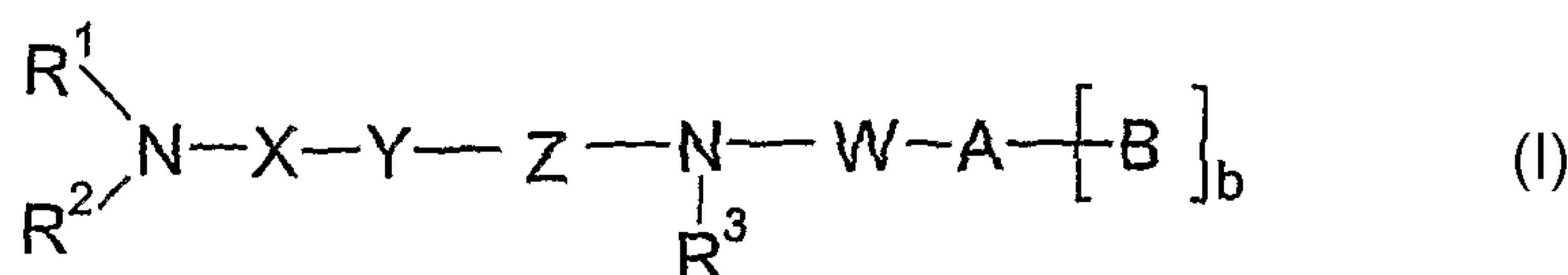




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(54) Titre : DERIVES D'ACIDE 3-(4-PIPERIDINE-1YLMETHYL-PHENYL) PROPIONIQUE-PHENYLAMIDE ET
COMPOSES APPARENTES, UTILISES COMME ANTAGONISTES MCH (HORMONE DE CONCENTRATION EN
MELANINE) POUR LE TRAITEMENT DE TROUBLES DUS A L'ALIMENTATION
(54) Title: 3-(4-PIPERIDINE-1YLMETHYL-PHENYL)-PROPION ACID-PHENYLAMIDE-DERIVATIVES AND RELATED
COMPOUNDS USED IN THE FORM OF MCH ANTAGONISTS (MELANINE CONCENTRATING HORMONE) FOR
TREATING EATING DISORDERS



(57) **Abrégé/Abstract:**

The invention relates to amid compounds of general formula (I), wherein groups and residuals A, B, b, W, X, Y, Z, R1, R2 and R3 have significances given in a claim 1. In addition, said invention relates to drugs containing at least one type of inventive amid. Because of the antagonist activity of an MCH-receptor, the inventive drugs are suitable for treating metabolic disturbances and/or eating disorders, in particular adiposity, bulimia, anorexia, hyperphagia and diabetes.



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ABSTRACT

The invention relates to amid compounds of general formula (I), wherein groups and residuals A, B, b, W, X, Y, Z, R¹, R² and R³ have significances given in a claim 1. In addition, said invention relates to drugs containing at least one type of inventive amid. Because of the antagonist activity of an MCH-receptor, the inventive drugs are suitable for treating metabolic disturbances and/or eating disorders, in particular adiposity, bulimia, anorexia, hyperphagia and diabetes.

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**New amide-compounds with MCH antagonistic activity and medicaments
comprising these compounds**

5 The present invention relates to new amide compounds, the physiologically acceptable salts thereof as well as their use as MCH antagonists and their use in preparing a pharmaceutical preparation which is suitable for the prevention and/or treatment of symptoms and/or diseases caused by MCH or causally connected with MCH in some other way. The invention further relates to the use of a compound
10 according to the invention for influencing eating behaviour and for reducing body weight and/or for preventing an increase in the body weight of a mammal. The invention also relates to compositions and medicaments containing a compound according to the invention, and processes for preparing them. Further objects of this invention relate to processes for preparing the compounds according to the invention.

15

Background to the Invention

The intake of food and its conversion in the body is an essential part of life for all living creatures. Therefore, deviations in the intake and conversion of food generally
20 lead to problems and also illness. The changes in the lifestyle and nutrition of humans, particularly in industrialised countries, have promoted morbid overweight (also known as corpulence or obesity) in recent decades. In affected people, obesity leads directly to restricted mobility and a reduction in the quality of life. There is the additional factor that obesity often leads to other diseases such as, for example,
25 diabetes, dyslipidaemia, high blood pressure, arteriosclerosis and coronary heart disease. Moreover, high body weight alone puts an increased strain on the support and mobility apparatus, which can lead to chronic pain and diseases such as arthritis or osteoarthritis. Thus, obesity is a serious health problem for society.

30 The term obesity means an excess of adipose tissue in the body. In this connection, obesity is fundamentally to be seen as the increased level of fatness which leads to a health risk. There is no sharp distinction between normal individuals and those suffering from obesity, but the health risk accompanying obesity is presumed to rise continuously as the level of fatness increases. For simplicity's sake, in the present

invention, individuals with a Body Mass Index (BMI), which is defined as the body weight measured in kilograms divided by the height (in metres) squared, above a value of 25 and more particularly above 30, are preferably regarded as suffering from obesity.

5

Apart from physical activity and a change in nutrition, there is currently no convincing treatment option for effectively reducing body weight. However, as obesity is a major risk factor in the development of serious and even life-threatening diseases, it is all the more important to have access to pharmaceutical active substances for the prevention and/or treatment of obesity. One approach which has been proposed very recently is the therapeutic use of MCH antagonists (cf. *inter alia* WO 01/21577, WO 01/82925).

Melanin-concentrating hormone (MCH) is a cyclic neuropeptide consisting of 19 amino acids. It is synthesised predominantly in the hypothalamus in mammals and from there travels to other parts of the brain by the projections of hypothalamic neurones. Its biological activity is mediated in humans through two different glycoprotein-coupled receptors (GPCRs) from the family of rhodopsin-related GPCRs, namely the MCH receptors 1 and 2 (MCH-1R, MCH-2R).

20

Investigations into the function of MCH in animal models have provided good indications for a role of the peptide in regulating the energy balance, i.e. changing metabolic activity and food intake [1.2]. For example, after intraventricular administration of MCH in rats, food intake was increased compared with control animals. Additionally, transgenic rats which produce more MCH than control animals, when given a high-fat diet, responded by gaining significantly more weight than animals without an experimentally altered MCH level. It was also found that there is a positive correlation between phases of increased desire for food and the quantity of MCH mRNA in the hypothalamus of rats. However, experiments with MCH knock-out mice are particularly important in showing the function of MCH. Loss of the neuropeptide results in lean animals with a reduced fat mass, which take in significantly less food than control animals.

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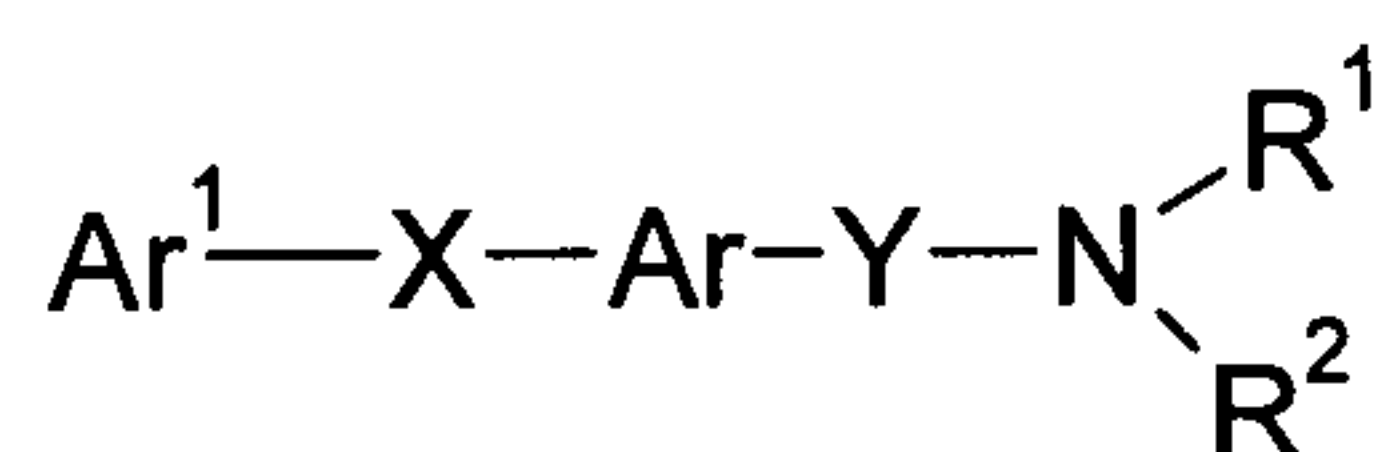
The anorectic effects of MCH are presumably mediated in rodents through the G-Galpa i-coupled MCH-1R [3-6], as, unlike primates, ferrets and dogs, no second MCH receptor subtype has hitherto been found in rodents. After losing the MCH-1R, knock-out mice have a lower fat mass, an increased energy conversion and, when fed
5 on a high fat diet, do not put on weight, compared with control animals. Another indication of the importance of the MCH system in regulating the energy balance results from experiments with a receptor antagonist (SNAP-7941) [3]. In long term trials the animals treated with the antagonist lose significant amounts of weight.

10 In addition to its anorectic effect, the MCH-1R antagonist SNAP-7941 also achieves additional anxiolytic and antidepressant effects in behavioural experiments on rats [3]. Thus, there are clear indications that the MCH-MCH-1R system is involved not only in regulating the energy balance but also in affectivity.

15 Literature:

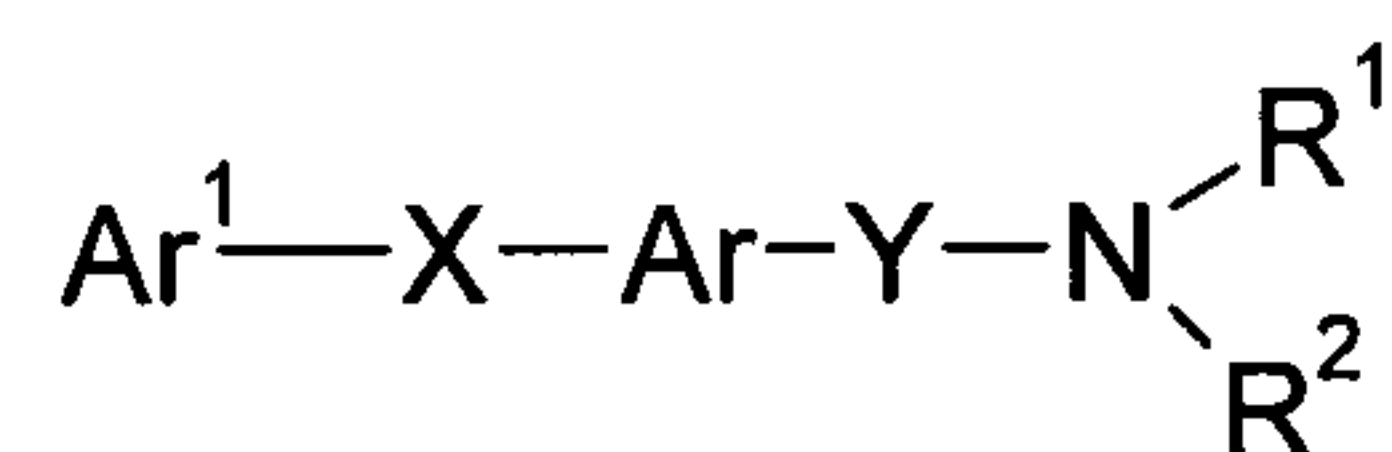
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- 20 3. Borowsky, B., et al., *Antidepressant, anxiolytic and anorectic effects of a melanin-concentrating hormone-1 receptor antagonist*. Nat Med, 2002. **8**(8): p. 825-30.
4. Chen, Y., et al., *Targeted disruption of the melanin-concentrating hormone receptor-1 results in hyperphagia and resistance to diet-induced obesity*.
25 Endocrinology, 2002. **143**(7): p. 2469-77.
5. Marsh, D.J., et al., *Melanin-concentrating hormone 1 receptor-deficient mice are lean, hyperactive, and hyperphagic and have altered metabolism*. Proc Natl Acad Sci U S A, 2002. **99**(5): p. 3240-5.
6. Takekawa, S., et al., *T-226296: A novel, orally active and selective melanin-concentrating hormone receptor antagonist*. Eur J Pharmacol, 2002. **438**(3): p.
30 129-35.

In the patent literature certain amine compounds are proposed as MCH antagonists. Thus, WO 01/21577 (Takeda) describes compounds of formula



wherein Ar¹ denotes a cyclic group, X denotes a spacer, Y denotes a bond or a spacer, Ar denotes an aromatic ring which may be fused with a non-aromatic ring, R¹ and R² independently of one another denote H or a hydrocarbon group, while R¹ and R² together with the adjacent N atom may form an N-containing hetero ring and R² with Ar may also form a spirocyclic ring, R together with the adjacent N atom and Y may form an N-containing hetero ring, as MCH antagonists for the treatment of obesity, *inter alia*.

Moreover WO 01/82925 (Takeda) also describes compounds of formula



wherein Ar¹ denotes a cyclic group, X and Y represent spacer groups, Ar denotes an optionally substituted fused polycyclic aromatic ring, R¹ and R² independently of one another represent H or a hydrocarbon group, while R¹ and R² together with the adjacent N atom may form an N-containing heterocyclic ring and R² together with the adjacent N atom and Y may form an N-containing hetero ring, as MCH antagonists for the treatment of obesity.

EP 0 237 678 A1 describes indole derivatives for the treatment of migraine. Example 4 mentions the compound N-[4-[[[(methylamino)sulphonyl]methyl]phenyl]-3-[2-(dimethylamino)-ethyl]-1-H-indole-5-propanamide oxalate.

JP 2000086603 describes propenamide derivatives which have a 2-hydroxypropoxy group, used as 5-HT_{1A} receptor antagonists.

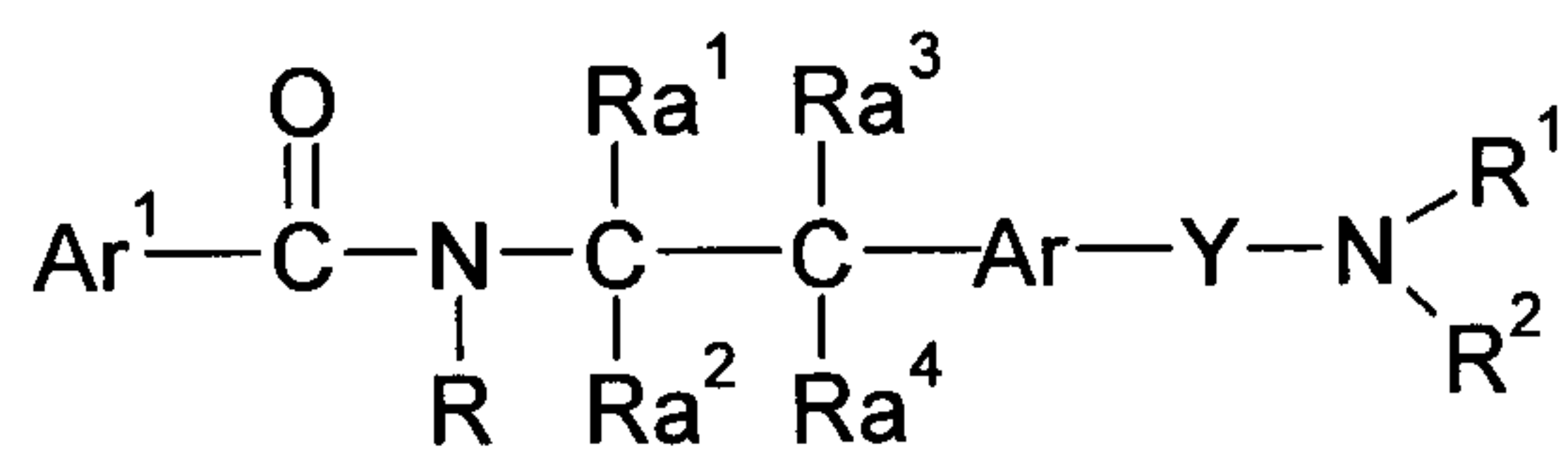
WO 99/29674 describes N-imidazolyl- and N-triazolylalkyl-phenyl-acetamide derivatives as inhibitors of the retinoid metabolism. The substance N-[4-[1-(1H-imidazol-1-yl)-2-methylpropyl]phenyl]-3-phenyl-2-propinamide is mentioned as compound number 198.

J. Krapcho et al. mention in J. Med. Chem. (1969), 12(1), 164-6 entitled "Immunosuppressive activity of 2'-(3-dimethylaminopropylthio)cinnamanilide (cinanserine) and related compounds" *inter alia* the compound 2'-[[3-(dimethylamino)propyl]thio]-3-phenyl-propiolanilide.

5

WO 2001002344 describes aminobenzoic acid derivatives as VEGF receptor antagonists and mentions, among others, the compound 2-(methylthio)-5-[[3-[4-(octadecylamino)phenyl]-1-oxopropyl]amino]-benzoic acid.

- 10 JP 04054118 proposes 4-(acylamino)phenols as 5-lipoxygenase inhibitors and mentions among others the compounds 4-amino-N-(4-hydroxy-3, 5-dimethylphenyl)-benzenepropanamide as well as 4-(dimethylamino)-N-(4-hydroxy-3, 5-dimethylphenyl)-benzenepropanamide.
- 15 The preparation of [[(benzoxazolylalkanoyl)amino]phenyl]alkanoates and their suitability as integrin receptor ligands are described in WO 2000049005. Mention is made *inter alia* of the compound β -methyl-4-[[3-[2-[(2-methylphenyl)amino]-6-benzoxazolyl]-1-oxopropylamino]-benzenepropanoic acid.
- 20 WO 2000005223 describes benzoxazole derivatives as inhibitors of the interaction between VCAM-1 and/or fibronectin and the integrin receptor VLA-4. Mention is made *inter alia* of the compound 4-[3-[[1-oxo-3-[2-(phenylamino)-6-benzoxazolyl]propyl]amino]phenoxy]-butanoic acid.
- 25 The preparation of carboxylic acid derivatives as EDG-1 receptor agonists is described in WO 2002092068. Mention is made *inter alia* of 2-chloro-5-[[1-oxo-3-[4-[(5-phenylpentyl)amino]phenyl]propyl]amino]-benzoic acid and the corresponding methyl ester.
- 30 Published International Application WO 2004/072018 proposes amine derivatives as antagonists of the MCH receptor. As well as compounds covered by general formula



, a number of different individual compounds

are also published.

5 Aim of the invention

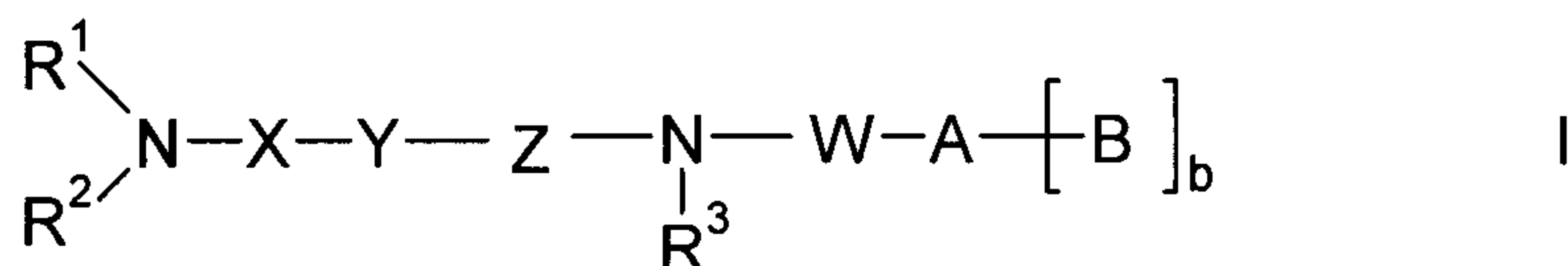
The aim of the present invention is to provide new amide compounds, particularly those which are effective as MCH antagonists.

The invention also sets out to provide new amide compounds which can be used to influence the eating habits of mammals and achieve a reduction in body weight, particularly in mammals, and/or prevent an increase in body weight.

The present invention further sets out to provide new pharmaceutical compositions which are suitable for the prevention and/or treatment of symptoms and/or diseases caused by MCH or otherwise causally connected to MCH. In particular, the aim of this invention is to provide pharmaceutical compositions for the treatment of metabolic disorders such as obesity and/or diabetes as well as diseases and/or disorders which are associated with obesity and diabetes. Other objectives of the present invention are concerned with demonstrating advantageous uses of the compounds according to the invention. The invention also sets out to provide a process for preparing the amide compounds according to the invention. Other aims of the present invention will be immediately apparent to the skilled man from the foregoing remarks and those that follow.

25 Object of the invention

In a first aspect the present invention relates to amide compounds of general formula I



wherein

R^1, R^2 independently of one another denote H, a C_{1-8} -alkyl or C_{3-7} -cycloalkyl group optionally mono- or polysubstituted by the group R^{11} , while a
5 -CH₂- group in position 3 or 4 of a 5-, 6- or 7-membered cycloalkyl group may be replaced by -O-, -S-, -NR¹³-, or a phenyl or pyridinyl group optionally mono- or polysubstituted by the group R^{12} and/or monosubstituted by nitro, or

10 R^1 and R^2 form a C_{2-8} -alkylene bridge, wherein

- one or two -CH₂- groups independently of one another may be replaced by -CH=N- or -CH=CH- and/or
- one or two -CH₂- groups independently of one another may be replaced by -O-, -S-, -SO-, -(SO₂)-, -C=N-O-R¹⁸, -CO-, -C(=CH₂)- or
15 -NR¹³- in such a way that heteroatoms are not directly joined together, and that a group -C=N-O-R¹⁸ or -CO- is not directly linked to the group R^1R^2N -,

20 while in the alkylene bridge defined hereinbefore one or more H atoms may be replaced by R^{14} , and

the alkylene bridge defined hereinbefore may be substituted by one or two identical or different carbo- or heterocyclic groups Cy such that the bond between the alkylene bridge and the group Cy is made

25

- via a single or double bond,
- via a common C atom forming a spirocyclic ring system,
- via two common adjacent C and/or N atoms forming a fused bicyclic ring system or
- via three or more C and/or N atoms forming a bridged ring system,

30 R^3 denotes H, C_{1-6} -alkyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-4} -alkyl or phenyl- C_{1-3} -alkyl,

X denotes a single bond or a C_{1-8} -alkylene bridge, wherein

- a $\text{-CH}_2\text{-}$ group which is not directly linked to the group $\text{R}^1\text{R}^2\text{N-}$ may be replaced by -CH=CH- or $\text{-C}\equiv\text{C-}$ and/or
- one or two non-adjacent $\text{-CH}_2\text{-}$ groups, which are not directly linked to the group $\text{R}^1\text{R}^2\text{N-}$, may be replaced independently of one another by -O- , -S- , -(SO)- , $\text{-(SO}_2\text{)-}$, -CO- or $\text{-NR}^4\text{-}$ in such a way that in each case two O, S or N atoms or an O and an S atom are not directly joined together,

while the bridge X may be connected to R^1 including the N atom linked to R^1 and X, forming a heterocyclic group, while the bridge X may additionally also be connected to R^2 including the N atom connected to R^2 and X, forming a heterocyclic group, and

while two C atoms or a C and an N atom of the alkylene bridge may be joined together by an additional C_{1-4} -alkylene bridge, and

a C atom may be substituted with R^{10} and/or one or two C atoms may be substituted in each case by one or two identical or different substituents selected from C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, C_{4-7} -cycloalkenyl and C_{4-7} -cycloalkenyl- C_{1-3} -alkyl, while two alkyl and/or alkenyl substituents may be joined together, forming a carbocyclic ring system, and

W denotes a single bond, while

25 Z denotes $\text{-C}\equiv\text{C-C(=O)-}$, $\text{-CR}^{7a}=\text{CR}^{7c}\text{-C(=O)-}$ or $\text{-CR}^{7a}\text{R}^{7b}\text{-CR}^{7c}\text{R}^{7d}\text{-C(=O)-}$, or

W denotes $\text{-C(=O)-C}\equiv\text{C-}$, while

Z denotes a single bond; and

30 Y has one of the meanings given for Cy,

while X may be connected to Y, forming a carbo- or heterocyclic group fused to Y, and/ or

optionally R^1 may be connected to Y, including the group X and the N atom connected to R^1 and X, forming a heterocyclic group fused to Y, and

5

A has one of the meanings given for Cy, while if the index b has the value 0, the group Cy does not have an amino group as substituent in the ortho position to the bridge W;

10

B has one of the meanings given for Cy,

b denotes the value 0 or 1,

15

Cy denotes a carbo- or heterocyclic group selected from one of the following meanings

20

- a saturated 3- to 7-membered carbocyclic group,
- a unsaturated 4- to 7-membered carbocyclic group,
- a phenyl group,
- a saturated 4- to 7-membered or unsaturated 5- to 7-membered heterocyclic group with an N, O or S atom as heteroatom,
- a saturated or unsaturated 5- to 7-membered heterocyclic group with two or more N atoms or with one or two N atoms and one O or S atom as heteroatoms,
- an aromatic heterocyclic 5- or 6-membered group with one or more identical or different heteroatoms selected from N, O and/or S,

25

while the above-mentioned 4-, 5-, 6- or 7-membered groups may be fused to a phenyl or pyridine ring via two common adjacent C atoms, and

30

in the above-mentioned 5-, 6- or 7-membered groups one or two non-adjacent $-CH_2-$ groups may independently of one another be replaced by a $-CO-$, $-C(=CH_2)-$, $-(SO)-$ or $-(SO_2)-$ group, and

the above-mentioned saturated 6- or 7-membered groups may also occur as bridged ring systems with an imino, N-(C₁₋₄-alkyl)-imino, methylene, C₁₋₄-alkyl-methylene or di-(C₁₋₄-alkyl)-methylene bridge, and

5 the above-mentioned cyclic groups may be mono- or polysubstituted by R²⁰ at one or more C atoms, in the case of a phenyl group may also additionally be monosubstituted by nitro, and/or one or more NH groups may be substituted by R²¹,

10 R⁴ has one of the meanings given for R¹⁷ or denotes C₂₋₆-alkenyl or C₃₋₆-alkynyl,

R^{7a}, R^{7c} denote H, F, Cl, C₁₋₄-alkyl or CF₃,

15 R^{7b}, R^{7d} denote H, F, C₁₋₄-alkyl, while R^{7b} and R^{7d} representing alkyl may be joined together to form a cyclopropyl group;

R¹⁰ denotes hydroxy, hydroxy-C₁₋₃-alkyl, C₁₋₄-alkoxy, C₁₋₄-alkoxy-C₁₋₃-alkyl, carboxy, C₁₋₄-alkoxycarbonyl, amino, C₁₋₄-alkyl-amino, di-(C₁₋₄-alkyl)-
20 amino, cyclo-C₃₋₆-alkyleneimino, amino-C₁₋₃-alkyl, C₁₋₄-alkyl-amino-C₁₋₃-alkyl, di-(C₁₋₄-alkyl)-amino-C₁₋₃-alkyl, cyclo-C₃₋₆-alkyleneimino-C₁₋₃-alkyl, amino-C₁₋₃-alkoxy, C₁₋₄-alkyl-amino-C₁₋₃-alkoxy, di-(C₁₋₄-alkyl)-amino-C₁₋₃-alkoxy, cyclo-C₃₋₆-alkyleneimino-C₁₋₃-alkoxy, aminocarbonyl, C₁₋₄-alkyl-aminocarbonyl, di-(C₁₋₄-alkyl)-aminocarbonyl or cyclo-C₃₋₆-
25 alkyleneimino-carbonyl,

R¹¹ denotes C₂₋₆-alkenyl, C₂₋₆-alkynyl, R¹⁵-O-, R¹⁵-O-C₁₋₃-alkyl, R¹⁵-O-CO-, R¹⁵-CO-O-, R¹⁶R¹⁷N-, cyano, R¹⁸R¹⁹N-CO- or Cy,

30 R¹² has one of the meanings given for R²⁰,

R¹³ has one of the meanings given for R¹⁷, with the exception of carboxy,

- 5 R^{14} denotes halogen, C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, R^{15} -O-, R^{15} -O-CO-, R^{15} -CO-, R^{15} -CO-O-, $R^{16}R^{17}N$, $R^{18}R^{19}N$ -CO, R^{15} -O- C_{1-3} -alkyl, R^{15} -O-CO- C_{1-3} -alkyl, R^{15} -O-CO-NH-, R^{15} -SO₂-NH, R^{15} -O-CO-NH- C_{1-3} -alkyl, R^{15} -SO₂-NH- C_{1-3} -alkyl, R^{15} -CO- C_{1-3} -alkyl, R^{15} -CO-O- C_{1-3} -alkyl, $R^{16}R^{17}N$ - C_{1-3} -alkyl, $R^{18}R^{19}N$ -CO- C_{1-3} -alkyl or Cy- C_{1-3} -alkyl,
- R^{15} denotes H, C_{1-4} -alkyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, phenyl, phenyl- C_{1-3} -alkyl, pyridinyl or pyridinyl- C_{1-3} -alkyl,
- 10 R^{16} denotes H, C_{1-6} -alkyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, C_{4-7} -cycloalkenyl, C_{4-7} -cycloalkenyl- C_{1-3} -alkyl, hydroxy- C_{2-3} -alkyl, C_{1-4} -alkoxy- C_{2-3} -alkyl, amino- C_{2-6} -alkyl, C_{1-4} -alkyl-amino- C_{2-6} -alkyl, di-(C_{1-4} -alkyl)-amino- C_{2-6} -alkyl or cyclo- C_{3-6} -alkyleneimino- C_{2-6} -alkyl,
- 15 R^{17} has one of the meanings given for R^{16} or denotes phenyl, phenyl- C_{1-3} -alkyl, pyridinyl, dioxolan-2-yl, -CHO, C_{1-4} -alkylcarbonyl, carboxy, hydroxycarbonyl- C_{1-3} -alkyl, C_{1-4} -alkoxycarbonyl, C_{1-4} -alkoxycarbonyl- C_{1-3} -alkyl, C_{1-4} -alkylcarbonylamino- C_{2-3} -alkyl, N-(C_{1-4} -alkylcarbonyl)-N-(C_{1-4} -alkyl)-amino- C_{2-3} -alkyl, C_{1-4} -alkylsulphonyl, C_{1-4} -alkylsulphonylamino- C_{2-3} -alkyl or N-(C_{1-4} -alkylsulphonyl)-N(C_{1-4} -alkyl)-amino- C_{2-3} -alkyl
- 20 R^{18} , R^{19} independently of one another denote H or C_{1-6} -alkyl,
- 25 R^{20} denotes halogen, hydroxy, cyano, C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, hydroxy- C_{1-4} -alkyl, R^{22} - C_{1-3} -alkyl or has one of the meanings given for R^{22} ,
- 30 R^{21} denotes C_{1-4} -alkyl, hydroxy- C_{2-3} -alkyl, C_{1-4} -alkoxy- C_{2-6} -alkyl, C_{1-4} -alkyl-amino- C_{2-6} -alkyl, di-(C_{1-4} -alkyl)-amino- C_{2-6} -alkyl, cyclo- C_{3-6} -alkyleneimino- C_{2-6} -alkyl, phenyl- C_{1-3} -alkyl, C_{1-4} -alkyl-carbonyl, C_{1-4} -alkoxy-carbonyl or C_{1-4} -alkylsulphonyl,

R²² denotes phenyl-C₁₋₃-alkoxy, cyclo-C₃₋₆-alkyleneimino-C₂₋₄-alkoxy, OHC, HO-N=HC, C₁₋₄-alkoxy-N=HC, C₁₋₄-alkoxy, C₁₋₄-alkylthio, carboxy, C₁₋₄-alkylcarbonyl, C₁₋₄-alkoxycarbonyl, aminocarbonyl, C₁₋₄-alkylamino-carbonyl, di-(C₁₋₄-alkyl)-aminocarbonyl, cyclo-C₃₋₆-alkyl-amino-carbonyl, cyclo-C₃₋₆-alkyleneimino-carbonyl, cyclo-C₃₋₆-alkyleneimino-C₂₋₄-alkyl-aminocarbonyl, phenyl-amino-carbonyl, C₁₋₄-alkyl-sulphonyl, C₁₋₄-alkyl-sulphinyl, C₁₋₄-alkyl-sulphonylamino, amino, C₁₋₄-alkylamino, di-(C₁₋₄-alkyl)-amino, C₁₋₄-alkyl-carbonyl-amino, cyclo-C₃₋₆-alkyleneimino, phenyl-C₁₋₃-alkylamino, N-(C₁₋₄-alkyl)-phenyl-C₁₋₃-alkylamino, acetylamino, propionylamino, phenylcarbonylamino, phenylcarbonylmethylamino, hydroxyalkylaminocarbonyl, (4-morpholinyl)carbonyl, (1-pyrrolidinyl)-carbonyl, (1-piperidinyl)carbonyl, (hexahydro-1-azepinyl)carbonyl, (4-methyl-1-piperazinyl)carbonyl, methylenedioxy, aminocarbonylamino or alkylaminocarbonylamino-,

while in the above-mentioned groups and radicals, particularly in A, B, W, X, Y, Z, R¹ to R⁴, R^{7a}, R^{7b}, R^{7c}, R^{7d}, R¹⁰ to R²², in each case one or more C atoms may additionally be mono- or polysubstituted by F and/or in each case one or two C atoms independently of one another may additionally be monosubstituted by Cl or Br and/or in each case one or more phenyl rings may independently of one another additionally comprise one, two or three substituents selected from the group F, Cl, Br, I, C₁₋₄-alkyl, C₁₋₄-alkoxy, difluoromethyl, trifluoromethyl, hydroxy, amino, C₁₋₃-alkylamino, di-(C₁₋₃-alkyl)-amino, acetylamino, aminocarbonyl, cyano, difluoromethoxy, trifluoromethoxy, amino-C₁₋₃-alkyl, C₁₋₃-alkylamino-C₁₋₃-alkyl and di-(C₁₋₃-alkyl)-amino-C₁₋₃-alkyl and/or may be monosubstituted by nitro, and

the H atom of a carboxy group present or an H atom bound to an N atom in each case may be replaced by a group which can be cleaved in vivo,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof,

while the following compounds according to provisos (M1) to (M14) are not included:

- (M1) N-[4-[[[(methylamino)sulphonyl]methyl]phenyl]-3-[2-(dimethylamino)-ethyl]-1-H-indole-5-propanamide oxalate,
- 5 (M2) 3-[2-[3-[3,6-dihydro-4-(2-naphthyl)-1(2H)-pyridinyl]-2-hydroxypropoxy]phenyl]-N-methyl-N-phenyl-2-propenamide,
- (M3) 3-[2-[2-hydroxy-3-[4-(1-naphthyl)-1-piperidinyl]propoxy]phenyl]-N-methyl-N-phenyl-2-propenamide,
- 10 (M4) 3-[2-[2-hydroxy-3-[4-(2-naphthyl)-1-piperidinyl]propoxy]phenyl]-N-methyl-N-phenyl-2-propenamide,
- (M5) 3-[2-[2-hydroxy-3-[4-(2-naphthalyl)-1-piperidinyl]propoxy]phenyl]-N-phenyl-2-propenamide,
- 15 (M6) N-[4-[1-(1H-imidazol-1-yl)-2-methylpropyl]phenyl]-3-phenyl-2-propinamide,
- (M7) 2'-[[3-(dimethylamino)propyl]thio]-3-phenyl-propiolanilide,
- 20 (M8) 2-(methylthio)-5-[[3-[4-(octadecylamino)phenyl]-1-oxopropyl]amino]-benzoic acid, including the trifluoroacetate salt,
- (M9) 4-amino-N-(4-hydroxy-3,5-dimethylphenyl)-benzenepropanamide,
- 25 (M10) 4-(dimethylamino)-N-(4-hydroxy-3,5-dimethylphenyl)-benzenepropanamide,
- (M11) β -methyl-4-[[3-[2-[(2-methylphenyl)amino]-6-benzoxazolyl]-1-oxopropylamino]-benzenepropanoic acid,
- 30 (M12) 4-[3-[[1-oxo-3-[2-(phenylamino)-6-benzoxazolyl]-propyl]amino]phenoxy]-butanoic acid,
- (M13) 2-chloro-5-[[1-oxo-3-[4-[(5-phenylpentyl)amino]phenyl]propyl]amino]-benzoic acid,

(M14) methyl 2-chloro-5-[[1-oxo-3-[4-[(5-phenylpentyl)amino]phenyl]propyl]amino]-benzoate.

- 5 In view of the individual compounds disclosed in WO 2004/072018 the following compounds are preferably not included either according to the invention:
- N-(4-pentyl-phenyl)-3-(4-pyrrolidin-1-ylmethyl-phenyl)-propionamide,
N-(4-bromo-phenyl)-3-(4-pyrrolidin-1-ylmethyl-phenyl)-propionamide,
N-(4'-chloro-biphenyl-4-yl)-3-(4-pyrrolidin-1-ylmethyl-phenyl)-propionamide,
10 N-(4-bromo-phenyl)-3-(4-pyrrolidin-1-ylmethyl-phenyl)-acrylamide,
N-(4'-chloro-biphenyl-4-yl)-3-(4-pyrrolidin-1-ylmethyl-phenyl)-acrylamide,
N-(4-bromo-2-fluoro-phenyl)-3-(4-pyrrolidin-1-ylmethyl-phenyl)-propionamide,
N-(4'-chloro-3-fluoro-biphenyl-4-yl)-3-(4-pyrrolidin-1-ylmethyl-phenyl)-propionamide.
- 15 The compounds according to the present invention, including the physiologically acceptable salts, are especially effective as antagonists of the MCH receptor, particularly the MCH-1 receptor, and exhibit very good affinity in MCH receptor binding studies. In addition, the compounds according to the invention have a high to
20 very high selectivity with regard to the MCH receptor. Generally the compounds according to the invention have low toxicity, they are well absorbed by oral route and have good intracerebral transitivity, particularly brain accessibility.

The invention also relates to the compounds in the form of the individual optical isomers, mixtures of the individual diastereomers, enantiomers or racemates, in the
25 form of the tautomers and in the form of the free bases or the corresponding acid addition salts with pharmacologically safe acids. The subject of the invention also includes the compounds according to the invention, including their salts, wherein one or more hydrogen atoms are replaced by deuterium.

- 30 This invention also includes the physiologically acceptable salts of the amide compounds according to the invention as described above and hereinafter.

Also covered by this invention are compositions containing at least one amide compound according to the invention and/ or a salt according to the invention optionally together with one or more physiologically acceptable excipients.

- 5 Also covered by this invention are pharmaceutical compositions containing at least one amide compound according to the invention and/ or a salt according to the invention optionally together with one or more inert carriers and/or diluents.

10 The invention also relates to the use of at least one amide compound according to the invention and/ or a salt according to the invention, including the compounds excluded by provisos (M1) to (M14), for influencing the eating behaviour of a mammal.

15 The invention also relates to the use of at least one amide compound according to the invention and/ or a salt according to the invention, including the compounds excluded by provisos (M1) to (M14), for reducing the body weight and/or for preventing an increase in the body weight of a mammal.

20 The invention also relates to the use of at least one amide compound according to the invention and/ or a salt according to the invention, including the compounds excluded by provisos (M1) to (M14), for preparing a pharmaceutical composition with an MCH-receptor-antagonistic activity, particularly with an MCH-1-receptor-antagonistic activity.

25 Moreover, the invention relates to the use of at least one amide compound according to the invention and/ or a salt according to the invention, including the compounds excluded by provisos (M1) to (M14), for preparing a pharmaceutical composition which is suitable for the prevention and/or treatment of symptoms and/or diseases which are caused by MCH or are otherwise causally connected with MCH.

30 The invention also relates to the use of at least one amide compound according to the invention and/ or a salt according to the invention, including the compounds excluded by provisos (M1) to (M14), for preparing a pharmaceutical composition which is suitable for the prevention and/or treatment of metabolic disorders and/or eating

disorders, particularly obesity, bulimia, bulimia nervosa, cachexia, anorexia, anorexia nervosa and hyperphagia.

5 This invention also relates to the use of at least one amide compound according to the invention and/ or a salt according to the invention, including the compounds excluded by provisos (M1) to (M14), for preparing a pharmaceutical composition which is suitable for the prevention and/or treatment of diseases and/or disorders associated with obesity, particularly diabetes, especially type II diabetes, complications of diabetes including diabetic retinopathy, diabetic neuropathy, diabetic
10 nephropathy, insulin resistance, pathological glucose tolerance, encephalorrhagia, cardiac insufficiency, cardiovascular diseases, particularly arteriosclerosis and high blood pressure, arthritis and gonitis.

Moreover, the invention relates to the use of at least one amide compound according
15 to the invention and/ or a salt according to the invention, including the compounds excluded by provisos (M1) to (M14), for preparing a pharmaceutical composition which is suitable for the prevention and/or treatment of hyperlipidaemia, cellulitis, fat accumulation, malignant mastocytosis, systemic mastocytosis, emotional disorders, affective disorders, depression, anxiety, sleep disorders, reproductive disorders,
20 sexual disorders, memory disorders, epilepsy, forms of dementia and hormonal disorders.

Another object of the invention is the use of at least one amide compound according to the invention and/ or a salt according to the invention, including the compounds
25 excluded by provisos (M1) to (M14), for preparing a pharmaceutical composition which is suitable for the prevention and/or treatment of micturition disorders, such as for example urinary incontinence, hyperactive urinary bladder, urgency, nycturia and enuresis.

30 Furthermore the invention relates to processes for preparing a pharmaceutical composition according to the invention, characterised in that at least one amide compound according to the invention and/ or a salt according to the invention is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

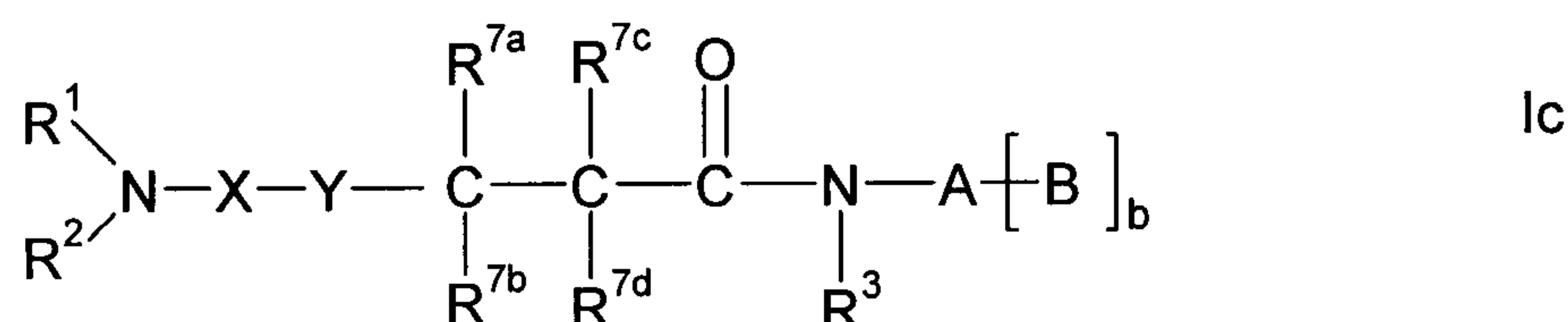
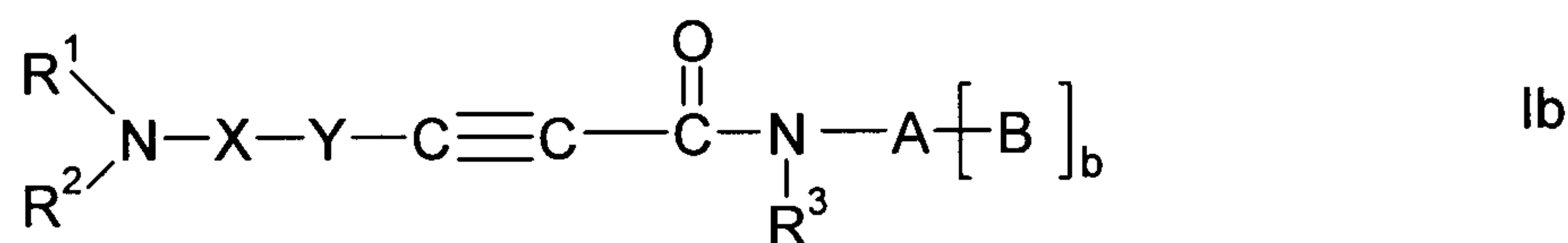
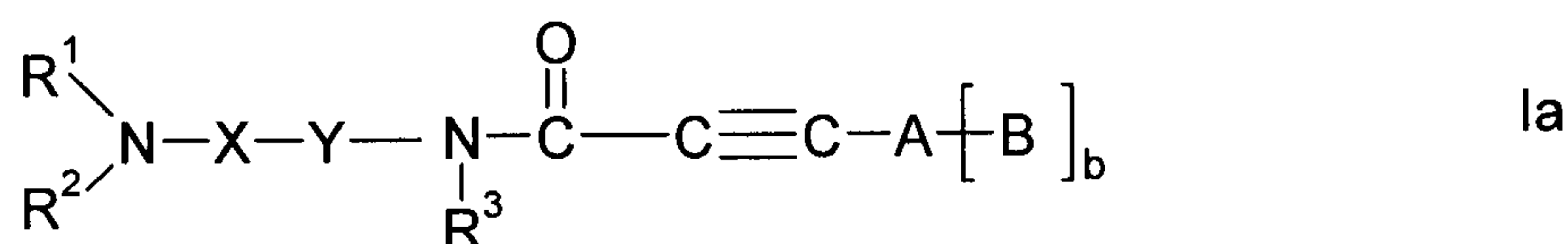
The invention further relates to a pharmaceutical composition containing a first active substance selected from the amide compounds according to the invention and/ or the corresponding salts, including the compounds excluded by provisos (M1) to (M14), as well as a second active substance selected from the group consisting of active substances for the treatment of diabetes, active substances for the treatment of diabetic complications, active substances for the treatment of obesity, preferably other than MCH antagonists, active substances for the treatment of high blood pressure, active substances for the treatment of hyperlipidaemia, including arteriosclerosis, active substances for the treatment of arthritis, active substances for the treatment of anxiety states and active substances for the treatment of depression, optionally together with one or more inert carriers and/or diluents.

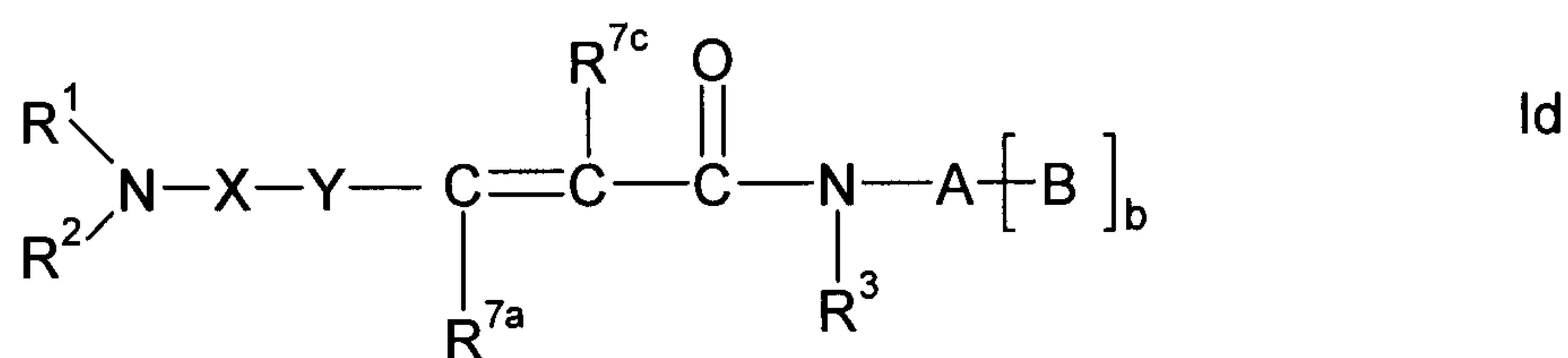
Detailed Description of the invention

Unless otherwise specified, the groups, residues and substituents, particularly A, B, W, X, Y, Z, R^1 to R^4 , R^{7a} , R^{7b} , R^{7c} , R^{7d} , R^{10} to R^{22} , and the index b have the meanings given hereinbefore.

If groups, residues and/or substituents occur more than once in a compound, they may have the same or different meanings in each case.

Preferred embodiments of this invention comprise compounds which may in each case be described by the following formulae Ia, Ib, Ic and Id:





wherein R^1 , R^2 , R^3 , R^{7a} , R^{7b} , R^{7c} , R^{7d} , X, Y, A, B and b have the meanings given above and hereinafter, particularly the meanings stated as being preferred.

Particularly preferred definitions of the groups R^{7a} , R^{7b} , R^{7c} , R^{7d} are H or methyl,
5 particularly H.

The preferred definitions of the individual groups and substituents given below refer to compounds of formula I according to the invention, particularly in each case to the four embodiments described by formulae Ia, Ib, Ic and Id.

10

Preferred meanings of the substituent R^3 are H, C_{1-4} -alkyl, C_{3-6} -cycloalkyl or C_{3-6} -cycloalkyl- C_{1-3} -alkyl; particularly H or C_{1-3} -alkyl. R^3 particularly preferably denotes H or methyl, particularly H.

15 The substituents R^1 and R^2 may have the meanings given above and hereinafter as separate groups or may be connected to one another as a bridge. For simplicity's sake, the preferred meanings of R^1 and R^2 as separate groups will be described first of all and then the preferred meanings of the groups R^1 and R^2 connected to one another to form a bridge. Preferred compounds according to the invention therefore
20 have one of the preferred meanings of R^1 and R^2 described below, as separate groups combined with one of the preferred meanings of R^1 and R^2 described hereinafter as groups connected to one another to form a bridge.

If R^1 and R^2 are not joined together via an alkylene bridge, R^1 and R^2 independently
25 of one another preferably denote a C_{1-8} -alkyl or C_{3-7} -cycloalkyl group optionally mono- or polysubstituted by the group R^{11} , while a $-\text{CH}_2-$ group in position 3 or 4 of a 5-, 6- or 7-membered cycloalkyl group may be replaced by $-\text{O}-$, $-\text{S}-$ or $-\text{NR}^{13}-$, or a

phenyl or pyridinyl group optionally mono- or polysubstituted by the group R^{12} and/or monosubstituted by nitro, while one of the groups R^1 and R^2 may also represent H.

Preferably the groups R^1 , R^2 independently of one another represent C_{1-6} -alkyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, hydroxy- C_{2-4} -alkyl, NC- C_{2-4} -alkyl, C_{1-4} -alkoxy- C_{2-4} -alkyl, C_{1-4} -alkoxy-carbonyl- C_{1-4} -alkyl, carboxyl- C_{1-4} -alkyl, amino- C_{2-4} -alkyl, C_{1-4} -alkyl-amino- C_{2-4} -alkyl, di-(C_{1-4} -alkyl)-amino- C_{2-4} -alkyl, cyclo- C_{3-6} -alkyleneimino- C_{2-4} -alkyl, pyrrolidin-3-yl, while the NH group may be substituted by R^{13} , pyrrolidinyl- C_{1-3} -alkyl, while the NH group may be substituted by R^{13} , piperidin-3-yl or -4-yl, while the NH group may be substituted by R^{13} , piperidinyl- C_{1-3} -alkyl, while the NH group may be substituted by R^{13} , tetrahydropyran-3-yl or -4-yl, tetrahydropyranyl- C_{1-3} -alkyl, tetrahydrofuran-3-yl, tetrahydrofuranyl- C_{1-3} -alkyl, phenyl, phenyl- C_{1-3} -alkyl, pyridyl or pyridyl- C_{1-3} -alkyl, while in the above-mentioned groups and radicals one or more C atoms may be mono- or polysubstituted by F and/or one or two C atoms, particularly one C atom may independently of one another be monosubstituted with Cl or Br, and the phenyl or pyridyl group may be mono- or polysubstituted by the group R^{12} defined hereinbefore and/or may be monosubstituted by nitro, and one of the groups R^1 , R^2 may also represent H. Preferably the above-mentioned cycloalkyl rings may be mono- or polysubstituted by substituents selected from hydroxy, hydroxy- C_{1-3} -alkyl, C_{1-3} -alkyl or C_{1-3} -alkyloxy, particularly hydroxy, hydroxymethyl, methyl and methoxy. Also preferably the C_{2-4} -alkyl bridges contained in hydroxy- C_{2-4} -alkyl and C_{1-4} -alkoxy- C_{2-4} -alkyl may additionally be monosubstituted by hydroxy, hydroxy- C_{1-3} -alkyl, C_{1-3} -alkyl or C_{1-3} -alkyloxy, particularly hydroxy, hydroxymethyl, methyl or methoxy. Preferred substituents R^{12} of the above-mentioned phenyl or pyridyl groups are selected from among F, Cl, Br, I, cyano, C_{1-4} -alkyl, C_{1-4} -alkoxy, difluoromethyl, trifluoromethyl, hydroxy, amino, C_{1-3} -alkylamino, di-(C_{1-3} -alkyl)-amino, acetylamino, aminocarbonyl, difluoromethoxy, trifluoromethoxy, amino- C_{1-3} -alkyl, C_{1-3} -alkylamino- C_{1-3} -alkyl and di-(C_{1-3} -alkyl)-amino- C_{1-3} -alkyl, while a phenyl group may also be monosubstituted by nitro.

30

Particularly preferred definitions of the groups R^1 and/or R^2 are selected from the group consisting of C_{1-6} -alkyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, tetrahydropyran-3 or -4-yl, tetrahydropyranyl- C_{1-3} -alkyl, piperidin-3 or -4-yl, while the NH group may be substituted by R^{13} , piperidinyl- C_{1-3} -alkyl, while the NH group may

be substituted by R^{13} , phenyl, pyridyl, phenyl- C_{1-3} -alkyl, pyridyl- C_{1-3} -alkyl, hydroxy- C_{2-4} -alkyl, C_{1-4} -alkoxy- C_{2-4} -alkyl, amino- C_{2-4} -alkyl, C_{1-4} -alkyl-amino- C_{2-4} -alkyl- and di-(C_{1-4} -alkyl)-amino- C_{2-4} -alkyl, while cycloalkyl rings may be mono-, di- or trisubstituted by substituents selected from hydroxy, hydroxy- C_{1-3} -alkyl, C_{1-3} -alkyl or C_{1-3} -alkyloxy, particularly hydroxy, hydroxymethyl, methyl and methoxy, and C_{2-4} -alkyl bridges contained in hydroxy- C_{2-4} -alkyl- and C_{1-4} -alkoxy- C_{2-4} -alkyl- may additionally be monosubstituted by hydroxy, hydroxy- C_{1-3} -alkyl, C_{1-3} -alkyl or C_{1-3} -alkyloxy, particularly hydroxy, hydroxymethyl, methyl or methoxy, and alkyl groups may be mono- or polysubstituted by F and/or monosubstituted by Cl, and one of the groups R^1 and R^2 may also represent H.

R^{13} preferably denotes H, C_{1-6} -alkyl, C_{1-4} -alkylcarbonyl or C_{1-4} -alkyloxycarbonyl. Particularly preferably R^{13} denotes H or C_{1-4} -alkyl, particularly H, methyl, ethyl or propyl.

Most particularly preferred definitions of the groups R^1 and/or R^2 are selected from the group consisting of methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, cyclopropyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, phenyl, pyridyl, phenylmethyl, pyridylmethyl, tetrahydropyran-4-yl, tetrahydropyran-4-yl-methyl, piperidin-4-yl, which may be substituted by R^{13} at the N atom, or piperidin-4-yl-methyl, which may be substituted by R^{13} at the N atom, while the ethyl, propyl and butyl groups mentioned may be monosubstituted by amino, methylamino or dimethylamino or mono- or disubstituted by hydroxy, methoxy or ethoxy, and the above-mentioned cycloalkyl rings may be mono- or disubstituted by hydroxy, hydroxymethyl or methyl, and methyl groups may be mono- or polysubstituted by fluorine, and one of the groups R^1 and R^2 may also represent H.

Examples of most particularly preferred definitions of the groups R^1 and/or R^2 are methyl, ethyl, n-propyl, i-propyl, 2-hydroxyethyl, 2-hydroxy-propyl, 3-hydroxypropyl, 2-hydroxy-2-methyl-propyl, 2-methoxyethyl, 3-amino-propyl, cyclopropyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, (1-hydroxycyclopropyl)methyl, phenyl, pyridyl, phenylmethyl, pyridylmethyl, tetrahydropyran-4-yl, N-methyl-piperidin-4-yl, N-(methylcarbonyl)-piperidin-4-yl and N-(tert.butyloxycarbonyl)-piperidin-4-yl, while

hydroxyalkyl groups may additionally be substituted by hydroxy, and one of the groups R^1 , R^2 may also represent H.

If the substituent R^1 has one of the meanings stated above as being preferred, but not
5 H, the substituent R^2 most particularly preferably denotes H, methyl, ethyl, n-propyl, i-propyl, 2-hydroxyethyl or 2-methoxyethyl.

Compounds according to the invention, particularly those which may be described by formula Ic or Id, are also preferred wherein one or both groups R^1 , R^2 represent one
10 or more groups selected from 2-hydroxyethyl, 2-hydroxy-2-methyl-propyl, 2-methoxyethyl, 3-amino-propyl, cyclopropyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, (1-hydroxycyclopropyl)methyl, phenyl, pyridyl, phenylmethyl, pyridylmethyl, tetrahydropyran-4-yl, N-methyl-piperidin-4-yl, N-(methylcarbonyl)-piperidin-4-yl and N-(tert.butyloxycarbonyl)-piperidin-4-yl, particularly 2-hydroxyethyl,
15 2-hydroxy-2-methyl-propyl, 2-methoxyethyl, tetrahydropyran-4-yl, cyclopropylmethyl and (1-hydroxycyclopropyl)methyl, while hydroxyalkyl groups may additionally be substituted by hydroxy.

Particularly preferably at least one of the groups R^1 , R^2 , most particularly preferably
20 both groups, have a meaning other than H.

If R^1 and R^2 form an alkylene bridge, this is preferably a C_{3-7} -alkylene bridge, wherein
- a $-CH_2-$ group not adjacent to the N atom of the R^1R^2N group may be replaced by $-CH=CH-$ and/or
25 - a $-CH_2-$ group which is preferably not adjacent to the N atom of the R^1R^2N- group may be replaced by $-O-$, $-S-$, $-C(=N-O-R^{18})-$, $-CO-$, $-C(=CH_2)-$ or $-NR^{13}-$, particularly preferably by $-O-$, $-S-$ or $-NR^{13}-$, in such a way that heteroatoms are not directly joined together and a group $-C=N-O-R^{18}$ or $-CO-$ is not directly linked to the group R^1R^2N- ,

30

while in the alkylene bridge defined hereinbefore one or more H atoms may be replaced by R^{14} , and

the alkylene bridge defined hereinbefore may be substituted by a carbo- or

heterocyclic group Cy in such a way that the bond between the alkylene bridge and the group Cy is made

- via a single or double bond,
- via a common C atom forming a spirocyclic ring system,
- 5 - via two common adjacent C and/or N atoms forming a fused bicyclic ring system or
- via three or more C and/or N atoms forming a bridged ring system.

R^{13} preferably denotes H, C_{1-6} -alkyl, C_{1-4} -alkylcarbonyl or C_{1-4} -alkyloxycarbonyl.

- 10 Particularly preferably R^{13} denotes H or C_{1-6} -alkyl, particularly H, methyl, ethyl or propyl.

Also preferably R^1 and R^2 form an alkylene bridge in such a way that R^1R^2N - denotes a group selected from azetidine, pyrrolidine, piperidine, azepan, 2,5-dihydro-1H-pyrrole, 1,2,3,6-tetrahydro-pyridine, 2,3,4,7-tetrahydro-1H-azepine, 2,3,6,7-tetrahydro-1H-azepine, piperazine wherein the free imine function is substituted by R^{13} , piperidin-4-one, piperidin-4-one-oxime, piperidin-4-one-O- C_{1-4} -alkyl-oxime, morpholine and thiomorpholine,

- 20 particularly a group selected from pyrrolidine, piperidine, 2,5-dihydro-1H-pyrrole, morpholine, thiomorpholine and piperazine, wherein the free imine function is substituted by R^{13} ,

- while according to the general definition of R^1 and R^2 one or more H atoms may be replaced by R^{14} , and/ or the above-mentioned groups may be substituted by one or two identical or different carbo- or heterocyclic groups Cy in a manner specified according to the general definition of R^1 and R^2 . Particularly preferred groups Cy for this are phenyl, C_{3-7} -cycloalkyl, aza- C_{4-7} -cycloalkyl, particularly phenyl, C_{3-6} -cycloalkyl, cyclo- C_{3-5} -alkyleneimino, as well as N- C_{1-4} -alkyl-(aza- C_{4-6} -cycloalkyl), while the cyclic groups Cy may be substituted as specified.
- 25
- 30

The alkylene bridge formed by R^1 and R^2 , wherein $-CH_2-$ groups may be replaced as specified, may be substituted, as described, by one or two identical or different carbo- or heterocyclic groups Cy.

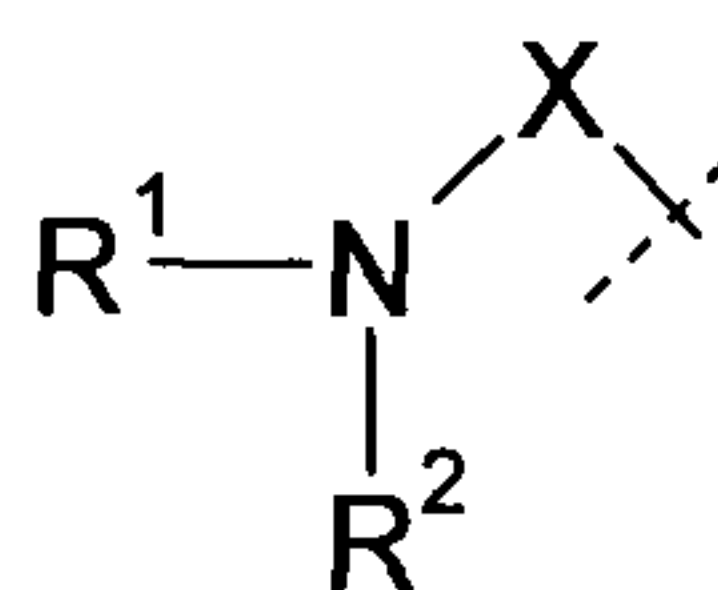
In the event that the alkylene bridge is linked to a group Cy via a single bond, Cy is preferably selected from the group consisting of C₃₋₇-cycloalkyl, cyclo-C₃₋₆-alkyleneimino, piperazinyl, 1H-imidazole, thienyl and phenyl, particularly C₃₋₆-cycloalkyl, pyrrolidinyl, piperidinyl and piperazinyl, which may be substituted as specified, and particularly the N atoms may be substituted by C₁₋₄-alkyl in each case.

In the event that the alkylene bridge is linked to a group Cy via a common C atom forming a spirocyclic ring system, Cy is preferably selected from the group consisting of C₃₋₇-cycloalkyl, aza-C₄₋₈-cycloalkyl, oxa-C₄₋₈-cycloalkyl, 2,3-dihydro-1H-quinazolin-4-one, particularly cyclopentyl and cyclohexyl, which may be substituted as specified, and particularly the N atoms may be substituted by C₁₋₄-alkyl in each case.

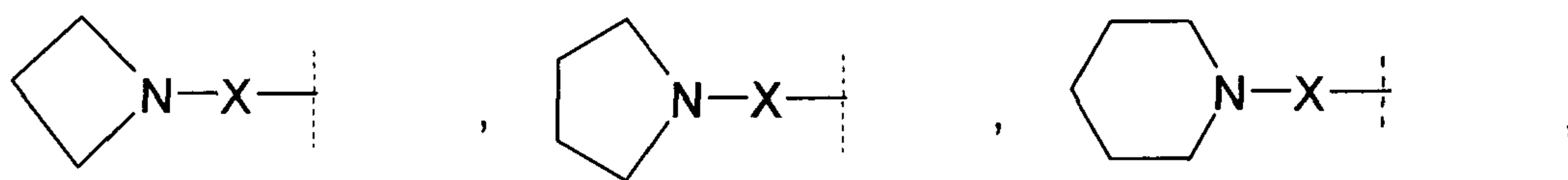
In the event that the alkylene bridge is linked to a group Cy via two common adjacent C and/or N atoms forming a fused bicyclic ring system, Cy is preferably selected from the group consisting of C₄₋₇-cycloalkyl, aza-C₄₋₇-cycloalkyl, phenyl, thienyl, particularly phenyl and pyrrolidinyl, which may be substituted as specified, and particularly the N atoms may be substituted by C₁₋₄-alkyl in each case.

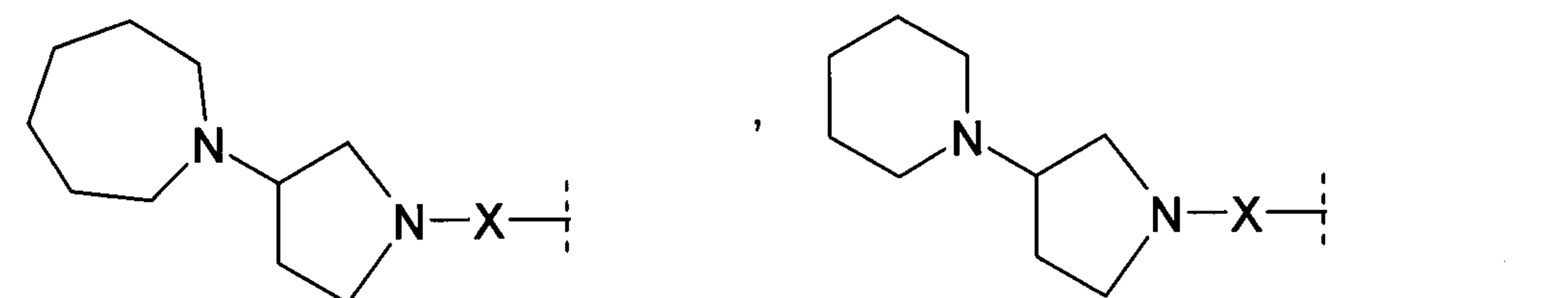
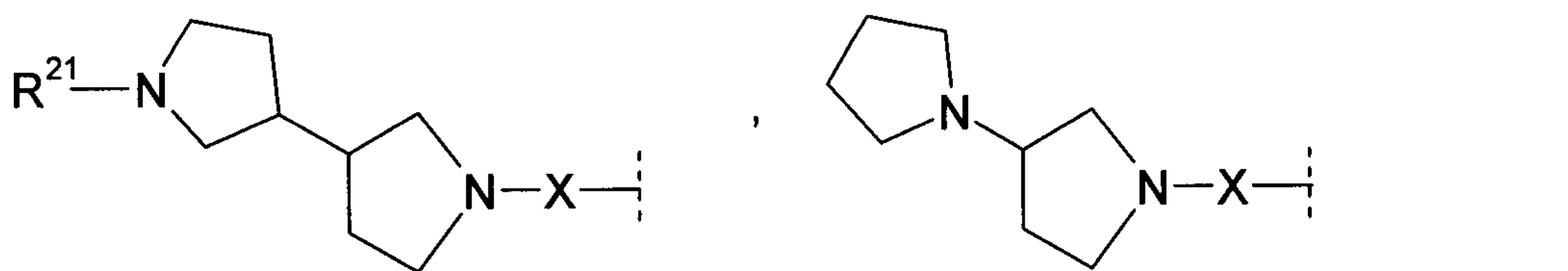
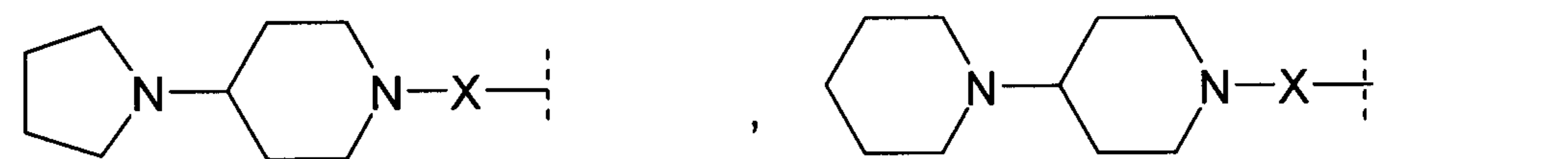
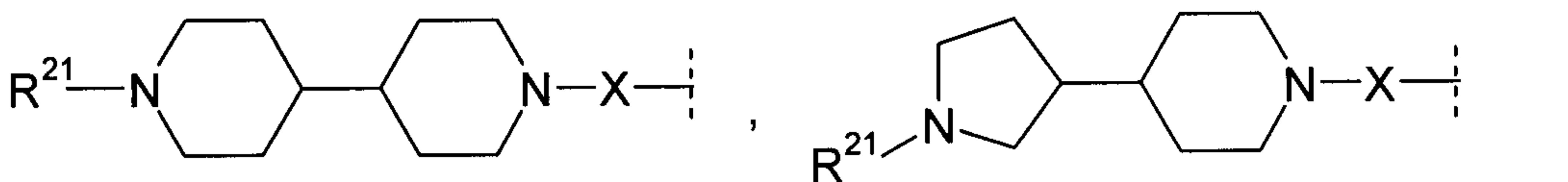
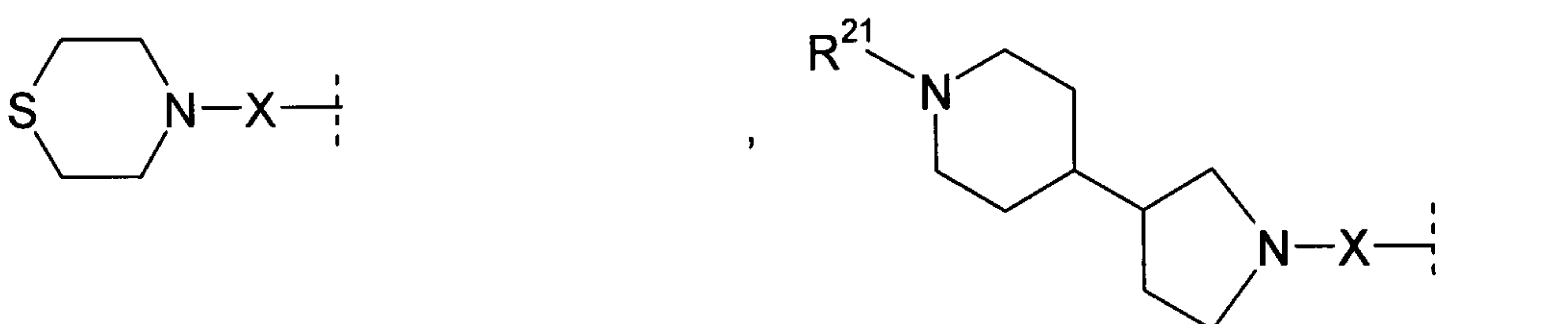
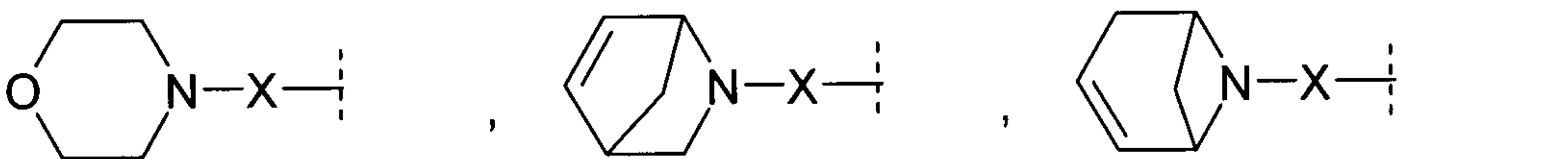
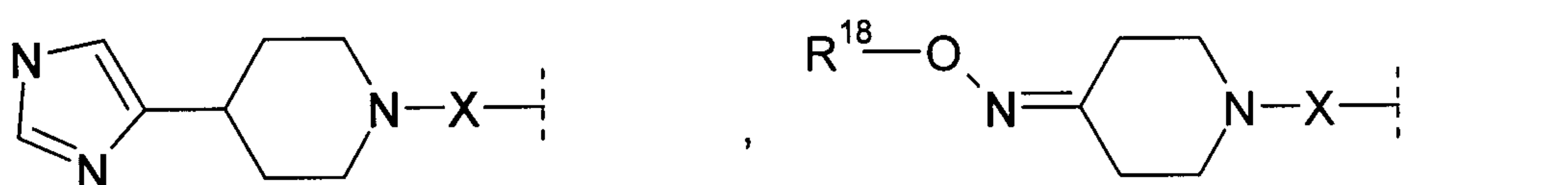
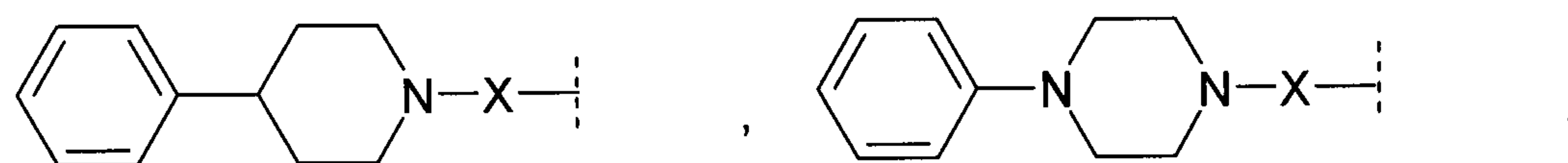
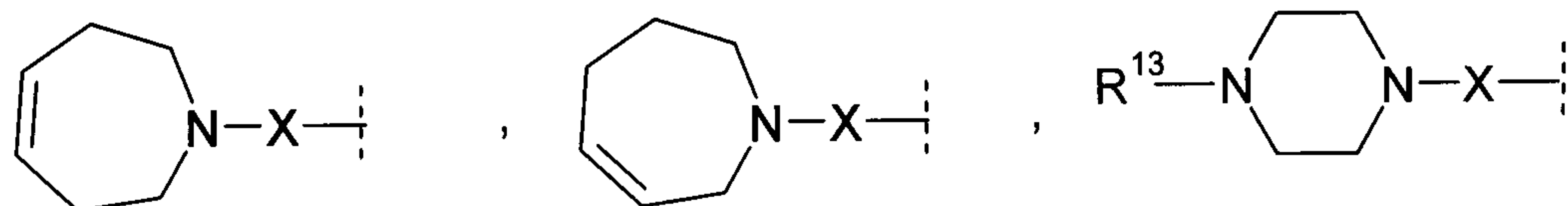
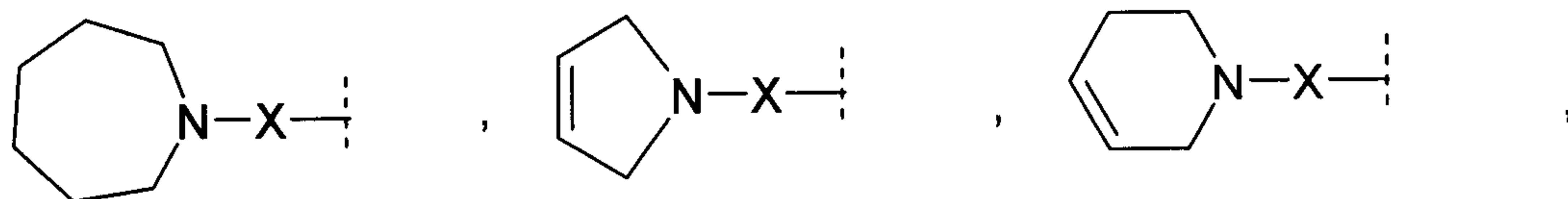
In the event that the alkylene bridge is linked to a group Cy via three or more C and/or N atoms forming a bridged ring system, Cy preferably denotes C₄₋₈-cycloalkane or aza-C₄₋₈-cycloalkane, particularly cyclopentane, cyclohexane, pyrrolidine or piperidine, while the N atoms may be substituted by C₁₋₄-alkyl in each case.

