

Design, Synthesis, and Identification of Silicon Incorporated Oxazolidinone Antibiotics with Improved Brain Exposure

B. Seetharamsingh,[†] Remya Ramesh,[†] Santoshkumar S. Dange,[†] Pankaj V. Khairnar,[†] Smita Singhal,[‡] Dilip Upadhyay,[‡] Sridhar Veeraraghavan,[§] Srikant Viswanadha,[§] Swaroop Vakkalanka,[§] and D. Srinivasa Reddy^{*,†}

[†]CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pune 411008, India

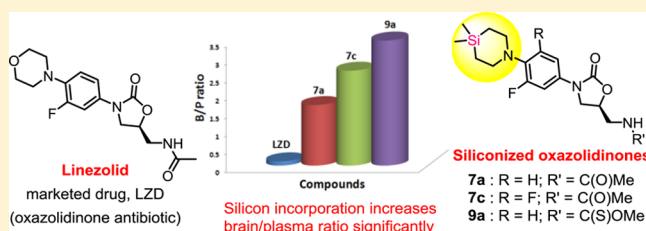
[‡]Daiichi Sankyo India Pharma Pvt. Ltd., Gurgaon, Haryana 122015, India

[§]Incozen Therapeutics Pvt. Ltd., Alexandria Knowledge Park, Turkapally, Rangareddy 500078, India

Supporting Information

ABSTRACT: Therapeutic options for brain infections caused by pathogens with a reduced sensitivity to drugs are limited. Recent reports on the potential use of linezolid in treating brain infections prompted us to design novel compounds around this scaffold. Herein, we describe the design and synthesis of various oxazolidinone antibiotics with the incorporation of silicon. Our findings in preclinical species suggest that silicon incorporation is highly useful in improving brain exposures. Interestingly, three compounds from this series demonstrated up to a 30-fold higher brain/plasma ratio when compared to linezolid thereby indicating their therapeutic potential in brain associated disorders.

KEYWORDS: Antibacterial, linezolid, oxazolidinone, brain exposure, sila analogue



Bacterial meningitis is a very severe condition with sudden onset of symptoms and death within hours. According to WHO statistics, bacterial meningitis affects more than 400 million people per year in the “African meningitis belt”. Of the 22 831 cases diagnosed in 2010 across 14 African countries, 2415 deaths were reported with a case-fatality ratio of 10.6%.¹ The diagnosis is done by investigating the cerebrospinal fluid of patients obtained by a lumbar puncture. Since meningitis is fatal, wide spectrum antibiotics are given even before the disease is actually confirmed. The choice of antibiotics depends on the pathogen that causes meningitis, the most common ones being *Streptococcus pneumoniae* and *Neisseria meningitidis*. Cephalosporin, ampicillin, vancomycin, and rifampin are some of the commonly used antibiotics for treating bacterial meningitis.² The central nervous system (CNS) is protected by the highly selective blood–brain barrier (BBB) that controls the entry of compounds into the brain. In a normal individual, the BBB efficiently protects the brain from pathogens that can easily cause infections in other parts of the body. While brain infections are not common, they can be difficult to treat in affected individuals due to the inability of drugs to cross the BBB. The BBB, therefore, makes drug delivery to the CNS a challenging task for medicinal chemists.^{3,4} In addition to permeability, development of resistance to existing antibiotics is yet another problem encountered in treatment of brain infections. Hence, a global demand and medical need exists to develop novel lipophilic antibiotics with better BBB penetration for treating brain infections.

Linezolid^{5,6} is the first oxazolidinone antibiotic to be marketed for clinical use that suppresses bacterial growth via inhibition of ribosomal protein synthesis. Linezolid binds to a site on the 50S ribosomal subunit near its interface with the 30S unit and thus prevents the formation of a 70S initiation complex.⁷ Linezolid’s broad spectrum of activity against virtually all Gram-positive bacteria, including methicillin resistant and vancomycin resistant bacteria, led to an increased usage of the drug and resulted in significant worldwide sales ever since its approval in 2000. However, only limited information has been established with respect to linezolid’s efficacy in treating infections of the central nervous system (CNS). The cerebrospinal fluid (CSF) penetration of linezolid, a limitation observed with other frontline antibiotics in the treatment of CNS infections, is relatively better. Although, it was not evaluated in a large number of patients suffering from CNS infections, positive clinical experience with linezolid was documented in the literature by a few groups.^{8,9} To increase the utility of linezolid in CNS infections, synthesis of novel compounds is necessary; in particular, by improving B/P ratios of drug concentrations. Sutezolid (PNU-100480)¹⁰ is another closely related molecule that falls in the oxazolidinone category and is currently in phase II clinical trials for the treatment of both drug resistant and sensitive tuberculosis. While

