One-pot Palladium-Catalyzed Synthesis And Antifungal Properties of Polycarbo- substituted Furo[3,2-c]quinolines

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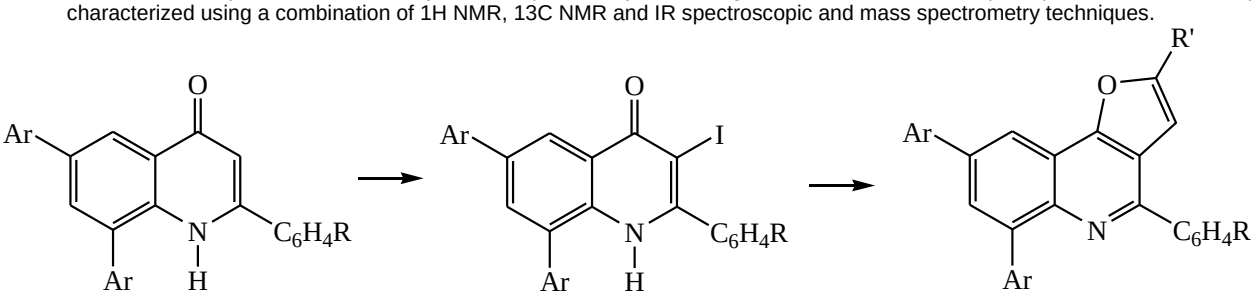
Abstract

A series of 2,6,8-triarylquinolin-4(1H)-ones were functionalized when treated with molecular iodine in the presence of sodium carbonate in tetrahydrofuran to afford the requisite 2,6,8-triaryl-3-iodoquinolin-4(1H)-ones. The latter were then subjected to two-step Sonogashira cross-coupling and tandem heteroannulation reaction with terminal alkynes in the presence of Pd(0)-CuI with triethylamine as a base in DMF-H2O mixture to afford exclusively the 2-substituted 4,6,8-triarylfuro[3,2-c]quinolines in a one-pot operation. The prepared polycarbo-substituted furoquinolines were subjected to preliminary screening for antimicrobial susceptibility. All the new compounds were characterized using a combination of 1H NMR, 13C NMR and IR spectroscopic and mass spectrometry techniques.



Keywords: Cross-coupling, Palladium-catalyzed, Sonogashira, Suzuki-Miyaura,Spectrscopy, 2,6,8-triarylquinolin-4(1H)-ones, 4,6,8-triarylfuro[3,2-c]quinolines, mass spectrometry

1.0 Introduction

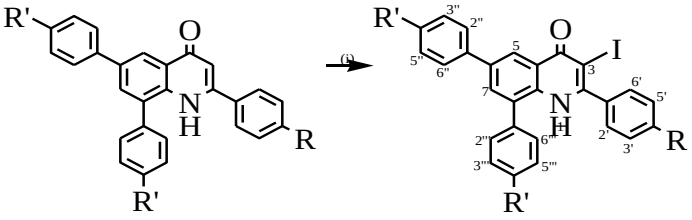
Annulated quinolines such as furoquinoline derivatives are of special interest due to a variety of physiological properties they possess, these include antiplasmodial, antifungal and antibacterial activity.[1],[2],[3],[4] These azoloquinoline derivatives are characterized by a five-membered heterocyclic furan ring with a single heteroatom fused to the main quinoline framework.[5],[6] They can either be linear or angular depending on the site of the main quinoline framework on which the furan ring is attached. Furoquinolines abound in nature and their synthesis continue to receive attention among organic chemists.[7],[8] Kolbisine and ptelatine are members of the naturally occurring furoquinolines,[9] a class of antimicrobially active alkaloids;[10] along with skimmianine, kokusaginine and maculine are present in a large number of rutaceous plants like *Galipea* and *Esenbeckia*.[9],[10] Kolbisine has been found to exhibit antifungal and antibacterial activities against both *Candida albicans* and *Salmonella typhi*, respectively.[2],[9] Kokusagnine, on the other hand, was found to exhibit antiplasmodial activity against *Plasmodium falciparum in vitro*.[1],[9] The mechanism of antimicrobial activity of furoquinolines is connected to their ability to bind DNA forming hydrogen bond using the oxygen atom in the furan ring.[11] In recent times, both linear and angular furoquinolines have exhibited promising immunosuppressive activity,[12] while the angular derivatives serves as anticancer agents.[13] The angular 4-anilinofuro[3,2-*c*]quinoline derivatives exhibited potent cytotoxicity against a full panel of NCI's 60 cancer cell lines.[13] They have therefore received much attention in a quest to efficiently develop more important furoquinolines. Many of the conventional synthetic methods employ tedious and low yielding ring upon ring approach and do not also allow for introduction of diverse substituents.[14],[15] Concerted efforts has been devoted to linear furoquinolines,[16],[17] there is scarcity of literature reports on the angular furoquinolines.[18]

Among the methods developed to date for the synthesis of furoquinolines is the Lewis acid catalyzed imino Diels- Alder reaction between *N*-benzylideanilines and nucleophilic olefins to yield a mixture of endo and exo furo[3,2-c]quinolines.[19]

Furthermore, angular furoquinolines were also previously prepared by cycloaddition through a 3-component reaction involving cyclohexanecarbaldehyde, methyl 3-(2-aminophenyl)propionate and ethyl α-(*p*-nitrophenyl)-α-isocyanate in methanol at room temperature then reflux in toluene to obtain 2-alkoxyfuro[2,3-c]quinoline.[20] Moreover, a 4-step oxidative cyclization of substituted 4-hydroxy-3-(methylbut-2-enyl)quinolin-2-ones with *m*-chloroperbenzoic acid to afford 8-substituted 2-(1-methylethyl)-5-methyl-4,5-dihydrofuro[3,2-c]quinolin-4-ones has also been reported.[9] Aza-Diels-Alder reaction of benzaldehyde derivatives with arylamines and 2,3-dihydrofuran in the presence of nano silica chromic acid as a catalyst afforded a mixture of disubstituted tetrahydrofuroquinolines cis and trans isomers in good yields.[21] Other approach to polysubstituted annulated quinolines bearing aryl substituents involves the use of halogenoquinolinones as substrates for metal catalyzed cross-couplings to incorporate the carbon-bearing substituents on the heterocyclic framework and in situ heteroannulation.[22],[23]

2.0 RESULTS AND DISCUSSION

Our 2-step approach to the polycabosubstituted furoquinolines involves the use of the known 2,6,8-triarylquinolin-4(1*H*)-ones **1a-h**.[24] To initiate our studies, we first prepared a series of 2,6,8-triaryl-3-iodoquinolin-4(1*H*)-ones **2a-h** as sole products in good yields through iodination of the corresponding NH-4-oxo derivatives when treated with molecular iodine in the presence of sodium carbonate in tetrahydrofuran at room temperature (Scheme 1). The ^{1}H NMR spectra of compounds **2a-h** reveals the absence of the signal for the singlet attributed to the olefinic proton displaced by the iodine at δ *ca*. 6.70 ppm. The corresponding ^{13}C NMR spectra show resonance for C-3 and C=O at δ *ca*.86.8 and 174.9 ppm, respectively. The IR spectra reveal absorption bands at ν_{max} *ca*. 3394 and 1644 cm^{-1} for NH and C=O, respectively. The accurately calculated *m/z* value with M+2 peak typical of ^{127}I isotope also confirmed the presence of iodine in the compounds.



