DOI: 10.1021/jm901300d

Synthesis and Antiplasmodial Activity of New Indolone *N*-Oxide Derivatives

Françoise Nepveu,*[,†,‡] Sothea Kim,[†,‡] Jeremie Boyer,[†,‡] Olivier Chatriant,[§] Hany Ibrahim,[†,‡] Karine Reybier,[†,‡] Marie-Carmen Monje,[†,‡] Severine Chevalley,[†,‡] Pierre Perio,[†,‡] Barbora H. Lajoie,[†,‡] Jalloul Bouajila,[†,‡] Eric Deharo,[†,‡] Michel Sauvain,[†,‡] Rachida Tahar,[∥] Leonardo Basco,[∥] Antonella Pantaleo,[⊥] Francesco Turini,[⊥] Paolo Arese,[⊥] Alexis Valentin,[†,‡] Eloise Thompson,[#] Livia Vivas,[#] Serge Petit,[§] and Jean-Pierre Nallet[§]

[†]*Université de Toulouse, UPS, UMR 152* (*Laboratoire de Pharmacochimie des Substances Naturelles et Pharmacophores Redox*), *F-31062 Toulouse cedex 9, France,* [‡]*IRD, UMR 152, F-31062 Toulouse cedex 9, France,* [§]*IDEALP-PHARMA, Bâtiment CEI, 66 Bd Niels Bohr, BP 2132, 69603 Villeurbanne cedex, France,* [∥]*Organisation de Coordination pour la Lutte Contre les Endémies en Afrique Centrale* (*OCEAC*), *BP 288, Yaoundé, Cameroun,* [⊥]*University of Turin Medical School* (*Dipartimento di Genetica, Biologia e Biochimica*), *Via Santena 5 bis, 10126 Torino, Italy, and* [#]*London School of Hygiene and Tropical Medicine* (*LSHTM*), *Keppel Street, London C1E 7HT, United Kingdom*

A series of 66 new indolone-*N*-oxide derivatives was synthesized with three different methods. Compounds were evaluated for in vitro activity against CQ-sensitive (3D7), CQ-resistant (FcB1), and CQ and pyrimethamine cross-resistant (K1) strains of *Plasmodium falciparum* (*P.f.*), as well as for cytotoxic concentration (CC_{50}) on MCF7 and KB human tumor cell lines. Compound **26** (5-methoxy-indolone-*N*-oxide analogue) had the most potent antiplasmodial activity in vitro (< 3 nM on FcB1 and = 1.7 nM on 3D7) with a very satisfactory selectivity index (CC_{50} MCF7/IC_{50} FcB1: 14623; CC_{50} KB/IC_{50} 3D7: 198823). In in vivo experiments, compound **1** (dioxymethylene derivatives of the indolone-*N*-oxide) showed the best antiplasmodial activity against *Plasmodium berghei,* 62% inhibition of the parasitaemia at 30 mg/kg/day.

1. Introduction

Because of multiple factors, the burden of malaria is currently increasing, the most important negative point being the development by *P. falciparum* (*P.f.*[a]) of resistance to cheap and effective drugs like chloroquine (CQ). One of the innovative approaches to antimalarial drug discovery is based on the identification of new drug targets and attendant inhibitor design. However, as recently reviewed,[1−4] most of clinically available antimalarial drugs were developed using pregene technology-era pharmacochemical approaches and the action mechanisms for the majority have not as yet been clarified.

Our approach was to identify novel antimalarial synthetic molecules by focusing our strategy on a chemical substructural motif (scaffold) critical for parasite growth. In antimalarial activity of artemisinin-like compounds,[5] the endoperoxide group plays a key role. It is the validated chemical scaffold and, because this substructural motif is a reducible or a pro-oxidant group, it can also be called a *redox pharmacophore*. From the pharmacological point of view, other powerful reducible chemical groups may also be able to disrupt cellular redox homeostasis. In past decades, many mono- and di-*N*-oxides derivatives have been reported for their antimalarial activities.[6−10] In these chemical series, the *N*-oxide group could be identified as a reducible group.

Our interest in the nitrone group [C═N^+-O^-] the chemical scaffold of radical spin traps led us to study the redox properties of some indolone derivatives.[11,12] We observed that 2-alkyl-indolone-*N*-oxides[13] were rapidly reduced in solution, leading to radical nitroxide intermediates, while 2-aryl indolone-*N*-oxides were stable in solution. Moreover, they gave very stable spin adducts by trapping oxygen or carbon-centered free radicals chemically or enzymatically produced. Previously, L. Lunazzi et al.[14] had also observed that under certain conditions, very long-lived radicals were generated via a proton attack from the solvent by heating up these indolones. Such chemical properties of *N*-oxide compounds were used to design bioreducible prodrugs such as tirapazamine derivatives with selective toxicity toward hypoxic cells.[15] This selectivity is based on the net reduction of the *N*-oxide moiety in the absence of oxygen, in a one or two-electron process-approach, by reductive enzymes. In addition, R. Danieli et al.[16] showed that indolone derivatives can be easily reduced by thiols. Recently, indazole *N*-oxide derivatives have been reported as antiprotozoal agents with a reduction mechanism.[17,18] Moreover, antituberculosis or antimycobacterial activities have been reported for some indolone-*N*-oxides.[19,20] Considering indolone-*N*-oxide properties, we hypothesized that their capacities to be reduced and generate stable radical intermediates and their reactivity with thiols may be critical for parasite growth within red blood cells (RBC). RBCs contain high levels of reductases and reductants, such as glutathione, and display a decrease in molecular oxygen concentration and an increase in reactive oxygenated species during parasite maturation. The preliminary assays in vitro were highly promising.

We therefore undertook the synthesis and study of in vitro and in vivo antiparasitic activity against *Plasmodium spp.* of a

*To whom correspondence should be addressed. Phone: +33-5-62-25-68-69. Fax: +33-5-62-25-98-02. E-mail: nepveu@cict.fr.

[a]Abbreviations: CQ, chloroquine; *P.f.*, *Plasmodium falciparum*; RBC, red blood cells; CC_{50}, 50% cytotoxic concentration; po, per oral route; 4-DMAP, 4-dimethylaminopyridine; DMSO, dimethyl sulfoxide; EFS, French blood bank; LDH, lactate dehydrogenase.

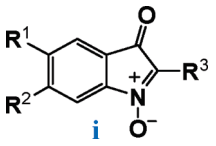


Figure 1. Structure of indolone *N*-oxide derivatives (**i**: compounds from **1** to **66**).

series of indolone *N*-oxides (Figure 1). We describe hereafter the synthesis and in vitro antiplasmodial activities assessed in CQ-sensitive (3D7), CQ-resistant (FcB1) and CQ and pyrimethamine cross-resistant (K1) strains of *Plasmodium falciparum* (*P.f.*). Hit optimization was carried out based on antiparasitic efficacy against the three strains, cytotoxicity against human cell lines, as well as physicochemical parameters. The study of in vivo activities was performed on *Plasmodium berghei* (NK65 and ANKA) murine models.

2. Chemistry

A series of 66 analogues of indolone *N*-oxides were prepared (Table 1). Three synthetic pathways were considered and successfully used in this work, which led to the desired indolone *N*-oxide derivatives (**i**: compounds from **1** to **66**) (Figure 1). Method 1 is based on 1,2-diketone intermediates **b**, which are cyclized via nitro group reduction to generate the corresponding indolone *N*-oxides **i**.[11,12] The 1,2-diketones were prepared by permanganate oxidation of a styrene precursor **a**, which is easily obtained by Wittig olefination of nitrobenzaldehydes with phosphonium ylides (Scheme 1).

Method 2[21] is a one-pot procedure based on Sonogashira coupling of *o*-iodo nitro-aryles **e** with terminal alkynes **f** and concomitant cyclization of *o*-(arylalkynyl)-nitroaryles intermediates **g** into indolone *N*-oxides (Scheme 2).[22,23] Method 3 derives from optimization of method 2 with the aim of improving yields, while increasing reaction kinetics. Specifically, method 3 was divided into two substeps: the first involved Sonogashira coupling as in method 2 as well as intermediate extraction, followed by an intramolecular cyclization using 4-dimethyl amino pyridine (4-DMAP) in refluxing pyridine (Scheme 3).[24−27] In some cases, using $AuBr_3$ as catalyst accelerated the reaction rate and improved the yield.[28] It must be mentioned that several *o*-bromo-nitroaryles (**e**) and 1-alkynes (**f**) used in this study to prepare indolone *N*-oxide analogues were also of synthetic origin (Schemes 2, 3). Compounds **e** were obtained by electrophilic nitration of *o*-bromoaryles aldehydes using fuming nitric acid/acetic acid mixture. Synthesis of 1-alkynes (**f**) involved the preparation of 1-(trimethylsilyl)-alkynes via Sonogashira coupling, followed by a desilylation step. Finally, *O*-benzyl-4-iodo-3-nitrophenol used to synthesize compounds **57** and **58** was obtained by *O*-benzylation of 4-iodo-3-nitrophenol (Scheme 4)

In comparing the methods used to synthesize indolone *N*-oxides, it is worth pointing out that method 3 requires 0.5−17 h to prepare a target molecule, albeit of low (20−30%) chemical yields, whereas methods 1 and 2 may require 1−2 weeks. However, method 1 itself is of key importance when considering that some stable *o*-(alkylalkynyl)-nitroaryles intermediates **g** failed to spontaneously cyclize into indolone *N*-oxides under Sonogashira conditions.[24]

To overcome difficulties in obtaining some targeted compounds according to previous methods, Sonogashira reactions were undertaken under microwave conditions; protocols were specifically adjusted for each reaction to obtain the expected compounds in a few minutes from low to moderate yield. Unfortunately, depending on the different substituents on aromatic rings, this easy protocol also failed in the synthesis of some designed indolones.

All of the compounds were chemically characterized by liquid chromatography (TLC and HPLC), infrared (IR), UV−visible, NMR (^{1}H and ^{13}C NMR), and mass spectrometry as well as elemental analysis. LogP values were calculated with VVCLAB software[29] and ranging between 0.62 and 4.79. Compound **57** is the most lipophilic in the series, and compound **51**, the least one. It appeared that lipophilicity has no detrimental effect on antiplasmodial activity (Table 1). Compounds were very poorly soluble in water except for salt forms (hydrochloride salt of the compounds **26**, **28**, and **30**). Studies of compound stability in solution showed that the compounds were stable in aprotic solvents (CH_3CN, $(CH_3)_2SO$) and less stable in polar and protic solvents (MeOH, H_2O) (data not shown).

Structure−Activity Relationship (SAR): Effect of Substituents on the Biological Activity. The compounds were designed according to the structure−activity relationship in considering the structure of the first hit identified, **1**. In addition, commercial chemical libraries were examined and, according to their molecular profile, some compounds were selected for testing. These procedures were helpful in pharmacophore determinations. All prepared compounds were tested at the primary level on a CQ-resistant *P. falciparum* strain (FcB1). This initial step identified the substituent effects of the indolone-*N*-oxide at either position 2, 5, or 6 (Figure 2).

Figure 2 presents the basic structure of indolone-*N*-oxide derivatives. The phenyl group (A) of the indolone moiety was found to be essential for antiplasmodial activity. Replacement of the phenyl group (A) by either pyridine (N at position 4 of the indolone moiety, compound **66**) or by pyridinium-*N*-oxide (N at position 5 of the indolone moiety, compound **65**) led to significant activity loss, IC_{50} was from 10- to 20-fold higher than their corresponding indolone analogue, compound **64**.

As shown in Figure 3, replacement of the phenyl group (R^3) (at position 2 of the indolone moiety) by an aliphatic chaine (*n*-propyl, **50**, or *i*-butyl, **49**) led to a significant loss of activity. Whereas functionalization of the phenyl moiety (R^3) by groups having a mesomeric effect (either +M: F, Cl, OCH_3, OPh or −M: NO_2) improved the activity, while groups with inductive effect (either +I: CH_3, C_2H_5, CH_2OH or −I: CF_3) decreased the activity.

As shown in Figure 4, comparable results were obtained with dioxymethylene derivatives of indolone-*N*-oxide, with the exception of compound **54** (IC_{50} measured by LDH method, see Supporting Information).

Figure 5 presents antiplasmodial activity of 2(4-methoxyphenyl)-indolone-*N*-oxide analogues. Substitutions at either position 5 or 6 of phenyl group (A) of the indolone moiety had no marked effect on IC_{50}. Therefore, substitutions at R^3 affected antiplasmodial activity to a greater extent than substitutions at the phenyl group of the indolone moiety (cf. Figures 3 and 4).

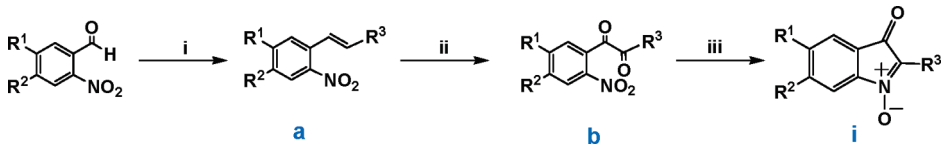
Figure 6 presents 5-methoxy-indolone-*N*-oxide analogues. Contrary to previous results (Figures 3, 4), substitutions at R^3 position had a slight effect on antiplasmodial activity, except when the substitution occurred at

Table 1. Structure of Indolone *N*-Oxide Analogues Obtained and Their in Vitro Antiplasmodial and Cytotoxic Activities

compd	R^1	R^2	R^3	Log P_{calc}[a] (VCCLAB)	IC_{50} (nM) FcB1 strain	CC_{50} (μM)[b] MCF7	selectivity index MCF-7/FcB1
1	O-CH_2-O		4′-chlorophenyl	2.07	75 ± 63	15.9	212
2	H	H	4′-phenoxyphenyl	3.51	264 ± 60	11.1	42
3	H	H	4′-hydroxymethyl phenyl	1.29	3950 ± 50	39.5	10
4	H	H	4′-methoxyphenyl	2.01	195 ± 20	> 39.5[c]	> 202
5	H	H	4′-6′-methoxy-naphthalen-2-yl	3.03	560 ± 15	15.3	66
6	O-CH_2-O		4′-6′-methoxy-naphthalen-2-yl	2.51	288 ± 30	25.6	89
7	O-CH_2-O		4′-phenoxyphenyl	3.00	165 ± 40	12.2	74
8	H	H	3′, 4′-dichlorophenyl	3.14	155 ± 20	13.7	88
9	OCH_3	H	4′-chlorophenyl	2.58	210 ± 10	21.5	102
10	OCH_3	OCH_3	4′-tolyl	2.25	265 ± 29	nd	nd
11	OCH_3	H	3′-trifluoromethyl-4′-chlorophenyl	3.32	50 ± 39	13.5	270
12	H	OCH_3	4′-chlorophenyl	2.57	150 ± 91	10.4	69
13	OCH_3	H	3′, 4′-dichlorophenyl	3.18	100 ± 7	81.0	81
14	O-CH_2-O		3′, 4′-dichlorophenyl	2.66	195 ± 2	7.4	38.1
15	O-CH_2-O		4′-ethoxyphenyl	1.98	156 ± 57	51.9	332
16	H	H	4′-tolyl	2.23	1770 ± 20	15	8.5
17	OCH_3	H	phenyl	2.00	184 ± 53	13.4	73
18	OCH_3	H	4′-tolyl	2.25	52 ± 48	> 37.5[c]	> 721
19	H	CF_3	4′-chlorophenyl	3.26	186 ± 15	3.1	16.5
20	OCH_3	H	4′-methoxy-naphthalen-2-yl	3.03	135 ± 45	14.4	107
21	OCH_3	H	4′-chlorobiphenyl-4-yl	4.06	630 ± 248	12.1	19
22	OCH_3	H	4′-methoxyphenyl	2.04	40 ± 39	> 35.3[c]	> 882
23	OCH_3	H	2′, 4′-dichlorophenyl	3.02	227 ± 9	> 31.0[c]	> 136
24	OCH_3	H	4′-phenoxyphenyl	3.51	193 ± 55	7.7	40
25	OCH_3	H	4′-trifluoromethoxyphenyl	2.90	20 ± 0	8.3	415
26	OCH_3	H	4′-dimethylaminophenyl	2.30	< 3	43.9	> 14,623
27	OCH_3	H	4′-isopropoxyphenyl	2.81	17 ± 2	> 32.1[c]	> 1,889
28	OCH_3	H	4′-diethylaminophenyl	3.34	131 ± 33	17.6	134
29	OCH_3	H	4′-methoxy-3′-tolyl	2.25	44 ± 4	> 33.6[c]	> 764
30	OCH_3	H	4′-aminophenyl	1.58	24 ± 19	12.7	528
31	H	OCH_3	4′-methoxyphenyl	2.03	106 ± 50	8.8	83.3
32	H	CF_3	4′-methoxyphenyl	2.72	135 ± 95	7.9	58.8
33	H	Cl	4′-methoxyphenyl	2.59	191 ± 0	22.2	116.5
34	H	CH_3	4′-methoxyphenyl	2.24	198 ± 26	14.9	75
35	H	OCF_3	4′-methoxyphenyl	2.88	133 ± 50	11.7	88.1
36	H	CH_3OCO	4′-mMethoxyphenyl	1.91	206 ± 9	40.2	194.9
37	OCH_3	H	4′-trifluoromethylphenyl	2.74	43 ± 23	11.7	273
38	OCH_3	H	4′-acetophenyl	2.05	256 ± 22	40.2	29.1
39	OCH_3	H	3′-chlorophenyl	2.60	21 ± 1	5.2	248
40	OCH_3	H	3′-methyl-4′-tolyl	2.48	37 ± 28	26	702.7
41	OCH_3	H	4′-acetamidophenyl	1.81	400 ± 232	7.4	18.5
42	OCH_3	H	4′-*tert*-butylphenyl	3.63	204 ± 14	11	53.9
43	OCH_3	H	2′-chlorophenyl	2.62	1130 ± 25	nd	nd
44	OCH_3	H	4′-chloro-3′-tolyl	2.80	3 ± 1	10.3	3,425
45	OCH_3	H	4′-carboxymethylphenyl	1.92	276 ± 45	7.1	25.6
46	OCH_3	H	2′-methyl-4′-methoxyphenyl	2.24	1043 ± 95	0.3	0.3
47	OCH_3	H	2′-thiophen-3-yl	1.93	270 ± 16	12.3	45.5
48	H	NO_2	4′-methoxyphenyl	1.97	345 ± 81	21.8	63.2
49	H	H	*i*-butyl	1.61	> 4500[c]	43.1	< 9
50	H	H	*n*-propyl	1.41	12160 ± 500	26.4	2
51	O-CH_2-O		ethyl	0.62	3560 ± 400	59.0	16
52	H	H	phenyl	1.96	889 ± 88	19.5	22
53	H	H	4′-fluorophenyl	2.06	120 ± 29	8.7	72.5
54	O-CH_2-O		4′-fluorophenyl	1.58	1710 ± 30	nd	nd
55	H	Cl	2′-thiophen-3-yl	2.45	130 ± 3	4.9	38
56	H	H	4′-nitrophenyl	1.96	56 ± 4	2.8	8.4
57	H	$PhCH_2O$	4′-phenoxyphenyl	4.79	665 ± 135	2.2	3.2
58	H	$PhCH_2O$	6′-methoxy-naphthalen-2-yl	4.37	730 ± 30	nd	nd
59	H	H	4′-chloro-3′-trifluoromethylphenyl	3.31	1045 ± 35	2.0	1.9
60	H	H	4′-ethylphenyl	2.81	2750 ± 150	> 39.8[c]	> 14
61	H	H	4′-trifluoromethylphenyl	2.71	1170 ± 80	34.3	29
62	OCH_3	OCH_3	phenyl	2.02	1890 ± 240	nd	nd
63	O-CH_2-O		phenyl	1.5	12720 ± 400	nd	nd
64	H	H	4′-chlorophenyl	2.54	272 ± 16	17.8	66
			chloroquine	4.63	151 ± 6	19.4	167
			sodium artesunate	2.41	6 ± 3	9.8	1633

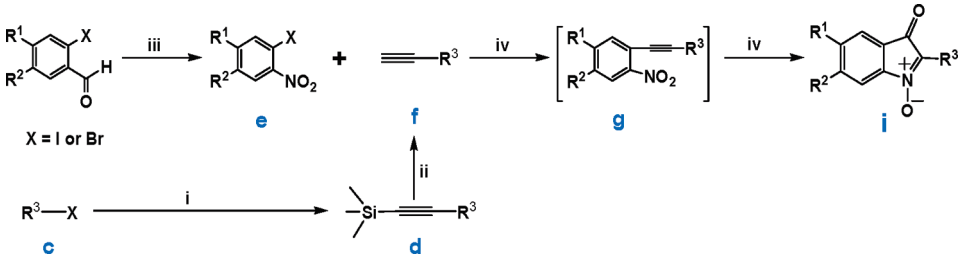
[a] LogP calculated with VCCLAB (http://www.virtuallaboratory.org/lab/alogps/start.html). [b] The drug concentration needed to cause 50% decrease of the cellular viability. [c] The highest tested concentration.

