Journal of Enzyme Inhibition and Medicinal Chemistry

ISSN: 1475-6366 (Print) 1475-6374 (Online) Journal homepage: informahealthcare.com/journals/ienz20

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To cite this article: Funda Tay, Leyla Yurttaş & Şeref Demirayak (2012) Synthesis of some N-[4-(benzothiazole-2yl) phenyl]-2-aryloxyacetamide derivatives and their anticancer activities, Journal of Enzyme Inhibition and Medicinal Chemistry, 27:4, 515-520, DOI: 10.3109/14756366.2011.599030

To link to this article: https://doi.org/10.3109/14756366.2011.599030

Published online: 08 Aug 2011.

Journal of Enzyme Inhibition and Medicinal Chemistry, 2012; 27(4): 515–520

ISSN 1475-6366 print/ISSN 1475-6374 online
DOI: 10.3109/14756366.2011.599030

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RESEARCH ARTICLE

Synthesis of some N-[4-(benzothiazole-2yl) phenyl]-2-aryloxyacetamide derivatives and their anticancer activities

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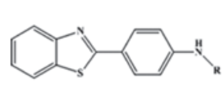
Abstract
In this study, some N-[4-(Benzothiazole-2-yl) phenyl]-2-aryloxyacetamide derivatives were prepared by reacting N-[4-(benzothiazole-2yl)phenyl]-2-chloroacetamide and different substituent phenol or thiophenol derivatives. The anticancer activities of the compounds obtained were investigated. It was observed that some of the compounds, namely **25** and **38**, showed notable anticancer activity.

Keywords: Benzothiazole, antitumour, non-small cell lung cancer, prostate cancer

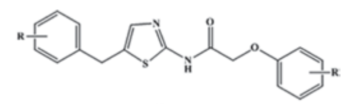
Introduction

Cytotoxic agents conventionally used in cancer treatment (conventional phase-specific purine, pyrimidine bases and non-phase-specific alkylating agents) are known to be toxic and have been criticized because of this, but will continue to be used until the introduction of less harmful agents. Another limitation of cancer treatment is that resistance to anticancer agents develops in tumor cells during clinical use. In addition to the aforementioned drugs, intensive investigation continues into new compounds targeting cancer-specific proteins and affecting different mechanisms, such as topoisomerase and telomerase inhibition[1–3].

In previous studies, 2-(4-aminophenyl) benzothiazole derivatives **I** were shown to have high antitumor activity *in vitro* and *in vivo*[4–6], mainly against breast, renal, colon, ovarian, lung and prostate cancers, despite their simple structures[7–10]. Analysis of structure-activity relationships showed that benzothiazole residues were essential for high activity. A phenyl ring on the 2-position of benzothiazole and alkyl and halogen residues on the 3-position were shown to be effective in increasing activity[10]. The binding of aminophenyl benzothiazoles to β-amyloid using for has been used for imaging and therapy in Alzheimer's disease.[11–12] The several differentially-substituted 2´-(3-aminophenyl)- and 2´-(4-aminophenyl) benzothiazoles were prepared as building blocks and their inhibitory activities were determined on kinase by initially testing *in vitro*[13]. In addition, other notable structures in terms of anticancer activity are compounds of aryloxy-acetamido-thiazole **II** residue. These compounds were reported to be effective therapeutic agents in prostate cancer[14].



I



II

In this study, 2-(aminoaryl)benzothiazole and aryloxy-acetamide residues were combined in a single structure in the light of the data above, N-[4-(Benzothiazole-2-yl) phenyl]-2-aryloxyacetamide compounds were obtained and their effects were evaluated against nine cancer types comprised of approximately sixty cell-lines.

Experimental

Chemistry

The synthesis of 2-(4-aminophenyl)benzothiazole molecules was done using Milestone microwawe reaction

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(Received 22 February 2011; revised 17 June 2011; accepted 18 June 2011)

apparatus. Melting points were determined by using an Electrothermal IA9000 digital melting point apparatus. Spectroscopic data were recorded on the following instruments: a Bruker Tensor 27 IR spectrophotometer; a ^{1}H-NMR (nuclear magnetic resonance) Bruker DPX-400 FT-NMR spectrophotometer, and an MS (mass spectroscopy) Agilent 1100 MSD spectrophotometer. Analyses for C, H and N were within 0.4% of the theoretical values. 4-(benzothiazole-2-yl)phenylamine and N-(4-benzothiazole-2-yl)phenyl-2-chloroacetamide were prepared according to the methods described in the literatüre[1,4]. Some characteristics of the compounds are given in Table 1 and the processes for their synthesis are shown in Scheme 1.

