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One pot synthesis of 4-(arylidene)-2-[5-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-thiazol-2-yl]-5-methyl-2,4-dihydro-pyrazol-3-ones *via* multi-component approach

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An efficient, one pot, four-component approach for the synthesis of 4-(arylidene)-2-[5-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-thiazol-2-yl]-5-methyl-2,4-dihydropyrazol-3-ones has been described. This synthesis involves the simultaneous formation of thiazole and pyrazole ring systems followed by condensation of different aldehydes on active methylene group of pyrazolone under Knoevenagel reaction conditions. The structures of newly synthesized compounds have been established on the basis of elemental analysis, IR, ^{1}H NMR and mass spectroscopic studies.

Keywords: Hantzsch-thiazole synthesis, pyrazolone, 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one, multi-component reaction, Knoevenagel reaction

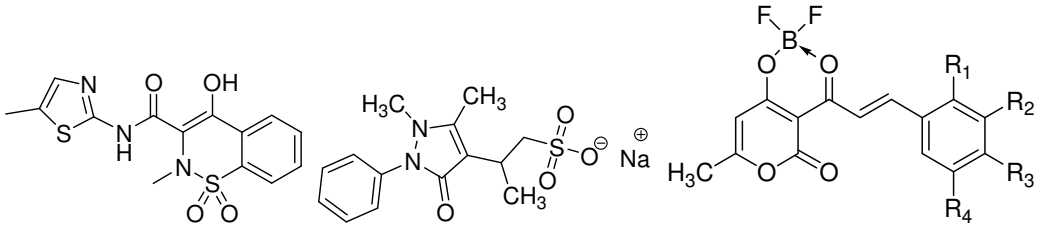
3-Acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one exhibits diverse chemistry[1]. It readily undergoes condensation reactions with a variety of bis-nucleophiles to give different heterocyclic systems, such as pyrazoles, benzothiazepines, benzodiazepines and pyrimidines[2-6]. 2-Pyrones and its derivatives constitute a large family of biologically active natural products, abundantly found in animals, insects, plants, bacteria, and microbial systems[7]. Particularly, 4-hydroxy-2-pyrones are considered as one of the important class of anti-HIV agents and exhibit a wide range of antimicrobial, antifungal, phytotoxic, cytotoxic and neurotoxic activities[8-10]. Some derivatives of 2-pyrone have enormous potential in the treatment of Alzheimer's disease[11,12]. Pyrazolone is a key pharmacophore which exhibits widespread pharmacological properties, such as anticancer[13], analgesic[14], anti-inflammatory[15], antipyretic[16], antioxidant[17] and antimicrobial[18] activity. Some of its derivatives are potential drugs for the treatment of fatal neurodegenerative diseases[19] and cardiovascular diseases[20]. Moreover; thiazole ring is of great importance in biological systems. Compounds having thiazole nucleus possess a broad range of biological activities such as anti-inflammatory[21], antibacterial[22] and antifungal[23] activity.

Meloxicam and Metamizole (or dipyrone) are commonly used drugs for a long time with thiazole and pyrazolone moiety respectively (**Figure 1**). Meloxican is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic effects, whilst metamizole has analgesic and antipyretic effect[24]. Dehydroacetic acid derivatives (**Figure 1**) and their boron difluoride complexes were experimentally confirmed by *in vitro* testing for their antiviral activity with respect to HIV-infected cells[25].

Thiazolyl pyrazolone motif can be synthesized in step-wise manner, for example, the solid phase reaction of ethyl 3-thiosemicarbazido-butanoate with phenacyl bromide afforded the corresponding ethyl 3-[(4-phenyl-2-thiazo-lyl)hydrazono]butanoate followed by heterocyclization on heating in ethanolic sodium-acetate[26]. One pot, multi-component synthetic protocol is more significant than the step wise approach in terms of efficiency, minimal waste production, energy or cost-effectiveness, and operational simplicity[27,28]. Hence, synthesizing the new substituted thiazolyl-pyrazolone derivatives *via* one pot multi-component approach is of vital significance.

