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DIKETOPIPERAZINE DERIVATIVES, A NEW SERIES OF
 PLATELET-ACTIVATING FACTOR INHIBITORS

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Some diketopiperazine derivatives (3a-f, 4a-f, and 5a-c) related to natural products (1 and 2) have been prepared and evaluated for their inhibition of platelet aggregation induced by platelet-activating factor (PAF).

KEYWORDS—diketopiperazine; platelet-activating factor; platelet aggregation; structure-activity relationship

Since the characterization of platelet-activating factor (PAF), an endogeneous mediator in allergic and inflammatory responses, research on PAF antagonists has increased to exploit a new type of agent for treating these diseases.¹⁾ As part of a research program for novel PAF inhibitors in our laboratories, the potent inhibitors bisdethiobis(methylthio)gliotoxin (1) and 3,6-bismethylthio-3-hydroxymethyl-6-phenylmethylpiperazine-2,5-dione (2) were isolated from *Penicillium terlikowskii* No. 5348²⁾ and *Penicillium citrinum* No. 2973,³⁾ respectively. In studying these natural products, we were interested in clarifying their structure-activity relationships to find more active compounds in these series. Both of these products have a diketopiperazine framework and a bis(methylthio) function as common structural units. To design molecules of compounds related to 1 and 2, we removed the C7 methylene (a) and disconnected the

Fig. 1

3a ; X=H , R=Me

3b ; X=Cl , R=Me

3c ; X=OMe, R=Me

3d ; X=H , R=Ph

3e ; X=Cl , R=Ph

3f ; X=OMe, R=Ph

4a ; X=H , R=Me

4b ; X=Cl , R=Me

4c ; X=OMe, R=Me

4d ; X=H , R=Ph

4e ; X=Cl , R=Ph

4f ; X=OMe, R=Ph

5a

5b ; X=H

5c ; X=Cl

Fig. 2

Chart 1

C13-N1 bond (b) in the structure of 1. These chemical variations lead to N-phenyl diketopiperazines (3, type A) and benzyldiketopiperazines (5, type B). The latter precisely corresponds to the structure of 2. Here we report the synthesis of these two compounds and their biological activities.

Compounds 3a,b⁴⁾ of the A type with cis configuration were prepared by a sequence of reactions (1. NBS/mCPBA, 2. AcSK, 3. I₂/HCl, 4. NaBH₄, 5. MeI)⁵⁾ starting from diketopiperazines 6 (X=H, Cl).⁶⁾ Alternatively, compound 3b⁴⁾ was prepared, together with the corresponding trans isomer 4b,⁴⁾ by a direct substitution of bromide 7 (X=Cl) with MeSNa. In the ¹H NMR spectrum of 3b, the diketopiperazine ring protons were by ca 0.25 ppm upfield from the protons of 4b (3b, 4.69, 4.90; 4b, 4.93, 5.14). This phenomenon was observed in general in this series of compounds and utilized in the structural assignment of these compounds. The related cis and trans compounds (3c-f and 4c-f)⁴⁾ were prepared using the direct substitution method.

Compounds of the B type were prepared as follows. Alkylation of diketopiperazine 9⁵⁾ with benzyl bromide (1 equiv/LiNPr₂ⁱ) gave the monobenzyl derivative 10, which was converted, via disulfide 11, to compound 5a⁴⁾ (1. BCl₃, 2. I₂, 3. NaBH₄, 4. MeI). Compounds 5b,c⁴⁾ were obtained from 9 by similar treatment after alkylation using 2 equivalent benzyl bromide and p-chlorobenzyl bromide (2 equiv/LiNPr₂ⁱ, respectively) of 9.

The compounds were evaluated in vitro by inhibition of a PAF-induced rabbit platelet aggregation and the results are summarized in comparison with those of 1 and 2 in Table I. In the compounds of the A type, without exception the cis compounds were more active than the corresponding trans isomers, particularly so in the S-phenyl series of compounds. The S-phenyl derivatives were more active than the corresponding S-methyl derivatives in the cis series, while the activities of the compounds in the trans series were entirely in reverse. Compound 3f was thus the most active in the A type of compounds. The three compounds prepared as the B type were all moderately active, but considerably less so than 3f.

