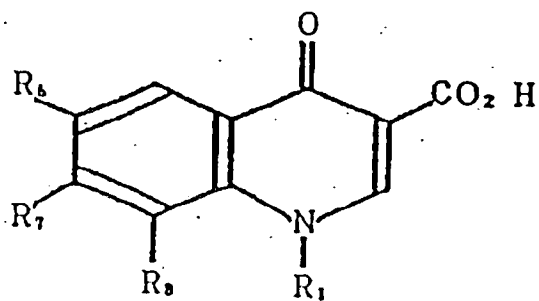
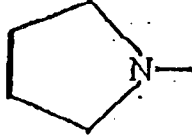
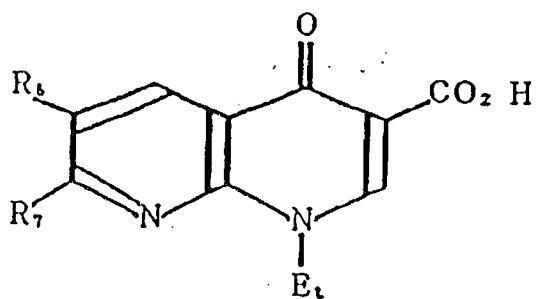


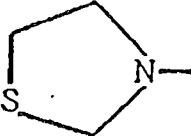
PYRIDONE CARBONIC ACID DERIVATIVES
ANTIBACTERIAL ACTIVITY

John M. Domagala, Lori Doyle Hanna, Carl L. Heifetz, Marland P. Hutt, Thomas P. Mich, Joseph P. Sanchez, and Marjorie Solomon, *Journal of Medicinal Chemistry*, **29**, 394 (1986).



R 6	R 7
F	H
NO ₂	H
F	
H	H ₂ NCH ₂ CH ₂ NH-



R 6	R 7
F	HON=CH-
NH ₂	CH ₃
F	

— BASIC STRUCTURES OF USED COMPOUNDS —

ANTIBACTERIAL ACTIVITY

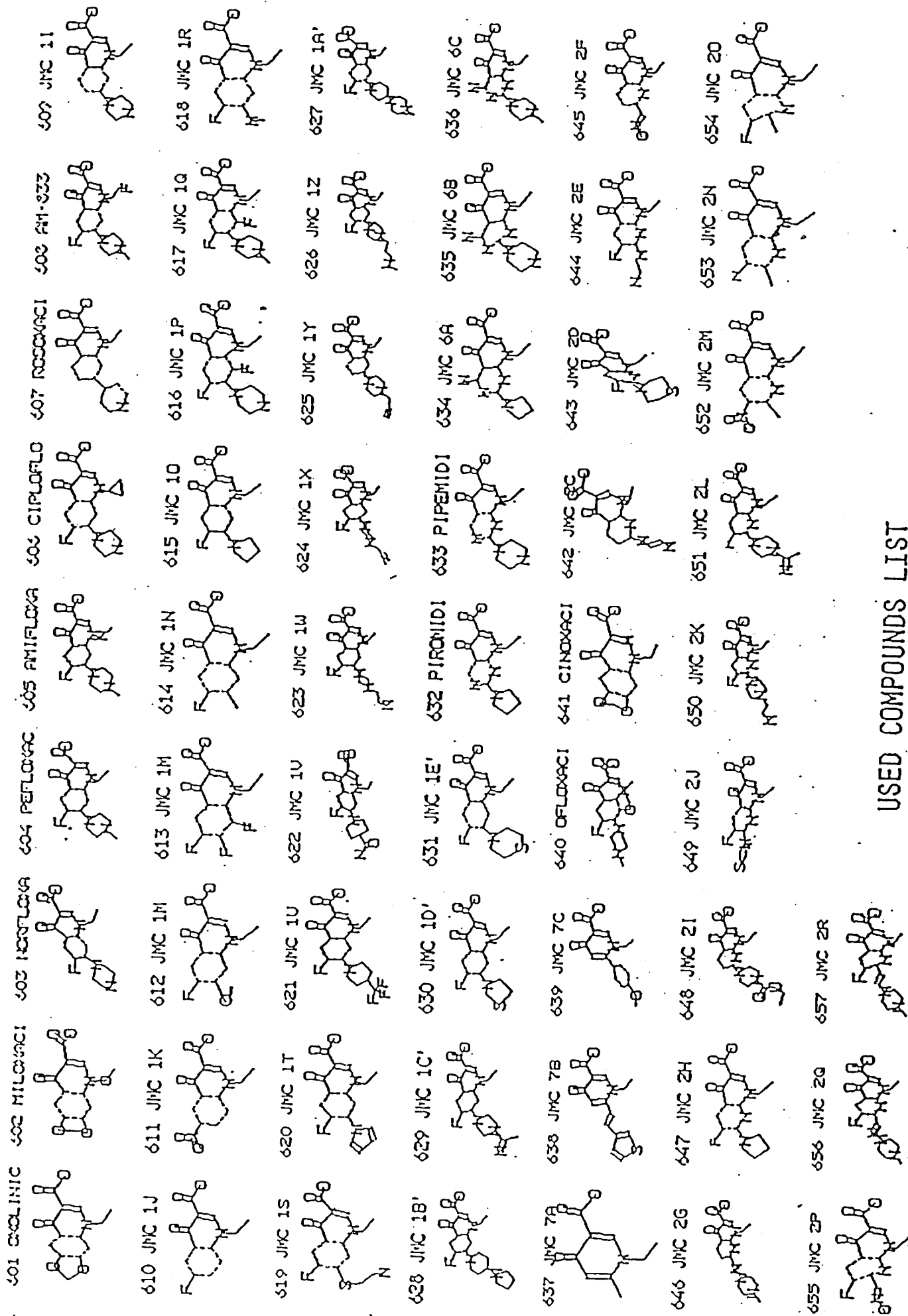
E. coli H560 MIC 0.1 ~ > 100.0 $\mu\text{g}/\text{mL}$

