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MAPPING THE ANTIMICROBIAL ACTIVITY OF INDOLOQUINOLINE AND NEOCRYPTOLEPINE ANALOGUES

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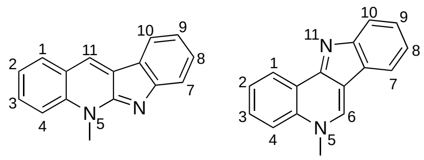
Abstract – A range of naturally occurring indoloquinolines, such as neocryptolepine and isocryptolepine, have been found to possess antimicrobial and anticancer activity. To broaden our understanding of this class of compound´s biological capacity we herein report the results of a screening campaign of a total of 9 11*H*-indolo[3,2-*c*]quinolines, 19 neocryptolepine analogues, and two isocryptolepine analogues towards a panel of both Gram-positive (*Enterococcus faecialis*, *Staphylococcus aureus*, and *Streptococcus agalactiae*) and Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) bacteria. The compounds were also tested for their cytotoxicity against human liver cells (HepG2) and human fetal lung fibroblast (MRC-5). Several of the compounds showed antimicrobial and cytotoxic activity, making them interesting for further optimization as antimicrobial or anticancer agents.

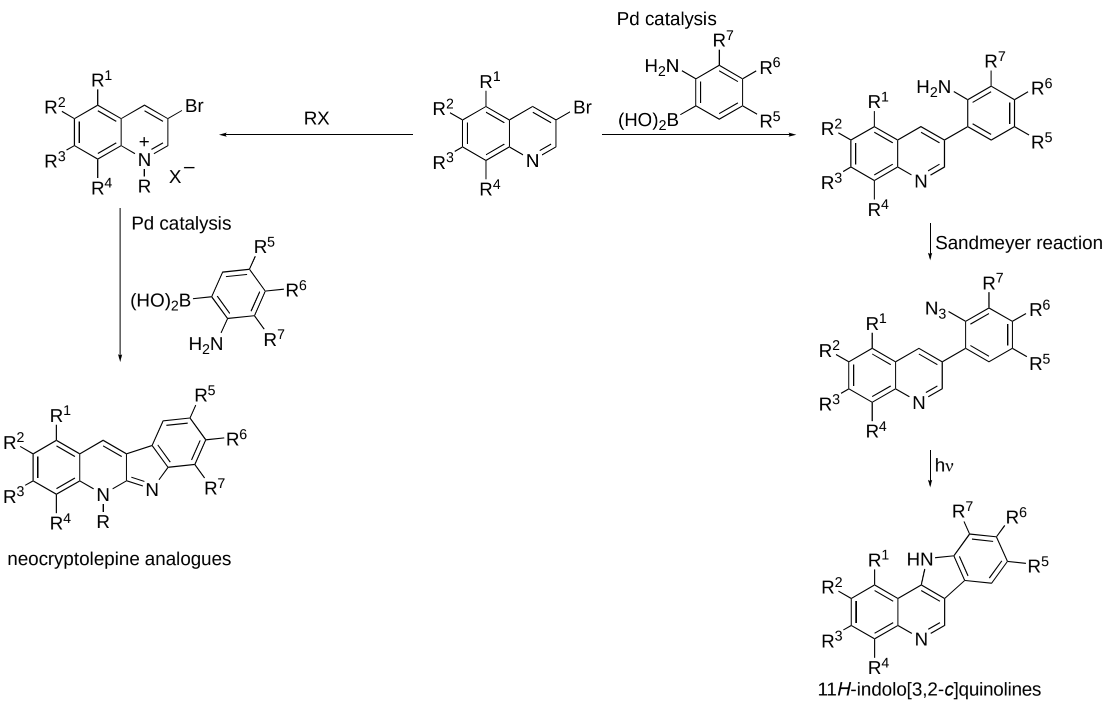
The indoloquinolines neocryptolepine (**1**) and isocryptolepine (**2**) (Figure 1) belongs to a class of tetracyclic *N*-heterocycles that are commonly found in natural products,[1] agrochemicals,[2] and drug candidates.[3] Due to the vast range of biological activity possessed by this group of compounds there has been a great interest in developing synthetic strategies for their preparation.[1,4] The broad variety of pharmacological properties found in this group of compounds therefore warrants further exploration.[1,5] Particular interesting is the activity some derivatives possess against methicillin-resistant *Staphylococcus aureus* (MRSA), a bacterial infection that is hampered by increasing antibiotic resistance, unresponsive to many broad-spectrum β-lactam antibiotics,[6] and drug-resistant biofilms, which are rapidly becoming a global health threat.[7]



neocryptolepine (**1**) isocryptolepine (**2**)

