西格列汀衍生物的设计、合成及降糖活性研究

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摘要: 本研究以西格列汀为起始原料, 应用不同类型的脂肪酰氯进行酰化反应, 得到目标化合物**Sd-01**～**Sd-10**。动物实验经吉林省药物研究院实验动物伦理委员会批准 (批准号: 2025001)。采用2型糖尿病小鼠模型对目标化合物进行了体内降糖活性评价, 构效关系分析, 并对其中活性较好的化合物进行了小鼠口服糖耐量测试。同时通过最大给药量试验对化合物进行初步安全性评价。结果表明, 该系列化合物具有良好的降糖活性与较高的安全性, 健康小鼠单次灌胃给药2 000 mg·kg^{-1}后未见行为异常及死亡情况。其中**Sd-06**的降糖活性与阳性对照药物西格列汀相当, **Sd-05**的降糖活性优于西格列汀, 此外**Sd-05**在30 mg·kg^{-1}剂量下能够明显改善正常小鼠的糖耐量, 活性优于西格列汀组 (50 mg·kg^{-1}), 具有进一步研究价值。

关键词: 西格列汀; 结构修饰; 构效关系; 降糖活性; 糖耐量

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Design, synthesis, and evaluation of hypoglycemic activity of sitagliptin derivatives

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Abstract: In this study ten new compounds **Sd-01**−**Sd-10** were synthesized *via* acylation from sitagliptin and various fatty acyl chlorides. Animal experiments approved by the Institutional Animal Care and Use Committee of Jilin Provincial Institute of Pharmaceutical Research (approval No. 2025001). The target compounds were evaluated for their *in vivo* hypoglycemic activity using a type 2 diabetic mouse model, with subsequent structure-activity relationship analysis and further assessment of the most active compounds *via* an oral glucose tolerance test. Meanwhile, a maximum feasible dose test was conducted in healthy mice for preliminary safety evaluation. The results indicated that this series of compounds exhibited promising hypoglycemic activity and a high level of safety, which was supported by the observation of no abnormal behavior or mortality in healthy mice after a single oral dose of 2 000 mg·kg^{-1}. Among them, **Sd-06** showed activity comparable to sitagliptin, whereas **Sd-05** was more potent. Notably, **Sd-05** at the lower dose of 30 mg·kg^{-1} effectively improved glucose tolerance in normal mice, surpassing the efficacy of sitagliptin at 50 mg·kg^{-1}, highlighting its value for further development.

Key words: sitagliptin; structural modification; structure-activity relationship; hypoglycemic activity; glucose tolerance

糖尿病是由于胰岛素分泌不足或作用缺陷引发的一种慢性代谢性疾病, 已成为21世纪继心脑血管疾病、癌症之后危害人类健康的三大疾病之一[1-3]。其临床分型主要包括1型糖尿病、2型糖尿病和妊娠期糖尿病等, 其中2型糖尿病占全部糖尿病病例的90%以上, 构成疾病负担的绝对主体[4-6]。西格列汀 (sitagliptin,

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图 1) 由默克公司研发, 于 2006 年 10 月获美国 FDA 批准用于治疗 2 型糖尿病[7]。作为该类药物中的开创性品种, 西格列汀已在包括中国在内的全球多数国家获得批准, 其市场表现突出, 2017 年全球销售额高达 59 亿美元, 持续位列全球畅销降糖药物之一[8]。然而, 西格列汀在临床应用中仍存在一定的局限性, 例如其功能相对单一, 对于糖尿病常伴随的心血管并发症风险缺乏额外的保护作用[9]; 此外, 其药代动力学性质也存在进一步优化的空间[10,11]。

