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SUPPORTING INFORMATION

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Synthesis

Compounds **2a**,[1] **2b**,[2] **2c-d**,[3] **2d**,[4] and **3a-b**[5] were prepared following literature procedures.

Antimicrobial assays

Microbroth Antimicrobial Assay: All microbroth antibiotic susceptibility testing was carried out in 96 well plates in accordance with Clinical Laboratory Standards Institute testing standards (2003) using the following pathogens: methicillin-resistant *Staphylococcus aureus* ATCC 33591 (MRSA), *S. warneri* ATCC 17917, vancomycin-resistant *Enterococcus faecium* EF 379 (VRE), *Pseudomonas aeruginosa* ATCC 14210, *Proteus vulgaris* ATCC 12454, and *Candida albicans* ATCC 14035. Compounds were tested in six replicates against each organism Compounds were re-suspended in sterile 20% DMSO and serially diluted to generate a range of twelve concentrations (256 μg/mL to 0.0625 μg/mL) in a final well volume concentration of 2% DMSO. Each plate contained eight uninoculated positive controls (media + 20% DMSO), eight untreated negative controls (Media +20% DMSO + organism), and one column containing a concentration range of a control antibiotic (vancomycin for MRSA and *S. warneri*, rifampicin for VRE, gentamycin for *P. aeruginosa*, ciprofloxacin for *P. vulgaris*, or nystatin for *C. albicans*). The optical density of the plate was recorded on a BioTek Synergy HT plate reader at 600 nm at time zero and then again after incubation of the plates for 22 h at 37 °C. After subtracting the time zero OD600 from the final reading the percentages of microorganism survival relative to vehicle control wells were calculated. MIC values were determined as the minimal concentration tested where 100% inhibition was observed for all replicates. IC_{50} values for each replicate were individually determined and used to calculate a mean IC_{50} and standard deviation for each compound in a given test condition.

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Compounds	*MRSA* MIC (μM)	*MRSA* IC_{50}±SD (μM)	*S. warneri* MIC (μM)	*S. warneri* IC_{50}±SD (μM)	*VRE* MIC (μM)	*VRE* IC_{50}±SD (μM)
1	24.7	10.4±4.1	12.4	9.1±0.5	12.4	5.0±1.2
2a	3.0	0.6±0.1	3.0	1.3±0.4	3.0	1.7±0.2
2b	23.6	0.4±0.1	23.6	17.7±1.2	47.1	19.1±6.6
2c	549.9	122±27	>550	339±32	137.5	62±3
2d	9.6	7.7±1.1	9.6	7.4±0.2	9.6	2.8±0.8
2e	9.1	3.0±2.0	9.1	3.7±0.1	9.1	3.5±0.1
3a	380.7	171±15	95.2	56.5±2.8	95.2	65.4±1.3
3b	404.8	83.8±6.5	101.2	38.7±2.1	>405	>405
vancomycin rifampicin	1.4	0.7±0.1	0.7	0.5±0.1	2.4	1.2±0.3

Compounds	*P. vulgaris* MIC (μM)	*P. vulgaris* IC_{50}±SD (μM)	*P aeruginosa* MIC (μM)	*P aeruginosa* IC_{50}±SD (μM)	*C. albicans* MIC (μM)	*C. albicans* IC_{50}±SD (μM)
1	>792	>792	>792	>792	>792	>792
2a	189.7	5.9±4.6	>759	>759	47.4	10.7±1.2
2b	754.0	176±12	>754	>754	>754	>754
2c	>550	>550	>550	>550	>550	>550
2d	>612	>612	>612	>612	>612	>612
2e	>585	>585	>585	>585	>585	>585
3a	>380	95±10	>380	>380	>380	>380
3b	404.8	104±21	>405	>405	>405	>405
ciprofloxacin gentamycin nystatin	0.2	ND	4.2	2.1±0.3	2.2	0.9±0.03

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Cell Lines and Growth Conditions

Human foreskin BJ fibroblast cells (ATCC CRL-2522) were grown and maintained in 15 mL of Eagle's minimal essential medium (Sigma M5650) supplemented with 10% fetal bovine serum (VWR#CA95043-976) and 100 μU penicillin and 0.1 mg/mL streptomycin (VWR#CA12001-692) in T75 cm^2 cell culture flasks (VWR#CABD353136) at 37 °C in a humidified atmosphere of 5% CO_2. Culture medium was refreshed every two to three days and cells were not allowed to exceed 80% confluency. Adult human epidermal keratinocytes (Heka) isolated from skin (Invitrogen#C-005-5C) were grown and maintained in 15 mL of EPilife medium (Invitrogen#M-EPI-500) supplemented with HKGS growth supplements (Invitrogen#S-001-5) (0.2% v/v bovine pituitary extract (BPE), 5 μg/mL bovine insulin, 0.18 μg/mL hydrocortisone, 5 μg/mL bovine transferrin, 0.2 ng/mL human epidermal growth factor) and 50μg/mL gentamicin (Sigma#G1397-10ML) in T75 cm^2 cell culture flasks (VWR#CABD353136) and incubated at 37 °C in a humidified atmosphere of 5% CO_2. Growth medium was refreshed every 2 d until the cells reached 50% confluency and then the medium was refreshed every 24 h until 80% confluency was obtained.

Cytotoxicity Assay

At 80% confluency, the cells were counted, diluted and plated into 96 well treated cell culture plates (VWR#29442-054) at a cell density of 10000 cells per well in 90 μL of respective growth medium. All media used for the assay were the same without the addition of antibiotics. The plates were incubated at 37 °C in a humidified atmosphere of 5% CO_2 to allow cells to adhere to the plates for 24 h before treatment. DMSO was used as the vehicle at a final concentration of 1% in the wells. All compounds to be tested were resolublized in sterile DMSO (Sigma#D2438) and a dilution series was prepared for each cell line using the respective cell culture growth medium of which 10 μL were added to the respective assay plate well yielding eight final concentrations ranging from 128 μg/mL to 1 μg/mL per well (final well volume of 100 μL) and incubated at 37 °C in a humidified atmosphere of 5% CO_2 for 24 h. All samples were tested in triplicate. Each plate contained eight uninoculated positive controls (media + 20% DMSO), eight untreated negative controls (Media +20% DMSO + cells), and one column containing a concentration range of zinc pyrithione. Alamar blue (Invitrogen#Dal1100) was added, 24 h after treatment, to each well at 10% of the culture volume (11 μL in 100 μL). Fluorescence was monitored using a BioTek Synergy HT plate reader at 530/25 excitation, 590/35 emission and 35 sensitivity at both time zero and 4 h after Alamar blue was added. After subtracting the time zero emission 590 nm measurement from the final reading the inferred percentage of microorganism survival relative to vehicle control wells were calculated and the IC_{50} was determined.

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Compounds	Keratinocyte (HeKa) MIC (μM)	Keratinocyte (HeKa) IC_{50}±SD (μM)	Fibroblast (BJ) MIC (μM)	Fibroblast (BJ) IC_{50}±SD (μM)
1	49.5	12.4±2.4	197.9	65±12
2a	23.7	10.7±2.3	11.9	7.7±0.2
2b	47.1	28.0±2.1	94.3	35.4±0.4
2c	>275	>275	>275	>275
2d	>306	>306	38.3	28.7±0.02
2e	>292	43.4±13.5	146.1	9.1±1.1
3a	>380	149±4	190.4	156±1
3b	12.7	<1.58	50.6	21.7±0.4
Zinc pyrithione	3.1	2.4±0.5	25.2	13.8±3.5

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