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Synthesis and Antitumor Activity of Some Rhodanine Derivatives

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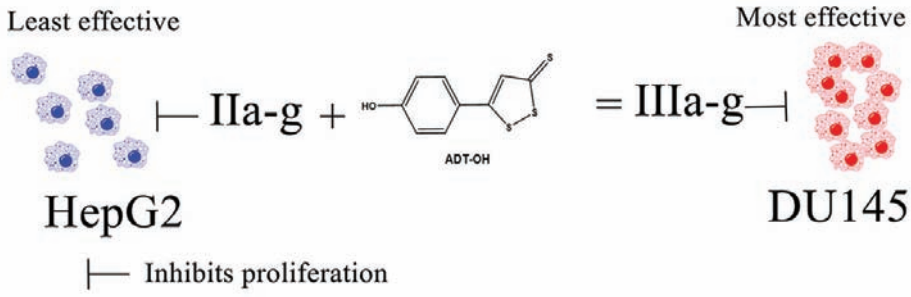
ABSTRACT Based on the WL-276, a series of novel compounds of rhodanine derivatives **III$_{a-g}$** was designed and synthesized to evaluate their antitumor activities. Compounds **II$_{a-g}$** were coupled with hydrogen sulfide donor 5-hydroxyphenyl-1,2-dithiocyclopenten-3-thione to obtain compounds **III$_{a-g}$**. Subsequently, we performed 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assays to detect antitumor activity. Compounds **III$_{a-f}$** and **II$_{a-g}$** showed strong anti-proliferation activities on HepG2 and DU145 cell lines. In general, the compounds **III** showed stronger activities than compounds II. Some of the compounds **II** had anti-proliferation effects on HepG2 and six compounds **III$_a$, III$_b$, III$_d$, III$_e$, III$_f$, and III$_g$** on DU145 cell lines were all stronger than the positive control 5-fluorouracil. The structures of all the synthesized compounds were confirmed by Fourier-transform infrared, ^{1}H NMR, and mass spectral data.



KEYWORDS Antitumor activity, H_2S donor, Rhodanine, WL-276.

INTRODUCTION

Rhodanine is widely used in verification and gravimetric determination of silver.[1,2] In recent years, a large number of studies have shown that Bcl-2 protein is the final regulator of cell apoptosis, and inappropriate survival of cells caused by its excessive expression might be one of the main causes of tumor formation and chemo-resistance.[3,4] As a result, the design and the development of antitumor drugs targeting Bcl-2 protein, has gradually become a hotspot of current research.[5,6] WL-276 show as **Figure 1**, a synthetic derivative of rhodanine, not only inhibits the protein expression of Bcl-2[7] but also shows strong inhibition activity against drug-resistant prostate adenocarcinoma PC-3 cell lines.[8,9] Hydrogen sulfide (H_2S) was previously considered to be harmful to the health of humans,[10] and later it was found that H_2S, as an important gas signaling molecule involved in important physiological processes, naturally exists in the human body.[11-14] In mammals, H_2S is mainly synthesized by cystathionine-β-synthase

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and cystathionine-γ-lyase (CSE), and the third pathway involves a combination of 3-thioltransferase and cysteine aminotransferases.[15,16] The pathway of H_2S production varies in different tissues or cells.[17] For instance, CSE mainly exists in the cardiovascular system, CBS is highly expressed in the nervous system, CSE and CBS can be detected simultaneously in the lungs, CBS is mainly found in airway blood vessels and epithelial cells, while CSE is mainly expressed in the lung parenchyma. H_2S exerts remarkable effects on angiogenesis, cytoprotection, and vasoactivity.[18,19] Endogenous H_2S has been demonstrated to be involved in the development of a variety of respiratory diseases and is able to regulate a variety of important physiological functions such as relaxing airways and pulmonary vessels, cell proliferation, apoptosis, oxidative stress, and inflammation. Endogenous H_2S has important physiological effects in the nervous system, circulatory system, and digestive system, and its metabolic abnormalities are associated with many diseases and are known as the third gaseous signaling molecule following nitric oxide and carbon monoxide.[20] Exogenous H_2S donor NaHS can inhibit the proliferation of T lymphocytes, human embryonic kidney cells HEK-293, and regulates the apoptosis of lymphocytes.[21] However, the half-life of H_2S is short and 5-hydroxyphenyl-1,2-dithiocyclopenten-3-thione (ADT-OH) is a compound that slowly releases the H_2S. Therefore, in our research, compounds **II** were synthesized from amino acids by cyclization and condensation and then conjugated with ADT-OH to obtain compounds **III** with an objective to evaluate the antitumor activity of the synthesized compounds.