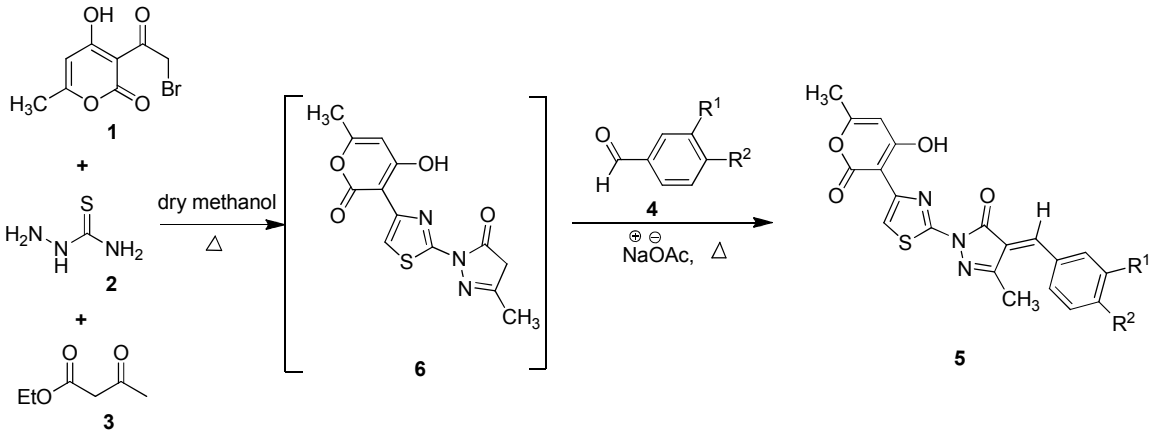
Results and Discussion

In continuation of the earlier work on the synthesis of biologically important heterocyclic systems[29,30], herein is reported a multi-component reaction that involves Hantzsch-thiazole synthesis and the formation of pyrazolone skeleton simultaneously. In this method, equimolar amounts of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one **1**, thiosemicarbazide **2** and ethyl acetoacetate **3** were taken in methanol and



(a) Meloxicam (b) Metamizole (c) Dehydroacetic acid derivatives

Figure 1 — Structures of common drug molecule and drug candidates



Scheme I — Synthesis of 4-(arylidene)-2-[5-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-thiazol-2-yl]-5-methyl-2, 4-dihydro-pyrazol-3-ones

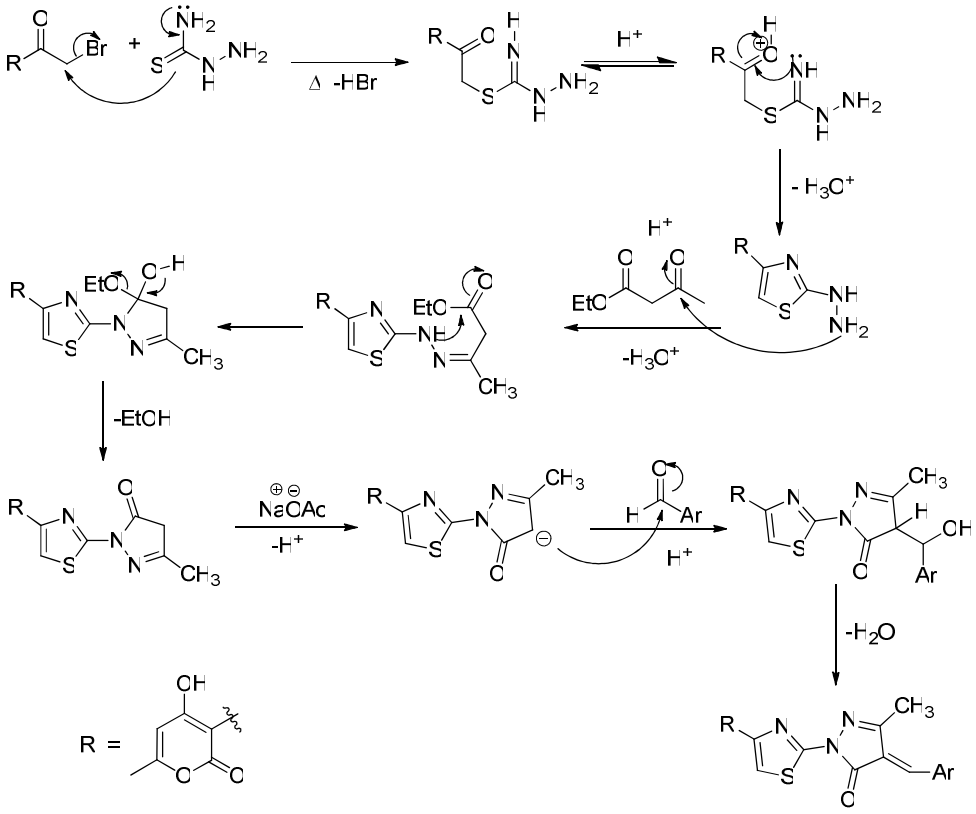
heated at 50-55°C which gave 2-[5-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-1,3-thiazol-2-yl]-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one having an active methylene group. Without isolating this intermediate, sodium acetate and aryl aldehyde **4** were added to the reaction mixture. This intermediate undergoes Knoevenagel condensation followed by an intramolecular dehydration to give the target products **5a-k** in good yields (**Scheme I, Table I**).

