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Structure and biological activity of endogenous and synthetic agonists of GPR119

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A G-protein-coupled receptor, GPR119, is a promising pharmacological target for a new class of hypoglycaemic drugs with an original mechanism of action, namely, increase in the glucose-dependent incretin and insulin secretion. In 2005, the first ligands were found and in the subsequent years, a large number of GPR119 agonists were synthesized in laboratories in various countries; the safest and most promising agonists have entered phase I and II clinical trials as agents for the treatment of type 2 diabetes mellitus and obesity. The review describes the major endogenous GPR119 agonists and the main trends in the design and modification of synthetic structures for increasing the hypoglycaemic activity. The data on synthetic agonists are arranged according to the type of the central core of the molecules.
The bibliography includes 104 references.

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1. Introduction

G-protein-coupled receptors (GPCRs) represent the most extensive family of eukaryotic transmembrane proteins, which control a multitude of physiological processes. These receptors have a common structure comprising one polypeptide with extracellular N-terminus, intracellular C-terminus and seven hydrophobic transmembrane domains (TM1 – TM7) linked to three extracellular (ECL1 – ECL3) and three intracellular (ICL1 – ICL3) loops. Approximately 800 receptors of the GPCR family have been detected in humans.[1]

There are several classifications of GPCRs. In terms of the homology of the amino acid sequence, they are subdivided into six classes and a large number of subtypes (families) and sub-subtypes (subfamilies): class A, rhodopsin-like (most numerous); class B, secretin receptor family; class C, metabotropic glutamate receptors; class D, fungal mating pheromone receptors; class E, cAMP-dependent receptors from the filamentous fungus *Dictyostelium discoideum*; and class F, signaling participants of a number of specific biochemical pathways. Classes D and E have not been found in vertebrate animals. Class A is subdivided by some authors (Bakir, Sezerman,[2] Horn *et al.*[3]) into the families of rhodopsin, peptides and amines; the amine family is, in turn, subdivided into the subfamilies of adrenoreceptors and dopamine, muscarine, serotonin and acetylcholine receptors.

According to the alternative GRAFS classification (this abbreviation is composed of the first letters of the name of

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each family), the GPCR receptors of vertebrates are subdivided into five groups.

1. The glutamate family, which includes the metabotropic glutamate receptors, calcium-sensing receptors and $GABA_B$ receptors (GABA is γ-aminobutyric acid), three type 1 taste receptors and a family of pheromone receptors (v2 receptors), which were found only in rodents.

2. The rhodopsin family includes receptors for a broad range of small molecules (neurotransmitters, peptides and hormones), olfactory receptors, visual pigments, type 2 taste receptors and five pheromone receptors (B1 receptors).

3. The adhesion family of the GPCR receptors is phylogenetically related to class B.

4. The Frizzled family includes signaling pathway receptors (Wnt and other).

5. Secretin family.

These families are, in turn, subdivided into subfamilies, depending on the endogenous ligands, which include ions, neurotransmitters, lipids, carbohydrates, nucleotides, amino acids, peptides and proteins.[1,4]

The G-protein-coupled receptors are involved in implementation of many functions, serve as pharmacological targets for more than 50% of drugs and are important potential targets for pharmacological studies and drug development.[1,2]

An approach based on stimulation of incretin secretion *via* activation of GPCR type receptors located on the intestinal enteroendocrine cells is now successfully applied in the design of drugs for the treatment of diabetes mellitus (DM) and obesity. Under physiological conditions, receptors of this group act as sensors for fatty acids (of various lengths), their derivatives, cellulose fermentation products and some other food components. Their activation results in enhanced secretion of incretins, which additionally stimulate insulin production and maintain the normal postprandial blood glucose. One of the key receptors of this group is GPR119, which is encoded in humans by one exon, with introns being located on the X-chromosome short arm (Xp26.1).[5]

GPR119 is expressed in intestinal L- and K-cells and in pancreatic β-cells. Also, it is encountered in several areas of rat brain, in particular, in cerebellum, cerebral cortex, vascular plexus, spinal ganglion, hippocampus and hypothalamus.[6,7] GPR119 refers to class A (rhodopsin type) G-protein coupled receptors, which mainly transmit the signal *via* cAMP by means of adenylyl cyclase-stimulating G-proteins (Gαs).[8] The activation of GPR119 increases the intracellular level of cAMP, resulting in glucose-dependent activation and enhanced insulin secretion in pancreatic β-cells. Furthermore, incretins protect the β-cells from apoptosis and increase cell proliferation. This dual mechanism of action means a pronounced hypoglycaemic action of GPR119 agonists without the risk of hypoglycaemia. Therefore, these compounds are considered to be promising drug candidates for the treatment of diabetes with an original mechanism of action (Fig. 1). This review is devoted to the description of chemical structures and hypoglycaemic action of the GPR119 agonists.

It has been found in experimental research and for healthy volunteers[9] that GPR119 agonists increase the level of circulating incretins, glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP) and peptide tyrosine-tyrosine (PYY); they reduce hyperglycaemia after the food intake or glucose load. Experiments have shown their cardio-, endothelio- and cerebroprotective activities. These pleiotropic effects, which are not inherent in the classical antidiabetic agents (which have, most often, only the hypoglycaemic action), can make these compounds more efficient for the therapy of diabetes mellitus and its complications.[10,11]

Thus, GPR119 agonists and drugs based on them may prove to be efficient for the prevention and/or treatment of

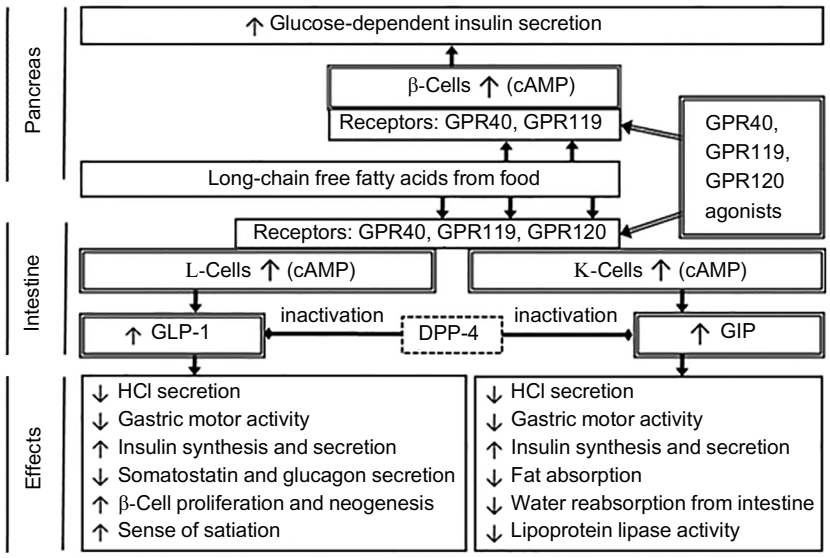


Figure 1. Mechanism of antidiabetic action of agonists of the receptors regulating incretin secretion. GPR40, GPR119 and GPR120 are located on intestinal L- and K-cells that release the key incretins (GLP-1 and GIP) and on pancreatic β-cells. The activation of these receptors increases the secretion of incretins and insulin, which leads to decreasing blood glucose concentration and induces some physiological effects, which are shown in the diagram. Development of synthetic receptor agonists is a promising approach to the design of new pharmaceutical antidiabetic drugs.

conditions such as carbohydrate and lipid metabolism disorders and the accompanying cerebral and myocardial ischemia.[12, 13]

Fatty acid derivatives that are able to activate GPR119 can either be components of the diet or be synthesized in intestine, thus having paracrine or autocrine action.[14] Furthermore, allosteric modulators are linked to GPR119 sites differing from the sites occupied by endogenous ligands; this is why, they are more selective.[15] Matsuda *et al.*[16] point out the existence of a common structure for most of the developed GPR119 agonists, namely, the methylsulfonyl-substituted phenyl group linked to a piperidinocarbamate moiety (or isostere).

The following abbreviations are used:
GPCR — G-protein-coupled receptor;
PYY — peptide tyrosine-tyrosine;
GIP — glucose-dependent insulinotropic polypeptide
GLP-1 — glucagon-like peptide-1;
DPP-4 — dipeptidyl-peptidase-4;
cAMP — cyclic adenosine monophosphate.

2. Natural endogenous GPR119 agonists

In 2001, Bonini *et al.*[17] reported *trans*-retinoic acid (all-*trans* retinoic acid, ATRA) called SNORF25 as the first potential endogenous ligand for GPR119.[5]

Lysophosphatidylcholine (LPC, **1**) was one of the first presumable endogenous agonists of GPR119. Compound **1** stimulated the glucose-dependent release of insulin and increased cAMP content in GPR119-transfected cells.[5]

Anandamide (*N*-arachidonoyl ethanolamide, AEA, **2**) is an endogenous cannabinoid transmitter, which belongs to the large group of *N*-acylethanolamines (NAES). Hydrolysis of AEA (**2**) affords free arachidonic acid.[18] Anandamide can be oxidized to prostamide E2 by cyclooxygenase-2.[19] Compound **2** affects many systems of the human body, including cardiovascular, nervous, and endocrine systems and the gastro-intestinal tract.[20]

Like another endogenous GPR119 agonist, *N*-oleoyl ethanolamide (OEA, **3**), AEA can regulate the eating behaviour. The GPR119 agonists, AEA (**2**) and OEA (**3**), are synthesized in the intestines and in the brain during fasting and satiety, respectively. Subsequently, AEA increases the food intake by activating cannabinoid receptors CB1, while OEA decreases the food intake by activating the receptors PPARα and/or GPR119;[21] this is accompanied by either decrease or increase in the cAMP content of the cells, respectively. It has been noted that, unlike LPC (**1**), OEA stimulates the intracellular synthesis of cAMP, which is followed by an increase in the insulin secretion only in the presence of glucose; this may be indicative of GPR119-independent effects of LPC.[22]

The introduction of OEA prevents an increase (or promotes a decrease) in the body weight, suppresses the appetite, changes the eating behaviour and motion activity of rats and enhances the absorption of fatty acids by adipocytes. Presumably, these effects are largely caused by increased secretion of incretins (GLP-1 and GIP) upon GPR119 activation.[23]

The GPR119 agonists, AEA and OEA, exert a neuroprotective effect in cerebral tissue injuries caused by impaired blood circulation or trauma.[24–26] Experimental studies demonstrated the ability of these compounds to retard the development of a neurodegenerative process by activating cannabinoid receptors (CB1 and CB2) and microglia.[27] However, the contribution of GPR119 to these effects is currently under discussion.