Figure 1. Structures of neocryptolepine (**1**) and isocryptolepine (**2**)

Our interest in this group of natural products and analogues has been driven from both an interest in their biological activity and the desire to develop new strategies for their preparation.[8] As a follow up from these activities, we recently reported the synthesis of a diverse library of 11*H*-indolo[3,2-*c*]quinolines and neocryptolepine analogues prepared from the same starting materials, viz. 3-bromoquinolines, by a Suzuki-Miyaura cross-coupling followed by an azidation-photochemical cyclization and a Pd(0)-catalyzed C-C bond formation followed by an intramolecular C-N bond formation, respectively (Scheme 1).[9] Herein we report the evaluation of their antimicrobial activity and cytotoxicity revealing interesting activities suggesting that the studied compounds might be suitable for future development into potent antimicrobial or anticancer agents.



Scheme 1. Overview of the synthetic strategy for the formation of neocryptolepine analogues and 11*H*-indolo[3,2-*c*]quinolines from 3-bromoquinolines

Our recently reported work efficiently produced a broad variation of substituted indoloquinolines (Figures 2 and 3).[9] These compounds were evaluated for their antimicrobial activity against five cell lines, viz. *Staphylococcus aureus*, *Escherichia coli*, *Enterococcus faecialis*, *Pseudomonas aeruginosa*, and *Streptococcus agalactiae* and for their cytotoxicity by screening against HepG2 (human liver) and MRC-5 (human fetal lung fibroblasts) (Table 1, Figure 3). Gentamicin, an antibiotic used to treat several types of bacterial infections,[10] was included as a positive control in the antimicrobial assays. Results from these studies are reported in Table 1 in addition to the results obtained for neocryptolepine (**1**) and isocryptolepine (**2**) from a previous study.[8c]

