35 **	69.10 ± 1.25 **	52.1 ± 1.30 *
5c	68.10 ± 1.25 **	70 ± 1.85 **	71.8 ± 1.35 **	55.4 ± 1.05 *
5d	65.40 ± 1.10 **	67 ± 1.50 **	70.20 ± 1.15 **	53.2 ± 1.20 *
6a	69.60 ± 1.55 **	72 ± 1.90 **	74.3 ± 1.50 **	58.8 ± 1.20 *
6b	69.1 ± 1.45 **	70 ± 1.80 **	72.6 ± 1.40 **	56.3 ± 1.10 *
6c	69.80 ± 1.60 **	73 ± 1.95 **	75.5 ± 1.55 **	59.8 ± 1.19 *
6d	69.4 ± 1.50 **	71 ± 1.85 **	73.5 ± 1.45 **	57.5 ± 1.15 *
7a	74.4 ± 1.10 **	77.5 ± 1.30 **	78.3 ± 1.20	64.4 ± 1.25 **
7b	70.1 ± 1.01 **	75.3 ± 1.50 **	76.5 ± 1.25	62.4 ± 1.20 **
7c	75.6 ± 1.20 **	78.4 ± 1.40 **	79.5 ± 1.35	65.6 ± 1.30 **
7d	72.2 ± 1.05 **	76.2 ± 1.45 **	77.6 ± 1.30	63.5 ± 1.35 **
Control	02.0 ± 0.36	05.0 ± 0.50	04.0 ± 0.58	04.0 ± 0.90
Diclofenac sodium	45.0 ± 0.96 *	54.3 ± 1.18 *	61 ± 1.50 *	38 ± 1.14 *

Each value represents the mean ± S.E (n = 6). Significance levels * p < 0.5, ** p < 0.001 as compared with respective control. Dose (20 mg/kg). For the selected tested compound. Drug in peripheral analgesic activity testing. The remaining compounds have the same activity in Peripheral analgesic activity testing.

3. Conclusions

The new ring systems prepared seem to be interesting for biological activity studies. Furthermore, the present investigation offers rapid and effective new procedures for the synthesis of the poly-condensed new heterocyclic ring systems. Compounds **6a–d** and **7a–d** exhibited potent anti-inflammatory and analgesic activities. It is worth mentioning that the incorporation of methoxy, dimethoxy, -furo[3,2-g]chromen, di- and tri-(piperazine or morpholine) and tetrahydropyrimido[1,6-a]pyrimidine moieties resulted in significant anti-inflammatory and analgesic activities. In conclusion,

we report herein a simple and convenient route for the synthesis of some new heterocyclic compounds based on furochromene pyrimidine derivatives for anti-inflammatory and analgesic evaluation.

4. Experimental

4.1. General

All melting points were taken on an Electrothermal IA 9100 series digital melting point apparatus (Shimadzu, Japan). Elemental analyses were performed at Vario EL (Elementar, Germany). Microanalytical data were processed in the microanalytical center, Faculty of Science, Cairo University and National Research Center. The IR spectra (KBr disc) were recorded using a Perkin-Elmer 1650 spectrometer (USA). ^1H -NMR spectra were determined using Jeol 270 MHz and Jeol JMS-AX 500 MHz (Jeol, Japan) spectrometers with Me_4Si as an internal standard. Mass spectra were recorded on an EI Ms-QP 1000 EX instrument (Shimadzu) at 70 eV. Pharmacological evaluations were done by the Pharmacology unit, Department of Pharmacognosy, Faculty of Pharmacy, Mansoura University, Egypt.

4.2. General Procedure for the Synthesis of 6-((4-Methoxy/4,9-dimethoxy)7-methylfuro[3,2-*g*]chromen-5-ylideneamino)-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-ones **1a,b**

A mixture of visnagen (2.3 g, 10 mmol) or khellin (2.6 g, 10 mmol) and 6-amino-2-thiouracil (1.43 g, 10 mmol), was refluxed in dimethylformamide (50 mL) for 6–8 h. The reaction mixture was cooled; the deposited precipitate was filtered off, washed with ethanol, dried, and recrystallized to obtain **1a,b** as crystalline products.

6-(4-Methoxy-7-methylfuro[3,2-*g*]chromen-5-ylideneamino)-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (1a). Obtained from visnagen as yellow crystals, m.p. 228–230 °C, crystallized from methanol (80% yield); IR (KBr, cm^{-1}): 3,390 (br, NHs), 3,030 (CH, aryl), 2,915 (CH, alkyl), 1,690 (CO), 1,630 (C=N); ^1H -NMR: 1.75 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 5.45 (s, 1H, H_{pyran}), 6.69 (s, 1H, H_{furan}), 6.74 (s, 1H, $\text{H}_{\text{benzene}}$), 6.90 (s, 1H, $\text{H}_{\text{pyrimidine}}$), 7.55 (s, 1H, H_{furan}), 10.40, 11.60 (2 br s, 2NH, D_2O exchangeable). ^{13}C -NMR: 23.3, 56.4 (2C, CH_3 , OCH_3), 93.5, 95.4, 99.7, 102.5, 108.4, 110.30, 147.1, 155.5, 157.4, 160.5, 162.3, 165.5, 166.3 (Ar-C), 169.2 (CO), 178.4 (CS). MS (70 eV, %) m/z , 355 (M^+ , 96%). Anal. Calc. for $\text{C}_{17}\text{H}_{13}\text{N}_3\text{O}_4\text{S}$ (355.37); Requires (Found): C, 57.46 (57.52); H, 3.69 (3.62); N, 11.82 (11.88); S, 9.02 (9.15).

6-(4,9-Dimethoxy-7-methylfuro[3,2-*g*]chromen-5-ylideneamino)-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (1b). Obtained from khellin as yellowish crystals, m.p. 240–242 °C, crystallized from dimethylformamide (82% yield); IR (KBr, cm^{-1}): 3,391 (br, NHs), 3,031 (CH, aryl), 2,914 (CH, alkyl), 1,688 (CO), 1,631 (C=N). ^1H -NMR: 1.74 (s, 3H, CH_3), 3.76 (s, 6H, 2 OCH_3), 5.46 (s, 1H, H_{pyran}), 6.68 (s, 1H, H_{furan}), 6.91 (s, 1H, $\text{H}_{\text{pyrimidine}}$), 7.54 (s, 1H, H_{furan}), 10.42, 11.62 (2 br s, 2NH, D_2O exchangeable). MS (70 eV, %) m/z 385 (M^+ , 90%). Anal. Calc. (Found) for $\text{C}_{18}\text{H}_{15}\text{N}_3\text{O}_5\text{S}$ (385.39): C, 56.10 (56.20); H, 3.92 (3.98); N, 10.90 (10.85); S, 8.32 (8.37).

