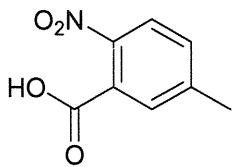
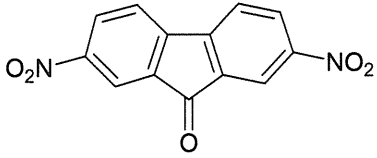
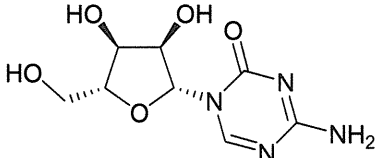
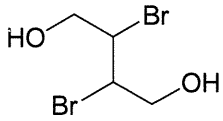

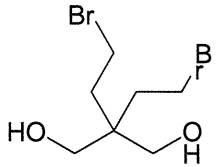
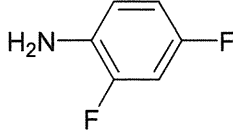
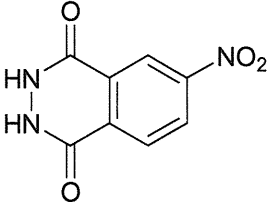
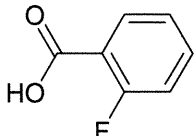
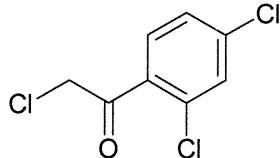
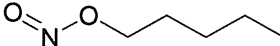
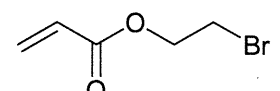
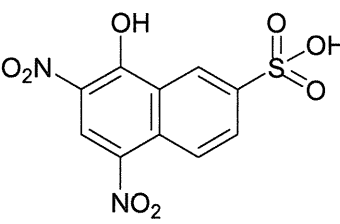
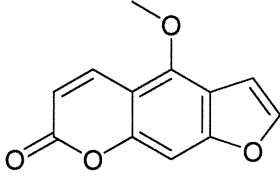
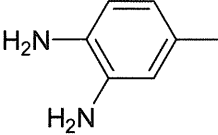
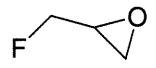

