DOI: 10.1070/RCR4624

Chemical approach to the design of effective antidiabetic agents

Artem D. Rogachev,[a, b] Sergey O. Kuranov,[a] Nariman F. Salakhutdinov [a, b]

[a] *N.N.Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences prosp. Akademika Lavrentieva 9, 630090 Novosibirsk, Russian Federation*
[b] *Novosibirsk State University ul. Pirogova 2, 630090 Novosibirsk, Russian Federation*

The review discusses the literature data on the structures of hypoglycemic compounds with different mechanisms of action. It is shown that many drugs acting on different biological targets have similar or identical structural moieties. Compounds containing a sulfonyl group, a 3-phenylpropanoic acid moiety or the indane ring, as well as derivatives of heterocyclic systems (quinoline, isoquinoline, benzoxazine, thiazolidine and so on) are presented. The approach to the design of multi-target hypoglycemic drugs by combining different pharmacophoric groups in one molecule is considered. The prospects of the use of these agents for the treatment of type 2 diabetes are discussed.
The bibliography includes 177 references.

Contents

I. Introduction 1313
II. Drug targets in the management of diabetes 1314
III. Main approaches to the design of multi-target drugs 1316
IV. Sulfonyl group-containing compounds 1318
V. Agents based on 3-phenylpropanoic acid 1320
VI. Compounds containing the indane ring and their heteroanalogues 1323
VII. Quinoline, isoquinoline and benzoxazine derivatives 1327
VIII. Compounds containing the thiazolidinedione moiety or its bioisosteres 1329
IX. Miscellaneous compounds 1331

I. Introduction

Type 2 diabetes (T2D) is a metabolic disorder characterized by the impaired regulation of blood sugar (glucose) levels. Currently, diabetes is approaching epidemic proportions. According to the World Health Organization (WHO), the total number of patients with diabetes is projected to rise above 350 million in 2030.[1] Type 2 diabetes is a multisystemic disease that affects metabolism, primarily of carbohydrates. This is associated with the blocking of interaction of the hormone insulin with tissues, resulting in that the body is unable to use insulin properly for glucose metabolism (insulin resistance). An increase in blood glucose levels leads to the development of nephropathy, retinopathy, atherosclerosis and cardiovascular diseases.

Currently, oral drugs used in the treatment of T2D include insulin sensitizers, which increase the sensitivity of the body to insulin (for example, biguanides, thiazolidinediones, glitazones), insulin secretagogues, which trigger insulin secretion in the body [for example, glucagon-like peptide 1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, sulfonylureas] α-glucosidase inhibitors, which retard the cleavage of oligosaccharides to glucose. According to the data from IMS Health,[2] all these compounds, except for sulfonylurea-based drugs, are included in the list of drugs most sold in the U.S. market in recent years.

The choice and use of a particular drug for the treatment of diabetes depend on the patient's condition and the degree of development of the diabetic state. Any drug has both advantages and drawbacks, sometimes very serious, which

A.D.Rogachev. Candidate of Chemical Sciences, Researcher at the NIOCH SB RAS and the NSU.
Telephone: +7(383)330 – 9747, e-mail: rogachev@nioch.nsc.ru
Current research interests: medicinal chemistry, natural compounds, high-performance liquid chromatography, mass spectrometry
S.O.Kuranov. Junior Researcher at the NIOCH SB RAS.
Telephone: +7(383)330 – 8870, e-mail: s.o.kuranov@chemomsu.ru
Current research interests: medicinal chemistry, organic synthesis, natural compounds
N.F.Salakhutdinov. Doctor of Chemical Sciences, Professor, Head of the Department of Medicinal Chemistry at the same Institute, Professor at the NSU.
Telephone: +7(383)330 – 9733, +7(383)214 – 2986,
e-mail: anvar@nioch.nsc.ru
Current research interests: synthesis, structures and properties of natural physiologically active compounds.

Received 23 December 2015
Translation: T.N.Safonova

© 2016 Russian Academy of Sciences and Turpion Ltd.

cause side effects. This gives impetus to the research aimed at searching for and synthesizing new effective low-toxic hypoglycemic compounds and investigating their properties.

The synthesis of multi-target drugs (MTD) (also called multifunctional compounds) is a new important area in the design of effective drugs. Such compounds possess several types of activity and their multifunctionality is provided by interactions with two or more molecular targets. The benefit of MTD is that they enable polytherapy of the disease using one active substance rather than a mixture of several components. The drawbacks of compositions of several drugs are a high probability of adverse effects and interactions of the drugs with each other, their different bioavailability and pharmacokinetics, *etc*. Investigations of the properties of one chemical compound and the selection of treatment strategies using this compound substantially simplify the task.

The number of diseases treatable with multifunctional compounds gradually increases. These are neurodegenerative diseases (Alzheimer's and Parkinson's diseases),[3,4] migraine,[5] immune system disorders.[6] Multi-target drugs promising for the treatment of malaria and tuberculosis,[7] cardioprotective agents,[8] anti-inflammatory and other medications are available. Approaches to the design of dual-action antibiotics are considered in the review.[9]

The structural features of some types of hypoglycemic compounds (for example, thiazolidinediones or DPP-4 inhibitors), as well as their properties and mechanisms of action are well known. Data on peroxisome proliferator-activated receptor gamma (PPARγ) agonists,[10,11] DPP-4 inhibitors[12,13] and GLP-1R agonists[14] are covered in a number of reviews. Such compounds are most commonly used and popular antidiabetic drugs. Numerous publications are devoted to the search for models and the development of *in vivo* and *in vitro* methods for investigating hypoglycemic properties of new derivatives.[15–21] The present review deals with the structural features of compounds exhibiting hypoglycemic activity and acting on different molecular targets. Attempts are made to find regular structural features of these compounds for the purpose of designing promising antidiabetic drugs, the activity of which is associated with the simultaneous action on several known targets.

II. Drug targets in the management of diabetes

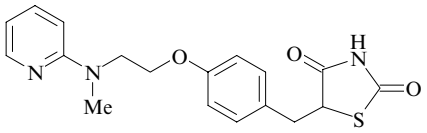
Most of biological targets and their use in diabetes therapy are considered in the review by Verspohl.[22] This Section summarizes the most popular targets, which have attracted attention of synthetic chemists employed in medicinal chemistry.

II.1. Peroxisome proliferator-activated receptors gamma

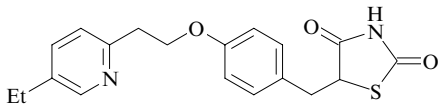
Peroxisome proliferator-activated receptors are a group of nuclear receptor proteins that function as transcription factors. They are activated by small lipophilic ligands that bind to the receptors and induce or suppress the transcription of numerous different genes, thus exerting considerable influence on cellular functions. The receptors PPARγ play an essential role in the regulation of glucose, lipid and cholesterol metabolism, thus making them attractive targets for drug design against diabetes, dyslipidemia and other components of metabolic syndrome.

In addition to PPARγ, two other subtypes of peroxisome proliferator-activated receptors were identified: alpha (PPARα) and beta/delta (PPARβ/δ). The PPARα subtype is found in liver, kidneys, adipose tissue and skin. This subtype is a molecular target mainly for fibrates that are used for the correction of lipid metabolism. The PPARβ/δ subtype is the least studied family of these receptors. It is assumed that these receptors play an essential regulatory role in fatty acid catabolism, energy metabolism and reverse cholesterol transport.[23] The PPARγ subtype has received the most attention due to the ability of these receptors to improve insulin sensitivity of tissues when insulin is in the activated state, *i.e*., upon exposure to antagonists. It was conclusively demonstrated that thiazolidinedione (TZD) derivatives are PPARγ agonists. The commercial drugs Rosiglitazone (**1**) and Pioglitazone (**2**) are examples of these compounds. Nevertheless, despite high hypoglycemic activity, these drugs have a number of adverse effects, such as a significant body weight gain, peripheral edema and an increased risk of cardiovascular events.

Structures 1, 2



1 (Rosiglitazone)



2 (Pioglitazone)

Rosiglitazone is often used as a reference sample in the experimental determination of activity of new PPARγ agonists and hypoglycemic compounds. The activating ability of new derivatives is usually evaluated taking the activation level of the receptor by Rosiglitazone (or another full agonist) as 100%, and the activity of other compounds is calculated with respect to this value. The concentration of the compound producing 50% of the maximal activation of the receptor (EC_{50}) is the experimental parameter that is employed to compare the activities. The ligand affinity for the receptor is assessed using a competitive test, in which the compound to be tested is replaced with tritium-labelled Rosiglitazone. This test provides an estimate of either the concentration at which 50% of Rosiglitazone molecules are replaced by the ligand (IC_{50}) or the constant characterizing the replacement

$$K_i = IC_{50}/\{1 + ([L]/K_d)\}$$

where [L] is the concentration of the ligand and K_d is the dissociation constant of the ligand – receptor complex.

Depending on the estimated value, the compounds are assigned to full or partial agonists or to selective receptor modulators. Full agonists are compounds that activate the receptor at the same level as or even stronger than Rosiglitazone. The advantage of these agonists is that they can be used in low concentrations; however, their side effects will be strong. Partial agonists are weak PPARγ activators that show the same activation profile as full agonists but have lower maximum activity.[10]

Selective PPARγ modulators (SPPARγM) are compounds capable of inducing a particular agonist or antagonist response of the receptor depending on the cellular environment. These are ligands that induce the specific effect of the receptor in a way different from that of full agonists.[24, 25]

There are quite a number of reviews, in which the PPARγ family is considered as targets for the treatment of many diseases. For instance, the possibilities of using PPARγ agonists for the treatment of not only diabetes but also inflammatory diseases are discussed by Pershadsingh.[26] The review[27] describes the discovery of thiazolidinediones as antidiabetic drugs, covers the data on characterization of PPAR families and their ligands and considers approaches to the drug design based on these compounds. The review[10] is devoted to the role of all types of PPAR as targets for the treatment of metabolic syndrome. Ramachandran *et al.*[11] summarize the data on chemical compounds acting as PPARγ agonists, dual PPARβ/γ agonists and PPARβ/γ, δ pan-agonists. The reviews[28 – 31] present the data on selective PPARγ modulators, describe a possible mechanism of their action and give examples of active compounds and results of biological assays.

II.2. Glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase IV inhibitors

Glucagon-like peptide-1 (GLP-1) is an incretin hormone released in response to food intake. This hormone plays an essential role in glucose homeostasis because it induces the β-cells of the pancreas to release insulin. The receptor for GLP-1 is called GLP-1R and it is activated by this peptide. The characteristic feature of GLP-1 is a very short lifetime in the body because this peptide is rapidly degraded by dipeptidyl peptidase 4. For this reason, drugs mimicking the action of the peptide, *i.e.*, drugs activating the GLP-1 receptor, or agents inhibiting the enzyme DPP-4 are used for the treatment of diabetes. The GLP-1R agonists that are currently used in the medical practice have a serious drawback, namely, being polypeptide compounds, they should be injected subcutaneously. Examples include Exenatide (**3**) and Liraglutide (**4**).

Structures 3, 4

H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH_2

3 (Exenatide)

H_2N-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser

n-$C_{15}H_{31}$–C(=O)–Glu–OH (N^6)

Phe-Glu-Lys-Ala-Ala-Gln-Gly-Glu-Leu-Tyr-Ser

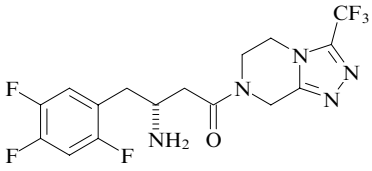
Ile-Ala-Trp-Leu-Val-Arg-Gly-Arg-Gly-CO_2H

4 (Liraglutide)

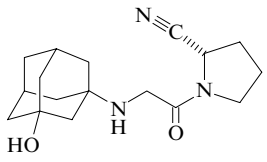
Currently, an extensive search for low-molecular-mass GLP-1R agonists is performed, and certain advances have been made. However, there are a few compounds possessing activity at a required level, and no commercial low-molecular-mass agents were approved for the medical use. The recent review[14] systematically considers the data on low-molecular-mass GLP-1R agonists.

Meanwhile, quite a number of DPP-4 inhibitors were synthesized. Let us mention Sitagliptin (**5**) and Vildagliptin (**6**) as commercial drugs, which are used either individually or in combination with other hypoglycemic agents. The schemes of the synthesis of popular DPP-4 inhibitors, including these compounds, are presented in the review.[32]

Structures 5, 6



5 (Sitagliptin)



6 (Vildagliptin)

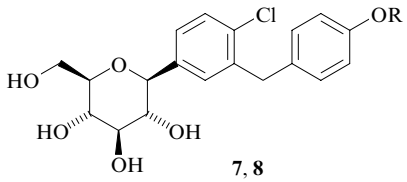
Data on synthetic DPP-4 inhibitors are summarized in numerous publications. For instance, inhibitors reported in the patent literature covering the 2006 – 2011 period are described in the review;[12] approaches to the development of popular commercial drugs are summarized by Gwaltney;[33] drugs containing a sulfonyl group were analyzed by Chen *et al.*;[34] Peters[13] systematically considered the data on cyanopyrrolidines that belong to one of the promising classes of hypoglycemic compounds. The meta-analysis of the data on the efficacy of DPP-4 inhibitors has been accomplished.[35]

II.3. Sodium-dependent glucose cotransporter 2 inhibitors and glucokinase activators

The inhibition of sodium-dependent glucose cotransporters 2 (SGLT2) is a promising rapidly evolving approach to the treatment of diabetes. The SGLT family comprises two representatives, SGLT1 and SGLT2, which are expressed mainly in kidneys and are involved in glucose reabsorption. The SGLT2 cotransporter subtype is involved in the transport of 90% – 98% of glucose excreted through the kidneys. Therefore, the regulation of this cotransporter is an important mechanism of maintenance of blood glucose levels:[36 – 38] the inhibition of SGLT2 leads to a decrease in glucose reabsorption in the kidneys and its excretion through urine and, as a consequence, to a reduction in blood plasma glucose levels. Most of known SGLT2 inhibitors are aryl derivatives of glucosides; however, promising agents belonging to other classes are also known.[39] Let us mention the commercial drugs Dapagliflozin (**7**), Empagliflozin (**8**) and Ipragliflozin (**9**). The approach to the synthesis of such compounds is described by Larson.[40]

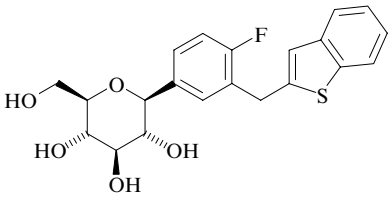
Glucokinase 4 is a hexokinase isozyme that is present in pancreatic cells and hepatocytes and that catalyzes the phosphorylation of six-carbon sugars. Glucokinase causes a rapid uptake of glucose from the blood in the liver. The transport of glucose into hepatocytes is accomplished by the transporters GLUT 2, the activity of which is not regulated by insulin levels.[41] In patients with type 2 diabetes, the glucokinase activity decreases by at least 50%.[42] The analysis and structural classification of glucokinase activators covered by patents during the 2008 – 2010 period are given in the review.[43] Piragliatin (**10**) serves as an example.

Structures 7 – 10

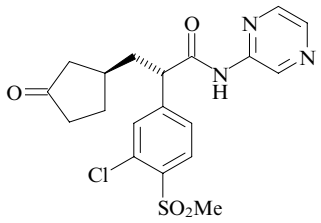


7, **8**

R = Et (**7**, Dapagliflozin),
(*S*)-oxolan-3-yl (**8**, Empagliflozin)



9 (Ipragliflozin)



10 (Piragliatin)

III. Main approaches to the design of multi-target drugs

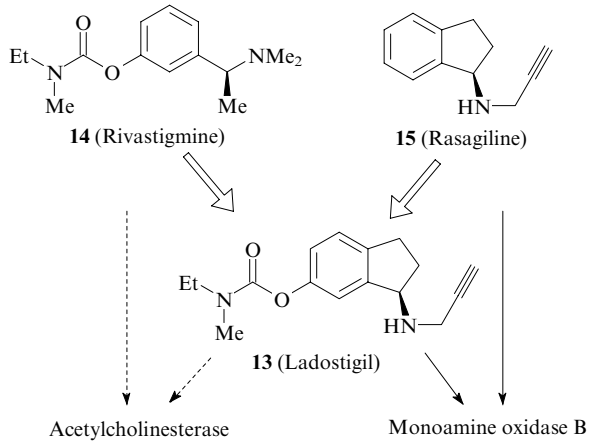
Multi-target agents are characterized and classified according to the method of design in the review.[44] Synthetic MTD are divided into two types: hybrid and chimeric. Compounds of the former type are constructed from two or more pharmacophores with different activities connected by linkers. Compounds of the latter type are designed by merging or fusing several pharmacophores through the overlap of their common moieties.

An example of hybrid MTD is compound **11**, which was prepared by combining moieties of two antimalarial agents — artemisinin and quinine.[45] The activity of hybrid **11** against the microorganisms *Plasmodium falsciparum* was higher than the activities of its components taken separately as well as an equimolar mixture. Capela *et al.*[46] conjugated artemisinin to peptidyl vinyl sulfones and synthesized compounds of general formula **12**, which also exhibited antimalarial activity.

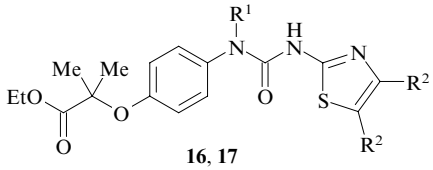
The synthesis of the drug Ladostigil (**13**) used for the treatment of Alzheimer's disease is an example of the design of chimeric MTD. This compound was constructed by combining moieties of two agents — the acetylcholinesterase inhibitor Rivastigmine (**14**) and the monoamine oxidase B inhibitor Rasagiline (**15**) (Scheme 1).[47] Compound **13** retained the inhibitory properties of the precursors against both enzymes and acquired neuroprotective properties.

A similar approach was applied by Li *et al.*[48] to synthesize urea derivatives acting as glucokinase activators and PPARγ agonists. In particular, chimeric compounds included the 2-phenyloxypropanoic acid moiety connected to the nitrogen-containing heteroaromatic ring and characteristic of fibrates (dual PPARα/γ agonists). Compounds **16** and **17** can serve as examples.

Scheme 1



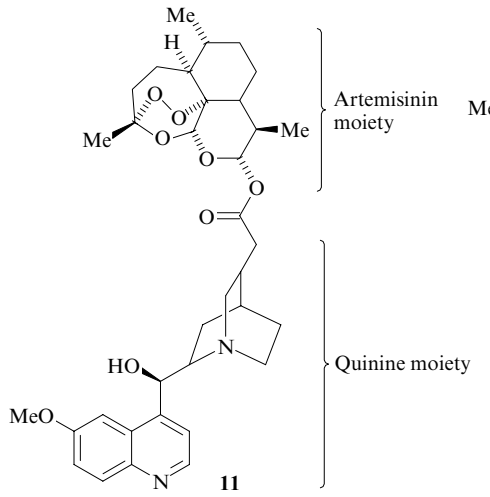
Structures 16, 17



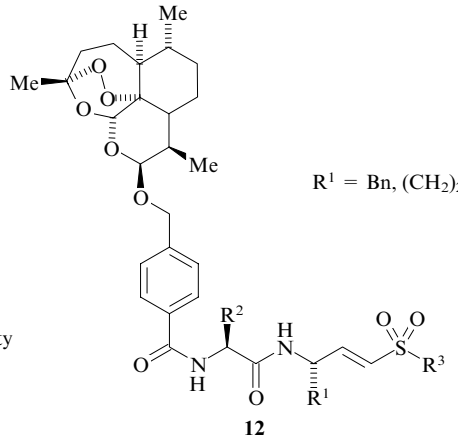
16, **17**

16: R^2 = H: R^1 = Et, iso-C_5H_{11}, EtO$(CH_2)_2$, 3-$FC_6H_4CH_2$;
17: R^2 – R^2 is benzo: R^1 = n-C_5H_{11}, iso-C_5H_{11}, All, cyclo-$C_5H_9CH_2$, 2-$FuCH_2$ (Fu is furyl)

Structures 11, 12



11



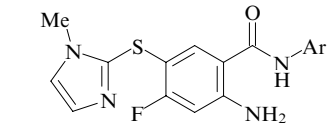
12

R^1 = Bn, $(CH_2)_2$Ph; R^2 = H, Bu^i, Bn; R^3 = Me, Ph

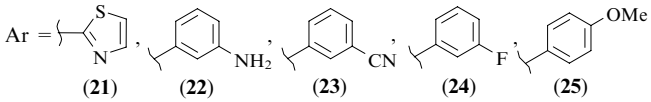
A series of chimeric MTD of general formula **20** (Scheme 2) were prepared in further research performed by Lu *et al.*[49] based on the structures of glucokinase activator **18** and the PPARγ agonist MK-767 (**19**). These compounds contain the benzamide group common to both precursors, the alkylaryl moiety acting as a glucokinase-activating pharmacophore, the thiazolidinedione ring characteristic of PPARγ agonists and a nitrogen-containing heterocycle. *In vitro* experiments showed high activity of the resulting compounds, which confirms the potential of this approach to the design of potent hypoglycemic agents.