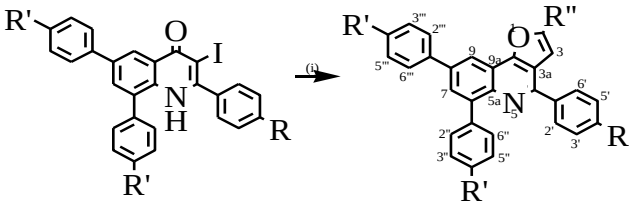
1a-h **2a-h**

Compd	R'	4'-R	% Yield 2
2a	H	H	81
2b	H	F	75
2c	H	Cl	74
2d	H	OMe	77
2e	F	H	72
2f	F	F	71
2g	F	Cl	75
2h	F	OMe	75

Reagents and conditions: (i) I_2, Na_2CO_3, THF, r t, 18 h

Scheme 1: Halogenation of 2,6,8-triarylquinolin-4(1*H*)-ones **1a-h**

With compounds **2a-h** in hand, we next explore these as substrates for palladium-catalyzed Sonogashira cross-coupling and tandem cyclization with terminal alkynes as coupling partners. We first reacted compound **2a** with phenylacetylene (1 equiv.) in the presence of $Pd(PPh_3)_4$ or 10% Pd/C as Pd(0) sources and triethylamine as a base in DMF under reflux as a reference starting point for exploration of the coupling reactions based on literature precedents.[25],[26] In both cases the reaction led to the formation of an inseparable mixture of products. We opted for the use of a $PdCl_2(PPh_3)_2$ as Pd(0) sources with copper iodide because copper is known to play a role in the transmetalation step with palladium and, in turn, promote intramolecular cyclization step in the catalytic cycle.[27] We then reacted **2a** with phenylacetylene (1 equiv.) and isolated the starting material and a product characterized using a combination of spectroscopic techniques as compound **3a** in (*ca*.50%) yield. Increasing the phenylacetylene to 1.5 equiv. afforded compound **3a** in 77% yield. These reaction conditions were extended to other derivatives of 2 using phenyl acetylene and 3-butyn-2-ol as coupling partners to afford the corresponding products **3b-h** in good yields (Scheme 2). The ^{1}H NMR spectra of the annulated compounds **3a-h** show the absence of signals corresponding to the NH and all the proton signals were observed in the aromatic region at δ *ca*. 7.06-8.55 ppm. The absence of resonance corresponding to the C=O in the ^{13}C NMR spectra also confirms the assigned structure. The IR spectra lacks the absorption bands at ν_{max} *ca*. 3394 and 1644 cm^{-1} for NH and C=O, respectively. The accurately calculated *m/z* values show the absence of the M+2 peak present in the precursors.



2a-h **3a-h**

Compd	R'	4'-R	R''	%Yield 3

3a	H	H	-C_6H_5	67
3b	H	F	-C_6H_5	71
3c	H	Cl	-C_6H_5	68
3d	H	OMe	-C_6H_5	66
3e	F	H	-C_6H_5	74
3f	F	F	-C_6H_5	67
3g	F	Cl	-C_6H_5	62
3h	F	OMe	-C_6H_5	63
3i	F	H	-$CHOHCH_3$	68

Reagents and conditions: (i) RCCH, $PdCl_2(PPh_3)_2$, CuI, Et_3N, DMF, 100 °C, 2 h

Scheme 2: Tandem metal-catalyzed alkynylation and heteroannulation of 2,6,8-triaryl-3-iodoquinolin-4(1*H*)-ones **2a-h**

3.0 Antimicrobial Screening

The antimicrobial screening of several of the synthesized compounds was undertaken, using the minimum inhibitory concentration (MIC) screening assay against six reference pathogens: *Staphylococcus aureus* (ATCC 25923, Gram-positive), *Enterococcus faecalis* (ATCC 29212, Gram-positive), *Escherichia coli* (ATCC 8739, Gram-negative), *Pseudomonas aureginosa* (ATCC 27858, Gram-negative), *Candida albicans* (ATCC 10231, yeast) and *Cryptococcus neoformans* (ATCC 14116, yeast) as described in Table 1.

The minimum inhibitory concentrations were determined using the INT micro well method.[28] The synthesized compounds were diluted in acetone so that starting concentrations of 5.00 mg/mL were introduced into the first well of a microtitre plate. The starting concentrations were diluted two-fold in each successive serial dilution. Where necessary, further dilutions were performed so that valid endpoint MIC values could be determined. Positive antimicrobial controls, ciprofloxacin for bacteria at starting stock concentrations of 10.00 µg/mL and amphotericin B for the yeasts at a starting concentration of 100 µg/mL were included in each assay to confirm antimicrobial susceptibility. Negative controls of acetone were included to evaluate the effect of the solvent on the growth of test micro-organisms. A broth control (media incubated without test organism) was included to confirm sterility. Cultures were streaked out onto Tryptone Soya agar to confirm purity. Bacterial cultures were grown overnight at 37 °C, diluted 1:100 and 100 µL inoculated into all wells at approximate inoculum concentrations of 1 x 10^6 colony forming units/mL. Incubation followed for 24 hours for bacterial and 37 °C for 48 hours for the yeasts. After incubation, a 0.40 mg/mL *p*-iodonitrotetrazolium violet solution was transferred into all inoculated wells (40 µL) and examined to determine a colour change in relation to concentration of microbial growth. Tests were performed at least in duplicate and in triplicate where results varied by more than one dilution factor.

Table 1: Antimicrobial Evaluation

Compd.	*Staph. aureus* (ATCC 25923)	*Ente. faecalis* (ATCC 29212)	*Esch. Coli* (ATCC 8739)	*Pseud. aureginosa* (ATCC 27858)	*C. albicans* (ATCC 10231)	*C. neoformans* (ATCC 14116)
3a	0.620	1.250	0.620	0.312	0.470	0.312
3b	0.620	2.50	0.620	0.312	0.470	0.312
3c	1.250	1.250	2.500	0.620	0.620	0.620
3d	0.620	2.500	0.940	0.312	2.500	0.470
3e	0.620	0.620	0.620	0.312	0.156	0.078
3f	1.250	0.620	0.312	1.250	0.156	0.078
3g	1.250	1.250	0.156	0.620	0.620	0.078
3h	0.620	0.620	1.250	0.312	0.156	0.078
3i	0.312	0.312	0.156	0.156	0.078	0.078
Ciprofloxacin Control µg/mL	0.310	0.310	0.160	0.630		
Amphotericin B µg/mL					2.50	1.250

Compounds **3e-i** were found to exhibit inhibitory activity against both *Candida albicans* and *Candida neoformans* (a fungal causative agent).[29],[30] The highest inhibitory effect against *Candida neoformans* was recorded by Compounds **3e**, **3f**, **3g, 3h** and **3i** with a MIC of 0.78 mg/ mL, while compound **3i** exhibited inhibition against *Candida albicans* with a MIC of 0.78 mg/ mL.

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In summary, hitherto unexplored series of polycarbosubstituted furo[3,2-c]quinolines were synthesized and were found to exhibit potential antifungal activities. It was widely believed the fluoro and oxo-substituents were necessary for the antimicrobial activity of the fluoroquinolones.[31],[32] The observed antifungal activity might be as a result of the quinolin-4(1*H*)-one moiety, the furan ring, the fluorine atom or the fluorophenyl substituents or a combination of all.

