·论 文·

新型5-氨基-2-(苄基硫代)噻唑-4-甲酰胺类化合物的设计、合成及抗肿瘤活性

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摘 要 为了寻找具有更好抗肿瘤活性的化合物,设计合成了一系列5-氨基-2-(苄基硫代)噻唑-4-甲酰胺衍生物。以2-氨基-2-氰基-乙酰胺为起始原料,合成了16个化合物 **DDO-5401** ~ **DDO-5416**;目标化合物结构经IR、^{1}H NMR和ESI-MS确证;采用MTT法对目标化合物进行5株肿瘤细胞(HCT116、HepG2、A549、MDA-MB-231、MCF-7)体外抗肿瘤活性测定。合成的化合物对肿瘤细胞尤其是A549细胞表现出了良好的抑制活性;构效关系研究表明,苯环上连有给电子基团的化合物抑制活性要好于连有吸电子基团的化合物。化合物 **DDO-5413** 的抑制活性最强,对乳腺癌细胞MDA-MB-231和MCF-7抑制活性好于阳性对照药达沙替尼,值得进一步研究。

关键词 5-氨基-2-(苄基硫代)噻唑-4-甲酰胺类衍生物;合成;抗肿瘤活性

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Design, synthesis and anti-tumor activity of novel 5-amino-2-(benzylthio) thiazole-4-carboxamide derivatives

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Abstract A series of 5-amino-2-(benzylthio) thiazole-4-carboxamide derivatives were designed and synthesized to discover novel compounds with anti-tumor activity. Compounds **DDO-5401-DDO-5416** were synthesized using 2-amino-2-cyanoacetamide as the start material. The structures of the synthesized compounds were confirmed by IR, ^{1}H NMR and ESI-MS. The *in vitro* anti-tumor activities of the synthesized compounds were determined by MTT assay in HCT116, HepG2, A549, MDA-MB-231 and MCF-7 cell lines. Target compounds showed good anti-tumor activity especially in A549 cell line. SAR study showed that electron donating groups were more favorable than electron absorption ones. Compound **DDO-5413** exhibited noteworthy activity in MDA-MB-231 and MCF-7 cell lines with IC_{50} value lower than the positive reference dasatinib. It suggested that **DDO-5413** might be the candidate for further investigation.

Key words 5-amino-2-(benzylthio) thiazole-4-carboxamide derivatives; synthesis; anti-tumor activity

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噻唑是咪唑、噁唑、三唑、吡啶等杂环的生物电子等排体,将一些药物结构中的咪唑、吡啶等杂环替换为噻唑后能够增强药物作用时间及药物作用效果,提高生物利用度[1-2],使其成为了新化学实体合成中重要的片段之一。在医药领域,许多天然或合成的化合物含有噻唑结构片段,并表现出了广泛的生物学活性[3-6]。分析其原因可能是噻唑环能与蛋白靶标形成多种类型的相互作用,同时,环上有多个取代位点,能够合成多种结构类型的化合物。

目前噻唑类抗肿瘤药物达沙替尼(dasatinib)、达拉菲尼(dabrafenib)、伊沙匹隆(ixabepilone)、噻唑呋林(tiazofurine)、博来霉素(bleomycin)等对肿瘤细胞的增殖抑制活性 IC_{50} 达到了微摩尔水平,已经成功应用于临床,并取得了良好的治疗效果[7-9](图 1)。

