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Synthesis and anticancer evaluation of thiazolyl–chalcones

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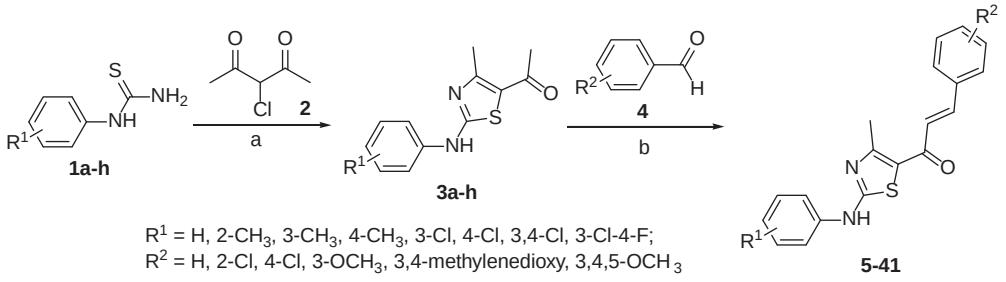
ABSTRACT

Thirty-seven (*E*)-1-(4-methyl-2-arylaminothiazol-5-yl)-3-arylprop-2-en-1-ones were synthesized via Claisen-Schmidt condensation of 1-(4-methyl-2-(arylamino)thiazol-5-yl)ethanone with the corresponding arylaldehydes. All these thiazolyl–chalcones were characterized and evaluated by MTT assay on human cancer cell lines BGC-823, PC-3, NCI-H460, BEL-7402 in vitro. Compounds **5**, **8**, **26**, **37** and **41** are effective against cancer cell lines with IC_{50}s below 10 μM. The antitumor activity in ICR mice bearing sarcoma 180 tumors indicates compounds **10** and **41** have moderate in vivo activity with 22–25% tumor-weight inhibition.

Molecules that possess sulfur atoms are universal and crucial in living organisms.[1] Thiazoles are an important kind of compounds containing one sulfur atom.[2] These heterocyclic moieties are existed in many natural products and synthetic drugs with a broad spectrum of pharmacological activities, including antibacterial sulfathiazole,[3,4] anticonvulsivant riluzole,[5] antiparkinsonian talipexole,[6] antiviral ritonavir,[7] and anticancer dasatinib.[8] Chalcones are also an important kind of compounds that are present in edible plants. They are the precursors of flavonoids and essential secondary metabolites in many plants and bacteria.[9] Chalcones exhibit a diversity of bioactivities, such as antioxidant, anticancer and anti-inflammatory activities.[10–12] Liu found that many piperidinyl chalcones have promising antiproliferative activities ($IC_{50} \leqslant 5$ μM).[10] To date, there were some thiazolyl–chalcones being reported. Patil studied synthesis of arylacrylothiazoles and their antifungal activity, but found none of them active.[13] However, there appears to be little in literature concerning such thiazolyl–chalcones with their anticancer activities. We attempted to investigate that whether introduction of thiazole groups into chalcones could enhance their anticancer activities or not.

In order to find novel thiazolyl–chalcones with high anticancer activities, we designed and synthesized a series of (*E*)-1-(4-methyl-2-arylaminothiazol-5-yl)-3-arylprop-2-en-1-ones **5**–**41**, outlined in Scheme 1. *N*-Aryl thioureas **1a**–**h** were prepared by known



Scheme 1. Synthesis of thiazolyl–chalcones. Reagents and conditions: (a) methanol, reflux, 54.2–77.5%; (b) KOH, THF, reflux, 11.8–81.3%.

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Table 1
Synthesis of thiazolyl–chalcones **5–41**

