Drugs of the Future 2002, 27(2): 132-139

CCC: 0377-8282/2002

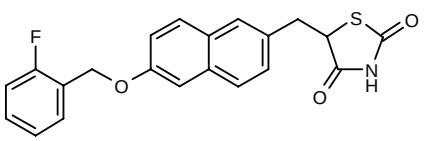
Netoglitazone

Prop INN; USAN

Antidiabetic
PPARα/PPARγ Agonist

MCC-555
RWJ-241947

5-[6-(2-Fluorobenzyloxy)naphthalen-2-ylmethyl]thiazolidine-2,4-dione



$C_{21}H_{16}FNO_3S$

Mol wt: 381.4290

CAS: 161600-01-7

CAS: 161599-99-1 (as sodium salt)

EN: 213009

Abstract

Diabetes mellitus is a worldwide health problem that affects more and more people every year. Several drugs are available for the treatment of diabetes mellitus including various insulin formulations, biguanides, sulfonylureas, α-glucosidase inhibitors, insulin secretagogues and insulin sensitizers. However, the search for more effective agents is ongoing. The insulin sensitizers or enhancers of insulin action improve insulin resistance in type 2 diabetes by increasing the sensitivity of cells to insulin and one novel class are the peroxisome proliferator-activated receptor (PPAR) agonists such as the thiazolidinediones or so-called glitazones. Thiazolidinediones (*e.g.*, troglitazone, rosiglitazone, pioglitazone), the first high-affinity PPARγ agonists discovered, do not increase insulin secretion or the number or affinity of insulin receptor binding sites but are thought to amplify postreceptor events in the insulin signaling cascade. Of these compounds, netoglitazone (MCC-555) which possesses both PPARα and PPARγ agonist activity has displayed potent preclincial activity and was selected for further clinical development as a treatment of diabetes. This article discusses the synthesis and the extensive pharmacological actions of this new agent.

Synthesis

Netoglitazone can be synthesized by two related ways:

a) Reduction of 6-hydroxynaphthalen-2-carboxylic acid (I) by means of trimethyl borate and BH_3.THF complex – obtained by reaction of $NaBH_4$ and dimethyl sulfate in THF – yields the naphthyl carbinol derivative (II), which is oxidized to aldehyde (III) with either manganese dioxide in DMF or acetone, mixtures of $CuCl_2$, $CuBr_2$ or $FeCl_3$ with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) in DMF or O_2, TEMPO and a ruthenium catalyst in chlorobenzene. Condensation of aldehyde (III) with thiazolidine-2,4-dione (IV) in 2-methoxyethanol, 2-propanol, DMF or DMSO gives 5-(6-hydroxynaphthalen-2-ylmethylene)thiazolidine-2,4-dione (V), which is then reduced with either H_2 over catalyst or cyclohexene to provide 5-(6-hydroxynaphthalen-2-ylmethyl)thiazolidine-2,4-dione (VI). Finally, compound (VI) is condensed with 2-fluorobenzyl chloride (VII) by means of NaH or KH in DMF, DMSO or NMP (1, 2). Scheme 1.

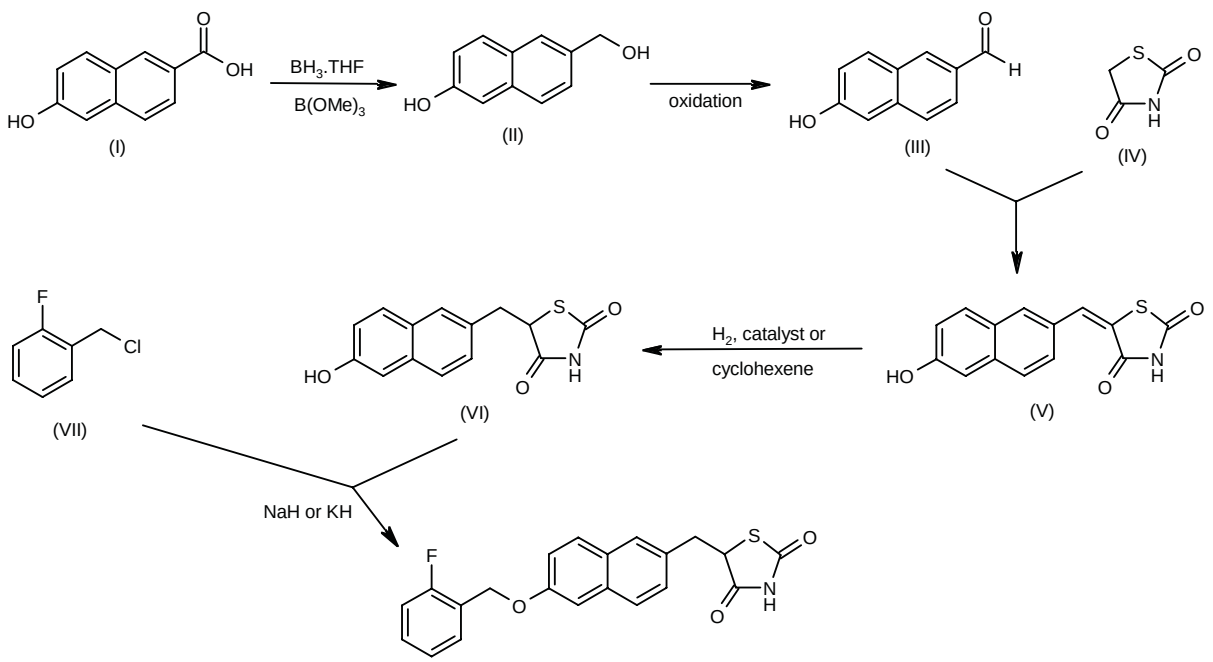
b) Reaction of aldehyde (III) with 2-fluorobenzyl alcohol (VIII) by means of triphenylphosphine and diethyl azodicarboxylate (DEAD) in THF furnishes 6-(2-fluorobenzyloxy)naphthalene-2-carbaldehyde (IX) , which is then reduced with $NaBH_4$ in ethanol/THF to give the naphthalenemethanol derivative (X). Halogenation of (X) by means of iodide, triphenylphosphine and imidazole in THF yields the naphthylmethyl iodide derivative (XI), which is finally condensed with thiazolidine-2,4-dione (IV) by means of HMPA and butyl lithium in THF (3). Scheme 2.

