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3-(4-PHENYL-1,2,4-TRIAZOL-3-YL)CHROMONES

T. V. Shokol, V. A. Turov, A. V. Turov, N. V. Krivokhizha, V. V. Semenyuchenko, and V. P. Khilya

The condensation of 4-phenyl-1,2,4-triazol-3-ylacetonitrile with 2-methyl-, 4-ethylresorcinol, and with pyrogallol gave α-(4-phenyl-1,2,4-triazol-3-yl)-2,4-dihydroxyacetophenones. Upon treatment with acid anhydrides and chlorides and subsequent hydrolysis these form 7-hydroxy-3-(4-phenyl)-1,2,4-triazol-3-yl)chromones with different substituents in both the benzene and the pyrone rings.

Keywords: 8-R^1-6-R^2-2-R^3-7-hydroxy-3-(4-phenyl-1,2,4-triazol-3-yl)chromones, α-(4-phenyl-1,2,4-triazol-3-yl)-3-R^1-5-R^2-2,4-dihydroxyacetophenones.

3-Hetarylchromones are now a rather broad class of compounds having different biological activity [1-3]. However, only isolated examples of triazole analogs of isoflavones are known (3-(4H-1,2,4-triazol-3-yl)-[4, 5], 3-(2H-1,2,3-triazol-4-yl)chromones [6], and 2,3-dihydro-3-(1H-1,2,4-triazol-1-yl)chromones [7]), with the latter patented as fungicides. The starting materials for their synthesis are the corresponding α-triazolyl-2-hydroxyacetophenones. 3-(4,5-Dihydro-1H-1,2,4-triazol-5-yl)chromones have been isolated amongst the products of the 1,3-dipolar cycloaddition of 3-(aryliminomethyl)chromones and C-acetylhydrazinoyl bromides [8].

With the aim of broadening the scope of triazole analogs of isoflavones we have synthesized a series of starting α-(4-phenyl-1,2,4-triazol-3-yl)-2,4-dihydroxyacetophenones (**1a-c**) with different substituents in the phenyl ring *via* condensation of 4-phenyl-1,2,4-triazol-3-ylacetonitrile with 2-methyl- and 4-ethylresorcinol and with pyrogallol. Modified Hoesch reaction conditions were used with boron trifluoride etherate as solvent and catalyst.

It should be noted that the products **1a,b** are obtained in chromatographically pure form and in high yields (78-80%) (as was found in the case of the condensation with the resorcinol (**1d**)) but the pyrogallol derivative **1c** was obtained in only 22% yield, very likely due to tarring of the reaction product.

Compounds **1** can exist in the ketone (**A**) and enolic (**B**) forms. Rapid recrystallization of compound **1b** from ethanol gave a 50% yield of a colorless product, the ^{1}H NMR spectrum of which (DMSO-d_6 solvent) showed the presence of a two-proton methylene singlet at 4.53 ppm and two low field singlets at 10.49 and 11.68 ppm which are assigned to the hydroxyl groups in the positions 4 and 2 of phenolic ring respectively. Thus the sample exists in the ketone form **A** only. After two weeks a light-yellow product is precipitated from the mother liquor whose ^{1}H NMR spectrum (DMSO-d_6) shows both the signal for the methylene group of ketone **A** at 4.53 ppm and also signals for a methine proton at 5.29 ppm and enolic proton at 14.09 ppm for the enol form (**B**) together with a double set of the remaining signals. Thus, in this case, we have shown the presence of keto-enol tautomerism with an isomer ratio of 84% (**A**) to 16% (**B**) as judged by the integrated intensities of the signals. With a more prolonged crystallization process the enol content of the sample is

