有机化学 DOI: 10.6023/cjoc202107001 综述与进展
Chinese Journal of Organic Chemistry REVIEW

基于二肽基肽酶 4 (DPP-4)靶点设计的五种降糖活性杂环合成及构效关系研究进展

孔媛芳[a] 杨 彬[a] 庄 严[a] 张京玉[a] 孙德梅*,[a] 董春红*,[b]
([a] 河南中医药大学药学院 郑州 450046)
([b] 河南中医药大学中医药科学院 郑州 450046)

摘要 糖尿病是我国慢性疾病中威胁人类健康的主要疾病, 治疗糖尿病的药物作用靶点主要有二肽基肽酶 4 (DPP-4)、单磷酸腺苷活化蛋白激酶(AMPK)、过氧化物酶体增殖物激活受体 γ (PPARγ)受体等, 其中以 DPP-4 为靶点的靶向药物研究是近几年的热点. DPP-4 抑制剂是治疗 2 型糖尿病的药物, 其最大的优点是不易诱发低血糖和增加体重. 据报道, 目前已上市的 DPP-4 靶向药物可引起胰腺炎和超敏等不良反应, 因此继续开发新型 DPP-4 抑制剂的降糖药物, 以避免不良反应发生值得进一步深入研究. 在系统的文献调研基础上, 总结出具有潜在的降糖活性杂环结构, 并通过计算机分子模拟对接, 针对DPP-4靶点, 最终筛选出5种易合成且降糖活性较高的杂环结构, 并对其合成路线及构效关系进行归纳总结分析, 为今后开发安全高效、结构新颖的 DPP-4 抑制剂的降糖药物提供研究基础.

关键词 糖尿病; 二肽基肽酶 4 (DPP-4)抑制剂; 分子对接; 合成方法; 构效关系

Research Progress on the Synthesis and Structure-Activity Relationship of Five Hypoglycemic Active Heterocycles Based on Dipeptidyl Peptidase 4 (DPP-4) Target Design

Kong, Yuanfang[a] Yang, Bin[a] Zhuang, Yan[a] Zhang, Jingyu[a]
Sun, Demei*,[a] Dong, Chunhong*,[b]
([a] *College of Pharmacy, Henan University of Chinese Medicine, Zhengzhou 450046*)
([b] *Academy of Chinese Medical Science, Henan University of Chinese Medicine, Zhengzhou 450046*)

Abstract Recently, diabetes has gradually become a main life-threatening disease in China. Drug targets for the treatment of diabetes mainly include dipeptidyl peptidase 4 (DPP-4), adenosine monophosphate-activated protein kinase (AMPK), peroxisome proliferator-activated receptor gamma (PPARγ) receptor and so on, in which targeted drug research targeting DPP-4 is a hot spot in recent years. DPP-4 inhibitor is a drug for the treatment of type 2 diabetes, and its biggest advantage is that it is not easy to induce hypoglycemia and increase weight. It is reported that the currently available DPP-4 targeted drugs can cause adverse reactions, such as pancreatitis and hypersensitivity. Therefore, it is worth further studying to continue to develop new hypoglycemic drugs for DPP-4 inhibitors to avoid adverse reactions. According to the systematic literature review, the potential heterocyclic structures with hypoglycemic activity are summarized and through computer molecular simulation docking, five kinds of heterocyclic structures with high hypoglycemic activity and easy synthesis are finally screened out based on DPP-4 target design. The synthesis routes and structure-activity relationships are summarized and analyzed, which provides a research basis for the development of safe, efficient and novel hypoglycemic drugs for DPP-4 inhibitors in the future.

Keywords diabetes; dipeptidyl peptidase 4 (DPP-4) inhibitor; molecular docking; synthesis methods; structure-activity relationship

* Corresponding authors. E-mail: jyzhang2004@hactcm.edu.cn; chunhong_dong@hactcm.edu.cn
Received July 1, 2021; revised September 30, 2021; published online November 9, 2021.
Project supported by the Zhongjing Scholars Research Funding of Henan University of Chinese Medicine (No. 00104311-2021-1-8), the Key Scientific Research Projects of Colleges and Universities in Henan Province (No. 20A350004), and the Natural Science Foundation of Henan Province (No. 202300410264).
河南中医药大学仲景高层次人才专项基金(No. 00104311-2021-1-8)、河南省高等学校重点科研项目(No. 20A350004)、河南省自然科学基金(No. 202300410264)资助项目.

1 Introduction

Diabetes is a metabolic disease characterized by hyperglycemia, which is caused by insulin secretion defects, impaired biological functions, or both. It can cause many complications in human organs, including the heart, brain, and kidney.[1] According to statistics, 0.67% of China's population suffered from diabetes in 1980, and this number has increased to 10.4% in just 33 years.[2] It has been forecast that the number of diabetes patients would reach 300 million worldwide in 2025 and 552 million in 2030.[3] Therefore, there is a need to develop highly effective hypoglycemic drugs for diabetes treatment.

The main targets of hypoglycemic drugs are dipeptidyl peptidase 4 (DPP-4), adenosine monophosphate-activated protein kinase (AMPK), peroxisome proliferator-activated receptor gamma (PPARγ) receptor, and fibroblast growth factor 21 and so on.[4] Among them, DPP-4 has recently become a hot research topic in the development of hypoglycaemic drugs which was used for the treatment of type 2 diabetes, which can inhibit the inactivation of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), improving the levels of endogenous GLP-1 and promoting the release of insulin from pancreatic β cells by GIP and it can also inhibit the secretion of glucagon from pancreatic α cells, thereby increasing the insulin levels and lowering the blood sugar.[5] At present, there are 12 kinds of DPP-4 inhibitors that have entered the market, and 4 drugs are in the clinical research stage and many new small DPP-4 inhibitors are in the preclinical research stage.[6]

The biggest advantage of antidiabetic drugs targeting DPP-4 is not easy to induce hypoglycemia and weight gain.[7] It is reported that the currently available DPP-4 targeted drugs can cause adverse reactions, such as pancreatitis and hypersensitivity.[8] All patients should be tested before application to avoid accidents. In 2015, the United States Food and Drug Administration (FDA) issued a safety statement, pointing out that if patients have persistent severe joint pain when using DPP-4 for treatment, they should report it in time and stop medication as appropriate.[9] DPP-4 inhibitors may also cause canceration in various tissues of the body and reduce the lysosomal activity caused by increased carcinogenicity in cells.[10] Meta-analysis showed that DPP-4 inhibitor increased the risk of heart failure.[11] Therefore, it is worth further studying to continue to develop new hypoglycemic drugs for DPP-4 inhibitors to avoid adverse reactions.

In order to avoid the adverse reactions of DPP-4 inhibitors, new hypoglycemic active drug molecules of DPP-4 were designed and developed. In this paper, we started by performing a search for chemical structures with hypoglycemic effect, and found 12 chemical frameworks with simple structures. Through being screened out with computer molecular simulation docking, five chemical structures with hypoglycemic activity of DPP-4 target, including benzopyran-2-one, hexahydropyrrolo[2,1-*b*]oxazole, pyrano[3,2-*c*]pyridone, pyrrolotriazine, and triazolopyrazine, were selected as they are highly active and easy to synthesize. The synthesis routes and structure-activity relationships are summarized and analyzed, which provides a research basis for the development of safe, efficient and novel hypoglycemic drugs for DPP-4 inhibitors in the future.

2 Screening of hypoglycemic heterocycles

Using "hypoglycemic compounds" as a keyword, we searched the CNKI database, Wanfang database, VIP Chinese journal service platform, SciFinder, TOP 200, Springer, PubMed, Elsevier, Wiley, American Chemical Society, and Royal Society of Chemistry databases, and related journal articles. More than 300 articles were found, and 12 chemical structures of hypoglycemic compounds were summarized. In particular, in the search, sitagliptin metformin, a hypoglycemic drug, appeared in the TOP 200 list in 2016 (Figure 1).

To understand the mechanisms of the hypoglycemic effect, 12 heterocyclic compounds exhibiting hypoglycemic activity were investigated.

Arylcoumarin compounds exhibit hypoglycemic activity among other pharmacological effects. By measuring the α-glucosidase inhibitory activity and the free radical activity of the advanced glycation end products (AGEs) form of these compounds, the benzopyran-2-one structure (**a**, Figure 1) was found responsible for the hypoglycemic activity. Hu *et al.*[12] synthesized 4-arylcoumarin and its anti-

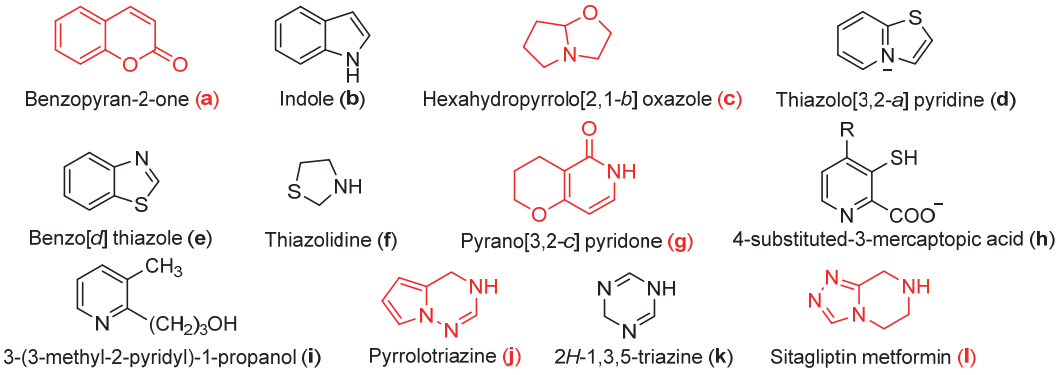
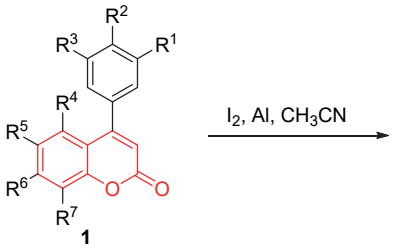


Figure 1 Chemical structures of 12 hypoglycemic compounds

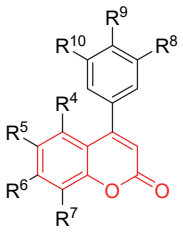
hypoglycemic activity *in vitro*. Both *α*-glucosidase and AGEs formation inhibitory activities were enhanced after demethylation, indicating that the hypoglycemic activity of these compounds can be enhanced when the methoxy group was demethylated to hydroxyl, and their IC_{50} values were shown in Table 1.