The plausible mechanism for the formation of product **5** can be proposed (**Scheme II**). The bromine atom of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one is replaced by a sulfur atom of thiosemicarbazide to yield an open-chain α-thio ketone, which under protonation proceeds to undergo intermolecular condensation to give 3-(2-hydrazino-thiazol-4-yl)-4-hydroxy-6-methyl-pyran-2-one **7**. This thiazolyl hydrazine intermediate undergoes cyclocondensation reaction with ethylacetoacetate to give 2-[4-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-thiazol-2-yl]-5-methyl-2,4-dihydro-pyrazol-3-one intermediate, which subsequently undergoes Knoevenagel condensation reaction with aldehyde on active methylene group to give the title compound **5**.

Table I — Synthesis of 4-(arylidene)-2-[5-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-thiazol-2-yl]-5-methyl-2, 4-dihydro-pyrazol-3-ones, **5a-k**

Entry	Compd	R^1	R^2	Reaction time (hr)	Yield (%)
1	**5a**	H	OCH_3	4.5	80
2	**5b**	OCH_3	OCH_3	4.5	83
3	**5c**	H	Cl	4	86
4	**5d**	H	$N(CH_3)_2$	4.5	82
5	**5e**	H	OH	5	77
6	**5f**	OH	OH	5	79
7	**5g**	NO_2	H	4.5	80
8	**5h**	H	CH_3	5	78
9	**5i**	H	H	5	86
10	**5j**	H	NO_2	4	87
11	**5k**	H	Br	4	81

All the structures of newly synthesized compounds have been confirmed by their spectral data. The ^{1}H NMR spectrum of compound **5a** shows prominent peaks for two CH_3 groups at δ 2.28 and 2.61. The-OCH_3 protons appeared at δ 3.90. Pyran proton appeared at δ 6.25. The methine proton and thiazole proton appeared at δ 7.90 and 8.26 respectively. The



Scheme II — Plausible mechanism

remaining protons were observed in the expected region. The ^{13}C NMR spectrum of **5a** also shows peaks at δ 19.2, 24.3, 55.6 and 163.8 for the two methyl,-OCH_3 and C=O of pyran respectively. The remaining carbons were observed in the expected region. All the above spectral data clearly indicate the formation of title products. Structural configuration of compound **5g** regarding *E/Z* configuration was obtained through ROESY experiment. As shown in **Scheme I**, the methine proton showed a through space coupling with aromatic *ortho* proton on benzene ring. The spectrum also revealed the absence of cross peak between methyl protons of pyrazolone at δ 2.24 and methine proton in the aromatic region. This confirms that the structure exists in (*E*) configuration. Thermodynamically the (*E*) structure is stable. Hence, it is formed exclusively.

