

### (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 Chem3D 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

AMES/QSAR International Collaborative Study のデータ 4021 件中の任意の 1000 件のなかの A グループ (47 件) 及び B グループ (79 件) の化合物について最安定構造 (最安定コンフォーマー) を計算した。(表 1, 表 2)

## 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

AMES/QSAR International Collaborative Study のデータ 4021 件中の任意の 1000 件のなかの A グループ (47 件) 及び B グループ (79 件) の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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H. Yamashita; Y. Demizu; T. Misawa; T. Shoda; M. Kurihara; Synthesis of a bis-cationic $\alpha,\alpha$ -disubstituted amino acid (9-amino-bispidine-9-carboxylic acid) and its effects on the conformational properties of peptides; *Tetrahedron*, 71, 2241-2245(2015)

Y. Demizu, H. Yamashita, T. Misawa, M. Doi, M. Tanaka, M. Kurihara; Effects of D-Leu residues on the helical secondary structures of L-Leu-based nonapeptides;

*Chem. Pharm. Bull.* 63, 218-224 (2015)

H. Yamashita; Y. Demizu; T. Misawa; T. Shoda; M. Kurihara; Synthesis of a bis-cationic $\alpha,\alpha$ -disubstituted amino acid (9-amino-bispidine-9-carboxylic acid) and its effects on the conformational properties of peptides; *Tetrahedron*, 71, 2241-2245(2015)

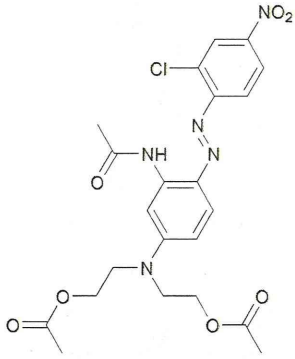
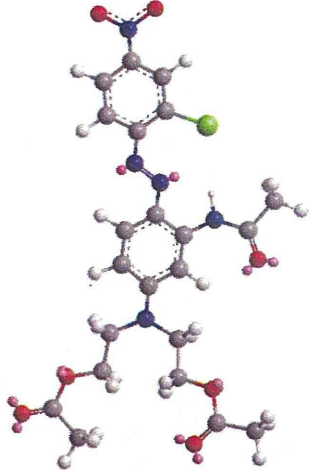
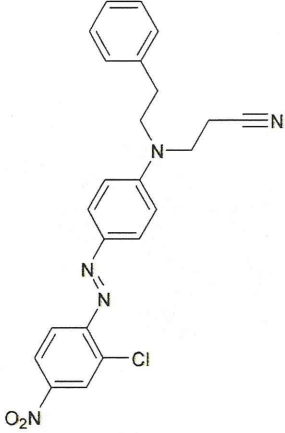
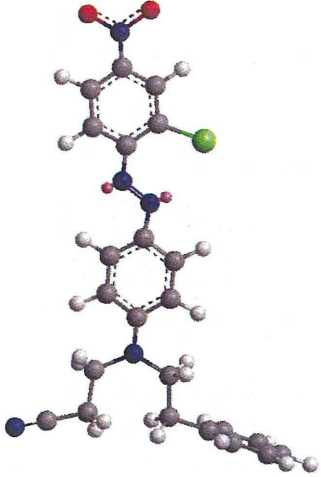
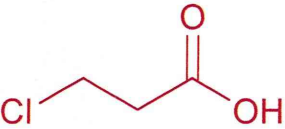
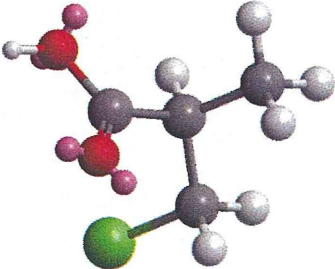
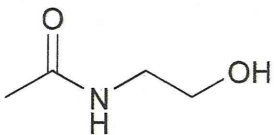
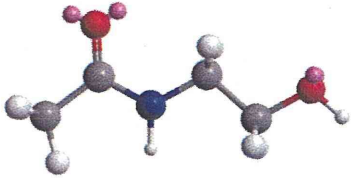
## 2. 学会発表

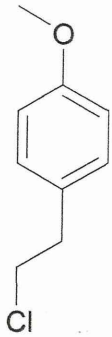
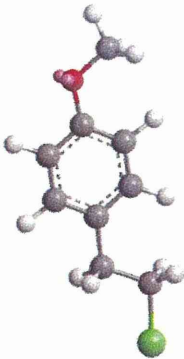
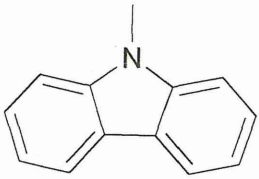
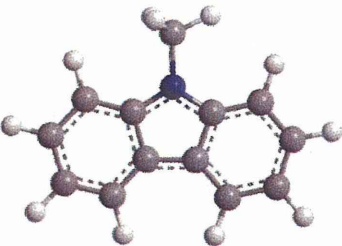
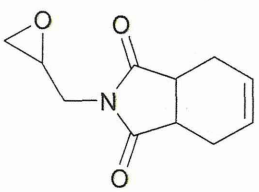
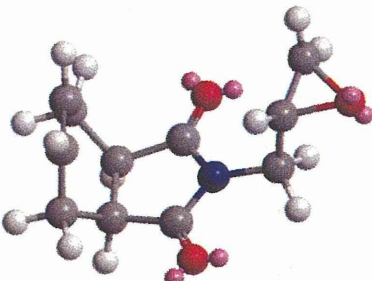
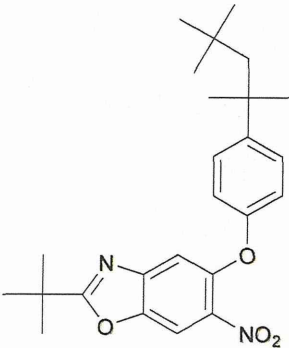
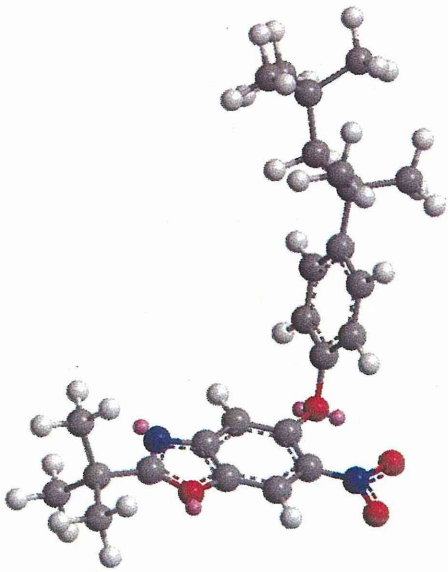
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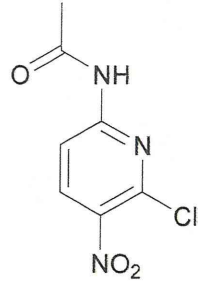
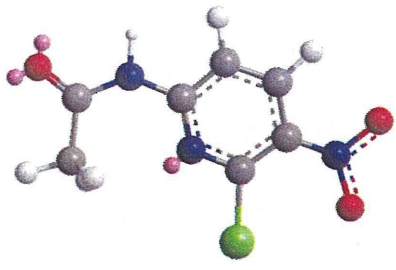
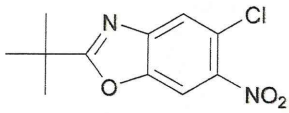
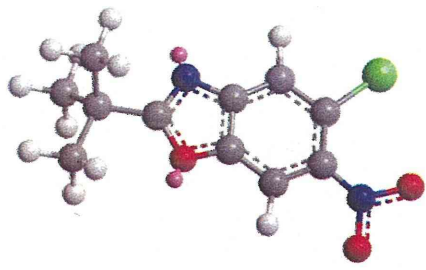
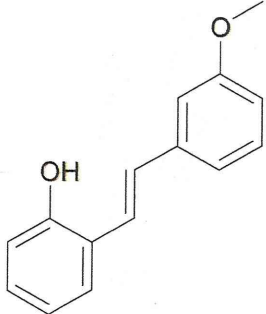
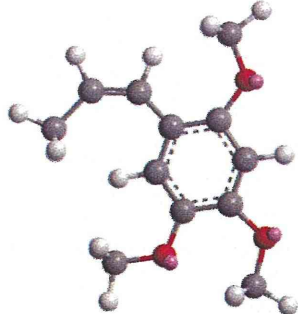
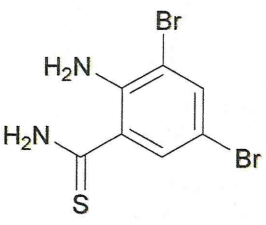
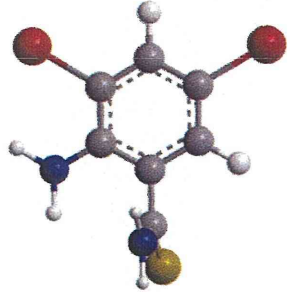
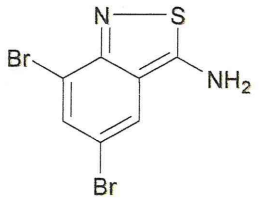
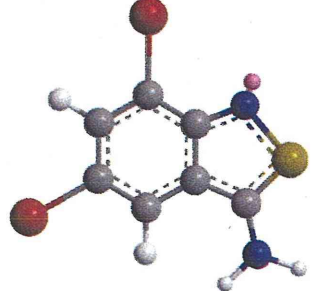
## H. 知的財産権の出願・登録状況