Introduction

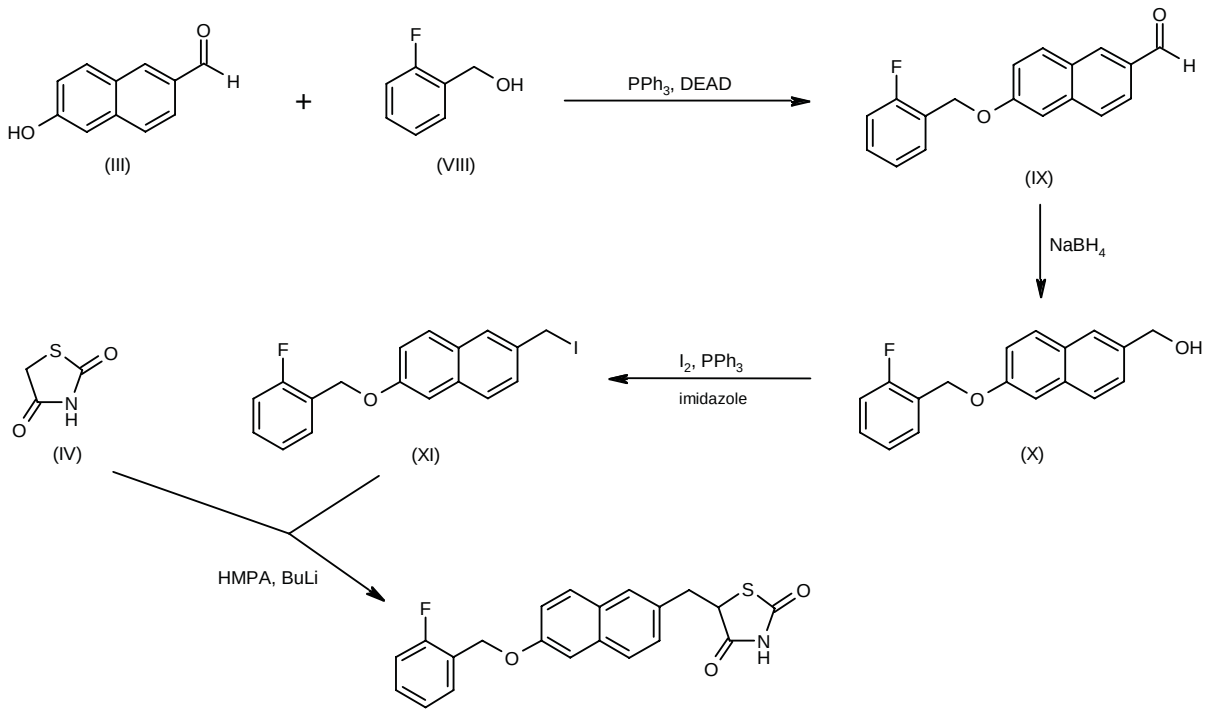
Diabetes mellitus includes several diseases that are characterized by chronic hyperglycemia with disturbances in fat, carbohydrate and protein metabolism due

L.A. Sorbera, J. Castañer, M. del Fresno, J. Silvestre. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

Scheme 1: Synthesis of Netoglitazone



Scheme 2: Synthesis of Netoglitazone



to abnormal insulin secretion and/or action. For the year 2000, the World Health Organization (WHO) reported that there were 154.4 million diabetics worldwide with no indication that prevalence is stabilizing. WHO predicts that there will be approximately 300 million individuals with diabetes by the year 2005 (4).

Diabetes is classified into 4 major subtypes. Type 1 diabetes, also known as juvenile-onset diabetes (previously referred to as insulin-dependent diabetes mellitus or IDDM), is due to the autoimmune destruction of pancreatic beta-cells resulting in the inability of the pancreas to produce insulin. Type 1 diabetes can be caused by autoimmune, genetic and/or environmental factors and accounts for 5-10% of all cases reported in the Western world. It usually develops before the age of 40 with most cases presenting before the age of 20. In contrast, type 2 diabetes, or adult-onset diabetes (previously referred to as non-insulin-dependent diabetes mellitus or NIDDM), accounts for over 90% of the reported diabetic cases reported in the Western world. In general, individuals suffering from type 2 diabetes produce sufficient amounts of insulin but they cannot use it effectively. Genetic predisposition and environmental factors contribute to its development and risk factors include obesity, physical inactivity, family history of diabetes, prior history of gestational diabetes, impaired glucose tolerance and race/ethnicity. Other types of diabetes are much less frequent and include gestational diabetes, drug-induced diabetes and diabetes secondary to illness or infection (4).

