Antihyperglycemic Activities of Cryptolepine Analogues: An Ethnobotanical Lead Structure Isolated from *Cryptolepis sanguinolenta*†

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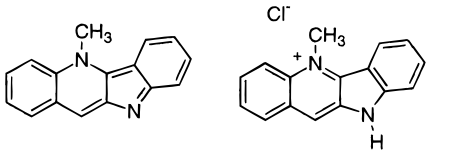
Cryptolepine (**1**) is a rare example of a natural product whose synthesis was reported prior to its isolation from nature. In the previous paper we reported the discovery of cryptolepine's antihyperglycemic properties. As part of a medicinal chemistry program designed to optimize natural product lead structures originating from our ethnobotanical and ethnomedical field research, a series of substituted and heterosubstituted cryptolepine analogues was synthesized. Antihyperglycemic activity was measured in vitro and in an NIDDM mouse model to generate the first structure−bioactivity study about the cryptolepine nucleus.

Introduction

Cryptolepine (**1**), a member of the indoloquinoline alkaloid family, is a rare example of a natural product whose synthesis was reported prior to its isolation from nature. Cryptolepine was first synthesized in 1906 by Fichter and Boehringer[1] for use as a possible dye while its isolation from *Cryptolepis triangularis* N. E. Br was first reported by Clinquart[2] 23 years later.[3−8] Cryptolepine-containing plants have been used by indigenous peoples of Africa as a dye,[9,10] and extracts obtained from various *Cryptolepis* sp. have a number of reported and current ethnomedical uses.[11] Cryptolepine and its hydrochloride salt (**2**) possess numerous biological properties, including antimalarial activity.[11] In previous papers we reported that cryptolepine (**1**) and its hydrochloride salt (**2**) possess antihyperglycemic properties[8] and that extracts of *Cryptolepis sanguinolenta* possess antihyperglycemic activity in non-insulin-dependent diabetes mellitus (NIDDM) rodent models and in humans.[12] Yet while the aqueous extract of *C. sanguinolenta* demonstrated a remarkable ability to lower fasting blood glucose levels in a patient study conducted in Ghana[12] and the glucose-lowering properties of cryptolepine hydrochloride were shown to be separate from an apparent anorexigenic effect,[8,12] we were faced with the prospect of separating these effects with future cryptolepine analogues, which would require extensive experimentation. Thus, as part of a medicinal chemistry program designed to optimize ethnobotanically generated leads,[13,14] we considered cryptolepine as a template for synthetic modification, recognizing that such optimization should address the reduced food consumption and body weight issues. A portion of this structure optimization study on the cryptolepine nucleus is reported below.



1 Cryptolepine **2** Cryptolepine Hydrochloride

Chemistry

Our earlier exploration into the synthesis of cryptolepine led to three synthetic routes being established.[8] Since these routes allowed for the preparation of structurally diverse cryptolepine analogues, all three synthetic strategies were pursued further. The first route began with the condensation reaction between a substituted indolyl acetate **3** and an isatin derivative **4**, affording quindoline carboxylic acids **5**. Decarboxylation in diphenyl ether followed by alkylation with methyl iodide using the Fichter conditions[1] or with methyl triflate afforded cryptolepine derivatives **7** and **8**, respectively. In most cases the hydroiodide and hydrotrifluoromethanesulfonate (hydrotriflate) salts were converted to their hydrochloride salts prior to biological testing using procedures described earlier[8] (Scheme 1).

When alkylation of quindoline **6** with ethyl iodide in methanol was attempted using the Fichter conditions,[1] a near 1:1 mixture of the ethyl and methyl derivatives **7** (R_5 = Et and Me, respectively) were obtained, presumably due to the formation of ethyl methyl ether and possible subsequent formation of methyl iodide, either of which could serve as the alkylating agent. This problem was eliminated when the solvent was changed from methanol to chloroform. Similarly using *ethanol-free* chloroform, the butyl, benzyl, and *p*-fluorobenzyl derivatives **11** were obtained.

4-Methoxycryptolepine hydrochloride **11j** was prepared according to the route shown in Scheme 2. Condensation of 1-acetyl-3-oxoindole[8] **12** with 2-nitro-3-methoxybenzaldehyde **13** using a catalytic amount of piperidine gave **14** as a mixture of *E*/*Z* isomers in 78−85% yield. Hydrogenation of **14** gave quindoline **15** in

† Dedicated to Professor Henry Rapoport on the occasion of his 79th birthday.

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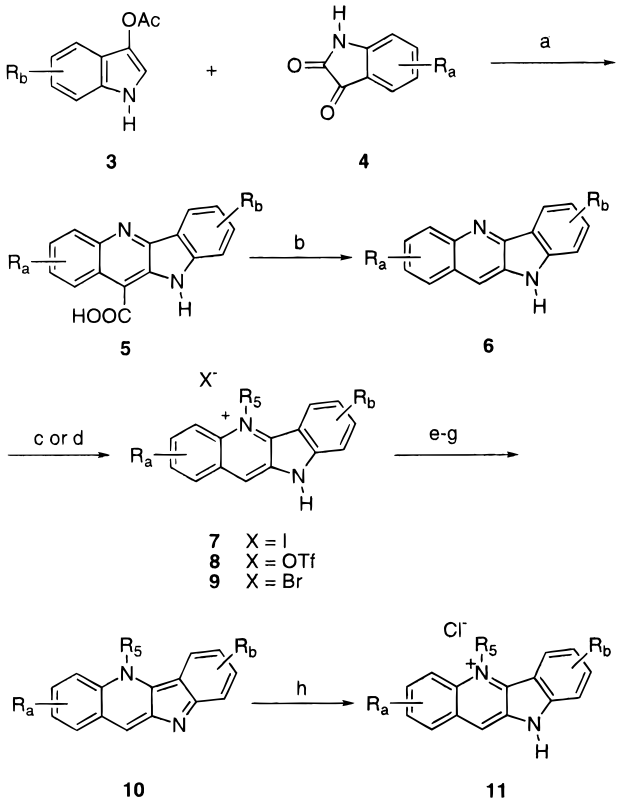
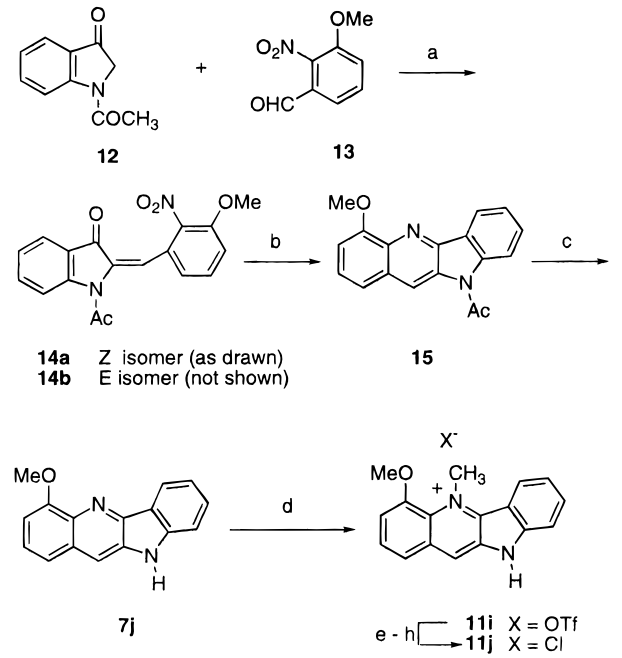
Scheme 1[a,b]



[a] (a) KOH, H_2O, N_2; (b) Ph_2O, 255 °C, 6 h; (c) R_5X, bomb, 120 °C; (d) MeOTf; (e) Na_2CO_3; (f) basic alumina, $CHCl_3$; (g) MeOH−$CHCl_3$; (h) HCl−Et_2O. [b] See Table 1 for definitions of R_a, R_b, and R_5.

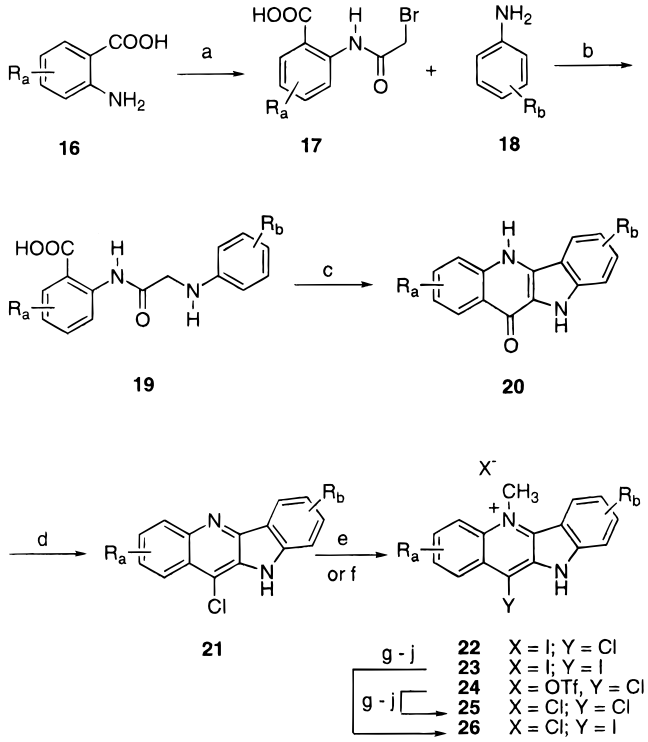
Scheme 2[a]



[a] (a) Piperidine (cat.), toluene/$CHCl_3$, 4 Å MS, room temperature; (b) H_2, Pd/C, MeOH; (c) KOH; (d) MeOTf, toluene, room temperature; (e) K_2CO_3; (f) basic alumina, $CHCl_3$; (g) $CHCl_3$−MeOH; (h) HCl.

53% yield after chromatography. Alkylation with methyl iodide and subsequent chromatography over basic alumina followed by acidification with HCl afforded the target methoxycryptolepine analogue. A more desirable approach to **11j** involved removal of the acetate protecting group prior to alkylation. Oftentimes quindoline **15** was difficult to purify, as it was contaminated with a reduction byproduct (**14** with double bond reduced). In these instances, it became necessary to resort to HPLC to obtain **15** free of this impurity. This problem was solved by removing the acetate group with KOH, providing **7j**, which was easily separated from the reduction byproduct. Alkylation with methyl triflate and counterion exchange provided 4-methoxycryptolepine hydrochloride **11j**.

Scheme 3[a,b]

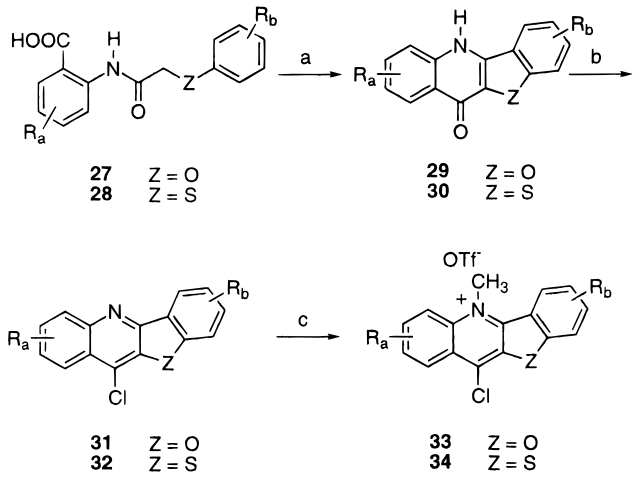


[a] (a) Bromoacetyl bromide, DMF/dioxane; (b) DMF; (c) PPA; (d) $POCl_3$; (e) MeI, MeOH, bomb; (f) MeOTf; (g) Na_2CO_3; (h) basic alumina, $CHCl_3$; (i) MeOH−$CHCl_3$; (j) HCl−Et_2O. [b] See Table 1 for definitions of R_a and R_b.