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Taras Shevchenko Kiev National University, Kiev 01033, Ukraine; e-mail: vkhilya@mail.univ.kiev.ua.
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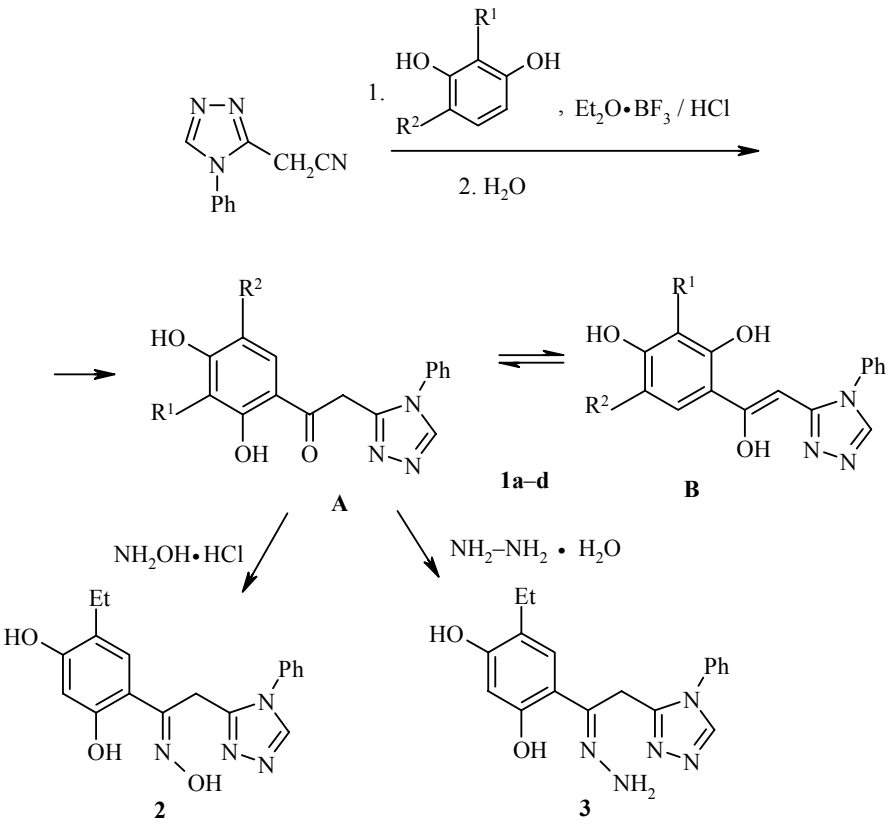


a R^1 = Me, R^2 = H; **b** R^1 = H, R^2 = Et; **c** R^1 = OH, R^2 = H; **d** R^1 = R^2 = H

increased, ^{1}H NMR showing that **1b** exists in DMSO-d_6 solution as 32% ketone **A** and 68% enol **B**. The isomer ratio is virtually equal in the less polar deuteroacetone (49% **A** to 51% **B**) but in the nonpolar chloroform it is present only in the keto form **A** (δ_{CH_2} = 4.28 ppm). In this sample an increase in temperature when recording the ^{1}H NMR spectrum in DMSO-d_6 from 0°C to 90°C causes the content of the keto form **A** to increase from 32% to 54% whereas the spectrum of the pure ketone **A** remains unchanged.

The presence of the keto-enol tautomerism is also observed in the ^{1}H NMR spectra of compounds **1a,c,d** recorded in DMSO-d_6. In this solution the products **1a** and **1d**, recrystallized respectively from ethanol and ethyl acetate, exist principally in the enol **B** form (94%) and contain only 6% of the ketone **A**. The yellow coloring of these samples is also evidence for the large enol content, in which a greater degree of conjugation of the phenol and triazole rings is achieved.

The ^{1}H NMR spectrum in DMSO-d_6 of the colorless pyrogallol derivative **1c** (recrystallized from aqueous DMF) shows principally the keto form **A** (87%) and 13% of the enol **B**. The given data points to a greater solubility of the enol form **B** of compounds **1a-d**. The rate of interconversion of the tautomers proved to be quite low and this allowed the isolation of the pure keto form **A** in the case of the product **1b**.

Thus the ratio of the tautomers **A** and **B** depends on the temperature, the solvent polarity, and on duration of the crystallization time.

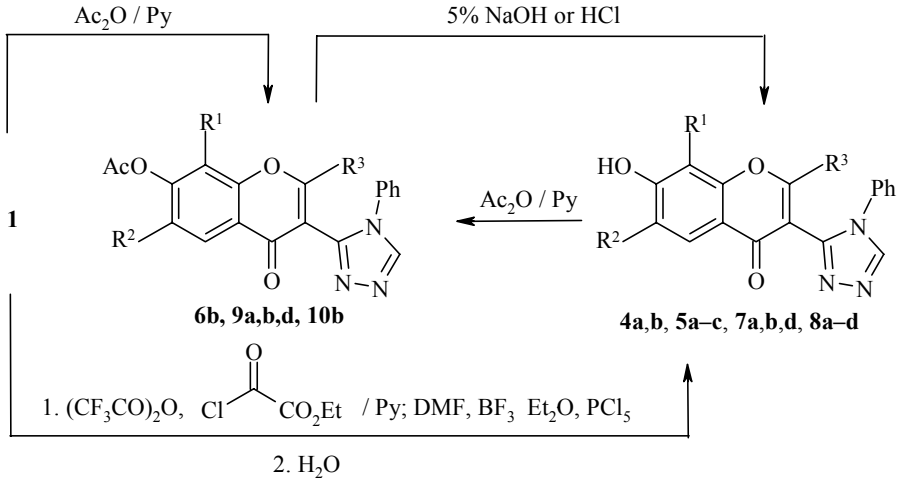
The IR spectra of compounds **1a-d** show strong absorption bands at 3080-3139 cm^{-1} (stretching vibrations of the 4-OH) group, 1627-1630 cm^{-1} (stretching of the carbonyl group), and 1505-1510 cm^{-1} (triazole ring).