4.0 Experimental

Commercially available solvents and reagents were used as supplied or purified by conventional methods before use. Melting points were determined on a Stuart melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained using a Varian Mercury 300 MHz Spectrometer at the University of South Africa and as $CDCl_3$ or DMSO-d_6 solution. The chemical shifts were referenced relative to the solvent peaks (δ_H 7.25 or δ_C 77.0 ppm for $CDCl_3$ and δ_H 2.50 or δ_C 40.0 ppm for DMSO-d_6) and are expressed in parts per million (ppm). The IR spectra were recorded as powders on a Digilab FTS 7000 series Win-Pro Fourier Transform Infrared Spectrometer equipped with a nitrogen cooled germanium crystal detector. Merck silica gel 60 F_{254} plates were used for thin layer chromatography (tlc) and the powder for column chromatography. High and low resolution mass spectra were recorded on a Waters API Q-TOF Ultima mass spectrometer at the University of Stellenbosch. Antimicrobial efficacy evaluation was done at the Department of Pharmacy and Pharmacology, Faculty of Health Sciences, University of Witwatersrand, South Africa. The synthesis and characterization of substrate 1 have been described elsewhere.[24]

4.1 Typical procedure for the synthesis of 2,6,8-triaryl-3-iodoquinolin-4(1*H*)-ones 2a-h

4.1.1. 2,6,8-Triphenyl-3-iodoquinolin-4(1*H*)-one (2a)

A mixture of **1a** (0.50 g, 1.3 mmol), I_2 (0.68 g, 2.7 mmol) and Na_2CO_3 (0.21 g, 2.0 mmol) in THF (20 mL) was stirred at room temperature for 18 hours. The mixture was quenched with saturated sodium thiosulphate solution and the precipitate was collected by filtration and washed with ice-cold water. The crude product was recrystallized in ethanol to afford **2a** as light brown solid, (0.48 g, 81%); mp 219-220 °C (EtOH); δ_H (300 MHz, $CDCl_3$): 7.39 (d, *J* 7.5 Hz, 2H), 7.44-7.57 (m, 11H), 7.72 (d, *J* 7.5 Hz, 2H), 7.84 (d, *J* 2.1 Hz, 1H), 8.45 (s, 1H), 8.70 (d, *J* 2.1 Hz, 1H); δ_C (75 MHz, $CDCl_3$) δ: 86.4, 121.8, 124.4, 127.2, 127.8, 128.5, 128.9, 129.0, 129.0, 129.1, 129.8, 130.5, 131.0, 132.1, 135.1, 136.0, 137.5 (C-1'"), 137.9 (C-1"), 139.5 (C-8), 151.3 (C-2), 175.2; IR (neat): ν_{max} (ATR) 3395, 3057, 1736, 1557, 1476, 892, 761, 654 cm^{-1}; *m/z*: 500 (100, M+H); HRMS (ES): MH^+; found 500.0411 $C_{27}H_{19}INO^+$: requires 518.0339

4.1.2. 2-(4-Fluorophenyl)-6,8-diphenyl-3-iodoquinolin-4(1*H*)-one 2b

Yield (0.45 g, 75%); mp 225-226 °C (EtOH); δ_H (300 MHz, $CDCl_3$): 7.18 (d, *J* 7.2 Hz, 2H), 7.36-7.58 (m, 10H), 7.72 (d, *J* 7.2 Hz, 2H), 7.84 (d, *J* 2.1 Hz, 1H), 8.40 (s, 1H), 8.68 (d, *J* 2.1 Hz, 1H); δ_C (75 MHz, $CDCl_3$): 86.6, 116.1 (d, $^2J_{CF}$ 21.9 Hz), 121.7, 124.4, 127.1, 127.8, 129.0, 129.0, 129.1, 129.9, 130.7 (d, $^3J_{CF}$ 8.9 Hz), 131.0, 132.2, 133.9 (d, $^4J_{CF}$ 3.4 Hz), 135.1, 135.9, 137.6, 139.4, 150.3, 163.7 (d, $^1J_{CF}$ 250.7 Hz), 175.1; ν_{max} (ATR) 3396, 3055, 1734, 1588, 1480, 837, 760, 696 cm^{-1}; *m/z* : 518 (100, M+H); HRMS (ES): MH^+; found 518.0411 $C_{27}H_{18}FINO^+$: requires 518.0339

4.1.3. 2-(4-Chlorophenyl)-6,8-diphenyl-3-iodoquinolin-4(1*H*)-one 2c

Yield (0.47 g, 74%); mp 246-248 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39 (2H, t, *J* 7.2 Hz, 3' & 5'-H), 7.44-7.58 (10H, m, Ph" & Ph'"-H), 7.72 (2H, d, *J* 7.2 Hz, 2' & 6'-H), 7.84 (1H, d, *J* 2.1 Hz, 7-H), 8.38 (1H, s, N-H), 8.69 (1H, d, *J* 2.1 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 86.5 (C-3), 121.8 (C-8), 124.4 (C-6), 127.2 (C-4"), 127.8 (C-4'"), 129.0 (C-4'), 129.1 (C-2" & 6"), 129.3 (C- 2'" & 6'"), 129.9 (C- 3" & 5"), 129.9 (C-3'" & 5'"), 131.0 (C-2' & 6'), 132.3 (C-3' & 5'), 135.1 (C-5), 135.9 (C-4a), 136.2 (C-7), 136.8 (C-1'), 137.7 (C- 1"), 137.9 (C- 1'"), 139.4 (C-8a), 150.1 (C-2), 175.1 (C-4); IR (neat): ν_{max} 3382, 3055, 1780, 1586, 1508, 1491, 1481, 1215, 1161, 1087, 1038, 1014, 940, 897, 829, 766 cm^{-1}; *m/z* (100, M+H) 534; HRMS (ES): MH^+; found 534.0123. Calculated for $[C_{27}H_{18}ClINO]^+$: requires 534.0043

4.1.4. 2-(4-Methoxyphenyl)-6,8-diphenyl-3-iodoquinolin-4(1*H*)-one 2d

Yield (0.51 g, 77%); mp 245-247 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.86 (3H, s, OCH_3), 6.98 (2H, t, *J* 7.2 Hz, 3' & 5'-H), 7.38-7.55 (10H, m, Ph" & Ph'"-H), 7.72 (2H, d, *J* 7.2 Hz, 2' & 6'-H), 7.83 (1H, d, *J* 2.1 Hz, 7-H), 8.43 (1H, s, N-H), 8.69 (1H, d, *J* 2.1 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 54.4 (OCH_3), 85.4 (C-3), 112.9 (C-8), 121.0 (C-6), 122.6 (C- 4"), 126.0 (C- 4'"), 126.7 (C-2" & 6"), 127.7 (C-2'" & 6'"), 128.0 (C-2' & 6'), 128.2 (C-3" & 5"), 128.5 (C-3'" & 5'"), 129.3 (C-3' & 5'), 129.4 (C-5), 130.8 (C-4a), 131.1 (C-7), 134.6 (C-1'), 135.5 (C-1'"), 136.0 (C-1"), 138.5 (C-8a), 151.1 (C-2), 159.9 (C-4'), 173.9 (C-4); IR (neat): ν_{max} 3377, 3050, 1784, 1595, 1505, 1478, 1221, 1157, 1026, 898, 786, 622, 610 cm^{-1}; *m/z* (100, M+H) 530; HRMS (ES): MH^+; found 530.0623. Calculated for $[C_{28}H_{21}INO_2]^+$: requires 530.0539