4.3. General Procedure for the Synthesis of 6-((4-Methoxy/4,9-dimethoxy)-7-methylfuro[3,2-g]chromen-5-ylideneamino)-2-methylsulfanyl-3H-pyrimidin-4-ones **2a,b**

To a warmed ethanolic KOH solution (prepared by dissolving 0.01 mol of KOH in 50 mL ethanol) was added each of **1a** (3.55 g, 10 mmol), or **1b** (3.85 g, 10 mmol), heating was continued for 30 min and the mixture was allowed to cool to room temperature, and methyl iodide (12 mmol) was added. The mixture was stirred under reflux for 6 hours, then cooled to room temperature and poured into cold water (100 mL). The solid product that precipitated was filtered off, washed with 100 mL water; the product was dried and crystallized to produce **2a,b**.

6-(4-Methoxy-7-methylfuro[3,2-g]chromen-5-ylideneamino)-2-methylsulfanyl-3H-pyrimidin-4-one (2a). Obtained from **1a** as white crystals, m.p. 275–277 °C, crystallized from dioxane (75% yield); IR (KBr, cm^{-1}): 3,385 (br, NH), 3,032 (CH, aryl), 2,918 (CH, alkyl), 1,686 (CO), 1,629 (C=N); $^1\text{H-NMR}$: 1.73 (s, 3H, CH_3), 2.68 (s, 3H, SCH_3), 3.75 (s, 3H, OCH_3), 5.50 (s, 1H, H_{pyran}), 6.67 (s, 1H, H_{furan}), 6.72 (s, 1H, $\text{H}_{\text{benzene}}$), 6.93 (s, 1H, $\text{H}_{\text{pyrimidine}}$), 7.53 (s, 1H, H_{furan}), 10.20 (brs, NH, D_2O exchangeable). MS (70 eV, %) m/z 369 (M^+ , 92%). Anal. Calc. (Found) for $\text{C}_{18}\text{H}_{15}\text{N}_3\text{O}_4\text{S}$ (369.39): C, 58.53 (58.50); H, 4.09 (4.14); N, 11.38 (11.45); S, 8.68 (8.73).

6-(4,9-Dimethoxy-7-methylfuro[3,2-g]chromen-5-ylideneamino)-2-methylsulfanyl-3H-pyrimidin-4-one (2b). Obtained from **1b** as a white powder, m.p. 293–295 °C, crystallized from methanol (70% yield); IR (KBr, cm^{-1}): 3,384 (br, NH), 3,030 (CH, aryl), 2,919 (CH, alkyl), 1,689 (CO), 1,630 (C=N); $^1\text{H-NMR}$: 1.75 (s, 3H, CH_3), 2.65 (s, 3H, SCH_3), 3.77 (s, 6H, 2 OCH_3), 5.49 (s, 1H, H_{pyran}), 6.68 (s, 1H, H_{furan}), 6.89 (s, 1H, $\text{H}_{\text{pyrimidine}}$), 7.52 (s, 1H, H_{furan}), 10.15 (br s, NH, D_2O exchangeable). $^{13}\text{C-NMR}$: 19.5, 23.2, 56.6, (4C, CH_3 , S- CH_3 , 2 OCH_3), 99.7, 101.5, 107.4, 109.2, 112.50, 127.1, 140.3, 145.1, 146.1, 149.2, 156.5, 157.5, 161.5, 165.3 (Ar-C), 169.4 (CO). MS (70 eV, %) m/z 399 (M^+ , 91%). Anal. Calc. (Found) for $\text{C}_{19}\text{H}_{17}\text{N}_3\text{O}_5\text{S}$ (399.42): C, 57.13 (57.20); H, 4.29 (4.25); N, 10.52 (10.57); S, 8.03 (8.18).

4.4. General Procedure for the Synthesis of 6-((4-Methoxy/4,9-dimethoxy)-7-methylfuro[3,2-g]chromen-5-ylideneamino)-2-(piperazin/morpholin)-1-yl-3H-pyrimidin-4-ones **3a-d**

To a warm solution of **2a** (3.69 g, 10 mmol) or **2b** (3.99 g, 10 mmol) in methanol (100 mL) was added the freshly distilled secondary aliphatic amines (piperazine and morpholine, 10 mmol). The reaction mixture was stirred under reflux for 8 h, and then allowed to cool to 0 °C for 12 h. The solid obtained was filtered, washed with water (100 mL), dried, and crystallized from the appropriate solvent to produce **3a-d**.

6-(4-Methoxy-7-methylfuro[3,2-g]chromen-5-ylideneamino)-2-piperazin-1-yl-3H-pyrimidin-4-one (3a). Obtained from **2a** and piperazine (0.86 g, 10 mmol) as a yellow powder, m.p. 215–217 °C, crystallized from ethanol (74% yield); IR (KBr, cm^{-1}): 3,390 (br, NH), 3,035 (CH, aryl), 2,922 (CH, alkyl), 1,690 (CO), 1,631 (C=N); $^1\text{H-NMR}$: 1.76 (s, 3H, CH_3), 2.67–2.73 (m, 8H, $\text{H}_{\text{piperazine}}$), 3.74 (s, 3H, OCH_3), 5.51 (s, 1H, H_{pyran}), 6.66 (s, 1H, H_{furan}), 6.70 (s, 1H, $\text{H}_{\text{benzene}}$), 6.90 (s, 1H, $\text{H}_{\text{pyrimidine}}$), 7.54 (s, 1H, H_{furan}), 9.75

(br s, NH, D₂O exchangeable), 10.25 (br s, NH, D₂O exchangeable). MS (70 eV, %) *m/z* 407 (M⁺, 88%). Anal. Calc. (Found) for C₂₁H₂₁N₅O₄ (407.42): C, 61.91 (61.88); H, 5.20 (5.10); N, 17.19 (17.22).

6-(4-Methoxy-7-methylfuro[3,2-*g*]chromen-5-ylideneamino)-2-morpholin-4-yl-3H-pyrimidin-4-one (3b). Obtained from **2a** and morpholine (0.87 g, 10 mmol) as yellowish crystals, m.p. 203–205 °C, crystallized from dioxane (76% yield); IR (KBr, cm^{−1}): 3,391 (br, NH), 3,034 (CH, aryl), 2,921 (CH, alkyl), 1,688 (CO), 1,629 (C=N); ¹H-NMR: 1.75 (s, 3H, CH₃), 3.10 (t, 4H, H_{morpholine}), 3.57 (t, 4H, H_{morpholine}), 3.72 (s, 3H, OCH₃), 5.52 (s, 1H, H_{pyran}), 6.67 (s, 1H, H_{furan}), 6.71 (s, 1H, H_{benzene}), 6.92 (s, 1H, H_{pyrimidine}), 7.53 (s, 1H, H_{furan}), 10.20 (br s, NH, D₂O exchangeable). ¹³C-NMR: 23.3, 48.4, 56.5, 71.8 (6C, CH₃, 4CH₂, OCH₃), 99.9, 101.1, 105.3, 106.9, 108.9, 112.40, 142.3, 145.1, 150.3, 154.2, 155.1, 156.3, 158.5, 160.1 (Ar-C), 169.1 (CO). MS (70 eV, %) *m/z* 408 (M⁺, 89%). Anal. Calc. (Found) for C₂₁H₂₀N₄O (408.14): C, 61.76 (61.70); H, 4.94 (4.90); N, 13.72 (13.63).