Table 1 *In vitro* hypoglycemic activity of compounds **1a**～**1d** and **2a**～**2d**



1

1a: R^1 = H, R^2 = OCH_3, R^3 = R^4 = R^5 = H, R^6 = R^7 = OH
1b: R^1 = R^2 = OCH_3, R^3 = H, R^4 = OH, R^5 = H, R^6 = OH, R^7 = H
1c: R^1 = R^2 = R^3 = OCH_3, R^4 = R^5 = H, R^6 = R^7 = OH
1d: R^1 = R^2 = OCH_3, R^3 = R^4 = R^5 = H, R^6 = R^7 = OH



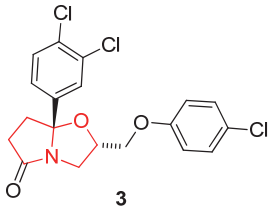
2

2a: R^1 = H, R^2 = OH, R^3 = R^4 = R^5 = H, R^6 = R^7 = OH
2b: R^1 = R^2 = OH, R^3 = H, R^4 = OH, R^5 = H, R^6 = OH, R^7 = H
2c: R^1 = R^2 = R^3 = OH, R^4 = R^5 = H, R^6 = R^7 = OH
2d: R^1 = R^2 = OH, R^3 = R^4 = R^5 = H, R^6 = R^7 = OH

Compd.	IC_{50}/(mg•L^{-1})	
	α-Glucosidase inhibitory activity	AGEs forming free radical activity
1a	＞1000	5.247±0.519
1b	＞1000	6.567±0.456
1c	＞1000	3.239±0.713
1d	＞1000	2.346±0.188
2a	＞1000	4.223±0.268
2b	0.469±0.042	2.453±0.069
2c	0.250±0.042	1.132±0.141
2d	1.020±0.062	0.623±0.016
Acarbose	0.042±0.002	—
Aminoguanidine Hydrochloride	—	28.255±0.657

Indole[13] (**b**, Figure 1) was also demonstrated as the basic structure with hypoglycemic effect in the indole-3-carboxylic acid derivative GY3, which can lower blood sugar levels by activating the AMPK pathway. By structural modification of GY3, ZG04 was obtained. With ZG04 as the lead compound, two compounds were modified at 1- and 3-positions. Their biological activity was tested in HepG2 cells, revealing that they have hypoglycemic activity. By studying the inhibitory activity against *α*-glucosidase, the measured IC_{50} range was from 0.53±0.01 μmol/L to 1.36±0.04 μmol/L. Compared with acarbose (IC_{50}=2.91±0.02 μmol/L), the synthesized indole derivatives enhanced the hypoglycemic activity.

Aicher *et al.*[14] synthesized a series of substituted tetrahydropyrrolo[2,1-*b*]oxazole-5(6*H*)-one and tetrahydropyrrolo[2,1-*b*]thiazole-5(6*H*)-one compounds (**c**, Figure 1) from amino alcohol or amino mercaptan and keto acid as substrates. These compounds were evaluated in a type 2 diabetes (noninsulin-dependent diabetes) model (*ob*/*ob* mice), and their blood sugar lowering efficacy *in vivo* was demonstrated. They can also enhance the utilization capacity of glucose in cultured L6 myocytes to achieve hypoglycemic effect. In obese, insulin-resistant cynomolgus monkeys, 21-day treatment with the compound **3** (2*S*) (Figure 2) substantially increased insulin sensitivity (S_I, +71±21%, p＜0.05), as determined by the Bergman minimal model while reducing basal (−36±11%, p＜0.05) and glucose stimulated (−35±11%, p＜0.05) insulin levels during an intravenous glucose tolerance test.



3

Figure 2 Structure of compound **3**

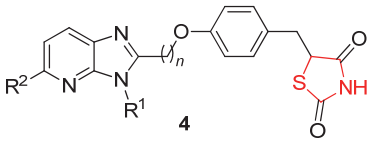
Blank *et al.*[15] prepared several substituted 2-arylthiazolo[3,2-*a*]pyridinium salts (**d**, Figure 1) and evaluated their hypoglycemic activity in rats fasted for 48 h. The common structure of these compounds is thiazolopyridine. Among the compounds prepared in this study, two compounds had the same hypoglycemic activity in 48 h fasted rats. At the oral dose of 102 mg of free alkali/kg (equivalent to 150 mg/kg perchlorate), these two compounds also significantly increased in liver triglyceride levels (a 200%～300% increase). At a low dose of 34 mg of free alkali/kg, one of the compounds still showed hypoglycemic activity but did not significantly increase the liver triglyceride. It also reduced blood glucose levels in streptozotocin-diabetic rats and normal feeding rats. At doses up to 136 mg of free alkali/kg (equivalent to 200 mg/kg perchlorate), no increase in liver triglycerides was observed in diabetic animals, indicating that the compound has a clear hypoglycemic effect.

The main pathological defect of T2DM patients is the decreased utilization of glucose in peripheral tissues,[16] and the resulting high blood glucose levels affect the transfer rate of glucose in skeletal muscle cells. Meltzer-Mats *et al.*[16] studied the effect of increasing glucose in skeletal muscle tissue under high glucose levels. For the drug transport, benzothiazole derivatives were designed and synthesized (**e**, Figure 1), and hypoglycemic activity

was found in experiments conducted with KKAY mice. Several synthetic structures were related to benzothiazole derivatives, one of which increased glucose uptake by 2.5- and 1.1-fold compared with carrier-treated and PT-1 cells. After subcutaneous injection of compound modification in mice with obesity gene, the blood glucose level could be reduced to the normal range.

Oguchi *et al.*[17] used pyridine as a substrate to synthesize a series of thiazole-2,4-dione derivatives (**f**, Figure 1), which are conformationally restricted analogs of rosiglitazone. The series was evaluated for its effect on hypoglycemic activity in genetically diabetic KK mice *in vivo* (Table 2).

Table 2 Hypoglycemic differentiation activities of thiazole-2,4-dione derivatives



4

Compd.	R^1	R^2	*n*	Decrease in blood glucose/%	
				18 h	21 h
4a	Me	H	0	−7.0±4.8	3.6±0.7
4b	Me	H	1	24.7±9.1	27.6±5.9
4c	Me	H	2	−5.6±6.2	13.0±9.3
4d	Me	H	3	−3.0±6.1	−9.3±18.3
4e	H	H	1	13.9±12.7	7.4±3.0
4f	Et	H	1	−19.5±8.7	2.4±8.3
4g	Ph	H	1	3.9±5.6	−3.4±22.4
4h	4-$ClC_6H_4CH_2$	H	1	24.5±8.2	−8.5±19.0
4i	4-$PhC_6H_4CH_2$	H	1	3.8±13.4	11.4±6.0
4j	Me	Cl	1	37.1±7.7	47.6±6.9

Qiao *et al.*[18] isolated a compound containing the structure of pyranopyridine (**g**, Figure 1) from the solid culture of the endophytic fungus Aspergillus. The activation of FGF21 by such compounds was proved by qRT-PCR. Under insulin resistance, FGF21 in HepG2 cells was significantly decreased. In the normal control group, the expression level of FGF21 could be effectively restored by administering 5 μmol/L compound. In addition, FGF21 was increased in a dose-dependent manner in the dose concentration range of 5～25 μmol/L. The above *in vitro* bioactivity analysis proved that pyran[3,2-*c*]pyridone structure has potential hypoglycemic activity and mechanism.

Blank *et al.*[19] reported that 3-mercapto-4-methylpicolinic acid (**h**, Figure 1) was one of very few compounds derived from 3-mercaptopicolinic acid (3-MPA) to have hypoglycemic activity. In order to find compounds with greater potency than 3-MPA, several 4-substituted 3-mercaptopicolinic acids (4-OMe, OC_6H_5, SMe, SH, C1, NH_2, Et) were prepared and used for animal experiments. The hypoglycemic activity was measured in 48 h fasted male rats weighing 200 g. Tail vein samples were obtained at 1, 2, and 4 h after administering 3-MPA. After testing, 1, 2 and 4 h, the blood glucose levels decreased by 30%, 42% and 45%, respectively. The hypoglycemic activity of 4-substituted analogs of 3-MPA was evaluated under the same conditions. The hypoglycemic effect of these compounds was not obvious. It can be proved that any modification of nature will reduce or destroy the hypoglycemic activity of 3-MPA.

Blank *et al.*[20] performed several structural modifications of 3-(3-methyl-2-pyridyl)-1-propanol (**i**, Figure 1), changing the positions of the methyl and alcohol side chains, the distance between the heterocycle and hydroxyl groups, and adding substituents, and they proved the hypoglycemic activity through animal experiments. Compounds were tested in rats fasted for 48 h at a dose of 150 mg/kg. After administration of test animals, liver triglycerides increased by about ten-fold (from 2.7±0.8 mg/g to 26.1±10.0 mg/g, $p<0.001$).

The structure of the DIV inhibitor drug alogliptin undergoes a skeleton transition from pyrimidinedione to a pyrrolotriazine structure,[21] which was then optimized to synthesize new pyrrolotriazines (**j**, Figure 1). All the new compounds were tested *in vitro* and *in vivo*, demonstrating hypoglycemic activity. Compared with the control drug alogliptin (IC_{50}=8.47 nmol/L), except for the four compounds with DPP-IV inhibitory activity (IC_{50}>9 nmol/L), the other compounds showed better activity. Some compounds showed potent hypoglycemic activity (IC_{50}<4 nmol/L), even 2～3.5 times higher than that of alogliptin.

Metformin (MET) is a commonly used drug for type 2 diabetes. However, it presents shortcomings such as incomplete absorption due to its high polarity. Li *et al.*[22] reacted MET with aldehydes and ketones to obtain dihydrotriazine compounds (**k**, Figure 1). According to the hypoglycemic animal experiment, the blood glucose levels of the three compounds were 7.45, 7.16 and 5.32 mmol/L, respectively, which were similar to those of metformin hydrochloride (5.01 mmol/L) and showed good hypoglycemic stability. Dihydrotriazine compounds are more lipophilic than metformin, which is conducive to the absorption of compounds and can be used as lead compounds for further study in the treatment of type 2 diabetes.

In addition, a hypoglycemic drug, sitagliptin and metformin, was searched in 2016 TOP 200 (**l**, Figure 1). Zhang[23] explored the curative effect of siglitine metformin on type 2 diabetes mellitus. They treated 82 patients in the observation group with siglitine metformin tablets and compared their postprandial 2 h blood glucose (2 h PBG) and fasting plasma glucose (FPG) (Table 3).

Table 3 Blood glucose indexes of patients [($x\pm s$), n=82]

Entry	FPG/(mol•L^{-1})		2 h PBG/(mol•L^{-1})	
	Before treatment	Post treatment	Before treatment	Post treatment
1	7.43±0.70	5.30±0.39	11.33±1.24	6.80±0.53
t	0.569	12.010	0.105	8.000
P	0.285	0.000	0.458	0.000

Based on this literature research, which afforded 12 kinds of heterocyclic compounds with hypoglycemic activity, the following research was performed to find heterocyclic hypoglycemic compounds with good hypoglycemic effect and simple synthetic routes.

3 Study on molecular docking

Taking DPP-4 as the target enzyme, the monomer structures of the 12 kinds of hypoglycemic backbones were respectively docked with DPP-4 using Autodock Vina. The calculation result is shown in Table 4, in which the molecule column represents the number of the 12 compounds. The total score column is given by the software based on the binding ability of the 12 compounds and DPP-4 as the target enzyme. When the score is negative, it shows that the compound can effectively combine with the protein. The greater the absolute score, the better the combination effect.

There are many modification positions in the structure of the heterocyclic compounds with hypoglycemic activity, which provides a platform for the design of lead compounds with strong targetability and high bioavailability.

Among the compounds depicted in Figure 1, compound **b** is cheap and its synthetic route does not need to be improved. Therefore, this article will not describe it. Compounds **i** and **h** are both pyridine compounds, which are easy to obtain and do not require further modification of their synthesis, so this article will not describe them.

