·论 文·

氟喹诺酮 C-3 羧基等排体的合成及抗肿瘤活性 V. 环丙沙星酰腙的合成及构效关系

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摘 要 为发现转化抗菌氟喹诺酮到抗肿瘤氟喹诺酮的策略及其构-效关系,用酰腙作为环丙沙星 C3 羧基的生物电子等排体,合成了 12 个未见报道的环丙沙星酰腙(**3a ~ 3l**)目标化合物。结果显示:体外对 SMMC-7721、L1210 和 HL60 3 种肿瘤细胞的抑制活性显著强于母体,但都低于对照药阿霉素,尤其对肝癌 SMMC-7721 细胞的活性与阿霉素相当。构效关系表明,取代链苯环带吸电子基团的活性强于供电子基团的活性,酰腙还原产物酰肼取代物的活性消失。结果说明酰腙可作为 C-3 羧基的等排体,酰腙亚胺双键是抗肿瘤活性所必需的药效团部位。

关键词 氟喹诺酮;酰腙;生物电子等排体;合成;抗肿瘤活性

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Synthesis and antitumor activity of fluoroquinolone C-3 isostere V: ciprofloxacin acylhydrazone derivatives

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Abstract To explore an efficient strategy for the transformation of antibacterial fluoroquinoles into antitumor fluoroquinolones and their structure-activity relationship, an acylhydrazone as bioisostere of the C-3 carboxylic group, twelve novel fluoroquinolone C-3 acylhydrazones **3a-3l** were synthesized from ciprofloxacin, respectively. The structures were characterized by element analysis and spectral data. The *in vitro* antitumor activity against SMMC-7721, L1210 and HL60 cell lines exhibited more significantly inhibitory activity than the parent, in which compounds with electron-withdrawing group were comparable to doxorubicin. SAR showed that compounds with electron-withdrawing group had more potency than those with electron-donating group, after reduction of acylhydrazone moiety, antitumor activity disappeared. Thus, it is necessary for an acylhydrazone as a bioisostere of the C-3 carboxylic group to develop antitumor fluoroquinolone lead compounds.

Key words fluoroquinolone; acylhydrazone; bioisostere; synthesis; antitumor activity

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基于拓扑异构酶(TOPO)不但是抗肿瘤药物的重要作用靶标,也是氟喹诺酮的抗菌作用靶酶,而且二者在结构和功能上具有相似性,因此对抗菌药氟喹诺酮进行合理结构修饰是开发抗肿瘤氟喹诺酮药物的有效途径[1-2]。虽然目前已认识到氟喹诺酮 C-3 羧基并非是抗肿瘤活性所必需的药效团,并可被杂环或稠杂环等羧基等排体替代[3-4],但这导致化合物的刚性较强、相对分子质量过大、

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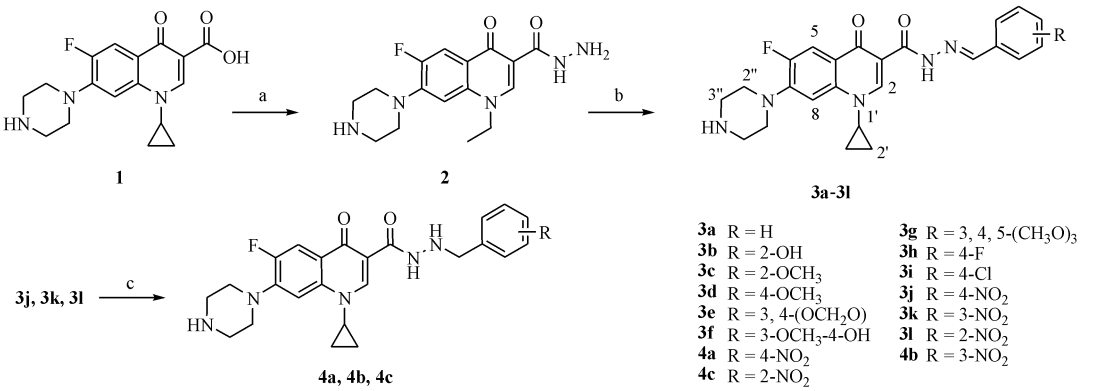
不利于成药性的发展[5]。有趣的是酰腙化合物不但具有与大分子靶标形成氢键的 N,O 供电子原子,同时其亚胺 N = C 双键也易与靶标大分子中的亲核基团(如 NH_2 和 SH)进行亲核加成,从而产生强的细胞毒活性[6]。同时已发现氟喹诺酮双酰腙类化合物具有强的抗肿瘤活性[7]。为此,为了进一步研究氟喹诺酮酰腙类的抗肿瘤构效关系,本文选择酰腙为环丙沙星 **1** 羧基的等排体,设计合成了12个未见文献报道的环丙沙星酰腙类化合物(**3a**~**3l**),并初步分析了其构效关系。

