# *N*-(1,5-二芳基-3-戊酮-1-基)-4-氨基苯甲酸的合成与 *α*-葡糖苷酶抑制活性初步研究

许　荟[1], 晏菊芳[2], 范　莉[1], 宋小礼[1], 唐雪梅[1], 杨大成[1*]

(1. 西南大学化学化工学院, 重庆 400715; 2. 成都地奥制药集团药物筛选中心, 四川 成都 610041)

**摘要**: 由 Mannich 反应直接合成了 16 个 *β*-氨基酮化合物, 制备方法简单、反应条件温和、产品易纯化, 收率达到 45%～90%。所制备的化合物通过 IR、ESI-MS、$^1$H NMR、$^{13}$C NMR 和 HR-MS 等方法进行了结构表征。*α*-葡糖苷酶抑制活性检测表明, 所合成的化合物对该酶的抑制活性顺序为: **2c** 最强, **2b**、**2h**、**1a**、**1f** 有一定的抑制活性。在此基础上, 对合成化合物的构-效关系进行了讨论。

**关键词**: 糖尿病; *α*-葡糖苷酶; *β*-氨基酮化合物; Mannich 反应

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# Synthesis and *α*-glucosidase inhibitory activity of *N*-(1,5-diaryl-3-pentone-1-yl)-4-aminobenzoic acid

XU Jin[1], YAN Ju-fang[2], FAN Li[1], SONG Xiao-li[1], TANG Xue-mei[1], YANG Da-cheng[1*]

(*1. School of Chemistry and Chemical Engineering, Southwest University, Chongqing 400715, China; 2. Chengdu Di Ao Pharmaceutical Group, Chengdu 610041, China*)

**Abstract**: In order to find highly active antidiabetic lead compound, sixteen 4-aminobenzoic acid derivatives were designed and synthesized directly through Mannich reaction in the solution of ethanol at 15–35 ℃ with facile method, mild reaction condition and high yield (45%–90%). Fifteen of them are new compounds. Their structures were confirmed by $^1$H NMR, $^{13}$C NMR, IR, ESI-MS and HR-MS. *α*-Glucosidase inhibitory activity of these compounds indicated that most of these compounds possess the activity with the order: **2c** > **2b** > **2h** > **1a** > **1f**. The structure-activity relationship of these 4-aminobenzoic acid derivatives was also discussed.

**Key words:** diabetes mellitus; *α*-glucosidase; *β*-amino ketone; Mannich reaction

糖尿病作为全球第三大非传染性疾病已经受到广泛的关注。目前抗Ⅱ型 ( 非胰岛素依赖型 ) 糖尿病药物分为四大类[1]: 磺酰脲类和非磺酰脲类促胰岛素分泌药物[2~5], 双胍类、噻唑烷二酮类等胰岛素增敏剂[6~10], 肝糖生成抑制剂[11]和 *α*-葡糖苷酶抑制剂等减缓糖吸收药物[12~14]。*α*-葡糖苷酶抑制剂类药物对Ⅰ、Ⅱ型糖尿病均适用, 其作用机制为竞争性抑制小肠黏膜上皮细胞表面的 *α*-葡糖苷酶, 从而延缓碳水化合物的分解和吸收, 缓解餐后高血糖症, 具有广泛的应用前景。然而, 由于该类药物使用时伴随腹泻、胃肠胀气等不良反应以及与其他降糖药联合使用时易引起低血糖[15], 这使得寻找新型、副作用小的*α*-葡糖苷酶抑制剂成为迫切需要。

为了发现新型 *α*-葡糖苷酶抑制剂, 必须借鉴已有药物的结构特点, 设计新型的抗糖尿病药物分子, 选择易于实现的合成方法。目前, 抗糖尿病药物种类很多, 结构类型各异。苯基丙酸类的 nateglinide (A4166)[4]、苯甲酸类型的 meglitinide 和 repaglinide[16]、*α*-烷氧-*β*-苯基丙酸的衍生物[17]、*L*-酪氨酸类衍生物[18]等分子中都含有羧基、氨基, 显示了这两种官能团的重要性; 另外这些分子多数都含有 2 个芳香环, 芳环之间间隔一定距离, 也就是说, 需要一个分子/结构

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*通讯作者 Tel: 13330280533, E-mail: hxydc@swu.edu.cn

单元 (linker) 将两个芳香环连接起来。Mannich 反应既是构筑有机分子骨架的重要方法, 也是将氮元素引入化合物的简便途径[19~22], 更重要的是, 该反应可以实现三组分之间的一步联结。某些 Mannich 反应的产物 (*β*-氨基酮), 具有抗炎[23, 24]、抗癌[24~28]、抗菌[29~31]等生物活性。作者研究发现, 某些*β*-氨基酮衍生物还具有抗雄激素活性[32], 这提示我们, 该类分子很有可能具有其他重要生物活性, 值得进一步研究。基于上述设想, 作者试图将对氨基苯甲酸 (类似于苯甲酸类抗糖尿病药物的药效团)、4-苯基-2-丁酮 (具有止咳的药理作用[33]) 或萘丁美酮 (具有消炎作用的上市药品) 作为原料, 通过 Mannich 反应合成新型的*β*-氨基酮衍生物, 以期获得具有新生物活性尤其是抗糖尿病活性的新化合物。合成实验发现, 4-苯基-2-丁酮或萘丁美酮与对氨基苯甲酸和芳香醛在较为温和的实验条件下发生 Mannich 反应, 可以直接得到 16 个 Mannich 碱 (**1a～2h**), 其中 15 个为新化合物, 反应式如图 1。