Table 4 Computer simulation results

Entry	Compound	Binding energy/(kJ•mol^{-1})
1	**a**	**−25.62**
2	**g**	**−22.68**
3	**j**	**−22.68**
4	**b**	−21.84
5	**i**	−21.42
6	**e**	−21
7	**l**	**−20.58**
8	**h**	−20.16
9	**d**	−19.32
10	**c**	**−17.64**
11	**k**	−17.64
12	**f**	−13.86

Compounds **e** and **d** are sulfur-containing compounds. Because of their strong odor, they are not selected for synthesis and will not be discussed further in this paper. Compound **k** has a single ring and is relatively easy to synthesize, and compound **f** has a higher score, indicating that the compound can be bound to proteins, but the absolute value of the score is the smallest, indicating poor binding effect with proteins, so it is not be discussed in detail here. The synthetic routes and the biological activities of the remaining five compounds need to be further investigated. The complexes of these five kinds of heterocyclic compounds with hypoglycemic activity and DPP-4 are shown in Figure 3.

4 Five hypoglycemic heterocycles for potential DPP-4 inhibitor

After comprehensive consideration, according to the selection principle of heterocyclic compounds with simple structure and many substitutable positions, five heterocyclic compounds of structure (**a**), (**c**), (**g**), (**j**), and (**l**) were screened out, namely, benzopyran-2-one, hexahydropyrrolo[2,1-*b*]oxazole, pyrano[3,2-*c*]pyridone, pyrrolotriazine, triazolopyrazine. Their synthetic routes and structure-activity relationships are discussed in the following sections.

4.1 Benzopyran-2-one

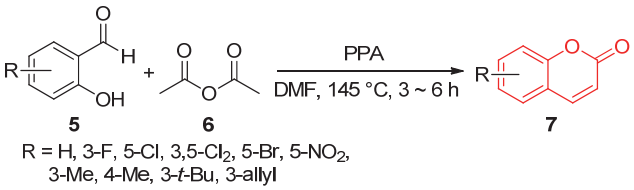
4.1.1 Derivative activity

The benzopyran-2-one (chromen-2-one, Coumarin) skeleton is shown in Figure 4.

The benzopyran-2-one ring system, which is present in numerous natural and synthetic products, displays varied bioactivities, such as anti-oxidant,[24] anti-inflammatory,[25] anti-human immunodeficiency virus (HIV),[26] anti-microbial,[27] anti-cancer,[28] and anti-tuberculosis[29] (Figure 5). Therefore, the synthesis and the applications of the benzopyran-2-one skeleton have gained widespread attention.

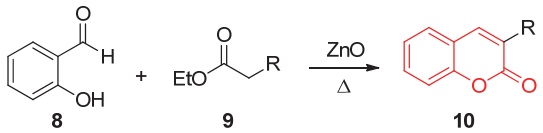
4.1.2 Synthetic route

Yang *et al.*[30] described a convenient procedure promoted by polyphosphoric acid (PPA) for the preparation of benzopyran-2-one from salicylaldehydes **5** and acetic anhydride (Scheme 1). This synthetic method is simple, and they could obtain different products with high yield.



Scheme 1 Synthetic route of compound **7**

Shakil *et al.*[31] reported an easily scalable method in which benzopyran-2-one derivatives were synthesized using ZnO as a catalyst (Scheme 2). They changed different solvents with the solvothermal method to synthesize ZnO morphologies. The catalytic activity of ZnO samples for benzopyran-2-one synthesis through the Knoevenagel condensation varied with morphology.



Scheme 2 Synthetic route of compound **10**

Song *et al.*[32] reported a general and straightforward protocol for di-/perfluoroalkylation of *ortho*-hydroxycinnamic esters **11** through a photoredox-catalyzed cascade

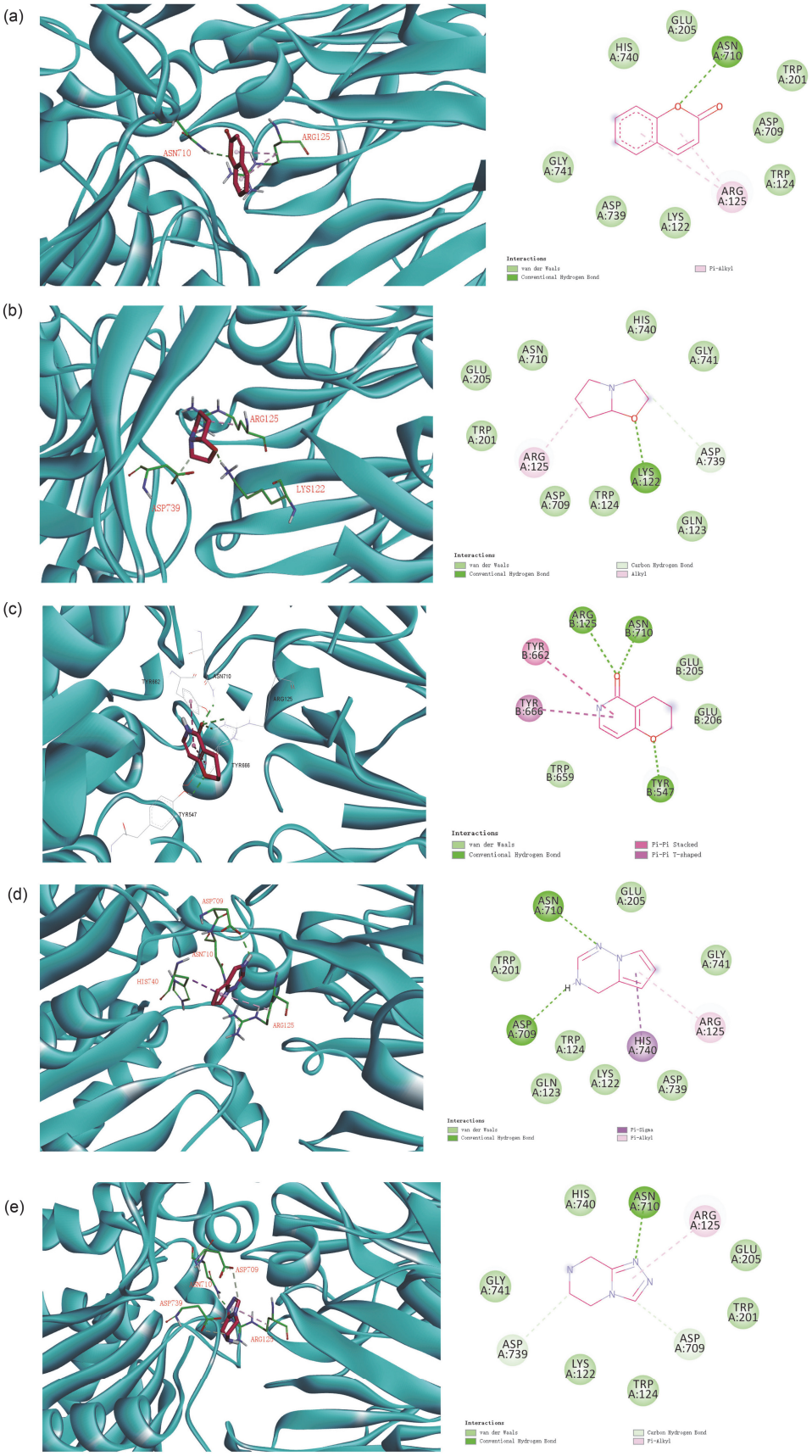


Figure 3 Complexes of five hypoglycemic heterocyclic compounds and DPP-4

(a) Complex of DPP-4 and benzopyran-2-one **a**; (b) Complex of DPP-4 and hexahydropyrrolo[2,1-*b*]oxazole **c**; (c) Complex of DPP-4 and pyrano[3,2-*c*]pyridine **g**; (d) Complex of DPP-4 and pyrrolotriazine **j**; (e) Complex of DPP-4 and triazolopyrazine l.

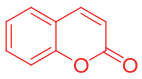


Figure 4 Skeleton of benzopyran-2-one (chromen-2-one, Coumarin)

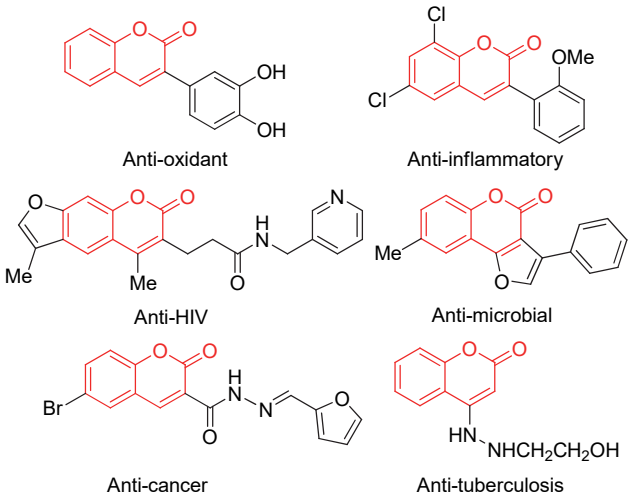
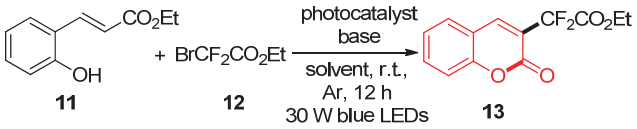


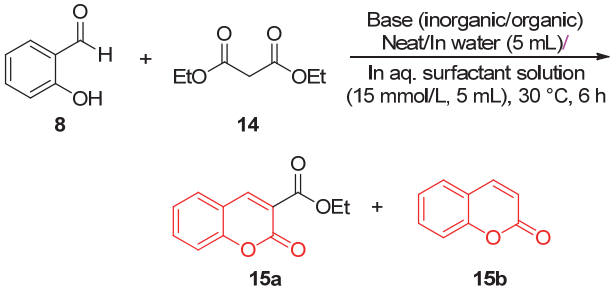
Figure 5 Various biological activities of benzopyran- 2-one ring

reaction to access several 3-fluoroalkylated coumarins (Scheme 3). The notable features of these reactions include mild reaction conditions, simple synthetic route, and excellent functional group compatibility.



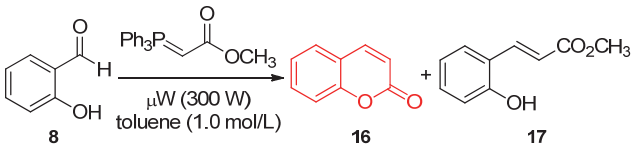
Scheme 3 Synthetic route of compound **13**

Vashishtha *et al.*[33] investigated the activity of various base catalysts for the Knoevenagel condensation of salicylaldehyde and diethyl malonate (DEM) in different reaction media (Scheme 4). In this work, they found an organic base surfactant micellar combined system with high efficiency and free of alkali/ metal catalyst. Besides, the organic base catalyst could be reused without losing its activity.



Scheme 4 Synthetic route of compounds **15a** and **15b**

Konrádová *et al.*[34] reported the synthesis of phenylpropanoids and benzopyran-2-one under microwave irradiation (Scheme 5). This reaction was characterized by one-pot synthesis and no phenol protecting group was required and high yields and selectivity were achieved.