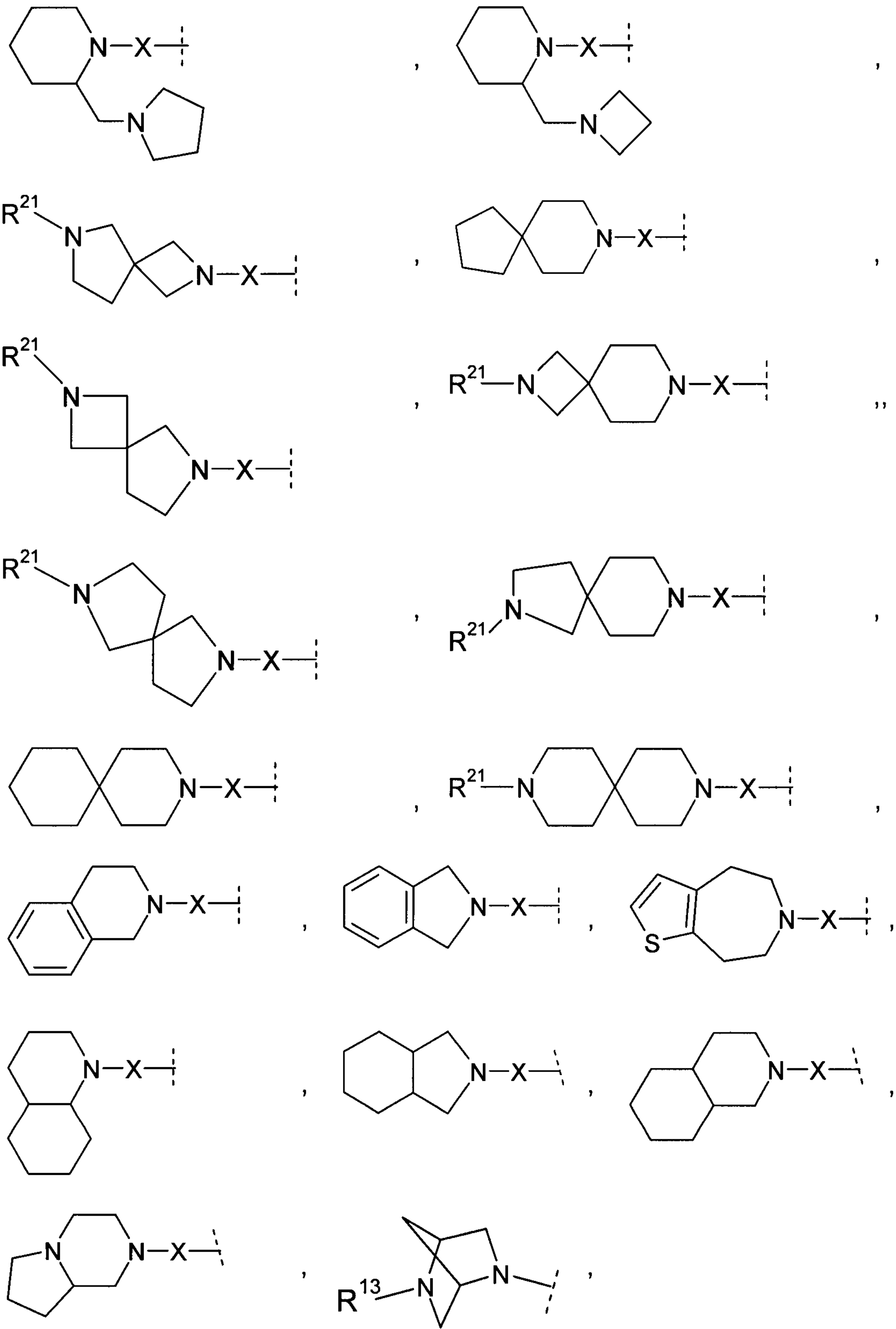
Particularly preferably the group

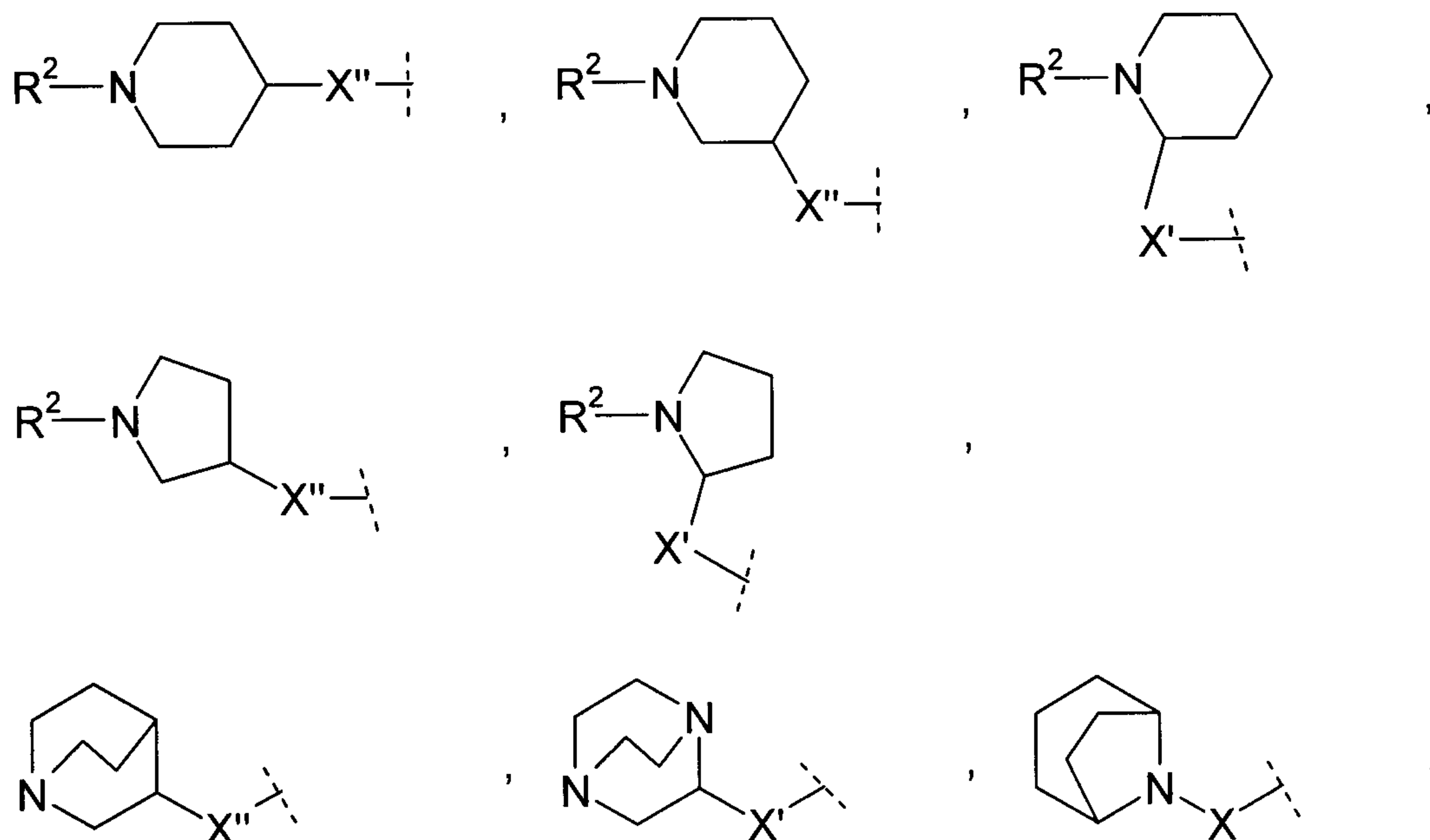


is defined according to one of the following partial formulae









while in the heterocycle formed by the group R^1R^2N - one or more H atoms may be replaced by R^{14} and/or a H atom may be substituted by Cy defined as C_{3-7} -cycloalkyl, which may be mono- or polysubstituted by R^{20} , particularly by F, hydroxy, C_{1-3} -alkyl, CF_3 , C_{1-3} -alkyloxy, OCF_3 or hydroxy- C_{1-3} -alkyl, and the ring connected to the

5 heterocycle formed by the group R^1R^2N - may be mono- or polysubstituted at one or more C atoms by R^{20} , and in the case of a phenyl ring may also additionally be monosubstituted by nitro and

10 X' , X'' independently of one another denote a single bond or C_{1-3} -alkylene and

in the event that the group Y is linked to X' or X'' via a C atom, may also denote $-C_{1-3}$ -alkylene-O-, $-C_{1-3}$ -alkylene-NH- or $-C_{1-3}$ -alkylene-N(C_{1-3} -alkyl)-, and

15

X'' additionally also denotes $-O-C_{1-3}$ -alkylene, $-NH-C_{1-3}$ -alkylene or $-N(C_{1-3}$ -alkyl)- C_{1-3} -alkylene and

in the event that the group Y is linked to X'' via a C atom, also denotes

20 $-NH-$, $-N(C_{1-3}$ -alkyl)- or $-O-$,

while in the meanings given for X' , X'' hereinbefore in each case a C atom

may be substituted by R^{10} , preferably by a hydroxy, ω -hydroxy- C_{1-3} -alkyl, ω -(C_{1-4} -alkoxy)- C_{1-3} -alkyl and/or C_{1-4} -alkoxy group, and/or one or two C atoms in each case may be substituted by one or two identical or different substituents selected from C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, C_{4-7} -cycloalkenyl and C_{4-7} -cycloalkenyl- C_{1-3} -alkyl, while two alkyl and/or alkenyl substituents may be joined together, forming a carbocyclic ring system, and

in X' , X'' independently of one another in each case one or more C atoms may be mono- or polysubstituted by F and/or in each case one or two C atoms independently of one another may be monosubstituted by Cl or Br and

wherein R^2 , R^{10} , R^{13} , R^{14} , R^{18} , R^{20} , R^{21} and X have the meanings given above and hereinafter.

Preferably X' , X'' independently of one another represent a single bond or C_{1-3} -alkylene and in the event that the group Y is linked to X' or X'' via a C atom, may also denote $-C_{1-3}$ -alkylene-O-, $-C_{1-3}$ -alkylene-NH or $-C_{1-3}$ -alkylene-N(C_{1-3} -alkyl), and X'' additionally also denotes $-O-C_{1-3}$ -alkylene, $-NH-C_{1-3}$ -alkylene or $-N(C_{1-3}$ -alkyl)- C_{1-3} -alkylene and in the event that the group Y is linked to X'' via a C atom, X'' also denotes $-NH$, $-N(C_{1-3}$ -alkyl)- or $-O-$. Particularly preferably X' , X'' independently of one another represent a single bond or methylene and in the event that the group Y is linked to X' or X'' via a C atom, also represent $-CH_2-O-$, $-CH_2-NH-$ or $-CH_2-N(C_{1-3}$ -alkyl)-, and in the event that the group Y is linked to X'' via a C atom, X'' also denotes $-NH-$, $-N(C_{1-3}$ -alkyl) or $-O-$.

In the preferred and particularly preferred meanings of R^1R^2N - listed above the following definitions of the substituent R^{14} are preferred: F, Cl, Br, C_{1-4} -alkyl, C_{2-4} -alkenyl, C_{2-4} -alkynyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, hydroxy, hydroxy- C_{1-3} -alkyl, C_{1-4} -alkoxy, ω -(C_{1-4} -alkoxy)- C_{1-3} -alkyl, C_{1-4} -alkyl-carbonyl, carboxy, C_{1-4} -alkoxy-carbonyl, hydroxy-carbonyl- C_{1-3} -alkyl, C_{1-4} -alkoxycarbonyl- C_{1-3} -alkyl, C_{1-4} -alkoxy-carbonylamino, C_{1-4} -alkoxy-carbonylamino- C_{1-3} -alkyl, amino, C_{1-4} -alkyl-amino, C_{3-7} -cycloalkyl-amino, $N-(C_{3-7}$ -cycloalkyl)- $N-(C_{1-4}$ -alkyl)-amino, di-(C_{1-4} -alkyl)-amino,

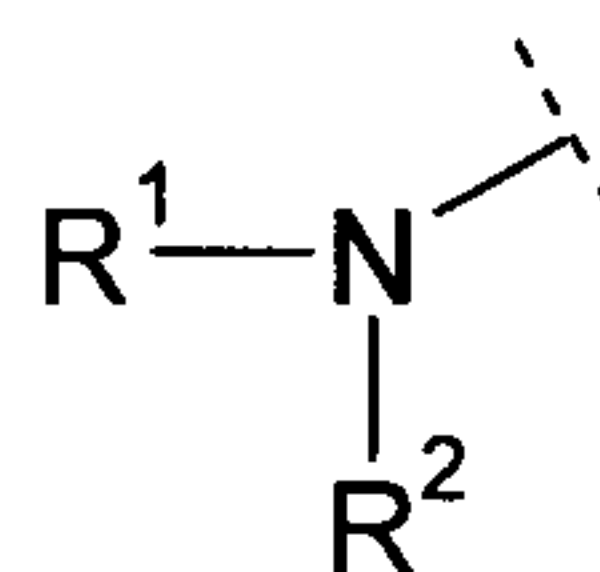
amino-C₁₋₃-alkyl, C₁₋₄-alkyl-amino-C₁₋₃-alkyl, C₃₋₇-cycloalkyl-amino-C₁₋₃-alkyl, N-(C₃₋₇-cycloalkyl)-N-(C₁₋₄-alkyl)-amino-C₁₋₃-alkyl, di-(C₁₋₄-alkyl)-amino-C₁₋₃-alkyl, cyclo-C₃₋₆-alkyleneimino-C₁₋₃-alkyl, aminocarbonyl, C₁₋₄-alkyl-amino-carbonyl, C₃₋₇-cycloalkyl-amino-carbonyl, N-(C₃₋₇-cycloalkyl)-N-(C₁₋₄-alkyl)-amino-carbonyl, di-(C₁₋₄-alkyl)-

5 amino-carbonyl, pyridinyl-oxy, pyridinyl-amino, pyridinyl-C₁₋₃-alkyl-amino. In the above meanings of the group R¹⁴ one or more C atoms may be mono- or polysubstituted by F and/or one or two C atoms independently of one another may be monosubstituted by Cl or Br, and in particular alkyl groups may be mono- or polysubstituted by fluorine.

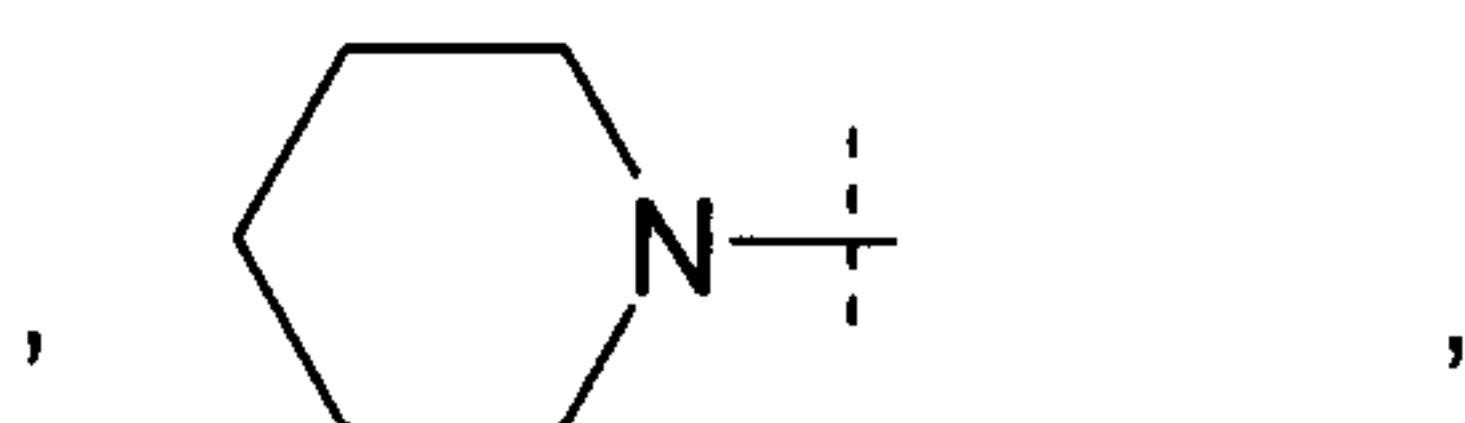
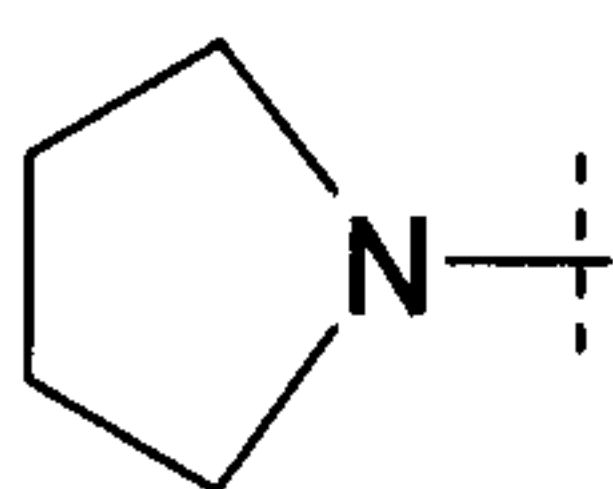
10 Most particularly preferred meanings of the substituent R¹⁴ are F, Cl, C₁₋₄-alkyl, C₃₋₆-cycloalkyl-C₁₋₃-alkyl, hydroxy, hydroxy-C₁₋₃-alkyl, C₁₋₄-alkoxy, C₁₋₄-alkoxy-C₁₋₃-alkyl, amino-C₁₋₃-alkyl, C₁₋₄-alkyl-amino-C₁₋₃-alkyl, C₃₋₇-cycloalkyl-amino-C₁₋₃-alkyl, N-(C₃₋₇-cycloalkyl)-N-(C₁₋₄-alkyl)-amino-C₁₋₃-alkyl, di-(C₁₋₄-alkyl)-amino-C₁₋₃-alkyl, cyclo-C₃₋₆-alkyleneimino-C₁₋₃-alkyl, aminocarbonyl and pyridylamino. In the above meanings of
15 the group R¹⁴ one or more C atoms, and particularly alkyl groups, may be mono- or polysubstituted by fluorine.

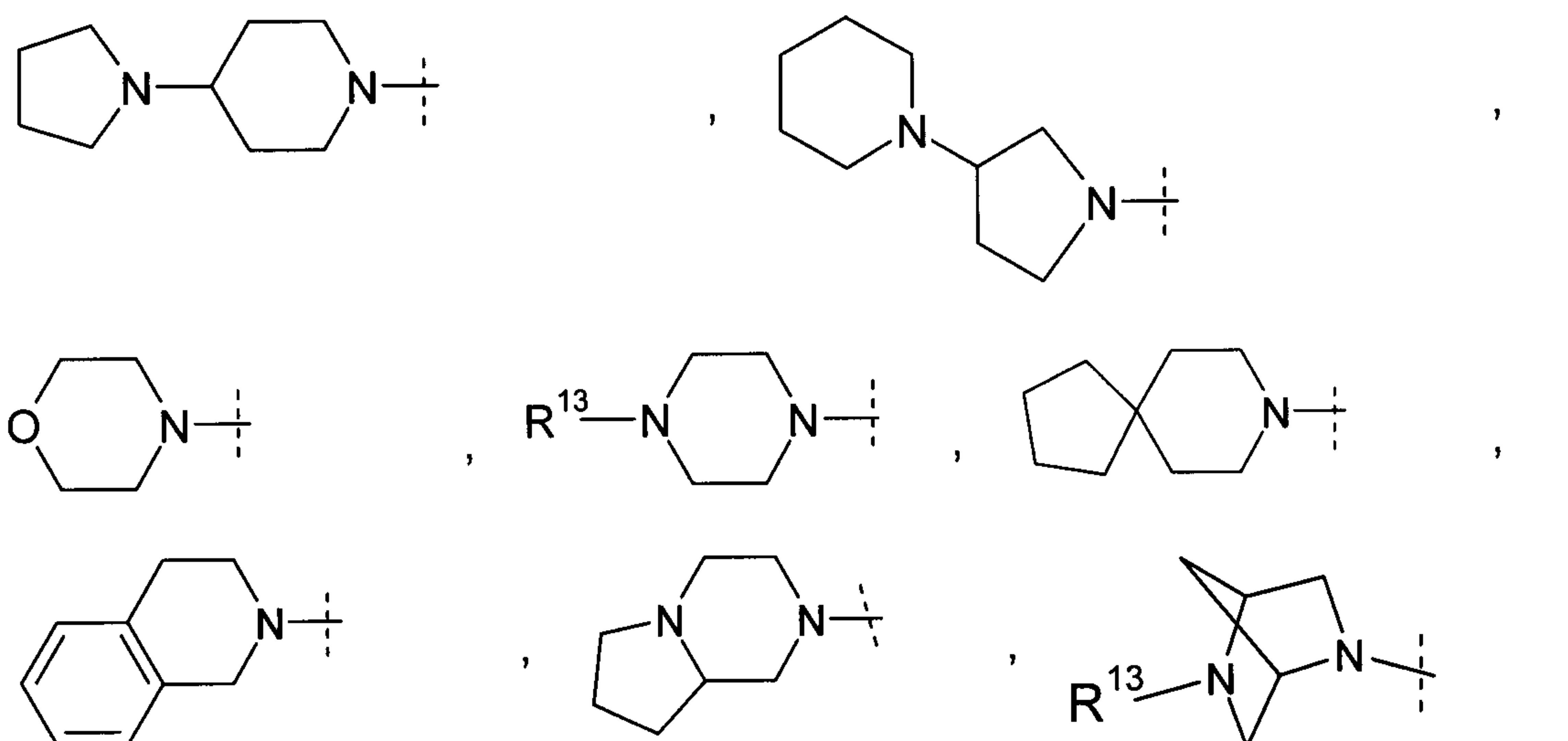
If in the heterocycle formed by the group R¹R²N- an H atom is replaced by Cy representing C₃₋₇-cycloalkyl, which may be mono- or polysubstituted by R²⁰, Cy
20 preferably denotes C₃₋₆-cycloalkyl and R²⁰ preferably denotes F, hydroxy, C₁₋₃-alkyl, CF₃, C₁₋₃-alkyloxy, OCF₃ or hydroxy-C₁₋₃-alkyl, particularly F, hydroxy, methyl, methoxy, CF₃, OCF₃ or hydroxymethyl. Particularly preferred meanings of Cy are C₃₋₆-cycloalkyl and 1-hydroxy-C₃₋₅-cycloalkyl.

Most particularly preferably the group



25 is defined according to one of the following partial formulae





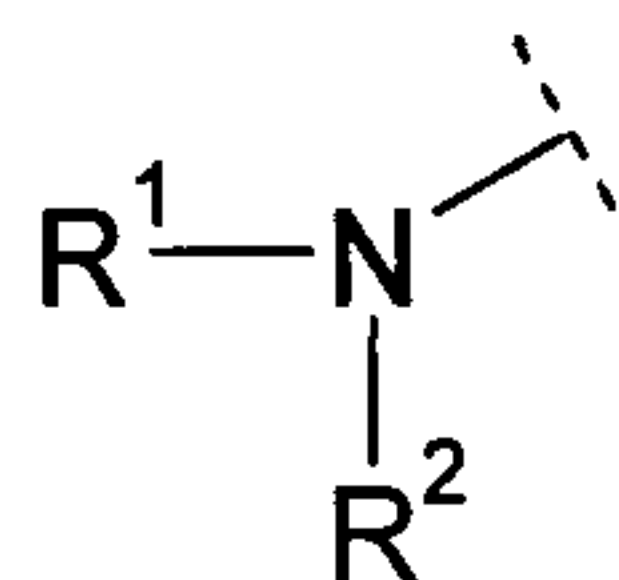
while in the heterocycle formed by the group R^1R^2N - one or more H atoms may be replaced by R^{14} and/or an H atom may be replaced by Cy representing C_{3-6} -cycloalkyl, which may be mono- or polysubstituted by R^{20} , particularly by F, hydroxy, C_{1-3} -alkyl, CF_3 , C_{1-3} -alkyloxy, OCF_3 or hydroxy- C_{1-3} -alkyl, particularly preferably by F, hydroxy, methyl, methoxy, CF_3 , OCF_3 or hydroxymethyl, and

the ring connected to the heterocycle formed by the group R^1R^2N - may be mono- or polysubstituted, preferably monosubstituted at one or more C atoms by R^{20} , or in the case of a phenyl ring may also additionally be monosubstituted by nitro and

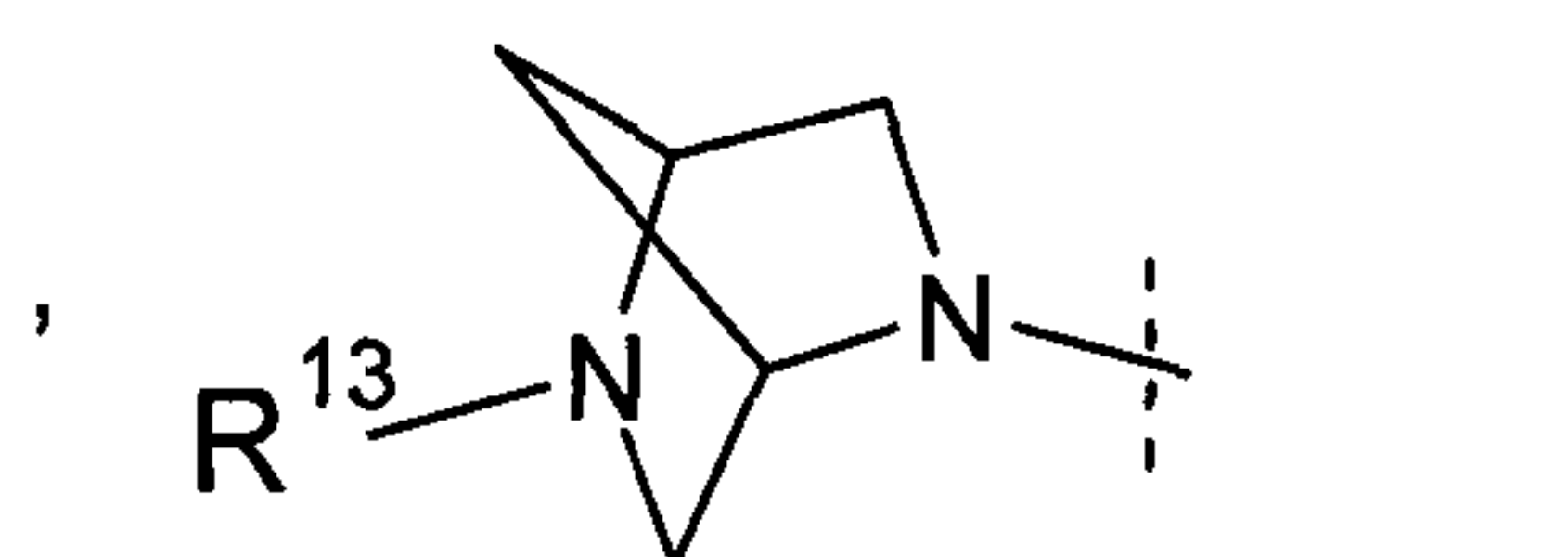
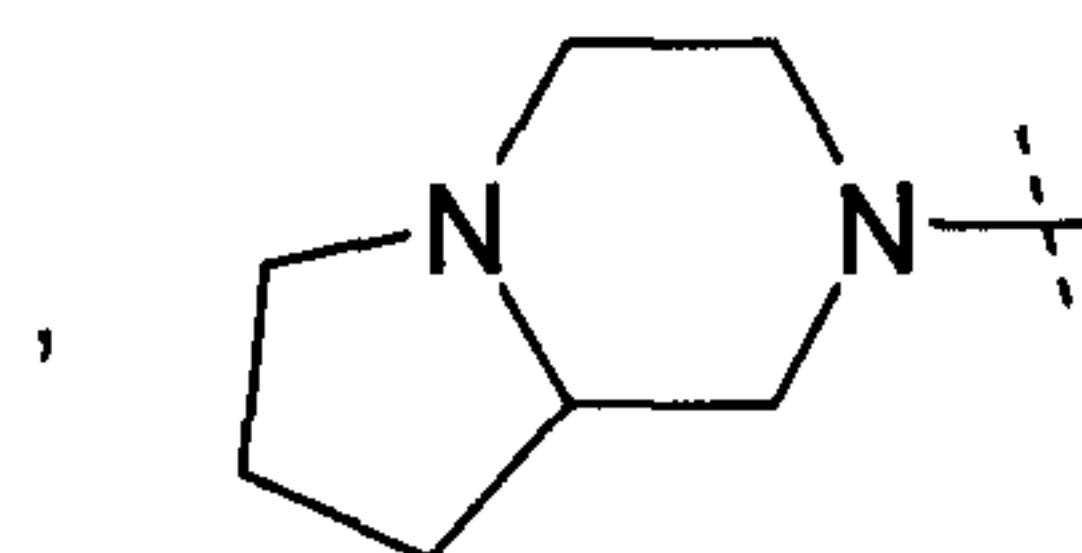
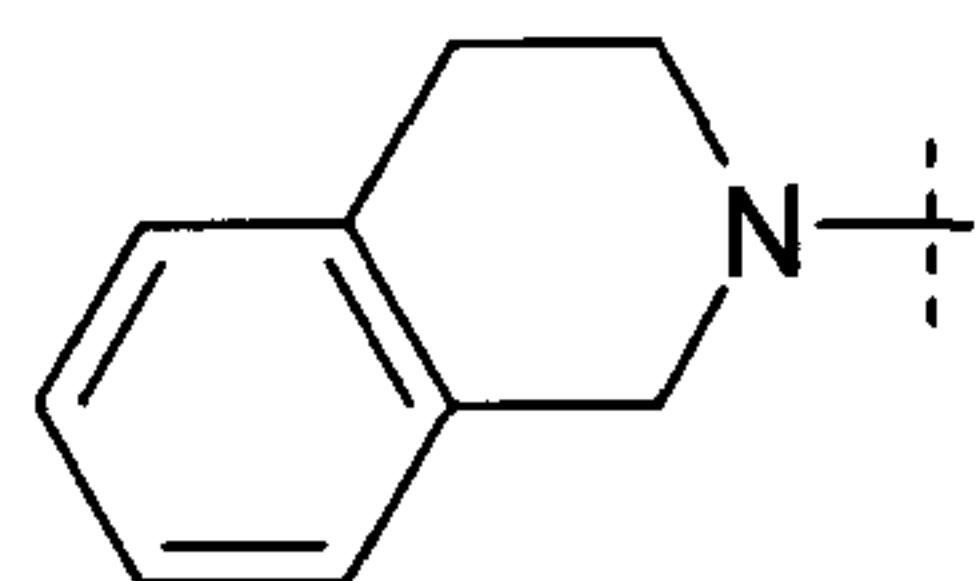
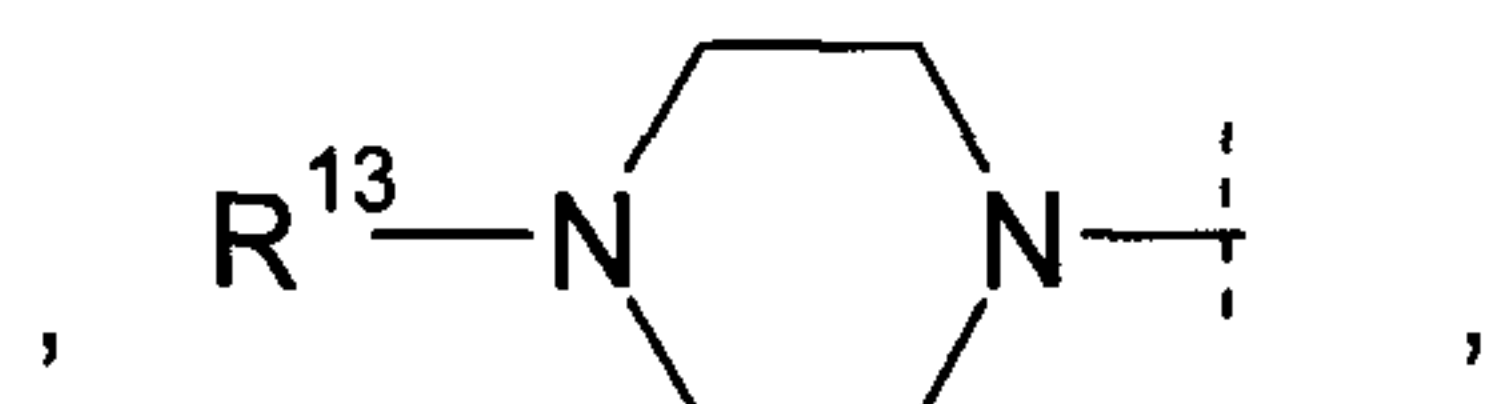
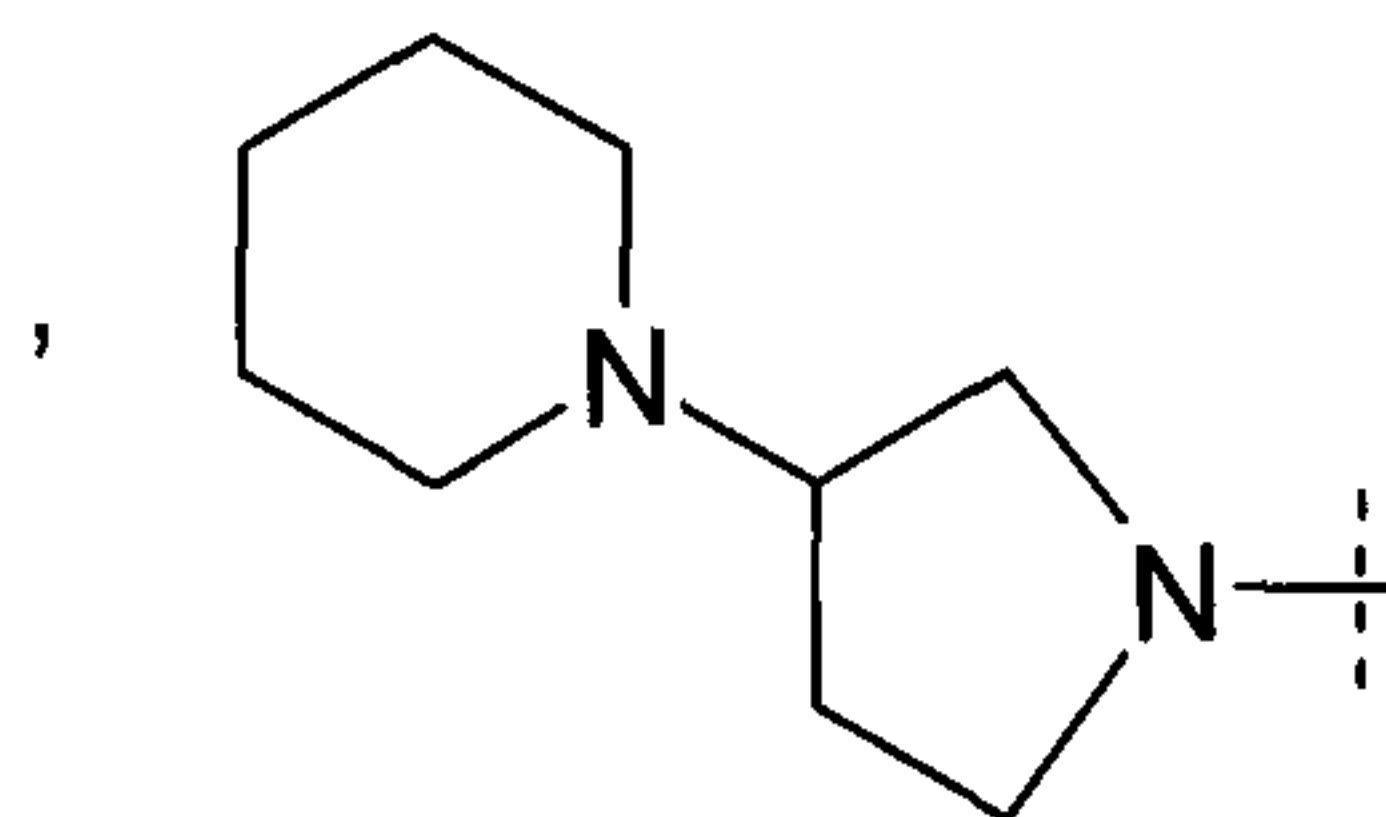
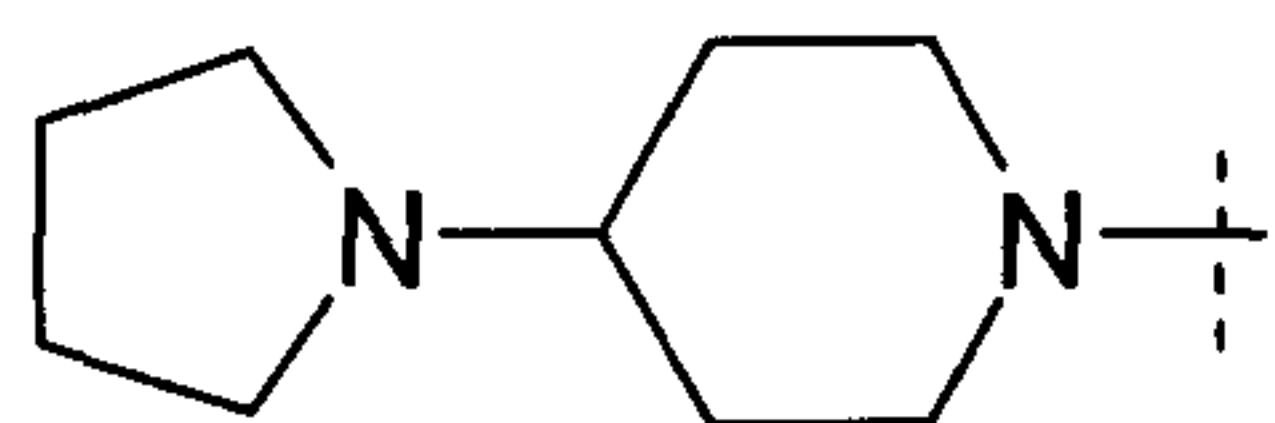
R^{14} in each case independently of one another denotes F, Cl, C_{1-4} -alkyl, C_{3-6} -cycloalkyl- C_{1-3} -alkyl, hydroxy, hydroxy- C_{1-3} -alkyl, C_{1-4} -alkyloxy, C_{1-4} -alkoxy- C_{1-3} -alkyl, pyridylamino or aminocarbonyl, while in each case one or more C atoms, particularly alkyl groups may additionally be mono- or polysubstituted by F; most particularly preferably denotes methyl, ethyl, propyl, trifluoromethyl, hydroxy, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1-hydroxy-1-methyl-ethyl, 1-hydroxycyclopropyl, methoxy, ethoxy, methoxymethyl, pyridylamino or aminocarbonyl; and

R^{13} is as hereinbefore defined, particularly denotes H or C_{1-3} -alkyl.

Compounds according to the invention, particularly those which may be described by formula Ic or Id, are also preferred, wherein the group

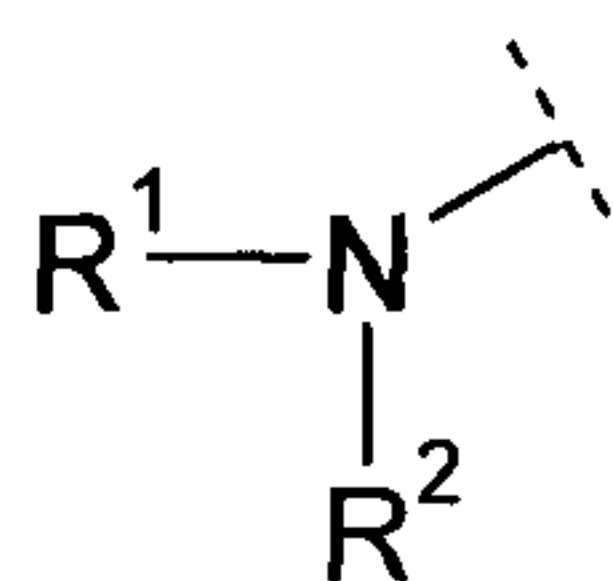


is defined according to one of the following partial formulae

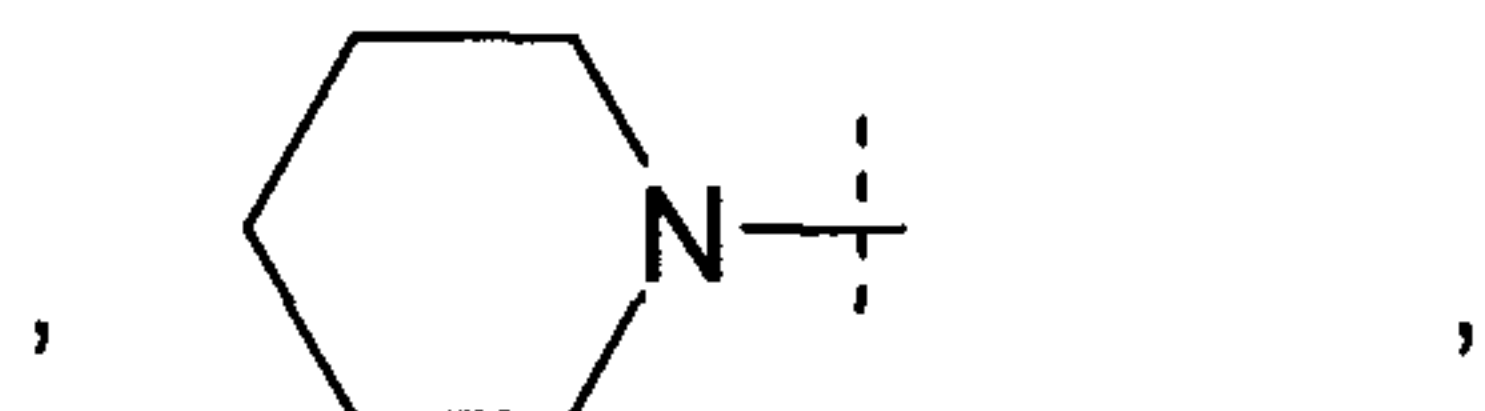
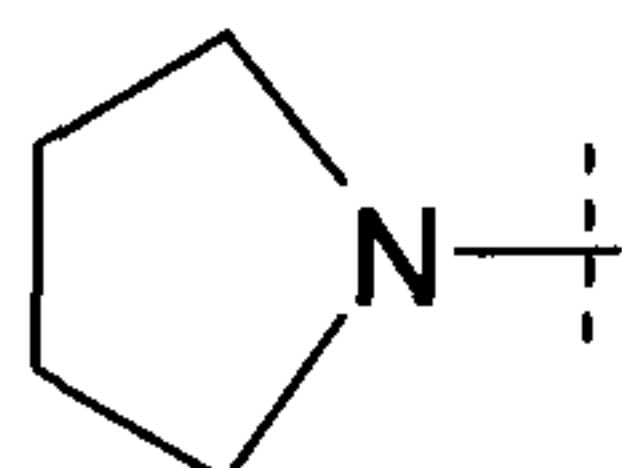


wherein H atoms may be replaced as specified hereinbefore and the ring connected to the heterocycle formed by the group $\text{R}^1\text{R}^2\text{N}-$ may be mono- or polysubstituted, preferably monosubstituted at one or more C atoms by R^{20} , in the case of a phenyl ring may also additionally be monosubstituted by nitro, or

wherein the group



is defined according to one of the following partial formulae



wherein at least one H atom of the heterocycle formed by the group $\text{R}^1\text{R}^2\text{N}-$ is substituted by a substituent selected from hydroxy, hydroxy- C_{1-3} -alkyl, 1-hydroxy- C_{3-5} -

cycloalkyl, C₁₋₄-alkyloxy and C₁₋₄-alkoxy-C₁₋₃-alkyl, and wherein additionally one or more, preferably one or two H atoms of the heterocycle formed by the group R¹R²N- may be replaced by the substituent R¹⁴ defined hereinbefore and/or an H atom of the heterocycle formed by the group R¹R²N- may be replaced by Cy representing C₃₋₆-
5 cycloalkyl, which may be mono- or polysubstituted by R²⁰, particularly by F, hydroxy, C₁₋₃-alkyl, CF₃, C₁₋₃-alkyloxy, OCF₃ or hydroxy-C₁₋₃-alkyl, particularly preferably by F, hydroxy, methyl, methoxy, CF₃, OCF₃ or hydroxymethyl.

10 Preferably X denotes a C₁₋₆-alkylene bridge, wherein

- a -CH₂ group not adjacent to the N atom of the R¹R²N- group may be replaced by -CH=CH- or -C≡C- and/or
- a -CH₂- group not adjacent to the N atom of the R¹R²N group may be replaced by -O-, -S-, -CO- or -NR⁴-, particularly preferably by -O-, -S- or -NR⁴-, in such a
15 way that in each case two O, S or N atoms or an O and an S atom are not directly joined together,

while R⁴ may be attached to Y, forming a heterocyclic ring system with one another,

20 while the bridge X may be connected to R¹ including the N atom linked to R¹ and X, forming a heterocyclic group, and

two C atoms or a C and an N atom of the alkylene bridge may be joined together by an additional C₁₋₄-alkylene bridge, and

25

a C atom may be substituted by R¹⁰ and/or one or two C atoms may each be substituted by one or two identical or different substituents selected from C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₃-alkyl, C₄₋₇-cycloalkenyl and C₄₋₇-cycloalkenyl-C₁₋₃-alkyl, while two alkyl and/or alkenyl substituents may be
30 joined together forming a carbocyclic ring system, particularly a cyclopropyl, cyclobutyl or cyclopentyl group.

Preferably, in the group X a -CH₂- group directly adjacent to the group R¹R²N- is not replaced by -O-, -S-, -(SO)-, -(SO₂)-, -CO- or -NR⁴-.

If in the group X one or two $-\text{CH}_2-$ groups independently of one another are replaced by $-\text{O}-$, $-\text{S}-$, $-(\text{SO})-$, $-(\text{SO}_2)-$, $-\text{CO}-$ or $-\text{NR}^4-$, these groups are preferably spaced from the $\text{R}^1\text{R}^2\text{N}-$ group by an alkylene bridge with at least 2 C atoms.

5

If in the group X two $-\text{CH}_2$ groups independently of one another are replaced by $-\text{O}-$, $-\text{S}-$, $-(\text{SO})-$, $-(\text{SO}_2)-$, $-\text{CO}-$ or $-\text{NR}^4-$, these groups are preferably separated from one another by an alkylene bridge with at least 2 C atoms.

- 10 If in the group X a $-\text{CH}_2-$ group of the alkylene bridge is replaced according to the invention, this $-\text{CH}_2-$ group is preferably not directly connected to a heteroatom, a double or triple bond.

- 15 Preferably the alkylene bridge X, X' or X'' has no imino groups or at most only one imino group. The position of the imino group within the alkylene bridge X, X' or X'' is preferably selected so that no aminal function is formed together with the amino group NR^1R^2 or another adjacent amino group, or two N atoms are not adjacent to one another.

- 20 If in X, X' or X'' a C atom is substituted, preferred substituents are selected from among the C_{1-4} -alkyl, C_{2-4} -alkenyl, C_{2-4} -alkynyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, hydroxy, ω -hydroxy- C_{1-3} -alkyl, ω -(C_{1-4} -alkoxy)- C_{1-3} -alkyl and C_{1-4} -alkoxy groups. Moreover in X, X' or X'' a C atom may be disubstituted and/or one or two C atoms may be mono- or disubstituted, while preferred substituents are selected from among
- 25 C_{1-4} -alkyl, C_{2-4} -alkenyl, C_{2-4} -alkynyl, C_{3-7} -cycloalkyl and C_{3-7} -cycloalkyl- C_{1-3} -alkyl, and two C_{1-4} -alkyl- and/or C_{2-4} -alkenyl substituents may also be joined together to form a saturated or monounsaturated carbocyclic ring.

- 30 Advantageously the group X representing C_{2-4} -alkylenoxy, particularly $-\text{CH}_2\text{CH}_2\text{CH}_2\text{O}-$, has no hydroxy substituent.

Most particularly preferred substituents of one or two C atoms in X, X' or X'' are selected from methyl, ethyl, n-propyl, i-propyl, cyclopropyl, cyclopropylmethyl, while

two alkyl substituents on one C atom may also be joined together to form a carbocyclic ring.

In the definitions of the substituents of the bridges X, X' and/or X'' and the definitions of the bridges X, X' and/or X'' themselves mentioned above and hereinafter, in each case one or more C atoms may additionally be mono- or polysubstituted by F and/or in each case one or two C atoms independently of one another may additionally be monosubstituted by Cl or Br.

10 If in the group X, X' or X'' one or more C atoms are substituted by a hydroxy and/or C₁₋₄-alkoxy group, the substituted C atom is preferably not immediately adjacent to another heteroatom.

Preferably X denotes an unbranched C₁₋₄-alkylene bridge and

15

in the event that the group Y is linked to X via a C atom, it also denotes -CH₂-CH=CH-, -CH₂-C≡C-, C₂₋₄-alkylenoxy or C₂₋₄-alkylene-NR⁴, particularly C₂₋₄-alkylenoxy or C₂₋₄-alkylene-NR⁴-,

20 while R⁴ may be connected to Y, forming a heterocyclic ring system,

while the bridge X may be connected to R¹, including the N atom connected to R¹ and X, forming a heterocyclic group, and

25 in X a C atom may be substituted by R¹⁰ and/or one or two C atoms may be substituted in each case by one or two identical or different substituents selected from C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₃-alkyl, C₄₋₇-cycloalkenyl and C₄₋₇-cycloalkenyl-C₁₋₃-alkyl, particularly selected from C₁₋₃-alkyl, while two alkyl and/or alkenyl substituents may be joined together, forming a
30 carbocyclic ring system, and

in the above-mentioned groups and radicals one or more C atoms may be mono- or polysubstituted by F and/or one or two C atoms independently of one another may be monosubstituted by Cl or Br and

R^1 , R^4 and R^{10} are as hereinbefore defined.

The substituent R^{10} preferably denotes a hydroxy, hydroxy- C_{1-3} -alkyl, C_{1-4} -alkoxy-
5 C_{1-3} -alkyl and/or C_{1-4} -alkoxy group, particularly hydroxy, hydroxymethyl or methoxy.

Preferred meanings of the substituent R^4 are H, C_{1-6} -alkyl and C_{3-6} -alkenyl.

Particularly preferably R^4 denotes H or C_{1-3} -alkyl. If R^4 is connected to Y forming a
heterocyclic ring system, particularly preferred meanings of R^4 are C_{2-6} -alkyl and C_{2-6} -
10 alkenyl.

In the event that R^4 is linked to Y forming a heterocyclic ring system, Y preferably
denotes phenyl and R^4 preferably denotes C_{2-6} -alkyl or C_{2-6} -alkenyl. Preferred
heterocyclic ring systems are indole, dihydroindole, quinoline, dihydroquinoline,
15 tetrahydroquinoline and benzoxazole.

Particularly preferably X denotes $-CH_2-$, $-CH_2-CH_2-$ or $-CH_2-CH_2-CH_2-$ and

in the event that the group Y is linked to X via a C atom (of the group Y), it may also
20 denote $-CH_2-CH=CH-$, $-CH_2-C\equiv C-$, $-CH_2-CH_2-O-$, $-CH_2-CH_2-CH_2-O-$ or
 $-CH_2-CH_2-NR^4-$ or $-CH_2-CH_2-CH_2-NR^4-$, particularly $-CH_2-CH_2-O-$, $-CH_2-CH_2-CH_2-O-$,
 $-CH_2-CH_2-NR^4-$ or $-CH_2-CH_2-CH_2-NR^4-$,

while R^4 may be connected to Y, forming a heterocyclic ring system,
25

while the bridge X may be connected to R^1 , including the N atom linked to R^1 and X,
forming a heterocyclic group, and

in X a C atom may be substituted by R^{10} and/or one or two C atoms independently of
30 one another may each be substituted by one or two identical or different C_{1-4} -alkyl
groups, while two alkyl groups may be joined together, forming a carbocyclic ring
system; preferably in X one or two C atoms may each be substituted independently of
one another by one or two identical or different C_{1-3} -alkyl groups, while two alkyl
groups may be joined together to form a carbocyclic ring system, particularly a

cyclopropyl group, and

in each case one or more C atoms may be mono- or polysubstituted by F and/or in each case one or two C atoms independently of one another may be monosubstituted
5 by Cl or Br, preferably in each case one or more C atoms may be mono- or polysubstituted by F.

Most particularly preferably, if the group Y is linked to X via a C atom (of the group Y), X denotes -CH₂-, -CH₂-CH₂-, -CH₂-CH₂-CH₂-, 1,1-cyclopropylene, -CH₂-CH₂-O-,
10 -CH₂-CH₂-CH₂-O-, -CH₂-CH₂-NR⁴- or -CH₂-CH₂-CH₂-NR⁴-, while these groups are unsubstituted or the alkylene bridge is substituted as specified, preferably mono- or disubstituted by methyl and/or fluorine.

The group R⁴ preferably only denotes vinyl if R⁴ is linked to Y forming a heterocyclic
15 ring system.

The group X preferably does not comprise a carbonyl group.

If Y denotes a fused bicyclic ring system, a preferred definition of the group X is a
20 single bond, -CH₂-, -CH₂-CH₂- or -CH₂-CH₂-CH₂-, particularly a single bond, -CH₂- or -CH₂-CH₂-, most particularly preferably -CH₂ or -CH₂-CH₂-, which may be substituted as specified.

In the event that the index b has the value 1, X particularly preferably denotes -CH₂-
25 or 1,1-cyclopropylene. X representing -CH₂- may be linked to Y forming a bicyclic ring system as specified, while for this purpose the -CH₂ bridge is substituted by C₂₋₃-alkyl. The -CH₂- bridge may comprise one or two substituents independently of one another selected from the group comprising C₁₋₃-alkyl, while two alkyl groups may be joined together, forming a carbocyclic ring system.

30 In the event that the index b has the value 0, X particularly preferably denotes -CH₂-CH₂-, -CH₂-CH₂-O-, -CH₂-CH₂-CH₂-O-, -CH₂-CH₂-NR⁴- or -CH₂-CH₂-CH₂-NR⁴-, while the above-mentioned groups may comprise one or two substituents independently of

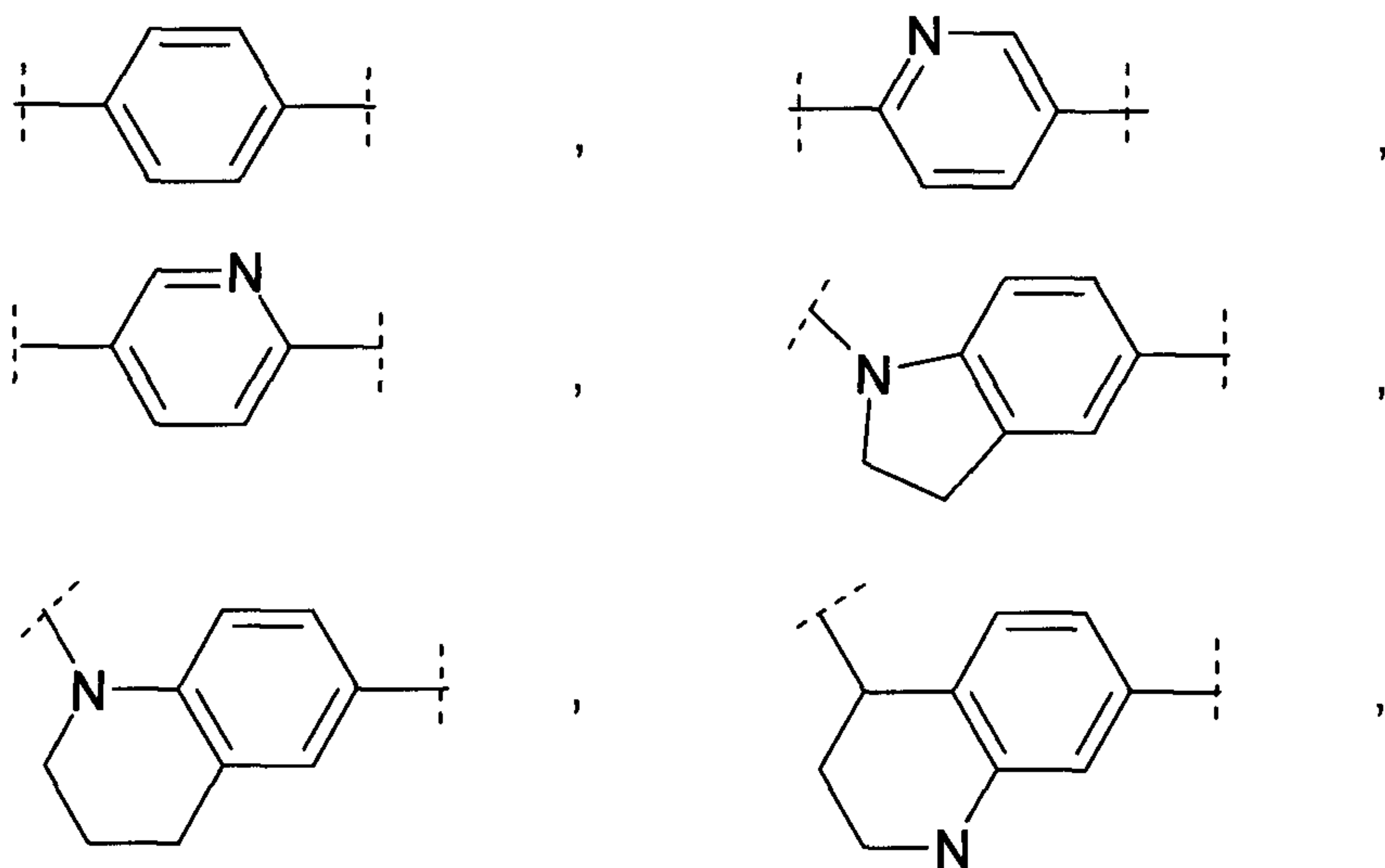
one another selected from the group comprising C₁₋₃-alkyl, while two alkyl groups may be joined together, forming a ring system.

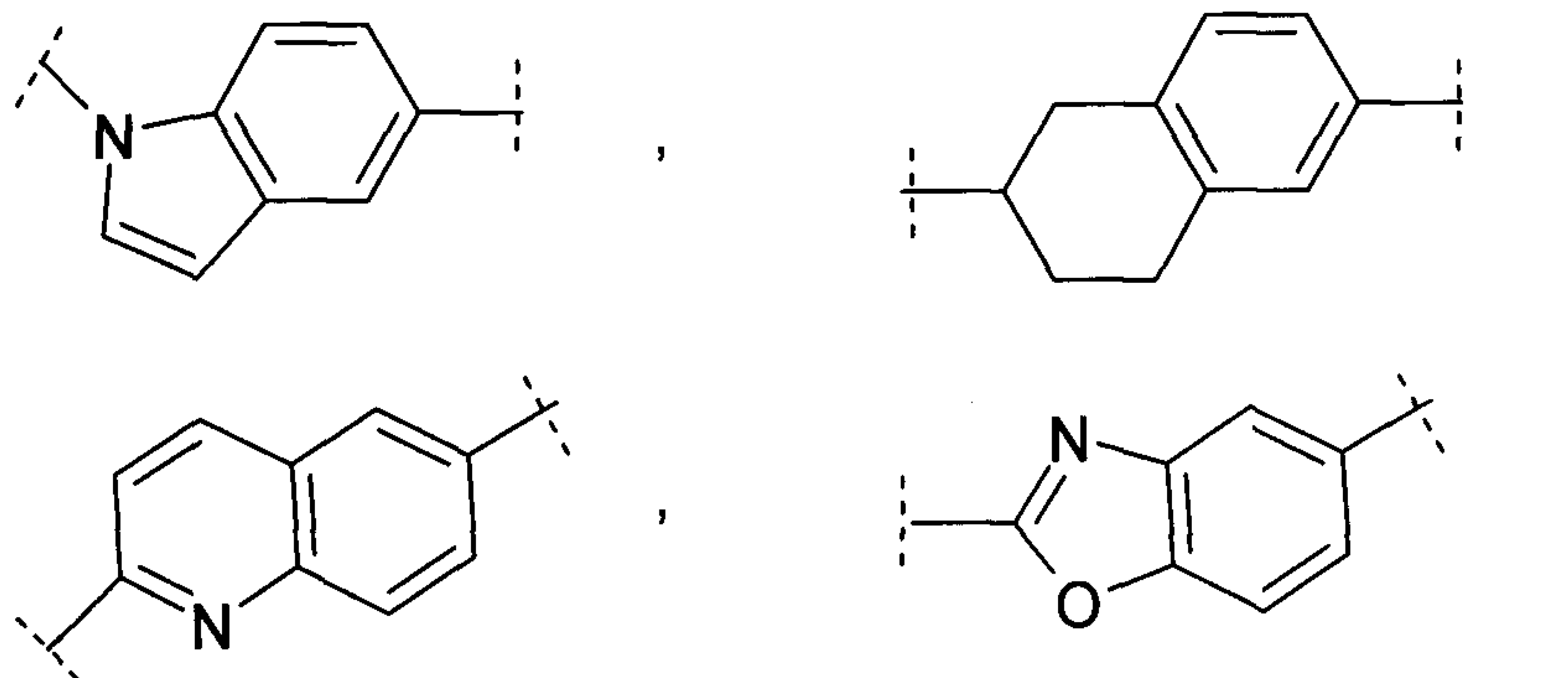
The bridge X may also represent a single bond. Preferably the bridge X only forms a single bond if Y denotes a bicyclic ring system. Also preferably, the bridge X may only represent a single bond if the compound according to the invention can be described according to one of the partial formulae Ia, Ib or Id, particularly according to one of the partial formulae Ia or Ib, most particularly preferably the partial formula Ib.

- 10 The group Y preferably has a meaning selected from among the bivalent cyclic groups phenyl, pyridinyl, naphthyl, tetrahydronaphthyl, indolyl, dihydroindolyl, quinolinyl, dihydroquinolinyl, tetrahydroquinolinyl, isoquinolinyl, dihydroisoquinolinyl, tetrahydro-isoquinolinyl or benzoxazolyl, while the above-mentioned cyclic groups may be mono- or polysubstituted at one or more C atoms by R²⁰, in the case of a phenyl group may also additionally be monosubstituted by nitro, and/or at one or more N atoms may be substituted by R²¹. R¹ may be connected to Y and/or X may be connected to Y as specified hereinbefore.

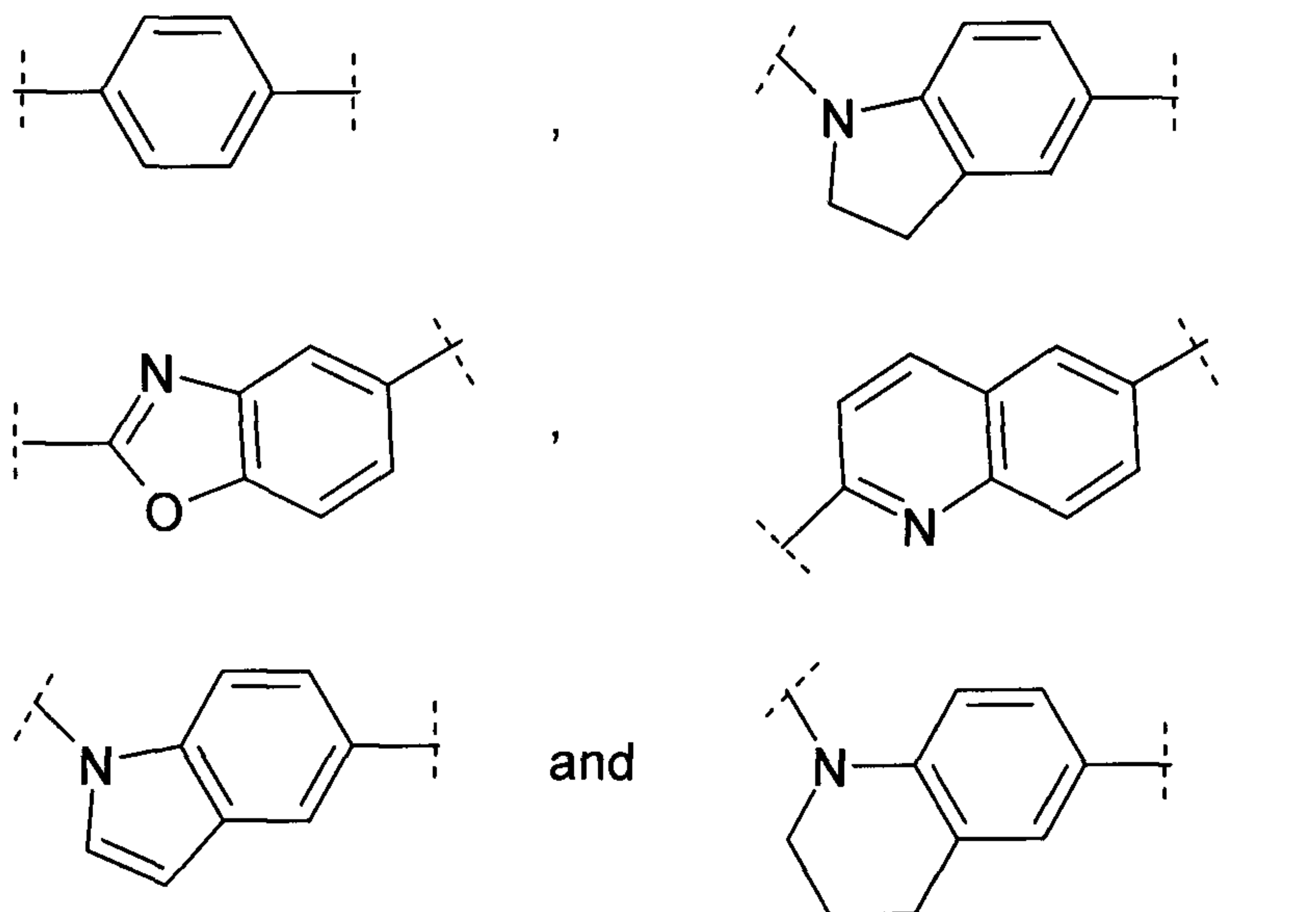
If the group Y denotes phenyl or pyridinyl, the bridges X and Z are preferably connected to the group Y in the para position.

Particularly preferably the group Y has a meaning selected from among the bivalent cyclic groups





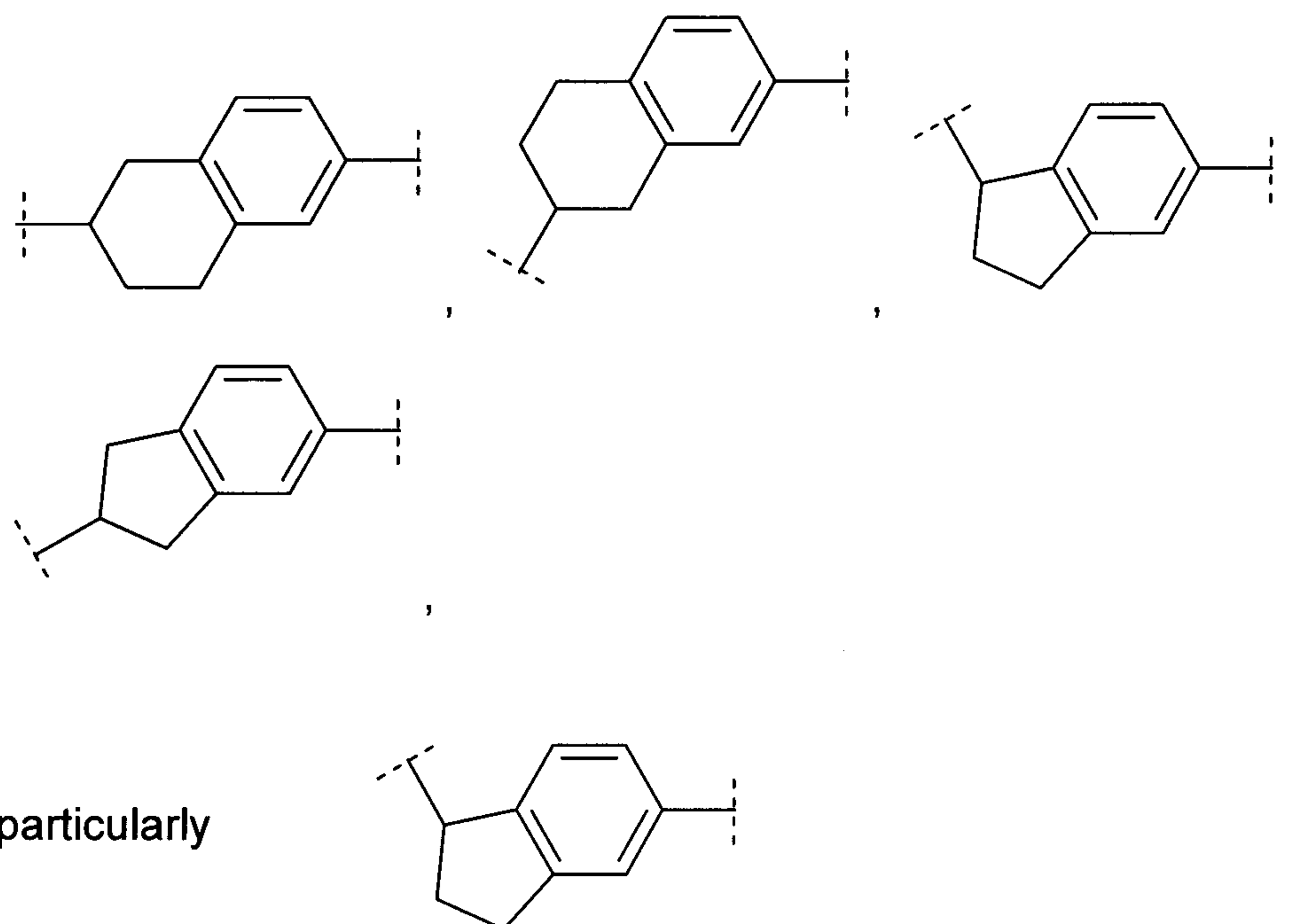
and in particular Y has one of the following meanings



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while the above-mentioned cyclic groups may be mono- or polysubstituted by R^{20} at one or more C atoms, in the case of a phenyl group may also additionally be monosubstituted by nitro, and/or one or more NH groups may be substituted by R^{21} .

