Communications to the Editor

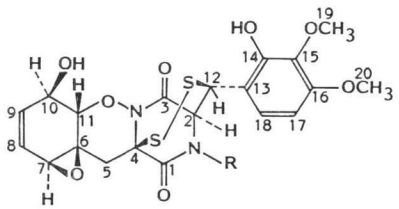
STRUCTURE OF FA-2097, A NEW MEMBER OF THE DIOXOPIPERAZINE ANTIBIOTICS

Sir:

An antibiotic gliovirin ($C_{20}H_{20}N_2O_5S_2$) produced by *Gliocladium virens,* is selectively active against members of the Oomycetes.[1] The structure of gliovirin has been established by NMR, mass spectral and X-ray crystallographic analysis as that depicted in Fig. 1. This demonstrated gliovirin to be a new member of the antibiotics containing a dioxopiperazine ring.[2] We have also reported the isolation, characterization and biological properties of a new antibiotic, FA-2097 (Ro 09-0542, $C_{21}H_{22}N_2O_5S_2$) characterized as a novel dioxopiperazine antibiotic by IR, NMR and mass spectroscopy.[3] By comparison of the spectroscopic properties of gliovirin and FA-2097, the structure of FA-2097 was established as *N*-methylgliovirin. In this communication, we describe the structural elucidation of FA-2097.

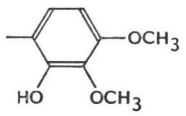
The UV spectrum of FA-2097 was almost identical to that of gliovirin,[2,3] indicating the presence in FA-2097 of the same chromophore (partial structure **3** in Fig. 2) as in gliovirin. This structure was also confirmed by the ^1H and ^{13}C NMR spectra of FA-2097 (Tables 1 and 2): ^1H NMR δ 3.69, 3.79 ($OCH_3 \times 2$), 6.56 (d, J=8.8 Hz, 1H), 7.32 (d, J=8.8 Hz, 1H); ^{13}C NMR δ 55.7 (q), 60.2 (q), 103.3 (d), 115.8 (s), 122.2 (d), 136.0 (s), 147.7 (s), 153.2 (s). Other signals in the ^1H and ^{13}C NMR spectra of FA-2097 were also observed at chemical shifts similar to those of gliovirin, except for an additional signal at δ 2.99 (s, 3H) in the ^1H NMR and one at δ 32.9 (q) in the ^{13}C NMR spectra of FA-2097, which are assignable to an *N*-methyl moiety. This observation suggested that FA-2097 was *N*-methylgliovirin, being consistent with the difference in molecular formula between gliovirin ($C_{20}H_{20}N_2O_5S_2$) and FA-2097 ($C_{21}H_{22}N_2O_5S_2$). This was supported by detailed analyses of the ^1H NMR spectrum of FA-2097 diacetate and the

Fig. 1.



Gliovirin (**1**) R=H
FA-2097 (**2**) R=CH_3

Fig. 2.



Partial structure **3**

Table 1. ^1H NMR data of gliovirin and FA-2097 in DMSO-d_6 with D_2O.

Proton	Gliovirin	FA-2097
2-CH	4.45 (d, J=1.4 Hz, 1H)	4.65 (d, J=1.5 Hz, 1H)
5-CH_2	2.57 (bs, 2H)	2.61 (d, J=13.9 Hz, 1H) 2.71 (d, J=13.9 Hz, 1H)
7-CH	3.10 (d, J=2 Hz, 1H)	3.13 (d, J=2.4 Hz, 1H)
8-=CH	5.87 (bd, J=10.8 Hz, 1H)	5.88 (bd, J=10.4 Hz, 1H)
9-=CH	5.76 (d, J=10.8 Hz, 1H)	5.75 (d, J=10.4 Hz, 1H)
10, 11-CH	4.27 (bs, 2H)	4.29 (bs, 2H)
12-CH	4.43 (d, J=1.4 Hz, 1H)	4.48 (d, J=1.5 Hz, 1H)
17-=CH	6.55 (d, J=8.9 Hz, 1H)	6.56 (d, J=8.8 Hz, 1H)
18-=CH	7.41 (d, J=8.9 Hz, 1H)	7.32 (d, J=8.8 Hz, 1H)
19 (20)-CH_3	3.65 (s, 3H)	3.69 (s, 3H)
20 (19)-CH_3	3.77 (s, 3H)	3.79 (s, 3H)
NCH_3		2.99 (s, 3H)

Chemical shifts are given in ppm (δ values) from internal TMS.

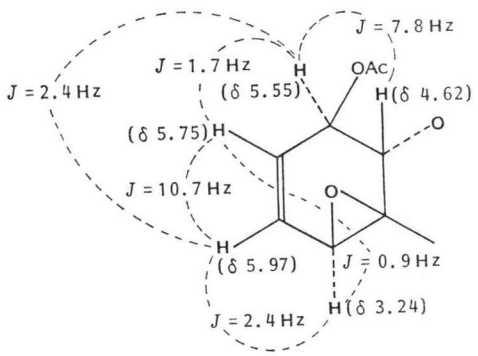
Table 2. ^{13}C NMR data of gliovirin and FA-2097 in DMSO-d_6.