4.1.5. 6,8-Bis(4-fluorophenyl)-3-iodo-2-phenylquinolin-4(1*H*)-one 2e

Yield (0.47 g, 72%); mp 240-241 °C (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.16 (2H, t, *J* 8.4 Hz, 3'" & 5'"-H), 7.25 (2H, t, *J* 8.4 Hz, 3" & 5"), 7.49-7.52 (7H, m, 2'" & 6'"-H and Ph'-H), 7.63-7.68 (2H, t, *J* 8.4 Hz, 2" & 6"-H), 7.75 (1H, d, *J* 2.1 Hz, 7-H), 8.35 (1H, s, N-H), 8.61 (1H, d, *J* 2.1 Hz, 5-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 86.4 (C-3), 115.9 (d, $^2J_{CF}$ 21.4 Hz, C-3" & 5"), 117.0 (d, $^2J_{CF}$ 21.4 Hz, C-3'" & 5'"), 121.7 (C-8), 124.4 (C-6), 128.4 (C-4'), 128.8 (d, $^3J_{CF}$ 8.0 Hz, C-2" & 6"), 130.1 (C-4a), 130.6 (C-5), 130.9 (d, $^3J_{CF}$ 8.0 Hz, C-2'" & 6'"), 131.7 (d, $^4J_{CF}$ 3.4 Hz, C-1"), 132.0 (C-2' & 6'), 135.1 (C-3' & 5'), 135.5 (d, $^4J_{CF}$ 3.4 Hz, C-1'"), 136.5 (C-1'), 137.8 (C-7), 151.4 (C-8a), 162.7 (d, $^1J_{CF}$ 247.2 Hz, C-4"), 163.0 (d, $^1J_{CF}$ 247.2 Hz, C-4'"), 175.0 (C-4); IR (neat): ν_{max} 3399, 3047, 1782, 1589, 1557, 1481, 1388, 1216, 1159, 1038, 1012, 898, 828, 783, 699, 647, 607 cm^{-1}; *m/z* (100, M+H) 536; HRMS (ES): MH^+; found 536.0320. Calculated for $[C_{27}H_{17}F_2INO]^+$: requires 536.0245

4.1.6. 2,6,8-Tris(4-fluorophenyl)-3-iodoquinolin-4(1*H*)-one 2f

Yield (0.47 g, 71%); mp 242-244 °C (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.14-7.28 (6H, m, 3', 3", 3"', 5', 5" & 5"'-H), 7.49 (4H, dd, *J* 3.6, 5.4 Hz, 2", 2"', 6" & 6"'-H), 7.69 (2H, dd, *J* 3.0, 5.4 Hz, 2' & 6'-H), 7.75 (1H, d, *J* 2.1 Hz, 7-H), 8.26 (1H, s, N-H), 8.62 (1H, d, *J* 2.1 Hz, 5-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 87.4 (C-3), 115.7 (d, $^2J_{CF}$ 21.4 Hz, C-3" & 5"), 116.4 (d, $^2J_{CF}$ 21.4 Hz, C-3"' & 5"'), 116.5 (d, $^2J_{CF}$ 21.4 Hz, C-3' & 5'), 122.8 (C-8), 129.4 (d, $^3J_{CF}$ 8.3 Hz, C-2" & 6"), 132.3 (d, $^3J_{CF}$ 8.3 Hz, C-2"' & 6"'), 132.3 (d, $^3J_{CF}$ 8.3 Hz, C-2' & 6'), 132.7 (C-6), 134.0 (C-4a), 135.2 (C-5), 135.5 (d, $^4J_{CF}$ 3.0 Hz, C-1"), 135.5 (d, $^4J_{CF}$ 3.0 Hz, C-1"'), 135.8 (d, $^4J_{CF}$ 3.0 Hz, C-1'), 136.6 (C-7), 147.1 (C-2), 153.2 (C-8a), 162.6 (d, $^1J_{CF}$ 243.7 Hz, C-4"), 162.8 (d, $^1J_{CF}$ 243.7 Hz, C-4"'), 163.3 (d, $^1J_{CF}$ 243.7 Hz, C-4'), 174.3 (C-4); IR (neat): ν_{max} 3381, 3066, 1780, 1589, 1503, 1481, 1218, 1158, 1097, 1040, 1014, 897, 839, 811, 797, 784, 618, 608 cm^{-1}; *m/z* (100, M+H) 554; HRMS (ES): MH$^+$; found, 554.0242. For $[C_{27}H_{16}F_3INO]^+$: requires, 554.0150

4.1.7. 6,8-Bis(4-fluorophenyl)-2-(4-chlorophenyl)-3-iodoquinolin-4(1*H*)-one 2g

Yield (0.48 g, 75%); mp 251-252 °C (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.33 (4H, dd, *J* 3.0, 5.4 Hz, 3", 3"', 5" & 5"'-H), 7.59 (4H, s, 2", 2"', 6" & 6"'-H), 7.72-7.76 (2H, dd, *J* 3.0, 5.4 Hz, 3' & 5'-H), 7.87 (2H, t, *J* 6.6 Hz, 2' & 6'-H), 7.89 (1H, d, *J* 2.1 Hz, 7-H), 8.41 (1H, d, *J* 2.1 Hz, 5-H), 11.15 (1H, s, N-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 87.2 (C-3), 116.3 (d, $^2J_{CF}$ 21.4 Hz, C-3" & 5"), 116.4 (d, $^2J_{CF}$ 21.4 Hz, C-3"' & 5"'), 122.8 (C-8), 128.7 (C-6), 129.2 (d, $^3J_{CF}$ 8.3 Hz, C-2" & 6"), 129.4 (d, $^3J_{CF}$ 8.3 Hz, C-2"' & 6"'), 131.8 (C-4'), 132.3 (d, $^4J_{CF}$ 3.0 Hz, C-1"), 132.7 (C-4a), 133.9 (d, $^4J_{CF}$ 3.0 Hz, C-1"'), 135.0 (C-5), 135.5 (C-2' & 6'), 135.8 (C-3' & 5'), 136.5 (C-5), 137.5 (C-7), 152.9 (C-8a), 162.6 (d, $^1J_{CF}$ 243.4 Hz, C-4"), 162.8 (d, $^1J_{CF}$ 243.4 Hz, C-4"'), 174.2 (C-4); IR (neat): ν_{max} 3382, 3055, 1781, 1586, 1507, 1492, 1481, 1215, 1161, 1087, 1014, 897, 828, 783, 766 cm^{-1}; *m/z* (100, M+H) 570; HRMS (ES): MH$^+$; found, 569.9911. For $[C_{27}H_{16}F_2ClINO]^+$: requires, 569.9855