Based on the analysis of the literature data, Zhang *et al.*[50] found the structural similarity between glucokinase (GK) activator **21** and glycogen phosphorylase (GP) inhibitor **22** containing the tetrasubstituted benzamide aromatic ring and the hetarylthio moiety. Compound **22** was found to exhibit moderate glucokinase-activating activity, thus providing the possibility of designing dual-action drugs based on this compound. A series of related derivatives, for example, compounds **23** – **25**, were synthesized. These compounds exhibited dual activity and hold promise for further investigations. The possible binding modes of these compounds to the enzymes were explored by molecular docking simulation, and the activity of these compounds against the mentioned targets was experimentally confirmed.

Structures 21 – 25



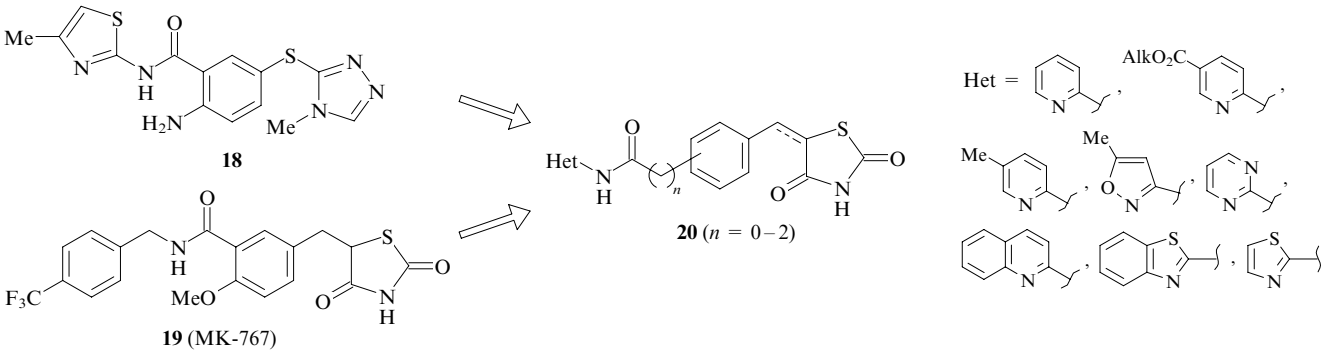
21 – **25**



(**21**) (**22**) (**23**) (**24**) (**25**)

Later, the search for the optimal structure of a hybrid molecule that would combine the properties of GK activators and GP imhibitors was accomplished.[51] For this purpose, model calculations were performed and the similarity between GK and GP, as well as the structural similarity between the known ligands of these enzymes were analyzed. It was concluded that the ligand molecule should be Y-shaped and at least two branches should be

Scheme 2

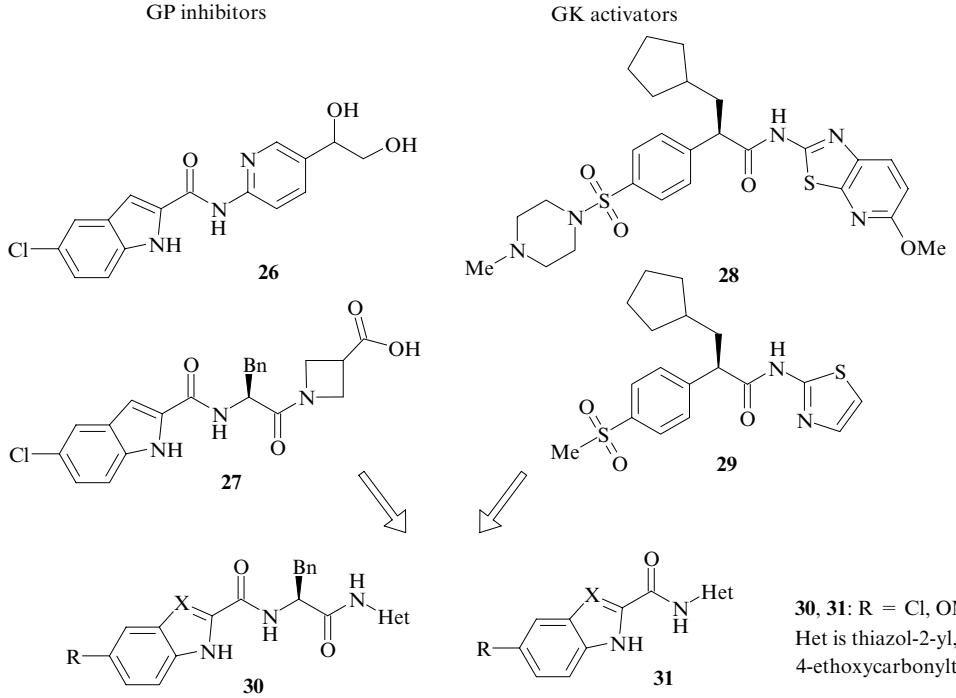


18

19 (MK-767)

20 (*n* = 0 – 2)

Scheme 3



GP inhibitors

GK activators

26

27

28

29

30

31

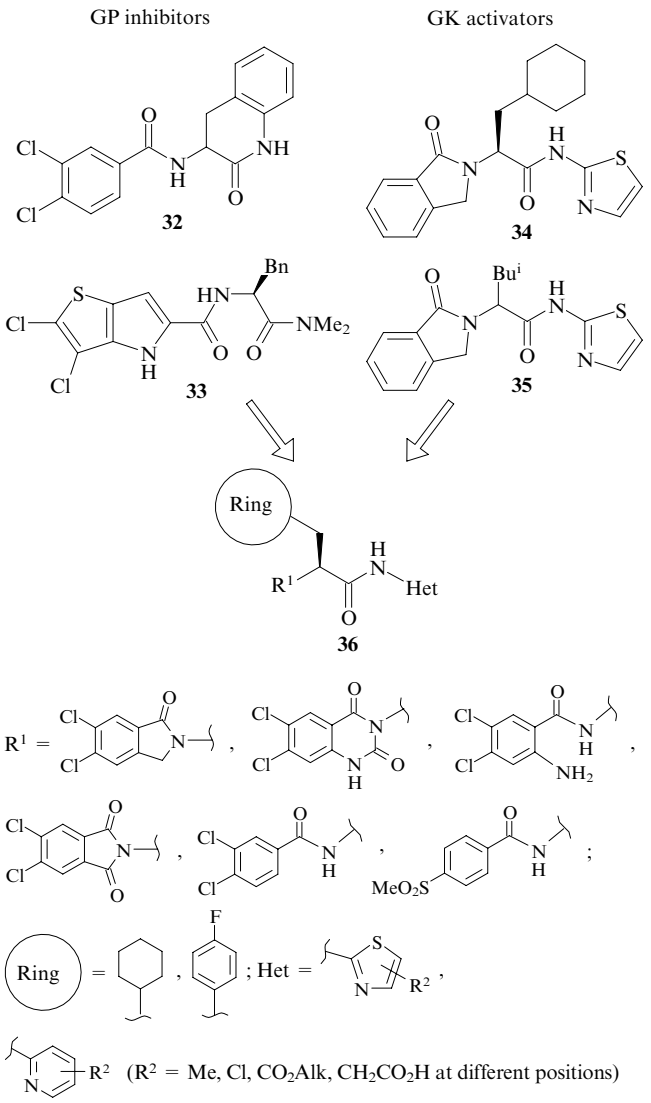
30, **31**: R = Cl, OMe; X = N, CH;
Het is thiazol-2-yl, 5-methoxycarbonylthiazol-2-yl, 4-ethoxycarbonylthiazol-2-yl, 2-Py (Py is pyridyl)

hydrophobic. Zhang *et al.*[51] suggested that the indole ring will provide the most efficient interaction with the enzyme GP and that the 2-aminohetaryl moiety can serve as a GK-activating pharmacophore.

Relying on the analysis of the results and based on the structures of several known ligands for GP (inhibitors **26**, **27**) and GK (activators **28**, **29**), Zhang *et al.*[51] proposed structures **26** and **27** (Scheme 3) as the basis for the design of dual-action drugs. Derivatives **30** and **31** were synthesized by linking the 2-aminoheteroaryl substituent to the indole (X = CH) or benzothiazole (X = S) moiety through a spacer. According to a similar principle, the structure of hybrid molecules of general formula **36** (Scheme 4) was proposed based on a combination of the structures of GP inhibitors (**32**, **33**) and GK activators (**34**, **35**).

Therefore, taking into account the multiplicity of factors that cause disturbance of glucose homeostasis in the human body and induce the development of T2D, as well as examples of MTD, we believe that the design of multifunctional drugs is a promising approach to the treatment of this disease. The development of new hypoglycemic MTD implies the analysis of the structures of the available agents with a known mechanism of action in order to determine the structural similarity or specific features of the chemical structures.

Scheme 4



IV. Sulfonyl group-containing compounds

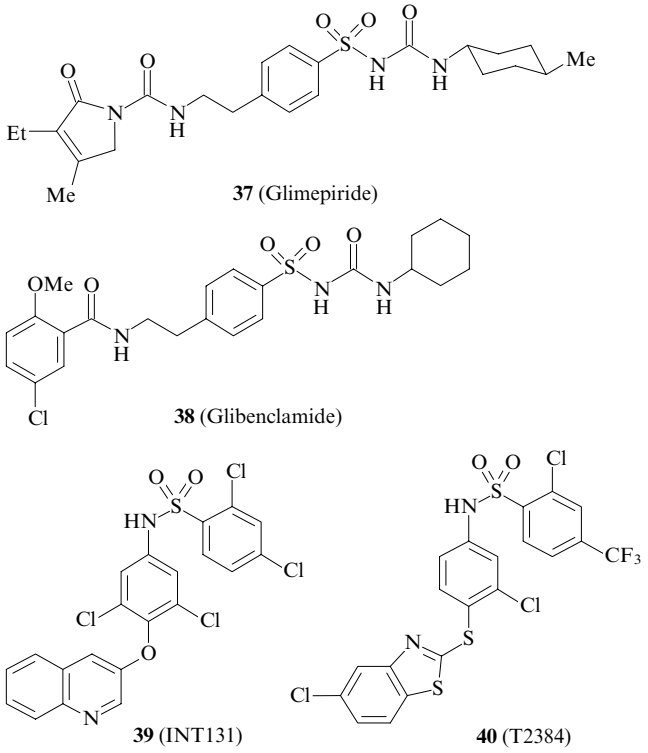
Antidiabetic compounds containing a sulfonyl group are summarized in the review.[34] The review focuses on sulfonamides and sulfones that are associated with 10 molecular targets, the action on which is critical for the regulation of glucose and insulin metabolism.

Sulfonylurea derivatives represent the first class of antidiabetic drugs approved for the medical use. These compounds are insulin secretagogues, which increase insulin secretion from the pancreas. It was found that the sulfonylureas Glimepiride (**37**) and Glibenclamide (**38**) specifically activate PPARγ, induce adipocyte differentiation, *i.e.*, they can act as regulators of not only sulfonylurea receptors but also of PPARγ. The activation level of PPARγ by compounds **37** and **38** is 16% and 25%, respectively, of that for Rosiglitazone. Consequently, these compounds are partial agonists or modulators of this receptor.[52]

When searching for antidiabetic PPARγ agonists containing a sulfonylurea moiety, we found a patent[53] that describes a series of sulfonyl derivatives of cyclohexylurea. The authors of the patent stated that these compounds are full or partial agonists or antagonists of PPARγ; however, they did not report any results of biological assays. Most of the compounds which are described in the patent[53] and which are agonists or modulators of PPARγ belong to sulfonamides.

The drug INT131 (**39**) is a selective PPARγ modulator. It shows a weak stimulation of adipocyte differentiation, enhances glucose tolerance in *Zucker* (*fa*/*fa*) rats and reduces the basal insulin level. The maximal efficacy of this drug is comparable to that of Rosiglitazone. Mean-

Structures 37 – 40

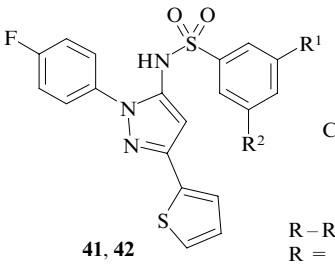


while, compound **39** has much less effect, as compared with other drugs, on heart and lung weights, body weight gain, the volume expansion and the plasma volume. Phase I and II clinical trials demonstrated that this compound is well-tolerated without any serious adverse events, and its antidiabetic activity is similar to that of thiazolidinedione agents.[54 – 56]

The compound T2384 (**40**) exhibited a similar action and proved to be a selective PPARγ ligand.[57] The crystallographic study showed that this agent can bind to the receptor in two different modes primarily *via* hydrophobic contacts, thus being distinct from full agonists. The affinity of the compound T2384 for the receptor was similar to that of Rosiglitazone, but its activating ability was approximately four times lower. Compound **40** inhibited the transactivation of PPARγ and the conversion of preadipocytes into adipocytes induced by Rosiglitazone. In experiments in *KKAy* mice, this compound demonstrated antidiabetic activity comparable to that of Rosiglitazone. Thus, it caused a dose-dependent decrease in plasma glucose levels. Besides, the drug T2384 antagonized the side effects induced by the Rosiglitazone treatment. At all the doses used, it did not cause a body weight gain and anemia. More importantly, the combined use of T2384 and Rosiglitazone decreased these side effects.

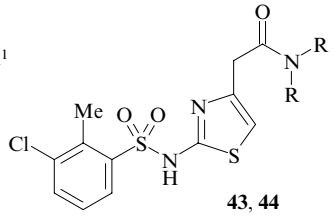
Compounds **41** and **42** were selected using the virtual screening performed by Lu *et al.*[58] These sulfonamides represent a new class of PPARγ ligands and demonstrate high selectivity to this receptor. Compound **41**, which had the best *in vitro* activity, was selected for further investigations. In the assay of adipogenic activity, this compound showed weaker activity compared to Rosiglitazone. The administration of compound **41** to *KKAy* mice led to a 35.7% reduction in glucose level. X-ray diffraction studies demonstrated that compounds **41** and **42** bind to the receptor without the formation of hydrogen bonds, which accounts for a low activation level.

Structures 41 – 45



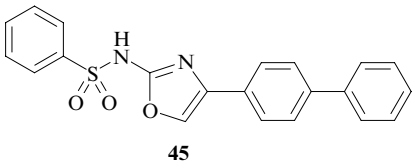
41, **42**

$R^1 = R^2 = CF_3$ (**41**);
$R^1 = F$, $R^2 = H$ (**42**)



43, **44**

R – R = $(CH_2)_2N(Me)(CH_2)_2 \cdot HCl$ (**43**),
R = Et (**44**)



45

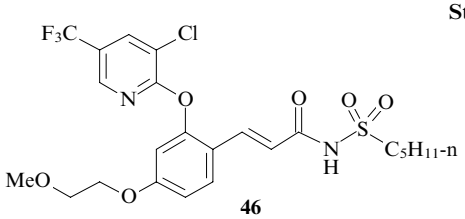
The $Ar-SO_2NH-$ Het5 moiety, where Het5 is a five-membered heterocycle, common to compounds **41** and **42** is present in derivatives **43** – **45**. The latter are inhibitors of the enzyme 11-β-hydroxysteroid dehydrogenase type 1 (11-β-HSD1), which catalyzes the conversion of cortisone to cortisol.[59, 60] The relation of this enzyme to T2D was shown in experiments in transgenic mouse models.[61, 62] The selective inhibition of 11-β-HSD1 holds promise in the treatment of this disease.[63, 64]

A new class of PPARγ agonists, which are neither thiazolidinediones nor carboxylic acids, has been described.[65, 66] Compound **46** was selected based on the analysis of the relationship between the structures of the compounds (the presence and the nature of substituents and functional groups) and the activity. This compound demonstrated high selectivity to the receptor, good metabolic stability and low cytotoxicity.

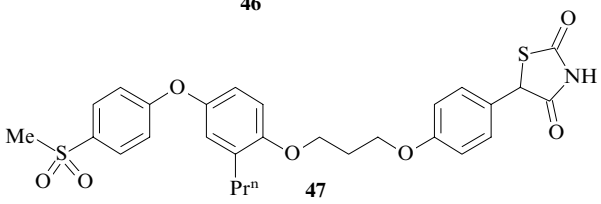
Much more compounds containing a sulfonyl group were studied as DPP-4 inhibitors or agents with a different mechanism of hypoglycemic effect. Compound **47** is an example of sulfones acting as PPARγ ligands.[67] It is highly probable that the agonist activity of this compound against PPARγ is associated with the presence of the TZD moiety; however, analogues of this compound lacking the methylsulfonyl group demonstrated lower bioavailability and(or) ability to activate this receptor.

It should be noted that compound **47** contains the $Ar-SO_2Me$ moiety, which may be present in compounds with a different mechanism of hypoglycemic effect. Thus, the introduction of the methanesulfonyl group into benzimidazole derivative **48** improved the selectivity of the resulting compound to the Ca channel.[68] Glucokinase-activating compounds **49** and **50** (Ref. 69) also contain the

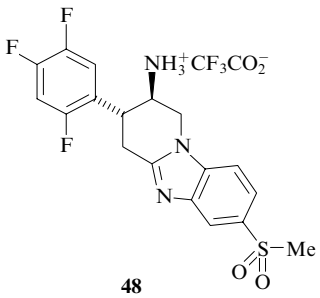
Structures 46 – 50



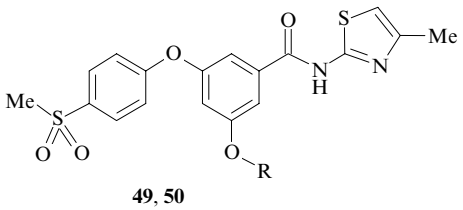
46



47



48



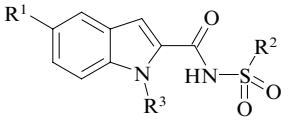
49, **50**

R = Pr^i (**49**), (*S*)-CH(Me)CH_2OH (**50**)

$MeSO_2-Ar-$ OAr moiety, which is present in PPARγ agonist **47**.

Hopkins *et al.*[70] synthesized a series of indole derivatives **51** containing a sulfonyl group. They found that *N*-sulfonyl-2-indole carboxamides are ligands for PPARγ. The study of the structure – activity relationship (SAR) showed that, in order to ensure the maximal binding to the receptor, the substituent R^2 should be aromatic, the substituent R^3 should be the benzyl group substituted at the *meta* position and the heteroaromatic indole ring should be unsubstituted; otherwise, the complete loss of activity takes place. The most potent compound in this series contains the following substituents: $R^1 = H$, $R^2 = 3\text{-}F_3CC_6H_4$, $R^3 = 3\text{-}BnOC_6H_4CH_2$.