2-Oleoylglycerol (2OG, **4**) is synthesized from the precursor, diacylglycerol, and metabolizes by the monoacylglycerol lipase (MAGL) enzyme to give oleic acid and glycerol.

In experiments on humans, oral administration of 2OG (**4**) caused an increase in the GLP-1 and GIP levels.[28] However, in mouse experiments, OEA (**3**) and the compound AR231453, a synthetic GPR119 agonist (**30**, see Section 3.6 below) induced a higher production of GLP-1 as compared with 2OG (**4**).[29]

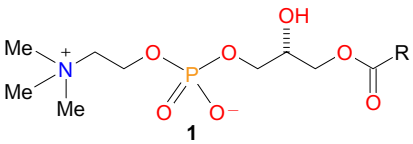
N-Oleoyl dopamine (OLDA, **5**) and 5-hydroxyeicosapentaenoic acid (5-HEPE, **6**) are also GPR119 agonists; however, they are not generated in the body under physiological conditions in amounts sufficient to produce a significant effect.[14] In *in vitro* experiments, the addition of OLDA (**5**) stimulated accumulation of cAMP in GPR119-transfected cells as efficiently as the addition of OEA (**3**) or highly efficient synthetic agonist AR231453 (**30**), while oral administration of OLDA (**5**) to mice considerably enhanced glucose utilization, thus decreasing the area under the glucose concentration–time curve (AUC) in the oral glucose tolerance test (OGTT).[30]

Other monoacylglycerols that are formed upon fat cleavage also show agonistic activities to GPR119; however, due to low concentration and selectivity to this receptor, it is impossible to determine their physiological role and possible pharmacological applications.[31]

Kumar *et al.*[32] investigated fatty acid amides and their activities towards GPR119. They have found that the ability of fatty acid amides to activate this receptor depends on the degree of saturation of acyl groups and the charge of their head groups. Also, it has been found that pretreatment of GPR119 with the agonists causes their desensitization to a degree correlated with the compound activity (half maximal effective concentration of the ligand, EC_{50}).

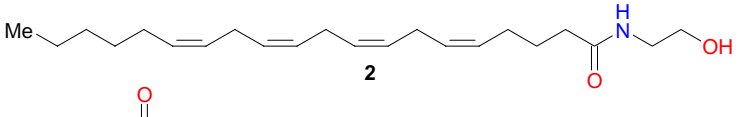
It was noted that increasing the number of double bonds in the molecule decreases the ability of these ligands to activate the receptors: compounds containing 1–2 double bonds have much higher efficiency and potential than those containing 3–6 double bonds. Indeed, oleoyl ethanolamide (**3**), linoleoyl ethanolamide (LEA, **7**), dihomo-γ-linolenoyl ethanolamide (DLEA, **8**), (7*Z*,10*Z*,13*Z*,16*Z*)-docosatetraenoyl ethanolamide (DTEA, **9**), eicosapentaenoyl ethanolamide (EPEA, **10**) and docosahexaenoyl ethanolamide

Structures 1–3

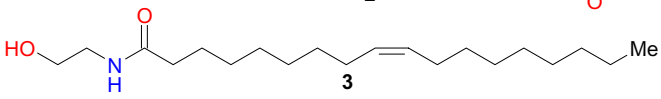


1

R is a fatty acid residue

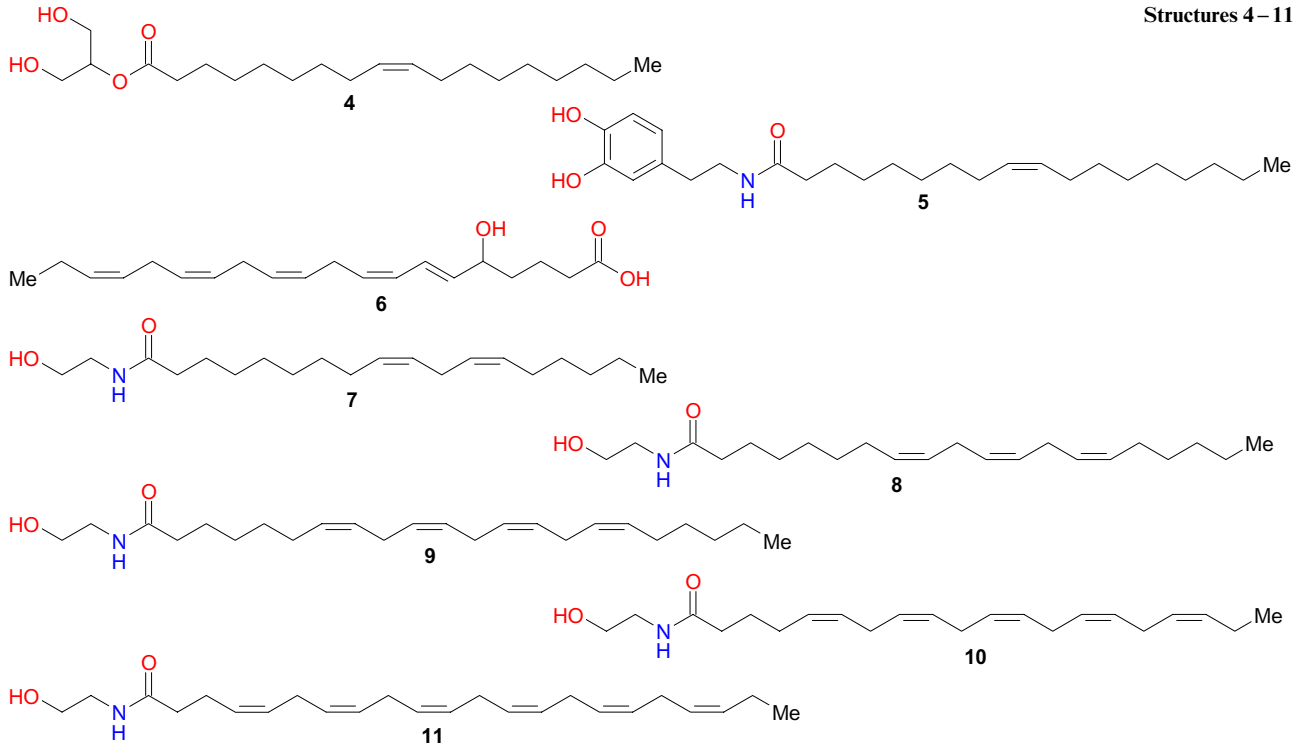


2



3

Structures 4 – 11



(DHEA, **11**) contain one, two, three, four, five and six double bonds, respectively, and OEA is most efficient among these compounds. It was also noted that the ethanolamide group is necessary for attaining the highest GPR119 activation.[32]

There are definite structural requirements to the head group of oleoyl amides. Compounds that could not activate GPR119 in the experiment [*N*-oleoylglycine (**12**), *N*-oleoylalanine (**13**) and *N*-oleoyl-γ-aminobutyric acid (**14**)] contain additionally a carboxyl group. The lack of activity can be attributed to either steric restrictions or the acidity of the carboxyl group.

In terms of the degree of desensitization of GPR119, the ligands have been arranged [31] in the following series:

OEA (**3**) > LEA (**7**) > DLEA (**8**) > DTEA (**9**) >
> EPEA (**10**) = DHEA (**11**)

The authors demonstrated that pretreatment of GPR119 with these ligands suppresses OEA-induced response to different degrees, also correlated with their ability to activate these receptors. This suggests that the indicated fatty acid amides target the same receptor binding sites. The suppression of the OEA-induced response may be related to desensitization of the receptors, competition between the ligands or a combination of receptor desensitization and ligand competition mechanisms.[32]

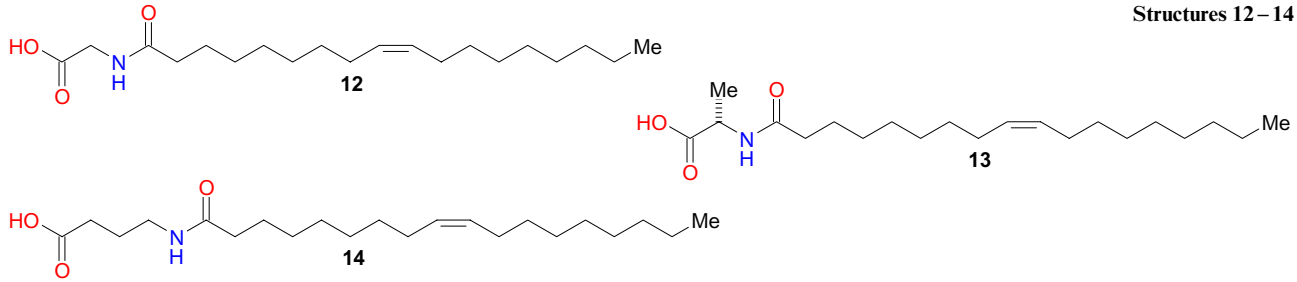
3. Synthetic agonists of GPR119

A complete classification of synthetic agonists of GPR119 is currently impossible, because many structures are not disclosed by patent holders. Nevertheless, the agonists available to date can be conventionally classified into several groups in terms of the central core structure.[33] Descriptions of these groups are given below.

3.1. Agonists with a six-membered heterocyclic core

As a result of high throughput screening, 4-(piperidino)pyrimidine derivative **15** was identified as an inverse agonist of GPR119 (IC_{50} = 84 μmol litre^{-1}, IC_{50} is the half maximal inhibitory concentration).[33] In the subsequent studies of structure – activity relationships, the trifluoromethylpyrazole moiety was replaced by a phenyl group linked to ester or other carbonyl-containing groups. Thus, agonists **16a** (EC_{50} = 1 μmol litre^{-1}) and **16b** (EC_{50} = 1.7 μmol litre^{-1}) were identified. Also, agonistic activity was found for derivatives that had a methylsulfonic or sulfonamide group and five-membered heterocycles as substituents in the benzene ring. The most pronounced increase in the

Structures 12 – 14



activity was noted when one functional group was located in position 4 of the benzene ring. The activity was retained when both ester and aniline linkers were present at the pyrimidine ring. In the agonists developed most recently, the sulfonyl aniline moiety was located in position 6, and the subsequent replacement of the ester group (*e.g.*, by an oxadiazole ring) resulted in the design of more active GPR119 agonists. The increase in substituent size from the methyl to ethyl group induced a more than 25-fold increase in the agonistic activity. Further increase in the substituent size and inclusion of branching into the ester group resulted again in increasing agonistic potential; *e.g.*, compound **17** demonstrated EC_{50} = 5.8 nmol litre^{-1}.