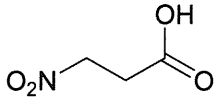
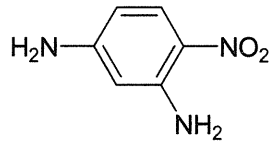
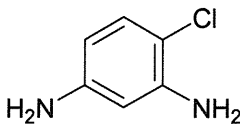
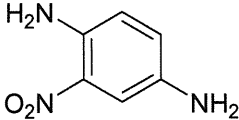
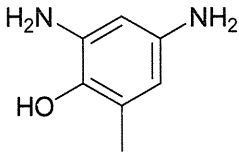
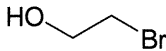
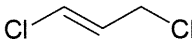
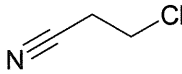
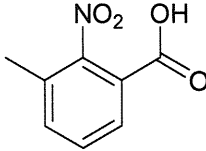
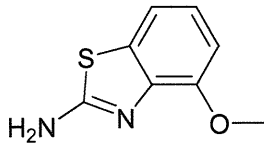
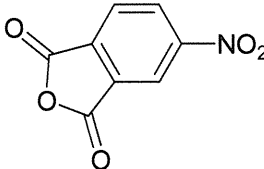
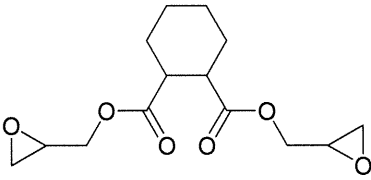
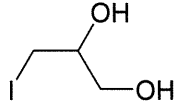
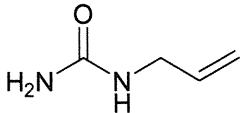
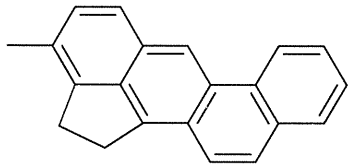
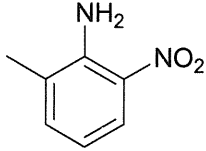
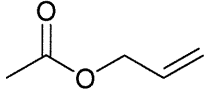
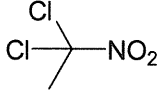
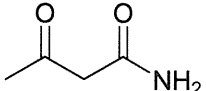
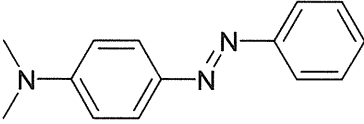
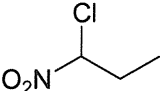
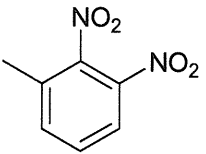
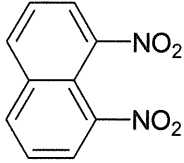
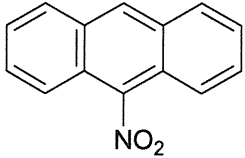
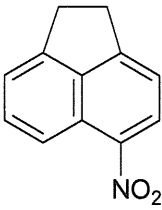
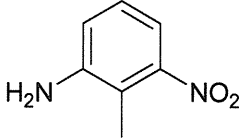
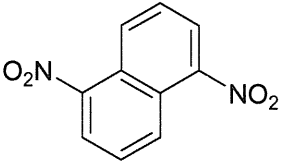
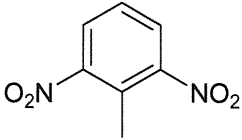
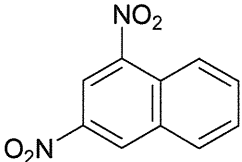
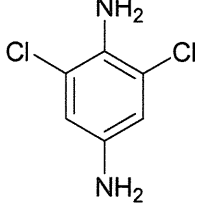
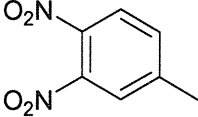
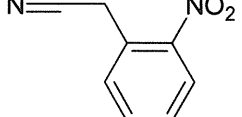
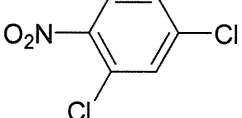


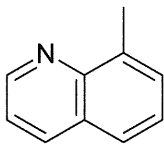
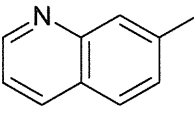
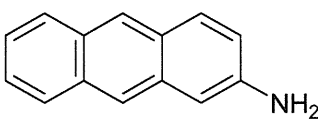
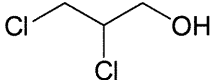
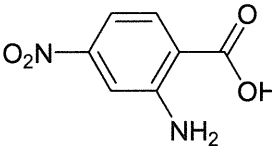
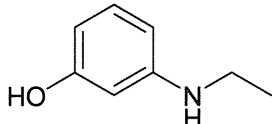
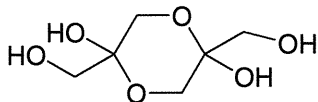
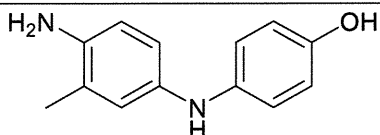
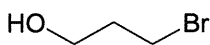
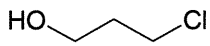
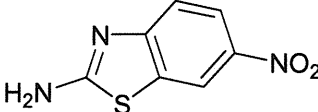
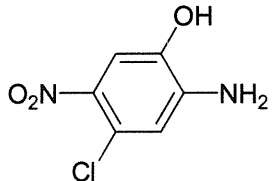
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300	31551-45-8		P
301	320-67-2		P
302	3234-02-4		P
303	3266-23-7		P
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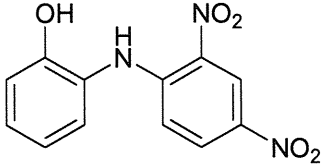
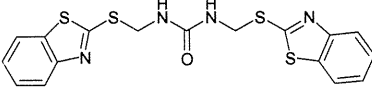
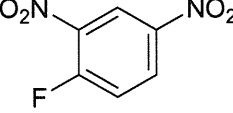


