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SYNTHESIS OF 6-ALKYL-4-[5-DIALKYLAMINOMETHYL-4-(4-METHYL-1,3-THIAZOL-2-YL)-1*H*-PYRAZOL-3-YL]-1,3-BENZENEDIOLS

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6-Alkyl-2-dialkylaminomethyl-7-hydroxy-3-(4-methyl-1,3-thiazol-2-yl)-4H-chromen-4-ones recyclized into 6-alkyl-4-[5-dialkylaminomethyl-4-(4-methyl-1,3-thiazol-2-yl)-1H-pyrazol-3-yl]-1,3-benzenediols under the influence of hydrazine hydrate.

Keywords: 6-alkyl-4-[5-dialkylaminomethyl-4-(4-methyl-1,3-thiazol-2-yl)-1*H*-pyrazol-3-yl]-1,3-benzenediols, 2-dialkylaminomethyl-3-thiazolylchromones, 3-aryl-4-hetarylpyrazoles, 2-chloromethyl-3-thiazolylchromones.

In the last 20 years there has been a steady growth in the number of publications devoted to the synthesis and study of pyrazole derivatives, including the functionalized 3-aryl-4-aryl(hetaryl)pyrazoles. This is explained by the broad spectrum of biological activity exhibited by these compounds and their potential use as structural blocks in the design of pyrazole-containing condensed systems with valuable properties [1-3]. A series of 3-aryl-4-aryl(hetaryl)pyrazole derivatives shows antiherpetic [4], antifungal, antibacterial [5], fungicidal, herbicidal, and growth regulating activity [6, 7]. Some of these have been studied as potential drugs for treatment of the nervous system (cerebral ischemia), diseases of the heart and gastrointestinal tract [8], they possess anti-inflammatory, analgesic, hypotensive, antiarrhythmic, thrombocyte antiaggregative [9], hypoglycemic, antiviral, and neuroleptic [4] effects. Derivatives of 3-(2,4-dihydroxyphenyl)-4-aryl(hetaryl)-pyrazole are recognized as a new class of $H_{SP}90$ inhibitors and may find use in the therapy of some types of cancer [10, 11].

The reactions of 3-(het)arylchromones with hydrazines are applicable for the synthesis of pyrazoles and have been used to prepare 2-(pyrazol-3-yl)phenol derivatives with het(aryl) substituents in position 4 and a variety of substituents (H, CF_3, Me, CO_2Et, CO_2H, $CONHNH_2$, CONHAlk, NH_2, $(CH_2)_2CO_2H$) in position 5 of the pyrazole ring [12, 13]. 2-(Pyrazol-3-yl)phenols with dialkylaminomethyl substituent in position 4 of the pyrazole ring were synthesized by recyclization of 3-dialkylaminomethylchromones under the influence of hydrazine hydrate [14].

In this paper, we present data on the assembly of pyrazolylthiazole bisheterocycles with dialkylaminomethyl substituents in position 5 of the pyrazole ring by starting from the 3-(4-methyl-1,3-thiazol-2-yl)chromone 2-dialkylaminomethyl derivatives **1a**,**c**,**d**, **2a**-**c**,**e**,**f** [15], or from the newly synthesized