反应收率为 40%～90%。它们的化学结构得到 IR、ESI-MS (表 1)、$^1$H NMR (表 2)、$^{13}$C NMR (表 3) 和 HR-MS (表 4)的确证。将所得到的化合物, 在抗糖尿病体外筛选模型上进行生物活性筛选, 发现它们对 *α*-葡糖苷酶有抑制作用, 其中 **2c** 对 *α*-葡糖苷酶有明显的抑制作用, **1a**、**1f**、**2b**、**2h** 也显示出了较好的抑制活性。由此发现*β*-氨基酮具有抗糖尿病活性, 为新型抗糖尿药物的研制发现了新的先导化合物。上述 Mannich 碱的其他生物活性尚在进一步研究中。

## 结果及讨论

合成 Mannich 碱的途径主要有两种: Mannich 反应合成法和间接合成法。Mannich 反应通常采用三组分一锅法[34, 35], 也有人选用 Schiff 碱与酮的缩合法[36]。Mannich 碱间接合成法有迈克尔加成法[37]、胺盐酸盐法[38]、胺交换法[28]、酮交换法[39, 40]等。本实验采用将三组分一锅法和 Schiff 碱与酮的缩合相结合的方法, 合成简便, 收率较高。

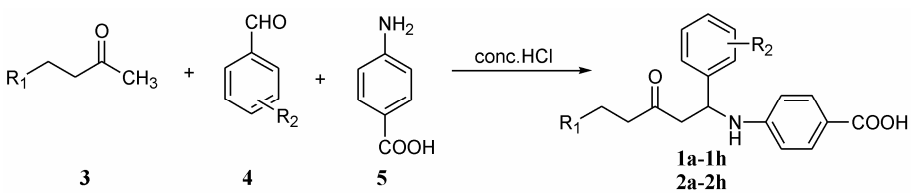
## 1　实验结果

Mannich 碱**(1a～2h)**的实验结果及分析数据见表 1～表 4。

## 2　结果讨论

芳香醛参与的 Mannich 反应, 多采用三组分一锅法或 Schiff 碱与酮的缩合法。在本课题组前期研究的基础上[41~44], 本文采用的方法是两段投料一锅反应法, 即在醛胺反应生成 Schiff 碱后, 直接加入酮组分与之反应。该法既省去了 Schiff 碱的分离步骤, 又避免了三组分一锅法难于判断反应完成程度的不便。

**2.1　反应影响因素**　甲醛参与的 Mannich 反应一般需加热回流, 作者前期研究的芳香醛参与的 Mannich 反应一般在 0～40 ℃条件下进行。在本实验考察范围内, 合成此类 *β*-氨基酮衍生物的难易差别很大。本文系统研究了反应条件, 试用了乙醇、乙醇-三氯甲烷、甲醇和三氯甲烷 4 种溶剂体系, 试验了浓盐酸、磷酸、冰醋酸、碘、氯化铁和氯化铝 6 种催化剂, 发现在温度为 25～30 ℃、催化剂为浓 HCl (0.1～0.2 mL)、在无水乙醇和乙醇-三氯甲烷体系中反应结果最好。温度太低 (0 ℃左右), 反应速率降低, 甚至不发生反应; 温度超过 45 ℃, 生成的产物会缓慢分解。盐酸过多或过少既会影响反应速度也会降低收率, 有时还决定反应是否进行。反应时间不宜过长, 延长反应时间容易导致产物分解, 所以适时监测反应对提高反应收率意义重大。这和作者以前的研究结果一致[41~44]。醛组分芳环上电子云密度对反应影响较大。间氯苯甲醛和 3, 4-二氯苯甲醛与 4-苯基-2-丁酮、对氨基苯甲酸难于发生 Mannich 反应, 和萘丁美酮参与的 Mannich 反应虽然可以发生, 但反应收率较低; 但对氯苯甲醛参与的上述 Mannich 反应, 不仅顺利发生而且收率较高。苯甲醛、间甲苯甲醛和胡椒醛, 与对氯苯甲醛相似, 反应较快且收率较高。含强吸电子基团的芳香醛, 如间硝基苯甲醛和对硝基苯甲醛, 其反应难易取决于取代基所处位置: 间硝基者反应较易发生, 收率也较高; 与之相反, 对硝基苯甲醛与 4-苯基-




**3**　**4**　**5**　**1a-1h** **2a-2h**

**1a**－**1h**: $R_1$ = $C_6H_5$-; **2a**－**2h**: $R_1$ = 6-Methoxy-2-naphthyl-;
$R_2$ = *m*-$CH_3$, *m*-$NO_2$, *p*-Cl, 3,4-$OCH_2O$, *p*-$NO_2$, H, *p*-OH, *p*-$OCH_3$, *m*-Cl, 3,4-diCl.

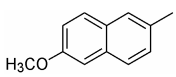
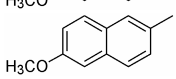
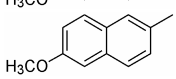
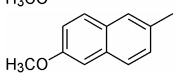
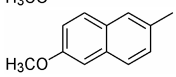
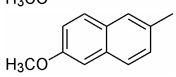
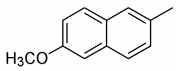
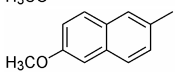
**Figure 1**　Mannich reaction of 4-aminobenzoic acid and aromatic aldehyde with 4-aryl-2-butanone

2-丁酮参与的反应收率较低, 在萘丁美酮参与的反应中未能得到对应的 Mannich 碱。对甲氧基苯甲醛, 不能发生反应或收率较低。幸运的是, 含强供电子基团的对羟基苯甲醛, 在本研究中都得到了对应的 Mannich 碱, 收率达到 60%左右。

