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Acetic acid mediated regioselective synthesis of 2,4,5-trisubstituted thiazoles by a domino multicomponent reaction†

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Acetic acid mediated regioselective synthesis of novel 2,4,5-trisubstituted thiazole derivatives has been reported by a domino reaction of thiosemicarbazide and aldehydes/ketones/isatin, to generate thiosemicarbazones (*in situ*) followed by addition of arylglyoxal and active methylene/activated C–H acids/pyrazole/indole in ethanol at 80 °C. The products are obtained in high yields by a simple work up. Metal free, short reaction time and high yields are some merits of this methodology.

Introduction

Thiazole scaffolds are present in a number of medicinally relevant compounds *e.g.*, sulfathiazole (**I**) is a short-acting sulfa drug which exhibits antibacterial activity,[1] abafungin (**II**) is a broad-spectrum potent antifungal agent,[2] compound **III** behaves as a nonsteroidal anti-inflammatory agent,[3] compound **IV** exhibits antimicrobial activity,[4a] compound **V** is cytotoxic,[4b] and nizatidine (**VI**) is a successful drug for the treatment of peptic ulcers and gastroesophageal disease (Fig. 1).[4c] Many other 2-hydrazinyl substituted thiazole motifs are known to show activities such as antimicrobial,[5] antitumour,[6] antibacterial and antifungal,[7] anti-inflammatory,[8] antimycobacterial,[9] and anticancer.[10]

Various methods have been reported for the synthesis of 1,3-thiazoles; *e.g.*, condensation of 1-alkynyl(phenyl)-λ^3-iodanes and thioamides/thioureas,[11] synthesis of thiazole amino acid derivatives by modified Hantzsch reaction,[12] and organocatalytic epoxidation of nitrostyrene followed by condensation with thioamides.[13] Condensation of arylglyoxals, cyclic 1,3-dicarbonyls and thioamides under exposure to microwaves at 130 °C,[14] domino reaction between 1,1,3,3-tetramethylguanidine, acetylenic esters and aryl isothiocyanates,[15] and one-pot tandem cyclization of aldehydes and cysteine esters as N and S sources in the presence of I_2/TBHP have also been used for the synthesis of thiazoles.[16] Catalyst free visible light mediated synthesis of multi-functionalized thiazoles by the reaction of phenacyl bromide and substituted thiourea,[17] catalyst free intramolecular cyclization of *N*-allylbenzothioamide[18] and NBS-mediated sequential reaction of 1,3-dicarbonyl compounds with mercaptonitrile salts have also been reported.[19] Balalaie *et al.* have reported $ZnCl_2$ mediated synthesis of dihydropyrimidinone and imidazoline-2-ones by the reaction of phenylglyoxal and nucleophiles with urea and *N*,*N*-dimethyl urea, respectively.[20a] Imidazo[1,2-*b*]pyrazole and imidazo[1,2-*a*]azine have been reported by a glyoxal based multicomponent reaction.[20b,c]

A literature survey revealed that in recent years, various methodologies have evolved for the synthesis of biologically active heterocycles.[21] In continuation of our efforts to develop efficient and green methodologies to construct biologically and medicinally important molecules,[22] we decided to investigate the synthesis of trisubstituted thiazoles by one-pot three component condensation of thiosemicarbazones, arylglyoxal and activated C–H acids.

Results and discussion

In this paper, we report regioselective synthesis of novel 2,4,5-trisubstituted thiazoles by one-pot condensation of arylthiosemicarbazones (generated *in situ*), arylglyoxal and activated C–H acids like 4-hyroxycoumarin, dimedone, cyclohexane-1,3-dione, 4-hydroxy-6-methyl-2-pyrone, cyclopentane-1,3-dione, 3-methyl-1*H*-pyrazol-5(4*H*)-one, 1,3-dimethylbarbituric acid, methyl 5-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate and indole in the presence of acetic acid as a catalyst. The reaction conditions were optimized by attempting reaction of equimolar amounts of thiosemicarbazide (**1a**), piperonaldehyde (**2a**), phenylglyoxal (**3a**) and 4-hydroxycoumarin (**4a**) under different conditions. Initially, the reaction was attempted by heating thiosemicarbazide (**1a**) and piperonaldehyde (**2a**) in ethanol at 80 °C in the presence of 10 mol% of *p*-toluenesulphonic acid (*p*-TSA). After the disappearance of the reactants (~30 min), phenylglyoxal (**3a**) and 4-hydroxycoumarin (**4a**) were added to the reaction mixture and the progress of the reaction was monitored by TLC using chloroform : methanol

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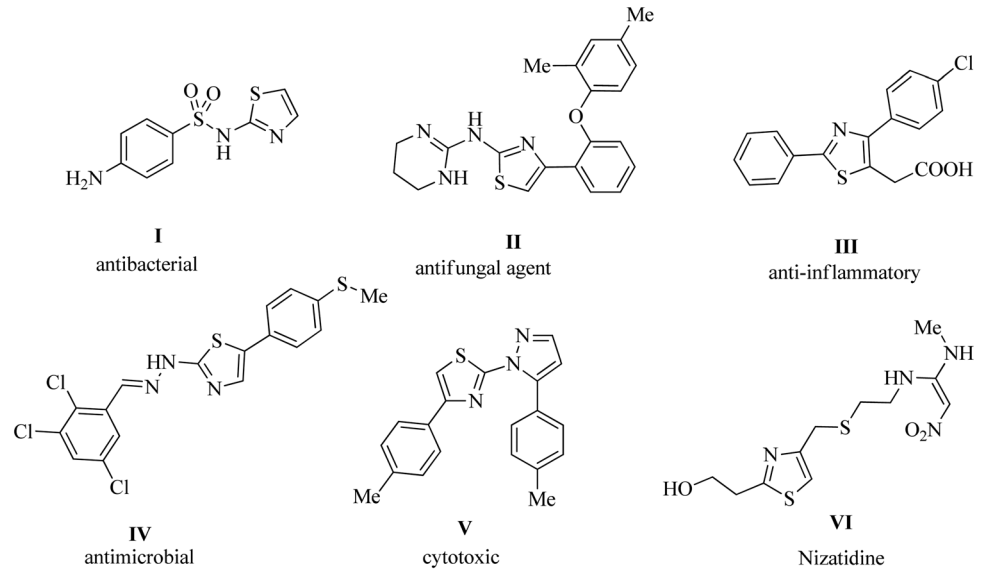


Fig. 1 Some medicinally important thiosemicarbazide and 1,3-thiazole skeletons.

