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A facile one-pot synthesis of thiazoles and thiazolyl-pyrazole derivatives via multicomponent approach

Santhosh Penta and Rajeswar Rao Vedula*

Department of Chemistry, National Institute of Technology, Warangal-506 004, A.P, India.

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Abstract: Thiazoles and thiazolyl-pyrazole derivatives have been efficiently synthesized under neat reaction conditions in excellent yields. Condensation of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one **(1)**, thiosemicarbazide (**2)** and various carbonyl compounds (**3 & 5)** gave corresponding thiazole (**4**) and thiazolyl-pyrazole derivatives **(6)** in excellent yields by using Hantzsch-Thiazole synthesis. The main advantage of this method is the short reaction time, high yields, simple workup and environmental benign process. The structures of newly synthesized compounds have been established by elemental analysis and spectral data.

Keywords: Thiazole; thiazolyl-pyrazole; 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one; multi-component approach; one-pot.

1. Introduction

Heterocycles are widely used in the development of modern pharmaceuticals, this being one of the reasons why continuous efforts are placed towards the design of amenable synthetic approaches for the synthesis of new heterocyclic systems. 3-Acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one (Dehydroacetic acid) is a versatile starting material and its derivatives find wider application in the synthesis of heterocyclic compounds.[1-8] Dehydroacetic acid is a pyran derivative and exhibit high biological activity.[9] For example, sodium dehydroacetate in rats induces severe hemorrhaging in multiple organs and prolongation of blood coagulation factors.[10] For instance, 4-hydroxy-2-pyrones are considered as one important class of anti-HIV agents and exhibit a wide range of antifungal, phytotoxic, antimicrobial, cytotoxic and neurotoxic activities.[11,12] Other 2-pyrone derivatives have shown a huge potential in the treatment of Alzheimer's diseases.[13] The nitrogen and sulfur heterocyclic systems are very interesting because of their physicochemical properties with relevance to the design of new drugs. In those compounds containing thiazole ring plays a prominent role in nature as they are found in numerous biologically active compounds. Thiazole ring systems are known to possess various pharmacological properties such as anti-tubercular, antifungal, analgesic and anti-cancer activity.[14-17] The thiazole derivatives niridazole and levamisole are used as antihelmintic drugs[18-19] and ritonavir is a antiretroviral drug from the protease inhibitor class used to treat HIV infection and AIDS.[20] Pyrazoles have emerged as a group of compounds possessing a broad spectrum of useful medicinal properties such as herbicides, fungicides and analgesics activities.[21-22] Schiff bases

* Corresponding author: E-mail: vrajesw@yahoo.com; Tel.: +91 9912186430; fax: +91 870 2459547.

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form a significant class of compounds in medicinal and pharmaceutical chemistry with several biological applications that include antibacterial, antifungal and antitumor activity.[23-29] Multi-component reactions (MCRs) involve domino processes "in which more than three different reactants directly get converted into their products by one-pot reaction''.[30] MCRs play an important role in modern organic chemistry, because they generally exhibit higher atom economy, selectivity, molecular complexity and diversity as well as produce fewer by-products compared to classical multistep synthesis.[31]

It is known that 2-aminothiazoles can be synthesized from α-bromoketone and a thiourea via a Hantzsch thiazole synthesis in high yields.[32-33] A literature survey revealed that, there are numerous routes reported for the synthesis of substituted thiazoles according to Hantzsch-thiazole synthesis.[34-36] These methods give excellent yields for thiazoles. However, for some substituted thiazoles low yields have been reported as a result of dehalogenation of the α-haloketone during the reaction.