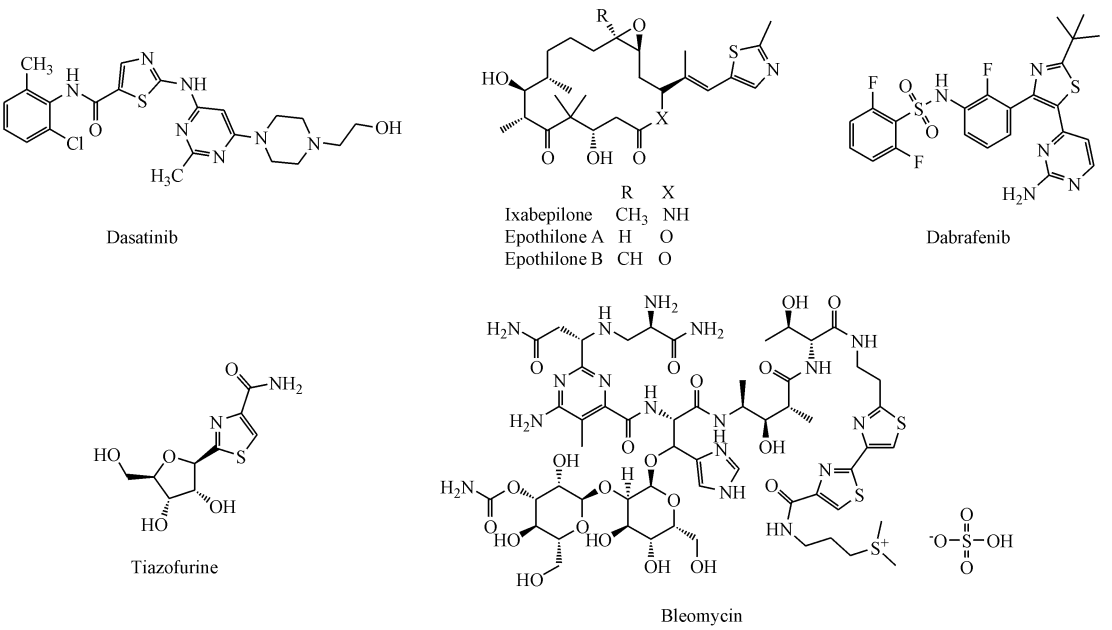
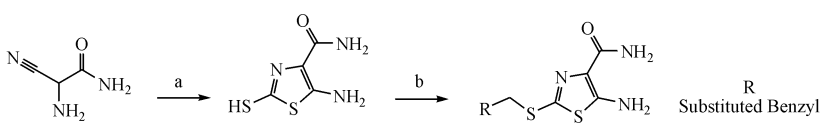


Figure 1　Structure of anti-tumor drugs with thiazole scaffold

为了获得具有较好抗肿瘤活性的化合物,对上述噻吩类抗肿瘤药物结构分析,应用拼合原理设计并合成了一系列具有 5-氨基-2-(苄基硫代)噻唑-4-甲酰胺结构片段的化合物 **DDO-5401 ~ DDO-5416**。该系列化合物表现出了良好的抗肿瘤活性,其中化合物 **DDO-5413** 对于肿瘤细胞的增殖抑制 IC_{50} 达到了微摩尔水平,具有进一步研究的价值。

1　合成路线

以 2-氨基-2-氰基乙酰胺为起始原料,与二硫化碳在甲醇回流条件下发生环合反应得到化合物 5-氨基-2-巯基噻唑-4-甲酰胺 **1a**[10],然后与取代的氯苄发生取代反应得到 **DDO-5401 ~ DDO-5416** 共 16 个终产物(表 1),合成方法见路线 1。



Scheme 1　Synthetic route of the target compounds **DDO-5401 - DDO-5416**

Reagents and conditions: (a) CS_2, MeOH, reflux, 5 d, 45.0%; (b) substituted benzyl chloride, K_2CO_3, DCM, reflux, 12 ~ 36 h, 15.6% -75.5%

2 实验部分

2.1 仪器和试剂

Melt-Temp Ⅱ熔点仪,温度计未校正;Bruker AV-300型核磁共振仪;$CDCl_3$和DMSO-d_6为溶剂,TMS为内标;IR采用KBr压片;Agilent 1946A-MSD型质谱仪(ESI-MS);柱色谱采用青岛海浪硅胶干燥剂厂生产的160~200目硅胶;薄层色谱采用烟台江友硅胶开发有限公司生产的GF_{254}薄层色谱硅胶。2-氨基-2-氰基乙酰胺(2-Amino-2-Cyanoacetamide,Acros);其他所用化学试剂均为分析纯或化学纯。人结肠癌细胞株HCT116、人肝癌细胞株HepG2、人肺癌细胞株A549、人乳腺癌细胞株MDA-MB-231、MCF-7(中国科学院典型培养物保藏委员会细胞库)。