Table 1 Optimization of the reaction conditions for the synthesis of compound **5a**[a]

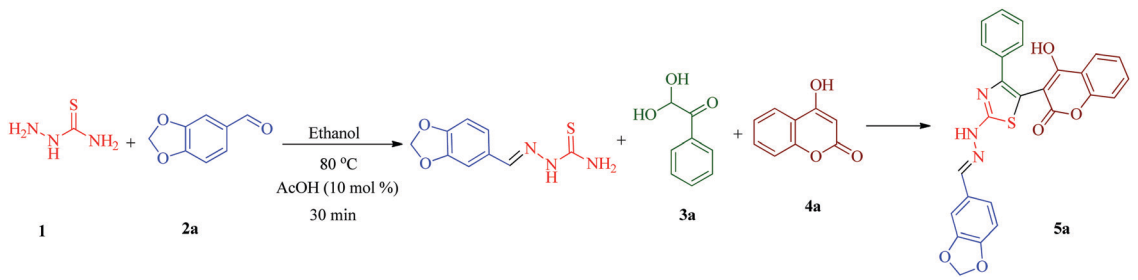
Entry	Catalyst[b]	Solvent	Time (min)	Yield[c] (%)
1	*p*TSA	EtOH	120	85
2	CH_3COOH	EtOH	60	92
3	CH_3COOH	MeOH	120	76
4	CH_3COOH	DCM	120	78
5	CH_3COOH	EG	120	81
6	CH_3COOH	PEG-400	120	82

[a] Reaction conditions: thiosemicarbazide (**1**) (1.0 mmol), aldehyde (**2a**) (1.0 mmol), phenylglyoxal (1.0 mmol), 4-hydroxycoumarin (**4a**) (1.0 mmol) and solvent (5 mL). [b] 10 mol% catalyst. [c] Isolated yield.

(95 : 5, v/v) as an eluent. The reaction was found to be completed after 120 min. The product was separated and identified as (*E*)-3-(2-(2-(benzo[*d*][1,3]dioxol-5-ylmethylene)hydrazinyl)-4-phenylthiazol-5-yl)-4-hydroxy-2*H*-chromen-2-one (**5a**) in 85% yield (Table 1, entry 1). The reaction was then repeated in ethanol using glacial acetic acid as a catalyst. To our delight, the reaction was complete in 60 min, and the product **5a** was isolated in 92% yield (Scheme 1) (Table 1, entry 2).

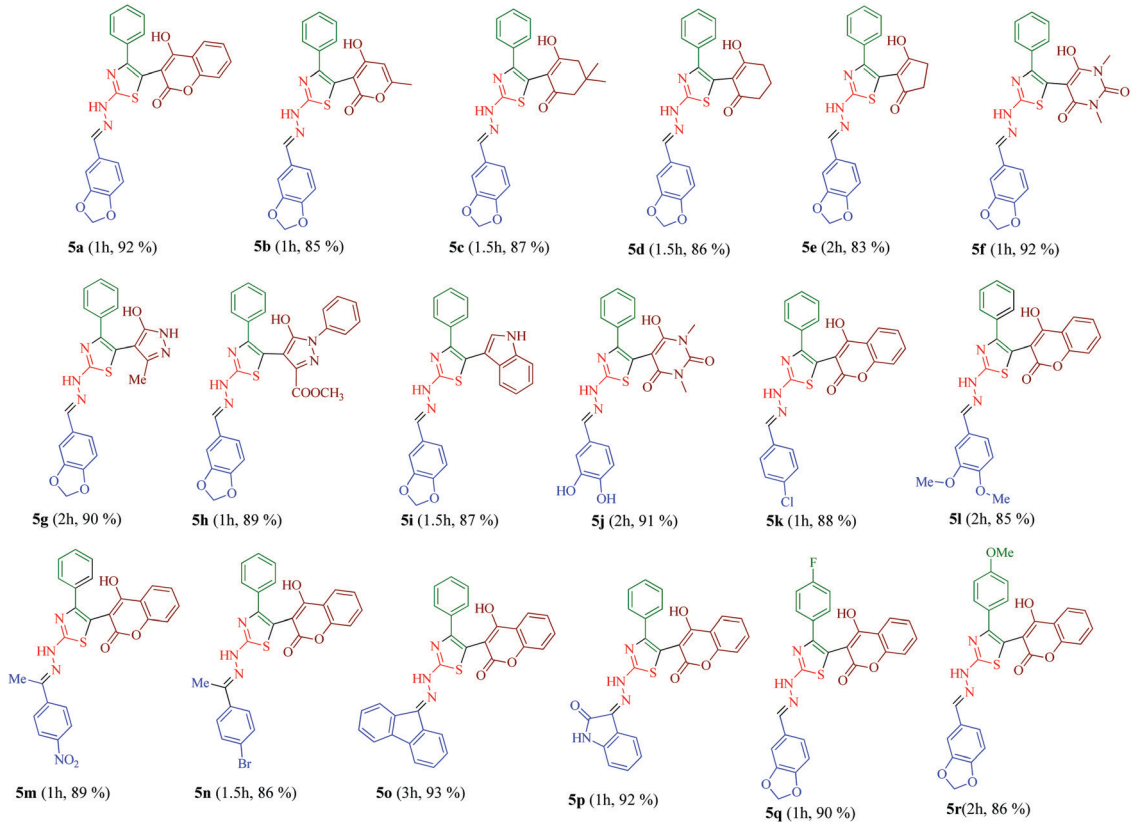
Reactions were then attempted in different solvents like methanol, DCM, EG and PEG-400 in the presence of 10 mol% of glacial acetic acid at 80 °C. The reactions were complete in 120 min and gave varying yields of the product (**5a**) from 76% to 82% (Table 1, entries 3–6). Therefore, it can be inferred from the results shown in Table 1 that the optimized reaction conditions for the synthesis of trisubstituted thiazole is one-pot four component condensation in ethanol at 80 °C in the presence of 10 mol% glacial acetic acid.