A series of 11-chlorocryptolepine analogues was prepared according to the route depicted in Scheme 3. A substituted anthranilic acid **16** was treated with bromoacetyl bromide to afford bromoacetyl derivative **17** (50−95%), which was treated with a substituted aniline **18** to provide anthranilic acid derivative **19** (50−90%). Acid-promoted cyclization of **19** with PPA gave quindolone **20**, which often was isolated only as the crude product and subsequently treated with $POCl_3$ to provide 11-chloroquindoline **21**.[15−19] The yield for this two-step transformation varied from 10 to 50% depending on the ring substituents. Alkylation of **21** with methyl iodide gave an inseparable mixture of the desired salt **22** and the product from halogen exchange **23**.[8] For this reason, the preferred procedure utilized methyl triflate as the alkylation agent which gave >95% yields of the hydrotriflate salt **24**. Conversion to the free base and subsequent treatment with HCl provided the target cryptolepine hydrochloride salts **25**.

Heterocyclic variation at position 10 was pursued, with the indolo nitrogen atom being replaced with oxygen, sulfur, and carbon. The requisite 11-chlorobenzofuro-[20,21] and 11-chlorobenzothienoquinolines[21] **31** and

Scheme 4[a,b]



27 Z = O, **28** Z = S

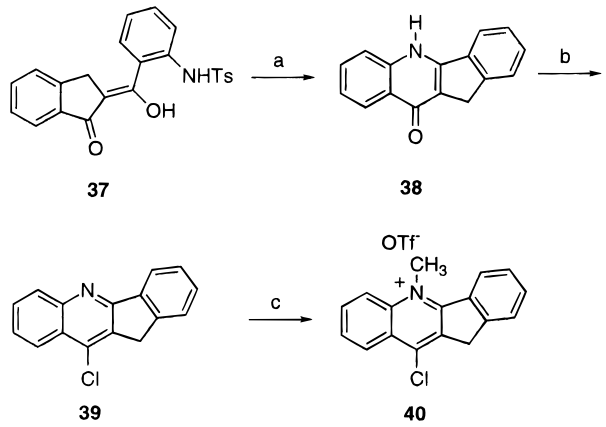
29 Z = O, **30** Z = S

31 Z = O, **32** Z = S

33 Z = O, **34** Z = S

[a] (a) PPA; (b) $POCl_3$; (c) MeOTf. [b] See Table 1 for definitions of R_a and R_b.

Scheme 5[a]



37 **38**

39 **40**

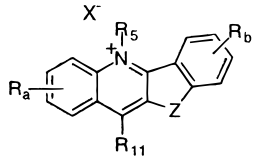
[a] (a) PPA; (b) $POCl_3$; (c) MeOTf.

32 were prepared according to literature or modified literature procedures (Scheme 4). Alkylation of **31** and **32** with methyl triflate gave the 11-chlorotriflate salts **33** and **34**.

Indenoquinoline derivative **40** (Scheme 5) required the synthesis of 11-oxo-5,11-dihydroindeno[1,2-*b*]quinoline **38**.[22] This was obtained by the *Thiele*−*Falk* reaction of *o*-phthalaldehyde **35** with 2-(*N*-tosylamino)-acetophenone[23] **36** and subsequent cyclization of the intermediate indanone **37** with PPA. Treatment of **38** with $POCl_3$ followed by alkylation with methyl triflate gave 11-chlorotriflate salt **40**.

The availability of the 11-chloro functionality in **24**, **25**, **33**, **34**, and **40** made it attractive to prepare a series of 11-substituted cryptolepine analogues. The 11-chloroquindoline and 2-fluoro-11-chloroquindoline systems (Z = NH, O, S, and CH_2) were chosen as representative substrates. Treatment of **24** or **25** (or the corresponding free base) with aniline, phenol, and 4-chlorothiophenol or thiophenol gave **41**, **42**, and **43** respectively (Scheme 6). All of these were converted into their chloride salts using the sodium carbonate/basic alumina procedure. In a similar manner, 4-chlorothiophenol was added to benzofuroquinoline **33** and indenoquinoline **40** to provide the 11-thiophenol derivatives **45** and **46**, respectively. 11-Phenyl derivatives **44** were prepared via phenylmagnesium bromide addition to the free base of **24**. The intermediate free bases were acidified with HCl to provide **44a**,**b** as their HCl salts.

Table 1. Cryptolepine Analogues



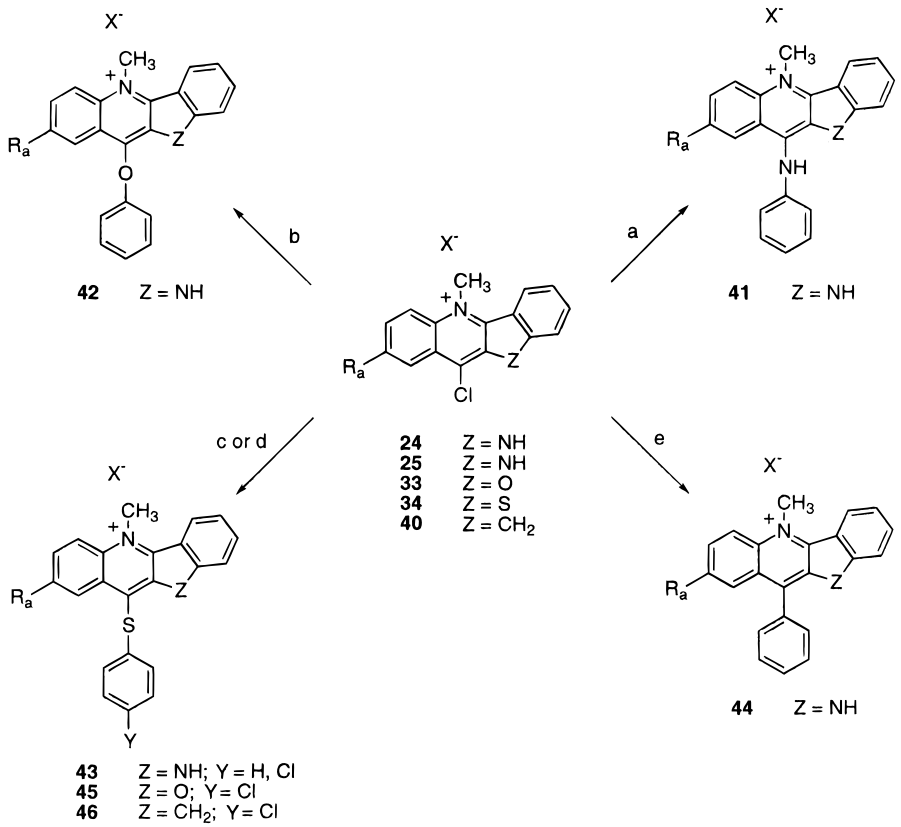
compd	R_a	R_5	R_b	R_{11}	Z	X
2	H	CH_3	H	H	NH	Cl
7a	H	CH_3	H	H	NH	I
11b	2-F	CH_3	H	H	NH	Cl
11c	H	CH_3	7-Br, 8-Cl	H	NH	Cl
11d	H	CH_3	6-Cl, 7-Br	H	NH	Cl
11e	H	Et	H	H	NH	Cl
11f	H	Bu	H	H	NH	Cl
11g	H	Bn	H	H	NH	Cl
11h	H	4-F-Bn	H	H	NH	Cl
11j	4-OMe	CH_3	H	H	NH	Cl
25k	H	CH_3	H	Cl	NH	Cl
25l	2-F	CH_3	H	Cl	NH	Cl
25m	H	CH_3	6-F	Cl	NH	Cl
25n	2-Cl	CH_3	H	Cl	NH	Cl
25o	1-Cl	CH_3	H	Cl	NH	Cl
25p	H	CH_3	8-F	Cl	NH	Cl
25r	H	CH_3	7-Ph	Cl	NH	Cl
25s[a]	H	CH_3	7-F	I	NH	Cl
25t[a]	H	CH_3	9-F	I	NH	Cl
33	H	CH_3	H	Cl	O	OTf
34	H	CH_3	H	Cl	S	OTf
40	H	CH_3	H	Cl	CH_2	OTf
41a	H	CH_3	H	NHPh	NH	Cl
41b	2-F	CH_3	H	NHPh	NH	Cl
42a	H	CH_3	H	OPh	NH	Cl
42b	2-F	CH_3	H	OPh	NH	Cl
43b	2-F	CH_3	H	4-Cl-PhS	NH	Cl
43c	H	CH_3	H	SPh	NH	Cl
44a	H	CH_3	H	Ph	NH	Cl
44b	2-F	CH_3	H	Ph	NH	Cl
45a	H	CH_3	H	4-Cl-PhS	O	OTf
46a	H	CH_3	H	4-Cl-PhS	CH_2	OTf
49	H	CH_3	H	COOMe	NH	I
50	H	CH_3	H	COOMe	NMe	I

[a] Contains 11-chloro impurity.

In Vitro Studies

The activity demonstrated by cryptolepine in the 3T3-L1 glucose transport assay[8] provided us with a useful method to screen analogues as they were prepared and to study the effect that substitution about and within the cryptolepine nucleus had on bioactivity. Most of the analogues shown in Table 1 were screened at three concentrations in the absence of added insulin, and the results are shown in Table 2. Our earlier study noted the importance of the N-5 methyl group for bioactivity, as the N-10 CH_3 regioisomer was inactive.[8] Increasing the lipophilicity of the substituent at N-5 increased the glucose transport activity **11f** (Bu) > **11e** (Et) > **2** (CH_3). Among the two N-5 benzyl derivatives prepared, benzyl (**11g**) was superior to the 4-fluorobenzyl derivative (**11h**) and equipotent with **11f**. In the absence of other factors, halogen or phenyl substitution on the ring system had a minimal effect on efficacy (**11b** vs **2**, **25n** vs **25k**) or decreased activity (**11c**, **25p**, **25r**). Likewise, the 11-chloro substituent reduced the activity of the cryptolepine analogue, possibly due to a deactivating effect (**25k** vs **2**, **25l** vs **11b**). Substitution at the 4-position with OMe (**11j**) or at the 6-position with fluorine (**25m**)

Scheme 6[a,b]



[a] Reagents: (a) aniline (80%); (b) phenol (60%); (c) 4-chlorothiophenol (66−75%); (d) thiophenol (63%); (e) PhMgBr (45%). For conversion to the chloride salts when Z = NH, the procedure in Scheme 1 was used. [b] See Table 1 for the definition of R_a and X.

improved activity, possibly due to an interaction between the methoxy or fluoro group and the N-5 methyl group altering the planarity of the molecule. A similar argument can be made for the simultaneous substitution at the 1- and 11-positions (**25o**), as this analogue displayed similar activity with the parent **2** and was more active than **25k** or **25n**.

Replacement of the nitrogen at the 10-position with oxygen (**33**), sulfur (**34**), and CH_2 (**40**) led to a reduction in the glucose transport activity, with the indenoquinoline derivative (**40**) showing activity only at the 30 μM concentration. Substitution at the 11-position with aniline (**41b**) maintained activity while substution with phenol (**42b**), 4-chlorothiophenol (**43b**), or phenyl (**44b**) appeared to reduce activity.

Some of the cryptolepine analogues which displayed significant glucose transport activity in the initial screen were investigated further at additional concentrations. As shown in Figure 1, an increase in the lipophilicity of the substituent at R_5 led to an increase in the glucose transport activity. With the butyl (**11f**) and benzyl (**11g**) derivatives, cellular toxicity was seen at the higher concentrations. The 4-methoxy derivative (**11j**) showed a marked improvement in glucose transport activity over cryptolepine hydrochloride (**2**), with cytotoxicity being observed at the higher concentration (30 μM). In contrast, the 2-fluoro derivative (**11b**) showed improved glucose transport across the concentration range without signs of cytotoxicity.

