

Synthesis and trypanocidal activity of substituted 2,4-diarylquinoline derivatives

Kola A. Oluwafemi^{a †}, Siyolise Phunguphunu^a, Sinalo Gqunu^a, Michelle Isaacs,^b Heinrich C. Hoppe^{b,c},
Rosalyne Klein,^{a,b*} and Perry T. Kaye^{a,b*}

^a Department of Chemistry, Rhodes University, Makhanda/Grahamstown, 6140, South Africa

^b Centre for Chemico- and Biomedical Research, Rhodes University, Makhanda/Grahamstown, 6140, South Africa

^c Department of Biochemistry and Microbiology, Rhodes University, Makhanda/Grahamstown, 6140, South Africa

Email: r.klein@ru.ac.za; p.kaye@ru.ac.za

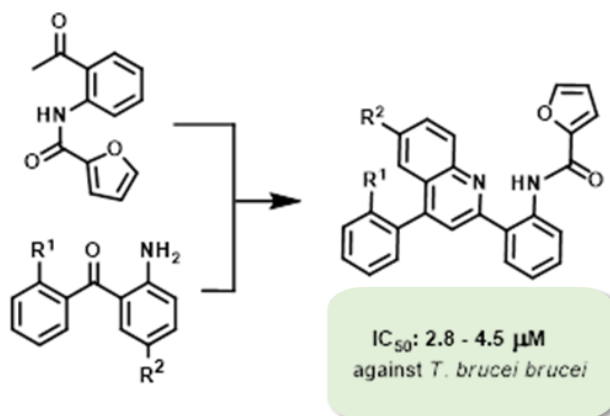
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Abstract

A small library of nine, novel 2,4-diarylquinoline derivatives has been prepared in high yield *via* convenient one- or two-step routes from a series of substituted 2-aminobenzophenones. None of the products exhibited toxicity at 20 μ M against human cervix adenocarcinoma (HeLa) cells, while many of them exhibited encouraging trypanocidal activity against *T. brucei brucei* (a parasite responsible for African cattle trypanosomiasis) - some with IC₅₀ values in the range 2.8 – 6.2 μ M.



Keywords: Synthesis, trypanocidal activity, diarylquinolines, *T. brucei brucei*

Introduction

African trypanosomiasis (Sleeping Sickness), regarded as one of the neglected tropical diseases (NTDs), is caused by parasitic infection by *Trypanosoma* species and is transmitted by Tsetse flies (*Glossina* spp.) which are endemic in Africa. Human African Trypanosomiasis (HAT) and Animal African Trypanosomiasis (AAT) are debilitating diseases which may prove fatal if not treated.¹⁻³ Efforts to eradicate the disease have included the use of nifurtimox **1**, pentamidine **2** and suramin **3**.⁴⁻⁶ Trypanothione reductase, farnesyl diphosphate synthase, 6-phospho-gluconate dehydrogenase, and UDP 4'-galactose epimerase are examples of trypanosomal enzymes currently receiving attention as drug targets.⁷ However, the range of available trypanocidal drugs is very limited; many have been in use for a long time and the development of resistance has been reported.^{4-6;8;9} There is, therefore, an urgent need to discover new and effective alternatives.⁴ *Plasmodium falciparum*, which is responsible for malaria, is also a parasitic protozoan, and various quinoline derivatives are well known for their antimalarial activity.¹⁰⁻¹⁶ In this communication, we report the synthesis of a series of novel 2,4-diarylquinoline derivatives and their evaluation for trypanocidal activity.

