1-环丙基-6-氟-7-(芳甲叉肼基)-喹诺酮羧酸的合成及抗菌抗肿瘤活性

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摘 要 为发现具有抗菌抗肿瘤活性的氟喹诺酮羧酸先导化合物,用芳腙类作为环丙沙星C-7哌嗪基的等排体,设计合成了15个新的1-环丙基-6-氟-7-(芳甲叉肼基)-喹诺酮羧酸(**4a**~**4o**)目标化合物,其结构经元素分析和光谱数据确证。目标化合物体外对金黄色葡萄球菌(*S. aureus*)和大肠埃希菌(*E. coli*)的抗菌活性弱于对照药环丙沙星,然而对人肝癌(SMMC-7721)株、鼠白血病细胞(L1210)和人白血病细胞(HL60)3种肿瘤细胞株的抑制活性强于环丙沙星,尤其是腙基芳香环上带吸电子取代基的化合物,其抗肿瘤活性显著高于供电子基的活性,其抑制活性与对照药阿霉素相当。这表明C-7哌嗪基的存在有利于提高其抗菌活性而不利于提高抗肿瘤活性,而C-7芳腙基的引入可提高抗肿瘤活性,进一步扩展了氟喹诺酮类化合物结构修饰的范围。

关键词 氟喹诺酮;腙;抗菌活性;抗肿瘤活性;合成

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Synthesis, antibacterial and antitumor activities of 1-cycloproyl-6-fluoro-7-(hydrazone)-quinolin-4(1*H*)-one-carboxylic acids

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Abstract To discover novel antibacterial and antitumor lead compounds derived from fluoroquinolone carboxylic acids, aryl hydrazone moiety as an isosteric replacement of the C-7 piperazine group of ciprofloxacin, fifteen new 1-cyclopropyl-6-fluoro-7-arylidenehydrazino-quinolin-4(1*H*)-one-3-carboxylic acids (**4a-4o**) as title compounds were designed and synthesized, respectively. The structures were characterized by elemental analysis and spectral data. The *in vitro* antibacterial assay of the title compounds against *S. aureus* and *E. coli* bacterial strains exhibited poorer activity than parent ciprofloxacin, however, the results of antitumor activity against SMMC-7721, L1210 and HL60 cell lines demonstrated stronger inhibitory activity than parent ciprofloxacin, especially compounds with electron-withdrawing aryl groups were comparable to doxorubicin. It suggests that it is favorable for an improvement of antitumor activity to introduce a functional arylhydrazone group instead of piperazine ring into the 7-position of fluoroquinolone skeleton.

Key words fluoroquinolone; hydrazone; antibacterial activity; antitumor activity; synthesis

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喹诺酮类抗菌药的构-效关系表明,喹啉-4-酮-3-羧酸是抗菌活性的基本药效结构,在喹啉环的6-和7-位分别引入氟原子和杂环哌嗪基有利于提高抗菌活性、并扩大其抗菌谱[1-2]。同时,基于其抗

