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A facile one-pot synthesis of 1,3,4-thiadiazine-5-yl-pyran-2-one derivatives via a multicomponent reaction

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A facile one-pot synthesis of 1,3,4-thiadiazine-5-yl-pyran-2-one derivatives via a multicomponent reaction

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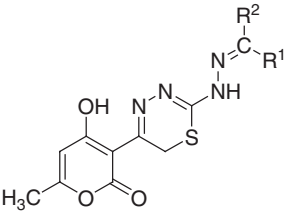
A facile synthesis of 1,3,4-thiadiazine-5-yl-pyran-2-one derivatives is achieved via a three-component reaction involving 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one, thiocarbohydrazide with various carbonyl compounds in one-pot under stirring. The main advantage of this procedure is the short reaction time, high yields, simple workup, and purification of products by non-chromatographic methods, *i.e.* by simple recrystallization from ethanol. The structures of newly prepared compounds have been established by elemental analysis and spectral data.



Keywords: 1,3,4-thiadiazine; 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one; thiocarbohydrazide; one-pot; multicomponent reactions

1. Introduction

Over the past several years, chemists have been aware of the environmental implications of their chemistry. Nowadays, they are trying to develop new synthetic methods, reaction conditions, and use of chemicals that reduce risks to humans and the environment. A multicomponent reaction (MCR), offering a straightforward route to generate complexity and diversity in a single operation, is an extremely powerful tool in combinatorial chemistry and drug discovery. However, if the one-pot MCRs could be carried out under solvent- and catalyst-free conditions, it would be most efficient synthetic methods of organic synthesis. MCRs are processes 'in which more than two educts directly get converted into their products by one-pot reaction'. MCRs play an important role in modern organic chemistry, because they generally exhibit higher atom economy and selectivity

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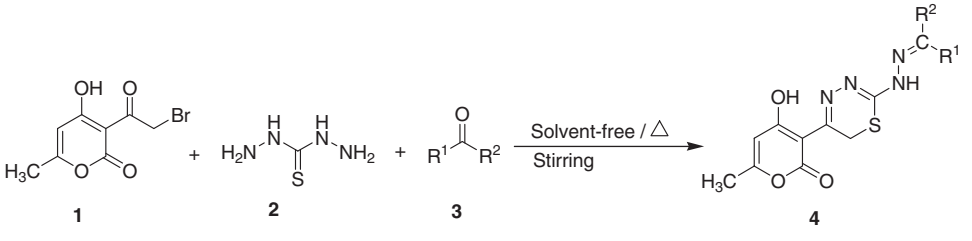
as well as produce fewer by-products compared with classical multistep synthesis. Further, in many cases, MCRs are easy to perform, inexpensive, and quick, consume less energy, and involve simple experimental procedures (*1–3*).

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 (*4–6*). Some 4-hydroxy-2-pyrans have also been tested as anticoagulant agents (*7*). 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 1,3,4-thiadiazines are biologically active compounds, many of these derivatives are used for cardiotonic and hypertensive activities (*8, 9*) and can be used for treatment of tumors and acquired immunodeficiency syndrome (*10*). A survey of literature reveals that much work remains to be done with 1,3,4-thiadiazines. Some heteroaryl-1,3,4-thiadiazines have been reported in the literature starting from phenacyl bromide or chloroacetic acid and pyrazolyl-1-thiocarbonylhydrazide (*11*). Schiff bases form a significant class of compounds in medicinal and pharmaceutical chemistry with several biological applications that include antibacterial, antifungal, and antitumor activity (*12–18*). Moreover, much interest has been focused on the biological activity of 1,3,4-thiadiazine derivatives. So we describe an efficient, solvent-free, one-pot method for the title compounds (Scheme 1).



