In vitro Efficacy of Novel Glucan Synthase Inhibitor, Ibrexafungerp (SCY-078), Against Multidrug- and Pan-resistant *Candida auris* Isolates from the Outbreak in New York

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Abstract

We report low MIC_{50} of Ibrexafungerp (SCY-078) for 102 *Candida auris* clinical and surveillance isolates from outbreak in New York. The group included *C. auris* with a variable resistance to antifungal drugs. Five pan-resistant *C. auris* isolates were susceptible to Ibrexafungerp with low MIC_{50} range of 0.12-1 μg/ml.

Introduction

Since its discovery in 2009, *Candida auris* has become a major concern as an emerging drug resistant, healthcare-related infection around the globe (1, 2). Beginning in 2013, the New York metropolitan area has suffered from a large, sustained outbreak of *C. auris* in hospitals and healthcare facilities (3). The latest NY data from 540 *C. auris* clinical isolates, *C. auris* isolates recovered from 11,035 patient surveillance specimens, and 3,672 environmental surveillance samples suggests the predominance of the South Asia Clade I with variable multidrug-resistance (4). There is a pressing public health need to test additional antifungal drugs for their efficacy against drug resistant *C. auris*.

Ibrexafungerp (formerly SCY-078), is an orally bioavailable, semi-synthetic modified compound of enfumafungin, a triterpene glycoside natural product (5, 6). Ibrexafungerp laboratory testing showed broad activity against *Candida* species including fluconazole-resistant *C. albicans*, and *C. auris* (7-9). We report *in vitro* activity of Ibrexafungerp against 102 *C. auris* isolates from NY comprising clinical and surveillance cases. The *C. auris* selection included variable resistance (resistance to one drug in one or two classes of antifungal drug) multidrug-resistant (resistance to two or more drugs between two classes of antifungal drugs) or pan-resistant (resistance to two or more azoles, all echinocandins, and amphotericin B).

Materials and Methods

A recent publication from our laboratory includes details about the processing, identification, and characterization of *C. auris* from the NY outbreak (4). Broth micro-dilution antifungal susceptibility testing was performed per Clinical and Laboratory Standards Institute reference method M27-A3 as described by Berkow et al. (7). Amphotericin B MIC_{100} was tested using E-test strips (bioMerieux USA, St. Louis, MO). We used CDC guidelines to assess antifungal resistance patterns in *C. auris* as breakpoints are not available for this pathogen (https://www.cdc.gov/fungal/candida-auris/c-auris-antifungal.html). We also used EUCAST recommendations as a surrogate breakpoint to determine resistance pattern to various antifungals (http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/AFST/Clinical_breakpoints/Antifungal_breakpoints_v_9.0_180212.pdf).

Results and Discussion

Ibrexafungerp MIC_{50} readings for 102 *C. auris* isolates are summarized in Tables 1-3. For 97 *C. auris* isolates with a variable resistance to antifungal drugs, Ibrexafungerp MIC_{50} range was 0.06-0.5 µg/ml, median and mode were 0.5 µg/ml, respectively (Table 1-2). All five pan-resistant *C. auris* isolates were susceptible to Ibrexafungerp with low MIC_{50} range of 0.12-1 (Table 3). Notably, Ibrexafungerp MIC_{50} range against our collection is well within the serum achievable concentrations reported from preclinical pharmacokinetics and pharmacodynamic studies, and murine models of disseminated candidiasis (10). Our laboratory findings expand earlier reports on *in vitro* efficacy of Ibrexafungerp against *C. auris* resistant to amphotericin B, flucytosine, itraconazole and isavuconazole (7, 9). The near universal fluconazole resistance, and unusually high resistance to azoles, echinocandins, polyene, and nucleoside inhibitors is a noticeable feature of *C. auris* isolates in the NY outbreak (3, 4). The exact mechanisms behind the observed resistance pattern remain unknown; with the exception of few isolates, all NY *C. auris* isolates belonged to South Asia clade, which is reported to have high drug-resistance (2). Our findings support enhanced evaluations of Ibrexafungerp including expanded clinical studies to better understand its therapeutic potential for *C. auris*.