Compds	Substituents		Yield (%)	Mp (°C)	^{1}H NMR ($CDCl_3$)	HRMS/elemental analysis[a]		
	R^1	R^2				C	H	N
5	3,4-Cl	H	49.6	213–215	7.79 (d, *J* = 15.2 Hz, 1H, =CH), 7.63–7.19 (m, 8H, Ar–H), 7.16 (d, *J* =15.2 Hz, 1H, =CH), 2.75 (s, 3H, CH_3)	M+H 389.0280 (389.0282)		
6	3,4-Cl	4-Cl	42.5	230–232	7.72 (d, *J* = 16 Hz, 1H, =CH), 7.60 (d, *J* = 2.8 Hz, 1H, Ar–H), 7.41 (d, *J* = 8.0 Hz, 2H, Ar–H), 7.48–7.43 (m, 2H, Ar–H), 7.39 (d, *J* = 8.0 Hz, 2H, Ar–H), 7.12 (d, *J* = 15.2 Hz, 1H, =CH), 2.74 (s, 3H, CH_3)	M+H 422.9885 (422.9892)		
7	3,4-Cl	4-OCH_3	64.4	215–217	7.76 (d, *J* = 15.2 Hz, 1H, =CH), 7.58 (d, *J* = 2.4 Hz, 1H, Ar–H), 7.44 (d, *J* = 8.8 Hz, 2H, Ar–H), 7.29–7.24 (m, 2H, Ar–H), 7.05 (d, *J* = 15.2 Hz, 1H, =CH), 6.94 (d, *J* = 8.8 Hz, 2H, Ar–H), 3.85 (s, 3H, OCH_3), 2.70 (s, 3H, CH_3)	M+H 419.0385 (419.0388)		
8	3,4-Cl	3-OCH_3	52.5	214–215	7.75 (d, *J* = 16 Hz, 1H, =CH), 7.60 (s, 1H, Ar–H), 7.49–7.21 (m, 4H, Ar–H), 7.18 (d, *J* = 15.2 Hz, 1H, =CH), 7.12 (m[c], 1H, Ar–H), 6.98 (d, *J* = 7.6 Hz, 1H, Ar–H), 3.87(s, 3H, OCH_3), 2.75(s, 3H, CH_3)	M+H 419.0392 (419.0388)		
9	3,4-Cl	3,4-methylenedioxy	45.0	237–239	7.69 (d, *J* = 16 Hz, 1H, =CH), 7.59 (d, *J* = 2.5 Hz, 1H, Ar–H), 7.47 (d, *J* = 9 Hz, 1H, Ar–H), 7.28 (d, *J* = 3.0 Hz, 1H, Ar–H), 7.12–7.10 (m, 2H, Ar–H), 6.98 (d, *J* = 15.5 Hz, 1H, =CH), 6.85 (d, *J* = 8.5 Hz, 1H, Ar–H), 6.04 (s, 2H, CH_2), 2.72 (s, 3H, CH_3)	b		
10	3,4-Cl	3,4,5-OCH_3	32.4	232–234	7.67(d, *J* = 15.6 Hz, 1H, =CH), 7.63 (d, *J* = 2.8 Hz, 1H, Ar–H), 7.46 (d, *J* = 9.2 Hz, 1H, Ar–H), 7.31 (dd, J_1 = 2.4 Hz, J_2 = 2.8 Hz, 1H, Ar–H), 7.02 (d, *J* = 15.2 Hz, 1H, =CH), 6.82 (s, 2H, Ar–H), 3.92 (s, 6H, 2×OCH_3), 3.90 (s, 3H, OCH_3), 2.72 (s, 3H, CH_3)	55.27 (55.12)	4.11 (4.21)	5.69 (5.84)
11	4-CH_3	3,4-methylenedioxy	27.8	228–230	7.65 (d, *J* = 15.5 Hz, 1H, =CH), 7.27–7.23 (m, 4H, Ar–H), 7.09 (d, *J* = 2.0 Hz, 1H, Ar–H), 7.07 (dd, J_1 = 1.5 Hz, J_2 = 1.5 Hz, 1H, Ar–H), 6.96 (d, *J* = 15.5 Hz, 1H, =CH), 6.82 (d, *J* = 8.5 Hz, 1H, Ar–H), 6.02 (s, 2H, CH_2), 2.66 (s, 3H, CH_3), 2.38 (s, 3H, CH_3)	66.89 (66.65)	4.57 (4.79)	7.53 (7.40)
12	4-CH_3	H	20.0	183–185	7.75 (d, *J* = 15.6 Hz, 1H, =CH), 7.60–7.58 (m, 2H, Ar–H), 7.40–7.39 (m, 3H, Ar–H), 7.25–7.19 (m, 4H, Ar–H), 7.15 (d, *J* = 15.2 Hz, 1H, =CH), 2.71 (s, 3H, CH_3), 2.40 (s, 3H, CH_3)	b		
13	4-CH_3	4-Cl	79.2	213–215	7.68 (d, *J* = 15.6 Hz, 1H, =CH), 7.52 (d, *J* = 8.8 Hz, 2H, Ar–H), 7.37 (d, *J* = 8.4 Hz, 2H, Ar–H), 7.25–7.20 (m, 4H, Ar–H), 7.09 (d, *J* = 15.6 Hz, 1H, =CH), 2.68 (s, 3H, CH_3), 2.38 (s, 3H, CH_3)	b		