Scheme 5 Synthetic route of compounds **16** and **17**

4.1.3 Structure-activity relationship

The structure-activity relationship of benzopyran-2-one is shown in Figure 6. When the methoxy demethylation at the C(3), C(4), and C(5) positions became hydroxyl, the antidiabetic activity of these compounds was enhanced. Considering the number of hydroxyls, the more the hydroxyls, the stronger the inhibitory activity against *α*-glucosidase and AGE formation. The hydroxylation of coumarin on the benzene ring at the C(4) position greatly influenced the inhibitory activity of *α*-glucosidase.[12]

When the C(5) position is *β*-*D*-glucopyranoside, it can stimulate insulin secretion and regulate hepatic glycogen metabolism to play an antidiabetic role. The most active compound possesses a free hydroxyl group at the C(7) position in the 4-phenylcoumarin core. The C(5) position of the sugar moiety (glucose vs. galactose) does not influence biological activity.[35]

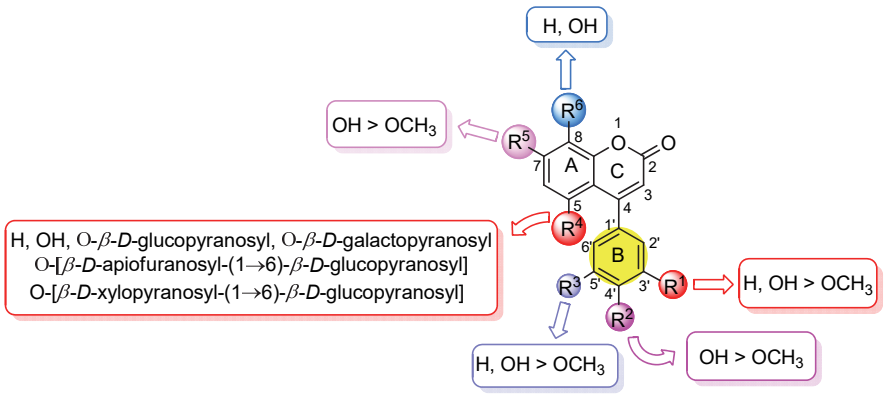


Figure 6 Structure-activity relationship of benzopyran-2-one

4.2 Hexahydropyrrolo[2,1-*b*]oxazole

4.2.1 Derivative activity

The hexahydropyrrolo[2,1-*b*]oxazole skeleton is shown in Figure 7.

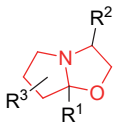


Figure 7 Skeleton of hexahydropyrrolo[2,1-*b*]oxazole

Hexahydropyrrolo[2,1-*b*]oxazole is the core unit of a wide range of promising bioactive compounds like anti-diabetic agents, anti-tumor agents, and cancer drug candidates, such as SLMP53-1 and DIMP53-1 (Figure 8).[36]

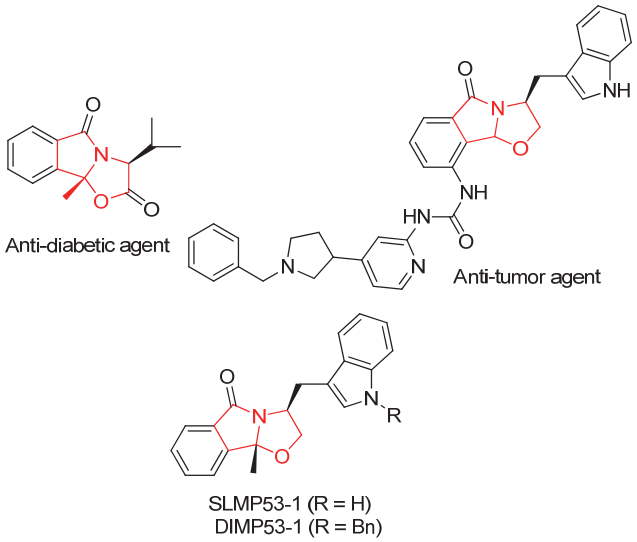
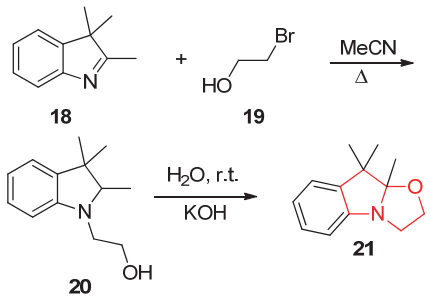


Figure 8 Various biological activities of hexahydropyrrolo[2,1-*b*]oxazole

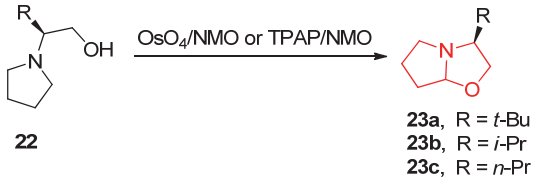
4.2.2 Synthetic route

Bao *et al.*[37] reported the synthesis of tetrahydrooxazole[3,2-*a*]indole (**21**) in 2019 using 2,3,3-trimethyl-3*H*-indole (**18**) and 2-bromoethanol (**19**) as substrates. The substitution reaction on the N atom afforded intermediate **20**, which then underwent self-cyclization to produce **21** (Scheme 6).



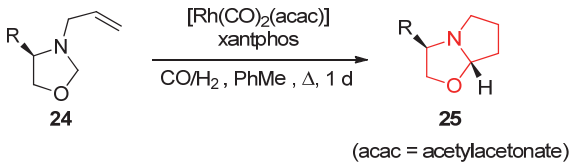
Scheme 6 Synthetic route of compound **21**

Chen *et al.*[38] reported that a catalytic amount of OsO_4 with NMO or a catalytic amount of tetrapropylammonium perruthenate (TPAP) with *N*-methylmorpholine *N*-oxide (NMO) is efficient reagents for the oxidative cyclization of saturated amino alcohols and different substituted pyrrolidine derivatives can be synthesized by this method (Scheme 7).



Scheme 7 Synthetic route of compounds **23a**～**23c**

In 2019, Vasylyev *et al.*[39] investigated a series of substituted chiral *N*-allyl oxazolidines **24** by modifying the allyl fragments and introducing electrophilic functional groups (formyl groups). The oxygen atom of the oxazolidine ring was found to affect the reaction intermediates, internal attack and cyclization reaction occured, and compound **25** was provided. The reaction is simple and applicable to a variety of *N*-allyl oxazolidine substrates with different R groups, and the products were obtained in high yield (Scheme 8).



Scheme 8 Synthetic route of compound **25**

4.2.3 Structure-activity relationship

The structure-activity relationship of hexahydropyrrolo-[2,1-*b*]oxazole is shown in Figure 9. Currently, this skeleton exhibits hypoglycemic activity only when it is replaced at positions C(8) and C(2). When the C(2) position is *S* configuration, the hypoglycemic activity is higher than the *R* configuration. When the C(2) position is CH_2XAr, where X is either oxygen or sulfur, the *in vitro* potency of this series in effecting glucose utilization, such as $CH_2O(4\text{-}ClC_6H_4)$ and $CH_2S(4\text{-}ClC_6H_4)$, increased. With $CH_2O(4\text{-}ClC_6H_4)$ at the C(2) position, the hypoglycemic activity was stronger. When the C(8) position was 4-Cl-C_6H_4, 4-$PhOC_6H_4$, 3,4-$Cl_2C_6H_4$, 4-$MeOC_6H_4$, 4-Cl-3-CF-C_6H_3, 4-FC_6H_4, 2-naphthyl, 4-biphenyl, or 4-pyridyl, the hypoglycemic activity was enhanced.[14]

4.3 Pyrano[3,2-*c*]pyridone

4.3.1 Derivative activity

The pyrano[3,2-*c*]pyridine skeleton is shown in Figure 10.

Some representative examples of biologically active benzopyran derivatives are shown in Figure 11.[40-42] Among them, isochromenones containing a six-membered

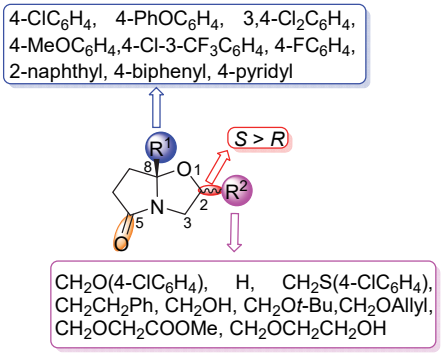


Figure 9 Structure-activity relationship of hexahydropyrrolo[2,1-*b*]oxazole

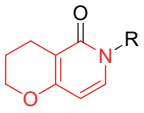


Figure 10 Skeleton of pyrano[3,2-*c*]pyridine

lactone ring possess potent biological functions, such as anti-cancer, anti-microbial, anti-inflammatory, anti-coagulant, and anti-HIV activities. The nitrogen-containing heterocycles quinolinones also have a broad range of biological properties including anti-cancer, anti-biotic, anti-viral, anti-bacterial, and anti-hypertensive activities.

4.3.2 Synthetic route

The synthesis of pyrano[3,2-*c*]pyridone derivatives usually requires the use of catalysts, which can be metal or nonmetal catalysts.

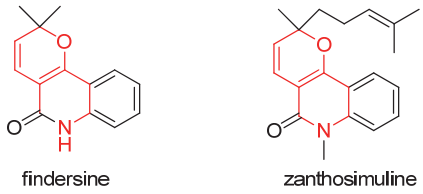
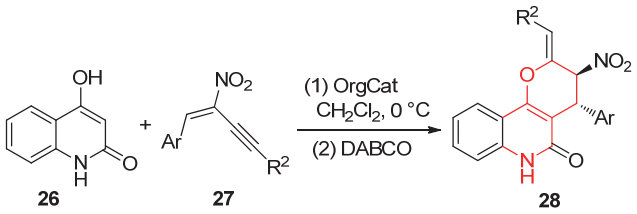


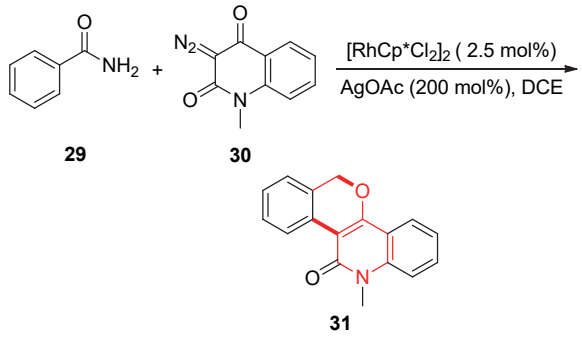
Figure 11 Various biological activities of pyrano[3,2-*c*]pyridine

Gurubrahamam *et al.*[43] studied the synthesis of pyrano-annulated scaffolds in high yield and excellent stereoselectivities using 1,3-nitroenynes with 4-hydroxycoumarin and 4-hydroxy-6-methyl-2-pyrone. The reaction proceeded through sequential conjugate addition, allene formation, intramolecular oxa-Michael 6-endo-dig cyclization and 1,4-diazabicyclo[2.2.2]octane (DABCO)-catalyzed olefin isomerization. A compound containing structure **g** was synthesized. The specific synthesis route is shown in Scheme 9.



