followed by quenching with triethylamine (6.8 mL, 48.8 mmol) and purification of the product by column chromatography as described for 1 afforded 3 as an oil; recrystallization of the product from 10 mL of *n*-hexane furnished 3 (0.27 g, 39%) as small colorless needles: mp 115–116.5 °C; ¹H NMR δ 0.93 (s, 9 H, *t*-Bu), 4.27 (s, 6 H, CH₂), 7.16 (dd, 1 H, J = 1.4 Hz, J = 7.7 Hz), 7.23–7.31 (m, 2 H), 7.71 (dd, 1 H, J = 1.7 Hz, J = 7.6 Hz); IR 2960, 2100 (NCS), 1600, 1470, 1330, 1240, 1125, 1000, 750 cm⁻¹; CIMS M + H = 306. Anal. (C₁₆H₁₉NO₃S) C, H, N.

1-(o-Nitrophenyl)-4-tert-butyl-2,6,7-trioxabicyclo[2.2.2]octane (15). Compound 11 (2.62 g, 8.94 mmol) in 80 mL of dry CH₂Cl₂ was treated with BF₃·OEt₂ (6.0 mL, 48.8 mmol) and stirred for 48 h at room temperture. Treatment of the reaction mixture with triethylamine (excess) and isolation of the product as described above for 9 afforded 15 (0.37 g, 14%) as colorless needles (2-propanol, 5 mL): mp 198–199 °C; ¹H NMR δ 1.04 (s, 9 H, t-Bu), 4.19 (s, 6 H, CH₂), 7.44 (m, 2 H), 7.55–7.93 (complex m, 2 H); IR 2960, 2900, 1530, 1370, 1330, 1125, 1000, 770, 740 cm⁻¹; CIMS M + H = 294. Anal. (C₁₅H₁₉NO₅) C, H, N. Attempts to improve the yield failed.

Biochemical and Biological Methods. Tissue Preparation. Adult male Sprague-Dawley rats (approximately 200 g) supplied by Taconic Farms (Germantown, NY) were decapitated, and the cerebral cortices removed on ice. The tissue was weighed and disrupted with a Brinkman Polytron (setting 5–6 for 15 s) in 50 volumes of 50 mM potassium phosphate buffer, pH 7.4, containing 100 mM sodium chloride. Cortical homogenates were centrifuged at 20000g (4 °C) for 20 min. The resulting pellets were resuspended in an equal volume of buffer containing sodium chloride and recentrifuged. This "washing" procedure was repeated a total of five times. The final pellet was resuspended in 10–15 volumes chloride free potassium phosphate buffer. Membranes were prepared and used on the same day as the assay.

For experiments in which cortical homogenates were pretreated with 1, 2, or 3 prior to incubation with the radioligand, aliquots of a twice-washed 1:15 cortical homogenate were incubated on ice for 1 h with 1 (60 nM), 2 (600–2400 nM), or 3 (600–2400 nM) in the presence of 200 mM sodium chloride. The reaction was terminated by dilution with approximately 10 volumes of potassium phosphate buffer, pH 7.4, containing 100 mM sodium chloride and centrifuged at 20000g, at 4 °C for 20 min. Resuspension of the pellet in the same volume of chloride containing buffer and centrifugation was carried out for a total of five washes. The final pellet was resuspended in 15 volumes of chloride-free buffer.

Receptor Binding. [³⁵S]**TBPS.** One hundred and fifty microliters of cortical homogenate (approximately 10 mg original wet weight) was added to tubes containing potassium phosphate buffer, pH 7.4, 200 mM NaCl, 2–5 nM [³⁵S]TBPS and unlabeled TBPS (0–160 nM) in a total volume of 500 μ L. Nonspecific binding was defined with use of 20 μ M picrotoxinin. Incubations were carried out at room temperature (25 °C) for 2 h and ter-

minated by rapid filtration over Whatman GF/B glass fiber filters with two 5-mL washes with ice-cold 50 mM potassium phosphate buffer. Radioactivity retained on the filters was determined by liquid scintillation spectrometry.

When inhibition of [35 S]TBPS binding was measured by the simultaneous addition of radioligand and acylators, 5 nM radioligand was employed with 5–1000 nM 1 and 50–10000 nM 2 and 3. For sequential addition of [35 S]TBPS and acylators, cortical homogenates were first incubated with 5 nM radioligand for 60 min. The acylators were then added and the incubations continued for an additional 60 min. All other conditions were maintained as discussed above.

Molecular Modeling. The optimized conformations of the thioureas 1a, 2a, and 3a (Figure 2) produced by acylation of a lysine residue by 1, 2, and 3, respectively, were obtained by MNDO calculations using SYBYL software (version 5.1, TRIPOS Assoc., a division of Evans and Sutherland, St. Louis, MO). Each optimized conformation was then subjected to conformational search with either (a) no constraint on the distance from the α -carbon in the lysine moiety $(C-\alpha)$ to C-4 (for numbering, see TBOB structure) in the cage portion of the molecule, or (b) a 13.6-13.8 Å C- α to C-4 distance constraint within 5 kcal/mol of the global energy minimum, or (c) a 15.6–15.7 Å C- α to C-4 distance constraint within 5 kcal/mol of the global energy minimum. Each conformation obtained from the conformational search routine was then optimized with use of Maximin2. The energies and distances reported in Table II are for the Maximin2 optimized conformations.

The global energy minimum conformations of TBOB, 1, 2, and 3 were also calculated by MNDO. The molecular dimensions (Figure 3) were obtained by measuring the distance from the center-line axis of each compound to the outside edge of the van der Waals radius of the most distant atom. For TBOB, the distance of a methyl hydrogen on the tert-butyl group to the center-line axis was found to be 3.21 Å. For the isothiocyanate derivatives, the distance from the sulfur atom was used; for the para isomer, this distance was determined to be 3.38 Å, while for the ortho and meta isomers, a distance range of 4.89-6.76 Å was found. The "effective diameters" were defined as the sum of the radii; for the isothiocyanate derivatives, the effective diameter was taken as the sum of the distance from the sulfur atom and the *tert*-butyl hydrogen to the center-line axis (Table II); for TBOB, the effective diameter was taken as twice the distance from one of the methyl hydrogens of the tert-butyl group to the center-line axis.

