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Structure-Activity Relationship (SAR) and Preliminary Mode of Action Studies of 3-Substituted Benzylthioquinolinium Iodide as Anti-opportunistic Infection Agents

Sidney Bolden Jr.[a], **Xue Y. Zhu**[a], **Jagan R Etukala**[a], **Comfort Boateng**[a], **Tryphon Mazu**[a], **Hernan Flores-Rozas**[a], **Melissa R. Jacob**[b], **Shabana I Khan**[b], **Larry A. Walker**[b], and **Seth Y. Ablordeppey**[a,*]

[a]College of Pharmacy and Pharmaceutical Sciences, Florida A&M University, Tallahassee, FL 32307, USA

[b]The National Center for the Development of Natural Products, Research Institute of Pharmaceutical Sciences, University of Mississippi, University, MS 38677, USA

Abstract

Opportunistic infections are devastating to immunocompromised patients. And in especially sub-Saharan Africa where the AIDS epidemic is still raging, the mortality rate was recently as high as 70%. The paucity of anti-opportunistic drugs, the decreasing efficacy and the development of resistance against the azoles and even amphotericin B have stimulated the search for new drugs with new mechanisms of action. In a previous work, we showed that a new chemotype derived from the natural product cryptolepine displayed selective toxicity against opportunistic pathogens with minimal cytotoxicity to normal cells. In this manuscript, we report the design and synthesis of substituted benzylthioquinolinium iodides, evaluated their anti-infective properties and formulated some initial structure-activity relationships around phenyl ring A from the original natural product. The sensitivity of the most potent analog **10l,** to selected strains of *C. cerevisiae* was also evaluated leading to the observation that this scaffold may have a different mode of action from its predecessor, cryptolepine.

Keywords

Substituted Quinolinium salts; benzylthioquinolinium iodides; antifungal agents; anti-opportunistic infections; cryptolepine; Craig plot; structure-activity relationships

1. Introduction

Systemic opportunistic infections (OIs) and especially fungal infectious diseases are a leading cause of morbidity and mortality worldwide and immuno-compromised individuals are especially vulnerable because their immune systems cannot successfully fight infections. [1] Thus, invasive fungal infections affect these individuals disproportionately, and antifungal agents offer the best treatment option.[2] Among the fungal species that dominate these OIs are: *Candida albicans, Aspergillus fumigatus* and *Cryptococcus neoformans*, with

*Corresponding author. Tel.: +1 850 599 3834; fax: +1 850 599 3934. seth.ablordeppey@famu.edu (S.Y. Ablordeppey).

mortality rates of 20–40%, 50–90%, and 20–70% respectively.[3, 4] *Candida* species are one of the most common causes of bloodstream infections and the treatment failure of invasive candidiasis is high. [5–11] *A. fumigatus* infections are most commonly found in specialized groups of patients that have had stem cell, heart, lung, and liver transplants with a mortality rate greater than 75% in this group and *C. neoformans* is responsible for meningitis, killing 650,000 people per year around the world.[3, 12]

Prior to the HIV/AIDS epidemic, the development of new classes of antifungal agents has been slow and sparse compared to antibacterial drug discoveries since serious fungal infections were less common. As a result, there are a limited number of classes of antifungal agents available to fight invasive fungal infections. The echinocandins are the most recent class of antifungal drugs and took about 30 years to evolve. Current combination drug treatment of cryptococcal meningitis infections uses the nucleic acid synthesis inhibitor flucytosine and the polyene ergosterol disruptor amphotericin B, which were discovered in the 1950s and 1960s, Azoles have the desirable properties of good tolerability and bioavailability and various triazoles have been used for the treatment of the fungal pathogen *C. albicans.* [2, 13] However, the overuse of these agents has resulted in the development of resistance to triazoles by specific species of *Candida*. For example, *Candida krusei* and *Candida glabrata* are inherently resistant to the triazole fluconazole, utilizing several resistance mechanisms including: efflux pump and ERG11 up regulation, and alterations in the ergosterol biosynthetic pathway. [14, 15] This increasing resistance development to current drugs may have a direct relationship on the health of the public.[14, 16]

We have previously shown that opening ring B of the natural product cryptolepine (**CLP**) and modifying the substituents on the nitrogen atoms resulted in the identification of new pharmacophores and leads for further development. [17] Furthermore, probing the N10 atom position with isosteres identified the sulfur isostere as having the best potential for further development.[18] Much of these efforts have been reported.[19] More recently, we reported the successful use of the 3D-QSAR molecular modeling method of CoMFA to predict the activity of a set of synthetic antifungal compounds with a high cross-validated correlation (q^2) of 0.815. [20] Subsequently, the model was validated to predict the activities of designed compounds prior to their synthesis and their biological activities have been shown to correlate very well with the CoMFA predicted activities (R = 0.80).[20] This model has inspired the design and the synthesis of the compounds in this manuscript.

The budding yeast *Saccharomyces cerevisiae* is widely used as a eukaryotic model organism. Yeast gene deletion strains provide a powerful tool to dissect biological pathways that play a role in drug response. [21–23] The use of small-molecules to modulate functions of target proteins is a powerful tool to study biological pathways with potential use in pharmacological intervention of human diseases. Yeast genome-wide screenings have provided significant information on the mechanism of targeted pathways.[24] In this study we tested the sensitivity of selected yeast gene deletion strains to compound **9l** to further investigate its mechanism of action.

In our continuing effort to obtain new anti-opportunistic infection agents with new mechanisms of action to overcome the resistance developed against current drugs on the market, we herein report the design, synthesis of a library of 3-substituted benzylthio quinolinium iodide salts, the evaluation of their antifungal and antibacterial activities against some of the common opportunistic pathogens associated with patients with compromised immune system diseases and the formulation of the structure-activity relationship (SAR).

2.0 Results and Discussion

2.1. Drug Design

We have previously reported that benzothieno[3,2-b]quinolinium iodide (**CLPI**), a sulfur bioisostere of cryptolepine demonstrated anti-infective properties against a number of selected fungal and bacterial pathogens.[25] Opening ring B to form **CLPIO** analogs also demonstrated anti-infective properties. In fact, analogs of **CLPIO** were not only more potent but also displayed less cytotoxicity against mammalian cells than cryptolepine, Figure 1.[26]

Thus, we selected **1** as a lead for further optimization using several optimization strategies. First, we explored the effect of the distance between the phenyl A & the S-atom. Secondly the hydrophobic (π-constants) and electronic space (σ) around phenyl A was explored (Fig 2), having previously demonstrated that substitution on the phenyl A resulted in significant changes in the activities against bacterial and fungal pathogens. [27,28] Selection of appropriate substituents was based on the Craig model of substituent selection to ensure that all possible combination of pi (π) and sigma (σ) (4 quadrants) was covered.

Next, phenyl A in compound **1** was replaced with a cyclohexyl ring (**2)** to find if aromaticity was required for the anti-infective activities. The effect of the absence of the phenylthio moiety from compound **1** was also evaluated for enhancement of anti-infective activities using compound **3** in which the phenylthio moiety was replaced with a similar lipophilic iodine group. The phenyl ring A was also replaced with a naphthalene ring (compound **4**) to explore the effect of extending aromaticity on the anti-infective activities. Finally, we replaced the sulfur with oxygen to form an oxygen isostere of **1,** that is compound **5**. Compound **5** was expected to aid our understanding of the role of the larger carbon sulfur bond angle compared to a carbon oxygen bond angle on the observed activities.

2.2. Synthesis

The synthesis of compound **1** was previously reported and required the conversion of 3-bromoquinoline (**6**) to 3-iodoquinoline (**7**) using the Finkelstein reaction.[25] Microwave irradiation was used to accelerate the copper-catalyzed carbon-sulfur bond formation reaction to provide the substituted benzylthioquinoline intermediates (**8a–r** and **8x–z**) (Scheme 1). [26] To obtain the 3-((cyanobenzyl)thio)quinoline intermediates (**8s–u**), cyanation of the appropriate 3-((bromobenzyl)thio)quinoline using copper(I) cyanide under Newman and Phillips reaction conditions. [29] Chemical demethylation of 3-((4-methoxybenzyl)-thio)quinoline whose synthesis was previously reported was accomplished using pyridine hydrochloride to afford intermediate 3-((4-hydroxybenzyl)-thio)quinoline (**8v**). [25] The final products, 3-[(substituted)-benzylthio]-1-(5-cyclohexylpentyl)-quinolin-1-ium iodides (**9a–z**) were obtained by the introduction of the 5-cyclohexylpentyl moiety onto the nitrogen using a new green chemistry inspired alkylation method (Scheme 1).

Compound **10** was obtained by coupling 3-iodoquinoline (**7**) with 2-phenylethanethiol instead of phenyl-methanethiol to form 3-(phenethylthio)quinoline (**10**). Compound **10** was then subjected to the microwave assisted N-alkylation procedure to yield the desired 1-(5-cyclohexylpentyl)-3-(phenethylthio)-quinolinium iodide (**11**).

Target compounds **2, 3, 4,** and **5** (Figure 3) were similarly obtained as described in Scheme 2 using cyclohexylthiol, 3-iodoquinoline (**7**), 2-naphthalenethiol and phenol respectively to obtain the corresponding penultimate products which were subsequently alkylated under microwave assisted conditions with 5-cyclohexylpentyl iodide. The detailed experimental description of each synthetic procedure can be found under the experimental section.

2.3 Antifungal activity and SAR

The results of the *in vitro* antifungal screening of the 3-((substituted-benzyl)thio)-1-(5-cyclohexylpentyl)quinolin-1-ium iodides (**9a–v**) are reported in Table 1. Target compounds were designed using substituents from the four quadrants of a Craig plot and each was placed at the *ortho, meta* and *para*-positions to explore the electronic and hydrophobic space around the benzylthio moiety and their effect on activity. Each of the resulting 3-(substituted benzyl)thio quinolinium target compounds was predicted using the previously developed CoMFA model.[20] The experimentally determined IC_{50}, MIC and MFC values for *C. neoformans*, *C. albicans* and *A. fumigatus* for compounds **9a–v**, are listed in Table 1. Amphotericin B, the gold standard antifungal agent, and fluconazole served as the positive controls. IC_{50} values of the compounds were ranked very potent, potent, active, moderate, weak or inactive (NA) for IC_{50} < 0.1, 0.1–1, 1–10, 10–15, >20 μg/mL or >50 μg/mL respectively. All of the target compounds **9a–v** showed potent to very potent antifungal activities against *C. neoformans*.

Compound **9a**, the unsubstituted 3-(benzylthio)-1-(5-cyclohexylpentyl)quinolin-1-ium iodide, supported the hypothesis that homologation by 1 methylene group enhances antifungal activity (Figure 2). The antifungal potency against *C. neoformans* increased from 0.5 μg/mL to 0.16 μg/mL when one methylene group was introduced between the thioether and the phenyl ring of compound **1**. However, when the distance was extended by inserting a second methylene group, the potency decreased from 0.16 μg/mL to 0.73 μg/mL and thus, suggesting that the optimal distance between the quinolinium and the phenyl ring was obtained by inserting only one methylene group. The 3-benzylthioquinolinium iodide scaffold was therefore selected for further optimization.

Beginning with compounds with positive σ and positive π values such as F, Br, CF_3 and Cl, at the *ortho, meta* and *para* positions of the phenyl ring A resulted in potent to very potent activities against *C. neoformans.* Fluoro substituents displayed activities lower than the unsubstituted analog with the *p*-substituent having the highest activity of the three. A similar trend was observed with the bigger bromo and trifluoro analogs (**9e–j**); these substituents having been suggested to demonstrate improved activities in our CoMFA model because of their bulky nature.

It is unclear why the *para* substituents consistently displayed the highest potencies but we further probed this by synthesizing and evaluating the *ortho* and *para* chloro analogs **9k** and **9l** respectively. Compound **9l** with IC_{50} of 0.05 μg/mL, exhibited the most potent antifungal activity for *C. neoformans* which is 4-fold more potent than amphotericin B (IC_{50} = 0.23 μg/mL for *C. neoformans*).

The methyl group was selected to represent substituents in the negative σ and positive π quadrant of the Craig plot. The compounds show potent activities against *C. neoformans* comparable to the CF_3 analogs with the para substituent having the highest potency. The displayed activities are however lower than that of the unsubstituted analog, **9a**. The methoxy substituent, **9p–r**, representing substituents from the negative σ and negative π quadrant also demonstrated potent activity with the *para* analog (**9r**) having the highest potency of the three and was equipotent to the unsubstituted analog. However, the more hydrophilic demethylated analog **9s**, displayed only moderate activity. Finally, we evaluated the representative of the positive σ and negative π quadrant using the cyano-substituted analogs **9t–v.** The result of the biological evaluation indicates that compared to **9s**, the *p*-OH analog which is also hydrophilic, the cyano analogs were 4 to 10-fold more potent against *C. neoformans*. This is consistent with the observation that the more important factor affecting activity is positive σ or electron withdrawing capacity of the substituents. Another observation of the activities in Table 1 reveals that compared to their potency against *C.*

neoformans, this library of compounds is less potent against *C. albicans* and *A. fumigatus*, although they maintain the general trends with the *p*-substituted analogs of each substituent group in general being the most potent against all fungi evaluated. Indeed, the *p*-chloro substituted analog (**9l**) is the most potent among all the other substituted analogs against all three pathogenic fungi. Thus, it would appear that a *p*-substituted electron withdrawing and lipophilic substituent demonstrates the highest potency in this library of compounds.

