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Synthesis and Antitumor Activity of Novel 1-(2′-Alkyl(or phenyl)thioethoxy)methyl-5-fluorouracils and Their Oxidation Products

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ABSTRACT: *A series of novel 1-(2′-alkyl(or phenyl)-thioethoxy)methyl-5-fluorouracils (***6***) were synthesized in three steps from 5-fluorouracil. They were oxidized into sulfoxide (***7***) and sulfone (***8***) derivatives by $NaIO_4$ and H_2O_2 30%/DEAD (diethyl azodicarboxylate), respectively, in high yields. In order to obtain structural information, sulfoxide* **7g** *was characterized by X-ray diffraction analysis. The preliminary bioassay indicated that the compounds* **6a** *and* **7g** *exhibit potential antitumor activity.* © 2004 Wiley Periodicals, Inc. Heteroatom Chem 15:543–548, 2004; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20059

INTRODUCTION

A large number of sulfur nucleosides, nucleotides, and oligonucleotides were synthesized for the purpose of finding new chemical therapeutic agents and biological tools. Some of them were developed as important tools in the study of protein and nucleic acid structures, functions and interactions, and antisense modulation of gene expression [1,2]. Many pyrimidine thionucleoside analogues also exhibit antitumor properties [3–5]. The introduction of a single sulfur atom into the nucleosides led to the efficient antiviral or antitumor agents. For example, lamivudine ((−)-L-β-1,3-oxathiolanyl cytosine) is used in the treatment of AIDS and chronic hepatitis B [6,7]; and 4′-thioFAC (1-(2-deoxy-2-fluoro-β-D-4-thio-*arabino*pentofuranosyl) cytosine) is shown to be a promising orally active antitumor agent [8].

The novel prodrug derivatives of 5-fluorouracil (5-FU) were developed [9–12]. They possess a broader spectrum of antitumor activity and lower toxicity. Some of 5-FU acyclonucleosides exhibited potential antitumors activity [13,14]. There has been little research done on the 5-FU acyclic thionucleoside. As part of our research program [15,16], we synthesized the title compounds, 1-(2′-alkyl(or phenyl)thioethoxy)methyl-5-fluorouracils, **6**, and their oxidation products **7, 8**. The synthetic route is shown in Scheme 1.

RESULTS AND DISCUSSION

*Synthesis of 1-(2′-Alkyl(or phenyl)thioethoxy)-methyl-5-fluorouracils (***6***), 1-(2′-Alkyl(or phenyl)sulfinylethoxy)methyl-5-fluorouracils (***7***), and 1-(2′-Alkyl(or phenyl)sulfonylethoxy)-methyl-5-fluorouracils (***8***)*

5-Fluorouracil (**1**) reacted with hexamethyldisilylazane (HMDS) by means of an improved procedure

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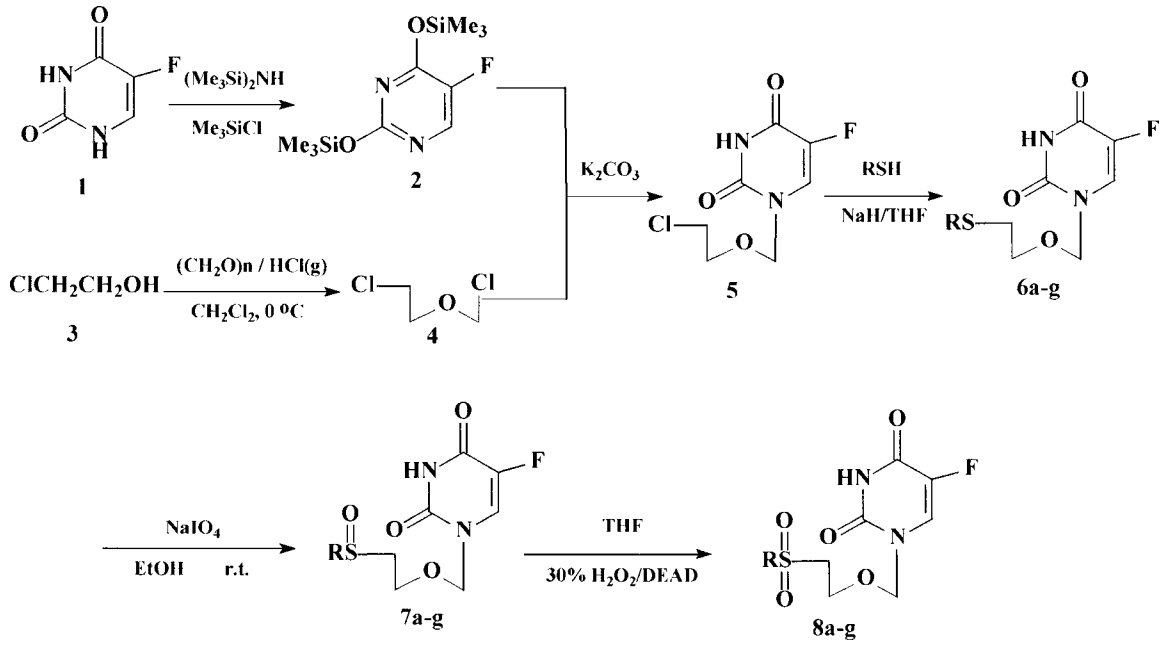
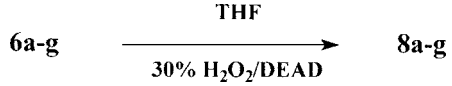


