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CONCISE ARTICLE

Synthesis and Biological Evaluation of N-(4-phenylthiazol-2-yl) Cinnamamide Derivatives as Novel Potential Anti-tumor Agents†

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In this study, a series of novel N-(4-phenylthiazol-2-yl) cinnamamide derivatives (**7a~8n**) were synthesized and evaluated for their anti-proliferative activities *in vitro* by MTT assay and the possible antitumor mechanism was also explored. The SAR analysis showed that the steric effect played an important role on the anti-tumor activity. The most potent analogue **8f** showed excellent inhibitions on the K562, Bel7402, A549 and Jurkat cells ranging from sub-micromolar to nanomolar concentration. Compound **8f** inhibited Jurkat cells with IC_{50} value of 0.035 μM with no apparent toxicity in different non-cancerous cells. Furthermore, it was suggested that the possible mechanism of **8f** might be associated with inducing cancer cells apoptosis on the results of flow cytometer analysis and Hoechst 33358 staining assays.

Introduction

Cancer continues to be a major public health problem in the world due to the highly cancer occurrence.[1] As some chemotherapy drugs had severely side effect or caused therapy resistance,[2, 3] efficiency and low toxicity drugs were imperative needed. Cancer cell survival status was related to various factors, including self-sufficiency in growth signals, evasion of programmed cell death (apoptosis), insensitivity to growth-inhibitory signals, sustained angiogenesis, limitless replicative potential, the tissue invasion and metastasis, in which the deregulation of apoptosis was believed to be a hallmark of most types of cancer.[4-6] Thus, compounds that restore apoptosis could be effective drugs to address uncontrolled proliferation cancer cells.[7]

Thiazole derivatives played a wide range of potential applications in many areas such as anti-bacteria, anti-fungal, anti-tubercular, anti-virals, anti-epileptic and anti-cancer activities.[8-13] As a thiazol-2-amine derivative, particularly, Dasatinib had been in clinical application successfully.[14] Apart from it, phenyl thiazole-2-amine derivatives had also been found potent anti-cancer activity, such as tubulin polymerization inhibitor CKD-516 which had significant growth inhibition against CT26 colon cancer *in vivo*.[15] In addition, another phenyl thiazole-2-amine derivative TR-644 showed potent microtubule depolymerizing activity, caused cell cycle arrest and inhibited angiogenesis.[16] On the other hands, some cinnamamide derivatives could also display potent anti-tumor effect through inducing apoptosis and coursing cell cycle arrest.[17-21] Conjugating different potent bioactivity structural moiety together might exhibit unpredictable effect and it might provide a method to find novel anti-cancer molecules.[22] Therefore, these findings prompted our further investigations on the anti-tumor effects of N-(4-phenylthiazol-2-yl) cinnamamide derivatives (Fig. 1).

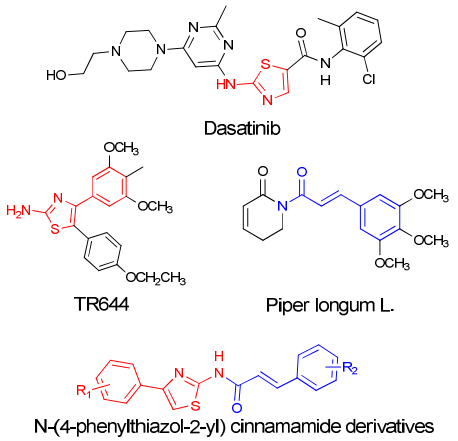


Fig.1 The chemical structures of the representative derivatives containing thiazol-2-amine, phenyl thiazole-2-amine and cinnamamide groups and the conjugating moiety designed.

From the conjugation ideal described above, we designed, synthesized and screened some N-(4-phenylthiazol-2-yl) cinnamamide derivatives through our privileged small molecule library. (*E*)-3-(4-morpholinophenyl)-N-(4-phenylthiazol-2-yl) acrylamide (compound **1**) was first found moderate inhibition (IC_{50}=12.58 μM) against chronic myeloid leukemia (CML) K562 cells in MTT assay (Fig. 2). In order to develop more potent anti-tumor agents, a series of novel N-(4-phenylthiazol-2-yl) cinnamamide derivatives compounds **7a~8n** were synthesized and evaluated for their anti-tumor activities.