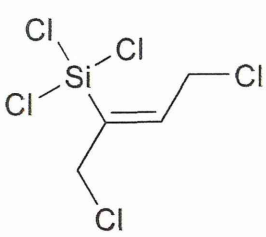
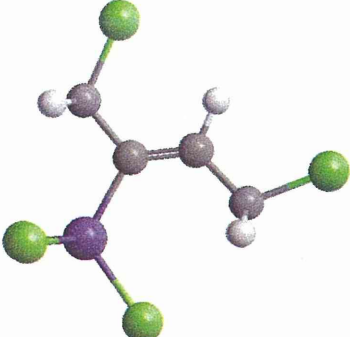
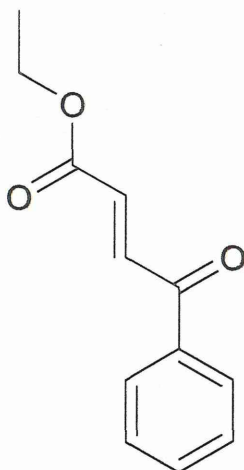
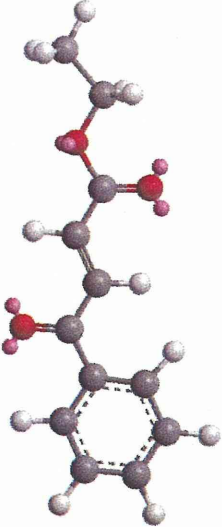
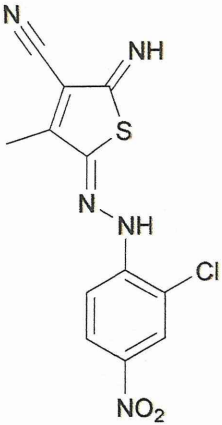
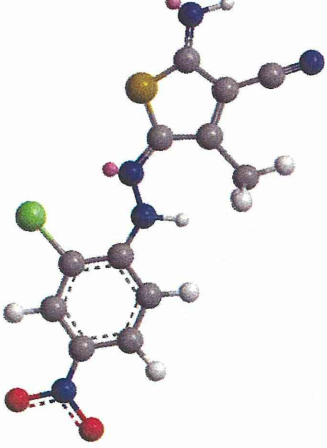
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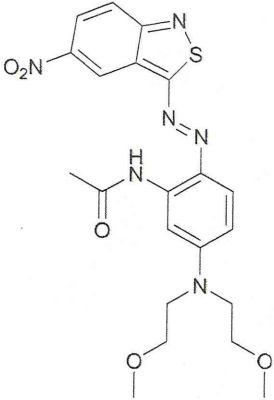
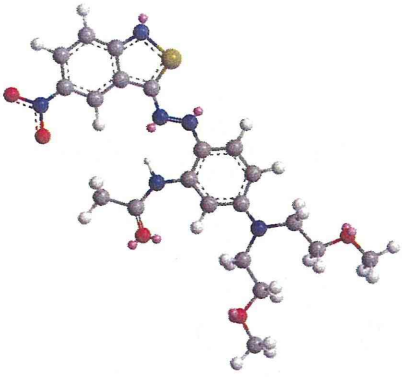
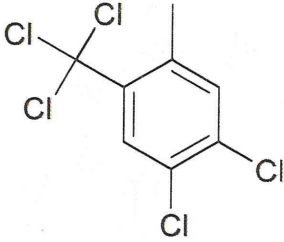
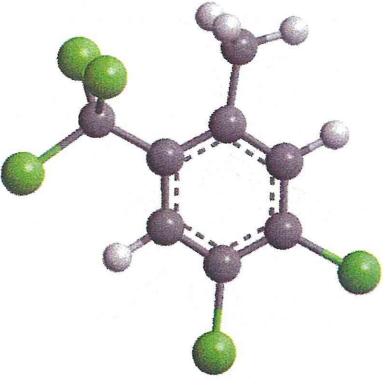
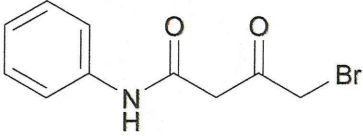
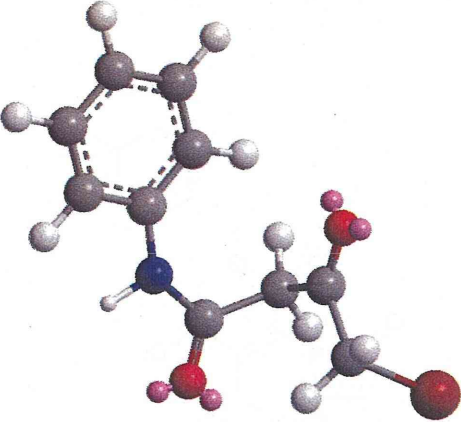
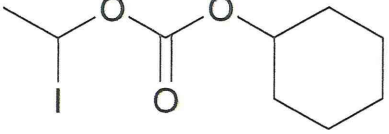
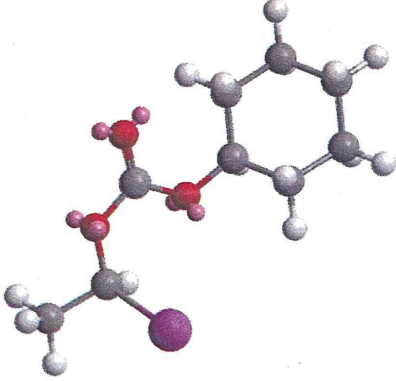
表 1