Scheme 1. Method 1 Used to Synthesize Indolone *N*-Oxide Derivatives (R^3 = Alkyl)[a]



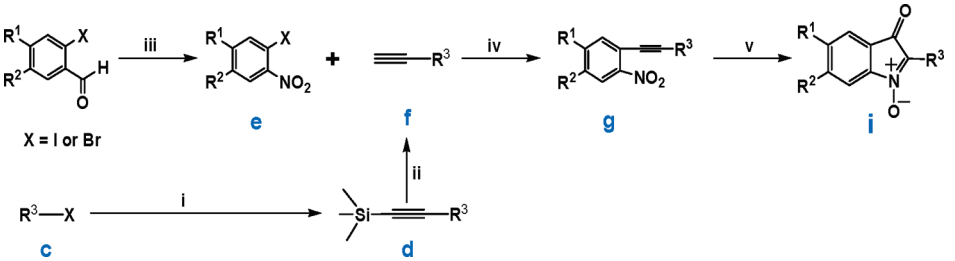
[a] Reagents and conditions: (i) $Ph_3PCH_2R^3Br$, NaOH, CH_2Cl_2, $Bu_4N^+Br^-$; (ii) $KMnO_4$, acetic anhydride, 0 °C; (iii) Zn, NH_4Cl, tetrahydrofuran, CH_2Cl_2.

Scheme 2. Method 2 Used to Synthesize Indolone *N*-Oxide derivatives (R^3 = Aryl)[a]



[a] Reagents and conditions: (i) $(CH_3)_3Si-C\equiv CH$, $Pd[(C_6H_5)_3P]_4$, CuI, Et_3N; (ii) CH_3OH, K_2CO_3; (iii) CH_3COOH, HNO_3 fuming; (iv) $Pd(PPh_3)_2Cl_2$, CuI, NEt_3, N_2, rt.

Scheme 3. Method 3 Used to Synthesize Indolone *N*-Oxide Derivatives (R^3 = Aryl)[a]



[a] Reagents and conditions: (i) $(CH_3)_3Si-C\equiv CH$, $Pd[(C_6H_5)_3P]_4$, CuI, Et_3N; (ii) CH_3OH, K_2CO_3; (iii) CH_3COOH, HNO_3 fuming; (iv) $Pd(PPh_3)_2Cl_2$, CuI, NEt_3, N_2, rt; (v) pyridine, 4-dimethylaminopyridine, reflux 140 °C.

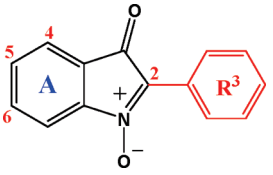
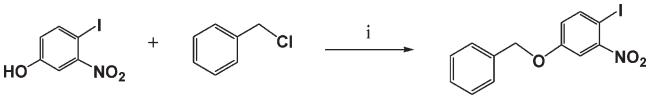


Figure 2. Indolone-*N*-oxide analogues.

Scheme 4. Synthesis of 4-Iodo-3-nitro Benzyloxy-benzene (**57e**, **58e**)[a]



[a] Reagents and conditions: (i) CH_3CH_2OH, K_2CO_3, 60 °C.

position 2 of the phenyl group (compounds: **43**, **46**). X-ray crystallographic studies of a similar compound (2-phenylisatogen) showed that isatogen and phenyl (R^3) rings were almost fully coplanar.[30] Hence substitution at position 2 led to a steric effect (hindrance) affecting the planarity system. Consequently, mesomeric-effect transmission from isatogen ring to phenyl ring would be inefficient due to low conjugation.

The conjugated system between nitrone group and ketonic function was found to be essential for an optimal in vitro antiplasmodial activity, while reduction of either nitrone or

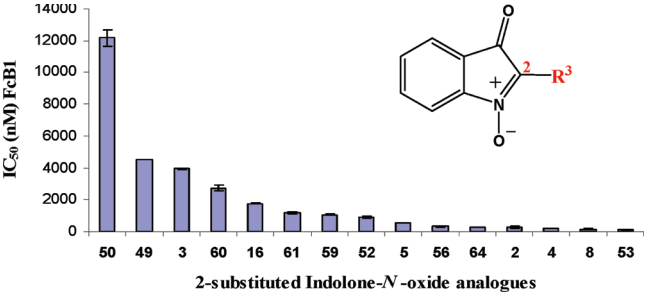


Figure 3. Comparison of antiplasmodial activity (IC_{50} [nM], strain FcB1) of 2-substituted indolone-*N*-oxides.

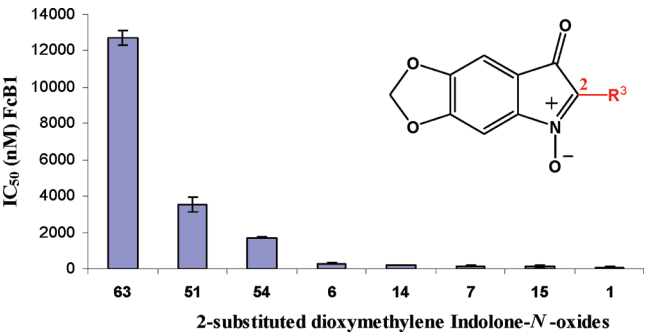


Figure 4. Comparison of antiplasmodial activity (IC_{50} (nM) FcB1) of dioxymethylene derivatives of indolone-*N*-oxides.

ketonic function led to a dramatic loss of activity (data not shown).

It was decided to analyze the possible capacity of the indolone-*N*-oxide derivatives to interact by stacking with heme. The malaria parasite does indeed break up hemoglobin inside RBC, releasing toxic-free heme. The parasite protects itself against heme toxicity by biocrystallizing around 30% of it into insoluble hemozoin. A compound that can inhibit this biocrystallization may be a potential antimalarial drug, as can the antimalarial chloroquine. The planarity of a molecule (conjugated system) may be indicative of a possible interaction with hemozoin. Several tests detecting such possible chemical drug/heme interaction are available. We used the assay developed by E. Deharo et al.[31] No relationship between antiplasmodial activity (IC_{50}/FcB1) and heme-inhibiting polymerization capacity in the biochemical assay was found in a series of seven compounds (see Supporting Information).

3. Biology

In Vitro Antiplasmodial Activity against *P. falciparum*. Initial testing was carried out on a chloroquine (CQ)-resistant strain of *P.f.* (Table 1). Several analogues displayed antiplasmodial activity in the low nanomolar range. Fourteen out of 66 synthetic compounds were found to be more potent in vitro against FcB1 than was chloroquine, with IC_{50}s lower than 100 nM (Table 1). Their cytotoxicity was evaluated on the MCF7 cell line. Selectivity index was defined as the ratio of CC_{50} value in MCF7 cells to IC_{50} value in CQ-resistant *P.f.* strain FcB1.

The best analogues, based on their selectivity index (SI > 200; MCF7/FcB1), were chosen for assays at the secondary level on a CQ-sensitive (3D7) and CQ and pyrimethamine-resistant (K1) strains of *P.f.* (Table 2). All tested compounds were found to be more potent than CQ against K1 strain. Three of them showed lower IC_{50} than that of artesunate against either 3D7 or K1 strains. Many compounds demonstrated equipotent activity against both CQ-sensitive and CQ-resistant strains. A comparison of IC_{50} values between *P.f.*-resistant and sensitive strains suggested relatively low levels of cross-resistance to CQ.[32] Resistance index (RI) values, calculated from comparison of IC_{50} values of resistant K1 or FcB1 and sensitive strains of *P. falciparum* 3D7 such as IC_{50} (K1 or FcB1)/IC_{50}(3D7), were found to be lower than those for CQ in the range 0.1−5.3 (K1) (Table 2). These compounds showed much lower resistance indices than those of CQ, suggesting that potential resistance to indolone structure is independent of chloroquine-resistance pathways.

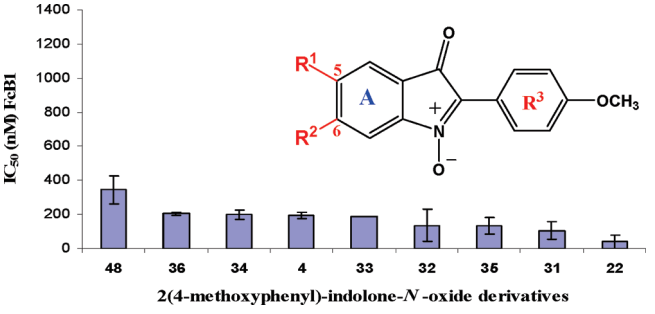


Figure 5. Comparison of antiplasmodial activity (IC_{50} (nM) FcB1) of 2(4-methoxyphenyl)-indolone-*N*-oxide analogues.

Cytotoxicity assayed on mammalian MCF7 and KB cell lines were in the μmolar range. CC_{50} values (MCF7) varied from 7.7 to 59.0 μM (Table 1) and from about 1 to 874 μM (KB) (Table 2). Most of the analogues tested at the secondary level had selectivity index greater than 200 (KB/3D7). Compounds that showed high selectivity (high selectivity index) are expected to offer the potential for safer therapy and constitute suitable candidates for further pharmacological studies.

In Vivo Antiplasmodial Activity against *Plasmodium berghei*. The best in vitro profiles displayed by indolone-*N*-oxide analogues, based on their potency, cytotoxicity, and selectivity index, led to the selection of some compounds for further in vivo evaluation against *P. berghei* strain. For compound **1**, the parasitaemia clearance in vivo in *P. berghei* (NK65 strain) was 81% at 48 mg/kg in a 4-day test. No acute toxicity was observed in Swiss female mice at a dose of ≤140 mg/kg (Table 3). Higher doses were not tested due to the lower solubility of the compound in DMSO at higher concentrations.

As shown in Table 4, compound **1** had the best antiplasmodial activity by intraperitoneal (ip) route of administration, while it showed the lowest activity by the oral route of administration. This could be explained by the first-pass effect, which leads to an extensive degradation of compound **1** when administered by the oral route. These results were confirmed by the metabolic studies of these compounds within mouse liver microsomes (Table 5). Further details and protocols are available in the Supporting Information. Compound **1** has the lowest half-life time, whereas compound **4** has the highest one. Therefore, no significant difference was observed between the

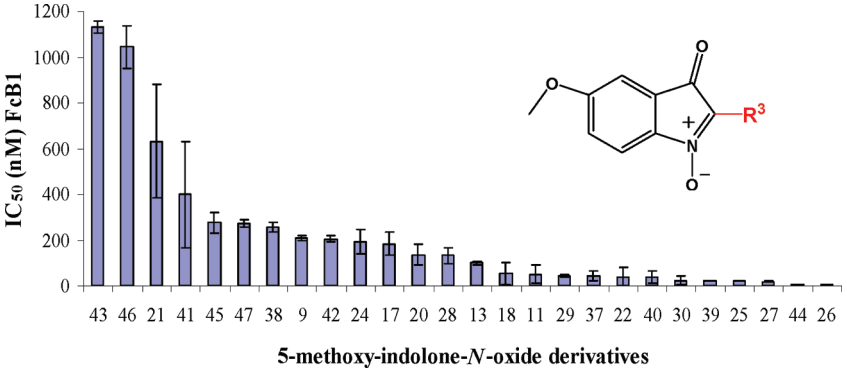


Figure 6. Comparison of antiplasmodial activity (IC_{50} (nM) FcB1) of 5-methoxy-indolone-*N*-oxide analogues.

Table 2. Selected Indolone *N*-Oxide Analogues and in Vitro Antiplasmodial and Cytotoxic Activities

compound	IC_{50} (nM) 3D7 strain	IC_{50} (nM) K1 strain	CC_{50} (μM) KB	selectivity index KB/3D7[a]	resistance index K1/3D7	resistance index FcB1/3D7
1	58 ± 17	88 ± 37	27.0	450	**1.5**	**1.3**
2	148 ± 12	60 ± 4	nd[b]	nd	**0.4**	**1.8**
4	101 ± 32	124 ± 44	457.0	4525	**1.2**	**1.9**
5	90 ± 28	40 ± 12	233.0	2589	**0.4**	**2.6**
6	72 ± 17	35 ± 8	nd	nd	**0.5**	**4.0**
7	285 ± 57	138 ± 14	nd	nd	**0.5**	**0.6**
8	98 ± 31	80 ± 39	570.0	5816	**0.8**	**1.6**
9	62 ± 37	59 ± 32	469.0	7564	**1.0**	**3.4**
11	69 ± 48	5 ± 5	< 1.4	< 20	**0.1**	**0.7**
18	27 ± 3	20 ± 8	56.0	2074	**0.7**	**1.9**
22	82 ± 38	16	874.0	10658	**0.2**	**0.5**
24	37 ± 48	< 1.5	5.6	151	**< 0.04**	**5.2**
25	30 ± 2	81 ± 22	11 ± 10	128	**2.7**	**0.7**
26	1.7	n.d.	338	198823	**nd**	**2.9**
27	32	81.3	321	10031	**2.5**	**0.5**
35	21 ± 0	112 ± 18	16 ± 0.4	86	**5.3**	**6.3**
37	< 0.5	1.9	110.0	> 220	**3.8**	**86.0**
39	139 ± 0	96 ± 47	64 ± 0.3	688	**0.7**	**0.2**
40	142 ± 3	178 ± 104	148 ± 107	980	**1.2**	**0.3**
chloroquine	35 ± 27	850 ± 57	44	1257	**24.3**	**4.3**
sodium artesunate	4 ± 3	4 ± 3	36.18 ± 8.09	9045	**1.0**	**1.5**

[a] SI 3D7 = cytotoxic (CC_{50}) (KB)/antiplasmodial (IC_{50}) (3D7) ratio. [b] nd: not determined.

Table 3. In Vivo Antimalarial Activity againt *P. berghei* (NK 65)

compd	ED_{50}[a] mg/kg/ 4days	parasitaemia clearance mg/kg/4 days ip/DMSO, %	toxicity in vivo ip/DMSO
1	16	81% at 48 mg/kg	No toxicity observed for a dose ≤140 mg/kg (limit of solubility in DMSO)
chloroquine	3	100% at 10 mg/kg	nd

[a] ED_{50}: effective dose required to achieve 50% parasitaemia clearance.

Table 4. In Vivo Antimalarial Activity against *P. berghei* (ANKA)

	% parasitaemia inhibition (at 30 mg/kg/day)	
compd	po, %[a]	ip, %[b]
1	14.5	62.1
4	32.4	40.5
26	20.9	15.3
27	25.1	30.4

[a] po: per oral route of administration. [b] ip: intrapretoneal route of administration.

Table 5. In Vitro Analysis of Compound Stability with Mouse Liver Microsomes

compd	half life (min)
1	< 1
4	16
26	6
27	6−7
verapamil hydrochloride	6

two administration routes (ip and po) for other compounds (**4**, **26**, and **27**).

5. Conclusion

The highest antiplasmodial activities were obtained for the 5-methoxy-indolone-*N*-oxide analogues (**26**, **27**). Compound **26** had the most potent antiplasmodial activity in vitro (< 3 nM on FcB1 and = 1.7 nM on 3D7) with a very satifactory selectivity index (CC_{50} MCF7/IC_{50} FcB1: > 14623; CC_{50} KB/IC_{50} 3D7: 198823).

Synthesis and screening of in vitro antiplasmodial activity and cytotoxicity of the novel series, indolone-*N*-oxide derivatives, identified promising antiplasmodial candidates based on their potency, selectivity index, and low cytotoxicity, rendering them as valid new leads for synthesizing new compounds that might improve the previous prototypes.

6. Materials and Methods

Commercial reagents were used as received without additional purification. Dichloromethane, acetonitrile, cyclohexane, and ethyl acetate were purchased from Fischer Bioblock (Strasbourg, France). Sodium sulfate, silica, silica gel 60 F-254 plates, ethanol, and methanol were purchased from VWR International (Strasbourg, France). Column chromatography for purification was carried out using 200−400 mesh chromagel. Flash chromatography was realized on CombiFlash (UVK-Lab. Toulouse, France). For molecular mass determination and purity control the following LC-PDA-MS^n system was used (Thermo electron Corporation), including an automatic injector with oven (Spectra System AS3000), a degasser (Spectra System SCM1000), and a quaternary pump (Spectra System P1000 XR) coupled to a photodiode array detector PDA (Spectra System UV6000LP), and an ion trap mass spectrometer (Finnigan LCQ Deca XP Max), using nitrogen as a nebulizing and drying gas. Data acquisition was performed using Finnigan Xcalibur software (version 1.4). Chromatographic separation was performed using analytical columns either Thermo Hypersil Hyperprep RP C-18 (8 μm, 150 mm × 4.6 mm) or Thermo BetaBasic RP C-4 (5 μm, 150 mm × 4.6 mm). For data acquisition we also used Waters Millenium32 software, version 3.2 (Waters, St. Quentin, France). Other mass spectrometers were employed for molecular mass determination such as MS-Nermag R10-10 spectrometer using electron ionization (Service Commun Toulouse, France), and GCT 1er WATERS using electron ionization and desorption chemical ionization (Service Commun Toulouse, France) for high-resolution mass determination. Elemental analyses were done using Perkin-Elmer 2400 series II CHNS/O Elemental analyzer (LCC, Toulouse, France).