- 10 The group Y may be linked to the group X forming a carbo- or heterocyclic group fused to Y. Preferred definitions of the groups -X-Y- linked to another are selected from the list comprising



- 5 while in the above-mentioned bicyclic groups the phenyl ring may be mono- or polysubstituted by R^{20} or may also additionally be monosubstituted by nitro, and the saturated carbocyclic ring may be mono- or disubstituted by C_{1-3} -alkyl.

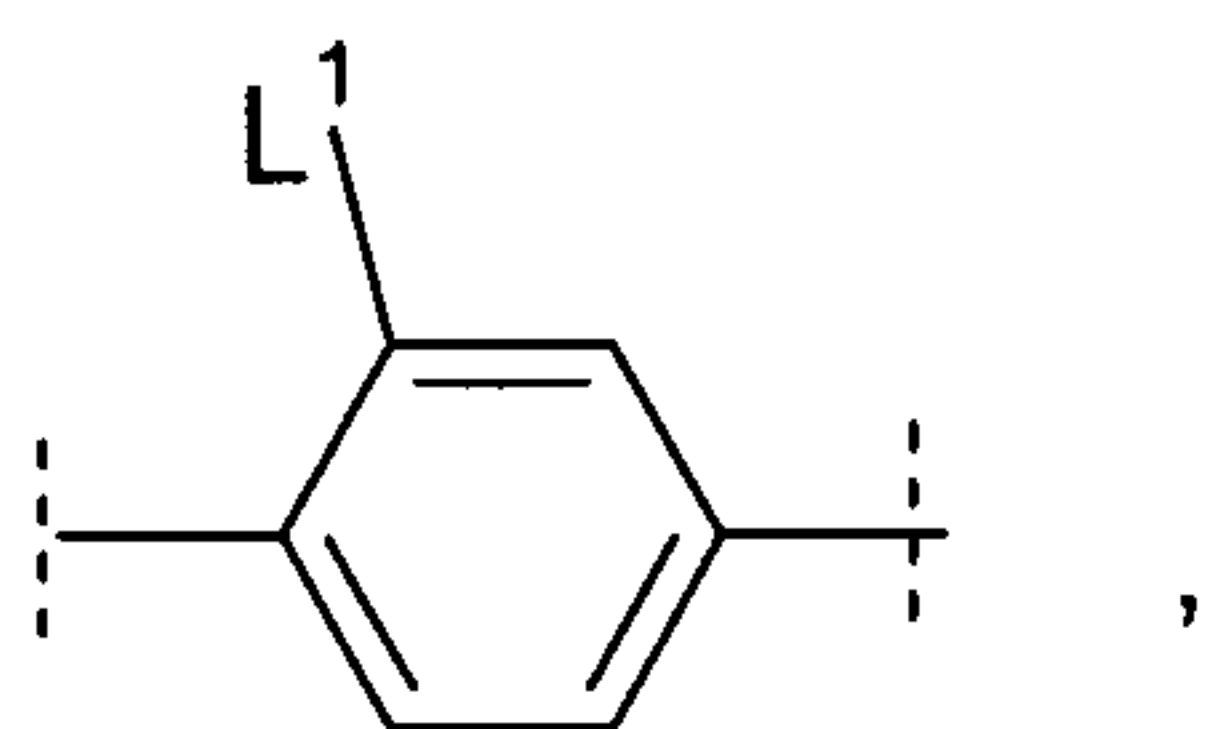
The group Y is preferably unsubstituted or mono- or disubstituted.

10

- Particularly preferred substituents R^{20} of the group Y are selected from the group consisting of fluorine, chlorine, bromine, cyano, nitro, C_{1-4} -alkyl, C_{2-6} -alkenyl, hydroxy, hydroxy- C_{1-3} -alkyl, C_{1-4} -alkoxy, trifluoromethyl, trifluoromethoxy, C_{2-4} -alkynyl, C_{1-4} -alkoxycarbonyl, C_{1-4} -alkoxy-1,3-alkyl, C_{1-4} -alkoxy-carbonylamino, amino, C_{1-4} -alkyl-amino, di- $(C_{1-4}$ -alkyl)-amino, aminocarbonyl, C_{1-4} -alkyl-amino-carbonyl, di- $(C_{1-4}$ -alkyl)-amino-carbonyl, $-CH=N-OH$ and $-CH=N-O-C_{1-4}$ -alkyl.
- 15

- Most particularly preferred substituents R^{20} of the group Y are selected from the group consisting of fluorine, chlorine, bromine, iodine, cyano, C_{1-3} -alkyl, C_{1-3} -alkoxy, C_{1-4} -alkoxycarbonyl, trifluoromethyl, trifluoromethoxy, amino, or, in the case of a phenyl ring, additionally nitro.
- 20

Most particularly preferably the group Y denotes substituted phenylene of the partial formula



wherein L^1 has one of the meanings given hereinbefore for R^{20} , preferably F, Cl, Br, I, CH₃, CF₃, OCH₃, OCF₃, methoxycarbonyl, ethoxycarbonyl, CN, amino or NO₂, or denotes H.

A preferred meaning of the group A is aryl or heteroaryl.

10 Preferably the group A is selected from among the cyclic groups phenyl, pyridinyl or naphthyl, which may be mono- or polysubstituted at one or more C atoms by R^{20} , and in the case of a phenyl ring may also additionally be monosubstituted by nitro, while the group A does not contain an amino group as substituent in the ortho position to the bridge W.

15

Preferably the group A has no substituent selected from the group consisting of C₁₋₄-alkyl-sulphonylamino, C₁₋₄-alkyl-carbonyl-amino, C₁₋₄-alkyl-sulphonylamino-C₁₋₃-alkyl, C₁₋₄-alkyl-carbonyl-amino-C₁₋₃-alkyl and phenylcarbonylamino. Other non-preferred substituents are aminocarbonyl, C₁₋₄-alkylaminocarbonyl, di-(C₁₋₄-alkyl)-aminocarbonyl, cyclo-C₃₋₆-alkyl-amino-carbonyl, cyclo-C₃₋₆-alkyleneimino-carbonyl, cyclo-C₃₋₆-alkyleneimino-C₂₋₄-alkyl-aminocarbonyl, phenyl-amino-carbonyl, aminocarbonyl-C₁₋₃-alkyl, C₁₋₄-alkylaminocarbonyl-C₁₋₃-alkyl, di-(C₁₋₄-alkyl)-aminocarbonyl-C₁₋₃-alkyl, cyclo-C₃₋₆-alkyl-amino-carbonyl-C₁₋₃-alkyl, cyclo-C₃₋₆-alkyleneimino-carbonyl-C₁₋₃-alkyl, cyclo-C₃₋₆-alkyleneimino-C₂₋₄-alkyl-aminocarbonyl-C₁₋₃-alkyl and phenyl-amino-carbonyl-C₁₋₃-alkyl.

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Moreover, the group A preferably has no substituent selected from the group consisting of nitro and tert-butyloxycarbonylamino in the ortho position to the bridge W in each case.

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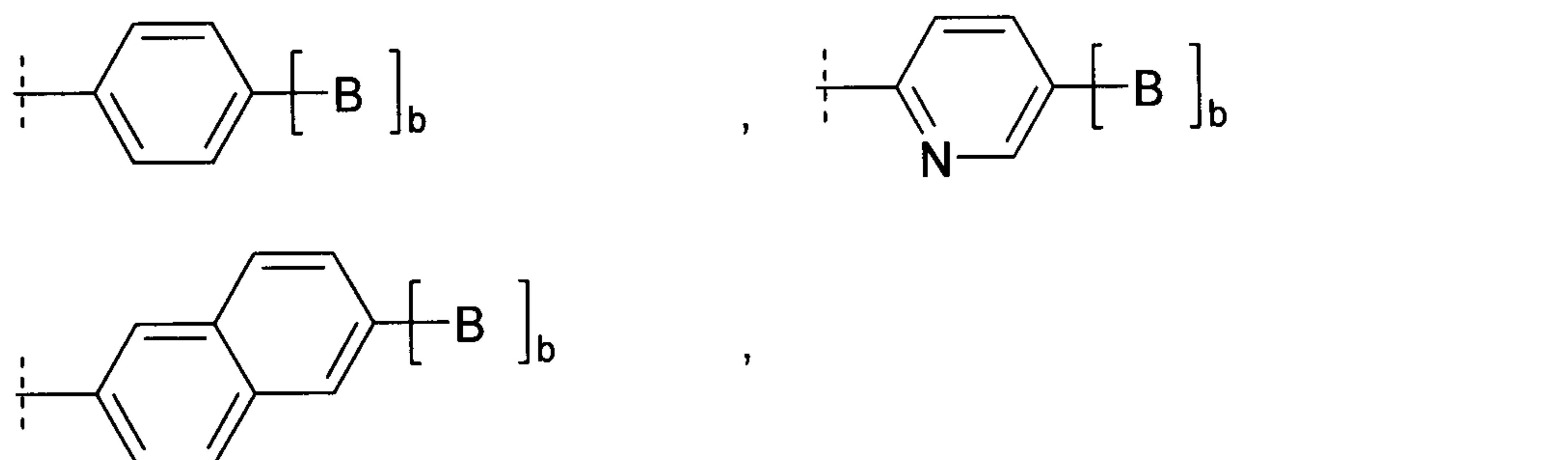
If b has the value 0, the group A is preferably mono-, di- or trisubstituted.

If b has the value 1, the group A is preferably unsubstituted or mono- or disubstituted.

If b has the value 1 and the group A is monosubstituted, the substituent is preferably

5 in the ortho position relative to the group W.

Most particularly preferably A is one of the following groups



10 while the groups listed may be mono- or polysubstituted by R^{20} as specified, while if the index b has the value 0, the group A does not have an amino group as substituent in the ortho position to the bridge W. The definitions phenyl and pyridyl given for the group A are preferred when b has the value 1.

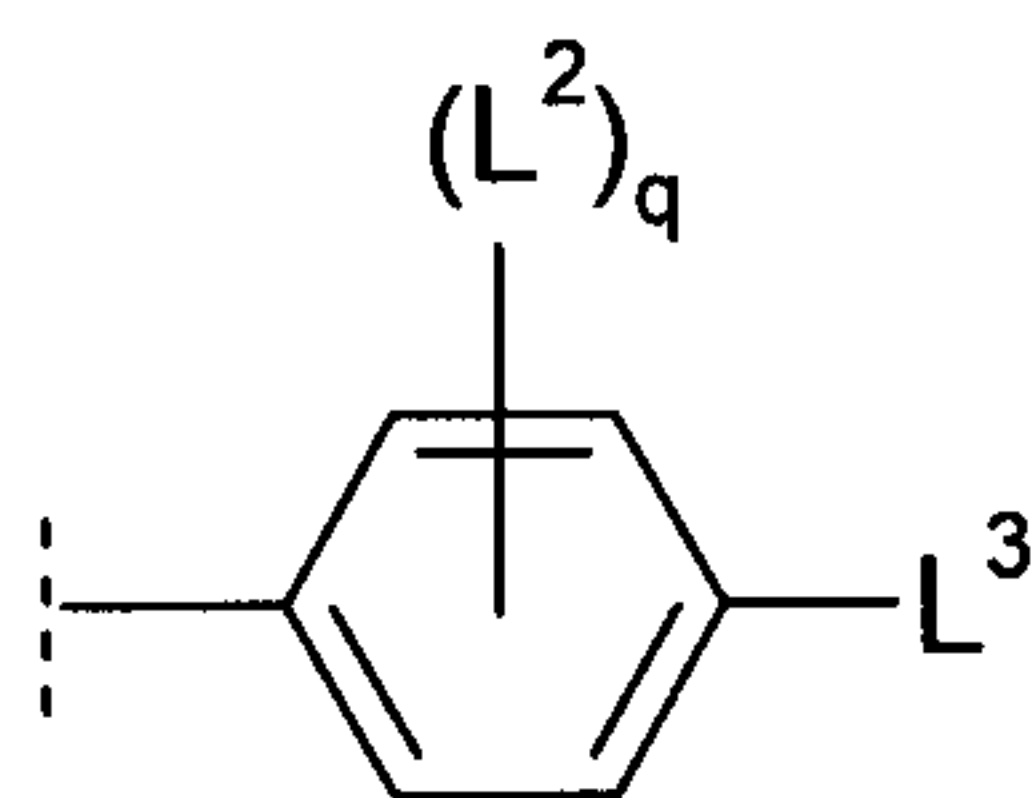
15 Particularly preferred substituents R^{20} of the group A are selected from among fluorine, chlorine, bromine, cyano, C_{1-4} -alkyl, C_{2-6} -alkenyl, -CHO, hydroxy, hydroxy- C_{1-3} -alkyl, C_{1-4} -alkoxy, trifluoromethyl, trifluoromethoxy, C_{2-4} -alkynyl, carboxy, C_{1-4} -alkoxycarbonyl, C_{1-4} -alkoxy- C_{1-3} -alkyl, C_{1-4} -alkoxy-carbonylamino, amino, C_{1-4} -alkyl-amino, di-(C_{1-4} -alkyl)-amino, cyclo- C_{3-6} -alkyleneimino, aminocarbonyl, C_{1-4} -alkyl-amino-carbonyl, di-(C_{1-4} -alkyl)-amino-carbonyl, -CH=N-OH and -CH=N-O- C_{1-4} -alkyl.

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Most particularly preferred substituents R^{20} of the group A are selected from among fluorine, chlorine, bromine, cyano, C_{1-4} -alkyl, C_{1-4} -alkoxy, trifluoromethyl, trifluoromethoxy, carboxy, C_{1-4} -alkoxycarbonyl, C_{1-4} -alkyl-amino- and di-(C_{1-4} -alkyl)-amino.

25

If b has the value 0, a particularly preferred meaning of the group A is substituted phenyl of the partial formula



wherein

L^2 has one of the meanings given for R^{20} or denotes H, preferably F, Cl, Br, I, CH₃, CF₃, OCH₃, OCF₃, CN or NO₂; particularly preferably F, Cl or Br;

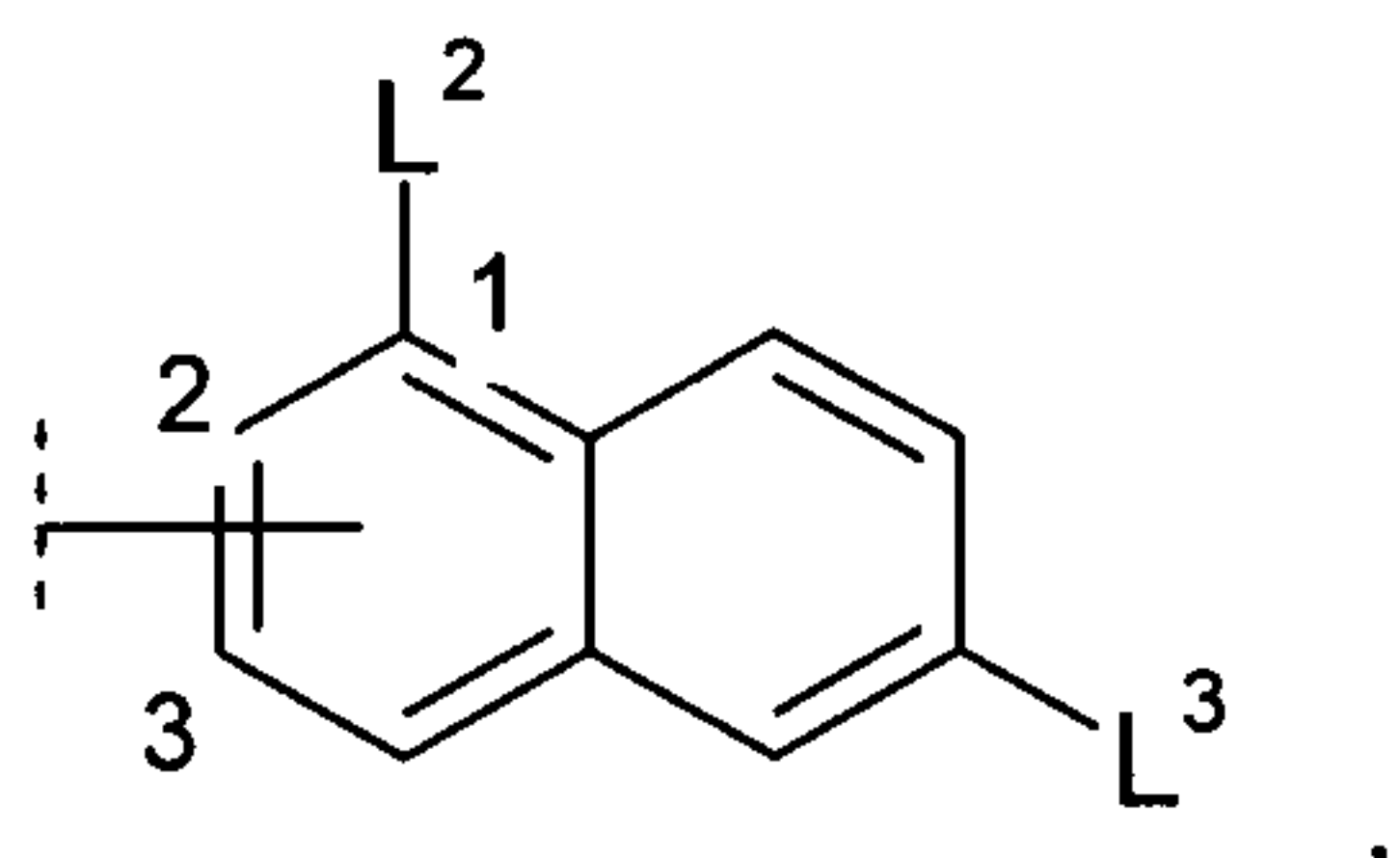
L^3 has one of the meanings given for R^{20} or denotes H, preferably F, Cl, Br, I, CF₃, OCF₃, CN, NO₂, C₁₋₄-alkyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₃-alkyl, C₁₋₄-alkoxy, C₃₋₇-cycloalkyl-O, C₃₋₇-cycloalkyl-C₁₋₃-alkoxy, -COO-C₁₋₄-alkyl or -COOH; particularly preferably F, Cl, Br, C₁₋₄-alkyl, CF₃, methoxy, OCF₃, CN or NO₂; most particularly preferably Cl, Br, CF₃ or NO₂;

q has the value 0, 1 or 2.

with the proviso that the phenyl group may only be at most monosubstituted by nitro.

Particularly preferably A is substituted phenyl according to the above partial formula, wherein q denotes 1 or 2 and/or at least one substituent L^2 is in the meta position to the substituent L^3 .

Another preferred partial formula for A, particularly where b has the value 0, is



wherein the bond to the group W is effected via the C atom in position number 2 or 3 and L^2 and L^3 are as hereinbefore defined.

In the event that b has the value 1, a preferred meaning of the group B is aryl or heteroaryl, which may be substituted as specified.

Preferred definitions of the group B are selected from the group consisting of phenyl, pyridyl, thienyl and furanyl. Particularly preferably, the group B denotes phenyl. The group B defined as specified may be mono- or polysubstituted by R^{20} , a phenyl group may additionally also be monosubstituted by nitro. Preferably the group B is mono-, di- or trisubstituted, particularly mono- or disubstituted. In the case of a monosubstitution the substituent is preferably arranged in the ortho or para position, particularly in the para position to the group A.

- 10 Particularly preferred substituents R^{20} of the group B are selected from the group consisting of fluorine, chlorine, bromine, cyano, nitro, C_{1-4} -alkyl, hydroxy, hydroxy- C_{1-3} -alkyl, C_{1-4} -alkoxy, trifluoromethyl, trifluoromethoxy, C_{2-4} -alkynyl, carboxy, C_{1-4} -alkoxycarbonyl, C_{1-4} -alkoxy- C_{1-3} -alkyl, C_{1-4} -alkoxy-carbonylamino, amino, C_{1-4} -alkyl-amino, di-(C_{1-4} -alkyl)-amino, cyclo- C_{3-6} -alkyleneimino, aminocarbonyl, C_{1-4} -alkyl-amino-carbonyl and di-(C_{1-4} -alkyl)-amino-carbonyl.

- Most particularly preferred substituents R^{20} of the group B are selected from the group consisting of fluorine, chlorine, bromine, cyano, CF_3 , C_{1-3} -alkyl, C_{1-4} -alkoxy and trifluoromethoxy or nitro; particularly fluorine, chlorine, bromine, methoxy, CF_3 and trifluoromethoxy.

Generally R^4 has one of the meanings given for R^{17} , preferably one of the meanings given for R^{16} .

- 25 Particularly preferred meanings of the substituent R^4 are H, C_{1-6} -alkyl and C_{3-6} -alkenyl. If R^4 is linked to Y forming a heterocyclic ring system, particularly preferred meanings of R^4 are C_{2-6} -alkyl and C_{2-6} -alkenyl.

- If R^{11} is a C_{2-6} -alkenyl or C_{2-6} -alkynyl group, the definitions $-CH=CH_2$, $-CH=CH(CH_3)$, $-CH=C(CH_3)_2$, $C\equiv CH$ and $-C\equiv C-CH_3$ are preferred.

The substituent R^{20} preferably has none of the following structural elements:

- a) $-CO$ -aryl or $-CO$ -heteroaryl, particularly $-CO$ -phenyl, while heteroaryl, aryl and phenyl may be substituted,

- b) $-C(=NH)-NH$, wherein the H atoms may be substituted and/or
c) $-NH-CO-NH$, wherein the H atoms may be substituted.

Generally preferred definitions of the group R^{20} are halogen, hydroxy, cyano, C_{1-4} -alkyl, C_{3-7} -cycloalkyl, C_{1-4} -alkoxy, C_{1-4} -alkoxycarbonyl or amino, while, as hereinbefore defined, in each case one or more C atoms may additionally be mono- or polysubstituted by F and/or in each case one or two C atoms independently of one another may additionally be monosubstituted by Cl or Br. Particularly preferably R^{20} denotes F, Cl, Br, I, OH, cyano, methyl, difluoromethyl, trifluoromethyl, ethyl, n-propyl, iso-propyl, methoxy, difluoromethoxy, trifluoromethoxy, ethoxy, n-propoxy, isopropoxy, methoxycarbonyl, ethoxycarbonyl or amino.

Preferred definitions of the group R^{21} are C_{1-4} -alkyl, C_{1-4} -alkylcarbonyl, C_{1-4} -alkoxycarbonyl, C_{1-4} -alkylsulphonyl, $-SO_2-NH_2$, $-SO_2-NH-C_{1-3}$ -alkyl, $-SO_2-N(C_{1-3}-alkyl)_2$ and cyclo- C_{3-6} -alkyleneimino-sulphonyl, while, as hereinbefore defined, in each case one or more C atoms may additionally be mono- or polysubstituted by F and/or in each case one or two C atoms independently of one another may additionally be monosubstituted by Cl or Br.

Most particularly preferred meanings of R^{21} are H, C_{1-4} -alkyl, C_{1-4} -alkylcarbonyl, C_{1-4} -alkoxycarbonyl, particularly H and C_{1-3} -alkyl.

Cy preferably denotes a C_{3-7} -cycloalkyl, particularly a C_{5-7} -cycloalkyl group, a C_{5-7} -cycloalkenyl group, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, aryl or heteroaryl, while aryl or heteroaryl preferably denotes a monocyclic or fused bicyclic ring system, and the above-mentioned cyclic groups may be mono- or polysubstituted by R^{20} at one or more C atoms, and in the case of a phenyl group may also additionally be monosubstituted by nitro, and/or one or more NH groups may be substituted by R^{21} .

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Preferred compounds according to the invention are those wherein one or more of the groups, radicals, substituents and/or indices have one of the meanings specified above as being preferred.

Particularly preferred compounds according to the invention are those wherein

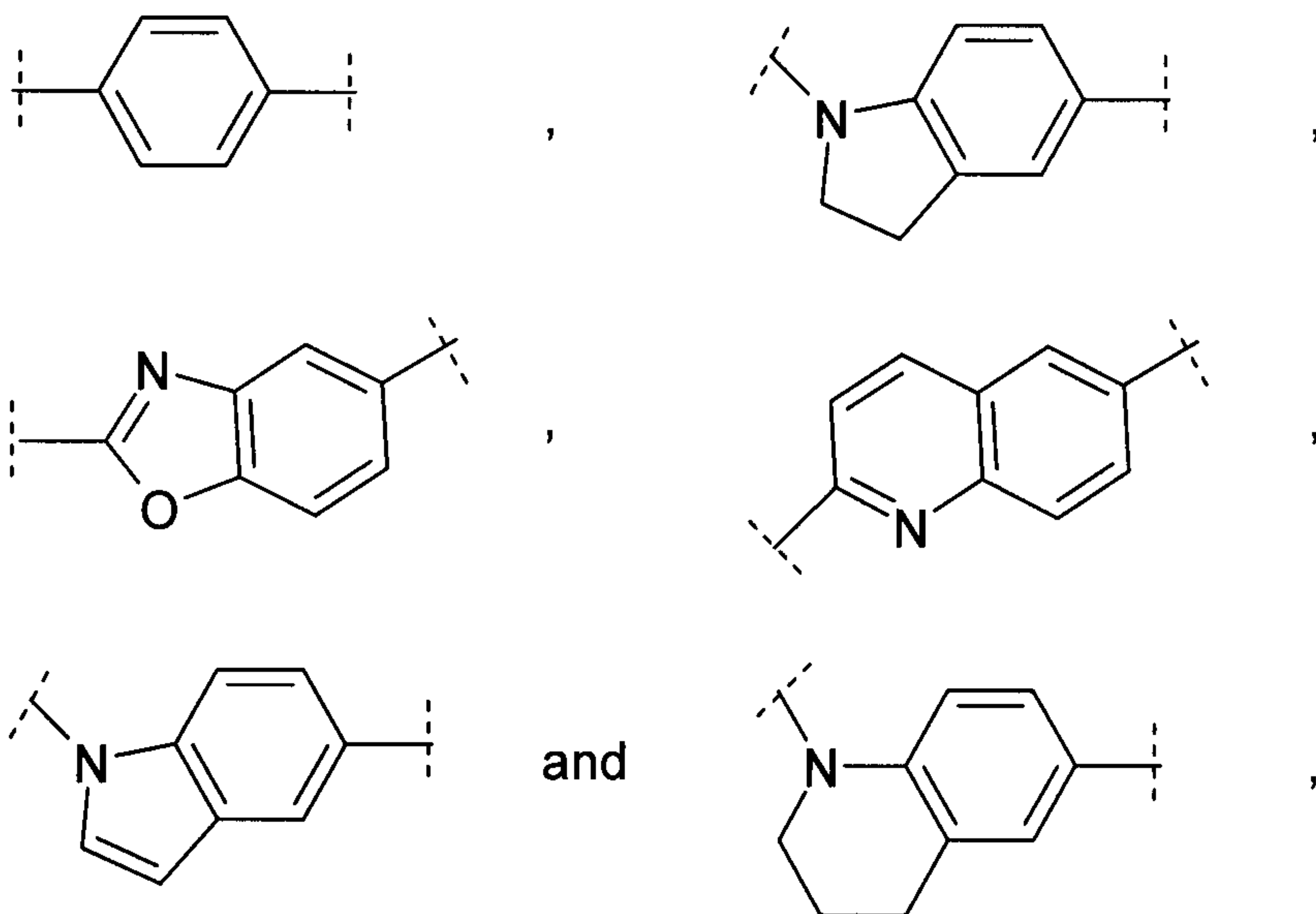
the bridge X denotes $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$ or 1,1-cyclopropylene, and

- 5 if the group Y is linked to X via a C atom (of the group Y), may also denote $-\text{CH}_2\text{CH}_2\text{O}-$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{O}-$, $-\text{CH}_2\text{CH}_2\text{NR}^4-$ or $-\text{CH}_2\text{CH}_2\text{CH}_2\text{NR}^4-$,

while the groups mentioned for X are unsubstituted or wherein the alkylene bridge as specified is preferably mono- or disubstituted by methyl and/or fluorine, while two

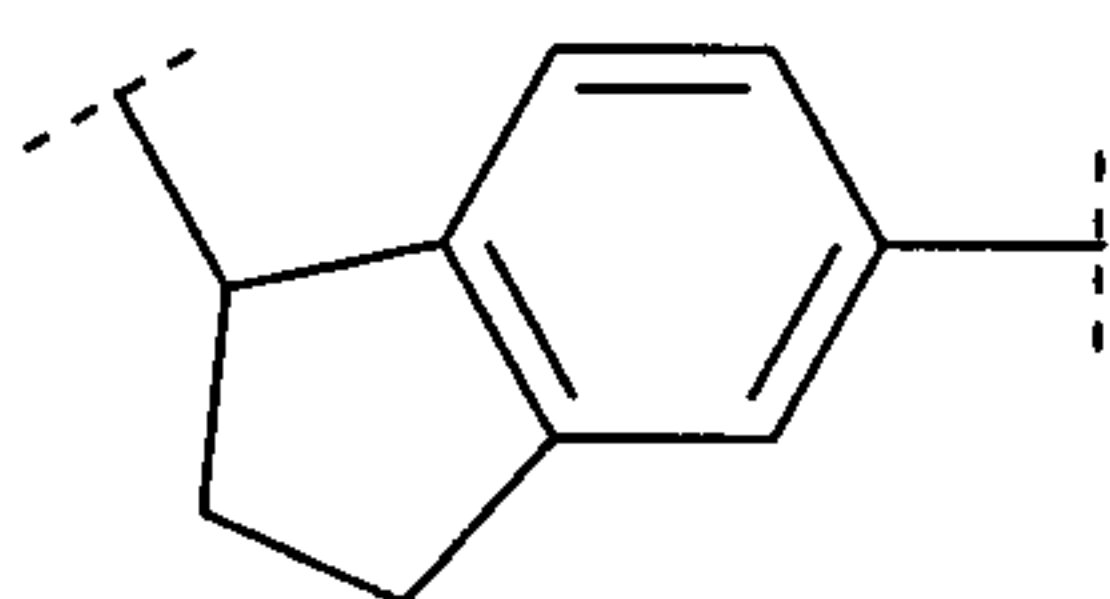
- 10 methyl groups may be joined together to form a cyclopropyl ring; and

the group Y has one of the following meanings



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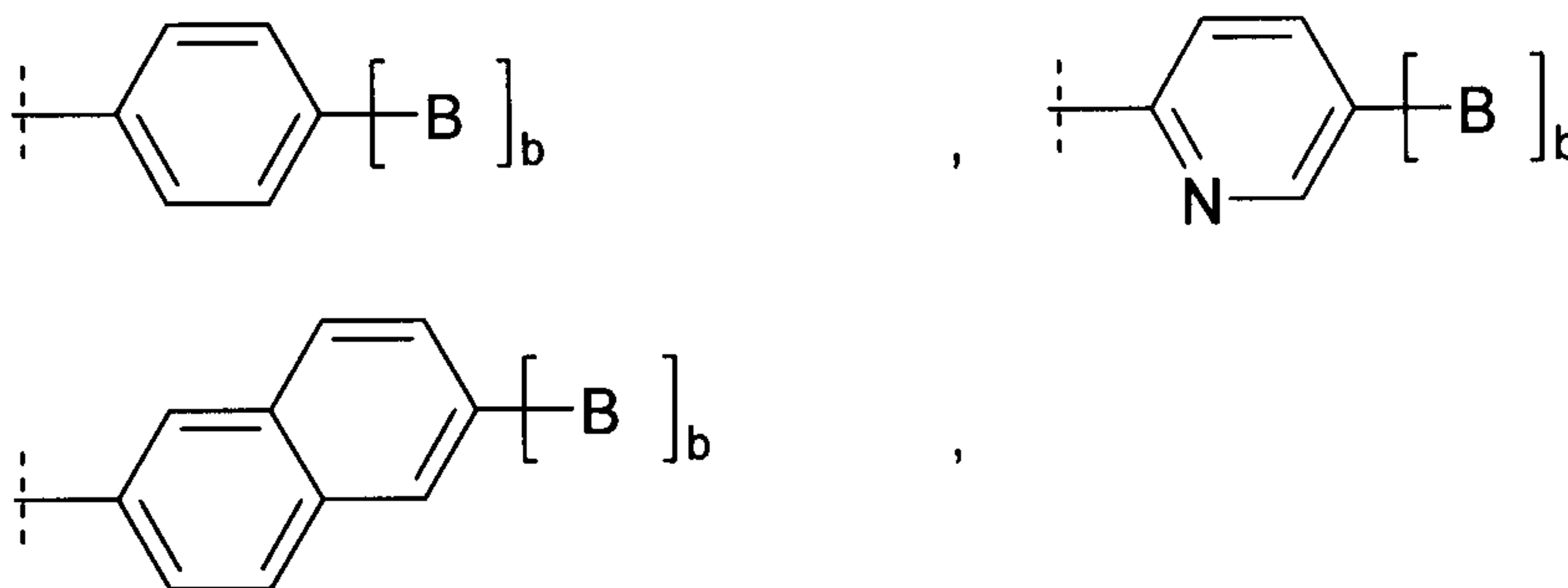
or the group Y is linked to the group X forming a carbo- or heterocyclic group fused to Y, while the group $-\text{X-Y}-$ denotes



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while the above-mentioned phenyl rings or the bicyclic groups containing heteroatoms may be mono- or polysubstituted by R^{20} and phenyl rings may also additionally be monosubstituted by nitro, and the saturated carbocyclic ring in the indane skeleton may be mono- or disubstituted by C_{1-3} -alkyl, and

the group A denotes one of the following partial formulae



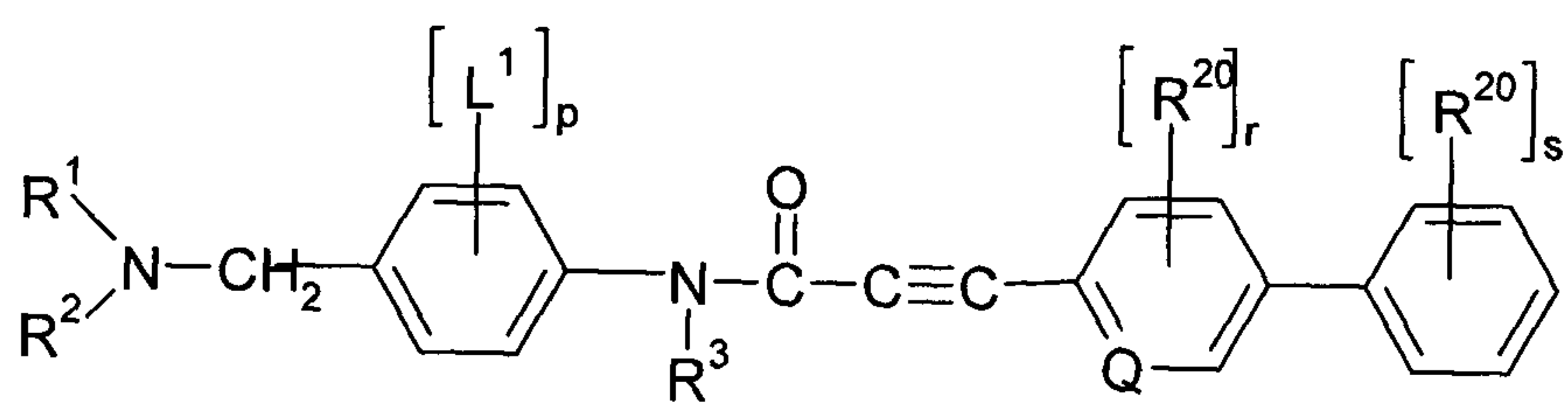
which may be mono- or polysubstituted by R^{20} , while if the index b has the value 0, the group A does not have an amino group as substituent in the ortho position to the bridge W, and

the group B denotes phenyl, which is mono- or polysubstituted by R^{20} , and

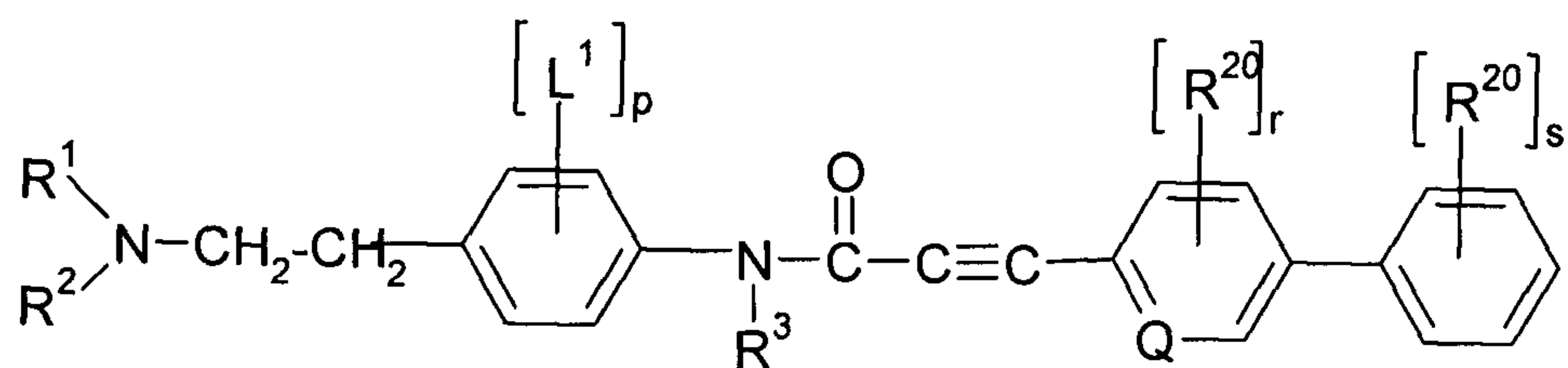
b denotes the value 0 or 1.

Most particularly preferred according to the invention are those compounds wherein A, B, b , X, Y, Z, R^1 , R^2 , R^3 and W independently of one another have one or more of the above-mentioned preferred meanings.

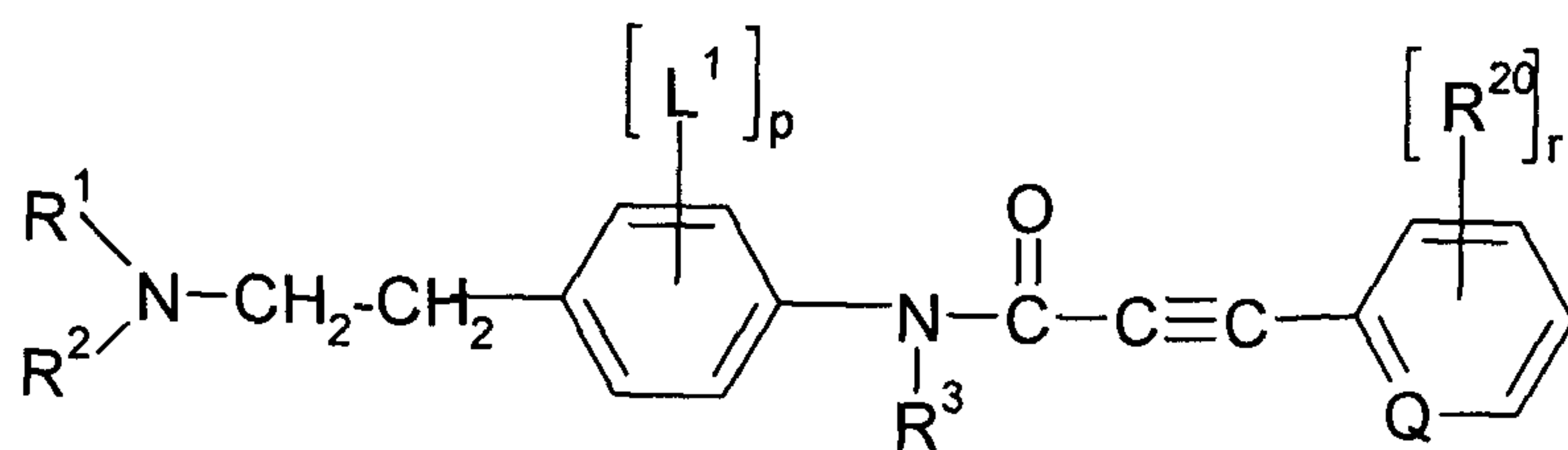
Preferred groups of compounds according to this invention can be described by the following formulae, particularly preferably by the formulae Ia.1, Ia.2a, Ia.2b, Ia.3, Ia.5, Ia.6, Ia.7, Ia.8, Ib.1, Ib.2, Ic.1 and Id.1



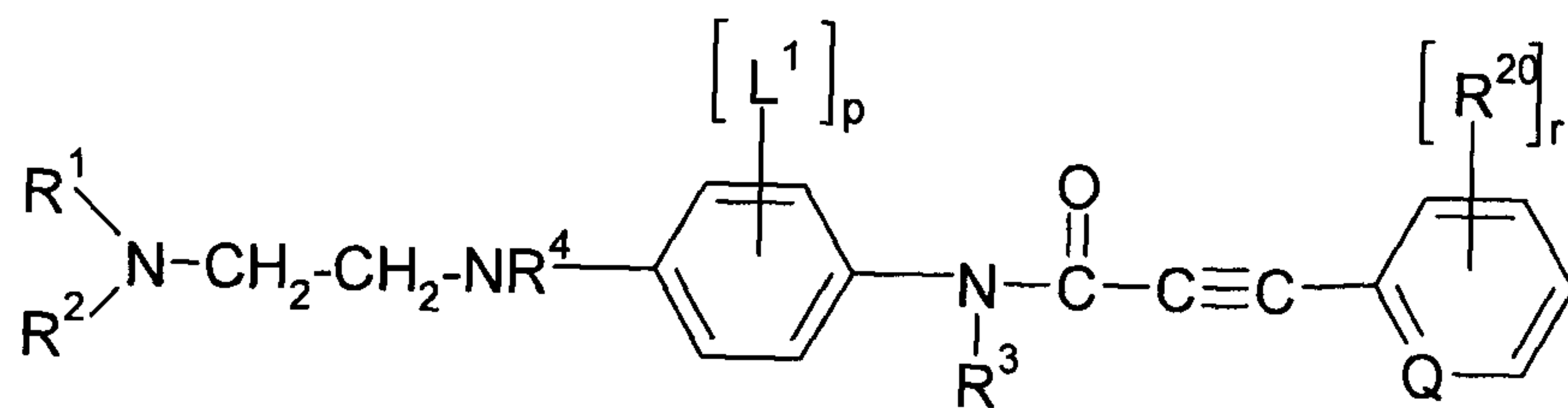
Ia.1



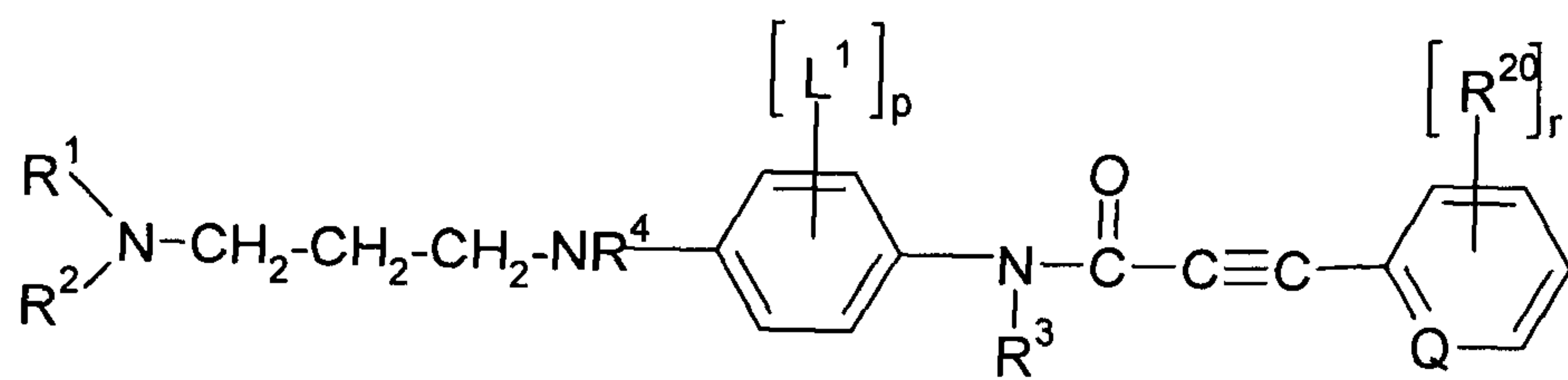
Ia.2a



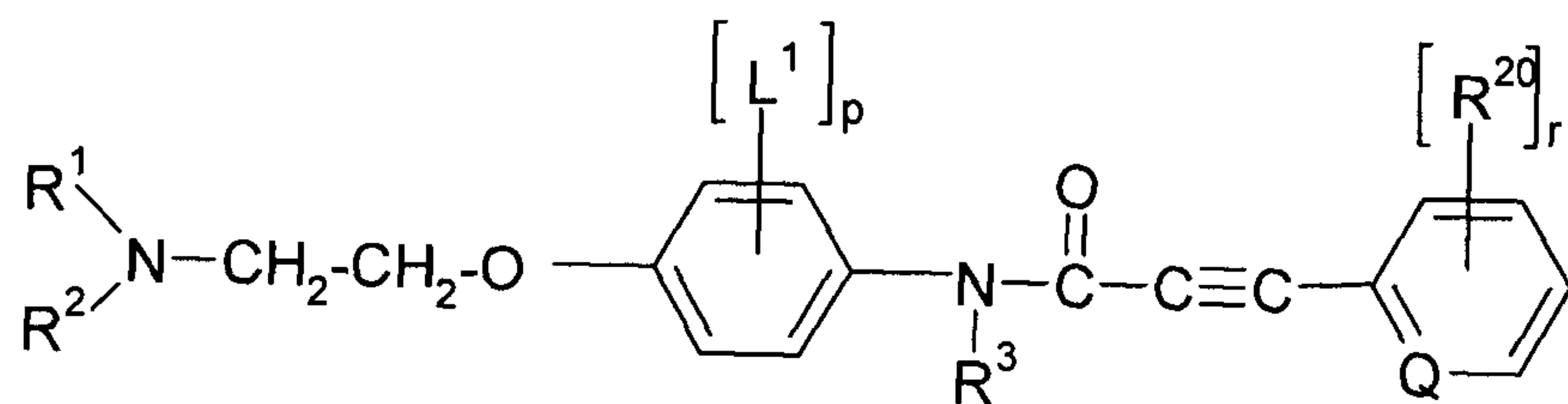
Ia.2b



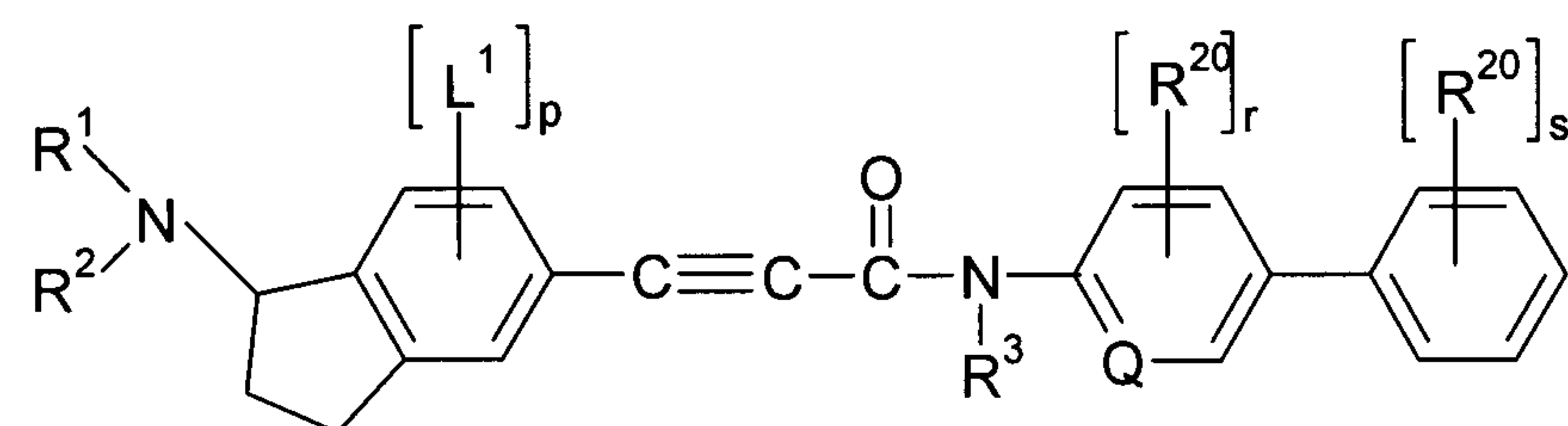
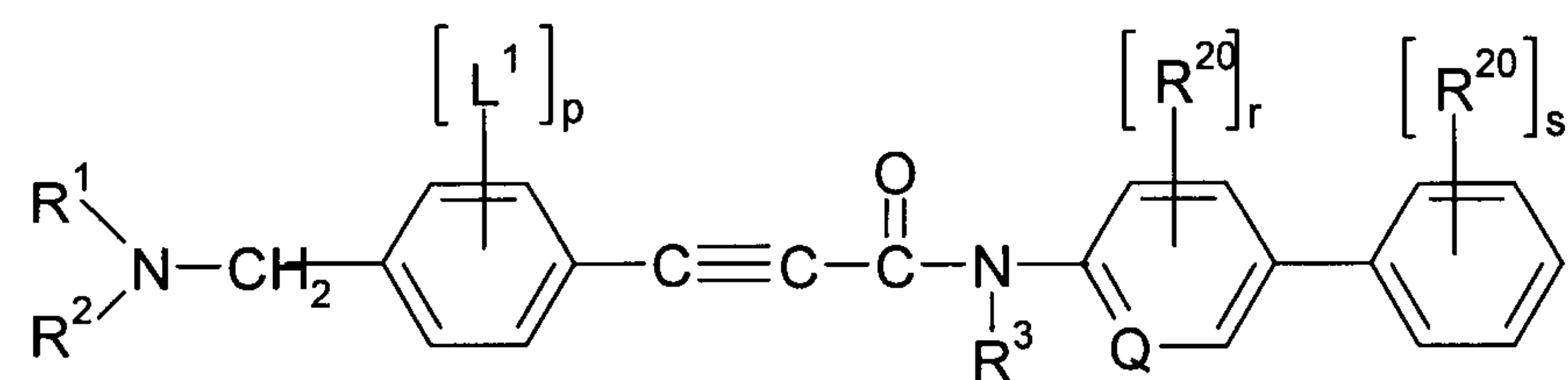
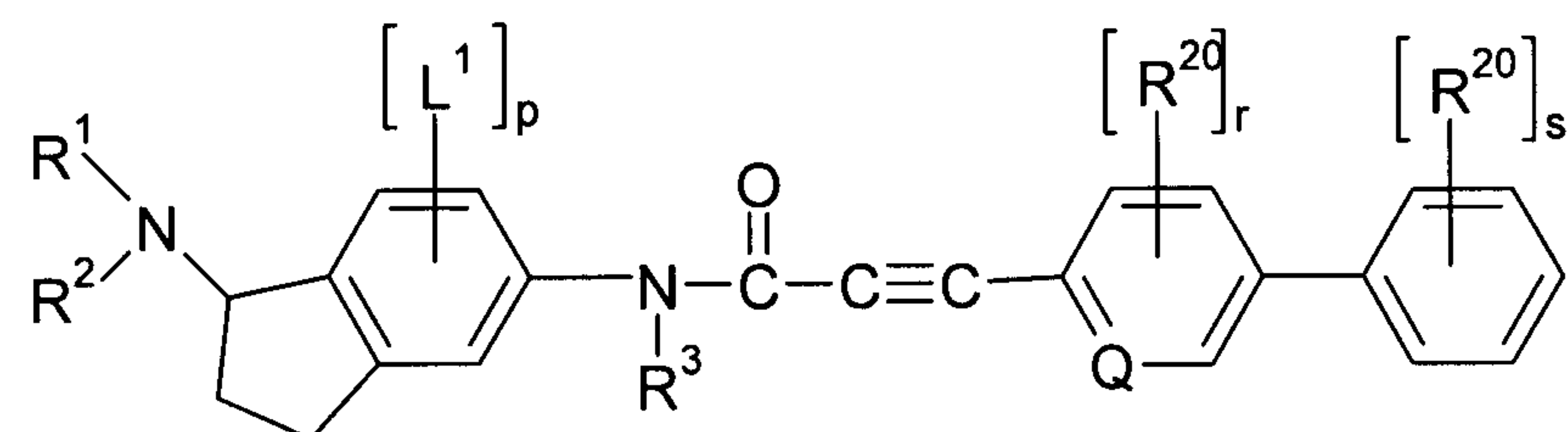
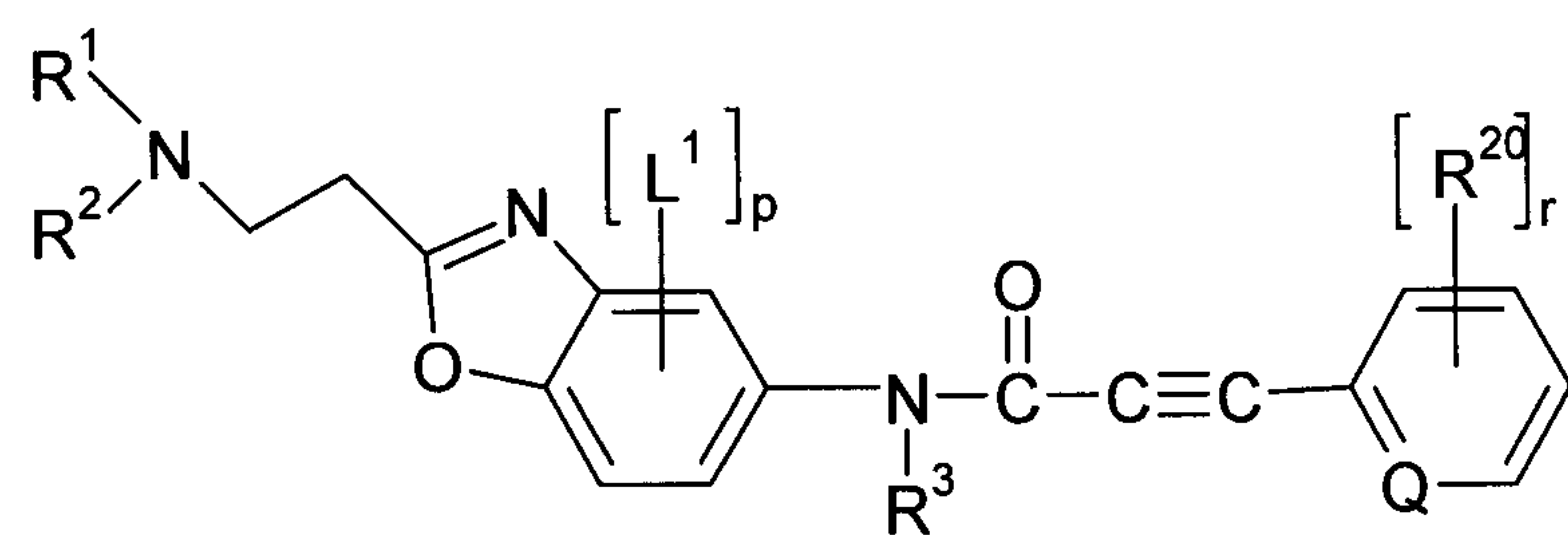
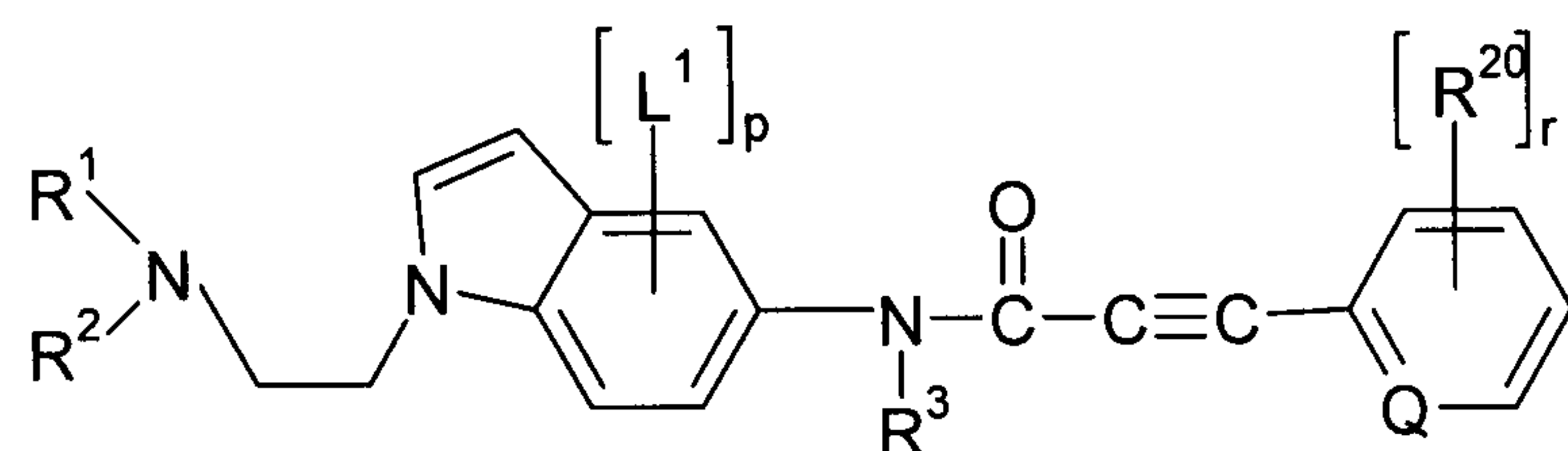
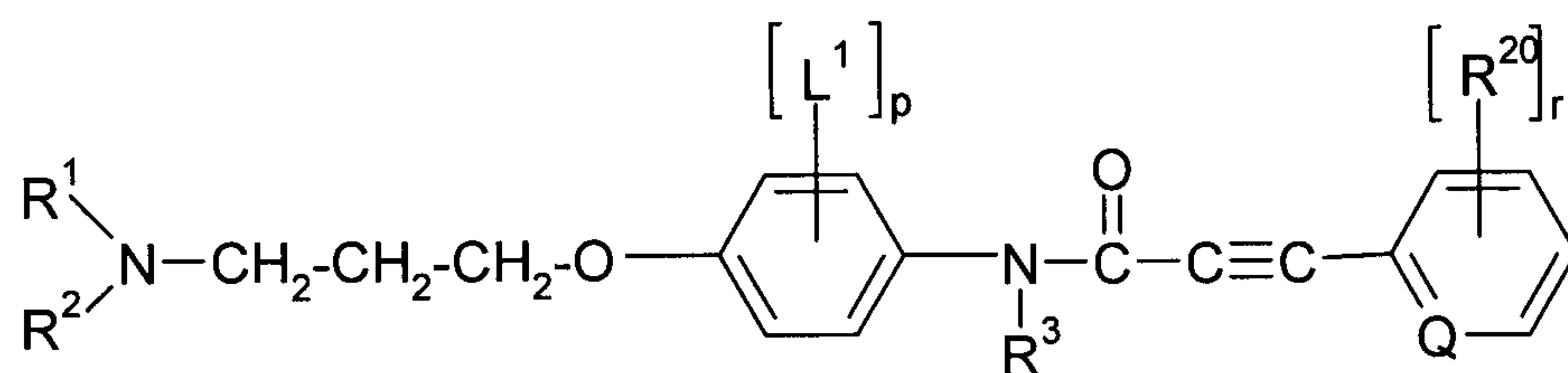
Ia.3

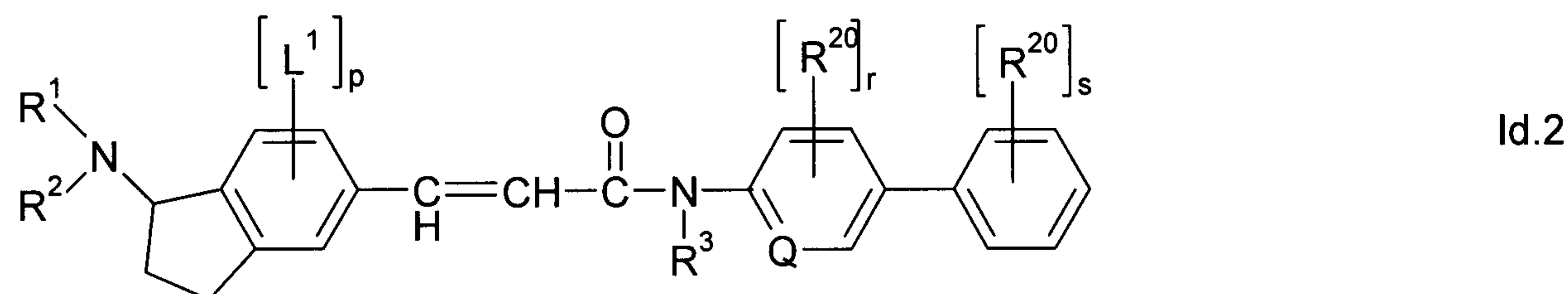
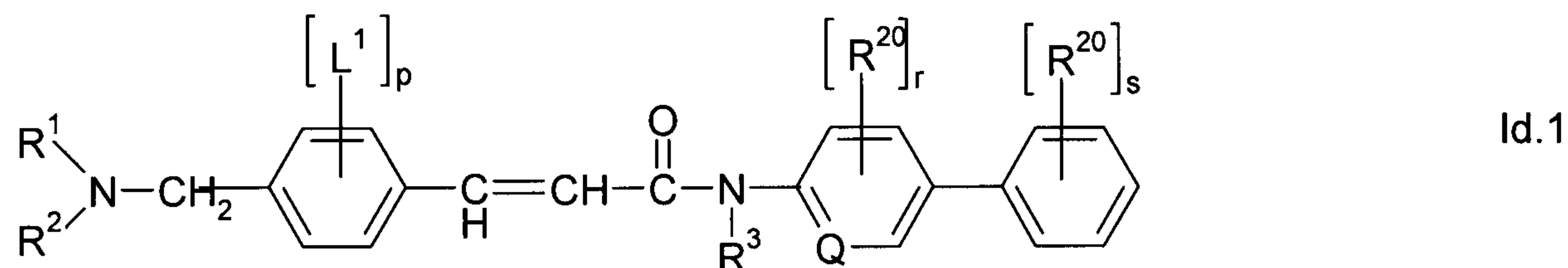
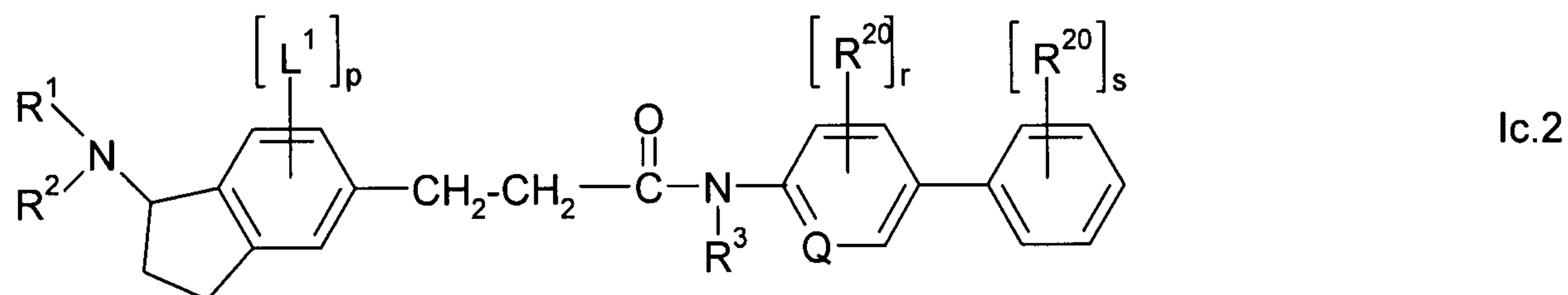
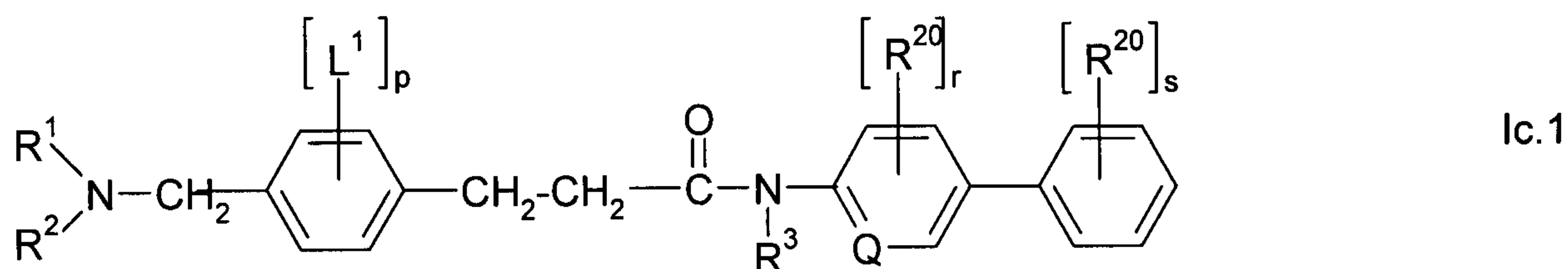


Ia.4



Ia.5



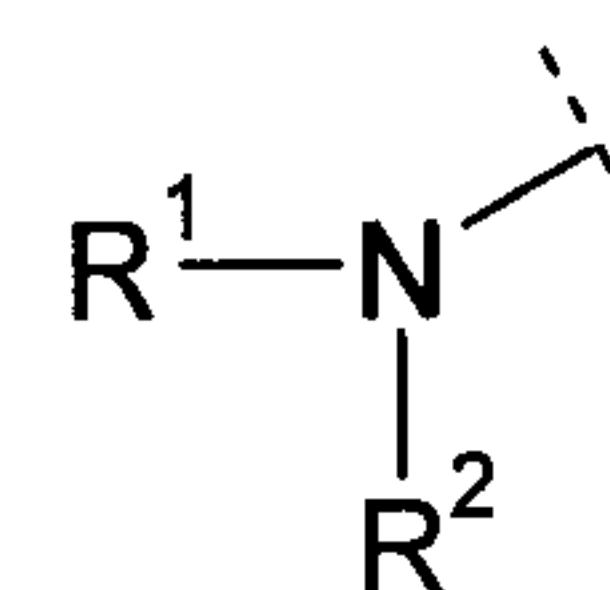


while the bridges X contained in formulae Ia.1 to Ia.8, Ib.1, Ic.1 and Id.1 representing -CH₂-, -CH₂-CH₂-, -CH₂-CH₂-NR⁴-, -CH₂-CH₂-CH₂-NR⁴-, -CH₂-CH₂-O- and -CH₂-CH₂-CH₂-O- may have one or two substituents selected independently of one another from the group consisting of C₁₋₃-alkyl and C₃₋₅-cycloalkyl, while two alkyl substituents may be joined together to form a C₃₋₆-cycloalkyl group; particularly preferably these bridges X, particularly representing -CH₂-, may have one or two methyl substituents, while two methyl substituents may be joined together to form a cyclopropyl group; and

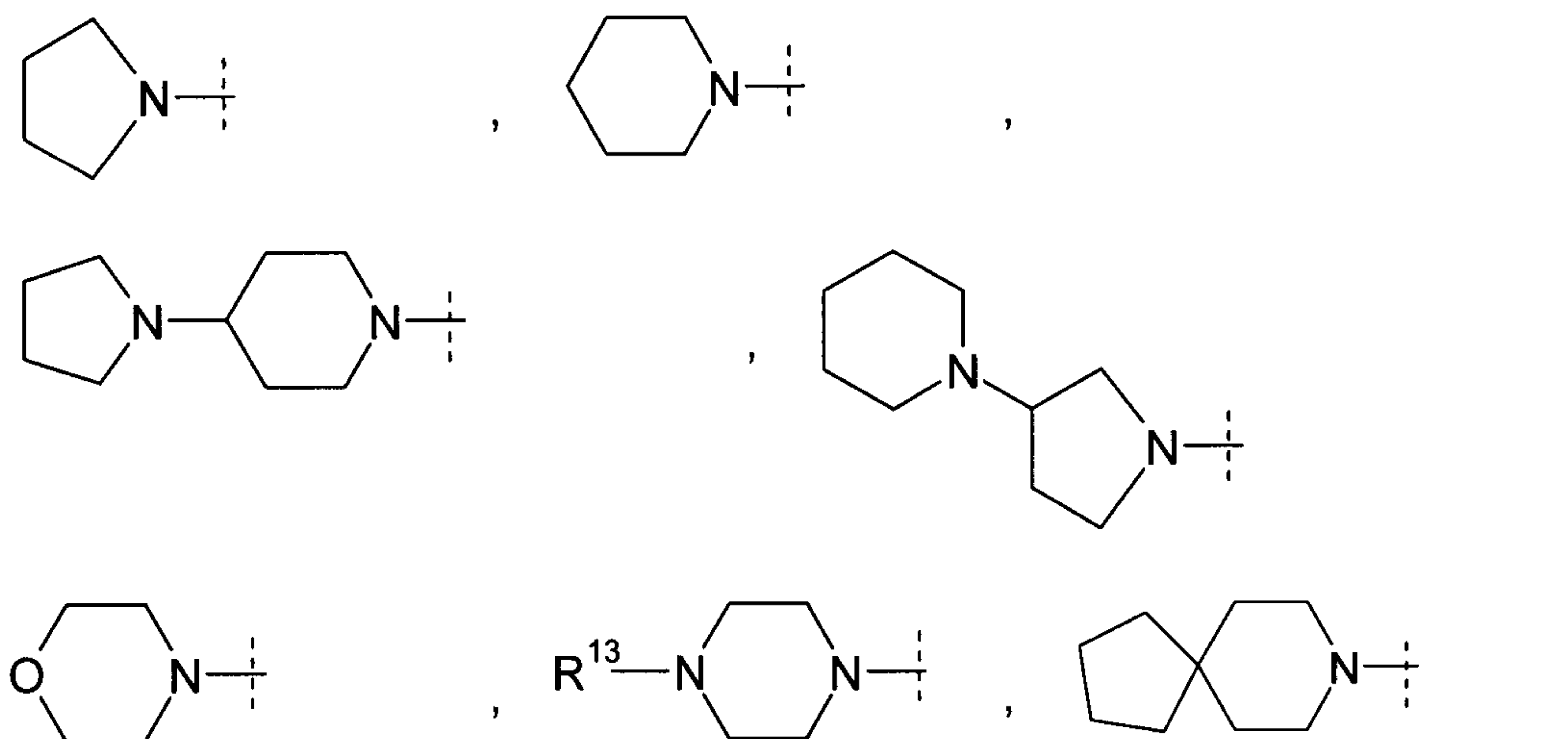
10 L¹, R¹, R², R³, R⁴ and R²⁰ have the meanings given above and substituents occurring more than once may have identical or different meanings; and particularly