Registry No. 1, 119963-45-0; 2, 119963-44-9; 3, 132981-30-7; 4, 99250-47-2; 5, 132981-25-0; 6, 132981-26-1; 7, 132981-27-2; 8, 132981-24-9; 9, 119963-47-2; 10, 119963-48-3; 11, 132981-28-3; 12, 133008-41-0; 13, 132981-29-4; 15, 132981-31-8; [^{35}S]-TBPS, 98774-25-5; p-O₂NC₆H₄COCl, 122-04-3; CSCl₂, 463-71-8; o-O₂NC₆H₄COCl, 610-14-0.

Benzyloxazolidine-2,4-diones as Potent Hypoglycemic Agents

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A series of benzyloxazolidine-2,4-diones, containing oxazole-based side chains, were found to lower blood glucose levels in the genetically obese ob/ob mouse. Incorporation of a benzofuran structural element in these compounds provides greatly enhanced in vivo potency. The syntheses and structure-activity relationships for this series are detailed.

Diabetes mellitus is a complex, chronic, progressive disease which eventually can adversely affect a number of

organs, as well as the nervous and vascular systems. Of the estimated six million individuals diagnosed with dia-

Table I. Glucose-Lowering Effects of Oxazolidinediones on Ob/ob Mice



							·			% glucose normalization ^b				
no.	R	x	Y	m	n	mp, °C	formula	prep methodª	25	10 mg/kg	5 mg/kg	1 mg/kg	0.5 mg/kg	0.2 mg/kg
15	Ph	0	0	1	1	163-165	C22H20N2O5	Ā				100*	28	
16	$4-(MeO)C_6H_4$	0	0	1	1	141-143	$C_{23}H_{22}N_2O_6$	в				80	53	
17	$3,5-(CF_3)_2C_6H_3$	0	0	1	1	167-170	C ₂₄ H ₁₈ F ₆ N ₂ O ₅ ^c	С					95*	14
18	2-furyl	0	0	1	1	148-151	$C_{20}H_{18}N_2O_6$	Α			24	14		
19	2-naphthyl	0	0	1	1	173-175	$C_{26}H_{22}N_2O_5^d$	Α				98*	100	46
20	cyclohexyl	0	0	1	1	209-214 dec	$C_{22}H_{25}N_2O_5Na\cdot 2H_2O$	С				61		
21	Ph	0	C(0)	1	1	198-200	$C_{23}H_{20}N_2O_5$	В			75	13		
22	2-naphthyl	\mathbf{S}	0	1	1	182-183	$C_{26}H_{22}N_2O_4S$	С					0	
23	Ph	0	0	1	0	19 9– 203	C ₂₁ H ₁₈ N ₂ O ₅ ^e					0		
24	Ph	0	0	0	1	158-160	$C_{21}H_{18}N_2O_5$	в			60			
25						142-144	$C_{26}H_{22}N_2O_5^{f}$	в			10	0		
26						7 9 -81	C ₂₈ H ₂₄ N ₂ O ₅ 1.25MeOH	в		40				
27						183-185	$C_{23}H_{16}N_2O_5$	в	0					
28						207-208	$C_{22}H_{18}N_2O_5$	В				9		

^a Method A is shown in Scheme I; Method B is shown in Scheme II; Method C is shown in Scheme IV. ^bNormalization relative to the ciglitazone effect at 50 mg/kg, which lowers blood glucose levels to that of the lean littermates. *p < 0.001. ^cCalcd: C, 54.55. Found: C, 53.95. ^dCalcd: C, 70.58. Found: C, 69.73. ^eCalcd: C, 66.66. Found: C, 65.98. ^fCalcd: C, 70.58. Found: C, 69.32.

betes mellitus in the United States,¹⁻³ ca. 90% are characterized as non-insulin dependent (NIDDM, type II). In addition, it has been estimated⁴ that nearly an equal number of type II diabetics remain undiagnosed. Because 80% of NIDDM patients are obese, diet and exercise are utilized as first-line therapies.⁵ Since dietary adherence is difficult for most patients, medication is necessary for many NIDDM patients. The most commonly employed oral hypoglycemics are the sulfonylureas (SU),^{6,7} whose mechanism of action probably involves insulin release.⁸ Both the first generation SU, e.g., tolbutamide (1),⁹ and



the second generation SU, e.g., glipizide, $(2)^{10}$ are valuable

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- (8) Lebovitz, H. E.; Feinglos, M. N. In Diabetes Mellitus, 3rd Ed.; Medical Examination Publishing Co.: New Hyde Park, NY, 1983; p 591.
- (9) (a) Haack, E. Arzneim.-Forsch. 1958, 8, 444. (b) Ruschig, H.; Korger, G.; Aumuller, N.; Wagner, H.; Weyer, R.; Bander, A.; Scholz, J. Arzneim.-Forsch. 1958, 8, 448.

therapies but possess disadvantages such as primary or secondary failure of efficacy as well as the potential for induction of hypoglycemia.³ The only other oral hypoglycemic drugs in use today are the biguanides, typified by metformin. These agents are limited to non-United States markets, however.¹¹ Numerous other nonsulfonylurea hypoglycemic compounds have been investigated clinically for treatment of NIDDM, but none of these have been sufficiently efficacious or well-tolerated to have reached market status.¹² Many of the newer agents reduce elevated glucose levels in animal models by non-insulin-releasing mechanisms and have been the subject of several recent reviews.^{13,14}

In 1982, workers at Takeda reported the preparation and hypoglycemic activity of a series of agents incorporating a range of weakly acidic heterocyclic functionalities. A series of benzylthiazolidine-2,4-diones were shown to effectively reduce insulin resistance or potentiate insulin action in genetically diabetic and/or obese animals.¹⁵ The prototypical agent, ciglitazone (3), was shown to lower plasma glucose levels in animal models of NIDDM but not in nondiabetic animal models.¹⁶ More recently, these

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- (11) The extent of biguanide therapy is minor and limited to some foreign markets, see: refs 5 and 6. For a review, see: Schafer, G. Diabetes Metab. 1983, 9, 148.
- (12) Acarbose, an α-glucosidase inhibitor, has recently been approved in Switzerland. See: Clissold, S. P.; Edwards, C. Drugs 1988, 24, 209.
- (13) Steiner, K. E.; Lien, E. L. Prog. Med. Chem. 1987, 24, 209.
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workers have identified a series of highly potent benzylthiazolidine-2,4-diones containing a 4-linked oxazole moiety, e.g. **4a**.¹⁷

With the interest in thiazolidine-2,4-diones¹⁸ as a potential therapeutic class of drugs for the treatment of NIDDM, our attention was directed toward the identification of other chemical series possessing similar hypoglycemic activity. During their profiling of other acidic heterocyclic ring systems related to thiazolidine-2,4-diones, including the analogous benzyloxazolidine-2,4-diones, the Takeda group showed that there is little or no hypoglycemic activity associated with these systems.¹⁵ In a more recent report,¹⁹ a series of phenyloxazolidine-2,4-diones were shown to cause improvements in glucose tolerance in fasted rats. It was reasoned that combination of the oxazolidine-2,4-dione functionality with the potent oxazole-based side chain (i.e. 4b) could potentiate the weak to moderate hypoglycemic activity observed in these earlier studies. This report details some of the structure-activity relationship (SAR) studies on this series.