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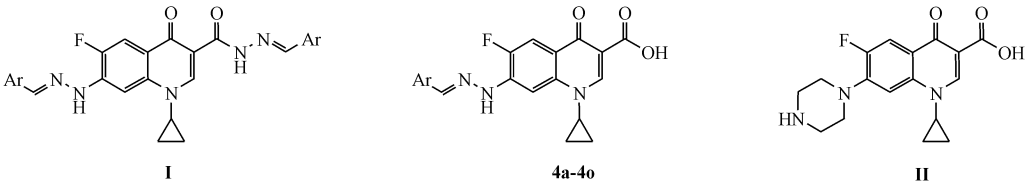
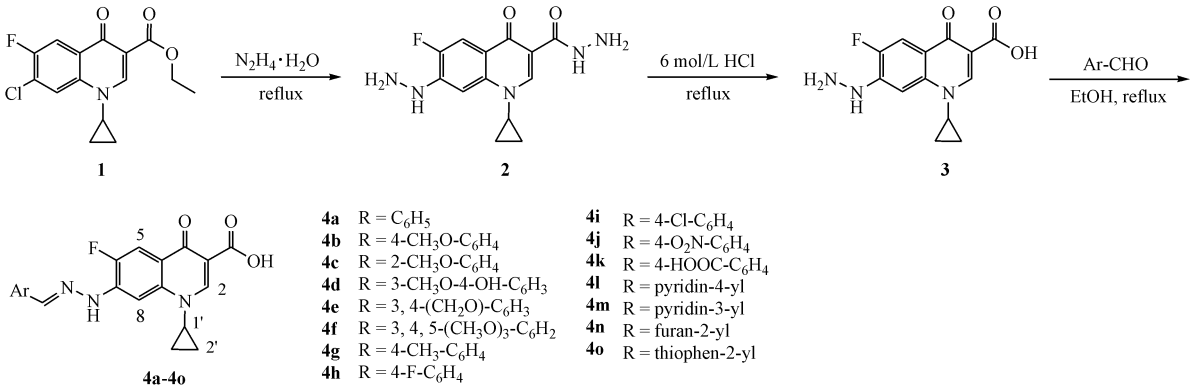
菌作用靶——拓扑异构酶也是抗肿瘤药物的重要作用靶点,且二者在功能和序列上具有相似性,因此氟喹诺酮有可能发展为抗肿瘤药物[3-4]。但对抗菌氟喹诺酮骨架如何修饰方可将其转化为抗肿瘤活性先导物,其精确的构效关系目前仍处于探索阶段[5]。结合前期的研究多关注于 C-3 羧基等排体的变化,而对 C-7 哌嗪的变化甚少,并所知 C-3 羧基的存在对抗肿瘤活性并非必要,可被腙类[6]和杂环[7]等替代。但是,保留 C-3 羧基、改变 C-7 哌嗪基所设计的新化合物将会对抗菌和抗肿瘤活性产生怎样的变化,有待进一步研究。基于前文 C-3/C-7 氟喹诺酮双腙的结构(Ⅰ)[8],保留其 C-7 芳腙基部分,把 C-3 酰腙还原为原有的 C-3 羧基,设计合成了环丙沙星(Ⅱ)类似物 C-7 芳腙取代的氟喹诺酮羧酸(**4a ~ 4o**),试图在保留抗菌活性的基础上提高其抗肿瘤活性。



1　合成路线

目标化合物 **4a ~ 4o** 的合成见路线 1。环丙沙星的前体羧酸酯 **1** 与肼同时发生酯的肼解和 C-7 氯原子的取代反应到 7-肼基氟喹诺酮酰肼 **2**[2],其在盐酸中通过酰肼的水解到 7-肼基氟喹诺酮-3-羧酸 **3**,然后分别与芳香醛缩合到 7-腙基氟喹诺酮-3-羧酸 **4a ~ 4o**。



Scheme 1　Synthetic route of compounds **4a-4o**

2　化学合成

2.1　仪器与试剂

上海申光 WK-1B 数字熔点仪测定;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。环丙羧酸酯(**1**)为市售工业级,7-肼基-6-氟-喹诺酮-3-酰肼 **2** 按前文[8]的方法制备,其它试剂均为市销分析纯。

2.2　1-环丙基-6-氟-7-肼基-喹啉-4(1*H*)-酮-3-羧酸(**3**)