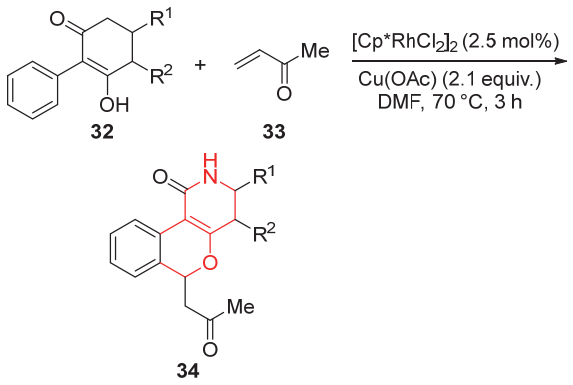
Scheme 9 Synthetic route of compound **28**

Shrestha *et al.*[44] investigated the construction of various functionalized isoquinolines by the Rh(III)-catalyzed cyclization reaction of 3-protected quinolinediones with unprotected arylamide. Benzamide and 3-diazoquinoline-2,4-dione were used as quinolinedione substrates, and a heterochromatic pyranopyridone structure was generated using [RhCp*Cl$_2$]$_2$ as catalyst. The specific synthetic route to ketone[4,3-*c*]quinoline-6,11-dione is shown in Scheme 10.



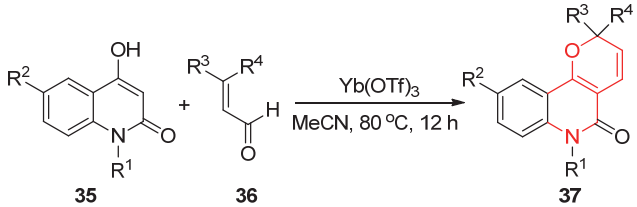
Scheme 10 Synthetic route of compound **31**

Bollikolla *et al.*[45] also used the [RhCp*Cl$_2$]$_2$ as catalyst for the synthesis of benzopyrans by C—H bond activation in 1,3-dicarbonyl compounds through OH-directed Rh-catalyzed vinylation. The specific synthesis route is shown in Scheme 11.



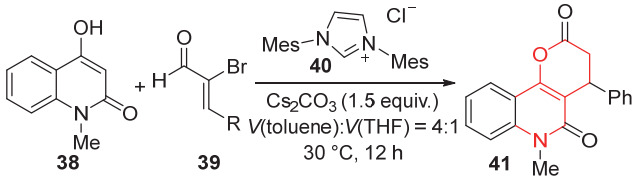
Scheme 11 Synthetic route of compound **34**

Neve *et al.*[46] used substituted 4-hydroxy-2-quinolinone as a substrate to synthesize the pyranopyridone structure under the catalysis of ytterbium triflate. The specific synthesis route is shown in Scheme 12.



Scheme 12 Synthetic route of compound **37**

Yetra *et al.*[47] also used *N*-substituted 4-hydroxy-2-quinolinone (**38**) as a substrate and synthesized the pyranopyridone (**41**) structure using cesium carbonate as a catalyst. The specific synthesis route is shown in Scheme 13.



Scheme 13 Synthetic route of compound **41**

4.3.3 Structure-activity relationship

The structure-activity relationship for pyrano[3,2-*c*]-pyridone is shown in Figure 12. When cyclohexane is substituted between C(3) and C(4), the skeleton can play a hypoglycemic effect. When the N(6) position is replaced by CH_3O, *in vitro* bioactive assays have indicated that the skeleton would exhibit a pronounced glucose uptake effect on liver HepG2 cells under both normal and insulin-resistant conditions with higher efficacy than metformin and lower cytotoxicity. When the N(6) position has hydroxyl substitution, by establishing L6 (rat myoblast)-derived cell lines, under the control of HKII promoter, HKII transcriptional activator would increase cell luci activity (HKII-luci signal), indicating that this skeleton is an HKII transcription activator.[48]

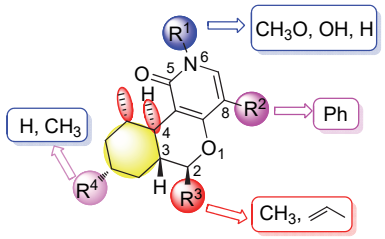


Figure 12 Structure-activity relationship of pyrano[3,2-*c*]pyridone

4.4 Pyrrolotriazine

4.4.1 Derivative activity

The study of pyrrolotriazine compounds, which contained many drug structures, is a hot topic of research (Figure 13). Pyrrolotriazine compounds can inhibit DPP-4 *in vitro* to reduce blood sugar.

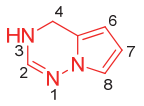
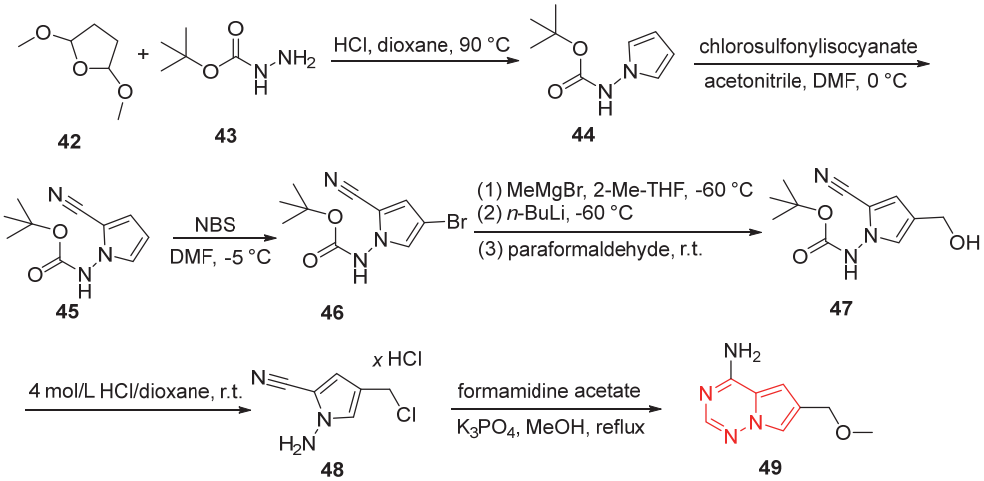


Figure 13 Skeleton of pyrrolotriazine

When the pyrrolotriazine skeleton is substituted at different positions, the resulting derivatives exhibit diverse activities. For example, the hypoglycemic activity is greatly enhanced by introducing piperidin-3-amine at 2-position, 2-methylbenzonitrile at 3-position, or benzenesulfinic acid at 6-position.[49] The introduction of 2,4-difluoro-5-(cyclopropylcarbamoyl) aniline at 4-position[50] provides the resulting pyrrolotriazine with inhibitory effect for VEGFR-2 kinase activity. When the 6-position is substituted, HER2 inhibitory activity is obtained.[51] For ester or ether substitution, the activity is low, whereas good activity is observed when substituting with acid or morpholine. This may be related to the ability of the side chain substituents to form hydrogen bonds. When the 2- and 7-positions of the pyrrolopyrazine structure are substituted by alkyl groups, ALK inhibitory activity is developed.[52] In addition, substitutions by morpholine at 4-position and pyrimidin-2-amine at 2-position are potent, metabolically stable class I PI3 kinase inhibitors with good enzymatic and cellular potency.[53]

4.4.2 Synthetic route

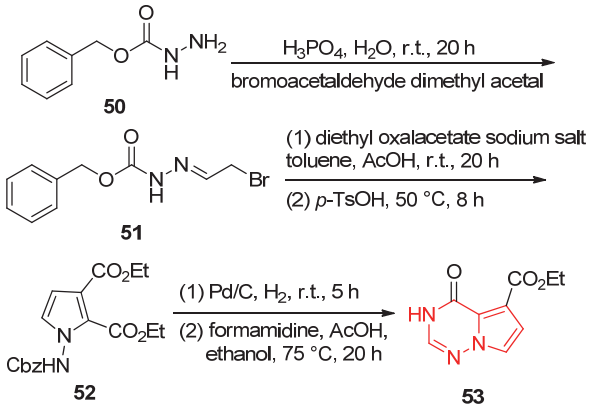
Collin *et al.*[54] reported the preparation of the pyrrolotriazine core structure **49** in six linear steps (Scheme 14). The synthesis started with an acid-catalyzed condensation reaction of commercially available 2,5-dimethoxytetrahydrofuran (**42**) with *tert*-butyl carbazate (**43**), afford-



Scheme 14 Synthetic route of compound **49**

ing the protected aminopyrrole **44** after crystallization. Introduction of the nitrile group at the C(1) of the pyrrole ring by electrophilic substitution afforded cyanopyrrole **45**, which was subjected to bromination at the C(4), leading to bromopyrrole **46**. The hydroxymethyl group was then installed in a subsequent three-step one-pot reaction. Treating the resulting pyrrole **47** with a hydrogen chloride solution in dioxane not only cleaved the butylcarbamate group but also converted the hydroxymethyl group into the corresponding chloromethyl **48**. This very reactive intermediate **48** could be directly converted into methoxymethylpyrrolotriazine **49** in a one pot, two-step reaction.

A different route was described by Qin *et al.*[55], as shown in Scheme 15. Mono carboxybenzyl (Cbz)-protected hydrazine **50** was reacted with bromoacetaldehyde dimethyl acetal to give **51**. Intermediate **51** was then reacted with the sodium salt of diethyl oxaloacetate, followed by cyclization in the presence of *para*-toluenesulfonic acid to give compound **52** in one pot. The Cbz group was removed before treatment with formamidine to obtain **53**.

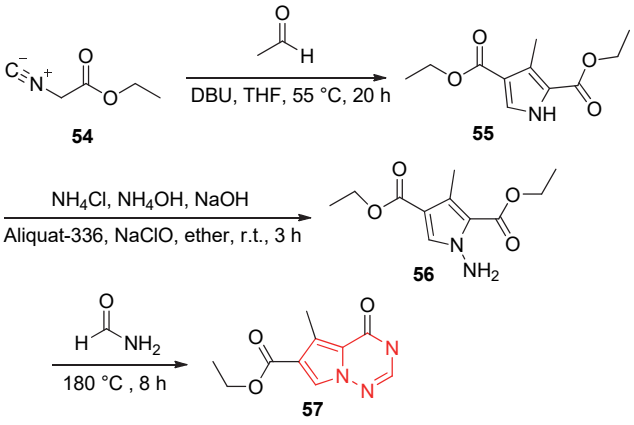


Scheme 15 Synthetic route of compound **53**

Compared with the first route, which is cumbersome and requires harsh reaction conditions and many steps, the second route is relatively simple, involving a one-pot reaction without isolation of intermediate products under mild conditions.

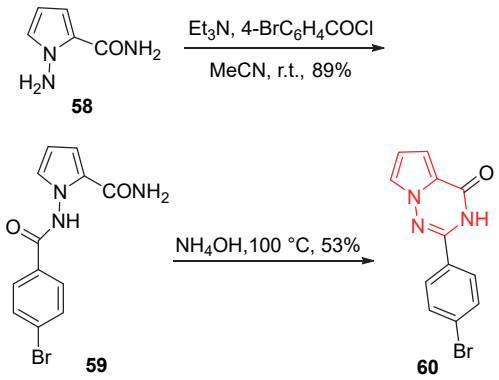
In 2018, Shi *et al.*[56] explored novel pyrrolo[2,1-*f*][1,2,4]triazine derivatives with improved anticancer efficacy as dual inhibitors of c-Met/VEGFR-2. Ethyl 2-isocyanoacetate (**54**) reacted with acetaldehyde to obtain diethyl 3-methyl-1*H*-pyrrole-2,4-dicarboxylate (**55**), which was then subjected to chlorination under alkaline conditions, undergoing substitution reaction of the N atom on the pyrrole ring to obtain compound **56**. The latter was then cyclized with formamide to produce compound **57** (Scheme 16).

