ABSTRACT
Diabetes is chronic metabolic disorder which growing fast ground world. Dipeptidyl peptidase IV (DPP4) inhibitors are proven in the treatment of type 2 diabetes. DPP4 is a target during controlling diabetes glycemic control. DPP4 inhibitors have been shown to be generally well tolerated, with a low risk of hypoglycemia and neutral weight gain, and have anticipated long-term beneficial effects on β-cell function. A number of DPP-4 inhibitor develop rapidly for management of type-2 diabetes. This article review development of synthetic sulphonamide derivative as a DPP-4 inhibitor from 2004 to 2017 and provide SAR, biological activities against DPP-4and selectivity over DPP-8/DPP-9.

KEYWORDS: DPP4 inhibitors, Sulfonamide derivative, type 2 diabetes.

INTRODUCTION
DPP-4 is involved in rapidly inactivating both GLP-1 and glucose-dependent insulinitotropic polypeptide (GIP), therefore prolonging half-life of GLP-1 (less than 2 min) and GIP (about 2–3 min). GLP-1 is a 30-amino acid peptide hormone made in the intestinal epithelial endocrine Cells. and GIP consists of 42 amino acids secreted predominantly in duodenal K cells in the proximal small intestine. The main actions of GLP-1 and GIP are to increase insulin biosynthesis, to promote beta cell proliferation and to reduce beta cell apoptosis, contributing to limiting postprandial glucose excursions. Therefore the mechanism of anti-hyperglycemic effect of DPP-4 inhibitors is associated with GLP and GIP.

DPP-4 inhibitors prevents the inactivation of the incretin hormone GLP-1, which contributes to insulin secretion stimulation, glucagon secretion inhibition and thereby glucose control
improvement. This is a kind of glucose-dependent manner explaining the low risk of hypoglycemia associated with DPP-4 inhibitors.

Human DPP-4 has 766 amino acids and consists in mainly three parts: a cytoplasmic tail (1 -- 6), a transmembrane region (7 -- 28) and an extracellular part (29 -- 766). The catalytic domain (508 -- 766) possesses the amino acidic triad Ser630, Asp708 and His740. The DPP-4 has two binding pockets/sites (S1 and S2); the S1 pocket consists of the catalytic triad and the S2 pocket (Arg125, Glu205, Glu206, Phe357, Ser209, Arg358).

Different models confirm that the presence of a primary amine, an aromatic ring and a variable substituent are essential on the core scaffold S2 pocket is responsible for the inhibitor selectivity on DPP-4 over DPP-8 and DPP-9 (Figure 2); in fact, residues Glu205 and Glu206 of S2 pocket are involved in salt bridge interactions with cationic groups. α-Amino acylpyrrolidine derivatives have also been explored to obtain reversible DPP-4 inhibitors; taking into account the selectivity of DPP-4 for Pro at the S1 position, DPP-4 inhibitors containing five-membered heterocyclic rings were designed, and despite the first target of DPP-4 inhibition, GLP-1 possessed an Ala residue at that position. Their inhibitory potency depends on the presence of an electrophile at the 2-position of the pyrrolidine ring, able to form an adduct with the Ser630 of the enzyme active site. Thus, small molecules bearing electrophiles able to interact with the catalytic serine have been mostly designed. Product-like inhibitors lacking an electrophile are more stable in biological media but generally less potent.

The mechanisms for the glucose-lowering action of DPP-4 inhibitors include GLP-1–dependent and GLP-1–independent mechanisms. Apart from GLP-1, other four possible bioactive peptides. GIP, oxyntomodulin, pituitary adenylate cyclase–activating peptide, and stromal cell–derived factor-1α.

Structure-activity relationships (SARs) for identifying potent DPP-4 inhibitors which provide useful information for developing potent DPP-4 drugs as type 2 diabetes treatments. Among these drugs are novel once-weekly dipeptidyl peptidase 4 inhibitors.

2-Cyano pyrrolidine derivatives are reported as potent and selective DPP-4 inhibitors for the treatment of T2DM. For potent DPP-4 activity and moderate selectivity against DPP-4 over other related enzymes including dipeptidyl peptidase-7 (DPP-7), DPP-8, and DPP-9. 2-Cyano
-pyrrolidine derivatives showed that cyanopyrrolidine was crucial for inhibitory activity, since it formed hydrogen bonds with OH-group of side-chain of Ser630 and carbonyl of side-chains of Glu205 and Glu206. Moreover, the enhanced binding affinity was explained by strong hydrogen bond between benzamide / triazole and Arg358, and π-π interaction between the benzyl group and Phe357.

