Synthesis and Antiplasmodial Activity of Aminoalkylamino-Substituted Neocryptolepine Derivatives

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A series of chloro- and aminoalkylamino-substituted neocryptolepine (5-methyl-5*H*-indolo[2,3-*b*]quinoline) derivatives were synthesized and evaluated as antiplasmodial agents. The evaluation also included cytotoxicity (MRC5 cells), inhibition of β-hematin formation, and DNA interactions (DNA−methyl green assay). Introduction of aminoalkylamino chains increased the antiplasmodial activity of the neocryptolepine core substantially. The most efficient compounds showed antiplasmodial activities in the nanomolar range. N^1,N^1-Diethyl-N^4-(5-methyl-5*H*-indolo[2,3-*b*]quinolin-8-yl)pentane-1,4-diamine **11c** showed an IC_{50} of 0.01 μM and a selectivity index of 1800.

Introduction

Plants are still important resources for the discovery of new drugs. The potential of natural compounds as new drug leads is clearly illustrated by the discovery and development of artemisinin-inspired endoperoxides as antimalarial drugs. The importance of artemisinins as antimalarials has encouraged research for other plant derived antiparasitic agents. A promising plant appeared to be *Cryptolepis sanguinolenta*. The roots of this climbing shrub are used in Central and West Africa in traditional medicine for the treatment of malaria. Its main alkaloid, cryptolepine (5-methyl-5*H*-indolo[3,2-*b*]quinoline) (**1**) has been shown to have potent antiplasmodial activity both against chloroquine-sensitive and chloroquine-resistant *Plasmodium falciparum* (Figure 1).[1,2] Further experiments indicated that cryptolepine inhibits the formation of β-hematin, a mechanism also responsible for the antiplasmodial activity of chloroquine (**2**). Unfortunately, cryptolepine is also a DNA intercalating agent and an inhibitor of topoisomerase II, resulting in a high level of cytotoxicity. It was speculated that substitution of cryptolepine could be favorable for more selective antimalarial activity by decreasing the DNA interfering action, and several series of substituted cryptolepines have been synthesized.[1,2] A dibromoanalogue, 2,7-dibromo-5-methyl-5*H*-indolo[3,2-*b*]-quinoline, was found 10 times more potent than cryptolepine, did not show cross-resistance with chloroquine, and appeared not toxic in mice but was still DNA-intercalating. Moreover, compounds with a 5*H*-indolo[3,2-*b*]quinoline core displayed antihyperglycemic, anticholinergic, and antiadrenergic activity.[1,2]

In a search for novel antimalarial compounds, we focused on minor alkaloids of *C. sanguinolenta* such as neocryptolepine (5-methyl-5*H*-indolo[2,3-*b*]quinoline, cryptotackieine) (**3**), isocryptolepine (5-methyl-5*H*-indolo[3,2-*c*]quinoline, cryptosanguinolentine) (**4**),[3,4] and the non-natural isoneocryptolepine (5-methyl-5*H*-indolo[2,3-*c*]quinoline) (**5**),[5−7] which also showed antiplasmodial activity against chloroquine-resistant *P. falciparum*. Neocryptolepine appeared to have lower affinity for DNA and topoisomerase II compared to cryptolepine.[8,9]

In a previous paper, we reported on the synthesis and biological activity of a series of substituted neocryptolepine derivatives. 2-Bromo-5-methyl-5*H*-indolo[2,3-*b*]quinoline (2-bromoneocryptolepine) was the most promising compound. It showed an IC_{50} of 4.0 μM against chloroquine resistant *P. falciparum* in the absence of obvious cytotoxicity (MRC5 cells: $IC_{50} > 32$ μM). It showed low affinity for DNA and no topoisomerase II inhibition. Inhibition of β-hematin formation could be demonstrated.[10,11] However, several analogues have been described for DNA interfering activity and are under investigation as anticancer drugs.[12,13]

In this paper, we report on the further exploration of the antimalarial potential of the neocryptolepine core. We tried to reduce the cytotoxicity by introducing halo-substituents as in 2-bromoneocryptolepine in order to reduce the DNA-intercalating properties of the parent compound. Therefore, a functional assay was used to measure DNA-interactions, i.e., the DNA−methyl green assay. In addition, we tried to improve the biological activity of the parent compound by substituting it with basic (aminoalkylamino) side chains. A basic side chain is indeed an important feature for the activity of chloroquine and is required for the accumulation into the food vacuole and, hence, for inhibition of hemozoin formation. Therefore, a functional assay was used to measure the inhibition of β-hematin formation, the in vitro process that is equivalent to hemozoin formation in the parasite. We prepared a series of neocryptolepine analogues with chloro-substituents, an N^1,N^1-diethylpentane-1,4-diamine group (the side chain of chloroquine), and a combination of both in various positions. This series was extended to other aminoalkylamino groups and to norneocryptolepine (quinindoline, 6*H*-indolo[2,3-*b*]quinoline) for the 11-substituted compounds.

During the course of our work, this strategy was applied to cryptolepine. 11-Substituted cryptolepine derivatives were reported, and these derivatives appeared more potent and less toxic than the parent compound although the selectivity ratios were still rather moderate (<50).[14] Basic side chain analogues of

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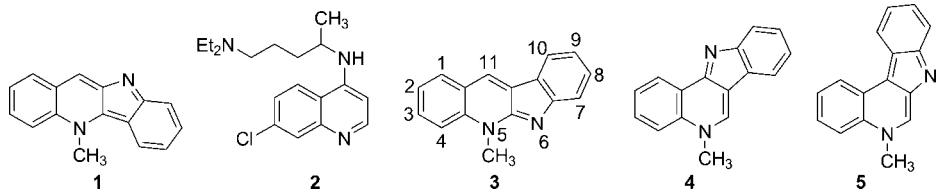


Figure 1. Structures of cryptolepine (**1**), chloroquine (**2**), neocryptolepine (**3**), isocryptolepine (**4**), and isoneocryptolepine (**5**).

norcryptolepine were reported as telomerase inhibitors.[15] Weak telomerase inhibiting properties had already been demonstrated for neocryptolepine.[16] Amino-substituted derivatives of neocryptolepine were not reported until now, apart from 11-anilino analogues of norneocryptolepine that were studied as anticancer agents.[17]

Chemistry

Several pathways for the synthesis of the neocryptolepine core have been developed. Cyclizations starting from a quinoline, an indole, and double cyclizations are described.

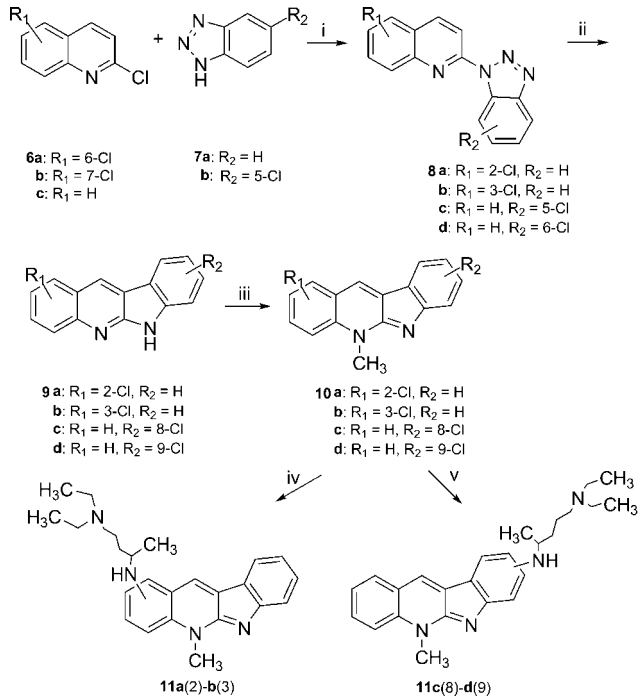
Double cyclizations include thermal biradical or Lewis acid induced cyclizations of *N*-[2-(alk-1-yn-1-yl)phenyl]-*N*′-phenylcarbodiimide[10,18−20] and *N*-[2-(alk-1-en-1-yl)phenyl]-*N*′-phenylcarbodiimides[21] and reductive cyclizations of 2,3-bis(2-nitrophenyl)propanoate derivatives.[22,23] Other methodologies start from (2-nitrobenzyl)triphenylphosphonium bromide and an aldehyde to construct the quinoline and indole ring consecutively.[24] Cyclizations starting from quinolines use 2-(1*H*-benzotriazol-1-yl)quinolines in a Graebe−Ullmann type reaction,[25,26] 2-azido-4-chloro-3-phenylquinoline in an intramolecular nitrene insertion reaction,[27] 2-(2-chloroquinolin-3-yl)aniline[28] or 3-(2-aminophenyl)-1-methylquinolin-2(1*H*)-one (after activation with $POCl_3$) in an intramolecular nucleophilic aromatic substitution reaction,[29] and *N*-phenylquinolin-2-amine via a heteroatom directed photoannulation.[30] Indole based strategies have been published starting from *N*-methylisatine,[31] 3-[(methylthio)methylene]-1,3-dihydro-2*H*-indol-2-one,[32] methyl 1*H*-indole-3-carboxylate,[33] or 2-chloro-1*H*-indole-3-carbaldehyde.[34]

Our general synthetic strategy was based on the amination of chloro-substituted neocryptolepines. The main reason for this is the incapability to perform a selective methylation of the quinoline nitrogen atom when the basic side chain is already present on the neocryptolepine nucleus. In addition, this approach offers the advantage to easily modify the basic side chain as it is introduced in the last reaction step. The chloroneocryptolepines were synthesized through two methods.