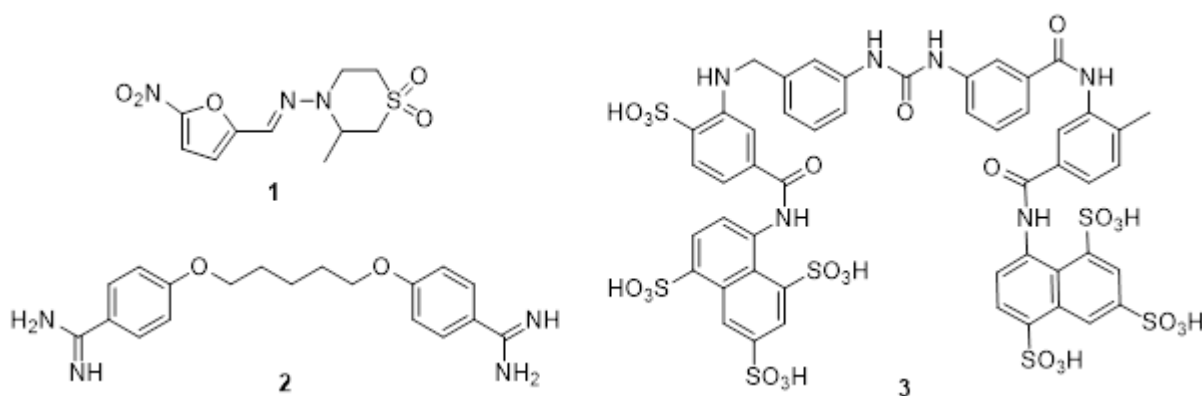


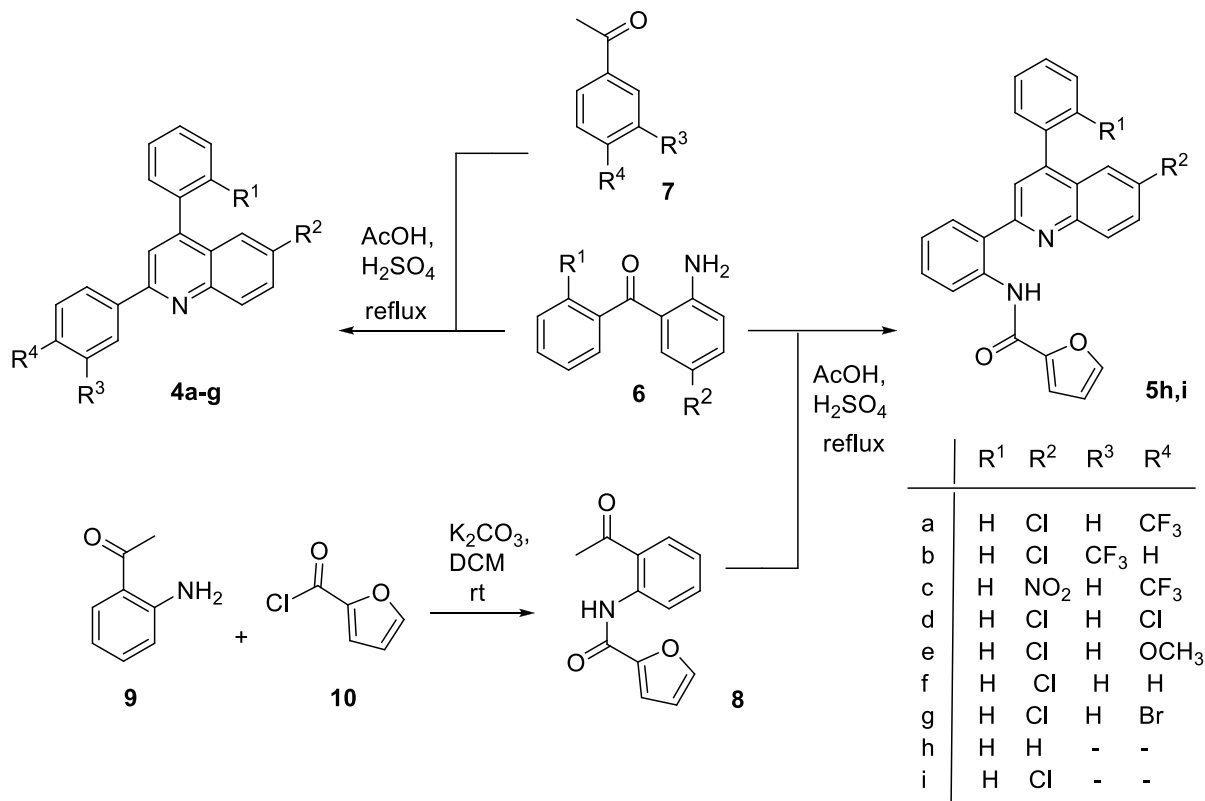
Figure 1. Structures of selected drugs used for the treatment of trypanosomiasis.

Results and Discussion

Access to both sets of 2,4-diarylquinoline derivatives **4a-g** and **5h,i** was achieved by adopting Friedländer-type methodology, involving the reaction of the common, 2-aminobenzophenones (**6**) with the variously substituted acetophenones (**7**) and (**8**), respectively (Scheme 1). Thus, in an approach similar to that used by Sankaran *et al.*¹⁷ in their synthesis of biquinoline- and quinoline-bearing chromenes, equal equivalents of the appropriate acetophenones (**7**) and 2-aminobenzophenones (**6**) were reacted in refluxing acetic acid in the presence of a catalytic quantity of sulphuric acid to give the desired substituted 2,4-diarylquinolines **4a-g** in yields ranging from 80 to 95% (Table 1).