6-(4,9-Dimethoxy-7-methylfuro[3,2-*g*]chromen-5-ylideneamino)-2-piperazin-1-yl-3H-pyrimidin-4-one (3c). Obtained from **2b** and piperazine (0.86 g, 10 mmol) as yellow crystals, m.p. 265–267 °C, crystallized from benzene (77% yield); IR (KBr, cm^{−1}): 3,390 (br, NH), 3,033 (CH, aryl), 2,920 (CH, alkyl), 1,685 (CO), 1,627 (C=N); ¹H-NMR: 1.73 (s, 3H, CH₃), 2.65–2.71 (m, 8H, H_{piperazine}), 3.76 (s, 6H, 2 OCH₃), 5.54 (s, 1H, H_{pyran}), 6.66 (s, 1H, H_{furan}), 6.95 (s, 1H, H_{pyrimidine}), 7.55 (s, 1H, H_{furan}), 9.80 (br s, NH, D₂O exchangeable), 10.30 (br s, NH, D₂O exchangeable). MS (70 eV, %) *m/z* 437 (M⁺, 86%). Anal. Calc. (Found) for C₂₂H₂₃N₅O₅ (437.45): C, 60.40 (60.35); H, 5.30 (5.39); N, 16.01 (16.21).

6-(4,9-Dimethoxy-7-methylfuro[3,2-*g*]chromen-5-ylideneamino)-2-morpholin-4-yl-3H-pyrimidin-4-one (3d). Obtained from **2b** and morpholine (0.87 g, 10 mmol) as a white powder, m.p. 254–256 °C, crystallized from hexane (75% yield); IR (KBr, cm^{−1}): 3,394 (br, NH), 3,031 (CH, aryl), 2,918 (CH, alkyl), 1,680 (CO), 1,625 (C=N); ¹H-NMR: 1.74 (s, 3H, CH₃), 3.12 (t, 4H, H_{morpholine}), 3.59 (t, 4H, H_{morpholine}), 3.75 (s, 6H, 2 OCH₃), 5.56 (s, 1H, H_{pyran}), 6.66 (s, 1H, H_{furan}), 6.97 (s, 1H, H_{pyrimidine}), 7.52 (s, 1H, H_{furan}), 10.26 (br s, NH, D₂O exchangeable). ¹³C-NMR: 23.24, 28.2, 56.6, 72.1 (7C, CH₃, 4 CH₂, 2 OCH₃), 99.3, 100.8, 106.9, 108.9, 112.2, 126.5, 140.1, 144.6, 145.4, 148.8, 158.7, 160.2, 162.3, 164.8 (Ar-C), 169.6 (CO). MS (70 eV, %) *m/z* 438 (M⁺, 85%). Anal. Calc. (Found) for C₂₂H₂₂N₄O₆ (438.43): C, 60.27 (60.30); H, 5.06 (5.12); N, 12.78 (12.70).

4.5. General Procedure for the Synthesis of (6-Chloro-2-(piperazin/morpholin)-1-yl-pyrimidin-4-yl)-(4-methoxy/4,9-dimethoxy)-7-methylfuro[3,2-*g*]chromen-5-ylidene)amines **4a–d**

A solution of **3a–d** (10 mmol) in dry dioxane (40 mL) was treated with 10 mL of phosphorus oxychloride, and the mixture was stirred under reflux for 7 h. The reaction mixture was allowed to cool to room temperature, and poured into cold water (100 mL), whereby a solid was separated, filtered off, and crystallized from the appropriate solvent to produce (**4a–d**).

(6-Chloro-2-piperazin-1-ylpyrimidin-4-yl)-(4-methoxy-7-methylfuro[3,2-*g*]chromen-5-ylidene)amine (4a). Obtained from **3a** (4.07 g, 10 mmol) as a brown powder, m.p. 281–283 °C, crystallized from methanol (82% yield); IR (KBr, cm^{−1}): 3,380 (br, NH), 3,025 (CH, aryl), 2,915 (CH, alkyl), 1,615

(C=N); $^1\text{H-NMR}$: 1.74 (s, 3H, CH_3), 2.75–2.81 (m, 8H, $\text{H}_{\text{piperazine}}$), 3.73 (s, 3H, OCH_3), 5.52 (s, 1H, H_{pyran}), 6.65 (s, 1H, H_{furan}), 6.71 (s, 1H, $\text{H}_{\text{benzene}}$), 6.95 (s, 1H, $\text{H}_{\text{pyrimidine}}$), 7.53 (s, 1H, H_{furan}), 9.82 (br s, NH, D_2O exchangeable). MS (70 eV, %) m/z 425 (M^+ , 84%). Anal. Calc. (Found) for $\text{C}_{21}\text{H}_{20}\text{ClN}_5\text{O}_3$ (425.87): C, 59.23 (59.20); H, 4.73 (4.68); N, 16.44 (16.33).

(6-Chloro-2-morpholin-4-yl-pyrimidin-4-yl)-(4-methoxy-7-methyl-furo[3,2-*g*]chromen-5-ylidene)-amine (**4b**). Obtained from **3b** (4.08 g, 10 mmol) as yellow crystals, m.p. 256–258 °C, crystallized from isopropanol (80% yield); IR (KBr, cm^{-1}): 3,020 (CH, aryl), 2,918 (CH, alkyl), 1,617 (C=N); $^1\text{H-NMR}$: 1.75 (s, 3H, CH_3), 3.11 (t, 4H, $\text{H}_{\text{morpholine}}$), 3.55 (t, 4H, $\text{H}_{\text{morpholine}}$), 3.72 (s, 3H, OCH_3), 5.54 (s, 1H, H_{pyran}), 6.67 (s, 1H, H_{furan}), 6.72 (s, 1H, $\text{H}_{\text{benzene}}$), 7.1 (s, 1H, $\text{H}_{\text{pyrimidine}}$), 7.55 (s, 1H, H_{furan}). MS (70 eV, %) m/z 426 (M^+ , 97%). Anal. Calc. (Found) for $\text{C}_{21}\text{H}_{19}\text{ClN}_4\text{O}_4$ (426.85): C, 59.09 (59.15); H, 4.49 (4.45); N, 13.13 (13.22).

