

医药与日化原料

噻吩并[2,3-*d*]嘧啶类衍生物的合成及抗肿瘤活性

刘波^{1,2}, 高慧², 张梦丹^{1,2}, 杨平², 宋新建^{1,2*}

(1. 湖北民族大学 生物资源保护与利用湖北省重点实验室, 湖北 恩施 445000; 2. 湖北民族大学 化学与环境工程学院, 湖北 恩施 445000)

摘要: 以 2-丁酮、丙二腈和单质硫为原料, 通过改良的 Gewald 反应制备了 2-氨基-3-氰基-4,5-二甲基噻吩 (I), I 再与三氯氧磷和三氟乙酸反应“一锅法”合成了 5,6-二甲基-2-三氟甲基-4-氯噻吩并[2,3-*d*]嘧啶 (II), 中间体 II 分别与不同取代苄胺反应制得了 16 种噻吩并[2,3-*d*]嘧啶类含氟衍生物 (III a~III p)。通过 ¹H NMR、¹³C NMR、FTIR、MS 和元素分析对目标化合物进行了表征, 并采用 X 射线单晶衍射测定了 5,6-二甲基-2-三氟甲基-4-苄氨基噻吩并[2,3-*d*]嘧啶 (III a) 的晶体结构。对目标化合物的体外抗肿瘤活性进行了评价。结果表明, III a、5,6-二甲基-2-三氟甲基-4-(3-氟苄氨基)噻吩并[2,3-*d*]嘧啶 (III c) 和 5,6-二甲基-2-三氟甲基-4-(3-氯苄氨基)噻吩并[2,3-*d*]嘧啶 (III f) 表现出良好的抗肿瘤活性, 化合物 III a 对 MCF-7 和 HepG2 细胞的半数抑制浓度 (IC₅₀) 分别为 2.01 和 2.44 μmol/L, III c 对 MCF-7 和 HepG2 细胞的 IC₅₀ 分别为 1.44 和 1.47 μmol/L, 二者的活性均远优于对照组吉非替尼 (Gefitinib)。

关键词: 噻吩并[2,3-*d*]嘧啶; 含氟衍生物; 晶体结构; 抗肿瘤活性; 合成; 医药原料

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Synthesis and antitumor activity of thieno[2,3-*d*]pyrimidine derivatives

LIU Bo^{1,2}, GAO Hui², ZHANG Mengdan^{1,2}, YANG Ping², SONG Xinjian^{1,2*}

(1. Hubei Key Laboratory of Biological Resources Protection and Utilization, Hubei Minzu University, Enshi 445000, Hubei, China; 2. School of Chemistry and Environmental Engineering, Hubei Minzu University, Enshi 445000, Hubei, China)

Abstract: 2-Amino-3-carbonitrile-4,5-dimethylthiophene (I) was firstly prepared from modified Gewald reaction of butan-2-one, malononitrile and elemental sulfur. Sixteen fluorinated thieno[2,3-*d*]pyrimidine derivatives (III a~III p) were then synthesized *via* substitution reaction of substituted benzylamines with key intermediate 4-chloro-5,6-dimethyl-2-(trifluoromethyl)thieno[2,3-*d*]pyrimidine (II), which was obtained directly from one-pot reaction of compound I and trifluoroacetic acid in presence of phosphorous oxychloride. These sixteen derivatives obtained were characterized by ¹H NMR, ¹³C NMR, FTIR, MS and elemental analysis with the crystal structure of compound 5,6-dimethyl-2-trifluoromethyl-4-benzylaminothieno[2,3-*d*]pyrimidine (III a) determined by X-ray single-crystal diffraction, and further evaluated for their *in vitro* antitumor performance. The results indicated that compounds III a, 5,6-dimethyl-2-trifluoromethyl-4-(3-fluorobenzyl)aminothieno[2,3-*d*]pyrimidine (III c) and 5,6-dimethyl-2-trifluoromethyl-4-(3-chlorobenzyl)aminothieno[2,3-*d*]pyrimidine (III f) exhibited good *in vitro* antitumor activity. The half inhibitory concentration (IC₅₀) of compound III a against MCF-7 and HepG2 cells were 2.01 and 2.44 μmol/L, respectively, while those of III c against MCF-7 and HepG2 cells were 1.44 and 1.47 μmol/L, respectively. Both of III a and III c displayed much better antitumor activity than the control group Gefitinib.

Key words: thieno[2,3-*d*]pyrimidine; fluorinated derivatives; crystal structure; antitumor activity; synthesis; drug materials

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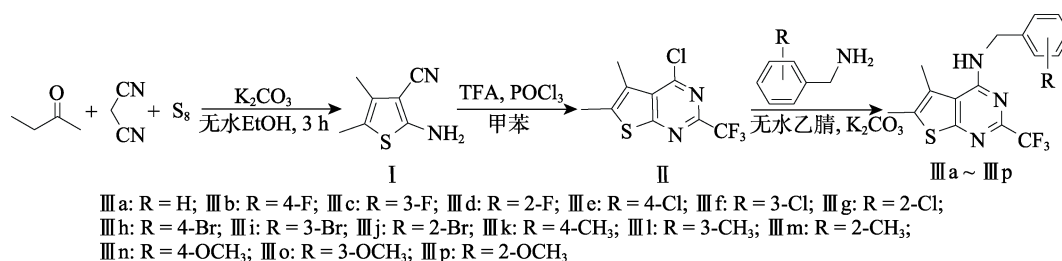
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作者简介: 刘波 (1990—), 男, 助理实验师, E-mail: liuboyao@163.com。联系人: 宋新建 (1975—), 男, 教授, E-mail: whxjsong@163.com。