14	4-CH_3	3-OCH_3	47.0	174–176	7.69 (d, *J* = 15.2 Hz, 1H, =CH), 7.31 (t, *J* = 8.0 Hz, 1H, Ar–H), 7.24–7.18 (m, 5H, Ar–H), 6.94 (dd, J_1 = 2.0 Hz, J_2 = 1.6 Hz, 1H, Ar–H), 7.11 (d, *J* = 15.2 Hz, 1H, =CH), 7.09 (m[c], 1H, Ar–H), 3.85 (s, 3H, OCH_3), 2.68 (s, 3H, CH_3), 2.37 (s, 3H, CH_3)	68.98 (69.20)	5.61 (5.53)	7.74 (7.69)
15	4-CH_3	2-Cl	27.5	205–206	8.12 (d, *J* = 15.6 Hz, 1H, =CH), 7.66 (dd, J_1 = 2.0 Hz, J_2 = 1.6 Hz, 1H, Ar–H), 7.43 (dd, J_1 = 1.6 Hz, J_2 = 1.6 Hz, 1H, Ar–H), 7.33–7.28 (m, 2H, Ar–H), 7.24–7.18 (m, 4H, Ar–H), 7.11 (d, *J* = 15.2 Hz, 1H, =CH), 2.69 (s, 3H, CH_3), 2.37 (s, 3H, CH_3)	b		
16	4-CH_3	3,4,5-OCH_3	44.4	203–205	7.66 (d, *J* = 15.6 Hz, 1H, =CH), 7.24 (d, *J* = 3.2 Hz, 4H, Ar–H), 7.00 (d, *J* = 15.2 Hz, 1H, =CH), 6.80 (s, 2H, Ar–H), 3.91 (s, 6H, 2×OCH_3), 3.90 (s, 3H, OCH_3), 2.70 (s, 3H, CH_3), 2.37 (s, 3H, CH_3)	65.32 (65.07)	5.66 (5.70)	6.74 (6.60)
17	H	3-OCH_3	15.1	170–172	7.72 (d, *J* = 15.6 Hz, 1H, =CH), 7.44 (t, *J* = 7.8 Hz, 2H, Ar–H), 7.38–7.30 (m, 3H, Ar–H), 7.20 (t, *J* = 6.8 Hz, 2H, Ar–H), 7.13 (d, *J* = 15.2 Hz, 1H, =CH), 7.11 (m[c], 1H, Ar–H), 6.95 (dd, J_1 = 1.6 Hz, J_2 = 2.0 Hz, 1H, Ar–H), 3.85 (s, 3H, OCH_3), 2.70 (s, 3H, CH_3)	68.60 (68.55)	5.27 (5.18)	7.81 (7.99)
18	H	H	31.3	196–197	7.75 (d, *J* = 15.2 Hz, 1H, =CH), 7.60 (dd, J_1 = 3.2 Hz, J_2 = 2.0 Hz, 2H, Ar–H), 7.45–7.36 (m, 7H, Ar–H), 7.21 (d, *J* = 7.6 Hz, 1H, Ar–H), 7.16 (d, *J* = 15.2 Hz, 1H, =CH), 2.71 (s, 3H, CH_3)	b		
19	H	2-Cl	13.0	174–176	8.13 (d, *J* = 15.6 Hz, 1H, =CH), 7.68 (dd, J_1 = 2.0 Hz, J_2 = 2.0 Hz, 1H, Ar–H), 7.46–7.42 (m, 3H, Ar–H), 7.37–7.29 (m, 4H, Ar–H), 7.21 (t, *J* = 7.4 Hz, 1H, Ar–H), 7.13 (d, *J* = 16 Hz, 1H, =CH), 2.71 (s, 3H, CH_3)	b		
20	H	4-Cl	35.3	200–202	7.69 (d, *J* = 15.2 Hz, 1H, =CH), 7.52 (d, *J* = 8.4 Hz, 2H, Ar–H), 7.44 (t, *J* = 7.8 Hz, 2H, Ar–H), 7.37 (d, *J* = 8.0 Hz, 4H, Ar–H), 7.21 (t, *J* = 7.4 Hz, 1H, Ar–H), 7.11 (d, *J* = 15.6 Hz, 1H, =CH), 2.69 (s, 3H, CH_3)	b		
21	H	3,4,5-OCH_3	22.4	250–252	7.67 (d, *J* = 15.2 Hz, 1H, =CH), 7.44 (t, *J* = 8.0 Hz, 2H, Ar–H), 7.37 (d, *J* = 7.6 Hz, 2H, Ar–H), 7.21 (t, *J* = 7.4 Hz, 1H, Ar–H), 7.02 (d, *J* = 15.2 Hz, 1H, =CH), 6.81 (s, 2H, Ar–H), 3.92 (s, 6H, 2×OCH_3), 3.90 (s, 3H, OCH_3), 2.72 (s, 3H, CH_3)	64.51 (64.37)	5.49 (5.40)	6.93 (6.82)
22	2-CH_3	4-Cl	19.0	204–206	7.67 (d, *J* = 15.2 Hz, 1H, =CH), 7.54–7.52 (m, 1H, Ar–H), 7.50 (d, *J* = 8.0 Hz, 2H, Ar–H), 7.36 (d, *J* = 8.4 Hz, 2H, Ar–H), 7.31 (d, *J* = 7.6 Hz, 2H, Ar–H), 7.24–7.20 (m, 1H, Ar–H), 7.05 (d, *J* = 15.6 Hz, 1H, =CH), 2.70 (s, 3H, CH_3), 2.35 (s, 3H, CH_3)	65.25 (65.12)	4.79 (4.65)	7.50 (7.59)

