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Design, synthesis and biological evaluation of novel pyrimidinedione derivatives as DPP-4 inhibitors

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ABSTRACT

A series of novel pyrimidinedione derivatives were designed and evaluated for *in vitro* dipeptidyl peptidase-4 (DPP-4) inhibitory activity and *in vivo* anti-hyperglycemic efficacy. Among them, the representative compounds **11**, **15** and **16** showed excellent inhibitory activity of DPP-4 with IC_{50} values of 64.47 nM, 188.7 nM and 65.36 nM, respectively. Further studies revealed that compound **11** was potent *in vivo* hypoglycemic effect. The structure–activity relationships of these pyrimidinedione derivatives had been discussed, which would be useful for developing novel DPP-4 inhibitors as treating type 2 diabetes.

Diabetes is a major global problem nowadays. It currently affects nearly 425 million people worldwide in 2017, and this number will rise to 700 million in 2045.[1] Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are both incretin hormones increasing insulin biosynthesis and therefore contributing to glycemic control.[2,3] However, both hormones are rapidly inactivated by the serine protease DPP-4, leading to limiting their therapeutic practicality. The idea of inhibiting DPP-4 was developed as a promising new therapy for type 2 diabetes mellitus (T2DM) 20 years ago.[4] To date, twelve DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin, alogliptin, linagliptin, anagliptin, gemigliptin, teneligliptin, evogliptin, omarigliptin, trelagliptin and gosogliptin) have been approved for the treatment of T2DM (Fig. 1).[5] Yet, there is still strong enthusiasm in developing novel DPP-4 inhibitors since some undesirable side effects exist in current drugs.[6]

Bromophenols are a set of natural products widely distributed in seaweed, most of which exhibit many biological activities, including hypoglycemic effect, anticancer, antioxidant, antimicrobial and other potent bioactivities.[7] In our previous study, a variety of bromophenols (Fig. 2), isolated from the red marine algae of the Rhodomelaceae family or synthesized derivatives, showed potent hypoglycemic effects *in vitro* and *in vivo*.[8–11] Herein, bromophenols are used as potent hypoglycemic agents and are considered as part of a new therapeutic strategy for treatment of type 2 diabetes.

The fully understanding of the interaction between DPP-4 enzyme and the bioactive substances plays a significant role in designing novel DPP-4 inhibitors. From the binding models we found that pyrimidinedione forms π-π interactions with Tyr547, which undergoes a conformational change in the S1 subsite; in addition, the cyanobenzyl group or the butynyl group binds to the S1 subsite.[12,13] Moreover, aminopiperidine is crucial for DPP-4 inhibitory activity, which forms salt bridge with Glu205, Glu206 and Tyr662 in S2 pocket.[14,15]

Synergistic activity is often attributed to molecular hybrids with different pharmacophores. Apart from pyrimidinedione core, we determined bromophenol, butynyl group, fluorocyanobenzyl or (*R*)-3-aminopiperidine as substituents. The widespread application of fluorine in drug design benefits from distinctive properties, including lipophilicity, eletrophilicity, metabolic stability, chemical stability, et al.[16] In view of these observations, a novel series of pyrimidinedione derivatives were designed and evaluated for *in vitro* DPP-4 inhibitory activity. Among these pyrimidinedione derivatives, compound **11** showed the most potent inhibitory activity of DPP-4 and was potent *in vivo* hypoglycemic effect. Structure-activity relationships (SARs) of these pyrimidinedione derivatives are also discussed in this paper.

It has been reported about the synthesis of benzyl bromide in our previous reports, as shown in Scheme 1 [17–19] The synthetic route of

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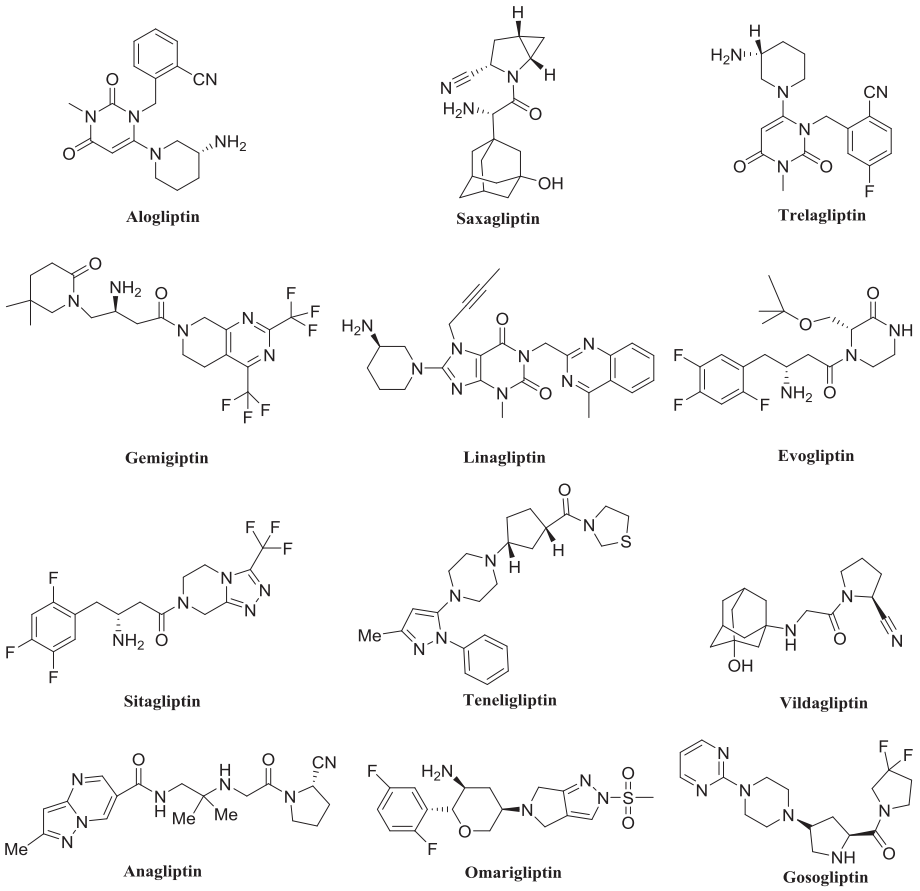


