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1,2,3-三氮唑衍生物的合成及其抑制幽门螺杆菌活性研究

吴凤艳,陈昌红,彭立望
(邵阳学院 生物与化学工程系,湖南 邵阳,422000)

摘　要:设计并合成了 15 个未曾见文献报道的 1-(2-(4-取代)苯氧乙基)-1H-1,2,3-三氮唑衍生物,并通过 NMR、IR、MS 确认了它们的结构.对合成条件进行了探讨,得出了叠氮化的最佳合成条件:卤代烃/叠氮化钠摩尔比为 1:1.5,反应温度为 65℃,幽门螺旋杆菌(HP)体外抑制活性测试结果表明,化合物 4c、5d、5k、5l 对 16 株 HP 表现出一定的抑制活性.

关键词:1,2,3-三氮唑;合成;幽门螺旋杆菌
中图分类号:R914.5　　**文献标识码**:A

Studies on the Synthesis and Anti-Helicobacter Pylori Activity of 1,2,3-Triazole Derivatives

WU Feng-yan, CHEN Chang-hong, PENG Li-wang
(Department of Biological and Chemical Engineering, Shaoyang University, Shaoyang, Hunan 422000, china)

Abstract: Fifteen unknown 1-(2-(4-subsitituted)phenyloxyethyl)-1,2,3-triazole derivatives winthout recorded report were synthesized, their structures were confirmed by NMR, IR, and MS. Synthetic conditions were discussed, the optimum reaction conditions were obtained as follows: n(RX):n(NaN3)=1:3, reaction temperature 65℃. The preliminary results against Helicobacter pylori (HP) indicated that four compounds 4c, 5d, 5k and 5l could show a high antibacterial activity against HP.

Key words: 1,2,3-triazole; synthesis; helicobacter pylori

据统计,世界上有60%以上的人感染了幽门螺旋杆菌(HP)[1,2].另外,由于抗菌药物的滥用,导致幽门螺杆菌对现有药物产生了耐药性,对治疗效果产生严重影响[3],因此,寻找新型高效低毒的抗菌药物成为当前药物研究热点之一.三氮唑类化合物由于其生物活性的多样性而备受关注,文献报

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作者简介:吴凤艳(1972-),女,湖南保靖人,助理实验师,研究方向:药物合成.

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道表明该类化合物具有一定抗菌活性[4].为了寻找新的含有 1,2,3- 三氮唑杂环结构的抗菌化合物,本文从对羟基苯甲醛出发,对位羟基与 1,2- 二氯乙烷进行醚化反应,引入 1,2,3- 三氮唑,然后再对醛基进行改造.所有未见文献报道的化合物都通过 NMR、IR、MS 对其结构进行了表征. 合成路线及结构见图 1.

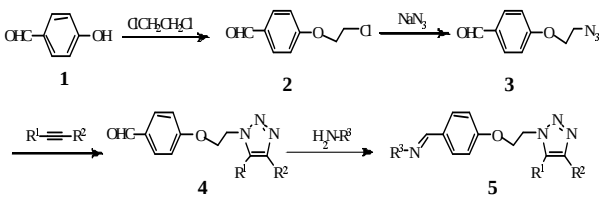

图 1　合成线路图

Fig.1 the syhthesis of target compounds

4a $R^1 = R^2 = CO_2CH_3$; 4b R^1 = H, $R^2 = CH_2OH$; 4c R^1 = H, $R^2 = CH_2Ph$; 5a $R^1 = R^2 = CO_2CH_3$, $R^3 = NHCSNH_2$; 5b $R^1 = R^2 = CO_2CH_3$, $R^3 = NHCONH_2$; 5c $R^1 = R^2 = CO_2CH_3$, R^3 = OH; 5d $R^1 = R^2 = CO_2CH_3$, $R^3 = OCH_3$; 5e R^1 = H, R^2 = CH2OH, $R^3 = NHCSNH_2$; 5f R^1 = H, $R^2 = CH_2OH$, $R^3 = NHCONH_2$; 5g R^1 = H, $R^2 = CH_2OH$, R^3 = OH; 5h R^1 = H, $R^2 = CH_2OH$, $R^3 = OCH_3$; 5i R^1 = H, $R^2 = CH_2Ph$, $R^3 = NHCSNH_2$; 5j R^1 = H, $R^2 = CH_2Ph$, $R^3 = NHCONH_2$; 5k R^1 = H, $R^2 = CH_2Ph$, R3 = OH; 5l R^1 = H, $R^2 = CH_2Ph$, $R^3 = OCH_3$.