The acetophenone component, *N*-(2-acetylphenyl)furan-2-carboxamide **8**, required for the synthesis of the 2-[2-(furoylamino)phenyl]quinoline analogues **5h,i** was specially prepared by reacting *o*-aminoacetophenone **9** with furoyl chloride **10** using potassium carbonate as a base in dichloromethane at room temperature. Subsequent reaction of compound **8** with the appropriate 2-aminobenzophenones (**6**) afforded the corresponding the 2-[2-(furoylamino)phenyl]quinolines **5i,j** in excellent yields (90-92%; Table 1).

Toxicity studies conducted against HeLa (human cervix adenocarcinoma) cells using a resazurin-based fluorescence assay, indicated that none of the synthesised compounds **4a-g** and **5h,i** showed any cytotoxicity at a concentration of 20 μM (Table 1 and Figure 2). On testing against *T. brucei brucei*, however, most of the compounds exhibited a measure of anti-trypanosomal activity - a number of them with very encouraging IC_{50} values (2.8 – 6.2 μM ; Table 1 and Figure 3).

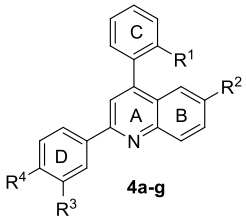
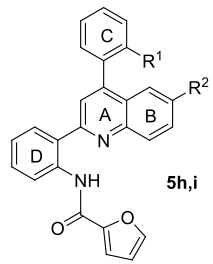


Scheme 1. Synthesis of 2,4-diarylquinolines **4a-g** and **5h,i**.

The bioassay data reveal a number of significant structure-activity relationship patterns.

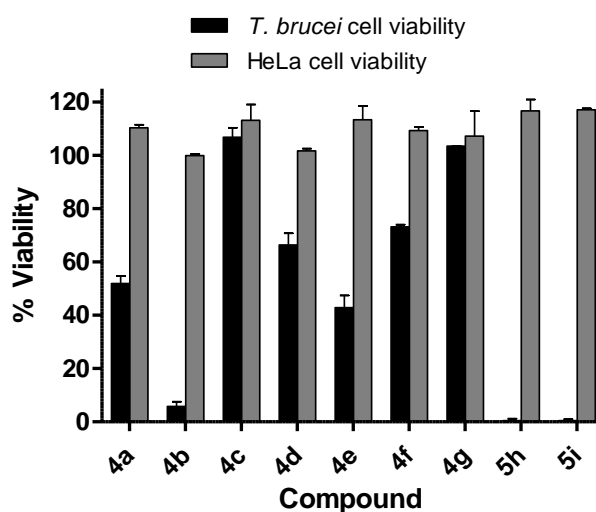
- The 2-[2-(furoylamino)phenyl]quinoline derivatives **5h** and **5i** both exhibited encouraging activity against *T. brucei brucei* at very low micromolar concentrations (IC_{50} : 2.8 – 4.5 μM), whereas only one of the 2-phenylquinoline analogues showed comparable activity (**4b**: IC_{50} : 6.2 μM).
- Compound **4b** is the only 2-phenylquinoline derivative to contain a *meta*-trifluoromethyl group (R^3) on the D-ring; moving the trifluoromethyl group (R^3) to the *para*-position, as in compound **4a**, decreases activity, increasing % *T. brucei brucei* viability from 6% for **4b** to 52% for **4a**.
- Changing the B-ring substituent (R^2) from Cl in **4a** to the strongly electron-withdrawing nitro group in compound **4c** effectively nullifies anti-trypanosomal activity with % *T. brucei brucei* viability increasing from 52% for **4a** to essentially 100% for **4c**.
- Compounds **4a**, **4b**, **4d** and **4e**, which contain the same B-ring substituent ($\text{R}^2 = \text{Cl}$) but differ in the nature of their D-ring substituents ($\text{R}^4 = \text{CF}_3$, Cl and OCH_3 , respectively) all show activity against *T. brucei brucei*, but when R^4 is changed to Br, as in compound **4g**, activity is lost altogether.

Table 1. Effect of compounds **4a-g** and **5h,i** at 20 μM on the viability of HeLa and *T.brucei brucei* cells

	R ¹	R ²	R ³	R ⁴	% Yield	% ^{b,c} HeLa cell viability	% ^{c,d} <i>T. brucei</i> Viability	
	4a	H	Cl	H	CF ₃	90	110 (1)	52 (3)
	4b	H	Cl	CF ₃	H	87	100 (1)	6 (2) (6.2 μM) ^a
	4c	H	NO ₂	H	CF ₃	80	113 (6)	107 (4)
	4d	H	Cl	H	Cl	93	102 (1)	66 (4)
	4e	H	Cl	H	OCH ₃	94	113 (5)	43 (5)
	4f	H	Cl	H	H	93	116 (7)	73 (8)
	4g	H	Cl	H	Br	95	107 (9)	104 (0.01)
	5h	H	H	-	-	92	117 (4)	0.5 (1) (4.5 μM) ^a
	5i	H	Cl	-	-	90	117 (6)	0.5 (0.5) (2.8 μM) ^a

^a IC₅₀ values in parentheses. ^b Emetine control: IC₅₀= 0.05 μM . ^c Standard deviation in parentheses.

