Electronic Supporting Information

Pharmaceutical Salts of Azole Anti-fungal Drugs: Physicochemical Behaviour and Activity Studies

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Figure ES11: Solution- based Abs. spectra of salts along with NDSA-2H at pH **2**.
Figure ES12: Solution- based Abs. spectra of salts along with NDSA-2H at pH **7**.
Figure ES13: P-XRD pattern of MIC compared with MIC left after solubility test.
Figure ES14: P-XRD pattern of KTC compared with KTC left after solubility test.
Figure ES15: P-XRD pattern of MIC-C compared with MIC-C left after solubility test.
Figure ES16: P-XRD pattern of KTC-C compared with KTC-C left after solubility test.

Table ES1: Antifungal activity (in terms of zone of inhibition) of MIC, MIC-C, KTC, and KTC-C against different human pathogenic fungal strains using disk diffusion assay.

S. No	**Strain**	**Zone of inhibition of KTC-C (cm)**	**Zone of inhibition of KTC (cm)**
1.	*C. albicans*	3.4	3.4
2.	*C. glabrata*	2.5	2.4
3.	*C. paropsilosis*	4	4
4.	*C. auris*	3.5	3.5
S. No	**Strain**	**Zone of inhibition of MIC-C (cm)**	**Zone of inhibition of MIC (cm)**
5.	*C. albicans*	1.6	1.6
6.	*C. glabrata*	1.6	1.5
7.	*C. paropsilosis*	1.6	1.8
8.	*C. auris*	1.6	1.6

Table ES2: Combinatorial impact of A) KTC and B) KTC-C with Polyene Amphotericin B (AmpB) against different pathogenic fungal strains.

A)

Strain	**MIC_{90} (µg/ml)**				**FICI**	**Interaction**
	AmpB (Alone)	**AmpB (Comb)**	**KTC (Alone)**	**KTC (Comb)**		
C. albicans	2	0.25	.00195	.00024	0.24	Synergistic
C. glabrata	4	2	0.25	0.125	1	No Interaction

C. paropsilosis	1	0.5	.0078	.0039	1	No Interaction
C. auris	4	1	.0625	.015625	0.5	Synergistic
ADCdr1-GFP	4	2	0.0312	0.01562	1	No Interaction
ADPdr5-GFP	8	4	0.0156	0.0078	1	No Interaction
ADCaMdr1-GFP	16	8	0.125	0.0625	1	No Interaction

B)

Strain	**MIC_{90} (µg/ml)**				**FICI**	**Interaction**
	AmpB (Alone)	**AmpB (Comb)**	**KTC-C (Alone)**	**KTC-C (Comb)**		
C. albicans	2	0.5	.0078	.00195	0.5	Synergistic
C. glabrata	4	1	0. 25	0.0625	0.5	Synergistic
C. paropsilosis	1	0.5	.0078	.0039	1	No Interaction
C. auris	4	2	.0625	.03125	1	No Interaction
ADCdr1-GFP	4	2	.03125	0.01562	1	No Interaction
ADPdr5-GFP	8	4	0.03125	0.01562	1	No Interaction
ADCaMdr1-GFP	16	8	0.25	0.125	1	No Interaction

Table ES3: Combinatorial impact of A) MIC and B) MIC-C with Polyene Amphotericin B (AmpB) against different pathogenic fungal strains

A)

Strain	**MIC_{90} (µg/ml)**				**FICI**	**Interaction**
	AmpB (Alone)	**AmpB (Comb)**	**MIC (Alone)**	**MIC (Comb)**		
C. albicans	2	1	.00195	.00097	1	No Interaction
C. glabrata	4	2	.0078	.0039	1	No Interaction
C. paropsilosis	1	0.5	.0078	.0039	1	No Interaction
C. auris	4	2	.0625	.03125	1	No Interaction
ADCDR1-GFP	4	2	0.25	0.125	1	No Interaction
ADPDR5-GFP	8	4	0.125	0.0625	1	No Interaction
ADCaMDR1-GFP	16	8	0.0039	0.00195	1	No Interaction

B)

Strain	MIC_{90} (µg/ml)				FICI	Interaction
	AmpB (Alone)	AmpB (Comb)	MIC-C (Alone)	MIC-C (Comb)		
C. albicans	2	1	.0039	.00195	1	No Interaction
C. glabrata	4	2	.0625	.03125	1	No Interaction
C. paropsilosis	1	0.5	.0625	.03125	1	No Interaction
C. auris	4	2	0.125	0.0625	1	No Interaction
ADCDR1-GFP	4	2	0.25	0.125	1	No Interaction
ADPDR5-GFP	8	4	0.125	0.0625	1	No Interaction
ADCaMDR1-GFP	16	8	0.0078	0.0039	1	No Interaction

Table ES4: Combinatorial Impact of A) KTC and B) KTC-C with Caspofungin (Echinocandin) against different pathogenic fungal strains

A)

Strain	MIC_{90} (µg/ml)				FICI	Interaction
	CSF (Alone)	CSF (Comb)	KTC (Alone)	KTC (Comb)		
C. albicans	.0625	.03125	.00195	.000007	0.5	Synergistic
C. glabrata	.03125	.015625	0.25	0.00097	0.5	Synergistic
C. paropsilosis	0.5	0.25	.0078	.000030	0.5	Synergistic
C. auris	.0078	.0039	.0625	.00024	0.5	Synergistic
ADCDR1-GFP	0.5	0.25	0.03125	0.0156	1	No Interaction
ADPDR5-GFP	.0625	0.03125	.0156	0.0078	1	No Interaction
ADCaMDR1-GFP	.0625	0.03125	0.125	0.00048	0.5	Synergistic