“Me-too”药物是新药研发中的重要策略之一, 指在已有原研药结构基础上进行优化或衍生化改造, 旨在获得疗效更优、活性更强或安全性更高的新化合物[12]。该策略不仅有助于突破现有药物的专利壁垒, 还能显著降低研发成本与风险, 为糖尿病等慢性疾病的临床治疗提供更多的药物选择[13]。西格列汀分子中的氨基是进行衍生化改造的理想位点。例如, Cadila 制药公司的专利 (WO2012017391A2) 系统性地报道了在西格列汀氨基位点连接各种氨基酸或肽链的一系列衍生物, 这些结构复杂的酰化衍生物 (如 GPL-2009-031, 图 1) 在体内外均表现出显著降糖效果, 证明了该修饰位点的巨大潜力[14]。另一方面, Xie 等[15]通过在西格列汀上引入不同链长的硝酸酯官能团, 成功设计出兼具强效降糖和一氧化氮释放功能的多功能分子 (如化合物 T4, 图 1), 展现了酰化修饰在增强活性和赋予新功能方面的价值。不仅如此, 该策略在维格列汀 (vildagliptin, 图 1) 中也取得了成功, 其仲胺氮原子的酰基化衍生物 (如 lipoyl vildagliptin 与 5-chlorovaleryl vildagliptin, 图 1) 被证实具有更显著的降糖效果和延长的药物半衰期[16,17]。这些研究共同表明, 对“列汀”类药物分子的氮原子进行酰基化修饰, 是一种能够有效改变药物理化性质、增强生物活性甚至引入附加药理作用的通用且可靠的策略。

基于上述成功经验, 本研究采用了一种系统而聚焦的策略: 使用一系列不同碳链长度的脂肪酰基对西格列汀分子的氨基进行衍生化改造 (图 2), 成功合成 10 个新型西格列汀衍生物。所有目标化合物均经核磁共振 (^{1}H NMR、^{13}C NMR) 与高分辨质谱 (HRMS-ESI) 确证结构, 并进一步通过小鼠体内降糖活性筛选实验评估其药理性能。通过构建这一结构相对简单的化合物库, 初步探索脂肪酰西格列汀疏水链长与其降糖活性之间的构效关系, 旨在获得生物活性更优、毒副作用更低的新型候选药物, 为西格列汀类“Me-too”药物的后续研发提供参考。

结果

1 目标化合物的设计

以脂肪酰氯与西格列汀氨基进行反应, 通过形成

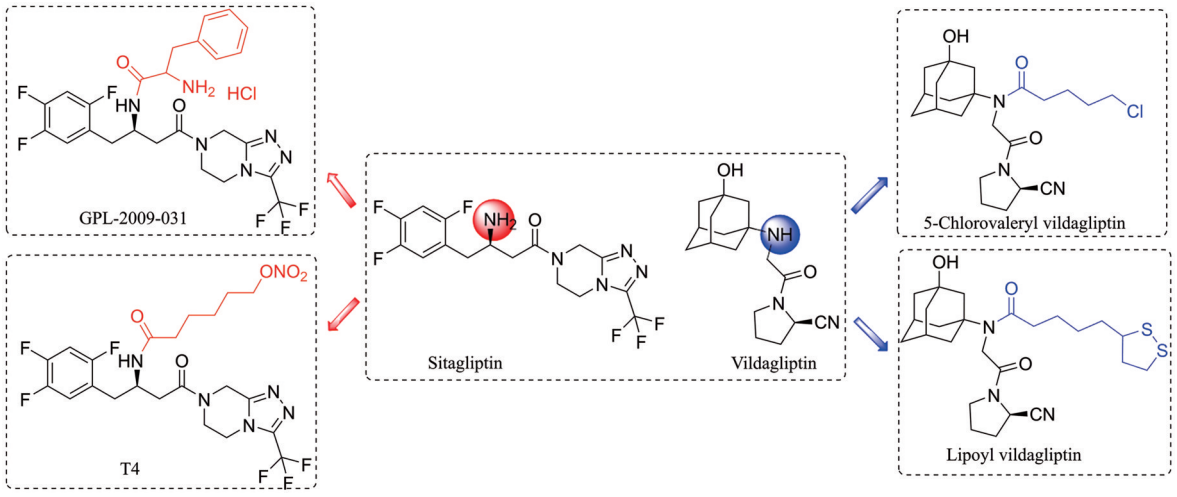


Figure 1 The application of me-too strategy in the structural optimization of sitagliptin and vildagliptin