4.1.8. 6,8-Bis(4-fluorophenyl)-2-(4-methoxyphenyl)-3-iodoquinolin-4(1*H*)-one 2h

Yield (0.48 g, 75%); mp 237-239 °C (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.82 (3H, s, OCH_3), 7.06 (2H, d, *J* 7.8 Hz, 3"' & 5"'-H), 7.35 (4H, dd, *J* 3.6, 5.4 Hz, 2"', 3" 5" & 6"'-H), 7.50 (2H, d, *J* 7.5 Hz, 2" & 6"-H), 7.75-7.84 (4H, m, 2', 3', 5' & 6'-H), 7.86 (1H, d, *J* 2.1 H, 7-H), 8.39 (1H, s, N-H), 11.0 (1H, d, *J* 2.1 Hz, 5-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 55.9 (OCH_3), 87.1 (C-3), 113.9 (C-8), 116.3 (d, $^2J_{CF}$ 21.3 Hz, C-3" & 5"), 116.4 (d, $^2J_{CF}$ 21.3 Hz, C-3"' & 5"'), 122.8 (d, $^3J_{CF}$ 8.3 Hz, C-2" & 6"), 129.4 (d, $^3J_{CF}$ 8.3 Hz, C-2"' & 6"'), 130.9 (C-6), 131.4 (C-3' & 5'), 132.5 (C-2' & 6'), 134.0 (d, $^4J_{CF}$ 3.0 Hz, C-1"), 134.0 (d, $^4J_{CF}$ 3.0 Hz, C-1"'), 135.4 (C-4a), 135.9 (C-5), 136.5 (C-7), 153.7 (C-8a), 160.8 (C-4'), 162.6 (d, $^1J_{CF}$ 243.3 Hz, C-4"), 162.8 (d, $^1J_{CF}$ 243.3 Hz, C-4"'), 174.3 (C-4); IR (neat): ν_{max} 3377, 3050, 1720, 1569, 1507, 1480, 1221, 1174, 1158, 1108, 1027, 834, 788, 623 cm^{-1}; *m/z* (100, M+H) 566; HRMS (ES): MH$^+$; found, 566.0438. For $[C_{28}H_{19}F_2INO_2]^+$: requires, 566.0350

4.2 Typical procedure for the synthesis of 2-substituted 4,6,8-triaryl-furo[3,2-c]quinoline derivatives 3a-i

4.2.1. 2,4,6,8-Tetraphenyl-furo[3,2-*c*]quinoline 3a

A mixture of **2a** (0.30 g, 0.6 mmol), $PdCl_2(PPh_3)_2$ (0.02 g, 0.03 mmol), CuI (0.011 g, 0.06 mmol) and Et_3N (0.34 mL, 2.4 mmol) in DMF (20 mL) in a three-necked round bottomed flask equipped with magnetic stirrer bar, condenser and rubber septum was stirred under argon for 1 hour. To this mixture was added phenyl acetylene (0.13 mL, 1.2 mmol) slowly via a syringe and the mixture was stirred at 100 °C for 2 hours under argon atmosphere. The mixture was cooled to room temperature and diluted with cold water (50 mL) and the product was taken up into $CHCl_3$ (3x50 mL). The combined organic layers were washed with water (2x20 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to afford **3a** as pale yellow solid, (0.23 g, 77%); mp 202-204 °C; R_f (10% ethyl acetate/ hexane) 0.72; δ_H (300 MHz, $CDCl_3$): 7.39-7.60 (m, 12H), 7.87 (d, *J* 8.7 Hz, 2H), 7.94 (d, *J* 8.7 Hz, 2H), 8.00 (d, *J* 8.7 Hz, 2H), 8.02 (d, *J* 2.1 Hz, 1H), 8.15 (d, *J* 8.7 Hz, 2H), 8.58 (d, *J* 2.1 Hz, 1H); δ_C (75 MHz, $CDCl_3$): 101.6, 117.0, 120.0, 125.0, 127.3, 127.5, 127.7, 127.8, 128.7, 128.9, 128.9, 129.0, 129.1, 129.2, 129.5, 129.9, 131.1, 139.0, 139.7, 139.8, 139.8, 140.6, 141.5, 142.3, 152.1, 156.4, 156.8; ν_{max} (ATR) 3069, 3032, 1590, 1482, 1365, 1010, 943, 874, 835, 791, 737, 690 cm^{-1}; *m/z* : 474 (100, M+H); HRMS (ES): MH$^+$, found: 474.1859 $C_{35}H_{24}NO^+$: requires, 474.1858.

4.2.2. 2,6,8-Triphenyl-4-(4-fluorophenyl)furo[3,2-*c*]quinoline 3b

Yield (0.32 g, 71%); mp 204-205 °C R_f (10% ethyl acetate/ hexane) 0.78; δ_H (300 MHz, $CDCl_3$): 7.21 (dd, *J* 3.9, 8.7 Hz, 2H), 7.39-7.57 (m, 10H), 7.87 (dd, *J* 6.0, 8.1 Hz, 4H), 8.00 (dd, *J* 4.5, 9.9 Hz, 3H), 8.12 (dd, *J* 2.7, 5.7 Hz, 2H), 8.54 (d, *J* 2.1 Hz, 1H); δ_C (75 MHz, $CDCl_3$): 101.3, 115.9 (d, $^2J_{CF}$ 21.4 Hz), 116.9, 119.7, 125.0 (d, $^3J_{CF}$ 8.0 Hz), 127.3, 127.5, 127.7, 127.8, 129.0, 129.0, 129.1, 129.1, 129.7, 130.6, 130.7, 131.1, 135.9 (d, $^4J_{CF}$ 3.2 Hz), 139.0, 139.8, 140.5, 141.4, 142.2, 150.9, 156.5, 156.7, 163.5 (d, $^1J_{CF}$ 247.6 Hz); IR (neat): ν_{max} 3052, 3033, 1600, 1485, 1366, 1227, 1154, 1012, 842, 793, 757, 691, 616 cm^{-1}; *m/z* : 492 (100, M+H); HRMS (ES): MH$^+$, found: 492.1764 $C_{35}H_{23}FNO^+$: requires, 492.1758

4.2.3. 2,6,8-Triphenyl-4-(4-chlorophenyl)furo[3,2-*c*]quinoline 3c

Yield (0.31 g, 68%); mp 245-246 °C; R_f (10% ethyl acetate/ hexane) 0.78; δ_H (300 MHz, $CDCl_3$): 7.43-7.55 (m, 12H), 7.88 (dd, *J* 1.5, 8.9 Hz, 4H), 8.02 (dd, *J* 1.5, 8.9 Hz, 4H), 8.09 (d, *J* 2.1 Hz, 1H), 8.56 (d, *J* 2.1 Hz, 1H); δ_C (75 MHz, $CDCl_3$): 101.2, 117.0, 119.7, 125.0, 127.4, 127.5, 127.7, 127.9, 128.9, 129.0, 129.0, 129.1, 129.2, 129.2, 129.7, 130.1, 131.1, 135.3, 138.2, 139.7, 140.4, 141.2, 142.2, 150.7, 156.6, 156.8; IR (neat): ν_{max} 3069, 3053, 3032, 1590, 1482, 1365, 1091, 1010, 873, 835, 791,

756, 737, 690, 643, 604 cm^{-1}; *m/z*: 508 (100, M+H); HRMS (ES): MH^+, found: 508.1479. $C_{35}H_{23}ClNO^+$: requires, 508.1468