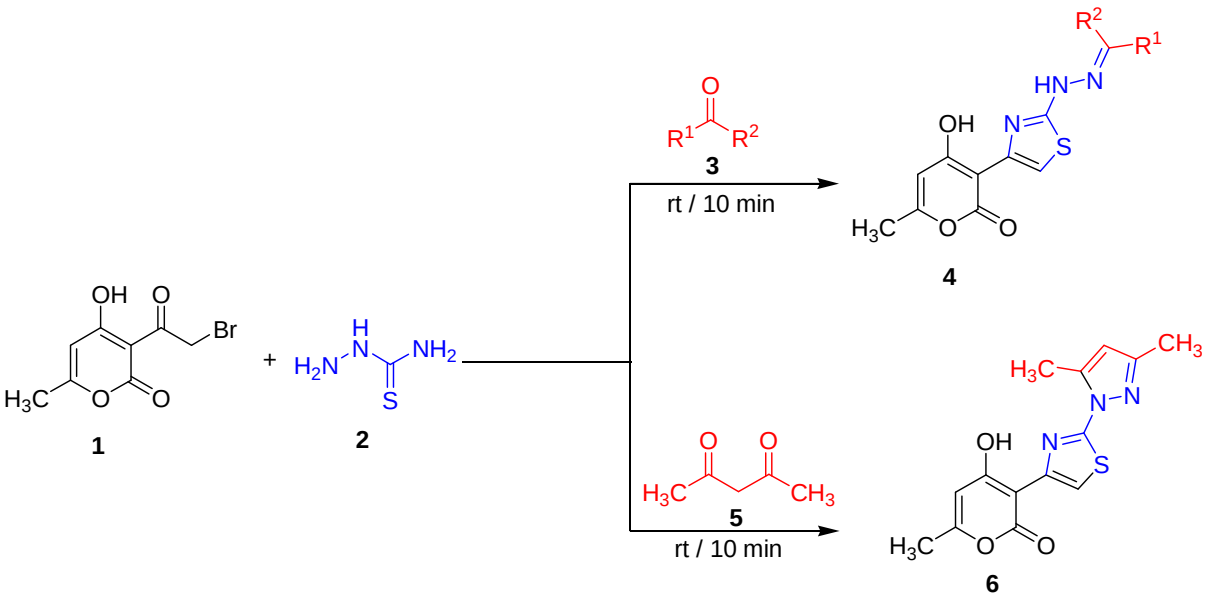
Based on the above observations and as a part of our research program in the synthesis of novel heterocyclic systems,[37-41] a facile route has been described for the synthesis of thiazoles and thiazolyl-pyrazole derivatives with pyran moiety via Hantzsch-thiazole multicomponent reaction.

2. Results and Discussion

Reaction of equimolar mixture of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (**1)**, thiosemicarbazide (**2)** and various carbonyl compounds (**3)** and acetyl acetone (**5)** on stirring at room temperature for period of 10 min resulted in the formation of 4-hydroxy-3-[2-(N′-substituted-hydrazino)-thiazol-4-yl]-6-methyl-pyran-2-one (**4a-j**) and 4-hydroxy-6-methyl-3-(2-(3,5-dimethyl-1*H*-pyrazol-1-yl)thiazol-4-yl)-2*H*-pyran-2-one derivatives (**6**) in good yields.

In this reaction, a plausible mechanism for the formation of **4** can be proposed. The bromine atom of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one is replaced by sulfur atom of thiosemicarbazide to yield an open chain α-thio ketone, which under trans-protonation proceeds to give 4-hydroxy thiazoline derivative. This subsequently undergoes dehydration to give 2-hydrazino thiazole derivative (*in situ*). This subsequently undergoes condensation reaction with various carbonyl compounds to give final product **4**. This is in accordance with modified Hantzsch-Thiazole synthesis. In the formation of thiazolyl-pyrazole **6** it is believed that first thioamide part of thiosemicarbazide undergoes condensation with loss of water and HBr molecules to gave cycloproduct of 3-(2-hydrazino-thiazol-4-yl)-4-hydroxy-6-methyl-pyran-2-one. This further undergoes to condensation with acetyl acetone to give final product. In this reaction, two heterocyclic ring systems, thiazole and a pyrazole, were developed simultaneously.

The IR spectrum of compound **4b** showed prominent peaks at 1731cm^{-1} for lactone, 3367 cm^{-1} to the hydroxyl of pyran ring. ^{1}H NMR of compound **4b** showed characteristic singlets for –CH_3 of pyran at δ 2.24, the C-5 proton of pyran ring singlet at δ 6.23, thiazole proton appeared as singlet at δ 7.81. The above spectral data confirmed the structure of compound **4b**. The ^{13}C NMR spectrum of **4b** also shows the peaks at δ 14.2 and 19.3 for two methyl carbons, 101.1 and 168.5 for C-5 of pyran carbon and C=O of pyran respectively. In the same way ^{1}H NMR of compound **6** showed characteristic singlets for –CH_3 of pyran at δ 2.22, the pyrazole methyl groups appeared as singlet at δ 2.27 and δ 2.62 respectively. The C-5 proton of pyran ring and pyrazole proton appeared as singlet at δ 6.30, while the thiazole proton appeared as singlet at δ 7.89. The remaining protons were observed in the expected region. The above spectral data confirmed the structure of the compound **6**. All the above spectral data clearly indicates the formation of title products.



