CHAPTER TWELVE

Beyond PPARs and Metformin: New Insulin Sensitizers for the Treatment of Type 2 Diabetes

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Contents

1. INTRODUCTION

Type 2 diabetes (T2D) is a chronic disease of elevated plasma glucose levels resulting from a failure of the pancreas to produce sufficient insulin and/or peripheral tissues to respond to insulin (i.e., insulin resistance). Prevalence of T2D has rapidly increased over the past decade in both the United States and the rest of the world, paralleling the rise of obesity, a known risk factor. In 2010, approximately 26-million Americans were considered diabetic, an 8% increase from 2008.[1] Major complications of T2D include nephropathy, retinopathy, and neuropathy. T2D doubles the risk for cardiovascular disease and stroke. The economic costs associated with T2D were estimated as $174 billion in 2007, the last year for which figures are available.[2]

T2D is managed through a combination of lifestyle interventions and/or pharmacological therapy. Bariatric surgery has been shown to provide

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remission from T2D but carries short-term risks.[3] Goals for T2D treatment have generally focused on reduction in glycosylated hemoglobin (HbA1c), a biomarker for plasma glucose. Lifestyle interventions, especially body weight loss and increased physical activity, can significantly lower HbA1c levels but are difficult to maintain over an extended period. Pharmacological treatment also results in lower HbA1c levels, but the effectiveness of such treatment can decrease over time. The choice of drugs is governed by a series of diabetes care algorithms which have been periodically updated, most recently in 2009.[4]

The past decade has seen the emergence of several new classes of anti-T2D drugs such as the dipeptidyl peptidase IV (DPPIV) inhibitors and incretin mimetics. The only insulin sensitizers currently on the market were launched in the 1990s when metformin and the thiazolidinediones (TZDs) pioglitazone and rosiglitazone received approval from the U.S. Food and Drug Administration. The TZDs are peroxisome proliferator-activated receptor γ (PPARγ) agonists that, when used as monotherapy, lower HbA1c levels more effectively than DPPIV inhibitors or glucagon-like peptide-1 mimetics and achieve greater durability than metformin,[4,5] However, the side effect and safety profiles of PPARγ agonists as a class have come into question.[6] The marketing of rosiglitazone was severely restricted in 2011. The non-TZD aleglitazar, a balanced PPARα/γ agonist in Phase III trials for the treatment of T2D and dyslipidemias, is the only current example of a full PPARγ agonist, albeit a nonselective PPAR modulator, in clinical development,[6,7] It has been proposed that selective and/or partial PPARγ modulators (SPPARγMs) such as INT131 might exhibit reduced side effects, but their efficacy is unproven.[8]

The discovery of non-PPARγ insulin sensitizers has attracted considerable interest. New insulin sensitizers would fill a much needed void in treatment options for T2D patients who no longer respond to metformin or cannot use pioglitazone due to its contraindications.[9] Only a few small molecule insulin sensitizers are currently in clinical development including imeglimin (a metformin analog), MSDC-0602 (a TZD analog with no PPARγ transactivation activity), VVP808 (a repurposed drug with ophthalmic activity), and AC-201 (a new formulation of diacerin),[10–13] Many other insulin sensitizers have been reported to show robust efficacy in animal models, although it is not known whether this efficacy will translate into humans. Herein, we review progress toward the next generation of insulin sensitizers, with a focus on synthetic agents that have demonstrated body weight-independent insulin-sensitizing efficacy in animal models.