Chemistry. The benzyloxazolidinediones in Tables I and II were prepared by one of three different synthetic approaches. The initial route selected, Scheme I, is based on previously reported alkylation reactions of N-phenyl-2,4-oxazolidinedione.²⁰ The requisite benzyl halides 6 were readily available in a two-step procedure from the known¹⁷ oxazole-containing benzaldehydes 5. Based on its ease of removal,²¹ the imide functionality of 2,4-oxazolidinedione was protected with a triphenylmethyl group. Generation of the 5-carboxylate dianion of N-(triphenylmethyl)-2,4oxazolidinedione using magnesium methyl carbonate²⁰ and reaction with the appropriate benzyl chloride provides the corresponding N-(triphenylmethyl)-protected benzyloxazolidinediones; however yields of >20% were never realized. Removal of the triphenylmethyl protecting group with neat trifluoroacetic acid provided the target oxazolidinediones. Given the low yields obtained in the alkylation step, alternative approaches to the benzyloxazolidinediones were explored.

Although 2,4-oxazolidinedione will not undergo basecatalyzed $^{\mathbf{\tilde{2}2}}$ condensations with aromatic aldehydes, 2-

- (18) For other efforts related to ciglitazone, see: (a) Meguro, K.; Fujita, T. U.S. Patent 4 687 777, 1987. (b) Yoshioka, T.; Kitazawa, G.; Kurumada, T.; Mitsuo, Y.; Hasegawa, K.; Fujita, T. AU-8654-122-A, 1985. (c) Kees, K.; Cheeseman, R. U.S. Patent 4 728 739, 1988. (d) Eggler, J.; Holland, G.; Johnson, M.; Volkmann, R. U.S. Patent 4 738 972, 1988.
- (19) Schnur, R. C.; Morville, M. J. Med. Chem. 1986, 29, 770.
- (20) Finkbeiner, H. J. Am. Chem. Soc. 1965, 87, 4588.
- (21) We would like to acknowledge Dr. R. Schnur for suggesting this protecting group and sharing experimental results from related systems.
- (22)For a review on the synthesis of oxazolidine-2,4-diones, see: Clark-Lewis, J. W. Chem. Rev. 1958, 58, 63.



^a(a) LiAlH₄, THF; (b) HCl(c), THF; (c) N-(triphenylmethyl)-2,4-oxazolidinedione, magnesium methyl carbonate, DMF; (d) CF₃COOH.

Scheme II^a



^a 2-Thio-2,4-oxazolidinedione, NaOAc, 140 °C, 0.2 Torr; (b) mchloroperbenzoic acid, DMF; (c) H_2 , Pd/C.

thio-2,4-oxazolidinedione has been reported to afford benzylidene derivatives of aromatic aldehydes.²³ Oxidative removal of sulfur, followed by reduction of the olefin, would afford the desired oxazolidinediones. This approach (Scheme II) was put into practice to prepare a majority of the oxazolidinediones in Tables I and II. Attempted condensations of the aromatic aldehydes (e.g. 7) with 2thio-2,4-oxazolidinedione, using the reported²³ conditions (sodium acetate/acetic acid), led to variable yields (25-60%) of the 2-thio-benzylidene derivatives 8. Since substantial amounts of starting materials were recovered from these reactions, an attempt was made to drive the equilibrium toward 8 by removing water during these condensations. Thus, when an intimate mixture of the aromatic aldehyde, 2-thio-2,4-oxazolidinedione, and sodium acetate are heated at 120-140 °C under vacuum (0.1 Torr) for 1-2 h, consistently good yields (50-70%) of the 2thiobenzylidene derivatives (e.g. 8) are obtained. Oxidative exchange of the thiocarbonyl for an oxocarbonyl with peracid, followed by catalytic hydrogenation, afforded the desired oxazolidinediones in excellent overall yields (70 - 90%).

Aldehydes 12 used for the preparation of the benzofuran-based oxazolidinediones in Table II were prepared via a five-step synthetic sequence (Scheme III). Basecatalyzed condensation of 5-bromosalicylaldehyde with the appropriate α -bromoacetyloxazole/thiazole 9 provides benzofurans 10. Removal of the ketone functionality in 10 was best accomplished by a two-step procedure involving reduction to the carbinol with sodium borohydride, followed by deoxygenation with triethylsilane.²⁴ Finally, aryl bromides 11 were converted to aldehydes 12 via the corresponding nitriles.

⁽¹⁷⁾ Meguro, K.; Fujita, T. EP-177-353, 1986.

Ushenko, N. K.; Gorizdra, T. E. Ukrain. Khim. Zhur. 1950, 16, (23)545; Chem. Abstr. 1954, 48, 11391b. West, C. T.; Donnelly, S. J.; Kooistra, D. A.; Doyle, M. P. J.

⁽²⁴⁾ Org. Chem. 1973, 38, 2675.

Table II. Glucose-Lowering Effects of Benzofuran-Based Oxazolidinediones on Ob/ob Mice



				· • · · ·	% glucose normalization ^b						
no.	R⁰	x	mp, °C	formula	5 mg/kg	1 mg/kg	0.5 mg/kg	0.2 mg/kg	0.1 mg/kg	0.05 mg/kg	0.025 mg/kg
29	Ph	0	189-191	C23H18N2O5-0.1EtOAc	100*			100*	92*	77°	65 ^d
30	$3-(Me)C_6H_4$	0	247 dec	$C_{24}H_{20}N_2O_5Na\cdot 2H_2O^e$			100*		90		
31	$4 - (Me)C_6H_4$	0	183-184	$C_{24}H_{20}N_2O_5$				100	40		
32	2-naphthyl	0	178 dec	$C_{27}H_{20}N_2O_5$		75		70	76		
33	cyclohexyl	0	98-99	C23H24N2O5Na-1.5H2O				91*	64		
34	Ph	S	148-151	$C_{23}H_{18}N_2O_4S$			0				

^aBenzofuran-based oxazolidinediones were prepared by using method B-see Scheme II. ^bNormalization relative to the ciglitazone effect of 50 mg/kg, which lowers blood glucose levels to that of the lean littermates. *p < 0.001. ^cAverage of three separate runs $\pm 20\%$. ^dAverage of three separate runs $\pm 28\%$. ^eCalcd: H, 4.86. Found: 4.09. ^fCalcd: H, 5.73. Found: 5.21.

