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含 1,2,4-三唑环的亚胺及酰亚胺类化合物的合成及生物活性

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摘要 以取代苯甲酸为原料, 经酯化、肼解、成盐和环化反应得到关键中间体 4-氨基-3-芳基-1,2,4-三唑-5-硫酮, 再分别与芳醛和邻苯二甲酸酐缩合得到亚胺及酰亚胺, 最后经硫醚化反应合成了 24 个新型的含有 1,2,4-三唑结构单元的亚胺及酰亚胺类化合物, 其结构经质谱、红外光谱、核磁共振及元素分析确认. 初步生物活性测试结果表明, 在实验浓度下大部分化合物表现出一定的杀菌活性, 尤其是化合物 **9**a, **9**d 和 **9**e 对水稻纹枯病菌的抑制活性与对照杀菌剂氟硅唑相当. 初步的细胞毒性实验结果表明, 化合物 **7**c, **7**f 和 **9**k 对人肺癌细胞(A549)的抑制活性与对照药品 5-氟尿嘧啶基本处于同一水平.

关键词 1,2,4-三唑; 杀菌活性; 抗肿瘤活性

中图分类号 O625 **文献标志码** A

1,2,4-三唑是一类具有广泛生物活性的五元含氮杂环化合物, 作为药物分子设计与合成的基本结构一直备受关注[1~3]. 在农药领域, 1,2,4-三唑类化合物作为杀菌剂、杀虫剂和除草剂的应用已有几十年的历史, 因其具有用量低和环境安全性好的特点, 目前仍是新农药分子设计、合成与生物活性研究中的热点[4~6]. 近年来, 三唑类化合物被发现具有广泛的药理活性, 如抗菌[7]、消炎[8]、抗过敏[9]、抗抑郁[10]、抗惊厥[11]和抗肿瘤[12,13]等活性. 亚胺及酰亚胺类化合物具有独特的分子结构, 其杂化轨道的 N 原子具有孤对电子, 有良好的配位能力, 常常表现出良好的抗癌[14~16]、抗菌[17]和抗病毒[18]等活性. 而 SCH_2 是具有生物相容性且能保持分子自由旋转的官能团, 有利于药物进入有机体与受体在合适的位置结合.

最近, 本课题组[19,20]根据生物活性叠加原理, 将活性功能团 1,2,4-三唑、含 SCH_2 官能团、亚胺以及酰亚胺片段进行组装, 合成了一系列具有良好抗肿瘤及杀菌活性的化合物. 为了筛选出活性更好的 1,2,4-三唑类先导化合物, 本文在前期研究的基础上, 分别对 1,2,4-三唑环的 3-位硫醚侧链、*N*4-位取代基和 5-位苯环的取代基进行了结构改造和修饰, 设计合成了标题化合物, 其结构经 ^{1}H NMR, IR, MS 及元素分析确认.

1 实验部分

1.1 仪器与试剂

Electrothermal 数字熔点测定仪; MERCURY-PLUS400 型核磁共振仪(氘代氯仿为溶剂, TMS 为内标); Micromass ZQ4000 型质谱仪; Vario El Ⅲ CHNSO 元素分析仪; Thermo Fisher Nicolet 6700 型红外光谱仪(KBr 压片); GF_{254}60 型薄层层析硅胶(青岛海洋化工厂).

所用试剂均为分析纯试剂, 使用前经常规处理; 4-氨基-3-(3,4,5-三甲氧基苯基)-5-巯基-1,2,4-三唑参照文献[21]方法制备, m. p. 226 ~ 227 ℃(文献值[21]: 228 ~ 230 ℃); 4-氨基-3-苯基-5-巯基-1,2,

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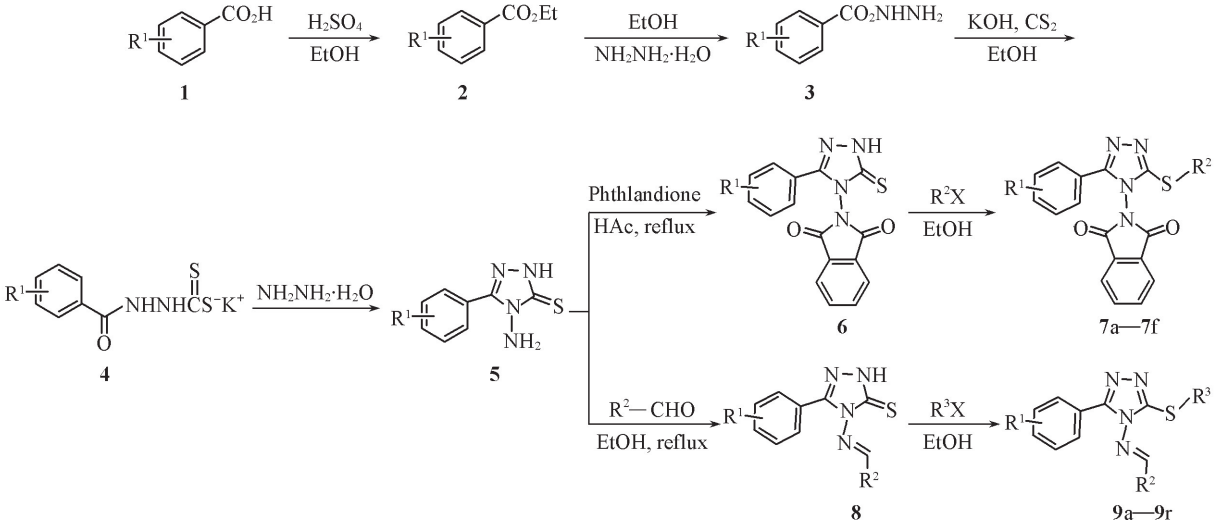
4-三唑参照文献[22]方法制备, m. p. 201 ~203 ℃(文献值[22]: 198 ~200 ℃).

1.2 实验过程

目标化合物的合成路线如 Scheme 1 所示.