噻吩并[2,3-*d*]嘧啶类化合物是一类结构独特的含氮稠杂环化合物, 具有广泛的生物活性, 如抑制 FLT3^[1]、PI3K^[2]、mTOR^[2]、表皮生长因子受体等激酶^[3]和微管蛋白活性^[4], 以及抗菌^[5]、抗病毒^[6]和抗肿瘤^[7-9]等。研究发现, 2-位和 4-位被取代的噻吩并[2,3-*d*]嘧啶类衍生物具有抗肿瘤^[10-11]、抗菌^[5]、抗病毒^[6]等许多药物活性。喹唑啉类酪氨酸激酶抑制剂是一类重要的抗癌药物, 如吉非替尼 (Gefitinib)、拉帕替尼 (Lapatinib)、埃罗替尼 (Erlotinib) 等。喹唑啉环作为一种化学结构基本单元, 是许多药物分子的重要组成部分。根据生物电子等排原理, 噻吩并[2,3-*d*]嘧啶环可视为喹唑啉环的生物电子等排体, 因其独特的结构和药理活性而常被用于抗癌药物分子设计, 噻吩并[2,3-*d*]嘧啶类化合物的抗肿瘤活性研究已屡见报道^[7-16]。

在药物分子的适当位置引入含氟基团可改变其理化性质, 如酸碱性、脂溶性和渗透效应等, 并可提高药物的代谢稳定性和靶向选择性, 因而含氟化合物已被广泛应用于医药和农药等领域^[8,17-18]。然而, 将含氟基团 (特别是三氟甲基) 引入到噻吩并[2,3-*d*]嘧啶环中还鲜有报道^[8]。为了从噻吩并[2,3-*d*]嘧啶类化合物中寻找高抗肿瘤活性的先导化合物, 并考察 *N*⁴-位苄基苯环上取代基的改变对抗肿瘤活性的影响, 本文在噻吩并[2,3-*d*]嘧啶环的 2-位引入三氟甲基、4-位引入不同的苄氨基, 设计并合成了 16 种噻吩并[2,3-*d*]嘧啶类含氟衍生物, 并以吉非替尼作为阳性对照组, 对其抗肿瘤活性进行研究, 为噻吩并[2,3-*d*]嘧啶类化合物的构效关系研究提供理论依据。

目标化合物的合成路线如下所示。



1 实验部分

1.1 主要试剂与仪器

所用试剂均为市售分析纯, 使用前均作无水处理。

Nicolet Avatar 370 型傅里叶变换红外光谱仪 (KBr 压片), 美国 Nicolet 公司; Thermo DSQ II 质谱仪 (EI 离子源), 美国 Thermo 公司; Avance-400 MHz 核磁共振波谱仪, 德国 Bruker 公司; Vario EL III CHNSO 型元素分析仪, 德国 Elementar 公司; X-4 型显微熔点测定仪, 北京泰克仪器有限公司; Bruker APEX-II 型 CCD 面探衍射仪, 德国 Bruker 公司。

1.2 化合物的制备

1.2.1 2-氨基-3-氟基-4,5-二甲基噻吩 (I) 的制备

向 100 mL 圆底烧瓶中加入 25 mL 无水乙醇, 搅拌下依次加入 0.72 g (10.00 mmol) 2-丁酮、0.66 g (10.00 mmol) 丙二腈、0.38 g (12.00 mmol) 单质硫、2.76 g (20.00 mmol) 碳酸钾, 回流反应 3 h。反应结束, 冷却至室温, 将反应液倒入 100 mL 冰水中, 析出大量固体, 抽滤得滤饼。经无水乙醇重结晶、60 °C 下减压干燥 2 h, 得 1.28 g 浅黄色固体 I, 产率 84%。¹HNMR (400 MHz, DMSO-*d*₆), δ: 6.88 (s, 2H, NH₂), 2.06 (s, 3H, 5-CH₃), 1.93 (s, 3H, 4-CH₃)。

1.2.2 5,6-二甲基-2-三氟甲基-4-氯噻吩并[2,3-*d*]嘧啶 (II) 的制备

冰水浴下, 向 50 mL 圆底烧瓶中加入 15 mL 甲苯,

搅拌下依次加入 1.52 g (10.00 mmol) 2-氨基-3-氟基-4,5-二甲基噻吩 (I)、1.5 mL (20.20 mmol) 三氟乙酸 (TFA) 和 3.0 mL (32.78 mmol) 新蒸的 POCl₃, 然后升温至 80 °C 反应 4 h。反应结束, 减压浓缩蒸去溶剂和剩余液体反应物。所得固体用乙酸乙酯 (10 mL×3 次) 溶解后过滤, 滤液减压浓缩后用正己烷重结晶, 再在 35 °C 下减压干燥 3 h, 得 1.79 g 淡黄色粉末状固体 II, 产率 67%。¹HNMR [400 MHz, (CD₃)₂CO], δ: 2.66 (s, 3H, 6-CH₃), 2.62 (s, 3H, 5-CH₃); ¹³CNMR [100 MHz, (CD₃)₂CO], δ: 173.1, 158.9, 153.9, 145.9, 135.5, 130.8, 126.1, 18.6, 18.4。