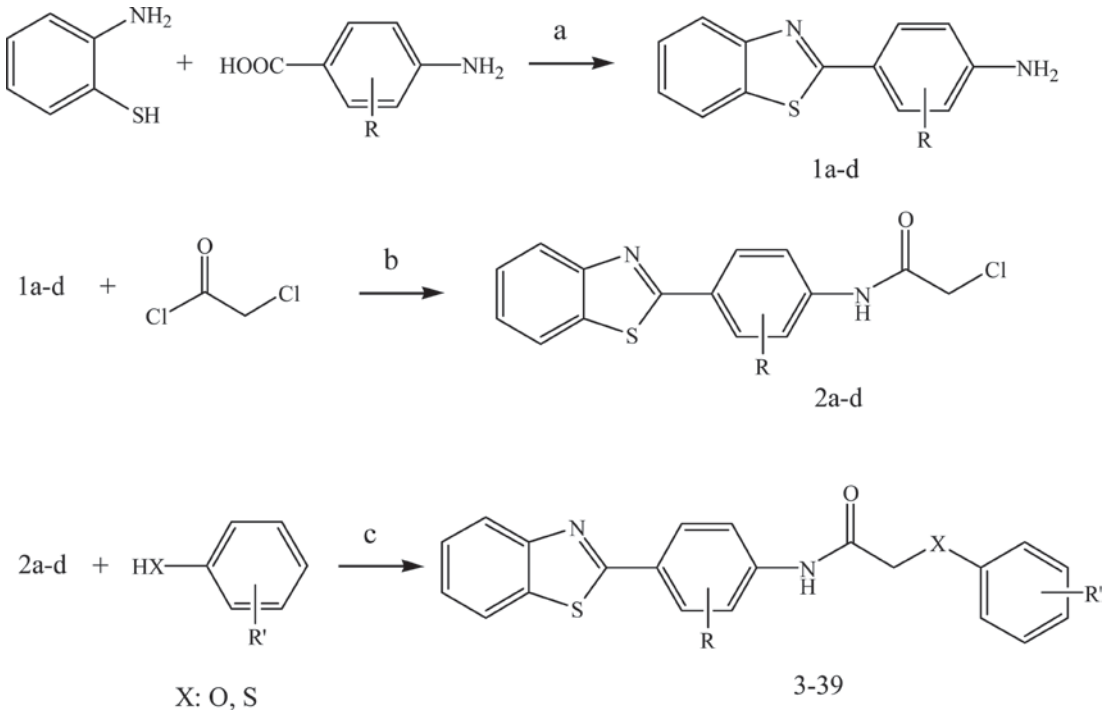
Table 1. Some characteristic of the compounds.