2. INSULIN SENSITIZERS

Insulin is a pleiotropic hormone involved in carbohydrate and lipid metabolism and cell proliferation. An insulin sensitizer improves insulin's ability to stimulate glucose utilization, leading to reduced plasma glucose.[14] At the level of tissues such as the liver, adipose tissue, or muscle, an insulin sensitizer may enhance the ability of insulin to decrease gluconeogenesis, inhibit lipolysis, or stimulate glucose uptake, respectively. The molecular mechanisms by which insulin sensitizers enhance the insulin response are varied and described in considerable detail elsewhere.[15]

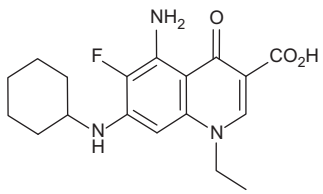
2.1. Insulin sensitizers that act within the insulin signaling pathway

The insulin/insulin receptor (IR) signaling cascade leading to activation of the phosphoinositide 3-kinase (PI3K)/Akt pathway is complex, involving many phosphorylation/dephosphorylation events and requiring an array of adaptor proteins and secondary signaling molecules.[16] In T2D, the system becomes dysregulated, with insulin losing its ability to inhibit gluconeogenesis or stimulate glycogenesis. Few opportunities for pharmacological modulation within this system have been identified to safely restore normal insulin signaling. Two novel classes of insulin sensitizers, protein tyrosine phosphatase-1b (PTP1b) inhibitors and type-II SH2-domain-containing inositol 5-phosphatase (SHIP2) inhibitors, are discussed below. The recently disclosed insulin sensitizers **1**–**3** (Fig. 12.1) also act within the IR pathway but are not discussed further here.[17–19]

2.1.1 PTP1b inhibitors

PTB1b negatively regulates insulin signaling by catalyzing the dephosphorylation of both the IR and insulin-receptor substrate-1 (IRS1). Genetic polymorphism data associate PTP1b with protection from and/or development of insulin resistance and diabetes in humans.[20] Ablation of PTP1b in mice improves insulin sensitivity and prevents weight gain on a high fat diet.[21]

The identification of small molecule PTP1b inhibitors with appropriate pharmacokinetic properties and selectivity has proven extremely challenging.[22] Many competitive PTP1b inhibitors are phosphotyrosine mimetics that contain a carboxylic or phosphonic acid (i.e., to drive binding affinity to the high-affinity catalytic site) and a large lipophilic tail seeking to

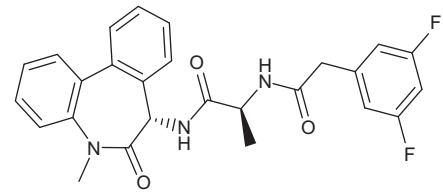


1 AS1842856

G6Pase mRNA IC50 = 0.13 μM (Fao cells)

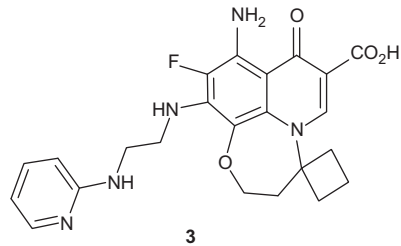
PEPCK mRNA IC_{50} = 0.037 μM (Fao cells)

Forkhead transcription factor-01 (Fox01) modulators



2

Notch/gamma-secretase inhibitors



3

Cell free IC50 = 0.004 μM

Cell IC50 = 3 μM

Glycogen synthase kinase-3alpha/beta inhibitors

Figure 12.1 Structures of insulin sensitizers **1**–**3** that act within the insulin signaling pathway.

maximize the additional binding energy that can be obtained from the shallow binding pocket.[23] These PTP1b inhibitors generally exhibit low ligand efficiency, poor cell activity, and suboptimal pharmacokinetic properties. Application of acidic isosteres has led to some improvement in ADME properties, but not sufficient to produce clinical candidates against the target.[24] An allosteric binding site on the enzyme has been identified but not yet successfully exploited in the design of oral inhibitors.[25] The discovery of new PTP1b inhibitors remains an active area of research, especially in academia, but further breakthroughs will be required to deliver orally active agents.[26]

While PTP1b does not appear to be druggable from a small molecule perspective, PTP1b protein levels can be modulated using antisense oligonucleotides (ASOs) that bind mRNA and reduce protein transcription. A PTP1b ASO ISIS113715 was advanced into Phase II clinical trials and shown to reduce plasma glucose and LDL-cholesterol in diabetic patients

without causing weight gain.[27] Development of ASO ISIS113715 has been reportedly suspended, replaced by a new ASO ISIS-PTP1B$_{RX}$ (structure unknown), currently in Phase I trials.[28]

