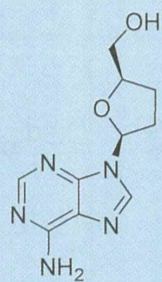
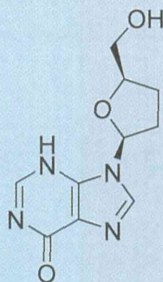

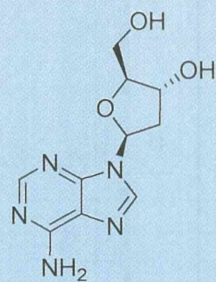
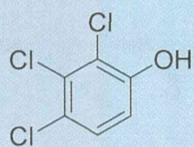
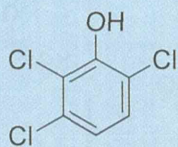
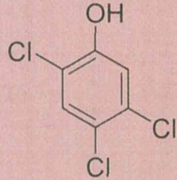

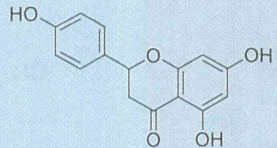
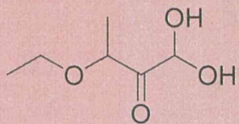
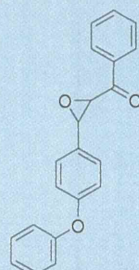
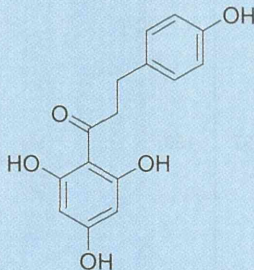
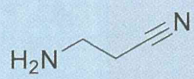
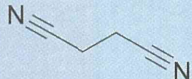
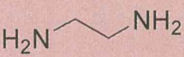
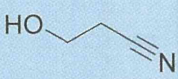
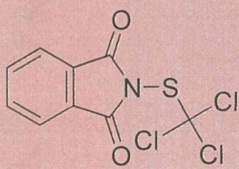
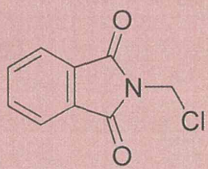
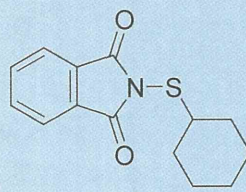
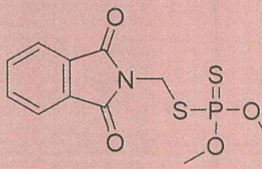
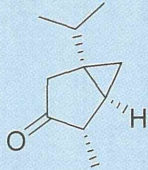
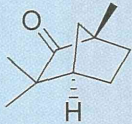
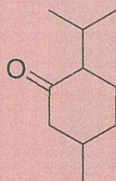
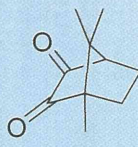
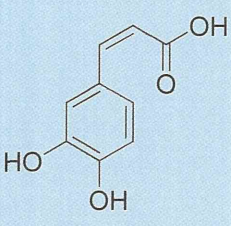
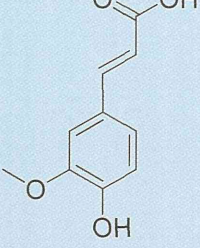
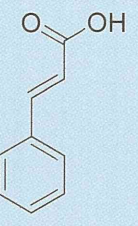
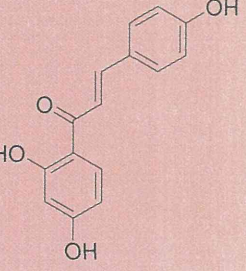
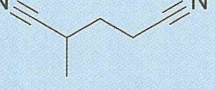
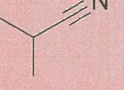

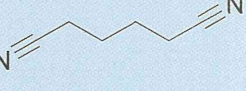
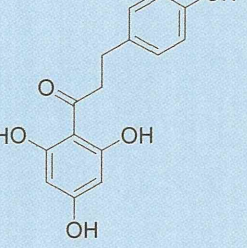
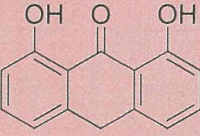
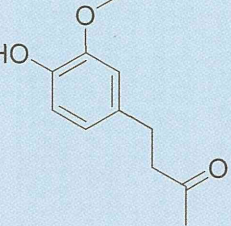
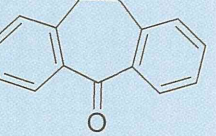