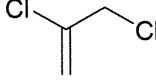
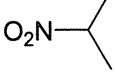
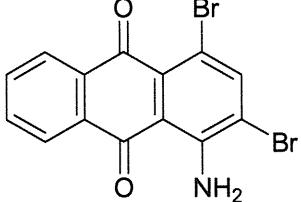
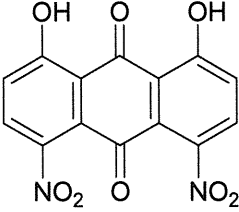
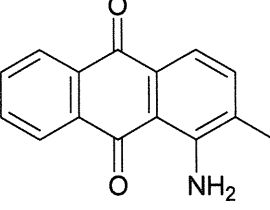
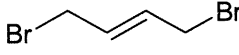
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309	463-04-7		P
310	4823-47-6		P
311	483-84-1		P
312	484-20-8		P
313	496-72-0		P
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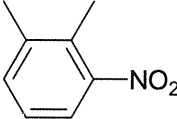
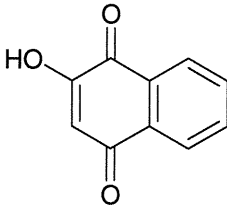
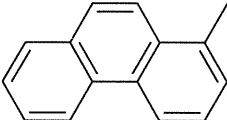
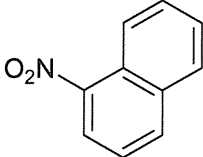
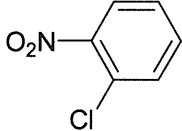
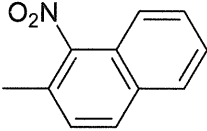
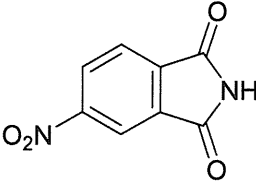
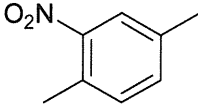
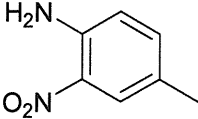
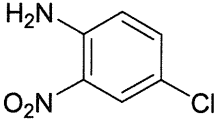
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321	540-51-2		P
322	542-75-6		P
323	542-76-7		P
324	5437-38-7		P
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326	5466-84-2		P
327	5493-45-8		P
328	554-10-9		P
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330	56-49-5		P
331	570-24-1		P
332	591-87-7		P
333	594-72-9		P
334	5977-14-0		P
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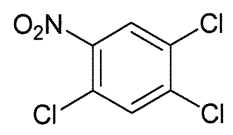
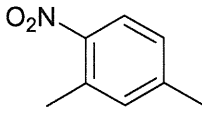
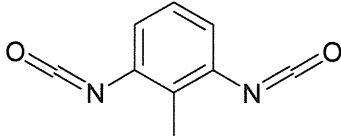
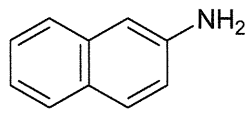
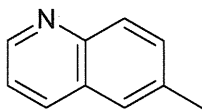
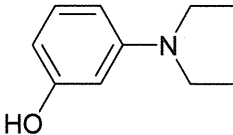
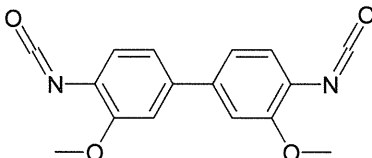
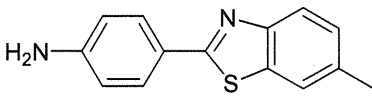
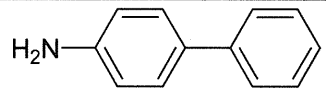
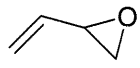
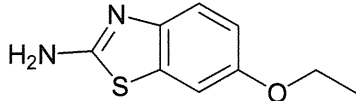
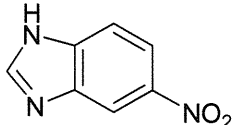
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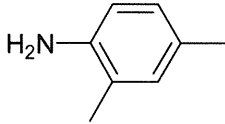
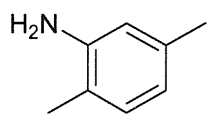
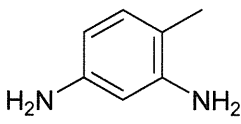
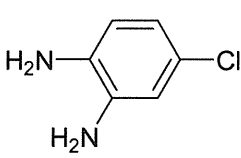
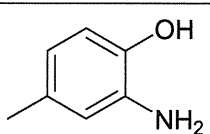
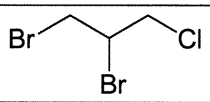
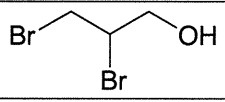
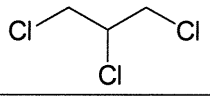
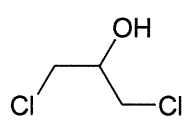
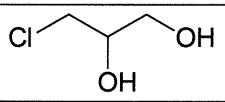
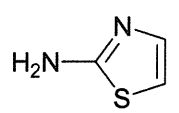
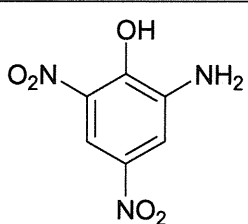
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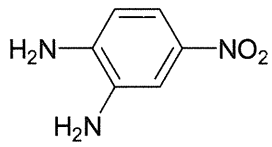
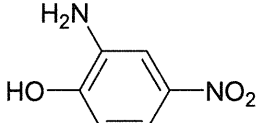
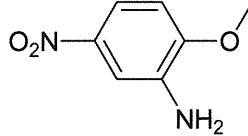
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厚生労働科学研究費補助金（化学物質リスク研究事業）  
分担研究報告書