1.2.3 目标化合物 (III a~III p) 的制备

向 50 mL 圆底烧瓶中依次加入 2.67 g (10.00 mmol) 5,6-二甲基-2-三氟甲基-4-氯噻吩并[2,3-*d*]嘧啶 (II)、10.00 mmol 取代苄胺、1.38 g (10.00 mmol) 碳酸钾和 25 mL 无水乙腈, 升温至 80 °C 反应, TLC 监测至反应结束 [洗脱剂: *V*(乙酸乙酯): *V*(石油醚) = 1 : 3]。减压浓缩后经柱层析 [吸附剂: 中性氧化铝, 展开剂: *V*(乙酸乙酯): *V*(石油醚) = 1 : 2] 分离得白色固体 III a~III p, 收率 79%~89%。

5,6-二甲基-2-三氟甲基-4-苄氨基噻吩并[2,3-*d*]嘧啶 (III a): 白色固体, 收率 86%, m.p. 107~108 °C; ¹HNMR [400 MHz, (CD₃)₂CO], δ: 7.48 (s, 1H, NH), 7.38~7.22 (m, 5H, Ar-H), 4.87 (s, 2H, Ar-CH₂), 2.59

(s, 3H, 6-CH₃), 2.48 (s, 3H, 5-CH₃); ¹³CNMR [100 MHz, (CD₃)₂CO], δ: 163.9, 157.8, 150.3, 139.3, 132.4, 128.3, 127.9, 126.9, 124.6, 121.7, 116.2, 44.3, 13.3, 12.5; IR (KBr), ν/cm⁻¹: 3438 (N—H), 1579 (C=N), 1334, 1193 (CF₃); EI-MS (M⁺), *m/z*, 实测值(计算值): 337.26 (337.09); 元素分析, C₁₆H₁₄F₃N₃S, 实验值(计算值): w(C) = 57.14% (56.96%), w(H) = 4.12% (4.18%), w(N) = 12.36% (12.46%)。

5,6-二甲基-2-三氟甲基-4-(4-氟苄氨基)噻吩并[2,3-*d*]嘧啶(III b): 白色固体, 收率 83%, m.p. 131~132 °C; ¹HNMR [400 MHz, (CD₃)₂CO], δ: 7.55 (s, 1H, NH), 7.51~7.05 (m, 4H, Ar—H), 4.85 (s, 2H, Ar—CH₂), 2.58 (s, 3H, 6-CH₃), 2.49 (s, 3H, 5-CH₃); ¹³CNMR [100 MHz, (CD₃)₂CO], δ: 163.9, 163.1, 160.7, 157.50, 149.9, 135.4, 132.4, 130.0, 121.6, 117.8, 114.9, 114.7, 43.7, 13.3, 12.52; IR (KBr), ν/cm⁻¹: 3514 (N—H), 1579 (C=N), 1334, 1166 (CF₃); EI-MS (M⁺), *m/z*, 实测值(计算值): 355.25 (355.08); 元素分析, C₁₆H₁₃F₄N₃S, 实验值(计算值): w(C) = 53.80% (54.08%), w(H) = 3.54% (3.69%), w(N) = 11.75% (11.83%)。

5,6-二甲基-2-三氟甲基-4-(3-氟苄氨基)噻吩并[2,3-*d*]嘧啶(III c): 白色固体, 收率 79%, m.p. 111~112 °C; ¹HNMR [400 MHz, (CD₃)₂CO], δ: 7.45 (s, 1H, NH), 7.34~6.98 (m, 4H, Ar—H), 4.89 (s, 2H, Ar—CH₂), 2.60 (s, 3H, 6-CH₃), 2.49(s, 3H, 5-CH₃); ¹³CNMR [100 MHz, (CD₃)₂CO], δ: 164.7, 162.3, 158.2, 150.6, 143.0, 133.2, 130.7, 125.3, 124.4, 122.3, 118.5, 115.4, 114.3, 44.6, 14.0, 13.2; IR (KBr), ν/cm⁻¹: 3493 (N—H), 1589 (C=N), 1330, 1200 (CF₃); EI-MS (M⁺), *m/z*, 实测值(计算值): 355.15 (355.08); 元素分析, C₁₆H₁₃F₄N₃S, 实验值(计算值): w(C) = 53.84% (54.08%), w(H) = 3.58% (3.69%), w(N) = 11.79% (11.83%)。

5,6-二甲基-2-三氟甲基-4-(2-氟苄氨基)噻吩并[2,3-*d*]嘧啶(III d): 白色固体, 收率 81%, m.p. 148~149 °C; ¹HNMR [400 MHz, (CD₃)₂CO], δ: 7.56 (s, 1H, NH), 7.31~7.09 (m, 4H, Ar—H), 4.93 (s, 2H, Ar—CH₂), 2.61 (s, 3H, 6-CH₃), 2.49 (s, 3H, 5-CH₃); ¹³CNMR [100 MHz, (CD₃)₂CO], δ: 164.0, 162.2, 159.8, 157.6, 149.9, 132.6, 130.1, 128.9, 126.0, 124.5, 124.1, 121.6, 117.9, 115.1, 33.3, 13.2, 12.5; IR (KBr), ν/cm⁻¹: 3457 (N—H), 1583 (C=N), 1334, 1164 (CF₃); EI-MS (M⁺), *m/z*, 实测值(计算值): 355.21 (355.08); 元素分析, C₁₆H₁₃F₄N₃S, 实验值(计算值): w(C) = 53.78% (54.08%), w(H) = 3.75% (3.69%), w(N) = 11.87% (11.83%)。

