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Notes

Synthesis of substituted 3-(3-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)imidazo-[2,1-*b*]thiazol-6-yl)-2*H*-chromen-2-ones and substituted 4-hydroxy-6-methyl-3-(6-phenylimidazo[2,1-*b*]thiazol-3-yl)-2*H*-pyran-2-one derivatives

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An easy, highly efficient and a new convenient two-step approach to the synthesis of 3-(3-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)imidazo[2,1-*b*]thiazol-6-yl)-2*H*-chromen-2-one derivatives and 4-hydroxy-6-methyl-3-(6-phenylimidazo[2,1-*b*]thiazol-3-yl)-2*H*-pyran-2-one derivatives is described. These compounds have been synthesized from 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one, thiourea, various 3-(2-bromoacetyl)-2*H*-chromen-2-ones and phenacyl bromides in good yields. The structures of newly prepared compounds have been confirmed by their analytical and spectral data.

Keywords: Imidazo thiazole, 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one, 3-(2-aminothiazol-4-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one, thiourea, acetic acid

Dehydroacetic acid (DHA) is a good starting material for the synthesis of different heterocyclic compounds[1]. DHA is biologically active and studies have shown that it has both antibiotic and anti fungal effects[2]. The compound of dehydroacetic acid is widely used as fungicide[3].

Imidazo [2, 1-*b*] thiazole derivatives have been reported to display potential antitumor activities against a variety of human cancer cell lines[4-9]. Imidazo-[2,1-*b*]thiazole scaffolds are known to exhibit broad spectrum of pharmacological activities, such as antifungal[10-12], antibacterial[12-15], anti-inflammatory[16] and antihypertensive properties[17]. Imidazothiazole derivatives have been shown to display potent antitumor and fungi static activities[18-20]. An imidazothiazole derivative, levamisole (the levo isomer of tetramisole) is a broad spectrum anthelmintic, also possess immuno-modulating and immuno-stimulating properties[21]. We designed the synthesis of novel substituted imidazo-thiazole derivatives starting from bromo dehydro-acetic acid and thiourea.

Reaction of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one **1** with thiourea resulted in the formation of 3-(2-aminothiazol-4-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one **3**. Condensation of 3-(2-aminothiazol-4-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one **3** with various 3-(2-bromoacetyl)-2*H*-chromen-2-ones / 2-bromo-1-phenylethanones in acetic acid for 9hr resulted in the formation of title compounds of 3-(3-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)imidazo-[2,1-*b*]thiazol-6-yl)-2*H*-chromen-2-one derivatives **4**, and 4-hydroxy-6-methyl-3-(6-phenylimidazo[2,1-b]thi-azol-3-yl)-2*H*-pyran-2-one derivatives **5** (**Scheme I**).

The structures of the newly prepared compounds **3**, **4** and **5** have been confirmed by analytical and spectral data.

The compound **3** showed in its IR spectrum characteristic peak for OH at 3384 cm^{-1} and NH_2 at 3291 cm^{-1} and lactone carbonyl at 1715 cm^{-1} and C=N at 1606 cm^{-1}. In the ^1H NMR (DMSO-d_6) spectrum, the compound showed a characteristic singlet at δ 7.12 for thiazole proton and NH_2 appeared at δ 8.18. In the mass spectrum, the compound exhibited $[M + H]^+$ ion at *m/z* 225.

