Synthesis, Characterization, and Anticancer Effect of Trifluoromethylated Aurone Derivatives

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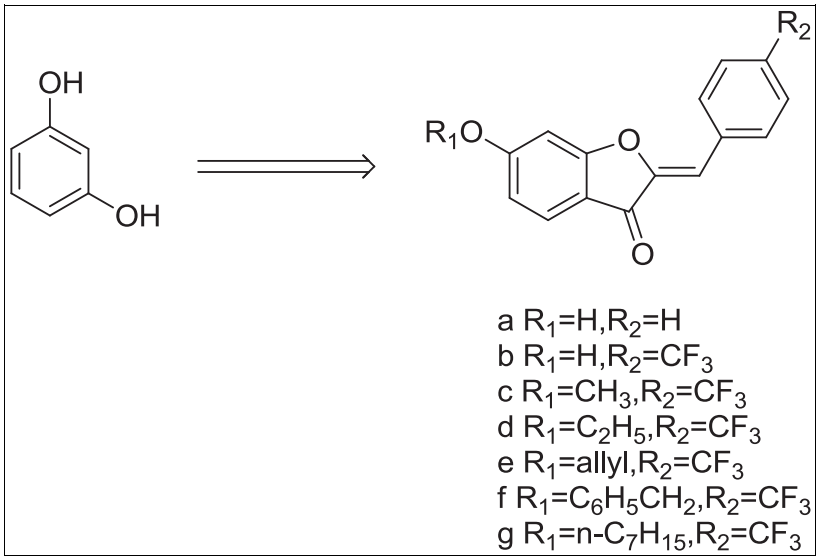

A series of trifluoromethylated aurone derivatives were synthesized, and the structure of 6-hydroxy-4-trifluoromethylated aurone was determined by single crystal X-ray analysis. Their anticancer activities against leucocythemia (HL-60) and colorectal adenocarcinoma (HT-29) were evaluated by the standard MTT method *in vitro* with 5-fluorouracil as a positive contrast drug. The results showed that all the (*Z*)-trifluoromethylated aurone derivatives had potential anticancer activities.

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INTRODUCTION

Acute leukemia is a neoplastic disease resulting from hyperplasia of myelohlast and other immature granulocyte. It can cause death rapidly without treatment [1]. Colorectal cancer is the third most common malignant tumors in Western countries [2], and it also has an increasing trend in China recently. Such diseases should be given due attention. Aurone is a heterocyclic chemical compound that has two isomers of the molecule, with (*E*)- and (*Z*)-configurations [3].

Most aurones are in the (*Z*)-configuration, which is the more stable configuration according to Austin Model 1 computation, but there are some in the (*E*)-configuration such as (*E*)-3′-O-β-D-glucopyranosyl-4,5,6,4′-tetrahydroxy-7,2′-dimethoxyaurone, found in *Gomphrena agrestis* [4]. The molecule contains a benzofuran element associated with a benzylidene linked in position 2. In aurone, a chalcone-like group is closed into a 5-membered ring instead of the 6-membered ring more typical of flavonoids [5]. Recently, aurones have received much attention because of their interesting biological activities, and these natural products and their synthetic analogues have proved to be promising bioactive compounds with a broad spectrum of activities including anticancer [6,7] and antioxidant [8,9] properties while they possess enzyme inhibitory [10,11] or enzyme inducing activity [12]. The aurone derivatives also have been used in the treatment of thyroid disease [13]. However, most of the anticancer activities were low. It is known that fluorine is the most electronegative element, and the van der Waals radius of fluorine is close to that of hydrogen. The introduction of the CF_3 group into organic molecules often changes their physiological, physical, and chemical properties dramatically, without the introduction of extra steric demand. Many efforts were made to introduce the trifluoromethyl group into different types of organic molecules for improving their stability and lipophilicity [14]. To our best knowledge, the introduction of fluorine moiety into the aryl part of the flavonoid molecule can enhance their biological activities including antibacterial activity, antifungal activity, and antiviral activity [15]. Earlier studies of B-ring

