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Structure–Activity Relationship of a New Series of Tricyclic Monoamine Oxidase Inhibitors of Pentanthrene Type

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This study was undertaken to evaluate the relationship between the structure and monoamine oxidase (MAO) inhibitory activity of a new series of tricyclic compounds, represented by tetrazolo-[5,1-*a*]phthalazine (Tetra-P), which are based on the pentanthrene skeleton (Fig. 1). Eleven tricyclic compounds analogous to Tetra-P were synthesized and tested as MAO inhibitors *in vitro*. Some of them, 1,2,3-triazolo[1,5-*a*]quinoline (Tri-Q), tetrazolo[5,1-*a*]isoquinoline (Tetra-I), 1,2,3-triazolo-[5,1-*a*]isoquinoline (Tri-I_2) and 1*H*-naphtho[1,2-*d*]triazole (Tri-N), were found to have potent MAO inhibitory effects almost equal to that of iproniazid or nialamide. In this series of compounds, the addition of the C ring to the bicyclic skeleton seemed to produce an increase in MAO inhibitory potency compared with the corresponding bicyclic compounds. The sequence of nitrogen atoms of the C ring appeared to be important for the MAO inhibitory effect. It was concluded that the electronic conditions around the C ring are critical for the interaction between MAO and these inhibitors.

Keywords——tetrazolo[5,1-*a*]phthalazine analogue; monoamine oxidase inhibitor; tricyclic compound; quantitative structure–activity relationship; competitive inhibition

In a previous paper, we reported that tetrazolo[5,1-*a*]phthalazine (Tetra-P) was formed from hydralazine, a useful antihypertensive agent, and nitrite ion in human saliva under acidic conditions.[1] Pharmacological tests using mice suggested that Tetra-P had an activity analogous to that of the well-known monoamine oxidase (MAO) inhibitor nialamide. Tetra-P consists of three rings (A, B, C) as shown in Fig. 1 and is a new kind of MAO inhibitor in its chemical structure. In our previous studies[2] several tricyclic compounds structurally analogous to Tetra-P were prepared and examined *in vitro* for inhibitory effects on rat brain mitochondrial MAO. Some of the compounds, Tetra-P, naphtetrazole (NTE), naphtriazole (NTR) and *s*-triazolo[3,4-*a*]phthalazine (Tri-P), were found to be new MAO inhibitors. In particular, NTE showed strong MAO inhibitory potency, almost equal to that of iproniazid. The present study was undertaken to determine the relationship between chemical structure, especially at the C ring, and MAO inhibitory effect in this series of tricyclic compounds. Eleven tricyclic compounds having analogous skeletons with Tetra-P were synthesized and tested for potency *in vitro* as MAO inhibitors. The results are reported here.

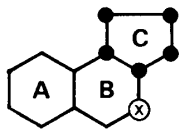


Fig. 1. Skeletal Structure of the Tricyclic Compounds

Materials and Methods

Compounds——All chemicals were of reagent grade, unless otherwise noted. The following compounds were synthesized by modifications of the methods already reported: 1,2,3-triazolo[1,5-*a*]quinoline (Tri-Q),[3] NTE and NTR, *s*-triazolo[3,4-*a*]isoquinoline (Tri-I_1) and tetrazolo[5,1-*a*]isoquinoline (Tetra-I),[4-6] 1,2,3-triazolo[5,1-*a*]isoquinoline (Tri-I_2).[3,7] Tetra-P and Tri-P were synthesized according to Haegele *et al.*[8] with some modification. 3*H*-Benz[*e*]indole (4,5-BI) and 1*H*-benz[*g*]indole (6,7-BI) were obtained according to Vorozhtsov and Kutkevichus[9] and Pennington *et al.*[10] 1*H*-Naphth[1,2-*d*]imidazole (Imi-N) and 1*H*-naphtho[1,2-*d*]triazole (Tri-N) were obtained according to the literature.[11-13] Each structure was identified on the basis of melting point, elemental analyses, and infrared, mass and nuclear magnetic resonance spectra.

