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Bioorganic & Medicinal Chemistry Letters
ELSEVIER
Bioorganic & Medicinal Chemistry Letters 14 (2004) 621–622

Synthesis and antitumor activity of 10-substituted benzylidene anthrone

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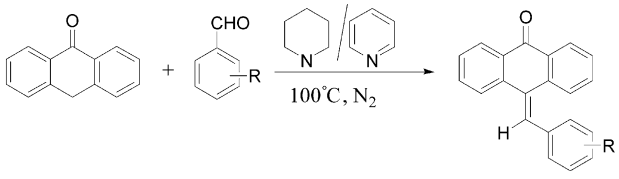
Received 24 July 2003; revised 18 November 2003; accepted 19 November 2003

Abstract—Fifteen compounds of 10-substituted benzylidene anthrone were prepared with moderate yield by reaction of anthrone and substituted benzaldehydes under the presence of pyridine and piperidine as catalyst. Their antitumor activities in vitro were evaluated. The results show that the electron-withdrawing substitutes decrease the activities, the electron-donor substitutes increase the activities; the compound with substitute at *ortho* or *para* position has stronger activities than that of compound with the same substitute but located at the *meta* position. There are six compounds which appear as strong effective inhibition for A-549 cancer cell growth. This is a kind of good leading compound which is worth researching further.

It was well known that many compounds containing anthraquinone skeleton have good bioactivities. Some of them are good antitumor medicines, such as, daunorubicin,[1] doxorubicin,[2] mitoxantrone,[3] bisantrene[4] and so on. It was reported that the derivatives of anthrone, 10-substituted benzylidene anthrone[5] and the Schiff base of anthrone with substituted anilines[6] also have good antitumor activities.

We are interested in how the substitutes in 10-substituted benzylidene anthrone affect the antitumor activities. Therefore, we designed fifteen 10-substituted benzylidene anthrones, in which the substitutes include electron-withdraw group and electron-donor and the same substitute but located at the *ortho*/*para* or *meta* position. These compounds were synthesized according to the literature method,[7–9] The synthetic reaction is shown in Scheme 1, the results are summarised in Table 1.

It was found that under literature reaction condition, the anthrone can be oxidated to anthraquinone even at room temperature. The ratio of conversion reached as high as 55%. With the addition of p-methoxy phenol as antioxidant, the reaction between anthrone and substituted benzaldehyde might proceed normally.[15]



Scheme 1.

Table 1. Synthesis of 10-substituted benzylidene anthrone

Entry	R	Mp(°C)[lit.]	Isolated yield (%)	Purity (HPLC)
1	H	118–119[117–118][10]	35.5	98.4
2	m-NO_2	171–173[170–172][11]	45.0	99.4
3*	p-F	105–108	23.3	99.6
4	o-OH	220–221[223–225][12]	81.6	99.3
5	p-OH	235–236[245–248][12]	35.6	99.7
6*	o-CH_3	90–93	14.0	99.2
7	m-CH_3	110–111[112–114][11]	40.5	99.6
8	P-CH_3	147–150[147–149][7]	74.3	99.4
9	o-OCH_3	149–152[146–147][7]	51.5	99.4
10*	m-OCH_3	113–115	75.3	99.1
11	P-OCH_3	142–145[142][13]	51.3	99.8
12	o-Cl	110–113[115][14]	69.5	99.1
13*	m-Cl	113–115	63.2	99.9
14	P-Cl	158–160–162[14]	31.6	99.1
15	3,4-diOCH_3	180–183[180–182][11]	68.7	97.4

*New compound; the structures of all compounds were characterized by IR/MS and HNMR, besides, the elemental analysis was also made for four new compounds.

Keywords: 10-Substituted benzylidene anthrone; Antitumor activity; Relationship between structures and activities.
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doi:10.1016/j.bmcl.2003.11.053

The antitumor activities of those compounds were evaluated in vitro using MTT method for P-388 cancer cell and SRB method for A-549 cancer cell. The results are shown in Tables 2 and 3, respectively.

It is clear from the data of Tables 2 and 3 that the compounds with electron-donor substitute such as CH_3, CH_3O, OH have more strong activities than that of those compounds with electron-withdrawing substitute such as Cl, F, NO_2. The compound without any substitute has no antitumor activity. It is also clear that the compounds with the electron-donor substitute at *ortho* or *para* position have stronger activities than that of compounds with the same substitutes but at *meta* position.

To the A-549 cancer cell, there are six compounds with electron-donor substitute at *ortho* or *para* which have strong bioactivity. To the P-388 cancer cell, there are two compounds having strong activity and three compounds having weak activity. All five compounds have electron-donor substitute at *ortho* or *para* position. So this kind of compound is a potential antitumor medicine which is worth to research further.