^d Pentamidine control: IC₅₀= 0.005 μM .

**Figure 2.** Graphical display of % HeLa and *T.brucei brucei* cell viability data with compounds **4a-g** and **5h,i** at 20 μM .

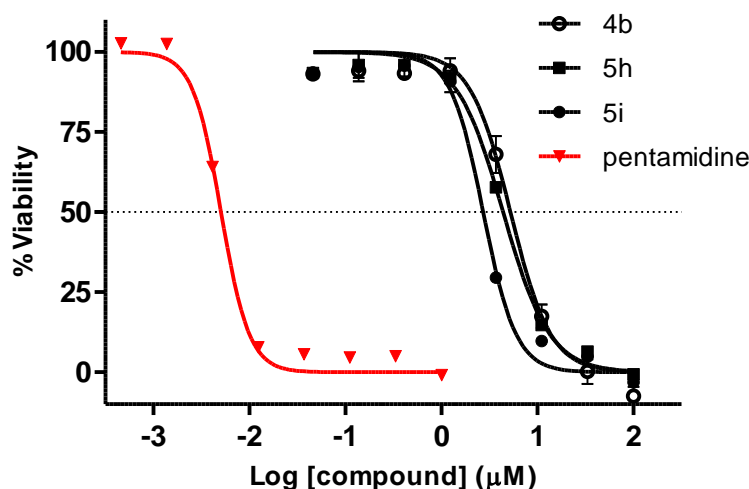


Figure 3. Dose-response curves showing the % viability of *T. brucei brucei* cells at various concentrations of compounds **4b**, **5h** and **5i** and the control, pentamidine.

Conclusions

In conclusion, convenient synthetic access to library of substituted 2,4-diphenylquinolines has been established and, although the mode of action is not known at present, it is apparent that a number of these compounds exhibit very encouraging anti-trypanosomal activity. Interesting structure-activity relationships have been identified, and the 2-[2-(furoylamino)phenyl]quinoline derivatives **5h,i**, in particular, are promising lead compounds for the development of novel trypanocidal agents.

Experimental Section

General. All chemicals were used as purchased from Sigma-Aldrich Chemical Co. Analytical thin layer chromatography (TLC) was performed using pre-coated silica gel plates. NMR spectra were recorded on Bruker 300, 400 and 600 MHz NMR spectrometers, chemical shifts were calibrated relative to the residual proton signal in DMSO- d_6 (2.5 ppm) and the NMR spectra were analysed using Mestrenova. IR Spectra were recorded on a Perkin Elmer Spectrum 100 FTIR spectrometer with a diamond window. Melting points were determined using a hot-stage apparatus and are uncorrected. HRMS analyses were conducted at Rhodes University and by the Central Analytical Facilities Unit at the University of Stellenbosch.

Representative synthetic methods, full characterisation data for the other novel compounds, and Bioassay protocols are detailed below. Bioassay reports and NMR spectra are provided in the Supplementary Material file.

N-(2-Acetylphenyl)furan-2-carboxamide 8. Potassium carbonate (172 mg, 1.5 eq.) was added to a solution of *o*-aminoacetophenone (1 mL, 8.3 mmol) in dichloromethane (30 mL), and the mixture was stirred at room temperature for 30 minutes. Furoyl chloride (0.8 mL, 8.3 mmol) was then added and the resulting mixture

stirred at room temperature for 1 hour, with the reaction progress being monitored by TLC. After the completion of the reaction, the mixture was extracted into DCM (2 × 60 mL), the organic solutions were combined, washed with deionized water (4 × 60 mL), dried with anhydr. potassium sulphate and filtered. The solvent was removed *in vacuo* and the residue was purified using column chromatography on silica gel [elution with ethyl acetate-hexane (2:1)] to afford ***N*-(2-acetylphenyl)furan-2-carboxamide (8)**. White solid (1.6 g, 84%), mp 52-54 °C (Found: MH⁺, *m/z* 230.0854. C₁₃H₁₂NO₃ requires 230.0817); δ_H/ppm (600 MHz; DMSO-*d*₆) 12.45 (1H, s, NH), 8.63 (1H, d, *J* 8.4 Hz, ArH), 8.10 (1H, dd, *J* 7.9, 0.9 Hz, ArH), 7.99 (1H, s, ArH), 7.64 (1H, m, ArH), 7.28 (1H, d, *J* 3.4 Hz, ArH), 7.24 (1H, m, ArH), 6.74 (1H, dd, *J* 3.4, 1.7 Hz, ArH) and 2.68 (3H, s, COCH₃); δ_C/ppm (150 MHz; DMSO-*d*₆) 203.5 and 156.2 (C=O), 147.5, 146.4, 139.4, 134.9, 132.5, 123.2, 122.8, 120.1, 115.8 and 112.9 (ArC) and 28.8 (CH₃).