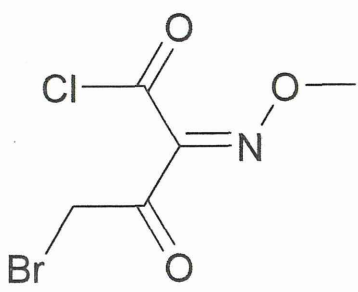
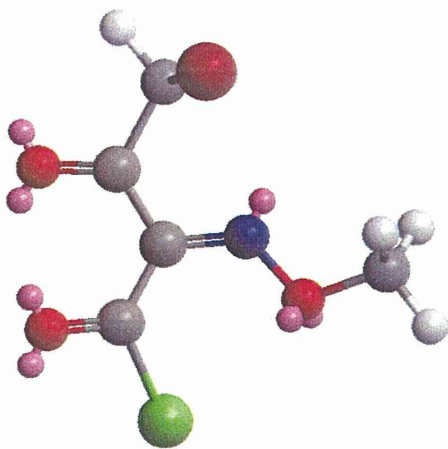
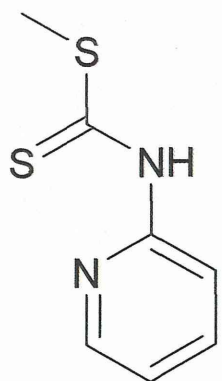
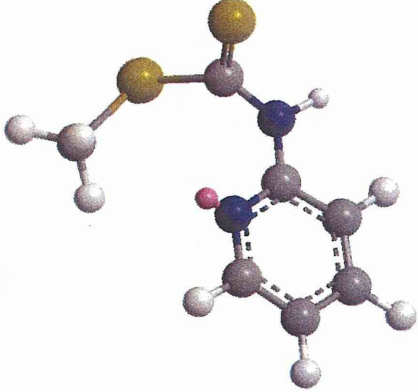
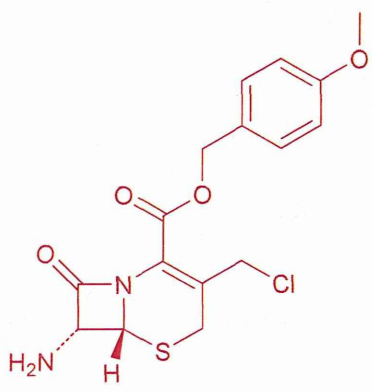
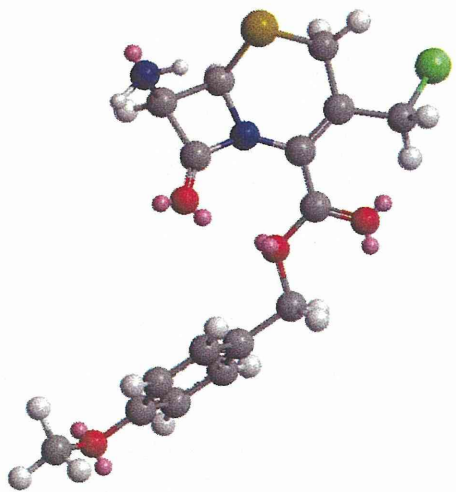
	A	最安定構造
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5	 <p>Chemical structure of 4-(chloromethyl)anisole, showing a benzene ring with a methoxy group (-OCH<sub>3</sub>) at the para position and a chloromethyl group (-CH<sub>2</sub>Cl) at the other para position.</p>	 <p>3D ball-and-stick model of 4-(chloromethyl)anisole, showing the spatial arrangement of atoms (Carbon in grey, Oxygen in red, Chlorine in green, Hydrogen in white).</p>
6	 <p>Chemical structure of indole, a bicyclic aromatic heterocycle consisting of a benzene ring fused to a pyrrole ring.</p>	 <p>3D ball-and-stick model of indole, showing the spatial arrangement of atoms (Carbon in grey, Nitrogen in blue, Hydrogen in white).</p>
7	 <p>Chemical structure of 2-(2-oxo-1,2,3,4-tetrahydrophthalazine-5-yl)oxirane, featuring a phthalazine ring system with a carbonyl group and an epoxide ring attached to the nitrogen atom.</p>	 <p>3D ball-and-stick model of 2-(2-oxo-1,2,3,4-tetrahydrophthalazine-5-yl)oxirane, showing the spatial arrangement of atoms (Carbon in grey, Nitrogen in blue, Oxygen in red, Hydrogen in white).</p>
8	 <p>Chemical structure of 2-(tert-butyl)-5-(tert-butylphenoxy)-3-nitroisoxazole, showing an isoxazole ring substituted with a tert-butyl group, a nitro group (-NO<sub>2</sub>), and a tert-butylphenoxy group.</p>	 <p>3D ball-and-stick model of 2-(tert-butyl)-5-(tert-butylphenoxy)-3-nitroisoxazole, showing the spatial arrangement of atoms (Carbon in grey, Nitrogen in blue, Oxygen in red, Hydrogen in white).</p>

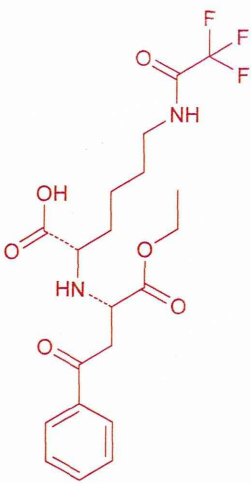
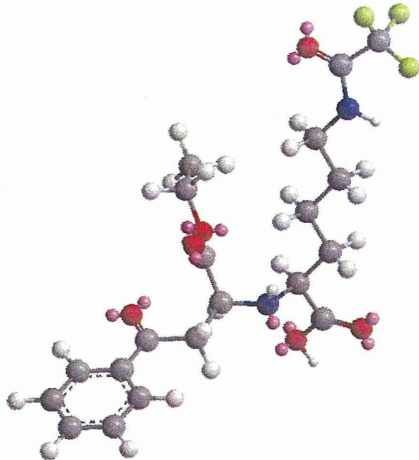
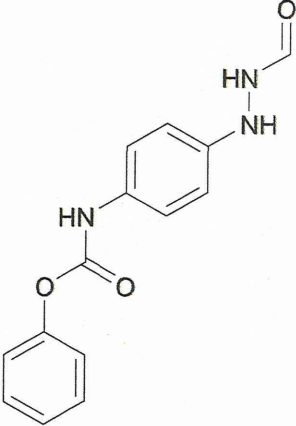
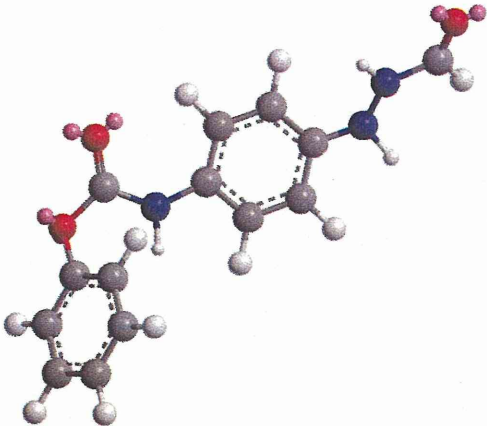
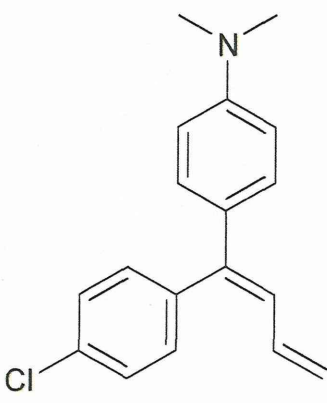
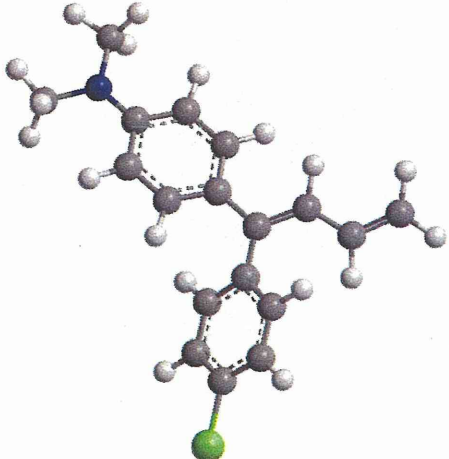
9	 <p>Chemical structure of 2-chloro-5-nitro-N-(2-oxoethyl)pyridine. It features a pyridine ring with a chlorine atom at the 2-position and a nitro group at the 5-position. An N-(2-oxoethyl) group is attached to the nitrogen atom at the 1-position.</p>	 <p>3D ball-and-stick model of 2-chloro-5-nitro-N-(2-oxoethyl)pyridine. The model shows the spatial arrangement of atoms, with carbon in grey, nitrogen in blue, oxygen in red, chlorine in green, and nitrogen in yellow.</p>
10	 <p>Chemical structure of 2-(2-chloro-5-nitrophenyl)isoxazole. It consists of an isoxazole ring attached to a benzene ring. The benzene ring has a chlorine atom at the 2-position and a nitro group at the 5-position.</p>	 <p>3D ball-and-stick model of 2-(2-chloro-5-nitrophenyl)isoxazole. The model shows the spatial arrangement of atoms, with carbon in grey, nitrogen in blue, oxygen in red, chlorine in green, and nitrogen in yellow.</p>
11	 <p>Chemical structure of 4-(3-hydroxyphenyl)but-3-en-2-one. It features a benzene ring with a hydroxyl group at the 3-position, connected via a propenyl chain to a carbonyl group.</p>	 <p>3D ball-and-stick model of 4-(3-hydroxyphenyl)but-3-en-2-one. The model shows the spatial arrangement of atoms, with carbon in grey, oxygen in red, and hydrogen in white.</p>
12	 <p>Chemical structure of 2,4-dibromo-5-aminothiobenzamide. It consists of a benzene ring with an amino group at the 5-position and two bromine atoms at the 2 and 4 positions. A thiobenzamide group is attached to the benzene ring.</p>	 <p>3D ball-and-stick model of 2,4-dibromo-5-aminothiobenzamide. The model shows the spatial arrangement of atoms, with carbon in grey, nitrogen in blue, sulfur in yellow, oxygen in red, and bromine in green.</p>
13	 <p>Chemical structure of 2-amino-4,6-dibromo-1,2,4-thiazole. It features a 1,2,4-thiazole ring with an amino group at the 2-position and two bromine atoms at the 4 and 6 positions.</p>	 <p>3D ball-and-stick model of 2-amino-4,6-dibromo-1,2,4-thiazole. The model shows the spatial arrangement of atoms, with carbon in grey, nitrogen in blue, sulfur in yellow, oxygen in red, and bromine in green.</p>