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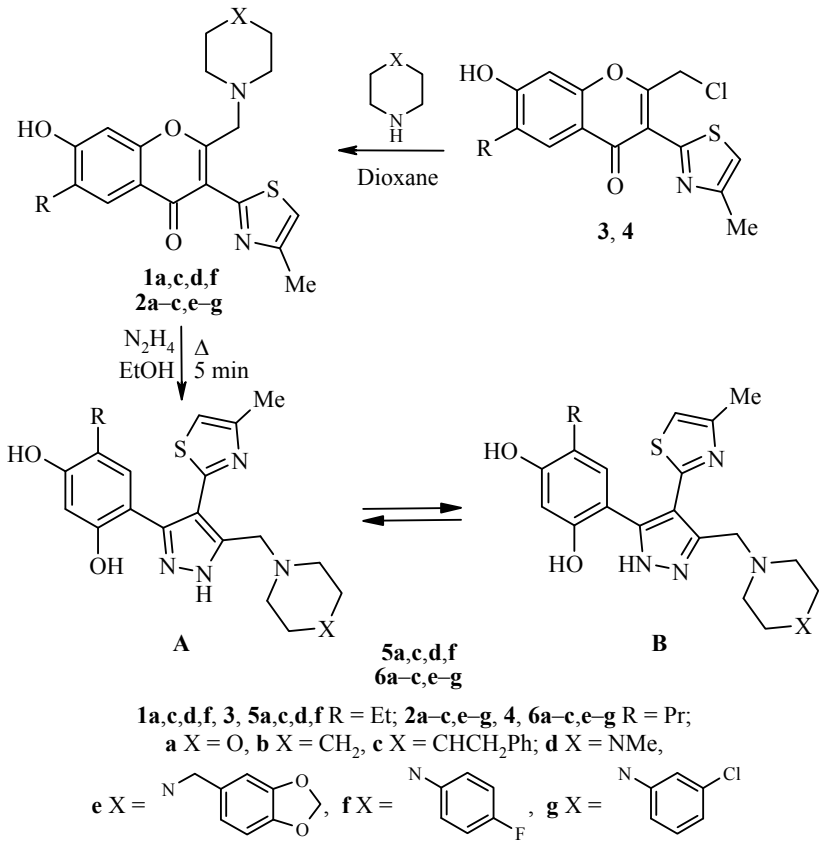
2-[4-(4-fluorophenyl)- and 2-[4-(3-chlorophenyl)piperazinomethyl]chromones **1f** and **2g.** The latter were obtained by amination of 2-chloromethylchromones **3** and **4** with 1-(4-fluorophenyl)- and 1-(3-chlorophenyl)piperazines by known methods [15, 16].

On refluxing compounds **1a**,**c**,**d**,**f** and **2a-c**,**e-g** for 5 min in ethanol with an excess of hydrazine hydrate, followed by dilution with water, the recyclization products **5a**,**c**,**d**,**f** and **6a-c**,**e-g** were isolated (Table 1).



Pyrazoles **5a**,**c**,**d**,**f** and **6a-c**,**e-g** were colorless crystalline compounds, insoluble in water, readily soluble in 2 N NaOH, and gave a characteristic blue color with an ethanolic solution of $FeCl_3$ as a result of chelate complex formation with the phenolic hydroxyl, suitably located close to the pyrazole ring nitrogen atom.

Characteristically, the ^1H NMR spectra of compounds **5a**,**c**,**d**,**f** and **6a-c**,**e-g** recorded in DMSO-d_6 contained three downfield singlets which exchanged with D_2O. The pyrazole ring NH proton gave the furthest downfield signal (12.58-13.13 ppm), while the hydroxyl protons gave signals at 9.11-10.18 ppm (Table 2). These signals were broadened as a result of proton exchange (interconversion of tautomers **A** and **B**). There was a doubling of NH proton signals (12.77 (**A**) and 13.13 ppm (**B**)) and the 3-OH proton signals (9.38 (**B**) and 9.44 ppm (**A**)) in the ^1H NMR spectrum of compound **6a**. The assignment of the tautomers **A** and **B** was based on the chemical shifts of the NH and 3-OH protons and their integrated intensities. The downfield signal among the two NH protons we assigned to the tautomer **B** because of its participation in an intramolecular hydrogen bond with the hydroxyl group oxygen atom, which is always associated with a paramagnetic shift. It followed from the integrated peak intensities that the 3-OH proton signal of the tautomer **A** was located downfield. The ratio of tautomers **A** and **B** was 7:3.