Several drugs are available for the treatment of diabetes mellitus including various insulin formulations (*e.g.*, very short-acting, short-acting, intermediate-acting, long-acting and biphasic insulins) in addition to biguanides, sulfonylureas, α-glucosidase inhibitors, insulin sensitizers and insulin secretagogues. Moreover, the search for new agents is ongoing. The insulin sensitizers or enhancers of insulin action improve insulin resistance in type 2 diabetes by increasing the sensitivity of cells to insulin. One novel class of insulin sensitizers that appear to be effective as a treatment for diabetes are peroxisome proliferator-activated receptor (PPAR) agonists such as the thiazolidinediones or so-called glitazones (4-8). PPARs are a family of transcription factors that play a crucial role in regulating the storage and catabolism of dietary fats and, since their cloning, they have become the target for the development of compounds to treat human metabolic diseases. Three PPAR subtypes have been identified, the α, γ and δ forms, which are products of distinct genes (9-14). The PPARγ subtype is mainly expressed in adipose tissue and 3 isoforms, PPARγ1, PPARγ2 and PPARγ3, exist with PPARγ1 the most prominent form (15-17). Studies have demonstrated that several endogenous fatty acids, eicosanoids, prostaglandins and their metabolites can modulate PPARγ activity, suggesting that these compounds may be the natural ligands for this receptor (6, 18-21). PPARγ forms heterodimers with another nuclear receptor, the 9-*cis*-retinoic acid receptor (RXR). PPARγ/RXR heterodimers bind to DNA and are the actual functional transcription factor within cells (22).

The PPARs are particularly attractive targets for antidiabetic therapy and PPAR agonists currently under development for the treatment of type 2 diabetes are shown in Table I. Thiazolidinediones (*e.g.*, troglitazone, rosiglitazone, pioglitazone) were the first high-affinity PPARγ agonists discovered and they have been developed for the last 15 years (23). These agents do not increase insulin secretion or the number or affinity of insulin receptor binding sites but are thought to amplify postreceptor events in the insulin signaling cascade (24, 25). Of these compounds, netoglitazone (MCC-555) which possesses both PPARα and PPARγ agonist activity has emerged as a promising agent for the treatment of diabetes and has been selected for further development.

Pharmacological Actions

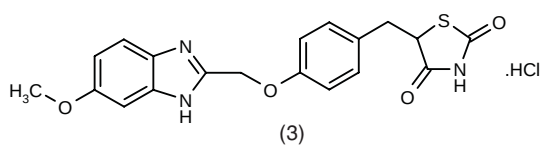
Netoglitazone displays dual PPARγ (EC_{50} = 3 μM) and PPARα (EC_{50} = 0.1 μM) agonism *in vitro* (26). Other thiazolidinediones have shown a good correlation between *in vivo* hypoglycemic activity and *in vitro* binding and activation of PPARγ. However, the antidiabetic activity of netoglitazone has been shown to be over 50-fold more potent in *in vivo* models of type 2 diabetes than would be expected based on its relatively low *in vitro* binding and activation of PPARγ. For example, results obtained from an in vitro radioligand binding assay revealed that netoglitazone was approximately 50-fold less potent than rosiglitazone in displacing [^{3}H]-rosiglitazone from bacterially expressed PPARγ (EC_{50} = 8 *vs.* 0.2 μM, respectively) (27). Moreover, netoglitazone was about 30-fold less effective than rosiglitazone in activating PPARγ in HEK293 cells transfected with PPARγ and PPRE luciferase reporter (ED_{50} = 3 *vs.* 0.1 μM, respectively) (26) and was 5-10-fold less active than rosiglitazone in inducing adipogenesis in both mouse and human preadipocytes (27, 28). On the other hand, netoglitazone was approximately 2.5-fold more potent than rosiglitazone in inducing the PPARγ target gene, aP2, in human preadipocytes; netoglitazone was effective at concentrations of 1-10 μM which are comparable to blood levels in animals treated with the agent. Thus, netoglitazone was more effective in inducing selective target gene expression which may explain the discrepancy between *in vitro* and *in vivo* activity seen for the agent (28). Table II summarizes *in vitro* activity of netoglitazone and other PPAR agonists in cell-based transactivation assays.

Further analysis of netoglitazone binding and activation of PPARγ revealed that the effects of netoglitazone binding are dependent on the cell type or DNA binding site. Therefore, the effect of netoglitazone is context-specific and it can act as a full agonist, partial agonist or antagonist. This context selectivity may also explain the potent antidiabetic effects seen *in vivo* despite its relatively low affinity for PPARγ *in vitro* (27).

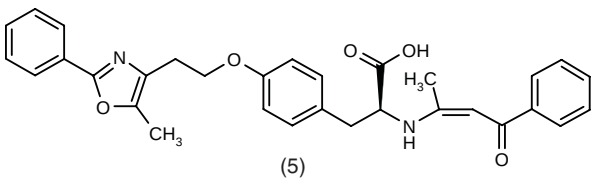
Netoglitazone activity was characterized in an *in vitro* study using isolated adult rat ventricular myocytes. Netoglitazone exposure (100 μM for 30 min or 10 μM for

Table I: PPAR agonists under development for the treatment of type 2 diabetes (from Prous Science Integrity®).