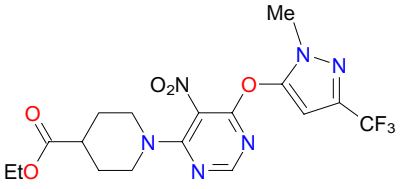
The oral administration of compounds **15** and **17** improved glucose utilization in mice and rats and had protective effect on the β-cells.[33]

Pyrimidine derivative **18** containing an terminal α-picoline moiety has been reported as a selective agonist of the receptors GPR119 of humans, dogs, monkeys, mice and rats. The compounds are readily soluble in water at pH 7; they do not affect the activity of liver enzymes and improve the glucose utilization in rats,[34] the AUC being decreased by 22%, 24% and 70% for 0.3, 3 and 30 mg kg^{-1} doses, respectively.

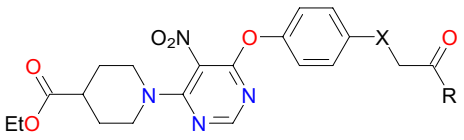
A patent[35] describes pyridine derivative **19** with a high activity (EC_{50} = 0.022 μmol litre^{-1}).

2-{[2-(4-Bromophenyl)-6-methylpyrimidin-4-yl]amino}ethanol (AS1269574, **20**) is the prototype of a series of 2,4,6-trisubstituted pyrimidines, which are efficient GPR119 agonists (for derivative **20**, EC_{50} = 2.5 μmol litre^{-1}). The compound AS1269574 increased the insulin secretion in the pancreatic β-cells of MIN-6 mice only at a high glucose level (16.8 μmol litre^{-1}),[36] but did not affect the fasting glycemia in experiments in healthy animals.

Structures 15 – 18

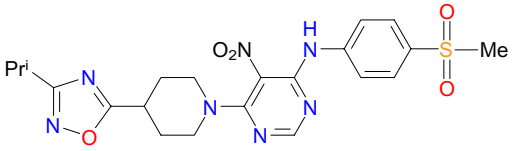


15

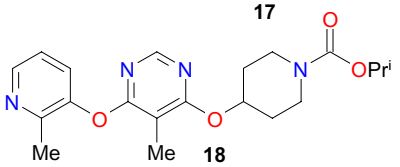


16a,b

X = C(O), R = OMe; X = CH_2, R = Me



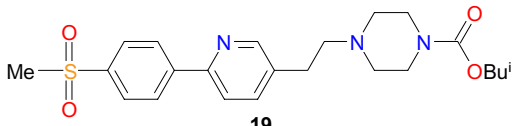
17



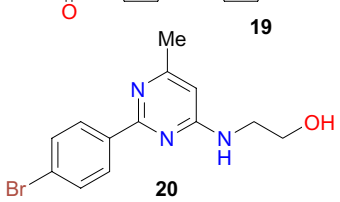
18

Subsequently, 2-(4-bromophenyl)-6-methyl-4-[2-(1-oxidopyridin-3-yl)ethylamino]pyrimidine (AS1535907, **21**) (Astellas Pharma) with EC_{50} = 1.5 μmol litre^{-1} has been synthesized by modification of compound **20**. Some researchers investigated the ability of new derivative **21** to increase the insulin secretion; not only the glucose-dependent mechanism of action of the compound has been established, but also the influence on the insulin secretion stage. In the isolated perfused pancreatic cells of rats without DM, the agent AS1535907 enhanced the first-stage insulin secretion at a 16.8 mmol litre^{-1} glucose level, but had no effect at a glucose concentration of 2.8 mmol litre^{-1}. As opposed to this, glibenclamide, an agent based on sulfonylurea, predominantly induced the second-stage insulin release at 16.8 mmol litre^{-1} glucose and markedly induced the insulin secretion at 2.8 mmol litre^{-1} glucose.[37,38] In *in vivo* studies on db/db mice, a single administration of AS1535907 at

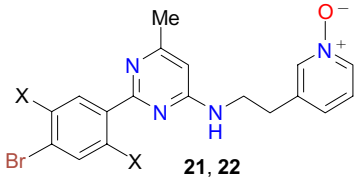
Structures 19 – 22



19



20



21, **22**

X = H (**21**), F (**22**)

10 μmol litre^{-1} concentration decreased the blood glucose level due to fast insulin secretion. It has been hypothesized that AS1535907 is able to stimulate the first-stage glucose-dependent insulin secretion and to cause faster and more physiological release of insulin than glibenclamide, which is very important for preventing the development of postprandial hyperglycaemia.[38]

Oshima *et al.*[39] reported the compound AS1669058 (Astellas Pharma) — 2-(4-bromo-3,5-difluorophenyl)-6-methyl-4-[2-(1-oxidopyridin-3-yl)ethylamino]pyrimidine (**22**) (as the oxalate) with EC_{50} = 0.044 μmol litre^{-1}; this product was also obtained by modification of AS1269574 (**20**).

The administration of AS1669058 to obese animals (db/db mice) was accompanied by enhancement of glucose utilization (decrease of AUC by 17%), a decrease in the glucose level by 22% and an increase in the insulin level by 28% compared with the control group.[39]

Negoro *et al.*[40] described a 4-amino-2-phenylpyrimidine derivative — (2*R*)-3-{[2-(4-chloro-2,5-difluorophenyl)-6-ethylpyrimidin-4-yl]amino}propane-1,2-diol **23** — as a potential GPR119 agonist with EC_{50} = 0.28 μmol litre^{-1}. This compound considerably decreased blood glucose and triglyceride levels in obese mice and had a protective action on the pancreatic β-cells.[40]

Zhang *et al.*[41] reported the discovery of *N*-arylsulfonyl-3-(pyridin-2-yloxy)aniline **24** with EC_{50} = 24 nmol litre^{-1} and E_{max} = 85% [E_{max} is the maximum possible effect (response) for this agonist; this parameter can be used to evaluate the relative efficiency of a drug].

Bristol Myers Squibb developed the compound BMS-903452 (**25**), which exhibited high activity in nanomolar concentrations (EC_{50} = 14 nmol litre^{-1}). Compound **25** was found to have a clear-cut hypoglycaemic activity *in vivo* when used in low doses (0.1–1 mg kg^{-1}), which was manifested as a decrease in the AUC relative to the control group by 14%, 37% and 40% for doses of 0.03, 0.1 and 1 mg kg^{-1}, respectively.[42]

Wacker *et al.*[42] reported the results of phase I clinical trials of BMS-903452. The agent was safe for healthy volunteers and well tolerated in any doses, with the elimination half-life being 36–51 h. Determination of the pharmacokinetic profile of the compound showed increase in the blood plasma concentration of the compound after 10 and 24 h, which corresponds to the food intake time of the patients and is indicative of possible enterohepatic circulation of the drug.

The compound GSK1292263 (below referred to as GSK263) — 3-isopropyl-5-{4-[6-(4-methylsulfonylphenyl)-pyridin-3-yloxymethyl]piperidin-1-yl}-1,2,4-oxadiazole (**26**) (EC_{50} = 6.9 nmol litre^{-1}) — developed by GlaxoSmith-Kline has reached phase II clinical trials, in which it showed good tolerability over a broad range of doses (10–800 mg) and rare undesirable effects (moderate headache, dizziness, skin hyperemia).[43,44]

The first administration of GSK263 is followed by a dose-dependent decrease in the AUC under glucose load; however, when the compound has been administered for two weeks, the hypoglycaemic activity and the ability to enhance the incretin and insulin secretion of the agent substantially decreases, but the ability to considerably increase the plasma level of total PYY after food intake is preserved. The agent GSK263 does not affect the GLP-1 and GIP concentrations, but, when introduced together with metformin, it increases the postprandial total GLP-1 level (up to 100 pmol litre^{-1}).[9]

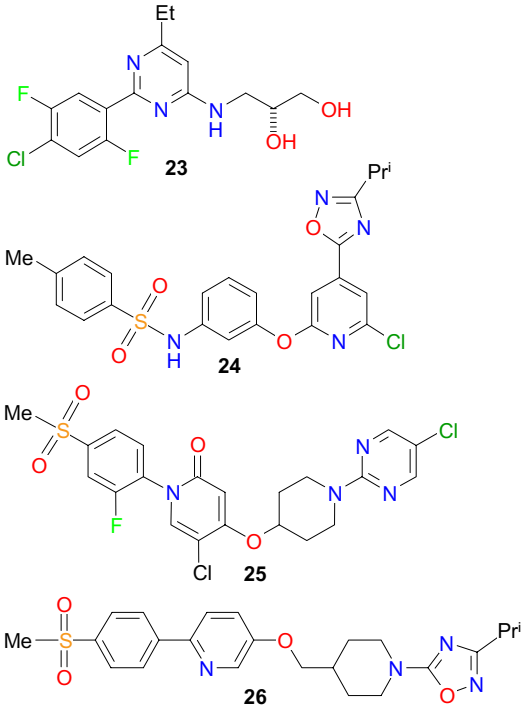
Nunez *et al.*[43] have studied the effect of GSK263, used either as single agent therapy or in combination with atorvastatin, on the lipid profile in the patients with dyslipidaemia (but without diabetes). The compound GSK263 in 800 mg dose substantially (by 20.7%) increased the high density lipoprotein (HDL) level and decreased the low-density lipoprotein (LDL) level by 21.8% and triglyceride level by 54.8% in comparison with placebo. In the authors' opinion,[43] GSK263 decreases the number and size of very low-density lipoprotein (VLDL) particles and chylomicrons, reduces the LDL and intermediate density lipoprotein (IDL) levels, increases the LDL particle size and increases the HDL particle amount and size, especially when used in combination with atorvastatin.