In Vivo Studies

Select cryptolepine analogues were tested under single dose conditions at 100 mg/kg in genetically altered obese diabetic mice (designated C57BL/KS-*db*/*db* or *db*/*db*). The results are shown in Table 3. The 4-methoxy derivative **11j** was the most efficacious derivative tested, lowering the plasma glucose level 58.3% 24 h postdose while showing improved food intake as compared with cryptolepine hydrochloride (**2**). The 2-fluoro derivative **11b** was also efficacious, lowering the plasma glucose level 42.5% 3 h postdose, with activity still being seen at 24 h. However, as with cryptolepine hydrochloride (**2**), this effect was accompanied by a large reduction in both mean body weight and food intake. The 7- and 9-fluoro, 11-iodo derivatives (**25s** and **25t**, respectively) were less active than **11b**, with **25s** showing less of an effect on the food consumption and mean body weight than did **11b** and **25t**. Substitution at the 11-position decreased the ability of the compound to lower plasma glucose based on the three analogues tested (**41b**, **42b**, and **44b**), with **41b** showing improvement in food consumption and body weight as well as demonstrating some activity. Heteroquindoline **33** was statistically inactive while showing no effect on food intake or body weight.

Substitution at the N-5 position dramatically altered the glucose-lowering ability and the in vivo toxicity of the cryptolepine analogue, possibly due to increased lipophilicity. In comparison with **2**, the ethyl derivative **11e** showed a faster onset of action at 3 h postdose, possibly due to pharmacokinetic differences, yet resulted in the death of two animals. The butyl derivative **11f** was acutely toxic at 100 mg/kg, resulting in the death of six out of eight animals. When **11e** and **11f** were tested at a lower dose (30 mg/kg), no activity and a trend toward activity was observed, respectively. With both

Table 2. In Vitro Glucose Transport Activity in 3T3-LI Adipocytes of Cryptolepine Analogues[a]

	% glucose transport[b,c]		
compd	3 μM	10 μM	30 μM
2	148 (*)	305 (**)	359 (**)
7a	134 (**)	163 (**)	287 (**)
11b	253 (***)	360 (***)	443 (****)
11c	104 (ns)	127 (*)	0.1 (ns)
11e	197 (***)	228 (****)	404 (****)
11f	561 (****)	868 (****)	490 (****)
11g	611 (***)	781 (***)	161 (*)
11h	168 (**)	248 (**)	323 (****)
11j	237 (****)	486 (****)	543 (****)
25k	107 (ns)	101 (ns)	0.33 (−)
25l	142 (*)	224 (***)	3.3 (−)
25m	143 (*)	457 (****)	6.4 (−)
25n	108 (ns)	138 (**)	215 (**)
25o	120 (ns)	282 (****)	352 (****)
25p	107 (ns)	159 (*)	6 (−)
25r	122 (*)	190 (****)	16 (−)
25s	115 (ns)	117 (ns)	0.92 (−)
25t	129 (*)	255 (***)	0.1 (−)
33	119 (ns)	114 (ns)	107 (ns)
34	96 (ns)	100 (ns)	110 (ns)
40	125 (ns)	119 (ns)	297 (****)
41b	325 (****)	208 (***)	0.9 (−)
42b	140 (**)	207 (***)	0.39 (−)
43b	128 (**)	154 (**)	13 (−)
44b	281 (****)	215 (*)	116 (ns)
45a	118 (ns)	142 (*)	141 (*)
46a	108 (ns)	110 (ns)	122 (ns)
49	63 (ns)	159 (**)	371 (****)
50	155 (**)	207 (***)	260 (****)

[a] 3T3-L1 glucose transport assay in the absence of added insulin. See ref 8 and procedure cited therein. Data is the average of triplicate runs. [b] p value in parentheses according to the following codes: **** $p < 0.0001$; *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$; ns denotes $p > 0.05$. [c] p as determined by Student's t-test, one tailed, independent.

derivatives, no effect on body weight or food intake was observed at the 30 mg/kg dose. Increasing the steric bulk at N-5 as in **11g** and **11h** resulted in two compounds which demonstrated an ability to lower plasma glucose with an improvement in the food intake and body weight parameters. Benzyl derivative **11g** lowered plasma glucose 15% 3 h postdose with no effect on food intake or body weight. 4-Fluorobenzyl derivative **11h** lowered plasma glucose 36.3% with improved food intake (3.1 vs 0.9 g for **2**).

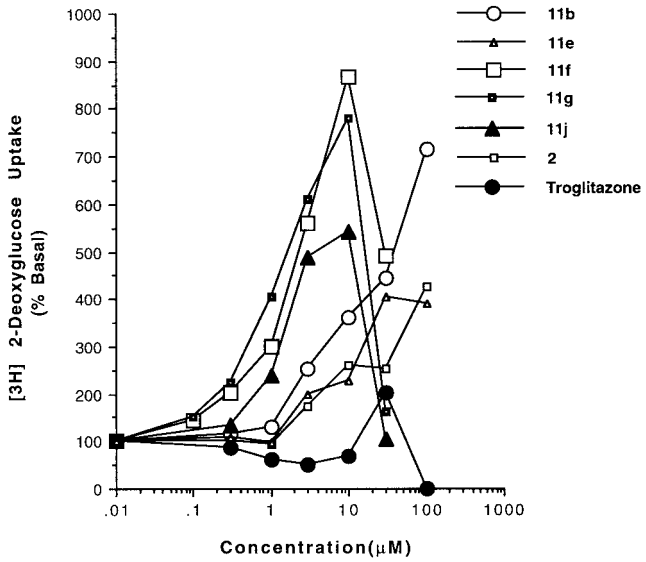


Figure 1. In vitro effect of chronic treatment of cryptolepine hydrochloride (**2**), its 2-fluoro derivative **11b**, its N-R_5 derivatives **11e**−**g**, and its 4-methoxy derivative **11j** on glucose transport in 3T3-L1 adipocytes (absence of insulin).

In an attempt to differentiate a glucose lowering effect with a cryptolepine analogue from an anorexigenic effect, a pair-fed experiment was conducted on a representative analogue. The 4-methoxy derivative **11j** was chosen on the basis of its ability to lower plasma glucose significantly and because concomitant effects in food intake were observed with this derivative. In this experiment, *db*/*db* mice were divided into a control group given free access to food and two pair-fed groups treated with either vehicle or 100 mg/kg of **11j**. Plasma glucose concentrations were measured 3 and 24 h postdose. While glucose concentrations were lower than control in both pair-fed groups, mice receiving **11j** treatment had significantly lower plasma glucose concentrations than did the vehicle-treated group (Table 4).

Table 3. In Vivo Results in *db*/*db* Mice of Selected Cryptolepine Analogues[a]

	dose,	plasma glucose, % change predose		ANOVA[b]		mean body weight, g/mouse		food intake,
compd	mg/kg	3 h	24 h	3 h	24 h	0 h	24 h	g/mouse/day
2	100	−16.4	−43.1	0.059	0.0002	41.0 ± 0.5	39.8 ± 0.5	0.9
11b	100	−42.5	−34.5	0.007	0.006	43.8 ± 0.7	41.9 ± 0.9	0.5
11c	100	−33.0	−18.9	0.011	0.037	45.5 ± 0.8	44.6 ± 0.6	2.8
11e	100	−23.2	−26.5	ns	0.021	44.6 ± 0.6	43.3 ± 1.0	1.0[c]
11e	30	−7.7	−4.1	ns	ns	41.7 ± 0.5	41.2 ± 0.6	5.1
11f	100	−33.8	−2.2	0.090	ns	45.8 ± 1.3	45.8 ± 1.2	2.6[d]
11f	30	4.0	−22.0	ns	0.1006	38.7 ± 0.8	38.6 ± 0.8	6.0
11g	100	−15.0	−20.0	0.0223	ns	39.3 ± 0.6	38.9 ± 0.7	5.1
11h	100	−36.3	−9.7	<0.0001	0.091	40.2 ± 1.2	39.0 ± 1.2	3.1
11j	100	−8.3	−58.3	ns	<0.0001	38.4 ± 0.7	37.1 ± 0.7	2.0
25s	100	−33.1	−13.2	0.026	ns	42.2 ± 1.4	41.8 ± 1.3	2.7
25t	100	19.9	−32.9	ns	0.15[e]	43.4 ± 0.7	41.4 ± 0.8	0.7
33	100	−17.9	−20.8	ns	ns[e]	40.6 ± 0.6	41.1 ± 0.6	4.9
41b	100	−10.5	−10.7	0.085	0.017	44.8 ± 0.6	44.2 ± 0.6	3.2
42b	100	−11.8	−7.5	0.049	0.044	46.6 ± 0.8	45.2 ± 1.0	1.6
44b	100	−11.2	−4.9	ns	ns	40.5 ± 0.9	40.4 ± 0.9	5.1
mean vehicle[f]	100	−3.2	−1.3			41.9 ± 0.8	41.8 ± 0.8	5.0

[a] Single dose experiments at $t = 0$ ($n = 8$, except **2**, where $n = 5$) in genetically altered obese diabetic mice (designated C57BL/KS-*db*/*db*). Plasma glucose levels measured at 3 and 24 h postdose. [b] Analysis of variance (one factor), ns = $p > 0.15$. Vehicle used as a negative control. Metformin used as a positive control. [c] Two animals died. [d] Six animals died. [e] Vehicle control dropped at 24 h in this experiment. [f] Mean values of seven treatment groups shown for comparison.

Table 4. Pair-Fed Experiment on 4-Methoxycryptolepine Hydrochloride (**11j**) in *db*/*db* Mice

	% change predose[b]		ANOVA	
treatment[a]	3 h	24 h	3 h	24 h
control	−9	2		
pair-fed control	−14	−43	ns	<0.001
pair-fed **11j**, 100 mg/kg	−15	−55*	ns	<0.001

[a] $n = 8$, single dose. [b] $p < 0.01$ (ANOVA) as compared to pair-fed control group.

Conclusion

On the basis of the ethnobotanically generated lead structure of cryptolepine, a series of substituted and heterosubstitued cryptolepine analogues have been synthesized, and their bioactivities have been measured in a 3T3-L1 glucose transport assay. While cryptolepine itself has been the subject of numerous biological studies, this report to our knowledge is the first structure−bioactivity study reported on the cryptolepine nucleus.[24] In this study, 33 analogues are reported. A select group of these synthesized analogues were further evaluated in genetically altered obese diabetic C57BL/KS-*db*/*db* mice. Most of the cryptolepine analogues that demonstrated in vitro activity, which were tested in vivo, also demonstrated in vivo activity. With most of the analogues that were tested in vivo, there appears to be a correlation between the ability of the compound to lower plasma glucose levels and the effect seen in the body weight and food intake parameters. Yet while it is possible that some of the analogues tested might manifest their ability to lower plasma glucose levels based on reduced food intake or based on a general toxic phenomenon (as with **11e** and **11f**), we have shown that two derivatives in this series, cryptolepine hydrochloride (**2**) and 4-methoxycryptolepine hydrochloride (**11j**), display true antihyperglycemic properties. One derivative, the N-5 benzyl analogue **11g**, exhibited a significant glucose lowering effect with no effect on food intake or body weight. Further results derived from this study which successfully address the food intake and body weight issues will be published in due course.

Experimental Section

General. General experimental conditions have been described.[8] Low-pressure liquid chromatography (LPLC) was performed on E. Merck 230−400 mesh silica gel using nitrogen pressure unless otherwise noted. Chromatography on cryptolepine salt derivatives was done on Fisher Activity I basic alumina using *ethanol-free chloroform*[8] or on Fisher neutral alumina.