ACTIVE CLASS

MIC 0.1 ~ 6.3 $\mu\text{g}/\text{mL}$ 27 COMPOUNDS

INACTIVE CLASS

MIC 12.5 ~ 100.0 $\mu\text{g}/\text{mL}$ 30 COMPOUNDS



USED DESCRIPTOR SET IN ORDER TO CHOOSE
LEAD CANDIDATES FROM THE GENERATED COMPOUNDS

(DOESN' T INCLUDE SBSTRUCTURE DESCRIPTORS)

- +1. TOTAL NUMBER OF PATHS/NUMBER OF ATOMS
- 2. NUMBER OF NITROGEN ATOMS IN STRUCTURE
- +3. NUMBER OF BASIS RINGS IN STRUCTURE
- 4. MINIMUM NUCLEOPHILIC SUPERDELOCALIZABILITY
- +5. TORSIONAL STRAIN ENERGY OF MOLECULE

DATA SET CONDITION

CLASS 1 (ACTIVE CLASS)	27 COMPOUNDS	
CLASS 2 (INACTIVE CLASS)	29 COMPOUNDS	TOTAL=56

* ONE COMPOUND WAS DELETED FROM THE ORIGINAL DATA SET TO KEEP DICHOTOMIZATION

DAN: 631
CLS: 1
+3
-2
-7
+5

DAN: 649
CLS: 1
bass Reg. No. 2
f-37
+14k
Superbe

DAN: 621
CLS: 1

DAN: 604
CLS: 1
pafloxacilin

DAN: 630
CLS: 1

DAN: 643
CLS: 1

DAN: 647
CLS: 1

DAN: 607
CLS: 1

DAN: 617
CLS: 1

DAN: 620
CLS: 1

DAN: 640
CLS: 1
Ofloxacin

DAN: 603
CLS: 1
Norfloxacin

DAN: 608
CLS: 1

DAN: 615
CLS: 1

DAN: 601
CLS: 1
Oxalimic

DAN: 605
CLS: 1
Amifloxacilin

DAN: 614
CLS: 1

DAN: 627
CLS: 1
JMC

DAN: 606
CLS: 1
Cuplofloxacin

DAN: 612
CLS: 1

DAN: 616
CLS: 1

DAN: 622
CLS: 1

DAN: 628
CLS: 1
JMC-

DAN: 648
CLS: 1

DAN: 659
CLS: 1

DAN: 602
CLS: 1

DAN: 629
CLS: 1

DAN: 618
CLS: 2
+3
