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# Design, Synthesis and Antitumor Activities of Novel 7-Arylseleno-7-deoxydaunomycinone Derivatives

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**Abstract**—7-Arylseleno-7-deoxydaunomycinone derivatives **3a–e** and 7-thiophenyl-7-deoxydaunomycinones (**7** and **8**) were synthesized and the antitumor activities of them were evaluated against human stomach cancer SGC-7901 and human leukaemia HL60. The cytotoxic assay show that seleno daunomycinone derivatives are much better inhibitory activity than thiodaunomycinone and the structure–activity relationship was discussed. 7-Deoxydaunomycinone **4** was obtained when selenophenols were used in excess and the possible mechanism was proposed.


## Introduction

Daunorubicin (**1a,** R = H, DAU) and Doxorubicin (**1b**, R = OH, DOX, Fig. 1) are clinically useful anthracycline antitumor agents currently. However, their clinical uses are hampered by a number of undesirable side effects, especially serious cardiotoxicity.[1] The mechanism of antibiotic action of DOX lies in its ability to intercalate between adjacent DNA base pairs causing topoisomerase II inhibition.[2,3] DNA binding data and the results of biological testing point out that the groups linked at C-7 and C-9 play an important role in the stabilization of the cleavable ternary complex drug-DNA–topoisomerase II via specific contacts.[2–4] The possible covalent bindings between C-7 and various biological nucleophiles have been sugessted as a root for the toxic side effects of daunorubicin and doxorubicin.[5] Many efforts have been made to modify the anthracyclines and try to develop analogues with high activity and low toxicity, and most of them maintain the sugar moiety.[6] Several analogues with various leaving group have been synthesized, and displacement of the 7-OH with O-, S- and C-nucleophiles has been described.[7] But the displacement of 7-OH of daunomycinone by selenium group has not been reported so far, and the replacement of glycoside oxygen by selenium group might possibly exhibit biological properties remarkably different from the glycosidic oxygen analogue, which might produce new molecules to be more accommodated in the minor groove of DNA. Selenium now was recognized as an essential nutriment and its deficiency can result in many diseases in human body, such as cancer,[8,9] cardiovascular disease,[10] loss of immunocompetence,[10] viral infections[10] and so on. On the other hand, selenium can be a chemopreventive agent to remedy and retard cancers.[9] In this work, displacement of oxygen atom at C-7 of daunomycinone **2** with arylseleno group was explored. 7-Arylseleno-daunomycinone derivatives were synthesized and their antitumor activities were evaluated against human stomach cancer SGC-7901 and human leukaemia HL60 in vitro. In order to compare the antitumor activities of selenium and sulfur, we also synthesized 7-thiophenyl-7-deoxydaunomycinone analogues.

## Results and Discussion

### Chemistry

Usually, the catalysts used to synthesize the selenide from alcohol and selenols are acetic acid, trifluoroacetic acid, boron-trifluoride etherate and so on. In our experiment, trifluoroacetic acid (TFA), *p*-toluenesulfonic acid (*p*-TsOH), boron-trifluoride etherate, zinc chloride, acetic acid and hydrochloride were used to catalyze the synthesis of 7-arylseleno-7-deoxydaunomycinones **3** from daunomycinone **2** and selenophenols.

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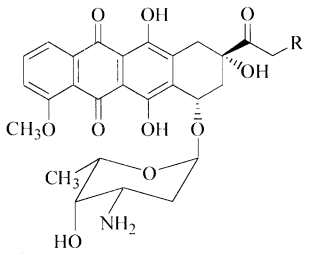
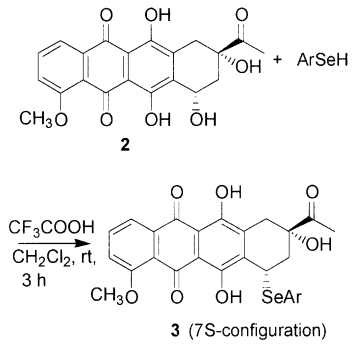



**Figure 1.** Structures of daunorubicin and doxorubicin.

As a result, trifluoroacetic acid, in dichloromethane at room temperature for 3 h, was the most potent and convenient catalyst for this reaction. The synthetic approach catalyzed by trifluoroacetic acid was depicted in Scheme 1. The experimental results, catalyzed by trifluoroacetic acid and other catalysts, are listed in Tables 1 and 2, respectively.

Displacement of 7-OH group in compound **2** should exist in formation of two isomers, that is, 7*S* and 7*R* configurations. In reaction conditions described above, only one isomer was obtained. The NMR spectra of compound **3a**–**f** show: H-7 as doublet at δ 4.87–4.95 ppm with a coupling constant of 2.4–3.6 Hz. According to literature reports[5,11] and comparing with the *J* (H-7, δ 5.31 ppm, $J = 3.8$ Hz) of daunomycinone **2**, the configuration of **3a**–**f** was determined as 7*S*-configuration.