Holmes *et al.*[57] used aminopyrrole **58** as the starting material, which was acylated with 4-bromobenzoyl chloride, affording compound **59**. The latter underwent self-cyclization in the presence of 30% ammonia in water, and triazone **60** was obtained in 53% yield after filtering with



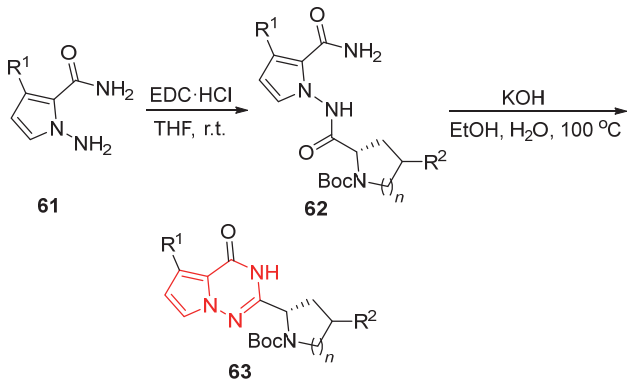
Scheme 16 Synthetic route of compound **57**

suction and washing with a small amount of acetonitrile (Scheme 17).



Scheme 17 Synthetic route of compound **60**

Jia *et al.*[58] reported a similar approach, in which the starting aminopyrrole was acylated and dehydrated to obtain pyrrolotriazine compound **63** (Scheme 18).



Scheme 18 Synthetic route of compound **63**

4.4.3 Structure-activity relationship

The structure-activity relationship for pyrrolotriazine is shown in Figure 14.[21] When C(7) is substituted by a benzene ring or *para*-methyl benzene ring, the compound has good inhibitory activity *in vitro*. When the R^1 is substituted

by fluorine atom, the hypoglycemic activity is enhanced significantly. Compared with the control drug alogliptin, the *in vitro* hypoglycemic activity was basically increased by about three times. However, when the C(7) position was substituted by phenyl *para*-fluoro or cyano, the hypoglycemic activity was slightly weaker than that of the control drug alogliptin. When C(7) was benzene ring and R^1 was fluorine atom substitution, *in vivo* experiments showed that when the dosage was less than 10 mg/kg, the blood glucose level of mice decreased with the increase of dosage, and the percentage of blood glucose decrease increased from 3.29% to 22.08% with the increase of dosage.

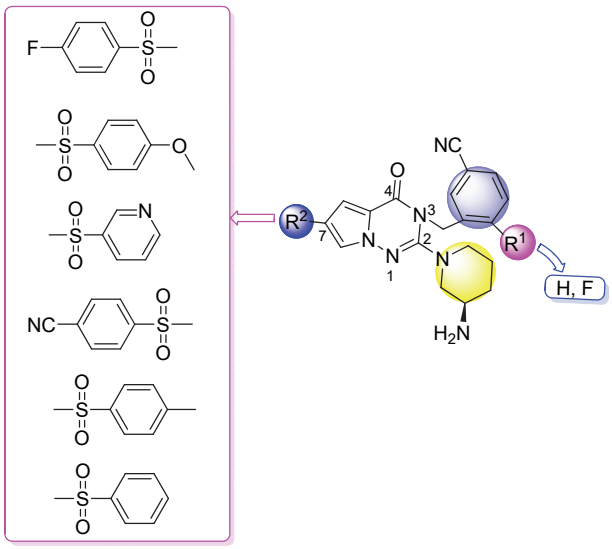


Figure 14 Structure-activity relationship of pyrrolotriazine

4.5 Triazolopyrazine

4.5.1 Derivative activity

There are many possible modifications of the N(7) and C(8) positions of the triazolopyrazine structure, which has been divided into three parts in Figure 15, among which the G_1 part is the basic structure of triazolopyrazine. When a ketone group is introduced at 3-position and an aryl group at 6-position, the resulting triazolopyrazine can serve as a new multifunctional scaffold for hAR antagonists.[59] Meanwhile, when a trifluoromethyl group is at 3-position, different R^1 substituents in the G_2 region afford different activities.[60] Thus, when R^1 is a hydrogen atom, an ethoxy group, or a fluorine atom, the compound has an excellent antimalaria effect against plasmodium falciparum. When R^1 is aminobenzothiazole, good antituberculosis activity against mycobacterium tuberculosis H37Rv strain is obtained. Finally, the presence of an alkyl group as R^2 substituent in the G_3 region provides anticonvulsant activity.[61]

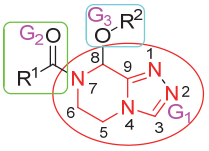
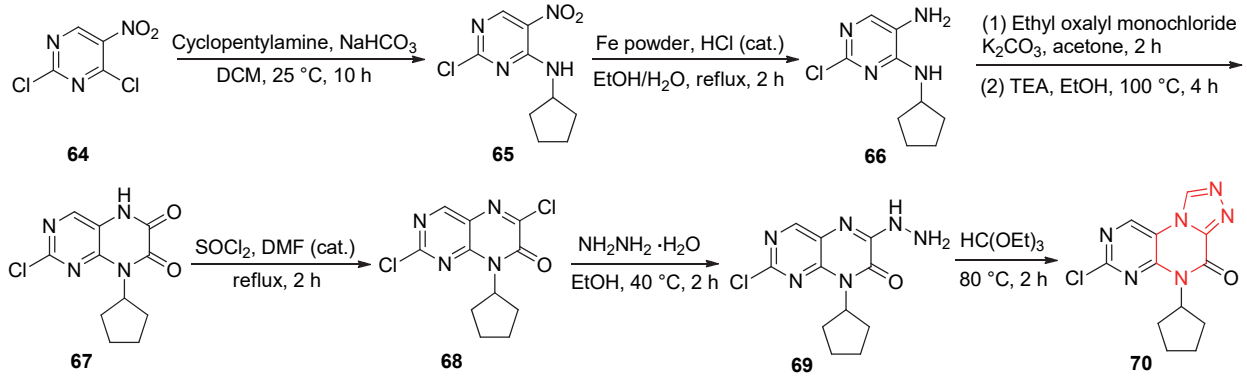


Figure 15 Skeleton of triazolopyrazine

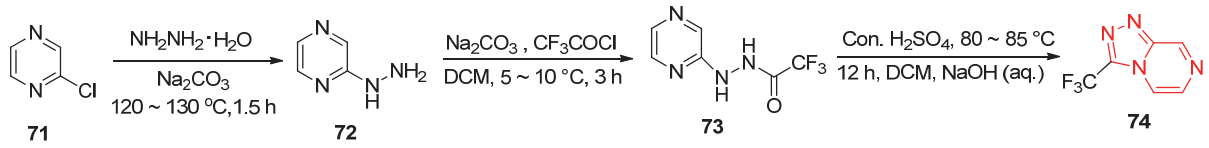
4.5.2 Synthetic route

Hou *et al.*[62] used 2,4-dichloro-5-nitropyrimidine (**64**) as a starting material, which reacted with cyclopentylamine to give compound **65**. The latter was then reduced using iron powder and catalytic amounts of concentrated HCl in EtOH/H_2O to obtain amide intermediate **66**, which afforded **67** upon treatment with oxalyl chloride monoethyl ester in acetone. Compound **67** was converted to the final product **68** by refluxing in $SOCl_2$. Subsequently, the intermediate **69** was available via hydrazinolysis of intermediate **68** with 80% hydrazine monohydrate in EtOH at 40 ℃. Intermediate **69** was treated with trimethyl orthoformate under 80 ℃ to produce triazole compound **70** (Scheme 19).

Mannam *et al.*[63] reported a different route, in which 2-chloropyrazine (**71**) was treated with hydrazine monohydrate in the presence of sodium carbonate as a base at harsh temperature under optimized neat reaction conditions to obtain 2-hydrazinopyrazine (**72**) in high yield. The hydrazine intermediate **72** was reacted with trifluoroacetyl chloride in the presence of sodium carbonate (Na_2CO_3) to afford 2,2,2-trifluoro-*N*′-(pyrazin-2-yl)acetohydrazide (**73**). Compound **73** was cyclized in the presence of concentrated sulfuric acid to give 3-(trifluoromethyl)-1,2,4-triazolo[4,3-*a*]pyrazine (**74**) as a pale brown solid (Scheme 20).

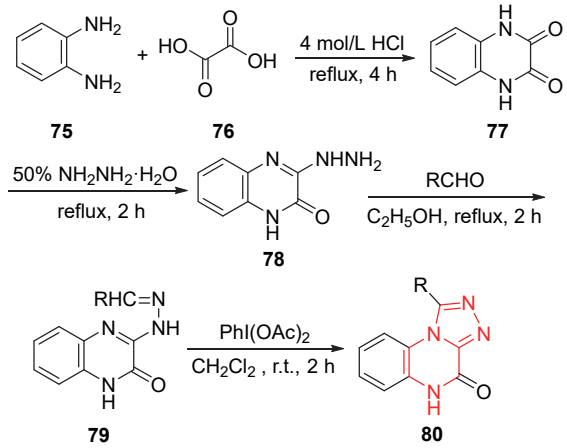


Scheme 19 Synthetic route of compound **70**



Scheme 20 Synthetic route of compound **74**

A series of [1,2,4]-triazolo[4,3-*a*]quinoxalin-4(5*H*)-ones that promoted photoinduced DNA cleavage were designed and synthesized by Sumran *et al.*[64] The synthesis started with the preparation of compound **77** by the reaction of *o*-phenylenediamine with oxalic acid in 4 mol/L HCl. Compound **77** was then treated with 50% hydrazine hydrate to obtain compound **78**, which was condensed with various aldehydes in ethanol under reflux to afford the corresponding key intermediates **79**. Then, derivatives **79** underwent intramolecular cyclization reaction via oxidation to generate compound **80** (Scheme 21).



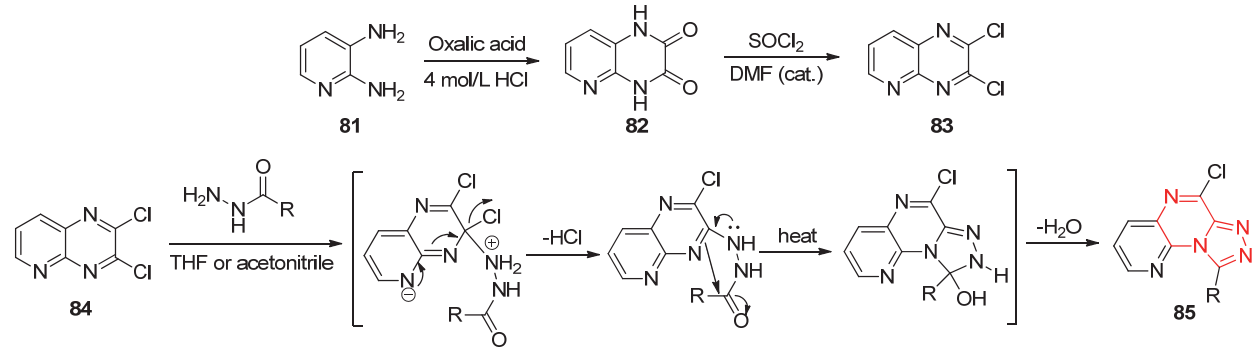
Scheme 21 Synthetic route of compound **80**

The one-pot synthesis of other triazolopyrazine derivatives, *i.e.*, 9-alkyl-6-chloropyrido[3,2-*e*]-[1,2,4]triazolo[4,3-*a*]pyrazines **85**, was reported by Unciti-Broceta *et al.*.[65] They prepared dichloride derivative **83** from 2,3-diaminopyridine (**81**) in very high yields. First, 5-azaquinoxaline ring **82** was obtained by reacting compound **81** with oxalic acid in 4 mol/L HCl aqueous solution. Then, compound **82** was treated with thionyl chloride and *N*,*N*-dimethylformamide (DMF) in catalytic amounts to obtain compound **83** (Scheme 22).