RESULTS AND DISCUSSION

Chemistry

The synthetic route for **II** and **III** is outlined in **Scheme 1**. Compound **I** was accessible through the reaction of amino-acid with CS_2 and sodium salt of chloroacetic acid.[22] Then, appropriate **I** was converted to **IIa–g** by their reaction with various aldehydes in the presence of ammonium acetate. Finally, compounds $\mathbf{II_{a–g}}$ were coupled with hydrogen sulfide donor ADT-OH to obtain compounds $\mathbf{III_{a–g}}$. We selected *N,N*-dicyclohexylcarbodiimide (DCC) as the condensing agent and used 4-dimethylaminopyridine (DMAP) as a catalyst.

The final yield depended on the reaction time. For example, in the synthesis of compound $\mathbf{III_a}$, the yield increased and then decreased with time (time – 10, 20, 30, 40, and 50 min; corresponding yield – 19.3%, 47.5%, 69.8%, 50.3%, and 23.4%). These data suggested that the yield was maximum at 30 min of reaction time. It was speculated that some by-products might have resulted due to the ester bond hydrolysis.

Antitumor activity

3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was performed to evaluate the effects of all target compounds on the proliferation of human hepatocellular carcinoma cell lines HepG2 and human prostate adenocarcinoma cell lines DU145 The results are summarized in **Table 1**.

The results of pharmacological screening revealed that except compound $\mathbf{II_b}$ compounds $\mathbf{II_a}$, $\mathbf{II_c}$, $\mathbf{II_d}$, $\mathbf{II_e}$, $\mathbf{II_f}$, and $\mathbf{II_g}$ exhibit strong inhibitory effects on the proliferation of HepG2 cells and DU145 cells. Conjugate compounds $\mathbf{III_a}$–$\mathbf{III_g}$ inhibited the proliferation of both HepG2 cells and had stronger inhibitory activity on DU145 cells. The antiproliferative potential of compounds $\mathbf{III_{a–b}}$ was observed in HepG2 cells and DU145 cells, of seven derivatives synthesized by coupling $\mathbf{II_{a–g}}$ with ADT-OH, compounds $\mathbf{II_c}$ to $\mathbf{II_g}$ reflected poorer antitumor activities than the positive control 5-fluorouracil (**5-FU**). However, compounds $\mathbf{III_d}$, $\mathbf{III_e}$, $\mathbf{III_f}$, and $\mathbf{III_g}$ had stronger antitumor activities on HepG2 than **5-FU**. The compounds $\mathbf{III_a}$ and $\mathbf{III_{b-d}}$ also had stronger antitumor activities on DU145 than **5-FU**.

NaHS could lead to DNA damage and the mechanism of action was to stabilize p53 as well as induce

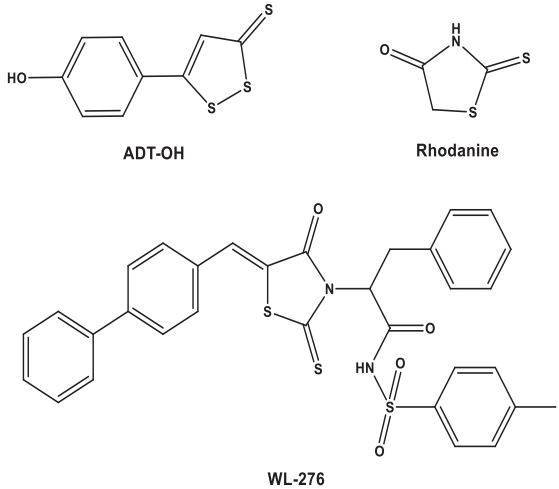
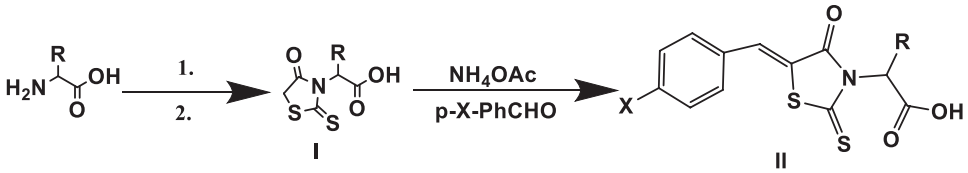
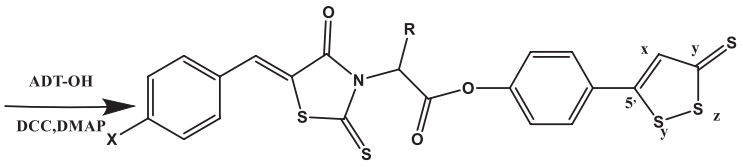