1 实验部分

1.1 仪器与试剂

核磁共振仪 Mercury- Plus300(美国 VARIAN);质谱仪 LCMS- 2010A(日本 岛津);熔点仪 WRS- 1B 数字熔点仪(上海精密科学仪器有限),未校正;红外光谱分析仪 VECTOR 22(德国 BRUKER).合成所用的试剂为分析纯或化学纯试剂,柱层析用硅胶为青岛海洋化工厂产品.

1.2 氯乙基醚化合物 2 的合成[5]

取 0.1mol 对羟基苯甲醛溶于 100mL 1,2- 二氯乙烷中,搅拌完全溶解后加入四丁基溴化铵 0.02mol,再从恒压滴液漏斗中缓慢加入 50mL 2M 的氢氧化钠水溶液,升温至 85℃并保持约 8h,TLC 跟踪反应进程.静置分出有机层,并用 1M 氢氧化钠溶液和水洗涤.无水硫酸钠干燥,减压除去溶剂,柱层析分离得到目标化合物.

1.3 叠氮化合物 3 的合成[6]

取中间体化合物 2 20mmol 溶于 30mL 的 DMF 中,搅拌下加入 30mmol 叠氮钠,65℃搅拌反应 12h.将反应液倒入 100mL 水中,二氯甲烷萃取物用水洗多次,无水硫酸镁干燥,浓缩得到化合物 3.

1.4 1- (2- (4- 甲酰基)苯氧乙基)- 1H- 1,2,3- 三氮唑 - 4,5- 二甲酸甲酯 4a 的合成[7]

取化合物 3 10mmol 和丁炔二酸二甲酯 11mmol 加入 30mL 甲苯中,120℃回流反应 4h.将反应液减压除去溶剂,得到暗红色液体,加入少量石油醚,大量固体析出,粗产品用石油醚与乙酸乙酯混合物重结晶,得到目标产物 4a.

4a:白色固体,m.p. 83- 85℃,产率 85%.IR (KBr, cm^{-1}) υ : 3005, 2954, 2881, 1738, 1687, 1599, 1512, 1317, 1238, 1063, 828; ^{1}H NMR (CDCl3) δ : 9.85 (s, 1H, CHO), 7.80 (d, 2H, J = 8.7 Hz, Ar- H), 6.90(d, 2H, J = 8.7 Hz, Ar- H), 5.09(t, 2H, J = 5.1 Hz, OCH_2), 4.45 (t, 2H, J = 5.1Hz, NCH2), 4.03 (s, 3H, OCH_3), 3.97 (s, 3H, OCH3). ^{13}C NMR (DMSO) δ : 191.8, 163.0, 160.7, 159.1, 132.4, 131.8, 130.8, 115.6, 67.1, 54.3, 53.3; ESI- MS (m/z): 356 (M+23, 100).

1.5 4- (2- (4- 羟甲基 - 1H- 1,2,3- 三氮唑)乙基氧苯甲醛 4b- 4c 的合成[8,9]

将 10 mmol 化合物 3a、11mmol 丙炔醇、2 mL 1M 的硫酸铜溶液和 10mmol 抗坏血酸钠溶于 45 mL 的二氧六环与水的混合物(体积比,2:1)中,室温下避光搅拌反应约 6h,TLC 跟踪反应至完全.加入 100mL 水,二氯甲烷萃取,有机物用水洗,无水硫酸钠干燥,浓缩得到粘稠状液体.用少量乙醚和乙醇洗涤后得粗品,再经重结晶得到目标化合物.

4b:白色粉末状固体,m.p. 107- 109℃,产率 80%.IR(KBr, cm^{-1}) υ : 3375, 3295, 3157, 2945, 2829, 2743, 1695, 1600, 1508, 1434, 1397, 1263, 1216, 1039, 830; ^{1}H NMR ($CDCl_3$) δ : 9.79 (s, 1H, CHO), 7.75 (d, J = 9.0 Hz, 3H, 2× ArH, NCH), 6.90 (d, J = 9.0Hz, 2H, ArH), 4.73 (t, J = 4.8 Hz, 4H, 2× CH_2), 4.38 (t, J = 4.8 Hz, 2H, CH_2); 13C NMR (CDCl3) δ : 191.8, 163.3, 148.8, 132.4, 130.7, 123.8, 115.7, 67.4, 55.8, 49.5; ESI- MS (m/z): 270(M+23,100).