SCHEME 1

of the literature [17] to give 2,4-di(trimethylsilyloxy)-5-fluoropyrimidine **2**. According to the standard chloromethyl ether method [18], the condensation of **2** with 2-(chloromethoxy)ethyl chloride **4**, obtained from 2-chloroethanol (**3**), gave the key intermediate **5** (79% yield) in the presence of anhydrous K_2CO_3. The compounds **6a–g** were obtained by the method for synthesis of unsymmetrical thioethers (NaH/RSH, THF) in yields of 93–98%; a slight excess of aqueous $NaIO_4$ [19] was added to a solution of compounds **6** in ethanol to afford compounds **7**. The resultant **7** were oxidized by 30% H_2O_2 to produce the sulfone derivatives **8** at very slow rates. However, when DEAD ($EtO_2CN{=}NCO_2Et$) was added to this system, the reaction was considerably accelerated to give **8** in high yields. The investigation of this reaction mechanism is under progress. The compounds **8** have also been obtained directly by oxidation of **6** with H_2O_2 30%/DEAD (Scheme 2).

The Structure of Products

All compounds **6–8** have been characterized by ^{1}H NMR, elemental analysis, and IR. Some of the experimental results of compounds **6–8** were listed in Tables 1 and 2.



SCHEME 2

In the ^{1}H NMR spectra of the title compounds (**6–8**), the methylene protons of the methoxy appear as a set of characteristic singlet peak in the range of δ 5.10–5.19. The protons of the ethylene group exhibit two sets of peaks at δ 2.66–3.09 and 3.69–3.73 (sulfides), 2.86–2.92 and 4.01–4.10 (sulfoxides), and 3.16–3.42 and 3.89–4.05 (sulfones). The hydrogens of another methylene (or methyl) linking with the sulfur atom display in the range of δ 2.09–2.53 (sulfides), 2.64–2.76 (sulfoxides), and 2.95–3.08 (sulfones). The ^{1}H NMR spectrum also reveals two sets of peaks at δ 7.36–7.42 (doublet), 8.98–9.90 (singlet), supporting the 5-fluorouracil structure. The IR spectra of compounds (**6–8**) showed normal stretching absorption bands indicating the existence of the groups NH (~3400 cm^{-1}), C=O (1694–1741), C=C (1654–1685), S=O (1037–1052), O=S=O (1160–1182, 1320–1349), C—O—C (1115–1139).

The Molecular Structure and Crystal Structure of Compound **7g**

In order to obtain information about the molecular structure of the compound **7g**, a single crystal of this compound was analyzed by X-ray diffraction. The colorless crystal of **7g**, $C_{13}H_{15}FN_2O_5S$ ($C_{13}H_{13}FN_2O_4S{\cdot}H_2O$), was obtained by evaporating from its saturated methanol solution. A crystal with the size of $0.25 \times 0.15 \times 0.05$ mm^3 was examined on a Bruker Smart 1000 four-circle diffractometer with Mo Kα radiation ($\lambda = 0.71073$ Å). The

TABLE 1 The Physical Constants and Elementary Analyses of Compounds **6a–g, 7a–g**, and **8a–g**

