



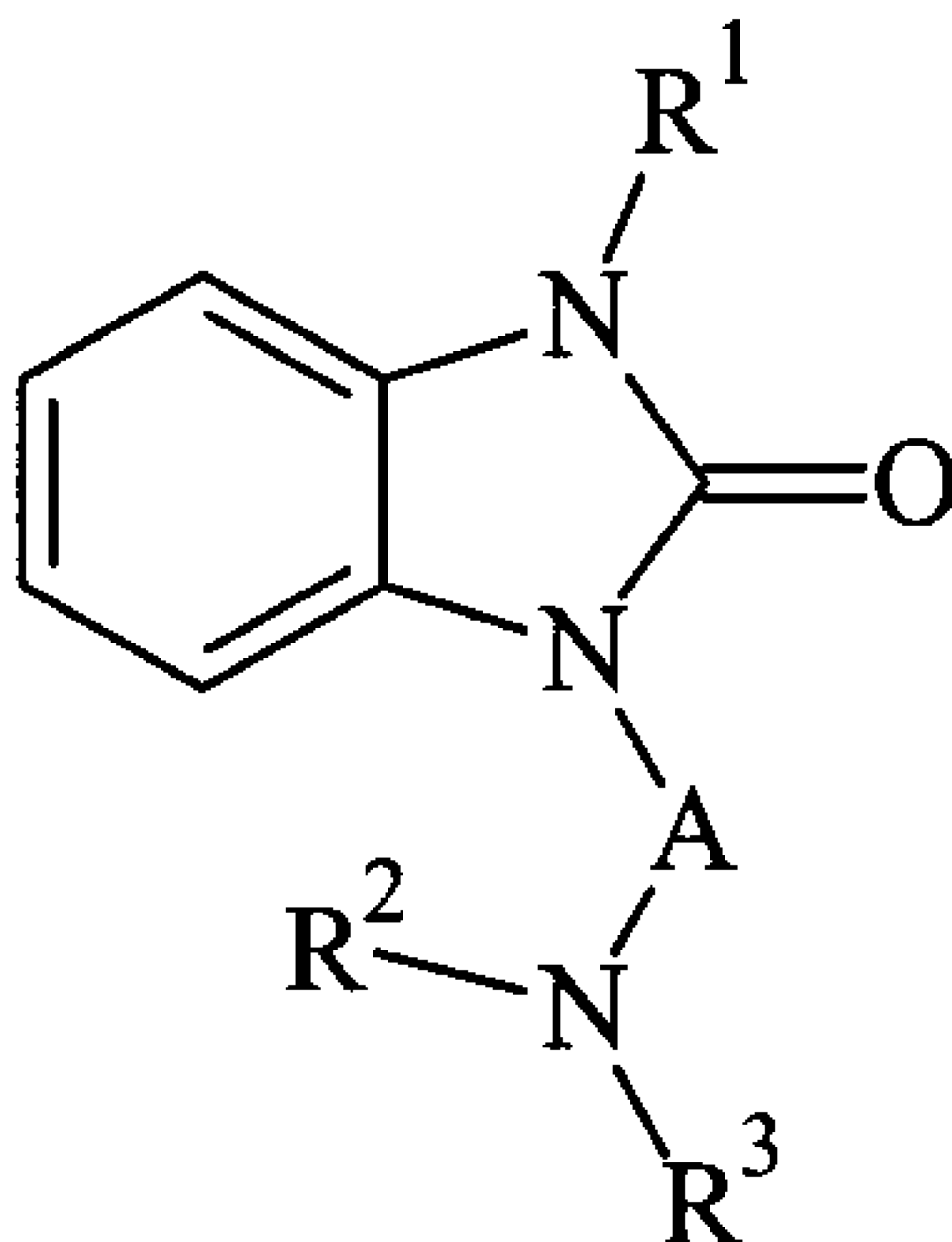
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(54) Titre : DERIVES BENZIMIDAZOLONE N,N'-DISUBSTITUES PRESENTANT UNE AFFINITE POUR LES
RECEPTEURS DE LA SEROTONINE ET DE LA DOPAMINE

(54) Title: NEW N, N'-DISUBSTITUTED BENZIMIDAZOLONE DERIVATIVES WITH AFFINITY AT THE SEROTONIN
AND DOPAMINE RECEPTORS



(I)

(57) Abrégé/Abstract:

The present invention relates to novel pharmacologically active N, N'-disubstituted benzimidazolone derivatives of general formula (I) where R¹, R², R³, and A are as defined in specification and claims, their pharmaceutically acceptable salts, to their preparation and their use for therapeutic purposes.



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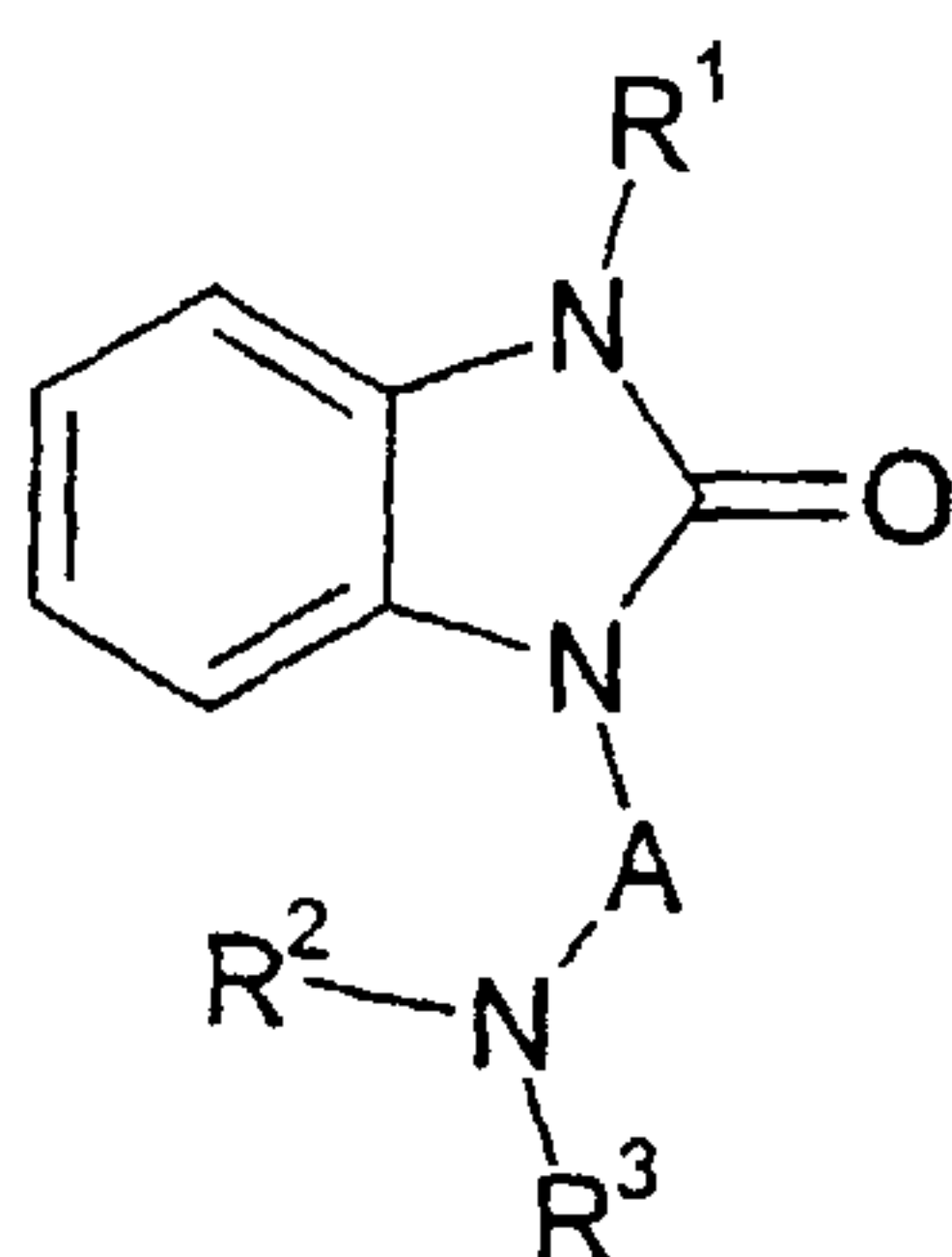
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AND DOPAMINE RECEPTORS

(I)

(57) Abstract: The present invention relates to novel pharmacologically
active N, N'-disubstituted benzimidazolone derivatives of general formula
(I) where R¹, R², R³, and A are as defined in specification and claims, their
pharmaceutically acceptable salts, to their preparation and their use for ther-
apeutic purposes.

New N,N'-disubstituted benzimidazolone derivatives with affinity at the serotonin and dopamine receptors

The present invention relates to novel pharmacologically active N,N'-disubstituted benzimidazolone derivatives and their addition salts which bind the serotonin or dopamine receptors, to their preparation and their use for therapeutic purposes. These compounds are able to discriminate the different serotonin and dopamine receptor subtypes like 5-HT_{1A}, 5-HT_{2A} and D₄ at which they can act as agonists or antagonists. Owing to this pharmacological activity, the present compounds are useful in the treatment of anxiety disorders, affective disorders such as depression, psychosis and schizophrenia, eating disorders, sexual disorders, Parkinson, stroke and traumatic brain injury.

Background of the invention

Serotonin (5-HT) and dopamine (DA) recognise several well defined cell surface receptor subtypes. Among these, 5-HT_{1A} and 5-HT_{2A} having a high and a low affinity for 5-HT, respectively, and D₄ at which DA has high affinity, have been implicated in many Central Nervous System disorders.

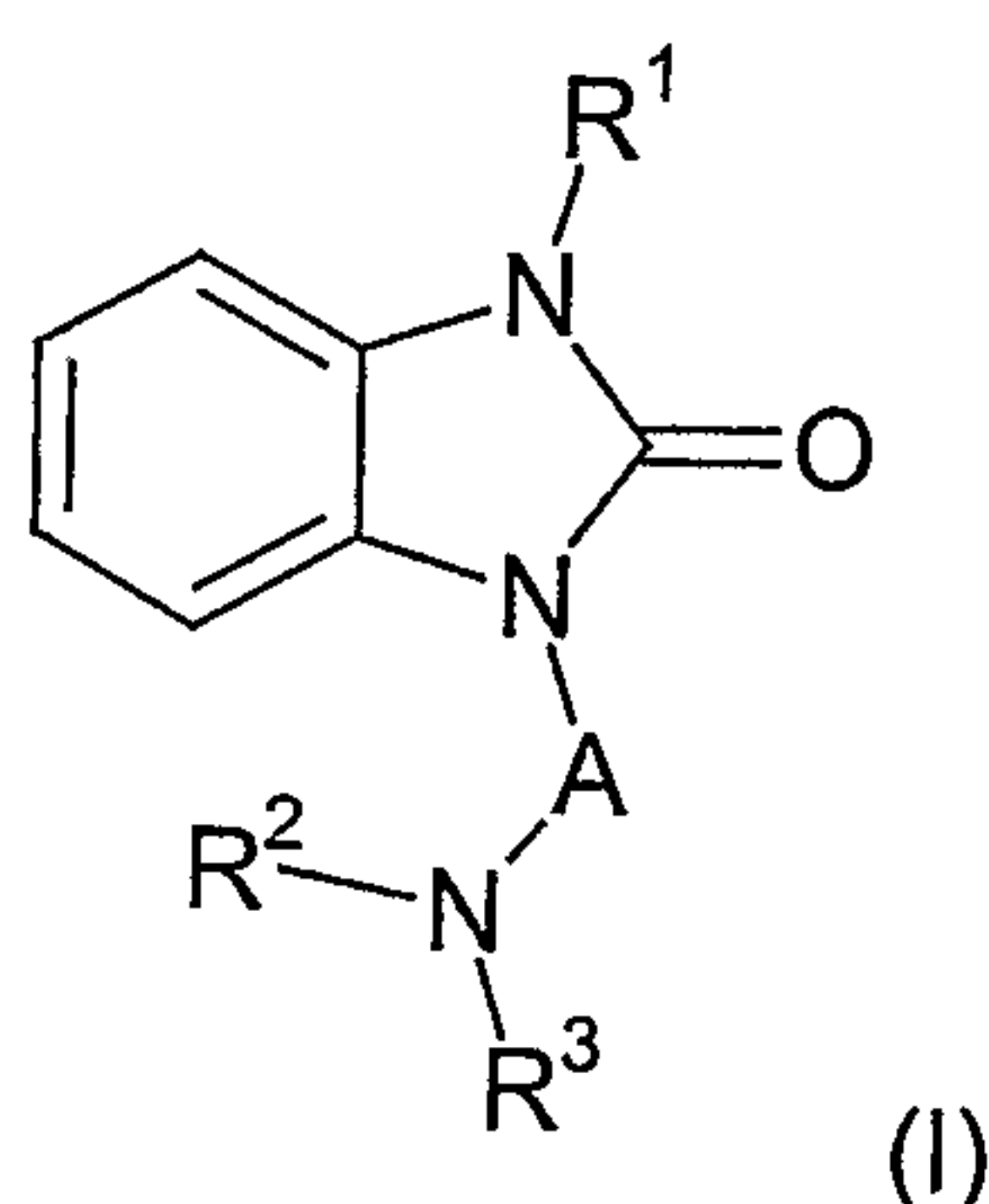
In the previous art, several classes of compounds able to interfere with the neurotransmission at 5-HT or DA receptor subtypes are known. Particularly, derivatives based on the core structure of the aryl piperazine and benzimidazolone have been described (e.g. GB 2023594, U.S. Pat. 3,472,854, U.S. Pat. 4,954,503, WO-9616949, WO-9501965 and WO-9833784), and targeted both to generic 5-HT or DA receptors and to a specific receptor subtype. In another patent (U.S. Pat. 5,576,318) are described compounds based both on the benzimidazolone and phenylpiperazine structures: in this latter case the described affinities are limited to 5-HT_{1A} and 5-HT_{2A} receptor subtypes.

Detailed description of the invention

Now we describe, and this is the object of the present invention, new derivatives of a benzimidazolone core structure. The N-substituents are alkyl chains bearing additional hydrophilic functional groups whereas the N'-substituents are alkyl or alkenyl spacers connecting the benzimidazolone scaffold to a large set of secondary amines bearing other diversity points. The compounds included in this invention possess an interesting affinity profile at the said serotonin and dopamine receptor subtypes: indeed some of them have a high and preferential affinity at a given site (e.g. 5-HT_{1A}, 5-HT_{2A} or D₄) whereas some others have a mixed affinity at the said receptors. Moreover a selected pool of compounds possesses an agonistic activity at the 5-HT_{1A} receptor coupled with an antagonistic activity at the 5-HT_{2A} receptor.

Owing to their peculiar profile, the present compounds may play a role in the regulation of neurotransmission at the serotonin and/or the dopamine sites and thus may be of value in the treatment of those diseases where an altered functioning of neurosignal transmission is present. Examples of these disorders include anxiety, depression, schizophrenia, Parkinson, sleep, sexual and eating disorders, stroke and brain injury. Particularly the compounds included in the present invention can be of value in the treatment of depression according to the mounting evidence that 5-HT_{1A} full agonists or high efficiency partial agonists are required for a robust antidepressant effect. In fact, electro physiology studies suggest that repeated administration of a variety of antidepressant treatments facilitate 5-HT_{1A} neurotransmission in the hippocampus, possibly through either an increased sensitivity of post-synaptic 5-HT_{1A} receptors or a decreased sensitivity of 5-HT_{1A} autoreceptors. Furthermore, there is some evidence from controlled clinical trials to support this suggestion. In addition the compound's ability to block the 5-HT_{2A} receptor is also of value: indeed, the stimulation of 5-HT_{1A} and 5-HT_{2A} receptors lead to opposite electrical events, inhibitory and excitatory, respectively. Thus only a concurrent activation of 5-HT_{1A} coupled with antagonism at 5-HT_{2A} receptors may completely and rapidly inhibit 5-HT post-synaptic cells, an important physiological event for antidepressant effects.

The present invention pertains to compounds of general formula (I)



wherein

R^1 denotes C₁-C₆-alkyl, preferably C₁-C₄-alkyl, being substituted by a group selected from OH, C₁-C₆-alkoxy, -OCONHC₁-C₆-alkyl, -OCONHC₁-C₆-alkyl, -NHSO₂C₁-C₆-alkyl and -NHCOC₁-C₆-alkyl, or

R^1 denotes C₁-C₆-alkyl, preferably C₁-C₄-alkyl, being substituted by a saturated or unsaturated 5- or 6-membered heterocycle containing one or two heteroatoms selected from the group consisting of nitrogen and oxygen, said heterocycle being optionally substituted by a group selected from C₁-C₄-alkyl, halogen and benzyl;

25771-774

3

R^2 and R^3 together with the nitrogen form a saturated or unsaturated 5- or 6-membered heterocyclic ring which may contain nitrogen or oxygen as an additional heteroatom, whilst the heterocyclic ring is substituted by a group
5 selected from phenyl, benzyl and diphenylmethyl, said group being optionally mono- or di-substituted by one or two groups selected from CF_3 , C_1-C_4 -alkyl, C_1-C_4 -alkoxy, phenyl, benzyl, halogen and OH, or

R^2 and R^3 together with the nitrogen form a saturated or
10 unsaturated 5- or 6-membered heterocyclic ring which may contain nitrogen or oxygen as an additional heteroatom, said heterocyclic ring being linked via a single bond, a methylene-bridge or spiro-connected to another saturated or unsaturated heterocyclic group containing one or two
15 heteroatoms selected from oxygen and nitrogen, said heterocyclic group being optionally mono- or di-substituted by a group selected from CF_3 , C_1-C_4 -alkyl, C_1-C_4 -alkoxy, phenyl, benzyl, halogen, =O and OH, or

R^2 and R^3 together with the nitrogen form a saturated or
20 unsaturated bi- or tricyclic heterocyclic ring-system which may contain nitrogen or oxygen as an additional heteroatom, said heterocyclic ring-system being optionally substituted by a group selected from CF_3 , C_1-C_4 -alkyl, C_1-C_4 -alkoxy, phenyl, benzyl, halogen, =O and OH;

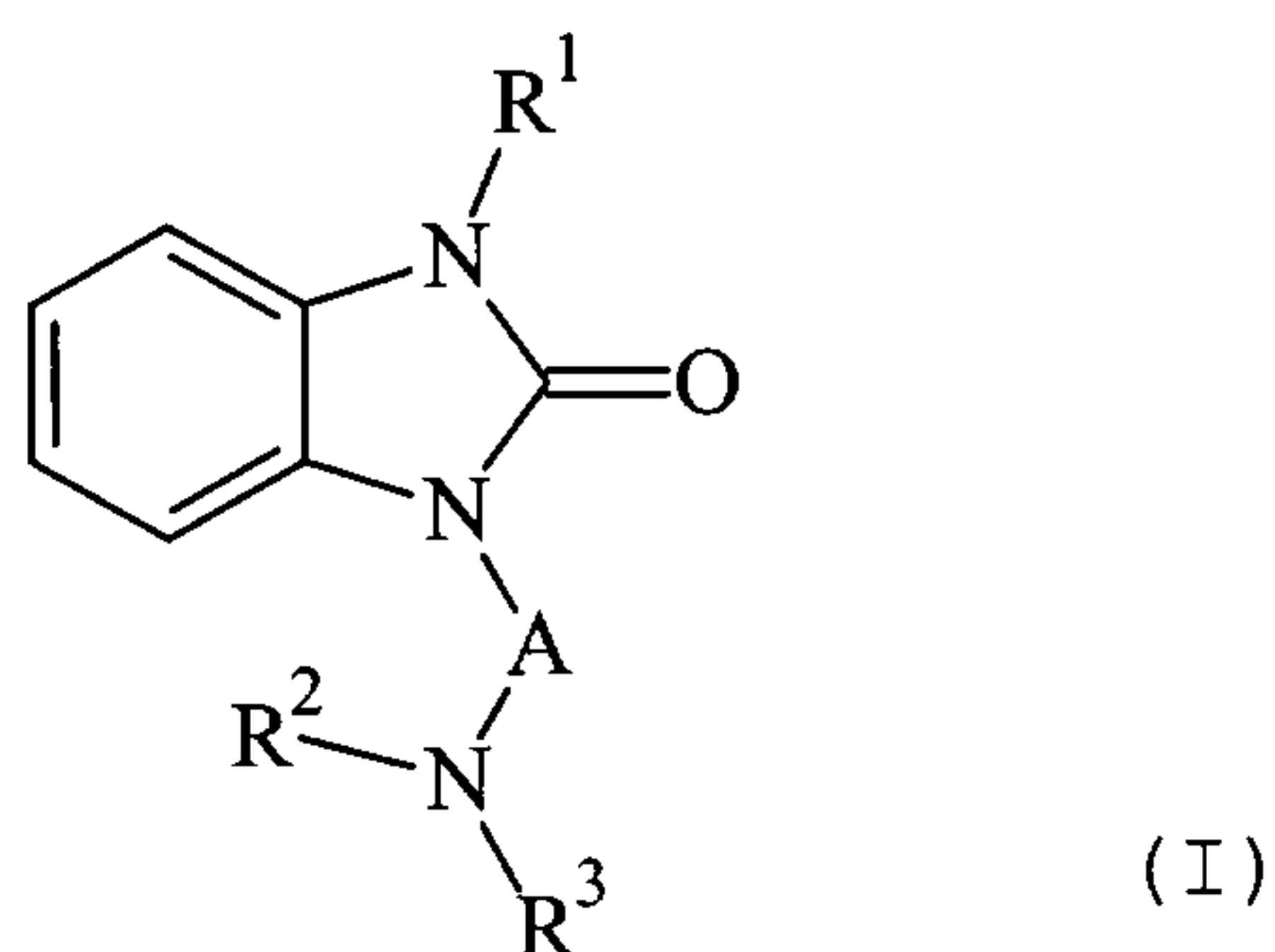
25 A denotes C_1-C_6 -alkylen, preferably C_1-C_4 -alkylen, C_2-C_6 -alkenylen, preferably C_2-C_4 -alkenylen, or C_2-C_6 -alkynylen, preferably C_2-C_4 -alkynylen,

or a pharmaceutically acceptable salt thereof.

According to one aspect of the present invention,
30 there is provided a compound of general formula (I)

25771-774

3a



5 wherein

R^1 denotes C_1 - C_6 -alkyl being substituted by a group selected from C_1 - C_6 -alkoxy, $-OCONHC_1$ - C_6 -alkyl, $-NHSO_2C_1$ - C_6 -alkyl and $-NHCOC_1$ - C_6 -alkyl

R^2 and R^3 together with the nitrogen to which each is
 10 attached form a saturated or unsaturated 5- or 6-membered heterocyclic ring which may contain nitrogen or oxygen as an additional heteroatom, whilst the heterocyclic ring is substituted by a group selected from phenyl, benzyl and diphenylmethyl, said group being unsubstituted, mono- or
 15 di-substituted by one or two groups selected from CF_3 , C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy, phenyl, benzyl, halogen and OH, or

R^2 and R^3 together with the nitrogen to which each is
 attached form a saturated or unsaturated 5- or 6-membered heterocyclic ring which may contain nitrogen or oxygen as an
 20 additional heteroatom, said heterocyclic ring being linked via a single bond, a methylene-bridge or spiro-connected to another saturated or unsaturated heterocyclic group containing one or two heteroatoms selected from oxygen and nitrogen, said heterocyclic group being unsubstituted, mono-
 25 or di-substituted by a group selected from CF_3 , C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy, phenyl, benzyl, halogen, and OH, or two hydrogen atoms from said heterocyclic group being optionally substituted by =O, or

25771-774

3b

R² and R³ together with the nitrogen to which each is attached form a saturated or unsaturated bi- or tricyclic heterocyclic ring-system which may contain nitrogen or oxygen as an additional heteroatom, said heterocyclic ring-system being unsubstituted or substituted by a group selected from CF₃, C₁-C₄-alkyl, C₁-C₄-alkoxy, phenyl, benzyl, halogen, and OH or two hydrogen atoms from said heterocyclic ring-system being optionally substituted by =O; and

A denotes C₁-C₆-alkylen, C₂-C₆-alkenylen or C₂-C₆-alkynylen, or a pharmaceutically acceptable salt thereof.

Preferred compounds are those of formula (I), wherein

R¹ denotes C₁-C₄-alkyl, preferably C₂-C₃-alkyl, being substituted by a group selected from OH, C₁-C₄-alkoxy, -OCONHC₁-C₄-alkyl, -OCONHC₁-C₄-alkyl, -NHSO₂C₁-C₄-alkyl and -NHCOC₁-C₄-alkyl, or

R¹ denotes C₁-C₄-alkyl, preferably C₂-C₃-alkyl, being substituted by a saturated or unsaturated 6-membered heterocycle containing one or two heteroatoms selected from the group consisting of nitrogen and oxygen;

R² and R³ together with the nitrogen form a saturated or unsaturated 5- or 6-membered heterocyclic ring which may contain nitrogen as an additional

heteroatom, whilst the heterocyclic ring is substituted by a group selected from phenyl, benzyl, diphenylmethyl, pyridinyl, pyrimidinyl, benzimidazolonyl and 3,4-methylenedioxybenzyl, said group being optionally mono- or di-substituted by a group selected from CF₃, C₁-C₄-alkyl, C₁-C₄-alkoxy, halogen and OH;

5

A denotes C₁-C₄-alkylen or C₂-C₄-alkenylen,
or a pharmaceutically acceptable salt thereof.

10 Also preferred compounds are those of formula (I), wherein

R¹ denotes ethyl, being substituted by a group selected from OH, OCH₃, OCH₂CH₃, -OCONHCH₃, -OCONHCH₂CH₃, -NHSO₂CH₃, -NHSO₂CH₂CH₃, -NHCOCH₃, -NHCOCH₂CH₃, morpholinyl, piperazinyl and piperidinyl

15 R² and R³ together with the nitrogen form a 6 membered saturated or unsaturated heterocyclic ring which may contain nitrogen as an additional heteroatom, whilst the heterocyclic ring is substituted by a group selected from phenyl, pyridinyl, pyrimidinyl, benzimidazolonyl, and substituted phenyl being mono- or di-substituted by a group selected from CF₃, CH₃, OCH₃, F and Cl;

20

A denotes C₁-C₄-alkylen or C₂-C₄-alkenylen,
or a pharmaceutically acceptable salt thereof.

25 Also of interest are compounds of formula (I), wherein

R¹ denotes ethyl, being substituted by a group selected from OH, OCH₃, -OCONHCH₂CH₃, -NHSO₂CH₃, -NHCOCH₃, morpholinyl and piperidinyl;

30 R² and R³ together with the nitrogen form a 6 membered saturated or unsaturated heterocyclic ring which may contain nitrogen as an additional heteroatom, whilst the heterocyclic ring is substituted by a group selected from pyridinyl, phenyl and substituted phenyl being mono- or di-substituted by a group selected from CF₃, CH₃, OCH₃, F and Cl;

35 A denotes ethylen, propylen, butylen or butenylen,
or a pharmaceutically acceptable salt thereof.

5

Of particular interest are compounds of formula (I), wherein

R¹ denotes ethyl, being substituted by a group selected from OH, OCH₃, - OCONHCH₂CH₃, -NHSO₂CH₃, -NHCOCH₃, morpholinyl and piperidinyl

5 R² and R³ together with the nitrogen form a ring selected from the group consisting of piperazin, piperidin and tetrahydropyridin, which is substituted by a group selected from pyridinyl, phenyl and substituted phenyl being mono- or di-substituted by a group selected from CF₃, CH₃ and Cl;

10 A denotes ethylen, butylen or butenylen, or a pharmaceutically acceptable salt thereof.

Furthermore preferred are compounds of formula (I), wherein

15 R¹ denotes ethyl, being substituted by a group selected from OH, OCH₃, - OCONHCH₂CH₃ and -NHSO₂CH₃;

R² and R³ together with the nitrogen form a piperazine-ring, being substituted by a group selected from trifluoromethylphenyl, methylphenyl, dimethylphenyl and chlorophenyl;

20

A denotes ethylen, butylen or butenylen, or a pharmaceutically acceptable salt thereof.

25 The most preferred compounds according to the invention are:

- 1-(2-methoxyethyl)-3-(4-{4-[3-(trifluoromethyl)-phenyl]-1-piperazinyl}-butyl)-1,3-dihydro-2H-benzimidazol-2-one;
- 1-{4-[4-(2,3-dimethylphenyl)-1-piperazinyl]-butyl}-3-(2-hydroxyethyl)-1,3-dihydro-2H-benzimidazol-2-one;
- 2-[2-oxo-3-(4-{4-[3-(trifluoromethyl)-phenyl]-1-piperazinyl}butyl)-2,3-dihydro-1H-benzimidazol-1-yl]-ethyl-ethylcarbamate;
- 1-(2-methoxyethyl)-3-(2-{4-[3-(trifluoromethyl)-phenyl]-1-piperazinyl}-ethyl)-1,3-dihydro-2H-benzimidazol-2-one;
- 1-{2-[4-(2,3-dimethylphenyl)-1-piperazinyl]-ethyl}-3-(2-methoxyethyl)-1,3-dihydro-2H-benzimidazol-2-one;
- 1-{2-[4-(3-chlorophenyl)-1-piperazinyl]-ethyl}-3-(2-hydroxyethyl)-1,3-dihydro-2H-benzimidazol-2-one;
- 2-[2-oxo-3-(2-{4-[3-(trifluoromethyl)-phenyl]-1-piperazinyl}-ethyl)-2,3-dihydro-1H-benzimidazol-1-yl]-ethyl-ethylcarbamate;

6

- 2-(3-{2-[4-(2,3-dimethylphenyl)-1-piperazinyl]-ethyl}-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)-ethyl-ethylcarbamate;
- N-[2-(3-{2-[4-(2,3-dimethylphenyl)-1-piperazinyl]-ethyl}-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)-ethyl]-methanesulfonamide;
- N-[2-(3-{(2Z)-4-[4-(3-methylphenyl)-1-piperazinyl]-2-butenyl}-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)-ethyl]-methanesulfonamide;
- N-[2-(3-{(2E)-4-[4-(3-chlorophenyl)-1-piperazinyl]-2-butenyl}-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)-ethyl]-methanesulfonamide;

If required, the compounds of general formulae (I) may be converted into the salts thereof, particularly, for pharmaceutical use, into the pharmaceutically acceptable salts thereof with an inorganic or organic acid. Suitable acids for this purpose include
 5 hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid. Moreover, mixtures of these acids may be used.

The alkyl groups meant here (including those which are components of other groups)
 10 are branched and unbranched alkyl groups having 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms, such as: methyl, ethyl, n-propyl, iso-propyl, butyl, iso-butyl, sec.-butyl, tert.-butyl, pentyl, iso-pentyl and hexyl.

The alkylen groups meant here are branched and unbranched alkyl-bridges having 1
 15 to 6 carbon atoms, preferably 1 to 4 carbon atoms, such as: methylen, ethylen, n-propylen, iso-propylen, butylen, iso-butylen, sec.-butylen, tert.-butylen, pentylen, iso-pentylen and hexylen.

Alkenyl groups (including those which are components of other groups) are the
 20 branched and unbranched alkenyl groups with 2 to 6 carbon atoms, preferably 2 to 4 carbon atoms, provided that they have at least one double bond, e.g. the alkyl groups mentioned above provided that they have at least one double bond, such as for example vinyl (provided that no unstable enamines or enolethers are formed), propenyl, iso-propenyl, butenyl, pentenyl and hexenyl.

25 Alkenylen groups are the branched and unbranched alkenyl-bridges with 2 to 6 carbon atoms, preferably 2 to 4 carbon atoms, provided that they have at least one double bond, e.g. the alkylen groups mentioned above provided that they have at least one double bond, such as for example vinylen (provided that no unstable enamines or enolethers are formed), propenylen, iso-propenylen, butenylen,
 30 pentylen and hexenylen.

If not otherwise specified the alkenyl- and alkenylen-groups mentioned above are to be understood as embracing optionally existing stereoisomers. Accordingly, for instance the definition 2-butenyl is to be understood as embracing 2-(Z)-butenyl and
5 2-(E)-butenyl, etc..

The term alkynyl groups (including those which are components of other groups) refers to alkynyl groups having 2 to 6, preferably 2 to 4 carbon atoms provided that they have at least one triple bond, e.g. ethynyl, propargyl, butynyl, pentynyl and
10 hexynyl.

Examples of N-linked 5- or 6-membered heterocyclic rings of general formula NR^2R^3 are as follows: pyrrole, pyrroline, pyrrolidine, piperidine, piperazine, morpholine, imidazole, imidazoline, imidazolidine, pyrazole, pyrazoline, pyrazolidine, preferably
15 morpholine, piperazine and piperidine.

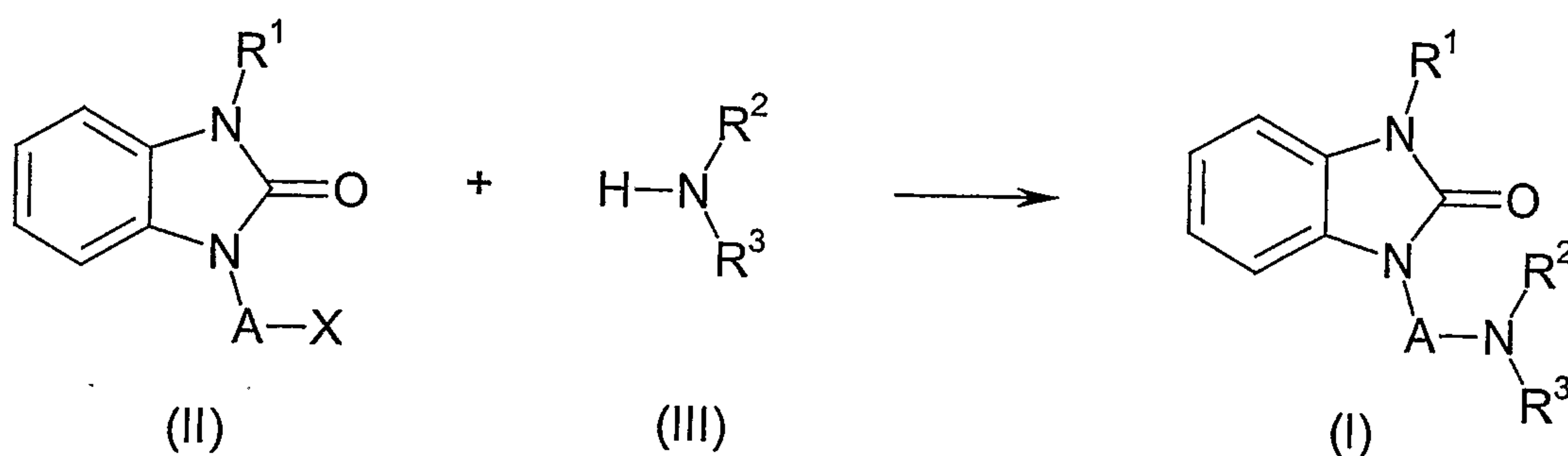
Examples of saturated or unsaturated bi- or tricyclic heterocyclic ring-system of formula NR^2R^3 which may contain nitrogen or oxygen as an additional heteroatom, are as follows: indole, tetrahydroindole, benzimidazole, benzoxazole, 1,2-
20 dihydroquinoline, 1,2-dihydroisochinoline, β -carboline, 9H-1,2,3,4-tetrahydro-pyridoindole and 9,10-dihydroacridine.

Halogen, stands for fluorine, chlorine, bromine or iodine, preferably chlorine or bromine.
25

"=O" means an oxygen atom linked by a double bond.

8

The compounds of general formula (I) may be conveniently prepared by a variety of synthetic processes analogous to those known in the art using conventional methods. For example these compounds may be prepared by alkylating the suitable secondary amine (III) with the proper benzimidazolone (II) bearing in the alkyl or alkenyl side chain suitable leaving group X such as halogen, methanesulfonate or 4-methylbenzenesulfonate (scheme 1).



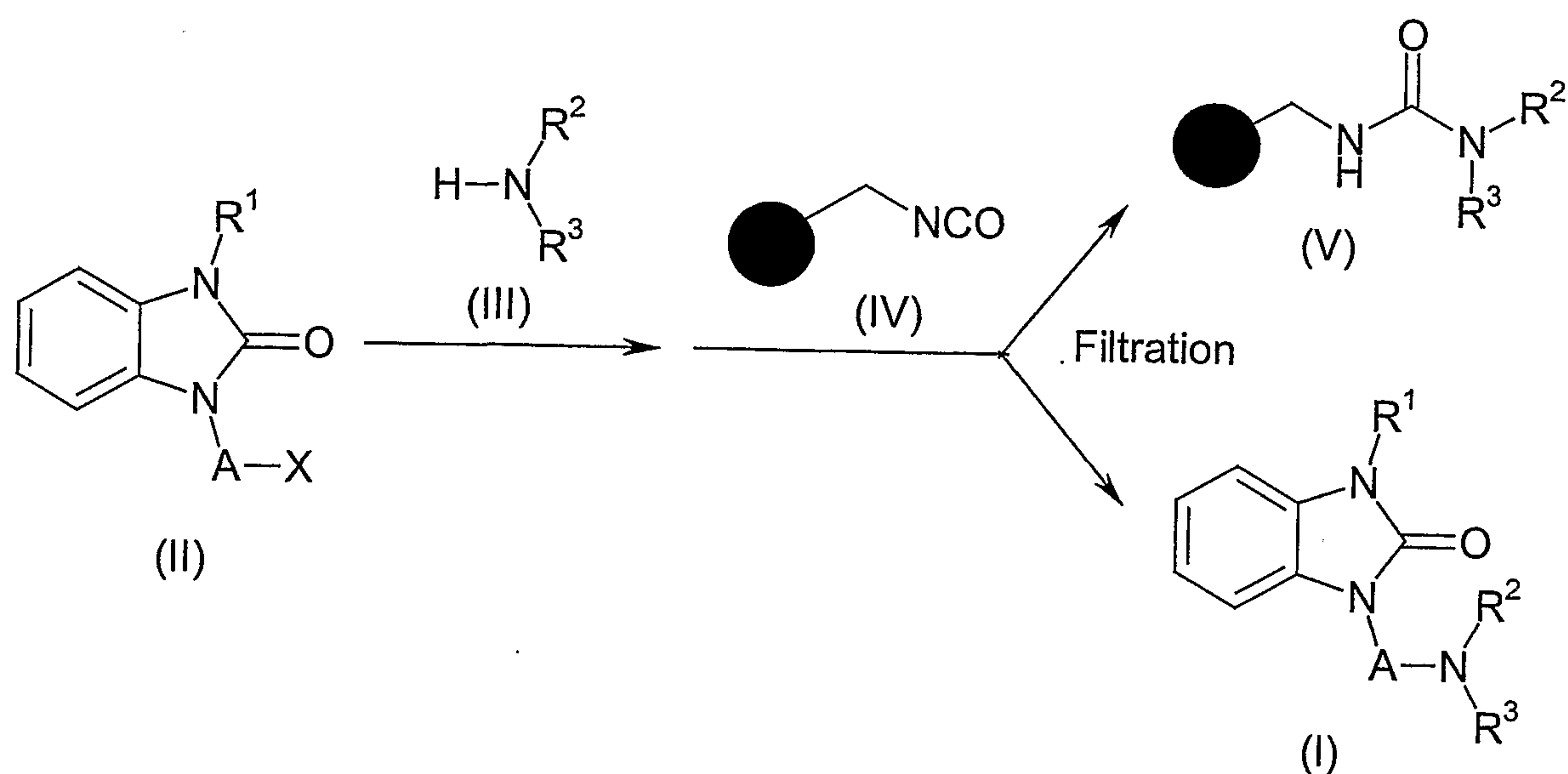
scheme 1:

The reaction conditions for the conventional synthesis of compounds of formula (I) according to scheme 1 are disclosed in EP 526 434 A1. Said reference additionally describes the possible synthetic pathways for the preparation of starting compounds (II).

According to a second option, the reaction sequence according to scheme 1 can not only be conducted via the conventional synthetic methods outlined in EP 526 434 A1 but, in the alternative, via combinatorial chemistry. For this approach a set of N-alkyl-N' halo alkyl/alkenyl benzimidazolones of formula (II) (from now on identified as Building Blocks or BB; see hereto table 1) was prepared via the traditional methods described in EP 526 434 A1 and then combinatorially reacted with the suitable secondary amines of formula (III) (table 2).

The process was carried out in a special apparatus consisting of a lower vial (reacting chamber) and an upper vial (condenser). Each compound was reacted with each amine in DMF under stirring at a temperature between 40 and 100°C preferably at 60 °C for 6 to 8 hours in the presence of Na₂CO₃. The excess amine was then scavenged at room temperature by introducing a polystyrene isocyanatemethyl resin of formula (IV) able to catch the excess amine as an urea of formula (V) immobilised on the solid support (scheme 2).

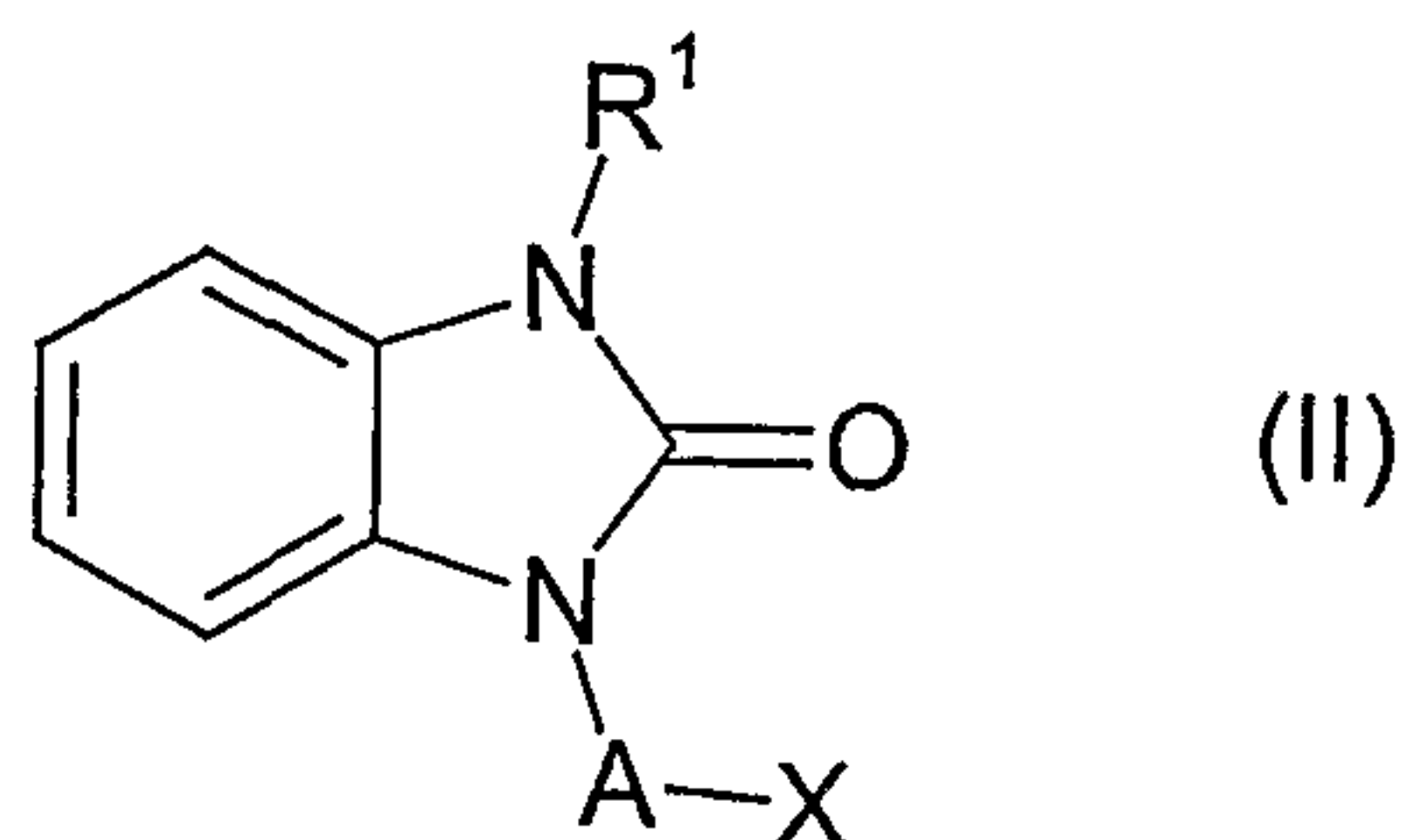
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Scheme 2:

The upper part of the reaction apparatus is substituted with another vial containing a
 5 frit inside and a connection to the vacuum. Filtration after turning over the apparatus
 and evaporation to dryness afforded the desired compounds of formula (I) in
 excellent yield and good purity. The parallel application of the aforementioned
 process to all of the compounds of formula (II) as shown in table 1 and all of the
 selected amines (III) as shown in table 2 allows the efficient synthesis of all of the
 10 compounds (I) according to the present invention.

Table 1: building blocks (BB) of formula (II) subjected to the process according to scheme 2



Building Block No.	Structure	Building Block No.	Structure
BB01		BB02	
BB03		BB04	
BB05		BB06	
BB07		BB08	
BB09		BB10	
BB11		BB12	

Table 1 (continued):

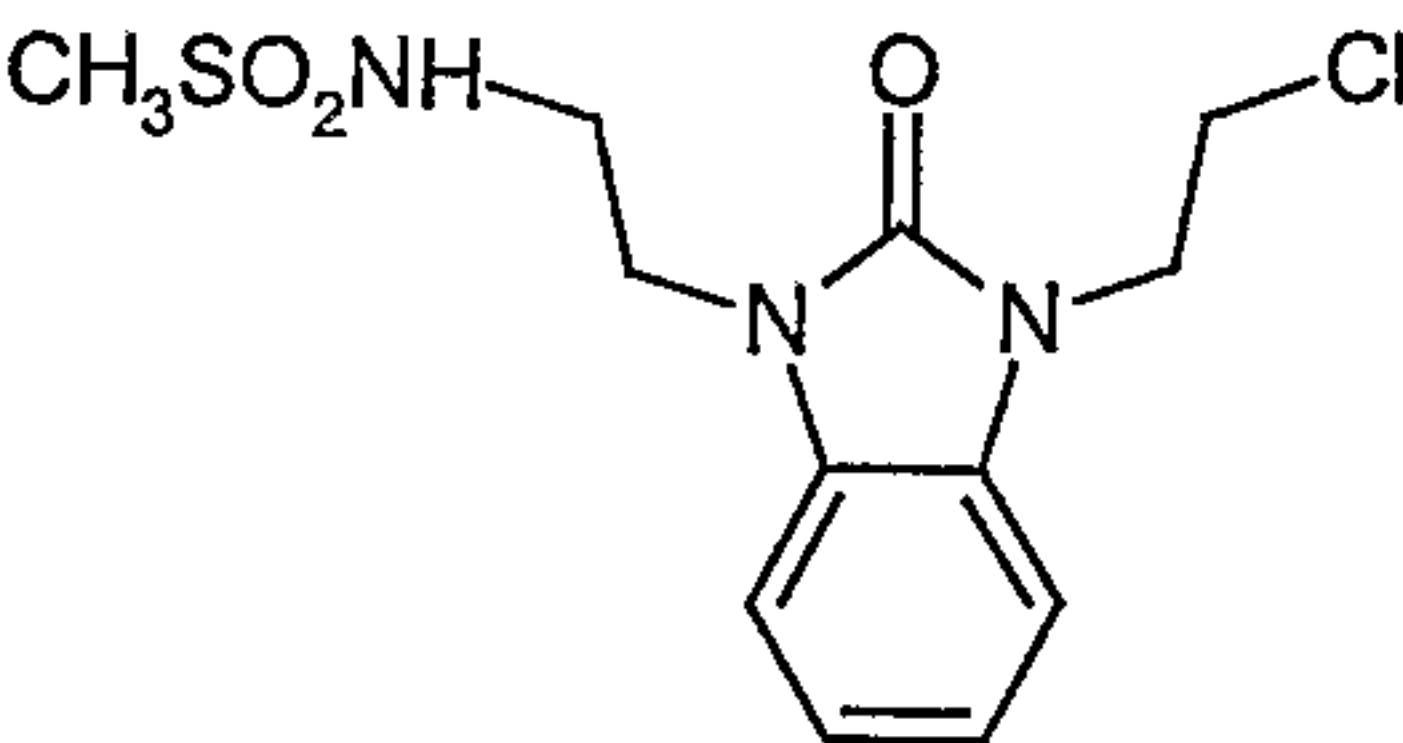
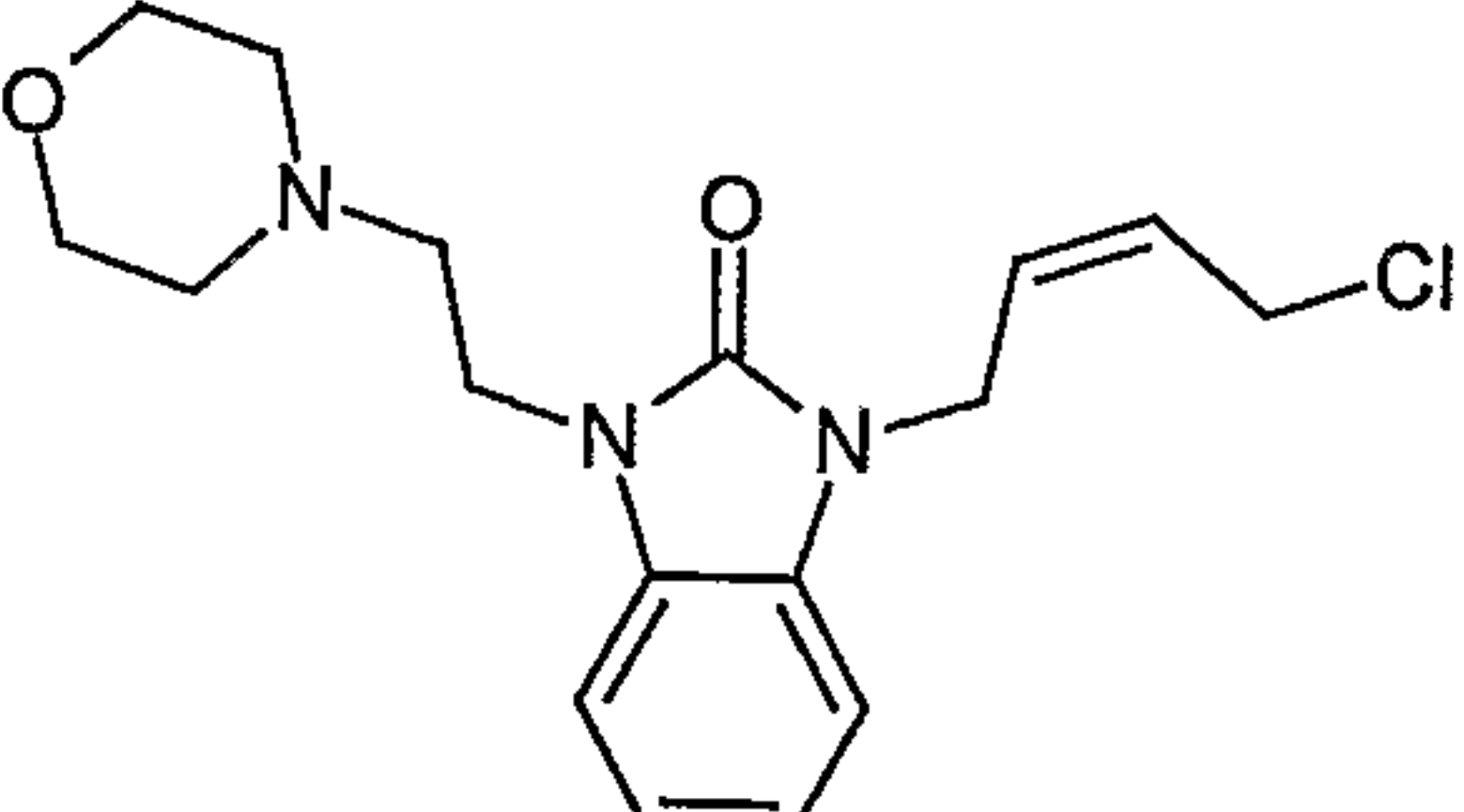
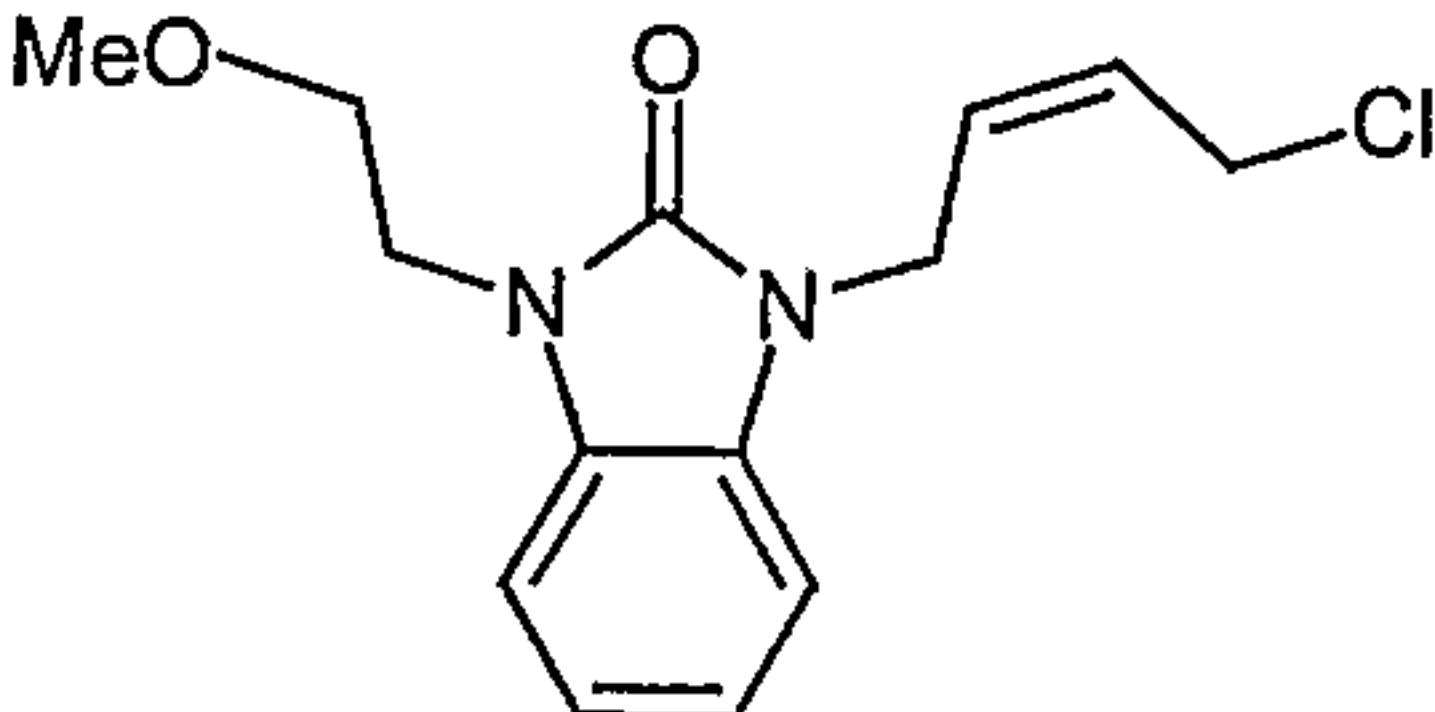
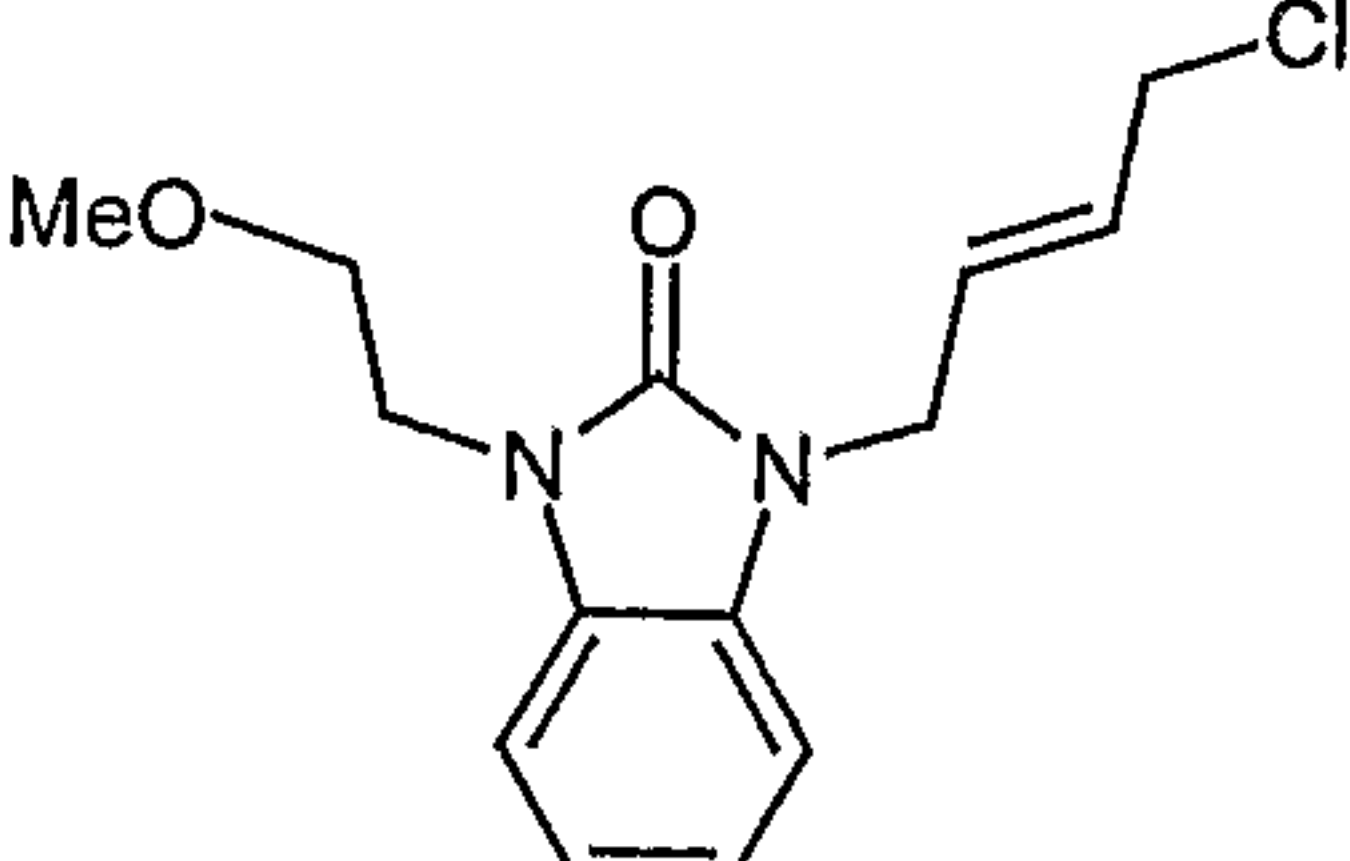
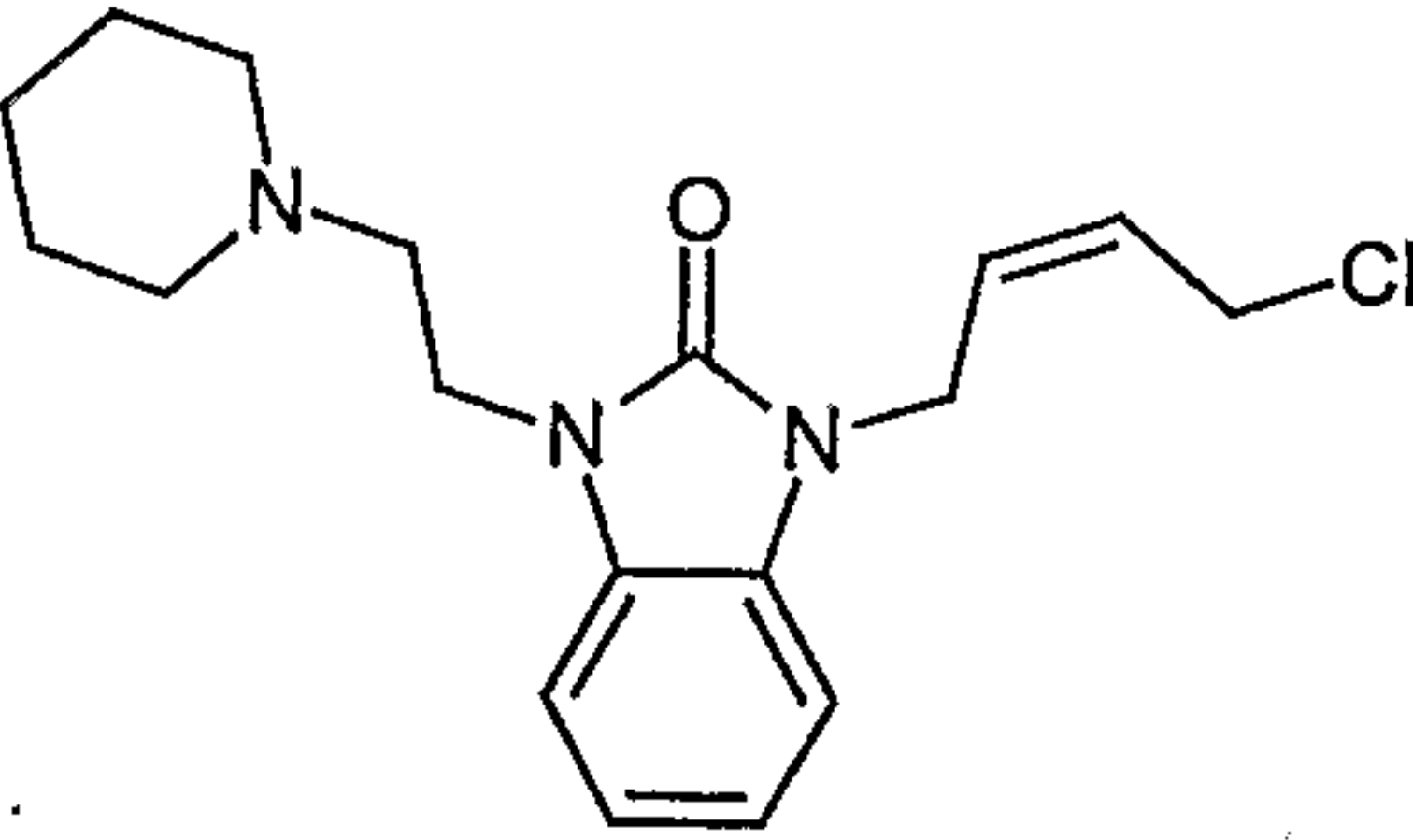
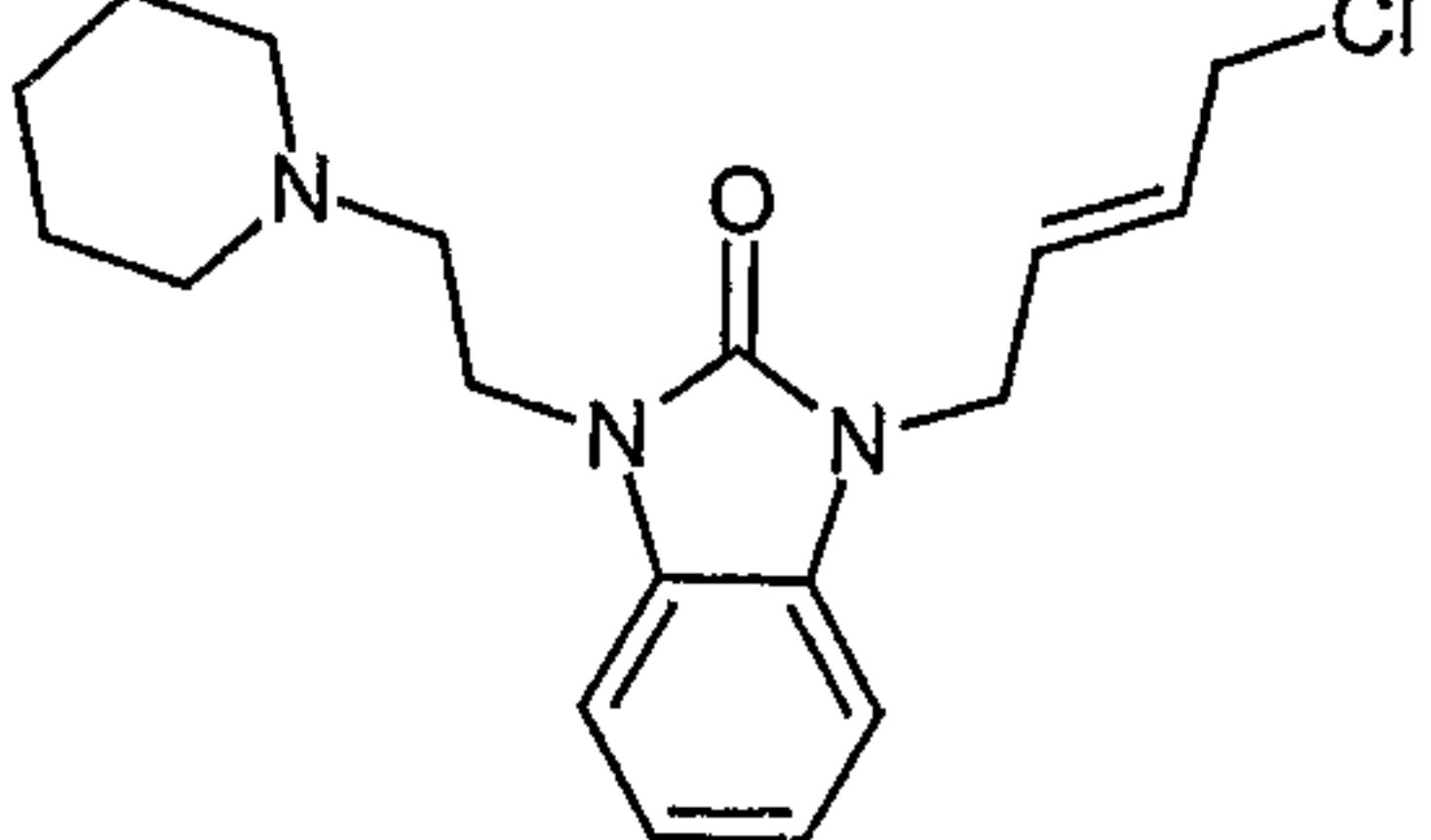
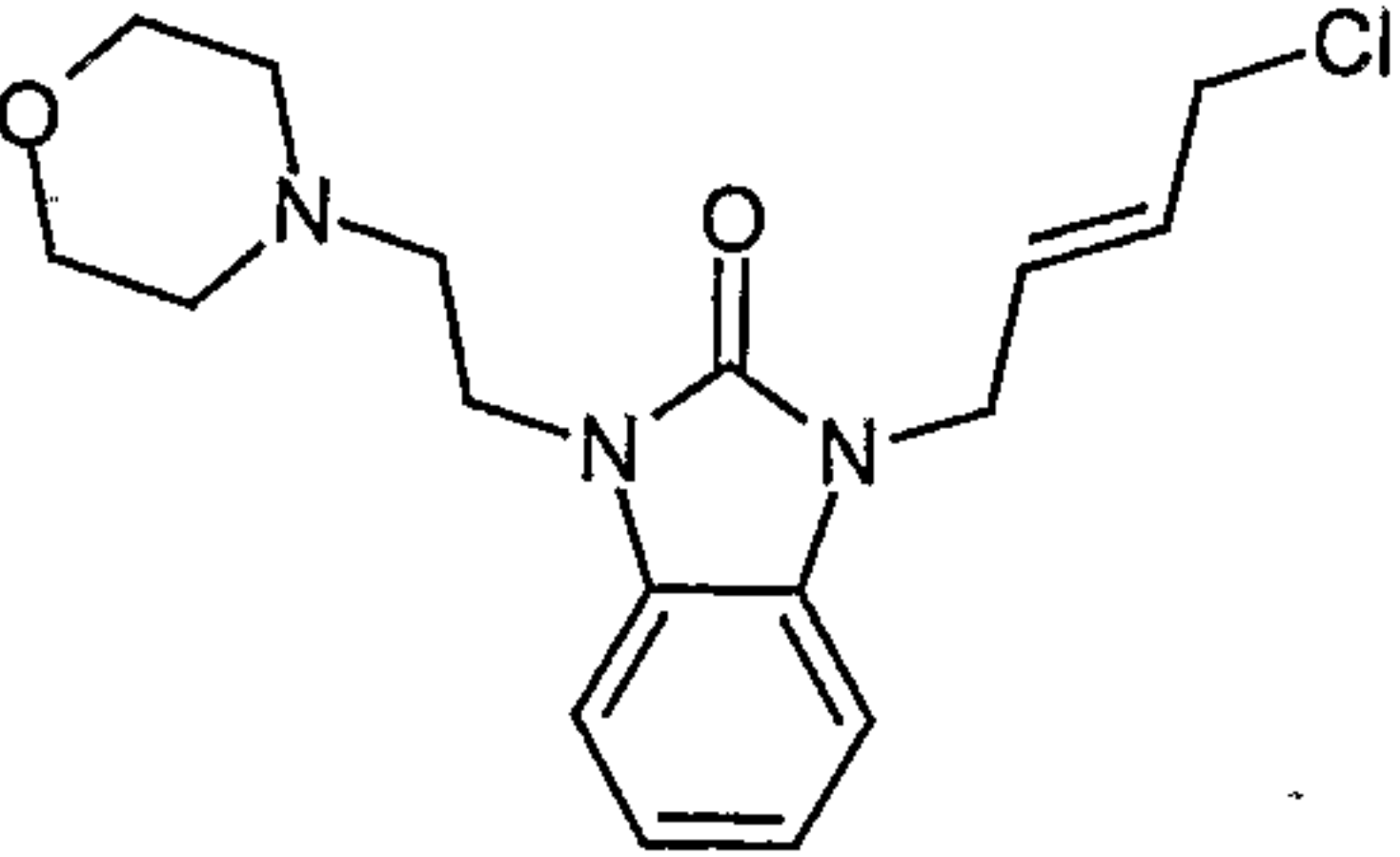
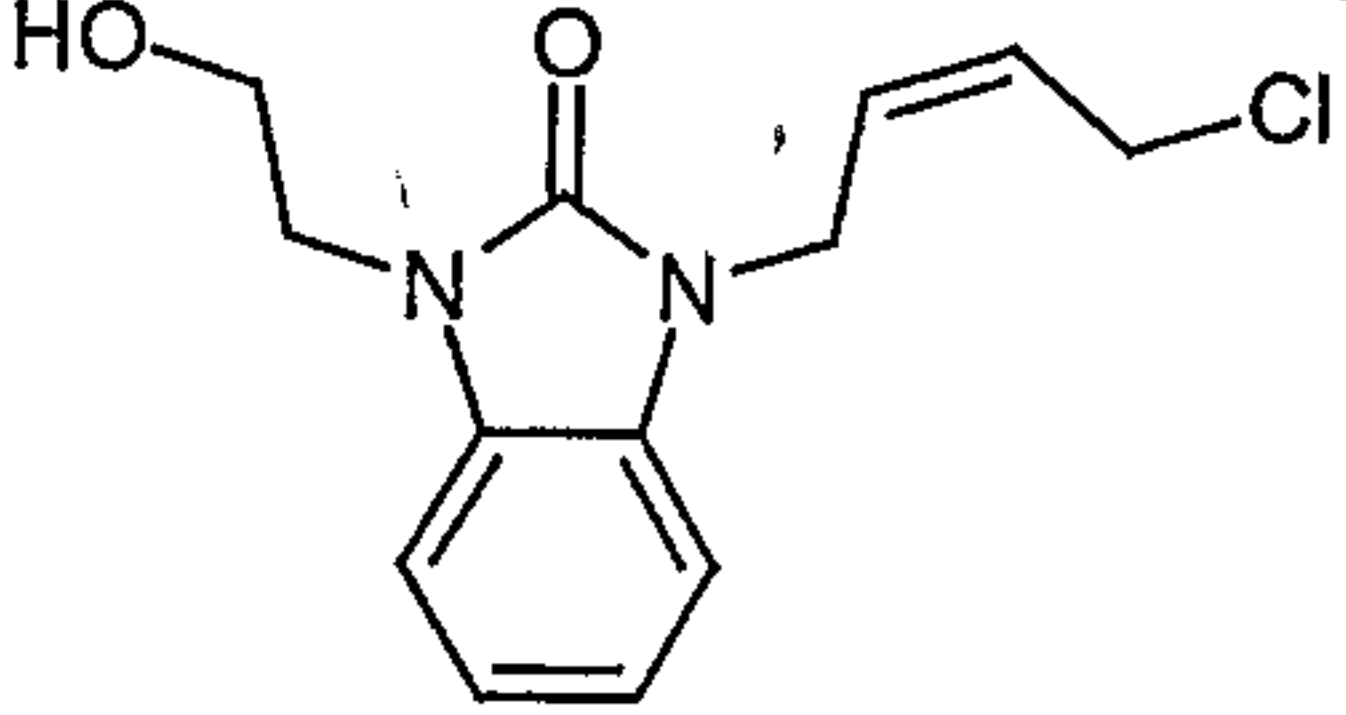
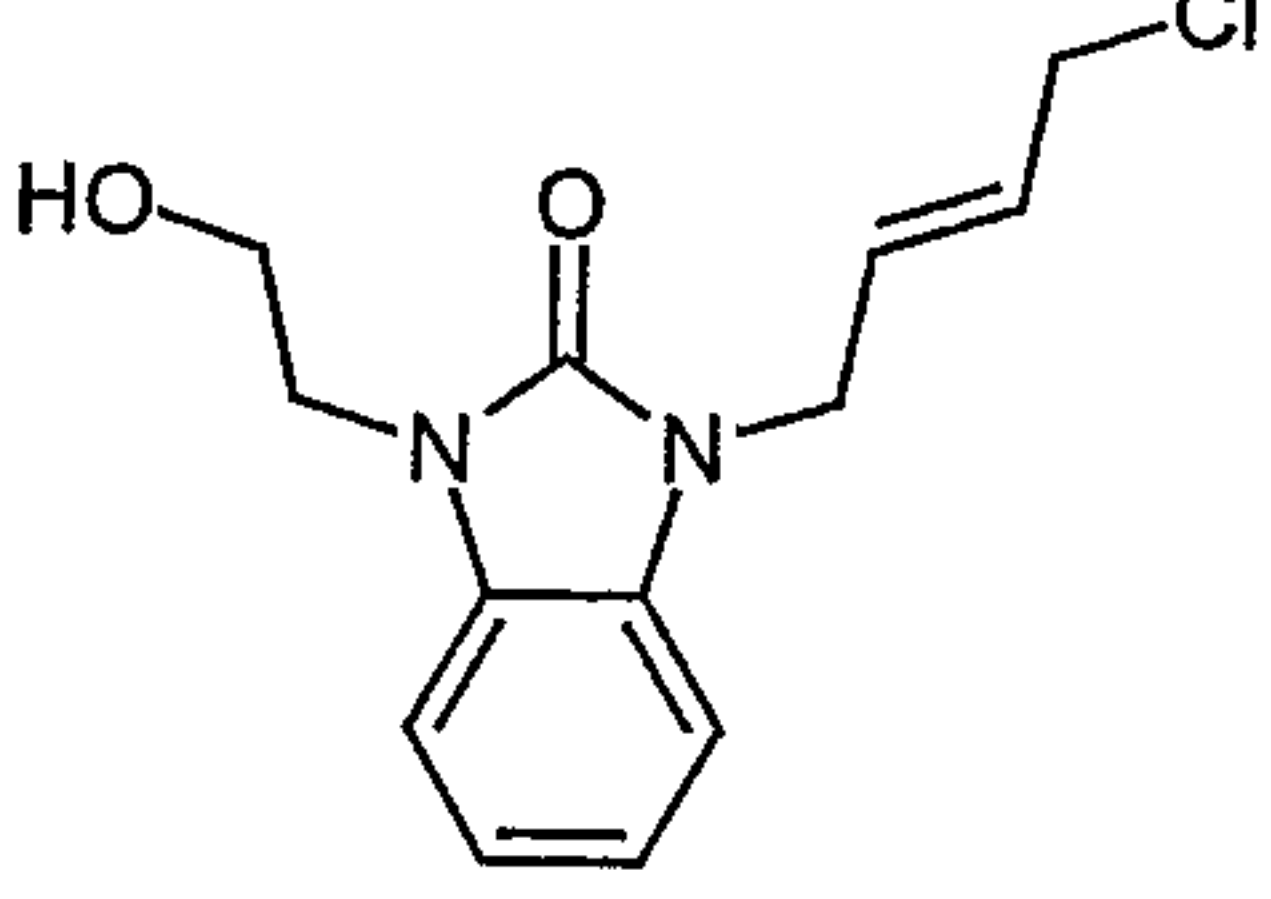
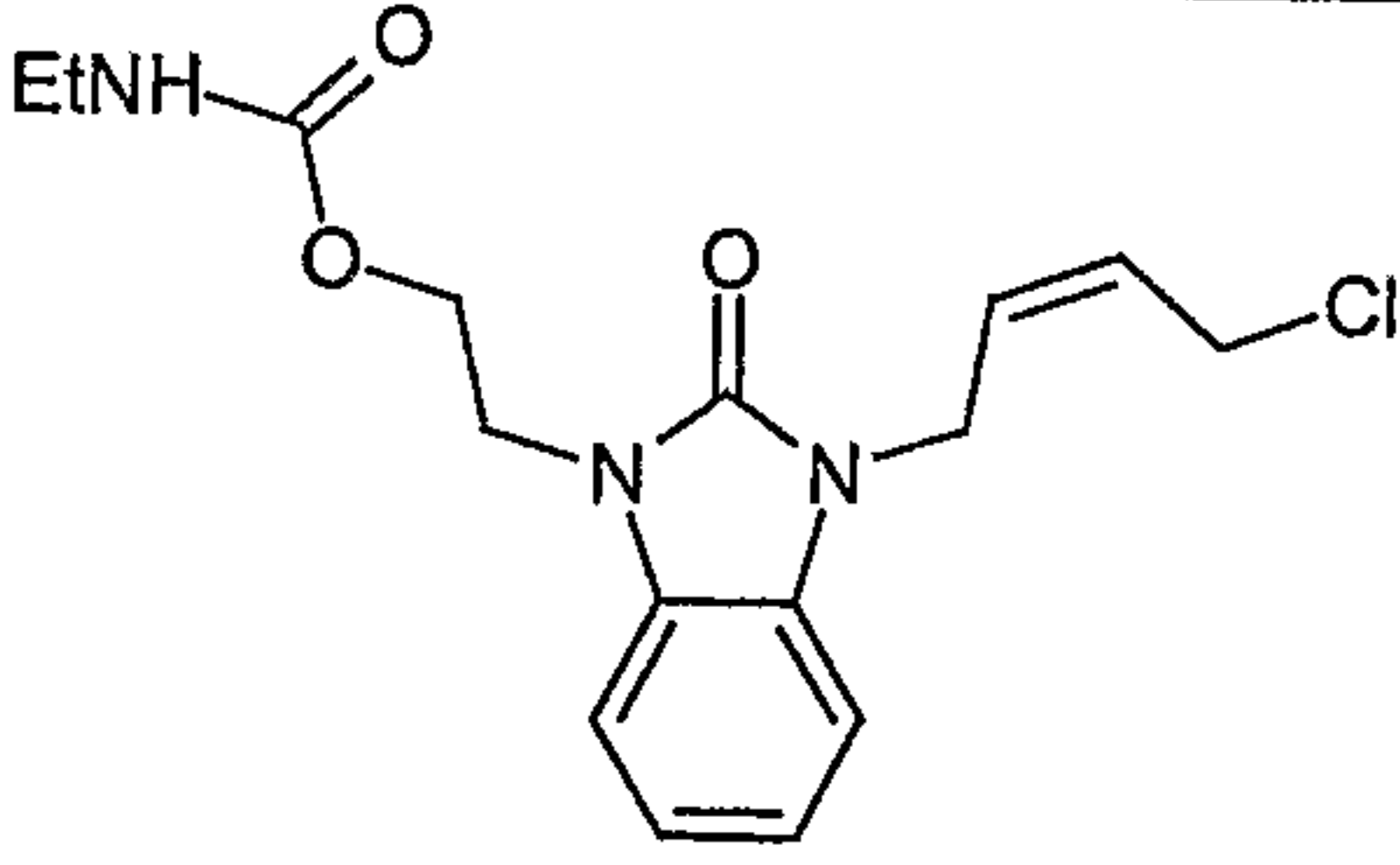
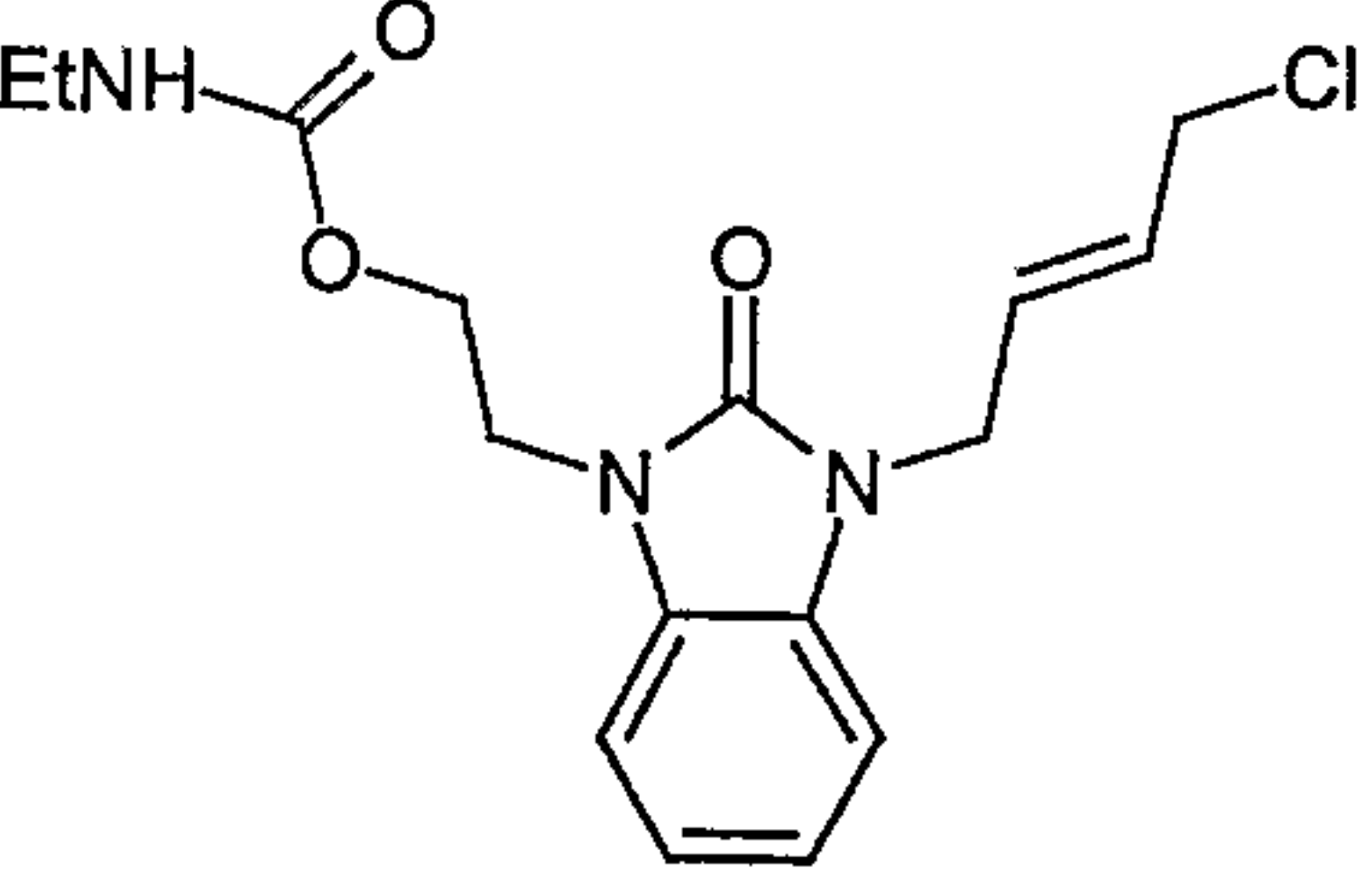
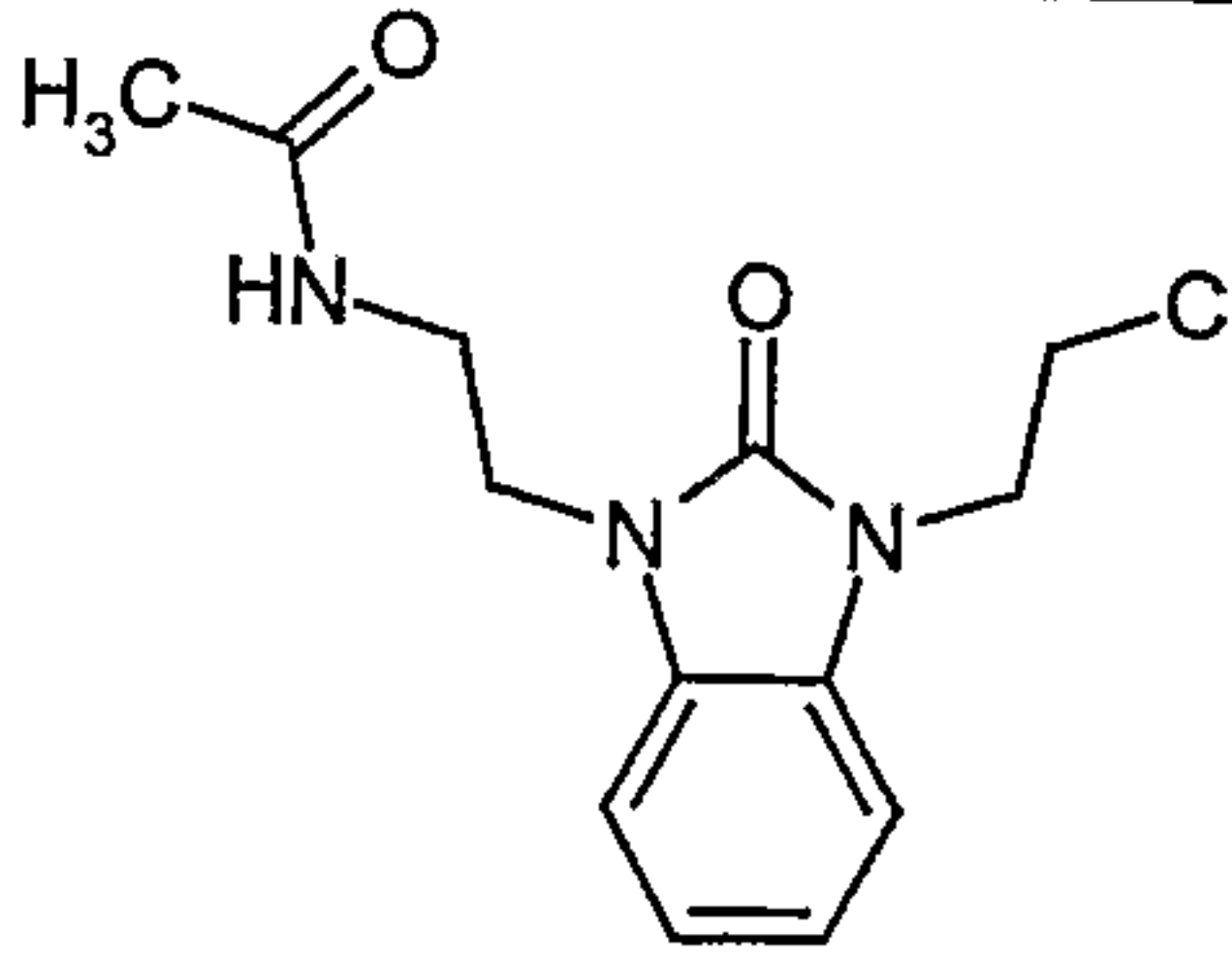
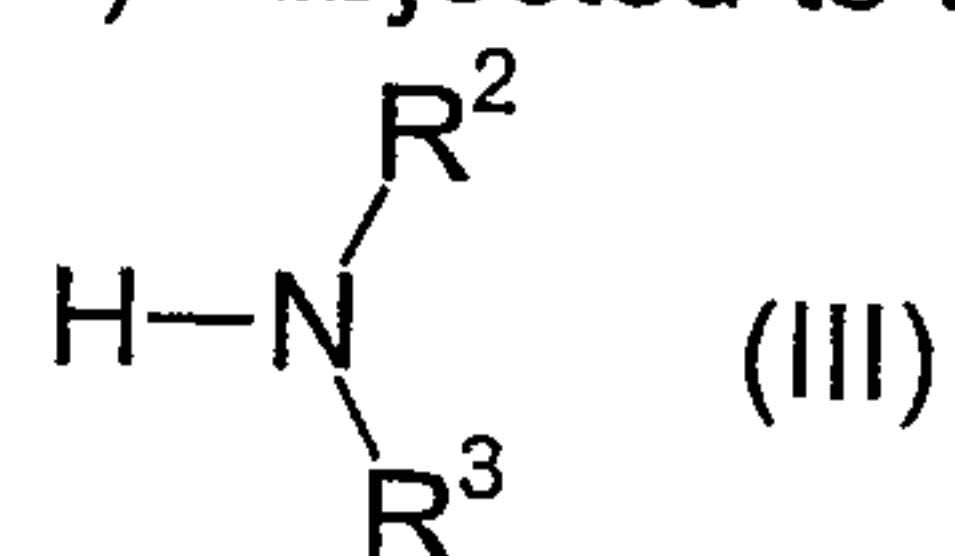
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BB15		BB16	
BB17		BB18	
BB19		BB20	
BB21		BB22	
BB23		BB24	

Table 1 (continued):

Building Block No.	Structure	Building Block No.	Structure
BB25		BB26	
BB27		BB28	

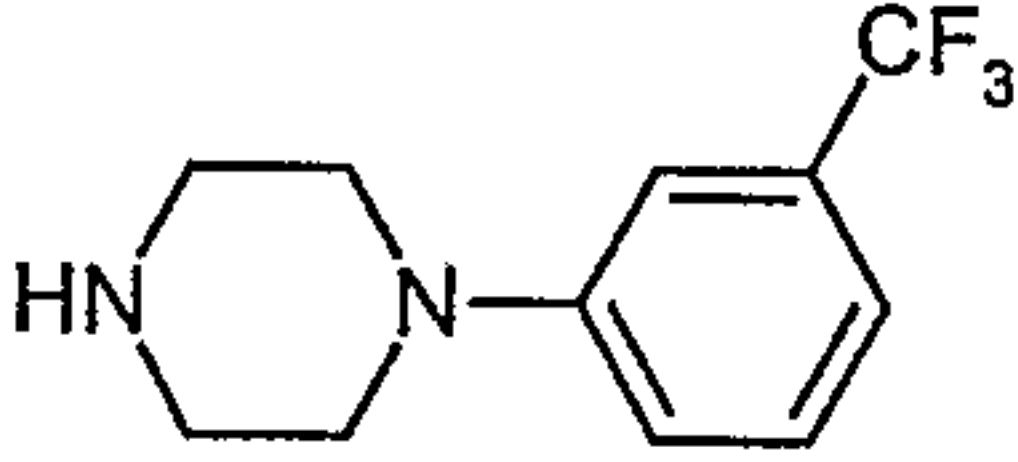
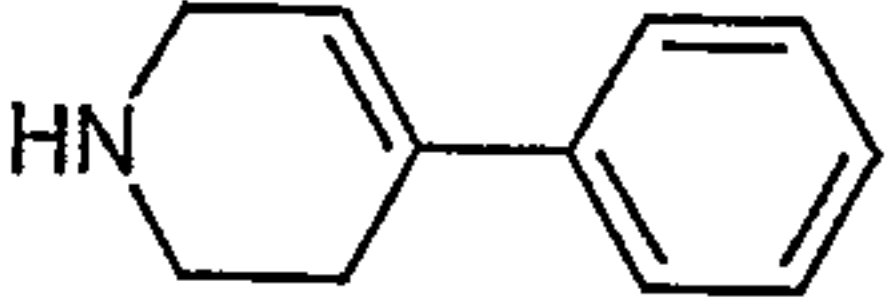
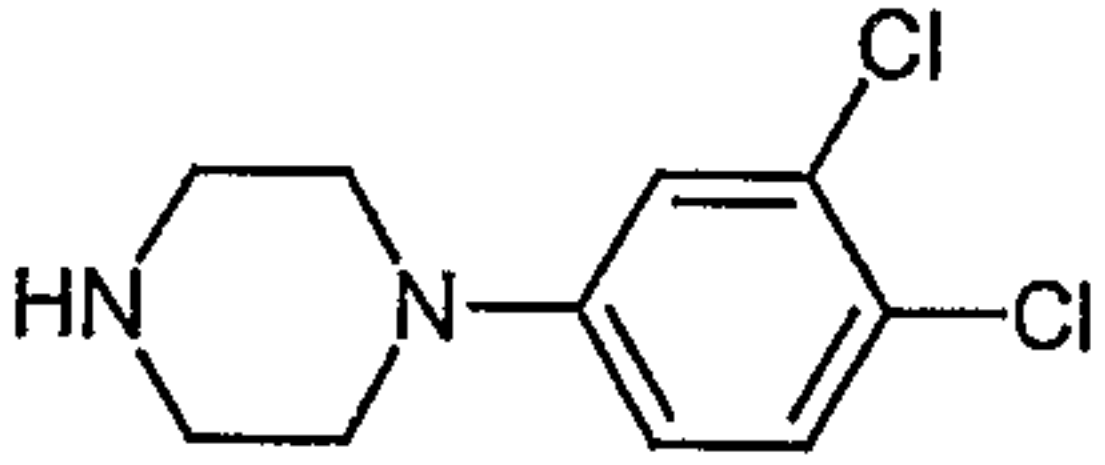
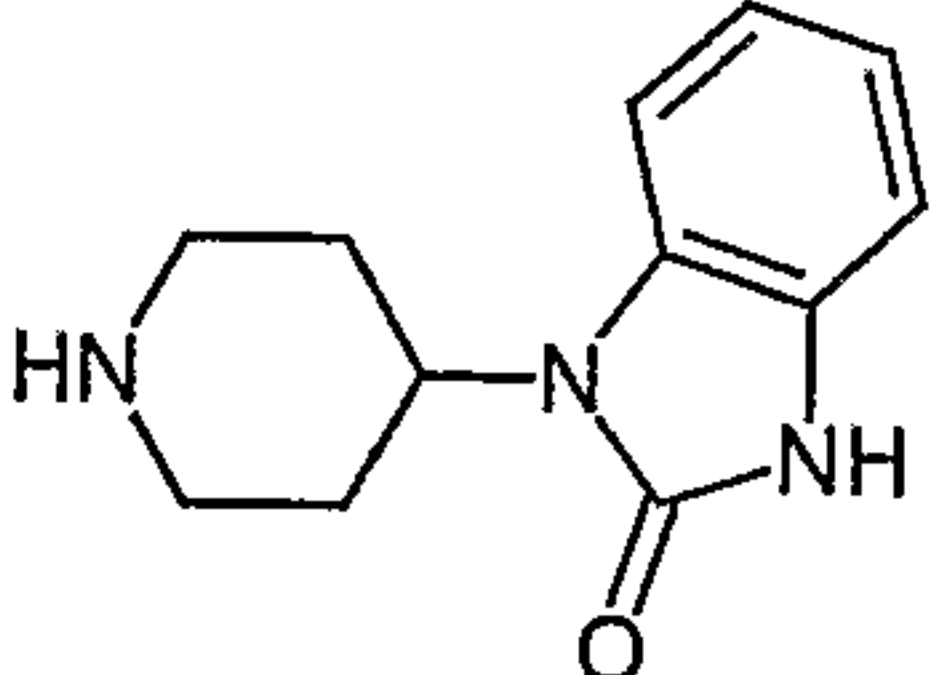
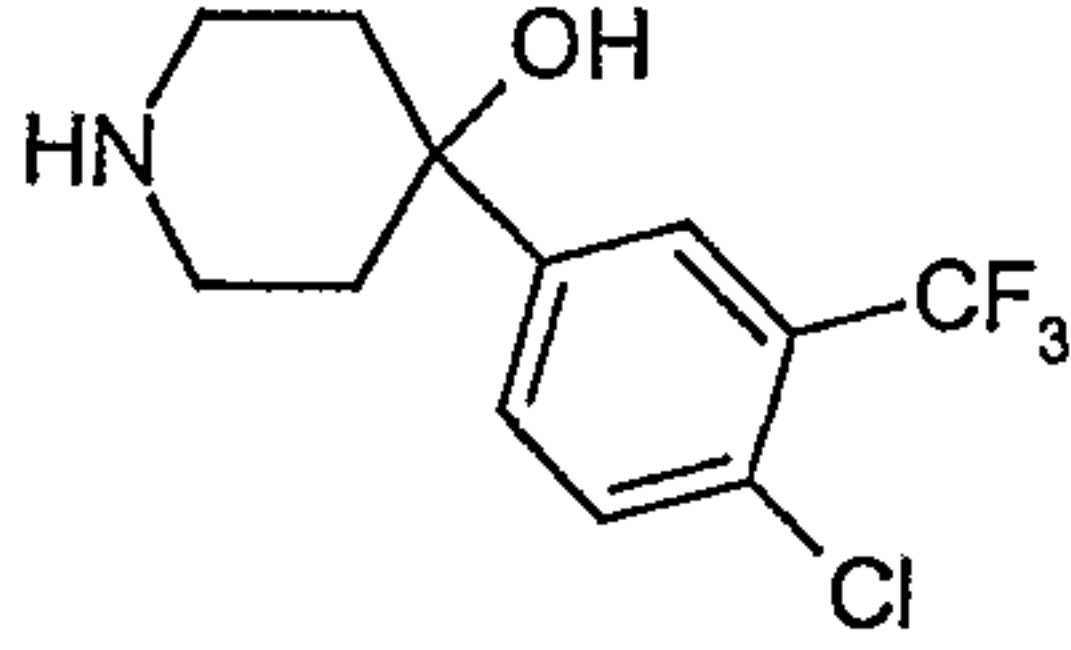
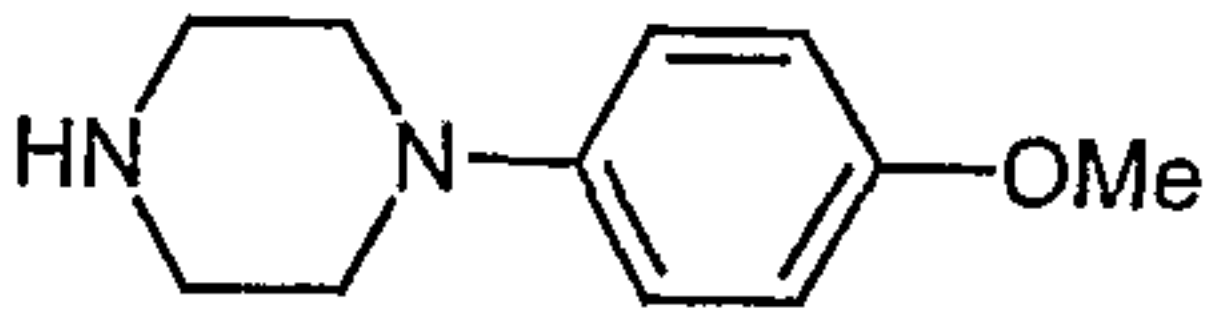
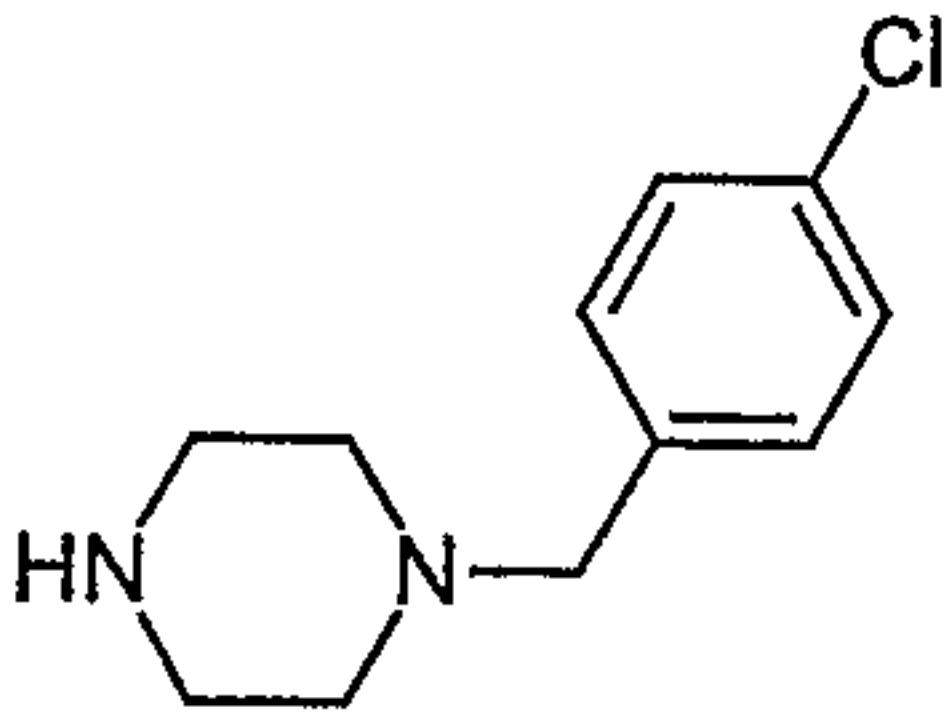
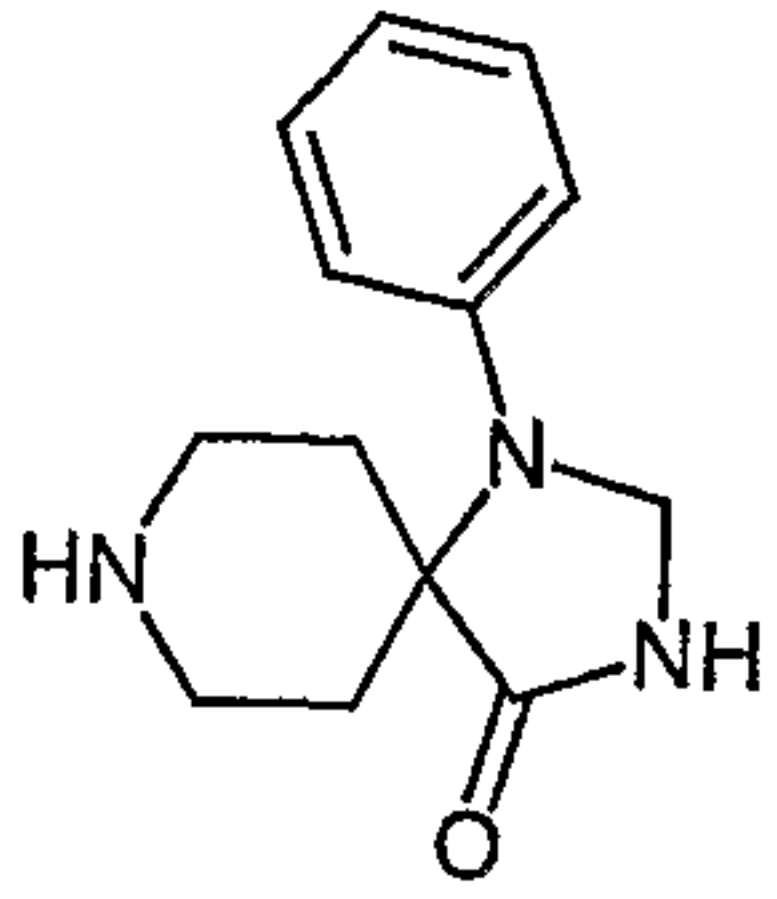
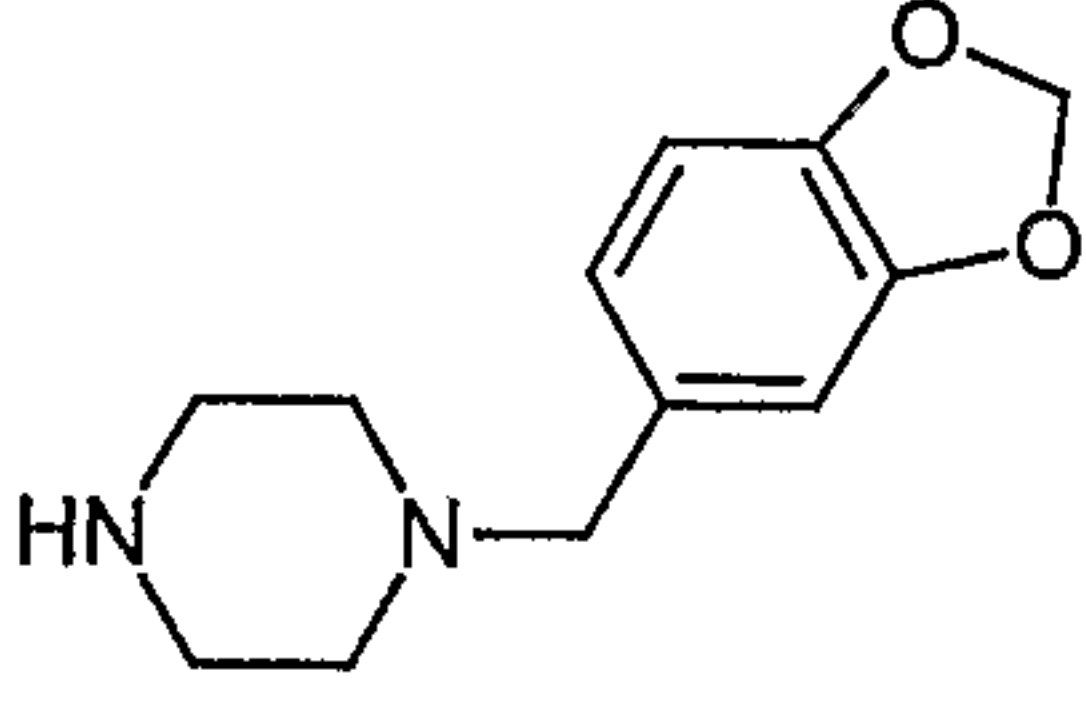
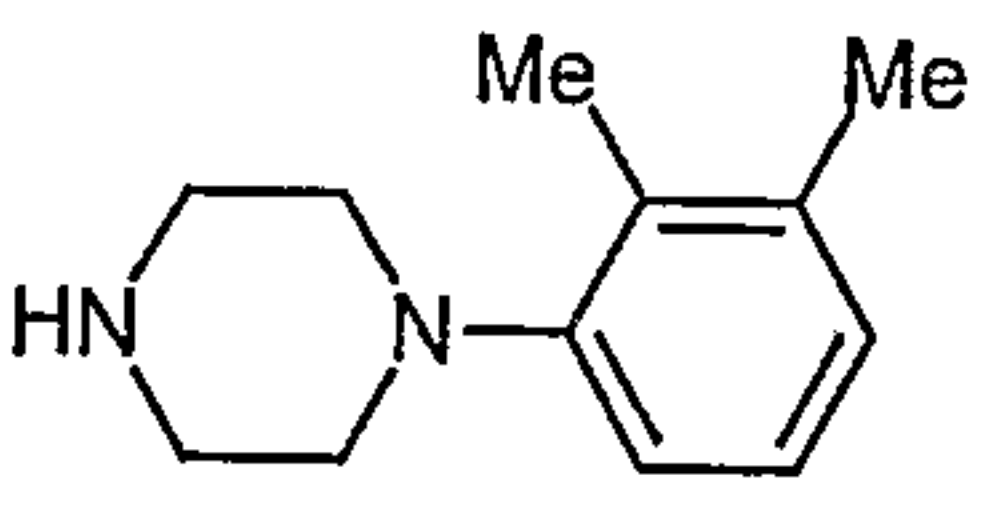
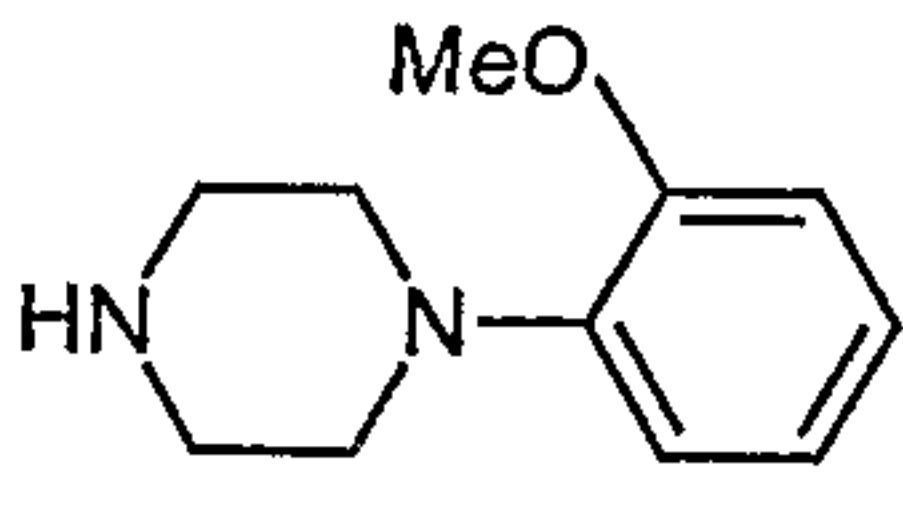
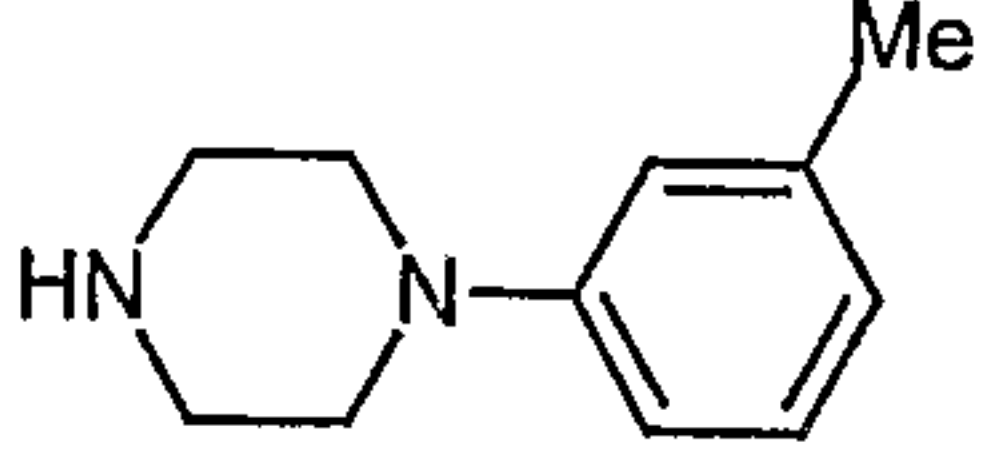
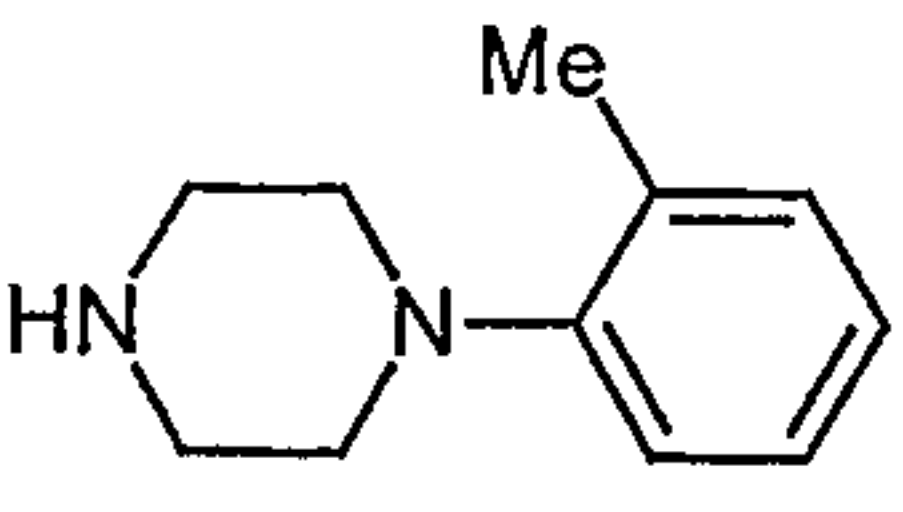
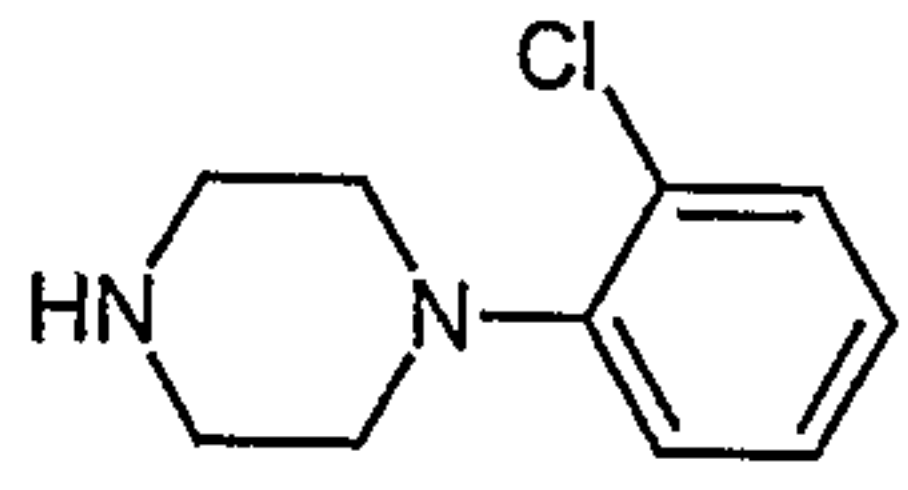
Table 2: Amines (AM) of formula (III) subjected to the process according to scheme 2



5

Amine No.	Structure	Amine No.	Structure
AM01		AM02	
AM03		AM04	
AM05		AM06	
AM07		AM08	

Table 2: (continued)

Amine No.	Structure	Amine No.	Structure
AM09		AM10	
AM11		AM12	
AM13		AM14	
AM15		AM16	
AM17		AM18	
AM19		AM20	
AM21		AM22	

For the pharmaceutical use the compounds of general formula (I) may be used as such or in the form of physiologically acceptable acid addition salts. The term "acid acceptable salts" includes both organic and inorganic acids such as maleic, citric tartaric, methanesulphonic, acetic, benzoic, succinic, gluconic, isethionic, glycinic.
5 lactic, malic, mucoic, glutammic, sulphamic and ascorbic acids; inorganic acids include hydrochloric, hydrobromic, nitric, sulfuric, or phosphoric acid.

According to a further feature of the present invention there are provided pharmaceutical compositions comprising as an active ingredient at least one
10 compound of formula (I), as before defined, or a physiologically acceptable addition salt thereof in addition with one or more pharmaceutical carrier, diluents or excipients. For pharmaceutical administration the compounds of general formula (I) and their physiologically acceptable acid addition salts may be incorporated into the conventional pharmaceutical preparation in solid, liquid or spray form. The
15 composition may, for example, be presented in a form suitable for oral, rectal, parenteral administration or for nasal inhalation: preferred forms includes for example, capsules, tablets, coated tables, ampoules, suppositories and nasal spray. The active ingredient may be incorporated in excipients or carriers conventionally used in pharmaceutical compositions such as, for example, talc, arabic gum, lactose,
20 gelatine, magnesium stearate, corn starch, aqueous or non aqueous vehicles, polyvynil pyrrolidone, semisynthetic glicerides of fatty acids, benzalcon chloride, sodium phosphate , EDTA, polysorbate 80.

In case it is desired to further increase the solubilty of the compounds of general formula (I) or of their physiologically acceptable salts surfactants, non ionic
25 surfactants such as PEG 400, cyclodextrin, metastable polymorphs, inert adsorbents such as bentonite, may be incorporated. Furthermore some techniques may be employed by preparing for example eutectic mixtures and/or solid dispersion by using mannitol, sorbitol, saccharose, succinic acid or physical modified forms by using hydrosoluble polymers, PVP, PEG 4000-20.000.
30 The compositions are advantageously formulated in dosage units, each dosage unit being adapted to supply a single dose of the active ingredient. Each dosage unit may conveniently contain from 0,01 mg to 100 mg, preferably from 0,1 to 50 mg.

However, it could be necessary to depart from the cited amounts, depending on the
35 body weight or on the administration route, on the individual response to the medicament, on the type of formulation and on the time, or time range, in which the administration is carried out. Therefore, it can be sufficient, in some cases, to use a lower amount then the cited minimum amount, whereas in other cases the higher range could be exceeded. When administering higher amounts, it would be advisable

15

to subdivide them in repeated administrations during the day. Moreover, the compounds of general formula (I) or the acid addition salts thereof can also be combined with other, different active substances.

- 5 The following examples illustrate the present invention, without limiting the scope thereof.

Examples of pharmaceutical formulation

10	A)	<u>Tablets</u>	for tablet
		Active substance	100 mg
		Lactose	140 mg
		Maize starch	240 mg
		Polyvinylpyrrolidone	15 mg
15		Magnesium stearate	5 mg
			500 mg

- 20 The finely ground active substance, lactose are part of maize starch are mixed. The mixture is sieved, wetted with a solution of polyvinylpyrrolidone in water, kneaded, finely granulated and dried. The granulate, the remaining maize starch and magnesium stearate are sieved and mixed together. The mixture is compressed to tablets of suitable form and size.

25	B)	<u>Tablets</u>	for tablet
		Active substance	80 mg
		Lactose	55 mg
		Maize starch	190 mg
		Microcrystalline cellulose	35 mg
30		Polyvinylpyrrolidone	15 mg
		Sodium carboxymethyl starch	23 mg
		Magnesium stearate	2 mg
			400 mg

35

The finely ground active substance, part of the maize starch, lactose, microcrystalline cellulose and polyvinylpyrrolidone are mixed. The mixture is sieved and worked up with the remaining maize starch and water, to obtain a granulate, which is dried and sieved. This is added with sodium carboxymethyl starch and magnesium stearate

and mixed, then the mixture is compressed to tablets of suitable size.

C)	<u>Solution for vials</u>	
	Active substance	50 mg
5	Sodium chloride	50 mg
	Water for injection	5 ml

The active substance is dissolved in water, optionally at pH of 5.5 to 6.5, and treated with sodium chloride as an osmolality agent. The resulting solution is filtered
10 apyrogenically, and the filtrate is placed in vials under asepsis conditions, then vials are sterilized and flame sealed. The vials contain 5 mg, 25 mg and 50 mg of active substance.

Experimental part

15 The following examples illustrate the preparation of all the new compounds included in the present invention. It should be understood that the invention is not limited to the given examples of chemical methods and processes for the preparation of the substances, as other conventional methods well known to those skilled in the art, are suitable too. In the following descriptions, each of the 28 Building Blocks prepared is
20 identified by its relevant Tag.

Part A) Preparation of the Building Blocks (BB) of formula (II)

Description 1

25 **1-[2-(1-piperidiny)-ethyl]-1,3-dihydro-2H-benzimidazol-2-one**

A solution of 1-isopropenyl-1,3-dihydro-2H-benzimidazol-2-one (35 g, 0.2 moles) in DMF (250 ml) was added dropwise to a suspension of 80% sodium hydride (6 g, 0.2 moles) in DMF (50 ml). The reaction mixture was first heated at 45 °C for 30 minutes, let to cool at room temperature and additional 80 % sodium hydride (7.2 g, 0.24
30 moles) was added. Then 1-(2-chloroethyl)-piperidine hydrochloride (44.16 g, 0.24 moles) was added portionwise and the reaction mixture was heated at 80-90 °C for 3 hrs. The mixture was then cooled at room temperature, adjusted to pH 3 with 37% aqueous HCl and heated at 80 °C for additional 2 hrs. The reaction mixture was poured into water and washed with ethyl acetate. The aqueous phase was adjusted
35 to pH 8-9 with a saturated sodium carbonate solution and extracted into ethyl acetate. The organic layer was taken to dryness to give an ivory solid which after crystallization from isopropyl ether afforded 22.9 g of the title compound. m.p. 123-125 °C.

According to the above described procedure, the following compound was prepared from the suitable intermediates:

1-[2-(4-morpholinyl)-ethyl]-1,3-dihydro-2H-benzimidazol-2-one

5 11.7 g; m.p. 122-126 °C.

Description 2

1-(2-methoxyethyl)-1,3-dihydro-2H-benzimidazol-2-one

10 Phenyl-2-oxo-2,3-dihydro-1H-benzimidazole-1-carboxylate (80 g, 0.315 moles) was added to a suspension of 80% sodium hydride (11.3 g, 0.378 moles) in DMF (500 ml) and heated at 35 °C for 1 hour. To the cooled solution 2-chloroethyl-methylether (43 ml, 0.472 moles) was added and the reaction mixture was heated at 100 °C for 4 hrs. The reaction mixture was poured into water and extracted with ethyl acetate. The combined extracts were taken to dryness to give 52 g of the protected intermediate.
15 This was suspended in methanol (500 ml), a solution of K₂CO₃ (44 g) in water (230 ml) was added and the mixture and stirred for 2 hrs at room temperature. After evaporation the reaction mixture was acidified and extracted into ethyl acetate. The organic layer was taken to dryness and from the crude oily residue, after
20 crystallization with isopropyl ether 21 g of the title compound were obtained as a white solid. m.p. 88 °C.

Description 3

1-[2-(tetrahydro-2H-pyran-2-yloxy)-ethyl]-1,3-dihydro-2H-benzimidazol-2-one

- 25 a) Phenyl-2-oxo-2,3-dihydro-1H-benzimidazole-1-carboxylate (50 g, 0.197 moles) was added to a suspension of 80% sodium hydride (7 g, 0.236 moles) in DMF (400 ml) and stirred for 1 hour at room temperature, then 2-(2 chloro-ethoxy)-tetrahydro-2H-pyran (34.8 ml, 0.236 moles) was added and the reaction mixture was heated at 100 °C for 7 hrs. The reaction mixture was then poured into water and extracted into ethyl acetate. The organic layer was taken to dryness to give
30 an oily residue.
- b) This residue (83 g) was dissolved in methanol, a solution of KOH (26 g in 260 ml water) was added and stirred for 2 hrs at room temperature. The methanol was evaporated and the residue was extracted into ethyl acetate. The organic layer was washed with an aqueous 5% HCl solution, dried and taken to dryness. The
35 oily residue was crystallized from diisopropyl ether to give 26 g of the title compound. m.p. 115 °C.

Description 4**1-(2-aminoethyl)-1,3-dihydro-2H-benzimidazol-2-one hydrochloride**

- 5 a) A suspension of Phenyl-2-oxo-2,3-dihydro-1H-benzimidazole-1-carboxylate (10 g, 39 mmol) and 80% sodium hydride (1.3 g, 43 mmol) in DMF (100 ml) was stirred at room temperature for 30 minutes. N-(2-bromoethyl)-phthalimide (10 g, 39 mmol) was added and the mixture heated at 100 °C for 12 hrs. The reaction mixture was then poured into 600 ml of water and stirred for 4 hrs at room temperature. The precipitated phthaloyl derivative was filtered off (white solid; 6.5 g).
- 10 b) This intermediate was suspended in methanol (70 ml), a 10% aqueous K₂CO₃ solution was added and the reaction mixture stirred overnight at room temperature. The methanol was evaporated, the residue was extracted with dichloro methane and the aqueous solution was acidified with 10% aqueous HCl to give the corresponding 2-carboxy-benzamido derivative which was filtered off
- 15 (5 g).
- c) To the crude intermediate were added 32 ml of a 15% aqueous HCl solution and the resulting suspension was heated at 90 °C for 3 hrs. After cooling, the solid was filtered off and the acidic solution was taken to dryness to give 1.5 g of the hydrochloride of the title compound as a pinkish solid. m.p. > 280 °C.
- 20

Description 5**N-[2-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)-ethyl]-acetamide**

- To a cooled solution of NaOH (0.41 g, 10 mmol) in water (5 ml) were simultaneously added 1-(2-aminoethyl)-1,3-dihydro-2H-benzimidazol-2-one
- 25 hydrochloride (0.7 g, 3.3 mmol) and a solution of acetic anhydride (0.37 ml, 3.9 mmol) in dioxane (10 ml). The reaction mixture was stirred for 2 hrs at room temperature and then taken to dryness. The residue was dissolved in water, adjusted to pH 4 with 10% aqueous HCl and extracted with CHCl₃. The organic layer was taken to dryness and from the crude residue 0.35 g of the title compound were
- 30 obtained after crystallization from diethyl ether. m.p. 153 °C.

Description 6**N-[2-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)-ethyl]-methanesulfonamide**

- To a solution of 1-(2-aminoethyl)-1,3-dihydro-2H-benzimidazol-2-one hydrochloride
- 35 (2.8 g, 13 mmol) in THF (30 ml) and triethyl amine (5.5 ml, 39 mmol) was added methanesulfonyl chloride (1.12 ml, 14 mmol) and the reaction mixture was stirred for 2 hrs at room temperature. The organic solvent was evaporated and the residue was partitioned into water and ethyl acetate. The organic layer was washed with saturated aqueous Na₂CO₃ solution and taken to dryness. The crude residue was

purified by flash chromatography (CH₂Cl₂-methanol 96-4) to give 0.5 g of the title compound as a white solid. m.p. 162-170 °C.

Description 7

5 **1-(2-chloroethyl)-3-[2-(tetrahydro-2H-pyran-2-yloxy)-ethyl]-1,3-dihydro-2H-benzimidazol-2-one**

Into a stirred solution of 1-[2-(tetrahydro-2H-pyran-2-yloxy)-ethyl]-1,3-dihydro-2H-benzimidazol-2-one (6.5 g, 25 mmoles) in DMF (40 ml) 80% sodium hydride (0.9 g, 30 mmoles) was added. After 30 minutes of stirring and heating 35 °C, 1-bromo-2-
10 chloro ethane (6.2 g, 48 mmoles) was added, the reaction temperature was increased at 90 °C and kept for 6 hrs then cooled at room temperature. The reaction mixture was poured into water, extracted with diethyl ether and the organic layer was taken to dryness. The residue was purified by flash chromatography (cyclohexane-ethyl acetate 50-50) to give 2.8 g of the title compound as a thick oil which was used
15 without any further purification.

According to the above described procedure, the following compounds were prepared from the suitable intermediates:

20 **1-(4-chlorobutyl)-3-[2-(tetrahydro-2H-pyran-2-yloxy)-ethyl]-1,3-dihydro-2H-benzimidazol-2-one**

The compound was purified by flash chromatography (cyclohexane-ethyl acetate 50-50). Thick oil.

25 **[BB09]: 1-(2-chloroethyl)-3-(2-methoxyethyl)-1,3-dihydro-2H-benzimidazol-2-one**
White solid. m.p. 55 °C., from diisopropyl ether

[BB01]: 1-(4-chlorobutyl)-3-(2-methoxyethyl)-1,3-dihydro-2H-benzimidazol-2-one

The compound was purified by flash chromatography (cyclohexane-ethyl acetate 50-
30 50). Thick oil.

[BB15]: 1-[(2Z)-4-chloro-2butenyl]-3-(2-methoxyethyl)-1,3-dihydro-2H-benzimidazol-2-one

The compound was purified by flash chromatography (cyclohexane-ethyl acetate 70-
35 30). Thick oil.

[BB24]: N-{2-[3-(2-chloroethyl)-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl]-ethyl}-acetamide

White solid. m.p. 140-142 °C., from acetone

5 **[BB06]: N-{2-[3-(4-chlorobutyl)-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl]-ethyl}-acetamide**

Ivory solid. m.p. 100 °C., from diethyl ether

Description 8

10 **1-[(2Z)-4-chloro-2-butenyl]-3-[2-(tetrahydro-2H-pyran-2-yloxy)-ethyl]-1,3-dihydro-2H-benzimidazol-2-one**

To a solution of 1-[2-(tetrahydro-2H-pyran-2-yloxy)-ethyl]-1,3-dihydro-2H-benzimidazol-2-one (12 g, 46 mmol) in DMF (120 ml) was added 80% sodium hydride (1.7 g, 55 mmol) and the mixture was stirred at room temperature for 1
15 hour. Cis 1,4-dichloro-2-butene (5.8 ml, 55 mmol) was dropped in and the reaction mixture was stirred for 3 hrs at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was taken to dryness and the residue was purified by flash chromatography (cyclohexane-ethyl acetate 70-30) to give 2.8 g of the title compound as a thick oil which was used without any
20 further purification.

According to the above described procedure, the following compounds were prepared from the suitable intermediates:

25 **1-[(2E)-4-chloro-2-butenyl]-3-[2-(tetrahydro-2H-pyran-2-yloxy)-ethyl]-1,3-dihydro-2H-benzimidazol-2-one**

The compound was purified by flash chromatography (cyclohexane-ethyl acetate 70-30). Waxy solid.

30 **[BB16]: 1-[(2E)-4-chloro-2-butenyl]-3-(2-methoxyethyl)-1,3-dihydro-2H-benzimidazol-2-one**

The compound was purified by flash chromatography (cyclohexane-ethyl acetate 70-30). Thick oil.

35 **[BB25]: N-(2-{3-[(2Z)-4-chloro-2-butenyl]-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl})-ethyl)-acetamide**

The compound was purified by flash chromatography (CH₂Cl₂-methanol 97-3). Waxy solid from diisopropyl ether, m.p. 118 °C.

[BB26]: N-(2-{3-[(2E)-4-chloro-2-butenyl]-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl}}-ethyl)-acetamide

White solid from diethyl ether, m.p. 108 °C.

5 **[BB13]: N-{2-[3-(2-chloroethyl)-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl]-ethyl}-methanesulfonamide**

The compound was purified by flash chromatography (CH₂Cl₂-methanol 98-2). White low melting solid.

10 **[BB07]: N-{2-[3-(4-chlorobutyl)-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl]-ethyl}-methanesulfonamide**

White solid, m.p. 104 °C from diethyl ether.

15 **[BB27]: N-(2-{3-[(2Z)-4-chloro-2-butenyl]-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl}-ethyl)-methanesulfonamide**

The compound was purified by flash chromatography (CH₂Cl₂-methanol 97-3). White solid, m.p. 83 °C from diethyl ether.

20 **[BB28]: N-2-{3-[(2E)-4-chloro-2-butenyl]-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl}-ethyl}-methanesulfonamide**

The compound was purified by flash chromatography (CH₂Cl₂-methanol 98-2). White solid, m.p. 98 °C from diethyl ether.

Description 9

25 **[BB08]: 1-(2-chloroethyl)-3-[(2-piperidiny)-ethyl]-1,3-dihydro-2H-benzimidazol-2-one**

A solution of 1-[2-(1-piperidiny)-ethyl]-1,3-dihydro-2H-benzimidazol-2-one (4 g, 16.3 mmoles) in DMF (50 ml) was added to a suspension of 80% sodium hydride (0.49 g, 16.3 mmoles) in DMF (25 ml) and the reaction mixture was heated under stirring for 30 minutes at 40 °C. The solution was slowly transferred (3 hrs) into a solution of 1-bromo-2-chloro-ethane (2.7 ml, 32.6 mmoles) in DMF (30 ml), the temperature was increased to 60 °C and stirred for 5 hrs. The reaction mixture was then taken to dryness under vacuum, the residue partitioned between 5% aqueous HCl and diethyl ether. The aqueous layer was adjusted to pH 9-10 with sodium carbonate and extracted with ethyl acetate. After evaporation and flash chromatography purification (CH₂Cl₂-methanol-NH₄OH 95-5-0.5) 2.2 g of the pure title compound was obtained as a clear oil.