4	R^1	R^2
(a)	H	p-Tolyl
(b)	H	p-Anisyl
(c)	H	o-Hydroxy phenyl
(d)	H	Phenyl
(e)	Me	Me

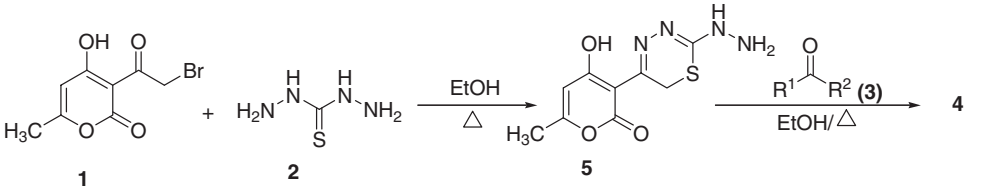
4	R^1	R^2
(f)	Me	Ph
(g)	Me	p-Tolyl
(h)	Me	p-Anisyl
(i)	Me	p-Chloro phenyl
(j)	Me	Et
(k)	$R^1 = R^2$ = Cyclohexylidene	

Scheme 1. One-pot and solvent-free synthesis of 1,3,4-thiadiazine-5-yl-pyran-2-one derivatives via three-component reaction.

2. Results and discussion

In continuation of our earlier work on the development of useful new synthetic methodologies (*19–24*), we observed that an equimolar mixture of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one, thiocarbohydrazide, and various carbonyl compounds on stirring at room temperature for a period of 30 min, followed by stirring at 50–60 °C for about 1 h resulted in the formation of the title compounds. The reaction path for the formations of products can be explained by the S-acylation of thiocarbohydrazide with **1**, followed by intramolecular cyclization to give pyran substituted 2-hydrazino-6H-1,3,4-thiadiazines. These underwent further condensation with carbonyl compounds to give the Schiff bases **4a**–**k** (Scheme 2).

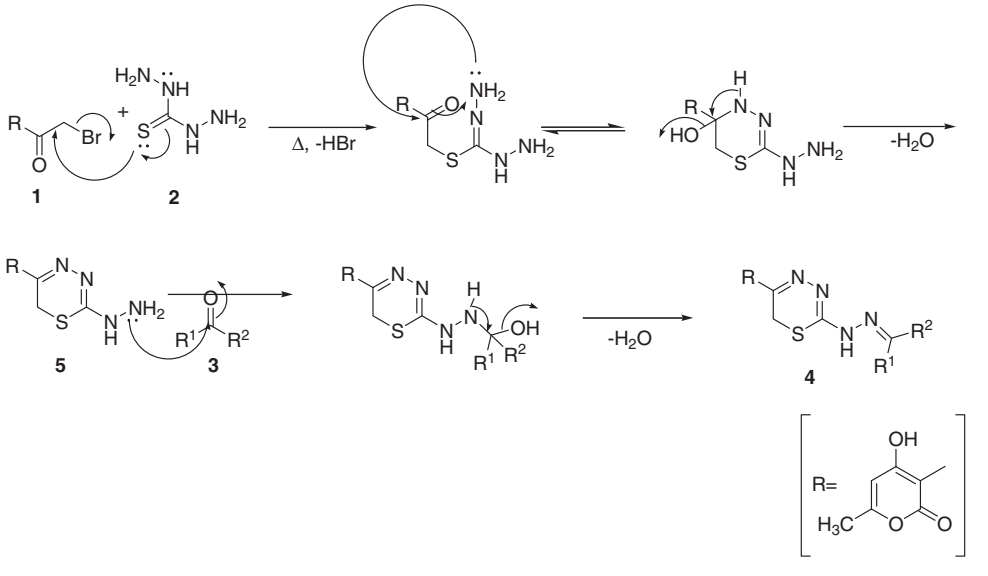
All the structures of newly synthesized compounds have been confirmed by their spectral data. The ^{1}H NMR spectrum of compound **4a** shows prominent peaks for –pyran CH_3 at δ 2.13, Ar$-CH_3$ at δ 2.33, CH_2 of thiadiazine at δ 4.65 and C-4 proton of pyran at δ 5.87. The ^{13}C NMR



Scheme 2. Two-step synthesis of 1,3,4-thiadiazine-5-yl-pyran-2-one derivatives.

spectrum of **4a** also shows the peaks at δ 19.9, 21.7, 107.1, and 163.4 for pyran methyl, CH_2 of thiadiazine, C-4 of pyran, and C=O of pyran, respectively. The remaining protons and carbons were observed in the expected region. All the above spectral data clearly indicates the formation of the title products.