2.2 化学合成

5-氨基-2-巯基噻唑-4-甲酰胺(**1a**) 2-氨基-2-氰基乙酰胺(4.950 g,50 mmol)溶于甲醇20 mL,加入二硫化碳10 mL,加热回流5d,TLC在碘的条件下显示反应完全。反应冷却后抽滤,固体用乙酸乙酯洗涤,干燥后得到土黄色固体**1a**(3.938 g,45.0%):mp:245.3~246.4 ℃;^{1}H NMR(DMSO-d_6,300 MHz) δ:(s,1H,-$\underline{NH_2}$),7.26(s,1H,-$\underline{NH_2}$),7.65(s,2H,-CO$\underline{NH_2}$);EI-MS *m/z* 173.98 $[M-H]^-$。

5-氨基-2-(苄基巯基)噻唑-4-甲酰胺(**DDO-5401**) 中间体**1a**(0.175 g,1 mmol)与苄基氯(114 μL,1 mmol)以K_2CO_3(0.207 g,1.5 mmol)为催化剂在二氯甲烷20 mL加热回流条件下反应。TLC在碘的条件下显示反应结束后浓缩,柱色谱分离,洗脱液为石油醚-乙酸乙酯(1:2),得到5-氨基-2-(苄基巯基)噻唑-4-甲酰胺(**DDO-5401**)白色固体,0.201 g,75.8%。mp:142.9~143.2 ℃;IR(KBr,ν):3 412.13,3 303.94,1 648.55,1 577.46,1 493.00,1 450.93,1 432.20,1 314.46,1 258.69,1 076.53,1 006.88,701.87,600.04;^{1}H NMR(300 MHz,DMSO-d_6) δ:4.29(2H,s,-$\underline{CH_2}$-Ar),7.03(1H,s,-$\underline{NH_2}$),7.16(1H,s,-$\underline{NH_2}$),7.19(2H,s,-CO$\underline{NH_2}$),7.24~7.32(5H,m,Ar-H);HRMS(ESI$^+$,*m/z*):Calcd. for $[C_{11}H_{11}N_3OS_2+H]^+$ 266.041 6 Found 266.041 7。

用类似的方法制备得到目标化合物**DDO-5402~DDO-5416**。

5-氨基-2-[(4-氟苄基)硫代]噻唑-4-甲酰胺(**DDO-5402**) 白色固体,0.188 g,66.3%。mp:112.3~114.0 ℃;IR(KBr,ν):3 414.18,3 240.62,3 133.58,2 360.69,1 658.80,1 638.26,1 617.17,1 561.06,1 508.81,1 485.91,1 441.76,1 424.44,1 261.02,1 227.03,1 100.22,1 015.82,1 000.65,838.48,799.90;^{1}H NMR(300 MHz,DMSO-d_6) δ:4.32(2H,s,-$\underline{CH_2}$-Ar),7.07(1H,s,-$\underline{NH_2}$),7.14(2H,d,-CO$\underline{NH_2}$),7.20(1H,s,-$\underline{NH_2}$),7.24(2H,d,J=8.64 Hz,Ar-H),7.39(2H,t,J=7.95 Hz,Ar-H);HRMS(ESI$^+$,*m/z*):Calcd. for $[C_{11}H_{10}FN_3OS_2+Na]^+$ 306.014 2,Found 306.014 6。

5-氨基-2-[(4-氯苄基)硫代]噻唑-4-甲酰胺(**DDO-5403**) 粉红色固体,0.191 g,63.7%。mp:163.7~165.9 ℃;IR(KBr,ν):3 413.80,3 367.05,3 243.91,3 131.58,2 963.18,1 657.64,1 599.75,1 561.07,1 490.71,1 443.16,1 422.52,1 261.32,1 096.29,1 016.25,836.48,802.14;^{1}H NMR(300 MHz,DMSO-d_6) δ:4.29(2H,s,-$\underline{CH_2}$-Ar),7.04(1H,s,-$\underline{NH_2}$),7.18(1H,s,-$\underline{NH_2}$),7.20(2H,s,-CO $\underline{NH_2}$),7.34(4H,d,J=8.82 Hz,Ar-H);HRMS(ESI$^+$,*m/z*):Calcd. for $[C_{11}H_{10}ClN_3OS_2+H]^+$ 300.002 7,Found 300.003 1。

