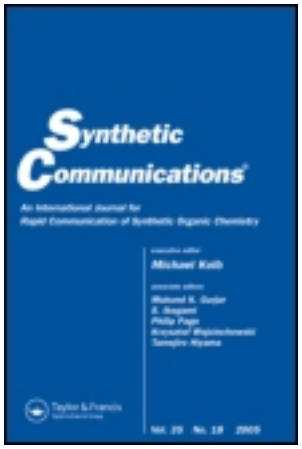

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New, Convenient, One-Pot Method for the Synthesis of Thiazolyl-pyrazolones from Dehydroacetic Acid Derivative via a Multicomponent Approach

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NEW, CONVENIENT, ONE-POT METHOD FOR THE SYNTHESIS OF THIAZOLYL-PYRAZOLONES FROM DEHYDROACETIC ACID DERIVATIVE VIA A MULTICOMPONENT APPROACH

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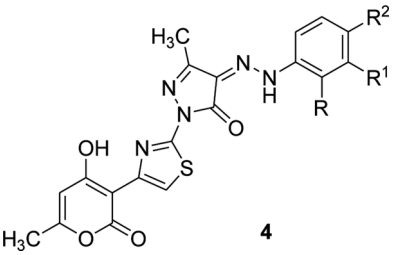
GRAPHICAL ABSTRACT



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Abstract *A convenient one-pot method for the synthesis of thiazolyl-pyrazolones was described in excellent yields. Reaction of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one with thiosemicarbazide and ethyl 2-(2-arylhydrazono)-3-oxobutanoates in anhydrous ethanol under reflux conditions afforded the corresponding 4-(2-arylhydrazono)-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 in good yields. The structures of newly synthesized compounds were established on the basis of elemental analysis, infrared,* ^1H *NMR, and mass spectroscopic studies.*

Keywords Aromatic primary amine; 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one; multicomponent reactions; one-pot synthesis; thiazolyl-pyrazolone; thiosemicarbazide

INTRODUCTION

Heterocycles are widely used in the development of modern pharmaceuticals. This is one of the reasons why continuous efforts are made toward the design of amenable synthetic approaches for the synthesis of new heterocyclic systems. The heterocyclic compounds thiazoles play a prominent role in nature as they are found in numerous biologically active compounds. Thiazole derivatives are exhibit significant biological activities such as antitubercular,[1] antifungal,[2] analgesic,[3] and anticancer activity.[4] Pyrazoles, as key substructures in a large variety of compounds with

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important medicinal and pesticidal properties, have attracted much attention.[5–7] Pyrazoles can be effectively utilized as antibacterial, antifungal, antiviral, antiparasitic, antitubercular, antidepressant, and insecticidal agents, and considerable attention has been focused on this class.[8–12] In addition, pyrazoles have played a crucial part in the development of heterocyclic chemistry and are also used extensively in organic synthesis.[13] 3-Acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one (dehydroacetic acid, DHA) is a versatile starting material, and its derivatives find wider application in the synthesis of heterocyclic compounds. [14–16]

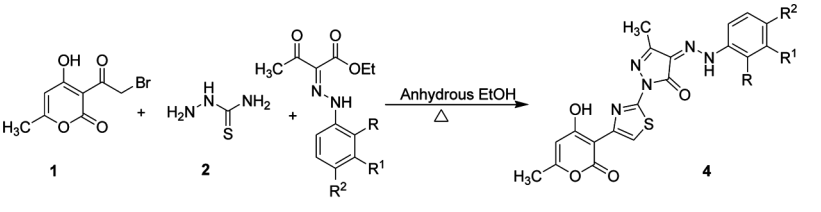
Multicomponent reactions (MCRs) are processes "in which more than two reactants directly get converted into their products by one-pot reaction."[17] MCRs play an important role in modern organic chemistry, because they generally exhibit great atom economy and selectivity as well as produce fewer by-products compared to classical multistep synthesis.[18] Further, in many cases, MCRs are easy to perform, inexpensive, and quick; consume less energy; and involve simple experimental procedures.[19] The first MCR was described in 1850 by Strecker,[20] and thereafter many such reactions have been reported in the literature.[21]