Structures 51

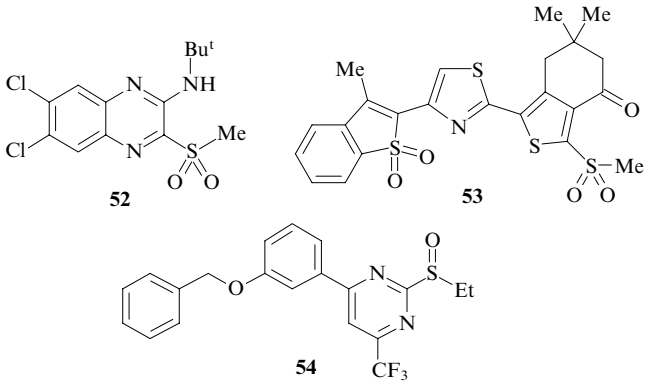


51

R^1 = H, Alk, Hal; R^2 = Ar; R^3 = Alk

Sulfonyl groups are present also in small-molecule GLP-1R agonists, for example in quinoxaline derivative **52**, compound **53** and sulfoxide **54**.[14]

Structures 52 – 54

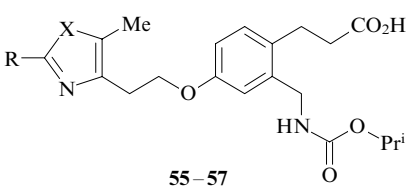


52 **53** **54**

V. Agents based on 3-phenylpropanoic acid

Quite a number of PPARγ ligands were synthesized based on 3-phenylpropanoic acid. Most of these compounds contain substituents at position 2 of propanoic acid. Achiral aminomethyl dihydrocinnamates synthesized by Warshawsky *et al.*[71] are examples of compounds without these substituents. Based on the results of *in vitro* experiments, several derivatives were chosen as selective PPARγ ligands and tested *in vivo* [in *db*/*db* mice and *ZDF* (Zucker diabetic fatty) rats]. All compounds demonstrated good hypoglycemic and hypolipidemic properties, analogues **55** – **57** being most potent.

Structures 55 – 57

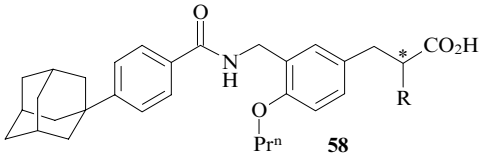


55 – **57**

55: R = 4-PhC_6H_4, X = O; **56**: R is 4-(pyrimidin-2-yl)phenyl, X = O; **57**: R is morpholino, X = S

Ohashi *et al.*[72] synthesized a series of optical isomers of 2-benzyl-substituted phenylpropanoic acid as selective PPARγ agonists starting from PPAR pan-agonist **58** (symbol β indicates the R substituent located above the plane). The *R* isomer of the most potent compound **59** was found to be more active than the *S* isomer. In further investigations, this research team synthesized cyclohexylmethyl [(*R*)-**60**, (*S*)-**60**] and phenethyl derivatives [(*R*)-**61**, (*S*)-**61**].[73] An analysis of their biological activity showed that a substituent at position 2 has a critical effect on the ability of the agent to activate PPARγ. The *R* isomer appeared to be more active in a pair of cyclohexylmethyl derivatives **60**, as well as in the case of benzyl derivative **59**, whereas the *S* isomer of phenethyl analogue **61** was more potent.

Structures 58 – 61



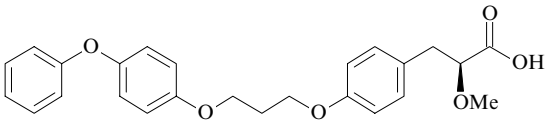
58

R = β-Et (**58**), Bn (**59**), cyclo-$C_6H_{11}CH_2$ (**60**), $Ph(CH_2)_2$ (**61**)

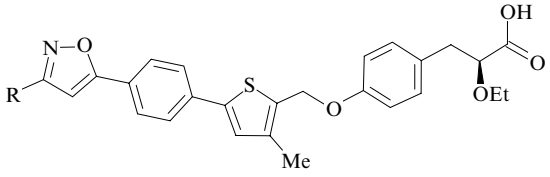
Many PPARγ agonists based on 3-phenylpropanoic acid contain alkoxy substituents at position 2. Martín *et al.*[74] synthesized 2-alkoxy-3-phenylpropanoic acid derivatives, some of which proved to be selective PPARγ agonists. Compound **62** demonstrated the best activity in *ZDF* rats. This compound normalized plasma glucose levels as effectively as Rosiglitazone, but the effective dose of this compound was four times lower.

The promising agents PAR-1622 (**63**) and PAM-1616 (**64**), which are 2-ethoxy derivatives of phenylpropanoic acid, were synthesized and characterized.[75 – 77] The compound PAR-1622 (**63**) is a partial PPARγ agonist. The oral administration of this agent to *db*/*db* mice caused a substantial decrease in glucose level [the effective dose producing 30% inhibition (ED_{30}) was 1.0 mg kg^{-1} per day]. Studies of the effect on the plasma volume in *ICR* mice showed that this compound did not cause hemodilution (volume expansion). The compound PAM-1616 (**64**) significantly improved hyperglycemia in *db*/*db* mice with little side effects.

Structures 62 – 64



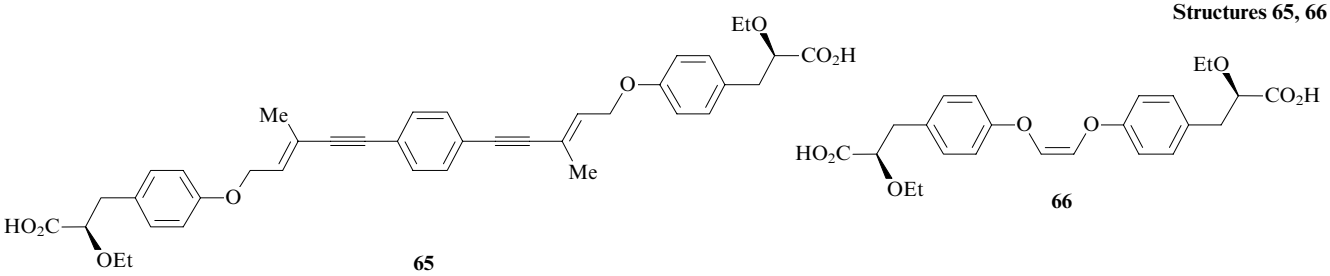
62



63, **64**

R = $MeOCH_2$ (**63**), Me (**64**)

Structures 65, 66



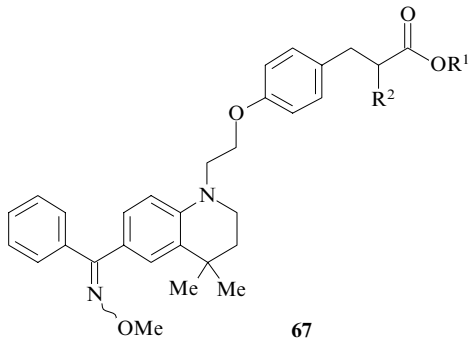
65 **66**

Sauerberg *et al.*[78] synthesized dimeric PPARγ ligands, which retained the agonist activity of the starting compounds against this receptor. According to the results of this study, the level of agonist activity of the ligands and their selectivity strongly depend on the structure. For compound **65**, this value is 119% (EC_{50} = 0.08 μmol litre^{-1}) of the activation level of the receptor by Rosiglitazone. The activity of compound **66**, which proved to be a selective PPARγ agonist, is 56% with EC_{50} = 15 μmol litre^{-1}. This corresponds to the range of values for partial agonists or modulators of the receptor.

It should be noted that, as opposed to compounds **62** – **64** with the *S* configuration of the chiral centre at position 2, the C(2) atom of the phenylpropanoic moiety in dimeric derivatives **65** and **66** has the *R* configuration. Taking into account these data and the activity of compounds **59** – **62**, it can be concluded that the type of the substituent rather than the configuration of the chiral centre plays a more essential role in the manifestation of activity.

The synthesis of a series of PPARγ ligands containing the 4,4-dimethyl-1,2,3,4-tetrahydroquinoline ring as a peripheral moiety was described by Parmenon *et al.*[79,80] In this series, compounds **67** and **68** demonstrated the highest activity and proved to be partial PPARγ agonists.

Structures 67, 68



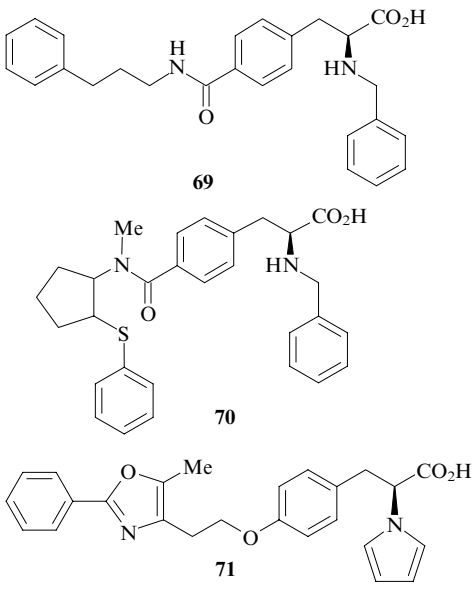
67

R^1 = Me, R^2 = $MeCO_2$ (**67**); R^1 = H, R^2 = 4-BzC_6H_4NH (**68**)

It should be noted that compound **67** did not bind to the receptor in *in vitro* experiments (K_i = 10 000 nmol litre^{-1}) but activated the latter (EC_{50} = 195 nmol litre^{-1}, 74% of the Rosiglitazone activation level). 2-Amino derivative **68** demonstrated high selectivity and affinity for PPARγ and was assigned to partial agonists of the receptor. Since the aim of the study was to find dual PPARα/γ agonists, *in vivo* experiments with compounds **67** and **68** were not performed. The form, in which these compounds were synthesized and tested (either as racemates or mixtures enriched in one of the optical isomers), was not reported.

A series of 2-amino derivatives of 3-phenylpropanoic acid are described in the patent.[81] It was found that these compounds are PPARγ agonists. Analogues **69** and **70** reduced glucose levels in *ZLR* (*Zucker lean rats*) rats. A series of derivatives possessing antidiabetic properties were synthesized from on L-tyrosine.[82] In this series, compound **71** proved to be most potent in rats [*Zucker* (*fa*/*fa*) line]. This compound caused a 40% and 24% reduction in plasma glucose and triglyceride levels, respectively, the high-density lipoprotein level being increased by 31%. The values of EC_{50} and K_i for this compound are 4.7 and 6.9 nmol litre^{-1}, respectively.

Structures 69 – 71



69 **70** **71**

The following regular features are evident from the analysis of the structure – activity relationship for 3-phenylpropanoic acid derivatives. First, all synthetic compounds having agonist activity against PPARγ can be represented by the structure shown in Fig. 1. This structure was reported by Parmenon *et al.*[79] and it is almost fully consistent with the scheme described in the review.[11] Second, in order to ensure the linear structure of the molecule, both linkers should be located in *para* positions of the aromatic ring. Third, in all cases where the 3-phenylpropanecarboxyl moiety contains a substituent at position 2, the C(2) atom has the *S* configuration. Apparently, this is true only for substituents with a small volume because, as it was shown for compounds **60** and **61**, the substituent has a critical effect on the activity of the compound.

In the literature, there are examples of the use of 2-amino-3-phenylpropanoic acid for the synthesis of a series of DPP-4 inhibitors containing a heterocyclic moiety

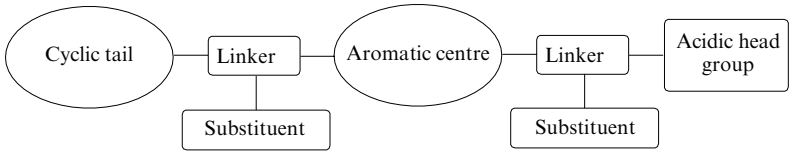
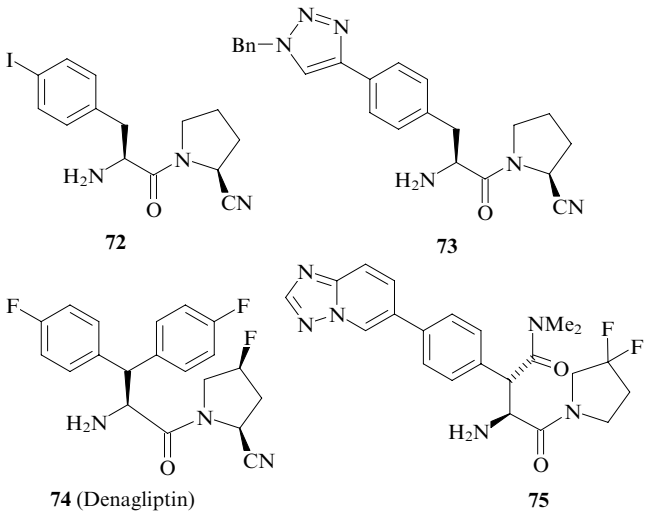


Figure 1. General structure of the typical synthetic PPARγ agonist (taken from the study of Parmenon *et al.*[79]).

attached to the carboxy group to form an amide bond. These are cyanopyrrolidines **72** and **73**, the drug Denagliptin (**74**) and compound **75** suggested as the substitution for the drug Sitagliptin.[83–85]

Structures 72 – 75

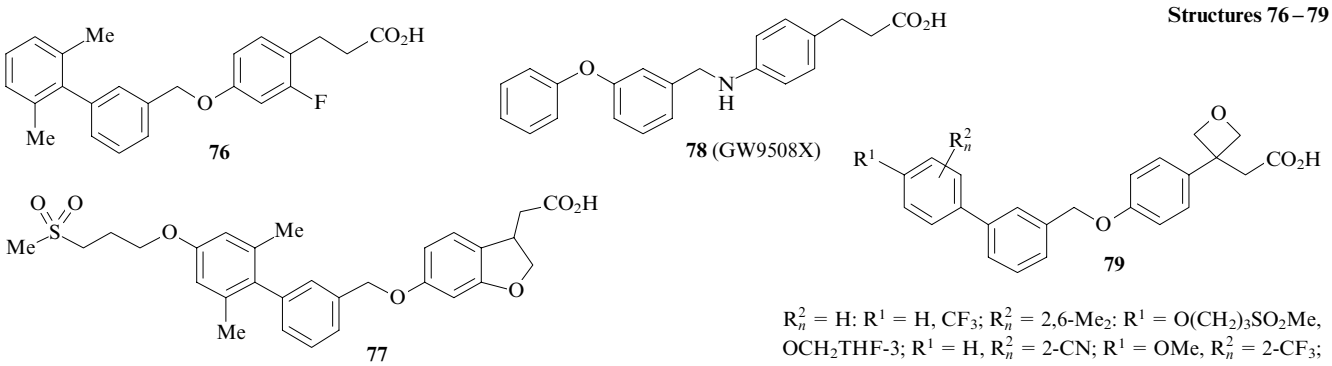


The free fatty acid receptor 1 (FFA1) belonging to G protein-coupled receptors (GPCR) is an important target for drugs that regulate blood glucose levels. It was suggested that the activation of this receptor stimulates insulin secretion depending on the blood glucose level,[86–88] and selective FFA1 agonists can serve as effective hypoglycemic agents.

Negoro *et al.*[89] described the search for the optimal structure of a selective FFA1 agonist. After preliminary experiments, benzyloxyphenylpropanoic acid was selected as the basis. After the structure optimization, the authors obtained compound **76**, which exhibited agonist activity in *in vitro* and *in vivo* experiments. Further modifications of this compound gave structure **77**, in which the β position of the acid aliphatic chain is involved in the heterocycle fused to the aromatic core.

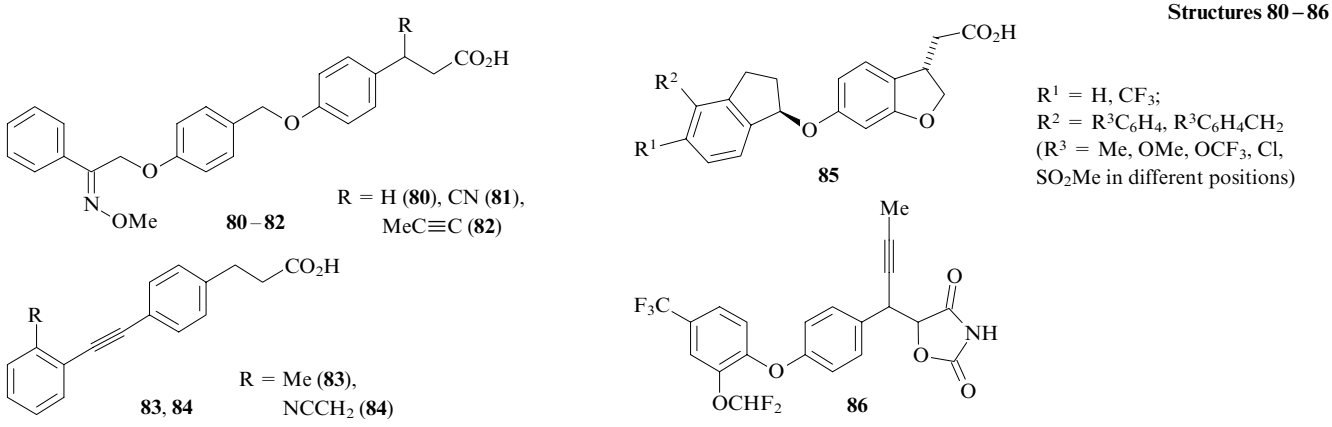
The design of new FFA1 receptor agonists has attracted attention of many research groups. Numerous compounds of this type were synthesized, many of which are currently under preclinical investigations. The structures of some agonists and the data on their efficacy, for example for compounds **78**–**86**, are considered in the review.[90]

Structures 76 – 79



R^2_n = H: R^1 = H, CF_3; R^2_n = 2,6-Me_2: R^1 = $O(CH_2)_3SO_2Me$, OCH_2THF-3; R^1 = H, R^2_n = 2-CN; R^1 = OMe, R^2_n = 2-CF_3; THF is tetrahydrofuryl

Structures 80 – 86



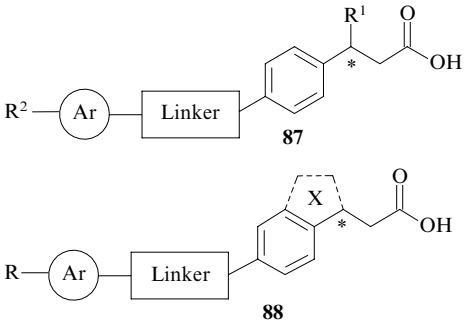


Figure 2. General structures of synthetic FFA1 agonists.[79]

Defossa and Wagner[90] suggested general formulae **87** and **88** to describe pharmacophoric groups of FFA1 agonists (Fig. 2). Low-molecular-mass substituents (R^1 in formula **87**) or cyclic moieties annulated with the aromatic ring (see structure **88**) can serve as linkers between the carboxy group and the aromatic ring. In the presence of such substituents, the configuration of the chiral centre has a considerable effect on the activity because the optical isomers exhibit different activities. The second aromatic moiety is a substituted monocyclic or bicyclic aryl (biaryl) group. The nature of the substituent R^2 may vary in a broad range. This region of the molecule can be modified to optimize the physicochemical properties, such as the polarity of the molecule, solubility and so on. A comparison of the structures of known PPARγ and FFA1 agonists shows their considerable similarity. This fact attests to a high probability of dual action for hypoglycemic agents of the phenylpropanoic acid series.