1. Further evaluation of the effect of various substitution patterns on antifungal activities are reported in Table 2.

Substitution of the bulky tertiary butyl group (**9w**) at the *p*-position of the scaffold did not improve activity but has a deleterious effect on activity with essentially no activity demonstrated at 20 μg/mL against both *C. albicans* and *A. fumigatus*. A 3,4-dichloro (**9x**), 3,5-ditrifluoromethyl (**9y**) and 2,4,6-trimethyl (**9z**) analogs displayed some activities but much lower than **9l**. As indicated earlier, activity is reduced when the methylene group in **9a** is extended to an ethylene chain as in compound **11**. Apparently, based on the activity of compounds **2** and **3**, the presence of the phenyl ring A is required. Compound **2**, with the phenyl ring A replaced by a cyclohexyl ring showed potent activity against *C. neoformans* but none was demonstrated against other fungi. Similarly, compound **3**, with no phenyl ring A (Ring A replaced with I), showed little or no activities against the fungi of interest. Extending aromaticity of phenyl ring A to a naphthalene (compound **4**) improved activity across the fungal spectrum and thus, confirms that aromaticity is required in the ring attached to the sulfur atom. Finally, replacing the sulfur atom with its oxygen isostere resulted in the loss of activity, as demonstrated in compounds **5a–b.** Interestingly, oxygen isosteres of the tetracyclic structure of cryptolepine, also resulted in compounds with little or no antifungal activity.

It was also of interest to evaluate the effect of these compounds on inherently resistant pathogens. Given that *C. albicans* and *C. glabrata* are the two most common pathogenic yeasts in humans, and *C. glabrata* and *C. krusei* show resistance to fluconazole, the two fungi were selected for this evaluation and the results of the screening are recorded in Table 3.[30] As shown, the compounds are more potent against *C. krusei* than *C. glabrata* although the general trends observed for the previous fungi including *C. albicans* are preserved. The *p*-substituted compounds overall remained the most active and compound **9l**, displayed the most potent activity among all the compounds against both *C. glabrata* and *C. krusei*. In fact, **9l** is equipotent to amphotericin B against the former and displays over 3-fold better activity against the latter. More importantly, when compared with fluconazole, compound **9l** is fungicidal to both pathogens with over 310-fold potency against *C. krusei*. Similarly, compound **4** demonstrated potent activity against both pathogens with over 79-fold fungicidal potency compared to fluconazole. Thus, these results are encouraging as they indicate the potential of these compounds in serving as replacement for fluconazole, in the treatment of emerging fungi and especially fluconazole-resistant fungi.

2.4 Cytotoxicity activity

The results of the cytotoxicity activity can be found in Table 1 and Table 2. The most active compound **9l** was found to show toxicity similar to the original lead compound cryptolepine. However, calculation of the selectivity index (SI = TC_{50}/IC_{50} = 26) demonstrated that **9l** has far more improved therapeutic profile than cryptolepine (0.61). On the other hand, all compounds except for **9g, 9i,** and **9j** did not demonstrate any cytotoxicity at 10 μg/mL. In fact compound **4** has the best therapeutic profile when measured by selectivity index, SI (>111) even when compared with amphotericin B (SI = 38). Thus, the cytotoxicity data confirms that the B-ring opened compounds have resulted in lower cytotoxicity than

cryptolepine and this scaffold has the potential to demonstrate selective toxicity along with potent anti-infective properties.

2.5 Sensitivity of *S. cerevisiae* deletion strains to antifungal compound, 9l

To further characterize the effect of **9l** on fungi, we determined the sensitivity of selected yeast strains to the compound. As shown in Figure 3, all strains displayed different sensitivity, with the *snf2* and *ydj1* mutants being the most sensitive. At 20 μmol/L concentration, the survival of the wild type strain to **9l** was 30%. Relative to the wild type, the *rad52* mutant, which is defective in homologous recombination, was 2.9-fold more sensitive, the mismatch repair mutant *msh2* was unaffected (1.1-fold more sensitive), while *snf2* and *ydj1* were highly sensitive (10-fold and 7.5-fold more sensitive, respectively). In comparison, exposure to cryptolepine resulted in a slow growth phenotype, with no significant difference in sensitivity between the strains tested, Figure 3. The *rad52* mutant strain displayed the highest sensitivity with 29% survival (3.5-fold over wild type), while *snf2* was 1.7-fold more sensitive than wild type, and *msh2* and *ydj1* were unaffected. At higher concentrations of cryptolepine (50 μmol/L), the strains displayed slower growth, but the same differential sensitivity as observed in lower concentrations, relative to wild type (data not shown).

The differential sensitivity to antifungal compound **9l** of the yeast deletions strains tested suggests a distinct mode of action. To assess the DNA damage potential of compound **9l**, we determined the sensitivity of the homologous recombination defective mutant *rad52*. Homologous recombination is essential for the repair of DNA double-strand breaks, which can arise from direct damage to DNA, or by inhibition of enzymes that act on DNA, such as topoisomerases. The *rad52* mutant was only slightly sensitive (2.9-fold higher than wild type) to **9l**. As comparison, other DNA damaging agents, such as topoisomerase II inhibitor doxorubicin, can inhibit *rad52* mutants more than 100-fold at similar concentrations [21]. In addition, *msh2* mutants are not significantly sensitive to **9l**, indicating that there is no increase in replication error. Neither are they more resistant, suggesting that no DNA damage, which requires mismatch repair for processing, is generated by **9l**.[23] However, **9l** considerably reduced the viability of the *snf2* strain, which is defective in chromatin remodeling. Mutations on *SNF2* have been shown to sensitize cells to various stresses, including some antibiotics, such as sulfanilamide and metals.[31, 32] The sensitivity of the *ydj1* strain, which is defective in an HSP40 co-chaperone essential for protein folding, suggests that **9l** may be causing cytotoxic stress which may lead to alteration of protein structure.[21] In comparison, cryptolepine was most effective on the *rad52* mutant strain consistent with its genotoxic properties.[33] Further investigation is necessary to elucidate the mechanism of action of **9l**.

3. Conclusion

In summary, we have optimized a series of 3-(substituted-benzyl)thio-1-(5-cyclohexyl-pentyl)quinolinium iodide salts (**9**) that were designed, interrogated using a CoMFA model developed for the purpose, synthesized using microwave assisted methodology, and characterized by ^{1}H-NMR. Overall, several compounds including **4**, **9a**, **d**, **g**, **j**, **l**, and **r** were more potent or equipotent to fluconazole and amphotericin B against *C. neoformans* and several other pathogenic opportunistic microorganisms including the inherently resistant *C. krusei* and *C. glabrata*. Using a systematic selection of substituents from a Craig plot, the designed analogs were predicted in silico using the previously developed CoMFA model. Compared to the actual biologically determined values, the CoMFA predictions were shown to be fairly accurate with a regression coefficient of 0.8. In addition, the 3-(substituted-benzyl)thio-1-(5-cyclohexylpentyl)quinolinium iodide salts showed low to no cytotoxicity in

Vero cells up to 10 μg/mL. The most potent analogs obtained, compounds **4** (SI >111) and **9l** (SI = 46) were more potent and displayed much more improved therapeutic profiles than CLP (SI = 0.61), fluconazole and amphotericin B (SI = 38).

Preliminary investigation to probe the mechanism of action of compound **9l** demonstrates that unlike its predecessor (CLP), the high sensitivity of compound **9l** to the *snf2* and *ydj1 S. cerevisiae* strains is not due to genotoxicity, and suggests that compound **9l** may be causing cytotoxic stress which may lead to alteration of protein structure.[21] In comparison, cryptolepine was most effective on the *rad52* mutant strain consistent with its genotoxic properties.[33] These preliminary results favor further exploration of compound **9l** to develop new antifungal compounds and to discover its mechanism of action.

4. Experimental

4.1. Materials and methods

Chemistry: All reagents were purchased from Sigma-Aldrich, Fischer Scientific, Alfa Aesar, Enamine, or Oakwood Products and were used without further purification. Microwave reactions were performed using a commercially available single-mode microwave Biotage Initiator, employing a 10 – 20 mL vial in a septum closed-vessel. Melting points were determined on an Electrothermal MEL-TEMP® 3.0 instrument and are uncorrected. ^{1}H NMR spectra were recorded on a Varian 300 MHz NMR spectrometer. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA and were within ±0.4% of the theoretical values where indicated by the symbols of the elements. FLASH chromatography was carried out on 12 g normal phase column of silica gel unless otherwise specified.

Genetic methods and strains: Yeast extract/peptone/dextrose (YPD) media was as described.[34, 35] Homozygous haploid deletion strains (parental strain BY4741: Mata his3Δ leu2Δ0 met15Δ0 ura3Δ0) were obtained from Thermo Scientific.

4.2. Synthesis of 1-(5-cyclohexylpentyl)-3-(cyclohexylthio)quinolin-1-ium iodide (2)

A mixture of CuI (20 mg, 0.10 mmol), K_2CO_3 (550 mg, 3.97 mmol), 3-iodoquinoline (500 mg, 1.96 mmol), cyclohexyl mercaptan (230 mg, 1.96 mmol), ethylene glycol (0.24 mL, 3.97 mmol), and 2-propanol (5 mL) was heated at 170°C un der nitrogen using microwave irradiation for 15 min. The reaction mixture was allowed to cool to rt, diluted with H_2O (20 mL) and extracted with EtOAc (3 x 30 mL). The organic fraction was washed with brine (150 mL), dried (Na_2SO_4) and concentrated by rotary evaporation at reduced pressure to yield the crude product. The crude product was purified with FLASH chromatography (EtOAc:Hexane, 0:10 to 20:80) to afford 3-(cyclohexylthio)-quinoline as a brown oil. Yield 42%; ^{1}H NMR ($CDCl_3$): δ 8.89 (s, 1H), 8.16 (s, 1H), 8.07 (d, 1H, *J* = 8.4 Hz), 7.77 (d, 1H, *J* = 7.8 Hz), 7.75 - 7.70 (m, 1H), 7.69 - 7.52 (m, 1H), 3.24 – 3.16 (m, 1H), 2.03 – 1.98 (m, 2H), 1.85 – 1.75 (m, 2H), 1.64 – 1.60 (m, 2H), 1.47 – 1.35 (m, 4H).

A mixture of 3-(cyclohexylthio)quinoline (26 mg, 0.10 mmol), 5-(iodopentyl)cyclohexane (38 mg, 0.60 mmol), and water (5 mL) was heated at 170°C using microwave irradiation for 15 minutes. The reaction mixture was allowed to cool to room temperature and diluted with EtOAc (10 mL) and extracted with EtOAc (3 x 30 mL). The organic fraction was sonicated to yield the crude product. The crude product was vacuum filtered using Et_2O to afford the pure 1-(5-cyclohexylpentyl)-3-(cyclohexylthio)quinolin-1-ium iodide as a yellow solid. Yield 20%, mp 158 – 160°C; ^{1}H-NMR (DMSO-d_6): δ 10.22 (s, 1H), 8.74 (s, 1H), 8.25 (d, 1H, *J* = 9.3 Hz), 8.15 (d, 1H, *J* = 7.8 Hz), 8.12 - 8.07 (m, 1H), 7.94 - 7.89 (m, 1H), 5.47 (t, 2H, *J* = 7.2 Hz), 4.21 - 4.14 (m, 1H), 2.11 - 2.06 (m, 4H), 1.77 - 1.75 (m, 2H), 1.70 - 1.61 (m, 6H), 1.56 - 1.46 (m, 5H), 1.35 - 1.25 (m, 4H), 1.21 - 1.12 (m, 6H), 0.90 - 0.80 (m, 2H). Anal. for $C_{26}H_{38}INS$

4.3. Synthesis of 1-(5-cyclohexylpentyl)-3-iodoquinolin-1-ium iodide (3)

A mixture of 3-iodoquinoline (1.0 g, 3.92 mmol), 5-(iodopentyl)cyclohexane (1.65 g, 5.88 mmol), and water (5 mL) was heated at 170°C using m icrowave irradiation for 15 minutes. The reaction mixture was allowed to cool to room temperature and diluted with EtOAc (10 mL) and extracted with EtOAc (3 x 30 mL). The organic fraction was sonicated to yield the crude product. The crude product was vacuum filtered on qualitative filter paper using Et_2O to afford the pure 1-(5-cyclohexylpentyl)-3-iodoquinolin-1-ium iodide as a yellow solid. Yield 19.6%, mp 207 – 209°C; ^{1}H-NMR (DMSO-d_6): δ 9.86 (s, 1H), 9.72 (s, 1H), 8.55 (d, 1H, *J* = 8.7 Hz), 8.36 - 8.33 (dd, 1H, *J* = 8.2 Hz, *J* = 1.47 Hz), 8.28 - 8.22 (m, 1H), 8.25 (t, 1H, *J* = 7.33 Hz), 4.95 (t, 2H, *J* = 7.91 Hz), 1.96 - 1.91 (m, 2H), 1.65-1.67 (m, 5H), 1.40 - 1.30 (m, 4H), 1.20 - 1.00 (m, 6H), 0.90 - 0.78 (m, 2H). Anal. for $C_{20}H_{27}I_2N$

4.4. Synthesis of 1-(5-cyclohexylpentyl)-3-(naphthalen-2-ylthio)quinolin-1-ium iodide (4)

A mixture of copper (I) iodide (19 mg, 0.10 mmol), Cs_2CO_3 (540 mg, 3.92 mmol), 3-iodoquinoline (500 mg, 1.96 mmol), naphthalene-2-thiol (0.21 mg, 1.96 mmol), ethylene glycol (0.24 mL, 3.92 mmol), and 2-propanol (5 mL) was heated at 170°C under nitrogen using microwave irradiation for 15 minutes. The reaction mixture was allowed to cool to room temperature and diluted with H_2O (20 mL) and extracted with EtOAc (3 x 30 mL). The organic fraction was washed with brine (150 mL), dried over anhydrous sodium sulfate, and concentrated by rotary evaporation at reduced pressure to yield the crude product. The crude product was purified with FLASH chromatography on a 12 g column using a gradient mobile phase (EtOAc:Hexane, 0:10 to 20:80) of EtOAc and hexane to afford 3-(naphthalen-2-ylthio)quinoline as a opaque solid. Yield 87%; ^{1}H NMR ($CDCl_3$): δ 8.87 (s, 1H), 8.10-8.07 (m, 2H), 7.91 (s, 1H), 7.85-7.79 (m, 2H), 7.77-7.68 (m, 3H), 7.57-7.47 (m, 2H), 7.45-7.26 (m, 2H).