The methylene group signals from the aminomethyl substituent in pyrazoles **5a**,**c**,**d**,**f** and **6a-c**,**e-g** was shifted upfield by 0.5 ppm in comparison with the analogous signal in the starting 2-dialkylaminochromones **1a**,**c**,**d**,**f** and **2a-c**,**e-g.**

Table 1. Physicochemical Characteristics of Pyrazoles **5a**,**c**,**d**,**f** and **6a-c**,**e-g**

Compound	Empirical formula	Found, % / Calculated, %				Mp, °C	Yield, %
		C	H	N	S		
5a	$C_{20}H_{24}N_4O_3S$	59.68 / 59.98	6.19 / 6.04	13.69 / 13.99	7.74 / 8.01	125-126	75
5c	$C_{28}H_{32}N_4O_2S$	68.77 / 68.82	6.90 / 6.60	11.47 / 11.47	6.55 / 6.56	119-120	82
5d	$C_{21}H_{27}N_5O_2S$	61.15 / 60.99	6.45 / 6.58	16.77 / 16.93	7.48 / 7.75	134-135	81
5f	$C_{26}H_{28}FN_5O_2S$	63.15 / 63.27	5.99 / 5.72	14.17 / 14.19	6.35 / 6.50	114-115	92
6a	$C_{21}H_{26}N_4O_3S$	60.57 / 60.85	6.53 / 6.32	13.51 / 13.52	7.70 / 7.73	114-115	90
6b	$C_{22}H_{28}N_4O_2S$	64.35 / 64.05	6.76 / 6.84	13.68 / 13.58	7.55 / 7.77	120-121	97
6c	$C_{29}H_{34}N_4O_2S$	68.99 / 69.29	6.92 / 6.82	11.09 / 11.15	6.34 / 6.38	105-106	67
6e	$C_{29}H_{33}N_5O_4S$	63.38 / 63.60	6.12 / 6.07	12.57 / 12.79	5.77 / 5.85	126-127	97
6f	$C_{27}H_{30}FN_5O_2S$	63.63 / 63.89	6.20 / 5.96	13.58 / 13.80	6.24 / 6.32	115-116	73
6g	$C_{27}H_{30}ClN_5O_2S$	61.59 / 61.88	5.95 / 5.77	13.56 / 13.36	5.94 / 6.12	94-95	78

The majority of the aromatic proton signals in compounds **5** and **6** were unequivocally assigned from their multiplicity. Less definite is the assignment of the two close singlets with chemical shifts of 6.93 and 6.85 ppm in the pyrazole **5c** and also the aliphatic proton signals of the amine group. For clear assignments we acquired the COSY-90 spectrum (Fig.1 and 2).

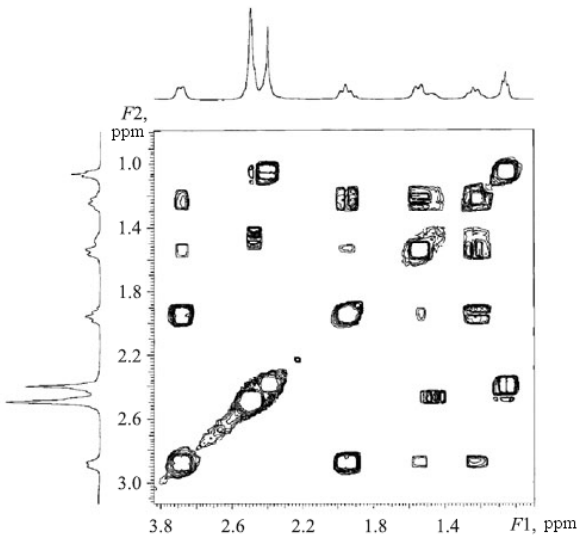


Fig.1. Fragment of the COSY spectrum, corresponding to the aliphatic proton signals of compound **5c**.