5-氨基-2-[(4-溴苄基)硫代]噻唑-4-甲酰胺(**DDO-5404**) 浅黄色固体,0.126 g,36.6%。mp:169.2~171.5 ℃;IR(KBr,ν):3 415.29,3 249.80,3 128.26,2 963.31,1 657.04,1 561.07,1 486.28,1 442.60,1 421.79,1 261.60,1 098.27,1 021.39,800.57;^{1}H NMR(300 MHz,DMSO-d_6) δ:4.30(2H,s,-$\underline{CH_2}$-Ar),7.07(1H,s,-$\underline{NH_2}$),7.23(3H,s,-CONH$_2$,-$\underline{NH_2}$),7.32(2H,d,J=7.74 Hz,Ar-H),7.52(2H,d,J=7.26 Hz,Ar-H);HRMS(ESI$^+$,*m/z*):Calcd. for $[C_{11}H_{10}BrN_3OS_2+H]^+$ 343.952 1,Found 343.952 2。

5-氨基-2-[(3-氟苄基)硫代]噻唑-4-甲酰胺(**DDO-5405**) 粉红色固体,0.186 g,65.6%。mp:109.3~110 ℃;IR(KBr,ν):3 552.71,3 415.51,3 255.29,3 133.20,1 659.02,1 637.90,1 616.97,1 560.84,1 487.75,1 443.17,1 422.92,1 260.93,1 098.73,1 021.05,800.88;^{1}H NMR(300 MHz,DMSO-d_6) δ:4.34(2H,s,-$\underline{CH_2}$-Ar),

7.08 ~ 7.14 (2H, m, -NH_2), 7.19 (1H, d, J = 2.67 Hz, -NH_2), 7.22 (4H, d, J = 5.37 Hz, Ar-H, -NH_2), 7.33 ~ 7.41 (1H, m, Ar-H); HRMS (ESI$^+$, m/z): Calcd. for [$C_{11}H_{10}FN_3OS_2$ + Na]$^+$ 306.014 2, Found 306.014 4。

5-氨基-2-[(2-氟苄基)硫代]噻唑-4-甲酰胺(**DDO-5406**)　浅黄色固体, 0.130 g, 60.0%。mp: 129.3 ~ 131.9 ℃; IR (KBr, ν): 3 464.36, 3 374.98, 3 262.17, 3 158.56, 1 654.26, 1 605.15, 1 579.97, 1 489.59, 1 440.59, 1 421.16, 1 225.06, 1 087.14, 1 012.10, 876.97, 769.48; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 4.32 (2H, s, -CH_2-Ar), 7.08 (1H, s, -NH_2), 7.12 (1H, d, J = 6.27 Hz, -NH_2), 7.18 (2H, t, J = 6.93 Hz, -CONH_2), 7.26 (2H, s, Ar-H), 7.31 ~ 7.43 (2H, m, Ar-H); HRMS (ESI$^+$, m/z): Calcd. for [$C_{11}H_{10}FN_3OS_2$ + Na]$^+$ 306.014 2, Found 306.014 4。

5-氨基-2-[(4-甲基苄基)硫代]噻唑-4-甲酰胺(**DDO-5407**)　粉红色固体, 0.172 g, 61.6%。mp: 165.1 ~ 167.6 ℃; IR (KBr, ν): 3 416.10, 3 366.67, 3 246.29, 3 130.64, 2 963.60, 2 360.39, 2 341.93, 1 658.09, 1 601.02, 1 563.67, 1 512.30, 1 486.29, 1 443.59, 1 424.21, 1 320.52, 1 261.64, 1 098.22, 1 022.17, 862.76, 800.81, 685.62, 518.52, 473.12; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.28 (3H, s, -CH_3), 4.28 (2H, s, -CH_2-Ar), 7.06 (1H, s, -NH_2), 7.13 (2H, d, J = 7.92 Hz, -CONH_2), 7.19 (1H, s, -NH_2), 7.22 (3H, d, J = 2.49 Hz, Ar-H), 7.25 (1H, s, Ar-H); HRMS (ESI$^+$, m/z): Calcd. for [$C_{12}H_{13}N_3OS_2$ + H]$^+$ 280.057 3, Found 280.057 5。