Compounds **1** undergo typical reactions at the carbonyl group. Treatment of the product **1b** with hydroxylamine hydrochloride in pyridine gives the oxime **2** and with hydrazine hydrate in alcohol the hydrazone **3**. The spectra of these compounds were recorded in DMSO-d_6 and showed signals for the ethyl group and

aromatic protons (Table 2) together with a typical methylene singlet at 4.16 ppm (oxime **2**) to 4.08 ppm (hydrazone **3**). The hydroxyl group protons of the oxime **2** absorb at low field at 9.41 (4-OH), 10.97 (2-OH), and 11.17 ppm (N–OH). In the spectrum of the hydrazone **3** the lowest field signal is the singlet for the 2-OH group proton at 12.65 ppm together with a two-proton amino group singlet at 6.62 ppm.

The ketones **1a-c** react with trifluoroacetic anhydride or ethoxalyl chloride in pyridine in the cold and cyclize to 6-R^2-8-R^1-7-hydroxy-3-(4-phenyl-1,2,4-triazol-3-yl)chromones with triflurometyl (**4a,b**) or carbethoxy substituents (**5a-c**) at position 2 of the molecule.

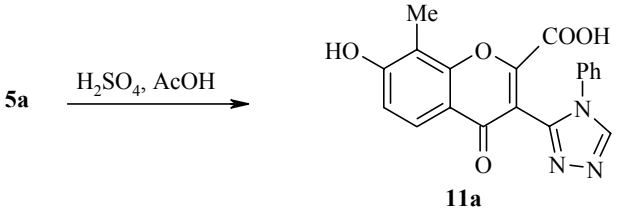
Treatment of the ketone **1b** with acetic anhydride in triethylamine at 130°C and subsequent work up of the reaction mixture with water gave 7-acetoxy-6-ethyl-2-methyl-3-(4-phenyl-1,2,4-triazol-3-yl)chromone (**6b**) which readily hydrolyzed using aqueous alcoholic base to give the target 7-hydroxy derivative **7b**. It was not possible to prepare the pure 7-acetoxy derivatives of 2-methylchromones under the same conditions (A) or in pyridine at 90-95°C [4] (B) from the ketones **1a,b** due to partial hydrolysis when treated with water hence the dry products underwent acid or base hydrolysis to give the 7-hydroxy-2-methylchromones **7a,d**. It should be noted that change of base or increase in temperature did not affect the yield of compound **7d** which was 57%, as in the study [4].



4a, **5a**, **7a–9a** R^1 = Me, R^2 = H; **4b–10b** R^1 = H, R^2 = Et; **5c**, **8c** R^1 = OH, R^2 = H;
4a,b $R^3 = CF_3$, **5a–c, 10b** $R^3 = CO_2Et$, **6b**, **7a,b,d** R^3 = Me, **8a–d, 9a,b** R^3 = H

The 7-hydroxy-3-(4-phenyl-1,2,4-triazol-3-yl)chromones unsubstituted at the position 2 had been prepared before using the Venkataraman method by refluxing the starting ketone **1d** with ethyl orthoformate in pyridine [4] or by treatment with acetoformic anhydride without a catalyst at room temperature [5]. Since the chromone **8b** prepared by us using the Venkataraman method could not be prepared in the pure state we have used a Vilsmeier formylation. This method allows the synthesis of the 7-hydroxychromones **8a,c**, unsubstituted in the position 2, and the previously obtained product **8d** [4, 5] in good yields over 1 h.

The existence of several functional groups in the target chromones leads to their modification. When treated with acetic anhydride in pyridine in the cold the 7-hydroxychromones **8a,b,d** and **5b** form the corresponding 7-acetoxy derivatives **9a,b,d** and **10b**. Acid hydrolysis of the ester group in the molecule **5a** gave the 7-hydroxy-8-methyl-3-(4-phenyl-1,2,4-triazol-3-yl)chromone-2-carboxylic acid **11a** (Table 1).