In view of the various biological activities of thiazoles and pyrazoles, our current studies are focused on the development of new routes for the synthesis of thiazolyl-pyrazolones with 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one. We have developed a one-pot, multicomponent reaction for the synthesis of substituted aryl hydrazono thiazolyl-pyrazolone derivatives. Hydrazono thiazolyl-pyrazolone derivatives were synthesized by Kalluraya et al.[22] in a stepwise manner. In this method, diazotization of ethyl acetoacetate with various aryldiazonium salts in the presence of sodium acetate in ethanol medium afforded the corresponding ethyl-2-arylhydrazono-3-oxobutyrates, which on reaction with thiosemicarbazide gave the respective thioamides. Reaction of these thioamides with 3-(2-bromoacetyl) coumarins in a dimethylformamide (DMF)–ethanol mixture gave the title products. However, this method has some limitations, such as harsh reaction conditions, and suffers from multistep synthesis, longer reaction times, and poor yields. Therefore there is still lack of a general, efficient, and one-pot method for the synthesis of substituted aryl hydrazono thiazolyl-pyrazolone.

RESULTS AND DISCUSSION

In continuation of our earlier work on the synthesis of different heterocyclic systems,[23–25] we report herein a facile, one-pot method for the synthesis of substituted phenyl hydrazono thiazolyl-pyrazolones from a three-component reaction. Reaction of an equimolar mixture of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (**1**), thiosemicarbazide (**2**), and ethyl 2-(2-phenylhydrazono)-3-oxobutanoate (**3**) under reflux in anhydrous ethanol gave the final products 4-(2-arylhydrazono)-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 (**4**) (Scheme 1).

In this reaction, a plausible mechanism for the formation of **4** can be proposed (Scheme 2). 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 *trans*-protonation proceeds to give 4-hydroxy thiazoline derivative (A). This subsequently undergoes dehydration to give 2-hydrazino thiazole



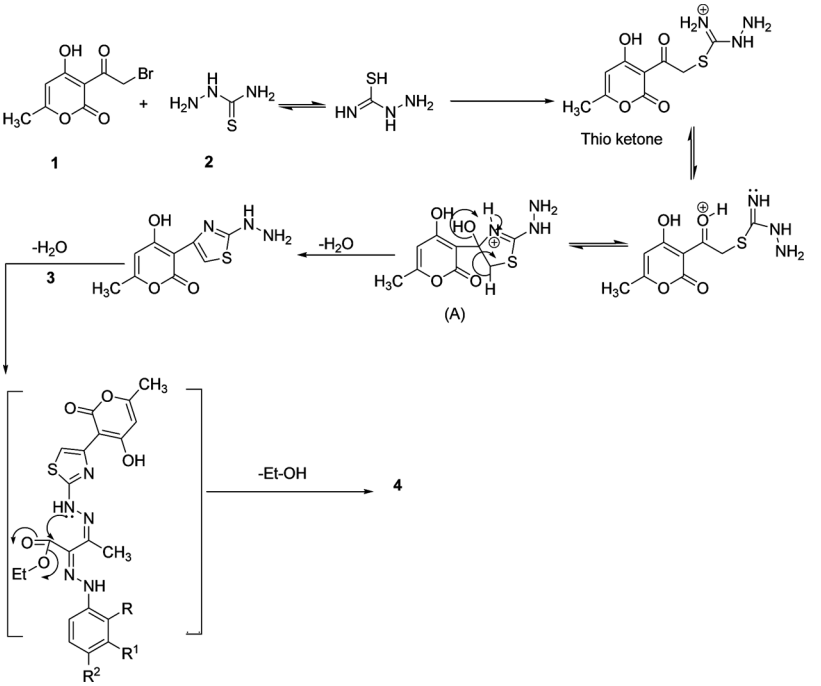
Compd	R	R^1	R^2
4 a	H	H	H
b	H	H	CH_3
c	CH_3	H	H
d	H	H	NO_2
e	H	NO_2	H
f	NO_2	H	H

Compd	R	R^1	R^2
g	OCH_3	H	H
h	H	OCH_3	H
i	H	H	OCH_3
j	H	H	Cl
k	COOH	H	H

Scheme 1. 4-(2-Arylhydrazono)-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.

derivative (in situ). This subsequently undergoes a condensation reaction with ethyl-2-(2-aryl hydrazono)-3-oxo butanoate to give final product **4**.