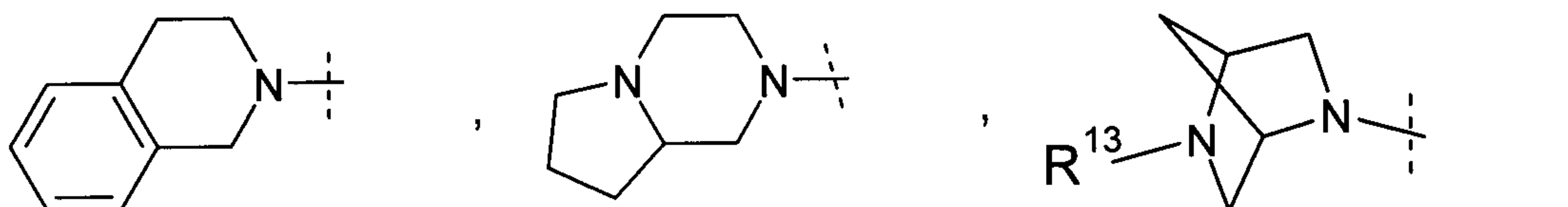
R^1 , R^2 independently of one another are selected from among C_{1-6} -alkyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, tetrahydropyran-3 or -4-yl, tetrahydropyranyl- C_{1-3} -alkyl, piperidin-3 or -4-yl, wherein the NH group may be substituted by R^{13} , piperidiny- C_{1-3} -alkyl, wherein the NH group may be substituted by R^{13} , phenyl, pyridyl, phenyl- C_{1-3} -alkyl, pyridyl- C_{1-3} -alkyl, hydroxy- C_{2-4} -alkyl, C_{1-4} -alkoxy- C_{2-4} -alkyl, amino- C_{2-4} -alkyl, C_{1-4} -alkyl-amino- C_{2-4} -alkyl and di-(C_{1-4} -alkyl)-amino- C_{2-4} -alkyl, while cycloalkyl rings may be mono-, di- or trisubstituted by substituents selected from hydroxy, hydroxy- C_{1-3} -alkyl, C_{1-3} -alkyl or C_{1-3} -alkyloxy, particularly hydroxy, hydroxymethyl, methyl and methoxy, and C_{2-4} -alkyl bridges contained in hydroxy- C_{2-4} -alkyl- and C_{1-4} -alkoxy- C_{2-4} -alkyl may additionally be monosubstituted by hydroxy, hydroxy- C_{1-3} -alkyl, C_{1-3} -alkyl or C_{1-3} -alkyloxy, particularly hydroxy, hydroxymethyl, methyl or methoxy, and alkyl groups may be mono- or polysubstituted by F and/or monosubstituted by Cl, and one of the groups R^1 and R^2 may also represent H; or

R^1 , R^2 are connected to each other in such a way that the group



is defined according to one of the following partial formulae





while in the heterocycle formed by the group R^1R^2N - one or more H atoms may be replaced by R^{14} and/or a H atom may be replaced by Cy representing C_{3-6} -cycloalkyl, which is mono- or polysubstituted by R^{20} , particularly with F, hydroxy, C_{1-3} -alkyl, CF_3 , C_{1-3} -alkyloxy, OCF_3 or hydroxy- C_{1-3} -alkyl, particularly preferably with F, hydroxy, methyl, methoxy, CF_3 , OCF_3 or hydroxymethyl, and

the ring attached to the heterocycle formed by the group R^1R^2N - may be mono- or polysubstituted, preferably monosubstituted at one or more C atoms by R^{20} , and in the case of a phenyl ring may also additionally be monosubstituted by nitro and

R^3 preferably denotes H or methyl,

R^{14} in each case independently of one another denotes F, Cl, C_{1-4} -alkyl, C_{3-6} -cycloalkyl- C_{1-3} -alkyl, hydroxy, hydroxy- C_{1-3} -alkyl, C_{1-4} -alkyloxy, C_{1-4} -alkoxy- C_{1-3} -alkyl, pyridylamino or aminocarbonyl, while in each case one or more C atoms may additionally be mono- or polysubstituted by F or in each case a C atom may be monosubstituted by Cl; most particularly preferably denotes methyl, ethyl, propyl, trifluoromethyl, hydroxy, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1-hydroxy-1-methyl-ethyl, methoxy, ethoxy, methoxymethyl, pyridylamino or aminocarbonyl; and

R^{13} denotes H, C_{1-4} -alkyl, C_{1-4} -alkylcarbonyl or C_{1-4} -alkyloxycarbonyl; particularly preferably denotes H or C_{1-3} -alkyl; and

Q denotes CH or N, while CH may be substituted by R^{20} ,

L^1 preferably denotes fluorine, chlorine, bromine, cyano, C_{1-3} -alkyl, C_{1-3} -alkoxy, trifluoromethyl, trifluoromethoxy, C_{1-4} -alkoxycarbonyl, amino or nitro;

particularly preferably denotes fluorine, chlorine, bromine, methyl, methoxy, trifluoromethyl, methoxycarbonyl, ethoxycarbonyl, cyano, amino or nitro;

p has the value 0 or 1,

R^{20} in each case independently of one another preferably denotes fluorine, chlorine, bromine, cyano, nitro, C_{1-4} -alkyl, C_{2-6} -alkenyl, hydroxy, hydroxy- C_{1-3} -alkyl, C_{1-4} -alkoxy, trifluoromethyl, trifluoromethoxy, C_{2-4} -alkynyl, carboxy, C_{1-4} -alkoxycarbonyl, C_{1-4} -alkoxy- C_{1-3} -alkyl, C_{1-4} -alkoxy-carbonyl-amino, amino, C_{1-4} -alkyl-amino, di- $(C_{1-4}$ -alkyl)-amino, aminocarbonyl, C_{1-4} -alkyl-amino-carbonyl, di- $(C_{1-4}$ -alkyl)-amino-carbonyl, while if the index b has the value 0, the group Cy does not have an amino group as substituent in the ortho position to the bridge W;

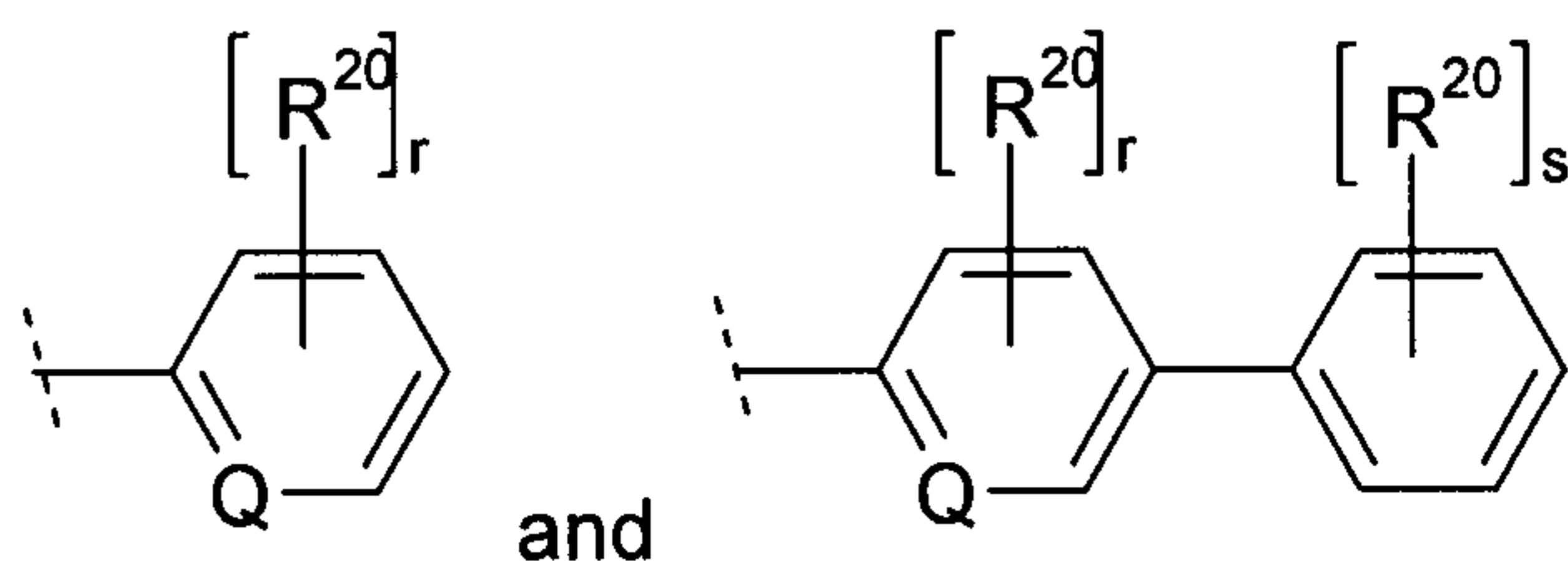
particularly preferably R^{20} is selected from fluorine, chlorine, bromine, cyano, nitro, C_{1-4} -alkyl, hydroxy, hydroxy- C_{1-3} -alkyl, C_{1-4} -alkoxy, trifluoromethyl, trifluoromethoxy, C_{2-4} -alkynyl, carboxy, C_{1-4} -alkoxycarbonyl- and C_{1-4} -alkoxy- C_{1-3} -alkyl;

most particularly preferably denotes fluorine, chlorine, bromine, cyano, CF_3 , C_{1-3} -alkyl, C_{1-4} -alkoxy and trifluoromethoxy or nitro;

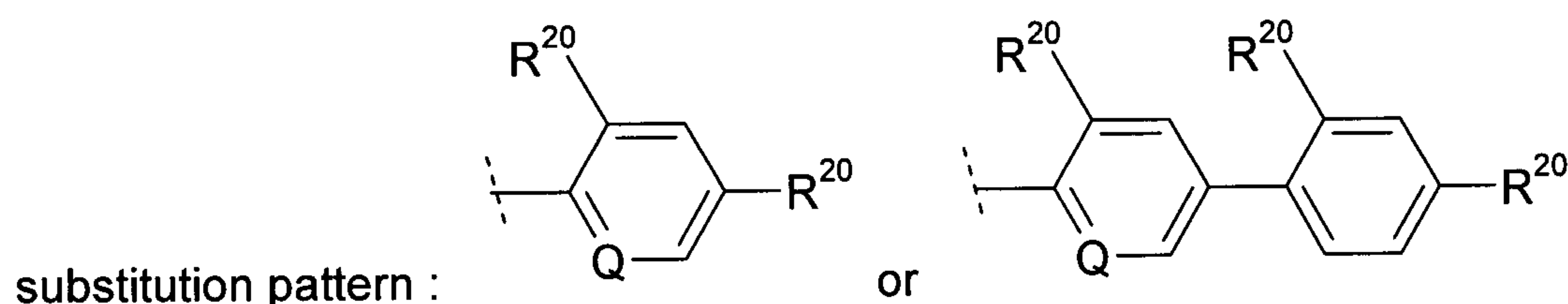
r, s in each case independently of one another have the value 0, 1, 2 or 3, preferably at least one index r or s does not denote the value 0, and

the compounds according to provisos (M1) to (M14) are not included.

The groups contained in formulae Ia.1 to Id.2



advantageously have the following



wherein R^{20} has one of the meanings given hereinbefore, including H, and substituents R^{20} occurring more than once may have the same or different meanings, and preferably at least one substituent R^{20} has a meaning other than H.

The compounds listed in the Examples and Tables, including the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof, are preferred according to the invention. Particularly preferred compounds are listed below, while the relevant Example number is given in square brackets:

3-(4-piperidin-1-ylmethyl-phenyl)-propynoic acid-(4'-methoxy-biphenyl-4-yl)-amide [1-8];

3-{4-[4-(pyridin-2-ylamino)-piperidin-1-ylmethyl]-phenyl}-propynoic acid-(4'-methoxy-biphenyl-4-yl)-amide [1-11];

3-(4-pyrrolidin-1-ylmethyl-phenyl)-propynoic acid-(4'-chloro-3-fluoro-biphenyl-4-yl)-amide [1.17];

3-[4-(4-methyl-piperidin-1-ylmethyl)-phenyl]-propynoic acid-(4'-chloro-2'-fluoro-biphenyl-4-yl)-amide [1-18];

3-[4-((R)-2-hydroxymethyl-pyrrolidin-1-ylmethyl)-phenyl]-propynoic acid-(4'-chloro-3-fluoro-biphenyl-4-yl)-amide [1-20];

3-[4-(4-hydroxy-piperidin-1-ylmethyl)-phenyl]-propynoic acid-(4'-chloro-3-fluoro-biphenyl-4-yl)-amide [1-21];

3-(4-pyrrolidin-1-ylmethyl-phenyl)-propynoic acid-(4'-chloro-biphenyl-4-yl)-methyl-amide [1-23];

3-(4-pyrrolidin-1-ylmethyl-phenyl)-propynoic acid-(4'-chloro-biphenyl-4-yl)-amide [1-33];

3-{4-[4-(1-hydroxy-1-methyl-ethyl)-piperidin-1-ylmethyl]-phenyl}-propynoic acid-(4'-chloro-biphenyl-4-yl)-amide [1-34];

3-[4-(4-methyl-piperidin-1-ylmethyl)-phenyl]-propynoic acid-(4'-chloro-biphenyl-4-yl)-amide [1-35];

- 3-[4-(4-methoxy-piperidin-1-ylmethyl)-phenyl]-propynoic acid-(4'-chloro-biphenyl-4-yl)-amide [1-36];
- 3-[4-(4-hydroxy-4-methyl-piperidin-1-ylmethyl)-phenyl]-propynoic acid-(4'-chloro-biphenyl-4-yl)-amide [1-37];
- 5 3-(4-piperidin-1-ylmethyl-phenyl)-propynoic acid-(4'-chloro-biphenyl-4-yl)-amide [1-38];
- 3-{4-[(cyclohexyl-ethyl-amino)-methyl]-phenyl}-propynoic acid-(4'-chloro-biphenyl-4-yl)-amide [1-52];
- 3-{4-[cyclopentyl-methyl-amino)-methyl]-phenyl}-propynoic acid-(4'-chloro-biphenyl-4-yl)-amide [1-425];
- 10 3-(1-pyrrolidin-1-yl-indan-5-yl)-propynoic acid-(4'-chloro-biphenyl-4-yl)-amide [2-3];
- 3-(4'-chloro-biphenyl-4-yl)-propynoic acid-(4-piperidin-1-ylmethyl-phenyl)-amide [3-6];
- 3-(4'-chloro-biphenyl-4-yl)-propynoic acid-[4-(4-methoxy-piperidin-1-ylmethyl)-phenyl]-amide [3-13];
- 15 3-(4'-chloro-biphenyl-4-yl)-propynoic acid-[4-(4-methyl-piperidin-1-ylmethyl)-phenyl]-amide [3-14];
- 3-(4'-chloro-biphenyl-4-yl)-propynoic acid-{4-[(cyclopropylmethyl-methyl-amino)-methyl]-phenyl}-amide [3-15];
- 3-(4'-chloro-biphenyl-4-yl)-propynoic acid-[4-(4-hydroxy-4-trifluoromethyl-piperidin-1-ylmethyl)-phenyl]-amide [3-17];
- 20 3-(4'-chloro-biphenyl-4-yl)-propynoic acid-[4-(4-hydroxy-1-piperidin-1-ylmethyl)-phenyl]-amide [3-18];
- 3-[5-(4-chloro-phenyl)-pyridin-2-yl]-propynoic acid-(4-piperidin-1-ylmethyl-phenyl)-amide [3-25];
- 25 3-[5-(4-chloro-phenyl)-pyridin-2-yl]-propynoic acid-[4-(3,5-dimethyl-piperidin-1-ylmethyl)-phenyl]-amide [3-29];
- 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[4-(2-diethylamino-ethoxy)-phenyl]-amide [3-38];
- 3-(2,4-dichloro-phenyl)-propynoic acid-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-amide [4-1];
- 30 3-(2,4-dichloro-phenyl)-propynoic acid-[3-methoxy-4-(2-diethylamino-ethoxy)-phenyl]-amide-hydrochloride [4-7];
- 3-(4-chloro-phenyl)-propynoic acid-[1-(2-pyrrolidin-1-yl-ethyl)-1*H*-indol-5-yl]-amide [4-10];

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[1-(2-pyrrolidin-1-yl-ethyl)-1*H*-indol-5-yl]-amide [4-11];

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[3-bromo-4-(2-diethylamino-ethoxy)-phenyl]-amide [4-15];

5 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[3-nitro-4-(2-diethylamino-ethoxy)-phenyl]-amide [4-17];

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[3-methoxy-4-(2-diethylamino-ethoxy)-phenyl]-amide-hydrochloride [4-20];

10 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[3-methyl-4-(2-diethylamino-ethoxy)-phenyl]-amide [4-21];

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[4-(3-diethylamino-ethoxy)-3-fluoro-phenyl]-amide [4-25];

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-{3-chloro-4-[2-(4-methyl-piperidin-1-yl)-ethylamino]-phenyl}-amide [4-27];

15 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[3-chloro-4-(2-diethylamino-ethyl)-phenyl]-amide [4-31];

3-(4-bromo-2-chloro-phenyl)-propynoic acid-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-amide [4-35];

20 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-{3-methoxy-4-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenyl}-amide [4-270];

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-{4-[2-(3,5-dimethyl-piperidin-1-yl)-ethoxy]-3-methoxy-phenyl}-amide [4-271];

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-{4-[2-(2,6-dimethyl-piperidin-1-yl)-ethoxy]-3-methoxy-phenyl}-amide [4-277];

25 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-{4-[2-(cyclopropylmethyl-methyl-amino)-ethoxy]-3-methoxy-phenyl}-amide-hydrochloride [4-278];

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-{4-[2-(cyclopropylmethyl-propyl-amino)-ethoxy]-3-methoxy-phenyl}-amide-hydrochloride [4-279];

30 (E)-*N*-(4'-chloro-biphenyl-4-yl)-3-[4-(4-methyl-piperidin-1-ylmethyl)-phenyl]-acrylamide [5-2];

(E)-*N*-(4'-chloro-biphenyl-4-yl)-3-[4-(4-methoxy-piperidin-1-ylmethyl)-phenyl]-acrylamide [5-4];

1-{4-[(E)-2-(4'-chloro-biphenyl-4-ylcarbamoyl)-vinyl]-benzyl}-piperidine-4-carboxylic acid amide [5-6];

(E)-N-(4'-chloro-biphenyl-4-yl)-3-(4-([methyl-(tetrahydro-pyran-4-yl)-amino]-methyl)-phenyl)-acrylamide [5-7];

(E)-N-(4'-chloro-biphenyl-4-yl)-3-[4-(4-hydroxymethyl-piperidin-1-ylmethyl)-phenyl]-acrylamide [5-8];

5 (E)-N-(4'-chloro-biphenyl-4-yl)-3-[4-((S)-3-hydroxy-pyrrolidin-1-ylmethyl)-phenyl]-acrylamide [5-9];

(E)-N-(4'-chloro-biphenyl-4-yl)-3-(4-pyrrolidin-1-ylmethyl-phenyl)-acrylamide [5-13];

(E)-N-(4'-chloro-biphenyl-4-yl)-3-(4-cyclopropylaminomethyl-phenyl)-acrylamide [5-14];

10 (E)-N-(4'-chloro-biphenyl-4-yl)-3-{4-[(cyclopropylmethyl-methyl-amino)-methyl]-phenyl}-acrylamide [5-17];

(E)-N-(4'-chloro-biphenyl-4-yl)-3-{4-[(cyclohexyl-methyl-amino)-methyl]-phenyl}-acrylamide [5-19];

(E)-N-(4'-chloro-biphenyl-4-yl)-3-{4-[(cyclohexyl-methyl-amino)-methyl]-phenyl}-

15 acrylamide [5-21];

(E)-N-(4'-chloro-biphenyl-4-yl)-3-[4-(2,6-dimethyl-morpholin-4-ylmethyl)-phenyl]-acrylamide [5-23];

(E)-3-[4-(8-aza-spiro[4,5]dec-8-ylmethyl)-phenyl]-N-(4'-chloro-biphenyl-4-yl)-acrylamide [5-25];

20 (E)-N-(4'-chloro-biphenyl-4-yl)-3-(4-[(2-hydroxy-2-methyl-propyl)-(2-methoxy-ethyl)-amino]-methyl)-phenyl)-acrylamide [5-27];

(E)-N-(4'-chloro-biphenyl-4-yl)-3-[4-(3-piperidin-1-yl-pyrrolidin-1-ylmethyl)-phenyl]-acrylamide [5-28]

N-(4'-chloro-biphenyl-4-yl)-3-[4-(4-methyl-piperidin-1-ylmethyl)-phenyl]-propionamide

25 [6-2];

N-(4'-chloro-biphenyl-4-yl)-3-[4-(4-methoxy-piperidin-1-ylmethyl)-phenyl]-propionamide [6-3];

N-(4'-chloro-biphenyl-4-yl)-3-(4-morpholin-4-ylmethyl-phenyl)-propionamide [6-4];

1-{4-[2-(4'-chloro-biphenyl-4-ylcarbamoyl)-ethyl]-benzyl}-piperidine-4-carboxylic acid
30 amide [6-5];

N-(4'-chloro-biphenyl-4-yl)-3-[4-(4-hydroxymethyl-piperidin-1-ylmethyl)-phenyl]-propionamide [6-6];

N-(4'-chloro-biphenyl-4-yl)-3-[4-((S)-3-hydroxy-pyrrolidin-1-ylmethyl)-phenyl]-propionamide [6-7];

N-(4'-chloro-biphenyl-4-yl)-3-[4-((*R*)-2-hydroxymethyl-pyrrolidin-1-ylmethyl)-phenyl]-propionamide [6-8];

N-(4'-chloro-biphenyl-4-yl)-3-[4-(4-hydroxy-4-methyl-piperidin-1-ylmethyl)-phenyl]-propionamide [6-9];

5 *N*-(4'-chloro-biphenyl-4-yl)-3-(4-pyrrolidin-1-ylmethyl-phenyl)-propionamide [6-11];

N-(4'-chloro-biphenyl-4-yl)-3-(4-[[methyl-(tetrahydro-pyran-4-yl)-amino]-methyl]-phenyl)-propionamide [6-12];

N-(4'-chloro-biphenyl-4-yl)-3-{4-[(cyclopropylmethyl-methyl-amino)-methyl]-phenyl}-propionamide [6-13];

10 *N*-(4'-chloro-biphenyl-4-yl)-3-(4-[(2-hydroxy-2-methyl-propyl)-(2-methoxy-ethyl)-amino]-methyl}-phenyl)-propionamide [6-14];

N-(4'-chloro-biphenyl-4-yl)-3-{4-[(cyclopropyl-methyl-amino)-methyl]-phenyl}-propionamide [6-15];

15 *N*-(4'-chloro-biphenyl-4-yl)-3-[4-(hexahydro-pyrrolo[1,2-*a*]pyrazin-2-ylmethyl)-phenyl]-propionamide [6-16];

N-(4'-chloro-biphenyl-4-yl)-3-(4-[(2-methoxy-ethyl)-methyl-amino]-methyl}-phenyl)-propionamide [6-17];

3-{4-[(benzyl-methyl-amino)-methyl]-phenyl}-*N*-(4'-chloro-biphenyl-4-yl)-propionamide [6-18];

20 *N*-(4'-chloro-biphenyl-4-yl)-3-(4-[[methyl-(tetrahydro-pyran-4-ylmethyl)-amino]-methyl]-phenyl)-propionamide [6-19];

N-(4'-chloro-biphenyl-4-yl)-3-(4-[[methyl-(2-phenoxy-ethyl)-amino]-methyl]-phenyl)-propionamide [6-20];

25 *N*-(4'-chloro-biphenyl-4-yl)-3-[4-(2,6-dimethyl-morpholin-4-ylmethyl)-phenyl]-propionamide [6-21];

N-(4'-chloro-biphenyl-4-yl)-3-{4-[(cyclohexyl-methyl-amino)-methyl]-phenyl}-propionamide [6-22];

N-(4'-chloro-biphenyl-4-yl)-3-[4-(5-methyl-2,5-diaza-bicyclo[2.2.1]hept-2-ylmethyl)-phenyl]-propionamide [6-23];

30 *N*-(4'-chloro-biphenyl-4-yl)-3-[4-(3-piperidin-1-yl-pyrrolidin-1-ylmethyl)-phenyl]-propionamide [6-25];

N-(4'-chloro-biphenyl-4-yl)-3-[4-((3*S*.5*R*)-3,5-dimethyl-piperidin-1-ylmethyl)-phenyl]-propionamide [6-26];

3-(4-[[3-amino-propyl)-methyl-amino]-methyl]-phenyl)-N-(4'-chloro-biphenyl-4-yl)-propionamide [6-27];

3-[4-(8-aza-spiro[4.5]dec-8-ylmethyl)-phenyl]-N-(4'-chloro-biphenyl-4-yl)-propionamide [6-28];

5 N-(4'-chloro-biphenyl-4-yl)-3-[4-((R)-3-hydroxy-pyrrolidin-1-ylmethyl)-phenyl]-propionamide [6-29];

N-(4'-chloro-biphenyl-4-yl)-3-{4-[(methyl-pyridin-3-ylmethyl-amino)-methyl]-phenyl}-propionamide [6-33];

10 N-(4'-chloro-biphenyl-4-yl)-3-{4-[(cyclohexyl-ethyl-amino)-methyl]-phenyl}-propionamide [6-35];

N-(4'-chloro-biphenyl-4-yl)-3-(4-cyclohexylaminomethyl-phenyl)-propionamide [6-39];

N-(4'-chloro-biphenyl-4-yl)-3-{4-[(cyclohexyl-isopropyl-amino)-methyl]-phenyl}-propionamide [6-40];

N-(4'-chloro-biphenyl-4-yl)-3-(4-cyclopentylaminomethyl-phenyl)-propionamide [6-41];

15 N-(4'-chloro-biphenyl-4-yl)-3-(4-[[ethyl-(2-hydroxy-2-methyl-propyl)-amino]-methyl]-phenyl)-propionamide [6-42];

including the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

20

Some expressions used hereinbefore and below to describe the compounds according to the invention will now be defined more fully.

25 The term halogen denotes an atom selected from among F, Cl, Br and I, particularly F, Cl and Br.

30 The term C_{1-n}-alkyl, where n has a value of 3 to 8, denotes a saturated, branched or unbranched hydrocarbon group with 1 to n C atoms. Examples of such groups include methyl, ethyl, n-propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, iso-pentyl, neo-pentyl, tert-pentyl, n-hexyl, iso-hexyl, etc. Substituted alkyl groups, such as for example the C₂₋₄-alkyl group in hydroxy-C₂₋₄-alkyl or C₁₋₄-alkoxy-C₂₋₄-alkyl, may also be branched or unbranched.

The term C_{1-n} -alkylene, where n may have a value of 1 to 8, denotes a saturated, branched or unbranched hydrocarbon bridge with 1 to n C atoms. Examples of such groups include methylene ($-CH_2-$), ethylene ($-CH_2-CH_2-$), 1-methyl-ethylene ($-CH(CH_3)-CH_2-$), 1,1-dimethyl-ethylene ($-C(CH_3)_2-CH_2-$), n -prop-1,3-ylene ($-CH_2-CH_2-$), 1-methylprop-1,3-ylene ($-CH(CH_3)-CH_2-CH_2-$), 2-methylprop-1,3-ylene ($-CH_2-CH(CH_3)-CH_2-$), etc., as well as the corresponding mirror-symmetrical forms.

The term C_{2-n} -alkenyl, where n has a value of 3 to 6, denotes a branched or unbranched hydrocarbon group with 2 to n C atoms and at least one $C=C$ -double bond. Examples of such groups include vinyl, 1-propenyl, 2-propenyl, iso-propenyl, 1,3-butadienyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl etc.

The term C_{2-n} -alkynyl, where n has a value of 3 to 6, denotes a branched or unbranched hydrocarbon group with 2 to n C atoms and a $C\equiv C$ triple bond. Examples of such groups include ethynyl, 1-propynyl, 2-propynyl, iso-propynyl, 1-butylnyl, 2-butylnyl, 3-butylnyl, 2-methyl-1-propynyl, 1-pentylnyl, 2-pentylnyl, 3-pentylnyl, 4-pentylnyl, 3-methyl-2-butylnyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl etc.

The term C_{1-n} -alkoxy denotes a C_{1-n} -alkyl-O- group, wherein C_{1-n} -alkyl is defined as above. Examples of such groups include methoxy, ethoxy, n -propoxy, iso-propoxy, n -butoxy, iso-butoxy, sec-butoxy, tert-butoxy, n -pentoxy, iso-pentoxy, neo-pentoxy, tert-pentoxy, n -hexoxy, iso-hexoxy etc.

The term C_{1-n} -alkylthio denotes a C_{1-n} -alkyl-S- group, wherein C_{1-n} -alkyl is defined as above. Examples of such groups include methylthio, ethylthio, n -propylthio, iso-propylthio, n -butylthio, iso-butylthio, sec-butylthio, tert-butylthio, n -pentylthio, iso-pentylthio, neo-pentylthio, tert-pentylthio, n -hexylthio, iso-hexylthio, etc.

The term C_{1-n} -alkylcarbonyl denotes a C_{1-n} -alkyl $-C(=O)-$ group, wherein C_{1-n} -alkyl is defined as above. Examples of such groups include methylcarbonyl, ethylcarbonyl, n -propylcarbonyl, iso-propylcarbonyl, n -butylcarbonyl, iso-butylcarbonyl, sec-

butylcarbonyl, tert-butylcarbonyl, n-pentylcarbonyl, iso-pentylcarbonyl, neo-pentylcarbonyl, tert-pentylcarbonyl, n-hexylcarbonyl, iso-hexylcarbonyl, etc.

The term C_{3-n}-cycloalkyl denotes a saturated mono-, bi-, tri- or spirocarbocyclic, preferably monocarbocyclic group with 3 to n C atoms. Examples of such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclododecyl, bicyclo[3,2,1]octyl, spiro[4,5]decyl, norpinyl, norbonyl, norcaryl, adamantyl, etc.

10 The term C_{5-n}-cycloalkenyl denotes a monounsaturated mono-, bi-, tri- or spirocarbocyclic group with 5 to n C atoms. Examples of such groups include cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclononenyl, etc.

15 The term C_{3-n}-cycloalkylcarbonyl denotes a C_{3-n}-cycloalkyl-C(=O) group, wherein C_{3-n}-cycloalkyl is as hereinbefore defined.

The term aryl denotes a carbocyclic, aromatic ring system, such as for example phenyl, biphenyl, naphthyl, anthracenyl, phenanthrenyl, fluorenyl, indenyl, pentalenyl, azulenyl, biphenylenyl, etc. A particularly preferred meaning of "aryl" is phenyl.

20

The term cyclo-C₃₋₇-alkyleneimino denotes a 4- to 7-membered ring which comprises 3 to 7 methylene units as well as an imino group, while the bond to the residue of the molecule is made via the imino group.

25 The term cyclo-C₃₋₇-alkyleneimino-carbonyl denotes a cyclo-C₃₋₇-alkyleneimino ring as hereinbefore defined which is linked to a carbonyl group via the imino group.

The term heteroaryl used in this application denotes a heterocyclic, aromatic ring system which comprises in addition to at least one C atom one or more heteroatoms selected from N, O and/or S. Examples of such groups are furanyl, thiophenyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,3,5-triazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl,

30

tetrazolyl, thiadiazinyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl (thianaphthenyl), indazolyl, benzimidazolyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, purinyl, quinazolinyl, quinozilanyl, quinolinyl, isoquinolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, azepinyl, diazepinyl, acridinyl, etc. The term heteroaryl also comprises the partially hydrogenated heterocyclic, aromatic ring systems, particularly those listed above. Examples of such partially hydrogenated ring systems are 2,3-dihydrobenzofuranyl, pyrrolinyl, pyrazolinyl, indolinyl, oxazolidinyl, oxazolinyl, oxazepinyl, etc. Particularly preferably heteroaryl denotes a heteroaromatic mono- or bicyclic ring system.

Terms such as aryl-C_{1-n}-alkyl, heteroaryl-C_{1-n}-alkyl, etc. refer to C_{1-n}-alkyl, as defined above, which is substituted with an aryl or heteroaryl group.

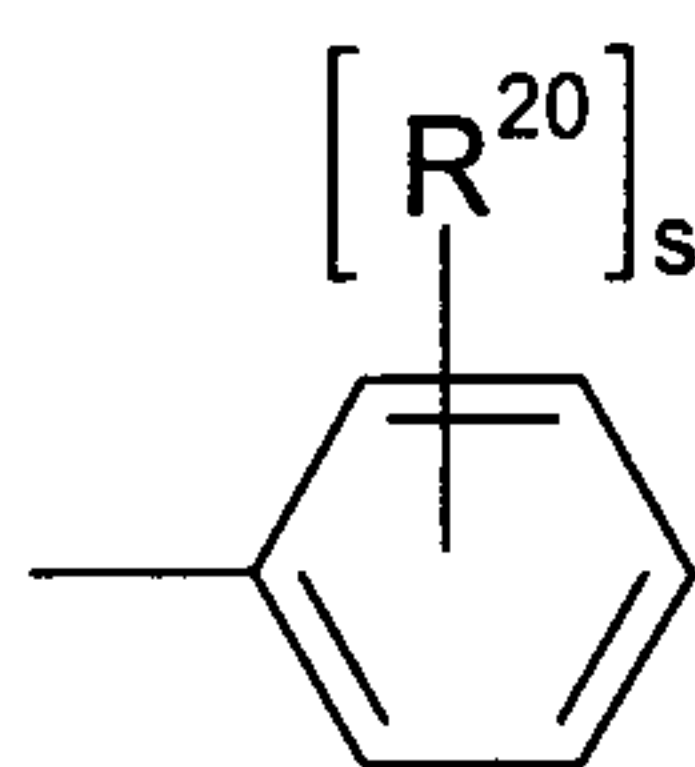
Many of the terms given above may be used repeatedly in the definition of a formula or group and in each case have one of the meanings given above, independently of one another.

The term "unsaturated", for example in "unsaturated carbocyclic group" or "unsaturated heterocyclic group", as used particularly in the definition of the group Cy, comprises in addition to the mono- or polyunsaturated groups, the corresponding, totally unsaturated groups, but particularly the mono- and diunsaturated groups.

The term "optionally substituted" used in this application indicates that the group thus designated is either unsubstituted or mono- or polysubstituted by the substituents specified. If the group in question is polysubstituted, the substituents may be identical or different.

The style used hereinbefore and hereinafter, according to which in a cyclic group a bond of a substituent is shown towards the centre of this cyclic group, unless otherwise stated, indicates that this substituent may be bound to any free position of the cyclic group carrying an H atom.

Thus in the example



the substituent R^{20} where $s = 1$ may be bound to any of the free positions of the phenyl ring; where $s = 2$ selected substituents R^{20} may differently from one another be bound to different free positions of the phenyl ring.

- 5 The H atom of any carboxy group present or an H atom bound to an N atom (imino or amino group) may in each case be replaced by a group which can be cleaved in vivo. By a group which can be cleaved in vivo from an N atom is meant, for example, a hydroxy group, an acyl group such as the benzoyl or pyridinoyl group or a C_{1-16} -alkanoyl group such as the formyl, acetyl, propionyl, butanoyl, pentanoyl or
- 10 hexanoyl group, an allyloxycarbonyl group, a C_{1-16} -alkoxycarbonyl group such as the methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert.butoxycarbonyl, pentoxycarbonyl, hexyloxycarbonyl, octyloxycarbonyl, nonyloxycarbonyl, decyloxycarbonyl, undecyloxycarbonyl, dodecyloxycarbonyl or hexadecyloxycarbonyl group, a phenyl- C_{1-6} -alkoxycarbonyl
- 15 group such as the benzyloxycarbonyl, phenylethoxycarbonyl or phenylpropoxycarbonyl group, a C_{1-3} -alkylsulphonyl- C_{2-4} -alkoxycarbonyl, C_{1-3} -alkoxy- C_{2-4} -alkoxy- C_{2-4} -alkoxycarbonyl or $R_eCO-O-(R_fCR_g)-O-CO-$ group wherein

R_e denotes a C_{1-8} -alkyl, C_{5-7} -cycloalkyl, phenyl or phenyl- C_{1-3} -alkyl group,

20

R_f denotes a hydrogen atom, a C_{1-3} -alkyl, C_{5-7} -cycloalkyl or phenyl group and

R_g denotes a hydrogen atom, a C_{1-3} -alkyl or $R_eCO-O-(R_fCR_g)-O$ group wherein

R_e to R_g are as hereinbefore defined,

25

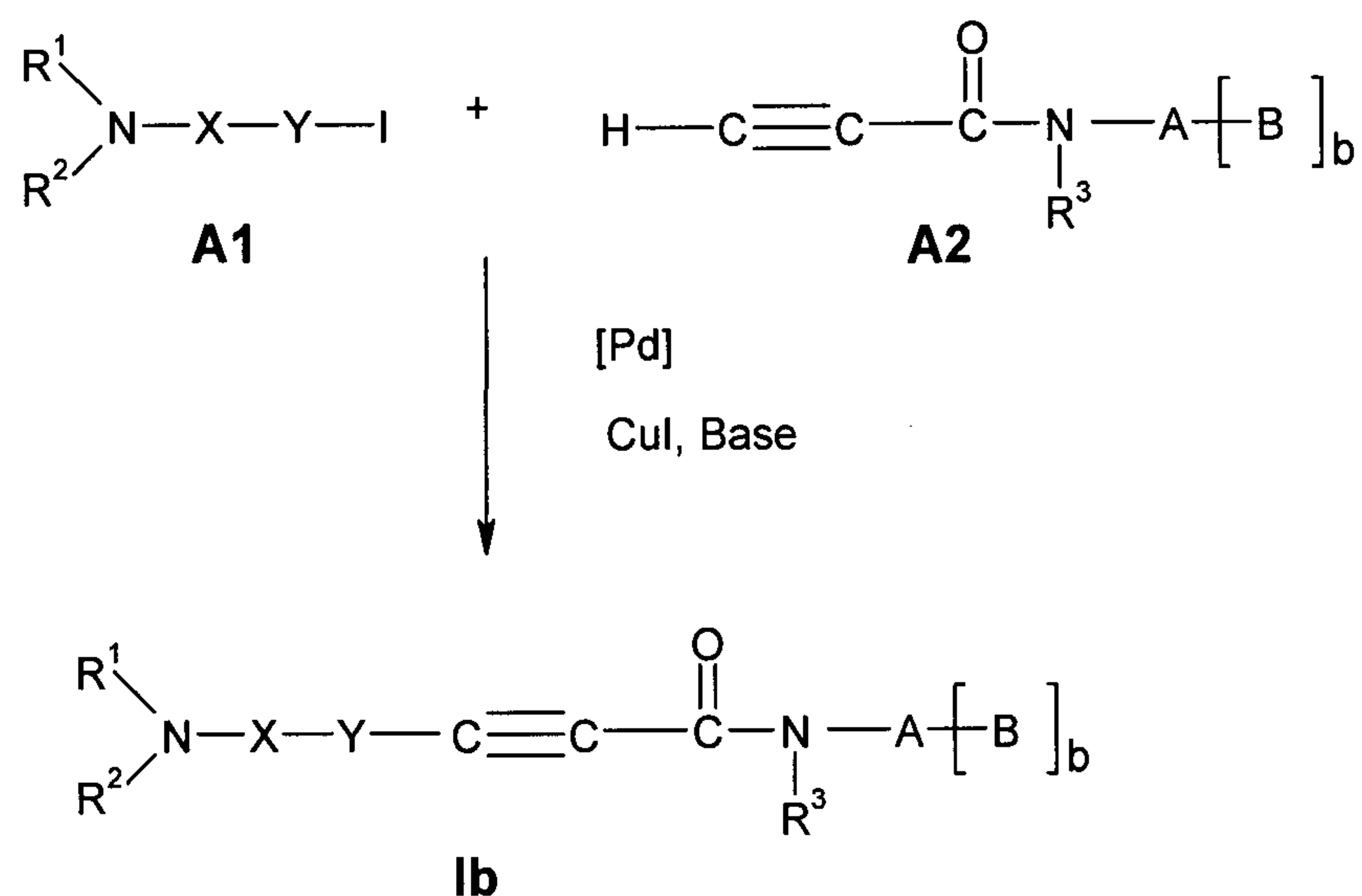
while the phthalimido group is an additionally possibility for an amino group, and the above-mentioned ester groups may also be used as a group which can be converted in vivo into a carboxy group.

The residues and substituents described above may be mono- or polysubstituted by fluorine as described. Preferred fluorinated alkyl groups are fluoromethyl, difluoromethyl and trifluoromethyl. Preferred fluorinated alkoxy groups are fluoromethoxy, difluoromethoxy and trifluoromethoxy. Preferred fluorinated alkylsulphinyl and alkylsulphonyl groups are trifluoromethylsulphinyl and trifluoromethylsulphonyl.

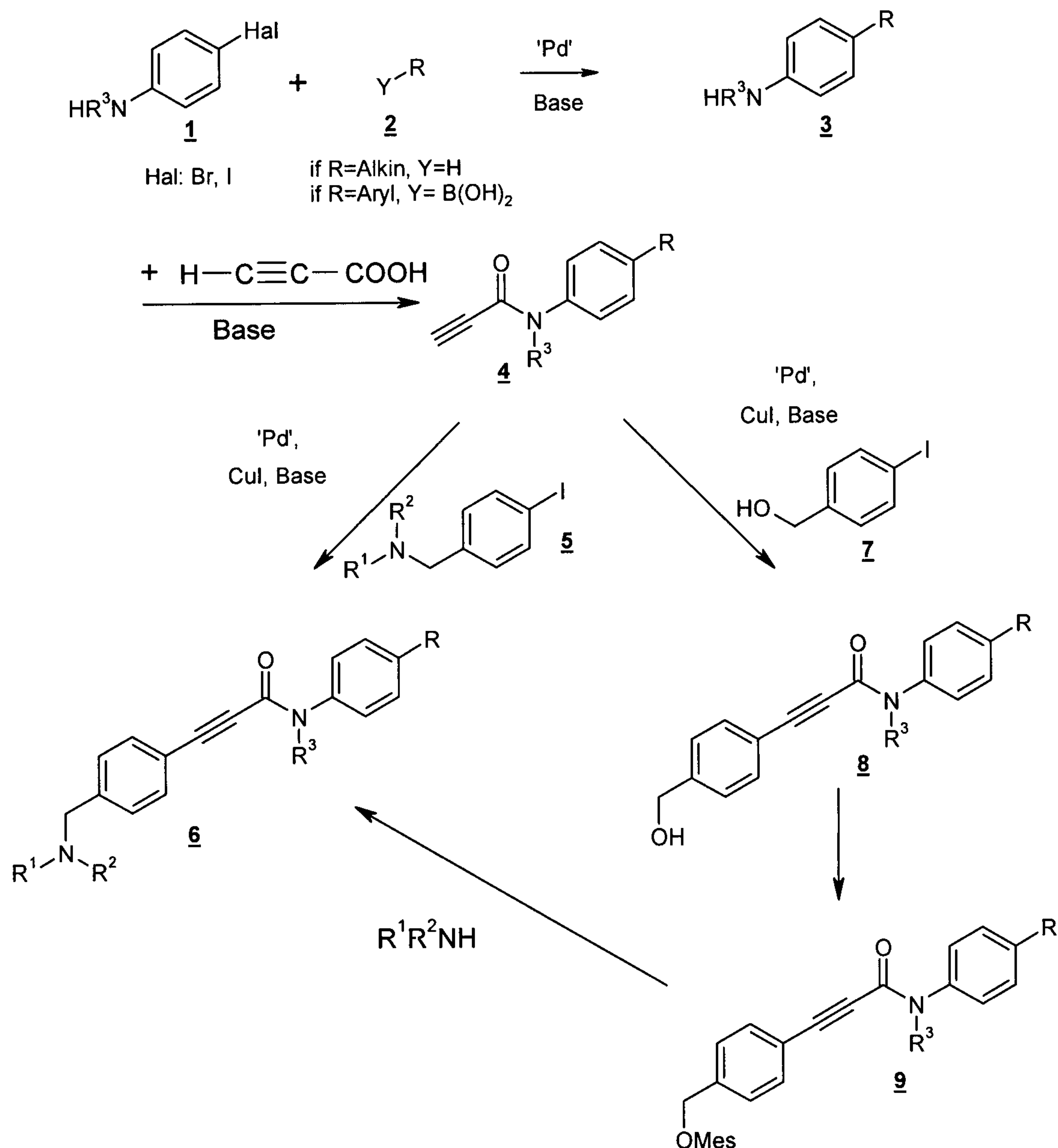
The compounds of general formula I according to the invention may have acid groups, predominantly carboxyl groups, and/or basic groups such as e.g. amino functions. Compounds of general formula I may therefore be present as internal salts, as salts with pharmaceutically useable inorganic acids such as hydrochloric acid, sulphuric acid, phosphoric acid, sulphonic acid or organic acids (such as for example maleic acid, fumaric acid, citric acid, tartaric acid or acetic acid) or as salts with pharmaceutically useable bases such as alkali or alkaline earth metal hydroxides or carbonates, zinc or ammonium hydroxides or organic amines such as e.g. diethylamine, triethylamine, triethanolamine *inter alia*.

The compounds according to the invention may be obtained using methods of synthesis which are known in principle. Preferably the compounds are obtained analogously to the methods of preparation explained more fully hereinafter, which are also an object of this invention. The abbreviations used hereinafter are defined in the introduction to the experimental section or are already familiar to those skilled in the art.

If the starting materials or intermediate products listed below contain groups R^1 , R^2 , R^3 , X, Y, Z, A or B with amine functions, these are preferably used in protected form, for example with a Boc, Fmoc or Cbz protective group, and liberated at the end of the reactions using standard methods.

Diagram 1:

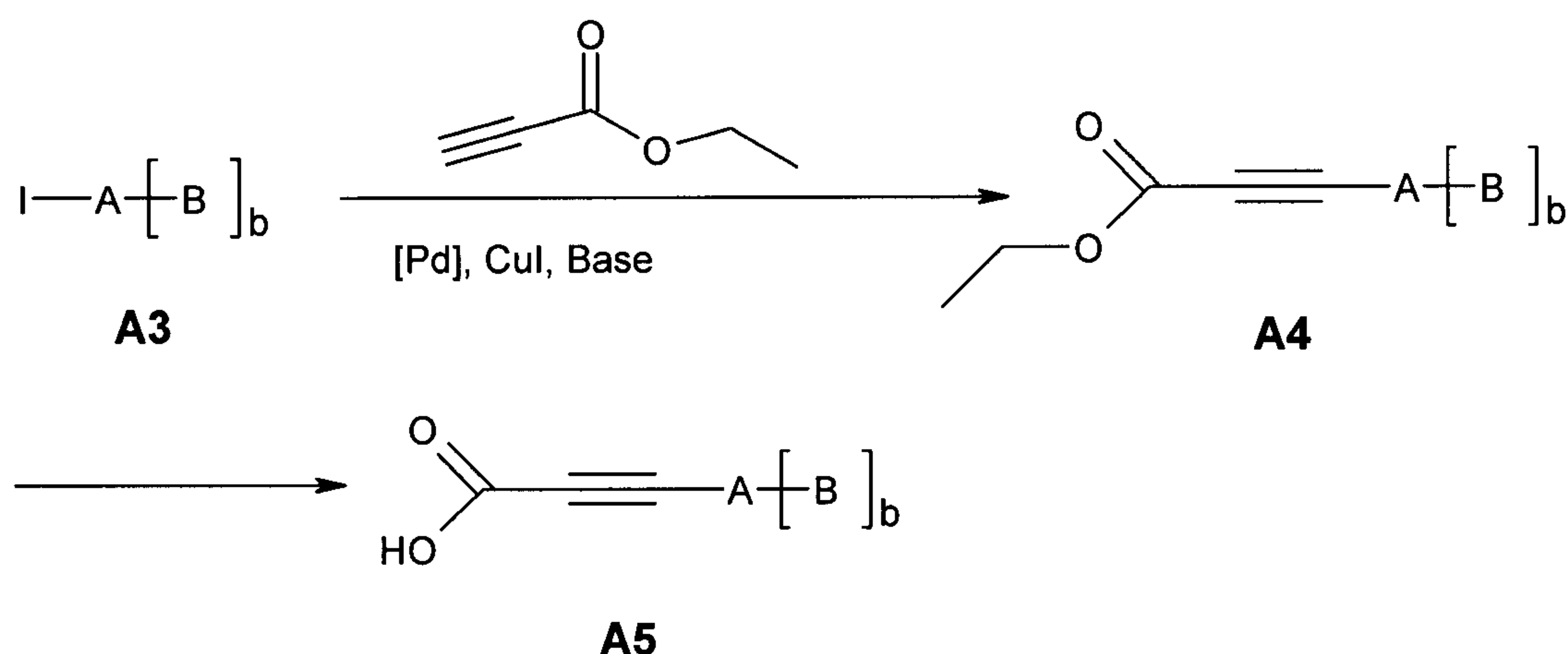
To obtain a compound of general formula Ib, a compound of general formula A1 is
 5 reacted with a compound of general formula A2 in a Sonogashira coupling in the
 presence of a catalyst such as for example palladium with or without ligands and
 copper iodide in a solvent such as for example dioxane, DMF, toluene, acetonitrile or
 THF or a mixture of solvents, using an amine base such as for example triethylamine
 or an inorganic base such as caesium carbonate at temperatures between -20 °C and
 10 200 °C.

Diagram 2:

In order to obtain compounds of formula 6, an aniline derivative of formula 1 is
 5 reacted with a compound of formula 2. If the compound 2 is an arylboric acid
 derivative, the reaction to the compound 3 is carried out in the presence of a catalyst
 such as for example palladium with or without ligands in a solvent or mixture of
 solvents comprising for example dioxane, DMF, toluene, THF or water using a base
 such as for example triethylamine or potassium carbonate at temperatures between
 10 ambient temperature and 200°C. Instead of the arylboric acid derivatives it is also
 possible to use organometallic aryl compounds such as for example tin or zinc
 compounds. If the compound 2 is an alkyne derivative, the reaction to obtain the

compound 3 is carried out as a Sonogashira coupling in the presence of a catalyst such as for example palladium with or without ligands and copper iodide in a solvent or mixture of solvents comprising for example dioxane, DMF, toluene, acetonitrile or THF using a base such as for example triethylamine at temperatures between -20°C and 200 °C. A compound of formula 4 is obtained by reacting a compound of formula 3 with propynecarboxylic acid in the presence of a base and activating reagents such as for example CDI, TBTU or DCC. Instead of the propynecarboxylic acid it is also possible to use propynecarboxylic acid chloride. Compounds of formula 4 may be reacted to compounds of formula 6 by a Sonogashira coupling as hereinbefore described. Alternatively a compound of formula 4 may be reacted with compound 7 in a Sonogashira coupling as described. The resulting compound of formula 8 is converted into the sulphonic acid derivative 9 by reacting with methanesulphonic acid chloride in the presence of a base such as triethylamine in an inert solvent such as for example dichloromethane at a temperature between 0°C and 50°C. For the reaction to a compound of formula 6 it is possible to use an analogous tosylate or a corresponding halogen compound instead of the mesylate 9. A compound of formula 9 is reacted with the corresponding amine in a solvent such as for example THF at a temperature between 0°C and 150 °C, producing a compound of formula 6.

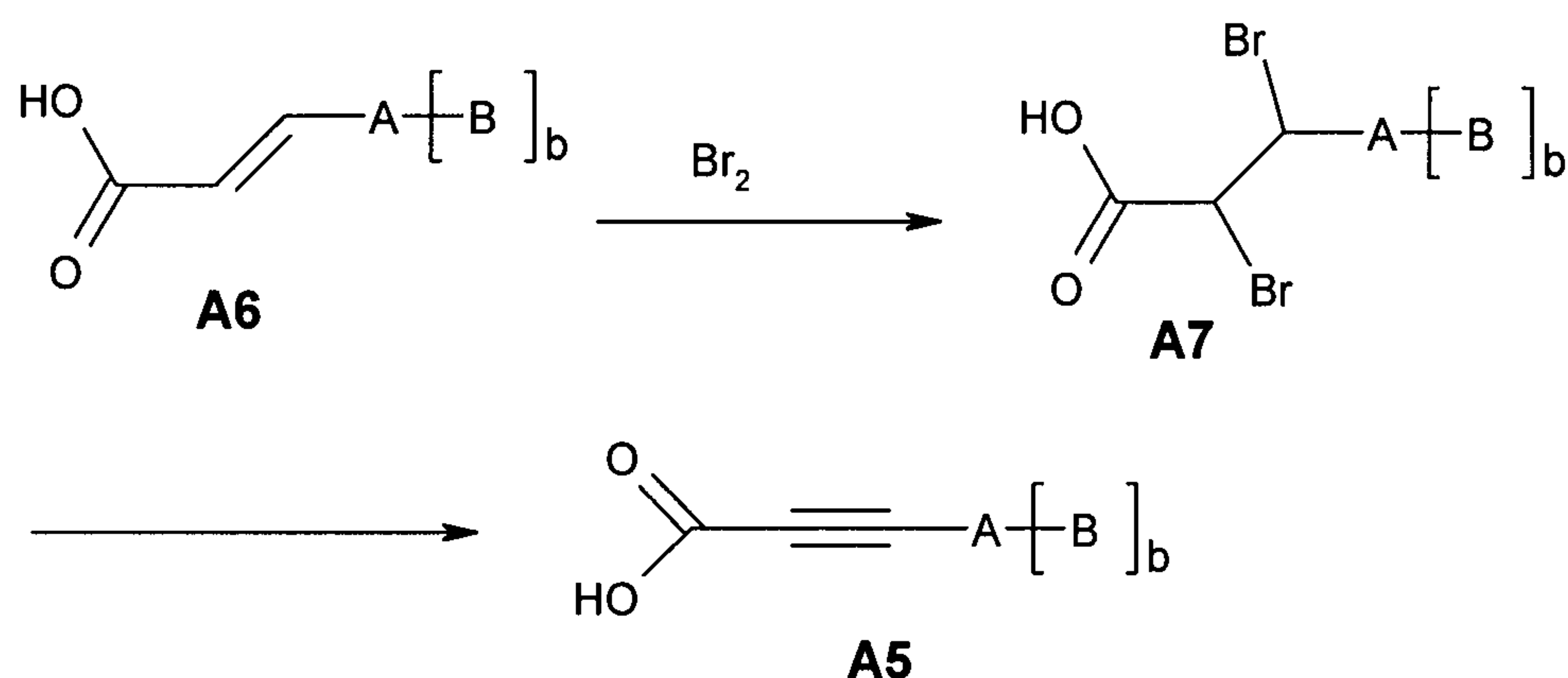
20 Diagram 3a:



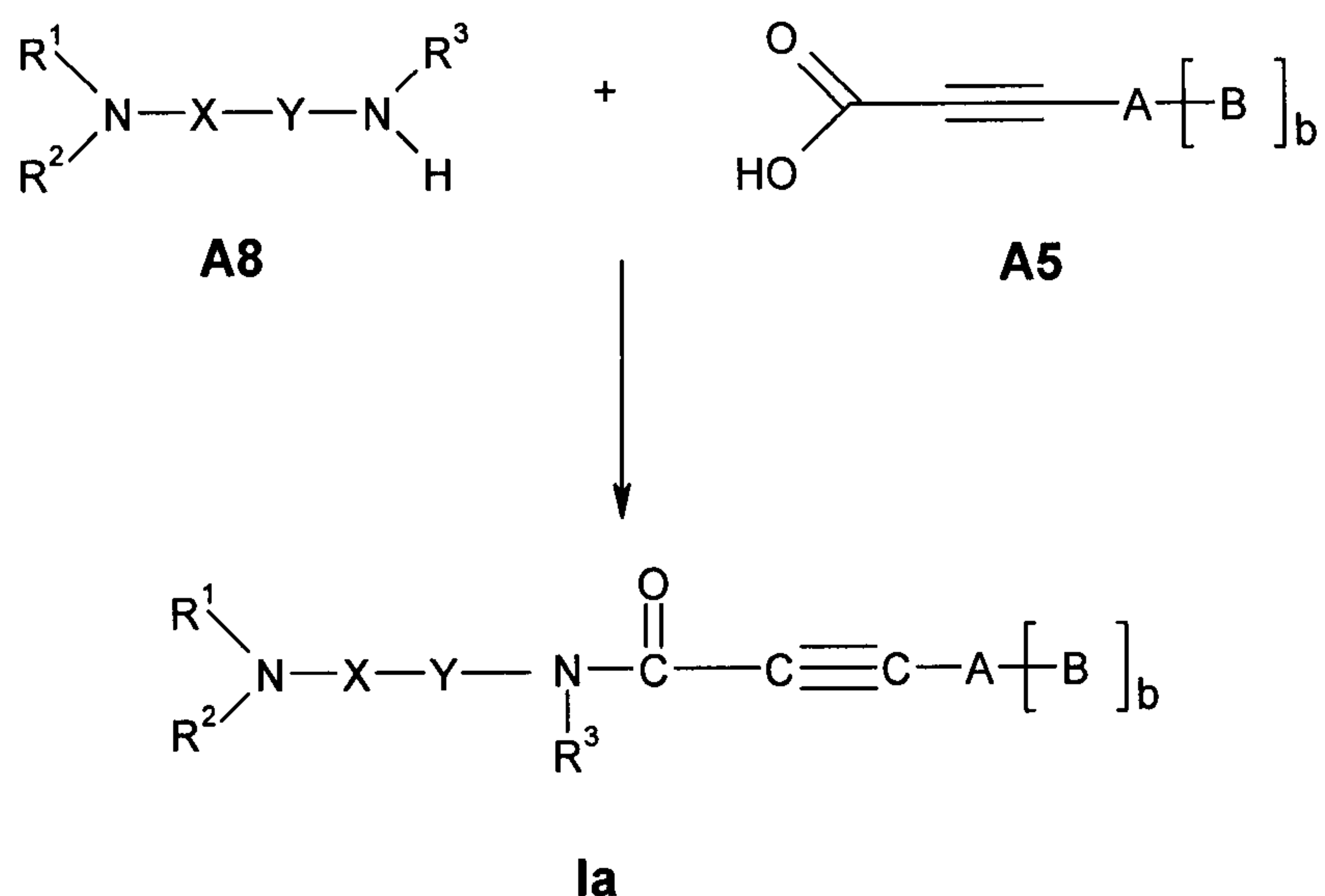
In order to obtain a compound of general formula A4, a compound of general formula A3 is reacted with an ester of propynoic acid, preferably with ethyl propynoate, in a Sonogashira coupling in the presence of a catalyst such as for example palladium with or without ligands and copper iodide in a solvent such as for example dioxane, DMF, toluene, acetonitrile or THF or a solvent mixture, using an amine base such as

for example triethylamine or an inorganic base such as caesium carbonate, at temperatures between -20°C and 200°C. The compound of general formula A4 is converted into a compound of general formula A5 in the course of an ester splitting. The ester splitting may take place in a solvent such as ethanol, dioxane or THF with or without the addition of water in the presence of an inorganic base such as sodium hydroxide, lithium hydroxide, potassium hydroxide or potassium carbonate at temperatures from 0°C to 150°C. Ester splitting is also possible in an organic solvent such as THF or dioxane in the presence of acid, for example aqueous hydrochloric acid or sulphuric acid.

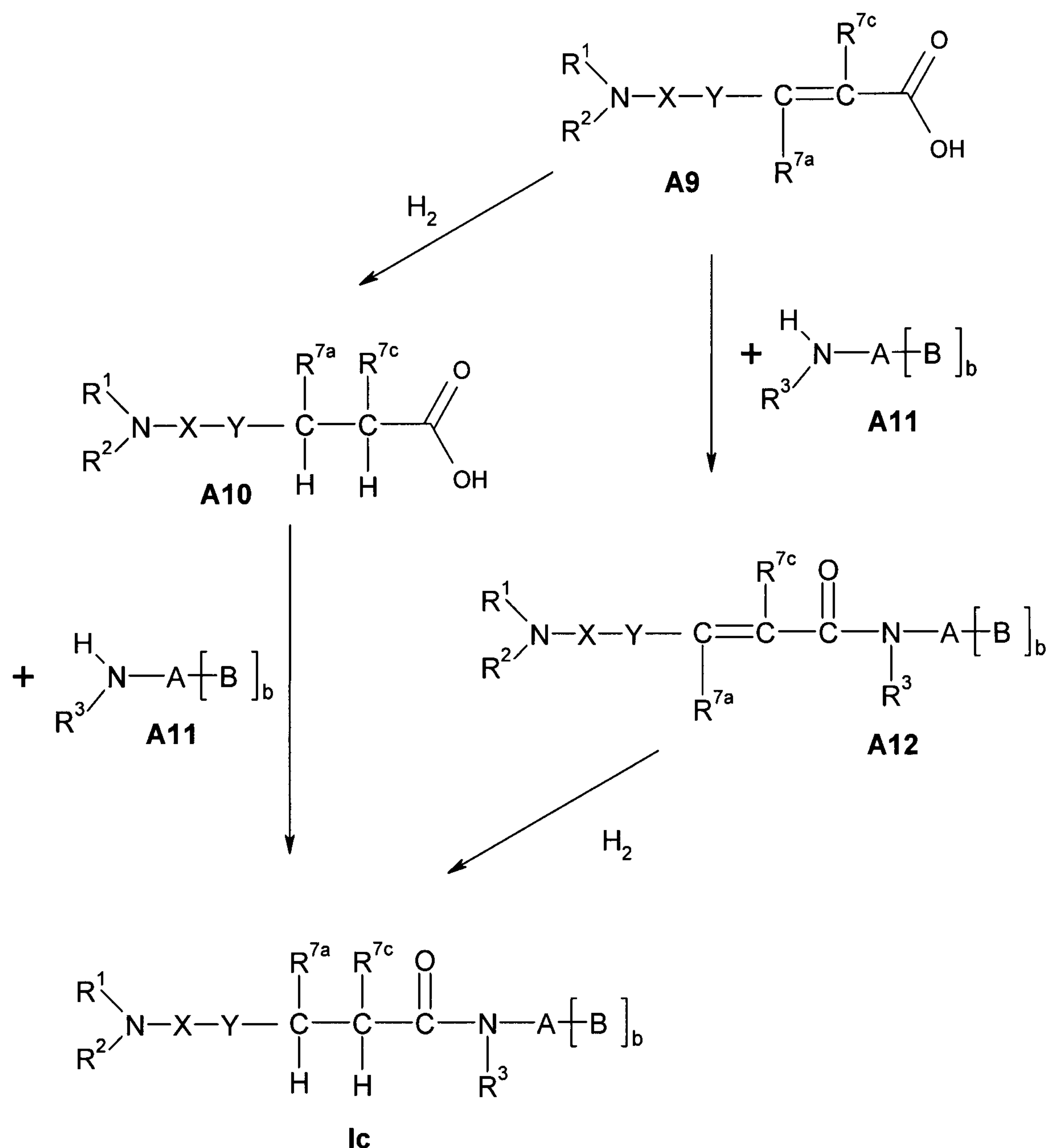
Diagram 3b:



A compound of general formula A5 may also be prepared by reacting a compound of general formula A7 in an organic solvent such as for example dioxane, ethanol or THF with or without the addition of water with a base such as potassium tert. butoxide, sodium hydroxide or sodium ethoxide at temperatures from 0°C to 150°C. However, it is also possible in this reaction to react a compound of general formula A7 with pyridine or quinoline at temperatures from 0°C to 150°C. A compound of general formula A7 is obtained by brominating a compound of general formula A6 in a solvent such as for example carbon tetrachloride at temperatures between -20°C to 100°C, preferably at temperatures between 0°C and ambient temperature.

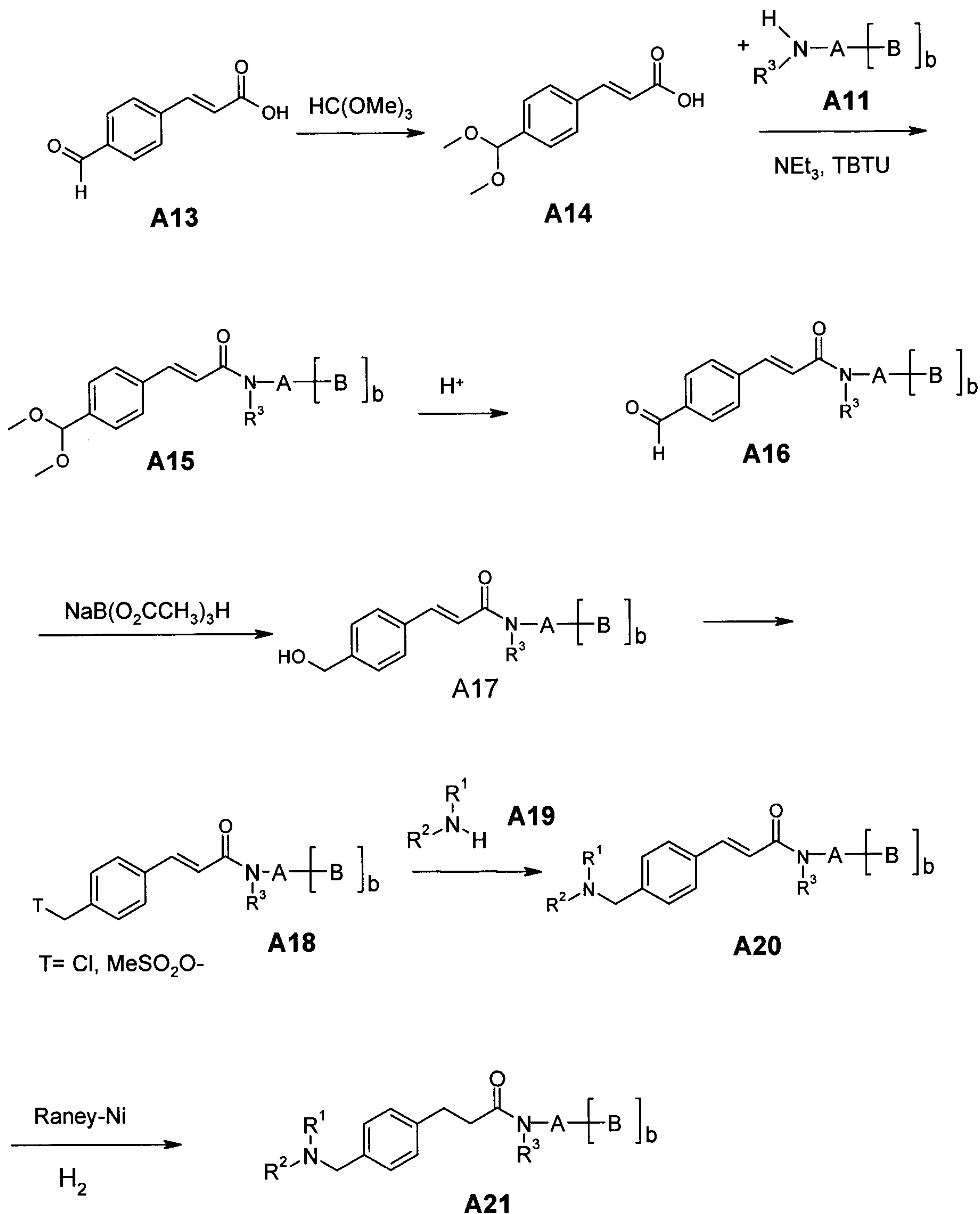
Diagram 3c:

- A compound of general formula 1a is obtained by reacting a compound of general formula A8 with a compound of general formula A5 in an organic solvent such as for example DMF, THF, dioxane, acetonitrile or toluene in the presence of a base such as for example triethylamine and activating reagents such as for example CDI, TBTU or DCC. Instead of the compound A5 it is also possible to use carboxylic acid chloride or a mixed anhydride of the compound A5 .
- 5

Diagram 4:

A compound of general formula **Ic** is advantageously obtained by hydrogenation of a compound of general formula **A12** in an organic solvent such as for example methanol, ethanol, THF or dioxane in the presence of a catalyst such as Raney nickel, palladium or platinum at temperatures between 0 °C and 150° C. The reaction of the compound **A12** to the compound **Ic** may however also take place in the presence of other hydrogen-transferring reagents. A compound of general formula **A12** is obtained by reacting a compound of general formula **A9** with a compound of general formula **A11** in an organic solvent such as for example DMF, THF, dioxane,

acetonitrile or toluene in the presence of a base such as for example triethylamine and activating reagents such as for example CDI, TBTU or DCC. Instead of the compound A9 it is also possible to use the carboxylic acid chloride of the compound A9. Compound Ic may also be obtained by reacting a compound of general formula A10 with a compound of general formula A11 under conditions as described above for the reaction of A9 and A11 to A12. The compound of general formula A10 may be obtained by reduction of a compound of general formula A9 analogously to the reaction of A12 to Ic.

Diagram 5:

A compound of general formula A21 may be obtained as follows. The cinnamic acid
 5 derivative A13 is converted by reaction with orthomethyl formate with or without an
 organic solvent such as for example methanol, THF or dioxane at temperatures
 between ambient temperature and 200 °C into the protected cinnamic acid derivative
 A14. This is reacted in the course of an amide linking with the amine of general

formula A11 in the presence of TBTU and triethylamine in an organic solvent such as for example DMF or THF at a temperature between 0 °C and ambient temperature, to obtain a compound of general formula A15. A compound of general formula A16 is obtained by the action of acid such as for example trifluoroacetic acid on the

5 compound A15 in a solvent such as for example dichloromethane, chloroform or water or combinations thereof at temperatures between 0 °C and 100 °C. Reduction of the compound A16 by the action of a hydride transfer agent such as sodium triacetoxyborohydride or sodium borohydride in an organic solvent such as for example THF in the presence of an acid such as acetic acid at temperatures between

10 0° C and 100° C yields a compound of general formula A17. Reacting A17 with methanesulphonic acid chloride in an organic solvent such as dichloromethane in the presence of a base such as triethylamine at temperatures between 0° C and 100° C yields a compound of general formula A18. To convert A17 into A18 it is also possible to react A17 with thionyl chloride. Compound A20 is obtained by reacting A18 with a

15 compound of general formula A19 in an organic solvent such as DMF, acetonitrile or THF at temperatures of 0°C and 100°C. A compound of general formula A21 is obtained by hydrogenation of a compound of general formula A20 in an organic solvent such as for example methanol, ethanol, THF or dioxane in the presence of a catalyst such as Raney nickel, palladium or platinum at temperatures between 0°C

20 and 150°C. The reaction of compound A20 to compound A21 may however also be carried out in the presence of other hydrogen-transferring reagents.

The compounds according to the invention may advantageously also be obtained by the processes described in the Examples that follow, and these may also be

25 combined with processes known to the skilled man from the literature, for example from WO 04/024702, WO 04/039780 and WO 04/039764.

Stereoisomeric compounds of formula (I) may chiefly be separated by conventional methods. The diastereomers are separated on the basis of their different physico-

30 chemical properties, e.g. by fractional crystallisation from suitable solvents, by high pressure liquid or column chromatography, using chiral or preferably non-chiral stationary phases.

Racemates covered by general formula (I) may be separated for example by HPLC on suitable chiral stationary phases (e.g. Chiral AGP, Chiralpak AD). Racemates which contain a basic or acidic function can also be separated via the diastereomeric, optically active salts which are produced on reacting with an optically active acid, for example (+) or (-)-tartaric acid, (+) or (-)-diacetyl tartaric acid, (+) or (-)-monomethyl tartrate or (+)-camphorsulphonic acid, or an optically active base, for example with (R)-(+)-1-phenylethylamine, (S)-(-)-1-phenylethylamine or (S)-brucine.