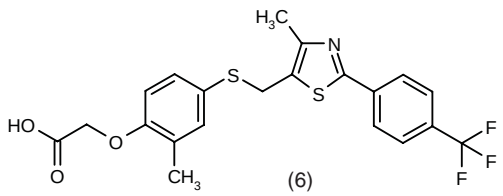
Drug	Source	Mechanism of Action	Phase
1. BMS-298585[1]	Bristol-Myers Squibb	PPARα agonist; PPARγ agonist	II
2. CLX-0921[1]	Calyx Therapeutics	PPARγ agonist	I
3. CS-011	Sankyo/Pfizer	PPARγ agonist	I
4. FK-614[1]	Fujisawa	PPARγ agonist	I
5. GW-409544X	GlaxoSmithKline/Ligand	PPARα agonist; PPARγ agonist	I
6. GW-501516	GlaxoSmithKline	PPARδ agonist	I
7. KRP-297	Kyorin/Merck & Co.	PPARα agonist; PPARγ agonist	II
8. Netoglitazone	Mitsubishi Pharma/Johnson & Johnson	PPARα agonist; PPARγ agonist	II
9. R-483[1]	Roche	PPARγ agonist	I
10. Ragaglitazar	Dr. Reddy's Res. Found./Novo Nordisk	PPARα agonist; PPARγ agonist	II
11. Reglitazar	Japan Tobacco/Pharmacia	PPARγ agonist	II
12. Tesaglitazar	AstraZeneca	PPARα agonist; PPARγ agonist	II



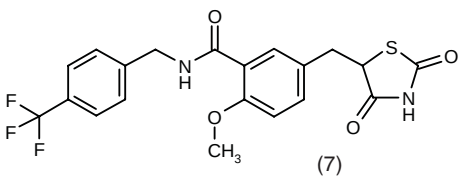
(3)



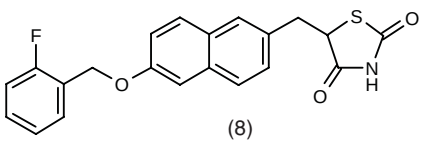
(5)



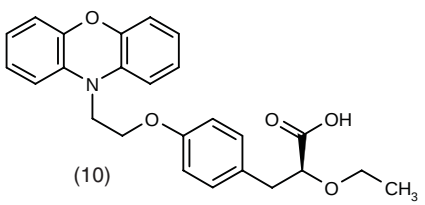
(6)



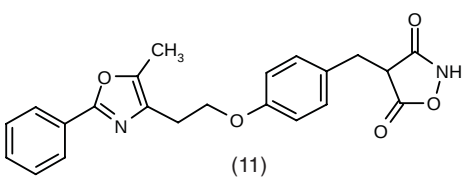
(7)



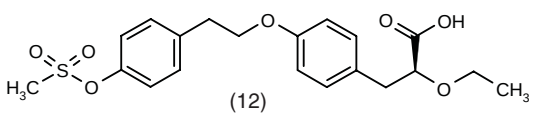
(8)



(10)



(11)



(12)

[1]Structure not yet detected

2 h) did not alter basal 3-*O*-methylglucose transport but did increase insulin (0.03 nM) action by 2-3-fold. Although treatment with the agent had no effect on autophosphorylation of the insulin receptor or on tyrosine phosphorylation of the insulin receptor substrate (IRS-1), a 2-fold increase in insulin action on IRS-1-associated phosphatidyl-inositol 3-kinase activity was observed. Further studies using cardiomyocytes from obese Zucker rats demonstrated that netoglitazone enhanced glucose transport and maximum insulin action by 2- and 1.6-fold, respectively, thus ameliorating insulin resistance. These effects were accompanied by a significant dephosphorylation of IRS-1 on Ser/Thr (29).

In vitro studies using isolated hepatocytes from Otsuka Long-Evans Tokushima fatty (OLETF) rats, an obese type 2 diabetes model, reported that incubation with alanine (10 mM) and netoglitazone (0.1 mM) significantly reduced glucose production. The agent had no effect on hepatocytes isolated from control rats nor did it influence alanine uptake. It was concluded that the effect of the agent was not via inhibition of alanine uptake but rather through suppression of the gluconeogenic pathway (30).

A study examining adipocytes and plasma leptin concentrations of male obese lean Zucker rats and Zucker diabetic (ZDF) rats treated with netoglitazone (10 mg/kg/day) for 21 days demonstrated that the agent caused a significant increase in gonadal white adipose tissue (WAT) mass in both obese (7.6 ± 0.3 *vs.* 6.4 ± 0.3 g in controls) and ZDF strains (7.0 ± 0.2 *vs.* 5.9 ± 002 g

Table II: Activity of PPAR agonists in cell-based transactivation assays (from Prous Science Integrity®).