5-氨基-2-[(3-甲基苄基)硫代]噻唑-4-甲酰胺(**DDO-5408**)　浅黄色固体, 0.158 g, 56.6%。mp: 94.3 ~ 96.4 ℃; IR (KBr, ν): 3 413.43, 3 371.26, 3 253.90, 3 128.89, 2 963.76, 1 660.52, 1 604.12, 1 560.97, 1 486.44, 1 442.56, 1 319.89, 1 260.00, 1 100.64, 999.24, 793.55; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.29 (3H, s, -CH_3), 4.28 (2H, s, -CH_2-Ar), 7.08 (2H, d, J = 7.32 Hz, -NH_2), 7.13 (2H, d, J = 7.92 Hz, -CONH_2), 7.19 (2H, s, -NH_2), 7.22 (2H, d, J = 3.00 Hz, Ar-H), 7.25 (1H, s, Ar-H); HRMS (ESI$^+$, m/z): Calcd. for [$C_{12}H_{13}N_3OS_2$ + Na]$^+$ 302.039 2, Found 302.039 4。

5-氨基-2-[(2-甲基苄基)硫代]噻唑-4-甲酰胺(**DDO-5409**)　黄色固体, 0.211 g, 75.5%。mp: 135.1 ~ 136.6 ℃; IR (KBr, ν): 3 461.18, 3 257.31, 3 154.39, 1 649.86, 1 598.64, 1 576.86, 1 485.92, 1 439.45, 1 418.89, 1 014.58, 724.99; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.35 (3H, s, -CH_3), 4.32 (2H, s, -CH_2-Ar), 7.09 (1H, d, J = 6.78 Hz, -NH_2), 7.14 (1H, d, J = 6.15 Hz, -CONH_2), 7.19 (3H, d, J = 3.54 Hz, Ar-H, -NH_2), 7.25 (3H, s, Ar-H); HRMS (ESI$^+$, m/z): Calcd. for [$C_{12}H_{13}N_3OS_2$ + Na]$^+$ 302.039 2, Found 302.039 1。

5-氨基-2-[(4-硝基苄基)硫代]噻唑-4-甲酰胺(**DDO-5410**)　红褐色固体, 0.174 g, 56.1%。mp: 149.3 ~ 151.1 ℃; IR (KBr, ν): 3 552.89, 3 442.21, 3 414.13, 3 296.04, 3 173.73, 2 962.99, 1 647.84, 1 617.75, 1 594.89, 1 519.56, 1 500.70, 1 432.16, 1 345.35, 1 315.02, 1 261.45, 1 092.25, 1 014.13, 859.88, 804.27; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 4.46 (2H, s, -CH_2-Ar), 7.09 (1H, s, -NH_2), 7.21 (1H, s, -NH_2), 7.24 (2H, s, -CONH_2), 7.64 (2H, d, J = 8.64 Hz, Ar-H), 8.20 (2H, d, J = 8.67 Hz, Ar-H); HRMS (ESI$^+$, m/z): Calcd. for [$C_{11}H_{10}N_4O_3S_2$ + H]$^+$ 311.026 7, Found 311.026 9。

5-氨基-2-[(3-硝基苄基)硫代]噻唑-4-甲酰胺(**DDO-5411**)　橘黄色固体, 0.159 g, 51.3%。mp: 144.5 ~ 146.1 ℃; IR (KBr, ν): 3 471.32, 3 390.23, 3 274.13, 3 124.16, 1 666.83, 1 637.87, 1 601.11, 1 573.99, 1 525.41, 1 484.13, 1 439.21, 1 421.79, 1 348.10, 1 328.45, 1 077.46, 1 010.84, 878.07, 816.05, 806.40, 783.15, 745.40, 692.81, 678.25, 492.81; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 4.46 (2H, s, -CH_2-Ar), 7.07 (1H, s, -NH_2), 7.20 (3H, s, -CONH_2, -NH_2), 7.60 (1H, t, J = 6.55 Hz, Ar-H), 7.80 (1H, d, J = 7.35 Hz, Ar-H), 8.11 (1H, d, J = 7.05 Hz, Ar-H), 8.26 (1H, s, Ar-H); HRMS (ESI$^+$, m/z): Calcd. for [$C_{11}H_{10}N_4O_3S_2$ + H]$^+$ 311.026 7, Found 311.026 6。

5-氨基-2-[(2-硝基苄基)硫代]噻唑-4-甲酰胺(**DDO-5412**)　鲜黄色固体, 0.146 g, 47.1%。mp: 114.7 ~ 115.2 ℃; IR (KBr, ν): 3 567.98, 3 465.11, 3 262.04, 3 150.09, 2 361.53, 2 344.48,