Scheme III^a



° (a) NaOMe, EtOH; (b) NaBH₄, THF, MeOH; (c) Et₃SiH, CF₃CO₂H; (d) CuCN, DMF, 150 °C, (e) 50% Al/Ni alloy, HCO₂H.

Scheme IV^a

$$\underbrace{\bigwedge_{N}}^{0} \underbrace{\bigwedge_{OH}}_{13}^{Me} + \underbrace{\bigwedge_{HO}}_{HO} \underbrace{\bigwedge_{N}}^{0} \underbrace{\bigwedge_{N}}_{NC(Ph)_{3}} \underbrace{a, b}_{0} 20$$

 a (a) Diethylazodicarboxylate, triphenylphosphine, THF; (b) CF₃COOH.

A third approach utilized for the preparation of oxazolidinediones in this study is outlined in Scheme IV. Coupling of oxazole-based alcohols (e.g. 13)¹⁷ with phenol 14^{25} under Mitsunobu conditions generates the requisite protected, ether-linked systems in a convergent manner in 30–60% yields. Deprotection (70–90%) with trifluoroacetic acid provides the target oxazolidinediones. Phenyloxazolidinedione 23 was prepared following the procedure previously reported by Schnur.¹⁹

Biological Procedures. The blood glucose lowering activities of these oxazolidinediones were measured with 6-8 week old C57BL/6J-ob/ob mice (obtained from Jackson Laboratories, Bar Harbor, ME). Animals were housed five per cage under standard animal care practices. After a five-day acclimation period, the animals were weighed and 25 μ L of blood was collected via the retroorbital sinus prior to any treatment. The blood sample was immediately diluted 1:5 with heparinized saline and held on ice for subsequent centrifugation and glucose analysis of the supernatant. Animals were then dosed (gavage) daily for four days with drug in vehicle or vehicle alone [0.25% (w/v) methylcellulose in water with no pH adjustment]. Animals were bled 24 hours after the fourth administration of drug or vehicle for blood glucose levels. The weight of each animal was recorded on days 1 and 5. The diluted plasma sample was analyzed for glucose with the VP Super System Autoanalyzer (Abbott Laboratories, Irving, TX), with the A-gent²⁶ glucose UV reagent system (hexokinase method).²⁷ Ciglitazone was dosed at 50 mg/kg as a positive control and results are reported in Table II as percent glucose normalization compared to the standard ciglitazone at 50 mg/kg. This dose of ciglitazone was sufficient to lower the pretreated blood glucose levels (276 \pm 11 mg/dL) of the ob/ob mice to that of their lean littermates $(207 \pm 9 \text{ mg/dL})$.

Results and Discussion

Based on the rather limited data available for the benzyl thiazolidinediones,^{17,28} SAR studies for the oxazolidinediones initially focussed on derivatives closely allied with

(28) Meguro, K.; Fujita, T. EP-208-420-A, 1987.

⁽²⁵⁾ We gratefully acknowledge Dr. S. Goldstein and P. Dambek for supplying 14 and the experimental procedures for the preparation of this intermediate.

⁽²⁶⁾ A registered trademark of Abbott Laboratories, Diagnostic Division. 820 Mission Street, So. Pasadena, CA 91030.

⁽²⁷⁾ A modification of the method of Richterich and Dauwalder, Schweiz. Med. Wochenschr. 1971, 101, 860.

4b. Those compounds prepared and screened for glucose-lowering activity in the genetically obese ob/ob mouse are shown in Table I. Oxazolidinedione 15 and related analogues were initially targeted, because previous studies on the thiazolidinediones^{17,28} suggested the 2-aryloxazolebased side chains to be the most potent compounds. This agent when dosed orally to ob/ob mice was able to normalize blood glucose to the level of the lean littermates at a dose of 1 mg/kg.

Substitutent effects in the 2-position of the oxazole ring were probed through the incorporation of functionalized aromatic and alkyl moieties (16-20). The focus of this limited study was to examine the degree to which in vivo activity was dependent on the lipophilicity of these agents. Based on calculated²⁹ log P's, the lipophilicity rank order for this series is $17 \sim 19 > 15 \sim 16 > 18 \sim 20$. Analysis of the glucose-lowering activity for this series of analogues reveals a trend toward enhanced potency with increasing lipophilicity. Because attention was diverted to a more potent series (vide infra) it remains to be determined at what point, if any, increasing lipophilicity leads to diminished in vivo effects.

A number of structural features of the oxazole side chain were examined to further define the breadth of activity for these oxazolidinediones. Substitution of a carbonyl group for the ether functionality (21 vs 15) or shortening (24) of the linker chain decreased activity. Earlier studies of the thiazolidinediones^{17,28} had shown the oxazoles linked in the 2-position to be significantly less active than the 4-substituted congeners; however there have been no reports where the side chain is attached in the 5-position. Compounds 25 and 26, prepared to follow up on this point,





are significantly less active than analogues linked at the 4-position (e.g. 15) of the oxazole. The lack of hypoglycemic activity associated with 5-linked homologues points to a fairly strict constraint on spatial orientation of the oxazole ring. In an attempt to clarify this point, benzoxazole derivative 27 was targeted as a conformationally restricted analogue of 15, where the ethyl linker and methyl group in the 5-position of 15 are constrained into the phenyl ring of the benzoxazole. Benzoxazole 27 was inactive at a dose 25-fold greater than that which normalized blood glucose levels by the parent lead, 15. It is unclear whether this decrease in potency is due to the oxazole ring in 27 being locked into an unfavorable conformation or if some unrelated physicochemical parameter(s) has been altered. The remaining side chain SAR issue addressed was to show that a simple replacement of the oxazole moiety with a closely related heterocycle (i.e. 19 to 22) significantly reduces activity.

A limited set of spatial orientation/electronic parameters were assessed for the benzyloxazolidinedione portion of these hypoglycemic agents. In contrast to the report¹⁹ which showed a series of phenyloxazolidinediones to be more potent than the corresponding benzyl oxazolidinediones, 23 was found to be >10-fold less effective than 15 in lowering blood glucose. Incorporation of unsaturation at the 5-position of the oxazolidinedione (28) also decreases potency.



