

## · 论 文 ·

培氟沙星 C-3 羧基等排体的合成及抗肿瘤活性(Ⅷ).  
均三唑硫醚酮缩氨基硫脲衍生物谢玉锁<sup>1</sup>, 高留州<sup>1</sup>, 闫 强<sup>1</sup>, 吴书敏<sup>1</sup>, 倪礼礼<sup>1</sup>, 黄文龙<sup>2</sup>, 赵 辉<sup>1\*</sup>, 胡国强<sup>1\*\*</sup>(<sup>1</sup>河南大学化学生物学研究所, 开封 475001; <sup>2</sup>中国药科大学新药研究中心, 南京 210009)

**摘要** 以均三唑杂环作为培氟沙星 C-3 羧基的等排体, 功能侧链-硫醚酮缩氨基硫脲为其修饰基, 设计合成了 12 个 C-3 均三唑硫醚酮缩氨基硫脲目标化合物 (**6a~6l**), 其结构经元素分析和光谱数据确证, 评价了它们体外对 SMMC-7721、L1210 和 HL60 3 种肿瘤细胞株的抗增殖活性。初步药理学实验结果表明: 目标化合物的抗肿瘤活性显著高于母体化合物 **1** 和相应中间体硫醚酮 (**5a~5l**), 尤其是苯环含羟基和氟原子的目标化合物  $IC_{50}$  已达到微摩尔水平, 与阳性对照药阿霉素的效力相当。这提示被功能基侧链修饰的唑杂环替代 C-3 羧基有利于提高其抗肿瘤活性。

**关键词** 培氟沙星; 均三唑; 硫醚酮; 缩氨基硫脲; 抗肿瘤活性**中图分类号** R914   **文献标志码** A   **文章编号** 1000-5048(2015)04-0416-05

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**Synthesis and antitumor activities of fluoroquinolone C-3 isosteres (VIII): s-triazole sulfide-one thiosemicarbazone derivatives from pefloxacin**XIE Yusuo<sup>1</sup>, GAO Liuzhou<sup>1</sup>, YAN Qiang<sup>1</sup>, WU Shumin<sup>1</sup>, NI Lili<sup>1</sup>, HUANG Wenlong<sup>2</sup>, ZHAO Hui<sup>1\*</sup>, HU Guoqiang<sup>1\*\*</sup><sup>1</sup>*Institute of Chemical Biology, Henan University, Kaifeng 475001;*<sup>2</sup>*Center of Drug Discovery, China Pharmaceutical University, Nanjing 210009, China*

**Abstract** To improve the antitumor activity of fluoroquinolones for a promising development of druggability, twelve novel fluoroquinolone C-3 s-triazole sulfide-one thiosemicarbazone derivatives (**6a~6l**) were designed and synthesized with a functionalized sulfide-one thiosemicarbazone as a modified side-chain for the C-3 bioisosteric s-triazole ring of pefloxacin (**1**). The structures were characterized by elemental analysis and spectral data. The *in vitro* antitumor activity of novel compounds against SMMC-7721, L1210 and HL60 cell lines was evaluated. The preliminary pharmacological results demonstrated that the title compounds exhibited more significantly antiproliferative activity than either the parent **1** or the corresponding sulfide-one intermediates (**5a~5l**). In particular, compounds bearing a hydroxyl group or a fluorine atom attached to benzene ring were comparable to the control doxorubicin with an  $IC_{50}$  value of micro-molar concentration, respectively. It suggests that an azole ring modified with functional side-chain instead of the C-3 carboxylic group is favorable to the improvement of antitumor activity.