**2.2 生物活性结果分析** 生物活性结果见表 4。结果显示, 在浓度为 10 μg·mL$^{-1}$时, 合成的 16 个化合物大部分对 α-葡糖苷酶有抑制活性, 其中 **2c** 有显著的抑制活性, 抑制率达到了 66.5%, **2b**、**2h**、**1a** 和 **1f** 也达到了 34.3%～48.5%; 在浓度为 100 μg·mL$^{-1}$时, 测试过的化合物几乎都有显著的抑制活性。

分子结构模拟发现, 1-芳基甲基酮、芳香醛和芳香胺生成的 Mannich 碱, 分子刚性很大, 三个芳环不在同一个平面; 4-芳基-2-丁酮 (4-苯基-2-丁酮和萘丁美酮)作为活性氢组分与芳香醛和芳香胺生成的 Mannich 碱, 由于芳环和羰基之间多了两个亚甲基使分子有一定的柔韧性, 体现在对 α-葡糖苷酶抑制活性上, 4-芳基-2-丁酮型 Mannich 碱 (后者) 较 1-芳基甲基酮型 (前者) 的活性更好 (前者活性另文发表); 即便是后者, 结构虽然相似, 但也有明显的活性差异, 如醛组分相同, 活性强度却是 **2c** (66.5%) > **1c** (–0.8%), **2h** (41.1%) > **1h** (6.6%), 表现为萘丁美酮系列的 Mannich 碱的生物活性总体较 4-苯基-2-丁酮系列的更好, 这可能与其空间结构的匹配性有关 (**2c**, **2h** 与阿卡波糖的三维空间结构见图 2)。同一系列分子, 当醛组分的取代基相同但取代位置不同时, 抑制率也有明显差异, 一般是对位取代产物的抑制活性优于间位, 如: **2c** (*p*-Cl) > **2d** (*m*-Cl), **1a** (*p*-$NO_2$) > **1b** (*m*-$NO_2$)。对于取代位置相同但取代基不同的醛组分, 所得产物的抑制率也不同, 如: **2c**(*p*-Cl)>**2h**(*p*-OH) > **2e** (H), **2d** (*m*-Cl) > **2f** (*m*-$CH_3$) > **2a** (*m*-$NO_2$), **2b** (3, 4-diCl) > **2g** (3, 4-$OCH_2O$), **1a** (*p*-$NO_2$) > **1f** (*p*-$OCH_3$) > **1d** (H) > **1h** (*p*-OH) > **1c** (*p*-Cl), **1b** (*m*-$NO_2$) > **1e** (*m*-$CH_3$)。由此可以看出, 化合物的生物活性, 既和取代基有关也和取代的位置相关。作者认为, 生物活性的影响因素是多方面的 (诸如电性、氢键、空间体积、分子刚柔性等), 本文所涉及化合物的生物活性的规律性有待进一步研究。

**Table 1** Partial experimental results of target compounds

| Compd. | $R_1$ | $R_2$ | Yield / % | mp / ℃ | MS (*m/z*, %) | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | $[M+1]^+$ | $[M+23]^+$ | A | B |
| **1a** | -$C_6H_5$ | *p*-$NO_2$ | 53.3 | 148–149 | 419 (100) | 441 (9) | 133 (7) | 120 (21) |
| **1b** | -$C_6H_5$ | *m*-$NO_2$ | 73.1 | 149–150 | 419 (100) | 441 (17) | / | 120 (25) |
| **1c** | -$C_6H_5$ | *p*-Cl | 67.2 | 162–163 | 408 (50) | 430 (24) | 133 (100) | 120 (92) |
| **1d** | -$C_6H_5$ | H | 90.1 | 144–145 | 374 (65) | 396 (25) | 133 (67) | 120 (100) |
| **1e** | -$C_6H_5$ | *m*-$CH_3$ | 83.0 | 163–164 | 388 (87) | 410 (32) | 133 (67) | 120 (100) |
| **1f** | -$C_6H_5$ | *p*-$OCH_3$ | 64.2 | 154–155 | 402 (6)* | 426 (43) | 133 (100) | 120 (51) |
| **1g** | -$C_6H_5$ | 3,4-$OCH_2O$ | 80.4 | 160–161 | 418 (10) | 440 (34) | 133 (52) | 120 (100) |
| **1h** | -$C_6H_5$ | *p*-OH | 60.5 | 125–127 | 388 (9)* | 412 (100) | 133 (37) | / |
| **2a** |  | *m*-$NO_2$ | 60.1 | 156–159 | 499 (100) | 521 (7) | 213 (9) | 271 (20) |
| **2b** |  | 3,4-diCl | 62.1 | 187–188 | 522 (100) | / | 213 (44) | 385 (34) |
| **2c** |  | *p*-Cl | 84.4 | 191–194 | 488 (98) | 510 (7) | 213 (100) | 351 (78) |
| **2d** |  | *m*-Cl | 45.0 | 157–159 | 488 (100) | / | 213 (33) | 351 (12) |
| **2e** |  | H | 72.3 | 193–194 | 454 (100) | 476 (12) | 213 (65) | 317 (45) |
| **2f** |  | *m*-$CH_3$ | 67.3 | 161–163 | 468 (100) | 490 (10) | 213 (47) | 331 (64) |
| **2g** |  | 3,4-$OCH_2O$ | 89.0 | 191–192 | 496 (8)* | 520 (25) | 213 (47) | 361 (27) |
| **2h** |  | *p*-OH | 57.8 | 192–193 | 468 (5)* | 492 (17) | 213 (100) | 333 (17) |