B)

Strain	MIC_{90} (µg/ml)				FICI	Interaction
	CSF (Alone)	CSF (Comb)	KTC-C (Alone)	KTC-C (Comb)		
C. albicans	.0625	.03125	.0078	.000030	0.5	Synergistic
C. glabrata	.03125	.015625	0.5	.0019	0.5	Synergistic
C. paropsilosis	0.5	0.25	.0078	.000030	0.5	Synergistic
C. auris	.0078	.0039	.0625	.00024	0.5	Synergistic

ADCDR1-GFP	0.5	0.25	.03125	0.0156	1	No Interaction
ADPDR5-GFP	.0625	0.03125	.03125	0.0156	1	No Interaction
ADCaMDR1-GFP	.0625	0.03125	0.25	0.00097	0.5	Synergistic

Table ES5: Combinatorial Impact of A) MIC and B) MIC-C with Caspofungin (Echinocandin) against different pathogenic fungal strains

A)

Strain	**MIC_{90} (µg/ml)**				**FICI**	**Interaction**
	CSF (Alone)	**CSF (Comb)**	**MIC (Alone)**	**MIC (Comb)**		
C. albicans	.0625	.03125	.00195	.000075	0.5	Synergistic
C. glabrata	.03125	.0156	.0078	.00030	0.5	Synergistic
C. paropsilosis	0.5	0.25	.0078	.00030	0.5	Synergistic
C. auris	.0078	.0039	.0625	.01562	0.74	No Interaction
ADCDR1-GFP	0.5	0.25	0.25	0.0625	0.75	No Interaction
ADPDR5-GFP	.0625	0.0312	0.125	0.0625	1	No Interaction
ADCaMDR1-GFP	.0625	0.0312	0.0039	0.00195	1	No Interaction

B)

Strain	**MIC_{90} (µg/ml)**				**FICI**	**Interaction**
	CSF (Alone)	**CSF (Comb)**	**MIC-C (Alone)**	**MIC-C (Comb)**		
C. albicans	.0625	.03125	.0039	.00015	0.5	Synergistic
C. glabrata	.03125	.0156	.0625	.0024	0.5	Synergistic
C. paropsilosis	0.5	0.25	.0625	.0024	0.5	Synergistic
C. auris	.0078	.0039	0.125	.03125	0.75	No Interaction
ADCDR1-GFP	0.5	0.25	0.25	0.0625	0.75	No Interaction
ADPDR5-GFP	0.0625	0.03125	0.0078	0.0039	1	No Interaction
ADCaMDR1-GFP	0.0625	0.03125	.0078	0.0039	1	No Interaction

Table ES6: Proteinase activity values of the *C. albicans* and *C. auris* strains treated with A) KTC and KTC-C, B) MIC and MIC-C. Diameter value is represented in centimeters. Relative enzyme activity is the enzyme activity relative to respective WT strain.

A)

S. No	Strain	Colony diameter (cm)	Total diameter (cm)	Enzyme activity*	Relative enzyme activity (to WT)
1.	*C. albicans* WT treated with KTC	0.8	2	2.5	0.83
2.	*C. albicans* WT treated with KTC-C	0.8	2.2	2.75	0.91
3.	*C. albicans* WT	0.8	2.4	3	1
4.	*C. auris* WT treated with KTC	0.6	1.5	2.5	0.83
5.	*C. auris* WT treated with KTC-C	0.6	1.4	2.33	0.77
6.	*C. auris* WT	0.7	2.1	3	1

B)

S. No	Strain	Colony diameter (cm)	Total diameter (cm)	Enzyme activity*	Relative enzyme activity (to WT)
1.	*C. albicans* WT treated with MIC	0.8	2.2	2.75	0.91
2.	*C. albicans* WT treated with MIC-C	0.8	2.3	2.875	0.95
3.	*C. albicans* WT	0.8	2.4	3	1
4.	*C. auris* WT treated with MIC	0.7	1.6	2.28	0.76
5.	*C. auris* WT treated with MIC-C	0.7	1.9	2.71	0.90
6.	*C. auris* WT	0.7	2.1	3	1

Table ES7: Crystallographic table of MIC-C.

Compound	1
CCDC no.	2305701
Sample ID	MAA-135
Empirical formula	C46 H36 Cl8 N4 O8 S2

Fw	628.59
temp(K)	150
Crystal system	Triclinic
Space group	*P*-1
a (Å)	13.6608(12)
b (Å)	14.1664(12)
c (Å)	15.0874(10)
α [º]	105.368(7)
β [º]	93.550(6)
γ [º]	116.078(9)
V [A^3]	2474.52
Z	2
D(calcd)[Mg/cm^3]	1.504
μ [mm^{-1}]	0.596
Θ range [◦]	25.000
Reflns collected	8713
Indep. Reflns	4657
GOF	1.013
$R1(I_0>2s(I_0))$	0.0408
wR2(all data)	0.2198

Table ES8: Calculated approximate weight of the parent drug left after the solubility studies.