A mixture of 3-(naphthalen-2-ylthio)quinoline (50mg, 0.20 mmol), 5-(iodopentyl)cyclohexane (84.1 mg, 0.30 mmol), and H_2O (5 mL) was heated at 170°C using microwave irradi ation for 15 min. The reaction mixture was allowed to cool to room temperature and diluted with EtOAc (10 mL) and extracted with EtOAc (3 x 30 mL). The pooled organic fraction was sonicated to yield the crude product. The crude product was vacuum filtered using Et_2O to afford the pure 1-(5-cyclohexylpentyl)-3-(naphthalen-2-ylthio)quinolin-1-ium iodide, **4** as a yellow solid. Yield 52.5%, mp 143 – 145°C; ^{1}H-NMR (DMSO-d_6): δ 9.68 (s, 1H), 9.21 (s, 1H), 8.56 (d, 1H, *J* = 10.5 Hz), 8.36 (d, 1H, *J* = 7,2 Hz), 8.24 - 8.19 (m, 1H), 8.16 (s, 1H), 8.02 - 7.97 (m, 2H), 7.93 - 7.83 (m, 2H), 7.58 - 7.55 (m, 3H), 5.02 - 4.97 (t, 2H, *J* = 6.9Hz), 1.99 - 1.70 (m, 2H), 1.69 - 1.49 (m, 5H), 1.35 - 1.15 (m, 4H), 1.19 - 0.99 (m, 6H), 0.89 - 0.69 (m, 2H). Anal. for $C_{30}H_{34}INS$

4.5. Synthesis of 1-(5-cyclohexylpentyl)-3-phenoxyquinolin-1-ium iodide (5a–b)

A mixture of copper (I) iodide (45.7 mg, 0.24 mmol), 3-iodoquinoline (500 mg, 1.96 mmol), phenol (369 mg, 3.92 mmol), Cs_2CO_3 (1.56 g, 3.92 mmol), and N-methyl pyrrolidione (NMP) (4 mL) was heated at 195°C using microwave irradiat ion for 2 hours. The reaction mixture was allowed to cool to room temperature and diluted with H_2O (20 mL) and extracted with EtOAc (3 x 30 mL). The organic fraction was washed with brine (150 mL), dried over anhydrous Na_2SO_4, and concentrated by rotary evaporation at reduced pressure to yield the crude product. The crude product was purified with FLASH chromatography on a 12 g column using a gradient mobile phase (EtOAc: Hexane, 0:10 to 20:80) of EtOAc and hexane to afford 3-phenoxyquinoline, as a white solid. Yield 55 %; ^{1}H NMR ($CDCl_3$): δ 8.80 (s, 1H), 8.03 (d, 1H, *J* = 8.4 Hz), 7.91 (d, 1H, *J* = 8.1 Hz), 7.78 (s, 1H), 7.70 - 7.64 (m, 1H), 7.60 - 7.54 (m, 1H), 7.48 - 7.43 (m, 2H), 7.25 - 7.20 (m 1H), 7.18 - 7.15 (m, 2H). To obtain the fluorinated analog, 4-fluorophenol was used in place of phenol to yield, 3-(4-fluoro-phenoxy)quinoline. Yield 64 %; ^{1}H NMR ($CDCl_3$): δ 8.80 (s, 1H), 8.00 (d, 1H, *J* =

8.4Hz), 7.88 (d, 1H, *J* = 8.1 Hz), 7.72 (s, 1H), 7.68-7.63 (m, 1H), 7.59 - 7.54 (m, 1H), 7.32 - 7.24 (m, 4H).

A mixture of 3-phenoxyquinoline or its 4-fluoro analog (0.23 mmol), 5-(iodopentyl)-cyclohexane (97 mg, 0.35 mmol), and H_2O (5 mL) was heated at 170°C using microwave irradiation for 15 min. The reaction mixture was allowed to cool to room temperature and diluted with EtOAc (10 mL) and extracted with EtOAc (3 x 30 mL). The organic fraction was sonicated, separated and solvent removed under reduced pressure to yield the crude product which was vacuum filtered using Et_2O to afford the pure as a yellow solid.

1-(5-cyclohexylpentyl)-3-phenoxyquinolin-1-ium iodide (5a)—Yield 8.23%, mp 143 – 146 °C; ^{1}H-NMR (DMSO-d_6): δ 9.77 (s, 1H), 8.81 (s, 1H), 8.57 (d, 1H, *J* = 8.7 Hz), 8.35 (d, 1H, *J* = 8.4 Hz), 8.16 - 8.11 (t, 1H, *J* = 7.2 Hz), 7.99 - 7.94 (t, 1H, *J* = 7.5 Hz), 7.55 - 7.50 (t, 2H, *J* = 8.4 Hz), 7.35 - 7.29 (t, 3H, *J* = 8.1 Hz), 5.07 - 5.02 (t, 2H, *J* = 8.1 Hz), 2.06 - 1.90 (m, 2H), 1.70 - 1.50 (m, 5H), 1.48 - 1.25 (m, 4H), 1.22 - 1.15 (m, 6H), 0.9 - 0.7 (m, 2H). Anal. for $C_{26}H_{32}INO$•0.07EtOAc

1-(5-cyclohexylpentyl)-3-(4-fluorophenoxy)quinolin-1-ium iodide (5b)—Yield 13.9%, mp 155 – 157°C; ^{1}H NMR (DMSO-d_6): δ 9.74 (s, 1H), 8.80 (s, 1H), 8.56 (d, 1H, *J* = 8.7 Hz), 8.35 (m, 1H), 8.14 (t, 1H, *J* = 7.2 Hz), 7.96 - 7.91 (m, 1H), 7.51 - 7.66 (m, 2H), 7.33 (m, 2H), 5.02 (t, 2H, *J* = 8.1 Hz), 2.12 - 1.96 (m, 2H), 1.75 - 1.55 (m, 5H), 1.50 - 1.27 (m, 4H), 1.19 - 1.13 (m, 6H), 0.9 - 0.7 (m, 2H). Anal. for $C_{26}H_{31}FINO$

4.6. Procedure for the synthesis of 3-iodoquinoline (7)

A mixture of 3-bromoquinoline (9.8 g, 4.73 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 100 °C and allowed to reflux under nitrog en for 48 hours according to the method of Klapars.[28] The progress of the reaction was monitored by TLC until 100% conversion was achieved. The reaction mixture was allowed to cool to room temperature, and then diluted with aq NH_3 (20 mL) followed by H_2O, and extracted with EtOAc (3 x 30 mL). The organic fraction was washed with brine (150 mL), dried (Na_2SO_4), and concentrated by rotary evaporation at reduced pressure to yield the pure product as a pale yellow solid. Yield (12 g, 100%). ^{1}H NMR ($CDCl_3$): 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).

4.7. General procedure for obtaining 3-[(substituted-benzyl)thio]quinolines (8a–r, w–z)

A mixture of CuI (20 mg, 0.10 mmol), Cs_2CO_3 (540 mg, 3.92 mmol), 3-iodoquinoline (500 mg, 1.96 mmol), substituted benzylthiol (0.21 mg, 1.96 mmol), ethylene glycol (0.22 mL, 3.92 mmol), and 2-propanol (2 mL) was heated at 170°C un der N_2 using microwave irradiation for 15 min. The reaction mixture was allowed to cool to room temperature, diluted with H_2O (20 mL) and extracted with EtOAc (3 x 30 mL). The organic fraction was pooled, washed with brine (150 mL), dried (Na_2SO_4) and concentrated under reduced pressure to yield the crude product which was purified using FLASH chromatography (EtOAc:Hexane, 0:10 to 20:80) to afford 3-[(substituted-benzyl)thio]quinoline.

4.7.1. 3-(Benzylthio)quinoline (8a)—Yield 77.1%; ^{1}H NMR ($CDCl_3$): δ 8.78 (s, 1H), 8.04 (d, 1H, *J* = 8.7 Hz), 7.98 (s, 1H), 7.70 – 7.66 (m, 3H), 7.52 (t, 1H, *J* = 6.0 Hz), 7.29 – 7.26 (m, 4H), 4.19 (s, 2H).

4.7.2. 3-((2-Bromobenzyl)thio)quinoline (8b)—Yield 70.9%; ^{1}H NMR ($CDCl_3$): δ 8.82 (s, 1H), 8.06 (d, 1H, *J* = 9.3 Hz), 8.02 (s, 1H), 7.72 – 7.70 (m, 1H), 7.70 – 7.67 (m, 1H), 7.58 – 7.51 (m, 2H), 7.18 (d, 2H, *J* = 6.3 Hz), 7.14 – 7.09 (m, 1H), 4.29 (s, 2H).

4.7.3. 3-((3-Bromobenzyl)thio)quinoline (8c)—Yield 89.5%; ^{1}H NMR ($CDCl_3$): δ 8.78 (s, 1H), 8.06 (d, 1H, *J* = 9.0 Hz), 7.999 (s, 1H), 7.72-7.56 (m, 2H), 7.56-7.51 (m, 1H), 7.469 (s, 1H), 7.39-7.35 (m, 1H), 7.17-7.10 (m, 2H), 4.13 (s, 2H).

4.7.4. 3-((4-Bromobenzyl)thio)quinoline (8d)—Yield 61.8%; ^{1}H NMR ($CDCl_3$): δ 8.78 (s, 1H), 8.06 (d, 1H, *J* = 9.0 Hz), 7.99 (s, 1H), 7.72 – 7.66 (m, 2H), 7.60 – 7.52 (m, 1H), 7.40 (d, 2H, *J* =6.6 Hz), 7.15 (d, 2H, *J* = 8.4 Hz), 4.12 (s, 2H).

4. 7.5. 3-((2-(Trifluoromethyl)benzyl)thio)quinoline (8e)—Yield 49.6%; ^{1}H NMR ($CDCl_3$): δ 8.80 (s, 1H), 8.07 (d, 1H, *J* = 9.0 Hz), 8.03 (s, 1H), 7.71-7.63 (m, 3H), 7.56-7.51 (m, 1H), 7.45-7.43 (m, 2H), 7.42-7.34 (m, 1H), 4.36 (s, 2H).

4. 7.6. 3-((3-(Trifluoromethyl)benzyl)thio)quinoline (8f)—Yield 82.0%; ^{1}H NMR ($CDCl_3$): δ 8.73 (s, 1H), 8.06 (d, 1H, *J* = 8.7 Hz), 7.98 (s, 1H), 7.72 – 7.97 (m, 2H), 7.57 – 7.54 (m, 1H), 7.54 – 7.49 (m, 2H), 7.44 – 7.35 (m, 2H), 4.21 (s, 2H).

4.7.7. 3-((4-(Trifluoromethyl)benzyl)thio)quinoline (8g)—Yield 55.7%; ^{1}H NMR ($CDCl_3$): δ 8.79 (s, 1H), 8.65 (d, 1H, *J* = 8.4 Hz), 7.98 (s, 1H), 7.73 – 7.67 (m, 2H), 7.57 – 7.52 (m, 1H), 7.54 (t, 2H, *J* = 8.4 Hz), 7.37 (d, 2H, J = 8.1 Hz), 4.21 (s, 2H).

4.7.8. 3-((2-Methylbenzyl)thio)quinoline (8h)—Yield 71.6%; ^{1}H NMR ($CDCl_3$): δ 8.79 (s, 1H), 8.06 (d, 1H, *J* = 8.7 Hz), 7.98 (s, 1H), 7.67 (t, 2H, *J* = 7.8 Hz), 7.52 (t, 1H, *J* = 8.1 Hz), 7.18 – 7.16 (m, 2H), 7.08 – 7.05 (m, 2H), 4.17 (s, 2H), 2.41 (s, 3H).

4.7.9. 3-((3-Methylbenzyl)thio)quinoline (8i)—Yield 73.5%; ^{1}H NMR ($CDCl_3$): δ 8.79 (s, 1H), 8.06 (d, 1H, *J* = 8.7 Hz), 7.95 (s, 1H), 7.66 – 7.61 (m, 2H), 7.52 – 7.46 (t, 1H, *J* = 7.2 Hz), 7.15 (t, 1H, *J* = 7.5 Hz), 7.06 (t, 3H, *J* = 8.4 Hz), 4.13 (s, 2H), 2.15 (s, 3H).

4.7.10. 3-((4-Methylbenzyl)thio)quinoline (8j)—Yield 71.6%; ^{1}H NMR ($CDCl_3$): δ 8.78 (s, 1H), 8.05 (d, 1H, *J* = 8.4 Hz), 7.99 (s, 1H), 7.66 (t, 2H, *J* = 7.5 Hz), 7.51 (t, 1H, *J* = 7.2 Hz), 7.17 (s, 2H, J=8.1 Hz), 7.08 (d, 2H, *J* = 7.8 Hz), 4.16 (s, 2H), 2.30 (s, 3H).