Fluorinated pyrrolidine amides were found to exhibit potent DPP-4 inhibitory activities. Molecular docking studies suggested that the difluoropyrrolidide moiety made extensive hydrophobic interactions with the side chains of Trp659, Val 656, Val711, Tyr631, Ser630, Tyr666, and Tyr662.

Glycine Based DPP-4 inhibitors were presented a series of piperidine derivatives as DPP-4 inhibitors, compound showed the highest potency against the enzyme of DPP-4.

Series of pyrrolidine-based inhibitors have most potent, long-lasting DPP-4 inhibitor with high selectivity against other related peptidases. The SAR analysis of heterocyclic ring contributed to inhibitory activity which was stacked with the side chain of Phe357 in the S2 sub site. Another group on heterocyclic compound trifluoromethyl, also interacted with Tyr585. Moreover, the enhanced binding affinity was explained by strong hydrogen bond between the carbonyl group of the amide bond and the side chains of Asn710 and Arg125.

The α-series, the β series also play an important role in discovering novel inhibitors of DPP-4. a series of β-alanine-based inhibitors as DPP-4 inhibitors. Benzyl side moiety was necessary since π-stacking interactions were observed with its surrounding residues Trp659 and Tyr666; the 2-cyanobenzyl substituent functioned as an H-bond acceptor to Arg125. The aminopiperidine formed an essential salt bridge with the backbone carboxylate of Glu205 and Glu206 in the S2 pocket, which was crucial for inhibitory activity.

SULFONAMIDE DERIVATIVE AS DPP-4 INHIBITORS-RELATED FROM 2004 TO 2017

Charles G. Caldwell et al., reported in 2004, (S)-3-fluoropyrrolidine showed good selectivity for DP-IV over quiescent cell proline dipeptidase (QPP). In modification of substituted 4-amino cyclohexyl glycine pyrrolidine lead structure. (S)- 3-fluoropyrrolidine showed good selectivity again DPP-4 over QPP. (S)- and (R) -3-fluoropyrrolidine showed good potency
with IC$_{50}$ value of 48 and 58 nM has good pharmacokinetic properties and was orally active in an oral glucose tolerance test in lean mice.$^{[12]}$

Jinyou Xu et al., designed in 2006, novel series of oxadiazole based amides have been shown to be potent DPP-4 inhibitors. The effect of changing the b-substituent in this series was improved by increasing the lipophilicity at the b-position isobutyl group, the cyclopropylmethyl group shows excellent selectivity over a variety of DPP-4 homologs.

Structural modification in a series of B-homophenyl alanine base DPP-4 inhibitor improve absorption across membrane while potency DPP-4 inhibition and selectivity maintain. In modification of side chain of amide with 1,2,4-oxadiazole and related heterocycle excellent oral bioavability and short half life.$^{[13]}$

Joseph L. Duffy et al., presented in 2007, a series of 4-aminocyclohexylglycine amides and sulfonamides improve the pharmacokinetic properties of the lead class while preserving the selectivity and the decreased influence of serum on intrinsic potency. Substitution of biaryl species in 1 or 2 with aryl sulfonamide 3 result loss of potency toward DPP-4. N-methyl toluyl sulfonamide derivative more potent.$^{[14]}$
Henry J. Tsai et al., showed in 2008 dipeptidyl derivatives with a sulfonamide moiety as DPP-IV inhibitors was a potent inhibitor (Ki539 nM), with a selectivity of 9160-fold over the DPP-II isozyme and elicits a hypoglycemic effect. 4-fluoro provides a reasonable inhibition constant of 39 nM suggesting the 4-position substitution is important. A strong but compact electrophile on the 4-position is favored in DPP-IV, but not in DPP-II. 4-fluoro provides has the highest IC50 value of 360 mM for DPP-II.\[15\]

Scott D. Edmondson et al., in 2008 discovered fluoroolefins possess excellent potency for DPP-4 inhibition. Potent and selective DPP-4 inhibitor were described in which a fluoroolefin moiety replaced a central amide bond. Fluoroolefin related to amide shows that fluoroolefin moiety chaves as an effective amide bioisostere in X-ray structure confirm the syn stereochemical assignment of potent DPP-4 inhibitor.\[26\]
Scott D. Edmondson et al., in 2009 presented a new series of DPP-4 inhibitors derived from piperidine-fused benzimidazoles. The improved DPP—4 potency of benzimidazole compared to phenyl triazole and phenyl imidazole. The addition of most substituents onto the benzimidazole improved DPP-4 inhibition potency. Polar substituents onto the 5-position of the benzimidazole ring typically resulted in enhancements in DPP-4 potency and QPP selectivity. The placement of polar electron donating substituents onto the 5-position of the benzimidazole ring also afforded potent and selective DPP-4 inhibitors such as a methanesulfonamide.\[^{[22]}\]