1 合成路线

目标化合物 **3a**~**3l** 的制备见路线1。环丙沙星 **1** 经肼化到相应的酰肼 **2**、与取代的苯甲醛缩合到目标化合物酰腙 **3a**~**3l**。其中,酰腙化合物 **3j**、**3k**、**3l** 经硼氢化钠还原得相应的酰肼取代物 **4a**、**4b**、**4c**。



Scheme 1 Synthetic route for ciprofloxacin acylhydrazone derivatives **3a-3l**
a: 80% $N_2H_4 \cdot H_2O$, reflux; b: Ar-CHO, EtOH, reflux; c: $NaBH_4$, MeOH, rt

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。环丙沙星(**1**)为市售品,环丙沙星酰肼(**2**)按文献[8]的方法制备,试剂均为市售分析纯。

2.2 化学合成

(取代)苯甲醛 1-环丙基-6-氟-7-哌嗪-1-基-喹啉-4(1*H*)-酮-3-甲酰腙(**3a**~**3l**)的合成通法

化合物 **2** 1.0 g(3.0 mmol)溶于无水乙醇(15 mL)中,加入等物质的量的苯甲醛或取代苯甲醛(3.0 mmol)和冰乙酸(0.1 mL),回流 10 h,放置析出固体,过滤,乙醇洗涤。用无水乙醇或 DMF-乙醇重结晶,得黄色固体目标化合物环丙沙星酰腙 **3a**~**3l**。

苯甲醛环丙沙星酰腙(**3a**),收率 86%,mp:243~245 ℃;^{1}H NMR(DMSO-d_6) δ:13.23(s,1H,CONH),8.73(s,1H,2-H),8.44(s,1H,N = CH),7.92(d,J = 13.2 Hz,1H,5-H),7.78~7.46(m,6H,8-H,Ph-H),3.81~3.78(m,1H,1′-H),3.28(t,J = 6.2 Hz,4H,2×2″-H),2.65(t,J = 6.2 Hz,4H,2×3″-H),1.16-1.27(m,4H,2×2×2′-H);MS (m/z):434[M + H]$^+$;Anal. calcd. for $C_{24}H_{24}FN_5O_2$(%):C 66.50,H 5.58,N 16.16;Found:C 66.74,H 5.36,N 16.38。

2-羟基苯甲醛环丙沙星酰腙(**3b**),收率 82%,mp:218~220 ℃;^{1}H NMR(DMSO-d_6) δ:13.18(s,1H,CONH),11.32(s,1H,OH),8.73(s,1H,2-H),8.32(s,1H,N = CH),7.86(d,J = 13.2 Hz,1H,5-H),7.53(d,J = 7.2 Hz,1H,8-H),7.36~6.68(m,4H,Ph-H),3.82~3.80(m,1H,1′-H),3.35~3.28(m,4H,2×2″-H),2.57(br,4H,2×3″-H),1.17-1.23(m,4H,2×2′-H);MS (m/z):450[M + H]$^+$;Anal. calcd. for $C_{24}H_{24}FN_5O_3$(%):C 64.13,H 5.38,N 15.58;Found:C 64.37,H 5.17,N 15.80。

2-甲氧基苯甲醛环丙沙星酰腙(**3c**),收率 72%,mp:152~154 ℃;^{1}H NMR(DMSO-d_6) δ:13.07(s,1H,CONH),8.67(s,1H,2-H),8.28(s,1H,N = CH),7.87(d,J = 13.2 Hz,1H,5-H),7.56(d,J = 7.2 Hz,1H,8-H),7.38~6.72(m,4H,Ph-H),3.87(s,3H,OCH_3),3.82~3.76(m,1H,1′-H),3.34~3.25(m,4H,2×2″-H),2.58(br,4H,2×3″-H),1.20~1.24(m,4H,2×2′-H);MS (m/z):464[M + H]$^+$;Anal. calcd. for $C_{25}H_{26}FN_5O_3$(%):C 64.78,H 5.65,N 15.11;Found:C 65.03,H 5.28,N 15.31。