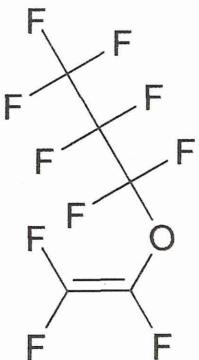
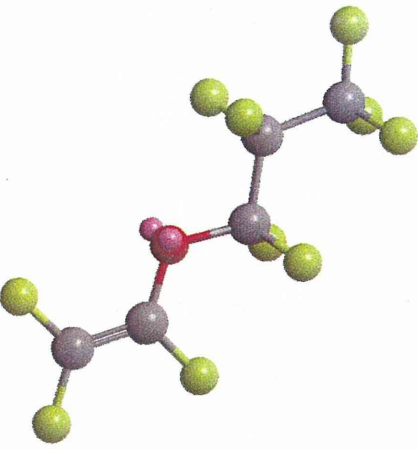
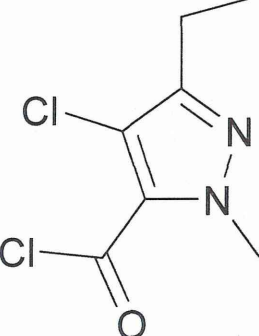
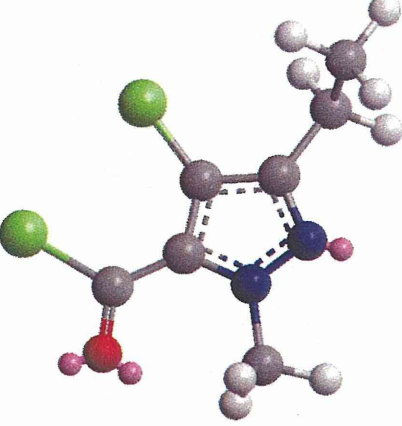
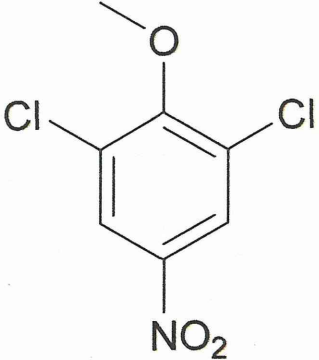
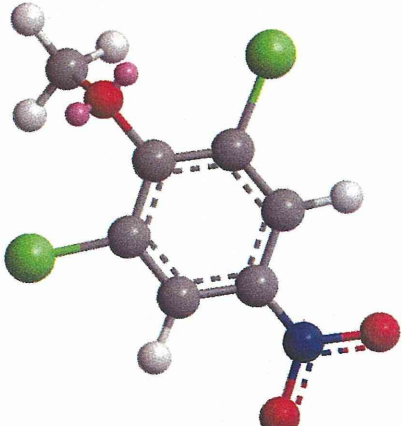
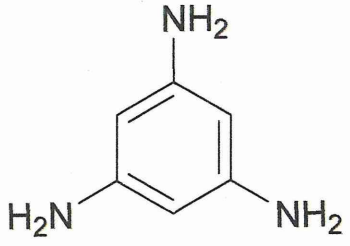
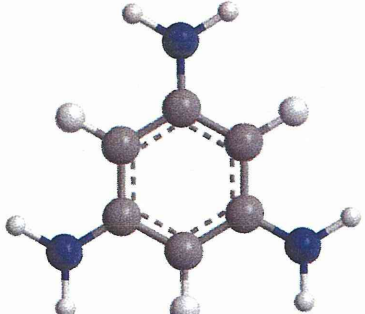
14	 <p>Chemical structure of a chlorinated silicon compound. It features a central silicon atom (Si) bonded to three chlorine atoms (Cl) and a carbon atom. This carbon atom is part of a double bond with another carbon atom, which is further bonded to a chlorine atom and a methylene group (-CH<sub>2</sub>-Cl).</p>	 <p>3D ball-and-stick model of the chlorinated silicon compound. The silicon atom is shown in purple, chlorine atoms in green, and carbon atoms in grey. Hydrogen atoms are shown in white.</p>
15	 <p>Chemical structure of ethyl 3-oxo-3-phenylacrylate. It consists of a central carbon-carbon double bond. One carbon is bonded to an ethoxy group (-OCH<sub>2</sub>CH<sub>3</sub>) and a carbonyl group (=O). The other carbon is bonded to a carbonyl group (=O) and a phenyl ring.</p>	 <p>3D ball-and-stick model of ethyl 3-oxo-3-phenylacrylate. Carbon atoms are grey, oxygen atoms are red, hydrogen atoms are white, and the phenyl ring is shown with dashed lines to indicate its planar structure.</p>
16	 <p>Chemical structure of a thiazole derivative. The thiazole ring is substituted with a cyano group (-C≡N), a methyl group (-CH<sub>3</sub>), and an imino group (=NH). It is also linked via an imine group (-N=NH-) to a benzene ring. The benzene ring is substituted with a chlorine atom (-Cl) and a nitro group (-NO<sub>2</sub>).</p>	 <p>3D ball-and-stick model of the thiazole derivative. Carbon atoms are grey, nitrogen atoms are blue, sulfur is yellow, oxygen atoms are red, hydrogen atoms are white, chlorine is green, and the nitro group is shown with dashed lines to indicate its planar structure.</p>