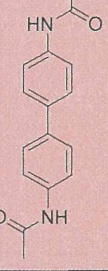
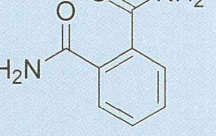
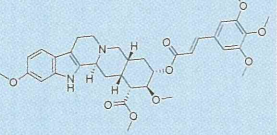
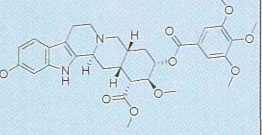
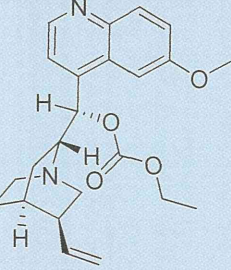
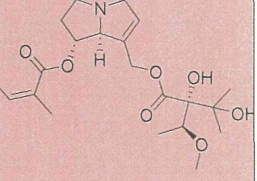
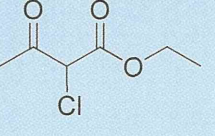
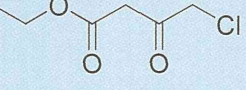
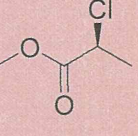
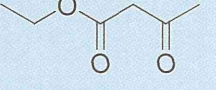
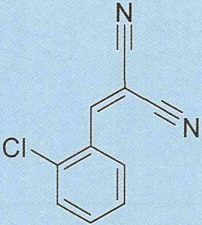
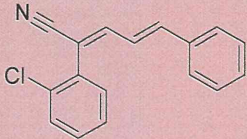
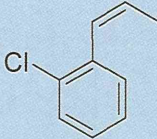
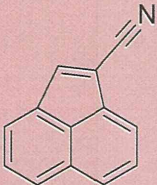


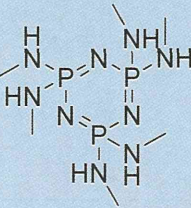
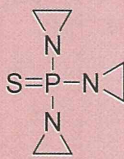
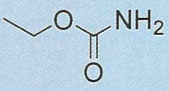
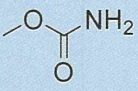
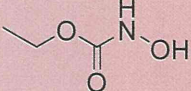
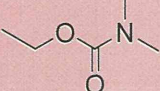
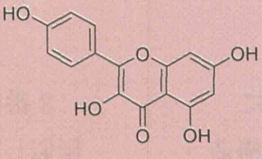
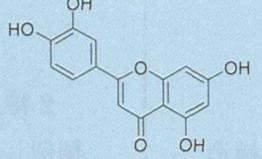
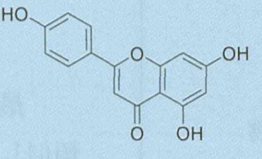
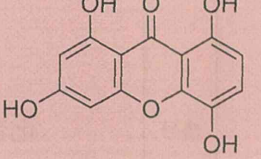
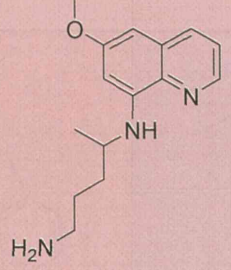
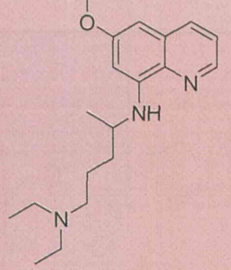
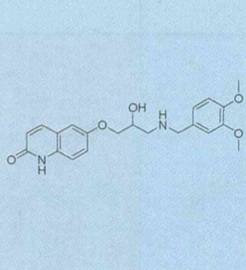
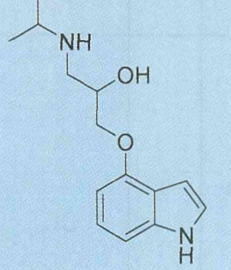
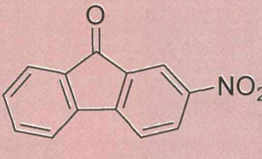
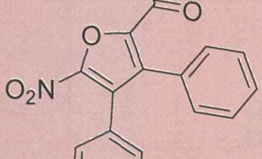
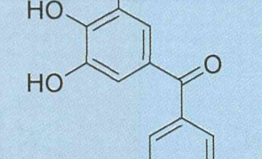
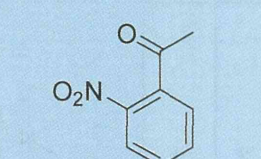
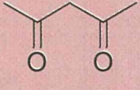
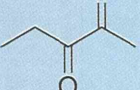
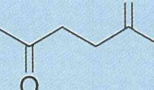
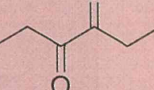