(6-Chloro-2-piperazin-1-yl-pyrimidin-4-yl)-(4,9-dimethoxy-7-methylfuro[3,2-*g*]chromen-5-ylidene)-amine (**4c**). Obtained from **3c** (4.37 g, 10 mmol) as a yellowish powder, m.p. 355–357 °C, crystallized from dimethylformamide (78% yield); IR (KBr, cm^{-1}): 3,391 (br, NH), 3,031 (CH, aryl), 2,922 (CH, alkyl), 1,616 (C=N); $^1\text{H-NMR}$: 1.71 (s, 3H, CH_3), 2.78–2.84 (m, 8H, $\text{H}_{\text{piperazine}}$), 3.74 (s, 6H, 2 OCH_3), 5.55 (s, 1H, H_{pyran}), 6.67 (s, 1H, H_{furan}), 7.12 (s, 1H, $\text{H}_{\text{pyrimidine}}$), 7.56 (s, 1H, H_{furan}), 9.85 (br s, NH, D_2O exchangeable). $^{13}\text{C-NMR}$: 23.4, 50.3, 56.6, 62.1 (7C, CH_3 , 4 CH_2 , 2 OCH_3), 99.8, 101.2, 105.2, 106.8, 108.8, 126.4, 140.1, 144.9, 145.2, 148.8, 156.5, 162.4, 164.7, 170.6, 179.8 (Ar–C). MS (70 eV, %) m/z 455 (M^+ , 78%). Anal. Calc. (Found) for $\text{C}_{22}\text{H}_{22}\text{ClN}_5\text{O}_4$ (455.89): C, 57.96 (57.90); H, 4.86 (4.81); N, 15.36 (15.32).

(6-Chloro-2-morpholin-4-yl-pyrimidin-4-yl)-(4,9-dimethoxy-7-methylfuro[3,2-*g*]chromen-5-ylidene)-amine (**4d**). Obtained from **3d** (4.38 g, 10 mmol) as a white powder, m.p. 340–342 °C, crystallized from hexane (76% yield); IR (KBr, cm^{-1}): 3,030 (CH, aryl), 2,916 (CH, alkyl), 1,615 (C=N); $^1\text{H-NMR}$: 1.72 (s, 3H, CH_3), 3.18 (t, 4H, $\text{H}_{\text{morpholine}}$), 3.63 (t, 4H, $\text{H}_{\text{morpholine}}$), 3.74 (s, 6H, 2 OCH_3), 5.54 (s, 1H, H_{pyran}), 6.67 (s, 1H, H_{furan}), 7.1 (s, 1H, $\text{H}_{\text{pyrimidine}}$), 7.53 (s, 1H, H_{furan}). MS (70 eV, %) m/z 456 (M^+ , 75%). Anal. Calc. (Found) for $\text{C}_{22}\text{H}_{21}\text{ClN}_4\text{O}_5$ (456.88): C, 57.83 (57.79); H, 4.63 (4.58); N, 12.26 (12.20).

4.6. General Procedure for the Synthesis of ((2,6-di-(Piperazin/morpholin))-1-yl-pyrimidin-4-yl)-((4-methoxy/4,9-dimethoxy)-7-methylfuro[3,2-*g*]chromen-5-ylidene)amines **5a–d**

To a warm solution of **4a–d** (10 mmol) in methanol (100 mL) was added the freshly distilled piperazine (10 mmol) or morpholine (10 mmol). The reaction mixture was stirred under reflux for 10 h, then allowed to cool to 0 °C for 12 h. The solid obtained was filtered, washed with water (100 mL), dried, and crystallized from appropriate solvent to produce **5a–d**.

(2,6-Di-piperazin-1-yl-pyrimidin-4-yl)-(4-methoxy-7-methylfuro[3,2-*g*]chromen-5-ylidene)amine (**5a**). Obtained from **4a** (4.25 g, 10 mmol) as yellow crystals, m.p. 261–263 °C, crystallized from ethanol (85% yield); IR (KBr, cm^{-1}): 3,390 (br, NH), 3,030 (CH, aryl), 2,931 (CH, alkyl), 1,620 (C=N); $^1\text{H-NMR}$: 1.72 (s, 3H, CH_3), 2.74–2.80 (m, 8H, $\text{H}_{\text{piperazine}}$), 3.13–3.19 (m, 8H, $\text{H}_{\text{piperazine}}$), 3.72 (s, 3H,

OCH₃), 5.54 (s, 1H, H_{pyran}), 6.68 (s, 1H, H_{furan}), 6.72 (s, 1H, H_{benzene}), 6.98 (s, 1H, H_{pyrimidine}), 7.55 (s, 1H, H_{furan}), 9.80–9.95 (br s, 2 NH, D₂O exchangeable). MS (70 eV, %) 475 (M⁺, 84%). Anal. Calc. (Found) for C₂₅H₂₉N₇O₃ (475.54): C, 63.14 (63.10); H, 6.15 (6.20); N, 20.62 (20.65).

(2,6-Di-morpholin-4-yl-pyrimidin-4-yl)-(4-methoxy-7-methylfuro[3,2-g]chromen-5-ylidene)amine

(5b). Obtained from **4b** (4.26 g, 10 mmol) as brown crystals, m.p. 246–248 °C, crystallized from ethanol (68% yield); IR (KBr, cm^{−1}): 3,031 (CH, aryl), 2,920 (CH, alkyl), 1,622 (C=N); ¹H-NMR: 1.75 (s, 3H, CH₃), 2.96–3.02 (m, 8H, H_{morpholine}), 3.63–3.69 (m, 8H, H_{morpholine}), 3.73 (s, 3H, OCH₃), 5.56 (s, 1H, H_{pyran}), 6.66 (s, 1H, H_{furan}), 6.70 (s, 1H, H_{benzene}), 7.2 (s, 1H, H_{pyrimidine}), 7.54 (s, 1H, H_{furan}). MS (70 eV, %) *m/z* 477 (M⁺, 86%). Anal. Calc. (Found) for C₂₅H₂₇N₅O₅ (477.51): C, 62.88 (62.80); H, 5.70 (5.68); N, 14.67 (14.55).

(4,9-Dimethoxy-7-methylfuro[3,2-g]chromen-5-ylidene)-(2,6-di-piperazin-1-yl-pyrimidin-4-yl)-amine

(5c). Obtained from **4c** (4.55 g, 10 mmol) as yellow crystals, m.p. 308–310 °C, crystallized from dioxane (73 % yield); IR (KBr, cm^{−1}): 3,395 (br, 2NH), 3,033 (CH, aryl), 2,921 (CH, alkyl), 1,624 (C=N); ¹H-NMR: 1.72 (s, 3H, CH₃), 2.73–2.79 (m, 8H, H_{piperazine}), 3.13–3.19 (m, 8H, H_{piperazine}), 3.75 (s, 6H, 2 OCH₃), 5.57 (s, 1H, H_{pyran}), 6.68 (s, 1H, H_{furan}), 7.1 (s, 1H, H_{pyrimidine}), 7.53 (s, 1H, H_{furan}), 9.83–9.98 (br s, 2NH, D₂O exchangeable). MS (70 eV, %) *m/z* 505 (M⁺, 93%). Anal. Calc. (Found) for C₂₆H₃₁N₇O₄ (505.57): C, 61.77 (61.70); H, 6.18 (6.13); N, 19.39 (19.32).