7a: R^1 =H, R^2 =4-$FC_6H_4CH_2$; **7**b: R^1 =H, R^2 =CH≡CCH_2; **7**c: R^1 =H, R^2 =4-$ClC_6H_4COCH_2$; **7**d: R^1 =H, R^2 =$C_6H_5CH_2$; **7**e: R^1 =H, R^2 =Me; **7**f: R^1 =H, R^2 =4-Me $C_6H_4COCH_2$; **9**a: R^1 =H, R^2 =C_6H_5, R^3 =Me; **9**b: R^1 =H, R^2 =C_6H_5, R^3 =$C_6H_5CH_2$; **9**c: R^1 =H, R^2 =C_6H_5, R^3 =CH_2C═CH_2; **9**d: R^1 =H, R^2 =C_6H_5, R^3 =4-$FC_6H_4CH_2$; **9**e: R^1 =H, R^2 =C_6H_5, R^3 =CH≡CCH_2; **9**f: R^1 =3,4,5-$(MeO)_3$, R^2 =3,4,5-$(MeO)_3C_6H_2$, R^3 =Me; **9**g: R^1 =3,4,5-$(MeO)_3$, R^2 =3,4,5-$(MeO)_3C_6H_2$, R^3 =CH_2C═CH_2; **9**h: R^1 =3,4,5-$(MeO)_3$, R^2 =3,4,5-$(MeO)_3C_6H_2$, R^3 =CH≡CCH_2; **9**i: R^1 =3,4,5-$(MeO)_3$, R^2 =3,4,5-$(MeO)_3C_6H_2$, R^3 =4-$FC_6H_4CH_2$; **9**j: R^1 =3,4,5-$(MeO)_3$, R^2 =3,4,5-$(MeO)_3C_6H_2$, R^3 =2-$ClC_6H_4CH_2$; **9**k: R^1 =3,4,5-$(MeO)_3$, R^2 =3,4,5-$(MeO)_3C_6H_2$, R^3 =4-$ClC_6H_4COCH_2$; **9**l: R^1 =3,4,5-$(MeO)_3$, R^2 =3,4,5-$(MeO)_3C_6H_2$, R^3 =$C_6H_5CH_2$; **9**m: R^1 =3,4,5-$(MeO)_3$, R^2 =4-FC_6H_4, R^3 =Me; **9**n: R^1 =3,4,5-$(MeO)_3$, R^2 =4-FC_6H_4, R^3 =$C_6H_5CH_2$; **9**o: R^1 =3,4,5-$(MeO)_3$, R^2 =4-FC_6H_4, R^3 =2-$ClC_6H_4CH_2$; **9**p: R^1 =3,4,5-$(MeO)_3$, R^2 =4-FC_6H_4, R^3 =4-$FC_6H_4CH_2$; **9**q: R^1 =3,4,5-$(MeO)_3$, R^2 =4-FC_6H_4, R^3 =CH≡CCH_2; **9**r: R^1 =3,4,5-$(MeO)_3$, R^2 =4-FC_6H_4, R^3 =CH_2C═CH_2.

Scheme 1 Synthetic routes of the title compounds

1.2.1 中间体 **6** 和 **8** 的合成及表征 2-[3-苯基-5-硫酮-1*H*-1,2,4-三唑-4(5*H*)-基]异吲哚-1,3-二酮(**6**)的合成: 将 1.92 g(10.0 mmol) 4-氨基-3-苯基-1*H*-1,2,4-三唑-5(4*H*)-硫酮和 1.63 g(11.0 mmol)邻苯二甲酸酐溶于 30 mL 冰醋酸中, 加热回流, 用 TLC 监测反应完成后, 减压除去溶剂, 用乙醇重结晶得淡黄色晶体 1.38 g, 收率 81%, m. p. 216 ~218 ℃. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 7.43(dd, J=10.6, 18.6 Hz, 2H, ArH), 7.51(d, J=7.6 Hz, 1H, ArH), 7.63(d, J=7.2 Hz, 2H, ArH), 7.87 ~7.91(m, 2H, ArH), 8.01(dd, J=3.0, 5.4 Hz, 2H, ArH), 11.12(s, 1H, NH); ESI-MS, m/z: 345.7 $[M+Na]^+$, 323.7$[M+1]^+$; IR(KBr), $\tilde{\nu}$/cm^{-1}: 3295, 2360, 1801, 1757, 1738, 1371, 1292, 719.

(*E*)-4-取代苯基亚氨基-3-(3,4,5-三甲氧基苯基)-1*H*-1,2,4-三唑-5(4*H*)-硫酮(**8**)的合成: 将 1.92 g(10.0 mmol) 4-氨基-3-苯基-1*H*-1,2,4-三唑-5(4*H*)-硫酮和 10.2 mmol 取代苯甲醛溶于 20 mL 无水乙醇中, 并加入 2 滴冰醋酸, 加热回流 2 ~3 h, 反应完成后, 冷却至室温, 析出大量固体, 过滤, 干燥, 用乙醇重结晶得无色或淡黄色晶体.

(*E*)-4-苯基亚氨基-3-苯基-1*H*-1,2,4-三唑-5(4*H*)-硫酮(**8**a): 无色晶体, 收率 89%, m. p. 167 ~168 ℃. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 7.48 ~7.57(m, 6H, ArH), 7.89(d, J=7.2 Hz, 2H, ArH), 7.95(t, J=6.4 Hz, 2H, ArH), 10.07(s, 1H, CH═N), 11.56(s, 1H, NH); ESI-MS, m/z: 303.7 $[M+Na]^+$, 281.7$[M+1]^+$; IR(KBr), $\tilde{\nu}$/cm^{-1}: 3110, 3055, 3027, 2999, 1573, 1504, 1483, 1276, 712, 680.

(*E*)-4-(3,4,5-三甲氧基苯基)亚氨基-3-(3,4,5-三甲氧基苯基)-1*H*-1,2,4-三唑-5(4*H*)-硫酮(**8**b):

无色晶体，收率 94%，m. p. 208 ~ 210 ℃. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 3.86(s, 6H, 2×OCH_3), 3.90(s, 9H, 3×OCH_3), 3.94(s, 3H, OCH_3), 7.15(s, 2H, ArH), 7.27(s, 2H, ArH), 9.76(s, 1H, CH═N), 11.38(s, 1H, NH); ESI-MS, *m/z*: 483.6[M+Na]$^+$, 461.7[M+1]$^+$; IR(KBr), $\tilde{\nu}$/cm^{-1}: 3262, 2360, 1594, 1507, 1471, 1455, 1134, 840.