-1
+5

DAN: 623
CLS: 2

DAN: 626
CLS: 2

DAN: 632
CLS: 2

DAN: 646
CLS: 2

DAN: 619
CLS: 2

DAN: 652
CLS: 2

DAN: 634
CLS: 2

DAN: 636
CLS: 2

DAN: 609
CLS: 2

DAN: 613
CLS: 2

DAN: 633
CLS: 2

DAN: 635
CLS: 2

DAN: 642
CLS: 2

DAN: 645
CLS: 2

DAN: 650
CLS: 2

DAN: 651
CLS: 2

DAN: 653
CLS: 2

DAN: 610
CLS: 2

DAN: 611
CLS: 2

DAN: 634
CLS: 2

DAN: 636
CLS: 2

DAN: 637
CLS: 2

DAN: 638
CLS: 2

DAN: 639
CLS: 2

DAN: 641
CLS: 2

DAN: 644
CLS: 2

DAN: 655
CLS: 2

DAN: 657
CLS: 2

DAN: 658
CLS: 2

DAN: 630
CLS: 2

DAN: 637
CLS: 2

DAN: 638
CLS: 2

DAN: 639
CLS: 2

DAN: 641
CLS: 2

DAN: 644
CLS: 2

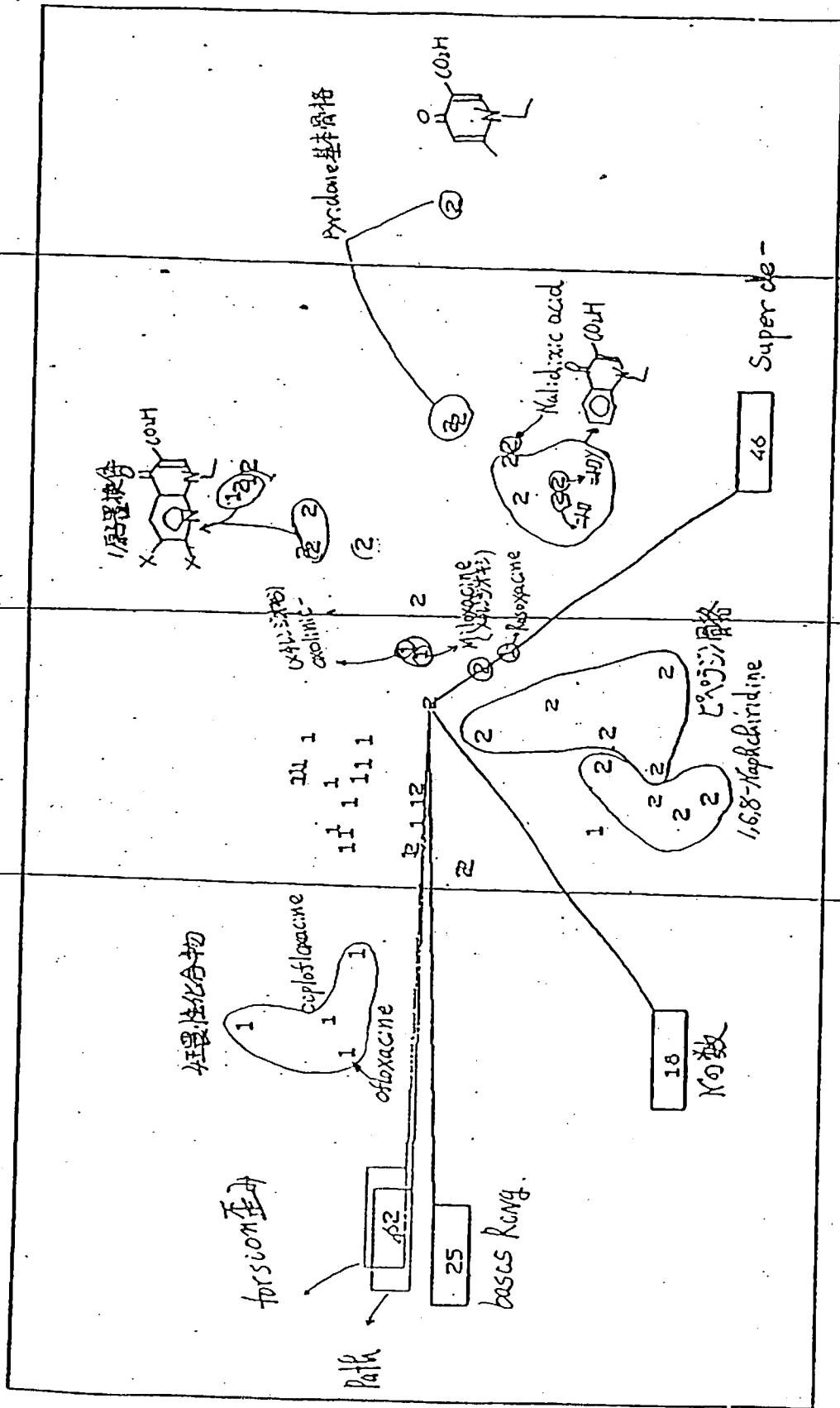
活性

不活性

独立環2個

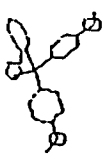
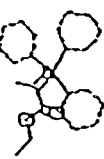

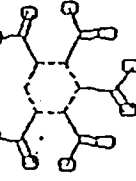
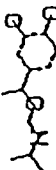
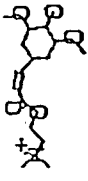
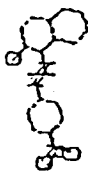
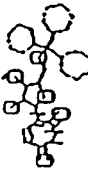
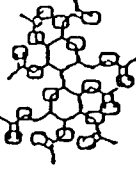
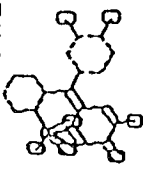
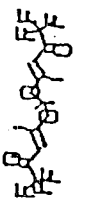
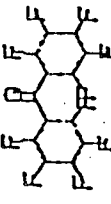
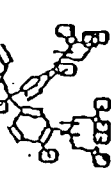
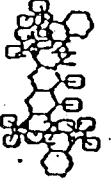
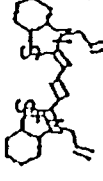
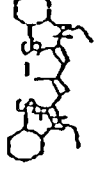