After the optimization of the reaction conditions, reactions of thiosemicarbazide (**1**), piperonaldehyde (**2a**) and phenylglyoxal (**3a**) were attempted with different nucleophiles such as 4-hydroxy-6-methyl-2-pyrone (**4b**), dimedone (**4c**), cyclohexane-1,3-dione (**4d**), pentane-1,3-dione (**4e**), 1,3-dimethylbarbituric acid (**4f**), 3-methyl-1*H*-pyrazol-5-ol (**4g**), methyl 5-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate (**4h**) and indole (**4i**) in ethanol in the presence of 10 mol% glacial acetic acid at 80 °C and phenylglyoxal and nucleophiles (activated C–H acids) were added in the same pot after the disappearance of aldehyde at ~30 min as monitored by TLC. All the reactions were complete in 1–2 h and gave the corresponding trisubstituted thiazoles (**5b–5i**) in high yields (Scheme 2) (Table 2). Subsequently, we also attempted reactions with different aldehydes/ketones under similar conditions. All the reactions were complete in 1–3 h and gave the corresponding products in good yields (Table 2, entries **5j–5p**).



Scheme 1

Table 2 Synthesis of 2,4,5-trisubstituted thiazoles[a,b]

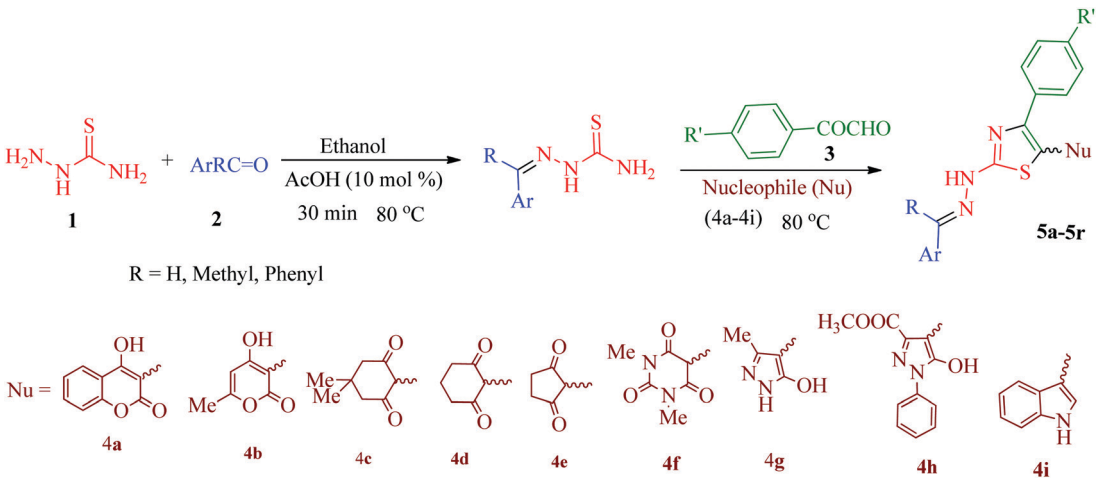


[a] Reaction conditions: thiosemicarbazide (**1a**) (1.0 mmol), aldehyde/ketone/isatin (1.0 mmol), arylglyoxal (1.0 mmol) and nucleophile (Nu) (**4a–4i**) (1.0 mmol) in 10 mol% AcOH in 5 mL of ethanol. [b] Isolated yields are given in brackets.

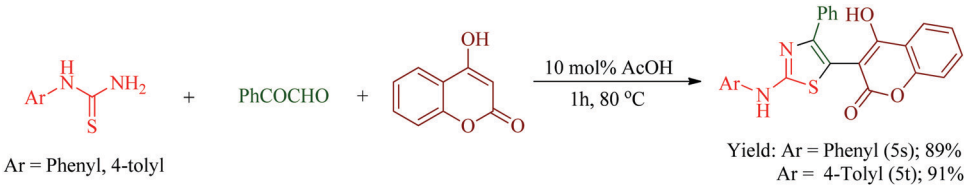
Reactions using substituted phenylglyoxal also yielded the corresponding thiazoles in high yields (Table 2, entries **5q–5r**).

The above protocol was also examined for the one-pot three component condensation of equimolar amounts of phenylglyoxal and 4-hydroxycoumarin with phenylthiourea & 4-tolylthiourea in place of thiosemicarbazone in ethanol in the presence of 10 mol% glacial acetic acid at 80 °C. The reactions proceeded smoothly and were complete in 1 h yielding the corresponding 4-hydroxy-3-(4-phenyl-2-(arylamino)thiazol-5-yl)-2*H*-chromen-2-one (Scheme 3).