4.2.4. 2,6,8-Triphenyl-4-(4-methoxyphenyl)furo[3,2-*c*]quinoline 3d

Yield (0.33 g, 66%); mp 200-201 °C; R_f (10% ethyl acetate/ hexane) 0.42; δ_H (300 MHz, $CDCl_3$): 3.89 (s, 3H), 7.07 (d, *J* 8.7 Hz, 2H), 7.39-7.56 (m, 10H), 7.87 (d, *J* 8.7 Hz, 2H), 7.94 (d, *J* 8.7 Hz, 2H), 8.00 (d, *J* 8.7 Hz, 2H), 8.02 (d, *J* 2.1 Hz, 1H), 8.12 (d, *J* 8.7 Hz, 2H), 8.56 (d, *J* 2.1 Hz, 1H); δ_C (75 MHz, $CDCl_3$): 55.4, 101.7, 114.1, 116.8, 117.0, 119.6, 124.9, 127.2, 127.5, 127.7, 127.7, 129.0 (2C), 129.9, 130.2, 131.1, 132.5, 138.8, 139.9, 140.6, 141.2, 142.3, 151.7, 156.2, 156.7, 160.6; IR (neat): ν_{max} 3047, 3003, 2959, 2836, 1603, 1482, 1366, 1303, 1246, 1171, 1032, 945, 836, 795, 758, 744, 698, 616 cm^{-1}; *m/z*: 504 (100, M+H); HRMS (ES): MH^+, found: 504.1970. $C_{36}H_{26}NO_2^+$: requires, 504.1964

4.2.5. 6,8-Bis(4-fluorophenyl)-2,4-diphenylfuro[3,2-*c*]quinoline 3e

Yield (0.35 g, 74%); mp 213-215 °C R_f (10% ethyl acetate/ hexane) 0.58; δ_H (300 MHz, DMSO-d_6): 7.18-7.24 (m, 4H), 7.39-7.57 (m, 7H), 7.82 (dd, *J* 2.7, 6.0 Hz, 2H), 7.88 (dd, *J* 2.7, 6.0 Hz, 2H), 7.91 (d, *J* 2.1 Hz, 1H), 7.99 (d, *J* 8.1 Hz, 2H), 8.11 (d, *J* 8.1 Hz, 2H), 8.47 (d, *J* 2.1 Hz, 1H); δ_C (75 MHz, DMSO-d_6): 101.6, 114.6 (d, $^2J_{CF}$ 21.3 Hz), 115.9 (d, $^2J_{CF}$ 21.3 Hz), 116.9, 117.0, 120.1, 125.0, 128.6, 128.8 (d, $^3J_{CF}$ 8.0 Hz), 129.0, 129.1, 129.2, 129.4, 129.8, 132.7 (d, $^3J_{CF}$ 8.0 Hz), 135.6 (d, $^4J_{CF}$ 3.2 Hz), 136.5 (d, $^4J_{CF}$ 3.2 Hz), 137.9, 139.6, 139.7, 140.5, 142.1, 152.2, 156.5, 156.6, 162.5 (d, $^1J_{CF}$ 245.3 Hz), 162.8 (d, $^1J_{CF}$ 245.3 Hz); IR (neat): ν_{max} 3051, 1600, 1509, 1366, 1012, 945, 830, 758, 690, 646 cm^{-1}; *m/z*: 510 (100, M+H); HRMS (ES): MH^+, found: 510.1663. $C_{35}H_{22}F_2NO^+$: requires, 510.1669

4.2.6. 4,6,8-Tris(4-fluorophenyl)-2-phenylfuro[3,2-*c*]quinoline 3f

Yield (0.36 g, 67%); mp 249-250 °C R_f (10% ethyl acetate/ hexane) 0.63; δ_H (300 MHz, DMSO-d_6): 7.20-7.27 (6H, m, 3, 3''' & 5''' and 2-Ph: 3, 4 & 5-H), 7.45 (2H, dd, *J* 0.9, 6.9 Hz, 2''' & 6'''-H), 7.54 (2H, dd, *J* 0.9, 6.9 Hz, 2'' & 6''-H), 7.80-789 (4H, m, 3'' & 5'' and 2-Ph: 2 & 6-H), 7.93 (1H, d, *J* 1.8 Hz, 7-H), 8.02 (2H, d, *J* 8.1 Hz, 3' & 5'-H), 8.12 (2H, d, *J* 8.1 Hz, 2' & 6'-H), 8.51 (1H, d, *J* 1.8 Hz, 9-H); δ_C (75 MHz, DMSO-d_6): 101.3, 114.6 (d, $^2J_{CF}$ 21.4 Hz), 115.7 (d, $^2J_{CF}$ 21.4 Hz), 115.9 (d, $^2J_{CF}$ 21.4 Hz), 116.9, 119.8, 125.0, 128.7, 129.1 (d, $^3J_{CF}$ 8.3 Hz), 129.2 (d, $^4J_{CF}$ 3.2 Hz), 129.6, 130.1, 130.6 (d, $^3J_{CF}$ 8.3 Hz), 132.6 (d, $^3J_{CF}$ 8.3 Hz), 135.5 (d, $^4J_{CF}$ 3.2 Hz), 135.7 (d, $^4J_{CF}$ 3.2 Hz), 136.4, 136.5, 137.9, 140.4, 142.0, 151.0, 155.9, 156.6, 162.5 (d, $^1J_{CF}$ 246.0 Hz), 162.8 (d, $^1J_{CF}$ 246.0 Hz), 163.6 (d, $^1J_{CF}$ 246.0 Hz); ν_{max} (ATR) 3049, 1602, 1509, 1485, 1154, 946, 868, 803, 756, 688 cm^{-1}; *m/z*: 528 (100, M+H); HRMS (ES): MH^+, found: 528.1577. $C_{35}H_{21}F_3NO^+$: requires, 528.1575

4.2.7. 6,8-Bis(4-fluorophenyl)-4-(4-chlorophenyl)-4-phenylfuro[3,2-*c*]quinoline 3g

Yield (0.36 g, 62%); mp 263-264 °C R_f (10% ethyl acetate/ hexane) 0.63; δ_H (300 MHz, DMSO-d_6): 7.18-7.26 (m, 4H), 7.44 (dd, *J* 6.9, 7.8 Hz, 2H), 7.53 (dd, *J* 6.3, 8.4 Hz, 4H), 7.79-7.88 (dd, *J* 3.3, 5.4 Hz, 4H), 7.93 (d, *J* 2.1 Hz, 1H), 8.04 (dd, *J* 8.1, 8.4 Hz, 4H), 8.51 (d, *J* 2.1 Hz, 1H); δ_C (75 MHz, DMSO-d_6): 101.2, 114.7 (d, $^2J_{CF}$ 21.4 Hz), 115.9 (d, $^2J_{CF}$ 21.4 Hz), 116.9, 117.0, 119.9, 125.0, 128.4, 128.8, 129.0, 129.1, 129.1, 129.6, 130.0, 132.6 (d, $^3J_{CF}$ 8.0 Hz), 132.6 (d, $^3J_{CF}$ 8.0 Hz), 135.5 (d, $^4J_{CF}$ 3.2 Hz), 136.5 (d, $^4J_{CF}$ 3.2 Hz), 138.1, 138.2, 140.5, 142.1, 150.9, 156.7, 156.8, 162.5 (d, $^1J_{CF}$ 245.0 Hz), 162.8 (d, $^1J_{CF}$ 245.0 Hz); ν_{max} (ATR) 3044, 2923, 2852, 1602, 1510, 1484, 1157, 944, 820, 741, 682 cm^{-1}; *m/z*: 544 (100, M+H); HRMS (ES): MH^+, found: 544.1279. $C_{35}H_{21}F_2ClNO^+$: requires, 544.1280

4.2.8. 6,8-Bis(4-fluorophenyl)-4-(4-methoxyphenyl)-4-phenylfuro[3,2-*c*]quinoline 3h