VI. Compounds containing the indane ring and their heteroanalogues

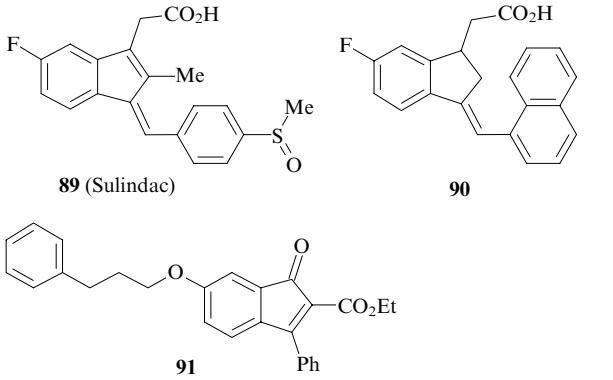
It should be noted that most of compounds described in this section are PPARγ ligands, act as full or partial agonists for this receptor or have a modulatory effect on the receptor. A number of examples of compounds containing the indane ring and exhibiting hypoglycemic activity are given above. Some of these derivatives are FFA1 receptor agonists, DPP-4 inhibitors, glycogen phosphorylase inhibitors and so on.

VI.1. Compounds with aromatic substituents

There are a few derivatives containing the indane ring, the hypoglycemic properties of which were investigated. In most cases, the interactions of these compounds with PPARγ were studied in order to choose the most active and potent agents. Felts *et al.*[91] synthesized a series of PPARγ agonists based on nonsteroidal anti-inflammatory drugs. An example is compound **90** synthesized based on the drug Sulindac (**89**). This compound exhibited pronounced agonist activity towards this receptor (EC_{50} = 0.1 μmol litre^{-1}).

Ahn *et al.*[92] were the first to found that indenones can act as PPARγ agonists. This research team synthesized a series of compounds, which proved to be full agonists of this receptor. Compound **91** was the most potent in this series (EC_{50} = 50 nmol litre^{-1}, 113% of the Rosiglitazone activation level). X-ray diffraction studies demonstrated that this compound binds to the receptor *via* a mechanism different from that of Rosiglitazone.

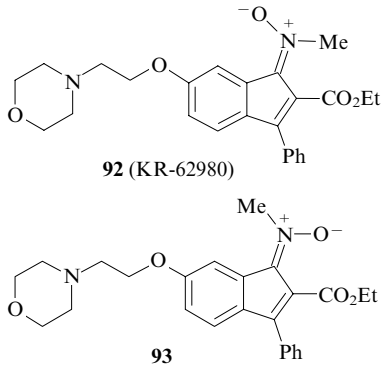
Structures 89 – 91



The investigation of the effect of substituents on the activity of compounds showed that indenones exhibit a cytotoxic effect, whereas indene N-oxides lack this property. Ahn *et al.*[93] studied the structure – activity relationship for a series of indene N-oxide derivatives and found that the methyl group at the N-oxide moiety, the benzylpropoxy group in the benzene ring, the phenyl moiety at position 3 of indene and the ethoxycarbonyl function at position 2 are optimal substituents.

Further investigations showed that the morpholinoethoxy group, which increases water solubility and overall bioavailability of the drug, is most suitable as a substituent in the benzene ring of indene. As a result, Ahn *et al.*[93] synthesized the compound KR-62980 (**92**) (EC_{50} = 15 nmol litre^{-1}, 30% of the Rosiglitazone activation level) as a promising antidiabetic agent. In order to perform the exhaustive analysis of the structure – activity relationship, the authors synthesized its geometric isomer **93**, which exhibited lower activity (EC_{50} = 40 nmol litre^{-1}).

Structures 92, 93



Kim *et al.*[94] investigated the antidiabetic properties of the drug KR-62980 (**92**) and demonstrated that this compound is a selective PPARγ modulator. In 3T3-L1 adipocytes, it induced the uptake of deoxyglucose labelled with tritium in proportion to the insulin level. The benefits of this compound are that it exhibited a weak adipogenic effect and had good bioavailability and biostability. The administration of KR-62980 to *C57BL/6J* mice for 14 days decreased the plasma glucose level with little side effects typical of Rosiglitazone (body weight gain, cardiac hypertrophy and hepatotoxicity).

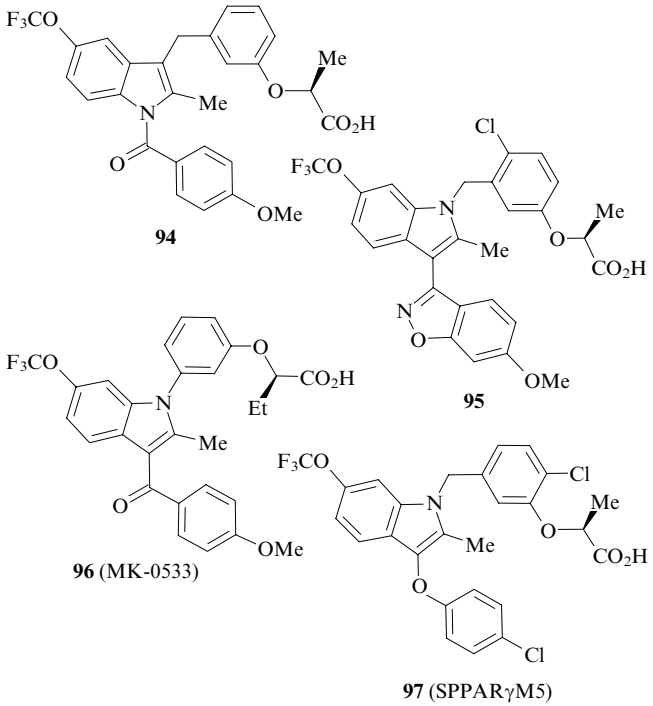
It should be emphasized that all the compounds described above contain either a free or esterified carboxy group. The position of this group in the molecule is such that these compounds can be considered as 3-phenylpropanoic acid derivatives containing rigidly fixed substituents in the α and β positions.

An analysis of the structures of PPARγ agonists **89** – **93** shows their similarity with general formula **88** proposed for FAA1 receptor agonists. These compounds are 3-phenylpropanoic acid derivatives containing cyclic moieties annulated to the aromatic ring. Therefore, it is likely that indane derivatives containing a carboxy group belong to dual-action agents and are promising for the design of multitarget hypoglycemic drugs.

VI.2. Indane analogues containing one heteroatom in the five-membered ring

In a series of studies[95–99] performed at the Merck, approaches to the search for and development of a promising indole-based antidiabetic drug are described. First, researchers synthesized a series of 3-benzyl-2-methylindoles, some of which proved to be selective PPARγ modulators. Compound **94** was shown to be the most promising agent. However, it was found that in the body, this compound is debenzylated to form inactive metabolites. Further modifications produced compound **95** possessing good activity; however, preclinical experiments demonstrated that the application of this compound causes undesirable side effects.

Structures 94 – 97



More recently, Acton III *et al.*[98] proposed the optimal structure of the agent (compound **96**, MK-0533). This compound exhibited hypoglycemic activity in *in vivo* experiments comparable to that of Rosiglitazone and Pioglitazone, while the application of MK-0533 did not cause cardiac hypertrophy, did not stimulate brown adipose tissue growth, caused an insignificant plasma volume expansion and did not increase the extracellular fluid volume.

The selective SPPARγM5 modulator (**97**) is another promising indole-based hypoglycemic drug.[99] This compound caused a 39% decrease in glucose levels and a 37% reduction in insulin levels in *db*/*db* mice. The oral administration of compound **97** to *Zucker* (*fa*/*fa*) rats demonstrated an antidiabetic effect (a decrease in plasma insulin, triglyceride and free fatty acid levels) at a dose of 2 mg kg^{-1}. This compound did not increase the extracellular fluid volume, did not induce cardiac hypertrophy and caused an insignificant increase in the cell cytoplasm (13% – 17%).

As can be seen from the formulae, compounds **94** – **97** have very similar structures. Acton III *et al.*[98] summarized the data on the relationship between the structure and the agonist activity of indole derivatives against PPARγ and presented these data by the formula (Fig. 3). It can be seen that even an insignificant change in the structure of the substituents can lead to a change in the activity against PPAR, in particular, against its γ subtype.

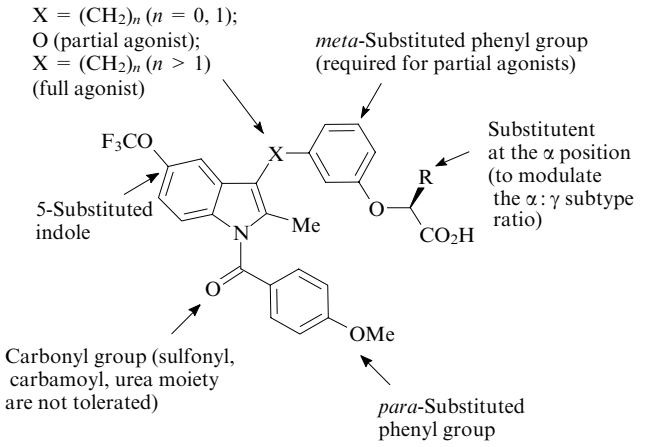
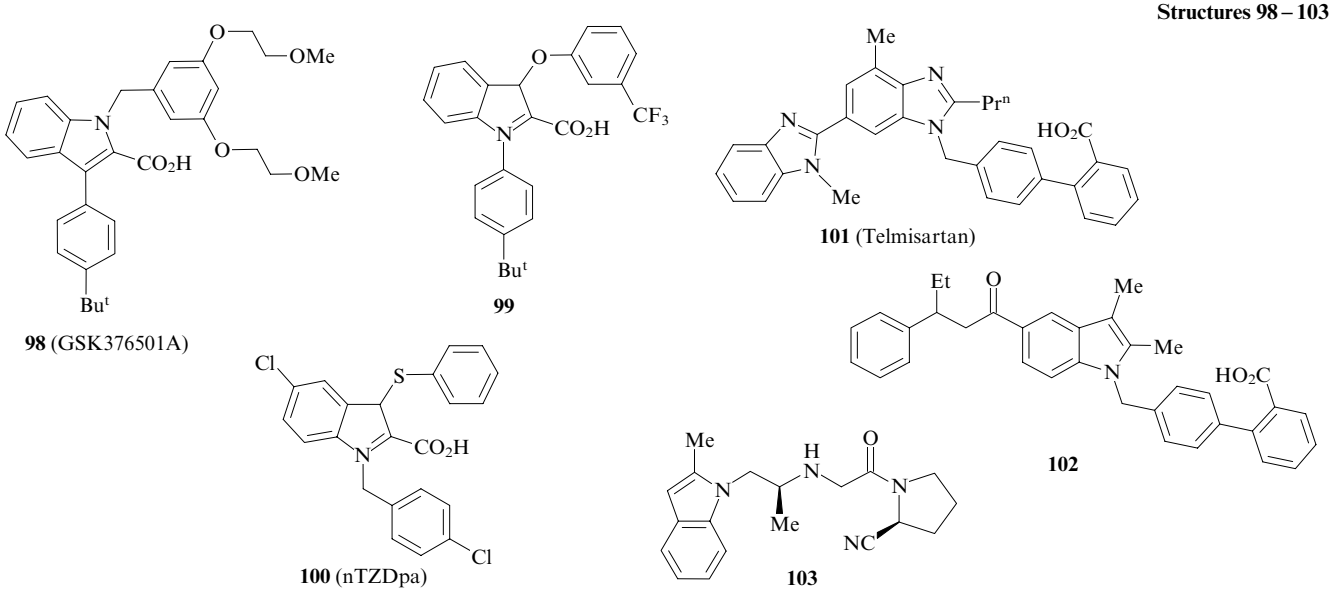


Figure 3. Influence of substituents on the activity of indole derivatives against PPAR (taken from Ref. 98).

Examples of indole derivatives containing the 4-(*tert*-butyl)phenyl substituent and acting as PPARγ agonists are available in the literature. A series of PPARγ modulators are included in the patent.[100] Although the synthesis of 68 compounds was described, the results of biological assays were reported only for six of them. The latter derivatives substantially decreased glucose levels in *ZDF* rats. The optimal synthesis pathway for compound **98** (GSK376501A), which is included in this patent, was described by Bullock *et al.*[101] However, the data on activity of this compound are not presented in the patent.[100] The change in the positions of the 4-(*tert*-butyl)phenyl group and the second aromatic substituent does not lead to the loss of activity of indole derivatives. For instance, compound **99**, which was assigned[102,103] to partial PPARγ agonists (EC_{50} = 13 nmol $litre^{-1}$, K_i = 12 nmol $litre^{-1}$, 31% of the Rosiglitazone activation level), exhibited good antidiabetic properties. This compound caused a 54% decrease in the blood plasma glucose level in mice (*db*/*db* line) compared to the control (Rosiglitazone) with lower body weight gain.

Structures 98 – 103



The compound nTZDpa (**100**) belonging to a new type of PPARγ ligands, was synthesized.[102, 104] This compound partially activated PPARγ (EC_{50} = 57 nmol litre^{-1}, IC_{50} = 12 nmol litre^{-1}, 25% of the Rosiglitazone activation level) with the simultaneous inhibition of Rosiglitazone in the case of their combined use. The treatment of animals (*C57BL/6J* mice fed a high-fat diet) with nTZDpa ameliorated hyperglycemia and hyperinsulinemia with an insignificant body weight gain and adipose tissue inflammation. Besides, the treatment with this agent was not accompanied by the development of cardiac hypertrophy.

A comparison of the structures of nTZDpa (**100**) and compound **94** shows that the phenylthio substituent in the former compound is bound to the indole C(3) atom. However, further investigations of compound **94** were not performed due primarily to its low resistance to metabolism accompanied by the removal of the benzyl group. In the case of the compound nTZDpa, the loss of the PhS moiety does not apparently take place.

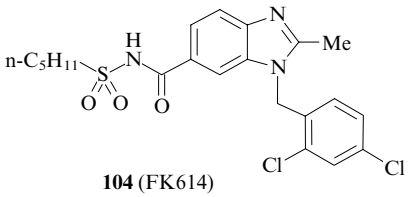
It was shown[105, 106] that the antihypertensive drug Telmisartan (**101**) partially activates PPARγ. High-carbohydrate high-fat diet-fed animals treated with Telmisartan had a ~10% lower body weight gain with a significant decrease in glucose and triglyceride levels compared to the control group. The administration of this compound to *KKAy* mice did not lead to a decrease in the glucose level but substantially reduced insulin, triglyceride and free fatty acid levels.

A series of new selective PPARγ modulators were synthesized based on Telmisartan (**101**). In the series of derivatives prepared by Lamotte *et al.*,[107] compound **102** proved to be most potent. This compound had a new binding mode to the receptor and was as effective as full agonists of this receptor in reducing glucose and triglyceride levels in *in vivo* experiments with less side effects. The values of EC_{50}, K_i and the activation level relative to Rosiglitazone were 0.8 nmol litre^{-1}, 8 nmol litre^{-1} and 31%, respectively.

Cyanopyrrolidines containing the indole moiety have been patented.[108] These compounds exhibited inhibitory activity against DPP-4. Compound **103** proved to be most potent.

The method for the synthesis of the benzimdazole derivative FK614 (**104**) and biological testing of this compound have been described.[109 – 112] The compound FK61 is a selective PPARγ ligand with specific transactivation properties, which are dependent on the environment of coactivators. The administration of the compound FK614 to *db/db* mice led to a significant reduction in the blood plasma glucose level (ED_{50} = 1.3 mg kg^{-1} comparable to the treatment with Rosiglitazone) and triglyceride level. This compound caused a decrease in glucose and insulin levels in *ob/ob* mice and improved glucose tolerance to sequential glucose loading. At the working doses at which PPARγ was activated and the antidiabetic effect was achieved, the drug FK614 (**104**) did not cause side effects and was safer than Rosiglitazone. The treatment of *ZDF* rats with this compound led to the improvement of impaired glucose tolerance and reduction in insulin resistance in peripheral tissues and the liver in a dose-dependent manner. The administration of FK614 to dogs with alloxan-induced diabetes mellitus improved glucose uptake by cells due to an increase in insulin sensitivity.

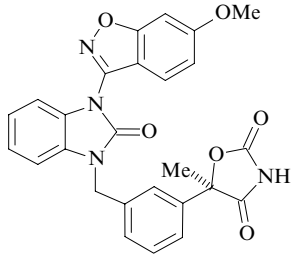
Structure 104



Liu *et al.*[113] synthesized a series of benzimidazolone carboxylic acids and oxazolidinediones. It was shown that the replacement of the indole moiety with the benzimidazolone group leads to a considerable increase in the selectivity to PPARγ. The benzisoxazole moieties were found to be most preferred as substituents. For example, compound **105** proved to be a selective PPARγ modulator (EC_{50} = 360 nmol litre^{-1}, IC_{50} = 83.1 nmol litre^{-1}, 85% of the

Rosiglitazone activation level). This compound exhibited antidiabetic properties comparable to those of Rosiglitazone in *db*/*db* mice and *Zucker* (*fa*/*fa*) rats with less side effects (fluid retention in the body, cardiac hypertrophy).

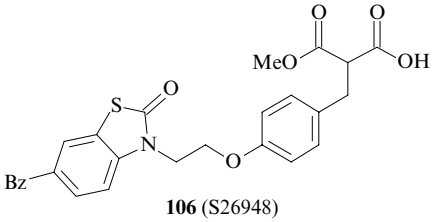
Structure 105



105

A series of 1,3-dicarbonyl compounds containing 2(3*H*)-benzazolonic heterocycles were synthesized and characterized.[114, 115] 6-Acyl-2(3*H*)-benzothiazolone derivatives with the 1,3-dicarbonyl group as the peripheral substituent were shown to be the most potent PPARγ agonists. In this series, monomethyl ester **106** (S26948) exhibited the highest PPARγ-activating ability and selectivity to PPARγ in *in vitro* experiments. This compound reduced blood glucose and triglyceride levels in mice (*ob*/*ob* line).

Structure 106

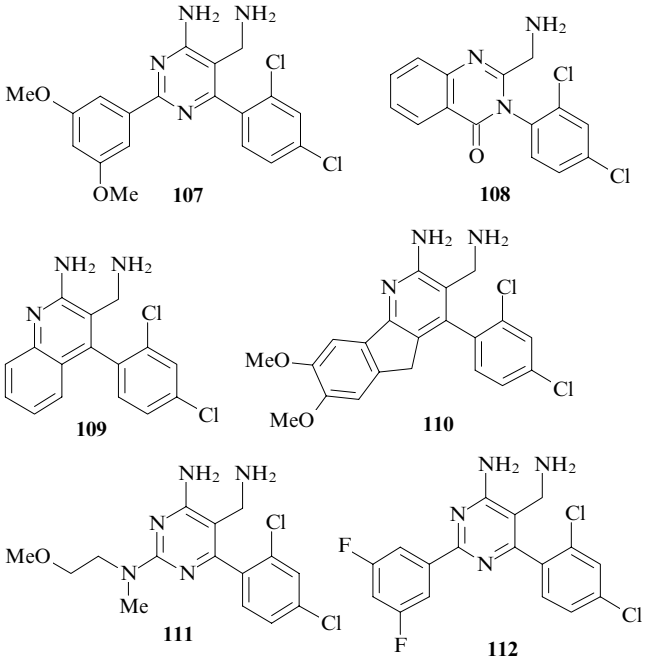


106 (S26948)

The detailed studies in animals (*ob*/*ob* and *db*/*db* mice, *ZDF* rats) showed that compound **106** exhibits pronounced antidiabetic properties without body weight gain or stimulation of adipogenesis. Moreover, this compound effectively corrected dyslipidemia and manifestations of atherosclerosis. However, the mechanism of these effects is unknown. Nevertheless, it should be noted that compound **106** contains the 3-phenylpropanoic acid moiety with a substituent in the *para* position of the aromatic ring. As it was shown in the preceding Section, this moiety is considered as a pharmacophore for ligands of the FFA1 receptor. This fact attests to a high probability of the hypoglycemic effect of compound **106** *via* at least two mechanisms.

