European Journal of Medicinal Chemistry 44 (2009) 3340–3344

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Short communication

Synthesis of new chiral 2,5-disubstituted 1,3,4-thiadiazoles possessing γ-butenolide moiety and preliminary evaluation of in vitro anticancer activity

Meng-Xue Wei [a], Lei Feng [a], Xue-Qiang Li [a,*], Xue-Zhang Zhou [b], Zhi-Hui Shao [c,**]

[a] Key Laboratory of Energy Sources and Chemical Engineering, Development Center of Natural Products and Medication and School of Chemistry and Chemical Engineering, Ningxia University, Yinchuan 750021, China
[b] Key Lab of Ministry of Education for Protection and Utilization of Special Biological Resources in Western China, School of Life Science, Ningxia University, Yinchuan 750021, China
[c] Key Laboratory of Medicinal Chemistry for Natural Resource (Yunnan University), Ministry of Education, Yunnan University, Kunming 650091, China

ARTICLE INFO

Article history:
Received 4 December 2008
Received in revised form
19 February 2009
Accepted 19 March 2009
Available online 27 March 2009

Keywords:
1,3,4-Thiadiazoles
Butenolide
X-ray crystallography
Hela cells
Growth inhibitory

ABSTRACT

A new series of chiral 1,3,4-thiadiazoles derivatives possessing γ-substituted butenolide moiety were synthesized and evaluated for in vitro anticancer properties. All the compounds showed good anticancer activities against Hela cell lines. Of all the studied compounds, compound **9e** exhibited the best inhibitory activity with an IC_{50} of 0.9 μM. After being treated with 0.1 μg/mL compound **9e** for 24 h, the growth inhibition rate of Hela cell lines was 59.2%.

1. Introduction

The identification of new compounds for the treatment of cancer is an important undertaking in pharmaceutical research. 1,3,4-Thiadiazole derivatives have received much attention due to their versatile biological properties [1–13]. In particular, a few differently substituted 1,3,4-thiadiazoles have been found to exhibit anticancer activities [14–18]. Besides, γ-substituted butenolide moiety represents a biological important entity that is present in natural products such as dysidiolide [19], andirolactone [20] and vallapin [21]. Dysidiolide and its derivatives have been found to possess varying anticancer properties [22–24].

In view of these above mentioned facts and an attempt to achieve new compounds with better anticancer properties, we designed and synthesized a new series of hybrid 1,3,4-thiadiazoles derivatives possessing γ-substituted butenolide moiety (Fig. 1) to evaluate their in vitro anticancer properties. To the best of our knowledge, the synthesis and anticancer activities of these compounds have not been reported so far.

2. Results and discussion

2.1. Chemistry

The enantiomerically pure γ-substituted butenolides **4** were prepared by the procedure shown in Scheme 1 [25,26]. Mucobromic acid **2** was easily accessible by the treatment of furfural **1** with Br_2/H_2O. The enantiomerically pure γ-substituted butenolides **4** were obtained via acetalization of mucobromic acid **2** by employing (−)-menthol and (+)-borneol as a chiral auxiliary, respectively and followed by resolution of the resulting diastereomers.

The 5-substituted-2-mercapto-1,3,4-thiadiazoles **8** were prepared as previously described (Scheme 2) [27]. The aroyl hydrazides **6** were obtained by reaction of the esters **5** with hydrazine in EtOH. Treatment of the hydrazides **6** with CS_2 under a basic condition (KOH/EtOH) gave the corresponding potassium aroyl dithiocarbazates **7**. Compounds **7** were then cyclized with cold concentrated sulfuric acid to provide the corresponding 5-substituted-2-mercapto-1,3,4-thiadiazoles **8** in good yields (60–90%). It should be noted that the yields of cyclization reaction of

* Corresponding author.
** Corresponding author. Tel.: +86 871 5031119; fax: +86 871 5035538.
E-mail addresses: lixq@nxu.edu.cn (X.-Q. Li), zhihui_shao@hotmail.com (Z.-H. Shao).