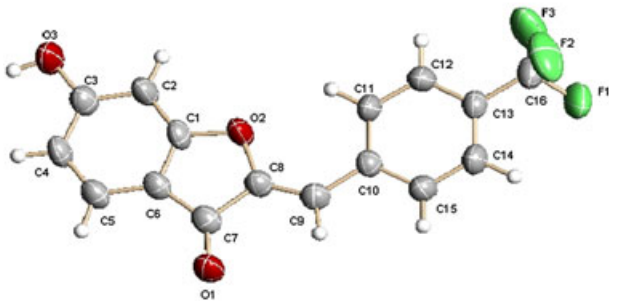


Figure 1. X-ray crystal Structure of compound **5**.

trifluoromethylated aurones in our laboratory showed some activities against SGC-7901 tumor cell [16]. In order to search for anticancer substances with high efficacy, low toxicity, and minimum side effects, we describe a series of aurone's synthesis and evaluate their anticancer activities against HL-60 and HT-29 cells, then confirm the configuration of trifluoromethylated aurone **5** by X-ray.

RESULTS AND DISCUSSION

Single crystal X-ray analysis of compound 5. The procedure as described in the experimental can smoothly convert resorcinol to compound **5**. To confirm its configuration, a yellow prismatic crystal of **5** with dimensions $0.314 \times 0.268 \times 0.087$ mm was mounted on a glass fiber with grease. Diffraction experiments were performed on graphite-monochromator diffractometer using the Φ–ω scan technique. The X-ray crystal structure of compound **5** is shown in Figure 1. It proves that compound **5** is in the (*Z*)-configuration. The packing diagram of compound **5** in a unit cell is shown in Figure 2. Refined cell dimensions and their standard deviations were obtained from Full-matrix least-squares on F^2. Empirical absorption

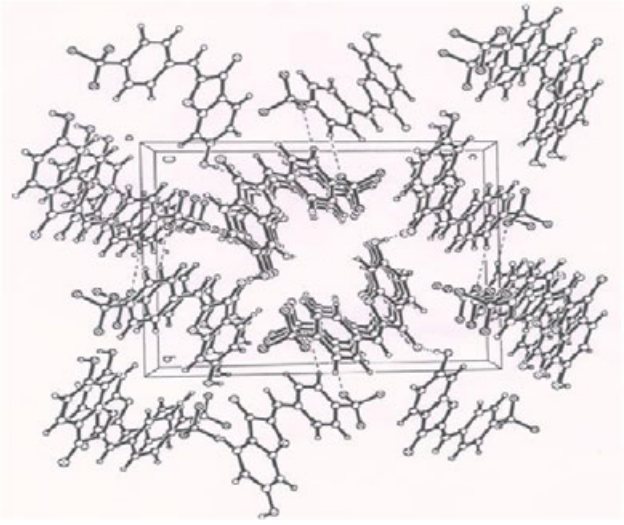


Figure 2. Unit-cell packing diagram of compound **5**.

Table 1

Crystal date and structure refinement for compounds **5**.

Identification code	Compounds **5**
Empirical formula	$C_{16}H_9F_3O_3$
Formula weight	306.23
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P2(1)/*n*
Unit cell dimensions	$a = 7.1950(11)$ Å $\alpha = 90°$ $b = 12.780(2)$ Å $\beta = 100.096(4)°$ $c = 15.066(3)$ Å $\gamma = 90°$
Volume	1363.9(4) Å^3
Z, calculated density	4, 1.491 Mg/m^3
Absorption coefficient	0.130 mm^{-1}
F(000)	624
Crystal size	$0.314 \times 0.268 \times 0.087$ mm
Theta range for data collection	2.10 to 28.26°
Limiting indices	$-9 \le h \le 8$, $-16 \le k \le 16$, $-15 \le l \le 20$
Reflections collected/unique	8181/3155 [R(int) = 0.0779]
Completeness to theta = 28.26	93.2%
Absorption correction	Sadabs
Max and min transmission	1.00000 and 0.64376
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3155/0/245
Goodness-of-fit on F^{-2}	0.745
Final R indices [$I > 2$sigma (I)]	$R_1 = 0.0466$, $wR_2 = 0.0723$
R indices (all data)	$R_1 = 0.1252$, $wR_2 = 0.0862$
Extinction coefficient	0.0059(6)
Largest diff. peak and hole	0.210 and -0.205 e·Å^{-3}

Table 2

Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters (Å$^2 \times 10^3$) of compound **5** (U(eq) is defined as one-third of the trace of the orthogonalized U_{ij} tensor).