肼基酰肼(**2**,10.0 g,34.4 mmol)溶于 6 mol/L 盐酸水溶液(200 mL),反应混合物搅拌回流反应至酰肼消失。减压蒸除溶剂,加水 100 mL 和适量的活性炭脱色 1 h。过滤,滤液用氨水调 pH 7.0。滤集产生的固体,用 5% 氢氧化钠溶液溶解所得的固体,用适量的活性炭在 60 ℃脱色 1 h。过滤,滤液用盐酸调 pH 7.0。滤集产生的固体,干燥。粗品用无水乙醇-DMF 重结晶,得黄色结晶(**3**),收率 56%,mp:216 ~ 218 ℃;^{1}H NMR(DMSO-d_6) δ: 14.48 (1H, br. s, COOH), 10.36 (1H, s, NH), 8.64(1H, s, 2-H), 8.15(1H, d, J = 13.2 Hz, 5-H), 7.84(1H, d, J = 6.2 Hz, 8-H), 4.16(2H, s, NH_2), 3.34 ~ 3.42 (1H, m, 1′-H), 1.24 ~ 1.16 (4H, m, 2′-H, 3′-H); MS (m/z): 278 [M + H]$^+$; Calcd. for $C_{13}H_{12}FN_3O_3$: 277.26。

1-环丙基-6-氟-7-(芳甲叉肼基)-喹啉-4(1*H*)-酮-3-羧酸(**4a**~**4o**)合成通法

肼基化物(**3**,0.5 g,1.8 mmol)与芳香醛(1.8 mmol)在无水乙醇(10 mL)中搅拌回流反应12 h。滤集产生的固体,用无水乙醇-DMF重结晶,得淡黄色结晶**4a**~**4o**。

1-环丙基-6-氟-7-(*N*′-苯甲叉肼基)-喹啉-4(1*H*)-酮-3-羧酸(**4a**) 收率84%,mp:235~237 ℃;^{1}H NMR(DMSO-d_6) δ:14.68(1H,br. s,COOH),10.53(1H,s,NH),8.67(1H,s,2-H),8.42(1H,s,CH=N),8.27(1H,d,J=13.2 Hz,5-H),7.84(1H,d,J=6.2 Hz,8-H),7.65~7.32(5H,m,Ph-H),3.32~3.28(1H,m,1′-H),1.27~1.18(4H,m,2′-H,3′-H);MS(*m/z*):366[M+H]$^+$;Calcd. 365.37;Anal. Calcd. for $C_{20}H_{16}FN_3O_3$:C 65.75,H 4.41,N 11.50;Found C 65.94,H 4.28,N 11.73。

1-环丙基-6-氟-7-(*N*′-对甲氧苯甲叉肼基)-喹啉-4(1*H*)-酮-3-羧酸(**4b**) 收率87%,mp:238~240 ℃;^{1}H NMR(DMSO-d_6) δ:14.73(1H,br. s,COOH),10.56(1H,s,NH),8.76(1H,s,2-H),8.46(1H,s,CH=N),8.34(1H,d,J=13.2 Hz,5-H),7.87(1H,d,J=6.2 Hz,8-H),7.66~7.46(4H,m,Ph-H),3.87(3H,s,OCH_3),3.37~3.32(1H,m,1′-H),1.28~1.21(4H,m,2′-H,3′-H);MS(*m/z*):396[M+H]$^+$;Calcd. 395.39;Anal. Calcd. for $C_{21}H_{18}FN_3O_4$:C 63.79,H 4.59,N 10.63;Found C 64.02,H 4.37,N 10.84。

1-环丙基-6-氟-7-(*N*′-邻甲氧苯甲叉肼基)-喹啉-4(1*H*)-酮-3-羧酸(**4c**) 收率73%,mp:216~218 ℃;^{1}H NMR(DMSO-d_6) δ:14.68(1H,br. s,COOH),10.54(1H,s,NH),8.78(1H,s,2-H),8.45(1H,s,CH=N),8.36(1H,d,J=13.2 Hz,5-H),7.88(1H,d,J=6.2 Hz,8-H),7.64~7.25(4H,m,Ph-H),3.89(3H,s,OCH_3),3.36~3.27(1H,m,1′-H),1.32~1.25(4H,m,2′-H,3′-H);MS(*m/z*):396[M+H]$^+$;Calcd. 395.39;Anal. Calcd. for $C_{21}H_{18}FN_3O_4$:C 63.79,H 4.59,N 10.63;Found C 63.93,H 4.44,N 10.80。