4-甲氧基苯甲醛环丙沙星酰腙(**3d**),收率 86%,mp:166~168 ℃;^{1}H NMR(DMSO-d_6) δ:13.05(s,1H,CONH),8.68(s,1H,2-H),8.26(s,1H,N = CH),7.84(d,J = 13.2 Hz,1H,5-H),7.57(d,J = 7.2 Hz,1H,8-H),7.43~6.68(m,4H,Ph-H),3.85(s,3H,OCH_3),3.83~3.75(m,1H,1′-H),3.32~3.24(m,4H,2×2″-H),2.63(br,4H,2×3″-H),1.22~1.27(m,4H,2×2′-H);MS (m/z):464[M + H]$^+$;

Anal. calcd. for $C_{25}H_{26}FN_5O_3$ (%): C 64.78, H 5.65, N 15.11; Found: C 64.93, H 5.47, N 15.28。

3,4-(二氧亚甲基)苯甲醛环丙沙星酰腙(**3e**),收率 93%, mp: 251 ~ 253 ℃; ^{1}H NMR (DMSO-d_6) δ: 13.24 (s, 1H, CONH), 8.69 (s, 1H, 2-H), 8.35 (s, 1H, N = CH), 7.86 (d, J = 13.2 Hz, 1H, 5-H), 7.53 ~ 7.02 (m, 4H, 8-H, Ph-H), 6.12 (s, 2H, OCH_2O), 3.81 ~ 3.77 (m, 1H, 1′-H), 3.36 ~ 3.28 (m, 4H, 2 × 2″-H), 2.57 ~ 2.52 (m, 4H, 2 × 3″-H), 1.22 ~ 1.27 (m, 4H, 2 × 2′-H); MS (m/z): 478 [M + H]$^+$; Anal. calcd. for $C_{25}H_{24}FN_5O_4$ (%): C 62.89, H 5.07, N 14.67; Found: C 63.10, H 4.89, N 14.84。

3-甲氧基-4-羟基-苯甲醛环丙沙星酰腙(**3f**),收率 87%, mp: 219 ~ 221 ℃; ^{1}H NMR (DMSO-d_6) δ: 13.21 (s, 1H, CONH), 10.87 (s, 1H, OH), 8.87 (s, 1H, 2-H), 8.28 (s, 1H, N = CH), 8.04 (d, J = 13.2 Hz, 1H, 5-H), 7.60 ~ 6.85 (m, 4H, 8-H, Ph-H), 3.87 (s, 3H, CH_3O), 3.83 ~ 3.80 (m, 1H, 1′-H), 3.35 ~ 3.26 (m, 4H, 2 × 2″-H), 2.58 ~ 2.53 (m, 4H, 2 × 3″-H), 1.20 ~ 1.26 (m, 4H, 2 × 2′-H); MS (m/z): 480 [M + H]$^+$; Anal. calcd. for $C_{25}H_{26}FN_5O_4$ (%): C 62.62, H 5.47, N 14.61; Found: C 62.83, H 5.36, N 14.78。

3,4,5-三甲氧苯甲醛环丙沙星酰腙(**3g**),收率 75%, mp: 179 ~ 181 ℃; ^{1}H NMR (DMSO-d_6) δ: 13.12 (s, 1H, CONH), 8.82 (s, 1H, 2-H), 8.37 (s, 1H, N = CH), 7.96 (d, J = 13.2 Hz, 1H, 5-H), 7.82 (d, J = 7.2 Hz, 1H, 8-H), 7.46 (s, 2H, Ph-H), 3.86, 3.88 (2s, 9H, 3 × CH_3O), 3.81 ~ 3.76 (m, 1H, 1′-H), 3.34 ~ 3.18 (m, 4H, 2 × 2″-H), 2.56 ~ 2.53 (m, 4H, 2 × 3″-H), 1.18 ~ 1.24 (m, 4H, 2 × 2′-H); MS (m/z): 524 [M + H]$^+$; Anal. calcd. for $C_{27}H_{30}FN_5O_5$ (%): C 61.94, H 5.78, N 13.38; Found: C 62.12, H 5.56, N 13.62。

