ANTI-MRSA ACTIVITY OF 1-(4-CHLOROPHENYL)-3-DICHLOROPHENYL- AND 3-TRICHLOROPHENYL-2-(1*H*-IMIDAZOL-1-YL)-2-PROPEN-1-ONE DERIVATIVES

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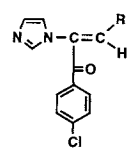
Substituted 1-(4-chlorophenyl)-2-(1*H*-imidazol-1-yl)-2-propen-1-one derivatives (**1**) including the 3-(2,4-dichlorophenyl) analog (**1b**) have been synthesized in our laboratories and found to show significant activities against Gram positive bacteria and fungi[1]. Recently, we synthesized a phenylpyrrole antibiotic, neopyrrolomycin (**2**) and its less chlorinated analogs, and clarified the significance of the dichlorophenyl or trichlorophenyl groups for biological activity including activity against methicillin-resistant *Staphylococcus aureus* species (MRSA)[2~4]. This has renewed interest in the synthesis and biological evaluation of several chlorinated phenyl analogs (**1a~1f**) of **1**, where R at the C-3 position is dichlorophenyl or trichlorophenyl groups.



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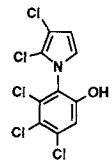

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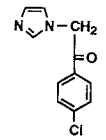

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Herein we report the synthesis and biological activity of the analogs (**1a~1f**) especially against MRSA.

A typical synthetic procedure is as follows[1].

To a hot solution of 2,3-dichlorobenzaldehyde (0.18 g, 1.03 mmol) in dry benzene were added piperidine (0.03 ml), acetic acid (0.012 ml) and then 1-(4-chlorophenyl)-2-(1*H*-imidazol-1-yl)ethanone (**3**: 0.2 g, 0.91 mmol), which was prepared as previously reported (mp 161.5°C)[1]. The resulting solution was refluxed with Dean-Stark trapping for 2 hours and evaporated to a residue, which was chromatographed on silica gel column with hexane - EtOAc (2 : 1) to give, after recrystallization from toluene, colorless crystals of **1a** (0.63 g) in 99%

Table 1. Melting points and ^{1}H NMR spectral data of 2-propen-1-one derivatives (**1a~1f**).

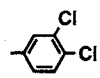
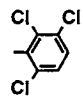
	R	Yield (%)	MP (°C)	^{1}H NMR ($CDCl_3$; δ ppm)
1a		99	133~134	7.76 7.56, 7.48, 7.45, 7.45, 7.44, 7.44, 7.13, 7.06, 6.87, 6.61
1b		91	134	7.73, 7.58~7.38, 7.15, 7.08, 6.88, 6.55
1c		86	103.5~104	7.66, 7.46, 7.36, 7.33, 7.26, 7.09, 6.89, 6.65
1d		93	111~111.5	7.66, 7.46, 7.45, 7.36, 7.27, 6.89, 6.80
1e		89	150~150.5	7.74, 7.48, 7.43, 7.16, 6.87, 6.60
1f		91	146.5~147.5	7.88, 7.47, 7.42, 7.36, 7.29, 7.06, 7.00, 6.76

Table 2. Antibacterial and antifungal activities of 2-propen-1-one derivatives (**1a**～**1f**)[a].

Test organism	MIC (μg/ml)					
	1a	**1b**	**1c**	**1d**	**1e**	**1f**
Staphylococcus aureus FDA209P	1.56	1.56	1.56	0.78	0.78	6.25
S. aureus Smith	1.56	1.56	3.12	1.56	0.78	6.25
Methicillin-resistant *S. aureus* No. 5	3.12	1.56	3.12	3.12	0.78	12.5
Methicillin-resistant *S. aureus* No. 17	3.12	1.56	1.56	3.12	1.56	12.5
Micrococcus luteus FDA16	3.12	0.78	1.56	1.56	1.56	0.78
Escherichia coli NIHJ	>50	>50	1.56	25	>100	>100
Candida pseudotropicalis F-2	3.12	1.56	<0.78	1.56	3.12	>50
C. albicans 3147	25	12.5	12.5	12.5	>50	>50
Cryptococcus neoformans F-10	3.12	0.78	0.78	3.12	3.12	3.12
Trichophyton asteroides 429	3.12	1.56	12.5	1.56	3.12	25

[a] MIC values were determined by agar dilution method using Mueller-Hinton agar for antibacterial tests with incubation at 37°C for 18 hours and a nutrient agar and 1% glucose for antifungal tests with incubation at 27°C for 42 hours.

yield: mp 133～134°C. The *E*-configuration was deduced from our previously reported X-ray crystallographic analysis of **1**[1].

Several chlorinated benzaldehydes (2,4-dichloro-, 3,4-dichloro-, 3,5-dichloro-, 2,3,5-trichloro- and 2,3,6-trichloro-benzaldehydes) were used for the aforesaid reaction in place of 2,3-dichlorobenzaldehyde to give the corresponding 2-propen-1-one derivatives (**1a**～**1f**) in high yields as shown in Table 1.

The biological activities of the compounds (**1a**～**1f**) against Gram-positive bacteria and fungi are shown in Table 2. All compounds except the 2,3,6-trichlorophenyl derivative (**1f**) exhibited similar good activity even against MRSA.

Now that 3-dichlorophenyl- and 3-trichlorophenyl-2-propen-1-one derivatives (**1a**～**1f**) have been readily synthesized and shown to have good activity, the industrial and clinical investigations are in due course.

Acknowledgments

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