0223-5234/$ – see front matter © 2009 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2009.03.023

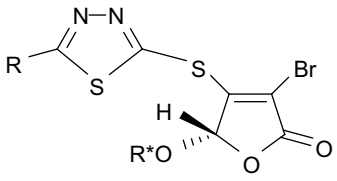
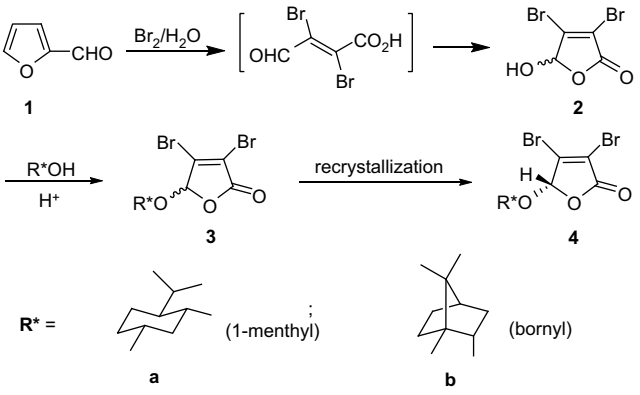


Fig. 1. The general structure of target compounds.



Scheme 1. Synthesis of compounds **4**.

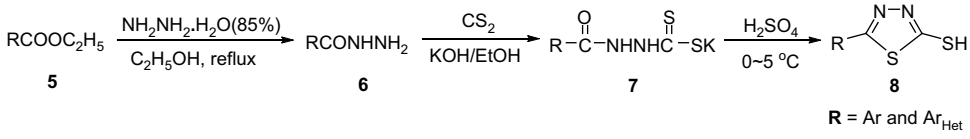
potassium aroyl dithiocarbazates were quite low (17–35%) in the previous literature [27]. After several attempts to improve the chemical yields of the cyclization reaction, we found that the quench procedure of the cyclization reaction dramatically affected the yields of products **8**. After the completion of the cyclization reaction, the addition of moderate quantities of $NH_3 \cdot H_2O$ to the reaction mixtures significantly improved the product yields.

The target compounds **9a–l** were prepared by tandem Michael addition–elimination reaction of γ-substituted butenolides **4** with 5-substituted-2-mercapto-1,3,4-thiadiazoles **8** (Scheme 3).

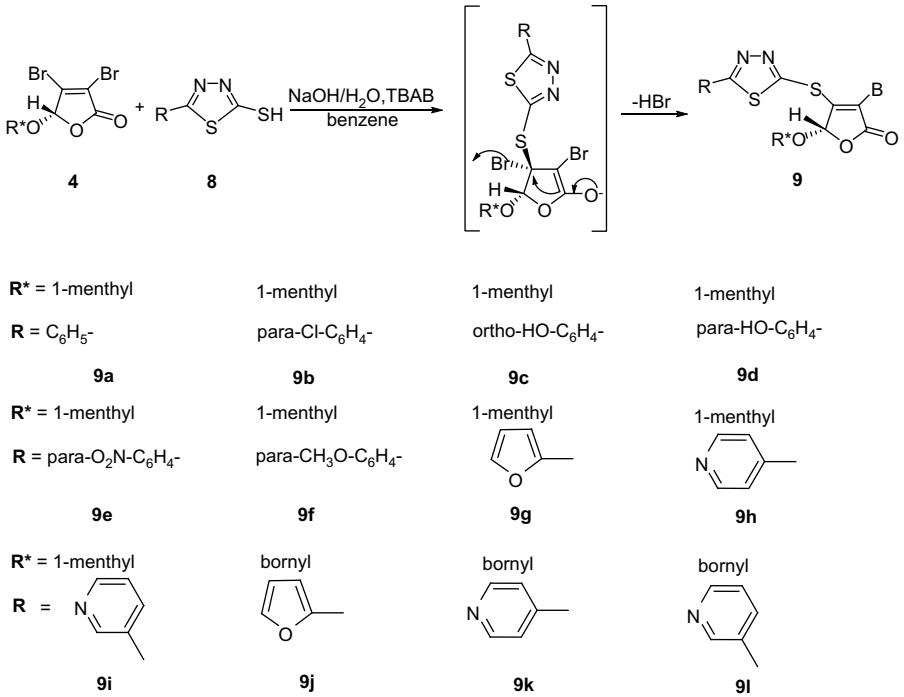
The structures of these new compounds **9** were characterized with IR, ^1H and ^{13}C NMR spectra. Physical and spectral data of compounds **9a–l** are reported in Table 1. Additionally, the structure of compound **9a** was corroborated by X-ray diffraction as shown in Fig. 2.

