Classification for the Structure-Activity Relationship Methods

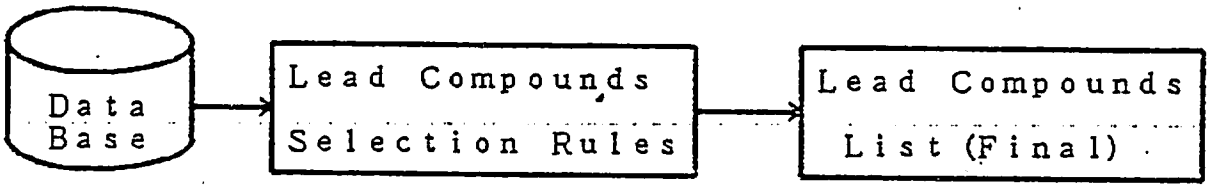
■ Based on a Lead Compound ■

- ☐ Lead Generation ☐
- ☐ Lead Optimization ☐
- ☐ Lead Evolution ☐

Lead Retrieval
Lead Access

1. Lead 化合物検索について　日本薬学会 (1981年 4月)
2. ピリドンカルボン酸の抗菌活性データを用いて 新規の(Lead) 抗菌活性薬物を探し出す (MACCSのALDRICHデータベースより)。

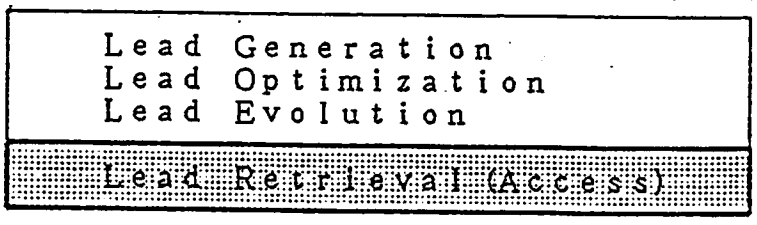
A Concept of the Lead Retrieval



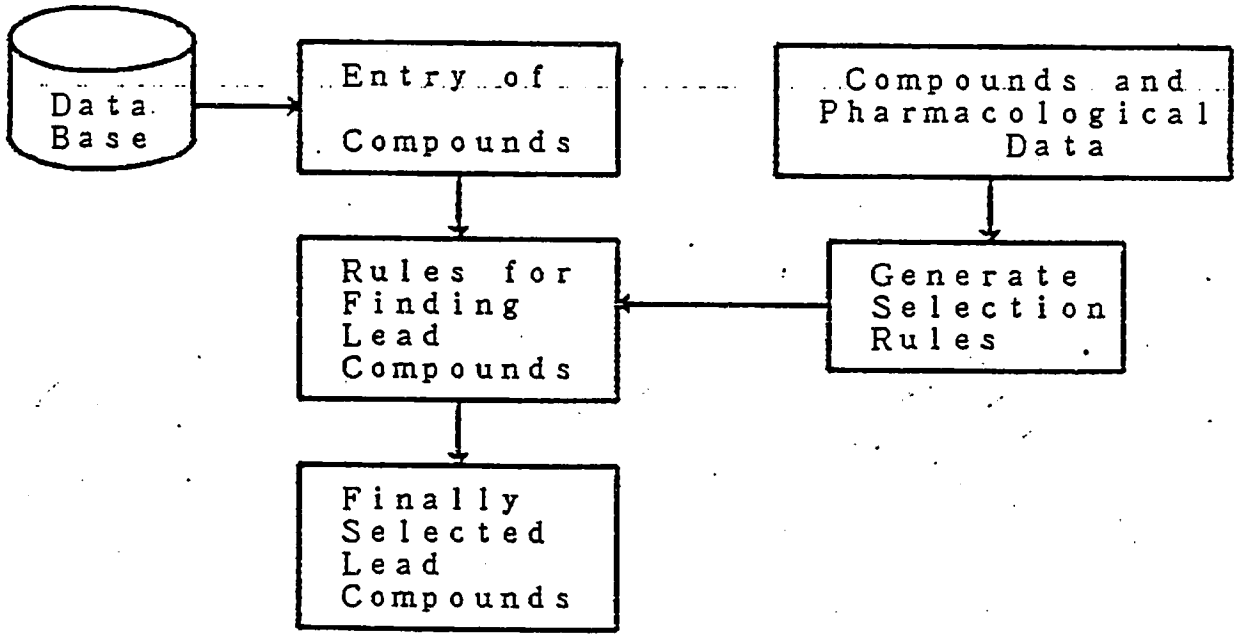
- ☐ In-house
  - MACCS
- ☐ Public
  - CAS
  - ISI
  - CIS
  - DARC