2-{[(1*S*)-1-[1-(3-Isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl]ethyl]oxy}-5-(4-methylsulfonylphenyl)pyrazine (GSK2041706A, or GSK706, **27**) (EC_{50} = 4 nmol litre^{-1}) has also been studied as a GPR119 agonist. Like agonist **26**, the compound GSK706 did not exhibit significant hypoglycaemic or anorexigenic activities in animals with primary (nutritional) obesity when used as single agent therapy. However, in some studies,[45,46] it has been shown that combined administration of GSK706 and metformin to animals kept on a high-fat diet resulted in a considerable increase in the efficiency of both agents. In particular, the GLP-1 level attained by combined treatment with GSK706 and metformin was 251% higher than that obtained for the control group. Meanwhile, when GSK706 (30 mg kg^{-1}) and metformin (100 mg kg^{-1}) were administered separately, this values were 40% and 120%, respectively. The same trend was observed for the total cholesterol and triglyceride levels: the administration of GSK706 decreased the levels by 19% and 12%, respectively, while the intake of metformin did not induce considerable changes in these characteristics. Meanwhile, a combination of GSK706 and metformin decreased the total cholesterol level by 31% and triglyceride level by 44%.[46]

Merck[47] has developed 4,4′-bipiperidine derivative **28**, exhibiting high activity towards GPR119 (EC_{50} < 10 nmol litre^{-1}). In GPR119-transfected Chinese hamster ovary (CHO) cells, this compound increased the intracellular cAMP level by a factor of almost five.[47] Studies of its pharmacological activity are still in progress.

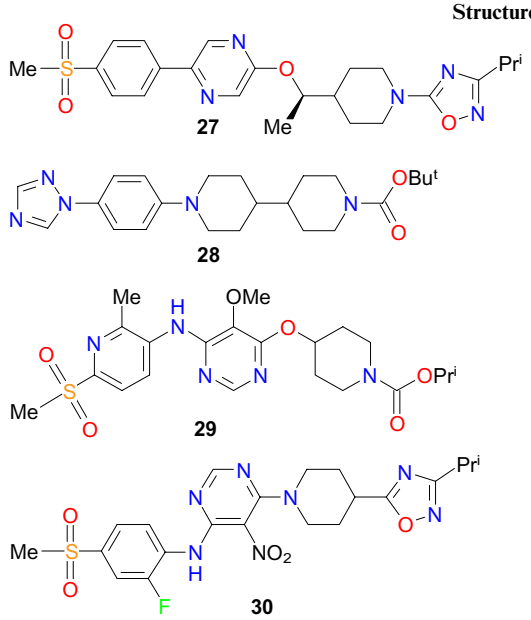
The compound APD597 (JNJ38431055) — isopropyl 4-{5-methoxy-6-[(2-methyl-6-methylsulfonylpyridin-3-yl)-amino]pyrimidin-4-yl}oxypiperidine-1-carboxylate (**29**) — has been developed when addressing the problem of inhibition of CYP2C9; this isoenzyme is inhibited by a number of bicyclic derivatives (compound **55**, see Section 3.3 below). Compound **29** belongs to the second generation of trisubstituted pyrimidine agonists and, according to *in vivo* studies, shows enhanced solubility, pharmacokinetics and metabolism as well as high activity.[5,48] However, as reported by Katz *et al.*,[49] clinical trials demonstrated insufficient therapeutic effects of the agent JNJ38431055 in type 2 diabetes (DM2) patients (single oral intake of 100 or 500 mg reduced the blood glucose level growth in the glucose tolerance test compared with placebo, but the use of several doses did not change the 24-hour average glucose level).[49,50]

Structures 23–26



The compound AR231453 (Arena Pharmaceuticals) — 2-fluoro-4-methylsulfonylphenyl{6-[4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidino]-5-nitropyrimidin-4-yl}amine (**30**) — is one of the most active GPR119 agonists. The high activity of this compound (EC_{50} = 0.68 nmol litre^{-1}) is associated with the presence of the nitropyrimidine core and the sulfonyl moiety.[45] Derivative **30** has a high selectivity to GPR119 and no affinity to other receptors. However, the possibility of systemic toxic effects on prolonged use of AR231453 has been suggested.[50, 51]

Structures 27 – 30



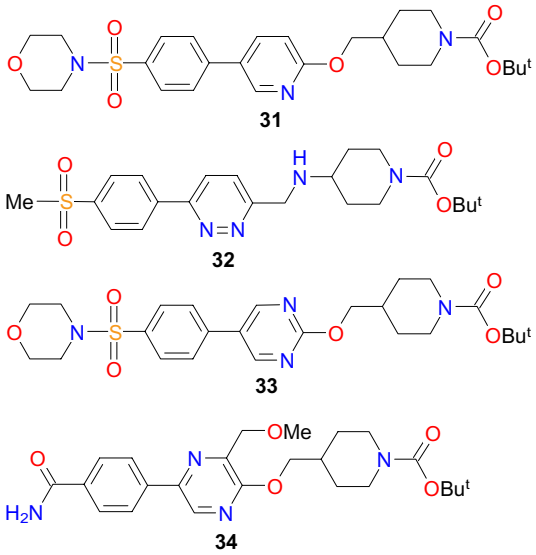
The compound AR231453 has shown pronounced antidiabetic action in many tests in various DM2 models (KK/Ay, ZDF, fa/fa, db/db and other mice); the hypoglycaemic action of AR231453 in a dose of 20 mg kg^{-1} was comparable with that of glibenclamide (30 mg kg^{-1}) based on sulfonylurea, but without the risk of hypoglycaemia development.[52, 53]

The simultaneous use of AR231453 (10 mg kg^{-1}) with a DPP-4 inhibitor, sitagliptin (1 mg kg^{-1}) in the C57BL/6 mice resulted in a synergistic increase in the active GLP-1 level (by a factor of four as compared with groups of animals administered with sitagliptin alone).[54]

Hothersall *et al.*[8] have found that the persistent effect of AR231453 is related to its slow dissociation (direct receptor-specific mechanism), whereas another highly active agonist, the compound MBX-2982 (**46**, see Section 3.2 below), is deposited in the receptor membrane (*i.e.*, there is a permanent ligand access in the binding site as a result of accumulation in the cell membrane in the close vicinity of the receptor). This emphasizes the importance of thorough investigation of mechanisms that determine the response to the action of GPR119 agonists.[8]

Compounds claimed by the Biovitrum company comprise a pyridine (**31**),[35] pyridazine (**32**),[55] pyrimidine (**33**)[56] or pyrazine (**34**)[57] core linked to the piperidine ring *via* an aminomethylene or oxymethylene linker. These compounds are characterized by EC_{50} = 22, 46 and 14 μmol litre^{-1}, respectively.[50] The investigations of the pharmacological activities of compounds of this series are currently in progress.

Structures 31 – 34

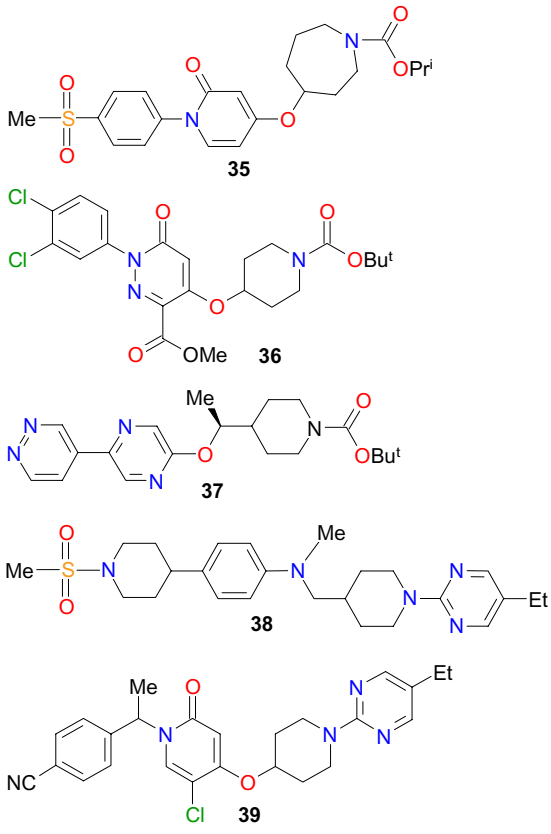


Molecules based on the 2-pyridone core containing a methylsulfonylphenyl substituent at nitrogen and various heterocycles linked to position 4 of the pyridine ring through an oxygen bridge have been prepared (an example is compound **35**).[58]

Pyridazone analogues (for example, compound **36**) have also been claimed as GPR119 modulators.[50, 58]

GlaxoSmithKline reported a series of GPR119 agonists based on six-membered aryl and hetaryl rings, in particular, compound **37**.[59]

Structures 35 – 39



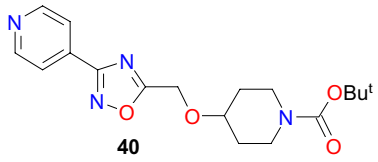
A number of GPR119 modulators contain a terminal sulfonamide group in the heterocyclic core (Novartis/IRM). Compound **38** administered to mice in a dose of 10 mg kg^{-1}, together with a DPP-4 inhibitor, induced an approximately 2.2-fold increase in the plasma concentration of active GLP-1 as compared with the group of animals that received only the DPP-4 inhibitor. In rat experiments, compound **38** induced a dose-dependent decrease in the glucose concentration, which was 31%, 48% and 56% for doses of 3, 10 and 30 mg kg^{-1}, respectively.[60–63]

Kim *et al.*[64] described the compound HD047703 (Hyundai Pharm, **39**). When administered to healthy animals (C57BL/6J mice) in a dose of 50 mg kg^{-1}, this compound decreased the AUC level after the oral glucose load to a degree comparable with that of the DPP-4 inhibitor (sitagliptin).[65] Prolonged (4 weeks) administration of compound **39** to animals with obesity (db/db mice) resulted in a threefold decrease in the fasting glucose level with a slight decrease in the body weight.