		IR (v, cm^{-1})							*Elementary Analysis (Calcd.%)*		
No.	*R*	*NH*	*C=O*	*C=C*	*S=O (or O=S=O)*	*C–O–C*	*Yield (%)*	*mp (°C)*	*C*	*H*	*N*
6a	Me	3419	1696	1657	–	1120	96	74–75	44.08(44.31)	5.46(5.59)	12.74(12.95)
6b	Et	3420	1694	1655	–	1129	95	59–60	46.57(46.94)	6.00(6.13)	11.82(12.16)
6c	Pr	3410	1703	1654	–	1130	97	61–62	49.16(49.16)	6.52(6.60)	11.69(11.47)
6d	Bu	3418	1697	1654	–	1115	93	54–55	51.12(51.14)	7.15(7.02)	10.95(10.84)
6e	Pent	3432	1740	1684	–	1122	94	56–57	52.77(52.92)	7.33(7.40)	10.06(10.29)
6f	$C_{12}H_{25}$	3422	1734	1682	–	1120	91	72–73	61.30(61.59)	9.09(9.25)	8.00(7.56)
6g	C_6H_5	3398	1741	1668	–	1132	94	92–93	52.42(52.69)	4.32(4.42)	9.51(9.45)
7a	Me	3419	1714	1670	1042	1120	95	112–113	41.67(41.37)	4.91(5.21)	12.10(12.06)
7b	Et	3414	1710	1665	1046	1120	90	120–121	43.78(43.89)	5.65(5.73)	11.31(11.37)
7c	Pr	3430	1718	1672	1045	1131	94	108–109	46.26(46.14)	6.18(6.20)	10.44(10.76)
7d	Bu	3428	1709	1670	1052	1138	95	104–105	48.07(48.16)	6.56(6.61)	10.24(10.21)
7e	Pent	3440	1712	1682	1045	1132	89	96–97	50.03(49.98)	6.63(6.99)	9.52(9.71)
7f	$C_{12}H_{25}$	3418	1719	1670	1046	1132	88	91–92	58.88(59.04)	8.67(8.86)	7.14(7.25)
7g	C_6H_5	3428	1719	1669	1037	1138	83	83–84	49.59(49.99)	4.19(4.33)	8.78(8.97)
8a	Me	3430	1705	1655	1165 1321	1123	89	159–160	38.94(38.70)	4.86(4.88)	11.16(11.29)
8b	Et	3409	1732	1654	1178 1325	1125	90	101–102	41.10(41.21)	5.25(5.38)	10.36(10.68)
8c	Pr	3450	1724	1667	1160 1325	1125	94	83–84	43.61(43.47)	5.63(5.84)	10.01(10.14)
8d	Bu	3438	1711	1685	1169 1320	1125	91	74–75	45.89(45.54)	6.36(6.25)	9.70(9.66)
8e	Pent	3401	1735	1671	1162 1334	1131	85	130–131	47.02(47.35)	6.50(6.62)	9.16(9.20)
8f	$C_{12}H_{25}$	3455	1709	1680	1170 1325	1139	78	128–129	56.85(56.69)	8.47(8.51)	6.66(6.96)
8g	C_6H_5	3418	1712	1665	1182 1349	1136	86	134–135	50.48(50.56)	4.24(4.50)	9.06(8.99)

compound **7g** crystallized in the orthorhombic space group *Pca*2 with cell dimensions $a = 12.878(3)$ Å, $b = 15.379(3)$ Å, $c = 7.6570(15)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, 1516.5(5) Å^3, $Z = 4$, and $D_c = 1.447$ Mg/m^3. The structure was solved by the direct method and refined by the full-matrix least squares on F^2, and the final crystallographic discrepancy (see Tables 3 and 4). The structure of compound **7g** is shown in the Fig. 1.

In the crystal cell (Fig. 2), there are two kinds of intermolecular hydrogen bonds. One forms between the O atom of sulfinyl group and the hydrogen atom of the imino group at the 3-position of 5-fluorouracil, the other between the O atom of the carbonyl group at the 4-position of 5-fluorouracil and the hydrogen atom of H_2O molecule.

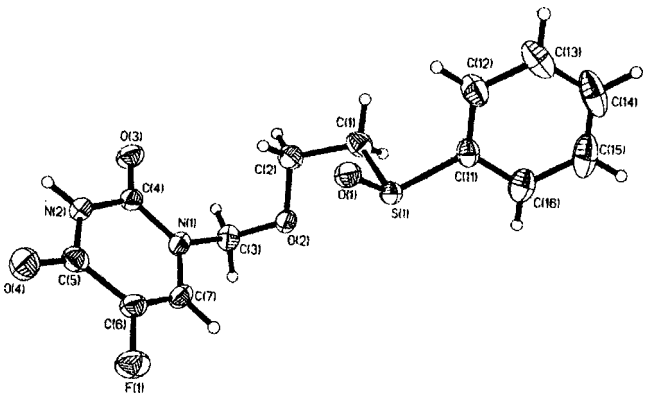


FIGURE 1 Molecular structure of compound **7g**.

Biological Assays

The preliminary biological activities were determined for the title compounds **6–8**. The anticancer activities given in Table 5 indicate that compound **6a** has potential inhibitory activities on P-388 (lymphocytic leukemia) and A-549 (human lung carcinoma) cell lines. Compound **7g** also has inhibiting activities on the A-549 cell lines.

EXPERIMENTAL

Elemental analyses were performed with a Chncorderd MT-3 elementary analyzer. NMR spectra were recorded with a Bruker AC-P200 spectrometer with TMS as the internal reference and $CDCl_3$ as the solvent. IR spectra were obtained on Shimadzu-435. Melting points were determined with a Thomas–Hoover melting point apparatus and are uncorrected. Column chromatography was performed on silica gel GF_{254} (Qing dao Hai yang Chemical Group Co. of China).