Comp.	R	R'	X	mp (°C)	Yield (%)	Molecular Formula	Analyses calc./found (%) C H N	
3	H	H	O	174	70	$C_{21}H_{16}N_2O_2S.1/2H_2O$	68.29 4.34	7.59
							68.19 4.33	7.60
4	H	4-Cl	O	222	78	$C_{21}H_{15}ClN_2O_2S.H_2O$	61.21 3.67	6.81
							61.01 3.63	6.77
5	H	3-Cl	O	233	74	$C_{21}H_{15}ClN_2O_2S.H_2O$	61.21 3.67	6.81
							61.01 3.63	6.77
6	H	2-Cl	O	207	72	$C_{21}H_{15}ClN_2O_2S.H_2O$	61.21 3.67	6.81
							61.01 3.63	6.77
7	H	4-OCH_3	O	176	75	$C_{22}H_{18}N_2O_3S$	67.6 4.65	7.17
							67.5 4.63	7.15
8	H	3-OCH_3	O	160	71	$C_{22}H_{18}N_2O_3S$	67.6 4.65	7.17
							67.5 4.63	7.15
9	H	2-OCH_3	O	132	68	$C_{22}H_{18}N_2O_3S$	67.6 4.65	7.17
							67.5 4.63	7.15
10	H	4-CH_3	O	198	73	$C_{22}H_{18}N_2O_2S.3H_2O$	61.67 4.20	6.54
							61.80 4.17	6.52
11	H	3-CH_3	O	222	69	$C_{22}H_{18}N_2O_2S.3H_2O$	61.67 4.20	6.54
							61.80 4.17	6.52
12	H	2-CH_3	O	159	67	$C_{22}H_{18}N_2O_2S.3H_2O$	61.67 4.20	6.54
							61.80 4.17	6.52
13	3-Cl	H	O	92	73	$C_{21}H_{15}ClN_2O_2S.H_2O$	61.38 3.68	6.79
							61.01 3.63	6.77
14	3-Cl	4-CH_3	O	266	76	$C_{22}H_{17}ClN_2O_2S.\ H_2O$	61.94 4.02	6.63
							61.82 3.98	6.55
15	3-Cl	3-CH_3	O	259	74	$C_{22}H_{17}ClN_2O_2S.\ H_2O$	61.94 4.02	6.63
							61.82 3.98	6.55
16	3-Cl	2-CH_3	O	186	71	$C_{22}H_{17}ClN_2O_2S.\ H_2O$	61.94 4.02	6.63
							61.82 3.98	6.55
17	3-Cl	4-Cl	O	204	78	$C_{21}H_{14}Cl_2N_2O_2S$	58.75 3.29	6.53
							58.71 3.29	6.52
18	3-Cl	3-Cl	O	214	75	$C_{21}H_{14}Cl_2N_2O_2S$	58.75 3.29	6.53
							58.71 3.29	6.52
19	3-Cl	2-Cl	O	224	70	$C_{21}H_{14}Cl_2N_2O_2S$	58.75 3.29	6.53
							58.71 3.29	6.52
20	3-Cl	4-OCH_3	O	161	73	$C_{22}H_{17}ClN_2O_3S.1/2H_2O$	60.90 3.92	6.46
							60.79 3.91	6.42
21	3-Cl	3-OCH_3	O	149	69	$C_{22}H_{17}ClN_2O_3S.1/2H_2O$	60.90 3.92	6.46
							60.79 3.91	6.42
22	3-Cl	2-OCH_3	O	162	64	$C_{22}H_{17}ClN_2O_3S.1/2H_2O$	60.90 3.92	6.46
							60.79 3.91	6.42
23	2-OCH_3	H	O	167	62	$C_{22}H_{18}N_2O_3S$	67.67 4.65	7.17
							67.63 4.61	7.15
24	2-OCH_3	4-CH_3	O	174	61	$C_{23}H_{20}N_2O_3S$	68.30 4.98	6.93
			O				68.27 4.97	6.91
25	2-OCH_3	4-Cl		181	66	$C_{22}H_{17}ClN_2O_3S.1/2H_2O$	60.90 3.92	6.46

(Continued)

Table 1. *(Continued)*.