4-氯-苯甲醛环丙沙星酰腙(**3h**),收率 86%, mp: 213 ~ 215 ℃; ^{1}H NMR (DMSO-d_6) δ: 13.17 (s, 1H, CONH), 8.86 (s, 1H, 2-H), 8.38 (s, 1H, N = CH), 8.03 (d, J = 13.2 Hz, 1H, 5-H), 7.96 (d, J = 7.5 Hz, 2H, Ph-H), 7.83 (d, J = 7.2 Hz, 1H, 8-H), 7.68 (d, J = 7.5 Hz, 2H, Ph-H), 3.80 ~ 3.78 (m, 1H, 1′-H), 3.38 ~ 3.22 (m, 4H, 2 × 2″-H), 2.67 ~ 2.58 (m, 4H, 2 × 3″-H), 1.23 ~ 1.25 (m, 4H, 2 × 2′-H); MS (m/z): 452 [M + H]$^+$; Anal. calcd. for $C_{24}H_{23}F_2N_5O_2$ (%): C 63.85, H 5.13, N 15.51; Found: C 64.02, H 5.31, N 15.74。

4-氯-苯甲醛环丙沙星酰腙(**3i**),收率 74%, mp: 157 ~ 159 ℃; ^{1}H NMR (DMSO-d_6) δ: 13.13 (s, 1H, CONH), 8.82 (s, 1H, 2-H), 8.35 (s, 1H, N = CH), 8.02 (d, J = 13.2 Hz, 1H, 5-H), 7.87 (d, J = 7.5 Hz, 2H, Ph-H), 7.81 (d, J = 7.2 Hz, 1H, 8-H), 7.66 (d, J = 7.5 Hz, 2H, Ph-H), 3.76 ~ 3.72 (m, 1H, 1′-H), 3.36 ~ 3.20 (m, 4H, 2 × 2″-H), 2.63 ~ 2.56 (m, 4H, 2 × 3″-H), 1.21 ~ 1.24 (m, 4H, 2 × 2′-H); MS (m/z): 468 [M + H]$^+$; Anal. calcd. for $C_{24}H_{23}ClFN_5O_2$ (%): C 61.60, H 4.95, N 14.97; Found: C 61.78, H 4.82, N 15.13。

4-硝基-苯甲醛环丙沙星酰腙(**3j**),收率 92%, mp: 263 ~ 265 ℃; ^{1}H NMR (DMSO-d_6) δ: 13.21 (s, 1H, CONH), 8.86 (s, 1H, 2-H), 8.47 (s, 1H, N = CH), 8.12 (d, J = 13.2 Hz, 1H, 5-H), 8.04 (d, J = 7.5 Hz, 2H, Ph-H), 7.86 (d, J = 7.2 Hz, 1H, 8-H), 7.73 (d, J = 7.5 Hz, 2H, Ph-H), 3.78 ~ 3.81 (m, 1H, 1′-H), 3.37 ~ 3.25 (m, 4H, 2 × 2″-H), 2.66 ~ 2.63 (m, 4H, 2 × 3″-H), 1.23 ~ 1.25 (m, 4H, 2 × 2′-H); MS (m/z): 479 [M + H]$^+$; Anal. calcd. for $C_{24}H_{23}FN_6O_4$ (%): C 60.25, H 4.85, N 17.56; Found: C 60.41, H 4.73, N 17.74。

3-硝基-苯甲醛环丙沙星酰腙(**3k**),收率 85%, mp: 232 ~ 234 ℃; ^{1}H NMR (DMSO-d_6) δ: 13.16 (s, 1H, CONH), 8.82 (s, 1H, 2-H), 8.44 (s, 1H, N = CH), 8.15 (d, J = 13.2 Hz, 1H, 5-H), 8.07 (d, J = 7.5 Hz, 2H, Ph-H), 7.88 (d, J = 7.2 Hz, 1H, 8-H), 7.75 (d, J = 7.5 Hz, 2H, Ph-H), 3.76 ~ 3.69 (m, 1H, 1′-H), 3.36 ~ 3.27 (m, 4H, 2 × 2″-H), 2.65 ~ 2.54 (m, 4H, 2 × 3″-H), 1.21 ~ 1.26 (m, 4H, 2 × 2′-H); MS (m/z): 479 [M + H]$^+$; Anal. calcd. for $C_{24}H_{23}FN_6O_4$ (%): C 60.25, H 4.85, N 17.56; Found: C 60.47, H 4.97, N 17.68。