Compound purity was determined by HPLC-UV and LC-PDA-MS methods and was found in the range 96−99%. The

separation was performed under a gradient mode using solvent A (water/0.05% trifluoroacetic acid) and solvent B (CH_3CN/0.05% trifluoroacetic acid). The gradient program was the following: at $t = 0$, solvents (80% A/20% B, v/v); at $t = 8$ min, solvents (0% A/100% B, v/v); at $t = 13$ min, solvents (0% A/100% B, v/v); column regeneration time was 7 min; the mobile phase was delivered at a flow rate of 1 mL/min. The injected volume was 10 μL. All the compounds were analyzed using C-18 column except the following compounds, which were analyzed using C-4 column (compounds **23**, **34**, **36**, **37**, **43**, **44**, **45**, **47**, and **48**). Melting points were determined on an Electrothermal 9300 capillary melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on an AC Bruker spectrometer at 300 or 500 MHz (^{1}H) and 75 or 125 MHz (^{13}C) using $CDCl_3$, CD_3CN, or $(CD_3)_2SO$ as solvents. Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (0 ppm) and the following multiplicity abbreviations were used: s, singlet; d, doublet; t, triplet; q, quatruplet; m, multiplet; dd, double of doublet; dt, double of triplet. IR spectra were recorded on a Perkin-Elmer PARAGON 1000 FT-IR spectrometer. UV−visible spectra were recorded on an Uvikon 931 Kontron spectrometer. High resolution mass spectrometry was used for some compounds (SCA, CNRS Vernaison, France).

6.1. Synthesis by Method 1 (Compounds 1, 15, 51−54). General Synthetic Procedure for Alkene Compounds a. To a solution of *o*-nitrobenzaldehyde (10.7 mmol) in dichloromethane (140 mL) was added the appropriate phosphonium salt (14.6 mmol). NaOH aqueous solution (50%) (12.8 mmol) and tetrabutylammonium chloride (54 mmol) were then added. The mixture was stirred at room temperature until complete disappearance of the starting product. It was then extracted by dichloromethane; the organic phase was washed with brine and dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by column chromatography (SiO_2) using dichloromethane as the eluant to give a mixture of *E*/*Z*-diastereoisomers.

5-[(*E*/*Z*)-2-Chlorophenyl)ethynyl]-6-nitro-1,3-benzodioxol (1a). Yield 87%. R_f 0.64 and 0.54 (cyclohexane/ethyl acetate, 70:30, v/v). IR (KBr) cm^{-1}: 1613, 1519, 1499, 1486, 1434, 1323, 1262, 1090, 1028, 930, 894, 815. ^{1}H NMR ($CDCl_3$, 200 MHz): (cis) δ 6.06 (s, 2H), 6.53 (s, 1H), 6.62 (d, $J = 12.0$ Hz, 1H), 6.85 (d, $J = 12.0$ Hz, 1H), 6.99 (d, $J = 8.5$ Hz, 2H), 7.15 (d, $J = 8.5$ Hz, 2H), 7.61 (s, 1H); (trans) δ 6.11 (s, 2H), 6.87 (d, $J = 16.0$ Hz, 1H), 7.07 (s, 1H), 7.31 (d, $J = 8.5$ Hz, 2H), 7.42, (d, $J = 8.5$ Hz, 2H), 7.49 (s, 1H), 7.60 (d, $J = 16.0$ Hz, 1H).

5-[(*E*/*Z*)-2-(4-Ethoxyphenyl)ethynyl-6-nitro-1,3-benzodioxol (15a). Yield 82%. R_f 0.59 and 0.52 (cyclohexane/ethyl acetate, 70:30, v/v). IR (KBr) cm^{-1}: 2971, 1642, 1605, 1511, 1482, 1325, 1259, 1175, 1120, 1033, 928, 873, 844, 815. ^{1}H NMR ($CDCl_3$, 200 MHz): (cis) δ 1.36 (t, $J = 7.0$ Hz, 3H), 3.96 (q, $J = 7.0$ Hz, 2H), 6.03 (s, 2H), 6.59 (d, $J = 11.8$ Hz, 1H), 6.61 (s, 1H), 6.69 (d, $J = 8.6$ Hz, 2H), 6.70 (d, $J = 11.8$ Hz, 1H), 6.98 (d, $J = 8.6$ Hz, 2H), 7.60 (s, 1H); (trans) δ 1.40 (t, $J = 7.0$ Hz, 3H), 4.03 (q, $J = 7.0$ Hz, 2H), 6.08 (s, 2H), 6.86 (d, $J = 8.6$ Hz, 2H), 6.88 (d, $J = 16.5$ Hz, 1H), 7.08 (s, 1H), 7.42 (d, $J = 8.7$ Hz, 2H), 7.47 (s, 1H), 7.58 (d, $J = 16.5$ Hz, 1H).

5-[(*E*/*Z*)-2-(4-Ethyl)ethynyl]-6-nitro-1,3-benzodioxol (51a). Yield 78%. R_f 0.55 (cyclohexane/ethyl acetate, 70:30, v/v). IR (KBr) cm^{-1}: 2957, 2885, 1607, 1519, 1503, 1477, 1327, 1254, 1036, 933, 876, 813. ^{1}H NMR ($CDCl_3$, 200 MHz): δ ppm 0.89 (t, $J = 7.5$ Hz, 3H), 0.99 (t, $J = 7.5$ Hz, 3H), 1.96 (m, 2H), 2.15 (m, 2H), 5.60 (dt, $J = 11.5$ and 7.5 Hz, 1H, cis), 5.97 (s, 2H), 6.00 (s, 2H), 6.02 (dt, $J = 15.6$ and 6.5 Hz, 1H, trans), 6.49 (d, $J = 11.4$ Hz, 1H, cis), 6.57 (s, 1H), 6.74 (d, $J = 15.2$ Hz, 1H, trans), 679 (s, 1H), 7.26 (s, 1H), 7.39 (s, 1H).

5-[(*E*/*Z*)-2-(4-Phenyl)ethenyl]-6-nitro-phenyl (52a). Yield 96%. R_f 0.78 and 0.73 (cyclohexane/ethyl acetate, 70:30, v/v). IR (KBr) cm^{-1}: 3056, 3028, 1627, 1604, 1571, 1519, 1495, 1443, 1344, 1302, 1142, 1076, 962, 920, 854, 783, 755, 698. ^{1}H NMR ($CDCl_3$, 200 MHz): δ ppm 6.75 (d, $J = 12.0$ Hz, 1H, cis), 6.89 (d, $J = 12.0$ Hz, 1H, cis), 7.08−8.13 (m, H arom + H alkene, trans). MS (EI): m/z 225 ($M^{+\cdot}$), 208, 180, 178, 176, 165, 152, 139, 119, 105, 92, 91, 77, 63, 51, 39.

5-[(*E*/*Z*)-2-(4-Fluorophenyl)ethynyl]-6-nitro-phenyl (53a). Yield 68.9%. R_f 0.71 and 0.74 (cyclohexane/ethyl acetate, 70:30, v/v). IR (KBr) cm^{-1}: 3070, 2923, 2851, 1630, 1601, 1570, 1628, 1476, 1446, 1343, 1302, 1232, 1158, 1097, 1013, 962, 856, 786, 698, 533. ^{1}H NMR ($CDCl_3$, 200 MHz): δ ppm (cis) 6.85 (dd, $J = 8.5$ Hz, $J = 2.1$ Hz, 2H), 6.90 (d, $J = 3.1$ Hz, 1H), 7.05 (m, 4H), 7.15 (d, $J = 9.0$ Hz, 1H), 7.4 (dd; $J = 7.1$ Hz, $J = 2.3$ Hz, 2H); (trans) δ 6.7 (d, $J = 12.2$ Hz, 1H), 7.23 (dd, $J = 4.6$ Hz, $J = 2.1$ Hz, 2H), 7.55 (m, 4H), 7.98 (d, $J = 11.9$ Hz, 1H), 8.1 (dd, $J = 9.5$ Hz, $J = 2.4$ Hz, 2H).

5[(*E*/*Z*)-2-(4-Fluorophenyl)ethynyl]-6-nitro-1,3-benzodioxol (54a). Yield 85.5%. R_f 0.60 and 0.50 (cyclohexane/ethyl acetate, 70:30, v/v). IR (KBr) cm^{-1}: 3125, 3015, 2928, 1614, 1608, 1519, 1506, 1486, 1321, 1261, 1233, 1158, 1027, 965, 812, 680, 521. ^{1}H NMR ($CDCl_3$, 200 MHz): (cis) δ 6.07 (s, 2H), 6.56 (s, 1H), 6.64 (d, $J = 11.9$ Hz, 1H), 6.92 (dd, $J = 3.3$ Hz, 2H), 7.06 (dd, $J = 3.6$ Hz, 2H), 7.09 (d, $J = 3.6$ Hz, 1H), 7.52 (s, 1H); (trans) δ 6.13 (s, 2H), 6.80 (s, 1H), 6.87 (dd, $J = 5.5$ Hz, 2H), 7.02 (d, $J = 5.2$ Hz, 1H), 7.48 (dd, $J = 5.5$ Hz, 2H), 7.53 (s, 1H), 7.62 (d, $J = 8.2$ Hz, 1H).

General Synthetic Procedure for Diketone Compounds b. To a stirred cooled solution (0−5 °C) of alkene (4.8 mmol) in acetic anhydride (32 mL) was added $KMnO_4$ (19.2 mmol) in small portions over a period of 20 min. After completion of the addition, the mixture was stirred in a cooling bath for 2 h. The reaction was then stopped by addition of ethyl acetate/cyclohexane (1:1, v/v) (32 mL) and an ice-cold solution of sodium bisulfite 10%. After stirring in the cooling bath for several minutes, the mixture was extracted by dichloromethane, and the organic phase was washed by an aqueous NaOH solution (1N), water, and dried over anhydrous $MgSO_4$. It was then concentrated by evaporation. The crude material obtained was purified by column chromatography (SiO_2) using cyclohexane/dichloromethane.

1-(4-Chlorophenyl)-2-(6-nitro-1,3-benzodioxol-5-yl)-1,2-ethanedione (1b). Yield 50%. R_f 0.51 (cyclohexane/ethyl acetate, 70:30, v/v). IR (KBr) cm^{-1}: 1691, 1673, 1583, 1506, 1483, 1424, 1325, 1266, 1148, 1094, 1030, 927, 881, 872, 858, 817, 781. ^{1}H NMR ($CDCl_3$, 200 MHz): δ ppm 6.21 (2H, s), 7.06 (s, 1H), 7.48 (d, $J = 8.4$ Hz, 2H), 7.56 (s, 1H), 8.09 (d, $J = 8.4$ Hz, 2H).

1-(4-Ethoxyphenyl)-2-(6-nitro-1,3-benzodioxol-5-yl)-1,2-ethanedione (15b). Yield 25%. R_f 0.33 (cyclohexane/ethyl acetate, 70:30, v/v). IR (KBr) cm^{-1}: 1690, 1649, 1598, 1565, 1514, 1483, 1426, 1327, 1265, 1171, 1140, 1073, 1031, 922, 865, 784, 756. ^{1}H NMR ($CDCl_3$, 200 MHz): δ ppm 1.46 (t, $J = 7.0$ Hz, 3H), 4.14 (q, $J = 7.03$ Hz, 3H), 4.14 (q, $J = 7.0$ Hz, 2H), 6.23 (s, 2H), 6.98 (d, $J = 9.0$ Hz, 2H), 7.08 (s, 1H), 7.58 (s, 1H), 8.16 (d, $J = 9.0$ Hz, 2H).

1-(4-Ethyl)-2-(6-nitro-1,3-benzodioxol-5-yl)-1,2-ethanedione (51b). Yield 50%; mp 81−82 °C. R_f 0.41 (cyclohexane/ethyl acetate, 70:30, v/v). IR (KBr) cm^{-1}: 2978, 2916, 1706, 1607, 1524, 1509, 1483, 1426, 1368, 1332, 1275, 1114, 1036, 927, 886, 873, 811. ^{1}H NMR ($CDCl_3$, 200 MHz): δ ppm 1.12 (t, $J = 7.2$ Hz, 3H), 2.98 (q, $J = 7.2$ Hz, 2H), 6.20 (s, 2H), 6.89 (s, 1H), 7.56 (s, 1H).

1-(4-Phenyl)-2-(6-nitro-1,3-benzodioxol-5-yl)-1,2-ethanedione (52b). Yield 60%. R_f 0.33 (cyclohexane/ethyl acetate, 70:30, v/v). IR (KBr) cm^{-1}: 3064, 1786, 1691, 1672, 1592, 1573, 1521, 1445, 1341, 1256, 1204, 1181, 1043, 1029, 977, 845, 803, 788, 765, 736, 713, 689, 637. ^{1}H NMR ($CDCl_3$, 200 MHz): δ ppm 7.48−7.90 (m, 6H), 8.25 (m, 3H).

1-(4-Fluorophenyl)-2-(6-nitrophenyl)-1,2-ethanedione (53b). Yield 30.7%. R_f 0.57 (cyclohexane/ethyl acetate, 70:30, v/v). IR (KBr) cm^{-1}: 3094, 2859, 1789, 1696, 1676, 1597, 1572, 1522, 1506, 1412, 1343, 1313, 1257, 1235, 1198, 1159, 1145, 872, 853, 782, 605. ^{1}H NMR ($CDCl_3$, 250 MHz): δ ppm 7.23 (t, $J = 9.7$ Hz, 1H), 7.78 (m, 2H), 7.8 (d, $J = 8.0$ Hz, 1H), 8.2 (dd, $J = 10.0$ and 2.0 Hz, 2H), 8.20 (dd, $J = 6.0$ and 2.0 Hz, 2H). ^{13}C NMR

($CDCl_3$, 75 MHz): δ ppm 115.8 (CH), 116.07 (CH), 124.1 (CH), 128.9 (C), 131.0 (CH), 132.4 (CH), 133.0 (C), 133.5 (CH), 133.6 (CH), 134.9 (CH), 164.9 (C), 168.3 (C), 186,4 (C), 189.8 (C).

1-(4-Butyl)-2-(6-nitro-1,3-benzodioxol-5-yl)-1,2-ethanedione (54b). R_f 0.40 (cyclohexane/ethyl acetate, 70:30, v/v). IR (KBr) cm^{-1}: 3115, 3069, 2923, 2852, 1703, 1676, 1598, 1521, 1504, 1484, 1428, 1326, 1270, 1231, 1149, 1035, 929, 884, 869, 856, 837, 780. ^1H NMR ($CDCl_3$, 250 MHz): δ ppm 6.26 (s, 2H), 7.01 (s, 1H), 7.21 (d, J = 7.5 Hz, 2H), 7.61 (s, 1H), 8.2 (d, J = 7.5 Hz, 2H).

General Synthetic Procedure for Indolone *N*-Oxide Analogues (i). To a solution of diketone (0.59 mmol) in THF (10 mL) was added a 10% aqueous solution of NH_4Cl (11 mL) and Zn (2.50 mmol). After 1 h of stirring at rt, the mixture was filtered, the two liquid phases separated, and the aqueous phase was extracted with dichloromethane. The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was dissolved in THF or dichloromethane (10 mL) and heated under reflux until complete disappearance of the intermediate hydroxylamine. After evaporation of the solvent, the crude product was purified by column chromatography (SiO_2) with toluene.

6-(4-Chlorophenyl)-7*H*-[1,3]dioxolo[4,5-*f*]indol-7-one-5-oxide (1). Yield 17.4%. R_f 0.61 (cyclohexane/ethyl acetate, 70:30, v/v); mp: 210−211 °C. UV (EtOH) λ_{max} nm (ε L·mol^{-1}·cm^{-1}): 298 (29 444). IR (KBr) cm^{-1}: 3101, 2906, 1707, 1584, 1521, 1465, 1370, 1301. ^1H NMR (CD_3CN, 500 MHz): δ ppm 6.21 (s, 2H), 7.12 (s, 1H), 7.24 (1s, 1H), 7.55 (dd, J = 2 Hz, J = 9 Hz; 2H), 8.58 (dd, J = 2 Hz, J = 9 Hz; 2H). ^{13}C NMR (CD_3CN, 125 MHz): δ ppm 97.0 (CH), 101.8 (CH), 103.9 (CH_2), 116.7 (C), 125.1 (C), 128.69 (CH × 2), 128.71 (CH × 2), 131.7 (C), 135.3 (C), 146.0 (C), 150.2 (C), 153.3 (C), 185.9 (C). MS (EI): m/z 301 ($M^{+\cdot}$), 284, 139, 120, 62. HR-MS [$M^{+\bullet}$] calcd for $C_{15}H_8NO_4Cl$ 301.0142, found 301.0141.

6-(4-Ethoxyphenyl)-7*H*-[1,3]dioxolo[4,5-*f*]indol-7-one-5-oxide (15). Yield 11.5%; mp 169−170 °C. R_f 0.58 (cyclohexane/ethyl acetate, 70:30, v/v). UV (EtOH) λ_{max} nm (ε L·mol^{-1}·cm^{-1}): 298 (38 790). IR (KBr) cm^{-1}: 1708, 1684, 1593, 1529, 1499, 1475, 1387, 1366, 1311, 1291, 1266. ^1H NMR ($CDCl_3$, 300 MHz): δ ppm 1.42 (t, J = 7.0 Hz, 3H), 4.09 (q, J = 7.0 Hz, 2H), 6.12 (s, 2H), 6.96 (d, J = 9.2 Hz, 2H), 6.98 (s, 1H), 7.13 (s, 1H), 8.63 (d, J = 9.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 14.8 (CH_3), 63.6 (CH_2), 97.3 (CH), 102.3 (CH), 103.1 (CH_2), 114.6 (CH × 2), 116.6 (C), 118.9 (C), 129.5 (CH × 2), 131.2 (C), 145.1 (C), 149.4 (C), 152.9 (C), 160.6 (C), 184.1 (C). MS (EI): m/z 311 ($M^{+\bullet}$), 283, 265, 190, 163, 149, 121, 119, 93, 77, 62. HR-MS [$M^{+\bullet}$] calcd for $C_{17}H_{13}NO_5$ 311.0794, found 311.0793.

6-Ethyl-7*H*-[1,3]-dioxolo[4,5-*f*]indol-7-one-5-oxide (51). Yield 5.1%. R_f 0.60 (cyclohexane/ethyl acetate, 70:30, v/v); mp: 136 °C. UV (EtOH) λ_{max} nm (ε L·mol^{-1}·cm^{-1}): 269 (30 035). IR (KBr) cm^{-1}: 3083, 2980, 1696, 1545, 1467, 1389, 1359, 1311, 1285. ^1H NMR ($CDCl_3$, 200 MHz): δ ppm 1.18 (t, J = 7.6 Hz, 3H), 2.61 (q, J = 7.6 Hz, 2H), 6.11 (s, 2H), 6.95 (s, 1H), 7.08 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): d 9.9 (CH_3), 15.2 (CH_2), 97.5 (CH), 102.5 (CH), 103.2 (CH_2), 117.0 (C), 139.1 (C), 144.4 (C), 149.6 (C), 152.5 (C), 185.9 (C). MS (EI): m/z 219 ($M^{+\bullet}$), 202 ($M^{+\bullet}$ −17), 174, 120, 62. HR-MS [$M^{+\bullet}$] calcd for $C_{11}H_9NO_4$ 219.0532, found 219.0532.