A: $[R_1CH_2CH_2CO]^+$; B: **1a–1h** 为$[C_6H_4CO_2H\text{-}p]^+$, **2a–2h** 为$[R_1CH_2CH_2COCH_2CHC_6H_4R_2]^+$; *为$[M-1]^-$

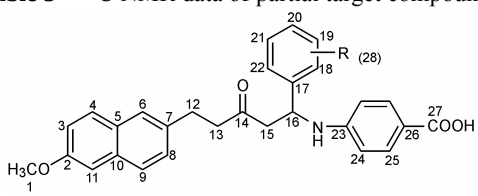
**Table 2**　$^1$H NMR and IR data of target compounds

| Compd. | $^1$H NMR ( $\delta$ / $10^{-6}$, designated hydrogen atom ) | IR ( $\nu_{max}$, $cm^{-1}$ ) |
|---|---|---|
| **1a** | 8.17 (2H, d, *J*=8.6 Hz, ArH), 7.67 (2H, d, *J*=8.6 Hz, ArH), 7.61 (2H, d, *J*=8.6 Hz, ArH), 7.25 (2H, d, *J*=7.8 Hz, ArH), 7.18~7.14 (3H, m, ArH), 6.56 (2H, d, *J*=8.6 Hz, ArH), 5.10 (1H, dd, *J*=3.9, 8.4 Hz, *CH), 3.08 (1H, dd, *J*=7.8, 16.8 Hz, $\underline{CH_2}$*CH), 2.88 (1H, dd, *J*=4.3, 16.9 Hz, $\underline{CH_2}$*CH), 2.83～2.77 (4H, m, $CH_2CH_2$) | 3 388(s), 3 000～2 500(br), 1 706(s), 1 661(s), 1 605(s) |
| **1b** | 8.29 (1H, s, ArH), 8.08 (1H, d, *J*=6.8 Hz, ArH), 7.89~7.87 (1H, m, ArH), 7.62 (1H, d, *J*=6.5 Hz, ArH), 7.60 (2H, d, *J*=8.6 Hz, ArH), 7.22 (2H, d, *J*=6.3 Hz, ArH), 7.18~7.15 (3H, m, ArH), 6.60 (2H, d, *J*=8.7 Hz, ArH), 5.14 (1H, dd, *J*=3.5, 8.3 Hz, *CH), 3.09 (1H, dd, *J*=7.9, 16.7 Hz, $\underline{CH_2}$*CH), 2.89 (1H, dd, *J*=4.9, 17.0 Hz, $\underline{CH_2}$*CH), 2.84～2.75 (4H, m, $CH_2CH_2$) | 3 377(s), 3 000～2 500(br), 1 705(s), 1 660(s), 1 607(s), 1 501(s) |
| **1c** | 7.60 (2H, d, *J*=8.5 Hz, ArH), 7.39 (2H, d, *J*=8.0 Hz, ArH), 7.37 (2H, d, *J*=8.0 Hz, ArH), 7.22 (2H, d, *J*=6.9 Hz, ArH), 7.18～7.15 (3H, m, ArH), 6.54 (2H, d, *J*=8.6 Hz, ArH), 4.95 (1H, dd, *J*=3.8, 8.6 Hz, *CH), 3.01 (1H, dd, *J*=7.6, 16.5 Hz, $\underline{CH_2}$*CH), 2.84～2.75 (5H, m, $CH_2CH_2$, $\underline{CH_2}$*CH) | 3 372(s), 3 000～2 500(br), 1 708(s), 1 669(s), 1 607(s), 1 496(s) |
| **1d** | 7.59 (2H, d, *J*=8.4 Hz, ArH), 7.38 (2H, d, *J*=7.4 Hz, ArH), 7.30 (2H, d, *J*=7.3 Hz, ArH), 7.28~7.14 (6H, m, ArH), 6.55 (2H, d, *J*=8.4 Hz, ArH), 4.93 (1H, dd, *J*=4.0, 8.6 Hz, *CH), 3.02 (1H, dd, *J*=7.3, 16.5 Hz, $\underline{CH_2}$*CH), 2.84～2.75 (5H, m, $CH_2CH_2$, $\underline{CH_2}$*CH) | 3 394(s), 3 000～2 500(br), 1 710(s), 1 688(s), 1 605(s), 1 496(s) |
| **1e** | 7.60 (2H, d, *J*=8.7 Hz, ArH), 7.26~7.14 (8H, m, ArH), 7.02 (1H, d, *J*=6.8 Hz, ArH), 6.54 (2H, d, *J*=8.7 Hz, ArH), 4.88 (1H, dd, *J*=4.5, 8.7 Hz, *CH), 3.00 (1H, dd, *J*=7.2, 16.5 Hz, $\underline{CH_2}$*CH), 2.86～2.74 (5H, m, $CH_2CH_2$, $\underline{CH_2}$*CH), 2.26 (3H, s, $CH_3$) | 3 366(s), 3 000～2 500(br), 1 703(s), 1 673(s), 1 606(s), 1 498(s) |
| **1f** | 7.59 (2H, d, *J*=8.7 Hz, ArH), 7.29 (2H, d, *J*=8.7 Hz, ArH), 7.22 (2H, d, *J*=6.9 Hz, ArH), 7.18~7.15 (3H, m, ArH), 6.85 (2H, d, *J*=8.6 Hz, ArH), 6.54 (2H, d, *J*=8.7 Hz, ArH), 4.87 (1H, dd, *J*=3.2, 8.2 Hz, *CH), 3.70 (3H, s, $OCH_3$), 2.99 (1H, dd, *J*=7.3, 16.3 Hz, $\underline{CH_2}$*CH), 2.83～2.72 (5H, m, $CH_2CH_2$, $\underline{CH_2}$*CH) | 3 393(s), 3 000～2 500(br), 1 710(s), 1 688(s), 1 604(s), 1 512(s) |
| **1g** | 7.60 (2H, d, *J*=8.5 Hz, ArH), 7.24 (2H, d, *J*=6.4 Hz, ArH), 7.18~7.15 (3H, m, ArH), 6.95 (1H, s, ArH), 6.85~6.80 (2H, m, ArH), 6.55 (2H, d, *J*=8.5 Hz, ArH), 5.95 (2H, s, $OCH_2O$), 4.86 (1H, dd, *J*=3.6, 8.1 Hz, *CH), 2.97 (1H, dd, *J*=7.2, 16.2 Hz, $\underline{CH_2}$*CH), 2.87～2.74 (5H, m, $CH_2CH_2$, $\underline{CH_2}$*CH) | 3 394(s), 3 000～2 500(br), 1 710(s), 1 689(s), 1 603(s), 1 488(s) |