5,6-二甲基-2-三氟甲基-4-(4-氯苄氨基)噻吩并[2,3-*d*]嘧啶(III e): 白色固体, 收率 84%, m.p. 166~168 °C; ¹HNMR [400 MHz, (CD₃)₂CO], δ: 7.51 (s, 1H, NH), 7.49~7.33 (m, 4H, Ar—H), 4.86 (s, 2H, Ar—CH₂),

2.59 (s, 3H, 6-CH₃), 2.49 (s, 3H, 5-CH₃); ¹³CNMR [100 MHz, (CD₃)₂CO], δ: 164.0, 157.5, 149.9, 138.3, 132.5, 132.2, 129.7, 128.2, 124.6, 121.6, 117.8, 43.7, 13.3, 12.6; IR (KBr), ν/cm⁻¹: 3470 (N—H), 1591 (C=N), 1332, 1185 (CF₃); EI-MS (M⁺), *m/z*, 实测值(计算值): 371.18 (371.05); 元素分析, C₁₆H₁₃ClF₃N₃S, 实验值(计算值): w(C) = 51.56% (51.69%), w(H) = 3.47% (3.52%), w(N) = 11.09% (11.30%)。

5,6-二甲基-2-三氟甲基-4-(3-氯苄氨基)噻吩并[2,3-*d*]嘧啶(III f): 白色固体, 收率 79%, m.p. 116~117 °C; ¹HNMR [400 MHz, (CD₃)₂CO], δ: 7.54 (s, 1H, NH), 7.45~7.25 (m, 4H, Ar—H), 4.87 (s, 2H, Ar—CH₂), 2.59 (s, 3H, 6-CH₃), 2.49(s, 3H, 5-CH₃); ¹³CNMR [100 MHz, (CD₃)₂CO], δ: 164.0, 157.5, 149.9, 141.8, 133.6, 132.5, 129.9, 128.1, 126.9, 126.5, 124.6, 121.6, 117.8, 43.9, 13.3, 12.5; IR (KBr), ν/cm⁻¹: 3455 (N—H), 1586 (C=N), 1332, 1187 (CF₃); EI-MS (M⁺), *m/z*, 实测值(计算值): 371.19 (371.05); 元素分析 C₁₆H₁₃ClF₃N₃S, 实验值(计算值): w(C) = 51.51% (51.69%), w(H) = 3.48% (3.52%), w(N) = 11.41% (11.30%)。

5,6-二甲基-2-三氟甲基-4-(2-氯苄氨基)噻吩并[2,3-*d*]嘧啶(III g): 白色固体, 收率 89%, m.p. 154~156 °C; ¹HNMR [400 MHz, (CD₃)₂CO], δ: 7.57 (s, 1H, NH), 7.44~7.27 (m, 4H, Ar—H), 4.96 (s, 2H, Ar—CH₂), 2.64 (s, 3H, 6-CH₃), 2.59 (s, 3H, 5-CH₃); ¹³CNMR [100 MHz, (CD₃)₂CO], δ: 164.0, 157.5, 150.3, 136.1, 132.9, 132.7, 129.9, 129.2, 128.8, 126.9, 124.5, 121.7, 117.9, 42.2, 13.3, 12.6; IR (KBr), ν/cm⁻¹: 3526 (N—H), 1579 (C=N), 1330, 1136 (CF₃); EI-MS (M⁺), *m/z*, 实测值(计算值): 371.24 (371.05); 元素分析, C₁₆H₁₃ClF₃N₃S, 实验值(计算值): w(C) = 51.58% (51.69%), w(H) = 3.46% (3.52%), w(N) = 11.28% (11.30%)。

5,6-二甲基-2-三氟甲基-4-(4-溴苄氨基)噻吩并[2,3-*d*]嘧啶(III h): 白色固体, 收率 81%, m.p. 163~164 °C; ¹HNMR [400 MHz, (CD₃)₂CO], δ: 7.50 (s, 1H, NH), 7.48~7.43 (m, 4H, Ar—H), 4.84 (s, 2H, Ar—CH₂), 2.59 (s, 3H, 6-CH₃), 2.49 (s, 3H, 5-CH₃); ¹³CNMR [100 MHz, (CD₃)₂CO], δ: 164.0, 157.4, 149.9, 138.8, 132.5, 131.2, 130.1, 124.6, 121.6, 120.3, 117.8, 43.7, 13.3, 12.5; IR (KBr), ν/cm⁻¹: 3481 (N—H), 1583 (C=N), 1334, 1168 (CF₃); EI-MS (M⁺), *m/z*, 实测值(计算值): 415.19 (415.00); 元素分析, C₁₆H₁₃BrF₃N₃S, 实验值(计算值): w(C) = 46.29% (46.17%), w(H) = 3.25% (3.15%), w(N) = 10.24% (10.09%)。