	x	*y*	*z*	*U*(eq)
O(1)	647(2)	8935(1)	7599(1)	61(1)
O(2)	1764(2)	6889(1)	6229(1)	55(1)
O(3)	−2892(3)	4330(1)	6490(1)	78(1)
C(1)	206(3)	6503(2)	6549(2)	48(1)
C(2)	−541(3)	5536(2)	6336(2)	57(1)
C(3)	−2117(3)	5274(2)	6702(2)	54(1)
C(4)	−2857(3)	5963(2)	7273(2)	52(1)
C(5)	−2053(3)	6916(2)	7479(2)	51(1)
C(6)	−472(3)	7199(2)	7110(1)	44(1)
C(7)	704(3)	8112(2)	7175(2)	48(1)
C(8)	2107(3)	7881(2)	6593(1)	47(1)
C(9)	3476(3)	8503(2)	6423(2)	48(1)
C(10)	4873(3)	8353(2)	5845(1)	43(1)
C(11)	4942(3)	7473(2)	5311(2)	51(1)
C(12)	6290(3)	7385(2)	4771(2)	53(1)
C(13)	7569(3)	8172(2)	4754(2)	45(1)
C(14)	7534(3)	9049(2)	5274(2)	56(1)
C(15)	6191(3)	9137(2)	5813(2)	53(1)
C(16)	8993(4)	8085(2)	4145(2)	62(1)
F(1)	10654(2)	8508(1)	4481(1)	88(1)
F(2)	8444(2)	8604(2)	3377(1)	114(1)
F(3)	9434(15)	7087(9)	3989(7)	122(4)
F(3′)	9110(30)	7249(15)	3759(12)	86(5)

Table 3

Selected bond lengths (Å) of compound **5**.

Bond	Bond lengths	Bond	Bond lengths
O(1)—C(7)	1.235(2)	C(8)—C(9)	1.324(3)
O(2)—C(8)	1.387(2)	C(9)—C(10)	1.454(3)
O(2)—C(1)	1.387(2)	C(10)—C(15)	1.386(3)
O(3)—C(3)	1.344(3)	C(10)—C(11)	1.388(3)
O(3)—H(9)	0.88(2)	C(11)—C(12)	1.375(3)
C(1)—C(2)	1.363(3)	C(12)—C(13)	1.380(3)
C(1)—C(6)	1.375(3)	C(13)—C(14)	1.373(3)
C(2)—C(3)	1.386(3)	C(14)—C(15)	1.01(2)
C(3)—C(4)	1.400(3)	C(16)—F(3)	1.227(15)
C(4)—C(5)	1.361(3)	C(16)—F(2)	1.329(3)
C(5)—C(6)	1.398(3)	C(16)—F(1)	1.332(3)
C(6)—C(7)	1.435(3)	C(16)—F(3′)	1.345(11)
C(7)—C(8)	1.497(3)		

Table 4

Selected bond angles (°) of compound **5**.

Bond angles	Bond angles value	Bond angles	Bond angles value
C(8)—O(2)—C(1)	106.68(16)	C(15)—C(10)—C(11)	118.1(2)
C(2)—C(1)—C(6)	124.3(2)	C(15)—C(10)—C(9)	118.3(2)
C(2)—C(1)—O(2)	123.4(2)	C(11)—C(10)—C(9)	123.5(2)
C(6)—C(1)—O(2)	112.3(2)	C(12)—C(11)—C(10)	120.6(2)
C(1)—C(2)—C(3)	116.2(2)	C(11)—C(12)—C(13)	120.3(2)
O(3)—C(3)—C(2)	117.2(2)	C(14)—C(13)—C(12)	119.6(2)
O(3)—C(3)—C(4)	121.6(2)	C(14)—C(13)—C(16)	120.6(2)
C(2)—C(3)—C(4)	121.2(2)	C(12)—C(13)—C(16)	119.8(2)
C(5)—C(4)—C(3)	120.7(2)	C(15)—C(14)—C(13)	120.1(2)
C(4)—C(5)—C(6)	118.9(2)	C(14)—C(15)—C(10)	121.3(2)
C(1)—C(6)—C(5)	118.5(2)	F(3′)—C(16)—F(1)	113.6(9)
C(1)—C(6)—C(7)	107.45(19)	F(3′)—C(16)—F(2)	93.2(11)
C(5)—C(6)—C(7)	134.0(2)	F(1)—C(16)—F(2)	103.8(2)
O(1)—C(7)—C(6)	130.9(2)	F(3′)—C(16)—F(3)	18.7
O(1)—C(7)—C(8)	124.4(2)	F(1)—C(16)—F(3)	103.2(5)
C(6)—C(7)—C(8)	104.7(2)	F(2)—C(16)—F(3)	111.3(5)
C(9)—C(8)—O(2)	124.0(2)	F(3′)—C(16)—C(13)	118.1(8)
C(9)—C(8)—C(7)	127.0(2)	F(1)—C(16)—C(13)	113.4(2)
O(2)—C(8)—C(7)	108.95(19)	F(2)—C(16)—C(13)	111.8(2)
C(8)—C(9)—C(10)	130.7(2)	F(3)—C(16)—C(13)	112.7(5)