Compound	R^1	R^2	Compound	R^1	R^2
4a	Me	Me	**4f**	$R^1 = R^2$ =	cyclohexylidine
4b	Me	Ph	**4g**	H	Ph
4c	Me	p-tolyl	**4h**	H	o-hydroxyphenyl
4d	Me	p-anisyl	**4i**	H	p-tolyl
4e	Me	Et	**4j**	H	p-anisyl

Scheme-1. One-pot synthesis of 4-hydroxy-3-[2-(N′-substitutedaryl-hydrazino)-thiazol-4-yl]-6-methyl-pyran-2-one **4a-j** and 4-hydroxy-6-methyl-3-(2-(3,5-di methyl-1*H*-pyrazol-1-yl)thiazol-4-yl)-2*H*-pyran-2-one **6.**

3. Conclusion

In conclusion, a facile one-pot reaction has been described for the synthesis of aryl and heteryl 2,4-disubstituted thiazoles and thiazolyl-pyrazole derivatives via multi-component approach using readily available starting materials. This method does not involve the use of volatile organic solvents thus it is an environmentally friendly process. These highly functionalized derivatives may be of interest for pharmaceutical purposes, yet to be explored.

4. Experimental

All the reagents and solvents were purchased from commercial sources and were used without further purification unless otherwise stated. 3-(2-Bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one[38] was prepared by literature procedure. Melting points were determined in open capillaries with a "Cintex" melting point apparatus Mumbai, India and were uncorrected. CHNS analysis was done by Carlo Erba EA 1108 automatic elemental analyzer. The purity of the compounds was checked by TLC plates (E. Merck Mumbai, India). IR spectra (KBr) were recorded on a Thermo Nicolet Nexus 670 spectrometer. ^{1}H-NMR spectra were recorded on a Bruker WM-400 spectrometer in δ ppm using TMS as standard. Mass spectra (EI-MS) were determined on Perkin Elmer (SCIEX API- 2000, ESI) at 12.5ev.

4.1. General procedure for the preparation of compounds 4a-j

An equimolar mixture of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (1mmol, 1eq) and thiosemicarbazide (1mmol, 1eq) with various carbonyl compounds (1 mL) on stirring at room temperature for about 10 min gave the solid. It was filtered and washed with cold methanol. The crude product recrystalized from ethanol.

4-Hydroxy-3-[2-(N'-isopropylidene-hydrazino)-thiazol-4-yl]-6-methyl-pyran-2-one (4a): Yield 92%; mp 182-184^{o}C, Color: light yellow; IR, υ, cm^{-1}: 1717(lactone C=O), 3251 (NH), 3370 (-OH). ^{1}H NMR (DMSO-d_6), δ, ppm: 1.96 (s, 6H, 2xCH$_3$), 2.23 (s, 3H, CH$_3$), 6.20 (s, 1H, pyran proton), 7.31 (s, 1H, thiazole), 11.11 (s, 1H, NH), 14.57 (s, 1H, OH). ^{13}C NMR (DMSO-d_6, δ ppm): 17.9 (CH$_3$), 19.3(CH$_3$), 24.7(CH$_3$), 93.8, 101.1, 103.3, 140.8, 152.9, 161.7, 162.0, 168.0, 168.6(C=O). ESI-MS 278 [M-H]$^{+}$. Anal. calcd. For $C_{12}H_{13}N_3O_3S$: C, 51.60; H, 4.69; N, 15.04, S, 11.48; Found: C, 51.5; H, 4.63; N,15.12; S, 11.52.