5,6-二甲基-2-三氟甲基-4-(3-溴苄氨基)噻吩并[2,3-*d*]嘧啶(III i): 白色固体, 收率 79%, m.p. 95~96 °C; ¹HNMR [400 MHz, (CD₃)₂CO], δ: 7.69 (s, 1H, NH), 7.50~7.28 (m, 4H, Ar—H), 4.87 (s, 2H, Ar—CH₂), 2.60

(s, 3H, 6-CH₃), 2.49(s, 3H, 5-CH₃); ¹³CNMR [100 MHz, (CD₃)₂CO], δ: 164.0, 157.4, 149.9, 142.1, 132.5, 131.0, 130.2, 129.9, 127.0, 124.6, 121.8, 121.6, 117.8, 43.8, 13.3, 12.6; IR (KBr), ν/cm⁻¹: 3451 (N—H), 1589 (C=N), 1336, 1197 (CF₃); EI-MS (M⁺), *m/z*, 实测值 (计算值): 415.19 (415.00); 元素分析, C₁₆H₁₃BrF₃N₃S, 实验值 (计算值): w(C) = 46.22% (46.17%), w(H) = 3.31% (3.15%), w(N) = 10.04% (10.09%)。

5,6-二甲基-2-三氟甲基-4-(2-溴苄氨基)噻吩并[2,3-*d*]嘧啶 (IIIj): 白色固体, 收率 84%, m.p. 127~128 °C; ¹HNMR [400 MHz, (CD₃)₂CO], δ: 7.63 (s, 1H, NH), 7.56~7.21 (m, 4H, Ar—H), 4.93 (s, 2H, Ar—CH₂), 2.65 (s, 3H, 6-CH₃), 2.51 (s, 3H, 5-CH₃); ¹³CNMR [100 MHz, (CD₃)₂CO], δ: 164.0, 157.5, 150.3, 137.7, 132.8, 132.6, 130.9, 128.9, 127.5, 124.5, 122.9, 121.6, 117.9, 44.9, 13.3, 12.6; IR (KBr), ν/cm⁻¹: 3479 (N—H), 1587 (C=N), 1330, 1197 (CF₃); EI-MS (M⁺), *m/z*, 实测值 (计算值): 415.19 (415.00); 元素分析, C₁₆H₁₃BrF₃N₃S, 实验值 (计算值): w(C) = 46.43% (46.17%), w(H) = 3.26% (3.15%), w(N) = 10.22% (10.09%)。

5,6-二甲基-2-三氟甲基-4-(4-甲氧基苄氨基)噻吩并[2,3-*d*]嘧啶 (IIIk): 白色固体, 收率 79%, m.p. 132~133 °C; ¹HNMR [400 MHz, (CD₃)₂CO], δ: 7.37 (s, 1H, NH), 7.28~7.12 (m, 4H, Ar—H), 4.82 (s, 2H, Ar—CH₂), 2.57 (3H, 6-CH₃), 2.48 (s, 3H, 5-CH₃), 2.28 (s, 3H, Ar—CH₃); ¹³CNMR [100 MHz, (CD₃)₂CO], δ: 163.9, 157.6, 150.4, 150.0, 136.4, 136.2, 132.3, 128.9, 127.9, 124.6, 121.7, 118.9, 117.7, 44.1, 20.2, 13.3, 12.5; IR (KBr), ν/cm⁻¹: 3473 (N—H), 1589 (C=N), 1334, 1180 (CF₃); EI-MS (M⁺), *m/z*, 实测值 (计算值): 351.28 (351.10); 元素分析, C₁₇H₁₆F₃N₃OS, 实验值 (计算值): w(C) = 57.97% (58.11%), w(H) = 4.53% (4.59%), w(N) = 12.06% (11.96%)。

5,6-二甲基-2-三氟甲基-4-(3-甲基苄氨基)噻吩并[2,3-*d*]嘧啶 (IIIl): 白色固体, 收率 82%, m.p. 101~102 °C; ¹HNMR [400 MHz, (CD₃)₂CO], δ: 7.31 (s, 1H, NH), 7.28~7.05 (m, 4H, Ar—H), 4.83 (s, 2H, Ar—CH₂), 2.58 (3H, 6-CH₃), 2.48(s, 3H, 5-CH₃), 2.29 (s, 3H, Ar—CH₃); IR (KBr), ν/cm⁻¹: 3471 (N—H), 1583 (C=N), 1332, 1183 (CF₃); ¹³CNMR [100 MHz, (CD₃)₂CO], δ: 163.9, 157.6, 150.0, 139.1, 137.7, 132.3, 128.7, 128.2, 127.7, 125.0, 124.6, 121.7, 117.7, 144.3, 20.5, 13.3, 12.5; EI-MS (M⁺), *m/z*, 实测值 (计算值): 351.28 (351.10); 元素分析, C₁₇H₁₆F₃N₃S, 实验值 (计算值): w(C) = 57.89% (58.11%), w(H) = 4.43% (4.59%), w(N) = 12.12% (11.96%)。