Symmetry transformations used to generate equivalent atoms.

corrections were applied on the basis of Sadabs, which resulted in transmission factors ranging from 0.64376 to 1.00000. The important crystal data: $C_{16}H_9F_3O_3$, $M_r = 306.23$, monoclinic, space group P2(1)/*n*, $a = 7.1950(11)$ Å, $b = 12.782(2)$ Å, $c = 15.066(3)$ Å, $\beta = 100.096(4)°$, $V = 1363.9(4)$ Å^3, $Z = 4$, $D_c = 1.491$ Mg/m^3, $F(000) = 624$, absorption coefficient 0.130 mm^{-1}. The detailed crystal data and structure refinement are shown in Table 1. Atomic coordinates and equivalent isotropic displacement parameter *U*(eq) are shown in Table 2. Bond lengths and angles are shown in Tables 3 and 4, respectively. Anisotropic displacement parameters are shown in Table 5. Hydrogen coordinates and isotropic displacement parameters are shown in Table 6. Torsion angles are shown in Table 7. It was observed that the whole molecule was planar with the torsion angle: C(7)—C(8)—C(9)—C(10) torsion angle is −178.1(2)°; C(8)—C(9)—C(10)—C(11) torsion angle is 2.7(4)°; and O(2)—C(1)—C(6)—C(5) torsion angle is 179.55(18)°.

Anticancer activity. All the trifluoromethylated aurone derivatives were tested for their anticancer activities *in vitro* against HL-60 and HT-29 by MTT-based assay. The assays were performed in 96-well plates essentially as described by Mosmann [17]. The results in Table 8 showed that all the trifluoromethylated aurone derivatives had potential anticancer activities. Although general structure–activity relationship of those trifluoromethylated aurone derivatives was not elucidated from these data, the

Table 5

Anisotropic displacement parameters (A$^2 \times 10^3$) of compound **5** (the anisotropic displacement factor exponent takes the form: $-2\pi^2[h^{-2}a^{*2}U_{11} + \cdots + 2hka^*b^*U_{12}]$.

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	64(1)	50(1)	76(1)	−11(1)	29(1)	1(1)
O(2)	62(1)	48(1)	66(1)	−6(1)	37(1)	−5(1)
O(3)	89(2)	55(1)	105(2)	−12(1)	57(1)	−23(1)
C(1)	50(2)	48(2)	52(2)	8(1)	26(1)	0(1)
C(2)	67(2)	47(2)	67(2)	−6(1)	38(2)	−5(1)
C(3)	62(2)	44(2)	62(2)	4(1)	26(1)	−2(1)
C(4)	52(2)	52(2)	61(2)	8(1)	31(1)	1(1)
C(5)	54(2)	47(2)	57(2)	4(1)	25(1)	9(1)
C(6)	45(1)	42(1)	49(2)	5(1)	17(1)	8(1)
C(7)	50(2)	47(2)	49(2)	4(1)	14(1)	8(1)
C(8)	53(2)	39(2)	53(2)	−1(1)	19(1)	1(1)
C(9)	50(2)	41(2)	53(2)	−3(1)	12(1)	2(1)
C(10)	44(1)	44(2)	43(1)	2(1)	12(1)	−1(1)
C(11)	51(2)	50(2)	57(2)	−7(1)	22(1)	−15(1)
C(12)	56(2)	53(2)	54(2)	−13(1)	19(1)	−9(1)
C(13)	41(1)	50(2)	47(2)	2(1)	11(1)	−6(1)
C(14)	54(2)	54(2)	63(2)	0(1)	22(1)	−15(1)
C(15)	57(2)	46(2)	57(2)	−8(1)	18(1)	−8(1)
C(16)	52(2)	79(2)	58(2)	0(2)	13(2)	−16(1)
F(1)	48(1)	129(2)	90(1)	−25(1)	21(1)	−26(1)
F(2)	83(1)	194(2)	72(1)	34(1)	32(1)	−3(1)
F(3)	119(5)	84(4)	189(9)	−14(4)	102(5)	11(3)
F(3′)	89(7)	102(11)	82(5)	−56(7)	56(5)	−51(8)