*2-(Chloromethoxy)ethyl Chloride (**4**)*

A suspension of 0.65 g (10 mmol) 2-chloroethanol and 0.70 g of paraformaldehyde in 18 mL of dry methylene chloride was cooled to 0°C. Dry hydrogen chloride was bubbled through the stirred suspension for 3 h until saturated. The mixture was allowed

TABLE 2 The ^{1}H NMR Data (δ) of Compound **6a–g**, **7a–g**, and **8a–g**

No	*^{1}H NMR (ppm)*
6a	2.09 (s, 3H, C$\underline{H}_3$S) 2.66 (t, 2H, $^3J_{HCCH}$ = 6.2 Hz, SC$\underline{H}_2$CH$_2$O) 3.73 (t, 2H, $^3J_{HCCH}$ = 6.2 Hz, SCH$_2$C$\underline{H}_2$O) 5.16 (s, 2H, OC$\underline{H}_2$O) 7.42 (d, 1H, $^3J_{HCCF}$ = 5.2 Hz, CF=C$\underline{H}$N) 9.90 (s, 1H, CON$\underline{H}$)
6b	1.22 (t, 3H, $^3J_{HCCH}$ = 7.4 Hz, C$\underline{H}_3$CH$_2$) 2.53 (q, 2H, $^3J_{HCCH}$ = 7.4 Hz, C$\underline{H}_2$S) 2.70 (t, 2H, $^3J_{HCCH}$ = 6.5 Hz, SC$\underline{H}_2$CH$_2$O) 3.72 (t, 2H, $^3J_{HCCH}$ = 6.5 Hz, SCH$_2$C$\underline{H}_2$O) 5.16 (s, 2H, OC$\underline{H}_2$O) 7.40 (d, 1H, $^3J_{HCCF}$ = 5.2 Hz, CF=C$\underline{H}$N) 9.45 (s, 1H, CON$\underline{H}$)
6c	0.95 (t, 3H, $^3J_{HCCH}$ = 7.3 Hz, C$\underline{H}_3$CH$_2$) 1.58 (m, 2H, CH$_3$C$\underline{H}_2$) 2.47 (t, 2H, $^3J_{HCCH}$ = 7.5 Hz, C$\underline{H}_2$S) 2.68 (t, 2H, $^3J_{HCCH}$ = 6.7 Hz, SC$\underline{H}_2$CH$_2$O) 3.71 (t, 2H, $^3J_{HCCH}$ = 6.7 Hz, SCH$_2$C$\underline{H}_2$O) 5.15 (s, 2H, OC$\underline{H}_2$O) 7.40 (d, 1H, $^3J_{HCCF}$ = 5.2 Hz, CF=C$\underline{H}$N) 9.45 (s, 1H, CON$\underline{H}$)
6d	0.89 (t, 3H, $^3J_{HCCH}$ = 6.9 Hz, C$\underline{H}_3$CH$_2$) 1.28–1.65 (m, 4H, 2×C$\underline{H}_2$) 2.52 (t, 2H, $^3J_{HCCH}$ = 7.3 Hz, C$\underline{H}_2$S) 2.69 (t, 2H, $^3J_{HCCH}$ = 6.0 Hz, SC$\underline{H}_2$CH$_2$O) 3.73 (t, 2H, $^3J_{HCCH}$ = 6.0 Hz, SCH$_2$C$\underline{H}_2$O) 5.16(s, 2H, OC$\underline{H}_2$O) 7.40 (d, 1H, $^3J_{HCCF}$ = 5.2 Hz, CF=C$\underline{H}$N) 9.31 (s, 1H, CON$\underline{H}$)
6e	0.86 (t, 3H, $^3J_{HCCH}$ = 6.9 Hz, C$\underline{H}_3$CH$_2$) 1.23–1.66 (m, 6H, 3×C$\underline{H}_2$) 2.50 (t, 2H, $^3J_{HCCH}$ = 7.4 Hz, C$\underline{H}_2$S) 2.68(t, 2H, $^3J_{HCCH}$ = 6.7 Hz, SC$\underline{H}_2$CH$_2$O) 3.71 (t, 2H, $^3J_{HCCH}$ = 6.7 Hz, SCH$_2$C$\underline{H}_2$O) 5.17 (s, 2H, OC$\underline{H}_2$O) 7.39 (d, 1H, $^3J_{HCCF}$ = 5.2 Hz, CF=C$\underline{H}$N) 9.28(s, 1H, CON$\underline{H}$)
6f	0.85 (t, 3H, $^3J_{HCCH}$ = 7.1 Hz, C$\underline{H}_3$CH$_2$) 1.19–1.62 (m, 20H, 10×C$\underline{H}_2$) 2.50 (t, 2H, $^3J_{HCCH}$ = 7.4 Hz, C$\underline{H}_2$S) 2.68 (t, 2H, $^3J_{HCCH}$ = 6.3 Hz, SC$\underline{H}_2$CH$_2$O) 3.69 (t, 2H, $^3J_{HCCH}$ = 6.3 Hz, SCH$_2$C$\underline{H}_2$O) 5.15 (s, 2H, OC$\underline{H}_2$O) 7.39 (d, 1H, $^3J_{HCCF}$ = 5.2 Hz, CF=C$\underline{H}$N) 9.18 (s, 1H, CON$\underline{H}$)