2.2. In vitro anticancer activity (MTT method)

All new synthesized compounds **9a–l** were evaluated for their in vitro anticancer activities against cervical cancer cell lines (HeLa). To our delight, all compounds **9a–l** displayed good inhibition activities on Hela cell lines (Table 2). Of all the studied compounds, compound **9e** exhibited the best inhibitory activity with an IC_{50} of 0.9 μM. Encouraged by these promising results, the growth inhibition rates of Hela cell lines with compounds **9a–l** at different concentrations (0.1–20 μM) were evaluated (Table 3). After being treated with 0.1 μg/mL compound **9e** for 24 h, the growth inhibition rate was 59.2%, while the growth inhibition rate of the more active compound **9h** ($IC_{50} = 1.3$ μM) was the highest (73.8%).



Scheme 2. Synthesis of compounds **8**.



Scheme 3. Synthesis of compounds **9a–l**.

Table 1
Physical properties and spectral data of compounds **9a–l**.

Compound	Mp (°C)	Yield (%)	IR (KBr) in cm^{-1}	^1H NMR ($CDCl_3$) δ in ppm	^{13}C NMR ($CDCl_3$) δ in ppm
9a	162–163	98	1784, 1596, 1557, 1492, 1456, 1313, 1212, 1129, 990	8.05–8.03 (m, 2H), 7.62–7.53 (m, 3H), 6.57 (s, 1H), 3.56 (1H, ddd, J = 10.8, 10.4, 4.4 Hz), 2.26–2.22 (m, 1H), 1.95–1.89 (m, 1H), 1.63–1.55 (m, 2H), 1.38 (m, 1H), 1.27–1.03 (m, 2H), 0.92 (d, J = 6.8 Hz, 3H), 0.88–0.81 (m, 2H), 0.79 (d, J = 6.8 Hz, 3H), 0.44 (d, J = 6.8 Hz, 3H)	167.0, 164.0, 156.6, 149.9, 132.6, 129.3, 126.9, 122.7, 117.0, 102.9, 83.3, 47.9, 42.1, 33.9, 31.5, 25.2, 22.7, 22.1, 20.9, 15.4
9b	133–134	95	1789, 1584, 1489, 1480, 1312, 1212, 1123, 992	7.48–7.45 (m, 2H), 6.49 (s, 1H), 3.48 (ddd, J = 10.8, 10.8, 4.8 Hz, 1H), 2.19–2.10 (m, 1H), 1.86–1.82 (m, 1H), 1.56–1.49 (m, 2H), 1.30 (m, 1H), 1.20–0.96 (m, 2H), 0.85 (d, J = 6.8 Hz), 0.81–0.74 (m, 2H), 0.71 (d, J = 6.8 Hz), 0.36 (d, J = 7.2 Hz)	165.2, 163.0, 155.9, 148.6, 138.0, 128.8, 127.2, 120.1, 116.3, 101.9, 82.4, 46.9, 41.1, 32.8, 30.5, 24.2, 21.7, 21.1, 19.9, 14.4
