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Synthesis and anti-tumor activity of novel ethyl 3-aryl-4-oxo-3,3*a*,4,6-tetrahydro-1*H*-furo[3,4-*c*]pyran-3*a*-carboxylates

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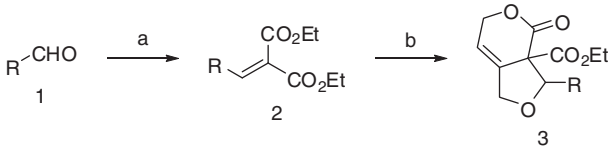
ABSTRACT

A series of ethyl 3-aryl-4-oxo-3,3*a*,4,6-tetrahydro-1*H*-furo[3,4-*c*]pyran-3*a*-carboxylates were prepared through the metal-catalyzed domino reaction of alkylidene malonates and 1,4-butynediol under a one-pot reaction condition at room temperature. Their in vitro anti-proliferative activities were subsequently evaluated in A549, QGY and HeLa cells. The majority of the compounds showed potent anti-tumor activity against HeLa cells. In particular, compound **3l** was the most potent compound with IC_{50} value of 5.4 μM. For the first time, the X-ray structure of the anti-tumor ethyl 3-aryl-4-oxo-3,3*a*,4,6-tetrahydro-1*H*-furo[3,4-*c*]pyran-3*a*-carboxylates is determined.

Cancer is the second leading cause of death worldwide and accounted for 7.6 million deaths in 2008 (WHO Fact sheet No. 297, February 2011). Consequently, various categories of anticancer drugs have been developed, such as: paclitaxe,[1] doxorubicin[2] and vinblastine[3] that have been used clinically for the treatment of breast, lung, stomach, prostate, colon, or pancreatic tumor or other solid tumors. However, undesirable side effects and extensive multi-drug resistance in cancer cells has been a major obstacle to successful cancer chemotherapy.[4] Hence, there is a pressing need for developing novel compounds that are able to overcome these obstacles while maintaining anti-cancer potency by preventing cancer cell proliferation.

Recently, domino reactions have been of great interest because of their capacity to generate molecular diversity within a minimum number of steps.[5] Among these reactions, metal-catalyzed [3+2] cycloaddition reaction is a particularly efficient approach, especially in the synthesis of five- and six-membered heterocycles.[6] We are interested in applying alkylidene malonates to the synthesis of oxygen-containing heterocycles, and part of our research is focused on the reaction between 1,4-butynediol and alkylidene malonates. Herein we report an efficient and straightforward method for the syntheses of ethyl 3-aryl-4-oxo-3,3*a*,4,6-tetrahydro-1*H*-furo[3,4-*c*]pyran-3*a*-carboxylate through the reaction of 1,4-butynediol with alkylidene malonates under Cu-catalyzed domino reaction condition. The in vitro anti-proliferative activities in various cancer cell lines were also evaluated.



Scheme 1. Reagents and conditions: (a) $CH_2(CO_2C_2H_5)_2$/piperidine/HOAc, toluene, reflux, 10–16 h, 70–82%; (b) 1,4-butynediol/NaH/CuI, THF, rt, 43–80%.

The ethyl 3-aryl-4-oxo-3,3*a*,4,6-tetrahydro-1*H*-furo[3,4-*c*]pyran-3*a*-carboxylates were synthesized according to Scheme 1 with 43–80% yield. With piperidine and glacial acetic acid as catalyst, the reaction of appropriate aryl formaldehydes **1** with diethyl malonate under refluxing condition afforded alkylidene malonates[7] **2**. Compound **2** (1 equiv) was reacted with 1,4-butynediol (1.5 equiv) in the presence of NaH (0.6 equiv) and CuI (0.1 equiv) at room temperature in THF, within 6 h, product **3** was obtained with 43–80% yield.[8] With an electron-withdrawing group or an electron-donating group on the aryl ring or heteroaromatic substitution being applied, the reaction could be performed smoothly. Nevertheless, an electron-withdrawing group on the aryl ring was slightly more favored than an electron-donating group. Furthermore, it should be noted that *para*-substituents help to form ethyl 3-aryl-4-oxo-3,3*a*,4,6-tetrahydro-1*H*-furo[3,4-*c*]pyran-3*a*-carboxylate, especially

