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Synthesis and Antitumor Activity of N-Triazol-5-yl-oxazolidin-4-one Derivatives.

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N-三氮唑基噁唑烷酮类衍生物合成及抗肿瘤活性研究

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摘要 以苯甲醛衍生物为起始物, 经多步反应合成了 15 个未见文献报道的 *N*-三氮唑基噁唑烷酮类衍生物. 探索发现 *N*-碘代丁二酰亚胺(NIS)以较高产率促进合成过程中的关键反应−分子内胺化反应, 此反应为分子内构建氮杂环提供了新的方法. 细胞毒活性测试表明, 化合物 **6a**、**6b** 和 **6c** 对人乳腺癌细胞 MDA-MB-231, **6a**、**6b** 和 **6d** 对宫颈癌细胞 HeLa 有一定的抑制活性.

关键词 *N*-三氮唑基噁唑烷酮; *N*-碘代丁二酰亚胺; 分子内胺化反应; 抗肿瘤活性

Synthesis and Antitumor Activity of *N*-Triazol-5-yl-oxazolidin-4-one Derivatives

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Abstract Fifteen novel *N*-triazol-5-yl-oxazolidin-4-ones were synthesized through a few of steps from the benzaldehydes. It was found that *N*-iodosuccinimide (NIS) can promote intramolecular amination reaction which is the key step of the syntheses, which will be used as new method for the intramolecular formation of nitrogen-containing heterocycles. Part of the compounds were evaluated for their anticancer activity. Among them, compounds **6a**, **6b** and **6c** showed moderate antiprolifiration activity toward human breast cancer cells MDA-MB-231 cell lines, while the mild activity of **6a**, **6b** and **6d** against human cervical cancer HeLa cell lines was confirmed *in vitro* assay.

Keywords *N*-triazol-5-yl-oxazolidin-4-one; *N*-iodosuccinimide; intramolecular amination ; antitumor activity

乳腺癌发病率呈逐年上升的趋势, 已跃居女性恶性肿瘤的首位[1]. 1,2,4-三氮唑衍生物具有抗菌、抗病毒、抗肿瘤等广泛的生物活性[2~6]. 如已上市伏氯唑(Vorozole)[7]和来曲唑(Letrozole)[8]等新一代高选择性芳香化酶抑制剂, 适用于治疗抗雌激素治疗无效的晚期绝经后乳腺癌患者以及乳腺癌早期的治疗. 而噁唑烷酮类是抗菌、抗病毒等作用的重要潜在药效团[9], 例如 2000 年上市的新型抗生素利奈唑胺(图 1)[10], 对甲氧西林敏感或耐药葡萄球菌、万古霉素敏感或耐药肠球菌、青霉素敏感或耐药肺炎链球菌均显示了良好的抗菌作用. 结合本课题组对三氮唑类化合物的合成及活性研究[11,12], 为使化合物结构具有多样性以利于进一步优化和拓展应用研究, 作者设计合成了噁唑烷酮环合物 **6**, 并以 2-(苄氧基)-*N*-(1,3-二苯基-1*H*-1,2,4-三唑-5-基)乙酰胺(**5a**)为底物, 借助 1,2,4-三氮唑水溶性较好且其诱导效应有利于酰胺氮对 C—H 键的插入反应性, 且以 1,2,4-三氮唑酰胺为氮源的胺化反应也稀少, 这也是课题组感兴趣的 C—N 键构建方法学研究的一部分[14], 拟集中在活性氮源的应用和拓展胺化反应, 发展在温和条件下获得新的生物活性化合物的方法, 为新药研究与开发奠定基础. 本文报道了以 *N*-碘代丁二酰亚胺(NIS)为氧化剂的一种有效和方便的苄位 C—H 键的分子内胺化方法, 在温和条

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件下以较高产率得到 1,2,4-三氮唑噁唑烷酮衍生物(Scheme 1). 同时, 作者对部分化合物的抗乳腺癌等活性进行了测试.

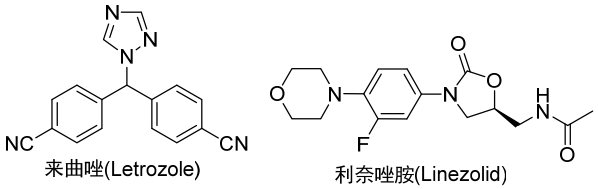


图 1 来曲唑和利奈唑胺的结构
Figure 1 Structures of letrozole and linezolid

1 结果与讨论

1.1 目标化合物合成及反应条件优化

以苯甲醛衍生物 **1** 为起始原料[11~13], 与单氰胺和叔丁醇钾以及 *N*-溴代丁二亚胺(NBS)反应合成 *N*-氰基苯甲亚胺酸甲酯类化合物 **2**, 然后与相应苯肼在甲醇回流条件下反应成环生成 1,2,4-三氮唑-5-胺类化合物 **3**, 与氯乙酰氯反应生成 2-氯-*N*-(1,3-二苯基-1*H*-1,2,4-三唑-5-基)乙酰胺衍生物 **4**, 以 *N*,*N*-二甲基甲酰胺(DMF)为溶剂, NaH 作碱, 与苯甲醇衍生物发生 Williamson 成醚反应, 得分子内胺化底物 **5**. 以 2-(苄氧基)-*N*-(1,3-二苯基-1*H*-1,2,4-三唑-5-基)乙酰胺(**5a**)为胺化反应底物探索氧化剂和催化剂对反应的影响, 最初用 $PhI(OAc)_2$ 和 I_2 体系进行分子内胺化关环, 得到目标 4-噁唑烷酮产物, 但收率仅 28%, 反应转化率低且副产物多. 优化改用 $PhI(CF_3CO_2)_2$ 作为氧化剂, 收率增加至 40%. 同时, 添加金属催化剂, 如 CuI 和 $Cu(CF_3SO_3)_2$, 但未见明显催化效果. 进一步条件优化表明, 只需加入 NIS, 反应效果最好(表 1).