(*E*)-4-对氟苯基亚氨基-3-(3,4,5-三甲氧基苯基)-1*H*-1,2,4-三唑-5(4*H*)-硫酮(**8c**)：淡黄色晶体，收率 93%，m. p. 191 ~ 193 ℃. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 3.84(s, 6H, 2×OCH_3), 3.89(s, 3H, OCH_3), 7.15 ~ 7.24(m, 4H, ArH), 7.91(s, 2H, ArH), 9.96(s, 1H, CH═N), 11.51(s, 1H, NH); ESI-MS, *m/z*: 411.7[M+Na]$^+$, 389.7[M+1]$^+$; IR(KBr), $\tilde{\nu}$/cm^{-1}: 3270, 2360, 1558, 1508, 1468, 1240, 1153, 837.

1.2.2　目标化合物 **7**a ~ **7**f 和 **9**a ~ **9**r 的合成　目标化合物 **7**a ~ **7**f 的合成：向 100 mL 单颈圆底烧瓶中加入 0.50 g(1.55 mmol) 中间体 **6**、0.26 g(1.86 mmol) 新炒的碳酸钾及 30 mL 无水乙醇，室温下搅拌 20 min，加入 1.55 mmol 卤代烃后加热回流继续反应，用 TLC 监测反应，约 6 ~ 8 h 后反应基本完全. 抽滤，减压浓缩，经硅胶柱层析[*V*(石油醚) : *V*(丙酮) = 8 : 1]得目标化合物 **7**a ~ **7**f.

2-(5-苯基-3-对氟苄硫基-4*H*-1,2,4-三唑-4-基)异吲哚-1,3-二酮(**7**a)：白色固体，收率 73%，m. p. 172 ~ 173 ℃. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 4.43(s, 2H, SCH_2), 6.94(t, *J* = 8.8 Hz, 2H, ArH), 7.30(dd, *J* = 5.2, 8.8 Hz, 2H, ArH), 7.37(d, *J* = 7.2 Hz, 3H, ArH), 7.58(t, *J* = 4.2 Hz, 2H, ArH), 7.87(dd, *J* = 3.2, 5.6 Hz, 2H, ArH), 7.94(dd, *J* = 2.8, 5.6 Hz, 2H, ArH); ESI-MS, *m/z*: 431.2[M+1]$^+$; IR(KBr), $\tilde{\nu}$/cm^{-1}: 3457, 3073, 1802, 1760, 1475, 1253, 726; 元素分析(%, $C_{23}H_{15}FN_4O_2S$ 计算值): C 64.49(64.18), H 3.61(3.51), N 12.97(13.02), S 7.24(7.45).

2-(3,5-二苯基-5-炔丙基硫基-4*H*-1,2,4-三唑-4-基)异吲哚-1,3-二酮(**7**b)：淡黄色固体，收率 71%，m. p. 125 ~ 127 ℃. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 2.25(s, 1H, ≡CH), 3.93(s, 2H, SCH_2), 7.40(dd, *J* = 7.0, 14.2 Hz, 3H, ArH), 7.58(d, *J* = 7.2 Hz, 2H, ArH), 7.89(d, *J* = 2.8 Hz, 2H, ArH), 7.96(d, *J* = 2.8 Hz, 2H, ArH); ESI-MS, *m/z*: 399.1[M+K]$^+$, 361.2[M+1]$^+$; IR(KBr), $\tilde{\nu}$/cm^{-1}: 3243, 1801, 1757, 1443, 1283, 645; 元素分析(%, $C_{19}H_{12}N_4O_2S$ 计算值): C 63.06(63.32), H 3.10(3.36), N 15.51(15.55), S 9.16(8.90).

2-[5-苯基-3-(2-对氯苯基-2-羰基硫基)-4*H*-1,2,4-三唑-4-基]异吲哚-1,3-二酮(**7**c)：淡黄色固体，收率 67%，m. p. 153 ~ 155 ℃. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 4.96(s, 2H, SCH_2), 7.37 ~ 7.47(m, 5H, ArH), 7.57(t, *J* = 2.1Hz, 2H, ArH), 7.87 ~ 7.96(m, 6H, ArH); ESI-MS, *m/z*: 475.2[M+1]$^+$; IR(KBr), $\tilde{\nu}$/cm^{-1}: 3081, 1802, 1757, 1673, 1462, 1235, 713; 元素分析(%, $C_{24}H_{15}ClN_4O_3S$ 计算值): C 60.32(60.70), H 2.98(3.18), N 11.59(11.80), S 6.93(6.75).

2-(5-苯基-3-苄硫基-4*H*-1,2,4-三唑-4-基)异吲哚-1,3-二酮(**7**d)：淡黄色固体，收率 74%，m. p. 138 ~ 140 ℃. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 4.47(s, 2H, SCH_2), 7.26 ~ 7.41(m, 8H, ArH), 7.58(d, *J* = 7.6 Hz, 2H, ArH), 7.86(d, *J* = 3.2 Hz, 2H, ArH), 7.94(t, *J* = 3.6 Hz, 2H, ArH); ESI-MS, *m/z*: 435.2[M+Na]$^+$, 413.3[M+1]$^+$; IR(KBr), $\tilde{\nu}$/cm^{-1}: 3062, 1804, 1757, 1706, 1454, 1296, 713; 元素分析(%, $C_{23}H_{16}N_4O_2S$ 计算值): C 67.07(66.97), H 3.66(3.91), N 13.51(13.58), S 7.95(7.77).

2-(3-甲硫基-5-苯基-4*H*-1,2,4-三唑-4-基)异吲哚-1,3-二酮(**7**e)：淡黄色固体，收率 71%，m. p. 117 ~ 119 ℃. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 2.69(s, 3H, SCH_3), 7.34 ~ 7.40(m, 3H, ArH), 7.56(d, *J* = 7.2 Hz, 2H, ArH), 7.87(dd, *J* = 3.2, 5.2 Hz, 2H, ArH), 7.96(dd, *J* = 3.2 Hz, *J* = 5.2 Hz, 2H, ArH); ESI-MS, *m/z*: 359.1[M+Na]$^+$, 337.3[M+1]$^+$; IR(KBr), $\tilde{\nu}$/cm^{-1}: 1797, 1756, 1467, 1299, 823; 元素分析(%, $C_{17}H_{12}N_4O_2S$ 计算值): C 60.92(60.70), H 3.55(3.60), N 16.69(16.66), S 9.71(9.53).