MAO Inhibitory Test *in Vitro*——Rat brain mitochondria were prepared by the method of Johnston.[14] MAO activity in rat brain mitochondria was assayed fluorometrically by using *p*-sulfamoylbenzylamine and benzylamine as the substrates of MAO-A and MAO-B, respectively, according to Nohta *et al.*[15] The MAO inhibitory potency of each compound was evaluated in terms of I_{50} value, the concentration of the compound required to cause 50% inhibition of the MAO activity.

Results and Discussion

Iproniazid and nialamide, which are potent MAO inhibitors, were used as reference standards in this investigation. Since all compounds tested showed nonselective inhibition of MAO-A and MAO-B, only the data for MAO-B are presented in this paper. The compounds could be classified into four groups: (A) quinoline group, (B) isoquinoline group, (C) phthalazine group, (D) naphthalene group according to their A and B rings (Fig. 1).

Figure 2 shows MAO inhibition curves obtained for iproniazid, nialamide, the bicyclic compounds and the tricyclic compounds synthesized this time. It is found that some of the new tricyclic compounds such as Tri-Q, Tetra-I, Tri-I_2 and Tri-N have potent MAO inhibitory effects almost equal to that of iproniazid or nialamide. The I_{50} values of all compounds were calculated from the corresponding MAO inhibition curves and are summarized in Table I.

Firstly, in the quinoline group (Table I(A)), the I_{50} values of Tri-Q, NTE and NTR were observed to be lower than that of quinoline, indicating greater inhibitory potency than that of quinoline. Tricyclic compounds of the isoquinoline group (Table I(B)) and the phthalazine group (Table I(C)) also showed stronger MAO inhibitory effects than the corresponding bicyclic compounds, except for Tri-I_1. In the naphthalene group (Table I(D)), although naphthalene itself had no potency, 6,7-BI, 4,5-BI, Imi-N and Tri-N showed remarkable MAO inhibitory potency. That is to say, the addition of the C ring to the bicyclic skeleton produced an increase in MAO inhibitory potency in this series of compounds.

Secondly, Table I(A) shows that the I_{50} values of Tri-Q and NTE were 1/16 and 1/20 of that of NTR, respectively. In the case of Tri-Q or NTE, the C ring contains a continuous run of three or four nitrogen atoms, while in NTR, the C ring contains three nitrogen atoms, only two of which are directly linked. Similarly, in the isoquinoline group, Tetra-I and Tri-I_2 which have continuous runs of nitrogen atoms in the C ring showed stronger MAO inhibitory potency than Tri-I_1 (Table I(B)). There was a similar tendency in the phthalazine group (Table I(C)). In the naphthalene group (Table I(D)), Tri-N showed a remarkable MAO inhibitory potency compared with 6,7-BI, 4,5-BI and Imi-N, which have one or two nitrogen atoms in the C ring. From these data, it seems that inhibitory effects of compounds that have continuous runs of nitrogen atoms in the C ring were more potent than those of compounds which have discrete nitrogen atoms. That is to say, the sequence of nitrogen atoms in the C ring is important for MAO inhibitory effect.

Thirdly, the nitrogen atom at the x-position shown in Fig. 1 did not play an important role in the MAO inhibitory action (Tetra-P *vs.* Tetra-I, Tri-P *vs.* Tri-I_1).

From the data mentioned above, it was concluded that the electronic conditions around