23	2-CH_3	2-Cl	51.6	181–183	8.11 (d, J = 15.6 Hz, 1H, =CH), 7.64 (dd, J_1 = 2.4 Hz, J_2 = 2.4 Hz, 1H, Ar–H), 7.53 (d, J = 8.8 Hz, 1H, Ar–H), 7.42 (dd, J_1 = 2.0 Hz, J_2 = 0.8 Hz, 1H, Ar–H), 7.33–7.27 (m, 4H, Ar–H), 7.23–7.20 (m, 1H, Ar–H), 7.07 (d, J = 15.2 Hz, 1H, =CH), 2.69 (s, 3H, CH_3), 2.35 (s, 1H, CH_3)	65.20 (65.12)	4.73 (4.65)	7.45 (7.59)
24	2-CH_3	3-OCH_3	16.5	173–176	7.69 (d, J = 15.6 Hz, 1H, =CH), 7.54 (d, J = 8.0 Hz, 1H, Ar–H), 7.34–7.29 (m, 3H, Ar–H), 7.23–7.16 (m, 2H, Ar–H), 7.09 (d, J = 15.6 Hz, 1H, =CH), 7.08 (m[c], 1H, Ar–H), 6.94 (dd, J_1 = 2.0 Hz, J_2 = 2.8 Hz, 1H, Ar–H), 3.84 (s, 3H, OCH_3), 2.70 (s, 3H, CH_3), 2.35 (s, 3H, CH_3)	69.25 (69.20)	5.71 (5.53)	7.56 (7.69)
25	2-CH_3	H	28.8	194–196	7.72 (d, J = 15.6 Hz, 1H, =CH), 7.58–7.53 (m, 3H, Ar–H), 7.38 (t, J = 3.2 Hz, 3H, Ar–H), 7.32 (t, J = 7.2 Hz, 2H, Ar–H), 7.23–7.19 (m, 1H, Ar–H), 7.10 (d, J = 15.6 Hz, 1H, =CH), 2.68 (s, 3H, CH_3), 2.35 (s, 3H, CH_3)	71.67 (71.83)	5.69 (5.42)	8.51 (8.38)
26	2-CH_3	3,4,5-OCH_3	28.0	146–148	7.63 (d, J = 15.6 Hz, 1H, =CH), 7.54 (d, J = 7.6 Hz, 1H, Ar–H), 7.34–7.31 (m, 2H, Ar–H), 7.22 (t, J = 7.6 Hz, 1H, Ar–H), 6.95 (d, J = 15.2 Hz, 1H, =CH), 6.78 (s, 2H, Ar–H), 3.90 (s, 6H, OCH_3), 3.88 (s, 3H, OCH_3), 2.66 (s, 3H, CH_3), 2.35 (s, 3H, CH_3)	65.23 (65.07)	5.81 (5.70)	6.75 (6.60)
27	3-CH_3	3-OCH_3	30.8	164–166	7.70 (d, J = 15.6 Hz, 1H, =CH), 7.32 (t, J = 7.4 Hz, 2H, Ar–H), 7.18 (t, J = 7.0 Hz, 2H, Ar–H), 7.14–7.10 (m[c], 2H, Ar–H), 7.13 (d, J = 15.6 Hz, 1H, =CH), 7.02 (d, J = 7.6 Hz, 1H, Ar–H), 6.94 (dd, J_1 = 2.0 Hz, J_2 = 2.4 Hz, 1H, Ar–H), 3.85 (s, 3H, OCH_3), 2.70 (s, 3H, CH_3), 2.40 (s, 3H, CH_3)	69.25 (69.20)	5.68 (5.53)	7.77 (7.69)
28	3-CH_3	H	33.8	173–175	7.76 (d, J = 15.2 Hz, 1H, =CH), 7.60 (dd, J_1 = 3.6 Hz, J_2 = 2.0 Hz, 2H, Ar–H), 7.41 (t, J = 3.2 Hz, 3H, Ar–H), 7.34–7.28 (m, 2H, Ar–H), 7.16 (d, J = 15.6 Hz, 1H, =CH), 7.16 (m[c], 2H, Ar–H), 2.72 (s, 3H, CH_3), 2.41 (s, 3H, CH_3)	71.75 (71.83)	5.60 (5.42)	8.57 (8.38)
29	3-CH_3	4-Cl	29.3	196–198	7.69 (d, J = 15.6 Hz, 1H, =CH), 7.52 (d, J = 8.8 Hz, 2H, Ar–H), 7.37 (d, J = 8.4 Hz, 2H, Ar–H), 7.31 (t, J = 8.0 Hz, 1H, Ar–H), 7.17 (d, J = 8.4 Hz, 1H, Ar–H), 7.14 (m[c], 2H, Ar–H), 7.11 (d, J = 15.6 Hz, 1H, =CH), 2.70 (s, 3H, CH_3), 2.40 (s, 3H, CH_3)	65.28 (65.12)	4.73 (4.65)	7.48 (7.59)
30	3-CH_3	3,4,5-OCH_3	11.8	190–192	7.66 (d, J = 15.2 Hz, 1H, =CH), 7.31 (t, J = 7.6 Hz, 1H, Ar–H), 7.18 (d, J = 8.8 Hz, 1H, Ar–H), 7.14 (s, 1H, Ar–H), 7.03 (m[c], 1H, Ar–H), 7.02 (d, J = 14.8 Hz, 1H, =CH), 6.81 (s, 2H, Ar–H), 3.91 (s, 6H, 2×OCH_3), 3.90 (s, 3H, OCH_3), 2.70 (s, 3H, CH_3), 2.40 (s, 3H, CH_3)	65.19 (65.07)	5.87 (5.70)	6.71 (6.60)