The structures of final products were also confirmed by synthesizing **4a** unambiguously. Reaction of equimolar mixture of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one, (1 mmol), thiocarbohydrazide (1 mmol) in ethanol gave 3-(2-hydrazino-6*H*-[1,3,4]thiadiazin-5-yl)-4-hydroxy-6-methyl-pyran-2-one **5**. This on reaction with **3** in ethanol gave the corresponding Schiff base **4a**. A plausible mechanism of formation of these compounds is presented in Scheme 3. The products obtained by both methods were found to be identical by mixed melting point measurements, Co-TLC and spectral data.



Scheme 3. Plausible mechanism.

3. Conclusion

We have developed a facile multicomponent and one-pot synthesis for the title compounds using readily available starting materials without application of any catalyst. When compared with the classical reaction conditions, these new synthetic methods have various advantages, such as good yields, shorter reaction time, inexpensive, and easy workup. These new derivatives may be beneficially utilized in drug research.

4. Experimental

4.1. *General*

All the reagents and solvents were pure, 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 (*25*) was prepared by a 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 Bruker WM-4(X) spectrometer (577 models). ^{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 12.5 ev.

4.2. *General procedure for the synthesis of compounds 4a–k*

3-(2-Bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one, (1 mmol), thiocarbohydrazide (1 mmol) and 1 ml of **3** were taken in a round bottom flask and stirred at room temperature for about 30 min. Then the reaction mixture was heated for about 1 h at 50–60 °C, cooled to room temperature, the solid separated was filtered, washed with cooled methanol, and recrystallized from ethanol to give yellow solids.

4.2.1. *4-Hydroxy-6-methyl-3-{2-[N′-(4-methyl-benzylidene)-hydrazino]-6H-[1,3,4]thiadiazin-5-yl}-pyran-2-one (**4a**)*

Color: yellow solid; yield 95%; mp. 247–248 °C; IR (KBr, υ max, cm^{-1}): 1602 (C=N), 1693 (C=O), 3174 (NH), 3311 (OH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.13 (s, 3H, pyran CH_3), 2.33 (s, 3H, ArCH_3), 4.65 (s, 2H, $-CH_2$ of thiadiazine), 5.87 (s, 1H, C-4 of pyran), 7.25 (d, 2H, J = 8.0 Hz, ArH), 7.55 (d, 2H, J = 8.0 Hz, ArH), 8.07 (s, 1H, =CH−Ar), 12.17 (s, 1H, −NH, D_2O, exchangeable), 15.64 (s, 1H, OH); ^{13}C NMR (DMSO-d_6, δ ppm): 19.4, 21.7, 22.5, 92.1, 107.1, 127.3, 128.2, 130.1, 131.9, 140.4, 145.5, 151.6, 154.7, 163.2, 163.4. Anal. calcd. for $C_{17}H_{16}N_4O_3S$: C, 57.29; H, 4.52; N, 15.72. Found: C, 57.21; H, 4.46; N, 15.66.

4.2.2. *4-Hydroxy-3-{2-[N′-(4-methoxy-benzylidene)-hydrazino]-6H-[1,3,4]thiadiazin-5-yl}-6-methyl-pyran-2-one (**4b**)*

Color: yellow solid; yield 84%; mp. 252–254 °C; IR (KBr, υ_{max}, cm^{-1}): 1608 (C=N), 1685 (C=O), 3176 (NH), 3311 (OH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.13 (s, 3H, pyran CH_3), 3.79 (s, 3H, OCH_3), 4.65 (s, 2H, $-CH_2$ of thiadiazine), 5.85 (s, 1H, C-4 of pyran), 7.00 (d, 2H, J = 8.0 Hz, ArH), 7.60 (d, 2H, J = 8.0 Hz, ArH), 8.05 (s, 1H, =CH−Ar), 12.10 (s, 1H, −NH, D_2O, exchangeable), 15.69 (s, 1H, OH); ^{13}C NMR (DMSO-d_6, δ ppm): 19.2, 21.8, 55.2, 91.2, 106.6, 114.3, 126.5, 128.2, 144.1, 154.0, 158.6, 160.6, 162.5, 162.6. Anal. calcd. for $C_{17}H_{16}N_4O_4S$: C, 54.83; H, 4.33; N, 15.04. Found: C, 54.80; H, 4.29; N, 14.96.