5,6-二甲基-2-三氟甲基-4-(2-甲基苄氨基)噻吩并[2,3-*d*]嘧啶 (III m): 白色固体, 收率 86%, m.p. 151~

152 °C; ¹HNMR [400 MHz, (CD₃)₂CO], δ: 7.42 (s, 1H, NH), 7.39~7.13 (m, 4H, Ar—H), 4.86 (s, 2H, Ar—CH₂), 2.60 (3H, 6-CH₃), 2.49 (s, 3H, 5-CH₃), 2.43 (s, H, Ar—CH₃); ¹³CNMR [100 MHz, (CD₃)₂CO], δ: 163.9, 157.6, 150.4, 150.0, 136.7, 135.9, 132.4, 128.0, 127.0, 124.6, 121.6, 118.9, 117.8, 42.2, 18.3, 13.3, 12.5; IR (KBr), ν/cm⁻¹: 3500 (N—H), 1587 (C=N), 1334, 1180 (CF₃); EI-MS (M⁺), *m/z*, 实测值 (计算值): 351.27 (351.10); 元素分析, C₁₇H₁₆F₃N₃S, 实验值 (计算值): w(C) = 58.25% (58.11%), w(H) = 4.84% (4.59%), w(N) = 12.20% (11.96%)。

5,6-二甲基-2-三氟甲基-4-(4-甲氧基苄氨基)噻吩并[2,3-*d*]嘧啶 (III n): 白色固体, 收率 79%, m.p. 133~134 °C; ¹HNMR [400 MHz, (CD₃)₂CO], δ: 7.42 (s, 1H, NH), 7.40~6.86 (m, 4H, Ar—H), 4.79 (s, 2H, Ar—CH₂), 3.76 (3H, OCH₃), 2.56 (s, 3H, 6-CH₃), 2.47 (s, 3H, 5-CH₃); ¹³CNMR [100 MHz, (CD₃)₂CO], δ: 163.9, 159.0, 157.5, 150.0, 132.3, 131.1, 129.3, 124.5, 121.7, 119.0, 117.7, 116.2, 113.7, 54.6, 44.0, 13.3, 12.5; IR (KBr), ν/cm⁻¹: 3506 (N—H), 1587 (C=N), 1332, 1185 (CF₃); EI-MS (M⁺), *m/z*, 实测值 (计算值): 367.28 (367.10); 元素分析, C₁₇H₁₆F₃N₃OS, 实验值 (计算值): w(C) = 55.41% (55.58%), w(H) = 4.44% (4.39%), w(N) = 11.51% (11.44%)。

5,6-二甲基-2-三氟甲基-4-(3-甲氧基苄氨基)噻吩并[2,3-*d*]嘧啶 (III o): 白色固体, 收率 81%, m.p. 116~117 °C; ¹HNMR [400 MHz, (CD₃)₂CO], δ: 7.26 (s, 1H, NH), 7.24~7.04 (m, 4H, Ar—H), 4.86 (s, 2H, Ar—CH₂), 3.78 (s, 3H, OCH₃), 2.60 (s, 3H, 6-CH₃), 2.50 (s, 3H, 5-CH₃); ¹³CNMR [100 MHz, (CD₃)₂CO], δ: 163.9, 159.9, 157.6, 150.0, 140.8, 132.4, 129.3, 124.6, 121.7, 120.05, 117.8, 113.5, 112.5, 54.5, 44.3, 13.3, 12.5; IR (KBr), ν/cm⁻¹: 3495 (N—H), 1577 (C=N), 1342, 1185 (CF₃); EI-MS (M⁺), *m/z*, 实测值 (计算值): 367.28 (367.10); 元素分析, C₁₇H₁₆F₃N₃OS, 实验值 (计算值): w(C) = 55.71% (55.58%), w(H) = 4.48% (4.39%), w(N) = 11.42% (11.44%)。

5,6-二甲基-2-三氟甲基-4-(2-甲氧基苄氨基)噻吩并[2,3-*d*]嘧啶 (III p): 白色固体, 收率 88%, m.p. 158~159 °C; ¹HNMR [400 MHz, (CD₃)₂CO], δ: 7.38 (s, 1H, NH), 7.29~6.88 (m, 4H, Ar—H), 4.85 (s, 2H, Ar—CH₂), 3.94 (s, 3H, OCH₃), 2.59 (s, 3H, 6-CH₃), 2.48 (s, 3H, 5-CH₃); ¹³CNMR [100 MHz, (CD₃)₂CO], δ: 163.7, 157.7, 150.4, 132.4, 129.2, 128.6, 126.3, 124.4, 121.6, 120.3, 117.8, 116.2, 110.5, 54.9, 40.4, 13.1, 12.5; IR (KBr), ν/cm⁻¹: 3530 (N—H), 1577 (C=N), 1330, 1187 (CF₃); EI-MS (M⁺), *m/z*, 实测值 (计算值): 367.28 (367.10); 元素分析, C₁₇H₁₆F₃N₃OS, 实验值 (计算值): w(C) = 55.61% (55.58%), w(H) = 4.12% (4.39%), w(N) = 11.24% (11.44%)。