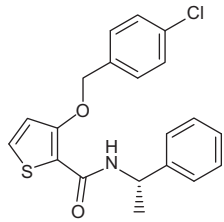
2.1.2 SHIP2 inhibitors (SHIP2i)

In the insulin signaling pathway, phosphatidylinositol 3,4,5-triphosphate (PIP3), a product of PI3K, activates Akt and other downstream kinases to initiate a cascade that results in translocation of glucose transporter type 4 (GLUT4) to the plasma membrane and glucose uptake into tissues. SHIP2 acts as a negative regulator of this pathway by catalyzing dephosphorylation of PIP3, thereby blocking IR signaling.[29] SHIP2 knockout and transgenic mouse studies, tissue selective knockdowns, and human genetics studies linking polymorphisms in SHIP2 with susceptibility to T2D support a role for this target in enhancing insulin sensitivity.[29] A thiophene derivative AS 1949490 (**4**, $IC_{50} = 0.6\ \mu M$, Fig. 12.2), discovered by high-throughput screening (HTS), was shown to increase phosphorylation of Akt and glucose uptake in L6 myoblasts treated with insulin.[30] When dosed at 300 mg/kg bid to *db/db* mice, **4** reduced plasma glucose levels by 23%. Since **4** does not contain an acidic "warhead" as required by many phosphatase inhibitors, this class of compounds may exhibit improved pharmacokinetic properties compared to PTP1b inhibitors.

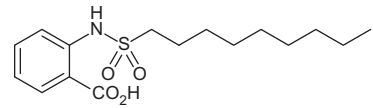
2.2. Insulin sensitizers that modulate lipid synthesis

Insulin resistance is often associated with accumulation of lipid derivatives in the liver and other tissues. Excess lipid deposition in the liver arises when hepatic uptake and synthesis of lipids exceeds hepatic clearance rates, via either oxidation or export as very low-density lipoprotein particles or as phospholipids into bile. Lipids that accrue in the liver come from dietary sources, elevated lipolytic activity in adipose tissue, or increased endogenous synthesis. It is not yet known whether fatty liver causes insulin resistance or insulin resistance causes the storage of excess fat in the liver. On the one hand, lipid intermediates are known to inhibit Akt signaling and activate serine kinases, with the latter able to phosphorylate IRS1, preventing its interaction with the IR.[31] On the other hand, the compensatory increases in plasma insulin arising from insulin resistance drive activation of the transcription factor sterol regulatory-element-binding protein-1c (SREBP-1c), which is a key regulator of FA synthesis.

Studies with transgenic animals and pharmacological tool compounds have shown that blocking the synthesis of saturated and (poly)unsaturated

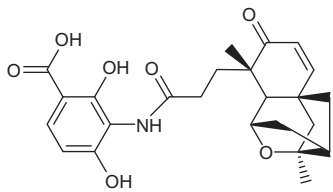


4 AS 1949490

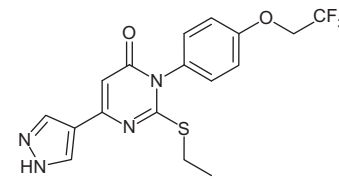


5 IC_{50} = 25 μM

Microsomal glycerol-3-phosphate acyltransferase inhibitor

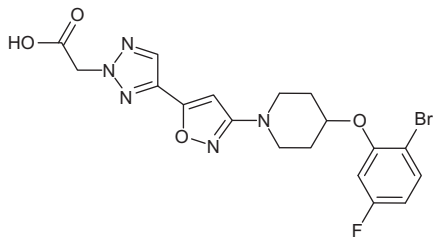


6 Fatty acid synthase IC_{50} = 0.1 μM

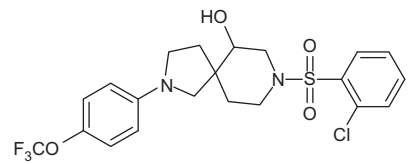


7 %inhibition @ 1 μM in HepG2 cells = 103%

Delta-5 desaturase inhibitor



8 Stearoyl CoA desaturase IC_{50} = 0.003 μM



9 Hormone sensitive lipase IC_{50} = 0.01 μM

Figure 12.2 Structures of SHIP2i **4** and insulin sensitizers **5**–**9** that can potentially modulate lipid levels.