4.7.11. 3-((2-Chlorobenzyl)thio)quinoline (8k)—Yield 70.0%; ^{1}H-NMR ($CDCl_3$): δ 8.78 (s, 1H), 8.06 (d, 1H, *J* = 9.0 Hz), 7.98 (s, 1H), 7.72 – 7.69 (m, 2H), 7.53 (t, 1H, *J* = 8.4 Hz), 7.26 – 7.17 (m, 4H), 4.14 (s, 2H).

4.7.12. 3-((4-Chlorobenzyl)thio)quinoline (8l)—Yield 50.5%; ^{1}H-NMR ($CDCl_3$): δ 8.78 (s, 1H), 8.05 (d, 1H, *J* = 8.7 Hz), 7.98 (s, 1H), 7.72 – 7.70 (m, 1H), 7.69 – 7.66 (m, 1H), 7.45 (t, 1H, *J* = 9.0 Hz), 7.26 – 7.25 (m, 2H), 7.23 – 7.18 (m, 2H), 4.14 (s, 2H).

4.7.13. 3-((2-Fluorobenzyl)thio)quinoline (8m)—Yield 87.1%; ^{1}H NMR ($CDCl_3$): δ 8.79 (s, 1H), 8.06 (d, 1H, *J* = 9.3 Hz), 8.02 (s, 1H), 7.71 – 7.66 (m, 2H), 7.56 – 7.50 (m, 1H), 7.23 – 7.20 (m, 2H), 7.04 – 6.98 (2H), 4.20 (s, 2H).

4.7.14. 3-((3-Fluorobenzyl)thio)quinoline (8n)—Yield 24.6%; ^{1}H NMR ($CDCl_3$): δ 8.78 (s, 1H), 8.06 (d, 1H, *J* =8.7 Hz), 7.98 (s, 1H), 7.65 (t, 2H, *J* = 6.3 Hz), 7.5 (t, 1H, *J* = 6.3 Hz), 7.26 – 7.18 (m, 1H), 7.04 – 7.00 (m, 2H), 6.94 (t, 1H, *J* =6.3 Hz), 4.15 (s, 2H).

4.7.15. 3-((4-Fluorobenzyl)thio)quinoline (8o)—Yield 45.1%; ^{1}H NMR ($CDCl_3$): δ 8.78 (s, 1H), 8.05 (d, 1H, *J* = 8.7 Hz), 7.98 (s, 1H), 7.71 – 7.66 (m, 2H), 7.54 (t, 1H, *J* = 8.7 Hz), 7.27 – 7.21 (m, 2H), 6.96 (t, 2H, *J* = 9.0 Hz), 4.15 (s, 2H).

4.7.16. 3-((2-Methoxybenzyl)thio)quinoline (8p)—Yield 52.2%; ^{1}H NMR ($CDCl_3$): δ 8.78 (s, 1H), 8.05 (s, 1H), 7.99 (s, 1H), 7.66 (t, 2H, *J* = 7.5 Hz), 7.52 (t, 1H, *J* = 6.3 Hz), 7.20 (d, 2H, *J* = 6.9 Hz), 6.80 (d, 2H, *J* = 6.9 Hz), 4.15 (s, 2H), 3.77 (s, 3H).

4.7.17. 3-((3-Methoxybenzyl)thio)quinoline (8q)—Yield 46.3%; ^{1}H NMR ($CDCl_3$): δ 8.78 (s, 1H), 8.05 (s, 1H), 7.99 (s, 1H), 7.66 (t, 2H, *J* = 7.5 Hz), 7.52 (t, 1H, *J* = 6.3 Hz), 7.20 (d, 2H, *J* = 6.9 Hz), 6.80 (d, 2H, *J* = 6.9 Hz), 4.15 (s, 2H), 3.77 (s, 3H).

4.7.18. 3-((4-Methoxybenzyl)thio)quinoline (8r)—Yield 30.0%; ^{1}H NMR ($CDCl_3$): δ 8.78 (s, 1H), 8.05 (s, 1H), 7.99 (s, 1H), 7.66 (t, 2H, *J* = 7.5 Hz), 7.52 (t, 1H, *J* = 6.3 Hz), 7.20 (d, 2H, *J* = 6.9 Hz), 6.80 (d, 2H, *J* = 6.9 Hz), 4.15 (s, 2H), 3.77 (s, 3H).

4.7.19. 3-((4-(Tert-butyl)benzylthio)quinoline (8w)—Yield 71.2%; ^{1}H NMR ($CDCl_3$): δ 8.82 (s, 1H), 8.04 (d, 1H, *J* = 8.7 Hz), 7.98 (s, 1H), 7.68 – 7.64 (m, 2H), 7.52 (t, 1H, *J* = 7.8 Hz), 7.33 – 7.26 (m, 2H), 7.26 – 7.21 (m, 2H), 4.18 (s, 2H), 1.26 (s, 9H).

4.7.20. 3-((3,4-dichlorobenzyl)thio)quinoline (8x)—Yield 46.3%; ^{1}H NMR($CDCl_3$):δ 8.78 (s, 1H), 8.06 (d, 1H, *J* = 9.0 Hz), 8.00 (s, 1H), 7.72 – 7.69 (t, 2H, *J* = 6.3 Hz), 7.57 – 7.52 (t, 1H, *J* = 7.8 Hz), 7.38 (s, 1H), 7.32 (d, 1H, *J* = 8.4 Hz), 7.05 (d, 1H, J=8.4 Hz), 4.10 (s, 2H).

4.7.21. 3-((3,5-bis(trifluoromethyl)benzyl)thio)quinoline (8y)—Yield 65%; ^{1}H NMR($CDCl_3$): δ 8.78 (s, 1H), 8.05 (d, 1H, *J* = 9.3 Hz), 8.01 (s, 1H), 7.71 – 7.66 (m, 2H), 7.56 – 7.50 (t, 1H, *J* = 8.1 Hz), 6.84 – 6.78 (m, 2H), 6.71 – 6.4 6(m, 1H), 4.12 (s, 2H).

4.7.22. 3-((2,4,6-trimethylbenzyl)thio)quinoline (8z)—Yield 73%; ^{1}H NMR ($CDCl_3$): δ 8.79 (s, 1H), 8.06 (d, 1H, *J* = 8.7 Hz), 7.98 (s, 1H), 7.70 - 7.65 (t, 2H, *J* = 7.8 Hz), 7.55 - 7.50 (t, 1H, *J* = 8.1 Hz), 7.18 - 7.16 (m, 2H), 4.15 (s, 2H), 2.41 (s, 9H).

4.8. General procedure for the synthesis of 3-((cyanobenzyl)thio)quinoline (8s–u)

A mixture of 3-(bromobenzyl)thio)quinoline ***8b–d*** (300 mg, 0.91 mmol) and copper (I) cyanide (160 mg, 1.8 mmol) was stirred for 6 hours at 200°C using microwave irradiation in NMP. The reaction mixture was diluted with H_2O, extracted with EtOAc (3 x 30 mL), the pooled organic fractions was washed with brine (150 mL), dried (Na_2SO_4) and concentrated by rotary evaporation at reduced pressure. The crude product was purified by FLASH chromatography (EtOAc:Hexane, 3:7) to afford 3-((cyanobenzyl)thio)quinoline.

4.8.1. 2-((Quinolin-3-ylthio)methyl)benzonitrile (8s)—Yield 42.2 %; ^{1}H NMR ($CDCl_3$): δ 8.74 (s, 1H), 8.21 (s, 1H), 8.07 (d, 1H, *J* = 8.7 Hz), 7.74 – 7.68 (m, 2H), 7.62 – 7.52 (m, 2H), 7.61 – 7.41 (m, 1H), 7.32 (t, 2H, *J* = 8.7 Hz), 4.33 (s, 2H).

4.8.2. 3-((Quinolin-3-ylthio)methyl)benzonitrile (8t)—Yield 20 %; ^{1}H NMR ($CDCl_3$): δ 8.78 (s, 1H), 8.06 (d, 1H, *J = 8.5 Hz), 7.98 (s, 1H), 7.74* –7.62 (m, 2H), 7.53 (t, 1H, *J* = 7.5 Hz), 7,45 (s, 1H), 7.36 (d, 1H, *J = 7.6 Hz), 7.19 – 7.07 (m, 2H), 4.12 (s, 2H).*

4.8.3. 4-((Quinolin-3-ylthio)methyl)benzonitrile (8u)—Yield 52.2%; ^{1}H NMR ($CDCl_3$): δ 8.78 (s, 1H), 8.08 (d, 1H, *J* = 6.9 Hz), 7.99 (s, 1H), 7.74 – 7.69 (m, 2H), 7.59 – 7.53 (m, 3H), 7.38 – 7.31 (d, 2H, *J* = 9.0 Hz), 4.18 (s, 2H).

4.9. Procedure for the synthesis of 3-((4-hydroxybenzyl)thio)quinoline (8v)

A mixture of 3-((4-methoxybenzyl)thio)quinoline ***8r***, (100 mg, 0.37 mmol) and pyridine hydrochloride (846 mg, 7.49 mmol) was stirred at 220 °C using microwave irradiation for 6 hours. The reaction mixture was diluted with H_2O, extracted with EtOAc (3 x 30 mL), the pooled organic fractions was washed with brine (150 mL), dried (Na_2SO_4), and concentrated by rotary evaporation at reduced pressure. The crude product was subjected to FLASH chromatography on a 12 g normal phase silica column (EtOAc:Hexane, 3:7) to afford 3-((4-hydroxybenzyl)thio)quinoline (***8v***) as a white solid. Yield 51.2%; ^{1}H NMR ($CDCl_3$): δ 9.35 (s, 1H), 8.76 (s, 1H), 8.28 (s, 1H), 7.97 (d, 1H, *J* = 8.7 Hz), 7.89 (d, 1H, J = 7.8 Hz), 7.70 (t, 1H, *J* = 7.2 Hz), 7.59 (t, 1H, *J* = 7.8 Hz), 7.18 (d, 2H, *J* = 7.8 Hz), 6.68 (d, 2H, *J* = 7.8 Hz), 4.29 (s, 2H).

4.10. General procedure for the synthesis of 3-((substituted-benzyl)thio)-1-(5-cyclohexyl-pentyl)quinolin-1-ium iodide (9a–z)

A mixture of 3-[(substituted-benzyl)thio]quinoline (56mg, 0.20 mmol), 5-(iodopentyl)cyclo-hexane (85 mg, 0.30 mmol), and H_2O (5 mL) was heated at 170°C using microwave irradiation for 15 min. The reaction mixture was allowed to cool to room temperature, diluted with EtOAc (10 mL) and extracted with EtOAc (3 x 30 mL). The organic fraction was sonicated to yield the crude product. The crude product was vacuum filtered using Et_2O to afford the pure 3-((substituted-benzyl)thio)-1-(5-cyclohexylpentyl)quinolin-1-ium iodide as a yellow solid.

4.10.1. 3-(Benzylthio)-1-(5-cyclohexylpentyl)quinolin-1-ium iodide (9a)—Yield 58%, mp 108 – 110°C; ^{1}H NMR (DMSO-d_6): δ 9.59 (s, 1H), 9.22 (s, 1H), 8.52 (d, 1H, *J* = 9.0 Hz), 8.31 (d, 1H, *J* = 5.1 Hz), 8.18 – 8.12 (m, 1H), 8.01 – 7.96 (m, 1H), 7.41 (d, 2H, *J* = 7.35 Hz), 7.34 – 7.21 (m, 3H), 4.96 (t, 2H, *J* = 7.5 Hz), 4.55 (s, 2H), 2.01 – 1.81 (m, 2H), 1.71 – 1.53 (m, 5H), 1.51 – 1.25 (m, 4H), 1.21 – 1.01 (m, 6H), 0.92 – 0.70 (m, 2H). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 149.9, 144.9, 136.3, 135.9, 135.2, 132.3, 130.1, 130.0, 129.9, 129.5, 129.5, 129.2, 129.2, 128.2, 119.4, 57.9, 40.7, 39.4, 39.1, 37.7, 37.1, 33.3, 30.0, 26.6, 26.5, 26.3, 26.2. Anal. for $C_{27}H_{34}INS$

4.10.2. 3-((2-Bromobenzyl)thio)-1-(5-cyclohexylpentyl)quinolin-1-ium iodide (9b)—Yield 23.5%, mp 126 – 128 °C; ^{1}H NMR (DMSO-d_6) δ 9.60 (s, 1H), 9.27 (s, 1H), 8.53 (d, 1H, *J* = 8.99 Hz), 8.31 (dd, 1H *J* = 1.45, 8.34 Hz), 8.17 (ddd, 1H, *J* = 1.49, 7.01, 8.75 Hz), 8.01 (ddd, 1H, *J* = 0.76, 7.19, 7.95 Hz), 7.64 (t, 1H, *J* = 1.81 Hz), 7.43 (ddt, 2H, *J* = 1.31, 3.93, 8.05 Hz), 7.25 (t, 1H, *J* = 7.82 Hz), 4.96 (t, 2H, *J* = 7.66 Hz), 4.54 (s, 2H), 1.98 – 1.80 (m, 2H), 1.71 – 1.48 (m, 6H), 1.37 – 1.29 (m 3H), 1.17 – 1.01 (m, 6H), 0.89 – 0.79 (m, 2H). Anal. for $C_{27}H_{33}INSBr•0.22H_2O$