The structures of newly prepared compounds have been established on the basis of elemental analysis and spectral data. The IR spectrum of compound **4b** showed prominent peaks at 1676 cm^{-1} for –C=O of pyrazolone, at 1694 cm^{-1} for lactone carbonyl, at 3374 cm^{-1} for –NH, and 3407 cm^{-1} for -OH, whereas the ^1H NMR of



Scheme 2. Plausible mechanism.

compound **4b** showed characteristic singlets for -CH_3 groups at δ 2.26, 2.33, and 2.35. The –NH proton appeared as a broad singlet at δ 13.20, and the –OH proton appeared at δ 14.47. The remaining spectral data confirmed the newly prepared compounds' structures (**4a–k**).

In conclusion, a novel, facile, one-pot, multicomponent reaction for the synthesis of 4-(2-arylhydrazono)-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 is presented. The advantages of this methodology are speed, good yield, simplicity, practicality, low cost, readily available components, and easy workup.

EXPERIMENTAL

All the reagents and solvents were pure, purchased from commercial sources, and used without further purification unless otherwise stated. 3-(2-Bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one[26] and ethyl 2-(2-arylhydrazono)-3-oxobutanoates[27] were prepared by the 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 thin-layer chromatography (TLC) plates (E. Merck, Mumbai, India). IR spectra (KBr) were recorded on a Bruker WM-4(X) spectrometer (577 model). ^{1}H NMR spectra were recorded on a Bruker WM-400 spectrometer in δ ppm using tetramethylsilane (TMS) as standard. Mass spectra (EI-MS) were determined on a Perkin Elmer instrument (SCIEX API-2000, ESI) at 12.5 eV.

General Procedure for the Synthesis of Compounds 4a–k

Compound **1** (1 mmol), thiosemicarbazide (1 mmol), and ethyl 2-(2-arylhydrazono)-3-oxobutanoate (1.2 mmol) were in anhydrous ethanol (10 mL) and heated at 80–85 °C for 4 h. The product obtained was cooled, filtered, washed with water, and recrystallized from anhydrous ethanol.

4-(2-Phenylhydrazono)-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 (4a)

Orange-yellow solid; yield 86%; mp 287–289 °C; IR (KBr, υ_{max}): 1585 (-C=N), 1660 (-C=O, pyrazolone), 1700 (lactone -C=O), 3375 (-NH), 3420 (-OH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.26 (s, 3H, -CH_3 of pyrone ring), 2.36 (s, 3H, CH_3 of pyrazolone), 6.25 (s, C_5 of pyrone ring), 7.20–7.30 (m, 1H, -ArH), 7.40–7.50 (m, 2H, -ArH), 7.60–7.80 (m, 2H, -ArH), 7.90 (s, 1H, thiazole proton), 13.17 (s, 1H, -NH), 14.23 (s, 1H, -OH). HRMS mass, calculated 409.08, found 408.0656. Anal. calcd. for $C_{19}H_{15}N_5O_4S$: C, 55.74; H, 3.69; N, 17.11. Found: C, 55.70; H, 3.74; N, 17.17.

4-(2-p-Tolylhydrazono)-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 (4b)

Light yellow solid; yield 82%; mp 273–275 °C; IR (KBr, υ_{max}): 1596 (-C=N), 1676 (-C=O, pyrazolone), 1694 (lactone -C=O), 3374 (-NH), 3407 (-OH). ^{1}H NMR

(400 MHz, DMSO-d_6): δ 2.26 (s, 3H, -CH_3 of pyrone ring), 2.34 (s, 6H, CH_3 of pyrazolone and Ar-CH_3), 6.27 (s, C_5 of pyrone ring) 7.33 (d, 2H, $J = 8$ -ArH), 7.67 (d, 2H, $J = 8$ ArH), 7.90 (s, 1H, thiazole proton), 13.20 (s, 1H, -NH), 14.47 (s, 1H, -OH). EI-MS 423 $[M + H]^+$. Anal. calcd. for $C_{20}H_{17}N_5O_4S$: C, 56.73; H, 4.05; N, 16.54. Found: C, 56.79; H, 4.12; N, 16.59.