31	3-CH_3	2-Cl	45.8	174–176	8.12 (d, J = 15.6 Hz, 1H, =CH), 7.68–7.66 (m, 1H, Ar–H), 7.44–7.42 (m, 1H, Ar–H), 7.33–7.29 (m, 3H, Ar–H), 7.18–7.16 (m[c], 2H, Ar–H), 7.13 (d, J = 15.2 Hz, 1H, =CH), 7.01 (d, J = 7.2 Hz, 1H, Ar–H), 2.69 (s, 3H, CH_3), 2.40 (s, 3H, CH_3)	65.30 (65.12)	4.53 (4.65)	7.44 (7.59)
32	4-Cl	H	38.8	199–202	7.76 (d, J = 15.2 Hz, 1H, =CH), 7.60 (dd, J_1 = 3.6 Hz, J_2 = 2.4 Hz, 2H, Ar–H), 7.41(dd, J_1 = 4.0 Hz, J_2 = 3.2 Hz, 4H, Ar–H), 7.38–7.33 (m, 3H, Ar–H), 7.15 (d, J = 15.2 Hz, 1H, =CH), 2.71 (s, 3H, CH_3)	[b]		
33	4-Cl	3-OCH_3	48.8	190–192	7.71 (d, J = 15.2 Hz, 1H, =CH), 7.40–7.31 (m, 5H, Ar–H), 7.19 (d, J = 7.6 Hz, 1H, Ar–H), 7.12 (d, J = 15.2 Hz, 1H, =CH), 7.10 (m[c], 1H, Ar–H), 6.96 (dd, J_1 = 2.0 Hz, J_2 = 2.4 Hz, 1H, Ar–H), 3.85 (s, 3H, OCH_3), 2.70 (s, 3H, CH_3)	62.60 (62.41)	4.82 (4.45)	7.45 (7.28)
34	4-Cl	4-Cl	40.9	242–244	7.70 (d, J = 15.6 Hz, 1H, =CH), 7.53 (d, J = 8.4 Hz, 2H, Ar–H), 7.41–7.33 (m, 6H, Ar–H), 7.10 (d, J = 15.2 Hz, 1H, =CH), 2.70 (s, 3H, CH_3)	[b]		
35	4-Cl	3,4,5-OCH_3	41.9	233–235	7.67 (d, J = 15.6 Hz, 1H, =CH), 7.36 (dd, J_1 = 8.8 Hz, J_2 = 8.4 Hz, 4H, Ar–H), 7.01 (d, J = 15.6 Hz, 1H, =CH), 6.81 (s, 2H, Ar–H), 3.92 (s, 6H, 2×OCH_3), 3.90 (s, 3H, OCH_3), 2.71 (s, 3H, CH_3)	59.25 (59.39)	4.79 (4.76)	6.43 (6.30)
36	4-Cl	4-OCH_3	27.0	211–212	7.72 (d, J = 15.2 Hz, 1H, =CH), 7.55 (d, J = 8.4 Hz, 2H, Ar–H), 7.36 (dd, J_1 = 9.2 Hz, J_2 = 7.2 Hz, 4H, Ar–H), 7.02 (d, J = 15.2 Hz, 1H, =CH), 6.92 (d, J = 8.4 Hz, 2H, Ar–H), 3.85 (s, 3H, OCH_3), 2.70 (s, 3H, CH_3)	[b]		
37	3-Cl	3-OCH_3	19.5	188–190	7.72 (d, J = 15.2 Hz, 1H, =CH), 7.43 (t, J = 2.0 Hz, 1H, Ar–H), 7.36–7.28 (m, 3H, Ar–H), 7.20 (d, J = 8.0 Hz, 1H, Ar–H), 7.15–7.10 (m[c], 2H, Ar–H), 7.14 (d, J = 15.6 Hz, 1H, =CH), 6.95 (dd, J_1 = 2.4 Hz, J_2 = 2.4 Hz, 1H, Ar–H), 3.86 (s, 3H, OCH_3), 2.71 (s, 3H, CH_3)	62.34 (62.41)	4.62 (4.45)	7.53 (7.28)
38	3-Cl	H	26.4	210–212	7.76 (d, J = 15.2 Hz, 1H, =CH), 7.62–7.59 (m, 2H, Ar–H), 7.43–7.40 (m, 4H, Ar–H), 7.36–7.28 (m, 2H, Ar–H), 7.16 (d, J = 15.2 Hz, 1H, =CH), 7.15–7.13 (m[c], 1H, Ar–H), 2.72 (s, 3H, CH_3)	64.49 (64.31)	4.41 (4.26)	7.73 (7.89)
39	3-Cl	4-Cl	13.5	207–209	7.70 (d, J = 15.6 Hz, 1H, =CH), 7.53 (d, J = 8.4 Hz, 2H, Ar–H), 7.43 (t, J = 2.0 Hz, 1H, Ar–H), 7.39–7.27 (m, 4H, Ar–H), 7.16 (m[c], 1H, Ar–H), 7.12 (d, J = 15.2 Hz, 1H, =CH), 2.71 (s, 3H, CH_3)	58.45 (58.62)	3.74 (3.62)	7.39 (7.20)
40	3-Cl	3,4,5-OCH_3	24.7	215–217	7.67 (d, J = 15.2 Hz, 1H, =CH), 7.44 (t, J = 2.0 Hz, 1H, Ar–H), 7.33–7.28 (m, 2H, Ar–H), 7.14 (d, J = 7.6 Hz, 1H, Ar–H), 7.03 (d, J = 15.2 Hz, 1H, =CH), 6.81 (s, 2H, Ar–H), 3.92 (s, 6H, 2×OCH_3), 3.90 (s, 3H, OCH_3), 2.71 (s, 3H, CH_3)	59.47 (59.39)	4.91 (4.76)	6.53 (6.30)
41	3-Cl,4-F	3,4,5-OCH_3	81.3	241–243	7.72 (d, J = 15.6 Hz, 1H, =CH), 7.59–7.05 (m, 5H, Ar–H), 7.02 (d, J = 15.2 Hz, 1H, =CH), 3.99 (s, 6H, 2×OCH_3), 3.96 (s, 3H, OCH_3), 2.79 (s, 3H, CH_3)	57.26 (57.08)	4.64 (4.35)	6.24 (6.05)