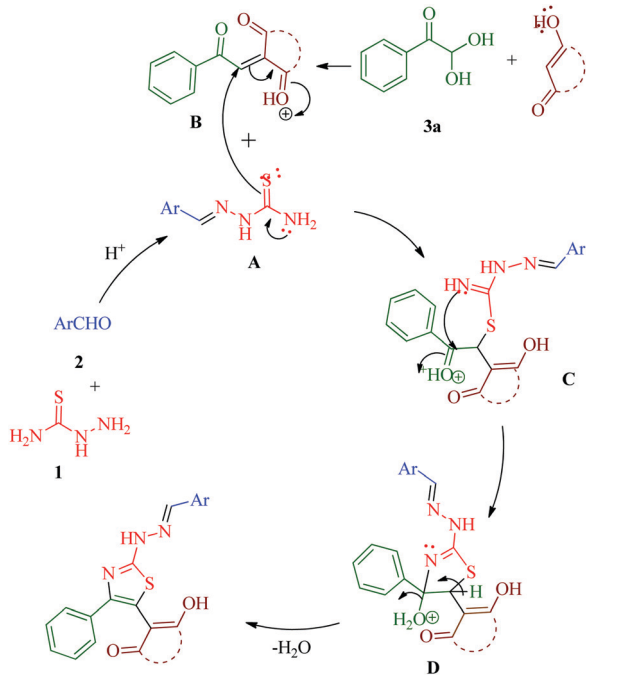
The proposed mechanism for the formation of thiazoles is depicted in Scheme 4. The reaction involves initial condensation of aldehydes/ketones/isatin and thiosemicarbazide to give thiosemicarbazone (**A**).[23] The condensation between phenylglyoxal



Scheme 2 Synthesis of 2,4,5-trisubstituted thiazoles.



Scheme 3 Synthesis of 2,4,5-trisubstituted thiazoles.



Scheme 4 Proposed mechanism for the synthesis of 2,4,5-trisubstituted thiazoles.

with cyclo-1,3-dione gives intermediate **B** which undergoes Michael addition with **A** followed by tautomerization to give **C**.[14] Intramolecular cyclization followed by loss of water gives the desired product **5**.

Conclusions

In conclusion, we have reported a facile one-pot metal free regioselective sequential synthesis of 2,4,5-trisubstituted thiazoles by condensation of aldehydes/ketones/isatin, thiosemicarbazide, phenylglyoxal and active methylene compounds/activated C–H acids in ethanol in the presence of glacial acetic acid (10 mol%) in excellent yields at 80 °C. The 2,4,5-trisubstituted thiazoles could also be obtained by replacing thiosemicarbazone, formed *in situ*, with arylthiourea.

Experimental

All the chemicals were commercially available and purchased from Sigma-Aldrich or Merck and used as received. Thin layer chromatography (GF-254) was used to monitor reaction progress. Melting points were measured on Buchi M-560 melting point apparatus and are uncorrected. IR (neat) spectra were recorded on a SHIMADZU spectrophotometer and the values are expressed as ν_{max} cm^{-1}. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Jeol JNM ECX-400P at 400 and 100 MHz respectively, using TMS as an internal standard. The chemical shift values are recorded on δ scale and the coupling constants (*J*) are in Hz. Mass spectral data were recorded on an Agilent 6200 Q-TOf (ESI-HRMS) mass spectrometer.

General procedure for the synthesis of 2,4,5-trisubstituted thiazoles (5a–5t)

A mixture of thiosemicarbazide (1) (1.0 mmol), aldehyde/ketone/isatin (2) (1.0 mmol), glacial acetic acid (10 mol%) and 5 mL of ethanol was taken in a 50 mL round bottomed flask mounted over a magnetic stirrer. The reactants were stirred magnetically in an oil-bath maintained at 80 °C and the progress of the reaction was monitored by TLC (eluent: chloroform : methanol, 95 : 5, v/v). After disappearance of the carbonyl compound (~30 min), arylglyoxal (1.0 mmol) and nucleophile (**4a–4i**) (1.0 mmol) were added to the reaction mixture and the heating was continued. The progress of the reaction was monitored by TLC (eluent: chloroform : methanol, 95 : 5, v/v) for the disappearance of arylglyoxal. After completion of the reaction, the mixture was cooled to room temperature. A solid product separated out which was filtrated at pump. The solid residue was washed with ethanol (5 mL). The products were characterized by IR, ^{1}H NMR, ^{13}C NMR and HRMS.

Spectral data

(*E*)-3-(2-(2-(Benzo[*d*][1,3]dioxol-5-ylmethylene)hydrazinyl)-4-phenylthiazol-5-yl)-4-hydroxy-2*H*-chromen-2-one (5a). Off white solid; m.p. 256–259 °C; IR (ν_{max} cm^{-1}) (neat): 3183, 1676, 1603, 1495, 1260, 1086, 750; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (bs, 1H, **OH**), 7.94 (s, 1H, **CH** imine), 7.85 (d, *J* = 8.0 Hz, 1H, Ar**H**), 7.67–7.60 (m, 1H, Ar**H**), 7.54 (d, *J* = 7.1 Hz, 2H, Ar**H**), 7.41–7.30 (m, 2H, Ar**H**), 7.25 (t, *J* = 7.5 Hz, 2H, Ar**H**), 7.18 (t, *J* = 7.2 Hz, 2H, Ar**H**), 7.06 (d, *J* = 8.1 Hz, 1H, Ar**H**), 6.91 (d, *J* = 8.0 Hz, 1H, Ar**H**), 6.01 (s, 2H, O**CH$_2$**O); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.2, 164.1, 161.9, 153.2, 149.0, 148.5, 141.9, 135.9, 133.5, 129.4, 128.7, 127.6, 124.7, 124.4, 122.7, 116.9, 116.3, 110.8, 109.0, 105.1, 102.0, 97.4; HRMS (ESI) calcd for $C_{26}H_{17}N_3O_5S$ $[M + H]^+$: 484.0967, found: 484.0963 $[M + H]^+$.