11a

TABLE 1. Characteristics of Compounds **1-11***

Compound	Empirical formula	Found, % / Calculated, % N	mp, °C	Yield, %
1a	$C_{17}H_{15}N_3O_3$	13.77 / 13.59	182	78
1b	$C_{18}H_{17}N_3O_3$	12.80 / 13.00	244-245	80
1c	$C_{16}H_{13}N_3O_4$	13.34 / 13.50	198	22
2	$C_{18}H_{18}N_4O_3$	16.67 / 16.56	249-250	91
3	$C_{18}H_{19}N_5O_2$	20.97 / 20.76	187-188	75
4a	$C_{19}H_{12}F_3N_3O_3$	10.76 / 10.85	217	82
4b	$C_{20}H_{14}F_3N_3O_3$	10.73 / 10.47	>300	60
5a	$C_{21}H_{17}N_3O_5$	10.95 / 10.74	138	52
5b	$C_{22}H_{19}N_3O_5$	10.51 / 10.37	200-201	71
5c	$C_{20}H_{15}N_3O_6$	10.77 / 10.68	212	86
6b	$C_{22}H_{19}N_3O_4$	11.10 / 10.79	190	58
7a	$C_{19}H_{15}N_3O_3$	12.79 / 12.61	206	40 (A), 72 (B)
7b	$C_{20}H_{17}N_3O_3$	12.33 / 12.10	>300	96
8a	$C_{18}H_{13}N_3O_3$	13.11 / 13.16	147	57
8b	$C_{19}H_{15}N_3O_3$	12.52 / 12.61	225	68
8c	$C_{17}H_{11}N_3O_4$	13.24 / 13.08	243	40
9a	$C_{20}H_{15}N_3O_4$	11.81 / 11.63	184	65
9b	$C_{21}H_{17}N_3O_4$	11.48 / 11.19	196	59
10b	$C_{24}H_{21}N_3O_6$	9.42 / 9.39	197-198	52
11a	$C_{19}H_{13}N_3O_5$	11.36 / 11.57	242	43

* Characteristics of compounds **1d, 7d-9d** ($R^1 = R^2 = R^3 = H$) were reported in [4]. Compounds **1a,b, 3, 5c, 7b-9b** were recrystallized from ethanol; **1c, 8a** from aqueous DMF; **2** from dioxane; **4a** from aqueous ethanol; **4b-5b** from acetonitrile; **5a, 7a** from methanol; **8c** from 2-propanol; **9a** from ether; **10b** from ethyl acetate; **11a** from acetic acid.

The 8-R^1-6-R^2-2-R^3-7-hydroxy-3-(4-phenyl-1,2,4-triazol-3-yl)chromones and their acetyl derivatives are colorless, crystalline materials. Typical features of their ^{1}H NMR spectra are a one-proton triazole 5-H singlet at 8.76-9.29, a five-proton phenyl multiplet in the range 7.38-7.71 ppm, and a low field one-proton 7-OH singlet at 10.31-11.21 ppm for the products **4, 5, 7, 8, 11** and three-proton acetoxy group singlet at 2.30-2.36 ppm for acetoxy derivatives **6** and **9**. The substituents at the position 2 in the synthesized chromones show the following signals: a singlet H-2 proton in **8** and **9** at 8.53-8.63 and 8.72-8.78 ppm respectively, a three-proton 2-methylchromone singlet at 2.30-2.39 ppm in **7b** and **6b**, and a three-proton triplet at 1.11-1.14 and two-proton quartet at 4.21-4.25 ppm corresponding to the ethyl group protons in the 2-carbethoxychromones **5b** and **10b**.