3.2. Five-membered heterocyclic agonists

Out of this group of compounds, 1,2,4-oxadiazole carbamate derivative **40** (PSN632408) was the first to be described as a GPR119 agonist.[33, 66]

Structure 40



40

Whereas endogenous GPR119 ligands increase, by analogy with GLP-1, both the insulin secretion and the concentration of intracellular Ca^{2+} and cAMP, oxadiazole derivatives affect these parameters in opposite directions. They possess an agonistic activity and efficiency similar to those of endogenous ligands [EC_{50} = 5.6 μmol $litre^{-1}$, E_{max} = 110% and EC_{50} = 3.2 μmol $litre^{-1}$, E_{max} = 100% for compounds **40** and OEA (**3**), respectively].[33, 67] The synthetic agonist PSN632408 (**40**) is less lipophilic and more selective to GPR119 than OEA and, unlike the endogenous ligand, it is efficiently absorbed.[13]

A number of studies[46, 68, 69] demonstrated that PSN632408 used in a dose of 10 mg kg^{-1} in combination with sitagliptin as a DPP-4 inhibitor (60 mg kg^{-1}) improves the weight and function of β-cells in animals with streptozotocin-induced diabetes mellitus, accelerates the cell neogenesis and prevents apoptosis. After 7 weeks of treatment, the weight of pancreatic β-cells was restored by 56% in the group that received combined therapy and by 39% and 45% in the groups that received only PSN632408 and sitagliptin, respectively. The authors also found a more than a twofold increase in the α-cell replication in animals that received only PSN632408 or only sitagliptin and a more than a fivefold increase for the group that received the combined therapy. The replication of α-cells and increase in the glucagon level may promote the formation of new β-cells, because glucagon is necessary for their formation and differentiation. Thus, the authors hypothesize that the DPP-4 inhibitor, the GPR119 agonist or their combination can be involved in the α- and β-cell differentiation.[68, 69]

Ning *et al.*[22] have compared the effects of PSN632408 (**40**), OEA (**3**) and another synthetic GPR119 agonist — 4-[5-(4-n-butylcyclohexyl)-1,2,4-oxadiazol-3-yl]pyridine (PSN375963, **41**) (EC_{50} = 8.4 μmol $litre^{-1}$) on the insulinoma MIN6c4 cells.

In the case of compounds **40** and **41**, the ability to increase the insulin secretion *in vitro* depended on the glucose concentration in the medium. At low glucose concentration (2.8 mmol $litre^{-1}$), these compounds did not stimulate the insulin secretion, which was simultaneously accompanied by a decrease in the cAMP production. This type of glucose-dependent action is inherent in the GPR119 agonists; however, the derivative PSN375963 also inhibited the cAMP production in the MIN6c4 cells at high (> 16 mmol $litre^{-1}$) concentrations of glucose.[22]

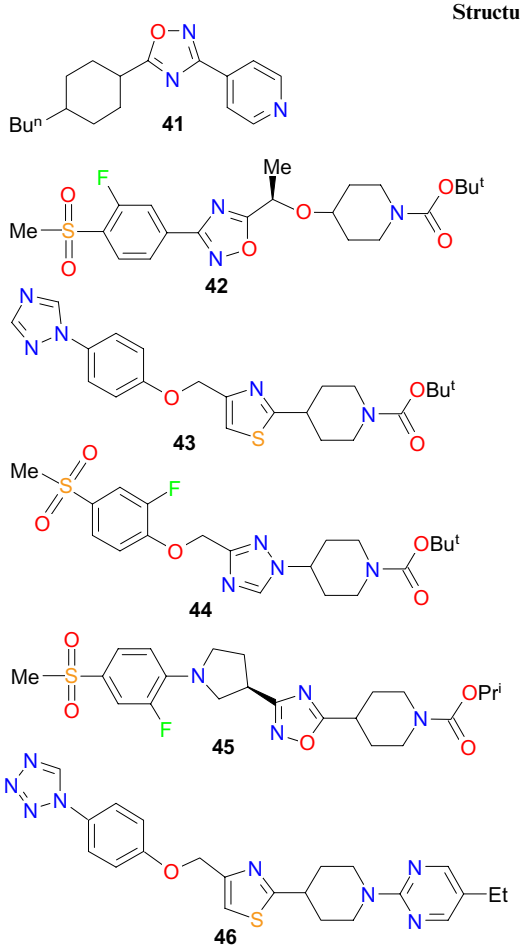
The replacement of the 4-pyridyl moiety in compound **40** by a 3-fluro-4-methylsulfonylphenyl moiety resulted in the formation of a new agonist with EC_{50} = 0.9 μmol $litre^{-1}$ and E_{max} = 375%. Modifications of the aromatic moiety after which the methylsulfonyl group was either replaced by H, Cl, Me or OMe or shifted to the neighbouring position 2 resulted in a decrease in the potential or complete inactivation. Subsequently, the additional introduction of the (*R*)-methyl group in the oxymethylene linker gave rise to the agent PSN119-2 (**42**, manufactured by Prosidion Ltd., EC_{50} = 0.4 μmol $litre^{-1}$, E_{max} = 358%). It is noteworthy that the *S*-isomer of this compound was much less efficient, so was a mixture of both isomers. This could make manufacture of the substance more complicated and more expensive; therefore, the structure optimization was continued; this gave rise to the new compound PSN821 (the structure was not disclosed). An analogue of derivative **42**, resulting from the replacement of the *tert*-butyl carbamate moiety by 5-isopropyl-1,2,4-oxadiazole one, has been patented. The new compound used in a dose < 100 mg kg^{-1} decreased significantly the glucose level and the amount of food consumed in experiments in obese mice and increased the insulin secretion in the HIT-T15 cells.[39, 70]

The compounds PSN119-2 (**42**) and PSN119-1 (**78**, see Section 3.5 below) were tested as agents for the treatment of obesity and metabolic syndrome; their anorexigenic potential was demonstrated in various obesity models. Shah and Kowalski[50] reported that PSN119-2 used in doses of 10 and 30 mg kg^{-1} improved the glucose utilization in rats upon oral administration, retarded the gastric emptying and reduced the food intake.

The agonistic activity was also exhibited by thiazole derivatives with a terminal triazole ring (for example, compound **43**) (Metabolex Inc.). According to a patent,[60] long-term (28 days) administration of compound **43** in 30 and 100 mg kg^{-1} doses to obese ZDF rats resulted not only in a decrease in the blood glucose and triglyceride levels, but also in a decrease in the glucose-stimulated peak insulin secretion; however, the compound also extended the insulin action time (the plasma insulin concentration decreased more slowly). The researchers cited believe that this sort of action could be useful in the therapy of diabetes mellitus in insulin-resistant patients.

A patent[71] describes 1,2,4-triazole derivative **44**. This compound increased the intracellular cAMP level *in vitro* by 69% with respect to the control. In glucose-loaded animals, compound **44** in a dose of 30 mg kg^{-1} increased the insulin secretion by 66% and improved glucose utilization, with the

Structures 41 – 46



AUC being decreased by 52% with respect to the control group.[71]

Pyrrolidinyl-1,2,4-oxadiazole **45** is a representative of a different chemical class of GPR119 agonists. These analogues also increase the intracellular cAMP level *in vitro*.[33, 61] Further modification of the molecules furnishes more stable or more selective agonists.

4-{[4-(1*H*-Tetrazol-1-yl)phenoxy]methyl}-2-[1-(5-ethylpyrimidin-2-yl)piperidin-4-yl]triazole (MBX-2982, **46**, Metabolex company) is a molecule based on a five-membered heterocyclic central core, which is directly linked to the piperidine ring *via* position 4 and to the benzene ring *via* the oxymethylene bridge. Compound **46** possesses a high agonistic activity to the receptor (EC_{50} = 10 μmol litre^{-1}), it is rapidly absorbed, and its elimination half-life is ~18 h.[5] According to Roberts,[72] in preclinical trials, MBX-2982 demonstrated an increase in the plasma GLP-1 and GIP levels, thus considerably increasing the insulin secretion and improving glucose utilization. The compound MBX-2982 decreases the concentration of glucose in DM2 patients in the fasted state and after food intake.[9] The administration of this compound to prediabetes patients in 100 and 300 mg doses restricted the growth in the glucose level after food intake by 26% and 37%, respectively, in comparison with the control group. In a five-day placebo-controlled rising dose study of MBX-2982 (25, 100, 300 and 600 mg), the deviations of the glucose level after food intake were statistically lower in all four groups of patients than in the control group, starting from 34% and up to 51%. In both studies, the use of MBX-2982 was safe and well tolerated without serious undesirable effects.[50]

3.3. Agonists based on bicyclic fused systems

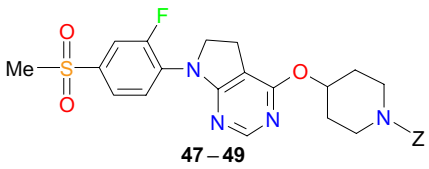
The compound GSK252A (**47**) (GlaxoSmithKline, EC_{50} = 40 nmol litre^{-1}) has a bicyclic dihydropyrrolopyrimidine core in the molecule and bears a structural analogy with GPR119 agonists in which pyrazolo[3,4-*d*]pyrimidine serves as the core.[50] In the dose of 30 mg kg^{-1}, the elimination half-life of GSK252A is 3.1 h, and its absolute bioavailability after oral administration is 60%.

According to Shah and Kowalski,[50] the administration of GSK252A (**47**) stimulated the GLP-1 production *in vitro*; the compound induced the glucose-dependent insulin secretion in islet cells of rats in the presence of 12 mmol litre^{-1} glucose, but did not affect the insulin production at low glucose levels (3 mmol litre^{-1}). The oral administration of GSK252A (10 mg kg^{-1}) to animals increased the concentrations of incretins GLP-1, GIP and PYY by factors of four, two and three, respectively. Under hyperglycaemia condition, this compound (10 mg kg^{-1}) improved glucose utilization, with AUC decreasing by 43%. After intravenous injection of glucose, GSK252A increased the peak concentration of insulin by 40%. The glucose infusion rate, with the retention of normal level, was approximately three times higher in rats administered with GSK252A than in the control group rats, which means that the agent can substantially enhance glucose utilization.[50]

Other compounds developed by GlaxoSmithKline are also known, for example, derivatives **48** and **49** containing a pyrrolopyrimidine core.[73, 74] While tested in C57BL/6 mice and SD rats, compound **49** induced a dose-dependent increase in the concentrations of circulating GIP and GLP-1 (oral doses of 3, 10, 30 and 60 mg kg^{-1} were used), increased the first (0 – 5 min) and second (15 – 90 min) stage glucose-stimulated insulin secretion and enhanced glucose utilization during the intravenous glucose tolerance test.[73] According to Shah and Kowalski,[50] in the oral glucose tolerance test, this compound decreased the AUC for glucose in animals by 28% (30 mg kg^{-1}) and 38% (10 mg kg^{-1}). During the insulin tolerance test for healthy animals, this derivative was found to enhance the tissue insulin sensitivity and can decrease the insulin resistance. Compounds **48** and **49** are described as having a therapeutic value for the treatment of diabetes and accompanying diseases: obesity, impaired glucose tolerance, insulin resistance and metabolic syndrome.[50, 73]

Molecules comprising a fused pyrimidine core, namely, 5,6,7,8-tetrahydropyrido[4,3-*d*]- and 5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4(3*H*)-ones substituted and unsubstituted at the pyridine nitrogen atom have been characterized in a patent [75] and meant for the treatment and/or prevention of obesity, diabetes and cardiovascular diseases. Compound

Structures 47 – 49

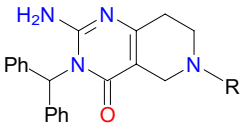


Z = CO_2Pr^i (**47**),  Br (**48**), CO_2Bu^t (**49**)

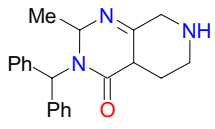
50 has been reported to enhance glucose utilization, with decreasing AUC, when administered in 3, 10 and 30 mg kg^{-1} oral doses before the glucose load.[75] This molecule activates GPR119 and stimulates cAMP production in GPR119-transfected cells (HEK293 line), with the EC_{50} values being in the range from 50 to 14 000 nmol litre^{-1}, and induces a steady decrease in the glucose level in mice with the genetic DM2 model.