lipids in the liver (Sections 2.2.1 and 2.2.2), or changing the composition of lipid intermediates, especially lipokines, in the total lipid pool (Sections 2.2.3 and 2.2.4) can lead to significant improvements in insulin sensitivity.[15] Other recently disclosed insulin sensitizers **5**–**9** have also been shown to modulate lipid levels but are not discussed further in this review (Fig. 12.2).[32–36] Insulin sensitizers that activate AMP-activated kinase (AMPK) to decrease lipid synthesis are described in greater detail in this issue of *Annual Reports* while those that inhibit acetyl-CoA carboxylase (ACC), a direct target of AMPK activators, have been reviewed in a past issue.[37]

2.2.1 DGAT inhibitors

The final step in triacylglycerol (TAG) synthesis involves the acylation of diacylglycerols by acyl CoA:diacylglycerol acyltransferase (DGAT) enzymes. Two isoforms, DGAT1 and DGAT2, have been identified, with the former localized mainly in the intestines and thought to play a role in the reesterification of hydrolyzed TAGs, and the latter in liver and adipose tissue. *Dgat*1$^{-/-}$ knockout mice are resistant to diet-induced obesity and hepatic steatosis and exhibit improved insulin sensitivity.[38] ASO knockdown of DGAT2 in rodent models was shown to decrease hepatic lipids and improve insulin sensitivity, without appearing to cause any overt toxicity.[39] A DGAT2 ASO ISIS-DGAT$_{RX}$ is currently in preclinical development.[28]

DGAT1 has been the subject of extensive research and patent activity, reviewed in detail elsewhere.[40] Since 2010, a few novel DGAT1 chemotypes have been disclosed, such as **10** ($IC_{50} = 0.089$ μM; Fig. 12.3).[41] Two DGAT1 inhibitors, PF-04620110 and AZD7687, have advanced into clinical trials for the treatment of T2D and obesity, but no longer appear to be under development.[42] It remains to be determined whether other classes of DGAT1 inhibitors will demonstrate insulin-sensitizing activities in humans.[42] The only published example of a small molecule inhibitor of DGAT2 is niacin, a weak noncompetitive inhibitor in HepG2 cells ($IC_{50} = 0.1$ mM).[43]

2.2.2 Adiponectin receptor agonists

Adiponectin is a hormone secreted by adipocytes and believed to act in muscle and liver to improve insulin sensitivity by stimulating FA oxidation, inhibiting FA synthesis (via activation of AMPK), and decreasing gluconeogenesis.[44] Adiponectin signals, in part, through two 7-transmembrane (7TM) receptors, AdipoR1 and AdipoR2, which differ from classical 7TM G-protein-coupled receptors (GPCRs) in that the carboxyl terminal domain is extracellular.[44] A series of spirocyclic derivatives such as **11** ($IC_{50} = 0.57$ μM; Fig. 12.3) was disclosed that reportedly activate AdipoR1 and stimulate ACC phosphorylation in cells overexpressing AdipoR1.[45] Compounds illustrated by **12** (AMPK EC_{50}'s = 0.5–1 μM) are structurally related to a series of benzylpiperidine derivatives exemplified by **13** (AMPK EC_{50}'s < 1 μM) that were discovered from an adiponectin binding displacement assay.[46,47] A 10-mer peptide analog ADP 355 (H-*D*-Asn-Ile-Pro-Nva-Leu-Tyr-*D*-Ser-Phe-Ala-*D*-Ser-NH_2) derived from the loop-β-sheet