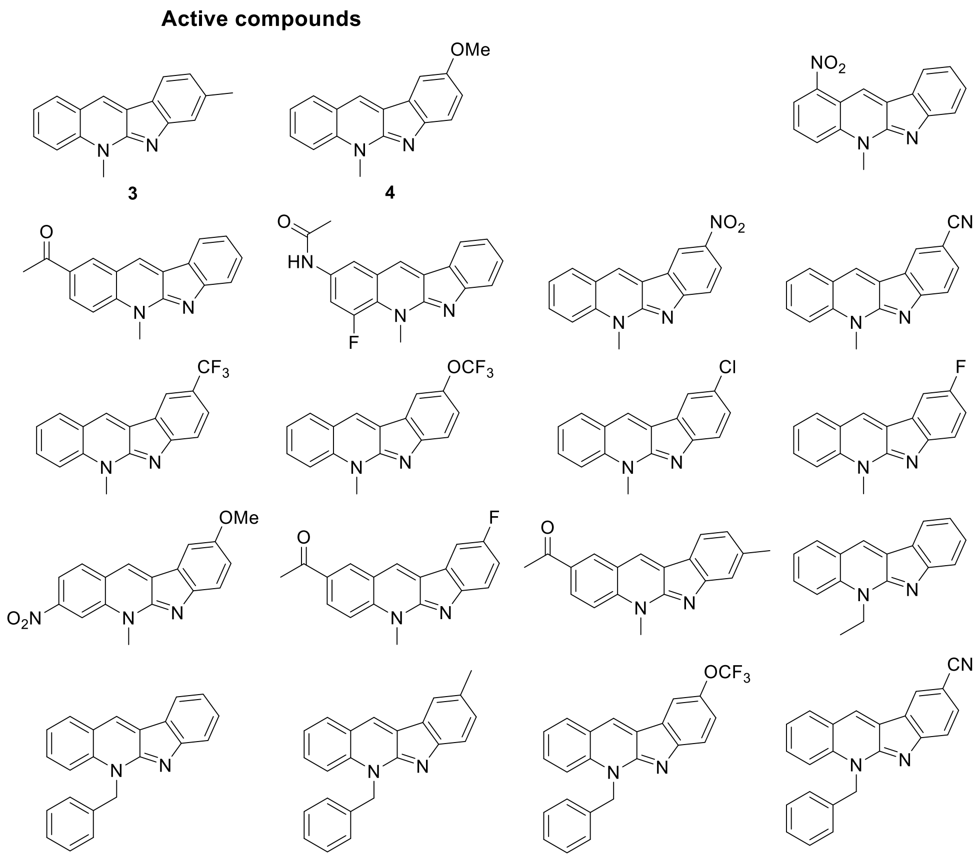


Figure 2. Neocryptolepine analogues included in this screening. Compounds **3** and **4** were active in our screening (Table 1).

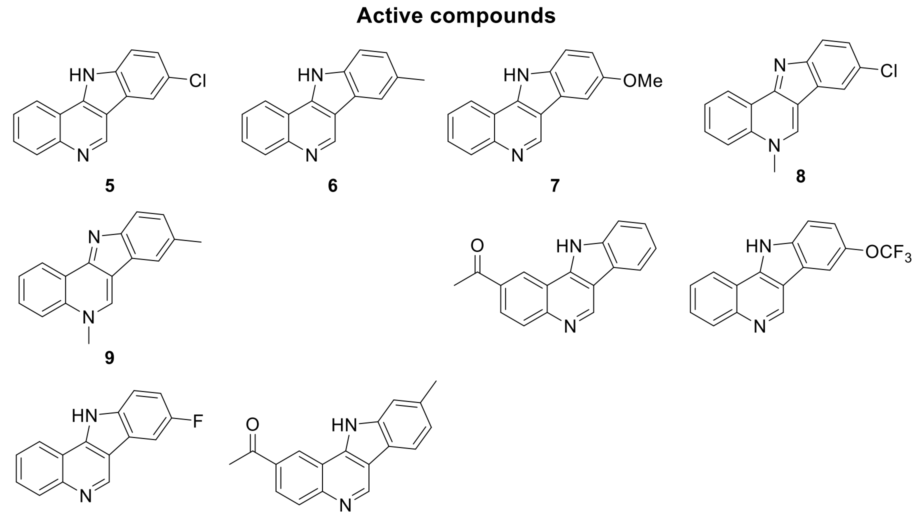


Figure 3. 11*H*-Indolo[3,2-*c*]quinolines screened in this study. Compounds **5-9** were active in our screening (Table 1).

Table 1. Minimum inhibition concentration (MIC) for isocryptolepine, neocryptolepine, and active neocryptolepine analogues, 11*H*-indolo[3,2-*c*]quinolines, and isocryptolepine analogues. Gentamicin was used as a positive control for the antimicrobial assays.

Compound	*E. faecalis*	*E. coli*	*P. aeruginosa*	*S. aureus*	*S. agalactiae*	HepG2	MRC-5
1[a]	>100 µM	>100 µM	>100 µM	>100 µM	100 µM	-	-
2[a]	100 µM	100 µM	>100 µM	100 µM	100 µM	-	-
3	75 µM	75 µM	>100 µM	75 µM	75 µM	25 µM	12.5 µM
4	100 µM	100 µM	>100 µM	100 µM	100 µM	100 µM	12.5 µM
5	>100 µM	>100 µM	>100 µM	25 µM	>100 µM	>100 µM	25 µM
6	>100 µM	75 µM	>100 µM	50 µM	100 µM	75 µM	25 µM
7	>100 µM	75 µM	>100 µM	75 µM	75 µM	50 µM	50 µM
8	75 µM	25 µM	>100 µM	50 µM	50 µM	6.25 µM	12.5 µM
9	75 µM	50 µM	>100 µM	75 µM	50 µM	75 µM	75 µM
Gentamicin	8 µM	0.13 µM	0.25 µM	0.06 µM	4 µM	-	-

[a]Data from reference 8c.