The general procedure for the synthesis of the 2,4-diarylquinolines (4a-g) and (5h,i) is illustrated by the following example. Conc. sulphuric acid (0.2 mL; CAUTION!) was added to a solution of 2-amino-5-chlorobenzophenone (150.6 mg, 0.7 mmol) and 4'-(trifluoromethyl)acetophenone (122.3 mg, 0.7 mmol) in acetic acid (10 mL). The resulting solution was stirred under a reflux condenser at 80 °C for 2 hours, during which the reaction progress was monitored by TLC. After completion of the reaction, the crude mixture was cooled to room temperature and then poured into ice-cold deionized water (150 mL). The resulting precipitate was filtered off, washed with cold deionized water (2 x 100 mL) and dried at room temperature for 24 hours. The dried material was washed with ethyl acetate (3 x 30 mL) to afford essentially pure **6-chloro-2-[4-(trifluoromethyl)phenyl]-4-phenylquinoline (4a)**. Yellow solid (242 mg, 90%), m.p.122-126 °C (Found: MH⁺, *m/z* 384.0770. C₂₂H₁₄ClF₃N requires 384.0767); δ_H/ppm (600 MHz; DMSO-*d*₆) 8.56 (2H, d, *J* 8.3 Hz, ArH), 8.23 (1H, d, *J* 9.0 Hz, ArH), 8.20 (1H, s, ArH), 7.91 (2H, d, *J* 8.3 Hz, ArH), 7.87 (1H, dd, *J* 9.0, 2.3 Hz, ArH), 7.80 (1H, d, *J* 2.3 Hz, ArH), 7.68 – 7.59 (5H, overlapping m, ArH); δ_C/ppm (150 MHz; DMSO-*d*₆) 155.2, 148.9, 147.0, 142.4, 137.1, 132.6, 132.4, 131.2, 130.1 (d, *J*_{C,F} = 31.7 Hz), 130.0, 129.5, 129.4, 128.9 (d, *J*_{C,F} = 12.5 Hz), 128.7, 126.7, 126.2 (dd, *J*_{C,F} = 7.6, 3.8 Hz), 124.4 and 120.5 [ArC].

Analytical data for other new compounds (4b-g) and (5h,i)

6-Chloro-2-[3-(trifluoromethyl)phenyl]-4-phenylquinoline (4b). Yellow solid (234 mg, 87%), mp 108-110 °C (Found: MH⁺, *m/z* 384.0773. C₂₂H₁₄ClF₃N requires 384.0767); δ_H/ppm (600 MHz; DMSO-*d*₆) 8.69 (1H, s, ArH), 8.66 (1H, d, *J* 7.9 Hz, ArH), 8.26 (1H, s, ArH), 8.23 (1H, d, *J* 9.0 Hz, ArH), 7.89 (1H, d, *J* 7.9 Hz, ArH), 7.85 (1H, dd, *J* 9.0, 2.3 Hz, ArH) and 7.8-7.6 (7H, series of overlapping signals, ArH); δ_C/ppm (150 MHz; DMSO-*d*₆) 154.6, 148.4, 146.5, 139.1, 136.7, 132.1, 131.8, 131.4, 130.7, 130.1, 129.9, 129.6, 129.0, 128.9, 126.4 (d, *J* 3.5 Hz), 126.2, 123.93, 123.85 (d, *J* 3.8 Hz), 123.4 (d, *J* 3.2 Hz), 119.8 [ArC].