分担研究課題：化学物質の構造の精密化、高度化に関する研究

研究分担者：出水庸介 国立医薬品食品衛生研究所有機化学部 第二室長

研究要旨

化学計算による化合物の精密な構造データの取得を行った。本年度プレカテゴリーライゼーション法で使用したデータセット（418 化合物）の全ての化合物の最安定構造（最安定コンフォーマー）を計算した。方法は、化学物質データベースのすべてについて分子力学計算（MMFF, OPLS2005 カ場等）を用いたコンフォメーション探索により最安定構造を計算した。ソフトウェアはシュレディンガー社の Macromodel を用いた。

A. 研究目的

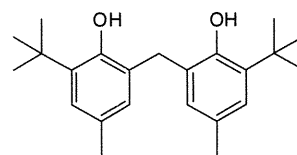
構造活性相関をより高度化するためには、そのもととなる化学物質の構造を高度化する必要がある。そこで化学計算による化学物質の精密な構造データの取得を目的とした。分子力学法と配座探索法（コンフォメーションサーチ）を用いて化学物質の精密な三次元構造を求めることとした。

B. 研究方法

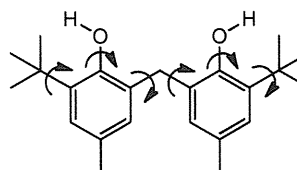
化学計算による化合物の精密な構造データの取得を行った。化学物質データベースのすべてについて分子力学計算（MMFF, OPLS2005 カ場等）を用いたコンフォメーション探索により最安定構造を計算した。ソフトウェアはシュレディンガー社の Macromodel を用いた。

最安定構造を求める方法論

(I) 初期座標の入力



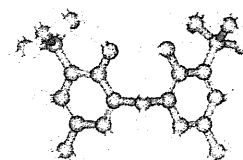
(II) 配座探索により最安定構造（グローバルミニマム）を求める



(III) ファイルフォーマットの変換



(IV) 最安定構造の表示



### (I) 初期座標の入力

グラフィカルユーザーインターフェース

(GUI) である Maestro 9.1 を用いて初期構造を入力した。構造異性体を含むと考えられる化学物質については、妥当と考えられる代表的な構造を用いた。分子力学計算で安定化を行い、構造を整えた。(ローカルミニマム)