The correlations in the COSY-90 spectrum differed in intensity. The greatest peak area corresponded to the geminal spin-spin coupling constants. The intensity of the correlated peaks decreased as the value of the spin-spin coupling constant decreased. This rule could be used to refine the assignments. For example, the signal at 2.89 ppm had one intense correlation with the signal of the geminal proton at 1.95 ppm and two correlations of lesser intensity with the vicinal proton signals at 1.55 and 1.21-1.25 ppm. The analogous consideration of all the other correlations permitted the full assignment of the signals (Fig.2).

The low intensity correlation between the aromatic proton signal at 6.93 ppm and the signal of the methyl protons at 2.40 ppm reflected the spin-spin coupling over four chemical bonds between the 4-methyl group of the thiazole ring and the neighboring H-5 proton (Fig. 2).

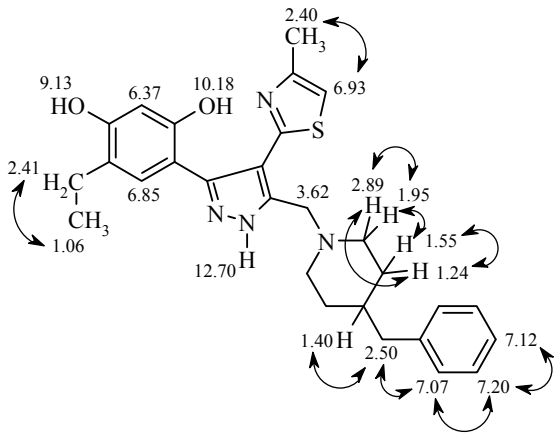


Fig. 2. Correlations found in the COSY spectrum of compound **5c.**

Thus, the synthesis of 6-alkyl-4-[5-dialkylaminomethyl-4-(4-methyl-1,3-thiazol-2-yl)-1*H*-pyrazol-3-yl]-1,3-benzenediols, potentially biologically active compounds, was carried out by the recyclization of 6-alkyl-2-di-alkylaminomethyl-7-hydroxy-3-(4-methyl-1,3-thiazol-2-yl)-4*H*-chromen-4-ones under the influence of hydrazine hydrate.

EXPERIMENTAL

The ^{1}H NMR spectra were acquired on a Varian Mercury 400 (400 MHz) instrument for DMSO-d_6 solutions with TMS as internal standard. A 4048×4048 matrix was used in the COSY-90 experiment. Elemental analyses were performed with a Perkin-Elmer CHN analyzer. Melting points were determined on a Boetius hot stage apparatus with a VEB Analytic PHMK 0.5 viewing adapter. The course of reactions and the purity of the obtained compounds were monitored by TLC on Silufol UV-254 plates with 9:1 $CHCl_3$–MeOH as eluent.

6-Ethyl-2-[4-(4-fluorophenyl)piperazinomethyl]-7-hydroxy-3-(4-methyl-1,3-thiazol-2-yl)-4*H*-chromen-4-one (1f). 1-(4-Fluorophenyl)piperazine (0.36 g, 2 mmol) was added to a solution of 2-chloro-methyl-6-ethyl-7-hydroxy-3-(4-methyl-1,3-thiazol-2-yl)-4*H*-chromen-4-one (**3**) (0.33 g, 1 mmol) in dioxane (10 ml). The mixture was refluxed for 40 min, maintained for 1 day at room temperature. The solvent was evaporated, the residue was triturated in water (50 ml), the precipitate was filtered off and recrystallized. Yield 0.40 g (83%). Mp 169-170°C (dioxane). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.23 (3H, t, *J* = 7.2, $CH_2C\underline{H}_3$); 2.48 (3H, s, CH_3); 2.67 (2H, q, *J* = 7.2, $C\underline{H}_2CH_3$); 2.73 (4H, br. s, CH_2NCH_2); 3.04 (4H, br. s, $\underline{CH}_2N(Ar)\underline{CH}_2$); 4.31 (2H, s, 2-$CH_2N$); 6.80-6.91 (5H, m, H-8, NC_6H_4F); 7.15 (1H, s, H-5'); 7.81 (1H, s, H-5); 10.67 (1H, s, 7-OH). Found, %: C 65.07; H 5.68; N 8.97; S 6.42. $C_{26}H_{26}FN_3O_3S$. Calculated, %: C 65.12; H 5.46; N 8.76; S 6.69.