(4,9-Dimethoxy-7-methylfuro[3,2-g]chromen-5-ylidene)-(2,6-di-morpholin-4-yl-pyrimidin-4-yl)-amine

(5d). Obtained from **4d** (4.56 g, 10 mmol) as a white powder, m.p. 332–334 °C, crystallized from hexane (78% yield); IR (KBr, cm^{−1}): 3,032 (CH, aryl), 2,920 (CH, alkyl), 1,630 (C=N); ¹H-NMR (DMSO-d₆, δ, ppm): 1.73 (s, 3H, CH₃), 2.97–3.04 (m, 8H, H_{morpholine}), 3.69–3.76 (m, 8H, H_{morpholine}), 3.73 (s, 6H, 2 OCH₃), 5.57 (s, 1H, H_{pyran}), 6.69 (s, 1H, H_{furan}), 7.2 (s, 1H, H_{pyrimidine}), 7.52 (s, 1H, H_{furan}). ¹³C-NMR: 23.2, 58.8, 56.6, 71.4 (11C, CH₃, 8CH₂, 2 OCH₃), 99.5, 100.2, 103.2, 106.9, 108.9, 126.5, 140.4, 145.1, 146.3, 148.9, 157.5, 161.5, 165.7, 169.7, 177.6 (Ar–C). MS (70 eV, %) *m/z* 507 (M⁺, 82%). Anal. Calc. (Found) for C₂₆H₂₉N₅O₆ (507.54): C, 61.53 (61.57); H, 5.76 (5.70); N, 13.80 (13.85).

4.7. General Procedure for the Synthesis of 3-Chloro-1-((4-methoxy/4,9-dimethoxy)-7-methyl-5H-furo[3,2-g]chromen-5-yl)-2,4-dimethyl-6,8-di(piperazin/morpholin)-1-yl-1,3,4,6-tetrahydro-2H-pyrimido-[1,6-a]pyrimidines **6a–d**

To a well stirred mixture of **5a–d** (10 mmol) and 3-chloropentane-2,4-dione (1.35 g, 10 mmol) in glacial acetic acid (40 mL), activated zinc dust (10.00 g) was added portionwise at room temperature over a period of 2 h. Stirring was continued for an additional 3 h. Thereafter, the reaction mixture was heated on a water bath (80–90 °C) for 3 h. The progress of reaction was monitored by TLC. After allowing the reaction mixture to cool to room temperature, it was poured into cold water (100 mL). The insoluble solid which separated was filtered, washed with water, dried and crystallized to produce **6a–d**.

3-Chloro-1-(4-methoxy-7-methyl-5H-furo[3,2-g]chromen-5-yl)-2,4-dimethyl-6,8-di-piperazin-1-yl-1,3,4,6-tetrahydro-2H-pyrimido[1,6-a]pyrimidine (6a**)**. Obtained from **5a** (4.75 g, 10 mmol) as a

yellowish powder, m.p. 350–352 °C, crystallized from dioxane (82% yield); IR (KBr, cm^{-1}): 3,395 (br, 2NH), 3,034 (CH, aryl), 2,932 (CH, alkyl), 1,632 (C=N); $^1\text{H-NMR}$: 1.15 (d, 6H, 2CH₃), 1.73 (s, 3H, CH₃), 2.63–2.69 (m, 8H, H_{piperazine}), 2.83–2.89 (m, 8H, H_{piperazine}), 3.14 (m, 2H, H_{dihydropyrimidine}), 3.73 (s, 3H, OCH₃), 3.92 (t, 1H, CH–Cl), 4.60 (s, 1H, H_{pyran}), 5.25 (s, 1H, H_{pyran}), 6.35 (s, 1H, H_{benzene}), 6.67 (s, 1H, H_{furan}), 6.83 (s, 1H, H_{pyrimidine}), 7.15 (s, 1H, H_{pyrimidine}), 7.51 (s, 1H, H_{furan}), 9.85, 9.96 (br s, 2NH, D₂O exchangeable). MS (70 eV, %) m/z 582 (M^+ , 80%). Anal. Calc. (Found) for C₃₀H₄₀ClN₇O₃ (582.14): C, 61.90 (61.85); H, 6.93 (6.90); N, 16.84 (16.75).

3-Chloro-1-(4-methoxy-7-methyl-5H-furo[3,2-g]chromen-5-yl)-2,4-dimethyl-6,8-di-morpholin-4-yl-1,3,4,6-tetrahydro-2H-pyrimido[1,6-a]pyrimidine (6b). Obtained from **5b** (4.77g, 10 mmol) as a yellow powder, m.p. 335–337 °C, crystallized from methanol (74% yield); IR (KBr, cm^{-1}): 3,028 (CH, aryl), 2,918 (CH, alkyl), 1,619 (C=N); $^1\text{H-NMR}$: 1.16 (t, 6H, 2CH₃), 1.72 (s, 3H, CH₃), 2.99–3.05 (m, 8H, H_{morpholine}), 3.14 (m, 2H, H_{pyrimidine}), 3.66–3.72 (m, 8H, H_{morpholine}), 3.75 (s, 3H, OCH₃), 3.94 (t, 1H, CH–Cl), 4.62 (s, 1H, H_{pyran}), 5.24 (s, 1H, H_{pyran}), 6.34 (s, 1H, H_{benzene}), 6.68 (s, 1H, H_{furan}), 6.75 (s, 1H, H_{pyrimidine}), 7.30 (s, 1H, H_{pyrimidine}), 7.52 (s, 1H, H_{furan}). MS (70 eV, %) m/z 584 (M^+ , 77%). Anal. Calc. (Found) for C₃₀H₃₈ClN₅O₅ (584.11): C, 61.69 (61.60); H, 6.56 (6.48); N, 11.99 (11.88).