[a] The data are experimental found by HRMS (APCI) or elemental analysis, and the data in the parentheses are calculated.
[b] Known compounds, see Ref. 13.
[c] Overlapped with =CH signals.

Table 2
Anticancer activities against BGC-823, PC-3, NCI-460, BEL-7402 cell lines in vitro[a]

Compds	Cancer cell inhibition, IC_{50} (μM)			
	BGC-823	PC-3	NCI-H460	BEL-7402
5	10.64	7.99	22.67	21.54
6	22.69	>25	>25	>25
7	>25	>25	>25	>25
8	8.35	10.10	20.07	>25
9	>25	>25	>25	>25
10	>25	19.33	>25	>25
11	>25	>25	>25	>25
12	>25	>25	>25	>25
13	>25	>25	>25	>25
14	>25	>25	>25	>25
15	>25	>25	>25	>25
16	>25	>25	>25	>25
17	14.29	>25	>25	>25
18	19.53	>25	>25	>25
19	22.76	>25	>25	>25
20	>25	>25	>25	>25
21	>25	>25	>25	>25
22	>25	>25	>25	>25
23	>25	>25	>25	>25
24	>25	>25	>25	>25
25	>25	>25	>25	>25
26	5.40	>25	6.32	10.28
27	>25	>25	>25	>25
28	13.62	11.68	21.83	>25
29	>25	>25	>25	>25
30	17.22	>25	19.83	>25
31	24.15	22.17	>25	>25
32	>25	24.60	>25	>25
33	>25	>25	>25	>25
34	>25	>25	>25	>25
35	>25	>25	22.00	>25
36	>25	>25	>25	>25
37	nt	>25	>25	>25
38	>25	>25	>25	>25
39	>25	>25	>25	>25
40	11.59	>25	>25	13.97
41	9.70	nt	6.31	nt
DDP	21.43	19.06	2.57	17.90

[a] Values presented are means of three experiments; nt = not tested.

methods in high yields.[14,15] 3-Chloropentane-2,4-dione **2** was prepared by acetylacetone and NCS (*N*-chlorosuccinimide) refluxing in carbon tetrachloride. The aminothiazoles **3a**–**h** were prepared by thioureas **1a**–**h** and **2** refluxing in methanol with 54.2–77.5% yields.[16] The desired thiazolyl–chalcones **5**–**41** were obtained by aminothiazoles **3a**–**h** condensed with the corresponding arylaldehydes **4** catalyzed by potassium hydroxide in refluxing THF.[17] The structures of compounds **5**–**41** were confirmed by IR, ^{1}H NMR, MS, HRMS or elemental analysis, and the results were summarized in Table 1. The configuration of compounds **5**–**41** is of the *trans* form, as the coupling constant of two protons on vinyl bond is above 15.0 Hz. For example, in ^{1}H NMR spectrum of compound **5**, there are two doublet peaks at 7.79 and 7.16 ppm with coupling constant J = 15.2 Hz.

All thiazolyl–chalcones **5**–**41** were evaluated by MTT assay on growth of human gastric cancer BGC-823, human prostate carcinoma PC-3, human lung carcinoma NCI-H460, hepatocellular carcinoma BEL-7402 cell lines. Cisplatin (DDP) was introduced as a positive control in the assay. The results were summarized in Table 2.