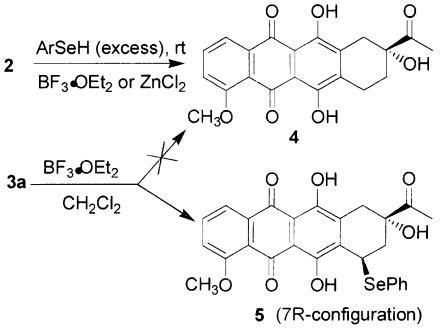

**Scheme 1.**

**Table 1.** Experimental results of the synthesis of compound **3a**–**e** catalyzed by TFA

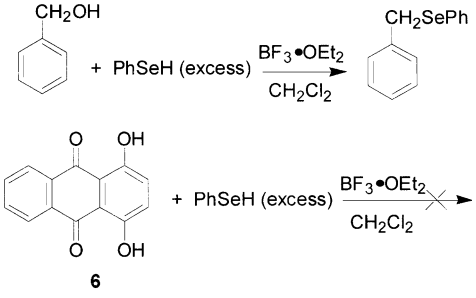
| Compd | Ar | Yield (%) | Mp (°C) |
|---|---|---|---|
| **3a** | $C_6H_5$ | 64.1 | 187–188.5 |
| **3b** | *p*-$MeC_6H_4$ | 70.2 | 173–175 |
| **3c** | *p*-$MeOC_6H_4$ | 71.7 | 167–170 |
| **3d** | *o*-$ClC_6H_4$ | 58.2 | 177.5–181 |
| **3e** | *m*-$MeC_6H_4$ | 78.3 | 168.5–169.5 |
| **3f** | Naphthyl | 74.8 | 96—99 |

Interestingly, when the molar ratio of **2** to selenophenols was 1:1 catalyzed by $BF_3{\cdot}OEt_2$ and $ZnCl_2$, the products **3** were obtained mainly. When selenophenols exceeds **2** by 2–3 times, however, 7-deoxydaunomycinone **4** was the main product at room temperature for 30 min. But at first 5 min reaction, **3** was detected on TLC. On the other hand, pure **3a** (7*S* configuration) was tested in the presence of $BF_3{\cdot}OEt_2$ in $CH_2Cl_2$, **4** was not found but **5** (7*R*-isomer, H-7, δ 4.98 ppm, dd, $J = 8.5$, 6.1 Hz) was obtained mainly (Scheme 2).

At same time, benzyl alcohol and 1,4-dihydroxy-anthraquinone **6** were reacted with excessive selenophenol catalyzed by $BF_3{\cdot}OEt_2$ in $CH_2Cl_2$, benzyl phenyl selenide was gained (identified by GC–MS) and **6** remained unchanged (Scheme 3). The above experiments suggested that selenophenol could not be a reducer to reduce quinone directly and the formation of **4** is related to the structure of daunomycinone. It is known that selenium has reductive properties and anthraquinone is



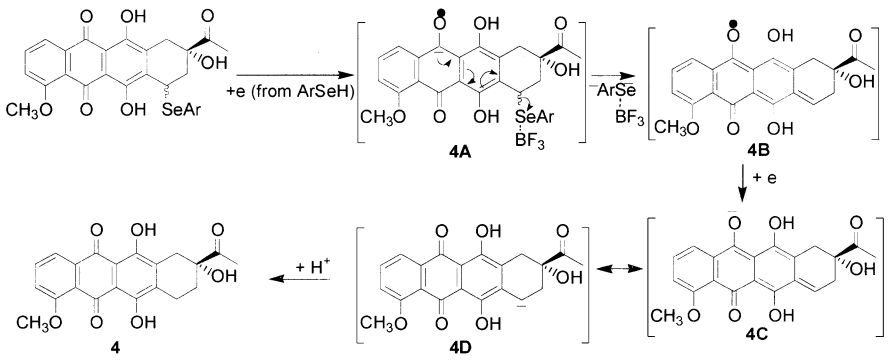

**Scheme 2.**




**Scheme 3.**

**Table 2.** Experimental results catalyzed by other catalysts

| Cat. | Solvent | Time | Temp (°C) | Yield (%) | Product |
|---|---|---|---|---|---|
| TFA | $CH_2Cl_2$ | 3 h | rt | 64.1 | **3a** (only) |
| *p*-TsOH | $CH_2Cl_2$ | 5 h | rt | 61.8 | **3a** (only) |
| $BF_3{\bullet}OEt_2$ | $CH_2Cl_2$ | 15 min | rt | 49.8 | **3a** (main) |
| | $CH_2Cl_2$ | 1 h | −15 | 58.7 | **3a** (only) |
| $ZnCl_2$ | $Cl(CH_2)_2Cl$ | 20 min | 80 | 51.2 | **3a** (main) |
| AcOH | Unreacted | | | | |
| HCl | Unreacted | | | | |