The Graebe−Ullman condensation,[25,26] starting from commercially available or prepared chloroquinolines **6** and chlorobenzotriazoles **7**, appeared the most versatile synthesis of neocryptolepines with substitutions on the A or D ring (2-, 3-, 8-, and 9-substitution). The Graebe−Ullman condensation was performed under thermolytic conditions and yielded intermediate 2-(1*H*-benzotriazol-1-yl)quinolines **8** and norneocryptolepines **9**. The 5-methyl group was introduced with iodomethane, giving rise to neocryptolepines **10.** As basic side chain, we used the chloroquine-derived N^1,N^1-diethylpentane-1,4-diamine. This chain was introduced on 2-, 3-, 8-, and 9-chloroneocryptolepines with a palladium-catalyzed amination reaction (Scheme 1).

First, we tried to implement the microwave-assisted amination protocol for aryl chlorides reported by us previously.[35] Unfortunately, these reaction conditions proved not very useful as the starting chloroneocryptolepines are only moderately soluble in toluene or dioxane. A better result was obtained when using the same catalyst system under more diluted conditions. The higher dilution prompted us to additionally select reflux conditions under classical heating.

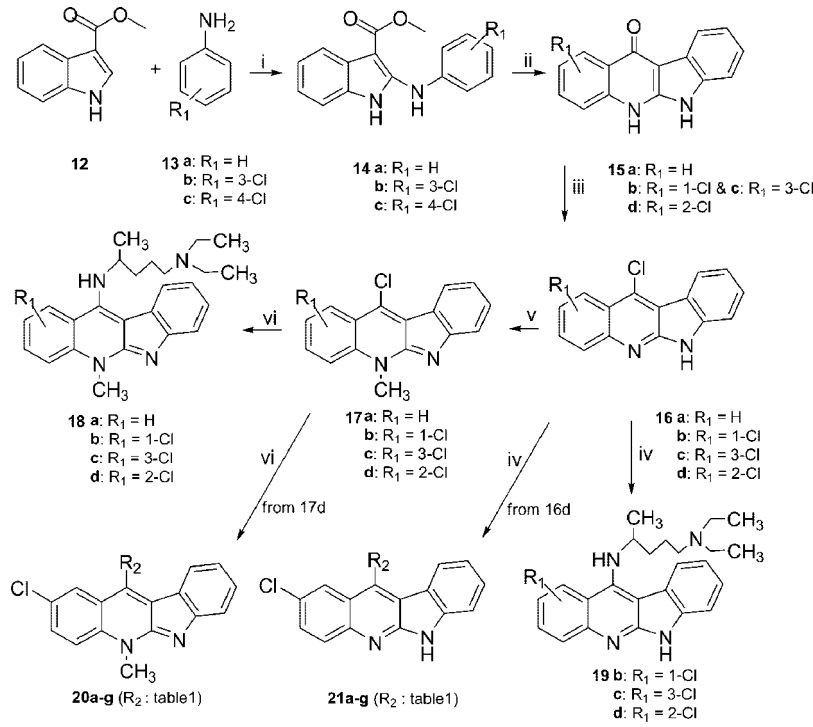
Scheme 1. Synthesis of Neocryptolepines with A or D-Ring Substitutions[a]



[a] Reagents and conditions: (i) 110−120 °C, 2 h. (ii) Polyphosphoric acid, 130 °C, 2−6 h, then 180 °C, 30 min. (iii) (a) MeI, dry THF, reflux, 18−24 h; (b) NH_4OH, CH_2Cl_2, room temperature. (iv) $Pd(OAc)_2$, DCPB, NaO*t*Bu, N^1,N^1-diethylpentane-1,4-diamine, toluene, reflux, 2 h. (v) $Pd(OAc)_2$, DTPB, NaO*t*Bu, N^1,N^1-diethylpentane-1,4-diamine, 1,4-dioxane, reflux, 2−24 h.

Neocryptolepines with a substitution in position 11 were prepared from 1*H*-methyl indole-3-carboxylate (**12**) and anilines **13** (Scheme 2).[33] The intermediate methyl 2-(phenylamino)-1*H*-indole-3-carboxylates (**14**), obtained via chlorination with *N*-chlorosuccinimide in the presence of 1,4-dimethylpiperazine, followed by addition of the aniline as trichloroacetate, were cyclized in boiling diphenyl ether to 5,6-dihydro-11*H*-indolo[2,3-*b*]quinolin-11-ones (**15**), which were dehydroxychlorinated with $POCl_3$ (**16a**). Methylation afforded 11-chloroneocryptolepine (**17a**), which was aminated via an S_NAr reaction in neat N^1,N^1-diethylpentane-1,4-diamine at high temperature, yielding target compound **18a.** Using 3- and 4-chloroanilines **13b−c** as starting materials, 1-, 2-, and 3-chlorosubstituted compounds **18b−d** were similarly obtained. The similarity of chloroneocryptolepines **18b−d** to chloroquine prompted us to prepare also their norneocryptolepine analogues **19b−d** by amination of compounds **16b−d** with N^1,N^1-diethylpentane-1,4-diamine via an S_NAr reaction. A series of analogues of **18d** (**20a−g**) and **19d** (**21a−g**) with other aminoalkylamino-substituents were synthesized by following the same synthetic strategy from **17** and **16**, respectively.

Scheme 2. Synthesis of Neocryptolepines with 11-Substitution[a]



[a] Reagents and conditions: (i) (a) *N*-Chlorosuccinimide, 1,4-dimethylpiperazine, CH_2Cl_2, 0 °C, 2 h; (b) trichloroacetic acid, **13a**−**c**, room temperature, 2 h. (ii) Diphenyl ether, reflux, 45 min-3 h. (iii) $POCl_3$, toluene, reflux, 6−12 h. (iv) N^1,N^1-Diethylpentane-1,4-diamine (for **18**) or appropriate amine (for **20**) (neat), 135−155 °C, 12 h. (v) (a) MeI, THF, reflux, 18−24 h; (b) NH_4OH, CH_2Cl_2, room temperature. (vi) N^1,N^1-Diethylpentane-1,4-diamine (for **19**) or appropriate amine (for **21**), 135−155 °C, 1−4 h.

All compounds used for biological screening and functional tests are listed in Table 1.

Results and Discussion

a. Antiplasmodial Activity and Cytotoxicity. All aminoalkylamino-substituted compounds and their chloro-substituted precursors were evaluated for in vitro antiplasmodial activity against a chloroquine-sensitive *P. falciparum* strain and for cytotoxicity on a human cell (MRC5) line.

All mono- and dichlorosubstituted neocryptolepines (**10a**−**d**, **17a**−**d**) and norneocryptolepines (**16b**−**d**) were poorly potent, showing lower activity than neocryptolepine. Most chloroneocryptolepines were less cytotoxic than the parent compound, except 11-chloroneocryptolepine **17a**, which was marginally more cytotoxic. Introduction of the N^1,N^1-diethylpentane-1,4-diamine side chain resulted in a substantial increase of the antiplasmodial activity. The 8-substituted compound **11c** appeared the most potent, with an IC_{50} of about 0.01 μM, which is as equally potent as the reference compound chloroquine. 11-Substituted neocryptolepine **18a** was less potent, but its activity increased by adding a chlorine substituent on the A-ring, as in compounds **18b**−**d**. Although it has been reported for cryptolepine as well as neocryptolepine derivatives that the presence of an *N*-methyl group is essential for antiplasmodial activity, removal of the 5-methyl group in compounds **18**, affording chloroquine like compounds **19**, resulted only in a 1- to 3-fold loss in potency.[10,36] This shows that not the *N*-methyl group as such, but rather the presence of a basic nitrogen atom, is important for the biological activity, i.e., accumulation in the acid food vacuole where hemozoin formation occurs. The cytotoxicity of the N^1,N^1-diethylpentane-1,4-diamine substituted compounds remained in the same range as the chloroneocryptolepines, compounds **11b**−**c**, **18d**, and **19d** showing the highest selectivity indices.

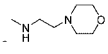
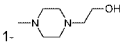
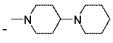
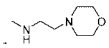
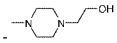
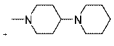
We also prepared a small series of 2-chloro-neo- and -norneocryptolepines with various aminoalkylaminogroups in position 11. Unfortunately, these compounds, **20a**−**g** and **21a**−**g**, although fairly potent, showed a remarkable increase in cytotoxicity.

b. DNA Interactions. Cryptolepine alkaloids are known as DNA intercalating agents and topoisomerase inhibitors, resulting in cytotoxicity. Although neocryptolepines are less prone to this interaction, we tested our compounds as DNA-interacting agents in the DNA−methyl green assay. Cryptolepine as well as neocryptolepine are active in this assay. It had been observed in our previous work on neocryptolepine derivatives that introduction of substituents such as bromine could lead to a decrease of DNA-interacting properties and a reduced cytotoxicity.[10,11] Indeed, all mono- and disubstituted chloro-derivatives of neocryptolepine **10a**−**d** and **17a**−**d** tested in this assay were inactive, as well as the dichlorinated nor-derivatives **16b**−**d**.

On the contrary, introduction of the N^1,N^1-diethylpentane-1,4-diamine side chain in various positions of neocryptolepine as in **11a**−**d** and **18a** did not result in a loss of DNA-interacting properties. However, an additional chloro-substituent in position 1 (**18b**) or 2 (**18d**), but not 3 (**18c**), yielded compounds showing no DNA-interacting activity in this assay. Nevertheless, when the 11-N^1,N^1-diethylpentane-1,4-diamine side chain of the 2-Cl derivative **18d** was replaced by a shorter basic side chain as in **20a**−**g**, the DNA interacting activity was restored.