3-Chloro-1-(4,9-dimethoxy-7-methyl-5H-furo[3,2-g]chromen-5-yl)-2,4-dimethyl-6,8-di-piperazin-1-yl-1,3,4,6-tetrahydro-2H-pyrimido[1,6-a]pyrimidine (6c). Obtained from **5c** (5.05g, 10 mmol) as a brown powder, m.p. 370–372 °C, crystallized from benzene (72% yield); IR (KBr, cm^{-1}): 3,390 (br, 2NH), 3,035 (CH, aryl), 2,924 (CH, alkyl), 1,620 (C=N); $^1\text{H-NMR}$: 1.17 (d, 6H, 2CH₃), 1.76 (s, 3H, CH₃), 2.70–2.76 (m, 8H, H_{piperazine}), 3.15 (m, 2H, H_{pyrimidine}), 3.18–3.24 (m, 8H, H_{piperazine}), 3.74 (s, 6H, 2 OCH₃), 3.93 (t, 1H, CH–Cl), 4.62 (s, 1H, H_{pyran}), 5.27 (s, 1H, H_{pyran}), 6.69 (s, 1H, H_{furan}), 6.85 (s, 1H, H_{pyrimidine}), 7.20 (s, 1H, H_{pyrimidine}), 7.52 (s, 1H, H_{furan}), 9.80–9.91 (br s, 2 NH, D₂O exchangeable). $^{13}\text{C-NMR}$: 22.1, 22.2, 23.1 (3C, 3 CH₃), 36.5, 45.5, 49.5 (3C, CH), 50.8 (2C, CH₂), 51.3 (4C, 4 CH₂), 52.3 (2C, 2 CH₂), 56.7 (2C, 2 OCH₃), 61.1, 65.2, 84.5 (3C, 3 CH), 101.1, 106.6, 107.1, 108.5, 125.9, 139.5, 142.3, 146.2, 148.7, 150.6, 165.4, 170.8 (Ar-C). MS (70 eV, %) m/z 612 (M^+ , 74%). Anal. Calc. for (Found) C₃₁H₄₂ClN₇O₄ (612.16): C, 60.82 (60.89); H, 6.92 (6.97); N, 16.02 (16.10).

3-Chloro-1-(4,9-dimethoxy-7-methyl-5H-furo[3,2-g]chromen-5-yl)-2,4-dimethyl-6,8-di-morpholin-4-yl-1,3,4,6-tetrahydro-2H-pyrimido[1,6-a]pyrimidine (6d). Obtained from **5d** (5.07 g, 10 mmol) as white crystals, m.p. 385–387 °C, crystallized from dioxane (69% yield); IR (KBr, cm^{-1}): 3,029 (CH, aryl), 2,921 (CH, alkyl), 1,629 (C=N); $^1\text{H-NMR}$: 1.16 (d, 6H, 2CH₃), 1.74 (s, 3H, CH₃), 2.93–2.99 (m, 8H, H_{morpholine}), 3.13 (m, 2H, H_{pyrimidine}), 3.66–3.72 (m, 8H, H_{morpholine}), 3.75 (s, 6H, 2 OCH₃), 3.95 (t, 1H, CH–Cl), 4.61 (s, 1H, H_{pyran}), 5.28 (s, 1H, H_{pyran}), 6.67 (s, 1H, H_{furan}), 6.88 (s, 1H, H_{pyrimidine}), 7.25 (s, 1H, H_{pyrimidine}), 7.55 (s, 1H, H_{furan}). MS (70 eV, %) m/z 614 (M^+ , 78%). Anal. Calc. (Found) for C₃₁H₄₀ClN₅O₆ (614.13): C, 60.63 (60.57); H, 6.56 (6.50); N, 11.40 (11.35).

4.8. General Procedure for the Synthesis of 1-((4-Methoxy/4,9-dimethoxy)-7-methyl-5H-furo[3,2-g]chromen-5-yl)-2,4-dimethyl-3,6,8-tri-(piperazin/morpholin)-1-yl-1,3,4,6-tetrahydro-2H-pyrimido[1,6-a]pyrimidines **7a–d**

To a warm solution of **6a–d** (10 mmol) in methanol (100 mL) was added freshly distilled piperazine (10 mmol) or morpholine (10 mmol). The reaction mixture was stirred under reflux for 12 h, and then allowed to cool to 0 °C for 12 h. The solid obtained was filtered, washed with water (100 mL), dried, and crystallized from the appropriate solvent to produce **7a–d**.

1-(4-Methoxy-7-methyl-5H-furo[3,2-g]chromen-5-yl)-2,4-dimethyl-3,6,8-tripiperazin-1-yl-1,3,4,6-tetrahydro-2H-pyrimido[1,6-a]pyrimidine (**7a**). Obtained from **6a** (5.82 g, 10 mmol) as yellow crystals, m.p. 300–302 °C, crystallized from ethanol (75% yield); IR (KBr, cm^{-1}): 3,398 (br, 3NH), 3,035 (CH, aryl), 2,930 (CH, alkyl), 1,630 (C=N); $^1\text{H-NMR}$: 1.12 (s, 6H, 2CH₃), 1.72 (s, 3H, CH₃), 2.38–2.44 (m, 8H, H_{piperazine}), 2.60–2.66 (m, 8H, H_{piperazine}), 2.80–2.86 (m, 8H, H_{piperazine}), 3.05 (s, 2H, H_{pyrimidine}), 3.1 (s, 1H, H_{pyrimidine}), 3.74 (s, 3H, OCH₃), 4.55 (s, 1H, H_{pyran}), 5.24 (s, 1H, H_{pyran}), 6.33 (s, 1H, H_{benzene}), 6.66 (s, 1H, H_{furan}), 6.80 (s, 1H, H_{pyrimidine}), 7.10 (s, 1H, H_{pyrimidine}), 7.53 (s, 1H, H_{furan}), 9.70, 9.80, 9.90 (3 br s, 3NH, D₂O exchangeable). MS (70 eV, %) m/z 631 (M^+ , 80%). Anal. Calc. (Found) for C₃₄H₄₉N₉O₃ (631.81): C, 64.63 (64.69); H, 7.82 (7.89); N, 19.95 (19.85).

1-(4-Methoxy-7-methyl-5H-furo[3,2-g]chromen-5-yl)-2,4-dimethyl-3,6,8-tri-morpholin-4-yl-1,3,4,6-tetrahydro-2H-pyrimido[1,6-a]pyrimidine (**7b**). Obtained from **6b** (5.84 g, 10 mmol) as pale yellow crystals, m.p. 296–298 °C, crystallized from hexane (79% yield); IR (KBr, cm^{-1}): 3,029 (CH, aryl), 2,920 (CH, alkyl), 1,623 (C=N); $^1\text{H-NMR}$: 1.10 (s, 6H, 2CH₃), 1.73 (s, 3H, CH₃), 2.36–2.42 (m, 8H, H_{morpholine}), 2.93–2.99 (m, 8H, H_{morpholine}), 3.04 (s, 2H, H_{pyrimidine}), 3.09 (s, 1H, H_{pyrimidine}), 3.64–3.70 (m, 8H, H_{morpholine}), 3.76 (s, 3H, OCH₃), 4.60 (s, 1H, H_{pyran}), 5.25 (s, 1H, H_{pyran}), 6.35 (s, 1H, H_{benzene}), 6.67 (s, 1H, H_{furan}), 6.78 (s, 1H, H_{pyrimidine}), 7.20 (s, 1H, H_{pyrimidine}), 7.51 (s, 1H, H_{furan}). $^{13}\text{C-NMR}$: 21.7, 21.8, 23.2 (3C, 3CH₃), 36.8, 45.8, 48.5 (3C, CH), 50.4 (2C, 2CH₂), 51.3 (2C, 2CH₂), 54.7 (2C, 2CH₂), 56.7 (1C, OCH₃), 71.7 (2C, 2CH₂), 72.1 (2C, 2CH₂), 72.4 (2C, 2CH₂), 92.2, 95.8, 99.8, 102.1, 107.2, 107.8, 108.3, 125.5, 139.2, 143.5, 145.2, 148.5, 150.3, 164.4, 169.8 (Ar–C). MS (70 eV, %) m/z 634 (M^+ , 82%). Anal. Calc. (Found) for C₃₄H₄₆N₆O₆ (634.77): C, 64.33 (64.28); H, 7.30 (7.35); N, 13.24 (13.30).