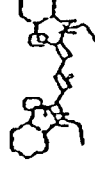

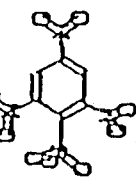
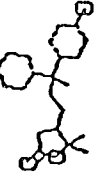
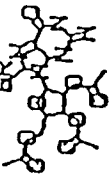
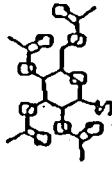
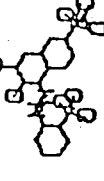
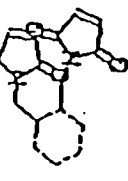
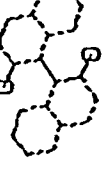
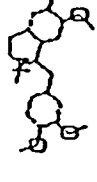


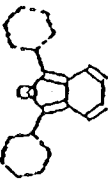
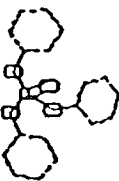
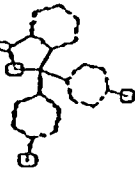
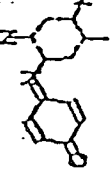
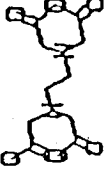

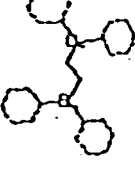
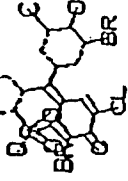
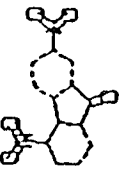
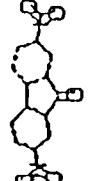
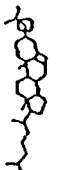
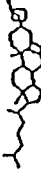
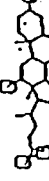

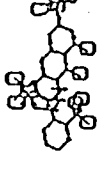
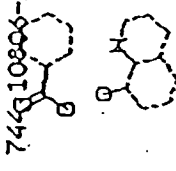
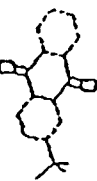

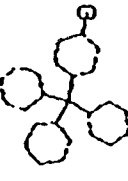
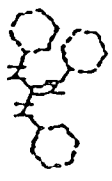
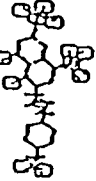
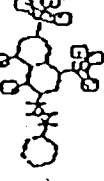
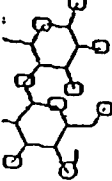
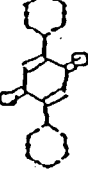
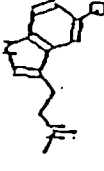