General Procedure A. 2-Fluoroquindoline-11-carboxylic Acid (5b). A nitrogen-purged solution of 3-fluoroisatin (4.71 g, 28.5 mmol) in 4 M KOH (135 mL) at 5 °C was added to a nitrogen-purged flask containing 3-indolyl acetate (5.00 g, 28.5 mmol). The mixture was mechanically stirred for 5 days at room temperature. Water (80 mL) was added, and the solution was heated at 70 °C for 20 min with air being drawn through the solution. The solution was filtered while hot through Celite, and the bed was rinsed with warm water (75 mL). The yellow filtrate was combined with an equal volume of ethanol (300 mL). The mixture was acidified to pH 2 with dilute HCl, chilled, and filtered. The filter cake was washed with water and ethanol, and then dried under high vacuum for 2 days to afford 4.91 g (61%) of **5b** as a bright yellow solid, mp > 243 °C: ^{1}H NMR (DMSO-d_6) δ 14.3 (broad s, 1H), 11.49 (s, 1H), 8.88 (dd, $J = 12.8$, $J = 2.8$, 1H), 8.34 (broad d, $J = 8.8$, 1H), 8.32 (d, $J = 9.2$, 1H), 7.79 (d, $J = 8.4$, 1H), 7.66 (ddd, $J = 8.4$, $J = 7.6$, $J = 1.2$, 1H), 7.62 (ddd, $J = 9.2$, $J = 7.6$, $J = 2.8$, 1H), 7.34 (ddd, $J = 8.0$, $J = 7.2$, $J = 0.8$, 1H); ^{13}C NMR (DMSO-d_6) δ 167.66, 160.45 ($J = 245$), 147.27 (d, $J = 2.3$), 144.44, 140.48, 132.87, 132.22 (d, $J = 10$), 130.51, 124.70 (d, $J = 11$), 121.22, 120.57, 120.48, 115.85 (d, $J = 27$), 112.70, 112.66, 109.80 (d, $J = 9$), 108.53 ($J = 26$); MS (EI, *m*/*z*) 280 (M^+). Anal. ($C_{16}H_9N_2O_2F\cdot0.5H_2O$) C, H, N.

General Procedure B. 2-Fluoroquindoline (6b). A mixture of **5b** (4.50 g, 16.1 mmol) and diphenyl ether (40 mL) was heated at 250 °C for 4 h. The mixture was cooled, petroleum ether (40 mL) was added, and the mixture was filtered. The filter cake was washed with petroleum ether (100 mL) and dried. The crude material was taken up into methanol (250 mL), and the insoluble portion was filtered and washed with additional methanol (2 × 75 mL). Concentration of the filtrate gave 2.47 g (65%) of **6b** as a brown solid, mp >246 °C: ^{1}H NMR (DMSO-d_6) δ 11.52 (s, 1H), 8.34 (d, $J = 8.0$, 1H), 8.28 (s, 1H), 8.24 (dd, $J = 9.2$, $J = 5.6$, 1H), 7.90 (dd, $J = 10$, $J = 2.8$, 1H), 7.65−7.52 (m, 3H), 7.29 (ddd, $J = 7.6$, $J = 6.8$, $J = 0.8$, 1H); ^{13}C NMR (DMSO-d_6) δ 158.96 (d, $J = 241$), 145.53, 143.97, 140.42, 132.86, 131.22 (d, $J = 10$), 129.83, 127.25 (d, $J = 10.6$), 121.31, 120.84, 119.54, 116.23 (d, $J = 27$), 112.47 (d, $J = 5.3$), 111.58, 110.01 (d, $J = 22$); MS (EI, *m*/*z*) 236 (M^+). Anal. ($C_{15}H_9N_2F$) C, H, N.

General Procedure C. 5-Ethylquindolinium Hydroiodide (7e). A suspension of quindoline[8] (1.0 g, 4.6 mmol) and ethyl iodide (3 mL, 37.7 mmol) was heated in a bomb at 135 °C for 15 h. The excess ethyl iodide was removed in vacuo, and the brown precipitate was collected, washed with ether, and dried, yielding 1.5 g (88%) of **7e**. Recrystallization from water gave bright yellow crystals, mp 256 °C (lit.[1] mp 222−223 °C): ^{1}H NMR (DMSO-d_6) δ 12.93 (s, 1H), 9.32 (s, 1H), 8.79 (d, $J = 9.2$, 1H), 8.66 (d, $J = 8.4$, 1H), 8.60 (d, $J = 8.0$, 1H), 8.18 (dd, $J = 7.6$, $J = 7.6$, 1H), 7.95 (t, $J = 8.0$, 2H), 7.87 (d, $J = 8.4$, 1H), 7.55 (dd, $J = 7.6$, $J = 7.6$, 1H), 5.55 (q, $J = 6.8$, 2H), 1.76 (t, $J = 7.2$, 3H); ^{13}C NMR (DMSO-d_6) δ 145.78, 136.92, 134.34, 133.94, 133.52, 132.71, 130.06, 127.09, 126.42, 125.50, 125.14, 121.81, 117.31, 113.37, 112.80, 47.33, 13.30; MS (EI, *m*/*z*) 247 (M^+). Anal. ($C_{17}H_{15}N_2I$) C, H, N.

5-Butylquindolinium Hydroiodide (7f). Reaction of quindoline (1.0 g, 4.6 mmol) and butyl iodide (3 mL, 26.4 mmol) according to general procedure C gave, after washing with 10% ethanol in ethyl ether and drying, 1.82 g (100%) of **7f** as a brown solid. Recrystallization from water gave **7f** as bright yellow crystals, mp 252−253 °C: ^{1}H NMR (DMSO-d_6) δ 12.96 (s, 1H), 9.34 (s, 1H), 8.77 (d, $J = 9.2$, 1H), 8.61 (dd, $J = 8.4$, $J = 1.2$, 1H), 8.54 (d, $J = 8.4$, 1H), 8.19 (ddd, $J = 8.4$, $J = 6.8$, $J = 1.6$, 1H), 7.96 (t, $J = 8.4$, 2H), 7.88 (d, $J = 8.4$, 1H), 7.58 (ddd, $J = 8.0$, $J = 6.8$, $J = 0.8$, 1H), 5.51 (t, $J = 7.2$, 2H), 2.09 (m, 2H), 1.69 (m, 2H), 1.00 (t, $J = 7.2$, 3H); ^{13}C NMR (DMSO-d_6) δ 145.78, 137.07, 134.64, 133.93, 133.52, 132.71, 130.07, 127.11, 126.40, 125.38, 125.29, 121.88, 117.55, 113.47, 112.89, 51.29, 30.11, 19.22, 13.83; MS (EI, *m*/*z*) 275 (M^+). Anal. ($C_{19}H_{19}N_2I\cdot0.86\ H_2O$) C, H, N.

General Procedure D. 2-Fluoro-5-methylquindolinium Hydrochloride (11b). A suspension of **6b** (0.50 g, 2.12 mmol) and methyl iodide (3.95 mL, 63.5 mmol) was heated at 150 °C for 24 h in a Parr bomb. The bomb was cooled, and the reaction mixture was concentrated. The orange residue was suspended in chloroform, adsorbed onto Na_2CO_3, and purified by chromatography over basic alumina. Elution with chloroform to remove unreacted starting material, and then elution with 2% methanol in chloroform gave violet fractions, which were collected and concentrated to a small volume (50 mL). The violet solution was acidified with a 1 M solution of HCl in ether to a bright yellow endpoint. The mixture was chilled, filtered, and then dried to give 0.41 g (68%) of **11b** as a bright orange solid, mp >246 °C: ^{1}H NMR (DMSO-d_6) δ 13.40 (s, 1H), 9.27 (s, 1H), 8.88 (dd, $J = 10$, $J = 4.4$, 1H), 8.80 (d, $J = 8.4$, 1H), 8.44 (dd, $J = 8.8$, $J = 2.8$, 1H), 8.11 (dd, $J = 10.4$, $J = 8.0$, 1H), 7.94 (dd, $J = 8.0$, $J = 8.0$, 1H), 7.85 (d, $J = 8.4$, 1H), 7.51 (dd, $J = 8.0$, $J = 8.0$, 1H), 5.05 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 159.35 ($J = 246$), 145.89, 138.28, 134.13, 134.03, 132.39, 127.39 (d, $J = 10.6$), 126.37, 123.62 (d, $J = 5.3$), 121.86

(d, $J = 27$), 121.41, 121.19 (d, $J = 9.0$), 113.70, 113.20, 112.65 (d, $J = 23.0$), 40.74; MS (LSIMS, *m/z*) 251 (M^+). HRMS (FAB$^+$, *m/z*) calcd for $C_{16}H_{12}N_2F^+$ 251.0984, found 251.0998. Anal. ($C_{16}H_{12}N_2ClF \cdot 1.25H_2O$) C, H, N.

General Procedure E. 5-Ethylquindolinium Hydrochloride (11e). 5-Ethylquindolinium hydroiodide **7e** (0.75 g, 2.0 mmol) was treated with a 5% solution of Na_2CO_3 (100 mL), extracted with chloroform (2 × 250 mL), and then the combined chloroform extract was concentrated to a small volume. Purification over basic alumina, first eluting with chloroform, and then eluting with 1−2% methanol in chloroform, gave a solution of the free base. The purple extract was evaporated to a small volume and acidified to a bright yellow endpoint with a 1.0 M solution of HCl in ether to give, after filtration and drying, 300 mg (53%) of **11e** as yellow crystals, mp 268.5−269 °C (dec): ^{1}H NMR (DMSO-d_6) δ 13.29 (s, 1H), 9.34 (s, 1H), 8.79 (d, $J = 9.2$, 1H), 8.66 (d, $J = 8.4$, 1H), 8.61 (dd, $J = 8.4$, $J = 1.6$, 1H), 8.19 (ddd, $J = 8.4$, $J = 6.8$, $J = 1.6$, 1H), 7.96 (t, $J = 7.2$, 2H), 7.90 (d, $J = 8.0$, 1H), 7.56 (ddd, $J = 8.4$, $J = 6.8$, $J = 1.2$, 1H), 5.56 (q, $J = 7.2$, 2H), 1.76 (t, $J = 7.6$, 3H); ^{13}C NMR (DMSO-d_6) δ 145.88, 136.93, 134.34, 133.92, 133.60, 132.68, 130.11, 127.07, 126.44, 125.50, 125.18, 121.75, 117.30, 113.43, 112.79, 47.32, 13.29. Anal. ($C_{17}H_{15}N_2Cl \cdot 0.86H_2O$) C, H, N.

5-Butylquindolinium Hydrochloride (11f). 5-Butylquindolinium hydroiodide (0.8 g, 2.0 mmol) was converted to its HCl salt according to general procedure E, affording 400 mg (63.5%) of **11f** as yellow crystals, mp 253−254 °C: ^{1}H NMR (DMSO-d_6) δ 13.55 (s, 1H), 9.35 (s, 1H), 8.76 (d, $J = 9.2$, 1H), 8.61 (d, $J = 8.4$, 1H), 8.52 (d, $J = 8.4$, 1H), 8.17 (dd, $J = 8.4$, $J = 8.4$, 1H), 7.94 (t, $J = 8.0$, 2H), 7.88 (d, $J = 8.4$, 1H), 7.55 (dd, $J = 8.0$, $J = 8.0$, 1H), 5.50 (t, $J = 7.6$, 2H), 2.08 (m, 2H), 1.69 (m, 2H), 1.00 (t, $J = 7.2$, 3H); ^{13}C NMR (DMSO-d_6) δ 145.85, 136.94, 134.58, 133.81, 133.53, 132.63, 130.09, 127.02, 126.36, 125.34, 125.22, 121.76, 117.51, 113.48, 112.75, 51.27, 30.11, 19.22, 13.83; MS (EI, *m/z*) 275 (M^+). HRMS (EI) calcd for $C_{19}H_{19}N_2^+$ 275.1548, found 275.1545. Anal. ($C_{19}H_{19}N_2Cl \cdot 1.5H_2O$) C, H, N.