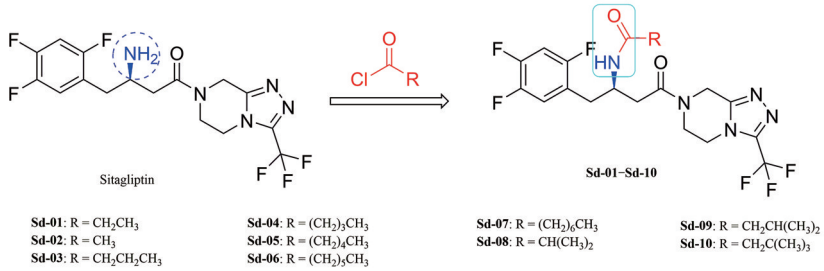


Figure 2 Sitagliptin derivatives **Sd-01**−**Sd-10**

不同链长的脂肪酰胺对西格列汀进行结构改造, 设计并合成了10个新型西格列汀衍生物 (图2), 并对其构效关系进行了探讨, 以期为后续开发西格列汀“Me-too”药物提供参考。

2　目标化合物的合成

西格列汀衍生物的合成路线如图2所示。以西格列汀为原料, 应用不同类型的脂肪酰氯进行酰化反应, 得到目标化合物**Sd-01**～**Sd-10**。其结构经^{1}H NMR、^{13}C NMR、HRMS-ESI确定, 理化性质及谱图数据见表1。

3　降糖药效学研究

小鼠在高脂饲料喂养4周后出现皮毛无光泽, 同时出现“三多一少”的症状, 即多饮、多食、多尿、体重减轻。

最大给药量试验结果表明, 健康小鼠一次性灌胃给予2 000 mg·kg^{-1}的化合物后, 状态无异常且无一例死亡, 初步证明该系列化合物在急性毒性层面具有较高的安全性。

Table 1　The characterization and physical properties of target compounds **Sd-01**–**Sd-10**

