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Original article

Optimization of 3-(phenylthio)quinolinium compounds against opportunistic fungal pathogens

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ABSTRACT

Ring-opened benzothieno[3,2-*b*]quinolinium salts (**3**) were designed and synthesized with substitution on the thiophene moiety. *In vitro* screenings were carried out against fungal pathogens including *Cryptococcus neoformans*, *Candida albicans*, *Candida glabrata*, *Candida krusei* and *Aspergillus fumigatus*. In all, by replacing the N-methyl group (**2**) with N-ω-phenylpentyl or ω-cyclohexylpentyl group to form substituted 3-(phenylthio)quinolinium compounds produced remarkable potencies, as high as 300-fold (cf, cryptolepine (**1**) = 250 μg/mL vs **11p** = 0.8 μg/mL for *C. albicans*) over the starting tetracyclic parent. In addition, all the N-ω-cyclohexylpentyl analogs produced superior activity against all the microorganisms tested than the N-ω-phenylpentyl substituted compounds. The potential of these compounds to induce toxicity in Vero cells was also investigated and the majority of them showed lower or no cytotoxicity at 10 μg/mL than amphotericin B, the gold standard in antifungal drug development. For instance, the trifluoromethyl substituted analogs (**11n-p**) have selectivity indices over 2-fold better than those of amphotericin B in *C. neoformans*. Overall, this ring-opened scafford of benzothienoquinolines, with substitution on the thiophenyl moiety, serves as a new lead for further development.

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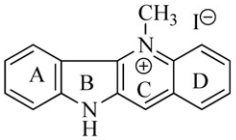
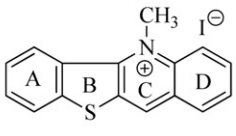
1. Introduction

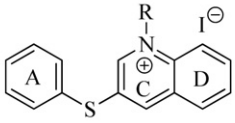
We recently reported that sulfur isosteres of cryptolepine (**1**), benzothieno[3,2-*b*]quinolinium salts (**2**), have the potential to become useful agents with broad antifungal properties and low cytotoxicity [1]. Cryptolepine [2], the original indoloquinoline alkaloid from which these compounds are derived, presumably acts in part by intercalating into DNA [3] and interfering with topoisomerase II [3,4]. We have hypothesized that opening the tetracyclic ring to form ring-opened analogs of cryptolepine might curtail DNA intercalation and decrease cytotoxicity. This hypothesis was tested indirectly by the synthesis and biological evaluation of ring B-opened analogs of cryptolepine and those of 5-alkylated benzothieno[3,2-*b*]quinolinium salts (**3**) [5a]. The results lend support to the hypothesis as these compounds were found to be more potent and less toxic than the parent cryptolepine and more potent than the benzothienoquinolinium salts from which they were derived [5b]. Consequently, in this paper, we have sought to optimize ring B-opened analogs of 5-alkylated benzothienoquinolinium salts (**3**) by synthesizing and evaluating additional ring-opened analogs and studying the structure-activity relationships involved in substituting on ring A in an attempt to increase selective toxicity to fungal pathogens that are commonly associated with AIDS.



5-Methyl-10*H*-Indolo[3,2-*b*]quinolinium Iodide, or Cryptolepine Hydroiodide (**1**)



5-Methyl-Benzothieno[3,2-*b*] quinolin-5-ium Iodide (**2**)



Ring-opened Analogs of 5-substituted Benzothienoquinolinium iodide (**3**)

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2. Results and discussion

2.1. Synthesis

The synthesis of the ring-opened analog, 1-alkylated-3-(phenylthio)quinolinium iodide (**3**), required 3-iodoquinoline (**5**) as the starting material. Compound **5** was obtained by employing Finkelstein reaction [6] to convert commercially available 3-bromoquinoline to the desired iodide. Using a copper-catalyzed carbon-sulfur bond formation reaction [7], substituted benzenethiols were reacted with 3-iodoquinoline to form substituted 3-(phenylthio)quinolines (**6**) (Scheme 1). The synthesis of 3-(hydroxyphenylthio)-quinoline (**7a-c**) was achieved by demethylation of 3-(methoxy phenylthio) quinoline (**6j-l**) using pyridine hydrochloride.

An alternate route to the preparation of 1-alkylated-3-(phenylthio)quinolinium iodide (Scheme 1) was employed [8] where appropriately substituted starting materials were unavailable. 3-Iodoquinoline was converted to *S-quinolin-3-yl benzothioate* (**8**) by reaction with thiobenzoic acid. Using the Cu-catalyzed C-S bond formation reaction adopted earlier, substituted-iodobenzenes were reacted with *S-quinolin-3-yl benzothioate* to obtain cyano-substituted 3-(phenylthio)quinolines (**9a-c**). Finally, to obtain the final target compounds, 3-[(substituted) phenylthio]quinolines were alkylated with appropriate alkyl halides to yield 3-(substituted-phenylsulfanyl)-1-(5-phenylpentyl)- (**10a-p**) or 3-(substituted-phenylsulfanyl)-1-(5-cyclohexylpentyl)- (**11a-p**) quinolinium iodides in good yields as shown in Scheme 2.

Substituents on phenyl ring A were selected using the Craig plot in order to explore the complete electronic and lipophilic space surrounding the phenylthio- moiety.

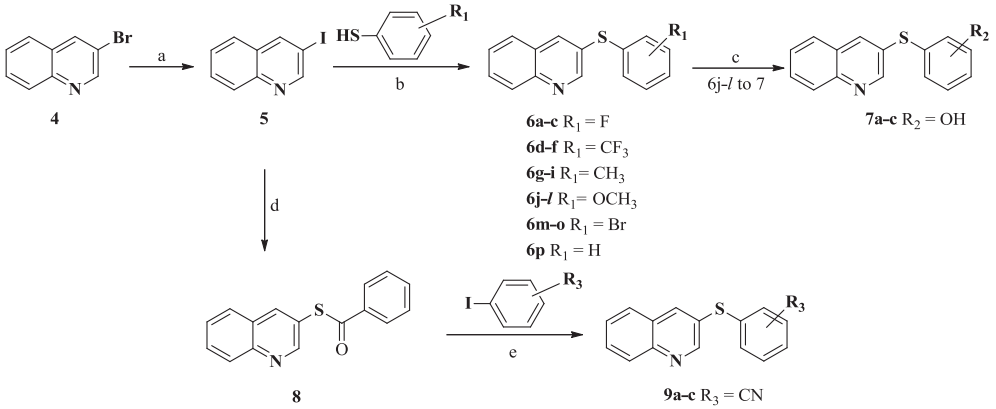
2.2. Biological evaluation

Previous studies in our laboratories have revealed that substitution on the ring of cryptolepine and 5-methyl benzothieno[3,2-*b*] quinolinium salt (**2**) enhanced potency and broadened anti-opportunistic activity profile [5,9]. This result was validated in murine models of cryptococcosis and candidiasis [5]. Further optimization, by opening the benzo[b]thiophene ring, has led to the identification of 1-substituted-3-(phenylthio)quinolinium iodide (**3**) as a potential anti-opportunistic agent [5]. It was of interest to explore a library of substituents on the benzenethiol moiety of 1-substituted-3-(phenylthio)quinolinium iodide since substitution here would have the most impact on the sulfur linking the rings. Thus, compounds **10a-p** were synthesized and evaluated against *Cryptococcus neoformans*,*Candida albicans* and *Aspergillus fumigatus* while **11a-p** were evaluated against additional pathogens *Candida glabrata* and *Candida krusei* since they were found to be more potent than **10a-p** and preliminary investigations showed them to have fungicidal properties. The inclusion of *C. glabrata* and *C. krusei* in the evaluations is related to their emerging status as microbes of health concern for immune-compromised populations. For example, the results of a recent study indicated that *C. glabrata* and *C. krusei* were the leading causes of candidemia in patients with hematologic malignancies [10]. It has also been reported that *C. krusei* is prevalent in bone marrow transplantation and accounts for 2–3% of all *Candida* bloodstream infections [11] and thus, is considered an emerging health concern.