Figure 1: Chemical structure of rhodanine, WL-276, and 5-hydroxyphenyl-1,2-dithiocyclopenten-3-thione





III

III_a, X=Br, R-$(CH_3)_2CHCH_2$
III_b, X=Br, R-$(CH_3)_2CH$
III_c, X=Cl, R-$(CH_3)_2CH$
III_d, X=Ph, R-$PhCH_2$
III_e, X=F, R-$(CH_3)_2CHCH_2$
III_f, X=F, R-$(CH_3)_2CH$
III_g, X=Cl, R-$(CH_3)_2CHCH_2$

Scheme 1: Synthetic route for rhodanine derivatives IIa–g and IIIa–g R = $(CH_3)_2CH_2$, etc.

Table 1: Antitumor activity of the target compounds on HepG2 and DU145

Compound	IC_{50}/(μmol/L)		Compound	IC_{50}/(μmol/L)	
	HepG2	DU145		HepG2	DU145
II_a	65.80	48.10	III_a	26.65	0.25
II_b	>100	81.10	III_b	11.03	2.46
II_c	20.42	48.70	III_c	42.75	21.26
II_d	62.00	52.20	III_d	2.11	5.33
II_e	21.32	41.23	III_e	2.75	1.26
II_f	23.01	43.32	III_f	2.34	3.12
II_g	20.25	45.45	III_g	18.09	10.12
5-FU	17.56	10.45	**5-FU**	7.11	2.42

downstream apoptotic protein such as p21, Bax, and cytochrome C. However, NaHS could not upregulate the levels of antiapoptotic protein Bc1-2.[23,24] The latest studies showed that the conjugate of NSAIDs and ADT-OH could inhibit tumor cell proliferation and induce tumor cell apoptosis. In addition, the antitumor activity of the conjugate was 28–2000 times stronger[25-27] then that of their traditional counterparts. It was because those H_2S donors could upregulate the level of pro-apoptotic protein Bax. Coupling H_2S donor ADT-OH with Bc1-2 inhibitor rhodanine derivatives could not only exhibit the expected antitumor effect but also significantly improved the antitumor activity of the compounds after coupling.

EXPERIMENTAL SECTION

Nuclear magnetic resonance (NMR), IR, and mass spectra were obtained using Varian Unity Inova 400 MHz NMR system, Nicolet Avatar 360 Fourier-transform infrared spectroscopy, Agilent 6220 LC/MSD TOF liquid chromatography, respectively. XT5 microscopic melting point apparatus was used to determine the melting point of synthesized compounds. BioTek ELISA was used for the result of MTT assay. Human hepatocellular carcinoma cell lines HepG2 and human prostate adenocarcinoma cell lines DU145 were bought from American type culture collection, USA. RPMI-1640 medium and MTT kit were bought from Sigma, USA. Dimethyl sulfoxide (DMSO) was bought from Guangzhou chemical reagent factory, China. Trypsin was bought from Shanghai Beyond Biotechnology, China. The synthetic route for compounds I is available in literature.[22] All chemical reagents used were commercially pure.

Synthesis of four compounds II_a to II_g

Compounds II_{a-g} were synthesized according to the previous study.[28,29]

Melting point of compounds II_{a-g}: II_a mp 237–239°C, II_b 241–245°C, II_c 240–242°C, II_d 253–256°C, II_e 224–226°C, II_f 227–229°C, II_g 241–244°C.

Synthesis of compounds III_{a-g}

Typical procedure for the synthesis of III_a Compound II_a (500 mg, 1.2 mmol), DCC (299 mg, 1.5 mmol), ADT-OH (326 mg, 1.4 mmol), and a catalytic amount of DMAP were dissolved in 20 mL dichloromethane. The mixture was

stirred at room temperature for 30 min and then filtered. The filtered cake was recrystallized from ethyl acetate and petroleum ether.