(*E*)-3-(2-(2-(Benzo[*d*][1,3]dioxol-5-ylmethylene)hydrazinyl)-4-phenylthiazol-5-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (5b). Off white solid; m.p. 180–182 °C; IR (ν_{max} cm^{-1}) (neat): 2970, 2945, 1742, 1584, 1371, 1252, 1032, 692; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.95 (bs, 1H, **OH**), 7.93 (s, 1H, **CH** imine), 7.53 (d, *J* = 7.3 Hz, 2H, Ar**H**),

7.30 (t, J = 7.6 Hz, 2H, Ar**H**), 7.26–7.17 (m, 2H, Ar**H**), 7.08 (d, J = 8.2 Hz, 1H, Ar**H**), 6.94 (d, J = 8.2 Hz, 1H, Ar**H**), 6.06 (s, 3H, **OCH$_2$O** + **CH** alkene), 2.21 (s, 3H, **CCH$_3$**), ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.6, 168.6, 167.5, 163.6, 163.3, 149.0, 148.5, 141.5, 136.4, 129.5, 128.6, 127.7, 127.4, 122.6, 111.8, 109.0, 105.0, 101.9, 100.5, 94.1, 21.6; HRMS (ESI) calcd for $C_{23}H_{17}N_3O_5S$ $[M + H]^+$: 448.0967, found: 448.0958 $[M + H]^+$.

(*E*)-2-(2-(2-(Benzo[*d*][1,3]dioxol-5-ylmethylene)hydrazinyl)-4-phenylthiazol-5-yl)-3-hydroxy-5,5-dimethylcyclohex-2-enone (5c). Yellow solid; m.p. 179–180 °C; IR (ν_{max} cm^{-1}) (neat): 3460, 2968, 1742, 1369, 1225, 1034; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (s, 1H, **CH** imine), 7.53 (d, J = 7.3 Hz, 2H, Ar**H**), 7.34–7.12 (m, 4H, Ar**H**), 7.06 (d, J = 7.8 Hz, 1H, Ar**H**), 6.93 (d, J = 7.8 Hz, 1H, Ar**H**), 6.05 (s, 2H, **OCH$_2$O**), 2.32 (bs, 2H, **COCH$_2$**CMe$_2$), 1.90 (bs, 2H, **COCH$_2$**CMe$_2$), 1.03 (s, 6H, 2 × **CH$_3$**); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.2, 166.7, 148.3, 148.0, 146.9, 140.6, 136.1, 129.2, 127.9, 127.1, 122.0, 113.1, 108.6, 106.5, 104.5, 101.5, 56.1, 31.5, 28.1, 21.1, 18.6; HRMS (ESI) calcd for $C_{25}H_{23}N_3O_4S$ $[M + H]^+$: 462.1488, found: 462.1476 $[M + H]^+$.

(*E*)-2-(2-(2-(Benzo[*d*][1,3]dioxol-5-ylmethylene)hydrazinyl)-4-phenylthiazol-5-yl)-3-hydroxycyclohex-2-enone (5d). Yellow solid; m.p. 226–228 °C; IR (ν_{max} cm^{-1}) (neat): 3007, 2970, 1742, 1646, 1368, 1227, 1028; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (s, 1H, **CH** imine), 7.63 (d, J = 7.3 Hz, 2H, Ar**H**), 7.35 (t, J = 7.6 Hz, 2H, Ar**H**), 7.26 (d, J = 7.8 Hz, 2H, Ar**H**), 7.12 (d, J = 7.8 Hz, 1H, Ar**H**), 6.99 (d, J = 8.2 Hz, 1H, Ar**H**), 6.10 (s, 2H, **OCH$_2$O**), 2.18–1.90 (m, 6H, **COCH$_2$CH$_2$CH$_2$**CO); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.2, 166.7, 148.4, 148.1, 146.5, 140.6, 136.2, 129.2, 128.1, 126.9, 122.1, 113.5, 108.6, 107.8, 104.6, 101.5, 21.1, 20.3; HRMS (ESI) calcd for $C_{23}H_{19}N_3O_4S$ $[M + H]^+$: 434.1175, found: 434.1164 $[M + H]^+$.

(*E*)-2-(2-(2-(Benzo[*d*][1,3]dioxol-5-ylmethylene)hydrazinyl)-4-phenylthiazol-5-yl)-3-hydroxycyclopent-2-enone (5e). Yellow solid; m.p. 252–253 °C; IR (ν_{max} cm^{-1}) (neat): 3408, 3009, 1740, 1628, 1447, 1250, 1034, 602; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (s, 1H, **CH** imine), 7.53 (q, J = 8.2 Hz, 2H, Ar**H**), 7.23 (m, 4H, Ar**H**), 7.07 (q, J = 7.8 Hz, 1H, Ar**H**), 6.92 (d, J = 8.2 Hz, 1H, Ar**H**), 6.03 (s, 2H, **OCH$_2$O**), 2.53–2.43 (bs, 4H, **COCH$_2$CH$_2$**CO); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.2, 166.8, 148.4, 148.0, 140.9, 136.2, 129.1, 128.0, 127.2, 127.0, 110.5, 109.4, 108.6, 104.6, 101.5, 30.5, 21.1; HRMS (ESI) calcd for $C_{22}H_{17}N_3O_4S$ $[M + H]^+$: 420.1018, found: 420.0999 $[M + H]^+$.

(*E*)-5-(2-(2-(Benzo[*d*][1,3]dioxol-5-ylmethylene)hydrazinyl)-4-phenylthiazol-5-yl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (5f). Yellow solid; m.p. >300 °C; IR (ν_{max} cm^{-1}) (neat): 2970, 1741, 1674, 1557, 1369, 1225, 762; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (s, 1H, **CH** imine), 7.53–7.41 (m, 4H, Ar**H**), 7.29 (dd, J = 15.8, 7.1 Hz, 4H, Ar**H**), 6.32 (s, 2H, **OCH$_2$O**), 3.08 (s, 6H, 2 × **NCH$_3$**), ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.0, 151.9, 149.1, 148.0, 128.3, 128.1, 127.7, 127.5, 123.4, 108.6, 105.0, 101.7, 27.8; HRMS (ESI) calcd for $C_{23}H_{19}N_5O_5S$ $[M + H]^+$: 478.1185, found: 478.1192 $[M + H]^+$.