TABLE 2. ^{1}H NMR Spectroscopic Characteristics of Compounds **1-11***

Compound	Chemical shifts, δ, ppm (*J*, Hz)
1	2
1a	6% **A** + 94% **B**: 1.94 (s, 3-CH_3) **A**, 1.97 (s, 3-CH_3) **B**, 4.55 (s, CH_2) **A**, 5.32 (s, CH) **B**, 6.31 (d, *J* = 8, H-5) **B**, 6.40 (d, *J* = 8, H-5) **A**, 6.98 (d, *J* = 8, H-6) **B**, 7.45 (m, C_6H_5) **A**, 7.58 (d, *J* = 8, H-6) **A**, 7.65 (m, C_6H_5) **B**, 8.61 (s, $H_{triazole}$-5) **A**, 8.80 (s, $H_{triazole}$-5) **B**, 9.69 (s, 4-OH) **B**, 10.41 (s, 4-OH) **A**, 12.31 (s, 2-OH) **A**, 14.12 (br. s, HO–C=) **B**, 2-OH **B** exchanged with D_2O
1b	**A**: 1.13 (3H, t, *J* = 7.5, 5-$\underline{CH_3}CH_2$); 2.47 (2H, q, *J* = 7.5, 5-$CH_3\underline{CH_2}$); 4.53 (2H, s, $CH_2C(O)$); 6.25 (1H, s, H-3); 7.44 (5H, m, C_6H_5); 7.52 (1H, s, H-6); 8.58 (1H, s, 5-$CH_{triazole}$); 10.49 (1H, s, 4-OH); 11.68 (1H, s, 2-OH)
	32% **A** + 68% **B**: 1.05 (t, *J* = 7.5, 5-$\underline{CH_3}CH_2$) **B**, 1.13 (t, *J* = 7.5, 5-$\underline{CH_3}CH_2$) **A**, 2.38 (q, *J* = 7.5, 5-$CH_3\underline{CH_2}$) **B**, 2.47 (q, *J* = 7.5, 5-$CH_3\underline{CH_2}$) **A**, 4.53 (s, $CH_2C(O)$) **A**, 5.29 (s, CH) **B**, 6.19 (s, H-3) **B**, 6.24 (s, H-3) **A**, 6.90 (s, H-6) **B**, 7.47 (m, C_6H_5) **A**, 7.51 (s, H-6) **A**, 7.66 (m, C_6H_5) **B**, 8.59 (s, $H_{triazole}$-5) **A**, 8.84 (s, $H_{triazole}$-5) **B**, 9.90 (s, 4-OH) **B**, 10.47 (s, 4-OH) **A**, 11.67 (s, 2-OH) **A**, 14.09 (br. s, HO–C=) **B**, 2-OH **B** exchanged with D_2O
1c	87% **A** + 13% **B**: 4.56 (s, CH_2CO) **A**, 5.34 (s, CH) **B**, 6.21 (d, *J* = 8, H-5) **B** 6.37 (d, *J* = 8, H-5) **A**, 6.68 (d, *J* = 8, H-6) **B**, 7.27 (d, *J* = 8, H-6) **A**, 7.46 (m, C_6H_5) **A**, 7.67 (m, C_6H_5) **B**, 8.63 (s, 5-$CH_{triazole}$) A, 8.85 (s, 5-$CH_{triazole}$) **B**, 10.01 (br. s, 4-OH) **A**, 11.79 (s, 2-OH) **A**, remaining protons exchanged with D_2O
1d	6% **A** + 94 % **B**: 4.53 (s, $CH_2C(O)$) **A**, 5.32 (s, CH) **B**, 6.10 (d, *J* = 1.5, H-3) **A**, 6.14 (d, *J* = 1.5, H-3) **B**, 6.21 (dd, $J_{3,5}$ = 1.5, $J_{5,6}$ = 8, H-5) **B**, 6.35 (dd, $J_{3,5}$ = 1.5, $J_{5,6}$ = 8, H-5) **A**, 7.13 (d, *J* = 8, H-6) **B**, 7.45 (d, *J* = 8, H-6) **A**, 7.47 (m, C_6H_5) **A**, 7.65 (m, C_6H_5) **B**, 8.61 (s, 5-$CH_{triazole}$) **A**, 8.85 (s, 5-$CH_{triazole}$) **B**, 9.89 (br. s, 4-OH) **B**, 10.50 (br. s, 4-OH) **A**, 11.75 (s, 2-OH) **A**, 14.14 (br. s, HO–C=) **B**, 2-OH exchanged with D_2O
2	1.07 (3H, t, *J* = 7.5, 5-$\underline{CH_3}CH_2$); 2.43 (2H, q, *J* = 7.5, $CH_3\underline{CH_2}$); 4.16 (2H, s, $CH_2C(O)$); 6.26 (1H, s, H-3); 6.99 (1H, s, H-6); 7.53 (5H, s, C_6H_5); 8.49 (1H, s, 5-$CH_{triazole}$); 9.41 (1H, s, 4-OH); 10.97 (1H, s, 2-OH); 11.17 (1H, s, N–OH)