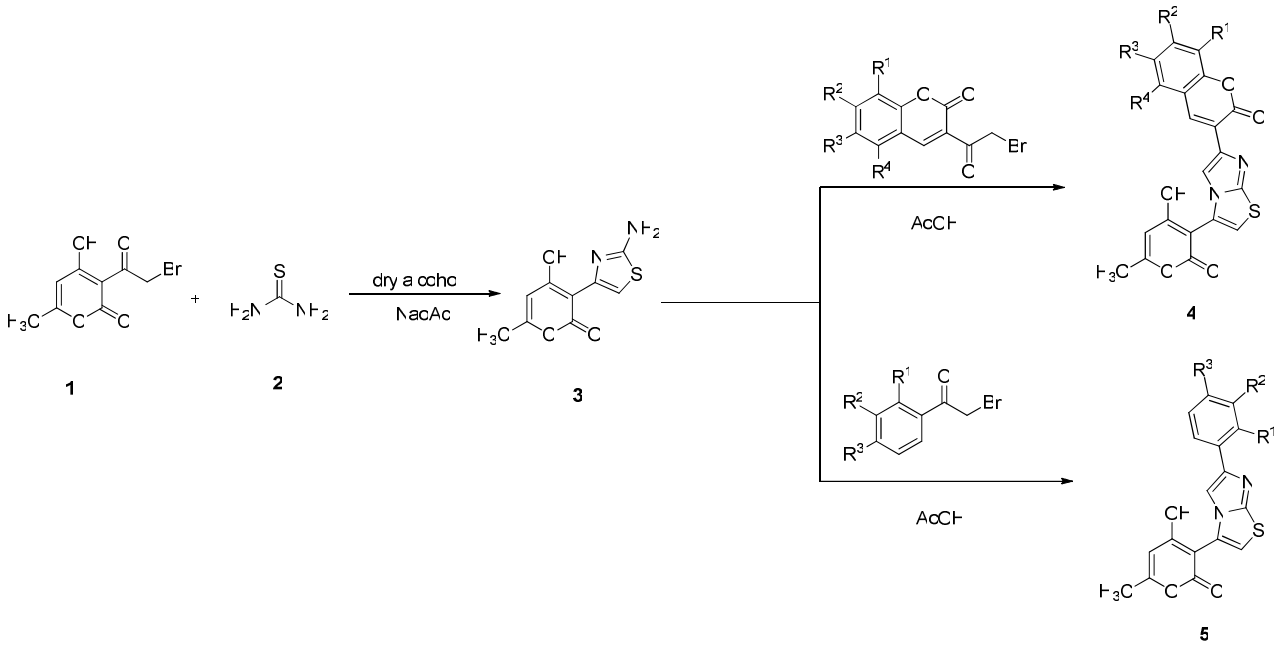
The compound **4a** showed in its IR spectrum characteristic peak for OH at 3440 cm^{-1} and pyran lactone carbonyl at 1721 cm^{-1} and chromen lactone carbonyl at 1708 cm^{-1} and C=N at 1601 cm^{-1}. In the ^1H NMR (DMSO-d_6) spectrum, the compound showed a characteristic singlet at δ 7.11 for thiazole proton, C_4-coumarin proton appeared at δ 8.68 and imidazole proton appeared at δ 8.46. In the mass spectrum, the compound exhibited $[M + H]^+$ ion at *m/z* 427.

Similarly the structures of the compounds **5** were confirmed by analytical and spectral data.

In conclusion, different substituted imidazo thiazole derivatives have been synthesized. This reaction proceeds smoothly in a good to excellent yields. In all cases, the products can be purified by simple recrystallization.

Experimental Section

All the reagents and solvents were pure, purchased from commercial sources and were used without any further purification unless otherwise stated. 3-(2-Bromoacetyl) - 4-hydroxy-6-methyl-2*H*-pyran-2-one[22] was prepared by literature procedure. Melting points



Compd	R^1	R^2	R^3	R^4
4a	Br	H	Br	H
4b	H	H	CH$_3$	H
4c	H	H	H	H
4d	5,6-benzo analogue of 4a			
4e	CH$_3$	H	CH$_3$	H

Compd	R^1	R^2	R^3
5a	H	H	CH$_3$
5b	H	H	CCH$_3$
5c	H	H	NO$_2$
5d	H	H	CH$_3$
5e	H	H	Br
5f	H	H	H
5g	CH$_3$	H	H

Scheme I — Synthesis of imidazo thiazole derivatives

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, Italy. 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 in spectrometer, Switzerland in δ ppm using TMS as standard. Mass spectra (EI-MS) were determined on (Liquid Chromatography Quadrupole) ion-trap mass spectrometer (Thermo Finnigan, San Jose, CA, USA).

General procedure for the synthesis of compound 3:

A mixture of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one **1** (1 mmol), thiourea **2** (1 mmol) and sodium acetate (1 mmol) was taken in 10 mL of dry alcohol. The reaction mixture was heated at 60°C for about 4 hr and then cooled to RT. The solid obtained was filtered, washed with water and purified by recrystallization from methanol.

3-(2-Aminothiazol-4-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one, 3. Colour: yellow solid; yield 90%. m.p. 267-69°C; IR (KBr): 3384 (OH), 3291 (NH_2), 1715 (O-C=O), 1606 cm^{-1} (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.21 (s, 3H, CH_3), 6.14 (s, 1H, pyran proton), 7.12 (s, 1H, thiazole proton), 8.18 (s, 2H, NH_2), 14.74 (s, 1H, OH); EI-MS: *m/z* 225 $(M+H)^+$. Anal. Calcd for $C_9H_8N_2O_3S$: C, 48.21; H, 3.60; N, 12.49. Found: C, 48.29; H, 3.68; N, 12.54%.