Let us analyze the structural similarities between the compounds described in Sections VI.1 and VI.2 and antidiabetic agents with a radically different mechanism of action. Thus, the compound FK614 (**104**) contains the n-pentylsulfonamide moiety, which is present in the structure of compound **46**.[65, 66] Note also that the PPARγ ligands — the compounds FK614 (**104**) and INT131 (**39**) — contain the 2,4-dichlorophenyl group characteristic of many DPP-4 inhibitors (see, for example, compounds **107**–**112**);[116] the PPARγ agonist — the compound T2384 (**40**) — bears the 2-chloro-4-trifluoromethylphenyl moiety similar in the nature to the 2,4-dichlorophenyl group.

Structures 107 – 112



107 **108** **109** **110** **111** **112**

The presence of the 2,4-dichlorophenyl substituent in these compounds promoted a 10 000-fold increase in their inhibitory activity against DPP-4 compared to analogues containing no chlorine atoms. The X-ray diffraction study provided an explanation for the enhancement of activity. According to results of X-ray diffraction, the dichlorophenyl moiety occupies very well the S1 pocket of the enzyme DPP-4.[117] It cannot be ruled out that the compounds INT131 (**39**), FK614 (**104**), *etc*. can simultaneously act as PPARγ agonists and DPP-4 inhibitors.

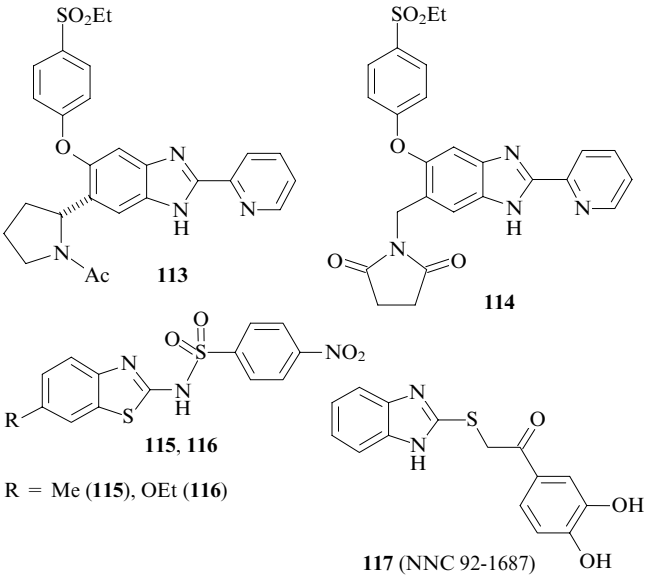
Compound **105** contains the oxazolidinedione ring as a pharmacophore. A series of agents including this heterocycle as the basis are described below (see Section VIII). It was demonstrated that oxazolidinediones can be more active than their thiazolidine analogues. The agent S26948 (**106**) contains the 3-phenylpropanoic acid moiety with the MeOC(O) substituent at position 2 characteristic of a series of compounds considered above. Structure **106** corresponds to the general pattern of the PPARγ agonist shown in Fig. 3.

A general consideration of 'six-membered + five-membered rings' (6 + 5) type compounds demonstrates that in most of these compounds, aromatic substituents are bound to the 6 + 5 core by one linker (either a carbon atom or a heteroatom). Apparently, this is the optimal distance allowing the substituent and the core to be close to each other and simultaneously enabling the rotation of the substituent with respect to the core, due to which the substituent can adopt a configuration favourable for the binding to the receptor.

Some benzimidazole derivatives exhibit a hypoglycemic effect with a different mechanism of action. Thus, compounds **113** and **114** are glucokinase activators.[118, 119] Compounds **115** and **116** are inhibitors of protein tyrosine phosphatase (PTP-1B), which is one of the most attractive targets for the treatment of T2D.[120, 121] The 2-thio-substituted benzimidazole derivative NNC 92-1687 (**117**) acts as

an antagonist of glucagon — the enzyme that causes the release of glycogen and stimulates gluconeogenesis.[122]

Structures 113 – 117



Therefore, numerous promising hypoglycemic agents with a different mechanism of action were synthesized based on indane, indole, benzimidazole and other 6 + 5-type heterocyclic compounds. These are not only full or partial agonists or selective modulators of PPARγ but also DPP-4 and glycogen phosphorylase inhibitors and activators of glucokinase and the FFA1 receptor. Apparently, the indane moiety and its heteroanalogues are not pharmacophores, which selectively interact with a particular receptor; however, their presence makes it possible to control the interaction of the agent with the biological target. Most likely, the arrangement of the substituents with respect to the 6 + 5 core does not play a key role in the activity of the compounds but it may be crucial for metabolic stability. Further investigations aimed at synthesizing new indole derivatives and related bicyclic compounds may lead to the design of compounds having a pronounced activity with small side effects.

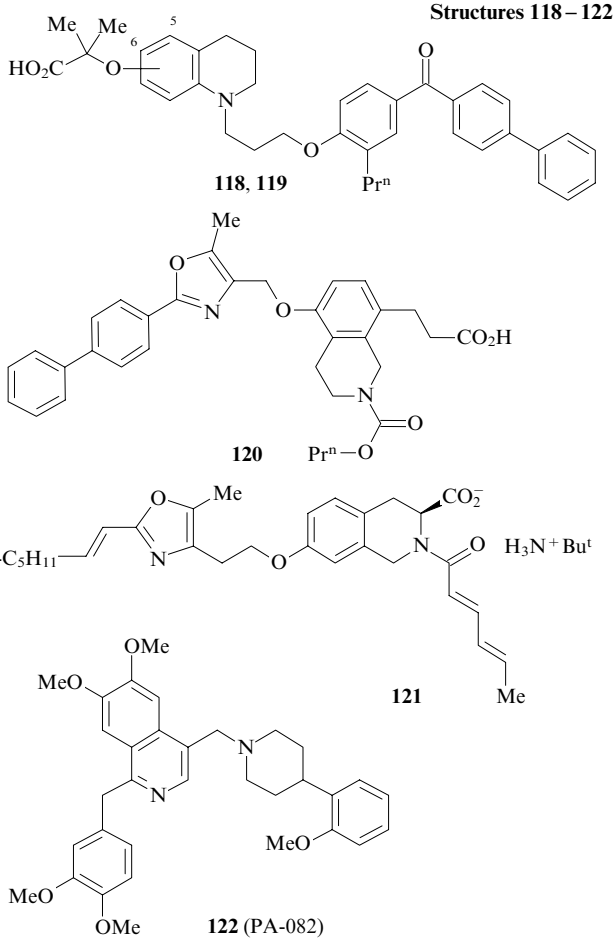
VII. Quinoline, isoquinoline and benzoxazine derivatives

Lin *et al.*[123] modified the known dual PPARα/γ agonist and synthesized a series of 1,2,3,4-tetrahydroquinoline derivatives as selective PPARγ agonists. Compounds **118** (5-isomer) and **119** (6-isomer) proved to be the most potent agents.

Henry *et al.*[124] synthesized a series of new tetrahydroisoquinolines, studied their activity against PPARγ and investigated antidiabetic properties. In this series, compound **120** proved to be a highly selective PPARγ ligand and was chosen for *in vivo* experiments. The administration of this compound to *db*/*db* mice at a dose of 30 mg kg^{-1} per day led to a reduction in the glucose level on the average by 41%. For *ZDF* rats, the minimum effective dose was 0.19 ± 0.09 mg kg^{-1}.

Tetrahydroisoquinoline derivative **121** exhibited the properties of a selective PPARγ agonist (EC_{50} =

Structures 118 – 122



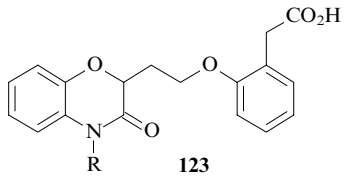
0.03 μmol litre^{-1}, 98% of the Rosiglitazone activation level).[125] Besides, this compound proved to be a PTP-1B inhibitor (IC_{50} = 1.18 μmol litre^{-1}). In a long-term experiment (14 days) in *KKAy* mice, this compound demonstrated the dose-dependent hypoglycemic effect; ED_{50} was 4.3 mg kg^{-1} per day. It was found that the administration of compound **121** to *SD* (Sprague Dawley) rats had no effect on the hematocrit value and red blood cell count as opposed to Rosiglitazone. Taking into account that the action of full PPARγ agonists is usually accompanied by the development of serious side effects, Otake *et al.*[125] concluded that the safer action of compound **121** was apparently attributed to its interactions with several targets.

Burgermeister *et al.*[126] synthesized the isoquinoline PA-082 derivative (**122**). This compound activated the receptor with 40% efficacy compared with Rosiglitazone (EC_{50} = 260 nmol litre^{-1}) and was characterized as a potential selective PPARγ modulator.

The rational design of benzoxazinone-based antidiabetic agents is described in patents and publications.[127 – 131] These studies resulted in the synthesis of new agonists, antagonists and modulators of PPARγ. The general structural formula **123** reflects the structure of the most potent compounds disclosed in the patent[129] (the activity was evaluated based on the ability of the compound to cause the expression of the *aP2* gene involved in lipid metabolism and energy balance). In the cited patent, it was shown that methyl esters of appropriate acids are not active.

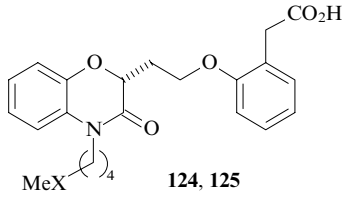
Rybczynski *et al.*[130] found that the introduction of a substituent into the benzoxazine moiety leads to a decrease

Structures 123 – 125



123

R = $F(CH_2)_6$, $HO(CH_2)_7$, *etc.*



124, **125**

X = CH_2 (**124**), O (**125**)

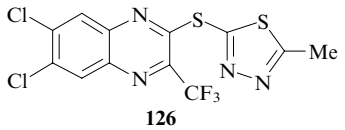
in the activity and that the *ortho* position of the carboxymethyl group in the benzene ring is the optimal one. Derivatives of this series were found to have a hypoglycemic effect, good bioavailability and metabolic stability in *db*/*db* mice.

Rybczynski *et al.*[131] demonstrated that compounds with a long aliphatic chain are most potent, substituted chains being preferred. The fluorine atom and the carbonyl and oxime groups proved to be appropriate substituents, whereas the carboxy or amide groups cause a decrease in the activity of the derivatives. It was also found that the configuration of the chiral centre plays an important role in the activity. Thus, the *R* isomers were shown to be most potent. The administration of the most promising compounds **124** and **125** to mice (*db*/*db* line) led to a dose-dependent decrease in plasma glucose levels.

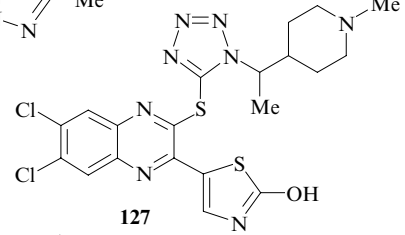
An analysis of the structure – activity relationship for the compounds considered in this Section demonstrates that it is very difficult to reveal molecular structural features and characteristic signs, which could indicate that these compounds belong to PPARγ ligands. Among the above structures, let us mention compounds **118**, **119** and **122** (see also Refs 127 – 131) containing bulky substituents only in the heterocycle and derivatives **120** and **121**, in which a bulky lipophilic moiety is attached to the aromatic heterocycle. Substituents are also quite diverse: linear saturated and unsaturated hydrocarbon chains, moieties with one or several aromatic rings and so on.

The literature data provide evidence that there are numerous hypoglycemic compounds that contain two annulated six-membered rings (6 + 6) and heteroatom(s) in one of the rings and that act on different molecular targets. For instance, the structures of GLP-1R agonists — quinoxalines **52** and **126** – **128** — are described in the review.[14] Compounds **52** and **126** contain small substituents in the quinoxaline moiety, whereas the substituents in the heterocyclic core of analogues **127** and **128** are rather bulky.

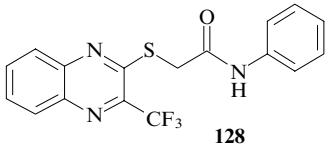
Structures 126 – 128



126



127



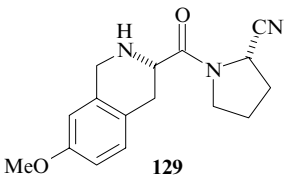
128

A large number of DPP-4 inhibitors based on quinoline and isoquinoline are included in the reviews.[68, 132] Examples are tetrahydroisoquinoline derivatives (**129**), xanthine derivatives (**130**), drug Linagliptin **131** and a series of quinolines and isoquinolines **132** – **135**.

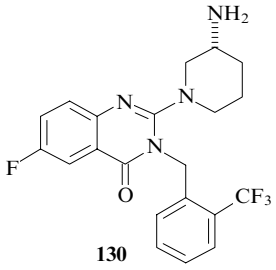
Iino *et al.*[133] described a series of quinazoline derivatives as glucokinase activators. Sulfophenyloxy derivative **136** proved to be the most promising compound in this series.

Consequently, heterocyclic compounds based on benzazines or their hydrogenated analogues hold promise as the starting compounds for the synthesis of potent hypoglycemic agents. It would be expected that slight modifications of the structures of these compound will lead to a change in the mechanism of hypoglycemic action (*i.e.*, the target for these

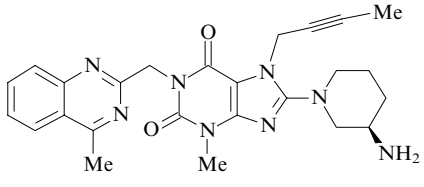
Structures 129 – 136



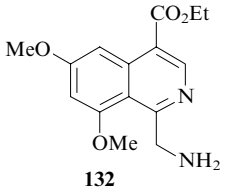
129



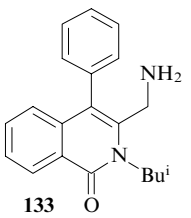
130



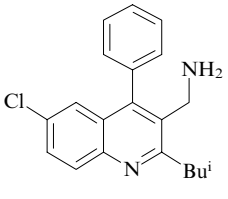
131 (Linagliptin)



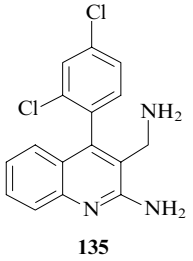
132



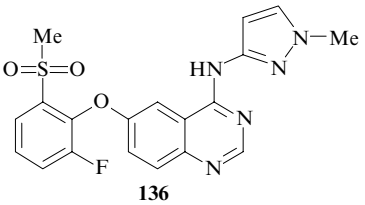
133



134



135



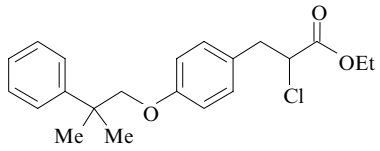
136

agents). These compounds might be multi-target drugs. In our opinion, investigations of the activity of known PPARγ agonists towards DPP-4 and GLP-1R is a useful and important problem (and, on the contrary, it is interesting to establish whether the known DPP-4 inhibitors and GLP-1R agonists are PPARγ agonists). To the best of our knowledge, such examples are lacking in the literature.

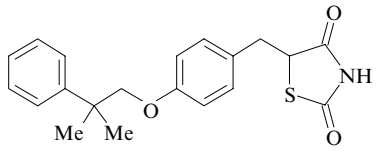
VIII. Compounds containing the thiazolidinedione moiety or its bioisosteres

The history of the development of hypoglycemic drugs based on thiazolidinediones is described in detail in the review.[27] The company Takeda Pharmaceuticals began research on the design of effective TZD-based antidiabetic drugs more than 20 years ago. It was found that the compound AL-294 (**137**), which was initially developed as a hypolipidemic agent, decreases blood sugar levels.[134] Further modifications of the structure of this compound in order to increase its efficacy and selectivity involved the bioisosteric replacement of the carboxy group with a heterocycle. This led to the discovery of the first unique TZD-based drug — AL-321 (**138**).[135]

Structures 137, 138



137 (AL-294)



138 (AL-321)

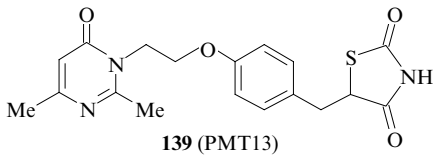
It was suggested that the compound prepared by the replacement of the carboxy group with the TZD moiety interacts with a new, previously unknown target involved in glucose metabolism. The optimization of the structure of this compound and the synthesis of other TZD-containing analogues resulted in the design of commercial drugs, including Rosiglitazone as the most popular and commonly used medication.[136] Compound **1** is the active ingredient of several drugs, some of which are included in top 100 drugs in the U.S. market. Nevertheless, despite the popularity and high activity, thiazolidinediones have a number of serious adverse effects. For instance, the drug Troglitazone was withdrawn from the market soon after the introduction because of numerous reports of hepatotoxicity during the clinical use. Edema, body weight gain and cardiovascular risk factors are other side effects caused by the treatment with TZD.

The PPARγ receptor, which plays a key role in adipogenesis, adipocyte differentiation, lipid and glucose homeostasis, insulin resistance and so on, is a validated target for thiazolidinediones.[137, 138] Due to the close relationship and the direct effect of PPARγ on the development of metabolic syndrome, an important task is to search for agonists of this receptor free of side effects in the body. Recently, it was found that thiazolidinediones are also FFA1 receptor agonist ligands,[139] their activating effect on the receptor is much longer-term compared with the known FFA1 ligands — lauric acid and the compound GW9508X (**78**). This observation suggests that derivatives containing the thiazolidinedione moiety or its bioisosteres can be assigned to multifunctional agents.

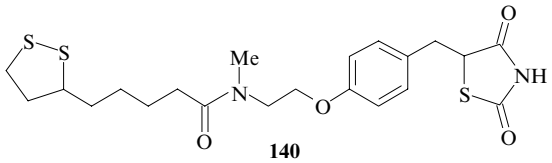
Ligands for PPARγ are considered in a number of reviews (see, for example, reviews [10, 27, 28]). Most of the ligands based on thiazolidinedione have the following structure: an aromatic ring containing a substituent at the *para* position is linked to the heterocyclic TZD moiety through a methylene group or a =CH bond. Meanwhile, ligands that have a different structure are also available. For instance, sulfonyl-containing TZD, in which a heterocyclic moiety is attached to the aromatic ring without a linker (see compound **47**), have been reported.[67]

Madhavan *et al.*[140] synthesized the hybrid molecule PMT13 (**139**), which combines the pyrimidinone and thiazolidinedione moieties, and studied its hypoglycemic properties. It was found that the efficacy of this compound is equivalent to that of Rosiglitazone. The administration of PMT13 to *db*/*db* mice led to a more pronounced reduction in blood plasma glucose and triglyceride levels compared to Rosiglitazone and Pioglitazone. The treatment of *Wistar* rats with this compound did not cause side effects.

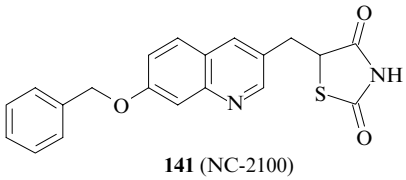
Structures 139 – 141



139 (PMT13)



140



141 (NC-2100)

α-Lipoic acid-based compound **140** activated PPARγ but it reduced only plasma triglyceride levels in *Zucker* (*fa*/*fa*) rats, while the plasma glucose level remained unchanged.[141] Chittiboyina *et al.*[141] attributed the absence of the hypoglycemic effect of this drug to the fact that mutations in *fa*/*fa* animals lead to a decrease in the affinity of lipoic acid-based ligands. These authors suggested that the hypoglycemic effect should be studied in high-fat diet-fed animals.

