# Hydroxyurea Derivatives as Hypoglycemic Agents

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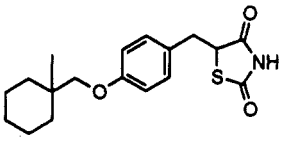
Non-insulin-dependent diabetes mellitus (NIDDM) is a disease typically characterized by peripheral insulin resistance, hyperglycemia, and obesity.[1] In addition to exercise and modified diet, glycemic control is often aided by the use of therapeutic agents.[2] The ones most commonly employed sulfonylureas[3] often suffer from primary or secondary failure as well as potentially fatal hypoglycemia.[4] This serious side effect is presumably due to the insulin-releasing properties of these drugs which persist even in the presence of low plasma glucose.[5] Additionally, some extra pancreatic actions of these compounds have recently been noted.[6] Other non-sulfonylurea compounds which do not have insulin-releasing properties have been investigated in NIDDM and are the subject of several recent reviews.[7]

Takeda, in 1982, reported on a series of compounds that apparently potentiate the action of insulin in the periphery.[8] The prototypical agent, ciglitazone (1), a 5-(4-alkoxybenzyl)thiazolidine-2,4-dione, was shown to lower blood glucose to normal levels in animal models of NIDDM but not in normal animals or insulin-dependent diabetes models.[9] This class of compounds appears to act via a mechanism that has a reduced risk of hypoglycemic episodes. Since that disclosure, several reports have appeared describing attempts to find more potent and better tolerated analogs.[10-12] The majority of the work reported thus far has explored replacements for the lipophilic tail (the methyl cyclohexylmethyl ether in 1) as well as moieties which may replace the phenyl ether. With few exceptions,[11-13] the acidic heterocyclic portion of the molecule has remained largely unexplored.[14] We chose to examine derivatives of the potent oxazolylethoxy backbone described by Meguro[10b,c] in which the acidic heterocycle is attached to this side chain at a nonenolizable site.[15] Our initial target was oxadiazoledione 3, in which C-5 of oxazolidinedione 2[12] is been replaced by a nitrogen.[16]



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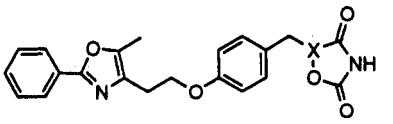
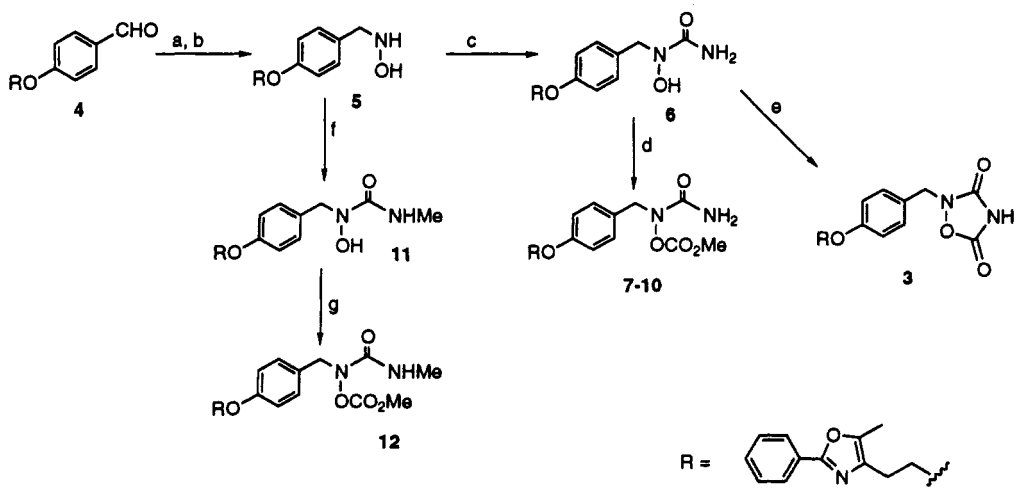


2 X = CH
3 X = N

These compounds were prepared (Scheme I) by the conversion of aldehyde 4[10b,c] to the oxime (96%, mp 149–151 °C) with hydroxylamine hydrochloride followed by reduction[17] with $NaBH_3CN$ in HCl/MeOH to the corresponding hydroxylamine 5 (97%, mp 99–100 °C). Treatment with excess potassium cyanate in acetic acid/water gave the desired hydroxyurea 6 (67%, mp 148–150 °C) which was readily converted into the oxadiazoledione 3 (72%, mp 195–197 °C) with ethyl chloroformate and 3 equiv of NaOH. If only 1 equiv of NaOH was utilized, carbonate derivatives 7–10 were isolated (7, 33%, mp 153–156 °C; 8, 17%, mp 130–133 °C; 9, 22%, mp 101–103 °C; 10, 11%, mp 130–132 °C). Carbalkoxylation occurred unambiguously on oxygen as evidenced by a major mass spectral fragment showing the loss of $-OCO_2R$.[18] Accordingly, *N*-methyl derivative 12 (29%, mp 134–135 °C) was isolated after treatment of 5 with methyl isocyanate in $CH_2Cl_2$ to give 11 (70%, mp 139–144 °C) followed by methyl chloroformate in $CH_2Cl_2$ with 1 equiv of $Et_3N$.