Yield (0.35 g, 63%); mp 221-222 °C R_f (10% ethyl acetate/ hexane) 0.40; δ_H (300 MHz, DMSO-d_6): 3.91 (s, 3H), 7.08 (d, *J* 8.7 Hz, 2H), 7.19-7.26 (m, 4H), 7.40-7.55 (m, 4H), 7.81 (dd, *J* 3.3, 6.0 Hz, 2H), 7.87 (dd, *J* 3.3, 6.0 Hz, 2H), 7.92 (d, *J* 2.1 Hz, 1H), 8.02 (d, *J* 8.7 Hz, 2H), 8.11 (d, *J* 8.7 Hz, 2H), 8.49 (d, *J* 2.1 Hz, 1H); δ_C (75 MHz, DMSO-d_6): 55.4, 101.7, 114.6 (d, $^2J_{CF}$ 21.4 Hz), 115.9 (d, $^2J_{CF}$ 21.4 Hz), 116.9, 117.0, 119.9, 125.0, 128.5, 129.0, 129.1 (d, $^3J_{CF}$ 8.0 Hz), 129.8, 130.2, 132.4, 132.7 (d, $^3J_{CF}$ 8.0 Hz), 135.7 (d, $^4J_{CF}$ 3.5 Hz), 136.6 (d, $^4J_{CF}$ 3.5 Hz), 137.6, 138.2, 140.2, 142.1, 151.9, 156.4, 156.6, 160.7, 162.4 (d, $^1J_{CF}$ 245.8 Hz), 162.8 (d, $^1J_{CF}$ 245.8 Hz); ν_{max} (ATR) 3044, 2923, 2852, 1602, 1510, 1484, 1157, 944, 820, 741, 682 cm^{-1}; *m/z*: 540 (100, M+H); HRMS (ES): MH^+, found: 540.1766. $C_{36}H_{24}F_2NO_2^+$: requires, 540.1775

4.2.9. 2-(2-Hydroxyethyl)-6,8-bis(4-fluorophenyl)-4-phenylfuro[3,2-*c*]quinoline 3i

A mixture of **2e** (0.50 g, 1.0 mmol), $PdCl_2(PPh_3)_2$ (0.04 g, 0.05 mmol), CuI (0.017 g, 0.1 mmol) and Et_3N (0.57 mL, 4.0 mmol) in DMF (30 mL)) in a three-necked round bottomed flask equipped with stirrer, condenser and rubber septum was stirred under argon for 1 hour. To this mixture was added 3-butyn-2-ol (0.20 mL, 2.0 mmol) slowly via a syringe and the mixture was stirred at 100 °C for 2 hours under argon atmosphere; work up and column chromatography on silica gel as described for **3e** afforded **3i** as pale yellow solid, (0.38 g, 68%); mp 245-246 °C; R_f (10% ethyl acetate/ hexane) 0.78; δ_H (300 MHz, DMSO-d_6): 1.90 (d, *J* 6.6 Hz, 3H), 2.41 (d, *J* 5.4 Hz, 1H), 5.34 (t, *J* 5.7 Hz, 1H), 7.25-7.39 (m, 4H), 7.58-7.69 (m, 4H), 7.92 (dd, *J* 3.6, 5.4 Hz, 2H), 8.02 (dd, *J* 3.6, 5.4 Hz, 2H), 8.06 (d, *J* 2.1 Hz, 1H), 8.20 (dd, *J* 1.5, 6.6 Hz, 2H), 8.57 (d, *J* 2.1 Hz, 1H); δ_C (75 MHz, DMSO-d_6): 21.7, 64.1, 102.5, 114.6 (d, $^2J_{CF}$ 21.4 Hz), 115.8 (d, $^2J_{CF}$ 21.4 Hz), 116.9, 118.9, 128.4, 128.6, 128.7, 128.9, 129.0 (d, $^3J_{CF}$ 8.0 Hz), 129.4, 132.7 (d, $^3J_{CF}$ 8.0 Hz), 135.6 (d, $^4J_{CF}$ 3.0 Hz), 136.4 (d, $^4J_{CF}$ 3.0 Hz), 137.8, 139.5, 140.4, 142.1, 152.3, 156.7, 157.0, 162.4 (d, $^1J_{CF}$ 247.5 Hz), 162.8 (d, $^1J_{CF}$ 247.5 Hz); ν_{max} (ATR) 3408, 3044, 2923, 2852, 1604, 1512, 1484, 1160, 940, 820, 742, 684 cm^{-1};

m/z: 478(100, M+H); HRMS (ES): MH^+, found: 478.1623. $C_{31}H_{22}F_2NO_2^+$: requires, 478.1619

Reference

1. Biavatti, MW; Vieira, PC; da Silva, MGF; Fernandes, JB; Victor, SR; Pagnocca, FC; Albuquerque, S; Caracelli, I; Zukerman-Schpector, J. Biological activity of Quinoline alkaloids from Raulinoa echinata And X-ray structure of Flindersiamine *J. Braz. Chem. Soc.*, **2002**, 13, 66-70.

2. Almeida, R; Penaflor, M; Simote, S; Bueno, O; Hebling, M; Pagnocca, F; Fernandes, J; Vieira, P; da Silva, M. Toxicity of substances isolated from Hebietta puberula *Bioassay Org. Br.*, **2007**, 2, 1-8.

3. Michael, JP. Indolizidine and quinolizidine alkaloids *Nat. Prod. Rep*., **2005**, 22, 627-646.

4. Basco, LK; Mitaku,S; Skaltsounis, AL; Ravelomanantsoa, N; Tillequin, F; Koch, M; Le Bras, J. In-vitro activities of furoquinolines and acridine alkaloids against plasmodium falciparum *Antimicrob. Agents Chemother*. **1994,** 38, 1169-1171.

5. Abass, M. Fused Quinolines: Recent Synthetic Approaches to Azoloquinolines. A Review *Heterocycles* **2005**, 65, 901-965.

6. Marchand, P; Puget, a; Le Baut, G; Emig, P; Czech, M; Gunther, E. Palladium(II)-catalyzed heterocyclisation of 8-arylethynyl-1,2,3,4- tetrahydroquinolines: a facile route to 2-aryl-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline derivatives *Tetrahedron*, **2005**, 61, 4035-4041.

7. Wansi, JD; Hussain, H; Tcho, AT; Kouam, SF; Specht, S; Sarite, SR; Hoeraul, A; Krohn, K. Antiplasmodial activities of furoquinoline alkaloids from *Teclea afzelii Phytother. Res.*, **2010**, 24, 775-777.

8. Michael, JP. Quinoline, quinazoline and acridone alkaloids *Nat. Prod. Rep*., **2002**, 19, 742-760.

9. Kuete, V; Wansi, JD; Mbaveng, AT; Kana Sop, MM; Tcho Tadjong, A; Penlap Beng, V; Etoa, F-X; Wandji, J; Marion Meyer, JJ; Lall, N. Antimicrobial activity of the methanolic extract and compounds from *Teclea afzelii* (Rutacea) *S. Afr. J. Bot*. **2008**, 74, 572-576.

10. Grundon, MF. The Alkaloids, (Ed. Brossi, A), Academic Press, New York, 1988, vol. 32, 341-349.

11. Hanawa, F; Fokialakis, N; Skaltsounis, AL. Photo-activated DNA binding and antimicrobial activities of furoquinoline and pyranoquinolone alkaloids from Rutacea *Planta Med*. **2004**, 70, 531-535.