6-Nitro-2-[4-(trifluoromethyl)phenyl]-4-phenylquinoline (4c). Yellow solid (126.2 mg, 80%), mp 192-194 °C (Found: MH⁺, *m/z* 395.1004. C₂₂H₁₄F₃N₂O₂ requires 395.1007); δ_H/ppm (600 MHz; DMSO-*d*₆) 8.71 (1H, s, ArH), 8.63 (2H, d, *J* 7.0 Hz, ArH), 8.54 (1H, d, *J* 9.1 Hz, ArH), 8.39 (1H, d, *J* 9.1 Hz, ArH), 8.37 (1H, s, ArH), 7.94 (2H, d, *J* 7.3 Hz, ArH), 7.75 (2H, d, *J* 6.0 Hz, ArH) and 7.72-7.63 (3H, m, ArH); δ_C/ppm (150 MHz; DMSO-*d*₆) 151.20 (m), 150.6, 150.2 (m), 145.4 (d, *J*_{C,F} = 6.6 Hz), 141.5 (d, *J*_{C,F} = 5.6 Hz), 136.2, 131.8, 129.8, 129.5, 129.1, 128.7, 125.9 (d, *J* 3.5 Hz), 124.5, 123.5, 122.5 and 120.8 [ArC].

6-Chloro-2-(4-chlorophenyl)-4-phenylquinoline (4d). White solid (140.1 mg, 93 %), mp 160-162 °C (Found: MH⁺, *m/z* 350.0506. C₂₁H₁₄Cl₂N requires 350.0503); δ_H/ppm (300 MHz; DMSO-*d*₆) 8.39 (2H, d, *J* 8.6 Hz, ArH), 8.19 (1H, d, *J* 9.0 Hz, ArH), 8.14 (1H, s, ArH), 7.85 (1H, dd, *J* 9.0, 2.4 Hz, ArH), 7.78 (1H, d, *J* 2.4 Hz, ArH) and 7.7-7.6 (7H, m, ArH); δ_C/ppm (75 MHz; DMSO-*d*₆) 155.0, 148.2, 146.5, 136.9, 136.7, 134.9, 131.9, 131.5, 130.5, 129.6, 129.2, 129.0, 128.9, 126.0, 123.9 and 119.6 (ArC).

6-Chloro-2-(4-methoxyphenyl)-4-phenylquinoline (4e). White solid (228 mg, 94 %), mp 128-130 °C (Found: MH⁺, *m/z* 346.1000. C₂₂H₁₇ClNO requires 346.0999); δ_H/ppm (400 MHz; DMSO-*d*₆) 8.28 (2H, d, *J* 8.8 Hz, ArH), 8.11 (1H, d, *J* 9.0 Hz, ArH), 8.01 (1H, s, ArH), 7.77 (1H, dd, *J* 9.0, 2.3 Hz, ArH), 7.71 (1H, d, *J* 2.2 Hz, ArH), 7.66-7.55 (5H, m, ArH), 7.08 (2H, d, *J* 8.8 Hz, ArH) and 3.83 (3H, s, OCH₃); δ_C/ppm (100 MHz; DMSO-*d*₆) 161.0, 156.0, 147.9, 146.7, 137.0, 131.8, 130.8, 130.6, 130.4, 129.6, 129.01, 128.99, 128.95, 125.7, 123.9, 119.3, 114.3 (ArC) and 55.4 (OCH₃).

6-Chloro-2,4-diphenylquinoline (4f). White solid (256.3 mg, 93%), mp 118-120 °C (Found: MH⁺, *m/z* 316.0934. C₂₁H₁₅ClN requires 316.0893); δ_H/ppm (400 MHz; DMSO-*d*₆) 8.33 (2H, d, *J* 6.6 Hz, ArH), 8.19 (1H, d, *J* 9.0 Hz, ArH), 8.09 (1H, s, ArH), 7.83 (1H, dd, *J* 9.0, 2.3 Hz, ArH), 7.77 (1H, d, *J* 2.3 Hz, ArH) and 7.66 – 7.52 (8H, overlapping m, ArH).

2-(4-Bromophenyl)-6-chloro-4-phenylquinoline (4g). White solid (150 mg, 95%); mp 166-168 °C (Found: MH⁺, *m/z* 393.9993. C₂₁H₁₄BrClN requires 393.9998); δ_H/ppm (600 MHz; DMSO-*d*₆) 8.30 (2H, d, *J* 8.0 Hz, ArH), 8.19 (1H, d, *J* 9.0 Hz, ArH), 8.11 (1H, s, ArH), 7.84 (1H, d, *J* 9.0 Hz, ArH), 7.77 (1H, s, ArH), 7.75 (2H, d, *J* 8.0 Hz, ArH) and 7.65-7.58 (5H, m, ArH); δ_C/ppm (150 MHz; DMSO-*d*₆) 155.6, 148.7, 147.0, 137.7, 137.2, 132.4, 132.3, 132.0, 131.1, 130.0, 129.9, 129.5, 129.4, 126.5, 124.4, 124.2 and 120.0 (ArC).