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Table 1
Synthesis of ethyl 3-aryl-4-oxo-3,3*a*,4,6-tetrahydro-1*H*-furo[3,4-*c*]pyran-3*a*-carboxylates[a]

Entry	3	Substrate R	NaH (equiv)	Temp (°C)	Time (h)	Yield[b] (%)
1	**3a**	Ph	0.6	20	6	62
2	**3b**	2-F-Ph	0.6	20	6	64
3	**3c**	4-F-Ph	0.6	20	6	72
4	**3d**	3-Cl-Ph	0.6	20	3	43
5	**3e**	4-Cl-Ph	0.6	20	6	77
6	**3f**	3,4-Cl_2-Ph	0.6	20	3	47
7	**3g**	4-Br-Ph	0.6	20	6	59
8	**3h**	4-*t*-Bu-Ph	0.6	20	6	51
9	**3i**	4-OCH_3-Ph	0.6	25	6	70
10	**3j**	3,4-$(OCH_3)_2$-Ph	0.6	25	6	56
11	**3k**	3,5-$(OCH_3)_2$-Ph	0.6	25	6	53
12	**3l**	3,4,5-$(OCH_3)_3$-Ph	0.6	30	6	52
13	**3m**	4-$N(CH_3)_2$-Ph	0.6	25	6	49
14	**3n**	4-NO_2-Ph	0.6	20	6	80
15	**3o**	2-Furanyl	0.6	20	6	66
16	**3p**	2-Thienyl	0.6	20	6	54
17	**3q**	2-Pyridyl	0.6	20	3	57

[a] Unless otherwise specified, the reaction was carried on 20.0 mmol scale in 50 mL of solvent.
[b] Isolated yield.

when the *para*-substituent was NO_2 or Cl. By that means, the reaction could easily produce pure compound **3** with high yield (Table 1, entries 5 and 14).

All the synthesized compounds were structurally characterized by ^{1}H NMR, ^{13}C NMR and mass spectral analysis.[9,10] For the first time, the X-ray crystallographic structure of ethyl 3-(3,5-dimethoxyphenyl)-4-oxo-3,3*a*,4,6-tetrahydro-1*H*-furo[3,4-*c*]pyran-3*a*-carboxylates (**3k**), a representative compound of the series of ethyl 3-aryl-4-oxo-3,3*a*,4,6-tetrahydro-1*H*-furo[3,4-*c*]pyran-3*a*-carboxylates with anti-tumor activity, is determined. The ORTEP III view of the molecule ethyl 3-(3,5-dimethoxyphenyl)-4-oxo-3,3*a*,4,6-tetrahydro-1*H*-furo[3,4-*c*]pyran-3*a*-carboxylate (**3k**) is shown in Figure 1 (CCDC 756985). It is worth noticing that although there are two chiral centers in the molecule of compound **3k**, only a pair of enantiomers was observed in X-ray single crystal. The C7 is a tertiary carbon which configuration was determined by the configuration of C3 during the formation of the rings. While the 3,3*a*-dihydro-1*H*-furo[3,4-*c*]pyran-4(6*H*)-one ring almost lies in one plane, the 3,5-dimethoxyphenyl and the ethyl carboxylate groups that link to C3 and C7, respectively, adopt an extended conformation.

The anti-tumor activities of ethyl 3-aryl-4-oxo-3,3*a*,4,6-tetrahydro-1*H*-furo[3,4-*c*]pyran-3*a*-carboxylates were subsequently evaluated in three human tumor cell lines: A549 (lung carcinoma), QGY (hepatoma) and HeLa (cervical carcinoma). All the compounds were assessed with quintuplicate dose-response assays indicated by certain growth parameters (colorimetric MTT assay) for their in vitro cytotoxic activities against the three human tumor cell lines. Dose–response curves were created by plotting cytotoxic effect against the $\log_{10}$ of the drug concentration for each cell line. Cytotoxic effects of each compound were determined by IC_{50} values, which represent the molar of drug concentration required to cause 50% growth inhibition. The biological screening results of ethyl 3-aryl-4-oxo-3,3*a*,4,6-tetrahydro-1*H*-furo[3,4-*c*]pyran-3*a*-carboxylate with 5-fluorouracil as a control for their anti-proliferative activities are summarized in Table 2.