Experimental Section

All the reagents and solvents were pure, purchased from commercial sources and were used as received unless otherwise stated. 3-(2-Bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one[31] was prepared by literature procedure. Melting points were determined in open capillaries with a "Stuart SPM-30" melting point apparatus and are uncorrected. CHNS analysis was carried out on Carlo Erba EA 1108 automatic elemental analyzer. The homogeneity of the compounds was checked by TLC plates. IR spectra (KBr) were recorded on a Thermo Nicolet Nexus 670 spectrometer. ^{1}H NMR spectra were recorded on a Bruker WM-400 spectrometer on the δ (ppm) scale using TMS as standard. Mass spectra (EI-MS) were determined on Perkin-Elmer (SCIEX API-2000, ESI) at 12.5 eV.

General procedure for the synthesis of compounds, 5a-k

3-(2-Bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (1 mmol), thiosemicarbazide (1 mmol) and ethyl acetoacetate (1 mmol) were taken in dry methanol (10 mL), heated at 50-55°C for about 2 hr. The reaction mixture was cooled RT, sodium acetate (2 mmol) and arylaldehyde (1.2 mmol) were added and further heated at 80-85°C for about 2-3 hr till the reaction was completed. The solid product obtained after cooling was collected and washed with water. The crude solid was purified by recrystallization from ethanol.

(*E*)-4-(4-Methoxybenzylidene)-1-(4-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl) thiazol-2-yl)-3-methyl-1*H*-pyrazol-5(4*H*)-one, 5a. Yellow solid; m.p. 285-87°C; IR (KBr): 1698 (C=O pyrazolone), 1727 (C=O lactone), 3305 cm^{-1} (OH); ^1H NMR (400 MHz, DMSO-d_6): δ 2.28 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 6.25 (s, 1H, pyran proton), 7.14 (d, 2H, *J* = 8.0 Hz, ArH), 7.80 (d, 2H, *J* = 8.0 Hz, ArH), 7.90 (s, 1H, =CH-Ar), 8.26 (s, 1H, thiazole); ^{13}C NMR (DMSO-d_6): δ 19.2, 24.3, 55.6, 99.9, 122.4, 123.2, 124.4, 127.0, 128.7, 129.2, 129.3, 130.4, 137.7, 140.8, 144.7, 145.6, 150.1,163.8, 192.2; EI-MS: *m/z* 423 $[M]^+$. Anal. Calcd for $C_{21}H_{17}N_3O_5S$: C, 59.57; H, 4.05; N, 9.92. Found: C, 59.52; H, 4.12; N, 9.87%.

(*E*)-4-(3,4-Dimethoxybenzylidene)-1-(4-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)thiazol-2-yl)-3-methyl-1*H*-pyrazol-5(4*H*)-one, 5b. Yellow solid; m.p. 237-39°C; IR (KBr): 1701 (C=O pyrazolone), 1746 (C=O lactone), 3304 cm^{-1} (OH); ^1H NMR (400 MHz, DMSO-d_6): δ 2.23 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 6.19 (s, 1H, pyran proton), 7.41 (d, 1H, *J* = 8.4 Hz, ArH), 7.63-7.65 (m, 2H, ArH), 7.71 (s, 1H, =CH-Ar), 8.24 (s, 1H, thiazole), 12.79 (s, 1H, OH); EI-MS: *m/z* 453 $[M]^+$. Anal. Calcd for $C_{22}H_{19}N_3O_6S$: C, 58.27; H, 4.22; N, 9.27. Found: C, 58.23; H, 4.25; N, 9.25%.

(*E*)-4-(4-Chlorobenzylidene)-1-(4-(4 - hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)thiazol-2-yl)-3-methyl-1*H*-pyrazol-5(4*H*)-one, 5c. Light brown solid; m.p. 274-76°C; IR (KBr): 1696 (C=O, pyrazolone) 1751 (C=O, lactone), 3304 cm^{-1} (OH); ^1H NMR (400 MHz, DMSO-d_6): δ 2.20 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 6.23 (s, 1H, pyran proton), 7.44 (d, 2H, *J* = 8.4Hz, ArH), 7.50 (s, 1H, =CH-Ar), 7.93 (d, 2H, *J* = 8.4 Hz, ArH), 8.37 (s, 1H, thiazole); ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.0, 25.6, 100.1, 115.5, 116.3, 122.1, 122.7, 123.4, 124.4, 126.7, 127.6, 128.9, 130.5, 130.6, 138.3, 151.6, 164.0, 191.1. Anal. Calcd for $C_{20}H_{14}ClN_3O_4S$: C, 56.14; H, 3.30; N, 9.82. Found: C, 56.19; H, 3.34; N, 9.91%.