Comp.	R	R'	X	mp (°C)	Yield (%)	Molecular Formula	Analyses calc./found (%) C H N		
							60.79	3.91	6.42
26	2-OCH_3	4-OCH_3	O	152	63	$C_{23}H_{20}N_2O_4S$	65.70	4.79	6.66
							65.67	4.80	6.68
27	2-CH_3	H	O	186	65	$C_{22}H_{18}N_2O_2S$	70.57	4.85	7.48
							70.49	4.81	7.51
28	2-CH_3	4-CH_3	O	157	64	$C_{23}H_{20}N_2O_2S$	71.11	5.19	7.21
							71.08	5.08	7.19
29	2-CH_3	2-CH_3	O	200	62	$C_{23}H_{20}N_2O_2S$	71.11	5.19	7.21
							71.08	5.08	7.19
30	2-CH_3	4-Cl	O	185	68	$C_{22}H_{17}ClN_2O_2S$	64.62	4.19	6.85
							64.59	4.19	6.83
31	2-CH_3	2-Cl	O	203	63	$C_{22}H_{17}ClN_2O_2S$	64.62	4.19	6.85
							64.59	4.19	6.83
32	2-CH_3	4-OCH_3	O	208	65	$C_{23}H_{20}N_2O_3S$	68.30	4.98	6.93
							68.25	4.95	6.92
33	2-CH_3	2-OCH_3	O	162	61	$C_{23}H_{20}N_2O_3S$	68.30	4.98	6.93
							68.25	4.95	6.92
34	H	H	S	94	60	$C_{21}H_{16}N_2OS_2.H_2O$	64.42	4.25	7.18
							63.95	4.06	7.10
35	H	4-Cl	S	211	67	$C_{21}H_{15}ClN_2OS_2$	61.38	3.68	6.82
							61.34	3.68	6.81
36	H	4-CH_3	S	115	63	$C_{22}H_{18}N_2OS_2.2H_2O$	61.90	4.22	6.50
							61.89	4.19	6.47
37	3-Cl	H	S	123	67	$C_{21}H_{15}ClN_2OS_2$	61.38	3.68	6.82
							61.35	3.67	6.79
38	3-Cl	4-Cl	S	102	74	$C_{21}H_{14}Cl_2N_2OS_2.3/2H_2O$	53.35	2.96	5.93
							53.28	2.95	5.91
39	3-Cl	4-CH_3	S	105	69	$C_{22}H_{17}ClN_2OS_2.2H_2O$	57.27	3.69	6.07
							57.25	3.65	6.05



Scheme 1. Synthesis of compounds 3–39. Reagents and conditions: **(a)** PPA/MW, 125°C, 35 minutes **(b)** DMF/Et_3N **(c)** acetonitril, K_2CO_3, heating at reflux.

General method for the preparation of N-[4-(benzothiazole-2-yl)phenyl)-2-phenoxyacetamide and N-[4-(benzothiazole-2-yl)phenyl)-2-thiophenoxyacetamide derivatives 3–33 and 34–39

A mixture of N-[4-benzothiazole-2-yl)phenyl]-2-chloroacetamide (1.65 mmol, 0.5 g), the appropriate substitue phenol or thiophenol derivatives (1.98 mmol) and K_2CO_3 (1.98 mmol, 0.3 g) in acetonitril was refluxed for 6 hours. The cooled mixture was filtered and recrystallized from DMSO/alcohol.

The characterization of compounds (25 and 38) showing high activity are given below. The remaining final compounds characterization are given as supporting data.

25: IR(KBr)υ_{max} (cm^{-1}): 3399 (N-H), 3050 (aromatic C-H), 2904 (aliphatic C-H), 1689 (C=O), 1605, 1539, 1499 (C=C, C=N), 1300-1000 (C-N), 1245 (C-O-C), 596 (C=C-S), 664 (C-S) NMR(400 MHz)(DMSO-d_6) δ (ppm): 3.72 (3H, s, OCH_3) 4.8 (2H, s, (-O-CH_2-)), 6.89 (2H, d, J:8.78 Hz, Ar-H), 7.05 (2H, d, J:8.34 Hz, Ar-H), 7.44 (1H, dt, J:7.62 Hz, J:7.52Hz, benzothiazole, C_6-H), 7.55 (1H, dt, J:7.64 Hz, J:7.49Hz, benzothiazole,C_5-H), 7.78 (1H, dd, J: 1.66 Hz, J: 1.64 Hz, Ar-H), 7.82 (1H, s, Ar-H), 8.12 (1H, d, J: 7.67 Hz, benzothiazole C_7-H), 8.21 (1H, d, J:7.68 Hz, Ar-H), 8.38 (1H, d, J: 8.29 Hz, benzothiazole C_4-H), 9.36 (1H, s, NH) MS (ES+): 425.1 (100%) M+1, 426.1 (26%) M+2, 427.1 (40.3%) M+3, 428.1 (10%) M+4.