Modulators of this class (Schering Plough) also include derivatives **51** and **52**.[75]

Structures 50 – 52



50, **51**

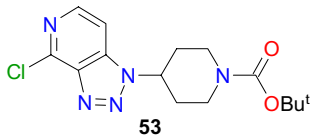


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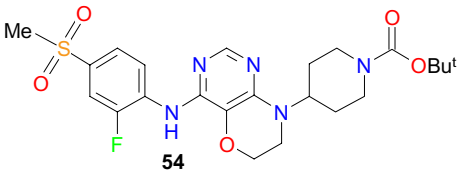
R = CMe_2Ph (**50**),
$CH(Me)C_6H_3F$-2-CF_3-4 (**51**)

Bicyclic agonists, compounds **53** and **54**, are described in patents,[76, 77] respectively. In *in vitro* studies, triazole derivative **53** showed EC_{50} = 19.49 μmol litre^{-1}, while oxazinopyrimidine derivative **54** had EC_{50} = 2.78 μmol litre^{-1} (Ref. 50).

Structures 53, 54



53



54

Isopropyl 4-{[1-(2-fluoro-4-methylsulfonyl-phenyl-)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}piperidine-1-carboxylate (**55**) (APD668; Arena Pharmaceuticals; also known as JNJ28630368) exhibited high activity towards GPR119 in various living organisms (hEC_{50} = 0.47, mEC_{50} = 0.98, rEC_{50} = 2.51 μmol litre^{-1}; the letters h, m and r designate EC_{50} values for humans, mice and rats, respectively). Apart from retarding the development of hyperglycaemia, this agent reduced the levels of triglycerides and free fatty acids and caused a moderate decrease in the body weight and food intake.[50]

However, APD668 (**55**) behaved as a strong inhibitor of the isoform CYP2C9 of the liver enzyme system (IC_{50} = 0.1 μmol litre^{-1}) and its hydroxylated metabolite is accumulated to a much higher degree in humans than in experimental animals. Although this metabolite did not possess high activity towards the target receptor, it had a high accumulation and long elimination half-life (~50 h). In order to solve the problem of CYP2C9 inhibition, alternative heterocyclic cores were used, the derivatives of which inhibited CYP2C9 to a considerably lower degree than pyrazolopyrimidine derivatives (see compound **29** in Section 3.1; for CYP2C9, the IC_{50} value is ~5.3 μmol litre^{-1}).

Zhang *et al.*[78] reported the agents ZSY-04 (**56**), ZSY-06 (**57**) and ZSY-13 (**58**). Compounds **56** and **57** are pyridopyrazinone derivatives, differing only in the substituent in the benzene ring, while derivative **58** contains a 3,6-disubstituted [1,2,4]triazolo[4,3-*b*]pyridazine core. In this study, all three compounds induced desensitization of GPR119 and glucose-dependent insulin secretion in the MIN6 cells, demonstrated high selectivity to GPR119 and did not activate other G-protein coupled receptors, in particular GPR40, GPR120, CB2, GLP-1R, GCGR, β2AR, DOR, KOR or MOR (in concentrations of up to 100 mmol litre^{-1}).[78]

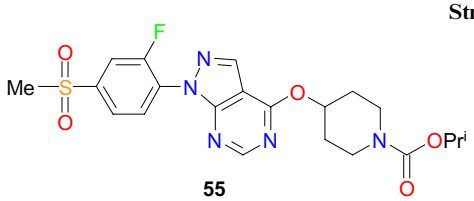
Gillespie *et al.*[79] described pyrazolo[3,4-*d*]pyrimidine derivative **59** as a potential GPR119 agonist (EC_{50} = 0.15 μmol litre^{-1}, E_{max} = 92%). In *in vivo* studies, preliminary injection of compound **59** (30 mg kg^{-1}) considerably enhanced the glucose utilization, which was manifested as a 44% decrease in the AUC compared with the control.

Wang *et al.*[80] presented a new class of GPR119 agonists based on 5-[2-(1-phenylsulfonyl-1,2,3,4-tetrahydroquinolin-7-yloxy)pyridin-4-yl]-1,2,4-oxadiazole with different substituents in the benzene and pyridine rings. One representative of this class is compound **60** with EC_{50} = 0.05 μmol litre^{-1}, E_{max} = 107%.

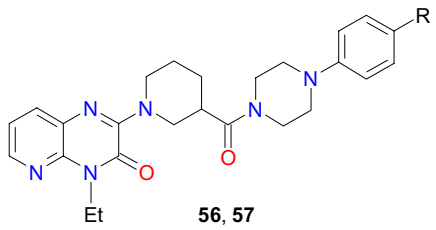
Yu *et al.*[81] reported *N*-[3-(1,3-dioxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-4-yloxy)phenyl]benzenesulfonamide derivative **61** as the GPR119 agonist with a high activity (EC_{50} = 16 nmol litre^{-1}); however, no data about the properties of this compound *in vivo* are available.

Sato *et al.*[82] described carbamate derivatives of indoline and indolinylpyrimidine as potential GPR119 agonists, in particular, 2-[1-(5-ethylpyrimidin-2-yl)piperidin-4-yl]propyl-7-fluoro-5-methylsulfonyl-2,3-dihydro-1*H*-indole-1-carboxy-

Structures 55 – 59

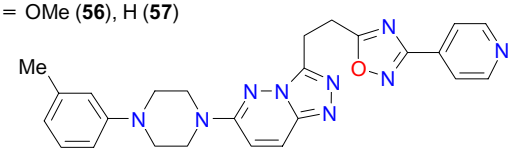


55

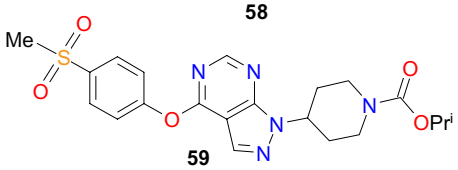


56, **57**

R = OMe (**56**), H (**57**)



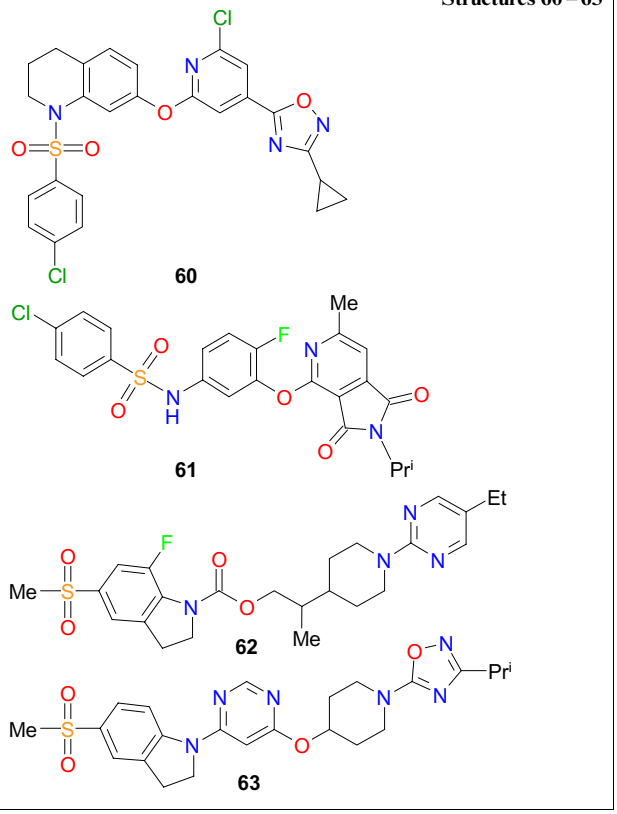
58



59

late (**62**) and 1-{6-[1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy]pyrimidin-4-yl}-5-methylsulfonyl-2,3-dihydro-1*H*-indole (**63**). Compounds **62** and **63** possess high activity: for racemic **62**, EC_{50} = 3.9 nmol litre^{-1}, while the second compound **63** is characterized by EC_{50} = 7.7 nmol litre^{-1}. Both derivatives increased the insulin secretion and decreased the AUC for glucose in the oral glucose tolerance test in Wistar rats, the agents being used in 10 and 30 mg kg^{-1} doses, respectively.