表 1 反应条件优化 [a]
Table 1 Optimization of the reaction conditions

Entry	Reagent	Catalyst	Yield/%
1	$PhI(OAc)_2/I_2$	—	28
2	$PhI(CF_3CO_2)_2/I_2$	—	40
3	$PhI(CF_3CO_2)_2$	$Cu(CF_3SO_3)_2$	42
4	NIS	$Cu(CF_3SO_3)_2$	50
5	NIS	CuI	48
6	NIS	—	54
7	NBS	—	Trace
8[b]	NIS	—	—

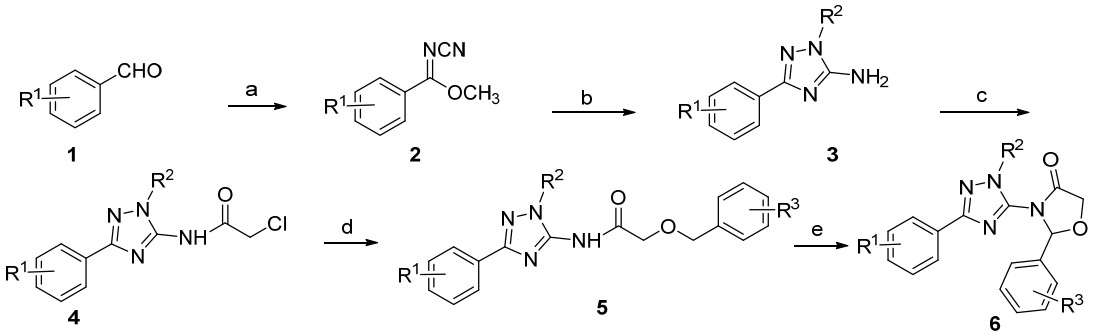
[a] Under daylight; [b] in the dark laboratory.

1.2 目标化合物的抗肿瘤活性

以苯达莫司汀(Bendamustine, 双功能基烷化剂)和伏立诺他(SAHA, HDAC 抑制剂)作为阳性药物对照[15,16]. 测试了部分目标化合物对人乳腺癌细胞 MDA-MB-231、MCF-7-TAM 和宫颈癌细胞 Hela 的体外细胞毒性(表 2). 实验结果表明化合物 **6a**、**6b** 和 **6c** 对 MDA-MB-231 细胞有一定的抗增生活性, 而 **6a**、**6b** 和 **6c** 对 HeLa 细胞有抑制作用, 但所有测试的化合物对 MCF-7-TAM 细胞无明显的抑制作用.

2 结论

报道了在温和条件下, 以 2-(苄氧基)-*N*-(1,3-二苯基-1*H*-1,2,4-三唑-5-基)乙酰胺类为底物, 通过 NIS 促进的分子内胺化环合方法得到 15 个未见文献报道的三氮唑 4-噁唑烷酮衍生物, 为分子内构建氮杂环提供了有效方法. 同时, 初步抗肿瘤活性测试结果表明三氮唑噁唑烷酮化合物具有一定的抗乳腺癌 MDA-MB-231 细胞活性及宫颈癌 Hela 细胞活性, 为发现包含三氮唑噁唑烷



5a, 6a: R^1 = H, R^2 = Ph, R^3 = H
5b, 6b: R^1 = 4-NO_2, R^2 = Ph, R^3 = H
5c, 6c: R^1 = 2-F, R^2 = Ph, R^3 = H
5d, 6d: R^1 = 4-Cl, R^2 = Ph, R^3 = H
5e, 6e: R^1 = 4-OCH_3, R^2 = Ph, R^3 = H
5f, 6f: R^1 = 4-F, R^2 = Ph, R^3 = H
5g, 6g: R^1 = 4-Br, R^2 = Ph, R^3 = H
5h, 6h: R^1 = 2,4-2Cl, R^2 = Ph, R^3 = H
5i, 6i: R^1 = H, R^2 = 3-ClPh, R^3 = H
5j, 6j: R^1 = H, R^2 = 4-FPh, R^3 = H
5k, 6k: R^1 = H, R^2 = 3-CH_3Ph, R^3 = H
5l, 6l: R^1 = H, R^2 = 2,5-2CH_3Ph, R^3 = H
5m, 6m: R^1 = H, R^2 = Ph, R^3 = 2-F
5n, 6n: R^1 = H, R^2 = Ph,R^3 = 4-CH_3
5o, 6o: R^1 = H, R^2 = Ph, R^3 = 4-Cl