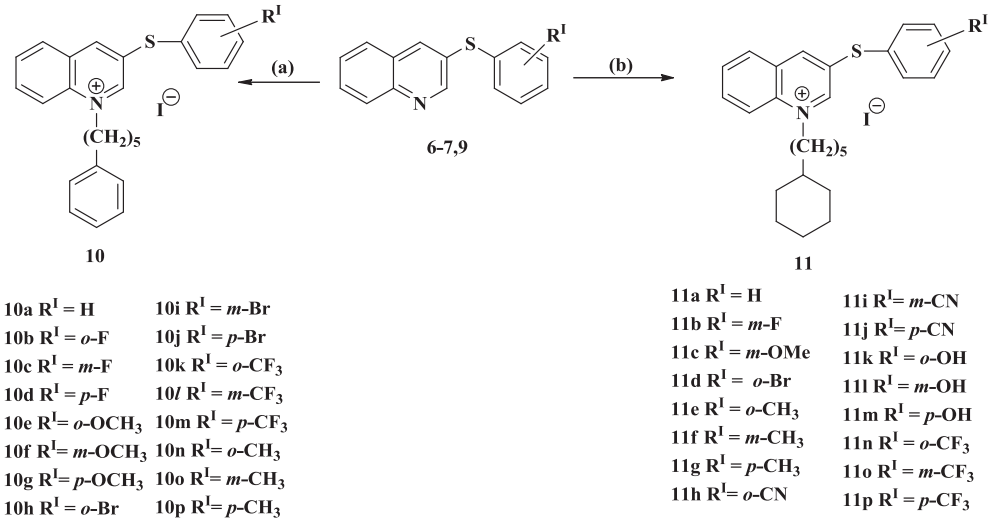
2.3. In-vitro evaluation

The results of the *in vitro* antifungal screening of substituted-3-(phenylthio)quinolinium iodides with the ω-phenylpentyl and ω-cyclohexylpentyl moieties are presented in Tables 1 and 2 respectively. When both IC_{50} and MIC values are between 1 and 10 μg/mL, the compounds are considered active, moderately active between 10 and 15 μg/mL and weak above 15 and up to 20 μg/mL. Compounds with activities above 20 μg/mL are considered inactive while activities below 1 μg/mL are considered very potent. Most of the compounds in the first group (Table 1) show potent activities against *C. neoformans* (Cn) and *C. albicans* (Ca) but are generally inactive against *A. fumigatus*. On the other hand, compounds in Table 2 are generally very potent not only against the three fungi but extend to *C. krusei* and *C. glabrata*, two emerging opportunistic pathogens. Both of these pathogens are more recent and are of significant concern in especially cancer patients. In addition to their enhanced potency, compounds **11a-p** in general are fungicidal at low concentrations against all the pathogens evaluated except for *A. fumigatus*.

Compound **10a**, the unsubstituted N-alkylated-3-phenylthioquinolinium salt, was previously reported [5] and support the initial hypothesis that ring-opening at the benzo[*b*]thiophene moiety and substitution of an ω-phenyl- or ω-cyclohexyl-pentyl group enhances activity against fungal pathogens. The effect of various substituents with varying electronic and lipophilic properties was evaluated by introducing substituents on the thiophenyl moeity with an ω-phenylpentyl group on the quinoline nitrogen. Compounds **10b-d** with fluoro substituents at *ortho*-, *meta*- and *para*- positions have only moderate to weak activity against two of the three pathogens excluding *C. albicans*. Activity against *C. albicans*



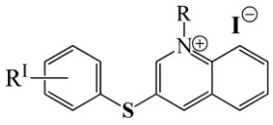
Scheme 1. Synthetic Procedure for 3-(substituted-phenylthio)quinoline. Reagents and Conditions: (a) CuI, $CH_3NHCH_2CH_2NHCH_3$, NaI, Dioxane, reflux under N_2, 110 °C, 48 h; (b) Substituted-benzenethiol, CuI, $HOCH_2CH_2OH$, K_2CO_3, *i*-PrOH, reflux under N_2, 110 °C, 48 h; (c) Py.HCl, 200–220 °C, 6 h; (d) Thiobenzoic acid, CuI, 1,10-phenanthroline, *i*-Pr_2EtN, Toluene, reflux under N_2, 110 °C 24 h (e) Substituted-benzene halide, CuI, $HOCH_2CH_2OH$, K_2CO_3, DMA, reflux under N_2, 110 °C, 48 h.



Scheme 2. Synthetic Procedure for 3-(substituted-phenylsulfanyl)-1-(5-alkyl)quinolinium iodide. Reagents and Conditions: (a) and (b) $C_6H_5(CH_2)_4CH_2$-I or $C_6H_{11}(CH_2)_4CH_2$-I, Tetramethylene sulfone, 110 °C, 12–16 h.

was much subdued compared to the other fungi under investigation. The electron-donating and weakly polar methoxy group did not fare any better. However, the effect of the larger, more lipophilic and electron-withdrawing bromo atom substituted at the *o*-, *m*- and *p*-positions (compounds **10h-j**) showed comparable activity to the unsubstituted compound. Interestingly, activity against *A. fumigatus* was much more significant than for any other substituted analog in the series. Compounds **10k-m**, the trifluoromethyl substituted analogs had similar activities as the bromo analogs except that they were essentially inactive against *A. fumigatus*. Finally, the electron-donating and lipophilic methyl group was evaluated. These had no significant activity against both *C. albicans* and *A. fumigatus* but retain comparable activity as the unsubstituted analog against *C. neoformans*. Overall, cytotoxicity in Vero cells was considered acceptable ($TC_{50} \geq 10$ μg/mL) for all analogs except for **10d**, the *o*-methoxy, **10o**, the *m*-methyl and **10p**, the *p*-methyl analogs.

Table 1
Antifungal activities of 3-(substituted-phenylsulfanyl)-1-(5-phenylpentyl)quinolinium iodide.



Compd[a] 10	R^I	R	IC_{50}/MIC/MFC (μg/mL)			TC_{50} (μg/mL)
			Cn	Ca	Af	
a	H	PP	1.5/5.0/>20	5.5/10/>20	NT/1.3/>20	NT
b	*o*-F	PP	9.5/20/>20	>20	9.0/20/>20	NC
c	*m*-F	PP	7.0/10/>20	>20	5.0/20/>20	NC
d	*p*-F	PP	15/20/>20	>20	9.0/20/>20	NC
e	*o*-OMe	PP	15/>20/>20	>20	8.0/>20/>20	4.3
f	*m*-OMe	PP	10/20/>20	>20	3.5/5.0/>20	>10
g	*p*-OMe	PP	15/20/<20	>20	4.5/20/>20	10
h	*o*-Br	PP	3.0/5.0/20	10/20/>20	1.0/2.5/>20	10
i	*m*-Br	PP	2.0/5.0/10	10/20/>20	2.5/10/>20	>10
j	*p*-Br	PP	2.0/10/10	8.5/20/>20	3.5/10/>20	NC
k	*o*-CF_3	PP	2.2/5.0/10	12/>20/>20	6.9/>20/>20	NC
l	*m*-CF_3	PP	2.1/5.0/10	14/>20/>20	17/>20/>20	NC
m	*p*-CF_3	PP	2.7/5.0/10	11/20/>20	15/>20/>20	10
n	*o*-CH_3	PP	4.0/5.0/20	>20	>20	NC
o	*m*-CH_3	PP	1.4/2.5/20	>20	20/>20/>20	8.8
p	*p*-CH_3	PP	1.2/2.5/5.0	>20	16/>20/>20	4.2
AmB			0.7/1.3/5.0	0.3/1.3/1.3	0.7/1.3/5.0	6.5[b]

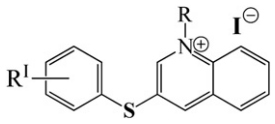
Abbreviations: Cn = *Cryptococcus neoformans*, Ca = *Candida albicans*, Af = *Aspergillus fumigatus*, AmB = Amphotericin B. R = PP = 5-Phenylpentyl-.

[a] All compounds were subjected to CHN analysis and each passed within 0.4% of the theoretical value. NT = Not Tested. IC_{50} = The concentration that affords 50% inhibition of growth; MIC = Minimum inhibitory concentration, is the lowest test concentration that allows no detectable growth. MFC = Minimum Fungicidal Concentration, is the lowest test concentration that kills the microorganism. TC_{50} = The concentration that is toxic to 50% of cells.

[b] TC_{50} value previously reported.[9] NC = No cytotoxicity observed on Vero cells at 10 μg/mL.

Next, the ω-phenylpentyl group was replaced with the more hydrophobic ω-cyclohexylpentyl group (Table 2) in line with previous observations that the latter enhanced activity even more [12]. Comparing the two unsubstituted analogs, the former (**10a**) and the latter (**11a**) showed the latter to be the more potent against all pathogens tested except for *A. fumigatus* where the reverse is the case. This observation was further probed using two *meta*-substituted analogs (**11b** and **11c**) and one *ortho*-substituted analog (**11d**) with similar results. Compounds **11e-g**, methyl-substituted analogs with electron donating and lipophilic characteristics provided a nice contrast with compounds **11h-j**, the cyano-substituted analogs with electron-withdrawing and hydrophilic characteristics. The results appear to suggest that the methyl substituents have marginally better activity against all pathogens although they also seem to have higher cytotoxicity. Comparing the electron-donating and hydrophilic hydroxy substituents (**11k-m**) with the electron-donating but lipophilic methyl substituents (**11e-g**), it would appear that lipophilicity rather than hydrophilicity was preferred for increased antifungal activity. Compounds **11n-p** with trifluoromethyl substituents at the *o*-, *m*- and *p*-positions respectively, also allowed for a head to head comparison of the effect of the ω-phenylpentyl- (**10k-m**) and ω-cyclohexylpentyl-(**11n-p**) substituents. Consistent with previous observations, the ω-cyclohexylpentyl group demonstrated superior potency against all five pathogens, including *C. glabrata* and *C. krusei*. Among the three cyclohexylpentyl substituted analogs however, the *p*-substituted trifluoromethyl analog **11p** showed the highest potencies similar in magnitude to those of amphotericin B. With no cytotoxicities observed at 10 μg/mL, the N-cyclohexylpentyl 3-phenylthio-quinolinium scaffold now constitutes a new anti-opportunistic infection pharmacophore warranting further development including *in vivo* efficacy evaluation. These investigations are currently ongoing.

Table 2
Antifungal activities of 3-(substituted-phenylsulfanyl)-1-(5- cyclohexylpentyl)quinolinium iodide.