4c: 白色粉末状固体,m.p. 98- 100℃,产率 90% .IR (KBr, cm- 1) υ :3125, 2831, 2743, 1687, 1596, 1506, 1430, 1245, 907, 828, 768, 700 ; ^{1}H NMR (CDCl3) δ : 9.88 (s, 1H, CHO), 7.93 (s, 1H,

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NCH), 7.81- 7.85(m, 4H, ArH), 7.43(t, J = 8.4Hz, J = 6.9Hz, 2H, ArH), 7.34 (t, J = 6.9Hz, 1H, ArH), 7.00(d, J = 8.7Hz, 1H, ArH), 4.86 (t, J = 5.1 Hz, 2H, OCH2), 4.51 (t, J = 5.1 Hz, 2H, NCH2); ^{13}C NMR (CDCl3) δ: 191.8, 163.3, 147.1, 132.4, 131.4, 130.7, 129.5, 128.5, 125.8, 122.6, 115.7, 67.3, 49.9; ESI- MS(m/z): 299(M+23,100).

1.6 希夫碱化合物(5a- 5l)的合成[10,11]

A. 氨基硫脲希夫碱合成法：称取1mmol取代芳醛, 0.091g(1mmol)氨基硫脲置于圆底烧瓶中,加入15mL乙醇为溶剂，回流过夜, 反应完全后静置冷却,出现沉淀.抽滤,固体物用95%乙醇重结晶,真空干燥,得纯品.

B. 氨基脲、羟胺、甲氧胺希夫碱合成法：称取1mmol取代芳醛溶于15mL乙醇中，另取1.1mmol氨基脲盐酸盐(盐酸羟胺、甲氧胺盐酸盐)用5M氢氧化钠水溶液中和至pH=6- 7,缓慢滴加到上述乙醇溶液中,回流5- 12h, 反应完全后静置冷却,出现白色晶体,抽滤,固体物用95%乙醇重结晶,真空干燥,得纯品.

5a: 白色固体,m.p. 173- 175℃，产率95%.IR (KBr, cm^{-1}) υ: 3461, 3303, 3151, 1743, 1600, 1507, 824; ^{1}H NMR (CDCl3) δ: 11.30 (s, 1H, NH), 8.10(s, 1H, NH), 7.95(s, 1H, CH=N), 7.91(s, 1H, NH), 7.70(d, 2H, *J* = 8.7 Hz, Ar- H), 6.86(d, 2H, *J* = 8.7 Hz, Ar- H), 5.00 (t, 2H, *J* = 4.8 Hz, OCH_2), 4.43 (t, 2H, *J* = 4.8Hz, NCH_2), 3.91 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3); 13C NMR ($CDCl_3$) δ: 178.2, 160.7, 159.5, 159.1, 142.6, 139.5, 131.9, 129.5, 128.1, 115.2, 66.8, 54.4, 53.4, 50.1; ESI- MS(m/z): 429(M+23,100).

5b: 白色固体,m.p. 172- 173℃，产率97%.IR (KBr, cm^{-1}) υ: 3516, 3379, 3203, 3068, 1757, 1688, 1582, 1511, 1431, 832; ^{1}H NMR ($CDCl_3$) δ: 10.09(s, 1H, NH), 7.74(s, 1H, CH=N), 7.61(d, 2H, *J* = 9.0 Hz, Ar- H), 6.84 (d, 2H, *J* = 9.0 Hz, Ar- H), 6.41 (s, 2H, NH), 5.00 (t, 2H, *J* = 4.8 Hz, OCH_2), 4.41 (t, 2H, *J* = 4.8Hz, NCH_2), 3.91(s, 3H, OCH_3), 3.86(s, 3H, OCH_3); 13C NMR ($CDCl_3$) δ:160.7, 159.2, 158.8, 157.5, 139.7, 139.5, 132.0, 128.8, 128.7, 115.2, 66.8, 54.4, 53.4, 50.1; ESI- MS(m/z): 413(M+23,100).