Parent drug	Total wt.	Wt. left at pH 2	Wt. left at pH 7
MIC	0.00416 mg	0.00202 mg	0.00104 mg
KTC	0.00523 mg	0.00123 mg	0.00160 mg

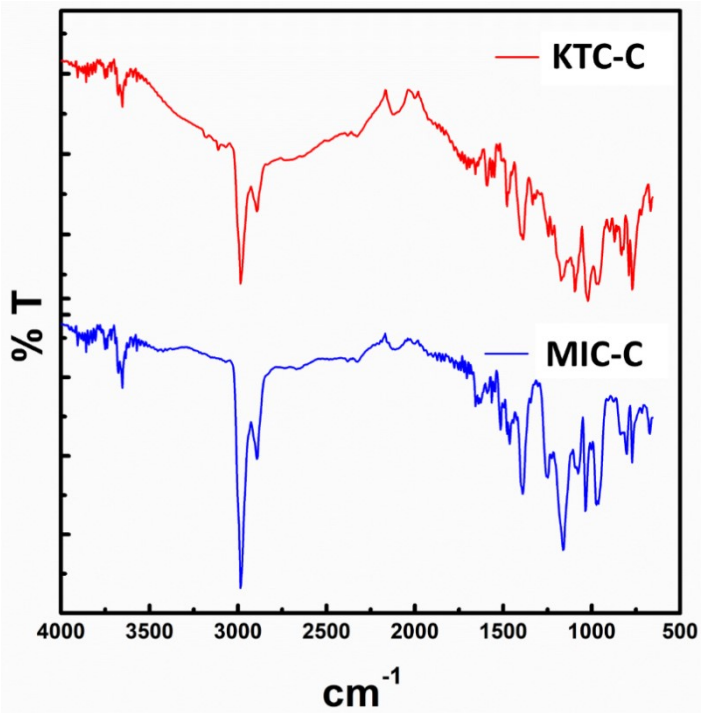

Figure ES1: FT-IR spectra of MIC-C and KTC-C recorded in neat form.

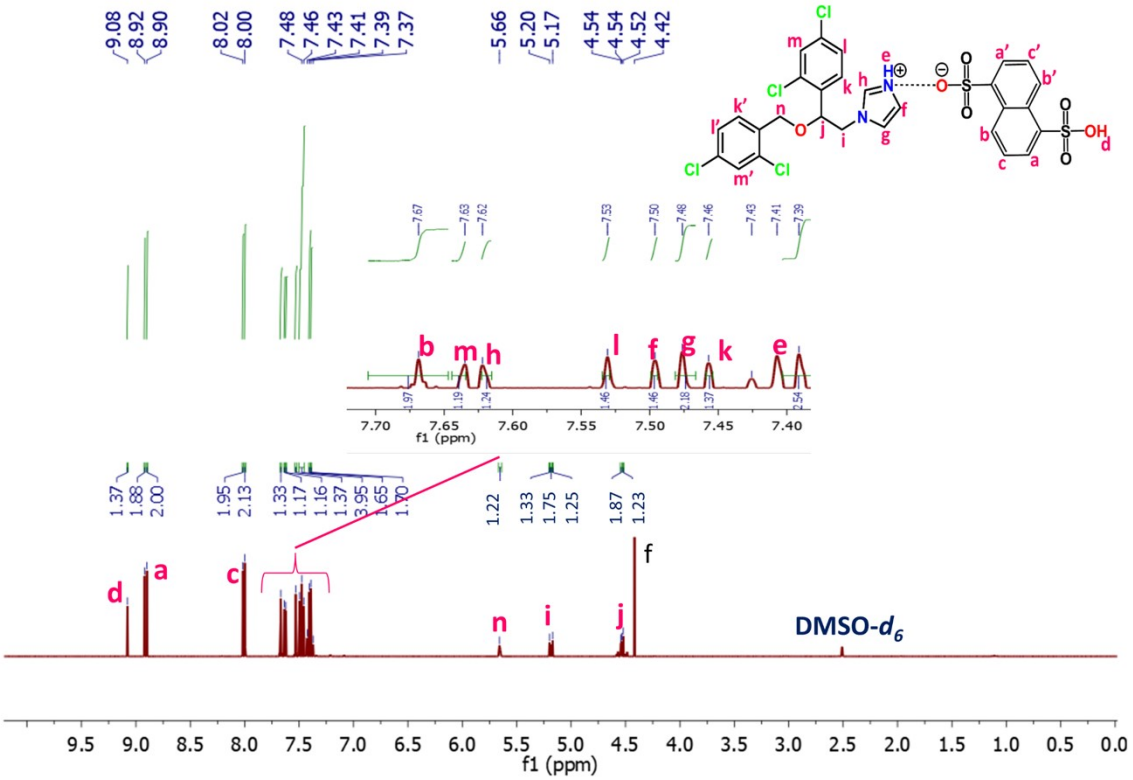

Figure ES2: [1]H-NMR Spectrum of MIC-C reported in DMSO-d_6 at 500 MHz.