Compd.	Properties, m.p., ^{1}H NMR, ^{13}C NMR, HRMS-ESI
Sd-01	White solid (70.0% yield); m.p. 183.3–183.5 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 7.69 (t, J = 8.9 Hz, 1H), 7.49–7.28 (m, 2H), 4.99 (s, 1H), 4.86 (s, 1H), 4.36–4.20 (m, 2H), 4.12–3.87 (m, 3H), 2.89 (dd, J = 13.6, 5.7 Hz, 1H), 2.76–2.62 (m, 3H), 1.99–1.78 (m, 2H), 0.83 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 169.80, 169.14, 156.36 (dd, J = 243.0, 9.8 Hz), 151.38 (d, J = 13.7 Hz), 148.23 (dd, J = 245.0, 13.7 Hz), 146.12 (dd, J = 240.0, 12.9 Hz), 142.98 (q, J = 39.6 Hz), 123.21 (d, J = 18.6 Hz), 119.50 (dd, J = 19.5, 6.3 Hz), 118.92 (q, J = 271.7 Hz), 105.88 (dd, J = 29.4, 21.0 Hz), 46.56, 44.03, 43.44, 42.51, 41.59, 37.93, 32.86, 22.90; HRMS-ESI: m/z Calcd. for $C_{19}H_{19}F_6N_5O_2$ [M+Na]$^+$ 486.144 3, found 486.133 1
Sd-02	White solid (72.3% yield); m.p. 159.6–169.1 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 7.78 (t, J = 8.6 Hz, 1H), 7.50–7.30 (m, 2H), 4.98 (s, 1H), 4.86 (d, J = 3.1 Hz, 1H), 4.31–4.22 (m, 2H), 4.10–4.06 (m, 1H), 3.97–3.93 (m, 2H), 2.87–2.85 (m, 1H), 2.75–2.57 (m, 3H), 1.69–1.61 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 172.93, 169.86 (d, J = 6.4 Hz), 156.42 (dd, J = 243.4, 9.9 Hz), 151.45 (d, J = 12.9 Hz), 148.25 (dd, J = 247.5, 13.7 Hz), 146.12 (dd, J = 240.0, 12.5 Hz), 143.04 (q, J = 38.8 Hz), 123.32 (d, J = 18.5 Hz), 119.66 (dd, J = 27.1, 6.5 Hz), 118.99 (q, J = 270.7 Hz), 105.81 (dd, J = 47.3, 27.3 Hz), 46.42, 43.79, 42.61, 41.69, 32.99, 29.03, 10.27; HRMS-ESI: m/z Calcd. for $C_{18}H_{17}F_6N_5O_2$ [M+Na]$^+$ 472.128 6, found 472.117 5
Sd-03	White solid (66.0% yield); m.p. 168.4–169.1 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 7.71 (t, J = 9.4 Hz, 1H), 7.51–7.28 (m, 2H), 5.07–4.93 (m, 1H), 4.85 (s, 1H), 4.45–3.83 (m, 5H), 2.89 (d, J = 13.9 Hz, 1H), 2.75–2.60 (m, 3H), 1.90 (t, J = 7.2 Hz, 1H), 1.82–1.81 (m, 1H), 1.37–1.31 (m, 2H), 0.67 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 171.94, 169.83 (d, J = 4.6 Hz), 156.40 (dd, J = 243.1, 9.8 Hz), 151.45 (d, J = 11.8 Hz), 148.25 (dd, J = 247.5, 13.6 Hz), 146.14 (dd, J = 242.4, 12.9 Hz), 143.03 (q, J = 38.9 Hz), 123.33 (d, J = 17.0 Hz), 119.64 (dd, J = 19.3, 6.2 Hz), 118.99 (q, J = 270.7 Hz), 105.94 (dd, J = 29.5, 20.9 Hz), 46.38, 44.09, 43.49, 42.62, 41.71, 37.92, 33.04, 19.00, 13.69; HRMS-ESI: m/z Calcd. for $C_{20}H_{21}F_6N_5O_2$ [M+Na]$^+$ 500.159 9, found 500.148 6
Sd-04	White solid (65.0% yield); m.p. 179.3–180.5 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 7.71 (dd, J = 11.1, 8.7 Hz, 1H), 7.49–7.39 (m, 1H), 7.38–7.30 (m, 1H), 5.07–4.93 (m, 1H), 4.86 (s, 1H), 4.41–4.19 (m, 2H), 4.13–3.85 (m, 3H), 2.91–2.87 (m, 1H), 2.70–2.64 (m, 3H), 1.92 (t, J = 7.3 Hz, 1H), 1.88–1.76 (m, 1H), 1.34–1.18 (m, 2H), 1.09–0.98 (m, 2H), 0.77–0.73 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 172.08, 169.83 (d, J = 3.8 Hz), 156.41 (dd, J = 243.0, 9.7 Hz), 151.45 (d, J = 11.1 Hz), 148.27 (dd, J = 247.5, 13.6 Hz), 146.13 (dd, J = 242.4, 12.1 Hz), 143.02 (q, J = 39.1Hz), 123.32 (d, J = 18.4 Hz), 119.68 (dd, J = 19.0, 6.1 Hz), 118.99 (q, J = 270.7 Hz), 105.93 (dd, J = 29.4, 21.0 Hz), 46.34, 44.10, 43.49, 42.63, 41.71, 35.57, 33.07, 27.79, 21.96, 14.01; HRMS-ESI: m/z Calcd. for $C_{21}H_{23}F_6N_5O_2$ [M+Na]$^+$ 514.175 6, found 514.164 4