5c: 白色固体,m.p. 94- 96℃，产率86%.IR (KBr, cm^{-1}) υ: 3228, 2962, 1733, 1606, 1564, 1517, 1451, 819; ^{1}H NMR ($CDCl_3$) δ: 10.98 (s, 1H, NOH), 8.02 (s, 1H, CH=N), 7.48 (d, 2H, *J* = 8.7 Hz, Ar- H), 6.86(d, 2H, *J* = 8.7 Hz, Ar- H), 5.00(t, 2H, *J* = 4.8 Hz, OCH_2), 4.40 (t, 2H, *J* = 4.8Hz, NCH_2), 3.91 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3); 13C NMR ($CDCl_3$) δ: 160.7, 159.2, 158.9, 148.0, 139.4, 132.0, 128.5, 127.0, 115.3, 66.8, 54.4, 53.4, 50.1; ESI- MS (m/z): 371(M+23,100).

5d: 白色固体,m.p. 57- 59℃，产率99%.IR (KBr, cm^{-1}) υ: 2953, 1736, 1606, 1553, 1512, 1467, 1433, 1336, 1242, 1058, 915, 827; ^{1}H NMR ($CDCl_3$) δ: 7.98 (s, 1H, CH=N), 7.48 (d, 2H, *J* = 8.7 Hz, Ar- H), 6.78(d, 2H, *J* = 8.7 Hz, Ar- H), 5.06(t, 2H, *J* = 5.1 Hz, OCH_2), 4.38 (t, 2H, *J* = 5.1Hz, NCH2), 4.02(s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3); 13C NMR ($CDCl_3$) δ:160.7, 159.4, 148.7, 139.5, 131.9, 129.0, 125.7, 115.4, 66.8, 62.1, 54.3, 53.3, 50.1; ESI- MS(m/z): 385 (M+23,100).

5e: 白色固体,m.p. 195- 197℃，产率91%.IR (KBr, cm^{-1}) υ: 3331, 3258, 3177, 1605, 1535, 1506, 1463, 830; ^{1}H NMR ($CDCl_3$) δ: 11.27 (s, 1H, NH), 8.07(s, 1H, NH), 8.01(s, 1H, CH=N), 7.96(s, 1H, NH), 7.70(d, 2H, J = 8.7 Hz, Ar- H), 6.94(d, 2H, J = 8.7 Hz, Ar- H), 5.15(t, 1H, J = 5.4Hz, OH), 4.74(t, 2H, J = 4.8 Hz, OCH_2), 4.50(d, 2H, J = 5.4Hz, OCH_2), 4.42(t, 2H, J = 4.8Hz, NCH_2); 13C NMR ($CDCl_3$) δ:159.8, 148.7, 142.7, 129.6, 127.9, 123.8, 115.5, 67.1, 55.8, 49.7; ESI- MS(m/z): 343(M+23,100).

5f: 白色固体,m.p. 190- 192℃，产率93%.IR (KBr, cm^{-1}) υ: 3455. 3279, 3135, 2955., 1743, 1671, 1606, 1583, 1509, 1245, 834;^{1}H NMR ($CDCl_3$) δ: 10.05 (s, 1H, NH), 8.01 (s, 1H, CH=N), 7.75 (s, 1H, NCH), 7.62(d, 2H, J = 8.4 Hz, Ar- H), 6.94(d, 2H, J = 8.4 Hz, Ar- H), 6.39(s, 2H, NH), 5.15(t, 1H, *J* = 5.1Hz, OH), 4.73 (t, 2H, *J* = 4.8 Hz, OCH_2), 4.50 (d, 2H, *J* = 5.1Hz, OCH_2), 4.42 (t, 2H, *J* = 4.8Hz, NCH_2); 13C NMR ($CDCl_3$) δ:159.1, 157.5, 139.8, 128.7, 128.6, 123.9, 115.4, 67.1, 55.8, 49.7; ESI- MS (m/z): 327 (M+23,100).