Carbon	Gliovirin*	FA-2097*
1 (3)	163.1 s	161.9 s
3 (1)	166.1 s	164.2 s
2	60.1† d	66.6 d
4	70.3 s	70.0 s
5	33.4 t	33.5 t
6	58.0 s	57.7 s
7	52.7† d	52.4 d
8	122.7 d	122.8 d
9	138.2 d	138.0 d
10	66.0 d	65.8 d
11	86.2 d	85.8 d
12	43.9 d	40.2 d
13	116.0 s	115.8 s
14	148.1 s	147.7 s
15	136.2 s	136.0 s
16	153.5 s	153.2 s
17	103.7 d	103.3 d
18	123.1 d	122.2 d
19	60.4 q	60.2 q
20	55.9 q	55.7 q
NCH_3		32.9 q

* Chemical shifts are given in ppm (δ values) downfield from TMS as an internal standard.

† Selective heteronuclear decoupling experiments have allowed the reassignment of the chemical shifts for these carbons.

Fig. 3.



Partial structure **4**

^{13}C NMR spectrum of FA-2097. The ^1H NMR spectrum of FA-2097 diacetate in $CDCl_3$ showed the presence of a ring structure (partial structure **4**) as shown in Fig. 3. Comparison of the ^{13}C NMR spectrum of FA-2097 with that of gliovirin showed that resonances of C-2 and C-12 carbons were displaced 6.5 ppm downfield (at δ 66.6 ppm) and 3.7 ppm upfield (at δ 40.2 ppm), respectively, from that of gliovirin. These shifts are consistent with the deshielding of nitrogen caused by *N*-methylation and the shielding caused by steric interaction between the *N*-methyl group and the C-12 hydrogen, respectively.

In order to compare the absolute configuration of gliovirin and FA-2097 both the optical rotations (measured on a Perkin-Elmer Model 241 polarimeter) and the rotatory dispersion curves (recorded on Cary Model 60) were determined. Gliovirin: $[\alpha]_D^{25}-97°$, $[\alpha]_{578}^{25}-102°$, $[\alpha]_{546}^{25}-117°$, $[\alpha]_{436}^{25}-197°$, $[\alpha]_{365}^{25}-263°$ (*c* 0.035, MeOH). FA-2097: $[\alpha]_D^{25}-208°$, $[\alpha]_{578}^{25}-219°$, $[\alpha]_{546}^{25}-251°$, $[\alpha]_{436}^{25}-462°$, $[\alpha]_{365}^{25}-825°$ (*c* 0.034, MeOH). Gliovirin: ORD (*c* 6.7×10^{-4}, MeOH) 25°, $[\phi]_{300}-1.13°\times10^4$, $[\phi]_{275}-3.75°\times10^4$, $[\phi]_{255}-1.50°\times10^4$, $[\phi]_{245}-2.6°\times10^4$, $[\phi]_{220}+3.0°\times10^4$. FA-2097: ORD (*c* 6.9×10^{-4}, MeOH) 25°, $[\phi]_{300}-2.3°\times10^4$, $[\phi]_{275}-4.0°\times10^4$, $[\phi]_{255}-1.2°\times10^4$, $[\phi]_{237}-3.0°\times10^4$, $[\phi]_{220}+2.5°\times10^4$. Due to the close similarity in optical properties between these two compounds we conclude that the absolute stereochemistry at the asymmetric centers of FA-2097 is identical with that of gliovirin. Thus, the structure of FA-2097 (Ro 09-0542) is determined to be *N*-methylgliovirin as shown in Fig. 1.

Acknowledgment

The authors wish to thank Miss Y. KODAMA for the NMR spectral data and Mr. T. KAMIYAMA for his technical assistance.

KAZUTERU YOKOSE
NOBORU NAKAYAMA
CHIKARA MIYAMOTO
TAMOTSU FURUMAI
HIROMI B. MARUYAMA

Department of Microbiology and Chemotherapy, Nippon Roche Research Center, 200 Kajiwara, Kamakura, Kanagawa 247, Japan

ROBERT D. STIPANOVIC
CHARLES R. HOWELL

U.S. Dept. of Agriculture, Agricultural Research Service, National Cotton Pathology Research Laboratory, P.O. Drawer JF College Station, Texas 77841, U.S.A.

(Received March 22, 1984)

References

1) HOWELL, C. R. & R. D. STIPANOVIC: Gliovirin, a new antibiotic from *Gliocladium virens*, and its role in the biological control of *Pythium ultimum*. Canad. J. Microbiol. 1983: 321~324, 1983
2) STIPANOVIC, R. D. & C. R. HOWELL: The structure of gliovirin, a new antibiotic from *Gliocladium virens*. J. Antibiotics 35: 1326~1330, 1982
3) MIYAMOTO, C.; K. YOKOSE, T. FURUMAI & H. B. MARUYAMA: A new epidithiodiketopiperazine group antibiotic, FA-2097. J. Antibiotics 35: 374~377, 1982