Having defined a broad set of SAR parameters for both the oxazole side chain and benzyloxazolidinedione portions of this series of glucose-lowering agents, our attention was directed toward preparation of a series of benzofuran analogues (Table II). Previous efforts³⁰ in our group have shown that analogues of ciglitazone (8) in which the conformational freedom of the side chain was reduced, via dihydrobenzofuran/-pyran formation, enhanced hypoglycemic activity. Because the incorporation of a dihydrobenzofuran/-pyran-based central core would introduce issues relating to diastereoisomers, the benzofuran subunit was selected. The parental analogue in this series, 29 is capable of "normalizing" blood glucose levels at a dose of 0.1 mg/kg, which represents as approximate 10-fold enhancement in potency relative to the "open-chain" analogue 15. Compound 29 did not reduce blood glucose levels below those found in the normal littermates (ob/-) at doses 100-fold greater than those exhibiting significant activity and thus these agents do not produce frank hypoglycemia, which is often observed clinically with the sulfonylureas.

A small set of compounds (30-33) with varying functionality at the 2-position of the oxazole ring exhibit potent glucose-lowering activity in the ob/ob mice. As for the ether-linked series (i.e. 22), substitution of a thiazole for the oxazole ring significantly reduces potency.

In summary, a series of benzyloxazolidine-2,4-diones has been shown to lower blood glucose levels in a rodent model of type II diabetes. Incorporation of a novel, benzofuran-based side chain resulted in the identification of agents with markedly enhanced hypoglycemic activity.

Experimental Section

All melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were carried out by the Analytical Department of Pfizer Central Research and results obtained for specified elements are within $\pm 0.4\%$ of the theoretical values unless otherwise denoted. ¹H NMR spectra of deuteriochloroform or DMSO-d₈ solutions (solvent utilized as an internal standard and deuterium lock) were recorded on a Varian XL-300 spectrometer. Literature procedures^{17,31} were employed to prepare the aldehydes, except for the benzofuran-based analogues utilized in methods A and B.

3-(Triphenylmethyl)-2,4-oxazolidinedione. A solution of potassium *tert*-butoxide (10 g, 92 mmol) and glycolamide (6.9 g, 92 mmol) and diethyl carbonate (13 g, 110 mmol) in anhydrous methanol (95 mL) was refluxed for 18 h. After cooling, solvent was removed in vacuo and saturated brine (25 mL) was added to the remaining solids. The reaction mixture was acidified to

⁽²⁹⁾ Calculations performed with MedChem-3.54, a software package supplied by Chemical Information System, Inc. Claremont, CA 91711.

⁽³⁰⁾ Clark, D. A.; Goldstein, S. W.; Volkmann, R. A.; Eggler, J. F.; Holland, G. F.: Hulin, B.; Stevenson, R. W.; Kreutter, D. K.; Gibbs, E. M.; Krupp, M. N.; Merrigan, P.; Kelbaugh, P. L.; Andrews, E. G.; Tichner, D. L.; Suleske, R. T.; Lamphere, C. H.; Rajeckas, F. J.; Kappeler, W. H.; McDermott, R. E.; Hutson, N. J.; Johnson, M. R. J. Med. Chem. 1991, 34, 319.

⁽³¹⁾ Clark, D. A.; Hulin, B.; Goldstein, S. W. EP-332-332-A, 1989.

pH = 2 with 6 N aqueous hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over sodium sulfate. Removal of solvent in vacuo afforded 2,4-oxazolidinedione (4.7 g, 50%) as a colorless solid: mp 85-88 °C; ¹H NMR (DMSO- d_6) δ 11.85 (br s, 1 H), 4.77 (s, 2 H).

To a solution of 2,4-oxazolidinedione (1.2 g, 11.9 mmol) and triethylamine (1.6 mL, 11.9 mmol) in dichloromethane (12 mL) was added chlorotriphenylmethane (3.3 g, 11.9 mmol) and the reaction was stirred at room temperature for 45 min. The thick reaction slurry was diluted into ethyl acetate, washed with water and saturated brine, and dried over sodium sulfate. Removal of solvent in vacuo afforded the title compound (4.0 g, 97%) as a colorless solid; mp 203-210 °C; ¹H NMR (DMSO- d_6) δ 7.52-7.13 (m, 15 H), 4.80 (s, 2 H).

Method A. 5-[4-[2-(5-Methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl]-2,4-oxazolidinedione (15). To a cooled (0 °C), stirred 1 M solution of lithium aluminum hydride (6.5 mL, 6.5 mmol) in diethyl ether was added dropwise a solution of 4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzaldehyde (2.0 g, 6.5 mmol) in THF (10 mL). The resulting solution was stirred for 0.5 h; water (0.2 mL), 20% NaOH (0.2 mL), and water (1 mL) were added in succession. The resulting solids were filtered off and washed with ethyl acetate (100 mL). The filtrates were combined and solvents were removed in vacuo to afford 4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl alcohol (1.7 g, 84%) as a waxy solid; mp 110-113 °C.

To a cooled (0 °C), stirred solution of 4-[2-(5-methyl-2phenyl-4-oxazolyl)ethoxy]benzyl alcohol (1.8 g, 5.8 mmol) in THF (10 mL) was added concentrated hydrochloric acid (4 mL) and the reaction mixture was then allowed to warm to room temperature. After stirring for 4 h, the reaction mixture was poured into ethyl acetate. The organic phase was washed with water and saturated brine and dried over sodium sulfate. Solvent was removed in vacuo to afford 4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl chloride (1.6 g, 86%); mp 88–90 °C.

A solution of 3-(triphenylmethyl)-2,4-oxazolidinedione (1.1 g, 3.2 mmol) in 2 M magnesium methyl carbonate in dimethylformamide (3 mL, 6.3 mmol) was heated at 85 °C for 0.5 h. This solution was transferred to a flask containing a 4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl chloride (0.7 g, 2.1 mmol) and the reaction was maintained at 85 °C for 3 h. The reaction was quenched into ice-cold 0.5 M aqueous hydrochloric acid (80 mL) and extracted with ethyl acetate (2×75 mL). The combined extracts were washed with water and saturated brine and dried over sodium sulfate. Solvent was removed in vacuo and the resulting oil was purified by flash chromatography over silica gel (30% ethyl acetate-hexanes) to afford N-(triphenylmethyl)-5-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl]-2,4-oxazolidinedione (0.23 g, 17%) as an oil.