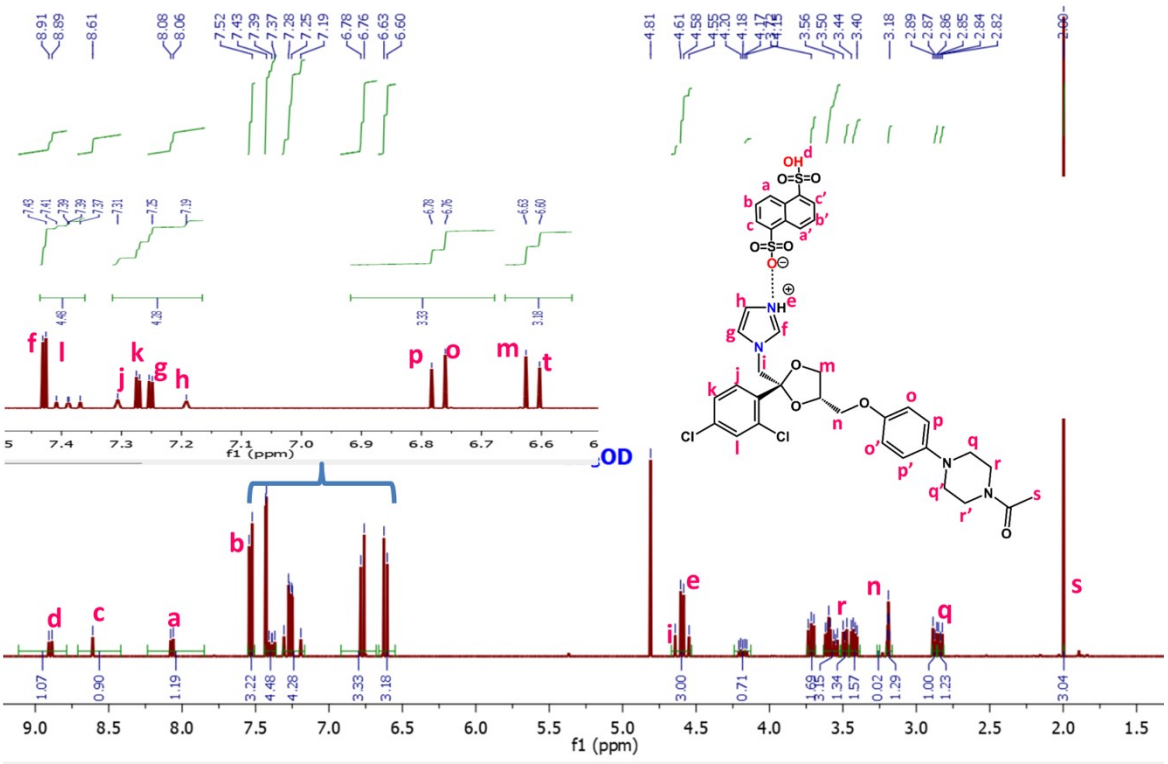

Figure ES3: ^{1}H-NMR Spectrum of KTC-C reported in CD_3OD at 500 MHz.