| **1h** | 7.60 (2H, d, *J*=8.5 Hz, ArH), 7.22 (2H, d, *J*=7.0 Hz, ArH), 7.20~7.13 (5H, m, ArH), 6.68 (2H, d, *J*=8.2 Hz, ArH), 6.54 (2H, d, *J*=8.5 Hz, ArH), 4.82 (1H, dd, *J*=3.2, 8.2 Hz, *CH), 2.97 (1H, dd, *J*=7.3, 16.2 Hz, $\underline{CH_2}$*CH), 2.86～2.72 (5H, m, $CH_2CH_2$, $\underline{CH_2}$*CH) | 3 393(s), 3 000～2 500(br), 1 711(s), 1 690(s), 1 604(s), 1 513(s) |
| **2a** | 8.30 (1H, s, ArH), 8.05 (1H, d, *J*=7.4 Hz, ArH), 7.89 (1H, d, *J*=7.6 Hz, ArH), 7.70~7.68 (2H, m, ArH), 7.67~7.65 (1H, m, ArH), 7.62 (2H, d, *J*=8.7 Hz, ArH), 7.57 (1H, s, ArH), 7.30 (1H, d, *J*=7.9 Hz, ArH), 7.26 (1H, s, ArH), 7.12 (1H, d, *J*=7.2 Hz, ArH), 6.60 (2H, d, *J*=8.6 Hz, ArH), 5.15 (1H, dd, *J*=4.7, 8.4 Hz, *CH), 3.85 (3H, s, $OCH_3$), 3.11 (1H, dd, *J*=8.9, 16.6 Hz, $\underline{CH_2}$*CH), 2.95~2.80 (5H, m, $CH_2CH_2$, $\underline{CH_2}$*CH) | 3 366(s), 3 000～2 500(br), 1 705(s), 1 676(s), 1 606(s), 1 504(s) |
| **2b** | 7.72 (1H, s, ArH), 7.69~7.67 (3H, m, 2ArH, NH), 7.64 (2H, d, *J*=8.7 Hz, ArH), 7.57~7.54 (2H, m, ArH), 7.39 (1H, d, *J*=7.9 Hz, ArH), 7.31 (1H, d, *J*=8.0 Hz, ArH), 7.26 (1H, s, ArH), 7.12 (1H, d, *J*=7.8 Hz, ArH), 6.58 (2H, d, *J*=8.6 Hz, ArH), 5.00 (1H, dd, *J*=4.8, 8.4 Hz, *CH), 3.86 (3H, s, $OCH_3$), 3.06 (1H, dd, *J*=9.2, 16.4 Hz, $\underline{CH_2}$*CH), 2.97~2.85 (4H, m, $CH_2CH_2$), 2.83 (1H, dd, *J*=4.6, 16.3 Hz, $\underline{CH_2}$*CH) | 3 384(s), 3 000～2 500(br), 1 708(s), 1 655(s), 1 607(s), 1 502(s) |
| **2c** | 7.70 (1H, d, *J*=7.7 Hz, ArH), 7.68 (1H, d, *J*=8.2 Hz, ArH), 7.61 (2H, d, *J*=8.6 Hz, ArH), 7.55 (1H, s, ArH), 7.41 (2H, d, *J*=8.4 Hz, ArH), 7.34 (2H, d, *J*=8.4 Hz, ArH), 7.31 (1H, d, *J*=9.0 Hz, ArH), 7.27 (1H, s, ArH), 7.12 (1H, d, *J*=8.9 Hz, ArH), 6.55 (2H, d, *J*=8.6 Hz, ArH), 4.96 (1H, dd, *J*=4.8, 8.5 Hz, *CH), 3.85 (3H, s, $OCH_3$), 3.04 (1H, dd, *J*=9.0, 16.5 Hz, $\underline{CH_2}$*CH), 2.96~2.85 (4H, m, $CH_2CH_2$), 2.81 (1H, dd, *J*=4.5, 16.4 Hz, $\underline{CH_2}$*CH) | 3 392(s), 3 000～2 500(br), 1 711(s), 1 691(s), 1 605(s), 1 490(s) |
| **2d** | 7.71 (1H, d, *J*=7.9 Hz, ArH), 7.69 (1H, d, *J*=7.4 Hz, ArH), 7.61 (2H, d, *J*=8.7 Hz, ArH), 7.56 (1H, s, ArH), 7.46 (1H, s, ArH), 7.36 (1H, d, *J*=7.6 Hz, ArH), 7.33 ~7.27 (3H, m, ArH), 7.26 (1H, s, ArH), 7.11 (1H, d, *J*=9.0 Hz, ArH), 6.56 (2H, d, *J*=8.6 Hz, ArH), 4.98 (1H, dd, *J*=4.2, 9.0 Hz, *CH), 3.85 (3H, s, $OCH_3$), 3.04 (1H, dd, *J*=8.8, 16.3 Hz, $\underline{CH_2}$*CH), 2.95~ 2.84 (4H, m, $CH_2CH_2$), 2.83 (1H, dd, *J*=4.9, 16.4 Hz, $\underline{CH_2}$*CH) | 3 385(s), 3 000～2 500(br), 1 708(s), 1 658(s), 1 605(s), 1 502(s) |
| **2e** | 7.70~7.68 (2H, m, ArH), 7.61 (2H, d, *J*=8.6 Hz, ArH), 7.56 (1H, s, ArH), 7.39 (2H, d, *J*=7.4 Hz, ArH), 7.28~7.25 (4H, m, ArH), 7.20 (1H, d, *J*=8.2 Hz, ArH), 7.12 (1H, d, *J*=8.3 Hz, ArH), 6.57 (2H, d, *J*=8.7 Hz, ArH), 4.96 (1H, dd, *J*=4.6, 8.9 Hz, *CH), 3.85 (3H, s, $OCH_3$), 3.05 (1H, dd, *J*=9.2, 16.4 Hz, $\underline{CH_2}$*CH), 2.94~2.83 (4H, m, $CH_2CH_2$), 2.80 (1H, dd, *J*=4.4, 16.2 Hz, $\underline{CH_2}$*CH) | 3 383(s), 3 000～2 500(br), 1 708(s), 1 656(s), 1 607(s), 1 502(s) |
| **2f** | 7.70~7.68 (2H, m, ArH), 7.61 (2H, d, *J*=8.6 Hz, ArH), 7.55 (1H, s, ArH), 7.29 (1H, d, *J*=8.2 Hz, ArH), 7.27 (1H, s, ArH), 7.18~7.15 (3H, m, ArH), 7.13 (1H, d, *J*=7.5 Hz, ArH), 7.02 (1H, s, ArH), 6.56 (2H, d, *J*=8.7 Hz, ArH), 4.90 (1H, dd, *J*=4.4, 8.8 Hz, *CH), 3.85 (3H, s, $OCH_3$), 3.03 (1H, dd, *J*=9.3, 16.4 Hz, $\underline{CH_2}$*CH), 2.94~2.80 (4H, m, $CH_2CH_2$), 2.77 (1H, dd, *J*=4.4, 16.4 Hz, $\underline{CH_2}$*CH), 2.25 (3H, s, $CH_3$) | 3 394(s), 3 000～2 500(br), 1 711(s), 1 689(s), 1 603(s), 1 486(s) |