**Scheme 4.**

an oxidant. It has been reported that anthracyclines could form an anthracycline radical in the body and this is the main reason why anthracyclines are cardiotoxic.[4,12] On the basis of the reports, we propose the following mechanism for the formation of **4** (Scheme 4). Further confirmation of this mechanism is under way.

Because boron-trifluoride etherate and zinc chloride are stronger Lewis acid than trifluoroacetic acid and *p*-toluenesulfonic acid, arylseleno group of **3** can not leave in the presence of TFA and *p*-TsOH as catalysts at room temperature, so main product was **3** no matter if the selenophenols were excessive or not.

The conversion from **3a** to **5** can be explained from the half-chair conformation of ring A in **3a** and **5** (Fig. 2). Selenophenyl group in **3a** was in the axial position, whereas it was in the equatorial orientation in **5**. Compound **5**, a thermodynamically controlled product, is more stable than **3a**, so **5** was obtained after a long time reaction. In another experiment conducted, after 6 h reaction of daunomycinone and selenophenol catalyzed by TFA at room temperature, compound **5** can be detected.

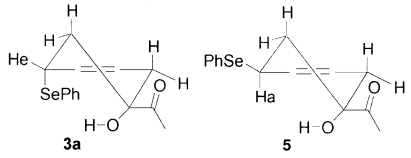



**Figure 2.** The conformation of **3a** and **5**.

**Table 3.** Cytotoxicities of new compounds **3a–e**, **7** and **8** against tumor cells

| Compd | Ar | $IC_{50}$ (μg/mL)[a] | |
|---|---|---|---|
| | | SGC-7901[b] | HL60[c] |
| **3a** | $C_6H_5$ | 21.7 | 68.2 |
| **3b** | *p*-$MeC_6H_4$ | 34.5 | 58.7 |
| **3c** | *p*-$MeOC_6H_4$ | 91.8 | 36.8 |
| **3d** | *o*-$ClC_6H_4$ | 23.8 | 76.1 |
| **3e** | *m*-$CH_3C_6H_4$ | 63.6 | 51.2 |
| **6A** | — | >100 | >100 |
| **6B** | — | >100 | >100 |
| DAU | — | 0.23 | 0.08 |

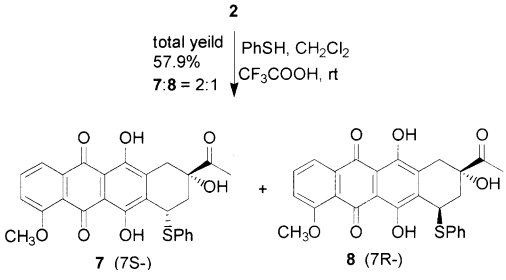
[a]Activity against tumor cells was measured by MTT-microculture tetrazolium assay.
[b]SGC-7901, human stomach cancer.
[c]HL60, human leukemia.

In order to compare the antitumor activity of selenium and sulfur analogues, we synthesized 7-thiophenyl-7-deoxydaunomycinone **7** and **8** from daunomycinone **2** and thiophenol catalyzed by $CF_3COOH$ and $BF_3{\cdot}OEt_2$, respectively. In contrast to seleno derivatives, 7*S*- and 7*R*-thiophenyl-7-deoxydaunomycinone were both obtained at any time, but **4** was not found even though the thiophenol was added in excess, probably because the reductive power of selenium is stronger than sulfur. The ratio of 7*S* (**7**):7*R* (**8**) was 2:1 from the reaction catalyzed by $CF_3COOH$ (Scheme 5).

## Biological Activity

Compounds **3a–e**, **7** and **8** were assayed for cytotoxicity by using cells of human stomach cancer SGC-7901 and human leukaemia HL60. Results are expressed in terms of inhibitory activity ($IC_{50}$, μg/mL) obtained by the MTT method. The results are listed in Table 3.