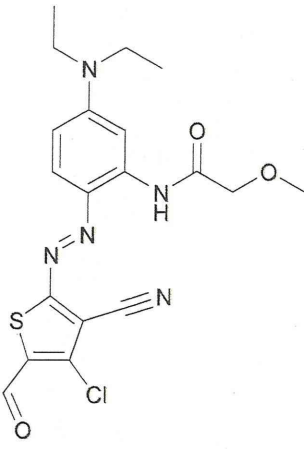
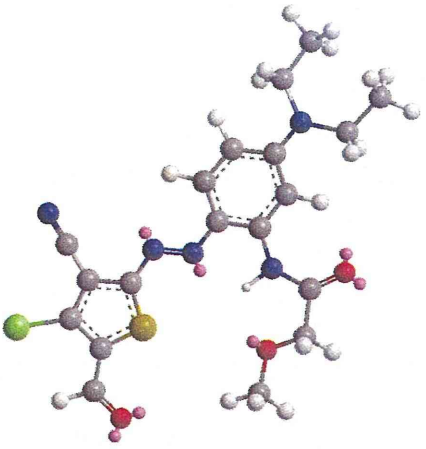
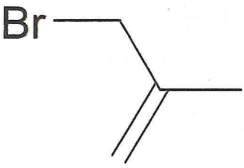
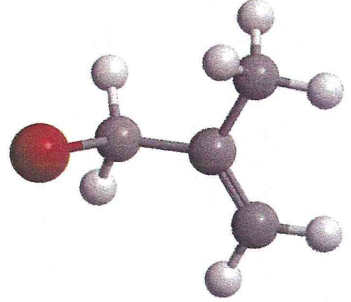
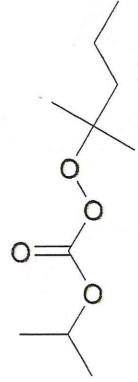
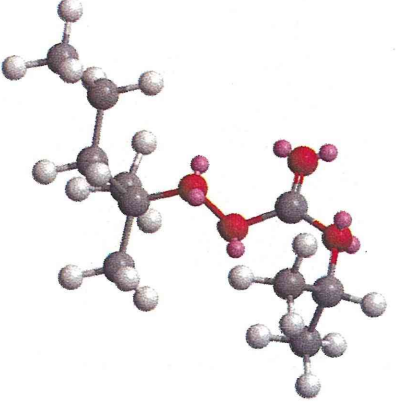
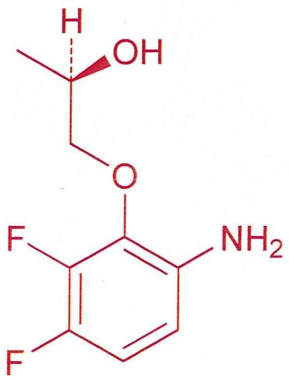
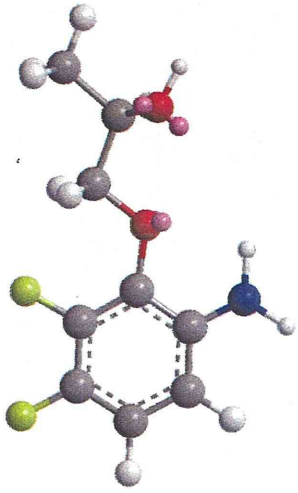
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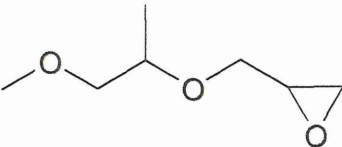
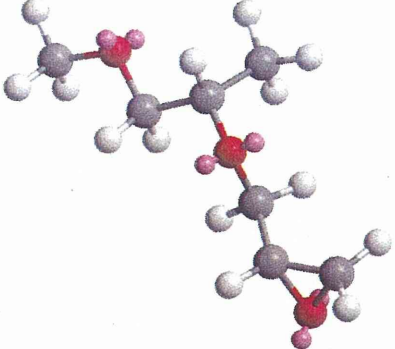
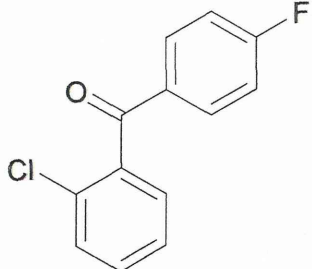
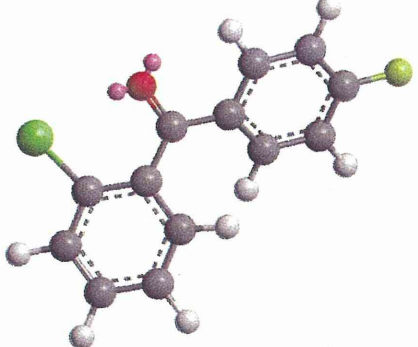
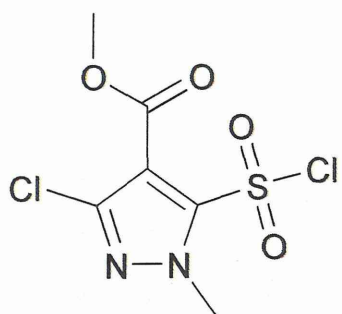
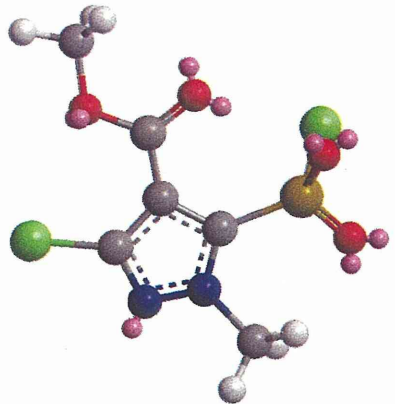
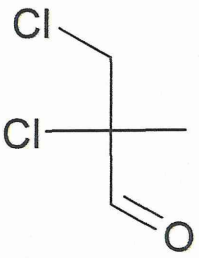
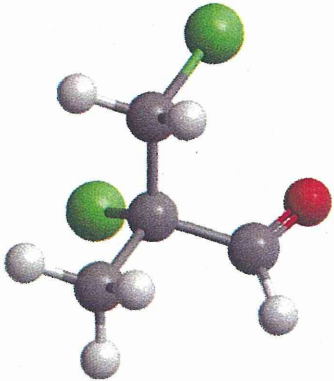
21	 <p>Chemical structure of 2-bromo-1-(chloroacetyl)ethanimine N-methyl ether. The structure shows a central carbon atom double-bonded to a nitrogen atom which is bonded to a methyl group. The central carbon is also single-bonded to a bromomethyl group and a chloroacetyl group.</p>	 <p>3D ball-and-stick model of 2-bromo-1-(chloroacetyl)ethanimine N-methyl ether. The model shows the spatial arrangement of atoms: carbon (grey), oxygen (red), nitrogen (blue), bromine (green), and chlorine (pink).</p>
22	 <p>Chemical structure of N-(pyridin-2-yl)thioacetamide. It consists of a pyridine ring attached to the nitrogen atom of a thioacetamide group.</p>	 <p>3D ball-and-stick model of N-(pyridin-2-yl)thioacetamide. The model shows the pyridine ring and the thioacetamide group in a 3D perspective.</p>
23	 <p>Chemical structure of a penicillin derivative. The structure shows a penicillin core with a 4-methoxyphenylacetamido group, a 2-chloroethyl group, and an amino group.</p>	 <p>3D ball-and-stick model of a penicillin derivative. The model shows the complex 3D structure of the penicillin core and its substituents.</p>

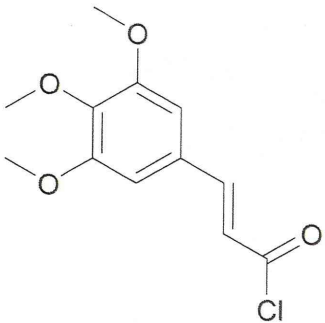
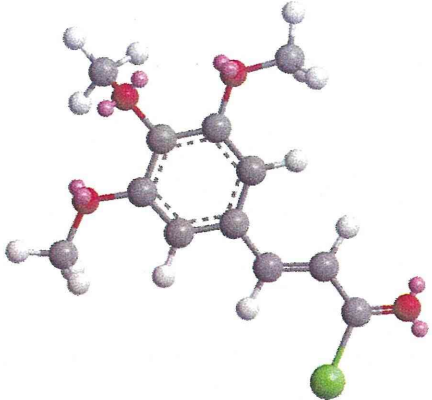
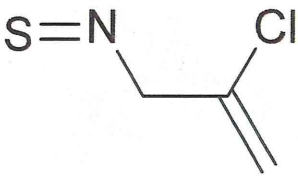
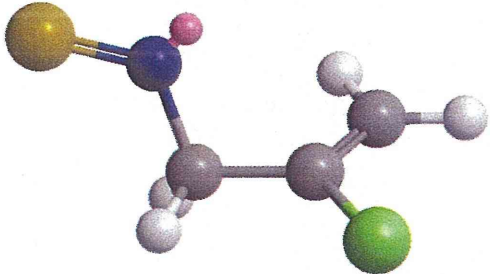
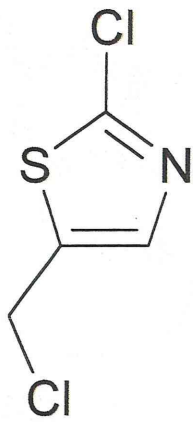
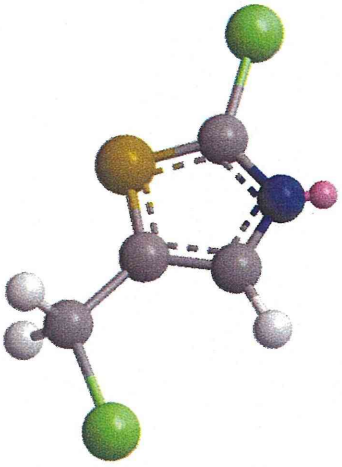
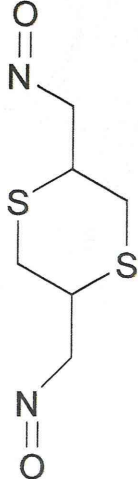
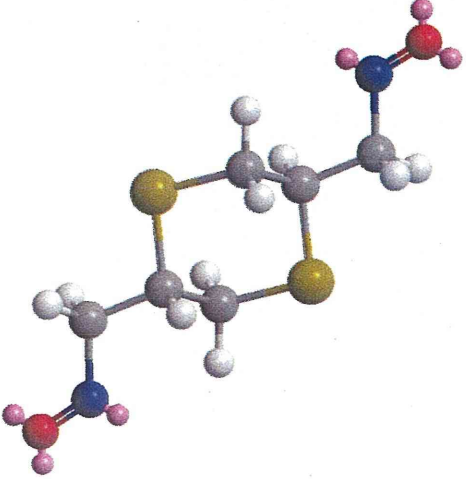