1.3 晶体结构测定

将目标化合物 5,6-二甲基-2-三氟甲基-4-苄氨基噻吩并[2,3-*d*]嘧啶(III a)的乙腈溶液在室温下缓慢挥发 5 d,得到无色针状晶体。使用 Bruker APEX-II CCD 面探衍射仪在 $2.06^\circ \leq \theta \leq 25.40^\circ$ 的范围内,以 φ - ω 扫描方式, Mo K_α 辐射 ($\lambda = 0.071073$ nm) 尺寸为 0.30 mm \times 0.20 mm \times 0.20 mm 的单晶,在 23 °C 温度下共收集 2930 个独立的衍射点,其中 1877 个可观测衍射点 [$I > 2\sigma(I)$], 等效点平均标准偏差 $R_{\text{int}} = 0.0308$ 。晶体结构通过 SHELXT-2014^[19] 程序直接解出,全部非氢原子由差值 Fourier 合成及差值电子密度函数修正得到。晶体的修正采用 SHELXL-2014^[20] 程序,全部非氢原子坐标及各向异性热参数经全矩阵最小二乘法进行最后修正,所有氢原子采用理论加氢,最终的偏离因子: $R = 0.0624$, $wR = 0.1628$ 。最终差值电子密度最高峰为 6.31×10^2 e/nm³, 最低峰为 -3.64×10^2 e/nm³, 最后一轮精修的最大偏移 $(\Delta/\sigma)_{\text{max}} = 0.010$, GOOF 值 $S = 0.817$ 。

2 结果与讨论

2.1 合成方法

本文以 2-丁酮、丙二腈和单质硫为原料,碳酸钾为催化剂,在无水乙醇中通过改良的 Gewald 反应制得 2-氨基-3-氰基-4,5-二甲基噻吩(I)。与文献^[21-23]报道的其他合成方法相比,本文以碳酸钾为催化剂^[24],以无水乙醇为溶剂,回流 3 h 完成反应,将反应液倒入水中直接析出固体,经无水乙醇重结晶得 I,产率高达 84%。以 K_2CO_3 作催化剂,廉价、绿色,能够在短时间内简便高效地合成出噻吩衍生物,反应机制参考文献^[23,25]。

关键中间体 5,6-二甲基-2-三氟甲基-4-氯噻吩并[2,3-*d*]嘧啶(II)通常是以 2-氨基-3-氰基噻吩为原料经多步法^[26-27]合成噻吩并[2,3-*d*]嘧啶-4-酮,再经三氯氧磷氯化制得。本实验以化合物 I、三氟乙酸和三氯氧磷为反应原料在甲苯溶剂中,于 80 °C 通过“一锅法”反应 4 h,一步合成出化合物 II,产率达 67%。与传统的合成方法相比,不仅操作简便、反应时间短,同时还方便地引入了三氟甲基基团。

2.2 结构表征

在 ¹HNMR 谱图中,各类质子的化学位移均清晰明显。苯环氢的化学位移出现在 δ 7.89~6.86 范围内,为多重峰;与苄基相连的 NH 质子的化学位移出现在 δ 7.50 左右,呈宽的弱吸收峰;苄基的亚甲基质子 ($ArCH_2$) 的化学位移出现在 δ 4.85 左右,为单峰;噻吩并[2,3-*d*]嘧啶环上 5-CH₃ 和 6-CH₃ 上质子的化学位移出现在 δ 2.65~2.48 左右,均为单峰。

IR 谱图中,特征官能团的吸收峰均可见。 3490 cm⁻¹ 附近出现目标化合物中 N—H 的伸缩振动吸收峰, 1577 cm⁻¹ 附近为 C=N 双键的伸缩振动吸收峰, 1334 cm⁻¹ 及 1180 cm⁻¹ 附近分别为 CF₃ 反对称和对称伸缩振动吸收峰。在 MS 谱图中,均出现明显的分子离子峰。

2.3 晶体结构

目标化合物 III a 的分子结构图如图 1 所示。晶体结构解析显示,晶体属单斜晶系, $P2_1/c$ 空间群,晶胞参数为: $a = 0.73551$ (18) nm、 $b = 1.1667$ (3) nm、 $c = 1.8641$ (5) nm、 $\alpha = 90^\circ$ 、 $\beta = 90.605$ (3)°、 $\gamma = 90^\circ$ 、 $V = 1.5995$ (7) nm³、 $Z = 4$ 、 $D_x = 1.401$ g/cm³、 $\mu = 0.235$ mm⁻¹、 $F(000) = 696.0$ 。

单晶衍射分析可知,在 III a 的分子结构中噻吩并[2,3-*d*]嘧啶环具有良好的共面性,与同一分子中的苯环形成了 $75.5(3)^\circ$ 的二面角。分子中 C(6)—N(3) 的键长 (0.1344 nm) 接近嘧啶环中 C—N 的键长,且都在正常的 C=N 双键 (0.127 nm) 和 C—N 单键键长 (0.147 nm) 之间,表明 N(3) 的孤对电子与嘧啶环形成了共轭, N(3) 与嘧啶环上的 N 原子都是 sp^2 杂化; C(6)—N(3) 键具有部分双键性质,并非结构式表现的单键形式; C(10)—N(3) 的键长为 0.1454 nm,是正常的 C—N 单键。