1-(4,9-Dimethoxy-7-methyl-5H-furo[3,2-g]chromen-5-yl)-2,4-dimethyl-3,6,8-tripiperazin-1-yl-1,3,4,6-tetrahydro-2H-pyrimido[1,6-a]pyrimidine (**7c**). Obtained from **6c** (6.12 g, 10 mmol) as a white powder, m.p. 340–342 °C, crystallized from dimethylformamide (72% yield); IR (KBr, cm^{-1}): 3,394 (br, NH), 3,032 (CH, aryl), 2,925 (CH, alkyl), 1,622 (C=N); $^1\text{H-NMR}$: 1.14 (s, 6H, 2CH₃), 1.74 (s, 3H, CH₃), 2.37–2.43 (m, 8H, H_{piperazine}), 2.62–2.68 (m, 8H, H_{piperazine}), 2.82–2.88 (m, 8H, H_{piperazine}), 3.08 (s, 2H, H_{pyrimidine}), 3.15 (s, 1H, H_{pyrimidine}), 3.76 (s, 6H, OCH₃), 4.58 (s, 1H, H_{pyran}), 5.22 (s, 1H, H_{pyran}), 6.67 (s, 1H, H_{furan}), 6.78 (s, 1H, H_{pyrimidine}), 6.92 (s, 1H, H_{pyrimidine}), 7.56 (s, 1H, H_{furan}), 9.75, 9.85, 9.95 (3 br s, 3 NH, D₂O exchangeable). MS (70 eV, %) m/z 661 (M^+ , 78%). Anal. Calc. (Found) for C₃₅H₅₁N₉O₄ (661.84): C, 63.52 (63.58); H, 7.77 (7.83); N, 19.05 (19.15).

1-(4,9-Dimethoxy-7-methyl-5H-furo[3,2-g]chromen-5-yl)-2,4-dimethyl-3,6,8-trimorpholin-4-yl-1,3,4,6-tetrahydro-2H-pyrimido[1,6-a]pyrimidine (**7d**). Obtained from **6d** (6.14g, 10 mmol) as yellow crystals, m.p. 355–357 °C, crystallized from dioxane (70% yield); IR (KBr, cm^{-1}): 3,030 (CH, aryl), 2,920 (CH, alkyl), 1,627 (C=N); $^1\text{H-NMR}$: 1.14 (s, 6H, 2CH₃), 1.72 (s, 3H, CH₃), 2.35–2.42 (m, 8H, H_{morpholine}), 2.85–2.92 (m, 8H, H_{morpholine}), 3.06 (s, 2H, H_{pyrimidine}), 3.10 (s, 1H, H_{pyrimidine}), 3.64–3.71 (m, 8H, H_{morpholine}), 3.74 (s, 6H, 2 OCH₃), 4.60 (s, 1H, H_{pyran}), 5.24 (s, 1H, H_{pyran}), 6.68 (s, 1H, H_{furan}), 6.83 (s, 1H, H_{pyrimidine}), 7.10 (s, 1H, H_{pyrimidine}), 7.54 (s, 1H, H_{furan}). MS (70 eV, %) m/z 664 (M⁺, 88%). Anal. Calc. (Found) for C₃₅H₄₈N₆O₇ (664.79): C, 63.23 (63.28); H, 7.28 (7.20); N, 12.64 (12.58).

5. Biological Evaluation

5.1. Animals

Female Sprague–Dawley rats (150–200 g) were used in the anti-inflammatory activity study. Swiss mice of both sexes weighing 25–30 g were used in analgesic activity tests. International principles and local regulations concerning the care and use of laboratory animals were taken into account. The animals had access to standard commercial diet and water *ad libitum* and were kept in rooms maintained at 22 ± 1 °C with a 12 h light-dark cycle.

5.2. Anti-Inflammatory Activity (Carrageenan-Induced Rat Hind Paw Edema Model)

The method adopted essentially resembles that described in the literature [17]. Distilled water was selected as vehicle to suspend the standard drugs and the test compounds. Sprague–Dawley rats were starved for 18 h prior to the experiment. The animals were weighed, marked for identification and divided into 28 groups each containing six animals. Edema was induced in the left hind paw of all rats by subcutaneous injection of 0.1 mL of 1% (w/v) carrageenan in distilled water into their footpads. The 1st group was kept as control and was given the respective volume of the solvent (0.5 mL distilled water). The 2nd to 16th groups were orally administered aqueous suspension of the synthesized compounds in dose of 20 mg/kg 1 h before carrageenan injection. The last group (standard) was orally administered diclofenac sodium at a dose of 20 mg/kg as an aqueous suspension [18]. The paw volume of each rat was measured immediately by a mercury plethysmometer, before carrageenan injection and then hourly for 3 h post administration of aqueous suspension of the synthesized compounds. The edema rate and inhibition rate of each group were calculated as follows: Edema rate (E)% = $(V_t - V_o)/V_o$, Inhibition rate (I)% = $(E_c - E_t)/E_c$ where V_o is the volume before carrageenan injection (mL), V_t is the volume at t h after carrageenan injection (mL), E_c and E_t are the edema rates of the control and treated groups, respectively.

5.3. Analgesic Activity Using Hot-Plate Test

The experiment was carried out as described in the literature [19], using a hot-plate apparatus, maintained at 53 ± 0.5 °C. The mice were divided into 28 groups of six animals each. The reaction time of the mice to the thermal stimulus was the time interval between placing the animal in the hot plate and when it licked its hind paw or jumped. The reaction time was measured prior to aqueous suspension of synthesized compounds and drug treatment (0 min). Group 1 was kept as normal control. The aqueous

suspension of synthesized compounds was orally administered to mice of groups 2–16 at doses of 20 mg/kg. Mice of group 17 (reference) were orally treated with diclofenac sodium at a dose of 20 mg/kg body wt. The reaction time was again measured at 15 min and repeated at, 30, 60 and 90 min after treatment. To avoid tissue damage to the mice paws, cut-off time for the response to the thermal stimulus was set at 60 s. The reaction time was calculated for each synthesized compound and drug-treated group.