6g	3.09 (t, 2H, $^3J_{HCCH}$ = 6.2 Hz, SC$\underline{H}_2$CH$_2$O) 3.73 (t, 2H, $^3J_{HCCH}$ = 6.2 Hz, SCH$_2$C$\underline{H}_2$O) 5.10 (s, 2H, OC$\underline{H}_2$O) 7.05–7.34 (m, 6H, CF=C$\underline{H}$N + C$_6\underline{H}_5$) 9.30 (s, 1H, CON$\underline{H}$)
7a	2.64 (s, 3H, C$\underline{H}_3$SO) 2.92 (m, 2H, OSC$\underline{H}_2$CH$_2$O) 4.03 (m, 2H, OSCH$_2$C$\underline{H}_2$O) 5.15 (s, 2H, OC$\underline{H}_2$O) 7.37 (d, 1H, $^3J_{HCCH}$ = 5.2 Hz, CF=C$\underline{H}$N) 8.98 (s, 1H, CON$\underline{H}$)
7b	1.31 (t, 3H, $^3J_{HCCH}$ = 7.1 Hz, C$\underline{H}_3$CH$_2$) 2.76 (m, 2H, C$\underline{H}_2$SO) 2.88 (m, 2H, OSC$\underline{H}_2$CH$_2$O) 4.01 (m, 2H, OSCH$_2$C$\underline{H}_2$O) 5.19 (s, 2H, OC$\underline{H}_2$O) 7.38 (d, 1H, $^3J_{FCCH}$ = 5.2 Hz, CF=C$\underline{H}$N) 9.18 (s, 1H, CON$\underline{H}$)
7c	1.06 (t, 3H, $^3J_{HCCH}$ = 7.5 Hz, CH$_3$C$\underline{H}_2$) 1.74 (m, 2H, CH$_3$C$\underline{H}_2$) 2.75 (m, 2H, C$\underline{H}_2$SO) 2.89 (m, 2H, OSC$\underline{H}_2$CH$_2$O) 4.02 (m, 2H, OSCH$_2$C$\underline{H}_2$O) 5.16 (s, 2H, OC$\underline{H}_2$O) 7.39(d, 1H, $^3J_{FCCH}$ = 5.2 Hz CF=C$\underline{H}$N) 9.50 (s, 1H, CON$\underline{H}$)
7d	0.92 (t, 3H, $^3J_{HCCH}$ = 7.5 Hz, C$\underline{H}_3$CH$_2$) 1.30–1.81 (m, 4H, 2×C$\underline{H}_2$) 2.73 (m, 2H, C$\underline{H}_2$SO) 2.86 (m, 2H, OSC$\underline{H}_2$CH$_2$O) 4.01 (m, 2H, OSCH$_2$C$\underline{H}_2$O) 5.19 (s, 2H, OC$\underline{H}_2$O) 7.38 (d, 1H, $^3J_{FCCH}$ = 5.1 Hz, CF=C$\underline{H}$N) 9.36 (s, 1H, CON$\underline{H}$)
7e	0.87 (t, 3H, $^3J_{HCCH}$ = 6.9 Hz, C$\underline{H}_3$CH$_2$) 1.37–1.74 (m, 6H, 3×C$\underline{H}_2$) 2.76 (m, 2H, C$\underline{H}_2$SO) 2.88 (m, 2H, OSC$\underline{H}_2$CH$_2$O) 4.03 (m, 2H, OSCH$_2$C$\underline{H}_2$O) 5.19 (s, 2H, OC$\underline{H}_2$O) 7.38 (d, 1H, $^3J_{FCCH}$ = 5.1 Hz, CF=C$\underline{H}$N) 9.53 (s, 1H, CON$\underline{H}$)
7f	0.82 (t, 3H, $^3J_{HCCH}$ = 6.8 Hz, C$\underline{H}_3$CH$_2$) 1.24–1.78 (m, 20H, 10×CH$_2$) 2.70 (m, 2H, C$\underline{H}_2$SO) 2.89 (m, 2H, OSC$\underline{H}_2$CH$_2$O) 4.02 (m, 2H, OSCH$_2$C$\underline{H}_2$O) 5.19 (s, 2H, OC$\underline{H}_2$O) 7.38 (d, 1H, $^3J_{FCCH}$ = 5.2 Hz, CF=C$\underline{H}$N) 9.23 (s, 1H, CON$\underline{H}$)
7g	3.01 (m, 2H, $^3J_{HCCH}$ = 6.2 Hz, OSC$\underline{H}_2$CH$_2$O) 3.89 (m, 1H, OSCH$_2$C$\underline{H}$HO) 4.10 (m, 1H, OSCH$_2$C$\underline{H}$HO) 5.13 (s, 2H, OC$\underline{H}_2$O) 7.39 (d, 1H, $^3J_{FCCH}$ = 5.2 Hz, CF=C$\underline{H}$N) 7.48–7.60 (m, 5H, C$_6\underline{H}_5$) 9.80 (s, 1H, CON$\underline{H}$)