2-[4-(3-Chlorophenyl)piperazinomethyl]-7-hydroxy-3-(4-methyl-1,3-thiazol-2-yl)-6-propyl-4*H*-chromen-4-one (2g) was obtained analogously from 2-chloromethyl-7-hydroxy-3-(4-methyl-1,3-thiazol-2-yl)-6-propyl-4*H*-chromen-4-one (**4**) and 1-(3-chlorophenyl)piperazine. Yield 0.41 g (79%). Mp 157-158°C (EtOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.99 (3H, t, *J* = 7.2, $(CH_2)_2C\underline{H}_3$); 1.65-1.68 (2H, m, $CH_2C\underline{H}_2CH_3$); 2.49 (3H, s, CH_3); 2.64 (2H, t, *J* = 7.2, $C\underline{H}_2CH_2CH_3$); 2.72 (4H, br. s, CH_2NCH_2); 3.15 (4H, br. s, $C\underline{H}_2N(Ar)C\underline{H}_2$); 4.31 (2H, s, 2-$CH_2N$); 6.71 (1H, d, *J* = 7.6, H-6"); 6.78 (1H, d, *J* = 7.6, H-4"); 6.81 (1H, s, H-2"); 6.90 (1H, s, H-8);

Table 2. ^{1}H NMR Spectra of Compounds **5a**,**c**,**d**,**f** and **6a-c**,**e-g**