According to a conventional method of separating isomers, the racemate of a compound of general formula (I) is reacted with one of the above-mentioned optically active acids or bases in equimolar amounts in a solvent and the resulting crystalline, diastereomeric, optically active salts thereof are separated using their different solubilities. This reaction may be carried out in any type of solvent provided that it is sufficiently different in terms of the solubility of the salts. Preferably, methanol, ethanol or mixtures thereof, for example in a ratio by volume of 50:50, are used. Then each of the optically active salts is dissolved in water, carefully neutralised with a base such as sodium carbonate or potassium carbonate, or with a suitable acid, e.g. with dilute hydrochloric acid or aqueous methanesulphonic acid and in this way the corresponding free compound is obtained in the (+) or (-) form.

The (R) or (S) enantiomer alone or a mixture of two optically active diastereomeric compounds covered by general formula I may also be obtained by performing the syntheses described above with a suitable reaction component in the (R) or (S) configuration.

As already mentioned, the compounds of formula (I) may be converted into the salts thereof, particularly for pharmaceutical use into the physiologically and pharmacologically acceptable salts thereof. These salts may be present on the one hand as physiologically and pharmacologically acceptable acid addition salts of the compounds of formula (I) with inorganic or organic acids. On the other hand, in the case of acidically bound hydrogen, the compound of formula (I) may also be converted by reaction with inorganic bases into physiologically and pharmacologically acceptable salts with alkali or alkaline earth metal cations as counter-ion. The acid addition salts may be prepared, for example, using hydrochloric acid, hydrobromic

acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, toluenesulphonic acid, benzenesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid. Moreover, mixtures of the above mentioned acids may be used. To prepare the alkali and alkaline earth metal salts of the compound of formula (I) with acidically bound hydrogen the alkali and alkaline earth metal hydroxides and hydrides are preferably used, while the hydroxides and hydrides of the alkali metals, particularly of sodium and potassium, are preferred and sodium and potassium hydroxide are most preferred.

10 The compounds according to the present invention, including the physiologically acceptable salts, are effective as antagonists of the MCH receptor, particularly the MCH-1 receptor, and exhibit good affinity in MCH receptor binding studies. Pharmacological test systems for MCH-antagonistic properties are described in the following experimental section.

15 As antagonists of the MCH receptor the compounds according to the invention are advantageously suitable as pharmaceutical active substances for the prevention and/or treatment of symptoms and/or diseases caused by MCH or causally connected with MCH in some other way. Generally the compounds according to the invention have low toxicity, they are well absorbed by oral route and have good intracerebral transitivity, particularly brain accessibility.

20 Therefore, MCH antagonists which contain at least one compound according to the invention are particularly suitable in mammals, such as for example rats, mice, guinea pigs, hares, dogs, cats, sheep, horses, pigs, cattle, monkeys and particularly humans, for the treatment and/or prevention of symptoms and/or diseases which are caused by MCH or are otherwise causally connected with MCH.

30 Diseases caused by MCH or otherwise causally connected with MCH are particularly metabolic disorders, such as for example obesity, and eating disorders, such as for example bulimia, including bulimia nervosa. The indication obesity includes in particular exogenic obesity, hyperinsulinaemic obesity, hyperplasmic obesity, hyperphyseal adiposity, hypoplasmic obesity, hypothyroid obesity, hypothalamic obesity, symptomatic obesity, infantile obesity, upper body obesity, alimentary

obesity, hypogonadal obesity, central obesity. This range of indications also includes cachexia, anorexia and hyperphagia.

Compounds according to the invention may be particularly suitable for reducing
5 hunger, reining in appetite, controlling eating behaviour and/or inducing a feeling of satiation.

In addition, the diseases caused by MCH or otherwise causally connected with MCH also include hyperlipidaemia, cellulitis, fatty accumulation, malignant mastocytosis,
10 systemic mastocytosis, emotional disorders, affectivity disorders, depression, anxiety states, reproductive disorders, sexual disorders, memory disorders, epilepsy, forms of dementia and hormonal disorders.

Compounds according to the invention are also suitable as active substances for the
15 prevention and/or treatment of other illnesses and/or disorders, particularly those which accompany obesity, such as for example diabetes, diabetes mellitus, particularly type II diabetes, hyperglycaemia, particularly chronic hyperglycaemia, complications of diabetes including diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, etc., insulin resistance, pathological glucose tolerance,
20 encephalorrhagia, cardiac insufficiency, cardiovascular diseases, particularly arteriosclerosis and high blood pressure, arthritis and gonitis.

MCH antagonists and formulations according to the invention may advantageously be used in combination with a dietary therapy, such as for example a dietary diabetes
25 treatment, and exercise.

Another range of indications for which the compounds according to the invention are advantageously suitable is the prevention and/or treatment of micturition disorders, such as for example urinary incontinence, hyperactive bladder, nycturia, enuresis,
30 while the hyperactive bladder and urinary incontinence may or may not be connected with benign prostatic hyperplasia.

The dosage required to achieve such an effect is conveniently, by intravenous or sub-cutaneous route, 0.001 to 30 mg/kg of body weight, preferably 0.01 to 5 mg/kg of

body weight, and by oral or nasal route or by inhalation, 0.01 to 50 mg/kg of body weight, preferably 0.1 to 30 mg/kg of body weight, in each case 1 to 3 x daily.

For this purpose, the compounds of formula I prepared according to the invention may
5 be formulated, optionally together with other active substances as described hereinafter, together with one or more physiologically acceptable excipients, inert conventional carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene
10 glycol, propylene glycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof, to produce conventional galenic preparations such as plain or coated tablets, capsules, powders, granules, solutions, emulsions, syrups, aerosols for inhalation, ointments or suppositories.

15 In addition to pharmaceutical compositions the invention also includes compositions containing at least one amide compound according to the invention and/ or a salt according to the invention optionally together with one or more physiologically acceptable excipients. Such compositions may also be for example foodstuffs which may be solid or liquid, in which the compound according to the invention is
20 incorporated.

For the above mentioned combinations it is possible to use as additional active substances particularly those which for example potentiate the therapeutic effect of an MCH antagonist according to the invention in terms of one of the indications
25 mentioned above and/or which make it possible to reduce the dosage of an MCH antagonist according to the invention. Preferably one or more additional active substances are selected from among

- active substances for the treatment of diabetes,
- active substances for the treatment of diabetic complications,
- 30 - active substances for the treatment of obesity, preferably other than MCH antagonists,
- active substances for the treatment of high blood pressure,
- active substances for the treatment of hyperlipidaemia, including arteriosclerosis,
- active substances for the treatment of arthritis,

- active substances for the treatment of anxiety states,
- active substances for the treatment of depression.

5 The above mentioned categories of active substances will now be explained in more detail by means of examples.

Examples of active substances for the treatment of diabetes are insulin sensitisers, insulin secretion accelerators, biguanides, insulins, α -glucosidase inhibitors, β 3 adreno-receptor agonists.

10

Insulin sensitisers include pioglitazone and its salts (preferably hydrochloride), troglitazone, rosiglitazone and its salts (preferably maleate), JTT-501, GI-262570, MCC-555, YM-440, DRF-2593, BM-13-1258, KRP-297, R-119702 and GW-1929.

15

Insulin secretion accelerators include sulphonylureas, such as for example tolbutamide, chloropropamide, tolazamide, acetohexamide, glycopyramide and its ammonium salts, glibenclamide, gliclazide, glimepiride. Further examples of insulin secretion accelerators are repaglinide, nateglinide, mitiglinide (KAD-1229) and JTT-608.

20

Biguanides include metformin, buformin and phenformin.

25

Insulins include those obtained from animals, particularly cattle or pigs, semisynthetic human insulins which are synthesised enzymatically from insulin obtained from animals, human insulin obtained by genetic engineering, e.g. from Escherichia coli or yeasts. Moreover, the term insulin also includes insulin-zinc (containing 0.45 to 0.9 percent by weight of zinc) and protamine-insulin-zinc obtainable from zinc chloride, protamine sulphate and insulin. Insulin may also be obtained from insulin fragments or derivatives (for example INS-1, etc.).

30

Insulin may also include different kinds, e.g. with regard to the onset time and duration of effect ("ultra immediate action type", "immediate action type", "two

phase type", "intermediate type", "prolonged action type", etc.), which are selected depending on the pathological condition of the patient.

α -Glucosidase inhibitors include acarbose, voglibose, miglitol, emiglitate.

β_3 Adreno receptor agonists include AJ-9677, BMS-196085, SB-226552, AZ40140.

Active substances for the treatment of diabetes other than those mentioned above include ergoset, pramlintide, leptin, BAY-27-9955 as well as glycogen phosphorylase inhibitors, sorbitol dehydrogenase inhibitors, protein tyrosine phosphatase 1B inhibitors, dipeptidyl protease inhibitors, glipazide, glyburide.

Active substances for the treatment of diabetic complications include for example aldose reductase inhibitors, glycation inhibitors and protein kinase C inhibitors, DPPIV blockers, GLP-1 or GLP-2 analogues and SGLT-2 inhibitors.

Aldose reductase inhibitors are for example tolrestat, epalrestat, imirestat, zenarestat, SNK-860, zopolrestat, ARI-50i, AS-3201.

An example of a glycation inhibitor is pimagedine.

Protein Kinase C inhibitors are for example NGF, LY-333531.

DPPIV blockers are for example LAF237 (Novartis), MK431 (Merck) as well as 815541, 823093 and 825964 (all GlaxoSmithkline).

GLP-1 analogues are for example Liraglutide (NN2211) (NovoNordisk), CJC1131 (Conjuchem), Exenatide (Amylin).

SGLT-2 inhibitors are for example AVE-2268 (Aventis) and T-1095 (Tanabe, Johnson&Johnson).

Active substances other than those mentioned above for the treatment of diabetic complications include alprostadiol, thiapride hydrochloride, cilostazol, mexiletine hydrochloride, ethyl eicosapentate, memantine, pimagedine (ALT-711).

5

Active substances for the treatment of obesity, preferably other than MCH antagonists, include lipase inhibitors and anorectics.

A preferred example of a lipase inhibitor is orlistat.

10

Examples of preferred anorectics are phentermine, mazindol, fluoxetine, sibutramine, baiamine, (S)-sibutramine, SR-141716, NGD-95-1.

15

Active substances other than those mentioned above for the treatment of obesity include lipstatin.

20

Moreover for the purposes of this application the active substance group of anti-obesity active substances also includes the anorectics, of which the β_3 agonists, thyromimetic active substances and NPY antagonists should be emphasised.

25

The range of substances which may be considered as preferred anti-obesity or anorectic active substances is indicated by the following additional list, by way of example: phenylpropanolamine, ephedrine, pseudoephedrine, phentermine, a cholecystokinin-A (hereinafter referred to as CCK-A) agonist, a monoamine reuptake inhibitor (such as for example sibutramine), a sympathomimetic active substance, a serotonergic active substance (such as for example dexfenfluramine, fenfluramine or a 5-HT_{2C} agonist such as BVT.933 or APD356), a dopamine antagonist (such as for example bromocriptine or pramipexol), a melanocyte-stimulating hormone receptor agonist or mimetic, an analogue of melanocyte-stimulating hormone, a cannabinoid receptor antagonist (Rimonabant, ACOMPLIA TM), an MCH antagonist, the OB protein (hereinafter referred to as leptin), a leptin analogue, a leptin receptor agonist, a galanine antagonist, a GI lipase inhibitor or reducer (such as for example orlistat). Other anorectics include bombesin agonists, dehydroepiandrosterone or its analogues, glucocorticoid receptor agonists and antagonists, orexin receptor antagonists,

30

urocortin binding protein antagonists, agonists of the Glucagon-like Peptide-1 receptor, such as for example exendin and ciliary neurotrophic factors, such as for example axokines. In this context mention should also be made of the forms of therapy which produce weight loss by increasing the fatty acid oxidation in the peripheral tissue, such as for example inhibitors of acetyl-CoA carboxylase.

Active substances for the treatment of high blood pressure include inhibitors of angiotensin converting enzyme, calcium antagonists, potassium channel openers and angiotensin II antagonists.

inhibitors of angiotensin converting enzyme include captopril, enalapril, alacepril, delapril (hydrochloride), lisinopril, imidapril, benazepril, cilazapril, temocapril, trandolapril, manidipine (hydrochloride).

Examples of calcium antagonists are nifedipine, amlodipine, efonidipine, nicardipine.

Potassium channel openers include levcromakalim, L-27152, AL0671, NIP-121.

Angiotensin II antagonists include telmisartan, losartan, candesartan cilexetil, valsartan, irbesartan, CS-866, E4177.

Active substances for the treatment of hyperlipidaemia, including arteriosclerosis, include HMG-CoA reductase inhibitors, fibrate compounds.

HMG-CoA reductase inhibitors include pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin, lipantil, cerivastatin, itavastatin, ZD-4522 and their salts.

Fibrate compounds include bezafibrate, clinofibrate, clofibrate and simfibrate.

Active substances for the treatment of arthritis include NSAIDs (non-steroidal antiinflammatory drugs), particularly COX2 inhibitors, such as for example meloxicam or ibuprofen.

- 5 Active substances for the treatment of anxiety states include chlordiazepoxide, diazepam, oxazolam, medazepam, cloxazolam, bromazepam, lorazepam, alprazolam, fludiazepam.

- 10 Active substances for the treatment of depression include fluoxetine, fluvoxamine, imipramine, paroxetine, sertraline.

The dosage for these active substances is conveniently $1/5$ of the lowest normal recommended dose up to $1/1$ of the normal recommended dose.

- 15 In another embodiment the invention also relates to the use of at least one alkyne compound according to the invention and/ or a salt according to the invention for influencing the eating behaviour of a mammal. This use is particularly based on the fact that compounds according to the invention may be suitable for reducing hunger, restricting appetite, controlling eating behaviour and/or inducing a feeling of satiety.
- 20 The eating behaviour is advantageously influenced so as to reduce food intake. Therefore, compounds according to the invention are advantageously used for reducing body weight. Another use according to the invention is the prevention of increases in body weight, for example in people who had previously taken steps to lose weight and are interested in maintaining their lower body weight. According to
- 25 this embodiment it is preferably a non-therapeutic use. Such a non-therapeutic use might be a cosmetic use, for example to alter the external appearance, or an application to improve general health. The compounds according to the invention are preferably used non-therapeutically for mammals, particularly humans, not suffering from any diagnosed eating disorders, no diagnosed obesity, bulimia, diabetes and/or
- 30 no diagnosed micturition disorders, particularly urinary incontinence. Preferably, the compounds according to the invention are suitable for non-therapeutic use in people whose BMI (body mass index), defined as their body weight in kilograms divided by their height (in metres) squared, is below a level of 30, particularly below 25.

The Examples that follow are intended to illustrate the invention:

Preliminary remarks:

As a rule, IR, ¹H-NMR and/or mass spectra have been obtained for the compounds prepared. Unless otherwise stated the R_f values were determined using ready-made silica gel 60 TLC plates F₂₅₄ (E. Merck, Darmstadt, Item no. 1.05714) without chamber saturation. The R_f values obtained under the heading Alox were determined using ready-made aluminium oxide 60 TLC plates F₂₅₄ (E. Merck, Darmstadt, Item no. 1.05713) without chamber saturation. The ratios specified for the eluants are based on units by volume of the solvents in question. The units by volume specified in the case of NH₃ relate to a concentrated solution of NH₃ in water. For chromatographic purification, silica gel made by Messrs Millipore (MATREXTM, 35-70 µm) is used. For chromatographic purification, Alox (E. Merck, Darmstadt, standardised aluminium oxide 90, 63-200 µm, Item no.: 1.01097.9050) is used. The HPLC data specified were measured under the parameters indicated below:

Analytical columns: Zorbax column (Agilent Technologies), SB (Stable Bond) - C18; 3.5 µm; 4.6 x 75 mm; column temperature: 30°C; flow: 0.8 mL / min; injection volume: 5 µL; detection at 254 nm (methods A and B).

Symmetry 300 (Waters), 3.5 µm; 4.6 x 75 mm; column temperature: 30°C; flow: 0.8 mL / min; injection volume: 5 µL; detection at 254 nm (method C)

Method A: water:acetonitrile:formic acid 9:1:0.01 towards 1:9:0.01 over 9 min

Method B: water:acetonitrile:formic acid 9:1:0.01 towards 1:9:0.01 over 4 min, then 6 min 1:9:0.01

method C: water:acetonitrile:formic acid 9:1:0.01 after 1:9:0.01 over 4 min, then 6 min 1:9:0.01

Preparative column: Zorbax column (Agilent Technologies), SB (Stable Bond) - C18; 3.5 µm; 30 x 100 mm; column temperature: ambient temperature; flow: 30 mL / min; detection at 254 nm.

In preparative HPLC purification, as a rule the same gradients are used which were used when obtaining the analytical HPLC data.

The products are collected under mass control, the fractions containing the product are combined and freeze-dried.

If there is no specific information as to the configuration, it is not clear whether there are pure enantiomers or whether partial or even total racemisation has taken place.

The following abbreviations are used above and hereinafter:

5		
	abs.	absolute
	Boc	tert-butoxycarbonyl
	Cbz	benzyloxycarbonyl
	CDI	N,N'-carbonyldiimidazole
10	CDT	1,1'-carbonyldi(1,2,4-triazole)
	DMF	N,N-dimethylformamide
	Et	ethyl
	ether	diethyl ether
	EtOAc	ethyl acetate
15	EtOH	ethanol
	Fmoc	9-fluorenylmethoxycarbonyl
	sat.	saturated
	semiconc.	semi-concentrated
	HCl	hydrochloric acid
20	HOAc	acetic acid
	HOBt	1-hydroxybenzotriazole-hydrate
	Hünig base	N-ethyldiisopropylamine
	HV	high vacuum
	i. vac.	in vacuo (under vacuum)
25	KOH	potassium hydroxide
	conc.	concentrated
	Me	methyl
	MeOH	methanol
	MTBE	methyl-tert-butylether
30	NaCl	sodium chloride
	NaOH	sodium hydroxide
	org.	organic
	Ph	phenyl
	RT	ambient temperature (approx. 20°C)

TBTU 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate

TEBAC triethylbenzylammonium chloride

TFA trifluoroacetic acid

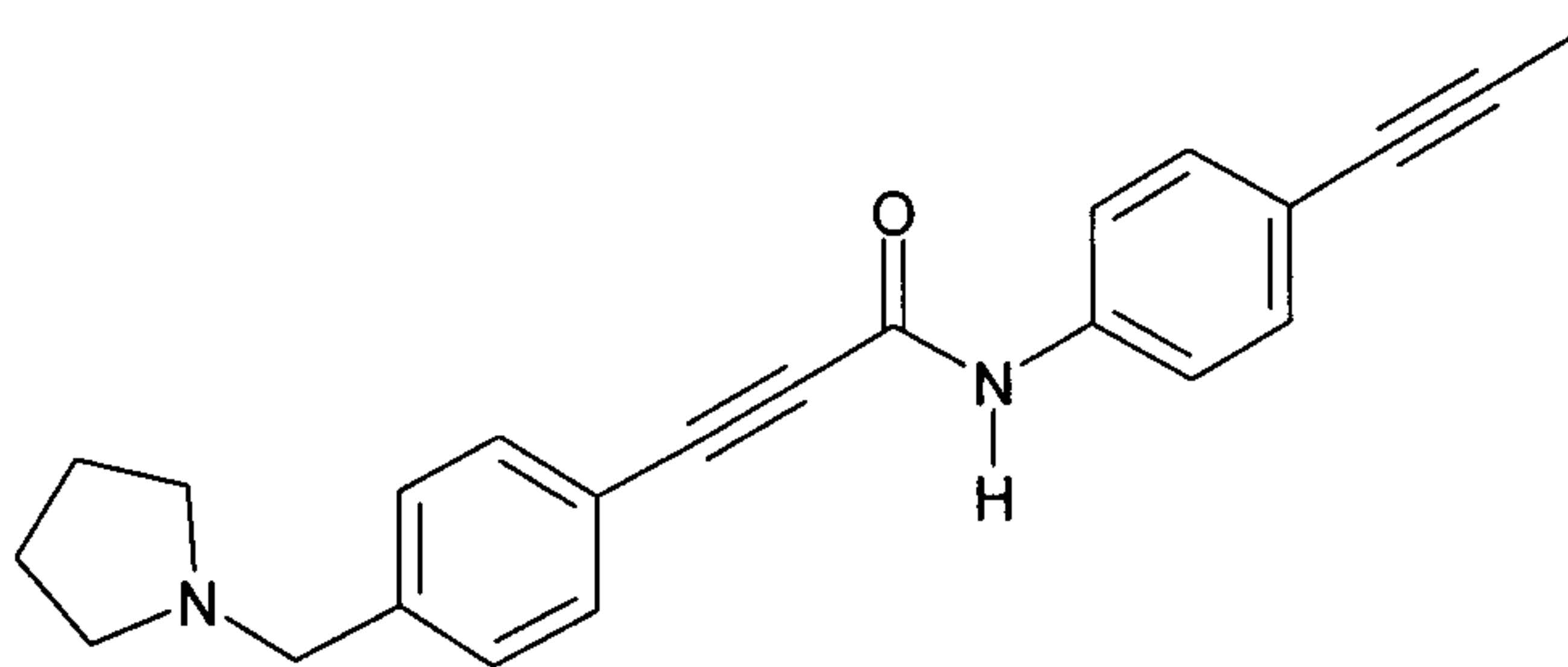
5 THF tetrahydrofuran

→* denotes the binding site of a group

In the structural formulae shown previously and hereinafter, as well as the H atoms at C atoms, the H atoms at O and N atoms, as in hydroxyl or amino groups, for example,
10 are generally not specifically shown for reasons of clarity.

Example 1.1:

3-(4-pyrrolidin-1-ylmethyl-phenyl)-propynoic acid- (4-prop-1-ynyl-phenyl)-amide



5 1.1.a. 4-prop-1-ynyl-phenylamine

5.47 g (25 mmol) 4-iodoaniline, 0.878 g (1.25 mmol) bistrisphenylphosphine palladium dichloride, 0.47 g (2.5 mmol) copper(I)iodide and 20 ml piperidine are placed in a pressure apparatus. Then 6.1 bar gaseous propyne are piped into the pressure apparatus, while the temperature rises to 39°C. It is therefore cooled with water. The mixture is stirred for two hours at ambient temperature and the reaction mixture is then extracted with ethyl acetate and water. The organic phase is dried over sodium sulphate, evaporated down and the residue purified by column chromatography on silica gel (eluant: cyclohexane/ ethyl acetate= 4:1).

Yield: 2.1 g (64 % of theoretical)

15 C₉H₉N (M= 131.17)

Calc.: Molecular ion peak (M+H)⁺: 132

Found: Molecular ion peak

(M+H)⁺: 132

1.1.b. propynoic acid- (4-prop-1-ynyl-phenyl)-amide

20 1.2 g (5.86 mmol) DCC are added to a solution of 375 mg (5.35 mmol) propynoic acid in 10 ml dichloromethane at 0°C and the mixture is stirred for 30 minutes. Then 0.7 g (5.35 mmol) 4-prop-1-ynyl-phenylamine, dissolved in dichloromethane, are slowly added dropwise and the mixture is stirred for two hours again at 0°C. The reaction mixture is then filtered through Celite and the filtrate is evaporated down. The purification is carried out by column chromatography on silica gel (eluant: dichloromethane/ethanol= 40:1).

Yield: 0.7 g (71.4 % of theoretical)

25 C₁₂H₉NO (M= 183.21)

Calc.: Molecular ion peak (M+H)⁺: 184
(M+H)⁺: 184

Found: Molecular ion peak

R_f value: 0.65 (silica gel, dichloromethane/ethanol/acetic acid 20:1)

5 1.1.c. 1-(4-iodobenzyl)-pyrrolidine

A solution of 5 g (16.83 mmol) 4-iodobenzyl bromide, 1.41 ml (17 mmol) pyrrolidine and 4.8 ml (34.43 mmol) triethylamine in 50 ml dichloromethane are stirred for 14 hours at ambient temperature. The reaction mixture is combined with water, the organic phase is separated off and dried over sodium sulphate.

10 Yield: 4 g (82.7 % of theoretical)

C₁₁H₁₄IN (M= 287.14)

Calc.: Molecular ion peak (M+H)⁺: 288
(M+H)⁺: 288

Found: Molecular ion peak

15 1.1.d. 3-(4-pyrrolidin-1-ylmethyl-phenyl)-propynoic acid- (4-prop-1-ynyl-phenyl)-amide

10 ml acetonitrile are degassed and combined with 0.35 ml (2 mmol) ethyldiisopropylamine and 0.2 g (0.69 mmol) 1-(4-iodobenzyl)-pyrrolidine. Then the mixture is again degassed and 13 mg copper(I)iodide, 34 mg tetrakis(triphenylphosphine) palladium and 137 mg (0.75 mmol) propynoic acid- (4-prop-1-ynyl-phenyl)-amide are then added in succession. The reaction mixture is stirred for 24 hours at ambient temperature and then combined with 60 mg propynoic acid- (4-prop-1-ynyl-phenyl)-amide. After 24 hours the mixture is evaporated down. The purification is carried out by column chromatography on silica gel (dichloromethane/ methanol/ ammonia = 30:1:0.1 to 20:1:0.1)

25 Yield: 24 mg (10 % of theoretical)

C₂₃H₂₂N₂O (M= 342.44)

Calc.: Molecular ion peak (M+H)⁺: 343
(M+H)⁺: 343

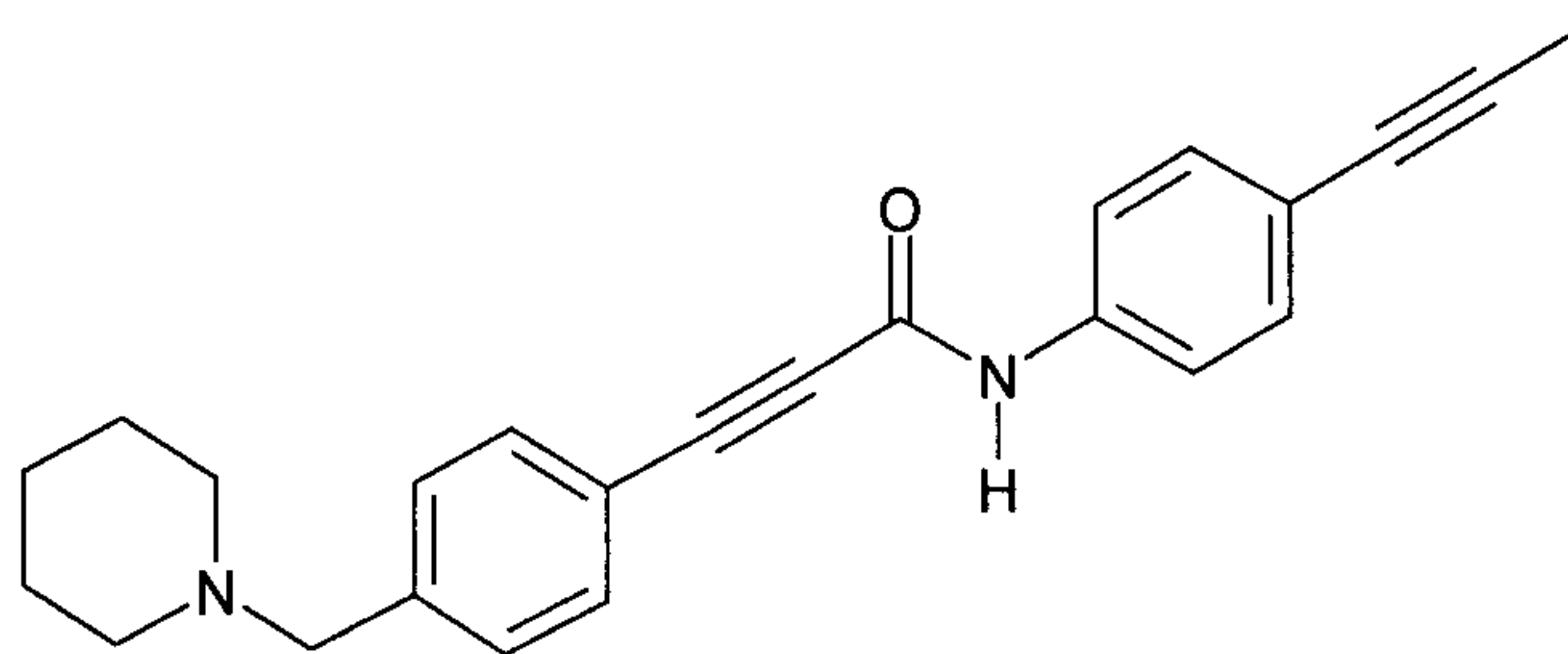
Found: Molecular ion peak

R_f value: 0.2 (silica gel, dichloromethane/ methanol/ ammonia = 10:1:0.1)

30

Example 1.2:

3-(4-piperidin-1-ylmethyl-phenyl)-propynoic acid- (4-prop-1-ynyl-phenyl)-amide



1.2.a. 3-(4-hydroxymethyl-phenyl)-propynoic acid-(4-prop-1-ynyl-phenyl)-amide

40 ml THF are degassed, combined with 2.62 g (8.03 mmol) caesium carbonate and
5 4-iodobenzylalcohol and again degassed. To this reaction mixture are added
successively 138 mg (0.12 mmol) tetrakis(triphenylphosphine) palladium, 53 mg (0.28
mmol) copper(I)iodide and 0.7 g (3.2 mmol) propynoic acid- (4-prop-1-ynyl-phenyl)-
amide. The mixture is stirred for 24 hours at ambient temperature and the reaction
mixture is then evaporated down. The purification of the residues is carried out by
10 column chromatography on silica gel (eluant: dichloromethane/ethanol= 60:1).

Yield: 0.5 g (57.8 % of theoretical)

C₁₉H₁₅NO₂ (M= 289.33)

Calc.: Molecular ion peak (M+H)⁺: 290

Found: Molecular ion peak

(M+H)⁺: 290

15 R_f value: 0.21 (silica gel, dichloromethane/ ethanol = 50:1)

1.2.b. -4-[(4-prop-1-ynyl-phenylcarbamoyl)-ethynyl]-benzyl methanesulphonate

0.14 ml (1.8 mmol) methanesulphonic acid chloride are slowly added dropwise at ambient temperature to a solution of 0.5 g (1.72 mmol) 3-(4-hydroxymethyl-phenyl)-propynoic acid (4-prop-1-ynyl-phenyl)-amide and 0.49 ml (3.6 mmol) triethylamine in 20 ml dichloromethane and the reaction mixture is stirred for two hours at ambient temperature. It is extracted three times with water and the organic phase is dried over sodium sulphate. The solvent is distilled off and the residue is stirred with diisopropylether.

25 Yield: 0.48 g (75.6 % of theoretical)

C₂₀H₁₇NO₄S (M= 367.42)

Calc.: Molecular ion peak (M+H)⁺: 368

Found: Molecular ion peak

(M+H)⁺: 368

R_f value: 0.48 (silica gel, dichloromethane/ ethanol = 20:1)

1.2.c. 3-(4-piperidin-1-ylmethyl-phenyl)-propynoic acid- (4-prop-1-ynyl-phenyl)-amide

A reaction mixture of 0.5 mg (0.13 mmol) 4-[(4-prop-1-ynyl-phenylcarbamoyl)-

ethynyl]-benzyl methanesulphonate, 0.028 ml (0.28 mmol) piperidine in 5 ml THF is

5 stirred for 14 hours at ambient temperature. The reaction mixture is evaporated down.

The purification is carried out by column chromatography on silica gel (eluant:

dichloromethane/ethanol= 25:1 to 15:1).

Yield: 13 mg (26.8 % of theoretical)

Melting point: 180-181°C

10 $C_{24}H_{24}N_2O$ (M= 356.47)

Calc.: Molecular ion peak $(M+H)^+$: 357

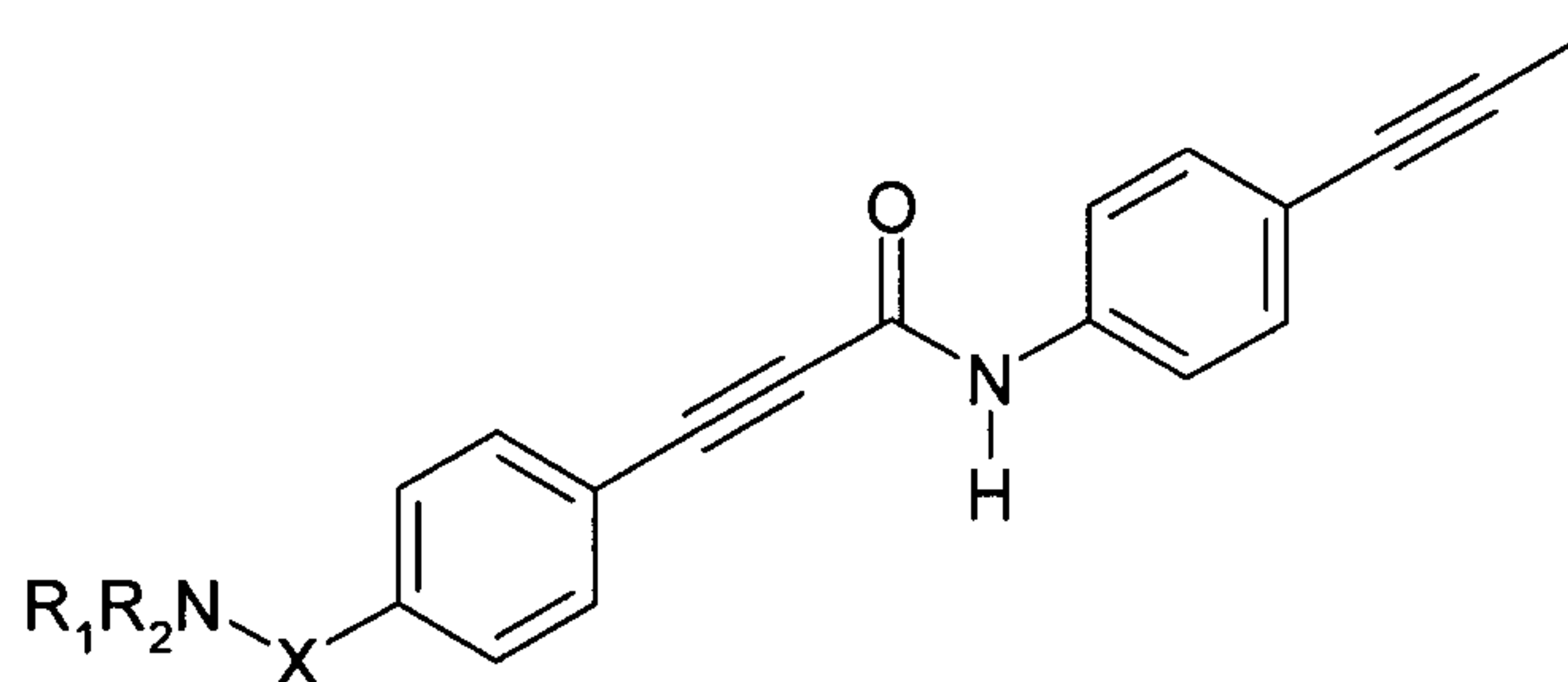
Found: Molecular ion peak

$(M+H)^+$: 357

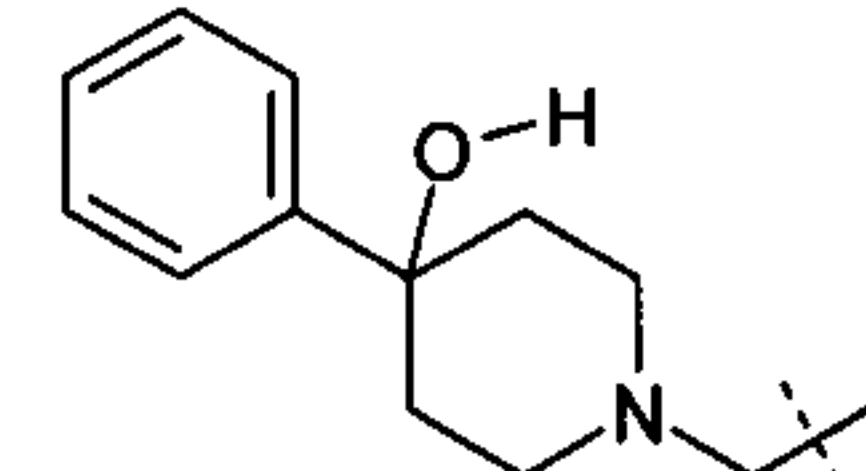
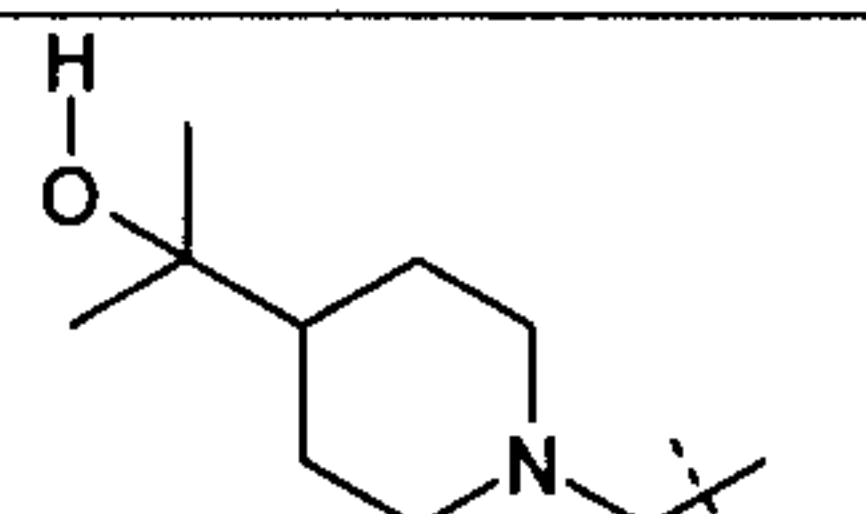
R_f value: 0.21 (silica gel, dichloromethane/ ethanol = 20:1)

15

The following compounds are prepared analogously to Example 1.2.c:



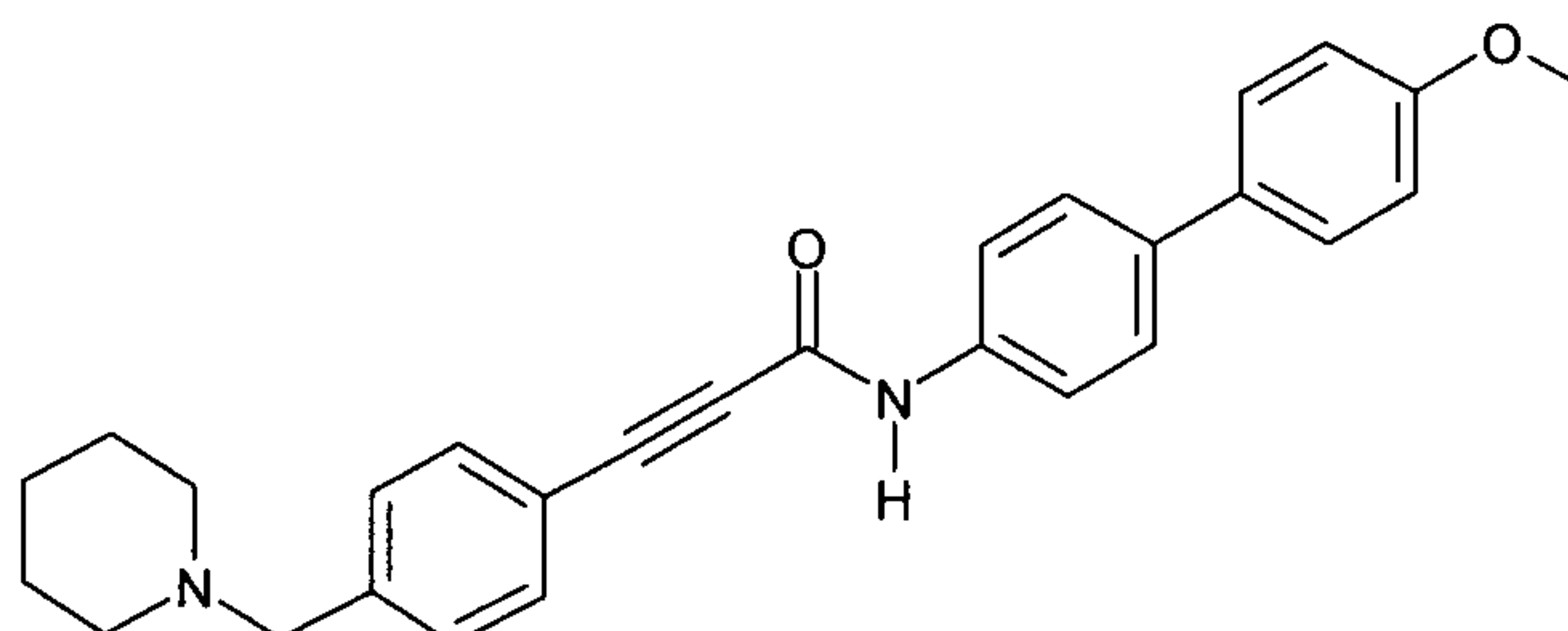
Example	R_1R_2N-X	educt	empirical formula	mass spectrum	mp [°C]	R_f value
1.3		1.2.b	$C_{25}H_{26}N_2O$	371 $[M+H]^+$	158-159	0.21 (A)
1.4		1.2.b	$C_{25}H_{26}N_2O_2$	387 $[M+H]^+$	176-177	0.3 (A)
1.5		1.2.b	$C_{29}H_{28}N_4O$	449 $[M+H]^+$	141	0.18 (A)

1.6		1.2.b	C ₃₀ H ₂₈ N ₂ O ₂	449 [M+H] ⁺	161.5	0.3 (A)
1.7		1.2.b	C ₂₇ H ₃₀ N ₂ O ₂	415 [M+H] ⁺	120	0.1 (A)

R_f value: A= (silica gel, dichloromethane/ethanol/ 20:1)

5 Example 1.8:

3-(4-piperidin-1-ylmethyl-phenyl)-propynoic acid-(4'-methoxy-biphenyl-4-yl)-amide



1.8.a. propynoic acid-(4'-methoxy-biphenyl-4-yl)-amide

10 Prepared analogously to Example 1.1.b from propynoic acid and 4'-methoxy-biphenyl-4-ylamine.

Yield: 1.3 g (17.2 % of theoretical)

C₁₆H₁₃NO₂ (M= 251.28)

Calc.: Molecular ion peak (M+H)⁺: 252

Found: Molecular ion peak

15 (M+H)⁺: 252

R_f value: 0.6 (silica gel, dichloromethane/ ethanol = 20:1)

1.8.b. 3-(4-hydroxymethyl-phenyl)-propynoic acid-(4'-methoxy-biphenyl-4-yl)-amide

20 Prepared analogously to Example 1.2.a from iodobenzylalcohol and propynoic acid-(4'-methoxy-biphenyl-4-yl)-amide.

Yield: 0.21 g (22.9 % of theoretical)

C₂₃H₁₉NO₃ (M= 357.41)

Calc.: Molecular ion peak (M+H)⁺: 358

Found: Molecular ion peak

(M+H)⁺: 358

R_f value: 0.35 (silica gel, dichloromethane/ ethanol = 20:1)

5

1.8.c. 4-[(4'-methoxy-bipheny-4-ylcarbamoyl)-ethynyl]-benzyl methanesulphonate

Prepared analogously to Example 1.2.b from 3-(4-hydroxymethyl-phenyl)-propynoic acid-(4'-methoxy-biphenyl-4-yl)-amide and methanesulphonic acid chloride.

Yield: 0.18 g (70.3 % of theoretical)

10 C₂₄H₂₁NO₅S (M= 435.50)

R_f value: 0.58 (silica gel, dichloromethane/ ethanol = 20:1)

1.8.d. 3-(4-piperidin-1-ylmethyl-phenyl)-propynoic acid- (4'methoxy -phenyl)-amide

Prepared analogously to Example 1.2.c from 4-[(4'-methoxy-bipheny-4-ylcarbamoyl)-ethynyl]-benzyl methanesulphonate and piperidine.

15

Yield: 5 mg (18.8 % of theoretical)

Melting point: 170⁰C

C₂₈H₂₈N₂O₂ (M= 424.54)

Calc.: Molecular ion peak (M+H)⁺: 425

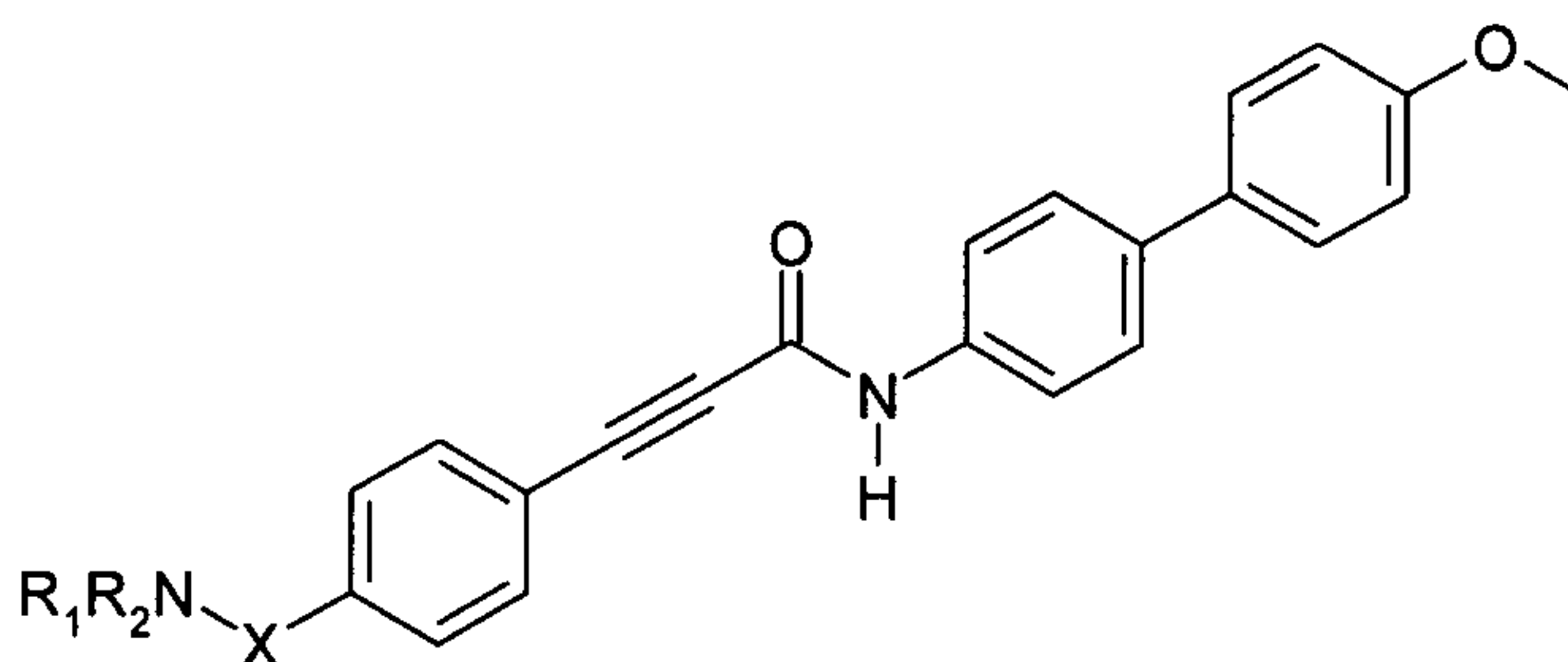
Found: Molecular ion peak

20 (M+H)⁺: 425

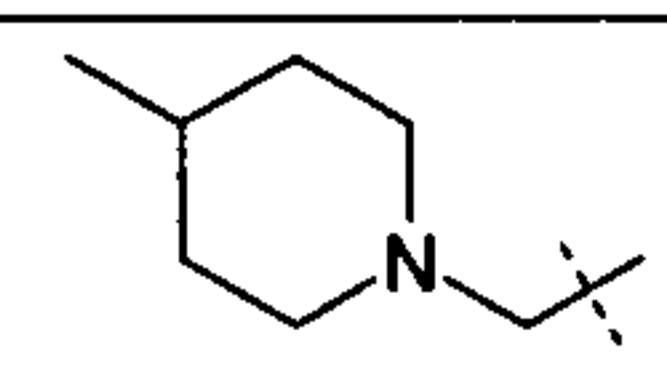
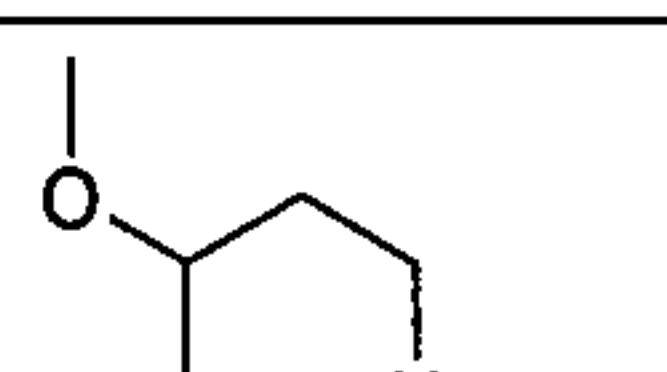
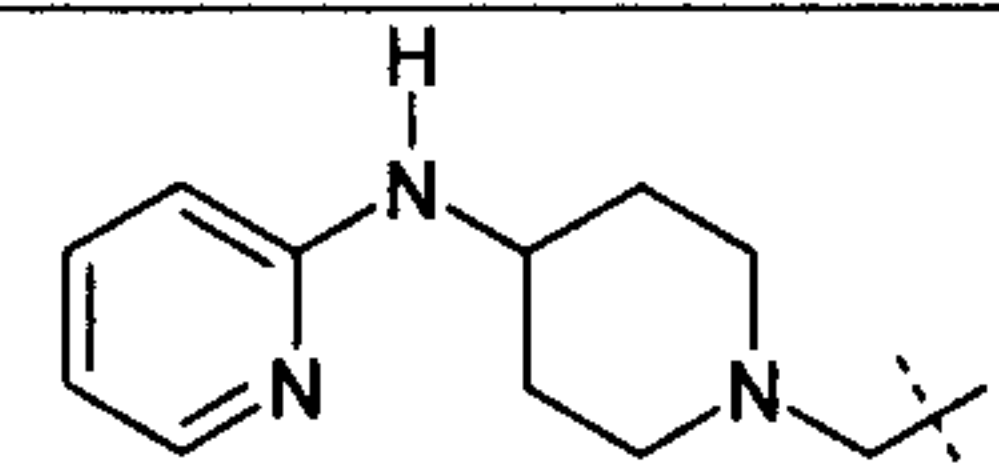
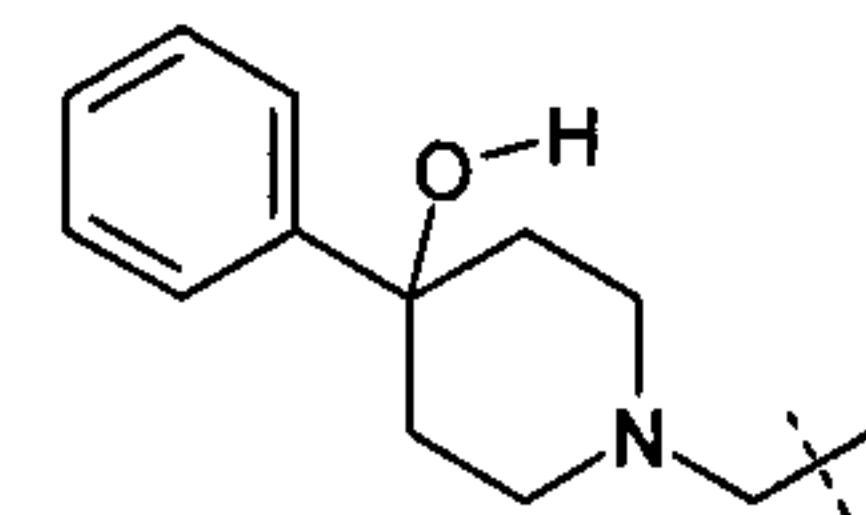
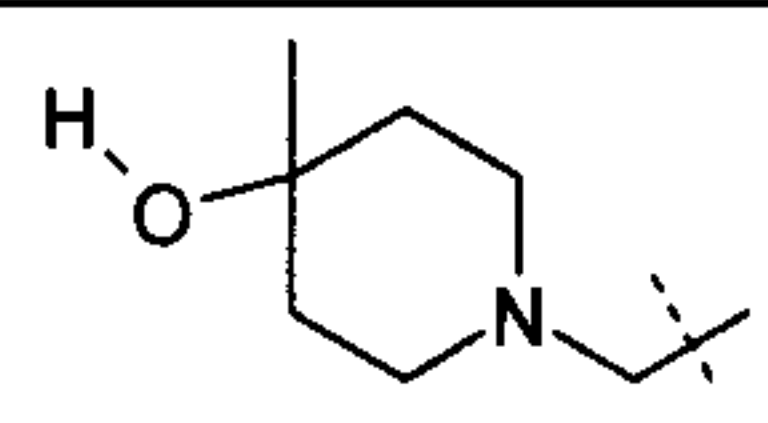
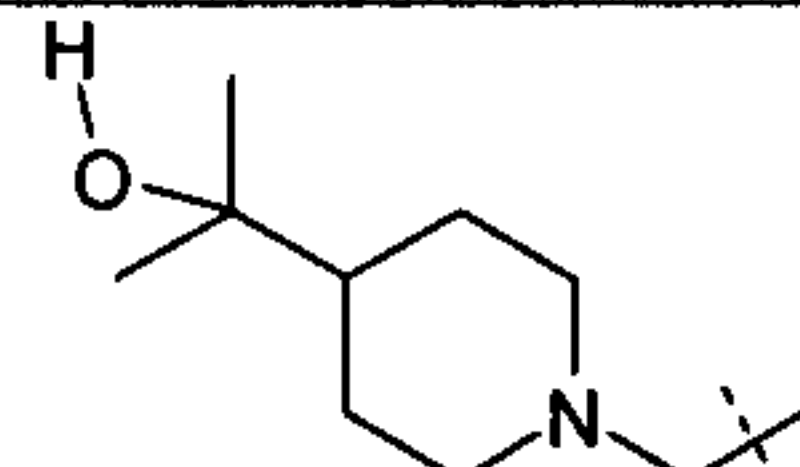
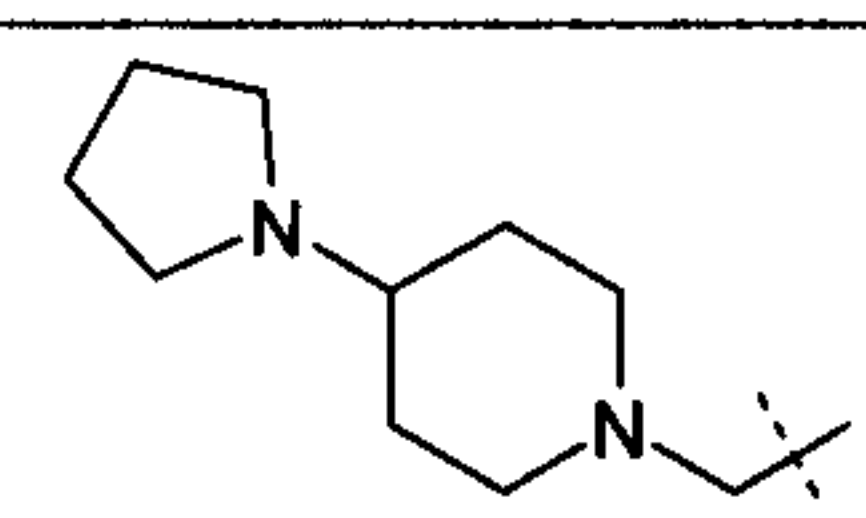
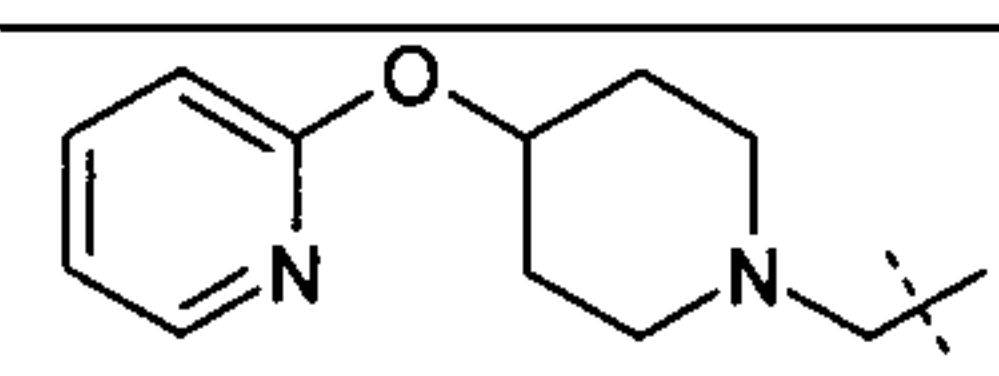
R_f value: 0.28 (silica gel, dichloromethane/ ethanol = 20:1)

The following compounds are prepared analogously to Example 1.8.d:

25



Example	R ₁ R ₂ N-X	educt	empirical formula	mass spectrum	mp [°C]	R _f value

1.9		1.8.c	C ₂₉ H ₃₀ N ₂ O ₂	439 [M+H] ⁺	168- 169	0.2 (A)
1.10		1.8.c	C ₂₉ H ₃₀ N ₂ O ₃	455 [M+H] ⁺	190.5	0.22 (A)
1.11		1.8.c	C ₃₃ H ₃₂ N ₄ O ₂	517 [M+H] ⁺	196- 197	0.15 (A)
1.12		1.8.c	C ₃₄ H ₃₂ N ₂ O ₃	517 [M+H] ⁺	167.5	0.2 (A)
1.13		1.8.c	C ₂₉ H ₃₀ N ₂ O ₃	455 [M+H] ⁺	156	0.35 (B)
1.14		1.8.c	C ₃₁ H ₃₄ N ₂ O ₃	483 [M+H] ⁺	192- 193	0.45 (B)
1.15		1.8.c	C ₃₂ H ₃₅ N ₃ O ₂	494 [M+H] ⁺	181- 182	0.05 (B)
1.16		1.8.c	C ₃₃ H ₃₁ N ₃ O ₃	518 [M+H] ⁺	196- 197	

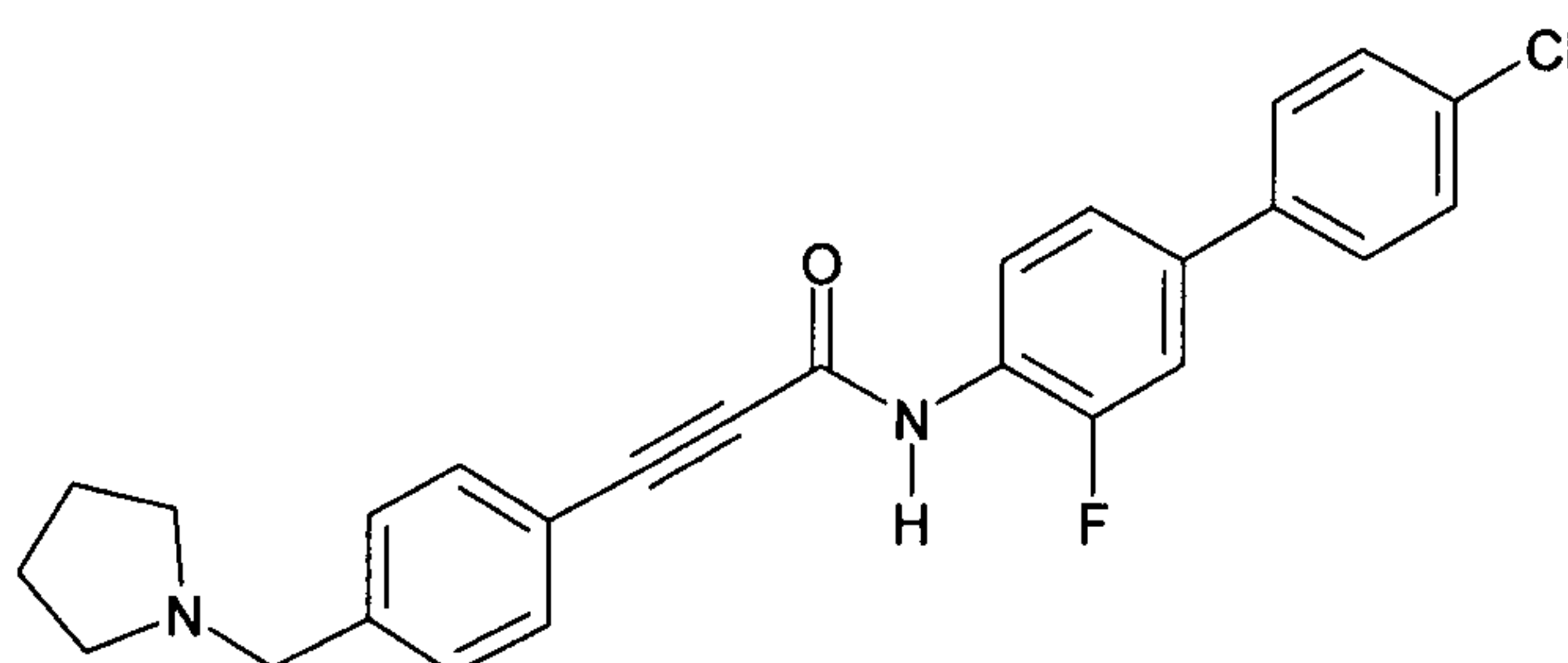
R_f value: A= (silica gel, dichloromethane/ethanol/ammonia 20:1)

B= (silica gel, dichloromethane/ethanol/ammonia 5:1)

5

Example 1.17:

3-(4-pyrrolidin-1-ylmethyl-phenyl)-propynoic acid-(4'-chloro-3-fluoro-biphenyl-4-yl)-amide



1.17.a. 4'-chloro-3-fluoro-biphenyl-4-ylamine

1.95 g (12.47 mmol) 4-chlorophenylboric acid, dissolved in 10 ml of methanol, and 3.9 g (36.79 mmol) sodium carbonate, dissolved in 10 ml of water, are added successively to a reaction mixture of 2.28 g (12 mmol) 4-bromo-2-fluoroaniline and 0.6 g (0.51 mmol) tetrakis(triphenylphosphine) palladium in 90 ml dioxane and stirred for 14 hours at 80°C. Then ethyl acetate is added and the reaction mixture is filtered. The filtrate is evaporated down and extracted with ethyl acetate and water. The organic phase is dried over sodium sulphate. The purification is carried out by column chromatography on silica gel (eluant: cyclohexane/ ethyl acetate= 3:1).

Yield: 2 g (75.2 % of theoretical)

C₁₂H₉FN (M= 221.66)

Calc.: Molecular ion peak (M+H)⁺: 222

Found: Molecular ion peak

(M+H)⁺: 222

R_f value: 0.41 (silica gel, cyclohexane/ethyl acetate 3:1)

1.17.b. propynoic acid-(4'-chloro-3-fluoro-biphenyl-4-yl)-amide

Prepared analogously to Example 1.1.b from 4'-chloro-3-fluoro-biphenyl-4-ylamine and propynoic acid.

Yield: 0.16 g (43.7 % of theoretical)

C₁₅H₉ClFNO (M= 273.69)

Calc.: Molecular ion peak (M+H)⁺: 274/276

Found: Molecular ion

peak (M+H)⁺: 274/276

R_f value: 0.3 (silica gel, cyclohexane/ethyl acetate 3:1)

1.17.c. 3-(4-pyrrolidin-1-ylmethyl-phenyl)-propynoic acid-(4'-chloro-3-fluoro-biphenyl-4-yl)-amide

Prepared analogously to Example 1.1.d from 1-(4-iodobenzyl)-pyrrolidine and propynoic acid-(4'-chloro-3-fluoro-biphenyl-4-yl)-amide.

Yield: 20 mg (13 % of theoretical)

Melting point: 136°C

C₂₆H₂₂ClFN₂O (M= 432.92)

Calc.: Molecular ion peak (M+H)⁺: 433/435/437

Found: Molecular ion

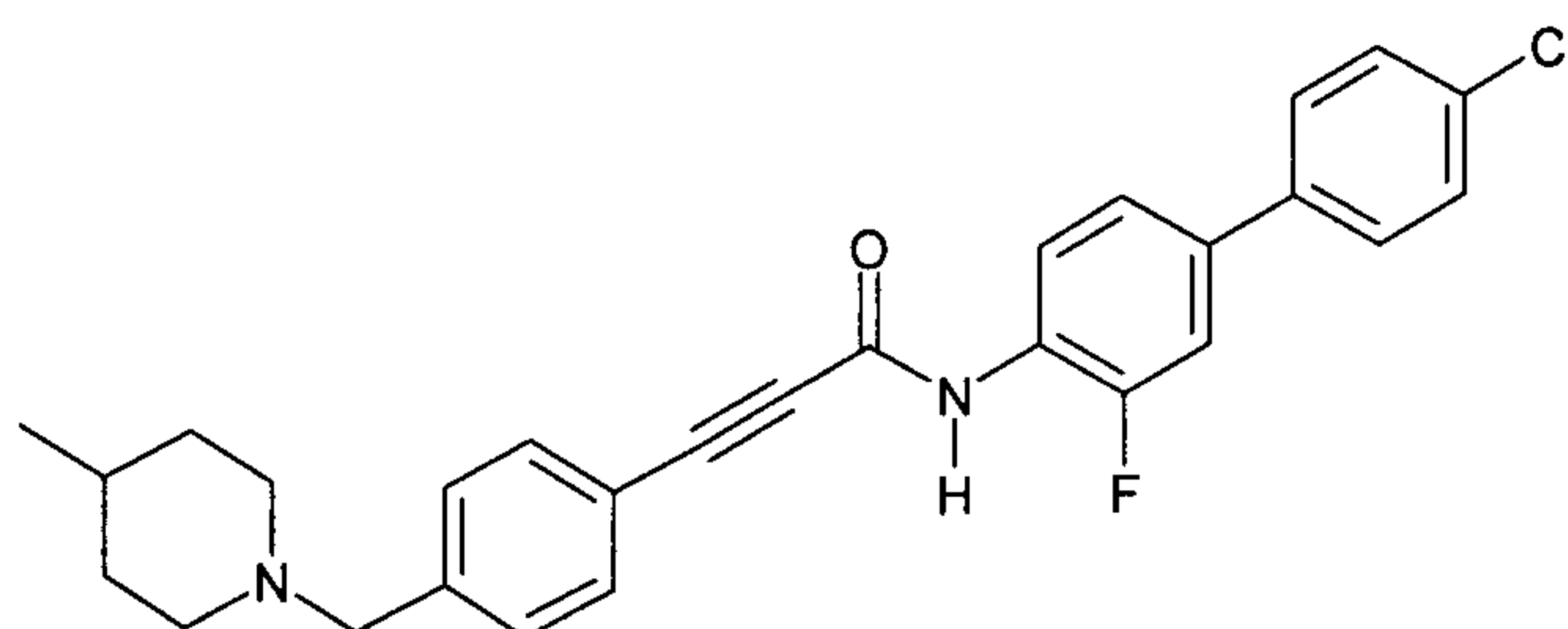
peak (M+H)⁺: 433/435/437

R_f value: 0.3 (silica gel, dichloromethane/ methanol/ ammonia = 10:1:0.1)

5

Example 1.18:

3-[4-(4-methyl-piperidin-1-ylmethyl)-phenyl]-propynoic acid-(4'-chloro-2'-fluoro-biphenyl-4-yl)-amide



10 1.18.a. 3-(4-hydroxymethyl-phenyl)-propynoic acid-(4'-chloro-2'-fluoro-biphenyl-4-yl)-amide

Prepared analogously to Example 1.2.a from propynoic acid-(4'-chloro-3-fluoro-biphenyl-4-yl)-amide and 4-iodobenzylalcohol.

Yield: 0.4 g (41 % of theoretical)

15 C₂₂H₁₅ClFNO₂ (M= 379.82)

Calc.: Molecular ion peak (M+H)⁺: 380/382

Found: Molecular ion

peak (M+H)⁺: 380/382

R_f value: 0.5 (silica gel, dichloromethane/methanol/ammonia=20:1:0.1)

20 1.18.b. 4-[(4'-chloro-2'-fluoro-biphenyl-4-ylcarbamoyl)-ethynyl]-benzyl methanesulphonate

Prepared analogously to Example 1.2.b from 3-(4-hydroxymethyl-phenyl)-propynoic acid-(4'-chloro-2'-fluoro-biphenyl-4-yl)-amide and methanesulphonic acid chloride.

Yield: 0.23 g (50 % of theoretical)

25 C₂₃H₁₇ClFN₂O₂S (M= 457.91)

Calc.: Molecular ion peak (M+H)⁺: 456/458

Found: Molecular ion peak

(M+H)⁺: 456/458

R_f value: 0.5 (silica gel, dichloromethane/ methanol/ ammonia = 20:1:0.1)

1.18.c. 3-[4-(4-methyl-piperidin-1-ylmethyl)-phenyl]-propynoic acid-(4'-chloro-2'-fluoro-biphenyl-4-yl)-amide

Prepared analogously to Example 1.2.c from 4-[(4'-chloro-2'-fluoro-biphenyl-4-ylcarbamoyl)-ethynyl]-benzyl methanesulphonate and 4-methylpiperidine.