30
35

According to the above described procedure, the following compounds were prepared from the suitable intermediates:

[BB02]: 1-(4-chlorobutyl)-3-[(2-(1-piperidiny)-ethyl)-1,3-dihydro-2H-benzimidazol-2-one

5 The compound was purified by flash chromatography (CH₂Cl₂-methanol-NH₄OH 95-5-0.5). Ivory solid, m.p. 82-87 °C from diethyl ether.

[BB12]: 1-(2-chloroethyl)-3-[2-(4-morpholinyl)-ethyl]-1,3-dihydro-2H-benzimidazol-2-one

10 The compound was purified by flash chromatography (CH₂Cl₂-methanol-NH₄OH 95-5-0.5). Thick oil.

[BB03]: 1-(4-chlorobutyl)-3-[2-(4-morpholinyl)-ethyl]-1,3-dihydro-2H-benzimidazol-2-one

15 The compound was purified by flash chromatography (CH₂Cl₂-methanol-NH₄OH 95-5-0.5). Clear oil.

Description 10

[BB14]: 1-[(2Z)-4-chloro-2-butenyl]-3-[2-(4-morpholinyl)-ethyl]-1,3-dihydro-2H-benzimidazol-2-one

20 A solution of 1-[2-(4-morpholinyl)-ethyl]-1,3-dihydro-2H-benzimidazol-2-one (4 g, 16.2 mmoles) in DMF (50 ml) was added dropwise to a suspension of 80% sodium hydride (0.49 g, 16.2 mmoles) in DMF (50 ml) and the mixture was heated under stirring at 45 °C for 30 minutes. This solution was slowly transferred (4 hrs) to a
25 solution of cis-1,4-dichloro-2-butene (3.43 ml, 32.4 mmoles) in DMF (20 ml). The reaction mixture was stirred overnight at room temperature, taken to dryness under vacuum and partitioned between ethyl acetate and water. From the organic solution after evaporation and flash chromatography purification (CH₂Cl₂-methanol-NH₄OH 95-5-0.5) 2.4 g of the title compound were obtained as an oil.

30

According to the above described procedure, the following compounds were prepared from the suitable intermediates:

[BB19]: 1-[(2E)-4-chloro-2-butenyl]-3-[2-(4-morpholinyl)-ethyl]-1,3-dihydro-2H-benzimidazol-2-one

35 The compound was purified by flash chromatography (CH₂Cl₂-methanol-NH₄OH 95-5-0.5). Thick oil.

[BB17]: 1-[(2Z)-4-chloro-2-butenyl]-3-[2-(1-piperidiny)-ethyl]-1,3-dihydro-2H-benzimidazol-2-one

The compound was purified by flash chromatography (CH₂Cl₂-methanol-NH₄OH 95-5-0.5). Thick oil.

5

[BB18]: 1-[(2E)-4-chloro-2-butenyl]-3-[2-(1-piperidiny) -ethyl]-1,3-dihydro-2H-benzimidazol-2-one

The compound was purified by flash chromatography (CH₂Cl₂-methanol-NH₄OH 95-5-0.5). Thick oil.

10

Description 11

[BB10]: 1-(2-chloroethyl)-3-(2-hydroxyethyl)-1,3-dihydro-2H-benzimidazol-2-one

A solution of 1-(2-chloroethyl)-3-[2-(tetrahydro-2H-pyran-2-yloxy)-ethyl]-1,3-dihydro-2H-benzimidazol-2-one (2.2 g) and a catalytic amount of p-toluensulfonic acid (0.1 g) in methanol (30 ml) was stirred at room temperature for 2 hrs. The reaction mixture was evaporated to dryness, the residue was dissolved in CH₂Cl₂ and washed with a saturated aqueous solution of K₂CO₃. The organic layer was taken to dryness to give 1.5 g of the title compound as white solid. m. p. 135 °C.

20 According to the above described procedure, the following compounds were prepared from the suitable intermediates:

[BB04]: 1-(4-chlorobutyl)-3-(2-hydroxyethyl)-1,3-dihydro-2H-benzimidazol-2-one
Thick oil.

25

[BB20]: 1-[(2Z)-4-chloro-2-butenyl]-3-(2-hydroxyethyl)-1,3-dihydro-2H-benzimidazol-2-one

White solid, m. p. 80 °C from diethyl ether.

30 **[BB21]: 1-[(2E)-4-chloro-2-butenyl]-3-(2-hydroxyethyl)-1,3-dihydro-2H-benzimidazol-2-one**

Ivory solid, m. p. 73 °C from diethyl ether.

Description 12

[BB11]: 2-[3-(2-chloroethyl)-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl]-ethyl-ethylcarbamate

5 1-(2-chloroethyl)-3-(2-hydroxyethyl)-1,3-dihydro-2H-benzimidazol-2-one (2.6 g, 11 mmoles) and ethyl isocyanate (20 ml) were refluxed under stirring for 6 hrs then left overnight at room temperature. The reaction mixture was taken to dryness and the residue was crystallized from diisopropyl ether to give 3 g of the title compound. m. p. 125 °C.

10 According to the above described procedure, the following compound was prepared from the suitable intermediate:

[BB05]: 2-[3-(4-chlorobutyl)-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl]-ethyl-ethylcarbamate

15 White solid, m. p. 75 °C from diethyl ether.

Description 13

[BB22]: 2-{3-[(2Z)-4-chloro-2-butenyl]-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl}-ethyl-ethylcarbamate

20 1-(4-chlorobutyl)-3-(2-hydroxyethyl)-1,3-dihydro-2H-benzimidazol-2-one (1.8 g, 6.8 mmoles) and ethyl isocyanate (6 ml) were stirred at room temperature for 48 hrs. The reaction mixture was then taken to dryness and the residue was crystallized from diethyl ether to give 1.8 g the title compound. m. p. 107 °C.

25 According to the above described procedure, the following compound was prepared from the suitable intermediate:

[BB23]: 2-{3-[(2E)-4-chloro-2-butenyl]-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl}-ethyl-ethylcarbamate

30 The compound was purified by flash chromatography (cyclohexane-ethyl acetate 50-50). White solid, m. p. 70 °C from diethyl ether.

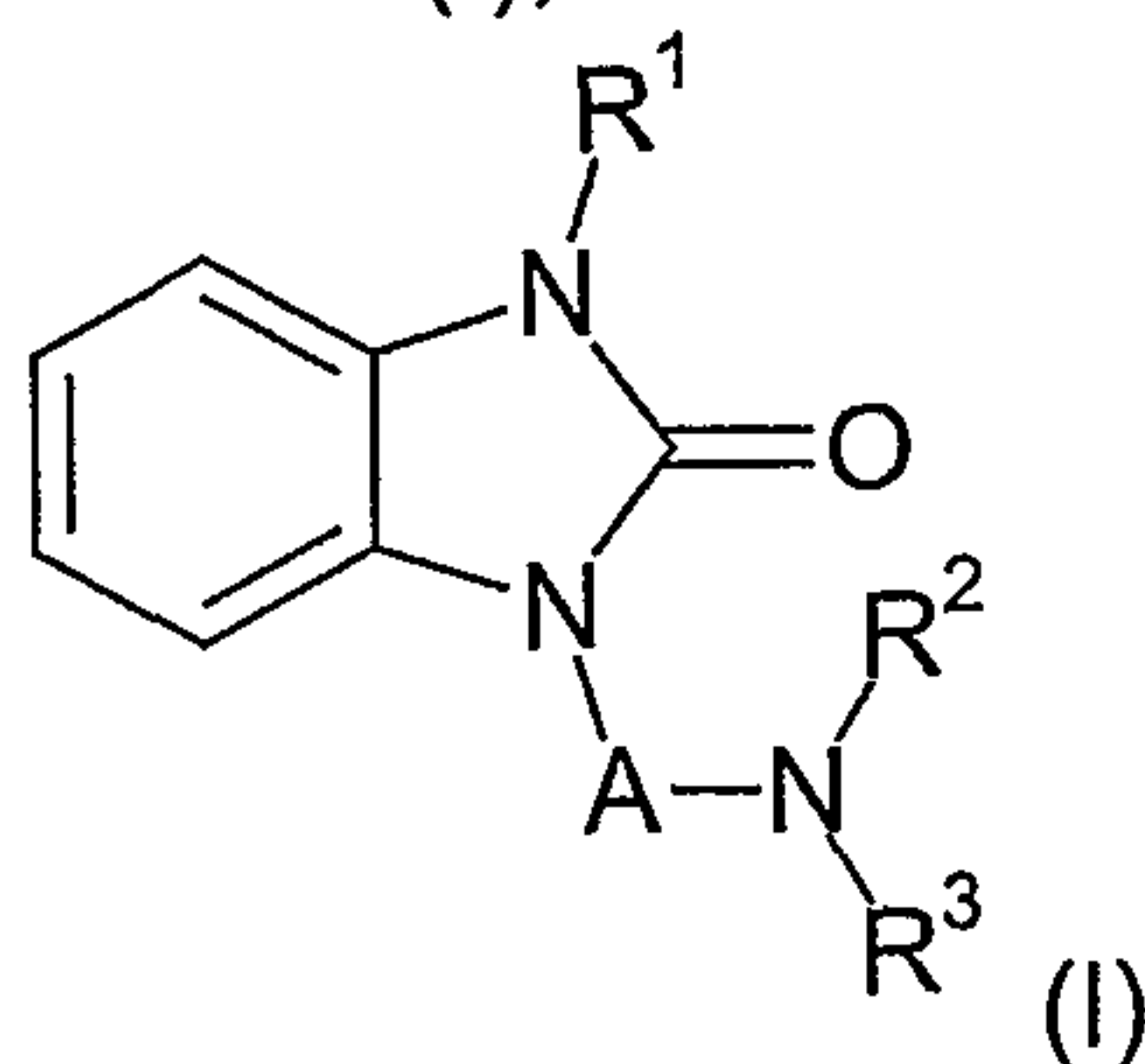
Part B) General method for the preparation of the compounds of formula (I)

5 A solution of each building block (II) (0,1mM) was reacted under stirring with each amine (0,2 mM) in anhydrous DMF (100 μ l) in the presence of Na₂CO₃ (0,3 mM) at a temperature ranging from room temperature to 100 °C, preferably between 60 °C and 80 °C, for about 6-8 hours. Isocyanatemethyl Polystyrene Resin (loading 0,23 meq/g), (0,2 mM) was introduced and the mixture was gently stirred at room temperature for 8 hours. The resin was then filtered off under vacuum, washed with 10 DMF, and filtered again. The collected solutions were evaporated to dryness in a speed-vac centrifuge. The compounds which were prepared according to the above described procedure are listed in Table 3.

15 Table 3 collects the structural formula of the synthetised compounds along with the corresponding characterising mass data (i.e. [M+H]⁺) obtained for each of the compounds according to the invention. The identification of the compounds and their purity was carried out by using positive APCI-LC/MS technique.

26

Table 3: compounds of general formula (I),



Comp. No	-R ¹	-A-		[M+H] ⁺
1				409
2				533
3				423
4				410
5				443
6				411
7				419
8				478
9				477
10				406

Table 3 (continued):

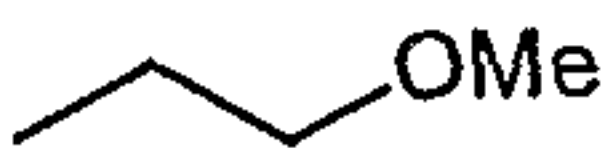
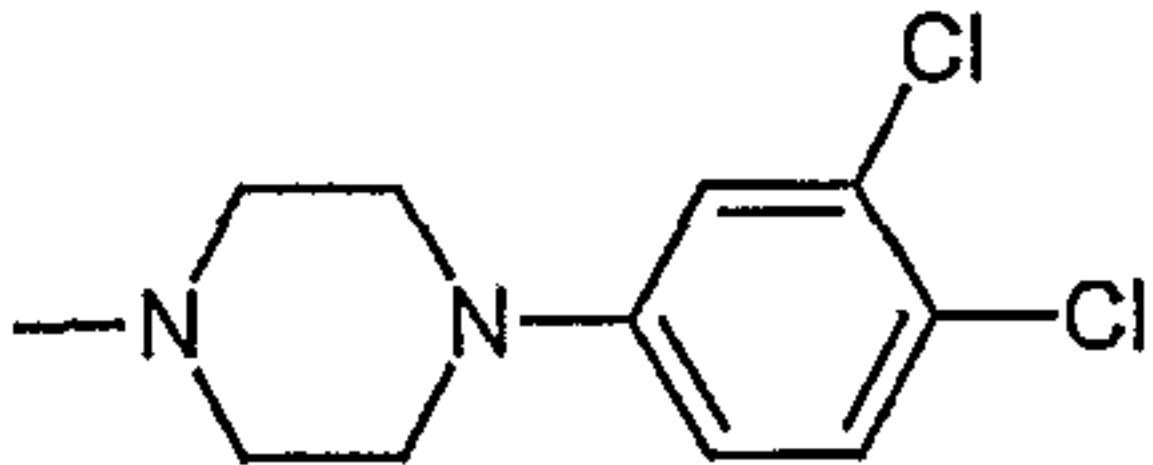
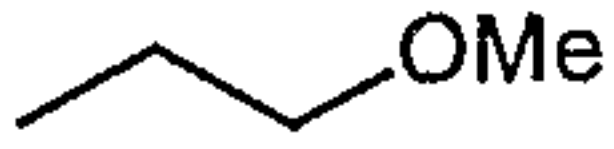
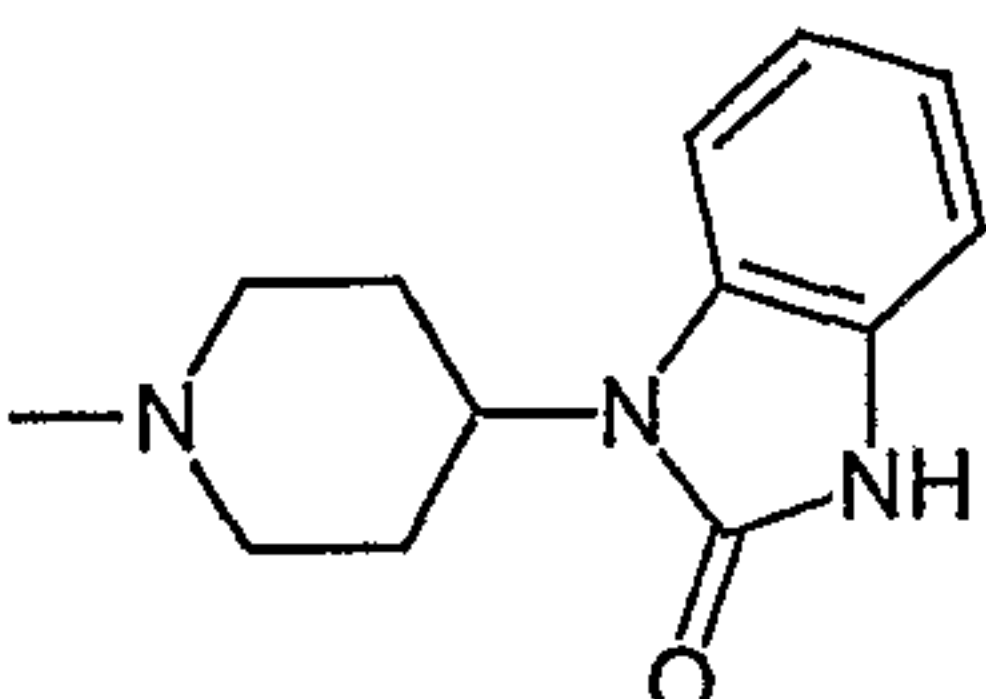
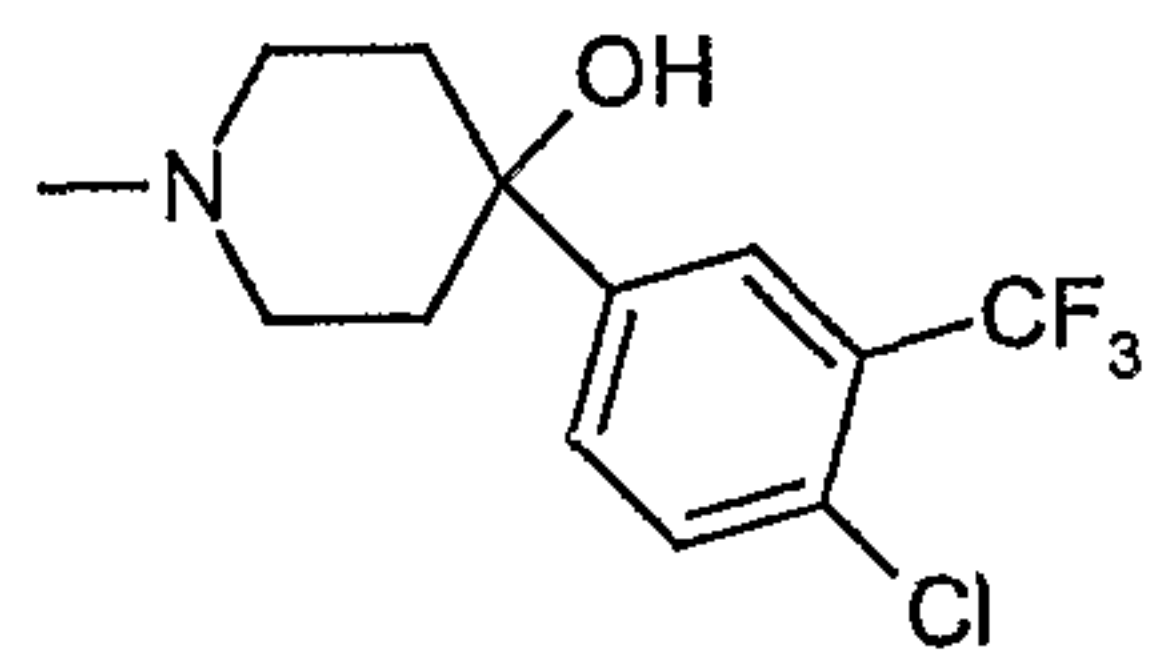
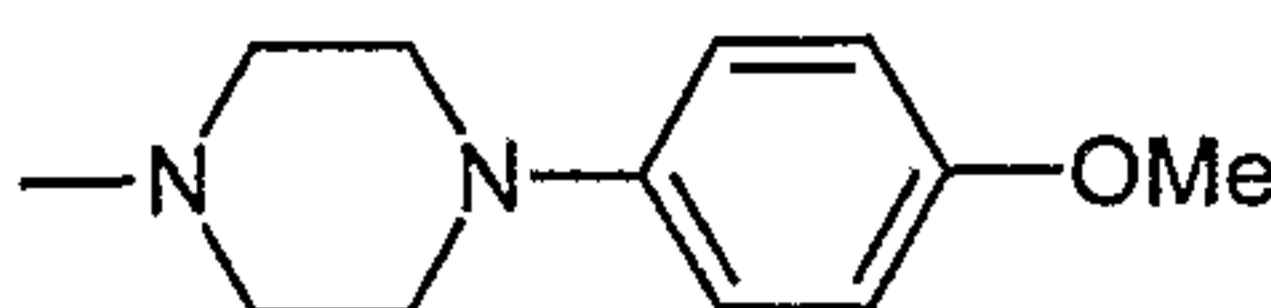
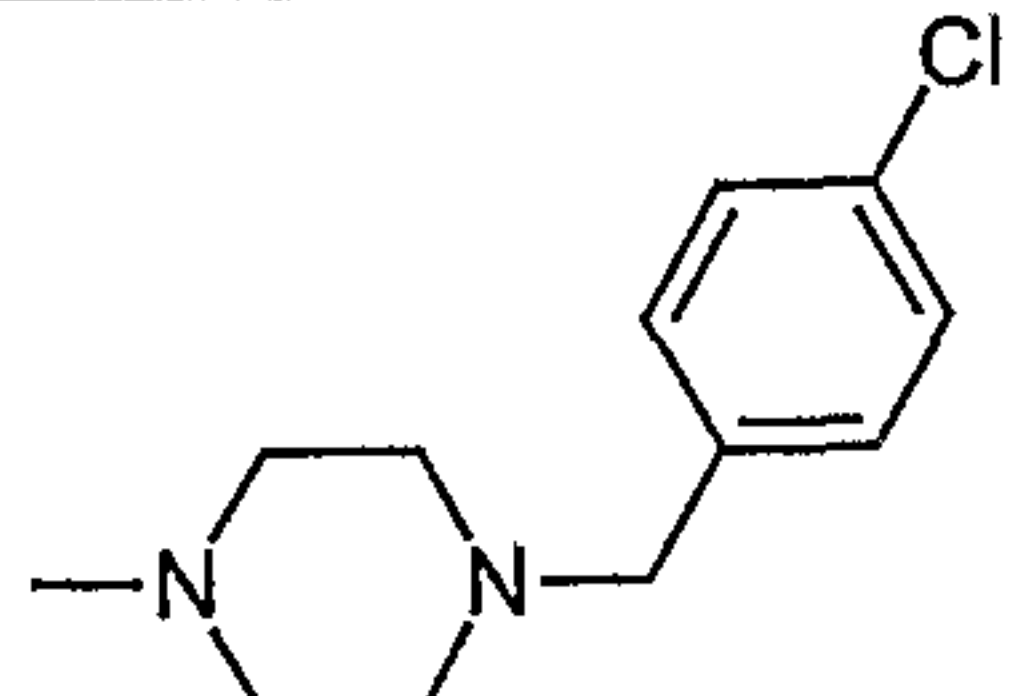
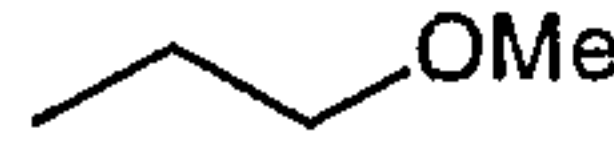
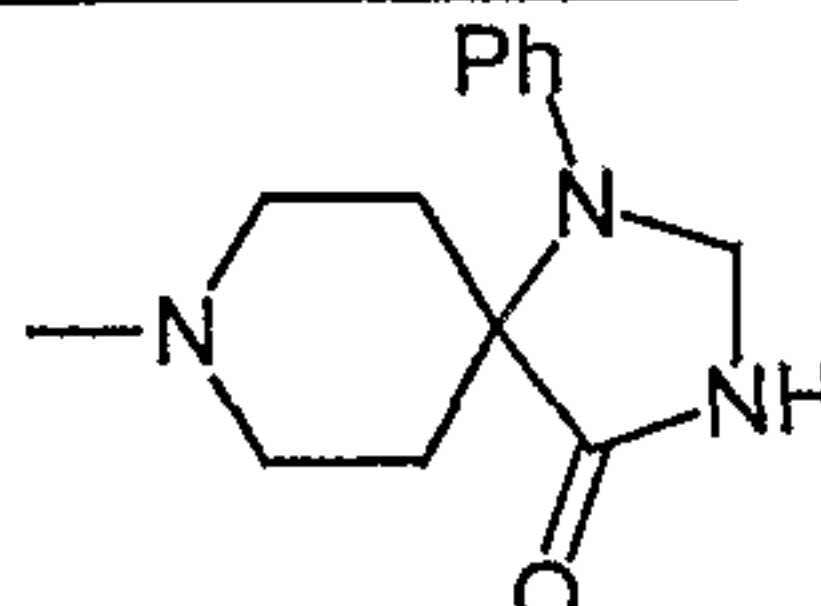
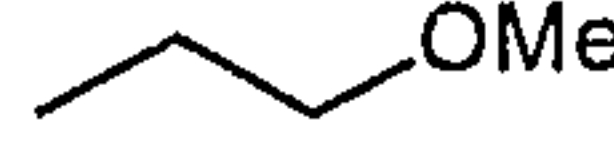
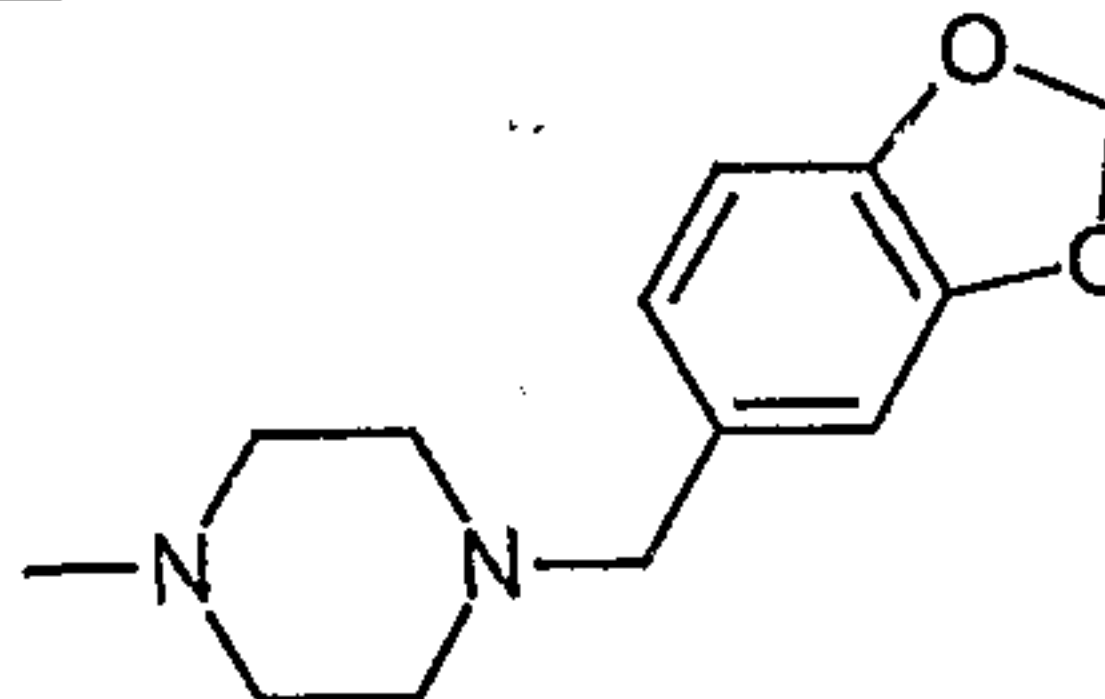
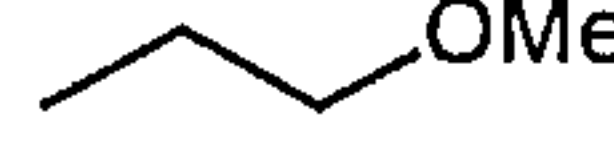
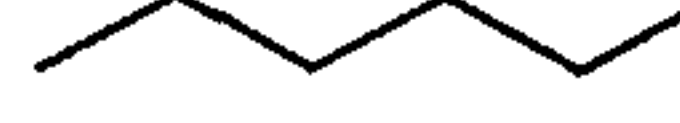
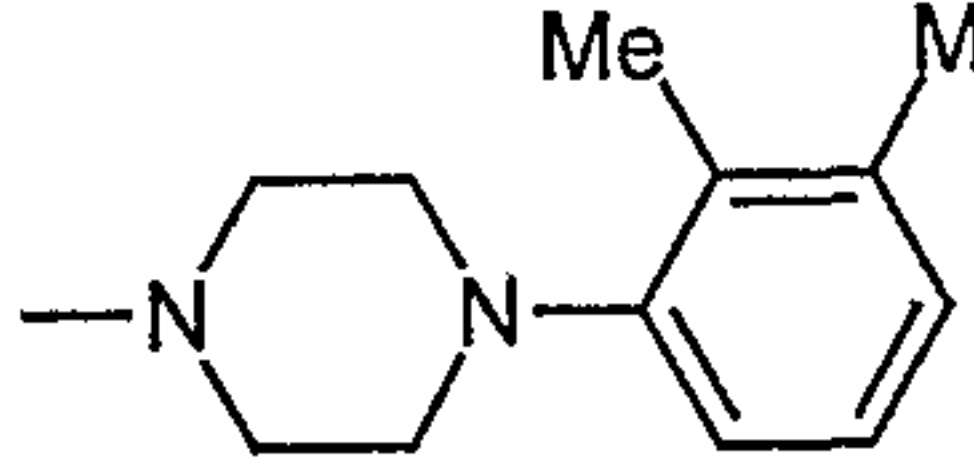
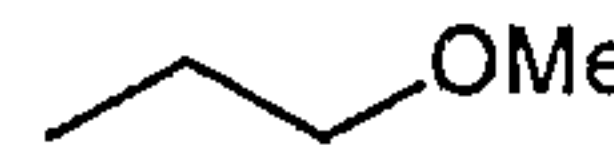
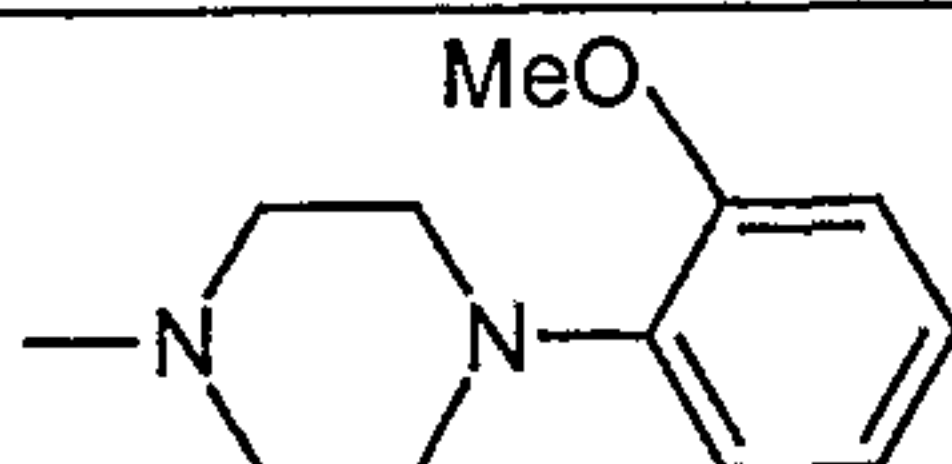
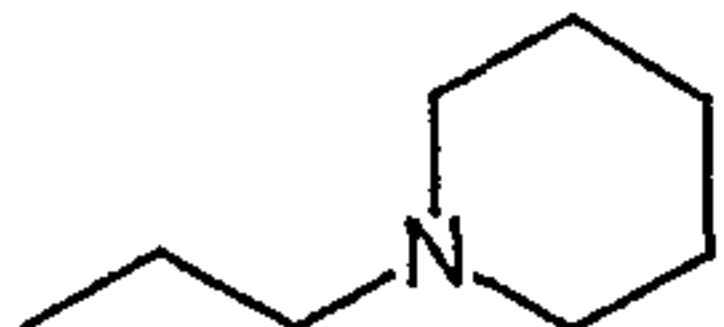
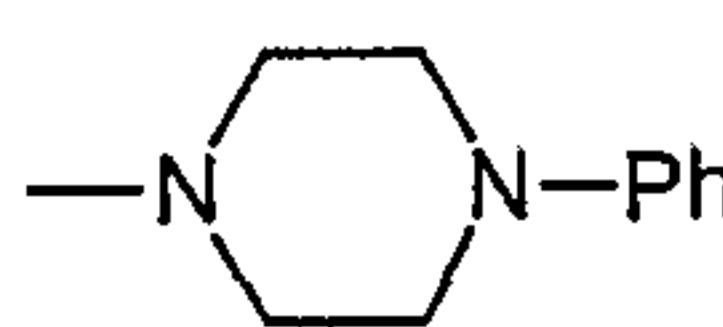
Comp. No	-R ¹	-A-	$\begin{array}{c} \text{R}^2 \\ \\ \text{---N---} \\ \\ \text{R}^3 \end{array}$	[M+H] ⁺
11				477
12				464
13				526
14				439
15				457
16				478
17				467
18				437
19				439
20				462

Table 3 (continued):

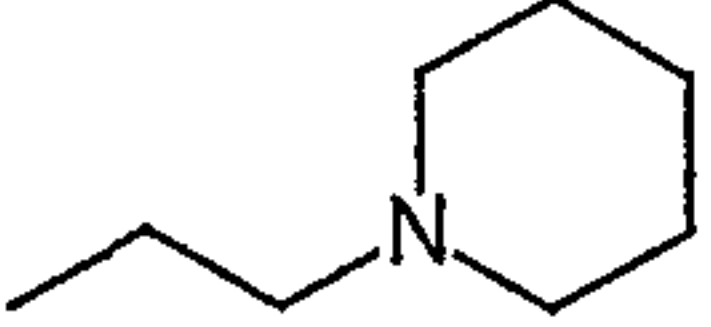
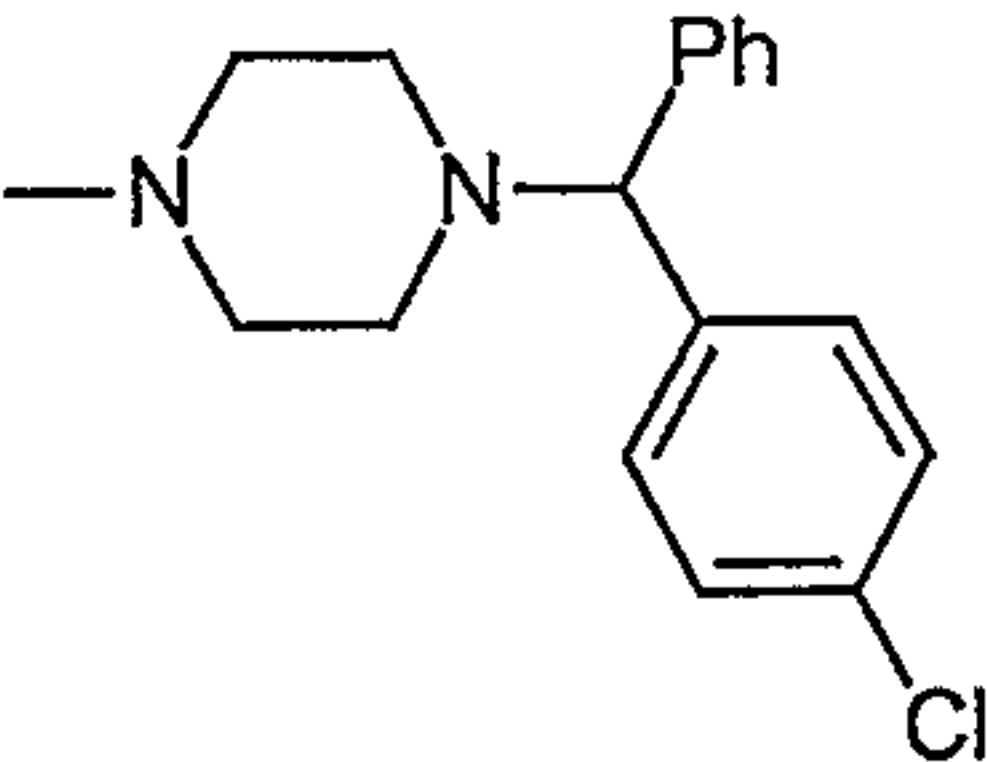
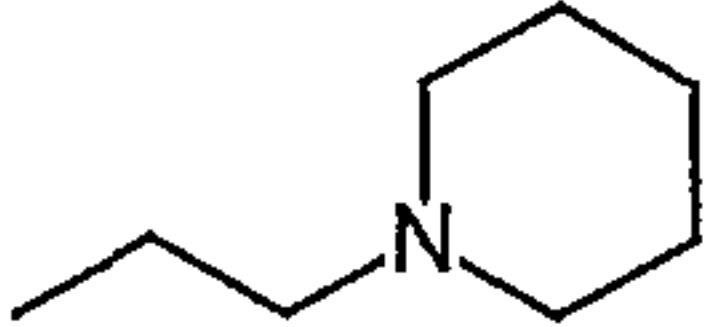
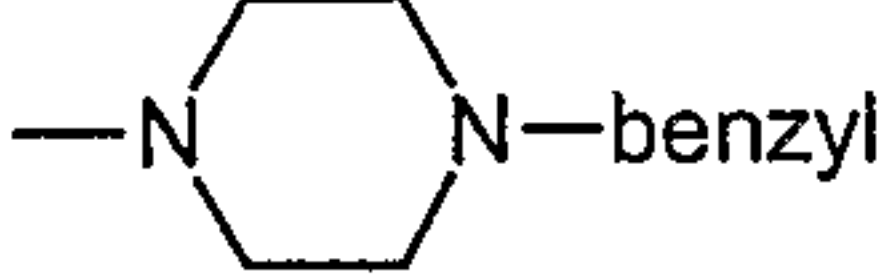
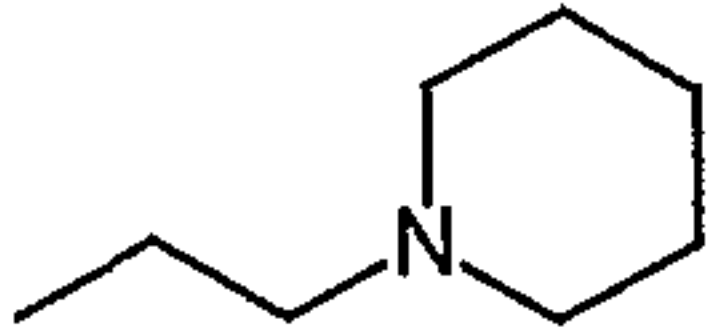
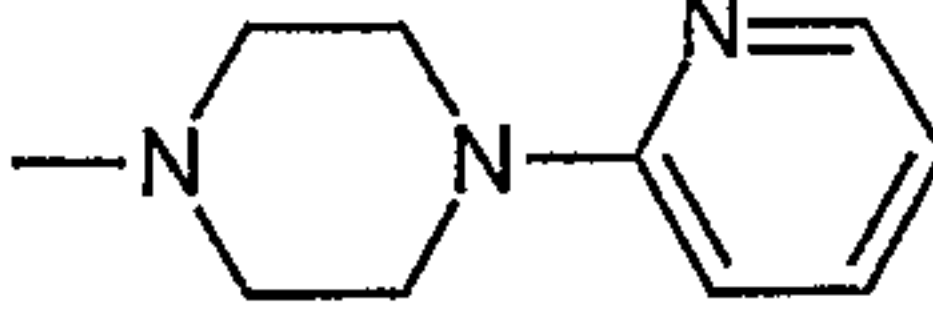
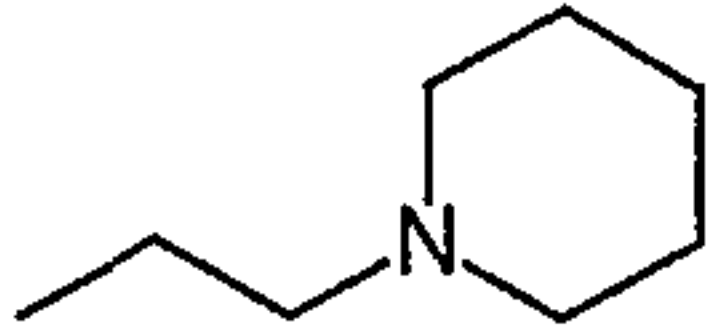
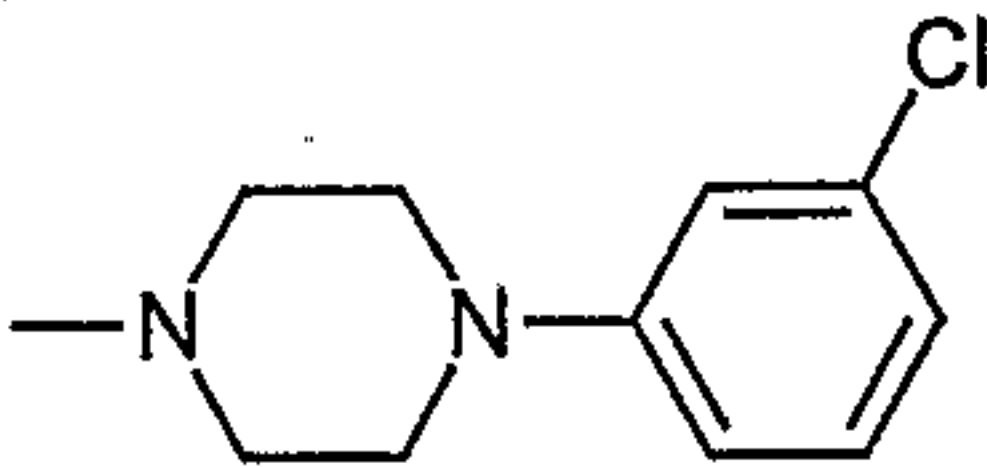
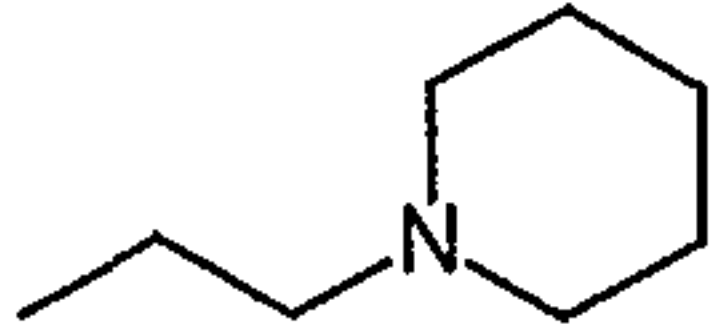
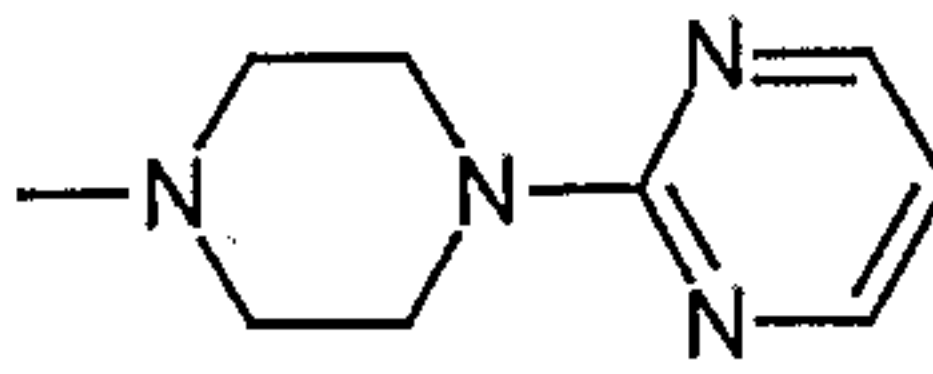
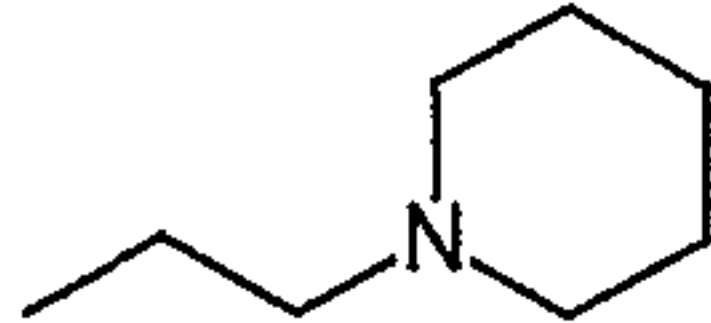
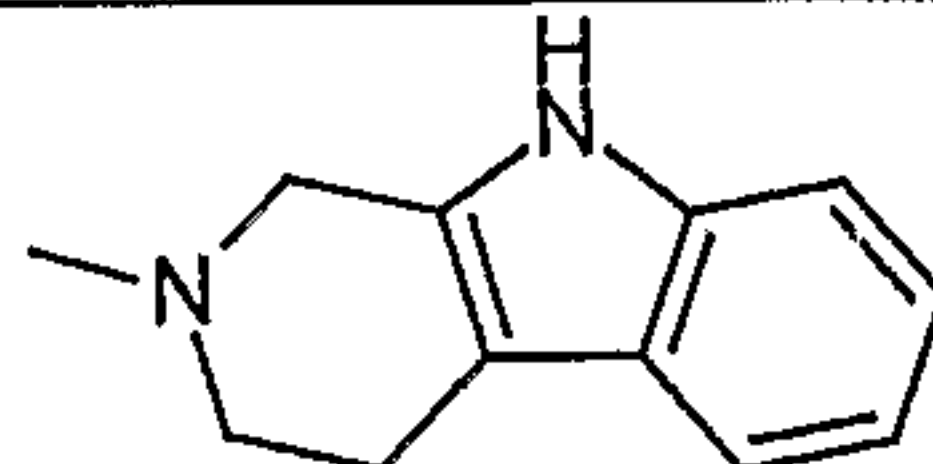
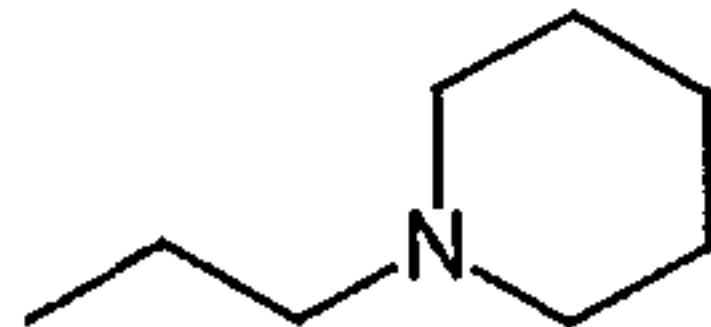
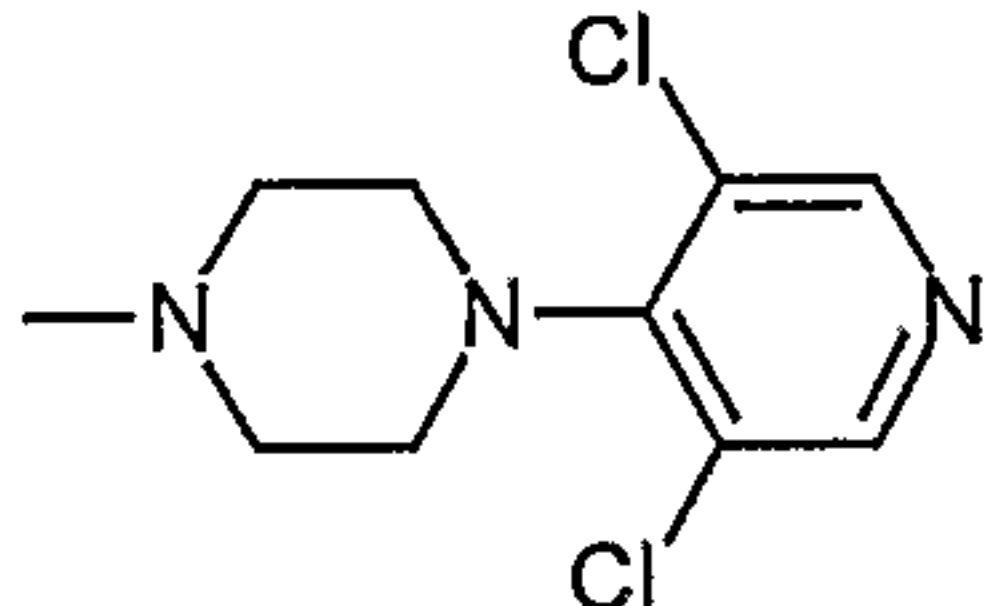
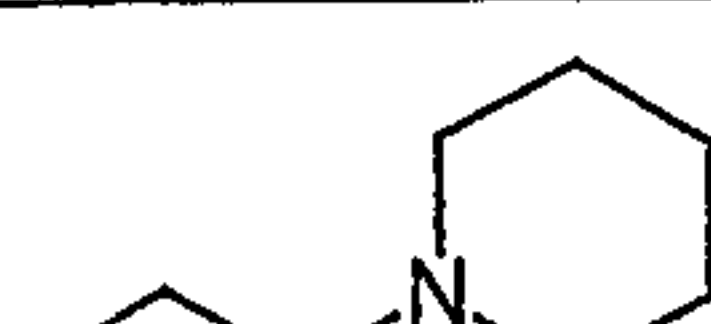
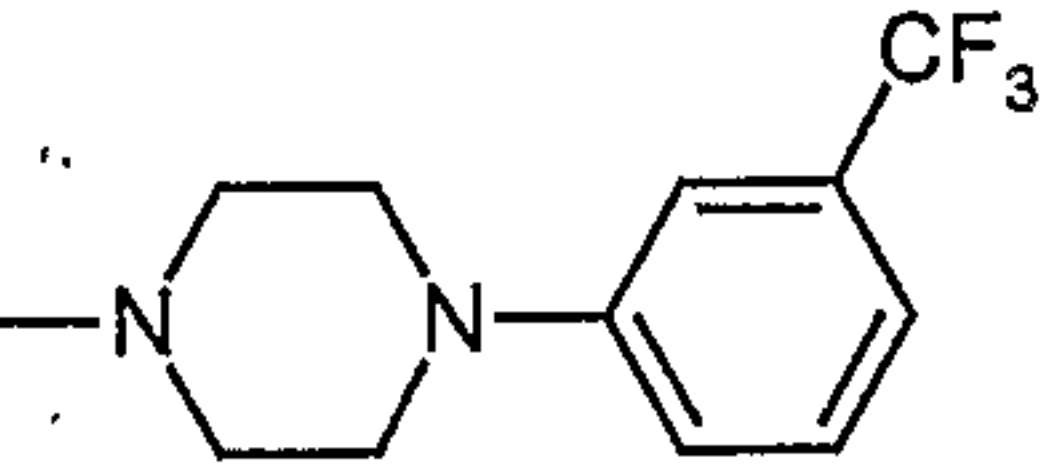
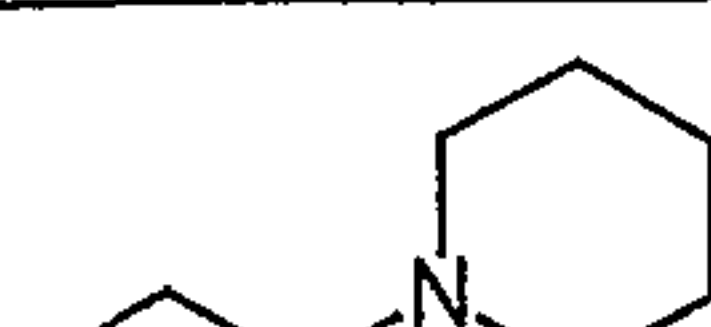
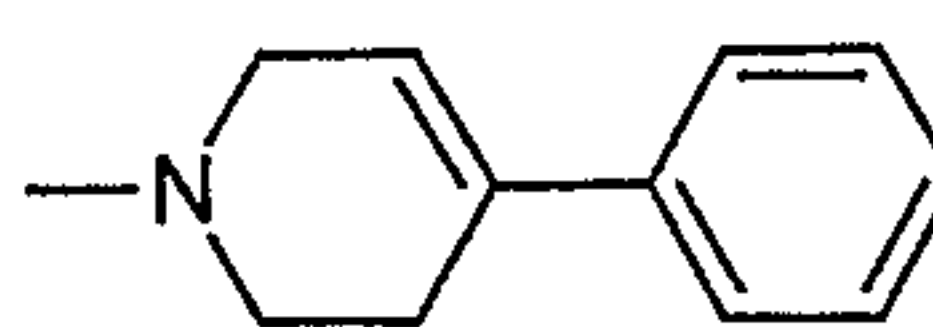
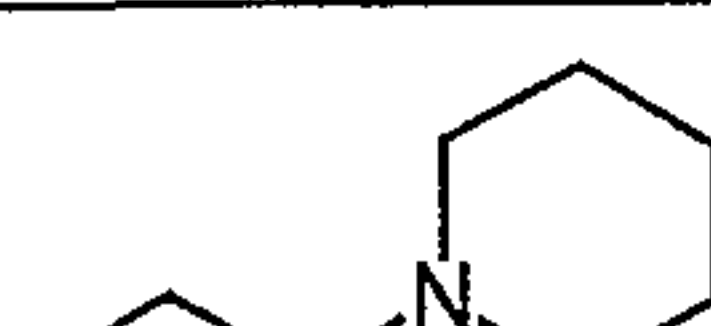
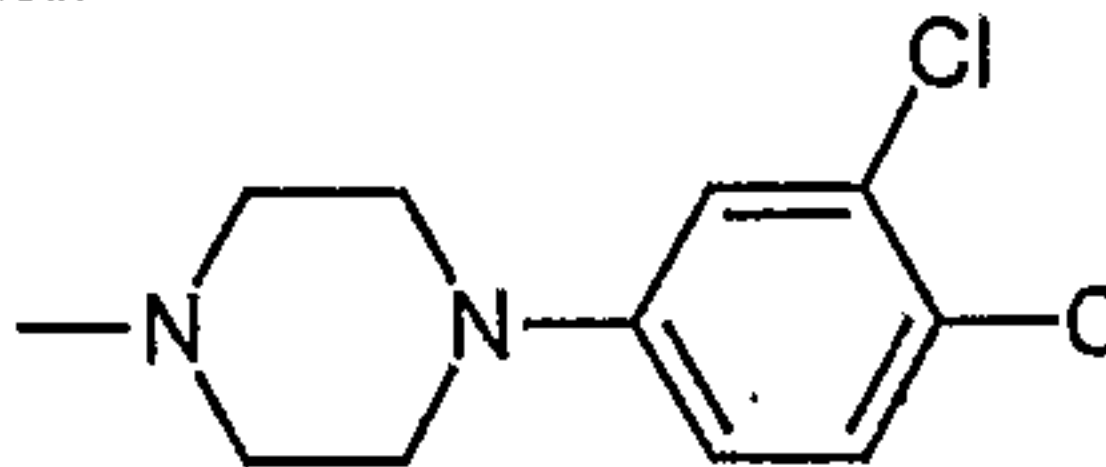
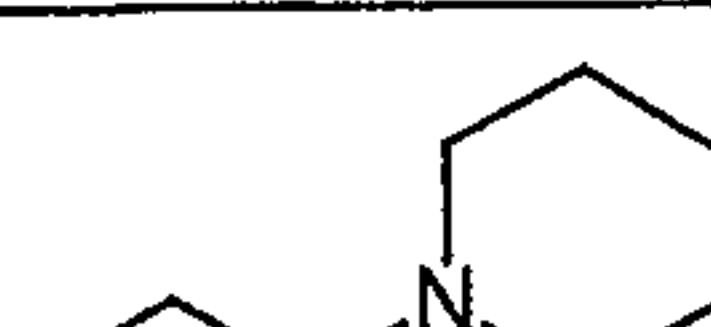
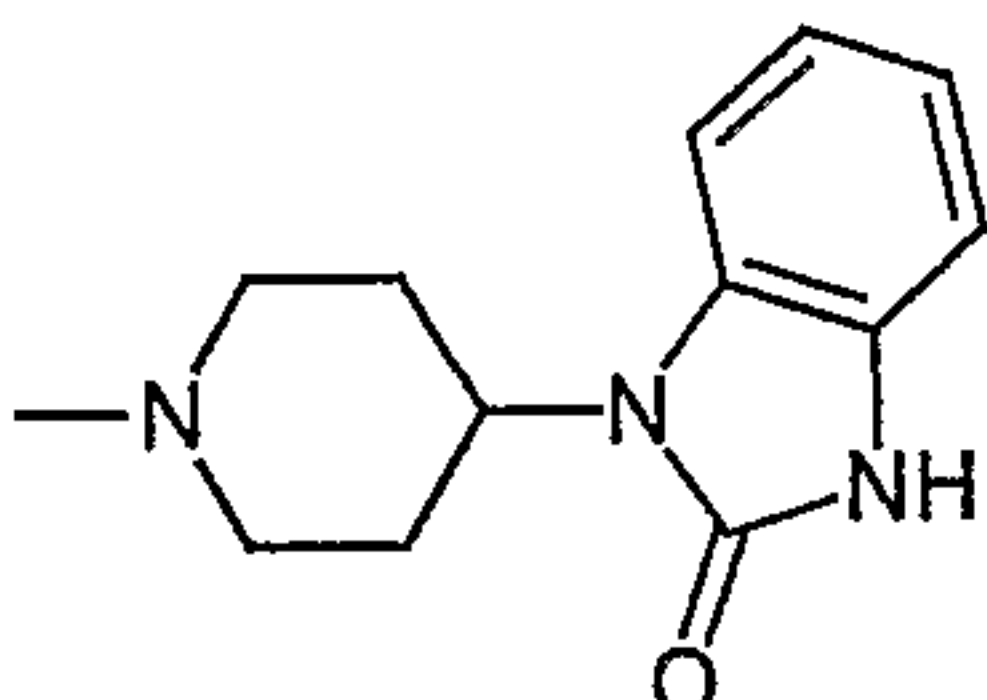
Comp. No	-R ¹	-A-	$\text{—N} \begin{matrix} \text{R}^2 \\ \text{R}^3 \end{matrix}$	[M+H] ⁺
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22				476
23				463
24				496
25				464
26				472
27				531
28				530
29				459
30				530
31				517

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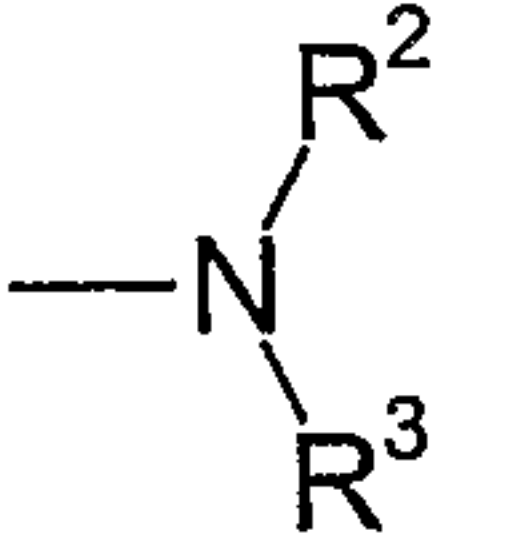
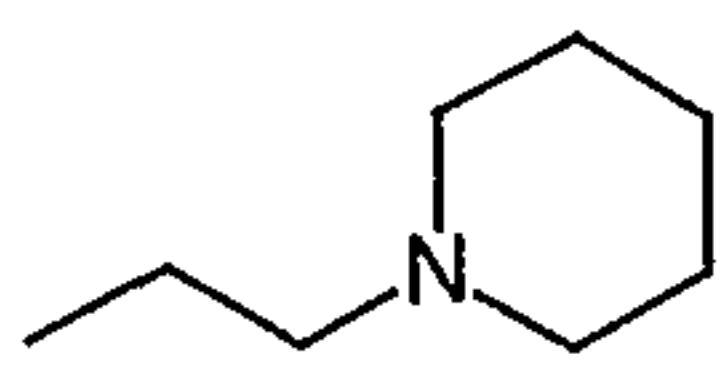
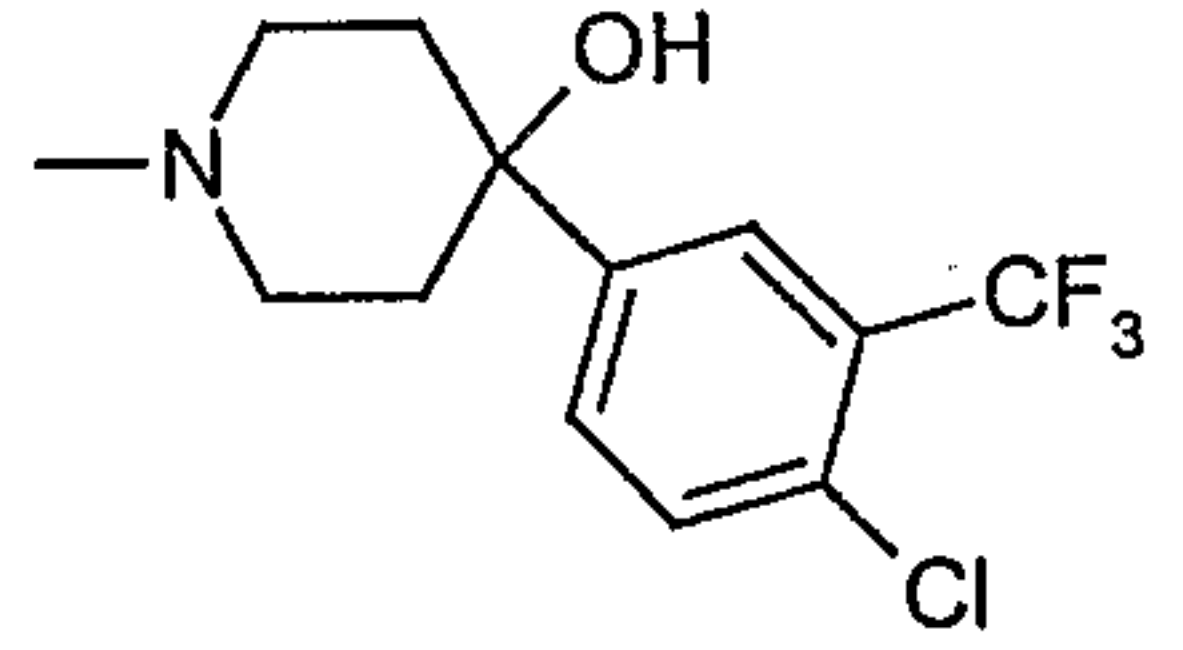
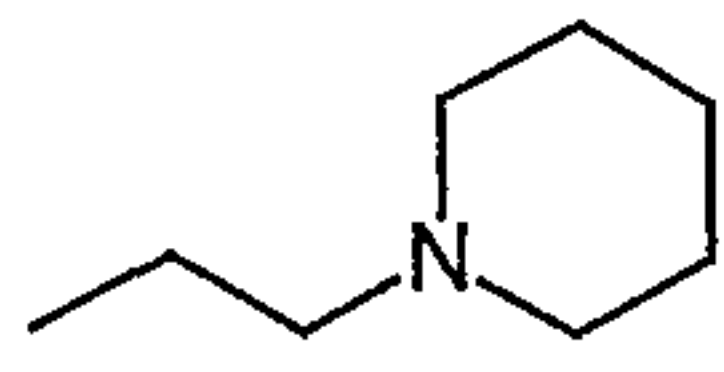
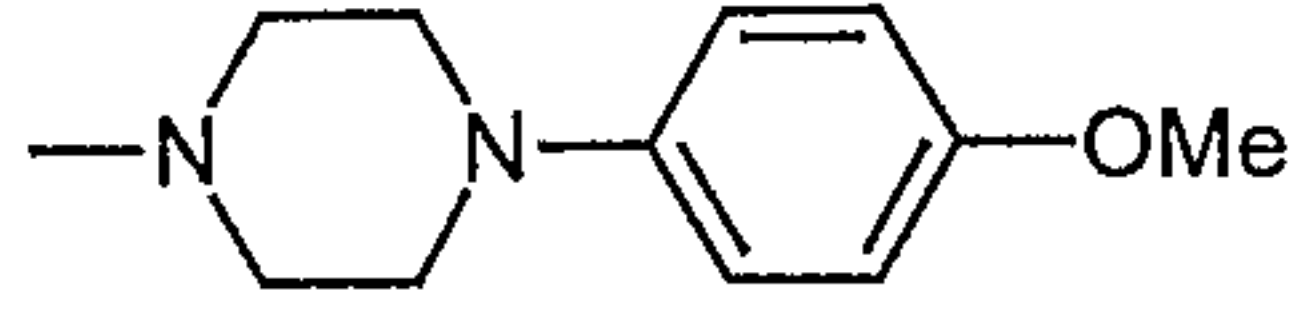
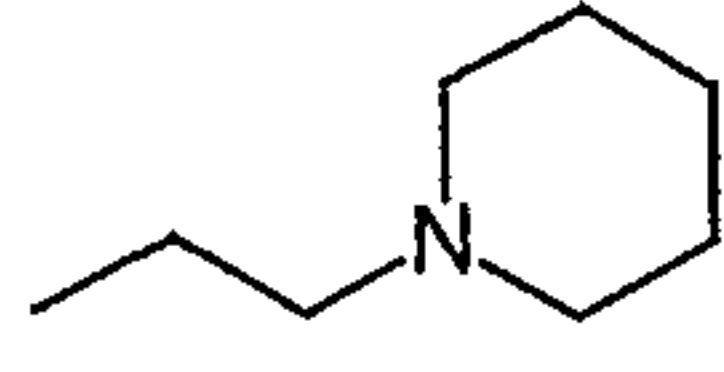
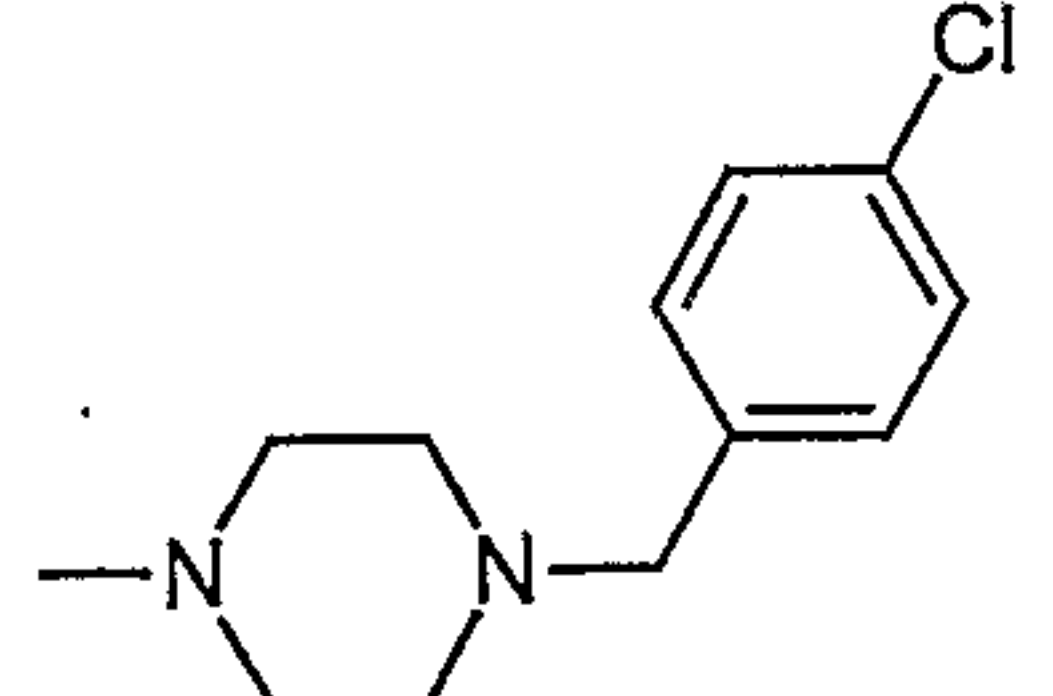
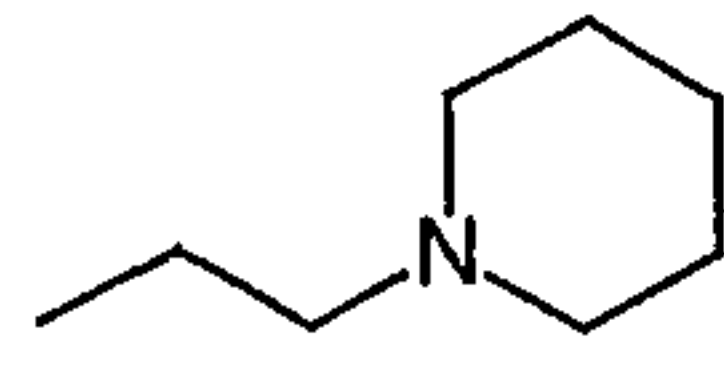
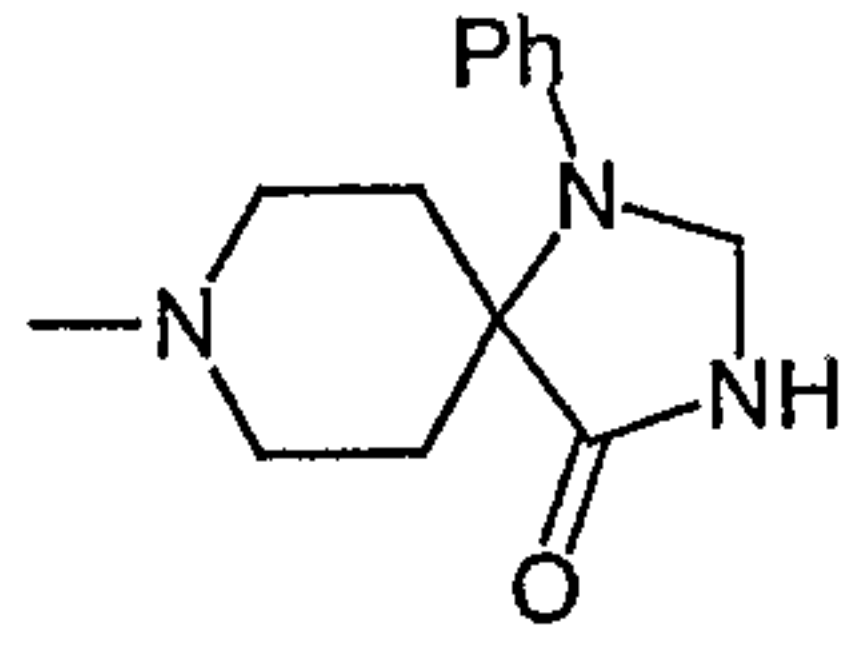
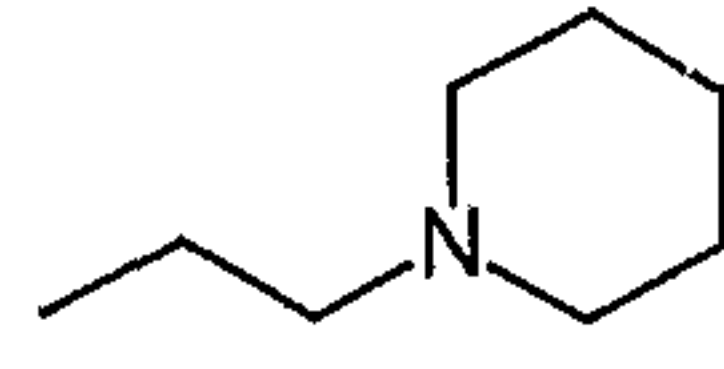
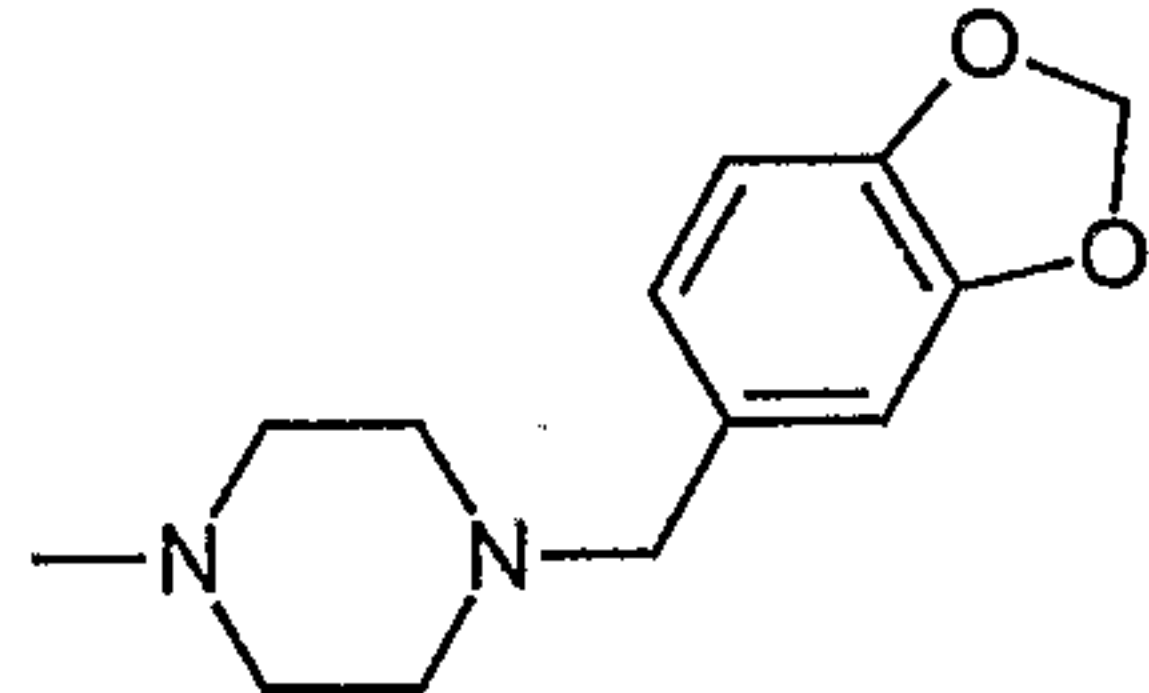
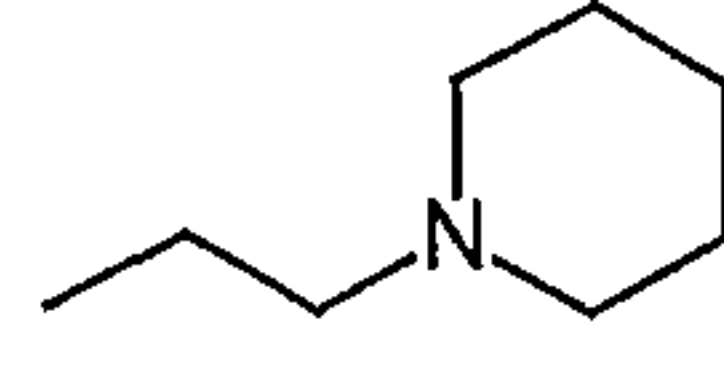
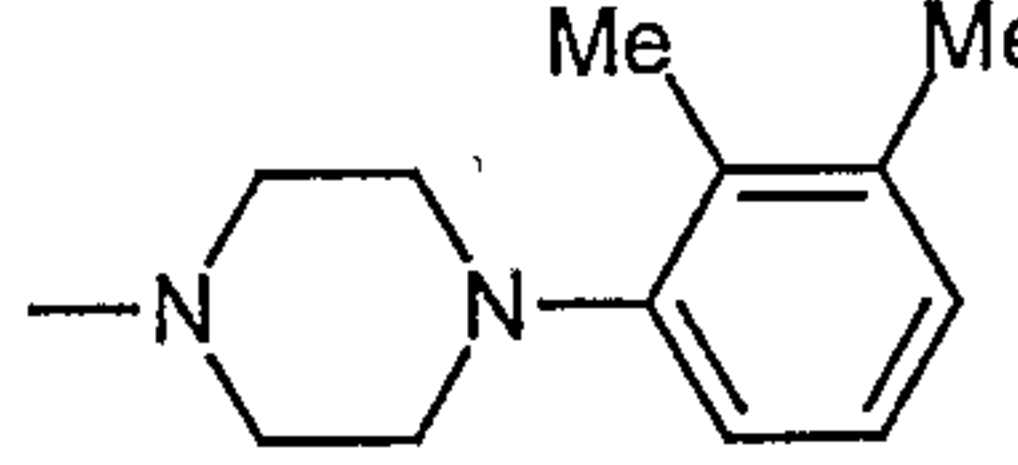
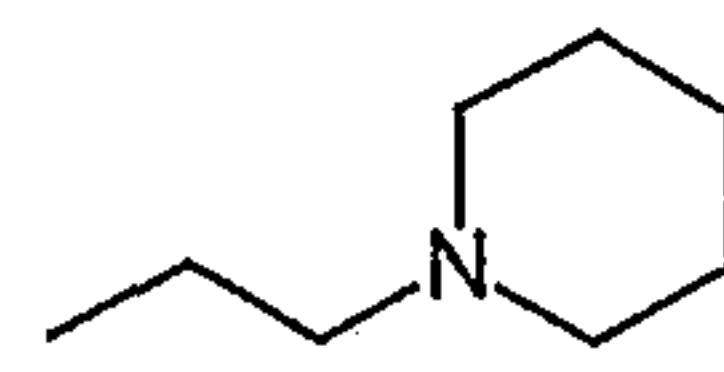
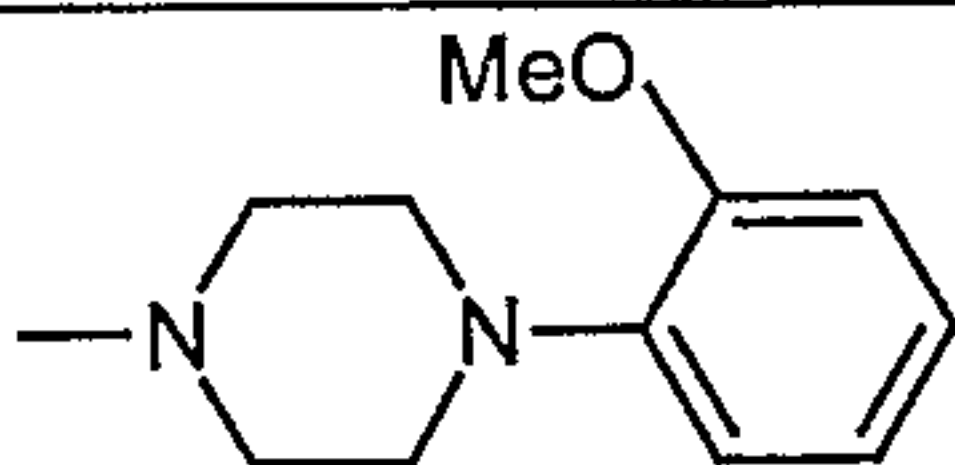
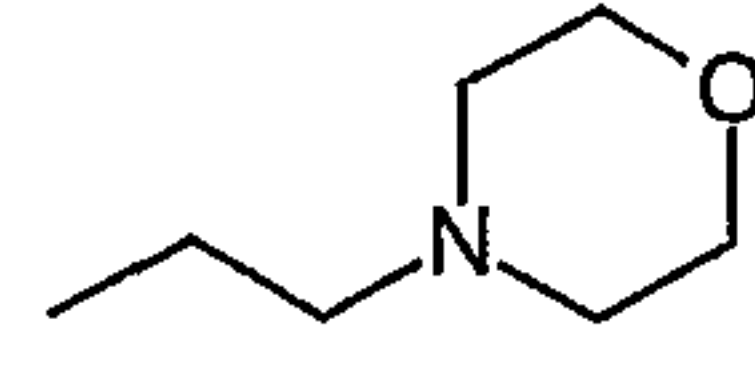
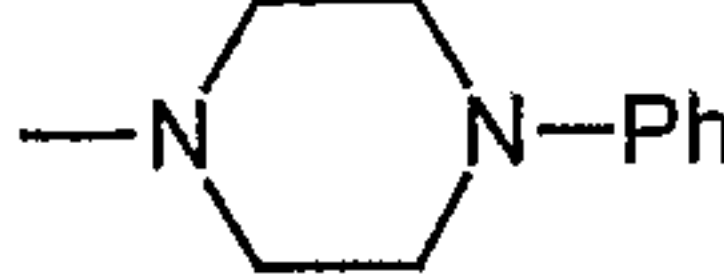
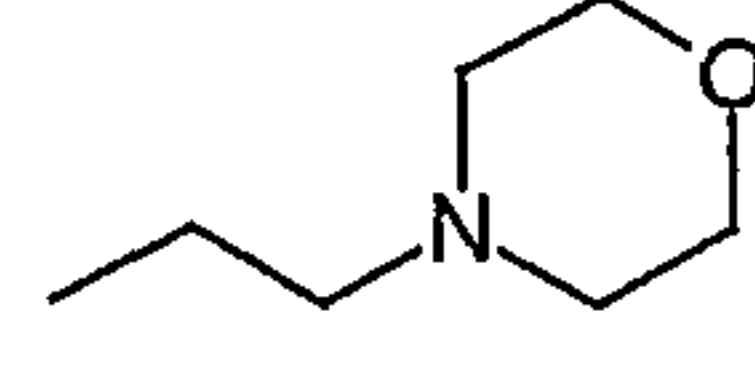
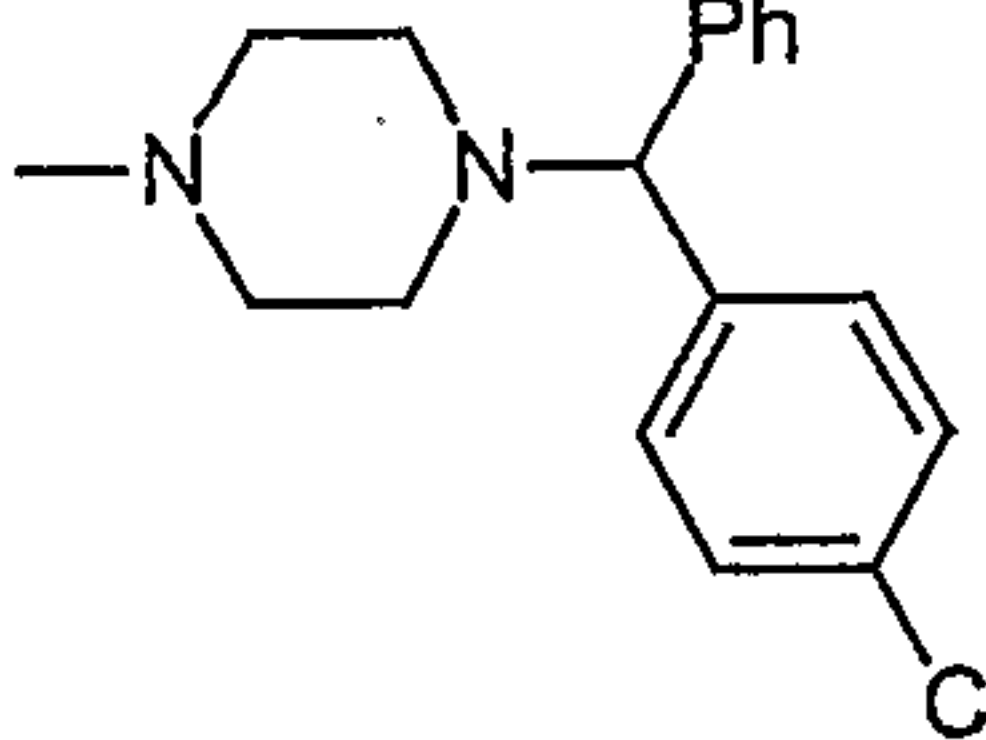
Comp. No	-R ¹	-A-		[M+H] ⁺
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38				492
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40				588

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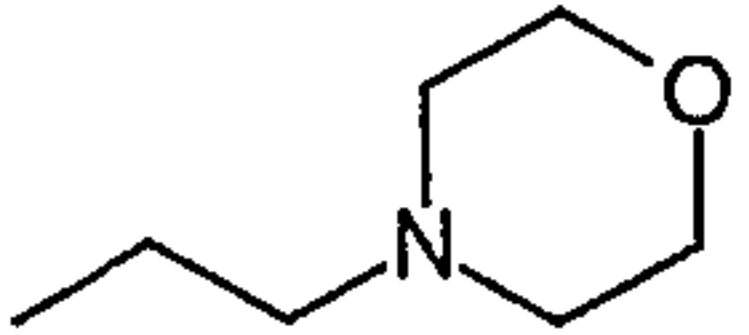
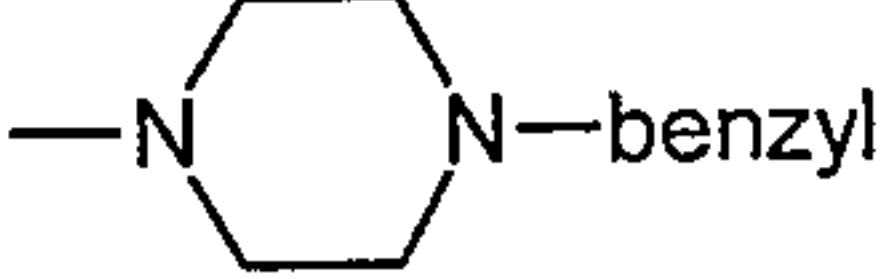
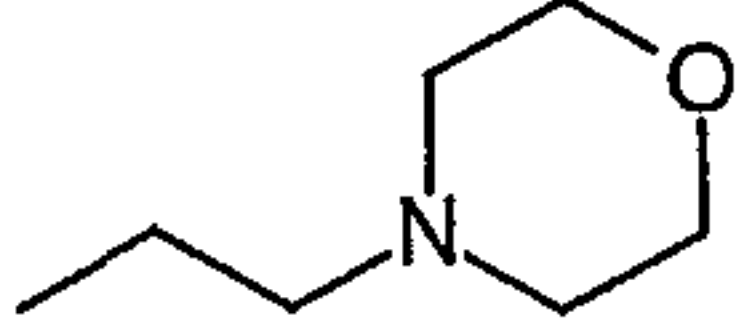
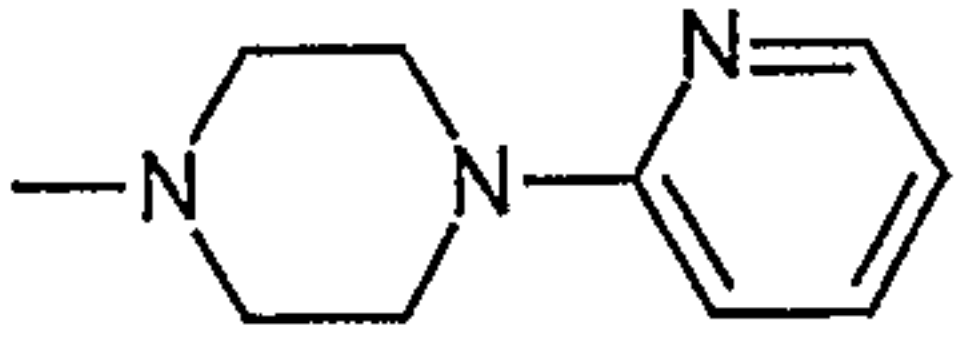
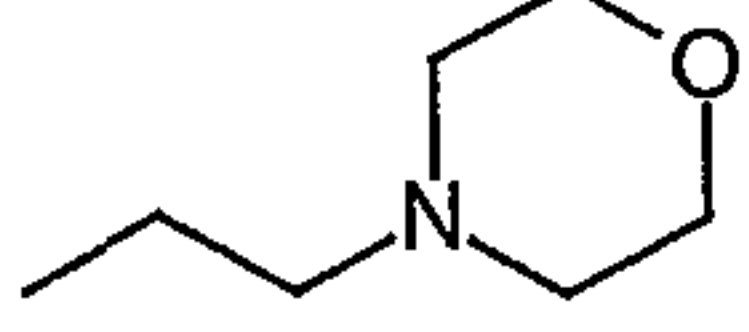
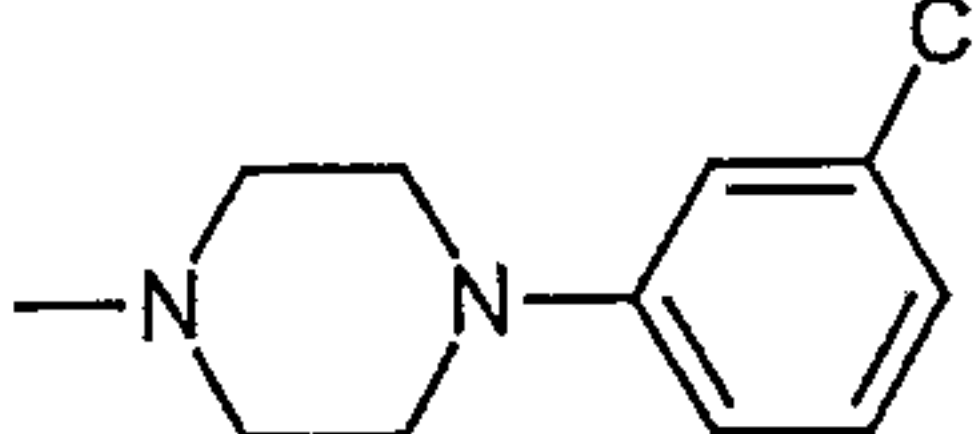
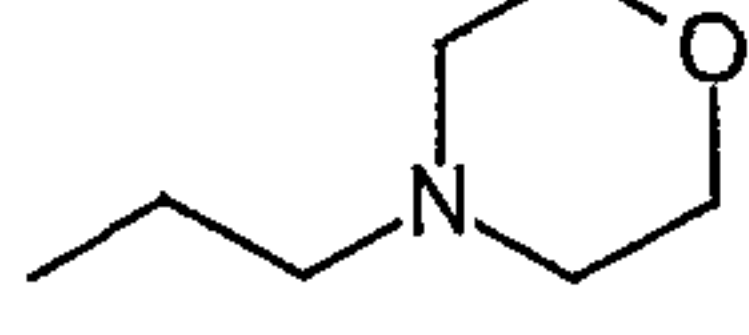
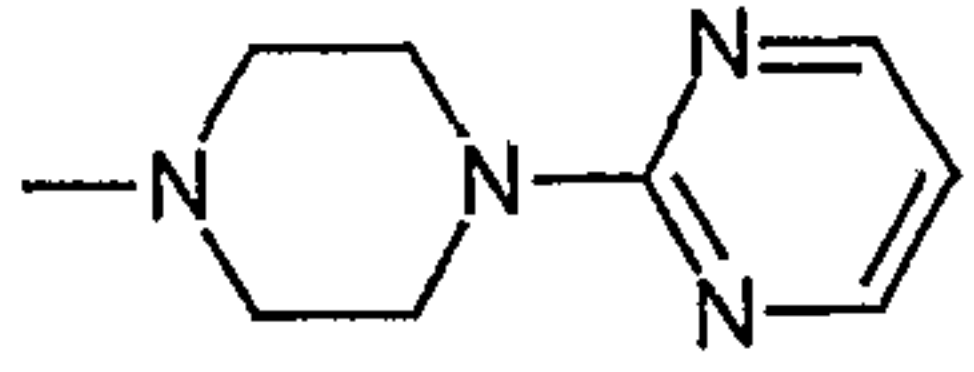
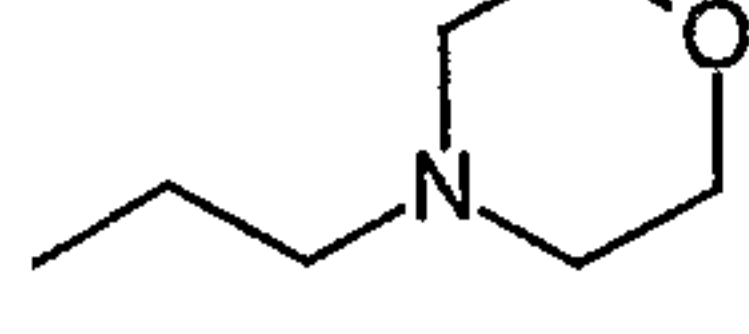
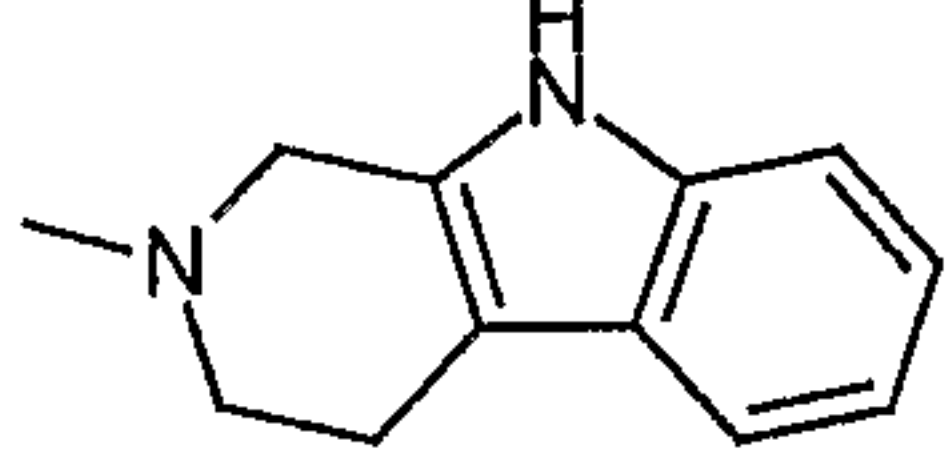
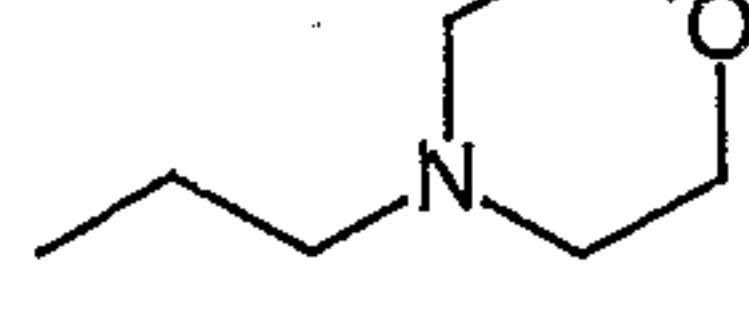
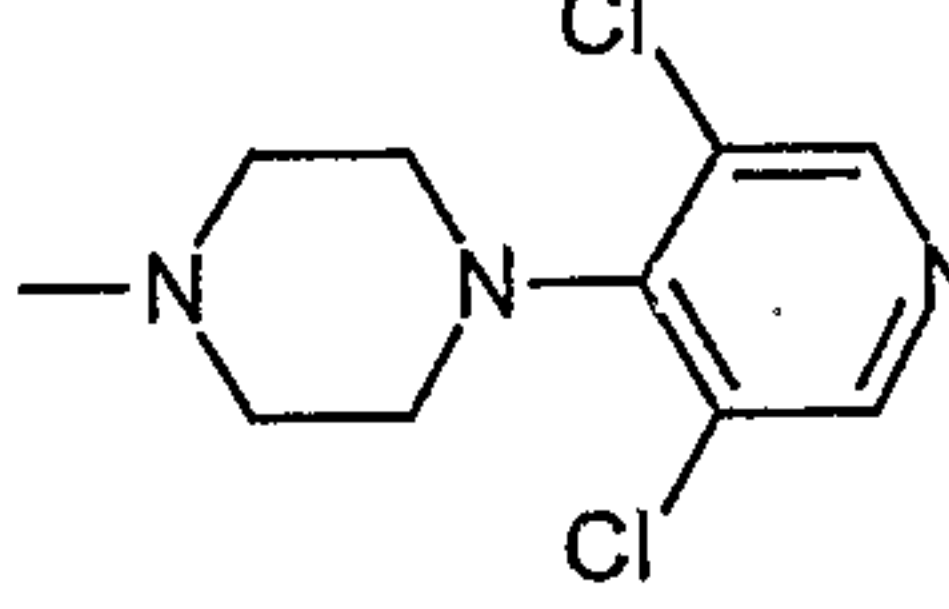
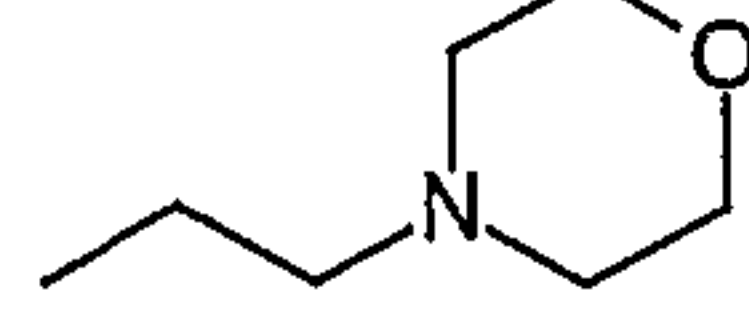
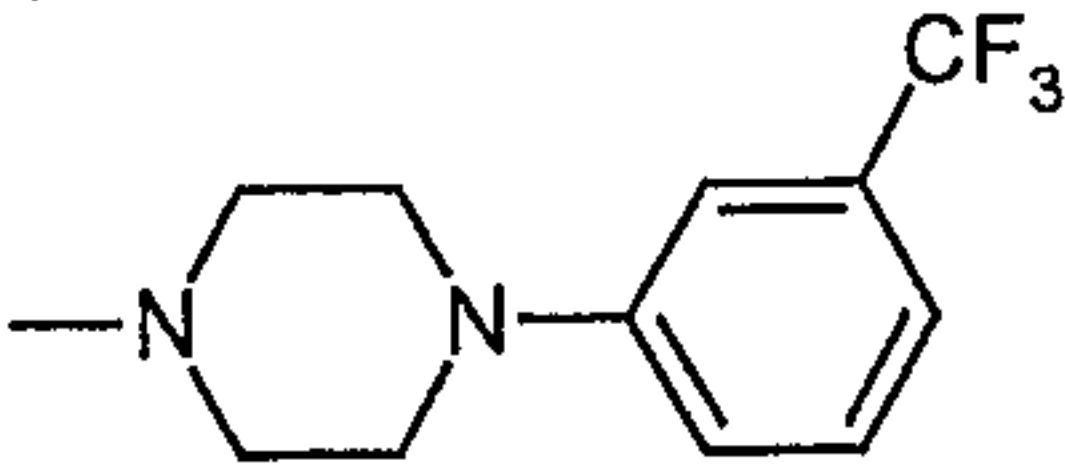
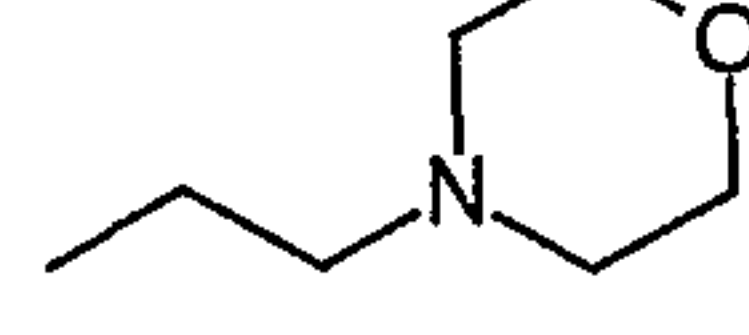
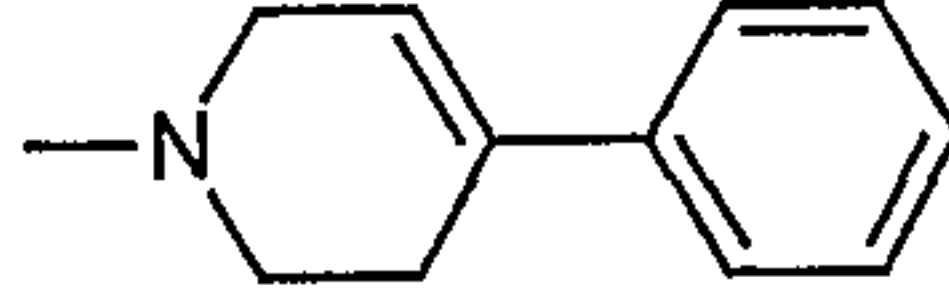
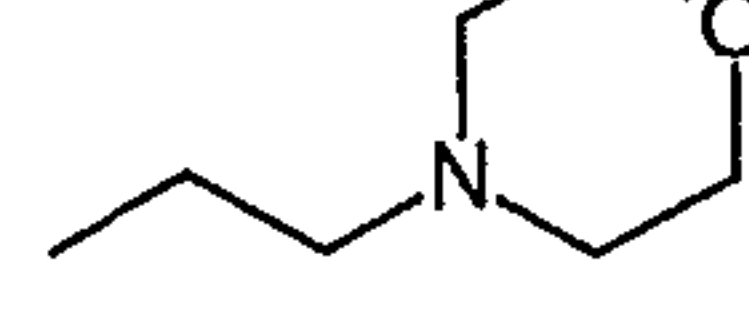
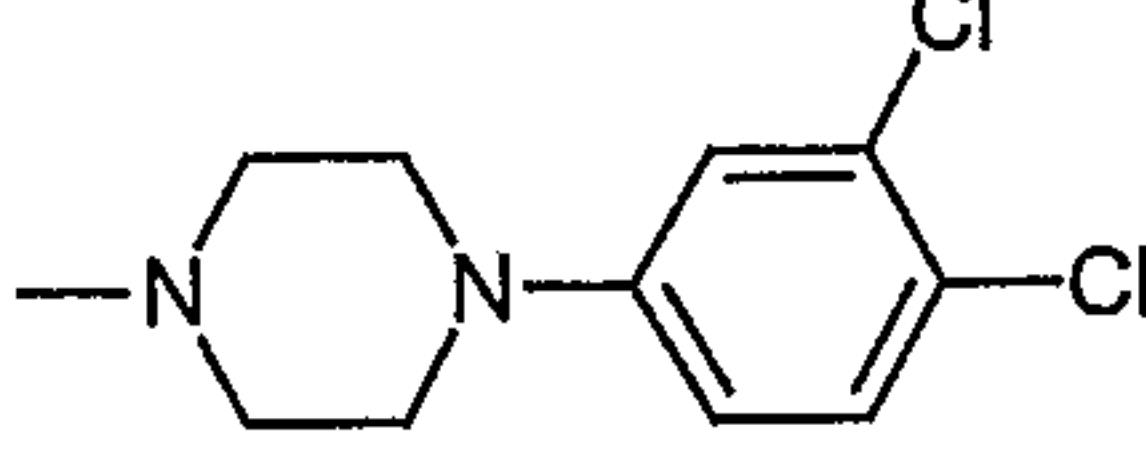
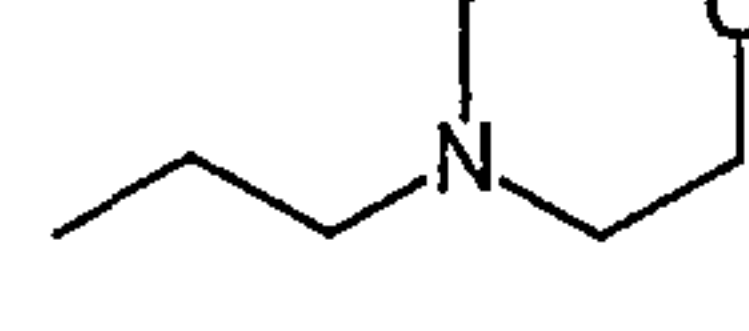
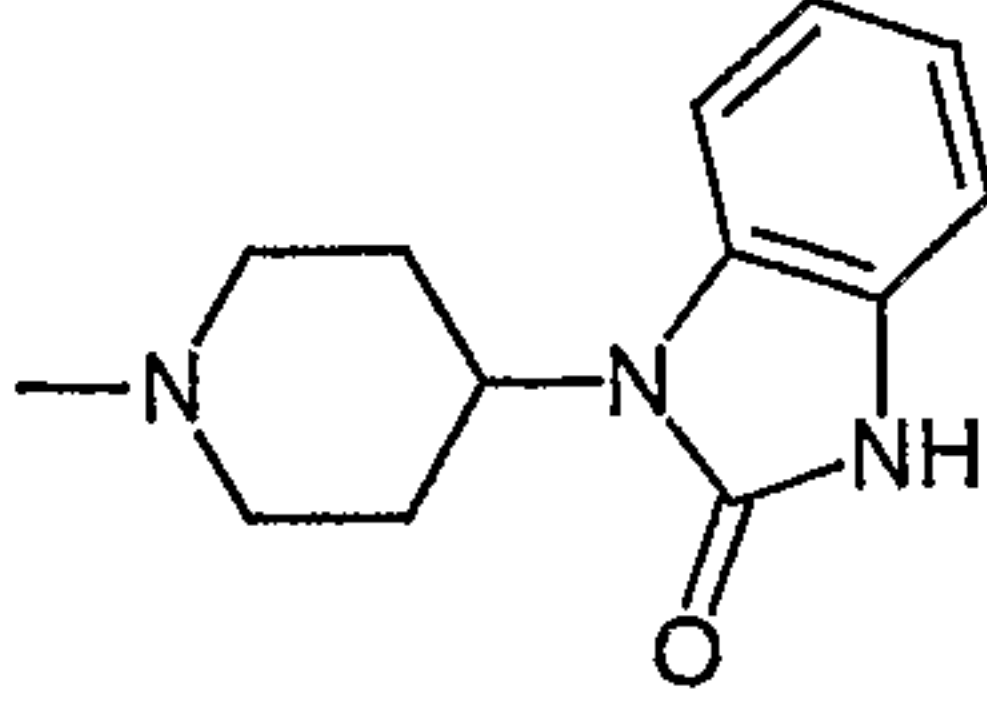
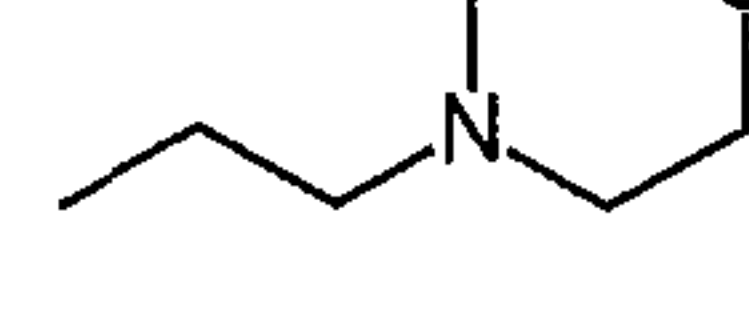
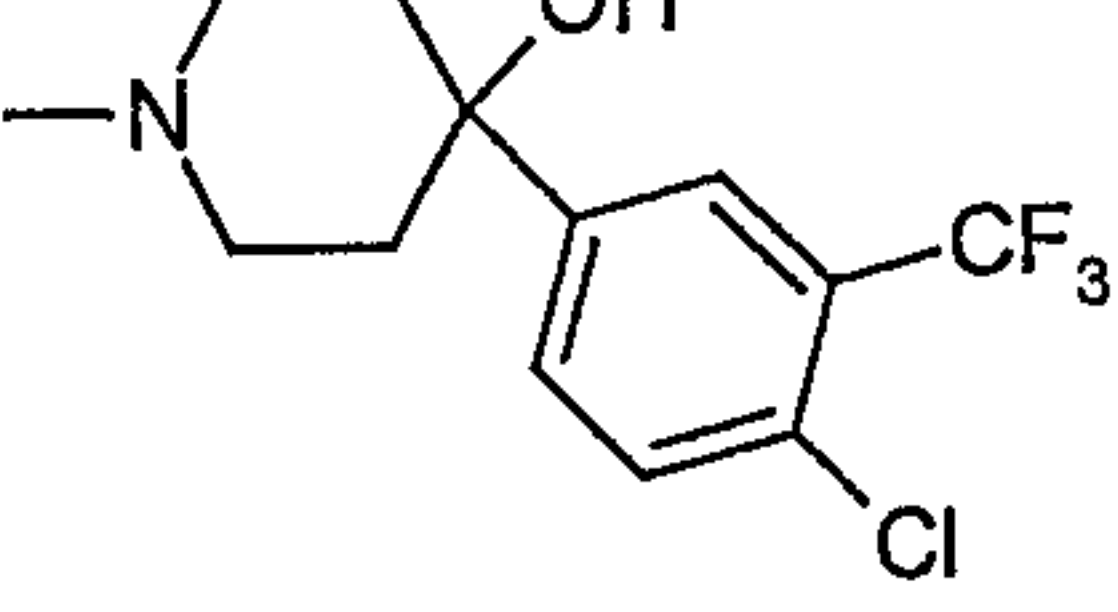
Comp. No	-R ¹	-A-	$\begin{array}{c} \text{R}^2 \\ \\ \text{---N---} \\ \\ \text{R}^3 \end{array}$	[M+H] ⁺
41				478
42				465
43				498
44				466
45				474
46				533
47				532
48				461
49				532
50				519
51				581

Table 3 (continued):

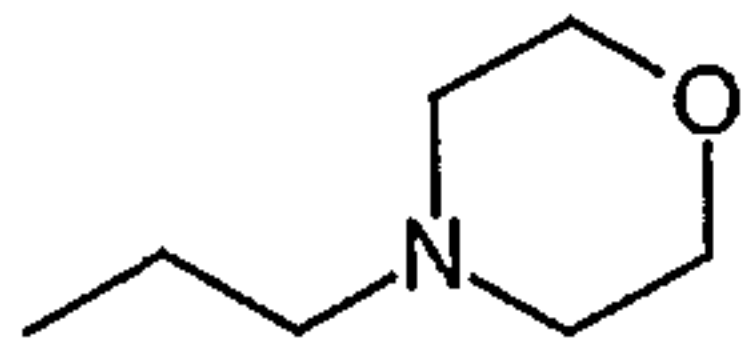
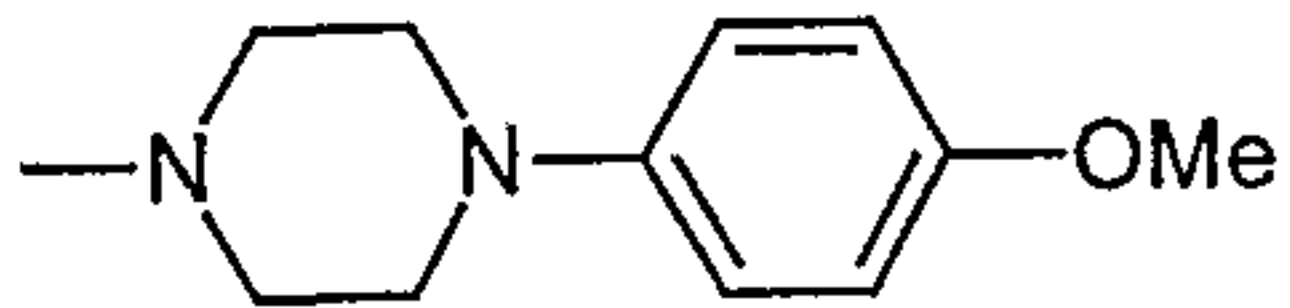
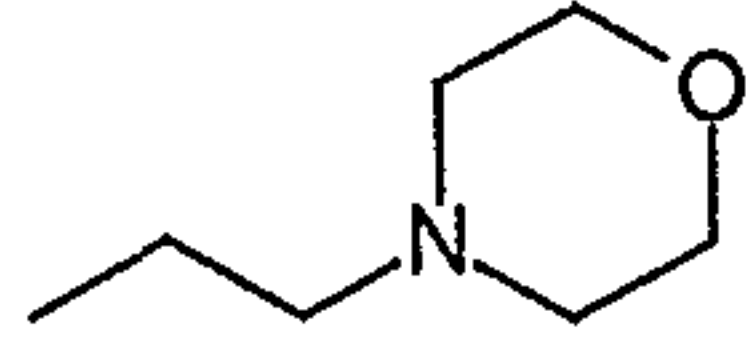
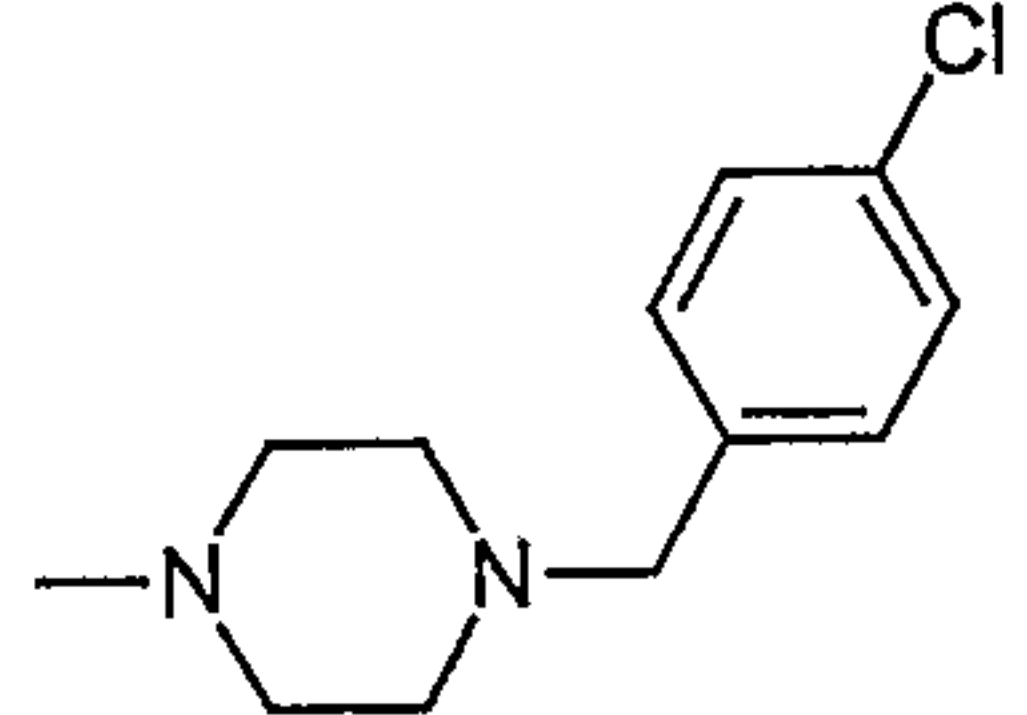
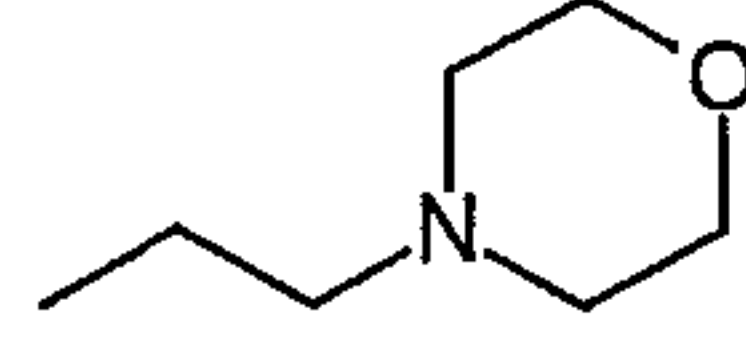
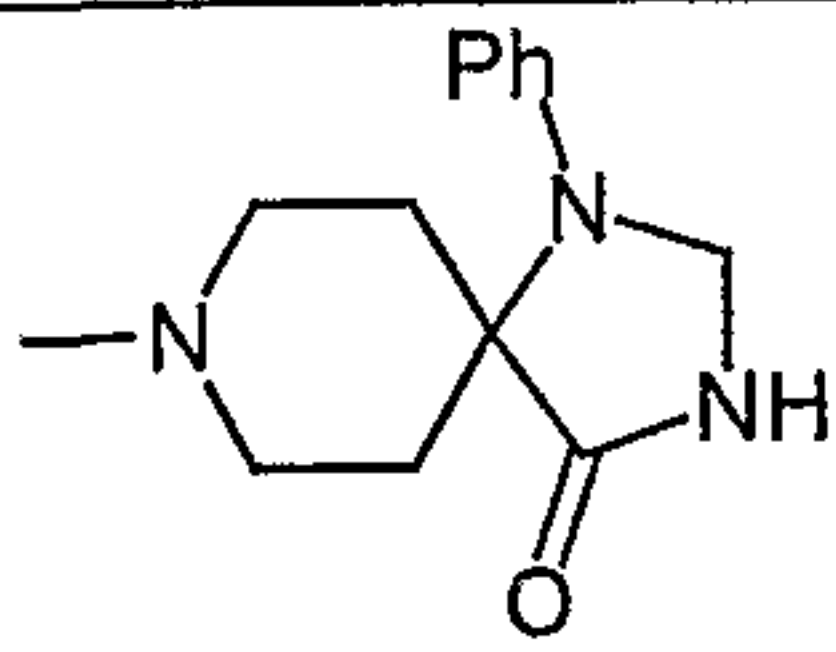
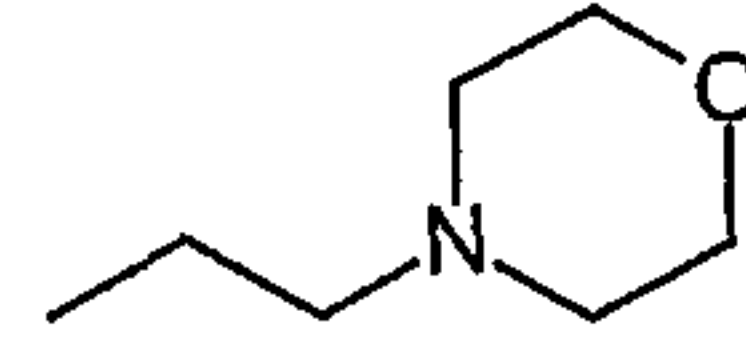
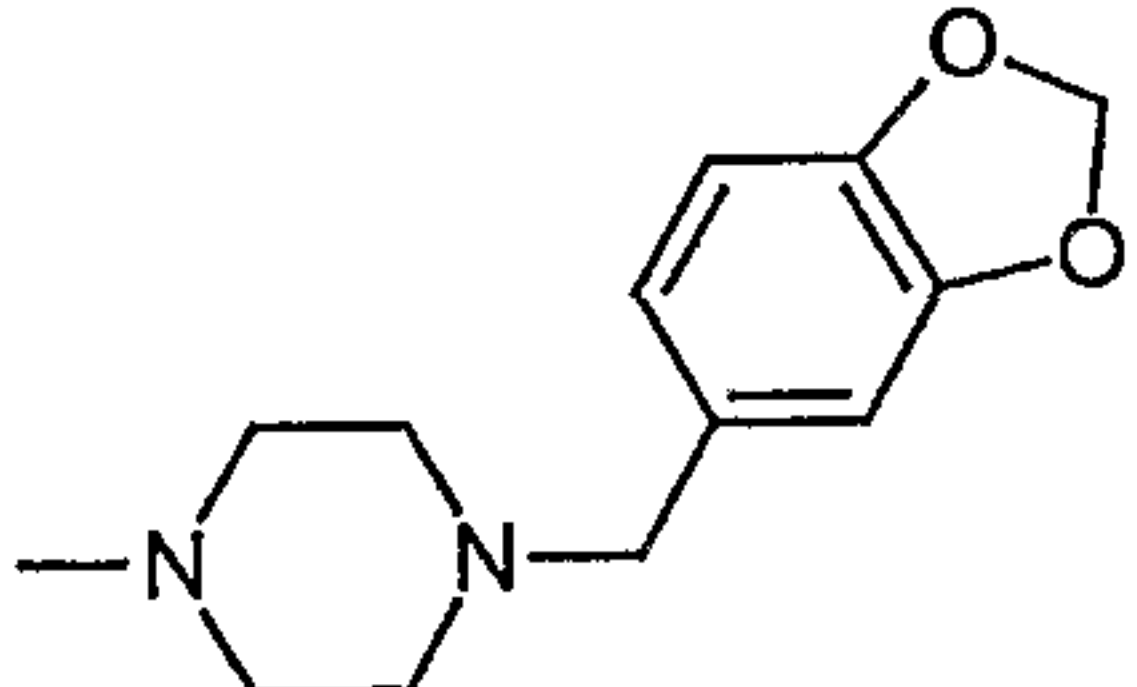
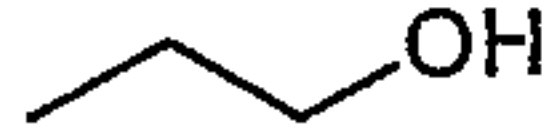
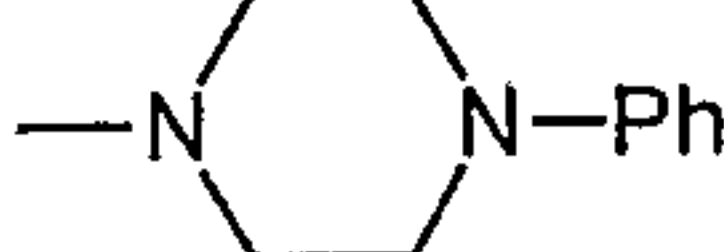
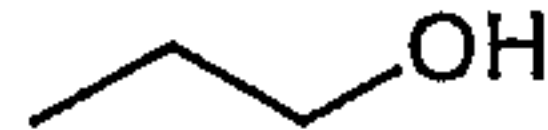
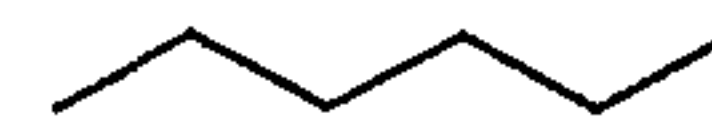
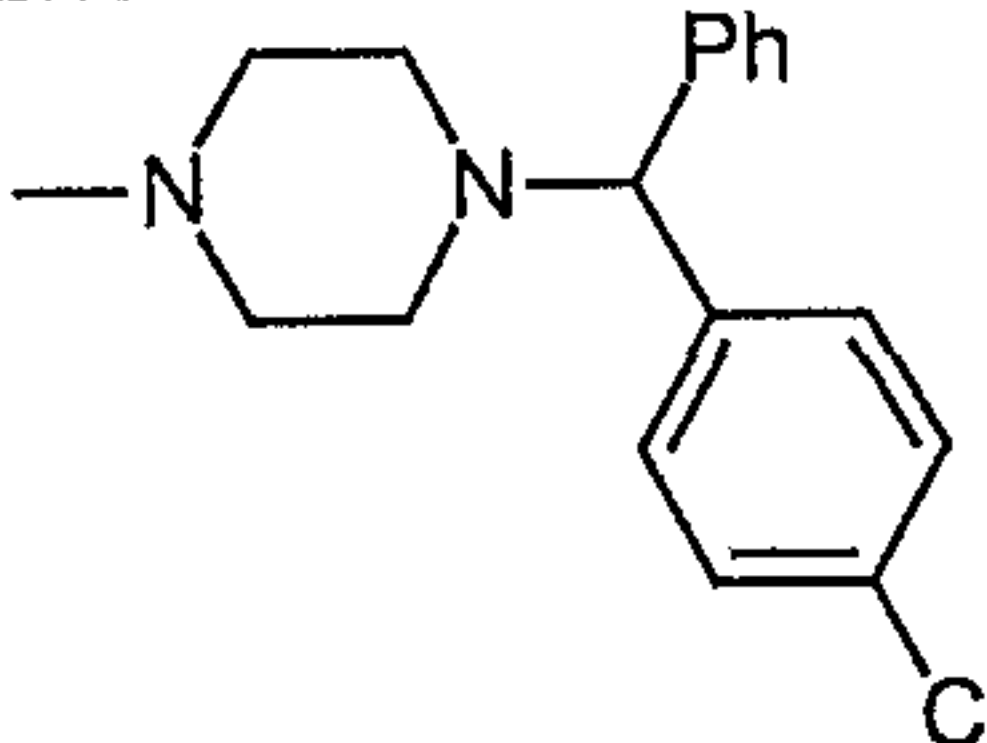
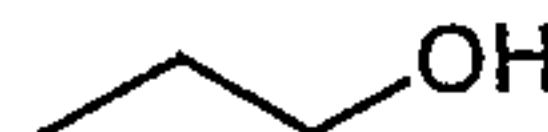
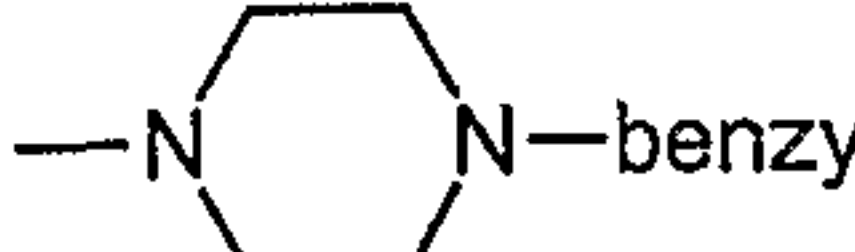
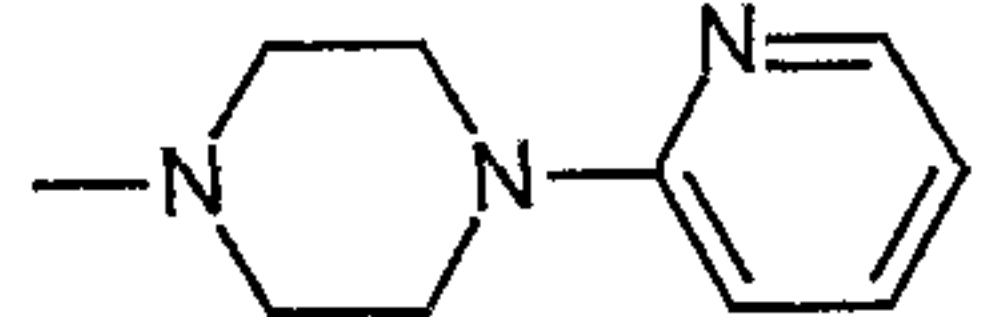
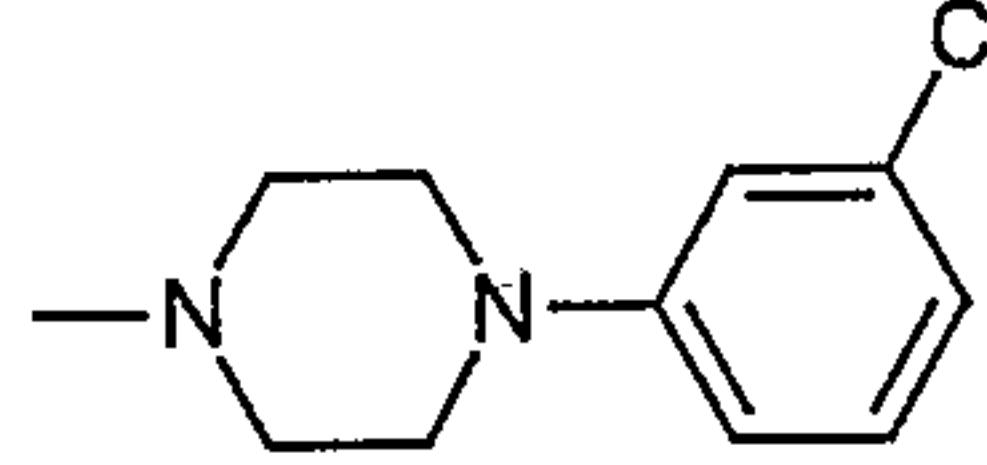
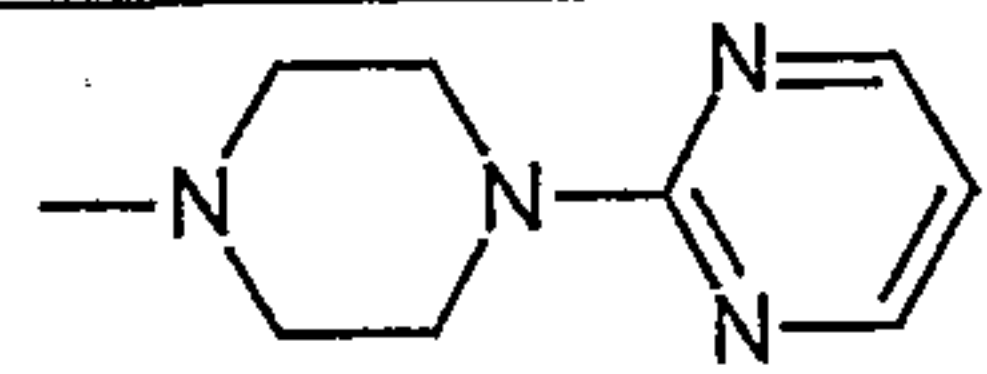
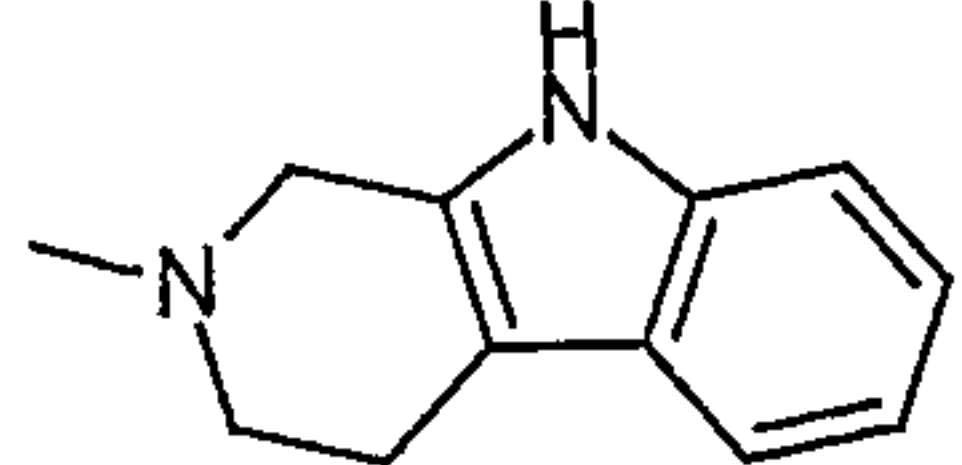
Comp. No	-R ¹	-A-	$\text{—N} \begin{matrix} \text{R}^2 \\ \text{R}^3 \end{matrix}$	[M+H] ⁺
52				494
53				512
54				533
55				522
56				395
57				419
58				409
59				396
60				429
61				397
62				405

Table 3 (continued):