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)
5a	1.03 (3H, t, ^3J = 7.2, $CH_2C\underline{H}_3$); 2.32 (3H, s, CH_3); 2.37 (2H, q, ^3J = 7.2, $C\underline{H}_2CH_3$); 2.49 (4H, br. s, CH_2NCH_2); 3.53 (4H, br. s, CH_2OCH_2); 3.76 (2H, s, 5'-CH_2N); 6.43 (1H, s, H-2); 6.84 (1H, s, H-5); 7.05 (1H, s, H-5"); 9.45 (1H, br. s, 3-OH); 9.69 (1H, br. s, 1-OH); 12.77 (1H, br. s, NH)
5c*	1.06 (3H, t, ^3J = 7.2, $CH_2C\underline{H}_3$); 1.21-1.25 (2H, m, $C\underline{H}_{eq}CHC\underline{H}_{eq}$); 1.38-1.43 (1H, m, $C\underline{H}CH_2Ph$); 1.55 (2H, d, ^2J = 12.8, $C\underline{H}_{ax}CHC\underline{H}_{ax}$); 1.95 (2H, t, ^2J = 12.8, $C\underline{H}_{eq}NC\underline{H}_{eq}$); 2.40-2.48 (7H, m, CH_3, $C\underline{H}_2CH_3$, $C\underline{H}_2Ph$); 2.89 (2H, d, ^2J = 10.4, $C\underline{H}_{ax}NC\underline{H}_{ax}$); 3.62 (2H, s, 5'-$CH_2$N); 6.37 (1H, s, H-2); 6.85 (1H, s, H-5); 6.93 (1H, s, H-5"); 7.07 (2H, d, ^3J = 7.6, H-2"',6"'); 7.12 (1H, t, ^3J = 7.6, H-4"'); 7.20 (2H, t, ^3J = 7.6, H-3"',5"'); 9.13 (1H, br. s, 3-OH); 10.18 (1H, br. s, 1-OH); 12.70 (1H, br. s, NH)
5d	1.03 (3H, t, ^3J = 7.2, $CH_2C\underline{H}_3$); 2.12 (3H, s, NCH_3); 2.32 (3H, s, 4"-CH_3); 2.39-2.50 (10H, m, $C\underline{H}_2CH_3$, 4CH_2 piperazine); 3.73 (2H, s, 5'-CH_2N); 6.42 (1H, s, H-2); 6.84 (1H, s, H-5); 7.06 (1H, s, H-5"); 9.47 (1H, br. s, 3-OH); 9.76 (1H, br. s, 1-OH); 12.78 (1H, br. s, NH)
5f	1.04 (3H, t, ^3J = 7.2, $CH_2C\underline{H}_3$); 2.35 (3H, s, CH_3); 2.41 (2H, q, ^3J = 7.2, $C\underline{H}_2CH_3$); 2.63 (4H, br. s, CH_2NCH_2); 3.05 (4H, br. s, $C\underline{H}_2N(Ar)C\underline{H}_2$); 3.86 (2H, s, 5'-$CH_2$N); 6.45 (1H, s, H-2); 6.87 (1H, s, H-5); 6.93-7.07 (5H, m, H-5", C_6H_4F); 9.48 (1H, br. s, 3-OH); 9.74 (1H, br. s, 1-OH); 12.81 (1H, br. s, NH)
6a	0.84 (3H, t, ^3J = 7.2, $(CH_2)_2C\underline{H}_3$); 1.46-1.49 (2H, m, $CH_2C\underline{H}_2CH_3$); 2.33-2.44 (9H, m, CH_3, $C\underline{H}_2CH_2CH_3$, CH_2NCH_2); 3.54 (4H, br. s, CH_2OCH_2); 3.77 (2H, s, 5'-CH_2N); 6.43 (1H, s, H-2); 6.82 (1H, s, H-5); 7.06 (1H, s, H-5"); 9.38 (0.3H, br. s, 3-OH (B)); 9.44 (0.7H, br. s, 3-OH (A)); 9.67 (1H, br. s, 1-OH); 12.77 (0.7H, br. s, NH (A)); 13.13 (0.3H, br. s, NH (B))
6b	0.87 (3H, t, ^3J = 7.2, $(CH_2)_2C\underline{H}_3$); 1.41-1.52 (8H, m, $CH_2C\underline{H}_2CH_3$, 3,4,5-CH_2 piperidine); 2.39-2.42 (9H, m, $C\underline{H}_2CH_2CH_3$, CH_3, CH_2NCH_2); 3.60 (2H, s, 5'-CH_2N); 6.37 (1H, s, H-2); 6.78 (1H, s, H-5); 6.95 (1H, s, H-5"); 9.11 (1H, br. s, 3-OH); 10.12 (1H, br. s, 1-OH); 12.58 (1H, br. s, NH)