Compd[a] $R^1$11	R	IC_{50}/MIC/MFC (μg/mL)					TC_{50} (μg/mL)	S.I.
		Cn	Ca	Cg	Ck	Af		Cn
aH	CP	0.5/1.3/2.5	2.7/5.0/10	15/20/20	0.7/1.3/2.5	8.6/10/>20	4.6	9.2
b*m*-F	CP	0.5/0.6/2.5	2.7/5.0/10	12/20/20	0.3/0.6/1.3	5.3/10/20	6.6	13
c *m*-OMe	CP	0.4/0.6/2.5	2.7/5.0/10	16/20/>20	0.6/1.3/1.3	5.5/10/20	4.5	11
d *o*-Br	CP	0.3/0.6/1.3	1.4/2.5/2.5	3.2/5.0/10	0.3/0.6/1.3	2.0/2.5/20	9.7	32
e *o*-CH_3	CP	0.3/0.6/1.3	1.7/5.0/10	13/20/20	0.6/1.3/1.3	4.8/10/>20	4.0	13
f *m*-CH_3	CP	0.2/0.3/0.4	1.4/2.5/5.0	5.5/10/10	0.4/0.6/1.3	3.5/5.0/5.0	3.7	19
g *p*-CH_3	CP	0.2/0.3/1.3	1.3/2.5/5.0	5.5/10/10	0.5/0.6/1.3	2.7/5.0/5.0	2.8	14
h *o*-CN	CP	1.1/1.3/10	3.3/10/10	12/20/20	0.7/2.5/5.0	5.0/19/20	10	9.1
i *m*-CN	CP	0.7/1.3/5.0	6.7/20/20	13/20/20	1.4/5.0/10	19/20/>20	NC	>14
j *p*-CN	CP	0.5/1.3/5.0	6.2/10/20	6.3/10/20	2.3/5.0/10	19/20/>20	NC	>20
k *o*-OH	CP	1.0/1.3/1.3	4.7/10/20	12/20/>20	4.4/10/10	3.9/10/>20	9.3	9.3
l *m*-OH	CP	1.3/2.5/5.0	3.5/10/20	>20	5.1/10/20	10/20/>20	NC	>7.7
m *p*-OH	CP	0.7/1.3/2.5	3.9/10/20	>20	1.5/5.0/5.0	7.9/20/>20	NC	>14
n *o*-CF_3	CP	0.3/0.6/1.3	1.1/2.5/2.5	3.0/5.0/10	1.1/1.3/1.3	1.8/5.0/5.0	NC	>33
o *m*-CF_3	CP	0.4/0.6/0.6	1.3/2.5/5.0	4.6/10/10	1.2/2.5/2.5	2.2/2.5/>20	NC	>25
p *p*-CF_3	CP	0.3/0.6/0.6	0.8/2.5/2.5	4.7/10/10	1.3/2.5/5.0	1.7/2.5/>20	NC	>33
AmB		0.7/1.3/5.0	0.3/1.3/1.3	0.6/1.3/2.5	0.9/2.5/2.5	0.7/1.3/5.0	6.5[b]	14

Abbreviations: Cn = *Cryptococcus neoformans*, Ca = *Candida albicans*, Cg = *Candida glabrata*, Ck = *Candida krusei*, Af = *Aspergillus fumigatus*, AmB = Amphotericin B. R = CP = 5-Cyclohexylpentyl-.

[a] All compounds were subjected to CHN analysis and each passed within 0.4% of the theoretical value. IC_{50} = The concentration that affords 50% inhibition of growth; MIC = Minimum inhibitory concentration, is the lowest test concentration that allows no detectable growth. MFC = Minimum Fungicidal Concentration, is the lowest test concentration that kills the microorganism. TC_{50} = The concentration that is toxic to 50% of cells.

[b] TC_{50} value previously reported NC = No cytotoxicity on Vero cells at 10 μg/mL. Selectivity Index (S.I.) = TC_{50}(Vero cells)/IC_{50} (Cn).

3. Conclusion

By opening the benzo[*b*]thiophene ring and replacing the N-methyl group with N-ω-phenylpentyl or ω-cyclohexylpentyl group to form substituted 3-(phenylthio)quinolinium compounds, we have obtained potencies as high as 300-fold (cf, cryptolepine = 250 μg/mL vs **11p** = 0.8 μg/mL for *C. albicans*) over the starting tetracyclic parent. Several of these analogs (**11a-p**) have also demonstrated significantly higher activity against *C. krusei* than the other pathogens tested. In addition, unlike their tetracyclic counterparts, these ring-opened analogs demonstrated fungicidal activity as well. The potential of these compounds to induce toxicity in Vero cells was also investigated. Except for the unsubstituted, methyl-substituted (**11e-f)** and *o*-OMe (**11c)** substituted analogs in the cyclohexylpentyl series, all of the compounds showed better cytotoxicity profile in Vero cells than amphotericin B and in fact most of them showed no cytotoxicity at10 μg/mL. In particular, the trifluoromethyl substituted analogs (**11n-p**) have selectivity indices over 2-fold better than those of amphotericin B in *C. neoformans*.

4. Experimental section

4.1. Chemistry

All reagents were purchased from Sigma–Aldrich, Fisher Scientific or Alfa Aesar and were used without further purification. Flash chromatography was performed with Davisil grade 634 silica gel. Analytical thin layer chromatography (TLC) was carried out on Merck TLC plates coated with silica gel 60 F_{254} (0.25 mm layer thickness); visualization was carried out using a UV lamp (254 nm). Melting points were determined on an Electrothermal MEL-TEMP® 3.0 device and are uncorrected. Nuclear Magnetic Resonance (^{1}HNMR) spectra were obtained on a Varian 300 MHz Mercury NMR Spectrometer. Elemental analyses were carried out by Atlantic Microlab, Inc., Norcross, GA, and were within 0.4% of the theory unless otherwise noted.

4.2. Procedure for the synthesis of 3-iodoquinoline, ***5***

The method of Klapars was used [6]. A mixture of 3-bromoquinoline (9.8 g, 47.3 mmol), CuI (0.45 g, 2.4 mmol), NaI (14.2 g, 94.5 mmol), *N, N*-dimethylethylenediamine (0.5 mL) and dioxane (47.3 mL) was stirred and heated to 110 °C and allowed to reflux under N_2 for 48 h. The reaction was monitored by TLC till the conversion reached 100%. The resulting mixture was allowed to cool to rt, diluted with 30% aqueous NH_3 (20 mL), then diluted with distilled H_2O and extracted with EtOAc (3 × 30 mL). The organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated by rotary evaporation at reduced pressure to yield the pure product in quantitative yield as a pale yellow solid. Yield 12 g, 100%. ^{1}HNMR ($CDCl_3$): δ 9.03 (d, 1H, J = 2.4 Hz), 8.54–8.53 (m, 1H), 8.08–8.04 (m, 1H), 7.76–7.69 (m, 2H), 7.59–7.53 (m, 1H).

4.3. General procedure for the synthesis of 3-[(substituted) phenylthio]quinoline, ***6a-p***

The method of Kwong was used [7]. A mixture of Cu (I) iodide (20 mg, 0.10 mmol), K_2CO_3 (540 mg, 3.92 mmol), 3-iodoquinoline (500 mg, 1.96 mmol), substituted benzenethiol (0.21 mL, 1.96 mmol), ethylene glycol (0.22 mL, 3.92 mmol) and 2-propanol (2 mL) was heated at 80 °C and allowed to reflux under N_2 for 30 h. After cooling to rt, the mixture was diluted with distilled H_2O (20 mL) and then extracted with EtOAc (3 × 15 mL). The pooled organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated by rotary evaporation at reduced pressure to provide a crude product. The crude product was purified by column chromatography on silica gel using hexane: EtOAc (9.8: 0.2)

to afford 3-[(substituted)phenylthio]quinoline. A typical reaction yield was found to be 90–95%.

4.3.1. 3-(2-fluorophenylthio)quinoline, ***6a***

Yield 94%; ^{1}HNMR ($CDCl_3$): δ 8.15 (d, 1H, J = 1.8 Hz), 8.09–8.05 (m, 2H), 7.70–7.64 (m, 2H), 7.54–7.48 (m, 1H), 7.36–7.26 (m, 2H), 7.14–7.05 (m, 2H).

4.3.2. 3-(3-fluorophenylthio)quinoline, ***6b***

Yield 90%; ^{1}HNMR ($CDCl_3$): δ 8.84 (d, 1H, J = 2.1 Hz), 8.19 (d, 1H, J = 1.8 Hz), 8.12–8.09 (m, 1H), 7.78–7.71 (m, 2H), 7.61–7.55 (m, 1H), 7.31–7.24 (m, 1H), 7.11–7.08 (m, 1H), 7.03–6.92 (m, 2H).

4.3.3. 3-(4-fluorophenylthio)quinoline, ***6c***

Yield 95%; ^{1}HNMR ($CDCl_3$): δ 8.77 (s, 1H), 8.08–8.05 (m, 1H), 7.97 (d, 1H, J = 2.4 Hz), 7.71–7.66 (m, 2H), 7.57–7.51 (m, 1H), 7.47–7.42 (m, 2H), 7.09–7.04 (m, 2H).