- ☐ Hansch-Fujita Method
- ☐ Pattern Recognition Method
- ☐ Drug Receptor Theory

- ☐ Calculate Similarity
- ☐ Check to Double Register of the Same Compounds



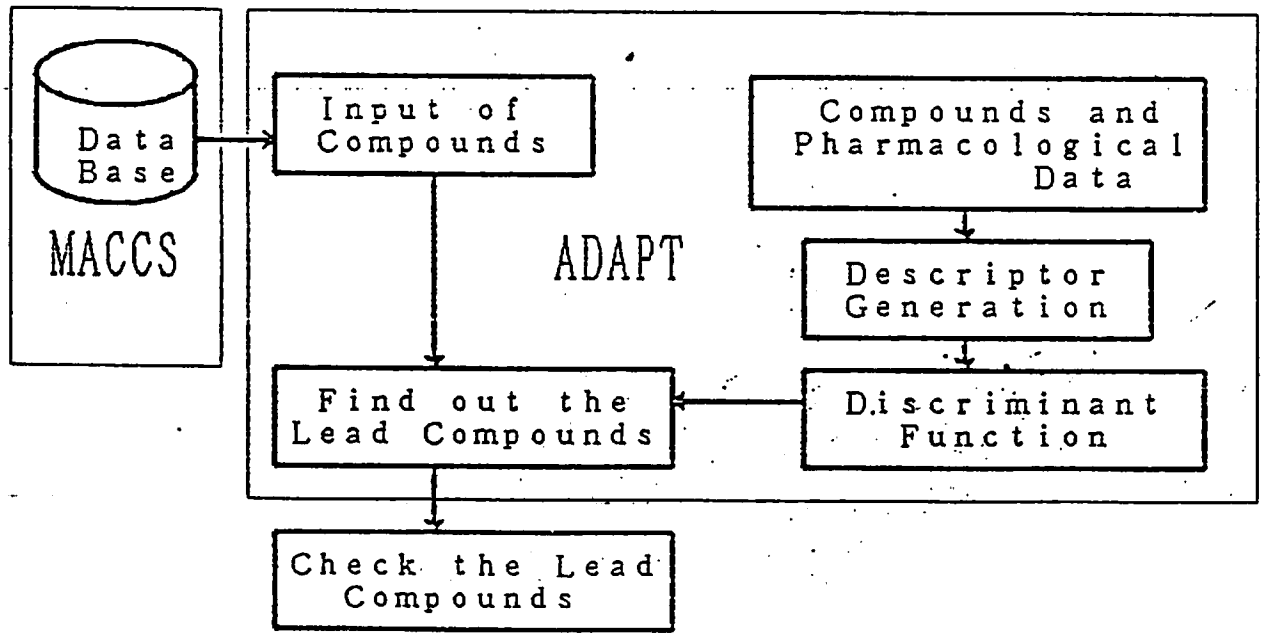
Flow Chart of the Lead Retrieval System



LEADS

Lead compounds Evaluation and Access Developpment System

LEADS System for the Lead Retrieval



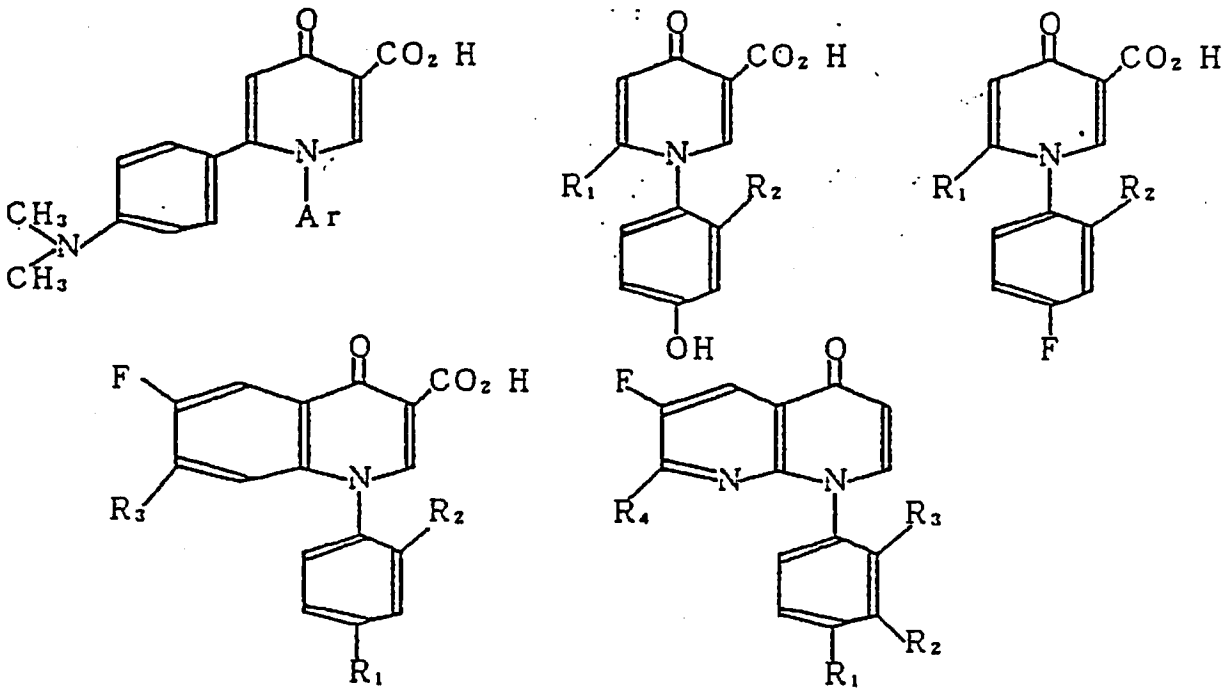
- ☐ Compound Data Base : ALDRICH in MACCS
- ☐ Finding Rule to the New Lead Compounds: Discriminant Function Generated by ADAPT

* MACCS: Molecular Access System
* ADAPT: Automated Data Analysys by Pattern recognition Toolkits

Antibacterial Agents

4-Pyridone-3-carboxylic acid

H. Narita, Y. Konishi, J. Nitta, H. Nagaki, I. Kitayama
Y. Watanabe, and I. Saikawa, YAKUGAKU ZASSHI,
106, 775 (1986)



Used Compounds

Total 108 Compounds were Used for the Pattern Recognition Study

56 Active Compounds
52 Not Active Compounds

Antibacterial Activity

☐ Staphylococcus aureus FDA 209P

MIC $\mu g/ml$

0.5 > Active compounds
0.5 < Not active compounds

Used Descriptors

63 Descriptors were Generated by ADAPT

- Various Feature Selection Methods were used to Select Descriptors

14 Descriptors were Finally Selected

1	FRAG	Number of Nitrogen Atoms
2	FRAG	Number of Aromatic Bonds
3	FRAG	Number of Ring Atoms
4	ALLP	Total Number of Paths (0~5)
5	ALLP	Total Number of Paths (20~46)
6	MOLC	Path-4 Molecular Connectivity
7	MOLC	Path-Cluster-4 Molecular Connectivity
8	BOMX	Maximum Bond Order
9	EDMX	Maximum Electron Density
10	LUMO	Lowest Unoccupied M.O.
11	FVMX	Maximum Free Valence Value
12	SNMN	Minimum Nucleophilic Superdelocalizability
13	STRA	Bond Strain Energy
14	STRA	Tortional Strain Energy