As shown in Table 3, seleno daunomycione derivatives showed inhibitory activity on the human stomach cancer SGC-7901 and the human leukaemia HL60, but lesser extent than DAU. Among compounds tested, 7-phenylselenodaunomycinone **3a** and 7-(*o*-chlorophenylseleno)daunomycinone **3d** were found to be highly cytotoxic against human stomach cancer, and 7-(*p*-methylphenylseleno)daunomycinone **3c** was found to be highly cytotoxic against human leukaemia HL60. On the other hand, seleno derivatives **3a–e** are much more potent than the thio analogues **7** and **8** regarding tested tumor cells, and the quinone radical intermediate **4A** or **4B** probably are the key reason on this fact. Seleno derivatives might form quinone radical intermediate **4A** or **4B** to intercalate between DNA base




**Scheme 5.**

pairs causing cytotoxicity, whereas thio derivatives do not have this ability. Further studies on the antitumor abilities of sulfur and selenium are under way.

## Conclusion

We have completed the synthesis and cytotoxic assay of novel 7-arylseleno-7-deoxydaunomycinone derivatives and 7-thiophenyl-7-deoxydaunomycinone analogues derived from daunomycinone. All synthesized seleno derivatives exhibited antitumor activities against human stomach cancer SGC-7901 and human leukaemia HL60. The cytotoxicity data suggest that the seleno derivatives are much more potent than the thio analogues.

## Experimental

Melting point was determined on a YANACO melting point apparatus and uncorrected. Infrared (IR) spectra were taken on a Nicolet 230 FT-IR spectrophotometer. Elemental analyses were performed on Carlo Elba 1106 instrument. $^1$H and $^{13}$C NMR spectra were recorded on AVANCE DMX500 using $CDCl_3$. Chemical shifts were reported at δ values in parts per million (ppm) and coupling constants (*J*) are given in hertz (Hz). MS spectra were recorded on ESQUIRE-LC-00075.

**General experimental procedure for the synthesis of 7-arylseleno-7-deoxydaunomycinone 3.** To a solution of **2** in $CH_2Cl_2$ (10 mL) was added selenophenols (1 equiv) and $CF_3COOH$ 0.5 mL, stirred at room temperature for 3 h, monitored by TLC. The reaction mixture quenched into water, washed with saturated $NaHCO_3$, water, extracted with $CH_2Cl_2$ (3×25 mL). The organic phase was dried with anhydrous $Na_2SO_4$ and then evaporated in vacuum. The residue was purified by silica gel column chromatography eluting with hexane/ dichloromethane/ acetate ester (4:4:1) and **3** was obtained in moderate to high yield.

**7-Phenylseleno-7-deoxydaunomycinone (3a).** A mixture of daunomycinone **2** (41 mg, 0.1 mmol), selenophenol (16 mg, 0.11 mmol) and trifluoroacetic acid (0.5 mL) was dissolved in dichloromethane and stirred for 3 h to give 35.5 mg of **3a** (64.1%) as a red powder. IR: 3444, 1695, 1617, 1583; $^1$H NMR: 14.02 (1H, s, OH), 13.40 (1H, s, OH), 8.03 (1H, d, $J$=7.7 Hz, ArH), 7.77 (3H, m, ArHArH), 7.39 (1H, d, $J$=8.4 Hz, ArH), 7.34 (3H, m, ArH), 4.95 (1H, d, $J$=3.7 Hz, H-7), 4.43 (1H, s, OH-9), 4.09 (3H, s, $OCH_3$), 3.19 (1H, d, $J$=18.7 Hz, H-10e), 3.01 (1H, d, $J$=18.7 Hz, H-10a), 2.55 (1H, dd, $J$=14.7, 5.2 Hz, H-8e), 2.49 (1H, d, $J$=14.7 Hz, H-8a), 2.39 (3H, s, $CH_3$); $^{13}$C NMR: 211.69 (C=O), 187.21 (C=O), 186.70 (C=O), 161.28 (C-4), 155.98 (C-6), 155.93 (C-11), 137.49 (C-2), 135.93 (C-6a), 135.80 (C), 135.42 (2×CH), 133.42 (C-12a), 131.47 (C-10a), 129.38 (2×CH), 128.59 (C), 121.22 (C-4a), 119.94 (C-3), 118.53 (C-1), 111.32 (C-5a), 110.70 (C-11a), 77.01 (C-9), 56.95 ($OCH_3$), 36.69 (C-7), 35.30 (C-8), 33.14 (C-10), 24.72 ($CH_3$). Anal. calcd for $C_{27}H_{22}O_7Se$: C, 60.34; H, 4.13. Found: C, 60.37; H, 4.11.