A solution of N-(triphenylmethyl)-5-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl]-2,4-oxazolidinedione (0.23 g, 0.36 mmol) in trifluoroacetic acid (1 mL) was stirred at room temperature for 0.5 h. The reaction was poured into ethyl acetate and extracted with water and saturated brine. The organic layer was dried over sodium sulfate and solvent was removed in vacuo. The resulting oil was purified by flash chromatography over silica gel (50% ethyl acetate-hexanes) to afford the title compound (85 mg, 61%) as a colorless solid: mp 163-166 °C; ¹H NMR (DMSO- d_6) δ 7.96-7.84 (m, 2 H), 7.54-7.42 (m, 3 H), 7.08 (d, 2 H), 6.84 (d, 2 H), 5.16 (t, 1 H), 4.17 (t, 2 H), 3.04 (q of AB pattern, 2 H), 2.90 (t, 2 H), 2.34 (s, 3 H).

General Procedure for Preparation of Benzofuran-Based Aldehydes. 2-[(5-Methyl-2-phenyl-4-oxazolyl)methyl]benzofuran-5-carboxaldehyde (7). To a slurry of 5-bromosalicylaldehyde (4.2 g, 21 mmol) in anhydrous ethanol (80 mL) was added sodium methoxide (1.1 g, 21 mmol). The resulting yellow slurry was stirred at room temperature for 15 min and then 4-(bromoacetyl)-5-methyl-2-phenyloxazole¹⁷ (6.0 g, 21 mmol) was added. An additional portion of sodium methoxide (0.27 g, 5 mmol) was added and the reaction was refluxed overnight. After cooling to room temperature, the solids were filtered off and washed with cold ethanol to afford (5-bromo-2-benzofuranyl)(5methyl-2-phenyl-4-oxazolyl)methanone (4.3 g, 53%) as an off-white solid; mp 211-212 °C (DMF-H₂O).

To a cooled (0 °C), stirred slurry of (5-bromo-2-benzofuranyl)(5-methyl-2-phenyl-4-oxazolyl)methanone (4.3 g, 11 mmol) in 50% tetrahydrofuran/methanol (75 mL) was added sodium borohydride (0.42 g, 11 mmol) portionwise over a 15-min period. The reaction mixture was stirred at room temperature for 1 h, and solvents were then removed in vacuo. The reaction mass was slurried in water (100 mL) and filtered. The solids were washed with water and methanol to afford (5-bromo-2-benzofuranyl)(5-methyl-2-phenyl-4-oxazolyl)methanol (3.8 g, 90%) as a white solid; mp 152–154 °C.

To a cooled (0 °C), stirred solution of (5-bromo-2-benzofuranyl)(5-methyl-2-phenyl-4-oxazolyl)methanol (1.4 g, 3.5 mmol) in trifluoroacetic acid (7 mL) was added triethylsilane (1.1 mL, 7.0 mmol). After 1 h, the reaction was diluted into ethyl acetate and was washed with water and saturated brine and dried over sodium sulfate. Solvent was removed in vacuo and purification by flash chromatography over silica gel (10% ethyl acetatehexanes) afforded (5-bromo-2-benzofuranyl)(5-methyl-2phenyl-4-oxazolyl)methane (1.3 g, 100%) as a yellow solid; mp 98-100 °C (MeOH).

A stirred solution of (5-bromo-2-benzofuranyl)(5-methyl-2phenyl-4-oxazolyl)methane (1.3 g, 3.5 mmol) and copper(I) cyanide (0.6 g, 7.0 mmol) in dimethylformamide (10 mL) was heated at 150 °C for 18 h. After cooling, the reaction was poured into concentrated ammonium hydroxide (40 mL) and extracted with ethyl acetate. The organic layer was washed with water and brine and dried over sodium sulfate. Solvent was removed in vacuo and purification by flash chromatography over silica gel (20% ethyl acetate-hexanes) afforded 2-[(5-methyl-2-phenyl-4-oxazolyl)methyl]benzofuran-5-carbonitrile (0.63 g, 58%) as a yellow solid; mp 139-140 °C (EtOAc-hexanes).

A slurry of 2-[(5-methyl-2-phenyl-4-oxazolyl)methyl]benzofuran-5-carbonitrile (0.62 g, 2.00 mmol) and 0.6 g of 50% nickel-aluminum alloy (Aldrich) in 70% aqueous formic acid was refluxed for 2 h. After cooling, the reaction mixture was filtered. The filtrate was added to ethyl acetate and extracted with 1 N aqueous sodium hydroxide and water and dried over sodium sulfate. Solvent was removed in vacuo to afford 2-[(5-methyl-2-phenyl-4-oxazolyl)methyl]benzofuran-5-carboxaldehyde (0.54 g, 87%) as a yellow solid: mp 116-118 °C; ¹H NMR (CDCl₃) δ 9.96 (s, 1 H), 7.98-7.90 (m, 3 H), 7.71 (d, 1 H), 7.44 (d, 1 H), 7.40-7.33 (m, 3 H), 6.59 (s, 1 H), 4.05 (s, 2 H), 2.34 (s, 3 H). The following aldehydes were prepared in a similar manner. 2-[[5-Methyl-2-(3-methylphenyl)-4-oxazolyl]methyl]benzofuran-5-carboxaldehyde: ¹H NMR (DMSO-d₈) & 10.0 (s, 1 H) 8.13 (s, 1 H), 7.83-7.77 (m, 4 H), 7.38-6.27 (m, 2 H), 6.82 (s, 1 H), 4.14 (s, 2 H), 2.40 (s, 3 H), 2.35 (s, 3 H). 2-[[5-Methyl-2-(4methylphenyl)-4-oxazolyl]methyl]benzofuran-5-carboxaldehyde: mp 128-129 °C; ¹H NMR (DMSO-d₆) δ 9.97 (s, 1 H), 8.12 (s, 1 H), 7.80-7.66 (m, 4 H), 7.27 (d, 2 H), 6.82 (s, 1 H), 4.15 (s, 2 H), 2.46 (s, 3 H), 2.40 (s, 3 H). 2-[[5-Methyl-2-(2naphthyl)-4-oxazolyl]methyl]benzofuran-5-carboxaldehyde: mp 153-155 °C; ¹H NMR (DMSO-d₆) δ 9.94 (s, 1 H), 8.42 (s, 1 H), 8.10-7.46 (m, 9 H), 6.82 (s, 1 H), 4.12 (s, 2 H), 2.42 (s, 3 H). 2-[(5-Methyl-2-cyclohexyl-4-oxazolyl)methyl]benzofuran-5-carboxaldehyde: oil; ¹H NMR (DMSO-d₆) δ 10.0 (s, 1 H), 8.16 (s, 1 H), 7.81 (d, 1 H), 7.71 (d, 1 H), 6.79 (s, 1 H), 4.03 (s, 2 H), 2.85-2.61 (m, 1 H), 2.26 (s, 3 H), 2.07-1.14 (m, 10 H). 2-[(5-Methyl-2-phenyl-4-thiazolyl)methyl]benzofuran-5-carboxaldehyde: mp 142–146 °C; ¹H NMR (DMSO- d_{θ}) δ 10.0 (s, 1 H), 8.11 (s, 1 H), 7.84-7.64 (m, 4 H), 7.48-7.36 (m, 3 H), 6.78 (s, 1 H), 4.31 (s, 2 H), 2.49 (s, 3 H).