Structures 60 – 63



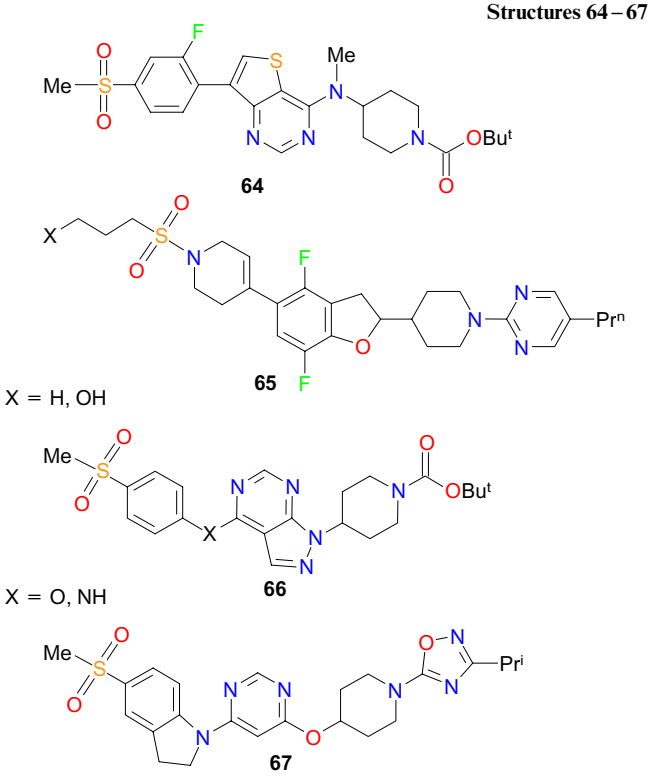
Jeon *et al.*[83] have described thienopyrimidine derivative **64** as an efficient agonist of GPR119. In ordinary mice experiments, this compound with EC_{50} = 3 nmol litre^{-1} induced a decrease in the AUC for glucose in the oral glucose tolerance test (15 mg kg^{-1} dose) in comparison with the control group and induced a dose-dependent increase in the insulin secretion in the TC-6 pancreatic β-cells.

Ye *et al.*[84] have studied dihydrobenzofuran derivatives **65**. These compounds were efficient GPR119 agonists *in vitro* (for X = H: EC_{50} = 2 nmol litre^{-1}, E_{max} = 119%; for X = OH: EC_{50} = 16 nmol litre^{-1}, E_{max} = 86%) and moderately inhibited the liver cytochrome system; however, animal experiments have not been reported as yet.

The company Roche has developed a series of pyrazolopyrimidine derivatives; the oxygen-bridged compound (**66**, X = O) proved to be 40 times more active than the analogue with the NH bridge (**66**, X = NH) (EC_{50} = 150 and 5740 nmol litre^{-1}, respectively).[85]

Takeda presented a series of agonists based on 5-(methylsulfonyl)indoline. When tested in animals (rats),[85] compound **67** containing an oxadiazole moiety (hEC_{50} = 7.7 nmol litre^{-1}) taken in a 10 mg kg^{-1} dose decreased the glucose variation in plasma and increased the glucose-dependent insulin secretion during the oral glucose tolerance test.

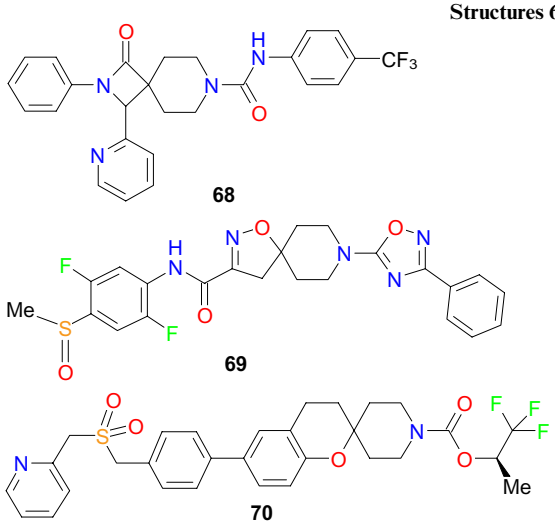
Structures 64 – 67



3.4. Polycyclic spiran agonists

Schering Plough Corporation has patented spiro derivatives of azetidine[86] and azetidinone[87] (for example, compound **68**) as agonists of GPR119. These spiro cycles are blockers of T-calcium channels (fast, low-threshold ones; these channels transfer the nociceptive signals in the peripheral and central nervous systems) and act as antagonists of vanilloid receptor 1 (transient receptor potential vanilloid 1, TRPV1) — an important integrator of pain and inflammatory stimuli — and antagonists of the Niemann – Pick C1 type protein (NPC1L1) — the key cholesterol absorption mediator. Thus, these molecules may be promising for drug

Structures 68 – 70



development for the treatment of pain syndrome as well as diabetes and obesity.[50, 86, 87]

Boehringer Ingelheim has reported[88] compounds containing the 1-oxa-2,8-diazaspiro[4.5]dec-2-enyl moiety; compound **69**, which was most effective among them, had EC_{50} = 21 nmol litre^{-1}.

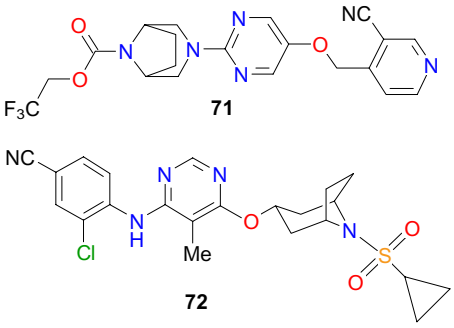
The company Kowa presented compound **70** with a spirocyclic structure. This derivative is a GPR119 agonist with hEC_{50} = 54 nmol litre^{-1}; however, no results of animal experiments have been published as yet.[85]

3.5. Polycyclic bridged agonists

Scott *et al.*[89] performed the search for GPR119 agonists based on 3,8-diazabicyclo[3.2.1]octane derivatives (for example, compound **71**). The authors varied the structure and conformation of molecules and studied their effect on the human and mouse GPR119. The effects of the agents on the human and mouse receptors (change in the cAMP) were considerably different, despite similar degrees of binding. Under the oral glucose load, the compounds had a hypoglycaemic action, the degree of which was correlated with the increase in the intracellular cAMP level *in vitro*.[89]

Xia *et al.*[90] reported 8-azabicyclo[3.2.1]octan-3-ol (nortropanol) derivative **72**, which exhibited high activity when used in a nanomolar concentration (EC_{50} = 3 nmol litre^{-1}, E_{max} = 96%), improved glucose utilization *in vivo* (30 mg kg^{-1}), with the AUC decreasing by 39%, and doubled the insulin level in comparison with the control group.

Structures 71, 72

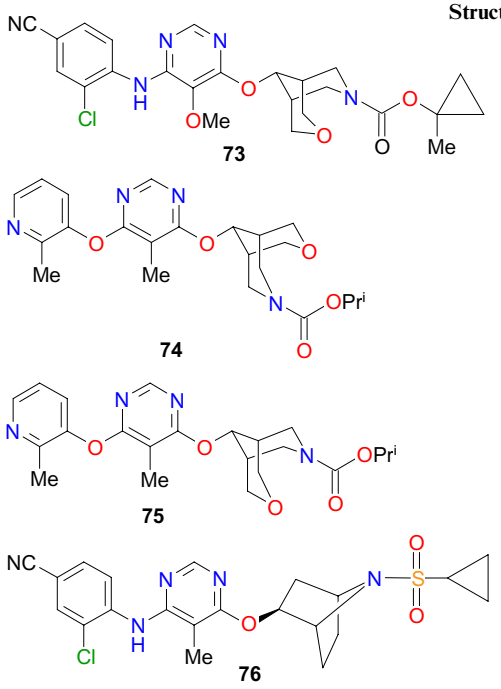


Dai *et al.*[91] described oxazabicyclononane derivative **73** (EC_{50} = 7 nmol litre^{-1}, E_{max} = 88%). When tested in mice, this compound exhibited a dose-dependent decrease in the AUC for glucose during the oral glucose tolerance test and was effective at low doses (starting from 0.1 mg kg^{-1}, it decreased the AUC by 40%, while for 3 mg kg^{-1} dose, the AUC decrease was 62%).

Pfizer disclosed the structure of oxazabicyclic compounds **74** and **75**. The former compound was the GPR119 agonist (hEC_{50} = 65 nmol litre^{-1}), while its isomer (compound **75**) showed antagonistic activity (K_b = 25 nmol litre^{-1}, K_b is the ligand binding constant). Measurements of pharmacokinetics of the former derivative showed a decrease in the bioavailability from 87% to 32% as the dose increased from 10 to 100 mg kg^{-1}; therefore, investigation of the whole series of compounds was discontinued.[85]

Merck reported one more molecule in which the replacement of the O-linked methylpyridinol moiety by the N-linked aniline moiety and the use of the cyclopropylsulfonamide group resulted in the development of a highly efficient GPR119 agonist (compound **76**) (EC_{50} = 3 nmol litre^{-1}). In the oral glucose tolerance test in mice, this compound in 10 and 30 mg kg^{-1} doses decreased the AUC by 30% and 39%, respectively.[85]

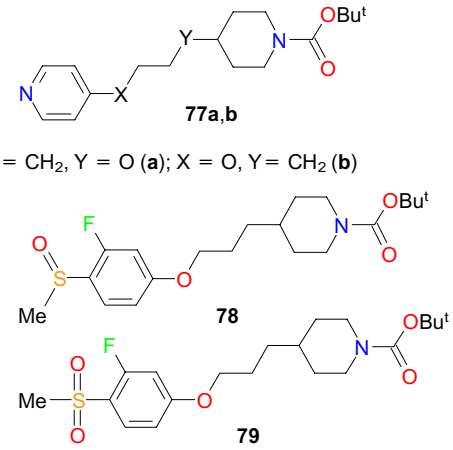
Structures 73 – 76



3.6. Agonists based on linear chains

Agonists of this type, for example, compounds **77** – **79**, contain a central acyclic oxyalkylene or alkylene moiety.[33] Initially, these compounds appeared good: they showed high activities in the screening phase (EC_{50} = 0.5 μmol litre^{-1} for **77b**), but turned out to have low efficiency in detailed investigations (E_{max} = 33%). The replacement of the pyridine ring by 3-fluoro-4-methylsulfonylphenyl moiety gave rise to analogues with exceptional activity and efficiency such as compound **79** (PSN119-1M) with EC_{50} = 0.2 μmol litre^{-1}, E_{max} = 392%. The pharmacological characteristics of racemic sulfoxide **78** (PSN119-1) have been studied in detail (EC_{50} = 0.5 μmol litre^{-1}, E_{max} = 407%).