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oxazolidinone antibiotics are typically bacteriostatic, their clinical activity is governed by the clinical dose as well as the pharmacokinetics. Other bacteriostatic agents such as tetracycline and chloramphenicol also possess good CSF penetration and are used in the treatment of bacterial meningitis.¹¹

Bioisosterism is one of the widely used methods for the efficient optimization of pharmacokinetic (PK) properties of a lead molecule.^{12–14} The incorporation of silicon into known drug scaffolds called the “silicon switch approach” has gained momentum in recent times.^{15–22} It is worth highlighting the efforts of Tacke’s group for their work on this interesting approach. In general, silicon analogues are more lipophilic than their carbon counterparts. Hence this strategy would be beneficial in CNS drug discovery wherein siliconized compounds could potentially display better blood–brain barrier (BBB) penetration. In our group, we are interested in synthesizing novel bioactive molecules with the incorporation of silicon.²³ Along these lines, we have designed and synthesized silicon analogues of the oxazolidinone antibiotics linezolid/sutezolid. We reasoned that the incorporation of silicon instead of an oxygen atom or sulfur atom in the morpholine/thiomorpholine ring can lead to a more lipophilic molecule, which was further supported by simple clogP calculations (Figure 1).^{24,25} Since the morpholine/thiomorpho-