Sd-05	White solid (65.0% yield); m.p. 161.7–162.5 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 7.71 (t, J = 9.8 Hz, 1H), 7.49–7.40 (m, 1H), 7.38–7.28 (m, 1H), 5.07–4.93 (m, 1H), 4.86 (s, 1H), 4.37–4.19 (m, 2H), 4.14–3.85 (m, 3H), 2.90 (dd, J = 14.1, 4.1 Hz, 1H), 2.71–2.62 (m, 3H), 1.91 (t, J = 7.3 Hz, 1H), 1.81 (q, J = 7.0 Hz, 1H), 1.35–1.27 (m, 2H), 1.21–1.10 (m, 2H), 1.09–0.91 (m, 2H), 0.78 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 172.12, 169.82 (d, J = 4.6 Hz), 156.39 (dd, J = 243.0, 9.6 Hz), 151.43 (d, J = 11.9 Hz), 148.27 (dd, J = 247.5, 13.6 Hz), 146.13 (dd, J = 242.4, 12.3 Hz), 143.02 (q, J = 39.3 Hz), 123.30 (d, J = 18.5 Hz), 119.67 (dd, J = 19.9, 9.2 Hz). 118.79 (q, J = 270.7 Hz), 105.85 (dd, J = 47.1, 29.1 Hz), 46.32, 43.79, 42.63, 41.72, 35.90, 33.02, 31.50, 28.55, 25.63, 22.38, 14.25; HRMS-ESI: m/z Calcd. for $C_{22}H_{25}F_6N_5O_2$ [M+Na]$^+$ 528.191 2, found 528.179 9
Sd-06	White solid (65.9% yield); m.p. 162.0–163.0 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 7.71 (t, J = 9.9 Hz, 1H), 7.47–7.39 (m, 1H), 7.38–7.30 (m, 1H), 5.07–4.93 (m, 1H), 4.86 (s, 1H), 4.37–4.19 (m, 2H), 4.10–3.87 (m, 3H), 2.92–2.86 (m, 1H), 2.71–2.62 (m, 3H), 1.91 (t, J = 7.2 Hz, 1H), 1.88–1.73 (m, 1H), 1.40–0.94 (m, 8H), 0.81 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 172.12, 169.82 (d, J = 4.6 Hz), 156.39 (dd, J = 243.0, 9.6 Hz), 151.43 (d, J = 11.9 Hz), 148.27 (dd, J = 247.5, 13.6 Hz), 146.14 (dd, J = 242.4, 12.3 Hz), 143.02 (q, J = 39.3 Hz), 123.30 (d, J = 18.5 Hz), 119.67 (dd, J = 19.9, 9.2 Hz), 118.79 (q, J = 270.7 Hz), 105.85 (dd, J = 47.1, 29.1 Hz), 46.32, 43.79, 42.63, 41.72, 38.31, 35.90, 33.02, 31.50, 28.55, 25.63, 22.38, 14.25; HRMS-ESI: m/z Calcd. for $C_{23}H_{27}F_6N_5O_2$ [M+Na]$^+$ 542.206 9, found 542.195 1
Sd-07	White solid (60.6% yield); m.p. 163.3–164.1 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 7.71 (t, J = 9.9 Hz, 1H), 7.49–7.28 (m, 2H), 5.07–4.93 (m, 1H), 4.86 (s, 1H), 4.40–4.21 (m, 2H), 4.13–3.81 (m, 3H), 2.90 (dd, J = 14.0, 4.3 Hz, 1H), 2.71–2.63 (m, 3H), 1.91 (t, J = 7.3 Hz, 1H), 1.81 (q, J = 7.2 Hz, 1H), 1.37–0.95 (m, 10H), 0.84 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 172.11, 169.82 (d, J = 4.8 Hz), 156.39 (dd, J = 243.1, 9.6 Hz), 151.43 (d, J = 11.7 Hz), 148.27 (dd, J = 247.5, 13.6 Hz), 146.14 (dd, J = 242.4, 12.9 Hz), 143.02 (q, J = 38.9 Hz), 123.29 (d, J = 18.5 Hz), 119.64 (dd, J = 19.3, 6.2 Hz), 118.98 (q, J = 270.7 Hz), 105.93 (dd, J = 48.5, 28.3 Hz), 46.30, 43.79, 42.63, 41.72, 38.81, 38.10, 35.87, 33.02, 31.60, 28.90, 25.67, 22.55, 14.31; HRMS-ESI: m/z Calcd. for $C_{24}H_{29}F_6N_5O_2$ [M+Na]$^+$ 556.222 5, found 556.211 0