Moreover, the possible mechanism of the most potent inhibitor (**8f**) was further investigated by flow cytometer as well as Hoechst 33358 staining. The results implied that its activity might be associated with inducing cancer cells apoptosis. To our best knowledge, none of the N-(4-phenylthiazol-2-yl) cinnamamide derivatives were reported to trigger apoptosis process as anti-cancer drugs.

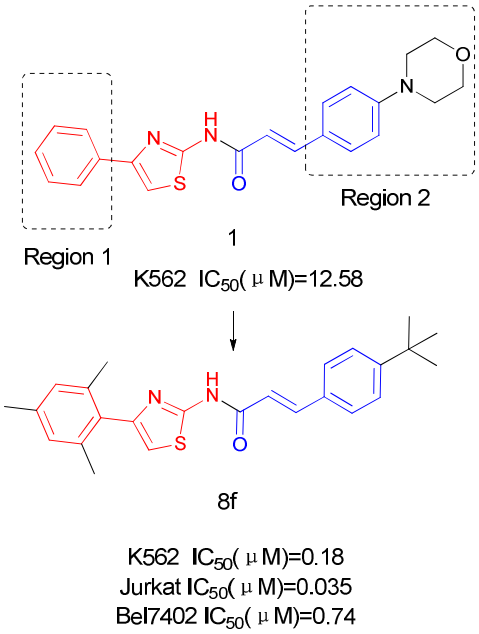
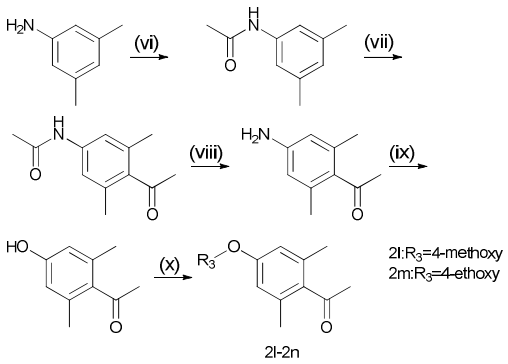


Fig.2 The structure of compound **1** and **8f**

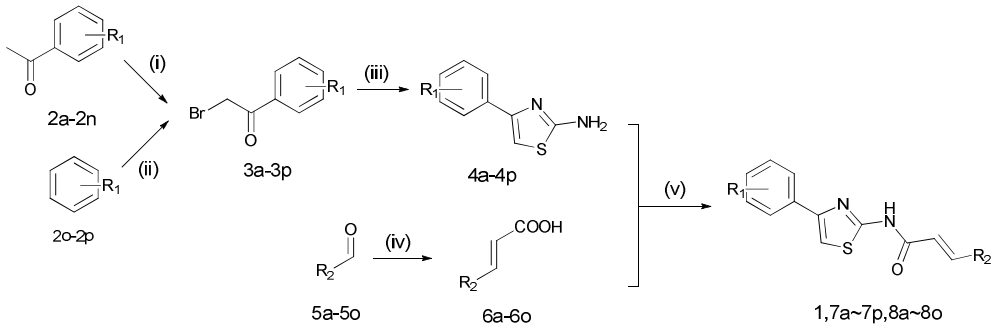
Results and discussion

Chemistry

The N-(4-phenylthiazol-2-yl) cinnamamide derivatives **1** and **7a~8o** could be prepared according to Scheme1. Bromination of **2a-2n** with Tetrabutylammonium tribromide afforded the α-bromination ketone **3a-3n**, and Friedel-Crafts acylation of commercial available **2o-2p** generated α-bromination ketone **3o-3p**. The crucial building block **4a-4p** was prepared by cyclizing **3a-3p** with thiocarbamide in refluxing alcohol.[23] Another key intermediates **6a-6o** were synthesized in light of Knoevenagel reaction from different aromatic aldehyde **5a-5o**.[24] Then condensation of various cinnamic acids **6a-6o** with **4a-4p** afforded corresponding products **7a-8o**. Synthetic approaches of the **2l** and **2n** were described in Scheme 2.[25] With using 3, 5-dimethylaniline as starting material, **2l-2n** could be prepared by five steps. All the structures of these compounds were determined by ^{1}H-NMR, ^{13}C-NMR and HR-MS.