1 647.96,1 576.59,1 518.77,1 481.86,1 418.84,1 340.46,1 324.75,1 263.53,1 231.71,1 196.47,1 122.18,1 009.32,784.27;^{1}H NMR(300 MHz,DMSO-d_6) δ:4.58(2H,s,-$\underline{CH_2}$-Ar),7.08(1H,s,-$\underline{NH_2}$),7.19(1H,s,-$\underline{NH_2}$),7.23(2H,s,-CO$\underline{NH_2}$),7.56(2H,d,J=9.21 Hz,Ar-H),7.66(1H,d,J=6.59 Hz,Ar-H),8.05(1H,d,J=8.37 Hz,Ar-H);HRMS(ESI$^+$,m/z):Calcd. for[$C_{11}H_{10}N_4O_3S_2$+H]$^+$ 311.026 7,Found 311.027 2。

5-氨基-2-{[4-(叔丁基)苄基]硫代}噻唑-4-甲酰胺(**DDO-5413**) 白色固体,0.191 g,61.1%。mp:146.3 ~ 148.7 ℃;IR(KBr,ν):3 467.68,3 374.71,3 260.47,3 170.71,2 962.06,1 645.22,1 591.38,1 573.92,1 496.50,1 424.21,1 365.57,1 317.17,1 267.93,1 242.27,1 106.98,1 015.65,839.01,787.12,663.41,560.60,519.75,500.04;^{1}H NMR(300 MHz,DMSO-d_6) δ:1.27(9H,s,-C($\underline{CH_3}$)$_3$),4.30(2H,s,-$\underline{CH_2}$-Ar),7.07(1H,s,-$\underline{NH_2}$),7.19(1H,s,-$\underline{NH_2}$),7.23(2H,s,-CO $\underline{NH_2}$),7.32(4H,dd,J=8.34,19.65 Hz,Ar-H);HRMS(ESI$^+$,m/z):Calcd. for[$C_{15}H_{19}N_3OS_2$+H]$^+$ 322.104 2,Found 322.104 3。

5-氨基-2-[(萘-1-甲基)硫代]噻唑-4-甲酰胺(**DDO-5414**) 粉红色固体,0.185 g,58.7%。mp:219.8 ~ 221.2 ℃;IR(KBr,ν):3 472.25,3 384.30,3 278.68,2 963.53,1 640.65,1 602.68,1 570.67,1 424.97,1 261.99,1 097.20,1 018.84,801.64;^{1}H NMR(300 MHz,DMSO-d_6) δ:4.81(2H,s,-$\underline{CH_2}$-Ar),7.08(1H,s,-$\underline{NH_2}$),7.23(3H,s,-$\underline{NH_2}$,-CO$\underline{NH_2}$),7.46(2H,s,Ar-H),7.57(2H,s,Ar-H),7.91(2H,d,J=1.86 Hz,Ar-H),8.19(1H,s,Ar-H);HRMS(ESI$^+$,m/z):Calcd. for[$C_{15}H_{13}N_3OS_2$+H]$^+$ 316.057 3,Found 316.057 1。

5-氨基-2-[(3-甲氧基苄基)硫代]噻唑-4-甲酰胺(**DDO-5415**) 白色固体,0.103 g,34.9%。mp:249.9 ~ 252.3 ℃;IR(KBr,ν):3 416.70,3 368.46,3 250.13,3 131.10,1 657.92,1 607.82,1 583.19,1 563.33,1 488.32,1 442.47,1 424.70,1 265.44,1 152.68,1 046.61,1 001.22,801.62;^{1}H NMR(300 MHz,DMSO-d_6) δ:3.73(3H,s,-O$\underline{CH_3}$),4.29(2H,s,-$\underline{CH_2}$-Ar),6.82(1H,d,J=8.37 Hz,-$\underline{NH_2}$),6.85(2H,s,-CO$\underline{NH_2}$),6.94(1H,s,-$\underline{NH_2}$),7.22(4H,s,Ar-H);HRMS(ESI$^+$,m/z):Calcd. for[$C_{12}H_{13}N_3NaO_2S_2$+Na]$^+$ 318.034 1,Found 318.033 7。