Reagents and conditions: (a) H_2NCN, NBS, *t*-BuOK, 50 ℃; (b) R^2NHNH_2.HCl, $(CH_3CH_2)_3N$, CH_3OH, reflux; (c) $ClCH_2COCl$, $(CH_3CH_2)_3N$, CH_2Cl_2, r.t.; (d) benzy alcohol or substituted benzyl alcohol, NaH, DMF, r.t.; (e) NIS, CH_2Cl_2, r.t., N_2, visible light

图式 1 目标化合物的合成路线
Scheme 1 Synthetic routes of the title compounds

表 2 目标化合物的体外抗肿瘤活性
Table 2 Antiproliferative activities of synthetic compounds

Compd.	IC_{50}/(μmol•L^{-1})		
	MDA-MB-231	MCF-7-TAM	HELA
6a	13.29	>20	13.91
6b	12.85	>20	>20
6c	12.28	>20	9.48
6d	>20	>20	11.83
6e	>20	>20	>20
6o	>20	>20	>20
Bendamustine	13.28	>20	>20
SAHA	3.62	3.52	4.52

酮类结构的抗肿瘤药物打下基础. 进一步结构修饰与构效关系研究正在进行之中.

3 实验部分

3.1 仪器与试剂

核磁共振仪为 Varian Mercury 400 MHz 型核磁共振仪和 Agilent 600MHz 型核磁共振仪($CDCl_3$ 为溶剂, TMS 为内标); VECTOR 22 红外光谱仪; Bruker Daltonics Data 分析 3.4 质谱仪和 Thermo LTQ Orbitrap-XL 质谱仪; YRT-3 熔点仪(天津市天大天发公司), 温度未经校正; HSGF 254 高效薄层层析硅胶板购于烟台汇友开发有限公司; HSGF 254 型薄层板硅胶(300～400 目)购于青岛海洋化工厂; 所用试剂如无特别说明均为分析纯, 所用溶剂均按常规方法进行干燥处理.

3.2 化合物合成

3.2.1 *N*-氰基苯甲亚氨酸甲酯类(**2**)、1,3-二苯基-1*H*-1,2,4-三唑-5-胺类(**3**)和 2-氯-*N*-(1,3-二苯基-1*H*-1,2,4-三唑-5-基)乙酰胺类(**4**)合成

化合物 **2**～**4** 均参照本课题组前期发表的文献合成, 表征数据与文献一致[11~13].

3.2.2 2-(苄氧基)-*N*-(1,3-二苯基-1*H*-1,2,4-三唑-5-基)乙酰胺类化合物(**5**)合成通法

氮气保护下, 在 10 mL 圆底烧瓶加入 2-氯-*N*-(1,3-二苯基-1*H*-1,2,4-三唑-5-基)乙酰胺类(0.3 mmol)和 NaH (1.2 mmol, 29.0 mg), 将相应苯甲醇(0.6 mmol)先溶于 3 mL 无水 DMF, 在冰浴下加入反应瓶, 室温反应至薄层色谱(TLC)检测原料反应完全后, 加入 60 mL 乙酸乙酯, 用饱和食盐水洗涤, 有机层经无水硫酸钠干燥后减压浓缩, 经柱层析分离纯化得化合物 **5**.

2-(苄氧基)-*N*-(1,3-二苯基-1*H*-1,2,4-三唑-5-基)乙酰胺(**5a**): 灰白固体, 产率 89%. m.p. 99～101 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.82 (s, 1H), 8.14 (d, *J*=6.4 Hz, 2H), 7.54～7.52 (m, 2H), 7.48～7.42 (m, 6H), 7.36～7.35 (m, 3H), 7.27～7.25 (m, 2H), 4.58 (s, 2H), 4.10 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) *δ*: 167.7, 160.6, 145.5, 136.6, 136.0, 130.3, 129.5, 128.8, 128.6, 128.4, 128.3, 127.9, 126.3, 123.7, 73.6, 69.0; IR (KBr) *v*: 3240, 3031, 3062, 1706, 1598, 1534, 1507, 1119, 1027, 727, 691 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{21}N_4O_2$ $[M+H]^+$ 385.1659, found 385.1660.

(苄氧基)-*N*-(3-(4-硝基苯基)-1-苯基-1*H*-1,2,4-三唑-5-基)乙酰胺(**5b**): 黄色固体, 产率 87%. m.p. 182～183 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.32 (q, *J*=9.2 Hz, 4H), 7.55～7.49 (m, 5H), 7.38～7.37 (m, 2H), 7.26 (s, 3H), 4.61 (s, 2H), 4.14 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) *δ*: 167.4, 158.8, 148.3, 146.1, 136.3, 136.2, 136.0, 129.7, 129.4, 128.7, 128.5, 127.9, 127.1, 123.8, 73.8, 69.1; HRMS (ESI) calcd for $C_{23}H_{20}N_5O_4$ $[M+H]^+$ 430.1510, found 430.1506.