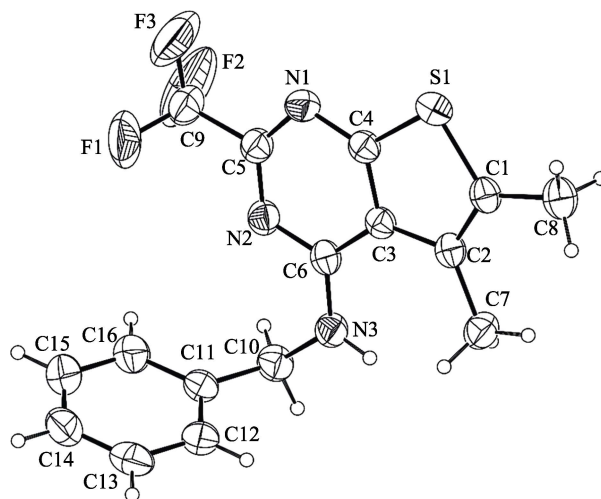


图 1 目标化合物 III a 的分子结构

Fig. 1 Molecular structure of compound III a

2.4 体外抗肿瘤活性

为了探讨目标化合物体外抗肿瘤活性,采用 MTT 法^[28]初步测试了其对乳腺癌细胞 (MCF-7) 和肝癌细胞 (HepG2) 的抑制活性,并以吉非替尼 (Gefitinib) 为阳性对照。体外抗肿瘤活性实验结果见表 1。

从表 1 可知,阳性对照组吉非替尼对 MCF-7 与 HepG2 的 IC₅₀ 分别为 14.68 和 24.94 μ mol/L,目标

物 III a、III c、III f 对 MCF-7 的 IC_{50} 分别为 2.01、1.44 和 23.30 $\mu\text{mol/L}$, III a、III c、III f、III i 对 HepG2 的 IC_{50} 分别为 2.44、1.47、8.71 和 10.91 $\mu\text{mol/L}$, 具有较好的抑制活性。可以看出, 目标物 III a 和 III c 对 MCF-7 和 HepG2 两种肿瘤细胞的抑制活性均优于阳性对照组吉非替尼, 且 III a、III c 对 MCF-7 与 HepG2 的 IC_{50} 相比吉非替尼降低了一个数量级, 具有深入研究的价值。

表 1 化合物 III a~III p 对 MCF-7 和 HepG2 的体外抗肿瘤活性

Table 1 *In vitro* antitumor activity of compounds III a~III p against MCF-7 and HepG2

序号	化合物	R	$IC_{50}/(\mu\text{mol/L})$	
			MCF-7	HepG2
1	III a	H	2.01	2.44
2	III b	4-F	52.36	> 100
3	III c	3-F	1.44	1.47
4	III d	2-F	> 100	> 100
5	III e	4-Cl	> 100	> 100
6	III f	3-Cl	23.30	8.71
7	III g	2-Cl	> 100	> 100
8	III h	4-Br	> 100	> 100
9	III i	3-Br	53.51	10.91
10	III j	2-Br	> 100	88.22
11	III k	4-CH ₃	> 100	> 100
12	III l	3-CH ₃	91.51	> 100
13	III m	2-CH ₃	> 100	> 100
14	III n	4-OCH ₃	> 100	> 100
15	III o	3-OCH ₃	> 100	> 100
16	III p	2-OCH ₃	> 100	> 100
对照	Gefitinib	—	14.68	24.94

构效关系分析发现, 在目标分子 N^4 -位苄基的苯环中引入吸电子取代基 (如卤素, 即 III b~III j) 对目标化合物抗肿瘤活性的影响大于供电子取代基 (如甲基、甲氧基, 即 III k~III p)。目标化合物的 N^4 -位苄基的苯环上有供电子基 (如甲基、甲氧基) 取代时抗肿瘤活性被削弱甚至无活性, 且其供电子能力越强则化合物的活性越差, 如: III k~III p 对 MCF-7 和 HepG2 的 IC_{50} 均大于 90 $\mu\text{mol/L}$; 抗肿瘤活性 III o < III l。目标化合物的 N^4 -位苄基的苯环间位被吸电子基 (如 F、Cl、Br) 取代时其抗肿瘤活性较高, 且卤原子的吸电子能力越强则化合物的活性越高 (如 III c > III f > III i), 尤其是苯环的间位被 F 原子取代时 (即 III c) 对 MCF-7 和 HepG2 的 IC_{50} 分别降低至 1.44 和 1.47 $\mu\text{mol/L}$, 对抗肿瘤活性提高最为显著。可见, 该噻吩并[2,3-*d*]嘧啶类衍生物的 N^4 -位苄基苯环上取代基的种类和位置均对化合物的抗肿瘤活性产生显著影响, 可为该类化合物的后续设计、合成及构效关系研究提供借鉴与理论参考。

3 结论

以 2-丁酮、丙二腈和单质硫为起始原料, 经三步反应合成出 16 种噻吩并[2,3-*d*]嘧啶类含氟衍生物, 收率为 79%~89%。并通过 $^1\text{H NMR}$ 、 $^{13}\text{C NMR}$ 、IR、EI-MS、元素分析和 X 射线单晶衍射方法证实了目标化合物的结构。体外抗肿瘤活性实验表明, 部分目标化合物 (如 III a、III c 和 III f) 对 MCF-7 和 HepG2 细胞表现出良好的抑制活性, 其中 III c 对 MCF-7 和 HepG2 的 IC_{50} 分别为 1.44 和 1.47 $\mu\text{mol/L}$, 其 IC_{50} 相比阳性对照组吉非替尼降低了一个数量级, 表明该化合物可作为抗肿瘤的先导化合物, 有待对其进行进一步结构优化及作用机制研究。

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