2-Phenyl-3*H*-indol-3-one 1-Oxide (52). Yield 1%. R_f 0.75 (cyclohexane/ethyl acetate 70:30, v/v); mp: 186 °C. UV (EtOH) λ_{max} nm (ε L·mol^{-1}·cm^{-1}): 285 (47458). IR (KBr) cm^{-1}: 3063, 1706, 1598, 1524, 1481, 1389, 1314. ^1H NMR ($CDCl_3$, 300 MHz): δ ppm 7.28−7.70 (m, 7H), 8.62−8.67 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 186.9 (C), 147.8 (C), 134.8 (CH), 133.0 (C), 131.2 (CH), 130.7 (CH), 128.5 (2 × CH), 127.9 (2 × CH), 125.9 (C), 122.8 (C), 121.6 (CH), 114.2 (CH). MS (EI): m/z 223 ($M^{+\bullet}$), 206, 177, 167, 151, 139, 130, 103, 90, 76, 63, 50, 39. HR-MS [$M^{+\bullet}$] calcd for $C_{14}H_9NO_2$ 223.0633, found 223.0635.

2-(4-Fluorophenyl)-3*H*-indol-3-one-*N*-oxide (53). Yield: 1%. R_f: 0.64 (cyclohexane/ethyl acetate 70/30, v/v). UV (CH_3CN) λ_{max}: 290 nm. IR (KBr) cm^{-1}: 3003, 2879, 1707, 1595, 1582, 1526, 1492, 1461, 1384, 1301, 1287. ^1H NMR ($CDCl_3$, 300 MHz): δ ppm 7.10−7.23 (m, 2H), 7.50−7.74 (m, 4H), 8.70−8.80 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 186.9 (C), 165.3 (C), 161.9 (C), 147.8 (C), 134.9 (CH), 131.2 (CH), 130.3 (CH), 130.2 (CH), 122.7 (C), 122.3 (C), 121.7 (CH), 115.9 (CH), 115.7 (CH), 114.2 (CH). MS (EI): m/z 241 ($M^{+\bullet}$), 224, 195, 184, 121, 107, 95, 76, 63, 50, 39.

6-(4-Fluorophenyl)-7*H*-[1,3]dioxolo-[4,5-f]indol-7-one-5-oxide (54). Yield 1%. R_f 0.56 (cyclohexane/ethyl acetate 70:30, v/v). UV (CH_3CN) λ_{max}: 295 nm. IR (KBr) cm^{-1}: 3100, 1703, 1604, 1588, 1535, 1502, 1477, 1390, 1371, 1316, 1231. ^1H NMR ($CDCl_3$, 300 MHz): δ ppm 6.17 (s, 2H), 7.04 (s, 1H), 7.14−7.21 (m, 2H), 7.26 (s, 1H), 8.66−8.70 (m, 2H). MS (EI): m/z 285 ($M^{+\bullet}$), 268, 212, 190, 171, 123, 95, 75, 62, 50, 39.

6.2. Synthesis by Method 2 (Compounds 2, 49−50, 56). 1-Iodo-2-nitrobenzene (19.4 mmol) was dissolved in freshly distilled triethylamine (100 mL) to which ethynyl derivative (19.4 mmol) was added. The reaction was stirred at room temperature under N_2 for 30 min, at which point dichloro-bis-(triphenylphosphine) palladium (0.4 mmol) and copper(I) iodide (1.4 mmol) were added. The mixture was stirred at room temperature for 5−7 days. The reaction mixture was filtered, the remaining solid was washed with ethyl acetate, and the combined solutions were evaporated to dryness, leaving an oily liquid. After solvent evaporation the crude product was purified by column chromatography (SiO_2). The product was then purified by recrystallization from toluene.

2-(4-Phenoxyphenyl)-3*H*-indol-3-one-*N*-oxide (2). Yield 34%. R_f 0.50 (cyclohexane/ethyl acetate 85:15, v/v); mp: 136−137 °C. UV (CH_3CN) λ_{max} nm (ε L·mol^{-1}·cm^{-1}): 287 (40798). IR (KBr) cm^{-1}: 3090, 1704, 1585, 1526, 1488, 1384, 1241. ^1H NMR ($CDCl_3$, 300 MHz): δ ppm 8.70 (d, J = 9.3 Hz, 2H), 7.68 (d, J = 3.9 Hz, 2H), 7.63 (d, J = 7.0 Hz, 1H), 7.49−7.57 (m, 1H), 7.38 (t, J = 7.5 Hz, 2H), 7.18 (t, J = 7.5 Hz, 1H), 7.09 (dd, J = 2.4 Hz, J = 9.3 Hz, 4H). NMR ^{13}C ($CDCl_3$, 75 MHz): δ ppm 187.1 (C), 159.6 (C), 155.7 (C), 148.0 (C), 134.9 (CH), 131.3 (CH), 130.0 (C), 129.9 (2CH), 129.8 (2CH), 124.4 (CH), 122.8 (C), 121.6 (CH), 120.6 (C), 120.0 (2CH), 117.8 (2CH), 114.1 (CH). HR-MS [$M^{+\bullet}$] calcd for $C_{20}H_{13}NO_3$ 315.0895, found 315.0892.

2-Isobutyl-3*H*-indol-3-one-*N*-oxide (49). Yield 1%. R_f 0.68 (cyclohexane/ethyl acetate 70:30, v/v); mp: 90 °C. UV (CH_3CN) λ_{max} nm (ε L•mol^{-1}•cm^{-1}): 245 (25700). IR (KBr) cm^{-1}: 2967, 1700, 1604, 1533, 1461, 1430, 1379, 1295, 1276. ^1H NMR ($CDCl_3$, 300 MHz): δ ppm 7.49−7.63 (m, 4H), 2.56 (d, J = 6.9 Hz, 2H), 2.17−2.26 (m, 1H), 0.98 (d, J = 6.6 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 187.1 (C), 147.4 (C), 138.9 (C), 134.3 (CH), 131.0 (CH), 123.1 (C), 121.4 (CH), 113.8 (CH), 30.2 (CH_2), 26.8 (CH), 22.8 ($2CH_3$). HR-MS [$M^{+\bullet}$] calcd for $C_{12}H_{13}NO_2$ 203.0946, found 203.0946.

2-Propyl-3*H*-indol-3-one-*N*-oxide (50). Yield 7%. R_f 0.52 (cyclohexane/ethyl acetate 70:30, v/v); mp: 58 °C. UV (CH_3CN) λ_{max} nm (ε L·mol^{-1}·cm^{-1}): 271 (24658). IR (KBr) cm^{-1}: 2962, 2927, 2872, 1698, 1599, 1532, 1464, 1434, 1381, 1345, 1285. ^1H NMR ($CDCl_3$, 300 MHz): δ ppm 7.48−7.62 (m, 4H), 2.65 (t, J = 7.5 Hz, 2H), 1.70 (m, J = 7.5 Hz, 2H), 1.02 (t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 187.0 (C), 147.4 (C), 139.3 (C), 134.3 (CH), 131.0 (CH), 123.1 (C), 121.3 (CH), 113.8 (CH), 23.2 (CH_2), 19.0 (CH_2), 14.1 (CH_3). MS-(−)APCI, m/z: 189 [$M^{-\bullet}$]. HR-MS [M + H]$^+$ calcd for $C_{11}H_{12}NO_2$ 190.0868, found 190.0876.

2-(4-Nitrophenyl)-3*H*-indol-3-one-*N*-oxide (56). Yield 18%. R_f 0.52 (cyclohexane /ehtyl acetate 70:30, v/v); mp: 246 °C. UV (CH_3CN) λ_{max} nm (ε L·mol^{-1}·cm^{-1}): 290 (21854). IR (KBr) cm^{-1}: 3132, 1715, 1594, 1512, 1482, 1388, 1344, 1314, 1288. ^1H NMR ($CDCl_3$, 500 MHz): δ ppm 8.94 (d, J = 8.7 Hz, 2H), 8.31 (d, J = 8.7 Hz, 2H), 7.75 (d, J = 4.5 Hz, 2H),

7.61−7.66 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ ppm 187.0 (C), 147.8 (C), 135.5 (C), 135.3 (CH), 132.0 (C), 132.1 (CH), 131.2 (C), 128.2 (2CH), 123.5 (C), 123.6 (2CH), 121.8 (CH), 114.6 (CH). MS-(−)APCI, *m/z*: 268 [$M^{-\bullet}$]. HR-MS $[M + H]^+$ calcd for $C_{14}H_9N_2O_4$ 269.0562, found 269.0581.

6.3. Synthesis by Method 3 (Compounds 3−48, 55, 57−66). 1-Iodo-2-nitroaryl (2 mmol) was dissolved in freshly distilled triethylamine (8 mL) to which ethynyl derivative (2 mmol) was added. The reaction was stirred at room temperature under N_2 for 10 min, and then dichloro-bis-(triphenylphosphine)-palladium (0.1 mmol) and copper(I) iodide (0.2 mmol) were added. The mixture was stirred at room temperature for 3 h. The reaction mixture was filtered. After solvent evaporation, the crude intermediate product was heated under reflux in the presence of pyridine (8 mL) and 4-dimethylaminopyridine (4-DMAP) (2 mmol) for a time-period varying between 2 h and 4 days. There are two other possibilities to carry out this protocol: The first one consists of catalyzing the reaction with $AuBr_3$ (3% molar) in either toluene or dichloromethane as solvent (compounds **22** and **26**). The second one consists of using the same reagents as the general protocol under microwaves conditions (Biotage Initiator 300W). These conditions are mentioned for each compound (**45−48**). The crude product was purified by column chromatography (SiO_2) using either dichloromethane/cyclohexane or petroleum ether/ethyl acetate or petroleum ether/dichloromethane. After concentration, the purified product was stirred with boiling ethanol and filtered at room temperature. When possible, the final compound was recrystallized from toluene.

2-(4-Hydroxymethylphenyl)-3*H*-indol-3-one-*N*-oxide (3). Yield 8%. R_f 0.64 (CH_2Cl_2/EtOH 94:6); mp: 199−200 °C. UV (CH_3CN) λ_{max} nm (ε L·mol^{-1}·cm^{-1}): 290 (33899). IR (KBr) cm^{-1}: 3268, 3083, 2904, 1701, 1597, 1526, 1493, 1458, 1385, 1284. ^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 8.95 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 4.8 Hz, 1H), 7.55 (t, J = 7.2 Hz, 2H), 7.40 (t, J = 7.2 Hz, 1H), 7.08 (s, 1H), 4.98 (s, J = 5.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 187.0 (C), 147.9 (C), 146.4 (C), 145.3 (C), 134.6 (CH), 132.1 (C), 131.1 (CH), 127.9 (2CH), 126.6 (2CH), 125.0 (C), 121.3 (CH), 114.0 (CH), 63.6 (CH_2). HR-MS $[M + H]^+$ calcd for $C_{15}H_{12}NO_3$ 254.0817, found 254.0821.

2-(4-Methoxyphenyl)-3*H*-indol-3-one-*N*-oxide (4). Yield 21%. R_f 0.55 (cyclohexane/ethyl acetate 70:30, v/v); mp: 188−189 °C. UV (CH_3CN) λ_{max} nm (ε L·mol^{-1}·cm^{-1}): 294 (38939). IR (KBr) cm^{-1}: 1702, 1599, 1530, 1492, 1460, 1380, 1301, 1262. ^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 8.74 (d, J = 9.3 Hz, 2H), 7.68 (dt, J = 4.5 Hz, J = 1.2 Hz, 2H), 7.61 (dt, J = 0.9 Hz, J = 7.2 Hz, 1H), 7.48−7.54 (m, 1H), 7.03 (d, J = 9.3 Hz, 2H), 3.89 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 187.3 (C), 161.4 (C), 148.0 (C), 134.8 (CH), 131.9 (C), 130.7 (CH), 129.8 (2CH), 122.8 (C), 121.5 (CH), 118.8 (C), 114.1 (2CH), 113.9 (CH), 55.4 (CH_3). HR-MS $[M + H]^+$ calcd for $C_{11}H_{12}NO_3$ 254.0817, found 254.0815.

2-(6-Methoxy-naphthalen-2-yl)-3*H*-indol-3-one-*N*-oxide (5). Yield 28%. R_f 0.47 (cyclohexane/ethyl acetate 70:30, v/v); mp: 209 °C. UV (CH_3CN) λ_{max} nm (ε L·mol^{-1}·cm^{-1}): 272 (50521). IR (KBr) cm^{-1}: 1700, 1600, 1517, 1480, 1456, 1393, 1335, 1286, 1261. ^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 9.30 (s, 1H), 8.70 (dd, J = 1.8 Hz, J = 9.0 Hz, 1H), 7.86 (dd, J = 9.0 Hz, J = 11.4 Hz, 2H), 7.72 (m, 2H), 7.66 (d, J = 6.9 Hz, 1H), 7.52−7.58 (m, 1H), 7.18 (td, J = 2.4 Hz, J = 9.0 Hz, 2H), 3.97 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 187.4 (C), 159.4 (C), 148.1 (C), 135.6 (C), 134.9 (CH), 132.3 (C), 131.1 (CH), 130.9 (CH), 128.6 (CH), 128.4 (C), 126.9 (CH), 124.5 (CH), 122.9 (C), 121.6 (CH), 121.4 (C), 119.4 (CH), 114.0 (CH), 105.7 (CH), 55.4 (CH_3). MS-(−)APCI, *m/z*: 303 [$M^{-\bullet}$]. HR-MS [$M^{+\bullet}$] calcd for $C_{19}H_{13}NO_3$ 303.0895, found 303.0881.

6-(6-Methoxy-naphthalen-2-yl)-7*H*-[1,3]-dioxolo[4,5-*f*]-indol-7-one-5-oxide (6). Yield 16.5%. R_f 0.40 (cyclohexane/ethyl acetate, 70:30, v/v); mp: 248−249 °C. UV (CH_3CN) λ_{max} nm (ε L·mol^{-1}·cm^{-1}): 306 (40572). IR (KBr) cm^{-1}: 1704, 1619, 1590, 1489, 1388, 1332, 1220. ^{1}H NMR ($CDCl_3$, 500 MHz): δ ppm 9.24 (s, 1H), 8.64 (dd, J = 1.5 Hz, J = 9.0 Hz, 2H), 7.86 (d, J = 9.0 Hz, 1H), 7.79 (d, J = 9.0 Hz, 1H), 7.12−7.20 (m, 3H), 7.06 (s, 1H), 6.16 (s, 2H), 3.95 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ ppm 186.3 (C), 159.5 (C), 153.0 (C), 143.2 (C), 135.6 (C), 131.0 (C), 130.9 (CH), 128.6 (C), 128.6 (CH), 127.9 (CH), 127.1 (CH), 123.6 (CH), 122.9 (C), 122.2 (C), 119.7 (CH), 115.8 (C), 106.2 (CH), 103.7 (CH_2), 102.1 (CH), 55.2 (CH_3). MS-(+)ESI, *m/z*: 348 $[M + H]^+$, 370 $[M + Na]^+$, 717 $[2M + Na]^+$. HR-MS [$M^{+\bullet}$] calcd for $C_{20}H_{13}NO_5$ 347.0794, found 347.0794.

6-(4-Phenoxylphenyl)-7*H*-[1,3]-dioxolo[4,5-*f*]- indol-7-one-5-oxide (7). Yield 33.5%. R_f 0.46 (cyclohexane/ethyl acetateethyl acetate, 70:30, v/v); mp: 168 °C. UV (CH_3CN) λ_{max} nm (ε L·mol^{-1}·cm^{-1}): 295 (52392). IR (KBr) cm^{-1}: 3098, 2914, 1706, 1589, 1523, 1491, 1475, 1388, 1362, 1310, 1262. ^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 8.67 (d, J = 9.0 Hz, 2H), 7.41 (t, J = 7.8 Hz, 2H), 7.23 (m, 2H), 7.07−7.11 (m, 4H), 7.04 (s, 1H), 6.16 (s, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 186.1 (C), 159.4 (C), 155.8 (C), 152.9 (C), 149.5 (C), 144.9 (C), 132.5 (C), 130.0 (2CH), 129.5 (2CH), 124.3 (CH), 120.8 (2C), 120.0 (2CH), 117.9 (2CH), 116.6 (C), 103.2 (CH_2), 102.3 (CH), 97.4 (CH). HR-MS [$M^{+\bullet}$] calcd for $C_{21}H_{13}NO_5$ 359.0794, found 359.0787.

2-(3,4-Dichloro-phenyl)-1-oxy-indol-3-one (8). Yield 78%; mp: 204.2−204.8 °C. UV (CH_3CN) λ_{max}: 286 nm. IR (CH_2Cl_2) cm^{-1}: 3040, 1705, 1590, 1510, 1420, 1384, 1265. ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm 7.55−7.60 (m, 2H), 7.65−7.72 (m, 3H), 8.57 (dd, J = 1.8 Hz, 8.7 Hz, 1H), 8.89 (d, J = 2.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 186.4 (C), 147.7 (C), 135.1 (CH), 134.7 (C), 133 (C), 131.7 (CH), 130.6 (CH), 130.3 (C), 129 (CH), 126.7 (CH), 125.7 (C), 122.6 (C), 121.9 (CH), 114.4 (CH). MS-(−)APCI, *m/z*: 291 [$M^{-\bullet}$]. HR-MS [$M^{+\bullet}$] calcd for $C_{14}H_7NO_2Cl_2$ 290.9854, found 290.9850.

2-(4-Chloro-phenyl)-5-methoxy-1-oxy-indol-3-one (9). Yield 60.8%; mp: 190.5−191.1 °C. UV (CH_3CN) λ_{max}: 290 nm. IR (KBr) cm^{-1}: 3104, 2951, 1702, 1639, 1598, 1519, 1481, 1433, 1384, 1283, 1248. ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm 3.91 (s, 3H), 7.08 (dd, J = 2.4 Hz, 8.4 Hz, 1H), 7.15 (d, J = 2.4 Hz, 1H), 7.46 (d, J = 8.7 Hz, 2H), 7.58 (d, J = 8.4 Hz, 1H), 8.59 (d, J = 8.7 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 186.6 (C), 162.6 (C), 140.7 (C), 136.2 (C), 131 (C), 128.8 (2 CH), 128.6 (2 CH), 124.6 (C), 124.5 (C), 118.4 (CH), 115.5 (CH), 108 (CH), 56.3 (CH_3). MS-(+)ESI, *m/z*: 288 $[M + H]^+$, MS-(−)ESI, *m/z*: 287 [$M^{-\bullet}$]. HR-MS $[M + H]^+$ calcd for $C_{15}H_{11}NO_3Cl$ 288.0427, found 288.0435.

5,6-Dimethoxy-1-oxy-2-*p*-tolyl-indol-3-one (10). Yield 1%. IR (KBr) cm^{-1}: 2998, 2839, 1698, 1651, 1594, 1525, 1485, 1220. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 2.41 (s, 3H), 3.97 (s, 3H), 4.04 (s, 3H), 7.13 (s, 1H), 7.26 (s, 1H), 7.29 (d, J = 8.4 Hz, 2H), 8.10 (d, J = 8.4 Hz, 2H). MS-(+)ESI, *m/z*: 298 $[M + H]^+$.

2-(4-Chloro-3-trifluoromethyl-phenyl)-5-methoxy-1-oxy-indol-3-one (11). Yield 41.1%; mp: 194.1−194.9 °C. IR (CH_2Cl_2) cm^{-1}: 3054, 2987, 1720, 1600, 1515, 1480, 1421, 1385, 1265. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 3.92 (s, 3H), 7.10 (dd, J = 8.4 Hz, 2.1 Hz, 1H), 7.18 (d, J = 2.1 Hz, 1H), 7.58−7.62 (m, 2H), 8.77 (dd, J = 1.8 Hz, 8.4 Hz, 1H), 9.07 (s, 1H). MS-(+)ESI, *m/z*: 356 $[M + H]^+$, 378 $[M + Na]^+$. HR-MS [$M^{+\bullet}$] calcd for $C_{16}H_9NO_3ClF_3$ 355.0223, found 355.0229.