**Key words** pefloxacin; s-triazole; sulfide-one; thiosemicarbazone; antitumor activity

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新药的创新起源于先导化合物的发现,而基于药效团的拼合和药物骨架的跃迁是构建先导物化学结构的有效策略<sup>[1]</sup>。同时对先导物的结构优化是促成其向成药性方向发展的重要环节<sup>[2]</sup>。氟喹诺酮药物以喹啉-4-酮-3-羧酸为基本骨架,因其抗菌作用靶标——拓扑异构酶也是抗肿瘤药物的重要作用靶点,由此可通过结构修饰将其抗菌活性转化为抗肿瘤活性<sup>[3-4]</sup>。基于此,本课题组前期报道了氟喹诺酮C-3羧基虽是抗菌活性所需的药效团,但并非是抗肿瘤活性所必要的,被其等排体如酰胺、唑杂环等替代可提高其抗肿瘤活性<sup>[5-6]</sup>。为进一步对唑杂环等排体的优化,考虑到缩氨基硫脲不但能与多种金属离子螯合产生重要的药理作用,常被用作一个重要的药效团来构建药物分子骨架,同时其许多衍生物因具有如抗病毒、抗菌、抗真菌、抗肿瘤活性等广泛的生物活性而引起药物化学工作者的重视<sup>[7]</sup>。尤其值得关注的是,一些杂环缩氨基硫脲类化合物的抗肿瘤作用靶点可能是DNA拓扑异构酶Ⅱ(Topo II),而该靶点是抗肿瘤药物研究的重要靶点<sup>[8]</sup>。为此,本研究利用药效团拼合原理,用均三唑杂环作为抗菌氟喹诺酮培氟沙星(1)C-3羧基的等排体,缩氨基硫脲作为等排体的

优化修饰基,并以硫醚链与氟喹酮骨架相连接,试图实现药效团的活性叠加,从而合成了新的C-3均三唑硫醚酮缩氨基硫脲目标化合物(6a~6l),并对其初步的构效关系进行分析。

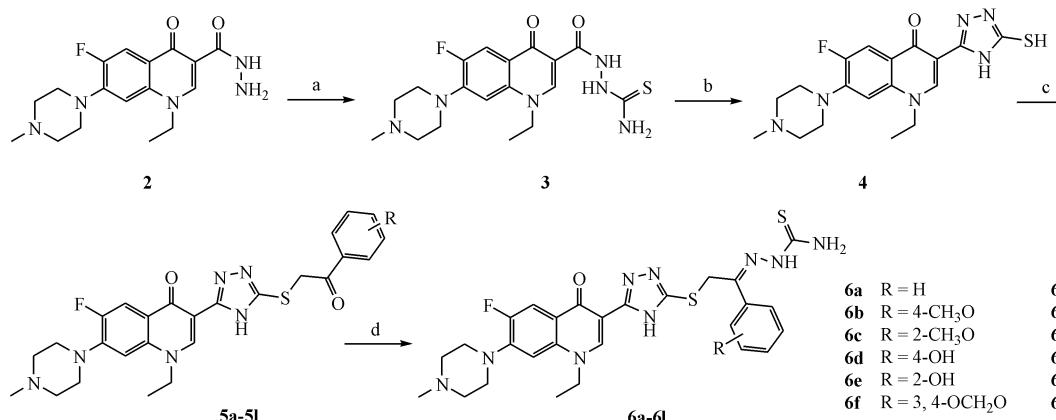
## 1 合成路线

目标化合物6a~6l的合成见路线1。培氟沙星酰肼2与硫氯化钾在酸性水溶液中发生缩合反应生成C-3酰胺基硫脲(3),接着化合物3在碱性水溶液中发生分子内环合反应得到C-3均三唑硫醇(4),它与溴代苯乙酮类发生亲核取代反应到C-3均三唑硫醚酮类中间体5a~5l。硫醚酮5a~5l分别与氨基硫脲反应制得相应的C-3均三唑硫醚酮缩氨基硫脲化合物6a~6l。

## 2 实验部分

### 2.1 材料

上海申光WK-1B数字熔点仪;德国Bruker公司Esquire LC型质谱仪;Bruker AM-400型核磁共振仪(TMS为内标);美国PE PE2400-II元素分析仪。C-3均三唑硫醇4按前期工作[6]的方法制备,试剂均为市销分析纯。