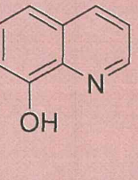
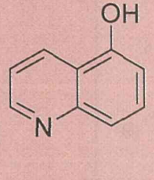
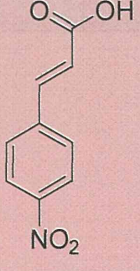
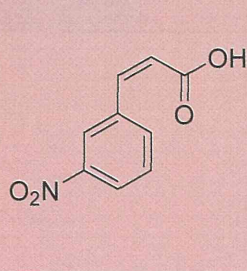
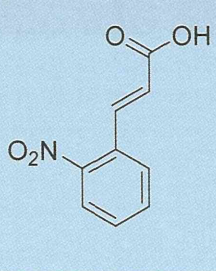
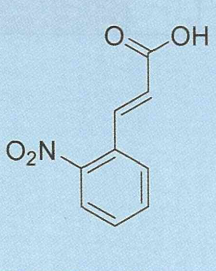


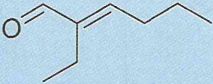
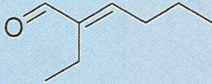
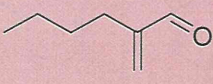
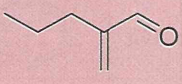

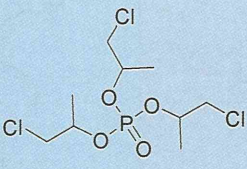
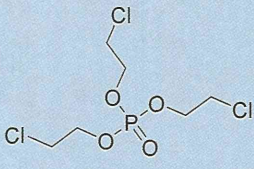



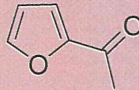
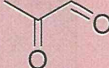


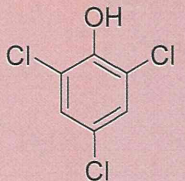
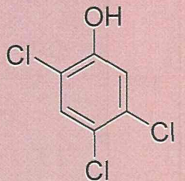
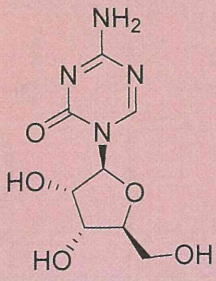
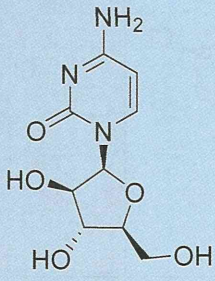
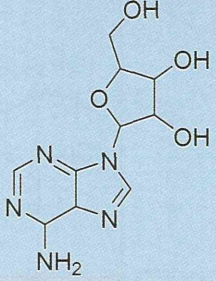

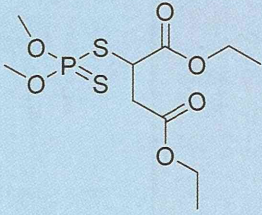
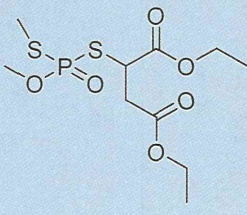
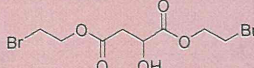
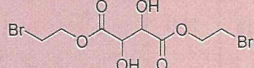
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42	185				
43	190				
44	191				
45	198				
46	199				

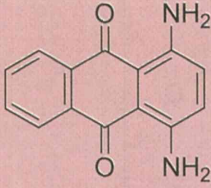
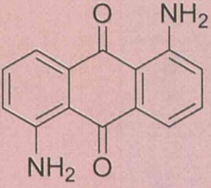
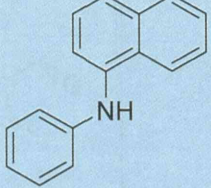
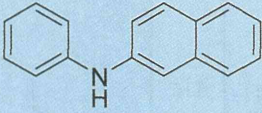
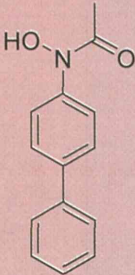
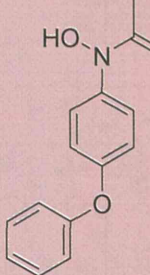
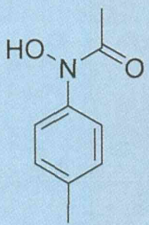
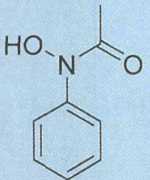
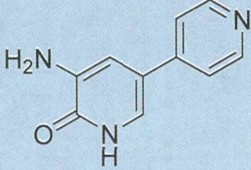
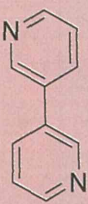
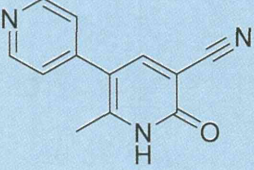