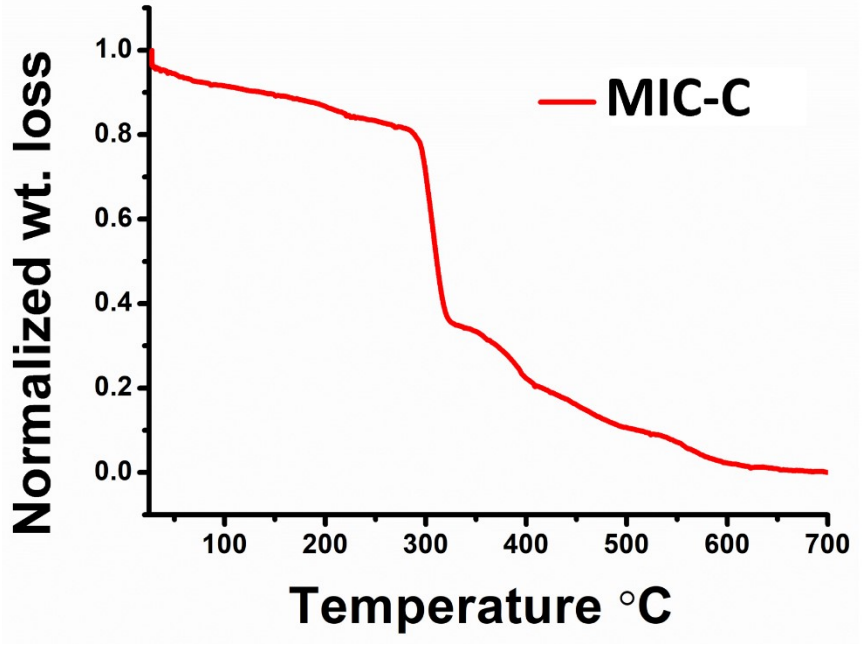

Figure ES4: TGA Profile of MIC-C

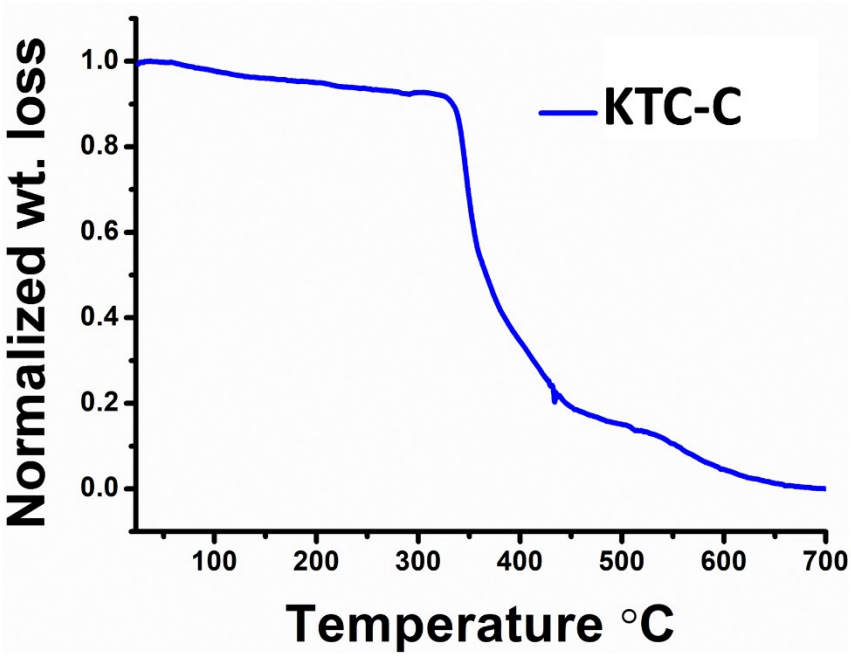

Figure ES5: TGA Profile of KTC-C

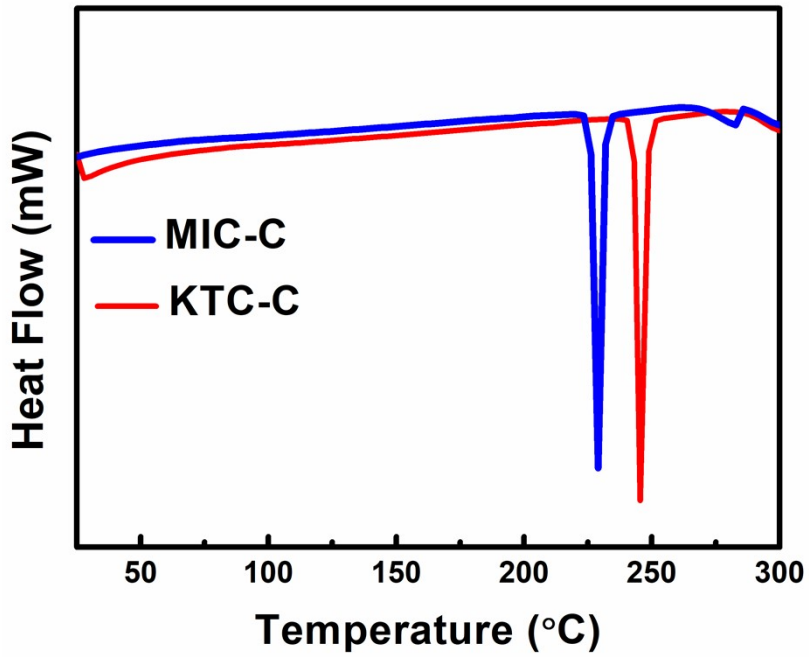

Figure ES6: DSC Curve of MIC-C and KTC-C.

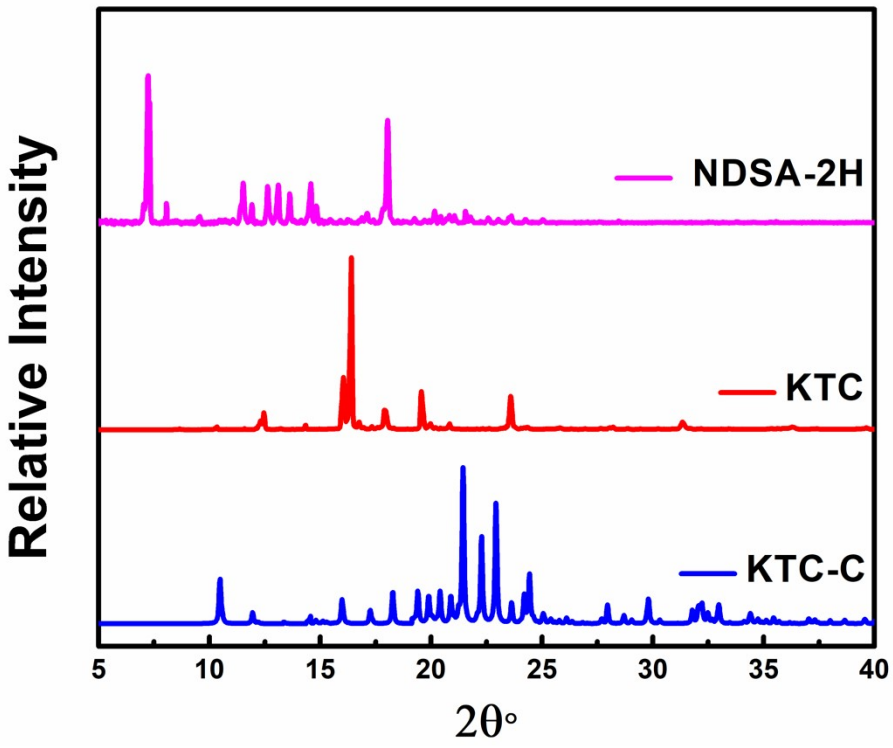

Figure ES7: P-XRD plots of KTC-C compared with precursors KTC and NDSA-2H.

