Pergamon

Bioorganic & Medicinal Chemistry Letters 9 (1999) 1927–1932

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

THE DESIGN AND SYNTHESIS OF ALS INHIBITORS FROM PHARMACOPHORE MODELS

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Received 22 March 1999; accepted 20 May 1999

Abstract: In search of new ALS inhibitors without the previous knowledge of receptor crystal structure, DISCO module was applied to produce 3D-pharmacophore models, which provided information to design novel molecules by 3D-database searching. Then a number of molecules were synthesized. Several of them have some ALS inhibitory activities.

Introduction:

Following with the rapid development of computer technology, Computer Aided Molecular Design (CAMD) has become a focus of attention in assisting the molecular design of some novel agrochemicals.

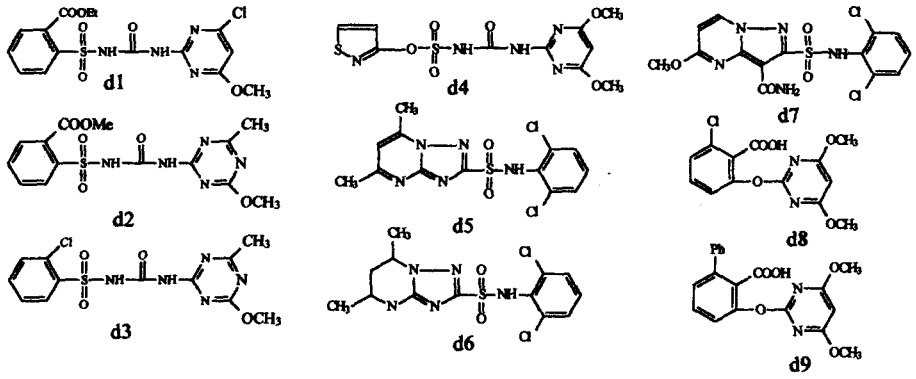
The research on the ALS enzyme inhibitors has been carried out consistently in our Laboratory. Since it is difficult to obtain ALS receptor crystal to clarify the relative mode of action, which restrain further development of new inhibitors. So a series of ligand molecules were calculated by using CoMFA method, and the 3D-QSAR results were obtained [1].

In order to explore new ALS inhibitors, another new DISCO module was adopted which translated the information of two-dimensional structures of active compounds into that of the three-dimension. Then the possible pharmacophore models could be displaced, which provide further information to design new molecules by 3D-database searching [2]. Afterwards, some molecules could be modified, synthesized and bio-assayed. In this way, the cycle of seeking potential leads can be found by using *Ligand Based Drug Design*, which is a promising method to contrive novel agrochemicals efficiently.

Method:

The 3D-pharmacophore models were built by using the molecular software package SYBYL/6.22[3] on Silicon Graphics Worksations. The 3D-datebase searching was carried by using ISIS/3D chemical information management software.

0960-894X/99/$ - see front matter
PII: S0960-894X(99)00301-7



Scheme 1

Aiming at the ALS enzyme inhibitors, we selected 9 compounds, which are different in structures and all known act on ALS enzyme with high activities [4] (Scheme 1). These compounds constituted a set of molecular database. After the DISCO module ran, molecule d6 was selected as the reference compound by system. In addition, we also selected molecule d1, which was synthesized in our Laboratory, as the reference. Then two classes 3D-pharmacophore models were obtained. The process followed as: Firstly, two kinds of preferential models were chosen (Figure1, 2). Secondly, their information was changed into 3D-query[5] (Figure 3,4). And last, based on 3D-query, relevant molecules were searched from the ACD-3D molecule database. Thus we obtained some molecules (Scheme 2), which have similar chemical features but are different in structures. Then molecule II and I were chosen to modify and synthesize.

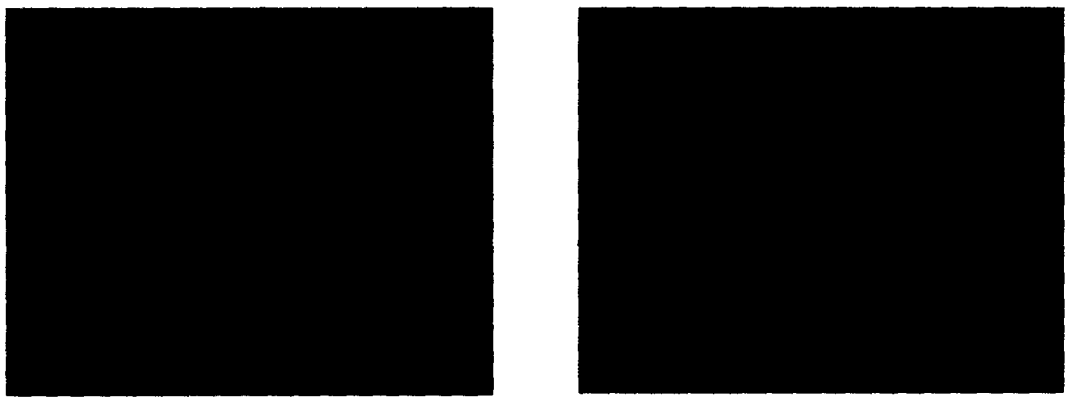


Figure 1. The pharmacophore model (d6 as reference). ***Figure 2.*** The pharmacophore model (d1 as reference).