2-[3-(2-羰基-2-对甲基苯基硫基)-5-苯基-4*H*-1,2,4-三唑-4-基]异吲哚-1,3-二酮(**7**f)：淡黄色固体，收率 79%，m. p. 122 ~ 124 ℃. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 2.40(s, 3H, Ar—CH_3), 4.99(s,

2H, SCH_2), 7.26(d, J=8.0 Hz, 2H, ArH), 7.39(dd, J=7.4, 13.4 Hz, 3H, ArH); 7.58(d, J=6.8 Hz, 2H, ArH), 7.88(t, J=3.4 Hz, 4H, ArH), 7.95(dd, J=3.2, 5.6 Hz, 2H, ArH); ESI-MS, m/z: 455.3[M+1]$^+$; IR(KBr), $\tilde{\nu}$/cm^{-1}: 3406, 1799, 1757, 1676, 1439, 1280, 712; 元素分析(%, $C_{25}H_{18}N_4O_3S$计算值): C 66.30(66.07), H 4.10(3.99), N 12.09(12.33), S 7.17(7.05).

目标化合物**9**a~**9**r的合成: 向25 mL圆底烧瓶中加入1.2 mmol中间体**8**和4.8 mL 0.01 g/mL氢氧化钠溶液, 室温下搅拌使其充分溶解得澄清液, 然后滴加1.1 mmol卤代烃的DMF溶液(1 mL). 用TLC监测反应完成后, 将反应混合物倒入水中, 析出白色或淡黄色固体, 静置, 抽滤, 用乙醇重结晶得目标化合物**9**a~**9**r.

(*E*)-3-甲硫基-5-苯基-*N*-苯亚甲基-4*H*-1,2,4-三唑-4-胺(**9**a): 白色固体, 收率86%, m.p. 87~89 ℃. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 2.77(s, 3H, SCH_3), 7.42~7.52(m, 5H, ArH), 7.58(t, J=7.4 Hz, 1H, ArH), 7.82(d, J=7.6 Hz, 2H, ArH), 7.89(dd, J=2.8, 6.4 Hz, 2H, ArH), 8.48(s, 1H, CH═N); ESI-MS, m/z: 317.0[M+Na]$^+$, 295.1[M+1]$^+$; IR(KBr), $\tilde{\nu}$/cm^{-1}: 3401, 1609, 1469, 1437, 1421, 999, 769, 691; 元素分析(%, $C_{16}H_{14}N_4S$ 计算值): C 65.32(65.28), H 4.61(4.79), N 19.08(19.03), S 10.51(10.89).

(*E*)-5-苯基-*N*-苯亚甲基-3-苄基硫基-4*H*-1,2,4-三唑-4-胺(**9**b): 白色固体, 收率78%, m.p. 111~112 ℃. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 4.50(s, 2H, SCH_2), 7.25~7.31(m, 3H, ArH), 7.35(dd, J=2.0, 7.6 Hz, 2H, ArH), 7.41~7.44(m, 3H, ArH), 7.48(t, J=7.6 Hz, 2H, ArH), 7.50~7.59(m, 1H, ArH), 7.75(t, J=4.2 Hz, 2H, ArH), 7.90~7.92(m, 2H, ArH), 8.28(s, 1H, CH═N); ESI-MS, m/z: 393.1[M+Na]$^+$, 371.1[M+1]$^+$; IR(KBr), $\tilde{\nu}$/cm^{-1}: 3296, 1610, 1494, 1450, 1417, 777, 706; 元素分析(%, $C_{22}H_{18}N_4S$ 计算值): C 71.43(71.31), H 4.80(4.90), N 15.23(15.12), S 8.54(8.66).

(*E*)-5-苯基-3-烯丙基甲硫基-*N*-苯亚甲基-4*H*-1,2,4-三唑-4-胺(**9**c): 白色固体, 收率83%, m.p. 91~93 ℃. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 3.90(d, J=7.2 Hz, 2H, SCH_2), 5.14(d, J=10.0 Hz, 1H, ═CH_a), 5.28(dd, J=1.2, 16.8 Hz, 1H, ═CH_b), 5.93~6.03(m, 1H, CH_2CH═), 7.41~7.45(m, 3H, ArH), 7.50(t, J=7.4 Hz, 2H, ArH), 7.57~7.60(m, 1H, ArH), 7.83(t, J=4.4 Hz, 2H, ArH), 7.91~7.93(m, 2H, ArH), 8.48(s, 1H, CH═N); ESI-MS, m/z: 343.4[M+Na]$^+$, 321.4[M+1]$^+$; IR(KBr), $\tilde{\nu}$/cm^{-1}: 3452, 1607, 1471, 1450, 1421, 989, 703; 元素分析(%, $C_{18}H_{16}N_4S$ 计算值): C 67.19(67.47), H 4.96(5.03), N 17.43(17.49), S 9.80(10.01).

(*E*)-5-苯基-*N*-苯亚甲基-3-对氟苄基硫基-4*H*-1,2,4-三唑-4-胺(**9**d): 白色固体, 收率69%, m.p. 79~81 ℃. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 4.56(s, 2H, SCH_2), 6.95(t, J=8.6 Hz, 2H, ArH), 7.31~7.35(m, 2H, ArH), 7.42(dd, J=3.6, 6.4 Hz, 3H, ArH), 7.48(t, J=7.4 Hz, 2H, ArH), 7.58(dd, J=4.0, 10.4 Hz, 1H, ArH), 7.76(t, J=4.2 Hz, 2H, ArH), 7.89~7.91(m, 2H, ArH), 8.32(s, 1H, CH═N); ESI-MS, m/z: 411.2[M+Na]$^+$, 389.2[M+1]$^+$; IR(KBr), $\tilde{\nu}$/cm^{-1}: 1598, 1508, 1471, 1452, 1220, 774, 701; 元素分析(%, $C_{22}H_{17}FN_4S$ 计算值): C 68.24(68.02), H 4.32(4.41), N 14.50(14.42), S 8.54(8.25).