3	0.90 (3H, t, *J* = 7.5, 5-$\underline{CH_3}CH_2$); 2.16 (2H, q, *J* = 7.5, 5-$CH_3\underline{CH_2}$); 4.08 (2H, s, $CH_2C(O)$); 6.15 (1H, s, H-3); 6.27 (1H, s, H-6); 6.62 (2H, br. s, NH_2); 7.59 (5H, m, C_6H_5); 8.55 (1H, s, 5-$CH_{triazole}$); 12.65 (1H, br. s, 2-OH); 4-OH exchanged with D_2O
4a	2.25 (3H, s, 8-CH_3); 7.06 (1H, d, *J* = 8, H-6); 7.33 (2H, m, H_{Ph}-2',6'); 7.73 (3H, m, H_{Ph}-3',4',5'); 7.71 (1H, d, *J* = 8, H-5); 8.91 (1H, s, $H_{triazole}$-5); 11.02 (1H, s, 7-OH)
4b	1.20 (3H, t, *J* = 7.5, 6-$\underline{CH_3}CH_2$); 2.64 (2H, q, *J* = 7.5, 6-$CH_3\underline{CH_2}$); 6.92 (1H, s, H-8); 7.32 (2H, s, H_{Ph}-2',6'); 7.43 (3H, s, H_{Ph}-3',4',5'); 7.71 (1H, s, H-5); 8.88 (1H, s, 5-$CH_{triazole}$); 11.21 (1H, s, 7-OH)
5a	1.16 (3H, t, *J* = 7.5, 2-$\underline{CH_3}CH_2O$); 2.27 (3H, s, 8-CH_3); 4.24 (2H, q, *J* = 7.5, 2-$CH_3\underline{CH_2}O$); 7.41 (1H, d, *J* = 8, H-6); 7.43 (5H, m, C_6H_5); 7.65 (1H, d, *J* = 8, H-5); 8.81 (1H, s, $H_{triazole}$-5); 10.85 (1H, s, 7-OH)
5b	1.11 (3H, t, *J* = 7.5, 2-$CO_2CH_2\underline{CH_3}$); 1.18 (3H, t, *J* = 7.5, 6-$\underline{CH_3}CH_2$); 2.62 (2H, q, *J* = 7.5, 6-$CH_3\underline{CH_2}$); 4.21 (2H, q, *J* = 7.5, 2-$CO_2\underline{CH_2}CH_3$); 6.92 (1H, s, H-8); 7.39 (5H, m, C_6H_5); 7.64 (1H, s, H-5); 8.87 (1H, s, 5-$CH_{triazole}$); 11.10 (1H, s, 7-OH)
5c	1.07 (3H, t, *J* = 7.5, 2-$CO_2CH_2\underline{CH_3}$); 4.21 (2H, q, 2-$CO_2\underline{CH_2}CH_3$); 7.08 (1H, d, *J* = 8, H-6); 7.29 (1H, d, *J* = 8, H-5); 7.44 (5H, m, C_6H_5); 9.29 (1H, s, 5-$CH_{triazole}$); 7-OH and 8-OH exchanged with D_2O
6b	1.17 (3H, t, *J* = 7.5 6-$\underline{CH_3}CH_2$); 2.35 (3H, s, 7-$CH_3C(O)O$); 2.39 (3H, s, 2-CH_3); 2.59 (2H, q, *J* = 7.5, 6-$CH_3\underline{CH_2}$); 7.38 (1H, s, H-8); 7.42 (5H, m, C_6H_5); 7.80 (1H, s, H-5); 8.87 (1H, s, 5-$CH_{triazole}$)
7a	2.23 (3H, s, 8-CH_3); 2.35 (3H, s, 2-CH_3); 6.91 (1H, d, *J* = 8, H-6); 7.39 (5H, m, C_6H_5); 7.59 (1H, d, *J* = 8, H-5); 8.81 (1H, s, 5-$CH_{triazole}$); 10.54 (1H, s, 7-OH)
7b	1.19 (3H, t, *J* = 7.5, 6-CH_3CH_2); 2.30 (3H, s, 2-CH_3); 2.59 (2H, q, *J* = 7.5, 6-CH_3CH_2); 6.81 (1H, s, H-8); 7.35 (5H, m, C_6H_5); 7.57 (1H, s, H-5); 8.77 (1H, s, 5-$CH_{triazole}$); 10.66 (1H, s, 7-OH)
7d	2.32 (3H, s, 2-CH_3); 6.78 (1H, s, H-8); 6.84 (1H, d, *J* = 8, H-6); 7.39 (5H, m, C_6H_5); 7.71 (1H, d, *J* = 8, H-5); 8.80 (1H, s, 5-$CH_{triazole}$); 10.67 (1H, s, 7-OH)
8a	2.25 (3H, s, 8-CH_3); 6.91 (1H, d, *J* = 8, H-6); 7.38 (5H, m, C_6H_5); 7.59 (1H, d, *J* = 8, H-5); 8.58 (1H, s, H-2); 8.76 (1H, s, 5-$CH_{triazole}$); 10.58 (1H, s, 7-OH)