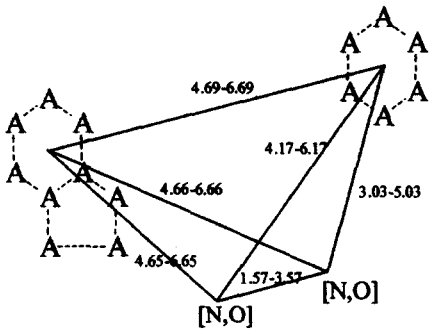


Figure 3. *The 3D-query from the pharmacophore model (d6 as reference).

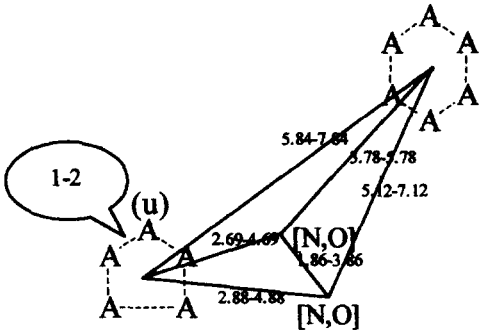
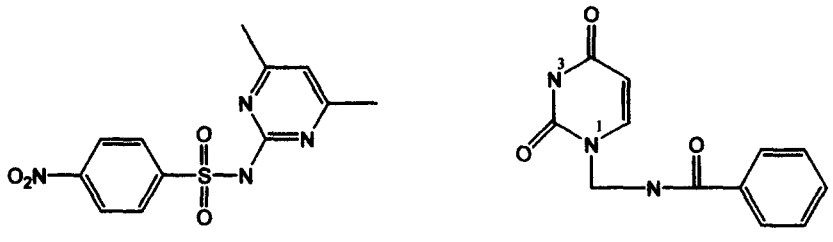


Figure 4. The 3D-query from the pharmacophore model (d1 as reference).

(*A means any atom; (u) marks the atom with unsaturated bonds; ... means any type of bond.)

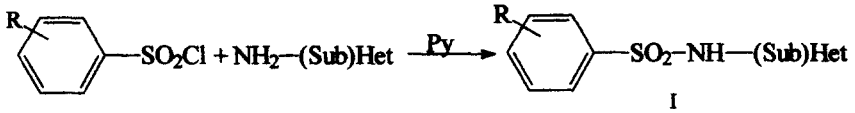


A B

Scheme2

Synthesis:

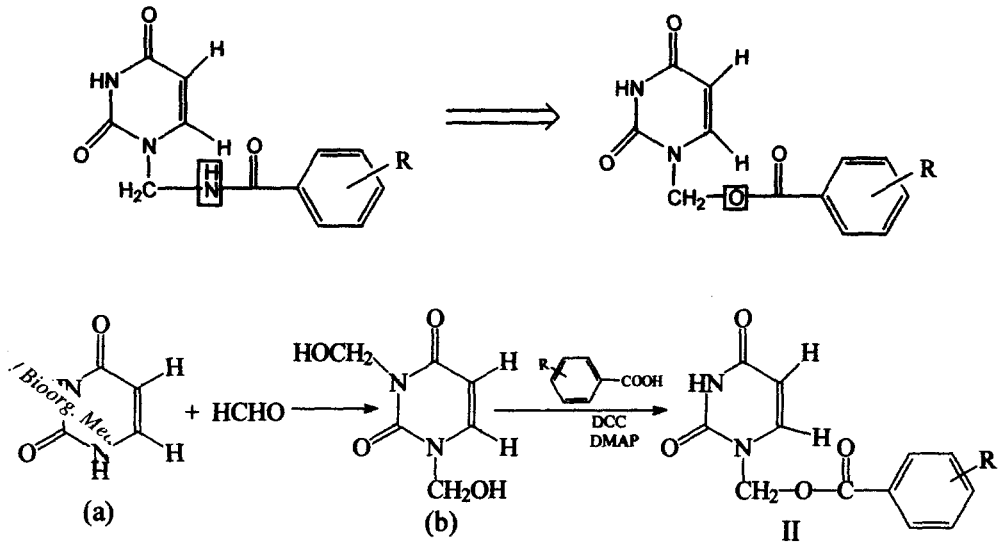
Since we have obtained the structure A from search result, we synthesized nine benzene sulfonic amide compounds I to screen for herbicidal lead (Scheme3). The reaction of benzene sulfonyl chloride with different heterocyclic amines in pyridine gave the corresponding compounds I.