Table 6

Hydrogen coordinates ($\times 10^4$) and parameters ($A^2 \times 10^3$) of compound **5**.

	x	*y*	*z*	*U*(eq)
H(1)	−40(30)	5071(15)	5949(13)	52(7)
H(2)	−3940(20)	5753(13)	7500(11)	42(6)
H(3)	−2500(30)	7433(15)	7873(14)	64(7)
H(4)	3490(20)	9154(13)	6725(11)	34(6)
H(5)	3980(30)	6944(16)	5297(13)	61(7)
H(6)	6340(20)	6762(14)	4419(12)	45(6)
H(7)	8470(30)	9621(18)	5225(14)	90(8)
H(8)	6150(30)	9738(14)	6169(12)	48(6)
H(9)	−3780(30)	4238(19)	6814(17)	98(10)

Table 7

Torsion angles (°) of compound **5**.

C(8)═O(2)─C(1)─C(2)	−179.6(2)
C(8)═O(2)═C(1)═C(6)	−0.4(2)
C(6)═C(1)═C(2)═C(3)	1.8(4)
O(2)═C(1)═C(2)═C(3)	−179.1(2)
C(1)═C(2)═C(3)═O(3)	179.2(2)
C(1)═C(2)═C(3)═C(4)	−1.4(4)
O(3)═C(3)═C(4)═C(5)	−180.0(2)
C(2)═C(3)═C(4)═C(5)	0.5(4)
C(3)═C(4)═C(5)═C(6)	0.1(4)
C(2)═C(1)═C(6)═C(5)	−1.3(4)
O(2)═C(1)═C(6)═C(5)	179.55(18)
C(2)═C(1)═C(6) – C(7)	179.1(2)
O(2)═C(1)═C(6)═C(7)	−0.1(3)
O(4)═C(5)═C(6)═C(1)	0.3(3)
C(4)═C(5)═C(6)═C(7)	179.8(2)
C(1)═C(6)═C(7)═O(1)	−179.9(2)
C(5)═C(6)═C(7)═O(1)	0.6(4)
C(1)═C(6)═C(7)═C(8)	0.5(2)
C(5)═C(6)═C(7)═C(8)	−179.0(2)
C(1)═O(2)═C(8)═C(9)	−178.7(2)
C(1)═O(2)═C(8)═C(7)	0.7(2)
O(1)═C(7)═C(8)═C(9)	−1.0(4)
C(6)═C(7)═C(8)═C(9)	178.7(2)
O(1)═C(7)═C(8)═O(2)	179.6(2)
C(6)═C(7)═C(8)═O(2)	−0.8(2)
O(2)═C(8)═C(9)═C(10)	1.3(4)
C(7)═C(8)═C(9)═C(10)	−178.1(2)
C(8)═C(9)═C(10)═C(15)	−178.3(2)
C(8)═C(9)═C(10)═C(11)	2.7(4)
C(15)═C(10)═C(11)═C(12)	0.3(3)
C(9)═C(10)═C(11)═C(12)	179.3(2)
C(10)═C(11)═C(12)═C(13)	0.1(4)
C(11)═C(12)═C(13)═C(14)	−0.5(4)
C(11)═C(12)═C(13)═C(16)	−177.7(2)
C(12)═C(13)═C(14)═C(15)	0.6(4)
C(16)═C(13)═C(14)═C(15)	177.8(2)
C(13)═C(14)═C(15)═C(10)	−0.2(4)
C(11)═C(10)═C(15)═C(14)	−0.3(3)
C(9)═C(10)═C(15)═C(14)	−179.3(2)
C(14)═C(13)═C(16)═F(3′)	173.2(12)
C(12)═C(13)═C(16)═F(3′)	−9.7(12)
C(14)═C(13)═C(16)═F(1)	36.6(4)
C(12)═C(13)═C(16)═F(1)	−146.2(2)
C(14)═C(13)═C(16)═F(2)	−80.4(3)
C(12)═C(13)═C(16)═F(2)	96.8(3)
C(14)═C(13)═C(16)═F(3)	153.3(5)
C(12)═C(13)═C(16)═F(3)	−29.5(6)

Table 8

The anticancer activities of the target compounds **5** and **6a–e** *in vitro*.