Scheme 1 Synthetic route of the title compounds 6a-6l from pefloxacin (1)

a; KSCN, HCl-H<sub>2</sub>O, reflux; b; NaOH, H<sub>2</sub>O, reflux; c; Ar-COCH<sub>2</sub>Br, EtOH, reflux; d; Thiosemicarbazide, HOAc, reflux

## 2.2 化学合成

1-乙基-6-氟-(4-甲基-哌嗪-基)-3-(5-苯甲酰甲硫基-4H-[1,2,4]三唑-3-基)-喹啉-4(1H)-酮(5a)的合成

C-3均三唑硫醇4(2.0 g, 5.2 mmol)与 $\alpha$ -溴代苯乙酮(1.2 g, 6.2 mmol)在无水乙醇(50 mL)中搅拌回流反应12 h。放置室温,过滤。粗品悬

浮于蒸馏水(50 mL)中,用碳酸氢钠饱和溶液调中性,滤集固体,干燥。用无水乙醇重结晶,得黄色结晶(5a)。用其他 $\alpha$ -溴代苯乙酮类与化合物4按同法制备1-乙基-6-氟-(4-甲基-哌嗪-基)-3-(5-取代苯甲酰甲硫基-4H-[1,2,4]三唑-3-基)-喹啉-4(1H)-酮(5b~5l),其理化性质和MS数据见表1。

**Table 1** Physical constants and spectral data of sulfide-one compounds **5a-5l**

Compd.	Yield/%	mp/°C	Elemental analysis (Calcd.)/%			MS (m/z) [M + H] <sup>+</sup> (Calcd.)
			C	H	N	
<b>5a</b>	86.4	186-188	61.82(61.64)	5.21(5.37)	16.83(16.59)	507(506.61)
<b>5b</b>	82.0	192-194	60.65(60.43)	5.32(5.45)	15.87(15.66)	537(536.63)
<b>5c</b>	73.5	176-178	60.57(60.43)	5.28(5.45)	15.83(15.66)	537(536.63)
<b>5d</b>	64.5	205-207	59.97(59.76)	5.38(5.21)	16.34(16.08)	523(522.61)
<b>5e</b>	58.6	192-194	59.68(59.76)	5.06(5.21)	16.31(16.08)	523(522.61)
<b>5f</b>	85.3	215-217	58.76(58.90)	5.15(4.94)	15.50(15.26)	551(550.62)
<b>5g</b>	75.2	193-195	59.56(59.35)	5.38(5.51)	15.02(14.83)	567(566.66)
<b>5h</b>	70.3	218-220	58.92(58.68)	5.07(5.29)	15.42(15.21)	553(552.63)
<b>5i</b>	76.5	182-184	62.50(62.29)	5.42(5.61)	16.37(16.14)	521(520.63)
<b>5j</b>	83.6	202-204	59.72(59.53)	4.87(5.00)	16.25(16.02)	525(524.60)
<b>5k</b>	73.0	172-174	57.86(57.72)	4.62(4.84)	15.76(15.53)	541(541.05)
<b>5l</b>	82.1	216-218	56.78(56.61)	4.63(4.75)	17.53(17.77)	552(551.60)

2-[5-[1-乙基-6-氟-7-(4-甲基哌嗪-1-基)-喹啉-4(1H)-酮-3-基]-4H-[1,2,4]三唑-3-基]- (取代)-苯乙酮缩氨基硫脲(**6a**~**6l**)合成通法

中间体**5**(2.0 mmol)溶于冰乙酸(15 mL)中,加入氨基硫脲(0.22 g, 2.4 mmol),混合物回流反

应12 h。减压蒸除溶剂,加水30 mL溶解,用适量的活性炭在50 °C搅拌脱色1 h。滤液用氨水调至中性,滤集产生的固体,水洗、干燥,无水乙醇重结晶,得淡黄色结晶目标物**6a**~**6l**,其理化性质和光谱数据见表2和3。