(*E*)-5-苯基-3-炔丙基硫基-*N*-苯亚甲基-4*H*-1,2,4-三唑-4-胺(**9**e): 白色固体, 收率85%, m.p. 77~79 ℃. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 2.28(t, J=2.6 Hz, 1H, ≡CH), 4.04(d, J=2.4 Hz, 2H, SCH_2), 7.44(t, J=3.4 Hz, 3H, ArH), 7.51(t, J=7.6 Hz, 2H, ArH), 7.58~7.61(m, 1H, ArH), 7.83(t, J=9.6 Hz, 2H, ArH), 7.90~7.93(m, 2H, ArH), 8.50(s, 1H, CH═N); ESI-MS, m/z: 341.1[M+Na]$^+$, 319.0[M+1]$^+$; IR(KBr), $\tilde{\nu}$/cm^{-1}: 3290, 3279, 1601, 1464, 1357, 1227, 699, 687; 元素分析(%, $C_{18}H_{14}N_4S$ 计算值): C 67.81(67.90), H 4.36(4.43), N 17.63(17.60), S 10.18(10.07).

(*E*)-3-甲硫基-5-(3,4,5-三甲氧基苯基)-*N*-(3,4,5-三甲氧基苯基亚甲基)-4*H*-1,2,4-三唑-4-胺(**9**f): 白色固体, 收率94%, m.p. 168~169 ℃. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 2.76(s, 3H, SCH_3),

3.83(s, 6H, 2×OCH_3), 3.87(s, 3H, OCH_3), 3.90(s, 6H, 2×OCH_3), 3.94(s, 3H, OCH_3), 7.08(s, 2H, ArH), 7.19(s, 2H, ArH), 8.37(s, 1H, CH═N); ESI-MS, *m/z*: 497.3[M+Na]$^+$, 475.3[M+1]$^+$; IR(KBr), $\tilde{\nu}$/cm^{-1}: 3357, 2975, 1577, 1467, 1359, 1244, 1123, 740; 元素分析(%, $C_{22}H_{26}N_4O_6S$ 计算值): C 55.77(55.68), H 5.32(5.52), N 11.98(11.81), S 6.66(6.76).

(*E*)-3-烯丙基硫基-5-(3,4,5-三甲氧基苯基)-*N*-(3,4,5-三甲氧基苯基亚甲基)-4*H*-1,2,4-三唑-4-胺(**9**g): 白色固体, 收率88%, m. p. 145～147 ℃. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 3.83(s, 6H, 2×OCH_3), 3.88(s, 3H, OCH_3), 3.91(s, 6H, 2×OCH_3), 3.92(d, *J*=4.8 Hz, 2H, SCH_2), 3.95(s, 3H, OCH_3), 5.16(d, *J*=10.0 Hz, 1H, ═CH_a), 5.28(dd, *J*=1.2, 17.2 Hz, 1H, ═CH_b), 5.94～6.04(m, 1H, CH_2CH═), 7.10(s, 2H, ArH), 7.24(s, 2H, ArH), 8.36(s, 1H, CH═N); ESI-MS, *m/z*: 523.4[M+Na]$^+$, 501.4[M+1]$^+$; IR(KBr), $\tilde{\nu}$/cm^{-1}: 3365, 2992, 2360, 1589, 1481, 1467, 1360, 1124, 720; 元素分析(%, $C_{24}H_{28}N_4O_6S$ 计算值): C 57.47(57.59), H 5.47(5.64), N 11.38(11.19), S 6.38(6.41).

(*E*)-3-炔丙基硫基-5-(3,4,5-三甲氧基苯基)-*N*-(3,4,5-三甲氧基苯基亚甲基)-4*H*-1,2,4-三唑-4-胺(**9**h): 白色固体, 收率79%, m. p. 182～184 ℃. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 2.29(t, *J*=2.4 Hz, 1H, ≡CH), 3.83(s, 6H, 2×OCH_3), 3.88(s, 3H, OCH_3), 3.91(s, 6H, 2×OCH_3), 3.95(s, 3H, OCH_3), 4.05(d, *J*=2.4 Hz, 2H, SCH_2), 7.09(s, 2H, ArH), 7.22(s, 2H, ArH), 8.38(s, 1H, CH═N); ESI-MS, *m/z*: 499.3[M+1]$^+$; IR(KBr), $\tilde{\nu}$/cm^{-1}: 3380, 3246, 2360, 1588, 1481, 1468, 1159, 1124, 722; 元素分析(%, $C_{24}H_{26}N_4O_6S$ 计算值): C 57.49(57.82), H 5.07(5.26), N 11.06(11.24), S 6.54(6.43).

(*E*)-5-(3,4,5-三甲氧基苯基)-3-对氟苄基硫基-*N*-(3,4,5-三甲氧基苯基亚甲基)-4*H*-1,2,4-三唑-4-胺(**9**i): 白色固体, 收率75%, m. p. 157～158 ℃. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 3.83(s, 6H, 2×OCH_3), 3.89(s, 9H, 3×OCH_3), 3.94(s, 3H, OCH_3), 4.44(s, 2H, SCH_2), 6.95(d, *J*=8.8 Hz, 2H, ArH), 7.01(s, 2H, ArH), 7.21(s, 2H, ArH), 7.34(d, *J*=5.6 Hz, 2H, ArH), 8.15(s, 1H, CH═N); ESI-MS, *m/z*: 591.3[M+Na]$^+$, 569.4[M+1]$^+$; IR(KBr), $\tilde{\nu}$/cm^{-1}: 3326, 1578, 1477, 1457, 1239, 1188, 1129; 元素分析(%, $C_{28}H_{29}N_4O_6S$ 计算值): C 59.26(59.14), H 5.30(5.14), N 9.95(9.85), S 5.55(5.64).

(*E*)-5-(3,4,5-三甲氧基苯基)-3-邻氯苄基硫基-*N*-(3,4,5-三甲氧基苯基亚甲基)-4*H*-1,2,4-三唑-4-胺(**9**j): 白色固体, 收率78%, m. p. 124～125 ℃. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 3.83(s, 6H, 2×OCH_3), 3.88(s, 3H, OCH_3), 3.90(s, 6H, 2×OCH_3), 3.94(s, 3H, OCH_3), 4.59(s, 2H, SCH_2), 7.01(s, 2H, ArH), 7.15～7.24(m, 4H, ArH), 7.35(dd, *J*=1.6, 7.6 Hz, 1H, ArH), 7.48(dd, *J*=1.8, 7.4 Hz, 1H, ArH), 8.18(s, 1H, CH═N); ESI-MS, *m/z*: 607.3[M+Na]$^+$, 585.3[M+1]$^+$; IR(KBr), $\tilde{\nu}$/cm^{-1}: 3458, 2995, 1608, 1481, 1469, 1242, 1127, 1006, 738; 元素分析(%, $C_{28}H_{29}N_4O_6S$ 计算值): C 57.41(57.48), H 4.93(5.00), N 9.45(9.58), S 5.60(5.48).