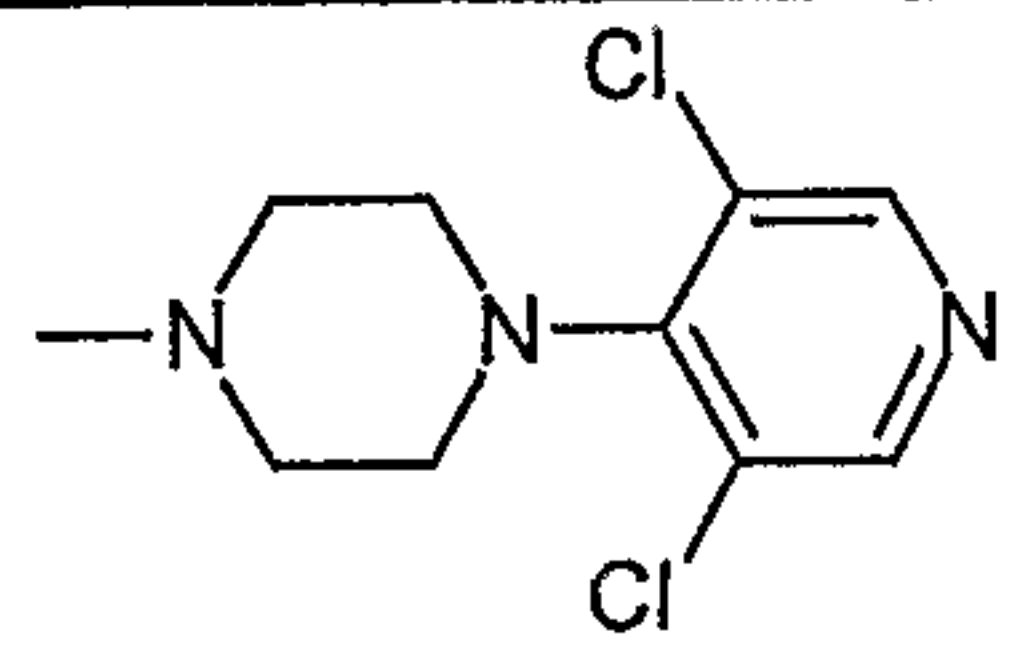
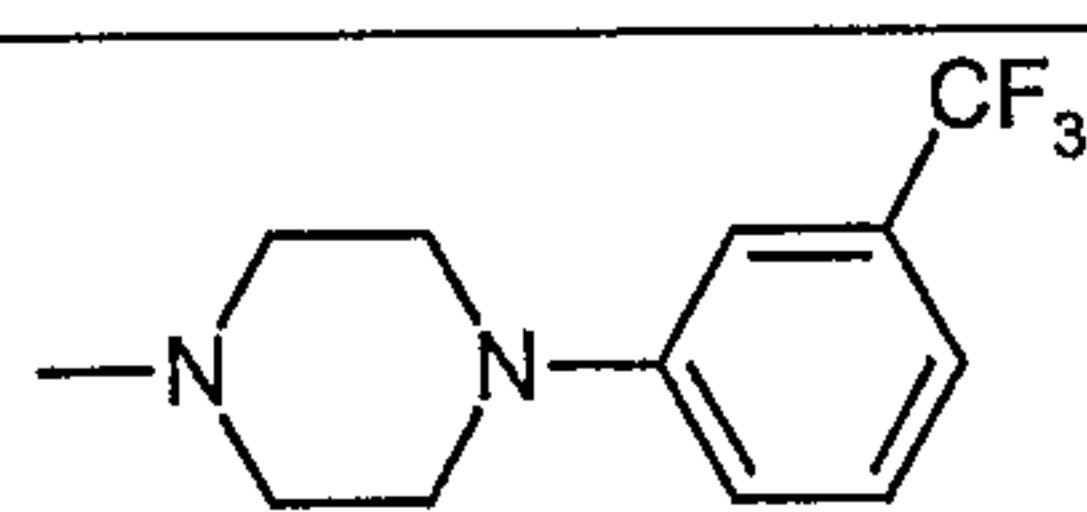
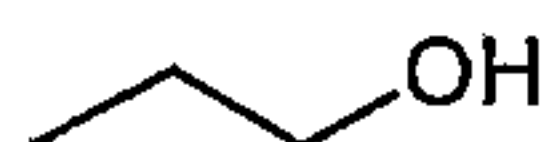
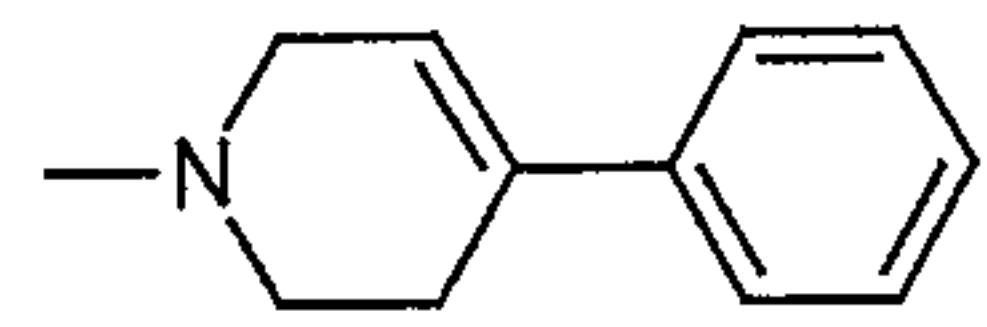
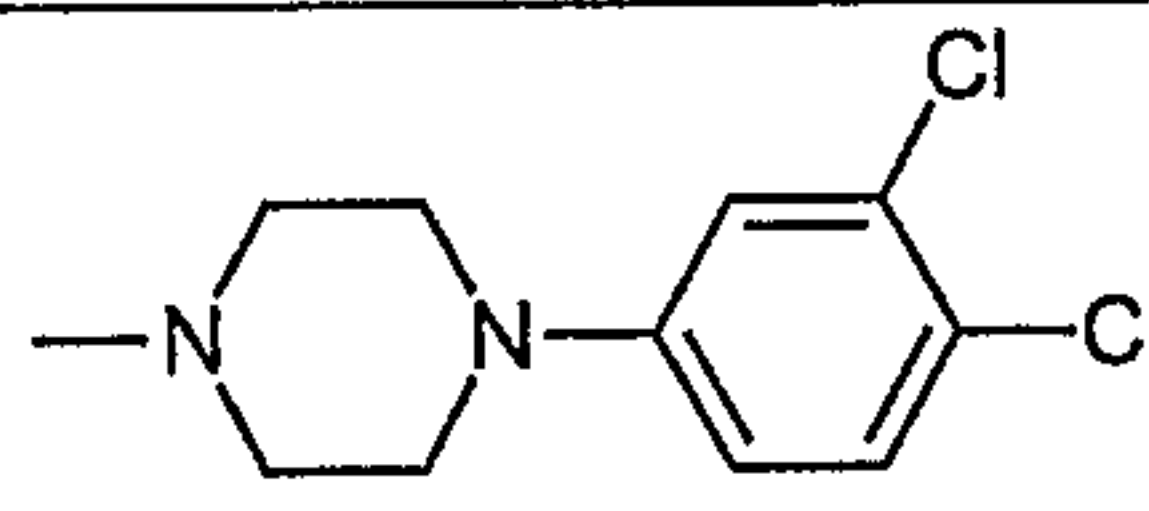
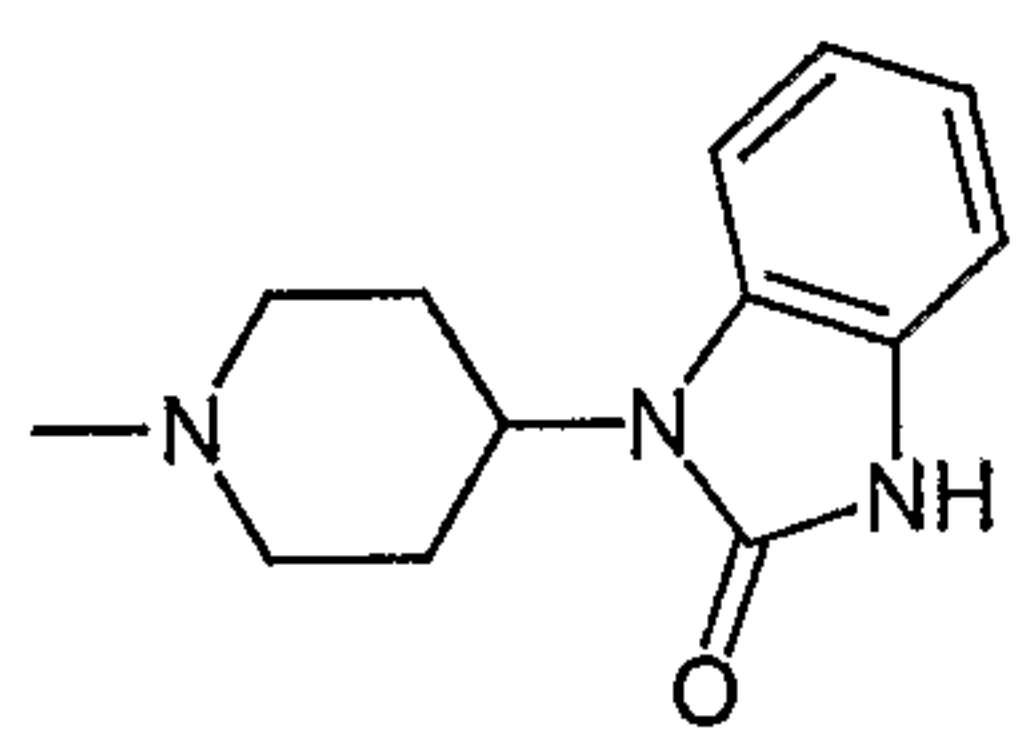
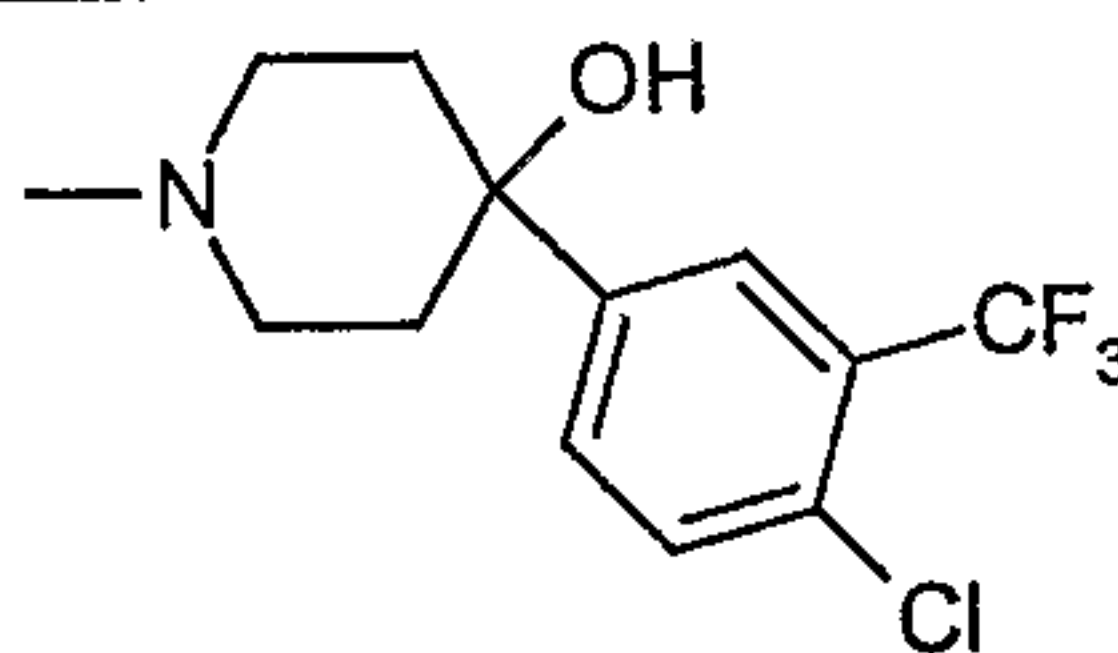
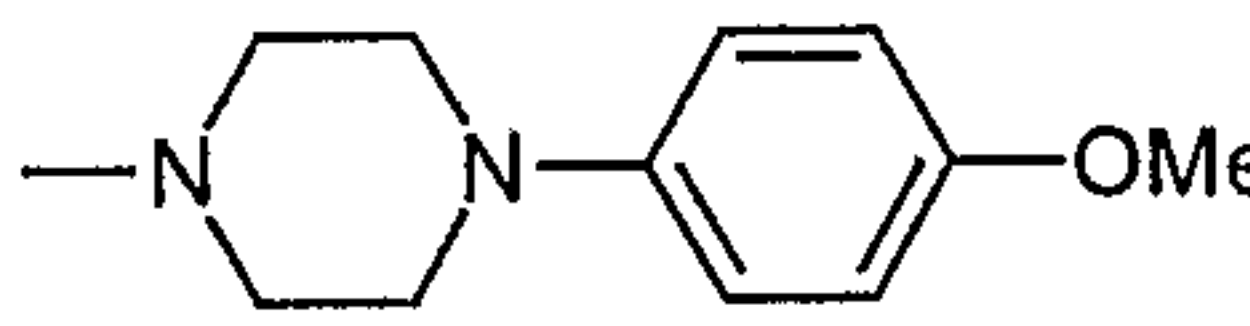
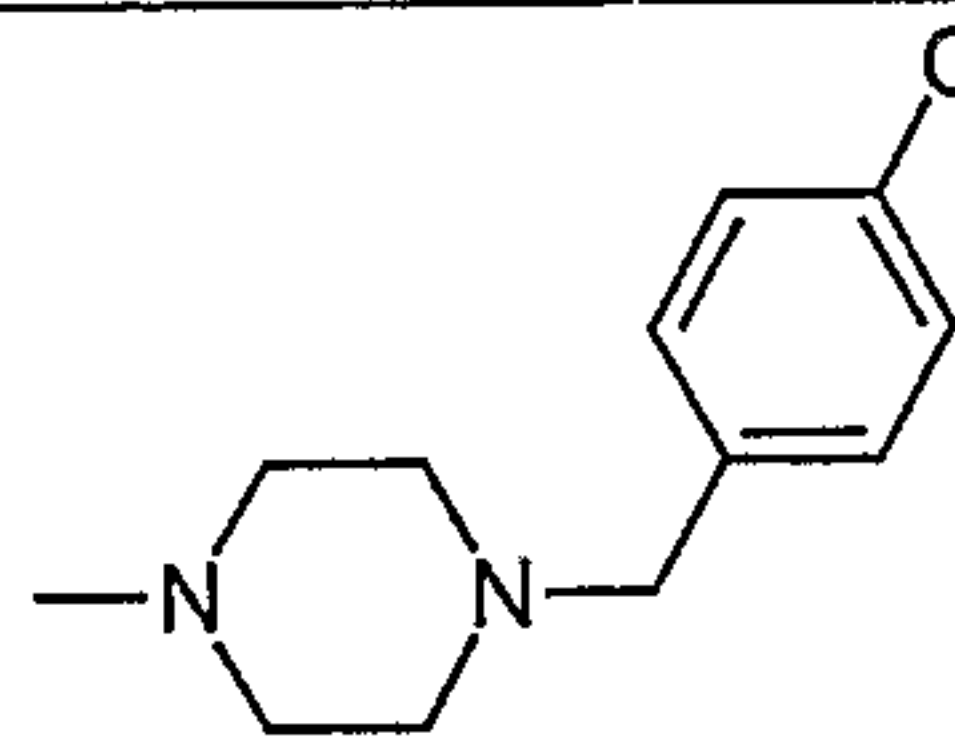
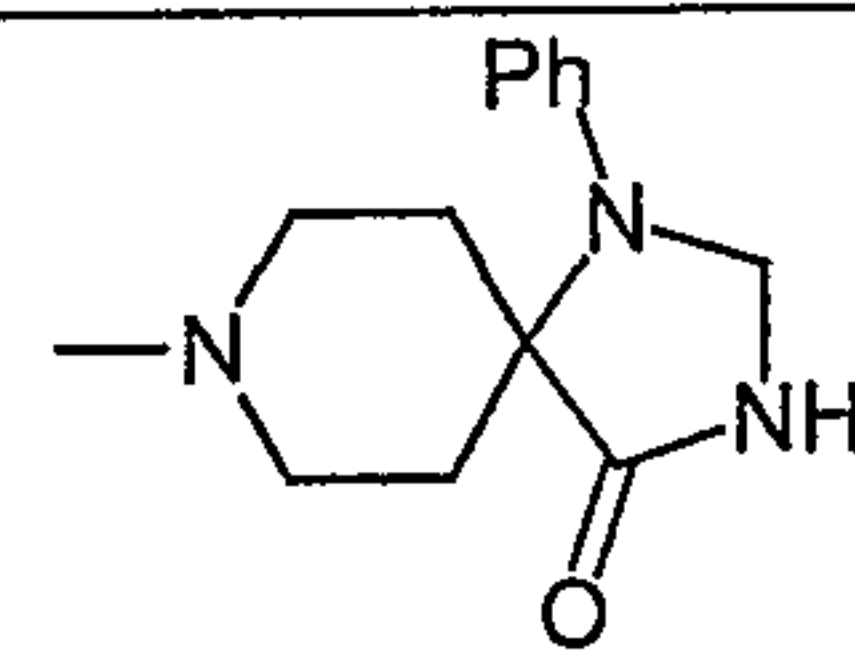
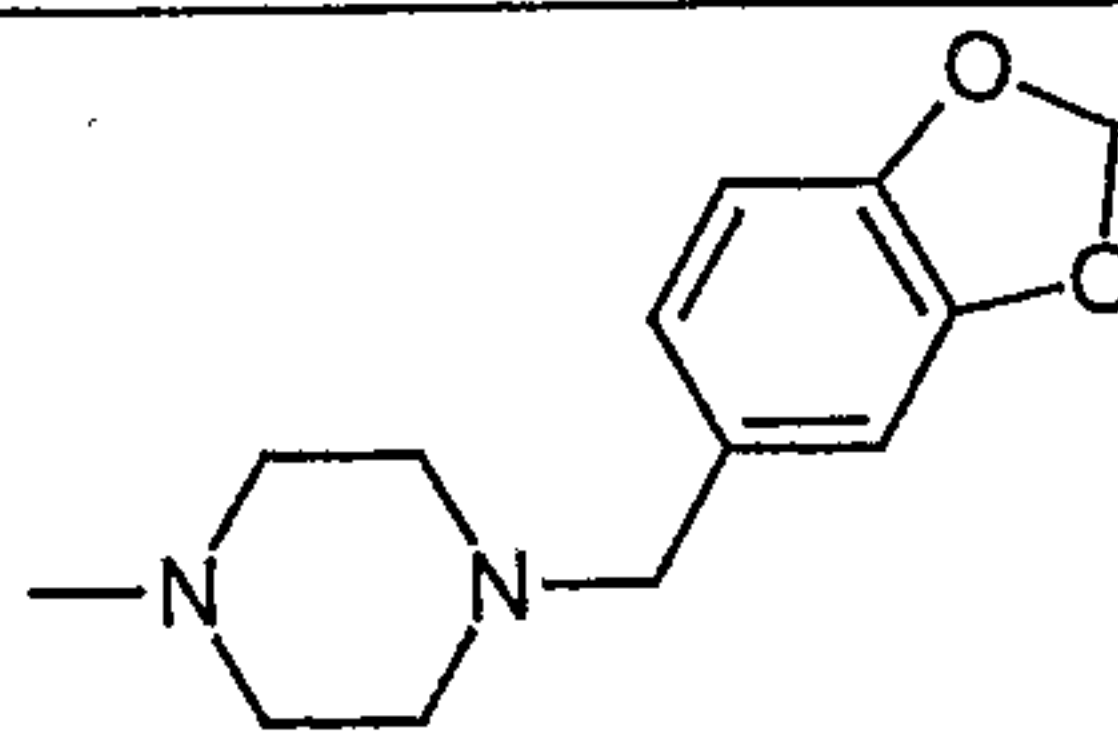
Comp. No	-R ¹	-A-	$\begin{array}{c} \text{R}^2 \\ \\ \text{---N---} \\ \\ \text{R}^3 \end{array}$	[M+H] ⁺
63				464
64				463
65				392
66				463
67				450
68				512
69				425
70				443
71				464
72				453

Table 3 (continued):

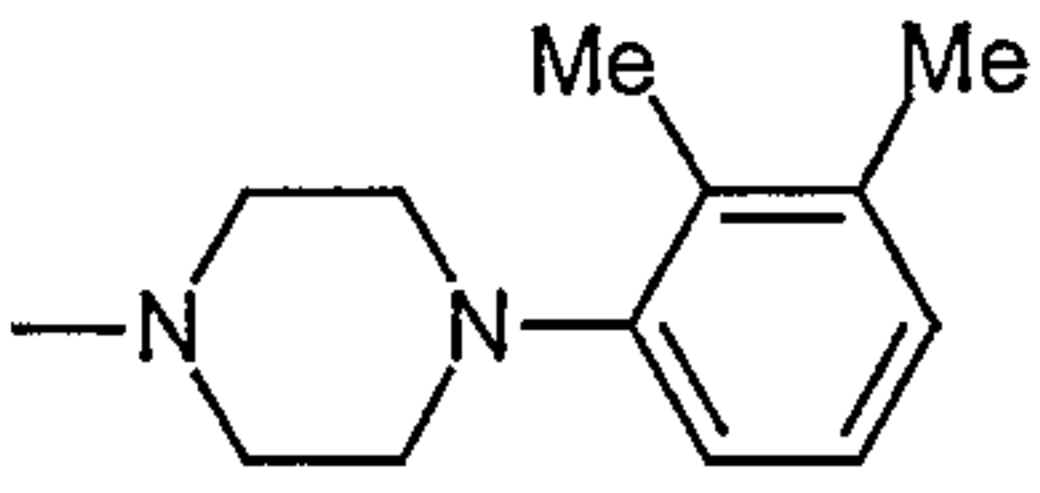
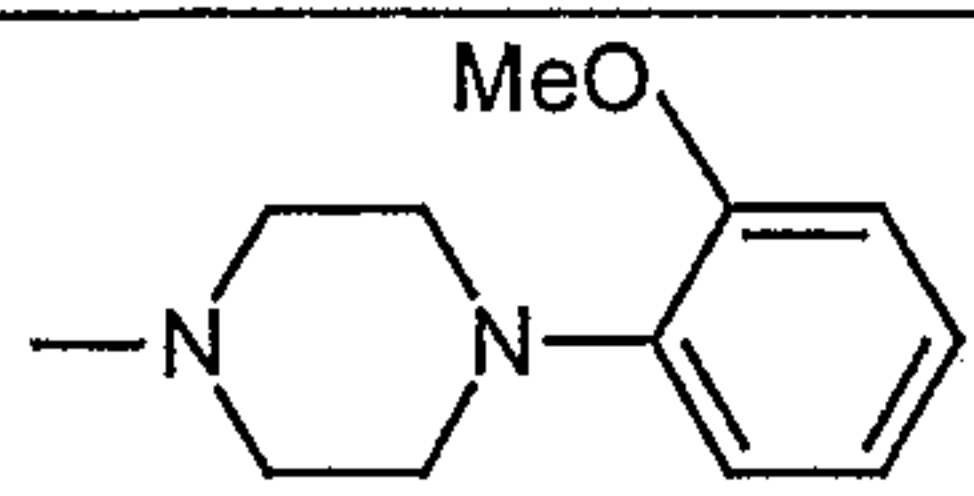
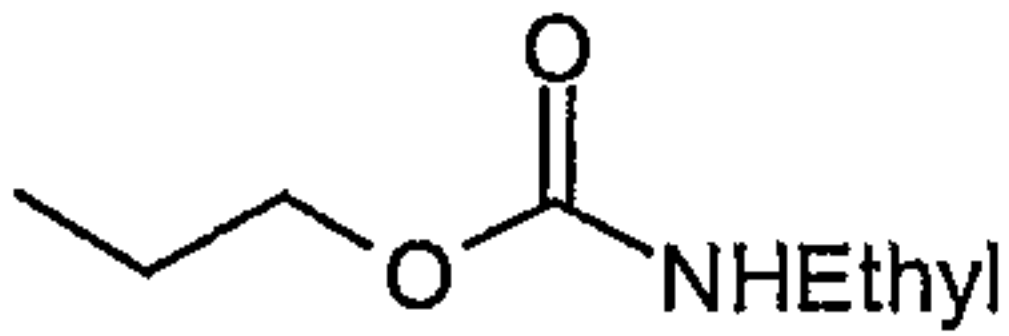
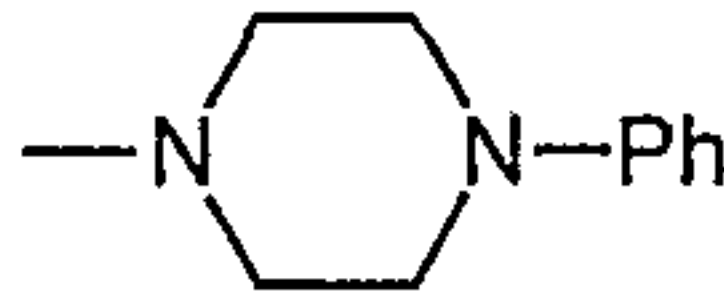
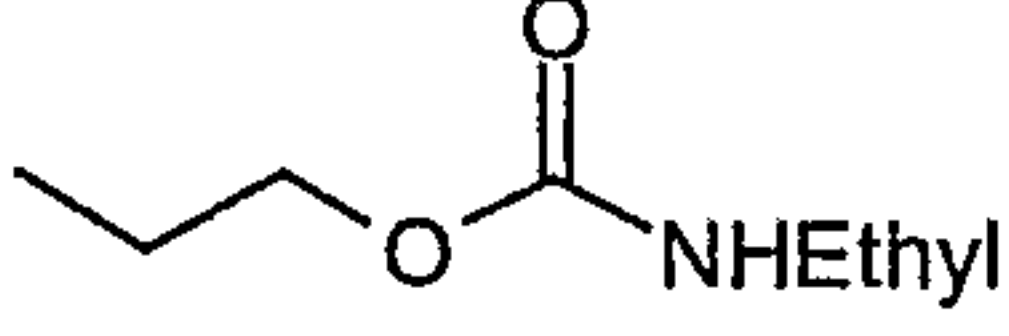
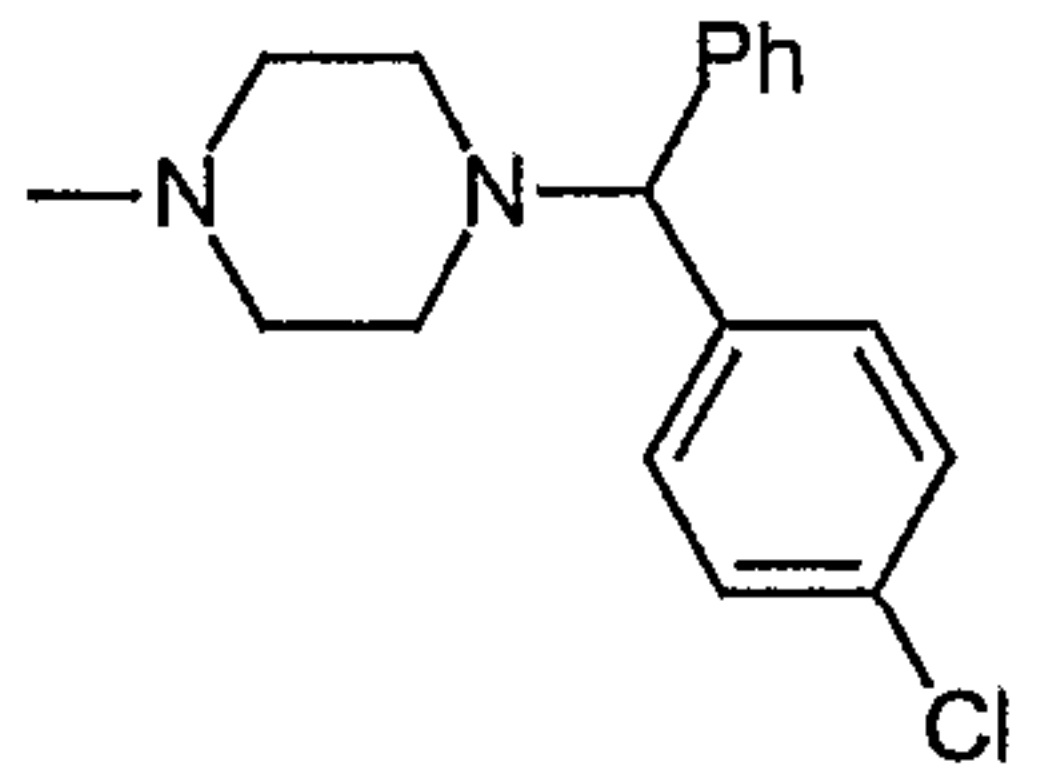
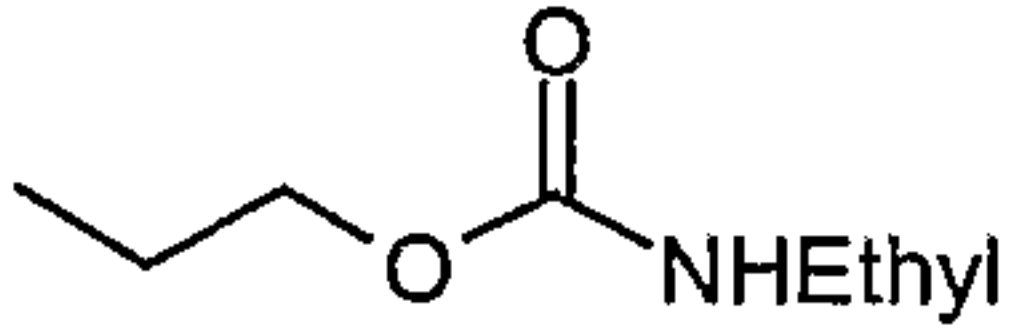
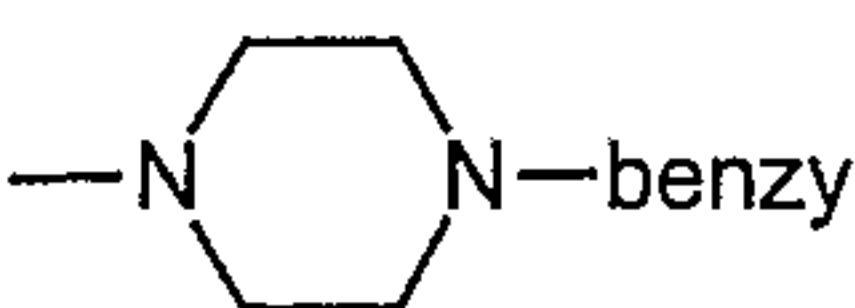
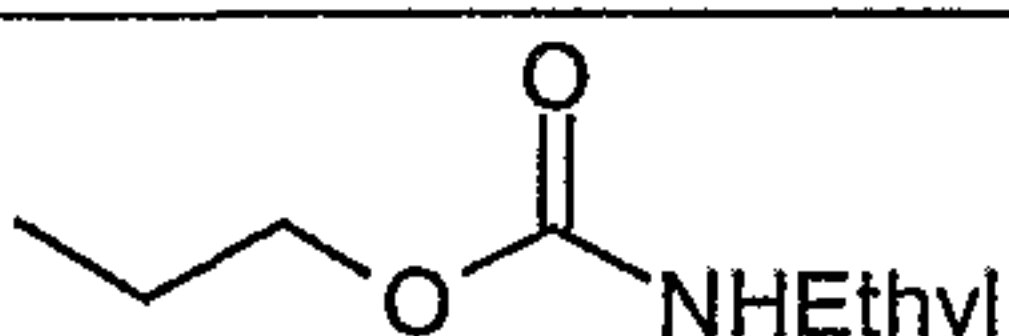
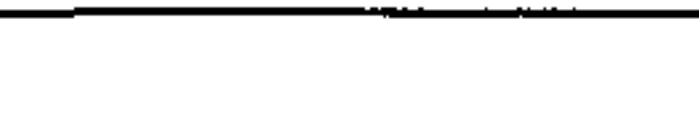
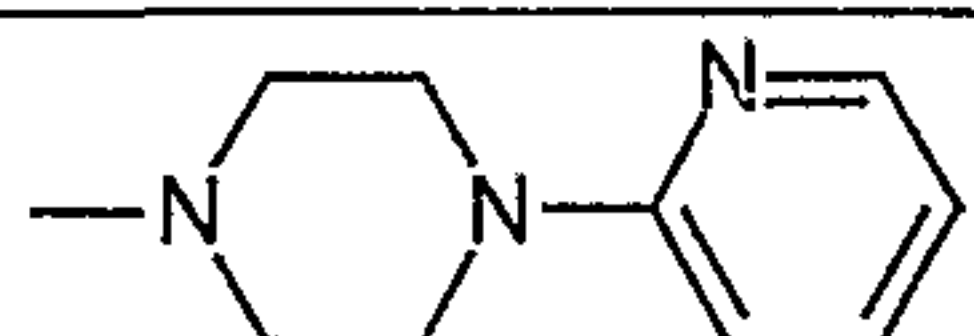
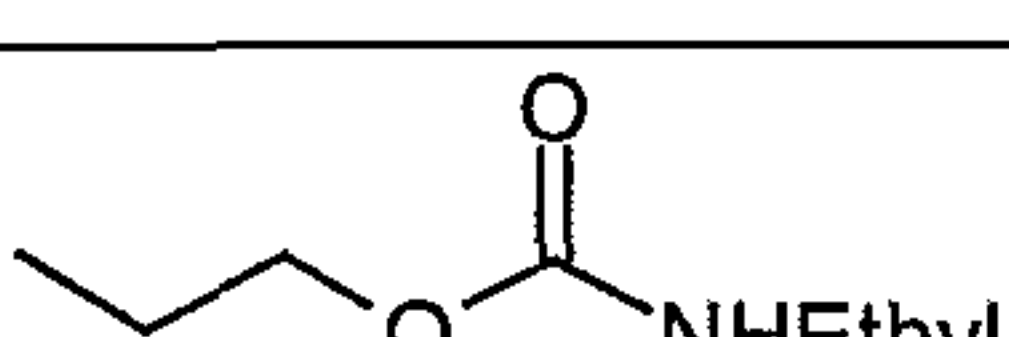
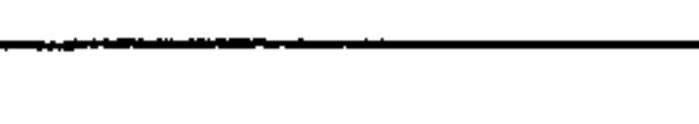
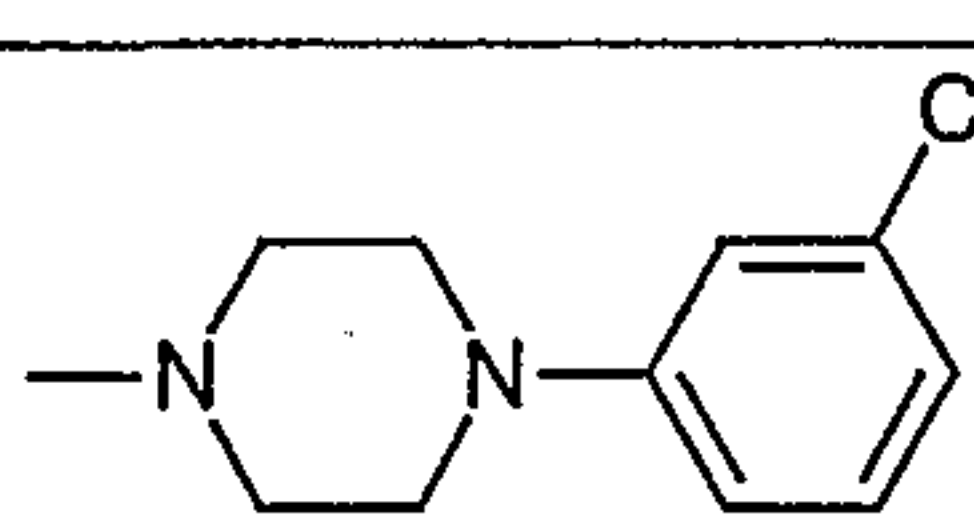
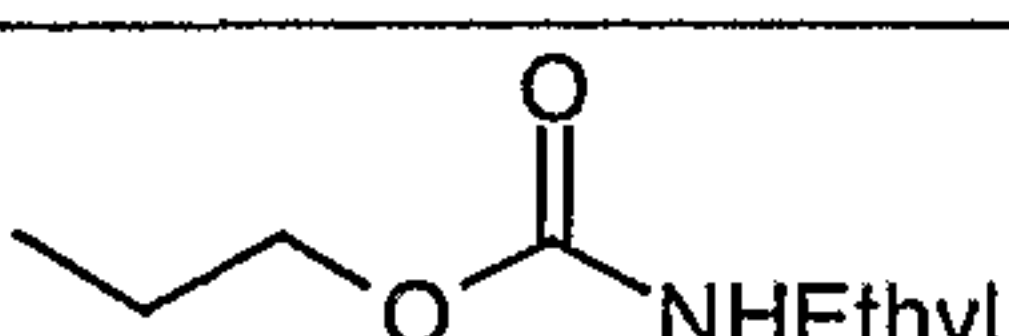
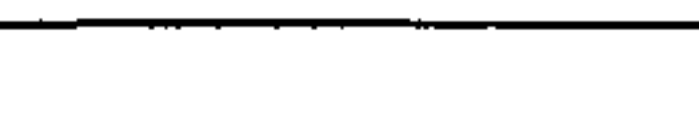
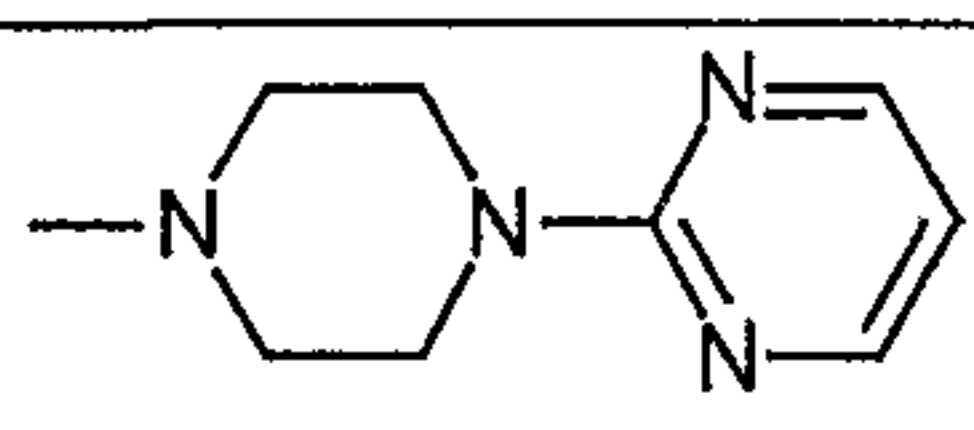
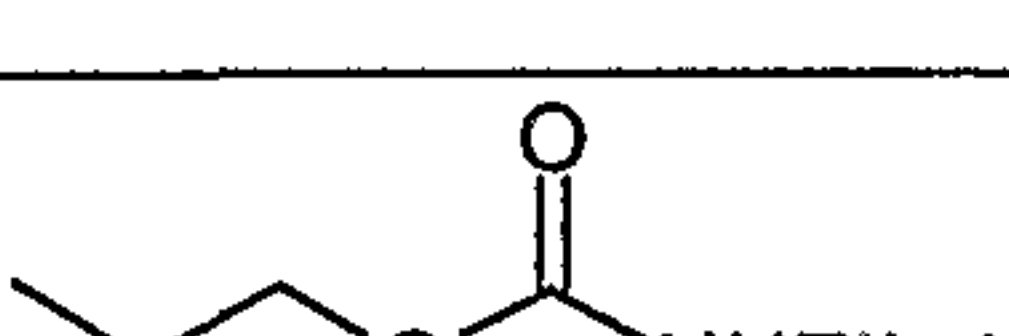
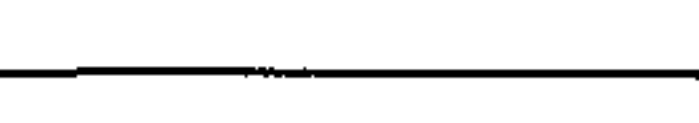
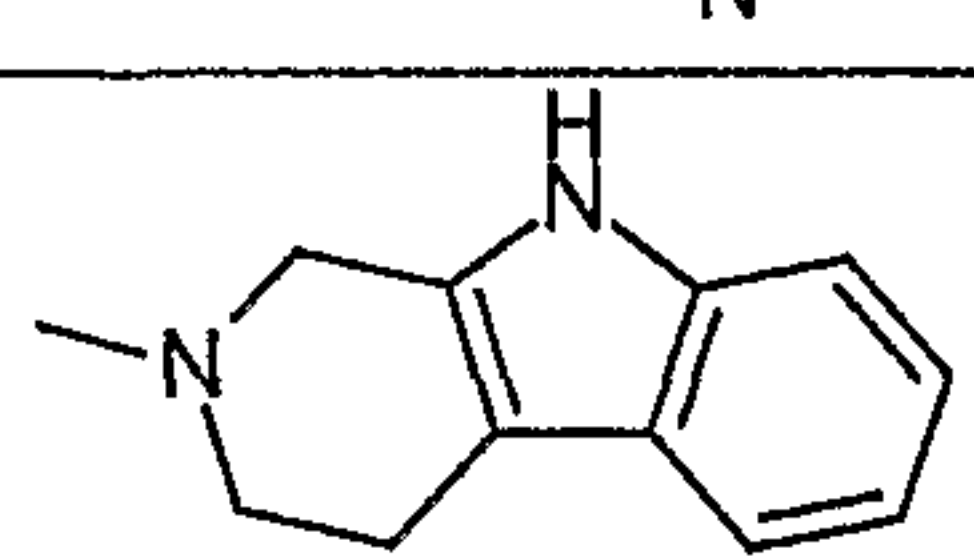
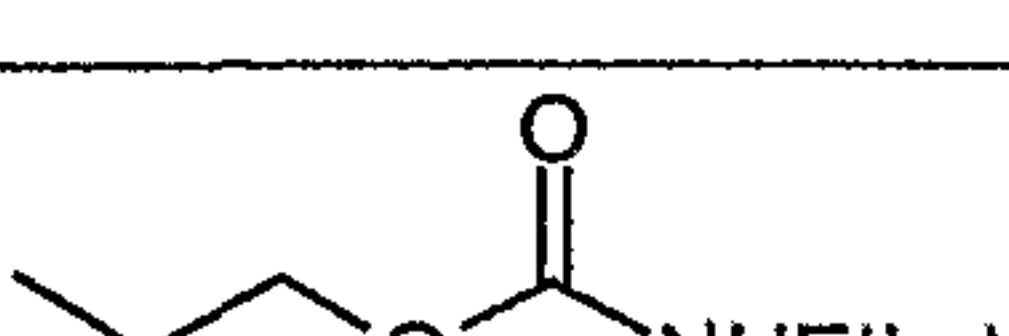
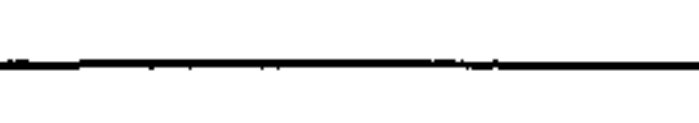
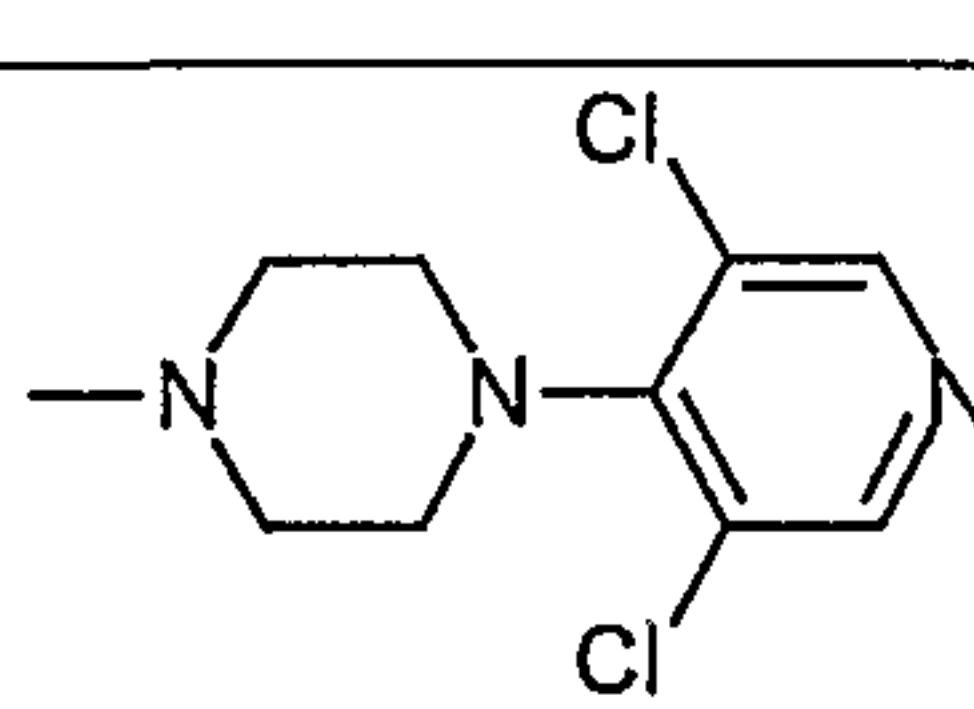
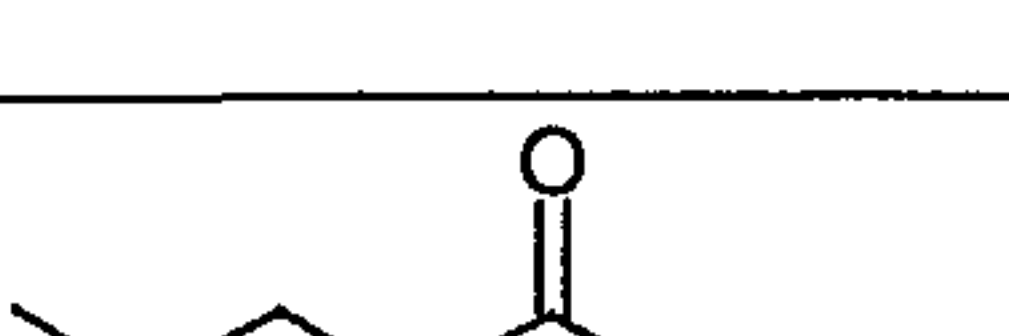
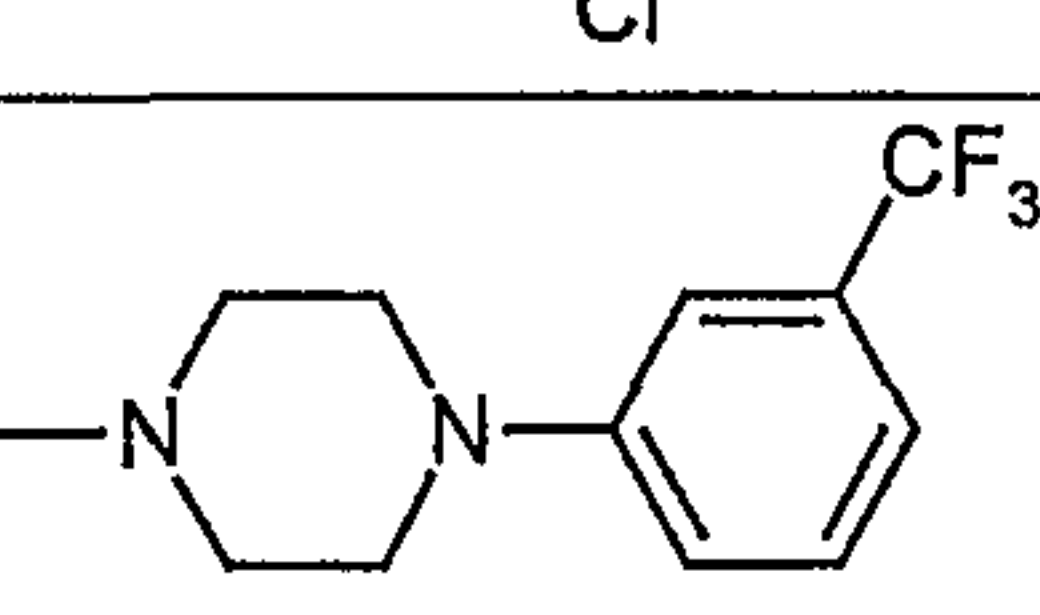
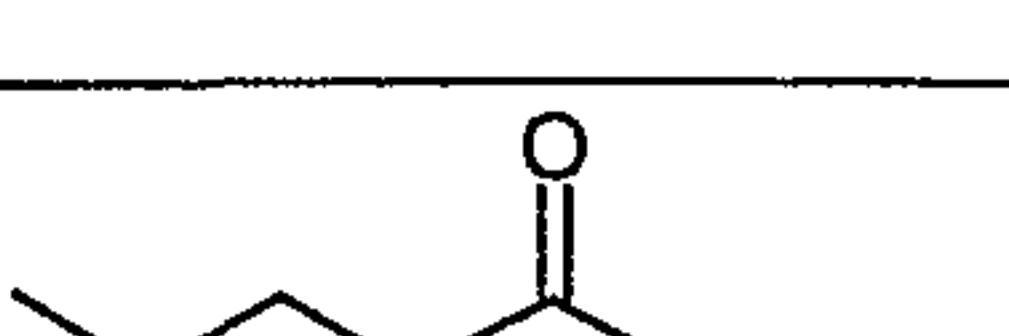
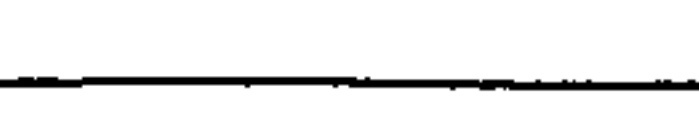
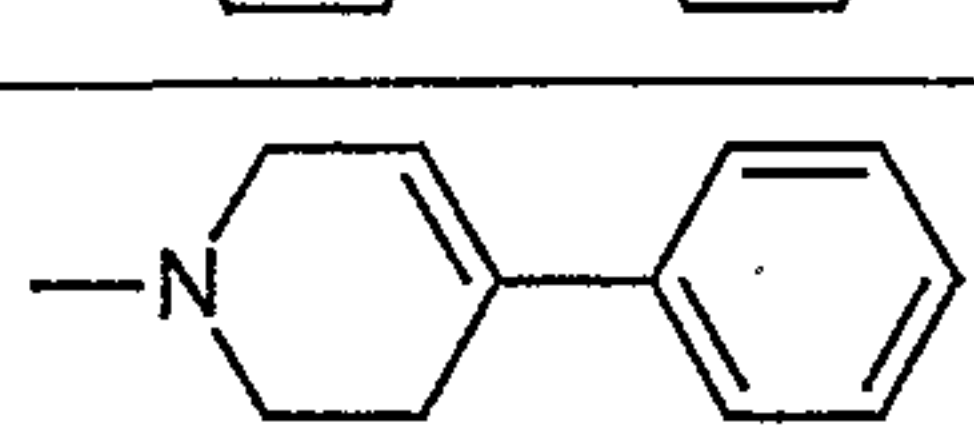
Comp. No	-R ¹	-A-	$\begin{array}{c} \text{R}^2 \\ \\ \text{---N---} \\ \\ \text{R}^3 \end{array}$	[M+H] ⁺
73				423
74				425
75				466
76				590
77				480
78				467
79				500
80				468
81				476
82				535
83				534
84				463

Table 3 (continued):

Comp. No	-R ¹	-A-	$\text{—N} \begin{matrix} \text{R}^2 \\ \text{R}^3 \end{matrix}$	[M+H] ⁺
85				534
86				521
87				583
88				496
89				514
90				535
91				524
92				494
93				496
94				480

Table 3 (continued):

Comp. No	-R ¹	-A-	$\begin{array}{c} \text{R}^2 \\ \\ \text{---N---} \\ \\ \text{R}^3 \end{array}$	[M+H] ⁺
95				480
96				500
97				436
98				560
99				450
100				437
101				470
102				438
103				446
104				505
105				504
106				433

Table 3 (continued):

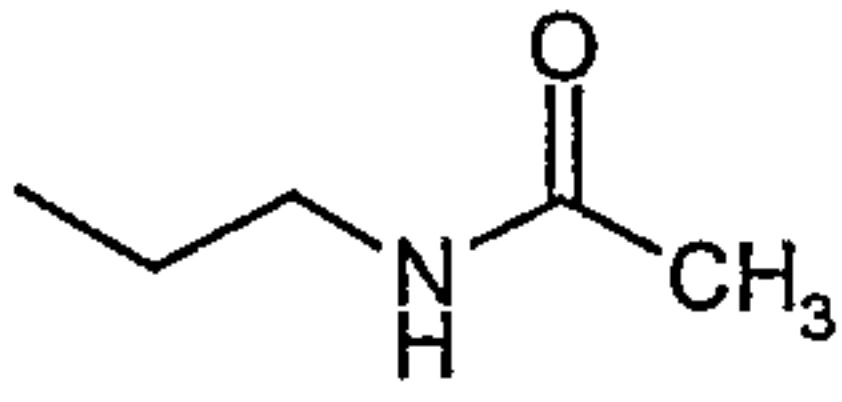
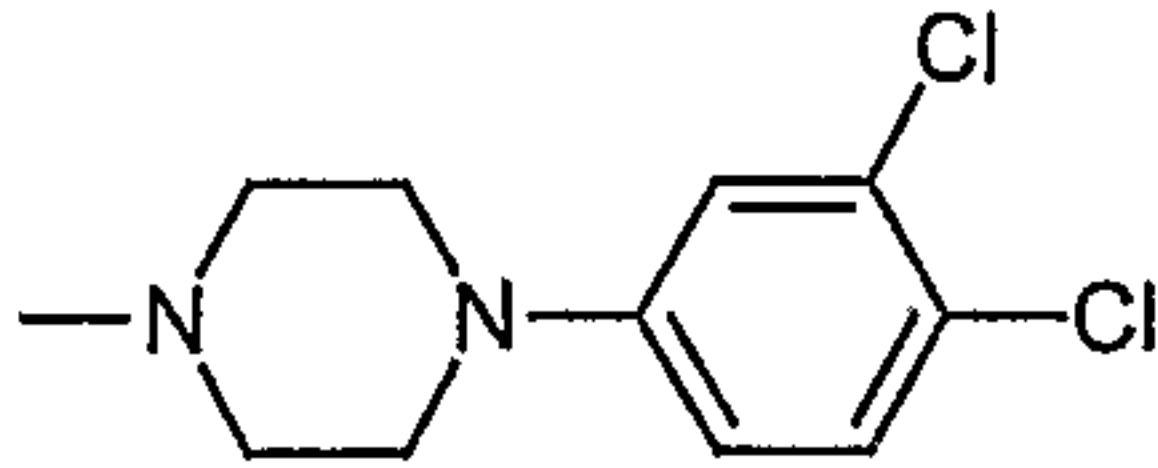
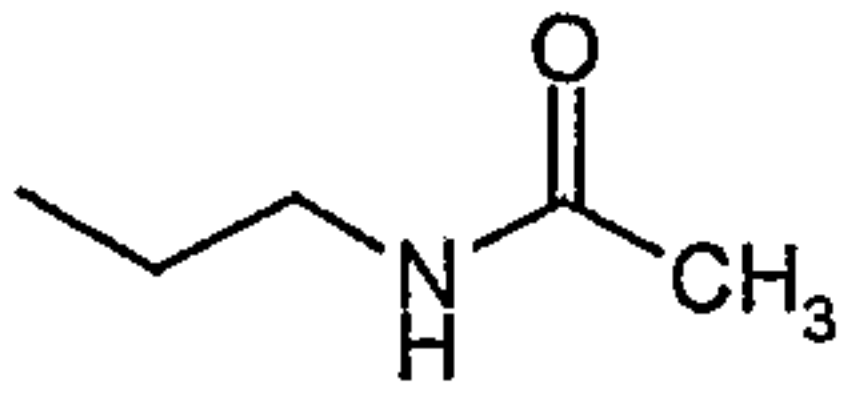
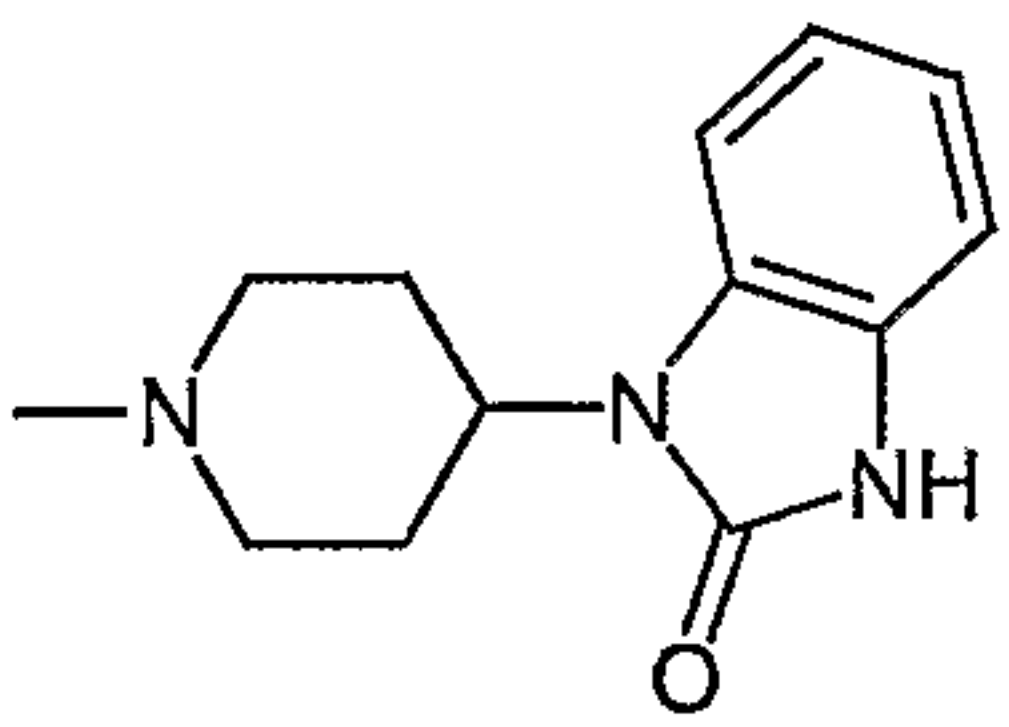
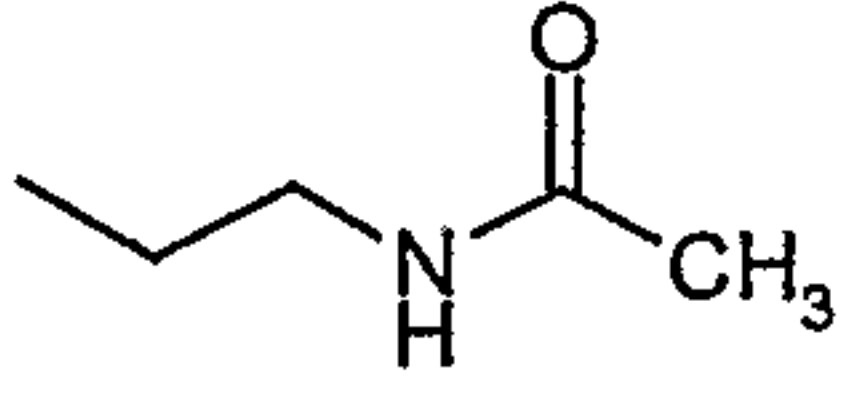
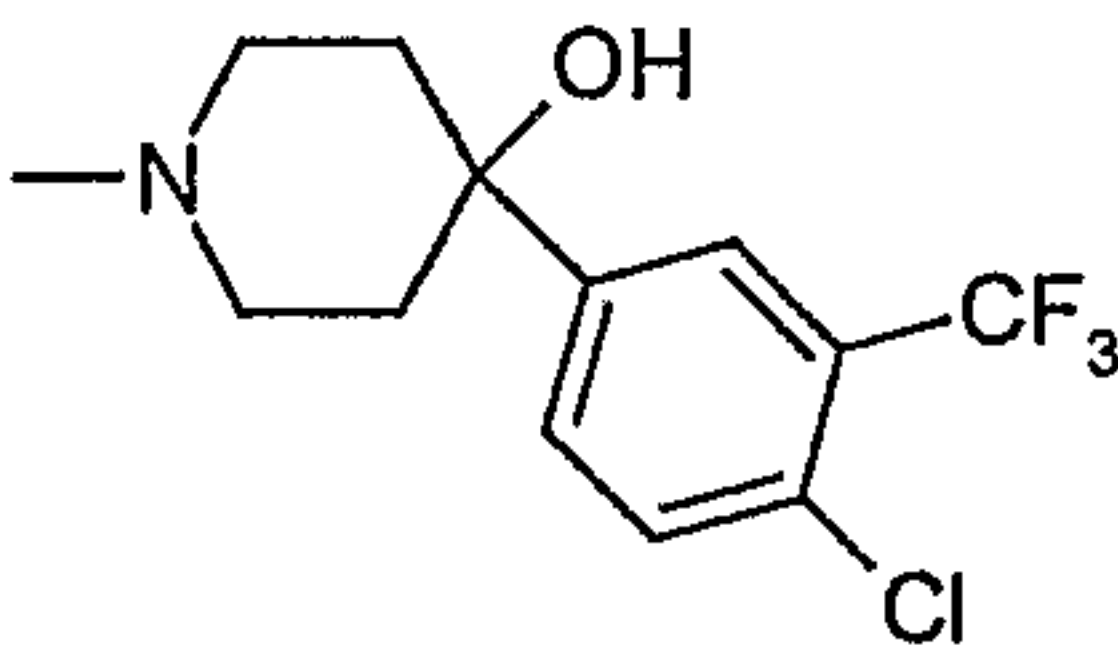
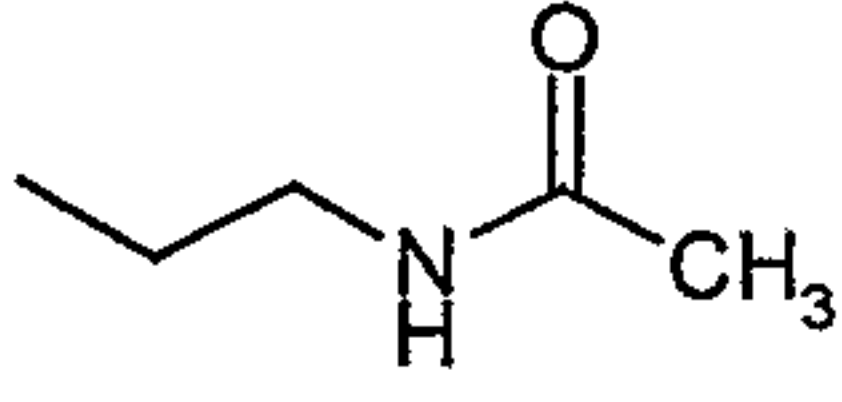
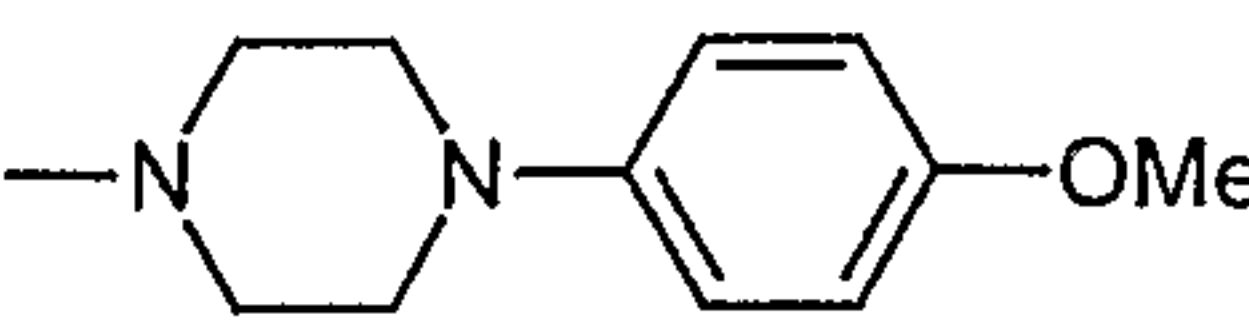
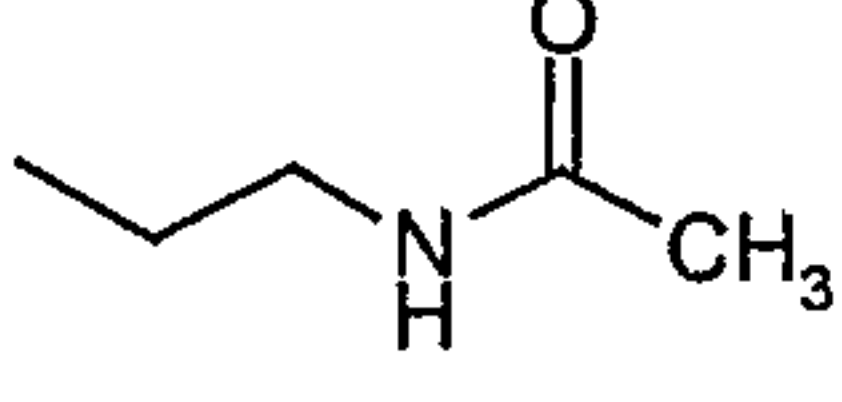
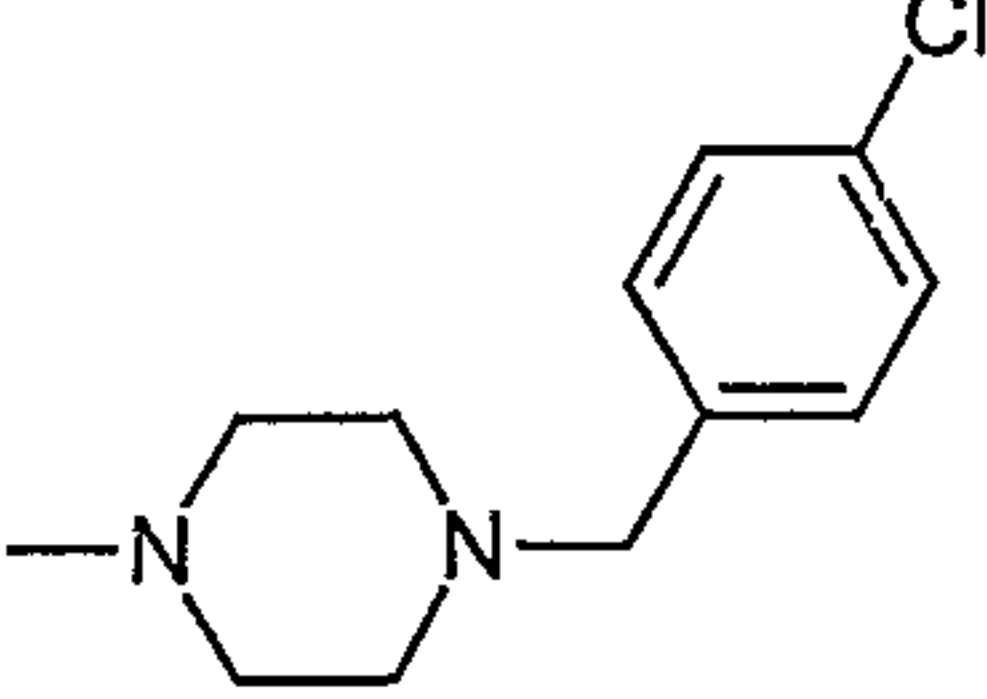
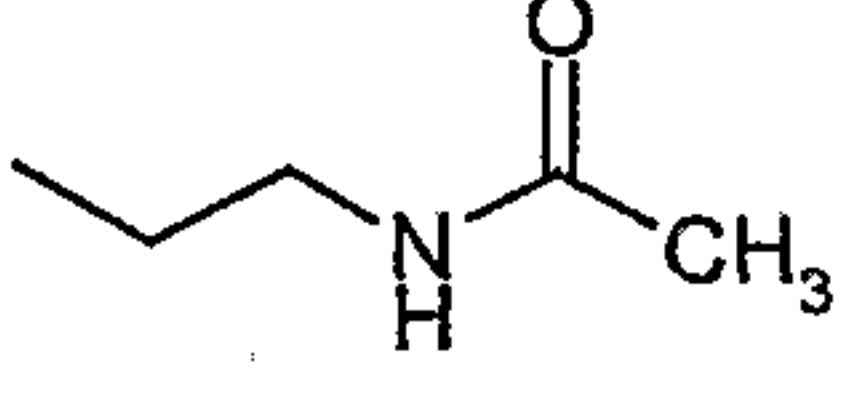
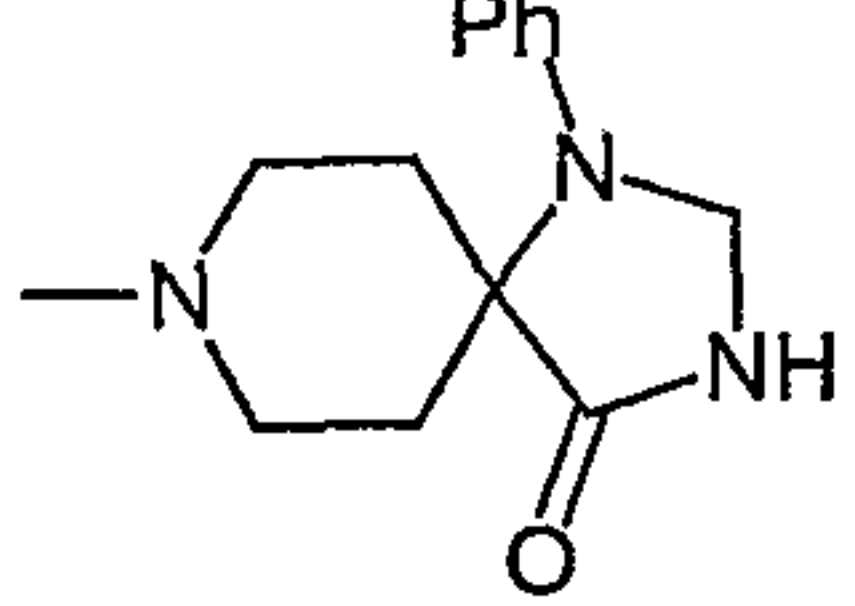
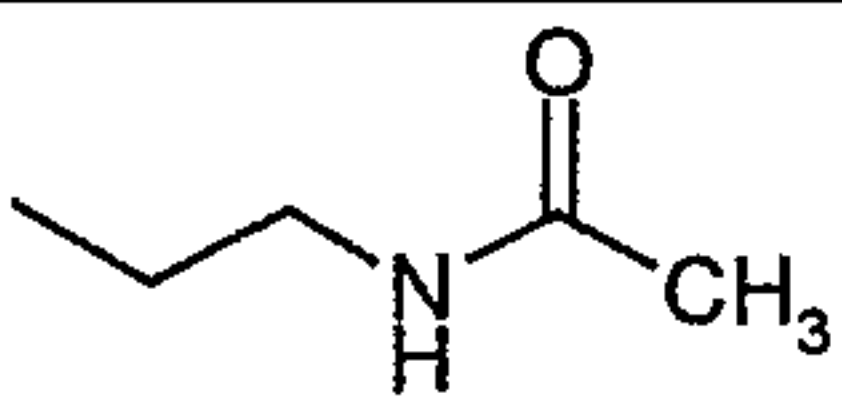
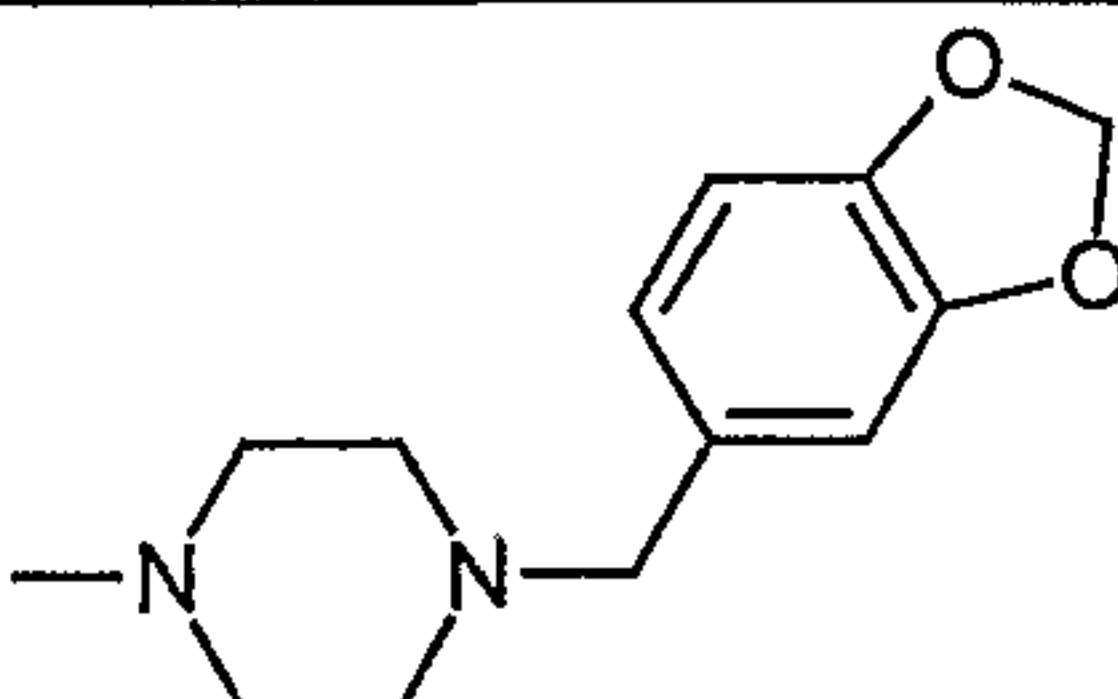
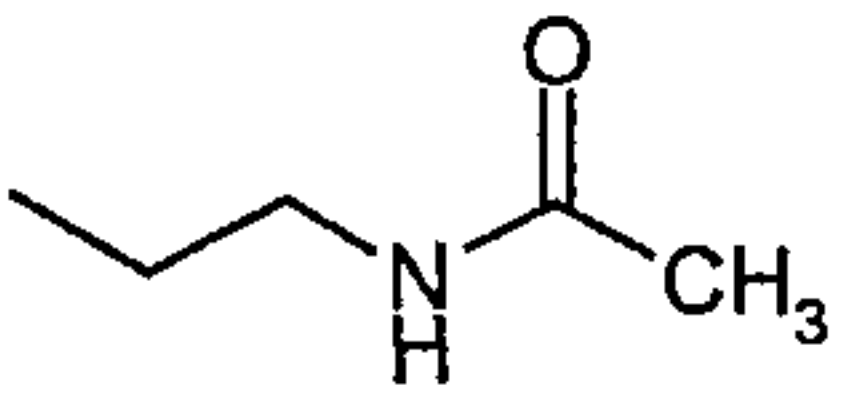
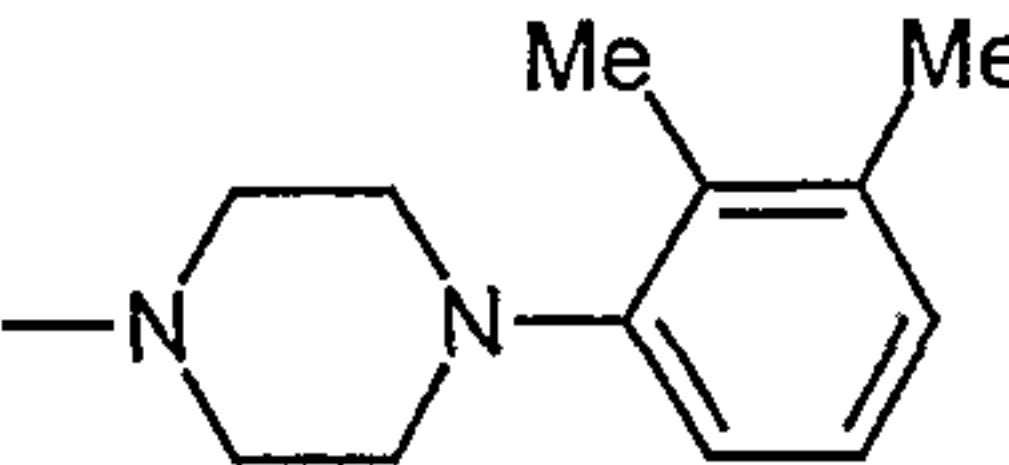
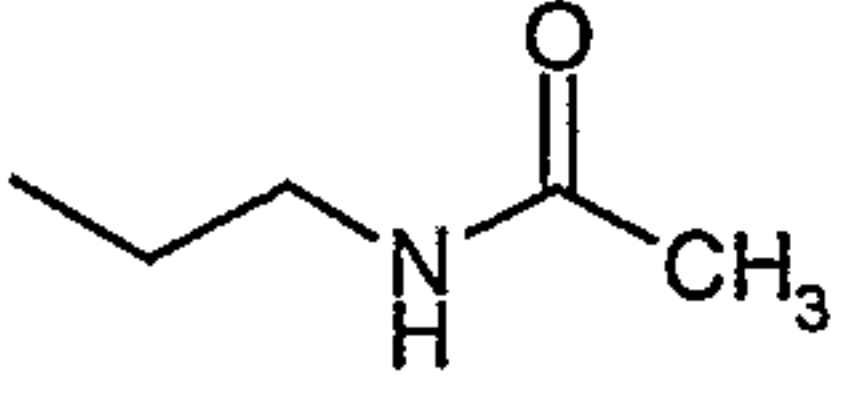
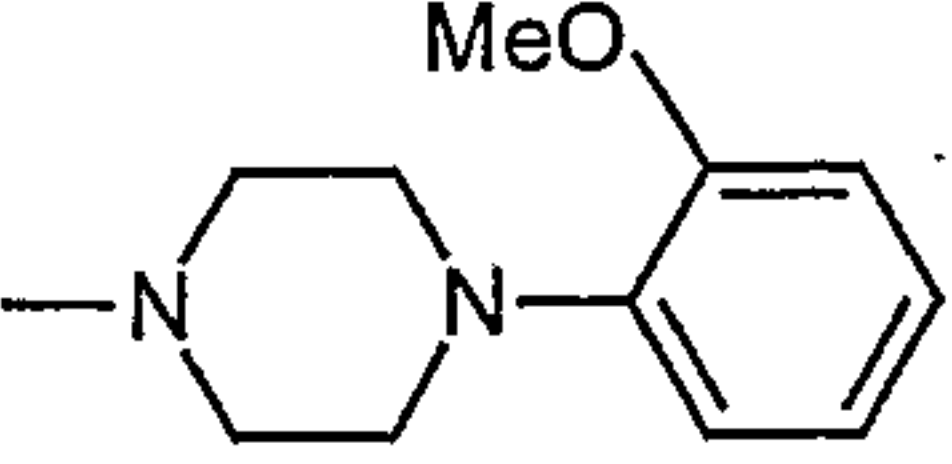
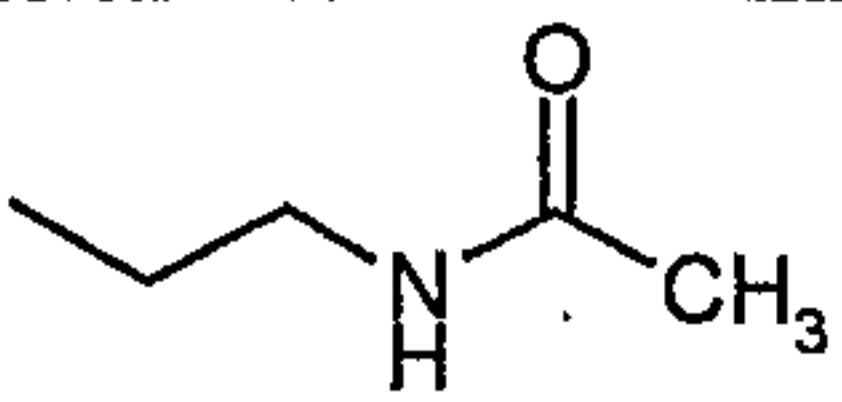
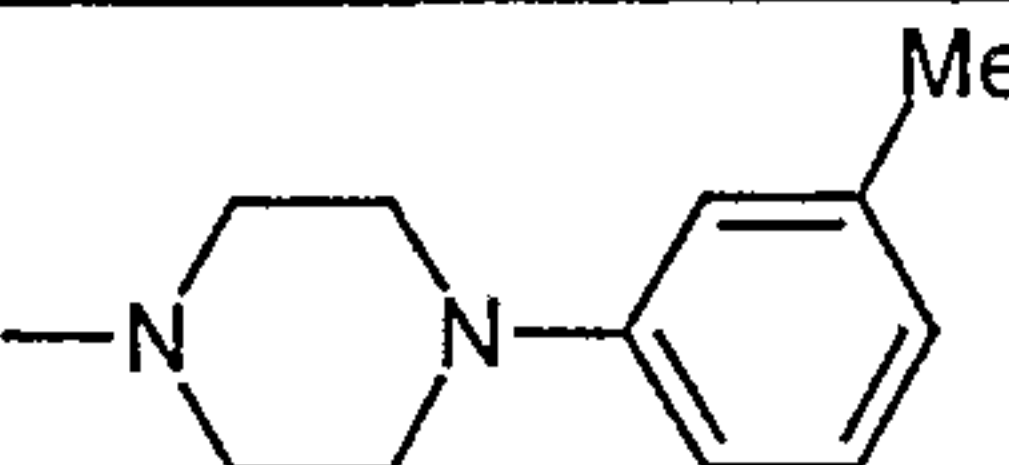
Comp. No	-R ¹	-A-	$\text{—N} \begin{matrix} \text{R}^2 \\ \text{R}^3 \end{matrix}$	[M+H] ⁺
107				504
108				491
109				553
110				466
111				484
112				505
113				494
114				464
115				466
116				450

Table 3 (continued):

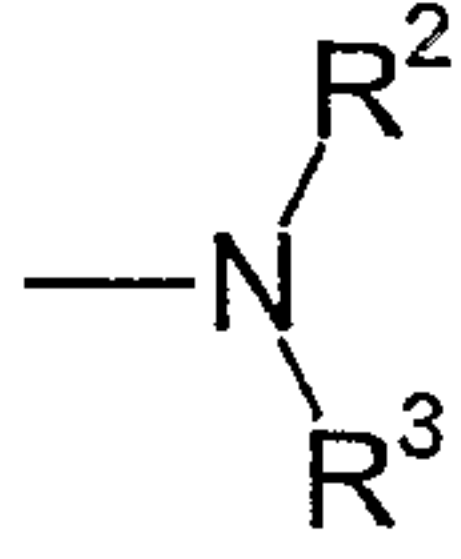
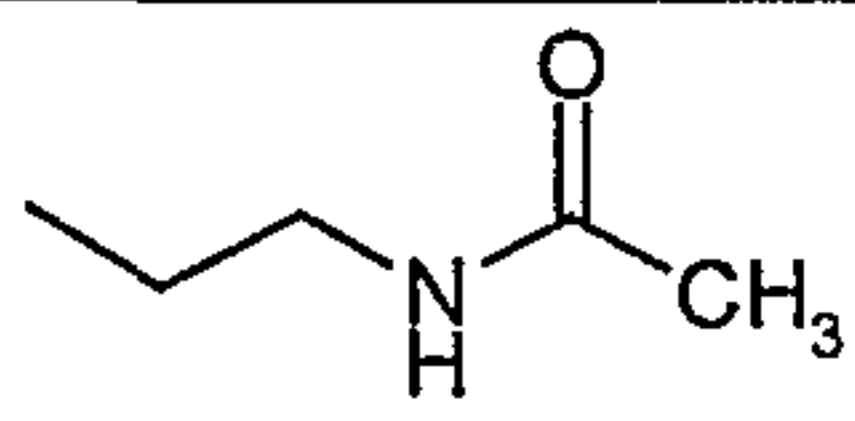
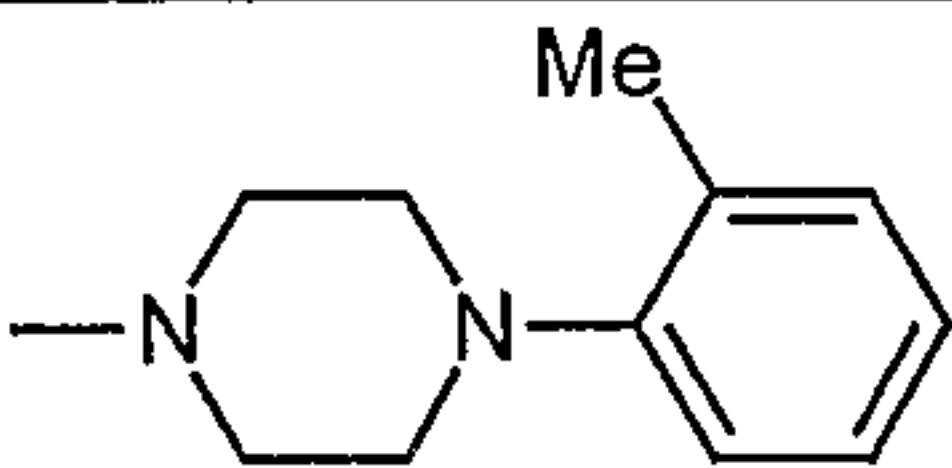
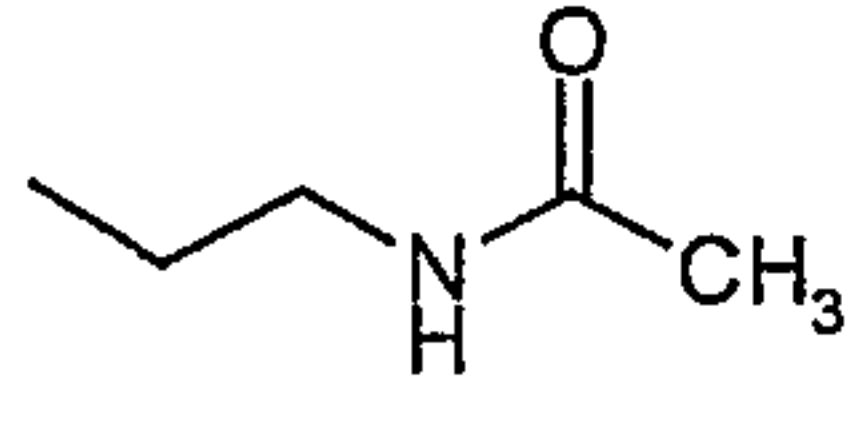
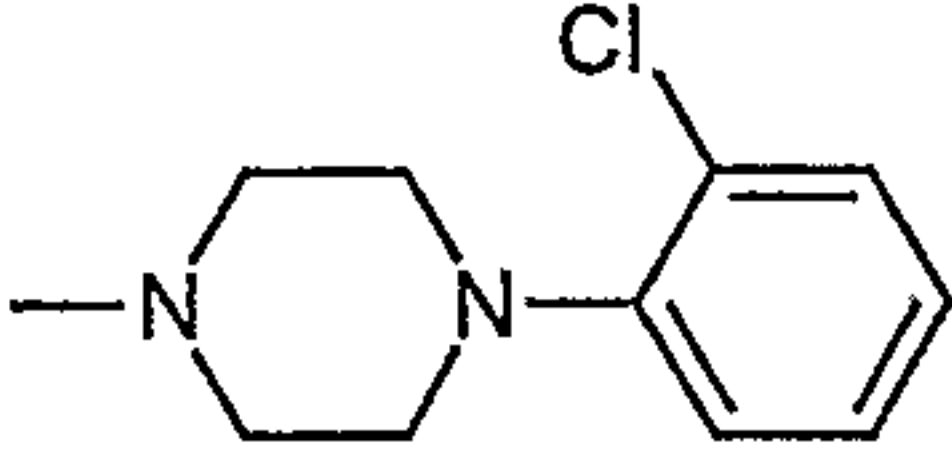
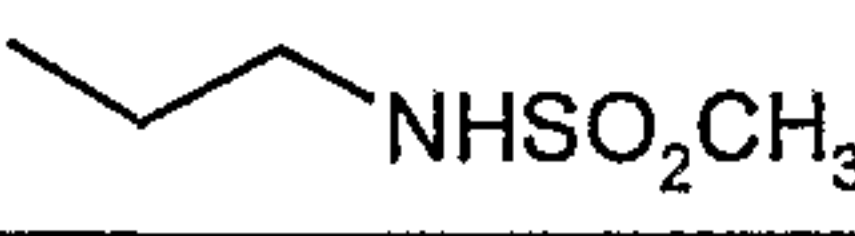
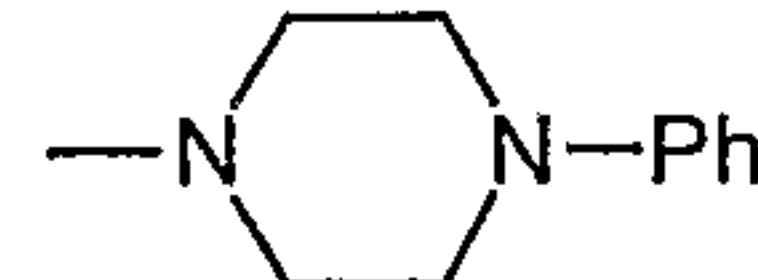
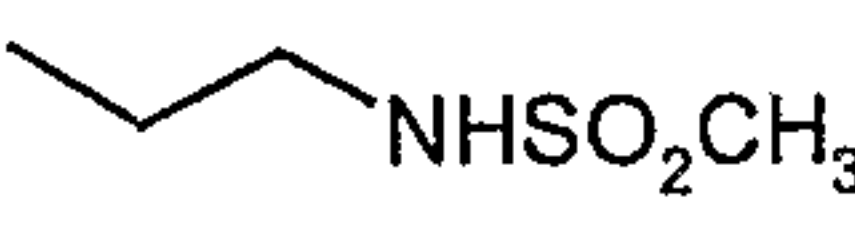
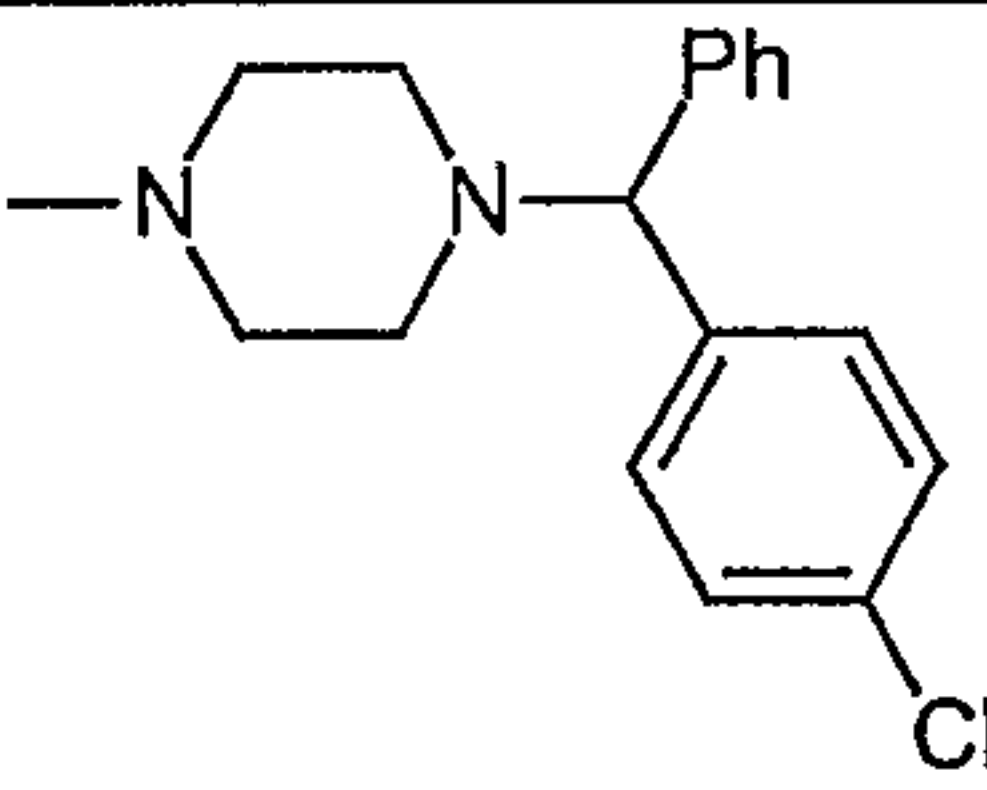
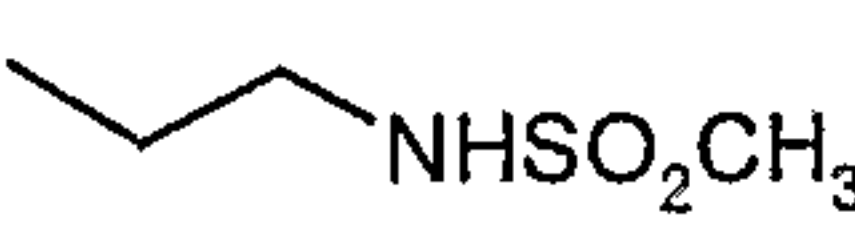
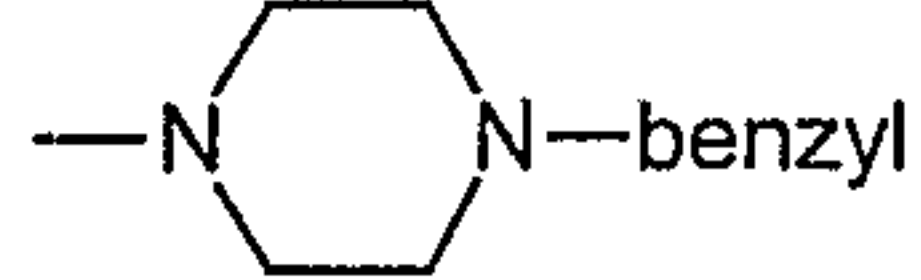
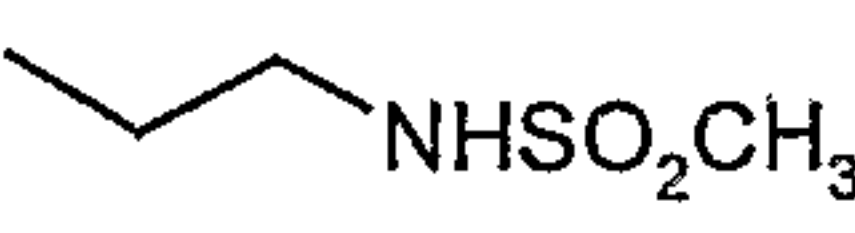
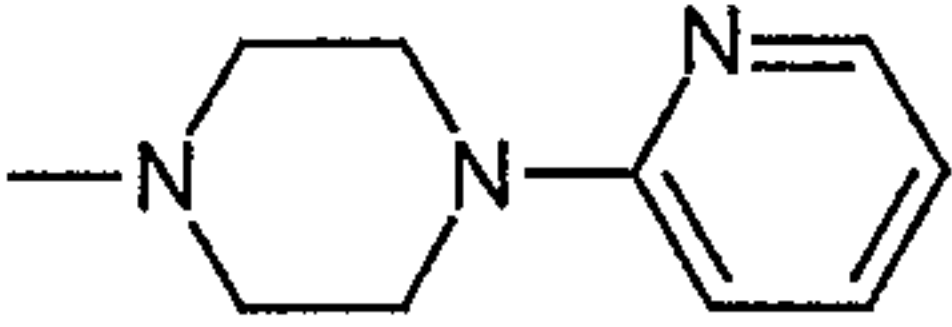
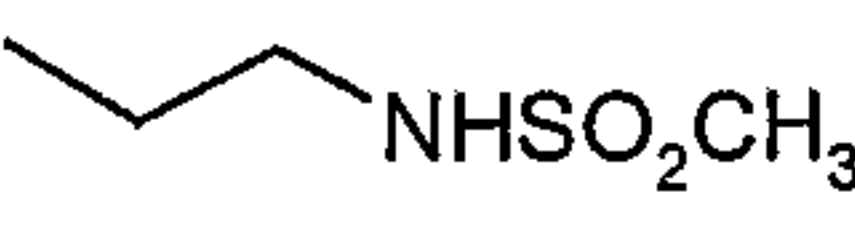
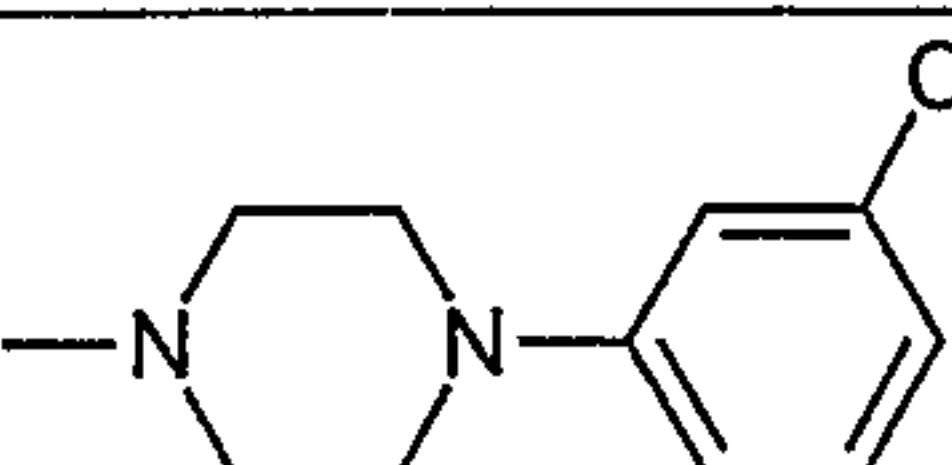
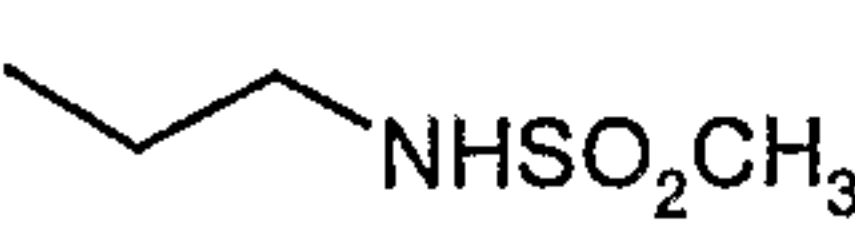
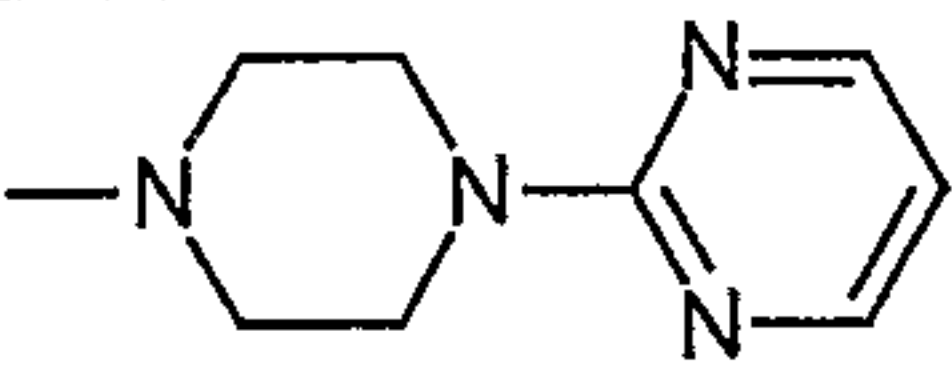
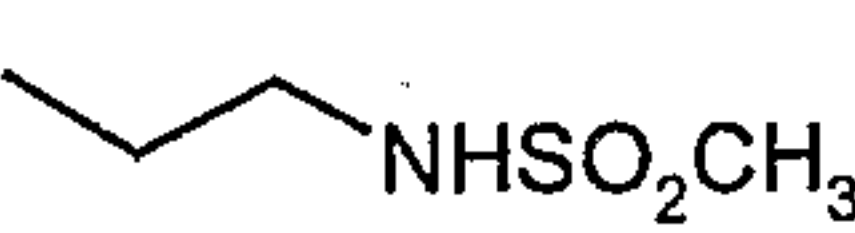
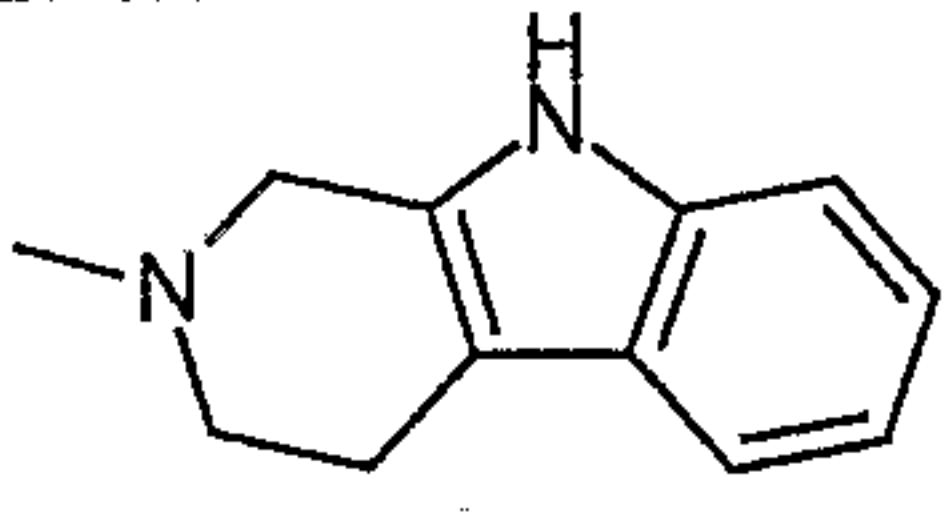
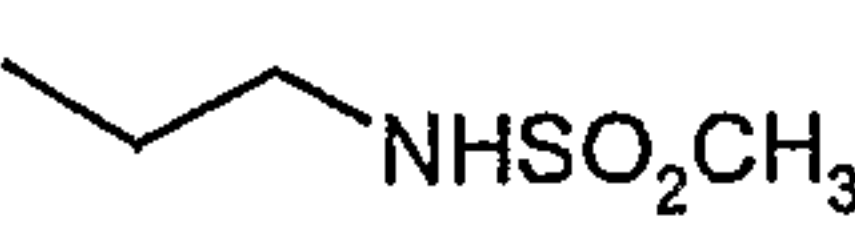
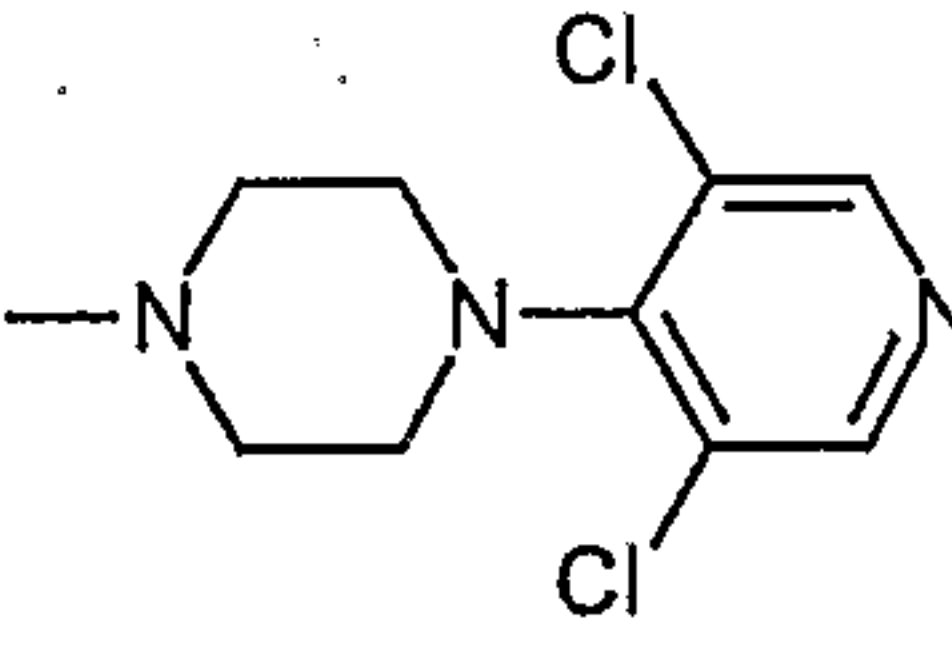
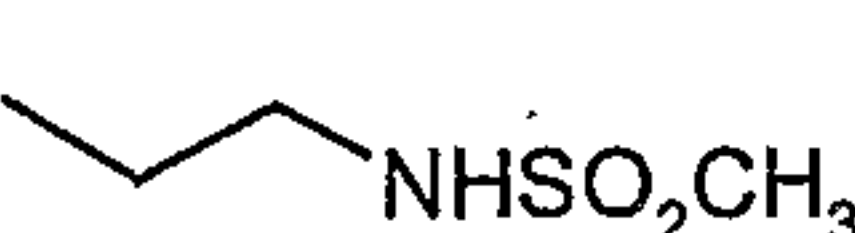
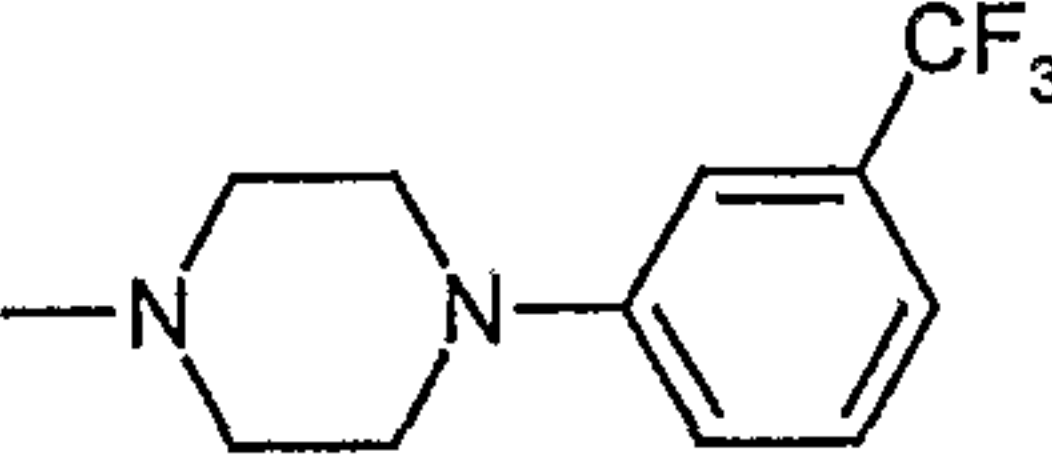
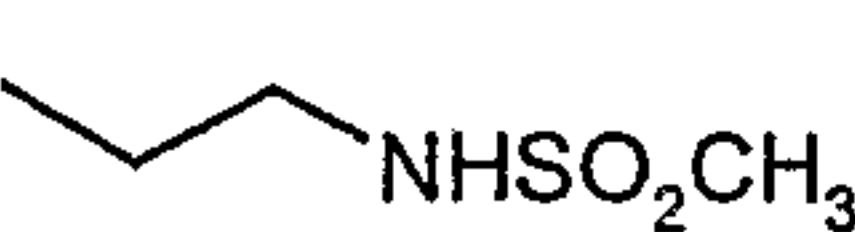
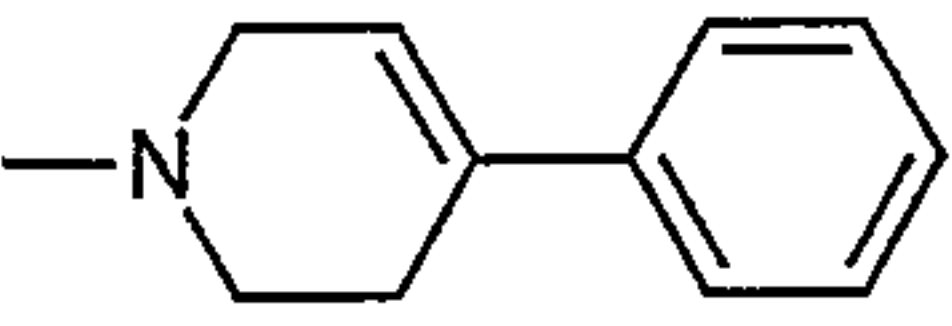
Comp. No	-R ¹	-A-		[M+H] ⁺
117				450
118				470
119				472
120				596
121				486
122				473
123				506
124				474
125				482
126				541
127				540
128				469

Table 3 (continued):

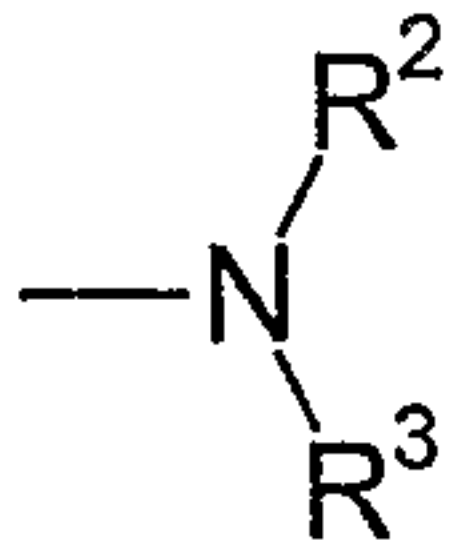
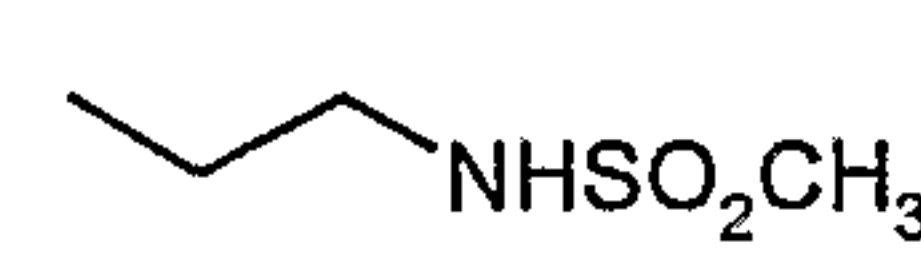
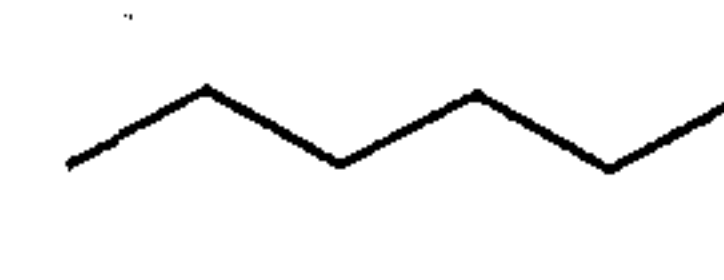
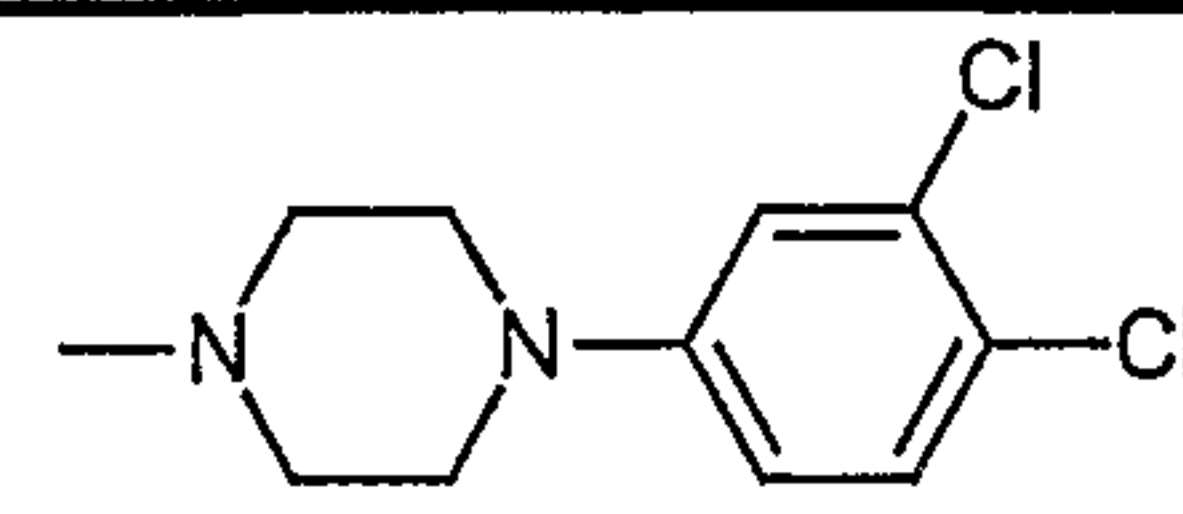
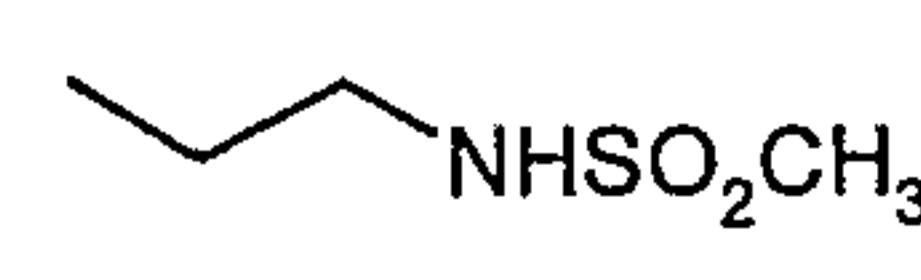
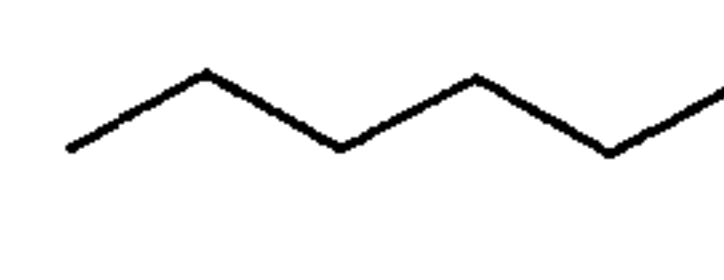
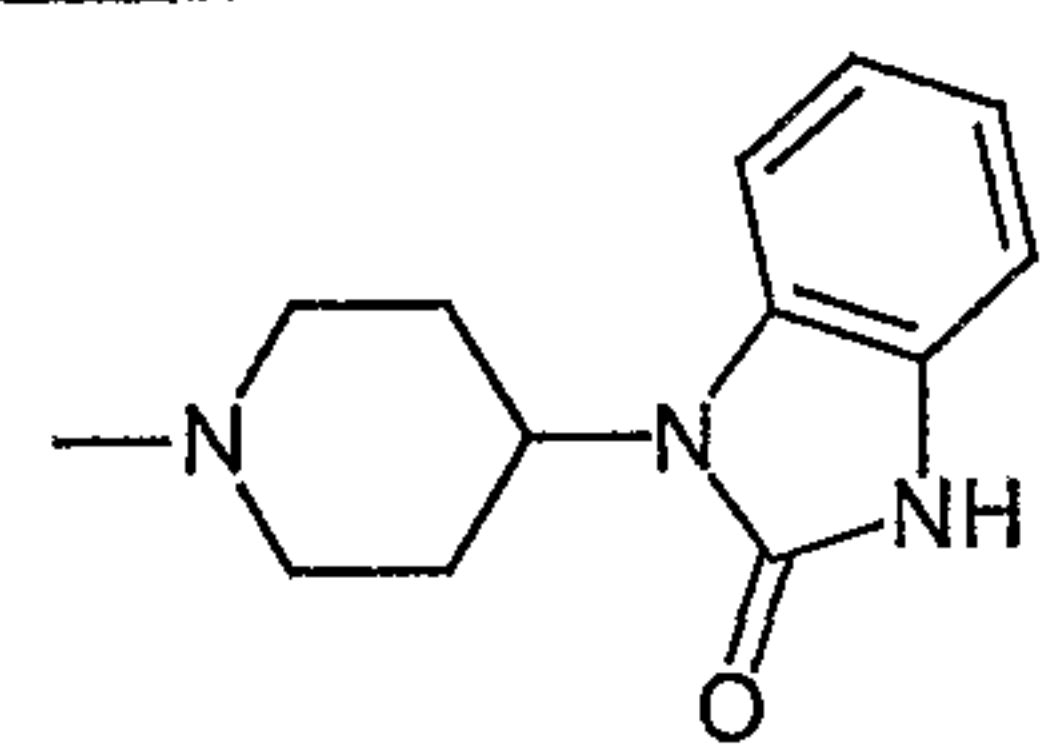
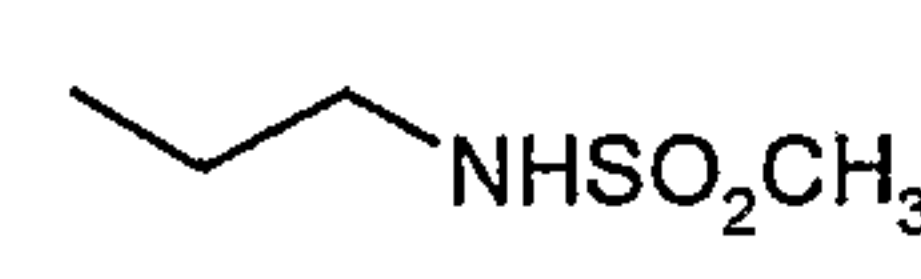
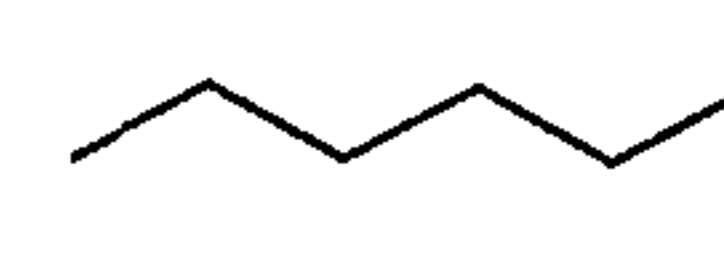
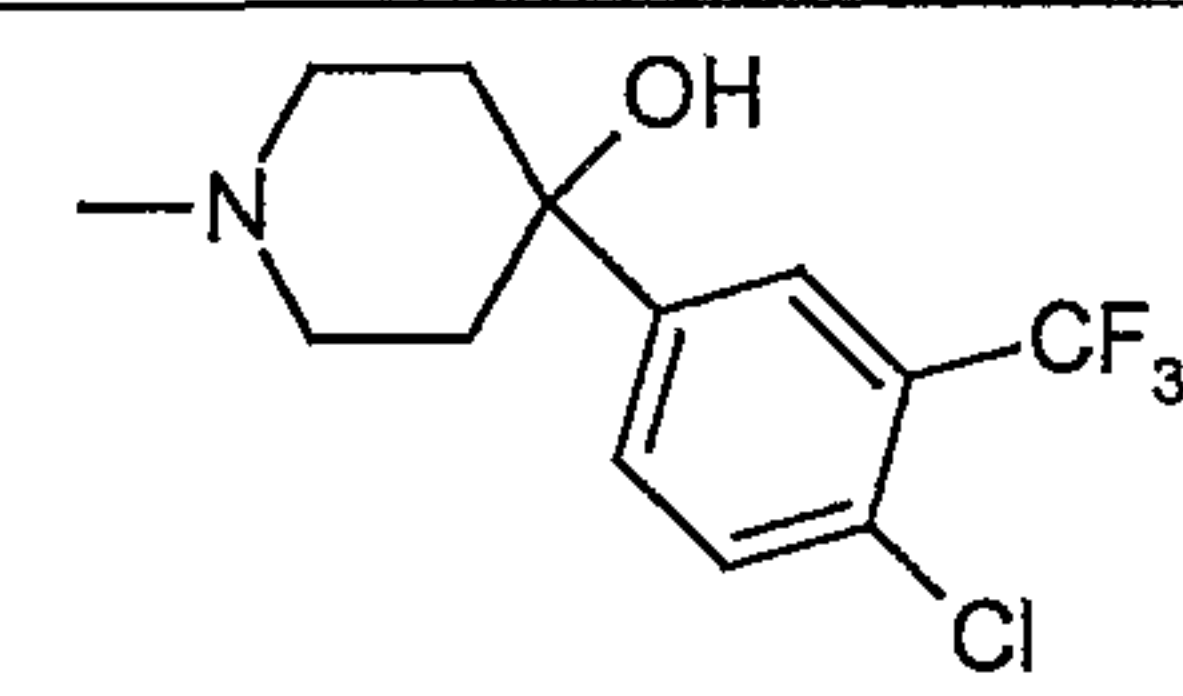
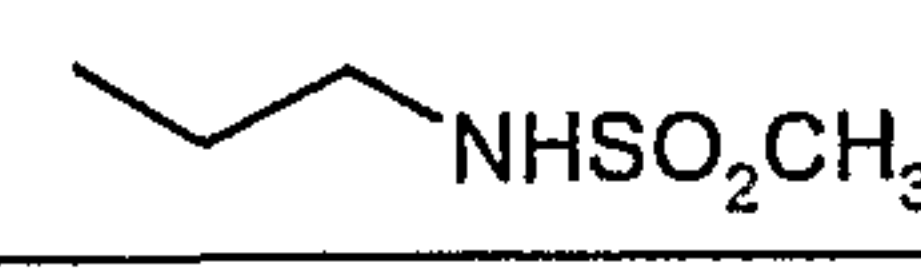
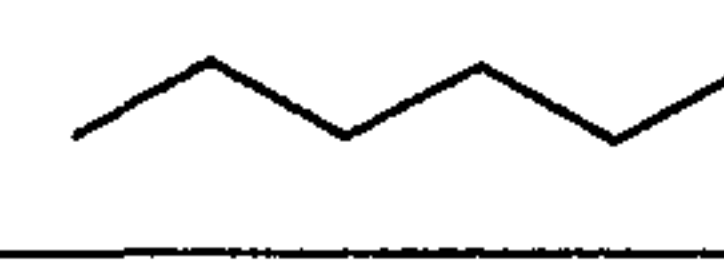
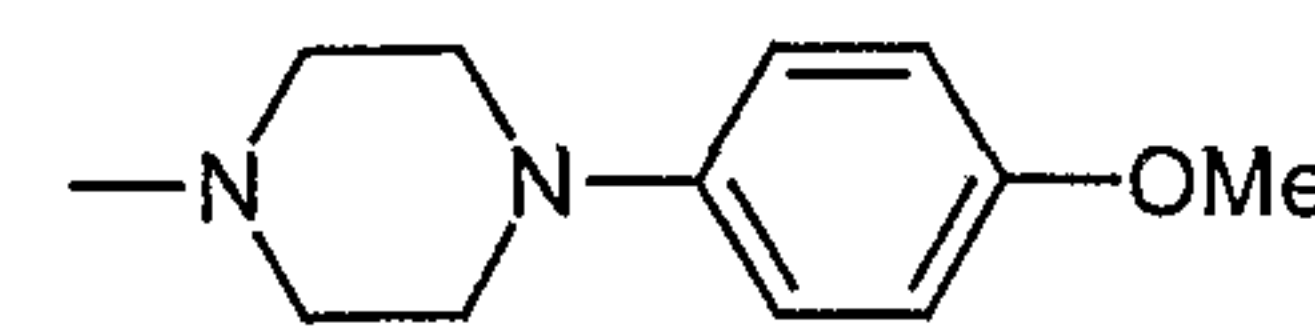
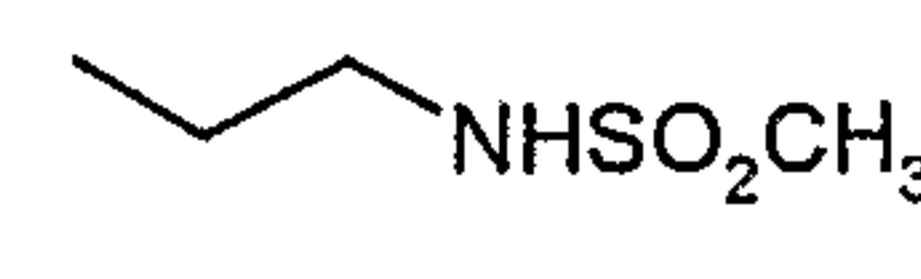
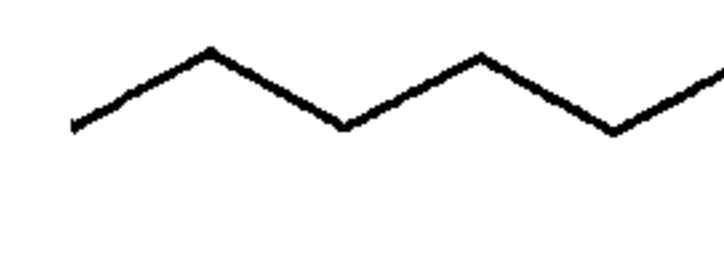
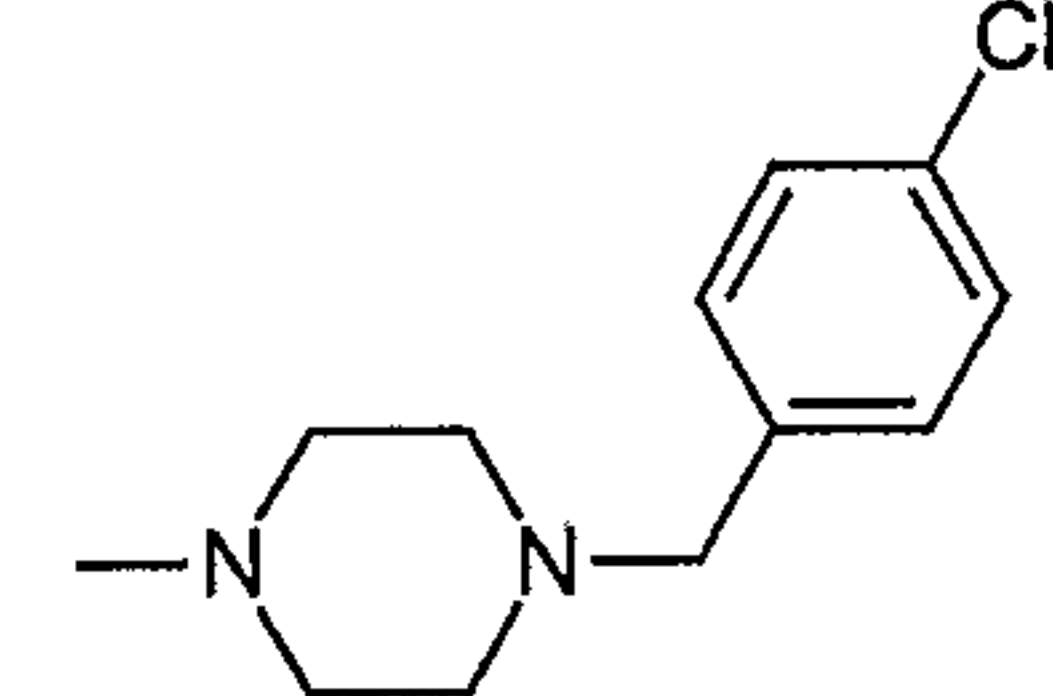
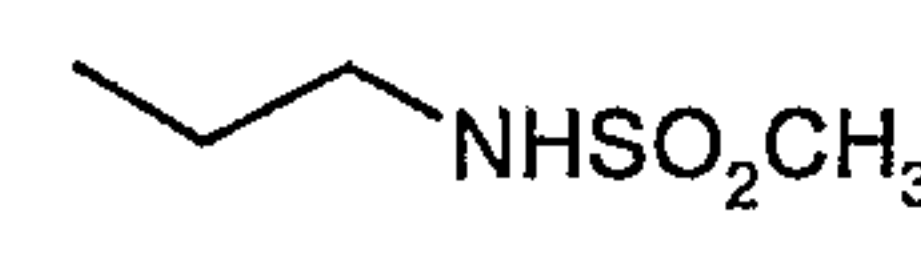
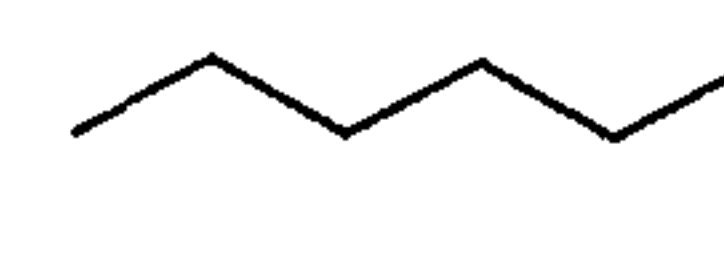
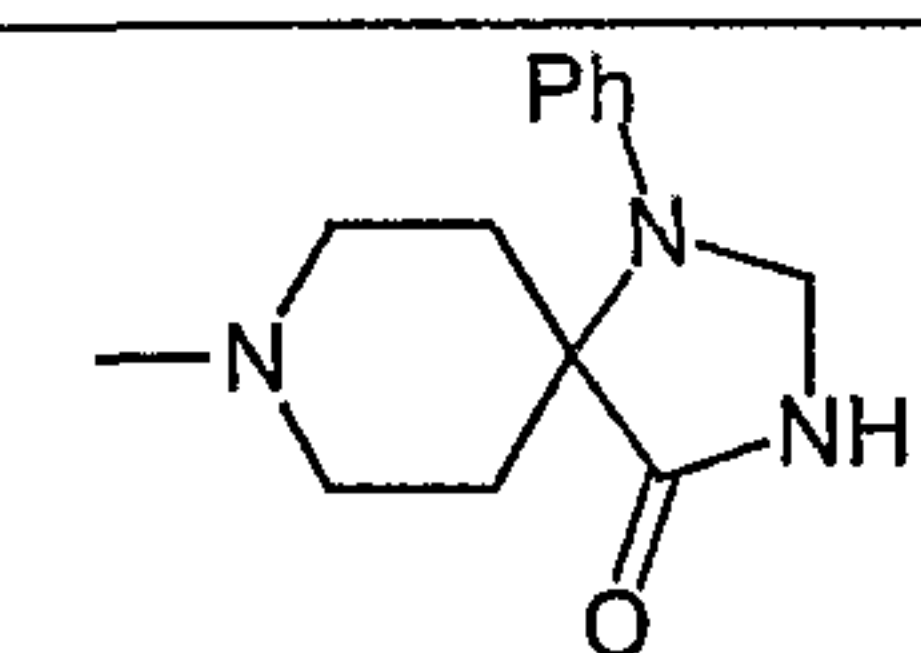
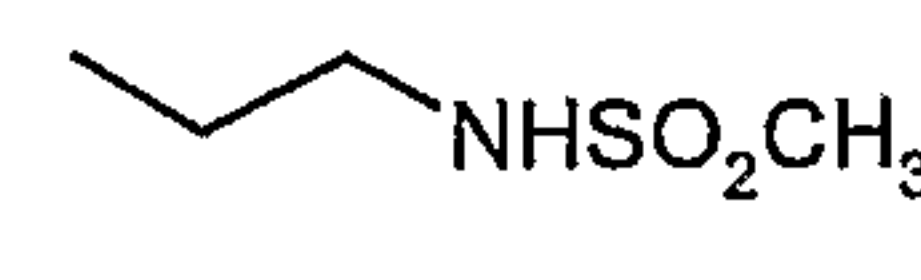
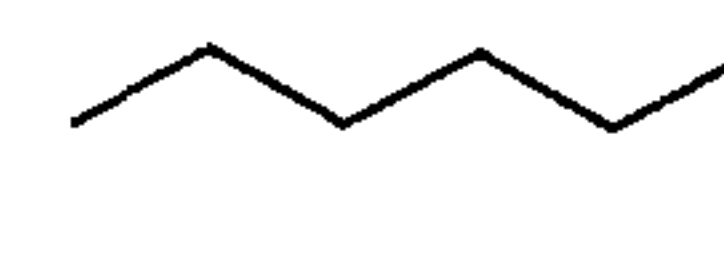
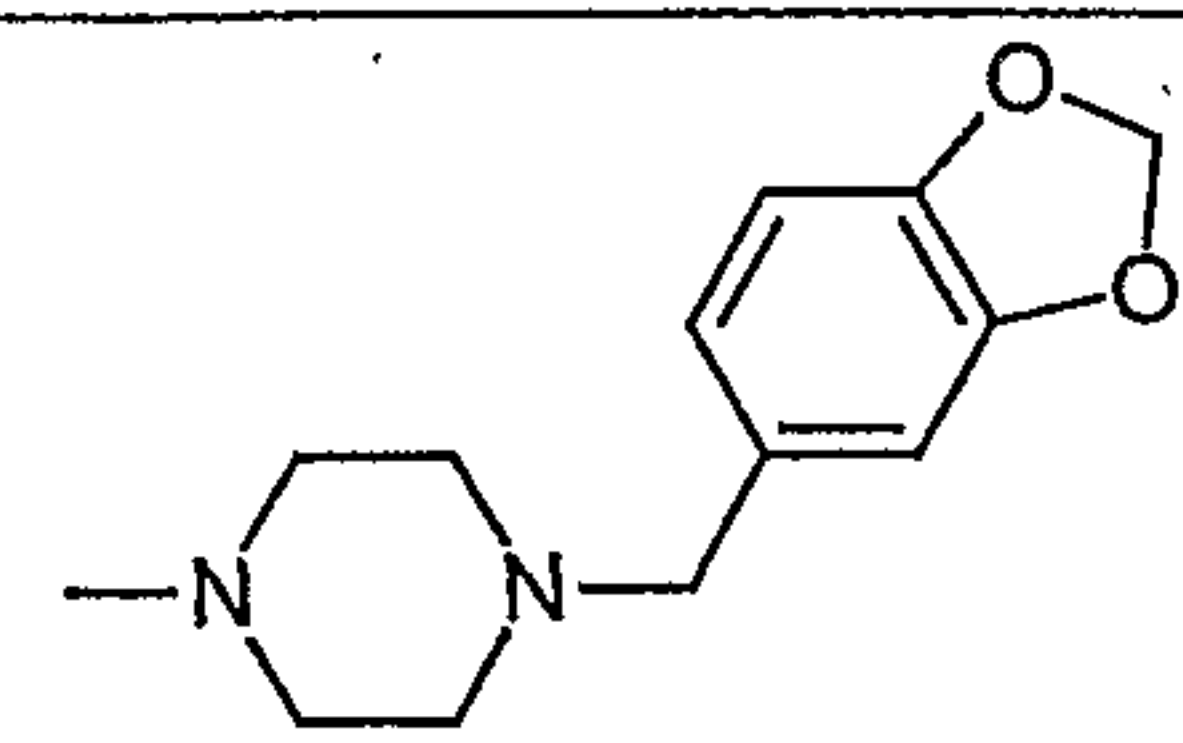
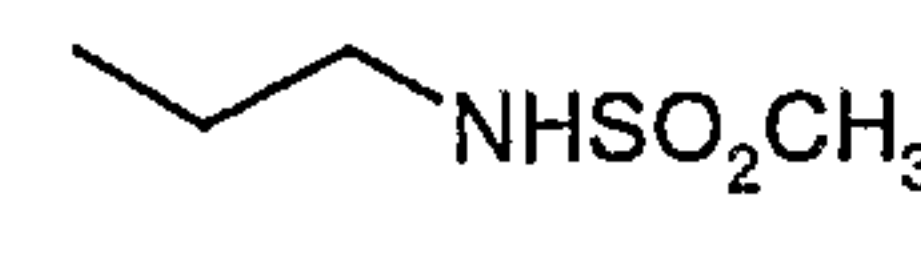
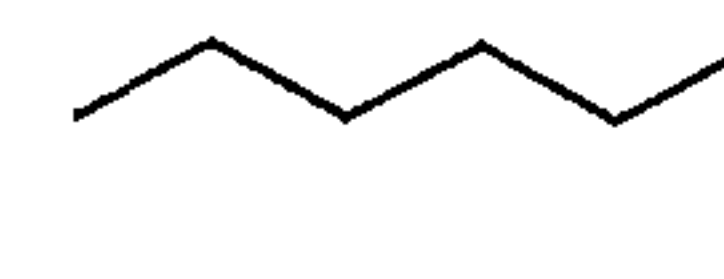
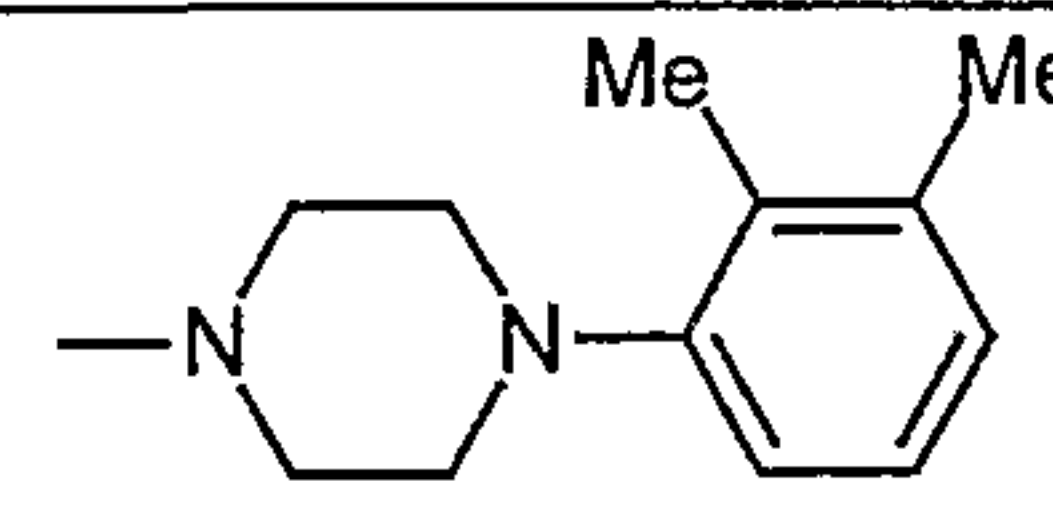
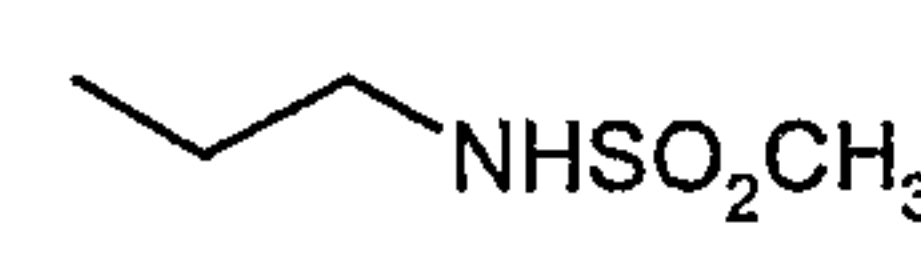
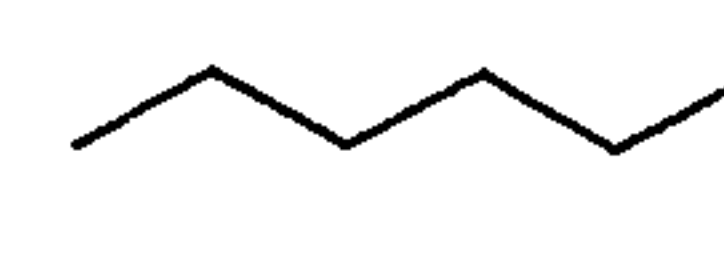
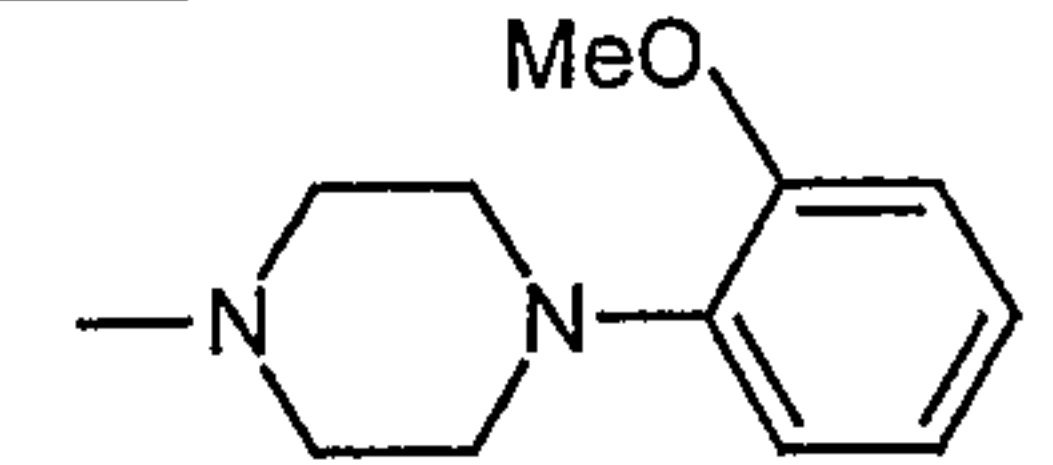
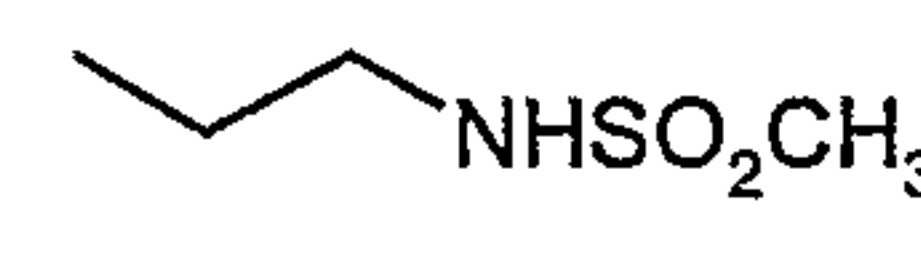
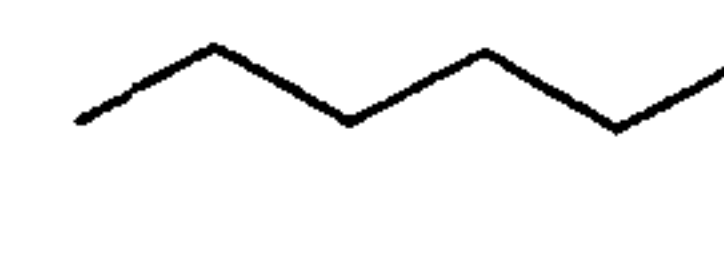
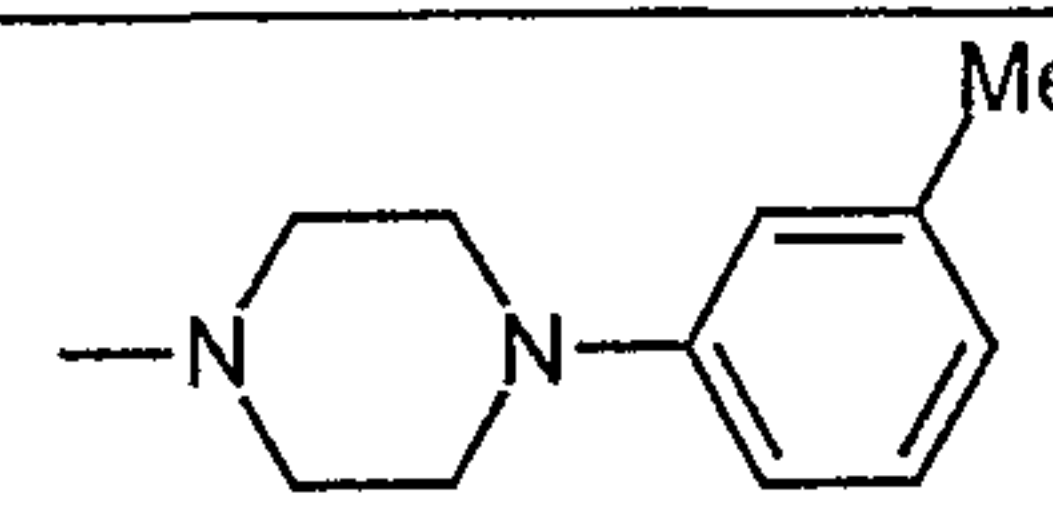
Comp. No	-R ¹	-A-		[M+H] ⁺
129				540
130				527
131				589
132				502
133				520
134				541
135				530
136				500
137				502
138				486