5-氨基-2-[(2-甲氧基苄基)硫代]噻唑-4-甲酰胺(**DDO-5416**) 黄色固体,0.046 g,15.6%。mp:252.7 ~ 254.9 ℃;IR(KBr,ν):3 451.26,3 367.37,3 258.73,3 155.77,2 963.44,1 652.80,1 599.09,1 578.29,1 491.86,1 430.32,1 261.73,1 000.86,1 024.35,800.23,757.63;^{1}H NMR(300 MHz,DMSO-d_6) δ:3.78(3H,s,-O$\underline{CH_3}$),4.22(2H,s,-$\underline{CH_2}$-Ar),6.86(1H,t,J=7.35 Hz,-$\underline{NH_2}$),6.98(1H,d,J=8.10 Hz,-$\underline{NH_2}$),7.04(1H,s,-CO$\underline{NH_2}$),7.21 ~ 7.28(5H,m,-CO$\underline{NH_2}$,Ar-H);HRMS(ESI$^+$,m/z):Calcd. for[$C_{12}H_{13}N_3NaO_2S_2$+H]$^+$ 296.052 2,Found 296.051 7。

2.3 体外抗肿瘤活性实验

采用MTT法评价了16个化合物对体外肿瘤细胞增殖的抑制活性[11],选用了人结肠癌细胞(HCT116)、人肝癌细胞(HepG2)、人肺癌细胞(A549)、人乳腺癌细胞(MDA-MB-231、MCF-7)共5株细胞,阳性对照药为噻唑类上市药物达沙替尼。

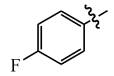
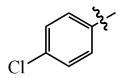
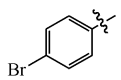
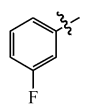
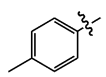
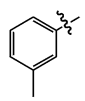
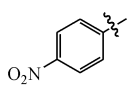
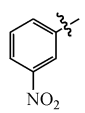
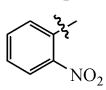
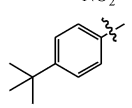
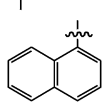
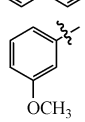
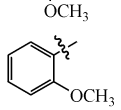
测试时,取处于指数生长期、状态良好的细胞(每孔4 000 ~ 5 000个细胞)接种于96孔培养板,24 h后加入不同的化合物,置于37 ℃、5% CO_2条件下培养48 h。每孔加入5 mg/mL MTT溶液20 μL,继续孵育4 h,吸弃孔内上清液,每孔加入DMSO 150 μL,振荡10 min,使结晶物充分溶解。酶标仪测定吸收度,结果见表1。

初步构效关系分析表明,当苯环上连有甲基、叔丁基等给电子基团时,化合物活性明显好于连有硝基、卤素等吸电子基团的化合物。

当苯环上连有体积较大的给电子取代基时,如含有叔丁基取代的化合物**DDO-5413**活性最好,一般来说邻位取代和间位取代活性优于对位取代活性,如苯环上连有甲基取代的3个化合物**DDO-5407**、**DDO-5408**和**DDO-5409**,邻位和间位取代时活性明显好于对位取代,且对位取代的**DDO-5407**即使在对化合物敏感性最高的A549细胞中抑制活性也仅达到16 μmol/L;苯环上连有甲氧基的邻位取代的化合物**DDO-5416**和间位取代的化合物**DDO-5415**活性在HCT116、A549、MCF-7细胞株中

抑制活性基本相当,而在 HepG2 和 MDA-MB-231 细胞株中差距较大,**DDO-5416** 的抑制活性明显好于 **DDO-5415**。

Table 1　Antiproliferation activity of compounds **DDO-5401** - **DDO-5416** against tumor cells ($\bar{x} \pm s, n = 3$)