2-(4-Chloro-phenyl)-6-methoxy-1-oxy-indol-3-one (12). Yield 5%. UV (CH_3CN) λ_{max}: 286 nm. IR (CH_2Cl_2) cm^{-1}: 3054, 3000, 1705, 1590, 1523, 1470, 1430, 1383, 1265. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 3.96 (s, 3H), 6.92 (dd, J = 2.1 Hz, 8.1 Hz, 1H), 7.24 (d, J = 2.1 Hz, 1H), 7.45 (d, J = 9.3 Hz, 2H), 7.55 (d, J = 8.1 Hz, 1H), 8.66 (d, J = 9.3 Hz, 2H). MS-(+)ESI, *m/z*: 288 $[M + H]^+$, 310 $[M + Na]^+$, MS-(−)ESI, *m/z*: 287 [$M^{-\bullet}$]. HR-MS [$M^{+\bullet}$] calcd for $C_{15}H_{10}NO_3Cl$ 287.0349, found 287.0349.

2-(3,4-Dichloro-phenyl)-5-methoxy-1-oxy-indol-3-one (13). Yield 23.4%; mp: 193−194 °C. IR (CH_2Cl_2) cm^{-1}: 3054, 2980,

1705, 1591, 1500, 1455, 1415, 1384, 1265. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 3.91 (s, 3H), 7.10 (d, J = 8.7 Hz, 1H), 7.15 (s, 1H), 7.52 (d, J = 8.7 Hz, 1H), 7.57 (d, J = 8.7 Hz, 1H), 8.52 (dd, J = 1.2 Hz, 8.7 Hz, 1H), 8.83 (s, 1H). MS-(+)ESI, m/z: 322 $[M + H]^+$, 344 $[M + Na]^+$. HR-MS $[M^{+\bullet}]$ calcd for $C_{15}H_9NO_3Cl_2$ 320.9959, found 320.9969.

6-(3,4-Dichloro-phenyl)-5-oxy-[1,3]-dioxolo[4,5-*f*]-indol-7-one (14). Yield 7%; mp: 270−271 °C. UV (CH_3CN) λ_{max}: 286 nm. IR (CH_2Cl_2) cm^{-1}: 3060, 2980, 1701, 1590, 1520, 1460, 1385, 1355, 1265. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 6.28 (s, 2H), 7.31 (s, 1H), 7.40 (s, 1H), 7.86 (d, J = 8.7 Hz, 1H), 8.47 (dd, J = 1.5 Hz, 9.0 Hz, 1H), 8.71 (d, J = 1.5 Hz, 1H). MS-(+)ESI, m/z: 336 $[M + H]^+$, 358 $[M + Na]^+$, MS-(−)ESI, m/z: 335 $[M^{-\bullet}]$. HR-MS $[M^{+\bullet}]$ calcd for $C_{15}H_7NO_4Cl_2$ 334.9752, found 334.9749.

1-Oxy-2-*p*-tolyl-indol-3-one (16). Yield 61%; mp: 214.4−215.3 °C. UV (CH_3CN) λ_{max}: 289 nm. IR (CH_2Cl_2) cm^{-1}: 3050, 2980, 1700, 1590, 1410, 1384, 1275, 1250. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 2.41 (s, 3H), 7.3 (d, J = 8.4 Hz, 2H), 7.48−7.56 (m, 1H), 7.61−7.69 (m, 3H), 8.56 (d, J = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 187.2 (C), 148 (C), 141.4 (C), 134.8 (CH), 132.3 (C), 131 (CH), 129.3 (2 CH), 127.8 (2 CH), 123.2 (C), 122.9 (C), 121.6 (CH), 114.1 (CH), 21.8 (CH_3). HR-MS $[M + H]^+$ calcd for $C_{15}H_{12}NO_2$ 238.0868, found 238.0881.

5-Methoxy-1-oxy-2-phenyl-indol-3-one (17). Yield 41%; mp: 135.3−135.7 °C. UV (CH_3CN) λ_{max}: 286 nm. IR (CH_2Cl_2) cm^{-1}: 3050, 2980, 1710, 1595, 1480, 1420, 1384, 1265. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 3.90 (s, 3H), 7.09 (d, J = 8.1 Hz, 1H), 7.16 (s, 1H), 7.42−7.60 (m, 4H), 8.58 (d, J = 6.9 Hz, 2H). MS-(−)ESI, m/z: 253 $[M^{-\bullet}]$, MS-(+)ESI, m/z: 254 $[M + H]^+$. HR-MS $[M^{+\bullet}]$ calcd for $C_{15}H_{11}NO_3$ 253.0739, found 253.0736.

5-Methoxy-1-oxy-2-*p*-tolyl-indol-3-one (18). Yield 13.4%; mp: 196.8−196.9 °C. IR (CH_2Cl_2) cm^{-1}: 3060, 3000, 1705, 1590, 1480, 1430, 1384, 1276. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 2.41 (s, 3H), 3.90 (s, 3H), 7.05 (dd, J = 2.4 Hz, 8.7 Hz, 1H), 7.14 (d, J = 2.4 Hz, 1H), 7.28 (d, J = 8.7 Hz, 2H), 7.57 (d, J = 8.7 Hz, 1H), 8.50 (d, J = 8.4 Hz, 2H). MS-(+)ESI, m/z: 268 $[M + H]^+$, 290 $[M + Na]^+$, 557 $[2M + Na]^+$. HR-MS $[M^{+\bullet}]$ calcd for $C_{16}H_{13}NO_3$ 267.0895, found 267.0900.

2-(4-Chloro-phenyl)-1-oxy-6-trifluoromethyl-indol-3-one (19). Yield 67.2%; mp: 167.3−167.5 °C. UV (CH_3CN) λ_{max}: 292 nm. IR (CH_2Cl_2) cm^{-1}: 3054, 1720, 1591, 1421, 1384, 1310, 1265. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.50 (d, J = 9.0 Hz, 2H), 7.78 (d, J = 8.1 Hz, 1H), 7.88 (d, J = 8.1 Hz, 1H), 7.96 (s, 1H), 8.66 (d, J = 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 185.4 (C), 147.9 (C), 137.5 (C), 132.4 (C), 129.1 (2 CH), 128.9 (2 CH), 128.8 (C), 125.4 (C), 123.9 (CH), 122.8 (CF_3), 122.1 (CH), 117.9 (C), 111.8 (CH). MS-(−)ESI, m/z: 325 $[M^{-\bullet}]$. HR-MS $[M^{+\bullet}]$ calcd for $C_{15}H_7NO_2ClF_3$ 325.0117, found 325.0116.

5-Methoxy-2-(-methoxy-naphtalen-2-yl)-1-oxy-indol-3-one (20). Yield 24.7%; mp: 203.8−204.1 °C. IR (CH_2CL_2) cm^{-1}: 3054, 2980, 1705, 1596, 1480, 1420, 1265. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 3.91 (s, 3H), 3.95 (s, 3H), 7.06−7.19 (m, 4H), 7.60 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 9.3 Hz, 1H), 7.87 (d, J = 8.7 Hz, 1H), 8.64 (dd, J = 2.1 Hz, 9 Hz, 1H), 9.22 (s, 1H). MS-(+)ESI, m/z: 334 $[M + H]^+$, 689 $[2M + Na]^+$. HR-MS $[M^{+\bullet}]$ calcd for $C_{20}H_{15}NO_4$ 333.1001, found 333.1005.

2-(4′-Chloro-biphenyl-4-yl)-5-methoxy-1-oxy-indol-3-one (21 >). Yield 43%; mp: 227.2−227.4 °C. IR (CH_2Cl_2) cm^{-1}: 3054, 2987, 1720, 1620, 1550, 1480, 1421, 1385, 1265. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 3.91 (s, 3H), 7.09 (dd, J = 2.4 and 8.4 Hz, 1H), 7.16 (d, J = 2.4 Hz, 1H), 7.43 (d, J = 8.7 Hz, 2H), 7.57−7.60 (m, 3H), 7.69 (d, J = 8.1 Hz, 2H), 8.69 (d, J = 8.1 Hz, 2H). MS-(+)ESI, m/z: 364 $[M + H]^+$, 386 $[M + Na]^+$, 749 $[2M + Na]^+$. HR-MS $[M^{+\bullet}]$ calcd for $C_{21}H_{14}NO_3Cl$ 363.0662, found 363.0676.

2-(4-Methoxy-phenyl)-5-methoxy-1-oxy-indol-3-one (22) (Catalyzed with $AuBr_3$ in Ahydrous Toluene 5 h at 0.5 °C). Yield 56%; mp: 196.0−196.8 °C. IR (CH_2Cl_2) cm^{-1}: 3053, 2980, 1700, 1602, 1525, 1480, 1420, 1384, 1263. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 3.87 (s, 3H), 3.89 (s, 3H), 6.99−7.07 (m, 3H), 7.13 (d, J = 2.7 Hz, 1H), 7.54 (d, J = 8.1 Hz, 1H), 8.66 (d, J = 9.0 Hz, 2H). MS-(+)ESI, m/z: 284 $[M + H]^+$, 589 $[2M + Na]^+$. HR-MS $[M^{+\bullet}]$ calcd for $C_{16}H_{13}NO_4$ 283.0845, found 283.0849.

2-(2−4-Dichloro-phenyl)-5-methoxy-1-oxy-indol-3-one (23). Yield 23.1%; mp: 180.5−180.9 °C. IR (CH_2Cl_2) cm^{-1}: 3054, 2980, 1709, 1614, 1524, 1473, 1434, 1397, 1358, 1265. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 3.92 (s, 3H), 7.11 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 7.20 (d, J = 2.4 Hz, 1H), 7.37−7.43 (m, 2H), 7.55 (d, J = 1.8 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H). MS-(+)ESI, m/z: 322 $[M + H]^+$. HR-MS $[M^{+\bullet}]$ calcd for $C_{15}H_9NO_3Cl_2$ 320.9959, found 320.9966.

5-Methoxy-1-oxy-2(4-phenoxy-phenyl)-indol-3-one (24). Yield 27.5%; mp: 157.3−159.3 °C. UV (CH_3CN) λ_{max}: 290 nm. IR (CH_2CL_2) cm^{-1}: 3060, 2980, 1700, 1587, 1520, 1485, 1420, 1384, 1265. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 3.90 (s, 3H), 7.07−7.20 (m, 7H), 7.39 (m, 2H), 7.56 (d, J = 8.4 Hz, 1H), 8.64 (d, J = 9.0 Hz, 2H). MS-(+)ESI, m/z: 346 $[M + H]^+$, 368 $[M + Na]^+$, 713 $[2M + Na]^+$; MS-(−)APCI, m/z: 345 $[M^{-\bullet}]$. HR-MS $[M^{+\bullet}]$ calcd for $C_{21}H_{15}NO_4$ 345.1001, found 345.1012.

5-Methoxy-1-oxy-2-(4-trifluoromethoxy-phenyl)-indol-3-one (25). Yield 6.1%; mp: 137.1−137.9 °C. IR (CH_2Cl_2) cm^{-1}: 3054, 2980, 1720, 1600, 1520, 1480, 1420, 1385, 1265. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 3.91 (s, 3H), 7.09 (dd, J = 8.4 and 2.1 Hz, 1H), 7.17 (d, J = 2.1 Hz, 1H), 7.32 (d, J = 9.0 Hz, 2H), 7.59 (d, J = 8.4 Hz, 1H), 8.70 (d, J = 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 186.5 (C), 162.7 (C), 150.0 (C), 140.6 (C), 130.8 (C), 129.2 (2 CH), 124.7 (C), 124.5 (C), 120.4 (CF_3), 120.6 (2 CH), 118.5 (CH), 115.6 (CH), 108.1 (CH), 56.3 (CH_3). MS-(+)ESI, m/z: 338 $[M + H]^+$. HR-MS $[M^{+\bullet}]$ calcd for $C_{16}H_{10}NO_4F_3$ 337.0562, found 337.0564.

2-(4-Dimethylamino-phenyl)-5-methoxy-1-oxy-indol-3-one (26d >) (Catalyzed with $AuBr_3$ in Anhydrous Dichloromethane 12 h at Room Temperature). Yield 5.8%; mp: 214.8−218.9 °C. UV (CH_3CN) λ_{max}: 332 nm. IR (CH_2Cl_2) cm^{-1}: 3054, 2980, 1690, 1602, 1540, 1480, 1420, 1383, 1265. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 3.06 (s, 6H), 3.88 (s, 3H), 6.76 (dm, J = 9.3 Hz, 2H), 7.03 (dd, J = 2.4 Hz, 8.4 Hz, 1H), 7.10 (d, J = 2.4 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 8.68 (dm, J = 9.3 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 187.8 (C), 161.5 (C), 151.2 (C), 141.4 (C), 132 (C), 129.1 (2 CH), 124.7 (C), 118.2 (CH), 114.6 (CH), 114.3 (C), 111.4 (2 CH), 107.8 (CH), 56.1 (CH_3), 40 (2 CH_3). MS-(+)ESI, m/z: 297 $[M + H]^+$, 615 $[2M + Na]^+$; MS-(−)APCI, m/z: 296 $[M^{-\bullet}]$. HR-MS $[M^{+\bullet}]$ calcd for $C_{17}H_{16}N_2O_3$ 296.1161, found 296.1159.

2-(4-Isopropoxy-phenyl)-5-methoxy-1-oxy-indol-3-one (27). Yield 4.7%; mp: 148.9−150.8 °C. UV (CH_3CN) λ_{max} nm (ε L·mol^{-1}·cm^{-1}): 302 (31250). IR (KBr) cm^{-1}: 2969, 2933, 1711, 1597, 1527, 1430, 1380, 1357. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 1.37 (d, J = 6.0 Hz, 6H), 3.89 (s, 3H), 4.65 (septuplet, J = 6 Hz, 1H), 6.98 (dm, J = 9.3 Hz, 2H), 7.05 (dd, J = 2.4 Hz, 8.7 Hz, 1H), 7.13 (d, J = 2.4 Hz, 1H), 7.54 (d, J = 8.7 Hz, 1H), 8.64 (dm, J = 9.3 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 187.2 (C), 162.1 (C), 159.6 (C), 139.4 (C), 130.9 (C), 129.4 (CH), 124.6 (C), 118.6 (C), 118.2 (2 CH), 115.5 (2 CH), 115.1 (CH), 107.9 (CH), 69.9 (CH), 56.2 (CH_3), 22 (2 CH_3). MS-(+)ESI, m/z: 312 $[M + H]^+$, 334 $[M + Na]^+$, 645 $[2M + Na]^+$. MS-(−)APCI, m/z: 311 $[M^{-\bullet}]$.

2-(4-Diethylamino-phenyl)-5-methoxy-1-oxy-indol-3-one (28). Yield 3.8%; mp: 168.6−171.5 °C. IR (CH_2Cl_2) cm^{-1}: 3054, 2980, 1700, 1601, 1530, 1482, 1384, 1265. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 1.21 (t, J = 6.9 Hz, 6H), 3.43 (q, J = 6.9 Hz, 4H), 3.88 (s, 3H), 6.73 (d, J = 9.0 Hz, 2H), 7.03 (dd, J = 2.4 Hz, 8.4 Hz, 1H), 7.09 (d, J = 2.4 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 8.65 (d, J = 9.0 Hz, 2H). MS-(+)ESI, m/z: 325 $[M + H]^+$. HR-MS $[M^{+\bullet}]$ calcd for $C_{19}H_{20}N_2O_3$ 324.1474, found 324.1483.

5-Methoxy-2(4-methoxy-3-methyl-phenyl)-1-oxy-indol-3-one (29). Yield 5%; mp: 192.9−193.6 °C. UV (CH_3CN) λ_{max}: 302 nm. IR (CH_2Cl_2) cm^{-1}: 3054, 2980, 1700, 1597, 1470, 1421, 1380, 1265. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 2.28 (s, 3H),

3.90 (s, 6H), 6.93 (d, J = 8.4 Hz, 1H), 7.06 (dd, J = 2.4 Hz, 6 Hz, 1H), 7.13 (d, J = 2.4 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H),8.48 (m, 1H), 8.55 (dd, J = 2.1 and 8.4 Hz, 1H). MS-(+)ESI, m/z: 298 $[M + H]^+$; MS-(−)APCI, m/z: 297 $[M^{-\bullet}]$. HR-MS $[M^{+\bullet}]$ calcd for $C_{17}H_{15}NO_4$ 297.1001, found 297.1011.

2-(4-Amino-phenyl)-5-methoxy-1-oxy-indol-3-one (30). Yield 3.3%; mp: 183.5−190.6 °C. IR (CH_2Cl_2) cm^{-1}: 3360, 3054, 2987, 1700, 1601, 1530, 1482, 1421, 1384, 1265. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 3.88 (s, 3H), 4.07 (s, NH_2), 6.74 (d, J = 9.0 Hz, 2H), 7.04 (dd, J = 2.4 and 8.4 Hz, 1H), 7.11 (d, J = 2.4 Hz, 1H), 7.52 (d, J = 8.4 Hz, 1H), 8.58 (d, J = 9.0 Hz, 2H). MS-(+)ESI, m/z: 269 $[M + H]^+$, 559 $[2M + Na]^+$. HR-MS $[M^{+\bullet}]$ calcd for $C_{15}H_{12}N_2O_3$ 268.0848, found 268.0858.

6-Methoxy-2-(4-methoxy-phenyl)-1-oxy-indol-3-one (31). Yield 5.6%; mp: 179.3−182.0 °C. IR (CH_2Cl_2) cm^{-1}: 3054, 2986, 1741, 1600, 1545, 1421, 1380, 1265. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 3.88 (s, 3H), 3.95 (s, 3H), 6.90 (d, J = 8.1 Hz, 1H), 7.02 (d, J = 9.0 Hz, 2H), 7.23 (s, 1H), 7.53 (d, J = 8.1 Hz, 1H), 8.75 (d, J = 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 186.2 (C), 165.7 (C), 161.4 (C), 150.9 (C), 132.6 (C), 129.9 (2 CH), 123.4 (CH), 119.0 (C), 115.2 (C), 114.8 (CH), 114.1 (2 CH), 101.2 (CH), 56.3 (CH_3), 55.4 (CH_3). MS-(+)ESI, m/z: 284 $[M + H]^+$, 589 $[2M + Na]^+$. HR-MS $[M + H]^+$ calcd for $C_{16}H_{14}NO_4$ 284.0923, found 284.0900.

2-(4-Methoxy-phenyl)-1-oxy-6-trifluoromethyl-indol-3-one (32). Yield 50%; mp: 178.8−180.0 °C. IR (CH_2Cl_2) cm^{-1}: 3054, 2987, 1740, 1610, 1421, 1390, 1265. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 3.89 (s, 3H), 7.03 (dm, J = 9.3 Hz, 2H), 7.13 (d, J = 9.0 Hz, 1H), 7.80 (d, J = 9.0 Hz, 1H), 7.92 (s, 1H), 8.73 (dm, J = 9.3 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 186.0 (C), 161.9 (C), 148.2 (C), 136.5 (C), 132.9 (C), 129.9 (2 CH), 128.2 (C), 128.1 (C), 125.5 (C), 124.7 (CF_3), 121.8 (CH), 118.3 (CH), 114.3 (2 CH), 111.4 (CH), 55.4 (CH_3). MS-(+)ESI, m/z: 322 $[M + H]^+$. HR-MS $[M + H]^+$ calcd for $C_{16}H_{11}NO_3F_3$ 322.0691, found 322.0711.