Compound	HL-60 (IC_{50} μmol/L)	HT-29(IC_{50} μmol/L)
4	3.74	9.12
5	1.54	8.90
6a	2.59	5.90
6b	1.65	9.12
6c	3.53	4.12
6d	3.46	4.12
6e	2.67	4.32
5-Fluorouracil	12.92	9.56

The given values are the average values of three experiments.

following points are noteworthy: (1) All the trifluoromethylated aurone derivatives (compounds **5** and **6a–e**) showed stronger cytotoxicity toward HL-60 cell than 6-hudroxy-aurone **4**. (2) Except compound **6b**, all the trifluoromethylated aurone derivatives showed better inhibitory activities toward HT-29 cell than 6-hudroxy-aurone **4**. (3) All the trifluoromethylated aurone derivatives showed better inhibitory activities toward HT-29 and HT-29 cell than 5-fluorouracil.

CONCLUSIONS

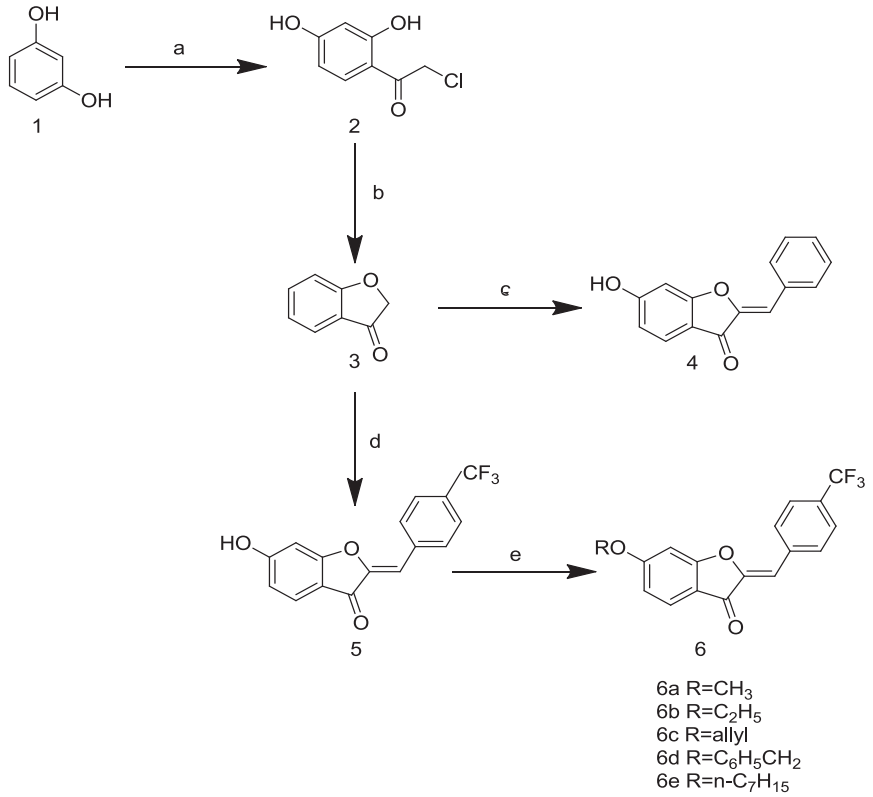
A series of trifluoromethylated aurone derivatives were synthesized, and the structure of 6-hydroxy-4-trifluoromethylated aurone was in the (*Z*)-configuration determined by single crystal X-ray analysis. All the (*Z*)-trifluoromethylated aurone derivatives had potential anticancer activities against leucocythemia (HL-60) and colorectal adenocarcinoma (HT-29).

EXPERIMENTAL

General. Analytical TLC was carried out with silica gel (HSGF 254). Melting points were determined with an X-5 digital micromelting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Bruker Avance 30 (Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences) (300 MHz) spectrometer, using $CDCl_3$ or CD_3COCD_3 as solvent and TMS internal standard. ^{19}F-NMR spectra were obtained on Bruker AM-300 (282 MHz). IR spectra were measured as KBr plates with a Shimadzu IR-440 infrared spectrometer. Elemental analyses were performed by Italian Carlo-Erba 1106. Reagents and solvents used were commercially available analytical grade materials used as supplied, without further purification.