Continued

| Compd. | $^1$H NMR ( $\delta$ / $10^{-6}$, designated hydrogen atom ) | IR ( $\nu_{max}$, $cm^{-1}$ ) |
|---|---|---|
| **2g** | 7.70~7.68 (2H, m, ArH), 7.61 (2H, d, *J*=8.2 Hz, ArH), 7.56 (1H, s, ArH), 7.29 (1H, d, *J*=8.2 Hz, ArH), 7.26 (1H, s, ArH), 7.11 (1H, d, *J*=8.9 Hz, ArH), 6.96 (1H, s, ArH), 6.85 (1H, d, *J*=8.0 Hz, ArH), 6.82 (1H, d, *J*=7.9 Hz, ArH), 6.57 (2H, d, *J*=8.3 Hz, ArH), 5.95 (2H, s, $OCH_2O$), 4.88 (1H, dd, *J*=4.4, 8.9 Hz, *CH), 3.85 (3H, s, $OCH_3$), 3.00 (1H, dd, *J*=9.2, 16.3 Hz, $\underline{CH_2}$*CH), 2.93~2.80 (4H, m, $CH_2CH_2$), 2.77 (1H, dd, *J*=4.5, 16.3 Hz, $\underline{CH_2}$*CH) | 3 396(s), 3 000～2 500(br), 1 710(s), 1 688(s), 1 604(s), 1 486(s) |
| **2h** | 7.71 (1H, d, *J*=7.1 Hz, ArH), 7.69 (1H, d, *J*=8.2 Hz, ArH), 7.61 (2H, d, *J*=8.6 Hz, ArH), 7.54 (1H, s, ArH), 7.28 (1H, d, *J*=8.1 Hz, ArH), 7.26 (1H, s, ArH), 7.18 (2H, d, *J*=8.4 Hz, ArH), 7.12 (1H, d, *J*=8.7 Hz, ArH), 6.69 (2H, d, *J*=8.4 Hz, ArH), 6.55 (2H, d, *J*=8.7 Hz, ArH), 4.84 (1H, dd, *J*=5.0, 8.4 Hz, *CH), 3.85 (3H, s, $OCH_3$), 3.00 (1H, dd, *J*=9.0, 16.2 Hz, $\underline{CH_2}$*CH), 2.92~2.79 (4H, m, $CH_2CH_2$), 2.76 (1H, dd, *J*=4.9, 16.4 Hz, $\underline{CH_2}$*CH) | 3 398(s), 3 000～2 500(br), 1 709(s), 1 659(s), 1 607(s), 1 509(s) |