6c	0.84 (3H, t, ^3J = 7.2, $(CH_2)_2C\underline{H}_3$); 1.17 (2H, m, $C\underline{H}_{eq}CHC\underline{H}_{eq}$); 1.44-1.48 (5H, m, $CH_2C\underline{H}_2CH_3$, $C\underline{H}CH_2Ph$, $C\underline{H}_{ax}CHC\underline{H}_{ax}$); 1.95 (2H, t, ^2J = 13.4, $C\underline{H}_{eq}NC\underline{H}_{eq}$); 2.30-2.32 (5H, m, CH_3, $C\underline{H}_2Ph$); 2.46 (2H, t, ^3J = 7.2, $C\underline{H}_2CH_2CH_3$); 2.87 (2H, br. s, $C\underline{H}_{ax}NC\underline{H}_{ax}$); 3.69 (2H, s, 5'-$CH_2$N); 6.42 (1H, s, H-2); 6.82 (1H, s, H-5); 7.07 (1H, s, H-5"); 7.13-7.17 (3H, m, H-2"',6"',4"'); 7.26 (2H, t, ^3J = 7.6, H-3"',5"'); 9.39 (1H, br. s, 3-OH); 9.76 (1H, br. s, 1-OH); 12.73 (1H, br. s, NH)
6e	0.83 (3H, t, ^3J = 7.2, $(CH_2)_2C\underline{H}_3$); 1.42-1.46 (2H, m, $CH_2C\underline{H}_2CH_3$); 2.31-2.45 (11H, m CH_3, $C\underline{H}_2CH_2CH_3$, CH_2NCH_2, $NC\underline{H}_2Ar$); 3.32 (4H, br. s, $C\underline{H}_2N(CH_2Ar)C\underline{H}_2$); 3.74 (2H, s, 5'-$CH_2$N); 5.97 (2H, s, OCH_2); 6.43 (1H, s, H-2); 6.71 (1H, d, ^3J = 6.4, H-7"'); 6.81-6.82 (3H, m, H-5,4"',6"'); 7.05 (1H, s, H-5"); 9.43 (1H, br. s, 3-OH); 9.74 (1H, br. s, 1-OH); 12.74 (1H, br. s, NH)
6f	0.83 (3H, t, ^3J = 6.8, $(CH_2)_2C\underline{H}_3$); 1.42-1.45 (2H, m, $CH_2C\underline{H}_2CH_3$); 2.32-2.34 (5H, m, CH_3, $C\underline{H}_2CH_2CH_3$); 2.61 (4H, br. s, CH_2NCH_2); 3.03 (4H, br. s, $C\underline{H}_2N(Ar)C\underline{H}_2$); 3.84 (2H, s, 5'-$CH_2$N); 6.45 (1H, s, H-2); 6.82 (1H, s, H-5); 6.90-7.04 (5H, m, H-5", C_6H_4F); 9.48 (1H, br. s, 3-OH); 9.69 (1H, br. s, 1-OH); 12. 81 (1H, br. s, NH)
6g	0.89 (3H, t, ^3J = 7.2, $(CH_2)_2C\underline{H}_3$); 1.46-1.49 (2H, m, $CH_2C\underline{H}_2CH_3$); 2.36 (2H, t, ^3J = 7.2, $C\underline{H}_2CH_2CH_3$); 2.40 (3H, s, CH_3); 2.65 (4H, br. s, CH_2NCH_2); 3.16 (4H, br. s, $C\underline{H}_2N(Ar)C\underline{H}_2$); 3.78 (2H, s, 5'-$CH_2$N); 6.39 (1H, s, H-2); 6.68 (1H, d, ^3J = 8.0, H-6"'); 6.77 (1H, d, ^3J = 8.0, H-4"'); 6.80 (1H, s, H-5); 6.84 (1H, s, H-5"); 6.90 (1H, s, H-2"'); 7.12 (1H, t, ^3J = 8.0, H-5"'); 9.11 (1H, br. s, 3-OH); 9.93 (1H, br. s, 1-OH); 12. 61 (1H, br. s, NH)

*Spin-spin coupling constants with values less than 4.0 Hz were not successfully measured because of the width of the signals.

7.14 (1H, t, *J* = 7.6, H-5"); 7.19 (1H, s, H-5'); 7.81 (1H, s, H-5); 10.33 (1H, br. s, 7-OH). Found, %: C 63.76; H 5.28; N 8.54; S 6.26. $C_{27}H_{28}ClN_3O_3S$. Calculated, %: C 63.58; H 5.53; N 8.24; S 6.29.

6-Alkyl-4-[5-dialkylaminomethyl-4-(4-methyl-1,3-thiazol-2-yl)-1*H*-pyrazol-3-yl]-1,3-benzenediols 5a,c,d,f and 6a-c,e-g (General Method). Hydrazine hydrate (0.1 g, 3.2 mmol) was added to a solution of 6-alkyl-2-dialkylaminomethyl-7-hydroxy-3-(4-methyl-1,3-thiazol-2-yl)-4*H*-chromen-4-one **1a**,**c**,**d**,**f** or **2 a-c**,**e-g**

(0.3 mmol) in EtOH (1 ml). The mixture was refluxed for 5 min, cooled, diluted with water (10 ml), then the precipitate was filtered off and recrystallized from aqueous EtOH.

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