4.10.3. 3-((3-Bromobenzyl)thio)-1-(5-cyclohexylpentyl)quinolin-1-ium iodide (9c)—Yield 19.6%, mp 115 – 117°C; ^{1}H NMR (DMSO-d_6): δ 9.55 (s, 1H), 9.23 (s, 1H), 8.50 (d, 1H, *J* = 8.7 Hz), 8.30 (d, 1H, *J* = 8.1 Hz), 8.16 (t, 1H, *J* = 6.9 Hz), 7.99 (t, 1H, *J* = 7.5 Hz), 7.50 – 7.45 (m, 2H), 7.37 – 7.33 (m, 2H), 4.95 (t, 2H, *J* = 7.5 Hz), 4.51 (s, 2H), 1.98 – 1.84 (m, 2H), 1.68 – 1.56 (m, 5H), 1.32 – 1.26 (m, 4H), 1.19 – 1.05 (m, 6H), 0.88 – 0.72 (m, 2H). Anal. for $C_{27}H_{33}INSBr•0.1H_2O$

4.10.4. 3-((4-Bromobenzyl)thio)-1-(5-cyclohexylpentyl)quinolin-1-ium iodide (9d)—Yield 21.4%, mp 92 – 94°C; ^{1}H NMR (DMSO-d_6): δ 9.56 (s, 1H), 9.24 (s, 1H), 8.52 (d, 1H, *J* = 9.0 Hz), 8.31 (dd, 1H, *J* = 8.0, 2.0 Hz,), 8.20 – 8.11 (m, 1H), 8.04 – 7.96 (m, 1H), 7.54 – 7.43 (m, 2H), 7.41 – 7.31 (m, 2H), 4.99 (t, 2H, *J* = 9.0 Hz), 4.53 (s, 2H), 1.94 – 1.80 (m, 2H), 1.70 – 1.52 (m, 6H), 1.38 – 1.22 (m, 3H), 1.17 – 1.06 (m, 6H), 0.89 – 0.70 (m, 2H). Anal. for $C_{27}H_{33}BrINS$

4.10.5. 1-(5-Cyclohexylpentyl)-3-((2-(trifluoromethyl)benzyl)thio)quinolin-1-ium iodide (9e)—Yield 18.1%, mp 145 – 147°C; ^{1}H NMR (DMSO-d_6): δ 9.68 (s, 1H), 9.31 (s, 1H), 8.56 (d, 1H, *J* = 8.7 Hz), 8.35 (d, 1H, *J* = 8.7 Hz), 8.20 (t, 1H, *J* = 7.2 Hz), 8.02 (t, 1H, *J* = 7.5 Hz), 7.76 (d, 1H, *J* = 7.5 Hz), 7.64 – 7.62 (m, 2H), 7.56-7.52 (m, 1H), 4.99 (t, 2H, *J* = 7.5 Hz), 4.66 (s, 2H), 1.97 – 1.91 (m, 2H), 1.65 – 1.60 (m, 5H), 1.40 – 1.30 (m, 4H), 1.18 – 1.11 (m, 6H), 0.90 – 0.79 (m, 2H). Anal. for $C_{29}H_{33}INSF_3$

4.10.6. 1-(5-Cyclohexylpentyl)-3-((3-(trifluoromethyl)benzyl)thio)quinolin-1-ium iodide (9f)—Yield 2.0%, mp 148 – 150°C; ^{1}H NMR (CD_3OD): δ 9.46 (s, 1H), 9.12 (s, 1H), 8.47 (d, 1H, *J* = 9.3 Hz), 8.30 (d, 1H, *J* = 8.4 Hz), 8.20 (t, 1H, *J* = 6.9 Hz), 7.99 (t, 1H, *J* = 8.1 Hz), 7.72-7.68 (m, 2H), 7.57 – 7.51 (m, 2H), 5.00 (t, 2H, *J* = 7.8 Hz), 4.59 (s, 2H), 2.10 – 1.96 (m, 2H), 1.76 – 1.64 (m, 5H), 1.43 – 1.37 (m, 4H), 1.28 – 1.19 (m, 6H), 0.90 – 0.84 (m, 2H). Anal. for $C_{29}H_{33}INSF_3$•$0.3H_2O$

4.10.7. 1-(5-Cyclohexylpentyl)-3-((4-(trifluoromethyl)benzyl)thio)quinolin-1-ium iodide (9g)—Yield 18.9%, mp 126 – 128°C; ^{1}H NMR (DMSO-d_6): δ 9.59 (s, 1H), 9.26 (s, 1H), 8.53 (d, 1H, *J* = 8.4Hz), 8.30 (d, 1H, *J* = 8.4 Hz), 8.17 (t, 1H, *J* = 7.5 Hz), 8.03 – 7.97 (m, 1H), 7.66 (d, 2H, *J* = 8.7 Hz), 7.63 (d, 2H, *J* = 8.7Hz), 4.96 (t, 2H, *J* = 7.2 Hz), 4.64 (s, 2H), 1.96 – 1.80 (m, 2H), 1.70 – 1.50 (m, 5H), 1.4 – 1.25 (m, 4H), 1.2 – 1.0 (m, 6H), 0.90 – 0.70 (m, 2H). Anal. for $C_{28}H_{33}F_3INS$

4.10.8. 1-(5-Cyclohexylpentyl)-3-((2-methylbenzyl)thio)quinolin-1-ium iodide (9h)—Yield 62.2%, mp 100 – 102°C; ^{1}H NMR (DMSO-d_6): δ 9.59 (s, 1H), 9.24 (s, 1H), 8.53 (d, 1H, *J* = 9.0 Hz), 8.31 (d, 1H, *J* = 8.1 Hz), 8.20-8.15 (m, 1H), 8.03-7.98 (m, 1H), 7.25-7.15 (m, 3H), 7.05 (t, 1H, *J* = 7.5 Hz), 4.95 (t, 2H, *J* = 7.8 Hz), 4.53 (s, 2H), 2.41 (s, 3H), 2.02-1.85 (m, 2H), 1.70-1.50 (m, 6H), 1.45-1.25 (m, 4H), 1.21-1.0 (m, 5H), 0.9-0.7 (m, 2H). Anal. for $C_{28}H_{36}INS$

4.10.9. 1-(5-Cyclohexylpentyl)-3-((3-methylbenzyl)thio)quinolin-1-ium iodide (9i)—Yield 5.4%; mp 100.4 – 102.3°C; ^{1}H NMR (DMSO-d_6): δ 9.60(s, 1H), 9.23 (s, 1H), 8.52 (d, 1H, *J* = 9.3 Hz), 8.31 (d, 1H, *J* = 7.2 Hz), 8.19 – 8.14 (m, 1H), 7.99 (t, 1H, *J* = 7.5 Hz), 7.23 – 7.15 (m, 3H), 7.06 – 7.04 (m, 1H), 4.99 (t, 2H, *J* = 7.5 Hz), 4.52 (s, 2H), 2.23 (s, 3H), 1.93 – 1.93 (m, 2H), 1.69 – 1.66 (m, 5H), 1.31 – 1.28 (m, 4H), 1.14 – 1.15 (m, 6H), 0.87 – 0.76 (m, 2H). ^{13}C-NMR(75 MHz, DMSO-d_6): δ 156.7, 149.8, 145.0, 138.3, 136.1, 135.9, 135.2, 132.4, 130.9, 130.1, 129.9, 129.6, 129.0, 128.8, 119.4, 57.9, 40.8, 39.1, 37.4, 37.3, 37.1, 33.3, 30.0, 29.2, 26.6, 26.5, 26.2, 21.3. Anal. for $C_{28}H_{36}INS$

4.10.10. 1-(5-Cyclohexylpentyl)-3-((4-methylbenzyl)thio)quinolin-1-ium iodide (9j)—Yield 56.0%, mp 100 – 102°C; ^{1}H NMR (DMSO-d_6): δ 9.57 (s, 1H), 9.21 (s, 1H), 8.51 (d, 1H, *J* = 9.0 Hz), 8.30 (d, 1H, *J* = 8.4 Hz), 8.18 – 8.12 (m, 1H), 8.01 – 7.96 (m, 1H), 7.31 – 7.26 (m, 2H), 7.12 – 7.08 (m, 2H), 4.98 (t, 2H, *J* = 8.7 Hz), 4.50 (s, 2H), 2.22 (s, 3H), 2.01 – 1.83 (m, 2H), 1.75 – 1.55 (m, 6H), 1.48 – 1.22 (m, 4H), 1.20 – 1.05 (m, 5H), 0.91 – 0.70 (m, 2H). Anal. for $C_{28}H_{36}INS$

4.10.11. 3-((2-Chlorobenzyl)thio)-1-(5-cyclohexylpentyl)quinolin-1-ium iodide (9k)—Yield 17.2%; mp 110 – 112°C; ^{1}H NMR (DMSO-d_6) δ 9.64 (s, 1H), 9.27 (s, 1H), 8.54 (d, 1H, *J* = 8.92 Hz), 8.32 (dd, 1H, *J* = 1.45, 8.28 Hz), 8.19 (ddd, 1H, *J* = 1.51, 6.99, 8.80 Hz), 8.04 – 7.97 (m, 1H), 7.47 (ddd, 2H, *J* = 1.74, 6.16, 7.54 Hz), 7.36 – 7.20 (m, 2H), 4.98 (t, 2H, *J* = 8.78 Hz), 4.59 (s, 2H), 1.95 – 1.82 (m, 2H), 1.70 – 1.53 (m, 6H), 1.43 – 1.19 (m, 3H), 1.13 (m, 6H), 0.90 – 0.69 (m, 2H). Anal. for $C_{27}H_{33}INSCl$

4.10.12. **3-((4-Chlorobenzyl)thio)-1-(5-cyclohexylpentyl)quinolin-1-ium iodide (*9l*)—**Yield 59.0%, mp 102 – 104°C; ^{1}H NMR (DMSO-d_6): δ 9.57 (s,1H), 9.24 (s,1H), 8.52 (d,1H, *J* = 9.0 Hz), 8.35 – 8.29 (dd, 1H, *J* = 1.2 Hz, *J* = 8.4 Hz), 8.19 – 8.14 (m, 1H), 8.02 – 7.97 (m, 1H), 7.44 – 7.40 (m, 2H), 7.41 – 7.35 (m, 2H), 4.98 (t, 2H, *J* = 9.0 Hz), 4.54 (s, 2H), 1.99 – 1.79 (m, 2H), 1.69 – 1.48 (m, 6H), 1.45 – 1.21 (m,4H), 1.20 – 1.00 (m,5H), 0.90 – 0.70 (m, 2H)). Anal. for $C_{27}H_{33}ClINS$

4.10.13. 1-(5-Cyclohexylpentyl)-3-((2-fluorobenzyl)thio)quinolin-1-ium iodide (9m)—Yield 12.2 %, mp 119 – 121°C; ^{1}H NMR (DMSO-d_6) δ 9.65 (s, 1H), 9.28 (s, 1H), 8.55 (d, 1H, *J* = 8.93 Hz), 8.32 (dd, 1H, *J* = 1.44, 8.30 Hz), 8.18 (dd, 1H, *J* = 1.61, 8.88 Hz), 8.05 – 7.96 (m, 1H), 7.47 – 7.39 (m, 1H), 7.33 (d, 1H, *J* = 8.23 Hz), 7.24 – 7.17 (m, 1H), 7.12 (m, 1H), 4.98 (t, 2H, *J* = 8.93 Hz), 4.57 (s, 2H), 1.99 – 1.83 (m, 2H), 1.61 (m, 6H), 1.39-1.21 (m, 3H), 1.21 – 1.01 (m, 6H), 0.89 – 0.74 (m, 2H). Anal. for $C_{27}H_{33}FINS$

4.10.14. 1-(5-Cyclohexylpentyl)-3-((3-fluorobenzyl)thio)quinolin-1-ium iodide (9n)—Yield 12.8%, mp 120 – 123°C; ^{1}H NMR (DMSO-d_6): δ 9.59 (s, 1H), 9.23 (s, 1H), 8.52 (d, 1H, *J* = 9.3 Hz), 8.30 (d, 1H, *J* = 6.9 Hz), 8.20 – 8.14 (m, 1H), 8.02 – 7.97 (m, 1H), 7.37 – 7.26 (m, 2H), 7.25 (s, 1H), 7.10 – 7.04 (m, 1H), 4.96 (t, 2H, *J* = 7.2 Hz), 4.56 (s, 2H), 1.99 – 1.69 (m, 2H), 1.68 – 1.46 (m, 5H), 1.44 – 1.18 (m, 4H), 1.17 – 1.06 (m, 6H), 0.99 – 0.69 (m, 2H). Anal. for $C_{27}H_{33}FINS$

4.10.15. 1-(5-Cyclohexylpentyl)-3-((4-fluorobenzyl)thio)quinolin-1-ium iodide (9o)—Yield 16.7%, mp 105 – 107°C; ^{1}H NMR (DMSO-d_6): δ 9.56 (s, 1H), 9.23 (s, 1H), 8.51 (d, 1H, *J* = 8.4 Hz), 8.33 – 8.29 (m, 1H), 8.19 – 8.14 (m, 1H), 8.02 – 7.97 (m, 1H), 7.46 – 7.42 (m, 2H), 7.15 – 7.09 (m, 2H), 4.96 (t, 2H, *J* = 9.0 Hz), 4.53 (s, 2H), 1.99 – 1.82 (m, 2H), 1.71 – 1.48 (m, 5H), 1.45 – 1.32 (m, 4H), 1.23 – 1.01 (m, 6H), 0.91 – 0.68 (m, 2H). ^{13}C-NMR(75 MHz, DMSO-d_6): δ 150.1, 145.4, 136.0, 135.3, 132.7, 132.7, 131.9, 131.6, 131.4, 130.9, 130.2, 130.1, 119.4, 115.8, 115.8, 58.0, 40.8, 37.4, 37.3, 33.3, 33.3, 30.0, 26.6, 26.5, 26.3, 26.2, 26.2. Anal. for $C_{27}H_{33}FINS$