6-Chloro-2-(4-methoxy-phenyl)-1-oxy-indol-3-one (33). Yield 8.8%; mp: 195−199 °C. IR (CH_2Cl_2) cm^{-1}: 3060, 2980, 1715, 1600, 1540, 1460, 1384, 1265. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 3.89 (s, 3H), 7.03 (d, J = 9.0 Hz, 2H), 7.48 (dd, J = 7.8 and 0.9 Hz, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.66 (d, J = 0.9 Hz, 1H), 8.73 (d, J = 9.0 Hz, 2H). MS-(+)ESI, m/z: 288 $[M + H]^+$, 310 $[M + Na]^+$, 597 $[2M + Na]^+$. HR-MS $[M^{+\bullet}]$ calcd for $C_{15}H_{10}NO_3Cl$ 287.0349, found 287.0352.

2-(4-Methoxy-phenyl)-6-methyl-1-oxy-indol-3-one (34). Yield 9.6%; mp: 177.6−178.4 °C. IR (CH_2Cl_2) cm^{-1}: 3040, 2980, 1699, 1600, 1527, 1499, 1435, 1378, 1299, 1264. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 2.51 (s, 3H), 3.88 (s, 3H), 7.02 (dm, J = 9.0 Hz, 2H), 7.28 (d, J = 7.8 Hz, 1H), 7.47 (s, 1H), 7.48 (d, J = 7.8 Hz, 1H), 8.73 (dm, J = 9.0 Hz, 2H). MS-(+)ESI, m/z: 268 $[M + H]^+$, 290 $[M + Na]^+$, 557 $[2M + Na]^+$. HR-MS $[M^{+\bullet}]$ calcd for $C_{16}H_{13}NO_3$ 267.0895, found 267.0894.

2-(4-Methoxy-phenyl)-1-oxy-6-trifluoromethoxy-indol-3-one (35). Yield 42%; mp: 173.6−174.4 °C. UV (CH_3CN) λ_{max}: 287 nm. IR (CH_2Cl_2) cm^{-1}: 3054, 2900, 1719, 1600, 1530, 1500, 1470, 1421, 1384, 1265. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 3.89 (s, 3H), 7.03 (dm, J = 9.0 Hz, 2H), 7.31 (d, J = 8.1 Hz, 1H), 7.54 (s, 1H), 7.65 (d, J = 8.1 Hz, 1H), 8.73 (dm, J = 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 185.7 (C), 161.8 (C), 153.9 (C), 149.8 (C), 132.9 (C), 129.9 (2 CH), 123.0 (CH), 122.1 (CH), 122.0 (C), 121.5 (CF_3), 118.5 (C), 114.2 (2 CH), 107.4 (CH), 55.4 (CH_3). MS-(+)ESI, m/z: 338 $[M + H]^+$. HR-MS $[M^{+\bullet}]$ calcd for $C_{16}H_{10}NO_4F_3$ 337.0562, found 337.0556.

2-(4-Methoxy-phenyl)-3-oxo-1-oxy-3*H*-indol-6-methyl carboxylate (36). Yield 7.2%; mp: 199.5−200.1 °C. IR (CH_2Cl_2) cm^{-1}: 3054, 2987, 1716, 1601, 1500, 1421, 1384, 1265. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 3.89 (s, 3H), 3.99 (s, 3H), 7.03 (dm, J = 9.3 Hz, 2H), 7.67 (d, J = 7.5 Hz, 1H), 8.23 (dd, J = 1.2 Hz, 7.5 Hz, 1H), 8.27 (d, J = 1.2 Hz, 1H), 8.72 (dm, J = 9.3 Hz, 1H). MS-(+)ESI, m/z: 312 $[M + H]^+$, 334 $[M + Na]^+$. HR-MS $[M^{+\bullet}]$ calcd for $C_{17}H_{13}NO_5$ 311.0794, found 311.0798.

5-Methoxy-1-oxy-2-(4-trifluoromethylphenyl)-indol-3-one (37). Yield 22.7%; mp: 192.9−193−8 °C. UV (CH_3CN) λ_{max}: 284 nm. IR (CH_2Cl_2) cm^{-1}: 3040, 2980, 1715, 1590, 1490, 1425, 1385, 1324, 1265. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 3.92 (s, 3H), 7.11 (dd, J = 2.4 and 8.4 Hz, 1H), 7.18 (d, J = 2.4 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 8.4 Hz, 2H), 8.74 (d, J = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 186.3 (C), 162.9 (C), 140.6 (C), 130.7 (C), 129.3 (C), 127.5 (4 CH), 125.4 (C), 124.9 (C), 123.8 (CF_3), 122.7 (C), 118.6 (CH), 115.8 (CH), 108.1 (CH), 56.3 (CH_3). MS-(+)ESI, m/z: 322 $[M + H]^+$. HR-MS $[M^{+\bullet}]$ calcd for $C_{16}H_{10}NO_3F_3$ 321.0613, found 321.0623.

2-(4-Acetyl-phenyl)-5-methoxy-1-oxy-indol-3-one (38). Yield 30.4%; mp: 205.3−206.1 °C. IR (CH_2Cl_2) cm^{-1}: 3054, 2980, 1680, 1596, 1480, 1415, 1384, 1265. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 2.64 (s, 3H), 3.92 (s, 3H), 7.11 (dd, J = 8.7 and 2.4 Hz, 1H), 7.18 (d, J = 2.4 Hz, 1H), 7.61 (d, J = 8.7 Hz, 1H), 8.06 (d, J = 8.4 Hz, 2H), 8.73 (d, J = 8.4 Hz, 2H). MS-(+)ESI, m/z: 296 $[M + H]^+$, 613 $[2M + Na]^+$. HR-MS $[M^{+\bullet}]$ calcd for $C_{17}H_{13}NO_4$ 295.0845, found 295.0848.

2-(3-Chlorophenyl)-5-methoxy-1-oxy-indol-3-one (39). Yield 7%; mp: 156.1−156.9 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 3.92 (s, 3H), 7.10 (dd, J = 8.4 and 2.4 Hz, 1H), 7.16 (d, J = 2.4 Hz, 1H), 7.41−7.43 (m, 2H), 7.58 (d, J = 8.4 Hz, 1H), 8.52 (m, 1H), 8.66 (s, 1H). MS-(+)ESI, m/z: 288 $[M + H]^+$, 310 $[M + Na]^+$.

Synthetic Procedure for 4′-Aryl-4-yl-trimethylsilane (39d). A mixture of trimethylsilylacetylene (5.03 mmol), triphenylphosphine (0.08 mmol), tetrakis(triphenylphosphine)palladium (0.042 mmol), and copper(I) iodide (0.13 mmol) in freshly distilled triethylamine (60 mL) was stirred for 10 min under N_2. 3-Chloro-iodobenzene (4.19 mmol) added and the mixture heated at 80 °C for 4 h. Diethylether (60 mL) was added to the cooled suspension. After filtration through a celite pad and evaporation of the solvent, an orange oily residue was obtained (965 mg). The crude product was purified by column chromatography (SiO_2) to produce a colorless oily liquid (883 mg). Yield: 100%

Synthetic Procedure for 4′-Ethynyl-aryl (39f). To a mixture of 4′-aryl-4-yl-trimethysilane (4.23 mmol) in methanol (30 mL) was added potassium carbonate (6.35 mmol). The mixture was stirred at room temperature for a night and then diluted with water (60 mL) and extracted with diethylether (120 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated to produce an orange oily liquid (443 mg). Yield: 77%

2-(3-Methyl-4-tolyl)-5-methoxy-1-oxy-indol-3-one (40). Yield 34%; mp: 167.2−169.4 °C. IR (CH_2Cl_2) cm^{-1}: 3054, 2986, 1710, 1600, 1484, 1421, 1385, 1265. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 2.32 (s, 3H), 2.34 (s, 3H), 3.91 (s, 3H), 7.06 (dd, J = 8.1 and 2.4 Hz, 1H), 7.15 (d, J = 2.4 Hz, 1H), 7.25 (d, J = 8.1 Hz, 1H), 7.56 (d, J = 8.1 Hz, 1H), 8.36 (d, J = 7.8 Hz, 1H), 8.39 (s, 1H). MS-(+)ESI, m/z: 282 $[M + H]^+$, 304 $[M + Na]^+$, 585 $[2M + Na]^+$. HR-MS $[M^{+\bullet}]$ calcd for $C_{17}H_{15}NO_3$ 281.1052, found 281.1053.

Synthetic Procedure for 4′-Aryl-4-yl-trimethysilane (40d). A mixture of 4-iodo-*o*-xylene (2.15 mmol), dichloro-bis-(triphenylphosphine)palladium (0.041 mmol), copper(I) iodide (0.0645 mmol) in freshly distilled triethylamine (5 mL) was stirred for 10 min under N_2. Trimethylsilylacetylene (3.23 mmol) added and the mixture heated at 80 °C for 2 h. After cooling, the solvent was evaporated and the crude product purified by column chromatography to produce a yellow oily liquid (386 mg). Yield: 88%

Synthetic Procedure for 4′-Ethynyl-aryl (40f). To a mixture of 4′-aryl-4-yl-trimethysilane (1.87 mmol) in methanol (5 mL) was added potassium carbonate (1.87 mmol). The mixture was stirred at room temperature for a night, diluted with water (15 mL), and extracted twice with diethylether (20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and evaporated to produce an orange oily liquid (183 mg). Yield: 75%

6.4. Synthesis by Method 3 (Compound 41). A mixture of 1-iodo-2-nitroaryl (7.12 mmol), dichloro-bis-(triphenylphosphine) palladium (0.14 mmol), and copper(I) iodide (0.36 mmol) in freshly distilled triethylamine (110 mL) was stirred for 10 min at 40 °C under N_2. Ethynyl derivative (8.54 mmol) was added, and the reaction mixture stirred at 40 °C for 6 h. After solvent evaporation, a brown solid was obtained (4.07 g). The crude product was purified by column chromatography (SiO_2) using petroleum ether/ethyl acetate (80:20 then 40/60) to produce an orange solid (1.1 g), corresponding to the uncyclized product. Yield: 58% (compound **41f** is commercially available).

Acetylation of the uncyclized product: the uncyclized product (0.75 mmol) was dissolved in dichloromethane (6 mL). DIPEA (1.16 mmol) was added and the mixture cooled to 0 °C. A solution of acetylchloride (0.83 mmol) in anhydrous dichloromethane (1 mL) added dropwise. The reaction mixture was stirred at room temperature for a night, washed with saturated $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and evaporated to produce a yellow solid (324 mg). Purification by column chromatography (SiO_2) using petroleum ether/ethyl acetate (90:10 then 50:50) produced a yellow solid (196 mg). Yield: 76%.

Cyclization of the acetylated product: the uncyclized product (0.63 mmol) was dissolved, under N_2, in anhydrous pyridine (5 mL). The reaction mixture was refluxed for 12 h, and solvent was removed. The crude product was purified by column chromatography (SiO_2) using petroleum ether/ethyl acetate (80:20 then 40:60) to give a solid (66 mg). Further purification was needed by suspending under reflux for 15 min this solid in ethanol. After cooling and filtering the suspension, a mauve solid (14 mg) was produced.

2-(4-Acetamidophenyl)-5-methoxy-1-oxy-indol-3-one (41). Yield 8%; mp: 249.1−254.1 °C. IR (CH_2Cl_2) cm^{-1}: 3320, 3054, 2980, 1690, 1585, 1485, 1420, 1384, 1265. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 2.22 (s, 3H), 3.91 (s, 3H), 7.08 (dd, J = 8.4 and 2.1 Hz, 1H), 7.14 (d, J = 2.1 Hz, 1H), 7.56−7.66 (m, 3H), 8.66 (d, J = 9 Hz, 2H). MS-(+)ESI, m/z: 333 $[M + Na]^+$. HR-MS $[M^{+\bullet}]$ Calcd for $C_{17}H_{14}N_2O_4$ 310.0954, found 310.0952.

2-(4-*tert*-Butylphenyl)-5-methoxy-1-oxy-indol-3-one (42). Yield 6%; mp: 141.7−143.6 °C. IR (CH_2Cl_2) cm^{-1}: 3054, 2980, 1690, 1600, 1483, 1415, 1384, 1265. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 1.35 (s, 9H), 3.91 (s, 3H), 7.07 (dd, J = 8.4 and 2.4 Hz, 1H), 7.16 (d, J = 2.4 Hz, 1H), 7.51−7.59 (m, 3H), 8.52 (d, J = 8.7 Hz, 2H). MS-(+)ESI, m/z: 310 $[M + H]^+$ (compound **42f** is commercially available). HR-MS $[M^{+\bullet}]$ calcd for $C_{19}H_{19}NO_3$ 309.1365, found 309.1359.

2-(2-Chlorophenyl)-5-methoxy-1-oxy-indol-3-one (43). Yield 28%; mp: 154.5−155.8 °C. UV (CH_3CN) λ_{max}: 268 nm. IR (CH_2Cl_2) cm^{-1}: 3060, 2940, 1710, 1600, 1535, 1475, 1420, 1384, 1263. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm), 3.92 (s, 3H), 7.11 (dd, J = 8.4 and 2.4 Hz, 1H), 7.21 (d, J = 2.4 Hz, 1H), 7.37 − 7.48 (m, 3H), 7.55 (dd, J = 8.4 Hz and 2.1 Hz, 1H), 7.64 (d, J = 8.1 Hz, 1H). MS-(+) ESI, m/z: 288 $[M + H]^+$, 310 $[M + Na]^+$, 597 $[2M + Na]^+$. MS-(−)APCI, m/z: 287 $[M^{-\bullet}]$. HR-MS $[M^{+\bullet}]$ calcd for $C_{15}H_{10}NO_3Cl$ 287.0349, found 287.0361.

Synthetic Procedure for 4′-Aryl-4-yl-trimethylsilane (43d). A mixture of 2-chloro-iodobenzene (6.3 mmol), tetrakis-(triphenylphosphine)palladium (0.126 mmol), and copper(I) iodide (0.19 mmol) in freshly distilled triethylamine (35 mL) was stirred for 10 min under N_2. Trimethylsilylacetylene (9.45 mmol) was added and the suspension heated at 80 °C for 4 h. After removal of the solvent and purification by column chromatography (SiO_2) using petroleum ether 100%, a yellow oily liquid (1.31 g) was produced. Yield: 100%

Synthetic Procedure for 4′-Ethynyl-aryl (43f). To a mixture of 4′-aryl-4-yl-trimethylsilane (7.7 mmol) in methanol (10 mL) was added potassium carbonate (11.55 mmol). The mixture was stirred at room temperature for 24 h and then diluted with water and extracted with diethylether. The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated to produce a yellow oily liquid (710 mg). Yield: 70%

2-(4-Chloro-3-tolyl)-5-methoxy-1-oxy-indol-3-one (44). Yield 19%; mp: 174.4−175.0 UV (CH_3CN) λ_{max}: 291 nm. IR (CH_2Cl_2) cm^{-1}: 3060, 3000, 1710, 1600, 1515, 1480, 1430, 1384, 1265. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 2.45 (s, 3H), 3.91 (s, 3H), 7.10 (dd, J = 8.4 and 2.1 Hz, 1H), 7.16 (d, J = 2.1 Hz, 1H), 7.46 (d, J = 8.1 Hz, 1H), 7.59 (d, J = 8.1 Hz, 1H), 8.42 (dd, J = 8.4 Hz and 2.1, 1H), 8.53 (s, 1H). MS-(+)ESI, m/z: 302 $[M + H]^+$, 324 $[M + Na]^+$. MS-(−)APCI, m/z: 301 $[M^{-\bullet}]$. HR-MS $[M^{+\bullet}]$ calcd for $C_{16}H_{12}NO_3Cl$ 301.0506, found 301.0504.

2-(4-Carboxymethylphenyl)-5-methoxy-1-oxy-indol-3-one (45d >) (Reaction Carried out under Microwave Conditions: 10 mn at 140 °C). Yield 2%; mp: 185.3−184.9 °C. IR (CH_2Cl_2) cm^{-1}: 3054, 3000, 1720, 1596, 1580, 1420, 1384, 1265. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 3.92 (s, 3H), 3.95 (s, 3H), 7.10 (dd, J = 8.7 and 2.1 Hz, 1H), 7.17 (d, J = 2.1 Hz, 1H), 7.59 (d, J = 8.7 Hz, 2H), 8.12 (d, J = 8.7 Hz, 2H), 8.39 (d, J = 8.4 Hz, 1H), 8.69 (d, J = 8.4 Hz, 2H). MS-(+)ESI, m/z: 312 $[M + H]^+$, 334 $[M + Na]^+$, 645 $[2M + Na]^+$. HR-MS $[M^{+\bullet}]$ calcd for $C_{17}H_{13}NO_5$ 311.0794, found 311.0794.

Synthetic Procedure for 4′-Aryl-4-yl-trimethylsilane (45d). A mixture of 4-iodo-methylbenzoate (6.25 mmol), copper(I) iodide (0.185 mmol), and dichloro-bis-(triphenylphosphine) palladium (0.125 mmol) in freshly distilled triethylamine (15 mL) was stirred under N_2. Trimethylsilylacetylene (9.58 mmol) was added and the mixture heated at 80 °C for 4 h. The suspension was cooled and evaporated. The crude product was purified by column chromatography (SiO_2) using petroleum ether/ethyl acetate (100:00 then 90:10) to produce a yellow solid (1.05 g). Yield: 72%

Synthetic Procedure for 4′-Ethynyl-aryl (45f). To a mixture of 4′-aryl-4-yl-trimethylsilane (4.52 mmol) in methanol (10 mL) was added potassium carbonate (4.52 mmol). The mixture was stirred at room temperature for 24 h and then diluted with water and diethylether. The organic layer dried over $MgSO_4$, filtered, and evaporated to produce a yellow solid (560 mg). Yield: 77%.

Synthesis of 4-Iodomethylbenzoate (Intermediate for 45d). 4-Iodobenzoic acid (8.06 mmol) was dissolved in anhydrous methanol (20 mL). Thionyl chloride (24.2 mmol) was added and the mixture refluxed for 6 h. Solvent was removed and the crude product treated with ethyl acetate and NaOH 1N. The organic layer was washed with a saturated solution of NaCl, dried over $MgSO_4$, filtered, and evaporated to produce a beige solid (139 mg). Yield: 78%.

2-(3-Methyl-4-methoxyphenyl)-5-methoxy-1-oxy-indol-3-one (46) (Reaction Carried out under Microwave Conditions: 10 mn at 150 °C). Yield 6.3%; mp: 170.8 − 171.3 °C. IR (CH_2Cl_2) cm^{-1}: 3040, 2980, 1700, 1603, 1480, 1415, 1384, 1265. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 2.31 (s, 3H), 3.84 (s, 3H), 3.91 (s, 3H), 6.87 (m, 2H), 7.07 (d, J = 9 Hz, 1H), 7.18 (d, J = 2.1 Hz, 1H), 7.33 (d, J = 9.6 Hz, 1H), 7.58 (d, J = 8.1 Hz, 1H). MS-(+)ESI, m/z: 298 $[M + H]^+$, 617 $[2M + Na]^+$ (compound **46f** is commercially available). HR-MS $[M^{+\bullet}]$ calcd for $C_{17}H_{15}NO_4$ 297.1001, found 297.1012.