5-Benzylquindolinium Hydrochloride (11g). Reaction of quindoline (1.0 g, 4.6 mmol) and benzyl bromide (3 mL, 8.5 mmol) in chloroform (5 mL) according to general procedure C for 48 h gave 1.78 g of crude hydrobromide salt. Purification on neutral alumina and conversion to the hydrochloride salt according to general procedure E gave 0.40 g (25%) of **11g** as yellow crystals, mp 241−242 °C: ^{1}H NMR (DMSO-d_6) δ 13.40 (s, 1H), 9.49 (s, 1H), 8.68 (d, $J = 8.4$, 1H), 8.53 (d, $J = 8.8$, 1H), 8.31 (d, $J = 8.4$, 1H), 8.12 (dd, $J = 7.6$, $J = 7.6$, 1H), 7.96 (dd, $J = 7.6$, $J = 7.6$, 1H), 7.90 (d, $J = 5.4$, 2H), 7.42−7.32 (m, 4H), 7.22 (m, 2H), 6.84 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 146.14, 138.11, 135.21, 134.16, 133.84, 133.28, 133.00, 130.23, 129.19, 128.14, 127.21, 126.41, 126.10, 126.02, 125.24, 121.65, 117.59, 113.53, 112.86, 54.89; MS (EI, *m/z*) 308 (M^+, free base). HRMS (EI) calcd for $C_{22}H_{16}N_2$ 308.1313, found 308.1309. HRMS (FAB) calcd for $C_{22}H_{17}N_2^+$ 309.1392, found 309.1387. Anal. ($C_{22}H_{17}N_2Cl \cdot 1.75H_2O$) C, H, N.

1-Acetyl-2-(3-methoxy-2-nitrophenylmethylene)-3-oxo-2,3-dihydroindole (14). Method A. To a mixture of 1-acetyl-3-oxoindole[8] (3.0 g, 17.14 mmol), 2-nitro-3-methoxybenzaldehyde (9.31 g, 51.43 mmol), and 4 Å molecular sieves (60 g) in toluene (250 mL) and chloroform (10 mL) was added 15 drops of piperidine. The mixture was stirred for 1 week during which time a yellow precipitate formed. The reaction mixture was diluted with dichloromethane to dissolve the precipitate. The molecular sieves were filtered off and washed several times with dichloromethane. The organic solution was concentrated and the crude product was purified by LPLC, eluting with dichloromethane, to give 5.86 g of unreacted 2-nitro-3-methoxybenzaldehyde and 4.9 g (85%) of **14** as a 2:1 mixture of *Z* and *E* isomers. Major isomer **14a**: ^{1}H NMR ($CDCl_3$) δ 8.22 (d, $J = 8.0$, 1H), 7.86 (ddd, $J = 7.6$, $J = 1.2$, $J = 0.4$, 1H), 7.71−7.68 (m, 1H), 7.48 (dd, $J = 8.0$, $J = 8.0$, 1H), 7.32 (ddd, $J = 7.6$, $J = 7.6$, $J = 0.8$, 1H), 7.14−7.06 (m, 3H), 3.97 (s, 3H), 1.98 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 184.7, 169.9, 151.7, 150.2, 137.5, 136.8, 136.1, 129.1, 125.2, 124.6, 123.3, 120.8, 117.5, 113.9, 113.3, 56.6, 24.7; MS (FAB, *m/z*) 339 (M + H^+). Minor isomer **14b**: ^{1}H NMR ($CDCl_3$) δ 8.00 (d, $J = 8.4$, 1H), 7.74−7.70 (m, 1H), 7.68−7.63 (m, 2H), 7.47 (t, $J = 8.0$, 1H), 7.25 (dt, $J = 7.6$, $J = 0.8$, 1H), 7.19 (dt, $J = 8.0$, $J = 0.8$, 1H), 7.14−7.06 (m, 1H), 3.94 (s, 3H), 2.65 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 182.9, 168.9, 151.3, 148.7, 136.5, 131.7, 130.8, 128.2, 124.8, 124.6, 123.9, 122.1, 119.8, 117.1, 112.8, 56.5, 26.7; MS (FAB, *m/z*) 339 (M + H^+). HRMS (FAB) calcd for $C_{18}H_{14}N_2O_5$+H^+ 339.0981, found 339.1010. Anal. ($C_{18}H_{14}N_2O_5$) C, H, N.

Method B. A solution of 1-acetyl-3-oxoindole[8] (3.0 g, 17.1 mmol), 2-nitro-3-methoxybenzaldehyde (4.65 g, 25.7 mmol), and piperidine (20 drops) in benzene (200 mL) was refluxed in a Dean−Stark apparatus for 4 h. During the first 3 h, the solvent in the trap was removed four times and replaced with freshly distilled benzene. After cooling, the solvent was removed and the residue was purified by LPLC, eluting with dichloromethane, to give 4.5 g (78%) of **14** as a 1:2 mixture of *Z* and *E* isomers.

4-Methoxyquindoline (7j). A mixture of **14** (6.0 g, 17.75 mmol, obtained via Method A) and 5% Pd/$CaCO_3$ (poisoned with lead, 1.5 g) in methanol (600 mL) was hydrogenated (balloon, 1 atm) at room temperature overnight. The catalyst was filtered over Celite, and the solvent was removed on a rotary evaporator to afford crude **15**. A solution of KOH (12.0 g) in methanol (180 mL) was added to crude **15**, and the mixture was stirred at room temperature for 30 min, during which the mixture turned dark brown. The mixture was poured into a saturated NH_4Cl solution and extracted several times with dichloromethane. The organic solutions were combined, washed with brine, dried over $MgSO_4$, and then concentrated. The crude product was purified by LPLC, eluting with dichloromethane and ethyl acetate 20:1, to give 1.82 g (41% yield over two steps) of **7j**, mp 204.5−205.2 °C: ^{1}H NMR (DMSO-d_6) δ 11.40 (s, 1H), 8.34 (d, $J = 8.0$, 1H), 8.22 (s, 1H), 7.66−7.54 (m, 3H), 7.44 (dd, $J = 8.0$, $J = 8.0$, 1H), 7.29 (dd, $J = 7.2$, $J = 7.2$, 1H), 7.06 (d, $J = 7.2$, 1H), 4.05 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 155.3, 144.3, 143.8, 135.5, 132.6, 129.3, 127.8, 125.0, 121.4, 121.2, 119.31, 119.27, 112.8, 111.4, 104.7, 55.4; MS (FAB, *m/z*) 249 (M + 1^+). HRMS (FAB) calcd for $C_{16}H_{12}N_2O$+H^+ 249.1028, found 249.1035.

General Procedure F. 4-Methoxy-5-methylquindolinium Hydrotrifluoromethanesulfonate (11i). A suspension of **7j** (570 mg, 2.3 mmol) in anhydrous toluene (30 mL) was treated with methyl triflate (1.88 g, 11.48 mmol) and the mixture was stirred at room temperature for 3 days. The reaction mixture was diluted with diethyl ether (100 mL). The solid was filtered, washed several times with ether, and then dried to give 742 mg (78%) of **11i** as a yellow solid. The product was recrystallized from methanol, mp 234.0−235.0 °C: ^{1}H NMR (DMSO-d_6) δ 12.81 (s, 1H), 9.19 (s, 1H), 8.68 (d, $J = 8.0$, 1H), 8.09 (dd, $J = 8.4$, $J = 0.8$, 1H), 7.94 (ddd, $J = 7.2$, $J = 7.2$, $J = 0.8$, 1H), 7.86−7.80 (m, 2H), 7.66 (dd, $J = 7.6$, $J = 1.2$, 1H), 7.51 (ddd, $J = 7.6$, $J = 7.6$, $J = 1.2$, 1H), 5.13 (s, 3H), 4.14 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 150.8, 145.8, 139.9, 133.9, 133.4, 128.5, 128.1, 127.6, 126.5, 124.7, 121.6, 121.3, 114.1, 113.3, 113.1, 57.0, 46.4; MS (FAB, *m/z*) 263 (M^+). HRMS (FAB) calcd for $C_{17}H_{15}N_2O^+$ 263.1184, found 263.1188. Anal. ($C_{18}H_{15}N_2F_3O_4S$) C, H, N.

General Procedure G. 4-Methoxy-5-methylquindolinium Hydrochloride (11j). A suspension of **11i** (700 mg, 1.70 mmol) in chloroform (200 mL) was shaken vigorously with a saturated K_2CO_3 solution (100 mL) in a separatory funnel. The purple chloroform extract was washed with aqueous K_2CO_3 solution (3×) and brine, dried over anhydrous K_2CO_3, and then concentrated. The residue was dissolved in chloroform (20 mL) and treated with a solution of HCl in ether (1.0 M, 20 mL). The yellow precipitate was filtered, washed several times with ether, and then dried. Recrystallization from methanol and acetone gave 430 mg (85%) of **11j**, mp 212.4−212.9 °C; ^{1}H NMR (DMSO-d_6) δ 13.24 (s, 1H), 9.22 (s, 1H), 8.68 (d, $J = 8.4$, 1H), 8.10 (dd, $J = 8.4$, $J = 0.8$, 1H), 7.93 (ddd, $J = 7.2$, $J = 7.2$, $J = 1.2$, 1H), 7.86−7.80 (m, 2H), 7.66 (dd, $J = 8.0$, $J = 0.8$, 1H), 7.50 (ddd, $J = 7.2$, $J = 7.2$, $J = 1.2$, 1H), 5.14 (s, 3H), 4.15 (s, 3H); ^{13}C NMR (DMSO-d_6) 150.7, 145.9, 139.8, 133.8,

133.4, 128.4, 128.0, 127.4, 126.4, 124.6, 121.6, 121.2, 113.9, 113.3, 113.1, 57.1, 46.6; MS (FAB, *m/z*) 263 (M^+). HRMS (FAB) calcd for $C_{17}H_{15}N_2O^+$ 263.1184, found 263.1169.

General Procedure H. 2-[(2-Bromoacetyl)amino]-5-fluorobenzoic Acid (17l). A solution of 2-amino-5-fluorobenzoic acid (15.0 g, 96.6 mmol) in DMF (35 mL) and dioxane (35 mL) was cooled to 0 °C. Bromoacetyl bromide (8.43 mL, 96.6 mmol) was added dropwise over a 20 min period, keeping the internal temperature between 0 and 1 °C. After the addition was completed, the ice bath was removed and stirring was continued overnight at room temperature. Water (300 mL) was added, and the light yellow precipitate which formed was filtered, washed with water until neutral, and then dried to give 25.4 g (95%) of **17l** as a white solid, mp 191.2−191.8 °C: ^{1}H NMR (acetone-d_6) δ 11.60 (s, 1H), 8.71 (dd, J = 9.2, J = 5.2, 1H), 7.80 (dd, J = 9.6, J = 3.2, 1H), 7.48−7.43 (m, 1H), 4.18 (s, 2H); ^{13}C NMR (acetone-d_6) δ 168.80, 165.71, 158.37 (d, J = 241.9), 138.56, 122.78 (d, J = 7.8), 122.70, 122.06 (d, J = 21.9), 117.98 (d, J = 24.0), 30.45; MS (EI, *m/z*) 275 (M^+). HRMS (EI) calcd for $C_9H_7NO_3BrF$ 274.9593, found 274.9594. Anal. ($C_9H_7NO_3BrF$) C, H, N.