1-环丙基-6-氟-7-[*N*′-(4-羟基-3-甲氧基)苯甲叉肼基]-喹啉-4(1*H*)-酮-3-羧酸(**4d**) 收率87%,mp:246~248 ℃;^{1}H NMR(DMSO-d_6) δ:14.75(1H,br. s,COOH),10.23,10.56(2H,s,OH,NH),8.84(1H,s,2-H),8.47(1H,s,CH=N),8.38(1H,d,J=13.2 Hz,5-H),7.87(d,J=6.2 Hz,8-H),7.68~7.42(m,3H,Ph-H),3.86(s,3H,OCH_3),3.37~3.31(m,1H,1′-H),1.34~1.22(1H,m,4H,2′-H,3′-H);MS(*m/z*):412[M+H]$^+$;Calcd. 411.39;Anal. Calcd. for $C_{21}H_{18}FN_3O_5$:C 61.31,H 4.41,N 10.21;Found C 61.54,H 4.28,N 10.45。

1-环丙基-6-氟-7-[*N*′-(3,4-二氧亚甲基)苯甲叉肼基]-喹啉-4(1*H*)-酮-3-羧酸(**4e**) 收率91%,mp>260 ℃;^{1}H NMR(DMSO-d_6) δ:14.77(1H,br. s,COOH),10.58(1H,s,NH),8.86(1H,s,2-H),8.45(1H,s,CH=N),8.37(1H,d,J=13.2 Hz,5-H),7.85(1H,d,J=6.2 Hz,8-H),7.64~7.38(3H,m,Ph-H),6.13(2H,s,OCH_2O),3.36~3.34(1H,m,1′-H),1.31~1.21(4H,m,2′-H,3′-H);MS(*m/z*):410[M+H]$^+$;Calcd. 409.38;Anal. Calcd. for $C_{21}H_{16}FN_3O_5$:C 61.61,H 3.94,N 10.26;Found C 61.83,H 4.15,N 10.48。

1-环丙基-6-氟-7-[*N*′-(3,4,5-三氧基)苯甲叉肼基]-喹啉-4(1*H*)-酮-3-羧酸(**4f**) 收率82%,mp:243~245 ℃;^{1}H NMR(DMSO-d_6) δ:14.75(1H,br. s,COOH),10.54(1H,s,NH),8.87(1H,s,2-H),8.43(1H,s,CH=N),8.36(1H,d,J=13.2 Hz,5-H),7.86(1H,d,J=6.2 Hz,8-H),7.58(2H,s,Ph-H),3.86,3.88(9H,2s,3×OCH_3),3.42~3.36(1H,m,1′-H),1.35~1.26(4H,m,2′-H,3′-H);MS(*m/z*):456[M+H]$^+$;Calcd. 455.45;Anal. Calcd. for $C_{23}H_{22}FN_3O_6$:C 60.66,H 4.87,N 9.23;Found C 60.87,H 4.69,N 9.46。

1-环丙基-6-氟-7-(*N*′-对甲基苯甲叉肼基)-喹啉-4(1*H*)-酮-3-羧酸(**4g**) 收率72%,mp:226~228 ℃;^{1}H NMR(DMSO-d_6) δ:14.73(1H,br. s,COOH),10.52(1H,s,NH),8.85(1H,s,2-H),8.37(1H,s,CH=N),8.25(1H,d,J=13.2 Hz,5-H),7.84(1H,d,J=6.2 Hz,8-H),7.66~7.25(4H,m,Ph-H),3.38~3.32(1H,m,1′-H),2.27(3H,s,CH_3),1.28~1.17(4H,m,2′-H,3′-H);MS(*m/z*):380[M+H]$^+$;Calcd. 379.39;Anal. Calcd. for $C_{21}H_{18}FN_3O_3$:C 66.48,H 4.78,N 11.08;Found C 66.71,H 4.55,N 11.31。