***4-Hydroxy-6-methyl-3-{2-[N'-(1-phenyl-ethylidene)-hydrazino]-thiazol-4-yl}-pyran-2-one (4b*)**: Yield 80%, mp 197-199^{o}C, Color: light yellow; IR, υ, cm^{-1}: 1731 (lactone C=O), 3247(NH), 3367(OH). ^{1}H NMR (DMSO-d_6), δ, ppm: δ 2.24 (s, 3H, CH$_3$), 2.35 (s, 3H, CH$_3$), 6.23 (s, 1H, pyran proton), 7.39-7.46 (m, 5H, ArH), 7.81 (s, 1H, thiazole), 11.57 (s, 1H, -NH), 14.50 (s, 1H, -OH). ^{13}C NMR (DMSO-d_6, δ ppm): 14.2(CH$_3$), 19.3(CH$_3$), 94.1, 101.1, 104.0, 125.8, 128.4, 129.1, 137.3, 142.2, 148.5, 161.5, 161.9, 168.2, 168.5(C=O). ESI-MS 340 [M-H]$^{+}$. Anal. calcd. For $C_{17}H_{15}N_3O_3S$: C, 59.81; H, 4.43; N, 12.31, S, 9.39; Found: C, 59.85; H, 4.40; N, 13.26; S, 9.34.

4-Hydroxy-6-methyl-3-{2-[N'-(1-p-tolyl-ethylidene)-hydrazino]-thiazol-4-yl}-pyran-2-one (4c): Yield 80%, mp 237-239^{o}C, Color: light yellow; IR , υ, cm^{-1}: 1727 (lactone C=O), 3248 (NH), 3377 (OH). ^{1}H NMR (DMSO-d_6), δ, ppm: 2.24 (s, 3H, CH$_3$), 2.32 (s, 3H, CH$_3$), 2.33 (s, 3H, CH$_3$), 6.22 (s, 1H, pyran proton), 7.25 (d, 2H, *J*=8.0Hz, ArH, part of AA'BB'), 7.41 (s, 1H, thiazole), 7.70 (d, 2H, *J*=8.4Hz, ArH, part of AA'BB'), 11.50 (s, 1H, -NH), 14.90 (s, 1H, -OH). ^{13}C NMR (DMSO-d_6, δ ppm): 14.2(CH$_3$), 19.3(CH$_3$), 20.8(CH$_3$), 93.9, 101.1, 104.0, 125.8, 129.0, 134.5, 138.8, 141.5, 148.9, 161.6, 161.9, 168.0, 168.5(C=O). ESI-MS 356 [M+H]$^{+}$. Anal. calcd. For $C_{18}H_{17}N_3O_3S$: C, 60.83; H, 4.82; N, 11.82, S, 9.02; Found: C, 60.78; H, 4.78; N, 11.76; S, 9.12.

4-Hydroxy-3-(2-{N'-[1-4-methoxy-phenyl)-ethylidene]-hydrazino}-thiazol-4-yl)-6-methyl-pyran-2-one (4d): Yield 82%, mp 232-234^{o}C, Color: light yellow; IR , υ, cm^{-1}: 1728 (lactone C=O), 3263 (NH), 3370 (OH). ^{1}H NMR (DMSO-d_6), δ, ppm: 2.24 (s, 3H, of CH$_3$), 2.31 (s, 3H, CH$_3$), 3.80 (s, 3H, OCH$_3$), 6.22 (s, 1H, pyran proton), 6.99 (d, 2H, *J*=8.8Hz, ArH), 7.40 (s, 1H, thiazole), 7.75 (d, 2H, *J*=8.8Hz, ArH), 11.47 (s, 1H, -NH), 14.87 (s, 1H, -OH). ^{13}C NMR (DMSO-d_6, δ ppm): 14.1(CH$_3$), 19.3(CH$_3$), 55.2(CH$_3$), 94.2, 101.1, 103.6, 113.8, 127.3, 129.8, 142.5, 148.3, 160.1, 161.5, 161.8, 168.3, 168.5(C=O). ESI-MS 372 [M+H]$^{+}$. Anal. calcd. For $C_{18}H_{17}N_3O_4S$: C, 58.21; H, 4.61; N, 11.31, S,8.63; Found: C, 58.26; H, 4.56; N, 11.34; S, 8.68.