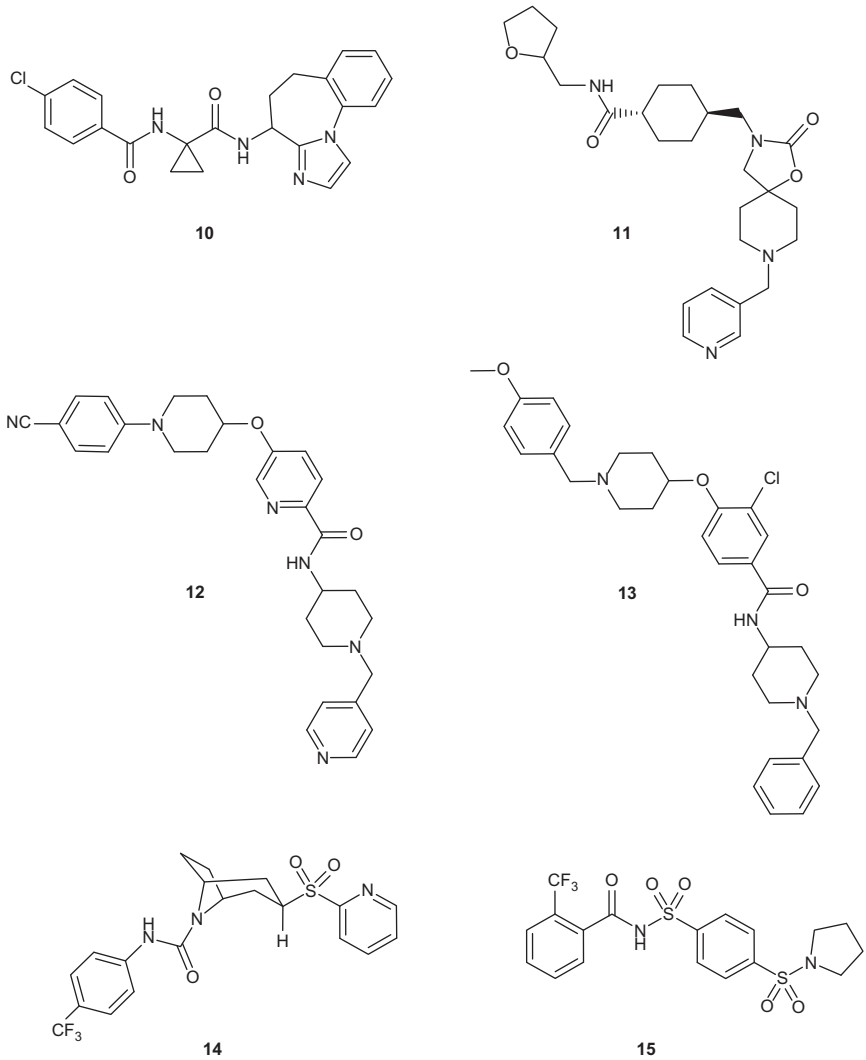


Figure 12.3 DGAT1 inhibitor **10**, adiponectin receptor mimetics **11**–**13**, and Elovl6 inhibitors **14**–**15**.

region of adiponectin has also been shown to activate adiponectin receptors, primarily AdipoR1, and stimulate downstream signaling, for example, AMPK.[48] The target specificity of ADP 355 was confirmed using siRNA technology. ADP 355 has been evaluated as an anticancer agent, but not as an insulin sensitizer.