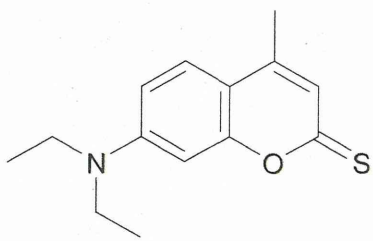
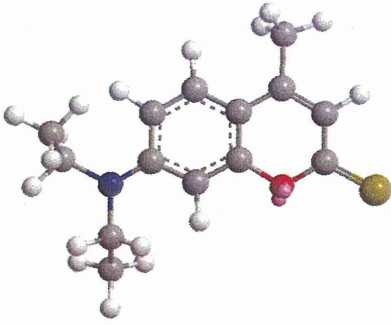
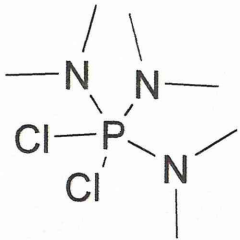
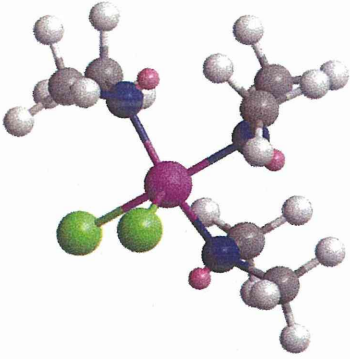
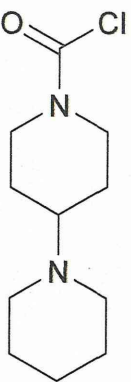
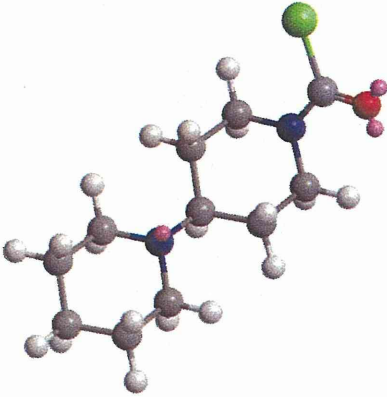
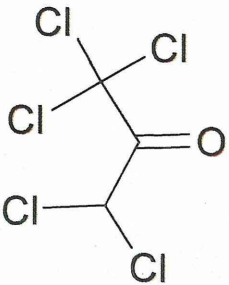
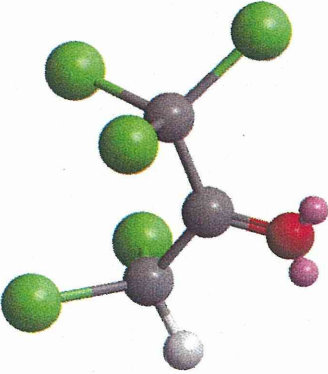
24	 <p>Chemical structure of a complex molecule featuring a benzene ring, a hydroxyl group, an amide group, and a trifluoromethyl group.</p>	 <p>3D ball-and-stick model of the molecule shown in row 24.</p>
25	 <p>Chemical structure of a molecule with a benzene ring, a carbonyl group, and a hydrazine group.</p>	 <p>3D ball-and-stick model of the molecule shown in row 25.</p>
26	 <p>Chemical structure of a molecule with a benzene ring, a chlorine atom, and a dimethylamino group.</p>	 <p>3D ball-and-stick model of the molecule shown in row 26.</p>

27	 <p>Chemical structure of hexafluorocyclopentadienone, showing a five-membered ring with a carbonyl group and six fluorine atoms.</p>	 <p>3D ball-and-stick model of hexafluorocyclopentadienone, showing the spatial arrangement of atoms.</p>
28	 <p>Chemical structure of 2-ethyl-4,5-dichloro-1-methyl-1H-imidazole-3-carbonyl chloride, showing a five-membered imidazole ring with an ethyl group, two chlorine atoms, a methyl group, and a carbonyl chloride group.</p>	 <p>3D ball-and-stick model of 2-ethyl-4,5-dichloro-1-methyl-1H-imidazole-3-carbonyl chloride, showing the spatial arrangement of atoms.</p>
29	 <p>Chemical structure of 1-methoxy-2,4-dichloro-5-nitrobenzene, showing a benzene ring with a methoxy group, two chlorine atoms, and a nitro group.</p>	 <p>3D ball-and-stick model of 1-methoxy-2,4-dichloro-5-nitrobenzene, showing the spatial arrangement of atoms.</p>
30	 <p>Chemical structure of 1,3,5-triaminobenzene, showing a benzene ring with three amino groups.</p>	 <p>3D ball-and-stick model of 1,3,5-triaminobenzene, showing the spatial arrangement of atoms.</p>

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39	 <p>Chemical structure of 3-(3,4,5-trimethoxyphenyl)acryloyl chloride, showing a benzene ring with three methoxy groups and an acryloyl chloride side chain.</p>	 <p>3D ball-and-stick model of 3-(3,4,5-trimethoxyphenyl)acryloyl chloride, showing the spatial arrangement of atoms.</p>
40	 <p>Chemical structure of 2-chloro-2-methylbut-3-en-1-yl isothiocyanate, showing a four-carbon chain with a terminal isothiocyanate group, a chlorine atom, and a methyl group.</p>	 <p>3D ball-and-stick model of 2-chloro-2-methylbut-3-en-1-yl isothiocyanate, showing the spatial arrangement of atoms.</p>
41	 <p>Chemical structure of 2-(chloromethyl)-4-chloro-1,3-thiazole, showing a five-membered thiazole ring with a chlorine atom at position 4 and a chloromethyl group at position 2.</p>	 <p>3D ball-and-stick model of 2-(chloromethyl)-4-chloro-1,3-thiazole, showing the spatial arrangement of atoms.</p>
42	 <p>Chemical structure of 1,3-dithiane-2,6-dione, showing a six-membered ring with two sulfur atoms and two carbonyl groups.</p>	 <p>3D ball-and-stick model of 1,3-dithiane-2,6-dione, showing the spatial arrangement of atoms.</p>