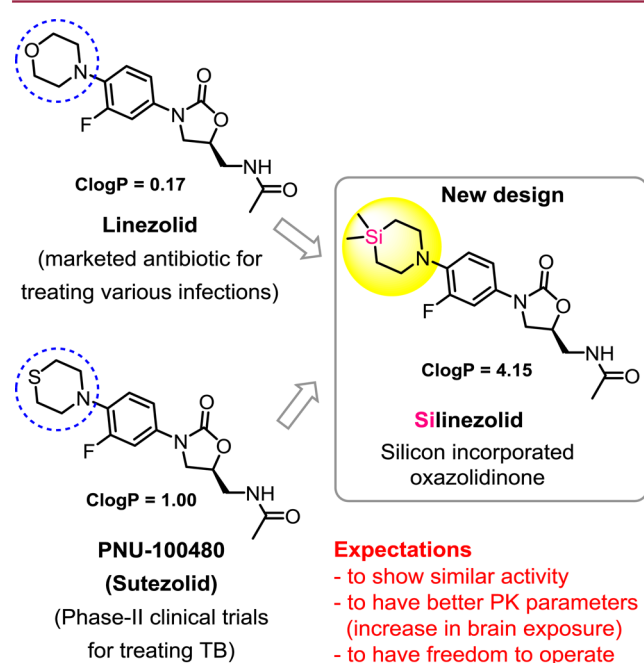


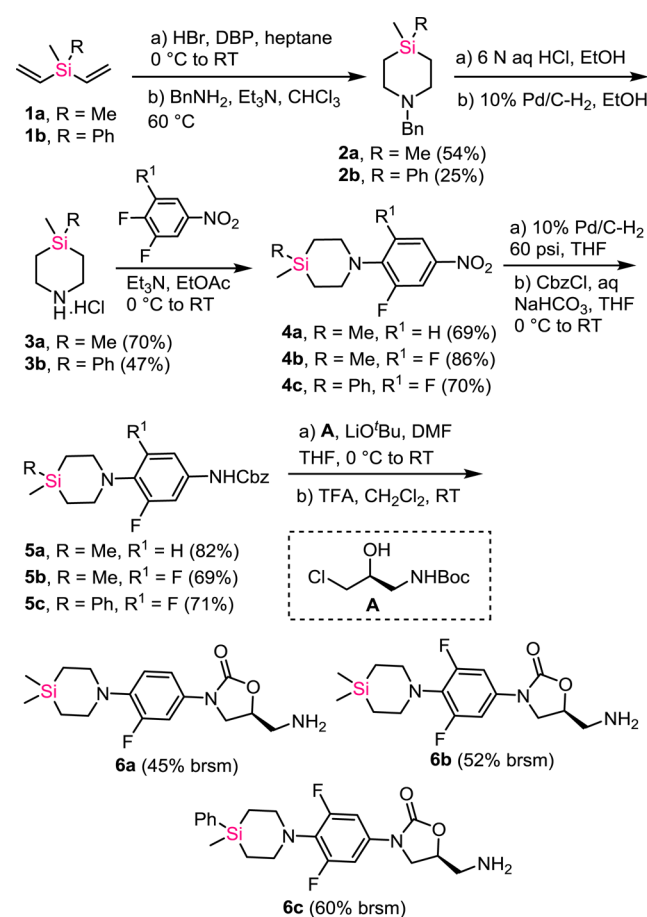
Figure 1. Design of silicon incorporated oxazolidinones.

line ring is not essential for activity and is amenable to different sterics around this moiety while retaining potency, we anticipated that the newly designed compounds would show similar activity to that of the parent. The details of experimental results are disclosed herein.²⁶

The chemical synthesis commenced with the preparation of 1,4-azasilananes **3a**²⁷ and **3b**²⁸ from commercially available divinylsilanes **1a** and **1b**. The treatment of HBr gas to vinylsilanes in heptane in the presence of a catalytic amount of dibenzoyl peroxide (DBP) gave bis(bromoethyl)silanes, which on reaction with benzylamine in CHCl₃ resulted in silapiperidines with benzyl protection **2a** and **2b**, respectively. The compounds **2a** and **2b** were debenzylated to give the key

silapiperidines **3a** and **3b**. These important intermediates were synthesized on multigram scale, which helped us to generate a library of silicon analogues of linezolid without much difficulty. The silapiperidines **3a** and **3b** on treatment with 3,4-difluoronitrobenzene and 3,4,5-trifluoronitrobenzene, resulted in compounds **4a–4c** by a simple nucleophilic aromatic substitution. The nitro group was reduced with H₂–Pd/C in THF followed by Cbz protection of the resulting amine in one pot to give the intermediates **5a–5c**. Compounds **5a–5c** were treated with chiral building block **A**²⁹ in the presence of LiO^tBu in dimethylformamide (DMF) to furnish the oxazolidinone core. Boc deprotection was achieved with trifluoroacetic acid (TFA) in CH₂Cl₂, and the salts were neutralized to afford the free amines **6a–6c** (Scheme 1).

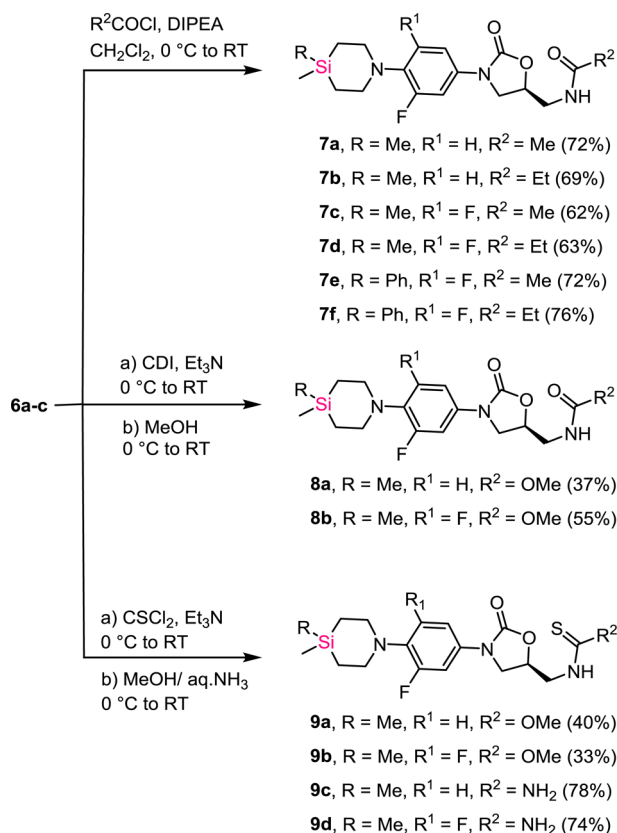
Scheme 1. Synthesis of Oxazolidinone Amines with Silicon Incorporation