Scheme 2 Reagents and conditions: (vi) Acetyl chloride, K_2CO_3, DCM, r.t., 2 h, 98.8%; (vii) Acetyl chloride, $AlCl_3$, DCM, 0 ℃-r.t., 3 h; (viii) 2N HCl, 80~100 ℃, 2 h, 97.5%; (ix) $NaNO_2$, HCl, H_2O, 0-100 ℃, 1.5 h, 33%; (x) Iodomethane or Iodoethane, K_2CO_3, Me_2CO, reflux, 99.6~99.8%.



1,2a-2p,3a-3p,4a-4p,7a~7p:
R_2=4-morpholinophenyl
1: R_1=H
a:R_1=*p*-OCH_3
b:R_1=*m*-OCH_3
c:R_1=*o*-OCH_3
d:R_1=*p*-F
e:R_1=*m*-F
f:R_1=*o*-F
g:R_1=*p*-CH_3
h:R_1=*m*-CH_3
i:R_1=*o*-CH_3
j:R_1=2,4-dimethyl
k:R_1=3,5-dimethyl
l:R_1=4-methoxy-2,6-dimethyl
m:R_1=4-ethoxy--2,6-dimethyl
n:R_1= 2,4,6-trifluoro
o:R_1=2,6-difluoro-4-methyl
p:R_1= 2,4,6-trimethyl

5a-5o,6a-6o,8a~8o:
R_1= 2,4,6-trimethyl
a:R_2=4-methoxyphenyl
b:R_2=4-ethoxyphenyl
c:R_2=4-(2-methoxyethoxy)phenyl
d:R_2=3,4,5-trimethoxyphenyl
e:R_2=4-methylphenyl
f:R_2=4-(*tert*-butyl)phenyl
g:R_2=4-fluorophenyl
h:R_2=4-bromophenyl
i:R_2=4-nitrophenyl
j:R_2=4-(trifluoromethyl)phenyl
k:R_2=4-chloro-3-(trifluoromethyl)phenyl
l:R_2=4-cyclopropylphenyl
m:R_2=(4-piperidin-1-yl)phenyl
n:R_2=pyridin-4-yl
o:R_2=phenyl

Scheme 1 Reagents and conditions: (i) Tetrabutylammonium tribromide, acetonitrile, 12 h; (ii) Bromoacetyl bromide, $AlCl_3$, DCM, 0 ℃, 5 min; (iii) Thiourea, EtOH, reflux, 3 h, 50~96%; (iv) Malonic acid, piperdine, pyridine, 115 ℃, 8 h, 60~97%; (v) EDCI, DMAP, DCM, r.t., 1 d, 29~80%.

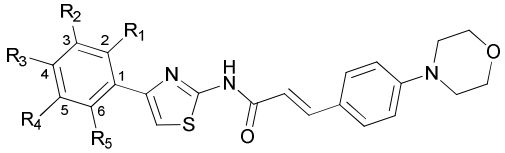
Biological evaluation

Cytotoxicity *in vitro*

The cytotoxicity of the synthesized compounds was tested on chronic myeloid leukemia cell line (K562) by the MTT assay,[26] and Paclitaxel was used as a positive control. The IC_{50} were expressed and summarized in Table 1~3. All the compounds exhibited activities ranging from 0.035 to 40.38 μM, and several compounds like **8f**, **8j**, **8l**, **7p** and **7l** were much more potent than Paclitaxel.

The SAR study mainly focused on the two parts of the hit compound **1**. Compounds **7a-7p** were synthesized to investigate the influence of the phenyl group in region 1 on the potency. A single substituent with suitable size on the phenyl ring could improve the activity, as illustrated by the fluoro substituted analogs **7d-7f** and methyl substituted analogs **7h-7i**, while a much bulkier group like methoxy (**7a-7c**) was detrimental to the potency. Substituent on *ortho*-position of the phenyl ring could improve the activity moderately, as illustrated by the single substituted analogs **7f**, **7i** and *di*-substituted analogue **7j**. *Tri*-substituted phenyl ring could improve the potency substantially, especially the introduction of methyl on both *ortho*-positions of phenyl ring (**7l**, **7m** and **7p**). Optimization on region 1 showed that 2, 4, 6-trimethyl phenyl was the most suitable group for anti-cancer activity.