Table 2. The inhibition ratio for A-549 growth

Compd	R	Concentration (mol/L)					Remark*
		10^{-4}	10^{-5}	10^{-6}	10^{-7}	10^{-8}	
1	H	95.4	79.9	9.8	1.0	4.4	n
2	m-NO_2	96.0	91.8	12.4	7.7	13.2	w
3	p-F	96.8	88.2	56.5	18.5	49.2	w
4	o-OH	96.3	94.8	89.3	83.0	85.2	s
5	p-OH	92.9	87.0	87.2	88.7	60.0	s
6	o-CH_3	90.9	84.8	18.5	0	5.7	n
7	m-CH_3	93.0	18.2	0	0	0	n
8	p-CH_3	95.2	91.8	90.0	92.7	84.7	s
9	o-OCH_3	89.3	81.7	85.7	86.8	66.3	s
10	m-OCH_3	95.8	92.5	25.1	38.1	6.2	w
11	p-OCH_3	90.0	84.7	87.0	85.4	84.8	s
12	o-Cl	89.9	53.0	0.3	6.0	5.9	n
13	m-Cl	97.1	92.0	62.9	5.7	12.5	w
14	p-Cl	96.0	87.3	41.9	33.6	41.7	w
15	3,4-diOCH_3	95.7	92.8	87.0	90.6	81.7	s

* n: 10^{-5}mol/L < 85%; w: 10^{-5} mol/L ≥ 85% or 10^{-6} mol/L > 50%; s: 10^{-6}mol/L ≥ 85% or 10^{-7} mol/L > 50%.

Table 3. The inhibition ratio for P-388 growth

Compd	R	Concentration (mol/L)					Remark*
		10^{-4}	10^{-5}	10^{-6}	10^{-7}	10^{-8}	
1	H	97.8	56.2	17.8	0	2.7	n
2	m-NO_2	89.8	55.8	23.9	22.1	30.7	n
3	p-F	83.3	31.4	18.4	10.3	5.2	n
4	o-OH	95.6	88.2	65.8	44.9	38.5	w
5	p-OH	100	72.0	41.6	27.1	42.8	n
6	o-CH_3	84.1	42.4	24.9	8.0	13.1	n
7	m-CH_3	53.3	7.2	0	0	0	n
8	p-CH_3	69.0	42.4	48.6	49.3	56.5	w
9	o-OCH_3	82.2	76.1	55.4	47.0	32.7	w
10	m-OCH_3	96.0	48.2	27.2	7.1	1.0	n
11	p-OCH_3	76.7	72.5	76.5	64.3	75.5	s
12	o-Cl	58.4	23.7	0	0	0	n
13	m-Cl	89.2	39.4	11.9	19.3	10.9	n
14	p-Cl	70.0	36.0	3.9	2.8	4.4	n
15	3,4-diOCH_3	95.7	80.2	56.0	53.6	50.9	s

Acknowledgements

The authors are thankful for the National Center for Drug screening, Shanghai, China to evaluate the antitumor activities. We also thank the National Natural Science Foundation of China for founding (project 20272053).

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15. Representative procedure: To a mixture of anthrone (3.9 g, 0.02 mol), 4-methoxy phenol(2.0 g, 0.016 mol) and 3-methoxy benzaldehyde (3.4 g, 0.025 mol) were added pyridine (30 mL) and piperidine (0.5 g, 0.006 mol). The air of the system was removed by aspirator, then put in the nitrogen gas, the operation was repeated three times. Then let the nitrogen gas bubble through the mixture all the time until the reaction finished. The reaction mixture was refluxed for 6 h. The anthrone was reacted completely by TLC test. The mixture was cooled down to room temperature and poured into methanol (75 mL). It was put in the refrigerator overnight. The precipitate was collected and recrystallized with ethanol to afford yellow crystal 4.7g, yield: 75.3%, mp: 113–115 °C, purity: 99.1% (HPLC). IR (KBr, cm^{-1}): 3061 (ArH), 3000 (=C–H), 2936 (–CH_3), 2832 (–CH_3), 1652 (C=O, s), 1600 (C=C, s), 1576, 1491, 1474, 1424, 1374, 1316, 1279, 1160, 1048, 932, 882, 782, 763, 684. ^{1}HNMR (400 MHz, $CDCl_3$): 3.71 (s, 3H, -OCH_3), 7.56 (s, 1H, =C–H), 6.83–8.30 (m, 12H, ArH). MS (*m*/*z*, %): 312 (M^+, 100), 311 (70), 297 (29), 281 (42), 268 (34), 252 (30), 239 (52), 120 (38). Elem. anal. ($C_{22}H_{16}O_2$) C, H: calcd (%), 84.59, 5.16, found (%), 84.32, 5.15.