These compounds were then evaluated in vivo for the ability lower blood glucose in the ob/ob mouse model.[19] While it was comforting to see that the hypoglycemic activity (Table I) of 3 was near that of its oxazolidinedione analog 2,[12] we were quite surprised to find similar potency for the methyl carbonate 7. The activity of this series is clearly at a maximum with the methyl derivative and rapidly declines with increasing alkoxy size. While the carbonates themselves may have intrinsic activity, we

**Scheme I**[a]



[a] Reagents: (a) $NH_2OH$ HCl, pyridine; (b) $NaBH_4$, HCl, MeOH; (c) KOCN, HOAc, $H_2O$; (d) 1 equiv of NaOH, $H_2O$, $ClCO_2R$; (e) 3 equiv of NaOH, $H_2O$, $ClCO_2Et$; (f) MeNCO, $CH_2Cl_2$; (g) $ClCO_2Me$, $Et_3N$, $CH_2Cl_2$.

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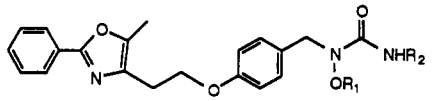
**Table I.** Hypoglycemic Effect in ob/ob Mice



| | | | % glucose normalization[a] | | | |
|---|---|---|---|---|---|---|
| no.[b] | $R_1$ | $R_2$ | 25 mg/kg | 10 mg/kg | 5 mg/kg | 1 mg/kg |
| 3 | –CO– | | 97* | 100* | NT[c] | 45* |
| 7 | $CO_2Me$ | H | 100* | 77* | 80* | 28* |
| 8 | $CO_2Et$ | H | | | 52* | |
| 9 | $CO_2{}^tBu$ | H | | | 50 | |
| 10 | $CO_2Ph$ | H | | | 25 | |
| 11 | H | Me | | | 25* | |
| 12 | $CO_2Me$ | Me | | | 25 | |

[a] Normalization relative to the effect of ciglitazone at 50 mg/kg which lowers blood glucose levels to that of lean littermates. [b] All compounds had C, H, and N analyses ± 0.4% of the theoretical value except 12 (N: calcd: 9.47; found: 8.85). [c] NT = not tested. *, $p < 0.05$.

**Table II.** Effect on GLUT 1 Glucose Transporter Expression in 3T3-L1 Adipocytes[a]

| | drug concentration (μm) | | |
|---|---|---|---|
| no. | 0.3 | 3 | 30 |
| 6 | 97.0 ± 5.6 | 109.8 ± 7.6 | 140.6 ± 10.5* |
| 3 | 109.7 ± 7.5 | 130.6 ± 5.6* | 142.3 ± 14.2* |
| 7 | 90.5 ± 13.0 | 113.0 ± 5.2 | 164.5 ± 13.9* |
| 1 | NT | NT | 151.3 ± 0.3* |

[a] Values are expressed as percentage (%) of basal, mean ± SE, after incubation with the compound at the specified concentration for 48 h. *, $p < 0.05$ when compared to control cells. NT = not tested.

cannot discount the possibility that they might be converted into 6 or 3 in vivo. It is, however, interesting to note that compound 6, when dosed at 50 mg/kg, produced a change in blood glucose that was not significantly different from control animals in the same assay. Also surprising is the potent activity of *N*-methylhydroxyurea 11 which caused a 25% drop in glucose when dosed at 5 mg/kg. It is conceivable that the disparity in activity between 11 and 6 might be due to differences in absorption/metabolism. Carboxymethylation of this material on oxygen, to give compound 12, does not improve activity, a trend not followed in the transformation of 6 to 7.

In order to better understand the intrinsic activity of this series, we examined compounds 3, 6, and 7 for the ability to increase glucose transporter expression in cell culture (after 48-h incubation with drug, in the absence of insulin, 3T3-L1 adipocytes were assayed by quantitative immunoblotting utilizing antibodies specific for GLUT 1).[20] The results (Table II) show that oxadiazoledione 3 is the most potent of the three compounds, effecting an increase in GLUT 1 glucose transporter at both 3 and 30 μM. Hydroxyureas 6 and 7 appear to be less potent, causing an upregulation of the protein only at 30 μM, although clearly they do possess intrinsic activity. The in vitro activity of compounds in this series is consistent with the activity seen in whole animals. Furthermore, the need to invoke a biotransformation of 7 into 3 or 6 for in vivo activity is unwarranted as 7 possesses activity in its own right.

In summary, the in vivo hypoglycemic activity found in the oxazolidinedione analog 2 was found to be retained when the epimerizable C-5 center was replaced with a nitrogen. This activity, as well as GLUT 1 glucose transporter upregulation, was further extended to the ring-opened carboalkoxylated hydroxyureas, the first acyclic non-carboxylic acid compounds[21] to show this potent biological effect.

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(16) This work has been disclosed in a patent application: WO 9203425; *Chem. Abstr.* **1992**, *117*, 26553s.

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(18) As additional proof of oxygen carbonylation, the $^1$H NMR signal for the NMe absorbance in **12**, 2.83 (d, $J$ = 5 Hz, 3H), upon treatment with $D_2O$, collapsed to a singlet. This doublet in **12** was presumably due to HNMe coupling and not restricted rotation of the isomeric nitrogen carbonylated material. We would like to thank a reviewer for suggesting this experiment.

(19) For biological procedures, see our earlier work in this area (ref 10m).

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(21) Hulin has patented a series of $\alpha$-substituted arylpropionic acids as hypoglycemic agents: US Patent 5 089 514.