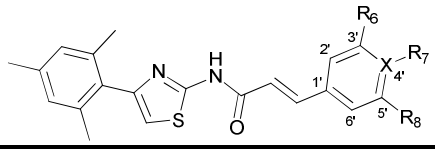
Table 1 The anti-proliferative activities of compounds 1, 7a~7p[a]



Cpd.	R_1	R_2	R_3	R_4	R_5	IC_{50} (μM) K562
1	H	H	H	H	H	12.58
7a	H	H	OCH_3	H	H	14.59
7b	H	OCH_3	H	H	H	25.16
7c	OCH_3	H	H	H	H	>90
7d	H	H	F	H	H	7.30
7e	H	F	H	H	H	5.73
7f	F	H	H	H	H	4.18
7g	H	H	CH_3	H	H	>90
7h	H	CH_3	H	H	H	7.51
7i	CH_3	H	H	H	H	3.74
7j	CH_3	H	CH_3	H	H	5.38
7k	H	CH_3	H	CH_3	H	>90
7l	**CH_3**	**H**	**OCH_3**	**H**	**CH_3**	**1.00**
7m	CH_3	H	OCH_2CH_3	H	CH_3	2.09
7n	F	H	OCH_3	H	F	30.31
7o	F	H	F	H	F	5.15
7p	**CH_3**	**H**	**CH_3**	**H**	**CH_3**	**0.61**
Paclitaxel						1.26

[a] IC_{50} value was average of three determinations and deviation from the average was <5% of the average value.

Table 2 The anti-proliferative activities of compounds 7p, 8a~8n[a]



Cpd.	R_6	R_7	R_8	X	IC_{50} (μM) K562
7p	**H**	**Morpholino**	**H**	**C**	**0.61**
8a	H	OCH_3	H	C	4.16
8b	H	OCH_2CH_3	H	C	2.48
8c	H	$OCH_2CH_2OCH_3$	H	C	1.49
8d	OCH_3	OCH_3	OCH_3	C	11.75
8e	H	CH_3	H	C	7.88
8f	**H**	**$C(CH_3)_3$**	**H**	**C**	**0.18**
8g	H	F	H	C	13.98
8h	H	Br	H	C	4.59
8i	H	NO_2	H	C	32.18
8j	**H**	**CF_3**	**H**	**C**	**0.48**
8k	H	Cl	CF_3	C	3.06
8l	**H**	**Cyclopropane**	**H**	**C**	**0.38**
8m	H	Piperidine	H	C	4.06
8n	H	-	H	N	9.39
8o	H	H	H	C	40.38
Paclitaxel					1.26

[a] IC_{50} value was average of three determinations and deviation from the average was <5% of the average value.

Compounds **8a-8o** were subsequently prepared to investigate the SAR on the region 2. As shown in Table 2, when the morpholino group was replaced by H atom (**8o**), a sharp loss of activity was observed, suggesting the substituent on *C4'*-position of phenyl ring was very important. Then we introduced different substituents on this position to investigate the electric and steric effects on the potency. A series of electron-donating alkyoxy substituted analogs were prepared and the potency improved as the increasing of size on the substituent (**8a-8c**), suggesting that a bulky group on this position was favorable. The same tendency could be found from the alky substituted derivatives **8e**, **8f** and **8l**. The introduction of substituent in *meta*-position was unfavorable for the activity, which can be illustrated by the *tri*-substituted analogue **8d**. The electron-withdraw substituted analogs exhibited comparable potency with electron-donating derivatives (**8g-8k**), suggesting that different electric effect group on this position was well tolerated. Altogether, the SAR of region 2 showed that bulky groups or flexible long chain groups on *C4'*-position could effectively increase the potency. Especially, **8f** got a 3-fold and 70-fold more potent activities compared with **7p** and **1,** respectively.

Further studying on the anti-proliferative activity of N-(4-phenylthiazol-2-yl) cinnamamide derivatives **8f**, **8j**, **8l** and **7p** and **7l** against a panel of human cancer cell lines were evaluated, including leukemia cell lines K562, MV4-11, Jurkat, breast cancer cell lines MDA-MB-468, MCF-7, lymphoma cell line LY-1, hepatocellular cell line Bel7402 and lung cancer cell

line A549. As shown in Table 3, all these compounds exhibited good inhibition on different cancer cells, especially on leukemia cell lines. Among these compounds, **8f** showed significant inhibition activities on Jurkat (IC_{50}=0.035 μM), MV4-11 (IC_{50}=0.11 μM) and K562 (IC_{50}=0.18 μM), apparently better than Paclitaxel. In addition, **8f** also showed moderate inhibition against A549 (IC_{50}=0.27 μM) and Bel7402 (IC_{50}=0.74 μM). Moreover, all these compounds showed no significant toxicity against the non-cancerous cell lines, including LO2, VERO and HEK293. Hence, the excellent anti-cancer efficiency and safety *in vitro* encouraged us to investigate the possible molecular mechanism of the lead compound **8f**.