**Table 2** Physical constants and spectral data of the target compounds **6a-6l**

Compd.	Yield/%	mp/°C	Elemental analysis (Calcd.)/%			MS (m/z) [M + H] <sup>+</sup> (Calcd.)
			C	H	N	
<b>6a</b>	57.8	216-218	56.17(55.94)	5.41(5.22)	21.93(21.74)	580(579.73)
<b>6b</b>	61.5	224-226	55.42(55.16)	5.07(5.29)	20.86(20.67)	610(609.75)
<b>6c</b>	52.6	206-208	55.38(55.16)	5.47(5.29)	20.83(20.67)	610(609.75)
<b>6d</b>	48.6	203-205	54.67(54.44)	5.27(5.08)	21.38(21.16)	596(595.73)
<b>6e</b>	45.6	195-197	54.68(54.44)	5.27(5.08)	21.38(21.64)	596(595.73)
<b>6f</b>	62.5	237-239	54.16(53.92)	4.71(4.85)	20.44(20.21)	624(623.74)
<b>6g</b>	52.4	213-215	54.68(54.44)	5.16(5.36)	19.84(19.70)	640(639.78)
<b>6h</b>	51.6	241-243	53.96(53.75)	5.36(5.15)	20.37(20.15)	626(625.75)
<b>6i</b>	57.2	213-215	56.81(56.64)	5.18(5.43)	21.44(21.23)	594(593.75)
<b>6j</b>	63.4	226-228	54.53(54.26)	4.74(4.89)	21.36(21.09)	598(597.72)
<b>6k</b>	47.8	205-207	52.96(52.80)	4.58(4.76)	20.70(20.53)	614(614.17)
<b>6l</b>	61.7	209-211	52.16(51.91)	4.53(4.68)	22.65(22.42)	625(624.72)

**Table 3** <sup>1</sup>H NMR data of the target compounds **6a-6l**

Compd.	<sup>1</sup> H NMR(400 MHz, DMSO-d <sub>6</sub> )
<b>6a</b>	1.36(3H, t, <i>J</i> = 7.0 Hz, CH <sub>3</sub> ), 2.32(3H, s, N-CH <sub>3</sub> ), 3.14-3.57(8H, m, piperazine-H), 4.48(2H, q, <i>J</i> = 7.0 Hz, CH <sub>2</sub> ), 4.72(2H, s, SCH <sub>2</sub> ), 7.19(1H, d, <i>J</i> = 6.8 Hz, 8-H), 7.55-7.71(3H, m, Ph-H), 7.84(1H, d, <i>J</i> = 13.2 Hz, 5-H), 7.86(1H, s, NH), 8.04~8.06(2H, m, Ph-H), 8.36, 8.31(2H, 2s, NH <sub>2</sub> ), 8.78(1H, s, 2-H), 13.78(1H, s, NH), 1.38(3H, t, <i>J</i> = 7.0 Hz, CH <sub>3</sub> ), 2.28(3H, s, CH <sub>3</sub> ), 3.18-3.68(8H, m, piperazine-H), 3.86(3H, s, OCH <sub>3</sub> ), 4.49(2H, q, <i>J</i> = 7.0 Hz, CH <sub>2</sub> ), 4.77(2H, s, SCH <sub>2</sub> ), 7.08(2H, d, <i>J</i> = 8.6 Hz, Ph-H), 7.21(1H, d, <i>J</i> = 6.8 Hz, 8-H), 7.94(1H, d, <i>J</i> = 13.2 Hz, 5-H), 7.87(1H, s, NH), 8.03(2H, d, <i>J</i> = 8.6 Hz, Ph-H), 8.34, 8.38(2H, 2s, NH <sub>2</sub> ), 8.77(1H, s, 2-H), 13.76(1H, s, NH)
<b>6b</b>	1.37(3H, t, <i>J</i> = 7.0 Hz, CH <sub>3</sub> ), 2.26(3H, s, CH <sub>3</sub> ), 3.17-3.58(8H, m, piperazine-H), 3.88(3H, s, OCH <sub>3</sub> ), 4.46(2H, q, <i>J</i> = 7.0 Hz, CH <sub>2</sub> ), 4.78(2H, s, SCH <sub>2</sub> ), 7.23-7.65(4H, m, Ph-H and 8-H), 7.95(1H, d, <i>J</i> = 13.2 Hz, 5-H), 7.06-8.86(2H, m, NH and Ph-H), 8.32, 8.36(2H, 2s, NH <sub>2</sub> ), 8.81(1H, s, 2-H), 13.76(1H, s, NH)
<b>6c</b>	1.38(3H, t, <i>J</i> = 7.0 Hz, CH <sub>3</sub> ), 2.27(3H, s, CH <sub>3</sub> ), 3.23-3.64(8H, m, piperazine-H), 4.47(2H, q, <i>J</i> = 7.0 Hz, CH <sub>2</sub> ), 4.81(2H, s, SCH <sub>2</sub> ), 6.89(2H, d, <i>J</i> = 8.8 Hz, Ph-H), 7.18(1H, d, <i>J</i> = 6.8 Hz, 8-H), and 8-H), 7.93-7.96(2H, m, Ph-H and 5-H), 7.87(1H, s, NH), 8.31, 8.35(2H, 2s, NH <sub>2</sub> ), 8.78(1H, s, 2-H), 10.54(1H, s, OH), 13.77(1H, s, NH)
<b>6d</b>	1.37(3H, t, <i>J</i> = 7.0 Hz, CH <sub>3</sub> ), 2.26(3H, s, CH <sub>3</sub> ), 3.17-3.58(8H, m, piperazine-H), 3.88(3H, s, OCH <sub>3</sub> ), 4.46(2H, q, <i>J</i> = 7.0 Hz, CH <sub>2</sub> ), 4.78(2H, s, SCH <sub>2</sub> ), 7.23-7.65(4H, m, Ph-H and 8-H), 7.95(1H, d, <i>J</i> = 13.2 Hz, 5-H), 7.06-8.86(2H, m, NH and Ph-H), 8.32, 8.36(2H, 2s, NH <sub>2</sub> ), 8.81(1H, s, 2-H), 13.76(1H, s, NH)