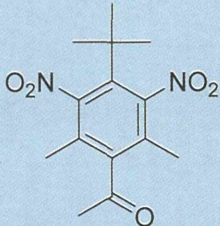
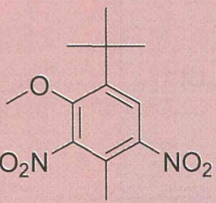
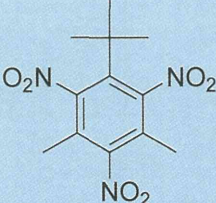
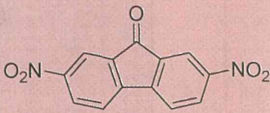
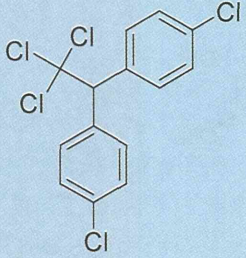
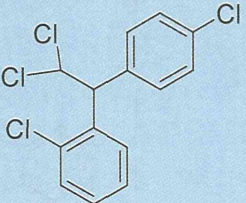
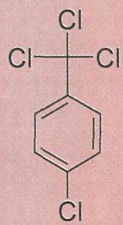
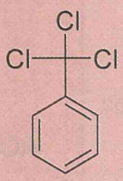
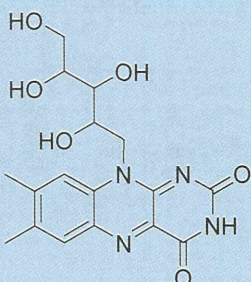
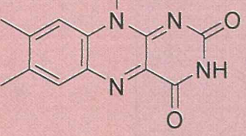
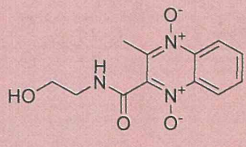
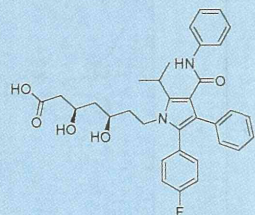
47	201				
48	203				
49	204				
50	209				
51	211				
52	214				

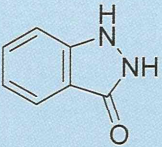
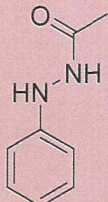
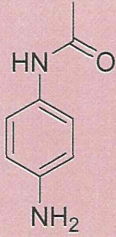
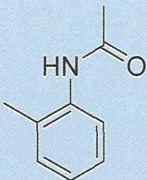
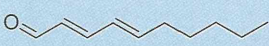
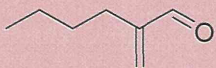
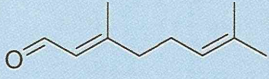
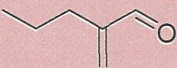


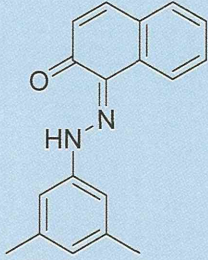

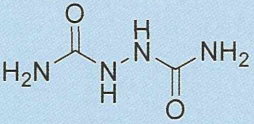
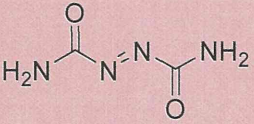
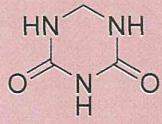
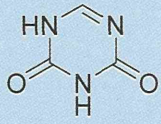
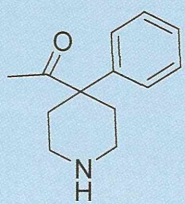
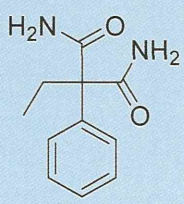