**Table 3** $^{13}$C NMR data of partial target compounds




| Compd. | $^{13}$C NMR ($\delta$/$10^{-6}$ , designated carbon atom) |
|---|---|
| **2a** | 206.9 (14), 167.5 (27), 156.9 (2), 151.2 (23), 148.1 (19), 145.9 (17), 136.3 (7), 133.7 (22), 132.9 (10), 131.2 (25), 130.1 (21), 128.9 (5), 128.7 (4), 127.8 (8), 126.8 (6), 126.0 (9), 122.2 (18), 121.3 (20), 118.6 (26), 118.0 (3), 112.0 (24), 105.8 (11), 55.3 (1), 51.6 (16), 49.7 (15), 43.5 (13), 28.9 (12) |
| **2b** | 206.9 (14), 167.5 (27), 156.9 (2), 151.3 (23), 144.7 (17), 136.3 (7), 132.9 (19), 131.9 (10), 131.3 (25), 130.8 (20), 129.6 (21), 128.9 (5), 128.8 (4), 128.7 (8), 127.8 (18), 127.2 (6), 126.9 (9), 126.0 (22), 118.7 (26), 118.0 (3), 112.1 (24), 105.9 (11), 55.3 (1), 51.3 (16), 49.7 (15), 43.6 (13), 28.9 (12) |
| **2c** | 207.1 (14), 167.5 (27), 157.0 (2), 151.4 (23), 142.3 (17), 132.9 (7), 131.6 (10), 131.1 (20), 130.3 (25), 130.2 (5), 129.0 (4), 128.9 (8), 128.7 (19, 21), 128.5 (18, 22), 127.8 (6), 126.0 (9), 118.6 (26), 117.8 (3), 112.0 (24), 105.9 (11), 55.3 (1), 51.8 (16), 50.0 (15), 43.7 (13), 28.9 (12) |
| **2d** | 207.1 (14), 167.5 (27), 156.9 (2), 151.5 (23), 144.7 (17), 134.2 (7), 133.3 (19), 132.4 (10), 131.6 (25), 130.1 (21), 129.1 (5), 129.0 (4), 128.5 (8), 127.6 (20), 127.5 (18), 127.1 (6), 126.4 (9), 125.1 (22), 119.0 (26), 118.9 (3), 113.6 (24), 106.2 (11), 55.9 (1), 53.0 (16), 49.9 (15), 43.5 (13), 28.9 (12) |
| **2e** | 207.3 (14), 167.6 (27), 156.9 (2), 151.7 (23), 143.3 (17), 136.3 (7), 132.9 (10), 131.2 (25), 129.0 (5), 128.8 (4), 128.6 (19, 21), 127.8 (8), 127.1 (20), 126.9 (6), 126.6 (18, 22), 126.0 (9), 118.6 (26), 117.5 (3), 111.9 (24), 105.9 (11), 55.3 (1), 52.4 (16), 50.3 (15), 43.7 (13), 28.9 (12) |
| **2f** | 207.4 (14), 167.6 (27), 156.9 (2), 151.7 (23), 143.3 (17), 137.7 (19), 136.3 (7), 132.9 (10), 131.2 (25), 129.0 (5), 128.7 (4), 128.5 (18), 127.8 (8, 21), 127.1 (6), 126.9 (9), 126.0 (20), 123.7 (22), 118.6 (26), 117.4 (3), 111.9 (24), 105.9 (11), 55.3 (1), 52.4 (16), 50.3 (15), 43.7 (13), 28.9 (12), 21.3 (28) |
| **2g** | 207.4 (14), 167.5 (27), 156.9 (2), 151.6 (23), 147.5 (19), 146.2 (20), 137.3 (17), 136.3 (7), 132.9 (10), 131.1 (25), 128.9 (5), 128.7 (4), 127.8 (8), 126.9 (6), 126.0 (9), 119.9 (22), 118.6 (26), 117.5 (3), 112.0 (21), 108.2 (24), 106.9 (18), 105.9 (11), 101.0 (28), 55.3 (1), 52.1 (16), 50.4 (15), 43.7 (13), 28.9 (12) |
| **2h** | 207.6 (14), 167.6 (27), 157.0 (20), 156.3 (2), 151.8 (23), 136.4 (17), 133.4 (7), 132.9 (10), 131.2 (25), 129.0 (5), 128.7 (4), 127.8 (8), 127.7 (18, 22), 126.9 (6), 126.0 (9), 118.6 (26), 117.3 (3), 115.3 (19, 21), 112.0 (24), 105.9 (11), 55.3 (1), 52.0 (16), 50.5 (15), 43.8 (13), 29.0 (12) |