Table 3 (continued):

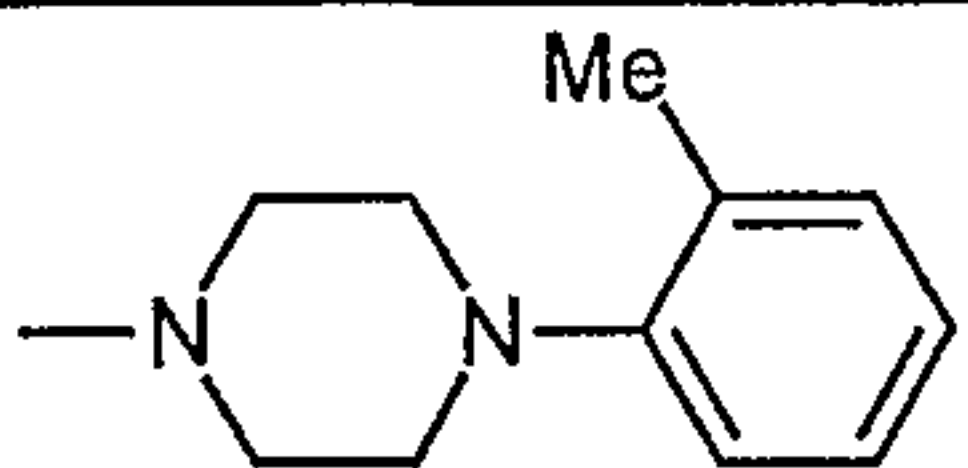
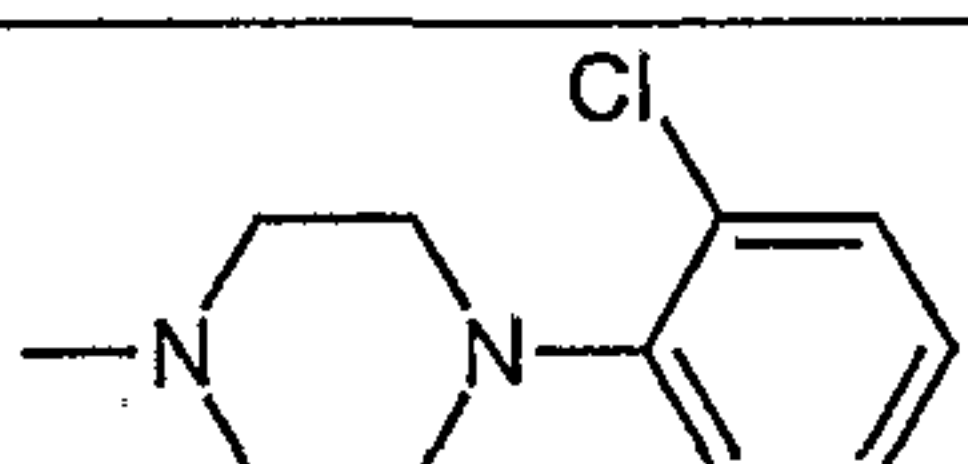
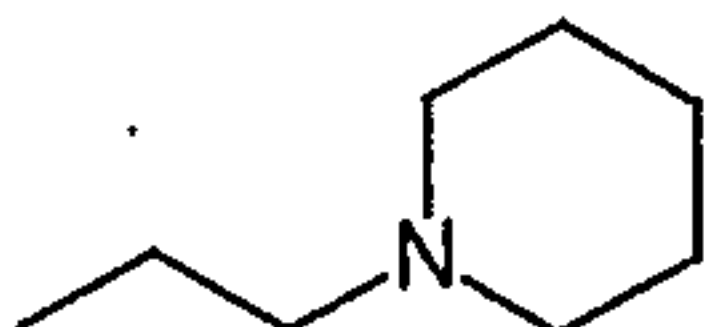
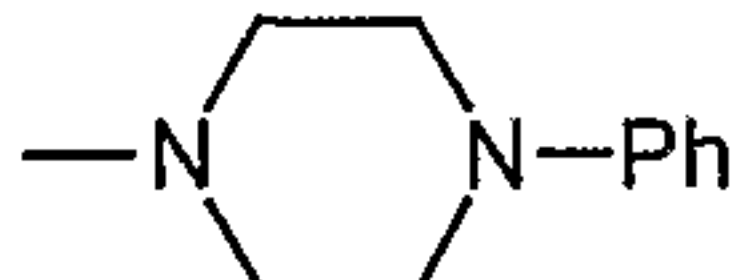
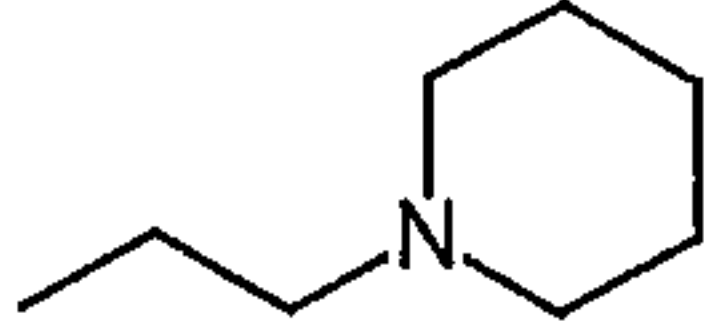
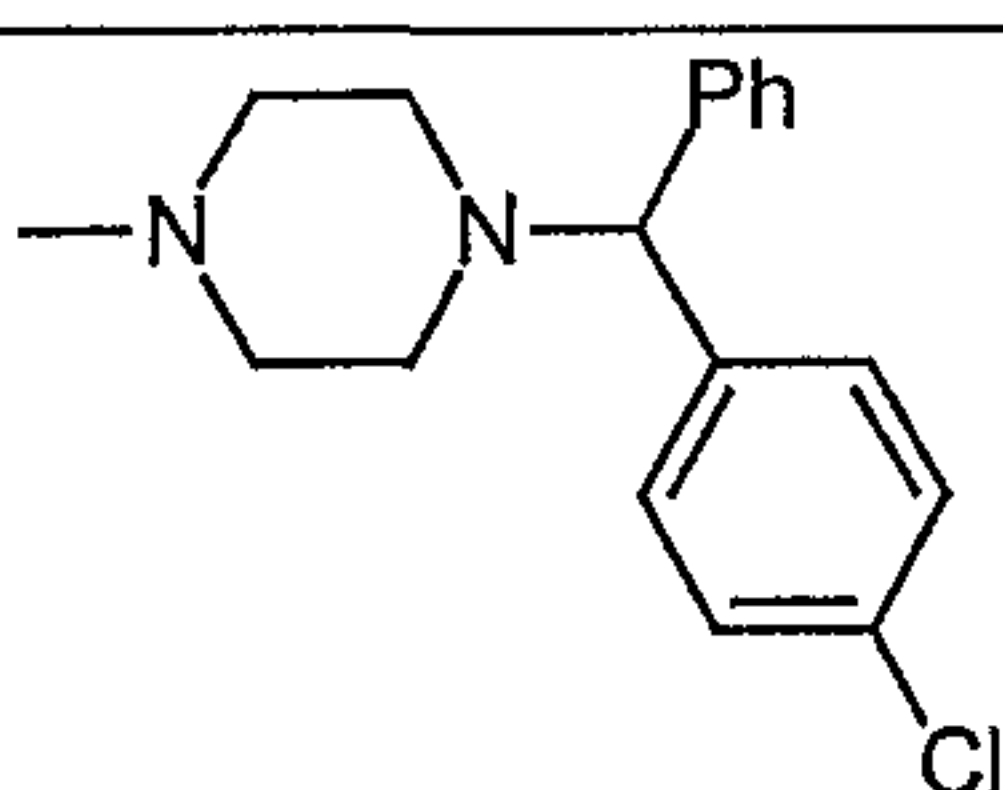
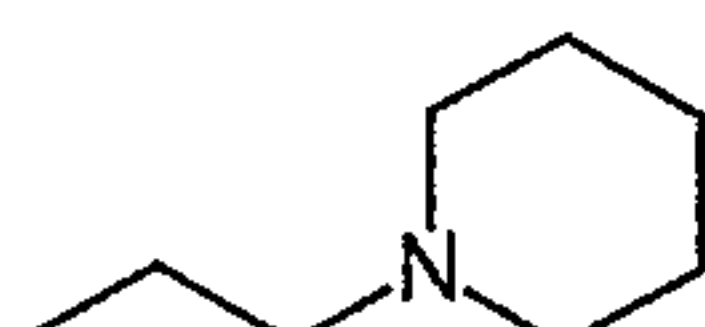
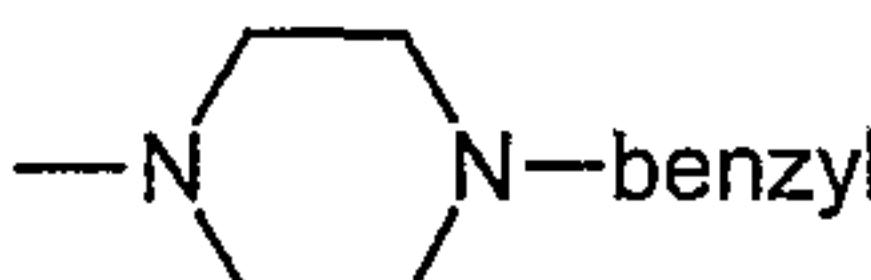
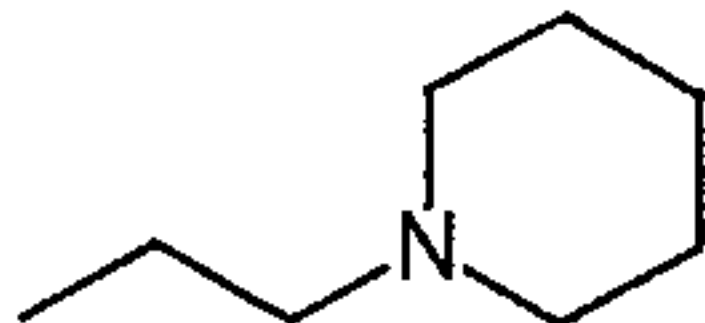
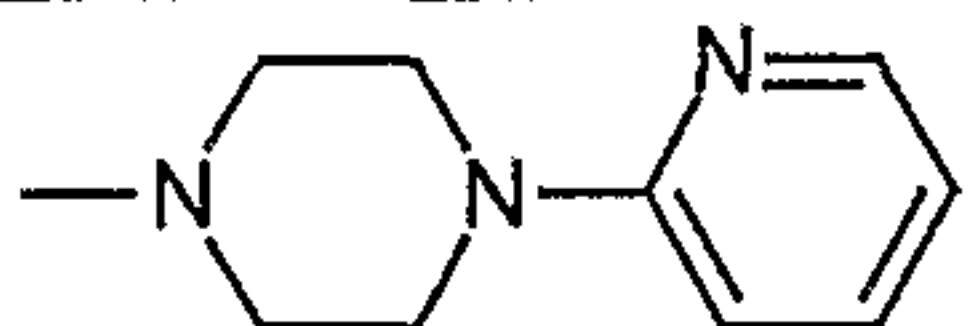
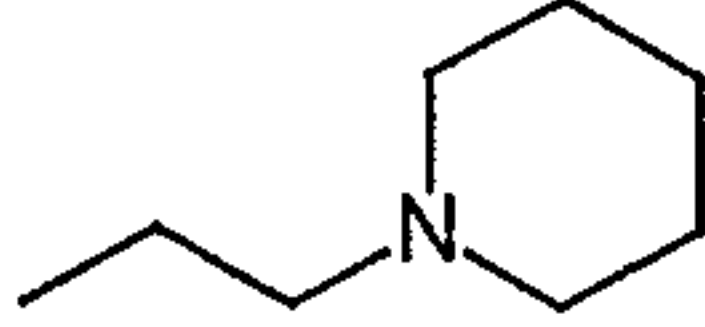
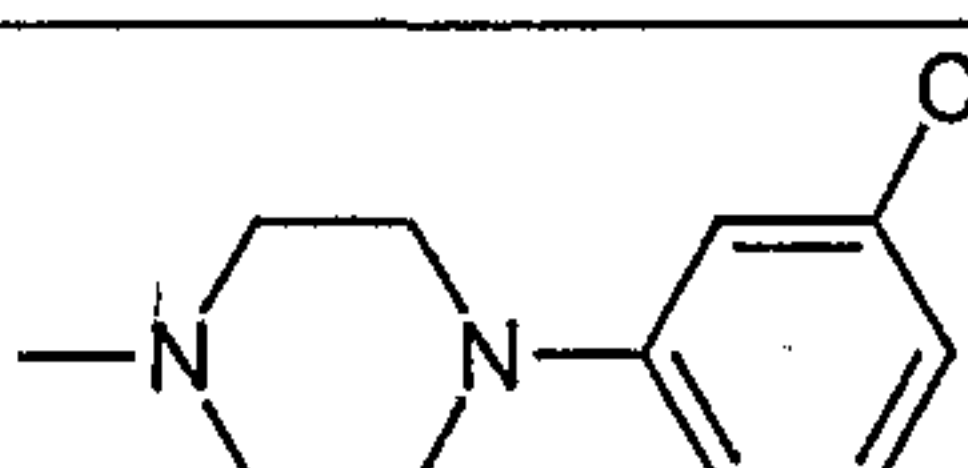
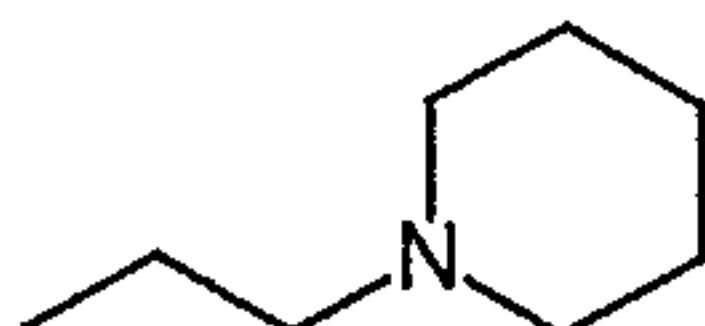
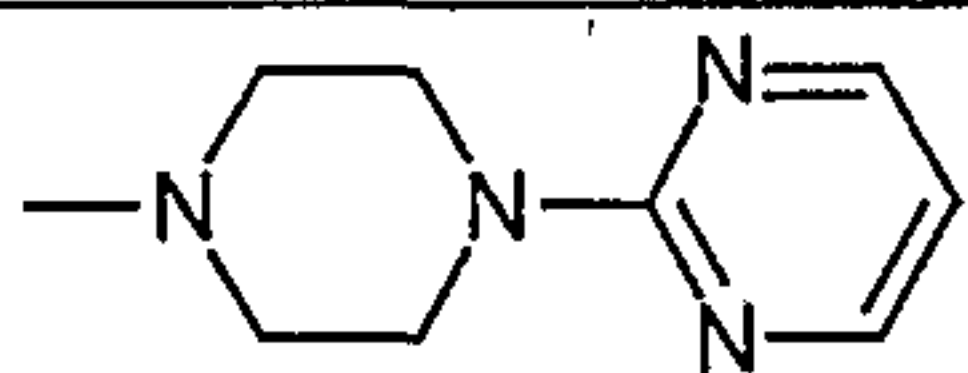
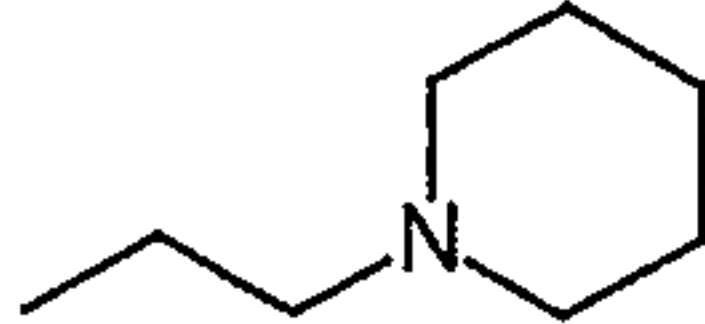
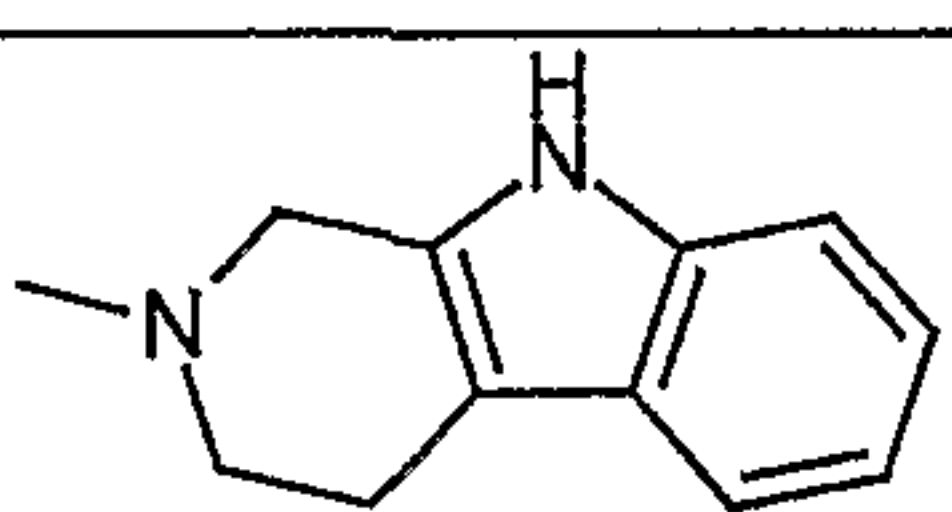
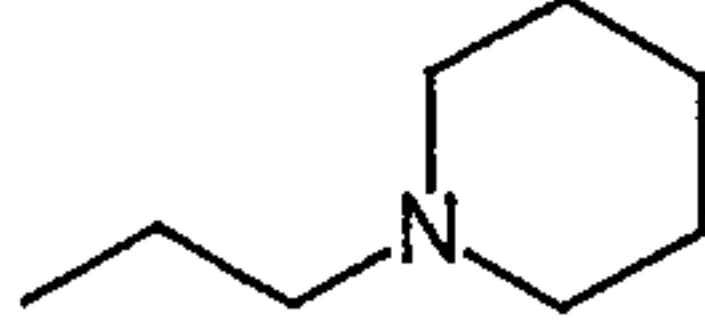
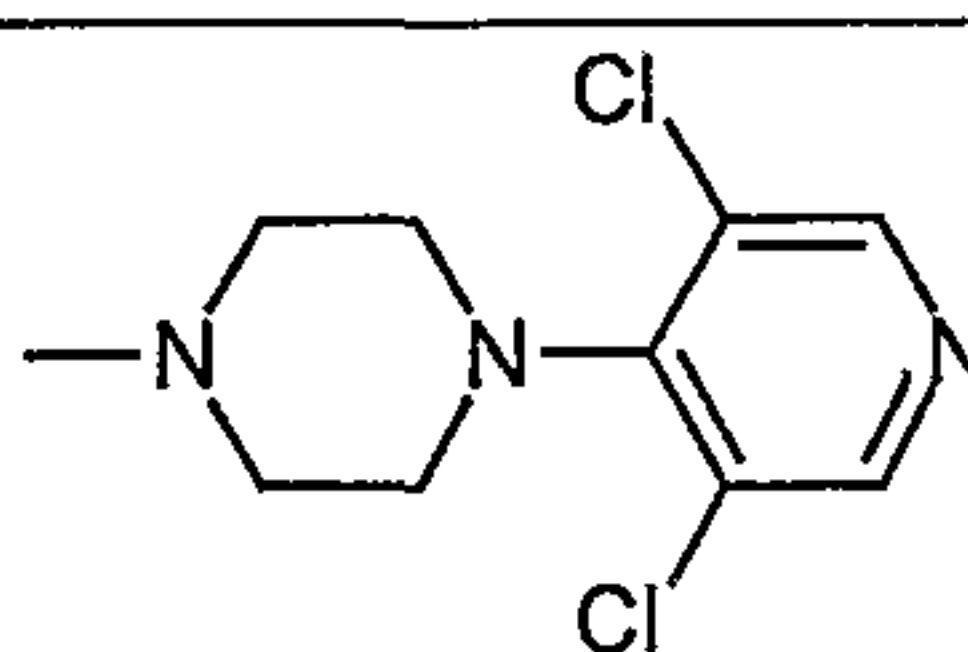
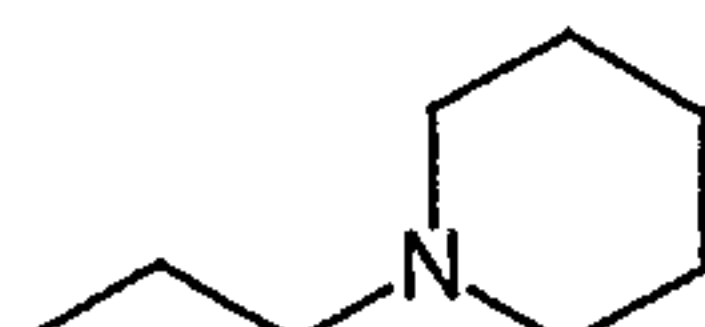
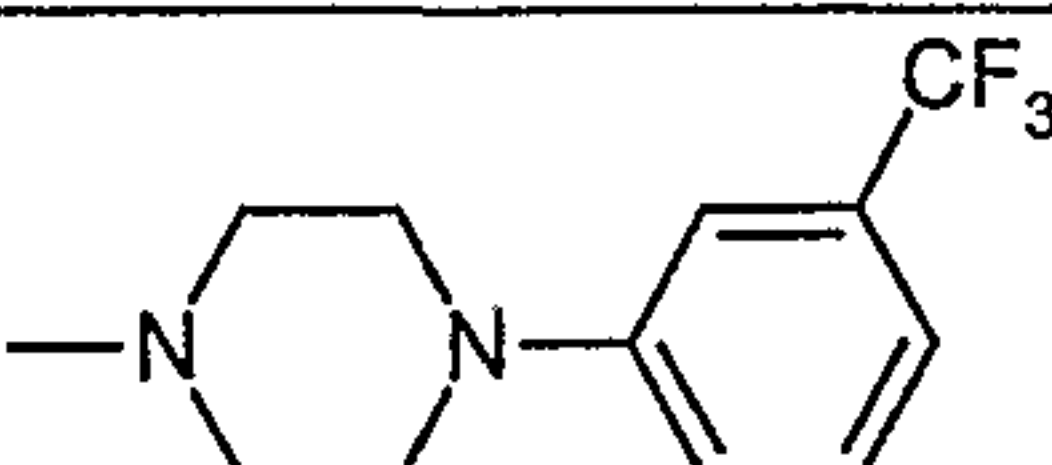
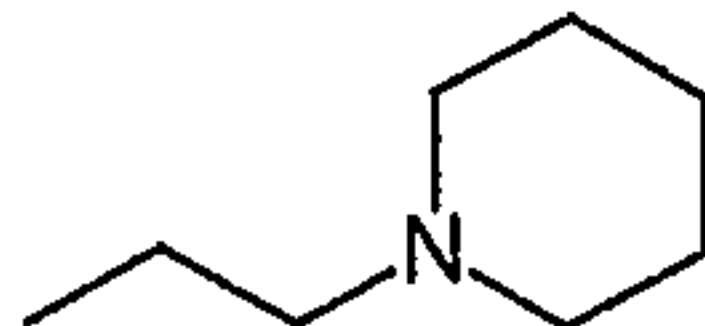
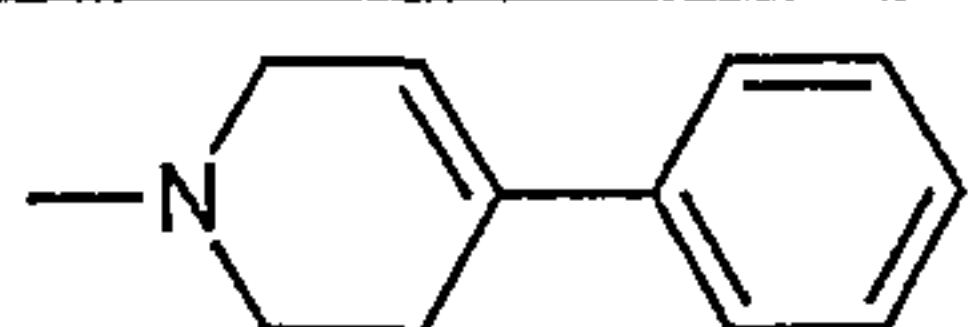
Comp. No	-R ¹	-A-	$\begin{array}{c} \text{R}^2 \\ \\ \text{---N---} \\ \\ \text{R}^3 \end{array}$	[M+H] ⁺
139				486
140				506
141				434
142				558
143				448
144				435
145				468
146				436
147				444
148				503
149				502
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Table 3 (continued):

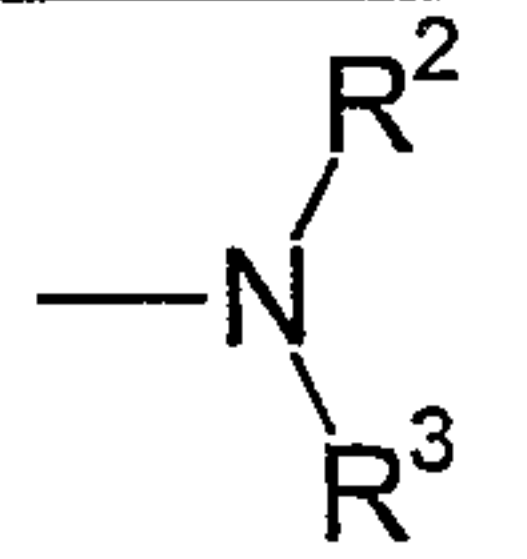
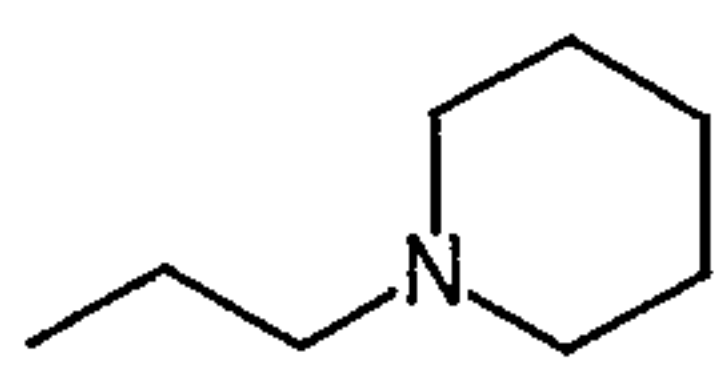
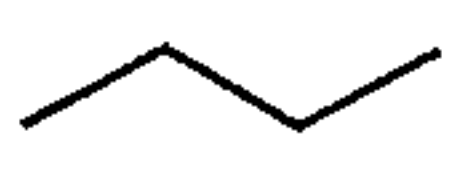
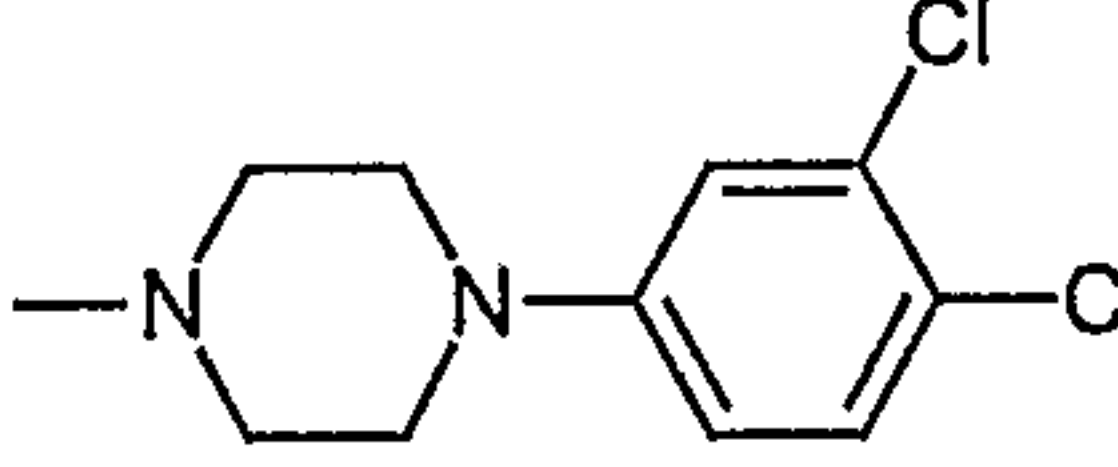
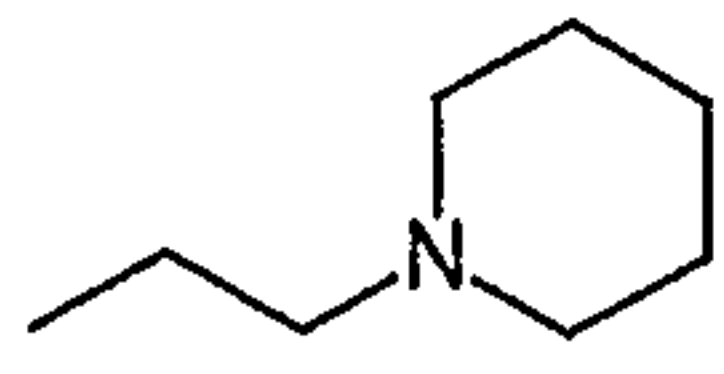
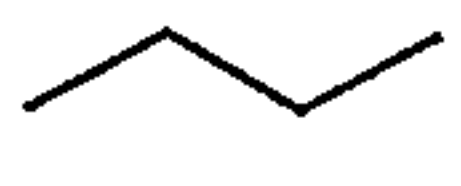
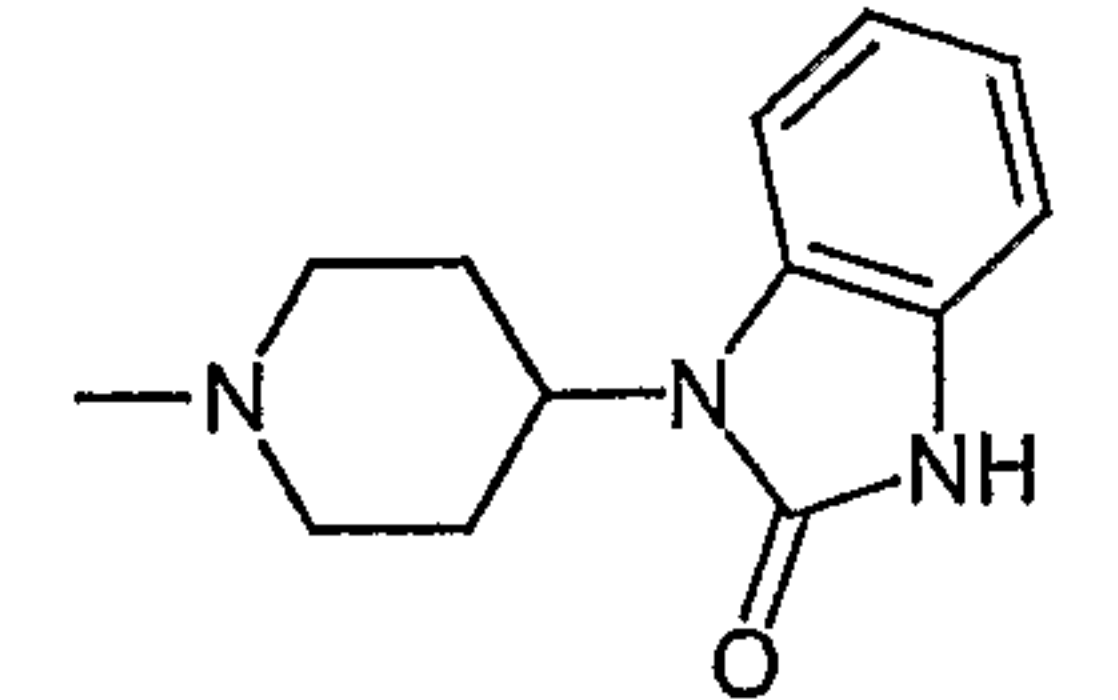
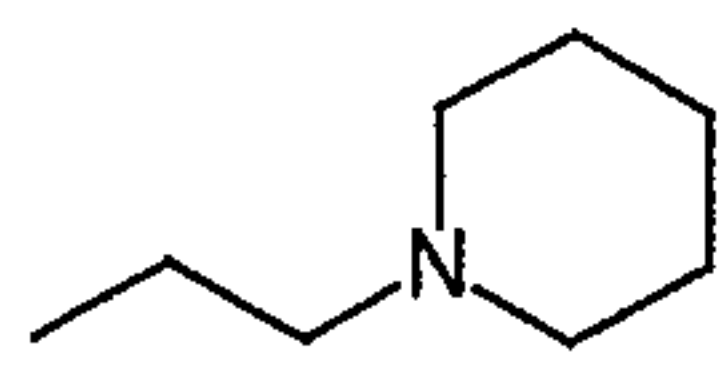
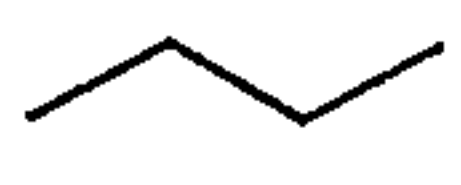
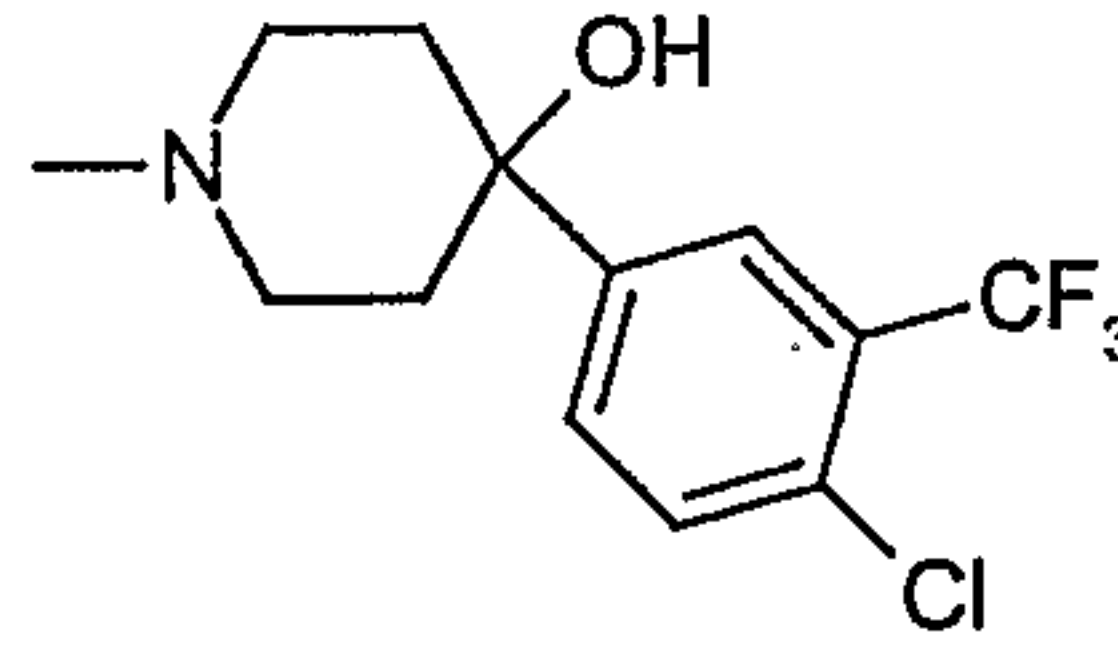
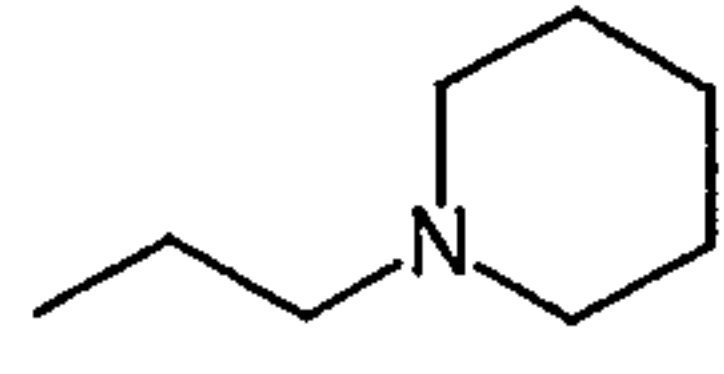
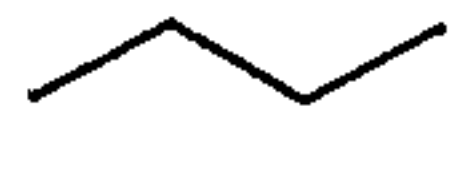
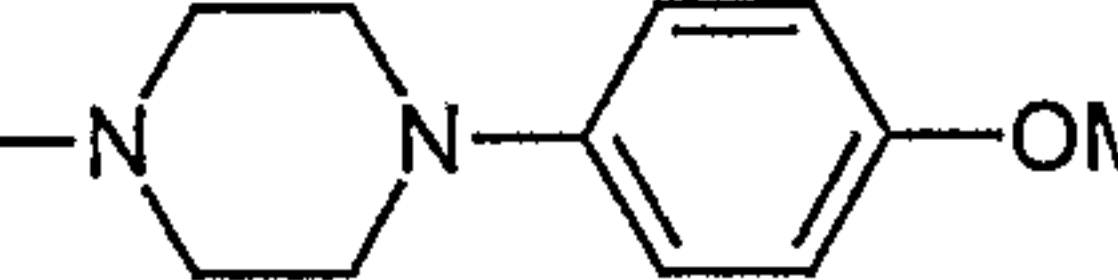
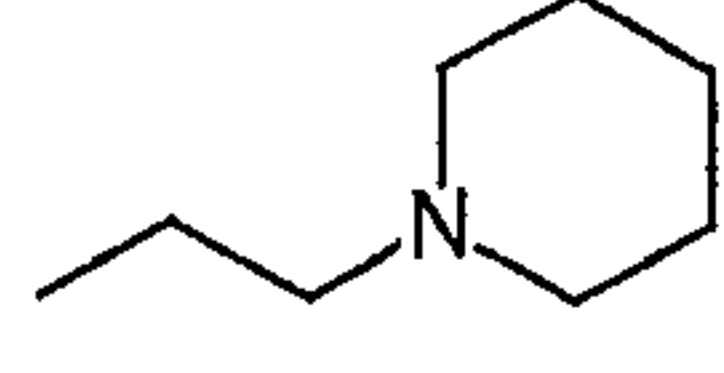
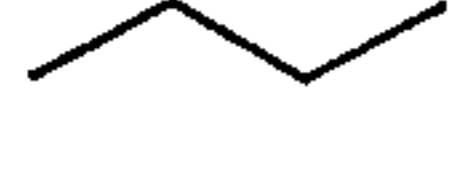
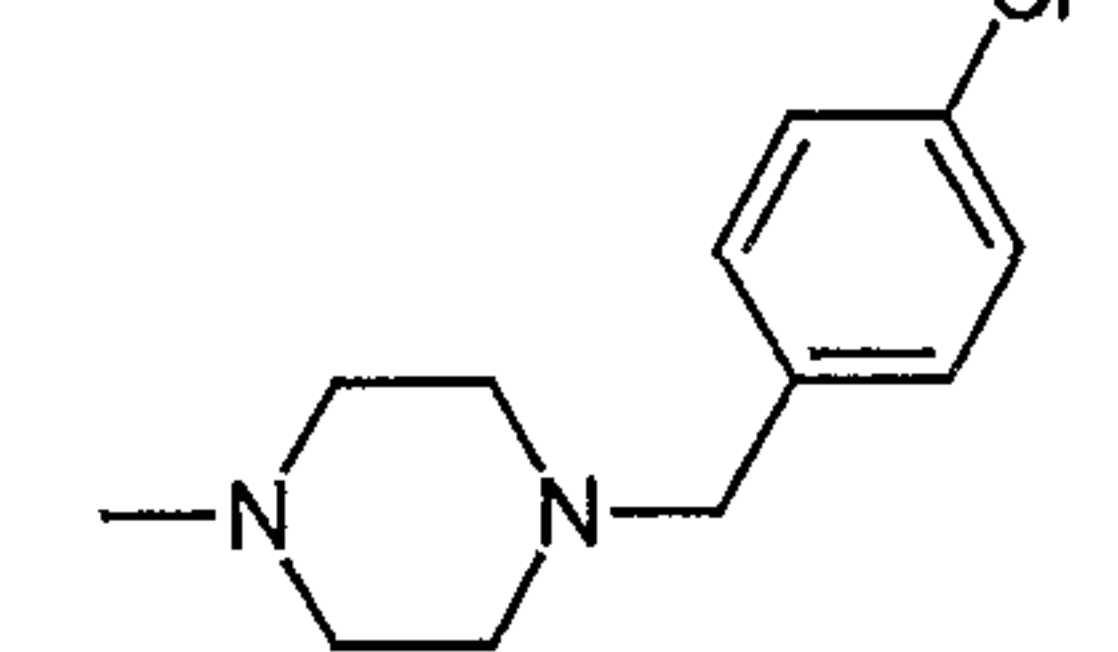
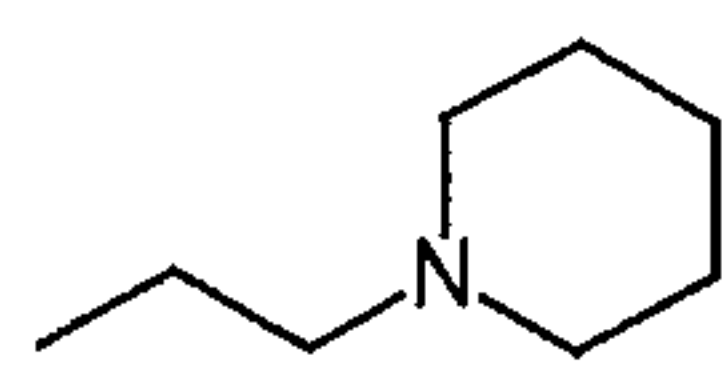
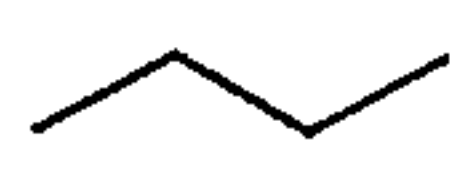
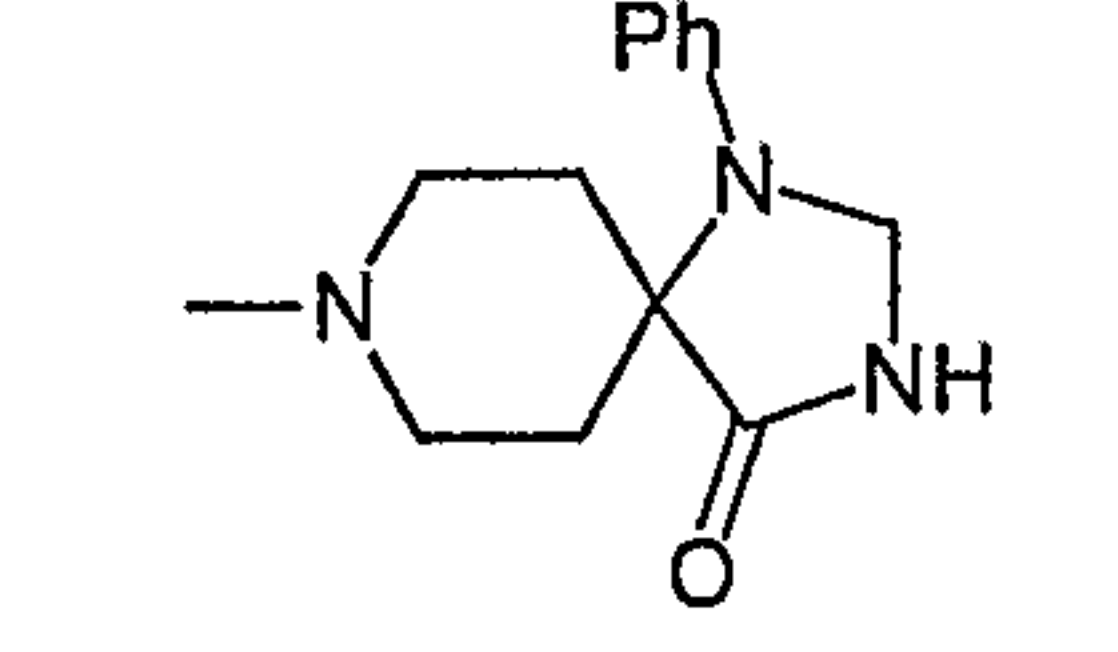
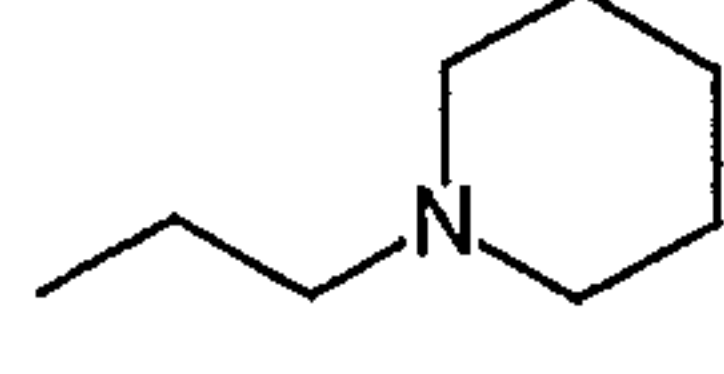
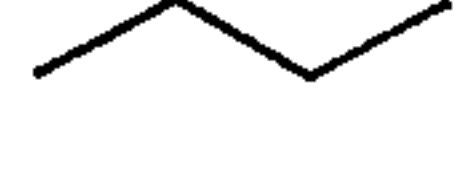
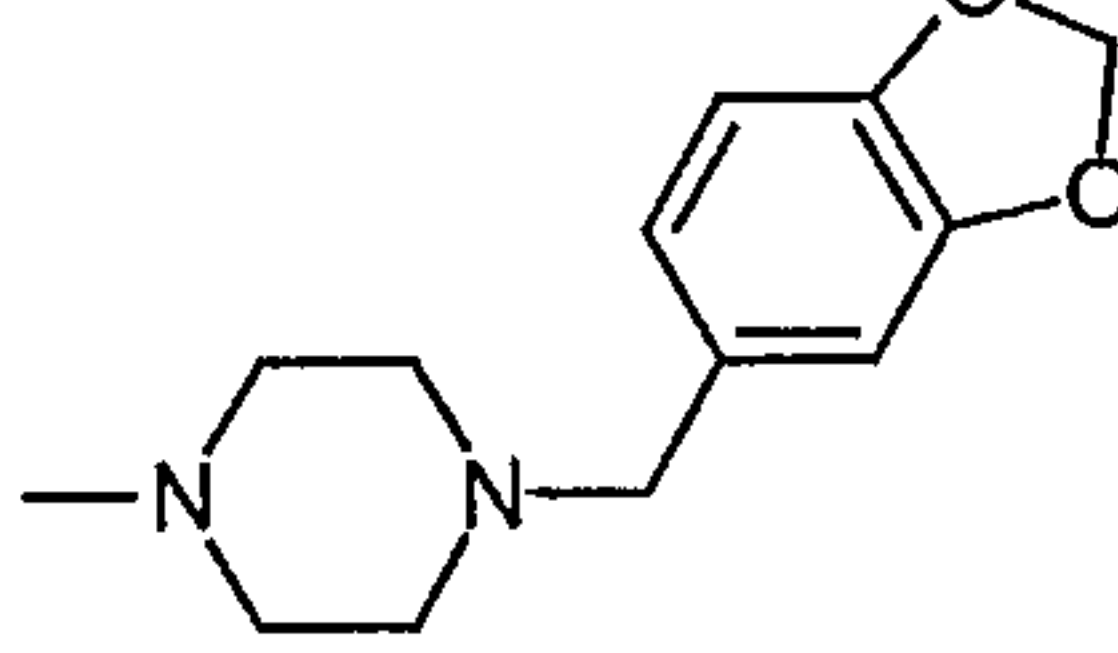
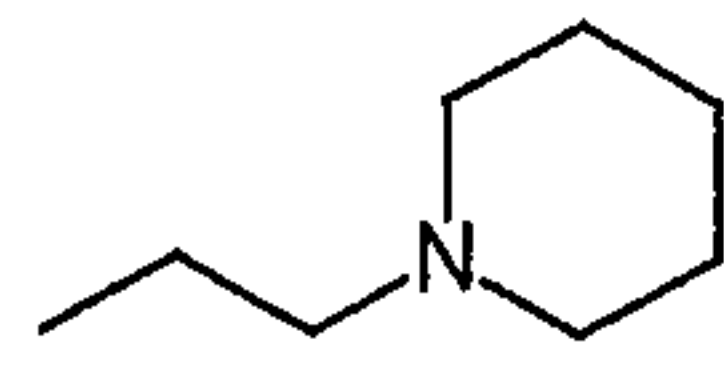
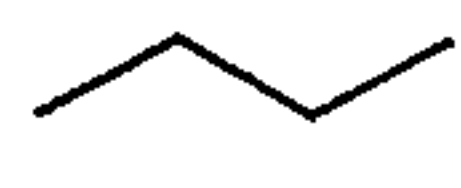
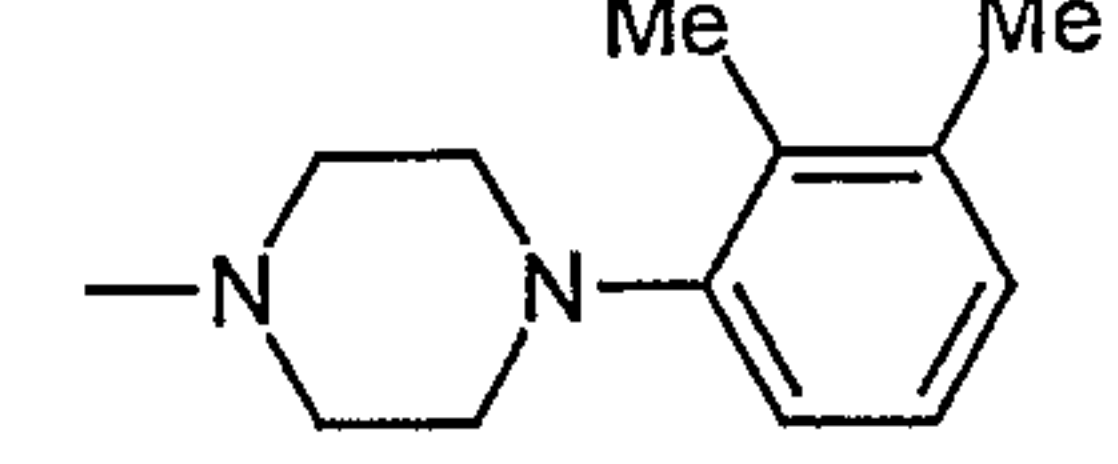
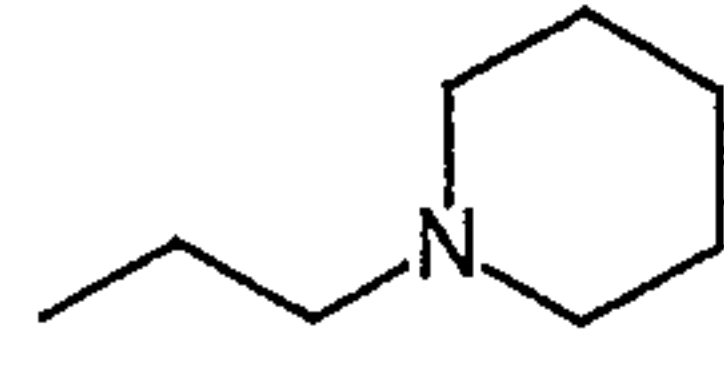
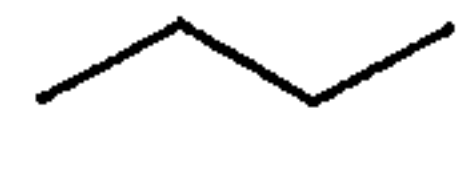
Comp. No	-R ¹	-A-		[M+H] ⁺
151				502
152				489
153				551
154				464
155				482
156				503
157				492
158				462
159				464

Table 3: (continued)

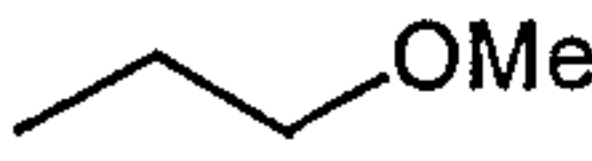
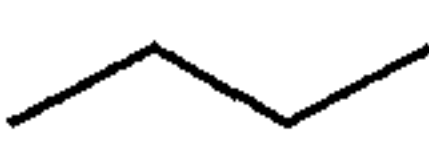
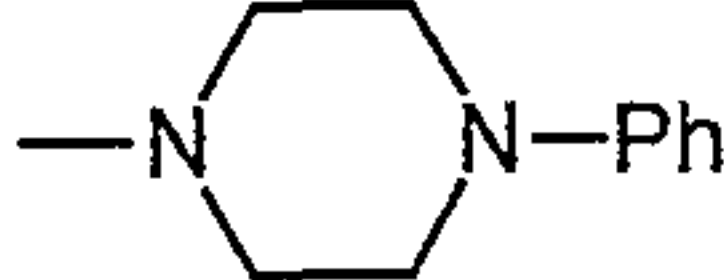
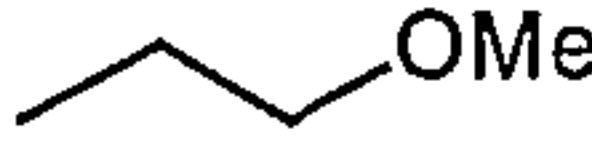
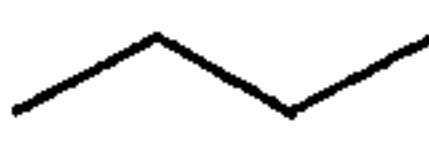
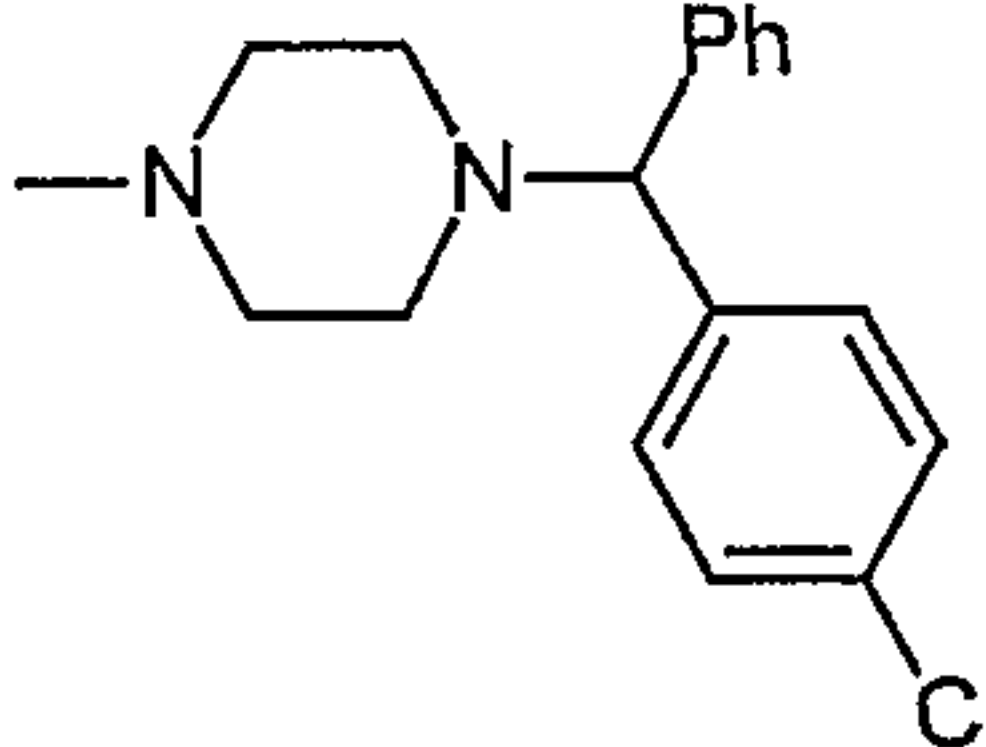
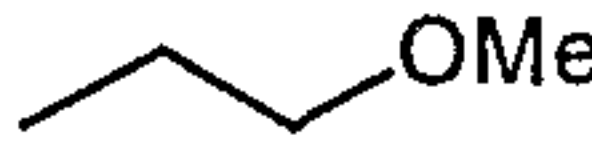
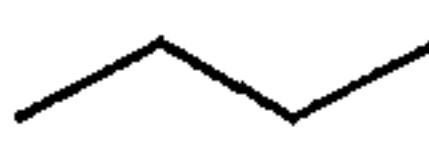
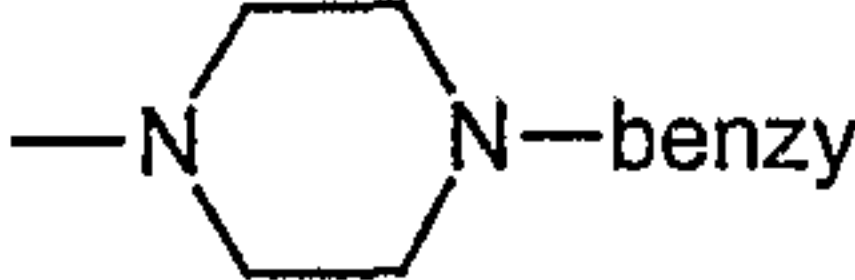
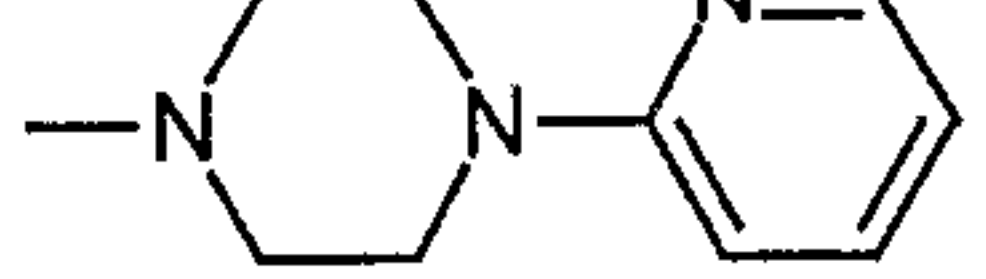
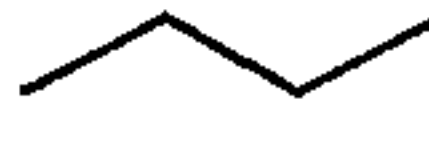
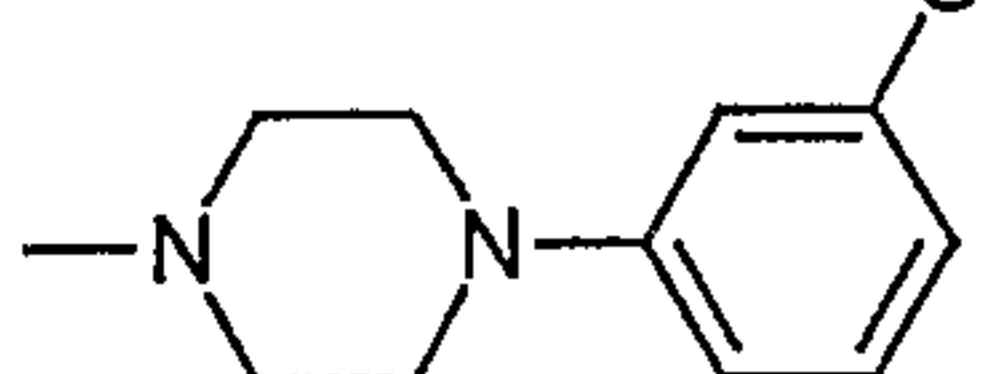
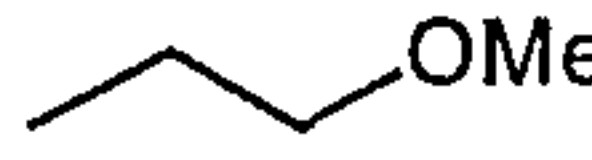
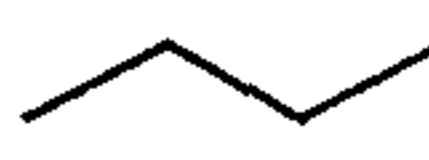
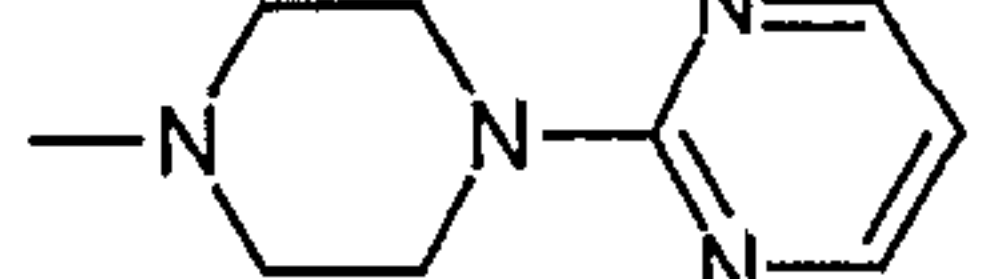
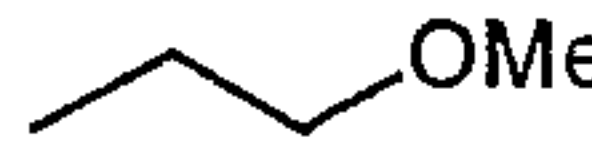
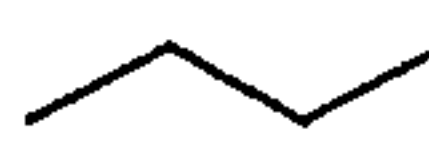
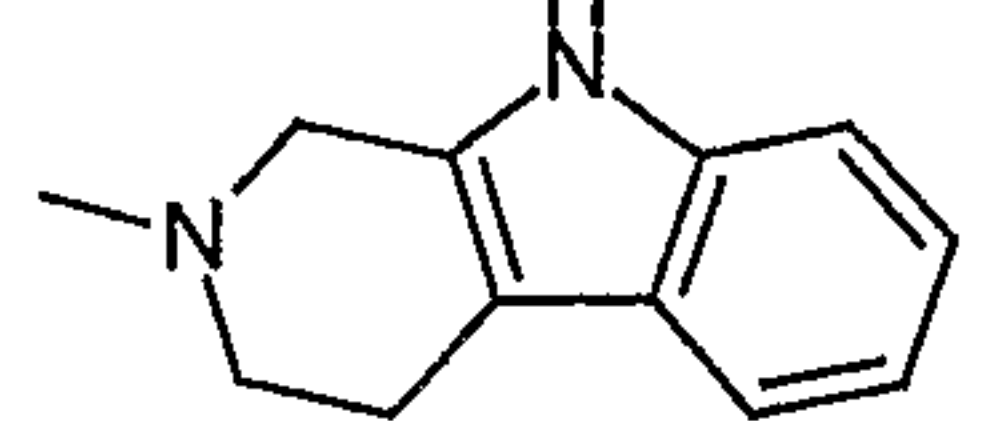
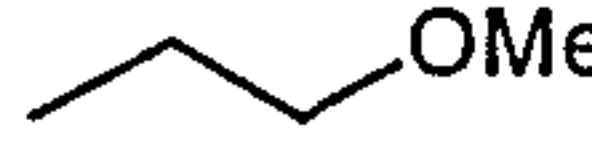
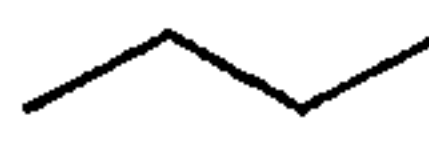
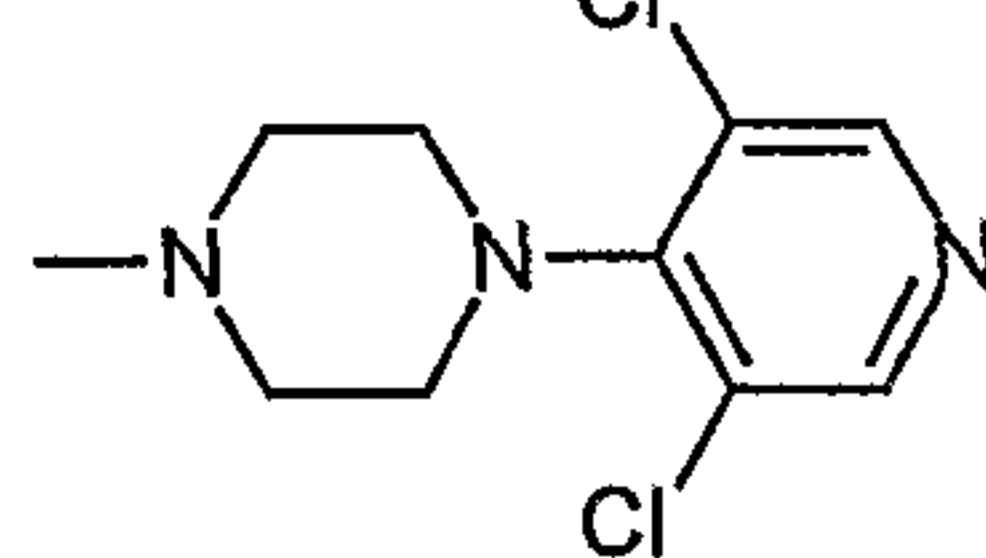
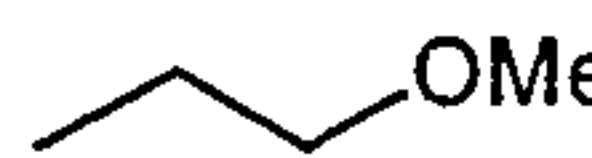
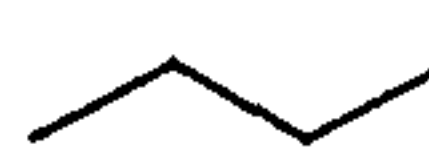
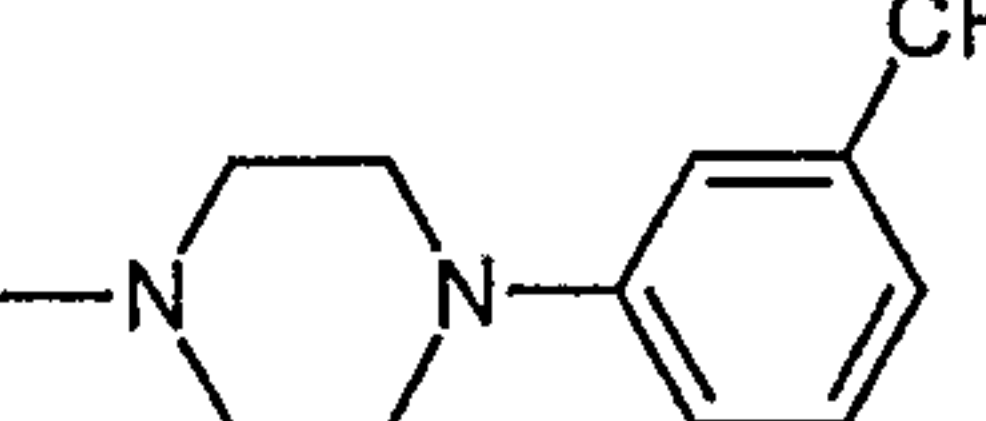
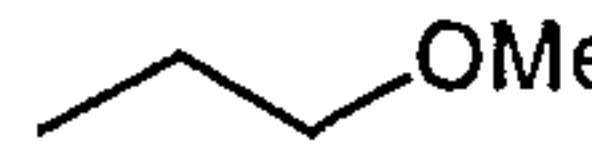
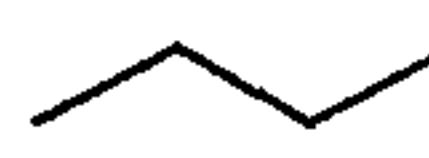
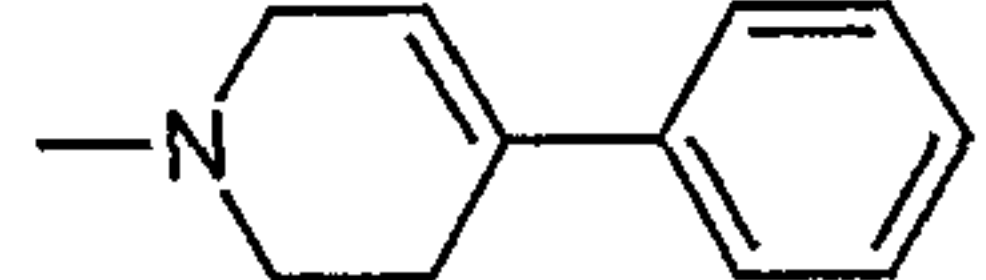
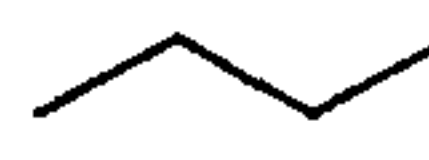
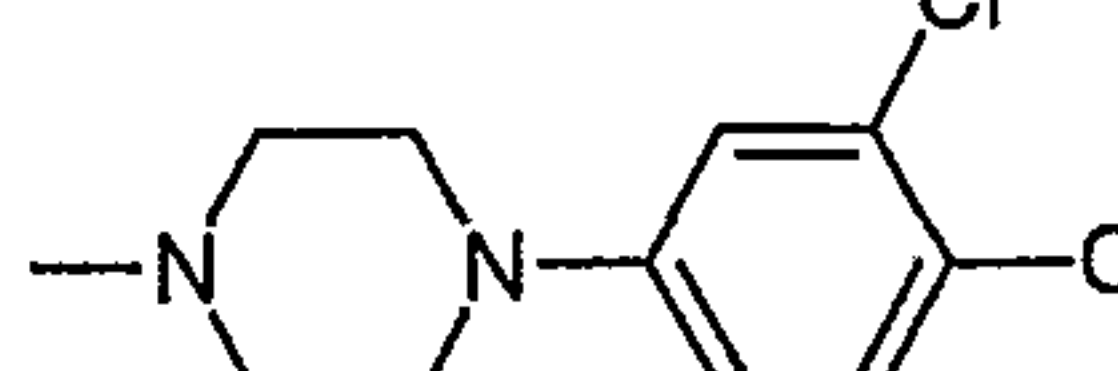
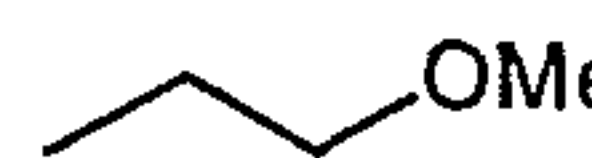
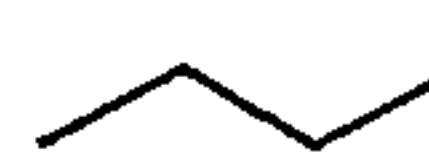
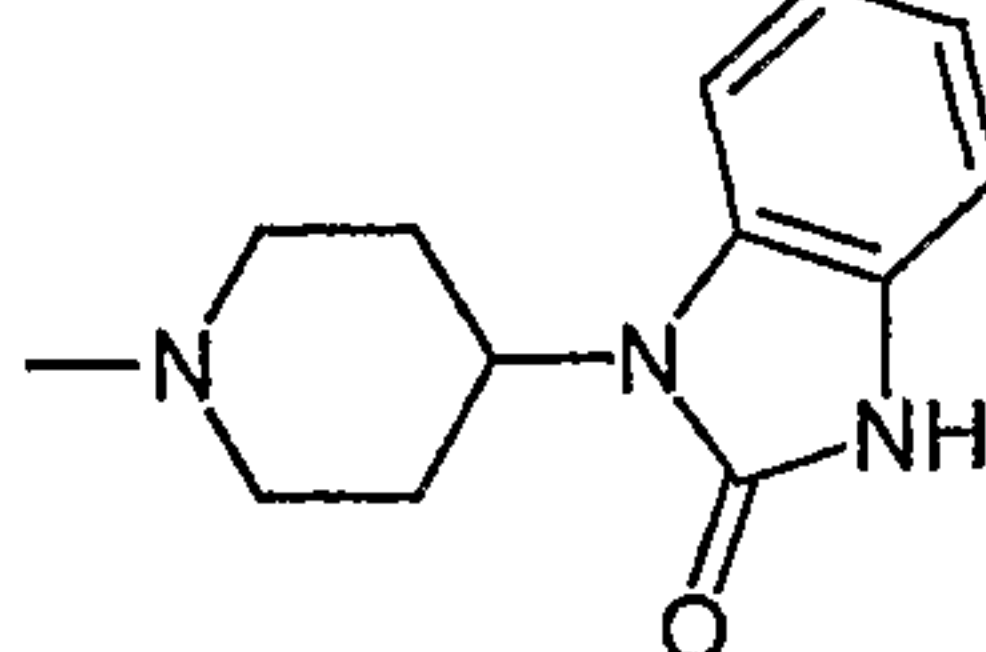
Comp. No	-R ¹	-A-	$\begin{array}{c} \text{R}^2 \\ \\ \text{---N---} \\ \\ \text{R}^3 \end{array}$	[M+H] ⁺
160				381
161				505
162				395
163				382
164				415
165				383
166				391
167				450
168				449
169				378
170				449
171				436

Table 3 (continued):

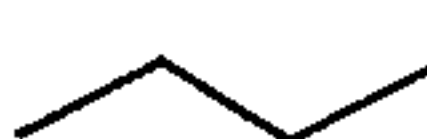
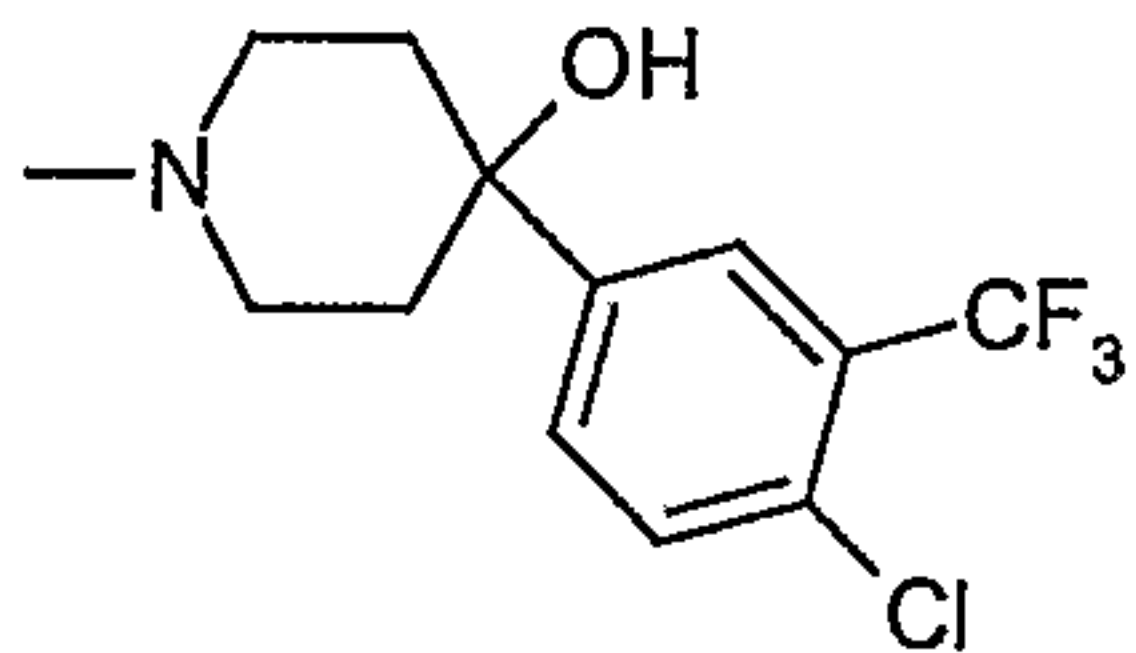
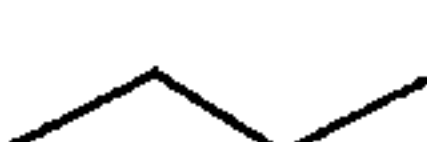
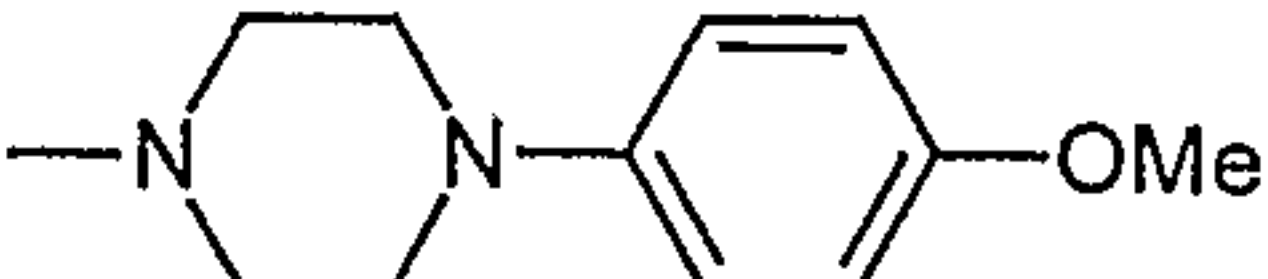
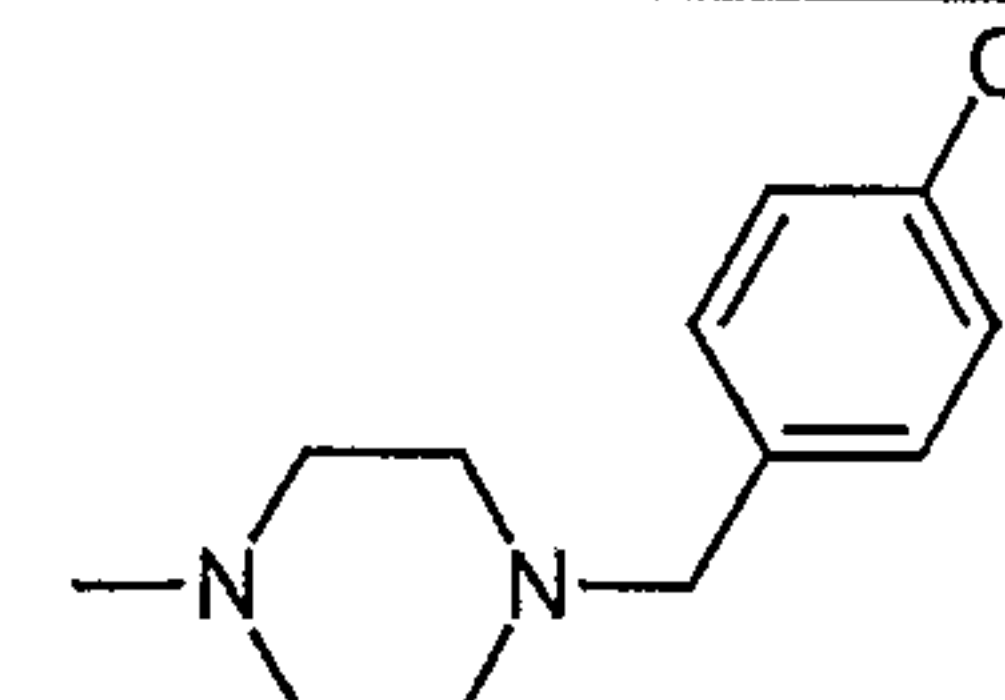
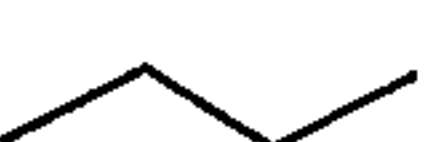
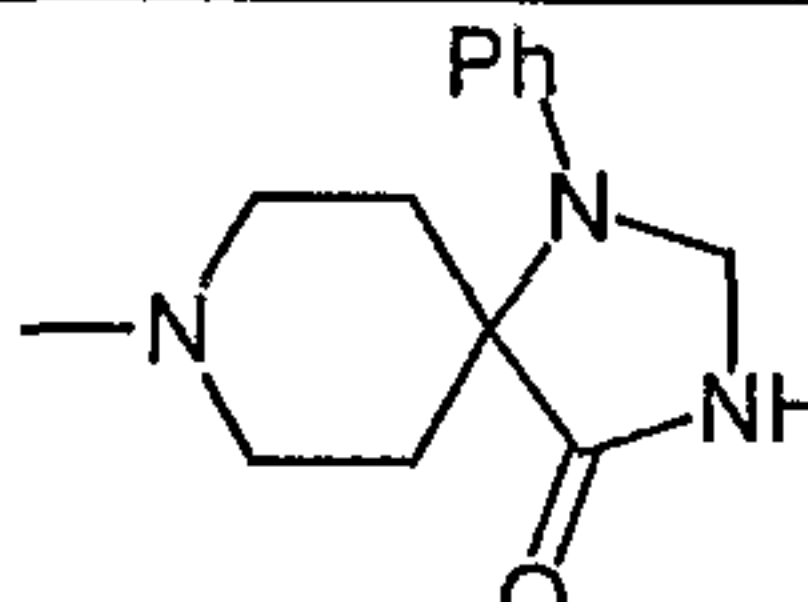
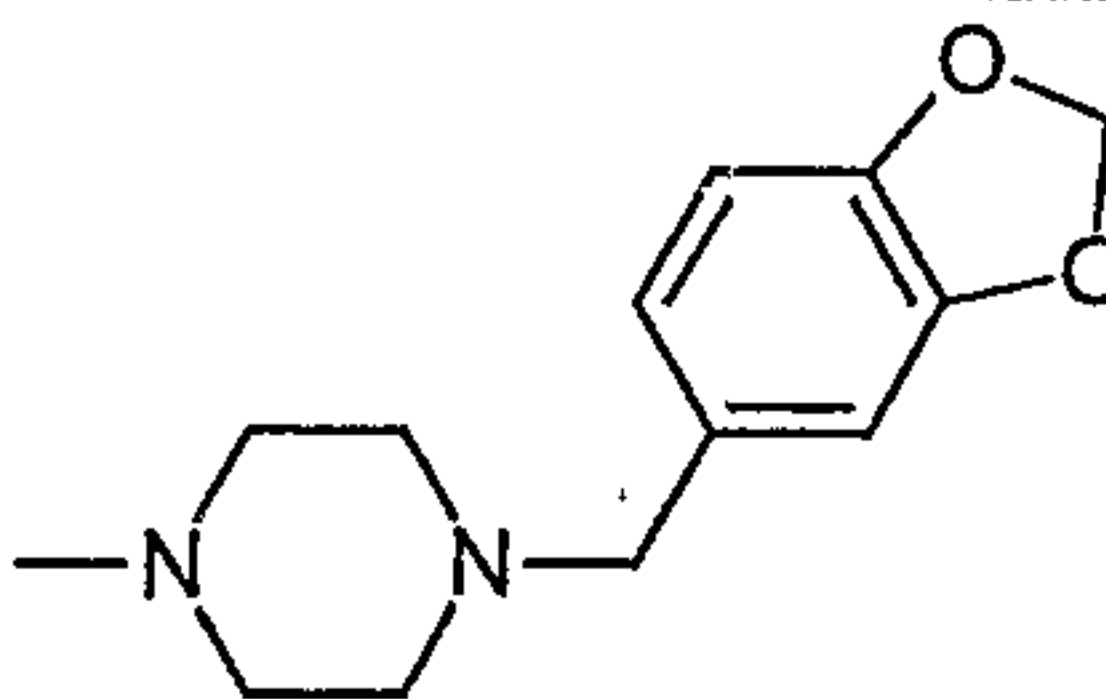
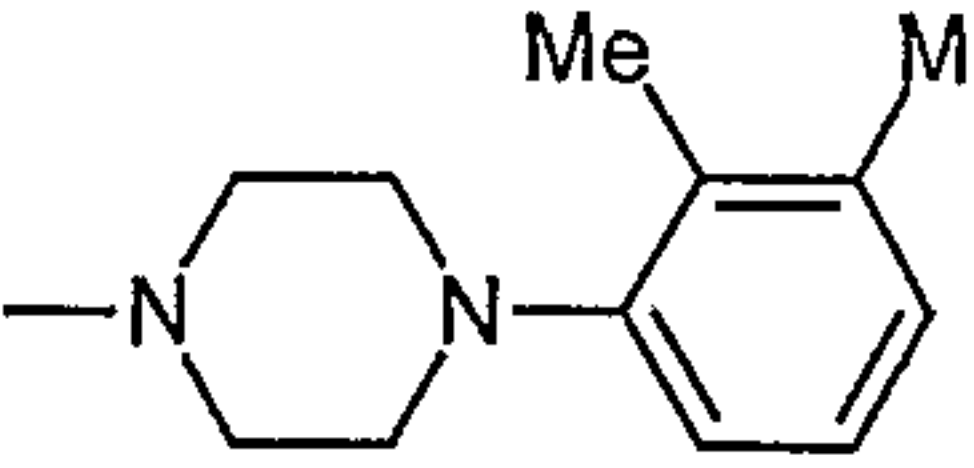
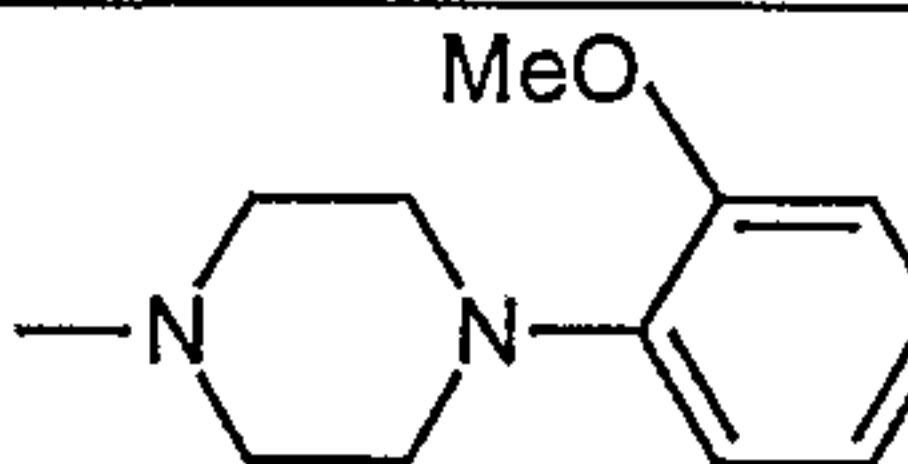
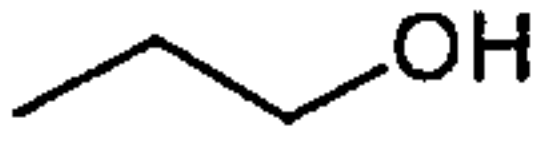
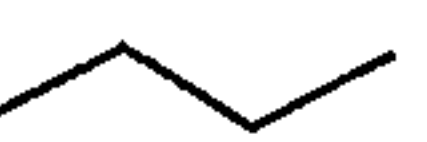
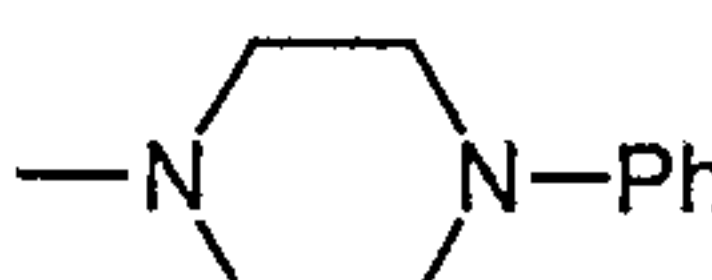
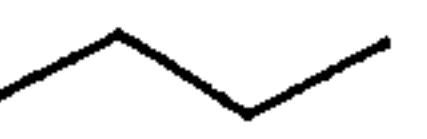
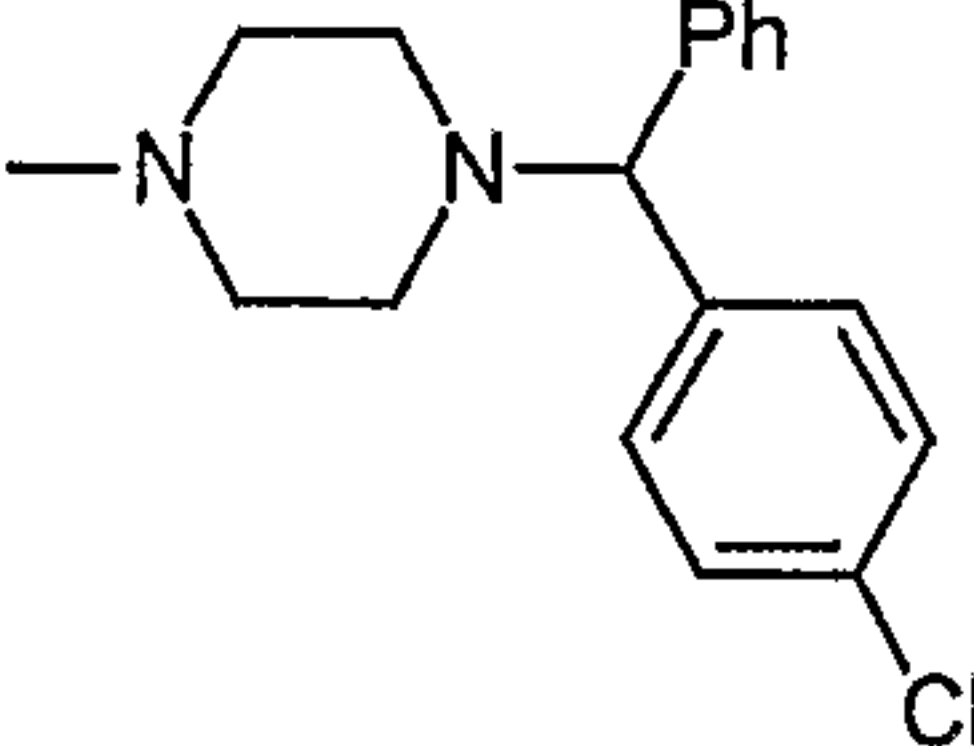
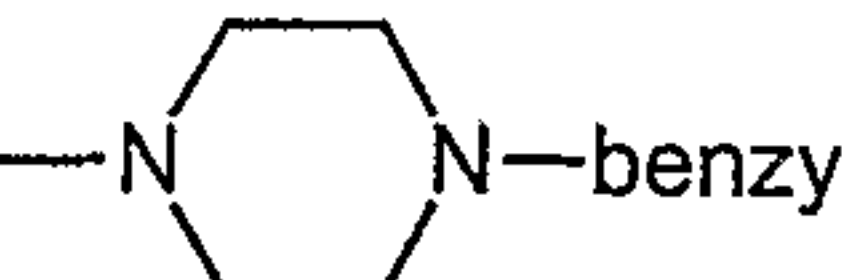
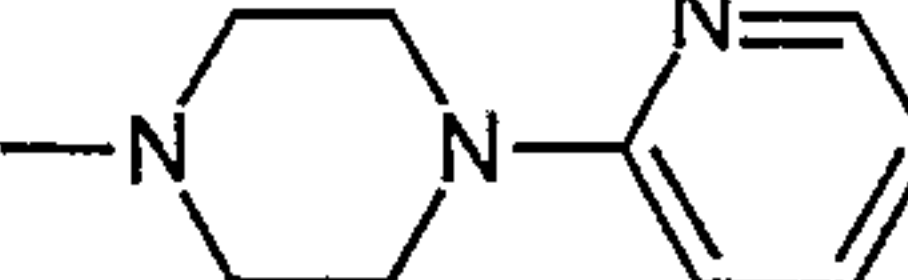
Comp. No	-R ¹	-A-	$\begin{array}{c} \text{R}^2 \\ \\ \text{---N---} \\ \\ \text{R}^3 \end{array}$	[M+H] ⁺
172				526
173				411
174				429
175				450
176				450
177				409
178				411
179				367
180				491
181				381
182				368

Table 3 (continued):

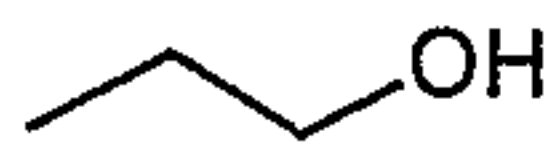
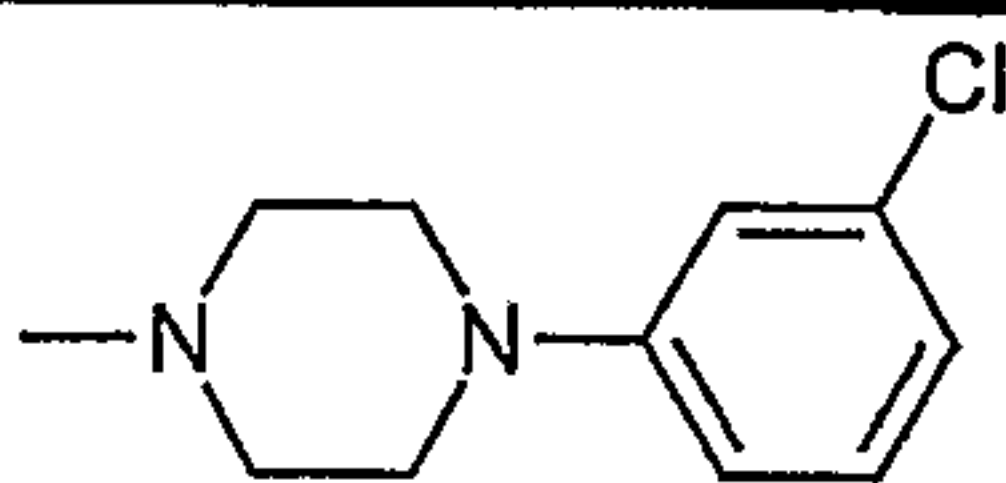
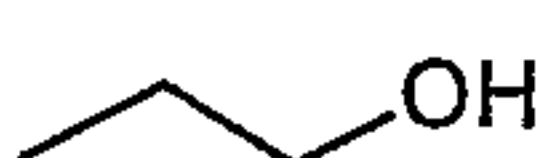
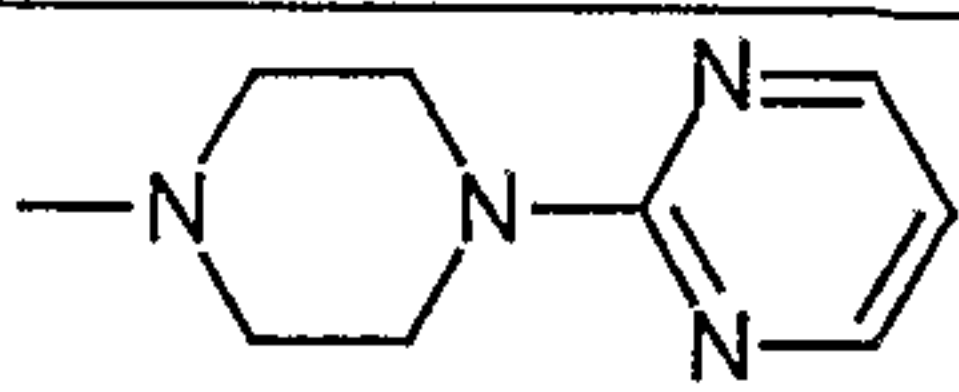
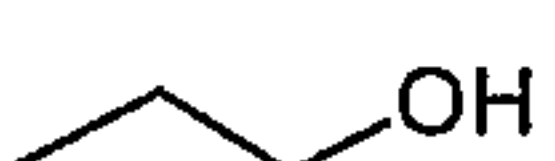
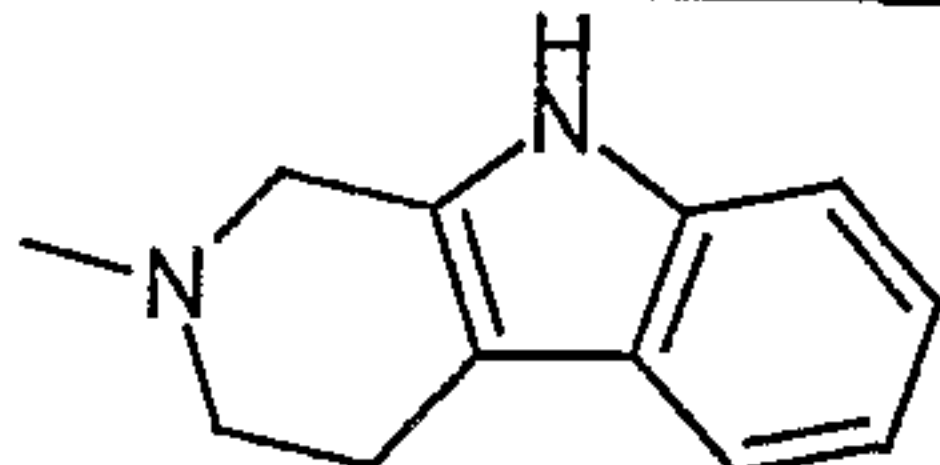
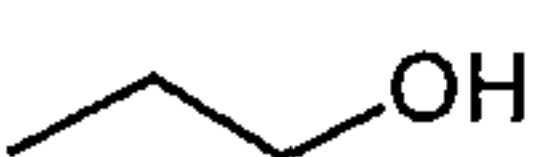
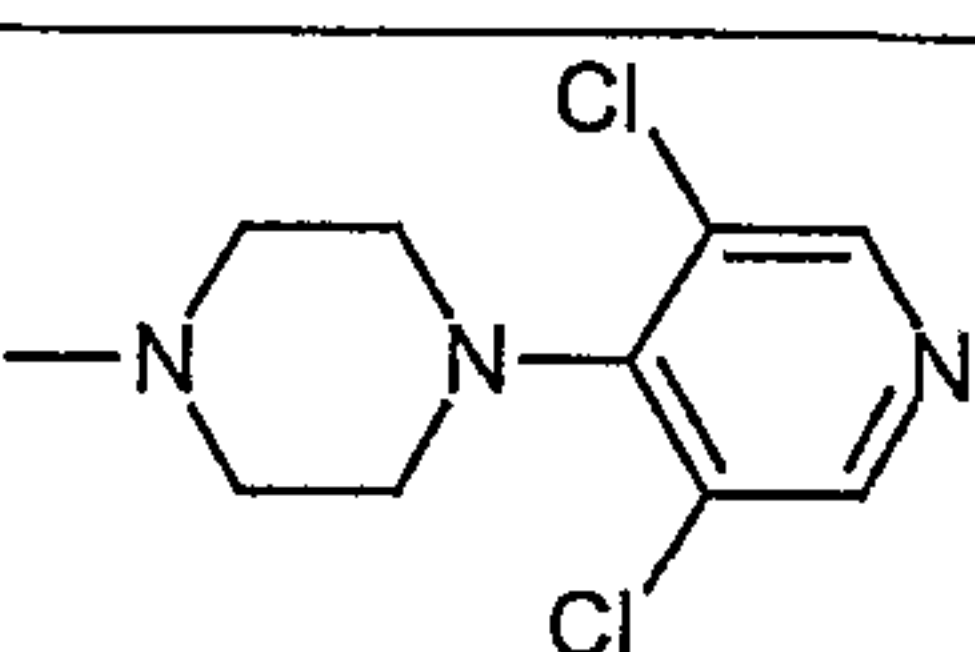
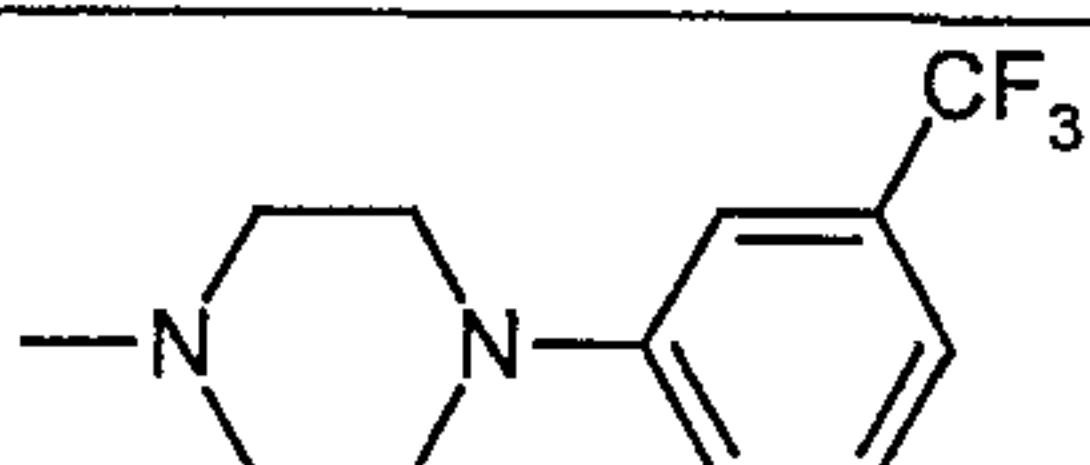
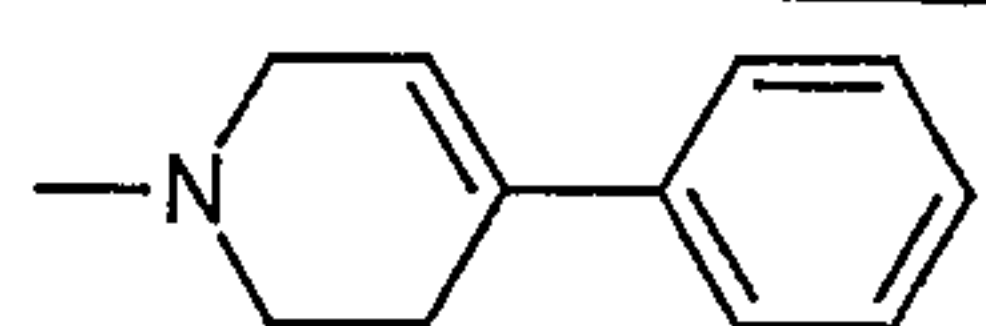
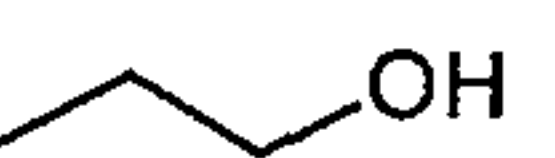
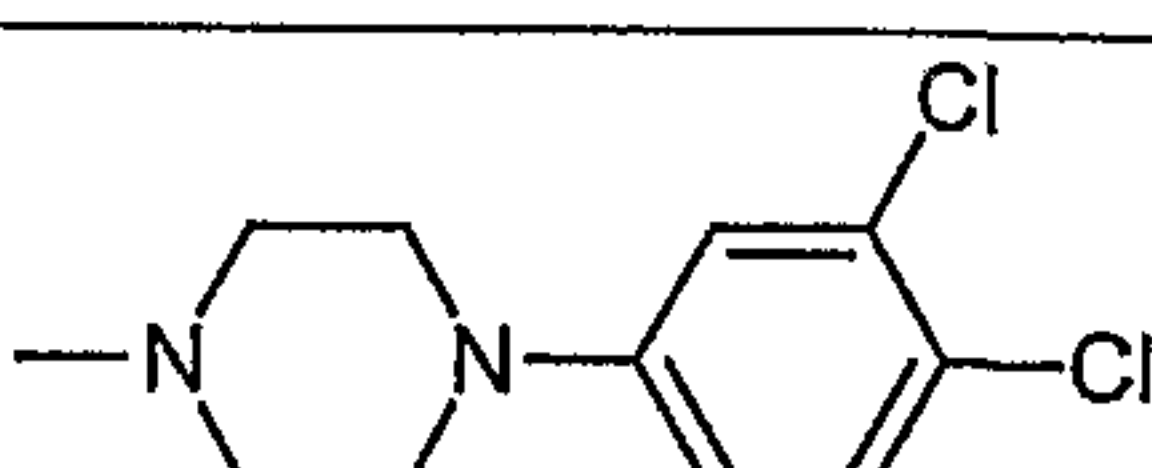
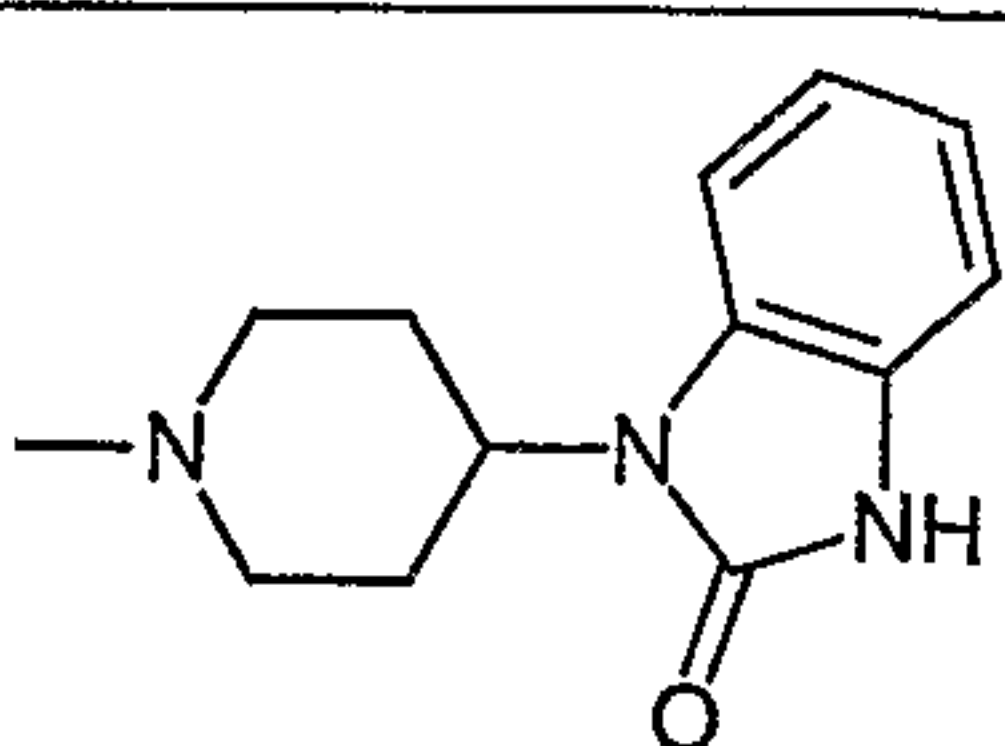
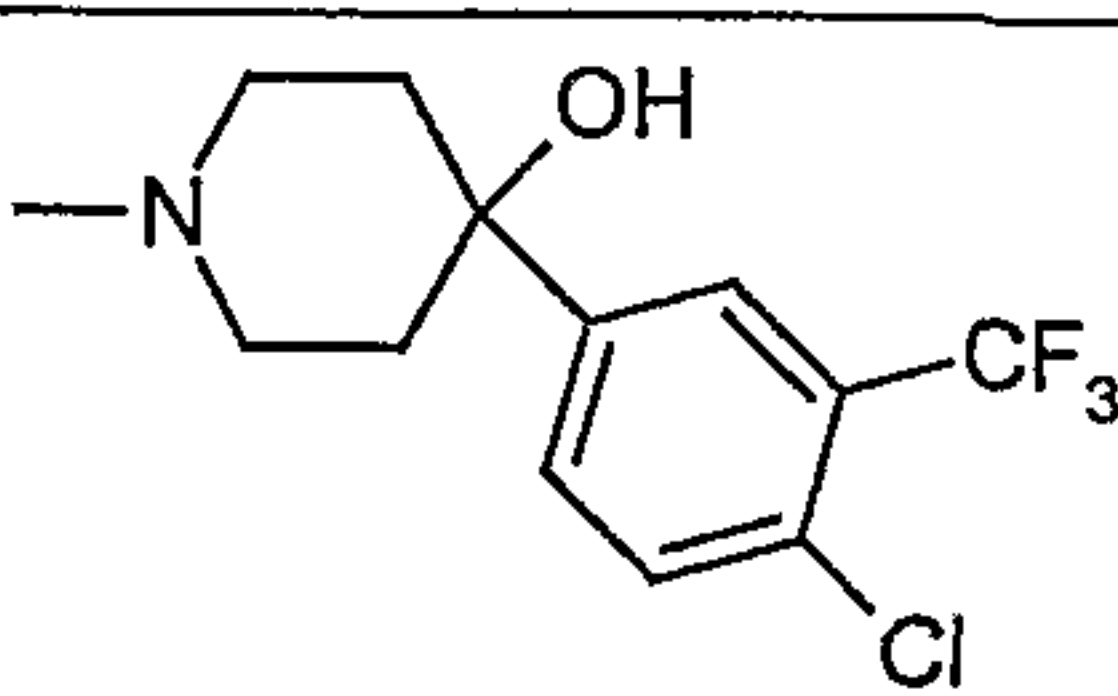
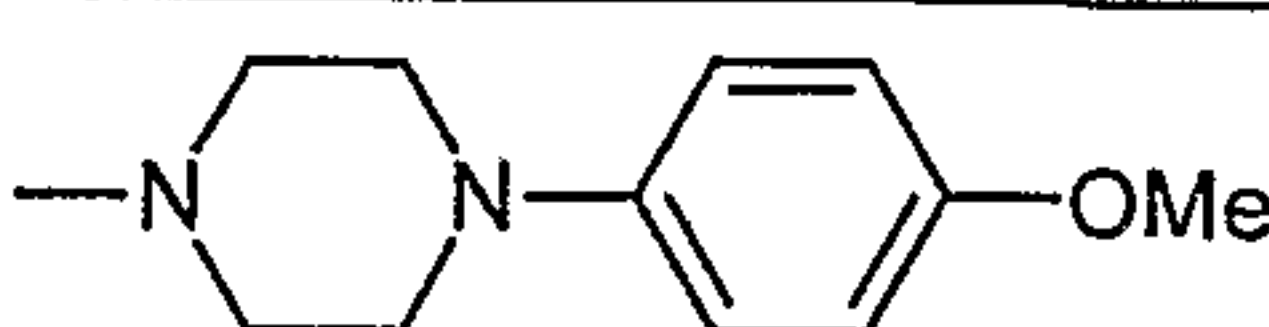
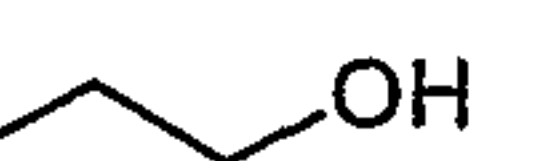
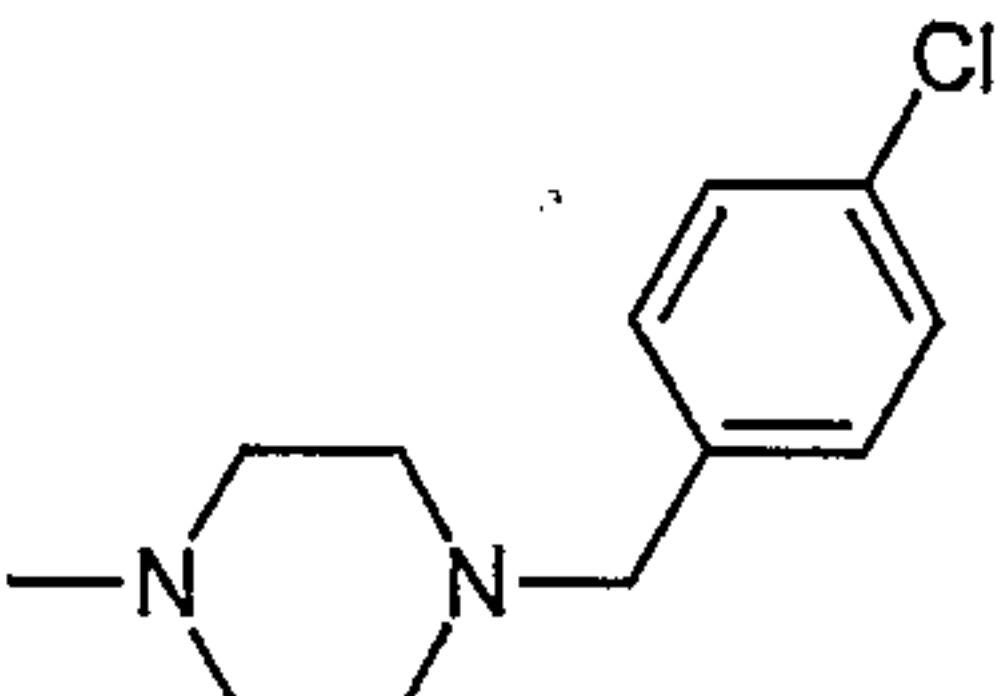
Comp. No	-R ¹	-A-	$\text{—N} \begin{matrix} \text{R}^2 \\ \text{R}^3 \end{matrix}$	[M+H] ⁺
183				401
184				369
185				377
186				436
187				435
188				364
189				435
190				422
191				484
192				397
193				415

Table 3 (continued):