5g: 黄色固体,m.p. 171- 173℃，产率78%.IR (KBr, cm^{-1}) υ: 3319, 3120, 2944, 1605, 1455, 1239, 1049, 831; ^{1}H NMR($CDCl_3$) δ: 10.95(s, 1H, NH), 8.03 (s, 1H, CH=N), 8.00(s, 1H, NCH), 7.49(d, 2H, *J* = 7.8 Hz, Ar- H), 6.94(d, 2H, *J* = 7.8 Hz, Ar- H), 4.73(t, 2H,

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J = 4.8 Hz, OCH_2), 4.50(s, 2H, OCH_2), 4.41(t, 2H, J = 4.8Hz, NCH_2); 13C NMR ($CDCl_3$) δ: 159.2, 148.7, 148.2, 128.5, 126.8, 123.8, 115.5, 67.1, 55.8, 49.6; ESI- MS(m/z): 285(M+23,100).

5h: **淡黄色固体**,m.p. 84- 87℃, **产率** 90%.IR (KBr, cm^{-1}) υ: 3557, 3400, 3147, 2938, 1604, 1511, 1245, 831; ^{1}H NMR ($CDCl_3$) δ: 7.99 (s, 1H, CH=N), 7.82(s, 1H, NCH), 7.51(d, 2H, J = 8.4 Hz, Ar- H), 6.85 (d, 2H, J = 8.4 Hz, Ar- H), 4.76- 4.82 (m, 4H, OCH_2), 4.39 (t, 2H,J= 4.5Hz, NCH_2); 13C NMR ($CDCl_3$) δ: 159.7, 148.7, 129.0, 125.6, 124.1, 115.5, 67.1, 62.2, 55.8, 49.7; ESI- MS(m/z): 299(M+23,100).

5i: **白色固体**,m.p. 200- 202℃, **产率** 91%.IR (KBr, cm^{-1}) υ: 3428, 3251, 3158, 1603, 1536, 1504, 1468, 1248, 826; ^{1}H NMR ($CDCl_3$) δ: 11.27 (s, 1H, NH), 8.63(s, 1H, NCH), 8.07(s, 1H, NH), 7.96(s, 1H, CH=N), 7.86 (s, 1H, NH), 7.83 (d, 2H, J = 6.9 Hz, Ar- H), 7.71(d, 2H, J = 8.4 Hz, Ar- H), 7.42(t, 2H, J = 6.9 Hz, Ar- H), 7.31 (t, 1H, J = 6.9 Hz, Ar- H), 6.97(d, 2H, J= 8.4 Hz, Ar- H), 4.81 (d, 2H, J = 5.1 Hz, OCH_2), 4.50 (t, 2H, J= 5.1Hz, NCH_2); 13C NMR ($CDCl_3$) δ: 178.2, 159.9, 147.1, 142.8, 131.4, 129.6, 128.5, 128.0, 125.8, 122.6, 115.5, 67.0, 50.0; ESI- MS (m/z): 389(M+23,100).

5j: **白色固体**,m.p. 211- 212℃, **产率** 86%.IR (KBr, cm^{-1}) υ: 3470, 3280,3135, 1715, 1584, 1249, 822; ^{1}H NMR ($CDCl_3$) δ: 10.05 (s, 1H, NH), 8.63(s, 1H, NCH), 7.83(d, 2H, J = 7.8 Hz, Ar- H), 7.74(s, 1H, CH=N), 7.61(d, 2H, J = 8.4 Hz, Ar- H), 7.43(t, 2H, J = 7.2 Hz, J = 7.8 Hz, Ar- H), 7.31 (t, 1H, J = 7.2 Hz, Ar- H), 6.95 (d, 2H, J = 8.4 Hz, Ar- H), 6.38 (s, 2H, NH), 4.81 (d, 2H, J = 4.8 Hz, OCH_2), 4.48 (t, 2H, J = 4.8Hz, NCH_2); 13C NMR ($CDCl_3$) δ: 159.2, 157.5, 147.0, 139.7, 131.4, 129.6, 128.7, 128.5, 122.6, 115.4, 67.0, 20.0; ESI- MS(m/z): 373 (M+23, 100).