**Table 4** The HR-MS and biological activity data of target compounds

| Compd. | Formula | HR-MS | | Conc.1 | | Inhibition /% | Conc.2 | | Inhibition /% |
|---|---|---|---|---|---|---|---|---|---|
| | | Calcd | Found | $\mu g \cdot mL^{-1}$ | $nmol \cdot mL^{-1}$ | | $\mu g \cdot mL^{-1}$ | $nmol \cdot mL^{-1}$ | |
| **1a** | $C_{24}H_{22}N_2NaO_5$ | 441.142 1 | 441.141 4 | 10 | 23.9 | 36.3 | 100 | 239.2 | 68.4 |
| **1b** | $C_{24}H_{22}N_2NaO_5$ | 441.142 1 | 441.140 2 | 10 | 23.9 | 19.8 | 100 | 239.2 | 80.8 |
| **1c** | $C_{24}H_{22}ClNNaO_3$ | 430.118 0 | 430.118 2 | 10 | 24.6 | –0.8 | 100 | 245.7 | 82.4 |
| **1d** | $C_{24}H_{23}NNaO_3$ | 396.175 0 | 396.157 4 | 10 | 26.8 | 19.8 | 100 | 268.1 | 63.1 |
| **1e** | $C_{25}H_{25}NNaO_3$ | 410.172 7 | 410.171 9 | 10 | 25.8 | 14.8 | 100 | 258.4 | 37.8 |
| **1f** | $C_{25}H_{25}NNaO_4$ | 426.167 6 | 426.167 8 | 10 | 24.8 | 34.3 | / | / | / |
| **1g** | $C_{25}H_{23}NNaO_5$ | 440.146 8 | 440.145 3 | 10 | 23.9 | –5.3 | 100 | 239.8 | 62.3 |
| **1h** | $C_{24}H_{23}NNaO_4$ | 412.151 9 | 412.152 9 | 10 | 25.7 | 6.6 | 100 | 257.1 | 70.8 |
| **2a** | $C_{29}H_{26}N_2NaO_6$ | 521.168 3 | 521.167 2 | 10 | 20.1 | 6.4 | / | / | / |
| **2b** | $C_{29}H_{25}Cl_2NNaO_4$ | 544.105 3 | 544.102 8 | 10 | 19.2 | 48.5 | / | / | / |
| **2c** | $C_{29}H_{26}ClNNaO_4$ | 510.144 3 | 510.143 0 | 10 | 20.5 | 66.5 | / | / | / |
| **2d** | $C_{29}H_{26}ClNNaO_4$ | 510.144 3 | 510.142 5 | 10 | 20.5 | 21.8 | / | / | / |
| **2e** | $C_{29}H_{27}NNaO_4$ | 476.183 2 | 476.185 1 | 10 | 22.1 | 10.2 | / | / | / |
| **2f** | $C_{30}H_{29}NNaO_4$ | 490.198 9 | 490.199 4 | 10 | 21.4 | 6.6 | / | / | / |
| **2g** | $C_{30}H_{27}NNaO_6$ | 520.173 1 | 520.173 5 | 10 | 20.1 | 7.9 | / | / | / |
| **2h** | $C_{29}H_{27}NNaO_5$ | 492.178 1 | 492.176 7 | 10 | 21.4 | 41.1 | / | / | / |
| | Acarbose | 645.57 | / | 100 | 154.9 | 74.1 | 100 | 154.9 | 74.1 |

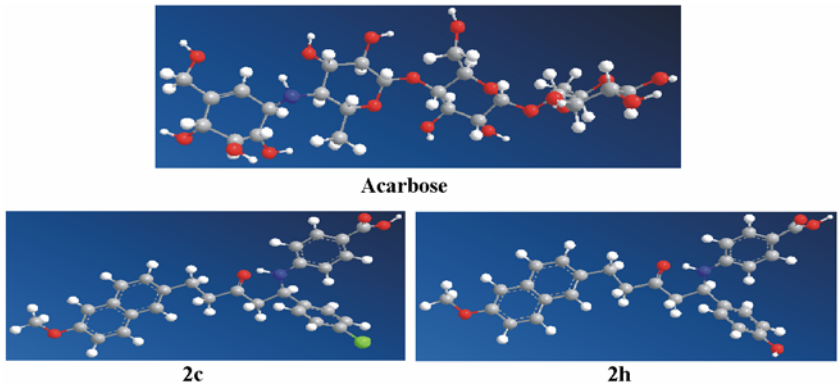



**Figure 2**　Three-dimensional structures of Acarbose and compounds **2c**, **2h**

## 结论

本文设计合成了 16 个 4-芳基-2-丁酮、芳香醛与对氨基苯甲酸生成的 Mannich 碱; 首次发现这些 *β*-氨基酮化合物对 *α*-葡糖苷酶具有不同程度的抑制活性, 其中 **2c** 有显著的抑制活性, 可作为新型抗糖尿病药物先导分子进一步研究。

## 实验部分

### 1　主要实验仪器及试剂

精密显微熔点测定仪 (X-6 型, 北京福凯仪器有限公司); FT-IR 红外光谱仪 (GX 型, USA; KBr 压片); 核磁共振仪 (AV-300, USA; TMS 为内标, DMSO-$d_6$ 为溶剂); 质谱仪 (Agilent 1946B ESI MS, USA); HR-MS (Bruker Daltonics Data Analysis 3.2, USA)。葡糖苷酶 (Sigma, G-0660), 葡萄糖检测试剂 (南京建成公司), 芳香醛、4-苯基-2-丁酮、萘丁美酮和对氨基苯甲酸为国产化学纯, 其余为国产分析纯。

### 2　Mannich 碱 (1a～2h)的一般合成方法

在 50 mL 圆底烧瓶中加入 2 mmol 的对氨基苯甲酸、2 mmol 芳香醛、2～4 mL 无水乙醇, 电磁搅拌。产生大量沉淀后, 加入 2 mmol 酮组分, 滴加 0.1～0.2 mL 浓盐酸, 继续搅拌。TLC 监测反应进程。反应完成后, 置于冰箱中过夜。次日抽滤, 滤饼水洗 (2×3 mL)、醇洗 (2×3 mL), 抽干得粗品。乙醇-丙酮混合溶剂重结晶, 干燥后得纯品。测定熔点, 进行 IR、$^1$H NMR、$^{13}$C NMR、ESI-MS 和 HR-MS 测定。

### 3　Mannich 碱的生物活性测定

100 μL 反应体系中含 0.02 U 葡糖苷酶、67 nmol·mL$^{-1}$ 磷酸钠缓冲液 (pH 6.8) 和样品, 同时设立空白对照 (不含酶和样品) 和阴性对照 (不含样品), 37 ℃反应 10 min, 加入 0.1 mol·mL$^{-1}$ 麦芽糖, 室温反应 10 min, 再加入 200 μL 的葡萄糖检测试剂, 混匀后 490 nm 测定 $A$ 值。根据 $A$ 值计算抑制率, 抑制率＝[1–($A_{样品}$–$A_{空白}$) / ($A_{阴性}$–$A_{空白}$)]×100。每个样品每个浓度设双复孔, 重复两次。

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