3-[2-(N'-sec-Butylidene-hydrazino]-thiazol-4-yl]-4-hydroxy-6-methyl-pyran-2-one(4e): Yield 80%, mp 216-218^{o}C, Color: light yellow; IR, υ, cm^{-1}: 1721 (lactone C=O), 3261 (NH), 3392 (OH). ^{1}H NMR (DMSO-d_6), δ, ppm: 1.06 (t, 3H, *J*=7.6Hz, CH$_3$), 1.94 (s, 3H, CH$_3$), 2.23 (s, 3H, CH$_3$), 2.29 (q, 2H, *J*=7.6Hz, CH$_2$), 6.20 (s, 1H, pyran proton), 7.33 (s, 1H, thiazole), 11.22 (s, 1H, NH), 14.82 (s, 1H, OH). ^{13}C NMR (DMSO-d_6, δ ppm): 10.3(CH$_3$), 16.7(CH$_3$), 19.3(CH$_3$), 31.0(CH$_2$), 93.5, 101.0, 103.5, 139.7, 156.9, 161.8, 162.1, 168.0, 168.6(C=O). EI-MS 293 [M]$^{+}$. Anal. calcd. For $C_{13}H_{15}N_3O_3S$: C, 53.23; H, 5.15; N, 14.32, S, 10.93; Found: C, 53.18; H, 5.10; N, 14.27; S, 10.88.

3-[2-(N'-Cyclohexylidene-hydrazino]-thiazol-4-yl]-4-hydroxy-6-methyl-pyran-2-one (4f): Yield 81%, mp 256-258^{o}C, Color: light yellow; IR, υ, cm^{-1}: 1737 (lactone C=O), 3252 (NH), 3420 (OH). ^{1}H NMR (DMSO-d_6), δ, ppm: 1.60-1.63 (m, 6H, 3xCH$_2$ of cyclohexyl), 2.23 (s, 3H, CH$_3$), 2.27-2.29 (m,

2H, CH_2), 2.43-2.46 (m, 2H, CH_2 of cyclohexyl), 6.21 (s, 1H, pyran proton), 7.33 (s, 1H, thiazole), 11.50 (s, 1H, -NH), 14.77 (s, 1H, -OH). ^{13}C NMR (DMSO-d_6, δ ppm): 19.4(CH_3), 24.8(CH_2), 25.5(CH_2), 26.7(CH_2), 27.7(CH_2), 34.6(CH_2), 93.0, 100.9, 104.0, 137.9, 160.1, 162.0, 162.4, 167.7, 168.6(C=O). ESI-MS 320 $[M+H]^+$. Anal. calcd. For $C_{15}H_{17}N_3O_3S$: C, 56.41; H, 5.37; N, 13.16, S, 10.04; Found: C, 56.37; H, 5.32; N, 13.12; S, 10.12.

3-[2-(N'-Benzylidene-hydrazino]-thiazol-4-yl]-4-hydroxy-6-methyl-pyran-2-one (4g): Yield 77%, mp 227-229°C, Color: light yellow; IR, υ, cm^{-1}: 1728 (lactone C=O), 3217 (NH), 3431 (OH). ^{1}H NMR (DMSO-d_6), δ, ppm: 2.24 (s, 3H, CH_3), 6.22 (s, 1H, pyran proton), 7.41-7.47 (m, 6H, 5ArH, $1H_2$ thiazole), 8.08 (s, 1H, CH=N), 12.47 (s, 1H, -NH), 14.88 (s, 1H, -OH). ^{13}C NMR (DMSO-d_6, δ ppm): 16.3(CH_3), 99.9, 128.4, 128.5, 129.0, 129.1, 152.3, 156.5, 161.1, 162.1, 162.8, 163.9, 166.7, 168.2(C=O). ESI-MS 328 $[M+H]^+$. Anal. calcd. For $C_{16}H_{13}N_3O_3S$: C, 58.70; H, 4.00; N, 12.84, S, 9.80. Found: C, 58.65; H, 3.96; N, 12.80; S, 9.75.

4-Hydroxy-3-{2-[N'-(2-hydroxy-benzylidene)-hydrazino]-thiazol-4-yl}-6-methyl-pyran-2-one (4h): Yield 87%, mp 243-245°C, Color: light yellow; IR, υ, cm^{-1}: 1707 (lactone C=O), 3207 (NH), 3370 (OH). ^{1}H NMR (DMSO-d_6), δ, ppm: 2.24 (s, 3H, CH_3), 6.23 (s, 1H, pyran proton), 6.85-6.92 (m, 4H, ArH), 7.33 (s, 1H, thiazole), 8.06 (s, 1H, CH=N), 11.32 (s, 1H, -NH), 14.82 (s, 1H, -OH). ^{13}C NMR (DMSO-d_6, δ ppm): 19.8(CH_3), 94.9, 101.4, 104.0, 116.5, 116.6, 119.7, 120.2, 126.7, 131.5, 143.4, 156.6, 161.8, 162.4, 167.3, 168.8(C=O). ESI-MS 342 $[M-H]^+$. Anal. calcd. For $C_{16}H_{13}N_3O_4S$: C, 55.97; H, 3.82; N, 12.24; S, 9.34; Found: C, 55.93; H, 3.78; N, 12.20; S, 9.30.