As previously reported by us, isocryptolepine (**2**) only has modest (100 µM) antimicrobial activity against four out of the five tested microbes while neocryptolepine (**1**) was inactive (> 100 µM) towards all strains, but one, namely *S. agalactiae* (100 µM).[8c] However, as anticipated it was possible to improve the activity by functionalization of the ring system. In total 19 diversely functionalized neocryptolepine analogues

(Figure 2) and 9 indoloquinolines (Figure 3) were screened for biological activity where seven of them showed activity of interest (Table 1).

Compound **3** had MIC values of 75 μM against all cell lines except *P. aeruginosa*, towards which it was inactive (>100 μM). Though less potent, the same trend was observed for compound **4**, having MIC values of 100 μM against the same cell lines as well as being inactive towards *P. aeruginosa*. Chlorinated compound **5** showed good inhibition of *S. aureus* (MIC = 25 μM), while its *N*-methylated counterpart **8** was highly effective against *E. coli* (MIC = 25 μM). 8-Chloroisocryptolepine (**8**) has previously been demonstrated by Whittell *et al.* to possess significant antiplasmodial activities.[11] Comparing the results for the two chloro-compounds, **5** and **8**, show that the activity against *S. aureus* decrease with the inclusion of an *N*-methyl group, while the activity against *E. coli* increases. Inclusion of the *N*-methyl group also increased the toxicity dramatically. The other evaluated isocryptolepine derivative **9** also showed poorer antimicrobial activity than 8-chloroisocryptolepine **8** against the same bacterial strain. Previous studies have shown that the *N*-methyl group is deemed pivotal to obtain certain biological activities seen in the indoloquinoline natural products,[12] however, 8-methyl-substituted compound **6** also showed significant activity against *S. aureus* (MIC = 50 μM), *E. coli* (MIC = 75 μM) and *S. agalactiae* (MIC = 100 μM). This illustrates that the methyl group functionalization in the scaffold is important, not necessarily the presence of an *N*-methyl group. Similar data was also obtained for the 8-methoxy-substituted compound **7**.

Cancer and bacterial infections are and will continue to be amongst the top lethal health concerns facing humanity.[13,14] A compromised immune system as a result of cancer treatment is a problem that sometimes is counteracted by simultaneously giving antibiotics to the patient. The combined effect of this dual treatment needs to be carefully evaluated since not all cancer treatments respond positively to the combination.[15] However, in some types of cancer treatment antibiotics are required. In this context the toxicity (antiproliferative) activity of compounds **5** and **8** in combination with their antimicrobial activity becomes interesting, which could in the future be a potential starting point for dual-purpose drug development. Such development is already taking place for peptide-based compounds.[16] The chlorinated indoloquinoline **5** possesses selective activity towards *S. aureus* (25 μM), a microbe that is ranked high on WHOs list over threats to human health where new antibiotics are needed,[17] and it also shows selective toxicity towards MRC-5 cells (25 μM). 8-Chloroisocryptolepine **8** shows interesting activity against the Gram-negative microbe *E. coli* (25 μM) and high toxicity (HepG2, 6.25 μM; MRC-5, 12.5 μM). Treatments against Gram-negative microbes are in particular interesting since they are dominating WHOs list of microbes that urgently require new antibiotics.[17,18]

In conclusion, we have evaluated 28 novel compounds in addition to neocryptolepine (**1**) and isocryptolepine (**2**) for their antimicrobial activity and toxicity. Amongst these compounds, seven showed antimicrobial activity and toxicity. In particular, compounds **5** and **8** showed interesting antimicrobial activity that can be further optimized while at the same time reducing the toxicity. In a longer time frame, work in the direction of developing dual purpose drugs for cancer treatment is also of interest, especially since such strategies has shown some potential for peptides.[16] Ongoing studies in our laboratories are directed towards following up these results.

EXPERIMENTAL

Synthesis

Detailed methods for the preparation of all compounds are described in Håheim *et al*.[9] Herein, general procedures for the formation of the target compounds are reported.