### (II) 配座探索により最安定構造(グローバルミニマム)を求める

配座探索 (Conformational Search) の方法は Macromodel の MCMM (Torsion sampling) 法を用いた。力場は MMFF, OPLS 2005 を用いた。1000 個の初期座標を発生させ、それぞれの安定配座を計算し、最もエネルギーの低いものを最安定コンフォーマー (最安定構造) とした。

### (III) ファイルフォーマットの変換

最安定構造の座標を mol2 ファイルに変換した。mol2 ファイルは生物活性値とデータセットを作る際の必要となる。

### (IV) 最安定構造の表示

分子表示ソフトウェア DS viewerPro 6.0 を用いて最安定構造を分子モデルで表示した。(別表 4 に表示)

## C. 研究結果

本年度作成したプレカテゴライゼーション法で使用したデータセット (418 化合物) の全ての化合物の最安定構造 (最安定コンフォーマー) を計算した。(別表 2)

## D. 考察

既存の毒性データベースにおける化合物の構造は不備が多い。2次元構造においてすら、特に構造異性体に関しては不明なものが多い。この構造を使って構造活性相関を行っても良い結果は得られない。今後、

構造をどのように扱うかは重要な問題になる。

## E. 結論

プレカテゴライゼーションで使用したデータセット (418 化合物) の全ての化合物の最安定構造を計算した。今後、分子の3次元構造を用いる構造活性相関の解析に使用できるようになった。今回化合物の3次元構造を構築するに当たって明らかになったが、既存の構造活性相関にどのような構造が用いられていたかは大いに検証されるべきである。

## F. 健康危機情報

特になし

## G. 研究発表

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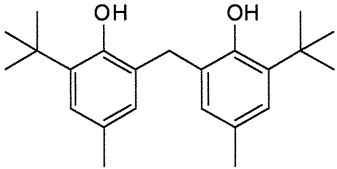
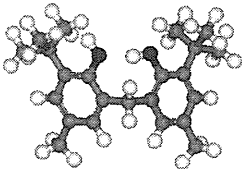
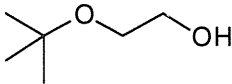
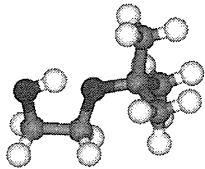
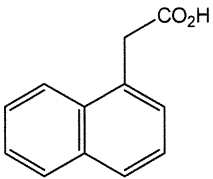
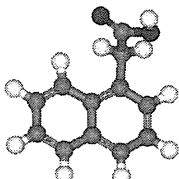
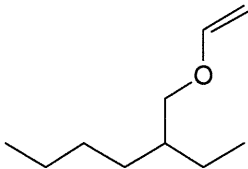
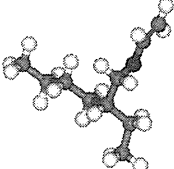
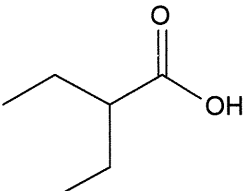
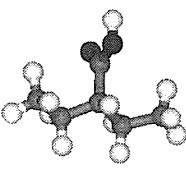
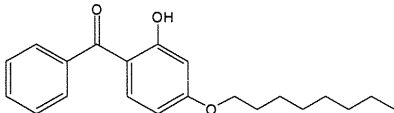
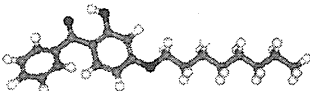
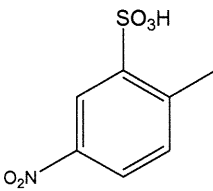
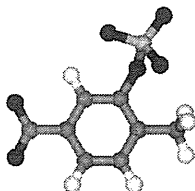
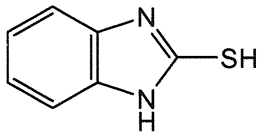
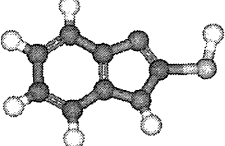
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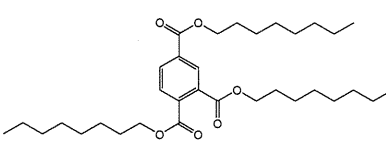
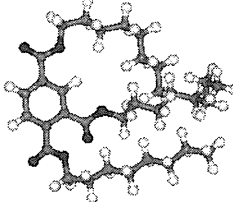
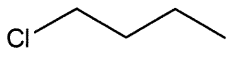
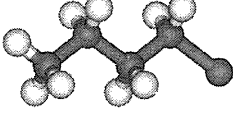
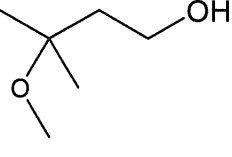
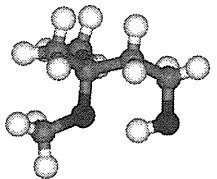
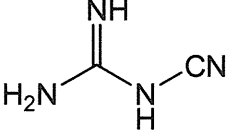
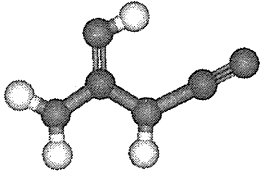
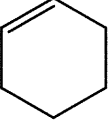
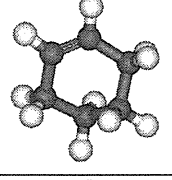
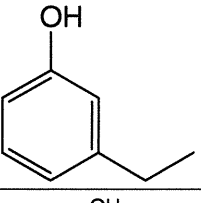
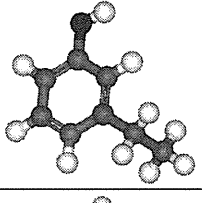
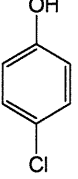
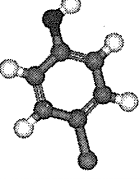
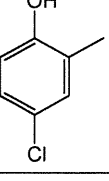
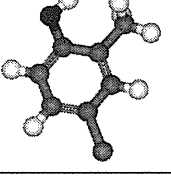
H. 知的財産権の出願・登録状況