4.10.16. 1-(5-Cyclohexylpentyl)-3-((2-methoxybenzyl)thio)quinolin-1-ium iodide (9p)—Yield 43.9%, mp 88 – 99°C; ^{1}H NMR (DMSO-d_6): δ 9.58 (s, 1H), 9.23 (s, 1H), 8.52 (d, 1H, *J* = 9.3 Hz), 8.30 (d, 1H, *J* = 8.4 Hz), 8.16 (t, 1H, *J* = 7.2 Hz), 7.99 (t, 1H, *J* = 7.5 Hz), 7.19 (t, 1H, *J* = 6.3 Hz), 6.98 (d, 2H, *J* = 8.1 Hz), 6.81 (d, 1H, *J* = 7.8 Hz), 4.96 (t, 2H, *J* = 7.5 Hz), 4.52 (s, 2H), 3.68 (s, 3H), 1.96 – 1.93 (m, 2H), 1.68 – 1.59 (m, 5H), 1.39 – 1.29 (m, 4H), 1.20 – 1.10 (m, 6H), 0.90 – 0.79 (m, 2H). Anal. for $C_{28}H_{36}INOS$

4.10.17. 1-(5-Cyclohexylpentyl)-3-((3-methoxybenzyl)thio)quinolin-1-ium iodide (9q)—Yield 23.4%, mp 127 – 129°C; ^{1}H NMR (DMSO-d_6): δ 9.58 (s, 1H), 9.23 (s, 1H), 8.52 (d, 1H, *J* = 9.3 Hz), 8.30 (d, 1H, *J* = 8.4 Hz), 8.16 (t, 1H, *J* = 7.2 Hz), 7.99 (t, 1H, *J* = 7.5 Hz), 7.20 (t, 1H, *J* = 6.3 Hz), 6.98 (d, 2H, *J* = 8.1 Hz), 6.81 (d, 1H, *J* = 7.8 Hz), 4.96 (t, 2H, *J* = 7.5 Hz), 4.52 (s, 2H), 3.68 (s, 3H), 1.96 – 1.93 (m, 2H), 1.68 – 1.59 (m, 5H), 1.39 – 1.29 (m, 4H), 1.20 – 1.10 (m, 6H), 0.90 – 0.79 (m, 2H). Anal. for $C_{28}H_{36}INOS$

4.10.18. 1-(5-Cyclohexylpentyl)-3-((4-methoxybenzyl)thio)quinolin-1-iumiodide (9r)—Yield 31.4%, mp 134 – 136°C; ^{1}H NMR (DMSO-d_6): δ 9.58 (s, 1H), 9.23 (s, 1H), 8.53 (d, 1H, *J* = 9.0 Hz), 8.32 (d, 1H, *J* = 6.9 Hz), 8.17 (t, 1H, *J* = 7.2 Hz), 7.99 (t, 1H, *J* = 7.8 Hz), 7.34 (d, 2H, *J* = 8.7 Hz), 6.86 (d, 2H, *J* = 6.9 Hz), 4.96 (t, 2H, *J* = 7.2Hz), 4.51 (s, 2H), 3.70 (s, 3H), 1.99 – 1.82 (m, 2H), 1.71 – 1.54 (m, 5H), 1.40 – 1.30 (m, 4H), 1.28 – 1.09 (m, 6H), 0.90 – 0.76 (m, 2H). ^{13}C-NMR(75 MHz, DMSO-d_6): δ 159.5, 146.8, 136.8, 136.6, 130.7, 130.7, 130.2, 129.9, 129.8, 127.8, 127.8, 119.5, 119.5, 114.5, 114.5, 58.8, 55.5, 40.7, 37.7, 37.5, 33.3, 33.3, 29.9, 27.6, 27.4, 26.2, 26.2, 25.8. Anal. for $C_{28}H_{36}INOS \cdot 3.5\ SiO_2$

4.10.19. 3-((2-Cyanobenzyl)thio)-1-(5-cyclohexylpentyl)quinolin-1-ium iodide (9s)—Yield 80.3%, mp 128 – 130 °C; ^{1}H NMR (DMSO-d_6) δ 9.67 (s, 1H), 9.29 (s, 1H), 8.60 – 8.47 (m, 1H), 8.33 (d, 1H, *J* = 8.3 Hz), 8.21 (dd, 1H, *J* = 8.9, 7.0 Hz), 8.03 (t, 1H, *J* = 7.7 Hz), 7.84 (d, 1H, *J* = 7.7 Hz), 7.68 – 7.42 (m, 3H), 4.98 (dd, 2H, *J* = 9.0, 6.0 Hz), 4.67 (s, 2H), 2.48 (dd, 2H, *J* = 3.7, 2.0 Hz), 1.93 (q, 2H, *J* = 8.3, 7.9 Hz), 1.64 (d, 4H, *J* = 12.9 Hz), 1.32 (s, 3H), 1.14 (q, 6H, *J* = 8.9, 5.8 Hz), 0.83 (t, 2H, *J* = 10.9 Hz). Anal. for $C_{28}H_{33}IN_2S$

4.10.20. 3-((3-Cyanobenzyl)thio)-1-(5-cyclohexylpentyl)quinolin-1-ium iodide (9t)—Yield 32.6%, mp 118 – 120 °C; ^{1}H NMR (DMSO-d_6) δ 9.63 (s, 1H), 9.26 (s, 1H), 8.55 (m, 1H), 8.32 (d, 1H, *J* = 8.14 Hz), 8.18 (dd, 1H, *J* = 7.99, 7.0 Hz), 8.01 (t, 1H, *J* = 7.63 Hz), 7.78 (d, 2H, *J* = 8.16 Hz), 7.65 – 7.40 (d, 2H, *J* = 8.2 Hz), 4.98 (t, 2H, *J* = 7.78 Hz), 4.65 (s, 2H), 1.98 – 1.81 (m, 2H), 1.63 (d, 5H, *J* = 12.87 Hz), 1.35 – 1.21 (m, 4H), 1.09 (m, 6H), 0.81 (m, 2H). Anal. for $C_{28}H_{33}IN_2S$

4.10.21. 3-((4-Cyanobenzyl)thio)-1-(5-cyclohexylpentyl)quinolin-1-ium iodide (9u)—Yield 12.6%, mp 132 – 134 °C; ^{1}H NMR (DMSO-d_6) δ 9.58 (s, 1H), 9.25 (s, 1H), 8.53 (d, 1H, *J* = 9.09 Hz), 8.32 (d, 1H, *J* = 8.14 Hz), 8.18 (t, 1H, *J* = 7.99 Hz), 8.01 (t, 1H, *J* = 7.59 Hz), 7.76 (d, 2H, *J* = 8.16 Hz), 7.60 (d, 2H, *J* = 8.19 Hz), 4.96 (t, 2H, *J* = 7.78 Hz), 4.63 (s, 2H), 1.98 – 1.81 (m, 2H), 1.63 (d, 5H, *J* = 12.87 Hz), 1.35 – 1.21 (m, 4H), 1.09 (dt, 6H, *J* = 6.48, 14.01 Hz), 0.81 (q, 2H, *J* = 11.87, 12.57 Hz). Anal. for $C_{28}H_{33}IN2S•0.25H_2O$

4.10.22. 1-(5-Cyclohexylpentyl)-3-((4-hydroxybenzyl)thio)quinolin-1-ium iodide (9v)—Yield 26.0%; mp 112 – 114°C; ^{1}H NMR (DMSO-d_6): δ 9.63 (s, 1H), 9.50 (s, 1H), 9.25 (s, 1H), 8.57 (d, 1H, *J* = 9.0 Hz), 8.37 (d, 1H, *J* = 8.4 Hz), 8.22 (t, 1H, *J* = 7.8 Hz), 8.05 (t, 1H, *J* = 7.5 Hz), 7.27 (d, 2H, *J* = 8.7 Hz), 6.73 (d, 2H, *J* = 8.7 Hz), 5.06 (t, 2H, *J* = 7.5 Hz), 4.51 (s, 2H), 2.00 – 1.96 (m, 2H), 1.71 – 1.67 (m, 5H), 1.39 – 1.36 (m, 4H), 1.32 – 1.11 (m, 6H), 0.90 – 0.84 (m, 2H). Anal. for $C_{27}H_{34}INOS$

4.10.23. 3-((4-(Tert-butyl)benzyl)thio)-1-(5-cyclohexylpentyl)quinolin-1-ium iodide (9w)—Yield 44.5%, mp 178 – 180°C; ^{1}H NMR (DMSO-d_6): δ 9.58 (s, 1H), 9.22 (s, 1H), 8.52 (d, 1H, *J* = 9.0 Hz), 8.30 (d, 1H, *J* = 8.1 Hz), 8.18 – 8.12 (m, 1H), 7.98 (t, 1H, *J* = 7.2 Hz), 7.32 (d, 2H, *J* = 9.3 Hz), 7.30 (d, 2H, *J* = 3.6 Hz), 4.96 (t, 2H, *J* = 8.1 Hz), 4.51 (s, 2H), 1.99 – 1.79 (m, 2H), 1.65 – 1.51 (m, 5H), 1.38 – 1.28 (m, 4H), 1.21 (s, 9H), 1.91 – 1.11 (m, 6H), 0.89 – 0.59 (m, 2H). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 151.1, 150.0, 145.5, 135.9, 135.7, 133.2, 132.6, 131.1, 130.1, 130.0, 129.3, 129.3, 125.9, 125.9, 119.8, 57.8, 40.8, 37.3, 37.1, 34.7, 33.2, 33.2, 31.5, 31.5, 31.5, 30.0, 26.6, 26.6, 26.5, 26.2, 26.2. Anal. for $C_{31}H_{42}INS$

4.10.24. 1-(5-cyclohexylpentyl)-3-((3,4-dichlorobenzyl)thio)quinolin-1-ium iodide (9x)—Yield 44.5%; mp 165 - 167°C; ^{1}H-NMR (DMSO-d_6): δ 9.56 (s, 1H), 9.25 (s, 1H), 8.52 (d, 1H, *J* = 9.0 Hz), 8.31 (d, 1H, *J* = 7.8 Hz), 8.20 - 8.15 (t, 1H, *J* = 7.2 Hz), 8.03 - 7.98 (m, 1H), 7.69 (s, 1H), 7.57 - 7.53 (dd, 1H, *J* = 3.9 Hz, *J* = 8.4 Hz), 7.41 - 7.36 (m, 1H), 4.98 - 4.93 (t, 2H, *J* = 8.1 Hz), 4.53 (s, 2H), 1.98 - 1.82 (m, 2H), 1.68 - 1.59 (m, 5H), 1.39 - 1.25 (m, 4H), 1.19 - 0.99 (m, 6H), 0.94 - 0.70 (m, 2H). Anal. for $C_{27}H_{32}Cl_2INS$

4.10.25. 3-((3,5-bis(trifluoromethyl)benzyl)thio)-1-(5-cyclohexylpentyl)quinolin-1-ium iodide (9y)—Yield 60.4%; mp 217 – 219°C; ^{1}H-NMR (DMSO-d_6): δ 9.61 (s, 1H), 9.26 (s, 1H), 8.53 (d, 1H, *J* = 9.0 Hz), 8.30 (d, 1H, *J* = 8.1 Hz), 8.22 – 8.16 (m, 1H), 8.11 (s, 2H), 8.04 - 7.99 (t, 1H, *J* = 7.8 Hz), 7.96 (s, 1H), 4.97 - 4.92 (t, 2H, *J* = 6.0 Hz), 4.69 (s, 2H), 1.99 - 1.78 (m, 2H), 1.70 - 1.49 (m, 5H), 1.46 - 1.20 (m, 4H), 1.19 - 0.99 (m, 6H), 0.96 - 0.69 (m, 2H). Anal. for $C_{29}H_{32}F_6INS$

4.10.26. 1-(5-cyclohexylpentyl)-3-((2,4,6-trimethylbenzyl)thio)quinolin-1-ium iodide (9z)—Yield 46.0%, mp 181 – 183°C; ^{1}H-NMR (DMSO-d_6): δ 9.61 (s, 1H), 9.28 (s, 1H), 8.54 (d, 1H, *J* = 8.7 Hz), 8.34 - 8.31 (dd, 1H, *J* = 8.1 Hz, *J* = 1.2 Hz), 8.20 - 8.14 (m, 1H), 8.04 - 7.99 (m, 1H), 6.89 (s, 2H), 5.01 - 4.96 (t, 2H, *J* = 7.8 Hz), 4.52 (s, 2H), 2.34 (s, 6H), 2.21 (s, 3H), 2.05 - 1.85 (m, 2H), 1.72 - 1.85 (m, 4H), 1.48 - 1.26 (m, 6H), 1.35 - 1.01 (m, 5H), 0.85-0.75 (m, 2H). Anal. for $C_{30}H_{40}INS$

4.11. Synthesis of 1-(5-cyclohexylpentyl)-3-(phenethylthio)quinolin-1-ium iodide (11)

A mixture of copper (I) iodide (18.7 mg, 0.09 mmol), Cs_2CO_3 (542 mg, 3.92 mmol), 3-iodoquinoline (500 mg, 1.96 mmol), 2-phenylethanethiol (0.542 mg, 3.92 mmol), ethylene glycol (0.24 mL, 3.92 mmol), and 2-propanol (5 mL) was heated at 170°C under nitrogen using microwave irradiation for 15 min. The reaction mixture was allowed to cool to room temperature and diluted with H_2O (20 mL) and extracted with EtOAc (3 x 30 mL). The pooled organic fractions was washed with brine (150 mL), dried over Na_2SO_4, and concentrated by rotary evaporation at reduced pressure to yield the crude product. The crude product was purified with FLASH chromatography (EtOAc:Hexane, 0:10 to 20:80) to afford 3-(phenethylthio)quinoline as a white solid. Yield 78 %; ^{1}H NMR ($CDCl_3$): δ 8.86 (s, 1H), 8.07 (d, 1H, *J* = 8.1 Hz), 8.04 (s, 1H), 7.74 (d, 1H, *J* = 9.0 Hz), 7.70 – 7.65 (m, 1H), 7.57 – 7.52 (m, 1H), 7.34 – 7.29 (m, 2H), 7.29 – 7.25 (m, 1H), 7.24 – 7.20 (m, 2H), 3.28 (t, 2H, *J* = 9.3 Hz), 2.98 (t, 2H, *J* = 8.4 Hz).