Soniya Nodoff et al., reported in 2009, increase molecular weight increase lipophilicity introduction of 3-Cl and 2,4,6-tri flouro phenyl moiety reduction size and lipophilicity of Sulfonamide cyclopropyl group provide potent and selectivity inhibitor of DPP-4. Balancing increase molecular weight increase lipophilicity C log P 1.82 resulted in significantly improve stability in rat, liver microsome $t_{1/2} > 2$ hr.\[^{[16]}\]
Reema Abu Khalaf et al., showed in 2013 N4-sulfonamidosuccinamic acid derivatives, it was found has the highest activity with 23% inhibition at 10 μM concentration. N4-sulfonamido-acrylic acid derivatives enclosing the amidino group showed the optimum inhibition N4-sulfonamidobenzoyl acetic acid derivatives had the highest activity with 25% inhibition (IC50= 33.5 μM).[17]

Radhika Sharma and Shubhangi S. Soman designed in 2014, the compounds presence of nitrile group at the P1 site is inevitable for the DPP-IV inhibition. Small molecules, sulfonamide derivatives of piperidine-3-carbonitrile and pyrrolidine-2-carbonitrile showed better inhibition with IC50 of 41.17 and 250.4 nM respectively which is comparable with the standard used for the assay (Vildagliptin) piperidine-3-carboxylic acid shows five-fold greater potency than (derived from L-proline).[20]
Peng-Fei Xiao et al., discovered in 2014, DPP4 with indole sulfonamide analogue are stable in liver microsome metabolic stability test. Only 2,4-disubstituted phenyl compound were tolerated and further modification caused significant activity less. which indicate P_1 pocket might be rigid and sensitive to substitution on phenyl ring.\textsuperscript{[18]}

Tao Jiang et al., presented in 2015, a series of sulfonamide derivatives introduction of fluorine atom on the phenyl moiety was of influence on improving inhibitory activities ethylation of the sulfonamide decreases the inhibitory activities all the sulfonamide derivatives exhibited excellent DPP4 inhibitory activity, with IC50 values ranging from sub-to single-digit nanomolar Steric and electronic effects did not appear to affect the binding activity to any appreciable extent, as small alkyl amides, cyclicamides represented in this group all displayed comparable activity.\textsuperscript{[23]}

Ping Chen et al., designed in 2015, Analogues of sulfonamide side chain at 3 position of the pyrazole moiety. Sulfonamide series imidazole sulfonamide which was ten times more potent than methyl sulfonamide in DPP-4 inhibition Sulfonamide group stabilized by addition hydrogen bond from with side chain of Y585 Sulfonamide analogs made in this study methyl
sulfonamide analog has longest half life clinical development suitable for once weekly dosing.\[^{21}\]

Radhika Sharma and Shubhangi S. Soman, discovered in 2016, A series of novel, non-proline mimetic, diamide derivatives of glycine were designed by substituting 1-(phenyl sulfonyl)piperidine-3-carboxamide at the P2 site and various secondary or tertiary amides at the P1 site. The binding affinity of the diamide derivatives of glycine (8.5 kcal/mol) for the DPP-4 enzyme was comparable with that of the marketed drug (Vildagliptin 6.7 kcal/mol) and hence was expected to show comparable potency.\[^{24}\]

Hai-De Gao et al., presented in 2016, The most active compound fluorine derivatives of sulfonamide 1,3,5- triazine thiazole was found as more potent inhibitor of DPP-4(2.32nM) than alogliptin as a standard. This compound showed in vivo DPP-4 inhibition accompanied with blood glucose lowering effect in experimental subject. It also found to possess favorable pharmacokinetic profile. Compound (30mg/kg) showed reduction in the area under the curve from 0 to 120 min (AUC) 0–120 min to 37.46%, which found approximately similar to the hypoglycemic profile of alogliptin (Standard). It also showed improvement of blood glucose level in dose-dependent manner in STZ-induced diabetic rats via significant improvement of insulin level and antioxidant enzyme systems.\[^{25}\]
CONCLUSION
DPP-IV inhibitors are a novel class of orally available molecules for the treatment of type 2 diabetes. There is more scope for designing newer DPP-4 inhibitor as antidiabetic. Most probable target for the evaluation under study is DPP-4 inhibitor which having improved efficacy by more selective DPP-4 inhibitor than DPP-8 and DPP-9 antidiabetic agent. Fewer side effect as compared with existing DPP-4 inhibitors with the aid of computer aided drug design concept a new DPP-4 inhibitor compound, can be design to improve therapeutic efficacy. Therefore it is expected that newly synthesis compound desired parameter.

REFERENCES