4.3.4. 3-(2-trifluoromethylphenylthio)quinoline, ***6d***

Yield 94%; ^{1}HNMR ($CDCl_3$): δ 8.82 (d, 1H, J = 2.1 Hz), 8.18 (s, 1H), 8.09 (d, 1H, J = 8.1 Hz), 7.77–7.71 (m, 3H), 7.60–7.55 (m, 1H), 7.39–7.34 (m, 2H), 7.26–7.23 (m, 1H).

4.3.5. 3-(3-trifluoromethylphenylthio)quinoline, ***6e***

Yield 95%; ^{1}HNMR ($CDCl_3$): δ 8.85 (s, 1H), 8.21 (d, 1H, J = 1.8 Hz), 8.13 (d, 1H, J = 8.1 Hz), 7.78–7.72 (m, 2H), 7.62–7.39 (m, 5H).

4.3.6. 3-(4-trifluoromethylphenylthio)quinoline, ***6f***

Yield 97%; ^{1}HNMR ($CDCl_3$): δ 8.87 (d, 1H, J = 1.8 Hz), 8.28 (d, 1H, J = 2.1 Hz), 8.12 (d, 1H, J = 8.4 Hz), 7.78 (t, 2H, J = 8.4 Hz), 7.60 (t, 1H, J = 6.9 Hz), 7.52 (d, 2H, J = 8.7 Hz), 7.36–7.28 (m, 2H).

4.3.7. 3-(2-methylphenylthio)quinoline, ***6g***

Yield 91%; ^{1}HNMR ($CDCl_3$): δ 8.74 (s, 1H), 8.07–8.04 (m, 1H), 7.83 (d, 1H, J = 2.1 Hz), 7.66–7.61 (m, 2H), 7.51–7.45 (m, 1H), 7.35–7.12 (m, 4H), 2.40 (s, 3H).

4.3.8. 3-(3-methylphenylthio)quinoline, ***6h***

Yield 96%; ^{1}HNMR ($CDCl_3$): δ 8.81 (d, 1H, J = 2.1 Hz), 8.05 (t, 2H, J = 2.4 Hz), 7.71–7.65 (m, 2H), 7.55–7.50 (m, 1H), 7.25–7.20 (m, 3H), 7.12–7.09 (m, 1H), 2.39 (s, 3H).

4.3.9. 3-(4-methylphenylthio)quinoline, ***6i***

Yield 92%; ^{1}HNMR ($CDCl_3$): δ 8.78 (d, 1H, J = 2.4 Hz), 8.06–8.03 (m, 1H), 7.95 (d, 1H, J = 3.0 Hz), 7.67–7.62 (m, 2H), 7.52–7.49 (m, 1H), 7.35–7.32 (m, 2H), 7.17 (d, 2H, J = 8.1 Hz), 2.39 (s, 3H).

4.3.10. 3-(2-methoxyphenylthio)quinoline, ***6j***

Yield 91%; ^{1}HNMR ($CDCl_3$,): δ 8.80 (d, 1H, J = 2.1 Hz), 8.09–8.04 (m, 2H), 7.72–7.66 (m, 2H), 7.56–7.50 (m, 1H), 7.35–7.20 (m, 2H), 6.96–6.91 (m, 2H), 3.86 (s, 3H).

4.3.11. 3-(3-methoxyphenylthio)quinoline, ***6k***

Yield 92%; ^{1}HNMR ($CDCl_3$): δ 8.83 (d, 1H, J = 2.4 Hz), 8.09–8.04 (m, 2H), 7.74–7.67 (m, 2H), 7.57–7.52 (m, 1H), 7.27–7.21 (m, 1H), 6.97–6.91 (m, 2H), 6.85–6.81 (m, 1H), 3.76 (s, 3H).

4.3.12. 3-(4-methoxyphenylthio)quinoline, ***6l***

Yield 94%; ^{1}HNMR ($CDCl_3$): δ 8.73 (d, 1H, J = 2.4 Hz), 8.05–8.01 (m, 1H), 7.80 (d, 1H, J = 2.1 Hz), 7.65–7.59 (m, 2H), 7.50–7.43 (m, 3H), 6.93–6.90 (m, 2H), 3.81 (s, 3H).

4.3.13. 3-(2-bromophenylthio)quinoline, ***6m***

Yield 95%; ^{1}HNMR ($CDCl_3$): δ 8.86 (d, 1H, J = 2.1 Hz), 8.22 (d, 1H, J = 2.4 Hz), 8.14–8.10 (m, 1H), 7.79–7.72 (m, 2H), 7.63–7.55 (m, 2H), 7.21–7.07 (m, 2H), 7.04–7.00 (m, 1H).

4.3.14. 3-(3-bromophenylthio)quinoline, ***6n***

Yield 90%; ^{1}HNMR ($CDCl_3$): δ 8.83 (s, 1H), 8.17 (d, 1H, J = 1.8 Hz), 8.12–8.09 (m, 1H), 7.77–7.70 (m, 2H), 7.60–7.54 (m, 1H), 7.47 (t, 1H, J = 1.8 Hz), 7.41–7.37 (m, 1H), 7.27–7.23 (m, 1H), 7.19–7.14 (m, 1H).

4.3.15. 3-(4-bromophenylthio)quinoline, ***6o***

Yield 92%; ^{1}HNMR ($CDCl_3$): δ 8.81 (d, 1H, J = 2.4 Hz), 8.10 (m, 2H), 7.75–7.69 (m, 2H), 7.59–7.53 (m, 1H), 7.46–7.42 (m, 2H), 7.26–7.21 (m, 2H).

4.3.16. 3-(phenylthio)quinoline, ***6p***

Yield 92%; ^{1}HNMR ($CDCl_3$): δ 8.81 (s, 1H), 8.08–8.06 (m, 2H), 7.71–7.25 (m, 8H).

4.4. General procedure for the synthesis of 3-(hydroxyphenylthio) quinoline ***7a-c***

A mixture of 3-(methoxyphenylthio)quinoline **(6j-l)** (100 mg, 0.37 mmol) and pyridine hydrochloride (864 mg, 7.49 mmol) was stirred for 6 h at 220 °C. The resulting mixture was diluted with distilled H_2O and extracted with EtOAc (3 × 15 mL). The pooled organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated by rotary evaporation at reduced pressure. The crude product was subjected to column chromatography on silica gel (hexane/EtOAc, 7: 3) to afford 3-(hydroxyphenylthio) quinoline as a solid. Yield 50–60%.

4.4.1. 3-(2-hydroxyphenylthio)quinoline, ***7a***

Yield 51%; ^{1}HNMR (DMSO-d_6): δ 8.72(s, 1H), 8.04 (d, 1H, J = 8.7 Hz), 7.70–7.40 (m, 6H), 7.10 (d, 1H, J = 7.8 Hz), 7.62–7.00 (t, 1H, J = 15 Hz), 6.54 (s, 1H).

4.4.2. 3-(3-hydroxyphenylthio)quinoline, ***7b***

Yield 60%; ^{1}HNMR (DMSO-d_6): δ 9.57 (s, 1H), 8.75 (d, 1H, J = 2.1 Hz), 8.37 (d, 1H, J = 2.1 Hz), 8.02–7.73 (m, 2H), 7.78–7.73 (m, 1H), 7.64–7.59 (m, 1H), 7.19–7.14 (m, 1H), 6.80–6.68 (m, 3H).

4.4.3. 3-(4-hydroxyphenylthio)quinoline, ***7c***

Yield 57%; ^{1}HNMR (DMSO-d_6): δ 9.84 (s, 1H), 8.66 (d, 1H, J = 2.4 Hz), 7.98–7.94 (m, 1H), 7.84–7.81 (m, 1H), 7.78–7.73 (m, 1H), 7.71–7.65 (m, 1H), 7.58–7.53 (m, 1H), 7.41–7.36 (m, 2H), 6.88–6.83 (m, 2H).

4.5. General procedure for the synthesis of S-quinolin-3-yl benzothioate ***8***

The method of Sawada was used [8]. A mixture of 3-iodoquinoline (5.4 g, 21.2 mmol), thiobenzoic acid (4.5 g, 32.60 mmol), CuI (400 mg, 2.1 mmol), 1,10-phenanthroline (780 mg, 4.3 mmol), *N, N*-diisopropylethylamine (10 mL, 43.00 mmol) in toluene (3 mL) was refluxed under N_2 for 24 h. After cooling to room temperature, the mixture was directly purified without performing liquid–liquid separation through column chromatography on silica gel (hexane/EtOAc, 9.6: 0.4) to afford *S*-quinolin-3-yl benzothioate. Yield 5.17 g, 90%; ^{1}HNMR ($CDCl_3$): δ 8.89 (1H, s), 8.38 (1H, brs), 8.16 (1H, d, J = 8.4 Hz), 8.05 (2H, m), 7.85 (1H, d, J = 8.4 Hz), 7.80 (1H, m), 7.63 (2H, m), 7.52 (2H, m).

4.6. General procedure for the synthesis of substituted-(quinolin-3-ylsulfanyl)-benzonitrile ***9a-c***

The method of Deng was used [13]. A mixture of *S*-quinolin-3-yl benzothioate (250 mg, 0.94 mmol), 2-iodobenzonitrile (280 mg, 1.22 mmol), ethylene glycol (0.11 mL, 1.88 mmol), Cu (I) iodide (89 mg, 0.47 mmol), K_2CO_3 (360 mg, 2.59 mmol) in *N, N*-

dimethylacetamide (4 mL) was heated at 110 °C for 48 h under N_2. The resulting mixture was diluted with EtOAc (3 × 20 mL), washed with brine (50 mL). The organic layer was dried over Na_2SO_4, and filtered. The filtrate was concentrated in *vacuo* and followed by column chromatography on silica gel to afford substituted-(quinolinylthio)benzonitrile. Yield 222 mg, 80–90%.