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Table 1. Detailed Ibrexafungerp MIC_{50} (µg/ml) for 98 clinical and surveillance isolates of *Candida auris*

C. auris	FZ	VOR	IZ	ISA	PZ	AND	CAS	MF	AP	FC	IBX
16-1	8	0.25	0.5	0.25	0.25	0.12	0.12	0.12	0.5	0.5	0.25
17-14	>256	2	0.5	0.5	0.12	4	2	4	0.75	0.032	0.25
17-15	>256	2	0.5	0.5	0.25	4	2	4	0.75	0.032	0.25
17-16	>256	2	0.5	0.5	0.12	4	2	4	1	0.023	0.25
17-12	32	0.5	0.06	0.015	0.03	8	8	8	1	0.032	0.25
17-18	>256	2	0.5	1	0.12	0.25	0.06	0.06	3	0.064	0.5
17-17	>256	4	0.5	0.5	0.06	0.25	0.03	0.06	3	0.064	0.25
17-13	>256	1	0.25	0.5	0.03	0.06	0.03	0.06	3	0.032	0.5
18-13	>256	0.5	0.12	0.12	0.03	0.12	0.03	0.12	1	32	0.25
18-5	>256	2	0.25	0.5	0.06	0.12	0.03	0.12	2	0.094	0.5
18-14	>256	1	0.25	0.5	0.03	0.06	0.015	0.06	1	0.047	0.5
18-15	>256	1	0.25	0.5	0.03	0.12	0.03	0.06	2	0.064	0.5
19-44	>256	2	1	1	0.25	4	16	1	1		0.5
19-45	>256	2	1	1	0.25	4	16	1	1		0.5
16-10	>256	2	0.5	1	0.25	0.25	0.06	0.12	2	0.032	0.25
16-11	8	0.06	0.5	0.03	0.25	0.25	0.25	0.12	0.25	0.064	0.25
16-12	>256	2	1	1	0.5	1	0.5	0.5	2	0.094	0.5
16-13	>256	2	1	2	0.5	1	0.5	0.5	2	0.047	0.25
16-14	>256	1	0.25	0.5	.12	0.12	0.25	0.25	2	0.047	0.25
16-15	>256	2	0.5	0.5	0.25	0.25	0.12	0.25	2	0.032	0.25
16-16	>256	1	0.5	0.5	0.25	0.12	0.06	0.12	2	0.047	0.25
16-17	>256	2	0.5	0.5	0.12	0.12	0.03	0.06	2	0.094	0.5
16-18	>256	2	0.5	0.5	0.12	0.12	0.03	0.06	1	0.125	0.5
16-19	8	0.12	0.5	0.06	0.25	0.25	0.5	0.25	0.25	0.094	0.25
16-2	2	0.015	0.015	0.01	0.008	0.06	0.03	0.03	0.094	0.023	0.25
16-20	>256	2	1	2	0.5	0.5	0.5	0.25	2	0.094	0.5
16-21	>256	2	0.5	0.5	0.12	0.12	0.06	0.06	1	0.047	0.5
16-22	>256	2	0.5	0.5	0.12	0.12	0.06	0.06	0.75	0.064	0.25
16-23	>256	2	1	1	0.5	1	1	0.25	2	0.094	0.5
16-24	>256	2	1	2	0.5	0.5	0.25	0.25	0.75	0.064	0.25
16-25	>256	2	0.5	1	0.5	1	0.5	0.5	3	0.064	0.25
16-26	>256	2	1	2	0.5	1	0.5	0.25	2	0.064	0.5
16-27	>256	2	0.5	1	0.25	0.25	0.12	0.12	2	0.032	0.5
16-28	>256	4	0.5	0.5	0.25	0.25	0.12	0.12	1	0.032	0.5
16-29	>256	2	0.5	0.5	0.25	0.25	0.06	0.12	2	0.032	0.5
16-3	4	0.03	0.015	0.008	0.008	0.06	0.03	0.06	0.094	0.032	0.25
16-30	>256	2	0.5	0.5	0.25	0.25	0.12	0.12	2	0.047	0.5
16-31	>256	2	0.5	0.5	0.25	0.25	0.12	0.12	2	0.094	0.5
16-32	>256	2	0.5	1	0.25	0.25	0.12	0.12	2	0.125	0.5
16-33	>256	1	0.5	0.5	0.12	0.25	0.06	0.06	2	0.064	0.25
16-34	>256	2	0.5	0.5	0.06	0.12	0.03	0.06	2	0.047	0.25
16-35	>256	2	0.5	1	0.25	0.25	0.25	0.25	1	0.125	0.25
16-36	>256	2	0.5	0.5	0.06	0.12	0.03	0.06	2	0.094	0.25
16-37	>256	2	0.5	1	0.25	0.25	0.06	0.12	2	0.125	0.25
16-39	>256	2	0.25	0.5	0.06	0.12	0.06	0.06	2	0.094	0.5
16-4	>256	0.5	0.5	0.25	0.12	0.12	0.06	0.12	1	0.032	0.5
16-40	>256	2	0.5	0.5	0.12	0.12	0.06	0.06	2	0.064	0.5
16-41	>256	2	0.5	0.5	0.12	0.12	0.03	0.06	1	0.032	0.5
16-5	>256	4	1	1	0.25	0.25	0.12	0.25	2	0.023	0.5
16-7	>256	2	0.5	1	0.25	0.25	0.25	0.25	2	0.094	0.5