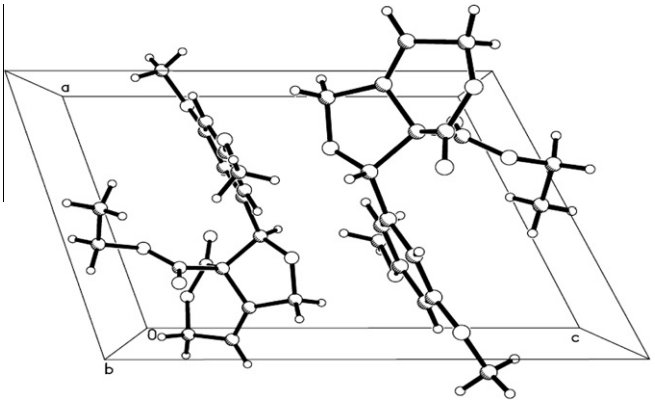

Figure 1. X-ray crystal structures of compound **3k** (CCDC 756985).

As shown in Table 2, the majority of newly synthesized compounds exhibited compound-specific potency against the HeLa cells. All these compounds possess a common ethyl 4-oxo-3,3*a*,4,6-tetrahydro-1*H*-furo[3,4-*c*]pyran-3*a*-carboxylate nucleus in which substitution at C-3 positions plays important roles in determining potency of ethyl 3-aryl-4-oxo-3,3*a*,4,6-tetrahydro-1*H*-furo[3,4-*c*]pyran-3*a*-carboxylates. Introduction of electron-donating moieties aryl ring (**3i**–**3l**) at C-3 position enhanced the anti-proliferative activity, and furthermore, multi-electron-donating substitution of aromatic ring at C-3 position displays higher anti-proliferative activity than single-electron-donating substitution of aryl ring at C-3 position. For instance, 3,4,5-trimethoxyphenyl substitution (**3l**) at C-3 position showed the best anti-proliferative activity (IC_{50} = 5.4 μM), that is much more effective than 4-methoxy-phenyl substitution at C-3 position. The compound (**3l**) also showed moderate anti-tumor activity against A549 cells (13.3 μM). However, introduction of an electron-withdrawing or a larger group substitution aromatic ring at C-3 position slightly decreased the activity. For instance, the compounds of 4-nitrophenyl (**3n**) and 4-*tert*-butyl-phenyl (**3h**) substitution at C-3 position only exhibited moderate activities, with IC_{50} of 53.4 and 23.4 μM, respectively. Furthermore, introduction of halo atom at C-3 aryl ring is detrimental to the activity (**3d**–**3g**), whereas replacement of 4-chlorophenyl (**3e**) or 4-bromophenyl (**3g**) group at C-3 position with 4-fluorophenyl yielded a compound (**3c**) with significant improved anti-tumor activity against HeLa cells. In addition, heteroaryl substitutions of **3o**–**3q** at C-3 position retained in vitro anti-tumor activity against HeLa cells. Lastly, all the ethyl

Table 2
Cytotoxic activities of ethyl 3-aryl-4-oxo-3,3*a*,4,6-tetrahydro-1*H*-furo[3,4-*c*]pyran-3*a*-carboxylates[a] (IC_{50}, μM)[b]

No.	Compound	HeLa	A549	QGY
1	**3a**	12.8	>10^3	>10^3
2	**3b**	22.1	>10^3	>10^3
3	**3c**	22.9	>10^3	>10^3
4	**3d**	>10^3	28.4	>10^3
5	**3e**	117.5	>10^3	>10^3
6	**3f**	72.4	>10^3	>10^3
7	**3g**	48.7	>10^3	>10^3
8	**3h**	25.4	>10^3	>10^3
9	**3i**	18.3	9.3	>10^3
10	**3j**	10.0	>10^3	>10^3
11	**3k**	16.0	>10^3	>10^3
12	**3l**	5.4	13.3	>10^3
13	**3m**	23.4	89.6	>10^3
14	**3n**	53.4	36.8	>10^3
15	**3o**	28.3	>10^3	>10^3
16	**3p**	30.4	>10^3	>10^3
17	**3q**	20.7	>10^3	>10^3
18	**5-FU**	16.1	5.6	14.1

[a] The cytotoxicity (as IC_{50} for each cell line) is the concentration of compound that reduced the optical density of treated cells by 50% with respect to untreated cells using the MTT assay.
[b] Data represent the mean values of three independent determinations.