(*E*)-4-(4-(Dimethylamino)benzylidene)-1-(4-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)thiazol-2-yl)-3-methyl-1*H*-pyrazol-5(4*H*)-one, 5d. Orange solid; m.p. 296-98°C; IR (KBr): 1701 (C=O, pyrazolone), 1740 (C=O, lactone), 3305 cm^{-1} (OH); ^1H NMR (400 MHz, DMSO-d_6): δ 2.28 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 3.02 (s, 6H,-$N(CH_3)_2$), 6.24 (s, 1H, pyran), 7.02 (d, 2H, *J* = 8.8 Hz, ArH), 7.32 (s, 1H, =CH-Ar), 8.04 (d, 2H, *J* = 8.8 Hz, ArH), 8.47 (s, 1H, thiazole proton), 14.77 (s, 1H, OH); EI-MS: *m/z* 436 $[M]^+$. Anal. Calcd for $C_{22}H_{20}N_4O_4S$: C, 60.54; H, 4.62; N, 12.84. Found: C, 60.59; H, 4.68; N, 12.90%.

(*E*)-4-(4-Hydroxybenzylidene)-1-(4-(4 - hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)thiazol-2-yl)-3-methyl-1*H*-pyrazol-5(4*H*)-one, 5e. Yellow solid; m.p. 194-96°°C; IR (KBr): 1698 (C=O, pyrazolone), 1738 (C=O, lactone), 3391 cm^{-1} (OH); ^1H NMR (400 MHz, DMSO-d_6): δ 2.26 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 5.93 (s, 1H, pyran), 6.92 (d, 2H, *J* = 8.8 Hz, Ar-H), 7.35 (s, 1H, =CH-Ar), 7.64 (d, 2H, *J* = 8.8 Hz, ArH), 8.20 (s, 1H, thiazole), 14.66 (s, 1H, OH), 14.70 (s, 1H, OH). Anal. Calcd for $C_{20}H_{15}N_3O_5S$: C, 58.67; H, 3.69; N, 10.26. Found: C, 58.62; H, 3.73; N, 10.29%.

(*E*)-4-(3,4-Dihydroxybenzylidene)-1-(4-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)thiazol-2-yl)-3-methyl-1*H*-pyrazol-5(4*H*)-one, 5f. Yellow-gray solid; m.p. 243-45°C; IR (KBr): 1696 (C=O, pyrazolone), 1722 (C=O, lactone), 3304 cm^{-1} (OH); ^1H NMR (400 MHz, DMSO-d_6): δ 2.28 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 6.15 (s, 1H, pyran proton), 6.67 (d, 1H, *J* = 7.6 Hz, ArH), 6.96-6.99 (m, 2H, ArH), 7.78 (s, 1H, =CH-Ar), 8.29 (s, 1H, thiazole). Anal. Calcd for $C_{20}H_{15}N_3O_6S$: C, 56.47; H, 3.55; N, 9.88. Found: C, 56.50; H, 3.58; N, 9.91%.

(*E*)-4-(3-Nitrobenzylidene)-1-(4 -(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)thiazol-2-yl)-3-methyl-1H-pyrazol-5(4*H*)-one, 5g. Light grey solid; m.p. 228-30°C; IR (KBr): 1698 (C=O, pyrazolone), 1742 (C=O, lactone), 3389 cm^{-1} (OH); ^1H NMR (400 MHz, DMSO-d_6): δ 2.24 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 6.21 (s, 1H, pyran proton), 7.26 (d, 1H, *J* = 7.6 Hz, ArH), 7.52-7.56 (m, 4H, 3H-ArH and 1H-=CH-Ar), 8.30 (s, 1H, thiazole). Anal. Calcd for $C_{20}H_{14}N_4O_6S$: C, 54.79; H, 3.22; N, 12.78. Found: C, 54.75; H, 3.25; N, 12.72%.