Fig. 1. Marketed DPP-4 inhibitors.

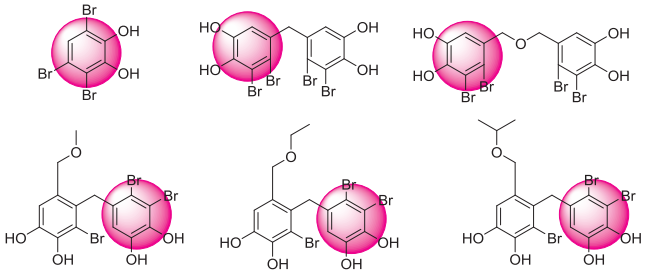
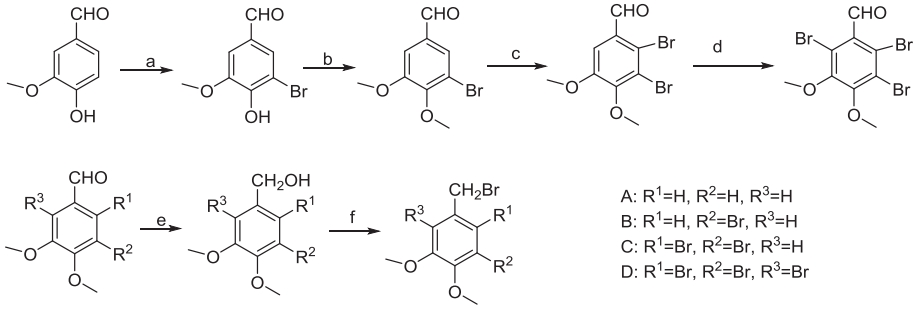


Fig. 2. Structures of bromophenol possessing hypoglycemic effect.

compounds **5–22** is depicted in Scheme 2[20,21] Briefly, the synthesis of pyrimidinedione derivatives was started from commercially available compound **1**. After alkylation of material **1** with 1-bromo-2-butyne or 2-cyanobenzo-5-fluorobenzyl bromide, the resulting precursor **2** was transformed into **3** through the *N*-alkylation. Compound **4** was obtained by a process of replacing the 6-chloro group with (*R*)-3-(Boc-Amino) piperidine. Finally, removal of Boc with TFA produced the final compounds **5–22**.

The inhibitory effects of compounds on DPP-4 activity were evaluated based on fluorescent probe.[22] In this part, we found that three compounds **11**, **15**, **16** showed potent inhibitory activity of DPP-4 at 100 nM with inhibitory rate of (100.12 ± 0.54)%, (95.59 ± 3.7)%, (98.84 ± 0.66)%, respectively (Table 1). As shown in Fig. 3, compounds **11**, **15** and **16** exhibited potent DPP-4 inhibitory activity, with IC_{50} values of 64.47 nM, 188.7 nM and 65.36 nM.

From the data of Table 1, we found that the degree of bromination of these compounds may have a close relationship with their DPP-4 inhibitory activity. For example, the number of bromine of compounds **11–14** gradually increases from 0 to 3. However, the DPP-4 inhibition rates of compounds **11–14** decrease from 100.12% to 0.66%. Similarly, compounds **6–8** were less potent than compound **5**. It could be found



Scheme 1. Reagents and conditions (a):Br_2, CH_3OH, 0 °C; (b): CH_3I, K_2CO_3, DMF, rt; (c): Br_2, CH_3COOH, Fe, 60 °C; (d): NBS, H_2SO_4, 0 °C; (e): $NaBH_4$, CH_3OH, 0 °C; (f):PBr_3, Et_3N, CH_2Cl_2, 0 ~ 15 °C;