5k: **白色固体**,m.p. 120- 122℃, **产率** 97%.IR (KBr, cm^{-1}) υ: 3407, 3129, 1606, 1512, 1465, 1251, 826; ^{1}H NMR ($CDCl_3$) δ: 10.95 (s, 1H, NH), 8.63(s, 1H, NCH), 8.03 (s, 1H, CH=N), 7.83 (d, 2H, J = 7.5 Hz, Ar- H), 7.49(d, 2H, J = 7.8 Hz, Ar- H), 7.45(t, 2H, J = 7.5 Hz, J = 7.2 Hz, Ar- H), 7.31 (t, 1H, J = 7.2 Hz, Ar- H), 6.96(d, 2H, J = 7.8 Hz, Ar- H), 4.81(d, 2H, J = 4.5 Hz, OCH_2), 4.47 (t, 2H, J = 4.5Hz, NCH_2); 13C NMR ($CDCl_3$) δ:159.3, 148.1, 147.0, 132.9, 131.4, 129.5, 126.9, 125.8, 122.6, 115.6, 67.0, 50.0; ESI- MS (m/z): 331(M+23,100).

5l: **白色固体**,m.p. 94- 96℃,**产率** 93%.IR(KBr, cm^{-1}) υ: 3125, 2938, 1606, 1511, 1051, 825; 1H NMR ($CDCl_3$) δ: 8.63 (s, 1H, NCH), 8.11 (s, 1H, CH=N), 7.83(d, 2H, J = 7.8 Hz, Ar- H), 7.51(d, 2H, J = 8.7 Hz, Ar- H), 7.42 (t, 2H, J = 7.2 Hz, J = 7.8 Hz, Ar- H), 7.30(t, 1H, J = 7.2 Hz, Ar- H), 6.96(d, 2H, J = 8.7 Hz, Ar- H), 4.81 (d, 2H, J = 5.1 Hz, OCH_2), 4.48(t, 2H, J = 4.5Hz, NCH_2), 3.83 (s, 3H, OCH_3); 13C NMR ($CDCl_3$) δ: 159.8, 148.7, 147.0, 131.3, 129.5, 128.5, 125.8, 125.6, 122.6, 115.6, 67.0, 62.2, 50.0; ESI- MS (m/z): 345(M+23,100).

1.7 抗幽门螺旋杆菌体外活性测试

样品稀释方法:以上样品先用相应溶媒将浓度配至 2560ug/mL,**按琼脂二倍稀释法进行二倍稀释.取无菌平皿编号后,于每个培养皿中加** 1mL **药液,再加入** 19mL **已加热融化的选择性培养基(融化后冷至** 50℃**时,加入** 10%**无菌脱纤维兔血),使培养皿中的药物终浓度为** 128、64、32……0.03、0.015、0.008ug/mL.

菌液配制:菌株于 37℃**微需氧环境培养** 2- 3 **天,取阳性者用于试验.选取** HP ATCC 11637 **与临床分离** Hp **致病菌株共** 17 **株,以接种环挑取单菌落稀释于生理盐水中,以** 0.5 **号麦氏比浊管比浊,接种菌量约为** 106CFU/mL.**采用多点接种仪**(Denley A400) **将细菌接种于含不同药物浓度的琼脂平皿表面. 接种后将培养皿置于** 37℃**微需氧环境培养** 2- 3 **天观察结果,以无菌生长的平皿培养基中所含药物最低浓度为对该菌的最低抑菌浓度**(Minimum inhibitory concentration, MIC).

2 结果与讨论

2.1 合成

叠氮化合物的合成最佳条件是叠氮钠投料量为 1.5 **当量,反应温度为** 65℃,**产率几乎** 100%.**为了得到单一立体构型** 4- **取代产物,采用了分类法来合成** 1,2,3- **三氮唑化合物:**1) **当为对称的炔时,在甲苯里回流数小时就可以反应完全,且后处理简单,产率高;**2) **当炔为不对称时,在** Cu[I]**的作用下反应速度明显加快,且只生成单一的** 4- **位立体构型产物.同时,为提高产物收率,炔烃需要稍微过量**

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表1 体外抗幽门螺旋杆菌活性表
Tab. 1 The measured results of anti- HP activity of the samples

Samples	MIC_{50}(ug/mL)	MIC_{90}(ug/mL)	MIC_{range}(ug/mL)
4a	>128	>128	>128
4b	>128	>128	>128
4c	128	>128	128->128
5a	>128	>128	>128
5b	>128	>128	>128
5c	>128	>128	>128
5d	128	>128	128->128
5e	>128	>128	>128
5f	>128	>128	>128
5g	>128	>128	>128
5h	>128	>128	>128
5i	>128	>128	>128
5j	>128	>128	>128
5k	128	>128	128->128
5l	128	>128	128->128
Metronidazole	>128	>128	>128
Clarithromycin	>128	>128	64->128