When testing in high concentration at 100 μg/mL, many thiazolyl–chalcones with low solubility were precipitated out partially that influenced the precision of MTT assay and the inhibition rates for most compounds exceeded 80% observed by microscope. From Table 2, some preliminary structure–activity relationships concerning the effect of substituents R^1 and R^2 could be drawn. Comparing the results of compounds **5**–**10** with the same R^1 substituent (R^1 = 3,4-Cl) but different R^2, it could be found that compounds **5** (R^2 = H) and **8** (R^2 = 3-OCH_3) have better anticancer activities. Moreover, compound **26** (R^2 = 3,4,5-OCH_3) has better activities among compounds **22**–**26** (R^1 = 2-CH_3), and **28** (R^2 = H) has better activities among **27**–**31** (R^1 = 3-CH_3), and **37** (R^2 = 3-OCH_3) have better activities among **37**–**40** (R^1 = 3-Cl). Therefore, substituents R^2 like H, 3-OCH_3, 3,4,5-OCH_3 may be positive to enhance the activities. On the other hand, comparing the activities of compounds **10**, **16**, **21**, **26**, **30**, **35**, **40** and **41**, they have the same R^2 (R^2 = 3,4,5-OCH_3) but different R^1. For prostate carcinoma PC-3 cell lines, compound **10** (R^1 = 3,4-Cl) has better activity, and for NCI-H460, BGC-823 and BEL-7402, compound **26** (R^1 = 2-CH_3) has better activities. Comparing the activities of compounds **8**, **14**, **17**, **24**, **27**, **33** and **37**, which have the same R^2 (R^2 = 3-OCH_3), it could be found that compound **8** (R^1 = 3,4-Cl) has better activities. Also, comparing the activities of compounds **5**, **12**, **18**, **25**, **28**, **32** and **38** with the same R^2 (R^2 = H), compounds **5** (R^1 = 3,4-Cl) and **28** (R^1 = 3-CH_3) have better activities. So the better substituent R^1 may be 3,4-Cl, 2-CH_3 or 3-CH_3 moieties.

Table 3
Antitumor efficacy of selected compounds **10** and **41** against S180 xenograft in mice[a]

Groups	Dose (mg/kg)	Ad.	No. animals[b]	TW (g)[c]	TWI (%)[d]
Control	—	Ip	10	2.52 ± 0.80	—
CTX	100	Ip	8	0.21 ± 0.05*	91.68
10	25	Ip	8	2.64 ± 0.70	—
10	50	Ip	8	1.89 ± 0.37	25.15
41	25	Ip	8	1.94 ± 0.74	22.97
41	50	Ip	8	1.95 ± 0.37	22.61

* p <0.01, compared to control.
[a] Values presented are means ± SD. Statistical analysis: student t-test.
[b] Number of mice tested in the group.
[c] Average tumor-weight after drug treatment.
[d] Percentage of tumor-weight inhibition versus control group.

Compounds **10** and **41** were also selected to evaluate their antitumor activity in vivo in ICR mice bearing sarcoma 180 cells. Cytophosphane (CTX) was used as a positive control and physiological saline as a blank control. The results presented in Table 3 showed that compound **10** through intraperitoneal injection (ip) administration at dose of 50 mg/kg, exhibited moderate experimental therapeutic efficacy by 25%, but no tumor inhibition was observed when the dose was decreased to 25 mg/kg. And compound **41** exhibited equivalent antitumor activity by about 23% at doses of 50 or 25 mg/kg. Anatomical observation found that compound **41**

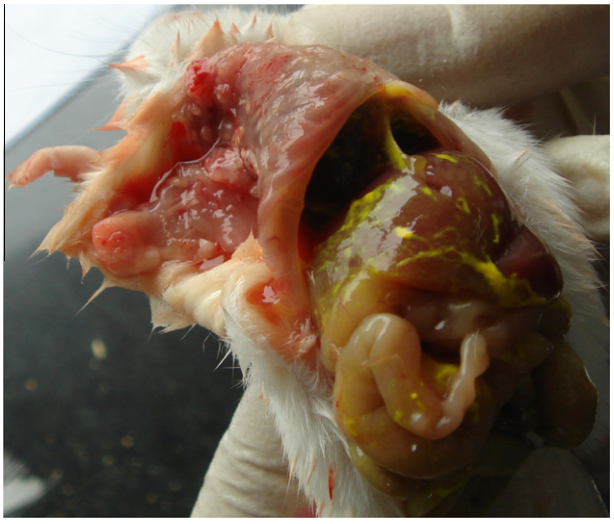

Figure 1. Anatomical observation indicating precipitation of compound **41** and intestinal obstruction in mouse.

precipitated partially in body and led to intestinal obstruction as shown in Figure 1.

In conclusion, we synthesized a series of thiazolyl–chalcones (*E*)-1-(4-methyl-2-arylaminothiazol-5-yl)-3-arylprop-2-en-1-ones and evaluated their activities against several cancer cell lines in vitro, and compounds **10** and **41** were tested antitumor activity in vivo against S180 xenograft in mice. Results showed the idea is true that introduction of thiazole groups into chalcones can improve their anticancer activities and some compounds exhibited potential anticancer activities. Further studies including the modification with solubility-enhancing groups are undertaken.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.09.041.