TABLE 2 (continued)

1	2
8b	1.17 (3H, t, *J* = 7.5, 6-CH_3CH_2); 2.60 (2H, q, *J* = 7.5, 6-CH_3CH_2); 6.89 (1H, s, H-8); 7.40 (5H, s, C_6H_5); 7.56 (1H, s, H-5); 8.53 (1H, s, H-2); 8.79 (1H, s, 5-$CH_{triazole}$); 10.58 (1H, s, 7-OH)
8c	6.90 (1H, d, *J* = 8, H-6); 7.23 (1H, d, *J* = 8, H-5); 7.40 (5H, m, C_6H_5); 8.63 (1H, s, H-2); 8.81 (1H, s, 5-$CH_{triazole}$); 9.48 (1H, s, 8-OH); 10.31 (1H, s, 7-OH)
8d	6.84 (2H, m, H-6 + H-8); 7.39 (5H, m, C_6H_5); 7.73 (1H, d, *J* = 8, H-5); 8.54 (1H, s, H-2); 8.76 (1H, s, 5-$CH_{triazole}$); 10.71 (1H, s, 7-OH)
9a	2.30 (3H, s, 7-$CH_3C(O)O$); 2.35 (3H, s, 8-CH_3); 7.18 (1H, d, *J* = 8, H-6); 7.42 (5H, m, C_6H_5); 7.80 (1H, d, H-5); 8.78 (1H, s, H-2); 8.81 (1H, s, 5-$CH_{triazole}$)
9b	1.17 (3H, t, *J* = 7.5, 6-CH_3CH_2); 2.35 (3H, s, 7-$CH_3C(O)O$); 2.57 (2H, q, *J* = 7.5, 6-CH_3CH_2); 7.41 (5H, m, C_6H_5); 7.46 (1H, s, H-8); 7.81 (1H, s, H-5); 8.72 (1H, s, H-2); 8.80 (1H, s, 5-$CH_{triazole}$)
9d	2.32 (3H, s, 7-$CH_3C(O)O$); 7.19 (1H, d, *J* = 8, H-6); 7.40 (5H, m, C_6H_5); 7.48 (1H, s, H-8); 7.95 (1H, d, *J* = 8, H-5); 8.74 (1H, s, H-2); 8.81 (1H, s, 5-$CH_{triazole}$)
10b	1.14 (3H, t, *J* = 7.5, 2-$CH_3CH_2OC(O)$); 1.20 (3H, t, *J* = 7.5, 6-CH_3CH_2); 2.36 (3H, s, 7-$CH_3C(O)O$); 2.61 (2H, q, *J* = 7.5, 6-CH_3CH_2); 4.25 (2H, q, *J* = 7.5, 2-$CH_3CH_2OC(O)$); 7.41 (5H, s, C_6H_5); 7.58 (1H, s, H-8); 7.88 (1H, s, H-5); 8.83 (1H, s, 5-$CH_{triazole}$)
11a	2.27 (3H, s, 8-CH_3); 7.00 (1H, d, *J* = 8, H-6); 7.40 (5H, m, C_6H_5); 7.66 (1H, d, *J* = 8, H-5); 8.98 (1H, s, 5-$CH_{triazole}$); 10.89 (1H, s, 7-OH); COOH exchanged with D_2O

* Spectra recorded in DMSO-d_6.

The IR spectra of the target chromones show absorption stretching bands for the cyclic carbonyl group at 1640-1660, the 7-OH group at 3420-3480, and the triazole ring at 1505-1510 cm^{-1}. The strong absorption band at 1770 cm^{-1} in the IR spectra of the 7-acetoxy derivatives are due to the stretching vibrations of the carbonyl group.

Hence, based on α-(4-phenyl-1,2,4-triazol-3-yl)-3-R^1-5-R^2-2,4-dihydroxyacetophenones, we have synthesized a series of 7-hydroxy-3-(4-phenyl-1,2,4-triazol-3-yl)chromones with differing substituents both in the benzene and pyrone rings

EXPERIMENTAL

The purity of the synthesized compounds was monitored using TLC on Silufol UV-254 plates eluting with a mixture of chloroform and methanol (9:1). ^1H NMR spectra were recorded using $CDCl_3$ or DMSO-d_6 on a Varian Mercury 400 spectrometer (400 MHz) using TMS as internal standard. IR Spectra were taken for KBr tablets on a Nexus 475 spectrometer.

α-(4-Phenyl-1,2,4-triazol-3-yl)-3-R^1-5-R^2-2,4-dihydroxyacetophenones 1a-d. A stream of dry hydrogen chloride was passed through a stirred solution of 4-phenyl-1,2,4-triazol-3-ylacetonitrile [9] (17 g, 0.1 mol) and resorcinol, 2-methylresorcinol, 4-ethylresorcinol, or pyrogallol (0.1 mol) in boron trifluoride etherate (100 ml) for 6 h at 50-60°C. After 12 h the mixture was transferred in portions into hot water (0.5 l) and refluxed for 2 h with 1 ml of sulfuric acid. It was then cooled, neutralized with ammonia solution to pH 4-5, and the precipitate was filtered off.

α-(Phenyl-1,2,4-triazol-3-yl)-5-ethyl-2,4-dihydroxy-acetophenone Oxime (2). A solution of the substituted ethylacetophenone **1b** (0.97 g, 3 mmol) and hydroxylamine hydrochloride (0.63 g, 9 mmol) was refluxed for 1 h in pyridine (4 ml). After 12 h it was poured into water (100 ml), triturated, and the crystallized precipitate was filtered off.

α-(Phenyl-1,2,4-triazol-3-yl)-5-ethyl-2,4-dihydroxyacetophenone Hydrazone (3). A solution of the ketone **1b** (0.97 g, 3 mmol) and hydrazine hydrate (0.5 g, 15 mmol) was refluxed for 1 h in ethanol (5 ml). The product was cooled and the precipitate was filtered off.