(*E*)-1-对氯苯基-5-(3,4,5-三甲氧基苯基)-2-[4-(3,4,5-三甲氧基苯基亚甲亚胺基)]-4*H*-1,2,4-三唑-3-硫基乙酮(**9**k): 白色固体, 收率76%, m. p. 149～151 ℃. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 3.82(s, 6H, 2×OCH_3), 3.88(s, 3H, OCH_3), 3.91(s, 6H, 2×OCH_3), 3.95(s, 3H, OCH_3), 4.91(s, 2H, SCH_2), 7.09(s, 2H, ArH), 7.18(s, 2H, ArH), 7.47(d, *J*=4.4 Hz, 2H, ArH), 7.99(d, *J*=8.8 Hz, 2H, ArH), 8.44(s, 1H, CH═N); ESI-MS, *m/z*: 635.2[M+Na]$^+$, 613.3[M+1]$^+$; IR(KBr), $\tilde{\nu}$/cm^{-1}: 3466, 2941, 1589, 1487, 1360, 1155, 1130, 770; 元素分析(%, $C_{29}H_{29}ClN_4O_7S$ 计算值): C 56.72(56.81), H 4.67(4.77), N 9.06(9.14), S 5.44(5.23).

(*E*)-5-(3,4,5-三甲氧基苯基)-3-苄基硫基-*N*-(3,4,5-三甲氧基苯基亚甲基)-4*H*-1,2,4-三唑-4-胺(**9**l): 白色固体, 收率73%, m. p. 141～142 ℃. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 3.82(s, 6H, 2×OCH_3), 3.87(s, 3H, OCH_3), 3.89(s, 6H, 2×OCH_3), 3.93(s, 3H, OCH_3), 4.49(s, 2H, SCH_2), 7.01(s, 2H, ArH), 7.23(s, 2H, ArH), 7.27～7.31(m, 3H, ArH), 7.35(dd, *J*=2.0 Hz, *J*=7.6 Hz,

2H, ArH), 8.13(s, 1H, CH═N); ESI-MS, *m/z*: 573.4[M+Na]$^+$, 551.4[M+1]$^+$; IR(KBr), $\tilde{\nu}$/cm^{-1}: 3432, 2937, 1578, 1524, 1457, 1239, 1128, 1006, 742; 元素分析(%, $C_{28}H_{30}N_4O_6S$ 计算值): C 61.34(61.08), H 5.38(5.49), N 10.32(10.18), S 5.63(5.82).

(*E*)-3-甲硫基-5-(3,4,5-三甲氧基苯基)-*N*-对氟苯基亚甲基-4*H*-1,2,4-三唑-4-胺(**9**m): 白色固体, 收率71%, m.p. 168~169 ℃. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 2.76(s, 3H, SCH_3), 3.80(s, 6H, 2×OCH_3), 3.87(s, 3H, OCH_3), 7.20(t, *J*=6.8 Hz, 4H, ArH), 7.87(dd, *J*=5.6, 8.4 Hz, 2H, ArH), 8.49(s, 1H, CH═N); ESI-MS, *m/z*: 425.7[M+Na]$^+$, 403.8[M+1]$^+$; IR(KBr), $\tilde{\nu}$/cm^{-1}: 2939, 1614, 1522, 1487, 1234, 1158, 1122, 850, 735; 元素分析(%, $C_{19}H_{19}FN_4O_3S$ 计算值): C 56.99(56.70), H 4.65(4.76), N 14.07(13.92), S 7.68(7.97).

(*E*)-5-(3,4,5-三甲氧基苯基)-3-苄基硫基-*N*-对氟苯基亚甲基-4*H*-1,2,4-三唑-4-胺(**9**n): 白色固体, 收率69%, m.p. 125~127 ℃. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 3.78(s, 6H, 2×OCH_3), 3.84(s, 3H, OCH_3), 4.44(s, 2H, SCH_2), 7.13~7.17(m, 4H, ArH), 7.23~7.25(m, 3H, ArH), 7.30(t, *J*=6.0 Hz, 2H, ArH), 7.76~7.79(m, 2H, ArH), 8.22(s, 1H, CH═N); ESI-MS, *m/z*: 501.7[M+Na]$^+$, 479.7[M+1]$^+$; IR(KBr), $\tilde{\nu}$/cm^{-1}: 2970, 2938, 1602, 1524, 1457, 1173, 1125, 738; 元素分析(%, $C_{25}H_{23}FN_4O_3S$ 计算值): C 62.50(62.75), H 4.78(4.84), N 11.78(11.71), S 6.93(6.70).

(*E*)-5-(3,4,5-三甲氧基苯基)-3-邻氯苄基硫基-*N*-对氟苯基亚甲基-4*H*-1,2,4-三唑-4-胺(**9**o): 白色固体, 收率69%, m.p. 125~127 ℃. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 3.79(s, 6H, 2×OCH_3), 3.86(s, 3H, OCH_3), 4.55(s, 2H, SCH_2), 7.14~7.19(m, 6H, ArH), 7.31(dd, *J*=1.4, 8.0 Hz, 1H, ArH), 7.42(d, *J*=1.6 Hz, 1H, ArH), 7.79(dd, *J*=5.4, 8.6 Hz, 2H, ArH), 8.32(s, 1H, CH═N); ESI-MS, *m/z*: 535.6[M+Na]$^+$, 513.6[M+1]$^+$; IR(KBr), $\tilde{\nu}$/cm^{-1}: 2952, 2932, 1614, 1601, 1486, 1461, 1152, 863, 774, 539; 元素分析(%, $C_{25}H_{22}ClFN_4O_3S$ 计算值): C 58.78(58.53), H 4.23(4.32), N 11.05(10.92), S 6.17(6.25).