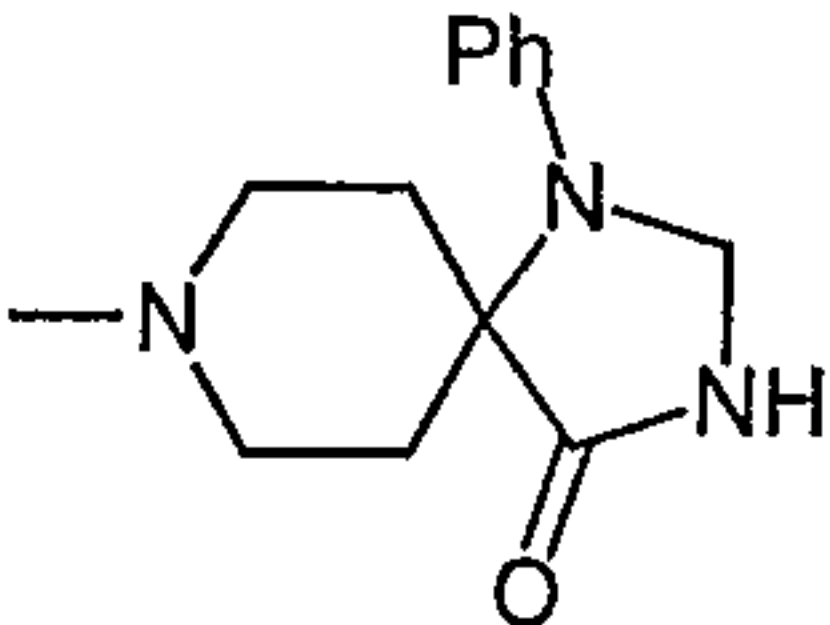
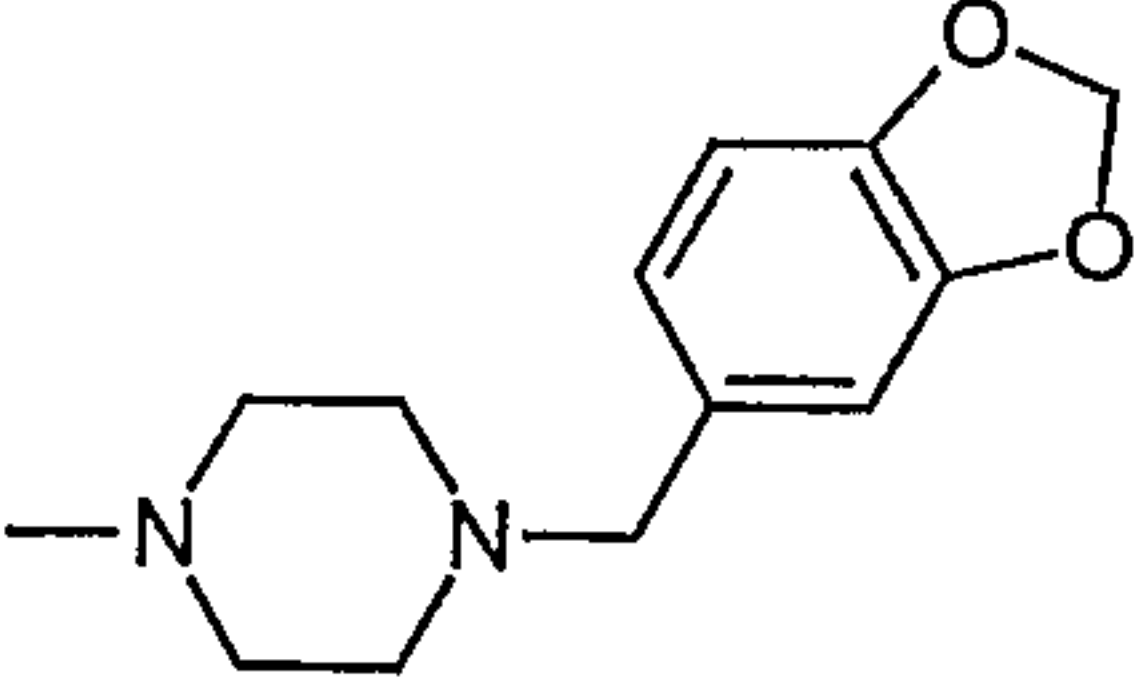
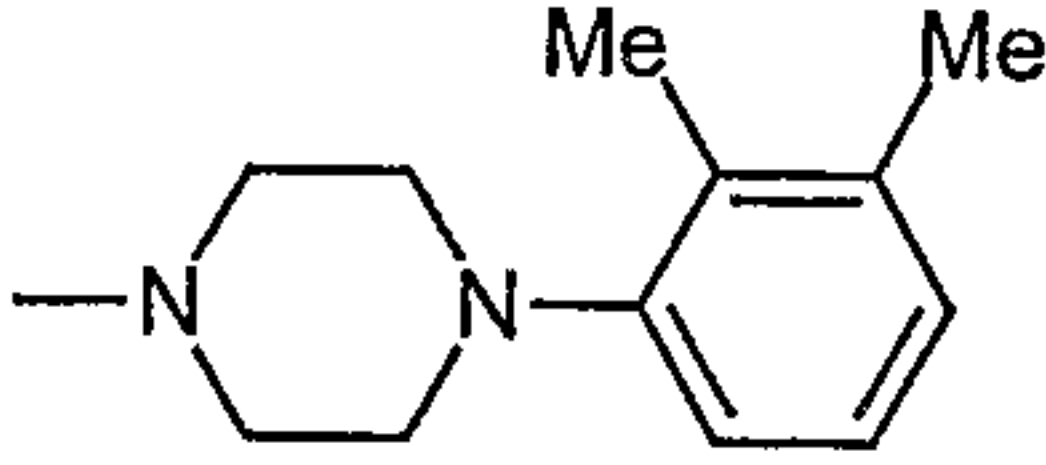
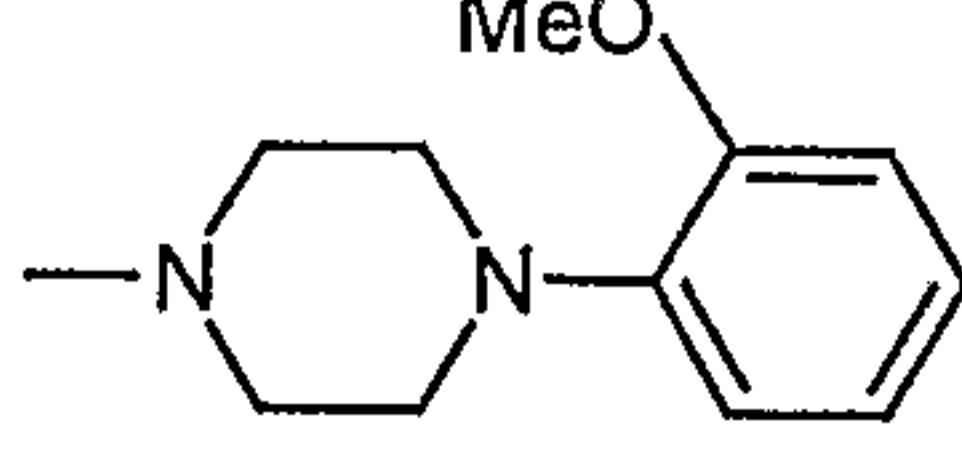
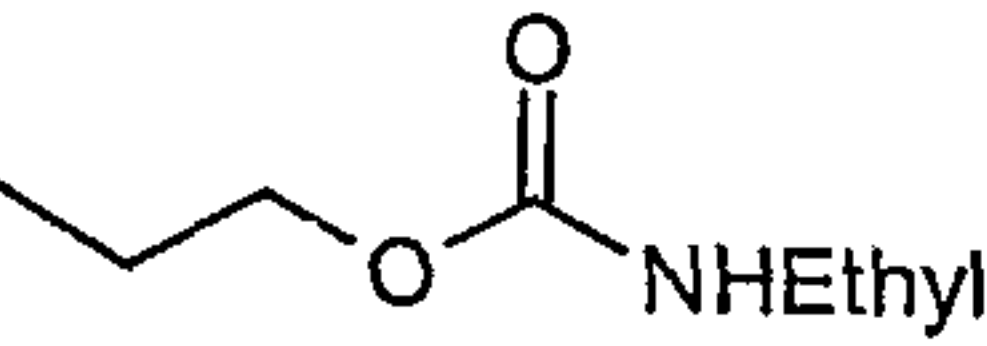
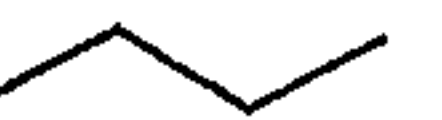
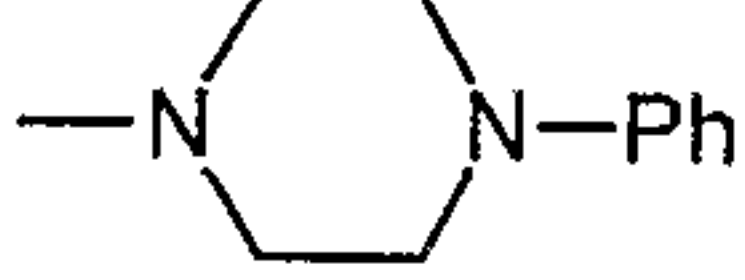
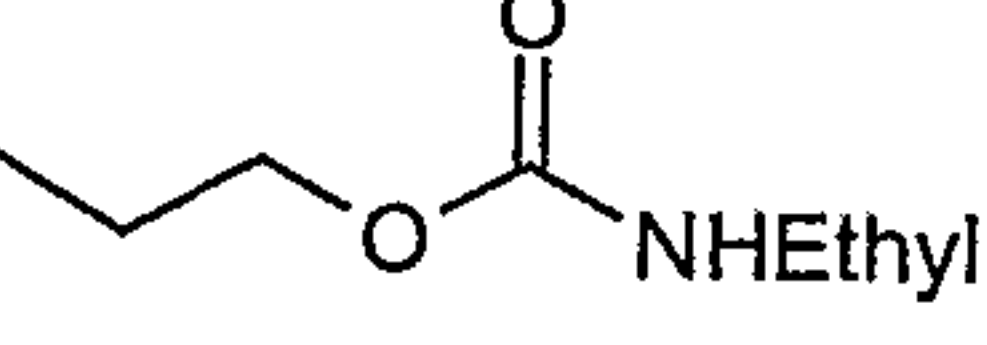
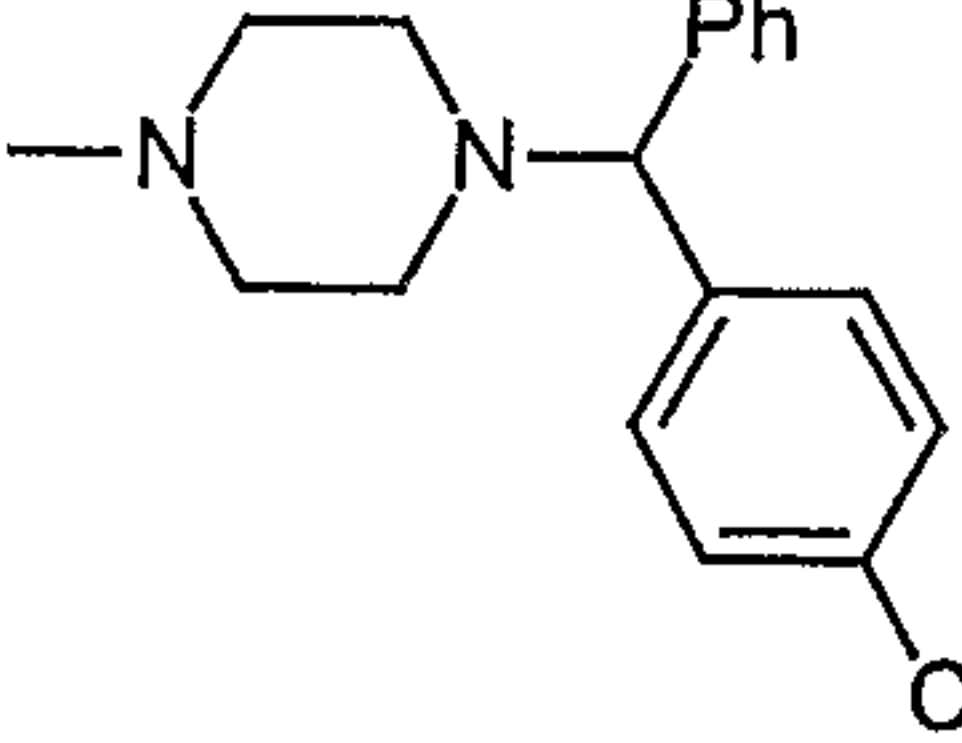
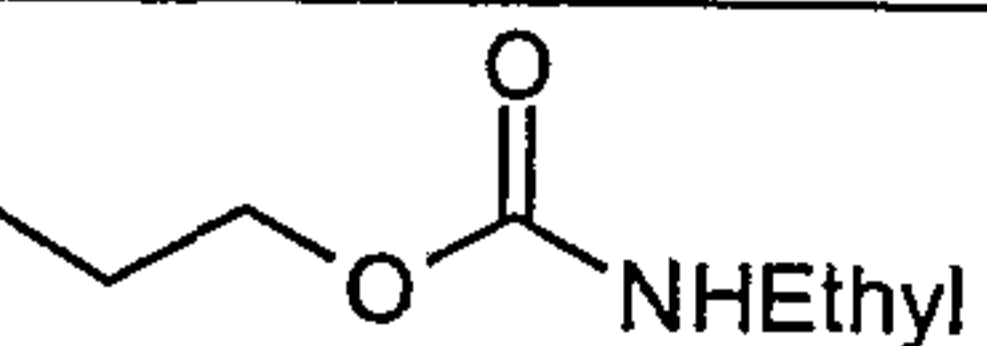
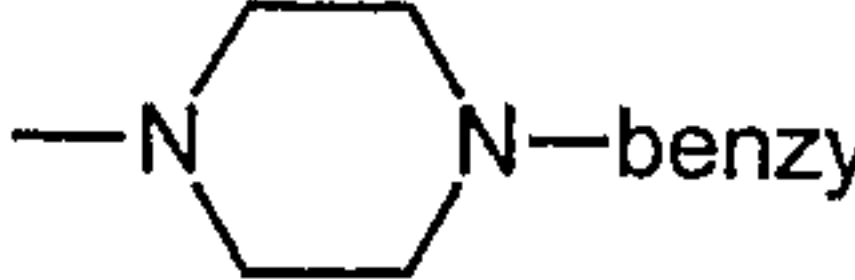
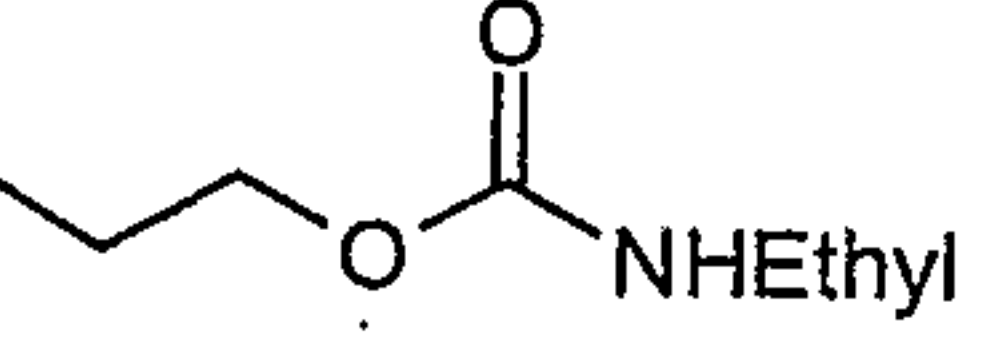
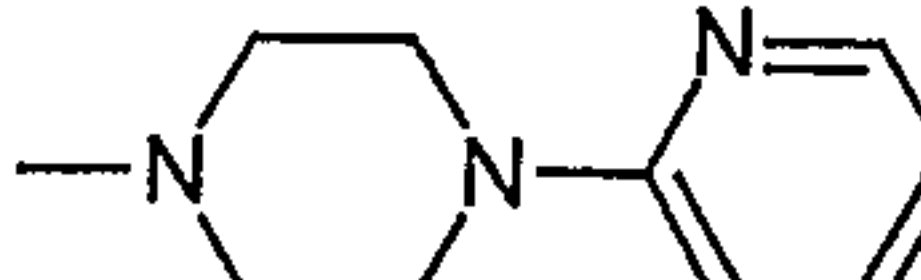
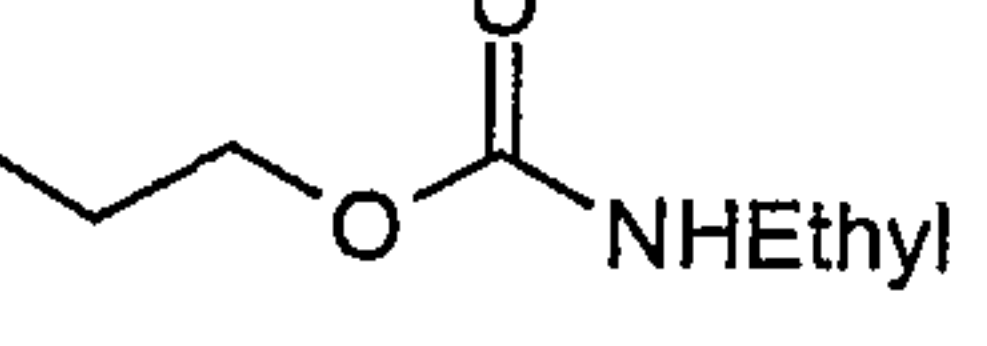
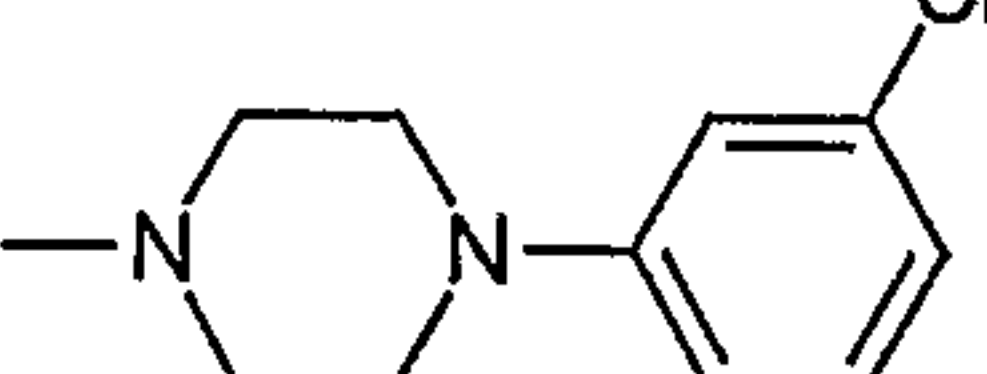
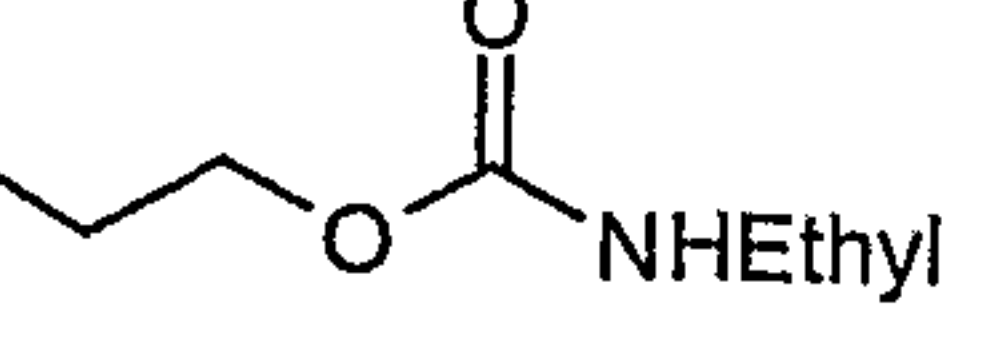
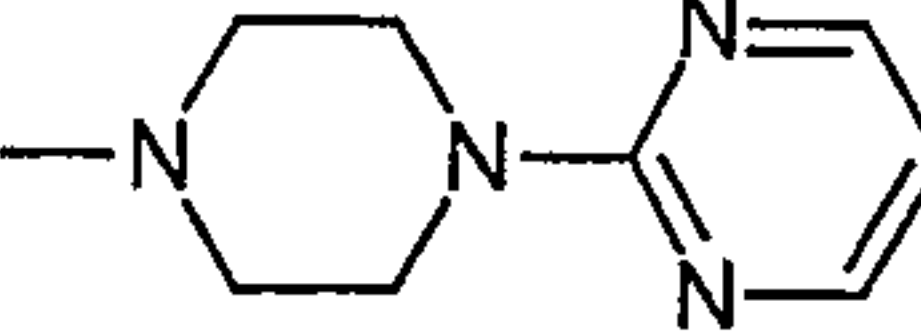
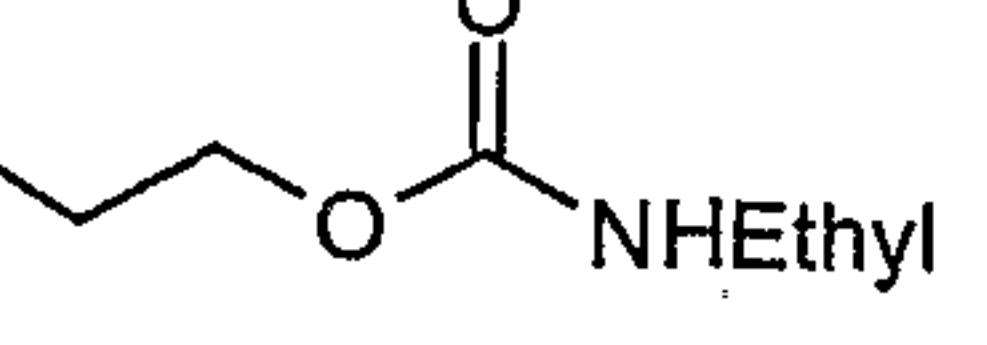
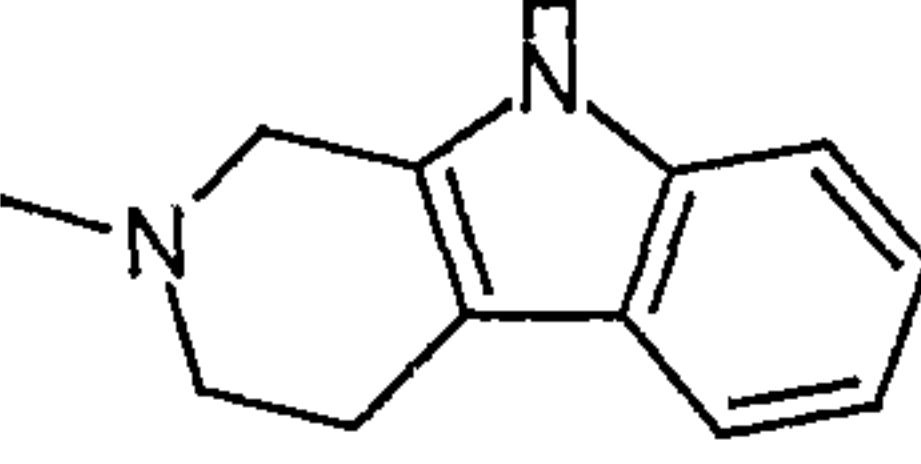
Comp. No	-R ¹	-A-	$\begin{array}{c} \text{R}^2 \\ \\ \text{---N---} \\ \\ \text{R}^3 \end{array}$	[M+H] ⁺
194				436
195				436
196				395
197				397
198				438
199				562
200				452
201				439
202				472
203				440
204				448

Table 3 (continued):

Comp. No	-R ¹	-A-	$\text{—N} \begin{matrix} \text{R}^2 \\ \text{R}^3 \end{matrix}$	[M+H] ⁺
205				507
206				506
207				435
208				506
209				493
210				555
211				468
212				486
213				507
214				496

Table 3 (continued):

Comp. No	-R ¹	-A-	$\begin{array}{c} \text{R}^2 \\ \\ \text{---N---} \\ \\ \text{R}^3 \end{array}$	[M+H] ⁺
215				466
216				468
217				452
218				452
219				472
220				436
221				560
222				450
223				437
224				470
225				438
226				446

Table 3 (continued):

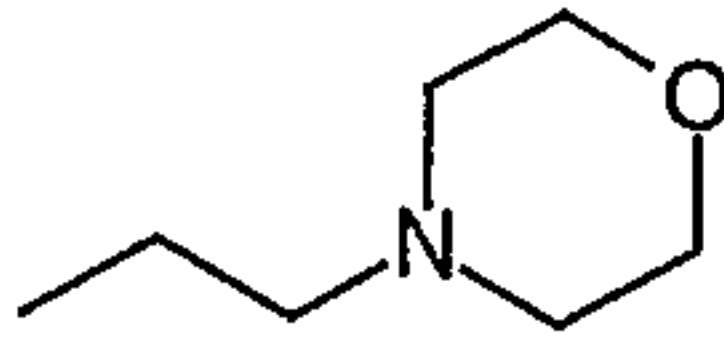
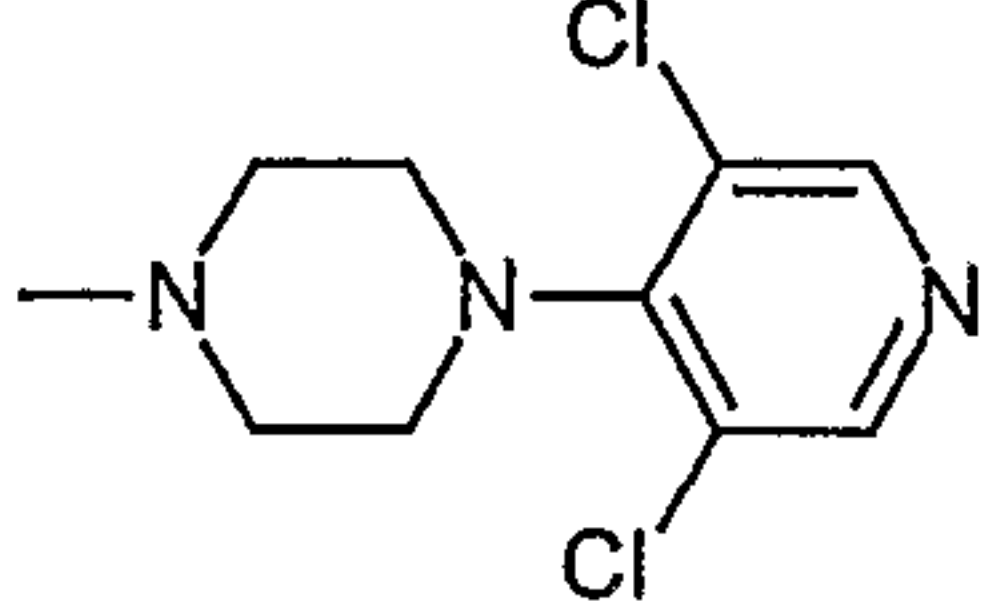
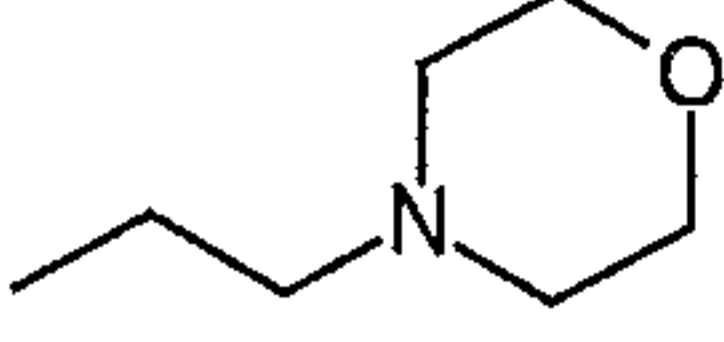
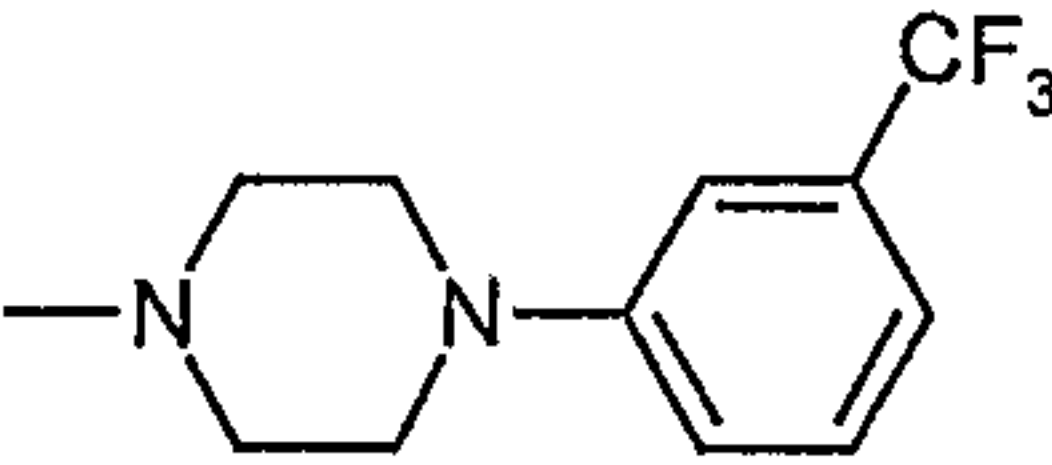
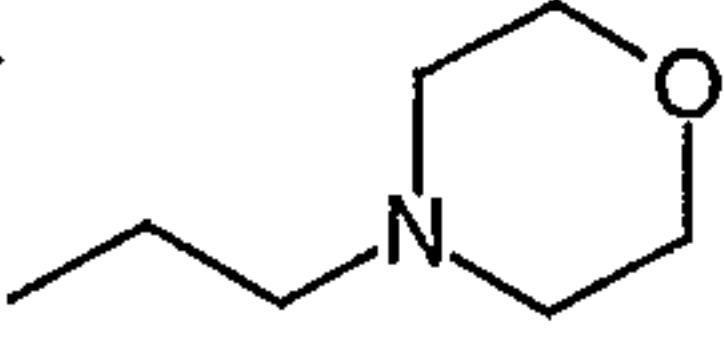
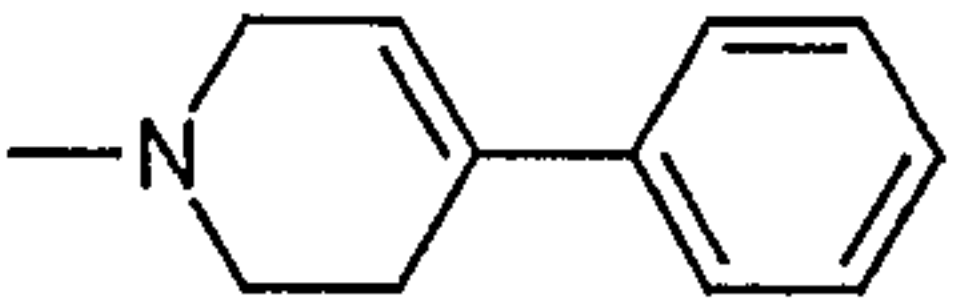
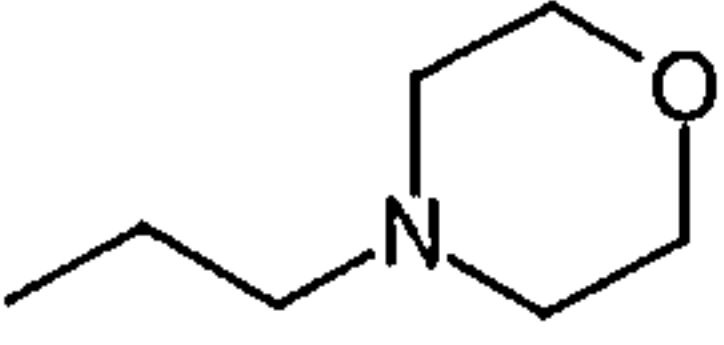
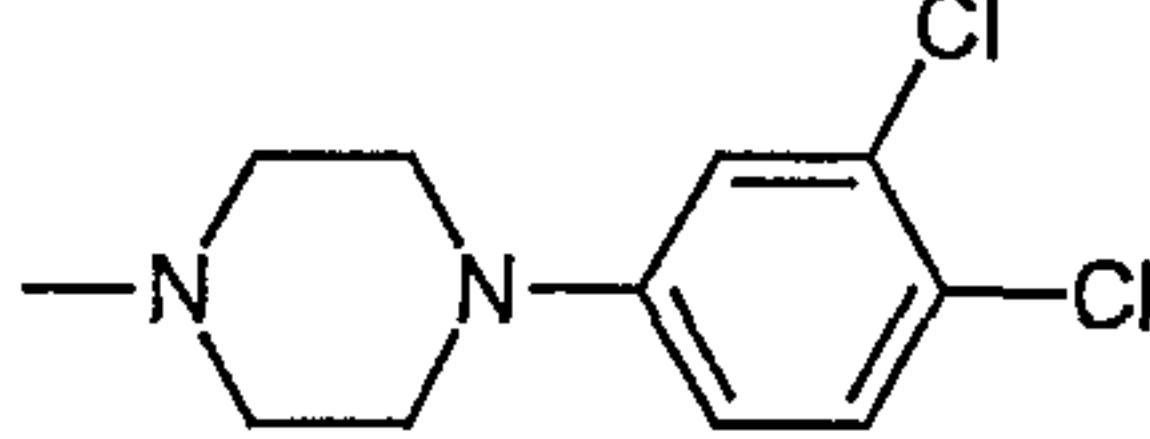
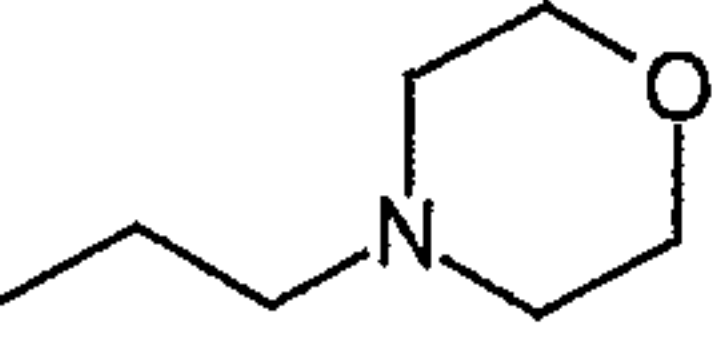
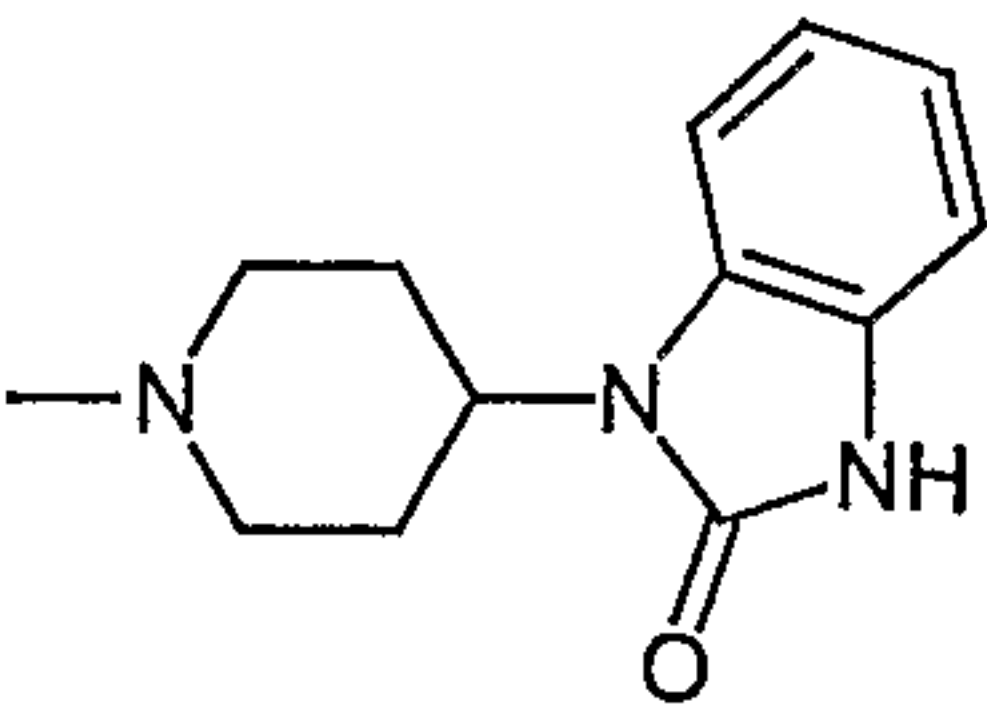
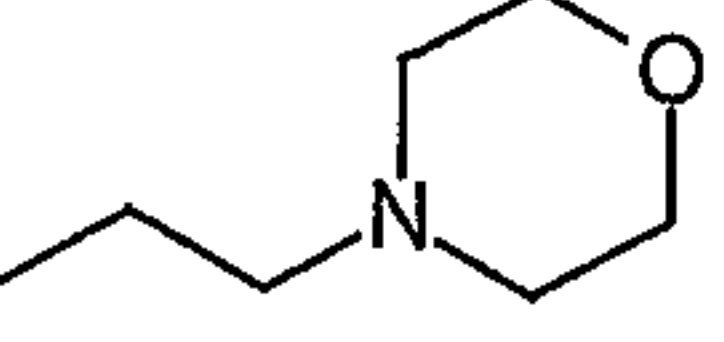
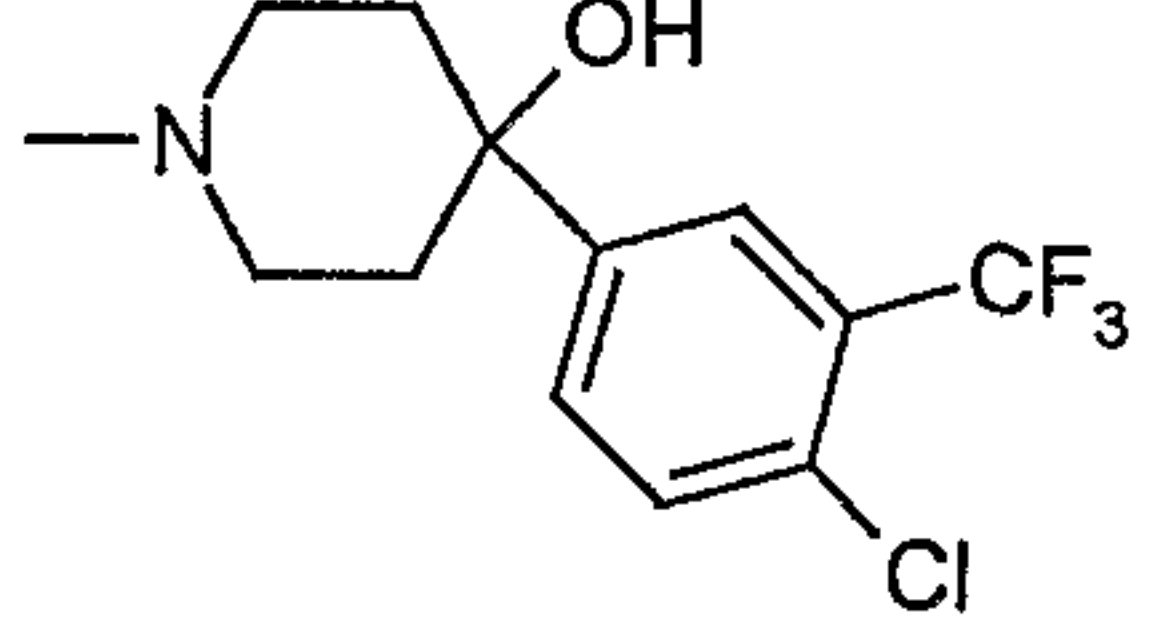
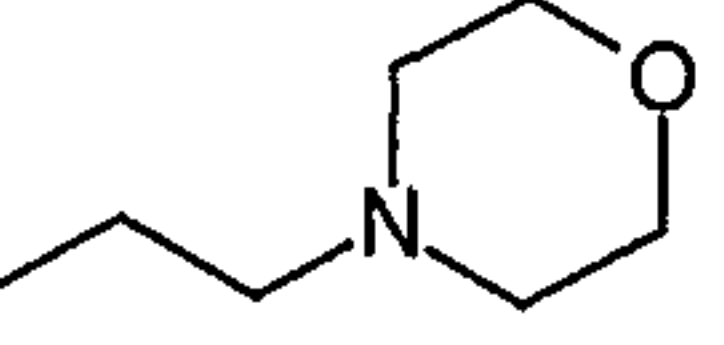
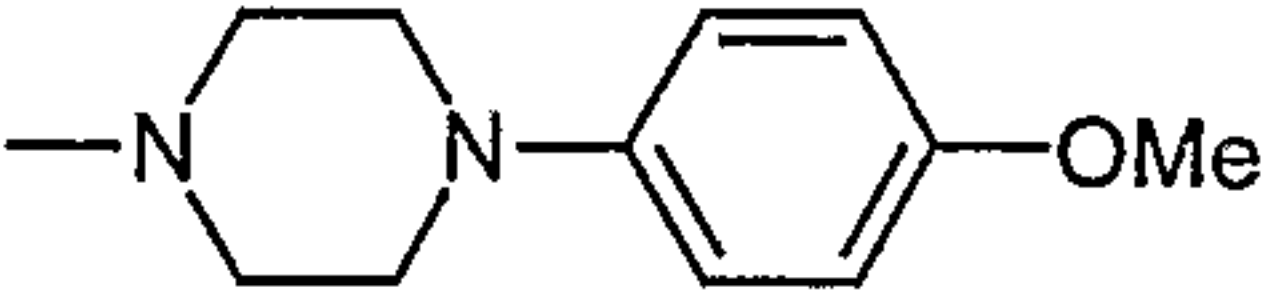
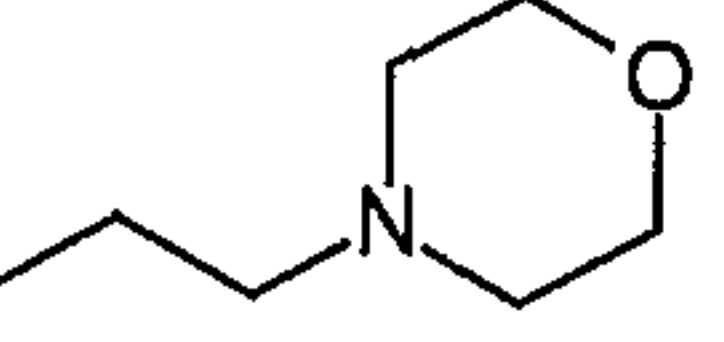
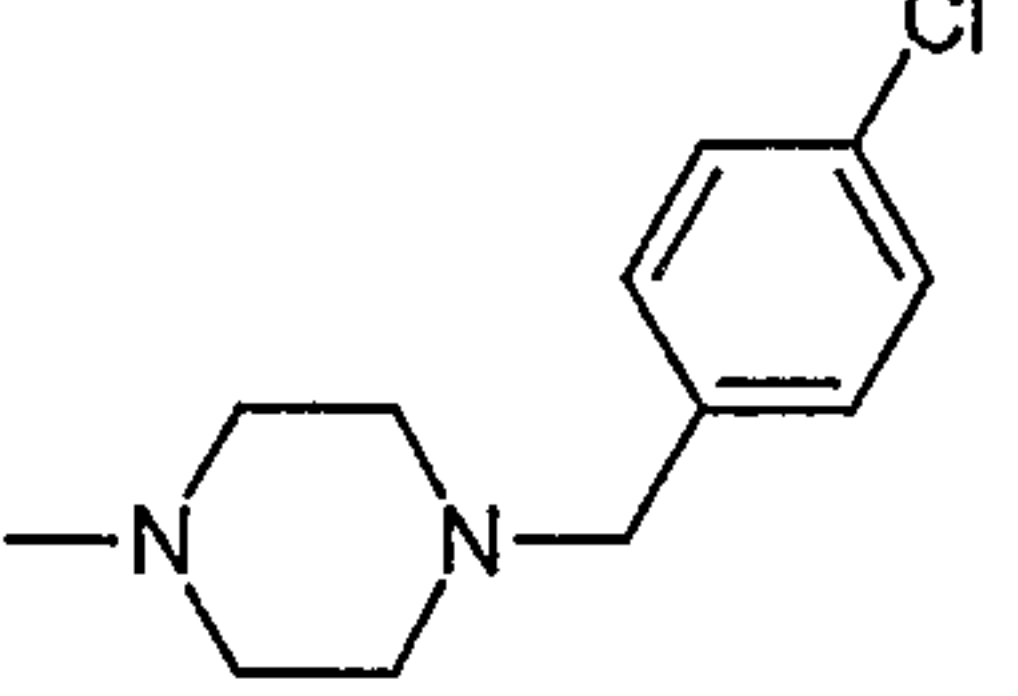
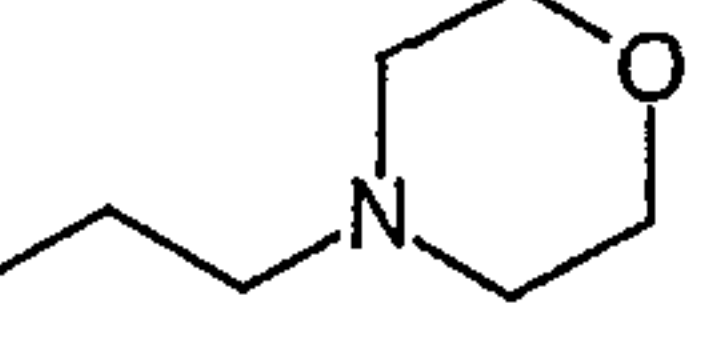
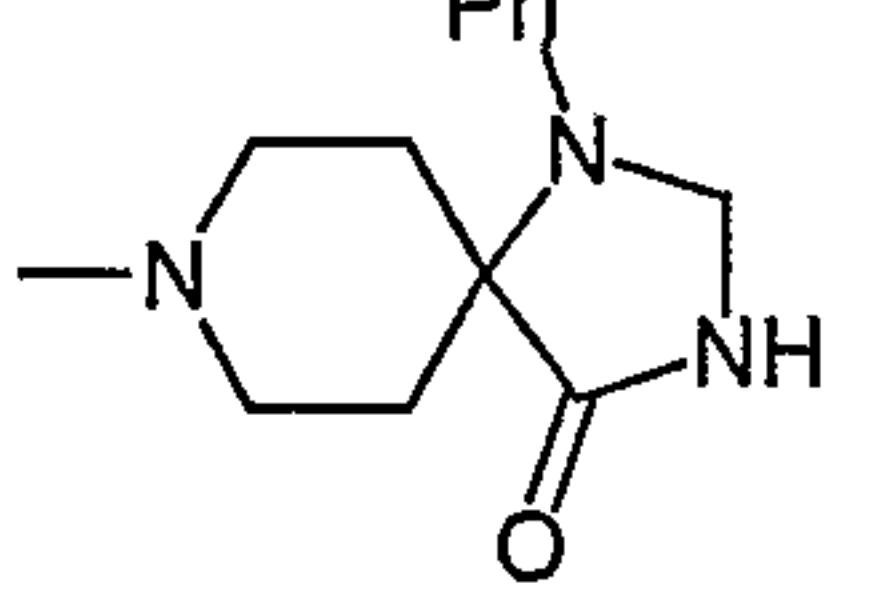
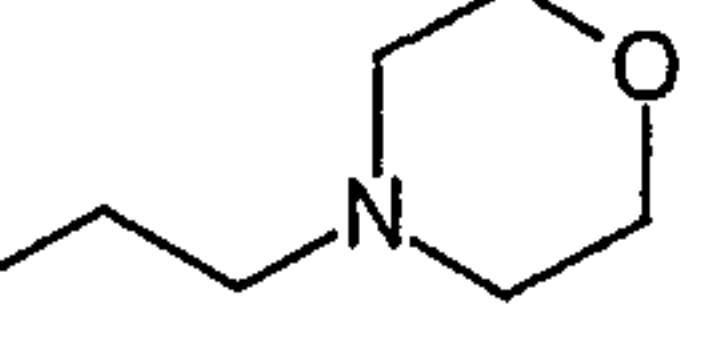
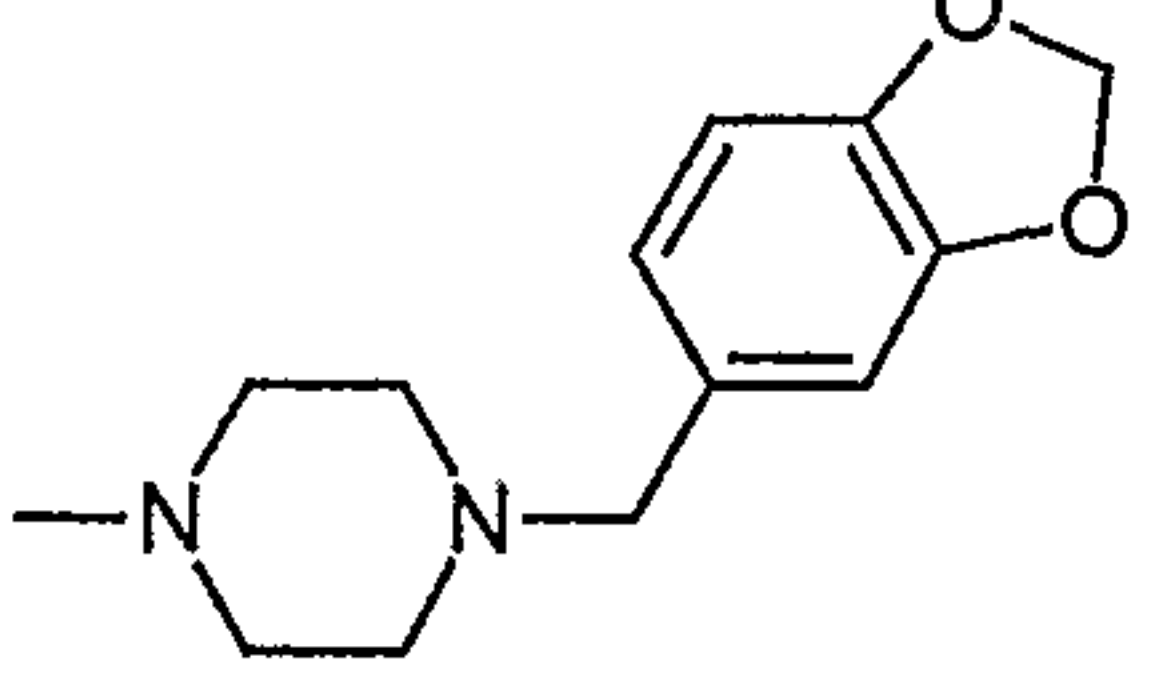
Comp. No	-R ¹	-A-	$\begin{array}{c} \text{R}^2 \\ \\ \text{---N---} \\ \\ \text{R}^3 \end{array}$	[M+H] ⁺
227				533
228				504
229				433
230				504
231				491
232				553
233				466
234				484
235				505
236				494

Table 3 (continued):

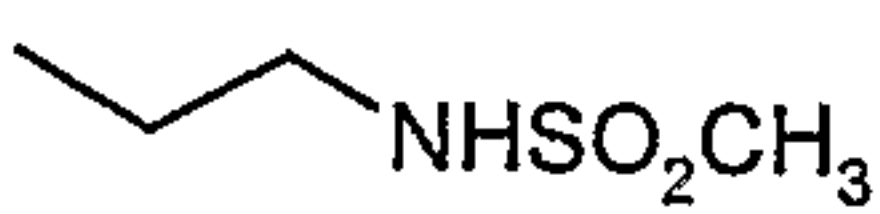
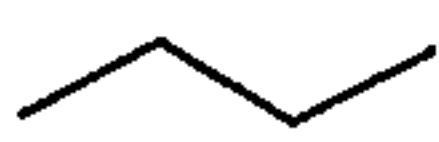
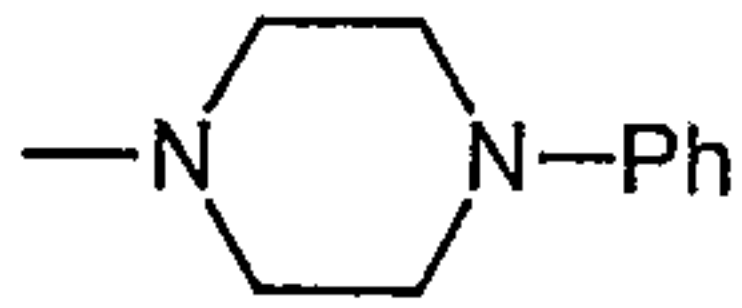
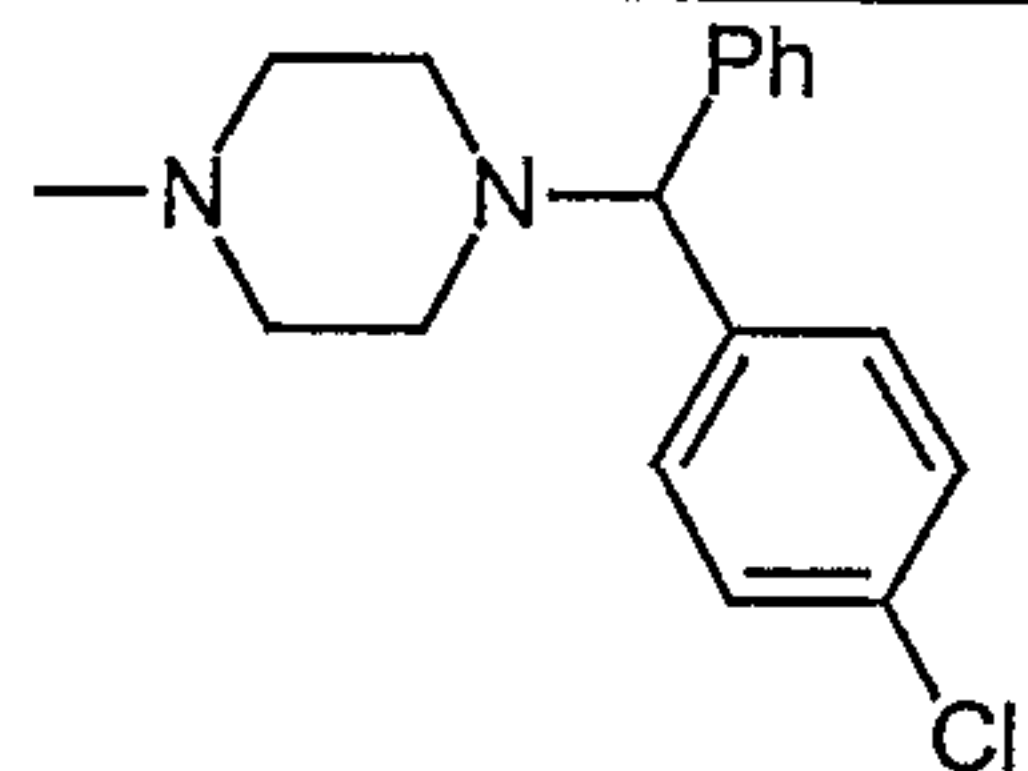
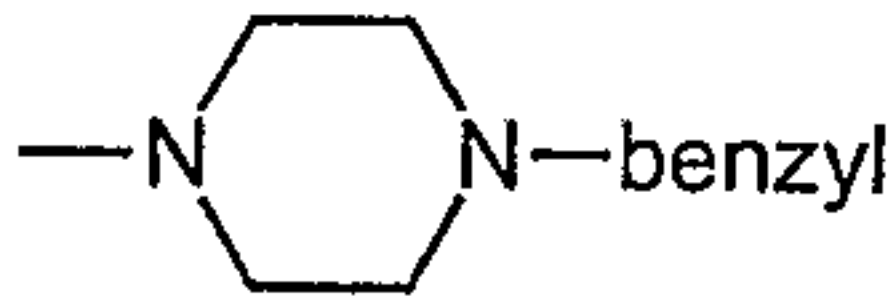
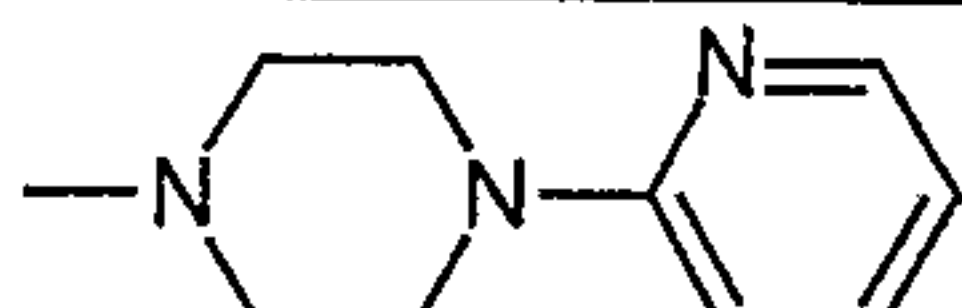
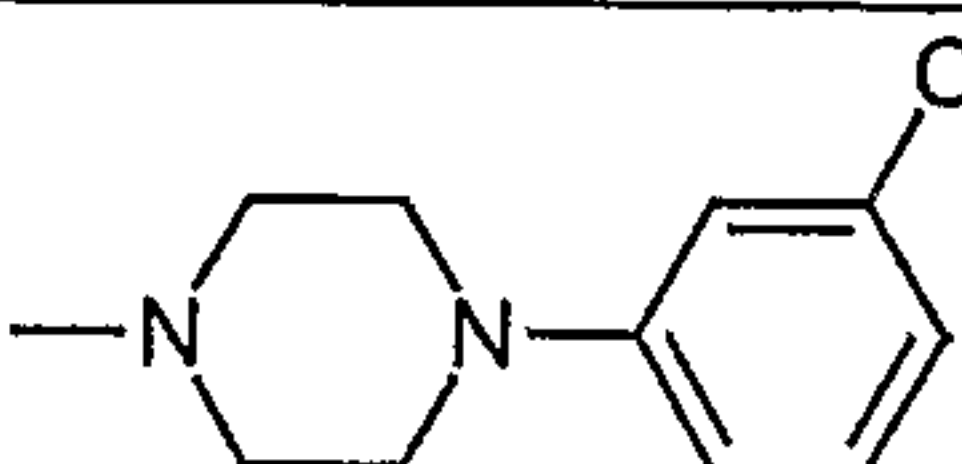
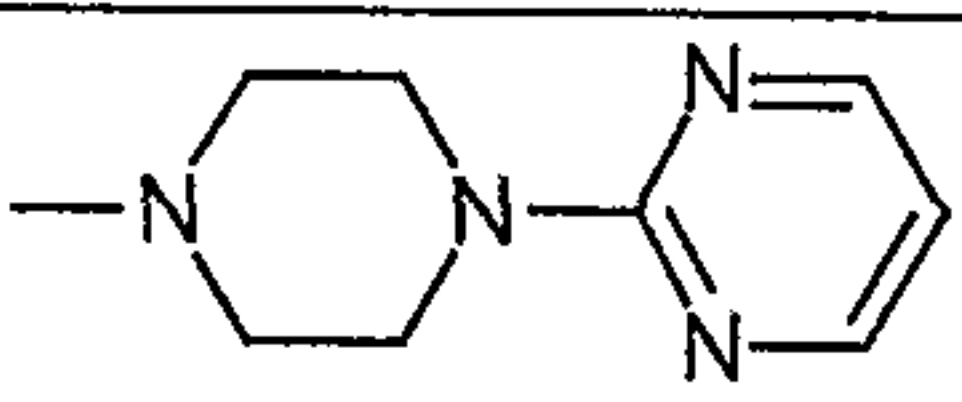
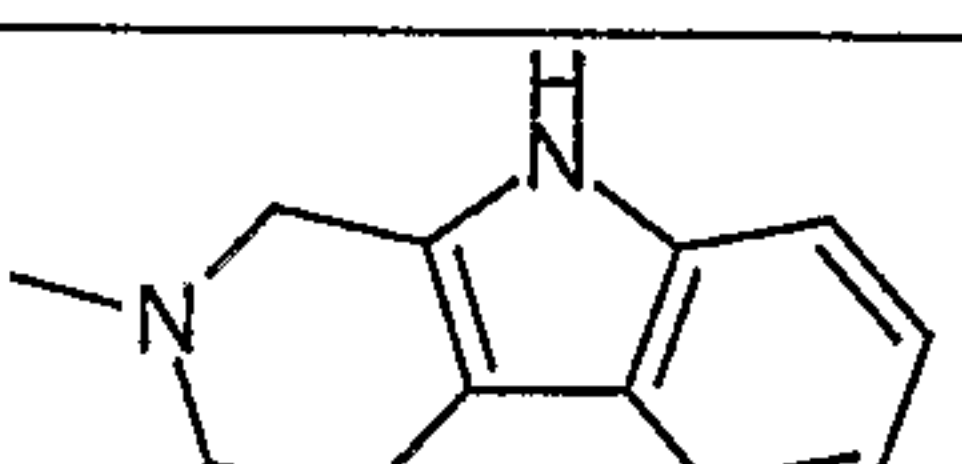
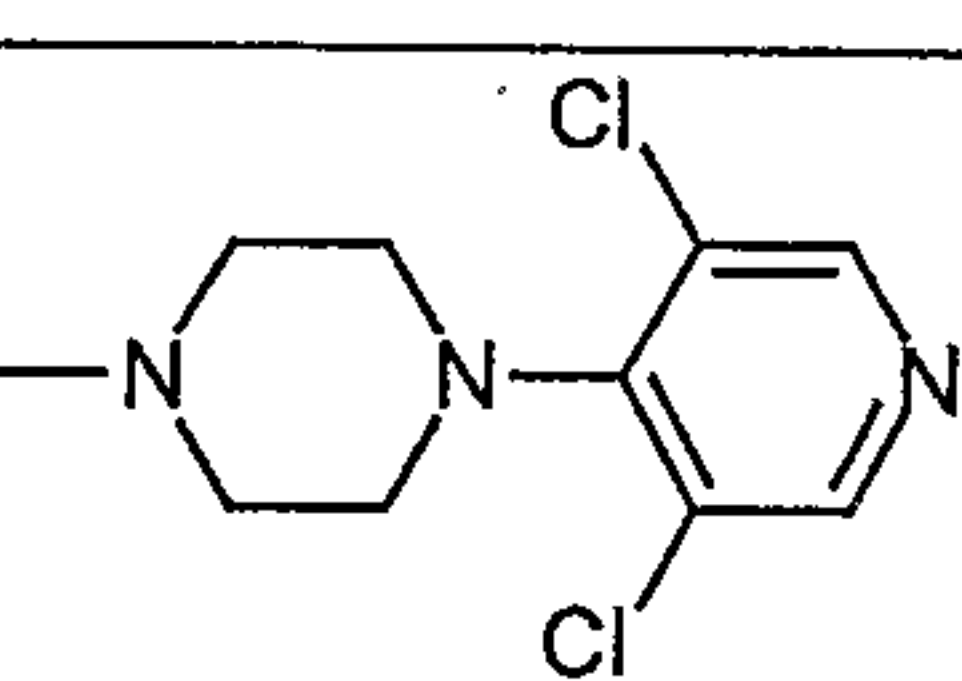
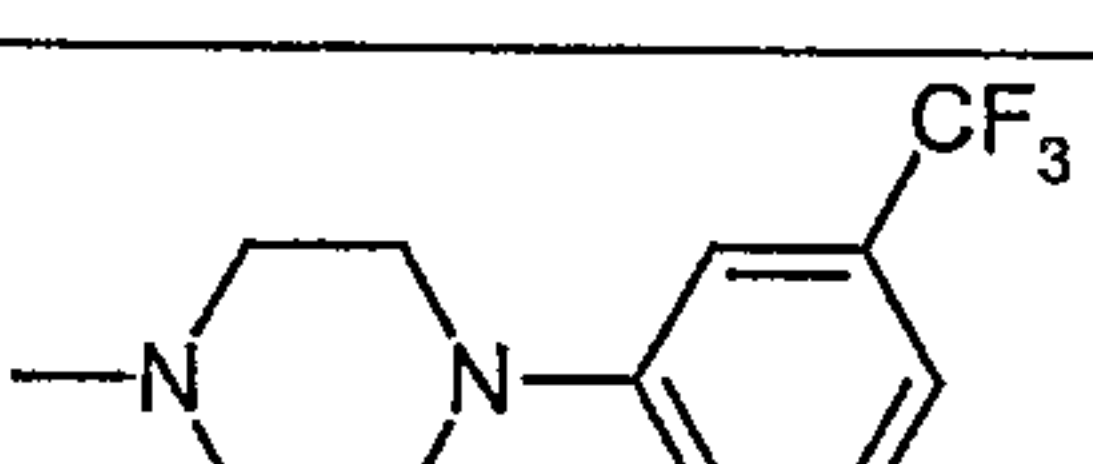
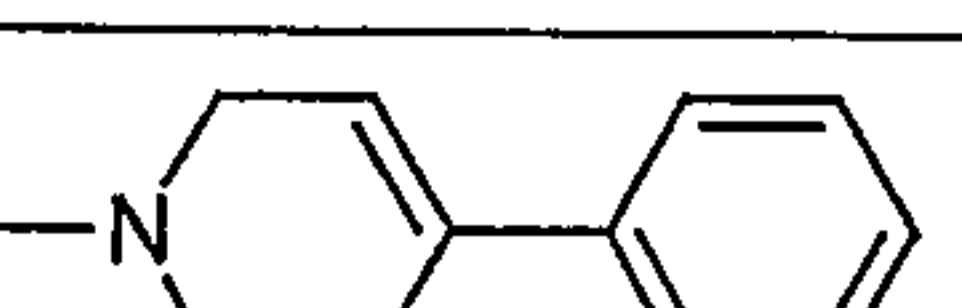
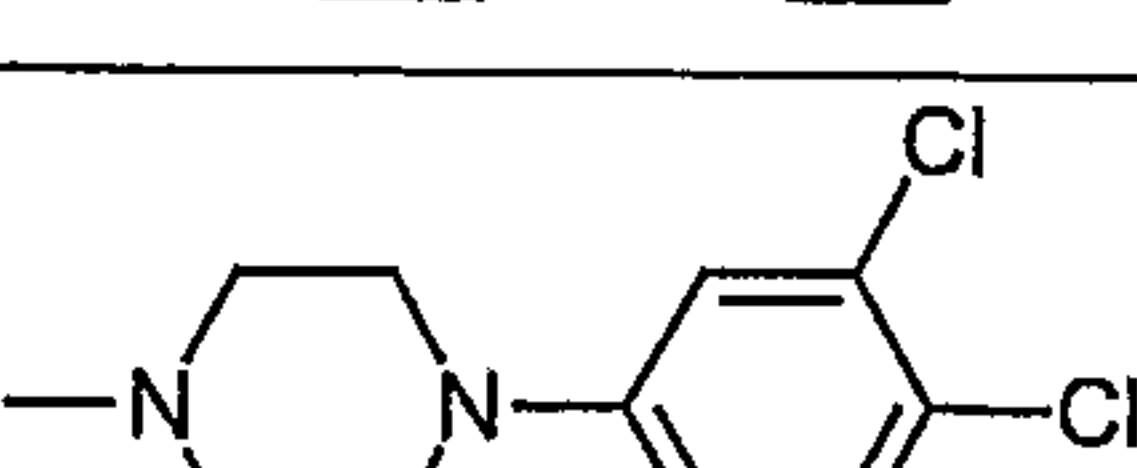
Comp. No	-R ¹	-A-	$\begin{array}{c} R^2 \\ \\ -N- \\ \\ R^3 \end{array}$	[M+H] ⁺
237				444
238				568
239				458
240				445
241				478
242				446
243				454
244				513
245				512
246				441
247				512

Table 3 (continued):

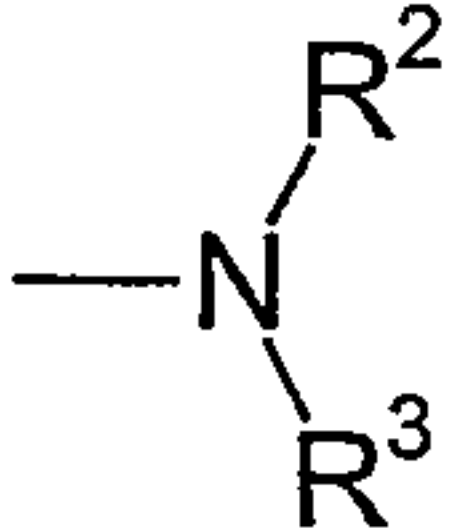
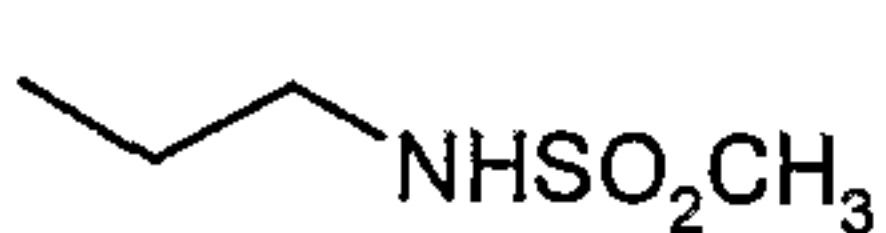
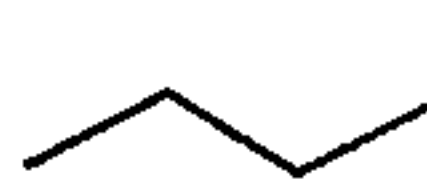
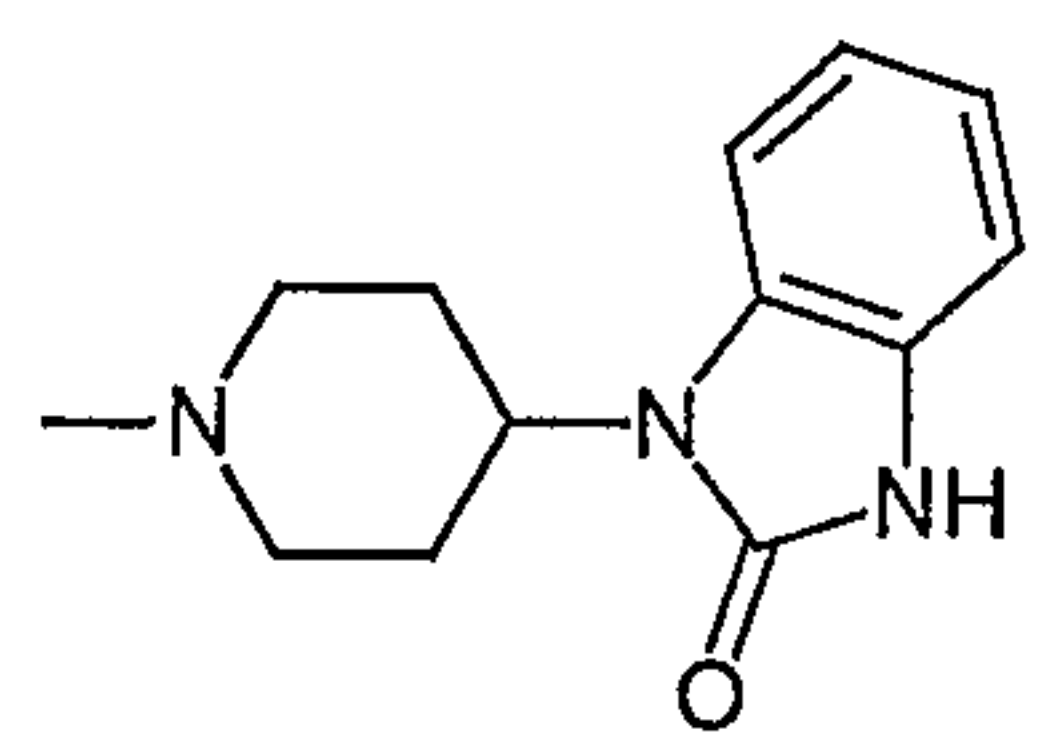
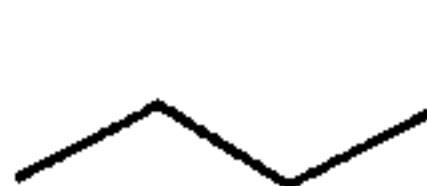
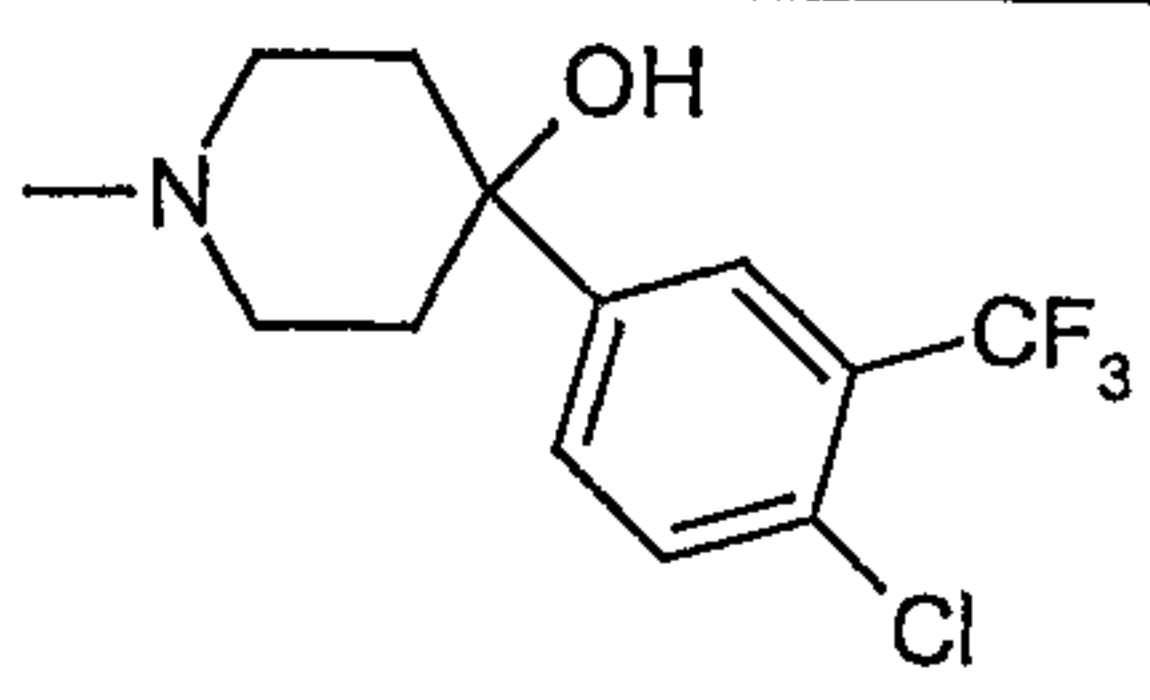
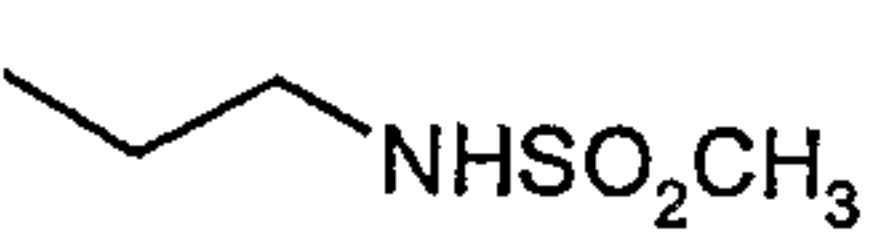
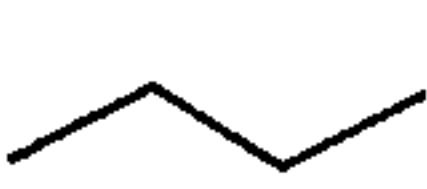
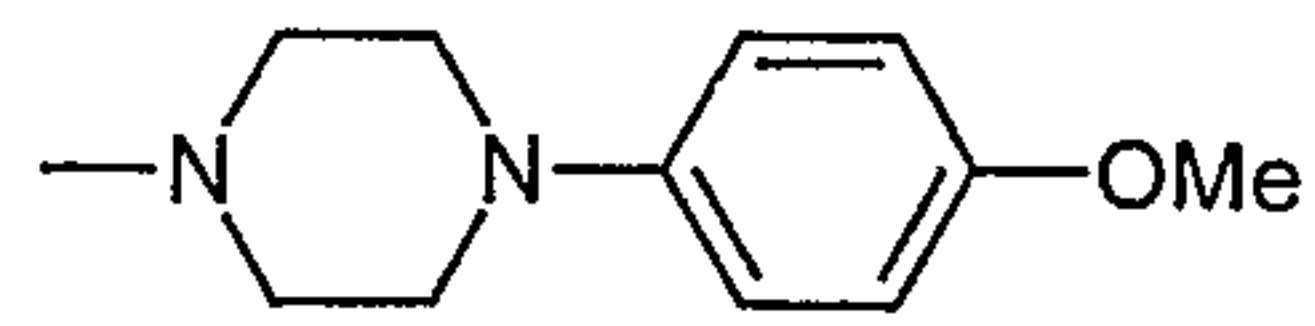
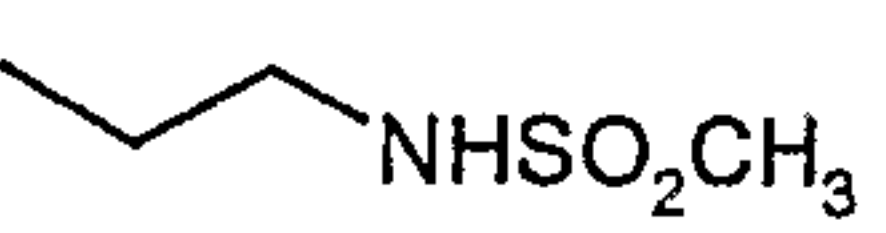
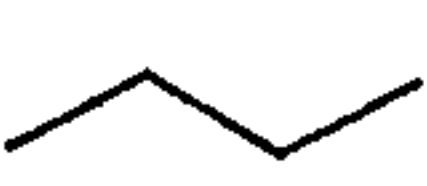
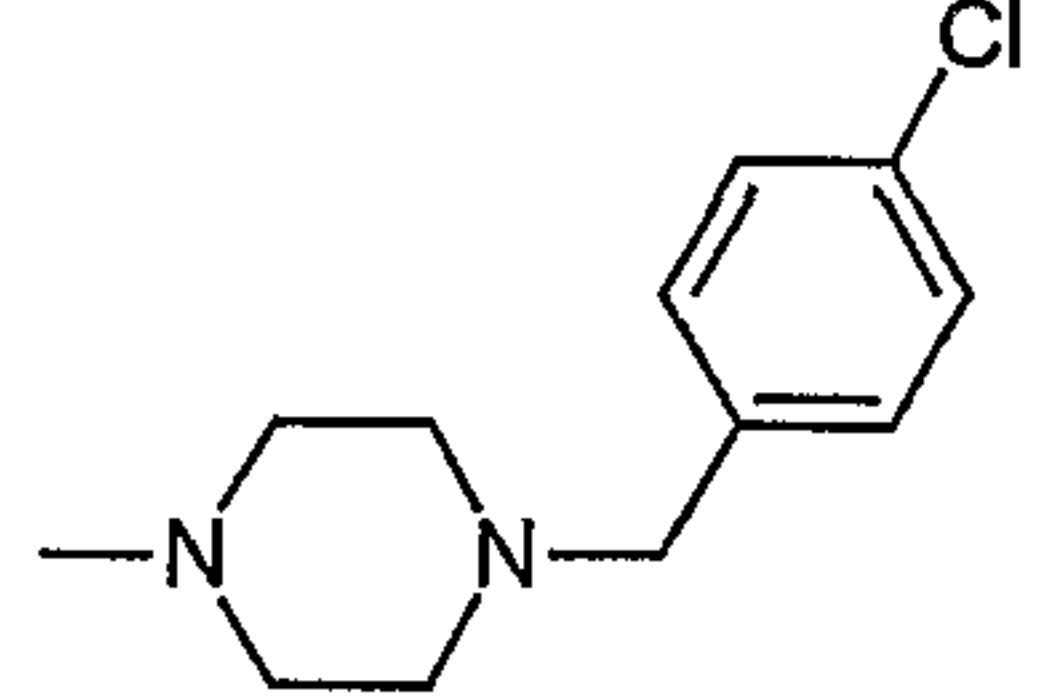
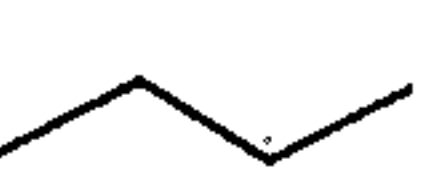
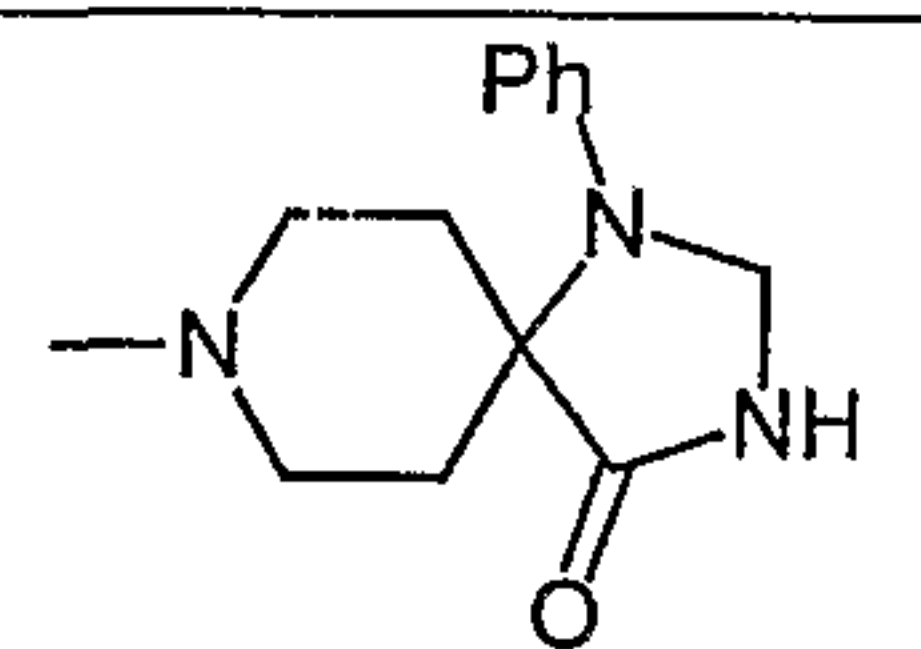
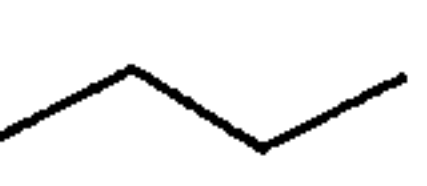
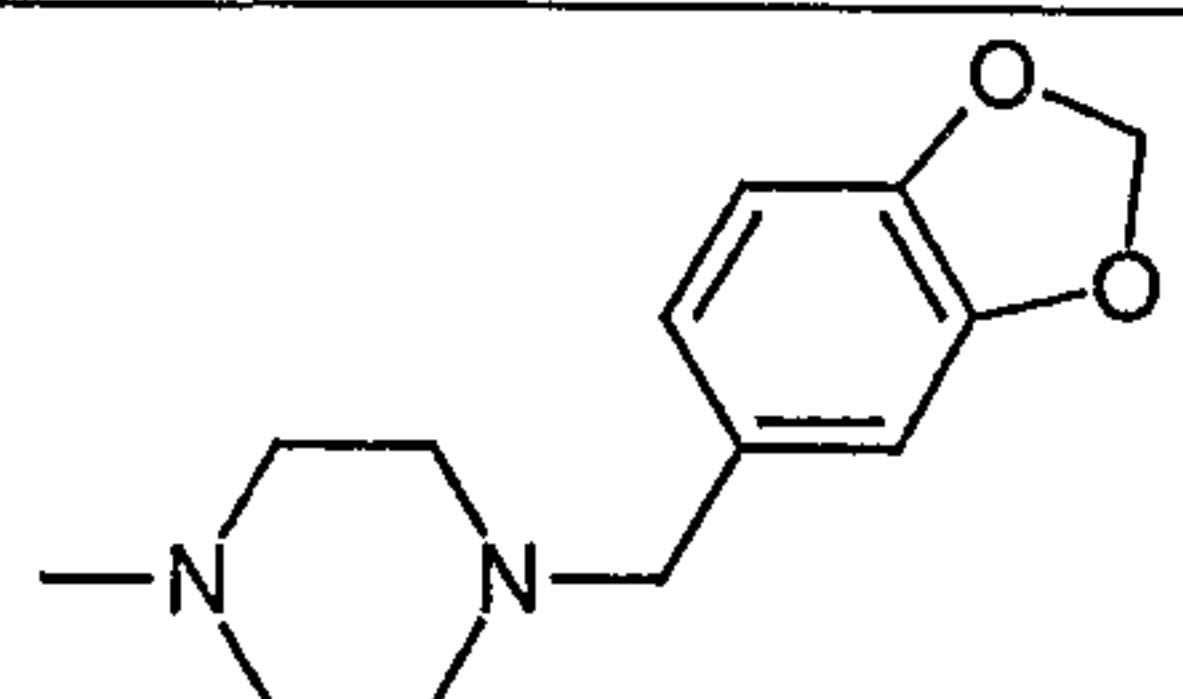
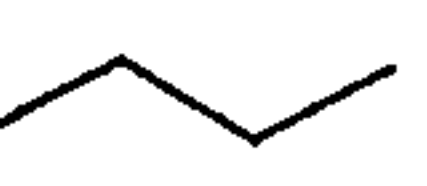
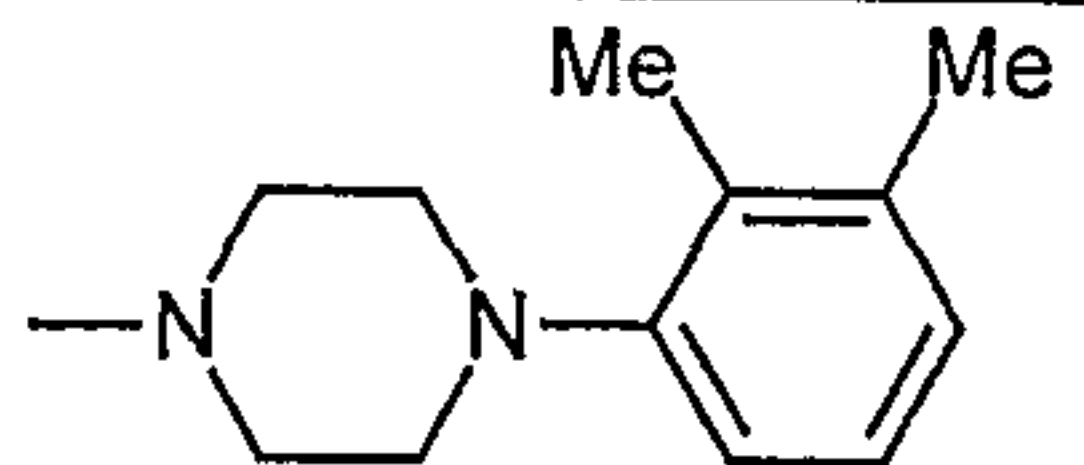
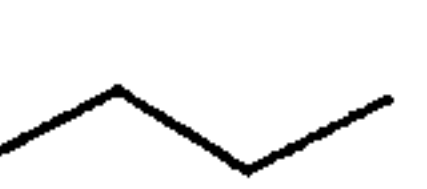
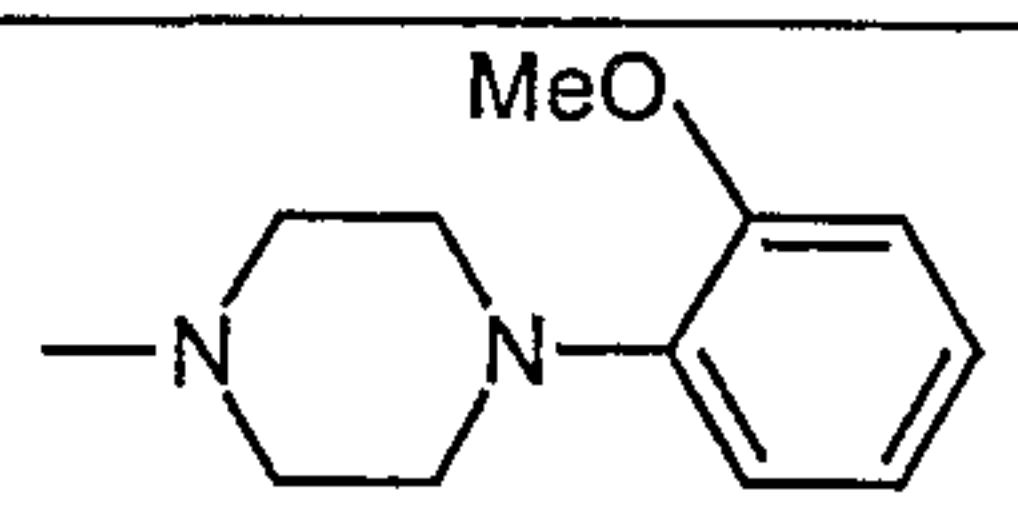
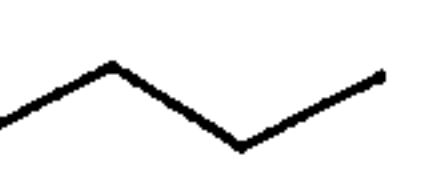
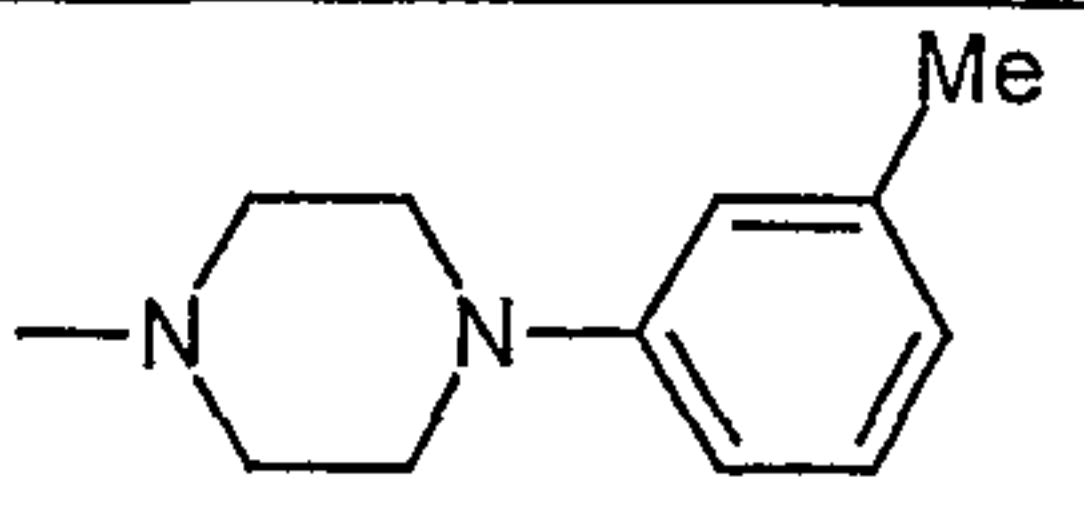
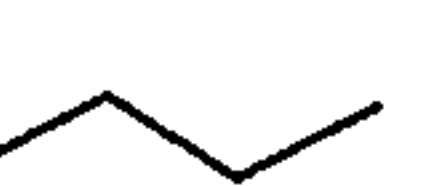
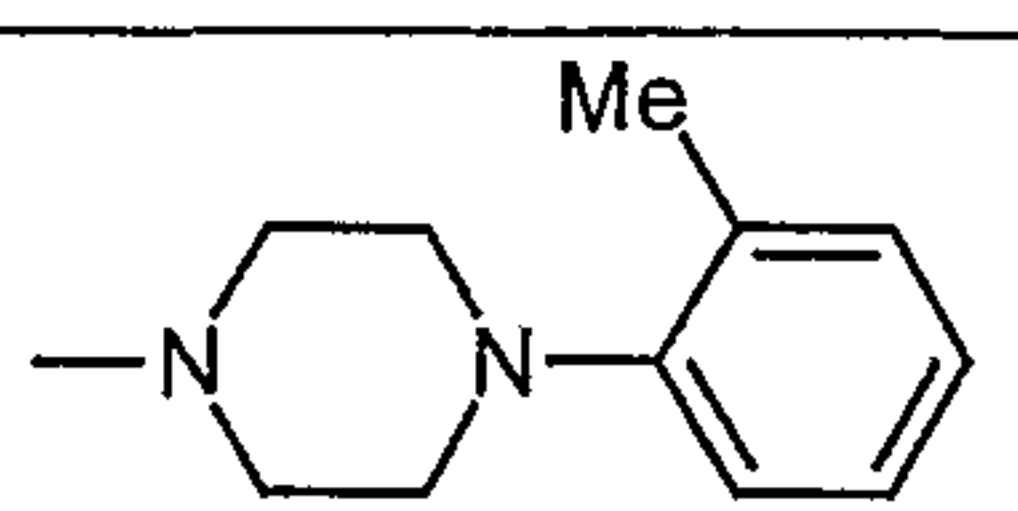
Comp. No	-R ¹	-A-		[M+H] ⁺
248				499
249				561
250				474
251				492
252				513
253				502
254				472
255				474
256				458
257				458

Table 3 (continued):

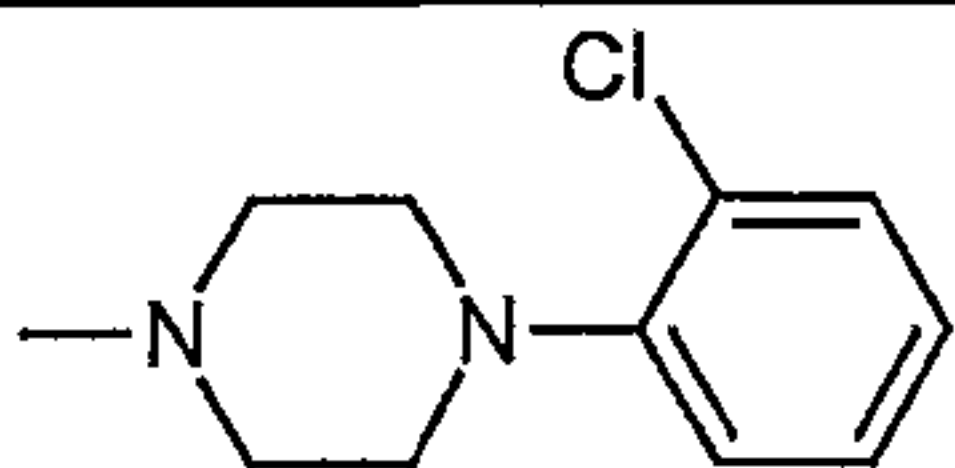
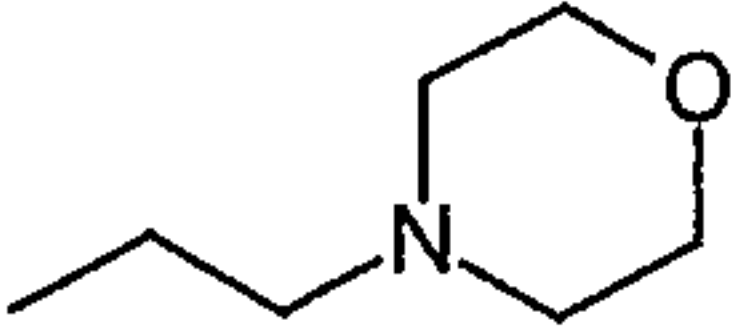
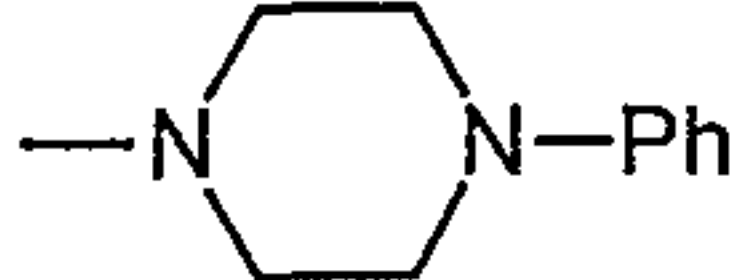
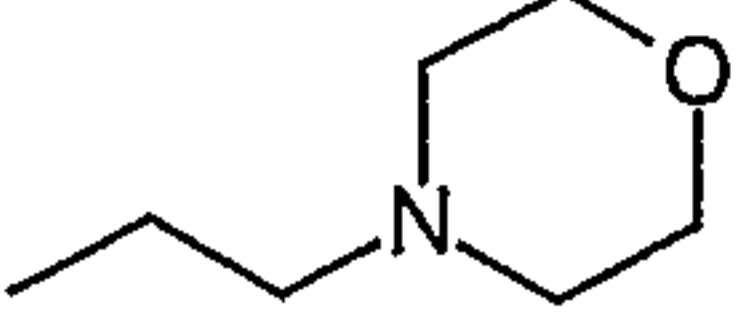
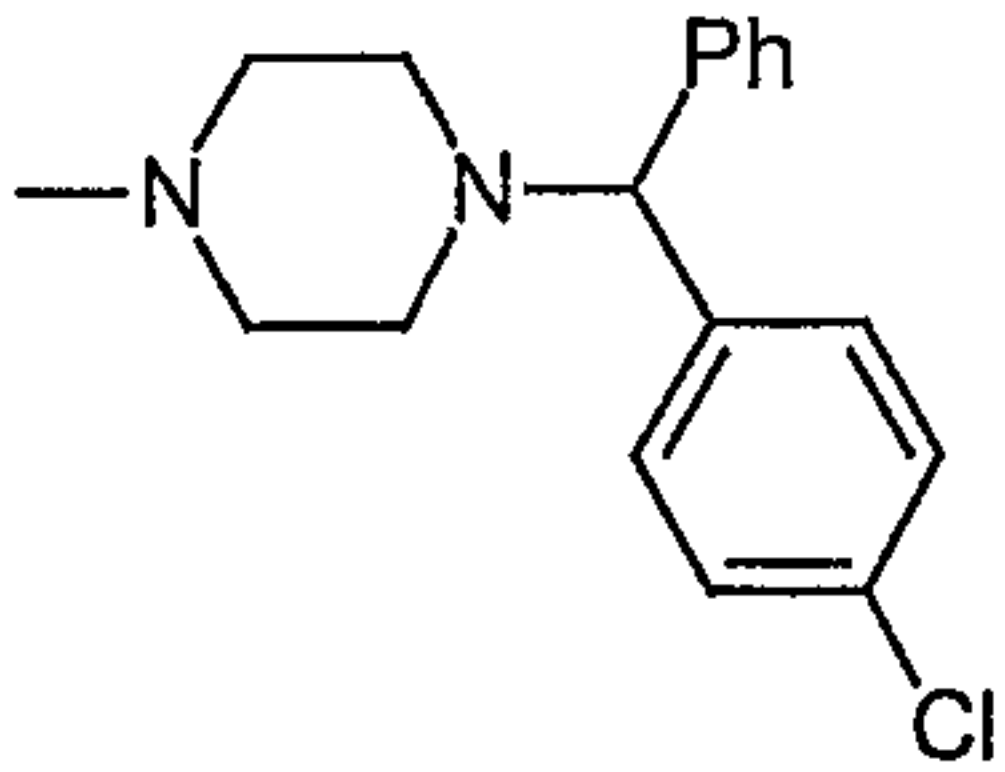
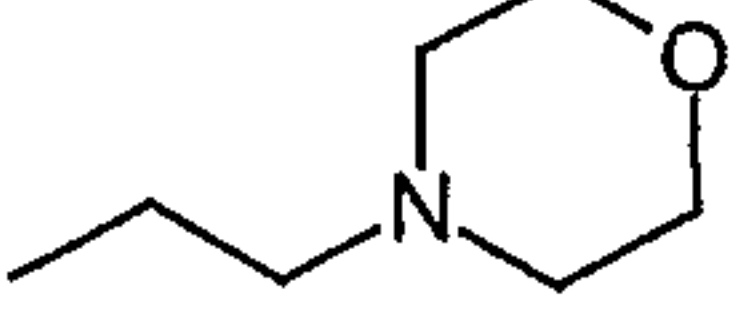
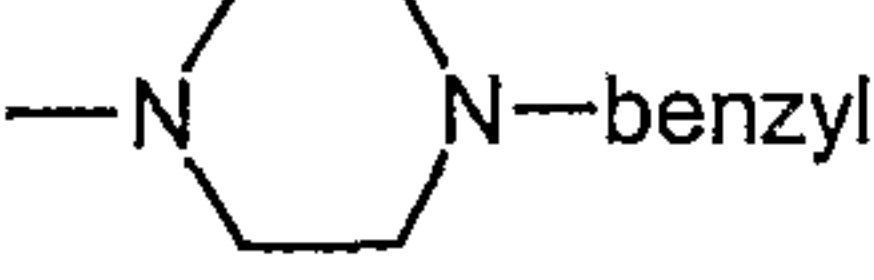
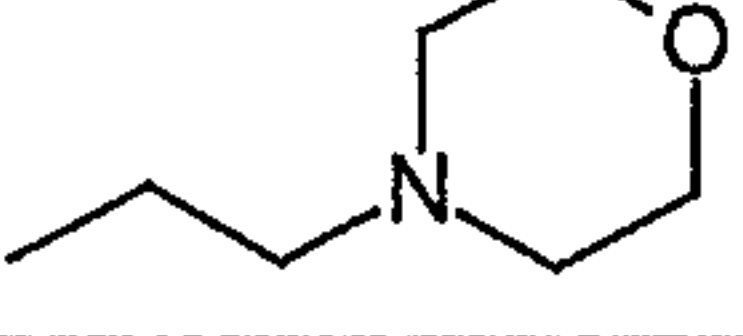
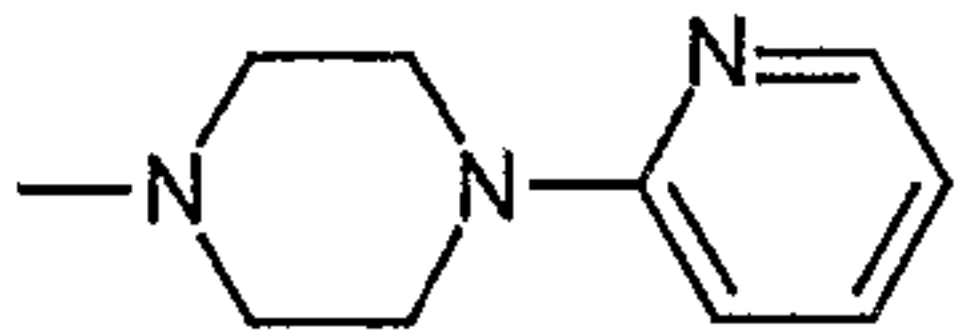
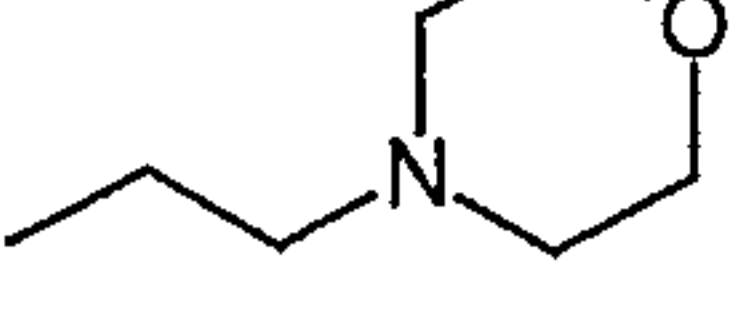
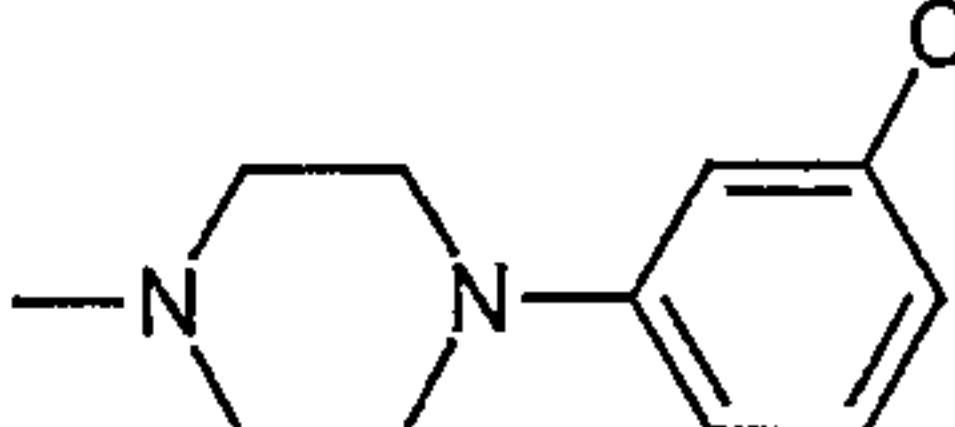
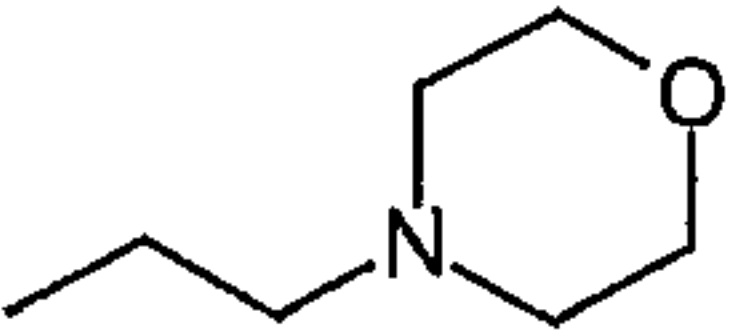
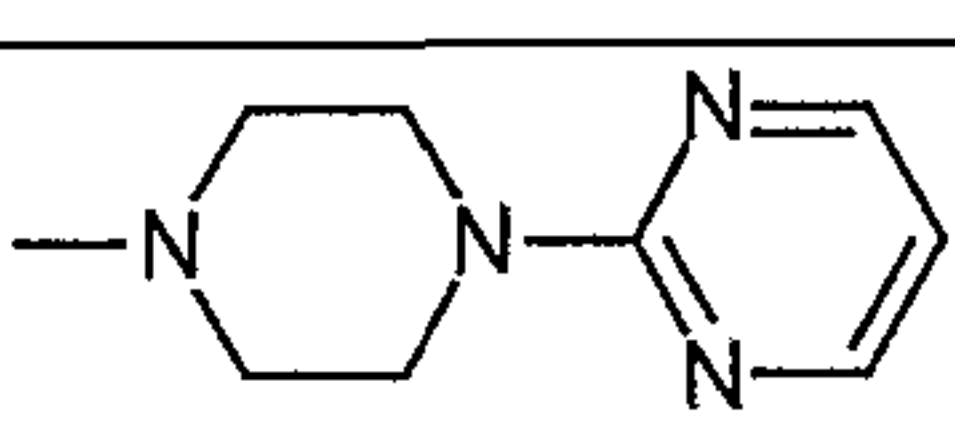
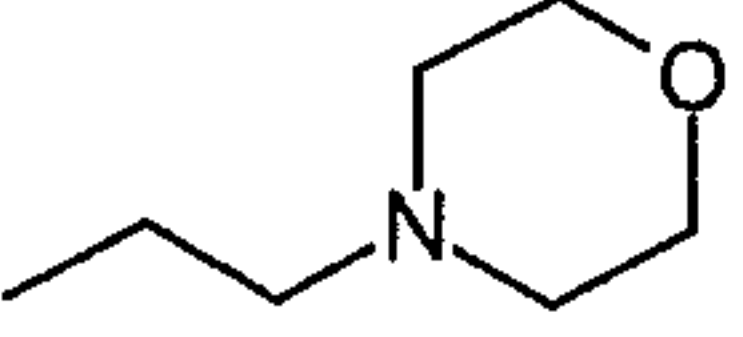
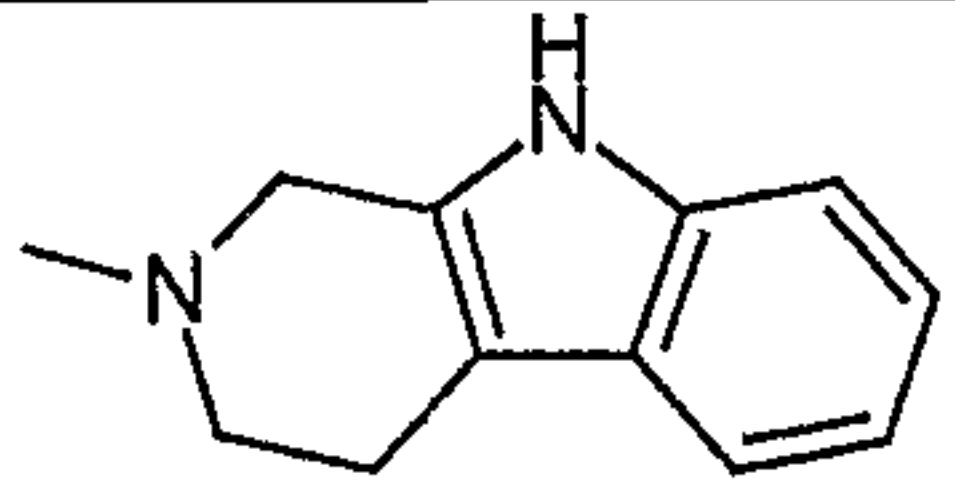
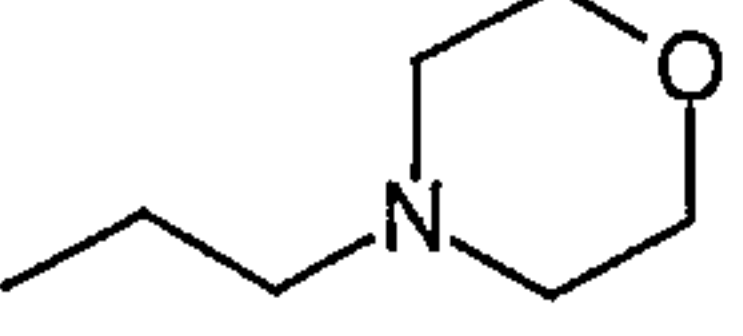
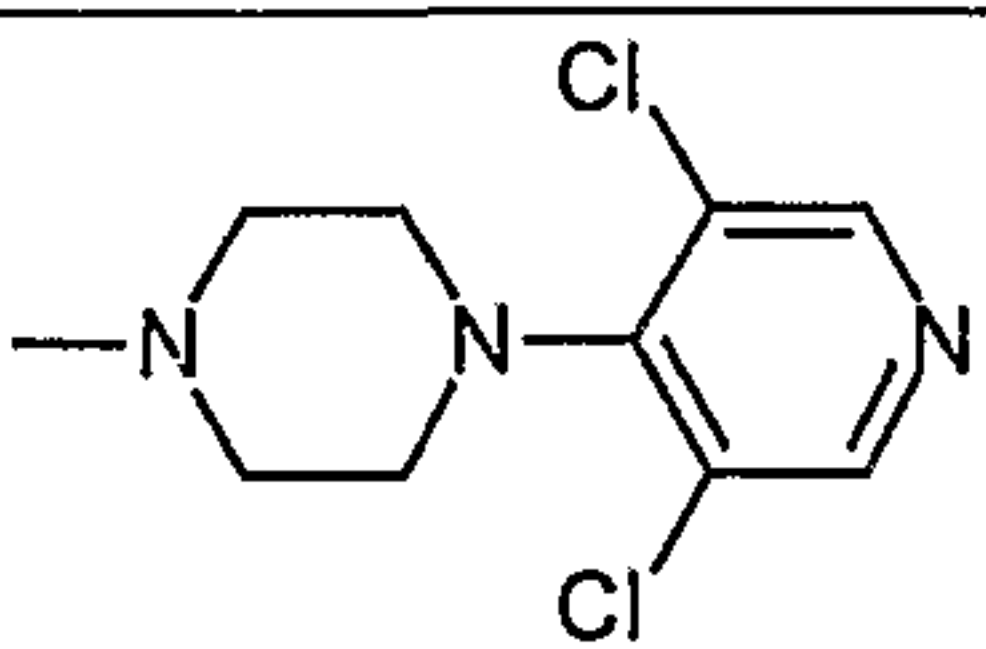
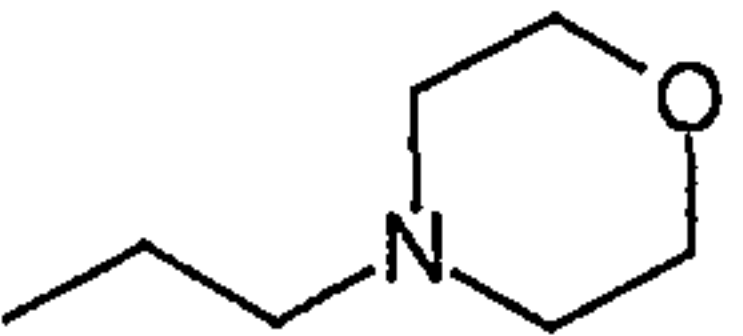
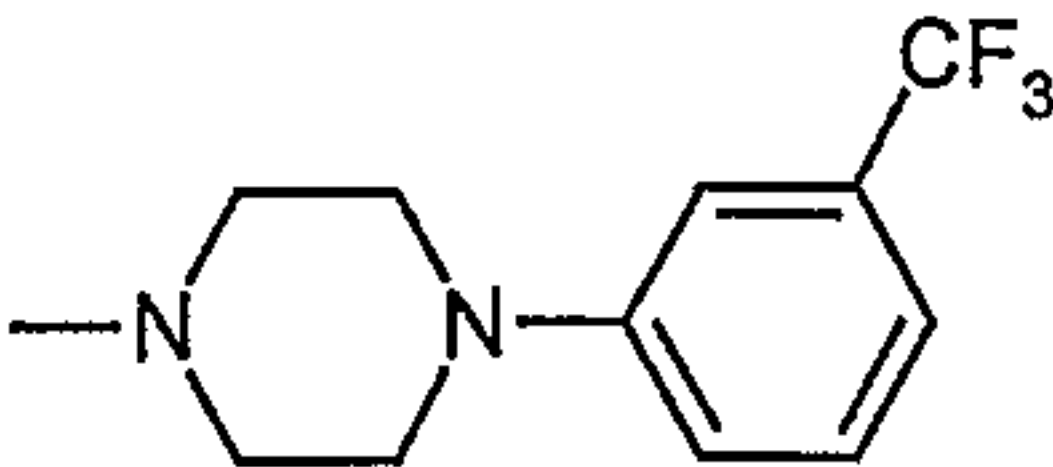
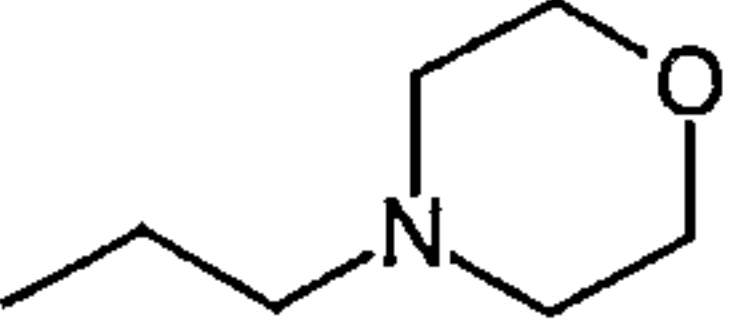
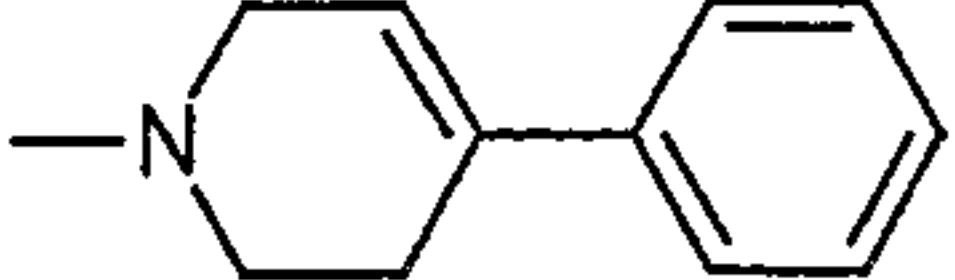
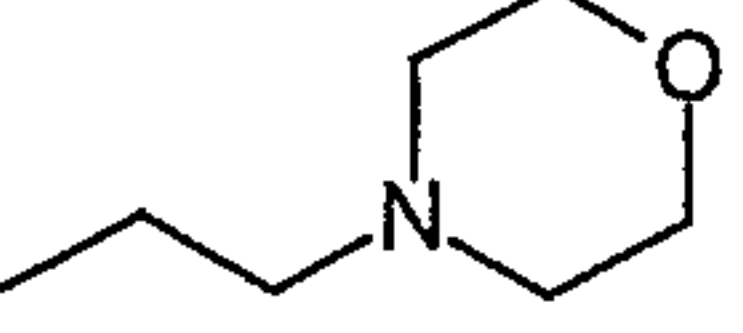
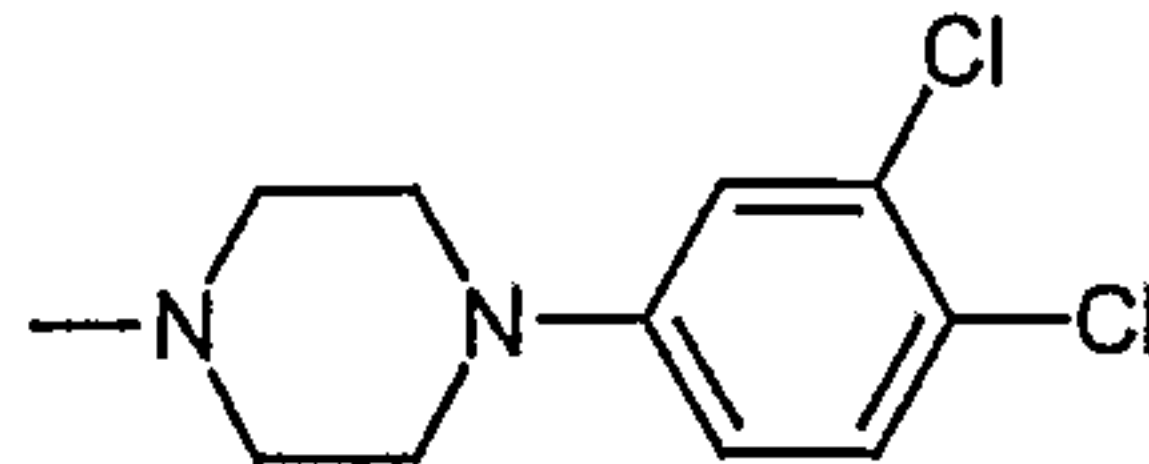
Comp. No	-R ¹	-A-	$\begin{array}{c} R^2 \\ \\ -N- \\ \\ R^3 \end{array}$	[M+H] ⁺
258				478
259				462
260				586
261				476
262				463
263				496
264				464
265				472
266				531
267				530
268				459
269				530

Table 3 (continued):

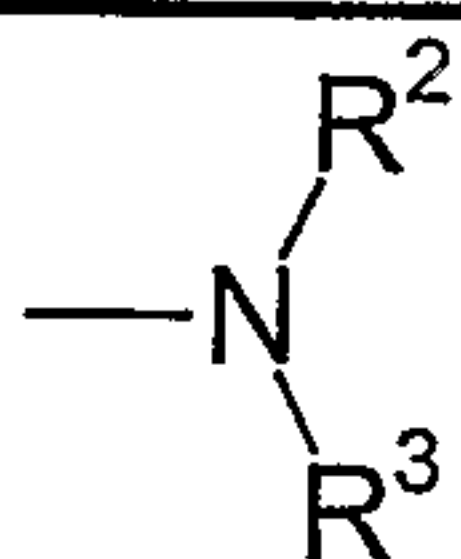
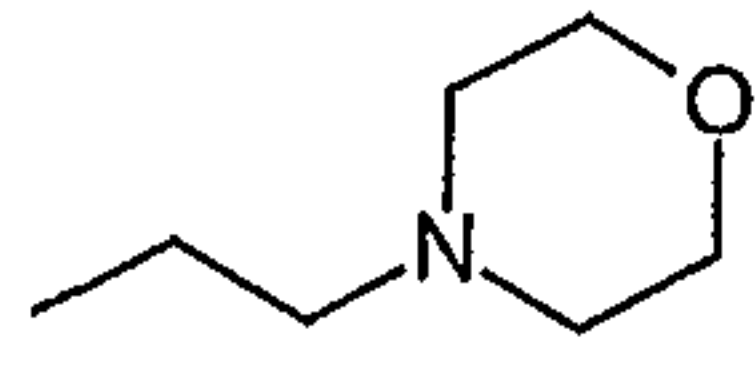
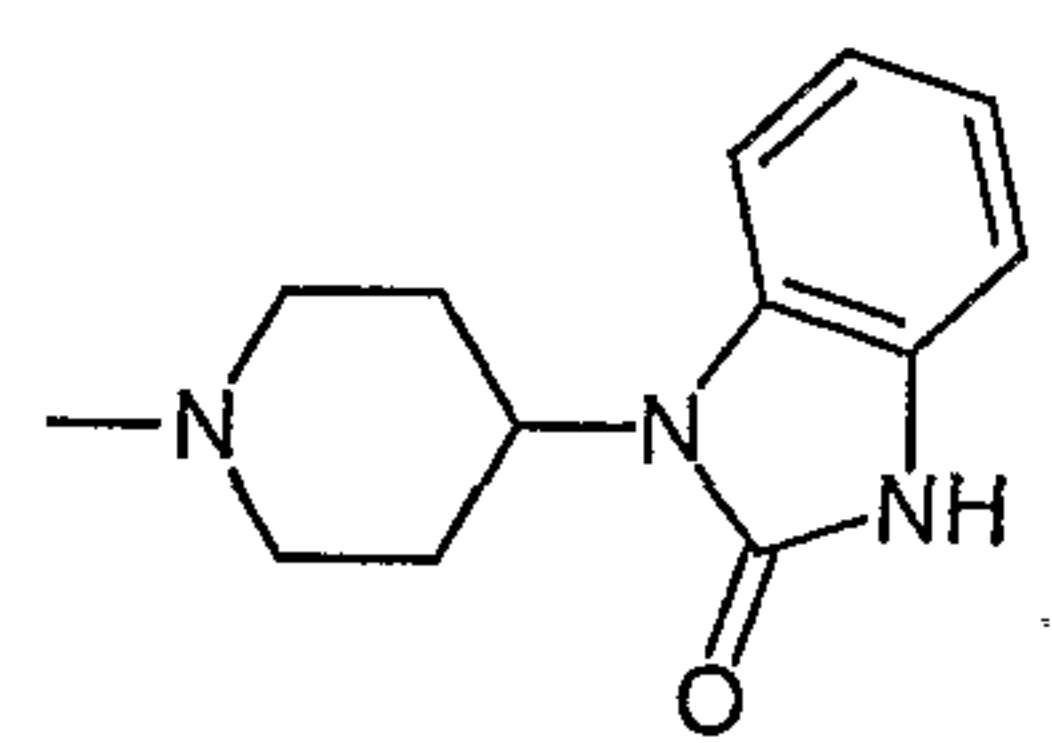
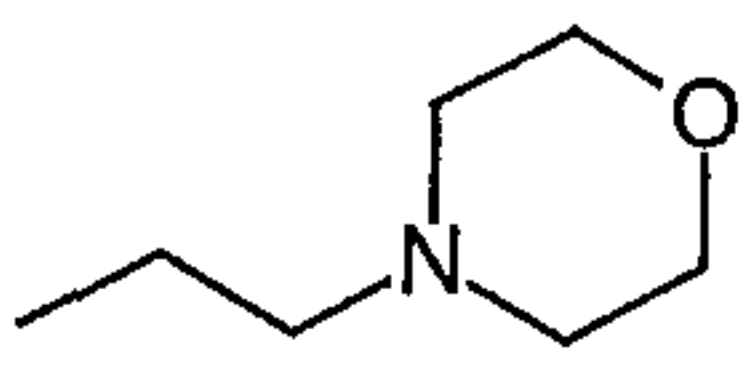
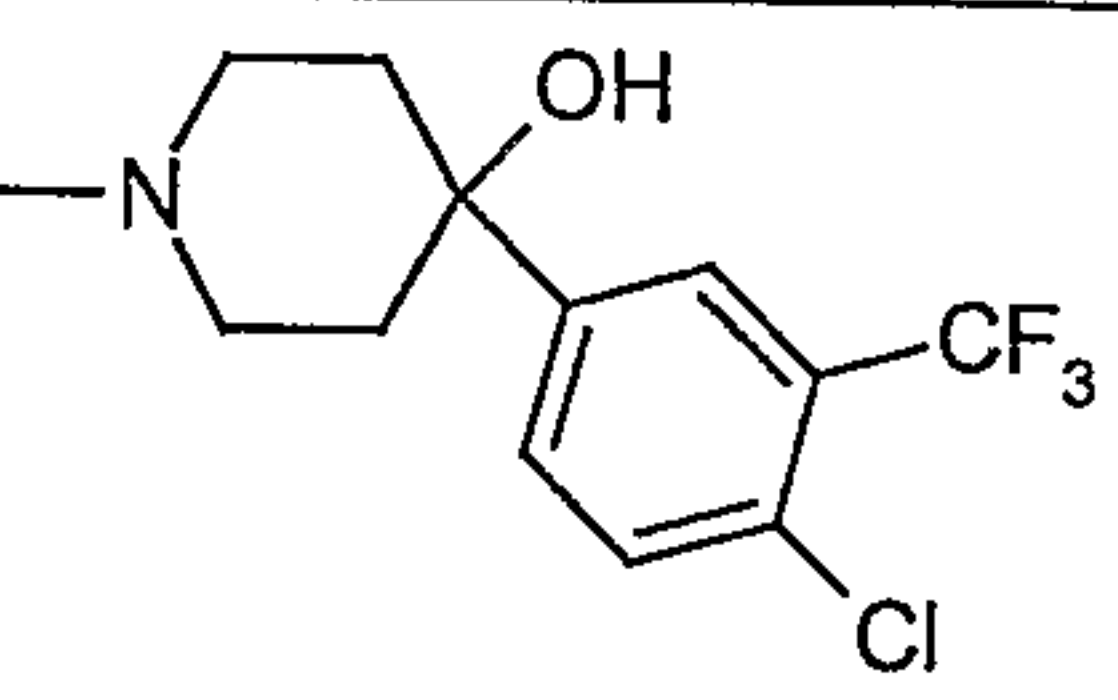
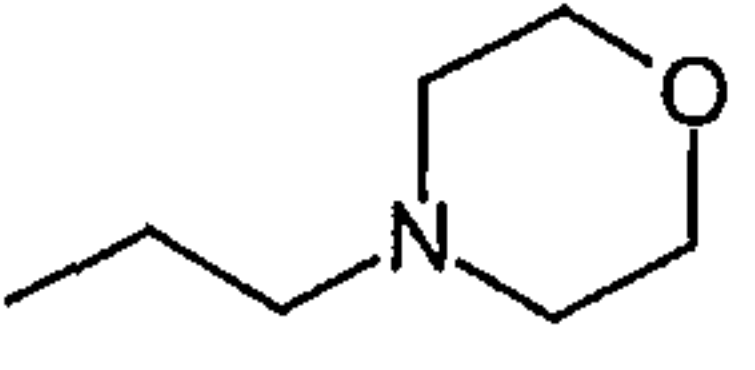
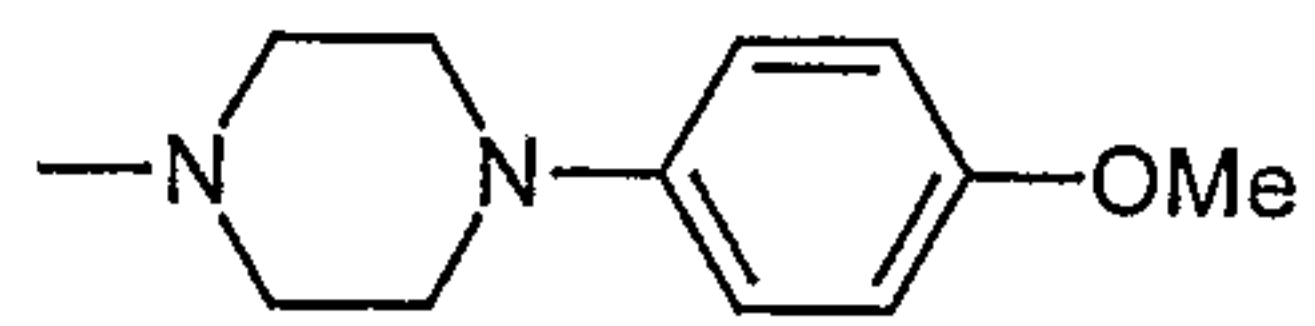
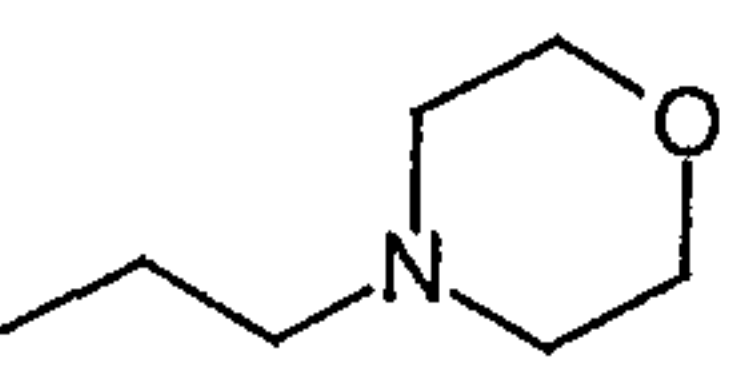
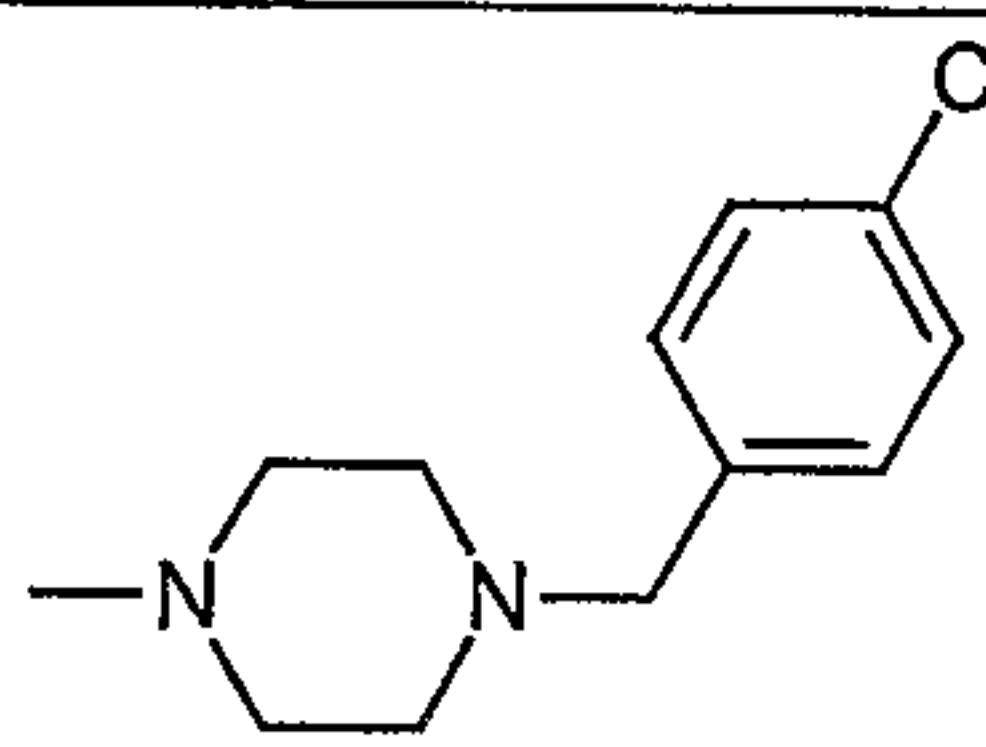
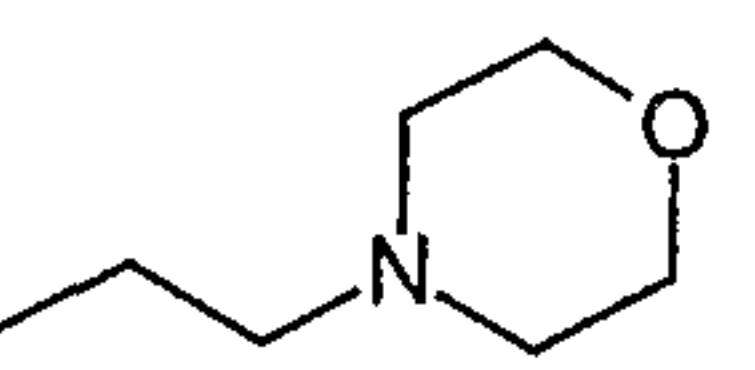
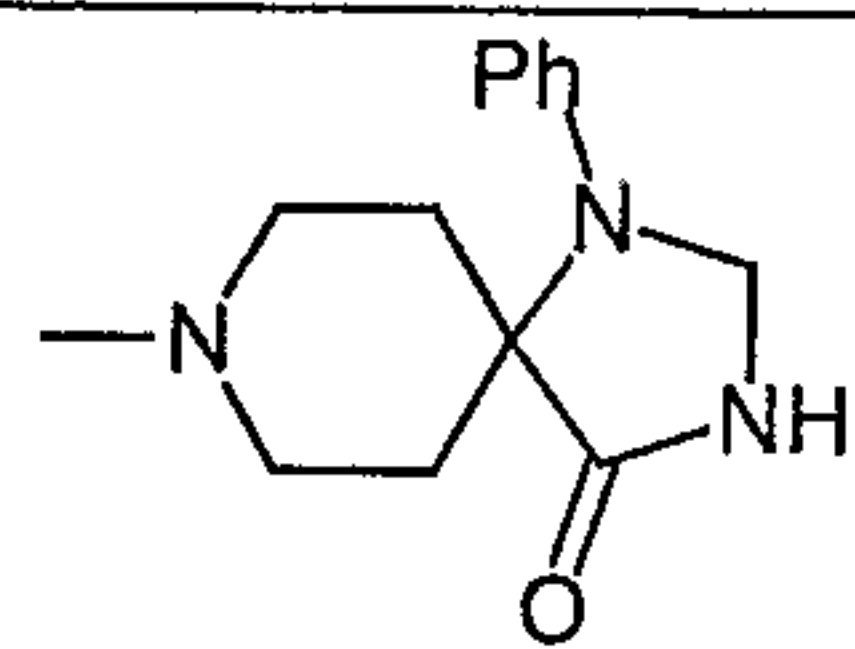
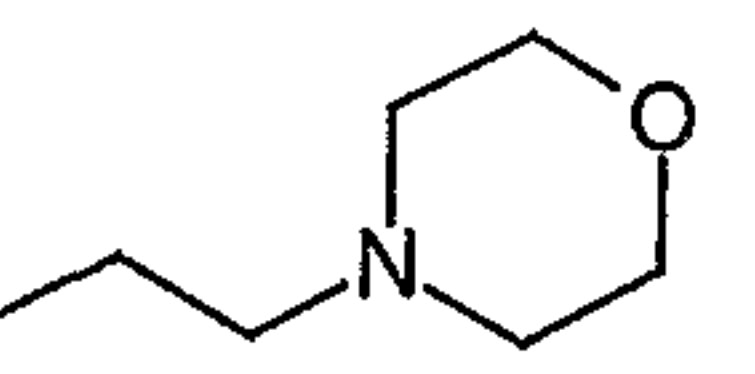
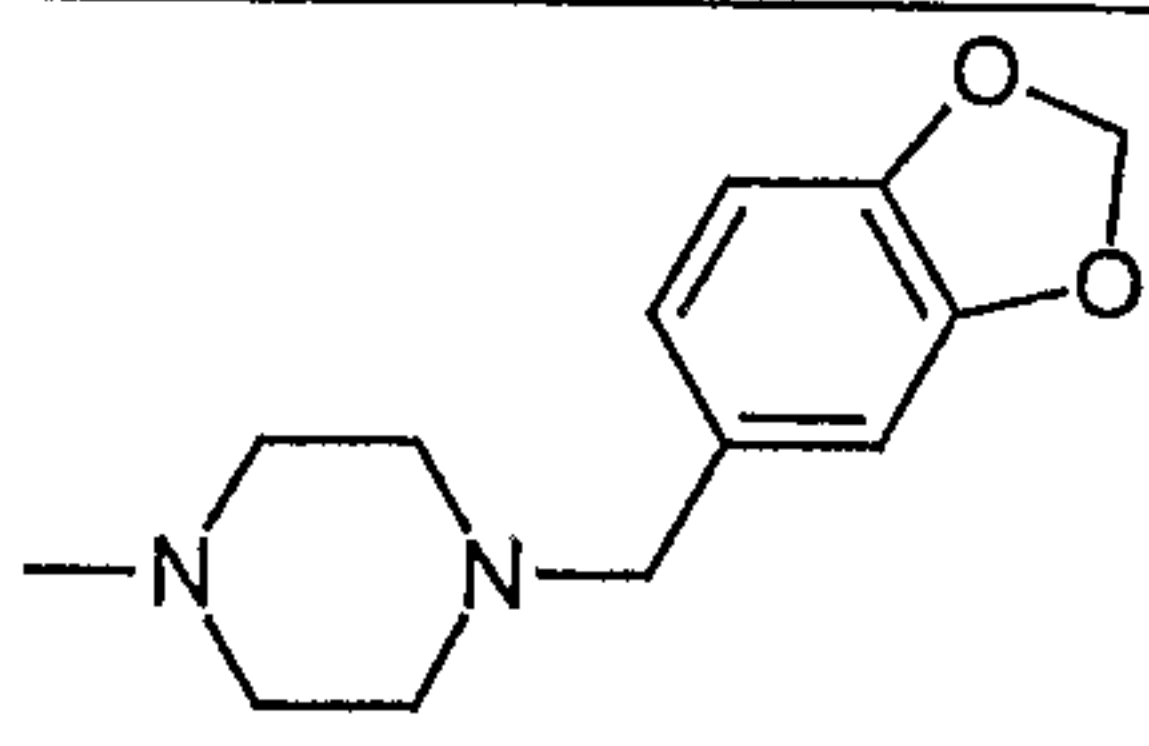
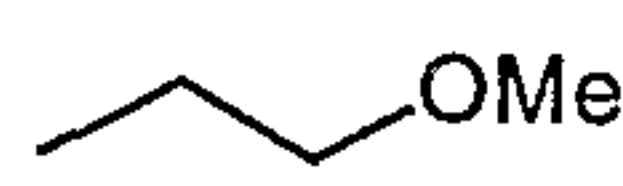
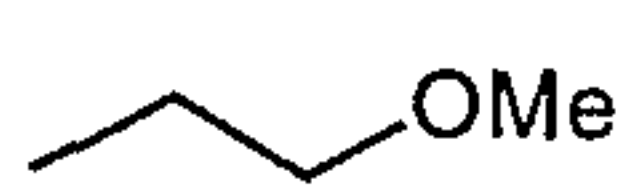
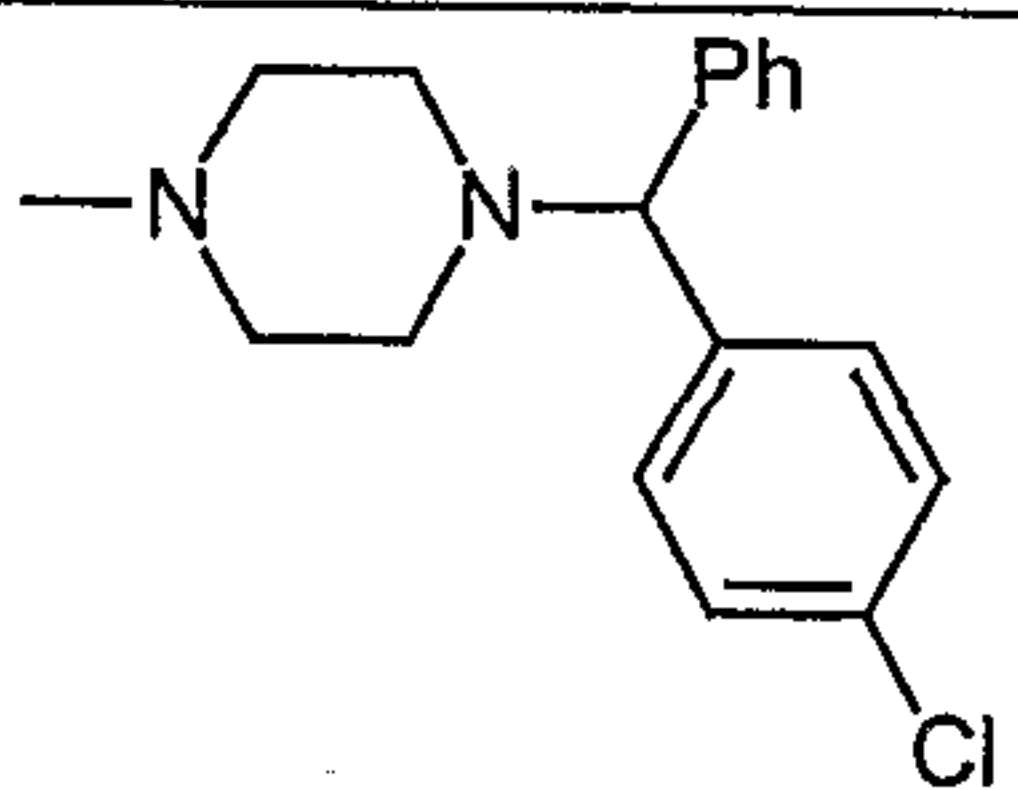
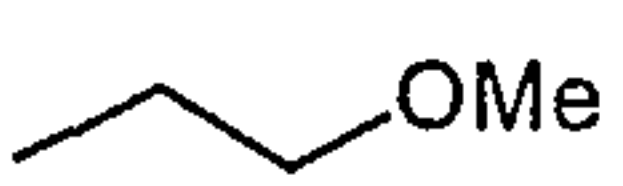
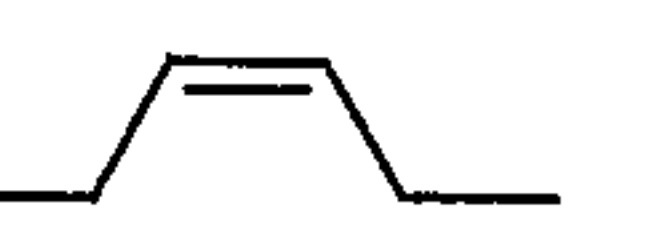
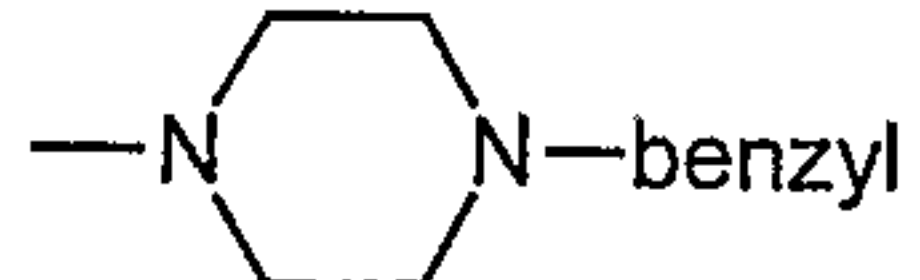
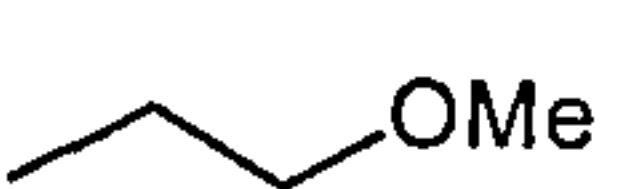
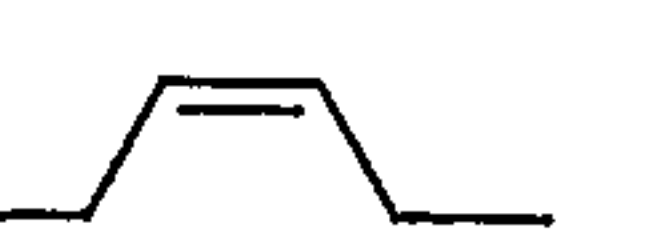
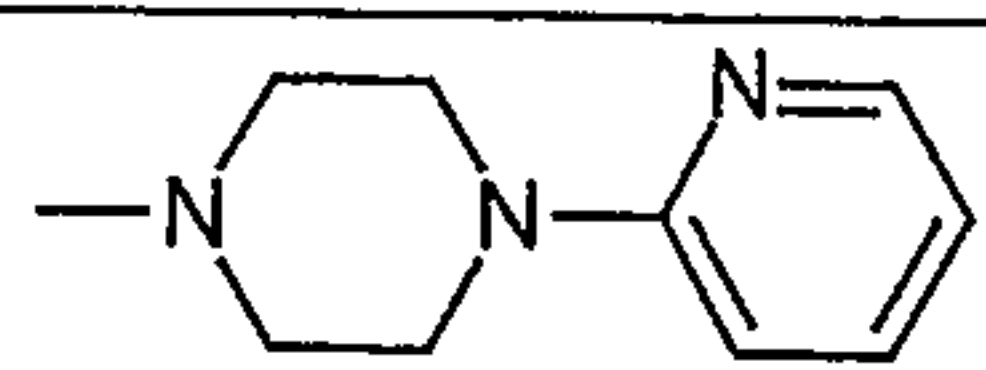
Comp. No	-R ¹	-A-		[M+H] ⁺
270				517
271				579
272				492
273				510
274				531
275				520
276				407
277				531
278				421
279				408