別表 6 : 最も構造が類似した 3 つの化合物のうち Ames 試験結果が 2 つ不一致のもの

	番号	化合物	最も類似した構造	2 番目に類似した構造	3 番目に類似した構造
1	4				
2	9				
3	27				
4	49	$\text{H}_2\text{B}-\text{BH}_2$	Si	C	Zn

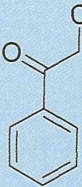
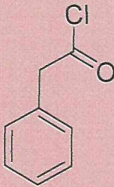
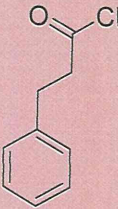
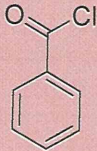
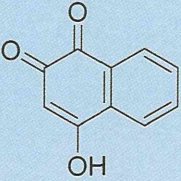
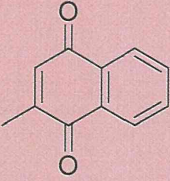

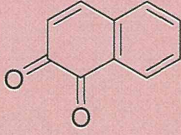
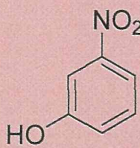
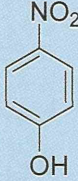
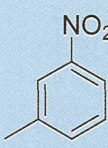
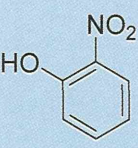
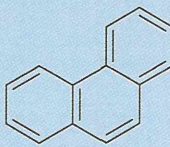
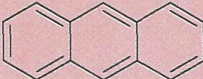
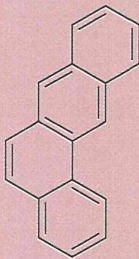
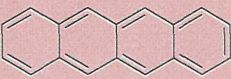
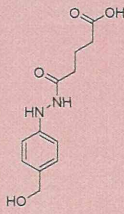
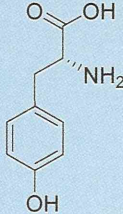
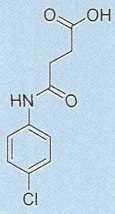
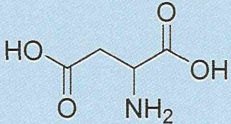
5	57				
6	63				
7	67				
8	74				
9	87				
10	109				

11	115				
12	135				
13	142				
14	143				
15	152				
16	153				

17	155				
18	157				
19	158				
20	172				
21	179				
22	180				

23	184				
24	192				
25	200				
26	205				
27	208				

別表 7 : 最も構造が類似した 3 つの化合物のうち Ames 試験結果が全て不一致のもの

	番号	化合物	最も類似した構造	2 番目に類似した構造	3 番目に類似した構造
1	43				
2	54				
3	64				
4	93				
5	112				

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

本年度は構造類似性に基づいた予測法の開発を目的とした。任意の 214 化合物を検証母集団とした。この検証母集団のターゲット分子の構造の精密化、高度化に対応するため、エネルギー安定構造である三次元構造を求めた。

最安定構造を求める方法論

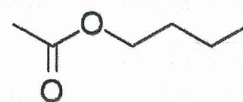
A. 研究目的

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ルサーチ）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。

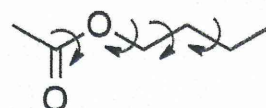
B. 研究方法

検証母集団の 214 化合物について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。方法は昨年度と同じ方法で行った。分子力学計算（MMFF, OPLS2005 力場等）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。

(I) 初期座標の入力



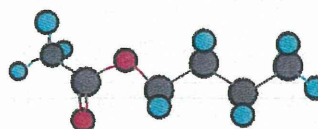
(II) 配座探索により最安定構造（グローバルミニマム）を求める



(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。

C. 研究結果

本プロジェクトで用いた、検証母集団の 214 化合物について最安定構造(最安定コンフォマー)を計算した。(表 1)

D. 考察

現在のところ 2次元の構造類似性による予測法を行っているが、3次元構造による構造類似性による予測法を検討することは非常に興味深い問題である。特に、最も構造類似性の高い化合物と活性が不一致のものについては化学構造及び立体構造による考察が必要であると考えられる。

E. 結論

本プロジェクトで用いた、検証母集団の 214 化合物について最安定構造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。現在のところ 2次元の構造類似性による予測法を行っているが、3次元構造による構造類似性による予測法を検討したい。

F. 健康危機情報

特になし

G. 研究発表

1. 論文発表

(論文発表-参考: コンピュータシミュレーションを含むもの)

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