**7-(4-Methylphenylseleno)-7-deoxydaunomycinone (3b).** A mixture of daunomycinone **2** (34 mg, 0.08), selenophenol (15 mg, 0.09 mmol) and trifluoroacetic acid (0.5 mL) was dissolved in dichloromethane and stirred for 3 h to give 33 mg of **3b** (70.2%) as a red powder. IR: 3441, 1695, 1618, 1538; $^1$H NMR: 14.04 (1H, s, OH), 13.40 (1H, s, OH), 8.07 (1H, d, $J$=7.6 Hz, ArH), 7.77 (1H, t, $J$=7.8 Hz, ArH), 7.65 (2H, d, $J$=7.8 Hz, ArH), 7.38 (1H, d, $J$=8.2 Hz, ArH), 7.14 (2H, d, $J$=7.8 Hz, ArH), 4.91 (1H, d, $J$=2.7 Hz, H-7), 4.09 (3H, s, $OCH_3$), 3.20 (1H, dd, $J$=18.7, 1.3 Hz, H-10e), 3.01 (1H, d, $J$=18.7 Hz, H-10a), 2.48 (1H, dd, $J$=14.8, 5.0 Hz, H-8e), 2.45 (1H, d, $J$=14.8 Hz, H-8a), 2.40 (3H, s, $CH_3$), 2.36 (3H, s, $CH_3$); $^{13}$C NMR: 211.79 (C=O), 187.17 (C=O), 186.64 (C=O), 161.26 (C-4), 155.91 (C-6), 155.84 (C-11), 139.20 (C-2), 137.27 (C-6a), 135.89 (C), 135.48 (2×CH), 133.51 (C-12a), 130.99 (C-10a), 129.48 (2CH), 128.48 (C), 121.31 (C-4a), 119.91 (C-3), 118.59 (C-1), 111.30 (C-5a), 110.78 (C-11a), 77.02 (C-9), 56.91 ($OCH_3$), 35.59 (C-7), 35.02 (C-8), 33.18 (C-10), 24.76 ($CH_3$), 21.56 ($CH_3$). Anal. calcd for $C_{28}H_{24}O_7Se$: C, 60.98; H, 4.39. Found: C, 61.02; H, 4.36.

**7-(4-Methoxyphenylseleno)-7-deoxydaunomycinone (3c).** A mixture of daunomycinone **2** (42 mg, 0.11 mmol), selenophenol (20 mg, 0.11 mmol) and trifluoroacetic acid (0.5 mL) was dissolved in dichloromethane and stirred for 3 h to give 43 mg of **3c** (71.7%) as a red powder. IR: 3433, 1695, 1617, 1583; $^1$H NMR: 14.07 (1H, s, OH), 13.40 (1H, s, OH), 8.03 (1H, d, $J$=7.7 Hz, ArH), 7.78 (1H, t, $J$=8.2 Hz, ArH), 7.68 (1H, d, $J$=8.7 Hz, ArH), 7.39 (1H, d, $J$=8.3 Hz, ArH), 6.85 (1H, d, $J$=8.7 Hz, ArH), 4.87 (1H, d, $J$=2.4 Hz, H-7), 4.60 (1H, s, OH-9), 4.10 (3H, s, $OCH_3$), 3.81 (3H, s, $OCH_3$), 3.18 (1H, d, $J$=18.7 Hz, H-10e), 3.01 (1H, d, $J$=18.7 Hz, H-10a), 2.46 (2H, m, H-8), 2.40 (3H, s, $CH_3$); $^{13}$C NMR: 211.89 (C=O), 187.18 (C=O), 186.65 (C=O), 161.26 (C-4), 160.46 (C), 156.02 (C-6), 155.86 (C-11), 137.87 (2CH), 137.41 (C-2), 135.93 (C), 135.74 (C), 135.70 (C-12a), 135.58 (C-10a), 121.28 (C-4a), 119.92 (C-3), 118.50 (C-1), 115.02 (2×CH), 111.31 (C-5a), 110.67 (C11a), 77.02 (C-9), 56.95 ($OCH_3$), 56.54 ($OCH_3$), 36.08 (C-7), 34.65 (C-8), 33.20 (C-10), 24.80 ($CH_3$). Anal. calcd for $C_{28}H_{24}O_8Se$: C, 59.27; H, 4.26. Found: C, 59.23; H, 4.23.

**7-(2-Chlorophenylseleno)-7-deoxydaunomycinone (3d).** A mixture of daunomycinone **2** (55 mg, 0.14 mmol), selenophenol (27 mg, 0.14 mmol) and trifluoroacetic acid (0.5 mL) was dissolved in dichloromethane and stirred for 3 h to give 46 mg of **3d** (58.2%) as a red powder. IR: 3433, 1708, 1617, 1538; $^1$H NMR: 13.77 (1H, s, OH), 13.36 (1H, s, OH), 7.98 (1H, d, $J$=7.65 Hz, ArH), 7.79 (1H, d, $J$=7.4 Hz, ArH), 7.74 (1H, t, $J$=8.0 Hz, ArH), 7.45 (1H, d, $J$=7.8 Hz, ArH), 7.34 (1H, d, $J$=8.2 Hz, ArH), 7.26 (1H, m, ArH), 7.19 (1H, m, ArH), 4.94 (1H, d, $J$=2.4 Hz, H-7), 4.10 (1H, s, OH-9), 4.05 (3H, s, OCH3), 3.15 (1H, d, $J$=18.6 Hz, H-10e), 3.01 (1H, d, $J$=18.6 Hz, H-10a), 2.67 (2H, m, H-8), 2.40 (3H, s, $CH_3$); $^{13}$C NMR: 211.05 (C=O), 187.10 (C=O), 186.56