3-aryl-4-oxo-3,3*a*,4,6-tetrahydro-1*H*-furo[3,4-*c*]pyran-3*a*-carboxylates didn't show anti-proliferative activity in QGY cells. Nevertheless, some of these compounds (**3d**, **3i**, **3l**, **3m** and **3n**) demonstrated moderate anti-proliferative activities in inhibiting A549 cell growth with IC_{50} at a micromolar range between 9.3 and 89.6 μM. Among these compounds, **3i** (IC_{50} = 9.3 μM) was the most potent one with anti-proliferative activity equivalent to the control drug 5-FU in A549 cells.

In conclusion, we have developed a simple one-pot synthesis of novel ethyl 3-aryl-4-oxo-3,3a,4,6-tetrahydro-1*H*-furo[3,4-*c*]pyran-3*a*-carboxylates and evaluated their anticancer activities in three human cancer cell lines. Most of the compounds showed potent anti-proliferative activities in HeLa cells. While a few of them showed moderate anti-proliferative activities in A549 cells. In particular, the compounds **3l** and **3i** were found to be the most potent compounds in HeLa and A549 cells, with IC_{50} values of 5.4 and 9.3 μM, respectively. Our ongoing experiments are being carried out to identify their cellular targets and to improve the potency and the selectivity of this series of compounds.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.04.003.