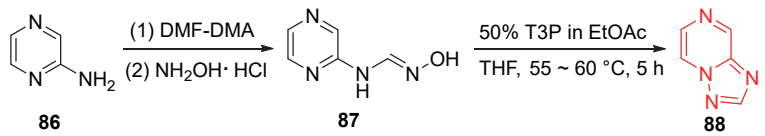
Ayothiraman *et al.*[66] reported the *N*′-hydroxy-*N*-formimidamides synthesized from 2-aminopyrazine and 3-aminoisoquinoline underwent efficient ring closure to provide the corresponding 1,2,4-triazoles **88** (Scheme 23). They have developed a general methodology for the cyclization of *N*′-hydroxy-*N*-formimidamides derived from *α*-aminoheteroarenes using T3P. The reactions proceeded under mild conditions, exhibited wide functional group tolerance, and provided the corresponding heteroaryl-fused 1,2,4-triazoles in moderate to excellent yields.

4.5.3 Structure-activity relationship

The structure-activity relationship for triazolopyrazine is shown in Figure 16. When the compound structure was oxidized at positions C(7)-C(8) and C(5)-C(6), they formed the core part of the sitagliptin heterocycle fragment of type 2 diabetes treatment drug. These fragments can be used to synthesize sitagliptin phosphate.[67] With a DPP-4 inhibitor, it is possible to completely prevent the *N*-terminal degradation of GLP-1 that occurs *in vivo*, resul-



Scheme 22 Synthetic route of compound **85**



Scheme 23 Synthetic route of compound **88**

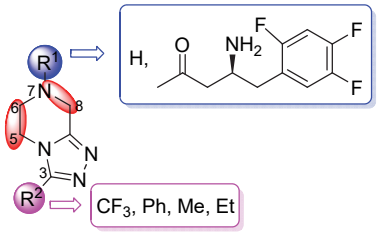


Figure 16 Structure-activity relationship of triazolopyrazine

ting in significant enhancement of its insulinotropic activity.[68]

5 Conclusion and outlook

In this paper, the synthetic methods and structure-activity relationship of five heterocyclic skeletons with hypoglycemic activity as potential DPP-4 inhibitors were summarized and analyzed (Figure 17). Through the search for "hypoglycemic compounds" as a keyword on websites and TOP 200 database, 12 kinds of heterocyclic compounds were obtained, which through the computer simulation design and taking DPP-4 as the target enzyme, and five heterocyclic compounds with hypoglycemic activity were found.

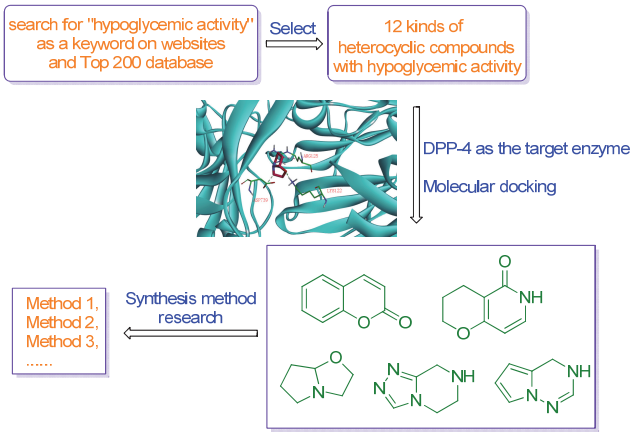


Figure 17 Research on five heterocyclic synthesis methods with hypoglycemic activity

According to literature, the hypoglycemic activity *in vitro* and *in vivo* of five heterocyclic compounds was summarized (Figure 18). The synthesis methods and structure-activity relationship were summarized and analyzed to provide research ideas for the development of hypoglycemic drugs based on DPP-4 targets, and five dominant skeletons were provided to lay the foundation for the future development of such drugs. However, there are still some problems that need to be further studied in this paper. The five heterocycles with hypoglycemic activity were only virtually screened through computer simulation, and the actual hypoglycemic activity needs to be further confirmed. Their synthesis routes were investigated only according to literature, and more economical and simple synthesis routes need to be explored. The mechanism of hypoglycemic activity also needs to be further studied.

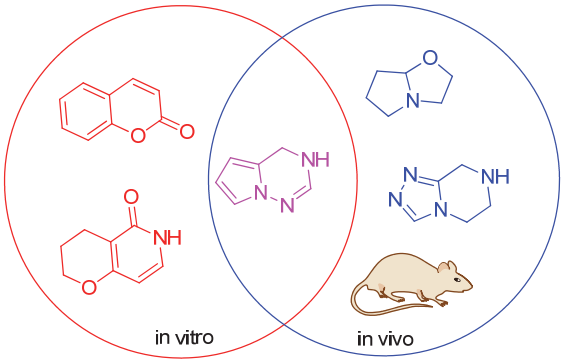


Figure 18 *In vitro* and *in vivo* activities of five hypoglycemic heterocyclic compounds

References

[1] Chakraborty, R.; Ahmed, A. B.; Saha, D. *Int. J. Curr. Pharm. Res.* **2019**, *4*, 60.

[2] Wang, L. M.; Gao, P.; Zhang, M.; Huang, Z. J.; Zhang D. D.; Deng, Q.; Li, Y. C.; Zhao, Z. P.; Qin, X. Y.; Jin, D. Y.; Zhou, M. G.; Tang, X.; Hu, Y. H.; Wang, L. H. *J. Am. Med. Assoc.* **2017**, *317*, 2515.

[3] Zimmet, P.; Shaw, J.; Alberti, K. G. M. M. *Diabetic Med.* **2003**, *20*, 693.

[4] Shen, W. *Chin. J. Misdiagn* **2011**, *11*, 8845 (in Chinese).
(谌卫, 中国误诊学杂志, **2011**, *11*, 8845.)

[5] (a) Liakos, C. I.; Papadopoulos, D. P.; Sanidas, E. A.; Markou, M. I.; Hatziagelaki, E. E.; Grassos, C. A.; Velliou, M. L.; Barbetseas, J. D. *Am. J. Cardiovasc. Drugs* **2020**, *21*, 262.
(b) Sun, Z. G.; Li, Z. N.; Zhu, H. L. *Mini-Rev. Med. Chem.* **2020**, *20*, 1709.

[6] Xiong, L. J.; Jin, Y.; Fang, Y. Y. *J. Shenyang Pharm. Univ.* **2020**, *37*, 181 (in Chinese).
(熊丽娟, 金一, 房元英, 沈阳药科大学学报, **2020**, *37*, 181.)

[7] Deacon C. F. *Diabetes* **2004**, *53*, 2181.

[8] Tang, Y. Z.; Tian, L. L.; Ni, C. L. *Med. Recapitulate* **2018**, *24*, 770 (in Chinese).
(汤云昭, 田琳琳, 倪长霖, 医学综述, **2018**, *24*, 770.)

[9] Dong, P. *J. Qiqihar Med. Univ.* **2019**, *40*, 218.

[10] Havale, S. H.; Pal, M. *Bioorg. Med. Chem.* **2009**, *17*, 1783.

[11] Rosenstock, J.; Perkovic, V.; Johansen, O. E.; Mark E. Cooper, M. E.; Kahn, S. E.; Marx, N.; Alexander, J. H.; Pencina, M.; Toto, R. D.; Wanner, C.; Zinman, B.; Woerle, H. J.; Baanstra, D.; Pfarr, E.; Schnaidt, S.; Meinicke, T.; George, J. T.; Eynatten, M. V.; McGuire, D. K. *J. Am. Med. Assoc.* **2018**. *321*, *69*.

[12] Hu, Y. H.; Sun, J.; Yang, J.; Wang, X. J. *Chem. Res.* **2018**, *29*, 357 (in Chinese).
(胡玉恒, 孙捷, 杨洁, 王晓静, 化学研究, **2018**, *29*, 357.)

[13] Thomas, D. A.; Bork, B.; Philip, A. B.; Leonard J. B.; Cheon, S. H.; Rhonda, O. D.; Jay, B. F.; William, S. F.; James, D. F.; Jiaping, G.; Douglas, C. K.; Gerald, G. K.; Christina, L. L.; Jeffrey, N.; Ronald, S.; Howard, C. S. *J. Med. Chem.* **1998**, *41*, 4.

[14] Aicher, T. D; Balkan, B.; Bell, P. A.; Brand, L. J.; Cheon, S. H.; Deems, R. O.; Fell, J. B.; Fillers, W. S.; Fraser, J. D; Gao, J.; Knorr, D. C.; Kahle, G. G.; Leone, C. L.; Nadelson, J.; Simpson, R.; Smith, H. C. *J. Med. Chem.* **1998**, *41*, 4556.

[15] Blank, B.; DiTullio, N. W.; Krog, A. J.; Saunders, H. L. *J. Med. Chem.* **1978**, *21*, 489.

[16] Meltzer-Mats, E.; Babai-Shani, G.; Pasternak, L.; Uritsky, N.; Getter, T.; Viskind, O.; Eckel, J.; Cerasi, E.; Senderowitz, H.; Sasson, S.; Gruzman, A. *J. Med. Chem.* **2013**, *56*, 5335.

[17] Oguchi, M.; Wada, K.; Honma, H.; Tanaka, A.; Kaneko, T.; Sakakibara, S.; Ohsumi, J.; Serizawa, N.; Fujiwara, T.; Horikoshi, H.; Fujita, T. *J. Med. Chem.* **2000**, *43*, 3052.

[18] Qiao, Y. B.; Xu, Q. Q.; Feng, W. Y.; Tao, L.; Li, X. N.; Liu, J. J.; Zhu, H. C.; Lu, Y. Y.; Wang, J. P.; Qi, C. X.; Xue, Y. B.; Zhang, Y.