Finally, it could be noted that the neocryptolepine derivatives **20a**−**g** showing DNA interacting activity in spite of the presence of a chloro-substituent lost this property by removing the *N*-methyl group as in **21a**−**g**. The latter observation is in agreement with the results obtained for the dichlorinated nor-derivatives **16b**−**d**. The absence of DNA-interacting properties is not necessarily accompanied by an absence of cytotoxicity,

Table 1. Biological Results: Cellular Toxicity (MRC5 cells), Antiplasmodial Activity (Pf), Selectivity Index (SI), Inhibition of β-Hematin Formation, and DNA Interaction of Substituted Neocryptolepines

		MRC5			Pf			SI	β-hematin formation		DNA interaction	
		IC_{50} μM	SD[a]	n[b]	IC_{50} μM	SD[a]	n[b]	MRC5/Pf	IC_{50} meq	SD[a]	IC_{50} μM	SD[a]
10a	2-Cl, 5-Me	> 64		2	52	16	2	> 1	1.31	0.20	> 1000	
10b	3-Cl, 5-Me	21	23	7	41.11	1.12	2	0.5	ND[c]		ND[c]	
10c	8-Cl, 5-Me	> 64		1	> 64		1	1	1.55	0.16	> 1000	
10d	9-Cl, 5-Me	> 64		1	29		1	> 2	1.23	0.17	> 1000	
17a	11-Cl, 5-Me	5	0.82	4	> 64		2	< 0.08	ND[c]		ND[c]	
17b	1-Cl, 11-Cl, 5-Me	34	26	3	39	22	2	0.9	no[d]		> 1000	
17d	2-Cl, 11-Cl, 5-Me	> 64		2	> 64		2	1	no[d]		> 1000	
17c	3-Cl, 11-Cl, 5-Me	27	33	3	> 64		2	< 0.4	1.14	0.15	ND[c]	
16b	1-Cl, 11-Cl	> 64		1	> 64		1	1	no[d]		> 1000	
16d	2-Cl, 11-Cl	> 64		1	> 64		1	1	no[d]		> 1000	
16c	3-Cl, 11-Cl	> 64		1	> 64		1	1	no[d]		> 1000	
11a	2-NHCH$(CH_3)(CH_2)_3NEt_2$, 5-Me	7.2	2.3	6	0.03	0	2	240	1.45		128	8
11b	3-NHCH$(CH_3)(CH_2)_3NEt_2$, 5-Me	16	8.8	6	0.015	0.007	2	1067	ND[c]		ND[c]	
11c	5-Me, 8-NHCH$(CH_3)(CH_2)_3NEt_2$	18	14	2	0.01	0.01	2	1800	4.40		219	4
11d	5-Me, 9-NHCH$(CH_3)(CH_2)_3NEt_2$	16	7.5	4	0.14	0.3	2	114	< 20% @ 5 meq[e]		446	187
18a	5-Me, 11-NHCH$(CH_3)(CH_2)_3NEt_2$	20	9	10	0.62	0.23	2	32	4.11		312	72
18b	1-Cl, 5-Me, 11-NHCH$(CH_3)(CH_2)_3NEt_2$	21	11	4	0.35	0.28	2	60	< 20% @ 5 meq[e]		> 1000	
18d	2-Cl, 5-Me, 11-NHCH$(CH_3)(CH_2)_3NEt_2$	29	25	4	0.043	0.004	2	674	< 20% @ 5 meq[e]		> 1000	
18c	3-Cl, 5-Me, 11-NHCH$(CH_3)(CH_2)_3NEt_2$	14	11	4	0.13	0.03	2	108	5.25	0.28	248	
19b	1-Cl, 11-NHCH$(CH_3)(CH_2)_3NEt_2$	20	4	3	1.2	1.1	2	17	3.05	0.08	> 1000	
19d	2-Cl, 11-NHCH$(CH_3)(CH_2)_3NEt_2$	> 64		2	0.12	0	2	> 533	2.30	0.11	> 1000	
19c	3-Cl, 11-NHCH$(CH_3)(CH_2)_3NEt_2$	15	3.9	3	0.14	0.14	2	107	4.43	0.20	> 1000	
20a	2-Cl, 5-Me, 11-NH$(CH_2)_2NMe_2$	< 0.25		1	< 0.25		1	1	no[d]		164	63
20b	2-Cl, 5-Me, 11- 	< 0.25		1	< 0.25		1	1	no[d]		186	6
20c	2-Cl, 5-Me, 11- 	0.37		1	0.69		1	0.5	no[d]		118	9
20d	2-Cl, 5-Me, 11- 	0.4		1	< 0.25		1	> 2	no[d]		645	39
20e	2-Cl, 5-Me, 11- 	1		1	2.1		1	0.5	no[d]		358	129
20f	2-Cl, 5-Me, 11- 	0.82		1	2.28		1	0.4	no[d]		376	228
20g	2-Cl, 5-Me ,11- 	4.4	3.6	2	2.46		1	2	no[d]		180	27
21a	2-Cl, 11-NH$(CH_2)_2NMe_2$	> 64		2	0.4	0.2	2	> 160	3.68	0.05	> 1000	
21b	2-Cl, 11- 	> 64		2	3	1.1	2	> 21	5.40	0.64	> 1000	
21c	2-Cl, 11- 	> 64		2	33		1	> 2	no[d]		> 1000	
21d	2-Cl, 11- 	15	11	3	0.38	0.18	2	39	1.53	0.42	> 1000	
21e	2-Cl, 11- 	3		1	2.46		1	1	2.09	0.12	> 1000	
21f	2-Cl, 11- 	2		1	2.34		1	0.9	2.00	0.17	> 1000	
21g	2-Cl, 11- 	2		1	< 0.25		1	> 8	2.20	0.23	> 1000	
3[f]	5-Me (Neocryptolepine)	11	1.4		27	5.7		0.4	5.97	0.22	93	10
[f]	2-Br, 5-Me	> 32			6	6.1		> 5	1.77	0.15	> 400	
2[f]	Chloroquine				0.01				2.56	0.31	ND[c]	

[a] SD = standard deviation. [b] *n* = number of independent measurements. [c] ND = not determined. [d] No inhibition of β-hematin formation at 5 meq. [e] Inhibition of β-hematin formation at 5 meq was less than 20%. [f] The data of these reference compounds are taken from reference 11.

indicating that other mechanisms of cytotoxicity may play a role as well. On the other hand, all compounds showing DNA-interacting activity are cytotoxic to various degrees, indicating that the assay is valid but not exclusive to predict cytotoxicity.

c. Inhibition of β-Hematin Formation. The antiplasmodial mechanism of action of chloroquine and analogues is based on inhibition of hemozoin formation from hematin. This process can be simulated in vitro by measuring the conversion of hemin (hematin as chloride) to β-hematin (synthetic hemozoin). In our previous research, we found that introduction of a chloro- or a bromo-substituent in position 2 or 3 of neocryptolepine increased the potency of the parent compound to inhibit β-hematin formation, yielding compounds more potent than chloroquine in this assay.[11]

In agreement with our previous work, the monochlorinated neocryptolepine derivatives **10a**,**c**,**d** showed a high inhibitory activity. In the series of the dichlorinated derivatives **17b**−**d** and **16b**−**d**, only **17c** was active. Nevertheless, **17c** showed no antiplasmodial activity. On the contrary, all neocryptolepine derivatives only containing a N^1,N^1-diethylpentane-1,4-diamine side chain in various positions **11a**−**d** and **18a** inhibited β-hematin formation, and the same was true for the chlorinated 11-N^1,N^1-diethylpentane-1,4-diamine derivatives **18b**−**d**. The activity was increased by removing the *N*-methyl group as in **19b**−**d**. All analogues of **18d** having a 2-Cl and 5-methyl substituent but a different basic side chain at position 11 (**20a**−**g**) were not active. However, the β-hematin inhibiting properties were restored by removal of the *N*-methyl group as in **21a**−**g** except for **21c**. This is exactly the opposite of that observed in the DNA−methyl green assay.

With regard to the β-hematin inhibitory assay, it should be noted that the amount of material needed to carry out the test is rather high and that the available amounts did not allow measurement of IC_{50} values >5 meq. In Table 1, all compounds showing no activity at 5 meq were marked as inactive, whereas some compounds such as **11d**, and **18b**,**d** showing some activity (<20% inhibition) at this concentration were marked as active. Since this assay has been developed quite recently, it is not completely clear yet which range of IC_{50} values has biological significance. Obviously also, IC_{50} values (much) higher than 5 meq may still be relevant because compounds such as **18b**,**d** did not show DNA interactions but had antiplasmodial activity in spite of a relatively low inhibitory activity of β-hematin formation (unless a completely different mechanism of action would be involved). On the other hand, this inhibitory activity is not necessarily associated with antiplasmodial activity (e.g., **10a**,**c**), possibly because the compound does not reach its target or is not sufficiently accumulated in the acid food vacuole. Taking this into account, the validity of the functional assay is demonstrated by the fact that all compounds containing a basic side chain (and hence are capable of accumulating in the acid food vacuole), and showing inhibition of β-hematin formation, are indeed antiplasmodially active. However, the range of measured IC_{50} values for inhibition of β-hematin formation was rather small (from 1 to >5 meq), and it was not possible to observe a more detailed correlation with the antiplasmodial activity. It should be noted that compound **21c**, which was surprisingly not active in the β-hematin inhibitory assay, was the only compound in the **21** series without a pronounced antiplasmodial activity.

Summarizing the results of both functional assays, DNA-interactions and inhibition of β-hematin formation, it can be concluded that our initial hypothesis that the antiplasmodial activity of parent compounds such as cryptolepine or neocryptolepine is due to a combination of nonselective DNA interactions that are accompanied by a general cytotoxicity and a selective mechanism of action, i.e., inhibition of hemozoin formation, still stands and is further confirmed. In the absence of inhibition of β-hematin formation, only DNA-interacting and cytotoxic compounds showed antiplasmodial activity. Compounds that are not active in both functional assays do not show a pronounced cytotoxicity or antiplasmodial activity.

d. In Vivo Activity. These results prompted us to evaluate compounds **18d** and **19d** in an in vivo drug screening model against *Plasmodium berghei* in Swiss mice. After daily intraperitoneal dosing at 50 mg/kg for five consecutive days, neocryptolepine analogue **18d** showed 100% reduction in parasitaemia on day 4, however, 50% of the animals died by day 7 due to drug toxicity. Administration of a lower dose (20 mg/kg intraperitoneal) was ineffective. The norcompound **19d** was less potent, as 100% reduction in parasitaemia could not be obtained.