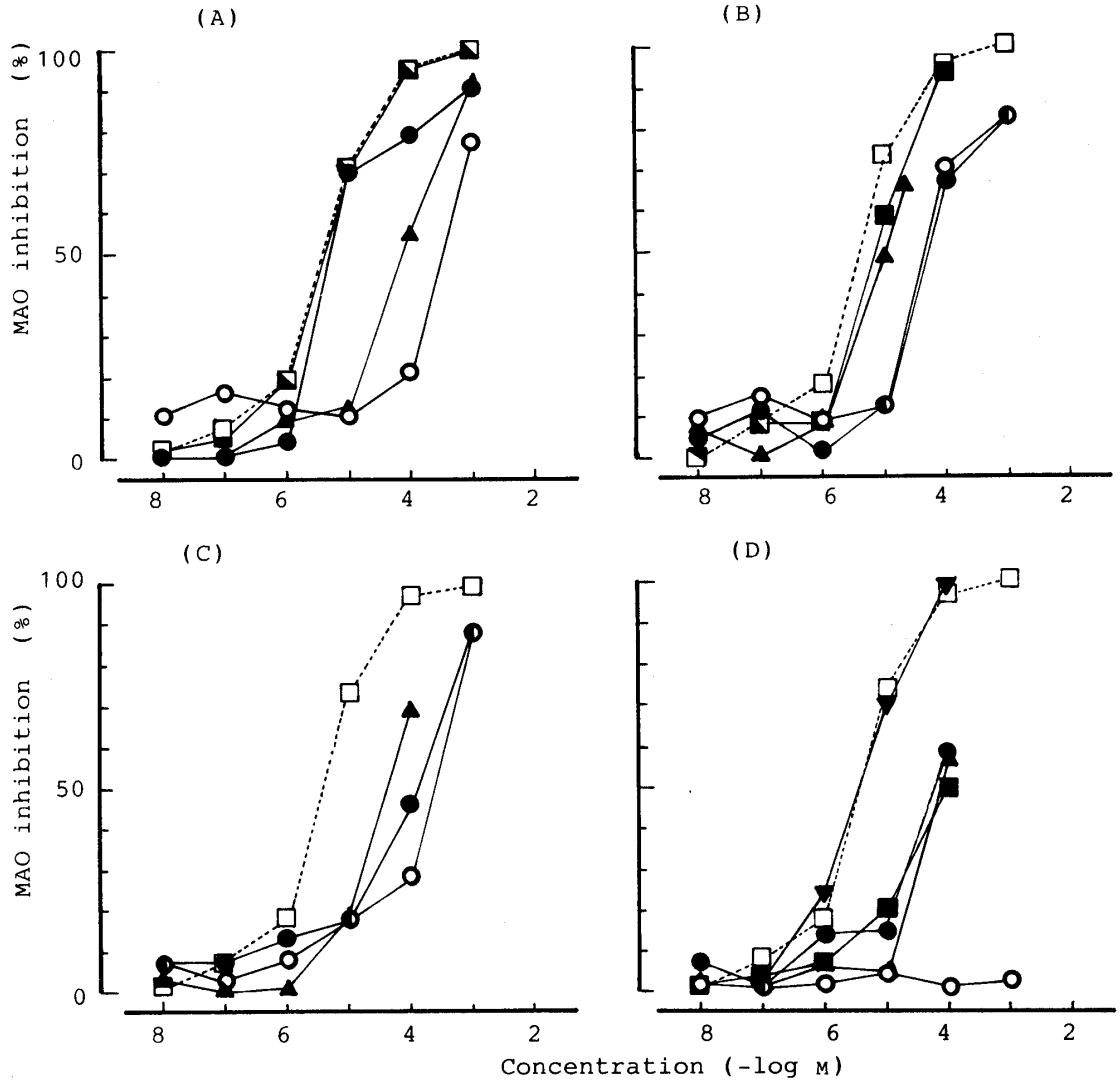


Fig. 2. Effects of the Concentration of the Tested Compounds of the (A) Quinoline Group, (B) Isoquinoline Group, (C) Phthalazine Group and (D) Naphthalene Group on the Inhibition of MAO

Rat brain mitochondrial fractions were incubated for 15 min at 37 °C with various concentrations of each compound. MAO activities were assayed using 0.095 mM benzylamine as the substrate, and were expressed as percent inhibition of the control. ---□---, iproniazid and nialamide (the curves overlapped each other).

(A) —○—, quinoline; —●—, Tri-Q; —▲—, NTR; —■—, NTE. (B) —○—, isoquinoline; —●—, Tri-I_1; —▲—, Tetra-I; —■—, Tri-I_2. (C) —○—, phthalazine; —●—, Tri-P; —▲—, Tetra-P. (D) —○—, naphthalene; —●—, 6,7-BI; —▲—, 4,5-BI; —■—, Imi-N; —▼—, Tri-N.