4-Hydroxy-6-methyl-3-{2-[N'-(4-methyl-benzylidene)-hydrazino]-thiazol-4-yl}-pyran-2-one (4i): Yield 80%, mp 237-239°C, Color: light yellow; IR, υ, cm^{-1}: 1717 (lactone C=O), 3242 (NH), 3366 (OH). ^{1}H NMR (DMSO-d_6), δ, ppm: 2.24 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 6.22 (s, 1H, pyran proton), 7.26 (d, 2H, *J*=8.0Hz, ArH, part of AA'BB'), 7.41 (s, 1H, thiazole), 7.59 (d, 2H, *J*=8.0Hz, ArH, part of AA'BB'), 8.05 (s, 1H, CH=N), 12.42 (s, 1H, NH), 14.82 (s, 1H, OH). ^{13}C NMR (DMSO-d_6, δ ppm): 19.4(CH_3), 21.0(CH_3), 94.0, 104.0, 126.6, 129.4, 129.6, 131.1, 134.0, 139.7, 144.2, 161.5, 162.1, 167.0, 168.4(C=O). ESI-MS 342 $[M+H]^+$. Anal. calcd. For $C_{17}H_{15}N_3O_3S$: C, 59.81; H, 4.43; N, 12.31, S, 9.39; Found: C, 59.77; H, 4.40; N, 12.28; S, 9.35.

4-Hydroxy-3-{2-[N'-(4-methoxy-benzylidene)-hydrazino]-thiazol-4-yl}-6-methyl-pyran-2-one (4j): Yield 78%, mp 273-275°C, Color: light yellow; IR, υ, cm^{-1}: 1712 (lactone C=O), 3234 (NH), 3438 (OH). ^{1}H NMR (DMSO-d_6), δ, ppm: 2.24 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 6.21 (s, 1H, pyran proton), 7.13 (d, 2H, *J*=8.4Hz, ArH), 7.39 (s, 1H, thiazole), 7.64 (d, 2H, *J*=8.4Hz, ArH), 8.03 (s, 1H, CH=N), 11.22 (s, 1H, -NH), 14.82 (s, 1H, -OH). ^{13}C NMR (DMSO-d_6, δ ppm): 19.5(CH_3), 55.3(OCH_3), 99.5, 113.7, 114.4, 129.1, 130.4, 131.3, 160.7, 161.7, 162.2, 163.8, 163.9, 164.2, 170.1(C=O). ESI-MS 358 $[M+H]^+$. Anal. calcd. For $C_{17}H_{15}N_3O_4S$: C, 57.13; H, 4.23; N, 11.76, S, 8.97; Found: C, 57.10; H, 4.20; N, 11.71; S, 8.92.

4.2. General procedure for the preparation of compounds 6

An equimolar mixture of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (1mmol, 1eq) and thiosemicarbazide (1mmol, 1eq) with acetyl acetone (1 mL) on stirring at room temperature for about 10 min gave the solid. It was filtered and washed with cold methanol. The crude product recrystalized from ethanol.

4-Hydroxy-6-methyl-3-(2-(3,5-dimethyl-1H-pyrazol-1-yl)-2H-pyran-2-one (6): Yield 88%, mp 217-219°C, Color: light yellow; IR, υ, cm^{-1}: 1727 (lactone C=O), 3437 (OH). ^{1}H NMR (DMSO-d_6), δ, ppm: 2.22 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 6.20 (s, 2H, pyran proton and pyrazole proton), 7.95 (s, 1H, thiazole), 13.27 (s, 1H, -OH). EI-MS 303 $[M]^+$. Anal. calcd. For $C_{14}H_{13}N_3O_3S$: C, 55.43; H, 4.32; N, 13.85, S, 10.57; Found: C, 55.40; H, 4.28; N, 13.81; S, 10.52.

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