General procedure for preparation of compounds 4a-e and 5a-g

A mixture of 3-(2-aminothiazol-4-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one **3** (1 mmol), and various 3-(2-bromoacetyl)-2*H*-chromen-2-ones/ 2-bromo-1-phenylethanones (1 mmol) was taken in 10 mL of glacial acetic acid. The reaction mixture was heated at 80°C for about 9 hr, cooled to RT. The solid obtained was filtered, washed with water and purified by recrystallization from ethanol, to give the title compounds of the **4a-e** and **5a-g**.

6,8-Dibromo-3-(3-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)imidazo[2,1-*b*] thiazol-6-yl)-2*H*-chromen-2-one, 4a. Colour: yellow solid; Yield 85%; m.p. 201-203°C; IR: 3440 (OH), 1721 (O-C=O), 1708 (O-C=O), 1601 cm^{-1} (C=N); ^1H NMR (400 MHz, DMSO-d_6): δ 2.21 (s, 3H, CH_3), 6.13 (s, 1H, pyran proton), 7.11 (s, 1H, thiazole proton), 8.19-8.31 (m, 3H, 2H Ar-H, 1H C_4-coumarin), 8.76 (s, 1H, imidazole proton), 14.73 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.1, 99.5, 103.0, 120.0, 122.0, 124.9, 126.9, 128.7, 129.6, 131.0, 132.1, 133.9, 135.0, 136.7, 142.0, 151.1, 157.2, 161.5, 164.3, 193.0; EI-MS: *m/z* 552 $(M+H)^{+2}$. Anal. Calcd for $C_{20}H_{10}Br_2N_2O_5S$: C, 43.66; H, 1.83; N, 5.09. Found: C, 43.60; H, 1.89; N, 5.21%.

6-Chloro-3-(3-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)imidazo[2, 1-*b*]thiazol-6-yl)-2*H*-chromen-2-one, 4b. Colour: yellow solid; Yield 85%; m.p. 239-41°C; IR: 3437 (OH), 1723 (O-C=O), 1705 (O-C=O), 1607 cm^{-1} (C=N); ^1H NMR (400 MHz, DMSO-d_6): δ 2.20 (s, 3H, CH_3), 6.13 (s, 1H, pyran proton), 7.11 (s, 1H, thiazole proton), 7.44-7.51 (m, 3H, Ar-H), 8.46 (s, 1H, C_4-coumarin proton); 8.68 (s, 1H, imidazole proton); 12.45 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.2, 98.9, 104.4, 117.8, 119.3, 121.2, 124.9, 126.9, 127.8, 128.5, 130.0, 131.8, 133.2, 137.0, 148.2, 152.8, 157.2, 162.4, 164.9, 193.1; EI-MS: *m/z* 427 $(M+H)^+$. Anal. Calcd for $C_{20}H_{11}ClN_2O_5S$: C, 56.28; H, 2.60; N, 6.56. Found: C, 56.34; H, 2.68; N, 6.63%.

3-(3-(4-Hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-imidazo[2,1-b]thiazol-6-yl)-2*H*-chromen-2-one, 4c. Colour: yellow solid; Yield 80%; m.p. 279-81°C; IR: 3440 (OH), 1719 (O-C=O), 1703 (O-C=O), 1605 cm^{-1} (C=N); ^1H NMR (400 MHz, DMSO-d_6): δ 2.21 (s, 3H, CH_3), 6.13 (s, 1H, pyran proton), 7.13 (s, 1H, thiazole proton), 7.59-7.81 (m, 4H, Ar-H), 8.44 (s, 1H, C_4-coumarin proton), 8.68 (s, 1H, imidazole proton), 12.82 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.3, 97.7, 103.1, 112.5, 116.3, 119.2, 121.5, 126.9, 127.7, 128.0, 128.6, 131.8, 135.7, 139.8, 146.1, 153.7, 157.5, 163.0, 165.9, 192.0. Anal. Calcd for $C_{20}H_{12}N_2O_5S$: C, 61.22; H, 3.08; N, 7.14. Found: C, 61.26; H, 3.18; N, 7.19%.