17-10	>256	2	0.5	1	0.5	0.5	0.25	0.25	2	0.094	0.25
17-11	>256	4	1	4	1	1	0.5	0.25	1	0.125	0.25
17-19	>256	2	1	1	0.25	0.25	0.06	0.12	3	32	0.25
17-20	128	0.5	0.25	0.25	0.06	0.12	0.03	0.06	1	0.047	0.25
17-21	>256	2	0.5	1	0.12	0.12	0.03	0.06	3	0.064	0.25
17-22	>256	2	0.5	0.5	0.12	0.25	0.06	0.06	0.75	0.023	0.25
17-25	>256	2	0.5	0.5	0.25	4	2	4	1	0.023	0.25
17-26	>256	4	1	2	0.5	0.5	0.25	0.12	2	32	0.25
17-27	>256	1	0.5	0.25	0.25	0.12	0.12	0.12	2	0.047	0.12
17-28	>256	2	1	1	0.5	0.03	0.03	0.06	0.75	0.094	0.06
17-2	>256	0.5	0.5	0.5	0.25	0.12	0.03	0.12	2	0.064	0.25
17-29	>256	4	1	2	0.5	0.5	0.25	0.25	1	0.047	0.25
17-30	>256	2	0.5	0.5	0.12	0.25	0.03	0.06	1	0.032	0.25
17-31	>256	2	0.5	1	0.25	0.25	0.25	0.25	1	0.19	0.25
17-3	>256	2	0.5	1	0.12	0.12	0.06	0.06	3	0.064	0.25
17-4	>256	2	0.5	0.5	0.5	0.12	0.03	0.25	3	0.125	0.25
17-5	>256	2	0.5	0.5	0.25	0.25	0.06	0.12	2	0.094	0.5
17-6	>256	2	0.5	1	0.5	0.5	0.25	0.5	3	0.064	0.25
17-7	>256	2	1	2	0.5	0.5	0.25	0.25	2	0.064	0.25
17-8	>256	2	0.25	0.25	0.12	0.12	0.015	0.06	3	0.064	0.5
17-9	>256	2	1	1	0.5	0.5	0.25	0.25	1	0.094	0.5
18-10	>256	1	0.25	0.5	0.06	0.06	0.03	0.06	1	0.047	0.5
18-11	>256	4	0.5	1	0.25	1	0.5	0.25	2	0.064	0.5
18-12	>256	2	1	1	0.25	0.25	0.25	0.12	2	32	0.5
18-23	>256	1	0.25	0.5	0.03	0.12	0.015	0.12	2	0.064	0.5
18-24	>256	2	0.25	0.5	0.06	0.12	0.06	0.06	2	0.064	0.5
18-25	>256	2	0.25	1	0.06	0.12	0.06	0.12	2	0.047	0.5
18-26	>256	2	0.25	0.5	0.03	0.12	0.03	0.06	2	0.064	0.5
18-3	>256	2	0.5	1	0.25	0.25	0.12	0.06	3	0.125	0.5
18-4	>256	2	1	1	0.25	0.25	0.12	0.12	2	>32	0.5
18-6	>256	2	0.25	0.5	0.06	0.25	0.06	0.12	2	0.094	0.5
18-7	>256	1	0.5	0.5	0.06	2	0.25	2	1	0.094	0.25
18-8	>256	2	0.5	0.5	0.25	0.12	0.06	0.06	2	0.094	0.5
18-9	>256	2	0.25	0.5	0.06	0.06	0.03	0.12	3	0.125	0.5
19-1	>256	2	0.5	0.5	0.12	0.5	0.25	0.12	0.75		0.5
19-10	>256	1	0.5	0.5	0.25	0.25	0.06	0.12	3		0.5
19-11	>256	1	1	1	0.25	0.25	0.25	0.12	1		0.5
19-12	>256	1	0.5	0.5	0.12	0.25	0.06	0.06	2		0.5
19-13	>256	1	0.5	0.5	0.25	0.25	0.12	0.12	1		0.5
19-14	>256	2	0.5	1	0.25	0.25	0.06	0.12	0.75		0.25
19-15	>256	1	0.5	0.25	0.12	0.25	0.06	0.12	2		0.5
19-16	>256	1	0.5	0.5	0.25	0.25	0.25	0.12	1		0.5
19-17	>256	2	1	1	0.25	0.5	0.25	0.25	1		0.5
19-18	>256	1	0.5	0.5	0.25	0.25	0.25	0.12	2		0.5
19-19	>256	2	1	1	0.5	0.5	0.25	0.25	2		0.5
19-2	>256	2	1	1	0.5	0.5	0.25	0.25	2		0.5
19-5	>256	1	1	0.5	0.5	1	0.5	0.5	2		0.5
Range	2->256	0.015-4	0.015-1	0.008-4	0.008-1	0.03-8	0.015-16	0.03-8	0.094-3	0.023->32	0.06-0.5
Median	>256	2	0.5	0.5	0.25	0.25	0.12	0.12	2	0.064	0.5
Mode	>256	2	0.5	0.5	0.25	0.25	0.06	0.12	2	0.064	0.5