5.4. Analgesic Activity (Acetic Acid Induced Writhing Response Model)

The compounds were selected for investigating their analgesic activity in acetic acid induced writhing response in Swiss albino mice, following the method described in literature [20]. One hundred and two mice were divided into 28 groups (six in each group) starved for 16 h, pretreated as follows, the 1st group which served as control positive orally received distilled water in appropriate volumes. The 2nd to 16th groups received the aqueous suspension of synthesized compounds orally at a dose of 20 mg/kg. The last group orally received diclofenac sodium at a dose of 20 mg/kg. After 30 min, each mouse was administrated 0.7% of an aqueous solution of acetic acid (10 mL/kg) and the mice were then placed in transparent boxes for observation. The number of writhes was counted for 20 min after acetic acid injection. The number of writhes in each treated group was compared to that of a control group. The number of writhing was recorded and the percentage protection was calculated using the following ratio: % protection = (control mean – treated mean/control mean) × 100.

Acknowledgements

The authors wish to express their most sincere thanks to Farid Abd-Elraheem Badria (Department of Pharmacognosy, Faculty of Pharmacy, Mansoura University 35516, Egypt) for carrying out the biological activity tests. The present work was supported by Department of Photochemistry (Heterocyclic unit); Chemical Industries Research Division, National Research Centre in Cairo, Egypt.

References

1. Dewar, H.A.; Grimson, T.A. Khellin in the treatment of angina of effort. *Br. Heart J.* **1950**, *12*, 54-60.
2. Vanachayangkul, P.; Byer, K.; Khan, S.; Butterweck, V. An aqueous extract of Ammi visnaga fruits and its constituents Khellin and Visnagen prevent cell damage caused by oxalate in renal epithelial cells. *Phytomedicine* **2010**, *17*, 653-658.
3. Abdel-Aal, E.A.; Daosukho, S.; El-Shall, H. Effect of supersaturation ratio and Khella extract on nucleation and morphology of kidney stones. *J. Crystal. Growth* **2009**, *311*, 2673-2681.
4. Vedaldi, D.; Caflleri, S.; Dall'Acqua, F.; Andrea, L.; Bovalini, L.; Martelli, P. Khellin, a naturally occurring furochromone, used for the photochemotherapy of skin diseases: mechanism of action. *Farmaco* **1988**, *4*, 333-346.
5. Trabalzini, L.; Martelli, P.; Bovalini, L.; Dall'Acqua, F.; Sage, E. Photosensitization of DNA of defined sequence by furochromones, Khellin and Visnagen. *J. Photochem. Photobiol. B: Bid.* **1990**, *7*, 317-336.

6. Leeuw, J.D.; Assen, Y.J.; van der Beek, N.; Bjerring, P.; Martino Neumann, H.A. Treatment of vitiligo with Khellin liposomes, ultraviolet light and blister roof transplantation. *J. Eur. Acad. Dermatol. Venereol.* **2011**, *25*, 74-81.
7. Ghate, M.; Kulkarni, M.V. Synthesis and anti-inflammatory activity of 4-(5'-acetyl-6'-hydroxy-3'-methylbenzofuran-2'-yl)coumarin and 6-acetyl-3,7-dimethyl-2-coumarin-4'-yl)furo[3,2-g]chromen-5-one. *Ind. J. Chem.* **2005**, *44B*, 1674-1678.
8. Frasinyuk, M.S.; Gorelov, S.V.; Bondarenko, S.P.; Khilya, V.P. Synthesis and properties of 4-(3-amino-2-benzofuranyl)-coumarins. *Chem. Heterocycl. Comp.* **2009**, *45*, 1261-1269.
9. Kittler, L.; Hradečná, Z.; Sühnel, J. Cross-link formation of phage lambda DNA in situ photochemically induced by the furocoumarin derivative angelicin. *Biochim. et Biophys. Acta* **1980**, *607*, 215-220.
10. Abeysekera, B.F.; Abramovski, Z.; Towers, G.H.N. Genotoxicity of the natural furochromones, Khellin and Visnagen and the identification of Khellin-thymine photoadduct. *Photochem. Photobiol.* **1983**, *38*, 311-315.
11. Schönberg, A.; Badran, N.; Starkowsky, N.A. Furo-chromones and coumarins. XIII. The dicoumarol analogs of bergapten, isopimpinellin and pimpinellin. *J. Am. Chem. Soc.* **1955**, *77*, 5438-5439.
12. Schönberg, A.; Badran, N.; Starkowsky, N.A. Furo-chromones and coumarins. XIV. 2-(3'-Pyridyl) analogs of Khellin and Visnagen. *J. Chem. Soc.* **1955**, *77*, 5439-5440.
13. El-Gazzar, A.B.A.; Youssef, M.M.; Youssef, A.M.S.; Abu-Hashem, A.A.; Badria, F.A. Design and synthesis of azolopyrimidoquinolines, pyrimido quinazolines as anti-oxidant, anti-inflammatory and analgesic activities. *Eur. J. Med. Chem.* **2009**, *44*, 609.
14. Shishoo, C.J.; Jain, K.S. Synthesis of some novel azido/ tetrazolothieno pyrimidines and their reduction to 2,4-diaminothieno[2,3-d]pyrimidines. *J. Heterocycl. Chem.* **1992**, *29*, 883-893.
15. Abu-Hashem, A.A.; Gouda, M.A.; Badria, F.A. Synthesis of some new pyrimido [2',1':2,3]thiazolo[4,5-b]quinoxaline derivatives as anti-inflammatory and analgesic agents. *Eur. J. Med. Chem.* **2010**, *45*, 1976.
16. El-Gazzar, A.B.A.; El-Enany, M.M.; Mahmoud, M.N. Synthesis, analgesic, anti-inflammatory and antimicrobial activity of some novel pyrimido[4,5-b]-quinolin-4-ones. *Bioorg. Med. Chem.* **2008**, *16*, 3261-3273.
17. Winter, C.A.; Risley, E.A.; Nuss, G.W. Carrageenan-induced edema in hind paw of the rats as an assay anti-inflammatory drugs. *Proc. Soc. Exp. Biol. Med.* **1962**, *111*, 544.
18. Mino, J.; Moscatelli, V.; Hnatyszyn, O.; Gorzalczy, S.; Acevedo, C.; Ferraro, G. Antinociceptive and antiinflammatory activities of artemisia copa extracts. *Pharmacol. Res.* **2004**, *50*, 59-63.
19. Aiyelero, O.M.; Ibrahim, Z.G.; Yaro, A.H. An Aalgesic and anti-inflammatory properties of the methanol leaf extract of Ficus Ingens (Moraceae) in rodents. *Nig. J. Pharm. Sci.* **2009**, *8*, 79-86.
20. Collier, D.J.; Dinnin, L.C.; Johnson, C.A.; Schneider, C. The abdominal response and its suppression by analgesic drugs in the mouse. *J. Pharmacol. Chemother.* **1968**, *32*, 295.