Conclusion

Neocryptolepine has been confirmed as a useful lead compound for the development of new antimalarial agents. Our initial goal to prepare synthetic derivatives with higher antiplasmodial activity and lower cytotoxicity could be achieved, resulting in several compounds with in vitro selectivity indices >500. Two compounds were selected for in vivo evaluation in infected mice, but they were not sufficiently potent or toxic to the animals. Further variations in substituents and substitution pattern may be necessary to obtain nontoxic compounds showing in vivo activity.

Experimental Section

General Methods. Starting materials were either commercially available or prepared as reported in literature (2,7-dichloroquinoline[37]). Anhydrous THF, toluene, and dioxane were obtained from Sigma-Aldrich or Acros. Moisture-sensitive reactions were done under a nitrogen or an argon atmosphere. Analytical thin-layer chromatography was performed on silica gel 60 F_{254} (Merck). Column chromatography was carried out on silica gel 60 (230−400 mesh, Merck). Characterization of all compounds was done with ^{1}H NMR and mass spectrometry. ^{1}H NMR spectra were recorded on a 400 MHz Bruker Avance DRX-400 spectrometer with NMR shifts being expressed in ppm downfield from internal TMS. NMR assignments for the regioisomers were determined on the basis of 2D experiments, and NMR coupling constants are reported in hertz. ES mass spectra were obtained from an Esquire 3000 plus ion trap mass spectrometer from Bruker Daltonics. Purity was verified using two diverse HPLC systems using respectively a mass and UV detector. Water (A) and ACN (B), were used as eluents. LC-MS spectra were recorded on an Agilent 1100 Series HPLC system using a Alltech Prevail C18 column (2.1 mm × 50 mm, 3 μm) coupled with an Esquire 3000plus as MS detector and a 5−100% B, 20 min-gradient was used with a flow rate of 0.2 mL/min. Then 0.1% formic acid was added to solvent A and B. Reversed phase HPLC was run on a Gilson instrument equipped with an Ultrasphere ODS column (4.6 mm × 250 mm, 5 μm). A 10−100% B, 35 min gradient was used with a flow rate of 1 mL/min. TFA (0.1%) was added to solvent A and B. The wavelength used was 214 nm. Flash chromatography was carried out using FlashMaster II (Jones Chromatography) using Merck silica gel 60 (230−400 mesh).

General Procedure for the Synthesis of 2-(1*H*-benzotriazol-1-yl)quinolines (8a−d). A mixture of chloroquinoline (**6**) (5 mmol) and benzotriazole (**7**) (5 mmol) was heated at 110−120 °C for 2 h until the exothermic reaction finished (TLC monitoring). After the mixture was cooled to room temperature, the resulting solid was dissolved in DMF (20 mL) and precipitated by slow addition of water. The resulting precipitate was collected by filtration, washed

with water, and dried to give a crude solid, which was recrystallized from EtOH to afford pure compounds **8** as colorless crystals.

2-(1*H*-Benzotriazol-1-yl)-6-chloroquinoline (8a). Yield: 1.30 g (93%), colorless crystals.

2-(1*H*-Benzotriazol-1-yl)-7-chloroquinoline (8b). Yield: 1.25 g (88.5%), colorless crystals.

2-(5-Chloro-1*H*-benzotriazol-1-yl)quinoline and 2-(6-Chloro-1*H*-benzotriazol-1-yl)quinoline (8c,d). Yield: 1.10 g (79%), colorless crystals obtained as an inseparable 1:1 mixture of two regioisomers.

General Procedure for the Synthesis of Chloro-6*H*-indolo[2,3-*b*]quinolines (9a−d). A mixture of **8a−d** (3 mmol) and polyphosphoric acid (15 mL) was heated at 130 °C for 2−6 h until the formation of N_2 had ceased. The mixture was heated at 180 °C for 30 min. The dark solution was allowed to attain room temperature, poured into ice water (30 mL), and neutralized with a saturated Na_2CO_3 solution until pH 8.5 was obtained. The product was extracted with CH_2Cl_2 (3 × 20 mL), the organic layer was dried over anhydrous Na_2SO_4, and evaporated in vacuo. The resulting light-yellow precipitate was purified with flash chromatography using EtOAc−hexane (1:1) as the eluent to afford pure compounds **9a** and **9b** and an inseparable 1:1 mixture of **9c** and **9d**.

2-Chloro-6*H*-indolo[2,3-*b*]quinoline (9a). Yield: 0.22 g (29%), light-yellow solid.

3-Chloro-6*H*-indolo[2,3-*b*]quinoline (9b). Yield: 0.23 g (30%), light-yellow solid.

8- and 9-Chloro-6*H*-indolo[2,3-*b*]quinoline (9c−d). Yield: 0.25 g (33.2%), light-yellow solid obtained as an inseparable 1:1 mixture of two regioisomers.

General Procedure for the Synthesis of Chloro-5-methyl-5*H*-indolo[2,3-*b*]quinolines (10a−d). Chloroindoloquinoline **9a−d** (1 mmol), THF (15 mL), and iodomethane (0.62 mL, 10 mmol) were heated at reflux under N_2 atmosphere (oil bath temperature: 68 °C) for 18−24 h under magnetic stirring in a round-bottom flask. After cooling to room temperature, the precipitated material was filtered off and rinsed well with THF. The residue was dissolved in MeOH (50 mL) and the solvent subsequently evaporated to dryness under reduced pressure. The crude product was purified by flash chromatography on silica gel using $CHCl_3$−MeOH (9:1) affording the hydroiodide salt of **10a−d** as yellowish−orange solids in 37−78% yield. To obtain the free base, the hydroiodide salt of **10a−d** was brought in a mixture of DCM (50 mL) and 30% ammonia in water (50 mL). The organic phase was separated and the aqueous phase subsequently extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness to yield **10a−d** as a red residue. Finally, the residue was purified by flash chromatography on silica gel using hexane−EtOAc (4:1) and hexane−EtOAc (1:1) as eluent to give pure **10a−d** as red solids. The regioisomeric mixture of **10c** and **10d** could be separated at this point using the same chromatographic conditions.

2-Chloro-5-methyl-5*H*-indolo[2,3-*b*]quinoline (10a). Yield: 0.23 g (86%), red solid. ^{1}H NMR ($CDCl_3$) δ 4.28 (s, 3H), 7.18 (m, 1H), 7.50 (m, 1H), 7.63 (m, 2H), 7.67 (d, 1H, J = 8.0 Hz), 7.88 (s, 1H), 7.98 (d, 1H, J = 7.6 Hz), 8.35 (s, 1H). HPLC: 214 nm; t_r 16.39 min 100%. LC/MS: t_r 12.5 min 100%. MS (ESI): m/z = 267 $[M + H]^+$.

3-Chloro-5-methyl-5*H*-indolo[2,3-*b*]quinoline (10b). Yield: 0.23 g (87%), red solid. ^{1}H NMR ($CDCl_3$) δ 4.28 (s, 3H), 7.18 (m, 1H), 7.50 (m, 1H), 7.63 (m, 2H), 7.67 (d, 1H, J = 8.0 Hz), 7.88 (s, 1H), 7.98 (d, 1H, J = 7.6 Hz), 8.35 (s, 1H). HPLC: 214 nm; t_r 15.95 min 100%. LC/MS: t_r 12.1 min 100%. MS (ESI): m/z = 267 $(M + H)^+$.

8-Chloro-5-methyl-5*H*-indolo[2,3-*b*]quinoline (10c). Yield: 0.16 g (60%). ^{1}H NMR ($CDCl_3$) δ 4.29 (s, 3H), 7.14 (m, 1H), 7.43 (m, 1H), 7.65 (m, 1H), 7.90 (d, 1H, J = 8.4 Hz), 7.75 (m, 1H), 7.84 (d, 1H, J = 8.4 Hz), 7.92 (m, 1H), 8.39 (s, 1H). HPLC: 214 nm; t_r 19.72 min 100%. LC/MS: t_r 12.1 min, 96%. MS (ESI): m/z = 267 $(M + H)^+$.

9-Chloro-5-methyl-5*H*-indolo[2,3-*b*]quinoline (10d). Yield: 0.08 g (30%). ^{1}H NMR ($CDCl_3$) δ 4.31 (s, 3H), 7.44 (m, 2H), 7.61 (d, 1H, J = 8.4 Hz), 7.71 (d, 1H, J = 8.4 Hz), 7.77 (m, 1H), 7.91 (m, 1H), 7.95 (d, 1H, J = 7.6 Hz), 8.44 (s, 1H). HPLC: 214 nm; t_r 19.67 min 100%. LC/MS: t_r 13.2 min 100%. MS (ESI): m/z = 267 $[M + H]^+$.

General Procedure for the Synthesis of N^1,N^1-diethyl-N^4-(5-methyl-5*H*-indolo[2,3-*b*]quinolin-2-yl)pentane-1,4-diamines (11a−d). A round-bottom flask was charged with chloroindoloquinoline (**10a−d**) (0.5 mmol), N^1,N^1-diethylpentane-1,4-diamine (0.75 mmol), and NaO*t*Bu (67.30 mg, 0.7 mmol) followed by dry toluene or dry dioxane (1 mL) in air. Subsequently, the flask was flushed with Ar for a few minutes under magnetic stirring. Then 1 mL of a stock solution of Pd catalyst (4 mol%) was added via a syringe and the flask was flushed with Ar for an additional 3 min. [Preparation of 4 mol % stock solution of the catalyst: A 250 mL bottle was charged with $Pd(OAc)_2$ as Pd(0) source (89.8 mg, 0.4 mmol), DCPB [2-(dicyclohexylphosphanyl)biphenyl] or DTPB [2-(di-*t*-butylphosphanyl)biphenyl] as ligand (0.8 mmol), and toluene (10 mL) in air. Subsequently, the bottle was flushed with argon for 10 min under magnetic stirring. The stock solutions were stored under an argon atmosphere. When DTPB was used as ligand for the catalyst, the stock solution was stirred for 16 h prior to its use.] The resulting mixture was heated at reflux (oil bath temperature: 105−110 °C) for 2−24 h under magnetic stirring and an argon atmosphere. After cooling to room temperature, CH_2Cl_2 (25 mL) was added and the suspension filtered over a pad of celite and rinsed with CH_2Cl_2 (30 mL). The solvent was removed under reduced pressure, and the residue purified by flash chromatography using DCM−2.0 N ammonia in MeOH (9:1) as the eluent to yield title compounds **11a−d**.