	PPAR Transactivation Assay pEC_{50}				
	PPARα		PPARγ		
Compound	Human	Mouse	Human	Mouse	Ref.
Ciglitazone	–	–	4.64	5.52	41, 42
Farglitazar	6.35-6.52	<5	8.70-9.47	9.46	25, 26, 41
Fenofibrate	4.49-4.52	4.74	3.52	3.60	25, 26
GW-7845	5.46	–	9.15	8.92	25
GW-9578	7.30	8.30	6.00	5.82	25
KRP-297	6.07-6.40	5.00	6.30-7.08	6.85	25, 26
Netoglitazone	7.00	–	5.09-5.52	–	26, 27
Pioglitazone	<5.0-5.18	<5.0	6.00-6.23	6.26	25, 26, 41, 43
Regaglitazar	5.49-5.52	–	6.22-6.24	–	26, 43
Reglitazar	5.70-5.72	5.37	6.40-7.08	7.05	26, 43
Rosiglitazone	<5.0-5.39	<5.0	6.80-7.37	7.12	25, 26, 41, 43
Troglitazone	<5.0	<5.0	6.01-6.27	6.11	25, 41, 43
Wy-14643	4.90-5.30	6.20	4.22-4.53	4.49	25, 43

in controls). Both strains of treated rats also exhibited a significant reduction in ob mRNA density, and consequently, plasma leptin concentrations were unaffected by treatment. Analysis of WAT from both strains revealed a higher cell density as compared to tissue from untreated animals, suggesting that netoglitazone promoted preadipocyte differentiation (31).

The efficacy of netoglitazone was demonstrated in several *in vivo* models of diabetes. Two studies showed the efficacy of the agent in the type 2 diabetic db/db mice model. In one study netoglitazone (1, 3, 10 or 30 mg/kg/day p.o.) was administered to db/db mice for 2 weeks. Treatment with the agent dose-dependently improved mean serum triglyceride (75.3 *vs.* 239.4 mg/dl), VLDL (1943.9 *vs.* 7152.1 mg/dl) and VLDL-triglyceride (19.6 *vs.* 142 mg/dl) levels with significant reductions seen at a dose of 30 mg/kg/day. The 10 mg/kg/day dose also resulted in significant reductions in VLDL and VLDL-triglyceride levels (32). Similar results were obtained in another study using db/db mice which compared the effects of netoglitazone (1, 3, 10 or 30 mg/kg/day p.o.) with troglitazone (200 or 400 mg/kg/day), pioglitazone (30 mg/kg/day) and rosiglitazone (30 mg/kg/day) after 8 weeks of treatment. Netoglitazone time- and dose-dependently lowered plasma glucose and triglycerides; reductions in glucose were significant with doses of 10 and 30 mg/kg/day (487.3 and 175.5 mg/dl, respectively, *vs.* 754.6 mg/dl in db/db controls) and reductions in triglycerides were significant with a dose of 30 mg/kg/day (89.4 *vs.* 280.5 mg/dl). Both pioglitazone and rosiglitazone also significantly lowered glucose levels (552.1 and 231.9 mg/dl, respectively) but troglitazone had no effect. Moreover, netoglitazone doses of 10 and 30 mg/kg significantly decreased HbA1c in a dose-dependent manner. In contrast, although rosiglitazone significantly reduced HbA1c levels, troglitazone and pioglitazone had no effect (33).

Netoglitazone (1, 3, 10 or 30 mg/kg/day p.o. for 4 days) was also effective in the KK-Ay diabetic/obese mouse model, in contrast to glibenclamide (1 mg/kg for 4 days) which had no significant effects. The 3, 10 and 30 mg/kg/day doses of netoglitazone all significantly decreased plasma glucose levels (425, 400 and 290 mg/dl *vs.* 605 mg/dl in controls). In addition, 30 mg/kg/day significantly lowered plasma insulin (140 *vs.* 645 mU/ml), triglycerides (320 *vs.* 720 mg/dl) and free fatty acid levels (1450 *vs.* 3150 mEq/l) (34). The *in vivo* activity of netoglitazone and other PPAR agents in genetically diabetic/obese mice is summarized in Table III.

Netoglitazone was effective in studies using obese fatty (fa/fa) Zucker rats and ZDF rats. Chronic treatment with the agent (10 and 30 mg/kg p.o. for 21 days) resulted in a decrease in nonesterified fatty acid levels and an increase in liver glycogen concentrations in both models as compared to controls. Treated obese Zucker rats also displayed a significant reduction in plasma glucose levels and triglyceride levels. Moreover, treatment with netoglitazone resulted in a significant improvement in insulin sensitivity since both treated obese Zucker rats (2.01 ± 0.19 mg/min) and ZDF rats (6.42 ± 1.03 mg/min) required significantly higher glucose infusion rates during a euglycemic hyperinsulinemic clamp to maintain stable glucose concentrations as compared to their respective obese controls (0.71 ± 0.17 mg/min and 2.09 ± 0.71 mg/min, respectively).Treatment of ZDF rats also enhanced insulin-induced suppression of hepatic glucose production (35).