9c	100–103	96	3285, 1790, 1589, 1549, 1489, 1312, 1227, 1136, 994	9.67 (s, 1H), 7.74–7.72 (m, 1H), 7.53–7.48 (m, 1H), 7.16–7.14 (m, 1H), 7.07–7.03 (m, 1H), 6.49 (s, 1H), 3.55 (ddd, J = 10.8, 10.4, 4.4 Hz, 1H), 2.25–2.22 (m, 1H), 1.93–1.86 (m, 1H), 1.65–1.56 (m, 2H), 1.38 (m, 1H), 1.28–1.03 (m, 2H), 0.92 (d, J = 6.8 Hz, 3H), 0.89–0.81 (m, 2H), 0.79 (d, J = 7.2 Hz, 3H), 0.46 (d, J = 6.8 Hz, 3H)	166.5, 163.9, 157.6, 156.0, 149.3, 134.7, 126.6, 120.4, 117.9, 117.8, 107.0, 102.9, 83.5, 48.0, 42.2, 33.8, 31.5, 25.3, 22.7, 22.1, 20.9, 15.4
9d	171–172	66	3388, 1750, 1613, 1508, 1491, 1314, 1291, 1226, 1135, 1006	7.96–7.92 (m, 2H), 7.00–6.97 (m, 2H), 6.53 (s, 1H), 5.59 (s, 1H), 3.54 (ddd, J = 10.8, 10.8, 6.4 Hz, 1H), 1.94–1.90 (m, 1H), 2.25–2.20 (m, 1H), 1.63–1.56 (m, 2H), 1.37 (m, 1H), 1.27–1.03 (m, 2H), 0.92 (d, J = 6.4 Hz, 3H), 0.88–0.81 (m, 2H), 0.79 (d, J = 6.8 Hz, 3H), 0.45 (d, J = 6.8 Hz, 3H)	167.0, 164.2, 159.4, 155.8, 150.2, 129.1, 116.7, 116.4, 115.3, 102.9, 83.4, 48.0, 42.2, 33.9, 31.5, 25.2, 22.7, 22.1, 21.0, 15.4
9e	124–125	83	1787, 1528, 1478, 1456, 1340, 1312, 1157, 1131, 997	8.37–8.33 (m, 2H), 8.19–8.16 (m, 2H), 6.50 (s, 1H), 3.49 (ddd, J = 10.8, 10.4, 4.4 Hz, 1H), 2.19–2.16 (m, 1H), 1.86–1.82 (m, 1H), 1.57–1.49 (m, 2H), 1.33 (m, 1H), 1.20–0.96 (m, 2H), 0.86 (d, J = 6.8 Hz, 3H), 0.81–0.75 (m, 2H), 0.71 (d, J = 7.2 Hz, 3H), 0.35 (d, J = 6.8 Hz, 3H)	164.1, 162.8, 157.4, 149.0, 148.0, 127.0, 126.9, 123.6, 117.2, 101.9, 82.5, 46.9, 41.1, 32.8, 30.5, 24.2, 21.7, 21.1, 19.9, 14.4
9f	133–134	92	1779, 1609, 1501, 1489, 1323, 1312, 1263, 1126, 998	7.98–7.96 (m, 2H), 7.04–7.02 (m, 2H), 6.53 (s, 1H), 3.90 (s, 3H), 3.55 (ddd, J = 11.2, 10.8, 4.0 Hz, 1H), 2.25–2.22 (m, 1H), 1.94–1.90 (m, 1H), 1.63–1.56 (m, 2H), 1.37 (m, 1H), 1.26–1.03 (m, 2H), 0.92 (d, J = 6.4 Hz, 3H), 0.88–0.85 (m, 2H), 0.79 (d, J = 6.8 Hz, 3H), 0.45 (d, J = 6.8 Hz, 3H)	167.1, 164.1, 163.0, 155.7, 150.2, 128.8, 116.6, 115.1, 114.8, 102.9, 83.3, 55.6, 48.0, 42.2, 33.9, 31.5, 25.2, 22.7, 22.1, 21.0, 15.4
9g	108–109	75	3158, 1787, 1582, 1481, 1457, 1368, 1316, 1217, 1130, 989	7.65–7.64 (m, 1H), 7.27–7.24 (m, 1H), 6.64–6.63 (m, 1H), 6.55 (s, 1H), 3.52 (ddd, J = 10.8, 10.8, 4.4 Hz, 1H), 2.25–2.19 (m, 1H), 1.82–1.78 (m, 1H), 1.63–1.55 (m, 2H), 1.37 (m, 1H), 1.26–1.02 (m, 2H), 0.91 (d, J = 6.8 Hz, 3H), 0.89–0.80 (m, 2H), 0.77 (d, J = 7.2 Hz, 3H), 0.45 (d, J = 6.8 Hz, 3H)	164.4, 161.2, 155.1, 152.4, 145.9, 144.6, 116.0, 112.9, 112.6, 103.1, 83.1, 48.0, 42.2, 33.9, 31.5, 25.2, 22.7, 22.1, 21.0, 15.6