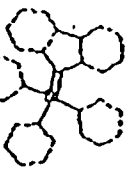
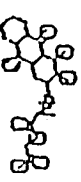
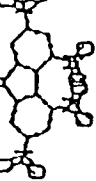
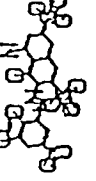
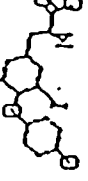
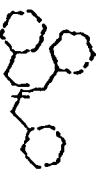
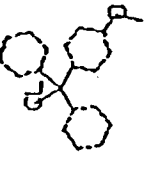
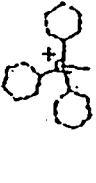

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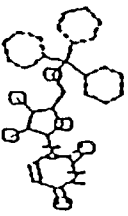
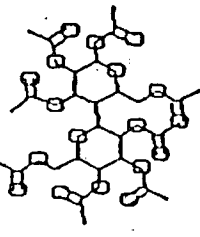
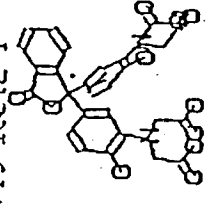
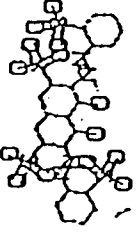
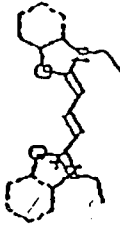
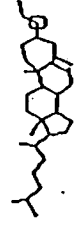
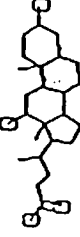
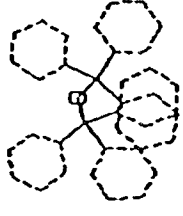
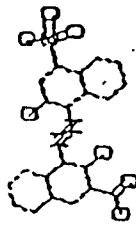
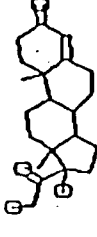
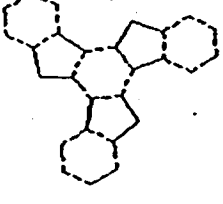
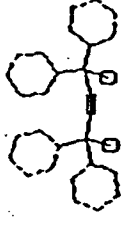
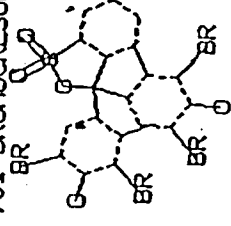
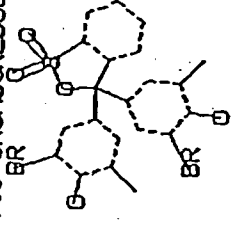
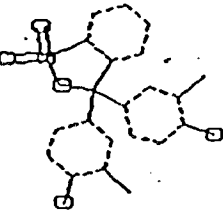
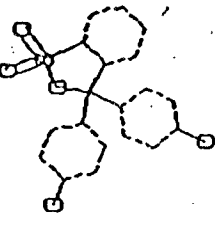
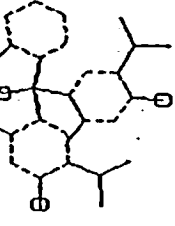
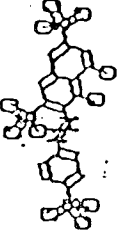
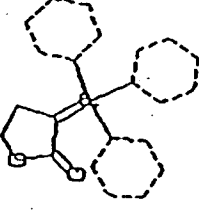
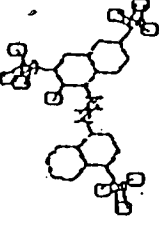
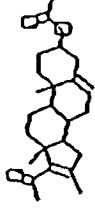
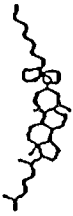
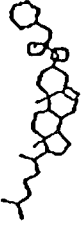
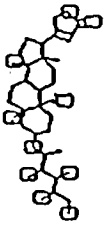
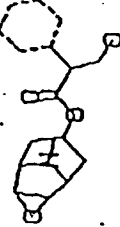
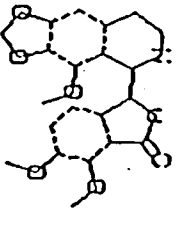
BIPLOT DISPLAY - AUTOSCALED DESCRIPTORS - % OF VAR: 80.99