(Continued)

Compd.	<sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> )
<b>6e</b>	1.37(3H, t, <i>J</i> = 7.0 Hz, CH <sub>3</sub> ), 2.26(3H, s, CH <sub>3</sub> ), 3.18-3.62(8H, m, piperazine-H), 4.47(2H, q, <i>J</i> = 7.0 Hz, CH <sub>2</sub> ), 4.82(2H, s, SCH <sub>2</sub> ), 7.16-7.23(4H, m, Ph-H and 8-H), 7.86(1H, s, NH), 7.88-7.95(2H, m, Ph-H and 5-H), 8.31, 8.34(2H, 2s, NH <sub>2</sub> ), 8.81(1H, s, 2-H), 10.56(1H, s, OH), 13.76(1H, s, NH)
<b>6f</b>	1.36(3H, t, <i>J</i> = 7.0 Hz, CH <sub>3</sub> ), 2.28(3H, s, CH <sub>3</sub> ), 3.16-3.57(8H, m, piperazine-H), 4.48(2H, q, <i>J</i> = 7.0 Hz, CH <sub>2</sub> ), 4.80(2H, s, SCH <sub>2</sub> ), 6.23(2H, s, OCH <sub>2</sub> O), 7.24-7.35(3H, m, Ph-H and 8-H), 7.86(1H, s, NH), 7.95(1H, d, <i>J</i> = 13.2 Hz, 5-H), 8.07(1H, s, Ph-H), 8.33, 8.37(2H, 2s, NH <sub>2</sub> ), 8.78(1H, s, 2-H), 13.77(1H, s, NH)
<b>6g</b>	1.37(3H, t, <i>J</i> = 7.0 Hz, CH <sub>3</sub> ), 2.32(3H, s, CH <sub>3</sub> ), 3.17-3.63(8H, m, piperazine-H), 3.85, 3.87(6H, 2s, 2OCH <sub>3</sub> ), 4.46(2H, q, <i>J</i> = 7.0 Hz, CH <sub>2</sub> ), 4.82(2H, s, SCH <sub>2</sub> ), 7.32-7.42(3H, m, Ph-H and 8-H), 7.87(1H, s, NH), 7.96(1H, d, <i>J</i> = 13.2 Hz, 5-H), 8.05(1H, s, Ph-H), 8.34, 8.30(2H, 2s, NH <sub>2</sub> ), 8.81(1H, s, 2-H), 13.77(1H, s, NH)
<b>6h</b>	1.36(3H, t, <i>J</i> = 7.0 Hz, CH <sub>3</sub> ), 2.28(3H, s, CH <sub>3</sub> ), 3.15-3.65(m, 8H, piperazine-H), 3.86(3H, s, OCH <sub>3</sub> ), 4.48(2H, q, <i>J</i> = 7.0 Hz, CH <sub>2</sub> ), 4.78(2H, s, SCH <sub>2</sub> ), 7.27-7.46(m, 3H, Ph-H and 8-H), 7.88(1H, s, NH), 7.95(1H, d, <i>J</i> = 13.2 Hz, 5-H), 8.07(1H, s, Ph-H), 8.32, 8.28(2H, 2s, NH <sub>2</sub> ), 8.83(1H, s, 2-H), 10.67(1H, s, OH), 13.76(1H, s, NH)