(*E*)-5-(3,4,5-三甲氧基苯基)-3-对氟苄基硫基-*N*-对氟苯基亚甲基-4*H*-1,2,4-三唑-4-胺(**9**p): 白色固体, 收率78%, m.p. 136~137 ℃. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 3.79(s, 6H, 2×OCH_3), 3.85(s, 3H, OCH_3), 4.42(s, 2H, SCH_2), 6.94(t, *J*=8.6 Hz, 2H, ArH), 7.17(t, *J*=7.2 Hz, 4H, ArH), 7.30(dd, *J*=5.4, 8.6 Hz, 2H, ArH), 7.79(dd, *J*=5.4, 8.6 Hz, 2H, ArH), 8.28(s, 1H, CH═N); ESI-MS, *m/z*: 519.6[M+Na]$^+$, 497.7[M+1]$^+$; IR(KBr), $\tilde{\nu}$/cm^{-1}: 2961, 2937, 1601, 1510, 1479, 1172, 1126, 860; 元素分析(%, $C_{25}H_{22}F_2N_4O_3S$ 计算值): C 60.63(60.47), H 4.38(4.47), N 11.41(11.28), S 6.73(6.46).

(*E*)-3-炔丙基硫基-5-(3,4,5-三甲氧基苯基)-*N*-对氟苯基亚甲基-4*H*-1,2,4-三唑-4-胺(**9**q): 白色固体, 收率85%, m.p. 147~148 ℃. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 2.26(t, *J*=2.6 Hz, 1H, ≡CH), 3.79(s, 6H, 3×OCH_3), 3.85(s, 3H, OCH_3), 4.00(d, *J*=2.4 Hz, 2H, SCH_2), 7.19(t, *J*=9.4 Hz, 4H, ArH), 7.87(dd, *J*=5.4, 8.6 Hz, 2H, ArH), 8.48(s, 1H, CH═N); ESI-MS, *m/z*: 449.6[M+Na]$^+$, 427.7[M+1]$^+$; IR(KBr), $\tilde{\nu}$/cm^{-1}: 3253, 2987, 1601, 1484, 1284, 1240, 1125, 860, 734, 543; 元素分析(%, $C_{21}H_{19}FN_4O_3S$ 计算值): C 59.39(59.14), H 4.32(4.49), N 13.49(13.14), S 7.39(7.52).

(*E*)-3-烯丙基硫基-5-(3,4,5-三甲氧基苯基)-*N*-对氟苯基亚甲基-4*H*-1,2,4-三唑-4-胺(**9**r): 白色固体, 收率76%, m.p. 115~116 ℃. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 3.78(s, 6H, 2×OCH_3), 3.84(s, 3H, OCH_3), 3.92(d, *J*=4.8 Hz, 2H, SCH_2), 5.11(d, *J*=10.0 Hz, 1H, ═CH_a), 5.25(dd, *J*=1.2, 17.2 Hz, 1H, ═CH_b), 5.87~5.96(m, 1H, CH_2CH═), 7.17(dd, *J*=6.8, 10.0 Hz, 4H, ArH), 7.87(dd, *J*=5.4, 8.6 Hz, 2H, ArH), 8.46(s, 1H, CH═N); ESI-MS, *m/z*: 451.7[M+Na]$^+$, 429.7[M+1]$^+$; IR(KBr), $\tilde{\nu}$/cm^{-1}: 3008, 2360, 1600, 1482, 1452, 1238, 1158, 1125, 863, 539; 元素分析(%, $C_{21}H_{21}FN_4O_3S$ 计算值): C 58.93(58.87), H 4.74(4.94), N 13.23(13.08), S 7.72(7.48).

2　结果与讨论

2.1　合　　成

亚胺的合成通常用相应的醛与氨基化合物在醇中回流反应或通过分水法制得. 由于 4-氨基-3-苯基-1*H*-1,2,4-三唑-5(4*H*)-硫酮(**5**)在乙醇中溶解性较差，且 4-位氨基的碱性较弱，亲核性不强，难以与醛反应. 加入少量的冰醋酸能明显改善该化合物的溶解性，同时也提供适宜的酸度，使亚胺中间体 **8** 得以顺利生成，并从反应体系中析出. 亚胺的碳氢化学位移单峰表明，席夫碱亚胺双键只存在一种几何异构，从稳定的趋向判断取代基应处于反式 *E*-式构型，说明化合物 **5** 与取代苯甲醛的缩合进程受热力学控制. 合成目标化合物 **9**a ~ **9**r 时，选用稀 NaOH 水溶液作碱，使 (*E*)-4-取代苯基亚氨基-3-(3,4,5-三甲氧基苯基)-1*H*-1,2,4-三唑-5(4*H*)-硫酮生成巯基负离子，能很好地与卤化苄发生亲核取代反应生成目标化合物. 而且随着反应进行，不溶于水的目标化合物会不断以沉淀形式析出，简化了实验操作，同时也减少了有机溶剂的使用量.

2.2　生物活性

2.2.1　抑菌活性　采用生长速率法，以香蕉枯萎菌(*Fusarium oxysporum f. sp. cubense*)、椰子灰斑菌(*Pestalotiopsis palmarum*)、橡胶棒孢菌(*Corynespora cmssiicola*)、芒果炭疽菌(*Colletotrichum gloeosporioides*)及水稻纹病菌(*Rhizoctonia solani*)为测试靶标，以广谱有机硅杀菌剂氟硅唑(Flusilazole)为对照药剂，进行了抑菌活性测定，普筛浓度为 150 mg/L，测试结果见表 1.

Table 1　Fungicidal activities of compounds 7a—7f and 9a—9r*

Compd.	Inhibitory ratio(%)				
	Fusarium oxysporum f. sp. cubense	*Pestalotiopsis palmarum*	*Corynespora cmssiicola* (*Berk & Curt.*) *Wei*	*Colletotrichum gloeosporioides PenZ*	*Rhizoctonia solani*
7a	++	−	−	−	+
7b	+	−	−	−	−
7c	−	−	−	−	+
7d	−	−	−	+	+
7e	+	−	−	−	−
7f	+	−	−	−	+
9a	++	+	+	+	++++
9b	−	−	−	−	++
9c	+	−	+	+	++
9d	++	++	−	+	++++
9e	+	−	+	+	++++
9f	−	−	−	−	+
9g	−	−	+	−	++
9h	−	−	−	+	++
9i	−	−	+	−	+
9j	−	+	−	−	+
9k	−	−	−	−	+
9l	−	−	−	++	++
9m	−	−	−	−	+
9n	−	+	−	−	++
9o	++	−	−	−	+
9p	−	−	+	−	++
9q	++	−	−	−	+
9r	−	−	+	−	++
Flusilazole	++++	++++	++++	+++	++++

* Rating system for the inhibition percentage: ++++ ≥90%; +++ ≥80%; ++ ≥60%; + ≥50%; − < 50%.