General Procedure I. 2-[2-[(Phenylamino)acetyl]amino]-5-fluorobenzoic Acid (19l). A solution of **17l** (22.4 g, 91 mmol) and aniline (26 mL, 285 mmol) in DMF (150 mL) was heated at 120 °C for 30 h. After cooling, the reaction mixture was poured into ice−water (800 mL), aqueous 5% KOH (100 mL) was added to solubilize the solid product and adjust the pH to 10−11, and then the mixture was extracted with dichloromethane (3 × 400 mL). The combined dichloromethane extracts were set aside and the aqueous layer was acidified to pH 3 with a solution of 5% HBr. The precipitate which formed was collected, washed with water, and then dried, yielding 19.6 g (75%) of **19l** as white crystals, mp 194−195 °C: ^{1}H NMR (acetone-d_6) δ 11.87 (s, 1H), 8.88 (dd, J = 9.6, J = 5.2, 1H), 7.71 (dd, J = 9.2, J = 3.2, 1H), 7.45−7.39 (m, 1H), 7.14−7.10 (m, 2H), 6.68−6.64 (m, 3H), 3.92 (s, 2H); ^{13}C NMR (acetone-d_6) δ 171.30, 168.14, 163.22, 157.97 (d, J = 241.3), 148.97, 138.66, 129.82, 122.60 (d, J = 7.1), 121.90 (d, J = 21.9), 118.63, 117.78 (d, J = 24.0), 113.67, 50.07; MS (EI, *m/z*) 288 (M^+). HRMS (EI) calcd for $C_{15}H_{13}N_2O_3F$ 288.0910, found 288.0914.

2-[2-[[(3-Fluorophenyl)amino]acetyl]amino]benzoic Acid (19m). Reaction of 2-[(2-bromoacetyl)amino]benzoic acid[16] (**19k**) (8.00 g, 31.0 mmol) and 3-fluoroaniline (7.45 mL, 77.5 mmol) in DMF (80 mL) at 80 °C for 8 h according to general procedure I gave 7.00 g (78%) of **19m** as a gray solid, mp 209 °C: ^{1}H NMR (DMSO-d_6) δ 13.5 (bs, 1H), 11.94 (s, 1H), 8.70 (d, J = 8.4, 1H), 7.94 (dd, J = 7.8, J = 1.4, 1H), 7.60 (ddd, J = 8.0, J = 8.0, J = 1.4, 1H), 7.15−7.07 (m, 2H), 6.83 (bs, 1H), 6.43−6.35 (m, 3H), 3.88 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 170.29, 169.12, 163.25 (d, J = 240.3), 150.17 (d, J = 10.6), 140.52, 134.18, 131.13, 130.43 (d, J = 10.6), 122.73, 119.40, 115.98, 108.42, 103.09 (d, J = 21.2), 98.97 (d, J = 25), 48.48; MS (EI, *m/z*) 388 (M^+). HRMS (EI) calcd for $C_{15}H_{13}N_2O_3F$ 288.0910, found 288.0915.

5,11-Dihydro-2-fluoro-11-oxo-10*H*-indolo[3,2-b]quinoline (2-Fluoro-11-quindolone) (20l). A mixture of **19l** (4.5 g, 15.8 mmol) and polyphosphoric acid (PPA, 150 g) was heated with mechanical stirring at 130 °C for 2 h. The reaction mixture was poured into ice−water (1.2 L), neutralized with saturated KOH solution, and then extracted with EtOAc (2 × 750 mL). The extract was washed with water and brine, dried (Na_2SO_4), and then concentrated to give 2.25 g (56.3%) of **20l** as a yellow solid, mp >270 °C. A portion of this material was purified by LPLC, eluting with EtOAc−MeOH (5:1): ^{1}H NMR (DMSO-d_6) δ 12.65 (s, NH), 11.75 (s, NH), 8.18 (d, J = 8.0, 1H), 7.99 (dd, J = 9.6, J = 2.4, 1H), 7.79 (dd, J = 8.8, J = 4.4, 1H), 7.60 (ddd, J = 10.8, J = 8.0, J = 2.4, 1H), 7.53−7.45 (m, 2H), 7.21 (dd, J = 7.6, J = 7.6, 1H); ^{13}C NMR (DMSO-d_6) δ 166.37, 156.77 (d, J = 237), 138.85, 135.75, 129.34, 127.71, 123.46 (d, J = 5.7), 122.67, 120.91, 120.27 (d, J = 7.7), 119.65 (d, J = 25.3), 118.99, 115.74, 112.66, 108.75 (d, J = 21.8); MS (EI, *m/z*) 252 (M^+).

2-Fluoro-11-chloroquindoline (21l). A solution of **20l** (6.0 g, 23.8 mmol) in $POCl_3$ (60 mL) was refluxed for 2 h. The reaction mixture was cooled, poured into ice, neutralized with a cold saturated solution of KOH while keeping the internal temperature below 45 °C, and then extracted with EtOAc (3 × 500 mL). The combined EtOAc extract was washed with water and brine, dried (Na_2SO_4), and then concentrated. Purification by LPLC, eluting with EtOAc−hexane (1:6), gave 3.5 g (54.5%) of **21l** as a yellow solid, mp 208.5−210.0 °C: ^{1}H NMR (DMSO-d_6) δ 11.89 (s, NH), 8.32 (s, J = 9.6, 1H), 8.30 (d, J = 8.4, 1H), 7.90 (dd, J = 10.4, J = 2.8, 1H), 7.69−7.60 (m, 3H), 7.33 (ddd, J = 8.0, J = 6.8, J = 1.2, 1H); ^{13}C NMR (DMSO-d_6) δ 159.98 (d, J = 243.4), 145.83, 144.00, 140.83, 132.25 (d, J = 9.8), 130.46, 130.42, 124.45 (d, J = 9.9), 121.62, 121.10, 120.39, 116.93 (d, J = 25.8), 112.06, 105.52 (d, J = 24.3); MS (EI, *m/z*) 270 (M^+). Anal. ($C_{15}H_8N_2ClF\cdot0.25H_2O$) C, H, N.

General Procedure J. 6-Fluoro-11-chloroquindoline (21m) and 8-Fluoro-11-chloroquindoline (21p). A suspension of **19m** (6.75 g, 23.4 mmol) in PPA (420 g) was heated at 140 °C for 5 h with mechanical stirring. The mixture was poured over ice (1 L) and placed in an ice bath where the internal temperature was kept below 45 °C while the mixture was neutralized to pH 7 with a saturated KOH solution (total volume 2 L). The resulting precipitate was filtered, washed with water (250 mL), and then dried under high vacuum at 45 °C for several days to afford 7.37 g of a mixture of 6-fluoro-11-quindolone and 8-fluoro-11-quindolone as a green solid: MS (FAB, *m/z*) 253 ($M + H^+$).

The crude mixture obtained above (7.29 g) was refluxed in $POCl_3$ (60 mL) for 3 h, cooled, and then slowly poured over ice (1 L). The mixture was neutralized to pH 7 with a cold slurry of aqueous KOH while maintaining an internal temperature below 45 °C with an external ice bath. The aqueous portion (1.3 L) was extracted with chloroform (5 × 400 mL). The combined organic extracts were washed with water (600 mL) and brine (600 mL), dried (Na_2SO_4), filtered, and then concentrated. The crude product was adsorbed onto neutral alumina with acetone. Chromatography over neutral alumina, eluting with EtOAc−hexane (1:5 gradiated to 1:4), and then rechromatography of mixed fractions in the same manner afforded 0.21 g (4% overall) of **21m** and 1.39 g (22% overall) of **21p** as yellow solids.

Characterization of **21m**: mp 241.8 °C; TLC R_f 0.39 (ethyl acetate−hexane (1:2)); ^{1}H NMR (DMSO-d_6) δ 12.09 (s, 1H), 8.28−8.25 (m, 2H), 7.79−7.71 (m, 2H), 7.65 (ddd, J = 8.0, J = 8.0, J = 5.6, 1H), 7.44 (d, J = 8.0, 1H), 7.10 (dd, J = 10.4, J = 8.0, 1H); ^{13}C NMR (DMSO-d_6) δ 157.70 (d, J = 254.0), 145.86 (d, J = 8.5), 144.19, 143.68, 131.54 (d, J = 9.2), 129.81, 129.41, 127.07, 126.71, 123.37, 122.08, 118.15, 109.26 (d, J = 18.1), 108.20 (d, J = 3.0), 106.10 (d, J = 18.3); MS (FAB, *m/z*) 271 ($M + H^+$). Anal. ($C_{15}H_8N_2FCl\cdot0.75H_2O$) C, H, N.

Characterization of **21p**: mp 240.5 °C; TLC R_f 0.47 (ethyl acetate−hexane (1:2)); ^{1}H NMR (DMSO-d_6) δ 11.95 (s, 1H), 8.34 (dd, J = 8.4, J = 5.6, 1H), 8.24 (m, 2H), 7.74 (ddd, J = 17.6, J = 6.8, J = 1.6, 1H), 7.72 (ddd, J = 17.6, J = 6.8, J = 1.6, 1H), 7.32 (dd, J = 9.6, J = 2.4, 1H), 7.14 (ddd, J = 9.6, J = 8.8, J = 2.4, 1H); ^{13}C NMR (DMSO-d_6) δ 163.80 (d, J = 244.9), 145.35 and 145.21 and 145.08 (two carbons), 144.03, 130.44, 129.19, 127.05, 126.37, 123.51 (d, J = 10.7), 123.35, 122.17, 118.06, 117.91, 108.41 (d, J = 24.1), 98.57 (d, J = 26.9); MS (FAB, *m/z*) 271 ($M + H^+$). Anal. ($C_{15}H_8N_2FCl\cdot0.88H_2O$) C, H, N.

2-Fluoro-5-methyl-11-chloroquindolinium Hydrotrifluoromethanesulfonate (24l). Reaction of **21l** (1.56 g, 5.76 mmol) and methyl triflate (1.89 g, 11.52 mmol) in anhydrous toluene (50 mL) for 1 day according to general procedure F gave 2.40 g (96%) of **24l** as an orange solid, mp 297.5−299.5 °C: ^{1}H NMR (DMSO-d_6) δ 13.29 (s, 1H), 8.97 (dd, J = 10.0, J = 4.4, 1H), 8.82 (d, J = 8.4, 1H), 8.41 (dd, J = 9.6, J = 3.2, 1H), 8.26−8.18 (m, 1H), 7.99 (ddd, J = 8.4, J = 8.4, J = 0.8, 1H), 7.84 (d, J = 8.4, 1H), 7.57 (ddd, J = 8.4, J = 8.4, J = 0.8, 1H), 5.04 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 160.50 (d, J = 250.5),

145.92, 138.99, 134.85, 132.88, 132.54, 127.60 (d, J = 5.0), 126.74, 124.96 (d, J = 9.9), 122.48 (d, J = 10.0), 122.39 (d, J = 26.9), 122.26, 114.47, 113.49, 108.46 (d, J = 25.4), 40.99; MS (EI, m/z) 285 (M^+), 287 ($M + 2^+$). HRMS (FAB, m/z) calcd for $C_{16}H_{11}N_2ClF^+$ 285.0595, found 285.0597. Anal. ($C_{17}H_{11}N_2O_3ClF_4S$) C, H, N.

General Procedure K. 2-Fluoro-5-methyl-11-chloroquindolinium Hydrochloride (25l). A suspension of **24l** (2.34 g, 5.38 mmol), anhydrous Na_2CO_3 (100 g), and chloroform (~100 mL) was sonicated and then concentrated to dryness. The adsorbate was loaded onto a basic alumina column and eluted with chloroform to remove the minor quindoline impurity. Elution with 2−4% methanol in chloroform gave 1.48 g (97%) of 11-chloro-5-methylquindoline as a purple solid.