Table I. Inhibitory Activity of Diketopiperazine Derivatives^{a)}

Compound	IC ₅₀ (uM)	Compound	IC ₅₀ (uM)
<u>1</u>	4.0	<u>4b</u>	15.4
<u>2</u>	16.9	<u>4c</u>	8.0
<u>3a</u>	16.9	<u>4d</u>	54.8
<u>3b</u>	7.3	<u>4e</u>	28.8
<u>3c</u>	5.2	<u>4f</u>	42.2
<u>3d</u>	5.2	<u>5a</u>	12.3
<u>3e</u>	1.7	<u>5b</u>	9.7
<u>3f</u>	0.69	<u>5c</u>	8.3

a) IC₅₀ is the concentration of a compound required for 50% inhibition of rabbit platelet aggregation induced by PAF (20 nM).

In conclusion, the most active PAF inhibitor was 3f. It had no effect on platelet aggregations induced by collagen, arachidonic acid, or ADP,⁷⁾ thus proving to be a PAF-specific inhibitor.

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REFERENCES AND NOTES

- 1) For reviews on PAF antagonists, see e.g. a) J.J.Godfroid and P.Braquet, *Trends Pharmacol. Sci.*, **7**, 368(1986); b) P.Braquet and J.J.Godfroid, *Trends Pharmacol. Sci.*, **7**, 397(1986); c) M.N.Chang, *Drugs Future*, **11**, 869(1986).
- 2) M.Okamoto, K.Yoshida, I.Uchida, M.Nishikawa, M.Kohsaka, and H.Aoki, *Chem. Pharm. Bull.*, **34**, 340(1986).
- 3) Unpublished data.
- 4) Physical data of the compounds prepared in the present study:
3a; mp 98-101°C, NMR(4.70 and 4.96). 3b; mp 113-115°C, NMR(2.26(3H,s, S-Me), 2.33(3H,s, S-Me), 3.15(3H,s, N-Me), 4.69(1H,s, H₂ or H₅), 4.70(1H,s, H₅ or H₂), and 7.38(4H,s). 3c; mp 80-83°C, NMR(4.69 and 4.90). 3d; mp 185-186°C, NMR(4.41 and 4.80). 3e; mp 194-196°C, NMR(4.39 and 4.71). 3f; mp 197-198°C, NMR(4.42 and 4.79). 4b; mp 153-155°C, NMR(2.10(3H,s, S-Me), 2.18(3H,s, S-Me), 3.17(3H,s, N-Me), 4.93(1H,s, H₂ or H₅), 5.14(1H,s, H₅ or H₂), 7.25(2H,d,J=8Hz), and 7.43(2H,d,J=8). 4c; mp 167-170°C, NMR(4.96 and 5.14). 4d; mp 147-149°C, NMR(5.10 and 5.33). 4e; mp 147-149°C, NMR(5.04 and 5.26). 4f; mp 172-173°C, NMR(5.06 and 5.25). 5a; mp 118-119°C. 5b; mp 98-99°C, NMR(2.20(6H,s, S-Me), 2.92(2H,d,J=15, benzyl-CH₂), 3.14(6H,s, N-Me), 3.36(2H,d,J=15, benzyl-CH₂), 6.7-7.3(10H,m). 5c; mp 148-150°C, NMR(2.25(6H,s), 2.93(2H,d,J=15), 3.12(6H,s), 3.60(2H,d,J=15), 6.76(4H,d,J=8), and 7.07(4H,d,J=8).
- 5) The syntheses of 4a,b were carried out according to the method adopted for the synthesis of glyotoxin. T.Fukuyama, S.Nakatsuka and Y.kishi, *Tetrahedron* **37**,2045(1981).
- 6) The compounds of 6 were synthesized by Ullmann-type reaction of substituted iodobenzenes and glycine-sarcosine anhydride.
- 7) Details will be reported elsewhere.

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