(C=O), 161.24 (C-4), 156.27 (C-6), 156.02 (C-11), 138.49 (C-2), 138.31 (C-6a), 136.73 (CH), 135.90 (C), 135.77 (CH), 133.35 (C-12a), 132.71 (C-10a), 129.73 (CH), 129.45 (CH), 127.33 (C), 121.27 (4a), 119.90 (C-3), 118.47 (C-1), 111.22 (C-5a), 110.50 (C-11a), 76.76 (C-9), 56.93 ($OCH_3$), 36.39 (C-7), 34.75 (C-8), 32.97 (C-10), 24.47 ($CH_3$). Anal. calcd for $C_{27}H_{21}O_7SeCl$: C, 56.71; H, 3.70. Found: C, 56.73; H, 3.66.

**7-(3-Methylphenylseleno)-7-deoxydaunomycinone (3e).** A mixture of daunomycinone **2** (51 mg, 0.13 mmol), selenophenol (22 mg, 0.13 mmol) and trifluoroacetic acid (0.5 mL) was dissolved in dichloromethane and stirred for 3 h to give 55 mg of **3e** (78.3%) as a red powder.: IR: 3447, 1695, 1617, 1582; $^1$H NMR: 14.00 (1H, s, OH), 13.33 (1H, s, OH), 7.96 (1H, d, $J=7.6$ Hz, ArH), 7.23 (1H, t, $J=8.0$ Hz, ArH), 7.57 (1H, s, ArH), 7.53 (1H, d, $J=7.6$ Hz, ArH), 7.34 (1H, d, $J=8.3$ Hz, ArH), 7.21 (1H, q, $J=7.6$ Hz, ArH), 7.14 (1H, d, $J=7.5$ Hz, ArH), 4.91 (1H, d, $J=3.6$ Hz, H-7), 4.06 (3H, s, $OCH_3$), 3.18 (1H, dd, $J=18.6$, 1.0 Hz, H-10e), 2.95 (1H, d, $J=18.6$ Hz, H-10a), 2.52 (1H, dd, $J=14.8$, 5.1 Hz, H-8e), 2.46 (1H, d, $J=14.8$ Hz, H-8a), 2.40 (3H, s, $CH_3$), 2.38 (1H, s, $CH_3$); $^{13}$C NMR: 211.89 (C=O), 187.10 (C=O), 186.62 (C=O), 161.26 (C-4), 155.95 (C-6), 155.86 (C-11), 139.22 (C-2), 137.30 (C-6a), 135.89 (C), 135.73 (C), 133.59 (C-12a), 132.36 (CH), 130.99 (C-10a), 129.44 (CH), 129.18 (CH), 128.85 (C), 121.31 (C-4a), 119.89 (C-3), 118.54 (C-1), 111.29 (C-5a), 110.69 (C-11a), 77.10 (C-9), 56.93 ($OCH_3$), 35.51 (C-7), 34.98 (C-8), 33.15 (C-10), 24.79 ($CH_3$), 21.55 ($CH_3$). Anal. calcd for $C_{28}H_{24}O_7Se$: C, 60.98; H, 4.39. Found: C, 60.95; H, 4.39.

**7-Naphthylseleno-7-deoxydaunomycinone (3f).** A mixture of daunomycinone **2** (33 mg, 0.083 mmol), selenophenol (17 mg, 0.084 mmol) and trifluoroacetic acid (0.5 mL) was dissolved in dichloromethane and stirred for 3 h to give 36 mg of **3f** (74.8%) as a red powder. IR: 3461, 1710, 1613, 1582; $^1$H NMR: 14.00 (1H, s, OH), 13.26 (1H, s, OH), 8.29 (1H, d, $J=8.3$ Hz, ArH), 8.03 (1H, d, $J=7.7$ Hz, ArH), 7.88 (3H, m, ArH), 7.78 (1H, t, $J=8.1$ Hz, ArH), 7.58 (2H, m, ArH), 7.43 (1H, d, $J=7.7$ Hz, ArH), 7.39 (1H, d, $J=8.4$ Hz, ArH), 4.91 (1H, d, $J=3.6$ Hz, H-7), 4.06 (3H, s, $OCH_3$), 3.18 (1H, dd, $J=18.6$, 1.0 Hz, H-10e), 2.95 (1H, d, $J=18.6$ Hz, H-10a), 2.52 (1H, dd, $J=14.8$, 5.1 Hz, H-8e), 2.46 (1H, d, $J=14.8$ Hz, H-8a), 2.40 (3H, s, $CH_3$), 2.38 (1H, s, $CH_3$); MS (ESIsource, positive): 611 $(M+Na)^+$. Anal. calcd for $C_{31}H_{24}O_7Se$: C, 63.38; H, 4.12. Found: C, 63.41; H, 4.14.

