SYNTHESIS AND ANTIBACTERIAL ACTIVITIES OF LESS CHLORINATED ANALOGS OF NEOPYRROLOMYCIN

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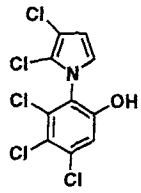
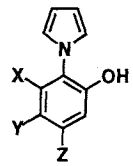
Neopyrrolomycin (**1**) isolated from cultured broth of *Streptomyces* sp. is an optically active and structurally unique phenylpyrrole antibiotic.[1] Very recently, (+)- and (−)-neopyrrolomycins (**1**)[2] and their analogs[3] were synthesized from 3,5-dichloroanisole in our laboratories.[4] Herein we report the synthesis of a variety of less chlorinated analogs (**2**～**14**) and their structure-activity relationship.

All analogs (**2**～**14**) were synthesized from 2-aminoanisoles **15a**～**15d** by our procedures as reported previously.[2~4] The compound **15a** (oil) was prepared from 3,5-dichlorophenol by nitration with fum. HNO_3 in AcOH successively followed by methylation with Me_2SO_4 to give **24** (mp 72～74°C) and reduction on Pd-C in 34% yield. Compound **15b** (oil) was prepared from **25**[5] by reduction with $Na_2S_2O_4$ in 58% yield. Both compounds **15c** and **15d** are commercially available.

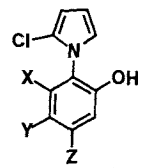
Reaction of **15a**～**15d** with 2,5-dimethoxytetrahy-



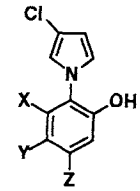
1: Neopyrrolomycin



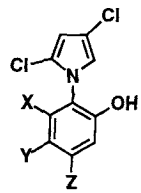
2: X = Z = Cl, Y = H
3: X = Cl, Y = Z = H
4: Y = Cl, X = Z = H
5: X = Y = Z = H



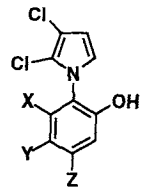
6: X = Z = Cl, Y = H
7: X = Cl, Y = Z = H



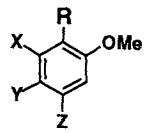
8: X = Cl, Y = Z = H
9: X = Y = Z = H



10: X = Cl, Y = Z = H
11: Y = Cl, X = Z = H
12: X = Y = Z = H



13: X = Z = Cl, Y = H
14: X = Cl, Y = Z = H



a: X = Z = Cl, Y = H
b: X = Cl, Y = Z = H
c: Y = Cl, X = Z = H
d: X = Y = Z = H

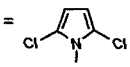
15: R = NH_2

16: R =

17: R =

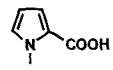
18: R =

19: R =



20: R =

21: R =



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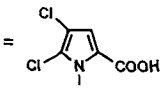
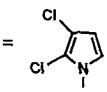
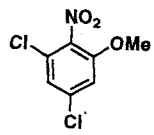
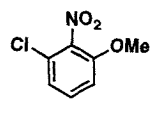


23: R =





24



25

Table 1. Antibacterial and antifungal activities of neopyrrolomycin analogs.[a]

Test organism	MIC (μg/ml)						
	1[b]	**2**	**3**	**4**	**5**	**6**	**7**
Citrobacter freundii IFO 12681	50	>50	>50	>100	>100	>50	>50
Enterobacter cloacae IFO 12935	25	1.56	>50	100	100	12.5	>50
Escherichia coli NIHJ JC-2	50	1.56	>50	100	100	12.5	>50
Klebsiella pneumoniae IFO 3317	12.5	0.10	12.5	25	25	0.78	25
Proteus vulgaris GN 5298	25	0.78	>50	100	100	3.13	>50
Pseudomonas aeruginosa IFO 3445	50	>50	>50	>100	>100	>50	>50
Serratia marcescens 3759	50	>50	>50	100	>100	>50	>50
Streptococcus epidermidis IFO 13889	0.39	3.13	>50	100	>100	1.56	50
Enterococcus faecalis IFO 12964	0.78	25	>50	100	>100	3.13	>50
E. faecium IFO 12367	0.20	25	>50	50	>100	1.56	50
Staphylococcus aureus IFO 12732	0.20	0.78	>50	50	>100	1.56	50
Methicillin-resistant *S. aureus* 4[c]	0.20	0.78	>50	50	>100	0.78	50
Methicillin-resistant *S. aureus* 69[c]	0.20	1.56	>50	50	>100	1.56	50
Candida albicans IFO 1269	3.13	25	>50	50	>100	12.5	>50
C. albicans IFM 40009	6.25	25	>50	50	>100	12.5	>50
Cryptococcus neoformans TIMM 0354	0.39	3.13	25	12.5	50	1.56	12.5
C. neoformans TIMM 0362	≤0.20	3.13	25	6.25	25	1.56	6.25
Aspergillus fumigatus TIMM 0063[d]	6.25	6.25	50	6.25	50	6.25	50
A. fumigatus IMF 4942[d]	6.25	12.5	50	12.5	100	6.25	50