These oxazolidinone amines **6a–6c** were treated with acetyl chloride and propionyl chloride to give the corresponding amides **7a–7f**. Treatment of amines **6a** and **6b** with carbonyldiimidazole (CDI) followed by addition of methanol produced two methylcarbamate derivatives **8a** and **8b**.²⁹ The reaction of amines **6a** and **6b** with thiophosgene followed by methanol yielded the thiocarbamates **9a** and **9b**. Similarly, quenching with aqueous ammonia resulted in the thiourea derivatives **9c** and **9d** (Scheme 2).

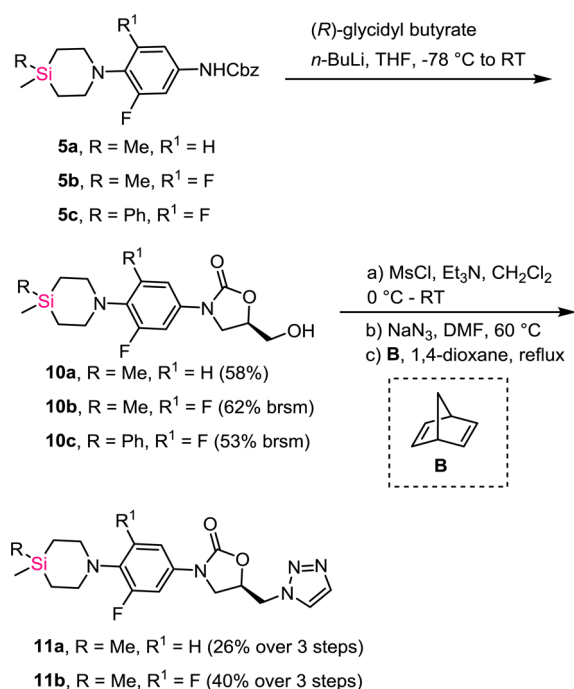
For the generation of compounds with varying structural features, compounds **5a–5c** were treated with *n*-BuLi and (*R*)-glycidyl butyrate to furnish the hydroxyl derivatives **10a–10c**. The alcohols **10a** and **10b** were converted to the corresponding

Scheme 2. Synthesis of Target Oxazolidinones with Silicon Incorporation



mesylates and the mesylate group was displaced with azide. The azide on heating with norbornadiene underwent a 1,3-dipolar cycloaddition followed by retro Diels–Alder reaction to furnish the triazoles **11a** and **11b**, respectively (Scheme 3).

Scheme 3. Synthesis of Triazole-Based Oxazolidinones



After synthesizing several silicon analogues, the antibacterial activity was assessed against various strains. MIC (minimum inhibitory concentration) of NCEs were determined by microbroth dilution method against facultative bacteria. The screening results of all compounds are provided in the Supporting Information. Among the screened oxazolidinones, the compounds **7a**, **7c**, **7d**, **9a**, and **9d** were more active against a majority of the bacterial strains tested. Compound **7a**, which is the closest linezolid analogue of all the compounds synthesized, showed good potency, but 4–8-fold less potent compared to linezolid across the strains. Introduction of additional fluorine atom on to aromatic ring (**7c**) resulted in a modest improvement in the potency. The compound with thiocarbamate functionality **9a** was the most potent compound in the series with activity comparable to that of linezolid. The presence of phenyl group on silicon resulted in a loss of potency (see Supporting Information). The alcohols **10a–10c** were found to be less potent. In general the addition of fluorine atom in the aromatic ring enhanced the antibacterial activity. However, addition of a fluorine atom onto the aromatic ring resulted in a marked decrease in potency (**9a** vs **9b**, see Supporting Information) in compounds belonging to the thiocarbamate series. After analysis of the structural features present in some of the potent oxazolidinones reported in literature, compounds **11a** and **11b** were prepared with triazole moieties in place of *N*-acyl group.³⁰ However, we did not observe significant activity with these compounds.