**7*S*- and 7*R*-thiophenyl-7-deoxydaunomycinone (7, 8).** To a solution of **2** (155 mg, 0.4 mmol) in $CH_2Cl_2$ (15 mL) was added thiophenol (59 mg, 0.54 mmol) and $CF_3COOH$ 1 mL, stirred at room temperature for 36 h, monitored by TLC. The reaction mixture quenched into water, washed with saturated $NaHCO_3$, water, extracted with $CH_2Cl_2$ (3×25 mL). The organic phase was dried with anhydrous $Na_2SO_4$ and then evaporated in vacuum. The residue was isolated by silica gel column chromatography eluting with hexane/dichloromethane/acetone (6:6:1) to give **7** (75 mg) as a red powder and **8** (39 mg) as a red powder with 57.9% total yield.

**7.** Mp 182–185 °C; IR: 3381, 1699, 1616, 1584, 1421, 1279, 1212, 1078, 1033; $^1$H NMR: 14.12 (1H, s, OH), 13.36 (1H, s, OH), 8.04 (1H, d, $J=7.6$ Hz, ArH), 7.78 (1H, t, $J=8.3$ Hz, ArH), 7.69 (2H, m, ArH), 7.39 (4H, m, ArHArH), 5.05 (1H, s, OH-9), 4.92 (1H, d, $J=4.2$ Hz, H-7), 4.09 (3H, s, $OCH_3$), 3.27 (1H, dd, $J=18.9$, 1.6 Hz, H-10e), 3.03 (1H, d, $J=18.9$ Hz, H-10a), 2.41 (3H, s, $CH_3$), 2.33 (1H, d, $J=14.8$ Hz, H-8e), 2.21 (1H, dd, $J=14.8$, 5.0 Hz, H-8a); $^{13}$C NMR: 212.0 (C=O), 187.0 (C=O), 186.65 (C=O), 161.04 (C-4), 155.73 (C-6), 155.60 (C-11), 135.60 (C-2), 134.73 (C-6a), 134.46 (C), 134.01 (C-12a), 133.49 (2×CH), 129.372 (2×CH), 128.58 (CH), 121.02 (C-4a), 119.72 (C-3), 118.40 (C-1), 111.26 (C-5a), 110.93 (C-11a), 76.79 (C-9), 56.72 ($OCH_3$), 42.00 (C-7), 33.32 (C-8), 32.67 (C-10), 24.73 ($CH_3$). Anal. calcd for $C_{27}H_{22}O_7S$: C, 66.11; H, 4.52. Found: C, 66.08; H, 4.57.

**8**: Mp 96–98 °C; IR: 3482, 1713, 1616, 1584, 1411, 1285, 1212, 1067; $^1$H NMR: 14.00 (1H, s, OH), 13.57 (1H, s, OH), 8.03 (1H, d, $J=7.6$ Hz, ArH), 7.77 (1H, t, $J=8.1$ Hz, ArH), 7.39 (3H, m, ArH+ArH), 7.30 (3H, m, ArH), 5.01 (1H, dd, $J=8.0$, 4.7 Hz, H-7), 4.09 (3H, s, $OCH_3$), 3.72 (1H, s, OH-9), 3.04 (1H, dd, $J=18.9$, 2.3 Hz, H-10e), 2.69 (1H, d, $J=18.9$ Hz, H-10a), 2.57 (1H, dd, $J=14.8$, 4.7 Hz, H-8e), 2.32 (4H, m, $CH_3$+H-8a); $^{13}$C NMR: 210.02 (C=O), 187.09 (C=O), 186.74 (C=O), 161.09 (C-4), 155.57 (C-6), 155.20 (C-11), 137.47 (C-2), 135.72 (C-6a), 153.53 (C), 134.94 (C), 134.36 (2×CH), 133.30 (C), 129.01 (2×CH), 128.54 (CH), 121.17 (C-4a), 119.72 (C-3), 118.42 (C-1), 111.73 (C-5a), 111.04 (C-11a), 78.06 (C-9), 56.74 ($OCH_3$), 39.43 (C-7), 38.53 (C-8), 30.90 (C-10), 24.02 ($CH_3$). Anal. calcd for $C_{27}H_{22}O_7S$: C, 66.11; H, 4.52. Found: C, 66.13; H, 4.56.