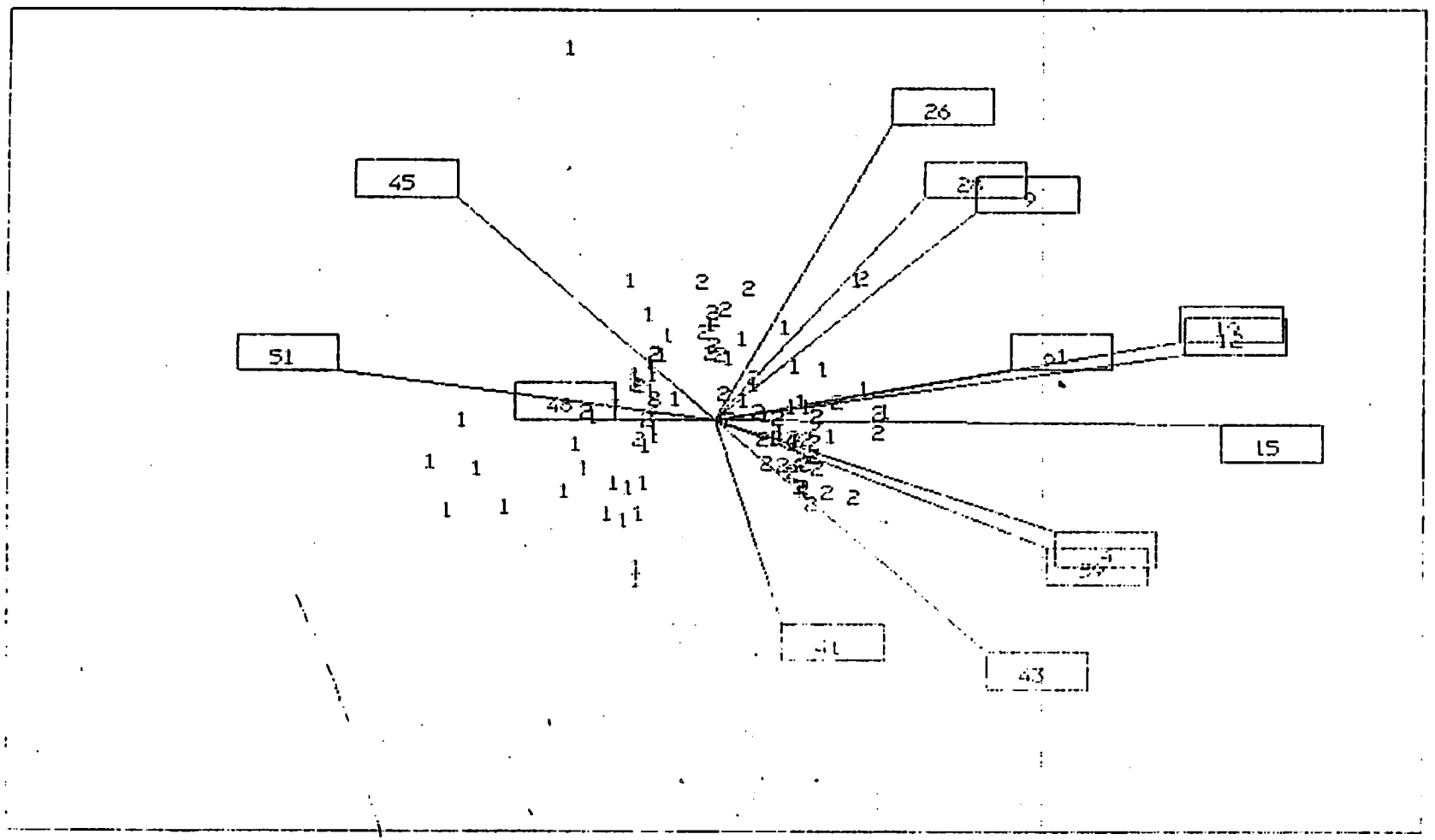
Results of Pattern Recognition Methods

Methods	Active	Not Active	Total
L. L. M.	100. 0	100. 0	100. 0
SIMPLEX	94. 2	92. 0	93. 1
TILSQ	100. 0	100. 0	100. 0
BAQ	100. 0	82. 0	91. 2
BAL	94. 2	92. 0	93. 1
KNN			
K=1	80. 8	80. 0	80. 4
K=3	86. 5	78. 0	82. 4

* 6 Compounds were Removed from the Initial (108 Compounds) Data Set

Active Class=50 (2 Compounds were Removed)
Not Active Class=52 (4 Compounds were Removed)
Total=102 Compounds

BIPLOT DISPLAY - AUTOSCALED DESCRIPTORS



SECOND

FIRST PRINCIPAL AXIS

Test Results by the Lead Retrieval System

■ Compounds ■

□ 200 Compounds from the ALDRICH DATA BASE
□ Selected at Random

■ Discriminant Function ■

□ Generated by the Linear Learning Machine in ADAPT

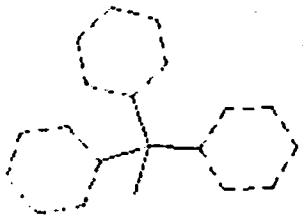
$$Y = 0.164W_1 - 0.052W_2 - 0.518W_3 + 0.193W_4 + 0.166W_5 + 0.245W_6 - 0.407W_7 + 0.506W_8 - 0.144W_9 - 0.098W_{10} + 0.112W_{11} - 0.077W_{12} - 0.081W_{13} - 0.315W_{14} + 0.019W_{N+1}$$

■ 20 Compounds were Finally Selected as the New Lead Compounds (Antibacterial Agents)