SECOND

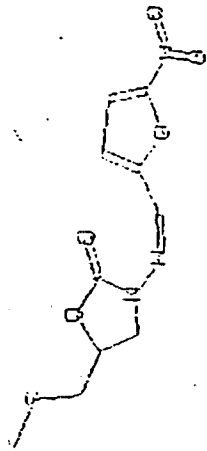
4环
FIRST PRINCIPAL AXIS
3环
单环

701 4,4'-DI	702 (CARBETH)	703 11 HENEI	704 10042-0	705 DEXTRO L	706 10049-3	707 PARA RED	708 10143-5	709 ALFIA-O
								
710 PYROCATE	711 CUPRIC T	712 DECAFLUO	713 10212-1	714 SULFONAZ	715 10247-4	716 3,3PR-DI	717 10249-0	718 10-NONAD
								
719 PICRYLSU	720 10416-7	721 8-BROMOG	722 BETA-DEX'	723 THIRIN I	724 N,MPR-OR	725 1,1'-BI-	726 DL-LAUDA	727 OCTADECY
								
728 TETRAETH	729 1,3-DIPH	730 TRIPHENY	731 PHENOLPH	732 10628-3	733 ETHYLENE	734 10640-2	735 ETHYLENE	736 10696-8
								
737 10709-3	738 2,7-DINI	739 10717-4	740 10718-2	741 DEOXYCHO	742 TRIPENTA	743 ARSENAZO	744 10806-5	745 2-TERT.-
								
746 OXOTIEMO	747 PARA-TRI	748 10977-0	749 11039-6	750 11066-8	751 D-(PLUS)	752 11287-9	753 11341-7	754 BIS-(TRI)
								
755 11391-3	756 ALIZARIN	757 2,4,5,7-	758 12797-3	759 12803-1	760 TRIBENZY	761 PARA-ANI	762 (HEPARYL)	763 TRIS-(EU)
								

709 10143-5		709 ALPHA-D-CELL		713 10212-1		714 SULFONAZO II		717 10249-0		740 10718-2		741 DECYCYCHOLIC	
754 BIS-(TRIPHEN		764 3-HYDROXY-4		773 13213-6		775 13223-3		783 13465-1		901 BROMOCRESOL		903 BROMOCRESOL	
907 CRESOL RED,		911 PHENOL RED,		913 THYMOLPHTHAL		916 2(P-SULFOPE		918 11478-2		939 AMARANTH (C.		953 3BETA-HYDROX	
964 CHOLESTERYL		965 12526-1		966 12532-6		980 SCOPOLAMINE		998 14630-7					

<CR> TO CLEAR:

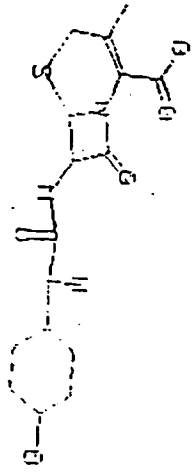
~~50~~ THIFURATEL



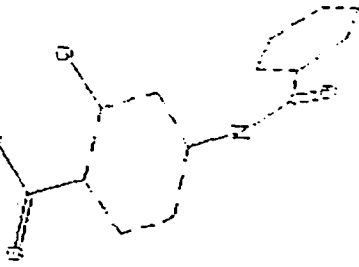
517 SULFANILAMILIDE DELI



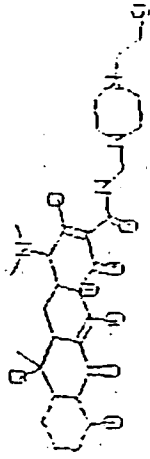
~~518~~ CEFADROXIL



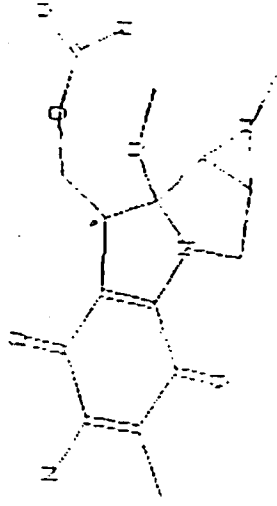
513 BENZANIDE DELI



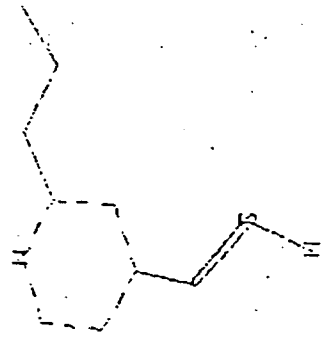
515 PIRACYCLINE



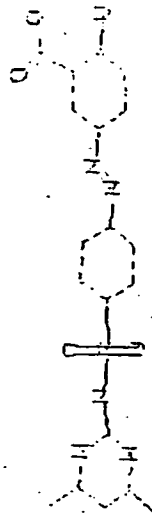
~~516~~ PUSFIBONACIN



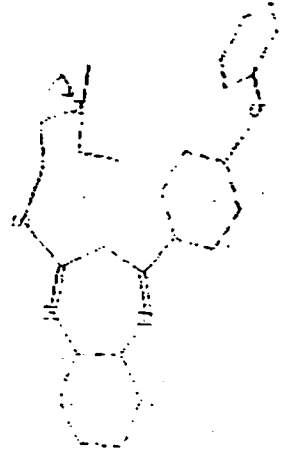
511 LOSTIPAMIDE



512 SALAZOSULFADIMINE



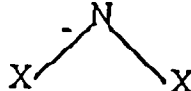
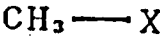
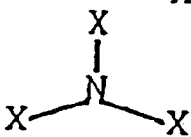
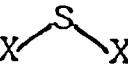

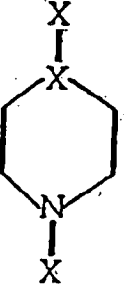

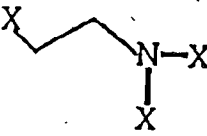


~~514~~ THEOPHYLLIN



CONCLUSION AND REMARKS

- EASY TO FIND OUT SOME LEAD CANDIDATES FROM COMPOUND DATA BASE
 - FIND OUT LEAD CANDIDATES, EVEN IF THE DIFFERENCES OF STRUCTURE ARE GREAT
 - THIS METHOD CAN HANDLE A LARGE NUMBER OF COMPOUNDS WITHIN A SHORT TERM
 - THIS METHOD CAN CHECK VARIOUS KINDS OF ACTIVITIES AT A TIME
 - PRACTICAL USE OF COMPOUND PROPERTY
-

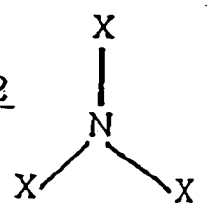
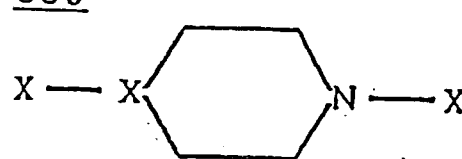
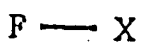

STARTING SUBSTRUCTURE LIST

		NNZ TOTAL		NNZ TOTAL	
<u>SS1</u>		11	11	<u>SS6</u>	 56 78
<u>SS2</u>		57	112	<u>SS7</u>	 6 6
<u>SS3</u>	 36 44	36	44	<u>SS8</u>	 19 20
<u>SS4</u>	 57 218	57	218	<u>SS9</u>	 35 109
<u>SS5</u>	 37 85	37	85	<u>SS10</u>	 52 53

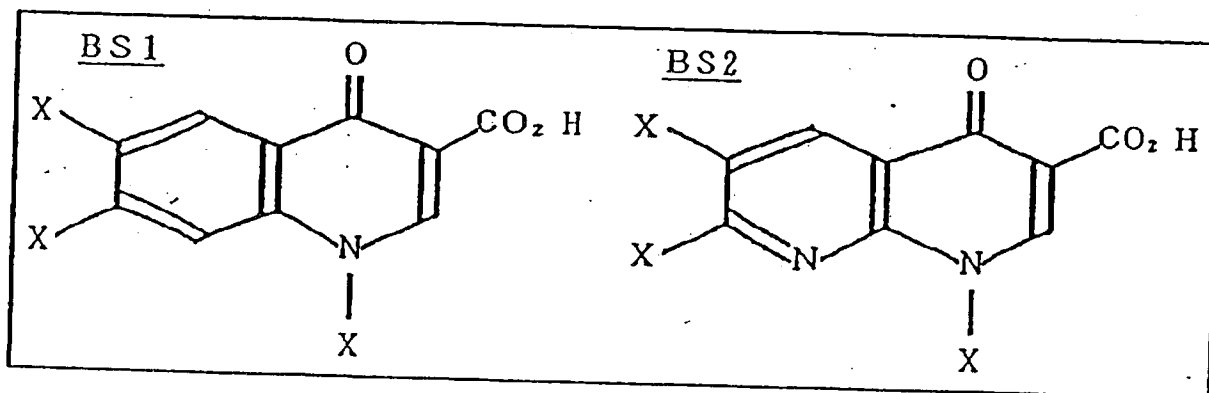
* X MEANS ALL KINDS OF ATOM EXCEPT HYDROGEN