1-环丙基-6-氟-7-(*N*′-对氯苯甲叉肼基)-喹啉-4(1*H*)-酮-3-羧酸(**4h**)　收率 88%, mp: 253 ~ 255 ℃; ^{1}H NMR (DMSO-d_6) δ: 14.81 (1H, br. s, COOH), 10.63 (1H, s, NH), 8.87 (1H, s, 2-H), 8.43 (1H, s, CH = N), 8.27 (1H, d, J = 13.2 Hz, 5-H), 7.86 (1H, d, J = 6.2 Hz, 8-H), 7.74 ~ 7.58 (4H, m, Ph-H), 3.44 ~ 3.35 (1H, m, 1′-H), 1.31 ~ 1.26 (4H, m, 2′-H, 3′-H); MS (m/z): 384 [M + H]$^+$; Calcd. 383.36; Anal. Calcd. for $C_{20}H_{15}F_2N_3O_3$: C 62.66, H 3.94, N 10.96; Found C 62.88, H 4.15, N 11.18。

1-环丙基-6-氟-7-(*N*′-对氯苯甲叉肼基)-喹啉-4(1*H*)-酮-3-羧酸(**4i**)　收率 76%, mp: 218 ~ 220 ℃; ^{1}H NMR (DMSO-d_6) δ: 14.76 (1H, br. s, COOH), 10.58 (1H, s, NH), 8.86 (1H, s, 2-H), 8.41 (1H, s, CH = N), 8.25 (1H, d, J = 13.2 Hz, 5-H), 7.83 (1H, d, J = 6.2 Hz, 8-H), 7.68 ~ 7.52 (4H, m, Ph-H), 3.42 ~ 3.30 (1H, m, 1′-H), 1.28 ~ 1.22 (4H, m, 2′-H, 3′-H); MS (m/z): 400 [M + H]$^+$; Calcd. 399.81; Anal. Calcd. for $C_{20}H_{15}ClFN_3O_3$: C 60.08, H 3.78, N 10.51; Found C 60.24, H 4.62, N 10.74。

1-环丙基-6-氟-7-(*N*′-对硝基苯甲叉肼基)-喹啉-4(1*H*)-酮-3-羧酸(**4j**)　收率 93%, mp: 256 ~ 258 ℃; ^{1}H NMR (DMSO-d_6) δ: 14.95 (1H, br. s, COOH), 10.66 (1H, s, NH), 8.93 (1H, s, 2-H), 8.48 (1H, s, CH = N), 8.34 (1H, d, J = 13.2 Hz, 5-H), 7.88 (1H, d, J = 6.2 Hz, 8-H), 7.76 ~ 7.63 (4H, m, Ph-H), 3.46 ~ 3.42 (1H, m, 1′-H), 1.35 ~ 1.28 (4H, m, 2′-H, 3′-H); MS (m/z): 411 [M + H]$^+$; Calcd. 410.36; Anal. Calcd. for $C_{20}H_{15}FN_4O_5$: C 58.54, H 3.68, N 13.65; Found C 58.76, H 3.85, N 13.84。

1-环丙基-6-氟-7-(*N*′-对羧基苯甲叉肼基)-喹啉-4(1*H*)-酮(**4k**)　收率 88%, mp: 245 ~ 247 ℃; ^{1}H NMR (DMSO-d_6) δ: 15.17, 13.36 (1H, 2br. s, 2 × COOH), 10.68 (1H, s, NH), 9.16 (1H, s, 2-H), 8.63 (1H, s, CH = N), 8.47 (1H, d, J = 13.2 Hz, 5-H), 8.28 ~ 7.64 (5H, m, Ph, 8-H), 3.47 ~ 3.43 (1H, m, 1′-H), 1.43 ~ 1.26 (4H, m, 2′-H, 3′-H); MS (m/z): 410 [M + H]$^+$; Calcd. 419.38; Anal. Calcd. for $C_{21}H_{16}FN_3O_5$: C 61.61, H 3.94, N 10.26; Found C 61.83, H 3.77, N 10.50。