General procedure for *N*-alkylation to obtain quinolinium halides

To a solution of 3-bromoquinoline in an appropriate amount of solvent, the alkylation reagent (5-10 equiv.) was added and the resulting mixture was stirred at the relevant temperature under an argon atmosphere until completion as indicated by TLC analysis. The formed precipitate was thoroughly washed with *n*-hexanes, filtered and dried to give the target quinolinium salt.

General procedure for the Suzuki-Miyaura cross-coupling and cyclization reaction forming neocryptolepine analogues

To a solution of quinolinium salt (1 equiv.) in an appropriate amount of DME under an argon atmosphere was added boronic acid (1.2-1.3 equiv.), an aq. solution of Cs_2CO_3 (3.2-4.2 equiv.), and $Pd(PPh_3)_4$ (5 mol%). The resulting reaction mixture was stirred at 80 °C until completion as indicated by TLC analysis. The crude mixture was then allowed to cool to rt and the volatiles were removed under reduced pressure. The concentrate was evaporated onto celite and purified by column chromatography using relevant eluents to give the target compounds.

General procedure for Suzuki-Miyaura cross-coupling reaction

To a solution of haloquinoline (1 equiv.) in an appropriate amount of EtOH under an argon atmosphere was added boronic acid (1.5 equiv.), an aq. solution of K_2CO_3 (3.5 equiv. in an appropriate amount of water), and $PdCl_2$(dppf) (5 mol%). The resulting reaction mixture was stirred at 60 °C until completion as indicated by TLC analysis. The crude mixture was then allowed to cool to rt and the volatiles were removed under reduced pressure. The concentrate was evaporated onto celite and purified by column chromatography using relevant eluents to give the target compounds.

General procedure for diazotization-azidation (Sandmeyer reaction)

Biaryl (1 equiv.) was dissolved in an appropriate amount of aq. HCl (37%) and the mixture was cooled to 0 °C using an ice bath. Then, ice-cooled aq. $NaNO_2$ (0.4 M) was added dropwise, and the resulting mixture was stirred at 0 °C for 1.5 h. An ice-cooled aq. solution of NaN_3/NaOAc (2.1 equiv.:14 equiv. in an appropriate amount of water) was added dropwise and the mixture was stirred for 1 h while the temperature was kept at 0 °C. The reaction mixture was quenched by addition of appropriate amounts of sat. aq. K_2CO_3 and subsequently extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were washed (1 x 20 mL water, 1 x 20 mL brine), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The concentrate was then evaporated onto celite and purified by column chromatography using relevant eluents to give the target compounds.

General procedure for photocyclization forming 11*H*-indolo[3,2-*c*]quinolines

Aryl azide (1 equiv.) in 150 mL of an appropriate solvent was bubbled with a steady flow of argon as the mixture was irradiated at ambient temperature with a 125 W medium-pressure (254-579 nm) mercury-vapor lamp until completion as indicated by TLC analysis. The volatiles were then removed under reduced pressure and the concentrate was evaporated onto celite. Finally, the crude mixture was purified by column chromatography using relevant eluents to give the target compounds.

General antimicrobial testing

All compounds for antimicrobial testing were diluted to a final assay concentration of 40 mL, 0.4% DMSO, and tested in full dose-response using three concentrations per log dose (16 points with a concentration range of 0.33 nM-40 mM, for reference compounds: 21 points with a concentration of 0.01 nM-40 mM). All compounds for antiplasmodial testing were diluted to a final assay concentration of 40 mL, 0.4% DMSO, and tested in full dose-response using three concentrations per log dose (16 points with a concentration range of 0.4 nM-40 mM, for reference compounds: 16 points with a concentration rage of 0.4 nM-40 mM for chloroquine and puromycin: 0.001 nM-0.1 mM for artemisinin). Compounds tested in the antiproliferative assays were tested in 11 dilution points (0.02 mM-40 mM or 0.04 mM-80 mM).