2-硝基-苯甲醛环丙沙星酰腙(**3l**),收率 81%, mp: 213 ~ 215 ℃; ^{1}H NMR (DMSO-d_6) δ: 13.24 (s, 1H, CONH), 8.87 (s, 1H, 2-H), 8.41 (s, 1H, N = CH), 8.09 (d, J = 13.2 Hz, 1H, 5-H), 8.02 (d, J = 7.5 Hz, 2H, Ph-H), 7.85 (d, J = 7.2 Hz, 1H, 8-H), 7.68 (d, J = 7.5 Hz, 2H, Ph-H), 3.76 ~ 3.71 (m, 1H, 1′-H), 3.40 ~ 3.31 (m, 4H, 2 × 2″-H), 2.68 ~ 2.62 (m, 4H, 2 × 3″-H), 1.19 ~ 1.25 (m, 4H, 2 × 2′-H); MS (m/z): 479 [M + H]$^+$; Anal. calcd. for $C_{24}H_{23}FN_6O_4$ (%): C 60.25, H 4.85, N 17.56; Found: C 60.38, H 4.68, N 17.72。

N′-硝基苄基-1-环丙基-6-氟-7-哌嗪-1-基-喹啉-4(1*H*)-酮-3-甲酰肼(**4a**,**4b**,**4c**)的合成

N′-硝基苄基-环丙沙星酰腙 **3**(1.0 g, 2.1 mmol)悬浮于干甲醇(20 mL)中,冰浴下慢慢滴加等物质量的硼氢化钠(76.0 mmg, 2.1 mmol)甲醇液(10 mL),常温搅拌 2 h,减压蒸干溶剂。加入蒸馏水(10 mL)分散残留物,用冰乙酸酸化至 pH 5.0,加入适量活性炭脱色,过滤。滤液用浓氨水碱化至 pH 8.0,放置析出固体,过滤,水涤。用无水乙醇重结晶,得固体目标化合物环丙沙星酰腙取代物 **4a**,**4b**,**4c**。

N′-(4-硝基苄基)-1-环丙基-6-氟-7-哌嗪-1-基-喹啉-4(1*H*)-酮-3-甲酰肼(**4a**),收率 81%, mp: 215 ~ 217 ℃; ^{1}H NMR (DMSO-d_6) δ: 13.18 (s, 1H, CONH), 8.78 (s, 1H, 2-H), 8.36 (s, 1H, N = CH), 7.85 (d, J = 13.2 Hz, 1H, 5-H), 7.82 ~ 7.58 (m, 5H, 8-H, Ph-H), 4.56 (br. s, 1H, NH), 3.78 ~ 3.74 (m, 1H, 1′-H), 3.55 (s, 2H, NCH_2), 3.31 ~ 2.62 (m, 8H, piperazine-H), 2.27 (s, 3H, NCH_3), 1.32 ~ 1.16 (m, 4H, CH_2CH_2); MS (m/z): 481 [M + H]$^+$; Anal. calcd. for $C_{24}H_{25}FN_6O_4$ (%): C 59.99, H 5.24, N 17.49; Found: C 60.18, H 5.42, N 17.71。

N′-(3-硝基苄基)-1-环丙基-6-氟-7-哌嗪-1-基-喹啉-4(1*H*)-酮-3-甲酰肼(**4b**),收率 74%, mp: 204 ~ 206 ℃; ^{1}H NMR (DMSO-d_6) δ: 13.17 (s, 1H, CONH), 8.82 (s, 1H, 2-