SUBSTRUCTURE LIST USED BY THE RECOM PROGRAM

□ SUBSTRUCTURES HAVING POSSITIVE SIGN ON THE DISCRIMINANT FUNCTION

SIGN	SSID	SIGN	SSID
+	<u>SS2</u>	+	<u>SS8</u>
			
+	<u>SS3</u>	+	<u>SS10</u>
			

□ BASIC SUBSTRUCTURES OF PYRIDONE DERIVATIVES



FINALLY SELECTED NINE DESCRIPTOR SET
(USED ONLY BY THE SBSTRUCTURE DESCRIPTORS)

- 1. ALL-PATH CALC OF SS1 IN STRUCTURE
- +2. ALL-PATH CALC OF SS2 IN STRUCTURE
- +3. MOST (+) σ CHARGE OF ATOMS IN SS8
- 4. MOST (+) σ CHARGE OF ATOMS IN SS9
- +5. MOST (+) σ CHARGE OF ATOMS IN SS10
- 6. MOST (-) σ CHARGE OF ATOMS IN SS2
- +7. MOST (-) σ CHARGE OF ATOMS IN SS10
- +8. MOLAR REFRACTION OF SS3 IN STRUCTURE
- 9. APPEARANCE NUMBER OF SS5 IN STRUCTURE

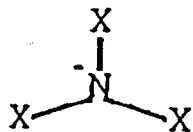
CLASS:1 27 COMPOUNDS
CLASS:2 29 COMPOUNDS TOTAL 56 COMPOUNDS

* ONE COMPOUND WAS DELETED FROM THE ORIGINAL
DATA SET TO KEEP DICHOTOMIZATION

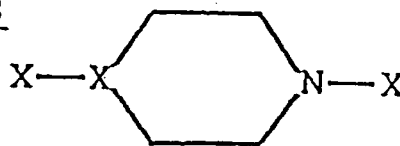
OPERATION FLOW OF GENERATING STRUCTURES
BY USING RECOM PROGRAM

1. CHOOSE SUBSTRUCTURES WHICH HAVE POSITIVE SIGN ON THE DISCRIMINANT FUNCTION

SS2



SS8



SS3

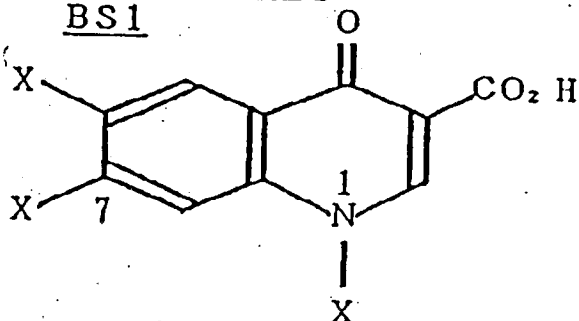


SS10

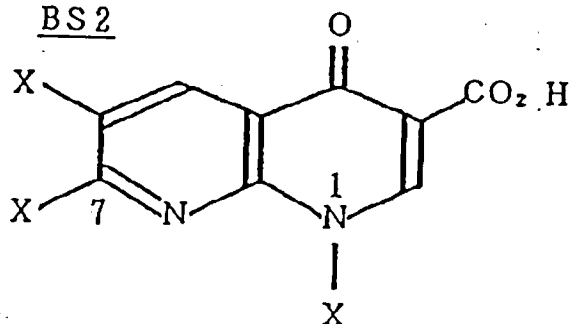


2. DETERMINE BASIC SUBSTRUCTURES WHICH INCLUDE QUINOLINE- AND 1,8-NAPHTHYRIDINE STRUCTURES USED ON THE RECOM PROGRAM WITH OTHER SUBSTRUCTURES

BS1



BS2



3. GENERATE STRUCTURES BY USING THE RECOM PROGRAM

4. DELETE COMPOUNDS BASED ON CHEMICAL REASONS

- ① FLUORINE SHOULD NOT CONNECT NITROGEN ATOM
- ② 1-AND 7-POSITION SHOULD BE LINKED AT LEAST FOUR ATOMS