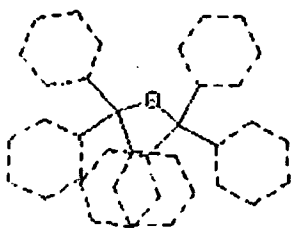
□ Discriminant Values of the New Lead Compounds

$-1000 \geq$ Discriminant Value ≥ -2000	16 Compounds
$-2000 \geq$ Discriminant Value	4 Compounds

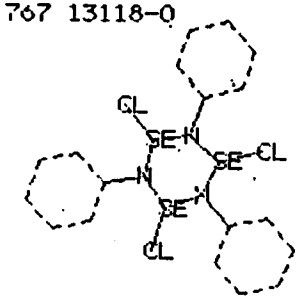
795 13705-7



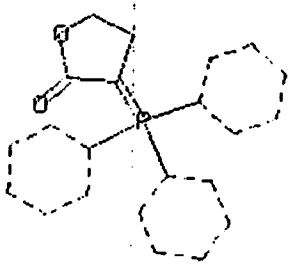
754 BIS-(TRIPHENYLTIN)



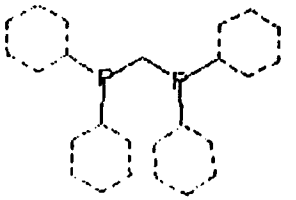
767 13118-0



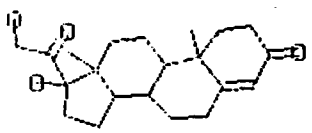
918 11478-2



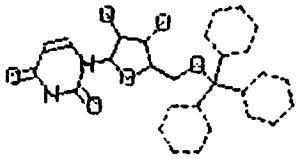
977 12756-6



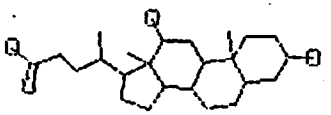
773 13213-6



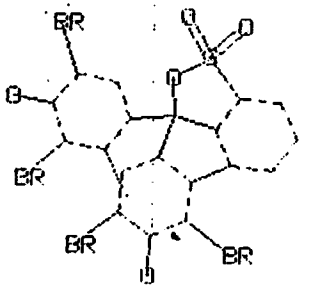
708 10143-5



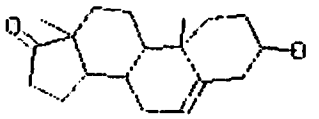
741 DEOXYCHOLIC ACID, 9



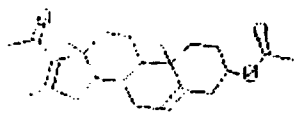
901 BROMOCRESOL GREEN,



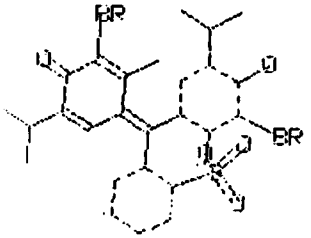
968 DEHYDROISOANDROSTER



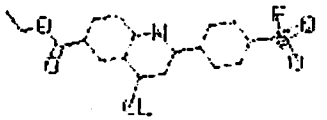
953 3BETA-HYDROXY-16-ME



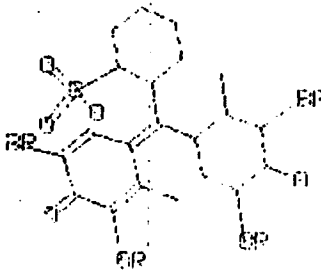
905 BROMOTHYMOL BLUE, W



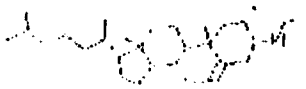
982 ETHYL 4-CHLORO-2-(P



902 BROMOCRESOL GREEN,

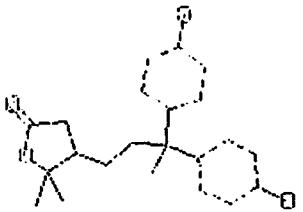


740 10718-2

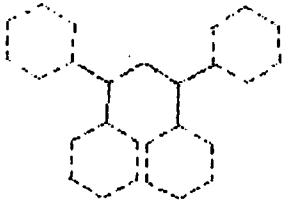


952 12229-7

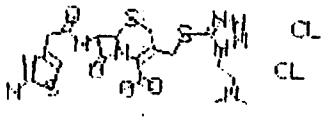
780 10416-7



976 12755-8



9 CEFOTIAM



930 12194-0