FZ			VOR			IZ			ISA			PZ			AND			CAS			MF			AP			FC			IBX		
Range	Median	Mode	Range	Median	Mode	Range	Median	Mode	Range	Median	Mode	Range	Median	Mode	Range	Median	Mode	Range	Median	Mode	Range	Median	Mode	Range	Median	Mode	Range	Median	Mode	Range	Median	Mode
2 - >256	>256	>256	0.015 - 4	2	2	0.015 - 1	0.5	0.5	0.008 - 4	0.5	0.5	0.008 - 1	0.25	0.25	0.03 - 8	0.25	0.25	0.015 - 16	0.12	0.06	0.03 - 8	0.12	0.12	0.094 - 3	2	2	0.023 - >32	0.064	0.064	0.06 – 0.5	0.5	0.5

Table 2. Summary Ibrexafungerp MIC_{50} (µg/ml) for 98 clinical and surveillance isolates of *Candida auris*

Table 3. Ibrexafungerp MIC_{50} data for pan-resistant *Candida auris*

Candida auris	**MIC_{50}**										
	FZ	**VOR**	**IZ**	**ISA**	**PZ**	**AND**	**CAS**	**MF**	**AP**	**FC**	**IBX**
17-24#	**>256**	**2**	**0.5**	**0.5**	**0.25**	**4**	**>16**	**4**	**2**	**0.064**	**0.5**
18-2#	**>256**	**2**	**1**	**1**	**0.25**	**8**	**2**	**4**	**2**	**0.064**	**0.12**
19-4#	**>256**	**2**	**0.5**	**0.5**	**0.25**	**4**	**2**	**4**	**2**	**NA**	**0.5**
19-42#	**>256**	**2**	**1**	**1**	**0.25**	**4**	**16**	**4**	**2**	**NA**	**1**
19-43#	**>256**	**2**	**1**	**1**	**0.25**	**4**	**16**	**4**	**2**	**NA**	**1**

#Pan-resistant
AP (E-test)
NA not available