***N*^{1},*N*^{1}-Diethyl-*N*^{4}-(5-methyl-5*H*-indolo[2,3-*b*]quinolin-2-yl)pentane-1,4-diamine (11a).** Yield: 0.11 g (58%). ^{1}H NMR ($CDCl_3$) δ 1.06 (t, 6H, J = 7.6 Hz), 1.29 (d, 3H, J = 6.4 Hz), 1.63 (m, 4H), 2.48 (t, 2H, J = 6.8 Hz), 2.58 (q, 4H, J = 7.2 Hz), 3.62 (m, 1H), 3.87 (s, 1H), 4.34 (s, 3H), 7.07 (m, 1H), 7.12 (m, 1H), 7.19 (m, 1H), 7.52 (m, 1H), 7.60 (d, 1H, J = 8.8 Hz), 7.72 (d, 1H, J = 8.0 Hz), 8.03 (d, 1H, J = 7.2 Hz), 8.43 (s, 1H). HPLC: 214 nm; t_r 15.03 min 100%. LC/MS: t_r 9.15 min 100%. MS (ESI): m/z = 389 $[M + H]^+$.

***N*^{1},*N*^{1}-Diethyl-*N*^{4}-(5-methyl-5*H*-indolo[2,3-*b*]quinolin-3-yl)pentane-1,4-diamine (11b).** Yield: 0.11 g (55%). ^{1}H NMR ($CDCl_3$) δ 1.05 (t, 6H, J = 7.6 Hz), 1.28 (d, 3H, J = 6.4 Hz), 1.64 (m, 4H), 2.46 (t, 2H, J = 6.8 Hz), 2.55 (q, 4H, J = 7.2 Hz)), 3.69 (m, 1H), 4.29 (s, 3H), 6.63 (s, 1H), 6.65 (d, 1H, J = 9.2 Hz), 7.17 (m, 1H), 7.45 (m, 1H), 7.51 (m, 1H), 7.70 (m, 2H), 7.96 (d, 1H, J = 7.2 Hz), 8.36 (s, 1H). HPLC: 214 nm; t_r 15.68 min 100%. LC/MS: t_r 11.2 min 100%. MS (ESI): m/z = 389 $(M + H)^+$.

***N*^{1},*N*^{1}-Diethyl-*N*^{4}-(5-methyl-5*H*-indolo[2,3-*b*]quinolin-8-yl)pentane-1,4-diamine (11c).** Yield: 0.13 g (67%). ^{1}H NMR ($CDCl_3$) δ 1.04 (t, 6H, J = 7.2 Hz), 1.27 (d, 3H, J = 6.0 Hz), 1.60 (m, 4H), 2.47 (t, 2H, J = 7.2 Hz), 2.57 (q, 4H, J = 7.2 Hz), 3.65 (m, 1H), 4.04 (d, 1H, J = 8.0 Hz), 4.32 (s, 3H), 6.45 (m, 1H), 6.92 (d, 1H, J = 2.0 Hz), 7.38 (m, 1H), 7.67 (m, 2H), 7.76 (d, 1H, J = 8.4 Hz), 7.88 (d, 1H, J = 7.6 Hz), 8.17 (s, 1H). HPLC: 214 nm; t_r 16.04 min 100%. LC/MS: t_r 10.4 min 96%. MS (ESI): m/z = 389 $[M + H]^+$.

N^1,N^1-Diethyl-*N*^{4}-(5-methyl-5*H*-indolo[2,3-*b*]quinolin-9-yl)pentane-1,4-diamine (11d). Yield: 0.054 g (28%). ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 6H, J = 7.2 Hz), 1.27 (d, 3H, J = 6.0 Hz), 1.60 (m, 4H), 2.83 (t, 2H, J = 7.2 Hz), 2.90 (q, 4H, J = 7.2 Hz), 3.61 (m, 1H), 4.32 (s, 3H), 5.93 (m, 1H), (6.90 (m, 1H), 7.40 (m, 2H), 7.57 (d, 1H, J = 8.8 Hz), 7.73 (m, 2H), 7.97 (d, 1H, J = 8.4 Hz), 8.52 (s, 1H). HPLC: 214 nm; t_r 15.95 min 100%. LC/MS: t_r 13.2 min 97%. MS (ESI): m/z = 389 $[M + H]^+$.

General Procedure for the Synthesis of Methyl 2-(Phenylamino)-1*H*-indole-3-carboxylates (14a−c). To a solution of methyl 1*H*-indole-3-carboxylate (**12**) (2.08 g, 11.9 mmol) in CH_2Cl_2 (50 mL) at 0 °C under argon, 1,4-dimethylpiperazine (0.75 g, 6.56 mmol) and *N*-chlorosuccinimide (1.75 g, 13.1 mmol) were added. The reaction mixture was allowed to stand at 0 °C for 2 h, and a solution of trichloroacetic acid (0.5 g, 3 mmol) and the appropriate aniline **13a−c** (23.4 mmol) in CH_2Cl_2 (50 mL) was added and the reaction mixture was allowed to attain room temperature. After 2 h, the reaction mixture was washed with 10% aqueous $NaHCO_3$ and

1.0 M aqueous HCl and finally with water and brine. The resulting solution was dried, filtered, and evaporated. The residue was chromatographed using hexane−EtOAc (3:1) as eluent to yield title compounds **14a**−**c**.

Methyl 2-(Phenylamino)-1*H*-indole-3-carboxylate (14a). Yield: 1.77 g (56%).

Methyl 2-[(3-Chlorophenyl)amino]-1*H*-indole-3-carboxylate (14b). Yield: 1.68 g (47%).

Methyl 2-[(4-Chlorophenyl)amino]-1*H*-indole-3-carboxylate (14c). Yield: 1.75 g (49%).

General Procedure for Synthesis of 5,6-Dihydro-11*H*-indolo[2,3-*b*]quinolin-11-one (15a−d). The ester **14a**−**c** (4 mmol) was heated for 45 min to 3 h in diphenyl ether (5 mL) at reflux (250 °C), and the reaction mixture was allowed to attain room temperature. The solid formed was isolated by filtration and washed with a large quantity of diethyl ether, yielding title compounds **15a**−**d**.

5,6-Dihydro-11*H*-indolo[2,3-*b*]quinolin-11-one (15a). Yield: 0.60 g (65%).

1-Chloro-5,6-dihydro-11*H*-indolo[2,3-*b*]quinolin-11-one and 3-Chloro-5,6-dihydro-11*H*-indolo[2,3-*b*]quinolin-11-one (15b−c). Yield: 0.94 g (88%), as an inseparable 1:1 mixture of two regioisomers.

2-Chloro-5,6-dihydro-11*H*-indolo[2,3-*b*]quinolin-11-one (15d). Yield: 0.57 g (53%).

General Procedure for Synthesis of 11-Chloro-6*H*-indolo[2,3-*b*]quinolines (16a−d). A solution of **15a**−**d**. (2.17 mmol) in dry toluene (5 mL) and $POCl_3$ (5 mL) was refluxed for 6−12 h. The reaction mixture was cooled, poured into ice, neutralized with a cold saturated solution of $NaHCO_3$ while keeping the internal temperature below 30 °C, and then extracted with CH_2Cl_2 (3 × 30 mL). The combined CH_2Cl_2 extract was washed with water and brine, dried (anhydrous Na_2SO_4), and then concentrated. Purification by flash chromatography, eluting with EtOAc−hexane (1:1) afford **16a**−**d** as yellow solids. The 1- and 3-Cl derivatives were separated during this procedure.

11-Chloro-6*H*-indolo[2,3-*b*]quinoline (16a). Yield: 0.38 g (69%). ^{1}H NMR (DMSO-d_6) δ 7.31 (m, 1H), 7.59 (m, 3H), 7.82 (m, 1H), 8.05 (1H, d, J = 8.5 Hz), 8.37 (d, 1H, J = 8.5 Hz), 8.54 (d, 1H, J = 7.7 Hz), 12.02 (s, 1H). MS (ESI): m/z = 253 $[M + H]^+$.

1,11-Dichloro-6*H*-indolo[2,3-*b*]quinoline (16b). Yield: 0.08 g (13%). ^{1}H NMR (DMSO-d_6) δ 7.45 (s, 1H), 7.65 (m, 1H), 7.75 (m, 3H), 8.12 (d, 1H, J = 8.0 Hz), 8.71 (d, 1H, J = 7.2 Hz), 12.20 (s, 1H). HPLC: 214 nm; t_r 19.67 min 100%. LC/MS: t_r 13.2 min 100%. MS (ESI): m/z = 287 $[M + H]^+$.

3,11-Dichloro-6*H*-indolo[2,3-*b*]quinoline (16c). Yield: 0.24 g (38%). ^{1}H NMR (DMSO-d_6) δ 7.36 (m, 1H), 7.55 (d, 1H, J = 8.4 Hz), 7.65 (m, 2H), 8.07 (d, 1H, J = 2.0 Hz), 8.36 (d, 1H, J = 9.2 Hz), 8.50 (d, 1H, J = 8.0 Hz), 12.18 (s, 1H). MS (ESI): m/z = 287 $[M + H]^+$.