The purple base was dissolved in chloroform (20 mL) and acidified to a yellow endpoint with a 1 M solution of HCl in ether. The product was filtered, washed with ether, dried, and then recrystallized from chloroform−methanol (5:1), using a minimum amount of ether to facilitate crystallization, providing 1.42 g (90%) of **25l** as yellow crystals, mp 211.8−212.5 °C: ^{1}H NMR (DMSO-d_6) δ 13.55 (s, 1H), 8.99 (dd, J = 10.0, J = 4.4, 1H), 8.82 (d, J = 8.4, 1H), 8.40 (dd, J = 9.2, J = 2.8, 1H), 8.25−8.18 (m, 1H), 7.99 (ddd, J = 8.4, J = 8.4, J = 0.8, 1H), 7.88 (d, J = 8.0, 1H), 7.56 (ddd, J = 8.4, J = 8.4, J = 0.8, 1H), 5.04 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 160.48 (d, J = 250.5), 146.01, 138.95, 134.75, 132.85, 132.53, 127.58 (d, J = 5.6), 126.71, 124.94 (d, J = 10.6), 122.51 (d, J = 9.3), 122.33 (d, J = 27.5), 122.20, 114.42, 113.56, 108.44 (d, J = 25.4), 40.02; MS (EI, m/z) 285 (M^+), 287 ($M + 2^+$). Anal. ($C_{16}H_{12}N_2ClF\cdot 2.6H_2O$) C, H, N.

6-Fluoro-5-methyl-11-chloroquindolinium Hydrochloride (25m). Hydrotriflate salt **24m** was prepared from **21m** (0.11 g, 3.9 mmol) and methyl triflate (0.11 mL, 0.97 mmol) according to general procedure F. The hydrotriflate salt was converted to its hydrochloride salt according to general procedure G. Purification on basic alumina (chloroform−EtOAc (1:0 to 4:1), then 2% methanol in chloroform) and reconversion to the hydrochloride salt according to general procedure K gave 0.11 g (98%) of **25m** as a bright orange solid, mp 232−233.2 °C (dec): ^{1}H NMR (DMSO-d_6/CD_3OD 1:1 v/v) δ 8.64 (d, J = 9.2, 1H), 8.63 (dd, J = 8.0, J = 1.2, 1H), 8.18 (ddd, J = 9.2, J = 6.6, J = 1.2, 1H), 8.00 (ddd, J = 8.4, J = 6.2, J = 1.2, 1H), 7.89−7.84 (m, 1H), 7.59 (dd, J = 8.4, J = 0.4, 1H), 7.22 (ddd, J = 13.6, J = 8.0, J = 0.8, 1H), 4.98 (s, 3H). HRMS (EI) calcd for $C_{16}H_{10}N_2Cl_2F$ 284.0516, found 284.0534. Anal. ($C_{16}H_{11}N_2Cl_2F\cdot 1.5H_2O$) C, H, N.

11-Chloro-5-methylbenzofuro[3,2-b]quinoline Trifluoromethanesulfonate (33). A suspension of **31** (0.40 g, 1.58 mmol) in anhydrous toluene (15 mL) was treated with methyl triflate (0.52 g, 0.36 mL, 200 mol %). The reaction mixture was stirred for 20 h at room temperature, diluted with ether, and then filtered and dried to give 0.41 g (62%) of **33**, mp 221−223 °C: ^{1}H NMR (DMSO-d_6) δ 8.90 (d, J = 8.0, 1H), 8.88 (d, J = 8.0, 1H), 8.73 (dd, J = 8.0, J = 1.2, 1H), 8.38 (ddd, J = 8.2, J = 7.2, J = 1.2, 1H), 8.22 (dd, J = 8.2, J = 0.8, 1H), 8.19−8.14 (m, 2H), 7.83 (ddd, J = 7.6, J = 4.4, J = 1.2, 1H), 5.01 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 159.53, 145.04, 142.89, 137.44, 136.69, 134.57, 130.32, 129.93, 127.05, 126.02, 125.43, 124.73, 119.23, 116.62, 113.80, 40.00; MS (FAB, m/z) 268 (M^+). HRMS (FAB) calcd for $C_{16}H_{11}NOCl^+$ 268.0529, found 268.0545.

11-Chloro-5-methylbenzothieno[3,2-b]quinolinium Trifluoromethane-sulfonate (34). A solution of **32** (0.16 g, 0.59 mmol) in anhydrous toluene (12 mL) was treated with methyl triflate (0.081 mL, 120 mol %), and the reaction mixture was stirred for 20 h at room temperature. The yellow product which formed was filtered, triturated with EtOAc for 24 h, filtered, and then dried to give 97 mg (38%) of **34**, mp 187−189 °C: ^{1}H NMR (DMSO-d_6) δ 9.01 (d, J = 8.0, 1H), 8.95 (d, J = 9.2, 1H), 8.69 (d, J = 8.4, 1H), 8.53 (d, J = 8.0, 1H), 8.43 (dd, J = 8.8, J = 8.8, 1H), 8.21 (dd, J = 8.0, J = 8.0, 1H), 8.09 (dd, J = 7.6, J = 7.6, 1H), 7.89 (dd, J = 8.0, J = 8.0, 1H), 5.07 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 148.34, 143.68, 143.11, 139.34, 135.72, 133.95, 130.59, 130.08, 128.35, 127.10, 125.12, 124.89, 122.81, 119.88, 117.13, 42.79; MS (FAB, m/z) 284 (M^+) MS (−FAB, m/z) 149 (OTf^-). HRMS (FAB) calcd for $C_{16}H_{11}NClS^+$ 284.0301, found 284.0313.

11-Chloro-5-methylindeno[1,2-*b*]quinolinium Trifluoromethanesulfonate (40). A solution of **39** (0.09 g, 0.35 mmol) in anhydrous toluene (8 mL) was treated with methyl triflate (0.05 mL, 0.42 mmol). The reaction mixture was stirred for 20 h at room temperature. Ether (50 mL) was added, and the mixture was stirred for 1 h. The product was filtered, dried, refluxed for 1 h with benzene, filtered while hot, and then dried again to afford 0.11 g (77%) of **40**, mp 193−194 °C: ^{1}H NMR (DMSO-d_6) δ 8.82 (d, J = 8.8, 1H), 8.72 (d, J = 8.0, 1H), 8.60 (dd, J = 8.0, J = 1.2, 1H), 8.32 (ddd, J = 8.8, J = 6.8, J = 1.2, 1H), 8.13 (ddd, J = 8.0, J = 6.8, J = 0.8, 1H), 8.01 (d, J = 7.6, 1H), 7.95 (dd, J = 7.6, J = 7.6, 1H), 7.79 (dd, J = 7.2, J = 7.2, 1H) 4.88 (s, 3H), 4.51 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 157.70, 148.30, 144.16, 139.51, 136.34, 134.85, 134.71, 133.09, 130.04, 128.83, 126.80, 125.39, 124.86, 119.81, 40.97, 34.97; MS (FAB, m/z) 266 (M^+); MS (FAB, m/z) 149 (OTf^-).

General Procedure L. 2-Fluoro-5-methyl-11-(phenylamino)quindolinium Hydrochloride (41b). A solution of 2-fluoro-5-methyl-11-chloroquindoline (freebase of **25l**) (530 mg, 1.86 mmol) and aniline (0.75 g, 8.06 mmol) in 2-ethoxyethanol (50 mL) was heated at 120 °C for 10 min. During this time the color of the reaction mixture changed from purple to yellow, and a yellow precipitate formed. After cooling, the reaction mixture was diluted with ether (100 mL). The precipitate was collected, washed thoroughly with ether, and then dried to give 555 mg (79%) of **41b**, mp 280 °C (sublimed): ^{1}H NMR (DMSO-d_6) δ 11.31 (s, NH), 10.62 (s, NH), 8.64 (d, J = 8.0, 2H), 8.47 (d, J = 10.8, 1H), 8.04 (dd, J = 8.0, J = 8.0, 1H), 7.77−7.68 (m, 2H), 7.47−7.39 (m, 3H), 7.29−7.22 (m, 3H), 4.83 (s, 3H); ^{13}C NMR (acetone-d_6) δ 152.50 (d, J = 245), 136.01, 132.03 (d, J = 3.0), 130.95, 130.52, 127.76, 125.68, 123.12, 119.52, 117.72, 115.57, 115.32, 115.08, 113.86 (d, J = 9.6), 113.37, 112.07 (d, J = 9.7), 107.81, 106.57, 101.60 (d, J = 24.7), 32.13; MS (EI, m/z) 342 (M^+). HRMS (FAB) calcd for $C_{22}H_{17}N_3F^+$ 342.1406, found 342.1433. Anal. ($C_{22}H_{17}N_3ClF$) C, H, N.

2-Fluoro-5-methyl-11-(phenoxy)quindolinium Hydrochloride (42b). Reaction of 2-fluoro-5-methyl-11-chloroquindoline (510 mg, 1.79 mmol) and phenol (1.5 g, 15.96 mmol) in 2-ethoxyethanol (50 mL) at 100 °C for 10 min according to general procedure L gave 410 mg (60.5%) of **42b**, mp 249.5−249.8 °C: ^{1}H NMR (DMSO-d_6) δ 12.94 (s, 1H), 8.98 (dd, J = 10.0, J = 4.4, 1H), 8.84 (d, J = 8.4, 1H), 8.16 (ddd, J = 10.0, J = 8.0, J = 2.8, 1H), 8.01 (dd, J = 8.8, J = 2.8, 1H), 7.94 (ddd, J = 8.4, J = 6.8, J = 0.8, 1H), 7.77 (d, J = 8.4, 1H), 7.55 (ddd, J = 8.4, J = 6.8, J = 0.8, 1H), 7.44−7.40 (m, 2H), 7.22 (dd, J = 8.4, J = 8.4, 1H), 7.15−7.12 (m, 2H), 5.06 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 159.65 (d, J = 248), 156.97, 145.58, 144.49 (d, J = 5.2), 141.74, 134.57, 134.30, 130.29, 127.14, 126.18, 124.21, 122.41 (d, J = 7.7), 122.23 (d, J = 9.0), 122.02 (d, J = 9.8), 121.85, 116.10, 114.57, 113.51, 106.46 (d, J = 26.2), 40.60; MS (EI, m/z) 342 ($M - H^+$). HRMS (FAB) calcd for $C_{22}H_{16}N_2FO^+$ 343.1247, found 343.1222. HRMS (EI) calcd for $C_{22}H_{15}N_2F$ 342.1168, found 342.1183. Anal. ($C_{22}H_{16}N_2OClF\cdot 2H_2O$) C, H, N.

2-Fluoro-5-methyl-11-[(4-chlorophenyl)thio]quindolinium Hydrochloride (43b). Reaction of 2-fluoro-5-methyl-11-chloroquindoline (56 mg, 0.21 mmol) and 4-chlorothiophenol (36 mg, 120 mol %) in 2-ethoxyethanol (5 mL) according to general procedure L gave 60 mg (73%) of **43b**, mp 254−256 °C: ^{1}H NMR (DMSO-d_6) δ 13.16 (s, 1H), 9.00 (dd, J = 10.0, J = 4.4, 1H), 8.85 (d, J = 8.4, 1H), 8.37 (dd, J = 9.6, J = 2.8, 1H), 8.15 (ddd, J = 10.0, J = 7.6, J = 2.8, 1H), 7.98 (dd, J = 8.0, J = 8.0, 1H), 7.87 (d, J = 8.4, 1H), 7.57 (dd, J = 7.6, J = 7.6, 1H), 7.38−7.33 (m, 4H), 5.10 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 160.35 (d, J = 249), 146.23 (146.04), 138.84, 138.10 (137.95), 134.86, 132.62, 132.32, 131.99, 130.40, 129.60, 128.51 (d, J = 5.3), 126.91, 125.68 (d, J = 2.0), 122.64 (d, J = 9.8), 122.08, 121.49 (d, J = 25.6), 114.51, 113.59, 109.66 (d, J =

25.1), 41.24; MS (FAB, *m*/*z*) 393 (M^+). HRMS (FAB) calcd for $C_{22}H_{15}N_2ClFS^+$ 393.0629, found 393.0618. Anal. ($C_{22}H_{15}N_2Cl_2FS \cdot 1.25H_2O$) C, H, N.