2-(3-(4-Hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-imidazo[2, 1-*b*]thiazol-6-yl)-3*H*-benzo[*f*]chromen-3-one, 4d. Colour: yellow solid; Yield 80%; m.p. 209-11°C; IR: 3433 (OH), 1725 (O-C=O), 1708 (O-C=O), 1608 cm^{-1} (C=N); ^1H NMR (400 MHz, DMSO-d_6): δ 2.20 (s, 3H, CH_3), 6.12 (s, 1H, pyran proton), 7.10 (s, 1H, thiazole proton), 7.64-7.70 (m, 2H, Ar-H), 7.79-7.83 (m, 2H, Ar-H), 8.10-8.12 (m, 2H, Ar-H), 8.39 (s, 1H, C_4-coumarin proton), 8.69 (s, 1H, imidazole proton), 12.79 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.1, 99.8, 103.1, 115.4, 116.6, 118.1, 119.3, 120.5, 121.1, 124.0, 126.0, 128.2, 128.9, 130.6, 131.8, 133.1, 134.3, 136.0, 145.2, 151.0, 157.1, 161.6, 164.2, 193.1. Anal. Calcd for $C_{24}H_{14}N_2O_5S$: C, 65.15; H, 3.19; N, 6.33. Found: C, 65.08; H, 3.23; N, 6.26%.

6, 8-Dichloro-3-(3-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)imidazo[2,1-*b*]thiazol-6-yl)-2*H*-chromen-2-one, 4e. Colour: yellow solid; Yield 75%; m.p. 262-64°C; IR: 3437 (OH), 1718 (O-C=O), 1704 (O-C=O), 1604 cm^{-1} (C=N); ^1H NMR (400 MHz, DMSO-d_6): δ 2.20 (s, 3H, CH_3), 6.11 (s, 1H, pyran proton), 7.10 (s, 1H, thiazole proton), 7.61 (d, 1H, Ar-H), 7.93 (d, 1H, Ar-H), 8.46 (s, 1H, C_4-coumarin proton), 8.68 (s, 1H, imidazole proton), 12.41 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.1, 98.4, 103.8, 112.4, 116.2, 119.0, 121.7, 126.9, 127.9, 128.0, 128.9, 132.2, 136.0, 138.9, 146.3, 152.6, 158.8, 163.0, 166.0, 192.1. Anal. Calcd for $C_{20}H_{10}Cl_2N_2O_5S$: C, 52.08; H, 2.19; N, 6.07. Found: C, 52.18; H, 2.24; N, 6.18%.

3-(6-(4-Chlorophenyl)imidazo[2,1-*b*]thiazol-3-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one, 5a. Colour: yellow solid; Yield 85%; m.p. 277-79°C; IR: 3400 (OH), 1719 (O-C=O), 1605 cm^{-1} (C=N); ^1H NMR (400 MHz, DMSO-d_6): δ 2.21 (s, 3H, CH_3), 6.11 (s, 1H, pyran proton), 7.18 (s, 1H, thiazole proton), 7.67 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.78 (d, 2H, *J* = 8.0 Hz, Ar-H), 8.67 (s, 1H, imidazole proton), 12.39 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.1, 98.3, 101.0, 110.1, 120.9, 127.0, 127.9, 129.0, 133.9, 134.2, 138.6, 141.0, 157.2, 164.2, 188.2; EI-MS: *m/z* 359 $(M+H)^+$. Anal. Calcd for $C_{17}H_{11}ClN_2O_3S$: C, 56.91; H, 3.09; N, 7.81. Found: C, 56.84; H, 3.14; N, 7.89%.

4-Hydroxy-3 - (6-(4-methoxyphenyl)imidazo[2,1-*b*]thiazol-3-yl)-6-methyl-2*H*-pyran-2-one, 5b. Colour: yellow solid; Yield 80%; m.p. 272-74°C; IR: 3379 (OH), 1720 (O-C=O), 1600 cm^{-1} (C=N); ^1H NMR (400 MHz, DMSO-d_6): δ 2.20 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 6.19 (s, 1H, pyran proton), 7.02 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.22 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.29 (s, 1H, thiazole proton), 8.86 (s, 1H, imidazole proton); ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.1, 56.1, 98.8, 102.9, 110.7, 112.7, 116.1, 124.6, 128.4, 131.4, 136.1, 147.7, 156.5, 161.9, 163.4, 191.5; EI-MS: *m/z* 355 $(M+H)^+$. Anal. Calcd for $C_{18}H_{14}N_2O_4S$: C, 61.01; H, 3.98; N, 7.90. Found: C, 61.18; H, 3.90; N, 7.82%.