9h	118–119	83	1790, 1590, 1485, 1413, 1375, 1315, 1210, 1134, 987	8.88–8.87 (m, 2H), 7.90–7.89 (m, 2H), 6.58 (s, 1H), 3.56 (ddd, J = 10.8, 10.4, 4.4 Hz, 1H), 2.25–2.22 (m, 1H), 1.93–1.89 (m, 1H), 1.64–1.56 (m, 2H), 1.38 (m, 1H), 1.28–1.04 (m, 2H), 0.93 (*d*, J = 6.8 Hz, 3H), 0.88–0.82 (m, 2H), 0.79 (d, J = 7.2 Hz, 3H), 0.42 (d, J = 7.2 Hz, 3H)	165.1, 163.8, 158.5, 151.2, 149.1, 129.7, 120.1, 118.2, 103.0, 83.5, 47.9, 42.2, 33.8, 31.5, 25.2, 22.7, 22.1, 20.9, 15.4
9i	121–123	89	1780, 1590, 1465, 1421, 1368, 1218, 1311, 1135, 995	9.04–9.03 (m, 1H), 8.72–8.71 (m, 1H), 8.22–8.19 (m, 1H), 7.44–7.41 (m, 1H), 6.55 (s, 1H), 3.56 (ddd, J = 10.4, 10.4, 4.0 Hz, 1H), 2.16–2.15 (m, 1H), 1.76–1.72 (m, 1H), 1.56–1.48 (m, 2H), 1.31 (m, 1H), 1.20–0.96 (m, 2H), 0.85 (d, J = 6.8 Hz, 3H), 0.81–0.71 (m, 2H), 0.69 (d, J = 6.8 Hz, 3H), 0.45 (d, J = 6.8 Hz, 3H)	166.7, 163.2, 156.4, 151.7, 150.8, 147.8, 133.8, 124.5, 123.2, 115.9, 102.3, 82.2, 46.9, 41.2, 32.8, 30.5, 24.2, 21.7, 21.1, 20.1, 14.6
9j	161–163	60	3128, 1783, 1591, 1490, 1374, 13431, 1321, 1221, 1136, 997	7.65–7.56 (m, 1H), 7.26–7.25 (m, 1H), 6.65–6.64 (m, 1H), 6.44 (s, 1H), 3.83 (dd, J = 5.2 Hz, 1H), 2.22–2.21 (m, 1H), 1.75–1.10 (m, 6H), 0.76 (s, 6H), 0.46 (s, 3H)	164.2, 161.4, 154.2, 153.3, 145.9, 144.5, 113.6, 112.9, 112.7, 103.6, 88.7, 49.2, 47.5, 44.8, 36.5, 27.9, 26.4, 19.5, 18.7, 13.0
9k	150–152	69	1788, 1596, 1475, 1410, 1314, 1207, 1183, 1135, 995	8.90 (s, 2H), 7.93–7.92 (m, 2H), 6.47 (s, 1H), 3.91 (dd, J = 8.8 Hz, 1H), 2.27–2.21 (m, 1H), 1.75–1.10 (m, 6H), 0.77 (d, J = 5.6, 6H), 0.48 (s, 3H)	165.2, 163.7, 157.8, 151.1, 149.9, 129.7, 120.2, 115.9, 103.6, 89.2, 49.3, 47.4, 44.8, 36.4, 27.8, 26.4, 19.4, 18.7, 13.1
9l	147–148	69	1781, 1587, 1463, 1405, 1340, 1312, 1218, 1133, 995	9.30–9.15 (m, 1H), 8.82 (m, 1H), 8.29–8.27 (m, 1H), 7.56–7.34 (m, 1H), 6.52 (s, 1H), 3.89–3.85 (m, 1H), 2.26–2.20 (m, 1H), 1.75–1.10 (m, 6H), 0.78–0.74 (m, 6H), 0.42 (s, 3H)	168.2, 164.1, 156.4, 152.9, 150.7, 148.8, 135.0, 134.1, 124.3, 114.3, 103.7, 88.7, 49.2, 47.4, 44.8, 36.5, 27.8, 26.4, 19.5, 18. 7, 13.0