4.6.1. 2-(quinolin-3-ylsulfanyl)-benzonitrile, ***9a***

Yield 90%; ^{1}HNMR ($CDCl_3$): δ 8.86 (d, 1H, J = 1.8 Hz), 8.32 (d, 1H, J = 2.4 Hz), 8.13 (d, 1H, J = 8.4 Hz), 7.81–7.23 (m, 7H).

4.6.2. 3-(quinolin-3-ylsulfanyl)-benzonitrile, ***9b***

Yield 84%; ^{1}HNMR ($CDCl_3$): δ 8.85 (d, 1H, J = 2.4 Hz), 8.27–8.26 (m, 1H), 8.15–8.11 (m, 1H), 7.80–7.36 (m, 7H).

4.6.3. 4-(quinolin-3-ylsulfanyl)-benzonitrile, ***9c***

Yield 87%; ^{1}HNMR ($CDCl_3$): δ 8.88 (d, 1H, J = 2.4 Hz), 8.35–8.34 (m, 1H), 8.16–8.13 (m, 1H), 7.82–7.49 (m, 5H), 7.25–7.22 (m, 2H).

4.7. General procedure for the synthesis of 3-(substituted-phenylsulfanyl)-1-(5-phenylpentyl) quinolinium iodide, ***10a-p***

3-(Substituted-phenylthio)quinoline (100 mg, 0.39 mmol) was added to 1-(5-iodopentyl)benzene (130 mg, 0.470 mmol) in tetramethylene sulfone (0.5 mL). The mixture was heated at 110 °C for 12–16 h in a sealed pressure tube. After cooling to rt, EtOAc (15 mL) was added to precipitate the solid. The precipitate was collected, washed with additional EtOAc and dried to a powdery product, 3-(substituted-phenylsulfanyl)-1-(5-phenylpentyl)quinolinium iodide.

4.7.1. 3-(phenylsulfanyl)-1-(5-phenylpentyl)quinolinium iodide, ***10a***

Yield 162 mg, 75%; Mp 166–167 °C; ^{1}HNMR (DMSO-d_6): 9.69 (1H, s), 9.17 (1H, s), 9.57 (1H, d, J = 9.0 Hz), 8.39 (1H, d, J = 8.0 Hz), 8.23 (1H, t, J = 7.5 Hz), 8.02 (1H, t, J = 7.5 Hz), 7.50 (5H, m), 7.24 (2H, t, J = 7.0 Hz), 7.15 (3H, m), 5.02 (2H, t, J = 7.4 Hz), 2.54 (2H, t, J = 7.4 Hz), 1.98 (2H, m), 1.60 (2H, m), 1.39 (2H, m). Anal. Calcd for $C_{26}H_{26}INS \cdot 0.2H_2O$: C 60.63; H 5.09; N 2.72. Found: C 60.60; H 5.02; N 2.73.

4.7.2. 3-(2-fluorophenylsulfanyl)-1-(5-phenylpentyl)quinolinium iodide, ***10b***

Yield 109 mg, 53%; Mp 134–136 °C; ^{1}HNMR (CD_3OD): δ 9.47 (d, 1H, J = 2.1 Hz), 8.93 (d, 1H, J = 0.9 Hz), 8.47 (d, 1H, J = 9 Hz), 8.30–8.19 (m, 2H), 8.03–7.97 (m, 1H), 7.71–7.65 (m, 1H), 7.59–7.56 (m, 1H), 7.36–7.29 (m, 2H), 7.23–7.17 (m, 2H), 7.14–7.09 (m, 3H), 5.04 (t, 2H, J = 7.5 Hz) 2.60 (t, 2H, J = 7.2 Hz), 2.10–2.05 (m, 2H), 1.74–1.64 (m, 2H), 1.46–1.38 (m, 2H). Anal. Calcd for $C_{26}H_{25}FINS$: C 58.98; H 4.76; N 2.65. Found: C 58.75; H 4.72; N 2.66.

4.7.3. 3-(3-fluorophenylsulfanyl)-1-(5-phenylpentyl)quinolinium iodide, ***10c***

Yield 120 mg, 58%; Mp 148–149 °C; ^{1}HNMR (CD_3OD): δ 9.43 (d, 1H, J = 2.1 Hz), 9.0 (s, 1H), 8.45 (d, 1H, J = 9 Hz), 8.29–8.173 (m, 2H), 8.0–7.95 (m, 1H), 7.50–7.42 (m, 1H), 7.36–7.30 (m, 2H), 7.21–7.04 (m, 6H), 4.99 (t, 2H, J = 7.5 Hz), 2.56 (t, 2H, J = 7.2 Hz), 2.07–1.99 (q, 2H, J = 7.2 Hz) 1.7–1.6 (m, 2H), 1.40–1.34 (q, 2H, J = 7.8 Hz). Anal. Calcd for $C_{26}H_{25}FINS$: C 58.98; H 4 0.76; N 2.65. Found: C 59.08; H 4.80; N 2.61.

4.7.4. 3-(4-fluorophenylsulfanyl)-1-(5-phenylpentyl)quinolinium, iodide ***10d***

Yield 168 mg, 81%; Mp 175–176 °C; ^{1}HNMR (CD_3OD): δ 8.82 (s, 1H), 8.45 (d, 1H, J = 9 Hz), 8.27–8.16 (m, 2H), 8.01–7.95 (m, 1H), 7.73–7.68 (m, 2H), 7.36 (d, 1H, J = 2.1 Hz), 7.30–7.08 (m, 7H), 5.02 (t, 2H, J = 7.8 Hz), 2.60 (t, 2H, J = 7.2 Hz), 2.10–2.00 (m, 2H), 1.72–1.66 (m, 2H), 1.43–1.37 (m, 2H). Anal. Calcd for $C_{26}H_{25}FINS$: C 58.98; H 4.76; N 2.65. Found: C 58.80; H 4.76; N 2.66.

4.7.5. 3-(2-methoxyphenylsulfanyl)-1-(5-phenylpentyl) quinolinium iodide, ***10e***

Yield 186 mg, 92%; Mp 121–124 °C; ^{1}HNMR (CD_3OD): δ 9.3 (d, 1H, J = 2.1 Hz), 8.7 (d, 1H, J = 1.5 Hz), 8.45 (d, 1H, J = 9 Hz), 8.25–8.14 (m, 2H), 7.99–7.94 (m, 1H), 7.62–7.52 (m, 2H), 7.23–7.06 (m, 7H), 5.02 (t, 2H, J = 6.9 Hz), 3.78 (s, 3H), 2.6 (t, 2H, J = 7.2 Hz), 2.09–2.00 (m, 2H), 1.71–1.63 (m, 2H), 1.43–1.37 (m, 2H).Anal. Calcd for $C_{27}H_{28}OINS$: C 59.89; H 5.21; N 2.59. Found: C 59.84; H 5.17; N 2.63.

4.7.6. 3-(3-methoxyphenylsulfanyl)-1-(5-phenylpentyl) quinolinium iodide, ***10f***

Yield 166 mg, 82%; Mp 158–159 °C; ^{1}HNMR (CD_3OD): δ 9.34 (d, 1H, J = 1.5 Hz), 8.89 (s, 1H), 8.45 (d, 1H, J = 9 Hz), 8.28–8.17 (m, 2H), 8.02–7.96 (m, 1H), 7.44–7.21 (m, 1H), 7.22–7.04 (m, 8H), 5.02 (t, 2H, J = 7.2 Hz), 3.80 (s, 3H), 2.59 (t, 2H, J = 7.2 Hz), 2.10–2.04 (m, 2H), 1.70–1.65 (m, 2H), 1.42–1.39 (m, 2H). Anal. Calcd for $C_{27}H_{28}OINS$: C 59.89; H 5.21; N 2.59. Found: C 59.82; H 5.28; N 2.64.

4.7.7. 3-(4-methoxyphenylsulfanyl)-1-(5-phenylpentyl) quinolinium iodide, ***10g***

Yield 180 mg, 89%; Mp 164–166 °C; ^{1}HNMR (CD_3OD): δ 9.24 (d, 1H, J = 2.1 Hz), 8.65 (d, 1H, J = 1.8 Hz), 8.41 (d, 1H, J = 9 Hz), 8.21–8.12 (m, 2H), 7.98–7.92 (m, 1H), 7.63–7.60 (m, 2H), 7.20–7.17 (m, 2H), 7.14–7.08 (m, 5H), 4.99 (t, 2H, J = 7.2 Hz), 3.85 (s, 3H), 2.59 (t, 2H, J = 7.5 Hz), 2.08–2.00 (m, 2H), 1.70–1.65 (m, 2H), 1.40–1.35 (m, 2H). Anal. Calcd for $C_{27}H_{28}OINS$: C 59.89; H 5.21; N 2.59. Found: C 59.60; H 5.22; N 2.62.