8a	2.95 (s, 3H, C$\underline{H}_3$SO$_2$) 3.31 (t, 2H, $^3J_{HCCH}$ = 5.5 Hz, O$_2$SC$\underline{H}_2$CH$_2$O) 3.89 (t, 2H, $^3J_{HCCH}$ = 5.5 Hz, O$_2$SCH$_2$C$\underline{H}_2$O) 5.15 (s, 2H, OC$\underline{H}_2$O) 7.39 (d, 1H, $^3J_{FCCH}$ = 5.1 Hz, CF=C$\underline{H}$N) 9.32 (s, 1H, CON$\underline{H}$)
8b	1.35 (t, 3H, $^3J_{HCCH}$ = 7.2 Hz, C$\underline{H}_3$CH$_2$) 3.01 (q, 2H, $^3J_{HCCH}$ = 7.2 Hz, C$\underline{H}_2$SO$_2$) 3.16 (t, 2H, $^3J_{HCCH}$ = 5.9 Hz, O$_2$SC$\underline{H}_2$CH$_2$O) 4.01 (t, 2H, $^3J_{HCCH}$ = 5.9 Hz, O$_2$SCH$_2$C$\underline{H}_2$O) 5.16 (s, 2H, OC$\underline{H}_2$O) 7.39 (d, 1H, $^3J_{FCCH}$ = 5.0 Hz, CF=C$\underline{H}$N) 9.34 (s, 1H, CON$\underline{H}$)
8c	1.04 (t, 3H, $^3J_{HCCH}$ = 7.8 Hz, C$\underline{H}_3$CH$_2$) 1.86 (m, 2H, CH$_3$C$\underline{H}_2$) 3.05 (t, 2H, $^3J_{HCCH}$ = 7.9 Hz, C$\underline{H}_2$SO$_2$) 3.28 (t, 2H, $^3J_{HCCH}$ = 5.9 Hz, O$_2$SC$\underline{H}_2$CH$_2$O) 4.03 (t, 2H, $^3J_{HCCH}$ = 5.9 Hz, O$_2$SCH$_2$C$\underline{H}_2$O) 5.16 (s, 2H, OC$\underline{H}_2$O) 7.39 (d, 1H, $^3J_{FCCH}$ = 5.2 Hz, CF=C$\underline{H}$N) 9.29 (s, 1H, CON$\underline{H}$)
8d	0.98 (t, 3H, $^3J_{HCCH}$ = 7.6 Hz, C$\underline{H}_3$CH$_2$) 1.39–1.91 (m, 4H, 2×C$\underline{H}_2$) 3.08 (t, 2H, $^3J_{HCCH}$ = 7.2 Hz, C$\underline{H}_2$SO$_2$) 3.22 (t, 2H, $^3J_{HCCH}$ = 6.8 Hz, O$_2$SC$\underline{H}_2$CH$_2$O) 4.05 ((t, 2H, $^3J_{HCCH}$ = 6.8 Hz, O$_2$SCH$_2$C$\underline{H}_2$O) 5.17 (s, 2H, OC$\underline{H}_2$O) 7.37 (d, 1H, $^3J_{FCCH}$ = 5.2 Hz, CF=C$\underline{H}$N) 9.18(s, 1H, CON$\underline{H}$)
8e	0.85 (t, 3H, $^3J_{HCCH}$ = 7.6 Hz, C$\underline{H}_3$CH$_2$) 1.40–1.88 (m, 6H, 3×CH$_2$) 3.02 (t, 2H, $^3J_{HCCH}$ = 7.4 Hz, C$\underline{H}_2$SO$_2$) 3.25 (t, 2H, $^3J_{HCCH}$ = 6.5 Hz, O$_2$SC$\underline{H}_2$CH$_2$O) 4.02 (t, 2H, $^3J_{HCCH}$ = 6.5 Hz, O$_2$SCH$_2$C$\underline{H}_2$O) 5.19 (s, 2H, OC$\underline{H}_2$O) 7.39 (d, 1H, $^3J_{FCCH}$ = 5.2 Hz, CF=C$\underline{H}$N) 9.25 (s, 1H, CON$\underline{H}$)
8f	0.80 (t, 3H, $^3J_{HCCH}$ = 7.2 Hz, C$\underline{H}_3$CH$_2$) 1.26–1.89 (m, 20H, 10×C$\underline{H}_2$) 3.05 (t, 2H, $^3J_{HCCH}$ = 7.4 Hz, C$\underline{H}_2$SO$_2$) 3.23 (t, 2H, $^3J_{HCCH}$ = 6.2 Hz, O$_2$SC$\underline{H}_2$CH$_2$O) 4.02 (t, 2H, $^3J_{HCCH}$ = 6.2 Hz, O$_2$SC$\underline{H}_2$CH$_2$O) 5.17 (s, 2H, OC$\underline{H}_2$O) 7.36 (d, 1H, $^3J_{FCCH}$ = 5.3 Hz, CF=C$\underline{H}$N) 9.39 (s, 1H, CON$\underline{H}$)
8g	3.42 (m, 2H, O$_2$SC$\underline{H}_2$CH$_2$O) 4.04 (m, 2H, O$_2$SCHC$\underline{H}_2$O) 5.19 (s, 2H, OC$\underline{H}_2$O) 7.36 (d, 1H, $^3J_{FCCH}$ = 5.3 Hz, CF=C$\underline{H}$N) 7.55–7.90 (m, 5H, C$_6\underline{H}_5$) 9.88 (s, 1H, CON$\underline{H}$)