2,11-Dichloro-6*H*-indolo[2,3-*b*]quinoline (16d). Yield: 0.49 g (79%). ^{1}H NMR (DMSO-d_6) δ 7.37 (m, 1H), 7.56 (d, 1H, J = 8.0 Hz), 7.64 (m, 1H), 7.82 (m, 1H), 8.07 (d, 1H, J = 9.2 Hz), 8.34 (d, 1H, J = 2.4 Hz), 8.53 (d, 1H, J = 7.6 Hz), 12.10 (s, 1H). MS (ESI): m/z = 287 $[M + H]^+$.

General Procedure for the Synthesis of 11-Chloroneocryptolepines (17a−d). A suspension of **16a**−**d** (0.5 mmol) in dry THF (10 mL) and iodomethane (0.31 mL, 5.0 mmol) was heated at 85 °C for 18−24 h under argon atmosphere. After cooling to room temperature, the precipitated material was filtered off and rinsed with THF (20 mL) to afford the hydroiodide salt of **16a**−**d** as orange solids. The free base was liberated from its hydroiodide by treatment with 28−30% ammonia in water and extraction with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, the solvent was evaporated, and the red residue was purified by flash chromatography using hexane−EtOAc (1:2) as the eluent to afford title compounds **17a**−**d** as red solids.

11-Chloro-5-methyl-5*H*-indolo[2,3-*b*]quinoline (17a). Yield: 0.10 g (75%). ^{1}H NMR ($CDCl_3$) δ 4.34 (s, 3H), 7.30 (m, 1H), 7.51 (m, 1H), 7.73 (m, 3H), 8.36 (d, 1H, J = 8.4 Hz), 8.44 (m, 1H), 8.87 (d, 1H, J = 8.4 Hz). HPLC: 214 nm; t_r 16.79 min 100%. LC/MS: t_r 11.9 min 94%. MS (ESI): m/z = 267 $[M + H]^+$.

1,11-Dichloro-5-methyl-5*H*-indolo[2,3-*b*]quinoline (17b). Yield: 0.09 g (60%). ^{1}H NMR ($CDCl_3$) δ 4.29 (s, 3H), 7.30 (m, 1H), 7.45 (m, 1H), 7.60 (m, 1H), 7.72 (m, 1H), 8.32 (d, 1H, J = 8.8 Hz), 8.24 (d, 1H, J = 8.8 Hz), 8.38 (d, 1H, J = 7.6 Hz). HPLC: 214 nm; t_r 20.55 min 97.97%. LC/MS: t_r 13.2 min 100%. MS (ESI): m/z = 301 $[M + H]^+$.

3,11-Dichloro-5-methyl-5*H*-indolo[2,3-*b*]quinoline (17c). Yield: 0.10 g (68%). ^{1}H NMR ($CDCl_3$) δ 4.26 (s, 3H), 7.29 (m, 1H), 7.59 (d, 1H, J = 7.2 Hz), 7.65 (d, 1H, J = 8.8 Hz), 7.69 (m, 1H), 7.71 (m, 1H), 8.38 (m, 1H), 8.40 (d, 1H, J = 7.6 Hz). HPLC: 214 nm; t_r 19.47 min 71.02%. LC/MS: t_r 13.5 min 85%. MS (ESI): m/z = 301 $[M + H]^+$.

2,11-Dichloro-5-methyl-5*H*-indolo[2,3-*b*]quinoline (17d). Yield: 0.11 g (73%). ^{1}H NMR ($CDCl_3$) δ 4.35 (s, 3H), 7.27 (t, 1H, J = 7.6 Hz), 7.53 (dd, 1H, J = 0.8 Hz), 7.58 (d, 1H, J = 8.4 Hz), 7.63 (d, 1H, J = 8.0 Hz), 7.7 (m, 2H), 8.5 (d, 1H, J = 7.6 Hz). HPLC: 214 nm; t_r 17.86 min 82.51%; LC/MS: t_r 13.2 min 87%. MS (ESI): m/z = 301 $[M + H]^+$.

General Procedure for the Synthesis of 11-Aminoalkylaminoneocryptolepines (18a−d) and (20a−g). Chloroindoloquinoline **17a**−**d** (0.3 mmol) and an excess of the appropriate aminoalkylamine (3.0 mmol) were heated together at 135−155 °C for 1−4 h. TLC monitoring was used to ensure the completion of reaction. The resulting brown crude oil was purified by flash chromatography using CH_2Cl_2−2 N ammonia in MeOH (9:1) as the eluent to yield pure **18a**−**d** and **20a**−**g** as yellowish−orange solids.

***N*^{1},*N*^{1}-Diethyl-*N*^{4}-(5-methyl-5*H*-indolo[2,3-*b*]quinolin-11-yl)pentane-1,4-diamine (18a).** Yield: 0.09 g (77%). ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 6H, J = 9.2 Hz), 1.38 (d, 3H, J = 6.4 Hz), 1.68 (m, 4H), 2.36 (t, 2H, J = 7.2 Hz), 2.42 (q, 4H, J = 6.8 Hz), 4.29 (s, 3H), 4.33 (s, 1H), 5.10 (d, 1H, J = 10.8 Hz), 7.21 (m, 1H), 7.39 (m, 1H), 7.46 (m, 1H), 7.75 (m, 3H), 7.91 (d, 1H, J = 7.6 Hz), 8.17 (d, 1H, J = 8.4 Hz). HPLC: 214 nm; t_r 14.22 min 100%. LC/MS: t_r 10.3 min 100%. MS (ESI): m/z = 389 $[M + H]^+$.

***N*^{4}-(1-Chloro-5-methyl-5*H*-indolo[2,3-*b*]quinolin-11-yl)-*N*^{1},*N*^{1}-diethyl-pentane-1,4-diamine (18b).** Yield: 0.11 g (85%). ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 6H, J = 9.2 Hz), 1.38 (d, 3H, J = 6.4 Hz), 1.61 (m, 4H), 2.36 (t, 2H, J = 7.2 Hz), 2.42 (q, 4H, J = 6.8 Hz), 4.22 (m, 1H), 4.29 (s, 3H), 4.93 (d, 1H, J = 10.8 Hz), 7.2 (t, 1H, J = 7.6 Hz), 7.37 (dd, 1H, J = 1.6, 7.2 Hz), 7.54 (t, 1H, J = 7.2 Hz), 7.71 (m, 2H), 8.24 (d, 1H, J = 8.8 Hz), 8.30 (d, 1H, J = 7.6 Hz). HPLC: 214 nm; t_r 14.8 min 95%. LC/MS: t_r 13.2 min 100%. MS (ESI): m/z = 423 $[M + H]^+$.

***N*^{4}-(3-Chloro-5-methyl-5*H*-indolo[2,3-*b*]quinolin-11-yl)-*N*^{1},*N*^{1}-diethyl-pentane-1,4-diamine (18c).** Yield: 0.10 g (79%). ^{1}H NMR ($CDCl_3$) δ 1.04 (t, 6H, J = 7.2 Hz), 1.4 (d, 3H, J = 6.0 Hz), 1.70 (m, 4H), 2.55 (t, 2H, J = 6.8 Hz), 2.61 (q, 4H, J = 7.2 Hz), 4.20 (m, 1H), 4.28 (s, 3H), 5.10 (d, 1H, J = 10.8 Hz), 7.23 (m, 1H), 7.45 (m, 1H), 7.66 (m, 2H), 7.67 (d, 1H, J = 8.0 Hz), 7.89 (d, 1H, J = 7.6 Hz), 8.18 (s, 1H). HPLC: 214 nm; t_r 15.29 min 97.40%. LC/MS: t_r 15.2 min 93%. MS (ESI): m/z = 423 $[M + H]^+$.

***N*^{4}-(2-Chloro-5-methyl-5*H*-indolo[2,3-*b*]quinolin-11-yl)-*N*^{1},*N*^{1}-diethyl-pentane-1,4-diamine (18d).** Yield: 0.09 g (71%). ^{1}H NMR ($CDCl_3$) δ 0.96 (t, 6H, J = 7.2 Hz), 1.36 (d, 3H, J = 6.4 Hz), 1.70 (m, 4H), 2.40 (t, 2H, J = 7.2 Hz), 2.47 (q, 4H, J = 7.2 Hz), 4.21 (m, 1H), 4.23 (s, 3H), 4.91 (d, 1H, J = 10.4 Hz), 7.21 (t, 1H, J = 7.2 Hz), 7.33 (dd, 1H, J =7.20, 2.0 Hz), 7.46 (t, 1H, J = 8.0 Hz), 7.66 (d, 1H, J = 8.0 Hz), 7.76 (d, 1H, J = 8.0 Hz), 7.87 (d, 1H, J = 7.6 Hz), 8.09 (d, 1H, J = 8.8 Hz). HPLC: 214 nm; t_r 14.23 min 100%. LC/MS: t_r 14.58 min 97%. MS (ESI): m/z = 423 $[M + H]^+$.

***N*^{1}-(2-Chloro-5-methyl-5*H*-indolo[2,3-*b*]quinolin-11-yl)-*N*^{2},*N*^{2}-dimethylethane-1,2-diamine (20a).** Yield: 0.09 g (83%). ^{1}H NMR ($CDCl_3$) δ 2.41 (s, 6H), 2.59 (t, 2H, J = 5.6 Hz), 3.85 (q, 2H, J = 3.2 Hz), 4.25 (s, 3H), 6.57 (br s, 1H), 7.21 (t, 1H, J = 7.2 Hz), 7.45 (t, 1H, J = 7.2 Hz), 7.62 (m, 2H), 7.76 (d, 1H, J = 8.0 Hz), 8.08 (d, 1H, J = 8.0 Hz), 8.20 (d, 1H, J = 2.0 Hz). HPLC: 214 nm; t_r 11.67 min 100%. LC/MS: t_r 9.2 min 100%. MS (ESI): m/z = 353 $[M + H]^+$.