(*E*)-4-(2-(2-(Benzo[*d*][1,3]dioxol-5-ylmethylene)hydrazinyl)-4-phenylthiazol-5-yl)-3-methyl-1*H*-pyrazol-5-ol (5g). White solid; m.p. 258–269 °C; IR (ν_{max} cm^{-1}) (neat): 3167, 2972, 1742, 1562, 1439, 1251, 1036; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.27 (s, 2H, **OH**, **NH**), 7.92 (s, 1H, **CH** imine), 7.55 (s, 2H, Ar**H**), 7.37–6.89 (m, 6H, Ar**H**), 6.04 (s, 2H, **OCH$_2$O**), 1.75 (s, 3H, **CCH$_3$**), ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.4, 159.4, 148.4, 148.0, 146.0, 140.9, 138.6, 135.9, 129.1, 128.2, 127.2, 127.0, 122.1, 112.2, 108.6, 104.7, 101.5, 94.2, 10.5; HRMS (ESI) calcd for $C_{21}H_{17}N_5O_3S$ $[M + H]^+$: 420.1130, found: 420.1113 $[M + H]^+$.

(*E*)-Methyl 4-(2-(2-(benzo[*d*][1,3]dioxol-5-ylmethylene)hydrazinyl)-4-phenylthiazol-5-yl)-5-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate (5h). White solid; m.p. 246–248 °C; IR (ν_{max} cm^{-1}) (neat): 1715, 1601, 1445, 1246, 1031, 760; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 12.01 (bs, 1H, **OH**), 7.94 (s, 1H, **CH** imine), 7.71 (d, J = 7.6 Hz, 2H, Ar**H**), 7.60–7.45 (m, 4H, Ar**H**), 7.35 (t, J = 7.4 Hz, 1H, Ar**H**), 7.30–7.21 (m, 2H, Ar**H**), 7.21–7.13 (m, 2H, Ar**H**), 7.11–7.03 (m, 1H, Ar**H**), 6.91 (d, J = 8.1 Hz, 1H, Ar**H**), 6.02 (s, 2H, OCH$_2$O), 3.59 (s, 3H, **COOCH$_3$**); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 167.5, 162.3, 152.3, 149.0, 148.5, 141.6, 141.0, 138.4, 136.1, 129.7, 129.5, 128.6, 127.9, 127.7, 123.0, 122.7, 110.2, 109.0, 105.1, 102.0, 96.5, 52.0; HRMS (ESI) calcd for $C_{28}H_{21}N_5O_5S$ $[M + Na]^+$: 562.1161, found: 562.1162 $[M + Na]^+$.

(*E*)-2-(2-(Benzo[*d*][1,3]dioxol-5-ylmethylene)hydrazinyl)-5-(1*H*-indol-3-yl)-4-phenylthiazole (5i). White solid; m.p. 231–232 °C; IR (ν_{max} cm^{-1}) (neat): 2914, 1628, 1493, 1443, 1246, 1028, 737; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 11.35 (s, 1H, **NH**), 7.94 (s, 1H, **CH** imine), 7.58–7.48 (m, 2H, **ArH**), 7.40 (d, J = 8.1 Hz, 2H, ArH), 7.25–6.99 (m, 7H, **ArH**), 6.94–6.82 (m, 2H, **ArH**), 5.99 (s, 2H, OCH$_2$O); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 172.7, 166.1, 148.9, 148.5, 145.1, 141.4, 136.8, 136.4, 129.5, 128.5, 128.2, 127.5, 126.6, 126.0, 122.5, 122.2, 119.9, 115.6, 112.4, 109.0, 106.6, 105.1, 101.9, HRMS (ESI) calcd for $C_{25}H_{18}N_4O_2S$ $[M + H]^+$: 439.1229, found: $[M + H]^+$ 439.1243.

(*E*)-5-(2-(2-(3,4-Dihydroxybenzylidene)hydrazinyl)-4-phenylthiazol-5-yl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (5j). White solid; m.p. >300 °C; IR (ν_{max} cm^{-1}) (neat): 3456, 3100, 1657, 1560, 1435, 1277, 754; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (s, 1H, **CH** imine), 7.55 (d, J = 9.7 Hz, 2H, Ar**H**), 7.42–7.08 (m, 5H, Ar**H**), 6.97 (s, 1H, Ar**H**), 6.07 (s, 2H, OCH$_2$O), 3.09 (s, 6H, 2 × **NCH$_3$**), ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 161.1, 152.0, 148.4, 145.9, 132.7, 128.1, 127.5, 124.9, 120.8, 117.3, 115.7, 112.6, 27.7; HRMS (ESI) calcd for $C_{22}H_{19}N_5O_5S$ $[M + H]^+$: 466.1185, found: 466.1192 $[M + H]^+$.

(*E*)-3-(2-(2-(4-Chlorobenzylidene)hydrazinyl)-4-phenylthiazol-5-yl)-4-hydroxy-2*H*-chromen-2-one (5k). Off white solid; m.p. 268–270 °C; IR (ν_{max} cm^{-1}) (neat): 3165, 1676, 1605, 1526, 1086, 752, 692; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.32 (bs, 1H, **OH**), 8.01 (s, 1H, **CH** imine), 7.86 (d, J = 6.6 Hz, 1H, Ar**H**), 7.63 (d, J = 8.5 Hz, 3H, Ar**H**), 7.58–7.51 (m, 2H, Ar**H**), 7.47–7.40 (m, 2H, Ar**H**), 7.40–7.36 (m, 1H, Ar**H**), 7.36–7.30 (m, 1H, Ar**H**), 7.29–7.22 (m, 2H, Ar**H**), 7.18 (t, J = 7.3 Hz, 1H, Ar**H**); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.1, 164.0, 161.9, 153.2, 149.6, 140.7, 135.8, 134.2, 133.9, 133.5, 129.5, 128.8, 128.1, 127.6, 124.8, 124.5, 116.9, 116.3, 111.2, 97.4; HRMS (ESI) calcd for $C_{25}H_{16}ClN_3O_3S$ $[M + H]^+$: 474.0679, found: 474.0678 $[M + H]^+$ and 476.0658 $[M + H + 2]^+$.