5 Yield: 13 mg (21 % of theoretical)

Melting point: 149-150°C

C₂₈H₂₆ClFN₂O (M= 460.98)

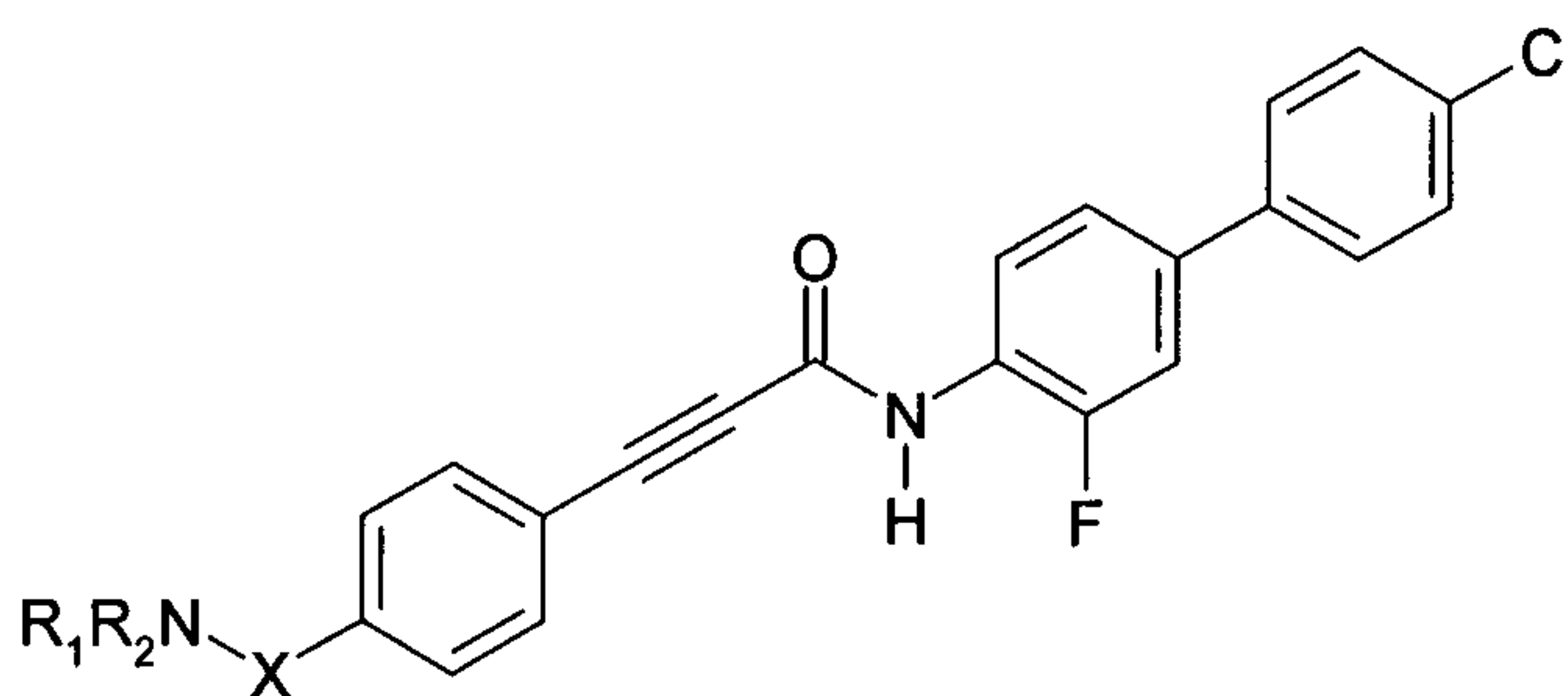
Calc.: Molecular ion peak (M+H)⁺: 461/463

Found: Molecular ion peak

(M+H)⁺: 461/463

10 R_f value: 0.3 (silica gel, dichloromethane/ methanol/ ammonia = 20:1:0.1)

The following compounds were prepared analogously to Example 1.2.c:



Example	R ₁ R ₂ N-X	educt	empirical formula	mass spectrum	mp [°C]	R _f value
1.19		1.18.b	C ₂₈ H ₂₅ ClFN ₃ O ₂	488/490 [M+H] ⁺	222- 223	0.1 (A)
1.20		1.18.b	C ₂₇ H ₂₄ ClFN ₂ O ₂	463/465 [M+H] ⁺	146- 148	0.25 (A)
1.21		1.18.b	C ₂₇ H ₂₄ ClFN ₂ O ₂	463/465 [M+H] ⁺	164- 165	0.3 (B)
1.22		1.18.b	C ₂₆ H ₂₂ ClFN ₂ O ₂	449/451 [M+H] ⁺		0.3 (A)

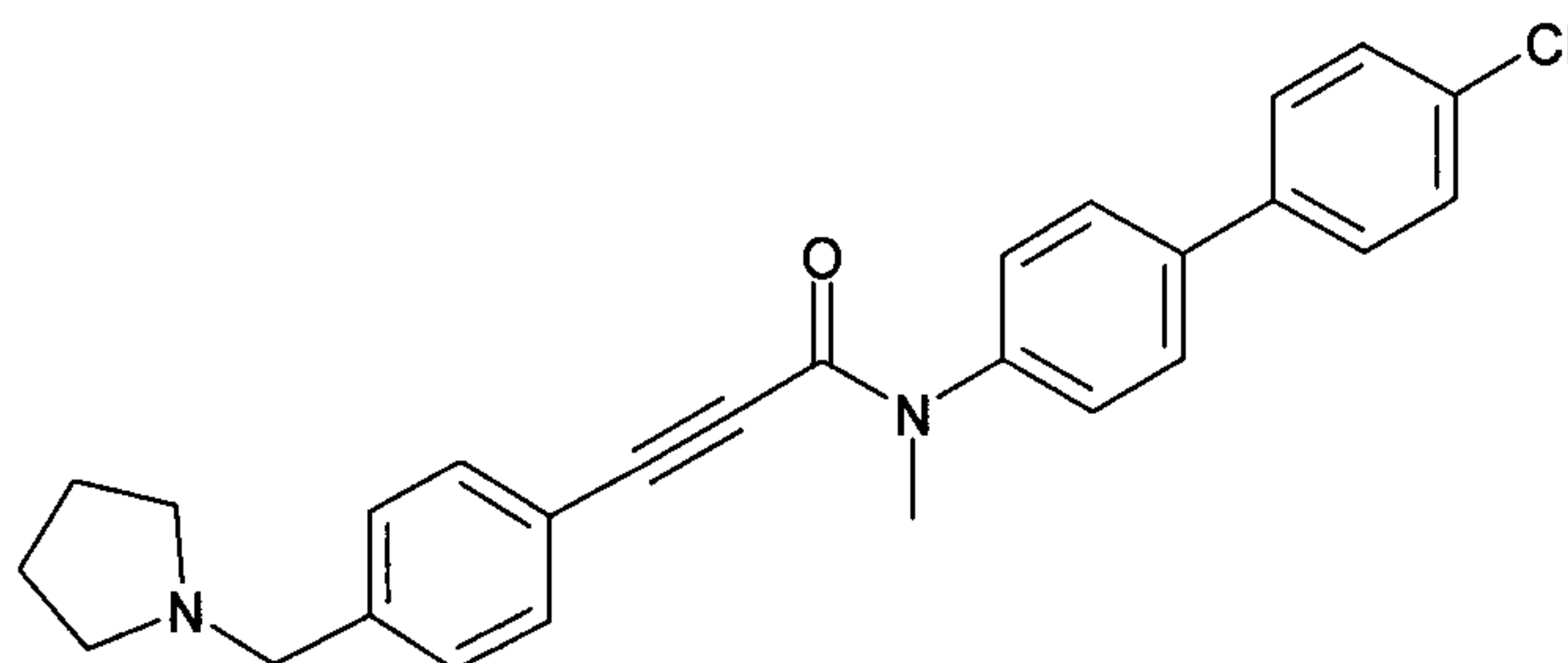
15

R_f value: A= (silica gel, dichloromethane/ethanol/ammonia 20:1:0.1)

B= (silica gel, dichloromethane/methanol/ammonia 10:1:0.1)

Example 1.23:

3-(4-pyrrolidin-1-ylmethyl-phenyl)-propynoic acid-(4'-chloro-biphenyl-4-yl)-methyl-amide



5

1.23.a. propynoic acid-(4'-chloro-biphenyl-4-yl)-amide

Prepared analogously to Example 1.1.b from 4'-chloro-biphenyl-4-ylamine and propynoic acid.

Yield: 0.4 g (29.2 % of theoretical)

10 **C₁₅H₁₀ClNO (M= 255.70)**

Calc.: Molecular ion peak (M+H)⁺: 256/258

Found: Molecular ion

peak (M+H)⁺: 256/258

R_f value: 0.35 (silica gel, dichloromethane/ ethanol 20:1)

15 1.23.b. propynoic acid-(4'-chloro-biphenyl-4-yl)-methyl-amide

75 mg (1.72 mmol) sodium hydride (55%) are added to a solution of 0.4 g (1.56 mmol) propynoic acid-(4'-chloro-biphenyl-4-yl)-amide in 10 ml THF at 0°C and stirred for one hour at this temperature. Then 0.098 ml (1.56 mmol) methyl iodide are added dropwise and the mixture is stirred for 14 hours, while the reaction mixture is allowed to come up to ambient temperature. Then the reaction mixture is extracted with water and ethyl acetate and the organic phase is dried over sodium sulphate. The purification is carried out by column chromatography on silica gel (eluant: cyclohexane/ ethyl acetate= 3:1).

20

Yield: 0.15 g (35.6 % of theoretical)

25 **C₁₆H₁₂ClNO (M= 269.73)**

Calc.: Molecular ion peak (M+H)⁺: 270/272

Found: Molecular ion

peak (M+H)⁺: 270/272

R_f value: 0.61 (silica gel, cyclohexane/ ethyl acetate 1:1)

1.23.c. 3-(4-pyrrolidin-1-ylmethyl-phenyl)-propynoic acid-(4'-chloro-biphenyl-4-yl)-methyl-amide

Prepared analogously to Example 1.1.d from 1-(4-iodobenzyl)-pyrrolidine and propynoic acid-(4'-chloro-biphenyl-4-yl)-methyl-amide.

Yield: 38 mg (25.4 % of theoretical)

Melting point: 161-164⁰C

C₂₇H₂₅ClN₂O (M= 428.96)

Calc.: Molecular ion peak (M+H)⁺: 429/431

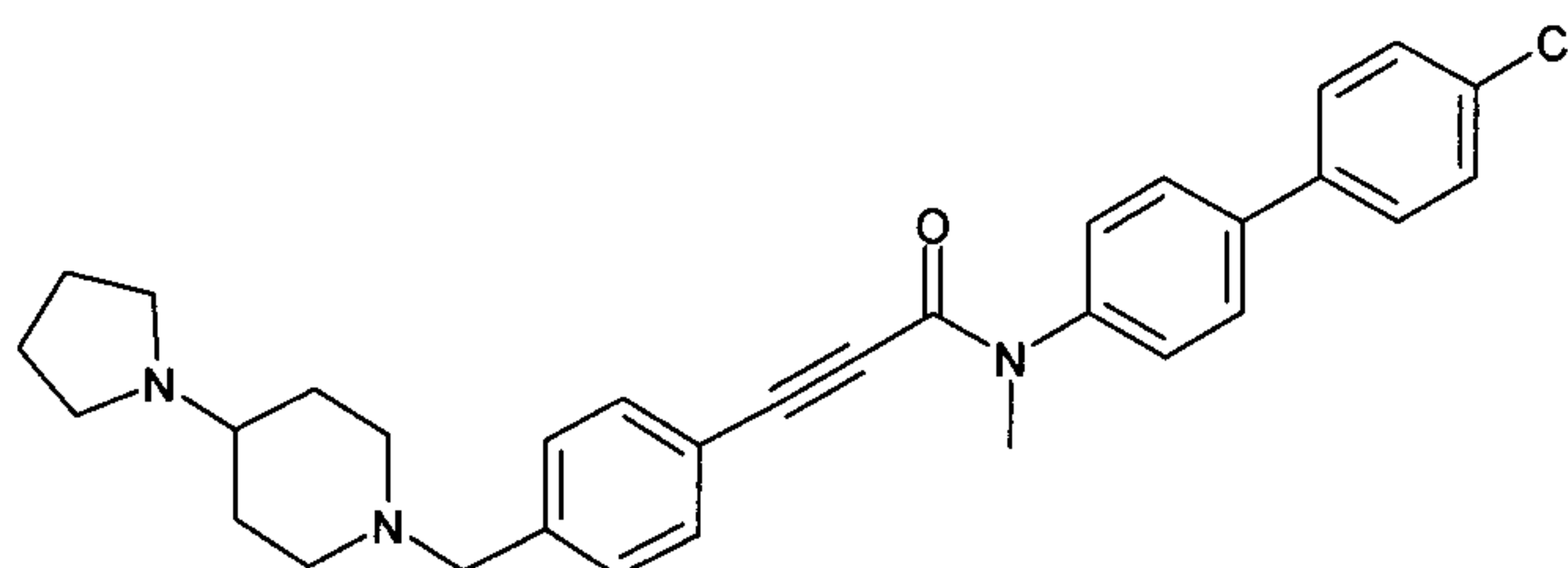
Found: Molecular ion

peak (M+H)⁺: 429/431

R_f value: 0.41 (silica gel, dichloromethane/ methanol/ ammonia = 10:1:0.1)

Example 1.24:

3-[4-(4-pyrrolidin-1-yl-piperidin-1-ylmethyl)-phenyl]-propynoic acid-(4'-chloro-biphenyl-4-yl)-methyl-amide-ditrifluoroacetate



1.24.a. 1-(4-iodobenzyl)-4-pyrrolidin-1-yl-piperidine

Prepared analogously to Example 1.1.c from 4-iodobenzyl bromide and 4-pyrrolidin-1-yl-piperidine.

Yield: 0.57 g (51% of theoretical)

C₁₆H₂₃IN₂ (M= 370.28)

Calc.: Molecular ion peak (M+H)⁺: 371

Found: Molecular ion peak

(M+H)⁺: 371

R_f value: 0.3 (silica gel, dichloromethane/ ethanol 20:1)

1.24.b. 3-[4-(4-pyrrolidin-1-yl-piperidin-1-ylmethyl)-phenyl]-propynoic acid-(4'-chloro-biphenyl-4-yl)-methyl-amide-ditrifluoroacetate

Prepared analogously to Example 1.1.d from 1-(4-iodobenzyl)-4-pyrrolidin-1-yl-piperidine and propynoic acid-(4'-chloro-biphenyl-4-yl)-methyl-amide.

Yield: 5 mg (4 % of theoretical)

Melting point: 161-164⁰C

5 $C_{32}H_{34}ClN_3O \times 2 CF_3CO_2H$ (M= 740.14)

Calc.: Molecular ion peak (M+H)⁺: 512/514

Found: Molecular ion

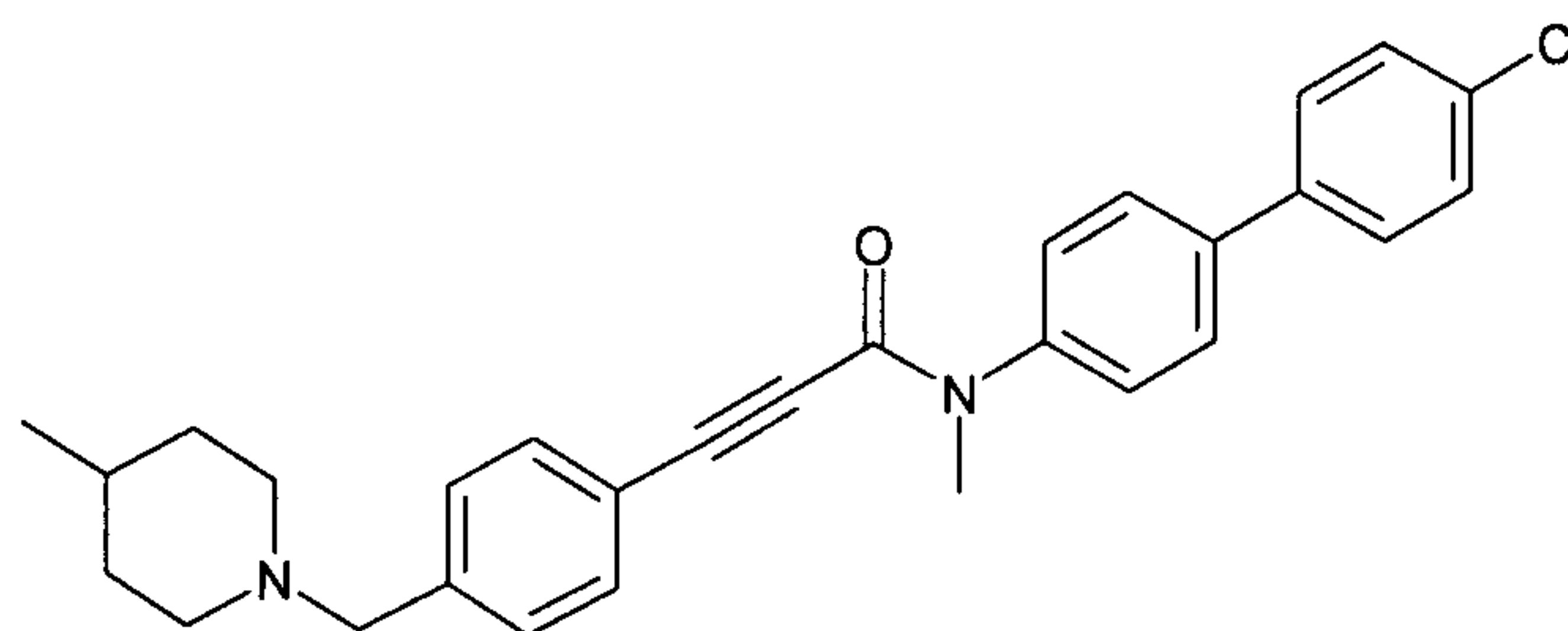
peak (M+H)⁺: 512/514

R_f value: 0.41 (silica gel, dichloromethane/ methanol/ ammonia = 10:1:0.1)

10

Example 1.25:

3-[4-(4-methyl-piperidin-1-ylmethyl)-phenyl]-propynoic acid-(4'-chloro-biphenyl-4-yl)-methyl-amide



15 1.25.a. 3-(4-hydroxymethyl-phenyl)-propynoic acid-(4'-chloro-biphenyl-4-yl)-methyl-amide

Prepared analogously to Example 1.2.a from 4-iodobenzylalcohol and propynoic acid-(4'-chloro-biphenyl-4-yl)-methyl-amide.

Yield: 0.52 g (90 % of theoretical)

20 $C_{23}H_{18}ClNO_2$ (M= 375.85)

Calc.: Molecular ion peak (M+H)⁺: 376/378

Found: Molecular ion

peak (M+H)⁺: 376/378

R_f value: 0.4 (silica gel, dichloromethane/ methanol/ ammonia = 10:1:0.1)

25 1.25.b. 4-[[4-(4'-chloro-biphenyl-4-yl)-methyl-carbamoyl]-ethynyl]-benzyl methanesulphonate

Prepared analogously to Example 1.2.b from 3-(4-hydroxymethyl-phenyl)-propynoic acid-(4'-chloro-biphenyl-4-yl)-methyl-amide.

Yield: 0.54 g (100 % of theoretical)

$C_{24}H_{20}ClNO_4S$ (M= 453.94)

Calc.: Molecular ion peak (M+H)⁺: 454/456

Found: Molecular ion

peak (M+H)⁺: 454/456

5

1.25.c. 3-[4-(4-methyl-piperidin-1-ylmethyl)-phenyl]-propynoic acid-(4'-chloro-biphenyl-4-yl)-methyl-amide

Prepared analogously to Example 1.2.c from 4-[[4-(4'-chloro-biphenyl-4-yl)-methyl-carbamoyl]-ethynyl]-benzyl methanesulphonate and 4-methylpiperidine.

10 Yield: 8 mg (16 % of theoretical)

$C_{29}H_{29}ClN_2O$ (M= 457.02)

Calc.: Molecular ion peak (M+H)⁺: 457/459

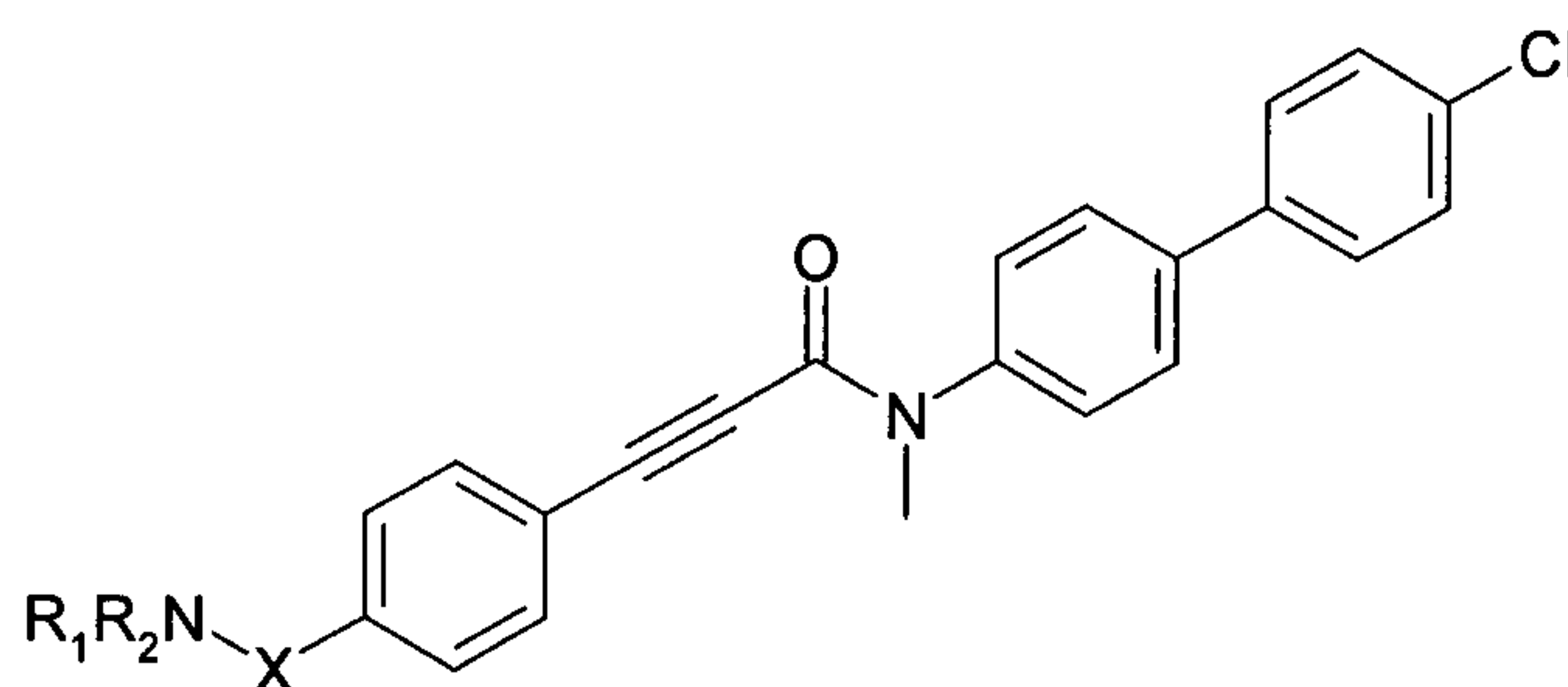
Found: Molecular ion

peak (M+H)⁺: 457/459

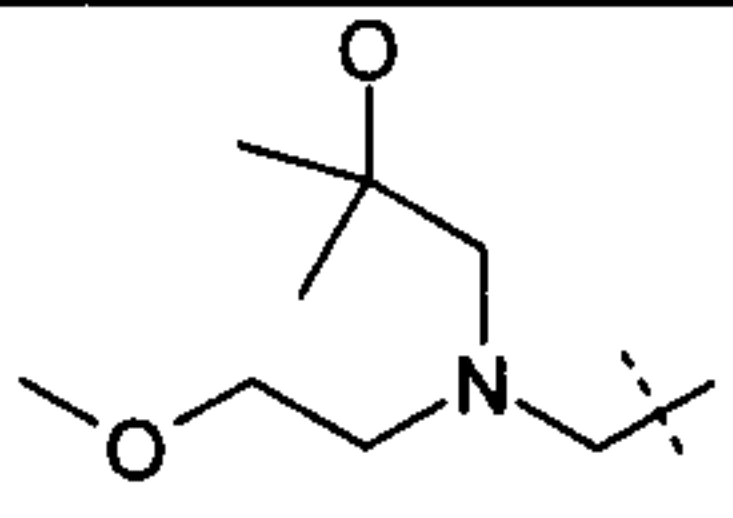
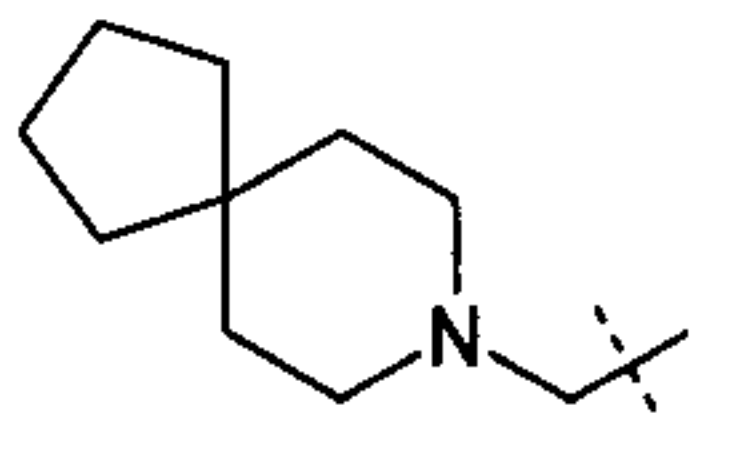
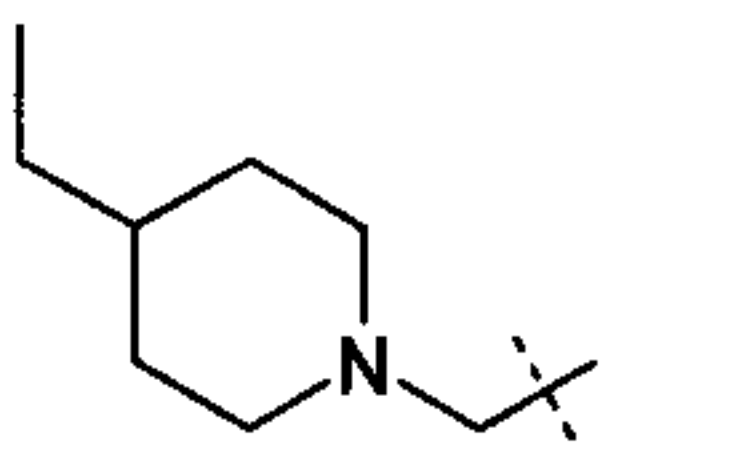
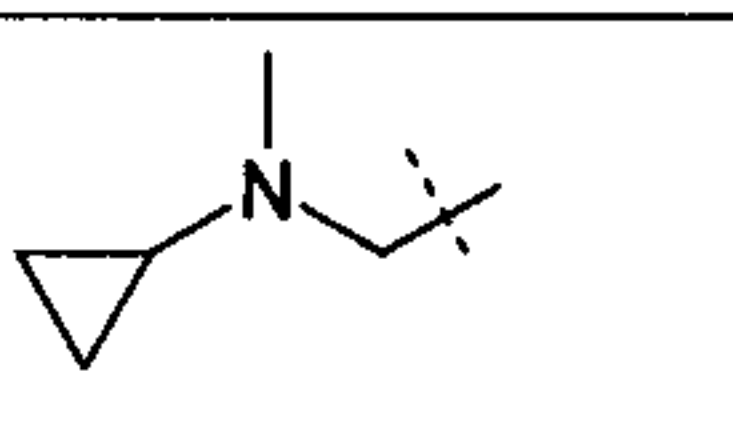
R_f value: 0.41 (silica gel, dichloromethane/ methanol/ ammonia = 10:1:0.1)

15

The following compounds are prepared analogously to Example 1.2.c:



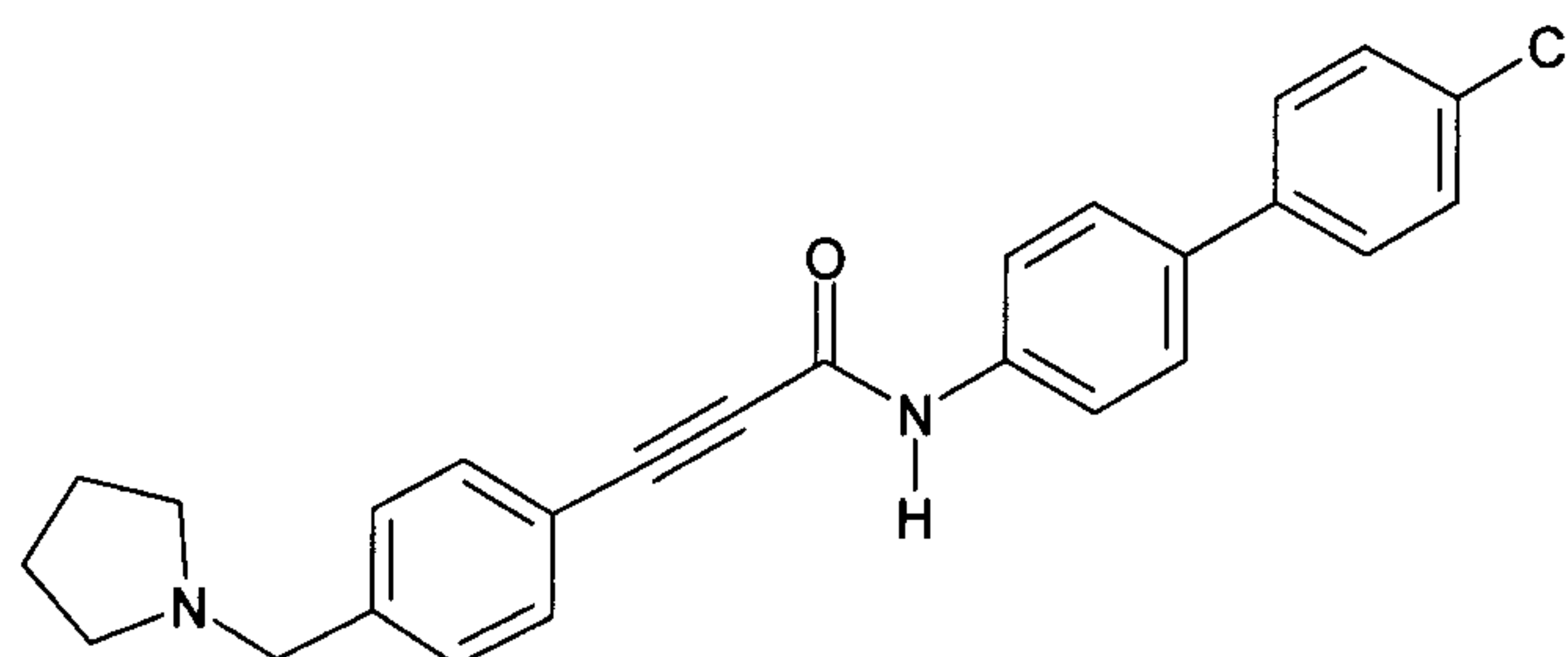
Example	R ₁ R ₂ N-X	educt	empirical formula	mass spectrum	mp [°C]	R _f value
1.26		1.25.c	$C_{29}H_{29}ClN_2O_2$	473/475 [M+H] ⁺	163.5	
1.27		1.25.c	$C_{28}H_{27}ClN_2O$	443/445 [M+H] ⁺	131.5	
1.28		1.25.c	$C_{29}H_{29}ClN_2O_2$	473/475 [M+H] ⁺	147- 148	

1.29		1.25.c	C ₃₀ H ₃₃ ClN ₂ O ₃	505/507 [M+H] ⁺	134	
1.30		1.25.c	C ₃₂ H ₃₃ ClN ₂ O	497/499 [M+H] ⁺	190	
1.31		1.25.c	C ₃₀ H ₃₁ ClN ₂ O	471/473 [M+H] ⁺	166	
1.32		1.25.c	C ₂₇ H ₂₅ ClN ₂ O	429/431 [M+H] ⁺	148- 149	

R_f value: A= (silica gel, dichloromethane/methanol/ammonia 10:1:0.1)

5 Example 1.33:

3-(4-pyrrolidin-1-ylmethyl-phenyl)-propynoic acid-(4'-chloro-biphenyl-4-yl)-amide



1.33.a. 1-(4-trimethylsilanylethynyl-benzyl)-pyrrolidine

A reaction mixture of 1 g (3.48 mmol) 1-(4-iodobenzyl)-pyrrolidine, 5 ml piperidin, 105
10 mg (0.091 mmol) tetrakis(triphenylphosphine) palladium and 10 mg (0.053 mmol)
copper(I)iodide is cooled to 0°C. At this temperature 0.59 ml (4.18 mmol)
trimethylsilylacetylene is added dropwise and then the cooling bath is removed. It is
stirred for three hours at ambient temperature, then combined with a saturated
aqueous ammonium chloride solution and extracted with dichloromethane. The
15 organic phase is dried over sodium sulphate. The purification is carried out by column
chromatography on silica gel (eluant: cyclohexane/ ethyl acetate= 1:1).

Yield: 0.75 g (83.6 % of theoretical)

C₁₆H₂₃NSi (M= 257.45)

Calc.: Molecular ion peak (M+H)⁺: 258
(M+H)⁺: 258

Found: Molecular ion peak

1.33.b. 1-(4-ethynyl-benzyl)-pyrrolidine

5 A solution of 0.75 g (2.91 mmol) 1-(4-trimethylsilanylethynyl-benzyl)-pyrrolidine in 10 ml dichloromethane and 10 ml of methanol is combined with 2.4 ml of a 1M sodium hydroxide solution and stirred for three hours at ambient temperature. The reaction mixture is evaporated down and the residue is extracted with water and ethyl acetate. The organic phase is stirred with activated charcoal, filtered and then dried over
10 sodium sulphate.

Yield: 0.4 g (74.1 % of theoretical)

C₁₃H₁₅N (M= 185.27)

Calc.: Molecular ion peak (M+H)⁺: 186
(M+H)⁺: 186

Found: Molecular ion peak

15

1.33.c. (4-pyrrolidin-1-ylmethyl-phenyl)-propynoic acid

5.98 ml (14.85 mmol) of a 1.6 M butyllithium solution in n-hexane are added dropwise to a solution of 2.3 g (12.41 mmol) 1-(4-ethynyl-benzyl)-pyrrolidine in 50 ml THF at
20 -78⁰C and stirred for one hour at this temperature. Then dry ice is added to the reaction mixture. Then the reaction mixture is allowed to come up to ambient temperature and stirred for 14 hours. The reaction mixture is combined with dilute hydrochloric acid and extracted with dichloromethane. The organic phase is separated off and dried over sodium sulphate. The sodium sulphate is separated off
25 and the solvent is removed.

Yield: 0.3 g (10.5 % of theoretical)

C₁₄H₁₅NO₂ (M= 229.28)

Calc.: Molecular ion peak (M+H)⁺: 230
(M+H)⁺: 230

Found: Molecular ion peak

30 R_f value: 0.15 (silica gel, dichloromethane/ methanol/ ammonia = 9:1:0.1)

1.33.d. 3-(4-pyrrolidin-1-ylmethyl-phenyl)-propynoic acid-(4'-chloro-biphenyl-4-yl)-amide

A solution of 0.3 g (1.30 mmol) (4-pyrrolidin-1-ylmethyl-phenyl)-propynoic acid, 0.27 g (1.32 mmol) 4'-chloro-biphenyl-4-ylamine, 0.42 g (1.32 mmol) TBTU and 0.18 ml (1.32 mmol) triethylamine in 30 ml DMF is stirred for 14 hours at ambient temperature. The reaction mixture is evaporated down and the residue is extracted with water and dichloromethane. The organic phase is dried over sodium sulphate. The purification is carried out by column chromatography on silica gel (eluant: dichloromethane/ethanol= 10:1).

Yield: 0.095 g (17.5 % of theoretical)

Melting point: from 180°C

10 C₂₆H₂₃ClN₂O (M= 414.93)

Calc.: Molecular ion peak (M+H)⁺: 415/417
peak (M+H)⁺: 415/417

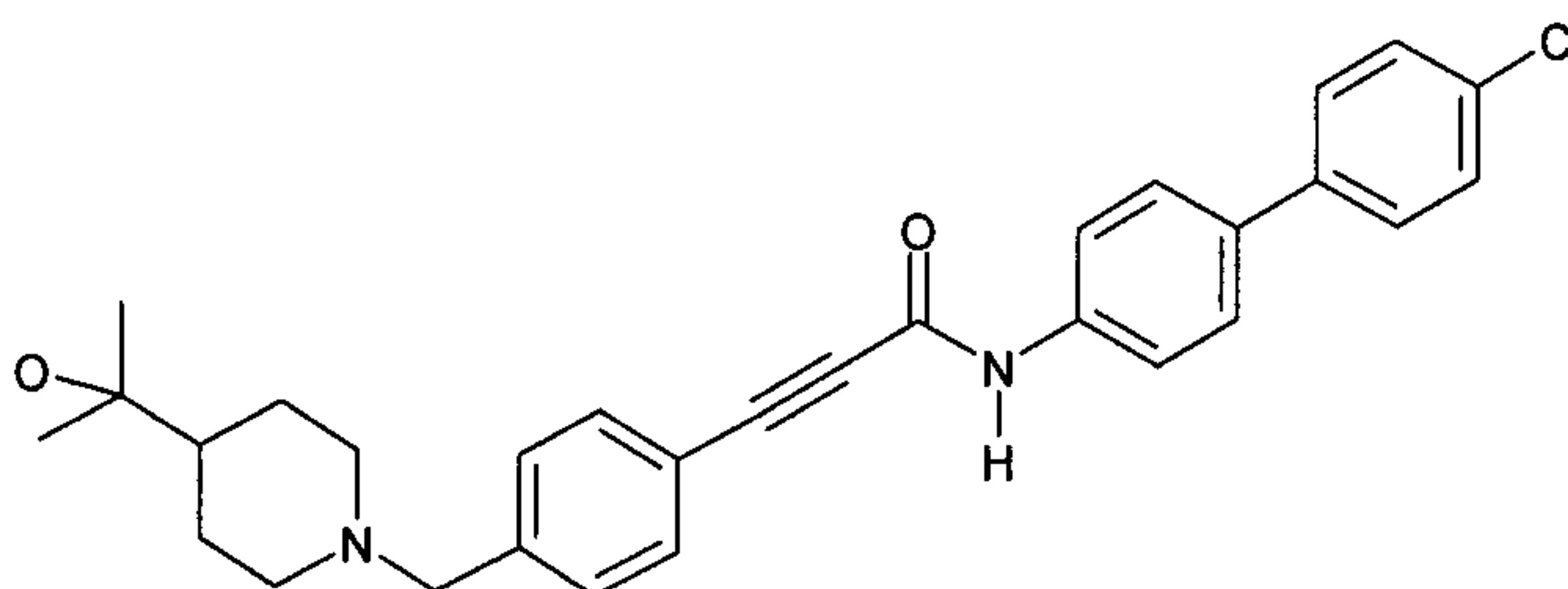
Found: Molecular ion

R_f value: 0.3 (silica gel, dichloromethane/ ethanol = 5:1)

15

Example 1.34:

3-{4-[4-(1-hydroxy-1-methyl-ethyl)-piperidin-1-ylmethyl]-phenyl}-propynoic acid-(4'-chloro-biphenyl-4-yl)-amide



20 1.34.a. 2-[1-(4-iodobenzyl)-piperidin-4-yl]-propan-2-ol

Prepared analogously to Example 1.1.c from 4-iodobenzyl bromide and 2-piperidin-4-yl-propan-2-ol.

Yield: 1.01 g (67% of theoretical)

C₁₅H₂₂INO (M= 359.25)

25 Calc.: Molecular ion peak (M+H)⁺: 360
(M+H)⁺: 360

Found: Molecular ion peak

R_f value: 0.4 (silica gel, dichloromethane/ ethanol 20:1)

1.34.b. 3-{4-[4-(1-hydroxy-1-methyl-ethyl)-piperidin-1-ylmethyl]-phenyl}-propynoic
30 acid-(4'-chloro-biphenyl-4-yl)-amide

Prepared analogously to Example 1.1.d from 2-[1-(4-iodobenzyl)-piperidin-4-yl]-propan-2-ol and propynoic acid-(4'-chloro-biphenyl-4-yl)-amide.

Yield: 45 mg (30 % of theoretical)

Melting point: 194-195°C

5 $C_{30}H_{31}ClN_2O_2$ (M= 487.04)

Calc.: Molecular ion peak (M+H)⁺: 487/489

Found: Molecular ion

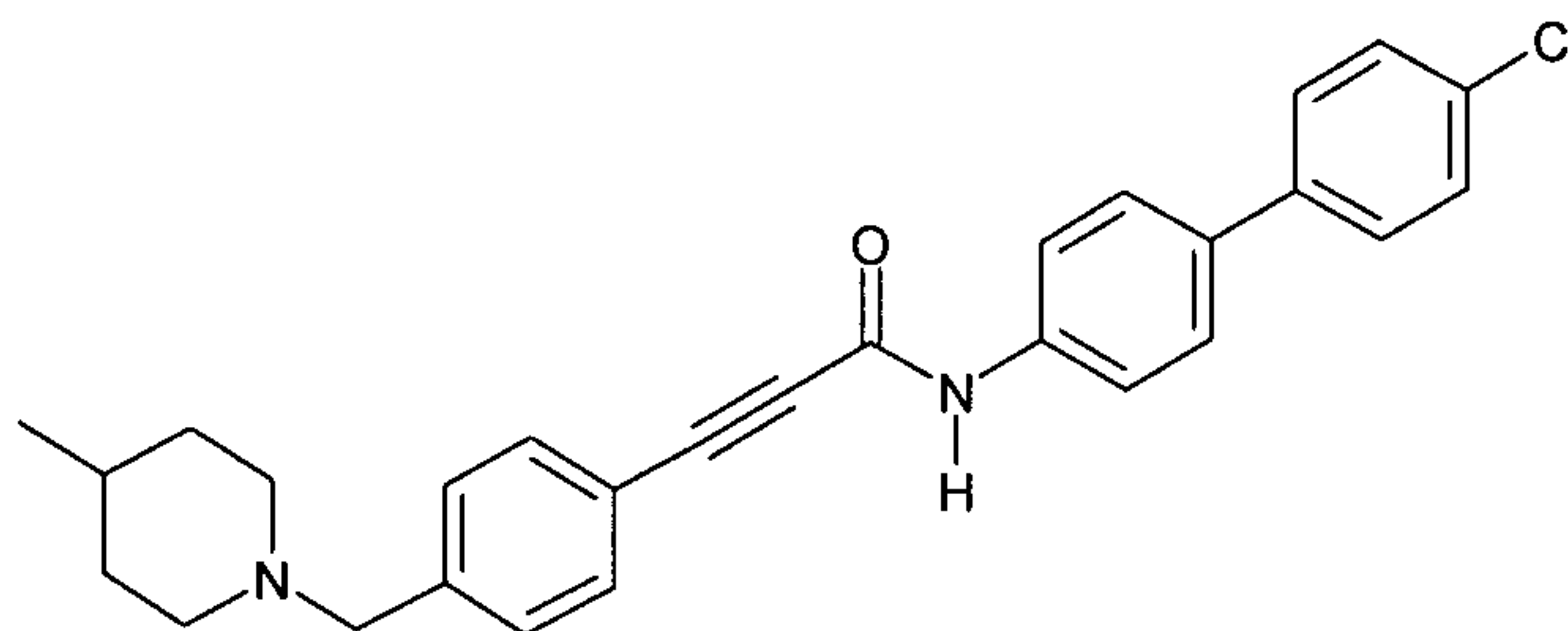
peak (M+H)⁺: 487/489

R_f value: 0.3 (silica gel, dichloromethane/ methanol/ ammonia = 10:1:0.1)

10

Example 1.35:

3-[4-(4-methyl-piperidin-1-ylmethyl)-phenyl]-propynoic acid-(4'-chloro-biphenyl-4-yl)-amide



15 1.35.a. 1-(4-iodobenzyl)-4-methyl-piperidine

Prepared analogously to Example 1.1.c from 4-iodobenzyl bromide and 4-methyl-piperidine.

Yield: 0.95 g (71.6% of theoretical)

$C_{13}H_{18}IN$ (M= 315.20)

20 Calc.: Molecular ion peak (M+H)⁺: 316

Found: Molecular ion peak

(M+H)⁺: 316

R_f value: 0.6 (silica gel, dichloromethane/ ethanol 20:1)

25 1.35.b. 3-[4-(4-methyl-piperidin-1-ylmethyl)-phenyl]-propynoic acid-(4'-chloro-biphenyl-4-yl)-amide

Prepared analogously to Example 1.1.d from 1-(4-iodobenzyl)-4-methyl-piperidine and propynoic acid-(4'-chloro-biphenyl-4-yl)-amide.

Yield: 50 mg (27 % of theoretical)

$C_{28}H_{27}ClN_2O$ (M= 442.99)

Calc.: Molecular ion peak (M+H)⁺: 443/445
peak (M+H)⁺: 443/445

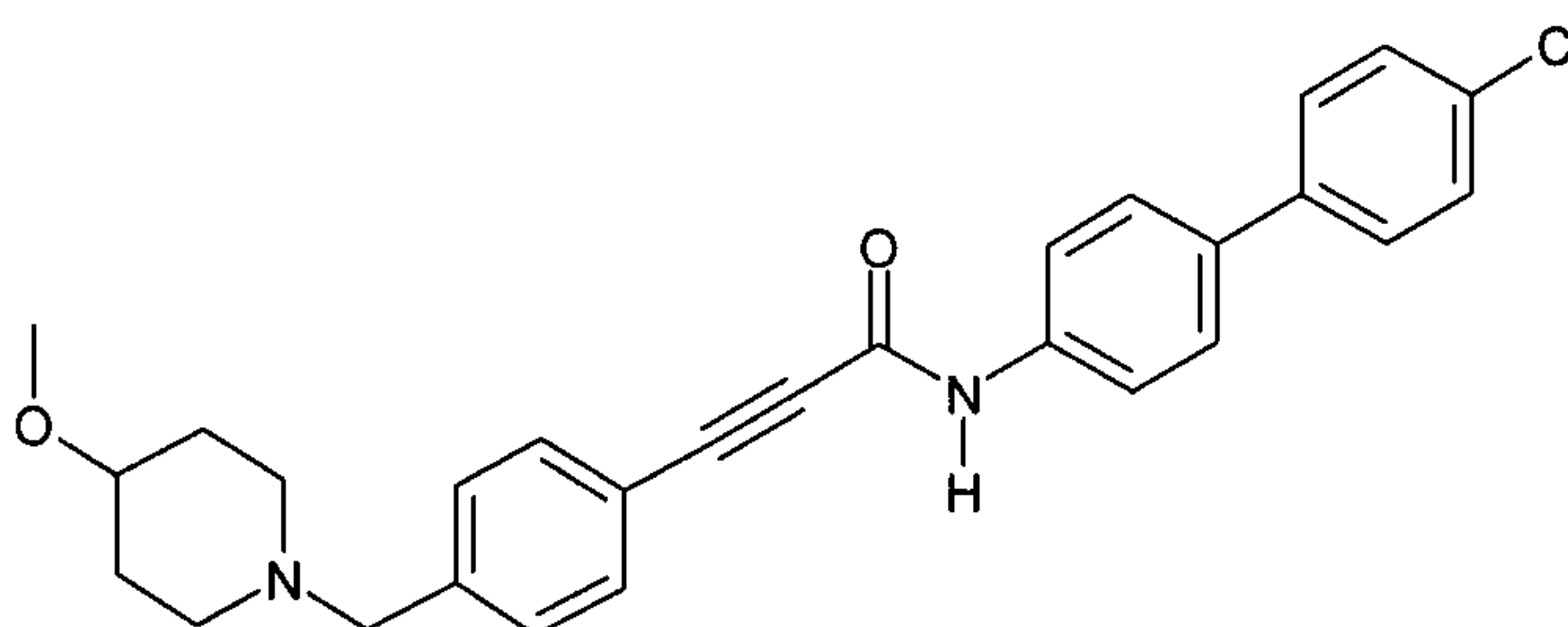
Found: Molecular ion

R_f value: 0.45 (silica gel, dichloromethane/ methanol = 10:1)

5

Example 1.36:

3-[4-(4-methoxy-piperidin-1-ylmethyl)-phenyl]-propynoic acid-(4'-chloro-biphenyl-4-yl)-amide



10 1.36.a. 1-(4-iodobenzyl)-4-methoxy-piperidine

Prepared analogously to Example 1.1.c from 4-iodobenzyl bromide and 4-methoxy-piperidine.

Yield: 0.93 g (66.7% of theoretical)

C₁₃H₁₈INO (M= 331.19)

15 Calc.: Molecular ion peak (M+H)⁺: 332
(M+H)⁺: 332

Found: Molecular ion peak

R_f value: 0.55 (silica gel, dichloromethane/ ethanol 20:1)

20 1.36.b. 3-[4-(4-methoxy-piperidin-1-ylmethyl)-phenyl]-propynoic acid-(4'-chloro-biphenyl-4-yl)-amide

Prepared analogously to Example 1.1.d from 1-(4-iodobenzyl)-4-methoxy-piperidine and propynoic acid-(4'-chloro-biphenyl-4-yl)-amide.

Yield: 25 mg (13 % of theoretical)

Melting point: 145-146 C

25 C₂₈H₂₇ClN₂O₂ (M= 458.99)

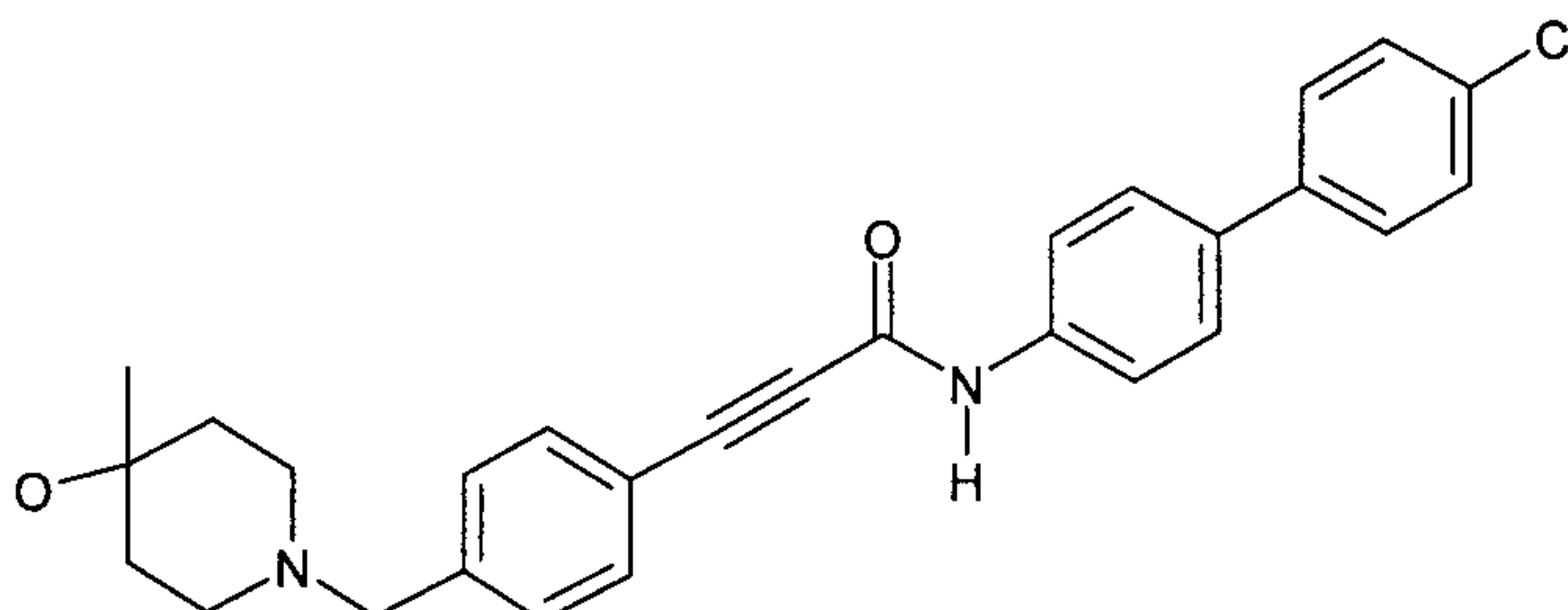
Calc.: Molecular ion peak (M+H)⁺: 459/461
peak (M+H)⁺: 459/461

Found: Molecular ion

R_f value: 0.4 (silica gel, dichloromethane/ methanol = 10:1)

Example 1.37:

3-[4-(4-hydroxy-4-methyl-piperidin-1-ylmethyl)-phenyl]-propynoic acid-(4'-chloro-biphenyl-4-yl)-amide



5 1.37.a. 1-(4-iodobenzyl)-4-methyl-piperidin-4-ol

Prepared analogously to Example 1.1.c from 4-iodobenzyl bromide and 4-methyl-piperidin-4-ol.

Yield: 0.22 g (30% of theoretical)

C₁₃H₁₈INO (M= 331.19)

10 Calc.: Molecular ion peak (M+H)⁺: 332
(M+H)⁺: 332

Found: Molecular ion peak

R_f value: 0.45 (silica gel, dichloromethane/ ethanol 20:1)

15 1.37.b. 3-[4-(4-hydroxy-4-methyl-piperidin-1-ylmethyl)-phenyl]-propynoic acid-(4'-chloro-biphenyl-4-yl)-amide

Prepared analogously to Example 1.1.d from 1-(4-iodobenzyl)-4-methyl-piperidin-4-ol and propynoic acid-(4'-chloro-biphenyl-4-yl)-amide.

Yield: 25 mg (13 % of theoretical)

Melting point: 192-193 C

20 C₂₈H₂₇ClN₂O₂ (M= 458.99)

Calc.: Molecular ion peak (M+H)⁺: 459/461
peak (M+H)⁺: 459/461

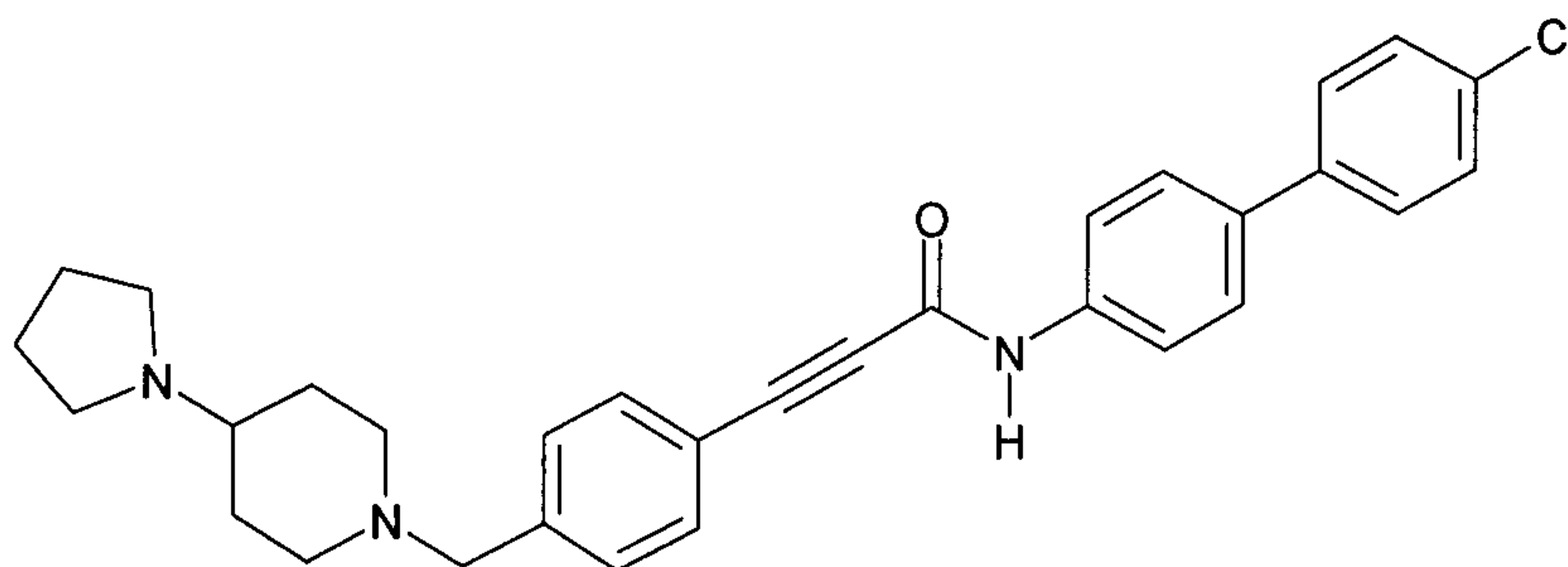
Found: Molecular ion

R_f value: 0.2 (silica gel, dichloromethane/ methanol = 10:1)

25

Example 1.38:

3-[4-(4-pyrrolidin-1-yl-piperidin-1-ylmethyl)-phenyl]-propynoic acid-(4'-chloro-biphenyl-4-yl)-amide



1.38.a. 3-[4-(4-pyrrolidin-1-yl-piperidin-1-ylmethyl)-phenyl]-propynoic acid-(4'-chloro-biphenyl-4-yl)-amide

Prepared analogously to Example 1.1.d from 1-(4-iodobenzyl)-4-pyrrolidin-1-yl-piperidine and propynoic acid-(4'-chloro-biphenyl-4-yl)-amide.

Yield: 15 mg (7 % of theoretical)

Melting point: 191-192 C

C₃₁H₃₂ClN₃O (M= 498.07)

Calc.: Molecular ion peak (M+H)⁺: 498/500

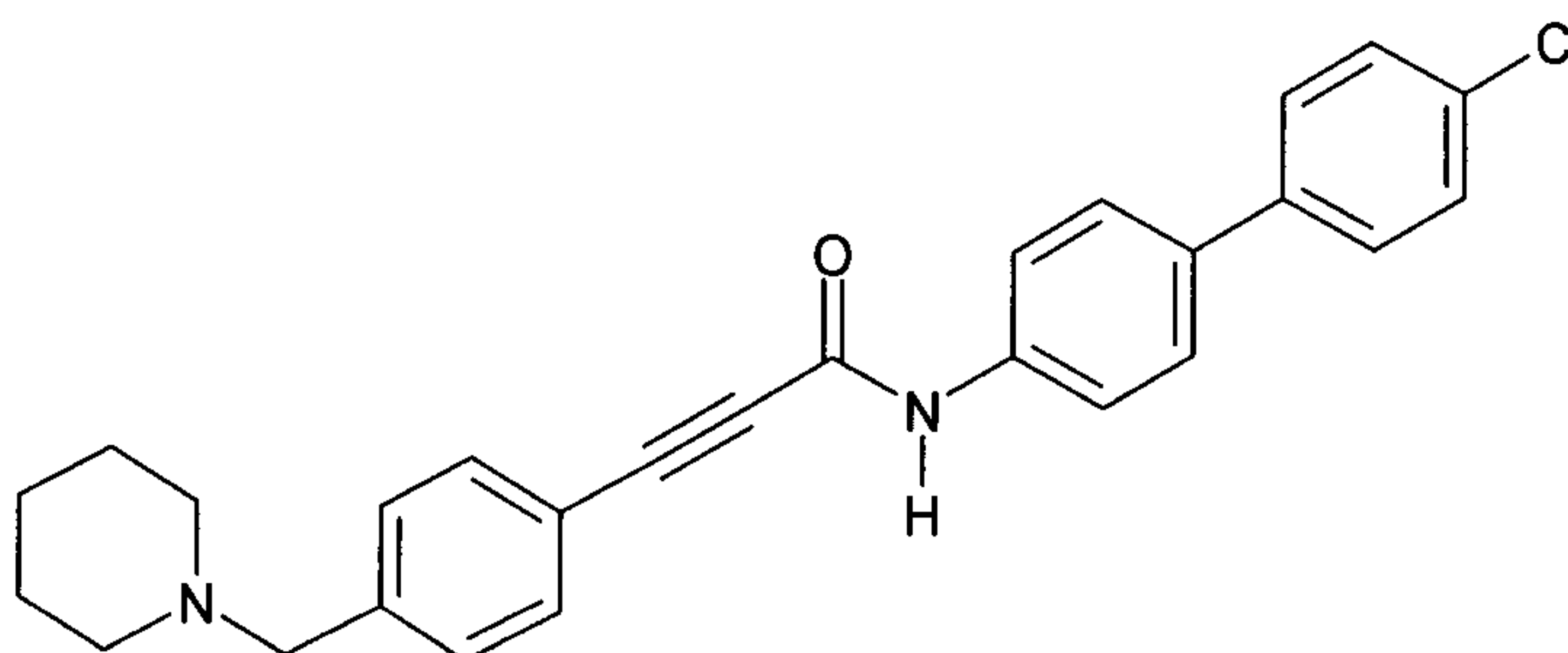
Found: Molecular ion

peak (M+H)⁺: 498/500

R_f value: 0.45 (silica gel, dichloromethane/ methanol/ammonia = 10:1:0.1)

Example 1.39:

3-(4-piperidin-1-ylmethyl-phenyl)-propynoic acid-(4'-chloro-biphenyl-4-yl)-amide



1.39.a. 1-(4-iodobenzyl)-piperidine

Prepared analogously to Example 1.1.c from 4-iodobenzyl bromide and piperidine.

Yield: 0.85 g (67% of theoretical)

C₁₂H₁₆IN (M= 301.17)

Calc.: Molecular ion peak (M+H)⁺: 322

Found: Molecular ion peak

(M+H)⁺: 302

R_f value: 0.55 (silica gel, dichloromethane/ ethanol 20:1)

1.39.b. 3-(4-piperidin-1-ylmethyl-phenyl)-propynoic acid-(4'-chloro-biphenyl-4-yl)-amide

Prepared analogously to Example 1.1.d from 1-(4-iodobenzyl)-piperidine and propynoic acid-(4'-chloro-biphenyl-4-yl)-amide.

5 Yield: 6 mg (4 % of theoretical)

Melting point: 179.5 C

C₂₇H₂₅ClN₂O (M= 428.96)

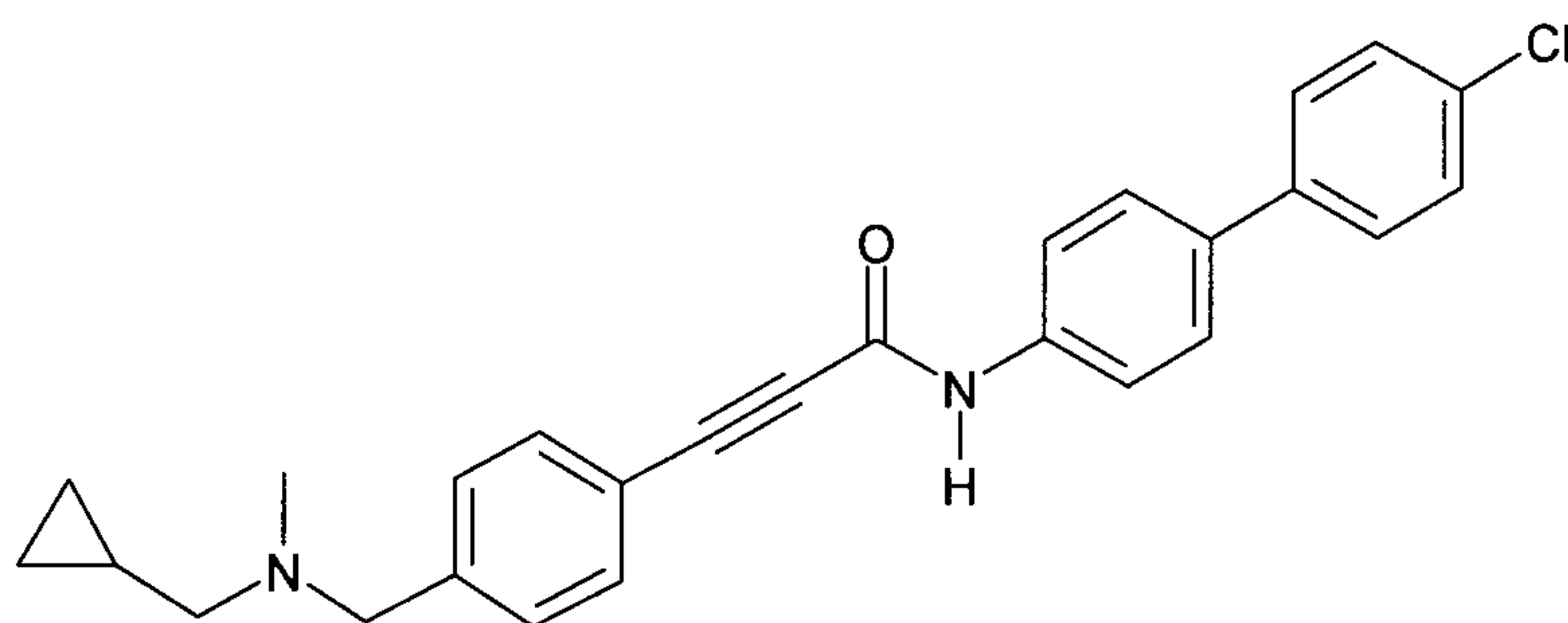
Calc.: Molecular ion peak (M+H)⁺: 429/431
peak (M+H)⁺: 429/431

Found: Molecular ion

10 R_f value: 0.5 (silica gel, dichloromethane/ methanol/ammonia = 10:1:0.1)

Example 1.40:

3-{4-[cyclopropylmethyl-methyl-amino)-methyl]-phenyl}-propynoic acid-(4'-chloro-biphenyl-4-yl)-amide



15

1.40.a. propynoic acid-(4'-chloro-biphenyl-4-yl)-amide

36 ml of a 1 molar DCC solution in dichloromethane are added dropwise at -10°C to a solution of 4.9 g (70 mmol) propynoic acid in 120 ml dichloromethane and the mixture is stirred for 30 min. Then 7 g (34.37 mmol) 4'-chloro-biphenyl-4-ylamine, dissolved in dichloromethane, are slowly added dropwise and the mixture is stirred for 2 h at -8°C. The reaction mixture is then filtered through Celite, washed again with methanol and the filtrate is evaporated down. The purification is carried out by column chromatography on silica gel (eluant: cyclohexane/ethyl acetate=6:1 to 2:1)

25 Yield: 7.6 g (95 % of theoretical)

C₁₅H₁₀ClNO (M=255.70)

Calc.: Molecular ion peak (M+H)⁺: 256/8 (Cl)
peak (M+H)⁺: 256/8 (Cl)

Found: Molecular ion

R_f value: 0.2 (silica gel, cyclohexane/ethyl acetate 1:1)

1.40.b 3-(4-hydroxymethyl-phenyl)-propynoic acid-4'-chloro-biphenyl-4-yl)-amide

10 g (30.69 mmol) caesium carbonate and 2.4 g (10.26 mmol) 4-iodobenzylalcohol are placed in 120 ml THF and cooled to -15°C in the ice/methanol bath, rinsed with argon and degassed. To this reaction mixture are added successively 660 mg (0.57 mmol) tetrakis(triphenylphosphine) palladium and 240 mg (1.26 mmol) copper(I)iodide and the mixture is again degassed. 3.2 g (12.52 mmol) propynoic acid-(4'-chloro-biphenyl-4-yl)amide are finally added. The mixture is stirred for 24 hours at ambient temperature and the reaction mixture is then evaporated down. The residue is extracted with water and ethyl acetate. The organic phase is dried over sodium sulphate, evaporated down and the residue is purified by column chromatography on silica gel (eluant: dichloromethane/methanol= 30:1).

Yield: 2 g (54 % of theoretical)

$C_{22}H_{16}ClNO_2$ (M= 361.82)

Calc.: Molecular ion peak (M+H)⁺: 362/4 (Cl)

Found: Molecular ion

peak (M+H)⁺: 362/4 (Cl)

R_f value: 0.35 (silica gel, dichloromethane/ ethanol/ammonia 20:1:0.1)

1.40.c. 3-(4-chloromethyl-phenyl)-propynoic acid-(4'-chloro-biphenyl-4-yl)-amide

0.45 ml (5.81 mmol) methanesulphonic acid chloride are slowly added dropwise at ambient temperature to a solution of 2 g (3.87 mmol) 3-(4-hydroxymethyl-phenyl)-propynoic acid-4'-chloro-biphenyl-4-yl)-amide and 1.56 ml (11.2 mmol) triethylamine in 100 ml dichloromethane and the reaction mixture is stirred for 24 hours at ambient temperature. It is extracted three times with water and the organic phase is dried over sodium sulphate. The solvent is distilled off and the residue is stirred with diisopropylether and suction filtered.

Yield: 0.8 g (54 % of theoretical)

$C_{22}H_{15}Cl_2NO$ (M= 380.27)

Calc.: Molecular ion peak (M+H)⁺: 380/2/4 (Cl₂)

Found: Molecular ion

peak (M+H)⁺: 380/2/4 (Cl₂)

R_f value: 0.7 (silica gel, dichloromethane/ ethanol = 50:1)

1.40.d. 3-{4-[cyclopropylmethyl-methyl-amino)-methyl]-phenyl}-propynoic acid-(4'-chloro-biphenyl-4-yl)-amide

A reaction mixture of 70 mg (0.18 mmol) 3-(4-chloromethyl-phenyl)-propynoic acid-(4'-chloro-biphenyl-4-yl)-amide, 19 mg (0.19 mmol) cyclopropylmethyl-methylamine and 51 mg (0.37 mmol) potassium carbonate in 5 ml acetone is agitated for 24 hours at reflux temperature. The reaction mixture is evaporated down. The residue is extracted between water and ethyl acetate. The organic phase is dried over sodium sulphate, evaporated down and the residue is purified by column chromatography on silica gel (eluant: dichloromethane/methanol= 100:0 to 50:50).