Table 3 The anti-proliferation activities of selective compounds and Paclitaxel against various cancer cell lines and non-cancerous cell lines [a]

Cell Lines	Cell Type	IC_{50} (μ M)[a]					
		8f	**8j**	**8l**	**7p**	**7l**	**Paclitaxel**
K562	Leukemia	**0.18**	**0.48**	0.38	0.61	1.00	1.26
MV4-11		**0.11**	3.65	1.41	6.42	2.73	0.75
Jurkat		**0.035**	1.15	1.24	9.05	1.24	0.69
MCF-7	Breast cancer	>30	>30	7.76	19.96	1.45	9.66
MDA-MB-468		>30	1.53	15.72	>30	>30	0.31
LY-1	Large B cell lymphoma	1.54	3.69	1.63	11.65	>30	0.18
Bel7402	Hepatocellular carcinoma	**0.74**	34.13	6.58	10.60	9.65	>10
A549	Lung adenocarcinoma	**0.27**	**0.20**	1.17	4.29	1.56	0.74
LO2	non-cancerous cells	>90	>90	>90	>90	>90	n.d*
VERO		>90	>90	>90	>90	>90	n.d
HEK293		>90	>90	>90	>90	>90	n.d

[a] Cancer cells and non-cancerous cells were all test for 96h. IC_{50} value was average of three determinations and deviation from the average was <5% of the average value. *n.d. means no detection.

Analysis of apoptosis by Flow Cytometry (FCM) and Hoechst staining

Based on the anti-cancer activation of N-(4-phenylthiazol-2-yl) cinnamamide derivatives, **8f** was chosen for further study its possible mechanism against the most sensitive cell lines, including K562, A549, Jurkat and Bel7402. As indicated in Fig. 3A, when treated with 3.3 μM **8f**, the percentage of apoptotic cells in K562, Jurkat, A549 and Bel7402 were 21.04%, 14.64%, 23.13% and 48.15%, respectively. As shown in Fig. 3B and 3C, **8f** induced apoptosis against Bel7402 cell line in a concentration-dependent manner, from 5.37%, 25.37%, 51.97% and 61.35% after treated with 0.37, 1.1, 3.3 and 10 μM **8f** for 48 h, respectively. The apoptosis-inducing effect was further confirmed by florescence microscopic Hoechst 33358-stained Bel7402 cells, as indicated by bright blue fluorescent cells and condensed nuclei. These results implied that **8f** inhibited the cancer cell proliferation by inducing apoptosis.

Experimental

(A)Cell Culture

The human Bel-7402 cell line was obtained from the China Centre for Type Culture Collection (CTCCC, Wuhan, China). LO2 and VERO cell lines were purchased from Shanghai Institute of Cell Resource Centre of Life Science (Shanghai, China). All other cell lines were acquired from the American Type Culture Collection. Cells were cultured in high glucose type Dulbecco's modified Eagle medium (DMEM) or low glucose type RPMI 1640 medium (Gibco BRL, Grand Island, N.Y.) supplemented with 10 % fetal bovine serum (FBS; Gibco, Auckland, N.Z.), 100 units/mL penicillin and 100μL streptomycin in a humid chamber at 37℃ under 5% CO_2 in atmosphere.

(B)Cell viability assay

For all *in vitro* assays, the dosage was diluted in relevant medium with a final DMSO concentration of less than 0.1 %. The MTT assay was used to measure the cell viability after compounds treatment. Cells were seeded in 96-well micro-plates at a density of 2~5*10^3 cells per well, and then, cultured for 24 h. After treatment with various concentrations of compound for 96 h, 20 μL of MTT solution(5 mg mL^{-1}) was added to each well and incubated 2~4 h at 37 ℃. After that, the supernatant fluid was removed and 150 μL of DMSO was added to dissolve the formazan crystal produced by living cells for 10~20 min. Then, 96-well microplates were read on Spectra MAX M5 microplate spectrophotometer at 570 nm for O.D. values. Statistical analyses were carried out in Graphpad Prism 5 (GraphPad Software Inc.).