3. Conclusion

In summary, a series of new chiral 1,3,4-thiadiazoles derivatives possessing γ-substituted butenolide moiety have been synthesized and their in vitro anticancer activity against cervical cancer cells has been evaluated. All the target compounds exhibited good anticancer activities. Compound **9e** with an IC_{50} of 0.9 μM was found to be the most active. This might have relationship with the hydrophile ability of nitro group on the benzene ring. Further studies of SAR of these compounds and the cytostatic properties of these compounds in other tumour cell lines are in progress.

4. Experimental

4.1. Chemistry

Thin-layer chromatography (TLC) was carried out on silica GF254 plates (Qingdao Haiyang Chemical Co., Ltd, China). All the melting points were determined on a WRS-1B digital melting point apparatus and are uncorrected. IR spectra were recorded on an FTIR-8400S spectrometer as KBr discs. ^1H NMR and ^{13}C NMR spectra were obtained with a Bruker Avance III 400 MHz spectrometer in chloroform-*d* ($CDCl_3$) and tetramethylsilane (TMS) was used as an internal standard. Diffraction measurement was made on a Bruker AXS SMART 1000 CCD diffractometer with graphite-monochromatized Mo Kα radiation (λ = 0.71073 Å). All chemicals were used as received without further purification unless otherwise stated.

4.1.1. General procedure for compounds ***9a–l***

To a solution of 0.1 N NaOH (11 mL) was sequentially added tetrabutyl ammonium bromide (TBAB) (0.11 mmol), compound **8** (1.1 mmol) and compounds **4** in PhH or $CHCl_3$ (5 mL). The resulting mixture was stirred at room temperature, and the reaction was monitored by TLC. On completion of the reaction (2–48 h), the mixture was extracted and the organic layer was washed with saturated $NaHCO_3$ and saturated brine, respectively. Then the organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The purification of the residue by silica gel

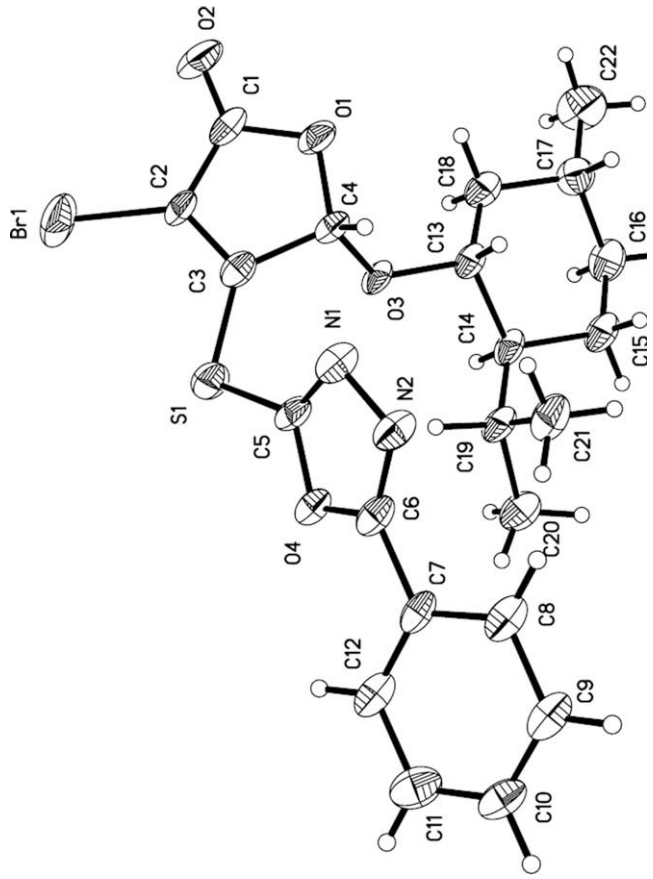


Fig. 2. ORTEP view of the crystal structure of compound **9a**.

Table 2
In vitro anticancer activities against Hela cell lines with compounds **9a–l** ($n = 3$).