Upon completion of *in vitro* testing of antibacterial activities, three out of the five best compounds (**7a**, **7c**, and **9a**) from this series were selected for ADME and physicochemical property studies. Specifically, solubility across the pH range, stability in plasma, stability in microsomes, and plasma protein binding were evaluated (results compiled in Table 1). Compound **7a** was soluble across the pH range tested with values being similar to that of linezolid. The solubility of compounds **7c** and **9a** was also comparable to linezolid at acidic pH; however, it was decreased at higher pH conditions. All silicon compounds demonstrated very good plasma stability profile similar to that of linezolid. All three compounds (**7a**, **7c**, and **9a**), along with linezolid, were screened for their microsomal metabolic stability in three different species (mouse, rat, and human). Compounds **7a** and **7c** were moderately stable in both mouse and human liver microsomes with **7c** being superior among the two. Compound **9a** showed poor stability in rodent liver microsomes, but it showed better stability in human microsomes. In the case of plasma protein binding studies, we found striking difference between linezolid and sila compounds. All three compounds, **7a**, **7c**, and **9a**, were strongly bound to the plasma proteins. Hence, this can be an advantage for the improvement in BBB penetration. Although free drug concentrations are generally associated with greater antimicrobial activity, the success of telavancin and daptomycin reflect the benefit associated with high protein binding (lower clearance, longer half-life, and longer duration of action). The discrepancy in findings can be attributed to the difference in the static *in vitro* test systems vis-à-vis the dynamic nature in an *in vivo* setting wherein several factors such as binding affinity of the drug to the proteins, transport across barriers, physiological conditions, and metabolism play a major role.³¹ Based on the overall *in vitro* profile, compound **7a** was selected for detailed *in vivo* pharmacokinetic studies in mice (results are compiled in the table provided in the Supporting Information). Although compound **7a** demonstrated 100% bioavailability and similar

Table 1. *In Vitro* PhysChem and ADME Data

compd	solubility (μM) at pH					% plasma stability		% metabolic stability in liver microsomes (after 30 min)			% human PPB
	1.2	2.2	4.5	7.4	10.2	rat	human	mouse	rat	human	
LZD	50	50	50	49	50	100.0	100.0	100.0	88.3	100.0	26.04
7a	50	50	41	40	41	97.3	100.0	40.8	10.8	48.9	94.33
7c	48	43	20	17	20	94.7	100.0	68.4	9.6	69.8	99.60
9a	48	47	9	2	2	100.0	100.0	15.2	5.7	43.0	100.00

Table 2. Brain PK Comparison of 7a, 7c, 9a, and LZD^a

route	7a			7c			9a			LZD		
	brain	plasma	B/P ratio	brain	plasma	B/P ratio	brain	plasma	B/P ratio	brain	plasma	B/P ratio
dose	10	10		10	10		10	10		10	10	
N	2	2		2	2		2	2		2	2	
C _{max}	1.33	1.05	1.27	5.58	2.02	2.76	1.47	0.37	3.96	0.45	3.65	0.12
AUC _{0-t}	3.01	1.78	1.69	14.74	5.80	2.54	3.11	0.87	3.57	0.83	7.58	0.11
AUC _{0-inf}	3.05	1.80	1.69	16.44	6.21	2.65	3.24	0.93	3.49	0.90	7.70	0.12

^aUnits for brain: C_{max} = $\mu\text{g/g}$, AUC_{0-t} = $\mu\text{g}\cdot\text{h/g}$, AUC_{0-inf} = $\mu\text{g}\cdot\text{h/g}$. Units for plasma: C_{max} = $\mu\text{g/mL}$, AUC_{0-t} = $\mu\text{g}\cdot\text{h/mL}$, AUC_{0-inf} = $\mu\text{g}\cdot\text{h/mL}$.