Table 3 (continued):

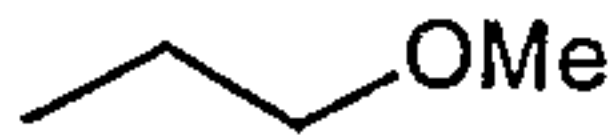
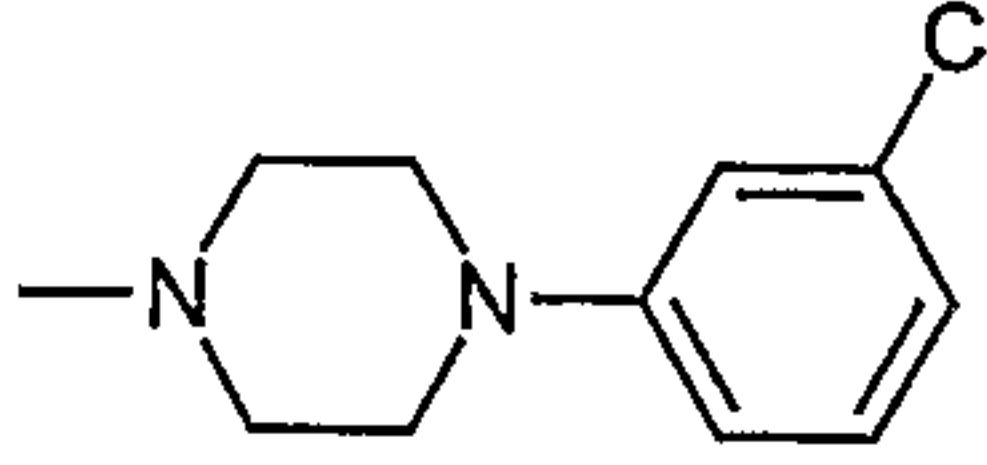
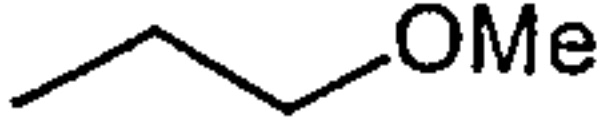
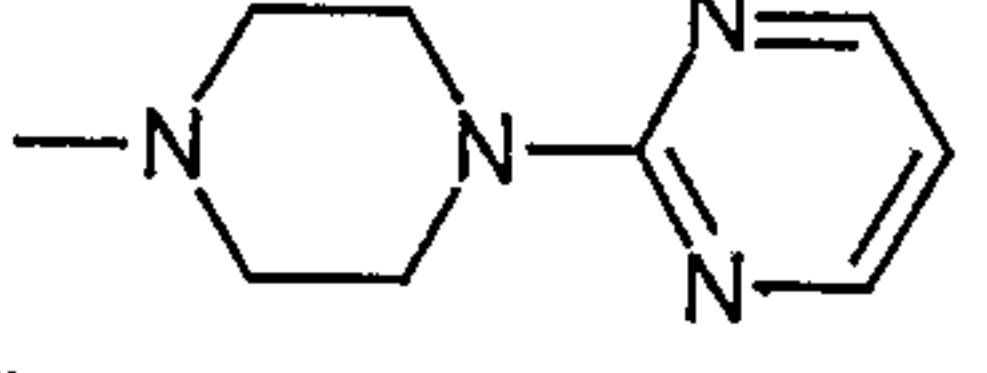
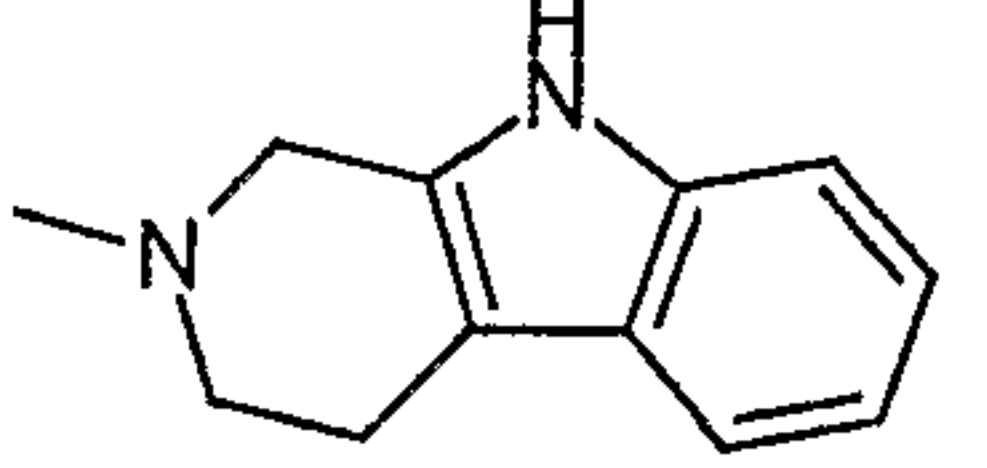
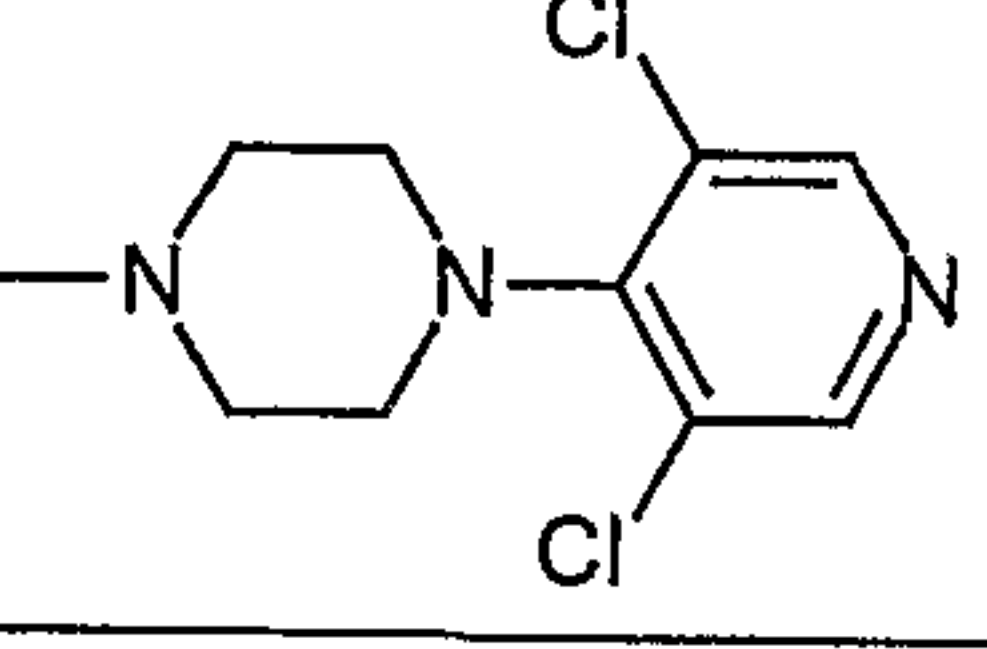
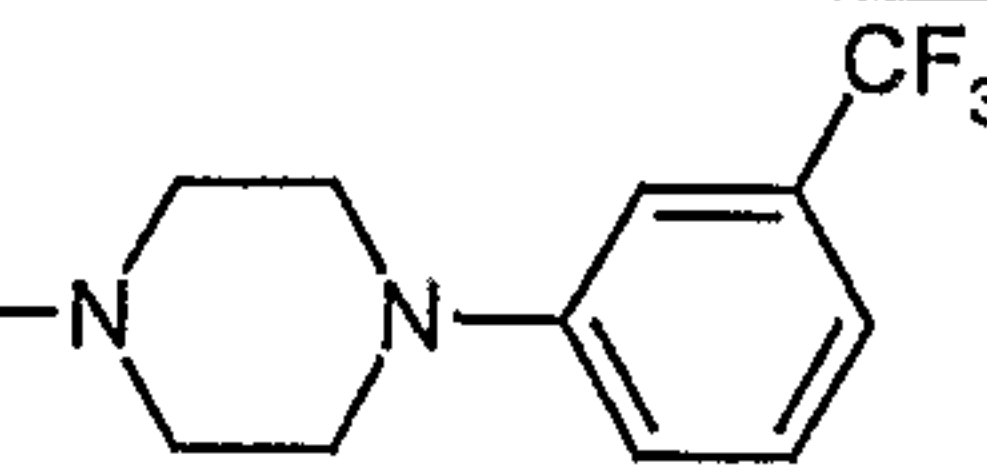
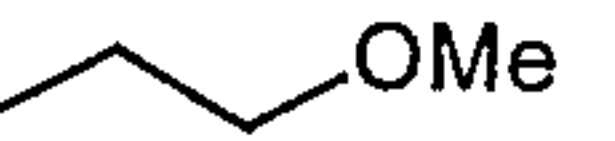
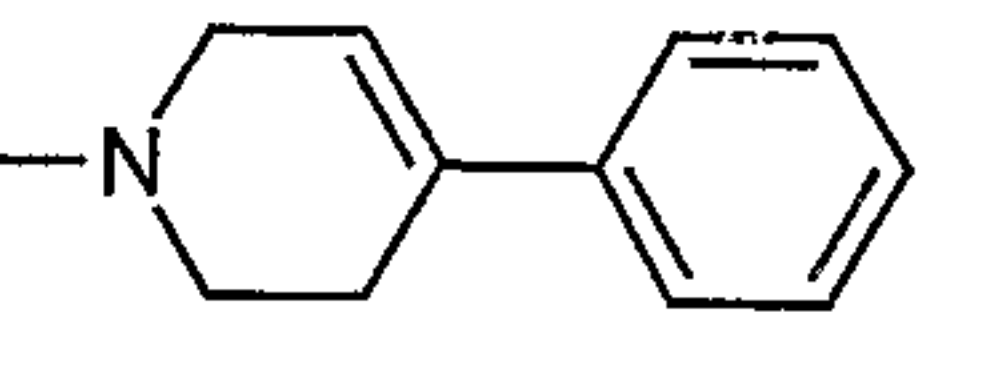
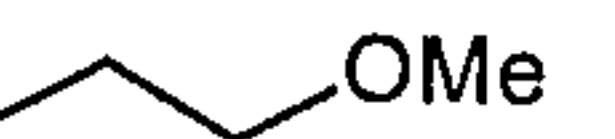
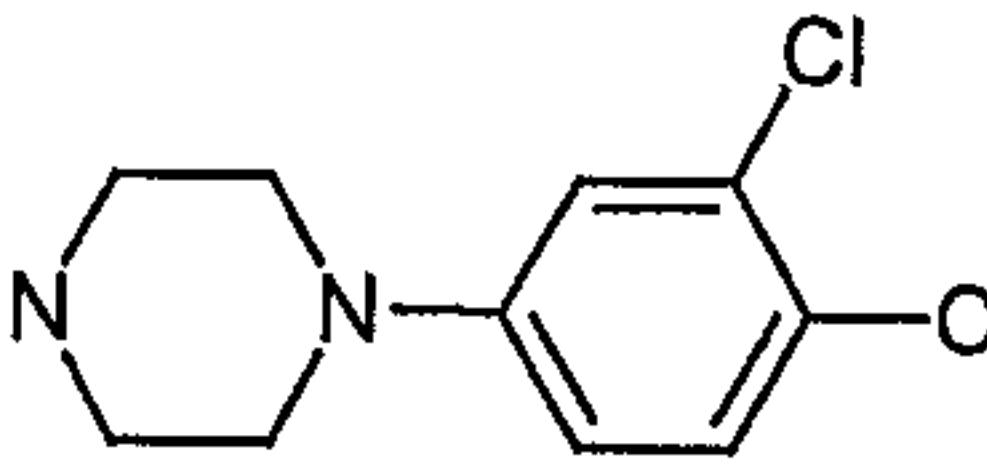
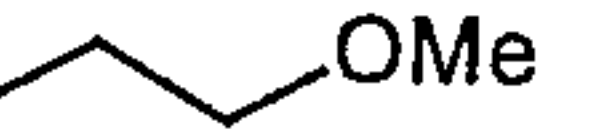
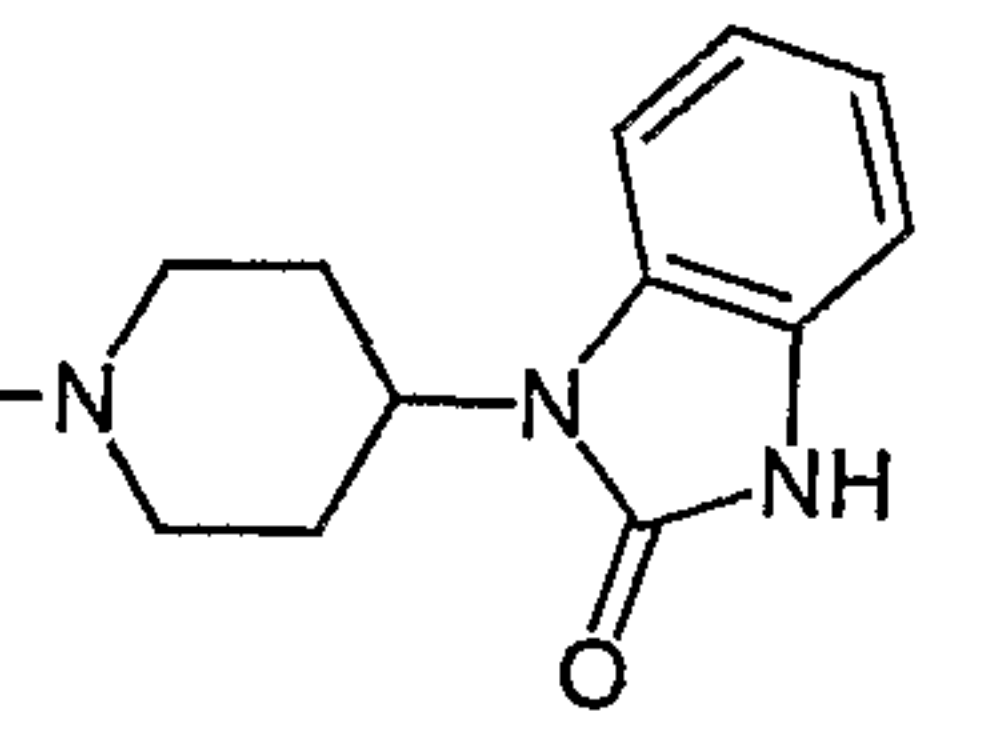
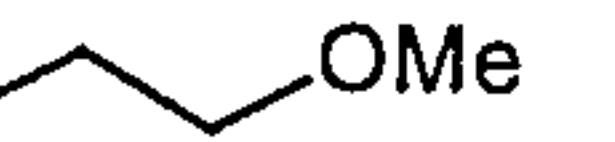
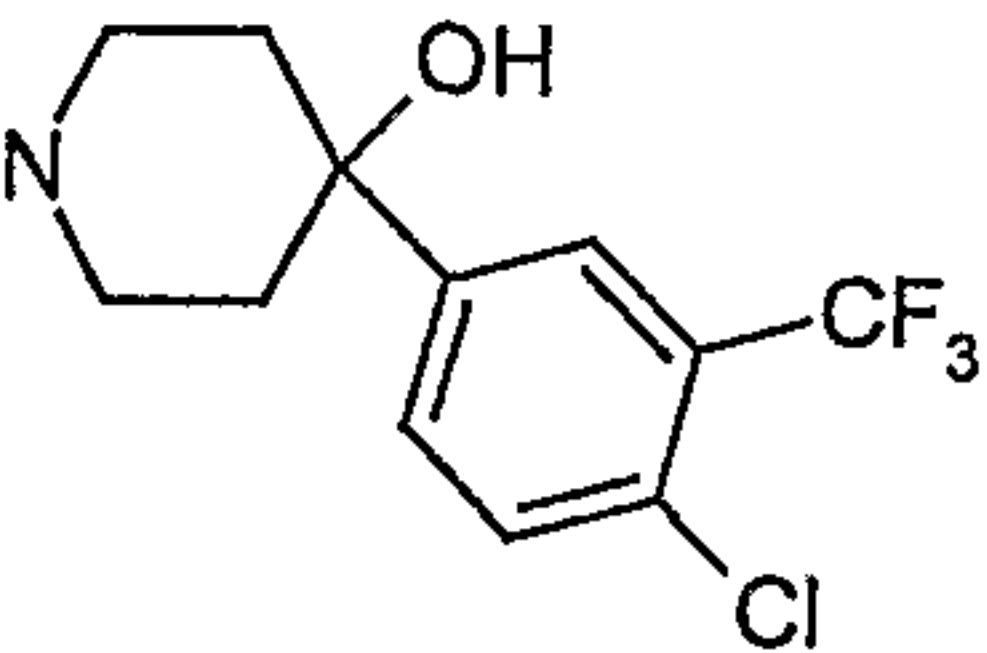
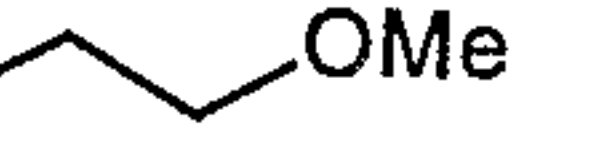
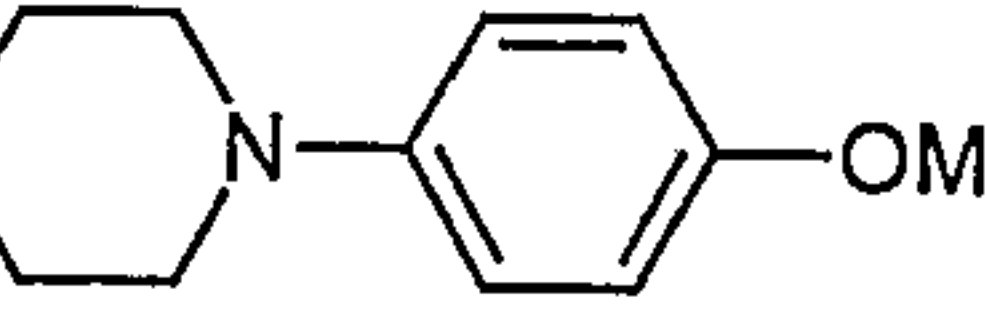
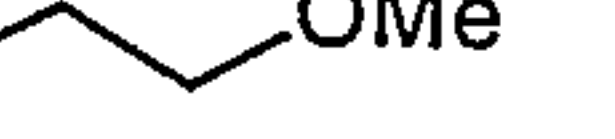
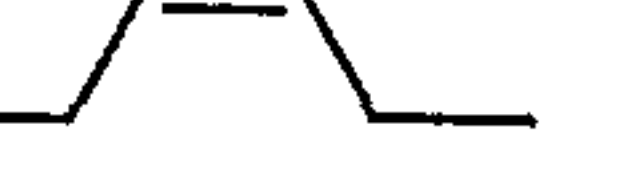
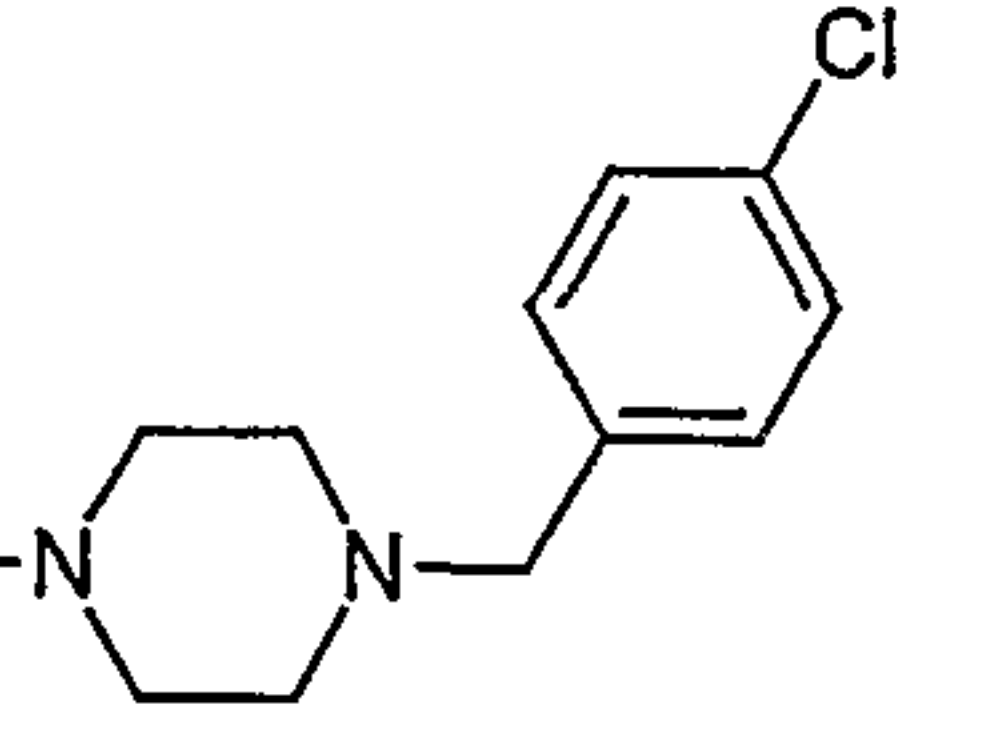
Comp. No	-R ¹	-A-	$\begin{array}{c} \text{R}^2 \\ \\ \text{---N---} \\ \\ \text{R}^3 \end{array}$	[M+H] ⁺
280				441
281				409
282				417
283				476
284				475
285				404
286				475
287				462
288				524
289				437
290				455

Table 3 (continued):

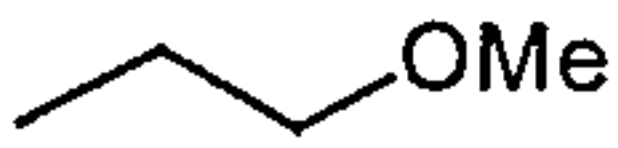
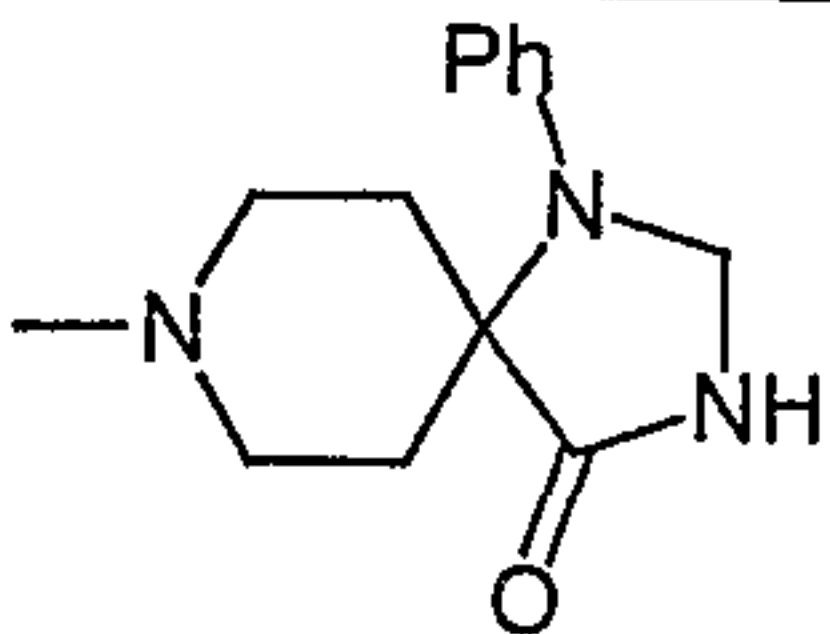
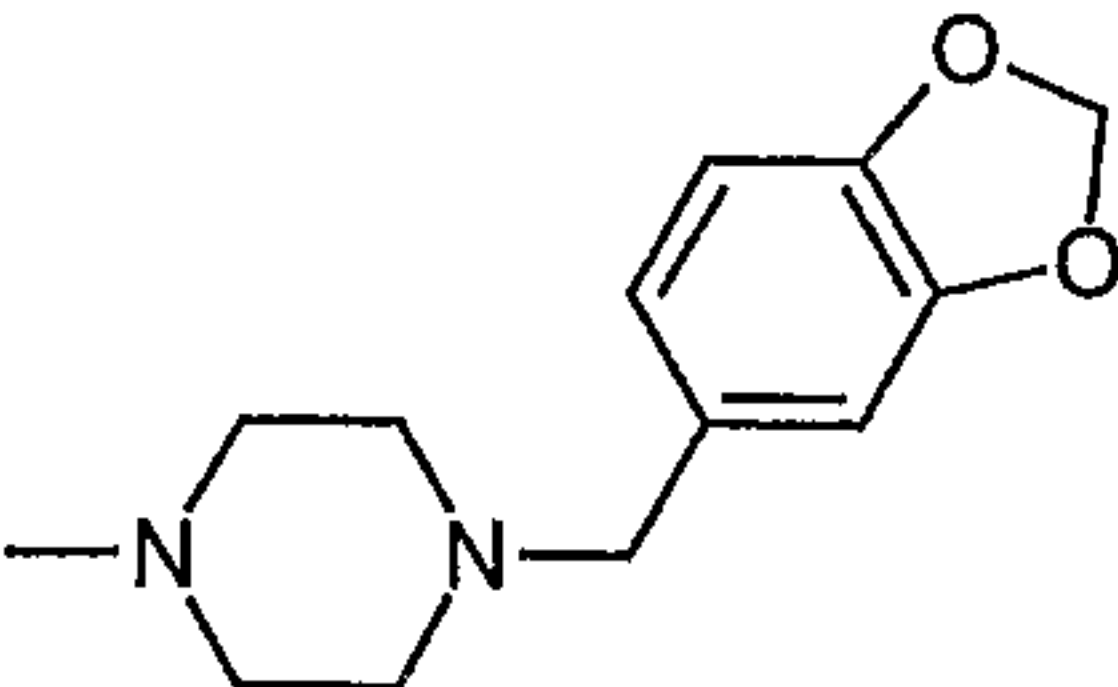
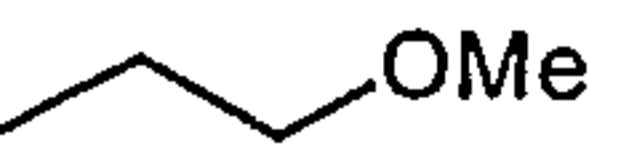
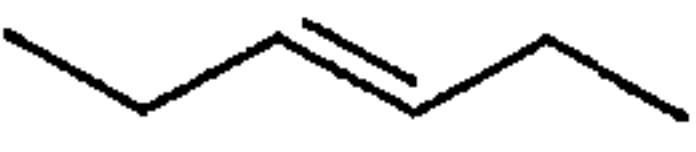
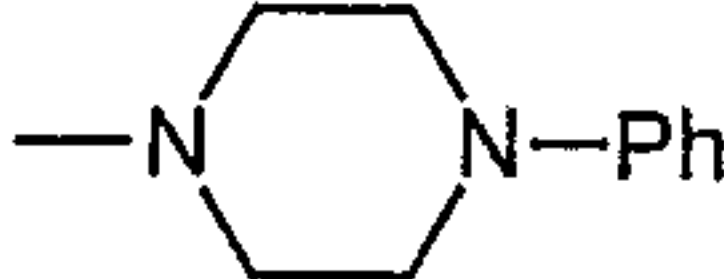
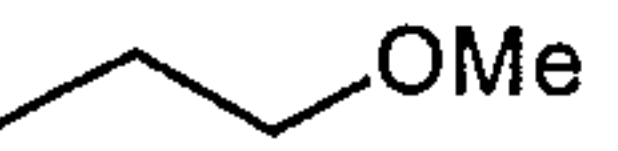
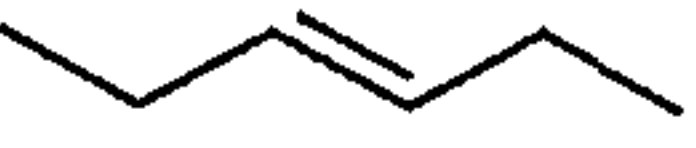
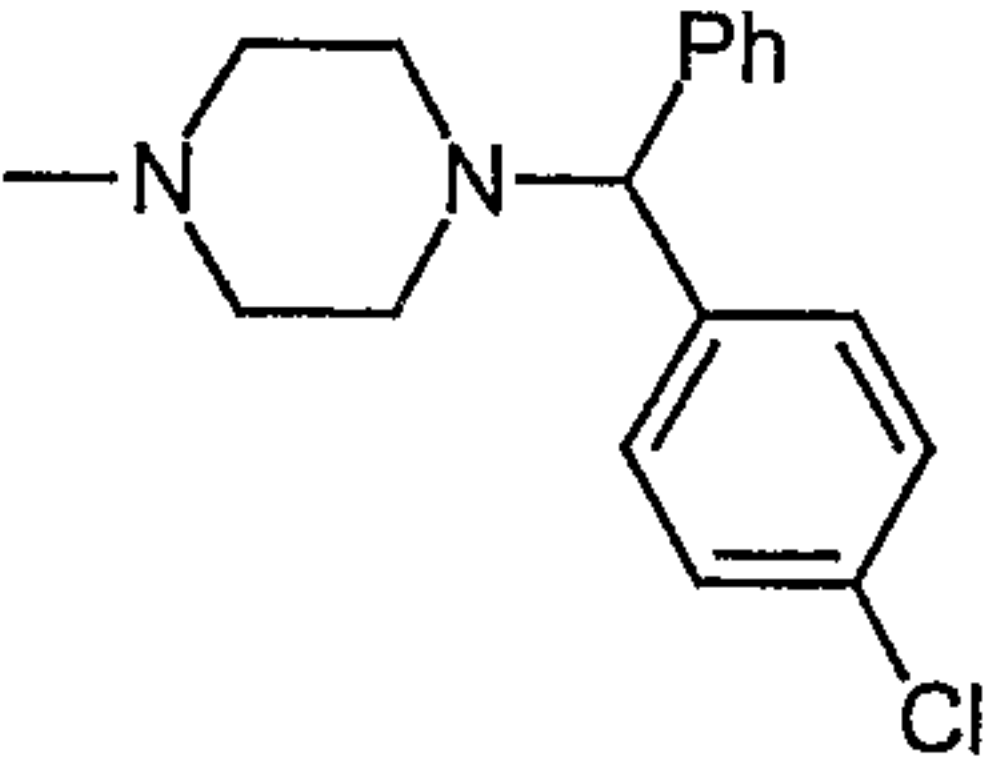
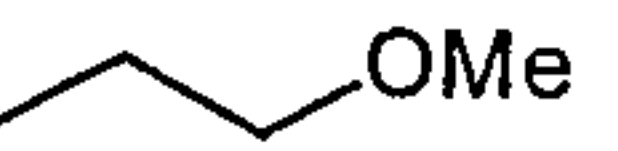
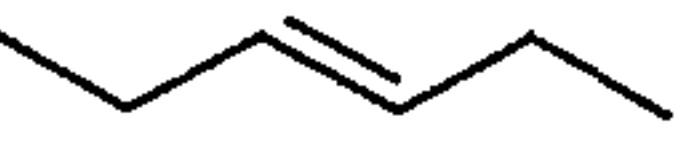
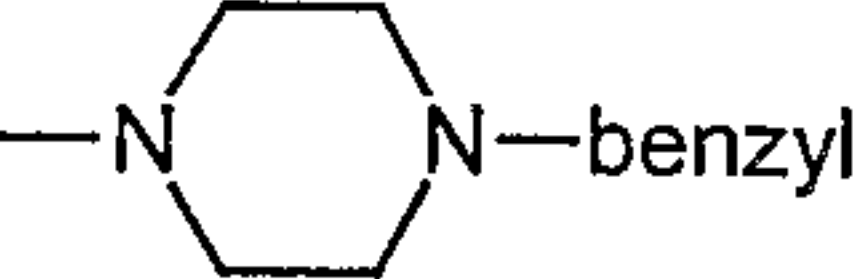
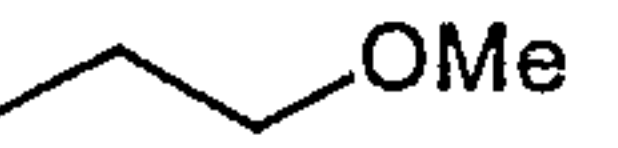
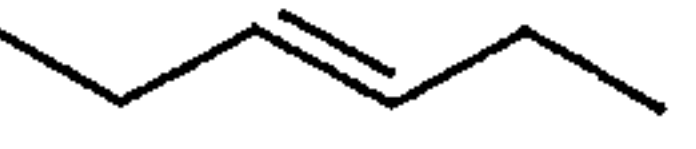
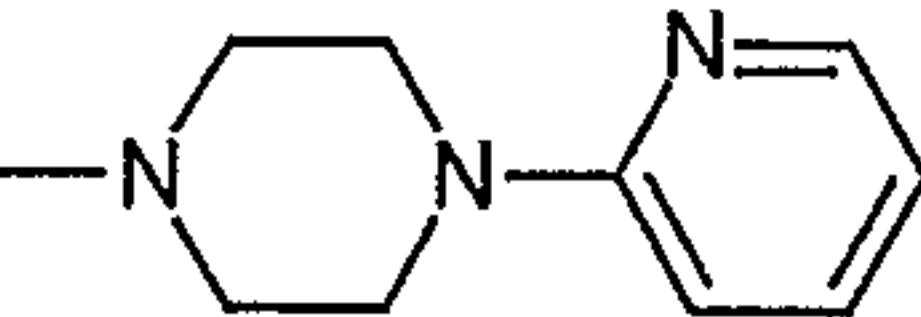
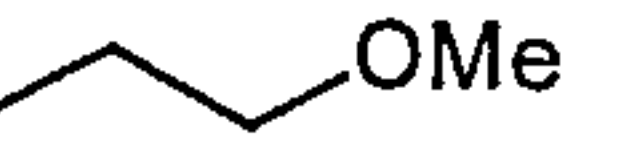
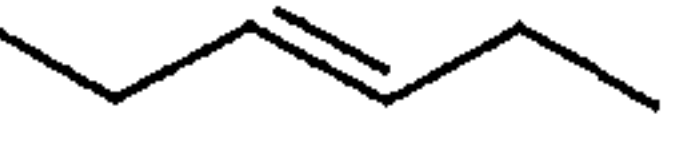
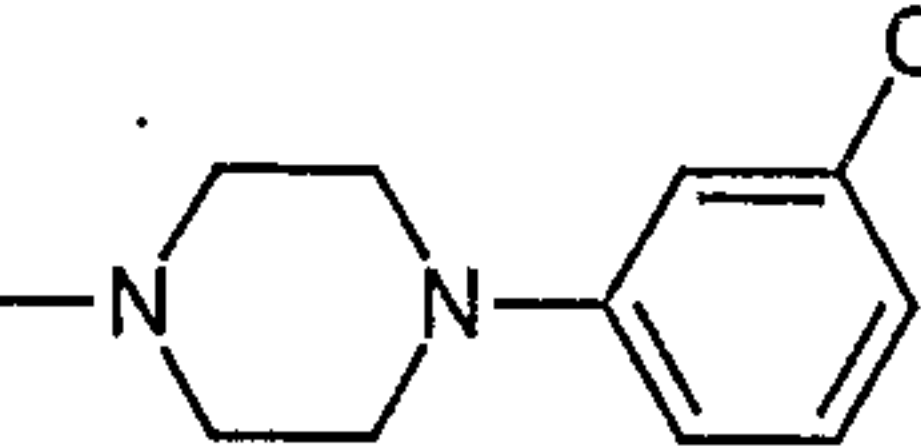
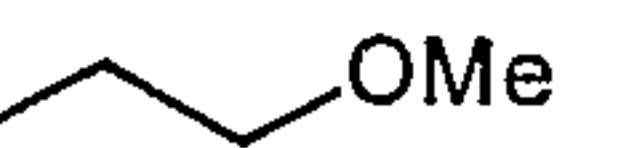
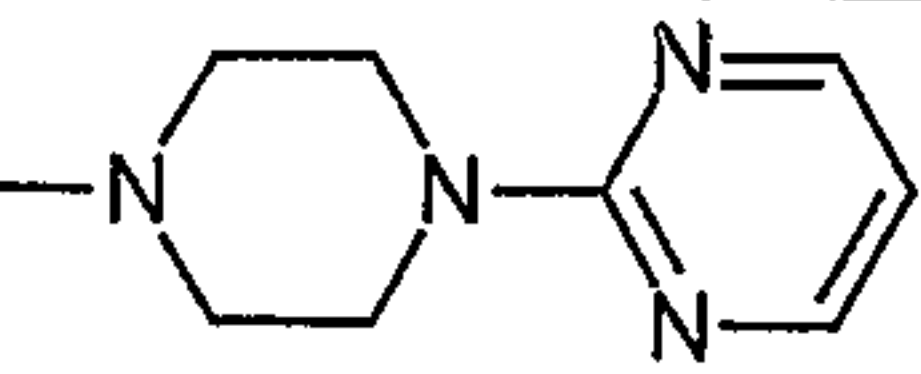
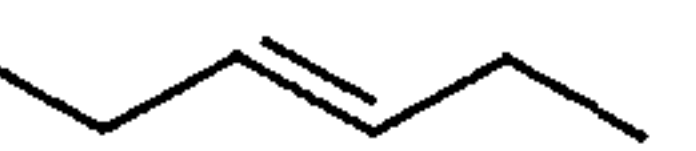
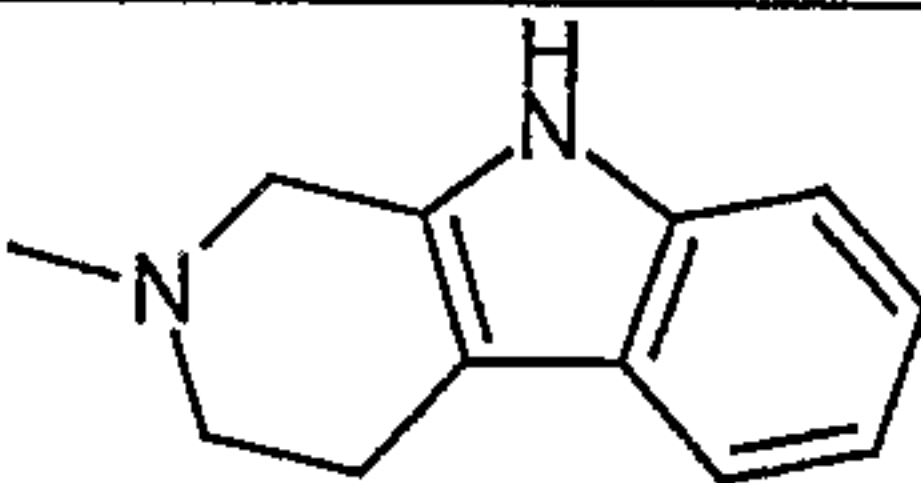
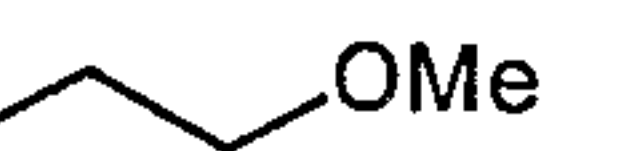
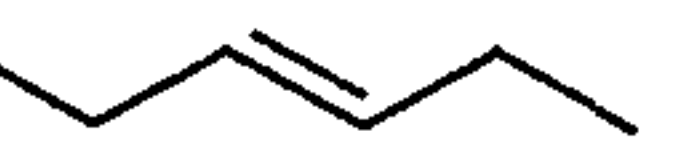
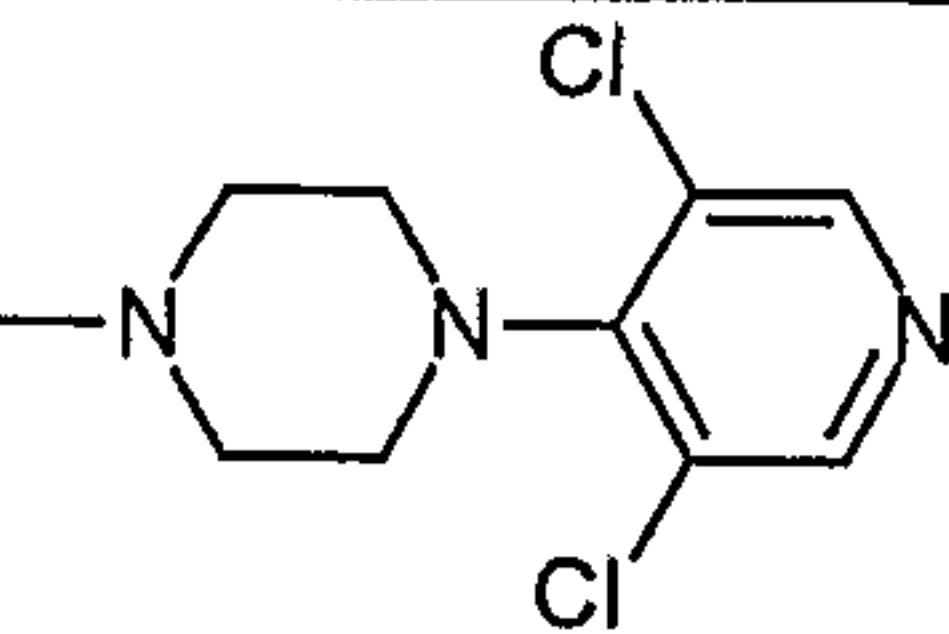
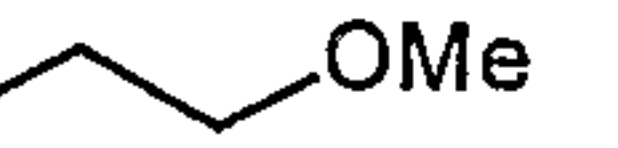
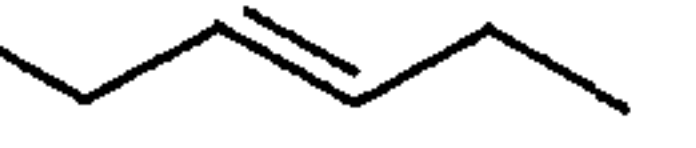
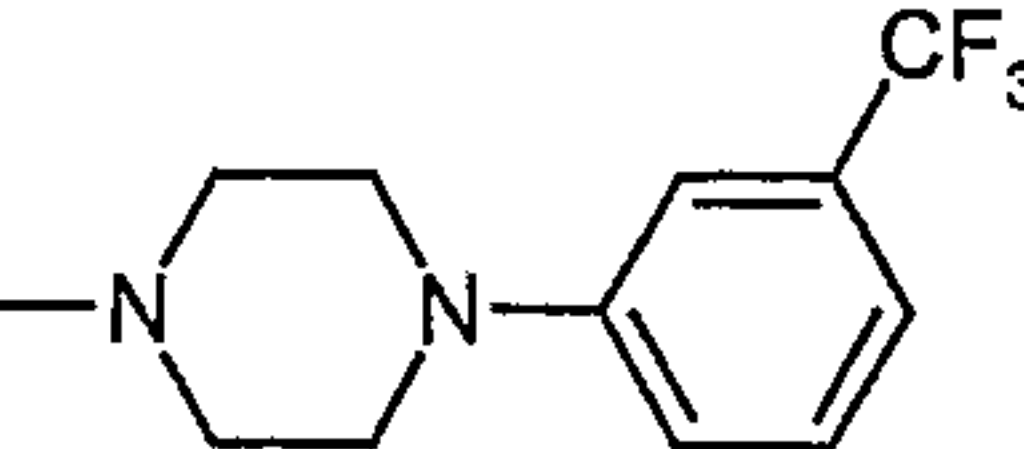
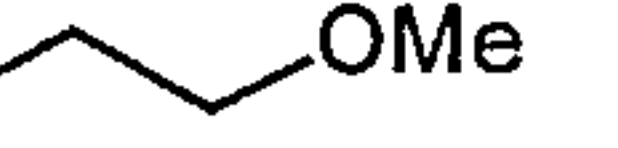
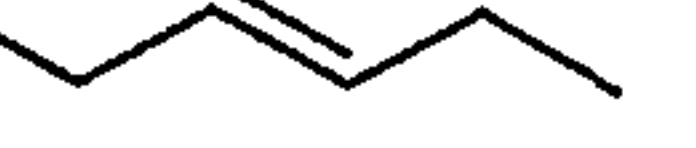
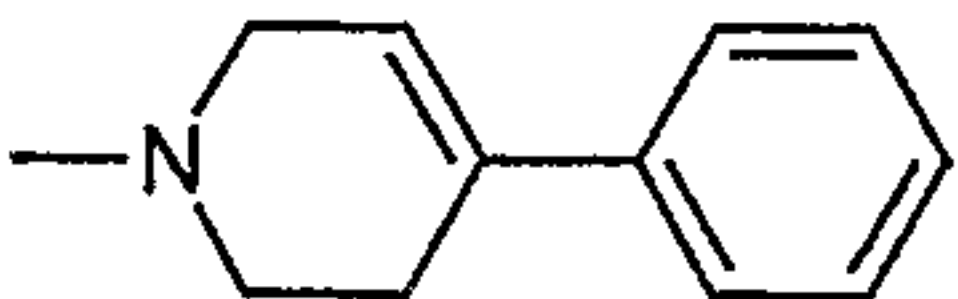
Comp. No	-R ¹	-A-	$\begin{array}{c} \text{R}^2 \\ \\ \text{---N---} \\ \\ \text{R}^3 \end{array}$	[M+H] ⁺
291				476
292				465
293				407
294				531
295				421
296				408
297				441
298				409
299				417
300				432
301				475
302				404

Table 3 (continued):

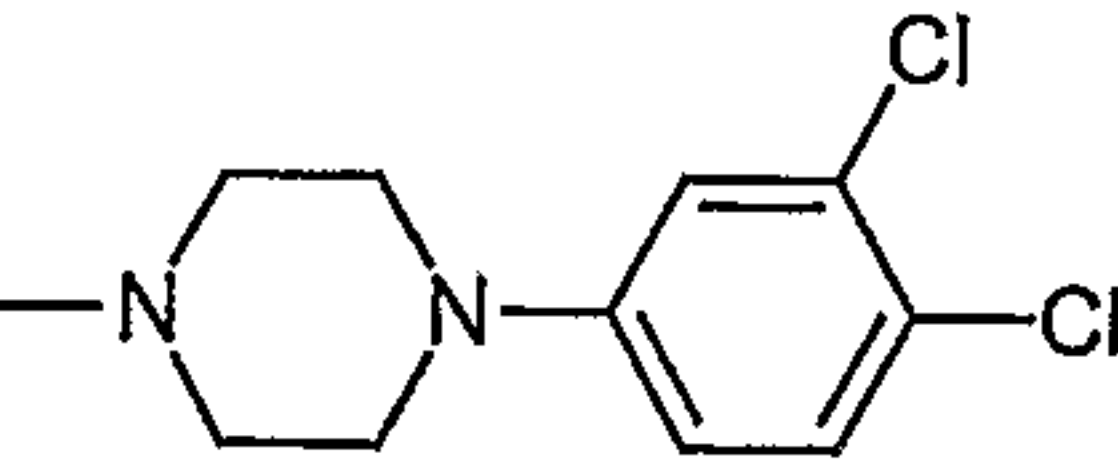
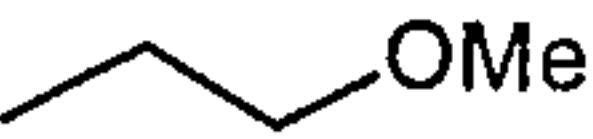
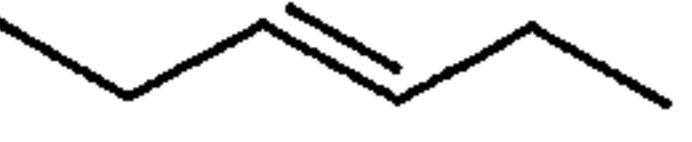
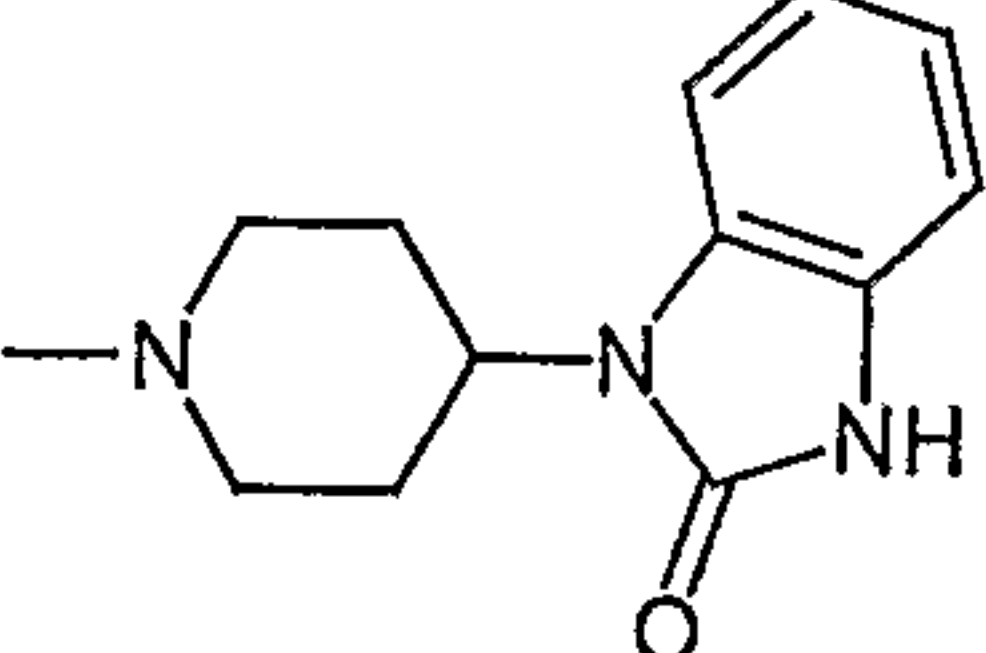
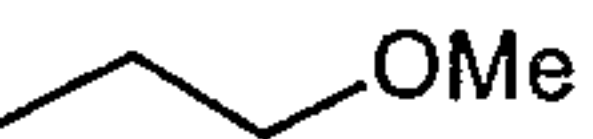
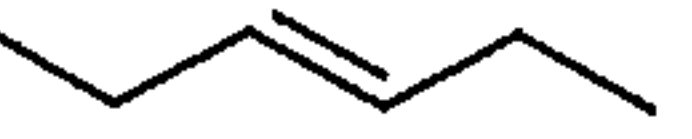
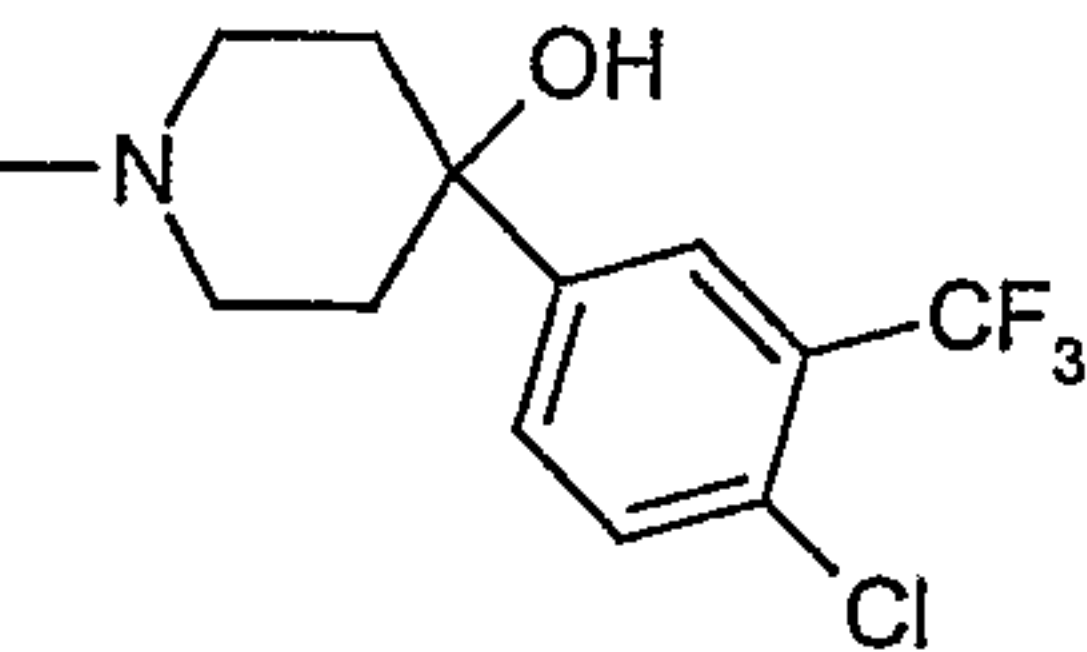
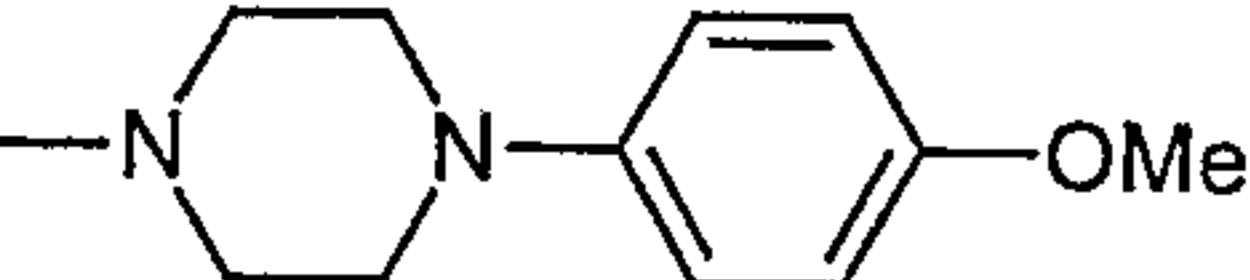
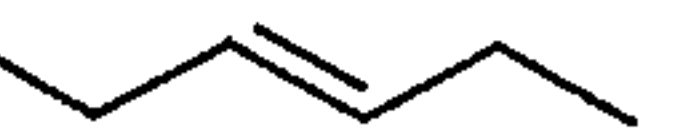
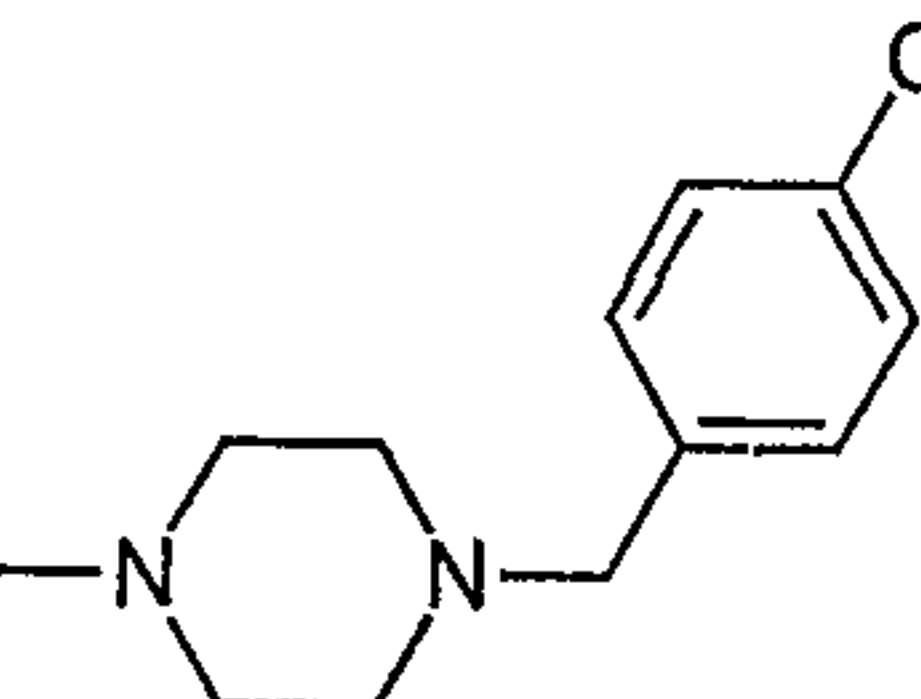
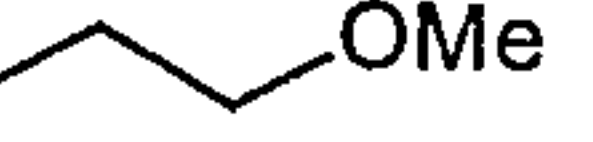
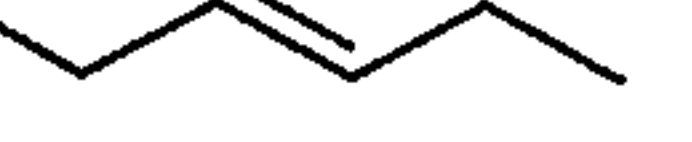
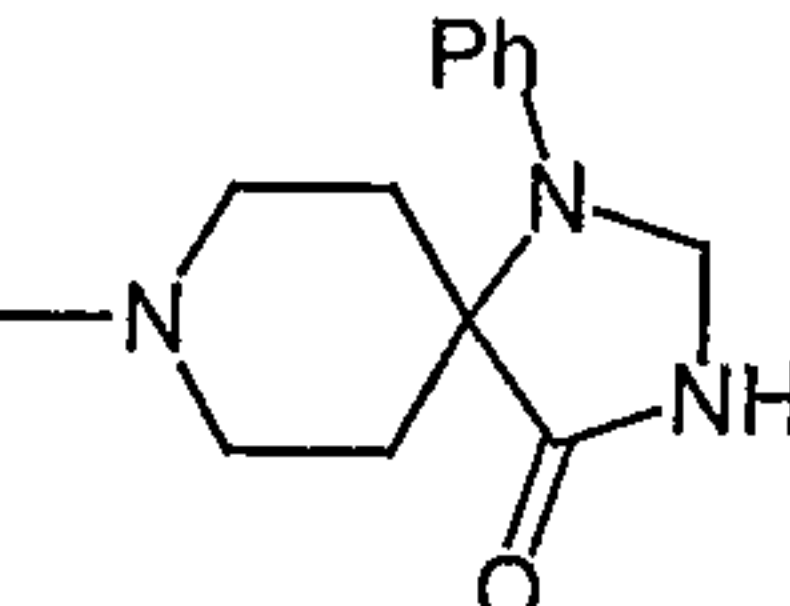
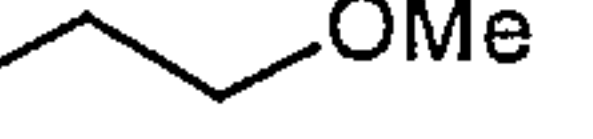
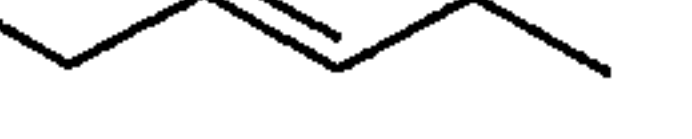
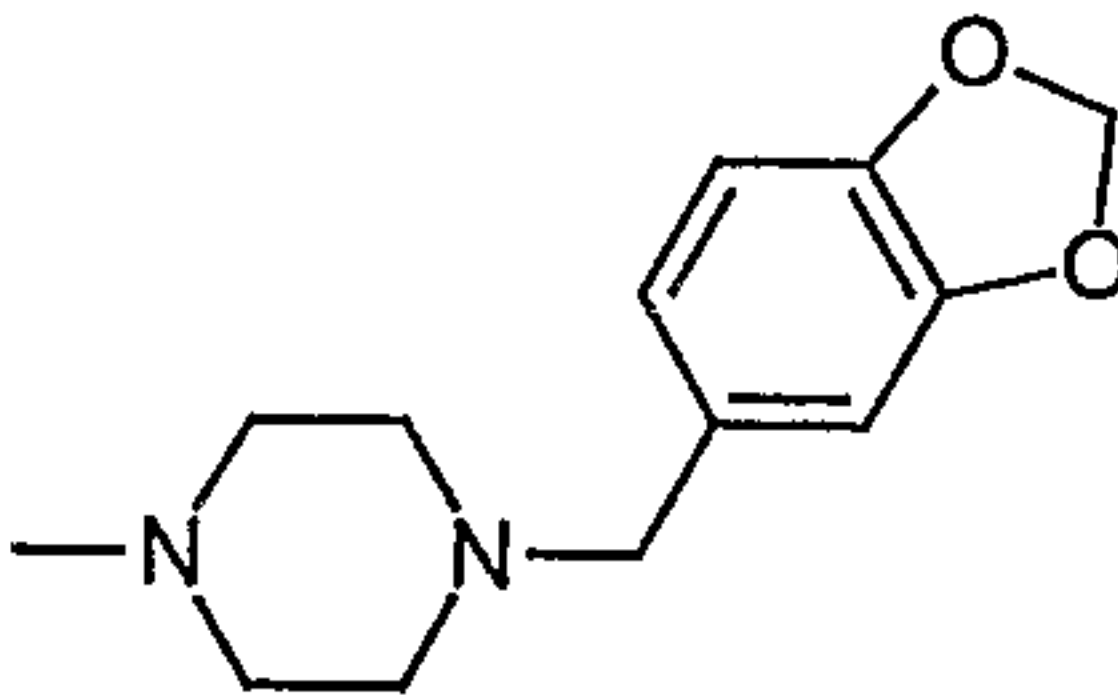
Comp. No	-R ¹	-A-	$\begin{array}{c} \text{R}^2 \\ \\ \text{---N---} \\ \\ \text{R}^3 \end{array}$	[M+H] ⁺
303				475
304				462
305				524
306				437
307				455
308				476
309				465

Table 3 (continued):

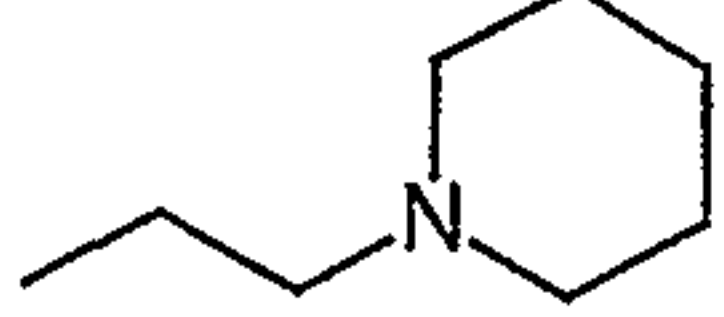
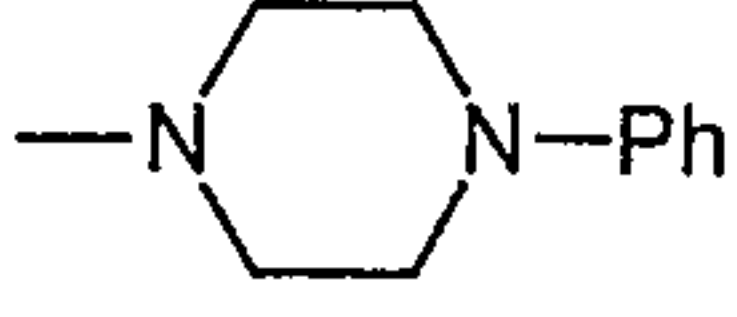
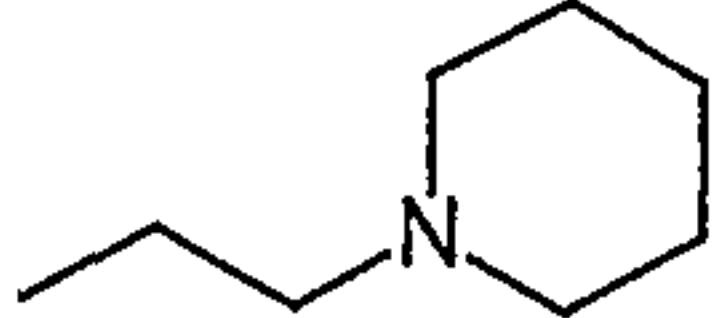
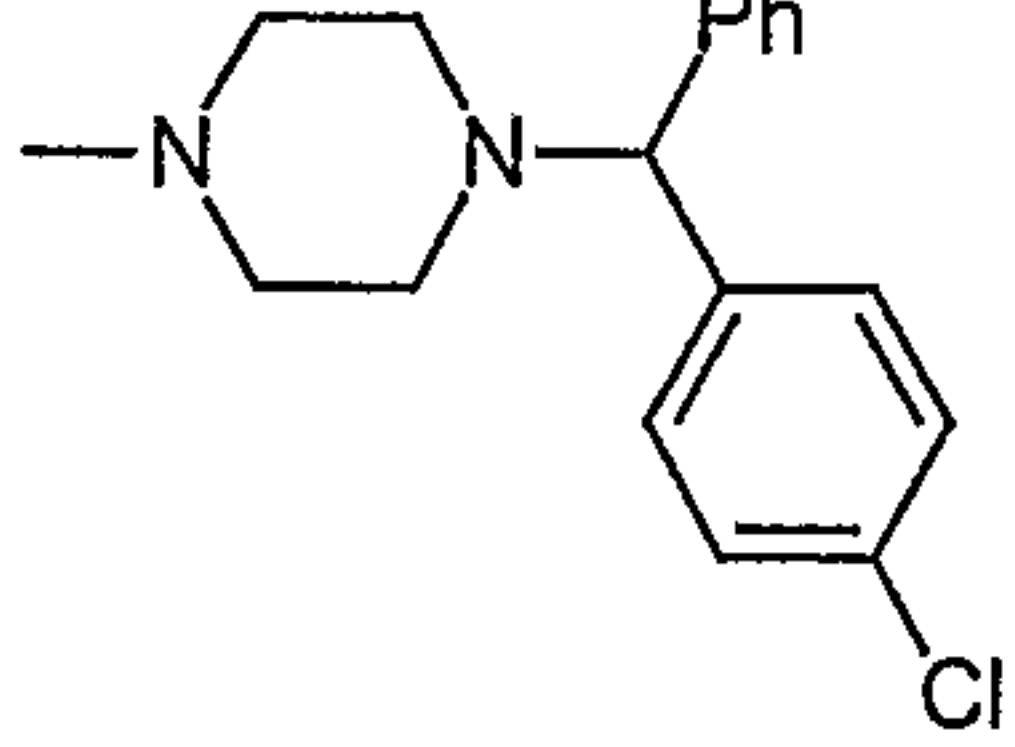
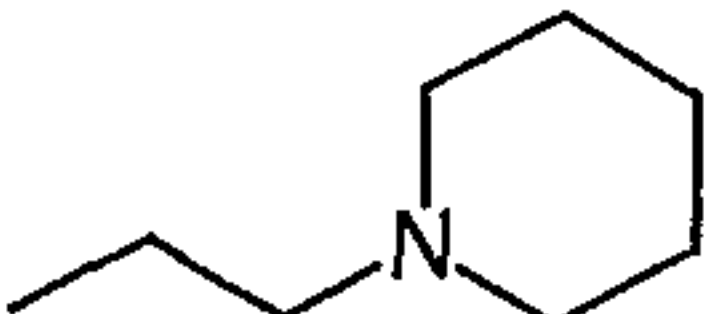
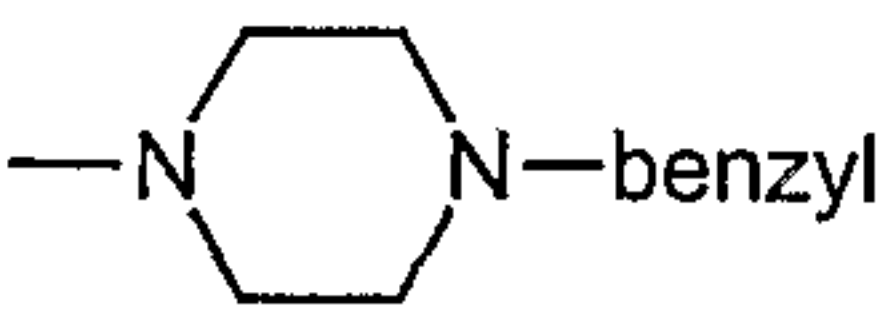
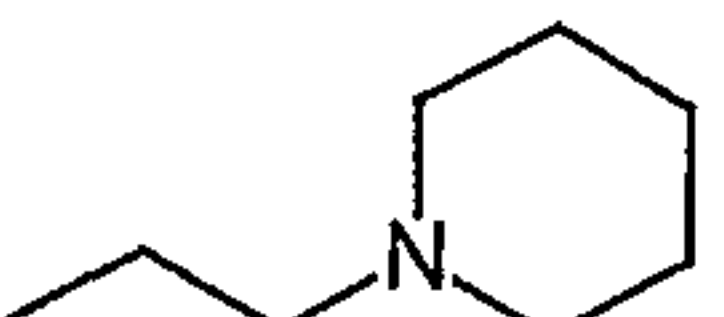
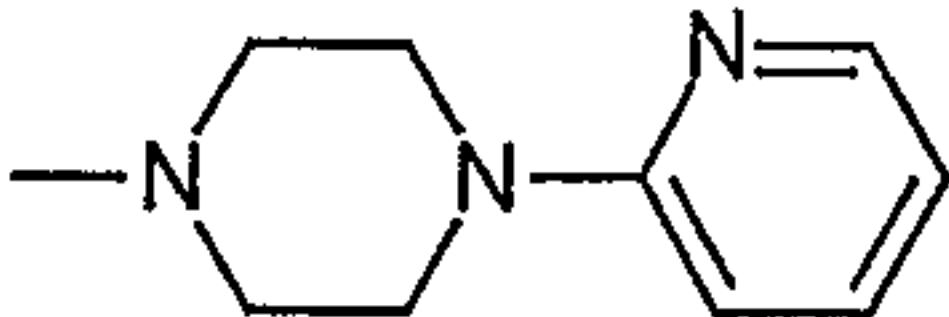
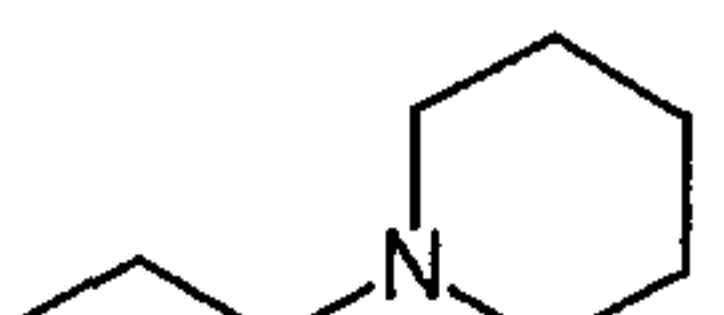
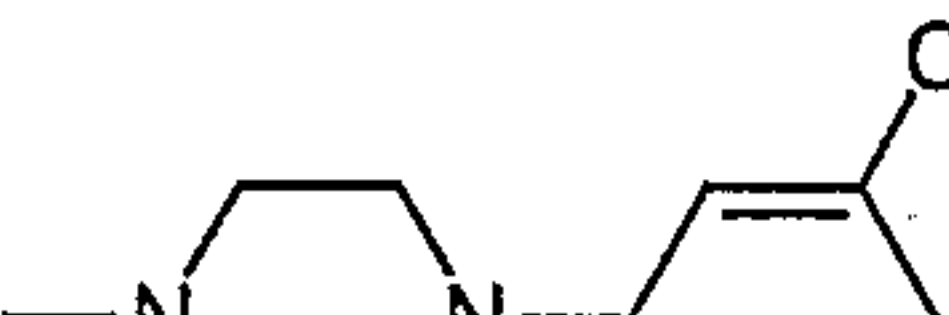
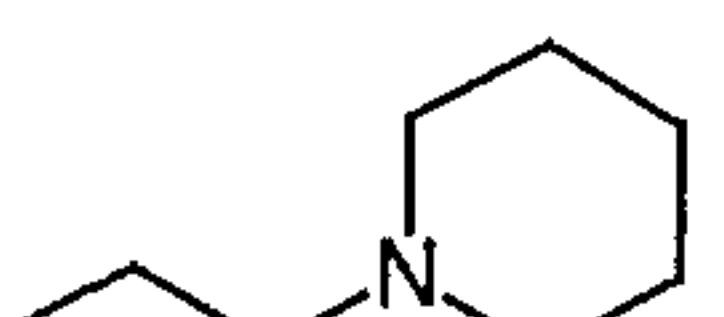
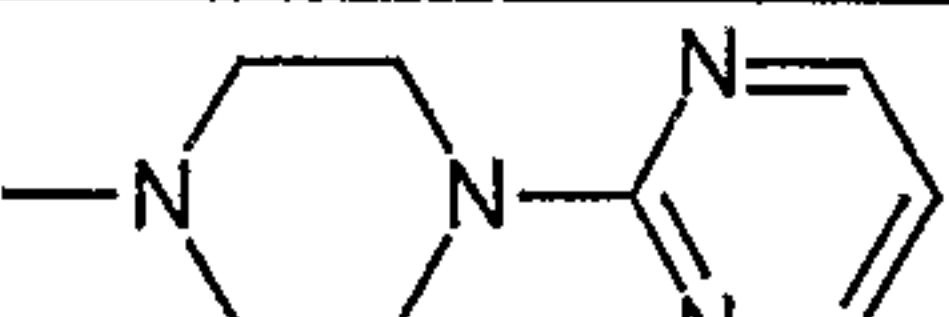
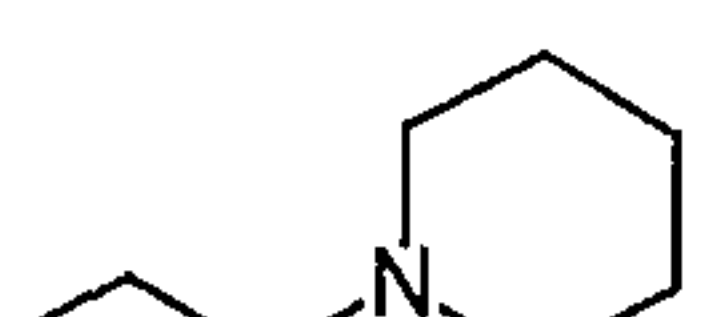
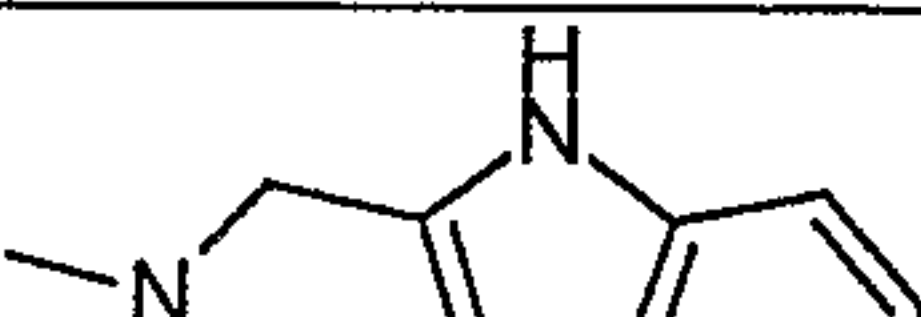
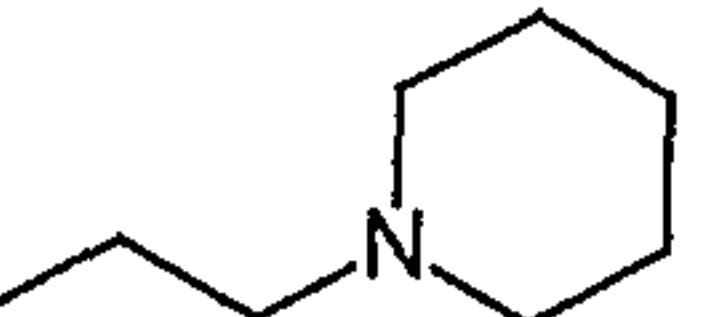
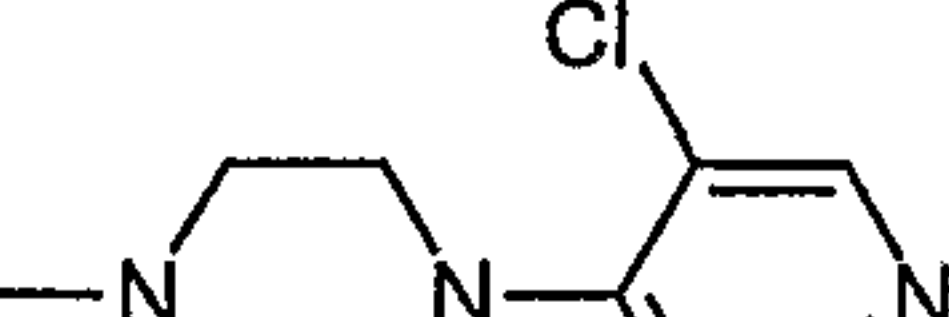
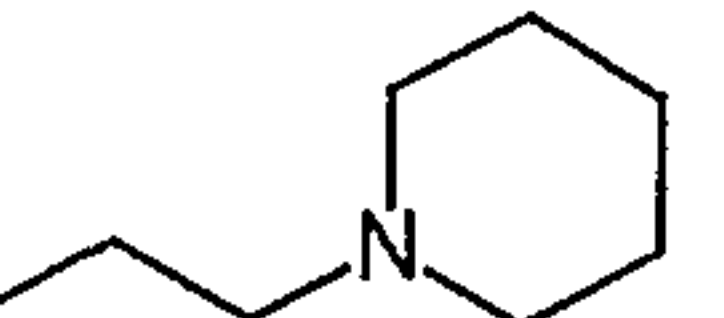
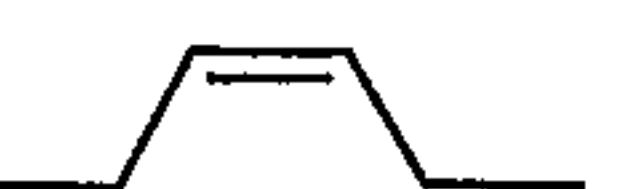
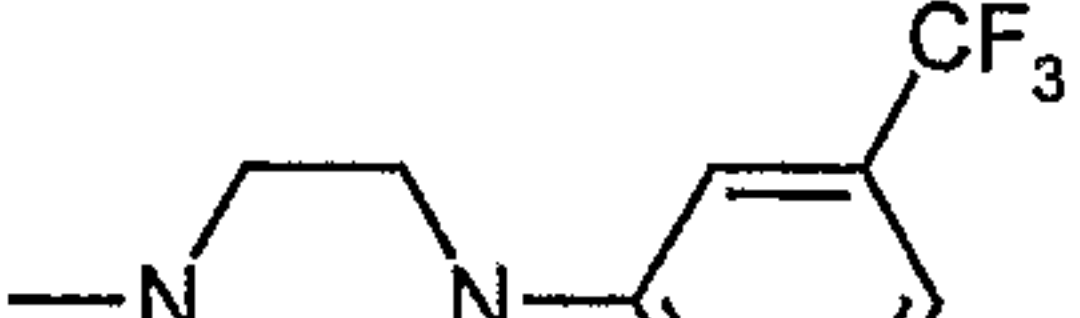
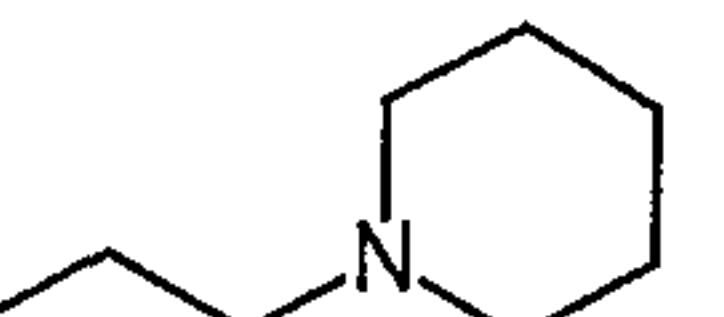
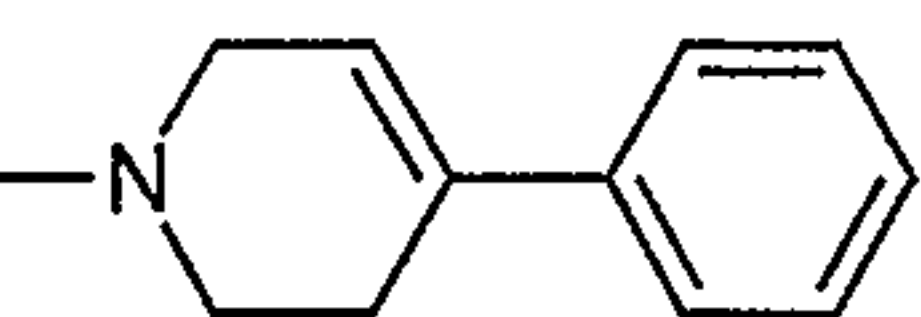
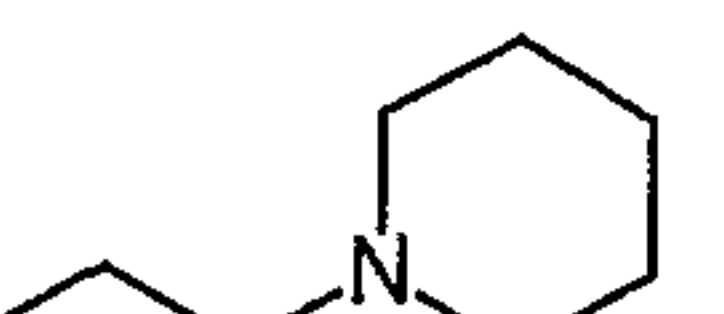
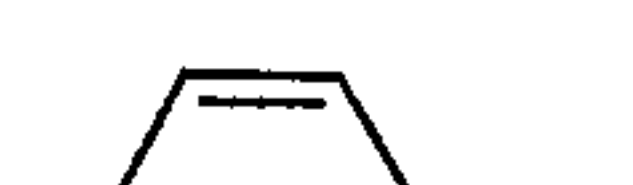
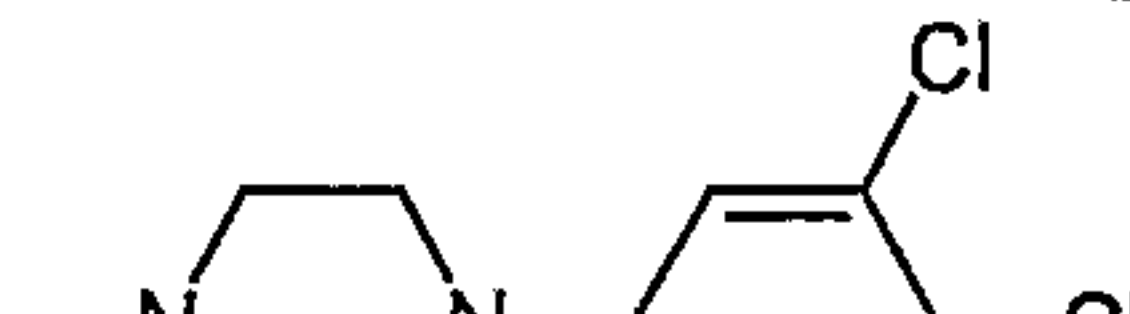
Comp. No	-R ¹	-A-	$\text{—N} \begin{matrix} \text{R}^2 \\ \text{R}^3 \end{matrix}$	[M+H] ⁺
310				460
311				584
312				474
313				461
314				694
315				462
316				470
317				465
318				528
319				457
320				528

Table 3 (continued):

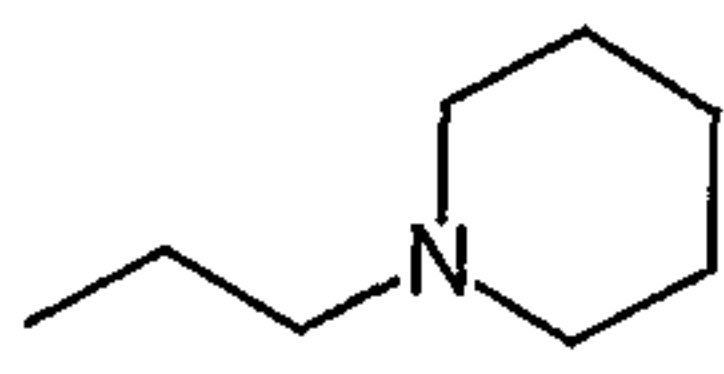
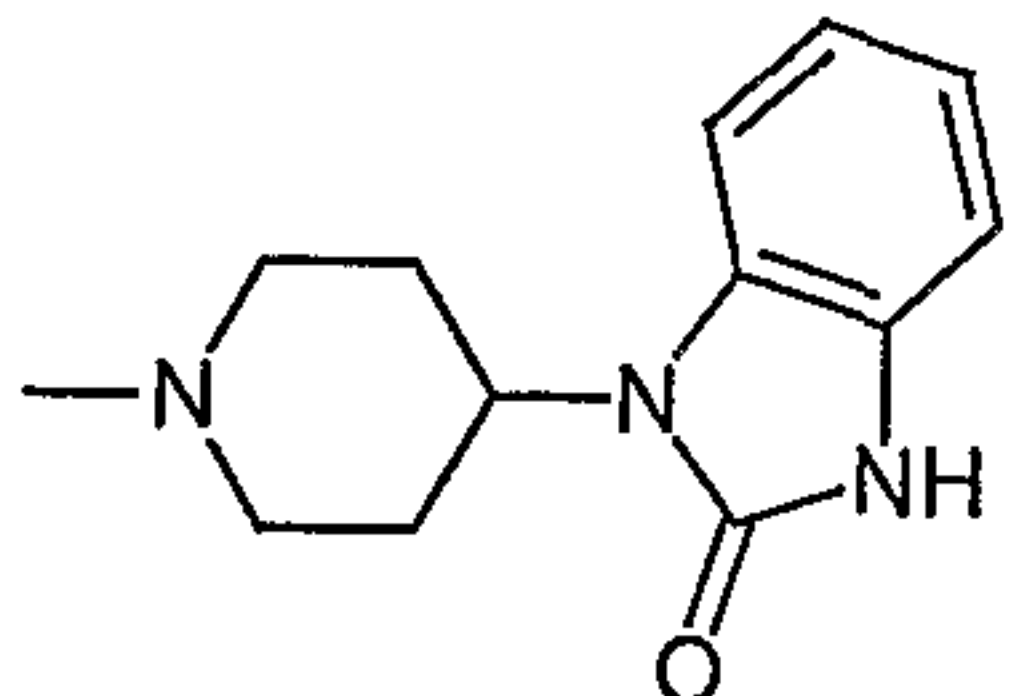
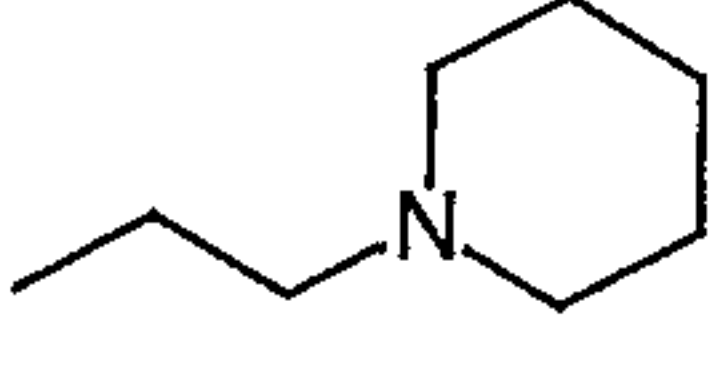
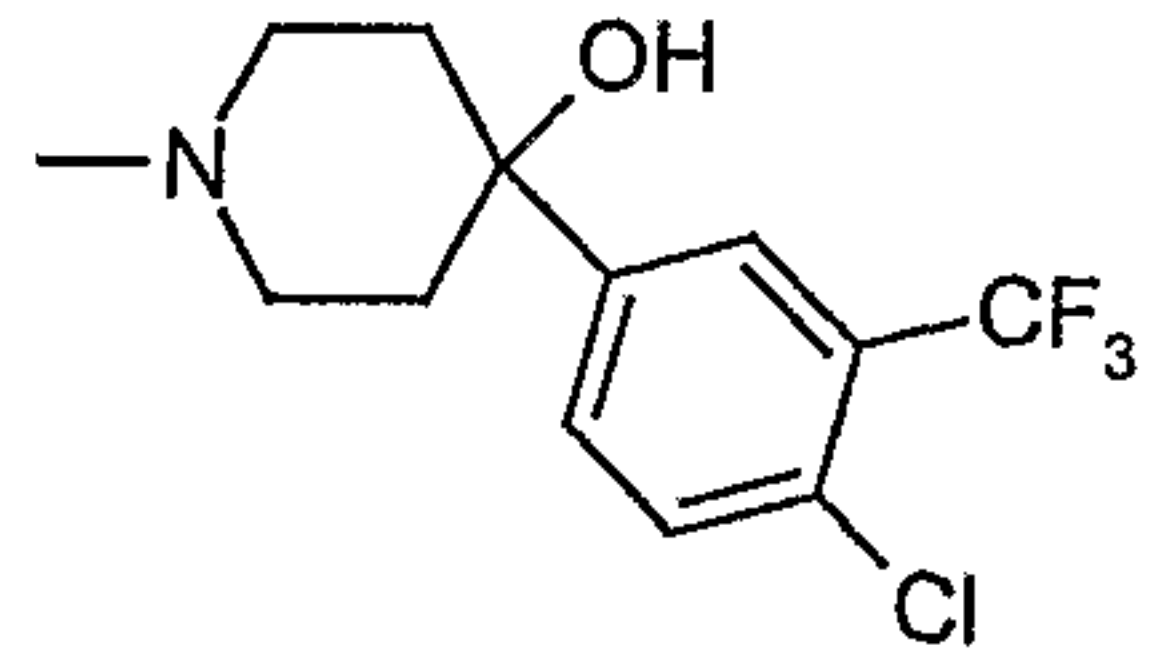
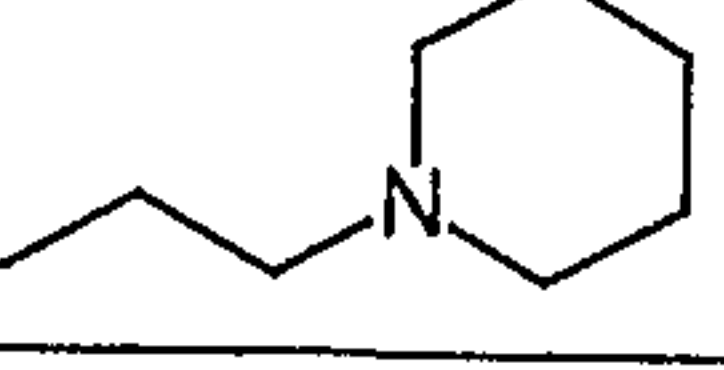
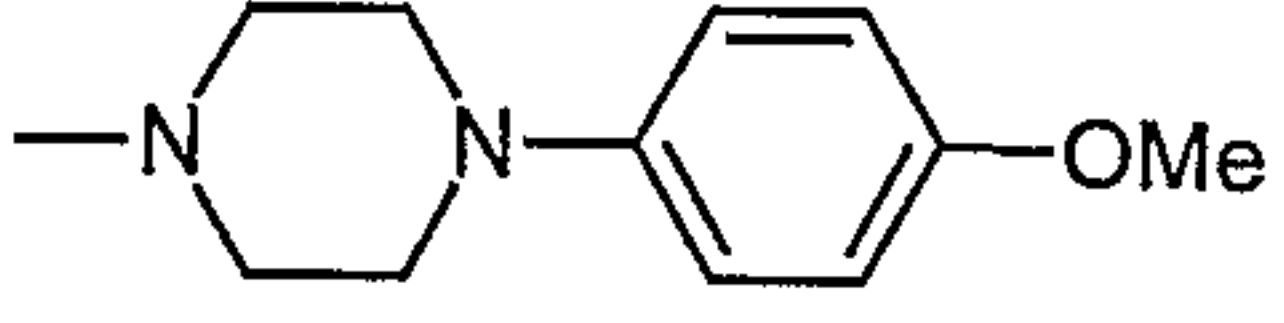
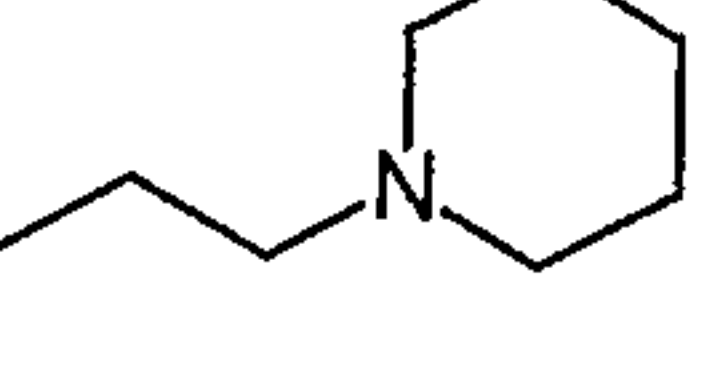
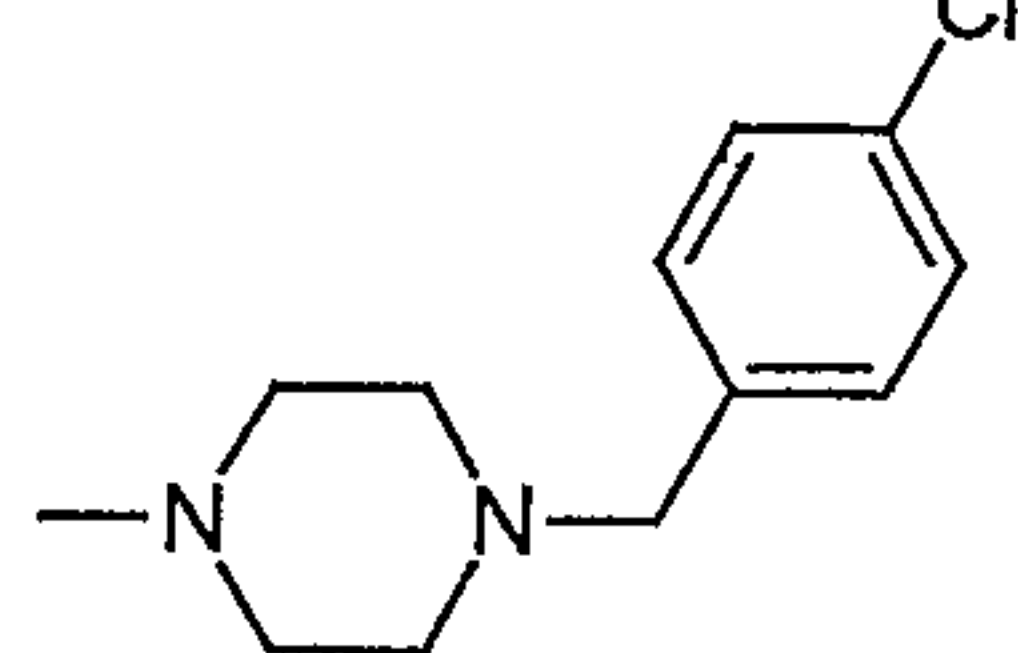
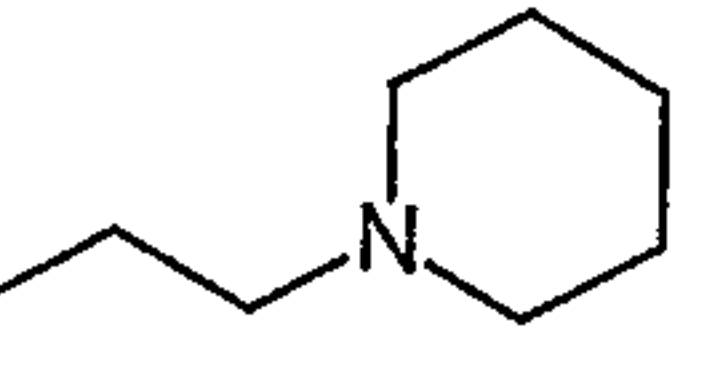
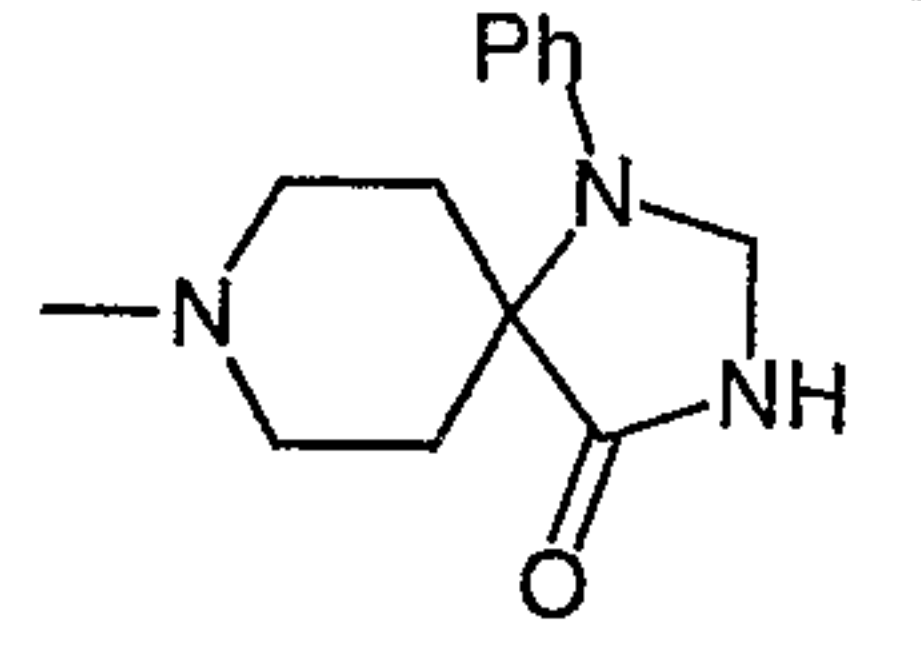
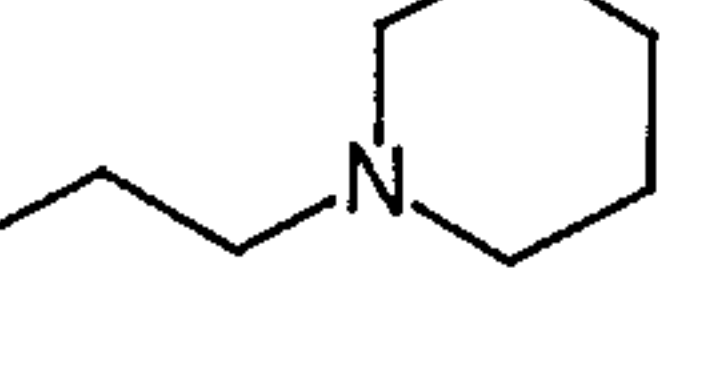
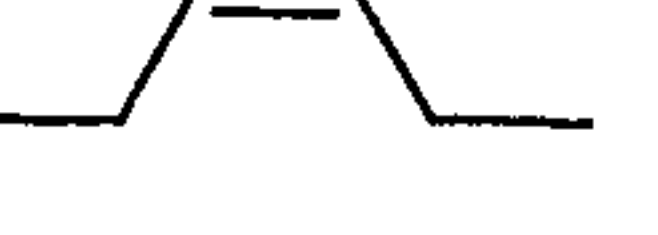
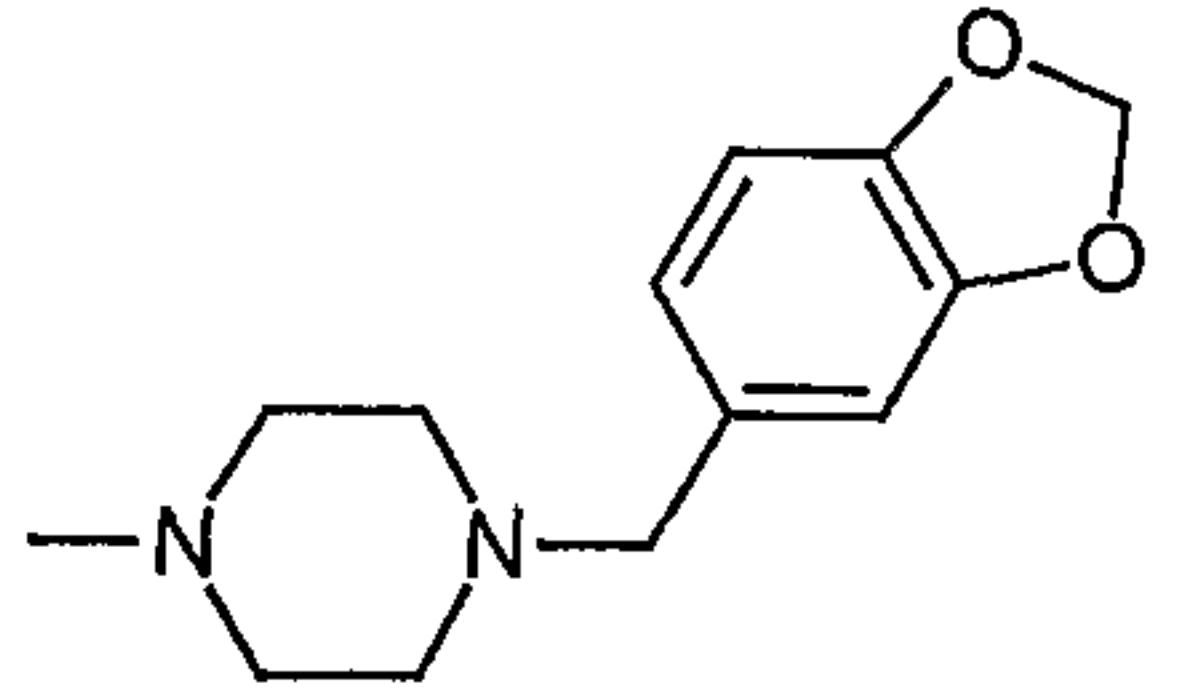
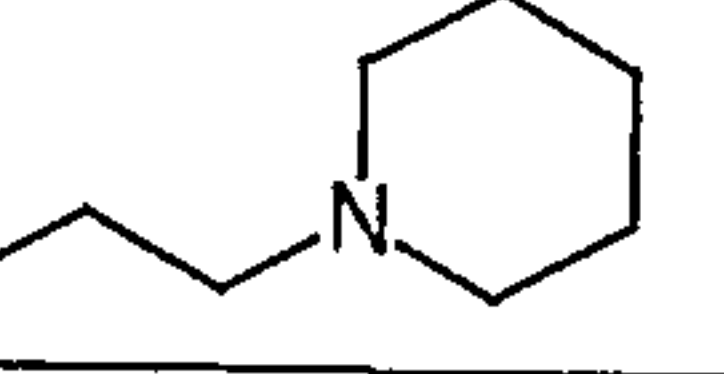
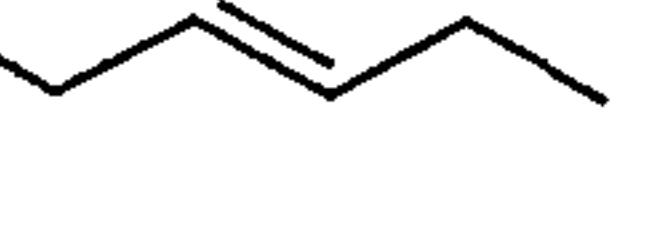
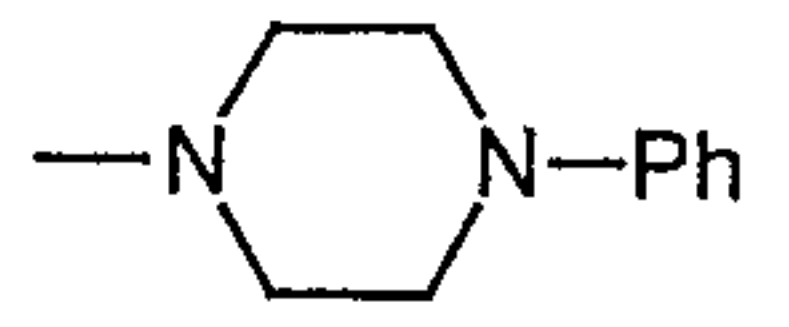
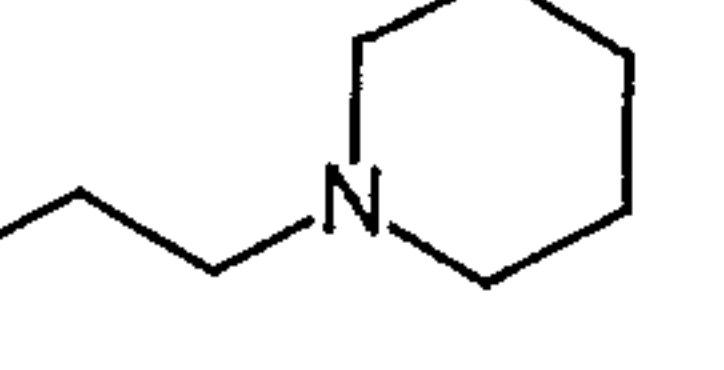
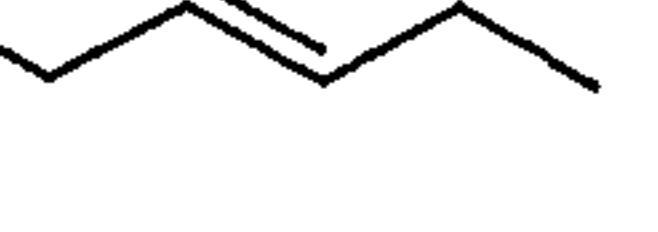
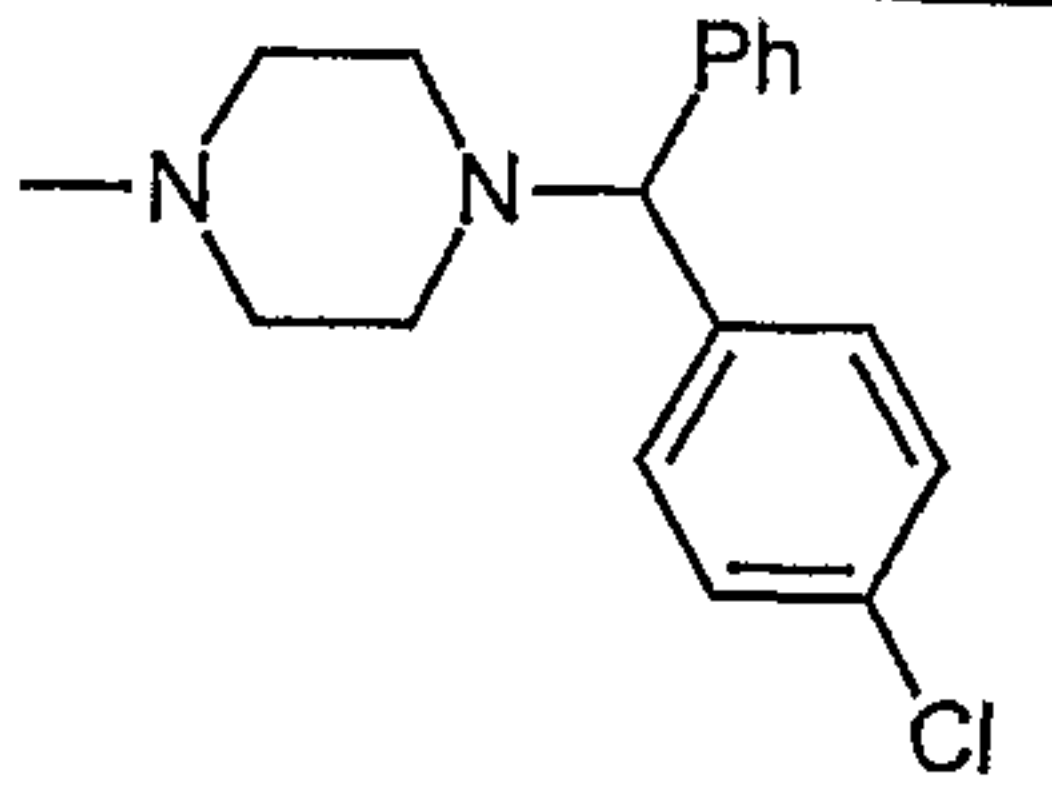
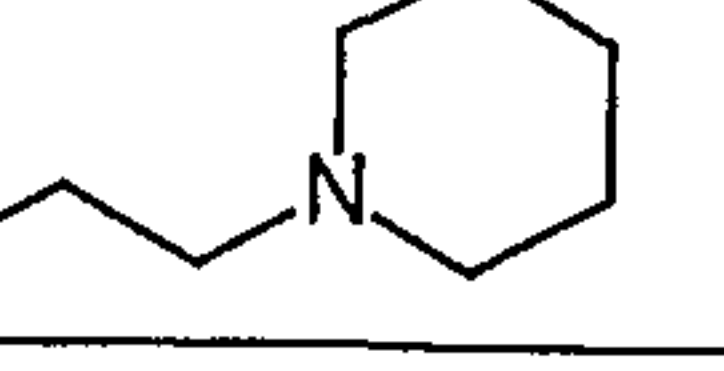
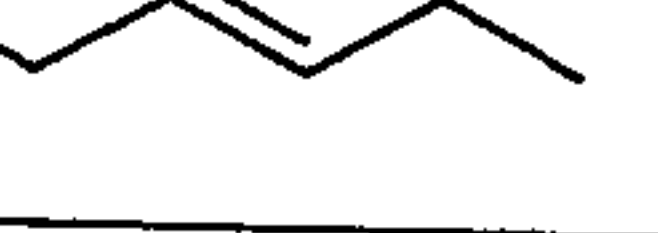
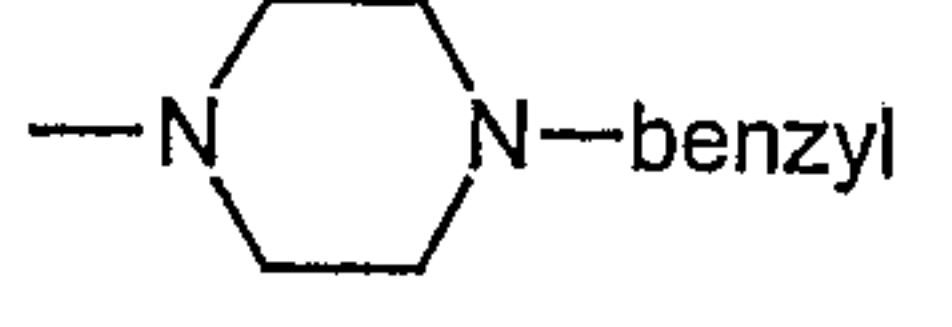
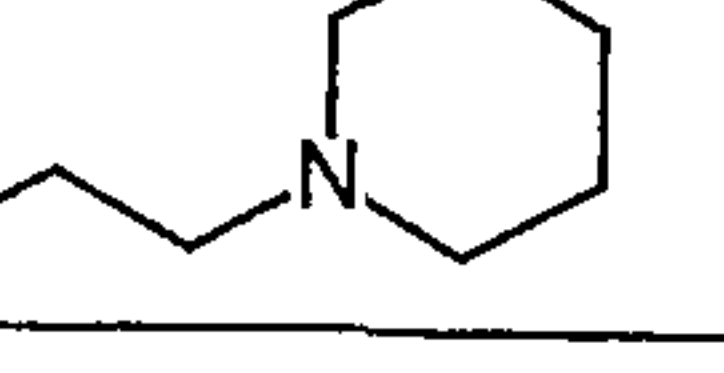
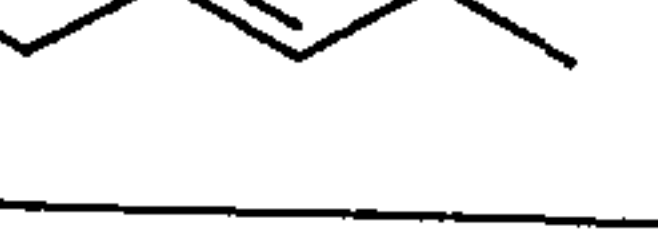
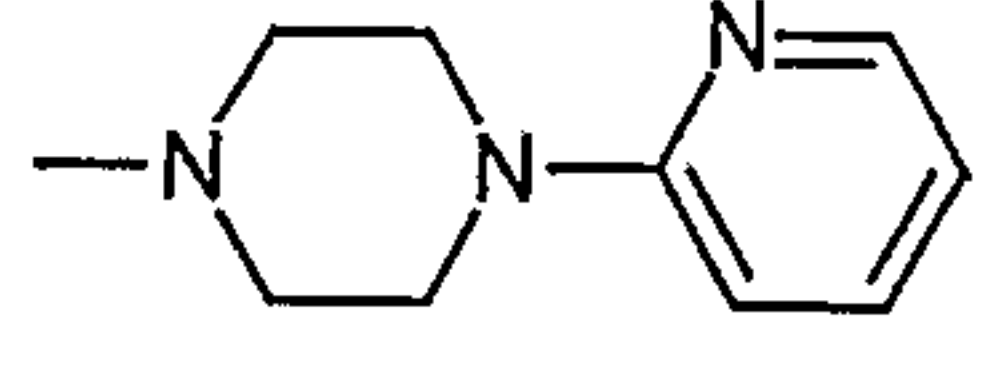
Comp. No	-R ¹	-A-	$\begin{array}{c} \text{R}^2 \\ \\ \text{---N---} \\ \\ \text{R}^3 \end{array}$	[M+H] ⁺
321				515
322				577
323				490
324				508
325				529
326				518
327				460
328				584
329				474
330				461

Table 3 (continued):