A mixture of 3-(phenethylthio)quinoline (100 mg, 0.40 mmol), 5-(iodopentyl)cyclohexane (168 mg, 0.60 mmol), and H_2O (5 mL) was heated at 170°C using microwave irradi ation for 15 min. The reaction mixture was allowed to cool to room temperature and diluted with EtOAc (10 mL) and extracted with EtOAc (3 x 30 mL). The organic fraction was sonicated to yield the crude product. The crude product was vacuum filtered using Et_2O to afford the pure 1-(5-cyclohexylpentyl)-3-(phenethylthio)quinolin-1-ium iodide (**5**) as a yellow solid. Yield 37.4%, mp 104 - 106°C; ^{1}H-NMR (DMSO-d_6): 9.58 (s, 1H), 9.19 (s, 1H), 8.51 (d, 1H, *J* = 9.0Hz), 8.30 (d, 1H, *J* = 8.1Hz), 8.17 - 8.12 (m, 1H), 8.01 - 7.96 (t, 1H, *J* = 7.8 Hz), 7.30 - 7.23 (m, 2H), 7.27 - 7.22 (m, 2H), 7.17 - 7.11 (m, 1H), 4.99 - 4.94 (t, 2H, *J* = 7.5 Hz), 3.58 - 3.53 (t, 2H, *J* = 7.2 Hz), 3.00 - 2.95 (t, 2H, *J* = 7.5 Hz), 1.99 - 1.85 (m, 2H), 1.72 - 1.49 (m, 5H), 1.44 - 1.25 (m, 4H), 1.25 - 1.10 (m, 6H), 0.91 - 0.69 (m, 2H). Anal. for $C_{28}H_{36}INS$

5. Biological Activity

5.1. Anti-fungal and anti-bacterial testing

Compounds were evaluated in vitro against a panel of microorganisms including *C. albicans* ATCC 90028 (*Ca*), *Candida krusei* ATCC 6258 (*Ck*), *C. neoformans* ATCC 90113 (*Cn*), *S. aureus* ATCC 29213 (*Sa*), *Methicillin-resistant S. aureus* ATCC 33591(*MRSA*), *A. fumigatus* ATCC 204305 (*Af*), and *M. intracellulare* ATCC 23068 (*Mi*) as previously reported [36] All organisms were obtained from the American Type Culture Collection (Manassas, Va.). Susceptibility testing was performed using a modified version of the NCCLS methods [36–38] for all organisms except for *M. intracellulare*, for which the modified Alamar blue procedure [39] was followed. Briefly, samples (dissolved in DMSO) were serially diluted by using 0.9% saline and transferred in duplicate to 96-well microplates. Microbial inocula were prepared after comparison of the absorbance (at 630 nm) of cell suspensions to the 0.5 McFarland standard and dilution of the suspensions in broth (Sabouraud dextrose and cation-adjusted MuellereHinton broth [Difco] for the fungi and bacteria, respectively, and 5% Alamar blue [BioSource International] in Middlebrook 7H9 broth with oleic acid albumin dextrose catalase enrichment for *M. intracellulare*) to afford recommended inoculum sizes. Microbial inocula were added to the samples to

achieve a final volume of 200 mL and final sample concentrations starting with 20 μg/mL. Growth, solvent, and medium controls were included on each test plate. The plates were read at either 530 nm or excitation and emission wavelengths of 544 and 590 nm (Alamar Blue method) prior to and after incubation. Percent growth was calculated and plotted with the concentration tested to afford the concentration that inhibits 50% of growth (IC_{50}).

5.2. Cytotoxicity assay

In vitro cytotoxicity against mammalian kidney fibroblast (VERO) cells was determined. The assay was performed in 96-well tissue culture-treated microplates and compounds were tested up to a highest concentration of 10 mg/mL as described earlier [36]. 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 dye assay [36]. 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.

5.3. *S. cerevisiae* sensitivity to antifungal compounds

The concentration of compound **9l** used to compare the relative sensitivity of the *S. cerevisiae* strains was determined using the wild type strain, to yield approximately a 30% survival. Final concentration used was 20 μmol/L. for both **9l** and cryptolepine. For sensitivity determination, strains were grown to exponential phase (OD_{600}~0.6) in YPD, washed and resuspended in water. Serial dilutions were spotted onto plates containing different concentrations of the antifungal compound. Sensitivity tests were performed in triplicate.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- SAR around ring A of substituted benzylthioquinolinium iodides (SBIs) is presented
- SBIs may serve as novel anti-opportunistic infection agents.
- SBIs appear to utilize a different mechanism of action from their predecessor, cryptolepine
- SBIs are novel agents with improved therapeutic profile than several drugs on the market.

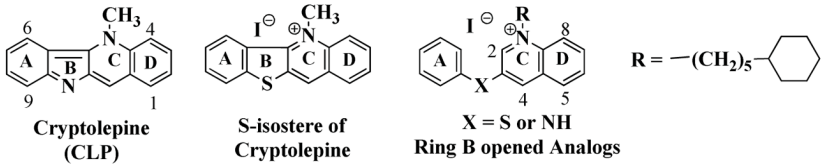


Figure 1.
Cryptolepine, CLP Sulfur bioisostere, and ring B opened Analogs.

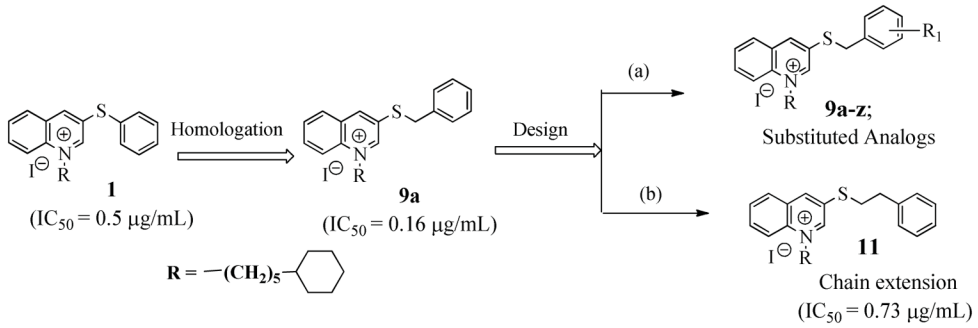


Figure 2.

Design Strategies: (a) Exploration of the hydrophobic and electronic space around phenyl ring A; (b) The effect of homologation on the activity/potency (IC_{50}) of compounds.

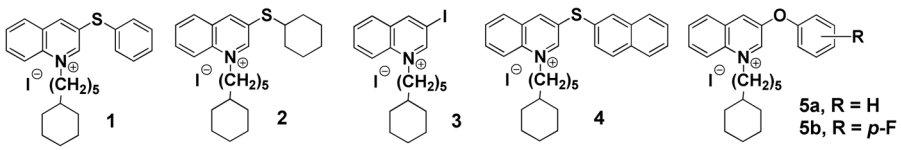


Figure 3.
Structures of the Scaffolds considered in the manuscript

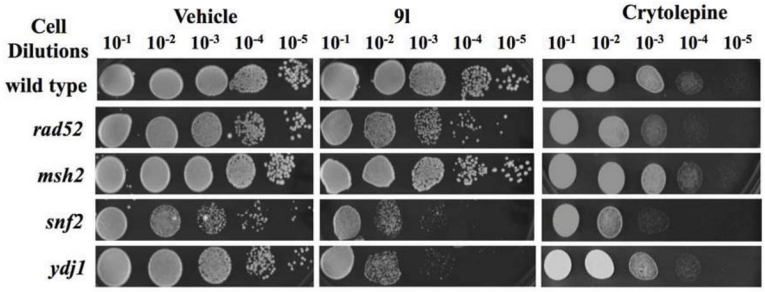
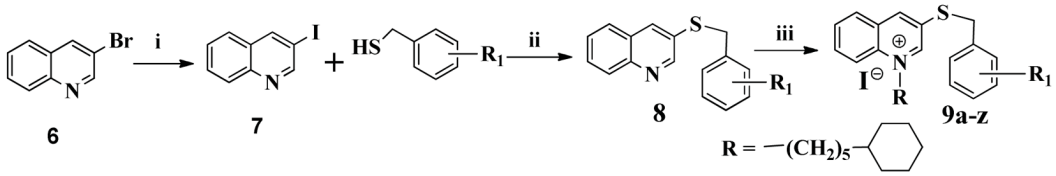


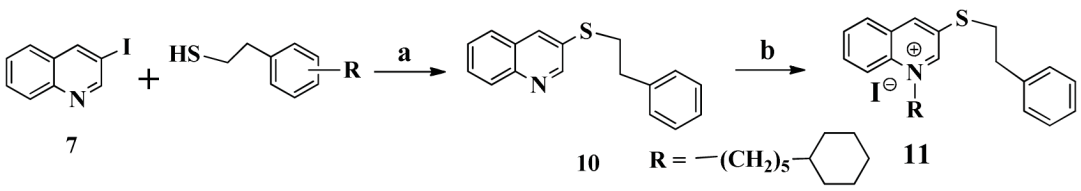
Figure 3.

Sensitivity of selected deletion mutant strains to **9l** and cryptolepine. Cells were grown to exponential phase, washed, resuspended and serial dilutions were spotted onto YPD media containing 20 μmol/L of the compound or control plates containing drug vehicle. Survival of the strains was calculated relative to growth on plates with no compound.



Scheme 1.

Synthetic Procedure for 3-((substituted benzyl)thio)-1-(5-cyclohexylpentyl)quinolin-1-ium iodide. Reagents and conditions: (i) CuI, $CH_3NH(CH_2)_2NHCH_3$, NaI, Dioxane, reflux, 110°C, 48h; (ii) CuI, Cs_2CO_3, $HOCH_2CH_2OH$, , i-PrOH, N_2, MWAS, 170 °C, 1/4h; (iii) $C_6H_{11}(CH_2)_4CH_2$-I, H_2O, MWAS, 170°C, 1/4h

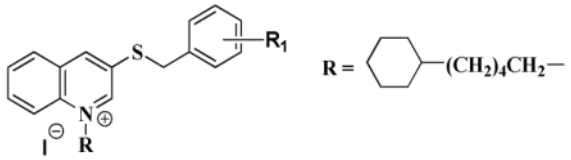


Scheme 2.

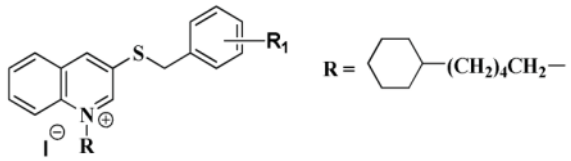
Synthetic Procedure for 3-((substituted phenethyl)thio)-1-(5-cyclohexylpentyl)quinolin-1-ium iodide (5a). Reagents and conditions: (a) CuI, $HOCH_2CH_2OH$, Cs_2CO_3, i-PrOH, N_2, MWAS, 170 °C, 15 min; (b) $C_6H_{11}(CH_2)_4CH_2$-I, H_2O, MWAS, 170 °C, 15 min.

Table 1

Antifungal activities of 3-((substituted-benzyl)thio)-1-(5-cyclohexylpentyl)quinolin-1-ium iodide.