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9. *General experimental procedure for synthesis of ethyl 3-aryl-4-oxo-3,3a,4,6-tetrahydro-1H-furo[3,4-c]pyran-3a-carboxylates*: NaH (60% in mineral oil, 12 mmol) was added to a solution of but-2-yne-1,4-diol (30 mmol) in THF (50 mL) under nitrogen, and the solution was stirred for 5 min at room temperature. alkylidene malonate (**2**, 20 mmol) and CuI (2 mmol) were then added successively. When plenty of target compound were observed by TLC, the reaction mixture was quenched by dropwise addition of a 20% solution of HCl, immediately cooled to room temperature. The mixture was further diluted and extracted twice with CH_2Cl_2, and the organics washed successively with saturated solution of brine, and water. The organic extracts were dried over $MgSO_4$, filtered, concentrated, and the residue purified by flash column chromatography to afford compound **3**.
10. Selected data for compounds **3a**–**q**: Compound **3a**: White solid; mp: 59.7–60.4 °C. IR: 3462, 3068, 3033, 2977, 2931, 2862, 1728, 1495, 1458, 1386, 1313, 1232, 1185, 1088, 1056, 1022, 985, 958, 921, 862, 806, 754, 700 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.69–7.72 (m, 1H), 7.27–7.37 (m, 1H), 6.06–6.08 (m, 1H), 5.48 (s, 1H), 4.95 (d, *J* = 13.8 Hz, 1 H), 4.83–4.86 (m, 2H), 4.62 (d, *J* = 13.8 Hz, 1H), 3.73 (q, *J* = 6.9 Hz, 2H), 0.81 (t, *J* = 6.9 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.42, 164.77, 141.64, 136.24, 127.98, 127.67, 126.77, 115.61, 83.91, 68.64, 67.52, 64.17, 62.06, 53.36, 13.28 ppm. ESIMS: *m*/*s* (%):311.81 $[M+Na]^+$. Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.53; H, 5.65. Compound **3c**: white solid; mp: 107.3–107.9 °C. IR: 3466, 3114, 3076, 3021, 2984, 2936, 2914, 2878, 2858, 2030, 1915, 1752, 1724, 1604, 1508, 1459, 1447, 1413, 1382, 1367, 1346, 1301, 1233, 1186, 1158, 1102, 1070, 1056, 1015, 982, 965, 922, 868, 854, 835, 819, 803, 786, 739, 712 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.68–7.73 (m, 2H), 7.00–7.05 (m, 2H), 6.05–6.08 (m, 1H), 5.42 (s, 1H), 4.96 (d, *J* = 13.8 Hz, 1 H), 4.83–4.85 (m, 2H), 4.63 (d, *J* = 13.8 Hz, 1 H), 3.80 (q, *J* = 7.2 Hz, 2H), 0.87 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.45, 164.75, 164.20, 160.93, 141.61, 132.01, 128.75, 128.74, 115.75, 114.74, 83.44, 68.68, 67.63, 64.09, 62.25, 13.46 ppm. ESIMS: *m*/*s* (%): 329.76 $[M+Na]^+$. Anal. Calcd for $C_{16}H_{15}FO_5$: C, 62.74; H, 4.94. Found: C, 62.57; H, 4.77. Compound **3i**: white solid, mp: 95.4–95.9 °C. IR: 3462, 3435, 3074, 3007, 2986, 2964, 2937, 2917, 2860, 2840, 2360, 2045, 1940, 1908, 1723, 1610, 1583, 1511, 1452, 1421, 1386, 1358, 1303, 1246, 1175, 1112, 1083, 1032, 983, 967, 921, 852, 837, 816, 797, 775, 74 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.61(d, *J* = 9.0 Hz, 2H), 6.86(d, *J* = 9.0 Hz, 2H), 6.02–6.06 (m, 1H), 5.40(s, 1H), 4.95 (d, *J* = 11.7 Hz, 1 H), 4.81–4.84 (m, 2H), 4.61(d, *J* = 11.7 Hz, 1 H), 3.78–3.85 (m, 5H), 0.9(t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 77 MHz): δ 167.51, 164.94, 159.45, 141.98, 128.18, 115.55, 113.16, 83.93, 68.59, 67.56, 64.17, 62.16, 55.15, 13.51 ppm. ESIMS: *m*/*s* (%): 351.7 $[M+Na]^+$. Anal. Calcd for $C_{17}H_{18}O_6$: C, 64.14; H, 5.70. Found: C, 54.33; H, 5.67. Compound **3l**. white solid; mp: 124.4–124.8 °C. IR: 3432, 3078, 2998, 2961, 2936, 2870, 2838, 1751, 1722, 1592, 1508, 1463, 1421, 1385, 1359, 1328, 1235, 1215, 1188, 1127, 1081, 1062, 1006, 989, 964, 913, 849, 832, 804, 785, 716 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.00 (s, 2H), 6.07 (m, 1H), 5.40 (s, 1H), 4.99 (d, *J* = 13.8 Hz, 1H), 4.83–4.85 (m, 2H), 4.65 (d, *J* = 13.8 Hz, 1H), 3.80–3.87 (m, 11H), 0.88 (t, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.60, 164.87, 153.73, 141.96, 137.58, 131.83, 115.69, 103.95, 83.91, 68.76, 67.61, 64.32, 62.25, 60.75, 56.10, 13.56 ppm. ESIMS: *m*/*s* (%): 379.45 $[M+H]^+$. Anal. Calcd for $C_{19}H_{22}O_8$: C, 60.31; H, 5.86. Found: C, 60.41; H, 5.89%. Compound **3q**: red oil, IR: 3442, 3087, 3057, 2974, 2928, 2862, 1728, 1458, 1386, 1369, 1323, 1184, 1058, 1025, 984, 958, 921, 857, 806, 763, 713 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.62(s, 1H), 7.69–7.80 (m, 2H), 7.30 (s, 1H), 6.05 (d, *J* = 2.7 Hz, 1H), 5.45 (s, 1H), 4.92 (d, *J* = 10.5 Hz, 1H), 4.74–4.82 (m, 2H), 4.63 (d, *J* = 15.0 Hz, 1H), 3.82 (q, *J* = 7.2 Hz, 2H), 0.81 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.86, 164.41, 154.90, 147.12, 139.65, 138.17, 122.82, 116.17, 83.39, 69.16, 67.78, 62.81, 62.25, 13.28 ppm. ESIMS: *m*/*s* (%): 312.17 $[M+Na]^+$. Anal. Calcd for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.42; H, 5.37; N, 4.77.