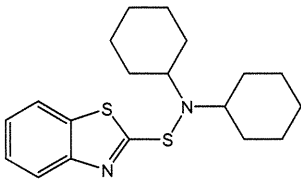
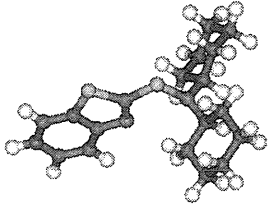
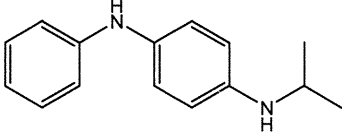
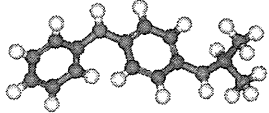
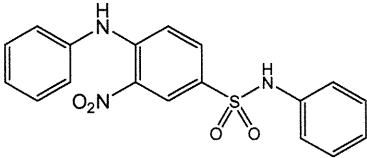
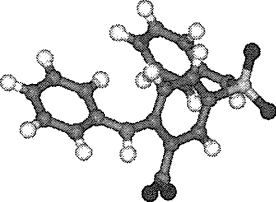
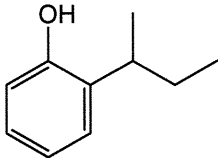
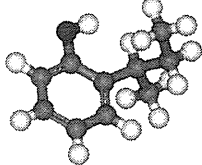
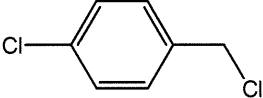
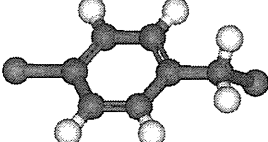
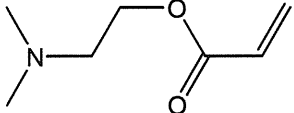
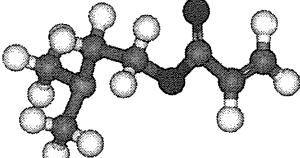
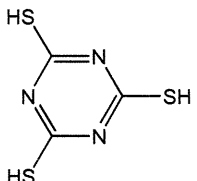
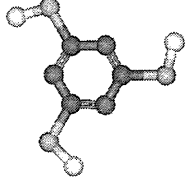