2-(苄氧基)-*N*-(3-(2-氟苯基)-1-苯基-1*H*-1,2,4-三唑-5-基)乙酰胺(**5c**): 淡黄色固体, 产率 85%. m.p. 104～106 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.94 (s, 1H), 8.10 (t, *J*=7.2 Hz, 1H), 7.53～7.44 (m, 5H), 7.39～7.34 (m, 4H), 7.26～7.15 (m, 4H), 4.57 (s, 2H), 4.09 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 167.8, 161.1, 159.4, 157.3, 145.4, 136.6, 136.1, 131.0, 130.1, 129.5, 129.0, 128.6, 128.4, 128.0, 127.9, 127.0, 124.1, 123.8, 116.5, 116.4, 73.4, 69.1; HRMS (ESI) calcd for $C_{23}H_{20}FN_4O_2$ $[M+H]^+$ 403.1565, found 403.1562.

2-(苄氧基)-*N*-(3-(4-氯苯基)-1-苯基-1*H*-1,2,4-三唑-5-基)乙酰胺(**5d**): 淡黄色固体, 产率 80%. m.p. 129～132 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.76 (s, 1H) , 8.08 (d, *J*=8.4 Hz, 2H), 7.53～7.44 (m, 5H), 7.41 (d, *J*=8.4 Hz, 2H), 7.37～7.36 (m, 2H), 7.27～7.25 (m, 3H), 4.60 (s, 2H), 4.11 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 167.5, 159.8, 145.6, 136.4, 136.0, 135.4, 129.6, 129.0, 128.8, 128.7, 128.5, 127.9, 127.7, 123.8, 73.7, 69.1; HRMS (ESI) calcd for $C_{23}H_{20}ClN_4O_2$ $[M+H]^+$ 419.1269, found 419.1269.

2-(苄氧基)-*N*-(3-(4-甲氧基苯基)-1-苯基-1*H*-1,2,4-三唑-5-基)乙酰胺(**5e**): 淡黄色固体, 产率 75%. m.p. 95～97 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.07 (d, *J*=8.8 Hz, 2H), 7.53 (d, *J*=6.8 Hz, 2H), 7.48～7.42 (m, 3H), 7.36～7.25 (m, 5H), 6.97 (d, *J*=8.8 Hz, 2H), 4.58 (s, 2H), 4.10 (s, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 167.8, 160.7, 145.4, 136.6, 136.1, 129.5, 128.7, 128.6, 128.3, 127.9, 127.8, 123.7, 122.9, 113.8, 73.6, 69.1, 55.2; HRMS (ESI) calcd for $C_{24}H_{23}N_4O_3$ $[M+H]^+$ 415.1765,

found 415.1767.

2-(苄氧基)-*N*-(3-(4-氟苯基)-1-苯基-1*H*-1,2,4-三唑-5-基)乙酰胺(**5f**): 淡黄色固体, 产率 92%. m.p. 110～112 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.80 (s, 1H), 8.14～8.11 (m, 2H), 7.53～7.43 (m, 6H), 7.36～7.35 (m, 2H), 7.27～7.25 (m, 2H), 7.12 (t, J=7.8 Hz, 2H), 4.59 (s, 2H), 4.11 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 167.5, 164.5, 162.8, 160.0, 145.6, 136.5, 136.0, 129.6, 129.0, 128.7, 128.5, 128.3, 127.9, 126.6, 123.8, 115.6, 115.4, 73.7, 69.1; HRMS (ESI) calcd for $C_{23}H_{20}FN_4O_2$ $[M+H]^+$ 403.1565, found 403.1561.

2-(苄氧基)-*N*-(3-(4-溴苯基)-1-苯基-1*H*-1,2,4-三唑-5-基)乙酰胺(**5g**): 灰白色固体, 产率 75%. m.p. 139～141 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.88 (s, 1H), 8.00 (d, J=8.8 Hz, 2H), 7.54 (d, J=8.4 Hz, 2H), 7.51～7.49 (m, 2H), 7.47～7.33 (m, 6H), 7.25～7.24 (m, 2H), 4.56 (s, 2H), 4.09 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.6, 159.8, 145.6, 136.4, 136.0, 131.6, 129.3, 129.0, 128.6, 128.4, 127.9, 123.7, 73.7, 69.0; HRMS (ESI) calcd for $C_{23}H_{20}BrN_4O_2$ $[M+H]^+$ 463.0764, found 463.0764.

2-(苄氧基)-*N*-(3-(2,4-二氯苯基)-1-苯基-1*H*-1,2,4-三唑-5-基)乙酰胺(**5h**): 灰白色固体, 产率 90%. m.p. 106～108 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.88(s, 1H), 7.91 (d, J=8.4 Hz, 1H), 7.58～7.44 (m, 6H), 7.35～7.26 (m, 6H), 4.58 (s, 2H), 4.10 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.6, 145.5, 136.4, 136.0, 135.5, 133.5, 132.2, 130.4, 129.6, 129.4, 129.0, 128.7, 128.4, 128.3, 127.9, 127.0, 123.7, 123.4, 73.7, 69.1; HRMS (ESI) calcd for $C_{23}H_{19}Cl_2N_4O_2$ $[M+H]^+$ 453.0879, found 453.0880.