General procedure for the synthesis of 6-hydroxy-4′-trifluoromethylated aurone 5 and some alkylated derivatives of 5. The synthetic route started from resorcinol. Condensation of resorcinol with chloroacetonitrile catalyzed by $ZnCl_2$ and followed by hydrolysis with HCl gas provided ketone **2** [18]. Treatment of **2** with sodium methoxide in MeOH gave benzofuranone **3**. Condensation of **3** with α,α,α-trifluoro-*p*-tolualdehyde in the presence of excess NaOH in H_2O/EtOH and followed by acidification with aqueous HCl gave the expected compound **5** (Scheme 1). The alkylation of **5** was

Scheme 1. Conditional and reagent: (a) $ClCH_2CN$, HCl(g); (b) NaOMe; (c) C_6H_5CHO/NaOH, NaOMe; (d) α,α,α-trifluoro-*p*-tolualdehyde/NaOH, HCl; (e) RX/K_2CO_3.



carried out with alkyl halides in the presence of K_2CO_3 in acetone to afford compounds **6a-e** (Scheme 1). In order to confirm the structure of these compounds, our research group bred the single crystal of compound **5** in acetone successfully.

The same procedure as described above can smoothly convert resorcinol to 6-hydroxy-aurone **4** via intermediates **2** and **3** (Scheme 1).

6-Hydroxy-4′-trifluoromethylated aurone (5). Yield 45%. m.p. 166–167°C. IR υ_{max} (cm^{-1}, KBr): 1416, 1458, 1500, 1530, 1580, 1614, 1643, 1683, 1778 (C═O), 2899, 2965, 3072; ^{1}H-NMR (300 MHz, CD_3COCD_3): δ 6.781 (s, 1H), 6.822 (dd, 1H, *J* = 2.1, 7.8 Hz), 6. 864 (d, 1H, *J* = 2.1 Hz), 7.656 (d, 2H, *J* = 8.4 Hz), 7.821 (d, 1H, *J* = 7.8 Hz), 8.174 (d, 2H, *J* = 8.4 Hz), 10.118 (s, 1H); ms (EI, 70 eV) *m/z*: 305 (100.00), 63 (89.26), 92 (86.98), 237 (81.48), 306 (M^+, 51.14), 108 (49.43), 69 (40.98), 159 (39.83); ^{19}F-NMR (282 MHz): –70.772. *Anal*. Calcd for $C_{16}H_9F_3O_3$: C, 62.75; H, 2.96. Found: C, 62.69; H, 2.97.

6-Methoxy-4′-trifluoromethylated aurone (6a). Yield 62.3%. m.p. 227–230°C. IR υ_{max} (cm^{-1}, KBr): 1416, 1446, 1501, 1593, 1609, 1659, 1702 (C═O), 2959; ^{1}H-NMR (300 MHz, $CDCl_3$): 3.974 (s, 3H), 6.798 (s, 1H), 6.818 (dd, 1H, *J* = 2.1, 7.8 Hz), 7.710 (d, 1H, *J* = 2.1 Hz), 7.715 (d, 2H, *J* = 8.4 Hz), 7.747 (d, 1H, *J* = 7.8 Hz), 8.004 (d, 2H, *J* = 8.4 Hz); ms (EI, 70 eV) *m/z*: 319 (100.00), 320 (M^+, 60.41), 251 (24.18), 57 (22.11), 43 (15.95), 63 (12.95), 321 (11.35), 69 (11.34); ^{19}F-NMR (282 MHz): –70.493. *Anal*. Calcd for $C_{17}H_{11}F_3O_3$: C, 63.75; H, 3.46. Found: C, 63.53, H, 3.51.