12. Butenschon, I; Moller, K; Hansel, W. Angular Methoxy-substituted Furo- and pyranoquinolinones as Blockers of the Voltage-Gated Potassium Channel kv1.3 *J. Med. Chem*., **2001**, 44, 1249-1256

13. Chen, Y-L; Chen, I-L; Wang, T-C; Han, C-H; Tzeng, C-C. Synthesis and anticancer evaluation of certain 4-anilinofuro[3,2-c]quinoline derivatives *Eur. J. Med. Chem*. **2005**, 40, 928-934.

14. (a) Godard, A; Jacquelin, JM; Queguiner, G. A new synthesis of 2,3-dihydrofuro[2,3-b], [2,3-c] and [3,2-c]quinolines *J. Heterocyl. Chem*. **1988**, 25, 1053-1054 (b) Pirrung, MC; Blume, F. Rhodium-Mediated Dipolar Cycloaddition of Diazoquinolinediones *J. Org. Chem*. **1999**, 64, 3642-3649.

15. Crousse, B; Begue, JP; Bonnet-Delpon, D. Synthesis of 2-CF3-Tetrahydroquinolines and Quinolone Derivatives from CF3-*N*-Arylaldimine *J. Org. Chem*. **2000**, 65, 5009-5013.

16. Godet, T; Vaxelaire, C; Michel, C; Milet, A; Belmont, P. Silver versus Gold catalysis in Tandem Reactions of Carbonyl Functions onto Alkynes: A versatile Access to Furoquinoline and Pyranoquinoline Cores *Chem. Eur. J*. **2007**, 13, 5632-5641

17. Zhang, Z; Zhang, Q; Sun, S; Xiong, T; Liu, Q. Dehydration induced conversions from a Single-Chain Magnet Into a Metamagnet in a Homometallic Nanoporous Metal-Organic Framework *Angew. Chem*. **2007**, 119, 1756.

18. Chen, J-J; Duh, C-Y; Huang, H-Y; Chen, I-S. Furoquinolin alkaloids and cytotoxic Constituents from the Leaves of Melicope semecarpifolia *Planta Med*. **2009**, 69, 542-546.

19. Mahesh, H; Reddy, C; Venkateshwar Reddy, K; Srinivasa Raju,PVK; Reddy, VV. Imino Diels-Alder Reactions: Efficient Synthesis of Pyrano and Furoquinolines catalyzed by $ZrCl_4$ *Synthestic Comm*. **2004**, 34, 4089-4101.

20. Bouma, MJ; Masson, G; Zhu, J. Exploiting the Divergent Reactivity of Isocyanates: One-pot Three-Components Synthesis of Functionalized Angular Furoquinolines *Eur. J. Org. Chem*. **2012**, 475-479.

21. Gharib, A; Jahangir, M. Catalytic Synthesis of Pyrano- and Furoquinolines Using Nano Silica Chromic Acid at Room Temperature *Org. Chem. Inter.*, **2013**, 1-7.

22. Venkataram S; Barange, DK; Pal, M. One-pot Synthesis of 2-substituted furo[3,2-c]quinolines via tandem coupling – cyclization under Pd/C-Copper Catalysis *Tetrahed. Lett.*, **2006**, 7317-7322.

23. Rocha, DHA; Pinto, DCG; Silva, AMS. Synthesis and cyclisation studies of (*E*)-2-aryl-1-methyl-3-styrylquinolin-4(1H)-ones Tetrahedron, **2015**, 71, 7717-7721.

24. Mphahlele, MJ; Oyeyiola, FA. Suzuki-Miyaura cross-coupling of 2-aryl-6,8-dibromo-1,2,3,4-tetrahydroquinolin-4-ones and subsequent dehydrogenation and oxidative aromatization of the resulting 2,6,8-triaryl-1,2,3,4-tetrahydroquinolin-4-ones *Tetrahedron*, **2011**, 67, 6819-6825.

25. Testa, ML; Larmatina, L; Mingoia, F. A new entry to the Substituted Pyrrolo[3,2,1-*ij*]quinoline derivatives of biological by intramolecular heteroannulation of internal imines *Tetrahedron*, **2004**, 60, 5873-5880.

26. Kang, SK; Park, SS; Kim, SS; Choi, JK; Yum, EK. Synthesis of 1,2,3,-trisubstituted pyrrolo[3,2-*c*]quinolines via palladium-catalyzed heteroannulation with internal alkynes *Tetrahed. Lett*. **1999**, 40, 4379-4382.

27. Layek, M; Rao, AVD; Gajare, V; Kalita, D; Barange, DP; Islam, A; Mukkanti, K; Pal, M. C-N bond forming reaction under copper catalysis: a new synthesis of 2-substituted 5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolines *Tetrahed. Lett*., **2009**, 50, 4878-4881.

28. National Committee for Clinical Laboratory Standards-Methods of Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically, 6th ed. Approved Standard M7-A6, Wayne, PA: NCCLS, 2003

29. Varma, A; Swinne,D; Staib,F; Bennett, JE; Kwon-Chung, KJ. Diversity of Dna fingerprints in *Cryptococcus neoformans J. Clin. Microbbiol*. **1995**, 33, 1807-1814.

30. Klepser, ME; Pfaller, MA. Variation in Electrophoretic Karyotype and antifungal Susceptibility of Clinical isolates of *Cryptococcus neoformans* at a University-affiliated Teaching Hospital from 1987 to 1994 *J. Clin. Microbiol*. **1998**, 36, 3653-3656

31. [a] Domaga, JM, Antimicrobial Quinolones: A Comparative Analysis of Antimicrobial Agents for Mycobacterium tuberculosis *J. Antimicrob. Chemother*., **1994**, 33, 685-706 [b] Kolaszkowska, A; Kolaszkowska, M. Drug Resistance Mechanisms and their Regulation in New albicans Candida species *J. Antimicrob. Chemother*. **2016**, 71, 1438-1450

32. Chu, D; Fernandez, P; Claiborne, A; Shen, L; Pernet, A. Structure-activity Relationships in Quinolone Antibacterial: design, synthesis and biological activities of novel Isothiazoloquinolones *Drugs Exp. Clin. Res*., **1988**, 14, 379-383

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Table 1: Antimicrobial Evaluation

Compd.	*Staph. aureus* (ATCC 25923)	*Ente. faecalis* (ATCC 29212)	*Esch. Coli* (ATCC 8739)	*Pseud. aureginosa* (ATCC 27858)	*C. albicans* (ATCC 10231)	*C. neoformans* (ATCC 14116)
3a	0.620	1.250	0.620	0.312	0.470	0.312
3b	0.620	2.50	0.620	0.312	0.470	0.312
3c	1.250	1.250	2.500	0.620	0.620	0.620
3d	0.620	2.500	0.940	0.312	2.500	0.470
3e	0.620	0.620	0.620	0.312	0.156	0.078

3f	1.250	0.620	0.312	1.250	0.156	0.078
3g	1.250	1.250	0.156	0.620	0.620	0.078
3h	0.620	0.620	1.250	0.312	0.156	0.078
3i	0.312	0.312	0.156	0.156	0.078	0.078
Ciprofloxacin						
Control µg/mL	0.310	0.310	0.160	0.630		
Amphotericin B µg/mL					2.50	1.250