2-Chloro-5-methyl-*N*-(2-pyrrolidin-1-ylethyl)-5*H*-indolo[2,3-*b*]quinolin-11-amine (20b). Yield: 0.08 g (70%). ^{1}H NMR ($CDCl_3$) δ 1.93 (m, 4H), 2.68 (m, 4H), 2.81 (t, 2H, J = 5.6 Hz), 3.88 (q,

2H, $J = 5.2$ Hz), 4.26 (s, 3H), 6.70 (br s, 1H), 7.20 (t, 1H, $J = 8.4$ Hz), 7.45 (t, 1H, $J = 8.4$ Hz), 7.64 (m, 2H), 7.77 (d, 1H, $J = 8.0$ Hz), 8.11 (d, 1H, $J = 8.0$ Hz), 8.24 (d, 1H, $J = 2.0$ Hz). HPLC: 214 nm; t_r 14.57 min 94.3%. LC/MS: t_r 13.2 min 100%. MS (ESI): $m/z = 409$ $[M + H]^+$.

2-Chloro-5-methyl-*N*-(2-morpholin-4-ethyl)-5*H*-indolo[2,3-*b*]quinolin-11-amine (20c). Yield: 0.10 g (87%). ^{1}H NMR ($CDCl_3$) δ 2.61 (m, 4H), 2.68 (t, 2H, $J = 6.8$ Hz), 3.87 (m, 4H), 3.9 (q, 2H, $J = 3.8$ Hz), 4.27 (s, 3H), 6.43 (br s, 1H), 7.22 (t, 1H, $J = 7.6$ Hz), 7.42 (m, 2H), 7.59 (m, 1H), 7.81 (d, 1H, $J = 8.8$ Hz), 8.14 (d, 1H, $J = 8.0$ Hz), 8.50 (s, 1H). HPLC: 214 nm; t_r 11.89 min 100%. LC/MS: t_r 10.7 min 97%. MS (ESI): $m/z = 395$ $[M + H]^+$.

2-Chloro-*N*-[(1-ethylpyrrolidin-2-yl)methyl]-5-methyl-5*H*-indolo[2,3-*b*]quinolin-11-amine (20d). Yield: 0.09 g (79%). ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3H, $J = 7.2$ Hz), 1.50 (m, 1H), 1.68 (m, 4H), 1.82 (m, 1H), 1.85 (m, 1H), 2.80 (m, 1H), 3.02 (m, 1H), 3.45 (m, 1H), 3.82 (m, 1H), 4.02 (m, 1H), 4.26 (s, 3H), 6.82 (m, 1H), 7.20 (t, 1H, $J = 7.2$ Hz), 7.65 (m, 2H), 7.76 (d, 1H, $J = 8.0$ Hz), 8.10 (d, 1H,, $J = 8.0$ Hz), 8.21 (d, 1H, $J = 2.0$ Hz). HPLC: 214 nm; t_r 12.44 min 100%. LC/MS: t_r 9.7 min 100%. MS (ESI): $m/z = 393$ $[M + H]^+$.

2-Chloro-5-methyl-11-(4-methylpiperazin-1-yl)-5*H*-indolo[2,3-*b*]quinoline (20e). Yield: 0.089 g (81%). ^{1}H NMR ($CDCl_3$) δ 2.53 (s, 3H), 2.81 (t, 4H, $J = 4.8$ Hz), 3.61 (t, 4H, $J = 4.4$ Hz), 4.34 (s, 3H), 7.27 (m, 1H), 7.54 (t, 1H, $J = 7.2$ Hz), 7.70 (s, 2H), 7.74 (d, 1H, $J = 7.6$ Hz), 8.33 (d, 1H, $J = 7.6$ Hz), 8.50 (s, 1H). HPLC: 214 nm; t_r 9.98 min 100%. LC/MS: t_r 8.8 min 100%. MS (ESI): $m/z = 365$ $[M + H]^+$.

2-{4-(2-Chloro-5-methyl-5*H*-indolo[2,3-*b*]quinolin-11-yl)piperazin-1-yl}ethanol (20f). Yield: 0.09 g (76%). ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 1H), 2.80 (t, 2H, $J = 5.2$ Hz), 2.91 (t, 4H, $J = 4.4$ Hz), 3.61 (t, 4H, $J = 4.8$ Hz), 3.78 (t, 2H, $J = 5.2$ Hz), 4.33 (s, 3H), 7.26 (m, 1H), 7.54 (t, 1H, $J = 8.40$ Hz), 7.68 (m, 2H), 7.74 (d, 1H, $J = 8.0$ Hz), 8.27 (d, 1H, $J = 7.6$ Hz), 8.47 (s, 1H). HPLC: 214 nm; t_r 9.67 min 100%. LC/MS: t_r 8.7 min 94%. MS (ESI): $m/z = 395$ $[M + H]^+$.

11-(1,4′-Bipiperidin-1′-yl)-2-chloro-5-methyl-5*H*-indolo[2,3-*b*]quinoline (20g). Yield: 0.09 g (65%). ^{1}H NMR ($CDCl_3$) δ 1.26 (m, 2H), 1.72 (m, 4H), 2.02 (m, 2H), 2.14 (m, 2H), 2.70 (m, 5H), 3.54 (m, 2H), 3.67 (m, 2H), 4.33 (s, 3H), 7.24 (m, 1H), 7.53 (t, 1H, $J = 7.6$ Hz), 7.68 (m, 2H), 7.74 (d, 1H, $J = 7.6$ Hz), 8.24 (d, 1H, $J = 8.0$ Hz), 8.43 (s, 1H). HPLC: 214 nm; t_r 12.64 min 100%. LC/MS: t_r 9.7 min 95%. MS (ESI): $m/z = 433$ $[M + H]^+$.

General Method for the Synthesis of 11-Aminoalkylaminonorneocryptolepines (19b−d) and (21a−g). A mixture of **16b−d** (0.40 mmol) and an excess of the appropriate aminoalkylamine (4 mmol) was heated slowly from room tempertaure to 135 °C over 1 h with stirring and subsequently heated at 155 °C for 12 h with continued stirring to drive the reaction to completion (TLC monitoring). The resulting brownish residue was purified by flash chromatography using CH_2Cl_2−MeOH (9:1) as the eluent to yield **19b−d** and **21a−g** as colorless viscous oils.

***N*^{4}-(1-Chloro-6*H*-indolo[2,3-*b*]quinolin-11-yl)-*N*^{1},*N*^{1}-diethyl-pentane-1,4-diamine (19b).** Yield: 0.19 g (73%). ^{1}H NMR ($CDCl_3$) δ 0.96 (t, 6H, $J = 7.2$ Hz), 1.29 (d, 3H, $J = 6.4$ Hz), 1.47 (m, 2H), 1.57 (m, 2H), 2.35 (t, 2H, $J = 7.2$ Hz), 2.48 (q, 4H, $J = 7.2$ Hz), 4.11 (m, 1H), 6.8 (d, 1H, $J = 10.8$ Hz), 7.3 (m, 1H), 7.38 (m, 1H), 7.47 (m, 2H), 7.53 (d, 1H, $J = 7.6$ Hz), 7.92 (d, 1H, $J = 8.0$ Hz), 7.99 (dd, 1H, $J = 8.0$, 1.2 Hz), 11.37(s, 1H). HPLC: 214 nm; t_r 14.57 min 94.3%. LC/MS: t_r 13.2 min 100%. MS (ESI): $m/z = 409$ $[M + H]^+$.

***N*^{4}-(3-Chloro-6*H*-indolo[2,3-*b*]quinolin-11-yl)-*N*^{1},*N*^{1}-diethyl-pentane-1,4-diamine (19c).** Yield: 0.13 g (82%). ^{1}H NMR ($CDCl_3$) δ 0.94 (t, 6H, $J = 7.2$ Hz), 1.35 (d, 3H, $J = 6.4$ Hz), 1.60 (m, 2H), 1.67 (m, 2H), 2.38 (t, 2H, $J = 7.2$ Hz), 2.45 (q, 4H, $J = 7.2$ Hz), 4.20 (m, 1H), 4.70 (d, 1H, $J = 10.8$ Hz), 7.31 (m, 1H), 7.48 (t, 1H, $J = 7.6$ Hz), 7.54 (d, 1H, $J = 7.6$ Hz), 7.88 (d, 1H, $J = 8.0$ Hz), 7.96 (d, 1H, $J = 8.0$ Hz), 7.99 (d, 1H, $J = 7.6$ Hz), 8.09 (m, 1H), 11.01(s, 1H). HPLC: 214 nm; t_r 15.41 min 94.14%. LC/MS: t_r 13.9 min 100%. MS (ESI): $m/z = 409$ $[M + H]^+$.

***N*^{4}-(2-Chloro-6*H*-indolo[2,3-*b*]quinolin-11-yl)-*N*^{1},*N*^{1}-diethyl-pentane-1,4-diamine (19d).** Yield: 0.09 g (56%). ^{1}H NMR ($CDCl_3$) δ 0.96 (t, 6H, $J = 7.2$ Hz), 1.36 (d, 3H, $J = 6.4$ Hz), 1.62 (m, 2H), 1.73 (m, 2H), 2.42 (t, 2H, $J = 7.2$ Hz), 2.47 (q, 4H, $J = 7.2$ Hz), 4.20 (m, 1H), 4.65 (d, 1H, $J = 10.8$ Hz), 7.29 (m, 1H), 7.46 (m, 2H), 7.62 (m, 1H), 7.93 (d, 1H, $J = 9.2$ Hz), 8.00 (d, 1H, $J = 8.8$ Hz), 8.14 (d, 1H, $J = 2.4$ Hz), 11.32 (s, 1H). HPLC: 214 nm; t_r 14.63 min 99.14%. LC/MS: t_r 14.2 min 100%. MS (ESI): $m/z = 409$ $[M + H]^+$.