4-[(2-Phenylbenzoxazol-5-yl)oxy]benzaldehyde. A stirred solution of 2,5-dihydroxybenzophenone³² (11.5 g, 53.6 mmol), hydroxylamine hydrochloride (5.6 g, 80.5 mmol), and pyridine (10.5 mL) in anhydrous ethanol (140 mL) was refluxed for 5 h. After cooling, the reaction was diluted into ethyl acetate, washed with water and brine, and dried over sodium sulfate. Removal of solvent in vacuo provided 2,5-dihydroxybenzophenone oxime (12.8 g, 100%) as a dark oil, which was taken on without further purification.

To a cooled (0 °C), stirred solution of 2,5-dihydroxybenzophenone oxime (12.8 g, 53.6 mmol) in acetonitrile (32 mL) and dimethylformamide (10 mL) was added phosphorus oxychloride (5.2 mL, 56 mmol) dropwise. The reaction was stirred at 0 °C

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for 40 min and then quenched into 0.7 M sodium acetate and extracted with ethyl acetate. The organic layer was washed with water and brine and dried over sodium sulfate. Removal of solvent in vacuo and purification by flash chromatography over silica gel (25% ethyl acetate-hexanes) afforded 2-phenylbenzoxazol-5-ol (5.92 g, 52%) as a colorless solid; mp 173-175 °C.

To a stirred solution of 2-phenylbenzoxazol-5-ol (5.83 g, 27.6 mmol) and 4-fluorobenzonitrile (5.69 g, 47.0 mmol) in dimethylformamide was added sodium hydride (0.93 g, 39 mmol) and the reaction was refluxed for 2 h. After cooling, the reaction was diluted into ethyl acetate and washed with water and brine and dried over sodium sulfate. Removal of solvent in vacuo afforded 4-[(2-phenylbenzoxazol-5-yl)oxy]benzonitrile (8.6 g, 100%) as a dark solid, which was taken on without further purification. A small portion was recrystallized from ethyl acetate; mp 149–152 °C.

Under the conditions described for the preparation of benzofuran-based aldehydes (see above), 4-[(2-phenylbenzoxazol-5yl)oxy]benzonitrile (3.1 g, 10 mmol) was converted to 4-[(2phenylbenzoxazol-5-yl)oxy]benzaldehyde (2.9 g, 92%): mp 88–91 °C (MeOH); ¹H NMR (CDCl₃) δ 9.88 (s, 1 H), 8.26–8.14 (m, 2 H), 7.82 (d, 2 H), 7.65–7.40 (m, 5 H), 7.12–6.95 (m, 3 H).

Method B. 5-[2-[(5-Methyl-2-phenyl-4-oxazolyl)methyl]-5-benzofuranylmethyl]-2,4-oxazolidinedione (29). An intimate mixture of 2-[(5-methyl-2-phenyl-4-oxazolyl)methyl]-5-benzofurancarboxaldehyde (1.6 g, 4.9 mmol), 2-thio-2,4-oxazolidinedione²³ (0.9 g, 7.3 mmol), and anhydrous sodium acetate (1.2 g, 15 mmol) were heated at 120 °C under vacuum (0.1 Torr) for 1.5 h. After cooling, the reaction solids were poured into ethyl acetate (400 mL)/water (100 mL) and the pH of the aqueous layer was adjusted to \sim 4 with 1 N aqueous hydrochloric acid. The organic layer was washed with water and saturated brine and dried over sodium sulfate. Solvent was removed in vacuo and the solids were triturated with cold methanol to afford 5-[2-[[(5-methyl-2-phenyl-4-oxazolyl)methyl]-5-benzofuranyl]methylidene]-2-thio-2,4-oxazolidinedione (1.1 g, 54%) as a colorless solid; mp 233-236 °C. Purification of the residue from the methanol washes by flash chromatography over silica gel (50% ethyl acetate-hexanes) afforded an additional 0.39 g (19%) of product.

To a cooled (0 °C) solution of 5-[2-[[(5-methyl-2-phenyl-4-oxazolyl)methyl]-5-benzofuranyl]methylidene]-2-thio-2,4-oxazolidinedione (2.3 g, 5.5 mmol) in dimethylformamide (40 mL) was added*m*-chloroperbenzoic acid (1.5 g, 7.1 mmol) and the resulting reaction was stirred at room temperature for 2.5 h. The reaction was diluted in ethyl acetate and washed with water and brine and dried over sodium sulfate. Solvent was removed in vacuo, and the resulting mixture was purified by flash chromatography over silica gel (50%, 70% ethyl acetate-hexanes) to afford 5-[2-[[(5-methyl-2-phenyl-4-oxazolyl)methyl]-5-benzofuranyl]-methylidene]-2,4-oxazolidinedione (1.5 g, 66%); mp 185-200 °C dec.

To a solution of 5-[2-[[(5-methyl-2-phenyl-4-oxazolyl)methyl[-5-benzofuranyl]methylidene]-2,4-oxazolidinedione (1.5 g, 3.6 mmol) in THF (20 mL) was added 1.5 g of 10% palladium-on-carbon (sulfur resistant, Engelhard) and the reaction mixture was hydrogenated on a Parr shaker at 40 psi overnight at room temperature. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography over silica gel (40% ethyl acetate-hexanes) to afford the title compound (1.0 g, 68%) as a colorless solid: mp 190-191 °C; ¹H NMR (DMSO- d_{6}) δ 7.92-7.84 (m, 2 H), 7.50-7.42 (m, 3 H), 7.41 (d, 1 H), 7.35 (s, 1 H), 7.04 (d, 1 H), 6.60 (s, 1 H), 5.23 (t, 1 H), 4.06 (s, 2 H), 3.18 (q of AB pattern, 2 H), 2.40 (s, 3 H).