2-Fluoro-5-methyl-11-phenylquindolinium Hydrochloride (44b). A suspension of 2-fluoro-5-methyl-11-chloroquindoline (300 mg, 0.35 mmol) in dry dioxane (30 mL) was added to a 1.0 M solution of phenylmagnesium bromide in ether (6 mL, 6.0 mmol) at room temperature. The reaction mixture was stirred for 1 h at room temperature and then heated for 1 h at 50 °C. The reaction mixture was cooled, poured into ice−water (300 mL), left to stand overnight, and then extracted with EtOAc (4 × 50 mL) and chloroform (4 × 50 mL). The combined chloroform and ethyl acetate extract was washed with water, dried, and then concentrated. The residue was purified on a basic alumina column, eluting 0.5−1.5% methanol in chloroform. The product containing fractions were combined, acidified with 1.0 M HCl solution in ether, and then filtered to give 175 mg (45.8%) of **44b** as a yellow solid, mp 251.4−251.8 °C: ^{1}H NMR (DMSO-d_6) δ 12.44 (s, NH), 9.00 (dd, J = 9.2, J = 4.4, 1H), 8.85 (d, J = 8.4, 1H), 8.17 (dd, J = 7.6, J = 7.6, 1H), 7.93 (dd, J = 7.8, J = 7.8, 1H), 7.81−7.70 (m, 6H), 7.62 (dd, J = 9.6, J = 2.8, 1H), 7.54 (dd, J = 7.2, J = 7.2, 1H), 5.12 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 159.66 (d, J = 249.1), 146.35, 138.27, 136.45, 134.13, 132.80 (d, J = 4.2), 131.15, 130.34, 129.94, 129.60, 129.39, 126.20 (d, J = 9.9), 121.88 (d, J = 9.1), 121.72, 121.66, 121.46, 114.01, 113.49, 109.94 (d, J = 24.1), 49.94; (LSIMS, *m*/*z*) 327 (M^+). HRMS (FAB) calcd for $C_{22}H_{16}N_2F^+$ 327.1297, found 327.1281.

Biological Assays. In Vitro Glucose Transport Assay (without Exogenously Added Insulin): [^{3}H]-2-Deoxy-D-glucose Uptake in Differentiated 3T3-L1 Adipocytes. Compounds were initially screened at three concentrations: 3, 10, and 30 μM. Compounds of interest were evaluated further at 0.1, 0.3, 1, 3, 10, 30 μM final concentrations or at 0.3, 1, 3, 10, 30, and 100 μM final concentrations. Adipocytes were treated (in triplicate) for 18 h with a test compound at the appropriate concentration. Details of this assay have been previously described.[8]

In Vivo Studies Using *db*/*db* Mice. The testing protocol in *db*/*db* mice has been previously described.[8]

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Supporting Information Available: Experimental procedures and characterization data for all compounds not described above (26 pages). Ordering information is given on any current masthead page.

References

(1) Fichter, F.; Boehringer, R. Ueber Chindolin. (Over Quindoline.) *Chem. Ber.* **1906**, *39*, 3932−3942.
(2) Clinquart, E. Sur la composition chimique de *Cryptolepis triangularis*, plante congolaise. (On the Chemical Composition of *Cryptolepis triangularis*, Plants from the (Belgian) Congo.) *Bull. Acad. R. Med. Belg.* **1929**, *9*, 627−635.
(3) It is possible that the accepted structure for cryptolepine was actually isolated 45 years after its initial synthesis by Fichter and Boehringer. Clinquart isolated a purple compound in 1929 (mp 160 °C), assumed to possess a primary NH_2 group, from the roots of *C. triangularis* N. E. Br. collected in Kisantu (Belgian Congo). He named this compound cryptolepine and proposed the formula $C_{14}H_{17}N_2O_4$ (see ref 2). Delvaux isolated a purple base in 1931 (mp 193−194 °C) from the same plant material which he named cryptolepine and proposed the formula $C_{17}H_{16}N_2O$ (see refs 4 and 5). The accepted formula for cryptolepine, $C_{16}H_{12}N_2$, was first isolated as a purple solid (mp 175−178 °C) by Gellért in 1951 from *C. sanguinolenta* (see ref 6). Gellért assigned the structure of (**1**) to cryptolepine. The structure of cryptolepine was recently verified by NMR spectroscopy in 1991 by Tackie et al. (see ref 7) and by unambiguous synthesis in 1998 by Bierer et al. (see ref 8).
(4) Delvaux, E. Sur la Cryptolépine. (On Cryptolepine.) *J. Pharm. Belg.* **1931**, *13*, 955−959.
(5) Delvaux, E. Sur la Cryptolépine. (On Cryptolepine.) *J. Pharm. Belg.* **1931**, *13*, 973−977.
(6) Gellért, E.; Raymond-Hamet; Schlittler, E. Die Konstitution des Alkaloids Cryptolepin. (The Constitution of the Alkaloid Cryptolepine.) *Helv. Chim. Acta* **1951**, *34*, 642−651.
(7) Tackie, A. N.; Sharaf, M. H. M.; Schiff, P. L., Jr.; Boye, G. L.; Crouch, R. C.; Martin, G. E. Assignment of the Proton and Carbon NMR Spectra of the Indoloquinoline Alkaloid Cryptolepine. *J. Heterocycl. Chem.* **1991**, *28*, 1429−1435.
(8) Bierer, D. E.; Fort, D. M.; Mendez, C. D.; Luo, J.; Imbach, P. A.; Dubenko, L. G.; Gerber, R. E.; Litvak, J.; Lu, Q. Zhang, P.; Reed, M. J.; Waldeck, N.; Bruening, R. C.; Noamesi, B. K.; Hector, R. F.; Carlson, T. J.; King, S. R. Ethnobotanical-Directed Discovery of the Antihyperglycemic Properties of Cryptolepine: Its Isolation from *Cryptolepis sanguinolenta*, Synthesis, and In Vitro and In Vivo Activities. *J. Med. Chem.* **1998**, *41*, 894−901.
(9) Dalziel, J. M. African Leather Dyes. *Kew Bull.* **1926**, 225−238.
(10) Dalziel, J. M. *The Useful Plants of West Tropical Africa*; Crown Agents for Overseas Governments and Administrations: London, 1955; 2nd reprint, p 387.
(11) See ref 8 and references therein.
(12) Luo, J.; Fort, D. M.; Carlson, T. J.; Noamesi, B.; nii-Amon-Kotei, D.; King, S. R.; Tsai, J.; Quan, J.; Hobensack, C.; Lapresca, P.; Waldeck, N.; Mendez, C. D.; Jolad, S. D.; Bierer, D. E.; Reaven, G. M. Cryptolepine, A Potentially Useful New Antihyperglycaemic Agent Isolated from *Cryptolepis sanguinolenta*: An Example of the Ethnobotanical Approach to Drug Discovery. *Diabetic Med.* **1998**, *15*, 367−374.
(13) Bierer, D. E.; Carlson, T. J.; King, S. R. Integrating Indigenous Knowledge, Tropical Medicinal Plants, Medicine, Modern Science and Reciprocity into a Novel Drug Discovery Approach. *Network Sci.* **1996**, *2* (No. 5) (http://www.awod.com/ netsci/Issues/May96/feature2.html).
(14) Bierer, D. E.; Dener, J. M.; Dubenko, L. G.; Gerber, R. E.; Litvak, J.; Peterli, S.; Peterli-Roth, P.; Truong, T. V.; Mao, G.; Bauer, B. E. Novel 1,2-Dithiins: Synthesis, Molecular Modeling Studies, and Antifungal Activity. *J. Med. Chem.* **1995**, *38*, 2628−2648.
(15) Yamato, M.; Takeuchi, Y.; Chang, M.; Hashigaki, K.; Tsuruo, T.; Tashiro, T.; Tsukagoshi, S. Synthesis and Antitumor Activity of Fused Quinoline Derivatives. *Chem. Pharm. Bull.* **1990**, *38*, 3048−3052.
(16) Yamato, M.; Takeuchi, Y.; Chang, M.; Hashigaki, K. Synthesis and Antitumor Activity of Fused Quinoline Derivatives. II. Novel 4- and 7-Hydroxyindolo-[3,2-b]quinolines. *Chem. Pharm. Bull.* **1992**, *40*, 528−530.
(17) Görlitzer, K.; Stockmann, R.; Walter, R. D. Gegen Malaria wirksame 10*H*- Indolo[3,2-b]chinolin-11-yl-amine. Part 1: Phenol-Mannich-Basen vom Amodiaquin- und Cycloquin-Typ. (Antimalarial 10*H*-Indolo[3,2-b]quinolin-11-ylamines. Part I: Phenol-Mannich Bases of the Amodiaquine and Cycloquine Type.) *Pharmazie* **1994**, *49*, 231−235.
(18) Görlitzer, K.; Weber, J. Anellierte Chinoline, 6. Mitt. 10*H*-Indolo-[3,2-b]chinoline (Fused Quinolines VI: 10*H*-Indolo[3,2-b]quinoline). *Arch. Pharm. (Weinheim)* **1981**, *314*, 852−861.
(19) Chang, M.; Takeuchi, Y.; Hashigaki, K.; Yamato, M. Synthesis of 7-Substituted Indolo[3,2-b]quinoline Derivatives. *Heterocycles* **1992**, *33*, 147−152.
(20) Sunder, S.; Peet, N. P. Synthesis of Benzofuro[3,2-b]quinoline-6(*11H*)one and Derivatives. *J. Heterocycl. Chem.* **1978**, *15*, 1379−1382.
(21) Görlitzer, K.; Weber, J. Anellierte Chinoline 4. Mitt. 11-Oxo-5, 11-dihydrobenzothieno[3,2-b][1]chinoline, S, S.-Dioxide und Thionierungsprodukte. (Fused Quinolines. Part 4. 5,11-Dihydrobenzothieno[3,2-b][1]quinolin-11-ones, S,S-Dioxides and Thionation Products.) *Arch. Pharm. (Weinheim)* **1980**, *314*, 76−84.
(22) Görlitzer, K. Untersuchungen an 1,3-Dicarbonylverbindungen, 11 Mitt. Anellierte Chinolone II, N- und O-Alkylierungsprodukte. (Studies on 1,3-Dicarbonyl Compounds, XI: Fused Quinolines II, N- and O-Alkylated Products.) *Arch. Pharm. (Weinheim)* **1979**, *312*, 254−261.

(23) Kempter, G.; Noack, H.; Russ, G. Heterocyclen aus Aminoketonen; Reaktionen monoalkylierter Amine mit aktiven Halogeniden. (Heterocycles from Amino Ketones: Reaction of Monoalkylated Amines with Active Halides.) *Z. Chem*. **1963**, *3*, 352−353.

(24) After this study was completed,[25] a report appeared which studied the effect that N-5 substitution of quindoline had on renal vasodilation and inhibition of platelet aggregation in a rat model. See: Oyekan, A. O.; Ablordeppy, S. Y. N-5 Alkylation of 3:4 Benz-Δ-carboline is a Requirement for Renal Vasodilation and Inhibition of Platelet Aggregation in the Rat. *Med. Chem. Res.* **1996**, *6*, 602−610.

(25) Bierer, D. E. Cryptolepine Analogs with Hypoglycemic Activity. U.S. Patent 5,681,958, October 28, 1997, filed June 7, 1995.

(26) Moran, K. In *Biodiversity and Human Health*; Grifo, F., Rosenthal, J., Eds.; Island Press: Washington, D.C., 1997; pp 243−263.

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