2-(苄氧基)-*N*-(1-(3-氯苯基)-3-苯基-1*H*-1,2,4-三唑-5-基)乙酰胺(**5i**): 白色固体, 产率 88%. m.p. 123～125 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.97 (s, 1H), 8.12～8.10 (m, 2H), 7.59 (s, 1H), 7.43 (d, J=5.6 Hz, 4H), 7.36～7.25 (m, 7H), 4.59 (s, 2H), 4.08 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.1, 160.7, 145.6, 137.9, 136.0, 135.1, 130.4, 129.9, 129.7, 128.8, 128.7, 128.5, 128.0, 126.3, 123.9, 121.4, 73.8, 69.0; HRMS (ESI) calcd for $C_{23}H_{20}ClN_4O_2$ $[M+H]^+$ 419.1269, found 419.1269.

2-(苄氧基)-*N*-(1-(4-氟苯基)-3-苯基-1*H*-1,2,4-三唑-5-基)乙酰胺(**5j**): 白色固体, 收率 80%. m.p. 116～118 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.83 (s, 1H), 8.12～8.10 (m, 2H), 7.51～7.48 (m, 2H), 7.43 (d, J=6.4 Hz, 3H), 7.37 (d, J=4.8 Hz, 3H), 7.28～7.26 (m, 2H), 7.15～7.10 (m, 2H), 4.59 (s, 2H), 4.08 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.9, 163.6, 161.1, 160.7, 145.7, 136.0, 132.8, 130.1, 129.6, 128.7, 128.5, 128.0, 126.3, 126.0, 125.9. 116.6, 116.3, 73.8, 69.1; HRMS (ESI) calcd for $C_{23}H_{20}FN_4O_2$ $[M+H]^+$ 403.1565, found 403.1561.

(苄氧基)-*N*-(3-苯基-1-(间甲苯基)-1*H*-1,2,4-三唑-5-基)乙酰胺(**5k**): 淡黄色固体, 收率 86%. m.p. 99～101 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.88 (s, 1H), 8.15～8.13 (m, 2H), 7.45～7.40 (m, 3H), 7.37 (s, 1H), 7.34～7.31 (m, 3H), 7.29 (d, J=7.2 Hz, 2H), 7.27～7.22 (m, 3H), 4.57 (s, 2H), 4.10 (s, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.6, 160.6, 145.5, 139.9, 136.4, 136.0, 130.3, 129.7, 129.4, 129.2, 128.6, 128.4, 128.4, 127.9, 126.4, 124.6, 120.6, 73.6, 69.1, 21.3; HRMS(ESI) calcd for $C_{24}H_{23}N_4O_2$ $[M+H]^+$ 399.1816, found 399.1811.

2-(苄氧基)-*N*-(1-(2,4-二甲基苯基)-3-苯基-1*H*-1,2,4-三唑-5-基)乙酰胺(**5l**): 泡沫状, 产率 65%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.64 (s, 1H), 8.14 (dd, J=1.6 Hz, 1.2 Hz, 2H), 7.45～7.38 (m, 3H), 7.34～7.33 (m, 3H), 7.17 (d, J=8.0 Hz, 4H), 7.07 (d, J=8.0 Hz, 1H). 4.51 (s, 2H), 4.05 (s, 2H), 2.37 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 167.2, 160.7, 146.7 140.3, 136.1, 135.3, 132.4, 132.2, 130.5, 129.4, 128.6, 128.4, 128.3, 127.7, 127.5, 126.5, 126.3, 73.6, 69.1, 21.2, 17.5; HRMS (ESI) calcd for $C_{25}H_{25}N_4O_2$ $[M+H]^+$ 413.1972, found 413.1971.

N-(1,3-二苯基-1*H*-1,2,4-三唑-5-基)-2-((2-氟苄基)氧基)乙酰胺(**5m**): 灰白色固体, 产率 88%. m.p. 103～108 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.92 (s, 1H), 8.13 (d, J=7.6 Hz, 2H), 7.52 (d, J=6.8 Hz, 2H), 7.46～7.38 (m, 6H), 7.35～7.25 (m, 2H), 7.12 (t, J=7.2 Hz, 1H), 7.05 (t, J=9.2 Hz, 1H), 4.63 (s, 2H), 4.12 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.6, 162.2, 160.7, 159.7, 145.5, 136.6, 130.5, 130.4, 130.3, 129.5, 128.8, 128.4, 126.3, 124.3, 123.8, 123.1, 115.6, 115.4 .69.3, 67.5; HRMS (ESI) calcd for $C_{23}H_{20}FN_4O_2$ $[M+H]^+$ 403.1565, found 403.1562.

N-(1,3-二苯基-1*H*-1,2,4-三唑-5-基)-2-((4-甲基苄基)氧基)乙酰胺(**5n**): 灰白色固体, 产率 86%. m.p. 116～117 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.80 (s, 1H), 8.15～8.13 (m, 2H), 7.55～7.53 (m ,2H), 7.51～7.39 (m, 6H), 7.18～7.14 (m, 4H), 4.55 (s, 2H), 4.08 (s, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.9, 160.6, 145.5, 138.2, 136.6, 133.0, 130.3, 129.4, 129.2, 128.7, 128.7, 128.4, 128.0, 126.3, 123.7, 73.5, 68.9, 21.1; HRMS (ESI) calcd for $C_{24}H_{23}N_4O_2$ $[M+H]^+$ 399.1816, found 399.1814.