4-(2-o-Tolylhydrazono)-1-(4-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)thiazol-2-yl)-3-methyl-1*H*-pyrazol-5(4*H*)-one (4c)

Orange-yellow solid; yield 80%; mp > 300 °C; IR (KBr, υ_{max}): 1543 (-C=N), 1663 (-C=O, pyrazolone), 1714 (lactone -C=O), 3367 (-NH) and 3425 (-OH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.26 (s, 3H, -CH_3 of pyrone ring), 2.38 (s, 3H, Ar-CH_3) 2.43 (s, 3H, CH_3 of pyrazolone), 6.29 (s, C_5 of pyrone ring), 7.20–7-40 (m, 3H, -ArH), 7.70–7.80 (m, 1H, -ArH), 7.90 (s, 1H, thiazole proton), 13.17 (s, 1H, -NH). EI-MS 423 $[M + H]^+$. Anal. calcd. for $C_{20}H_{17}N_5O_4S$: C, 56.73; H, 4.05; N, 16.54. Found: C, 56.78; H, 4.16; N, 16.59.

4-(2-(4-Nitrophenylhydrazono)-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 (4d)

Orange-yellow solid; yield 83%; mp 282–284 °C; IR (KBr, υ_{max}): 1607 (-C=N), 1679 (-C=O, pyrazolone), 1701 (lactone -C=O), 3351 (-NH), 3397 (-OH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.26 (s, 3H, CH_3 of pyrone ring) 2.37 (s, 3H, CH_3 of pyrazolone), 6.28 (s, C_5 of pyrone ring), 7.85–8.00 (m, 3H, -ArH), 8.20–8.40 (m, 2H, -1ArH and 1 thiazole proton), 13.30 (s, 1H, -NH), 14.40 (s, 1H, -OH). EI-MS 454 $[M + H]^+$. Anal. calcd. for $C_{19}H_{14}N_6O_6S$: C, 50.22; H, 3.11; N, 18.49. Found: C, 50.28; H, 3.16; N, 18.54.

4-(2-(3-Nitrophenylhydrazono)-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 (4e)

Yellow solid; yield 81%; mp 271–273 °C; IR (KBr, υ_{max}): 1594 (-C=N), 1688 (-C=O, pyrazolone), 1708 (lactone -C=O), 3387 (-NH), 3398 (-OH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.33 (s, 3H, -CH_3 of pyrone ring), 2.42 (s, 3H, CH_3 of pyrazolone), 6.27 (s, C_5 of pyrone ring), 8.01–8.20 (m, 4H, -ArH), 8.51 (s, 1H, thiazole proton), 13.26 (s, 1H, -NH), 14.41 (s, 1H, -OH). EI-MS 454 $[M + H]^+$. Anal. calcd. for $C_{19}H_{14}N_6O_6S$: C, 50.22; H, 3.11; N, 18.49. Found: C, 50.26; H, 3.15; N, 18.54.

4-(2-(2-Nitrophenylhydrazono)-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 (4f)

Orange-yellow solid; yield 78%; mp 294–296 °C; IR (KBr, υ_{max}): 1577 (-C=N), 1678 (-C=O, pyrazolone), 1704 (lactone -C=O), 3395 (-NH), 3489 (-OH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.27 (s, 3H, -CH_3 of pyrone ring), 2.40 (s, 3H, CH_3 of pyrazolone), 6.23 (s, C_5 of pyrone ring), 7.43–7.50 (m, 1H, -ArH), 7.90–8.00 (m, 2H, -ArH), 8.10–8.20 (m, 1H, -ArH), 8.4 (s, 1H, thiazole proton), 14.23 (s, 1H, -NH),

14.28 (s, 1H, -OH). EI-MS 454 $[M + H]^+$. Anal. calcd. for $C_{19}H_{14}N_6O_6S$: C, 50.22; H, 3.11; N, 18.49. Found: C, 50.27; H, 3.15; N, 18.54.

4-(2-(2-Methoxyphenylhydrazono)-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 (4g)

Orange-yellow solid; yield 86%; mp > 300 °C; IR (KBr, υ_{max}): 1595 (-C=N), 1678 (-C=O, pyrazolone), 1704 (lactone -C=O), 3357 (-NH), 3460 (-OH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.26 (s, 3H, -CH_3 of pyrone ring), 2.33 (s, 3H, CH_3 of pyrazolone), 3.99 (s, 3H, -OCH_3), 6.29 (s, C_5 of pyrone ring), 7.03–7.20 (m, 2H, -ArH), 7.70–7.80 (m, 2H, -ArH), 7.9 (s, 1H, thiazole proton), 13.20 (s, 1H, -NH), 14.34 (s, 1H, -OH). EI-MS 439 $[M + H]^+$. Anal. calcd. for $C_{20}H_{17}N_5O_5S$: C, 54.66; H, 3.90; N, 15.94. Found: C, 54.69; H, 3.96; N, 15.98.