I

Scheme 3

In addition, we also selected structure B, which belongs to Uracil derivative. Some N^3 substituted uracils were reported as herbicides [6,7]. But N^1 long chain substituted compounds were rarely reported as herbicides. Thus we selected N^1 substituted structure II as staring structure, modified group NH to atom O as bioisoster [8] and synthesized a series of compounds II (Scheme4). The synthesis of compounds II began with the reaction of uracil (**a**) and formaldehyde at 60°C to give 1,3-bishydroxymethyl uracil (b). Then the substituted benzoic acids were coupled with (b) in the presence of equal equiv DCC and a catalytic amount of DAMP in dry nitrile[9].



Scheme 4

Result and Discussion:

Preliminary bioassays were carried out on two category compounds. Their biological activity data IC_{50} were calculated by using the rape-root growth method [10, 11] (Table 1,2).

The results of biological tests indicated that some compounds synthesized have some extent of ALS inhibiting activities. That implied a starting point of designing novel structures of potential ALS inhibitors using CAMD without the previous knowledge of exact structure of the target enzyme. The exploring work still needs to be optimized in future.

Table 1. The biological activities of compounds I

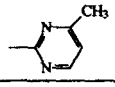
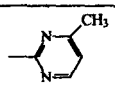
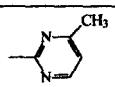
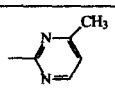
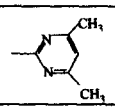
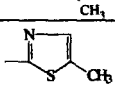
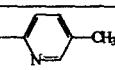
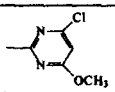
No.	(Sub) Aryl		I_{C50}(mol/L)
	R	(Sub)Het	
I_a	o-NO_2		$2.87x10^{-4}$
I_b	p-Br		$5.89x10^{-5}$
I_c	p-F		$3.89x10^{-5}$
I_d	2,5-2Cl		$9.72x10^{-5}$
I_e	2,5-2Cl		$3.30x10^{-5}$
I_f	2,5-2Cl		$>3.09x10^{-4}$
I_g	p-F		$1.52x10^{-4}$
I_h	2.5-2Cl		$8.47x10^{-5}$
I_i	p-F		$1.11x10^{-4}$

Table 2. The biological activities of compounds II

No.	R	I_{C50}(ppm)
II_a	m-CH_3	16.04
II_b	p-F	55.86
II_c	H	55.36
II_d	p-NO_2	>100
II_e	p-I	>100
II_f	p-Cl	51.29
II_g	o-OCH_3	>100
II_h	p-Br	55.38
II_i	2,6-2Cl, 4-CF_3	>100
II_j	p-OCH_3	>100

Acknowledgements:

This project was supported by the National Natural Science Foundation of China (Granted Number: 29772679) and the State Key Laboratory of Elemento-Organic Chemistry.

Thanks to the assistance to this project from Prof. Kaixian CHEN and Dr. Jianzhong CHEN, Shanghai Institute of Materia Medica.

References and notes:

1. Liu Jie; Li Zhengming; Wang Xia et al. *Science in China (Series B)* **1998**, 41 (1), 50.
2. Yvonne C.Martin; Mark G. Bures; Elizabeth A.Danaher; Jerry DeLazzer *Journal of Computer-Aided Molecular Design* **1993**, 7, 83.
3. Tripos Inc., 1699 South Hanley Road, St. Louis, Missouri 63144, USA.
4. Shimizu,T.; Nakayama, I.; Wada, N. and Abe, H. *J. Pest. Sci.* **1994**,19, 257.
5. Douglas R. Henry and Osman F. G. *http://www.ch.ic.ac.uk/ectoc/papers/guner/*.
6. Lutz Albert W. U.S.Patent 3,635,977, 1972; *Chem. Abstr.* **1972**, 76, 113244v.
7. Enomoto Masayuki; Takemura Susumu et al. Eur. Pat. Appl.EP 540,023, **1993**; *Chem. Abstr.* **1993**, 119, 139259k.
8. Toshio Fujita *Biosci. Biotech. Biochem.* **1996**,60(4), 557.
9. Suhail Ahmad; Shoichiro Ozaki; Toshio Nagase et al. *Chem.Pharm.Bull.***1987**, 35(10), 4137.
10. Swanson, C. P. *Bot. Gaz.* **1946**, 107, 507.
11. Ready, D.; Gramt,V.Q. *Bot. Gaz.* **1947**,109, 39.