(*E*)-3-(2-(2-(3,4-Dimethoxybenzylidene)hydrazinyl)-4-phenylthiazol-5-yl)-4-hydroxy-2*H*-chromen-2-one (5l). Off white solid; m.p. 254–256 °C; IR (ν_{max} cm^{-1}) (neat): 3441, 3144, 1674, 1587, 1528, 1462, 1092, 820; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07–7.97 (s, 1H, CH imine), 7.92–7.79 (m, 2H, Ar**H**), 7.65–7.48 (m, 3H, Ar**H**), 7.39–7.20 (m, 4H, Ar**H**), 7.14 (d, J = 8.0 Hz, 1H, Ar**H**), 6.94 (d, J = 8.2 Hz, 1H, Ar**H**), 6.82–6.58 (m, 1H, Ar**H**), 3.74 (s, 6H,

2 × OC**H**$_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.3, 166.5, 165.4, 164.2, 162.0, 153.2, 152.8, 150.8, 149.5, 147.5, 143.3, 135.1, 133.6, 132.3, 128.8, 127.7, 124.1, 121.3, 119.0, 116.9, 116.4, 112.1, 110.8, 108.6, 104.8, 97.1, 56.0, 55.8; HRMS (ESI) calcd for $C_{27}H_{21}N_3O_5S$[M + H]$^+$: 500.1280, found: 500.1292 [M + H]$^+$.

(*E*)-4-Hydroxy-3-(2-(2-(1-(4-nitrophenyl)ethylidene)hydrazinyl)-4-phenylthiazol-5-yl)-2*H*-chromen-2-one (5m). Yellow solid; m.p. 214–216 °C; IR (ν_{max} cm^{-1}) (neat): 3186, 1670, 1568, 1333, 1277, 754, 689; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (d, J = 8.9 Hz, 2H, Ar**H**), 7.95 (d, J = 8.9 Hz, 2H, Ar**H**), 7.85 (d, J = 7.4 Hz, 1H, Ar**H**), 7.66–7.53 (m, 3H, Ar**H**), 7.41–7.22 (m, 4H, Ar**H**), 7.19 (t, J = 7.2 Hz, 1H, Ar**H**), 2.34 (s, 3H, **C**H$_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.7, 169.4, 164.1, 161.9, 153.2, 149.3, 147.4, 144.8, 144.5, 135.6, 133.5, 128.8, 127.6, 127.0, 124.7, 124.4, 124.2, 116.9, 116.3, 111.8, 97.3, 21.5; HRMS (ESI) calcd for $C_{26}H_{18}N_4O_5S$ [M + H]$^+$: 499.1076, found: 499.1072 [M + H]$^+$.

(*E*)-3-(2-(2-(1-(4-Bromophenyl)ethylidene)hydrazinyl)-4-phenylthiazol-5-yl)-4-hydroxy-2*H*-chromen-2-one (5n). White solid; m.p. 239–240 °C; IR (ν_{max} cm^{-1}) (neat): 3252, 1663, 1603, 1489, 1082, 754, 700; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (d, J = 7.8 Hz, 1H, Ar**H**), 7.72–7.59 (m, 3H, Ar**H**), 7.55 (t, J = 6.0 Hz, 4H, Ar**H**), 7.42–7.29 (m, 2H, Ar**H**), 7.22 (m, 3H, Ar**H**), 2.28 (s, 3H, **C**H$_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.6, 164.0, 161.9, 153.2, 146.1, 137.6, 135.8, 133.5, 131.9, 128.7, 128.2, 127.6, 124.8, 124.4, 122.6, 116.9, 116.3, 111.2, 97.5, 14.3; HRMS (ESI) calcd for $C_{26}H_{18}BrN_3O_3S$ [M + H]$^+$: 532.0330, found: 532.0361 [M + H]$^+$ and 534.0341 [M + H + 2]$^+$.

3-(2-(2-(9*H*-Fluoren-9-ylidene)hydrazinyl)-4-phenylthiazol-5-yl)-4-hydroxy-2*H*-chromen-2-one (5o). Yellow solid; m.p. 261–262 °C; IR (ν_{max} cm^{-1}) (neat): 3227, 1695, 1605, 1532, 1179, 1076, 756; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (d, J = 7.0 Hz, 1H, Ar**H**), 7.82 (d, J = 8.2 Hz, 2H, Ar**H**), 7.76 (d, J = 8.3 Hz, 2H, Ar**H**), 7.68–7.58 (m, 1H, Ar**H**), 7.54–7.46 (m, 2H, Ar**H**), 7.45–7.22 (m, 9H, Ar**H**); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.5, 161.9, 153.2, 140.7, 139.3, 137.5, 133.7, 131.5, 130.3, 129.4, 129.0, 128.3, 127.9, 124.8, 124.5, 121.3, 120.7, 117.0, 116.2, 96.7; HRMS (ESI) calcd for $C_{31}H_{19}N_3O_3S$ [M + H]$^+$: 514.1225, found: 514.1226 [M + H]$^+$.

(*E*)-3-(2-(5-(4-Hydroxy-2-oxo-2*H*-chromen-3-yl)-4-phenylthiazol-2-yl)hydrazono)indolin-2-one (5p). Red solid; m.p. 280–284 °C; IR (ν_{max} cm^{-1}) (neat): 3068, 1705, 1676, 1612, 1545, 1153, 754; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.32 (s, 1H, **OH**), 11.24 (s, 1H, **NH**), 7.84 (m, 2H, Ar**H**), 7.67–7.60 (m, 1H, Ar**H**), 7.58 (d, J = 8.5 Hz, 1H, Ar**H**), 7.50–7.45 (m, 2H, Ar**H**), 7.40–7.27 (m, 4H, Ar**H**), 7.22 (d, J = 7.3 Hz, 1H, Ar**H**), 7.04 (t, J = 7.6 Hz, 1H, Ar**H**), 6.96–6.90 (m, 1H, Ar**H**); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.9, 164.4, 163.7, 161.9, 153.2, 150.3, 141.8, 135.3, 133.7, 132.7, 131.0, 128.9, 127.7, 124.8, 124.5, 123.0, 120.3, 117.0, 116.3, 114.7, 111.6, 96.7; HRMS (ESI) calcd for $C_{26}H_{16}N_4O_4S$ [M + H]$^+$: 481.0971, found: 481.0971 [M + H]$^+$.