6-Methoxy-4′-trifluoromethylated aurone (6b). Yield 66.4%. m.p. 149–151°C. IR υ_{max} (cm^{-1}, KBr): 1415, 1447, 1475, 1498, 1589, 1613, 1657, 1700 (C═O), 2980; ^{1}H-NMR (300 MHz, $CDCl_3$): 1.499 (t, 3H, *J* = 6.9 Hz), 4.175 (q, 2H, *J* = 6.9 Hz), 6.760 (dd, 1H, *J* = 2.1, 7.8 Hz), 6.784 (d, 1H, *J* = 2.1 Hz), 6.799 (s, 1H), 7.690 (d, 2H, *J* = 8.4 Hz), 7.715 (d, 1H, *J* = 7.8 Hz), 7.990 (d, 2H, *J* = 8.4 Hz); ms (EI, 70 eV) *m/z*: 333 (100.00), 334 (M^+, 92.51), 305 (77.39), 237 (20.55), 265 (19.59), 335 (17.93), 306 (15.58), 63 (7.45); ^{19}F-NMR (282 MHz): –73.059. *Anal*. Calcd for $C_{18}H_{13}F_3O_3$: C, 64.67; H, 3.92. Found: C, 65.45; H, 4.22.

6-Ethoxy-4′-trifluoromethylated aurone (6c). Yield 82.2%. m.p. 122–124°C. IR υ_{max} (cm^{-1}, KBr): 1417, 1448, 1494, 1602, 1617, 1660, 1707 (C═O); ^{1}H-NMR (300 MHz, $CDCl_3$): 4.664–4.691 (m, 2H), 5.369–5.515 (m, 2H), 6.033–6.126 (m, 1H), 6.787 (s, 1H), 6.814 (d, 1H, *J* = 2.1 Hz), 7.671 (d, 2H, *J* = 7.8 Hz), 7.675 (d, 1H, *J* = 7.5 Hz), 7.719 (dd, 1H, *J* = 2.1, 7.5 Hz), 7.978 (d, 2H, *J* = 7.8 Hz); ms (EI, 70 eV) *m/z*: 346 (M^+, 100.00), 345 (83.84), 41 (26.47), 347 (21.66), 305 (18.62), 236 (18.19), 327 (12.72), 277 (12.24); ^{19}F-NMR (282 MHz): –56.761. *Anal*. Calcd for $C_{19}H_{13}F_3O_3$: C, 65.89; H, 3.78. Found: C, 65.76; H, 3.99.

6-Benzyloxy-4′-trifluoromethylated aurone (6d). Yield 89.6%. m.p. 148–149°C. IR υ_{max} (cm^{-1}, KBr): 1417, 1446, 1471, 1496, 1593, 1610, 1656, 1699 (C═O); ^{1}H-NMR (300 MHz, $CDCl_3$): 5.221 (s, 2H), 6.815 (s, 1H), 6.880 (dd, 1H, *J* = 2.1, 9.0 Hz), 7.425–7.470 (m, 5H), 7.456 (d, 1H, *J* = 2.1 Hz), 7.703 (d, 2H, *J* = 7.8 Hz), 7.747 (d, 1H, *J* = 9.0 Hz), 7.996 (d, 2H, *J* = 7.8 Hz); ms (EI, 70 eV) *m/z*: 91 (100.00), 396 (M^+, 24.75), 92 (8.76), 65 (7.15), 236 (6.75), 397 (6.26), 63 (6.25), 377 (4.25); ^{19}F-NMR (282 MHz): –74.146. *Anal*. Calcd for $C_{23}H_{15}F_3O_3$: C, 69.70; H, 3.81. Found: C, 69.76; H, 3.91.

6-Heptyloxy-4′-trifluoromethylated aurone (6e). Yield 82.2%. m.p. 112–113°C. IR υ_{max} (cm^{-1}, KBr): 1414, 1447, 1476, 1497, 1592, 1612, 1656, 1699 (C═O), 2926, 2957; ^{1}H-NMR (300 MHz, $CDCl_3$): 0.887 (t, 3H, J = 6.9 Hz), 0.925–1.873 (m, 10H), 4.079 (t, 2H, J = 6.9 Hz), 6.756 (dd, 1H, J = 2.1, 9.0 Hz), 6.773 (d, 1H, J = 2.1 Hz), 6.777 (s, 1H), 7.677 (d, 2H, J = 7.8 Hz), 7.696 (d, 1H, J = 9.0 Hz), 7.972 (d, 2H, J = 7.8 Hz); ms (EI, 70 eV) *m/z*: 305 (100.00), 404 (M^+, 72.77), 306 (45.08), 237 (29.49), 403 (22.04), 405 (18.99), 57 (16.12), 307 (9.87); ^{19}F-NMR (282 MHz): –67.871. *Anal*. Calcd for $C_{23}H_{15}F_3O_3$: C, 69.70; H, 3.81. Found: C, 69.76; H, 3.91.

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