4.2.3. *4-Hydroxy-3-{2-[N′-(2-hydroxy-benzylidene)-hydrazino]-6H-[1,3,4]thiadiazin-5-yl}-6-methyl-pyran-2-one (**4c**)*

Color: yellow solid; yield 87%; mp. 296–298 °C; IR (KBr, υ_{max}, cm^{-1}): 1604 (C=N), 1683 (C=O), 3189 (NH), 3376 (OH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.15 (s, 3H, pyran CH_3),

4.65 (s, 2H, $-CH_2$ of thiadiazine), 5.91 (s, 1H, C-4 of pyran), 7.32–7.62 (m, 4H, ArH), 7.87 (s, 1H, =CH−Ar), 11.57 (s, 1H, −NH, D_2O, exchangeable). ^{13}C NMR (DMSO-d_6, δ ppm): 19.5, 92.7, 99.8, 102.5, 116.2, 119.5, 128.8, 129.9, 131.4, 132.3, 154.7, 157.3, 162.3, 163.2, 163.8, 169.1. Anal. calcd. for $C_{16}H_{14}N_4O_4S$: C, 53.62; H, 3.94; N, 15.63. Found: C, 53.58; H, 3.90; N, 15.59.

4.2.4. *3-[2-(N′-Benzylidene)-hydrazino)-6H-[1,3,4]thiadiazin-5-yl]-4-hydroxy-6-methyl-pyran-2-one (**4d**)*

Color: yellow solid; yield 85%; mp. >300 °C; IR (KBr, υ_{max}, cm^{-1}): 1610 (C=N), 1689 (C=O), 3169 (NH), 3407 (OH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.13 (s, 3H, pyran CH_3), 4.65 (s, 2H, $-CH_2$ of thiadiazine), 5.87 (s, 1H, C-4 of pyran), 7.40–7.72 (m, 5H, ArH), 8.07 (s, 1H, =CH−Ar) 11.10 (s, 1H, −NH, D_2O, exchangeable), 15.64 (s, 1H, OH); ^{13}C NMR (DMSO-d_6, δ ppm): 19.2, 21.8, 106.5,126.6, 127.3, 128.7, 128.8, 129.8, 130.0, 133.9, 144.5, 154.1, 162.8, 174.8. Anal. calcd. for $C_{16}H_{14}N_4O_3S$: C, 56.13; H, 4.12; N, 16.36. Found: C, 56.09; H, 4.10; N, 16.31.

4.2.5. *4-Hydroxy-3-[2-(N′-(isopropylidene)-hydrazino]-6H-[1,3,4]thiadiazin-5-yl]-6-methyl-pyran-2-one (**4e**)*

Color: yellow solid; yield 92%; mp. 202–206 °C; IR (KBr, υ_{max}, cm^{-1}): 1610 (C=N), 1689 (C=O), 3165 (NH), 3327 (OH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.93 (s, 3H, pyran CH_3), 2.13 (s, 6H, $2CH_3$), 4.54 (s, 2H, $-CH_2$ of thiadiazine), 5.87 (s, 1H, C-4 of pyran), 11.10 (s, 1H, −NH, D_2O, exchangeable), 15.64 (s, 1H, OH); ^{13}C NMR (DMSO-d_6, δ ppm): 16.5, 19.9, 21.7, 22.5, 92.1, 107.1, 151.6, 154.7, 161.2, 163.4, 167.0, 182.7. ESI-MS 295 $[M+H]^+$; Anal. calcd. for $C_{12}H_{14}N_4O_3S$: C, 48.97; H, 4.79; N, 19.04. Found: C, 48.91; H, 4.71; N, 19.94.

4.2.6. *4-Hydroxy-6-methyl-3-[2-[N′-(1-phenyl-ethylidene)-hydrazino]-6H-[1,3,4]thiadiazin-5-yl}-pyran-2-one (**4f**)*

Color: yellow solid; yield 90%; mp. 286–288 °C; IR (KBr, υ_{max}, cm^{-1}): 1610 (C=N), 1685 (C=O), 3159 (NH), 3325 (OH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.15 (s, 3H, pyran CH_3), 2.32 (s, 3H, =C−CH_3, 4.64 (s, 2H, $-CH_2$ of thiadiazine), 5.90 (s, 1H, C-4 of pyran), 7.40–7.42 (m, 5H, ArH) 11.50 (s, 1H, −NH, D_2O, exchangeable). ^{13}C NMR (DMSO-d_6, δ ppm): 16.9, 19.8, 22.5, 91.5, 107.1, 121.5, 127.4, 128.2, 130.1, 131.9, 150.8, 153.7, 161.5, 165.0, 170.6. Anal. calcd. for $C_{17}H_{16}N_4O_3S$: C, 57.29; H, 4.52; N, 15.72. Found: C, 57.22; H, 4.49; N, 15.68.