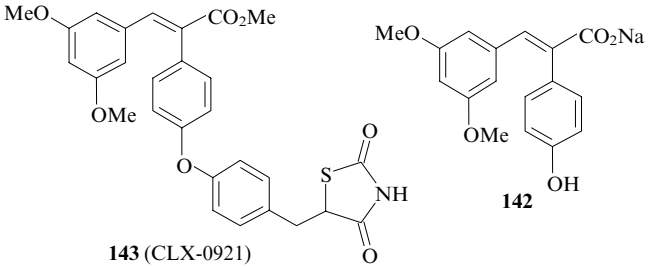
The compound NC-2100 (**141**) containing the TZD moiety attached to two fused aromatic rings (quinoline core)[142] is also inconsistent with the general structural pattern of TZD agonists for PPARγ. Investigations of the properties of compound **141** showed that the latter activates both PPARγ and PPARα in CV-1 line cells. Nevertheless, only the γ-subtype of the PPA receptor was activated in *KKAy* mice with EC_{50} 10 – 30 times higher compared to the reference compound (Pioglitazone). Despite a low ability of compound **141** to activate PPARγ, the administration of

this compound to *KKAy* mice even at low doses led to a decrease in blood glucose levels in the animals. Besides, this drug caused an insignificant body weight gain and adipose tissue accumulation. This behaviour may indicate that the hypoglycemic effect of the agent NC-2100 (**141**) is associated not only with agonist properties with respect to PPARγ but also with its interaction with other biological targets.

A very interesting and, in our opinion, promising approach to the search for new antidiabetic agents was proposed in the studies,[143, 144] in which derivatives of 2-phenyl-substituted cinnamic acid were synthesized and their hypoglycemic properties were evaluated. It was found that compounds having a double bond in the *E* configuration are the most potent agents in this series, whereas *Z* isomers or their analogues with the reduced double bond exhibit much lower activity, if at all.

The thiazolidinedione heterocycle was attached to the salt of 2-(4-hydroxyphenyl)cinnamic acid **142**, which exhibited weak hypoglycemic properties. Despite low *in vitro* activity, the resulting compound CLX-0921 (**143**) had a significant hypoglycemic effect in *ob*/*ob* mice, a decrease in plasma triglyceride and fatty acid levels being observed. The hypoglycemic effect of CLX-0921 was confirmed in experiments in *ZDF* rats and *db*/*db* mice. In all experiments in animals, no body weight gain was observed, except for *ZDF* rats, in which the weight gain was 13%.

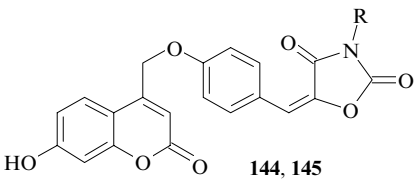
Structures 142, 143



143 (CLX-0921) **142**

A similar approach to the synthesis of hypoglycemic compounds was employed by Shukla *et al.*[145] This research group prepared a series of coumarin derivatives containing TZD and its bioisosteres, such as the oxazolidinedione and imidazolidinedione moieties. In *in vivo* experiments (*Wistar male* rats with Streptozotocin-induced diabetes), the derivatives containing the oxazolidinedione moiety proved to be more effective than those containing the thiazolidinedione or imidazolidinedione moiety. In the series of the synthesized compounds, compounds **144** and **145** were found to be most potent. This study is a good illustration of the rational design of new drugs through the attachment of a known pharmacophore to a natural moiety.

Structures 144, 145



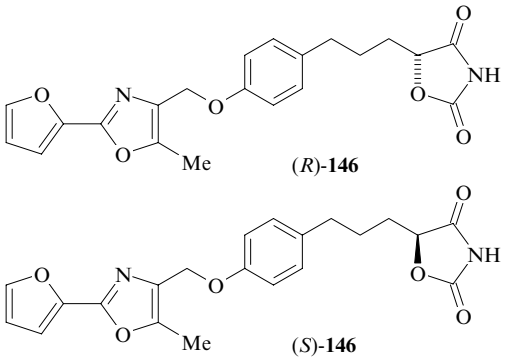
144, **145**

R = H (**144**), Bn (**145**)

Momose *et al.*[146] found that oxazolidinedione derivatives can be more active than the corresponding TZD. Two new classes of thiazolidine-2,4-diones and oxazolidine-2,4-diones containing the ω-(azolylalkoxyphenyl)alkyl substituent at position 5 were synthesized and their hypoglycemic properties were evaluated. In this series, compound **146** was the most interesting and potent. Both stereoisomers of this compound were synthesized. Further investigations demonstrated that epimer (*R*)-(+)-**146** has a stronger hypoglycemic effect in *KKAy* mice (ED_{25} = 0.56 mg kg^{-1} per day *versus* more than 1.5 mg kg^{-1} per day for the *S* isomer) and *Wistar* rats (ED_{25} = 0.05 and 0.362 mg kg^{-1} per day). The authors of the cited study attributed the antidiabetic properties of this compound to its ability to activate PPARγ. In all experiments, the isomer (*R*)-(+)-**146** was more active than Pioglitazone used as the standard.

Despite the fact that similar results were obtained in other studies,[145, 146] it should be noted that there are significant differences between the structure of compound **146** and the structures of oxazolidinedione derivatives **144** and **145**. First, the heterocycle contains a tertiary carbon atom giving rise to a chiral centre. Second, the oxazolidinedione moiety of compound **146** is linked to the aromatic core by a bridge of three CH_2 groups, whereas most of TZD agents contain a CH_2 or =CH group as a linker.

Structures 146

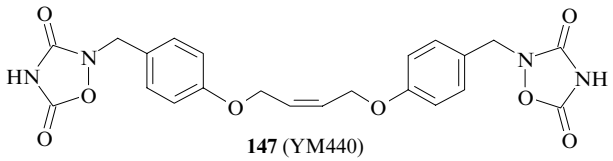


(*R*)-**146**

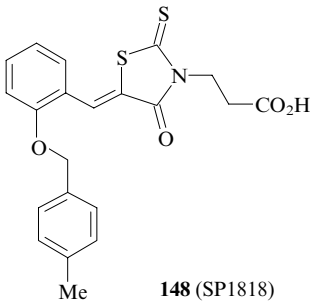
(*S*)-**146**

Interesting results were obtained by Shimaya and coworkers.[147, 148] The authors synthesized the compound YM440 (**147**), which insignificantly activated the PPARγ receptor (EC_{50} = 110 μmol $litre^{-1}$) but was bound to the latter with the affinity (K_i = 4.0 μmol $litre^{-1}$) comparable to that of Troglitazone and Pioglitazone (K_i = 3.1 μmol $litre^{-1}$). The hypoglycemic activity of the compound YM440 in *db*/*db* mice was comparable to the activity of

Structures 147, 148



147 (YM440)



148 (SP1818)

the thiazolidinedione drugs Troglitazone and Pioglitazone, but the administration of this drug did not cause a body weight gain. The hypoglycemic effect was observed 7 days after the administration of the agent was stopped, whereas the action of the reference drugs Rosiglitazone and Troglitazone ceased much faster.

It was demonstrated that PPARγ agonists can be synthesized based on rhodanine.[149–151] The 5-benzylidene moiety was shown to be required for the binding of this class of compounds to the receptor. The presence of simple substituents (OMe, OEt, 2-carboxyfuryl, aminocarbonylmethoxy) in this moiety has no effect on the activity of the compound but the introduction of the arylalkyl group gives rise to the activating ability and increases the affinity for the receptor. The ability of the drug to bind to the receptor is also influenced by the length of the chain containing the carboxy group. It was found that the trimethylene chain is the group of choice. The authors studied the binding mechanism of rhodanine derivatives to the receptor and demonstrated that electrostatic interactions of the carboxyethyl group play an important role in this process, whereas the function of the rhodanine heterocycle in the binding to PPARγ is somewhat different from that of the thiazolidinedione moiety. A series of derivatives were synthesized and the most potent and promising compound SP1818 (**148**) was characterized. This compound was found to be a selective partial receptor agonist; the activation level was 70% ($EC_{50} \sim 1$ μmol litre^{-1}) of the Rosiglitazone activation level. Experimens in 3T3-L1 cells demonstrated that the agent SP 1818 significantly stimulates glucose metabolism in adipose tissue. Park *et al.*[151] also believed that this compound interacts with a receptor site different from that for Rosiglitazone and more weakly stimulates adipocyte differentiation, resulting is less side effects (in particular, lower body weight gain).

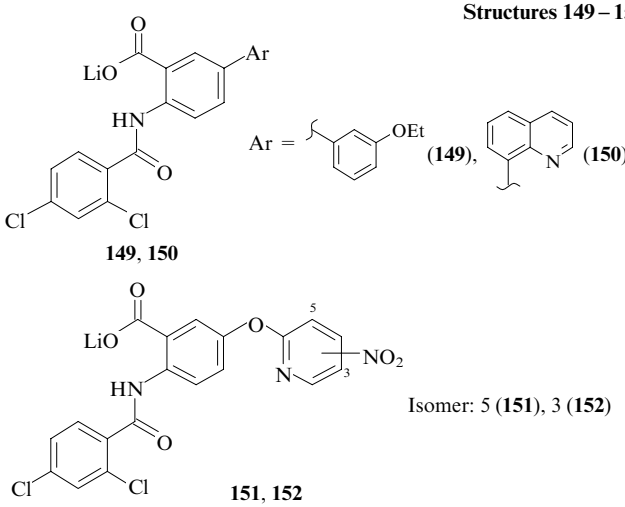
Therefore, thiazolidinediones, the pharmacological action of which is accompanied by effects that are not typical of selective PPARγ agonists (reduction in glucose levels in the absence of body weight gain, low activity against PPARγ with a pronounced hypoglycemic effect and so on) have been reported. It is quite probable that the overall hypoglycemic effect of some compounds described in this section, which have low affinity for PPARγ, is associated with the interaction with the FFA1 receptor or other targets. This fact should be taken into account in the design of new thiazolidinedione-based antidiabetic drugs.

IX. Miscellaneous compounds

Thor *et al.*[152] synthesized a series of salts of 5-substituted 2-benzoylaminobenzoic acids acting as both dual PPARα/γ agonists and selective PPARγ agonists. Compounds **149** – **152** proved to be the most potent PPARγ agonists. It was shown that these compounds interact with the active site different from that for Rosiglitazone. These compounds contain the 2,4-dichlorophenyl moiety, which is present in many DPP-4 inhibitors.

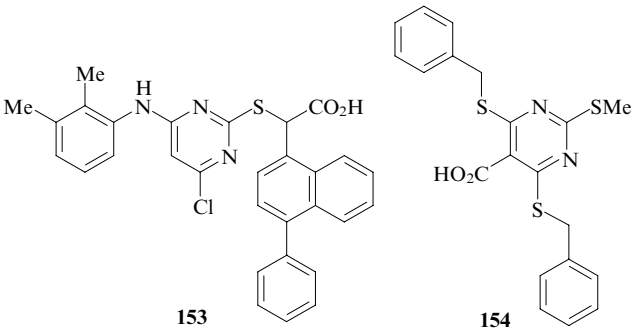
Pyrimidine derivatives **153** and **154** (Refs 153 and 154, respectively) are PPARγ agonists structurally similar to DPP-4 inhibitors. Thieme *et al.*[153] demonstrated that compound **153** belongs to selective PPARγ modulators; the activation level of PPARγ is 45% with EC_{50} = 4.5 μmol litre^{-1}. It was found that the binding mode of

Structures 149 – 152



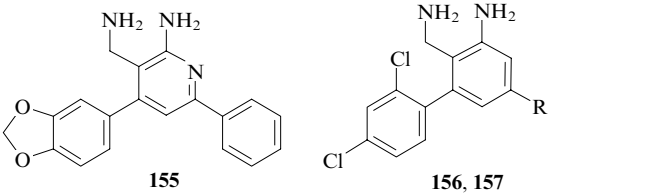
compound **154** to the receptor is different from that of full agonists. This compound exhibited an excellent hypoglycemic effect in *db*/*db* mice but it caused a body weight gain as the side effect comparable to that of Rosiglitazone.

Structures 153, 154



Compounds **153** and **154** are structurally similar to aminomethylpyrimidine DPP-4 inhibitors **155** – **157** considered in the review.[132] The main feature of these compounds is the presence of the aminomethyl function adjacent to the amino group in the pyrimidine ring. Although the aminomethyl substituent is absent in compounds **153** and **154**, their hypoglycemic effect is associated not only with the agonist activity against PPARγ but also with the inhibitory activity against DPP-4.

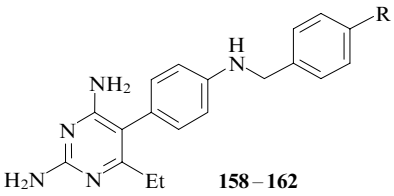
Structures 155 – 157



R = Ph (**156**), N(Me)$(CH_2)_2$OMe (**157**)

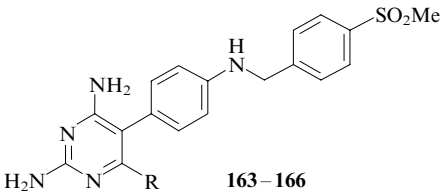
An extensive series of diaminopyrimidines, for example compounds **158** – **166**, which are ghrelin receptor antagonists, were synthesized.[155–157] The polypeptide ghrelin and its receptor play a key role in glucose homeostasis, and the use of receptor antagonists holds promise for the treatment of type 2 diabetes.[158, 159]

Structures 158 – 169

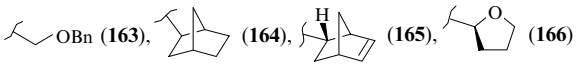


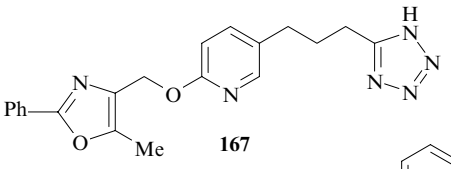
158 – 162

R = Cl (**158**), SO_2Me (**159**), NO_2 (**160**), CN (**161**), CH(Me)OH (**162**)

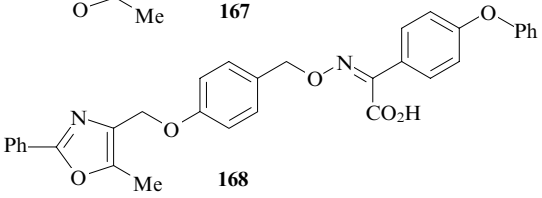


163 – 166

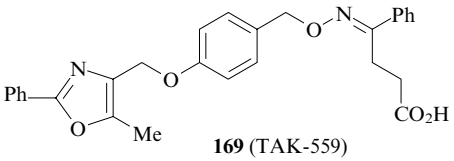
R =  (**163**), (**164**), (**165**), (**166**)



167



168



169 (TAK-559)

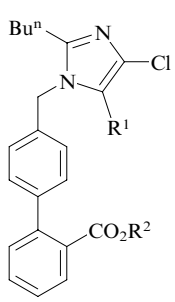
Takeda researchers[160] synthesized a series of 5-(4-alkoxyarylalkyl)-1*H*-tetrazole derivatives and demonstrated that these compounds have high hypoglycemic activity. Compound **167** proved to be the most potent agent. It activated PPARγ at low doses and reduced plasma glucose and triglycride levels in *KKAy* mice (ED_{25} = 0.084 and 0.13 mg kg^{-1} per day, respectively) and *Wistar Fatty* rats (ED_{25} = 0.0873 and 0.0277 mg kg^{-1} per day, respectively).

In further studies, this research team synthesized oxyiminoacetic acid derivatives.[161, 162] Relying on the structure of compound **168**, which exhibited a good antidiabetic effect in *KKAy* mice, the authors analyzed the structure – activity relationship and found that the insertion of a carbon chain between the imine nitrogen atom and the carboxy group leads to a considerable enhancement of the activity against PPARγ. The administration of the resulting compound **169** (TAK-559) to *KKAy* mice substantially reduced plasma glucose and triglyceride levels without body weight gain. Besides, this compound had good bioavailability after oral administration.

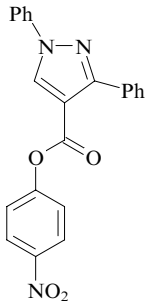
A comparison of the structures of compounds **167 – 169** shows that all these compounds fit within the general formula of PPARγ ligands. These molecules have a lipophilic aromatic tail, an aromatic core in the centre with the 1,4-arrangement of the substituents and a polar head group. Compound **169** contains a butanoic acid with an imine substituent at the C(3) atom as a polar head group. This group can be considered as an analogue of FFA1-activating 3-phenylpropanoic acids described above. Apparently, other effective hypoglycemic drugs will be prepared by means of further modifications of this compound.

The synthesis of a series of imidazole derivatives as selective PPARγ agonists is included in the patent.[163] According to the results of biological assays, all compounds were inactive against PPARα; imidazoles **170 – 174** proved to be the most potent selective PPARγ agonists.

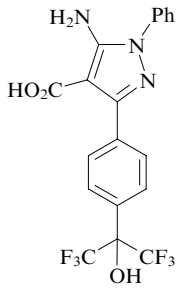
Structures 170 – 176



170 – 174



175 (SP3415)



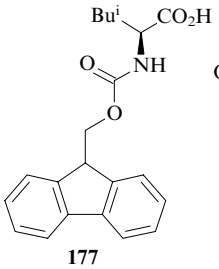
176

R^1 is dioxolan-2-yl: R^2 = H (**170**), Me (**171**);
R^2 = Me: R^1 = CHO (**172**), CH_2OBn (**173**), CH=NBn (**174**)

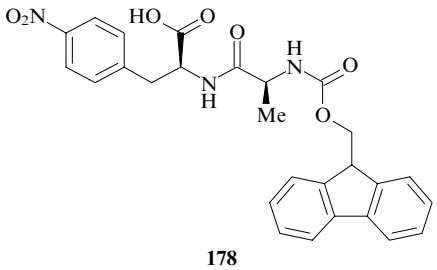
Choi *et al.*[164] characterized the compound SP3415 (**175**) as a partial PPARγ agonist. This pyrazole derivative has high affinity for the receptor, but its agonist properties are rather weak. In the case of the combined action with Rosiglitazone, the agent SP3415 inactivates the agonist effect of the former. The structurally similar compound is described in the patent,[165] the authors of which synthesized malonyl-coenzyme A decarboxylase (MCD) inhibitors. This enzyme plays a key role in lipid and glucose metabolism and its inhibition provides an approach to the treatment of diabetes and obesity.[166] Among the compounds which are listed in this patent and are considered as potent MCD inhibitors, let us mention pyrazole **176** containing two aryl moieties and the carboxy function as substituents.

The compound Fmoc-L-leucine **177** (Fmoc is 9-fluorenylmethoxycarbonyl) is one of the first selective PPARγ modulators.[167] It was found that two molecules of this ligand are required for the binding to one receptor molecule. This compound is a weak activator but it is a strong insulin sensitizer and has a weak adipogenic effect compared to thiazolidinediones. We found no structures analogous to compounds **177** among DPP-4 inhibitors and

Structures 177, 178



177

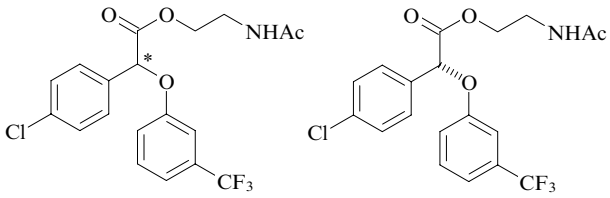


178

GLP-1R agonists; however, examples of the synthesis of Fmoc derivatives of amino acids as PPAR agonists (compound **178**) and anti-inflammatory agents are available in the literature.[168, 169]

Halofenate (**179**) is a known drug with an alternative treatment. Clinical trials of a racemic mixture of this drug as a hypolipidemic and hypouricemic agent demonstrated that this drug significantly decreases glucose and insulin levels in patients with diabetes but not in patients with normal glucose levels. Allen *et al.*[170] found that this compound is a selective PPARγ modulator. It rapidly decreases glucose and insulin levels in *ob*/*ob* mice. The long-term administration (28 days) of this compound to insulin-resistant rats enhances insulin sensitivity comparable to Rosiglitazone, but it does not cause body weight gain in animals. The compound MBX-102 (**180**) is an optically active (−)-isomer of Halofenate and has all properties inherent in the latter. Compound **180** is presently under clinical trials both as an antidiabetic agent and a drug for the treatment of gout.[171]

Structures 179, 180

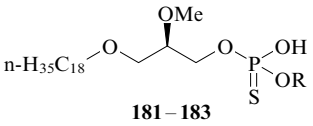


179 (Halofenate) **180** (MBX-102)

Liberato *et al.*[172] determined the crystal structure of the PPARγ domain that binds to the receptor ligand and found that the ligand-binding pocket can be occupied by medium-chain fatty acids. The authors confirmed that C8:0 – C10:0 acids bind to the PPARγ domain in an *in vitro* experiment and demonstrated that these acids are low-potent partial receptor agonists.