H. *J. Nat. Prod.* **2019**, *82*, 2925.
[19] Blank, B.; DiTullio, N. W.; Deviney, L.; Roberts, J. T.; Magnani, A.; Billig, M.; Saunders, H. L. *J. Med. Chem.* **1977**, *20*, 1572.
[20] Blank, B.; DiTullio, N. W.; Krog, A. J.; Saunders, H. L. *J. Med. Chem.* **1979**, *22*, 840.
[21] Li, C. J.; Le, Z. P.; Zhao, C. S. *Chin. J. New Drugs* **2014**, *23*, 2195 (in Chinese).
(李翠娟, 乐治平, 赵传生, 中国新药杂志, **2014**, *23*, 2195.)
[22] Li, Z. Y.; Wang, J. T.; Gu, Y. Q.; Tang, L. *Chem. Reagents* **2013**, *35*, 114 (in Chinese).
(李志燕, 王建塔, 古元琴, 汤磊, 化学试剂, **2013**, *35*, 114.)
[23] Zhang, C. L. *Heilongjiang Med. J.* **2019**, *32*, 1095 (in Chinese).
(张春玲, 黑龙江医药, **2019**, *32*, 1095.)
[24] Veselinovic, J. B.; Veselinovic, A. M.; Vitnik, Z. J.; Vitnik, V. D.; Nikolic, G. M. *Chem. Biol.* **2014**, *214*, 49.
[25] Arora, R. K.; Kaur, N.; Bansal, Y.; Bansal, G. *Acta Pharm. Sin. B* **2014**, *4*, 368.
[26] Mahajan, D. H.; Pannecouque, C.; De, C. E.; Chikhalia, K. H. *Arch. Pharm. (Weinheim, Ger.)* **2009**, *342*, 281.
[27] Sabry, N. M.; Mohamed, H. M.; Khattab, E. S.; Motlaq, S. S.; El-Agrody, A. M. *Eur. J. Med. Chem.* **2011**, *46*, 765.
[28] Miri, R.; Nejati, M.; Saso, L.; Khakdan, F.; Parshad, B.; Mathur, D.; Parmar, V. S.; Bracke, M. E.; Prasad, A. K.; Sharma, S. K.; Firuzi, O. *Pharm. Biol.* **2016**, *54*, 105.
[29] Manvar, A.; Malde, A.; Verma, J.; Virsodia, V.; Mishra, A.; Upadhyay, K.; Acharya, H.; Coutinho, E.; Shah, A. *Eur. J. Med. Chem.* **2008**, *43*, 2395.
[30] Yang, L. S.; Wang, Y.; Wang, E. H.; Yang, J.; Pan, X.; Liao, X.; Yang, X. S. *Synth. Commun.* **2020**, *50*, 3080.
[31] Shakil, M.; Meguerdichian, A. G.; Tasnim, H.; Shirazi, A. A.; Seraji, M. S.; Suib, S. L. *Inorg. Chem.* **2019**, *58*, 5703.
[32] Song, D.; Wang, C. M.; Ye, Z. P.; Xia, P. J.; Deng, Z. X.; Xiao, J. A.; Xiang, H. Y.; Yang, H. *J. Org. Chem.* **2019**, *84*, 7480.
[33] Vashishtha, M.; Mishra, M.; Shah, D. O. *Green Chem.* **2016**, *18*, 1339.
[34] Konrádová, D.; Kozubíková, H.; Doležal, K.; Pospíšil, J. *Eur. J. Org. Chem.* **2017**, *2017*, 5204.
[35] Guerrero-Analco, J.; Medina-Campos, O.; Brindis, F.; Bye, R.; Pedraza-Chaverri, J.; Navarrete, A.; Mata, R. *Phytochemistry* **2007**, *68*, 2087.
[36] Soares, J.; Espadinha, M.; Raimundo, L.; Ramos, H.; Gomes, A. S.; Gomes, S.; Loureiro, J. B.; Inga, A.; Reis, F.; Gomes, C.; Santos, M. M. M.; Saraiva, L. *Mol. Oncol.* **2017**, *11*, 612.
[37] Bao, B.; Bai, S.; Fan, J.; Su, J.; Wang, W.; Yu, D. *Dyes Pigm.* **2019**, *171*, 107778.
[38] Chen, W. L.; Wang, L. Y.; Li, Y. J. *Eur. J. Org. Chem*. **2020**, *1*, 103.
[39] Vasylyev, M.; Alper, H. *Angew. Chem., Int. Ed*. **2009**, *48*, 1287.
[40] Elmore, S. W.; Coghlan, M. J.; Anderson, D. D.; Pratt, J. K.; Green, B. E.; Wang, A. X.; Stashko, M. A.; Lin, C. W.; Tyree, C. M.; Miner, J. N.; Jacobson, P. B.; Wilcox, D. M.; Lane, B. C. *J. Med. Chem*. **2001**, *44*, 4481.
[41] Wu, C. S.; Lin, Z. M.; Wang, L. N.; Guo, D. X.; Wang, S. Q.; Liu, Y. Q.; Yuan, H. Q.; Lou, H. X. *Bioorg. Med. Chem. Lett*. **2011**, *21*, 3261.
[42] Zan, L. F.; Qin, J. C.; Zhang, Y. M.; Yao, Y. H.; Bao, H. Y.; Li, X. *Chem. Pharm. Bull. (Tokyo)* **2011**, *59*, 770.
[43] Gurubrahamam, R.; Gao, B. F.; Chen, Y. M.; Chan, Y. T.; Tsai, M. K.; Chen, K. *Org. Lett*. **2016**, *18*, 3098.
[44] Shrestha, R.; Khanal, H. D.; Lee, Y. R. *RSC Adv*. **2019**, *9*, 17347.
[45] Bollikolla, H. B.; Choppakatla, S.; Polam, N.; Thripuram, V. D.; Chidipudi, S. R. *Asian J. Org. Chem*. **2017**, *6*, 1598.
[46] Neve, J. E.; Wijesekera, H. P.; Duffy, S.; Jenkins, I. D.; Ripper, J. A.; Teague, S. J.; Campitelli, M.; Garavelas, A.; Nikolakopoulos, G.; Le, P. V.; de A. Leone, P.; Pham, N. B.; Shelton, P.; Fraser, N.; Carroll, A. R.; Avery, V. M.; McCrae, C.; Williams, N.; Quinn, R. J. *J. Med. Chem*. **2014**, *57*, 1252.
[47] Yetra, S. R.; Roy, T.; Bhunia, A.; Porwal, D.; Biju, A. T. *J. Org. Chem*. **2014**, *79*, 4245.
[48] Zhang, C.; Jin, L.; Mondie, B.; Mitchell, S. S.; Castelhano, A. L.; Cai, W. Z.; Bergenhem, N. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1433.
[49] Zhang, Z.; Wallace, M. B.; Feng, J.; Stafford, J. A.; Skene, R. J.; Shi, L.; Lee, B.; Aertgeerts, K.; Jennings, A.; Xu, R.; Kassel, D. B.; Kaldor, S. W.; Navre, M.; Webb, D. R.; Gwaltney, S. L. *J. Med. Chem*. **2011**, *54*, 510.
[50] Cai, Z. W.; Wei, D.; Borzilleri, R. M.; Qian, L.; Kamath, A.; Mortillo, S.; Wautlet, B.; Henley, B. J.; Jeyaseelan, R. S.; Tokarski, J.; Hunt, J. T.; Bhide, R. S.; Fargnoli, J.; Lombardo, L. J. *Bioorg. Med. Chem. Lett*. **2008**, *18*, 1354.
[51] Awale, M.; Mohan, C. G. *J. Mol. Graphics Modell.* **2008**, *26*, 1169.
[52] Ke, Z.; Lu, T.; Liu, H.; Yuan, H.; Ran, T.; Zhang, Y.; Yao, S.; Xiong, X.; Xu, J.; Xu, A.; Chen, Y. *J. Mol. Struct*. **2014**, *1067*, 127.
[53] Dugar, S.; Hollinger, F. P; Kuila, B.; Arora, R.; Sen, S.; Mahajan, D. *Bioorg. Med. Chem. Lett*. **2015**, *25*, 3142.
[54] Collin, M. P.; Lobell, M.; Hubsch, W.; Brohm, D.; Schirok, H.; Jautelat, R.; Lustig, K.; Bomer, U.; Vohringer, V.; Heroult, M.; Grunewald, S.; Hess, S. H. *Med. Chem.* **2018**, *13*, 437.
[55] Qin, L. Y.; Ruan, Z.; Cherney, R. J.; Dhar, T. G. M.; Neels, J.; Weigelt, C. A.; Sack, J. S.; Srivastava, A. S.; Cornelius, L. A. M.; Tino, J. A.; Stefanski, K.; Gu, X.; Xie, J.; Susulic, V.; Yang, X.; Yarde, C. M.; Skala, S.; Bosnius, R.; Goldstein, C.; Davies, P.; Ruepp, S.; Salter, C. L.; Bhide, R. S.; Poss, M A. *Bioorg. Med. Chem. Lett*. **2017**, *27*, 855.
[56] Shi, W.; Qiang, H.; Huang, D. D.; Bi, X. Z.; Huang, W. L.; Qian, H. *Eur. J. Med. Chem*. **2018**, *158*, 814.
[57] Holmes, J. L.; Almeida, L.; Barlaam, B.; Croft, R. A.; Dishington, A. P.; Gingipalli, L.; Hassall, L. A.; Hawkins, J. L.; Ioannidis, S.; Johannes, J. W.; McGuire, T. M.; Moore, J. E.; Patel, A.; Pike, K. G.; Pontz, T.; Wu, X. Y.; Wang, T.; Zhang, H. J.; Zheng, X. L. *Synthesis* **2016**, *48*, 1226.
[58] Jia, H.; Dai, G.; Su, W.; Xiao, K.; Weng, J.; Zhang, Z.; Wang, Q.; Yuan, T.; Shi, F.; Zhang, Z.; Chen, W.; Sai, Y.; Wang, J.; Li, X.; Cai, Y.; Yu, J.; Ren, P.; Venable, J.; Rao, T.; Edwards, J. P.; Bembenek, S. D. *J. Med. Chem*. **2019**, *62*, 4936.
[59] Falsini, M.; Squarcialupi, L.; Catarzi, D.; Varano, F.; Betti, M.; Dal, B. D.; Marucci, G.; Buccioni, M.; Volpini, R.; De, V. T.; Cavalli, A.; Colotta, V. *J. Med. Chem*. **2017**, *60*, 5772.
[60] Jethava, D. J.; Acharya, P. T.; Vasava, M. S.; Bhoi, M. N.; Bhavsar, Z. A.; Rathwa, S. K.; Rajani, D. P.; Patel, H. D. *J. Mol. Struct*. **2019**, *1184*, 168.
[61] Guan, L. P.; Zhang, R. P.; Chang, Y.; Gan, X. X. *Asian J. Chem*. **2013**, *25*, 3660.
[62] Hou, Y. L.; Zhu, L. Y.; Li, Z. W.; Shen, Q.; Xu, Q. L.; Li, W.; Liu, Y. J.; Gong, P. *Eur. J. Med. Chem*. **2019**, *163*, 690.
[63] Mannam, M. R.; Devineni, S. R.; Pavuluri, C. M.; Chamarthi, N. R.; Kottapalli, R. S. P. *Phosphorus, Sulfur Silicon Relat. Elem.* **2019**, *194*, 922.
[64] Sumran, G.; Aggarwal, R.; Mittal, A.; Aggarwal, A.; Gupta, A. *Bioorg. Chem*. **2019**, *88*, 102932.
[65] Unciti-Broceta, A.; Pineda-de-las-Infantas, M. J.; Díaz-Mochón, J. J.; Romagnoli, R.; Baraldi, P. G.; Gallo, M. A.; Espinosa, A. *J. Org. Chem*. **2005**, *70*, 2878.
[66] Ayothiraman, R.; Bandaru, D.; Paranthaman, R.; Fenster, M.; Eastgate, M. D.; Vaidyanathan, R. *Org. Process Res. Dev*. **2019**, *23*, 2510.
[67] Li, C. *M.S. Thesis* Fudan University, Shanghai, **2010** (in Chinese).
(李超, 硕士论文, 复旦大学, 上海, 2010.)
[68] Deacon, C. F.; Hughes, T. E.; Holst, J. J. *Diabetes* **1998**, *47*, 764.

(Cheng, F.)