(*E*)-3-(2-(2-(Benzo[*d*][1,3]dioxol-5-ylmethylene)hydrazinyl)-5-(4-fluorophenyl)thiazol-4-yl)-4-hydroxy-2*H*-chromen-2-one (5q). Off white solid; m.p. 262–264 °C; IR (ν_{max} cm^{-1}) (neat): 3176, 1672, 1603, 1497, 1227, 837, 750; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.09 (bs, 1H, **OH**), 7.94 (s, 1H, **CH** imine), 7.86 (d, J = 7.8 Hz, 1H, Ar**H**), 7.67–7.60 (m, 1H, Ar**H**), 7.60–7.51 (m, 2H, Ar**H**), 7.41–7.28 (m, 2H, Ar**H**), 7.18 (s, 1H, Ar**H**), 7.13–7.03 (m, 3H, Ar**H**), 6.90 (d, J = 8.0 Hz, 1H, Ar**H**), 6.01 (s, 2H, OC**H**$_2$O); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.3, 164.0, 163.2, 161.9, 160.7, 153.2, 149.0, 148.5, 141.9, 133.5, 132.5, 129.6, 129.6, 124.7, 124.5, 122.7, 116.9, 116.4, 115.7, 115.5, 110.7, 109.0, 105.1, 102.0, 97.3; HRMS (ESI) calcd for $C_{26}H_{16}FN_3O_5S$ [M + H]$^+$: 502.0873, found: 502.0875 [M + H]$^+$.

(*E*)-3-(2-(2-(Benzo[*d*][1,3]dioxol-5-ylmethylene)hydrazinyl)-4-(4-methoxyphenyl)thiazol-5-yl)-4-hydroxy-2*H*-chromen-2-one (5r). Off white solid; m.p. 265–266 °C; IR (ν_{max} cm^{-1}) (neat): 1618, 1595, 1448, 1254, 1028, 826, 752; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 1H, C**H** imine), 7.86 (d, J = 7.8 Hz, 1H, Ar**H**), 7.71–7.59 (m, 1H, Ar**H**), 7.48 (d, J = 8.8 Hz, 2H, Ar**H**), 7.43–7.29 (m, 2H, Ar**H**), 7.17 (s, 1H, Ar**H**), 7.05 (d, J = 8.1 Hz, 1H, Ar**H**), 6.90 (d, J = 8.0 Hz, 1H, Ar**H**), 6.82 (d, J = 8.8 Hz, 2H, Ar**H**), 6.01 (s, 2H, OC**H**$_2$O), 3.66 (s, 3H, OC**H**$_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.1, 164.1, 162.0, 159.1, 153.2, 149.0, 148.5, 141.8, 133.4, 129.4, 128.9, 128.5, 124.7, 122.7, 116.9, 116.4, 114.1, 109.0, 105.0, 102.0, 97.5, 55.5; HRMS (ESI) calcd for $C_{27}H_{19}N_3O_6S$ [M + H]$^+$: 514.1073, found: 514.1094 [M + H]$^+$.

4-Hydroxy-3-(4-phenyl-2-(phenylamino)thiazol-5-yl)-2*H*-chromen-2-one (5s). Off white solid; m.p. 224–226 °C; IR (ν_{max} cm^{-1}) (neat): 3323, 3262, 1724, 1682, 1601, 1491, 745, 685; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.31 (s, 1H, **NH**), 7.89 (d, J = 8.2 Hz, 1H, Ar**H**), 7.72 (d, J = 8.2 Hz, 2H, Ar**H**), 7.63 (d, J = 7.8 Hz, 2H, Ar**H**), 7.44–7.28 (m, 7H, Ar**H**), 7.23 (t, J = 7.1 Hz, 1H, Ar**H**), 6.96 (t, J = 7.3 Hz, 1H, Ar**H**); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.3, 163.2, 161.9, 153.2, 149.4, 141.7, 135.8, 133.6, 129.6, 128.8, 127.7, 124.8, 124.5, 121.9, 117.5, 116.9, 116.3, 97.1; HRMS (ESI) calcd for $C_{24}H_{16}N_2O_3S$ [M + H]$^+$: 413.0960, found: 413.0959 [M + H]$^+$.

4-Hydroxy-3-(4-phenyl-2-(*p*-tolylamino)thiazol-5-yl)-2*H*-chromen-2-one (5t). Off white solid; m.p. 210–212 °C; IR (ν_{max} cm^{-1}) (neat): 3264, 1676, 1605, 1524, 1092, 822, 696; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.19 (s, 1H, **NH**), 7.88 (d, J = 8.2 Hz, 1H, Ar**H**), 7.73–7.51 (m, 5H, Ar**H**), 7.44–7.18 (m, 5H, Ar**H**), 7.14 (d, J = 8.2 Hz, 2H, Ar**H**), 2.25 (s, 3H, Ar**C**H$_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.2, 163.5, 161.9, 153.2, 149.3, 139.2, 135.9, 133.5, 130.8, 130.0, 128.8, 128.0, 127.7, 124.7, 124.4, 117.7, 116.9, 116.3, 109.9, 97.1, 20.9; HRMS (ESI) calcd for $C_{25}H_{18}N_2O_3S$ [M + H]$^+$: 427.1116, found: 427.1112 [M + H]$^+$.

Conflicts of interest

There are no conflicts to declare.

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