A series of analogues of lysophosphatidic acid, which are LPA_3 receptor ligands, were synthesized in order to determine the structure – activity relationship. It was found that some of these compounds (for example, thiophosphates **181** – **183**) act as PPARγ agonists and also as activators that are only slightly less effictive than Rosiglitazone.[173 – 175]

Structures 181 – 183

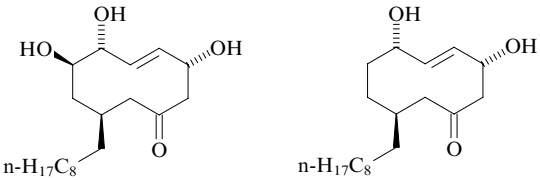


181 – **183**

R = Me (**181**), Bu^n (**182**), cyclo-C_6H_{11} (**183**)

Several antidiabetic agents were proposed based on natural compounds. For example, the lactones seimatopolide A (**184**) and seimatopolide B (**185**) isolated from the extract of the plant *Seimatosporium discosioides* proved to be PPARγ agonists.[176] The EC_{50} values for these compounds are 1.15 and 11.05 μmol litre^{-1}, respectively.

Structures 184, 185



184 (seimatopolide A) **185** (seimatopolide B)

Bhalla *et al.*[177] demonstrated that *N*-acetylfarnezidecysteine (AFC, **186**) is either a full or partial PPARγ agonist. The administration of AFC to mice with diabetes induced by feeding high-fat diet led to a substantial decrease in glucose level. In this case, the body weight gain in animals was 5.8%, whereas the body weight gain in mice treated with Rosiglitazone was 14%.

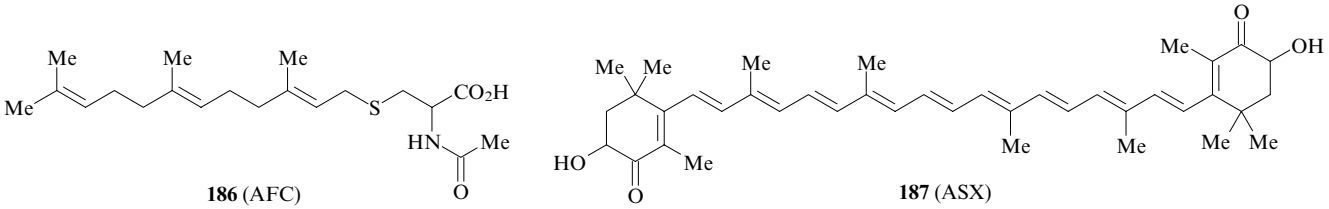
The carotenoid astaxanthin (ASX, **187**) binds to PPARγ in a dose-dependent manner, but it does not cause activation of the reporter gene under the control of PPARγ, although it inhibited the PPARγ-dependent expression induced by Rosiglitazone. The compound ASX did not stimulate 3T3-L1 cell differentiation but inhibited the differentiation induced by Rosiglitazone. Therefore, it was concluded that ASX is a PPARγ modulator, the action of which depends on the cellular microenvironment.

The structures of compounds **181** – **187**, which are PPARγ ligands, and the character of their hypoglycemic effect that differs from that of Rosiglitazone suggest that these compounds can act as activators of the FFA1 receptor or exhibit a hypoglycemic effect but with a different mechanism.

* * *

An analysis of the literature data shows that many hypoglycemic compounds that act on different biological targets contain similar or even identical structural moieties responsible for biological activity. Taking into account the fact that the agent can interact simultaneously with several targets, the search for new hypoglycemic drugs should not be limited to testing the activity of compounds for one of the targets. Apparently, the affinity of the molecules for other targets should be at least calculated, if it is possible. In our opinion, the screening in *in vitro* experiments is the approach of choice.

Structures 186, 187



186 (AFC) **187** (ASX)

Type 2 diabetes is a disease associated with the complex impairment of glucose metabolism and causing many complications. Therefore, the synthesis of multifunctional agents seems to be a promising approach to the rational design of new effective drugs for the treatment of this disease. The synthesis of compounds containing a combination of different pharmacophores, such as the thiazolidinedione ring, the cyanopyrrolidine moiety, *etc*., should be mentioned as one of approaches that holds promise for the development of multi-target drugs. The introduction of known pharmacophores into natural compounds, which have particular hypoglycemic properties, has also a potential for the development of antidiabetic drugs.

References

1. S Wild, G Roglic, A Green, R Sicree, H King *Diabetes Sare* **27** 1047 (2004)
2. M Bartholow *Pharmacy Times* (July) 2012; http://www.pharmacytimes.com/publications/issue/2012/july2012/top-200-drugs-of-2011
3. M L Bolognesi, R Matera, A Minarini, M Rosini, C Melchiorre *Curr. Opin. Chem. Biol.* **13** 303 (2009)
4. A Brunschweiger, P Koch, M Schlenk, F Pineda, P Küppers, S Hinz, M Köse, S Ullrich, J Hockemeyer, M Wiese, J Heer, C E Müller *ChemMedChem* **9** 1704 (2014)
5. A González-Hernández, M Condés-Lara *Headache* **54** 197 (2014)
6. Patent RF 2527273 (2014)
7. K Li, L A Schurig-Briccio, X Feng, A Upadhyay, V Pujari, B Lechartier, F L Fontes, H Yang, G Rao, W Zhu, A Gulati, J H No, G Cintra, S Bogue, Y L Liu, K Molohon, P Orlean, D A Mitchell, L Freitas-Junior, F Ren, H Sun, T Jiang, Y Li, R-T Guo, S T Cole, R B Gennis, D C Crick, E Oldfield *J. Med. Chem.* **57** 3126 (2014)
8. C Liu, W Guo, X Shi, M A Kaium, X Gu, Y Z Zhun *Eur. J. Med. Chem.* **46** 3996 (2011)
9. A N Tevyashova, E N Olsufyeva, M N Preobrazhenskaya *Russ. Chem. Rev.* **84** 61 (2015)
10. C Pirat, A Farce, N LebeMgue, N Renault, C Furman, R Millet, S Yous, S Speca, P Berthelot, P Desreumaux, P Chavatte *J. Med. Chem.* **55** 4027 (2012)
11. U Ramachandran, R Kumar, A Mittal *Mini-Rev. Med. Chem.* **6** 563 (2006)
12. L Mendieta, T Tarrago, E Giralt *Expert Opin. Ther. Pat.* **21** 1693 (2011)
13. J-U Peters *Curr. Top. Med. Chem.* **7** 579 (2007)
14. F S Willard, A B Bueno, K W Sloop *Exp. Diabetes Res.* **2012** ID 709893 (2012)
15. Y Zhang, R Proenca, M Maffei, M Barone, L Leopold, J M Friedman *Nature (London)* **372** 425 (1994)
16. K Kobayashi, T M Forte, S Taniguchi, B Y Ishida, K Oka, L Chan *Metabolism* **49** 22 (2000)
17. H Iwatsuka, A Shino, Z Suzuoki *Endocrinol. Jpn.* **17** 23 (1970)
18. A S Reddi, R A Camerini-Davalos *Adv. Exp. Med. Biol.* **246** 7 (1988)
19. S F Greene, P R Johnson, K C Eiffert, M R Greenwoodt, J S Stern *Obes. Res.* **2** 432 (1994)
20. L M Zucker, T F Zucker *J. Hered.* **52** 275 (1961)
21. *Animal Models in Diabetes Research (Ser. Methods in Molecular Biology* Vol. 933) (Eds H-G Joost, H Al-Hasani, A Schürmann) (New York: Humana Press, 2012)
22. E J Verspohl *Pharmacol. Rev.* **64** 188 (2012)
23. S Luquet, C Gaudel, D Holst, J Lopez-Soriano, C Jehl-Pietri, A Fredenrich, P A Grimaldi *Biochim. Biophys. Acta* **1740** 313 (2005)
24. S Higgins, A M DePaoli *Am. J. Clin. Nutr.* **91** 267S (2010)
25. G Chinetti-Gbaguidi, J-C Fruchart, B Staels *Curr. Opin. Pharmacol.* **5** 177 (2005).
26. H A Pershadsingh *Expert Opin. Invest. Drugs* **13** 215 (2004)
27. N Cho, Y Momose *Curr. Top. Med. Chem.* **8** 1483 (2008)
28. B L Balint, L Nagy *Endocr. Metab. Immune Disord. Drug Targets* **6** 33 (2006)
29. F Zhang, B E Lavan, F M Gregoire *PPAR Res.* **2007** ID 32696 (2007)
30. S Dagdelen *Recent Pat. Endocr. Metab. Immune Drug Discov.* **2** 24 (2008)
31. L S Doshi, M K Brahma, U A Bahirat, A V Dixit, K V S Nemmani *Expert Opin. Invest. Drugs* **19** 489 (2010)
32. N Mulakayala, U Reddy CH, J Iqbal, M Pal *Tetrahedron* **66** 4919 (2010)
33. S L Gwaltney *Curr. Top. Med. Chem.* **8** 1545 (2008)
34. X Chen, S Hussain, S Parveen, S Zhang, Y Yang, C Zhu *Curr. Med. Chem.* **19** 3578 (2012)
35. T Karagiannis, P Paschos, K Paletas, D R Matthews, A Tsapas *Br. Med. J.* **344** e1369 (2012)
36. E M Wright, B A Hirayama, D F Loo *J. Int. Med.* **261** 32 (2007)
37. I Idris, R Donnelly *Diabetes Obes. Metab.* **11** 79 (2009)
38. S L Anderson, J C Marrs *Ann. Pharmacother.* **46** 590 (2012)
39. A-R Li, J Zhang, J Greenberg, T W Lee, J Liu *Bioorg. Med. Chem. Lett.* **21** 2472 (2011)
40. G L Larson *Chim. Oggi. Chem. Today* **33** 37 (2015)
41. J F Caro, S Triester, V K Patel, E B Tapscott, N L Frazier, G L Dohm *Horm. Metab. Res.* **27** 19 (1995)
42. B Willms, P Ben-Ami, H D Söling *Horm. Metab. Res.* **2** 135 (1970)
43. R Sarabu, S J Berthel, R F Kester, J F Tilley *Expert Opin. Ther. Pat.* **21** 13 (2011)
44. Y Bansal, O Silakari *Eur. J. Med. Chem.* **76** 31 (2014)
45. J J Walsh, D Coughlan, N Heneghan, C Gaynora, A Bell *Bioorg. Med. Chem. Lett.* **17** 3599 (2007)
46. R Capela, R Oliveira, L M Gonçalves, A Domingos, J Gut, P J Rosenthal, F Lopes, R Moreira *Bioorg. Med. Chem. Lett.* **19** 3229 (2009)
47. O Weinreb, S Mandel, O Bar-Am, M Yogev-Falach, Y Avramovich-Tirosh, T Amit, M B H Youdim *Neurotherapeutics* **6** 163 (2009)
48. Y Li, K Tian, A Qin, L Zhang, L Huo, L Lei, Z Shen, H Song, Z Feng *Eur. J. Med. Chem.* **76** 182 (2014)
49. J Lu, L Lei, Y Huan, Y Li, L Zhang, Z Shen, W Hu, Z Feng *ChemMedChem* **9** 922 (2014)
50. L Zhang, H Li, Q Zhu, J Liu, L Chen, Y Leng, H Jiang, H Liu *Bioorg. Med. Chem.* **17** 7301 (2009)
51. L Zhang, X Chen, J Liu, Q Zhu, Y Leng, X Luo, H Jiang, H Liu *Eur. J. Med. Chem.* **58** 624 (2012)
52. S Fukuen, M Iwaki, A Yasui, M Makishima, M Matsuda, I Shimomura *J. Biol. Chem.* **280** 23653 (2005)
53. Patent WO 2004066963 (2004)
54. L S Higgins, C S Mantzoros *PPAR Res.* **2008** Article ID 936906 (2008)
55. A Motani, Z Wang, J Weiszmann, L R McGee, G Lee, Q Liu, J Staunton, Z Fang, H Fuentes, M Lindstrom, J Liu, D H T Biermann, J Jaen, N P C Walker, R M Learned, J L Chen, Y Li *J. Mol. Biol.* **386** 1301 (2009)
56. U Kintscher, M Goebel *Curr. Opin. Invest. Drugs* **10** 381 (2009)
57. Y Li, Z Wang, N Furukawa, P Escaron, J Weiszmann, G Lee, M Lindstrom, J Liu, X Liu, H Xu, O Plotnikova, V Prasad, N Walker, R M Learned, J L Chen *J. Biol. Chem.* **283** 9168 (2008)
58. I-L Lu, C-F Huang, Y-H Peng, Y-T Lin, H-P Hsieh, C-T Chen, T-W Lien, H-J Lee, N Mahindroo, E Prakash, A Yueh, H-Y Chen, Ch M V Goparaju, X Chen, C-C Liao, Y-S Chao, J T-A Hsu, S-Y Wu *J. Med. Chem.* **49** 2703 (2006)

59. P Alberts, C Nilsson, G Selen, L O Engblom, N H Edling, S Norling, G Klingstrom, C Larsson, M Forsgren, M Ashkzari, C E Nilsson, M Fiedler, E Bergqvist, B Ohman, E Bjorkstrand, L B Abrahmsen *Endocrinology* **144** 4755 (2003)
60. J Xiang, M Ipek, V Suri, W Massefski, N Pan, Y Ge, M Tam, Y Xing, J F Tobin, X Xu *Bioorg. Med. Chem. Lett.* **15** 2865 (2005)
61. H Masuzaki, J Paterson, H Shinyama, N M Morton, J J Mullins, J R Seckl, J S Flier *Science* **294** 2166 (2001)
62. J M Paterson, N M Morton, C Fievet, C J Kenyon, M C Holmes, B Staels, J R Seckl, J J Mullins *Proc. Natl. Acad. Sci. USA* **101** 7088 (2004)
63. C Hale, M Wang *Mini-Rev. Med. Chem.* **8** 702 (2008)
64. R Ge, Y Huang, G Liang, X Li *Curr. Med. Chem.* **17** 412 (2010)
65. K Rikimaru, T Wakabayashi, H Abe, H Imoto, T Maekawa, O Ujikawa, K Murase, T Matsuo, M Matsumoto, C Nomura, H Tsuge, N Arimura, K Kawakami, J Sakamoto, M Funami, C D Mol, G P Snell, K A Bragstad, B C Sang, D R Dougan, T Tanaka, N Katayama, Y Horiguchi, Y Momose *Bioorg. Med. Chem.* **20** 714 (2012)
66. K Rikimaru, T Wakabayashi, H Abe, T Tawaraishi, H Imoto, J Yonemori, H Hirose, K Murase, T Matsuo, M Matsumoto, C Nomura, H Tsuge, N Arimura, K Kawakami, J Sakamoto, M Funami, C D Mol, G P Snell, K A Bragstad, B C Sang, D R Dougan, T Tanaka, N Katayama, Y Horiguchi, Y Momose *Bioorg. Med. Chem.* **20** 3332 (2012)
67. H Koyama, J K Boueres, W Han, E J Metzger, J P Bergman, D F Gratale, D J Miller, R L Tolman, K L MacNaul, J P Berger, T W Doebber, K Leung, D E Moller, J V Heck, S P Sahoo *Bioorg. Med. Chem. Lett.* **13** 1801 (2003)
68. Y Liu, Y Hu, T Liu *Curr. Med. Chem.* **19** 3982 (2012)
69. T Iino, D Tsukahara, K Kamata, K Sasaki, S Ohyama, H Hosaka, T Hasegawa, M Chiba, Y Nagata, J Eiki, T Nishimura *Bioorg. Med. Chem.* **17** 2733 (2009)
70. C R Hopkins, S V O'Neil, M C Laufersweiler, Y Wang, M Pokross, M Mekel, A Evdokimov, R Walter, M Kontoyianni, M E Petrey, G Sabatakos, J T Roesgen, E Richardson, T P Demuth Jr *Bioorg. Med. Chem. Lett.* **16** 5659 (2006)
71. A M Warshawsky, C A Alt, J T Brozinick, A R Harkness, E D Hawkins, J R Henry, D P Matthews, A R Miller, E A Misener, C Montrose-Rafizadeh, G A Rhodes, Q Shen, J A Vance, U E Udodong, M Wang, T Y Zhang, R W Zink *Bioorg. Med. Chem. Lett.* **16** 6328 (2006)
72. M Ohashi, T Oyama, I Nakagome, M Satoh, Y Nishio, H Nobusada, S Hirono, K Morikawa, Y Hashimoto, H Miyachi *J. Med. Chem.* **54** 331 (2011)
73. M Ohashi, I Nakagome, J Kasuga, H Nobusada, K Matsuno, M Makishima, S Hirono, Y Hashimoto, H Miyachi *Bioorg. Med. Chem.* **20** 6375 (2012)
74. J A Martín, D A Brooks, L Prieto, R González, A Torrado, I Rojo, B López de Uralde, C Lamas, R Ferritto, M D Martín-Ortega, J Agejas, F Parra, J R Rizzo, G A Rhodes, R L Robey, C A Alt, S R Wendel, T Y Zhang, A Reifel-Miller, C Montrose-Rafizadeh, J T Brozinick, E Hawkins, E A Misener, D A Briere, R Ardecky, J D Fraser, A M Warshawsky *Bioorg. Med. Chem. Lett.* **15** 51 (2005)
75. M K Kim, Y N Chae, H S Kim, S H Choi, M H Son, S H Kim, J K Kim, H S Moon, S K Park, Y A Shin, J G Kim, C H Lee, J I Lim, C Y Shi *Arch. Pharm. Res.* **32** 721 (2009)
76. Patent WO 02100813 (2002)
77. M K Kim, Y N Chae, S H Choi, H S Moon, M H Son, M H Bae, H H Choi, Y Hur, E Kim, Y H Park, C S Park, J G Kim, J I Lim, C Y Shin *Eur. J. Pharmacol.* **650** 673 (2011)
78. P Sauerberg, J P Mogensen, L Jeppesen, L A Svensson, J Fleckner, J Nehlin, E M Wulff, I Pettersson *Bioorg. Med. Chem. Lett.* **15** 1497 (2005)
79. C Parmenon, J Guillard, D-H Caignard, N Hennuyer, B Staels, V Audinot-Bouchez, J-A Boutin, C Dacquet, A Ktorzae, M-C Viaud-Massuard *Bioorg. Med. Chem. Lett.* **18** 1617 (2008)
80. C Parmenon, J Guillard, D-H Caignard, N Hennuyer, B Staels, V Audinot-Bouchez, J-A Boutin, C Dacquet, A Ktorza, M C Viaud-Massuard *Bioorg. Med. Chem. Lett.* **19** 2683 (2009)
81. Patent WO 200063161 (2000)
82. K G Liu, M H Lambert, A H Ayscue, B R Henke, L M Leesnitzer, W R Oliver Jr , K D Plunket, H E Xu, D D Sternbach, T M Willson *Bioorg. Med. Chem. Lett.* **11** 3111 (2001)
83. M Engel, T Hoffmann, L Wagner, M Wermann, U Heiser, R Kiefersauer, R Huber, W Bode, H-U Demuth, H Brandstetter *Proc. Natl. Acad. Sci. USA* **100** 5063 (2003)
84. Patent WO 2003002531 (2003)
85. S D Edmondson, A Mastracchio, R J Mathvink, J He, B Harper, Y-J Park, M Beconi, J Di Salvo, G J Eiermann, H He, B Leiting, J F Leone, D A Levorse, K Lyons, R A Patel, S B Patel, A Petrov, G Scapin, J Shang, R S Roy, A Smith, J K Wu, S Xu, B Zhu, N A Thornberry, A E Weber *J. Med. Chem.* **49** 3614 (2006)
86. Y Itoh, Y Kawamata, M Harada, M Kobayashi, R Fujii, S Fukusumi, K Ogi, M Hosoya, Y Tanaka, H Uejima, H Tanaka, M Maruyama, R Satoh, S Okubo, H Kizawa, H Komatsu, F Matsumura, Y Noguchi, T Shinohara, S Hinuma, Y Fujisawa, M Fujino *Nature (London)* **422** 173 (2003)
87. H Shapiro, S Shachar, I Sekler, M Hershfinkel, M D Walker *Biochem. Biophys. Res. Commun.* **335** 97 (2005)
88. K Fujiwara, F Maekawa, T Yada *Am. J. Physiol. Endocrinol. Metab.* **289** E670 (2005)
89. N Negoro, S Sasaki, S Mikami, M Ito, M Suzuki, Y Tsujihata, R Ito, A Harada, K Takeuchi, N Suzuki, J Miyazaki, T Santou, T Odani, N Kanzaki, M Funami, T Tanaka, A Kogame, S Matsunaga, T Yasuma, Y Momose *ACS Med. Chem. Lett.* **1** 290 (2010)
90. E Defossa, M Wagner *Bioorg. Med. Chem. Lett.* **24** 2991 (2014)
91. A S Felts, B S Siegel, S M Young, C W Moth, T P Lybrand, A J Dannenberg, L J Marnett, K Subbaramaiah *J. Med. Chem.* **51** 4911 (2008)
92. J H Ahn, M S Shin, S H Jung, S K Kang, K R Kim, S D Rhee, W H Jung, S D Yang, S J Kim, J R Woo, J H Lee, H G Cheon, S S Kim *J. Med. Chem.* **49** 4781 (2006)
93. J H Ahn, M S Shin, S H Jung, J A Kim, H M Kim, S H Kim, S K Kang, K R Kim, S D Rhee, S D Park, J M Lee, J H Lee, H G Cheon, S S Kim *Bioorg. Med. Chem. Lett.* **17** 5239 (2007)
94. K R Kim, J H Lee, S J Kim, S D Rhee, W H Jung, S-D Yang, S S Kim, J H Ahn, H G Cheon *Biochem. Pharmacol.* **72** 446 (2006)
95. Patent WO 2004020409 (2004)
96. Patent WO 2006099077 (2006)
97. K Liu, R M Black, J J Acton III, R Mosley, S Debenham, R Abola, M Yang, R Tschirret-Guth, L Colwell, C Liu, M Wu, C F Wang, K L MacNaul, M E McCann, D E Moller, J P Berger, P T Meinke, A B Jones, H B Wood *Bioorg. Med. Chem. Lett.* **15** 2437 (2005)