1-环丙基-6-氟-7-(*N*′-吡啶-4-甲叉肼基)-喹啉-4(1*H*)-酮(**4l**)　收率 86%, mp > 260 ℃; ^{1}H NMR (DMSO-d_6) δ: 15.12 (1H, s, COOH), 9.13 (1H, s, 2-H), 8.85 (2H, d, J = 7.6 Hz, Py-H), 8.64 (2H, d, J = 7.6 Hz, Py-H), 8.54 (1H, s, CH = N), 8.43 (1H, d, J = 13.2 Hz, 5-H), 8.06 (1H, d, J = 6.2 Hz, 8-H), 3.48 ~ 3.44 (1H, m, 1′-H), 1.37 ~ 1.32 (4H, m, 2′-H, 3′-H); MS (m/z): 367 [M + H]$^+$; Calcd. 366.35; Anal. Calcd. for $C_{19}H_{15}FN_4O_3$: C 62.29, H 4.13, N 15.29; Found C 62.46, H 4.33, N 15.51。

1-环丙基-6-氟-7-(*N*′-吡啶-3-甲叉肼基)-喹啉-4(1*H*)-酮(**4m**)　收率 81%, mp > 260 ℃; ^{1}H NMR (DMSO-d_6) δ: 15.12 (1H, s, COOH), 9.07 (1H, s, 2-H), 8.89 (2H, d, J = 7.6 Hz, Py-H), 8.67 ~ 8.52 (3H, m, Py-H, CH = N), 8.41 (1H, d, J = 13.2 Hz, 5-H), 7.94 (1H, d, J = 6.2 Hz, 8-H), 3.45 ~ 3.38 (1H, m, 1′-H), 1.35 ~ 1.28 (4H, m, 2′-H, 3′-H); MS (m/z): 367 [M + H]$^+$; Calcd. 366.35; Anal. Calcd. for $C_{19}H_{15}FN_4O_3$: C 62.29, H 4.13, N 15.29; Found C 62.54, H 3.96, N 15.48。

1-环丙基-6-氟-7-(*N*′-呋喃-2-甲叉肼基)-喹啉-4(1*H*)-酮(**4n**)　mp: 253 ~ 255 ℃; ^{1}H NMR (DMSO-d_6) δ: 14.93 (1H, s, COOH), 9.13 (1H, s, 2-H), 8.48 (1H, m, CH = N), 8.38 (1H, d, J = 13.2 Hz, 5-H), 7.86 ~ 7.23 (4H, m, 8-H, furan-H), 3.42 ~ 3.35 (1H, m, 1′-H), 1.33 ~ 1.26 (4H, m, 2′-H, 3′-H); MS (m/z): 356 [M + H]$^+$; Calcd. 356.33; Anal. Calcd. for $C_{18}H_{14}FN_3O_4$: C 60.85, H 3.97, N 11.83; Found C 61.05, H 3.84, N 11.68。

1-环丙基-6-氟-7-(*N*′-噻吩-2-甲叉肼基)-喹啉-4(1*H*)-酮(**4o**)　mp: 247 ~ 249 ℃; ^{1}H NMR (DMSO-d_6) δ: 14.96 (1H, s, COOH), 9.03 (1H, s, 2-H), 8.57 (1H, m, CH = N), 8.44 (1H, d, J = 13.2 Hz, 5-H), 8.17 ~ 7.36 (4H, m, 8-H, thiophene-H), 3.44 ~ 3.37 (1H, m, 1′-H), 1.38 ~ 1.25 (4H, m, 2′-H, 3′-H); MS (m/z): 372 [M + H]$^+$; Calcd. 371.39; Anal. Calcd. for $C_{18}H_{14}FN_3O_3S$: C 58.21, H 3.80, N 11.31; Found C 58.43, H 3.72, N 11.52。