Growth Inhibition Assay

To determine and quantify antimicrobial activity, a bacteria growth inhibition assay in liquid media was executed. Compounds **1-7** were tested against *Staphylococcus aureus* (ATCC 25923), *Escherichia coli*

(ATCC 259233), *Enterococcus faecialis* (ATCC 29122), *Pseudomonas aeruginosa* (ATCC 27853) and *Streptococcus agalactiae* (ATCC 12386); all strains from LGC Standards (Teddington, UK). *S. aureus*, *E. coli*, and *P. aeruginosa* were grown in Muller Hinton broth (275730, Becton, Franklin Lakes, NJ, USA). *E. faecalis* and *S. agalactiae* were cultured in brain hearth infusion broth (53286, Sigma, St. Louis, MO, USA). Fresh bacterial colonies were transferred in the respective medium and incubated at 37 °C overnight. The bacterial cultures were diluted to a culture density representing the log phase and mL/well were pipetted into a 96-well microtiter plate (734-2097, NunclonTM, Thermo Scientific, Waltham, MA, USA). The final cell density was 1500-15.000 colony forming units/well. The compound was diluted in 2% (v/v) DMSO in D_2O, providing a final assay concentration of 50% of the prepared sample, since 50 mL of sample in DMSO/water were added to 50 mL bacterial culture. After adding the samples to the plates, they were incubated overnight at 37 °C and the growth was determined by measuring the optical density at $\lambda = 600$ nm (OD600) with a 1420 Multilabel Counter VICTOR3TM (Perkin Elmer, Waltham, MA, USA). A water sample was used as a reference control, growth medium without bacteria was used as a negative control and dilution series of Gentamicin (A2712, Merck, Darmstadt, DE) from 32 to 0.01 mg/mL was used as positive control and visually inspected for bacterial growth. The positive control was used as a system suitability test and the results of the antimicrobial assay were only considered valid when positive control was passed. The final concentration of DMSO in the assays was ≤ 2% (v/v) and was known to have no effect in the tested bacteria. The data was processed using GraphPad Prism 8.

Cytotoxicity assay

The antiproliferative activities of **1** were evaluated against the melanoma cell line, the hepatocellular carcinoma cell line HepG2 (ATCC, HB-8065™), and the non-malignant lung fibroblast cell line MRC5 (ATCC, CCL-171™) in an MTS in vitro cell proliferation assay. The compounds were tested in concentrations from 1.56-100 µM against both cell lines. HepG2 was cultured and assayed in MEM Earle's (F0325, Biochrom) supplemented with 5 mL non-essential amino acids (K0293, Biochrom) and 1 mM sodium pyruvate (L0473, Biochrom). MRC5 was cultured and assayed in MEM Eagle (M7278, Sigma-Aldrich) supplemented with 5 mL non-essential amino acids, 1 mM sodium pyruvate and 0.15% (w/v) sodium bicarbonate (L1713, Biochrom). In addition, all media were supplemented with 10% fetal bovine serum (FBS, S1810, Biowest), 10 µg/mL Gentamicin (A2712, Biochrom) and 5 mL glutamine stable (200 mM per 500 mL medium, X0551, Biowest). Briefly, the cells were seeded in 96-well microtiter plates (Nunclon Delta Surface, VWR) at 4000 cells/well for MRC5 and 20,000 cells/well for HepG2. After incubation for 24 h in 5% CO_2 at 37 °C, the media was replaced, and compound added generating a total volume of 100 µL/well. MRC5 were incubated for 72 h before assaying, and HepG2 for 24 h. Subsequently, 10 µL of CellTiter 96® AQueous One Solution Reagent (G358B, Promega) was added to each well and the plates were incubated for 1 h at 37 °C. Following this, the absorbance was measured at 490 nm with a Tecan Spark Multimode Microplate reader. Negative controls were cells assayed with their respective cell media, and positive controls were cells treated with 10% DMSO (D4540, Sigma-Aldrich). Percent cell survival was calculated using the equation below. The data was visualized using GraphPad Prism 8.4.2 and IC50 was calculated. The built-in ROUT method was used to detect and remove outliers from the dataset (Q = 1%).

Percent (%) cell survival: ((absorbance treated wells-absorbance positive control))/((absorbance negative control-absorbance positive control)) x 100.

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