Similar method was used for the synthesis of compounds $\mathbf{III}_{b-g}$.[30]

III_a: Red solid, yield 69.8%, mp 187.2–188.6°C. ^{1}H NMR ($CDCl_3$) δ: 0.98 (d, 3H, *J* = 6.6 Hz, CH_3), 1.04 (d, 3H, *J* = 6.5 Hz, CH_3), 1.59–1.68 (m, 1H, CH), 2.21–2.36 (m, 2H, CH_2), 5.59–5.95 (m, 1H, CH), 7.22 (d, 2H, *J* = 8.5Hz, ArH), 7.37 (d, 2H, *J* = 8.6 Hz ArH), 7.67 (d, 2H, *J* = 8.7 Hz, ArH), 7.70 (s, 1H, = CH). IR (KBr, ν, cm^{-1}): 1769.9 (C = 0), 1711.0 (C = 0), 1600.8 (C = C), 1581.9 (C = C); HR-MS m/z: Calcd. For $C_{25}H_{20}BrNO_3S_5$ [M +H] $^+$: 621.9303, Found: 621.9280.

III_b: Red solid, yield 73.4%, mp 159.5–160.7° C. ^{1}H NMR ($CDCl_3$) δ: 0.91 (d, 3H,*J* = 6.9 Hz, CH_3), 1.33 (d, 3H, *J* = 6.5 Hz, CH_3), 2.94–3.05 (m, 1H, CH), 5.52 (m, 1H, *J* = 9.4 Hz, CH), 7.21 (d, 2H, *J* = 8.6 Hz, ArH), 7.37–7.39 (m, 3H, ArH, =CH), 7.63–7.67 (m, 4H, ArH), 7.72 (s, 1H, =CH). IR (KBr, ν, cm^{-1}): 1777.3 (C = 0), 1706.4 (C = 0), 1601.1 (C = C), 1582.2 (C = C); HR-MS m/z: Calcd. For $C_{24}H_{18}BrNO_3S_5$ [M + H]$^+$: 607.9146, Found: 607.9122.

III_c: Red solid, yield 70.1%, mp 164.3–165.2°C. ^{1}H NMR ($CDCl_3$) δ: 0.91 (d, 3H, *J* = 6.9 Hz, CH_3), 1.33 (d, 3H, *J* = 6.5 Hz, CH_3), 2.94–3.03 (m, 1H, CH), 5.52 (m, 1H, *J* = 8.6 Hz, CH), 7.21 (d, 2H, *J* = 8.7 Hz, ArH), 7.38 (s, 1H, = CH), 7.44–7.49 (m, 4H, ArH), 7.66 (d, 2H, *J* = 8.7 Hz, ArH), 7.74 (s, 1H, = CH). IR (KBr, ν, cm^{-1}): 1777.0 (C = 0), 1704.4 (C = 0), 1601.6 (C = C), 1583.3 (C = C); HR-MS m/z: Calcd. For $C_{24}H_{18}ClNO_3S_5$ [M +H]$^+$: 563.965, Found: 563.9644.

III_d: Red solid, yield 68.5%, melting point 168.4–171.4 ℃. ^{1}H NMR ($CDCl_3$) δ: 3.55–3.65 (m, 2H, CH_2), 6.27–6.32 (m, 1H, CH), 7.17–7.30 (m, 5H, ArH), 7.29 (d, 2H, *J* = 8.7 Hz, ArH), 7.41 (d, 1H, *J* = 7.1 Hz, ArH), 7.46–7.51 (m, 2H, ArH, =CH), 7.71–7.75 (m, 4H, ArH), 7.80 (s, 1H, =CH), 7.87 (t, 3H, *J* = 7.7 Hz, ArH), 7.99 (d, 2H, *J* = 8.7 Hz, ArH). 7.71–7.75 (m, 4H, ArH). 1771.3 (C = 0), 1704.6 (C = 0), 1590.5 (C = C), 1520.7 (C = C); HR-MS m/z: Calcd. For $C_{34}H_{23}NO_3S_5$ [M+H]$^+$: 654.0354, Found: 654.0346.

III_e: Red solid, yield 73.4%, mp 157.5–161.2°C. ^{1}H NMR ($CDCl_3$) δ: 0.98 (d, 3H, *J* = 6.6 Hz, CH_3), 1.04 (d, 3H, *J* = 6.5 Hz, CH_3), 1.59–1.68 (m, 1H, CH), 2.21–2.36 (m, 2H, CH_2), 5.59–5.95 (m, 1H, CH), 7.22 (d, 2H, *J* = 8.5Hz, ArH), 7.37 (d, 2H, *J* = 8.6 Hz ArH), 8.02 (d, 2H, *J* = 7.49 Hz, ArH), 7.68 (s, 1H, = CH). IR (KBr, ν, cm^{-1}): 1769.9 (C = 0), 1711.0 (C = 0), 1600.8 (C = C), 1581.9 (C = C); HR-MS m/z: Calcd. For $C_{25}H_{20}FNO_3S_5$ [M + H] $^+$: 561.9303, Found: 561.9280.