# Compounds		IC_{50}/MIC/MFC (μg/mL)			Cytotoxicity TC_{50} (μg/mL)
Label	**R_1**	***C. neoformans***	***C. albicans***	***A. fumigatus***	
9a	H	0.16/0.31/0.63	1.6/5.0/5.0	5.7/10/20	**NC**
9b	o-F	0.63/1.3/1.3	2.7/5.0/5.0	6.5/20/20	**NC**
9c	m-F	0.39/0.63/0.63	1.8/5.0/5.0	5.6/10/20	**NC**
9d	p-F	0.37/0.63/0.63	1.9/5.0/5.0	5.2/10/10	**NC**
9e	o-Br	0.69/1.3/2.5	4.0/10/10	9.6/20/20	**NC**
9f	m-Br	0.56/0.63/1.3	2.6/5.0/5.0	4.8/10/10	**NC**
9g	p-Br	0.22/0.63/0.63	0.50/1.3/2.5	2.4/5.0/5.0	**NC**
9h	o-CF_3	0.42/0.63/1.3	0.97/2.5/5.0	3.7/5.0/10	**NC**
9i	m-CF_3	0.28/0.63/0.63	1.2/2.5/2.5	1.9/2.5/2.5	**NC**
9j	p-CF_3	0.25/0.31/0.31	1.4/2.5/2.5	2.9/5.0/5.0	**7.9**
9k	o-Cl	1.5/2.5/5.0	5.6/10/20	17 /20/20	**NC**
9l	p-Cl	0.05/0.08/0.08	0.33/0.63/0.63	0.69/1.3/1.3	**1.3 (SI = 26)**
9m	o-CH_3	0.39/0.63/ND	1.4/2.5/ND	4.1/10/ND	**NC**
9n	m-CH_3	0.42/0.63/0.63	2.0/5.0/5.0	5.8/10/10	**5.0**
9o	p-CH_3	0.25/0.31/0.31	1.4/2.5/5.0	4.5/10/10	**6.8**
9p	o-OCH_3	0.34/0.63/2.5	2.8/5.0/5.0	9.8/20/>20	**NC**
9q	m-OCH_3	0.35/0.63/2.5	4.8/10/10	10.9/20/>20	**NC**
9r	p-OCH_3	0.18/0.31/0.63	1.2/5.0/5.0	5.4/10/10	**NC**
9s	p-OH	4.9/10/10	11/20/20	16 /20/20	**NC**
9t	o-CN	0.5/1.3/2.5	1.6/5.0/10	11/20/20	**NC**



# Compounds			IC50/MIC/MFC (μg/mL)		Cytotoxicity TC50 (μg/mL)
Label	**R1**	***C. neoformans***	***C. albicans***	***A. fumigatus***	
9u	m-CN	1.1/2.5/5.0	4.3/10/20	8.6/20/20	**NC**
9v	p-CN	0.81/2.5/2.5	2.5/5.0/10	8.6/20/20	**NC**
Cryptolepine		NT/12.5/>25	250 (MIC)	NT	**3.2 (SI < 0.13*)**
Fluconazole		0.21/6.3/13	0.12 /NA/NA	NT	**NT**
Amphotericin_B		0.20/0.63/0.63	0.20/0.62/1.3	0.70/1.3/5.0	**7.6 (SI = 38)**

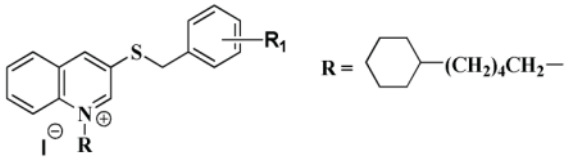
NT = Not tested; IC_{50} = The concentration that affords 50% inhibition of growth; MIC = Minimum inhibitory concentration and is the lowest test concentration that allows no detectable growth; MFC = Minimum fungicidal concentration and is the lowest test concentration that kills the organism; NC = No cytotoxicity observed at 10 μg/mL. TC_{50} = The concentration that is toxic to 50% of cells. SI = is the selectivity index estimated as TC_{50}/IC_{50} against *C. neoformans*.

*For CLP, MIC was used to estimate the SI instead of IC_{50}.

#The antifungal activities of 9a–c, e–g, and p–s were predicted using a CoMFA model and the actual activities were reported elsewhere to validate the model.

Table 2

Antifungal Activities of Other Analogs



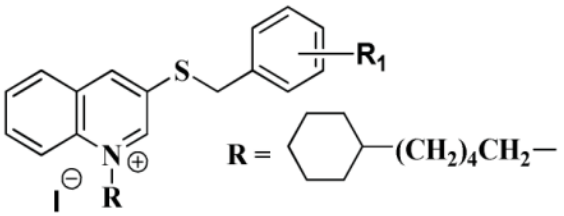
Compounds		IC_{50}/MIC/MFC (μg/mL)			Cytotoxicity TC_{50} (μg/mL)
R_1	Label	*C. neoformans*	*C. albicans*	*A. fumigatus*	
9a	**H**	0.16/0.31/0.63	1.6/5.0/5.0	5.7/10/20	**NC**
#**9w**	p-t-Bu	0.52/1.3/10	20/>20/>20	>20/>20/>20	**NC**
9x	3,4-di-Cl	0.45/0.63/0.63	1.1/2.5/2.5	2.8/5/5	**NC**
9y	3,5-di-CF_3	0.63/1.3/1.3	2.8/5.0/5.0	>20/>20/>20	**NC**
9z	2,4,6-triCH_3	0.32/0.63/0.63	>20/>20/>20	2.3/5/5	**NC**
2	Cyclohex_anal	1.2/2.5/2.5	>20/>20/>20	>20/>20/>20	**NC**
3	3IQ	5.8/10/10	>20/>20/>20	>20/>20/>20	**NC**
4	Naphthalene	0.09/0.16/0.16	0.42/1.3/2.5	1.2/2.5/2.5	**NC (SI > 111)**
5a	O-Ph	>20/>20/>20	>20/>20/>20	>20/>20/>20	**NC**
5b	O-Ph(p-F)	8.62/10/10	>20/>20/>20	>20/>20/>20	**NC**
11	Et_homolog	0.73/1.3/1.3	3.6/>20/>20	19/>20/>20	**NC**
CLP	Cryptolepine	12.5 (MIC)	250 (MIC)	NT	**3.2**
	Amph B	0.20/0.63/0.63	0.20/0.62/1.3	0.70/1.3/5.0	**7.6 (SI =38)**

NT = Not tested; IC_{50} = The concentration that affords 50% inhibition of growth; MIC = Minimum inhibitory concentration and is the lowest test concentration that allows no detectable growth; MFC = Minimum fungicidal concentration and is the lowest test concentration that kills the organism; NC = No toxicity on Vero cells at 10 μg/mL; TC_{50} = The concentration that is toxic to 50% of cells. SI = is the selectivity index estimated as TC_{50}/IC_{50} against *C. neoformans*.

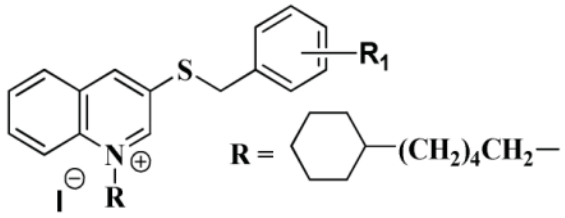
#The antifungal activity of **9w** was predicted using a CoMFA model and the actual activities were reported elsewhere to validate the model.

Table 3

Effect of Target Compounds on inherently Resistant Fungal Pathogens



Compounds		IC_{50}/MIC/MFC (μg/mL)	
Label	**R_1**	***C. glabrata***	***C. krusei***
9a	H	2.9/5.0/5.0	0.71/1.3/1.3
9b	o-Br	6.3/20/20	1.4/2.5/2.5
9c	m-Br	2.6/5.0/5.0	0.49/1.3/1.3
9d	p-Br	1.3/2.5/2.5	0.14/0.63/0.63
9e	o-CF_3	3.4/10/10	0.49/1.3/1.3
9f	m-CF_3	1.4/2.5/2.5	0.40/0.63/0.63
9g	p-CF_3	1.6/5.0/5.0	0.49/0.63/0.63
9h	o-CH_3	2.7/5.0/NT	0.43/1.3/NT
9i	m-CH_3	2.8/5.0/5.0	1.4/2.5/2.5
9j	p-CH_3	2.7/5.0/5.0	0.46/1.3/1.3
9k	o-Cl	6.0/10/10	0.34/2.5/2.5
9l	p-Cl	0.44/1.3/1.3	0.07/0.16/0.16
9m	o-F	2.8/5.0/5.0	0.84/2.5/2.5
9n	m-F	3.3/5.0/10	0.67/2.5/2.5
9o	p-F	3.1/5.0/5.0	0.27/1.3/1.3
9p	o-OCH_3	8.2/20/20	0.75/2.5/2.5
9q	m-OCH_3	9.7/20/20	0.88/2.5/2.5
9r	p-OCH_3	3.0/10/10	0.37/0.63/1.3
9s	o-CN	7.9/20/20	0.56/1.3/1.3
9t	m-CN	>20/>20/>20	1.5/5.0/5.0
9u	p-CN	4.7/10/10	1.1/2.5/2.5
9v	p-OH	11/20/20	5.7/10/10
9w	p-tBu	>20/>20/>20	1.2/20/20
9x	3,4-di-Cl	3.0/5.0/5.0	0.30/1.3/1.3
9y	3,5-di-CF_3	>20/>20/>20	17/>20/>20
9z	2,4,6-triCH_3	1.7/5.0/5.0	0.44/0.63/0.63
2	Cyclohex_anal	15/>20/>20	0.35/2.5/2.5
3	3IQ	>20/>20/>20	1.7/10/10

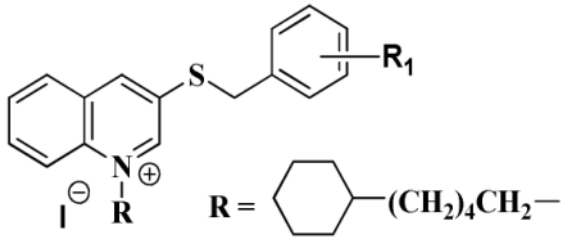


Compounds		IC_{50}/MIC/MFC (μg/mL)	
Label	**R_1**	***C. glabrata***	***C. krusei***
4	Naphthalene	0.87/2.5/2.5	0.09/0.63/0.63
5a	O-Ph	>20/>20/>20	>20/>20/>20
5b	O-Ph(p-F)	>20/>20/>20	>20/>20/>20
11	Et_homolog	9.5/20/>20	0.69/5.0/5.0
Fluconazole		27/NA/NA	27/50/50
Amphotericin_B		0.22/0.63/1.3	0.22/0.62/1.3

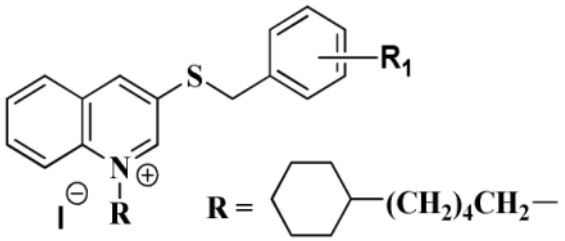
NT = Not tested; NA = Not active at 20 μg/mL; IC_{50} = The concentration that affords 50% inhibition of growth; MIC = Minimum inhibitory concentration and is the lowest test concentration that allows no detectable growth; MFC = Minimum fungicidal concentration and is the lowest test concentration that kills the fungus.

Table 4

Effect of Target Compounds on Selected Pathogenic Opportunistic Bacteria



Compounds		IC_{50}/MIC/MBC (μg/mL)		
Label	**R_1**	***S. aureus***	***MRSA***	***M. intracellulare***
9a	H	0.23/0.31/10	0.33/0.63/1.3	4.0/5.0/20
9b	o-Br	0.73/1.3/2.5	0.74/1.3/2.5	16/20/20
9c	m-Br	0.44/0.63/1.3	0.37/0.63/1.3	6.5/10/10
9d	p-Br	0.34/0.63/2.5	0.34/0.63/2.5	6.9/10/10
9e	o-CF_3	0.42/0.63/1.3	0.41/0.63/1.3	3.5/5.0/5.0
9f	m-CF_3	0.42/0.63/0.63	0.21/0.31/0.63	3.2/5.0/5.0
9g	p-CF_3	0.40/0.63/1.3	0.40/0.63/1.3	6.1/10/10
9h	o-CH_3	0.19/0.31/1.3	0.22/0.63/1.3	3.4/5.0/5.0
9i	m-CH_3	0.40/0.63/2.5	0.56/1.3/2.5	7.2/10/10
9j	p-CH_3	0.28/0.63/1.3	0.36/0.63/1.3	4.7/10/10
9k	o-Cl	0.77/1.3/5	0.74/1.3/5	13/20/20
9l	p-Cl	0.05/0.16/0.31	0.06/0.16/0.31	1.6/2.5/2.5
9m	o-F	0.40/0.63/2.5	0.73/1.3/2.5	6.7/10/10
9n	m-F	0.64/1.3/2.5	0.72/1.3/2.5	7.2/10/10
9o	p-F	0.39/0.63/2.5	0.49/1.3/2.5	7.5/10/10
9p	o-OCH_3	0.31/0.63/5	0.35/0.63/5	3.0/5.0/5.0
9q	m-OCH_3	0.28/0.63/1.3	0.33/0.63/1.3	3.7/5.0/5.0
9r	p-OCH_3	0.18/0.31/2.5	0.36/0.63/2.5	1.7/2.5/2.5
9s	o-CN	0.26/2.5/2.5	0.34/0.63/5.0	2.2/2.5/5.0
9t	m-CN	0.68/1.3/5.0	0.97/2.5/10	6.8/10/10
9u	p-CN	0.69/1.3/2.5	0.72/1.3/5.0	4.8/5.0/10
9v	p-OH	1.8/5.0/5.0	2.2/5.0/5.0	>20/>20/>20
9w	p-tBu	>20/>20/>20	12/20/>20	>20/>20/>20
9x	3,4-di-Cl	0.50/2.5/2.5	0.18/1.3/1.3	4.5/5.0/10
9y	3,5-di-CF3	NA/NA/NA	1.3/2.5/10	3.1/5.0/5.0
9z	2,4,6-triCH3	0.34/0.63/1.3	0.23/0.63/0.63	2.9/5.0/5.0
2	Cyclohex_	0.74/1.3/10	1.2/2.5/10	8.4/10/10



Compounds		IC50/MIC/MBC (μg/mL)		
Label	**R_1**	***S. aureus***	***MRSA***	***M. intracellulare***
3	3IQ_Salt	18/>20/>20	>20/>20/>20	>20/>20/>20
4	Napht	0.34/0.63/2.5	0.35/0.63/2.5	4.2/5.0/10
5a	O-Ph	19/>20/>20	>20/>20/>20	>20/>20/>20
5b	O-Ph(p-F)	14/20/>20	14/>20/>20	20/20/20
11	Ethyl_homolog	0.73/1.3/10	1.2/2.5/10	12/20/2020
	Cipro	0.14/0.5/1	0.11/0.5/1	0.005/0.45/1

NT = Not tested; IC_{50} = The concentration that affords 50% inhibition of growth; MIC = Minimum inhibitory concentration and is the lowest test concentration that allows no detectable growth; MBC = Minimum bactericidal concentration and is the lowest test concentration that kills the bacteria.