2-(2-Thiophen-3-yl)-5-methoxy-1-oxy-indol-3-one (47) (Reaction Carried out under Microwave Conditions: 10 mn at 140 °C). Yield 11%; mp: 171.9−172.6 °C. IR (CH_2Cl_2) cm^{-1}: 3060, 2980, 1710, 1600, 1480, 1420, 1384, 1265. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 3.90 (s, 3H), 7.05 (dd, J = 8.1 and 3 Hz, 1H), 7.15 (d, J = 2.7 Hz, 1H), 7.43 (m, 1H), 7.55 (d, J = 8.1 Hz, 1H), 8.24 (d, J = 4.8 Hz, 1H), 8.94 (d, J = 3 Hz, 1H). MS-(+)ESI, m/z: 260 $[M + H]^+$, 282 $[M + Na]^+$ (compound **47f** is commercially available). HR-MS $[M^{+\bullet}]$ calcd for $C_{13}H_9NO_3S$ 259.0303, found 259.0298.

2-(4-Methoxyphenyl)-6-nitro-1-oxy-indol-3-one (48) (Reaction Carried out under Microwave Conditions: 30 mn at 140 °C). Yield 48%; mp: 266.9−270.3 °C. IR (CH_2Cl_2) cm^{-1}: 3050, 2980, 1715, 1596, 1520, 1410, 1383, 1265. ^1H NMR ($(CD_3)_2SO$, 300 MHz) δ (ppm) 3.87 (s, 3H), 7.18 (d, J = 8.1 Hz, 2H), 7.92 (d, J = 6 Hz, 1H), 8.21 (d, J = 1.8 Hz, 1H), 8.46 (m, 1H), 8.60 (d, J = 7.5 Hz, 2H). MS-(+)ESI, m/z: 299 $[M + H]^+$. HR-MS $[M^{+\bullet}]$ calcd for $C_{15}H_{10}N_2O_5$ 298.0590, found 298.0591.

Synthetic Procedure for 4′-Aryl-4-yl-trimethylsilane (48d). A mixture of 4-bromo-anisole (29.9 mmol), tetrakis(triphenylphosphine)palladium (0.595 mmol), and copper(I) iodide (1.497 mmol) in freshly distilled triethylamine (15 mL) was stirred for 10 min under N_2. Trimethylsilylacetylene (44.9 mmol) was added dropwise. The suspension was heated to 80 °C for 3 days. Solvent was removed. The crude product was purified by column chromatography (SiO_2) using petroleum ether 100% as an elutent to produce a yellow solid (2.61 g). Yield: 46%

Synthetic Procedure for 4-Ethynyl-aryl (48f). To a mixture of 4′-aryl-4-yl-trimethylsilane (11.94 mmol) in methanol (105 mL) was added potassium carbonate (17.91 mmol). The suspension stirred at room temperature for 18 h and then diluted with water (215 mL) and extracted with diethylether (400 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated to produce a yellow oily liquid (344 mg). Yield: 22%

2-(3-Thiophene)-6-chloro-3*H*-indol-3-one-*N*-oxide (55). Yield 3%. R_f 0.61 (cyclohexane/ethyl acetate, 80/20, v/v); mp: 174 °C. UV (DMF) λ_{max} nm (ε L·mol^{-1}·cm^{-1}): 293 (nd). IR (KBr) cm^{-1}: 1715, 1600, 1541, 1499, 1458, 1425, 1363, 1346, 1204. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 9.15 (s, 1H), 8.26 (d, J = 6.0 Hz, 1H), 7.67 (s, 1H), 7.47−7.51 (m, 2H), 7.52 (d, J = 3.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 184.9 (C), 148.9 (C), 141.3 (2C), 130.8 (CH), 130.0 (CH), 126.0 (CH), 125.9 (CH), 122.7 (CH), 121.1 (2C), 115.1 (CH).

Intermediate 4-Iodo-3-nitrobenzyloxybenzene (57e−58e). To a mixture of 4-iodo-3-nitro-phenol (3 mmol), benzyle chloride (6 mmol), and ethanol (5 mL) was added pulverized anhydrous K_2CO_3 (2.3 mmol). The reaction was stirred at 60 °C during 15 h. The reaction mixture was filtered and the precipitate was washed with ethyl acetate (100 mL). The filtrate was washed with the brine solution (2 × 100 mL) and then dried on Na_2SO_4. The crude product obtained after evaporation was purified by recrystallization from cyclohexane. Yield 67%. R_f 0.64 (cyclohexane/ethyl acetate 85:15, v/v).

2-(6-Phenoxyphenyl)-6-benzyloxy-3*H*-indol-3-one-*N*-oxide (57old >). Yield 4%. R_f 0.46 (cyclohexane/ethyl acetate, 85:15, v/v); mp: 148 °C. UV (DMF) λ_{max} nm (ε L·mol^{-1}·cm^{-1}): 288 (44536). IR (KBr) cm^{-1}: 1707, 1643, 1586, 1527, 1493, 1378, 1284, 1247. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 10.13 (d, J = 9.0 Hz, 2H), δ (ppm) 9.85 (s, 1H), 8.66−8.72 (m, 4H), 8.47−8.59 (m, 4H), 8.28−8.35 (m, 5H), 8.21 (dd, J = 2.1 and 8.1 Hz, 1H), 6.05 (s, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 187.0 (C), 165.8 (C), 160.6 (C), 157.2 (C), 151.9 (C), 137.4 (C), 133.3 (C), 131.5 (2CH), 131.2 (2CH), 130.0 (2CH), 129.6 (CH), 129.1 (2CH), 125.7 (CH), 124.7 (CH), 122.7 (C), 121.2 (2CH), 119.0 (2CH), 117.1 (CH), 116.8 (C), 103.5 (CH), 72.0 (CH_2). MS-(−)APCI, m/z: 421 [M$^{-\cdot}$]. HR-MS [M$^{+\cdot}$] calcd for $C_{27}H_{19}NO_4$ 421.1314, found 421.1322.

2-(6-Methoxynaphtyl)6-benzyloxy-3*H*-indol-3-one-*N*-oxide (58). Yield 7%. R_f 0.32 (cyclohexane/ethyl acetate, 85:15, v/v); mp: 192 °C. UV (DMF) λ_{max} nm (ε L·mol^{-1}·cm^{-1}): 275 (47086). IR (KBr) cm^{-1}: 1702, 1620, 1466, 1388, 1304, 1268. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 9.65 (s, 1H), 9.04 (dd, J = 1.5 Hz, J = 9.0 Hz, 2H), 7.94 (d, J = 9.0 Hz, 1H), 7.89 (d, J = 9.0 Hz, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 2.0 Hz, 1H), 7.27−7.30 (m, 2H), 7.36 (t, J = 7.0 Hz, 1H), 7.43 (t, J = 8.0 Hz, 2H), 7.09 (dd, J = 1.5 Hz, J = 9.0 Hz, 2H), 5.23 (s, 2H), 3.78 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 186.1 (C), 164.7 (C), 159.6 (C), 150.0 (C), 136.3 (C), 135.9 (C), 133.1 (C), 131.1 (CH), 128.7 (2CH), 128.6 (C), 128.6 (CH), 128.0 (2CH), 127.1 (CH), 124.9 (CH), 123.7 (CH), 123.6 (CH), 122.2 (C), 119.7 (CH), 115.8 (C), 116.0 (CH), 106.2 (CH), 102.4 (CH), 70.9 (CH_2), 55.2 (CH_3). MS-(+)APCI, m/z: 410 [M + H]$^+$.

2-(4-Chloro-3-trifluoromethyl-phenyl)-1-oxy-indol-3-one (59). Yield 19%; mp: 205.1−205.2 °C. IR (CH_2Cl_2) cm^{-1}: 3040, 1705, 1590, 1510, 1420, 1384, 1265. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.58−7.78 (m, 5H), 8.81 (dd, J = 2.1 and 8.7 Hz, 1H), 9.13 (d, J = 2.1 Hz, 1H). MS-(+)ESI, m/z: 326 [M + H]$^+$. HR-MS [M$^{+\bullet}$] calcd for $C_{15}H_7NO_2ClF_3$ 325.0117, found 325.0130.

2-(4-Ethyl-phenyl)-1-oxy-indol-3-one (60). Yield 31%; mp: 178.4−178.6 °C. UV (CH_3CN) λ_{max} nm (ε L·mol^{-1}·cm^{-1}): 294 (20845). IR (CH_2Cl_2) cm^{-1}: 3060, 2980, 1700, 1595, 1535, 1490, 1420, 1384, 1265. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 1.27 (t, J = 7.5 Hz, 3H), 2.70 (q, J = 7.5 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.50−7.58 (m, 1H), 7.62−7.70 (m, 3H), 8.58 (d, J = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 187.2 (C), 147.9 (C), 147.6 (C), 134.8 (CH), 132 (C), 130.9 (CH), 128.2 (2 CH), 127.9 (2 CH), 123.3 (C), 122.9 (C), 121.6 (CH), 114.1 (CH), 29.1 (CH_2), 15.2 (CH_3). MS-(+)ESI, m/z: 252 [M + H]$^+$. HR-MS [M + H]$^+$ calcd for $C_{16}H_{14}NO_2$ 252.1025, found 252.1034.

1-Oxy-2-(4-trifluoromethyl-phenyl)indol-3-one (61). Yield 18%; mp: 210.0−210.3 °C. UV (CH_3CN) λ_{max} nm (ε L·mol^{-1}·cm^{-1}): 291 (11516). IR (CH_2Cl_2) cm^{-1}: 3054, 2980, 1705, 1590, 1540, 1495, 1420, 1384, 1265. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.56−7.77 (m, 6H), 8.78 (d, J = 7.8 Hz, 2H). MS-(+)ESI, m/z: 292 [M + H]$^+$. HR-MS [M$^{+\bullet}$] calcd for $C_{15}H_8NO_2F_3$ 291.0507, found 291.0505.

5,6-Dimethoxy-1-oxy-2-phenyl-indol-3-one (62). Yield 7%. IR (KBr) cm^{-1}: 2939, 2835, 1740, 1700, 1647, 1593, 1568, 1519, 1435, 1330, 1300. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 3.97 (s, 3H), 4.04 (s, 3H), 7.14 (s, 1H), 7.27 (s, 1H), 7.42−7.54 (m, 3H), 8.60−8.64 (m, 2H). MS-(+)ESI, m/z: 284 [M + H]$^+$, 306 [M + Na]$^+$. HR-MS [M + H]$^+$ calcd for $C_{16}H_{14}NO_4$ 284.0923, found 284.0930.

5-Oxy-6-phenyl-[1,3]dioxolo-[4,5-*f*]indol-7-one (63). Yield 28%; mp: 175.5−176.9 °C. UV (CH_3CN) λ_{max}: 268 nm. IR (CH_2Cl_2) cm^{-1}: 2980, 2900, 1700, 1590, 1520, 1490, 1460, 1384, 1275. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 6.15 (m, 2H), 7.04 (s, 1H), 7.19 (s, 1H), 7.45−7.49 (m, 3H), 8.59 (d, J = 6.9 Hz, 2H). MS-(+)ESI, m/z: 268 [M + H]$^+$, 290 [M + Na]$^+$; MS-(−)ESI, m/z: 267 [M$^-$]. HR-MS [M + H]$^+$ calcd for $C_{15}H_{10}NO_4$ 268.0610, found 268.0621.

2-(4-Chlorophenyl)-1-oxy-indol-3-one (64). Yield 20%; mp: 177.0−177.1 °C. UV (CH_3CN) λ_{max}: 280 nm. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.46 (d, J = 12.0 Hz, 2H), 7.54−7.61 (m, 1H), 7.64−7.73 (m, 3H), 8.66 (d, J = 12.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 186.7 (C), 147.8 (C), 136.7 (C), 135 (CH), 131.9 (C), 131.4 (CH), 128.98 (2 CH), 128.91 (2 CH), 124.4 (C), 122.7 (C), 121.8 (CH), 114.3 (CH). MS-(+)ESI, m/z: 258 [M + H]$^+$; MS-(−)APCI, m/z: 257 [M$^{-\bullet}$]. HR-MS [M + H]$^+$ calcd for $C_{14}H_9NO_2Cl$ 258.0322, found 258.0329.

2-(4-Chlorophenyl)-1,5-dioxypyrrolo(3,2-*c*)pyridine (65). Yield 29.3%; mp: 242−243 °C. ^{1}H NMR ($(CD_3)_2SO$, 300 MHz) δ (ppm) 7.67 (d, J = 8.7 Hz, 2H), 7.76 (d, J = 6.3 Hz, 1H), 8.5 (d, J = 8.7 Hz, 3H), 8.63 (s, 1H). MS-(+)ESI, m/z: 275 [M + H]$^+$. HR-MS [M$^{+\bullet}$] calcd for $C_{13}H_7N_2O_3Cl$ 274.0145, found 274.0140.

2-(4-Chlorophenyl)-1-oxy-pyrrolo[3,2-*b*]pyridin-3-one (66). Yield 75.2%; mp: 196−197 °C. UV (CH_3CN) λ_{max} nm (ε L·mol^{-1}·cm^{-1}) 293 (25066). IR (CH_2Cl_2) cm^{-1}: 3040, 1710, 1590, 1525, 1480, 1420, 1384, 1265. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.48 (d, J = 8.4 Hz, 2H), 7.59 (dd, J = 5.1 Hz, 7.8 Hz, 1H), 8.00 (d, J = 7.8 Hz, 1H), 8.66 (d, J = 8.4 Hz, 2H), 8.82 (d, J = 5.1 Hz, 1H). MS-(+)ESI, m/z: 259 [M + H]$^+$.

Intermediate 4-Chloro-biphenyle Used to Synthesize (21c). Iodobenzene (10.0 mmol), 4-chlorophenylboronic acid (14 mmol), palladium acetate (0.3 mmol), 1,4-diazabicyclo-(2,2,2)octane (0.6 mmol), and potassium carbonate were dissolved in DMF (7 mL) and mixed with acetone (110 mL). The mixture was kept under reflux for 7 h. It was then concentrated by evaporation. The residue was subsequently resuspended in water and extracted 3 times by dichloromethane. The organic phases were collected and washed once with water and then dried over anhydrous $MgSO_4$, filtered, and evaporated. The crude product was purified by column chromatography (SiO_2) using petroleum ether as an eluant. Yield 58%.

Intermediate 4-Chloro-4′-iodo-biphenyle (21c). To a mixture of 4-chloro-biphenyle (5.7 mmol), acetic acid (2.4 mL), iodine (2.86 mmol), and sulphuric acid (0.66 mL) was added dropwise

fuming nitric acid (0.115 mL). The mixture was stirred at 35−40 °C for 18 h and then diluted in a mixture of water/dichloromethane. The organic phase was washed with water until pH 4−5 and then dried with $MgSO_4$, filtered, and concentrated by evaporation. The residue was purified by column chromatography (SiO_2) using petroleum ether as an eluant. Yield 74%.

Intermediate 1-Iodo-4-isopropoxy-benzene (27c). To a mixture of 4-iodophenol (3.95 mmol) in DMF (7 mL), isopropyl bromide (4.34 mmol) and potassium carbonate (4.42 mmol) were added. The reaction was stirred under reflux for 4 h. The crude product obtained after evaporation was dissolved in a mixture of petroleum ether and sodium hydroxide 1 N (50:50, v/v). The organic phase dried over anhydrous $MgSO_4$, filtered, evaporated, and purified by column chromatography (SiO_2) using petroleum ether as an eluant. Yield 55%.

General Synthetic Procedure for Intermediate 4′-Aryl-4-yl-trimethylsilane (21d, 27d, 29d, 59d). To a mixture of 4-halogeno-aryl (1.59 mmol) and trimethylsilylacetylene (2.39 mmol) in triethylamine (10 mL) were added tetrakis(triphenylphosphine)palladium (0.0239 mmol) and copper(I) iodide (0.0477 mmol). The mixture was stirred at 80 °C for 4 h. After evaporation, the residue was purified by column chromatography (SiO_2) using petroleum ether as an eluant.

General Synthetic Procedure for Intermediate 4′-Ethynyl-aryl (21f, 27f, 29f, 59f). To a mixture of 4′-aryl-4-yl-trimethylsilane (1.2 mmol) in methanol (20 mL) was added potassium carbonate (0.192 mmol). The mixture was stirred at room temperature for a night. The mixture was diluted in dichloromethane. The organic phases were then washed with a saturated solution of sodium bicarbonate, dried over anhydrous $MgSO_4$, filtered, and evaporated. The pure product was purified by column chromatography (SiO_2) eluant petroleum ether.

General Synthetic Procedure for Intermediate *o*-Bromo-nitroaryl (52e, 53e). To a mixture of acetic acid (210 mL) and fuming nitric acid (46 mL) cooled in ice was added dropwise *o*-bromobenzaldehyde (46 mmol) for 20 min in keeping the temperature below 10 °C. The mixture was stirred at 10 °C for 2 h, and then kept in a mixture of ice/water. The precipated product was filtered and washed several times with water and then dried.

6.4. Determination of Log P. Values of Log P_{calc} were calculated with software from Virtual Computational Chemistry Laboratory (VCCLAB http://www.virtuallaboratory.org/lab/alogps/start.html).

6.5. *P. falciparum* in Vitro Culture and Parasite Growth Inhibition Assays. 6.5.1. Initial Testing Carried out in Toulouse (France). RPMI 1640 medium (BioWhittaker, Cambrex (cat. no. BE12-702F), Belgium) containing L-glutamine (BioWhittaker, cat. no. BE17-605E), 25 mM HEPES (BioWhittaker, cat no. 17-737F), and 10% human serum (EFS, Toulouse, France) was used to cultivate *P. falciparum*. Human RBCs (group O±) for parasite culture were obtained from EFS in transfusion vials. They were extensively washed with RPMI medium to discard plasma and leukocytes. Leucocyte-free erythrocytes were stored at 50% hematocrit (1 volume of RPMI + 1 volume of packed RBC) for a maximum period of 21 days. *P.f.* asexual blood stage parasites were propagated by incubation at 37 °C in *P.f.* culture media at 3−5% hematocrit in controlled atmosphere (5% CO_2, 100% relative humidity).[33] Parasitized RBCs were maintained in 25 cm^2 culture flasks (TPP, Switzerland, ref 90025). Reference drugs, chloroquine (CQ), and artemether (ART) were obtained from Sigma (ref C6628) and Cambrex, respectively. CQ was dissolved in culture medium and ART in ethanol (stock solutions: 10 mg/mL) and stored at −20 °C prior to testing. For drug assays, serial drug dilutions were made in *P.f.* culture media and added to 96-well (TPP) culture plates. All drugs were tested in triplicate. *Plasmodium*-infected RBCs were distributed at 2% parasitaemia (2% hematocrit) in 96-well microtiter plates with different drug concentrations and incubated for 48 h at 37 °C and 5% of CO_2. [^{3}H]-Hypoxanthine (Perkin-Elmer) was added 24 h after the beginning of incubation. At the end of incubation (48 h), microtiter plates were frozen and thawed, and each well was harvested onto a glass-fiber filter paper. The quantity of incorporated [^{3}H]-hypoxanthine was determined with a β-counter (1450-Microbeta Trilux, Wallac-PerkinElmer). Growth-inhibition percentages were plotted as a semilogarithmic function of drug concentration. The IC_{50} values were determined by linear regression analysis on the linear segments of the curves. Assays were repeated three times. Controls were carried out to assess the background (negative control) and parasite growth (positive control).