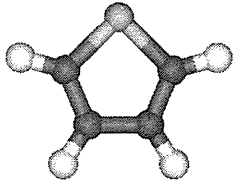
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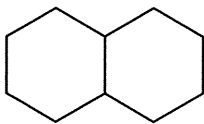
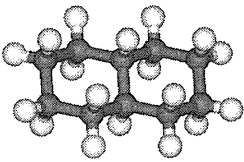
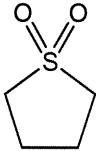
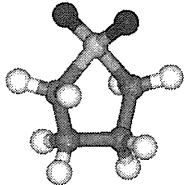

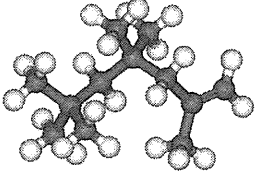
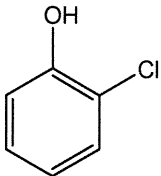
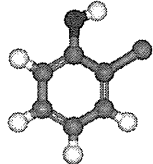
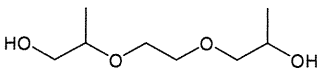
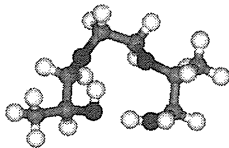
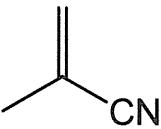
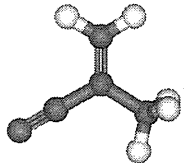
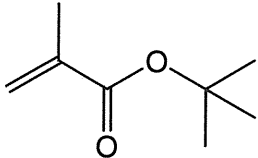
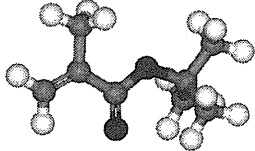


別表 2

	化合物名	構造式	三次元構造
1	2,2'-メチレン ビス(6-tert-ブ チル- <i>p</i> -クレゾ ール)		
2	2-tert-ブトキ シエタノール		
3	1-ナフチル酢 酸		
4	2-エチルヘキシル=ビ ニル=エーテル		
5	2-エチル酪酸		
6	2-ヒドロキシ -4-(オクチルオ キシ)ベンゾフ ェノン		
7	2-メチル-5-ニ トロベンゼン スルホン酸		
8	2-メルカプト ベンツイミダ ゾール		

9	1,2,4-ベンゼン トリカルボン 酸トリオクチ ル		
10	1-クロロプタ ン		
11	3-メトキシ-3- メチル-1-ブタ ノール		
12	シアノグアニ ジン		
13	シクロヘキセ ン		
14	3-エチルフェ ノール		
16	4-Chloro-o-cresol		
17	4-クロロ-o-ク レゾール		

18	N,N-ジシクロ ヘキシル-2-ベン ゾチアゾール スルフェン アミド		
19	N-フェニル-N'- イソプロピル p-フェニレン ジアミン		
20	ディスパーズ イエロー 42		
21	o-sec-ブチルフ ェノール		
22	$\alpha$ ,4-ジクロロ トルエン		
23	アクリル酸 2-(ジメチルア ミノ)エチルエ ステル		
24	トリチオシア ヌル酸		
25	チオフェン		

26	デカヒドロナ フタレン [ピシ クロ [4,4,0] デカン]		
27	テトラヒドロ チオフェン -1,1-ジオキシ ド		
28	トリイソブチ レン		
29	2-クロロフェ ノール		
30	トリプロピレ ングリコール		
31	メタクリロニ トリル		
32	メタクリル酸 tert-ブチルエ ステル		
33	2,3,6-トリメチ ルフェノール	