Test organism	MIC (μg/ml)						
	8	**9**	**10**	**11**	**12**	**13**	**14**
Citrobacter freundii IFO 12681	>50	>50	>12.5	>50	>50	100	>100
Enterobacter cloacae IFO 12935	>50	>50	>12.5	>50	>50	12.5	100
Escherichia coli NIHJ JC-2	>50	>50	>12.5	>50	>50	12.5	100
Klebsiella pneumoniae IFO 3317	25	50	>12.5	25	25	1.56	25
Proteus vulgaris GN 5298	50	>50	>12.5	50	50	3.13	50
Pseudomonas aeruginosa IFO 3445	>50	>50	>12.5	>50	>50	100	>100
Serratia marcescens 3759	>50	>50	>12.5	>50	>50	50	>100
Streptococcus epidermidis IFO 13889	50	50	12.5	6.25	12.5	0.78	6.25
Enterococcus faecalis IFO 12964	50	>50	12.5	6.25	50	0.78	6.25
E. faecium IFO 12367	25	50	6.25	1.56	50	0.39	6.25
Staphylococcus aureus IFO 12732	50	50	12.5	6.25	12.5	0.39	6.25
Methicillin-resistant *S. aureus* 4[c]	25	50	6.25	3.13	12.5	0.20	6.25
Methicillin-resistant *S. aureus* 69[c]	50	50	12.5	6.25	12.5	0.20	6.25
Candida albicans IFO 1269	50	50	12.5	6.25	50	6.25	12.5
C. albicans IFM 40009	50	25	12.5	6.25	50	6.25	25
Cryptococcus neoformans TIMM 0354	6.25	3.13	3.13	1.56	6.25	0.39	3.13
C. neoformans TIMM 0362	6.25	6.25	3.13	1.56	6.25	0.39	3.13
Aspergillus fumigatus TIMM 0063[d]	25	6.25	12.5	6.25	6.25	3.13	12.5
A. fumigatus IMF 4942[d]	25	6.25	12.5	6.25	12.5	6.25	12.5

[a] MIC values were determined by an agar dilution method using mueller Hinton agar for antibacterial tests with incubation at 37°C for 18 hours and a Sabouraud Dextrose agar for antifungal tests with incubation at 30°C for 24 hours.

[b] K salt.

[c] Clinical isolate.

[d] Incubation: 48 hours.

Table 2. ^{1}H NMR data of neopyrrolomycin analogs.

No	δ ppm
2	5.35 (2H, brs), 6.43 (2H, t, J=2 Hz), 6.70 (2H, t, J=2 Hz), 7.00 (1H, d, J=2 Hz), 7.10 (1H, d, J=2 Hz)
3	5.23 (1H, s), 6.44 (2H, t, J=2 Hz), 6.73 (2H, t, J=2 Hz), 6.95 (1H, dd, J=8, 2 Hz), 7.05 (1H, dd, J=8, 2 Hz), 7.25 (1H, t, J=8 Hz)
4	5.28 (1H, s), 6.40 (2H, t, J=2 Hz), 6.85 (2H, t, J=2 Hz), 6.97 (1H, d, J=9 Hz), 7.25 (2H, m)
5	5.27 (1H, s), 6.38 (2H, t, J=2 Hz), 6.83 (2H, t, J=2 Hz), 7.00 (2H, m), 7.27 (2H, m)
6	5.35 (1H, brs), 6.33 (2H, m), 6.60 (1H, m), 7.01 (1H, d, J=2 Hz), 7.10 (1H, d, J=2 Hz)
7	5.18 (1H, s), 6.37 (2H, m), 6.67 (1H, m), 7.00 (1H, dd, J=8, 2 Hz), 7.31 (1H, t, J=8 Hz)
8	5.15 (1H, s), 6.36 (1H, m), 6.63 (2H, m), 6.93 (1H, dd, J=8, 2 Hz), 7.03 (1H, dd, J=8, 2 Hz), 7.25 (1H, t, J=8 Hz)
9	5.22 (1H, s), 6.33 (1H, m), 6.77 (2H, m), 7.03 (2H, m), 7.23 (2H, m)
10	5.30 (1H, s), 6.28 (1H, d, J=2 Hz), 6.63 (1H, d, J=2 Hz), 6.98 (1H, dd, J=8, 2 Hz), 7.08 (1H, dd, J=8, 2 Hz), 7.33 (1H, t, J=8 Hz)
11	5.25 (1H, brs), 6.23 (1H, d, J=2 Hz), 6.68 (1H, d, J=2 Hz), 6.98 (1H, d, J=9 Hz), 7.18 (1H, d, J=2 Hz), 7.30 (1H, dd, J=9, 2 Hz)
12	5.12 (1H, s), 6.25 (1H, d, J=2 Hz), 6.72 (1H, d, J=2 Hz), 7.07 (3H, m), 7.38 (1H, m)
13	5.68 (1H, brs), 6.38 (1H, d, J=4 Hz), 6.58 (1H, d, J=4 Hz), 7.02 (1H, d, J=2 Hz), 7.11 (1H, d, J=2 Hz)
14	5.45 (1H, s), 6.40 (1H, d, J=4 Hz), 6.63 (1H, d, J=4 Hz), 6.98 (1H, dd, J=8, 2 Hz), 7.08 (1H, dd, J=8, 2 Hz), 7.32 (1H, t, J=8 Hz)