Continued

Compd.	Properties, m.p., ^{1}H NMR, ^{13}C NMR, HRMS-ESI
Sd-08	White solid (47.4% yield); m.p. 208.6−209.8 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 7.65 (t, J = 9.0 Hz, 1H), 7.49−7.27 (m, 2H), 5.01 (s, 1H), 4.85 (s, 1H), 4.44−4.19 (m, 2H), 4.06 (d, J = 5.4 Hz, 1H), 4.00−3.90 (m, 2H), 2.93−2.85 (m, 1H), 2.72−2.58 (m, 3H), 2.25−2.07 (m, 1H), 0.87−0.75 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 176.05, 169.91, 156.39 (dd, J = 242.8, 9.7 Hz), 151.44 (d, J = 12.9 Hz), 148.22 (dd, J = 247.5, 13.6 Hz), 146.08 (dd, J = 241.4, 12.0 Hz), 143.04 (q, J = 39.0 Hz), 123.34 (d, J = 19.6 Hz), 119.76 (dd, J = 19.1, 9.1 Hz), 118.98 (q, J = 271.7 Hz),105.85 (dd, J = 45.5, 29.3 Hz), 46.16, 43.78, 42.20, 38.32, 34.52, 33.01, 19.86, 19.56; HRMS-ESI: *m/z* Calcd. for $C_{20}H_{21}F_6N_5O_2$ $[M+Na]^+$ 500.159 9, found 500.148 7
Sd-09	White solid (47.4% yield); m.p. 208.6−209.8 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 7.71 (t, J = 9.6 Hz, 1H), 7.50−7.25 (m, 2H), 5.08−4.93 (m, 1H), 4.85 (s, 1H), 4.44−4.22 (m, 2H), 4.13−3.83 (m, 3H), 2.89 (dd, J = 13.7, 4.3 Hz, 1H), 2.76−2.63 (m, 3H), 1.85−1.72 (m, 2H), 1.70 (d, J = 5.6 Hz, 1H), 0.73−0.68 (d, J = 6.1 Hz, 3H), 0.65 (d, J = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C:171.40, 169.83, 156.38 (dd, J = 243.2, 9.4 Hz), 151.44 (d, J = 11.0 Hz), 148.26 (dd, J = 247.5, 13.7 Hz), 146.14 (dd, J = 241.4, 11.6 Hz), 143.03 (q, J = 38.9 Hz), 123.30 (dd, J = 18.5, 5.1 Hz), 119.67 (dd, J = 19.0, 6.5 Hz), 118.98 (q, J = 271.7 Hz), 106.03 (dd, J = 27.2, 18.9 Hz), 46.37, 45.19, 43.80, 42.46, 41.73, 38.45, 33.07, 25.87, 22.38; HRMS-ESI: *m/z* Calcd. for $C_{21}H_{23}F_6N_5O_2$ $[M+Na]^+$ 514.175 6, found 514.164 3
Sd-10	White solid (23.8% yield); m.p. 151.1−151.8 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 7.66 (t, J = 8.7 Hz, 1H), 7.49−7.30 (m, 2H), 5.09−4.93 (m, 1H), 4.92−4.77 (m, 1H), 4.39 (d, J = 10.3 Hz, 1H), 4.32−4.18 (m, 1H), 4.14−3.80 (m, 3H), 2.87 (dd, J = 14.0, 4.5 Hz, 1H), 2.76−2.57 (m, 3H), 1.90−1.62 (m, 2H), 0.76 (d, J = 2.7 Hz, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 170.74, 169.80, 156.39 (dd, J = 243.2, 9.8 Hz), 151.43 (d, J = 9.0 Hz), 148.25 (dd, J = 247.5, 13.6 Hz), 146.16 (dd, J = 242.4, 13.1 Hz), 143.02 (q, J = 38.8 Hz), 123.29 (d, J = 18.7 Hz), 119.69 (dd, J = 18.7, 6.1 Hz), 118.98 (q, J = 271.7 Hz), 105.89 (dd, J = 29.4, 21.0 Hz), 49.29, 46.33, 43.79, 42.20, 38.80, 38.09, 33.00, 30.60, 29.81; HRMS-ESI: *m/z* Calcd. for $C_{22}H_{25}F_6N_5O_2$ $[M+Na]^+$ 528.191 2, found 528.179 9

降血糖活性筛选实验结果表明 (表2), 设计合成的10个新化合物中除**Sd-02**、**Sd-03**外均具有降糖活性, 其中**Sd-06**的降糖活性与阳性对照药物西格列汀相当, **Sd-05**的降糖活性优于西格列汀。

口服糖耐量试验结果显示 (表3), **Sd-05**在30 mg·kg^{-1}剂量下能够明显改善正常小鼠的糖耐量, 活性优于西格列汀组 (50 mg·kg^{-1}), 表明西格列汀衍生物**Sd-05**表现出良好的降血糖作用, 在改善糖代谢紊乱、维持血糖稳定方面优于现有的西格列汀, 具有进一步开发应用的意义。

4 构效关系研究

由表2数据可以发现, 直链脂肪酰基衍生物 (**Sd-01**～**Sd-07**) 的活性呈现碳链长度依赖性: 当碳原子数为6或7时 (**Sd-05**、**Sd-06**), 化合物表现出最优的降糖活性, 其效果与阳性药西格列汀相当甚至更优; 而碳链较短 (2～5) 或过长 (= 8) 均导致活性减弱, 呈现出一种“先增强后减弱”的规律。与之相比, 支链脂肪酰基衍生物 (**Sd-08**～**Sd-10**) 的降糖活性普遍较弱, 这可能是由于支链引入所带来的空间位阻, 影响了药物分子的体内代谢过程或与靶点的相互作用。