2-[2-(Furan-2-carboxamido)phenyl]-4-phenylquinoline (5h). Gray solid (180 mg, 92%), mp 176-180 °C (Found: MH⁺, *m/z* 391.1453. C₂₆H₁₉N₂O₂ requires 391.1447); δ_H/ppm (600 MHz; DMSO-*d*₆) 13.82 (1H, s, NH), 8.62 (1H, d, *J* 8.1 Hz, ArH), 8.40 (1H, d, *J* 8.4 Hz, ArH), 8.22 (1H, d, *J* 7.5 Hz, ArH), 8.10 (1H, s, ArH), 8.04 (1H, s, ArH), 7.98 (1H, m, ArH), 7.9-7.3 (8H, series of overlapping m, ArH), 7.32 (2H, m, ArH) and 6.77 (1H, s, ArH); δ_C/ppm (150 MHz; DMSO-*d*₆) 156.8 (C=O), 155.8, 148.1, 145.8, 137.5, 137.1, 130.85, 130.84, 130.5, 130.3, 129.6, 128.9, 128.8, 128.6, 127.6, 125.4, 125.3, 124.6, 124.0, 121.3, 120.9, 115.3, 112.8 and 99.6 (ArC).

6-Chloro-2-[2-(furan-2-carboxamido)phenyl]-4-phenylquinoline (5i). Gray solid (191 mg, 90%), mp 150-156 °C (Found: MH⁺, *m/z* 425.1053. C₂₆H₁₈ClN₂O₂ requires 425.1057); δ_H/ppm (600 MHz; DMSO-*d*₆) 13.68 (1H, s, NH), 8.62 (1H, d, *J* 8.0 Hz, ArH), 8.38 (1H, d, *J* 8.8 Hz, ArH), 8.21 (1H, d, *J* 7.3 Hz, ArH), 8.09 (2H, d, *J* 13.4 Hz, ArH), 7.98 (1H, d, *J* 8.8 Hz, ArH), 7.80 (1H, s, ArH), 7.7-7.6 (5H, m, ArH), 7.55 (1H, d, *J* 8.6 Hz, ArH), 7.28 (2H, s, ArH) and 6.77 (1H, d, *J* 13.4 Hz, ArH); δ_C/ppm (150 MHz; DMSO-*d*₆) 157.3 and 155.8 (C=O), 148.9, 148.0, 145.8, 144.7, 137.5, 136.5, 134.0, 132.1, 132.0, 131.32, 131.31, 130.8, 130.3, 129.5, 129.1, 128.9, 128.5, 128.4, 125.4, 124.9, 124.0, 121.8, 121.3, 115.3 and 112.8 (ArC). **Note.** Doubling of certain C-13 signals attributed to rotamerism of the amide moiety.

Bioassay protocols

Cytotoxicity determination. To assess the overt cytotoxicity of the compounds, HeLa (human cervix adenocarcinoma) cells cultured in DMEM medium containing 10% fetal bovine serum and antibiotics (penicillin, streptomycin, amphotericin B) in a 5% CO₂ 37°C incubator were plated in 96-well plates at a density of 2 x 10⁴ cells per well. After an overnight incubation to allow cell adhesion, test compounds were added to a final concentration of 20 μM and incubation continued for 48 hours. Residual cell viability was determined by adding resazurin to a final concentration of 50 μM and measuring fluorescence (EX₅₆₀/EM₅₉₀) in a Spectramax M3 plate reader (Molecular Devices) after a 4-hour incubation. Fluorescence readings were converted to % cell viability in compound-treated wells relative to untreated controls, after subtracting background readings obtained from wells without cells. Compounds were tested in duplicate wells. Emetine was used as a control drug standard.

Anti-trypanosomal assay. To assess trypanocidal activity, *T.b. brucei* (strain 427) trypomastigotes were seeded in 96-well plates at a density of 2.4 x 10⁴ cells per well in medium consisting of IMDM containing 25 mM

HEPES, 10% fetal bovine serum, 1 mM hypoxanthine, antibiotics (penicillin, streptomycin) and HMI-9 supplement. After an overnight incubation at 37°C in a 5% CO₂ incubator, compounds were added to a final fixed concentration of 20 µM or as 3-fold serial dilutions, and incubation continued for 24 hours. Resazurin was added to a final concentration of 50 µM and, after an additional 24-hour incubation, fluorescence (EX₅₆₀/EM₅₉₀) was measured in Spectramax M3 plate reader. Fluorescence readings were converted to % parasite viability in compound-treated wells relative to untreated controls, after subtracting background readings obtained from wells without cells. Compounds were tested in duplicate wells. Pentamidine was used a control drug standard

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Supplementary Material

The ¹H- and ¹³C-NMR spectra for all new compounds **8**, **4a-g**, and **5h,i** and the bioassay reports and data are provided in the Supplementary Material file.