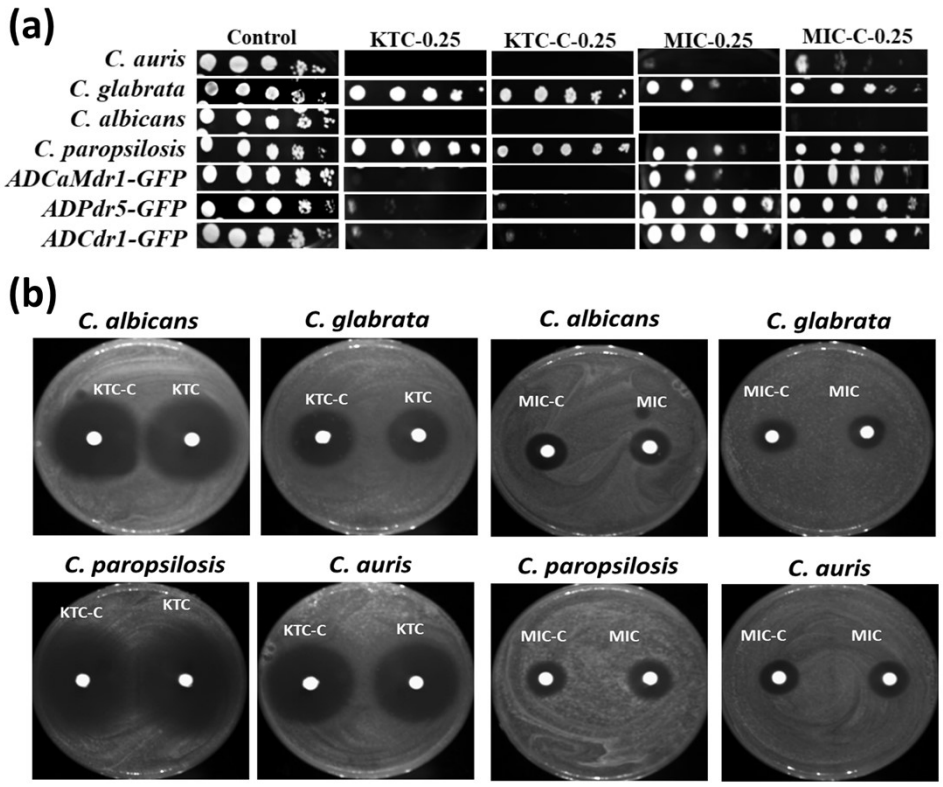

Figure ES8. Drug Susceptibility Assays (A) Spot assay results of different *Candida* and drug transporter over-expressing yeast strains in the presence of MIC, MIC-C, KTC and KTC-C drugs (µg/ml). A fivefold serial dilution of 0.1 OD of each strain was spotted on control and drug-treated plates, and (B) Disk diffusion assay displaying a comparative zone of inhibition of different Wild type *Candida* strains in the presence of MIC, MIC-C, KTC and KTC-C.

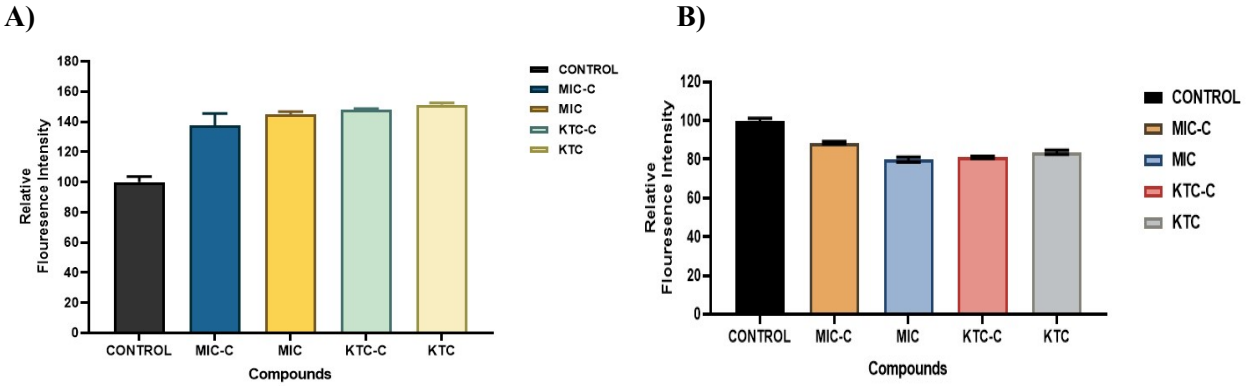

Figure ES9: The effect of compounds (KTC, KTC-C, MIC, and MIC-C) on a) membrane depolarisation and b) on cytoplasmic and cell membrane integrity of *C. albicans* cells. The data are shown as means ± SD.