Table 3. Antibacterial Activity of Selected Compounds against *S. pneumoniae* and *N. meningitidis*

strain	7a ^b	7c ^b	9a ^b	LZD ^b
<i>S.pneumoniae</i> ATCC 49619	8	16	4	0.5
<i>S.pneumoniae</i> ATCC 6303	4	8	4	0.5
<i>S.pneumoniae</i> 6303 LZD ^R	>32	>32	32	32
<i>S.pneumoniae</i> ATCC 700904 Pen ^R , erm+ve	4	16	4	1
<i>N.meningitidis</i> ^a E-63	32	>32	32	8
<i>N.meningitidis</i> ^a M-1	>32	>32	32	8
<i>N.meningitidis</i> ^a 306	>32	>32	32	8
<i>N.meningitidis</i> ^a E-95	>32	>32	32	8
<i>N.meningitidis</i> ^a 184	>32	>32	32	8

^aClinical isolates. ^bMIC values are measured in $\mu\text{g/mL}$.

half-life as compared to linezolid, it was inferior in terms of C_{max}, AUC, and clearance. However, the volume of distribution (V_d) of 7a was twice that of linezolid, which can be attributed to its high plasma protein binding. Next, we decided to understand BBB penetrating potential of the silicon compounds, which was the main objective of this project. Toward this goal, all three selected compounds, i.e., 7a, 7c, and 9a were administered through oral route and various parameters were measured. The details of experimental protocol and all the measurements are placed in the Supporting Information. Interestingly, all the three compounds displayed significant brain penetration. Compounds 7a, 7c, and 9a had a 14-, 22-, and 29-fold higher B/P ratios compared to linezolid (see Table 2). These ratios were calculated using AUC measurements. Calculations using C_{max} also gave similar ratios. It is worth highlighting that actual brain concentrations of the silicon compounds 7a, 7c, and 9a are much superior with respect to linezolid. Out of the three compounds, 7c was the best in terms of actual drug concentration (C_{max} = 5.58 $\mu\text{g/g}$ and AUC = 16.44 $\mu\text{g}\cdot\text{h/g}$). As the siliconized linezolid analogues displayed impressive B/P ratio, we became interested in testing these compounds against selected bacterial strains (*S. pneumoniae* and *N. meningitidis*) that cause brain infections.² The MIC values generated using various strains suggest that all three compounds possess comparable activity with respect to *S. pneumoniae* (Table 3).³² However, in the case of *N. meningitidis* strains, only compound 9a showed significant activity and other two compounds 7a and 7c did not show the activity up to 32

$\mu\text{g/mL}$. Although the antibacterial potencies are less when compared to the marketed drug linezolid, the higher B/P ratio of silicon compounds suggest that incorporation of silicon is beneficial in terms of BBB penetration.

In conclusion, we have designed and synthesized various oxazolidinones with the incorporation of silicon. Three compounds 7a, 7c, and 9a were identified as potential lead molecules from the present series, demonstrating up to 30-fold higher B/P ratio as compared to the marketed antibiotic drug, linezolid. These results can be considered as an initial step toward the development of brain penetrant oxazolidinone antibiotics. The demonstrated concept with the incorporation of silicon into known drug scaffold to improve CNS exposures can also be applied to other classes of compounds. Profiling of selected compounds in brain infected preclinical models is the future course of action and the goal is to further optimize the identified compounds toward the development of an antibiotic that can be useful in treating CNS infections.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmmedchemlett.5b00213.

Experimental details; compound characterization details; screening details; antibacterial data for all the compounds; protocols for pharmacokinetic studies including brain PK; data from mice PK experiments (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: ds.reddy@ncl.res.in.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

DEDICATION

This work is dedicated to Professor Sourav Pal, Indian Institute of Technology, Bombay and former Director, CSIR-NCL, Pune on the occasion of his 60th birthday.

ABBREVIATIONS

NCE, new chemical entity; brsm, based on recovered starting material; LZD, linezolid; ADME, absorption, distribution, metabolism, excretion; N , number of subjects; AUC, area under the curve; $t_{1/2}$, half-life; K_{el} , elimination rate constant; Cl_z, clearance; BA, bioavailability; B/P ratio, brain to plasma ratio; PPB, plasma protein binding

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(32) We have also determined the cytotoxicity of compounds **7a**, **7c**, and **9a** following 24 h incubation with human hepatoma (HepG2) and tracheal epithelial cells (HTEpiC). Compounds **7c** and **9a** were nontoxic at $>10 \mu\text{M}$ concentration in both HepG2 and HTEpiC cells. However, the IC_{50} of compound **7a** incubation was $9 \mu\text{M}$ in HepG2 cells and $5 \mu\text{M}$ in HTEpiC cells. Details are provided in the [Supporting Information](#).