drofuran gave the corresponding pyrroles **16a**~**16d**. **16a**: 64%, mp 86~90°C; **16b**: 90%, mp 80~82°C; **16c**: 75%, oil; **16d**: 50%, oil. De-*O*-methylation of **15a**~**15d** with $AlCl_3$ in benzene led to the neopyrrolomycin analogs **2**~**5**. **2**: 84%, mp 68~69°C; **3**: 91%, mp 89~92°C; **4**: 77%, oil; **5**: 86%, oil.

Selective chlorination of **16a**~**16d** with *N*-chlorosuccinimide (NCS) in DMF at room temperature provided **17a** and **17c** exclusively but mixtures of **17b** and **18b**, and **17d** and **18d**. **17a**: 56%, oil; **17b**: 55%, oil; **18b**: 13%, oil; **17c**: 68%, mp 53~55°C; **17d**: 43%, oil; **18d**: 5%, oil. De-*O*-methylation of **17a** and **17b** with $AlCl_3$ gave **6** and **7**, respectively. **6**: 33%, oil; **7**: 98%, mp 55°C (dec). Similar deprotection of **18b** and **18d** yielded **8** and **9**, respectively. **8**: 85%, mp 70~72°C; **9**: 78%, oil.

Further chlorination of **17b**~**17d** with NCS in DMF at 50°C followed by de-*O*-methylation produced the 2,4-dichloropyrrole derivatives **10**, **11** and **12** through the migration of a chlorine atom.[3,4] **10**: 40%, oil; **11**: 56%, mp 72~74°C; **12**: 50%, oil.

Regioselective bromination of **16a** and **16b** with *N*-bromosuccinimide in DMF at room temperature gave **20a** and **20b**. **20a**: 90%, oil; **20b**: 68%, oil. Lithiation with *n*-BuLi followed by treatment with CO_2 gas gave the carboxylic acids **21a** and **21b**, which were chlorinated by trichloroisocyanuric acid[2~4] to give **22a** and **22b**, respectively. **22a**: 83%, mp 215~217°C; **22b**: 70%, mp 205~208°C. These products were decarboxylated by heating with Cu powder in quinoline, followed by de-*O*-methylation with $AlCl_3$ in benzene, to afford the neopyrrolomycin analogs **13** and **14**. **13**: 40%, oil; **14**: 70%, oil.

All analogs **2**~**14** showed antibacterial and/or antifungal activities as shown in Table 1. Remarkably, the simple 3,5-dichlorophenol analog **2** showed strong antibacterial activities against Gram-positive and -negative bacteria, but analogs **3**, **4** and **5** showed little activities. Also, the 3,5-dichlorophenol analogs **6** and **13** displayed stronger activities than the corresponding 3-chlorophenol analogs **7** and **14**. These findings suggest that the chlorine atom at the C-5 position of the benzene ring is essential for appearance of strong antibacterial activities.

The ^{1}H NMR (90 MHz, $CDCl_3$) of the target molecules (**2**~**14**) are summarized in Table 2.

Acknowledgments

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References

1) NOGAMI, T.; Y. SHIGIHARA, N. MATSUDA, Y. TAKAHASHI, H. NAGANAWA, H. NAKAMURA, M. HAMADA, Y. MURAOKA, T. TAKITA, Y. IITAKA & T. TAKEUCHI: Neopyrrolomycin, a new chlorinated phenylpyrrole antibiotic. J. Antibiotics 43: 1192~1194, 1990

2) TATSUTA, K. & M. ITOH: Total synthesis of chlo-

rinated phenylpyrrole antibiotics, (+)- and (−)-neopyrrolomycins. Tetrahedron Lett. 34: 8443～8444, 1993

3) TATSUTA, K. & M. ITOH: Synthesis and biological evaluation of neopyrrolomycin analogs. J. Antibiotics 47: 262～265, 1994

4) TATSUTA, K. & M. ITOH: Total synthesis of (+)- and (−)-neopyrrolomycins, chlorinated phenylpyrrole antibiotics. Bull. Chem. Soc. Jpn., in press.

5) KIMURA, T.; N. WATANABE, M. MATSUI, K. HAYASHI, H. TANAKA, I. OHTSUKA, T. SAEKI, M. KOGUSHI, H. KABAYASHI, K. AKASAKA, Y. YAMAGISHI, I. SAITOU & I. YAMATSU: Structure-activity relationship of a series of phenylureas linked to 4-phenylimidazole. Novel potent inhibitors of acyl-CoA: Cholesterol O-acyltransferase with antiatherosclerotic activity. 2. J. Med. Chem. 36: 1641～1653, 1993