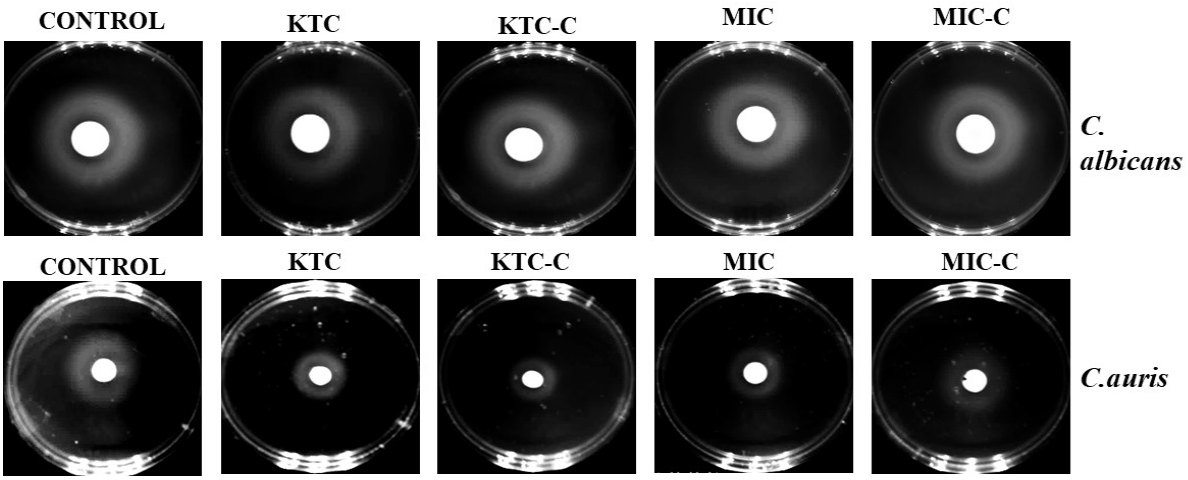

Figure ES10: Proteinase activity determination of *C. albicans* and *C. auris* strains in the presence of MIC, MIC-C, KTC and KTC-C on the solid YBD medium containing yeast extract, BSA, and glucose. The proteinase activity could be seen as the formation of respective zones of protein degradation around each strain. *C. albicans* and *C. auris* WT cells without any drug treatment were taken as respective controls. The proteinase activity (represented in arbitrary units; A.U) of each sample was estimated by dividing the diameter of the precipitation zone plus the colony diameter by the diameter of the colony alone.

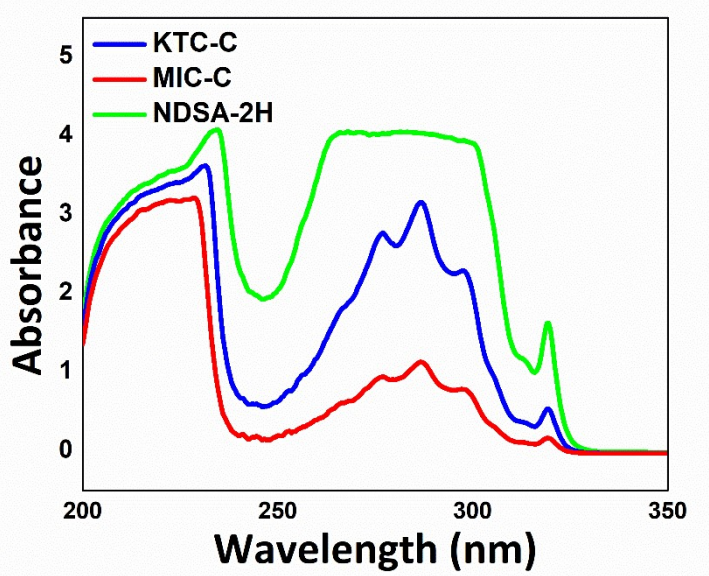

Figure ES11: Solution- based Abs. spectra of salts along with NDSA-2H at pH **2**.

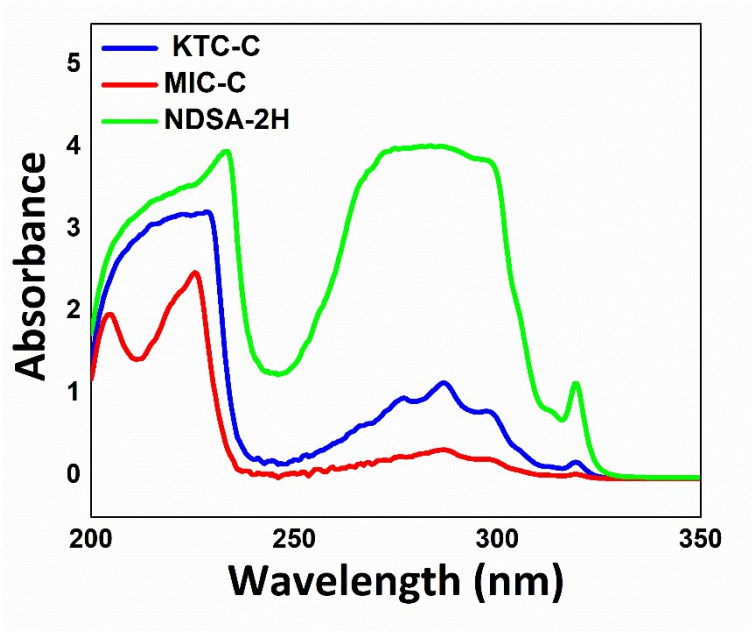

Figure ES12: Solution- based Abs. spectra of salts along with NDSA-2H at pH 7.

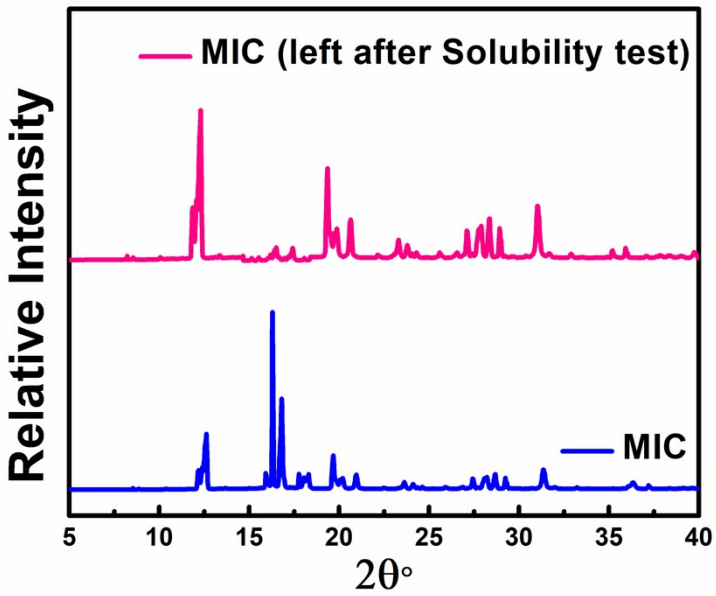

Figure ES13: P-XRD pattern of MIC compared with MIC left after solubility test.