Experiments using young (6 week old) prediabetic ZDF rats with impaired glucose tolerance demonstrated that chronic treatment with netoglitazone (10 mg/kg p.o. for 28 days) was capable of preventing development of overt diabetes through maintenance of β-cell function and improvements in insulin sensitivity. Not only were blood glucose levels consistently less in treated ZDF rats as compared to controls but plasma insulin levels were maintained throughout the treatment period as compared to a 40% reduction seen in controls. At 8 weeks of age, the rise in body weight was maintained in treated ZDF

Table III: In vivo *activity of PPAR agonists in genetically diabetic/obese mice (from Prous Science Integrity®).*

Compound	Hypoglycemia		Insulinemia decrease	Triglyceride levels decrease	Ref.
	ED_{25}	ED_{50}	ED_{50}	ED_{50}	
Ciglitazone	47	–	–	–	44
Farglitazar	–	0.6	1.2	0.1	26
Fenofibrate	–	>100	–	>100	26
KRP-297	–	0.3	4.5	5.0	26
Netoglitazone	2.7	<3.0	<3.0	<3.0	26
Pioglitazone	4.6-14	2.3-30	15-31	0.4-26.7	26, 27, 43-46
Regaglitazar	–	0.4-2.1	0.3	0.1	26, 47
Reglitazar	38	238	234	206	45, 46
Rosiglitazone	7.1	0.5-0.87	0.07-0.7	0.14	26, 27, 43
Troglitazone	170-283	>323	>323	>323	44, 46

ED_{25} and ED_{50} expressed in mg/kg/day p.o.

animals as compared to an attenuation seen in untreated controls. Treated ZDF rats also displayed an improvement in insulin sensitivity in that they required a higher glucose infusion rate during a euglycemic hyperinsulinemic clamp (36).

Another *in vivo* study also using young (6 week old) prediabetic ZDF rats further demonstrated the protective effects of netoglitazone on pancreatic β-cells. Treatment with the agent (10 mg/kg p.o. for 28 days) partially protected pancreatic β-cells from apoptosis and cellular damage. These effects may be due to the netoglitazone-induced normalization in pancreatic nitric oxide synthase (NOS) activity (860 ± 93 *vs.* 1439 ± 124 fmol/mg protein in diabetic controls); nitrate/nitrite levels were also reduced in treated animals (4.01 ± 0.68 *vs.* 6.31 ± 0.79 nmol/mg protein in diabetic controls). It was concluded that damage of pancreatic β-cells may involve an excess in nitric oxide production and that netoglitazone may protect these cells via inhibition of NOS induction (37).

The insulin sensitizing effects of netoglitazone (about 0.17 mg/kg/day p.o. for 4 weeks) were also demonstrated in obese cynomolgus monkeys with abnormal glucose tolerance but no hyperglycemia. Although fasted plasma glucose levels were unchanged with treatment, plasma insulin levels were decreased by about 50%. Treatment also inhibited the increase in glucose (by 30%) and insulin (by 50%) observed in control obese monkeys and increased the glucose tolerance rate or K value 1.8 times (38).

The safety of netoglitazone was shown in *in vivo* studies using rats and cynomolgus monkeys where the agent had no significant hematological or cardiac side effects. Although rats treated with pioglitazone or rosiglitazone at doses of more than 100 mg/kg displayed dose-dependent reductions in hemoglobin and/or hematocrit and cardiac hypertrophy, netoglitazone-treated animals had only slight anemia with doses of 1000 mg/kg and no alterations in the heart. Further testing of netoglitazone (10, 30, 100 and 300 mg/kg for 13 weeks) in monkeys demonstrated that the agent did not induce anemia or cardiac hypertrophy (39).

Clinical Studies

Netoglitazone is currently undergoing phase II trials as a treatment for type 2 diabetes (40).

Source

Mitsubushi Pharma Corp. (JP); licensed to Johnson & Johnson (US) worldwide.

References

1. Qu, J., Ichikawa, S., Iwane, H. (Mitsubishi Chemical Corp.). *6-Hydroxy-2-naphthylcarbinol and process for the preparation thereof.* WO 0073252.

2. Ueno, H., Ohe, T., Suehiro, I., Sekiya, T. (Mitsubishi Chemical Corp.). *Preparation method of naphthalene derivs.* JP 1998139768.

3. Ueno, H., Oe, T., Suehiro, I., Nakamura, F. (Mitsubishi Chemical Corp.). *Naphthalene derivs.* EP 0604983, JP 1994247945, US 5594016.

4. Prous Science Drug R&D Backgrounders: *Diabetes mellitus (online publication).* Updated February 5, 2002.

5. Lehmann, J.M., Moore, L.B., Smith-Oliver, T.A., Wilkison, W.O., Willson, T.M., Kliewer, S.A. *An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor γ (PPARγ).* J Biol Chem 1995, 270: 12953-6.

6. Forman, B.M., Tontonoz, P., Chen, J., Brun, R.P., Spiegelman, B.M., Evans, R.M. *15-Deoxy-Δ12,14-prostaglandin J_2 is a ligand for the adipocyte determination factor PPARγ.* Cell 1995, 83: 803-12.

7. Lambe, K.G., Tugwood, J.D. *A human peroxisome-proliferator-activated receptor-γ is activated by inducers of adipogenesis, including thiazolidinedione drugs.* Eur J Biochem 1996, 239: 1-7.

8. Berger, J., Bailey, P., Biswas, C., Cullinan, C.A., Doebber, .W., Hayes, N.S., Saperstein, R., Smith, R.G., Leibowitz, M.D. *Thiazolidinediones produce a conformational change in peroxisomal proliferator-activated receptor-γ. Binding and activation correlate with antidiabetic actions in db/db mice.* Endocrinology 1996, 137: 4189-95.