8-R^1-6-R^2-7-Hydroxy-2-(4-phenyl-1,2,4-triazol-3-yl)-2-trifluoromethylchromones (4a,b). Trifluoroacetic anhydride (8.4 g, 40 mmol) was added dropwise with stirring to a solution of the ketone **1a,b** (10 mmol) in pyridine (10 ml) cooled to 0°C. The product was held at room temperature for 48 h, poured into iced water (100 ml), and the precipitate was filtered off.

8-R^1-6-R^2-2-Carbethoxy-7-hydroxy-3-(4-phenyl-1,2,4-triazol-3-yl)chromones (5a-c) were synthesized by the preceding method from the corresponding ketones **1a-c** (10 mmol) and ethoxalyl chloride (3 g, 22 mmol) (for compounds **1a,b**) or 33 mmol (for compound **1c**).

7-Acetoxy-6-ethyl-2-methyl-3-(4-phenyl-1,2,4-triazol-3-yl)chromone (6b). A solution of the substituted ethylacetophenone (3.23 g, 10 mmol), acetic anhydride (5.1 g, 50 mmol) and triethylamine (5 g, 50 mmol) was heated at 130-140°C for 2 h. After cooling the solution was poured into water (100 ml) and the precipitate was filtered off.

6-Ethyl-7-hydroxy-2-methyl-3-(4-phenyl-1,2,4-triazol-3-yl)chromone (7b). A 5% solution of sodium hydroxide (1.5 ml) and water (5 ml) were added to a solution of the 7-acetoxy derivative **6b** (0.6 g, 1.5 mmol) in ethanol (10 ml). The mixture was refluxed for 5 min, poured into water (100 ml), neutralized with hydrochloric acid to pH 7, and the precipitate was filtered off.

7-Hydroxy-2,8-dimethyl-3-(4-phenyl-1,2,4-triazol-3-yl)chromone (7a). A. A mixture of the substituted methylacetophenone **1a** (4.63 g, 15 mmol), acetic anhydride (7.1 g, 70 mmol) and triethylamine (8.3 g, 60 mmol) was heated at 130-140°C on an oil bath while the reaction was monitored by TLC. The cooled reaction mixture was poured into a mixture of water (100 ml) and hydrochloric acid (5 ml) and the precipitate was filtered off. It was transferred to a mixture of methanol (20 ml) and sulfuric acid (1 ml) and refluxed with the reaction monitored chromatographically, cooled, and the precipitate was filtered off.

B. A mixture of compound **1a** (4.5 g, 14.6 mmol) and acetic anhydride (8.2 g, 80 mmol) in pyridine (25 ml) was heated at 90-95°C for 5 h and then cooled and poured into ice. The tar was triturated in water until formation of a precipitate which was filtered off, dissolved in a minimum amount of alcohol, and refluxed for 30 s with 5% sodium hydroxide solution (3 ml). The product was diluted with water (50 ml), acidified with hydrochloric acid to pH 4-5, and the precipitate was filtered off.

7-Hydroxy-2-methyl-3-(4-phenyl-1,2,4-triazol-3-yl)chromone (7d) was prepared similarly to compound **7a** using method A in 57% yield.

8-R^1-6-R^2-7-Hydroxy-3-(4-phenyl-1,2,4-triazol-3-yl)chromones (8a-d). Boron trifluoride etherate (8.46 g, 60 mmol) was added dropwise with stirring to a solution of the corresponding dihydroxyacetophenone **1a-d** (10 mmol) in DMF (15 ml, 0.2 mol). Phosphorus pentachloride (2.3 g, 11 mmol) was added portionwise and the product was held for 30 min at 70-80°C. The mixture was poured into water (100 ml), refluxed for 30 min, cooled, and the precipitate was filtered off. The yield of **7-hydroxy-3-(4-phenyl-1,2,4-triazol-3-yl)chromone** (**8d**, $R^1 = R^2 = R^3 = H$) was 57%.

2-R^3-6-R^2-8-R^1-7-Acetoxy-3-(4-phenyl-1,2,4-triazol-3-yl)chromones (9a,b,d, 10b). A solution of the corresponding 7-hydroxy product **8a,b,d** or **5b** (1.5 mmol) in a mixture of acetic anhydride (0.61 g, 6 mmol) and pyridine (0.5 g, 6 mmol) was held at room temperature for 24 h. The precipitated product was filtered off (in the case of the products **9a,d**) or poured into water (50 ml) and filtered to give the precipitated **7-acetoxy-3-(4-phenyl-1,2,4-triazol-3-yl)chromone (9b)** and compound **10b**.

7-Hydroxy-8-methyl-3-(4-phenyl-1,2,4-triazol-3-yl)chromone-2-carboxylic Acid (11a). A solution of the carbethoxychromone **5a** was refluxed in a mixture of acetic acid (2.3 ml) and conc. H_2SO_4 (0.75 ml) for 15 min, held for 12 h, and the precipitate was filtered off.

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