4-[5-[N-(Triphenylmethyl)-2,4-dioxooxazolidinyl]methyl]phenol (14).²⁵ A solution of 3-(triphenylmethyl)-2,4oxazolidinedione (150 g, 0.44 mol) in 2 M magnesium methyl carbonate (0.44 L, 0.87 mol) in dimethylformamide was heated at 90 °C for 1.5 h. This solution was then added over a 10-min period to a solution of 4-(chloromethyl)phenyl acetate³³ (53.8 g, 0.29 mol) in dimethylformamide (50 mL) at room temperature. The reaction was then heated at 90 °C for 1 h, cooled, added to 1 N aqueous hydrochloric acid (1 L) and extracted with ethyl acetate. The organic layer was washed with water and dried over sodium sulfate. Solvent was removed in vacuo and purification by flash chromatography over silica gel (hexanes then 30% ethyl acetate-hexanes) afforded the title compound (61.8 g, 47%) as an off-white solid; mp 158–161 °C. Anal. Calcd for $C_{29}H_{23}NO_4$: C, 77.49; H, 5.16; N, 3.12. Found: C, 77.11; H, 5.15; N, 3.04.

Method C. 5-[4-[2-(2-Cyclohexyl-5-methyl-4-oxazolyl)ethoxy]benzyl]-2,4-oxazolylidinedione (20). To a stirred solution of 2-(2-cyclohexyl-5-methyl-4-oxazolyl)ethanol¹⁷ (0.9 g, 4.2 mmol), 4-[5-[N-(triphenylmethyl)-2,4-dioxooxazolidinyl]methyl]phenol (14; 2.0 g, 4.6 mmol) and triphenylphosphine (1.3 g, 5.0 mmol) in THF (25 mL) was added diethyl azodicarboxylate (0.7 mL, 4.6 mmol). The reaction mixture was stirred at room temperature for 26 h, poured into water, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and solvent removed in vacuo. The residue was purified by flash chromatography over silica gel (6% p-dioxane-toluene) to afford N-(triphenylmethyl)-5-[4-[2-(2-cyclohexyl-5-methyl-4-oxazolyl)ethoxy]benzyl]-2,4-oxazolidinedione (1.2 g, 44%) as an oil: ¹H NMR (CDCl₃) δ 7.30–6.82 (m, 19 H), 4.77 (t, 1 H), 4.23 (t, 2 H), 3.14 (q of AB pattern, 2 H), 2.86 (t, 2 H), 2.72-2.54 (m, 1 H), 2.20 (s, 3 H), 2.00-1.10 (m, 10 H).

A solution of N-(triphenylmethyl)-5-[4-[2-(2-cyclohexyl-5methyl-4-oxazolyl)ethoxy]benzyl]-2,4-oxazolidinedione in trifluoroacetic acid (10 mL) was stirred at room temperature for 0.5 h. The reaction mixture was diluted into ethyl acetate, washed with water and saturated brine, and dried over sodium sulfate. Solvent was removed in vacuo and the residue was purified by flash chromatography over silica gel (20% *p*-dioxane-toluene) to afford the title compound (0.46 g, 90%) as an oil; ¹H NMR (CDCl₃) δ 7.05 (d, 2 H), 6.71 (d, 1 H), 4.97 (t, 1 H), 4.00 (t, 2 H), 3.12 (q of AB pattern, 2 H), 2.80 (t, 2 H), 2.78-2.64 (m, 1 H), 2.18 (s, 3 H), 2.00-1.16 (m, 10 H).

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Registry No. 5, 103788-59-6; 6, 132646-28-7; 7, 132646-34-5; 7 (ketone), 132646-31-2; 7 (alcohol), 132672-20-9; 7 (5-bromo), 132646-32-3; 8, 132646-43-6; 9 (2-Ph), 103788-62-1; 13, 132646-47-0; 14, 132646-46-9; 15, 132646-30-1; 16, 132646-50-5; 17, 132646-51-6; 18, 132646-52-7; 19, 132646-53-8; 20, 132646-49-2; 21, 132672-21-0; 22, 132646-54-9; 23, 132646-55-0; 24, 132646-56-1; 25, 132646-57-2; 26, 132646-60-7; 27, 132646-61-8; 28, 132646-62-9; 29, 132646-45-8; **30**, 132672-22-1; **31**, 132646-58-3; **32**, 132646-59-4; **33**, 132672-23-2; 34, 132672-24-3; ClCPh₃, 76-83-5; glycolamide, 598-42-5; diethyl carbonate, 105-58-8; 2,4-oxazolidinedione, 2346-26-1; 5-bromosalicylaldehyde, 1761-61-1; 3-(triphenylmethyl)-2,4-oxazolidinedione, 132646-26-5; 4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl alcohol, 132646-27-6; N-(triphenylmethyl)-5-[4-[2-(5methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl]-2,4-oxazolidinedione, 132646-29-8; 2-[(5-methyl-2-phenyl-4-oxazolyl)methyl]benzofuran-5-carbonitrile, 132646-33-4; 2-[[5-methyl-2-(3-methylphenyl)-4-oxazolyl]methyl]benzofuran-5-carboxaldehyde, 132646-35-6; 2-[[5-methyl-2-(4-methylphenyl)-4-oxazolyl]methyl]benzofuran-5-carboxaldehyde, 132646-36-7; 2-[[5methyl-2-(2-naphthyl)-4-oxazolyl]methyl]benzofuran-5-carboxaldehyde, 132646-37-8; 2-[[5-methyl-2-cyclohexyl-4-oxazolyl]methyl]benzofuran-5-carboxaldehyde, 132646-38-9; 2-[(5methyl-2-phenyl-4-thiazolyl)methyl]benzofuran-5-carboxaldehyde, 132646-39-0; 2.5-dihydroxybenzophenone, 2050-37-5; 2.5-dihydroxybenzophenone oxime, 132646-40-3; 2-phenylbenzoxazol-5-ol, 116496-29-8; 4-fluorobenzonitrile, 1194-02-1; 4-[(2phenylbenzoxazol-5-yl)oxy]benzonitrile, 132646-41-4; 4-[(2phenylbenzoxazol-5-yl)oxy]benzaldehyde, 132646-42-5; 2-thio-2,4-oxazolidinedione, 2346-24-9; 5-[2-[[(5-methyl-2-phenyl-4-oxazolyl)methyl]-5-benzofuranyl]methylidene]-2,4-oxazolidinedione, 132646-44-7; 4-(chloromethyl)phenyl acetate, 39720-27-9; N-(triphenylmethyl)-5-[4-[2-(2-cyclohexyl-5-methyl-4-oxazolyl)ethoxy]benzyl]-2,4-oxazolidinedione, 132646-48-1.

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