2.3　抗菌和抗肿瘤活性测试

2.3.1　抗菌活性　对合成的 15 个新目标化合物

(**4a**~**4o**)及对照品环丙沙星(CFX),用DMSO配成128 mg/L的供试液,采用标准试管二倍稀释法测定其对金黄色葡萄球菌(*S. aureus* ATCC25923)和大肠埃希菌(*E. coli* ATCC25922)的体外最低抑菌浓度(MICs)。结果表明,15个目标化合物的MICs均大于16.0 mg/L,其抗菌活性低于环丙沙星的活性(MIC≤2.0 mg/L)。

2.3.2 *抗肿瘤活性* 15个目标化合物(**4a**~**4o**)及对照品蒽醌类抗肿瘤药阿霉素(DOX)及母体环丙沙星,用DMSO配成1.0×10^{-2} mol/L浓度的储备液,用RPMI 1640稀释到所需浓度(0.1,1.0,10.0,30.0,50.0 mol/L),按文献[7]的方法测定他们各自对人肝癌细胞(SMMC-7721)、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1。

Table 1 *In vitro* antitumor activity of compounds **4a-4o** against SMMC-7721, L1210 and HL60 tumor cells

Compd.	IC_{50}/(μmol/L)		
	SMMC-7721	L1210	HL60
4a	11.3±1.4	20.6±1.8	25.7±2.4
4b	13.6±1.5	24.6±2.3	28.5±1.7
4c	10.7±1.2	14.6±1.4	17.8±1.5
4d	7.3±0.6	8.7±1.0	15.6±1.4
4e	26.8±2.0	29.3±1.8	32.6±2.4
4f	31.8±2.6	35.7±2.3	37.6±2.3
4g	26.5±1.8	31.5±2.6	34.6±2.7
4h	6.3±0.6	8.8±0.7	10.5±1.1
4i	18.6±1.7	23.4±1.2	27.8±1.6
4j	2.7±0.3	5.8±0.5	7.4±0.5
6k	3.1±0.2	4.6±0.4	5.6±0.3
6l	2.7±0.3	5.8±0.5	7.4±0.5
6m	3.6±0.2	7.3±0.4	8.6±0.5
4n	3.8±0.5	6.6±0.4	7.8±0.6
4o	6.4±0.3	8.7±0.6	11.2±1.3
DOX	2.8±0.6	2.4±0.3	3.5±0.4
CFX	>100	>100	>100

DOX: Doxorubicin; CFX: Ciprofloxacin

体外抗肿瘤测试结果(表1)表明,15个目标化合物的抗肿瘤活性虽然不及对照品阿霉素,但其IC_{50}小于40.0 μmol/L,活性强于母体药物环丙沙星($IC_{50}\geq100$ μmol/L),说明C-7哌嗪基的存在对抗菌活性的贡献较大,但对提高抗肿瘤活性的意义不大。同时,本研究目标化合物的抗肿瘤活性与前文报道[8]的C-3/C-7双腙的活性相比也无显著的变化,这进一步表明C-3羧基并非抗肿瘤活性所必需的活性药效基团。初步的构效关系表明,当芳腙苯环带有游离羟基、氟原子或吸电子基团(如硝基和羧基)的化合物显示出较强的抗肿瘤活性;把苯环用芳香杂环(如吡啶、呋喃或噻吩等)替代的化合物,其抗肿瘤活性也显著增强。从电性上分析,芳杂环也为吸电子基,从而可提高芳腙亚胺双键的亲电性,有利于与作用靶点大分子中的亲核功能基如巯基、氨基等发生加成反应形成细胞毒性。为此,氟喹诺酮C-7哌嗪基不是抗肿瘤活性的优选药效团,可用强的亲电性功能基替代。然而,C-3羧基应作如何相应的变化仍值得进一步探讨。

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