5 小结

本研究基于“Me-too”药物研发策略, 设计并合成了10个新型西格列汀脂肪酰胺衍生物, 系统评价其小鼠体内降糖活性并初步探讨了构效关系。结果表明, 化合物**Sd-05**在2型糖尿病模型中表现出优于西格列汀的降糖活性, 且在口服糖耐量试验中以更低剂量 (30 mg·kg^{-1}) 展现出更佳的血糖调控能力。构效关系分析揭示直链脂肪酰基衍生物的降糖活性呈碳链长度依赖性, C6或C7链长为最佳结构单元, 而支链结构则不利于活性发挥。最大给药量试验证实, 该系列化合物在2 000 mg·kg^{-1}剂量下对健康小鼠无急性毒性, 安全性良

Table 2 The *in vivo* hypoglycemic activity of compounds **Sd-01**−**Sd-10**. n = 10, $\bar{x} \pm s$. $^*P < 0.05$, $^{**}P < 0.01$ *vs* model group; $^{\triangle\triangle}P < 0.01$ *vs* sitagliptin group; $^{\diamond\diamond}P < 0.01$ *vs* blank control group

Group	Blood glucose/mmol·L^{-1}	
	Prior to dosing	On day 8
Blank control group	7.03 ± 1.09	6.73 ± 0.96
Model group	21.76 ± 3.06	28.72 ± 3.76$^{\diamond\diamond}$
Sitagliptin group	20.35 ± 4.24	19.05 ± 7.84**
Sd-01	21.68 ± 3.61	24.35 ± 4.15*
Sd-02	21.78 ± 3.38	26.23 ± 4.92
Sd-03	21.59 ± 2.40	25.58 ± 7.23
Sd-04	21.58 ± 2.89	23.36 ± 4.22*
Sd-05	20.92 ± 2.89	17.72 ± 4.40$^{**\triangle\triangle}$
Sd-06	21.75 ± 2.80	19.75 ± 5.72**
Sd-07	21.69 ± 3.14	21.26 ± 5.57*
Sd-08	21.01 ± 2.64	23.41 ± 4.22*
Sd-09	21.6 ± 2.06	24.30 ± 2.72*
Sd-10	20.63 ± 1.85	24.10 ± 3.83*

Table 3 Oral glucose tolerance test for compound **Sd-05**. n = 10, $\bar{x} \pm s$. $^{**}P < 0.01$ *vs* sitagliptin group; $^{\triangle\triangle}P < 0.01$ *vs* blank control group

Group	Time/min				
	−30	0	30	60	90
Blank control	6.88 ± 1.01	7.02 ± 0.84	14.52 ± 2.72	11.95 ± 1.36	9.90 ± 1.06
Sitagliptin	6.78 ± 1.02	7.20 ± 1.10	10.04 ± 1.45$^{\triangle\triangle}$	9.76 ± 1.28$^{\triangle\triangle}$	8.70 ± 1.31$^{\triangle\triangle}$
Sd-05	6.83 ± 1.06	7.29 ± 1.05	9.15 ± 0.87$^{**\triangle\triangle}$	8.90 ± 1.32$^{**\triangle\triangle}$	8.05 ± 0.97$^{**\triangle\triangle}$

好。该研究为西格列汀类药物的优化提供了新思路, 其深入的作用机制研究将作为后续工作重点开展。

实验部分

1　主要仪器与试验材料

实验所用试剂均为市售分析纯或化学纯。西格列汀 (HEW220803-5, 湖北威德利化学试剂有限公司); 链脲佐菌素 (CR2410070, 武汉赛维尔生物科技有限公司); 基础维持饲料 (2107632500015257, 辽宁长生生物技术股份有限公司); 高脂饲料 (QC202502152125011, 玉书生物科技有限公司); 无水柠檬酸 (J00121B, 美伦生物有限公司); 二水合柠檬酸三钠 (20130109, 北京化工厂); 羧甲基纤维素钠 (F20020928, 中国医药上海化学试剂公司); 血糖试纸 (77-2306061-44, 九州通医疗器械集团有限公司)。