**7*R*-Selenophenyl-7-deoxydaunomycinone (5).** To a solution of **2** (96 mg, 0.24 mmol) in $CH_2Cl_2$ (15 mL) was added thiophenol (73.8 mg, 0.24 mmol) and $BF_3{\bullet}OEt_2$ 0.5 mL, stirred at room temperature for 8 h, monitored by TLC. The reaction mixture quenched into water, washed with saturated $NaHCO_3$, water, extracted with $CH_2Cl_2$ (3×25 mL). The organic phase was dried with anhydrous $Na_2SO_4$ and then evaporated in vacuum. The residue was isolated by silica gel column chromatography eluting with hexane/dichloromethane/acetate ester (5:5:1) to give **5** (51.6 mg, 40.7%) as a red powder. Mp 73–75 °C; IR: 3443, 1696, 1617, 1583; $^1$H NMR: 14.05 (1H, s, OH), 13.36 (1H, s, OH), 8.00 (1H, d, $J=7.54$ Hz, ArH), 7.75 (1H, t, $J=8.0$ Hz, ArH), 7.42 (2H, d, $J=7.0$ Hz, ArH), 7.36 (2H, m, ArH+ArH), 7.25 (2H, m, ArH), 4.98 (1H, dd, $J=8.5$, 6.1 Hz, H-7), 4.08 (3H, s, $OCH_3$), 3.68 (1H, s, OH-9), 2.93 (1H, dd, $J=16.2$, 2.7 Hz, H-10e), 2.50 (1H, dd, $J=15.4$, 5.9 Hz, H-8e), 2.32 (2H, m, H-10a+H-8a), 2.20 (3H, $OCH_3$); $^{13}$C NMR: 210.39 (C=O), 187.28 (C=O), 186.73 (C=O), 161.31 (C-4), 155.75 (C-6), 155.61 (C-11), 139.43 (C-2a), 137.28 (2×CH), 136.00 (C-6a), 135.74 (C), 134.08 (C-12a), 131.84 (C-10a), 129.43 (C), 129.26 (2×CH), 123.51 (C-4a), 119.89 (C-3), 118.56 (C-1), 111.72 (C-5a), 110.89 (C-11a), 78.13 (C-9), 56.96 ($OCH_3$), 38.87 (C-7), 32.39 (C-8), 31.07 (C-10), 24.15

($CH_3$). Anal. calcd for $C_{27}H_{22}O_7Se$: C, 60.34; H, 4.13. Found: C, 60.38; H, 4.09.

### Antitumor test procedures in vitro

**Human stomach cancer SGC-7901.** 200 μL SGC-7901 cell suspensions ($5\times10^4$ cells/mL) were dispensed into each well of 96-well flat-bottom culture plates (Costar). After 56 h culture with the agents, the cells were incubated with MTT (250 μg/mL) for anther 4 h. Then the medium was removed, and 200 μL of $Me_2SO$ was added to each well of the 96-well plate to solubilize the MTT formazan produced by the viable SGC-7901 cells. Absorbance at 570 nm ($A_{570}$) was measured with an enzyme-linked-immunosorbent-assay (ELISA) plate reader (Dynatech MR4000). Analysis of the relationship between measured $A_{540}$ and number of viable SGC-7901 cells indicated that cell densities at $2.5\times10^4$ $\sim80\times10^4$ cells/mL gave rise to a detectable and relatively linear range of absorbance values ($r=0.989$).

**Human leukaemia HL60.** 200 μL HL60 cell suspensions ($5\times10^4$ cells/mL) were dispensed into each well of 96-well flat bottom culture plates (Costar). After 44 h culture with the agents, the cells were incubated with MTT (250 μg/mL) for anther 4 h. Then, the plate was centrifugalized, the medium was removed and 200 μL of DMSO was added to each well of the 96-well plate to solubilize the MTT formazan produced by the viable HL60 cells. Absorbance at 570 nm ($A_{570}$) was measured with an enzyme-linded-immunosorbent-assay (ELISA) plate reader (Dynatech MR4000). Analysis of the relationship between measured $A_{540}$ and number of viable HL60 cells indicated that cell densities at $2.5\times10^4$ $\sim80\times10^4$ cells/mL gave rise to a detectable and relatively linear range of absorbance values ($r=0.989$).

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