(C)Analysis of apoptosis by Flow Cytometry (FCM)

To investigate the apoptosis effect of **8f**, we analysed the percentage of apoptotic cells by FCM after propidium iodide (PI) staining. Briefly, cells were seeded into 2 mL of medium/well in 6-well plates for 24 h and treated with various concentrations of **8f** for another 48 h. Then the cells were washed twice with cold PBS, and next stained PI solution (containing 50 μg mL^{-1} PI and 20μg mL^{-1} RNAase in 0.1 %

sodium citrate plus 0.1 % Triton X-100). The results were tested by FCM (Becton-Dickinson, USA) and analysed by Flow Jo software.

(D)Morphological analysis by Hoechst staining

Morphological changes associated with apoptosis in Bel7402 cells were detected by Hoechst 33358 staining. Briefly, cells were plated in 6-well plates and cultured for 24 h, followed by **8f** treatment for another 48 h. The cells were fixed with paraformaldehyde 15 min and washed twice with PBS. Then, the cells were stained with Hoechst 33358 solutions (5 μg mL-1, in PBS) and examined under fluorescence microscope to identify the nuclear morphology of the apoptotic cells.

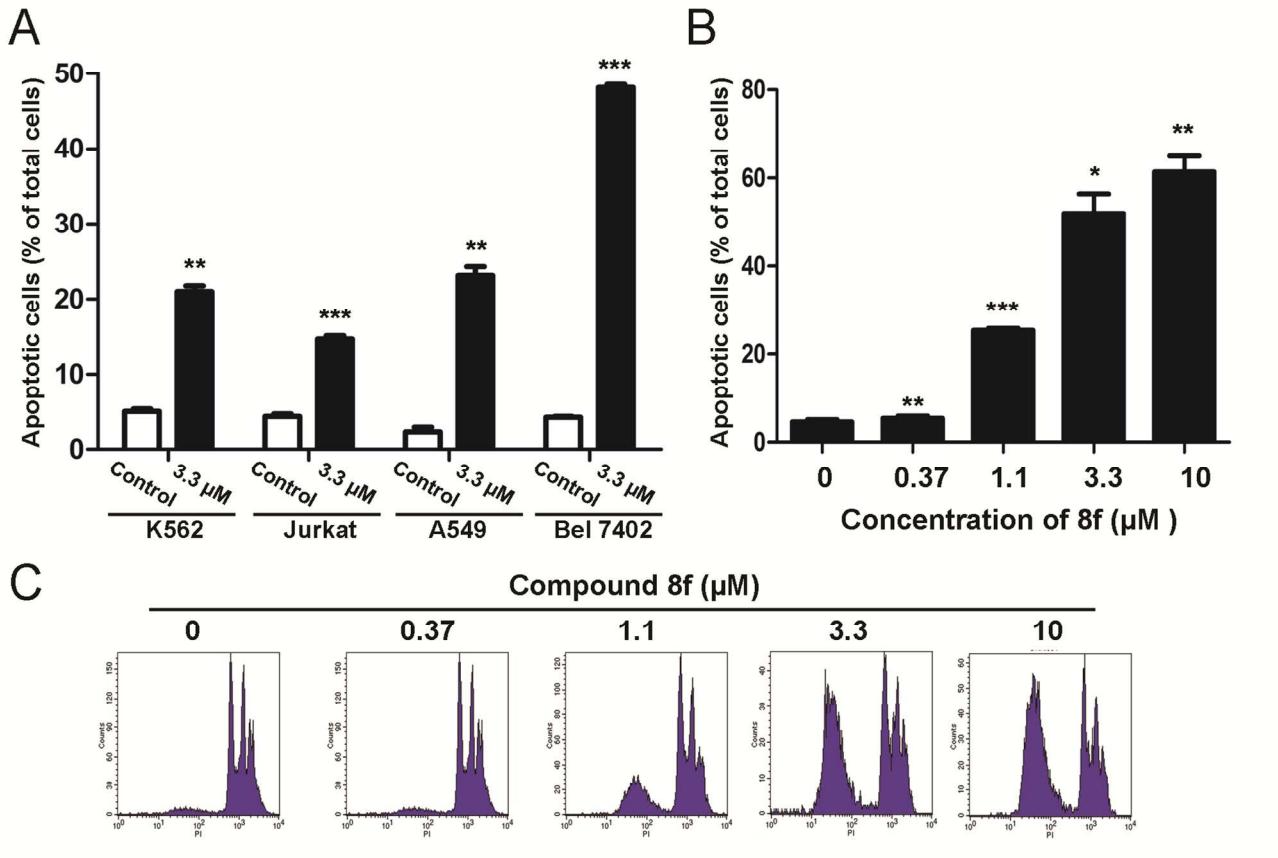


Fig3. Effect of **8f** on the induction of apoptosis: (A) Statistical results of apoptosis assays presented as surviving cells (percentage of untreated control), inducing K562, Jurkat, A549, Bel7402, after treatment with 0.37 or 3.3 μM **8f** for 48 hours. (B) and (C) Flow cytometric analysis and statistical results of PI-stained Bel7402 cells incubation with varying concentrations of **8f** (0.37 μM, 1.1 μM, 3.3 μM, 10 μM) for 48 hours. Date are expressed as mean ± SD. for at least 3 independent experiments (*p<0.05;**p<0.01; ***p<0.001 vs. Vehicle control).

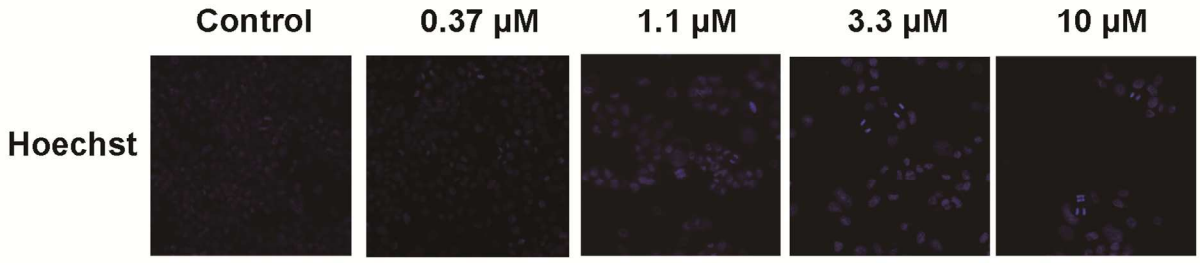