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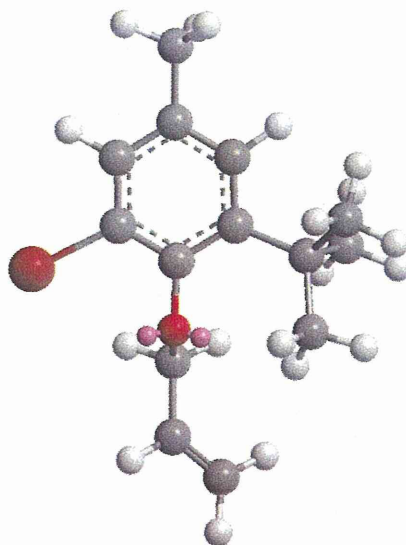
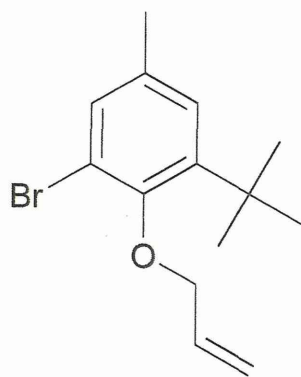
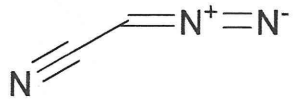
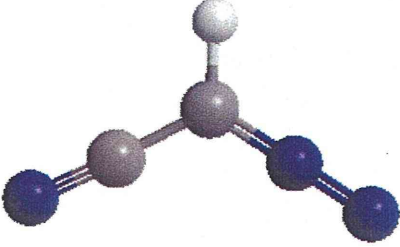
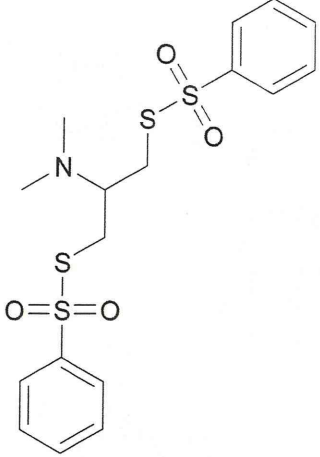
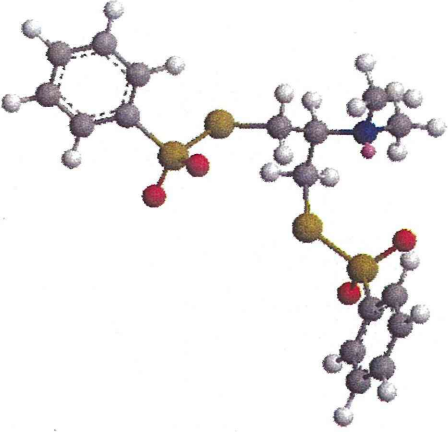
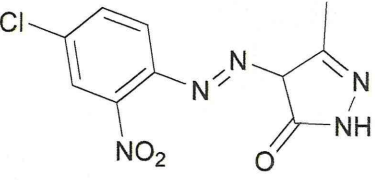
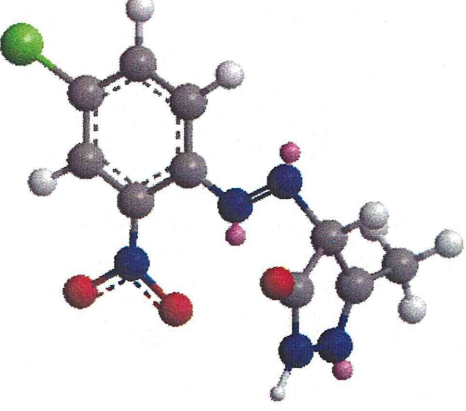
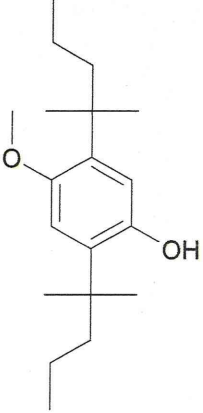
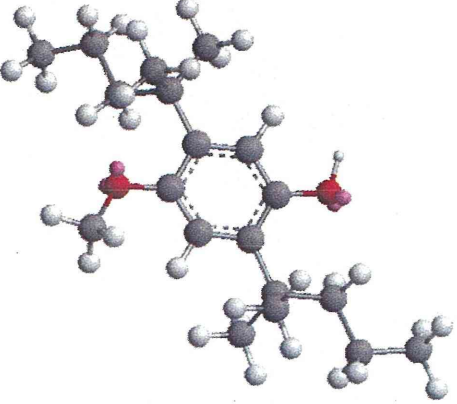
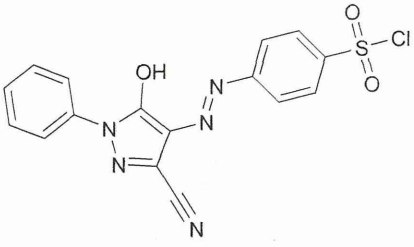
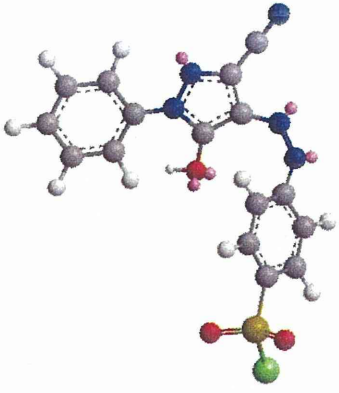
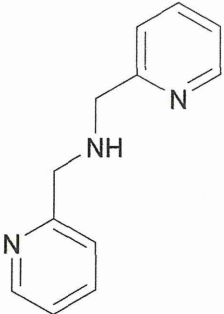
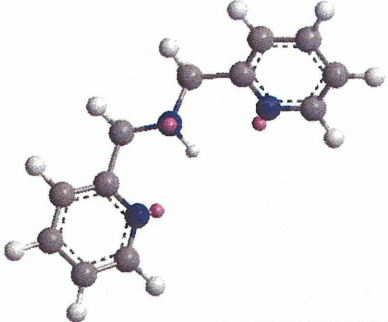
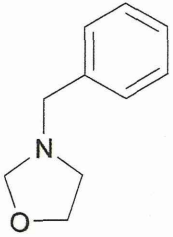
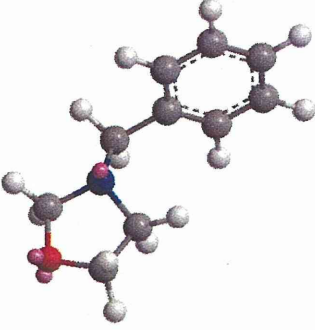
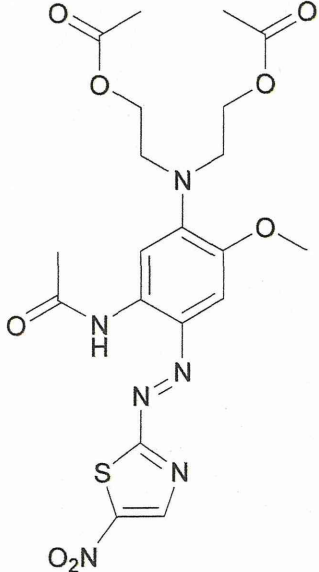
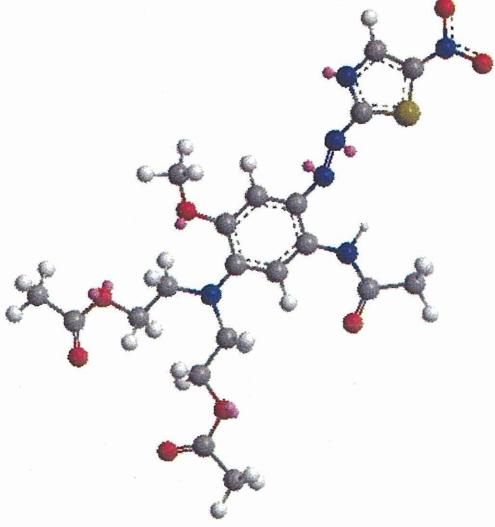
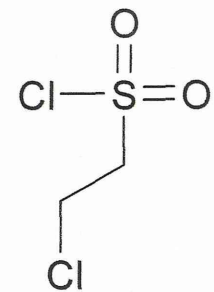
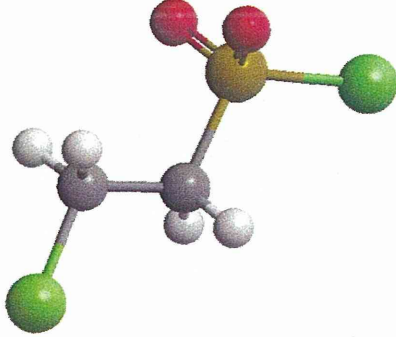
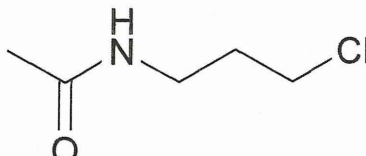
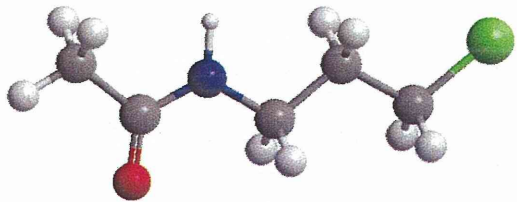
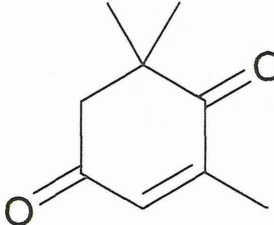
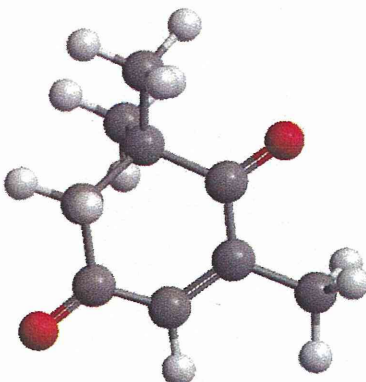
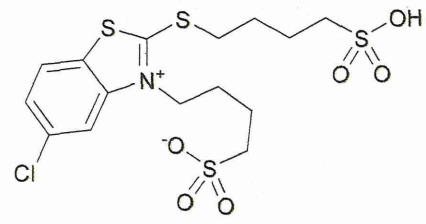
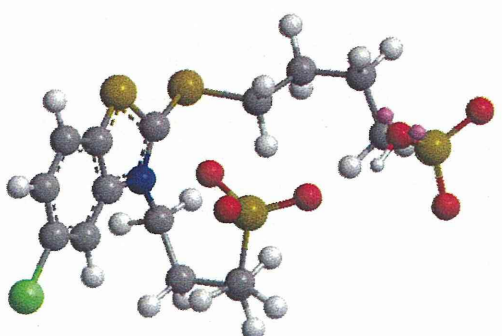