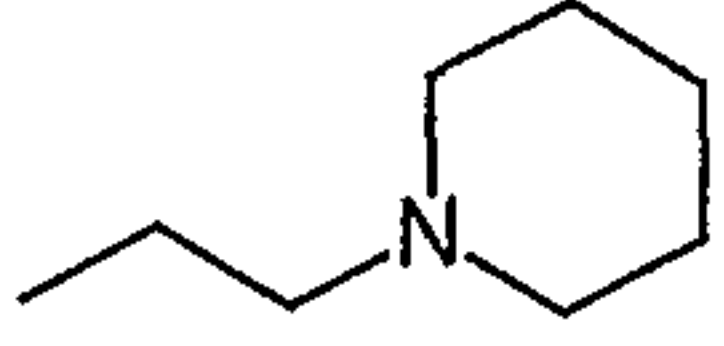
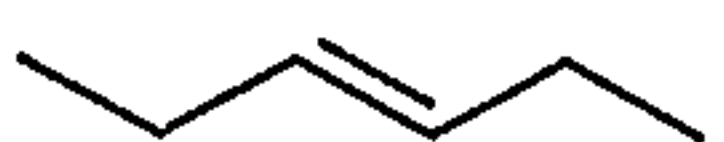
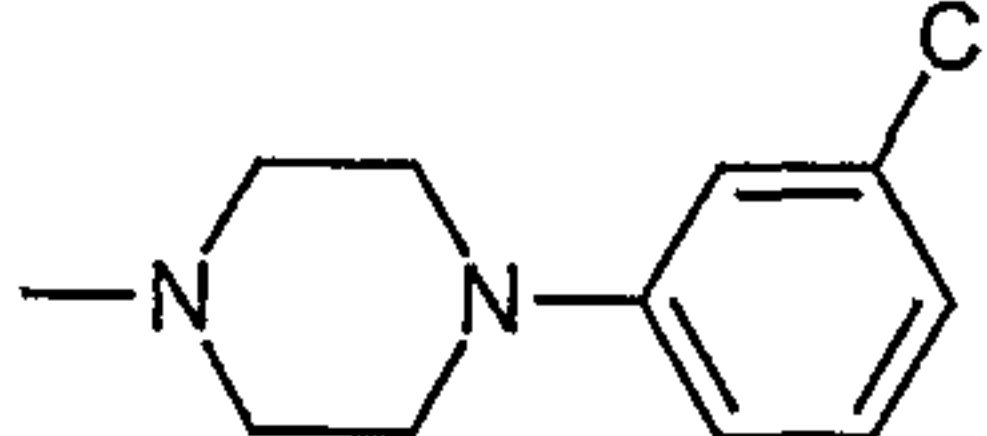
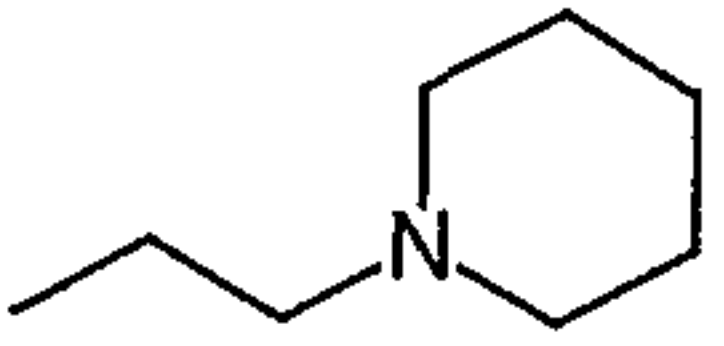
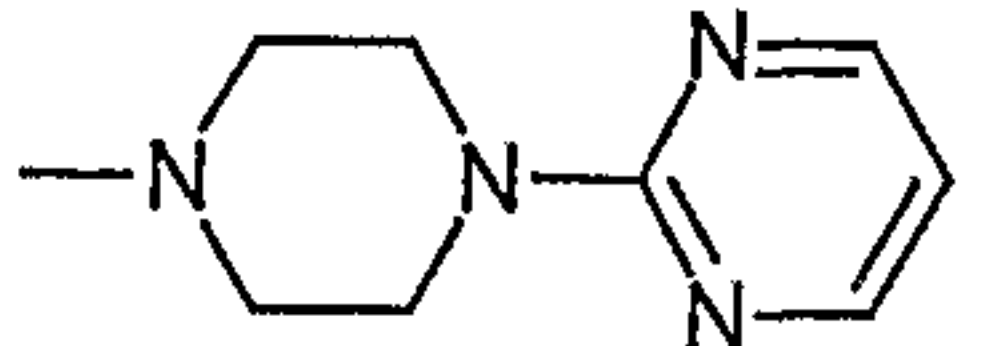
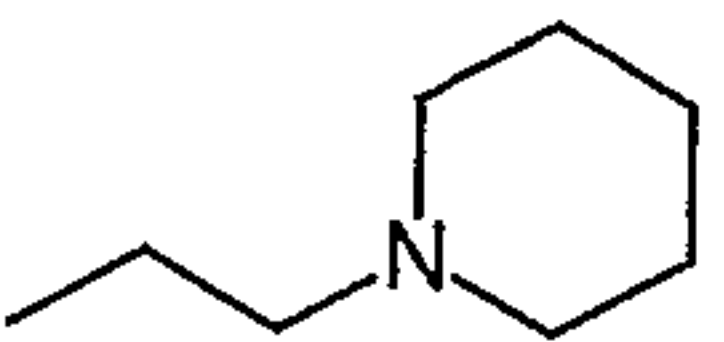
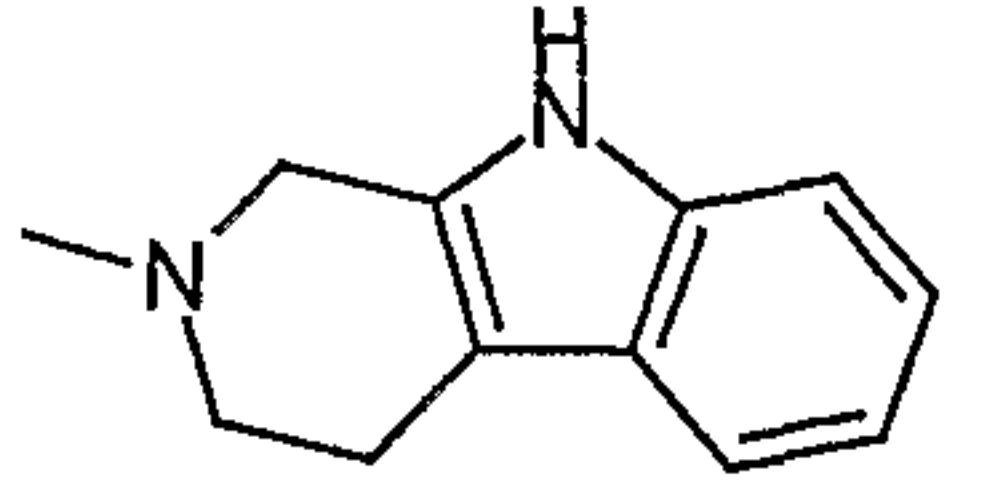
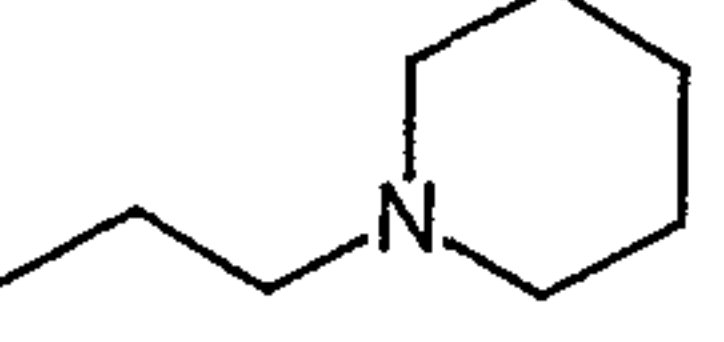
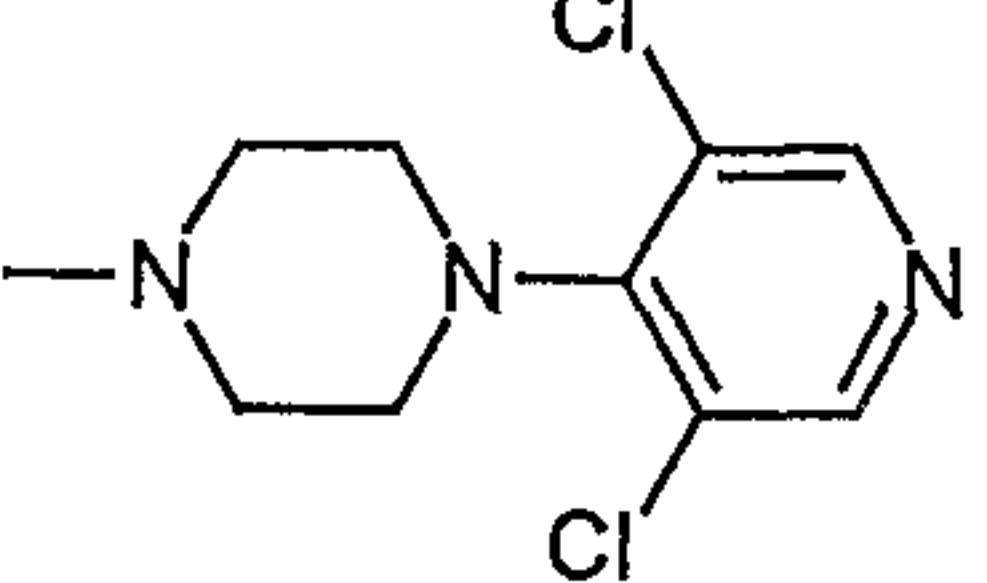
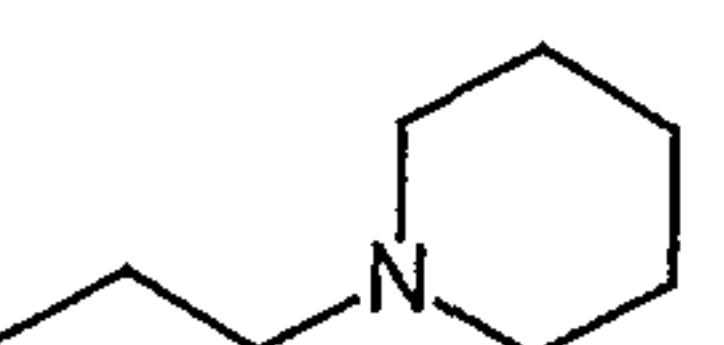
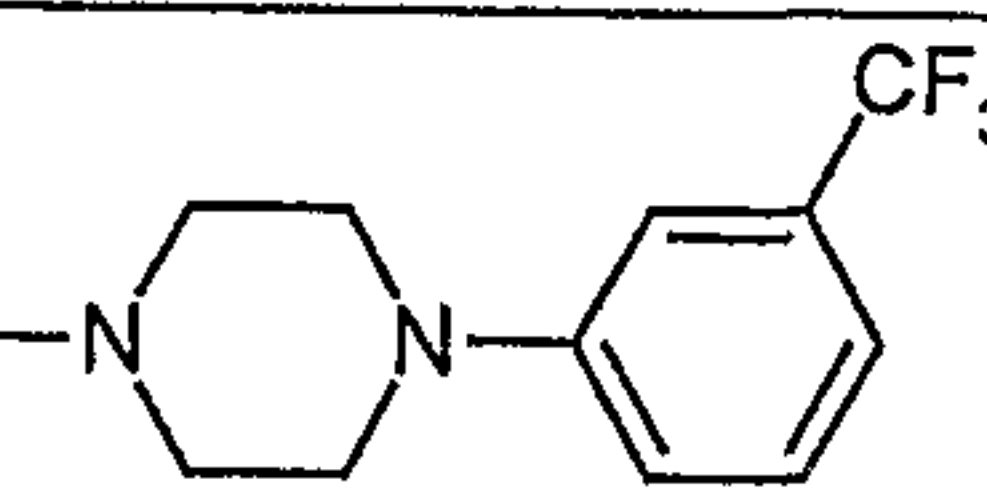
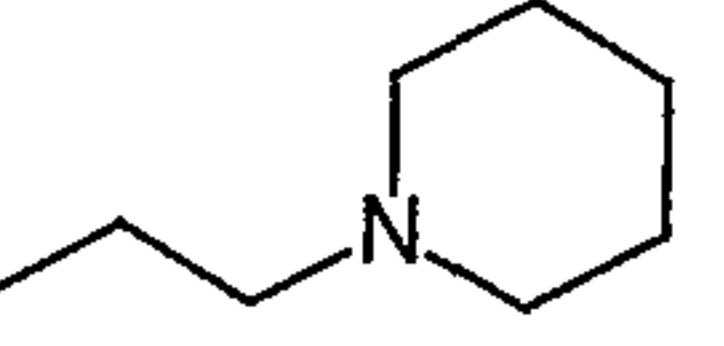
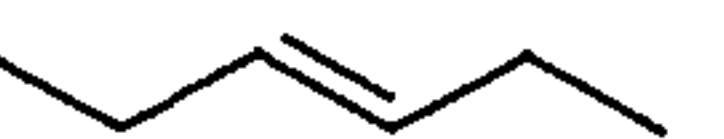
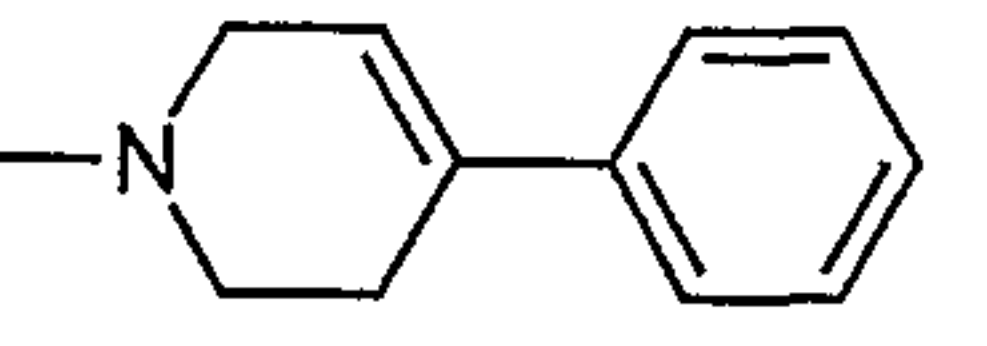
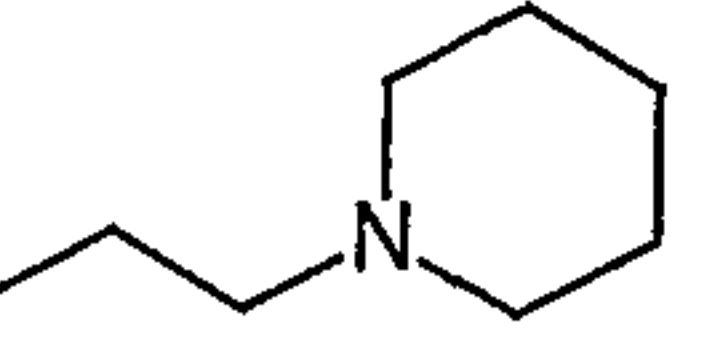
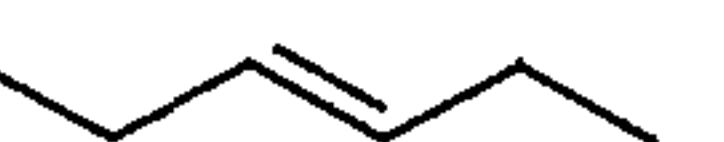
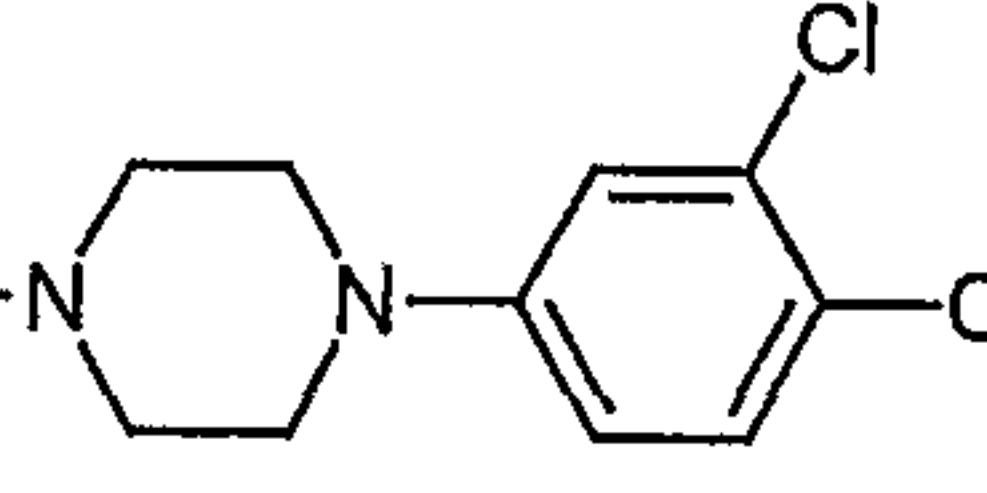
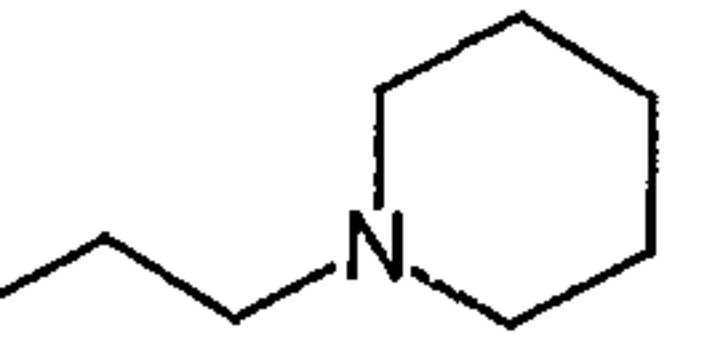
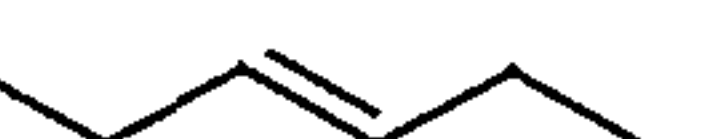
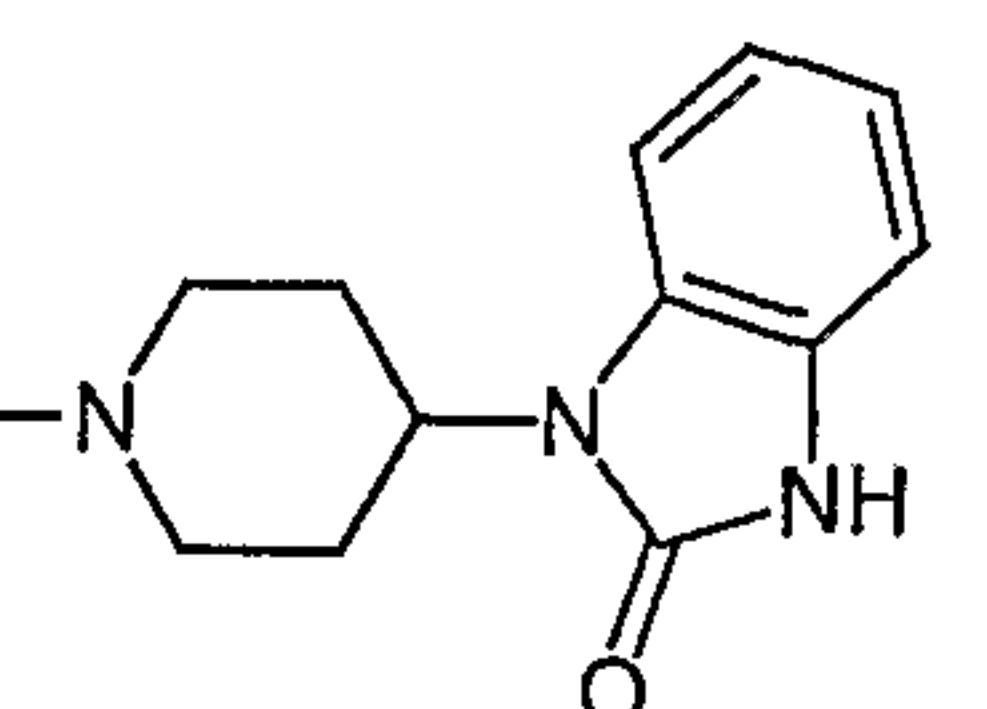
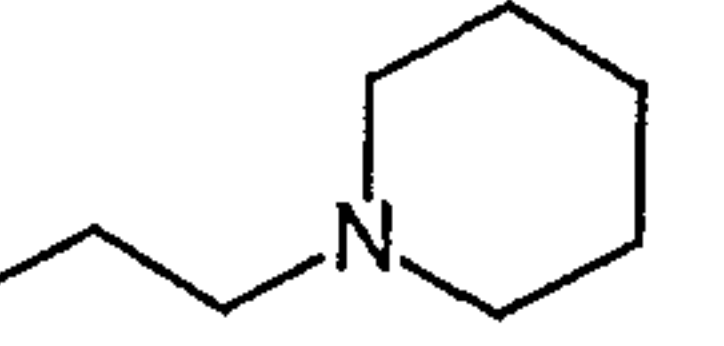
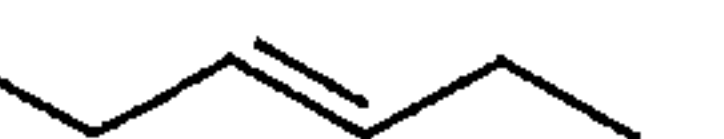
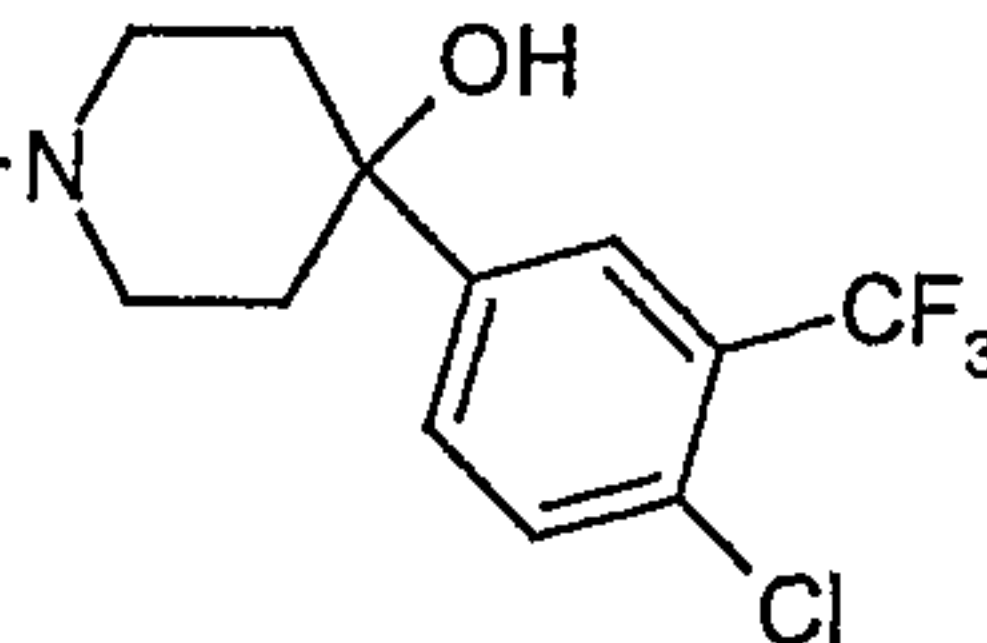
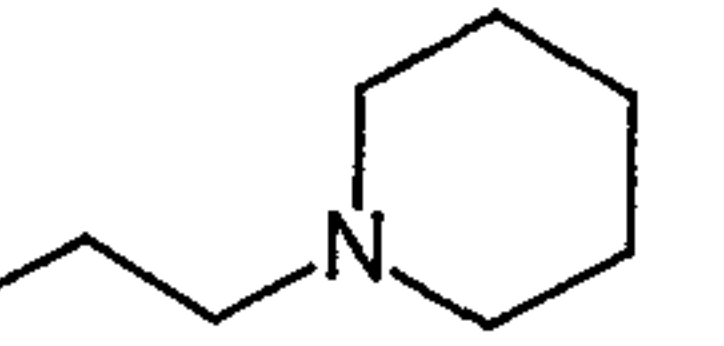
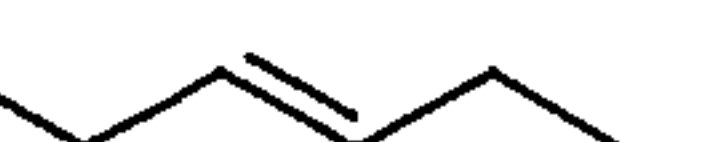
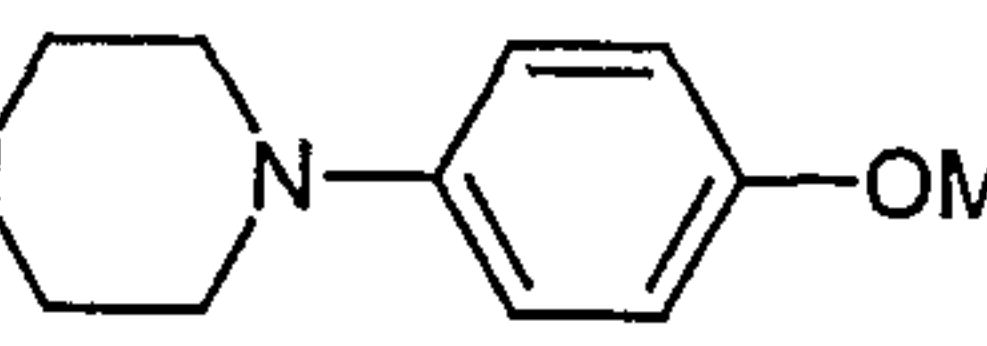
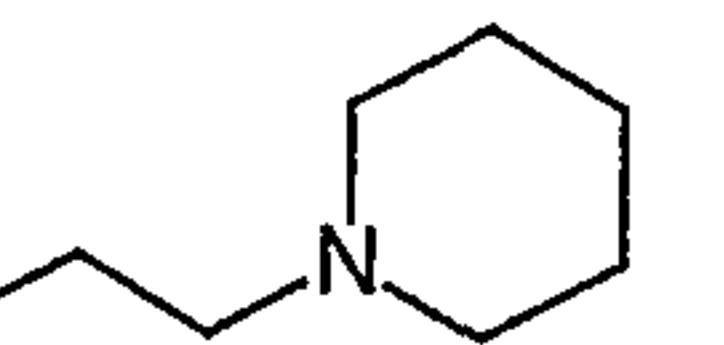
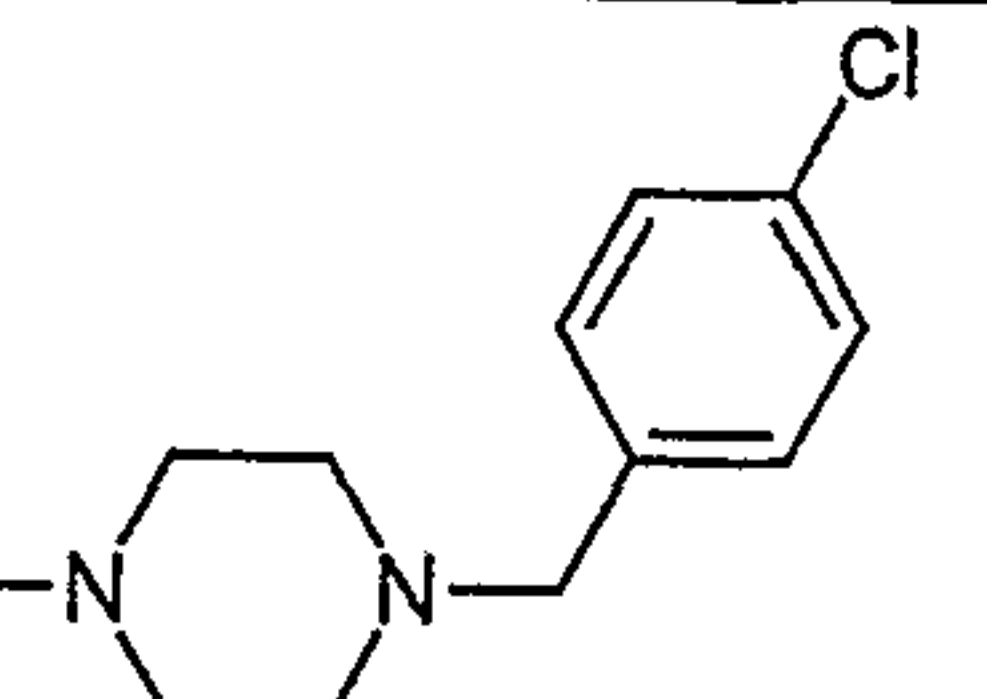
Comp. No	-R ¹	-A-	$\begin{array}{c} \text{R}^2 \\ \\ \text{---N---} \\ \\ \text{R}^3 \end{array}$	[M+H] ⁺
331				494
332				462
333				470
334				465
335				528
336				457
337				528
338				515
339				577
340				490
341				508

Table 3 (continued):

Comp. No	-R ¹	-A-	$\begin{array}{c} R^2 \\ \\ -N- \\ \\ R^3 \end{array}$	[M+H] ⁺
342				529
343				518
344				462
345				586
346				476
347				463
348				496
349				464
350				472
351				467
352				530

Table 3 (continued):

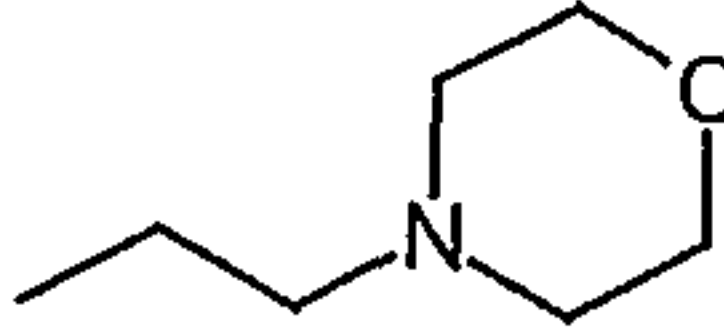
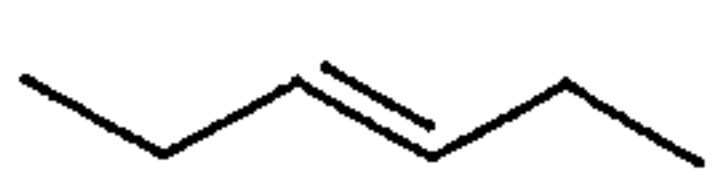
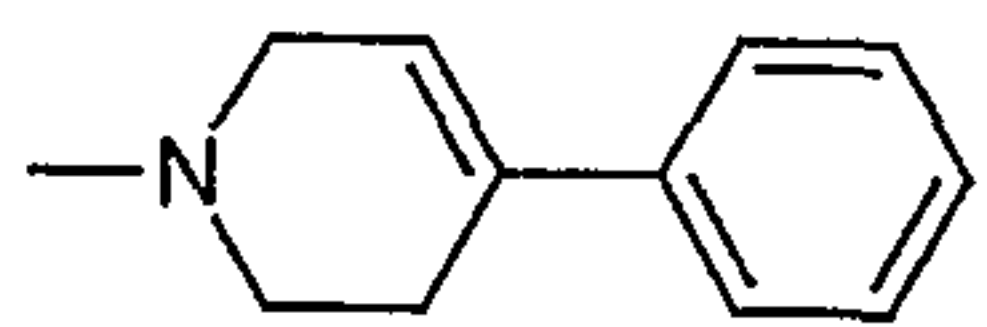
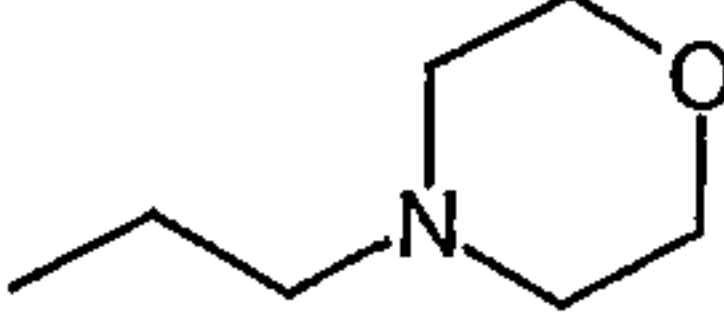
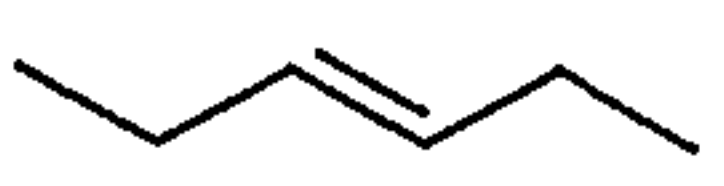
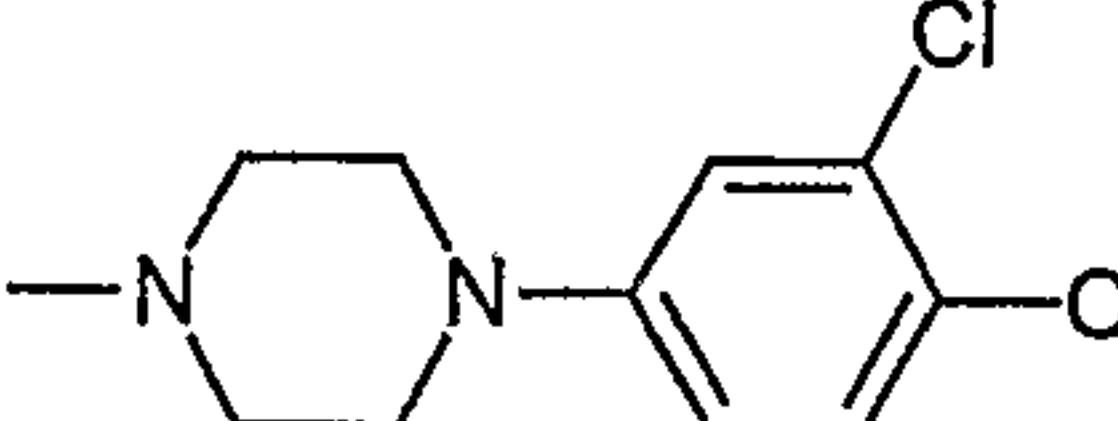
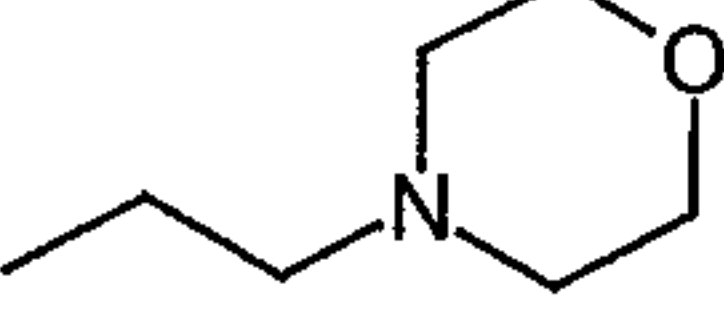
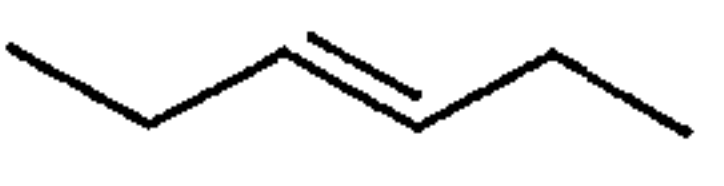
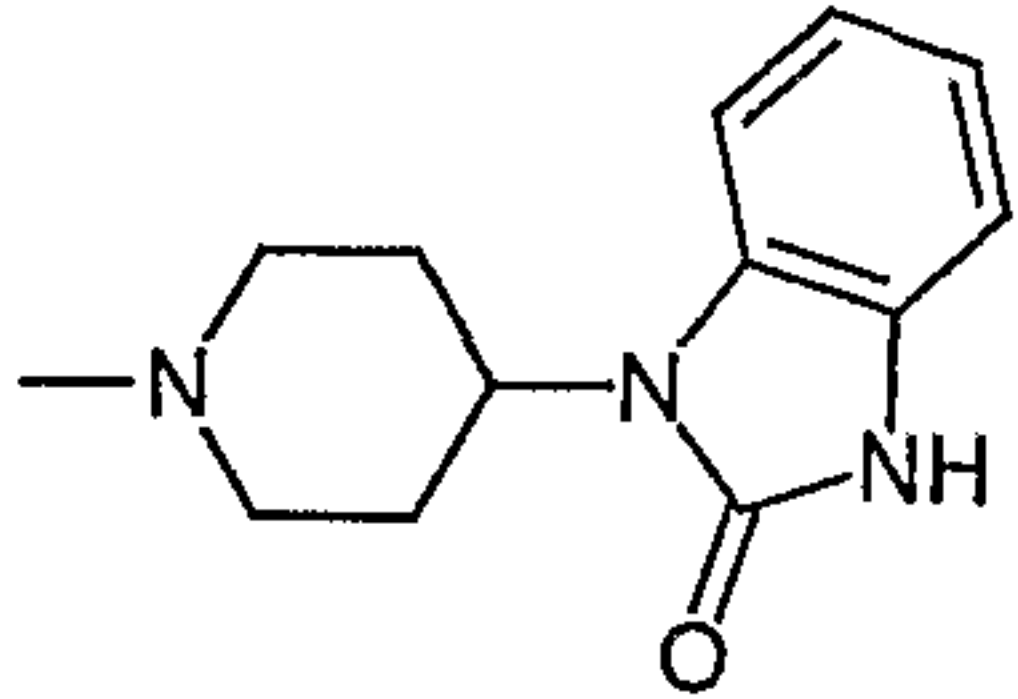
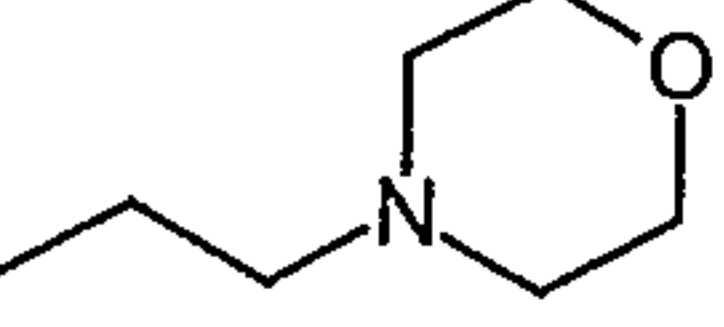
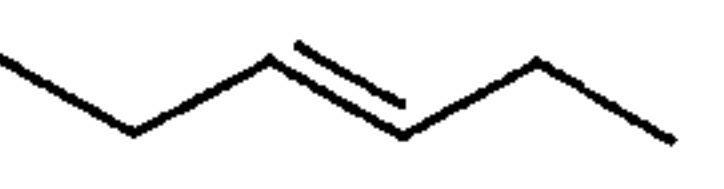
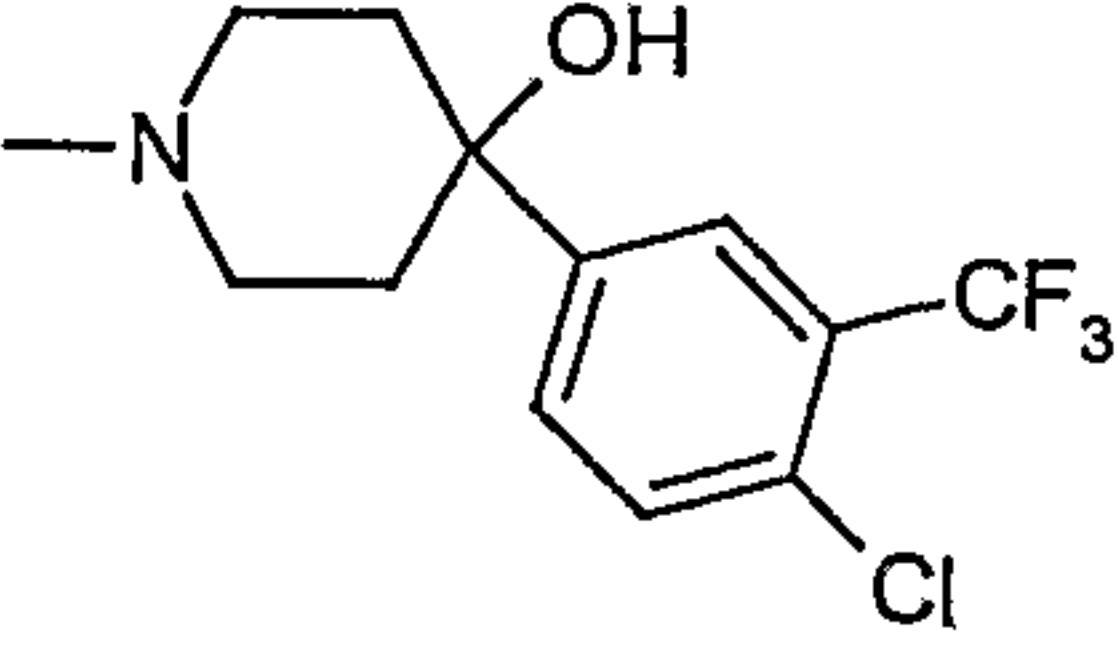
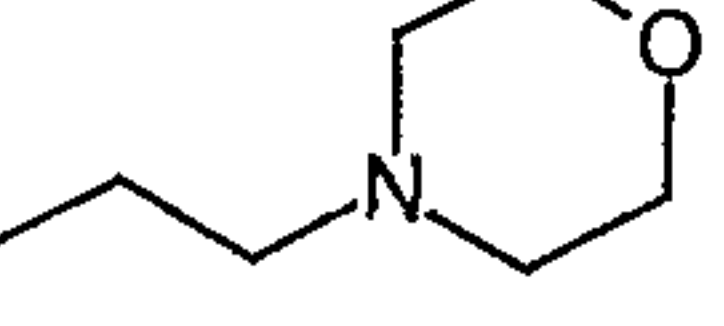
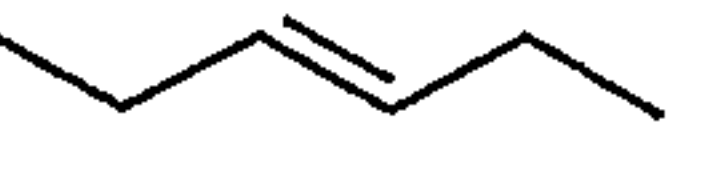
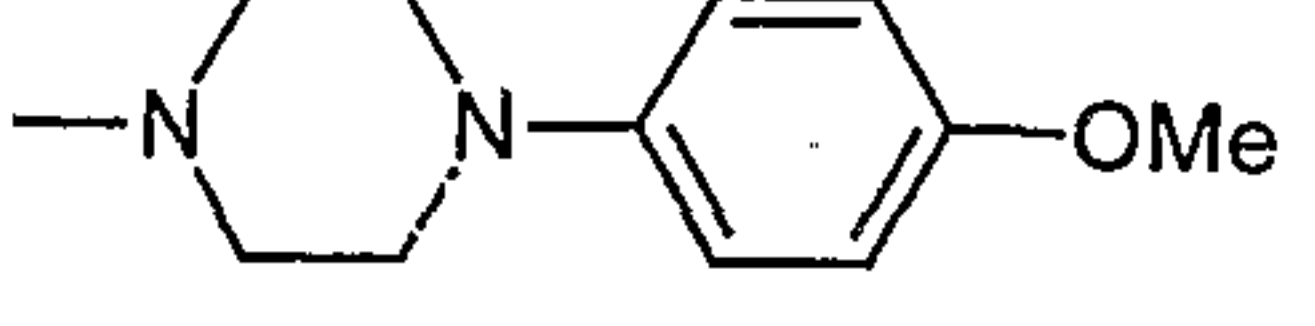
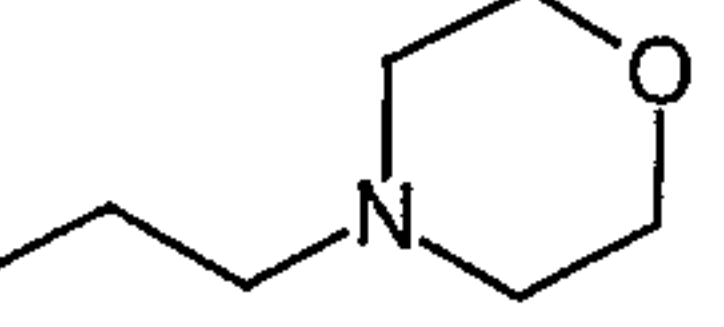
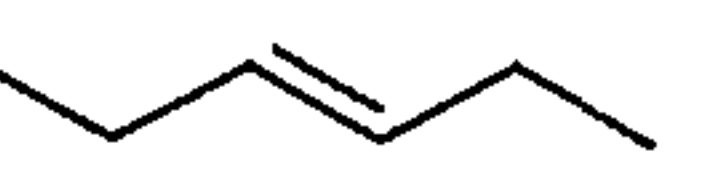
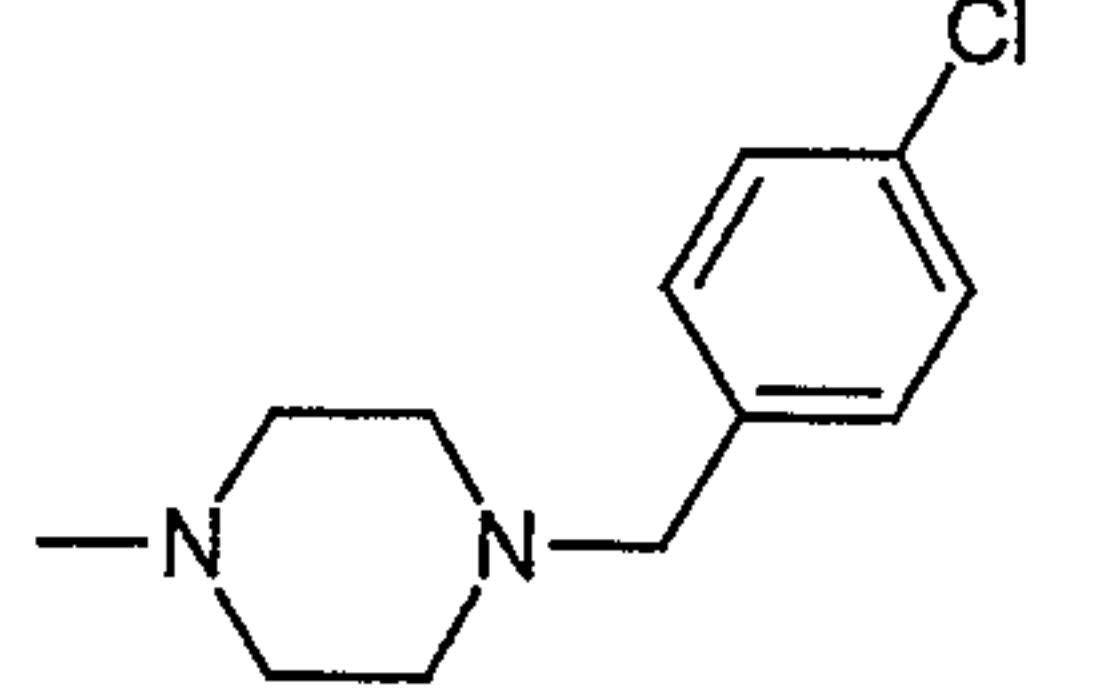
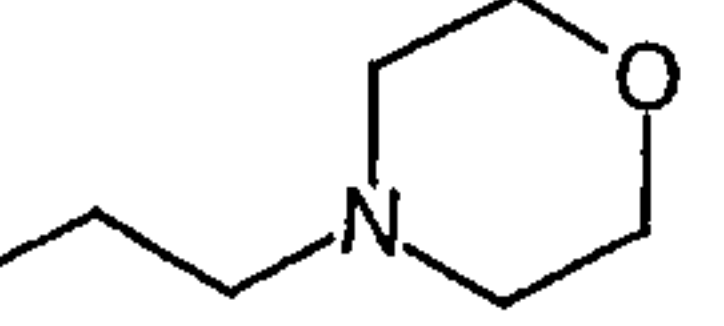
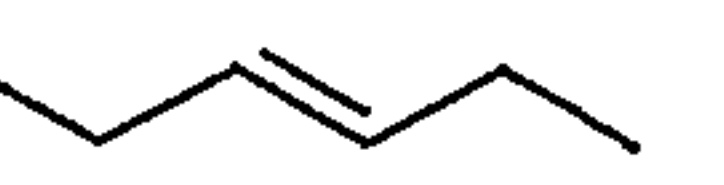
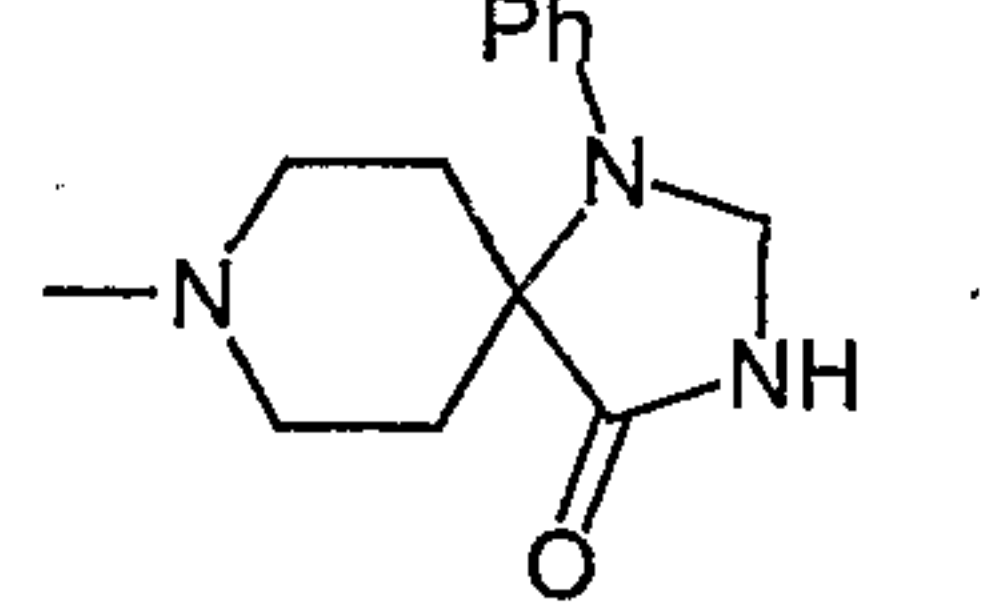
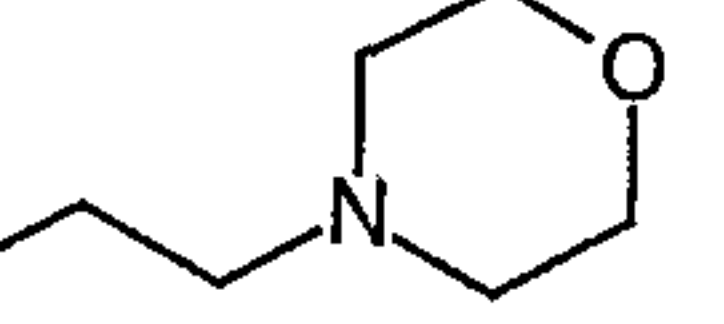
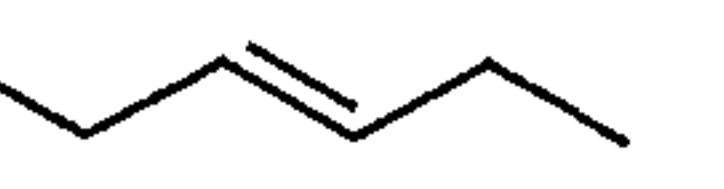
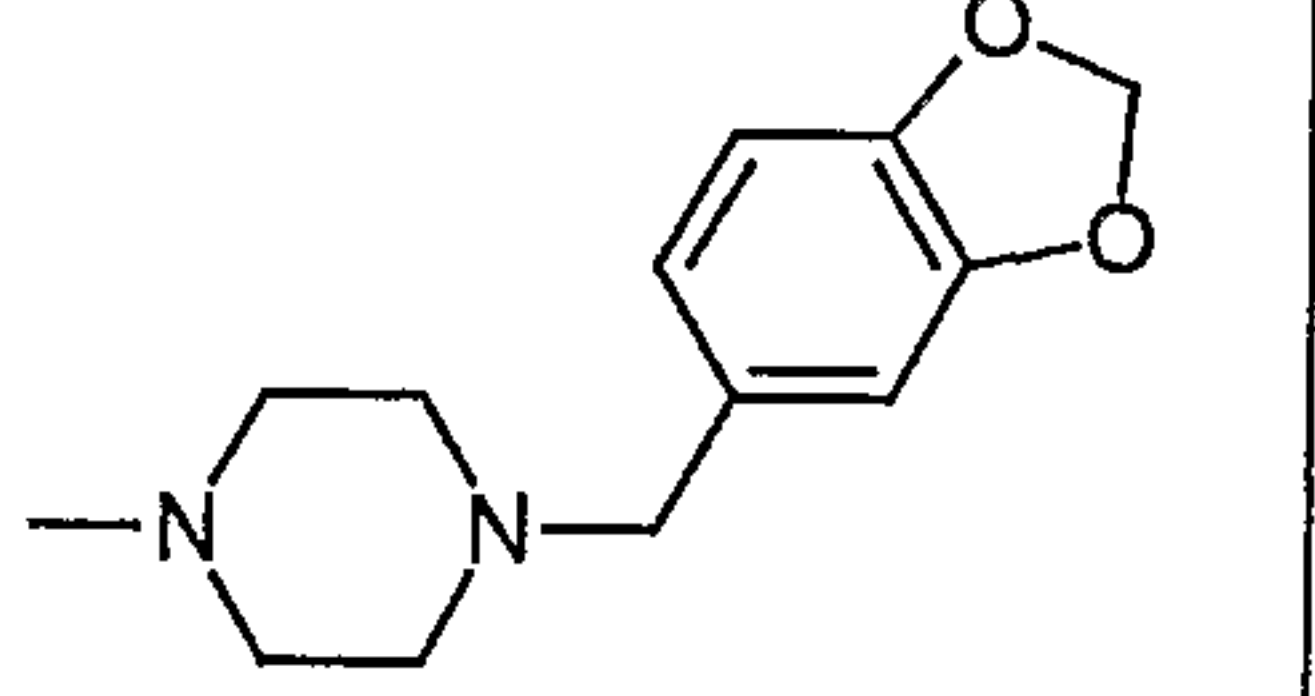
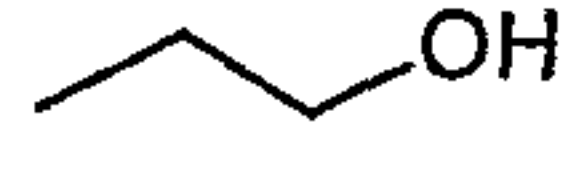
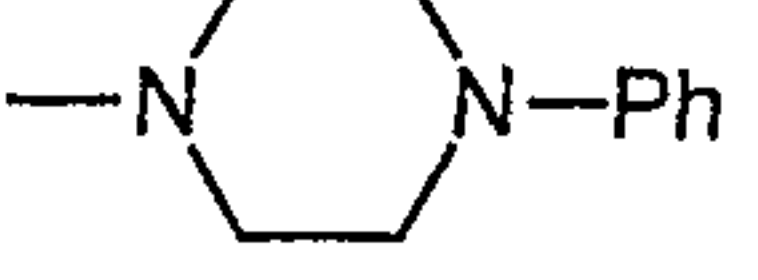
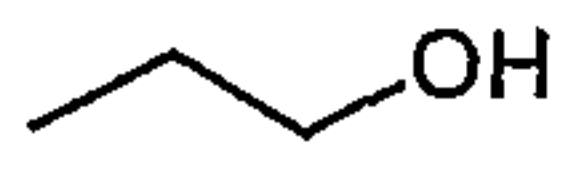
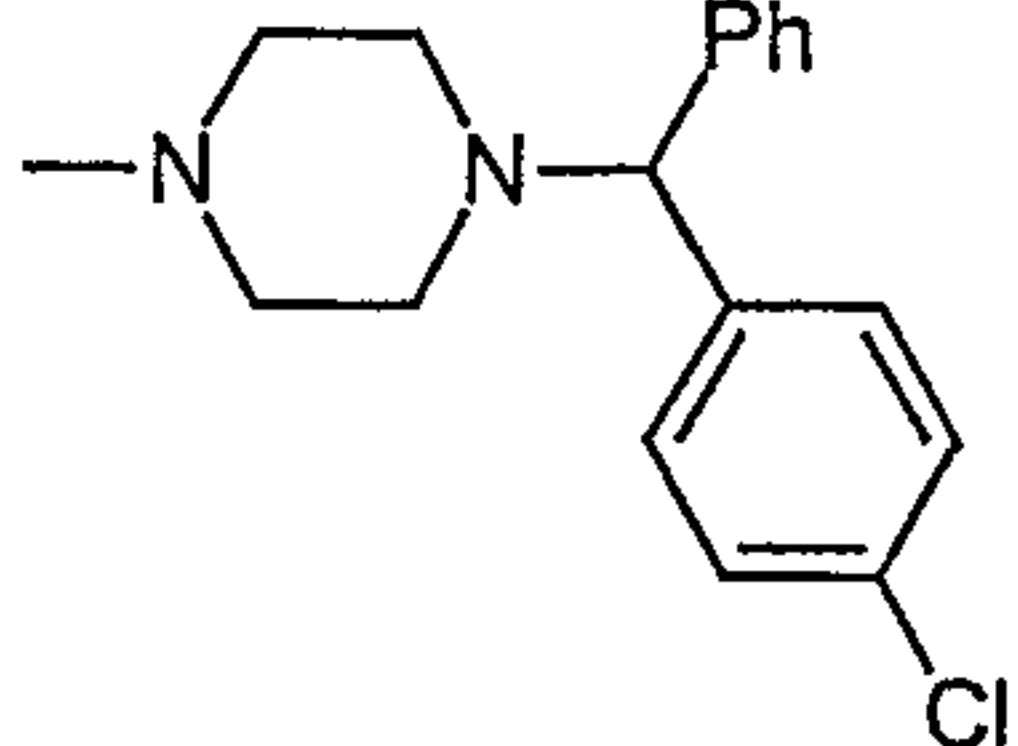
Comp. No	-R ¹	-A-	$\begin{array}{c} \text{R}^2 \\ \\ \text{---N---} \\ \\ \text{R}^3 \end{array}$	[M+H] ⁺
353				459
354				530
355				517
356				579
357				492
358				510
359				531
360				520
361				393
362				517

Table 3 (continued):

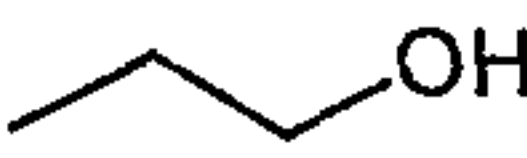
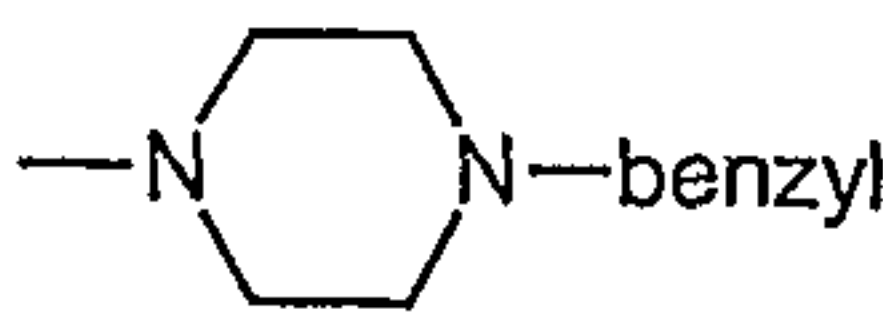
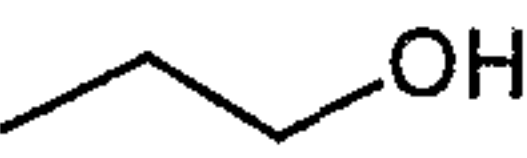
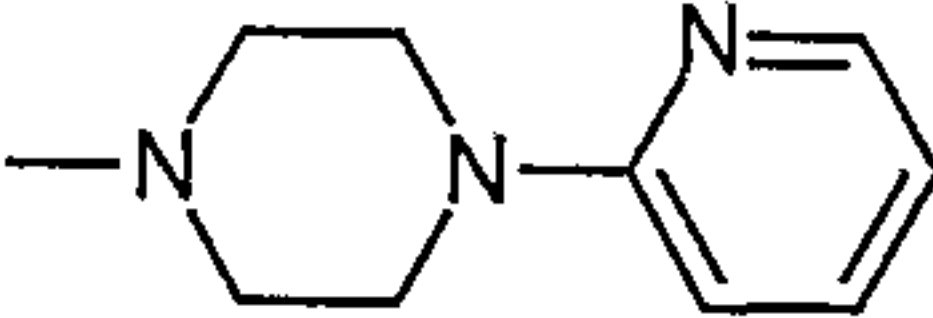
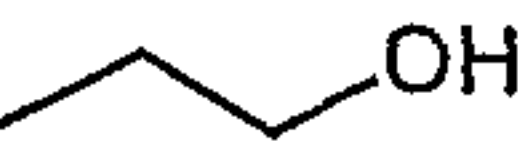
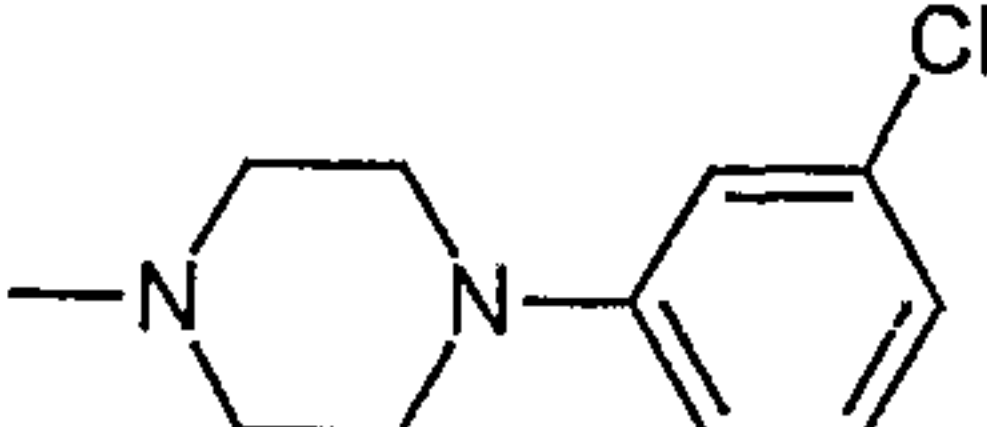
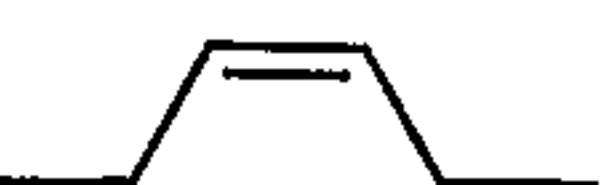
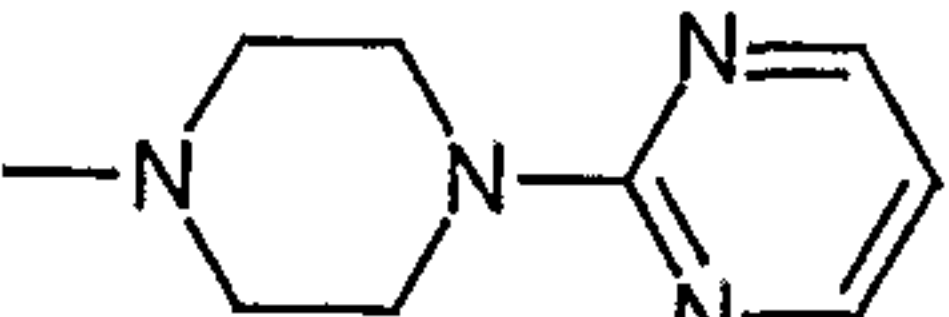
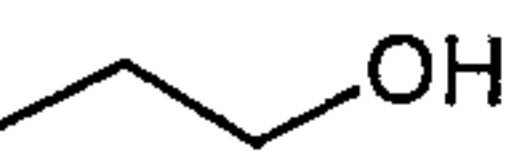
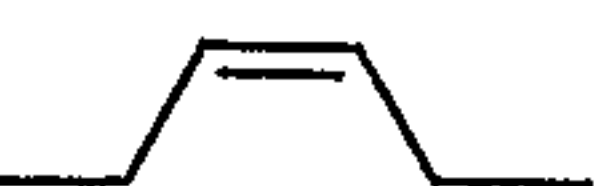
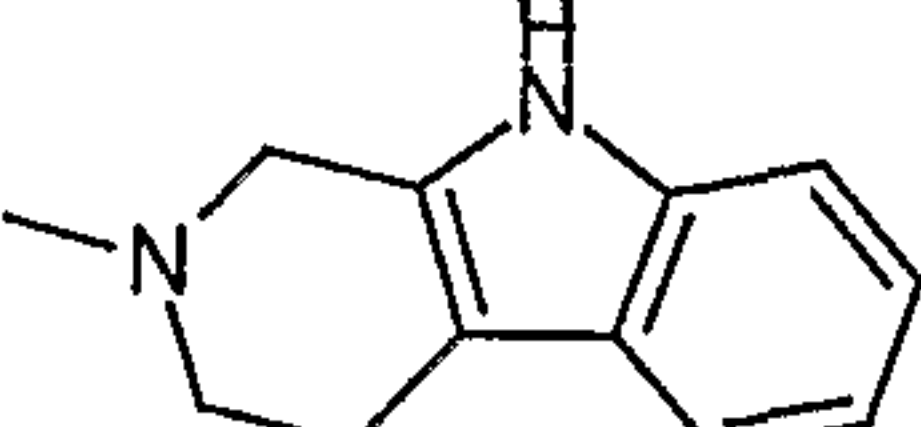
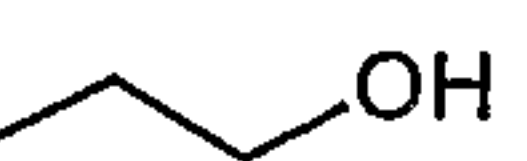
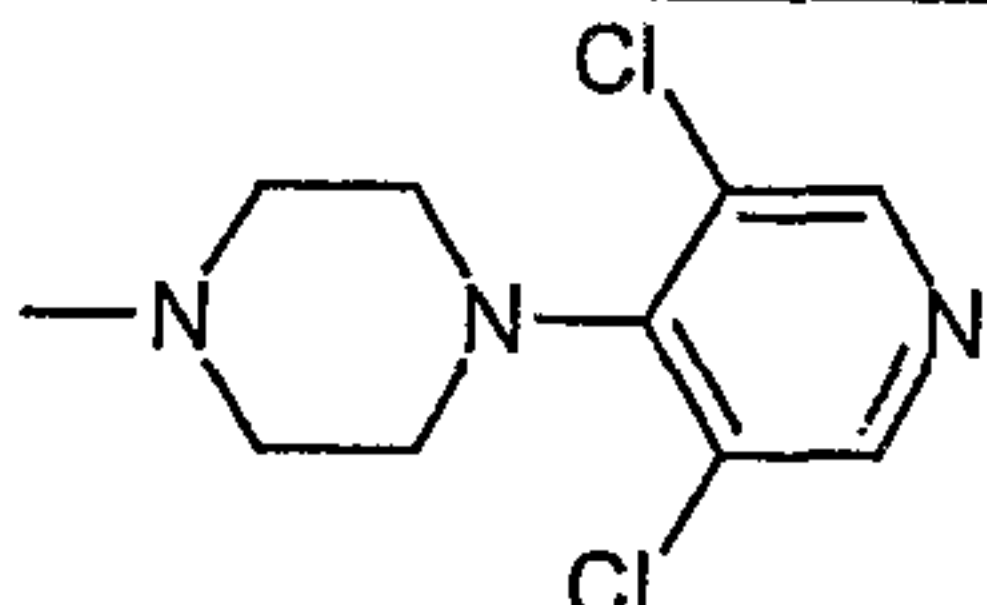
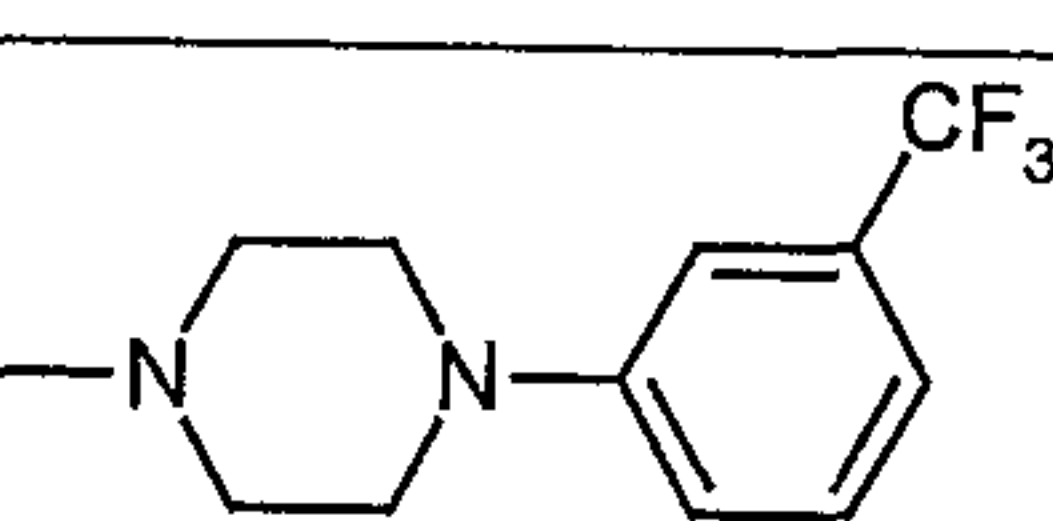
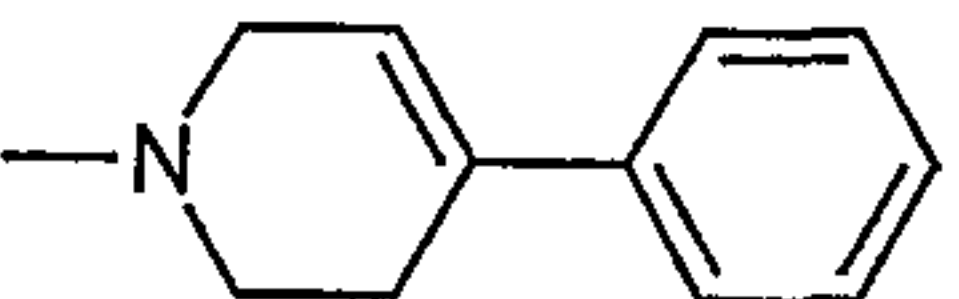
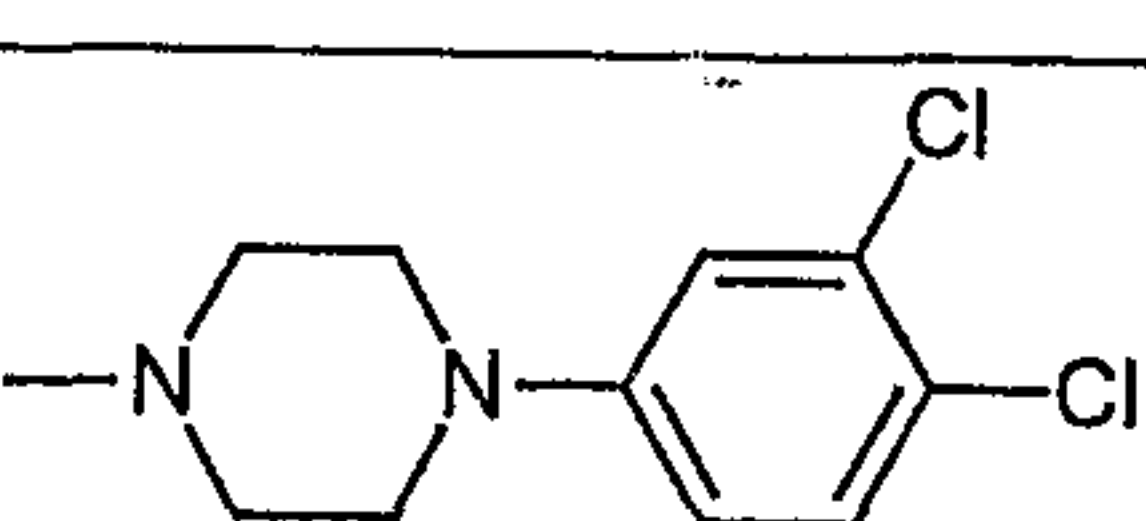
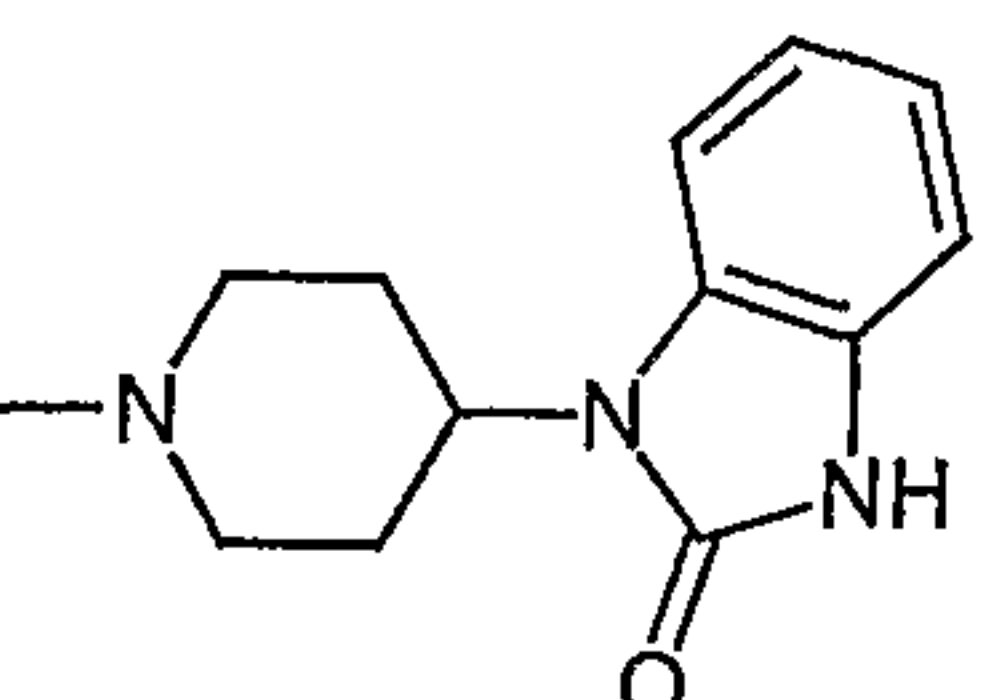
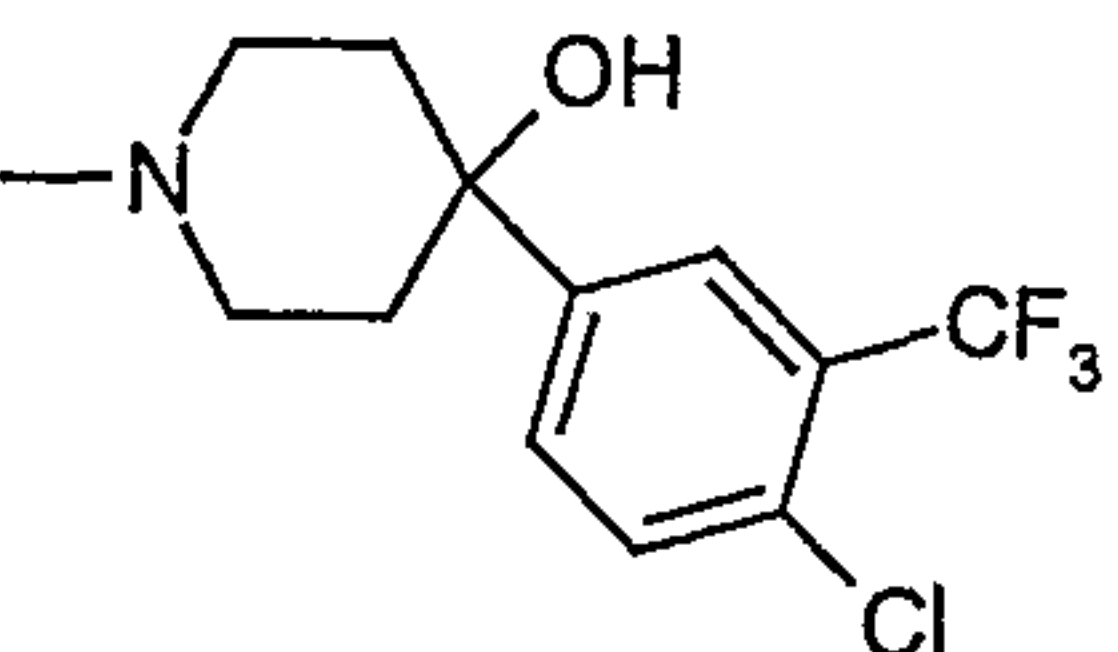
Comp. No	-R ¹	-A-	$\begin{array}{c} R^2 \\ \\ -N- \\ \\ R^3 \end{array}$	[M+H] ⁺
363				407
364				394
365				427
366				395
367				403
368				476
369				461
370				390
371				461
372				448
373				510

Table 3 (continued):

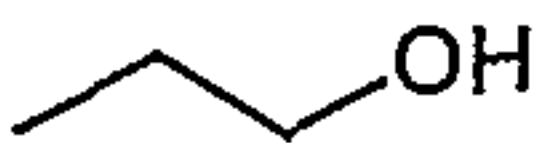
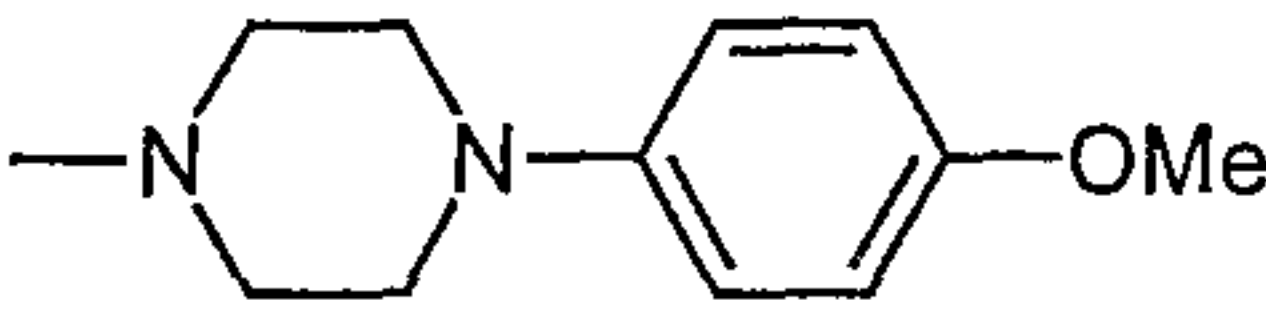
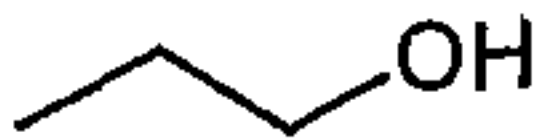
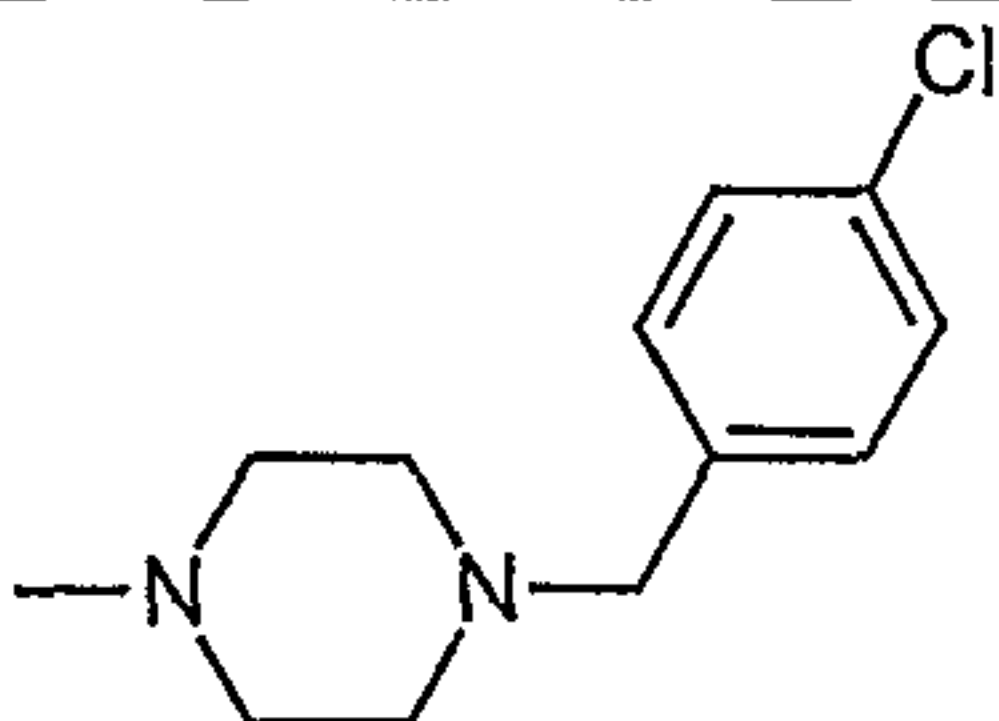
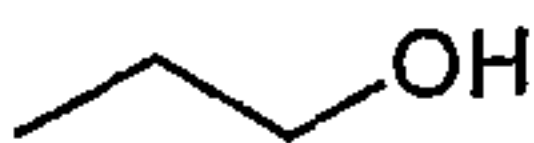
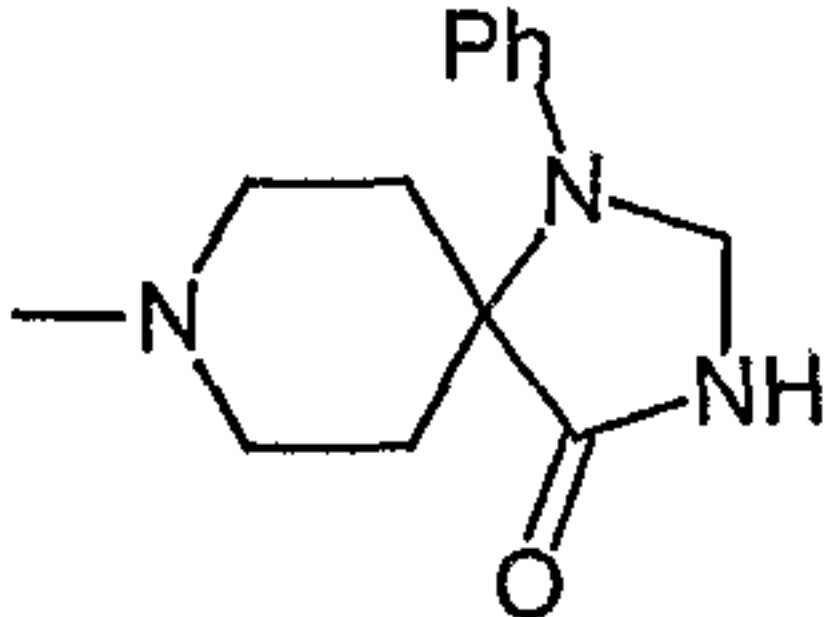
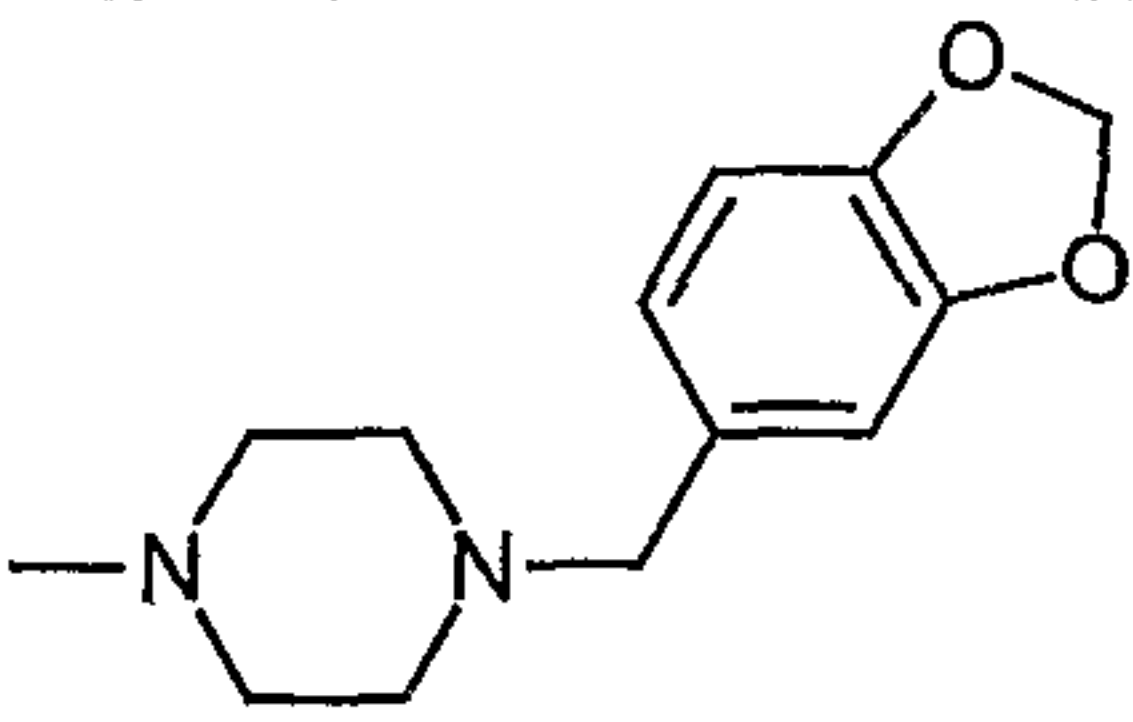
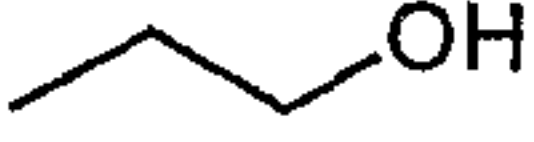
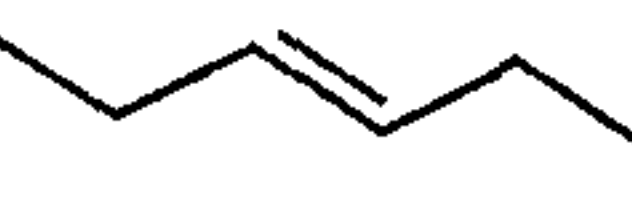
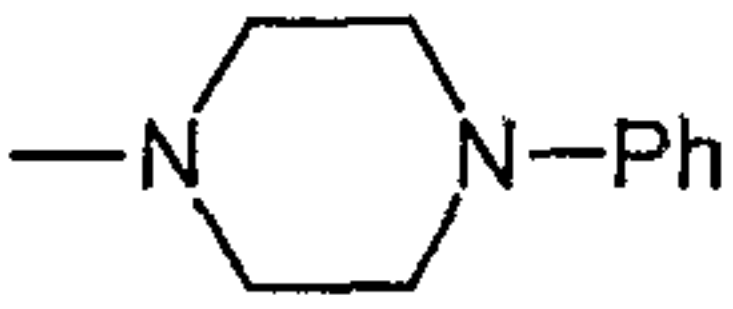
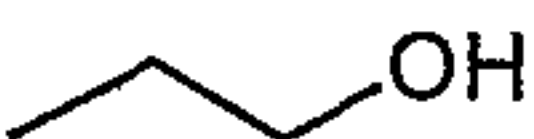
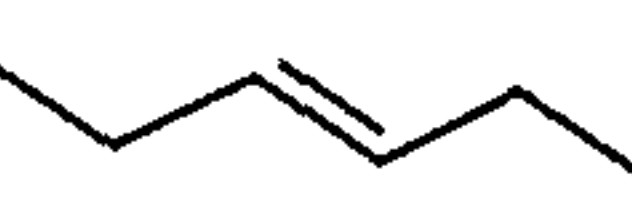
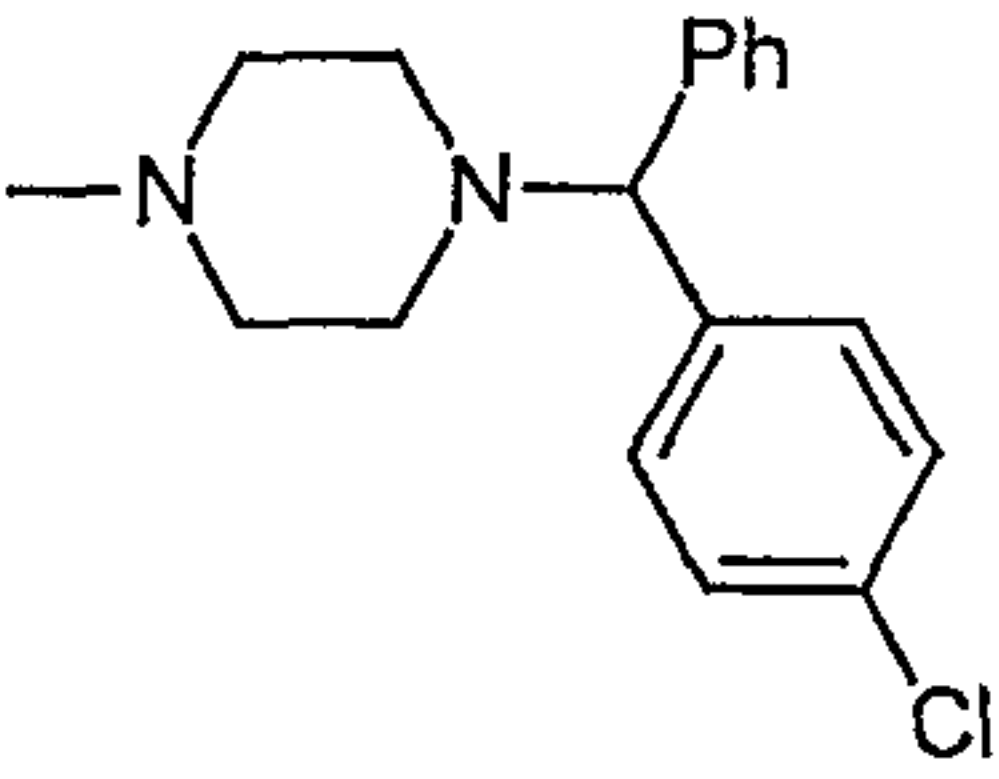
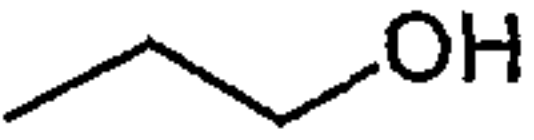
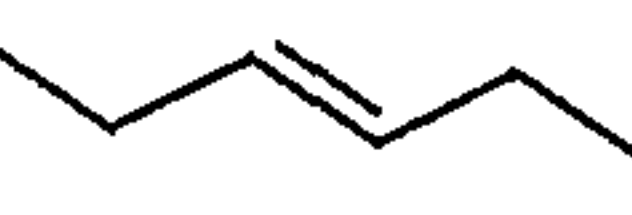
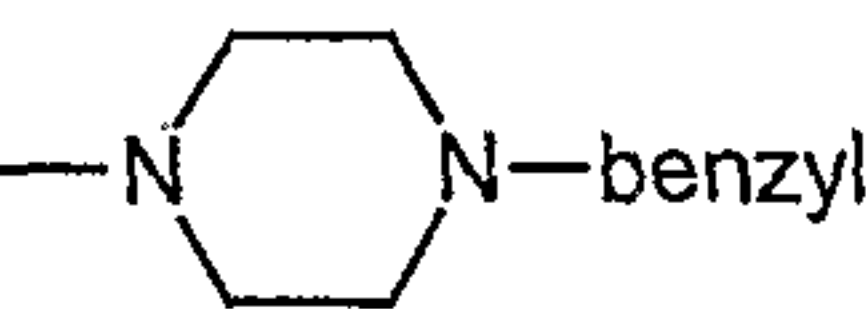
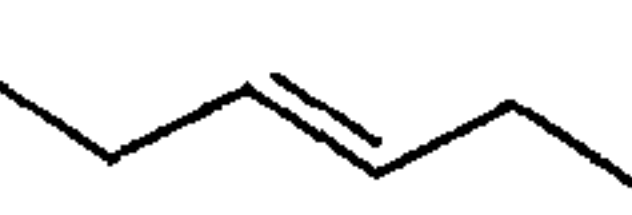
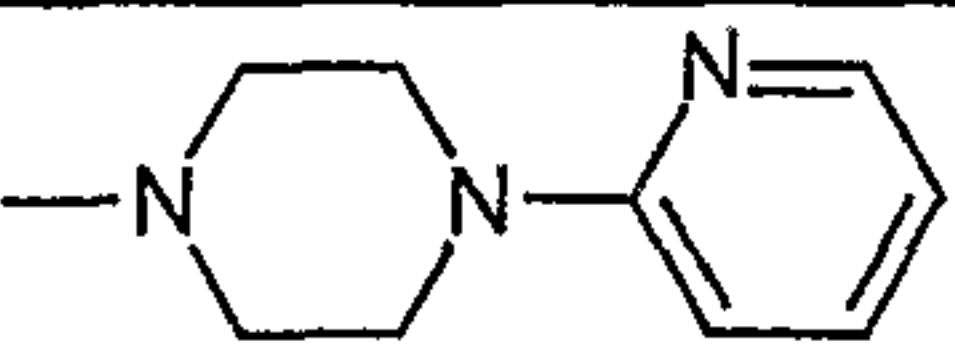
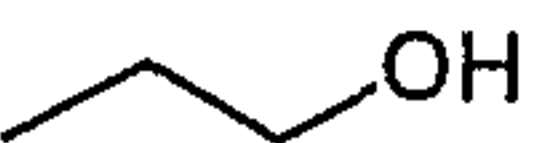
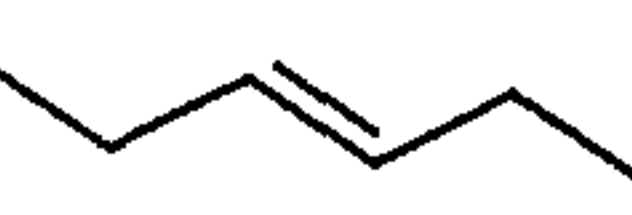
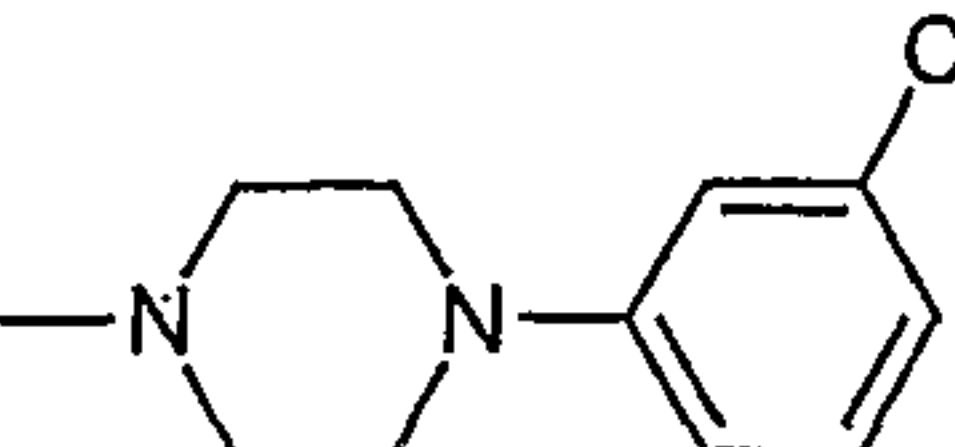
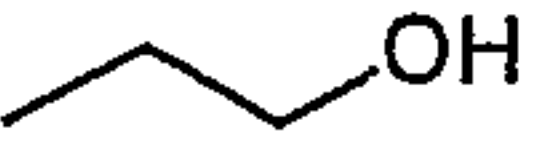
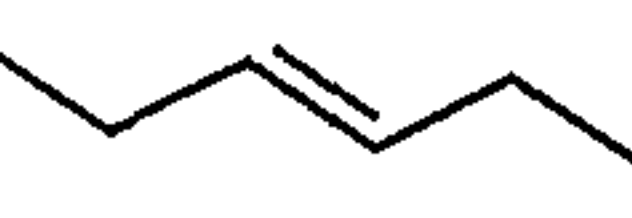
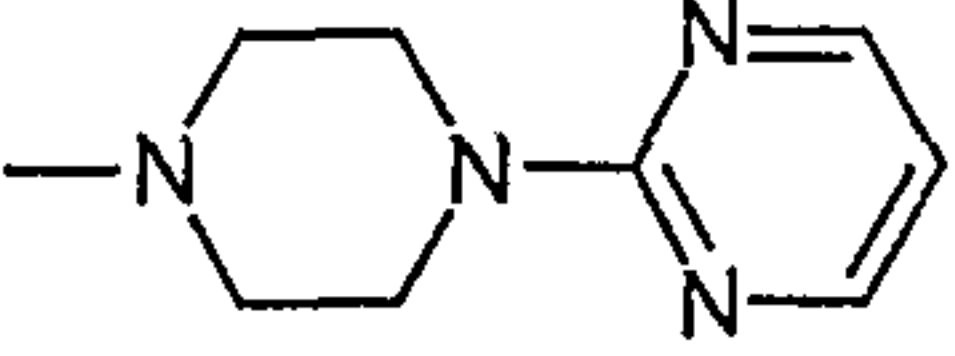
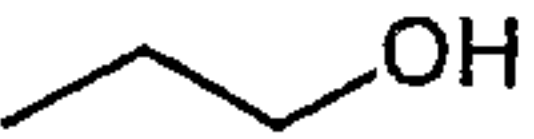
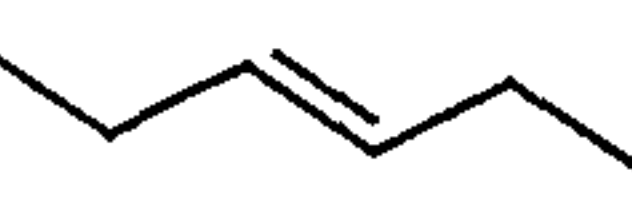
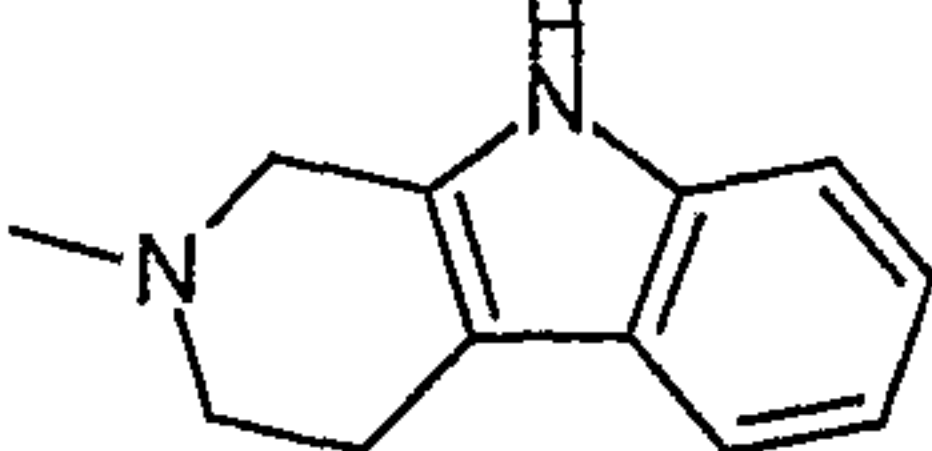
Comp. No	-R ¹	-A-	$\begin{array}{c} \text{R}^2 \\ \\ \text{---N---} \\ \\ \text{R}^3 \end{array}$	[M+H] ⁺
374				423
375				441
376				462
377				451
378				393
379				517
380				407
381				394
382				427
383				395
384				403

Table 3 (continued):

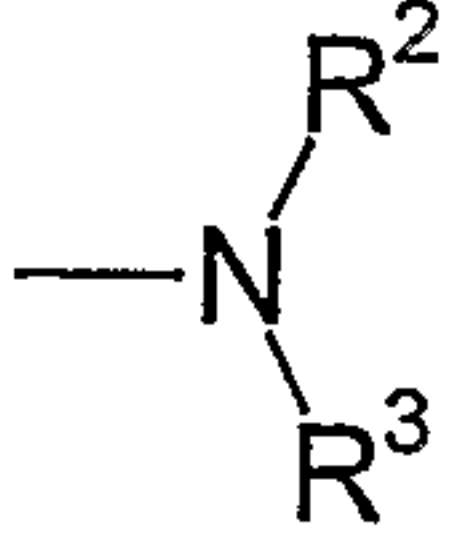
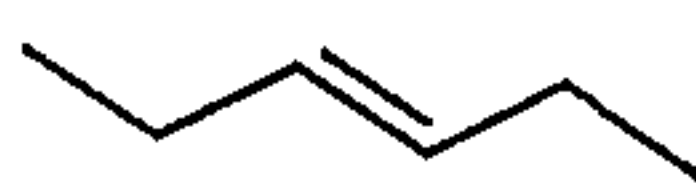
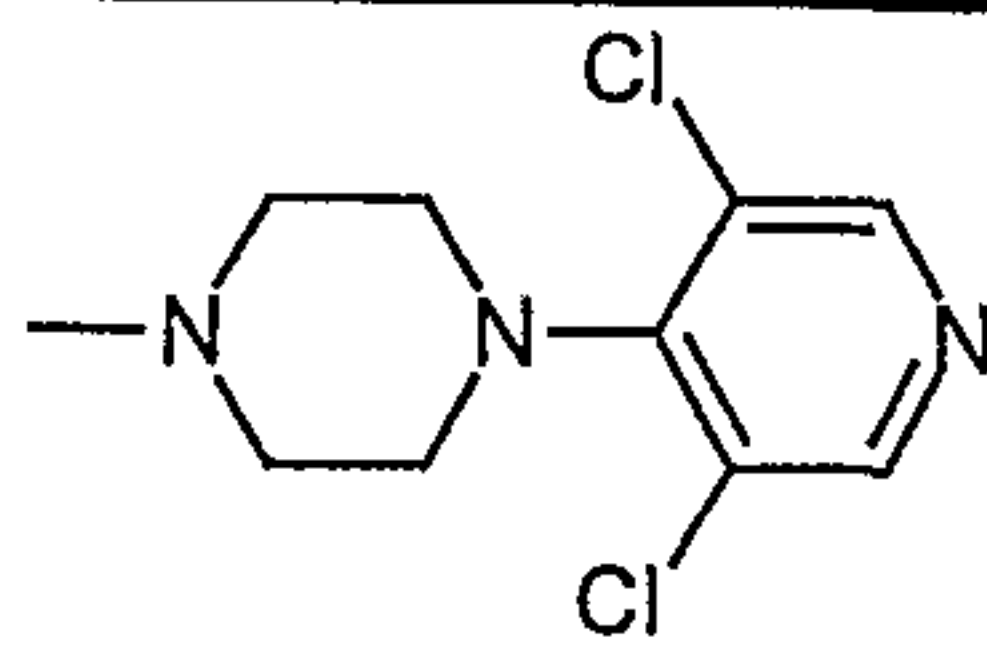
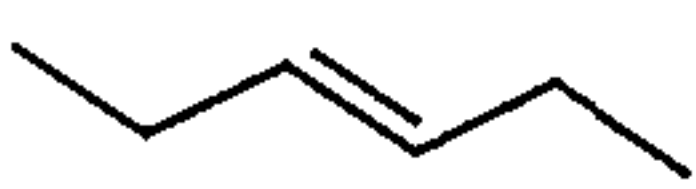
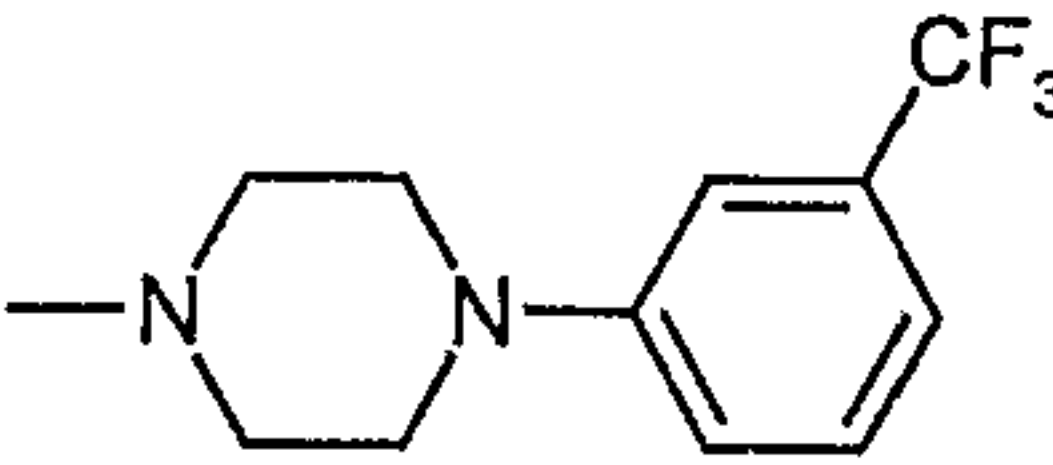
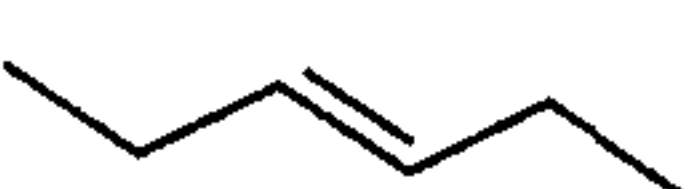
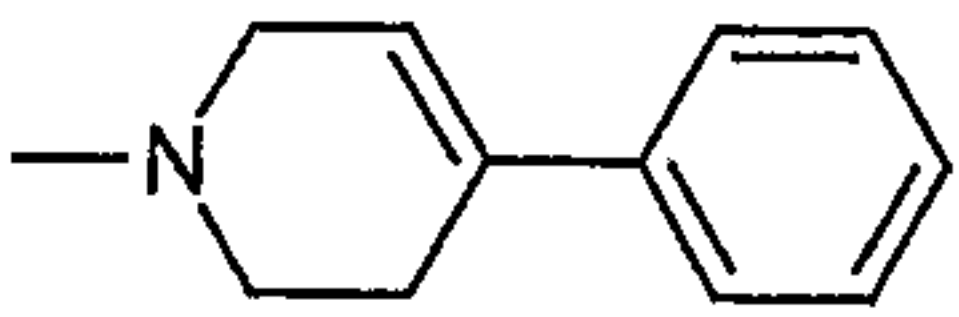
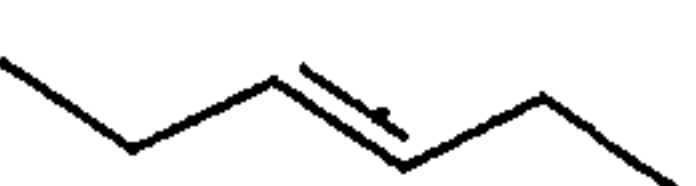
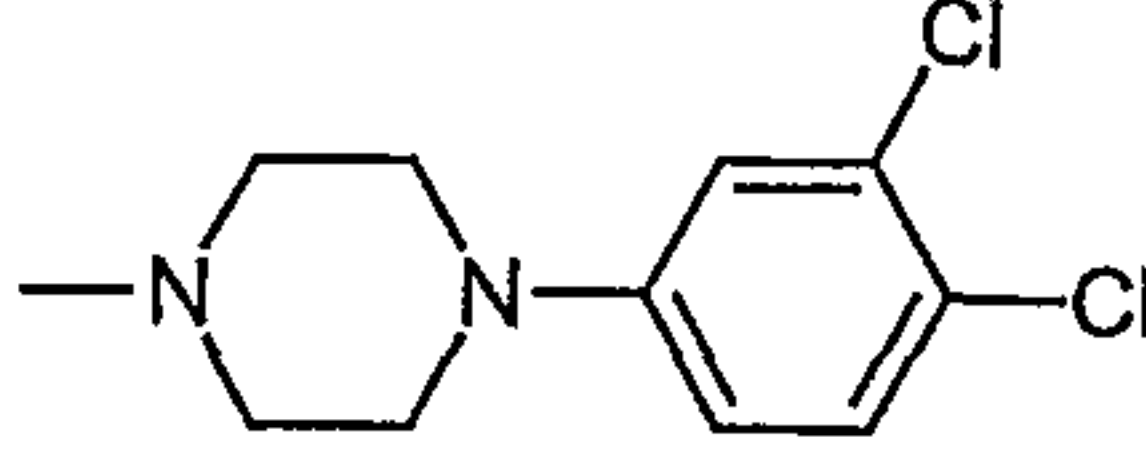
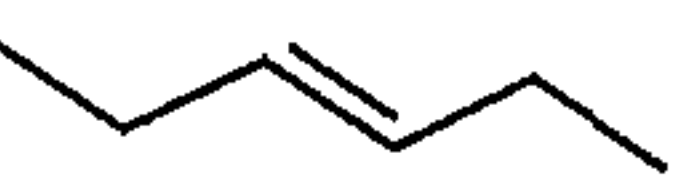
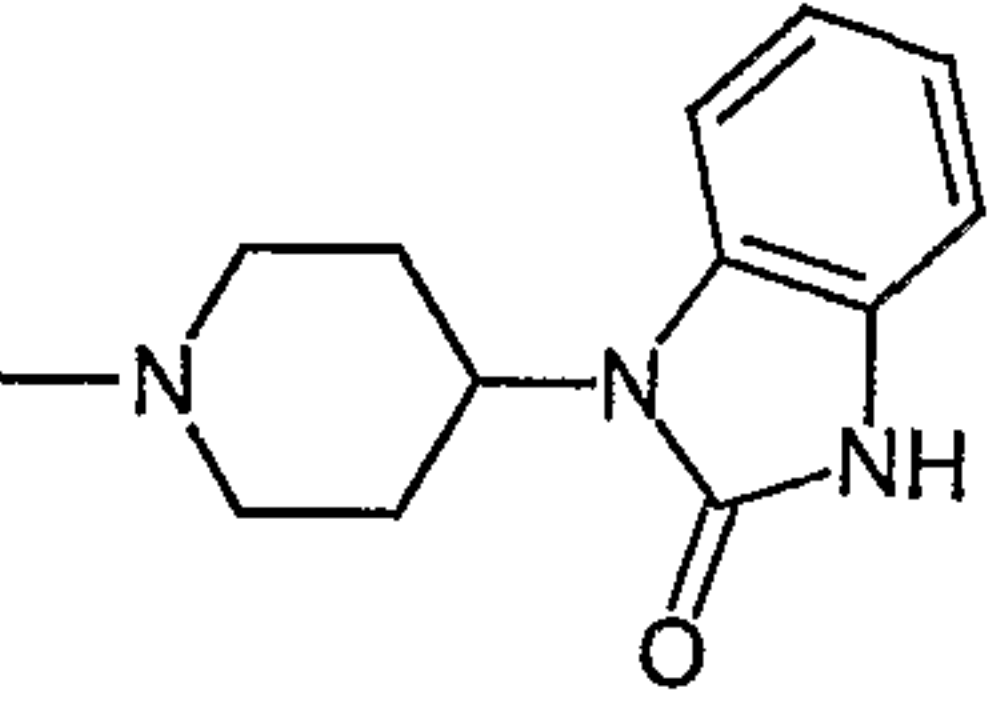
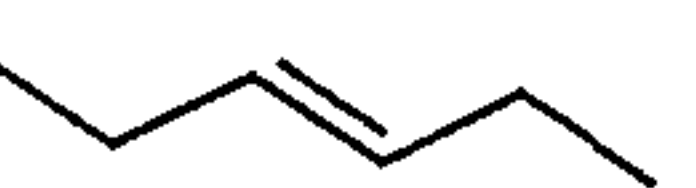
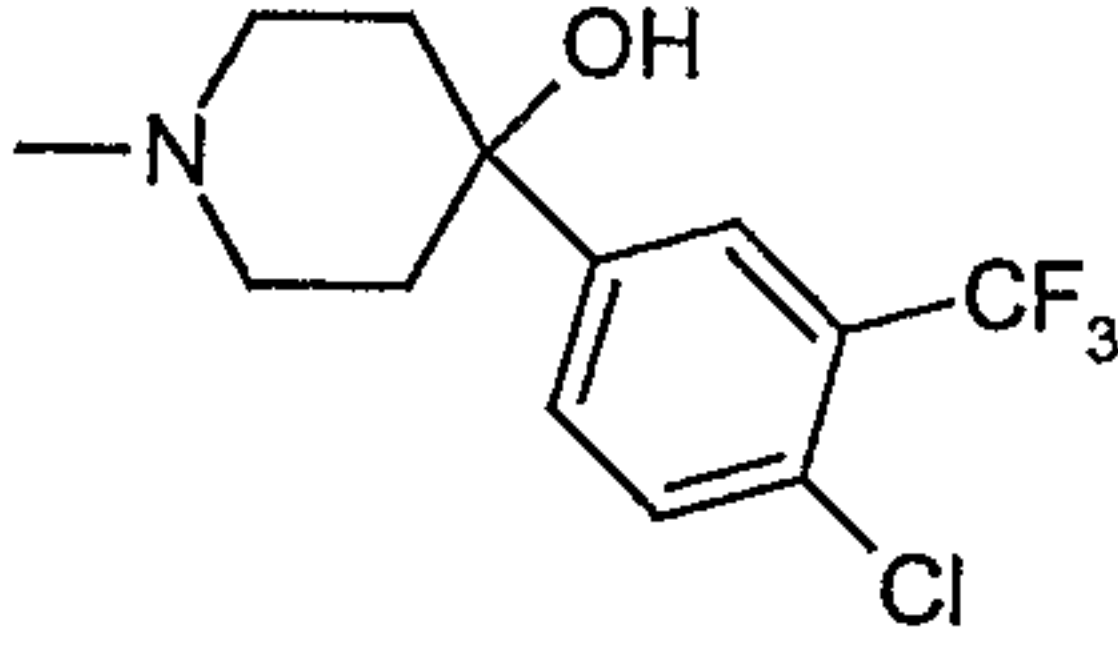
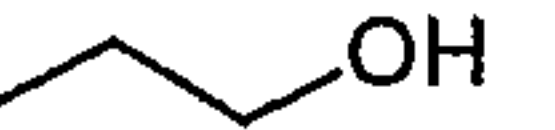
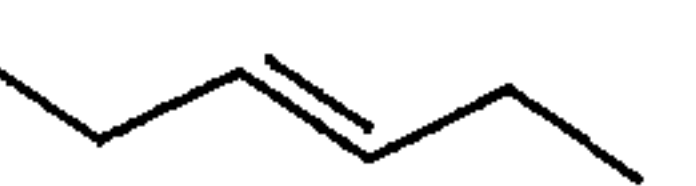
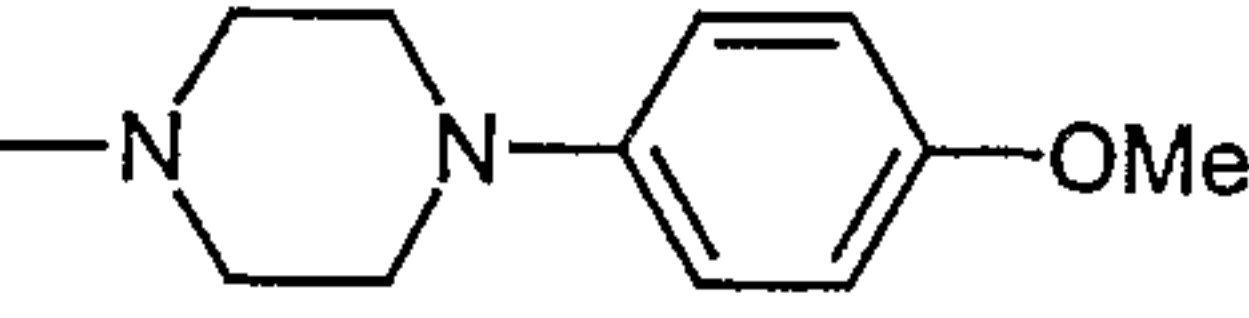
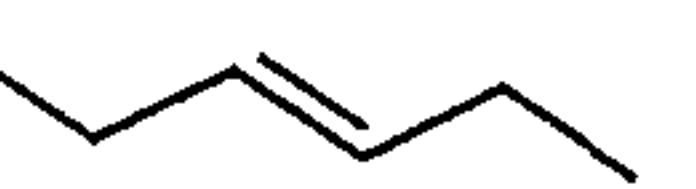
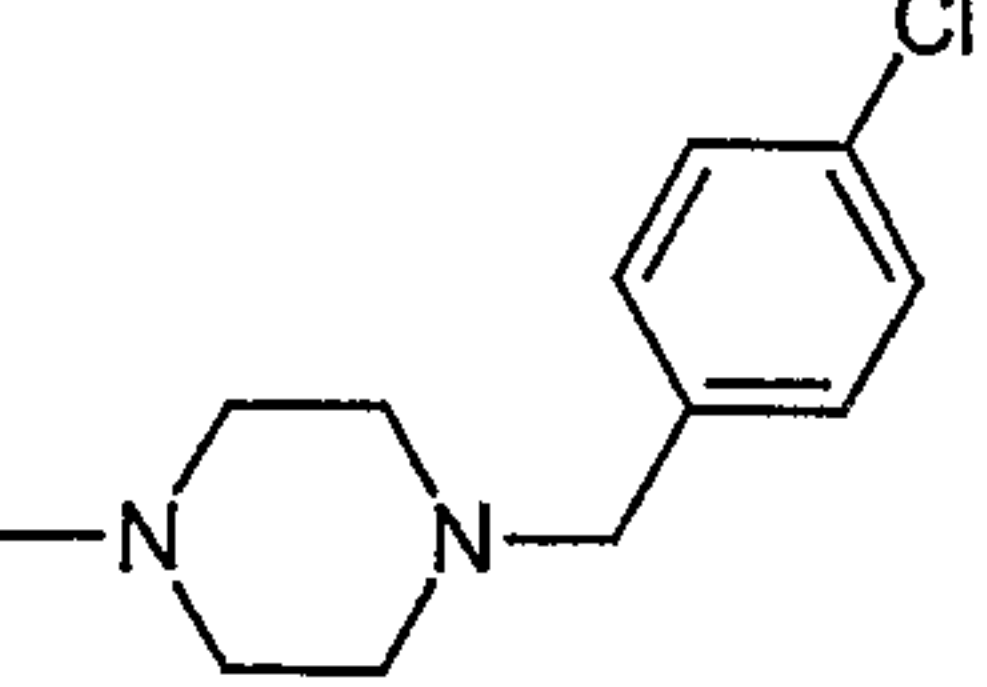
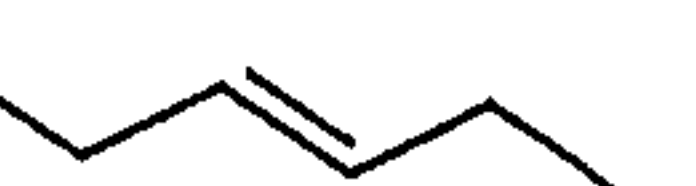
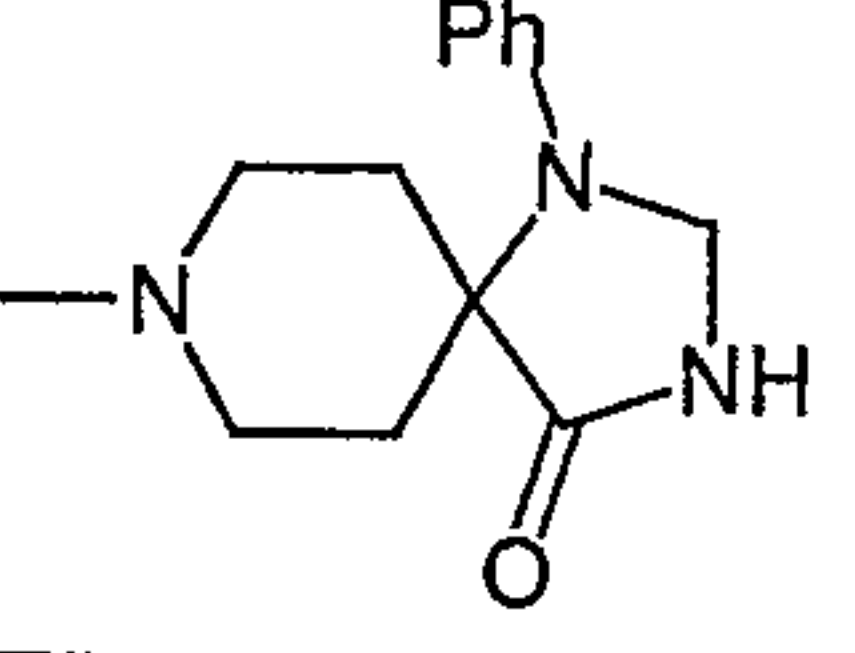
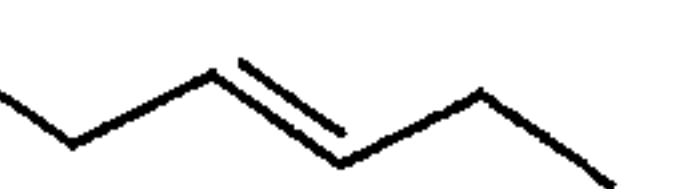
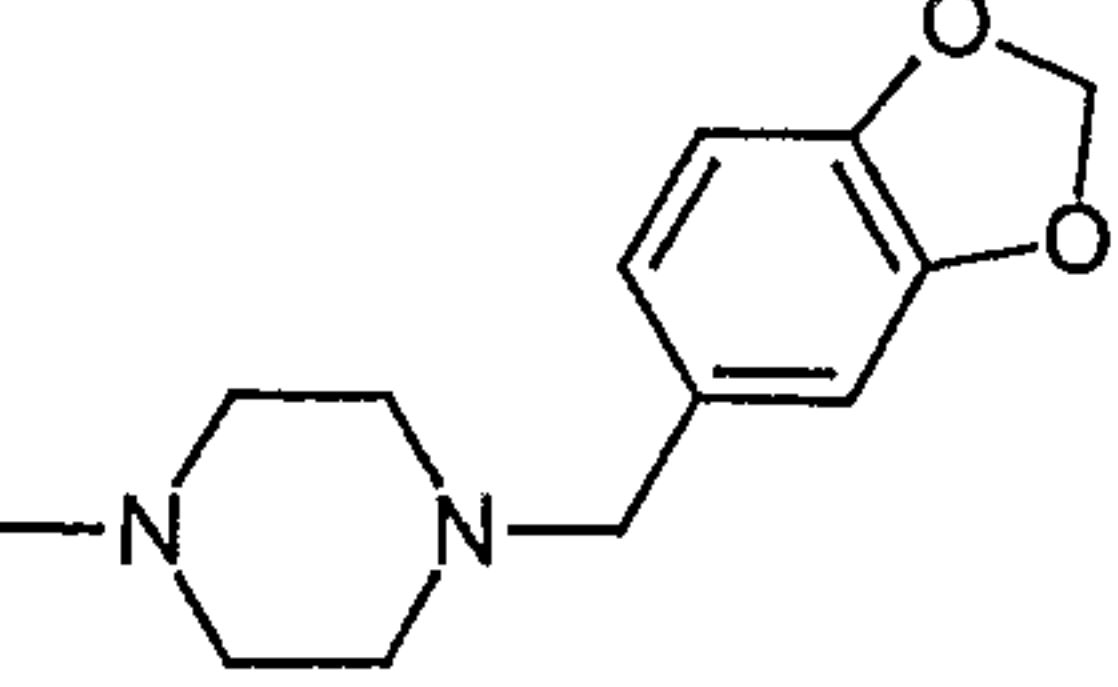
Comp. No	-R ¹	-A-		[M+H] ⁺
385				476
386				461
387				390
388				461
389				448
390				510
391				423
392				441
393				462
394				451

Table 3 (continued):

Comp. No	-R ¹	-A-	$\begin{array}{c} \text{R}^2 \\ \\ \text{---N---} \\ \\ \text{R}^3 \end{array}$	[M+H] ⁺
395				464
396				588
397				478
398				465
399				699
400				466
401				474
402				469
403				532
404				461
405				532

Table 3 (continued):

Comp. No	-R ¹	-A-	$\text{—N} \begin{matrix} \text{R}^2 \\ \text{R}^3 \end{matrix}$	[M+H] ⁺
406				519
407				581
408				494
409				512
410				533
411				522
412				464
413				588
414				478
415				465

Table 3 (continued):

Comp. No	-R ¹	-A-	$\text{—N} \begin{matrix} \text{R}^2 \\ \text{R}^3 \end{matrix}$	[M+H] ⁺
416				498
417				466
418				474
419				469
420				532
421				461
422				532
423				519
424				581
425				494
426				512

Table 3 (continued):

Comp. No	-R ¹	-A-	$\begin{array}{c} \text{R}^2 \\ \\ \text{---N---} \\ \\ \text{R}^3 \end{array}$	[M+H] ⁺
427				533
428				522
429				408
430				532
431				422
432				409
433				442
434				410
435				418
436				477
437				476

Table 3 (continued):

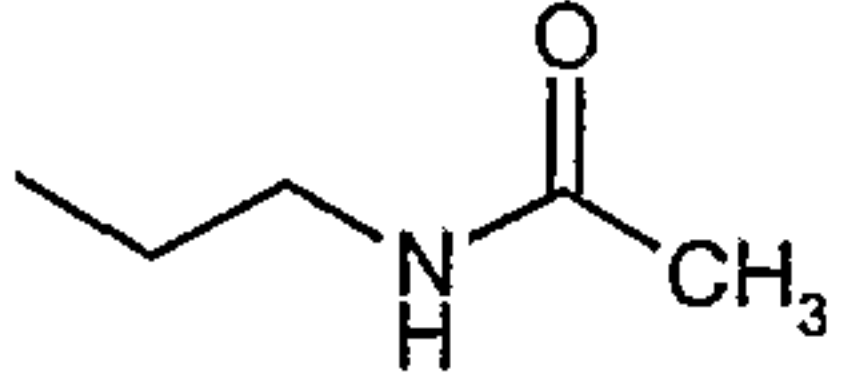
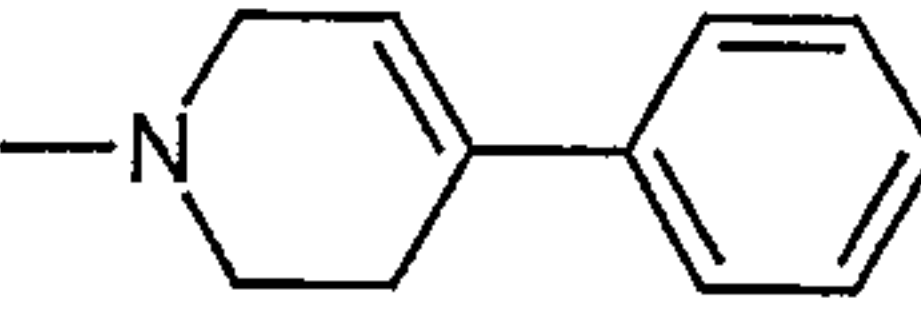
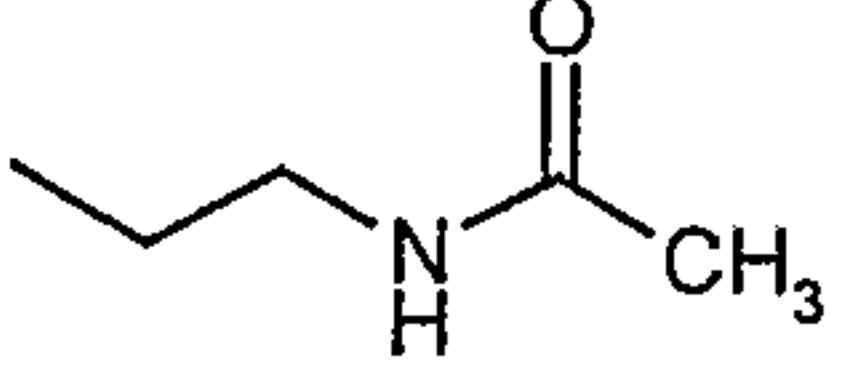
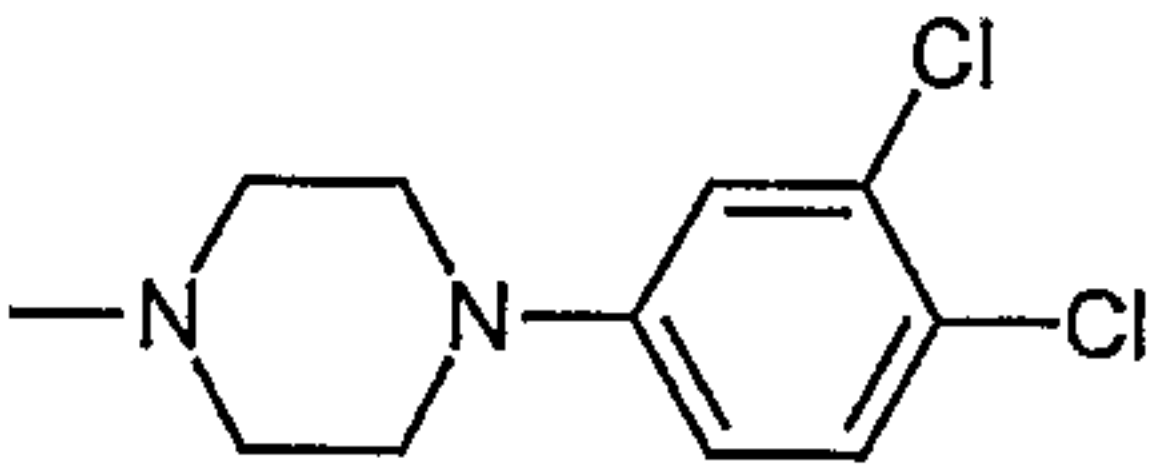
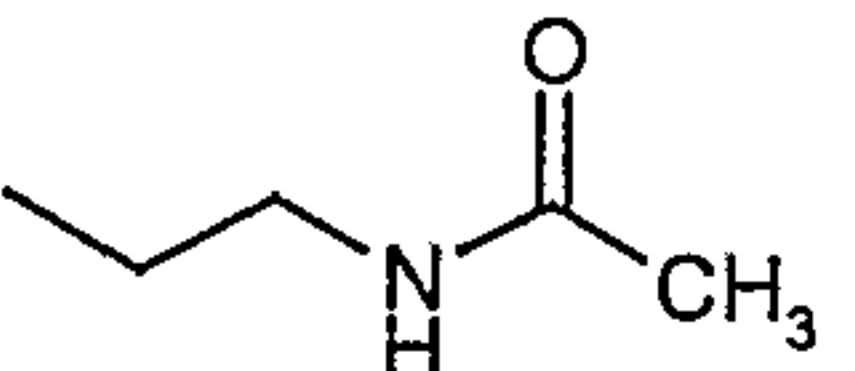
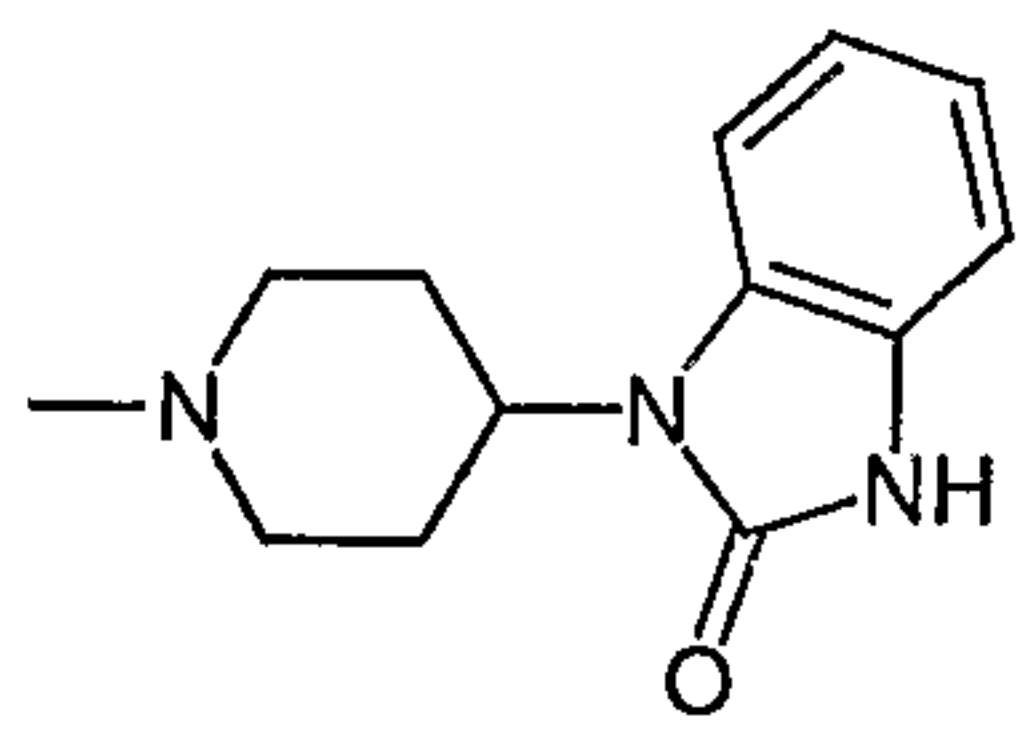
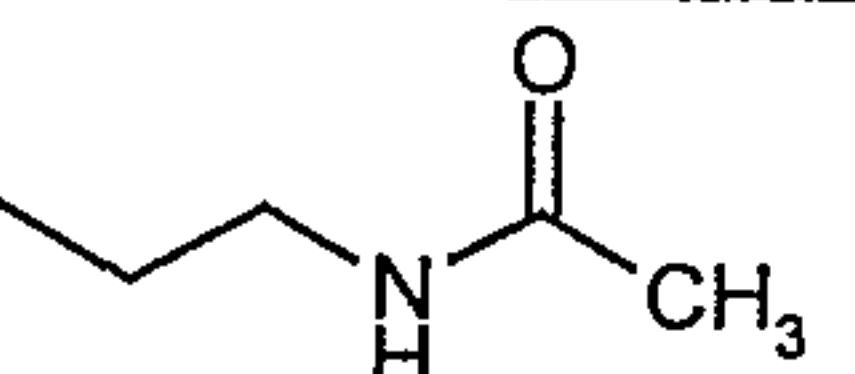
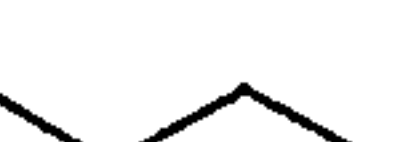
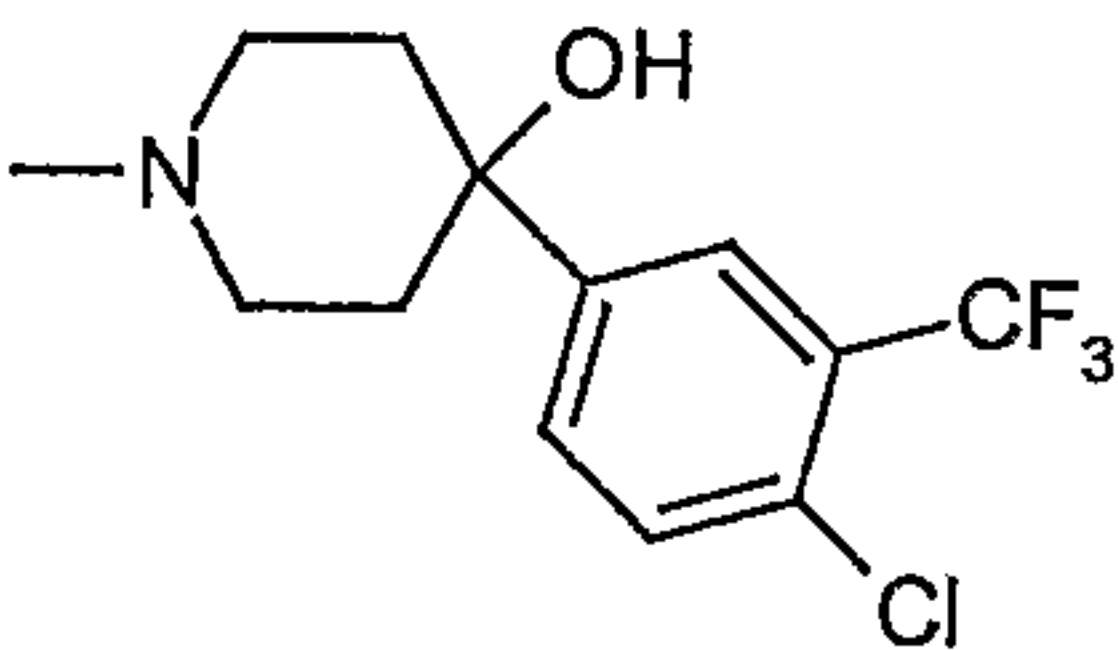
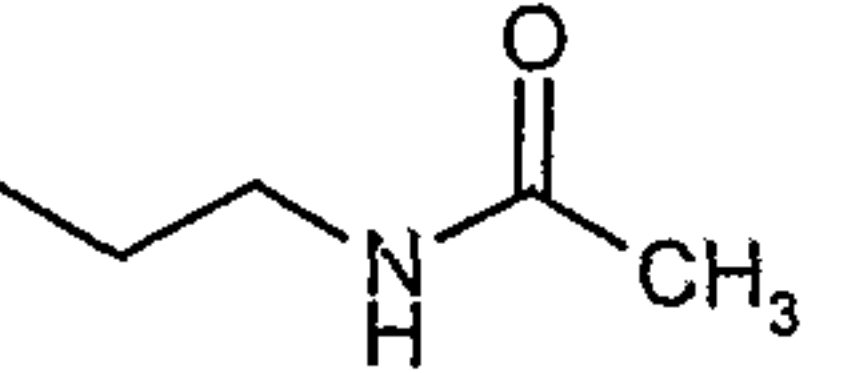
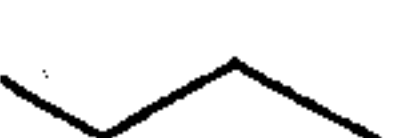
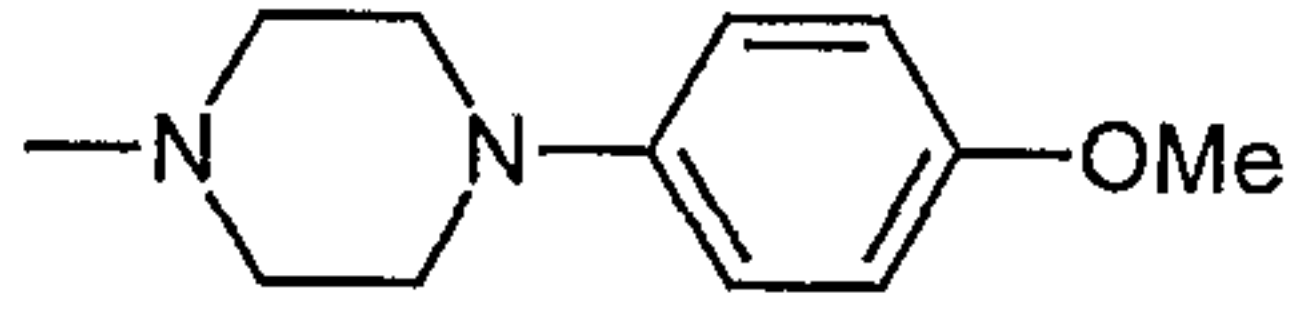
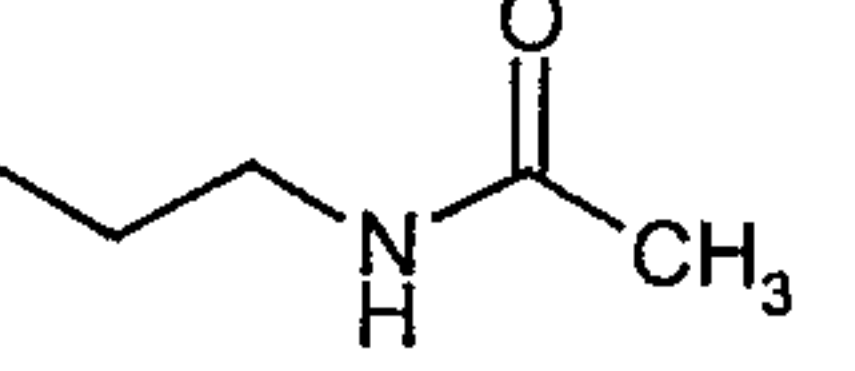
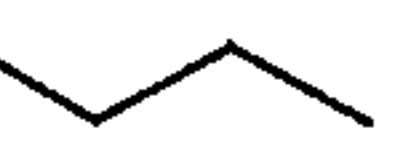
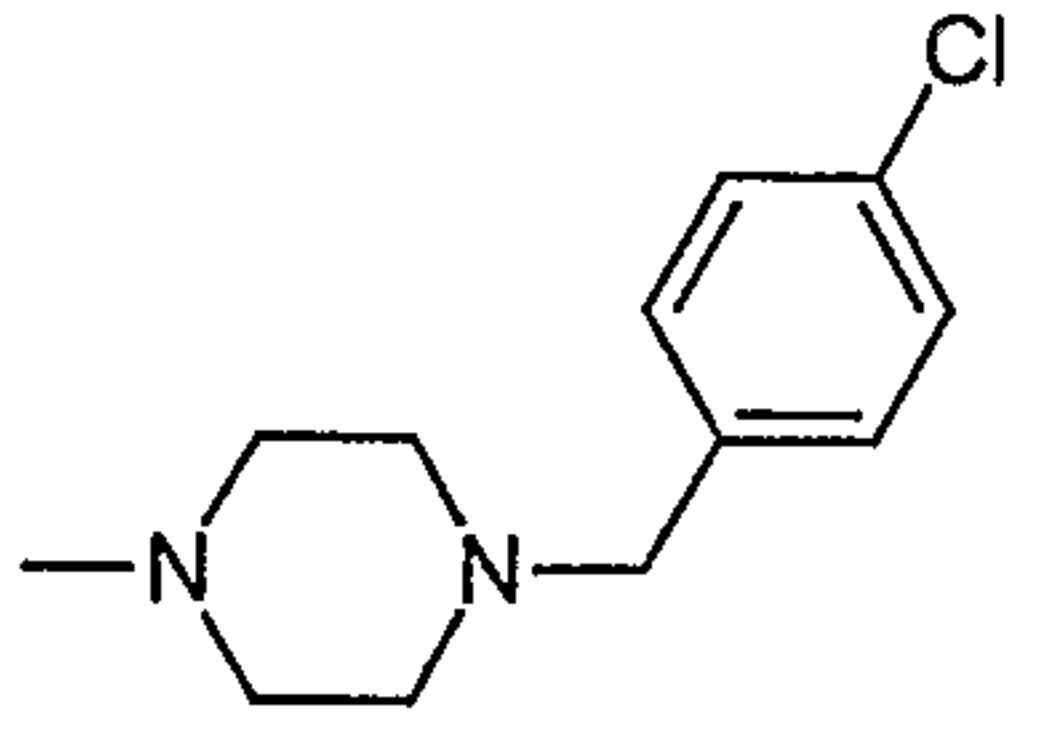
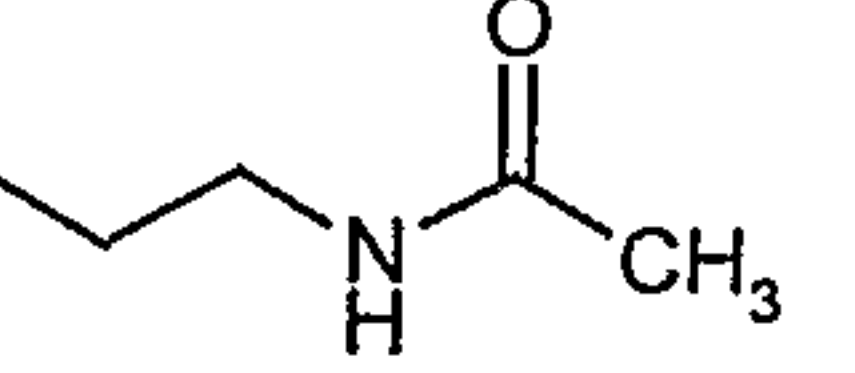
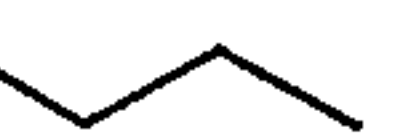
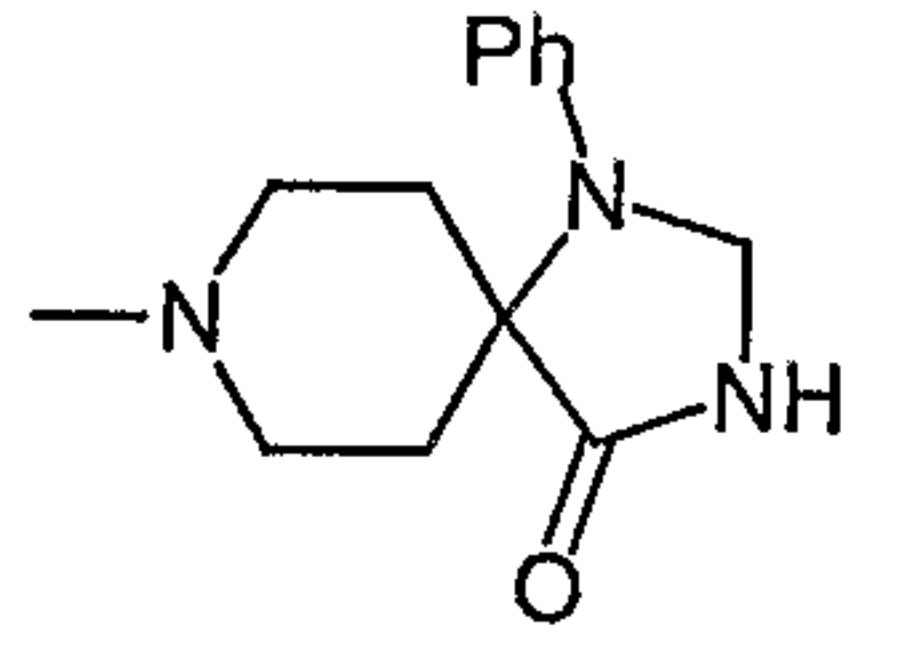
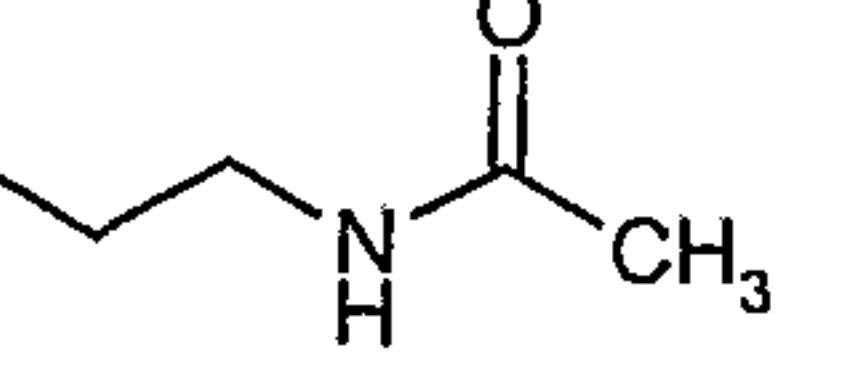
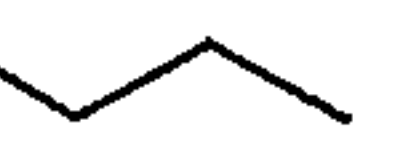
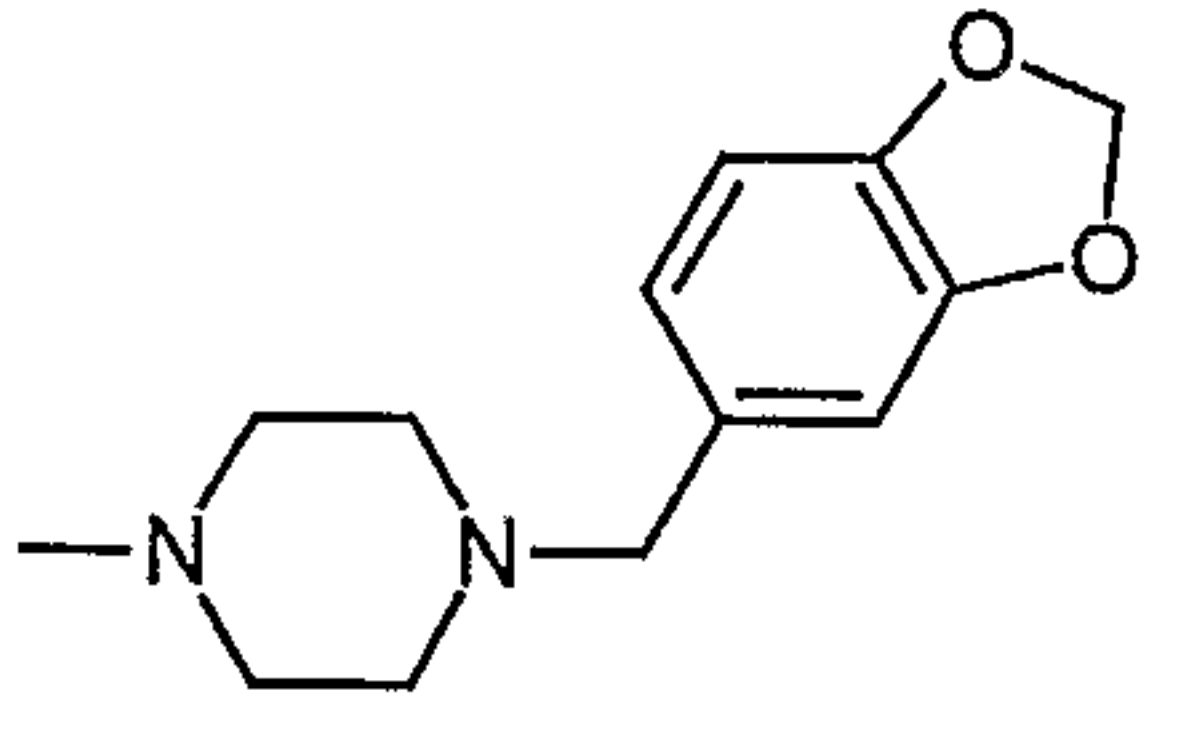
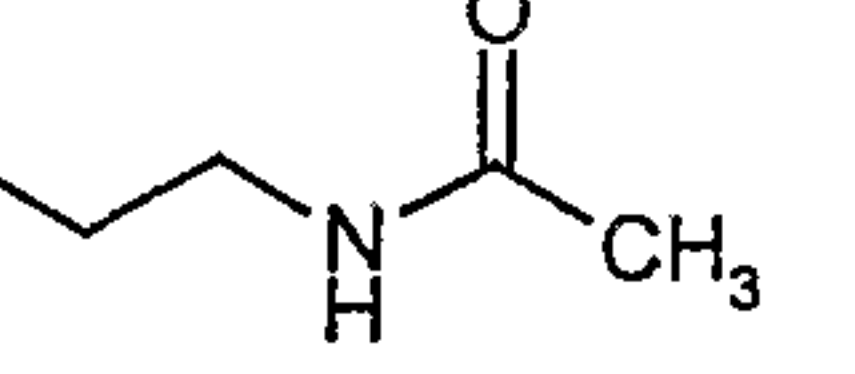
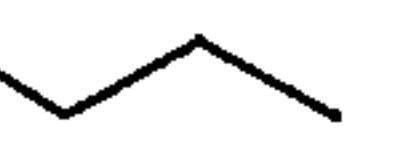
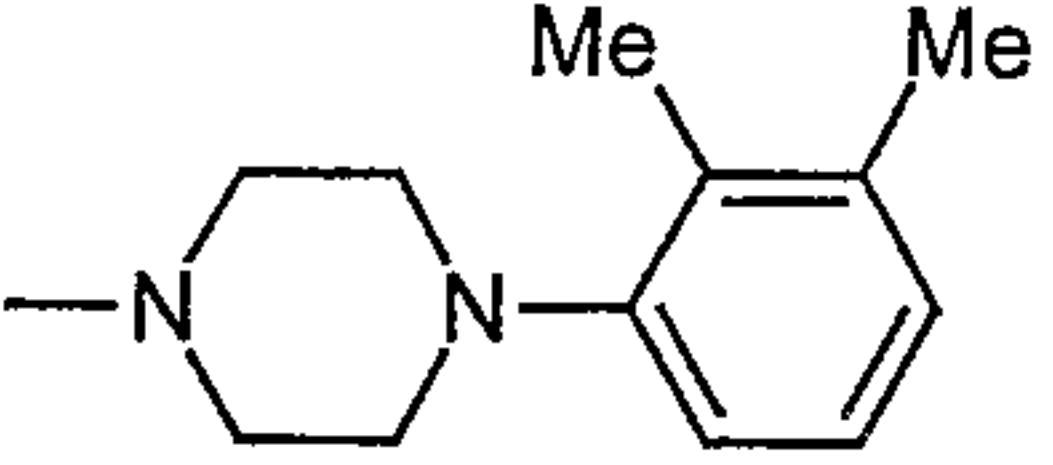
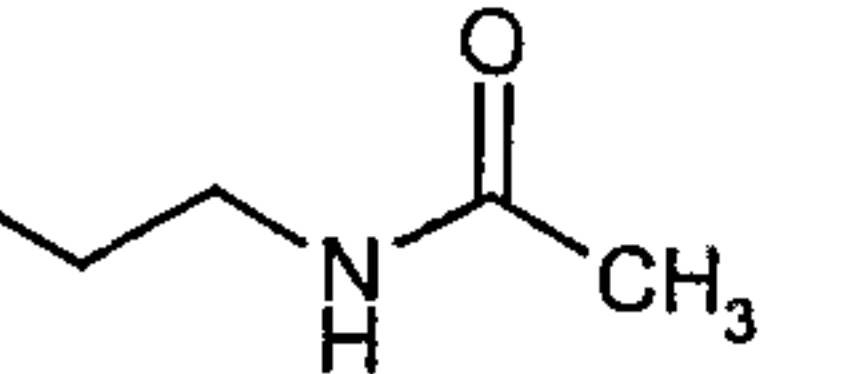
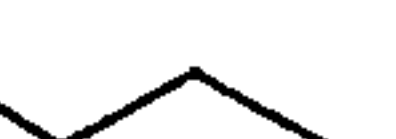
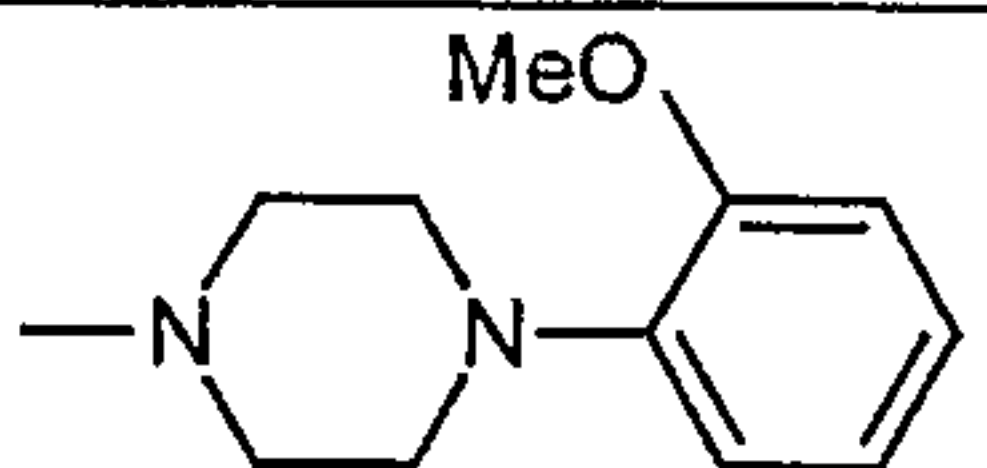
Comp. No	-R ¹	-A-	$\begin{array}{c} \text{R}^2 \\ \\ \text{---N---} \\ \\ \text{R}^3 \end{array}$	[M+H] ⁺
438				405
439				476
440				463
441				525
442				438
443				456
444				477
445				466
446				436
447				438