2-((4-氯苄基)氧基)-*N*-(1,3-二苯基-1*H*-1,2,4-三唑-5-基)乙酰胺(**5o**): 白色固体, 产率89%. m.p. 135～136 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.13 (dd, J=2 Hz, 1.6 Hz, 2H), 7.55～7.53 (m, 2H), 7.50～7.42 (m, 6H), 7.33 (d, J=8.4 Hz, 2H), 7.19 (d, J=8.4 Hz, 2H), 4.55 (s, 2H), 4.11 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.5, 160.6, 145.5, 136.6, 134.6, 134.2, 130.2, 129.5, 129.3, 129.2, 128.9, 128.8, 128.5, 126.3, 123.8, 72.9, 69.2; HRMS (ESI) calcd for $C_{23}H_{20}ClN_4O_2$ $[M+H]^+$ 419.1269, found 419.1268.

3.2.3 (1,3-二苯基-1*H*-1,2,4-三唑-5-基)-2-苯基噁唑烷-4-酮类合成通法

氮气保护下, 在 Schlenk 管中加入 2-(苄氧基)-*N*-(1,3-二苯基-1*H*-1,2,4-三唑-5-基)乙酰胺类(0.2 mmol), NIS (0.4 mmol, 90 mg)及 4 mL 无水二氯甲烷, 于可见光下室温反应45 h, 加入40 mL二氯甲烷, 依次用10% 硫代硫酸钠溶液, 饱和食盐水洗涤, 有机层经无水硫酸钠干燥后减压浓缩, 经柱层析分离纯化得目标化合物 **6**.

(1,3-二苯基-1*H*-1,2,4-三唑-5-基)-2-苯基噁唑烷-4-酮(**6a**): 灰白色固体, 产率 54%. m.p. 115～117 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.10 (d, J=6.4 Hz, 2H), 7.45～7.31 (m, 7H), 7.25～7.19 (m, 6H), 6.57 (s, 1H), 4.62, 4.54 (ABq, J=14.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.6, 161.2, 144.0, 136.3, 134.7, 130.4, 130.1, 129.7, 129.1, 128.6, 127.2, 126.3, 124.3, 93.2, 68.1; IR (KBr) ν: 3068, 2989, 1742, 1594, 1527, 1501, 1247, 1073, 754, 692 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{19}N_4O_2$ $[M+H]^+$ 383.1503, found 383.1501.

3-(3-(4-硝基苯基)-1-苯基-1*H*-1,2,4-三唑-5-基)-2-苯基-噁唑烷-4-酮(**6b**): 淡黄色固体, 产率 58%. m.p. 69～71 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.29 (t, J=9.2 Hz, 4H), 7.47～7.34 (m, 5H,), 7.30～7.20 (m, 5H), 6.56 (s, 1H), 4.53～4.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.6, 159.2, 148.4, 136.2, 134.6, 130.6, 129.5, 129.2, 128.7, 127.2, 127.0, 124.3, 123.9, 93.1, 68.0; HRMS (ESI) calcd for $C_{23}H_{18}N_5O_4$ $[M+H]^+$ 428.1353, found 428.1352.

3-(3-(2-氟苯基)-1-苯基-1*H*-1,2,4-三唑-5-基)-2-苯基噁唑烷-4-酮(**6c**): 黄色固体, 产率 60%. m.p. 141～143 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.04 (t, J=7.2 Hz, 1H), 7.42～7.33 (m, 5H), 7.28～7.16 (m, 8H), 6.58 (s, 1H), 4.62, 4.54 (ABq, J=14.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.6, 161.6, 159.0, 157.9, 143.9, 137.8, 136.2, 134.7, 131.2, 130.5, 130.0, 129.2, 129.1, 128.6, 127.2, 124.6, 124.3, 124.1, 116.7, 116.5, 93.1, 68.1; HRMS (ESI) calcd for $C_{23}H_{18}FN_4O_2$ $[M+H]^+$ 401.1408, found 401.1409.

3-(3-(4-氯苯基)-1-苯基-1*H*-1,2,4-三唑-5-基)-2-苯基噁唑烷-4-酮(**6d**): 泡沫状, 产率 61%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.02 (d, J=8.4 Hz, 2H), 7.43～7.33 (m, 6H), 7.32～7.17 (m, 6H) , 6.54 (s, 1H), 4.53～4.64 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.8, 160.3, 144.2, 137.8, 136.1, 135.7, 134.6, 130.5, 129.3, 129.2, 128.9, 128.7, 127.6, 127.2, 124.3, 124.0, 93.2, 68.0; HRMS (ESI) calcd for $C_{23}H_{18}ClN_4O_2$ $[M+H]^+$ 417.1113, found 417.1111.

3-(3-(4-甲氧基苯基)-1-苯基-1*H*-1,2,4-三唑-5-基)-2-苯基噁唑烷-4-酮(**6e**): 黄色固体, 产率 72%. m.p. 50～54 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (d, J=6.4 Hz, 2H), 7.39～7.19 (m, 9H), 6.96 (d, J=7.2 Hz, 2H), 6.56 (s, 1H), 4.61, 4.53 (ABq, J=14.0 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.6, 161.1, 160.8, 143.9, 136.4, 134.8, 130.4, 129.1, 129.0, 128.6, 127.7, 127.1, 124.3, 122.9, 113.9, 93.1, 68.0, 55.3; HRMS (ESI) calcd for $C_{24}H_{21}N_4O_3$ $[M+H]^+$ 413.1608, found 413.1612.