抑菌活性测试结果表明，所有目标化合物对香蕉枯萎菌、椰子灰斑菌、橡胶棒孢菌及芒果炭疽菌均表现出较弱的抑菌活性；而大部分化合物对水稻纹枯病菌有较明显的抑制活性，尤其是化合物 **9**a，**9**d 和 **9**e 的抑菌效果近似于杀菌剂氟硅唑，具有进一步研究的价值. 总体来看，亚胺类 1,2,4-三唑衍生

物(**9**a ~ **9**r) 对水稻纹枯病菌的抑制活性要优于酰亚胺类化合物(**7**a ~ **7**f), 表明亚胺基团的引入有利于提高化合物的抑菌活性. 对于亚胺类化合物(**9**a ~ **9**r), 当与三唑环直接相连的苯环上取代基 R^1 为 H (**9**a ~ **9**e)时, 其抑菌活性要明显优于 R^1 为 3,4,5-$(MeO)_3$ 的化合物 **9**f ~ **9**l 以及 R^1 为 4-F 取代基的化合物 **9**m ~ **9**r, 表明在 5-位苯环上引入取代基不利于提高化合物的抑菌活性. 此外, 与其它化合物相比, 化合物 **9**a, **9**d 和 **9**e 的抑菌活性最高, 表明三唑环 3-位硫醚上的取代基对目标化合物的抑菌活性有明显的影响.

2.2.2 *抗肿瘤活性* 以 5-氟尿嘧啶(5-Fu)为对照药物, 采用四甲基偶氮唑盐微量酶反应比色法(MTT)测定了目标化合物 **7**a ~ **7**f 和 **9**a ~ **9**r 对人肺癌细胞(A549)、乳腺癌细胞(MD-MBA-231)和前列腺癌细胞(PC-3M)的体外抗肿瘤活性, 测试结果如表 2 所示.

Table 2 IC_{50} values of target compounds 7a—7f and 9a—9r against A549, MD-MBA-231 and PC-3M*

Compd.	$IC_{50}/(\mu mol \cdot L^{-1})$			Compd.	$IC_{50}/(\mu mol \cdot L^{-1})$		
	A549	MD-MBA-231	PC-3M		A549	MD-MBA-231	PC-3M
7a	>200	>200	>200	**9**h	>200	>200	>200
7b	>200	>200	>200	**9**i	>200	>200	91.6
7c	38.3	>200	>200	**9**j	>200	>200	98.0
7d	>200	>200	>200	**9**k	36.7	147.5	60.7
7e	>200	>200	>200	**9**l	>200	>200	>200
7f	44.6	>200	>200	**9**m	>200	>200	>200
9a	>200	>200	34.1	**9**n	>200	89.6	>200
9b	>200	>200	97.9	**9**o	>200	>200	59.8
9c	>200	>200	>200	**9**p	>200	>200	>200
9d	104.6	59.8	>200	**9**q	>200	>200	61.3
9e	>200	>200	41.1	**9**r	>200	>200	>200
9f	>200	>200	99.2	5-Fu	35.4	14.2	22.6
9g	>200	>200	73.2				

* IC_{50} values mean of three experiments in replicate.

体外抗肿瘤活性筛选结果表明, 部分化合物具有较好的肿瘤抑制活性. 化合物 **7**c, **7**f 和 **9**k 对人肺癌细胞(A549)的 IC_{50} 值分别为 38.3, 44.6 和 36.7 μmol/L, 与对照药品物 5-氟尿嘧啶的肿瘤抑制活性(IC_{50} = 35.4 μmol/L)基本处于同一水平. 此外, 化合物 **9**k 对 MD-MBA-231 和 PC-3M 癌细胞的 IC_{50} 值分别为 147.5 和 60.7 μmol/L, 体现出较为广谱的肿瘤抑制活性. 本文在考察三唑环上不同取代基对目标化合物抗肿瘤活性的影响时, 并未发现明显的规律. 对此类化合物的合成和抗肿瘤活性的深入研究正在进行中.

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Syntheses and Biological Activities of Novel Imine and Imide Derivatives Bearing 1,2,4-Triazole Moiety†

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Abstract According to active groups combination principle, a series of novel imine and imide derivatives bearing 1,2,4-triazole moiety was designed and synthesized. The key intermediate 3-substituted phenyl-4-amino-1,2,4-triazole-5-thiones was synthesized by esterification, hydrazinolysis, salt and cyclization reactions, and then was condensed with aromatic aldehydes and isobenzofuran-1,3-dione to obtain imine and imide derivatives, which were subjected to the thioetherification with suitable halides (RX) to produce the corresponding 24 novel imine and imide derivatives bearing 1,2,4-triazole moiety. The structures of target compounds were fully characterized by ^{1}H NMR, IR, mass spectroscopy and elemental analysis. The preliminary bioassay results showed that most of the compounds possessed certain fungicidal activities. At the concentration of 150 mg/L, the inhibition rates of compounds **9**a, **9**d and **9**e against *Rhizoctonia solani* were very similar with the commercial fungicide Flusilazole. Meanwhile, the preliminary structure-activity relationships (SAR) were discussed in order to investigate the essential structures required for their bioactivities. In addition, their *in vitro* antitumor activities were evaluated against three cancer cell lines [human alveolar epithelial cells (A549), human breast cancer cells (MD-MBA-231) and human prostate cancer cells (PC-3M)] by the methyl thiazolyl tetrazolium (MTT) chromatometry method with Fluorouracil as a positive contrast drug. The bioassay data indicated that compounds **7**c, **7**f and **9**k showed similar antiproliferation with Fluorouracil against A549 cell lines with IC_{50} values of 38.3, 44.6 and 36.7 μmol/L, respectively. Most interestingly, compound **9**k also exhibited a broad spectrum of antitumor activity against MCF-7 and MKN45 with IC_{50} values of 147.5 and 60.7 μmol/L, respectively.

Keywords 1,2,4-Triazole; Fungicidal activity; Antitumor activity

(Ed.: P, H, N, K)

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