4-(2-(3-Methoxyphenylhydrazono)-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 (4h)

Orange-yellow solid; yield 76%; mp > 300 °C; IR (KBr, υ_{max}): 1595 (-C=N), 1678 (-C=O, pyrazolone), 1704 (lactone -C=O), 3377 (-NH), 3411 (-OH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.28 (s, 3H, -CH_3 of pyrone ring), 2.41 (s, 3H, CH_3 of pyrazolone), 3.87 (s, 3H, -OCH_3), 6.02 (s, C_5 of pyrone ring), 6.82 (d, 1H, $J = 8$ Hz, ArH), 7.02 (d, 2H, $J = 8$ Hz, -ArH), 7.32 (t, 1H, $J = 8$ Hz, -ArH), 7.96 (s, 1H, thiazole proton), 13.22 (s, 1H, -NH), 14.39 (s, 1H, -OH). EI-MS 439 $[M + H]^+$. Anal. calcd. for $C_{20}H_{17}N_5O_5S$: C, 54.66; H, 3.90; N, 15.94. Found: C, 54.69; H, 3.95; N, 15.91.

4-(2-(4-Methoxyphenylhydrazono)-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 (4i)

Orange-yellow solid; yield 80%; mp > 300 °C; IR (KBr, υ_{max}): 1595 (-C=N), 1678 (-C=O, pyrazolone), 1707 (lactone -C=O), 3367 (-NH), 3417 (-OH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.26 (s, 3H, -CH_3 of pyrone ring), 2.38 (s, 3H, CH_3 of pyrazolone), 3.79 (s, 3H, -OCH_3), 6.27 (s, C_5 of pyrone ring), 6.90–7.10 (m, 3H, -ArH), 7.60–7.80 (m, 2H, 1-ArH and 1H of thiazole). EI-MS 439 $[M + H]^+$. Anal. calcd. for $C_{20}H_{17}N_5O_5S$: C, 54.66; H, 3.90; N, 15.94. Found: C, 54.61; H, 3.96; N, 15.98.

4-(2-(4-Chlorophenylhydrazono)-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 (4j)

Orange-yellow solid; yield 87%; mp 290–293 °C; IR (KBr, υ_{max}): 1557 (-C=N), 1696 (-C=O, pyrazolone), 1702 (lactone -C=O), 3390 (-NH), 3407 (-OH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.26 (s, 3H, -CH_3 of pyrone ring), 2.35 (s, 3H, CH_3 of pyrazolone), 6.28 (s, 1H, C_5 of pyrone ring), 7.06 (d, 2H, -ArH), 7.07 (d, 2H, -ArH), 7.90 (s, 1H, thiazole proton), 13.07 (s, 1H, -NH), 14.38 (s, 1H, -OH). EI-MS 443 $[M + H]^+$. HRMS mass calculated 443.05; found, 444.0527. Anal. calcd. for $C_{19}H_{14}ClN_5O_4S$: C, 51.41; H, 3.18; N, 15.78. Found: C, 54.69; H, 3.94; N, 15.99.

2-(*N*′{1-[4-(4-Hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)thiazol-2-yl)-3-methyl-5-oxo-1,5-dihydro-pyrazol-4-ylidene}-hydrazino)-benzoic Acid (4k)

Orange-yellow solid; yield 81%; mp > 300 °C; IR (KBr, υ_{max}): 1590 (-C=N), 1677 (-C=O, pyrazolone), 1710 (lactone -C=O), 3357 (-NH), 3421 (-OH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.25 (s, 3H, -CH_3 of pyrone ring), 2.37 (s, 3H, CH_3 of pyrazolone), 6.26 (s, C_5 of pyrone ring), 7.25 (d, 1H, $J = 8$ Hz, ArH), 7.60–7.70 (m, 2H, -ArH), 7.90–8.10 (m, 2H, 1-ArH and 1H of thiazole), 14.52 (s, 1H, -NH), 14.73 (s, 1H, -COOH), 15.06 (s, 1H, -OH). EI-MS 453 $[M + H]^+$. Anal. calcd. for $C_{20}H_{15}N_5O_6S$: C, 52.98; H, 3.33; N, 15.45. Found: C, 15.95; H, 3.39; N 15.49.

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