References

1. Malvy, D.; Chappuis F. *Clin Microbiol Infect.*, **2011**, 17, 986-995.
<https://doi.org/10.1111/j.1469-0691.2011.03536.x>
2. Pollitt L.C.; MacGregor, P.; Matthews, K.; Reece, S.E. *Trends Parasitol.*, **2011**, 27, 197-203.
<https://doi.org/10.1016/j.pt.2011.01.004>
3. Simarro, P.P.; Jannin, J.; Cattand, P. *PLOS medicine*. **2008**, 5, e55.
<https://doi.org/10.1371/journal.pmed.0050055>
4. Wilkinson, S.R.; Kelly, J.M. *Expert Reviews in Mol Med.*, **2009**, 11, e31.
<https://doi.org/DOI.org/10.1017/S1462399409001252>
5. Barrett, MP *PLoS pathog.*, **2010**, 6, e1001204.
<https://doi.org/DOI.org/10.1371/journal.ppat.1001204>
6. Fairlamb. A.H. *Trends Parasitol.*, **2003**, 19, 488-494.
<https://doi.org/DOI.org/10.1016/j.pt.2003.09.002>
7. Scotti, L.; Mendonça, F.J.B.; da Silva, M.S.; Scotti, M.T. *Curr Protein Pept Sci.*, **2016**, 17(3), 243-259
<https://doi.org/10.2174/1389203717999160226173754>
8. Baker, N.; de Koning, H.P.; Mäser, P.; Horn, D. *Trends Parasitol.*, **2013**, 29, 110118.
<https://doi.org/DOI.org/10.1016/j.pt.2012.12.005>

9. Chitanga, S.; Marcotty, T.; Namangala, B.; den Bossche P.V.; Abbeelee, J.V.D.; Delespaux, V. *PLoS Negl Trop Dis.*, **2011**, 5(12), e1454.
<https://doi.org/10.1371/journal.pntd.0001454>
10. Foley, M.; Tilley, L. *Pharmacol Ther.*, **1998**, 79, 55-87.
[https://doi.org/10.1016/s0163-7258\(98\)00012-6](https://doi.org/10.1016/s0163-7258(98)00012-6)
11. O'Neill, P.M.; Bray, P.G.; Hawley, S.R.; Ward, S.A.; Park, B.K. *Pharmacol Ther.*, **1998**, 77, 29-58.
[https://doi.org/10.1016/s0163-7258\(97\)00084-3](https://doi.org/10.1016/s0163-7258(97)00084-3)
12. Homewood, C.A.; Warhurst, D.C.; Peters, W.; Baggaley, V.C. *Nature* **1972**, 235, 50-52.
<https://doi.org/10.1038/235050a0>
13. Hawley, S.R.; Bray, P.G.; Mungthin, M.; Atkinson, J.D.; O'Neill, P.M.; Ward, S.A. *Antimicrob Agents Chemother.*, **1998**, 42, 682-686.
<https://doi.org/10.1128/AAC.42.3.682>
14. Roberts, L.; Egan, T.J.; Joiner, K.A.; Hoppe, H.C. *Antimicrob Agents Chemother.*, **2008**, 52, 1840-1842.
<https://doi.org/10.1128/AAC.01478-07>
15. Ressurreição, A.S.; Gonçalves, D.; Siteo, A.R.; Albuquerque, I.S.; Gut, J.; Góis, A.; Gonçalves, L.M.; Bronze, M.R.; Hanscheid, T.; Biagini, G.A.; Rosenthal, P.J.; Prudêncio, M.; O'Neill, P.; Mota, M.M.; Lopes, F.; Moreira, R. *J. Med. Chem.*, **2013**, 56, 7679-7690.
<https://doi.org/10.1021/jm4011466>
16. Rodrigues, T.; da Cruz, F.P.; Lafuente-Monasterio, M.J.; Gonçalves, D.; Ressurreição, A.S.; Siteo, A.R.; Bronze, M.R.; Gut, J.; Schneider, G.; Mota, M.M.; Rosenthal, P.J.; Prudêncio, M.; Gamo, F.; Lopes, F.; Moreira, R. *J. Med Chem.*, **2013**, 56, 4811-4815.
<https://doi.org/10.1021/jm400246e>
17. Sankaran, M.; Chandraprakash, K.; Uvarani, C.; Vennila, K.; Velmurugan, D.; Mohan, P. *Synlett.* **2012**, 23, 2858-2864.
<https://doi.org/10.1055/s-0032-1317488>

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