<b>6i</b>	1.36(3H, t, <i>J</i> = 7.0 Hz, CH <sub>3</sub> ), 2.24, 2.40(6H, 2s, 2CH <sub>3</sub> ), 3.07-3.53(8H, m, piperazine-H), 4.46(2H, q, <i>J</i> = 7.0 Hz, CH <sub>2</sub> ), 4.78(2H, s, SCH <sub>2</sub> ), 6.87(2H, d, <i>J</i> = 8.2 Hz, Ph-H), 7.31(1H, d, <i>J</i> = 6.8 Hz, 8-H), 7.92(1H, d, <i>J</i> = 13.2 Hz, 5-H), 7.86(1H, s, NH), 7.94(2H, d, <i>J</i> = 8.2 Hz, Ph-H), 8.31, 8.28(2H, 2s, NH <sub>2</sub> ), 8.75(1H, s, 2-H), 13.76(1H, s, NH)
<b>6j</b>	1.38(3H, t, <i>J</i> = 7.0 Hz, CH <sub>3</sub> ), 2.26(3H, s, CH <sub>3</sub> ), 3.15-3.58(8H, m, 8H, piperazine-H), 4.48(2H, q, <i>J</i> = 7.0 Hz, CH <sub>2</sub> ), 4.82(2H, s, SCH <sub>2</sub> ), 7.25(2H, d, <i>J</i> = 8.2 Hz, Ph-H), 7.36(1H, d, <i>J</i> = 6.8 Hz, 8-H), 7.88(1H, s, NH), 7.95(1H, d, <i>J</i> = 13.2 Hz, 5-H), 8.12(2H, d, <i>J</i> = 8.2 Hz, Ph-H), 8.33, 8.36(2H, 2s, NH <sub>2</sub> ), 8.83(1H, s, 2-H), 13.77(1H, s, NH)
<b>6k</b>	1.36(3H, t, <i>J</i> = 7.0 Hz, CH <sub>3</sub> ), 2.25(3H, s, CH <sub>3</sub> ), 3.13-3.56(8H, m, piperazine-H), 4.46(2H, q, <i>J</i> = 7.0 Hz, CH <sub>2</sub> ), 4.80(2H, s, SCH <sub>2</sub> ), 7.23(2H, d, <i>J</i> = 8.5 Hz, Ph-H), 7.34(1H, d, <i>J</i> = 6.8 Hz, 8-H), 7.85(s, NH), 7.91(1H, d, <i>J</i> = 13.2 Hz, 5-H), 8.07(d, <i>J</i> = 8.5 Hz, 2H, Ph-H), 8.30, 8.34(2s, 2H, NH <sub>2</sub> ), 8.81(s, 1H, 2-H), 13.76(1H, s, 1H, NH)
<b>6l</b>	1.39(3H, t, <i>J</i> = 7.0 Hz, CH <sub>3</sub> ), 2.28(3H, s, CH <sub>3</sub> ), 3.24-3.67(8H, m, piperazine-H), 4.52(2H, q, <i>J</i> = 7.0 Hz, CH <sub>2</sub> ), 4.86(2H, s, SCH <sub>2</sub> ), 7.36(1H, d, <i>J</i> = 6.8 Hz, 8-H), 7.56(2H, d, <i>J</i> = 8.5 Hz, Ph-H), 7.88(1H, s, NH), 7.97(1H, d, <i>J</i> = 13.2 Hz, 5-H), 8.12(2H, d, <i>J</i> = 8.5 Hz, Ph-H), 8.35, 8.38(2H, 2s, NH <sub>2</sub> ), 8.85(1H, s, 2-H), 13.78(1H, s, NH)