3-(3-(4-氟苯基)-1-苯基-1*H*-1,2,4-三唑-5-基)-2-苯基噁唑烷-4-酮(**6f**): 粘状固体, 产率 75%. m.p. 105～107 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.09～8.06 (m, 2H), 7.42～7.32 (m, 4H), 7.25～7.18 (m, 6H), 7.12 (t, J=8.8 Hz, 2H), 6.55 (s, 1H), 4.62,4.54 (ABq, J=14.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.6, 165.0, 162.5, 160.5, 144.2, 136.3, 134.7, 130.5, 129.2, 128.6, 128.3, 128.2, 127.2, 124.3, 115.7, 115.5, 93.2, 68.0; HRMS (ESI) calcd for $C_{23}H_{18}FN_4O_2$ $[M+H]^+$ 401.1408, found 401.1407.

3-(3-(4-溴苯基)-1-苯基-1*H*-1,2,4-三唑-5-基)-2-苯基噁唑烷-4-酮(**6g**): 黄色泡沫状, 产率 58%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.96 (d, J=8.4 Hz, 2H), 7.57 (d, J=8.4 Hz, 2H), 7.45～7.32 (m, 4H), 7.27～7.17 (m, 6H), 6.54 (s, 1H), 4.51～4.64 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 170.6, 160.4, 144.3, 136.3, 134.7, 131.8, 130.5, 129.2, 129.1, 128.6, 127.8, 127.2, 124.3, 124.0, 93.1, 68.0; HRMS (ESI) calcd for $C_{23}H_{18}BrN_4O_2$ $[M+H]^+$ 461.0608, found 461.0603.

3-(3-(2,4-二氯苯基)-1-苯基-1*H*-1,2,4-三唑-5-基)-2-苯基噁唑烷-4-酮(**6h**): 淡黄色固体, 产率 55%. m.p. 98～101 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.83 (d, J=8.4 Hz, 1H), 7.52 (d, J=2 Hz, 1H), 7.43～7.32 (m, 5H), 7.30～7.02 (m, 6H), 6.57 (s, 1H), 4.51～4.64 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.5, 159.0, 143.8, 136.2, 135.8, 134.6, 133.6, 132.0, 130.6, 129.3, 129.2, 128.7,

127.8, 127.2, 127.1, 124.2, 93.2, 68.1; HRMS (ESI) calcd for $C_{23}H_{17}Cl_2N_4O_2$ [M+H]$^+$ 451.0723, found 451.0721.

3-(1-(3-氯苯基)-3-苯基-1*H*-1,2,4-三唑-5-基)-2-苯基噁唑烷-4-酮(**6i**): 灰白色固体, 产率 65%. m.p. 125～126 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.10 (s, 2H), 7.45 (s, 3H), 7.38～7.32 (m, 3H), 7.29～7.19 (m, 5H), 7.05 (s, 1H), 6.61 (s, 1H), 4.65, 4.57 (ABq, J=14.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 170.4, 161.4, 144.1, 137.2, 134.7, 130.5, 130.0, 129.9, 129.8, 129.2, 128.6, 127.0, 126.2, 124.6, 122.2, 93.0, 68.0; HRMS (ESI) calcd for $C_{23}H_{18}ClN_4O_2$ [M+H]$^+$ 417.1113, found 417.1112.

3-(1-(4-氟苯基)-3-苯基-1*H*-1,2,4-三唑-5-基)-2-苯基噁唑烷-4-酮(**6j**): 淡黄色固体, 产率 51%. m.p. 128～130 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.09 (d, J=6.8 Hz, 2H), 7.44 (d, J=6.4 Hz, 3H), 7.34 (q, J=4.8 Hz, 1H), 7.26 (d, J=4.8 Hz, 4H), 7.16～7.12 (m, 2H), 7.06 (t, J=8.4 Hz, 2H), 6.59 (s, 1H), 4.62, 4.55 (ABq, J=14.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.6, 163.9, 161.3, 144.3, 134.9, 132.4, 130.5, 130.1, 129.8, 128.7, 128.6, 127.1, 126.6, 126.5, 126.2, 116.2, 115.9, 93.1, 68.1; HRMS (ESI) calcd for $C_{23}H_{18}FN_4O_2$ [M+H]$^+$ 401.1408, found 401.1406.

2-苯基-3-(3-苯基-1-(间甲苯基)-1*H*-1,2,4-三唑-5-基)(**6k**): 灰白色固体, 收率 58%. m.p. 77～79 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.11 (d, J=4.8 Hz, 2H), 7.44～7.32 (m, 4H), 7.29～7.20 (m, 6H), 7.03 (d, J=7.6 Hz, 1H), 6.87 (s, 1H), 6.58 (s, 1H), 4.61, 4.53 (ABq, J=14.8 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.4, 161.3, 139.2, 136.2, 134.9, 130.3, 129.9, 129.6, 128.8, 128.5, 127.1, 126.2, 125.2, 121.3, 93.0, 68.0; HRMS (ESI) calcd for $C_{24}H_{21}N_4O_2$ [M+H]$^+$ 397.1659, found 397.1657.