Compound	IC_{50} (μM)	Compound	IC_{50} (μM)
9a	3.0	**9g**	1.7
9b	2.2	**9h**	1.3
9c	2.9	**9i**	5.6
9d	2.6	**9j**	1.3
9e	0.9	**9k**	3.0
9f	3.7	**9l**	3.4

The IC_{50} values represent the compound concentration (μM) required to inhibit tumour cell proliferation by 50%.

Table 3
Growth inhibition rates of Hela cell lines with compounds **9a–l** at different concentrations.

Compound	Inhibition rates (%)				
	0.1 μM	1 μM	5 μM	10 μM	20 μM
9a	56.1	59.1	40.6	28.1	29.7
9b	51	58.2	29.3	35.1	26.8
9c	58.9	61.2	37.5	42.3	33.4
9d	60.6	59.4	36.0	44.4	36.0
9e	59.2	47.6	30.0	34.5	24.5
9f	56.4	55.6	47.1	35.6	32.9
9g	55.6	54.3	29.4	36.9	27.2
9h	73.8	51.3	33.9	26.8	22.3
9i	56.4	59.5	52.3	32.8	33.0
9j	50.9	51.4	31.1	28.6	34.3
9k	51.8	55.1	44.9	39.4	40.6
9l	58.9	56.3	45.4	40.5	36.3

column chromatography or crystallization yielded the desired compounds **9a–l**.

4.1.2. Crystal data for ***9a***

$a = 12.4791$ (13) Å, $b = 6.6726$ (8) Å, $c = 14.5108$ (19) Å, $\beta = 109.796$ (2)°, monoclinic crystal system with space group $P2_1$, $V = 1.1369$ (2) nm^3, $Z = 2$, $\mu = 1.930\ mm^{-1}$, $D_c = 1.441\ g/cm^3$, $T = 298$ (2), $0.45 \times 0.17 \times 0.12$ mm.

4.2. Pharmacology

Cells (1×10^4 in 100 μL) were seeded on 96-well plates in triplicate. Following a 24-h-culture at 37 °C, the medium were replaced with fresh medium at various concentrations (0.5, 1, 5, 10, 20 μg/mL) of compounds **9a–l** in a final volume of 110 μL. At the same time, set drug-free medium negative control well, and solvent control well of the same volume of dimethyl sulfoxide (DMSO). Cells were incubated at 37 °C for 24 h. Then 20 μL of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) (2 mg/mL in a phosphate buffer solution (PBS)) was added to each well, incubated for an additional 4 h, the plates were centrifuged at 1000 r/min for 10 min, then the medium was removed. MTT formazan precipitates were dissolved in 100 μL of DMSO, shaken mechanically for 10 min and then read immediately at 570 nm in a plate reader (Opsys MR, Denex Technology, USA).

Cell inhibition rate = $[A_{570}$ (negative control well) − A_{570} (dosing well)]/A_{570} (negative control well) × 100%.

Acknowledgements

We thank Major State Basic Research Development Program of China (2007CB21602), National Natural Science Foundation of China (20702044), Key Project of Chinese Ministry of Education (203143), and Natural Science Foundation of Ningxia Province of China (NZ0606) for financial support. We also thank a reviewer for his invaluable suggestions on our work.