## 2.3 抗肿瘤活性评价

对合成的12个C-3均三唑硫醚酮(**5a**~**5l**)及其缩氨基硫脲目标化合物(**6a**~**6l**)和对照蒽醌类抗肿瘤药阿霉素及母体培氟沙星用DMSO配成 $1.0 \times 10^{-2}$  mol/L浓度的储备液。按文献[9]的方法测定对人肝癌细胞(SMMC-7721)、小鼠白血病细胞(L1210)和人白血病细胞(HL60)的半数抑制浓度( $IC_{50}$ )，结果见表4。

体外抗增殖活性结果表明，12个C-3均三唑硫醚酮中间体(**5a**~**5l**)和12个C-3均三唑硫醚酮缩氨基硫脲目标化合物(**6a**~**6l**)对3种试验肿瘤细胞株的半数抑制浓度均低于其前体药培氟沙星，表明均三唑杂环可作为C-3羧基的等排体。初步构效关系表明：当等排体均三唑修饰侧链硫醚酮转化为相应的硫醚酮缩氨基硫脲侧链时其活性明显提高，同时苯环带有羟基或氟原子的化合物其抗肿瘤活性高于其他取代基化合物的活性，如酚羟基化合物**6d**、**6e**、**6h**和氟苯基化合物**6j**的 $IC_{50}$ 已达到微摩尔级，其活性与对照药阿霉素相当，具有发展为先导物的潜力。苯环羟基的存在有利于与靶点

的结合部位形成氢键有关，而苯环氟原子的存在能够提高化合物穿透细胞膜的能力，有利于提高其抗肿瘤活性。基于此，氟喹诺酮C-3羧基并非是抗肿瘤活性所必要药效团，唑杂环作为C-3羧基的等排体且被功能侧链进一步修饰优化有利于提高抗肿瘤活性。

**Table 4** Antiproliferative activity of compounds (**5a**~**5l** and **6a**~**6l**) against SMMC-7721, L1210 and HL60 tumor cells

Compd.	IC <sub>50</sub> /(μmol/L)		
	SMMC-7721	L1210	HL60
<b>5a/6a</b>	33.7/10.6	42.8/17.6	48.3/27.6
<b>5b/6b</b>	38.6/14.2	51.6/15.3	43.4/20.6
<b>5c/6c</b>	27.6/8.7	38.5/12.7	34.2/11.6
<b>5d/6d</b>	25.3/4.6	30.8/8.6	28.3/6.5
<b>5e/6e</b>	21.7/3.2	26.2/7.4	26.8/5.2
<b>5f/6f</b>	41.5/17.3	53.2/17.6	45.3/22.8
<b>5g/6g</b>	36.2/15.7	47.3/16.2	42.8/20.7
<b>5h/6h</b>	22.6/3.8	27.5/7.2	25.8/4.7
<b>5i/6i</b>	41.6/14.8	47.8/15.2	45.8/18.6
<b>5j/6j</b>	18.4/2.7	21.6/5.2	19.3/4.5
<b>5k/6k</b>	41.7/16.3	52.4/18.6	45.2/23.5
<b>5l/6l</b>	45.2/21.7	56.8/23.5	48.7/20.4
Doxorubicin	2.8	1.6	3.0
Pefloxacin	>100	>100	>100

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