4-Hydroxy-6-methyl-3-(6-(4-nitrophenyl)imidazo-[2,1-*b*]thiazol-3-yl)-2*H*-pyran-2-one, 5c. Colour: yellow

solid; Yield 75%; m.p. 280-82°C; IR: 3389 (OH), 1724 (O-C=O), 1599 cm^{-1} (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.23 (s, 3H, CH_3), 6.17 (s, 1H, pyran proton), 7.22 (s, 1H, thiazole proton), 7.55 (d, 2H, *J* = 8.0 Hz, Ar-H), 8.19 (d, 2H, *J* = 8.4 Hz, Ar-H), 8.66 (s, 1H, imidazole proton), 12.33 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.0, 100.4, 101.1, 114.4, 124.2, 128.1, 129.2, 130.7, 135.2, 141.9, 149.2, 154.6, 162.3, 163.5, 191.4. Anal. Calcd for $C_{17}H_{11}N_3O_5S$: C, 55.28; H, 3.00; N, 11.38. Found: C, 55.21; H, 2.94; N, 11.44%.

4-Hydroxy-6-methyl-3-(6-(p-tolyl)imidazo[2,1-*b*]thiazol-3-yl)-2*H*-pyran-2-one, 5d. Colour: yellow solid; Yield 80%; m.p. 265-67°C; IR: 3439 (OH), 1715 (O-C=O), 1607 cm^{-1} (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.21 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 6.12 (s, 1H, pyran proton), 7.17-7.44 (m, 5H, 1H thiazole, 4H Ar-H), 8.68 (s, 1H, imidazole proton), 12.78 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.1, 24.2, 99.1, 103.0, 115.5, 121.0, 127.1, 128.0, 129.1, 132.2, 133.6, 137.0, 140.5, 161.7, 164.2, 193.2. Anal. Calcd for $C_{18}H_{14}N_2O_3S$: C, 63.89; H, 4.17; N, 8.28. Found: C, 63.81; H, 4.24; N, 8.34%.

3-(6-(4-Bromophenyl)imidazo[2,1-*b*]thiazol-3-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one, 5e. Color: yellow solid; Yield 85%; m.p. 270-72°C; IR: 3413 (OH), 1719 (O-C=O), 1606 cm^{-1} (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.20 (s, 3H, CH_3), 6.10 (s, 1H, pyran proton), 7.18 (s, 1H, thiazole proton), 7.80 (d, 2H, *J* = 7.2 Hz, Ar-H), 8.11 (d, 2H, *J* = 8.0 Hz, Ar-H), 8.67 (s, 1H, imidazole proton), 13.00 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.1, 99.6, 101.0, 112.3, 121.0, 121.6, 122.7, 130.6, 133.6, 134.3, 136.7, 142.0, 163.1, 164.9, 173.2. Anal. Calcd for $C_{17}H_{11}Br\ N_2O_3S$: C, 50.63; H, 2.75; N, 6.95. Found: C, 50.60; H, 2.81; N, 6.91%.

4-Hydroxy-6-methyl-3-(6-phenylimidazo[2, 1-*b*]-thiazol-3-yl)-2*H*-pyran-2-one, 5f. Colour: yellow solid; Yield 80%; m.p. 269-71°C; IR: 3398 (OH), 1717 (O-C=O), 1599 cm^{-1} (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.23 (s, 3H, CH_3), 6.20 (s, 1H, pyran proton), 6.87-6.92 (m, 2H, Ar-H), 7.22-7.27 (m, 4H, 1H thiazole, 3H Ar-H), 8.65 (s, 1H, imidazole proton), 12.38 (s, 1H, OH). Anal. Calcd for $C_{17}H_{12}\ N_2O_3S$: C, 62.95; H, 3.73; N, 8.64. Found: C, 62.99; H, 3.82; N, 8.56%.

3-(6-([1, 1'-Biphenyl]-4-yl)imidazo[2,1-*b*]thiazol-3-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one, 5g. Colour: yellow solid; Yield 78%; m.p. 258-60°C; IR: 3437 (OH), 1717 (O-C=O), 1604 cm^{-1} (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.23 (s, 3H, CH_3), 6.17 (s, 1H, pyran proton), 7.15 (s, 1H, thiazole proton), 7.44-7.78 (m, 5H, Ar-H), 7.86 (d, 2H, *J* = 8.4 Hz Ar-H), 8.09 (d, 2H, *J* = 8.4 Hz Ar-H), 8.68 (s, 1H, imidazole proton), 12.50 (s, 1H, OH). Anal. Calcd for $C_{23}H_{16}\ N_2O_3S$: C, 68.98; H, 4.03; N, 7.01. Found: C, 68.91; H, 4.18; N, 7.18%.

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