Yield: 30 mg (38 % of theoretical)

Melting point: 181°C

C₂₇H₂₅ClN₂O (M= 428.95)

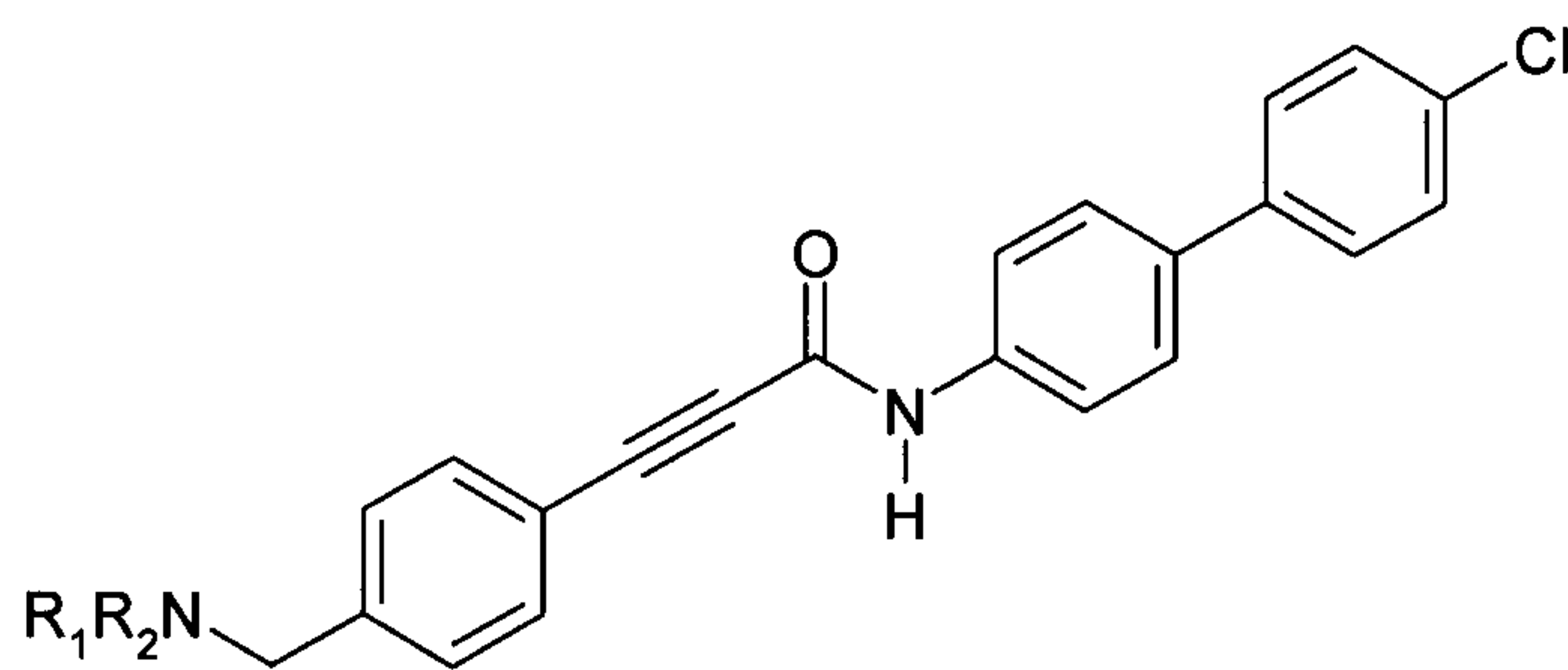
Calc.: Molecular ion peak (M+H)⁺: 429/31(Cl)

Found: Molecular ion

peak (M+H)⁺: 429/31(Cl)

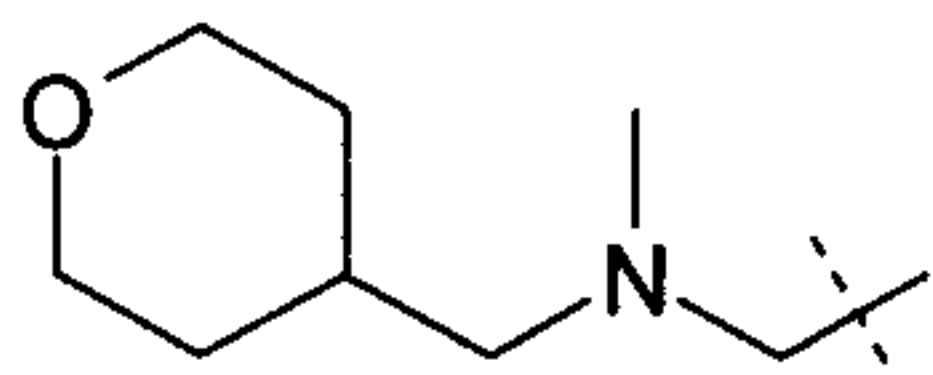
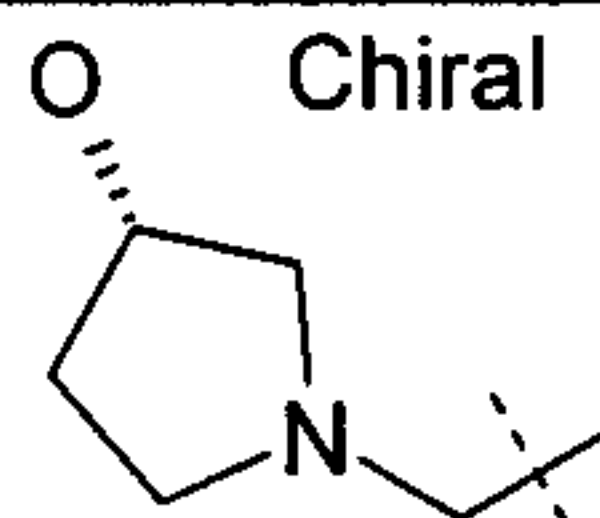
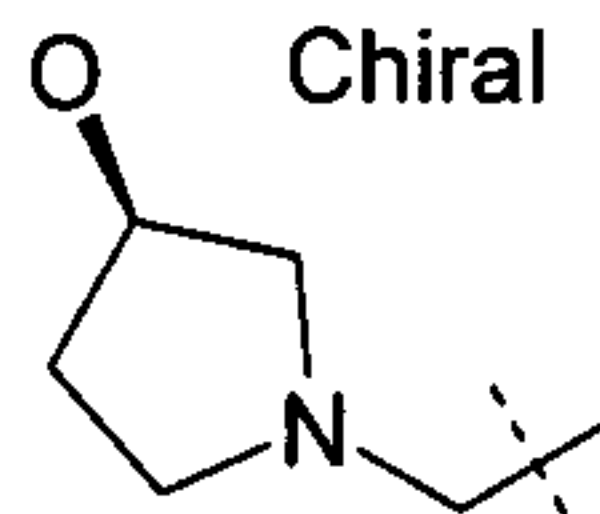
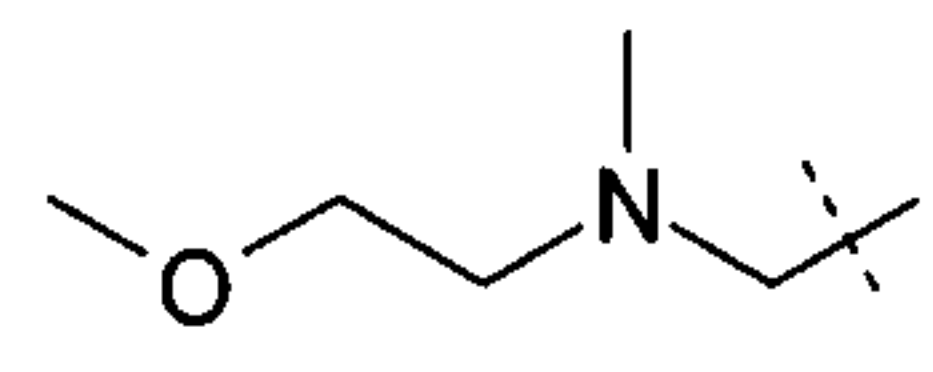
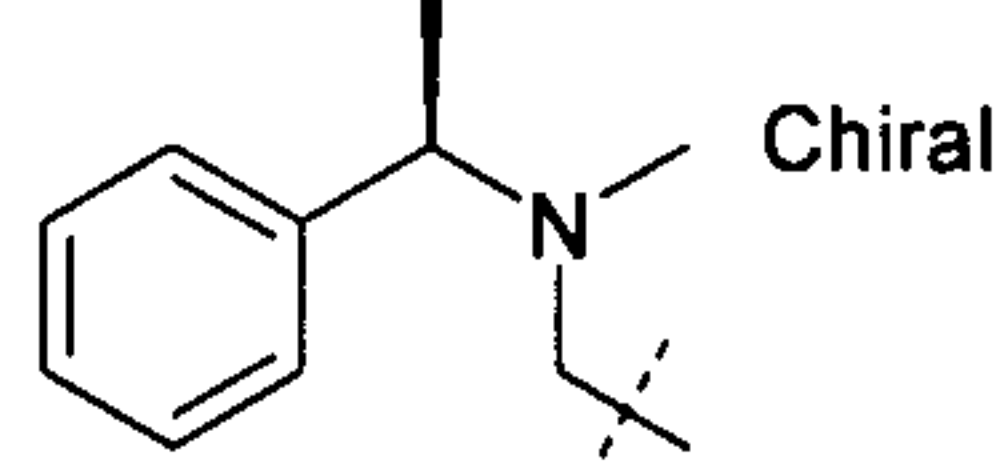
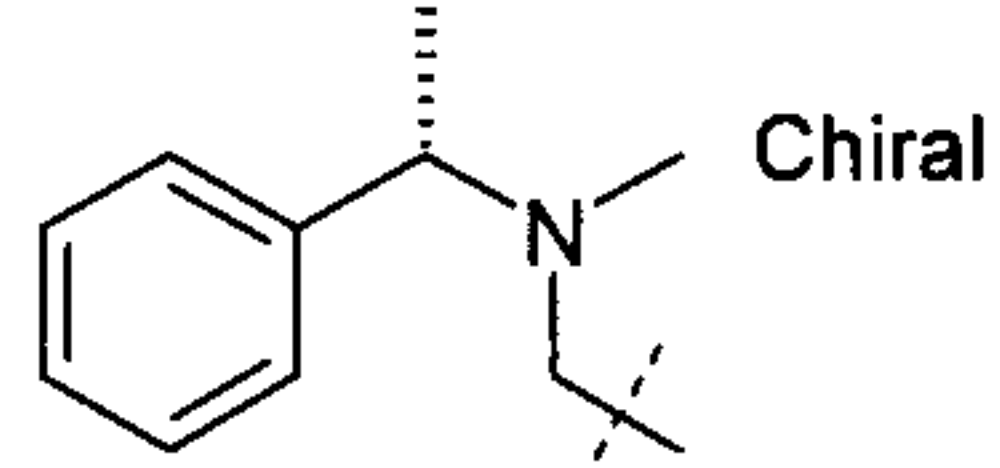
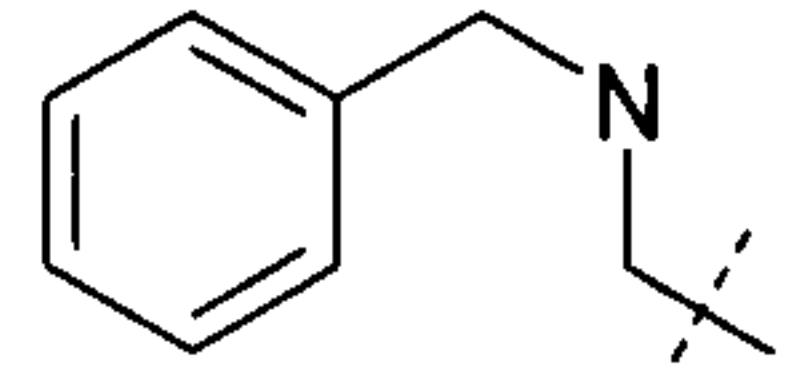
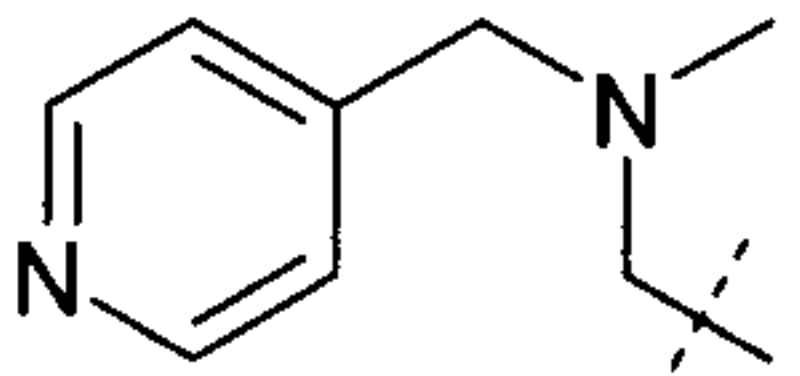
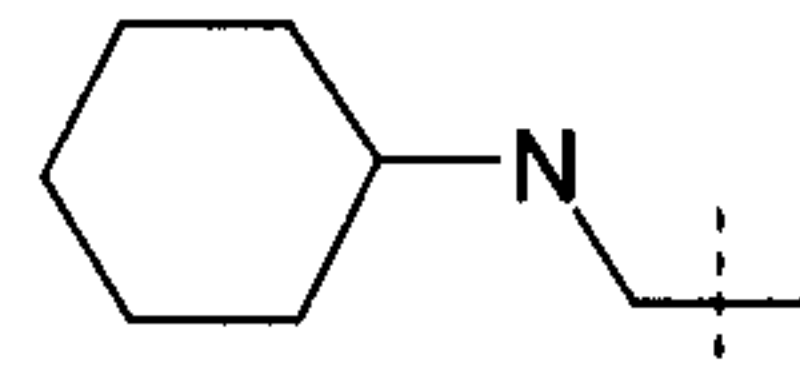
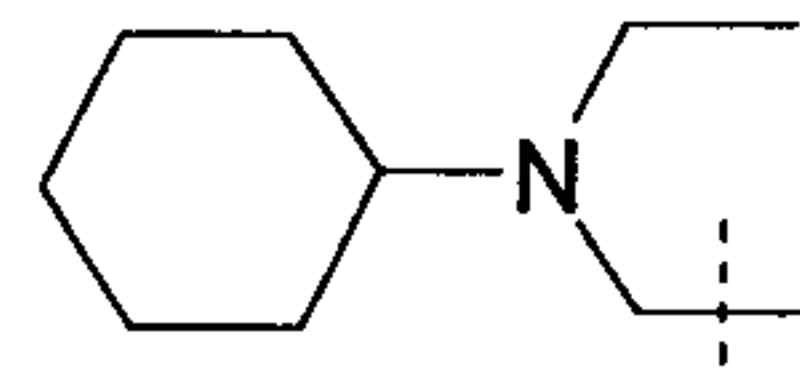
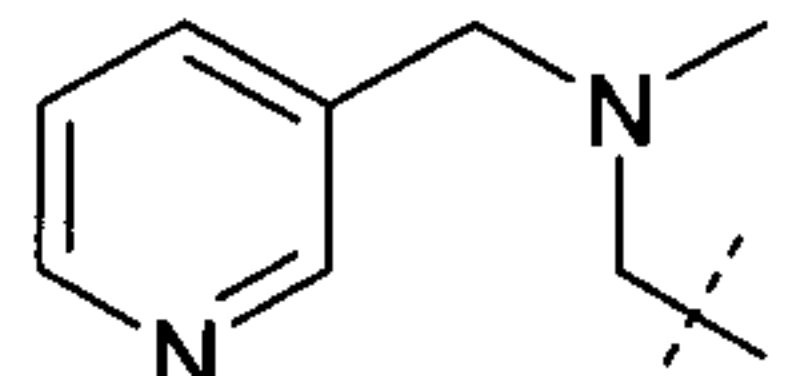
R_f value: 0.5 (silica gel, dichloromethane/ ethanol/ammonia = 20:1:0.1)

The following compounds are prepared analogously to Example 1.40.d:



20

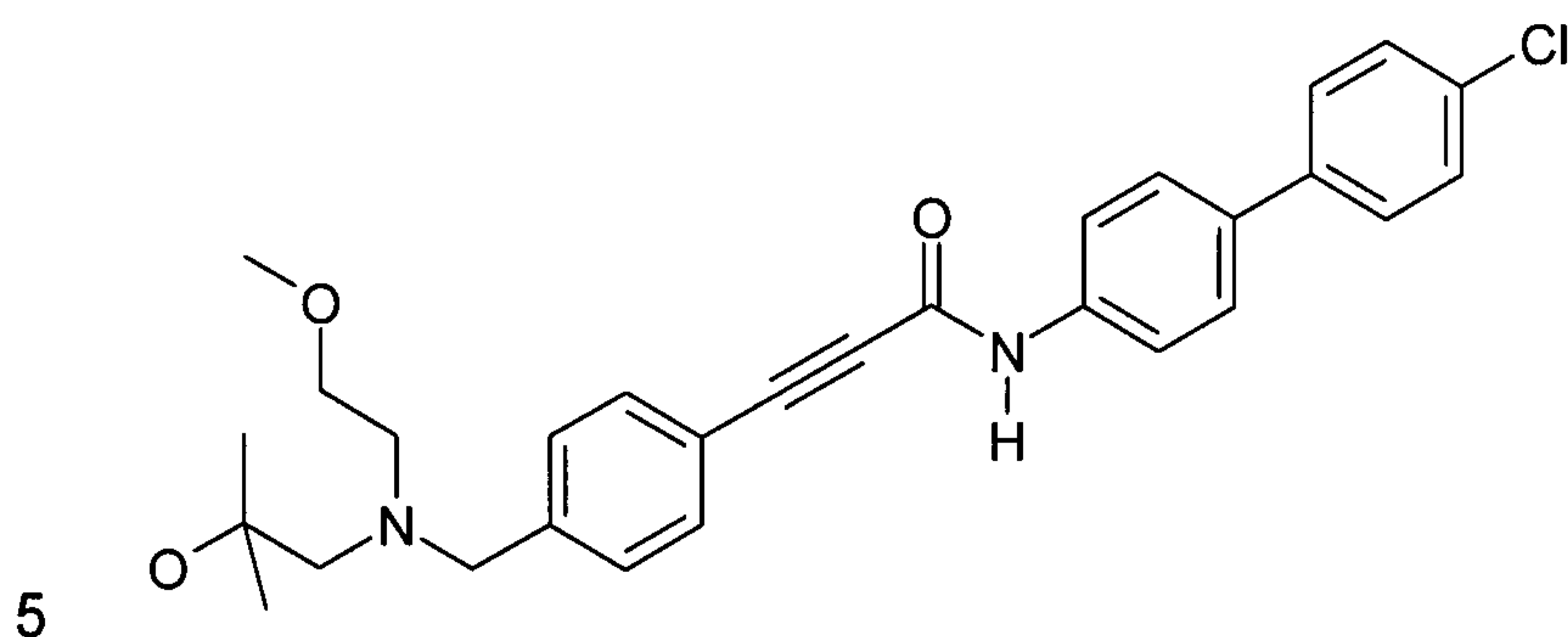
Example	R ₁ R ₂ N-X	educt	empirical formula	mass spectrum	mp [°C]	R _f value
1.41		1.40.c	C ₂₈ H ₂₇ ClN ₂ O ₂	459/61 (Cl) [M+H] ⁺	196	0.35 (A)
1.42		1.40.c	C ₂₉ H ₂₉ ClN ₂ O	457/9 (Cl) [M+H] ⁺	215	0.4 (A)

1.43		1.40.c	C ₂₉ H ₂₉ ClN ₂ O ₂	473/5 (Cl) [M+H] ⁺	181- 182	0.5 (A)
1.44		1.40.c	C ₂₆ H ₂₃ ClN ₂ O ₂	431/3 (Cl) [M+H] ⁺	175	0.15 (A)
1.45		1.40.c	C ₂₆ H ₂₃ ClN ₂ O ₂	431/3 (Cl) [M+H] ⁺	135- 136	0.15 (A)
1.46		1.40.c	C ₂₆ H ₂₅ ClN ₂ O ₂	433/5 (Cl) [M+H] ⁺	149	0.3 (A)
1.47		1.40.c	C ₃₁ H ₂₇ ClN ₂ O	479/81 (Cl) [M+H] ⁺	162- 164	0.3 (B)
1.48		1.40.c	C ₃₁ H ₂₇ ClN ₂ O	479/81 (Cl) [M+H] ⁺	165- 166	0.3 (B)
1.49		1.40.c	C ₂₉ H ₂₃ ClN ₂ O	451/3 (Cl) [M+H] ⁺	150- 154	0.2 (B)
1.50		1.40.c	C ₂₉ H ₂₄ ClN ₃ O	466/68 (Cl)	186	0.1 (B)
1.51		1.40.c	C ₂₈ H ₂₇ ClN ₂ O	443/5 (Cl)	223,5- 224	0.2 (B)
1.52		1.40.c	C ₃₀ H ₃₁ ClN ₂ O	471/3 (Cl)	156- 157	0.2 (B)
1.53		1.40.c	C ₂₉ H ₂₄ ClN ₃ O	466/68 (Cl)	175- 176	

R_f value: A= (silica gel, dichloromethane/ethanol/ammonia 20:1:0.1)

B= (silica gel, dichloromethane/ethanol/ammonia 50:1:0.1)

3-(4-[(2-hydroxy-2-methyl-propyl)-(2-methoxy-ethyl)amino]-methyl)-phenyl)-propionic acid-(4'-chloro-biphenyl-4-yl) amide trifluoroacetate



A reaction mixture of 70 mg (0.18 mmol) 3-(4-chloromethyl-phenyl)-propynoic acid-(4'-chloro-biphenyl-4-yl)-amide, 19 mg (0.19 mmol) 1-(2-methoxy-ethylamino)-2-methyl-propan-2-ol and 51 mg (0.37 mmol) potassium carbonate in 5 ml acetone is agitated for 24 hours at reflux temperature. The reaction mixture is evaporated down. The residue is extracted between water and ethyl acetate. The organic phase is dried over sodium sulphate, evaporated down and the residue is purified by column chromatography first of all on silica gel (eluant: dichloromethane/methanol= 100:0 to 50:50) and then on RP-18 (eluant: water + 0.1% trifluoroacetic acid / acetonitrile + 0.1% trifluoroacetic acid=100:0 to 50:50).

Yield: 11 mg (11 % of theoretical)

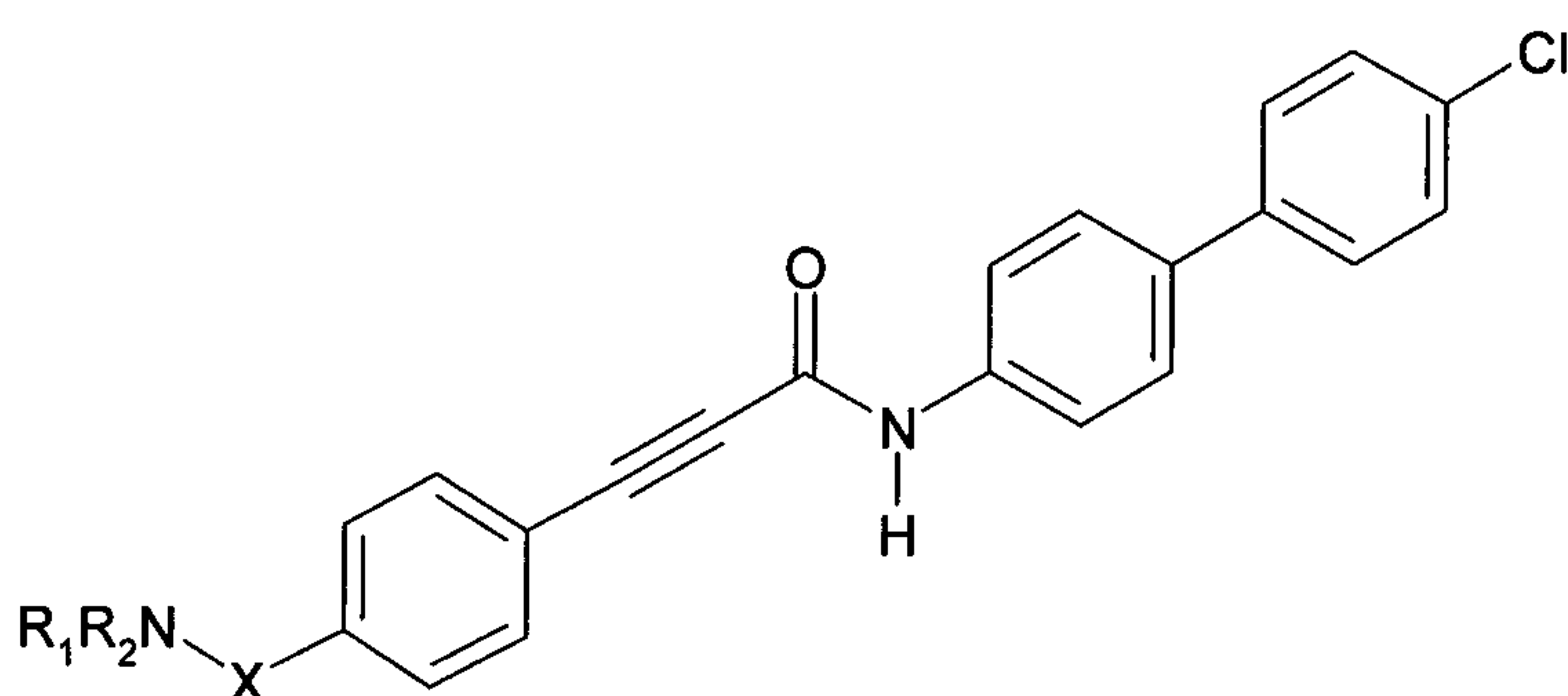
$C_{29}H_{31}ClN_2O_3 \cdot C_2HF_3O_2$ (M= 605.04)

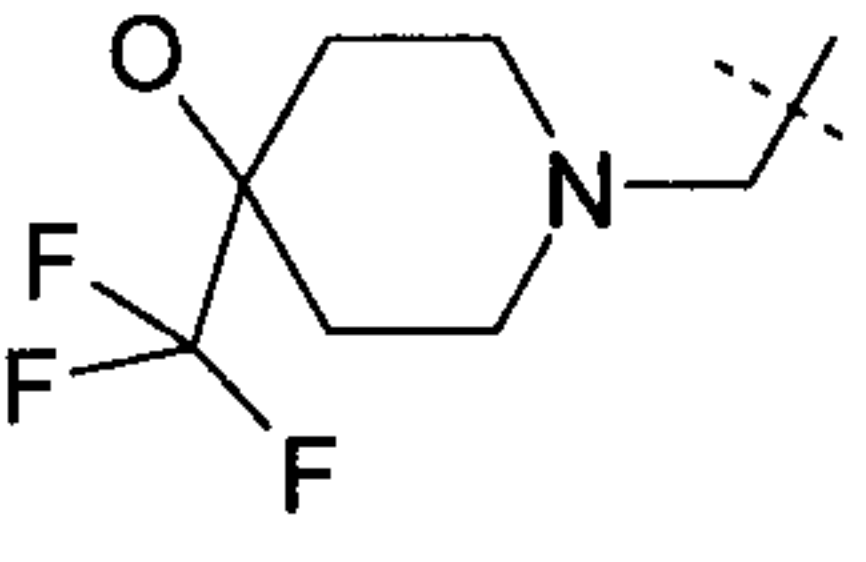
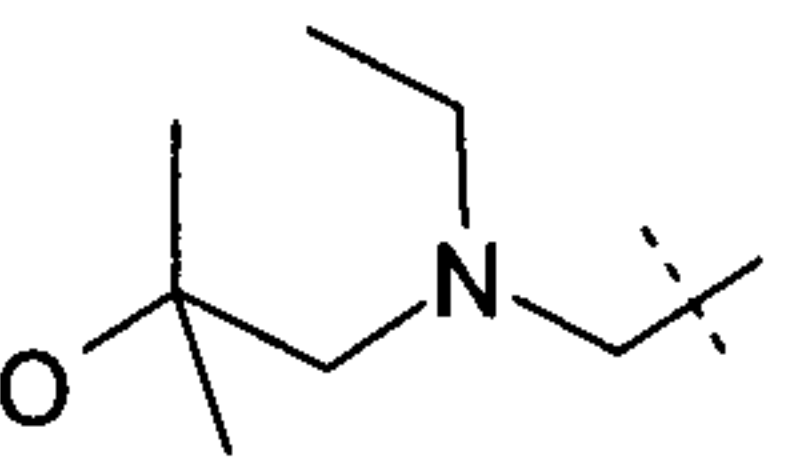
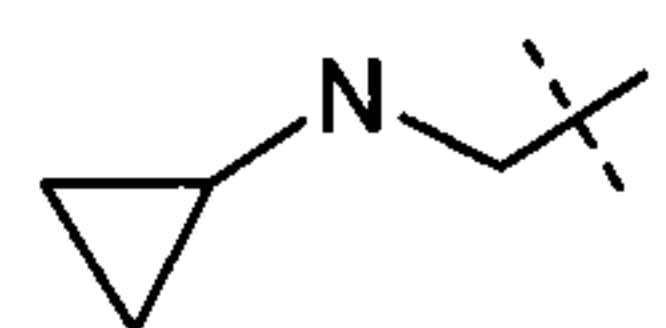
Calc.: Molecular ion peak (M+H)⁺: 491/93 (Cl)

Found: Molecular ion peak

(M+H)⁺: 491/93 (Cl)

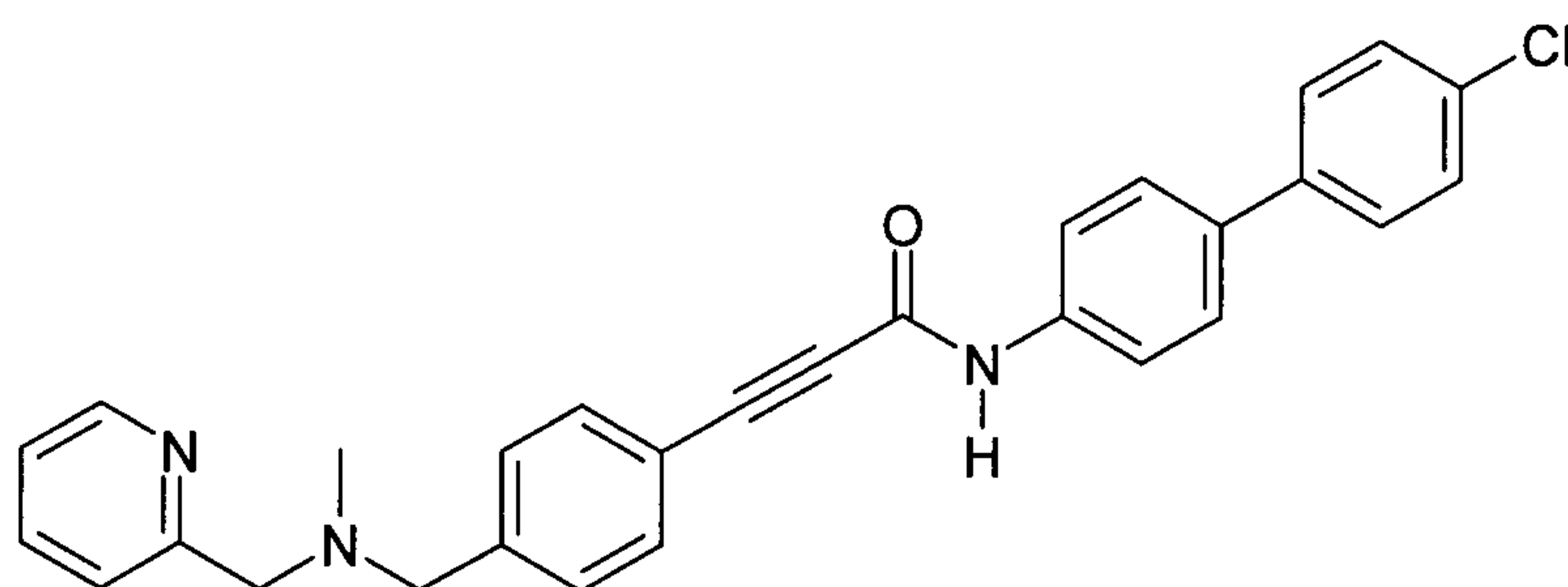
The following compounds are prepared analogously to Example 1.54:



Example	R ₁ R ₂ N-X	educt	empirical formula	mass spectrum	mp [°C]
1.55		1.40.c	C ₂₈ H ₂₄ ClF ₃ N ₂ O ₂	513/15 (Cl)	70-78
1.56		1.40.c	C ₂₈ H ₂₉ ClN ₂ O ₂	461/63 (Cl)	
1.57		1.40.c	C ₂₅ H ₂₁ ClN ₂ O	401/3 (Cl)	224-225

5 Example 1.58:

3-{4-[(methyl-pyridin-2-ylmethyl-amino)-methyl-phenyl]-propynoic acid-(4'-chloro-biphenyl-4-yl)amide



10

A reaction mixture of 55 mg (0.15 mmol) 3-(4-chloromethyl-phenyl)-propynoic acid-(4'-chloro-biphenyl-4-yl)-amide, 18.3 mg (0.159 mmol) methyl-pyridin-2-ylmethyl-amine and 51 mg (0.37 mmol) potassium carbonate in 5 ml acetone is agitated for 24 hours at reflux temperature. The reaction mixture is evaporated down. The residue is triturated with water and diisopropylether and the product is suction filtered and dried in the air.

Yield: 20 mg (30 % of theoretical)

Melting point: 217-218 °C

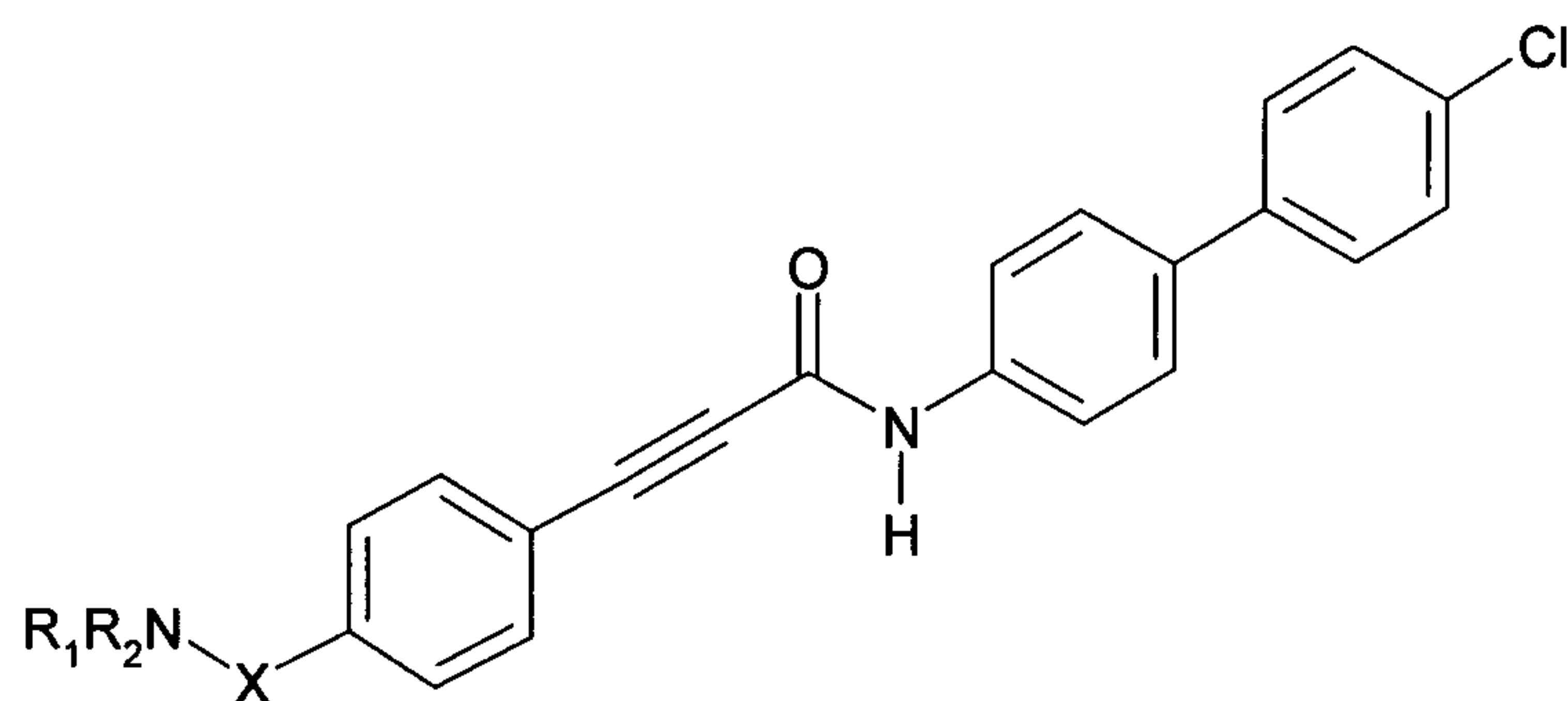
20 C₂₉H₂₄ClN₃O (M= 465.97)

Calc.: Molecular ion peak (M+H)⁺: 466/468 (Cl)

Found: Molecular ion

peak (M+H)⁺: 466/468 (Cl)

The following compound is prepared analogously to Example 1.58:

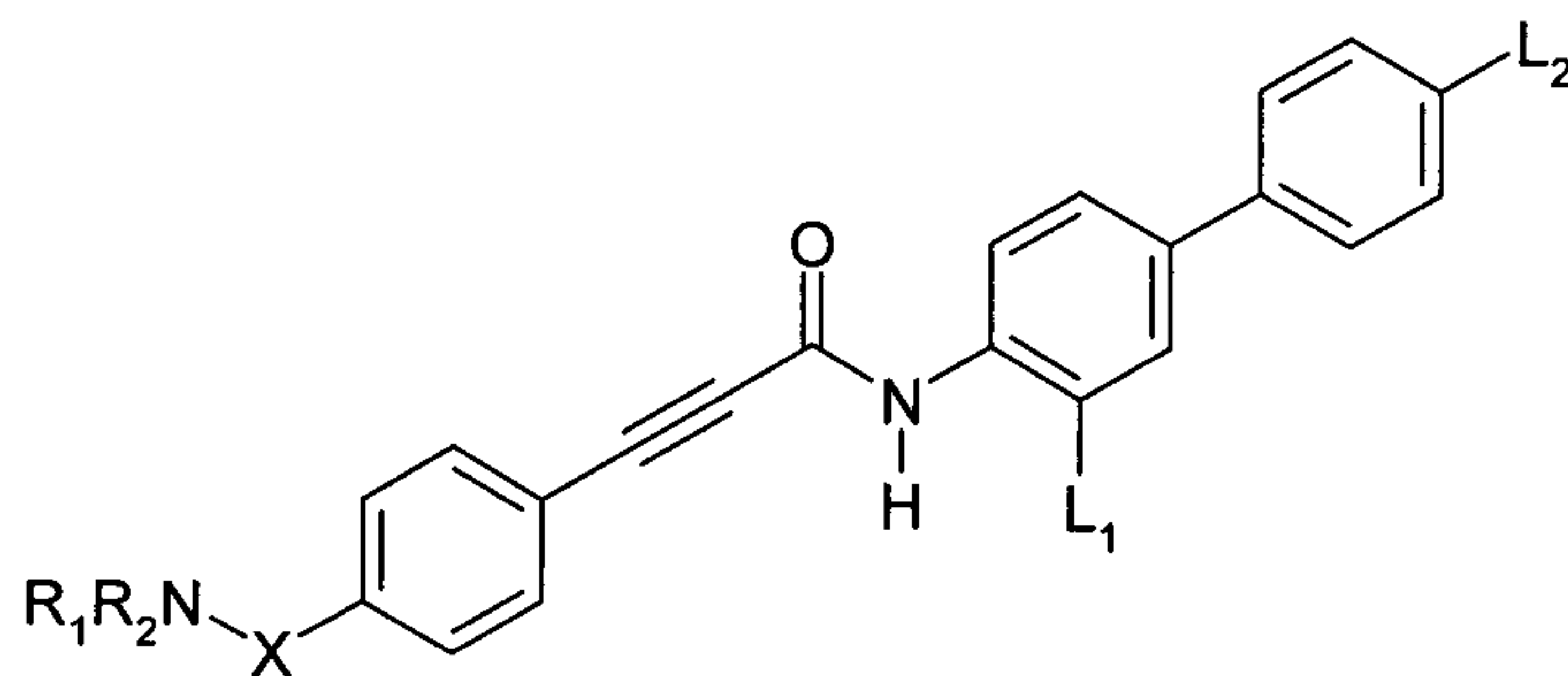


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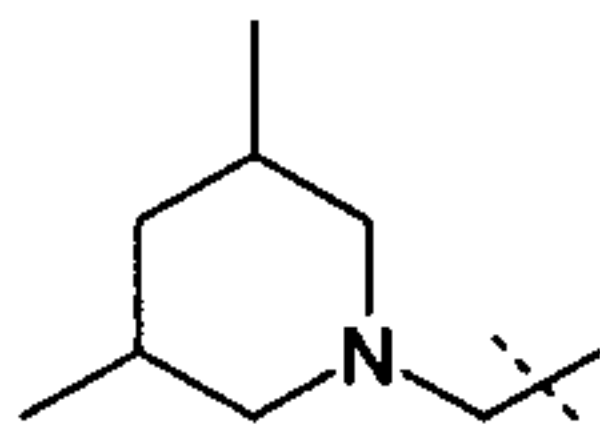
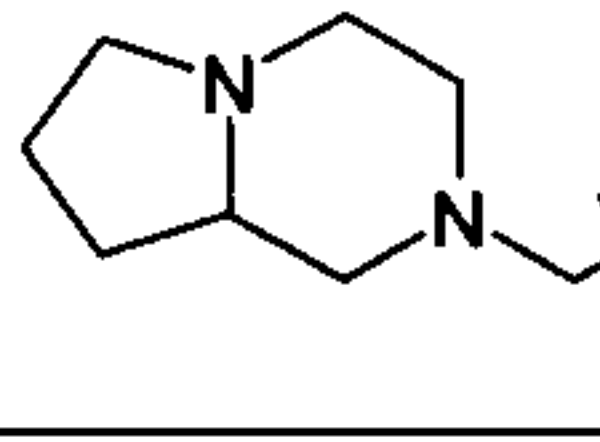
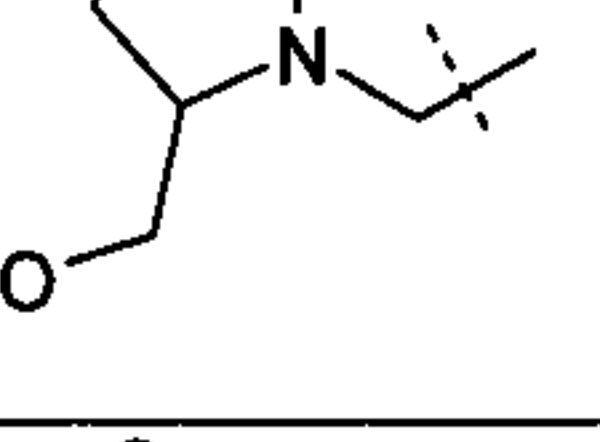
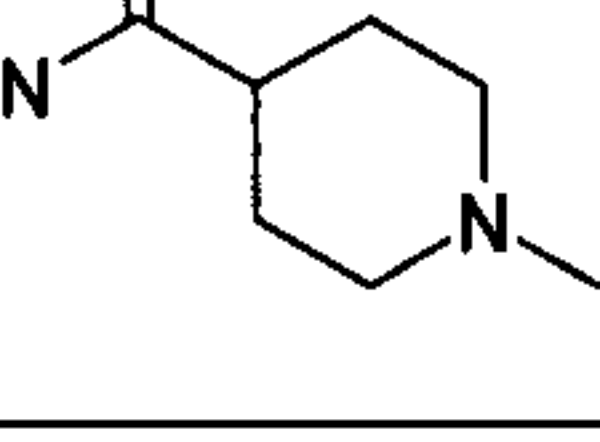
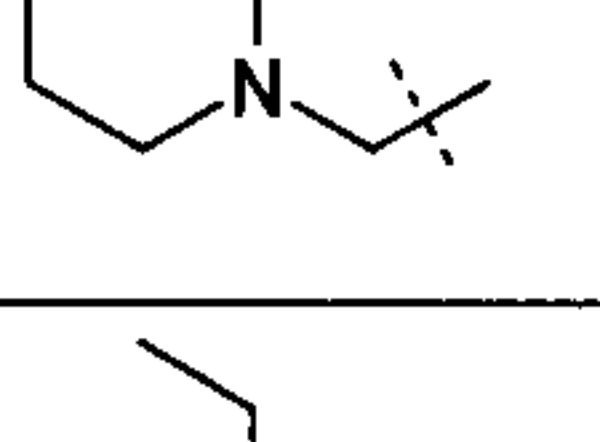
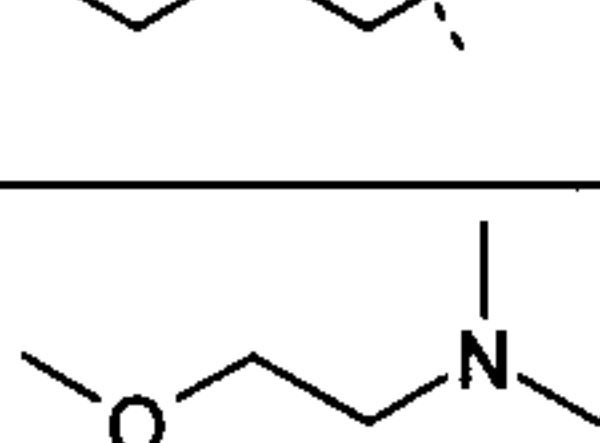
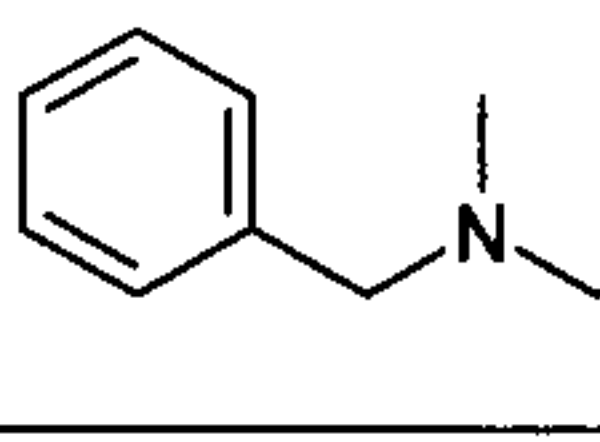
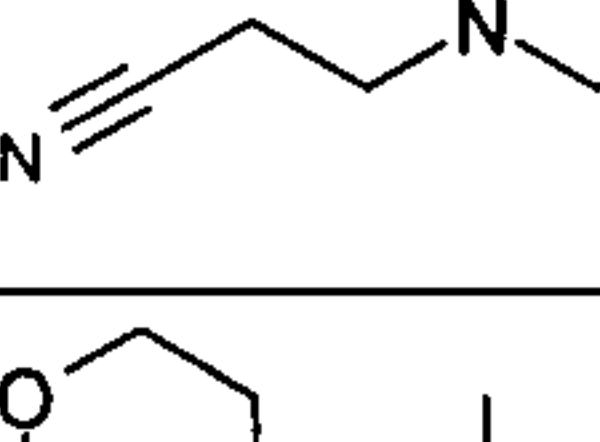
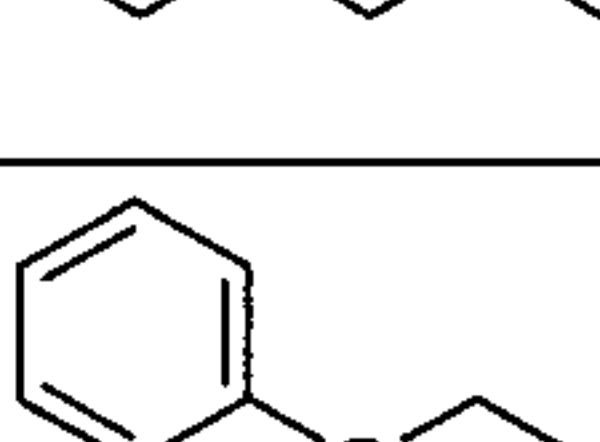
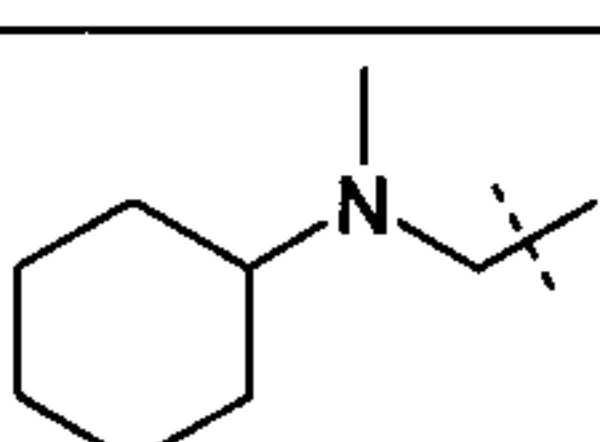
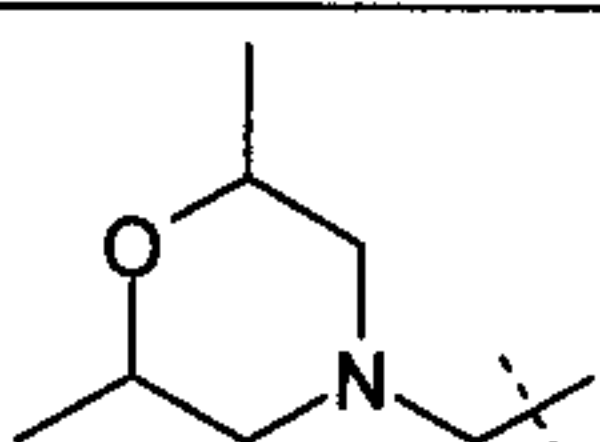
Example	R ₁ R ₂ N-X	educt	empirical formula	mass spectrum	mp [°C]
1.59		1.40.c	C ₂₇ H ₂₅ ClN ₂ O	429/31/33 (Cl)	195- 196

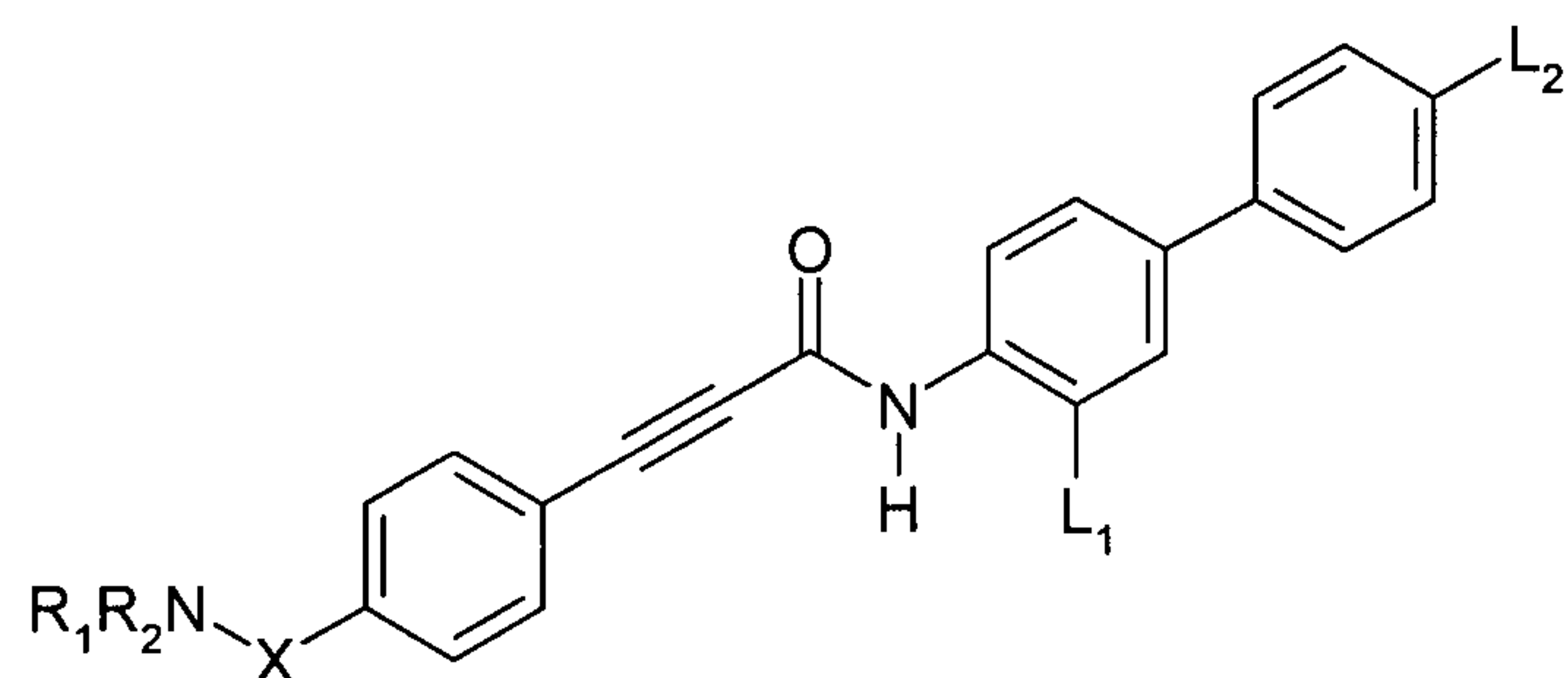
The following compounds are prepared analogously to Example 1.2.c:

10

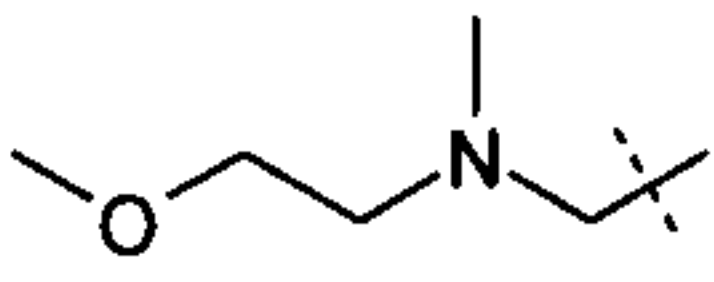
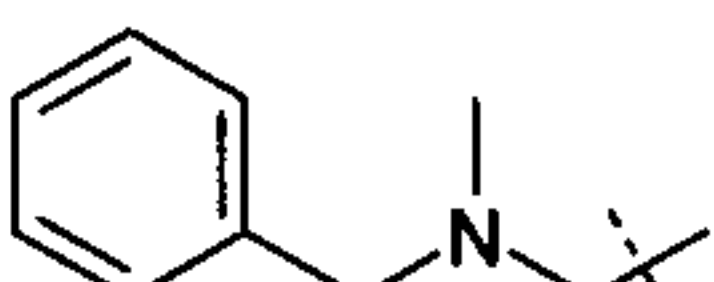
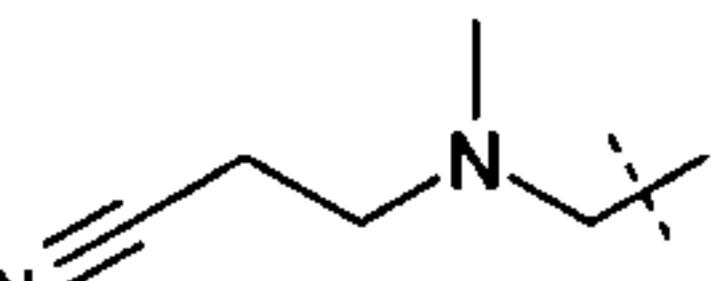
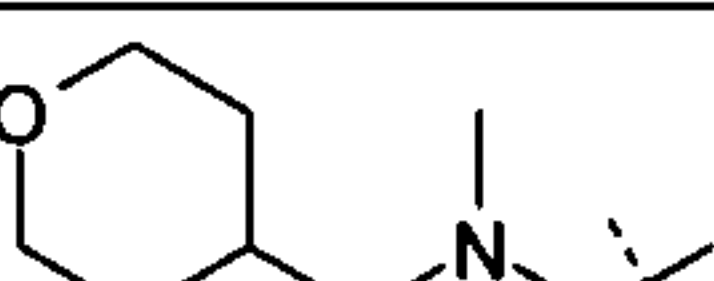
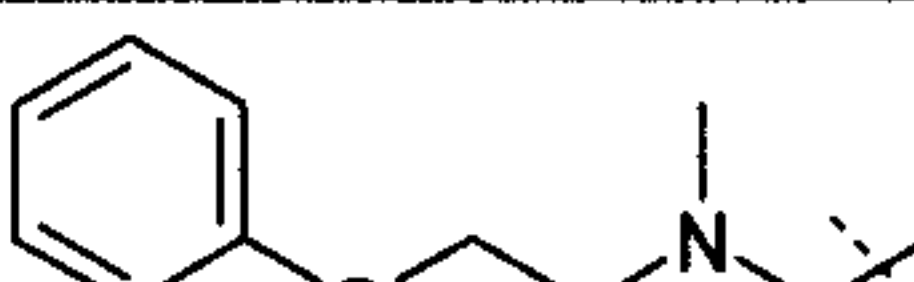
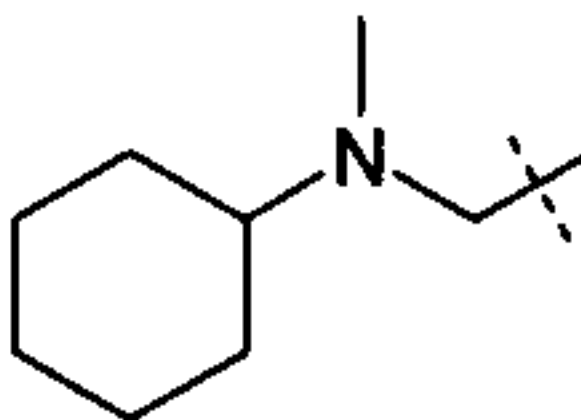
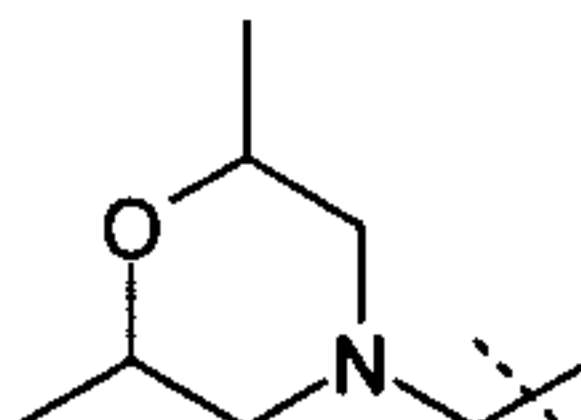


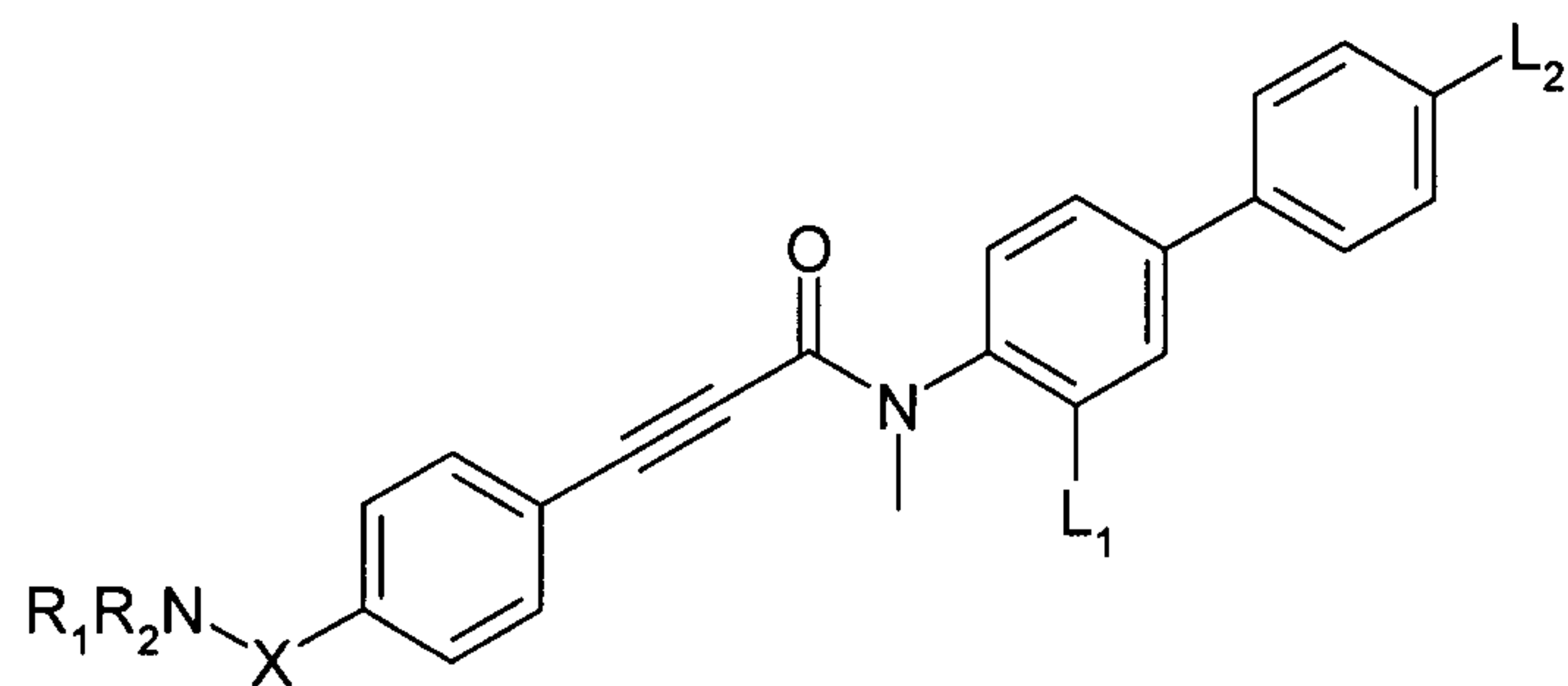
Example	R ₁ R ₂ N-X	L ₁	L ₂
1.60		H	Cl
1.61		H	Cl
1.62		H	Cl

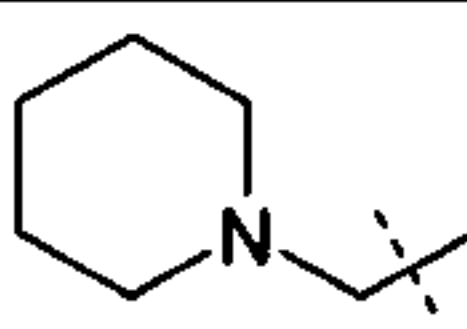
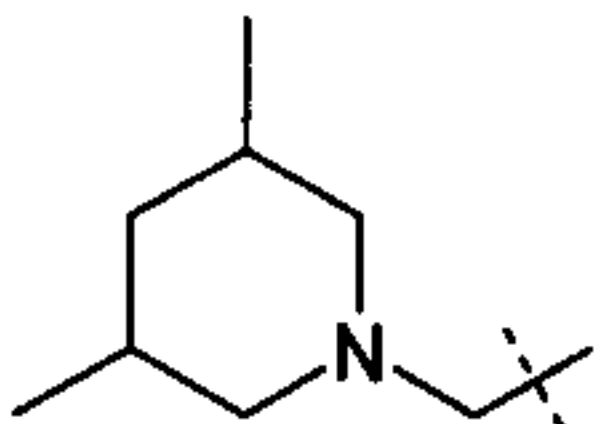
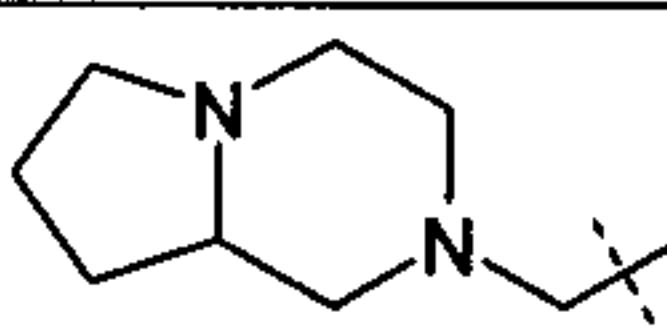
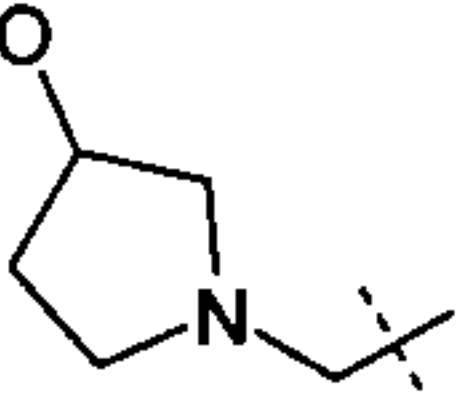
1.63		H	Cl
1.64		H	Cl
1.65		H	Cl
1.66		H	Cl
1.67		H	Cl
1.68		H	Cl
1.69		H	Cl
1.70		H	Cl
1.71		H	Cl
1.72		H	Cl
1.73		H	Cl
1.74		H	Cl
1.75		H	Cl

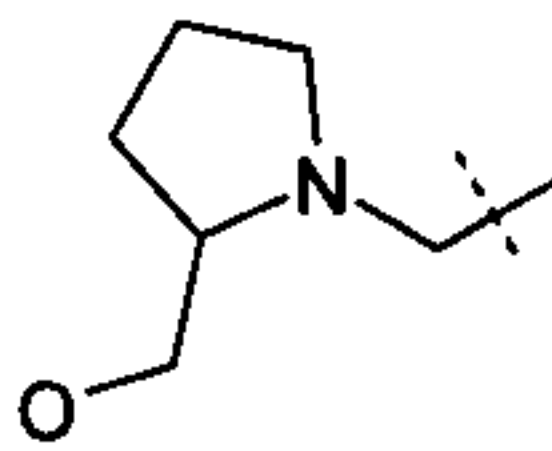
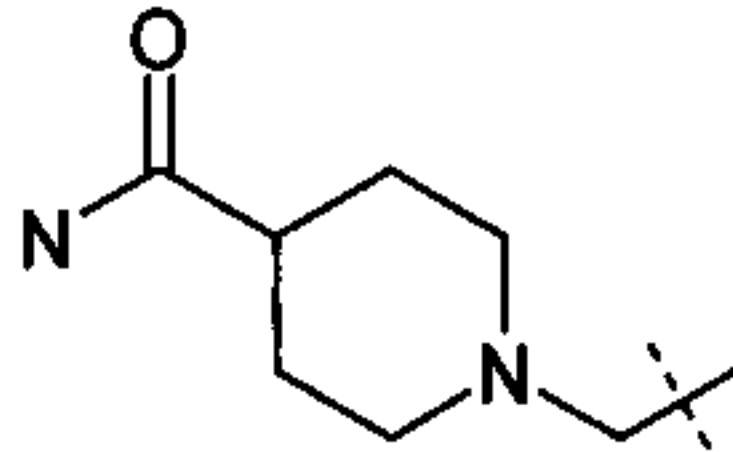
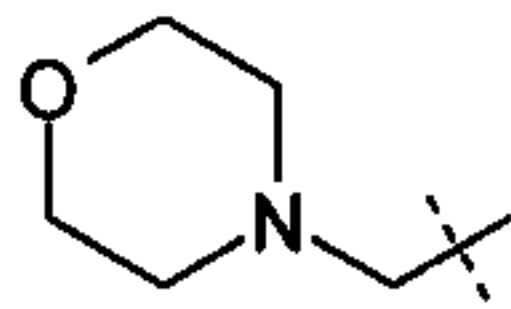
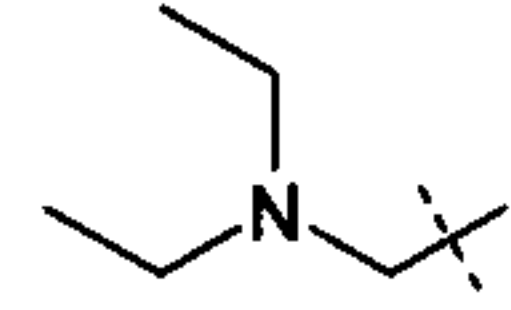
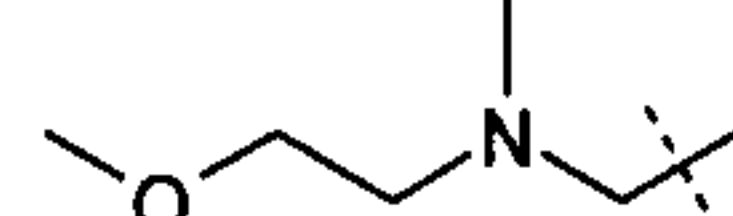
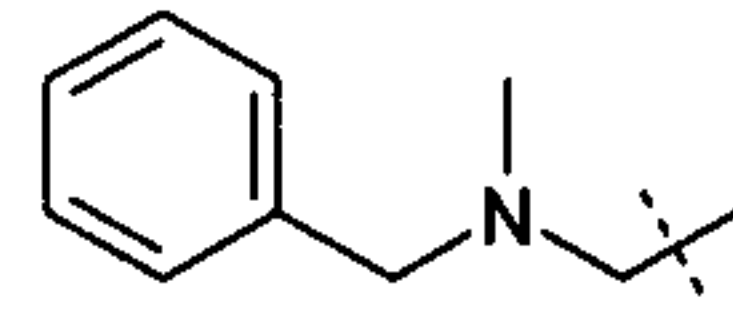
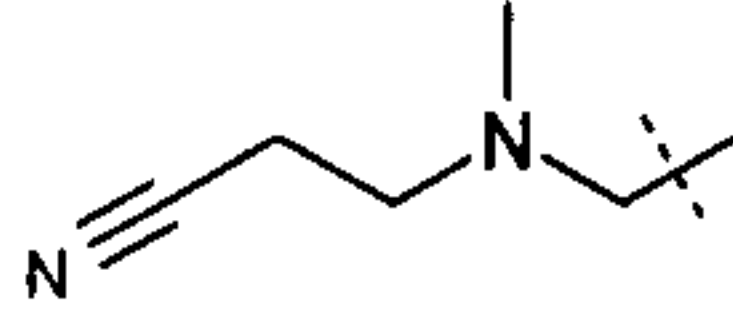
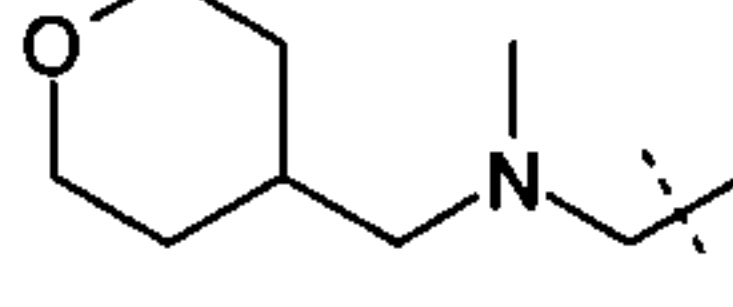
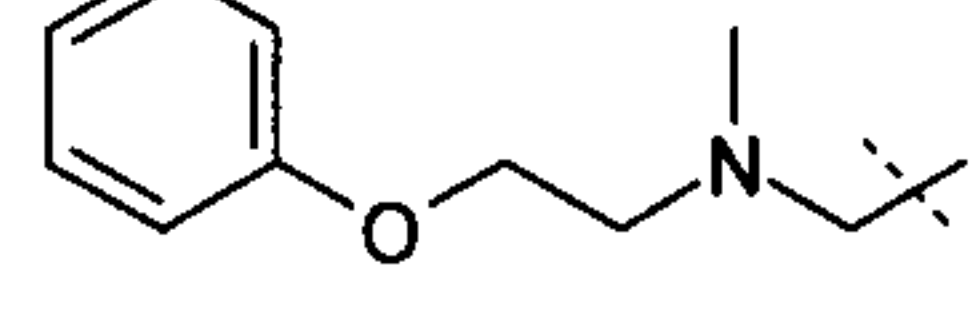
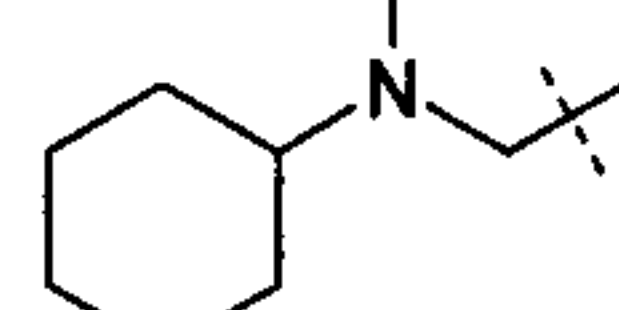
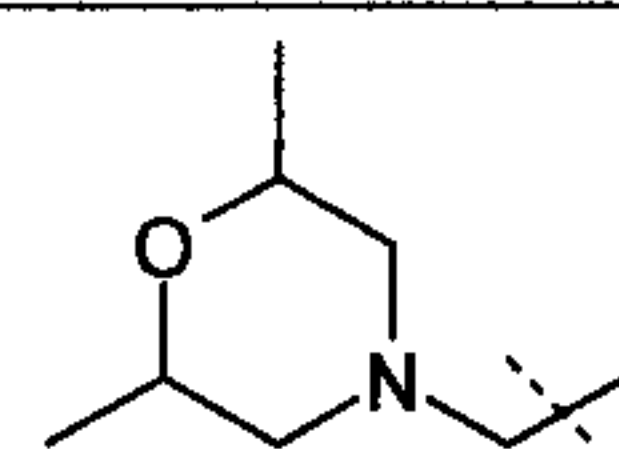


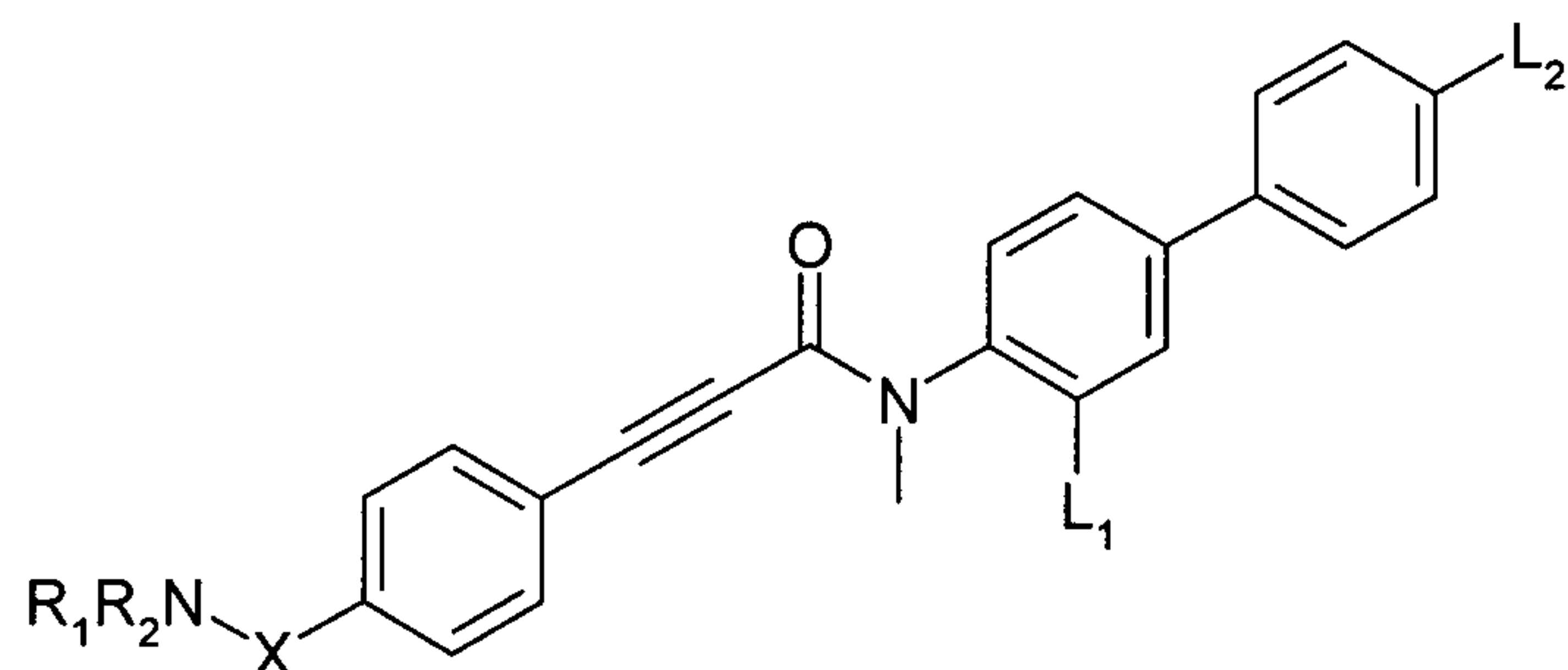
Example	$\text{R}_1\text{R}_2\text{N-X}$	L_1	L_2
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1.77		F	Cl
1.78		F	Cl
1.79		F	Cl
1.80		F	Cl
1.81		F	Cl
1.82		F	Cl
1.83		F	Cl
1.84		F	Cl
1.85		F	Cl
1.86		F	Cl
1.87		F	Cl