采用全自动熔点仪 (MPA100型, 美国Optimelt公司) 测定化合物熔点; ^{1}H NMR和^{13}C NMR谱图通过液体超导核磁共振谱仪 (Avance neo 400 MHz型, 美国Bruker公司) 测定; 质谱采用高分辨质谱仪 (Q Exactive型, 美国ThermoFisher公司) 测定。采用血糖仪 (GLM-77型, 中国九州通医疗器械集团有限公司) 测定小鼠血糖。

昆明小鼠, SPF级, 体质量为18～20 g, 由辽宁长生生物技术股份有限公司提供, 合格证号为210726250100354。动物实验经吉林省药物研究院实验动物伦理委员会批准 (批准号2025001)。

2　化学合成

将西格列汀 (5 g, 12.28 mmol)、碳酸钾 (2.45 g, 18.41 mmol) 溶于无水二氯甲烷中, 降温至0 ℃以下, 搅拌下缓慢滴加不同类型的酰氯溶液 (13.26 mmol), 滴加完毕后室温进行反应, TLC监测反应进程。反应完毕后, 将反应液用适量水稀释, 并用稀盐酸调节溶液pH至弱酸性。水层用二氯甲烷萃取, 有机相用无水硫酸钠干燥, 过滤, 蒸除二氯甲烷得到粗品, 粗品用无水乙醇进行重结晶得到目标化合物**Sd-01**～**Sd-10**。

3　药效学实验

3.1　2型糖尿病小鼠模型的建立[18,19]　取昆明小鼠, 雌雄各半, 所有动物自由饮水进食, 活动不限。动物室温度为20～25 ℃, 湿度为40%～70%。适应性喂养3天。选择10只小鼠作为空白对照组, 始终喂养正常饲料, 其余小鼠全部建立糖尿病模型, 即采用高脂饲料进行喂养4周。观察记录各组小鼠在实验期间的体质量和外观形态的变化, 如毛色、运动功能、代谢物是否正常及有无异常分泌物等, 评估动物一般状态变化。

喂养4周后, 高脂饲料喂养组禁食12 h, 按50 mg·kg^{-1}腹腔注射链脲佐菌素STZ, 连续注射5天。继续饲养1周后, 12 h禁食不禁水, 断尾取血, 用血糖仪测量血糖。之后隔天测血糖, 共测3次, 血糖值均 ⩾ 11.11 mmol·L^{-1}为稳定高血糖小鼠, 作为模型动物。

3.2　最大给药量试验[20]　为评估化合物的初步安全性, 进行了最大给药量试验。健康小鼠适应性饲养3天, 按2 000 mg·kg^{-1}的最大可行剂量一次性灌胃给药, 连续观察14天, 记录小鼠的一般行为状态、中毒表现及死亡情况。

3.3　小鼠体内降糖活性测试　将建模成功的小鼠进行分组。组别为模型组、西格列汀组、西格列汀衍生物组 (**Sd-01**～**Sd-10**), 每组10只, 雌雄各半, 给予高脂饲料。空白对照组继续给予正常饲料喂养。西格列汀组每日小鼠灌胃给予西格列汀混悬液, 西格列汀衍生物组每日给予西格列汀衍生物混悬液, 给药剂量都为50 mg·kg^{-1}。模型组和空白对照组按0.1 mL· (10 g)$^{-1}$小鼠给予0.25%羧甲基纤维素钠溶液。连续给药7天, 第7日晚禁食, 第8日早用血糖仪测空腹血糖。给药前空腹平均血糖值和第8天平均血糖值测量结果见表2。

3.4　Sd-05口服糖耐量测试[11,21]　昆明小鼠, 体重18～20 g, 雌雄各半, 随机分为3组, 每组10只。实验前小鼠禁食不禁水12 h, 空白对照组给予空白溶媒 (0.25%的羧甲基纤维素钠), 西格列汀组灌胃给予西格列汀混悬液, 给药剂量为50 mg·kg^{-1}, **Sd-05**组小鼠灌胃给予**Sd-05**混悬液, 给药剂量为30 mg·kg^{-1}。给药后, 断尾取血, 测定血糖值 (记为−30 min)。给药30 min后测定血糖值记为0 min, 之后立即按20 mg·kg^{-1}灌胃给予葡萄糖溶液 (质量浓度为2 mg·mL^{-1}), 并于30、60、90、120 min测定血糖值, 测量结果见表3。

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利益冲突: 本文所有作者声明不存在利益冲突关系。

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