3-(1-(2,4-二甲基苯基)-3-苯基-1*H*-1,2,4-三唑-5-基)-2-苯基噁唑烷-4-酮(**6l**): 淡黄色固体, 产率 59%. m.p. 88～92 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.09 (d, J=8.0 Hz, 2H), 7.45～7.25 (m, 8H), 7.05 (s, 1H), 6.98 (d, J=8.0 Hz, 1H), 6.78 (s, 1H), 6.55 (s, 1H), 4.55, 4.46 (ABq, J=14.8 Hz, 2H), 2.36 (s, 3H), 1.76 (s, 3H); ^{13}C NMR(100 MHz, $CDCl_3$) δ: 170.4, 161.0, 145.1, 140.0, 135.8, 135.2, 132.6, 131.8, 130.5, 129.5, 128.6, 128.5, 127.6, 126.7, 126.4, 126.2, 93.0, 67.8, 21.2, 17.1; HRMS (ESI) calcd for $C_{25}H_{23}N_4O_2$ [M+H]$^+$ 411.1816, found 411.1813.

(1,3-二苯基-1*H*-1,2,4-三唑-5-基)-2-(2-氟苯基)噁唑烷-4-酮(**6m**): 棕色固体, 产率 54%. m.p. 110～112 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.09～8.07 (m, 2H), 7.42～7.43 (m, 7H), 7.34～7.24 (m, 3H), 7.02 (t, J=7.6 Hz, 1H), 6.97 (t, J=9.4 Hz, 1H), 6.80 (s, 1H), 4.63, 4.52 (ABq, J=14.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.3, 162.3, 161.3, 159.8, 143.8, 136.5, 132.2, 132.1, 130.2, 129.6, 129.2, 129.1, 128.5, 126.3, 124.3, 124.2, 116.2, 116.0, 89.0, 67.8; HRMS (ESI) calcd for $C_{23}H_{18}FN_4O_2$ [M+H]$^+$ 401.1408, found 401.1408.

(1,3-二苯基-1*H*-1,2,4-三唑-5-基)-2-(对甲苯基)噁唑烷-4-酮(**6n**): 淡黄色固体, 产率 63%. m.p. 111～112 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.10 (d, J=7.6 Hz, 2H), 7.42 (q, J=7.2 Hz, 6H), 7.24～7.22 (m, 2H), 7.15 (d, J=7.6 Hz, 2H), 7.02 (d, J=8.0 Hz, 2H), 6.53 (s, 1H), 4.60, 4.51 (ABq, J=14.8 Hz, 2H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.6, 161.2, 144.1, 140.5, 136.4, 131.7, 130.2, 129.6, 129.2, 129.0, 128.5, 127.1, 126.2, 124.3, 93.1, 68.0, 21.2; HRMS (ESI) calcd for $C_{24}H_{21}N_4O_2$ [M+H]$^+$ 397.1659, found 397.1658.

2-(4-氯苯基)-3-(1,3-二苯基-1*H*-1,2,4-三唑-5-基)噁唑烷-4-酮(**6o**): 粘状固体, 产率 64%. m.p. 94～96 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.11～8.09 (m, 2H), 7.46～7.42 (m, 6H), 7.22～7.12 (m, 6H), 6.54 (s, 1H), 4.63, 4.56 (ABq, J=14.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 170.5, 161.3, 143.8, 136.4, 136.2, 133.2, 130.1, 129.8, 129.2, 129.1, 128.8, 128.6, 128.5, 126.2, 124.2, 92.4, 68.0; HRMS (ESI) calcd for $C_{23}H_{18}ClN_4O_2$ [M+H]$^+$ 417.1113, found 417.1110.

3.3 初步体外抗肿瘤活性测试

将乳腺癌细胞系 MDA-MB-231 和 MCF-7 及宫颈癌细胞系 HeLa 常规地补充在有 10% FBS, 4 mmol/L 谷氨酰胺, 1 mmol/L 丙酮酸钠, 100 IU/mL 青霉素, 100 μg/mL 链霉素和 0.25 μg/mL 两性霉素的培养基里, 置于 37 ℃, 5% CO_2 的培养箱内培养, 以细胞每孔 5×10^3 的密度接种在 96 孔板中培养 24 h, 分别按不同剂量浓度加入苯达莫司汀、伏立诺他及合成的三氮唑-4-噁唑烷酮化合物, 并孵育 72 h 后加入 20 μL 刃天青钠处理 2 h, 使用 Victor 微量滴定荧光计(Perkin-Elmer, USA)在 560 nm(激发), 590 nm(发射)记录荧光. IC_{50} 为与用最大量二甲基亚砜(DMSO)(0.25%)处理的细胞相比(视为 100%), 抑制 50%细胞增殖所需的化合物浓度.

辅助材料(Supporting Information) 化合物 **5a**～**5o**, **6a**～**6o** 的 ^{1}H NMR、^{13}C NMR 图谱. 这些材料可以免费从本刊网站(http://sioc-journal.cn/)上下载.

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