(*E*)-2-[4-(4-Hydroxy-6-methyl - 2-oxo-2*H*-pyran-3-yl)-thiazol-2-yl]-5-methyl-4-(4-methyl-benzylidene)-2, 4-dihydro-pyrazol-3-one, 5h. Gray solid; m.p. 253-55°C; IR (KBr): 1699 (C=O, pyrazolone), 1755 (C=O, lactone), 3397 cm^{-1} (OH); ^1H NMR (400 MHz, DMSO-d_6): δ 2.28 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 2.86 (s, 3H, CH_3), 6.21 (s, 1H, pyran proton), 7.13 (d, 2H, *J* = 8.8 Hz, ArH), 7.77 (s, 1H, =CH-Ar), 7.87 (d, 2H, *J* = 8.8, ArH), 8.25 (s, 1H, thiazole proton). Anal. Calcd for $C_{21}H_{17}N_3O_4S$: C, 61.90; H, 4.21; N, 10.31. Found: C, 61.94; H, 4.25; N, 10.39%.

(*E*)-4-Benzylidene-1-(4-(4- hydroxy - 6-methyl-2-oxo-2*H*-pyran-3-yl)thiazol-2-yl)-3-methyl-1*H*-pyrazol-

5(4*H*)-one, 5i. Gray solid; mp: 185-87°C; IR (KBr): 1678 (pyrazolone), 1742 (C=O, lactone), 3392 cm^{-1} (OH); ^1H NMR (400 MHz, DMSO-d_6): δ 2.20 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 6.20 (s, 1H, pyran proton), 7.14-7.24 (m, 6H, 5H-ArH and 1H-=CH-Ar), 8.32 (s, 1H, thiazole proton). Anal. Calcd for $C_{20}H_{15}N_3O_4S$: C, 61.06; H, 3.84; N, 10.68. Found: C, 61.12; H, 3.87; N, 10.72%.

(*E*)-4-(4-Nitrobenzylidene)-1-(4 - (4-hydroxy-6-methyl-2-oxo - 2*H* - pyran-3-yl)thiazol-2-yl)-3-methyl-1*H*-pyrazol-5(4*H*)-one, 5j. Light grey solid; m.p. 261-63°C; IR (KBr): 1696 (C=O, pyrazolone), 1750 (C=O, lactone), 3391 cm^{-1} (OH); ^1H NMR (400 MHz, DMSO-d_6): δ 2.28 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 6.21 (s, 1H, pyran proton), 7.31 (d, 2H, J = 8.8 Hz, ArH), 7.67 (s, 1H, =CH-Ar), 8.10 (d, 2H, J = 8.8Hz, ArH), 8.50 (s, 1H, thiazole). Anal. Calcd for $C_{20}H_{14}N_4O_6S$: C, 54.79; H, 3.22; N, 12.78. Found: C, 54.73; H, 3.18; N, 12.82%.

(*E*)-4-(4-Bromobenzylidene)-1-(4-(4 - hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)thiazol-2-yl)-3-methyl-1*H*-pyrazol-5(4*H*)-one, 5k. Brown solid; m.p. >300°C; IR (KBr): 1697 (C=O, pyrazolone), 1742 (C=O, lactone), 3392 cm^{-1} (OH); ^1H NMR (400 MHz, DMSO-d_6): δ 2.25 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 6.29 (s, 1H, pyran proton), 7.19 (d, 2H, J = 8.8Hz, ArH), 7.61 (s, 1H, =CH-Ar), 7.89 (d, 2H, J = 8.8 Hz, ArH), 8.46 (s, 1H, thiazole), 14.46 (s, 1H, OH). Anal. Calcd for $C_{20}H_{14}BrN_3O_4S$: C, 50.86; H, 2.99; N, 8.90. Found: C, 50.89; H, 2.96; N, 8.94%.

Conclusion

In this paper an efficient, one-pot method was developed for the synthesis of 4-(arylidene)-2-[5-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-thiazol-2-yl]-5-methyl-2,4-dihydro-pyrazol-3-ones in excellent yields. The experimental conditions are simple, inexpensive and mild. This multicomponent approach would be useful in the context of synthesis of molecular library for pharmacological applications. The biological activity test of these compounds is in progress.

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