III_f: Red solid, yield 65.1%; mp 165.1–169.3°C. ^{1}H NMR ($CDCl_3$) δ: 0.91 (d, 3H,*J* = 6.9 Hz, CH_3), 1.33 (d, 3H, *J* = 6.5 Hz, CH_3), 2.94–3.05 (m, 1H, CH), 5.52 (m, 1H, *J* = 9.4 Hz, CH), 7.21 (d, 2H, *J* = 8.6 Hz, ArH), 7.37–7.39 (m, 3H, ArH, =CH), 7.91–7.98 (m, 4H, ArH), 7.70 (s, 1H, =CH). IR (KBr, ν, cm^{-1}): 1777.3 (C = 0), 1706.4 (C = 0), 1601.1 (C = C), 1582.2 (C = C); HR-MS m/z: Calcd. For $C_{24}H_{18}FNO_3S_5$[M+H]$^+$: 547.9146, Found: 547.9122.

III_g: Red solid, production 69.3%; mp 184.3–185.2°C. ^{1}H NMR ($CDCl_3$)δ: 0.98 (d, 3H, *J* = 6.6 Hz, CH_3), 1.04 (d, 3H, *J* = 6.5 Hz, CH_3), 1.59–1.68 (m, 1H, CH), 2.21–2.36 (m, 2H, CH_2), 5.59–5.95 (m, 1H, *J* = 8.6 Hz, CH), 7.22 (d, 2H, *J* = 8.5 Hz, ArH), 7.37 (d, 2H, *J* = 8.6 Hz ArH), 7.67 (d, 2H, *J* = 8.7 Hz, ArH), 7.70 (s, 1H, = CH). IR (KBr, ν, cm^{-1}): 1777.0 (C = 0), 1704.4 (C = 0), 1601.6 (C = C), 1583.3 (C = C); HR-MS m/z: Calcd. For $C_{25}H_{20}ClNO_3S_5$ [M+H] $^+$: 578.1144., Found: 578.1144.

ANTITUMOR ACTIVITY

Drug preparation

At first, the compounds were dissolved in DMSO and diluted to the required concentrations in the RPMI-1640 medium, and six concentrations (1, 10, 20, 40, 80, and 160 μmol/L) were set for each compound. Next, MTT assay was conducted to evaluate the antitumor activity in vitro, with 5-FU used as a positive control.

Cell culture

RPMI-1640 medium with 10% fetal bovine serum was used for human hepatocellular carcinoma cell lines HepG2 and human prostate adenocarcinoma cell lines DU145, and 37°C, 5% CO_2 incubator were used for culturing.

Antitumor activity assay

One flask of cells in good condition and logarithmic growth phase was taken and digested with 0.25% trypsin to detach adherent cells to prepare a tube containing 5 × 10^6–6 × 10^6 cells/mL. Next, seeded a 96-well plate with 50 mL cell suspension per well incubated the 96-well plate at 37°C 5% CO_2 for 24 h. The next day, medium in the 96-well plate was removed and the tested compound was added at 50 mL per well. The negative control group and blank group were set with five duplicate wells for each group. After having cultured for 48 h, MTT solution (5 mg/mL) was added into 96-well plate (20 μL/well) and then incubated for 4 h. Then, culture solution with DMSO (150 μL/well) instead. At last, the ELISA used for observing the absorbance (A) of each well at 570 nm, and calculated cell inhibition rate. Each experiment was repeated at least 3 times. Cell inhibition rate (%) = (1-[experimental Group A – blank control Group A]/[negative control Group A – blank control group A])*100.

CONCLUSION

Compounds $\mathbf{III}_{a-f}$ and $\mathbf{II}_{a-g}$ showed strong anti-proliferation activities on HepG2 and DU145 cell lines. In general, the compounds **III** showed stronger activities than compounds **II**. Some of the compounds **II** had anti-proliferation effects on HepG2 and six compounds $\mathbf{III}_a$, $\mathbf{III}_b$, $\mathbf{III}_d$, $\mathbf{III}_e$, $\mathbf{III}_f$, and IIIg on DU145 cell lines were all stronger than the positive control 5-fluorouracil.

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