4.2.7. *4-Hydroxy-6-methyl-3-{2-[N′-(1-p-tolyl-ethylidene)-hydrazino]-6H-[1,3,4]thiadiazin-5-yl}-pyran-2-one (**4g**)*

Color: yellow solid; yield 89%; mp. 272–274 °C; IR (KBr, υ_{max}, cm^{-1}): 1617 (C=N), 1690 (C=O), 3177 (NH), 3378 (OH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.26 (s, 3H, pyran CH_3), 2.33 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 4.57, (s, 2H, $-CH_2$ of thiadiazine), 6.20 (s, 1H, C-4 of pyran), 7.26 (d, 2H, J = 8.0 Hz, ArH), 7.74 (d, 2H, J = 8.0 Hz, ArH). ^{13}C NMR (DMSO-d_6, δ ppm): 14.1, 19.5, 20.8, 22.4, 100.0, 125.7, 125.8, 126.1, 128.2, 128.9, 129.0, 129.1, 162.5, 162.9, 163.8, 167.4. Anal. calcd. for $C_{18}H_{18}N_4O_3S$: C, 58.36; H, 4.90; N, 15.12. Found: C, 58.31; H, 4.87; N, 15.10.

4.2.8. *4-Hydroxy-3-[2-{N′-[1-(4-methoxy-phenyl)-ethylidene]-hydrazino}-6H-[1,3,4]thiadiazin-5-yl}-6-methyl-pyran-2-one (**4h**)*

Color: yellow solid; yield 92%; mp. 212–214 °C; IR (KBr, υ_{max}, cm^{-1}): 1602 (C=N), 1689 (C=O), 3150 (NH), 3347 (OH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.28 (s, 3H, pyran CH_3), 2.41 (s, 3H, =C−CH_3), 3.84 (s, 3H, −OCH_3), 4.55 (s, 2H, −CH_2 of thiadiazine), 6.17 (s, 1H, C-4 of pyran), 6.97 (d, 2H, J = 8.8 Hz, ArH), 7.73 (d, 2H, J = 8.8 Hz, ArH), 11.50 (s, 1H, −NH, D_2O, exchangeable);^{13}C NMR (DMSO-d_6, δ ppm): 14.0, 19.5, 26.3, 55.2, 100.1, 113.8, 127.4, 127.7, 130.4, 160.2, 160.5, 162.6, 163.0, 163.6, 167.0, 169.4. Anal. calcd. for $C_{18}H_{18}N_4O_4S$: C, 55.95; H, 4.70; N, 14.50. Found: C, 55.91; H, 4.66; N, 14.47.

4.2.9. *3-(2-{N′-[1-(4-Chloro-phenyl)-ethylidene]-hydrazino}-6H-[1,3,4]thiadiazin-5-yl}-4-hydroxy-6-methyl-pyran-2-one (**4i**)*

Color: yellow solid; yield 87%; mp. 188–190 °C; IR (KBr, υ_{max}, cm^{-1}): 1600 (C=N), 1687 (C=O), 3157 (NH), 3324 (OH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.15 (s, 3H, pyran CH_3), 2.30 (s, 3H, =C−CH_3), 4.56 (s, 2H, −CH_2 of thiadiazine), 5.93 (s, 1H, C-4 of pyran), 7.50 (d, 2H, J = 8.0 Hz, ArH), 7.79 (d, 2H, J = 8.0 Hz, ArH). ^{13}C NMR (DMSO-d_6, δ ppm): 19.0, 21.1, 22.2, 91.0, 108.0, 127.6, 127.7, 128.5, 133.7, 133.9, 136.6, 151.9, 153.2, 162.5, 168.9. Anal. calcd. for $C_{17}H_{15}ClN_4O_3S$: C, 52.24; H, 3.87; N, 14.33. Found: C, 52.20; H, 3.84; N, 14.30.