9. Greene, M.E., Blumberg, B., McBride, O.W., Yi, H.F., Kronquist, K., Kwan, K., Hsieh, L., Greene, G., Nimer, S.D. *Isolation of the human peroxisome proliferator activated receptor γ cDNA: Expression in hematopoietic cells and chromosomal mapping.* Gene Expr 1995, 4: 281-99.

10. Issemann, I., Green, S. *Activation of a member of the steroid hormone receptor superfamily by peroxisome proliferators.* Nature 1990, 347: 645-50.

11. Kliewer, S.A., Forman, B.M., Blumberg, B., Ong, E.S., Borgmeyer, U., Mangelsdorf, D.J., Umesono, K., Evans, R.M. *Differential expression and activation of a family of murine peroxisome proliferator-activated receptors.* Proc Natl Acad Sci USA 1994, 91: 7355-9.

12. Schmidt, A., Endo, N., Rutledge, S.J., Vogel, R., Shinar, D., Rodan, G.A. *Identification of a new member of the steroid hormone receptor superfamily that is activated by a peroxisome proliferator and fatty acids.* Mol Endocrinol 1992, 6: 1634-41.

13. Zhu, Y., Alvares, K., Huang, Q., Rao, M.S., Reddy, J.K. *Cloning of a new member of the peroxisome proliferator-activated receptor gene family from mouse liver.* J Biol Chem 1993, 268: 26817-20.

14. *A unified nomenclature system for the nuclear receptor superfamily.* Cell 1999, 97: 161-3.

15. Fajas, L., Auboeuf, D., Raspe, E. at al. *The organization, promotor analysis, and expression of the human PPARγ gene.* J Biol Chem 1997, 272: 18779-89.

16. Xue, J.C., Schwarz, E.J., Chawla, A., Lazar, M.A. *Distinct stages in adipogenesis revealed by retinoid inhibition of differentiation after induction of PPARγ.* Mol Cell Biol 1996, 16: 1567-75.

17. Fajas, L., Fruchart, J.C., Auwerx, J. *PPARγ3 mRNA: A distinct PPARγ mRNA subtype transcribed from an independent promotor.* FEBS Lett 1998, 55-60.

18. Yu, K., Bayona, W., Kallen, C.B., Harding, H.P., Ravera, C.P., McMahon, G., Brown, M., Lazar, M.A. *Differential activation of peroxisome proliferator-activated receptors by eicosanoids.* J Biol Chem 1995, 270: 23975-83.

19. Kliewer, S.A., Lenhard, J.M., Willson, T.M., Patel, I., Morris, D.C. Lehmann, J.M. *A prostaglandin J_2 metabolite binds peroxisome proliferator-activated gamma and promotes adipocyte differentiation.* Cell 1995, 83: 813-9.

20. Krey, G., Braissant, O., L'Horset, F., Kalkhoven, E., Perroud, M., Parker, M.G., Wahli, W. *Fatty acids, eicosanoids, and hypolipidemic agents identified as ligands of peroxisome proliferator-activated receptors by coactivator-dependent receptor ligand assay.* Mol Endocrinol 1997, 11: 779-91.

21. Ricote, M., Li, A.C., Willson, T.M., Kelly, C.J., Glass, C.K. *The peroxisome proliferator activated receptor-γ is a negative regulator of macrophage activation.* Nature 1998, 391: 79-82.

22. Kliewer, S.A., Umesono, K., Noonan, D.J., Heyman, R.A., Evans, R.M. *Convergence of 9 cis retinoic acids and peroxisome proliferator signalling pathways through heterodimer formation of their receptors.* Nature 1992, 358: 771-4.

23. Hulin, B., McCarthy, P.A., Gibbs, E.M. *The glitazone family of antidiabetic agents.* Curr Pharm Des 1996, 2: 85-102.

24. Antihyperglycemic Thiazolidinediones: Ciglitazone and its Analogues. J.R. Colca and D.R. Morton (Eds.), Smith-Gordon, New York, 1990, 255-61.

25. Willson, T.M., Brown, P.J., Sternbach, D.D., Henke, B.R. *The PPARs: From orphan receptors to drug discovery.* J Med Chem 2000, 43: 527-50.

26. Wulff, E.M., Jeppesen, L., Bury, P.S., Mogensen, J.P., Fleckner, J., Andersen, A.-S.T., Wassermann, K., Sauerberg, P. *Characterisation of a future generation insulin sensitizers in vitro and in vivo.* Diabetes 2001, 50(Suppl. 2): Abst 2210-PO.

27. Reginato, M.J., Bailey, S.T., Krakow, S.L., Minami, C., Ishii, S., Tanaka, H., Lazar, M.A. *A potent antidiabetic thiazolidinedione with unique peroxisome proliferator-activated receptor γ-activating properties.* J Biol Chem 1998, 273: 32679-84.

28. Burris, T.P., Yang, M., Rybczynski, P.J., Combs, D.W., Demarest, K.T. *Characterization of a thiazolidinedione with PPARγ super agonist activity.* 81st Annu Meet Endocr Soc (June 12-15, San Diego) 1999, Abst P2-666.

29. Liu, L.S., Tanaka, H., Ishii, S., Eckel, J. *The new antidiabetic drug MCC-555 acutely sensitizes insulin signaling in isolated cardiomyocytes.* Endocrinology 1998, 139: 4531-9.