Structures 77 – 79

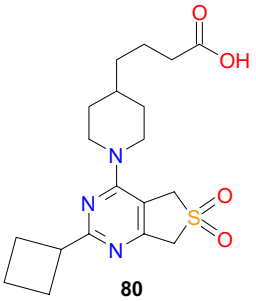


Compounds PSN119-1 (**78**) and PSN119-2 (**42**) (see Section 3.1 above) have been considered as agents for the treatment of obesity and metabolic syndrome; their anorexigenic potential has been shown in various obesity models. When tested in obese animals (ZDF rats), PSN119-1 (in a 50 mg kg^{-1} dose) induced a statistically significant decrease in the food intake, like the appetite regulator sibutramine (5 mg kg^{-1}). In the model of obesity caused by high-calorie diet, subchronic (3 weeks) administration of PSN119-1 (100 mg kg^{-1}) resulted in a considerable decrease in the glucose and insulin levels, fat tissue weight and plasma leptin level. In addition, subchronic oral administration of PSN119-1 to young db/db mice once a day in 100 mg kg^{-1} dose retarded the progression of diabetes mellitus.[33]

3.7. Miscellaneous synthetic GPR119 agonists

Yoshida *et al.*[36] reported that 4-[1-(2-cyclobutyl-6,6-dioxo-5,7-dihydrothieno[3,4-*d*]pyrimidin-4-yl)piperidin-4-yl]butanoic acid (**80**, AS1907417) increases the intracellular cAMP content and glucose-dependent insulin secretion in HEK293, NIT-1 and MIN-6-B1 cells. In healthy mice *in vivo*, the compound AS1907417 increased the glucose tolerance, but did not affect the plasma levels of insulin and glucose, whereas in obese db/db mice, it improved the lipid profile, increased the insulin concentration and decreased the glucose level.[92]

Structure 80



80

In compound **81** developed by Sanwa Kagaku Kenkyusho, the replacement of the amide group by a short aminoalkylene linker in combination with the terminal indanone moiety gave rise to a new GPR119 agonist (EC_{50} = 51 nmol litre^{-1}). This derivative induced a dose-dependent decrease in the growth of the blood glucose level during the oral glucose tolerance test in mice by 29% and 38% when used in 3 and 10 mg kg^{-1} doses, respectively.[85]

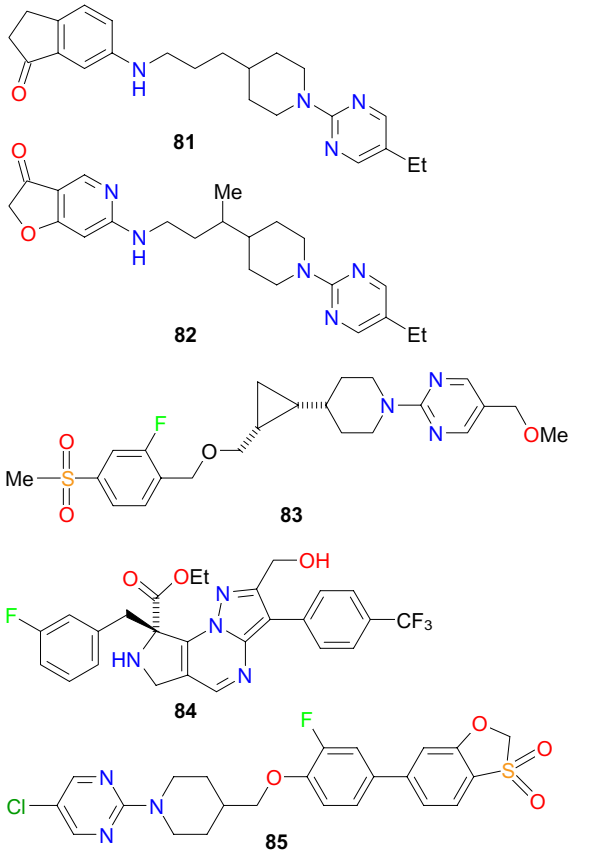
The modification of the main group and introduction of a methyl group into the linker produced a new racemic compound **82** (EC_{50} = 14 nmol litre^{-1}); according to Sakairi *et al.*,[93] this compound taken in 10 mg kg^{-1} dose retarded the gastric emptying and increased the total GLP-1 concentration in the blood plasma of the C57BL/6J mice.

Merck (Liu *et al.*[94]) has reported compound **83** with EC_{50} = 2.1 nmol litre^{-1}. In the oral glucose tolerance test in mice, this compound showed a dose-dependent decrease in the AUC for glucose by 16%, 20% and 29% in 0.3, 1 and 10 mg kg^{-1} doses, respectively; however, the compound MBX-2982 (**46**, see Section 3.2), taken as the positive control, was more efficient (40% for 10 mg kg^{-1} dose).

At the Genomics Institute of the Novartis Research Foundation, a new GPR119 agonist has been developed on the basis of tricyclic system **84** (EC_{50} = 5 nmol litre^{-1}, E_{max} = 99%). According to Azimioara *et al.*,[95] this compound taken in 30 mg kg^{-1} dose increased the active GLP-1 concentration in the healthy C57BL/6 mice twice as efficiently as the DPP-4 inhibitor. For animals with obesity (ZDF rats), the administration of compound **84** for two weeks enhanced glucose utilization, with the AUC under glucose load being decreased by 37% in comparison with the control group.[95]

Pharmacologists of the Volgograd State Medical University, together with chemists from the Chemical Diversity Research Institute (Khimki), developed the agent ZB-16 — 5-chloro-2-{4-[[4-(3,3-dioxo-1,3-benzoxathiol-6-yl)-2-fluorophenoxy]methyl]piperidin-1-yl}pyrimidine (**85**), which possesses high activity towards GPR119 (EC_{50} = 7.25 nmol litre^{-1}).[96]

Structures 81 – 85



The administration of ZB-16 to streptozotocin – nicotinamide-induced DM animal model decreases the glycaemic level[97] and improves the lipid profile and the functional state of endothelium.[98] A morphological examination of the pancreatic tissue of these animals has shown a greater area of insulin-positive material in the islets,[99] a lower content of the apoptosis marker (caspase 3) and a higher content of the proliferation marker (Ki67) for the test group that has received ZB-16 (1 mg kg^{-1}). It was also found that ZB-16 significantly increases the GLP-1 and insulin secretion both in intact animals and in animals with experimental diabetes mellitus.[100]

The administration of ZB-16 (oral, 4 weeks, 1 mg kg^{-1}) to animals kept on a high-fat and high-calorie diet induced a

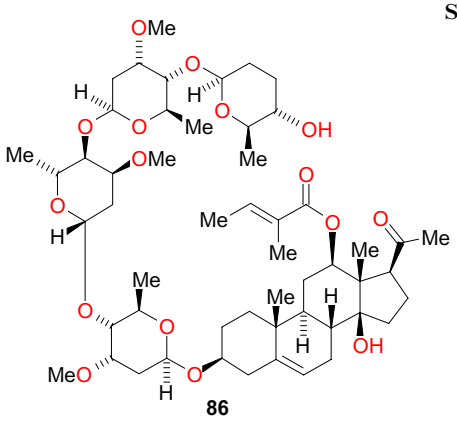
statistically significant decrease in the food intake and body weight and the blood LDL and triglyceride levels.[101]

Thus, the compound ZB-16 possesses pronounced antidiabetic properties associated with increasing GLP-1 and insulin secretion. In addition, the pleiotropic effects of GLP-1 may be responsible for the observed endothelioprotective action of ZB-16 in experimental DM.[98]

4. Plant extracts with agonistic activity

In recent years, plant extracts have attracted increasing attention as GPR119 agonists. Zhang *et al.*[102] have revealed agonistic activity to GPR119 of a steroid glycoside, Gordonoside F, the only biologically active component of *Hoodia Gordoni* (*Asclepiadaceae*) — 3β-*O*-[β-oleandropyranosyl-(1→4)-β-D-cymaropyranosyl-(1→4)-β-D-cymaropyranosyl-(1→4)-β-D-cymaropyranoside]-12β-tigloyl-14β-hydroxypregn-5-en-20-one (**86**).

Structure 86

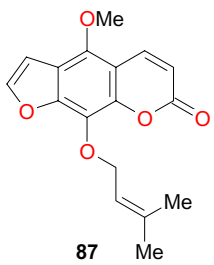


86

A patent[103] has disclosed the application of Gordonoside F as a GPR119 agonist for the preparation of drugs against diabetes and obesity. In healthy animals (C57BL/6 mice), Gordonoside F (200 mg kg^{-1}) caused a decrease in the food intake, while the extract of *H. Gordoni* induced a glucose-dependent increase in the plasma insulin and GLP-1 concentrations.[102]

Park *et al.*[104] reported the extract of *Angelica dahurica* (*Umbelliferae*) containing phellopterin (**87**) as the active component. Compound **87** is able to increase insulin secretion and improve glucose tolerance *in vivo*, presumably, owing to the agonistic activity to GPR119. The treatment of C57BL/6 mice with the *A. dahurica* extract (300 mg kg^{-1}) for three weeks induced a 8% decrease of the AUC under glucose load in comparison with the control group; however, the food intake of the two groups did not differ significantly.[104]

Structure 87



87

5. Conclusion

The discovery of the receptor GPR119, determination of its location and investigation of its functions have stimulated the search for synthetic agonists in order to develop a new class of hypoglycaemic pharmaceutical drugs with an original spectrum of pharmacological action.

The use of GPR119 agonists represents an absolutely new and unexplored approach to the incretin therapy of DM2 patients, in which the glucose-dependent insulin secretion increases *via* two additional mechanisms, by acting directly on the β-cells and in a mediated way *via* the increase of incretin (GLP-1 and GIP) secretion. The obvious potential benefits of GPR119 agonists include the decrease in the appetite and body weight and the absence of risk of hypoglycaemia development during the treatment. The combined use of a GPR119 agonist and a DPP-4 inhibitor (with the mechanism of protection of the secreted GLP-1) opens up new protocols for combined therapy of DM2. This strategy may not only ensure a better glycaemic control, but may also cause weight loss, which is especially important for patients with obesity. Design of the pharmaceutical drugs of this group would be useful for the development of not only pharmacology, but also fundamental science, as only this can extend the knowledge of the physiology of GPR119. The experience of development of synthetic GPR119 agonists has demonstrated that even a minor change in the structure of chemical compounds of various classes can considerably affect their efficiency and safety. The interest in GPR119 is not fading out, more and more patent applications describing compounds as GPR119 agonists are being published every year. In the future, they may become representatives of a new class of antidiabetic products, in particular, drugs that increase incretin secretion.

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