38:IR(KBr)υ_{max}(cm^{-1}):3249(N-H),3079(aromaticC-H), 2916 (aliphatic C-H), 1683 (C=O), 1600, 1531, 1477 (C=C, C=N), 1300-1000 (C-N), 734 (C=C-S) ^{1}H-NMR(400 MHz) (DMSO-d_6) δ (ppm): 3.94 (2H, s, (-S-CH_2-)), 7.5 (5H, m, Ar-H, benzothiazole, C_6-H), 7.59 (1H, dt, J:8.26 Hz, J: 8.26 Hz, benzothiazole C_5-H) 7.64 (1H, dd, J:2.11 Hz, J: 2.05 Hz, Ar-H), 8.02 (1H, d, J:2.04 Hz, Ar-H), 8.1 (1H, d, J:8.03 Hz, benzothiazole C_7-H), 8.19 (1H, d, J:7.81 Hz Ar-H), 8.27 (1H, d, J: 8.69 Hz, benzothiazole C_4-H), 10.70 (1H, s, NH) MS (ES+): 445(100%) M+1, 446 (27%) M+2, 447 (74%) M+3, 448(19%) M+4, 449 (20%) M+5.

Anticancer activity

The cyctotoxic and/or growth inhibitory effects of the compounds were evaluated *in vitro* against approximately 60 human tumor cell lines derived from nine neoplastic diseases, namely: leukemia (L), non-small cell lung cancer (NSCLC), colon cancer (CC), central nervous system cancer (CNSC), melanoma (M), ovarian cancer (OC), renal cancer (RC), prostate cancer (PC) and breast cancer (BC). The evaluation of anticancer activity was performed at the National Cancer Institute (NCI), Bethesda, USA. The *in vitro* screening program was based upon the use of multiple panels of 60 human tumor cell lines, against which our compounds were tested at 10-fold dilutions of five concentrations ranging from 10^{-4} to 10^{-8} M. The percentage growth was evaluated spectrophotometrically against controls not treated with test agents. A 48-hour continuous drug exposure protocol was followed and a sulforhodamine B (SRB) protein assay was used to estimate cell growth[15].

Result and discussion

Chemistry

N-[4-benzothiazole-2-yl]phenyl]-2-aryloxyacetamide derivatives were synthesized using the sequence of reactions depicted in Scheme 1. The initial compounds, 2-(4-aminophenyl)benzothiazoles **1a-d**, were prepared via polyphosphoric acid mediated oxidative condensation of 2-aminothiophenol with 4-aminobenzoic acid in microwave conditions.

N-[4-(benzothiazole-2-yl)phenyl]-2-chloroacetamide compounds **2a-d** were prepared by reacting 2-(4-aminophenyl)benzothiazole and chloroacetyl chloride in triethylamine and DMF to produce the halides.

The two groups of final compounds are N-[4-(benzothiazole-2-yl)phenyl)-2-phenoxyacetamide derivatives and N-[4-(benzothiazole-2-yl)phenyl)-2-(phenylthio) acetamide derivatives, derivative numbers **3–33** and **34–39** respectively. N-[4-(benzothiazole-2-yl)phenyl)-2-phenoxyacetamide derivatives **3–33**, were synthesized by reacting N-[4-(benzothiazole-2-yl)phenyl]-2-chloro acetamide and appropriate substituent phenols in acetonitrile solvent. The other derivatives, **34–39**, were synthesized by reacting N-[4-benzothiazole-2-yl)phenyl]-2-chloro acetamide and appropriate substituent thiophenols in acetonitrile solvent. The structures of the compounds obtained were elucidated using spectral data. In the IR spectra, characteristic amide carbonyl functions were observed in the 1709-1670 cm^{-1} region, both separately and as a single band. The NMR spectra of compounds **3–33** exhibited singlets resulting from resonances of the N-[4-(benzothiazole-2-yl)phenyl)-2-phenoxyacetamide residue assigned to –O-CH_2-protons at 4.7-4.8 ppm, and N-H protons at 9.3–10.92 ppm. N-[4-(benzothiazole-2-yl)phenyl]-2-phenylthio) acetamide derivative residue was assigned to –S-CH_2-protons at 3.85-3.94 ppm and N-H protons at 9.61–10.70 ppm. For the other compounds, the same protons were taking part in multiplets, because they were overlapping with aromatic and benzothiazole protons.

Anticancer activity

In the first step, compounds **3, 7, 13, 17, 20, 25, 26, 35** and **38** were selected by NCI for the anticancer tests. The selected compounds were evaluated *in vitro* against 60 human tumor cell lines derived from nine neoplastic diseases and the test results were determined as growth percentage values for 10^{-5} M concentration. The obtained growth percent values are shown in Table 2.