Fig4. Effect of **8f** on cell morphology. The fluorescence microscopic appearance of Hoechst 33358-stained Bel7402 cells which incubated with **8f** for 48 h

Conclusions

In conclusion, we described the discovery and optimization of N-(4-phenylthiazol-2-yl) cinnamamide derivatives as novel potential anti-tumor agents. These compounds were synthesized and evaluated for their anti-cancer activities *in vitro*. The SAR analysis showed that conformational restriction and steric effect played a crucial role on the anti-proliferation activities. The most potent analogue **8f** displayed excellent inhibitory activities against several human cancer cell lines at sub-micromolar to nanomolar concentrations, including K562, Bel7402, A549, MV4-11 and Jurkat, while no apparent toxicity to non-cancerous cells was observed. The further studies of the mechanism of action implied that **8f** might display its anti-cancer activity *via* inducing apoptosis, which was worthy of developing as an anti-cancer candidates.

In brief, our results provided interesting information for the design of novel N-(4-phenylthiazol-2-yl) cinnamamide derivatives with better anti-cancer potency. Further studies on the exact biological mechanisms and anti-tumor research *in vivo* are underway.

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Notes and references

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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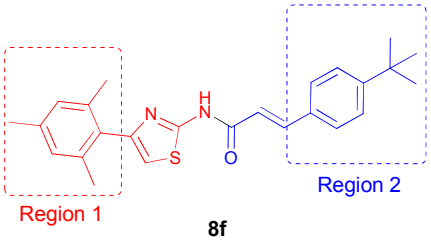
A series of N-(4-phenylthiazol-2-yl) cinnamamide derivatives were synthesized and evaluated bioactivity *in vitro* by MTT assay, further studies revealed that the activity might be associated with inducing cancer cells apoptosis.



8f

K562 IC_{50}(μ M)=0.18
Jurkat IC_{50}(μ M)=0.035
Bel7402 IC_{50}(μ M)=0.74
A549 IC_{50}(μ M)=0.27