References

[1] H.N. Dogan, A. Duran, S. Rollas, G. Sener, M.K. Uysal, D. Gulen, Bioorg. Med. Chem. 10 (2002) 2893–2898.
[2] H.N. Dogan, S. Rollas, H. Erdeniz, Il Farmaco 53 (1998) 462–467.
[3] S. Rollas, S. Karakus, B.B. Durgun, M. Kiraz, H. Erdeniz, Il Farmaco 51 (1996) 811–814.
[4] M.G. Mamolo, V. Falagiani, D. Zampieri, L. Vio, E. Banfi, G. Scialino, Il Farmaco 58 (2003) 631–637.
[5] A. Foroumadi, Z. Kiani, F. Soltani, Il Farmaco 58 (2003) 1073–1076.
[6] E.E. Oruc, S. Rollas, F. Kandemirli, N. Shvets, A.S. Dimoglo, J. Med. Chem. 47 (2004) 6760–6767.
[7] M.R. Stillings, A.P. Welbourn, D.S. Walter, J. Med. Chem. 29 (1986) 2280–2284.
[8] C.B. Chapleo, P.L. Myers, A.C. Smith, I.F. Tulloch, D.S. Walter, J. Med. Chem. 30 (1987) 951–954.
[9] F. Clerici, D. Pocar, G. Maddalena, A. Loche, V. Perlini, M. Brufani, J. Med. Chem. 44 (2001) 931–936.
[10] F. Vergne, P. Bernardelli, E. Lorthiois, N. Pham, E. Proust, C. Oliveira, A. Mafroud, F. Royer, R. Wrigglesworth, J.K. Schellhaas, M.R. Barvian, F. Moreau, M. Idrissi, A. Tertre, B. Bertin, M. Coupe, P. Berna, P. Soulard, Bioorg. Med. Chem. Lett. 14 (2004) 4607–4613.
[11] M. Amir, K. Shikha, Eur. J. Med. Chem. 39 (2004) 535–545.
[12] S. Schenone, C. Brullo, O. Bruno, F. Bondavalli, A. Ranise, W. Filippelli, B. Rinaldi, A. Capuano, G. Falcone, Bioorg. Med. Chem. 14 (2006) 1698–1705.
[13] Y. Song, D.T. Connor, A.D. Sercel, R.J. Sorenson, R. Doubleday, P.C. Unangst, B.D. Roth, V.G. Beylin, R.B. Gilbertsen, K. Chan, D.J. Schrier, A. Guglietta, D.A. Borneimer, R. Dyer, J. Med. Chem. 42 (1999) 1161–1169.
[14] T. Wang, Y.-H. Zhang, S. Yu, H. Ji, Y.-S. Lai, S.-X. Peng, Chin. Chem. Lett. 19 (2008) 928–930.
[15] W. Rzeski, J. Matysiak, M. Kandefer-Szerszen, Bioorg. Med. Chem. 15 (2007) 3201–3207.
[16] A. Senff-Ribeiro, A. Echevarria, E.F. Silva, S.S. Veiga, M.B. Oliveira, Anticancer Drugs 15 (2004) 269–275.
[17] N. Terzioglu, A. Gursoy, Eur. J. Med. Chem. 38 (2003) 781–786.
[18] A. Mastrolorenzo, A. Scozzafava, C.T. Supuran, Eur. J. Pharm. Sci. 11 (2000) 325–332.

[19] S.P. Gunasekera, P.J. McCarthy, M. Kelly-Borges, E. Lobkovsky, J. Clardy, J. Am. Chem. Soc. 118 (1996) 8759–8760.
[20] H. Avcibasi, H. Anil, Phytochemistry 26 (1987) 2852–2854.
[21] D.H. Miles, V. Chittawong, D.-S. Lho, A.-M. Payne, A.A. de La Cruz, E.D. Gomez, J.A. Weeks, J.L. Atwood, J. Nat. Prod. 54 (1991) 286–289.
[22] I.S. Marcos, M.A. Escola, R.F. Moro, P. Basabe, D. Diez, F. Sanz, F. Mollinedo, J. de la Iglesia-Vicente, B.G. Sierrac, J.G. Urones, Bioorg. Med. Chem. 15 (2007) 5719–5737.
[23] M. Takahashi, K. Dodo, Y. Sugimoto, Y. Aoyagi, Y. Yamada, Y. Hashimoto, R. Shirai, Bioorg. Med. Chem. Lett. 10 (2000) 2571–2574.
[24] D. Brohm, N. Philippe, S. Metzger, A. Bhargava, O. Muller, F. Lieb, H. Waldmann, J. Am. Chem. Soc. 124 (2002) 13171–13178.
[25] A. van Oeveren, J.F.G.A. Jansen, B.L. Feringa, J. Org. Chem. 59 (1994) 5999–6007.
[26] Q.-H. Chen, Z. Geng, B. Huang, Tetrahedron: Asymmetry 6 (1995) 401–404.
[27] M. Baron, C.V. Wilson, J. Org. Chem. 23 (1958) 1021–1023.