4.7.8. 3-(2-bromophenylsulfanyl)-1-(5-phenylpentyl)quinolinium iodide, ***10h***

Yield 102 mg, 55%; Mp 110–112 °C; ^{1}HNMR (CD_3OD): δ 9.43(d, 1H, J = 2.1 Hz), 8.98 (s, 1H), 8.5 (d, 1H, J = 9 Hz), 8.33–8.22 (m, 2H), 8.05–8.00 (m, 1H), 7.81–7.77 (m, 1H), 7.59–7.56 (m, 1H), 7.48–7.35 (m, 2H), 7.22–7.07 (m, 5H), 5.05 (t, 2H, J = 7.2 Hz), 2.6 (t, 2H, J = 7.5 Hz), 2.11–2.06 (m, 2H), 1.72–1.66 (m, 2H), 1.43–1.37 (m, 2H). Anal. Calcd for $C_{26}H_{25}BrINS$: C 52.90; H 4.27; N 2.37. Found: C 52.96; H 4.32; N 2.42.

4.7.9. 3-(3-bromophenylsulfanyl)-1-(5-phenylpentyl)quinolinium iodide, ***10i***

Yield 115 mg, 62%; Mp 156–157 °C; ^{1}HNMR (CD_3OD): δ 9.45 (d, 1H, J = 1.8 Hz), 9.04 (d, 1H, J = 1.5 Hz) 8.47 (d, 1H, J = 9.3 Hz), 8.33–8.21 (m, 2H), 8.05–7.99 (m, 1H), 7.79–7.78 (m, 1H), 7.65–7.61 (m, 1H), 7.57–7.54 (m, 1H) 7.42–7.36 (m, 1H), 7.22–7.07 (m, 5H), 5.03 (t, 2H, J = 7.5 Hz), 2.6 (t, 2H, J = 7.5 Hz), 2.12–2.05 (m, 2H), 1.72–1.67 (m, 2H), 1.38–1.43(m, 2H). Anal. Calcd for $C_{26}H_{25}BrINS$: C 52.90; H 4.27; N 2.37. Found: C 52.61; H 4.22; N 2.33.

4.7.10. 3-(4-bromophenylsulfanyl)-1-(5-phenylpentyl)quinolinium iodide, ***10j***

Yield 130 mg, 70%; Mp 178–179 °C; ^{1}HNMR (CD_3OD): δ 9.4 (d, 1H, J = 2.1 Hz), 8.97 (s, 1H), 8.46 (d, 1H, J = 8.4 Hz), 8.31–8.19 (m, 2H), 8.0 (t, 1H, J = 7.5 Hz), 7.67–7.63 (m, 2H), 7.65 (d, 2H, J = 9.0 Hz), 7.51 (d, 2H, J = 9.0 Hz), 7.14–7.08 (m, 3H), 5.02 (t, 2H, J = 7.2 Hz), 2.6 (t, 2H, J = 7.8 Hz), 2.10–2.00 (m, 2H), 1.71–1.66 (m, 2H), 1.42–1.36 (m, 2H). Anal. Calcd for $C_{26}H_{25}BrINS$: C 52.90; H 4.27; N 2.37. Found: C 52.76; H 4.28; N 2.49.

4.7.11. 3-(2-Trifluoromethyl-phenylsulfanyl)-1-(5-phenylpentyl) quinolinium iodide, ***10k***

Yield 60 mg, 32%; Mp 143–144 °C; ^{1}HNMR (CD_3OD): δ 9.44 (d, 1H, J = 1.8 Hz), 8.93 (s, 1H), 8.48 (d, 1H, J = 9 Hz), 8.31–8.21 (m, 2H),

8.04–7.92 (m, 2H), 7.66–7.69 (m, 3H), 7.17–7.22 (m, 2H), 7.08–7.14 (m, 3H), 5.04 (t, 2H, $J = 7.2$ Hz), 2.60 (t, 2H, $J = 7.2$ Hz) 2.15–2.05 (m, 2H), 1.74–1.64 (m, 2H), 1.46–1.38 (m, 2H). Anal. Calcd for $C_{27}H_{25}F_3INS$: C 55.96; H 4.35; N 2.42. Found: C 55.88; H 4.34; N 2.40.

4.7.12. 3-(3-Trifluoromethyl-phenylsulfanyl)-1-(5-phenylpentyl) quinolinium iodide, ***10l***

Yield 79.40 mg, 56%; Mp 151–152 °C; ^{1}HNMR (CD_3OD): δ 9.51 (d, 1H, $J = 1.8$ Hz), 9.08 (s, 1H), 8.52 (d, 1H, $J = 9$ Hz), 8.33–8.22 (m, 2H), 8.02 (t, 1H, $J = 8.1$ Hz), 7.93 (s, 1H), 7.77–7.75 (m, 2H), 7.66 (t, 1H, $J = 7.2$ Hz), 7.22–7.08 (m, 5H), 5.04 (t, 2H, $J = 7.5$ Hz), 2.60 (t, 2H, $J = 7.5$ Hz), 2.11–2.06 (m, 2H), 1.72–1.67 (m, 2H), 1.48–1.40 (m, 2H). Anal. Calcd for $C_{27}H_{25}F_3INS$: C 55.96; H 4.35; N 2.42. Found: C 55.92; H 4.31; N 2.44.

4.7.13. 3-(4-Trifluoromethyl-phenylsulfanyl)-1-(5-phenylpentyl) quinolinium iodide, ***10m***

Yield 29 mg, 26%; Mp 131–132 °C; ^{1}HNMR (CD_3OD): δ 9.54 (d, 1H, $J = 1.8$ Hz), 9.19 (s, 1H), 8.51 (d, 1H, $J = 9$ Hz), 8.37–8.25 (m, 2H), 8.04 (t, 1H, $J = 7.5$ Hz), 7.74–7.65 (m, 4H), 7.08–7.22 (m, 5H), 5.05 (t, 2H, $J = 7.5$ Hz), 2.60 (t, 2H, $J = 7.5$ Hz), 2.13–2.07 (m, 2H), 1.72–1.67 (m, 2H), 1.45–1.39 (m, 2H). Anal. Calcd for $C_{27}H_{25}F_3INS$: C 55.96; H 4.35; N 2.42. Found: C 55.72; H 4.32; N 2.48.

4.7.14. 3-(2-Methyl-phenysulfanyl)-1-(5-phenylpentyl)quinolinium iodide, ***10n***

Yield 156 mg, 75%; Mp 166–167 °C; ^{1}HNMR (CD_3OD): δ 9.28 (d, 1H, $J = 2.1$ Hz), 8.59 (s, 1H), 8.45 (d, 1H, $J = 8.7$ Hz), 8.21–8.14 (m, 2H), 7.96 (t, 1H, $J = 7.5$ Hz), 7.60 (d, 1H, $J = 7.5$ Hz), 7.47–7.46 (m, 2H), 7.37–7.32 (m, 1H), 7.22–7.07 (m, 5H), 5.01 (t, 2H, $J = 7.2$ Hz), 2.60 (t, 2H, $J = 7.2$ Hz), 2.45 (s, 3H), 2.14–2.04 (m, 2H), 1.71–1.66 (m, 2H), 1.41–1.36 (m, 2H). Anal. Calcd for $C_{27}H_{28}INS$: C 61.71; H 5.37; N 2.67. Found: C 61.44; H 5.36; N 2.58.

4.7.15. 3-(3-Methyl-phenysulfanyl)-1-(5-phenylpentyl)quinolinium iodide, ***10o***

Yield 194 mg, 93%; Mp 175–176 °C; ^{1}HNMR (CD_3OD): δ 9.31 (s, 1H), 8.83 (s, 1H), 8.46 (d, 1H, $J = 8.7$ Hz), 8.25–8.16 (m, 2H), 7.97 (t, 1H, $J = 7.8$ Hz), 7.47–7.33 (m, 4H), 7.21–7.07 (m, 5H), 5.01 (t, 2H, $J = 7.2$ Hz), 2.59 (t, 2H, $J = 7.5$ Hz), 2.37 (s, 3H), 2.09–2.04 (m, 2H), 1.70–1.65 (m, 2H), 1.41–1.36 (m, 2H). Anal. Calcd for $C_{27}H_{28}INS \cdot 0.3H_20$: C 61.08; H 5.32; N 2.64. Found: C 61.07; H 5.38; N 2.67.

4.7.16. 3-(4-Methyl-phenysulfanyl)-1-(5-phenylpentyl)quinolinium iodide, ***10p***

Yield 157 mg, 75%; Mp 179–181 °C; ^{1}HNMR (DMSO-d_6): δ 9.60 (d, 1H, $J = 2.1$ Hz), 9.02 (d, 1H, $J = 1.5$ Hz), 8.55 (d, 1H, $J = 9.0$ Hz), 8.36–8.34 (m, 1H), 8.22–8.16 (m, 1H), 7.98 (t, 1H, $J = 7.8$ Hz), 7.48 (d, 2H, $J = 7.8$ Hz), 7.31–7.11(m, 7H), 5.01 (t, 2H, $J = 7.2$ Hz), 2.56–2.40 (m, 2H), 2.33 (s, 3H), 2.01–1.91 (m, 2H), 1.64–1.54 (m, 2H), 1.40–1.30 (m, 2H). Anal. Calcd for $C_{27}H_{28}INS$: C 61.71; H 5.37; N 2.67. Found: C 61.83; H 5.47; N 2.80.