6.5.2. Secondary Testing Carried out in London (U.K.). Drug-sensitive 3D7 clone of the NF54 isolate (unknown origin) and chloroquine-, pyrimethamine-, and cycloguanil-resistant K1 strain (Thailand) came from MR4 (Malaria Research and Reference Reagent Resource Center, Manassas, VA). Parasites were maintained in tissue culture flasks in blood group A^+ human RBCs at 5% hematocrit in RPMI-1640 supplemented with 25 mM HEPES, 24 mM $NaHCO_3$, 0.2% w/v glucose, 0.03% L-glutamine, 150 μM hypoxanthine, and 0.5% Albumax II (Gibco, UK) in a 5% CO_2 incubator at 37 °C and the medium changed daily. Synchronization was achieved by a combination of 5% sorbitol and 60% Percoll gradient centrifugation as described elsewhere. The method used to assess parasite growth was based on the [^{3}H]hypoxanthine incorporation assay (with modifications, including the use of Albumax, rather than 10% human plasma, to supplement the culture medium.

Stock drug solutions were usually dissolved in 100% dimethylsulfoxide (Sigma, Dorset, UK) and a 2-fold dilution series (100, 50, 25, 12.5, 6.25, 3.125, 1.56, 0.78, 0.39, 0.20, 0.10, and 0.05 μM) of the drugs prepared in assay medium (RPMI-1640 supplemented with 0.5% Albumax II [Invitrogen], 0.2% w/v glucose, 0.03% L-glutamine, and 5 μM hypoxanthine) added to each well of 96-well plates in triplicate. Fifty μL of synchronous *P.f.* culture (0.5% parasitaemia) or uninfected RBCs were added to each well to a final hematocrit of 2.5%. All assays included chloroquine diphosphate (Sigma) and artesunate (WHO/TDR) as control drugs and control wells with untreated infected RBCs and uninfected RBCs.

Test plates were incubated at 37 °C in 5% CO_2, 95% air mixture for 24 h, at which point 20 μL (0.1 μCi/well) of [^{3}H]-hypoxanthine (Perkin-Elmer, Hounslow, UK) were added to each well. After shaking for 1 min using a plate shaker, the plates were returned to the incubator and incubated for an additional 24 h. The experiment was terminated by placing the plates in a −80 °C freezer.

Plates were thawed and harvested onto glass-fiber filter mats using a 96-well cell harvester (Harvester 96, Tomtec, Oxon, UK) and left to dry. After the addition of MeltiLex solid scintillant (PerkinElmer, Hounslow, UK), the incorporated radioactivity was counted using a Wallac 1450 Betalux scintillation counter (Wallac). Data acquired by the Wallac BetaLux scintillation counter were transferred onto a MICROSOFT EXCEL spreadsheet (Microsoft Corp.), and the IC_{50}/IC_{90} values of each drug were calculated by using XLFit (ID Business Solutions Ltd., UK) line fitting software.

6.6. In Vitro Cytotoxicity Assay. Cytotoxicity was estimated on human breast cancer cells (MCF7) at a primary level (Toulouse, France), The cells were cultured in the same conditions as those used for *P. falciparum*, except that 10% human serum was replaced by 10% fetal calf serum (Cambrex). After trypsinization, cells were distributed in 96-well plates at 2×10^4 cells/well in 100 μL of culture medium added to 100 μL of the same medium containing the tested compounds at various concentrations (the final concentrations in the wells were 1, 10, and 100 μg/mL).

Cell growth was estimated by a colorimetric assay based on XTT reduction.[34] After 48 h of contact between cells and test compounds, the culture medium was replaced by 50 μL of a

sodium 2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-2*H*-tetrazolium-5-carboxanilide inner salt (XTT) (Sigma, Saint Quentin Fallavier, France) in water solution (0.5 mg/mL), and cells were incubated for 180 min. XTT was converted into a formazan product, detected at 450 nm. IC_{50} values were determined graphically from dose−response curves (positive control being doxorubicin [Sigma]). Experiments were performed twice in triplicate

Cytotoxicity was evaluated on KB cell line at a secondary level (London, UK). The AlamarBlue (Accumed International Inc., USA) method was used to assess cytotoxicity to the KB cell line. Microtiter plates were seeded at a density of 4×10^4 KB cells/mL in RPMI 1640 culture medium supplemented with 10% heat-inactivated fetal calf serum (complete medium) (Seralab, Inc.) and incubated at 37 °C, 5% CO_2, 95% air mixture for 24 h, followed by compound addition to triplicate wells in a dilution series in complete medium. The positive control drug was podophyllotoxin (Sigma). Plates were incubated for a further 72 h, followed by the addition of 10 μL of Alamar-Blue (AccuMed International Inc.) to each well and incubation for 2−4 h at 37 °C, 5% CO_2, 95% air mixture. Fluorescence emission at 585 nm was measured in a SPECTRAMAX GEMINI plate reader (Molecular Devices Inc.) after excitation at 530 nm. ED_{50} values were calculated using XLFit (ID Business Solutions Ltd., UK) line fitting software.

6.7. In Vivo Assays. In vivo studies were approved by the appropriate institutional animal care and use committee.

The Primary Assay (Toulouse, France) with compound **1** of in vivo antimalarial efficacy was achieved using the *P. berghei* rodent malaria 4-day suppressive test. The compound was dissolved in 100% dimethyl sulfoxide (DMSO).

Animal and Conditions: mice, Swiss females, 20 ± 2 g; series: 10 animals per cage; control group: 10 animals; cages: standard; maintenance: conditioned air at 20 °C and 50−60% relative humidity; diet with standard food and water ad libitum.

Test Procedure, Day 0: Heparinized blood was taken from a donor mouse with approximately 30% parasitaemia and diluted in physiological saline to 10^8 parasitized RBC per mL. An aliquot of 0.1 mL (10^7 parasitized RBC) of this suspension was injected intraperitoneally (ip) into experimental groups of 10 mice. Two h postinjection, the experimental groups were treated with a single dose of test compound, prepared in appropriate dilution in DMSO of the stock solution in DMSO, by intraperitoneally (ip) route; compound **1** was tested at six different doses.

Day 1 to 3: 24, 48, and 72 h postinjection, the experimental group of mice were retreated again with the same dose and by the same route as on day 0.

Day 4: 24 h after the last treatment (i.e., 96 h postinjection), blood smears from all animals were prepared and stained with Giemsa. Parasitaemia was determined microscopically by counting 20 fields at approximately 100 RBC per field.

Activity was expressed as the difference between the mean value of the control group (taken as 100%) and those of the experimental group and calculated and expressed as percentage reductions (= activity) using the following equation:

$$\text{activity} = 100 - \left(\frac{\text{mean} - \text{parasitemia} - \text{treated}}{\text{mean} - \text{parasitemia} - \text{control}} \times 100 \right)$$

Other Assays were made in LSHTM with similar protocols (London, UK).

Full Suppressive 4-Day Peters' Test: In vivo tests were performed under the UK Home Office Animals (Scientific Procedures) Act 1986. The rodent malaria line used was the *P. berghei* ANKA (drug-susceptible). Swiss outbred 20 g male CD-1 mice (Charles Rivers, UK), were kept in specific pathogen-free conditions and fed ad libitum. For oral administration, compounds were dissolved in standard suspending formula (SSV) [0.5% sodium carboxymethylcellulose, 0.5% benzyl alcohol, 0.4% Tween 80, 0.9% NaCl (all Sigma)]. For intraperitoneal administration, compounds were dissolved in 0.05% Tween 80. Mice were infected intravenously with 2×10^6 infected red cells, randomized, and divided in groups of five mice for each dose (day 0). Oral treatment by gavage started 3 h postinfection and continued on day 1, 2, and 3 postinfection once a day. Parasitaemia was determined by microscopic examination of Giemsa stained blood films taken on day 4. Microscopic counts of blood films from each mouse were exported into a Microsoft Excel spreadsheet (Microsoft Corp.) and expressed as percentages of inhibition from the arithmetic mean parasitaemias of each group in relation to the untreated group. Dose−response curves were obtained and ED_{50} and ED_{90} values and 95% CI calculated using XLFit version 4 (ID Business Solutions Ltd., UK) line fitting software.

Acknowledgment. This work was supported by the European Union (Redox Antimalarial Drug Discovery, Read-Up, FP6-2004-LSH-2004-2.3.0-7, Strep no. 018602). Thanks are due to the Fondation Pierre Fabre for awarding a fellowship to S.K. We thank E. Pelissou, E. Augugliaro, S. Vomshied, A. Lallemand, A. Boyer, P. Lajoie, E. Najahi, S. Casties, B. Moukarzel, and Shereen Nasser for technical assistance.

Supporting Information Available: Hematin binding assays, metabolism of some selected compounds by liver microsomes, lactate dehydrogenase (LDH) assay, elemental analysis for some compounds, selected ^1H, ^{13}C NMR, and IR spectra, and references cited. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Biot, C.; Chibale, K. Novel approaches to antimalarial drug discovery. *Infect. Dis.: Drug Targets* **2006**, *6*, 173–204.
(2) Lanteri, C. A.; Johnson, J. D.; Waters, N. C. Recent advances in malaria drug discovery. *Recent Pat. Anti-Infect. Drug Discovery* **2007**, *2*, 95–114.
(3) Jochen, W.; Regina, O.; Hasson, J.; Martin, S. New antimalarial drugs. *Angew. Chem., Int. Ed.* **2003**, *42*, 5274–5293.
(4) Padmanaban, G.; Nagaraj, V. A.; Rangarajan, P. N. Drugs and drugs target against malaria. *Curr. Sci.* **2007**, *92*, 1545–1555.
(5) Krishna, S.; Bustamante, L.; Haynes, R. K.; Staines, H. M. Artemisinins: their growing importance in medicine. *Trends Pharmacol. Sci.* **2008**, *29*, 520–527.
(6) Aldana, I.; Ortega, M. A.; Jaso, A.; Zarranz, B.; Oporto, P.; Gimenez, A.; Monge, A.; Deharo, E. Anti-malarial activity of some 7-chloro-2-quinoxalinecarbonitrile-1,4-di-*N*-oxide derivatives. *Pharmazie* **2003**, *58*, 68–69.
(7) Marin, A.; Lima, L. M.; Solano, B.; Vicente, E.; Silanes, S. P.; Maurel, S.; Sauvain, M.; Aldana, I.; Monge, A.; Deharo, E. Antiplasmodial structure−activity relationship of 3-trifluoromethyl-2-arylcarbonylquinoxaline 1,4-di-*N*-oxide derivatives. *Exp. Parasitol.* **2008**, *118*, 25–31.
(8) Zarranz, B.; Jaso, A.; Aldana, I.; Monge, A.; Maurel, S.; Deharo, E.; Jullian, V.; Sauvain, M. Synthesis and antimalarial activity of new 3-arylquinoxaline-2-carbonitrile derivatives. *Arzneim. Forsch.* **2005**, *55*, 754–761.
(9) Zarranz, B.; Jaso, A.; Lima, L. M.; Aldana, I.; Monge, A.; Maurel, S.; Sauvain, M. Antiplasmodial activity of 3-trifluoromethyl-2-carbonylquinoxaline di-*N*-oxide derivatives. *Braz. J. Pharm. Sci.* **2006**, *42*, 357–361.
(10) Vicente, E.; Lima, L. M.; Bongard, E.; Charnaud, S.; Villar, R.; Solano, B.; Burguete, A.; Perez-Silanes, S.; Aldan, I.; Vivas, L.; Monge, A. Synthesis and structure−activity relationship of 3-phenylquinoxaline 1,4-di-*N*-oxide derivatives as antimalarial agents. *Eur. J. Med. Chem.* **2008**, *43*, 1903–1910.
(11) Génisson, V. B.; Bouniol, A. V.; Nepveu, F. A new general approach for the synthesis of 2-substisuted-3*H*-indol-3-one-*N*-oxide derivation. *Synlett* **2001**, *5*, 700–702.
(12) Boyer, J.; Génisson, V. B.; Nepveu, F. Access to unsymmetrical 1,2-diketone intermediates via benzeneseleninic anhydride-promoted oxidation: application to indolone-*N*-oxide synthesis. *J. Chem. Res.* **2003**, *8*, 507–508.

(13) Boyer, J.; Bernardes-Genisson, V.; Farines, V.; Souchard, J. P.; Nepveu, F. 2-Substituted-3*H*-indol-3-one-1-oxides: preparation and radical trapping properties. *Free Radical Res*. **2004**, *38*, 459–471.
(14) Lunazzi, L.; Pedulli, G. F.; Maccagnasi, G.; Mangini, A. Electron spin resonance study of free radicals thermally generated from isatogens. *J. Chem. Soc B* **1967**, 1072–1076.
(15) Cerecetto, H.; Gonzalez, M. *N*-Oxides as hypoxia selective cytotoxins. *Mini-Rev. Med. Chem*. **2001**, *1* (3), 219–223.
(16) Danieli, R.; Maccagnani, G.; Isatogens. II. Reduction of 2-aryl isatogens by thioalcohols and thiophenols. *Boll. Sci. Fac. Chim. Ind. Bologna* **1965**, *23*, 353–358.
(17) Gerpe, A.; Aguirre, G.; Boiani, L.; Cerecetto, H.; González, M.; Olea-Azar, C.; Rigol, C.; Maya, J. D.; Morello, A.; Piro, O. E.; Arán, V. J.; Azqueta, A.; López de Ceráin, A.; Monge, A.; Rojas, M. A.; Yaluff, G. Indazole *N*-oxide derivatives as antiprotozoal agents: synthesis, biological evaluation and mechanism of action studies. *Bioorg. Med. Chem*. **2006**, *14*, 3467–3480.
(18) Aguirre, G.; Cerecetto, H.; Di Maio, R.; González, M.; Seoane, G.; Denicola, A.; Ortega, M. A.; Aldana, I.; Monge, A. Benzo[1, 2-*c*]1,2,5-oxadiazole *N*-oxide derivatives as potential antitrypanosomal drugs. Structure−activity relationships. Part II. *Arch. Pharm*. **2002**, *335*, 15–21.
(19) Sahasrabudhe, A. B.; Kamath, H. V.; Bapat, B. V.; Sheshgiri, N. K. Antitubercular agents: Part III—Synthesis of substituted 2-arylisatogens. *Indian J. Chem*. **1980**, *19B*, 230–232.
(20) Hooper, M; Patterson, D. A.; Wibberley, D. G. Preparation and antibacterial activity of isatogens and related compounds. *J. Pharm. Pharmacol*. **1965**, *17*, 734–741.
(21) Rosen, G. M.; Tsai, P.; Barth, E. D.; Dorey, G.; Casara, P.; Spedding, M.; Halpern, H. J. A one-step synthesis of 2-(2-pyridyl)-3*H*-indol-3-one *N*-oxide: Is it an efficient spin trap for hydroxyl radical? *J. Org. Chem*. **2000**, *65*, 4460–4463.
(22) Sonogashira, K.; Tohda, Y.; Hagihara, N. A convenient synthesis of acetylenes: catalytic substitutions of acetylenic hydrogen with bromoalkenes, iodoarenes and bromopyridines. *Tetrahedron Lett*. **1975**, *16*, 4467–4470.
(23) Elangovan, A.; Wang, Y. H.; Ho, T. I. Sonogashira coupling reaction with diminished homocoupling. *Org. Lett*. **2003**, *5*, 1841–1844.
(24) Kim, S. Ph.D. thesis. 09−11−2007, no. TOU3-5139084. Université Toulouse-3, Toulouse, France, **2007**.
(25) Bond, C. C.; Hooper, M. Isatogens Part VI. Synthesis of isatogens via tolan (diphenylacetylene) intermediates. *J. Chem. Soc. C* **1969**, 2453–2460.
(26) Suvilo, I.; Bruskstus, A.; Tumkevicius, S. The first synthesis of novel 7-oxo-7H-pyrrolo[3,2-*d*]-pyrimidine 5-oxide from 1-(5-nitro-6-pyrimidinyl)-2-arylacetylenes. *Synlett* **2003**, *8*, 1151–1152.
(27) Berry, D. J.; Di Giovanna, C. V.; Metrick, S. S.; Murugan, R. Catalysis by 4-dialkylamino-pyridines. *Arkivoc*, **2001**, (i), 201−226.
(28) Naoki, A.; Kenichiro, S.; Yoshinori, Y. $AuBr_3$-catalyzed cyclisation of *O*-(alkynyl)nitrobenzenes. Efficient synthesis of isatogens and anthranils. *Tetrahedron Lett*. **2003**, *44*, 5675–5677.
(29) *ALOGPS 21*; http://www.virtuallaboratory.org/lab/alogps/; access date 10−11 July 2009.
(30) Adams, D. B.; Hooper, M.; Christopher, J. S.; Raper, S. E.; Stoddart, B. Isatogens: crystal structure, electron density calculations and ^{13}C nuclear magnetic resonance spectra. *J. Chem. Soc., Perkin Trans 1* **1986**, *6*, 1005–1010.
(31) Deharo, E.; Garcia, R. N.; Oporto, P.; Gimenez, A.; Sauvain, M.; Jullian, V.; Ginsburg, H. A non-radiolabelled ferriprotoporphyrin IX biomineralisation, inhibition test for the high throughput screening of antimalarial compounds. *Exp. Parasitol*. **2002**, *100*, 252–256.
(32) Guillon, J.; Grellier, P.; Labaied, M.; Sonnet, P.; Leger, J. M.; Deprez-Poulain, R.; Forfar-Bares, I.; Dallemagne, P.; Lemaitre, N.; Pehourcq, F.; Rochette, J.; Sergheraert, C.; Jarry, C. Synthesis, antimalarial activity, and molecular modeling of new pyrrolo[1,2-*a*]quinoxalines, bispyrrolo[1,2-*a*]quinoxalines, bispyrido[3,2-*e*]pyrrolo[1,2-*a*]pyrazines, and bispyrrolo[1,2-*a*]thieno[3,2-*e*]pyrazines. *J. Med. Chem*. **2004**, *47*, 1997–2009.
(33) Benoit, F.; Valentin, A; Pélissier, Y.; Diafouka, F.; Marion, C.; Kone-Bamba, D.; Koné, M.; Mallié, M.; Yapo, A.; Bastide, J. M. In vitro antimalarial activity of vegetal extracts used in west african traditional medicine. *Am. J. Trop. Med. Hyg*. **1996**, *54*, 67–71.
(34) Portet, B.; Fabre, N.; Roumy, V.; Gornitzka, H.; Bourdy, G.; Chevalley, S.; Sauvain, M.; Valentin, A.; Moulis, C. Activity-guided isolation of antiplasmodial dihydrochalcones and flavanones from *Piper hostmannianum* var. berbicense. *Phytochemistry* **2007**, *68*, 1312–1320.