2.2.3 Elovl6 inhibitors

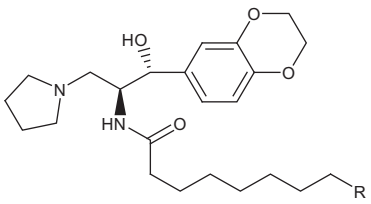
Elongation of very long chain fatty acids protein 6 (Elovl6) catalyzes the formation of C14-, C16-, and C18- saturated and unsaturated FAs from C12-, C14-, and C16- fatty acids, respectively, using malonyl CoA as a two carbon donor. Recent evidence suggests that the FA palmitoleate may act as a lipokine to stimulate muscle insulin action.[49] Genetic knockdown of Elov6 does not protect mice on a high fat diet from obesity or severe hepatic steatosis but does prevent the development of insulin resistance. Pharmacological inhibition using the Elov6 inhibitor **14** ($IC_{50} = 0.038$ μM; Fig. 12.3), however, did not recapitulate the insulin sensitivity phenotype observed in the knockout mice.[50] It was suggested that this may be due to selective inhibition of liver Elovl6 and a lack of inhibition in muscle and adipose tissue. No changes in the ratio of palmitoleate to palmitate were observed during the study. A novel series of Elov6 inhibitors exemplified by the acylsulfonamide **15** was recently disclosed (%inh @ 10 μM = 100%).[51]

2.2.4 GCS inhibitors (GCSi)

Excess production of sialic acid-containing glycosphingolipids such as ganglioside GM3 has been linked to insulin resistance through the formation of lipid rafts that disrupt the activity of the membrane-bound IR. Transgenic mice lacking GM3 due to the absence of GM3 synthase show improved insulin sensitivity.[52] Glucosylceramide synthase (GCS) is a glucosyltransferase that processes sphingolipid ceramides into glucosylceramides, intermediates in the production of GM3. GCSi Genz-123346 (**16**; $IC_{50} = 0.016$ μM; Fig. 12.4) modulates GM3 levels and improves glycemic control and insulin sensitivity in animal models of type 2 diabetes.[53] Genz-112638 (**17**; $IC_{50} = 0.009$ μM) is currently in Phase III clinical trials for type 1 Gaucher disease. A series of HTS-derived nonsphingosine inhibitors exemplified by **18** ($IC_{50} = 0.016$ μM) has been recently described.[54] No GCSi's are yet believed to be under clinical evaluation for the treatment of T2D.

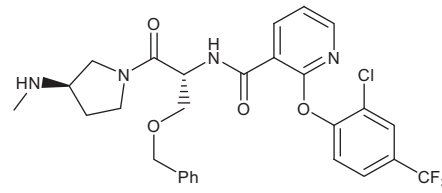
2.3. Insulin sensitizers that modulate inflammatory pathways

Proinflammatory cytokines secreted by adipocytes or resident macrophages can stimulate lipolysis (e.g., tumor necrosis factor α, TNF-α) or modulate the insulin signaling pathway, potentially by activating intracellular kinases such as c-Jun N-terminal kinase (JNK) and inhibitor of kappa B kinase (IKK) (e.g., TNF-α or interleukin 1, IL-1).[55,56] JNK can phosphorylate IRS1, preventing IRS1 binding to IR. JNK inhibitors such as **19** have been shown to improve insulin sensitivity (Fig. 12.4).[57] IKK activates



16 R = H; Genz-112638

17 R = Me; Genz-123346



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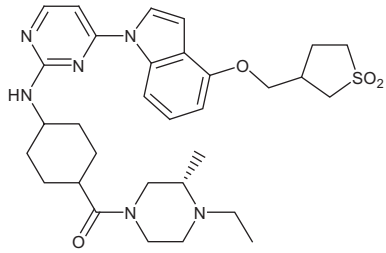
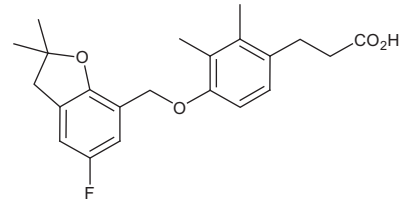
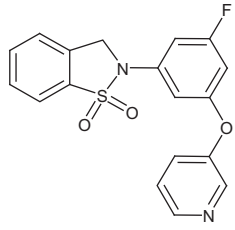


19 c-Jun N-terminal kinase IC_{50} = 0.019 μM



20



21

Figure 12.4 Structures of GCSi's **16**–**18**, JNK inhibitor **19**, and GPR120 agonists **20**–**21**.