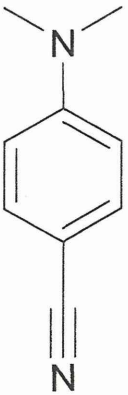
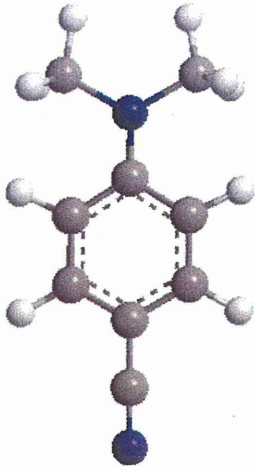
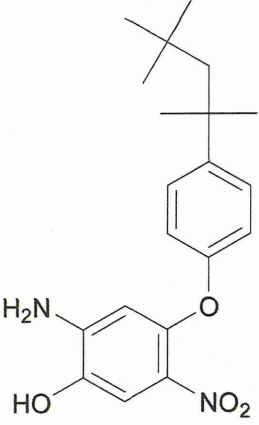
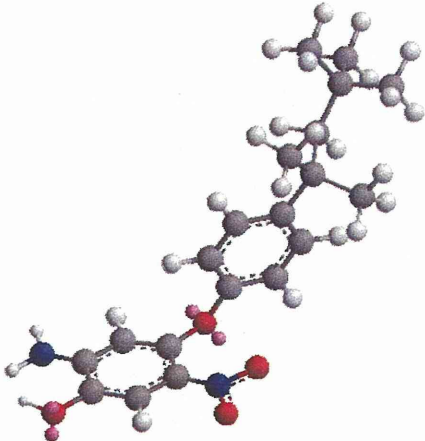
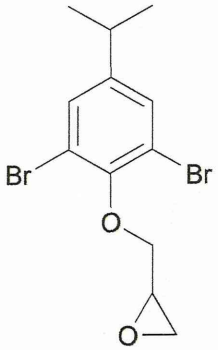
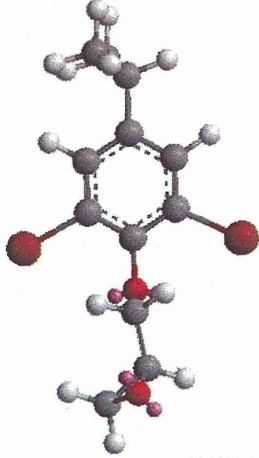
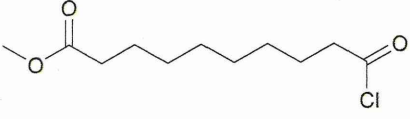
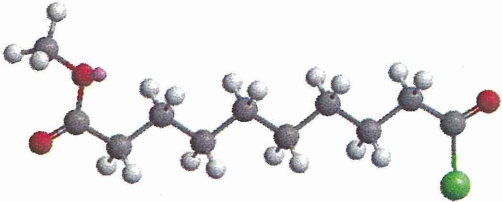
表 2

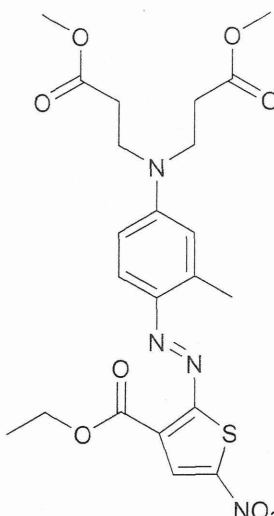
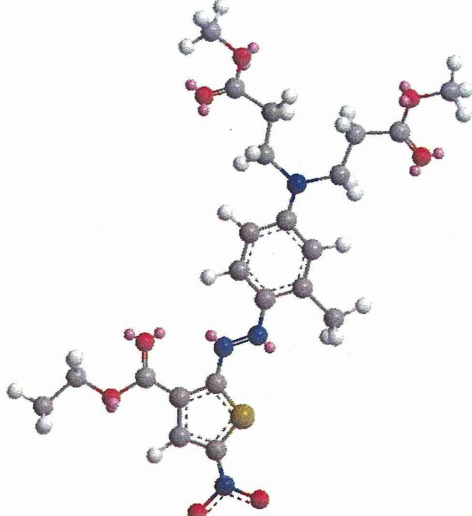
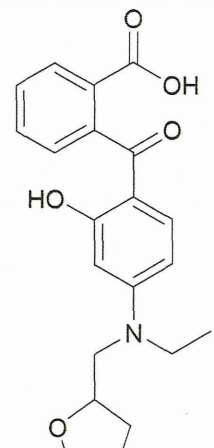
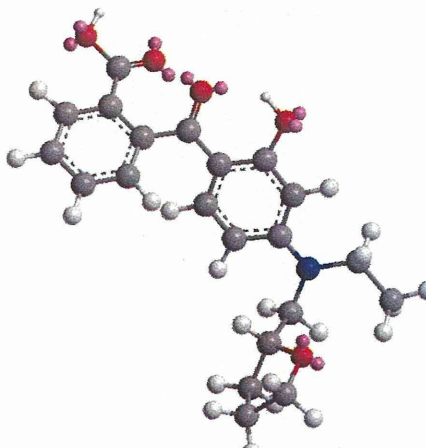
	B	最安定構造
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9	 <chem>ClCCS(=O)(=O)Cl</chem>	
10	 <chem>CC(=O)NCCCCl</chem>	
11	 <chem>CC(C)=CC(=O)C(C)C</chem>	
12	 <chem>Clc1ccc2c(c1)sc(cc2N+)S(=O)(=O)CCCCS(=O)(=O)O</chem>	

13	 <p>Chemical structure of N,N-dimethyl-4-cyanobenzamide, showing a benzene ring with a dimethylamino group (-N(CH<sub>3</sub>)<sub>2</sub>) at the para position and a cyano group (-C≡N) at the other para position.</p>	 <p>3D ball-and-stick model of N,N-dimethyl-4-cyanobenzamide, showing the spatial arrangement of atoms (carbon in grey, nitrogen in blue, oxygen in red, and hydrogen in white).</p>
14	 <p>Chemical structure of a complex amide, featuring a benzene ring with an amino group (-NH<sub>2</sub>), a hydroxyl group (-OH), and a nitro group (-NO<sub>2</sub>) at the 1, 2, and 4 positions, respectively. The ring is connected via an ether linkage (-O-) to a quaternary carbon atom, which is further substituted with a tert-butyl group and a phenyl ring.</p>	 <p>3D ball-and-stick model of the complex amide, showing the spatial arrangement of atoms (carbon in grey, nitrogen in blue, oxygen in red, and hydrogen in white).</p>
15	 <p>Chemical structure of a brominated amide, featuring a benzene ring with two bromine atoms (-Br) at the 3 and 5 positions, an isopropyl group (-CH(CH<sub>3</sub>)<sub>2</sub>) at the 1 position, and a propylene oxide ring attached via an ether linkage (-O-) at the 4 position.</p>	 <p>3D ball-and-stick model of the brominated amide, showing the spatial arrangement of atoms (carbon in grey, nitrogen in blue, oxygen in red, and hydrogen in white).</p>
16	 <p>Chemical structure of a long-chain amide, featuring a decane chain with a methyl ester group (-COOCH<sub>3</sub>) at one end and a chloroacetyl group (-COCl) at the other end.</p>	 <p>3D ball-and-stick model of the long-chain amide, showing the spatial arrangement of atoms (carbon in grey, nitrogen in blue, oxygen in red, and chlorine in green).</p>

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