4.8. General procedure for the synthesis of 3-(substituted-phenylsulfanyl)-1-(5-cyclohexylpentyl) quinolinium iodide, ***11a-p***

4.8.1. 3-(phenylsulfanyl)-1-(5-cyclohexylpentyl)quinolinium iodide, ***11a***

Yield 160 mg, 73%; Mp 174–176 °C; ^{1}HNMR (DMSO-d_6): δ 9.66 (d, 1H, $J = 2.1$ Hz), 9.16 (d, 1H, $J = 1.5$ Hz), 8.58 (d, 1H, $J = 9.0$ Hz), 8.38 (t, 1H, $J = 7.2$ Hz), 8.25–8.19 (m, 1H), 8.01 (t, 1H, $J = 7.5$ Hz), 7.56–7.41 (m, 5H), 5.01 (t, 2H, $J = 7.2$ Hz), 1.93–1.91 (m, 2H), 1.64–1.61 (m, 5H), 1.30–1.11 (m, 10H), 0.86–0.79 (m, 2H). Anal. Calcd for $C_{26}H_{32}INS$: C 60.34; H 6.23; N 2.71. Found: C 60.48; H 6.27; N 2.75.

4.8.2. 3-(3-fluorophenylsulfanyl)-1-(5-cyclohexylpentyl) quinolinium iodide, ***11b***

Yield 132 mg, 58%; Mp 141–142 °C; ^{1}HNMR (DMSO-d_6): δ 9.48 (d, 1H, $J = 1.8$ Hz), 9.06–8.95 (m, 1H), 8.52–8.48 (m, 1H), 8.32–8.19 (m, 2H), 8.04–7.97 (m, 1H), 7.73–7.21 (m, 4H), 5.05 (t, 2H, $J = 7.5$ Hz), 2.14–2.06 (m, 2H), 1.71–1.67 (m, 5H), 1.37–1.18 (m, 10H), 0.92–0.85 (m, 2H). Anal. Calcd for $C_{26}H_{31}FINS$: C 58.32; H 5.83; N 2.62. Found: C 58.23; H 5.80; N 2.55.

4.8.3. 3-(2-bromophenysulfanyl)-1-(5-cyclohexylpentyl) quinolinium iodide, ***11c***

Yield 100 mg, 59%; Mp 157–158 °C; ^{1}HNMR (CD_3OD): δ 9.46 (d, 1H, $J = 2.1$ Hz), 8.99 (s, 1H), 8.54 (d, 1H, $J = 8.7$ Hz), 8.32–8.22 (m, 2H), 8.01 (t, 1H, $J = 7.5$ Hz), 7.80–7.77 (m, 1H), 7.65–7.62 (m, 1H), 7.49–7.36 (m, 2H), 5.02 (t, 2H, $J = 7.5$ Hz), 2.09–2.05 (m, 2H), 1.70–1.66 (m, 5H), 1.38–1.12 (m, 10H), 0.91–0.84 (m, 2H). Anal. Calcd for $C_{26}H_{31}BrINS$: C 52.36; H 5.24; N 2.35. Found: C 52.18; H 5.24; N 2.27.

4.8.4. 3-(3-methoxyphenylsulfanyl)-1-(5-cyclohexylpentyl) quinolinium iodide, ***11d***

Yield 191 mg, 93%; Mp 147–148 °C; ^{1}HNMR (DMSO-d_6): δ 9.37 (d, 1H, $J = 2.1$ Hz), 8.91 (s, 1H), 8.49 (d, 1H, $J = 8.7$ Hz), 8.27–8.17 (m, 2H), 7.98 (t, 1H, $J = 7.5$ Hz), 7.42 (t, 1H, $J = 8.1$ Hz), 7.19–7.17 (m, 2H), 7.08–7.05 (m, 1H), 5.02 (t, 2H, $J = 7.2$ Hz), 3.81 (s, 3H), 2.07–2.02 (m, 2H), 1.70–1.67 (m, 5H), 1.25–1.17 (m, 10H), 0.88–0.85 (m, 2H). Anal. Calcd for $C_{27}H_{34}INOS$: C 59.23; H 6.26; N 2.56. Found: C 59.15; H 6.22; N 2.53.

4.8.5. 3-(2-trifluoromethyl-phenylsulfanyl)-1-(5-cyclohexylpentyl) quinolinium iodide, ***11e***

Yield 101 mg, 53%; Mp 172–173 °C; ^{1}HNMR (CD_3OD): δ 9.48 (d, 1H, $J = 2.1$ Hz), 8.95 (d, 1H, $J = 1.5$ Hz), 8.54 (d, 1H, $J = 9$ Hz), 8.31–8.21 (m, 2H), 8.03–7.92 (m, 1H), 7.95–7.92 (m, 1H), 7.76–7.67 (m, 3H), 5.07 (t, 2H, $J = 7.5$ Hz), 2.09–2.04 (m, 2H), 1.71–1.67 (m, 5H), 1.39–1.18 (m, 10H), 0.88–0.84 (m, 2H). Anal. Calcd for $C_{27}H_{31}F_3INS$: C 55.39; H 5.34; N 2.39. Found: C 55.32; H 5.43; N 2.42.

4.8.6. 3-(3-trifluoromethylphenysulfanyl)-1-(5-cyclohexylpentyl) quinolinium iodide, ***11f***

Yield 54 mg, 28%; Mp 137–140 °C; ^{1}HNMR (CD_3OD): δ 9.55 (d, 1H, $J = 1.8$ Hz), 9.10 (s, 1H), 8.54 (d, 1H, $J = 9$ Hz), 8.34–8.22 (m, 2H), 8.02 (t, 1H, $J = 8.1$ Hz), 7.94 (s, 1H), 7.85 (t, 1H, $J = 7.5$ Hz), 7.76 (d, 1H, $J = 7.8$ Hz), 7.67 (t, 1H, $J = 7.5$ Hz), 5.06 (t, 2H, $J = 7.8$ Hz), 2.07–2.05 (m, 2H), 1.70–1.67 (m, 5H), 1.38–1.17 (m, 10H), 0.91–0.84 (m, 2H). Anal. Calcd for $C_{27}H_{31}F_3INS \cdot 0.4H_20$: C 54.71; H 5.27; N 2.36. Found: C 54.73; H 5.25; N 2.31.

4.8.7. 3-(4-trifluoromethyl-phenylsulfanyl)-1-(5-cyclohexylpentyl) quinolinium iodide, ***11g***

Yield 25.8 mg, 13%; Mp 143–144 °C; ^{1}HNMR (CD_3OD): δ 9.58 (d, 1H, $J = 1.8$ Hz), 9.21 (s, 1H), 8.56 (d, 1H, $J = 9.0$ Hz), 8.37–8.25 (m, 2H), 8.04 (t, 1H, $J = 7.5$ Hz), 7.75–7.76 (m, 4H), 5.07 (t, 2H, $J = 7.2$ Hz), 2.08–2.05 (m, 2H), 1.70–1.67 (m, 5H), 1.39–1.37 (m, 10H), 0.88–0.84 (m, 2H). Anal. Calcd for $C_{27}H_{31}F_3INS$: C 55.39; H 5.34; N 2.39. Found: C 55.28; H 5.31; N 2.42.

4.8.8. 3-(2-methyl-phenysulfanyl)-1-(5-cyclohexylpentyl) quinolinium iodide, ***11h***

Yield 48 mg, 32%; Mp 162–163 °C; ^{1}HNMR (DMSO-d_6): δ 9.30 (d, 1H, $J = 1.8$ Hz), 8.62 (s, 1H), 8.47 (d, 1H, $J = 9.0$ Hz), 8.21–8.15 (m, 2H), 7.96 (t, 1H, $J = 6.9$ Hz), 7.63 (d, 1H, $J = 8.1$ Hz), 7.48–7.47 (m, 2H), 7.38–7.35 (m, 1H), 5.02 (t, 2H, $J = 7.5$ Hz), 2.47 (s, 3H), 2.05–2.00 (m, 2H), 1.71–1.67 (m, 5H), 1.36–1.18 (m, 10H), 0.88–0.85 (m, 2H). Anal. Calcd for $C_{27}H_{34}INS$: C 61.01; H 6.45; N 2.64. Found: C 61.24; H 6.43; N 2.62.

4.8.9. 3-(3-methyl-phenysulfanyl)-1-(5-cyclohexylpentyl) quinolinium iodide, ***11i***

Yield 135 mg, 71%; Mp 163–164 °C; ^{1}HNMR (CD_3OD): δ 9.35 (d, 1H, J = 2.1 Hz), 8.85 (s, 1H), 8.48 (d, 1H, J = 9.0 Hz), 8.26–8.17 (m, 2H), 7.97 (t, 1H, J = 8.1 Hz), 7.49–7.34 (m, 4H), 5.02 (t, 2H, J = 7.2 Hz), 2.38 (s, 3H), 2.07–2.00 (m, 2H), 1.70–1.67 (m, 5H), 1.37–1.17 (m, 10H), 0.91–0.85 (m, 2H). Anal. Calcd for $C_{27}H_{34}INS$: C 61.01; H 6.45; N 2.64. Found: C 60.92; H 6.56; N 2.63.