H),8.35(s,1H,N=CH),7.84(d,J=13.2 Hz,1H,5-H),7.80~7.61(m,5H,8-H,Ph-H),4.57(br.s,1H,NH),3.80~3.76(m,1H,1′-H),3.57(s,2H,NCH_2),3.35~2.58(m,8H,piperazine-H),2.29(s,3H,NCH_3),1.34~1.18(m,4H,CH_2CH_2);MS (m/z):481[M+H]$^+$;Anal. calcd. for $C_{24}H_{25}FN_6O_4$(%):C 59.99,H 5.24,N 17.49;Found:C 60.16,H 5.07,N 17.68。

N′-(2-硝基苄基)-1-环丙基-6-氟-7-哌嗪-1-基-喹啉-4(1*H*)-酮-3-甲酰肼(**4c**),收率72%,mp:216~218 ℃;^{1}H NMR(DMSO-d_6)δ:13.22(s,1H,CONH),8.78(s,1H,2-H),8.32(s,1H,N=CH),7.80(d,J=13.2 Hz,1H,5-H),7.83~7.64(m,5H,8-H,Ph-H),4.58(br.s,1H,NH),3.83~3.77(m,1H,1′-H),3.54(s,2H,NCH_2),3.37~2.62(m,8H,piperazine-H),2.32(s,3H,NCH_3),1.36~1.22(m,4H,CH_2CH_2);MS (m/z):481[M+H]$^+$;Anal. calcd. for $C_{24}H_{25}FN_6O_4$(%):C 59.99,H 5.24,N 17.49;Found:C 60.25,H 5.04,N 17.73。

3 抗肿瘤活性评价

对合成的12个环丙沙星酰腙(**3a~3l**)目标化合物及3个*N*′-(硝基苄基)环丙沙星酰肼(**4a**,**4b**,**4c**)进行抗肿瘤活性评价,将合成的化合物和对照品蒽醌类抗肿瘤药阿霉素(DOX)及母体环丙沙星(CFX)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,按文献[7]的方法,求出对人肝癌细胞(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 Inhibitory activities of acylhydrazones(**3a-3l**) against SMMC-7721,L1210 and HL60 tumor cells

Compd.	IC_{50}/(μmol/L)		
	SMMC-7721	L1210	HL60
3a	25.6±1.6	32.9±2.4	37.6±2.5
3b	18.3±1.5	27.3±2.4	30.7±2.8
3c	28.4±2.3	37.8±3.0	38.7±2.6
3d	30.5±2.7	38.8±3.2	42.4±2.7
3e	20.6±2.1	28.6±1.8	27.4±2.2
3f	28.4±1.8	37.3±2.7	40.5±2.3
3g	35.1±2.7	47.8±3.5	48.0±2.5
3h	27.6±1.3	38.7±3.0	42.5±2.7
3i	27.6±1.3	38.7±3.0	42.5±2.7
3j	10.5±1.2	18.4±1.4	23.6±2.2
3k	15.3±1.4	20.5±2.6	27.3±1.5
3l	9.6±1.0	23.6±1.6	28.8±1.3
4a	>100	>150	>150
4b	>100	>150	>150
4c	>100	>150	>150
DOX	1.8±0.5	3.7±0.7	3.2±0.4
PFX	>150	>150	>150

DOX:Doxorubicin;PFX:Profloxacin

体外抗肿瘤筛选结果(表1)表明,12个酰腙目标化合物对3种试验肿瘤细胞株抑制活性(<50.0 μmol/L)虽然低于阿霉素的活性,但均显著强于环丙沙星**1**(>150 μmol/L),尤其对肝癌细胞(SMMC-7721)的抑制活性高于对白血病细胞(L1210和HL60)的活性,显示出了一定的选择性。初步的构效关系表明,苯甲醛的取代基为吸电子基团如硝基时,其酰腙的抗肿瘤活性强于带供电子基如甲氧基化合物的活性,这可能是吸电子基团能够活化酰腙的亚胺N=C双键;同时,除酚羟基苯基外,随着苯环取代基体积的增大,活性降低。更有意义的是,对活性较强的硝基酰腙化合物(**3j**,**3k**,**3l**),其还原酰肼取代物(**4a**,**4b**,**4c**)的活性大大减低,表明抗肿瘤活性与酰腙亚胺N=C双键相关。由此可初步推测,由抗菌药氟喹诺酮发展抗肿瘤药氟喹诺酮保留其C-3羧基是不必要的,酰腙作为其等排体是必要的。

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