4.2.10. *3-(2-{N′-(sec-Butylidene-hydrazino)-6H-[1,3,4]thiadiazin-5-yl]-4-hydroxy-6-methyl-pyran-2-one (**4j**)*

Color: yellow solid; yield 89%; mp. 217–219 °C; IR (KBr, υ_{max}, cm^{-1}): 1617 (C=N), 1689 (C=O), 3189 (NH), 3364 (OH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.06 (t, 3H, J = 8 Hz, −CH_3), 1.94 (s, 3H, of CH_3 of pyran ring), 2.23 (s, 3H, −N=C−CH_3), 2.29 (q, 2H, J = 8 Hz, −N=C−CH_2), 4.65 (s, 2H, −CH_2 of thiadiazine), 6.18 (s, 1H, C-4 of pyran), 11.17 (s, 1H, −NH, D_2O, exchangeable). ^{13}C NMR (DMSO-d_6, δ ppm):14.5, 19.3, 24.9, 25.4, 26.7, 97.2, 102.7, 154.1, 159.7, 161.0, 162.9, 164.7, 168.6. Anal. calcd. for $C_{13}H_{16}N_4O_3S$: C, 50.64; H, 5.23; N, 18.17. Found: C, 50.60; H, 5.20; N, 18.13.

4.2.11. *3-[2-(N′-Cyclohexylidene-hydrazino)-6H-[1,3,4]thiadiazin-5-yl]-4-hydroxy-6-methyl-pyran-2-one (**4k**)*

Color: yellow solid; yield 86%; mp. 278–280 °C; IR (KBr, υ_{max}, cm^{-1}): 1619 (C=N), 1685 (C=O), 3163 (NH), 3375 (OH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.60–1.63 (m, 6H, −3CH_2 of cyclohexyl), 2.23 (s, 3H, CH_3 of pyran ring), 2.27–2.29 (m, 2H, CH_2 of cyclohexyl), 2.43–2.46 (m, 2H, CH_2 of cyclohexyl), 4.65 (s, 2H, −CH_2 of thiadiazine), 5.85 (s, 1H, C-4 of pyran), 12.10 (s, 1H, −NH, D_2O, exchangeable), 15.69 (s, 1H, −OH); ^{13}C NMR (DMSO-d_6, δ ppm): 19.3, 24.9, 25.4, 26.7, 27.2, 34.6, 41.3, 101.2, 102.7, 142.5, 157.1, 161.4, 161.7, 168.4, 168.6. Anal. calcd. for $C_{15}H_{18}N_4O_3S$: C, 53.88; H, 5.43; N, 16.75. Found: C,53.84; H, 5.40; N, 16.71.

4.3. *General procedure for the synthesis of 3-(2-hydrazino-6H-[1,3,4]thiadiazin-5-yl)-4-hydroxy-6-methyl-pyran-2-one (5)*

3-(2-Bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (1 mmol) and thiocarbohydrazide (1 mmol) are taken in 5 ml of anhydrous ethanol and refluxed for about 1 h. The yellow solid

obtained on cooling was filtered, washed with methanol, and recrystallized from ethanol to give yellow solid.

Color: yellow solid; yield 89%; mp. 265–267 °C; IR (KBr, υ_{max}, cm^{-1}): 1604 (C=N), 1690 (C=O), 3175 (NH), 3328 (OH). ^{1}H NMR (400 MHz, DMSO-d_6): 2.13 (s, 3H, CH_3 of pyran ring), 4.65 (s, 2H, $-CH_2$ of thiadiazine), 5.87 (s, 1H, C-4 of pyran), 10.05 (s, 1H, $-NH$, D_2O, exchangeable), 12.34 (s, $-NH_2$, D_2O exchangeable), 15.64 (s, 1H, $-OH$); EI-MS 254[M^+]. Anal. calcd. for $C_9H_{10}N_4O_3S$: C, 42.51; H, 3.96; N, 22.03. Found: C, 41.94; H, 3.84; N, 21.93.

4.4. *General procedure for the synthesis of 4a from 3-(2-hydrazino-6 H-[1,3,4] thiadiazin-5-yl)-4-hydroxy-6-methyl-pyran-2-one (5)*

A mixture of compound **5** (1 mmol) and **3** (1 mmol) in 5 ml of anhydrous ethanol was refluxed for about 1 h. The solid obtained was cooled, filtered, washed with methanol, and recrystallized from ethanol.

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