98. J J Acton III, T E Akiyama, C H Chang, L Colwell, S Debenham, T Doebber, M Einstein, K Liu, M E McCann, D E Moller, E S Muise, Y Tan, J R Thompson, K K Wong, M Wu, L Xu, P T Meinke, J P Berger, H B Wood *J. Med. Chem.* **52** 3846 (2009)
99. C H Chang, L A McNamara, M S Wu, E S Muise, Y Tan, H B Wood, P T Meinke, J R Thompson, T W Doebber, J P Berger, M E McCann *Eur. J. Pharmacol.* **584** 192 (2008)
100. Patent WO 2008028118 (2008)
101. K M Bullock, D Burton, J Corona, A Diederich, B Glover, K Harvey, M B Mitchell, M D Trone, R Yule, Y Zhang, J F Toczko *Org. Process Res. Dev.* **13** 303 (2009)
102. Patent WO 200130343A1 (2001)
103. J F Dropinski, T Akiyama, M Einstein, B Habulihaz, T Doebber, J P Berger, P T Meinke, G Q Shi *Bioorg. Med. Chem. Lett.* **15** 5035 (2005)
104. J P Berger, A E Petro, K L Macnaul, L J Kelly, B B Zhang, K Richards, A Elbrecht, B A Johnson, G Zhou, T W Doebber, C Biswas, M Parikh, N Sharma, M R Tanen, G M Thompson, J Ventre, A D Adams, R Mosley, R S Surwit, D E Moller *Mol. Endocrinol.* **17** 662 (2003)
105. S C Benson, H A Pershadsingh, C I Ho, A Chittiboyina, P Desai, M Pravenec, N Qi, J Wang, M A Avery, T W Kurtz *Hypertension* **43** 993 (2004)
106. T Takasu, H Kakuta, M Sasamata, S Yamagishi *Int. J. Biomed. Sci.* **2** 333 (2006)
107. Y Lamotte, P Martres, N Faucher, A Laroze, D Grillot, N Ancellin, Y Saintillan, V Beneton, R T Gampe Jr *Bioorg. Med. Chem. Lett.* **20** 1399 (2010)
108. Patent WO 2003037327A1 (2003)
109. H Minoura, S Takeshita, M Ita, J Hirosumi, M Mabuchi, I Kawamura, S Nakajima, O Nakayama, H Kayakiri, T Oku, A Ohkubo-Suzuki, M Fukagawa, H Kojo, K Hanioka, N Yamasaki, T Imoto, Y Kobayashi, S Mutoh *Eur. J. Pharmacol.* **494** 273 (2004)
110. H Uchino, T Kim, T K T Lam, H Yoshii, P Klement, W Williams, R Kawamori, A Giacca *Metab. Clin. Exp.* **54** 1250 (2005)
111. H Minoura, S Takeshita, T Yamamoto, M Mabuchi, J Hirosumi, S Takakura, I Kawamura, J Seki, T Manda, M Ita, S Mutoh *Eur. J. Pharmacol.* **519** 182 (2005)
112. T Fujimura, H Sakuma, S Konishi, T Oe, N Hosogai, C Kimura, I Aramori, S Mutoh *J. Pharmacol. Sci.* **99** 342 (2005)
113. W Liu, F Lau, K Liu, H B Wood, G Zhou, Y Chen, Y Li, T E Akiyama, G Castriota, M Einstein, C Wang, M E McCann, T W Doebber, M Wu, C H Chang, L McNamara, B McKeever, R T Mosley, J P Berger, P T Meinke *J. Med. Chem.* **54** 8541 (2011)
114. E Blanc-Delmas, N Lebegue, V Wallez, V Leclerc, S Yous, P Carato, A Farce, C Bennejean, P Renard, D-H Caignard, V Audinot-Bouchez, P Chomarat, J Boutin, N Hennuyer, K Louche, M C Carmona, B Staels, L Pgnicaud, L Casteilla, M Lonchampt, C Dacquet, P Chavatte, P Berthelota, D Lesieur *Bioorg. Med. Chem.* **14** 7377 (2006)
115. M C Carmona, K Louche, B Lefebvre, A Pilon, N Hennuyer, V Audinot-Bouchez, C Fievet, G Torpier, P Formstecher, P Renard, P Lefebvre, C Dacquet, B Staels, L Casteilla, L Pénicaud *Diabetes* **56** 2797 (2007)
116. D Hunziker, M Hennig, J U Peters *Curr. Top. Med. Chem.* **5** 1623 (2005)
117. J-U Peters, S Weber, S Kritter, P Weiss, A Wallier, M Boehringer, M Hennig, B Kuhn, B-M Loeffler *Bioorg. Med. Chem. Lett.* **14** 1491 (2004)
118. M Ishikawa, K Nonoshita, Y Ogino, Y Nagae, D Tsukahara, H Hosaka, H Maruki, S Ohyama, R Yoshimoto, K Sasaki, Y Nagata, J-i Eiki, T Nishimura *Bioorg. Med. Chem. Lett.* **19** 4450 (2009)
119. K Takahashi, N Hashimoto, C Nakama, K Kamata, K Sasaki, R Yoshimoto, S Ohyama, H Hosaka, H Maruki, Y Nagata, J-i Eiki, T Nishimura *Bioorg. Med. Chem.* **17** 7042 (2009)
120. G Navarrete-Vazquez, P Paoli, I Leun-Rivera, R Villalobos-Molina, J L Medina-Franco, R Ortiz-Andrade, S Estrada-Soto, G Camici, D Diaz-Coutiño, I Gallardo-Ortiz, K Martinez-Mayorga, H Moreno-Díaz *Bioorg. Med. Chem.* **17** 3332 (2009)
121. R Sarabu, J Tilley *Annu. Rep. Med. Chem.* **40** 167 (2005)
122. P Madsen, L B Knudsen, F C Wiberg, R D Carr *J. Med. Chem.* **41** 5150 (1998)
123. C-H Lin, Y-H Peng, M S Coumar, S K Chittimalla, C-C Liao, P-C Lyn, C-C Huang, T-W Lien, W-H Lin, J T-A Hsu, J-H Cheng, X Chen, J-S Wu, Y-S Chao, H-J Lee, C-G Juo, S-Y Wu, H-P Hsieh *J. Med. Chem.* **52** 2618 (2009)
124. J R Henry, Y Li, A M Warshawsky, J T Brozinick, E D Hawkins, E A Misener, D A Briere, C Montrose-Rafizadeh, R W Zink, N P Yumibe, R T Ajamie, B Wilken, V Devanarayan *Bioorg. Med. Chem. Lett.* **16** 6293 (2006)
125. K Otake, S Azukizawa, M Fukui, K Kunishiro, H Kamemoto, M Kanda, T Miike, M Kasai, H Shirahase *Bioorg. Med. Chem.* **20** 1060 (2012)
126. E Burgermeister, A Schnoebelen, A Flament, J Benz, M Stihle, B Gsell, A Rufer, A Ruf, B Kuhn, H P Mäki, J Mizrahi, E Sebokova, E Niesor, M Meyer *Mol. Endocrinol.* **20** 809 (2006)
127. Patent WO 200187860 (2001)
128. Patent WO 200187861 (2001)
129. Patent WO 200187862 (2001)
130. P J Rybczynski, R E Zeck, D W Combs, I Turchi, T P Burris, J Z Xu, M Yang, K T Demarest *Bioorg. Med. Chem. Lett.* **13** 2359 (2003)
131. P J Rybczynski, R E Zeck, J Dudash Jr, D W Combs, T P Burris, M Yang, M C Osborne, X Chen, K T Demarest *J. Med. Chem.* **47** 196 (2004)
132. B G Szczepankiewicz, R Kurukulasuriya *Curr. Top. Med. Chem.* **7** 569 (2007)
133. T Iino, Y Sasaki, M Bamba, M Mitsuya, A Ohno, K Kamata, H Hosaka, H Maruki, M Futamura, R Yoshimoto, S Ohyama, K Sasaki, M Chiba, N Ohtake, Y Nagata, J-i Eiki, T Nishimura *Bioorg. Med. Chem. Lett.* **19** 5531 (2009)
134. Y Kawamatsu, H Asakawa, T Saraie, K Mizuno, E Imamiya, K Nishikawa, Y Hamuro *Arzneim. Forsch./Drug Res.* **30** 751 (1980)
135. T Sohda, K Mizuno, H Tawada, Y Sugiyama, T Fujita, Y Kawamatsu *Chem. Pharm. Bull.* **30** 3563 (1982)
136. J M Lehmann, L B Moore, T A Smith-Oliver, W O Wilkison, T M Willson, S A Kliewer *J. Biol. Chem.* **270** 12953 (1995)
137. K Matsusue, M Haluzik, G Lambert, S H Yim, O Gavrilova, J M Ward, B Brewer Jr, M L Reitman, F J Gonzalez *J. Clin. Invest.* **111** 737 (2003)
138. A W Norris, L Chen, S J Fisher, I Szanto, M Ristow, A C Jozsi, M F Hirshman, E D Rosen, L J Goodyear, F J Gonzalez, B M Spiegelman, C R Kahn *J. Clin. Invest.* **112** 608 (2003)
139. N J Smith, L A Stoddart, N M Devine, L Jenkins, G Milligan *J. Biol. Chem.* **284** 17527 (2009)
140. G R Madhavan, R Chakrabarti, R K Vikramadithyan, R N V S Mamidi, V Balraju, B M Rajesh, P Misra, S K B Kumar, B B Lohray, V B Lohraya, R Rajagopalan *Bioorg. Med. Chem.* **10** 2671 (2002)
141. A G Chittiboyina, M S Venkatraman, C S Mizuno, P V Desai, A Patny, S C Benson, C I Ho, T W Kurtz, H A Pershadsingh, M A Avery *J. Med. Chem.* **49** 4072 (2006)
142. Y Fukui, S Masui, S Osada, K Umesono, K Motojima *Diabetes* **49** 759 (2000)

143. P Neogi, F J Lakner, S Medicherla, J Cheng, D Dey, M Gowri, B Nag, S D Sharma, L B Pickford, C Gross *Bioorg. Med. Chem.* **11** 4059 (2003)
144. D Dey, S Medicherla, P Neogi, M Gowri, J Cheng, C Gross, S D Sharma, G M Reaven, B Nag *Metabolism* **52** 1012 (2003)
145. S Shukla, P Kumar, N Das, N S H N Moorthy, S K Shrivastava, P Trivedi, R S Srivastava *Med. Chem.* **8** 834 (2012)
146. Y Momose, T Maekawa, T Yamano, M Kawada, H Odaka, H Ikeda, T Sohda *J. Med. Chem.* **45** 1518 (2002)
147. A Shimaya, E Kurosaki, R Nakano, R Hirayama, M Shibasaki, H Shikama *Metabolism* **49** 411 (2000)
148. E Kurosaki, R Nakano, A Shimaya, S Yoshida, M Ida, T Suzuki, M Shibasaki, H Shikama *Biochem. Pharmacol.* **65** 795 (2003)
149. Q Liu, Y Zhang, H Lu, Q Li, C Zhou, M Wang *Acta Pharmacol. Sin.* **28** 2033 (2007)
150. J Choi, Y Ko, H S Lee, Y S Park, Y Yang, S Yoon *Eur. J. Med. Chem.* **45** 193 (2010)
151. Y S Park, J Choi, K Kim, J S Lim, S Yoon, Y Yang *Biomol. Ther.* **18** 77 (2010)
152. M Thor, K Beierlein, G Dykes, A-L Gustavsson, J Heidrich, L Jendeberg, B Lindqvist, C Pegurier, P Roussel, M Slater, S Svensson, M Sydow-Bäckman, U Thornström, J Uppenberg *Bioorg. Med. Chem. Lett.* **12** 3565 (2002)
153. T M Thieme, R Steri, E Proschak, A Paulke, G Schneider, M Schubert-Zsilavecz *Bioorg. Med. Chem. Lett.* **20** 2469 (2010)
154. S Seto, K Okada, K Kiyota, S Isogai, M Iwago, T Shinozaki, Y Kitamura, Y Kohno, K Murakami *J. Med. Chem.* **53** 5012 (2010)
155. M D Serby, H Zhao, B G Szczepankiewicz, C Kosogof, Z Xin, B Liu, M Liu, L T J Nelson, W Kaszubska, H D Falls, V Schaefer, E N Bush, R Shapiro, B A Droz, V E Knourek-Segel, T A Fey, M E Brune, D W A Beno, T M Turner, C A Collins, P B Jacobson, H L Sham, G Liu *J. Med. Chem.* **49** 2568 (2006)
156. B Liu, M Liu, Z Xin, H Zhao, M D Serby, C Kosogof, L T J Nelson, B G Szczepankiewicz, W Kaszubska, V G Schaefer, H D Falls, C W Lin, C A Collins, H L Sham, G Liu *Bioorg. Med. Chem. Lett.* **16** 1864 (2006)
157. A Pasternak, S D Goble, R K de Jesus, D L Hreniuk, C C Chung, M R Tota, P Mazur, S D Feighner, A D Howard, S G Mills, L Yang *Bioorg. Med. Chem. Lett.* **19** 6237 (2009)
158. A F Muller, J A Janssen, L J Hofland, S W Lamberts, M Bidlingmaier, C J Strasburger, A J van der Lely *J. Clin. Endocrinol. Metab.* **86** 590 (2001)
159. J Svensson, L Lonn, J O Jansson, G Murphy, D Wyss, D Krupa, K Cerchio, W Polvino, B Gertz, I Boseaus, L Sjostrom, B A Bengtsson *J. Clin. Endocrinol. Metab.* **83** 362 (1998)
160. Y Momose, T Maekawa, H Odaka, H Ikeda, T Sohda *Chem. Pharm. Bull.* **50** 100 (2002)
161. H Imoto, E Imamiya, Y Momose, Y Sugiyama, H Kimura, T Sohda *Chem. Pharm. Bull.* **50** 1349 (2002)
162. H Imoto, Y Sugiyama, H Kimura, Y Momose *Chem. Pharm. Bull.* **51** 138 (2003)
163. Patent CN 101085772 (2007)
164. J Choi, Y Park, H S Lee, Y Yang, S Yoon *Bioorg. Med. Chem.* **18** 8315 (2010)
165. Patent WO 2002064136A3 (2002)
166. H Tang, Y Yan, Z Feng, R K de Jesus, L Yang, D A Levorse, K A Owens, T E Akiyama, R Bergeron, G A Castriota, T W Doebber, K P Ellsworth, M E Lassman, C Li, M S Wu, B B Zhang, K T Chapman, S G Mills, J P Berger, A Pasternak *Bioorg. Med. Chem. Lett.* **20** 6088 (2010)
167. S Rocchi, F Picard, J Vamecq, L Gelman, N Potier, D Zeyer, L Dubuquoy, P Bac, M F Champy, K D Plunket, L M Leesnitzer, S G Blanchard, P Desreumaux, D Moras, J P Renaud, J Auwerx *Mol. Cell* **8** 737 (2001)
168. Patent CN 101724017 (2012)
169. Patent WO 2013116682 (2013)
170. T Allen, F Zhang, S A Moodie, L E Clemens, A Smith, F Gregoire, A Bell, G E O Muscat, T A Gustafson *Diabetes* **55** 2523 (2006)
171. F M Gregoire, F Zhang, H J Clarke, T A Gustafson, D D Sears, S Favelyukis, J Lenhard, D Rentzeperis, L E Clemens, Y Mu, B E Lavan *Mol. Endocrinol.* **23** 975 (2009)
172. M V Liberato, A S Nascimento, S D Ayers, J Z Lin, A Cvoro, R L Silveira, L Martínez, P C Souza, D Saidemberg, T Deng, A A Amato, M Togashi, W A Hsueh, K Phillips, M S Palma, F A Neves, M S Skaf, P Webb, I Polikarpov *PLoS ONE* **7** e36297 (2012)
173. T M McIntyre, A V Pontsler, A R Silva, A St Hilaire, Y Xu, J C Hinshaw, G A Zimmerman, K Hama, J Aoki, H Arai, G D Prestwich *Proc. Natl. Acad. Sci. USA* **100** 131 (2003)
174. G D Prestwich, Y Xu, L Qian, J Gajewiak, G Jiang *Biochem. Soc. Trans.* **33** 1357 (2005)
175. L Qian, Y Xu, T Simper, G Jiang, J Aoki, M Umezu-Goto, H Arai, S Yu, G B Mills, R Tsukahara, N Makarova, Y Fujiwara, G Tigyi, G D Prestwich *ChemMedChem* **1** 376 (2006)
176. N T Hiep, Y H Choi, N Kim, S S Hong, S B Hong, B Y Hwang, H J Lee, S J Lee, D S Jang, D Lee *J. Nat. Prod.* **75** 784 (2012)
177. K Bhalla, B J Hwang, J H Choi, R Dewi, L Ou, J Mclenithan, W Twaddel, E Pozharski, J Stock, G D Girnun *J. Biol. Chem.* **286** 41626 (2011)