translocation of the transcription factor nuclear factor-κB (NF-κB), which regulates the expression of many proinflammatory genes, including TNF-α and IL-1. Both the JNK and IKK/NF-κB pathways are upregulated in insulin-resistant states in animal models and humans,[58,59]

2.3.1 GPR120 agonists

GPR120 is a GPCR that responds to long-chain FAs. This receptor was recently shown to be expressed in macrophages, where it is coupled to the β-arrestin pathway.[60] FA activation leads to recruitment of β-arrestin-2,

receptor internalization, and sequestration of proinflammatory proteins.[60] Omega-3 FAs such as docosahexaenoic acid are β-arrestin-biased GPR120 agonists (EC_{50}'s = 1–10 μM) that reduce inflammation in adipose tissue and improve insulin sensitivity in mice on a high fat diet.[60] Several GPR120 agonists, such as the carboxylic acid derivative **20** (EC_{50}'s = 1–10 μM; Fig. 12.4), have been disclosed.[61] These compounds appear to have been identified in assays measuring ligand-stimulated mobilization of intracellular calcium, another GPR120 signaling pathway thought to play a role in incretin secretion from the gastrointestinal tract. Compound **20** was shown to reduce glucose excursion in an IP glucose tolerance test (42% reduction @ 30 mg/kg po). A neutral series of GPR120 agonists, exemplified by **21** (EC_{50} = 0.18 μM), has also been identified. The activity of **21** for β-arrestin recruitment has not been reported.[62] No GPR120 agonists are reported to be clinical development.

2.4. Insulin sensitizers that act through other pathways

2.4.1 Ghrelin receptor antagonists

Ghrelin is an orexigenic peptide that contains a unique octanoyl group at Ser3. Its pharmacological activities are mediated via the ghrelin receptor (GHSR1a). Because of the role that ghrelin plays in stimulating food intake, GHSR1a antagonists were originally investigated as potential weight loss agents.[63] Recently, GHSR1a knockdown in mice and pharmacological inhibition using antagonists such as **22** (IC_{50} = 0.015 μM; Fig. 12.5) have been shown to enhance insulin sensitivity.[64,65] The ghrelin receptor is believed to possess high constitutive activity, suggesting that receptor modulation by an inverse agonist may lead to a differentiated profile compared to a neutral antagonist.[66] Neutral ghrelin antagonist **23** unexpectedly stimulated food intake in rodent models.[67] Recent disclosures include macrocyclic compounds such as **24** (IC_{50}'s = 0.001–0.01 μM),[68] and the inverse agonist **25**.[69] No ghrelin receptor antagonists are reported to be in clinical development.

2.4.2 CDK5 inhibitors

A novel mode of action was recently uncovered for PPARγ agonists such as rosiglitazone.[70] These agonists were shown to block cyclin-dependent kinase-5 (CDK5)-mediated phosphorylation of PPARγ, preventing PPARγ-mediated suppression of insulin responsive genes that regulate adipokines such as adiponectin. In human T2D patients treated with rosiglitazone, individual reductions in fasting plasma glucose and insulin