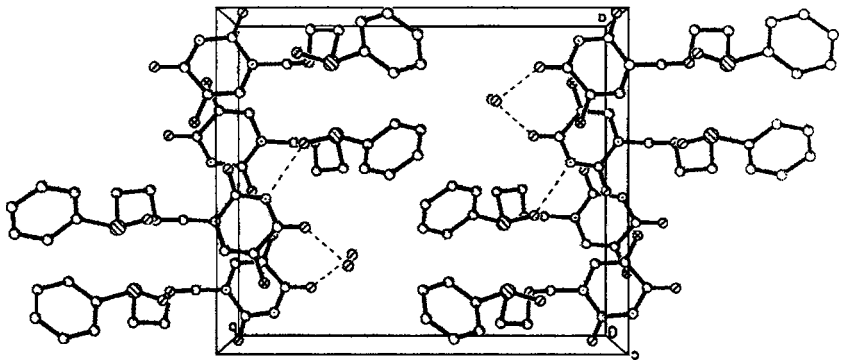


FIGURE 2 Molecular packing of compound **7g** in unit cell.

to stand in a refrigerator overnight and then dried over anhydrous $CaCl_2$. It was filtered and the solvent removed under reduced pressure to give an oily residue, which was used directly in the next step to prepare 1-(2′-chloroethoxy)methyl-5-fluorouracil (**5**).

*1-(2′-Chloroethoxy)methyl-5-fluorouracil (**5**)*

To a mixture of 5-fluorouracil (10 mmol, 1.30 g) and hexamethyldisilazane (4 mL) was added trimethylsilyl chloride (1 mL). The resultant suspension was refluxed for 3 h. The excess hexamethyldisilazane was removed from the reaction mixture in vacuo to give the crude silylation product of 5-fluorouracil as a solid, which was used in the next step without further purification.

A suspension of 0.2 g of anhydrous K_2CO_3 and 1.29 g (10 mmol) of $ClCH_2OCH_2CH_2Cl$ in 15 mL of dry CH_2Cl_2 was stirred at room temperature for 5 min under N_2 atmosphere. The crude silylation product of 5-fluorouacil was added into this system. The mixture was stirred overnight at room temperature. The resultant reaction mixture was adjusted to pH 7 with 0.1 M HCl and extracted with chloroform (3×60 mL). The organic extracts were combined and dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel flash chromatography to give **5** as a white solid (1.74 g, 78%); mp 103–104°C; ^{1}H MNR ($CDCl_3$, δ). 3.61 (t, 2H, $J = 5.6$ Hz) 3.86 (t, 2H, $J = 5.6$ Hz) 5.19 (s, 2H) 7.41 (d, 1H, $J = 5.2$ Hz) 9.76 (s, 1H).

*1-(2′-Alkyl(or phenyl)thioethoxy)methyl-5-fluorouracils (**6**)*

To a suspension of 0.312 g (6.5 mmol) of 50% NaH in THF (15 mL) was added dropwise 6 mmol of HSR (or PhSH) at 0°C. The reaction mixture was warmed to room temperature and stirred for 2 h, and then 0.67 g (3 mmol) of **5** was added to the reaction mixture and stirring was continued for 5 h. The resultant mixture was adjusted to pH 6–7 with 1 M HCl and extracted with $CHCl_3$ (3×50 mL). The organic layers were combined and dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was then purified by flash chromatography on silica gel ($CHCl_3$:CH_3OH = 20:1) to give **6**. The appropriate experimental data are listed in Tables 1 and 2.

When R=CH_3, chloride **5** was added to a solution of $NaSCH_3$ (5 mL), the mixture was stirred over 8 h, and then adjusted to pH 7. The reaction mixture was extracted with chloroform (3×50 mL). The organic phases were combined and dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was then purified by flash chromatography on silica gel ($CHCl_3$:CH_3OH = 20:1) to give **6a**. The appropriate experimental data are listed in Tables 1 and 2.