30. Mizubayashi, R., Nakamura, J., Hamada, Y., Nakayama, M., Chaya, S., Komori, H., Kiriyama, T., Kasuya, Y., Yasuda, Y., Hotta, N. *Acute effect of MCC-555 in isolated hepatocytes of Otsuka Long-Evans Tokushima fatty rats.* Diabetologia 43(Suppl. 1): A190.

31. Widdowson, P.S., Upton, R., Ishii, S., Williams, G. *The thiazolidinedione, MCC-555, reduces ob expression in mature adipocytes, but does not alter plasma leptin concentrations.* Br J Pharmacol 1998, 123(Suppl.) Abst 187P.

32. Ishii, S., Tanaka, H. *Effect of repeated administration of RWJ 241947/MCC-555, a novel insulin sensitizer, on serum lipoprotein levels in db/db mice.* Diabetes 2001, 50(Suppl. 2): Abst 577-P.

33. Ishii, S., Tanaka, H., Shiraishi, M. *Comparative effects of thiazolidinediones on plasma glucose and triglycerides in a mouse model of diabetes.* 37th Annu Meet Eur Assoc Study Diabetes (Sept 9-13, Glasgow) 2001, Abst 766.

34. Tanaka, H., Ishii, S., Shiraishi, M. *Hypoglycemic, hyperinsulinemia-improving and hypolipidemic effects of a novel insulin sensitizer in KK-A(Y) mice.* 37th Annu Meet Eur Assoc Study Diabetes (Sept 9-13, Glasgow) 2001, Abst 866.

35. Upton, R., Widdowson, P.S., Ishii, S., Tanaka, H., Williams, G. *Improved metabolic status and insulin sensitivity in obese fatty (fa/fa) Zucker rats and Zucker diabetic fatty (ZDF) rats treated with the thiazolidinedione, MCC-555.* Br J Pharmacol 1998, 125: 1708-14.

36. Pickavance, L., Widdowson, P.S., King, P., Ishii, S., Tanaka, H., Williams, G. *The development of overt diabetes in young Zucker diabetic fatty (ZDF) rats and the effects of chronic MCC-555 treatment.* Br J Pharmacol 1998, 125: 767-70.

37. Pickavance, L.C., Widdowson, P.S., Foster, J.R., Ishii, S., Tanaka, H., Williams, G. *The thiazolidinedione, MCC-555, prevents nitric oxide synthase induction in the pancreas of the Zucker diabetic fatty rat.* Brit J Pharmacol 128(Suppl.): Abst 116P.

38. Ishii, S., Hike, N., Yoshida, T. *The improving effect of MCC-555, an insulin sensitizer, on glucose tolerance in obese cynomolgus monkeys.* Diabetes 1999, 48(Suppl. 1): Abst 2006.

39. Ishii, S., Wasaki, M., Ohe, T., Ueno, H., Tanaka, H. *MCC-555: A highly potent thiazolidinedione lacking hematological and cardiac side-effects.* Diabetes 45(Suppl. 2): Abst 515.

40. *Research & developments.* Mitsubishi Pharma Corporation Web Site February 7, 2002.

41. Henke, B.R., Blanchard, S.G., Brackeen, M.F. et al. *N-(2-Benzoylphenyl)-L- tyrosine PPARγ agonists. 1. Discovery of a novel series of potent antihyperglycemic and antihyperlipidemic agents.* J Med Chem 1998, 41: 5020-36.

42. Willson, T.M., Cobb, J.E., Cowan, D.J., Wiethe, R.W., Correa, I.D., Prakash, S.R., Beck, K.D., Moore, L.B., Kliewer, S.A., Lehmann, J.M. *The structure-activity relationship between peroxisome proliferator-activated receptor γ agonism and the antihyperglycemic activity of thiazolidinediones.* J Med Chem 1996, 39: 665-8.

43. Sauerberg, P., Pettersson, I., Jeppesen, L. et al. *Novel tricyclic-α-alkyloxyphenylpropionic acids: dual PPARα/γ agonists with hypolipidemic and antidiabetic activity.* J Med Chem 2002, 45: 789-804.

44. Arakawa, K., Inamasu, M., Matsumoto, M. et al. *Novel benzoxazole 2,4 thiazolidinediones as potent hypoglycemic agents. Synthesis and structure activity relationships.* Chem Pharm Bull 1997, 45: 1984-93.

45. Shinkai, H., Onogi, S., Tanaka, M., Shibata, T., Iwao, M., Wakitani, K., Uchida, I. *Isoxazolidine-3,5-dione and noncyclic 1,3-dicarbonyl compounds as hypoglycemic agents.* J Med Chem 1998, 41: 1927-33.

46. Shibata, T., Matsui, K., Nagao, K., Shinkai, H., Yonemori, F., Wakitani, K. *Pharmacological profiles of a novel oral antidiabetic agent, JTT-501, an isoxazolidinedione derivative.* Eur J Pharmacol 1999, 364: 211-9.

47. Chakrabarti, R., Vikramadithyan, R.K., Suresh, J., Misra, P., Hiriyan, J., Rajagopalan, R. *(–) DRF 2725, a novel dual activator of PPARα and PPARγ with unique antidiabetic hypolipidemic activity*. Diabetes 2001, 50(Suppl. 2): Abst 432-P.