Table 3 (continued):

Comp. No	-R ¹	-A-	$\begin{array}{c} \text{R}^2 \\ \\ \text{---N---} \\ \\ \text{R}^3 \end{array}$	[M+H] ⁺
448				422
449				422
450				442
451				434
452				558
453				448
454				435
455				468
456				436
457				444
458				503
459				502

Table 3 (continued):

Comp. No	-R ¹	-A-	$\begin{array}{c} \text{R}^2 \\ \\ \text{---N---} \\ \\ \text{R}^3 \end{array}$	[M+H] ⁺
460				431
461				502
462				489
463				551
464				464
465				482
466				503
467				492
468				462
469				464

Table 3 (continued):

Comp. No	-R ¹	-A-	$\begin{array}{c} \text{R}^2 \\ \\ \text{---N---} \\ \\ \text{R}^3 \end{array}$	[M+H] ⁺
470				448
471				448
472				468
473				434
474				558
475				448
476				435
477				468
478				436
479				444
480				503
481				502

Table 3 (continued):

Comp. No	-R ¹	-A-	$\text{—N} \begin{matrix} \text{R}^2 \\ \text{R}^3 \end{matrix}$	[M+H] ⁺
482				431
483				502
484				489
485				551
486				464
487				482
488				503
489				492
490				462
491				464

Table 3 (continued):

Comp. No	-R ¹	-A-	$\text{—N} \begin{matrix} \text{R}^2 \\ \text{R}^3 \end{matrix}$	[M+H] ⁺
492				448
493				448
494				468
495				470
496				594
497				484
498				471
499				504
500				472
501				480
502				539
503				538

Table 3 (continued):

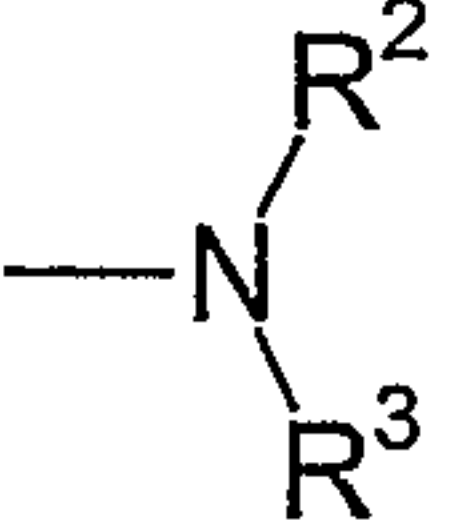
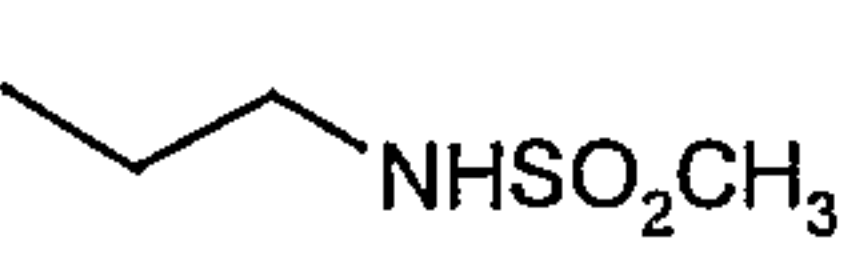
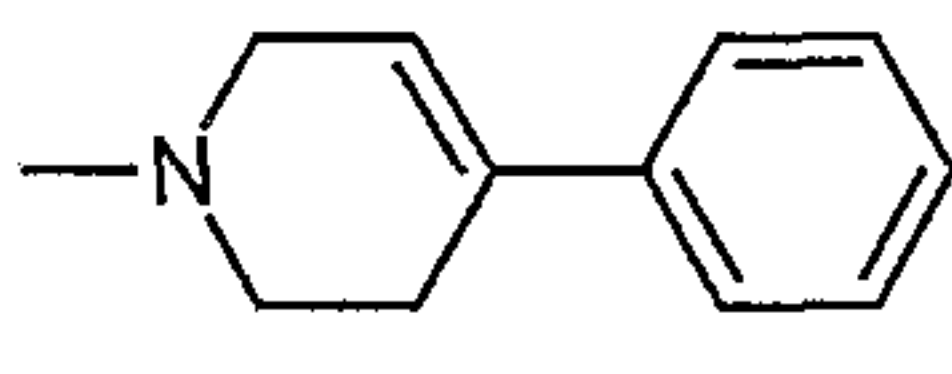
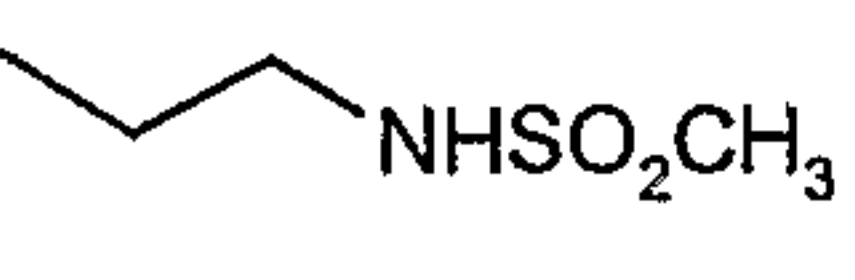
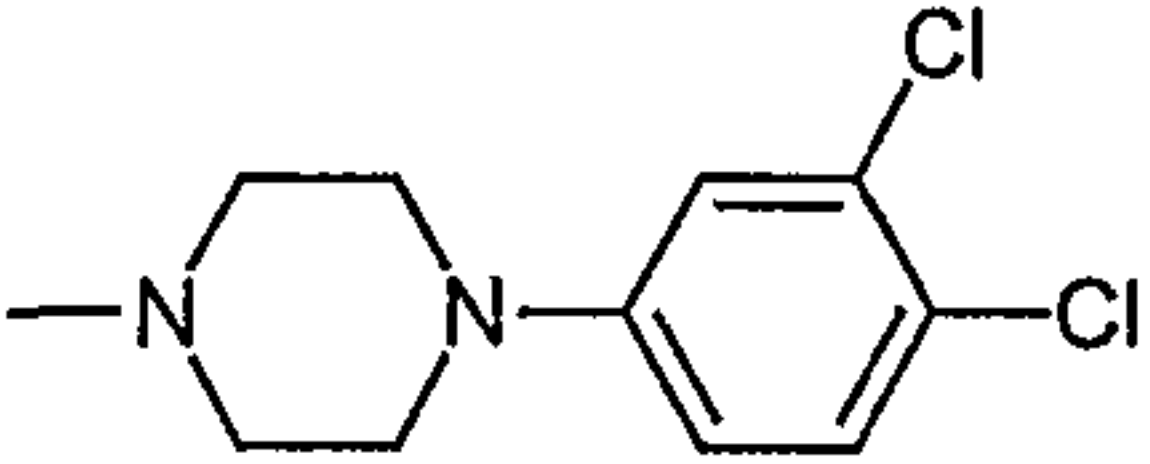
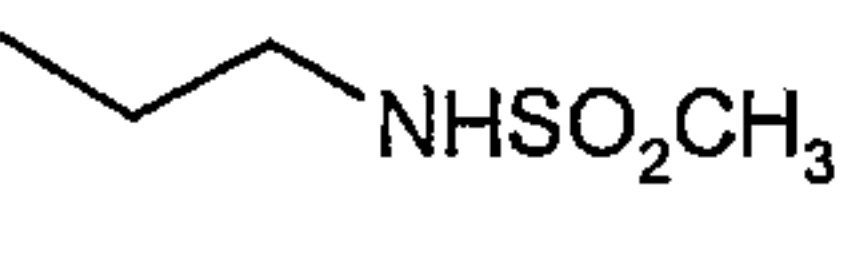
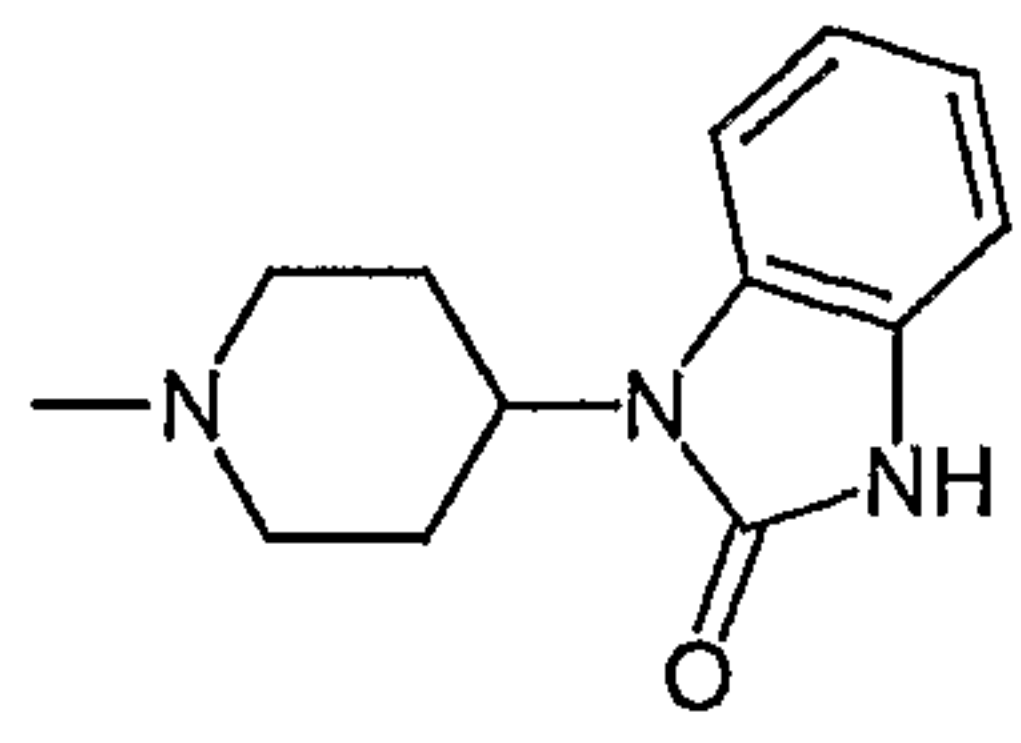
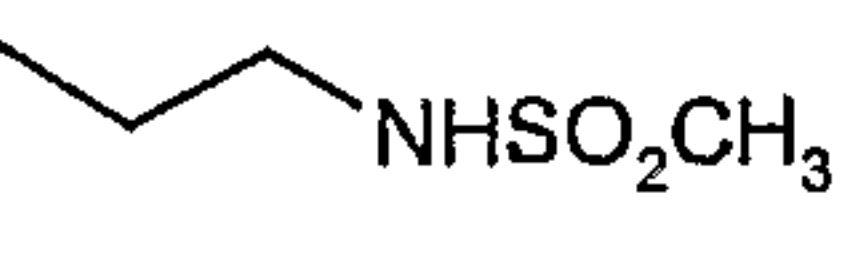
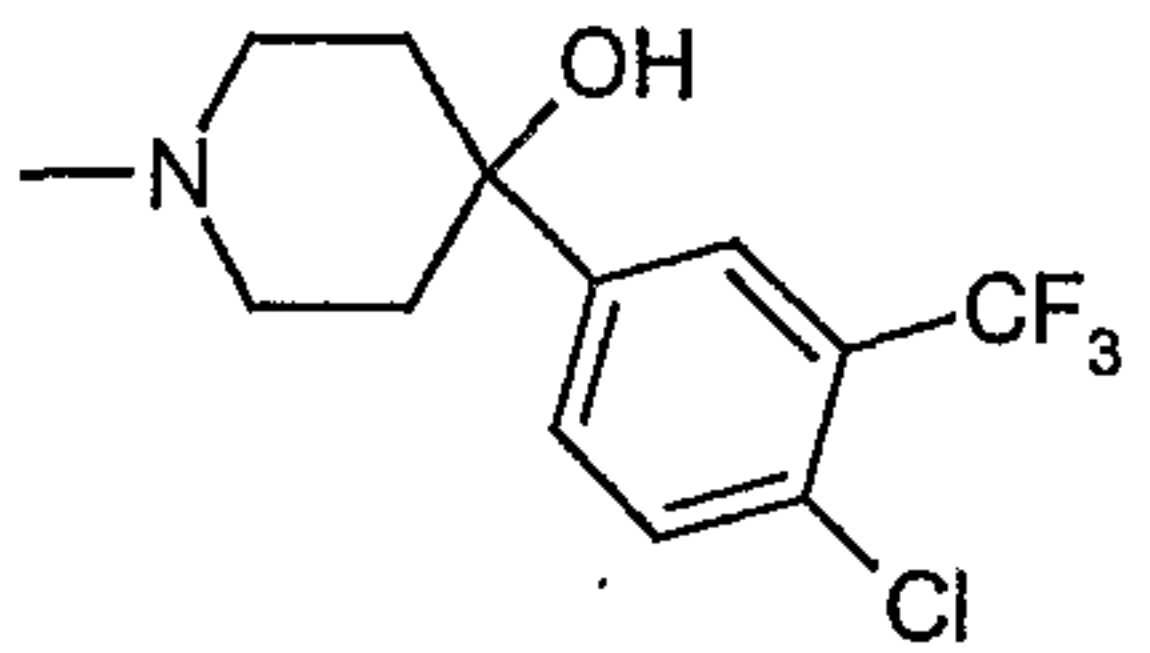
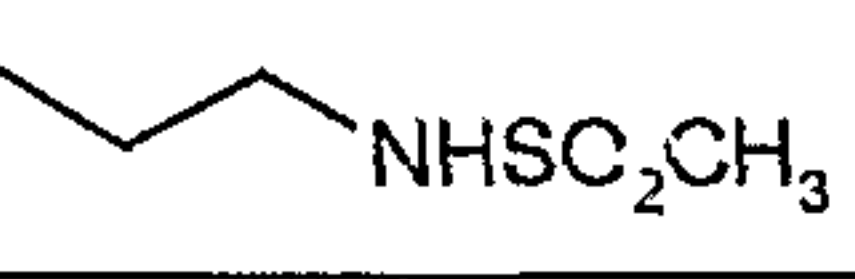
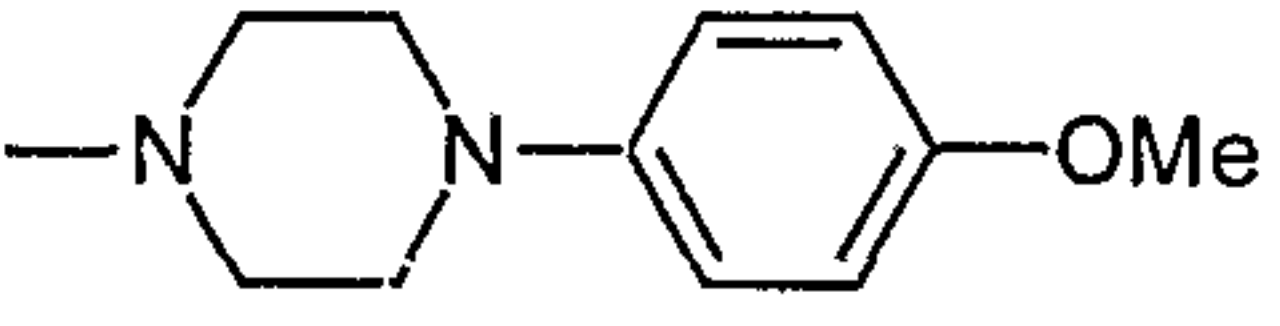
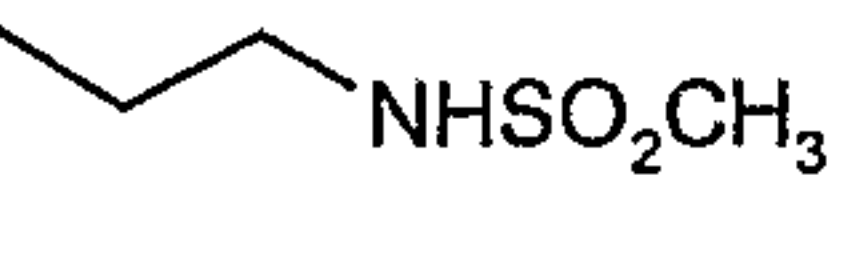
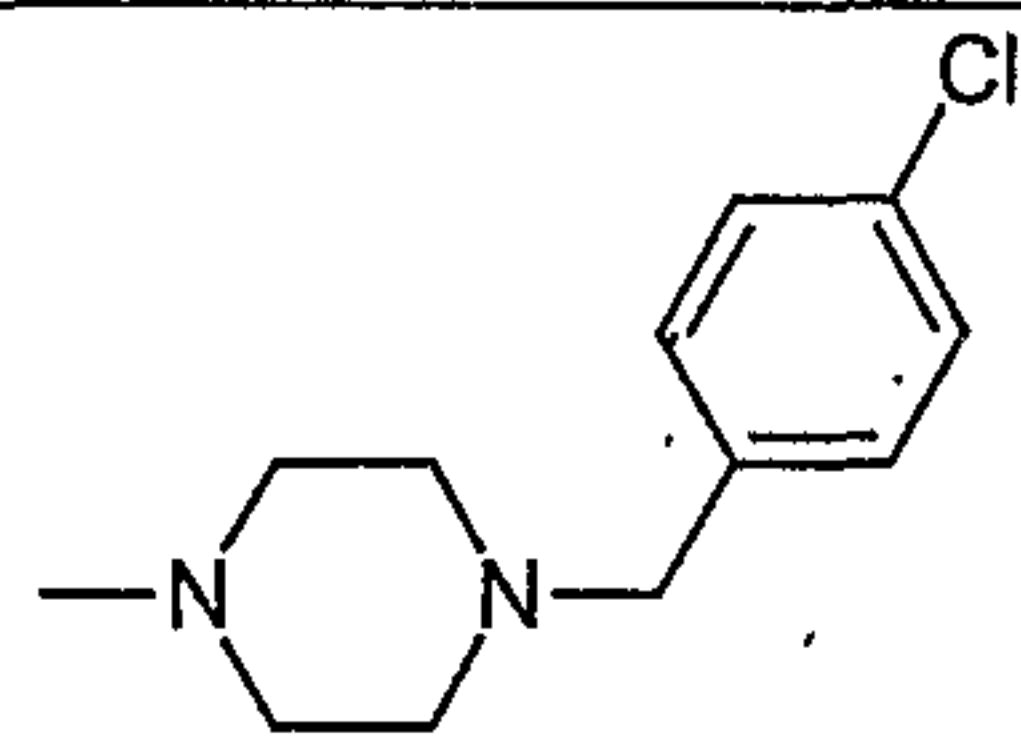
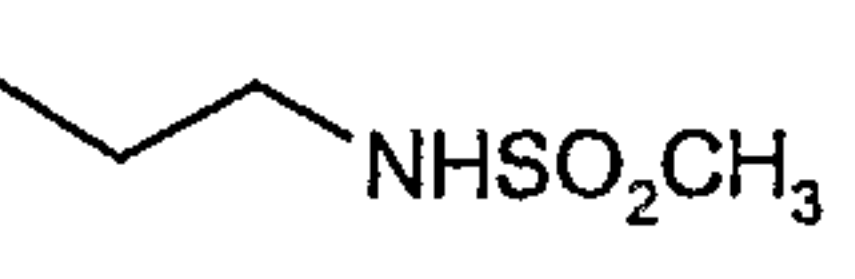
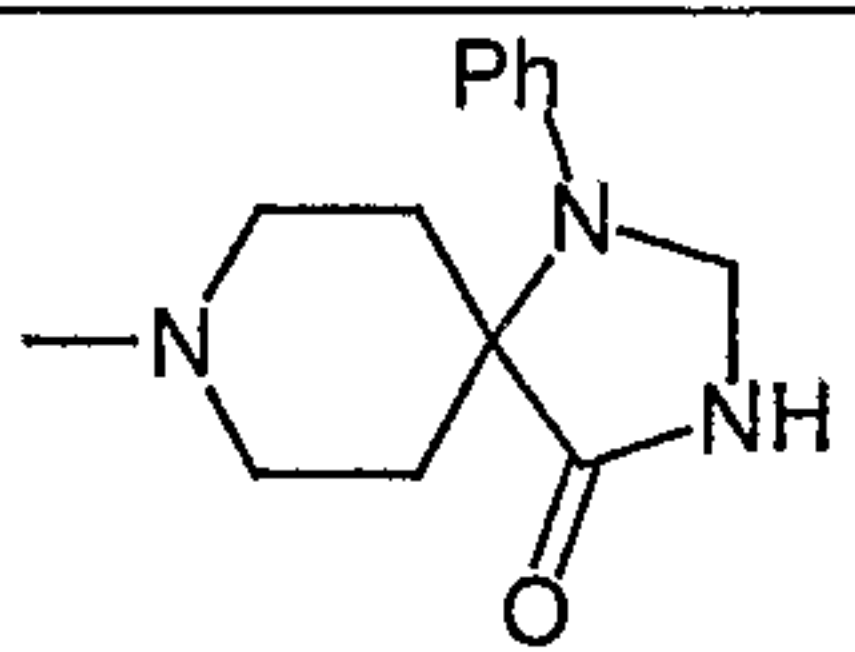
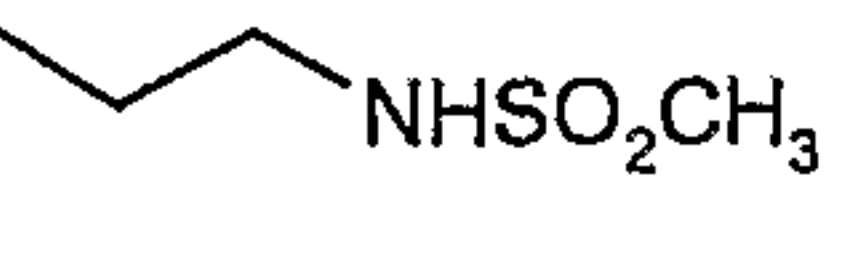
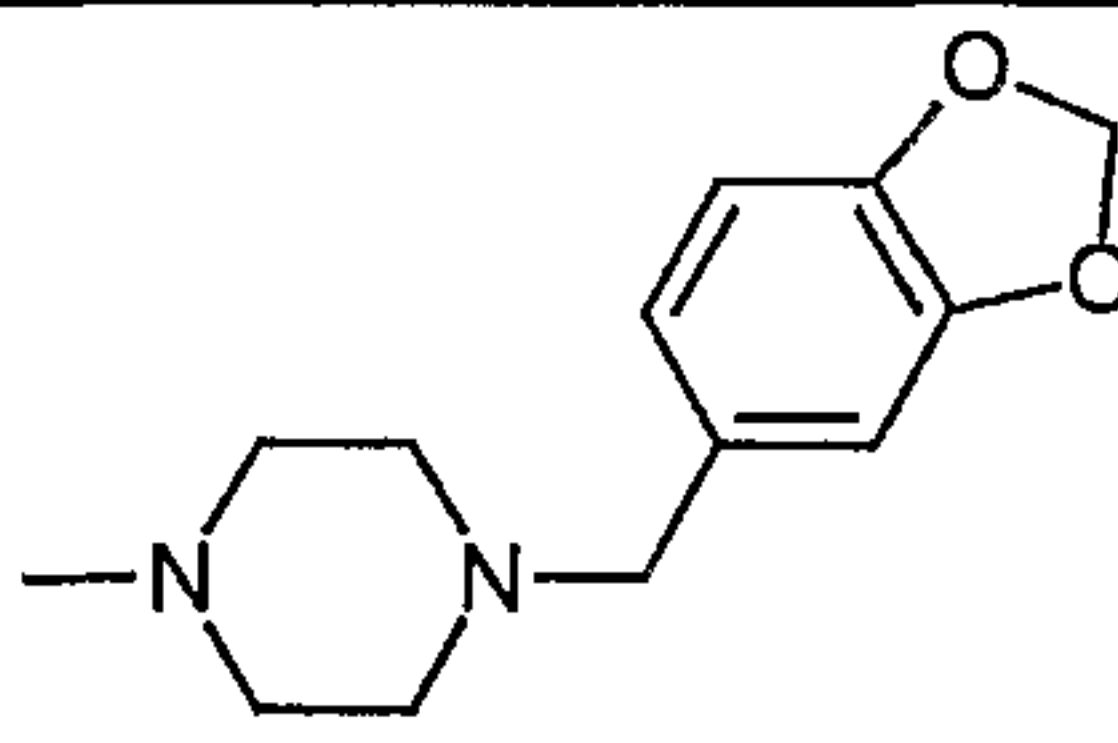
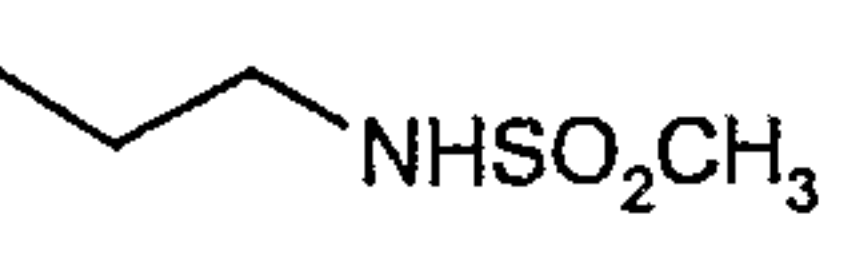
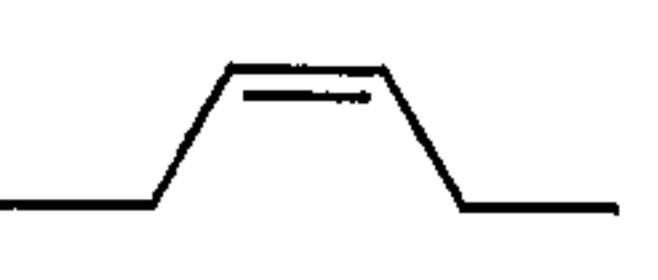
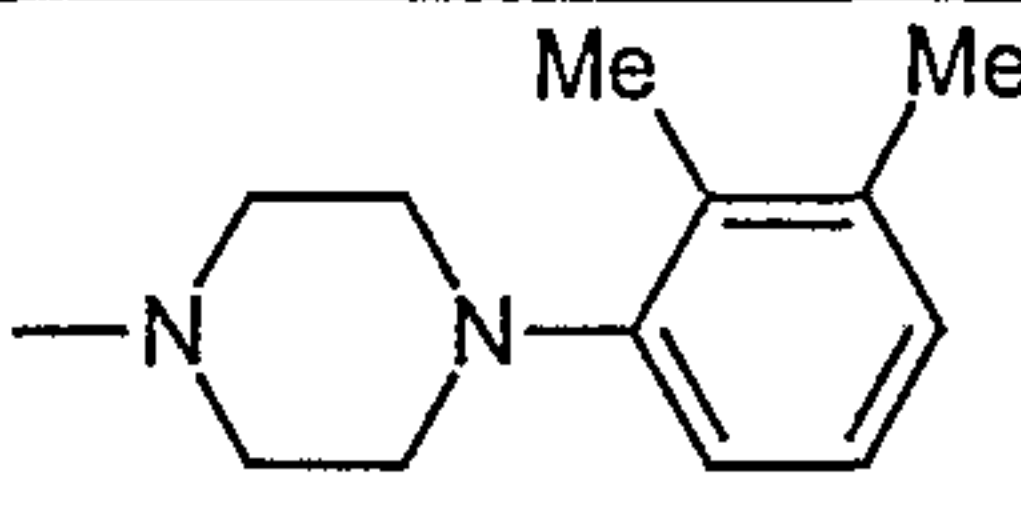
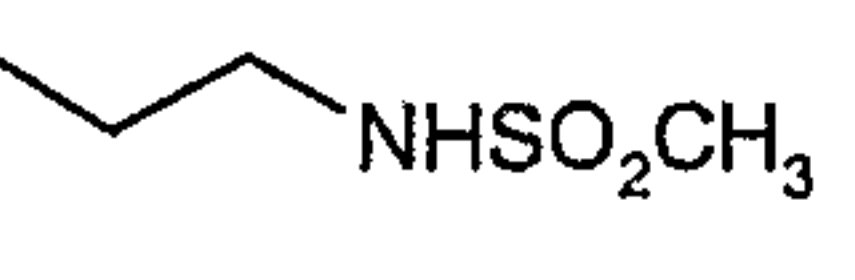
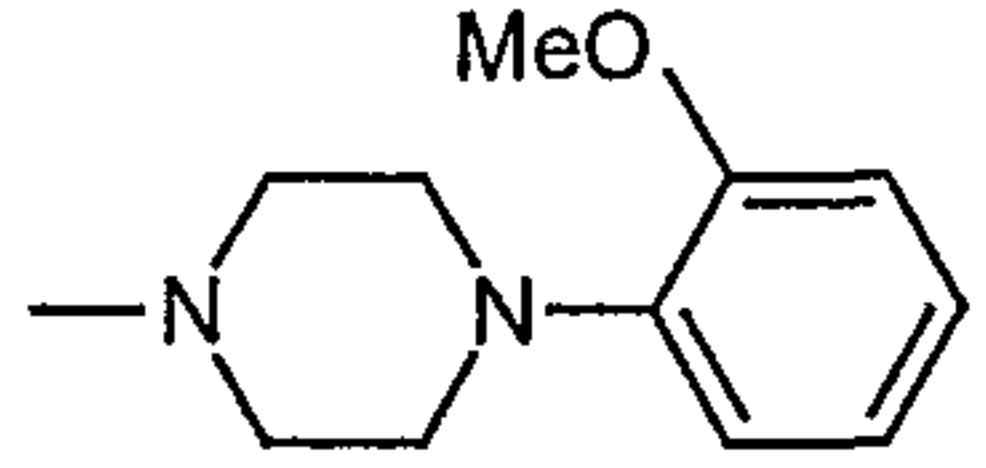
Comp. No	-R ¹	-A-		[M+H] ⁺
504				467
505				538
506				525
507				587
508				500
509				518
510				539
511				528
512				498
513				500

Table 3 (continued):

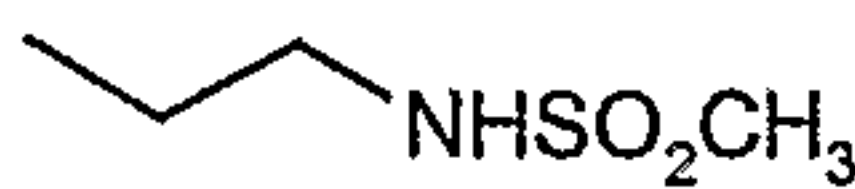
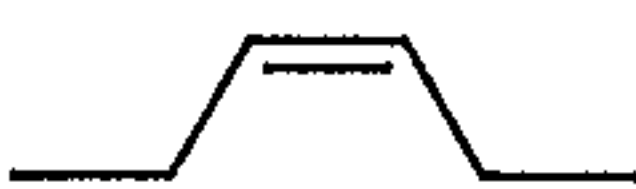
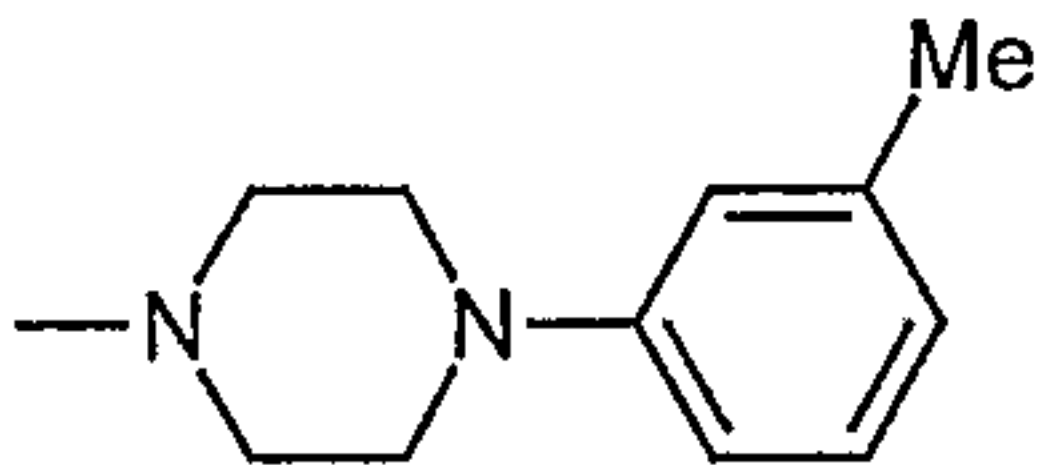
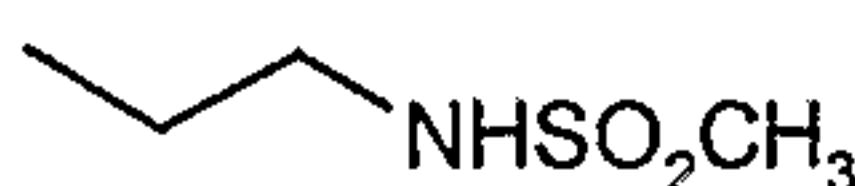
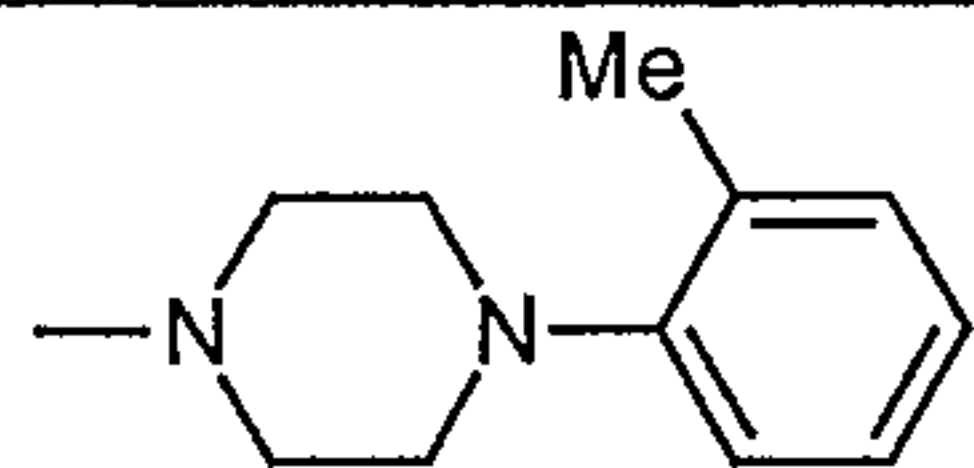
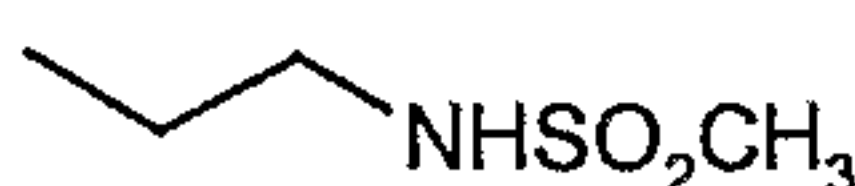
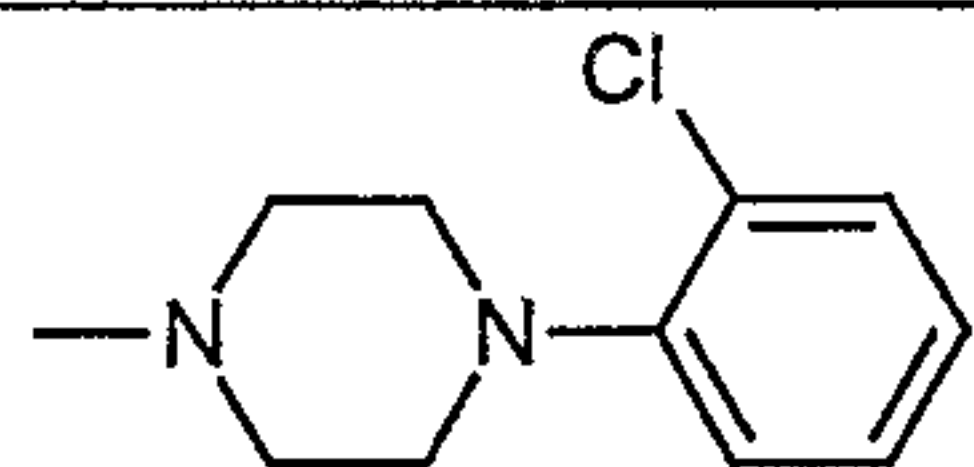
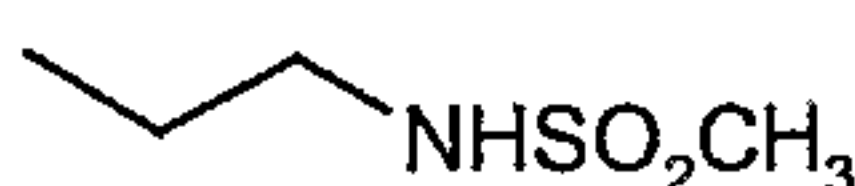
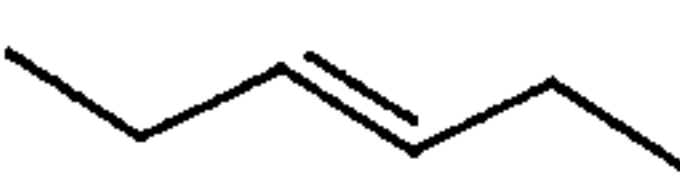
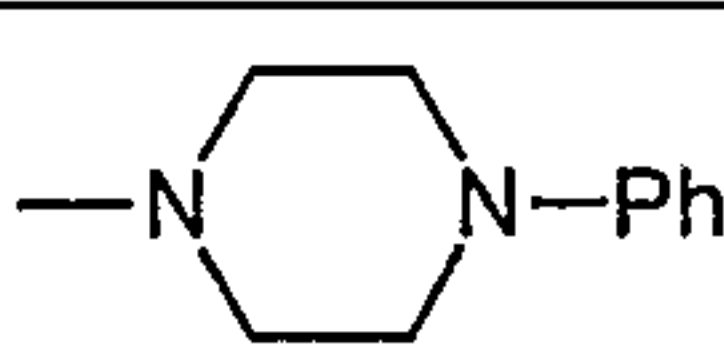
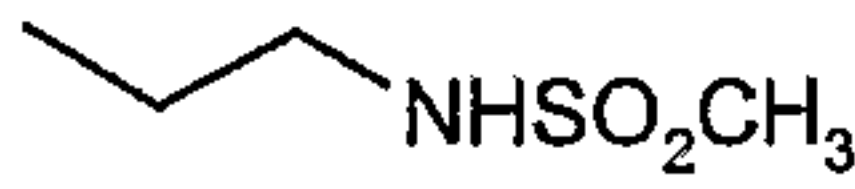
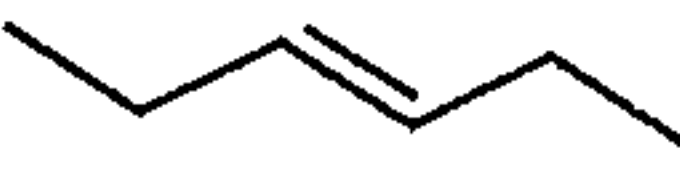
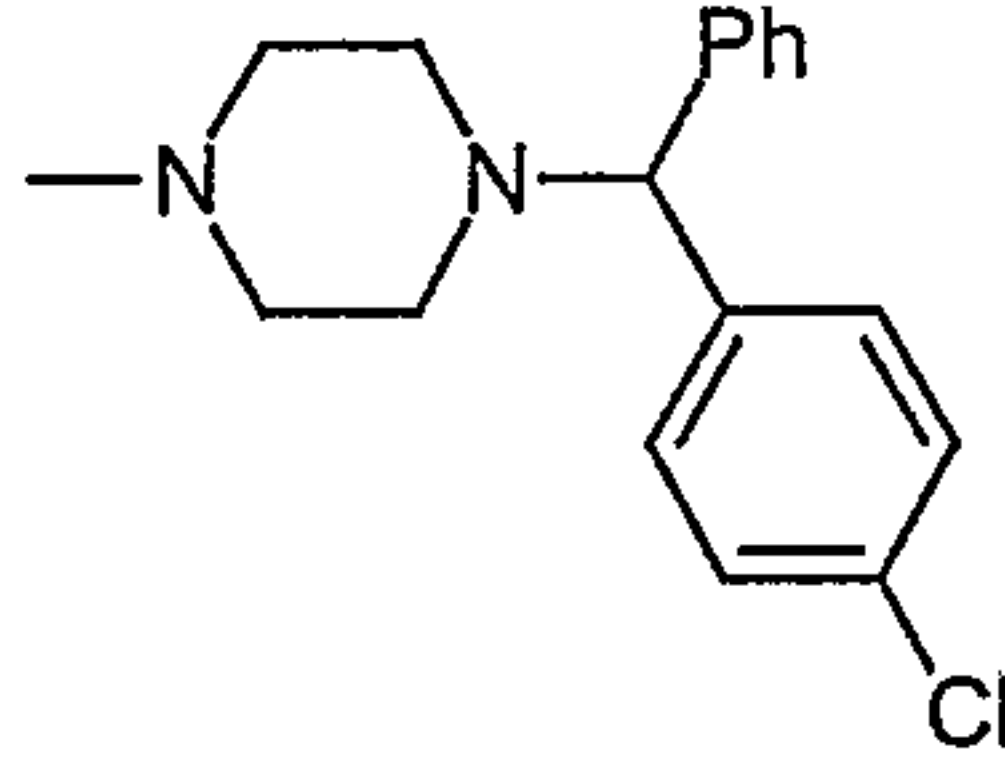
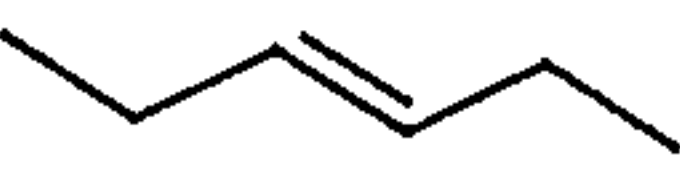
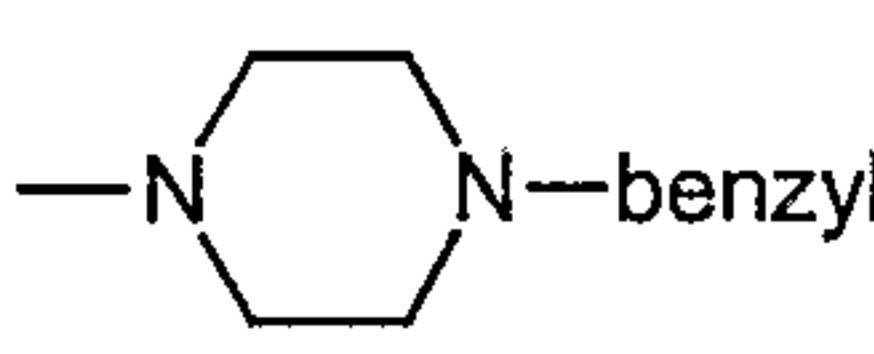
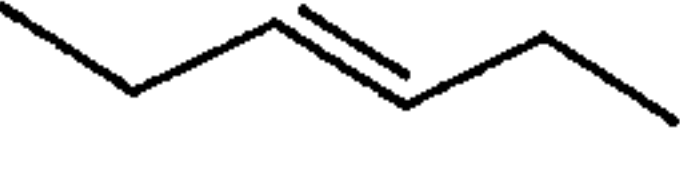
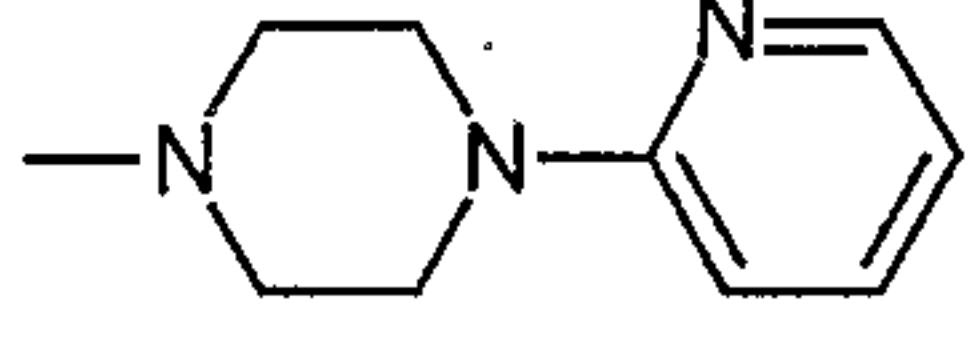
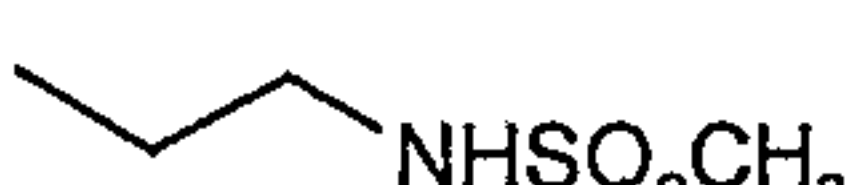
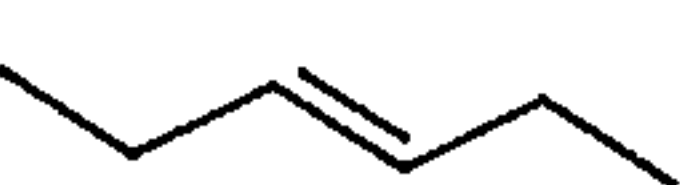
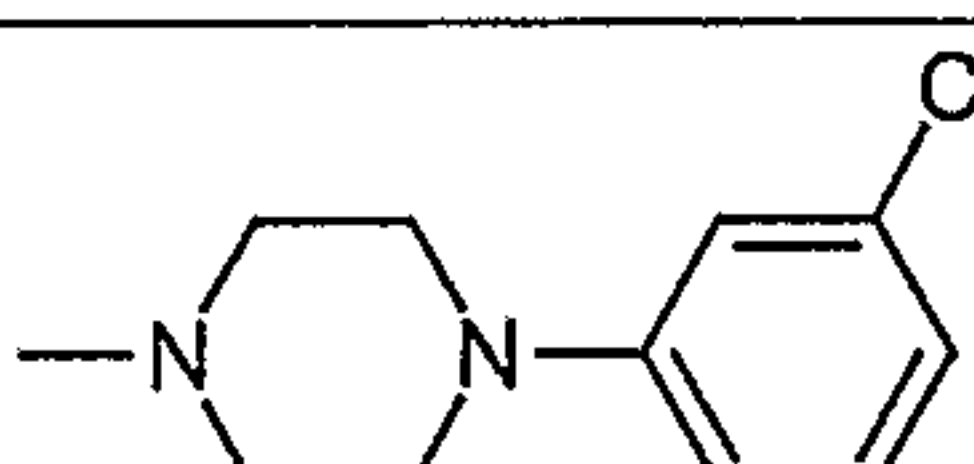
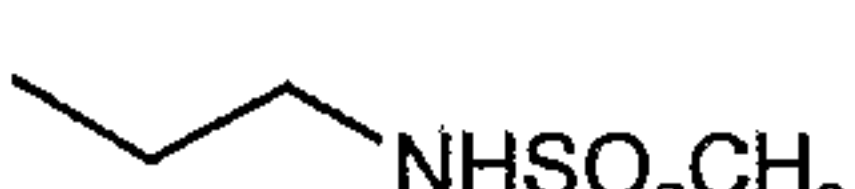
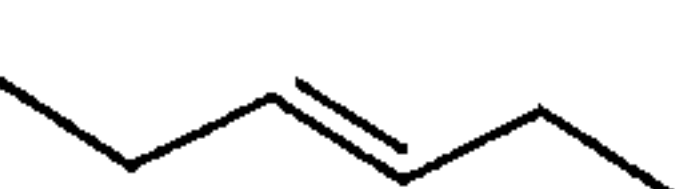
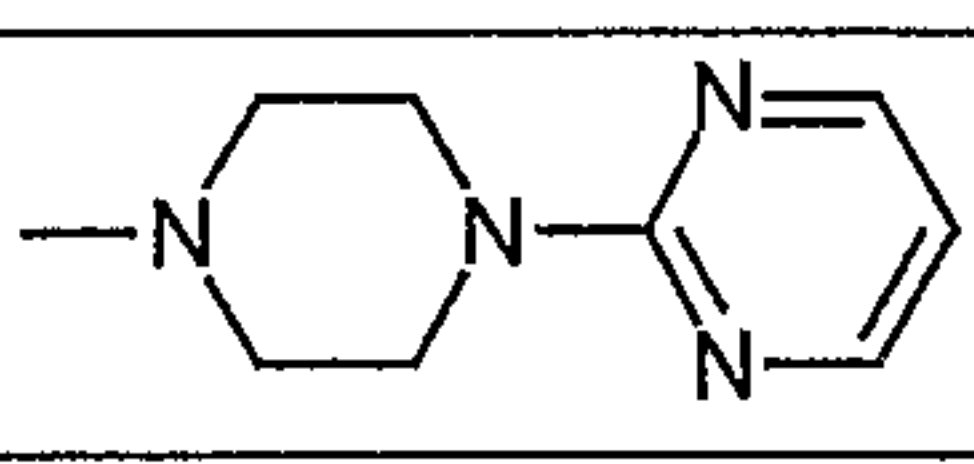
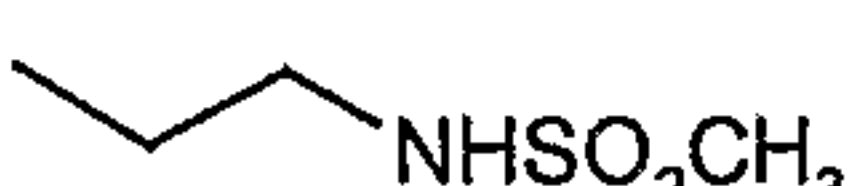
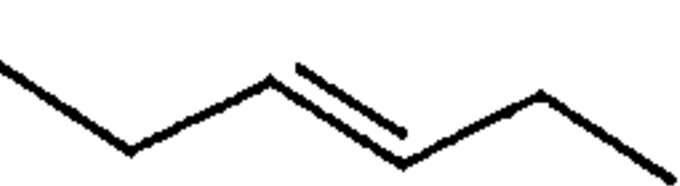
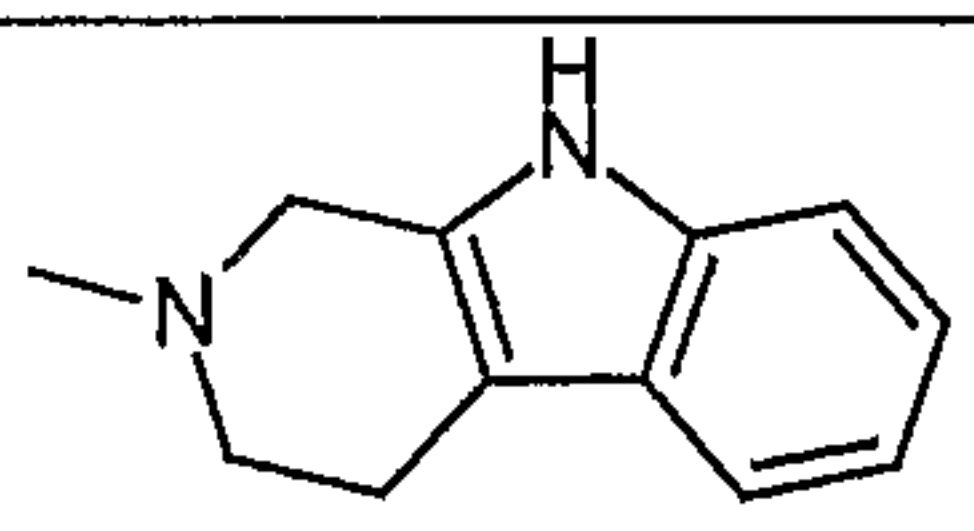
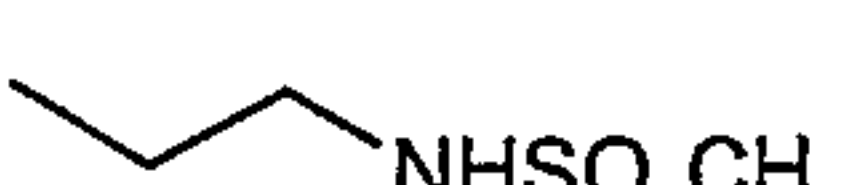
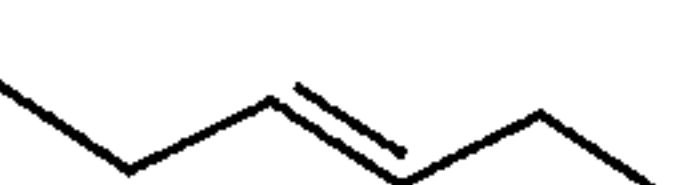
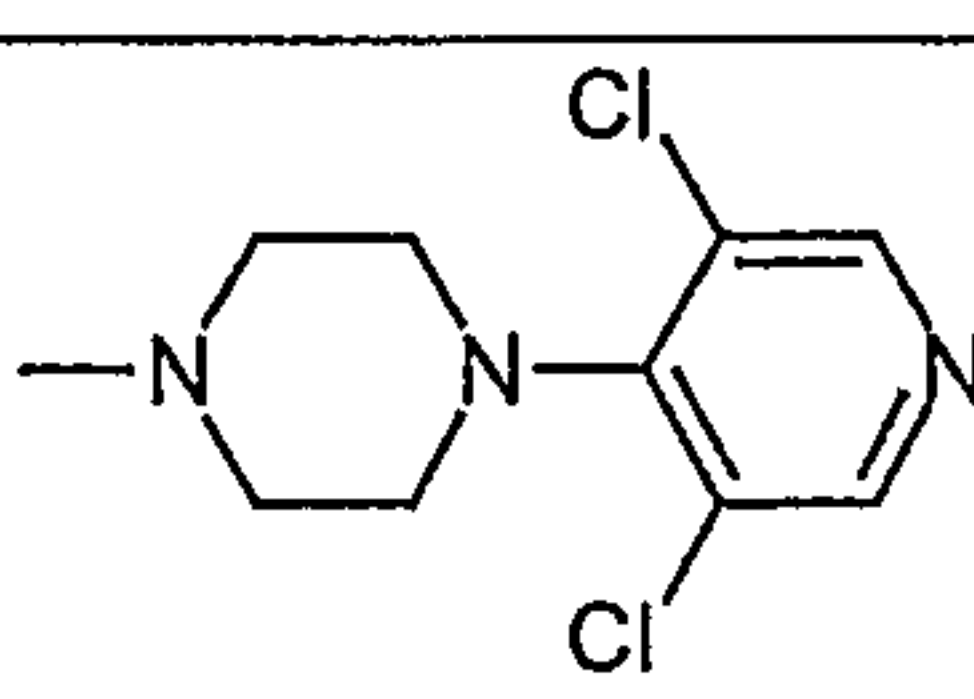
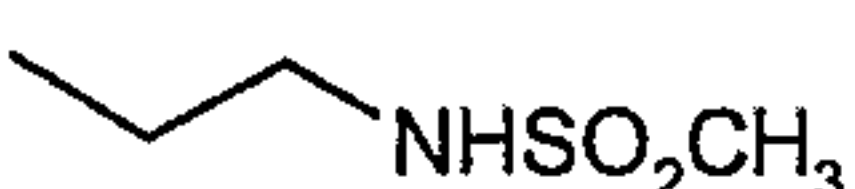
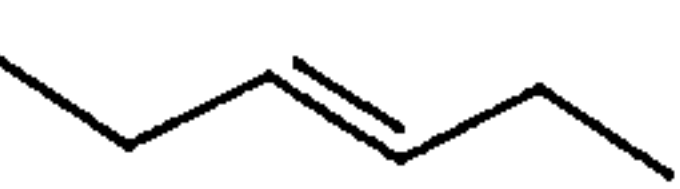
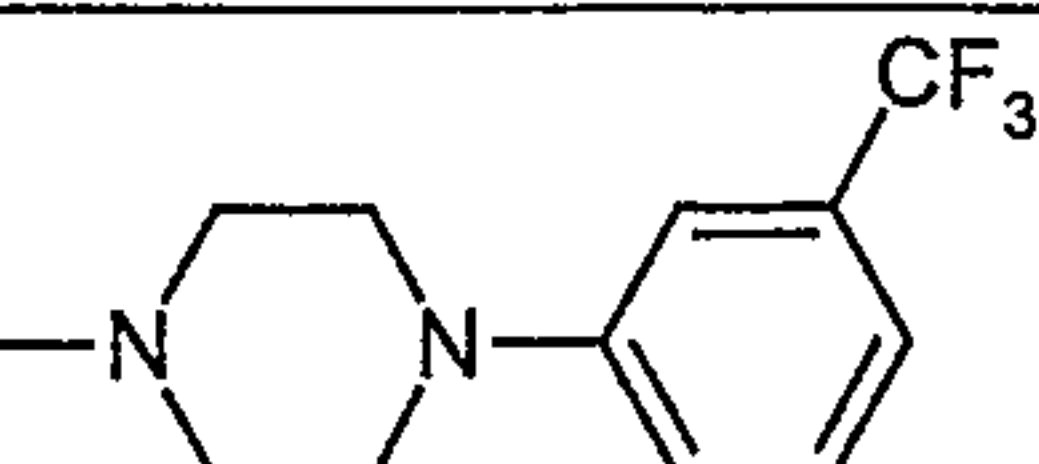
Comp. No	-R ¹	-A-	$\begin{array}{c} \text{R}^2 \\ \\ \text{---N---} \\ \\ \text{R}^3 \end{array}$	[M+H] ⁺
514				484
515				484
516				504
517				470
518				594
519				484
520				471
521				504
522				472
523				480
524				539
525				538

Table 3 (continued):

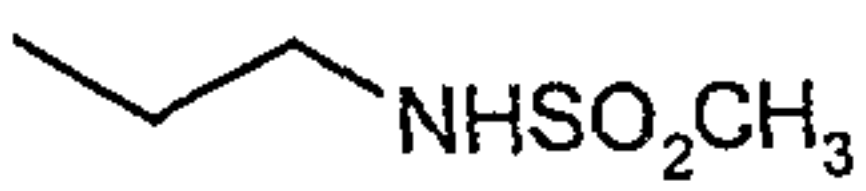
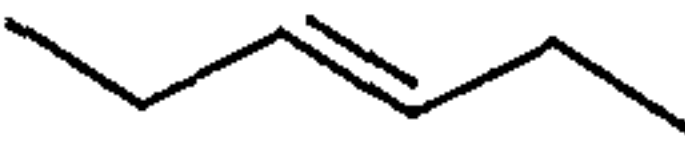
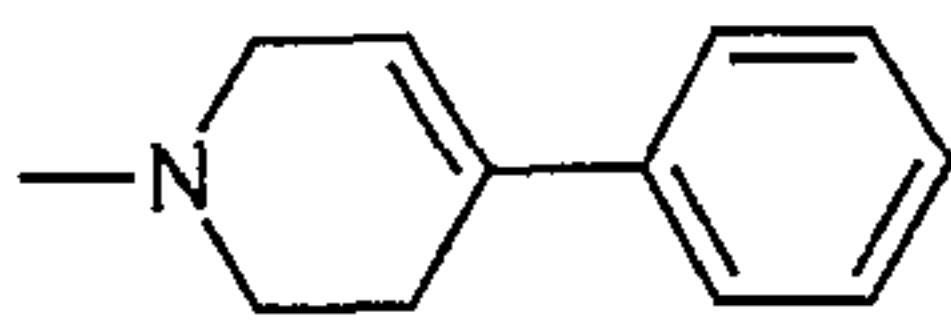
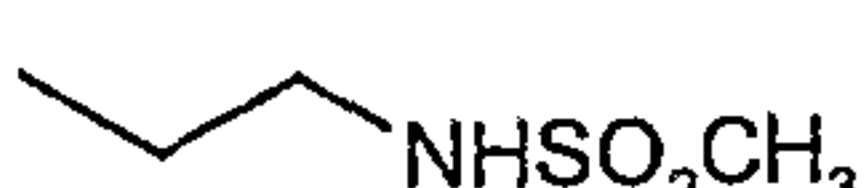
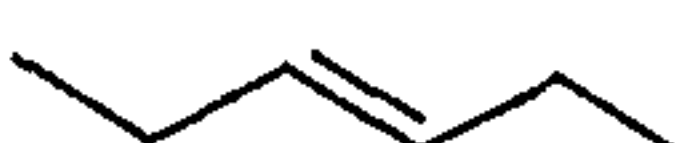
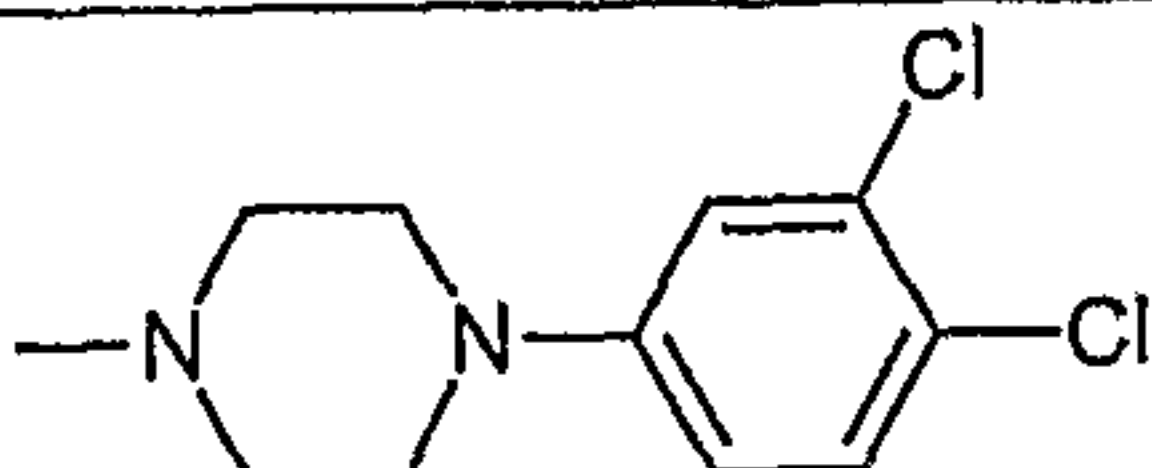
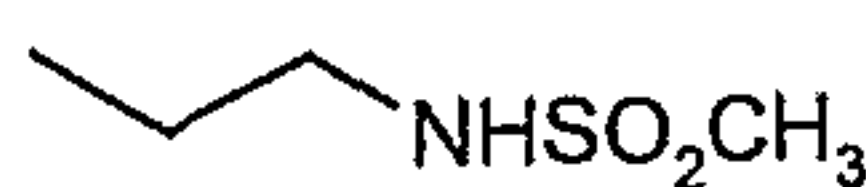
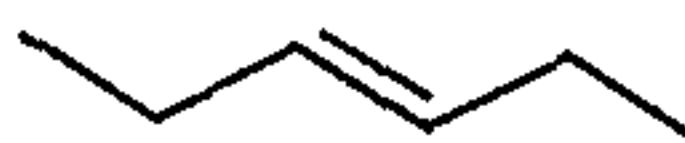
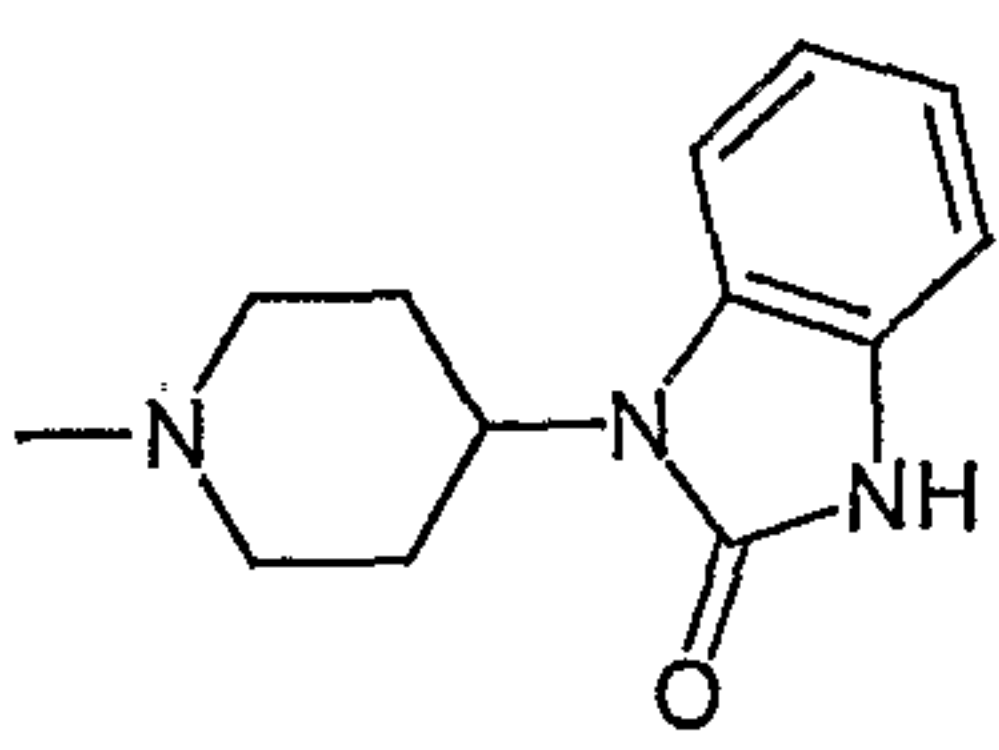
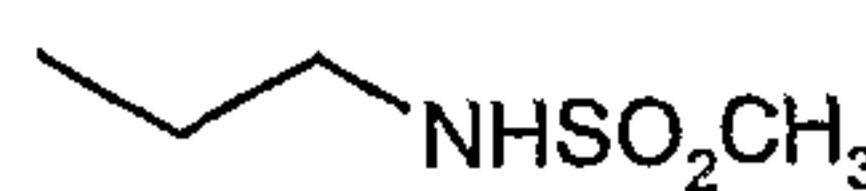
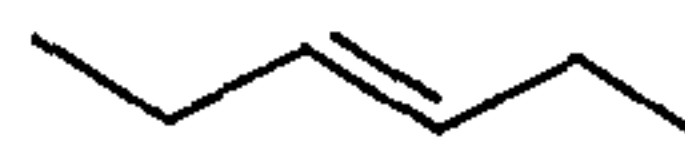
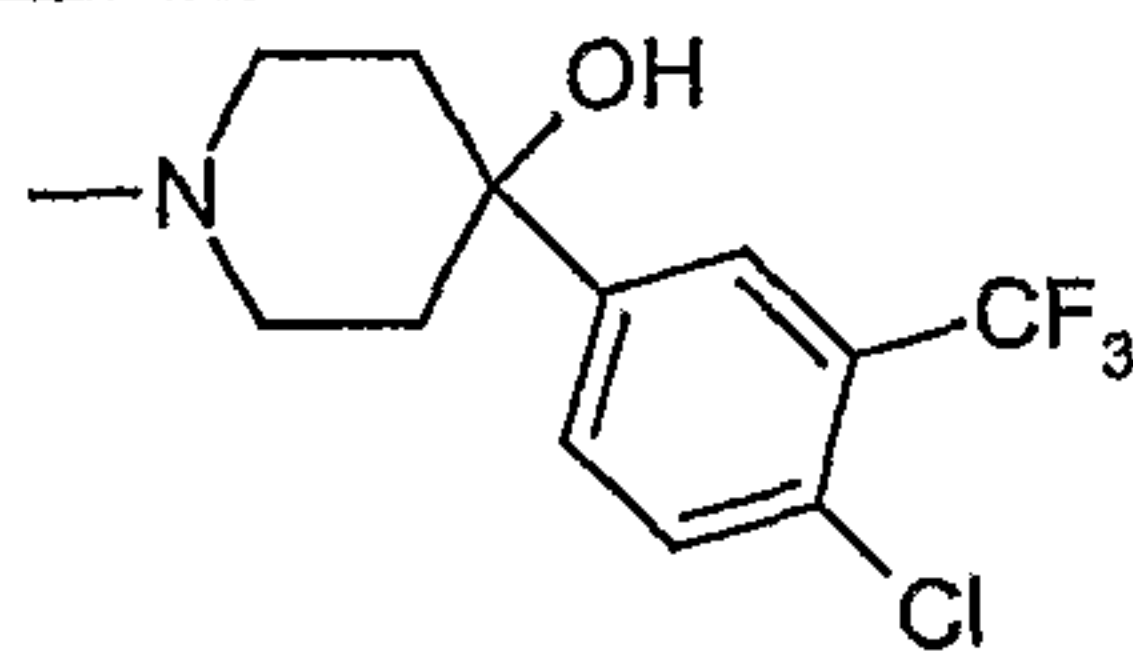
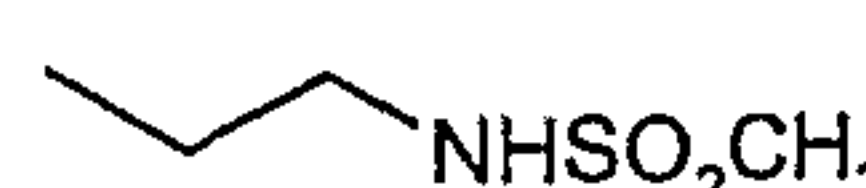
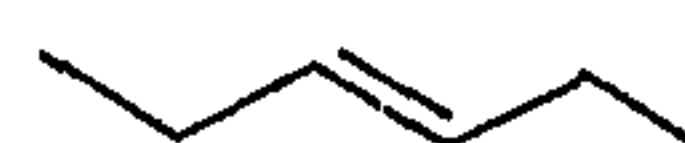
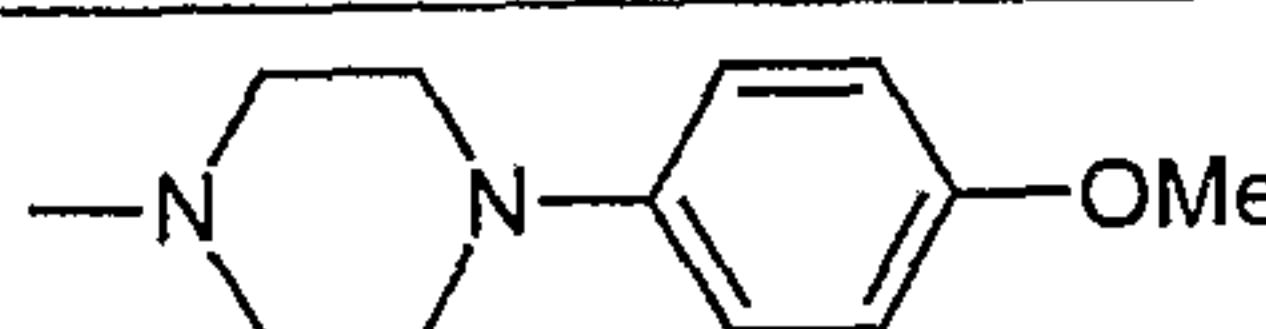
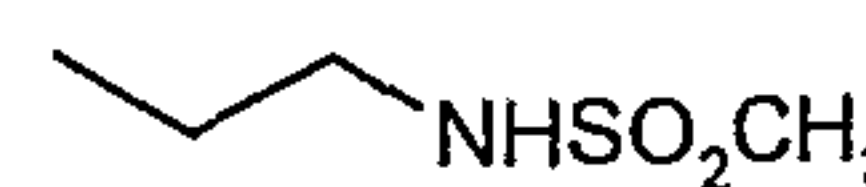
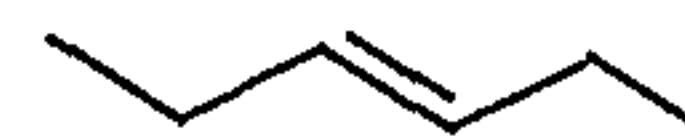
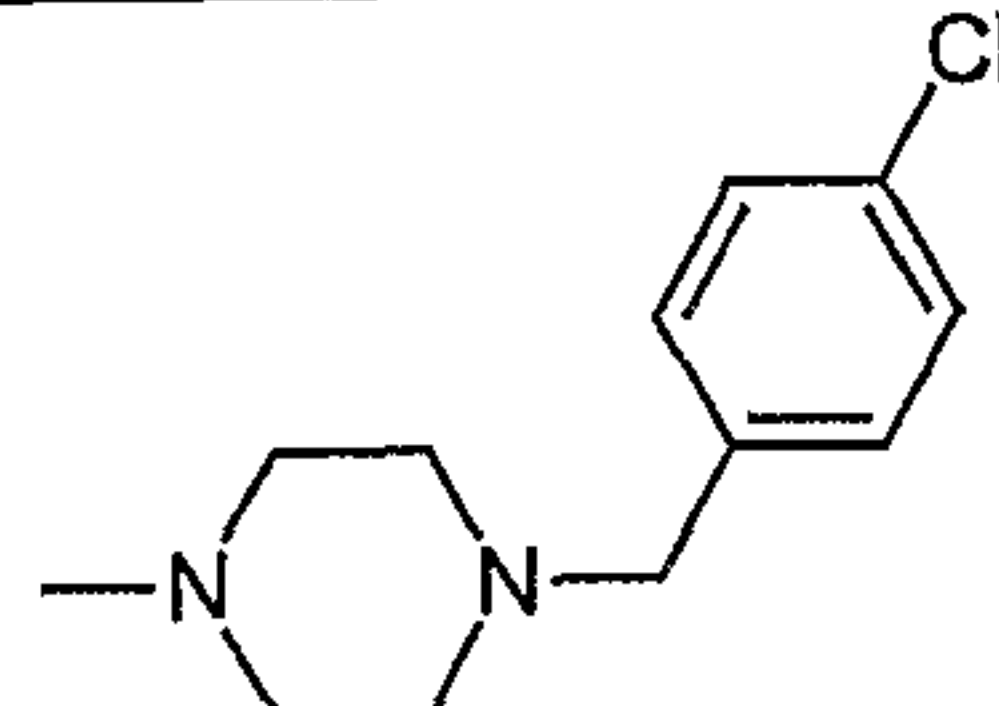
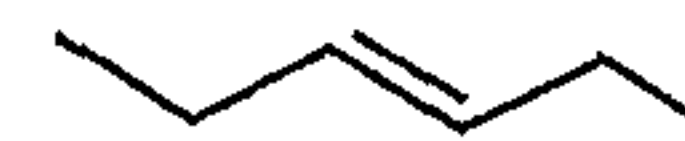
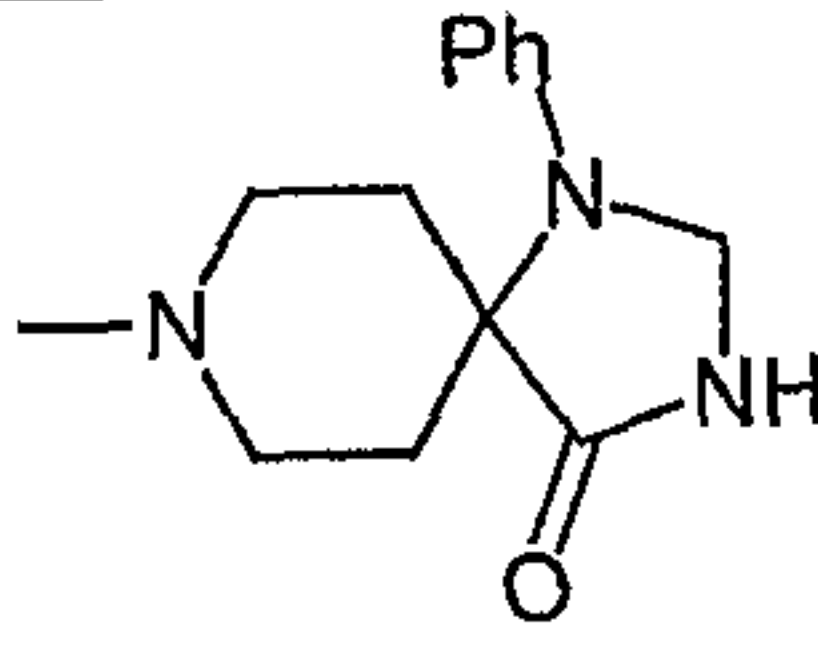
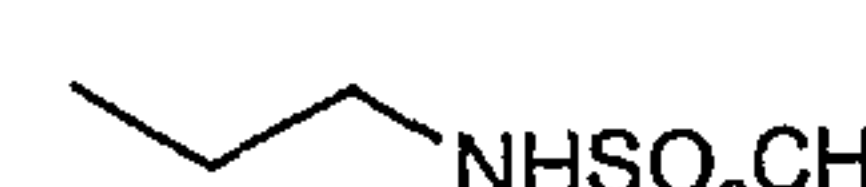
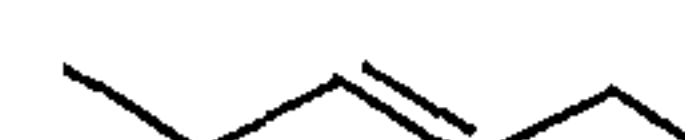
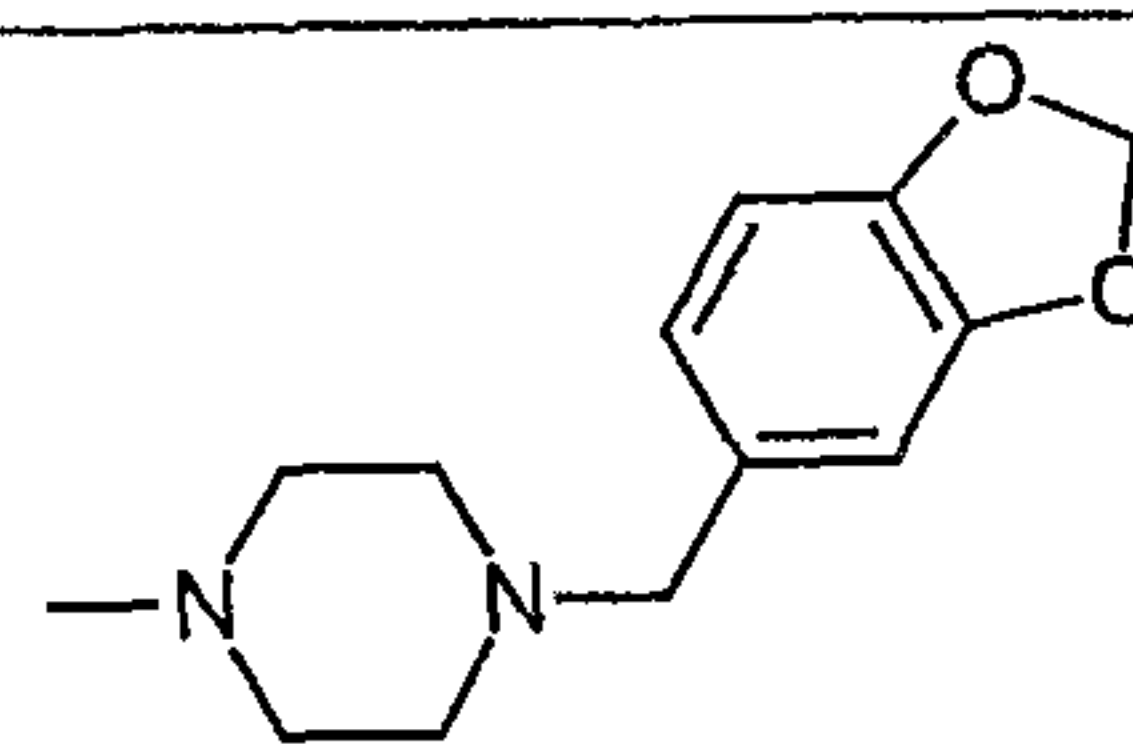
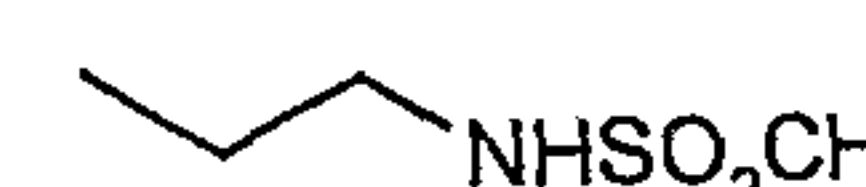
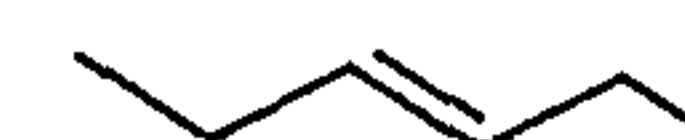
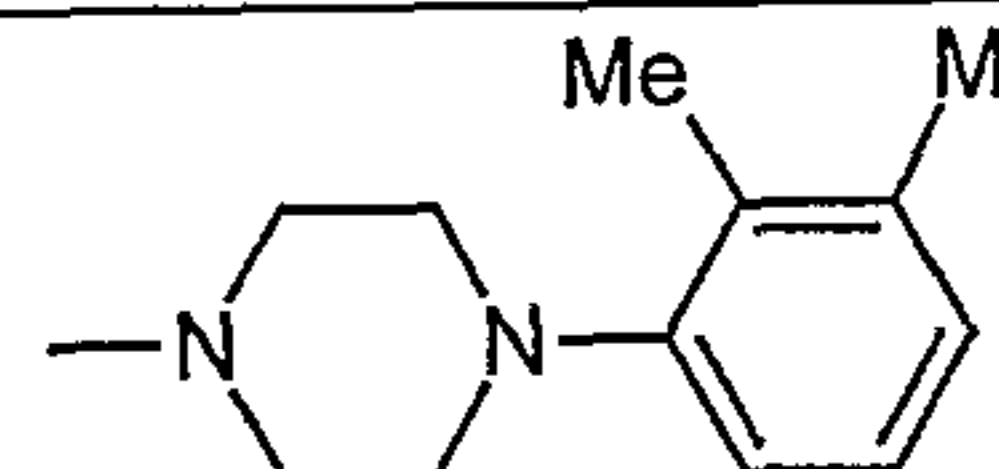
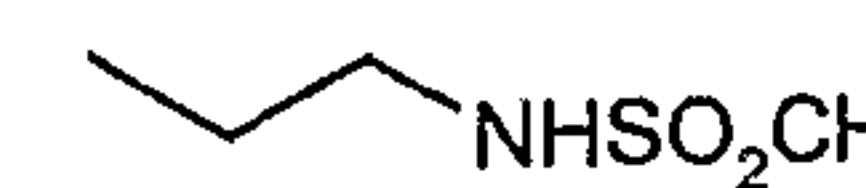
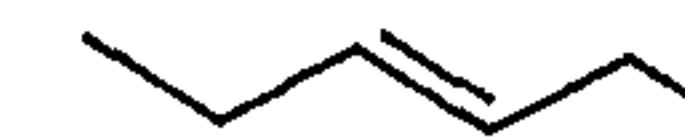
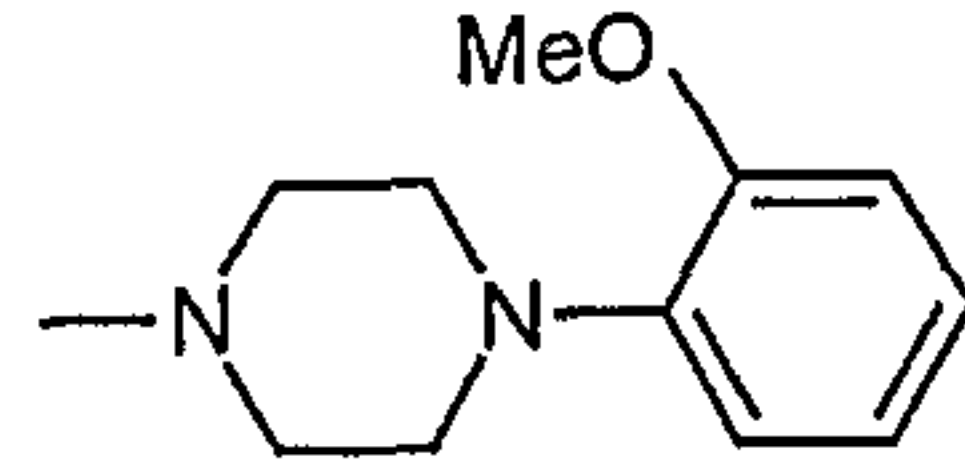
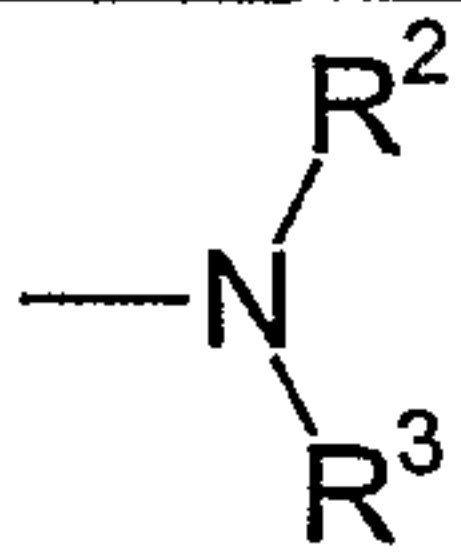
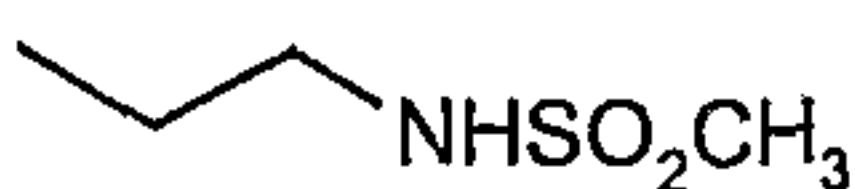
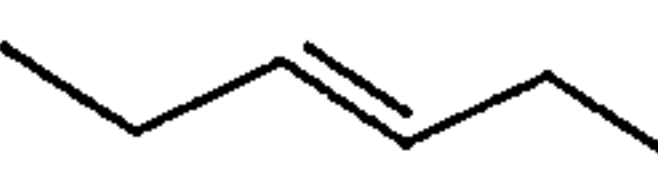
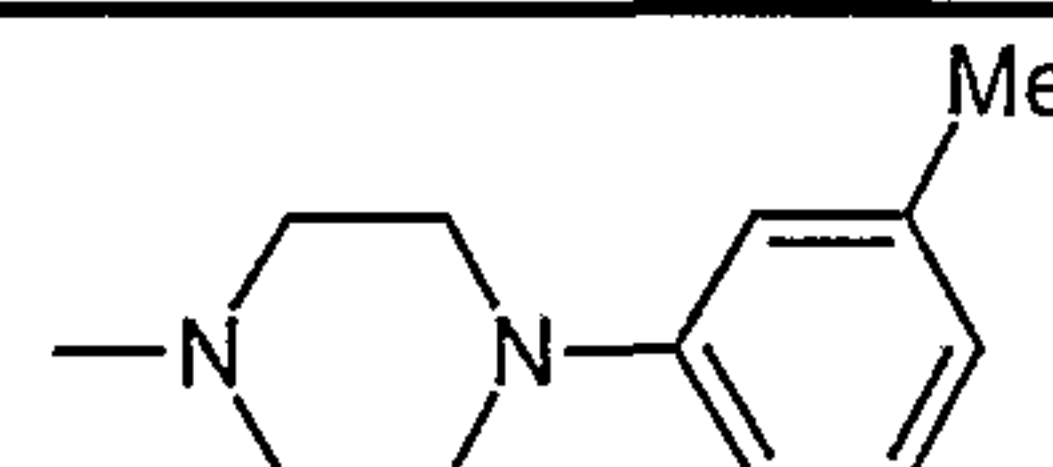
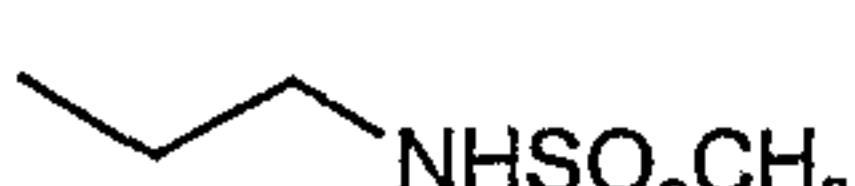
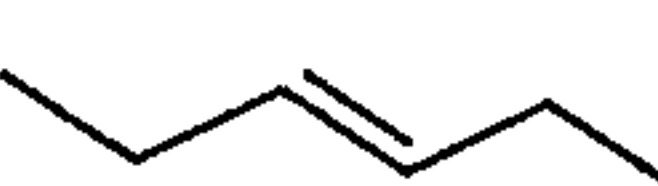
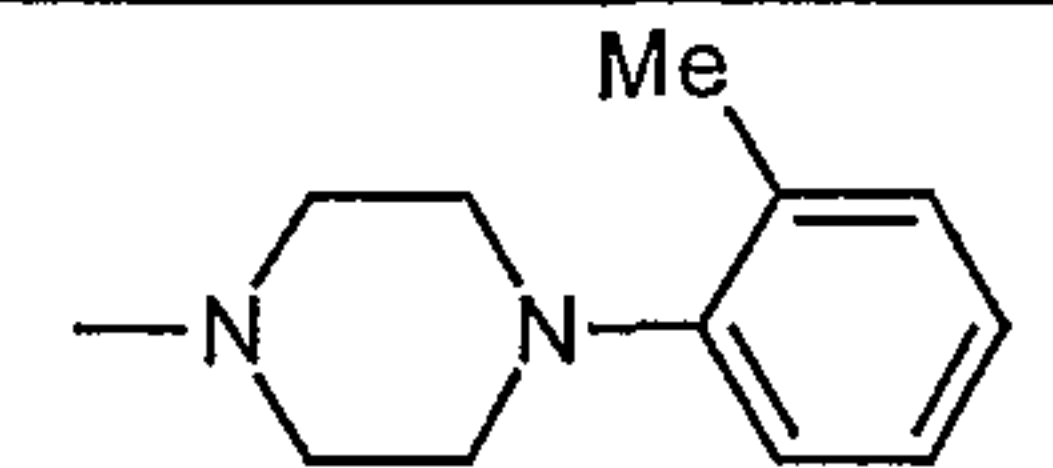
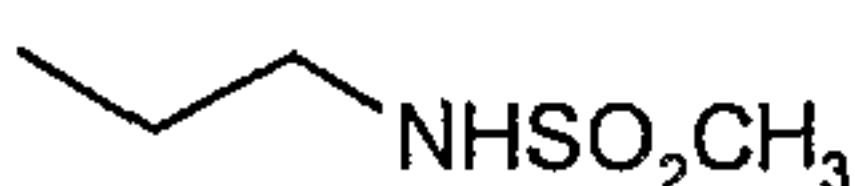
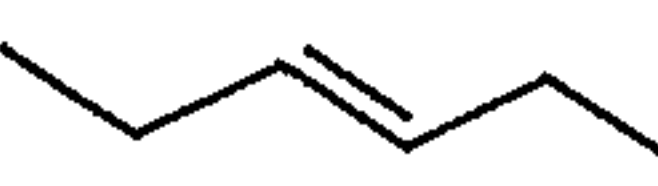
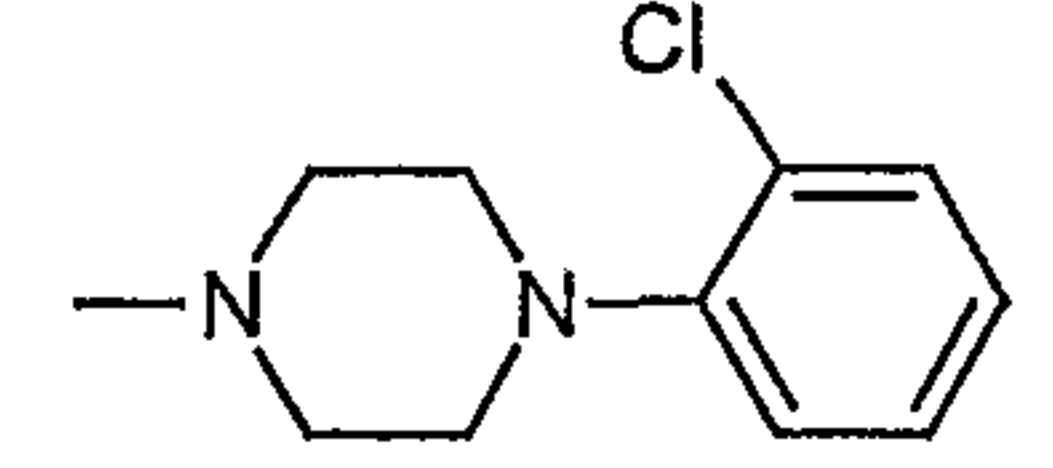
Comp. No	-R ¹	-A-	$\text{—N} \begin{matrix} \text{R}^2 \\ \text{R}^3 \end{matrix}$	[M+H] ⁺
526				467
527				538
528				525
529				587
530				500
531				518
532				539
533				528
534				498
535				500

Table 3 (continued):

Comp. No	-R ¹	-A-		[M+H] ⁺
536	 <chem>CCCN(S(=O)(=O)C)C</chem>	 <chem>CCC=CCC</chem>	 <chem>CC1=CC=C(N2CCN(CC2)C1)C</chem>	484
537	 <chem>CCCN(S(=O)(=O)C)C</chem>	 <chem>CCC=CCC</chem>	 <chem>CC1=CC=C(N2CCN(CC2)C1)C</chem>	484
538	 <chem>CCCN(S(=O)(=O)C)C</chem>	 <chem>CCC=CCC</chem>	 <chem>ClC1=CC=C(N2CCN(CC2)C1)C</chem>	504

The biological profile of the compounds object of this invention, was assessed by evaluating their activity at the 5-HT_{1A}, 5-HT_{2A} and D₄ receptors, according to the methods below described.

5 Receptor Binding studies

Receptor binding studies were carried out to determine the affinity of the compounds for 5-HT_{1A}, 5-HT_{2A} and D₄ receptors

5-HT_{1A} Radioligand Receptor Binding Assay

10 Membranes from CHO cells, expressing 5-HT_{1A} human receptors were suspended in incubation buffer.

Binding assay:

Binding assays were performed in MultiProbe 204 pipetting system (Packard),
15 according to a predetermined mapping, consistent with the software Screen. The compounds were tested in singlicate at one concentration (10^{-7} M) in a total volume of 1000 μ l. 980 μ l of diluted membranes, 10 μ l DMSO or unlabelled ligand and 10 μ l of [³H]-8-OH-DPAT (0.6-0.7 nM) were incubated for 60 min at 27 °C. The reaction was stopped by rapid filtration through Tomtec cell Harvester (48 wells) using
20 Filtermat B (presoaked in 0.1% PEI) filters. Filters were washed with ice-cold 50 mM Tris-HCl (pH 7.4) buffer (9 x 700 μ l), dried, covered with MeltiLex B/HS scintillator sheets (Wallac) and heated at 80-90 °C for about 10 min, transferred into plastic sample bags (Wallac), sealed and put into 1024 Beta Plate scintillation counter (Wallac). Non specific binding was determined in the presence of 5-HT (10^{-5} M).

25

Data analysis:

The specific radioligand binding to the receptor was defined by the difference between total binding and non specific binding, determined in the presence of an excess of unlabelled ligand. Results were expressed as percentage of control
30 specific binding obtained in the presence of the compounds.

The affinity values (IC₅₀) for the compounds were obtained by a non linear least squares regression analysis on the basis of a one binding site model.

5-HT_{1A} Functional assay (cAMP)

35 CHO/5-HT_{1A} cells were random seeded at a density of about 200,000/well in 24 well plates the day prior to the experiment. On the day of the experiment, cells were pretreated for 15 min at 37 °C with 500 μ M isobuthylmethylxantine (IBMX) dissolved in culture medium without serum. Wells were then divided in different groups in duplicate as follows: control, 10 μ M FSK, 10 μ M FSK + 1 μ M 5-HT as positive

standard and 10 μ M FSK + 10 μ M of the different compound under evaluation. Sample solutions were added and incubated for additional 15 min at 37 °C. After incubation, medium was aspirated and the reaction stopped by adding 200 μ l of lysis buffer. Plates were shaken for 5 min, then the lysate was removed and samples were
5 stored at 4 °C until the day of the assay. For the cAMP evaluation, samples were properly diluted and the cAMP content was measured by an enzymeimmunoassay system.

Data analysis:

10 Results are expressed as % inhibition of the cAMP accumulation induced by 10 μ M FSK.

D₄ Radioligand Receptor Binding Assay

15 Membranes from CHO cells, expressing D₄ human receptors were suspended in incubation buffer.

Binding assay:

Binding assays were performed in MultiProbe 204 pipetting system (Packard), according to a predetermined mapping, consistent with the software Screen. The
20 compounds were tested in singlicate at one concentration (10^{-7} M) in a total volume of 1000 μ l (980 μ l of diluted membranes, 10 μ l DMSO or unlabelled ligand and 10 μ l of [³H] YM-09151-2 (0.15-0.25 nM). After incubation for 120 min at 27 °C, the reaction was stopped by rapid filtration through Tomtec cell Harvester (48 wells) using Filtermat B (presoaked in 0.1% PEI) filters. Filters were washed with ice-cold
25 50 mM Tris-HCl (pH 7.4) buffer (9 x 700 μ l), dried, covered with MeltiLex B/HS (Wallac) scintillator sheets and heated in oven at 80-90 °C for about 10 min, transferred into plastic sample bags (Wallac), sealed and put into 1024 Beta Plate scintillation counter (Wallac). Non specific binding was determined in the presence of clozapine dissolved in DMSO to a final concentration of 10^{-5} M.

30

Data analysis:

The specific radioligand binding to the receptor was defined by the difference between total binding and non specific binding, determined in the presence of an excess of unlabelled ligand. Results were expressed as percentage of control
35 specific binding obtained in the presence of the compounds.

5 HT_{2A} Radioligand Receptor Binding Assay

Tissue preparation:

Rats (male Sprague-Dawley, 200-250 g) were used. Cerebral frontal cortex was homogenized in 10 volumes of ice cold 0.32 M sucrose in 5 mM Tris-HCl (pH 7.4) buffer. After centrifugation of the homogenate (1,000 x g for 10 min) the supernatant was then recentrifuged at 48,000x g for 15 min. The resulting pellet was gently homogenized in an equal volume of 50mM Tris-HCl buffer (pH 7.4) and incubated at 37° C for 10 minutes. Membranes were then collected by centrifugation as above described and finally resuspended in 10 volumes of 50mM Tris-HCl buffer (pH 7.4).

Binding assay:

For displacement experiments membranes (980 µl) were diluted in 50 mM Tris-HCl buffer (pH 7.4) to a final concentration of 1:100 (w/v); the tissue suspension was then incubated at 37 °C for 10 min in a final volume of 1 ml in the presence of 0.5 nM [³H]-Ketanserin. Non specific binding was determined by incubating similar samples with unlabelled methysergide (100 µM). After incubation, samples prepared in a 24 wells cell culture cluster (Costar) were rapidly filtered by Inotech cell harvester (IH 201 filters). The filters were washed three times with 2 ml ice-cold Tris-HCl buffer and placed in polyethylene vials, then 4 ml of Filter Count scintillation cocktail (Packard) were added. The radioactivity present was counted by liquid scintillation spectrometry.

Data analysis:

The affinity values (IC₅₀) for the compounds were obtained by a non linear least squares regression analysis on the basis of a one binding site model.

5 HT_{2A} Functional assay (PI turnover)

Tissue preparation:

Cross-chopped miniprisms (350 x 350 µm) were prepared from mouse whole cerebral cortices and incubated for 60 min at 37 °C in Krebs-Henseleit buffer containing 2 g/l glucose.

Functional assay:

Cerebral cortex miniprisms were distributed in vials and incubated for 30 min with approximately 170 nM [³H]-myoinositol (10-20 Ci/mmol) and 10 mM lithium chloride. Samples were divided in different groups in triplicate: control, 100 µM 5-HT, 10 and 30 µM flibanserin + 100 µM 5-HT, as standards, and 10 µM of the different compound under investigation + 100 µM 5-HT. When 5-HT was added the incubation continued for 45 min. Compounds under investigation and flibanserin were added

80

10 min before dispensing 5-HT. Incubation was terminated by the addition of 940 μ l chloroform-methanol (1: 2 v/v). Further aliquots of chloroform (310 μ l) and water (310 μ l) were added and labeled inositol phosphates (I Ps) were extracted from the aqueous phase by ion exchange chromatography using Dowex resin in the formate
5 form. After addition of 10 ml of PicoFluor 40 scintillation cocktail (Packard), the radioactivity present in an aliquot (400 μ l) of the aqueous extract was counted by liquid scintillation spectrometry.

Data analysis:

10 Results are expressed as % inhibition of the PI turnover accumulation induced by 100 μ M 5-HT.

15 The following tables (Tables 4 to 6) collect the biological data at the said receptors of the new compounds.

Table 4: % inhibition at 5-HT_{1A} and D₄ receptors

Comp. No.	5-HT _{1A} receptor binding assay % inhib. (10 ⁻⁷ M)	D ₄ receptor binding assay % inhib. (10 ⁻⁷ M)	Comp. No.	5-HT _{1A} receptor binding assay % inhib. (10 ⁻⁷ M)	D ₄ receptor binding assay % inhib. (10 ⁻⁷ M)
1	56	38	78	69	44
5	92	54	79	86	58
7	77	91	81	55	78
9	93	32	83	89	39
10	60	47	84	52	42
11	48	90	85	77	79
19	69	32	92	94	55
20	50	60	93	94	62
23	73	48	94	88	72
24	90	67	95	85	64
25	48	44	96	92	72
26	70	94	107	55	58
28	89	35	118	80	36
29	57	83	145	85	42
30	44	90	149	88	35
37	90	54	150	57	52
38	92	78	158	95	72
39	36	42	159	85	50
43	104	55	164	96	41
45	100	82	169	85	58
56	63	71	177	98	39
59	75	51	182	62	45
60	93	82	183	96	62
62	73	96	187	94	36
64	92	43	188	78	78
65	52	74	189	54	99
66	65	99	197	77	43
73	91	58	215	98	48
74	92	62	216	92	44
75	67	54	219	89	37

Table 4: % inhibition at 5-HT_{1A} and D₄ receptors (continued)

Comp. No.	5-HT _{1A} receptor binding assay % inhib. (10 ⁻⁷ M)	D ₄ receptor binding assay % inhib. (10 ⁻⁷ M)	Comp. No.	5-HT _{1A} receptor binding assay % inhib. (10 ⁻⁷ M)	D ₄ receptor binding assay % inhib. (10 ⁻⁷ M)
224	98	51	332	78	85
226	71	32	333	99	80
228	95	33	335	95	55
229	67	34	336	90	81
241	69	32	348	99	51
254	85	34	349	73	31
255	58	33	361	86	46
256	59	51	364	77	36
263	92	42	365	89	63
265	55	78	367	61	90
280	93	38	369	96	59
282	53	77	370	93	60
285	96	32	371	59	95
286	65	87	378	77	35
293	89	32	382	88	39
297	96	34	395	86	32
303	71	70	399	82	32
310	85	49	404	95	34
311	59	60	412	93	39
314	93	82	416	96	39
316	72	94	446	92	31
318	92	36	501	70	63
319	94	70	504	93	34
327	78	74	505	78	58
330	97	84	527	73	36
331	100	92	535	97	39

Table 5: 5-HT_{1A} agonist activity

Comp.d No.	5-HT _{1A}	
	receptor binding IC ₅₀ (nM)	cAMP % inhib.
5	13	63
9	9.9	48
37	16	44
60	6.2	65
64	12	52
73	13	45
83	15	64
158	13	48
164	4.2	73
168	5.0	71
177	3.3	76
183	7.2	66
187	8.2	44
202	1.7	72
206	2.1	80
215	0.85	83
217	5.2	68
219	15	61
228	6.0	82
254	7.4	66
263	8.8	63
284	4.9	82
285	5.2	47
296	8.2	82
297	7.9	74
301	2.6	83
310	15	63
314	7.1	44
318	3.1	61
330	7.9	62

Table 5: (continued)

Comp.d No.	5-HT _{1A}	
	receptor binding IC ₅₀ (nM)	cAMP % inhib.
333	16	67
335	3.5	69
347	13	65
348	3.5	57
352	4.1	79
365	15	82
369	3.5	84
370	4.4	52
381	44	79
382	11	64
386	6.7	82
403	5.5	84
404	2.1	60
415	14	82
416	7.9	77
420	1.8	87
421	0.66	56
446	7.3	81
459	8.8	86
468	3.1	66
472	3.1	67
481	11	82
499	5.0	74
503	2.8	87
504	3.6	50
512	0.59	68
514	7.9	67
520	8.1	70
521	0.61	67
525	1.5	87
536	9.5	55

Table 6: 5-HT_{2A} antagonist activity

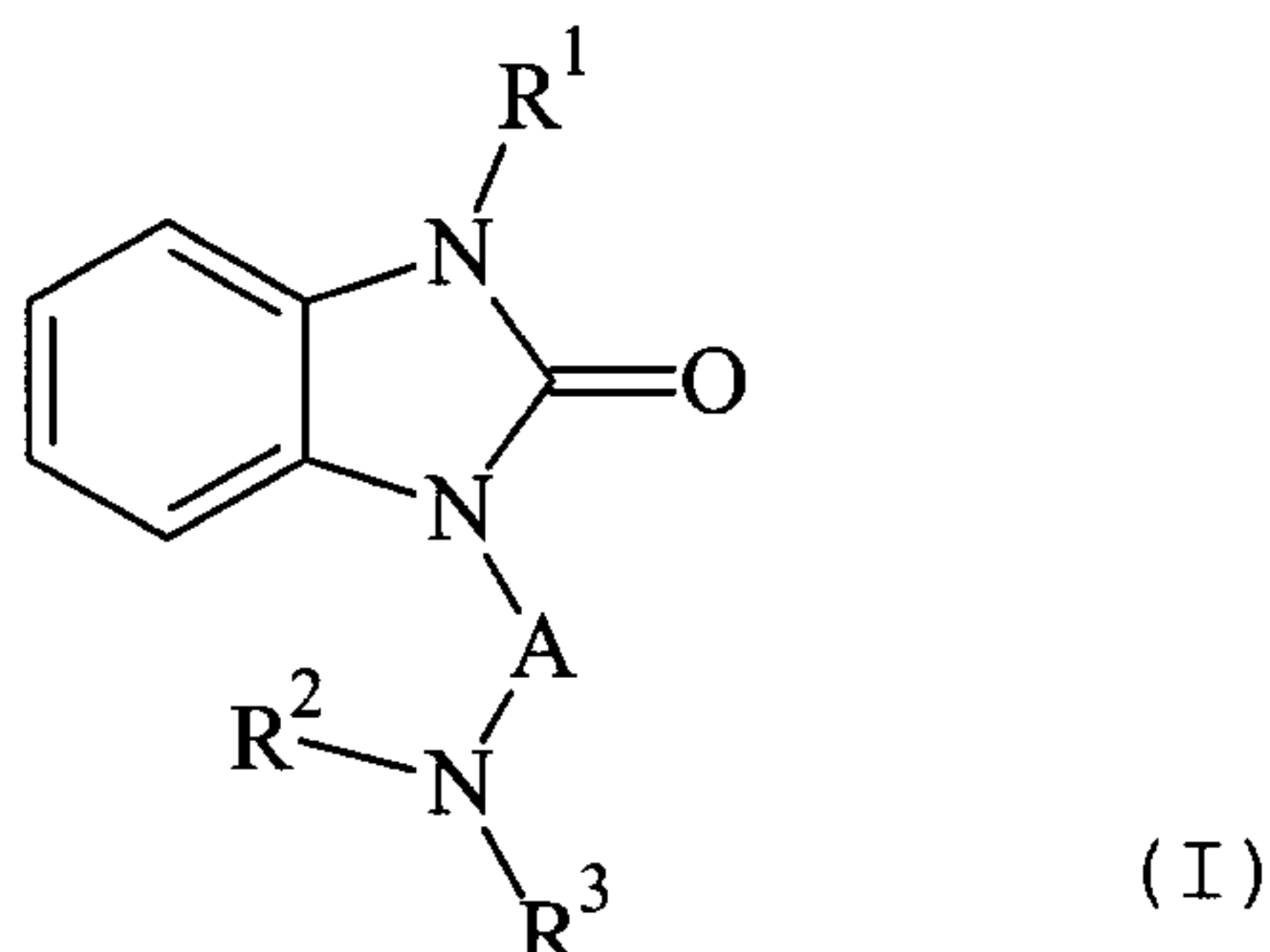
Comp.d No.	5-HT _{2A}	
	receptor binding IC ₅₀ (nM)	PI turnover % inhib.
9	16	45
73	0.90	42
83	43	86
168	46	22.00
177	7.7	39
183	27	12.00
206	17	90
215	3.2	83
254	65	64
514	74	41
521	30	48

25771-774

86

CLAIMS:

1. A compound of general formula (I)



wherein

R^1 denotes C_1 - C_6 -alkyl being substituted by a group selected from C_1 - C_6 -alkoxy, $-OCONHC_1$ - C_6 -alkyl, $-NHSO_2C_1$ - C_6 -alkyl and
10 $-NHCOC_1$ - C_6 -alkyl

R^2 and R^3 together with the nitrogen to which each is attached form a saturated or unsaturated 5- or 6-membered heterocyclic ring which may contain nitrogen or oxygen as an additional heteroatom, whilst the heterocyclic ring is
15 substituted by a group selected from phenyl, benzyl and diphenylmethyl, said group being unsubstituted, mono- or di-substituted by one or two groups selected from CF_3 , C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy, phenyl, benzyl, halogen and OH, or

R^2 and R^3 together with the nitrogen to which each is attached form a saturated or unsaturated 5- or 6-membered heterocyclic ring which may contain nitrogen or oxygen as an additional heteroatom, said heterocyclic ring being linked via a single bond, a methylene-bridge or spiro-connected to another saturated or unsaturated heterocyclic group
25 containing one or two heteroatoms selected from oxygen and nitrogen, said heterocyclic group being unsubstituted, mono- or di-substituted by a group selected from CF_3 , C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy, phenyl, benzyl, halogen, and OH, or two

25771-774

87

hydrogen atoms from said heterocyclic group being optionally substituted by =O, or

R² and R³ together with the nitrogen to which each is attached form a saturated or unsaturated bi- or tricyclic
5 heterocyclic ring-system which may contain nitrogen or oxygen as an additional heteroatom, said heterocyclic ring-system being unsubstituted or substituted by a group selected from CF₃, C₁-C₄-alkyl, C₁-C₄-alkoxy, phenyl, benzyl, halogen, and OH or two hydrogen atoms from said heterocyclic
10 ring-system being optionally substituted by =O; and

A denotes C₁-C₆-alkylen, C₂-C₆-alkenylen or C₂-C₆-alkynylen, or a pharmaceutically acceptable salt thereof.

2. A compound or salt according to claim 1, wherein

R¹ denotes C₁-C₄-alkyl being substituted by a group selected
15 from C₁-C₄-alkoxy, -OCONHC₁-C₄-alkyl, -NHSO₂C₁-C₄-alkyl and -NHCOC₁-C₄-alkyl

R² and R³ together with the nitrogen to which each is attached form a saturated or unsaturated 5- or 6-membered heterocyclic ring which may contain nitrogen as an
20 additional heteroatom, whilst the heterocyclic ring is substituted by a group selected from phenyl, benzyl, diphenylmethyl, pyridinyl, pyrimidinyl, benzimidazolonyl and 3,4-methylenedioxybenzyl, said group being unsubstituted, mono- or di-substituted by a group selected from CF₃,
25 C₁-C₄-alkyl, C₁-C₄-alkoxy, halogen and OH; and

A denotes C₁-C₄-alkylen or C₂-C₄-alkenylen.

25771-774

88

3. A compound or salt according to claim 1, wherein R^1 denotes ethyl, being substituted by a group selected from OCH_3 , OCH_2CH_3 , $-OCONHCH_3$, $-OCONHCH_2CH_3$, $-NHSO_2CH_3$, $-NHSO_2CH_2CH_3$, $-NHCOCH_3$, and $-NHCOCH_2CH_3$,

5 R^2 and R^3 together with the nitrogen to which each is attached form a 6-membered saturated or unsaturated heterocyclic ring which may contain nitrogen as an additional heteroatom, whilst the heterocyclic ring is substituted by a group selected from phenyl, pyridinyl, pyrimidinyl, benzimidazolonyl, and substituted phenyl being
10 mono- or di-substituted by a group selected from CF_3 , CH_3 , OCH_3 , F and Cl; and

A denotes C_1 - C_4 -alkylen or C_2 - C_4 -alkenylen.

4. A compound or salt according to claim 1, wherein

15 R^1 denotes ethyl, being substituted by a group selected from OCH_3 , $-OCONHCH_2CH_3$, $-NHSO_2CH_3$ and $-NHCOCH_3$,

R^2 and R^3 together with the nitrogen to which each is attached form a 6-membered saturated or unsaturated heterocyclic ring which may contain nitrogen as an
20 additional heteroatom, whilst the heterocyclic ring is substituted by a group selected from pyridinyl, phenyl and substituted phenyl being mono- or di-substituted by a group selected from CF_3 , CH_3 , OCH_3 , F and Cl; and

A denotes ethylen, propylen, butylen or butenylen.

25 5. A compound or salt according to claim 1, wherein

R^1 denotes ethyl, being substituted by a group selected from OCH_3 , $-OCONHCH_2CH_3$, $-NHSO_2CH_3$ and $-NHCOCH_3$,

25771-774

89

R^2 and R^3 together with the nitrogen to which each is attached form a ring selected from the group consisting of piperazin, piperidin and tetrahydropyridin, which is substituted by a group selected from pyridinyl, phenyl and substituted phenyl being mono- or di-substituted by a group selected from CF_3 , CH_3 and Cl ; and

A denotes ethylen, butylen or butenylen.

6. A compound or salt according to claim 1, wherein R^1 denotes ethyl, being substituted by a group selected from OCH_3 , $-OCONHCH_2CH_3$ and $-NHSO_2CH_3$;

R^2 and R^3 together with the nitrogen to which each is attached form a piperazine-ring, being substituted by a group selected from trifluoromethylphenyl, methylphenyl, dimethylphenyl and chlorophenyl; and

15 A denotes ethylen, butylen or butenylen.

7. A pharmaceutical composition comprising one or more compounds or salts according to any one of claims 1 to 6 and one or more pharmaceutically acceptable carriers.

8. A pharmaceutical composition according to claim 7 for treatment of one or both of an anxiety disorder and an affective disorder.

9. A pharmaceutical composition according to claim 7 for treatment of a disease selected from depression, psychosis, schizophrenia, eating disorders, sexual disorders, Parkinson, stroke and traumatic brain injury.

10. A use of a compound or salt according to any one of claims 1 to 6 in preparation of a pharmaceutical composition for treatment of one or both of an anxiety disorder and an affective disorder.

25771-774

90

11. A use of a compound or salt according to any one of claims 1 to 6 for preparation of a pharmaceutical composition for treatment of a disease selected from depression, psychosis, schizophrenia, eating disorders, sexual disorders, Parkinson, stroke and traumatic brain injury.

12. A use of a compound or salt according to any one of claims 1 to 6 for treatment of one or both of an anxiety disorder and an affective disorder.

10 13. A use of a compound or salt according to any one of claims 1 to 6 for treatment of a disease selected from depression, psychosis, schizophrenia, eating disorders, sexual disorders, Parkinson, stroke and traumatic brain injury.

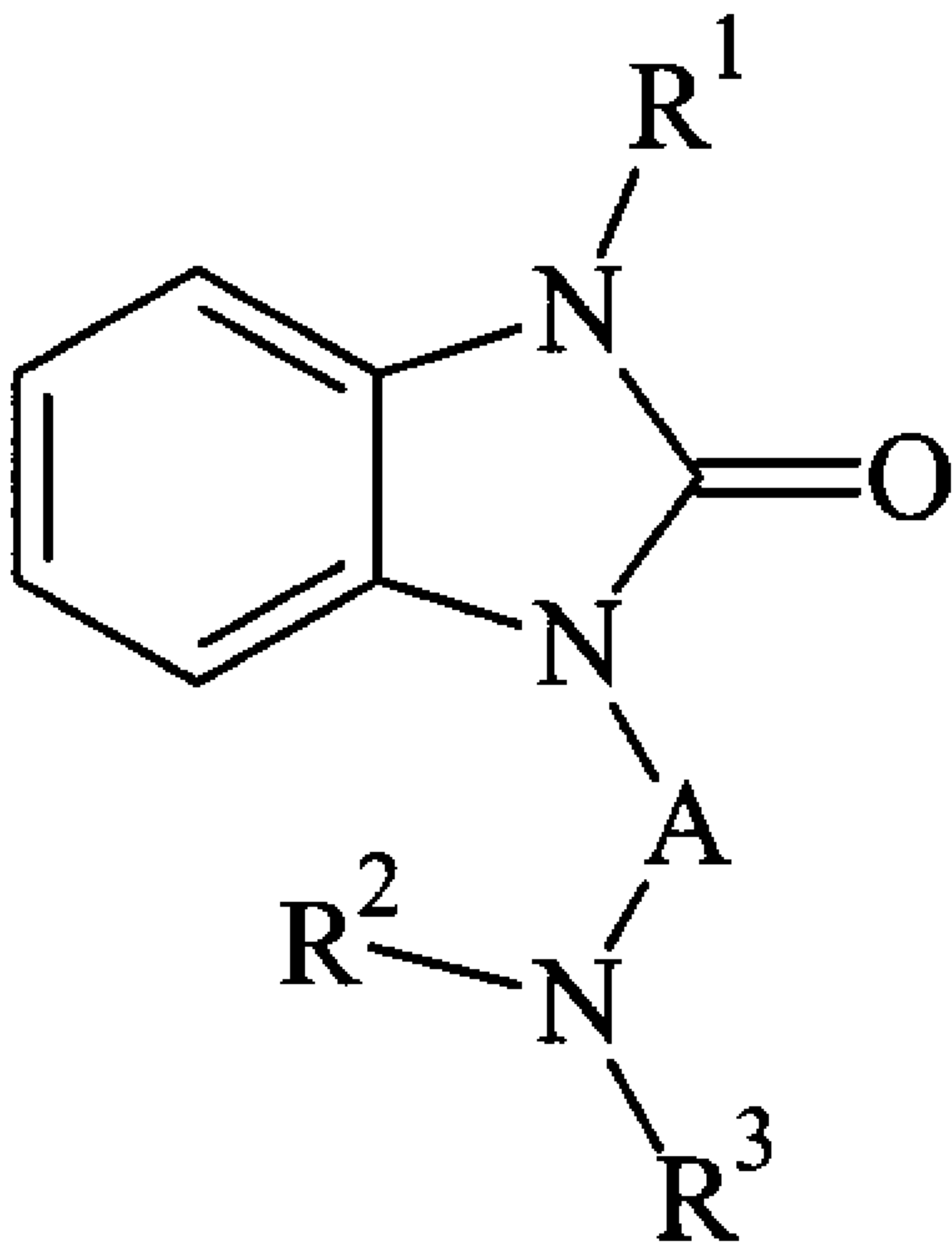
15 14. A compound or salt according to any one of claims 1 to 6 for treatment of one or both of an anxiety disorder and an affective disorder.

15. A compound or salt according to any one of claims 1 to 6 for treatment of a disease selected from depression, psychosis, schizophrenia, eating disorders, sexual disorders, Parkinson, stroke and traumatic brain injury.

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PATENT AGENTS



(I)