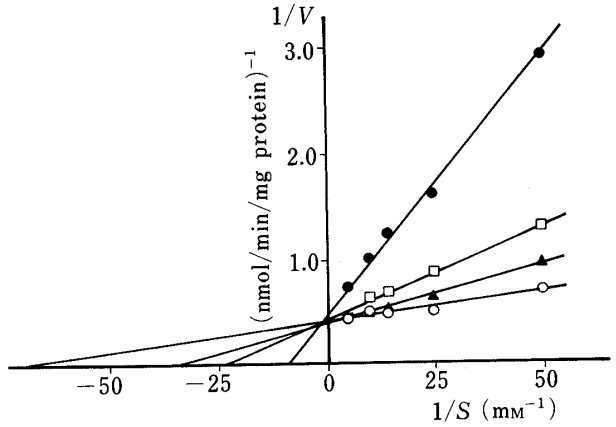
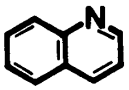
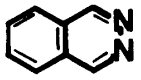
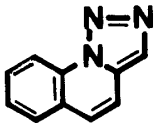
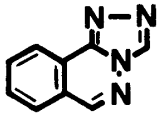
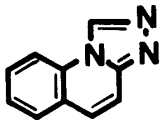
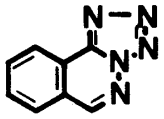
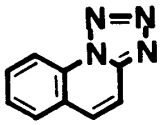
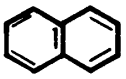
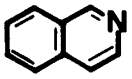
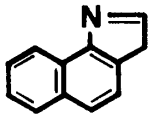
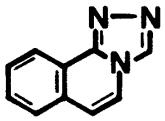
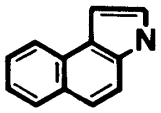
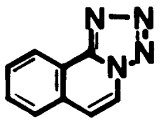
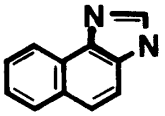
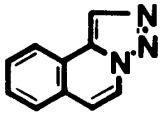
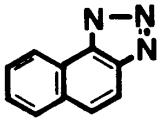


Fig. 3. Lineweaver–Burk Plot Showing the Inhibition of Rat Brain Mitochondrial MAO Activity by NTE

Benzylamine was used as the substrate at the concentrations (S) of 0.02, 0.04, 0.07, 0.1 and 0.2 mM. Reaction velocities (V) were measured after preincubation of mitochondrial samples for 15 min at 37 °C in the presence of the following NTE concentrations: zero (○), 10^{-6} M (▲), 3×10^{-6} M (□), 10^{-5} M (●), $K_i = 1.3\times10^{-6}$ M.

TABLE I. Results of MAO Inhibitory Test of All Compounds Using Rat Brain Mitochondrial Fraction

Formula	Name	I_{50} ($\times 10^{-6}$ M)	Formula	Name	I_{50} ($\times 10^{-6}$ M)
	Iproniazid	3.2			
	Nialamide	3.5			
(A) Quinoline group			(C) Phthalazine group		
	Quinoline	320		Phthalazine	250
	Tri-Q	5.0		Tri-P	100
	NTR	79		Tetra-P	40
	NTE	4.0	(D) Naphthalene group		
				Naphthalene	Inactive
(B) Isoquinoline group					
	Isoquinoline	50		6,7-BI	63
	Tri-I_1	71		4,5-BI	79
	Tetra-I	10		Imi-N	100
	Tri-I_2	7.1		Tri-N	3.6

the C ring are important for the interaction between MAO and these inhibitors.

Lineweaver–Burk plots of the kinetic data indicated that the inhibitions by Tetra-P, Tri-P, NTE and NTR were competitive for both MAO-A and MAO-B. Thus, only the data for NTE are shown in Fig. 3.

This is the first study to discuss the structure–MAO inhibitory activity relationship of the new series of tricyclic compounds which contain the pentanthrene skeleton. In order to formulate the quantitative structure–activity relationship (QSAR) for these MAO inhibitors and to develop a method for further studies on drug design such as central nervous system (CNS)-related drugs, we are now computerizing the data, in terms of physico-chemical parameters such as the partition coefficient and the electron density of each compound.

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