2.2 抗幽门螺旋杆菌活性及初步构效关系

化合物(4a-4c,5a-5l)对临床分离16株幽门螺旋杆菌(HpATCC11637,Hp05-1～Hp05-5,Hp05-9,Hp05-12,Hp05-14和Hp06-1-Hp06-8)进行了体外抗菌活性的筛选(Table 1).结果显示,化合物(4c、5d、5k、5l)对其中9株幽门螺旋杆菌(HpATCC11637,Hp05-3,Hp06-1－Hp06-7)表现出一定的抗菌活性,抑制活性都为MIC50＝128ug/mL.由此,可以推测:1)当三氮唑4位上为羟甲基取代时,几乎没有什么抗菌活性,而当三氮唑4位上为苯环取代时,表现出良好的抗菌活性,说明4位苯环取代是一个有效的基团,对提高其抑制幽门螺杆菌的活性有利;2)同时三氮唑4位4,5-同时取代是也有一定的抗菌活性,可以推测,在三氮唑的4位上引入不同的基团可能会对这类化合物的抑菌活性产生影响;3)当苯环上的醛基缩合成希夫碱时,所有的氨基脲、氨基硫脲希夫碱都没有表现出抗菌活性,而且反而使活性降低;羟胺、甲氧基胺希夫碱化合物表现出了一定的抗菌活性,特别是甲氧基胺,有增强抗菌活性的作用,因此,甲氧基胺希夫碱片段可能是一个有效的活性基团.

参考文献:

[1] Malfertheiner, P.; Micetti, P.; Price, A. The Year in Helicobacter pylori 1994 [M]. Current Science Ltd: London, 1994.

[2] Katsura, Y.; Nishino, S. Anti- Helicobacter pylori Agents. 3. 2- [(Arylalkyl) guanidino]- 4- furylthiazoles [J]. J. Med. Chem. 1999, 42(15): 2920- 2926.

[3] Katsura, Y.; Nishino, S. Anti- Helicobacter pylori Agents. 5. 2- (Substituted guanidino)- 4- arylthiazoles and Aryloxazole Analogues[J].J. Med. Chem. 2002, 45(1): 143- 150.

[4] Reck, F.; Zhou, F. Identification of 4- Substituted 1,2,3- Triazoles as Novel Oxazolidinone Antibacterial Agents with Reduced Activity against Monoamine Oxidase A[J]. J. Med. Chem. 2005, 48(2): 499- 506.

[5] Ian, R. Rationally Designed Analogs of Tamoxifen with Improved Calmodulin Antagonism[J]. J. Med. Chem. 1995, 38(2): 241- 248.

[6] Zhou, P. 4- (2- Aminoethoxy)- N- (phenylsulfonyl)indoles as novel 5- HT6 receptor ligands [J]. Bioorg. Med. Chem. Lett.2005, 15(5): 1393- 1396.

[7] Hartmuth C. K. Click Chemistry: Diverse Chemical Function from a Few Good Reactions [J]. Angew. Chem. Int. Ed. 2001, 40(11), 2004- 2021.

[8] Li, Z- M.; Seo, T. S.; Ju, J- Y. 1,3- Dipolar cycloaddition of azides with electron- deficient alkynes under mild condition in water[J]. Tetrahedron. Lett. 2004, 45(15): 3143- 3146.

[9] 成兰兴. 1H- 1,2,3- 三氮唑合成新工艺 [J]. 广东化工, 2011,38(213):65- 66.

[10] Surendra, N. Synthesis and anticonvulsant activity of 4- bromophenyl substituted aryl semicarbazones[J]. Eur. J. Med. Chem. 2000, 35(10): 879- 886.

[11] Jeong, T- S. (E)- Phenyl- and - heteroaryl- substituted O- benzoyl- (or acyl)oximes as lipoprotein- associated phospholipase A2 inhibitors [J]. Bioorg. Med. Chem. Lett. 2005, 15(5): 1525- 1527.

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