Compounds **25** and **38** showed notably low growth of 29.64% and 30.93%, respectively, against CNSC and PC cell lines. With respect to mean values, the same two compounds exhibited the lowest growth percent values of 50.94 and 59.73%, respectively. As required by the test methods, the compounds with a growth percentage lower than 75% were accepted for the further screening test. Thus, compounds **25** and **38** were used in the second

Table 2. Anticancer activity of some compounds as % growth.

Comp.	L	NSCLC	CC	CNSC	M	OC	RC	PC	BC	Mean
3	81.18	87.51	97.78	96.22	98.48	97.75	90.17	96.00	81.00	91.70
7	88.17	96.37	106.39	96.22	111.31	101.84	97.97	100.56	89.87	99.36
13	106.10	90.05	105.47	98.10	102.18	93.60	101.25	100.07	90.65	98.51
17	101.52	96.11	105.79	103.08	111.04	98.62	108.34	101.85	98.19	103.04
20	87.84	83.30	100.15	89.58	102.33	88.74	94.60	92.80	81.53	91.53
25	77.14	40.58	62.38	29.64	64.12	36.06	46.04	65.94	43.81	50.94
26	92.33	76.34	82.77	72.16	86.91	81.18	81.74	89.83	68.77	80.99
35	84.81	91.88	99.23	92.57	107.2	91.83	93.84	79.57	80.56	93.50
38	49.23	49.54	51.77	62.01	82.98	60.39	54.65	30.93	67.05	59.73

Table 3. Mean $logGI_{50}$ values of compounds **25** and **38** and control anticancer agents.

Comp.	L	NSCLC	CC	CNSC	M	OC	RC	PC	BC	MG_MID
25	–4.32	–5.42	–4.91	–5.11	–5.21	–5.26	–5.33	–5.26	–5.17	–5.14
38	–5.32	–5.38	–5.45	–5.22	–5.25	–5.34	–5.41	–5.62	–5.41	–5.36
A	–5.48	–5.17	–5.11	–5.12	–5.08	–5.18	–4.99	–4.49	–4.79	–5.09
B	–6.39	–6.20	–6.14	–6.18	–6.08	–6.45	–6.17	–6.41	–6.05	–6.20

A: Melphalan, **B:** Cisplatin.

stage of the study, in which the selected compounds were tested at 10-fold dilutions of five concentrations ranging from 10^{-4} to 10^{-8} M. The results are given as $logGI_{50}$ (GI_{50}: growth inhibition of 50%). The detailed test results are given in Table 3.

The test method stated that compounds having $logGI_{50}$ values greater than –4 are considered as inactive. It can be seen that the $logGI_{50}$ values for the compounds are less than –4. Therefore, we may conclude that the two compounds under investigation provide a notable activity level. Melphalan and cisplatin (cis-diaminodichloroplatinum) are two commonly used chemotherapeutic agents and are used as control anticancer agents. When the mean graph midpoint (MG-MID) values of the compounds melphalan and cisplatin (i.e. –5.09 and –6.20, respectively) are considered, it is observed that the two compounds provide high activity levels. The MG-MID values of the compounds are lower than that of the control compound, melphalan.

The present study analyzed the effect levels of 2-(aminoaryl)benzothiazole and aryloxyacetamide, two groups of compounds known to have an anticancer effect, after their residues were combined in a single structure. However, although the obtained compounds showed relatively high activity values, they did not achieve the same activity level as compounds containing both of the residues separately within their structures.

Compound **25** contained R: 2-OCH_3 and R': 4-Cl as a substituent and compound **38** contained R: 3-Cl and R': 4-Cl as substituents. Moreover, while compound **25** has an aryl ether structure, Compound 38 is an aryl thioether. Therefore, it is remarkable that the common feature of these most effective two compounds is the R' group being 4-CI. Except for this feature, it does not seem possible to establish a structure-activity relationship according to the structure of the compounds and substituents.

Acknowledgements

This work was supported by the Commission of Scientific Research Projects of Eskisehir Osmangazi University (ESOGU/200819010). The authors gratefully acknowledge the financial support by Eskişehir Osmangazi University. Authors also would like to thank to National Cancer Institue (NCI), Bethesda, MD, USA for in vitro screening of our compounds in human cancer cell lines.

Declaration of interest

The authors report no conflicts of interest.

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