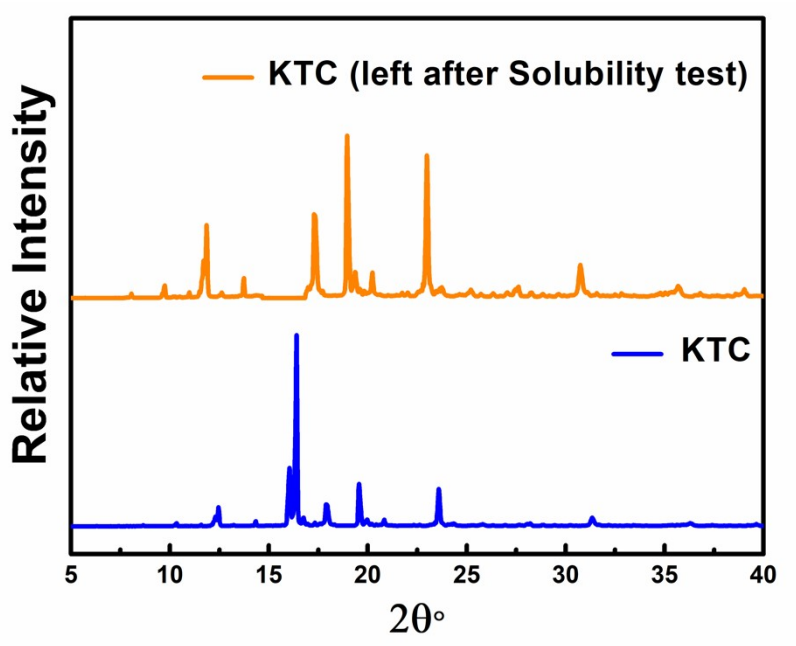

Figure ES14: P-XRD pattern of KTC compared with KTC left after solubility test.

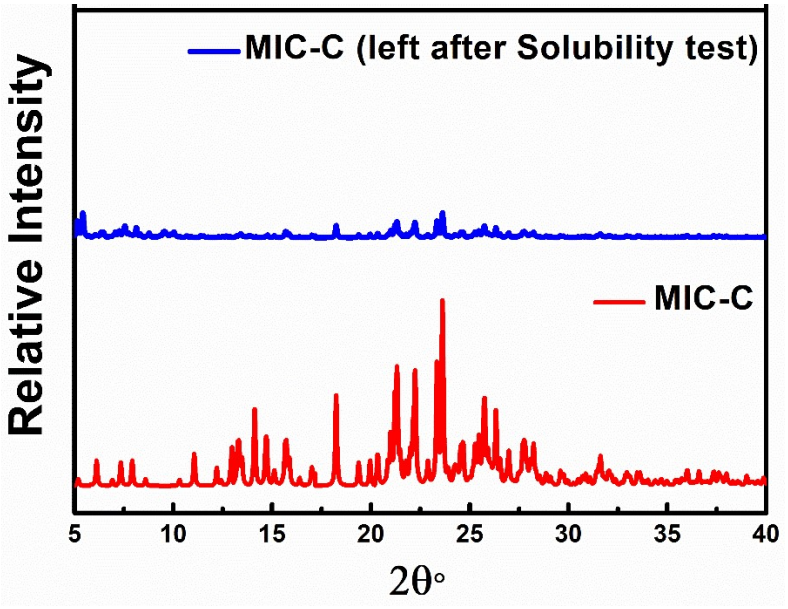

Figure ES15: P-XRD pattern of MIC-C compared with MIC-C left after solubility test.

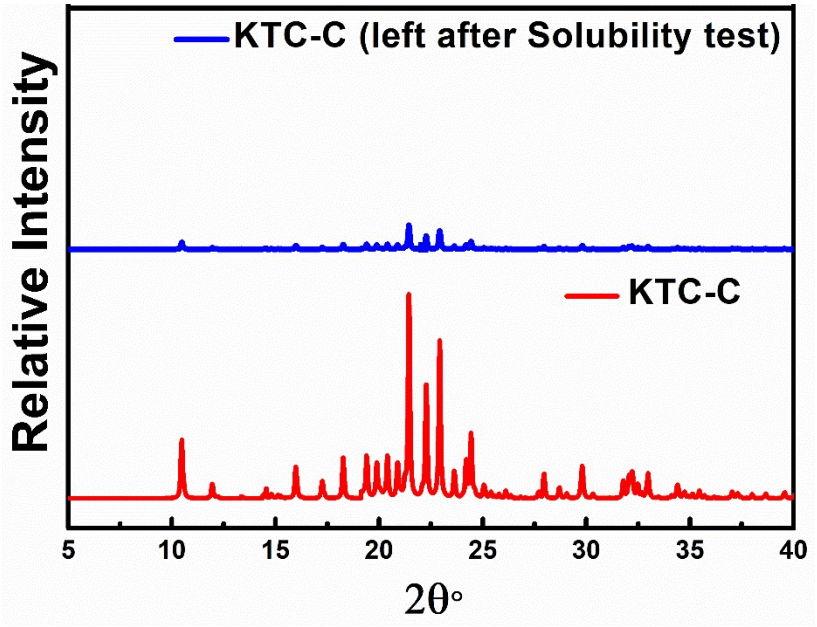

Figure ES16: P-XRD pattern of KTC-C compared with KTC-C left after solubility test.