***N*^{2}-(2-Chloro-6*H*-indolo[2,3-*b*]quinolin-11-yl)-*N*^{1},*N*^{1}-dimethyl-ethane-1,2-diamine (21a).** Yield: 0.10 g (73%). ^{1}H NMR (DMSO-d_6) δ 2.26 (s, 6H), 2.59 (br s, 2H), 3.77 (m, 2H), 6.36 (br s, 1H), 7.24 (m, 1H), 7.42 (m, 2H), 7.59 (m, 1H), 7.82 (d, 1H, $J = 8.8$ Hz), 8.10 (d, 1H, $J = 8.0$ Hz), 8.46 (s, 1H), 11.53(s, 1H). HPLC: 214 nm; t_r 12.09 min 100%. LC/MS: t_r 9.6 min 94%. MS (ESI): $m/z = 339$ $[M + H]^+$.

2-Chloro-*N*-(2-pyrrolidin-1-ylethyl)-6*H*-indolo[2,3-*b*]quinolin-11-amine (21b). Yield: 0.09 g (62%). ^{1}H NMR (DMSO-d_6) δ 1.70 (m, 4H), 2.50 (m, 4H), 2.73 (m, 2H), 3.77 (m, 2H), 6.40 (br s, 1H), 7.23 (m, 1H), 7.42 (m, 2H), 7.60 (m, 1H), 7.82 (d, 1H, $J = 8.8$ Hz), 8.12 (d, 1H, $J = 8.8$ Hz), 8.47 (s, 1H), 11.52 (br s, 1H). HPLC: 214 nm; t_r 12.1 min 100%. LC/MS: t_r 10.2 min 97%. MS (ESI): $m/z = 365$ $[M + H]^+$.

2-Chloro-*N*-(2-morpholin-4-ylethyl)-6*H*-indolo[2,3-*b*]quinolin-11-amine (21c). Yield: 0.12 g (77%). ^{1}H NMR (DMSO-d_6) δ 2.31 (br s, 4H), 2.55 (br m, 2H), 3.42 (br s, 4H), 3.76 (m, 2H), 6.33 (br m, 1H), 7.23 (m, 1H), 7.42 (m, 2H), 7.59 (m, 1H), 7.81 (d, 1H, $J = 8.8$ Hz), 8.14 (d, 1H, $J = 8.0$ Hz), 8.50 (s,1H), 11.51 (s, 1H). HPLC: 214 nm; t_r 12.28 min 100%. LC/MS: t_r 9.8 min 95%. MS (ESI): $m/z = 381$ $[M + H]^+$.

2-Chloro-*N*-[(1-ethylpyrrolidin-2-yl)methyl]-6*H*-indolo[2,3-*b*]quinolin-11-amine (21d). Yield: 0.11 g (75%). ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3H, $J = 7.2$ Hz), 1.62 (m, 1H), 1.75 (m, 2H), 1.85 (m, 1H), 2.34 (m, 2H), 2.78 (m, 1H), 3.05 (m, 1H), 3.46 (m, 1H), 3.87 (m, 1H), 4.02 (m, 1H), 6.52 (d, 1H, $J = 6.8$ Hz), 7.27 (m, 1H), 7.43 (t, 1H, $J = 7.6$), 7.49 (d, 1H, $J = 8.0$ Hz), 7.60 (m, 1H), 8.00 (d, 1H, $J = 9.2$ Hz), 8.21 (d, 1H, $J = 7.6$ Hz), 8.27 (d, 1H, $J = 2.4$ Hz), 11.51 (s, 1H). HPLC: 214 nm; t_r 12.25 min 100%. LC/MS: t_r 9.8 min 100%. MS (ESI): $m/z = 379$ $[M + H]^+$.

2-Chloro-11-(4-methylpiperazin-1-yl)-6*H*-indolo[2,3-*b*]quinolin (21e). Yield: 0.11 g (78%). ^{1}H NMR ($CDCl_3$) δ 2.50 (s, 3H), 2.82 (m, 4H), 3.49 (m, 4H), 7.34 (m, 4H), 7.75 (d, 1H, $J = 8.8$ Hz), 8.42 (s, 2H), 12.19 (br s,1H). HPLC: 214 nm; t_r 11.31 min 100%. LC/MS: t_r 11.3 min 100%. MS (ESI): $m/z = 351$ $[M + H]^+$.

2-{4-(2-Chloro-6*H*-indolo[2,3-*b*]quinolin-11-yl)piperazin-1-yl}ethanol (21f). Yield: 0.10 g (68%). ^{1}H NMR ($CDCl_3$) δ 2.80 (t, 2H, $J = 5.6$ Hz), 2.94 (m, 5H, $J = 4.8$ Hz), 3.62 (t, 4H, $J = 4.4$ Hz), 3.79 (t, 2H, $J = 5.2$ Hz), 3.52 (m, 2H), 7.33 (t, 1H, $J = 8$ Hz), 7.47 (d, 1H, $J = 7.6$ Hz), 7.52 (t, 1H, $J = 7.2$ Hz), 7.64 (m, 1H), 8.02 (d, 1H, $J = 8.8$ Hz), 8.48 (m, 2H), 10.10 (br s, 1H). HPLC: 214 nm; t_r 10.57 min 100%. LC/MS: t_r 8.7 min 95%. MS (ESI): $m/z = 381$ $[M + H]^+$.

11-(1,4′-Bipiperidin-1′-yl)-2-chloro-6*H*-indolo[2,3-*b*]quinoline (21g). Yield: 0.10 g (60%). ^{1}H NMR ($CDCl_3$) δ 1.72 (m, 6H), 2.03 (m, 2H), 2.15 (m, 2H), 2.71 (m, 5H), 3.52 (m, 2H), 3.66 (m, 2H), 7.33 (m, 1H), 7.45 (d, 1H, $J = 7.6$ Hz), 7.50 (t, 1H, $J = 7.6$ Hz), 7.61 (m, 1H), 8.00 (d, 1H, $J = 8.8$ Hz), 8.42 (m, 2H), 10.26 (s,1H). HPLC: 214 nm; t_r 13.46 min 100%. LC/MS: t_r 13 min 100%. MS (ESI): $m/z = 419$ $[M + H]^+$.

In Vitro Biological Screening Tests. Standard screening methodologies were adopted as described.[38] For antiplasmodial activity, the chloroquine-susceptible *P. falciparum* Ghana strain was used. Parasites were cultured in human erythrocytes at 37 °C under a low oxygen atmosphere (3% O_2, 4% CO_2, and 93% N_2) in RPMI-1640 culture medium. After 72 h exposure to the compounds, parasite multiplication was measured by the Malstat method.[39] Absorbance was spectrophotometrically read at 655 nm, and percentage growth inhibition was calculated compared to the negative blanks.

For cytotoxity evaluation, MRC-5 SV_2 cells (human fetal lung fibroblasts) were cultivated in MEM supplemented with L-glutamine (20 mM) and 5% FCS at 37 °C and 5% CO_2. For the assay, 10^4 MRC-5 cells/well were seeded onto the 96-well test plates containing the prediluted compounds and incubated at 37 °C and 5% CO_2 for 72 h. Cell viability was determined fluorimetrically after addition of resazurin.[40]

In Vivo Antiplasmodial Evaluation. Swiss mice are intraperitoneally infected with 4×10^8 erythrocytes infected with chloroquine-sensitive *P. berghei* (ANKA-strain) and intraperitoneally treated with the test compounds at 50 mg/kg for five consecutive days. On days 4 and 7, levels of parasitaemia are determined on Giemsa-stained blood smears. A more detailled description can be found in the Supporting Information.

DNA−Methyl Green Assay. The DNA−methyl green reagent was prepared by suspending 20 mg of DNA−methyl green (Sigma-Aldrich Chemie Gmbh, Steinheim, Germany) in 100 mL of 0.05 M Tris HCl buffer (pH 7.5) containing 7.5 mM $MgSO_4$ and stirred at 37 °C for 24 h. The samples were transferred to a 96-well microtiter plate, and the solvent was removed under vacuum. Then 200 μL of the DNA−methyl green reagent was added to the test compounds. The absorbance at 620 nm was measured at $t = 0$ and after 24 h of incubation at 25 °C. Cryptolepine was used as a positive control.[11] The IC_{50} value was calculated by comparing the initial and the final absorbance. It corresponds to the concentration where 50% displacement of methyl green from DNA occurs.[41]

Inhibition of β-Hematin Formation. This microassay was performed in a 96-well V-bottom microplate.[42] First, 50 μL of an 8 mM hemin (Sigma-Aldrich Chemie Gmbh, Steinheim, Germany) solution in DMSO was added to 50 μL of the test compound in water (or for water-insoluble compounds, 25 μL of a 16 mM hemin solution in DMSO was added to 25 μL of the test compound in DMSO, 50 μL of water was added afterward in order to keep the DMSO concentration constant at 25%). Then as a negative control, 50 μL of water was used instead of the test solution, and chloroquine (Sigma-Aldrich Chemie Gmbh, Steinheim, Germany) served as a positive control. Then 100 μL of an 8 M acetate buffer (pH 5) was added, and the plate was incubated at 37 °C for 18 h. After 15 min of centrifugation at 3000 rpm, the soluble fraction was removed and 200 μL of DMSO was added to the wells. The plate was centrifuged again for 15 min at 3000 rpm, and all supernatant was removed. The residual pellet of pure β-hematin remaining in the well was dissolved in 200 μL of 0.1 M NaOH solution. Then 75 μL from each well was transferred into a U-bottom microplate, and a serial 4-fold dilution in 0.1 M NaOH was prepared. The absorbance was measured at 414 nm using a microtiter plate reader. The IC_{50} value was calculated compared to the control (100% β-hematin formation).

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Supporting Information Available: A table with HPLC data demonstrating purity of target compounds, a detailled description of the in vivo drug screening model against *Plasmodium berghei* in Swiss mice, and spectroscopic details of the intermediate compounds **8a**, **8b**, **8c−d**, **9a**, **9b**, **9c−d**, **14a**, **14b**, **14c**, **15a**, **15b−c**, **15d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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