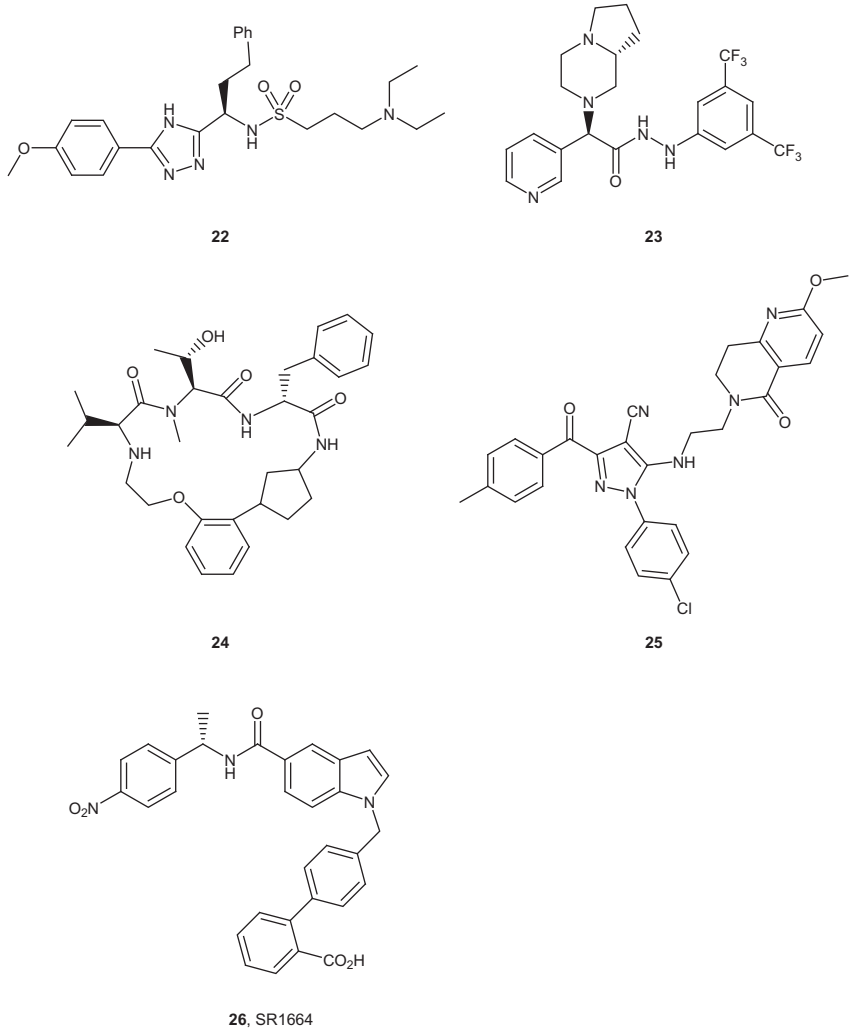


Figure 12.5 Structures of ghrelin receptor antagonists **22**–**25** and compound **26** that blocks CDK5-mediated phosphorylation of PPARγ.

levels correlated with the degree of agonist-induced inhibition of PPARγ phosphorylation.[70] Novel inhibitors of CDK5-mediated phosphorylation of PPARγ such as SR1664 (**26**; Fig. 12.5) have been disclosed which are devoid of PPARγ transcriptional agonism.[71] Compound **26** demonstrated equivalent glucose-lowering activity to rosiglitazone in rodent models but exhibited an improved profile with respect to weight gain, edema, and bone formation. It remains to be determined whether the efficacy and safety

profiles of agents such as **26** will translate to humans and differentiate from full PPARγ agonists and SPPARγMs.[7]

3. CONCLUSION

The rapid world-wide growth in the prevalence of T2D, combined with the limited durability of established antidiabetic medicines, suggests that a large medical need exists for new, safe, and effective treatments. While many gliptins and insulin secretagogues/incretin mimetics have been approved since 2000, and many others are in development, no new insulin sensitizers have reached the marketplace in recent years, attesting to the difficulty of discovering such drugs. The efficacy achieved with TZDs not only has set a high bar in terms of glucose lowering but also has illustrated the challenges and high demands of patients, prescribers, and payers on drug safety.

In the past decade, a greater understanding of the science underlying the molecular pathways that lead to insulin resistance has emerged. Accumulation of lipids in the liver and other tissues and the development of inflammation in adipose tissue and liver have been shown to play important roles in the development of T2D. While the number of druggable targets within the IR signaling cascade is limited, human genetic data and studies using transgenic rodent models have identified several promising targets involved in lipid metabolism and inflammatory pathways that could potentially be modulated to improve insulin sensitivity. Both small and large molecules with activities against some of these targets have shown promise in rodent models as insulin sensitizers. A formidable challenge in the coming years will be identifying targets for which rodent pharmacology, and equally importantly safety, will translate to robust and safe insulin sensitizing and glucose-lowering activities in humans to meet demands from the ever-growing population of T2D patients.

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