TABLE 3 Selected Bond Lengths (Å) of Compound **7g**

S(1)–O(1)	1.507(2)	O(4)–C(5)	1.216(4)	S(1)–C(11)	1.788(4)
F(1)–C(6)	1.351(4)	S(1)–C(1)	1.809(4)	C(1)–C(2)	1.508(5)
N(1)–C(7)	1.372(5)	C(5)–C(6)	1.434(5)	N(1)–C(4)	1.382(4)
C(6)–C(7)	1.325(5)	N(1)–C(3)	1.467(4)	C(11)–C(12)	1.376(6)
N(2)–C(4)	1.371(4)	C(11)–C(16)	1.383(5)	N(2)–C(5)	1.376(4)
C(12)–C(13)	1.377(6)	O(2)–C(3)	1.387(4)	C(13)–C(14)	1.360(7)
O(2)–C(2)	1.430(4)	C(14)–C(15)	1.369(8)	O(3)–C(4)	1.223(4)
C(15)–C(16)	1.402(7)				

TABLE 4 Selected Bond Angles (°) of Compound **7g**

O(1)–S(1)–C(11)	106.75(17)	O(4)–C(5)–C(6)	126.5(3)	O(1)–S(1)–C(1)	104.70(15)
N(2)–C(5)–C(6)	112.3(3)	C(11)–S(1)–C(1)	98.51(15)	C(7)–C(6)–F(1)	122.0(3)
C(7)–N(1)–C(4)	121.0(3)	C(7)–C(6)–C(5)	122.7(3)	C(7)–N(1)–C(3)	118.6(3)
F(1)–C(6)–C(5)	115.2(3)	C(4)–N(1)–C(3)	120.4(3)	C(6)–C(7)–N(1)	120.9(3)
C(4)–N(2)–C(5)	127.5(3)	C(12)–C(11)–C(16)	120.9(4)	C(3)–O(2)–C(2)	113.5(2)
C(12)–C(11)–S(1)	121.1(3)	C(2)–C(1)–S(1)	110.9(2)	C(16)–C(11)–S(1)	117.9(3)
O(2)–C(2)–C(1)	106.9(3)	C(11)–C(12)–C(13)	119.9(4)	O(2)–C(3)–N(1)	113.5(3)
C(14)–C(13)–C(12)	119.8(5)	O(3)–C(4)–N(2)	122.1(3)	C(13)–C(14)–C(15)	121.2(5)
O(3)–C(4)–N(1)	122.4(3)	C(14)–C(15)–C(16)	119.9(5)	N(2)–C(4)–N(1)	115.4(3)
C(11)–C(16)–C(15)	118.2(5)	O(4)–C(5)–N(2)	121.2(3)		

TABLE 5 Inhibitory Effects of Compounds **6–8** (10^{-5} M) on Cell Lines P-388 and A-549

Compounds	**6a**	**6b**	**6c**	**6d**	**6e**	**6f**	**6g**	**7a**	**7b**	**7c**	**7d**	**7e**	**7g**	**8a**	**8b**	**8c**	**8d**	**8e**	**8f**	**8g**
Inhibition rate (P-388) (%)	86	64	59	71	63	74	60	49	37	31	22	35	69	40	32	25	19	34	21	49
Inhibition rate (A-549) (%)	89	71	73	58	65	55	51	43	56	62	36	57	87	53	18	36	45	26	29	53

*1-(2′-Alkyl(or phenyl)sulfinylethoxy)methyl-5-fluorouracils (**7**)*

To a solution of compounds **6** (2 mmol) in 5 mL of ethanol was added dropwise (0.46 g, 2.1 mmol) of aqueous saturated $NaIO_4$ at room temperature, and the mixture was stirred overnight. The resultant mixture was poured into 10 mL of water and extracted with chloroform (3 × 30 mL). The organic layers were combined and dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was then purified by flash chromatography on silica gel ($CHCl_3$:CH_3OH = 15:1) to give **7**. The appropriate experimental data are listed in Tables 1 and 2.

*1-(2′-Alkyl(or phenyl)sulfonylethoxy)methyl-5-fluorouracils (**8**)*

0.5 mL of 30% H_2O_2 and 1.2 mmol of DEAD (diethyl azodicarboxylate) were added to a solution of 1 mmol of compounds **7** in THF (5 mL). The mixture was stirred at 50–55°C for 2 h. Additional DEAD was added, if necessary, to effect a complete reaction. The reaction mixture was continuously stirred at the same temperature for 1 h before pouring into H_2O (10 mL). The resultant mixture was extracted with chloroform (3 × 30 mL). The organic layers were combined and dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel ($CHCl_3$:CH_3OH = 10:1) to give **8**. The appropriate experimental data are listed in Tables 1 and 2.

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