Compd.	R	IC_{50}/(μmol/L)				
		HCT116	HepG2	A549	MDA-MB-231	MCF-7
DDO-5401		9.45 ± 0.31	38.57 ± 1.58	34.59 ± 1.91	34.89 ± 0.21	21.17 ± 0.93
DDO-5402		55.83 ± 1.49	33.88 ± 1.51	33.33 ± 0.58	51.61 ± 0.17	38.02 ± 1.41
DDO-5403		37.76 ± 0.68	33.43 ± 1.85	13.88 ± 0.38	34.51 ± 0.16	35.39 ± 1.73
DDO-5404		7.21 ± 0.48	32.88 ± 1.44	39.61 ± 0.71	16.41 ± 0.13	27.56 ± 1.32
DDO-5405		15.63 ± 0.54	21.38 ± 1.02	29.95 ± 0.60	22.37 ± 0.95	34.21 ± 1.57
DDO-5406		16.81 ± 0.60	34.31 ± 2.03	17.07 ± 0.84	23.81 ± 0.21	31.97 ± 1.42
DDO-5407		37.91 ± 1.08	22.61 ± 1.05	16.59 ± 0.85	38.10 ± 0.27	55.83 ± 1.49
DDO-5408		30.21 ± 1.78	11.57 ± 1.12	7.22 ± 0.55	7.10 ± 0.32	18.43 ± 1.28
DDO-5409		16.20 ± 0.68	26.12 ± 1.56	13.37 ± 0.90	8.84 ± 0.29	15.54 ± 1.07
DDO-5410		38.08 ± 0.74	50.48 ± 1.44	40.64 ± 0.53	7.38 ± 0.23	39.79 ± 1.21
DDO-5411		26.94 ± 0.71	52.95 ± 1.98	9.85 ± 0.90	21.07 ± 1.22	18.74 ± 1.30
DDO-5412		30.65 ± 0.90	36.95 ± 1.59	20.15 ± 0.92	30.75 ± 0.70	26.13 ± 3.55
DDO-5413		7.26 ± 1.19	20.35 ± 1.67	8.99 ± 0.86	4.40 ± 0.52	6.52 ± 0.66
DDO-5414		27.30 ± 1.31	30.71 ± 1.20	18.62 ± 0.98	22.52 ± 0.17	13.36 ± 1.08
DDO-5415		25.84 ± 0.75	48.92 ± 1.12	11.28 ± 1.24	40.27 ± 0.48	16.47 ± 0.94
DDO-5416		21.88 ± 0.60	36.38 ± 1.37	11.48 ± 0.74	13.87 ± 0.70	17.67 ± 1.48
Dasatinib		17.37 ± 1.48	28.09 ± 2.05	50.48 ± 1.44	12.75 ± 0.21	89.03 ± 1.55

当苯环上连有吸电子取代基团时,含有强吸电子取代基团(如硝基)取代的化合物活性最差;卤原子取代时活性顺序大致为溴 > 氯 > 氟,同样邻位取代和间位取代活性优于对位取代活性,如苯环含有硝基取代的化合物 **DDO-5410**、**DDO-5411**、**DDO-5412** 除了在 MDA-MB-231 细胞中对位取代的 **DDO-5410** 表现了较好的抑制活性外,其他 4 株细胞中对位取代的活性明显差于邻位和对位取代活性。

化合物对于 5 株肿瘤细胞增殖抑制活性具有一定的选择性。大多数的化合物对 A549 细胞的抑制活性要强于 HCT116 细胞和 MDA-MB-231 细胞,对 HepG2 细胞的抑制活性最差,说明了 A549 细胞对此类化合物敏感性更高。

化合物 **DDO-5413** 对 4 株细胞均具有良好的增殖抑制活性(IC_{50}在 4 ~ 9 μmol/L 之间),且化合物 **DDO-5413** 对 MDA-MB-231 和 MCF-7 细胞株的抑制活性略优于达沙替尼,对其他 3 株细胞的抑制活性略低于达沙替尼,具有进一步优化和开发的价值。

3 结 论

通过 MTT 抗肿瘤细胞增殖抑制实验对设计的含有 5-氨基-2-(苄基硫代)噻唑-4-甲酰胺结构片段的 16 个化合物进行测定,初步的构效关系分析表明,苯环上连有给电子取代基团时活性要优于吸电子取代基团,两种取代基团为邻位和对位取代时抑制活性要好于对位取代。大部分化合物对肿瘤细胞体外增殖表现出了较好的抑制活性,且化合物对不同肿瘤细胞表现出了一定的抑制活性差异,对 A549 细胞的抑制活性最好。化合物 **DDO-5413** 的肿瘤细胞增殖抑制活性最佳,对乳腺癌细胞的抑制活性较好,优于阳性对照药达沙替尼,对结肠癌细胞、肝癌细胞以及肺癌细胞的抑制活性略低于达沙替尼,具有进一步研究的价值。

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