References and notes

1. Fontecave, M.; Ollagnier-de-Choudens, S.; Mulliez, E. *Chem. Rev.* **2003**, *103*, 2149.
2. Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances*, 4th ed.; Thieme: Stuttgart, 2001.
3. Bharti, S. K.; Nath, G.; Tilak, R.; Singh, S. K. *Eur. J. Med. Chem.* **2010**, *45*, 651.
4. Gouda, M. A.; Berghot, M. A.; El-Ghani, G. E. A.; Khalil, A. M. *Eur. J. Med. Chem.* **2010**, *45*, 1338.
5. Medime, E.; Capan, G. *II Farmaco* **1994**, *49*, 449.
6. Gillespie, R. J.; Cliffe, I. A.; Dawson, C. E.; Dourish, C. T.; Gaur, S.; Giles, P. R.; Jordan, A. M.; Knight, A. R.; Lawrence, A.; Lerpiniere, J.; Misra, A.; Pratt, R. M.; Todd, R. S.; Upton, R.; Weiss, S. M.; Williamson, D. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2920.
7. Bell, F. W.; Cantrell, A. S.; Hogberg, M.; Jaskunas, S. R.; Johansson, N. G.; Jordan, C. L.; Kinnick, M. D.; Lind, P.; Morin, J. M.; Noreen, R.; Oberg, B.; Palkowitz, J. A.; Parrish, C. A.; Pranc, P.; Sahlberg, C.; Ternansky, R. J.; Vasileff, R. T.; Vrang, L.; West, S. J.; Zhang, H.; Zhou, X. X. *J. Med. Chem.* **1995**, *38*, 4929.
8. Cortes, J.; Rousselot, P.; Kim, D. W.; Ritchie, E.; Hamerschlak, N.; Coutre, S.; Hochhaus, A.; Guilhot, F.; Saglio, G.; Apperley, J.; Ottmann, O.; Shah, N.; Erben, P.; Branford, S.; Agarwal, P.; Gollerkeri, A.; Baccarani, M. *Blood* **2007**, *109*, 3207.
9. Kim, J. H.; Ryu, H. W.; Shim, J. H.; Park, K. H.; Withers, S. G. *ChemBioChem* **2009**, *10*, 2475.
10. Liu, X.-L.; Go, M.-L. *Bioorg. Med. Chem.* **2007**, *15*, 7021.
11. Henmi, K.; Hiwatashi, Y.; Hikita, E.; Toyama, N.; Hirano, T. *Biol. Pharm. Bull.* **2009**, *32*, 1109.
12. Gacche, R. N.; Dhole, N. A.; Kamble, S. G.; Bandgar, B. P. *J. Enzyme Inhib. Med. Chem.* **2008**, *23*, 28.
13. Patil, V. H.; Mane, R. A.; Ingle, D. B. *Indian J. Chem.* **1978**, *16B*, 1114.
14. Liu, B.; Gao, H. Q.; Zhou, X. J. *Chemistry (Hua Xue Tong Bao)* **1994**, *57*, 42.
15. Lin, Y.-F.; Hu, W.-X.; Yang, Z.-Y.; Wang, L.-G. *J. Zhejiang Univ. Technol.* **2007**, *35*, 27.
16. *General procedure for preparation of compounds* **3a**–**h**: To a stirred solution of 1-(3,4-dichlorophenyl)thiourea **1a** (11.05 g, 50 mmol) in methanol (100 mL) below 25 °C, was added a solution of 3-chloropentane-2,4-dione (6.73 g, 50 mmol) in methanol (15 mL). After addition, the reaction was kept at refluxing to reach completion. After cooling in ice, white solid was precipitated and treated with 5% K_2CO_3 to adjust pH to 7–8. Compound **3a** was filtered and crystallized from ethyl acetate, pale yellow crystals, 11.66 g (yield 77.5%), mp: 220–221 °C; IR ν_{max} (KBr)/cm^{-1}: 3270, 3070, 1604, 1587, 1546, 1472, 1362, 1318; ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ: 7.56 (d, J = 2.0 Hz, 1H, Ar–H), 7.47 (d, J = 8.5 Hz, 1H, Ar–H), 7.24 (dd, J_1 = 2.0 Hz, J_2 = 8.5 Hz, 1H, Ar–H), 2.65 (s, 3H, CH_3), 2.50 (s, 3H, CH_3CO); EIMS m/z (%): 300 (M^+, 80), 285 (100), 257 (12), 218 (7), 186 (6), 172 (7), 86 (13), 71 (9). Compounds **3b**–**h** was synthesized in the same manner by reaction of the corresponding N-substituted thioureas **1b**–**h** with 3-chloro-acetylaceton **2**, respectively.
17. *General procedure for preparation of compounds* **5**–**41**: To a cooled mixture of 1-(2-(3,4-dichlorophenylamino)-4-methylthiazol-5-yl)ethanone **3a** (3.01 g, 10 mmol), benzaldehyde (1.27 g, 12 mmol) and tetrahydrofuran (40 mL) in ice at about 5 °C, was added dropwise 40% aq potassium hydroxide (5.5 mL) and then the reaction mixture was allowed to reflux until completion (EtOAc/toluene = 2:1, monitored by TLC). It was then poured into icy water containing acetic acid (30 mL) and stood overnight in refrigerator. The precipitated was filtered and washed with H_2O, recrystallized from THF/EtOAc to get pure **5**, yellow-brown solid, 1.93 g (yield 49.6%), mp: 213–215 °C; IR ν_{max} (KBr)/cm^{-1}: 3443, 3287, 3110, 1642, 1608, 1542, 1474. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ: 7.79 (d, J = 15.2 Hz, 1H, =CH), 7.63–7.19 (m, 8H, Ar–H), 7.16 (d, J = 15.2 Hz, 1H, =CH), 2.75 (s, 3H, CH_3). HRMS (APCI): calcd for $C_{19}H_{14}^{35}Cl_2N_2OS$+H 389.0282. Found 389.0280. Compounds **6**–**41** were synthesized in the same manner.