4.8.10. 3-(4-methyl-phenysulfanyl)-1-(5-cyclohexylpentyl) quinolinium iodide, ***11j***

Yield 121 mg, 64%; Mp 157–158 °C; ^{1}HNMR (CD_3OD): δ 9.32 (d, 1H, J = 2.1 Hz), 8.77 (d, 1H, J = 1.8 Hz), 8.47 (d, 1H, J = 8.4 Hz), 8.23–8.15 (m, 2H), 7.96 (t, 1H, J = 7.8 Hz), 7.57–7.54 (m, 2H), 7.37 (d, 2H, J = 7.8 Hz), 5.02 (t, 2H, J = 7.8 Hz), 2.41 (s, 3H), 2.06–2.02 (m, 2H), 1.71–1.67 (m, 5H), 1.38–1.13 (m, 10H), 0.92–0.85 (m, 2H). Anal. Calcd for $C_{27}H_{34}INS$: C, 61.01; H, 6.45; N, 2.64. Found: C, 61.15; H, 6.53; N, 2.67.

4.8.11. 3-(2-cyanophenysulfanyl)-1-(5-cyclohexylpentyl) quinolinium iodide, ***11k***

Yield 96.3 mg, 57%; Mp 174–175 °C; ^{1}HNMR (DMSO-d_6): δ 9.76 (d, 1H, J = 1.8 Hz), 9.35 (d, 1H, J = 1.8 Hz), 8.61–8.59 (m, 1H), 8.43–8.40 (m, 1H), 8.30–8.25 (m, 1H), 8.07–7.99 (m, 2H), 7.73–7.56 (m, 3H), 5.02 (t, 2H, J = 7.5 Hz), 1.96–1.94 (m, 2H), 1.64–1.61 (m, 5H), 1.29–1.10 (m, 10H), 0.85–0.79 (m, 2H). Anal. Calcd for $C_{27}H_{31}IN_2S$: C 59.77; H 5.76; N 5.16. Found: C 59.99; H 5.85; N 5.09.

4.8.12. 3-(3-cyanophenysulfanyl)-1-(5-cyclohexylpentyl) quinolinium iodide, ***11l***

Yield 16.7 mg, 17%; Mp 162–164 °C; ^{1}HNMR (DMSO-d_6): δ 9.71 (d, 1H, J = 2.1 Hz), 9.36 (s, 1H), 8.61 (d, 1H, J = 9.0 Hz), 8.42 (d, 1H, J = 7.2 Hz), 8.29–8.24 (m, 1H), 8.07–7.97 (m, 2H), 7.85–7.81 (m, 2H), 7.63–7.58 (m, 1H), 5.00 (t, 2H, J = 7.2 Hz), 1.96–1.92 (m, 2H), 1.64–1.60 (m, 5H), 1.31–1.12 (m, 10H), 0.85–0.78 (m, 2H). Anal. Calcd for $C_{27}H_{31}IN_2S$: C 59.77; H 5.76; N 5.16. Found: C 59.76; H 5.82; N 5.13.

4.8.13. 3-(4-cyanophenysulfanyl)-1-(5-cyclohexylpentyl) quinolinium iodide, ***11m***

Yield 98.7 mg, 53%; Mp 149–150 °C; ^{1}HNMR (DMSO-d_6): δ 9.76 (d, 1H, J = 1.5 Hz), 9.47 (s, 1H), 8.63 (d, 1H, J = 9.0 Hz), 8.44 (d, 1H, J = 6.9 Hz), 8.32–8.27 (m, 1H), 8.09–8.04 (m, 1H), 7.83–7.81 (m, 2H), 7.60–7.57 (m, 2H), 5.01 (t, 2H, J = 7.2 Hz), 1.96–1.93 (m, 2H), 1.62–1.61 (m, 5H), 1.32–1.11 (m, 10H), 0.86–0.79 (m, 2H). Anal. Calcd for $C_{27}H_{31}IN_2S$: C 59.77; H 5.76; N 5.16. Found: C 59.93; H 5.81; N 5.17.

4.8.14. 3-(2-hydroxyphenysulfanyl)-1-(5-cyclohexylpentyl) quinolinium iodide, ***11n***

Yield 44 mg, 37%; Mp 172–174 °C; ^{1}HNMR (DMSO-d_6): δ 10.32 (s, 1H), 9.55 (s, 1H), 8.84 (s, 1H), 8.53 (d, 1H, J = 9.0 Hz), 8.34–8.31 (m, 1H), 8.15–7.95 (m, 2H), 7.41–7.29 (m, 2H), 7.01–6.86 (m, 2H), 4.99 (t, 2H, J = 6.6 Hz), 1.91–1.90 (m, 2H), 1.64–1.60 (m, 5H), 1.28–1.10 (m, 10H), 0.81–0.78 (m, 2H). Anal. Calcd for $C_{26}H_{32}INOS$: C 58.53; H 6.05; N 2.63. Found: C 58.57; H 6.10; N 2.75.

4.8.15. 3-(3-hydroxyphenysulfanyl)-1-(5-cyclohexylpentyl) quinolinium iodide, ***11o***

Yield 33 mg, 44%; Mp 129–131 °C; ^{1}HNMR (CD_3OD): δ 10.10 (s, 1H), 9.34 (d, 1H, J = 2.1 Hz), 8.88 (s, 1H), 8.48 (d, 1H, J = 8.7 Hz), 8.27–8.17 (m, 2H), 7.98 (t, 1H, J = 15.6 Hz), 7.32 (t, 1H, J = 7.8 Hz), 7.06–7.01 (m, 2H), 6.93–6.89 (m, 1H), 5.02 (t, 2H, J = 7.2 Hz), 2.14–2.00 (m, 2H), 1.70–1.67 (m, 5H), 1.38–1.36 (m, 10H), 0.88–0.80 (m, 2H). Anal. Calcd for $C_{26}H_{32}INOS$: C 58.53; H 6.05; N 2.63. Found: C 58.28; H 5.98; N 2.52.

4.8.16. 3-(4-hydroxyphenysulfanyl)-1-(5-cyclohexylpentyl) quinolinium iodide, ***11p***

Yield 30 mg, 26%; Mp 121–122 °C; ^{1}HNMR (DMSO-d_6): δ 10.05 (s, 1H), 9.51 (d, 1H, J = 1.8 Hz), 8.75 (s, 1H), 8.51 (d, 1H, J = 9.0 Hz), 8.32 (d, 1H, J = 7.5 Hz), 8.14 (t, 1H, J = 7.5 Hz), 7.92 (t, 1H, J = 7.8 Hz), 7.47 (d, 2H, J = 8.4 Hz), 6.91 (d, 2H, J = 8.7 Hz), 4.98 (t, 2H, J = 7.5 Hz), 1.96–1.92 (m, 2H), 1.65–1.61 (m, 5H), 1.28–1.06 (m, 10H), 0.83–0.79 (m, 2H). Anal. Calcd for $C_{26}H_{32}INOS$: C 58.53; H 6.05; N 2.63. Found: C 58.47; H 5.98; N 2.65.

4.9. Antifungal testing

All organisms were obtained from the American Type Culture Collection (Manassas, VA) and include *C. neoformans* ATCC 90113, *C. albicans* ATCC 90028, *C. glabrata* ATCC 90030, *C. krusei* ATCC 6258, and *A. fumigatus* ATCC 90906. Susceptibility testing was performed using a modified version of the CLSI methods [14] as described by Samoylenko et al. [15]. Amphotericin B (ICN Biomedicals, Ohio) was used as a positive control in each assay.

Briefly, DMSO solutions of samples were serially diluted in saline and transferred in duplicate to 96-well microplates. Microbial suspensions were diluted in broth to afford desired colony forming units/mL according to the 0.5 McFarland Standard [*C. albicans*: either Saboraud Dextrose broth (SDB) or RPMI 1640, *C. neoformans*: SDB, *A. fumigatus*: either YM broth (for MICs) or RPMI-1640 + 5% Alamar Blue (for IC_{50} determination). After adding microbial cultures to the samples affording a final volume of 200 μL and final test concentration starting with 20 μg/mL, plates were read prior to and after incubation using either fluorescence at 544ex/590em (*A. fumigatus*) using the Polarstar Galaxy Plate Reader (BMG LabTechnologies, Germany) or optical density at 630 nm using the EL-340 Biokinetics Reader (Bio-Tek Instruments, Vermont). Growth (saline only), solvent, and blank (media only) controls were included on each test plate. Drug control amphotericin B (ICN Biomedicals, Ohio) for fungi was included in each assay. Percent growth was calculated and plotted versus test concentration to afford the IC_{50} (sample concentration that affords 50% growth of the organism). The minimum inhibitory concentration (MIC) was determined by visually inspecting the plate, and is defined as the lowest test concentration that allows no detectable growth (for Alamar Blue assays, no color change from blue to pink).

4.10. Cytotoxicity assay

In vitro cytotoxicity was determined against mammalian kidney fibroblast (VERO) cells. The assay was performed in 96-well tissue culture-treated microplates and compounds were tested up to a highest concentration of 10 μg/mL as described earlier [16]. In brief, cells (25,000 cells/well) were seeded to the wells of the plate and incubated for 24 h. Samples were added and plates were again incubated for 48 h. The number of viable cells was determined by the neutral red assay as previously described [16]. IC_{50} values were determined from dose curves of growth inhibition versus concentration. Doxorubicin was used as a positive control, while DMSO was used as the negative (vehicle) control.

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