1.88		F	Cl
1.89		F	Cl
1.90		F	Cl
1.91		F	Cl
1.92		F	Cl
1.93		F	Cl
1.94		F	Cl

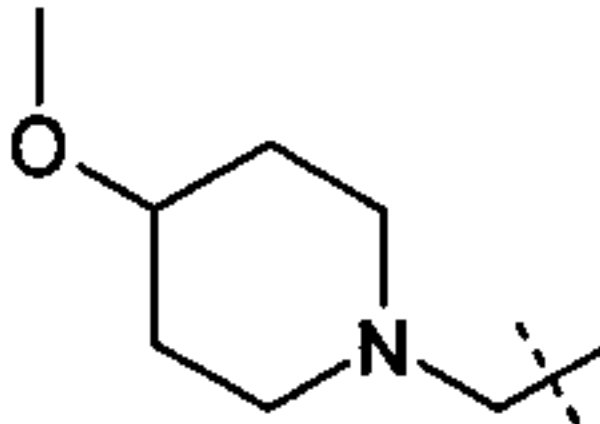
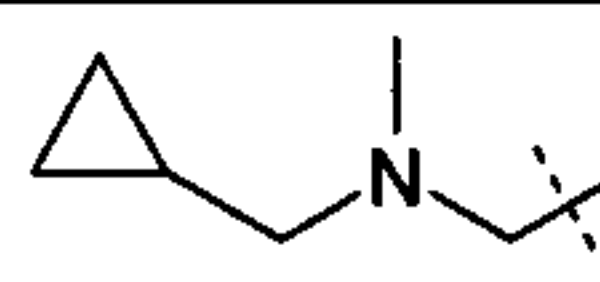
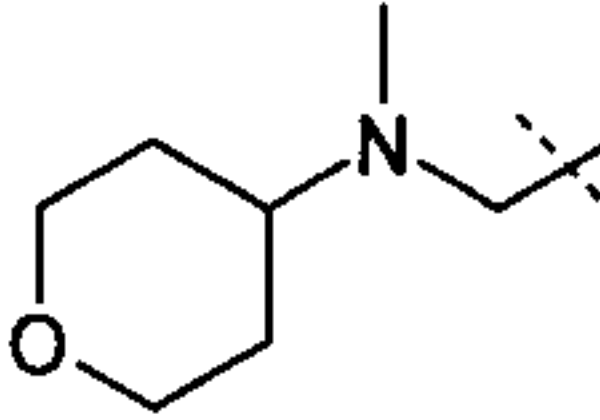
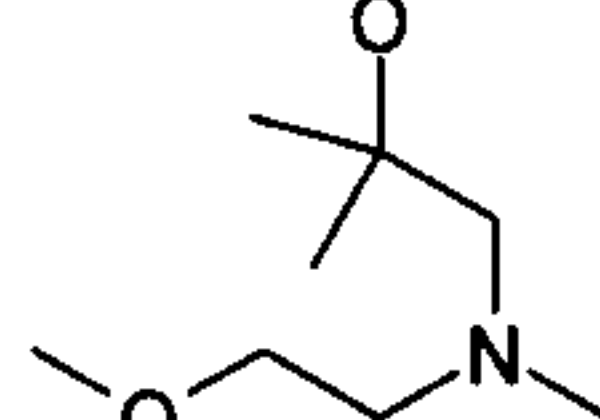
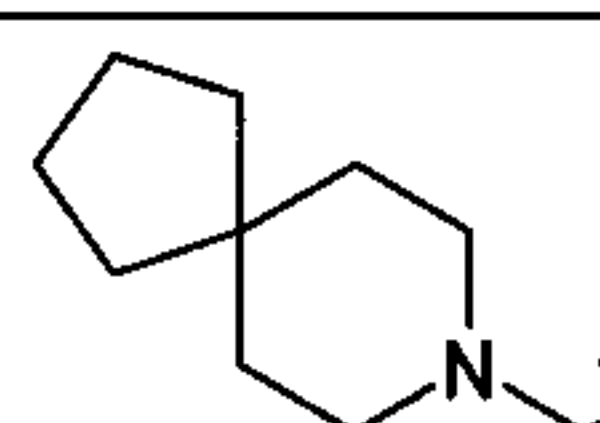
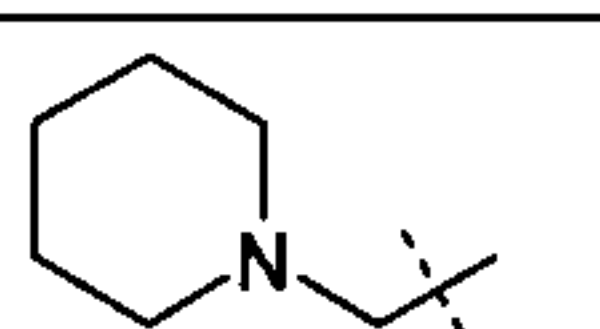
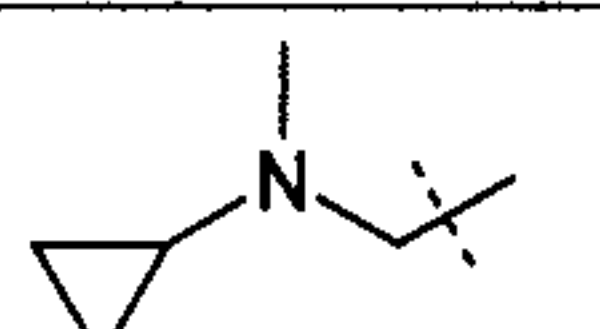
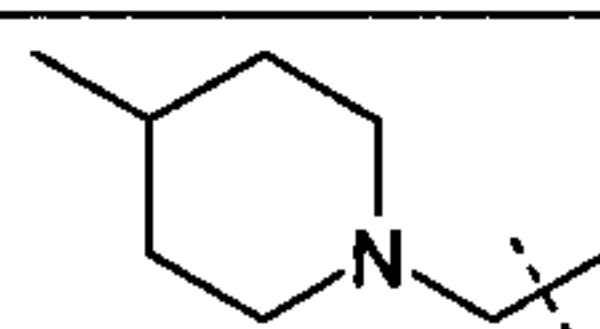
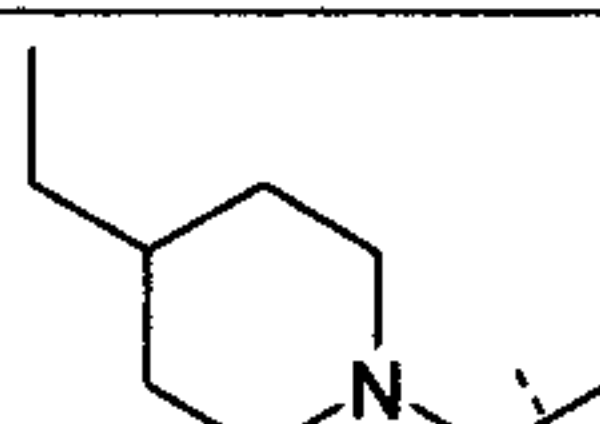
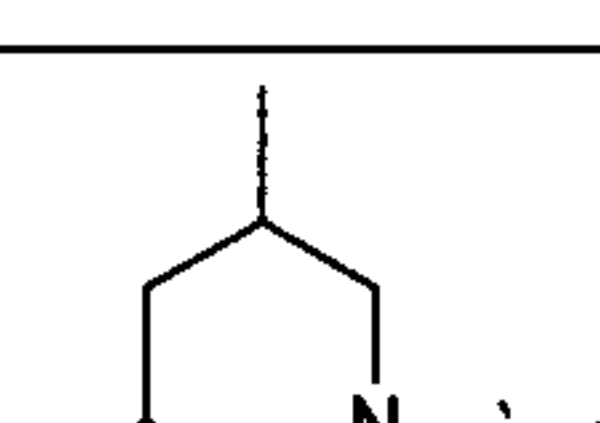
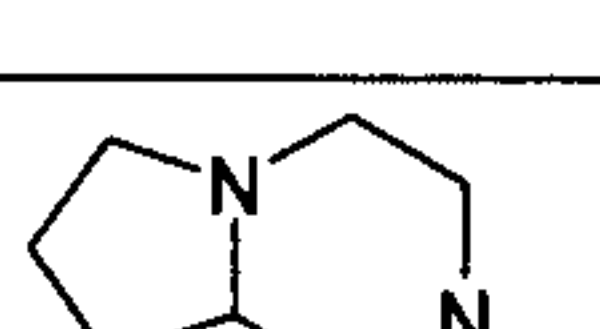
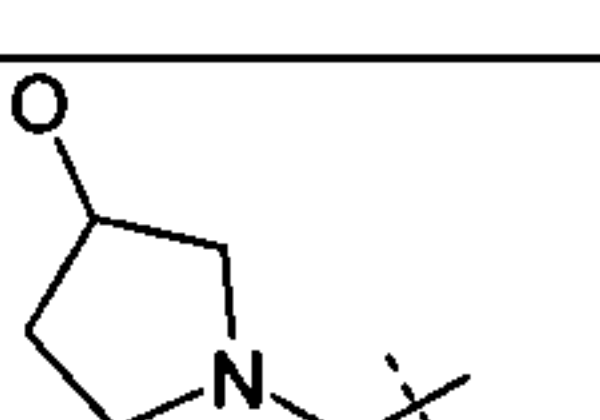
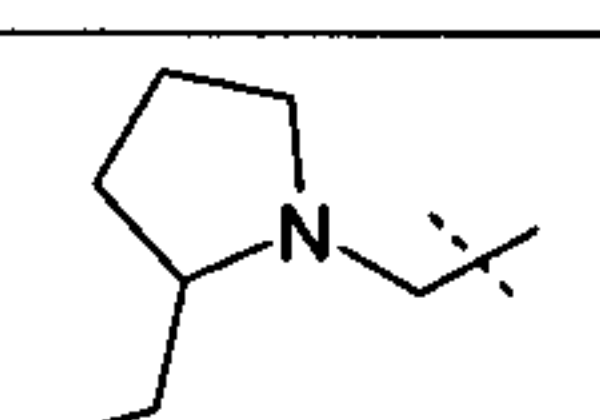
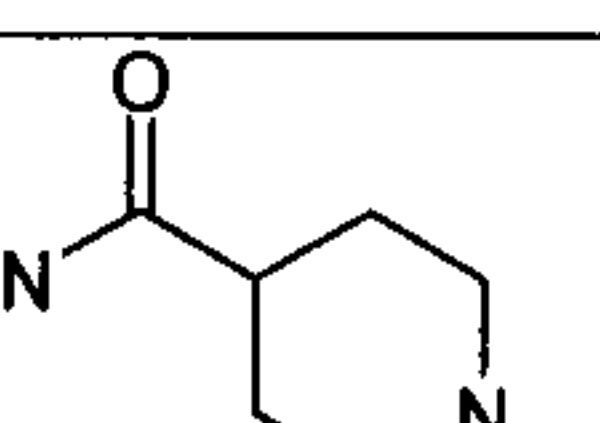
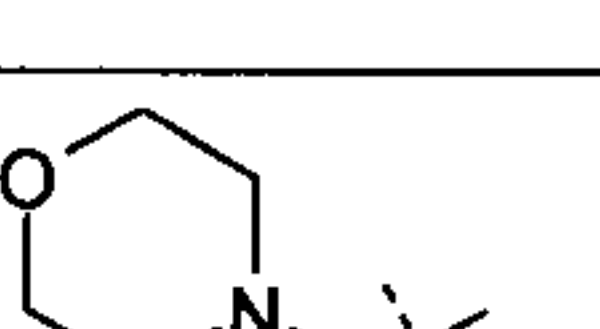


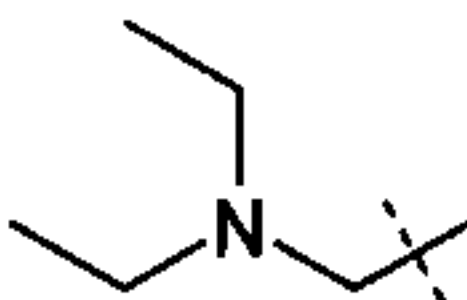
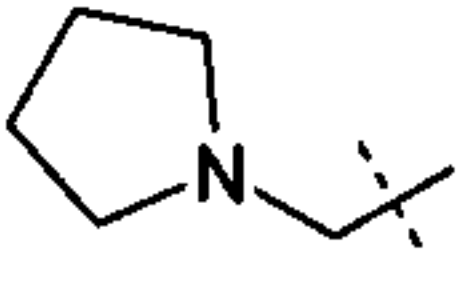
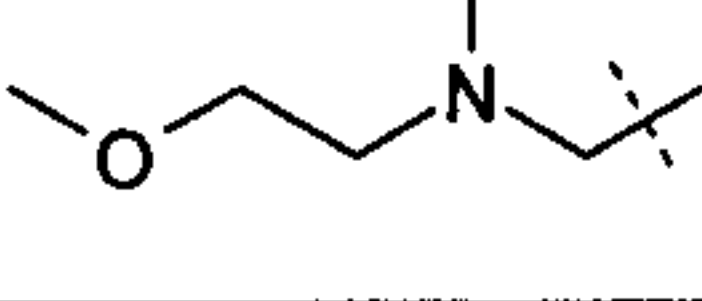
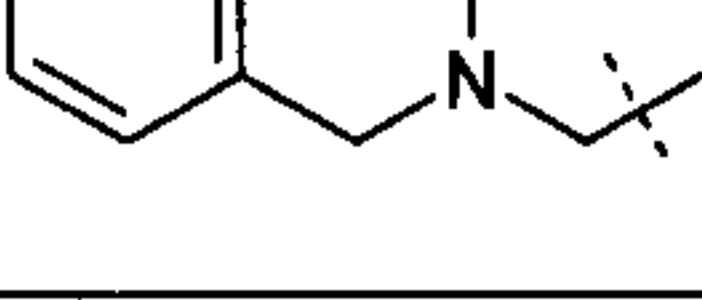
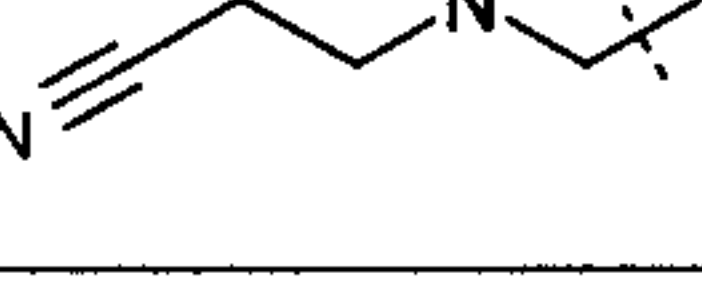
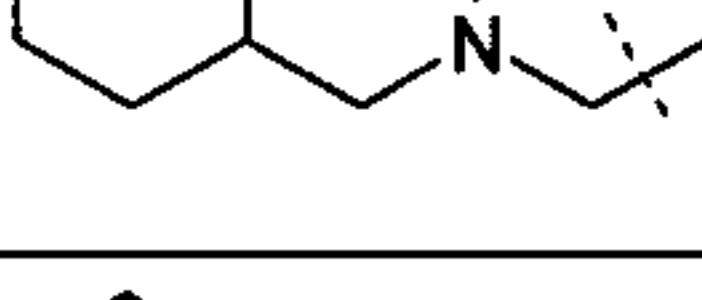
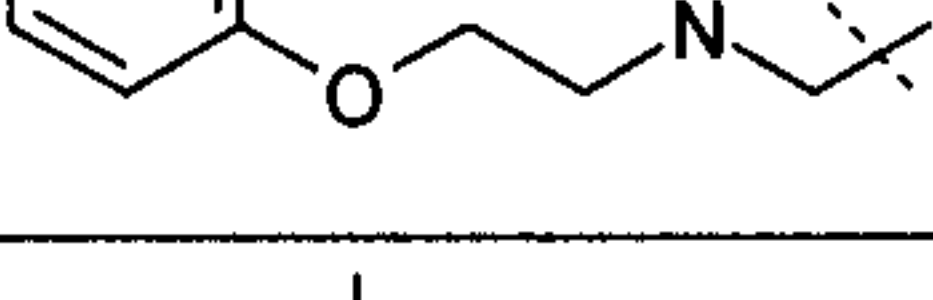
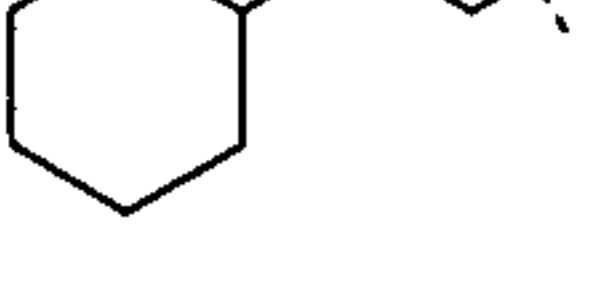
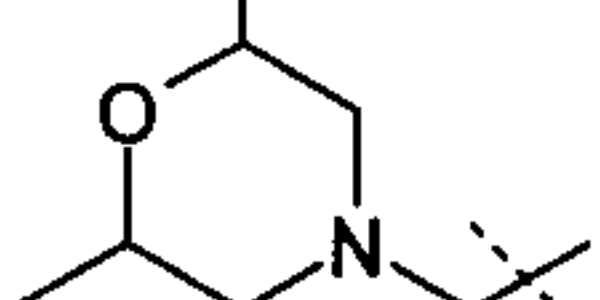
Example	R ₁ R ₂ N-X	L ₁	L ₂
1.95		H	Cl
1.96		H	Cl
1.97		H	Cl
1.98		H	Cl

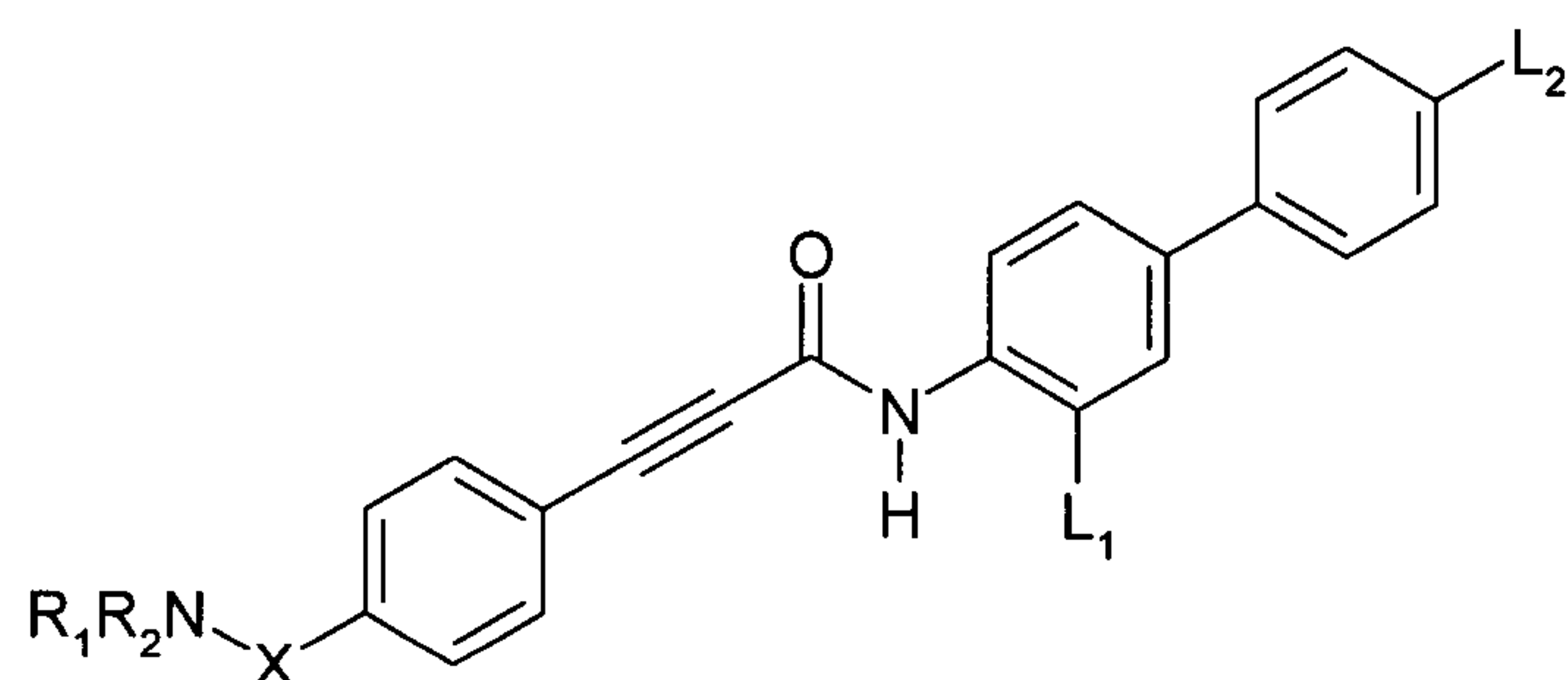
1.99		H	Cl
1.100		H	Cl
1.101		H	Cl
1.102		H	Cl
1.103		H	Cl
1.104		H	Cl
1.105		H	Cl
1.106		H	Cl
1.107		H	Cl
1.108		H	Cl
1.109		H	Cl

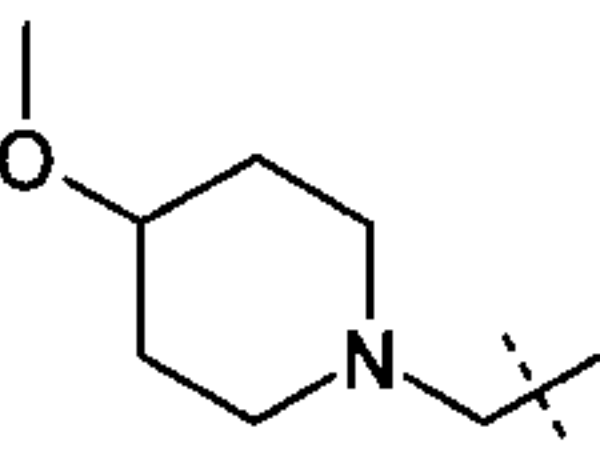
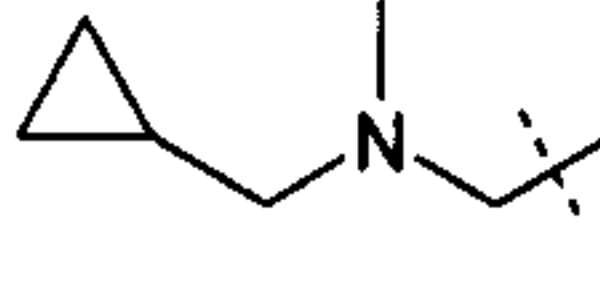
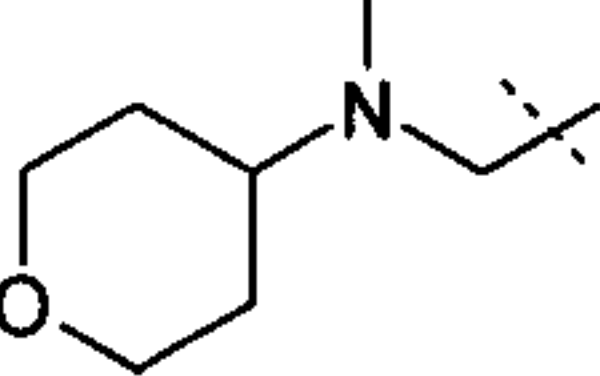


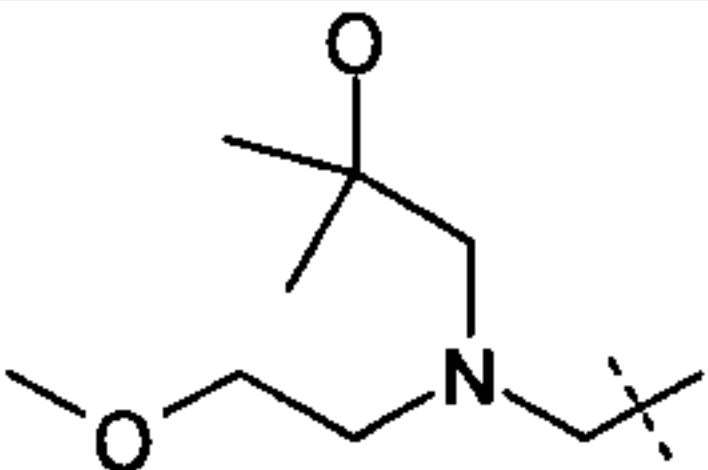
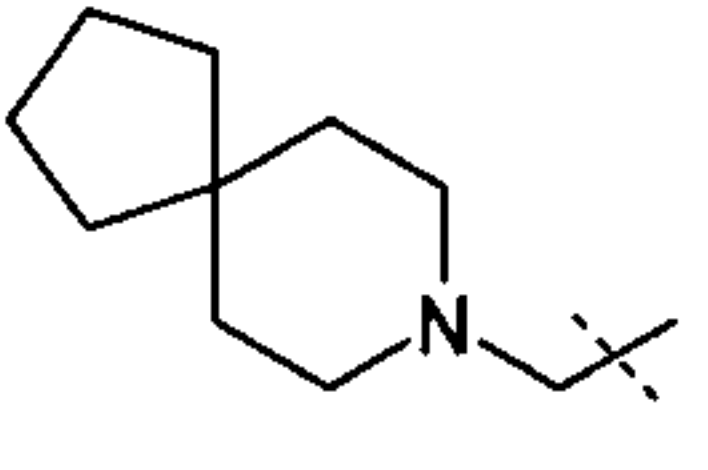
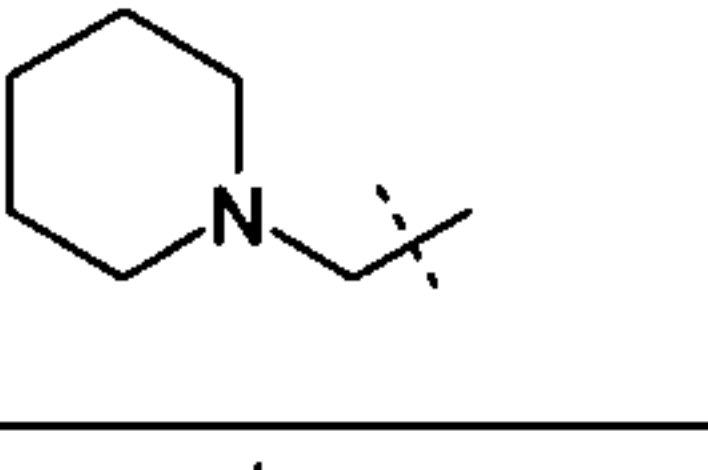
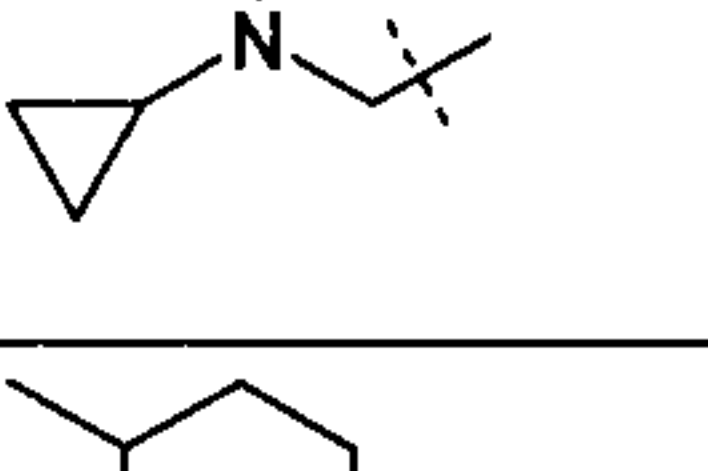
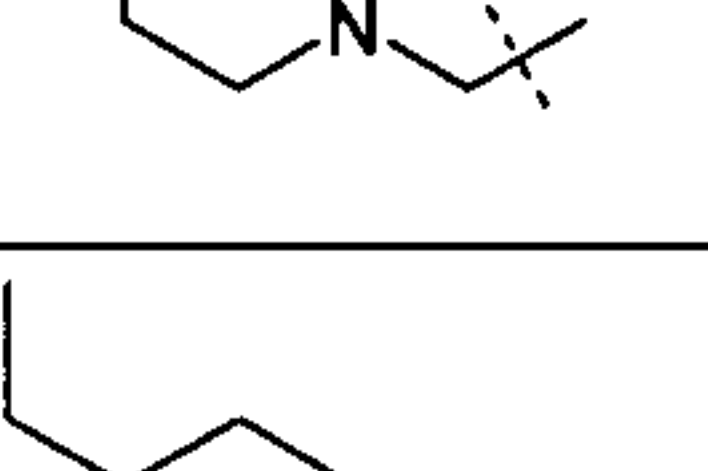
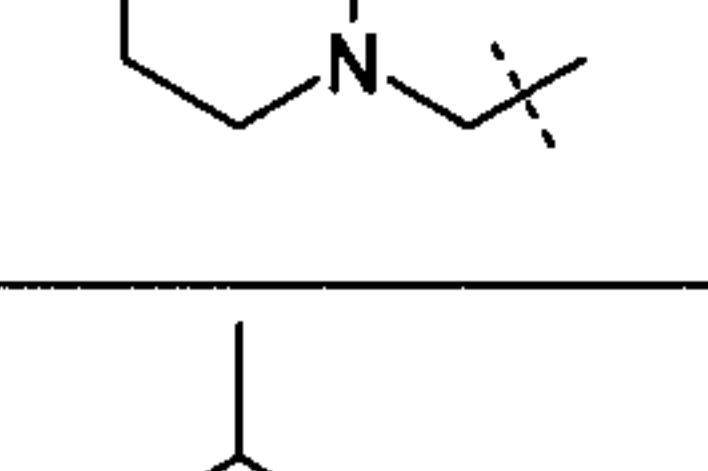
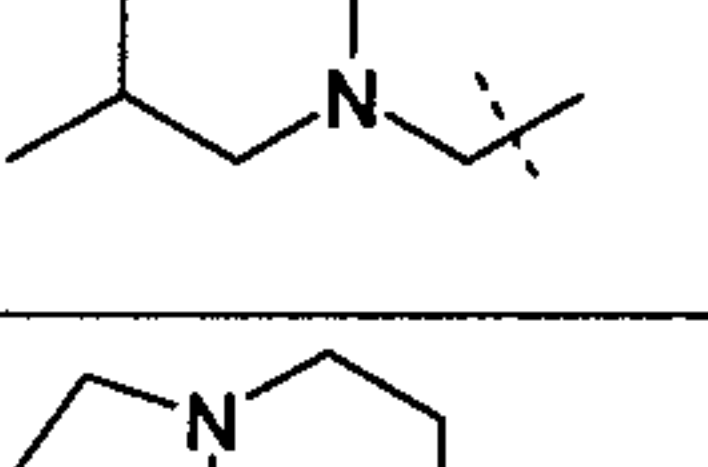
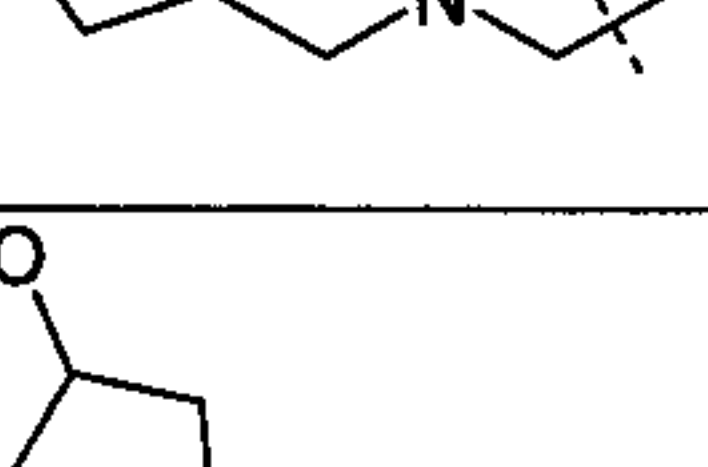
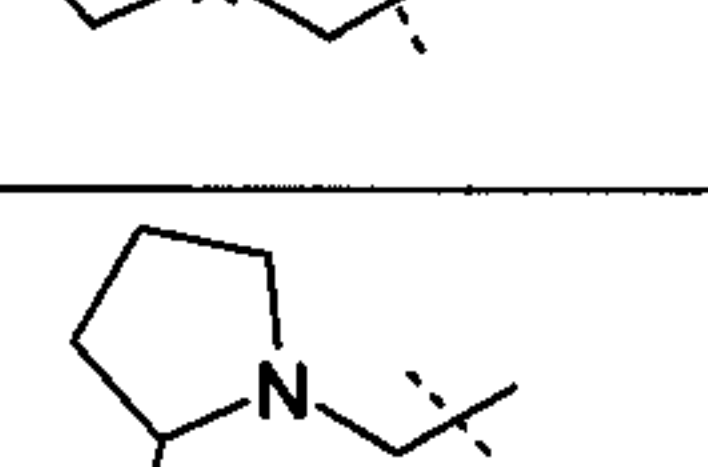
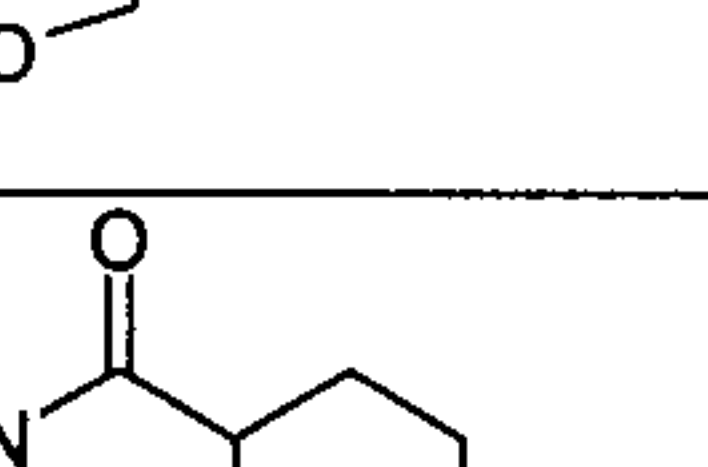
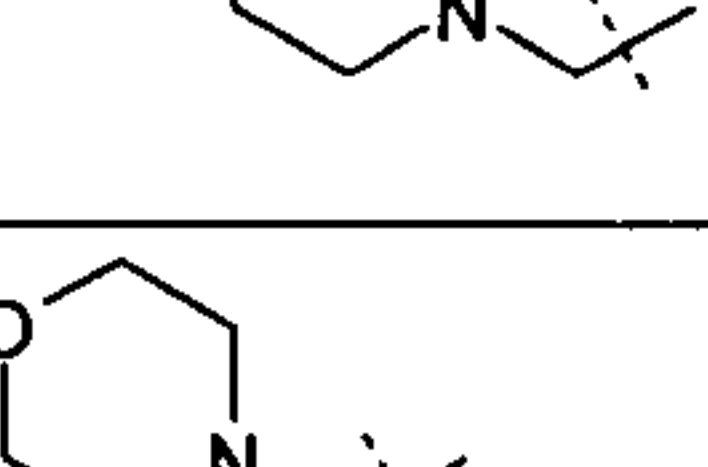
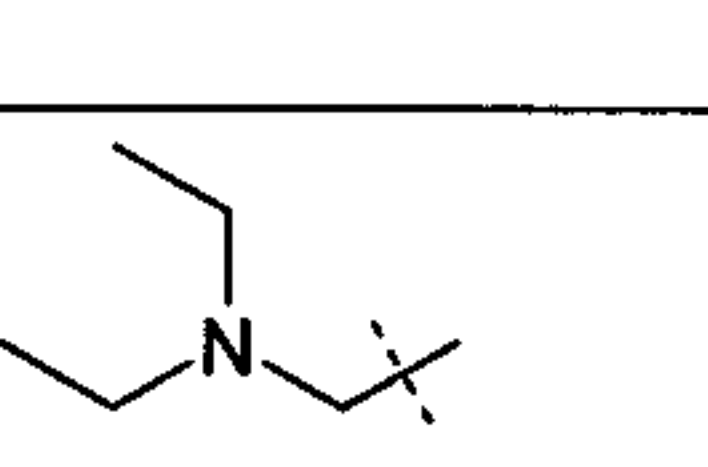
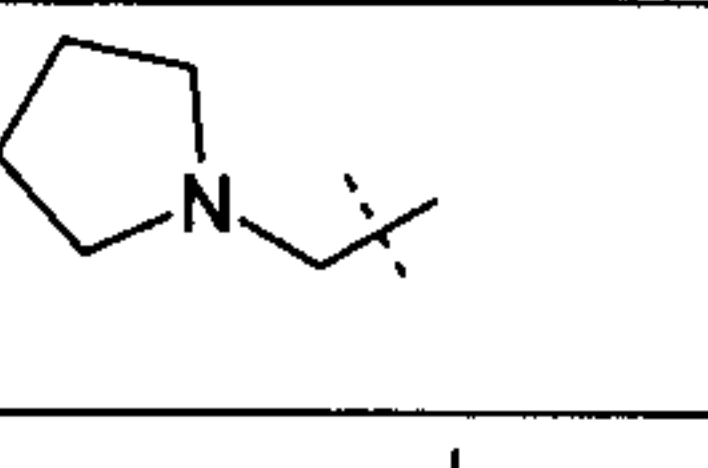
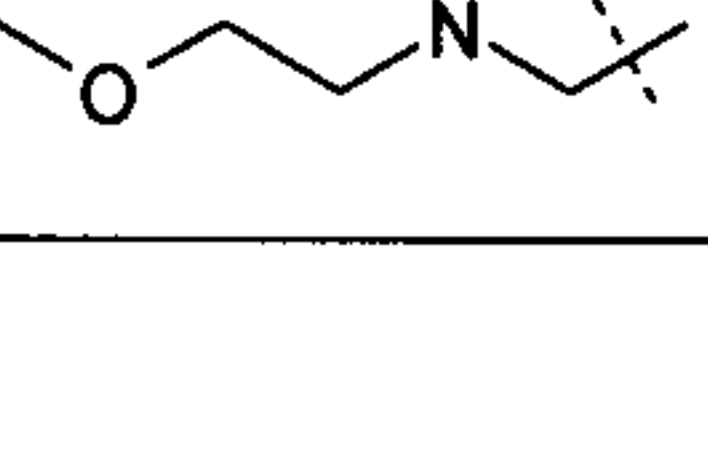
Example	R_1R_2N-X	L_1	L_2

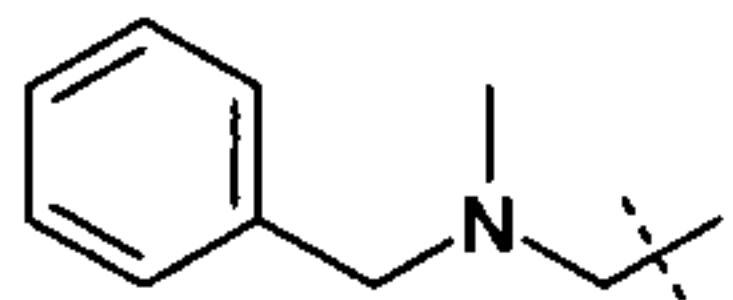
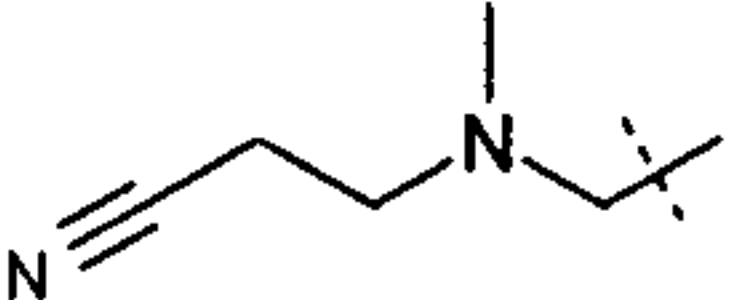
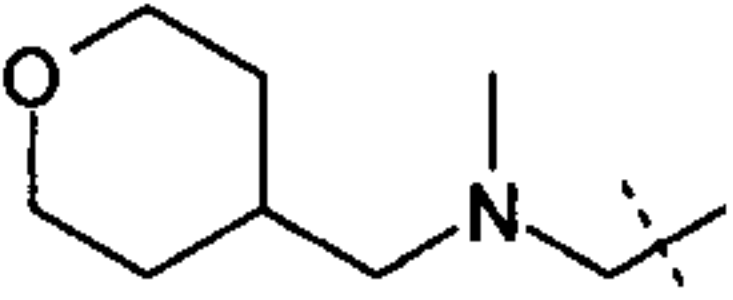
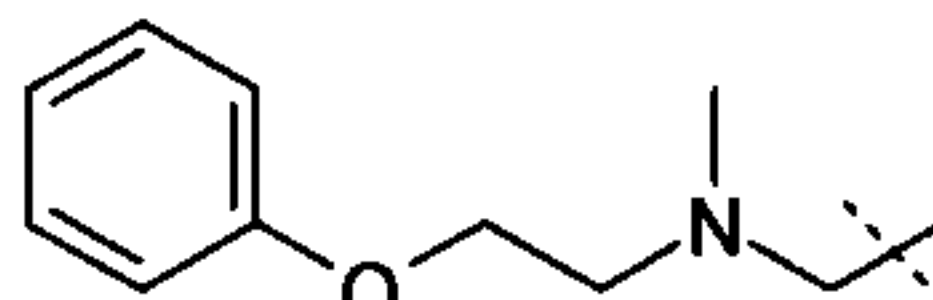
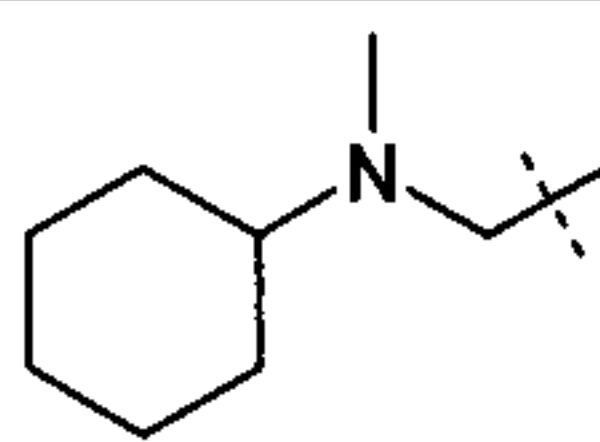
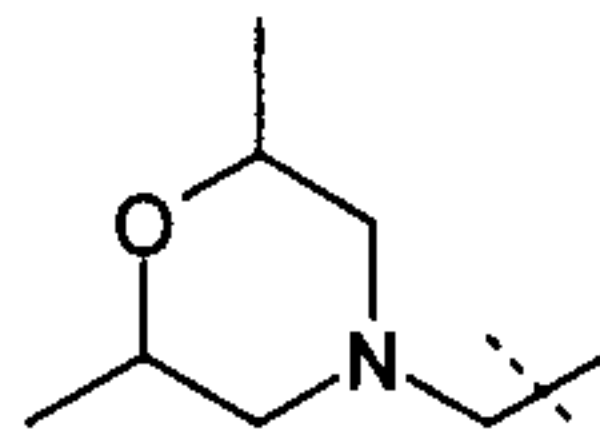
1.110		F	Cl
1.111		F	Cl
1.112		F	Cl
1.113		F	Cl
1.114		F	Cl
1.115		F	Cl
1.116		F	Cl
1.117		F	Cl
1.118		F	Cl
1.119		F	Cl
1.120		F	Cl
1.121		F	Cl
1.122		F	Cl
1.123		F	Cl
1.124		F	Cl

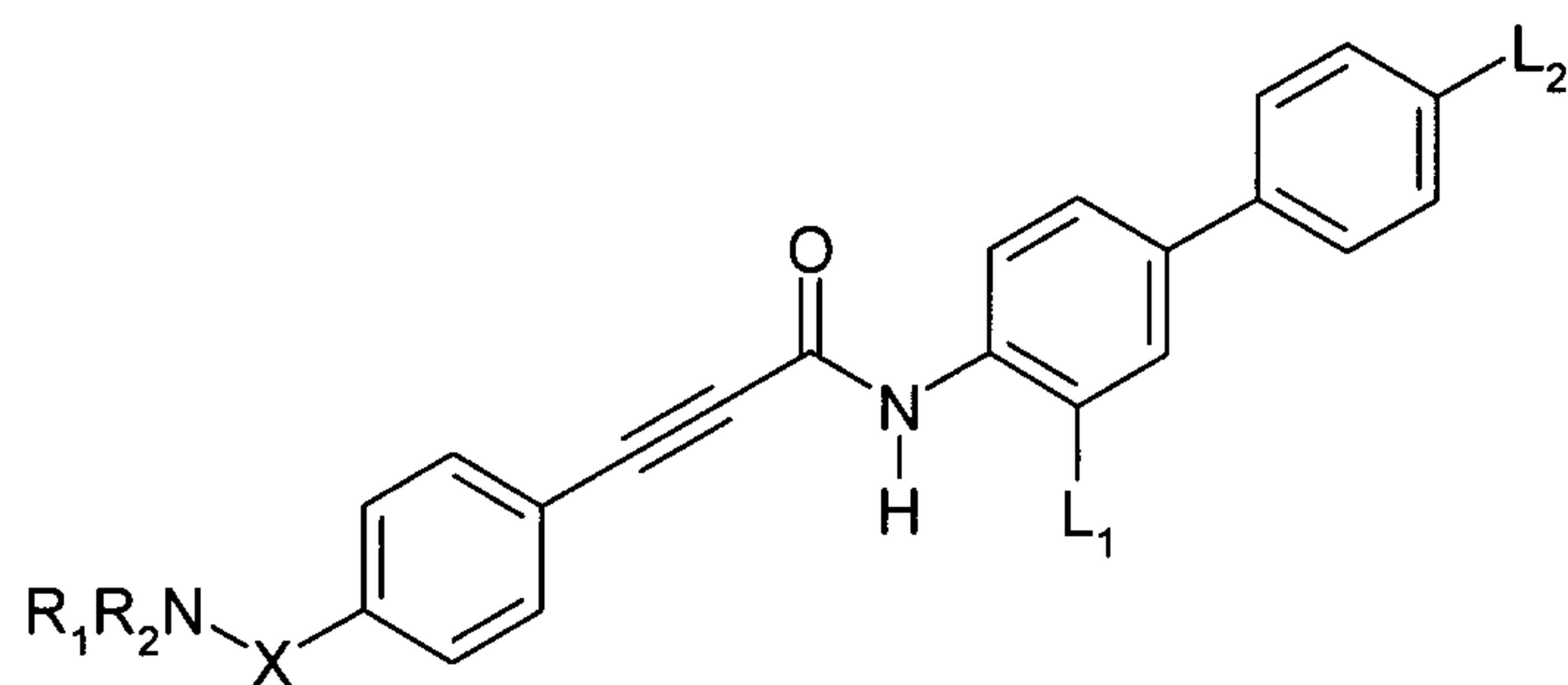
1.125		F	Cl
1.126		F	Cl
1.127		F	Cl
1.128		F	Cl
1.129		F	Cl
1.130		F	Cl
1.131		F	Cl
1.132		F	Cl
1.133		F	Cl

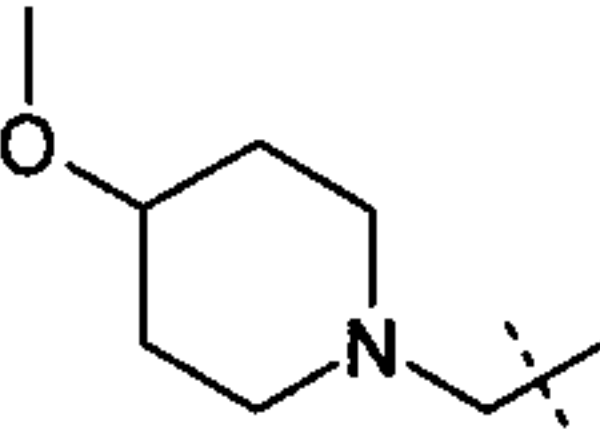
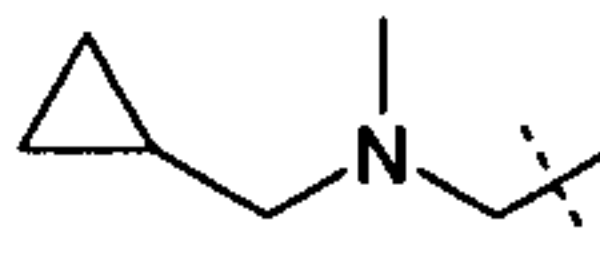
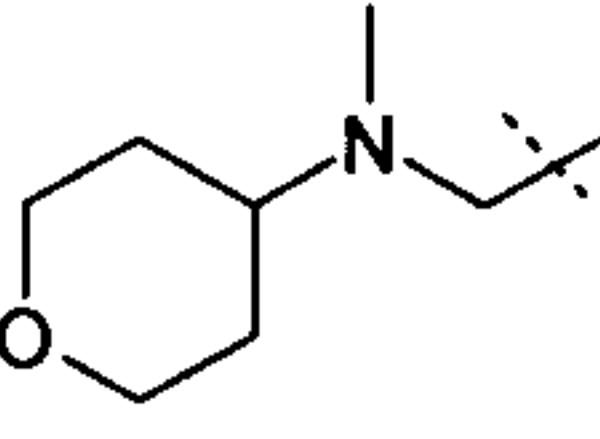
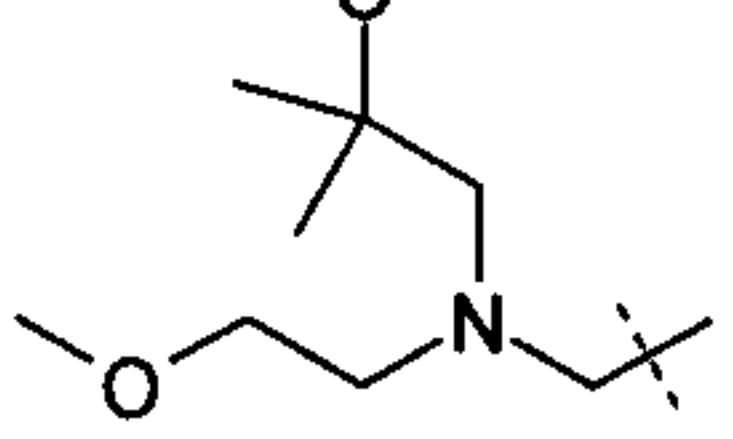
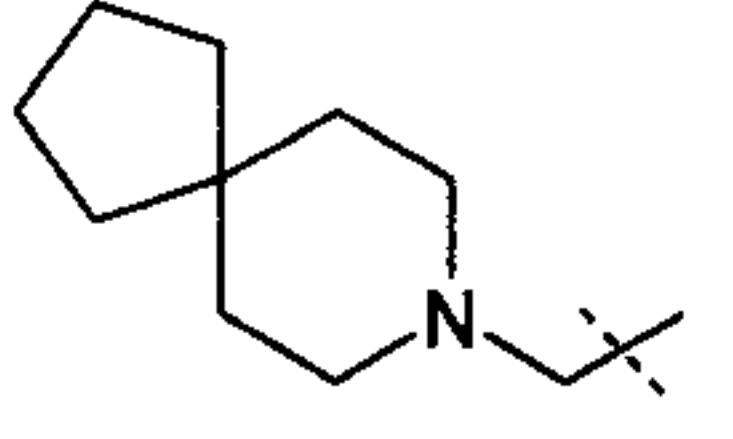


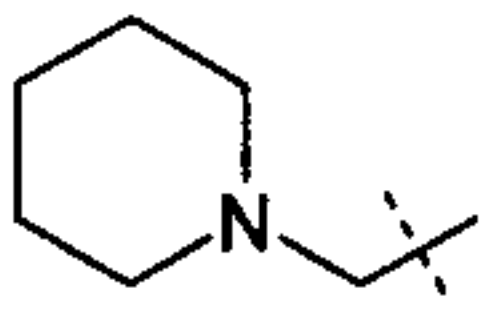
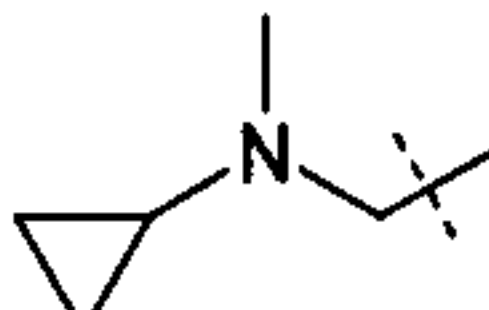
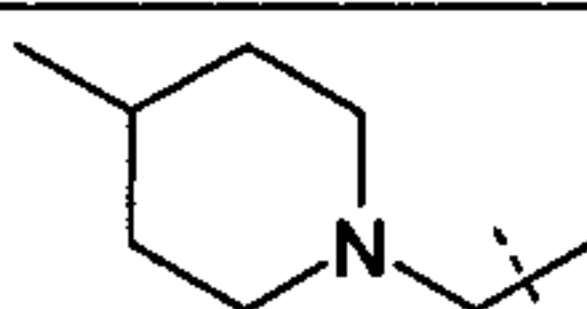
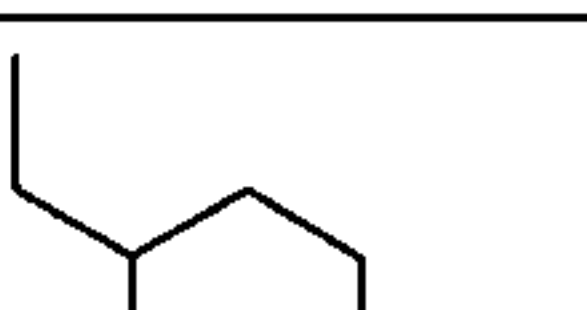
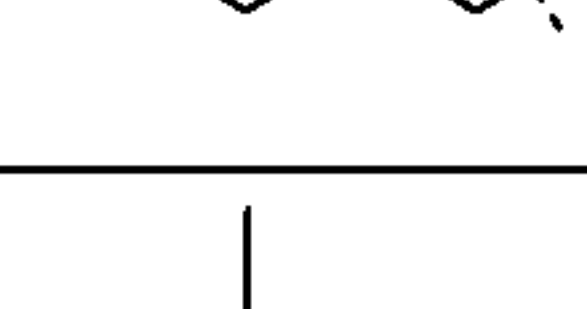
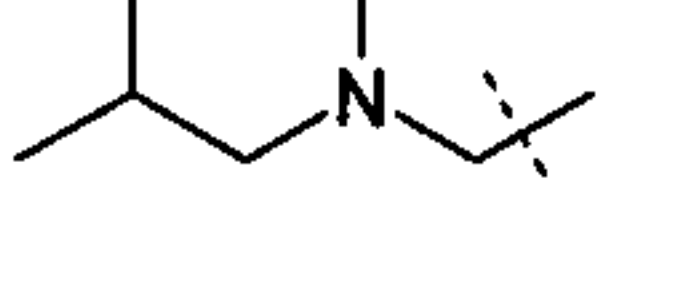
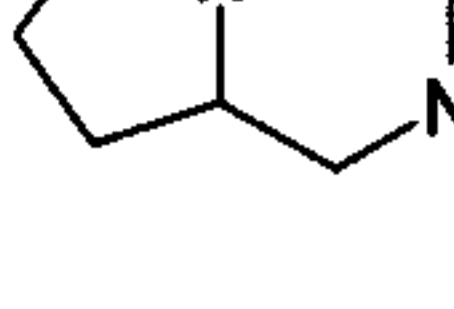
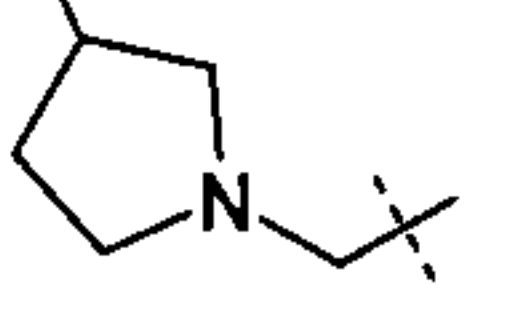
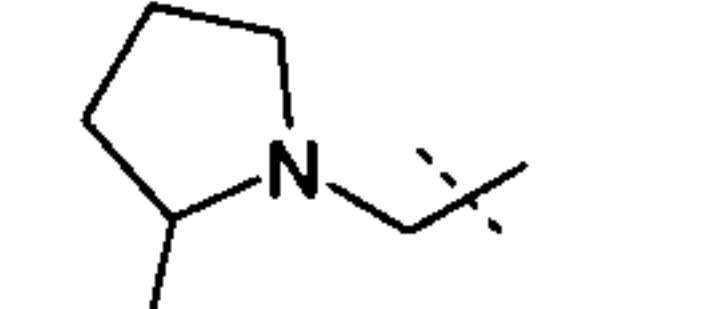
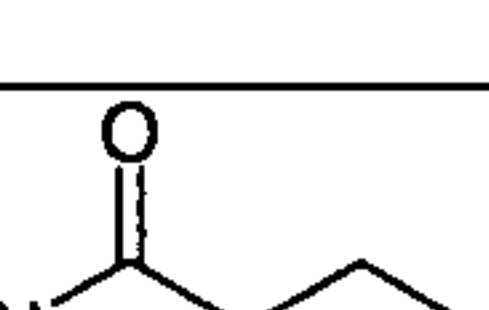
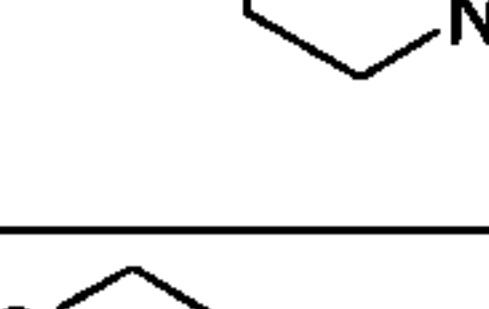
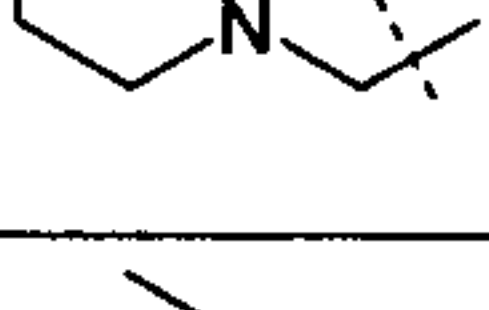
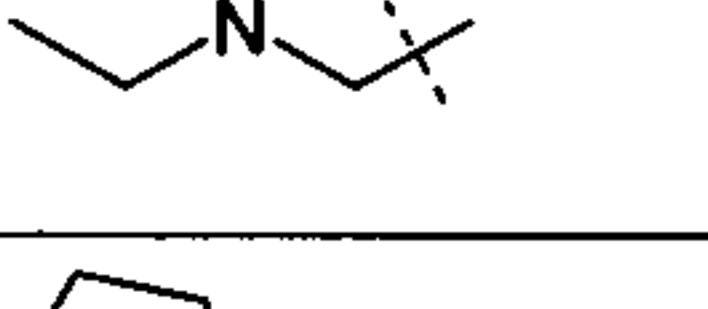
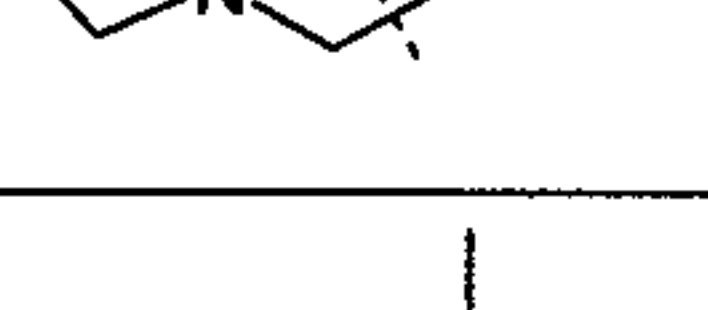
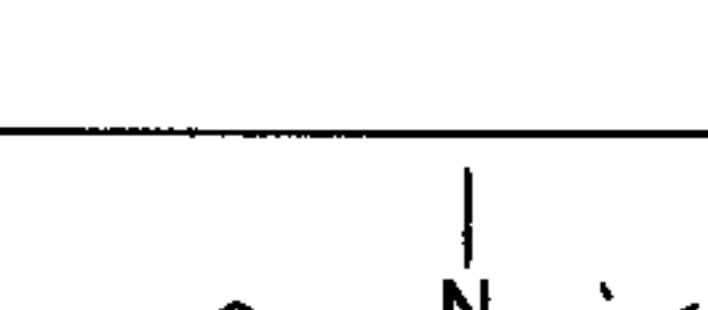
Example	R_1R_2N-X	L_1	L_2
1.134		H	CF ₃
1.135		H	CF ₃
1.136		H	CF ₃

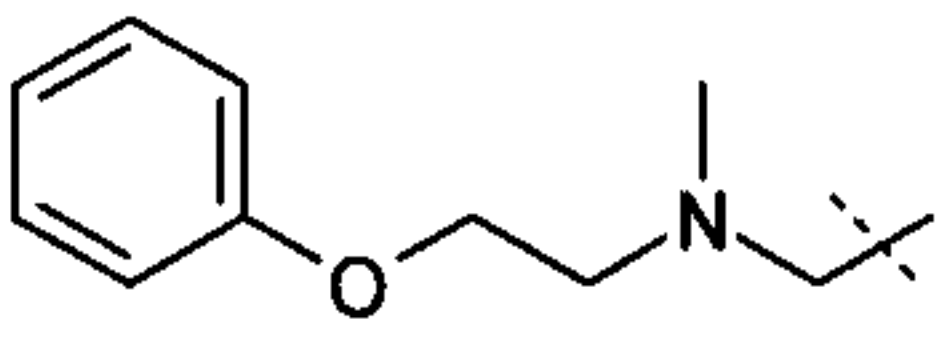
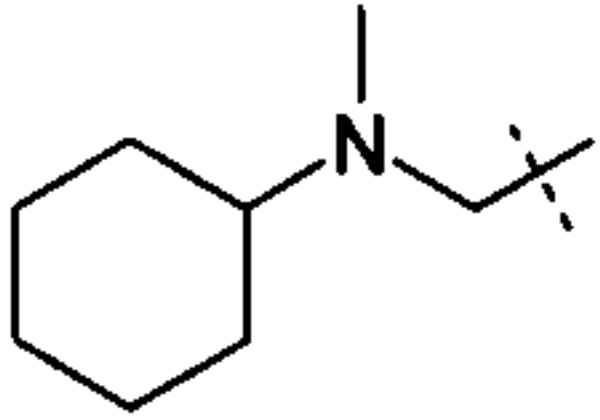
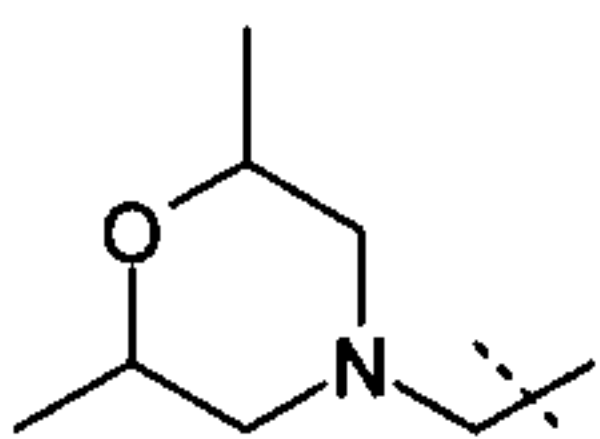
1.137		H	CF ₃
1.138		H	CF ₃
1.139		H	CF ₃
1.140		H	CF ₃
1.141		H	CF ₃
1.142		H	CF ₃
1.143		H	CF ₃
1.144		H	CF ₃
1.145		H	CF ₃
1.146		H	CF ₃
1.147		H	CF ₃
1.148		H	CF ₃
1.149		H	CF ₃
1.150		H	CF ₃
1.151		H	CF ₃

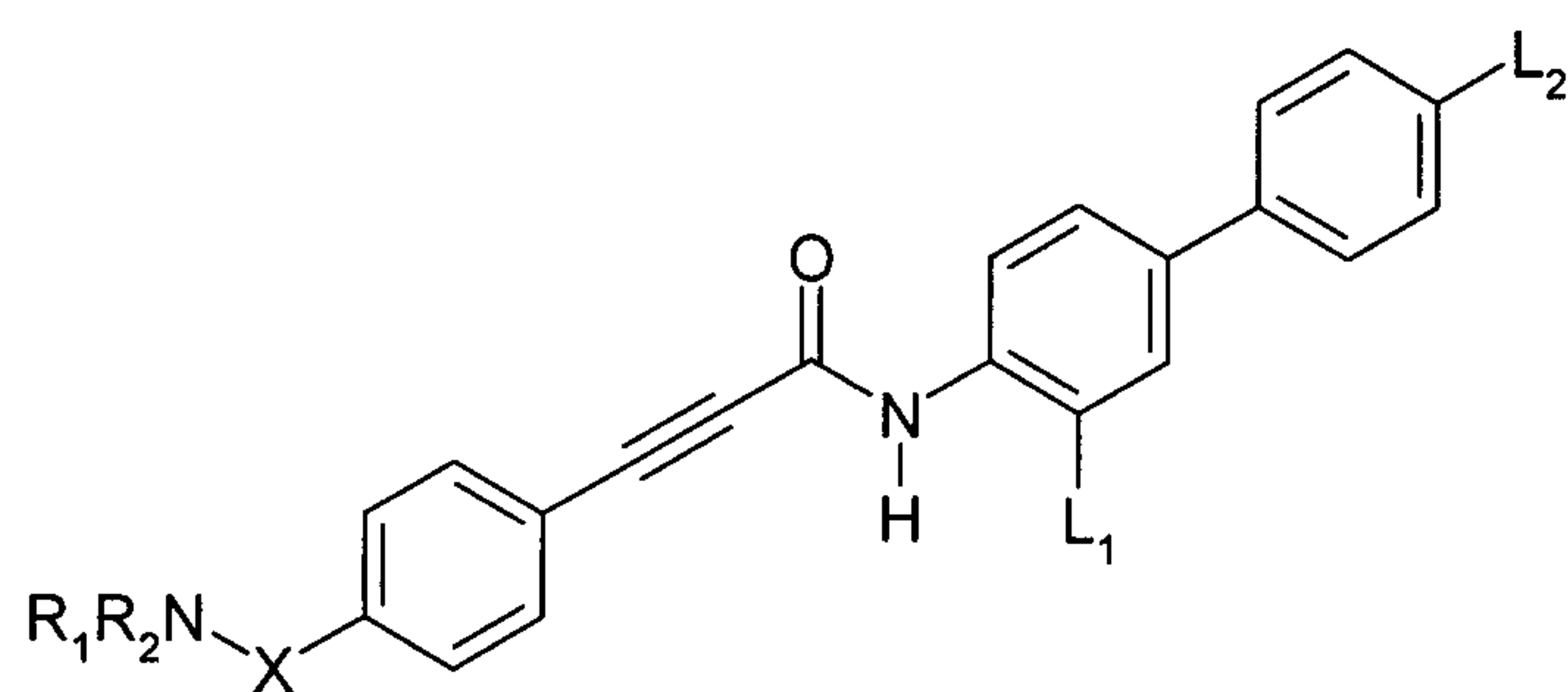
1.152		H	CF ₃
1.153		H	CF ₃
1.154		H	CF ₃
1.155		H	CF ₃
1.156		H	CF ₃
1.157		H	CF ₃

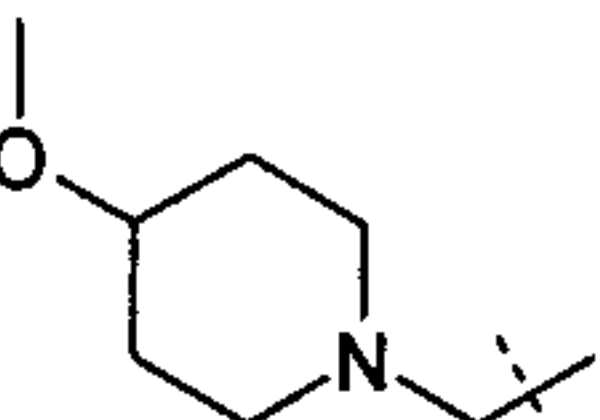
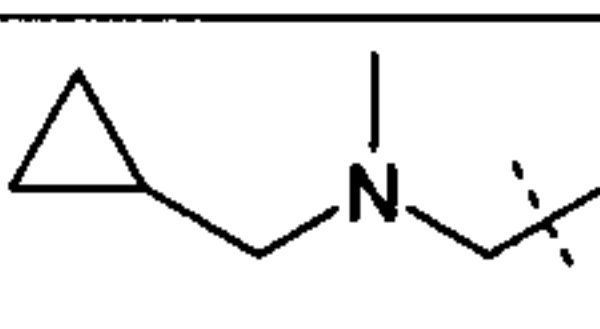
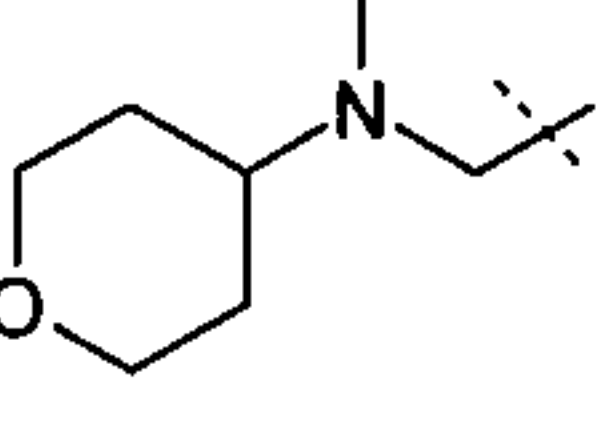
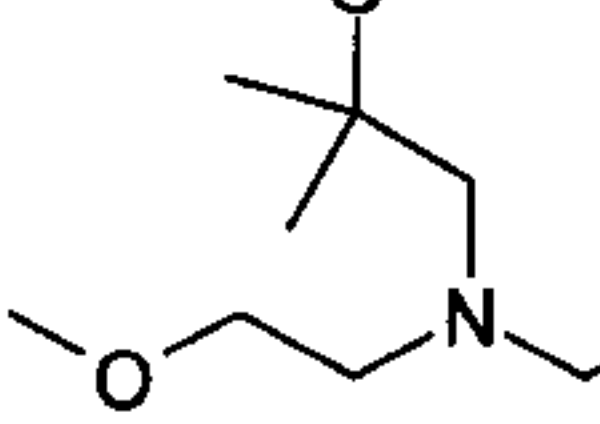
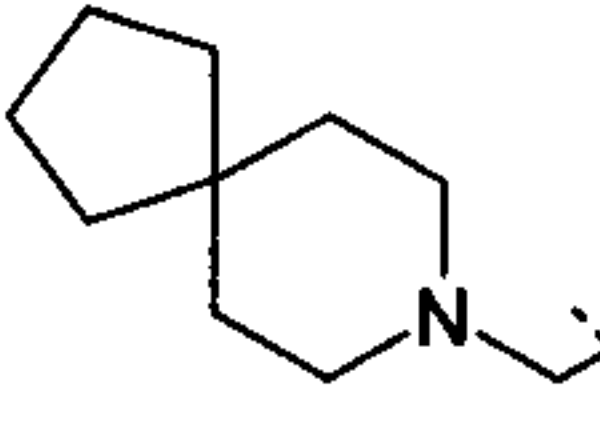
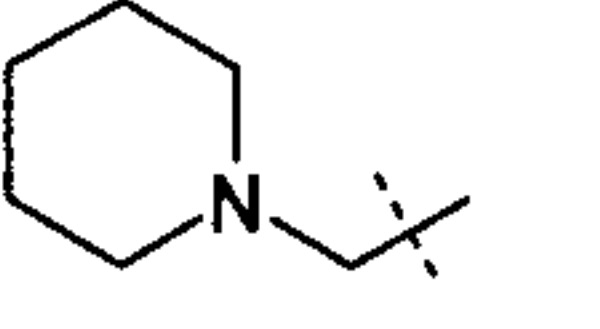
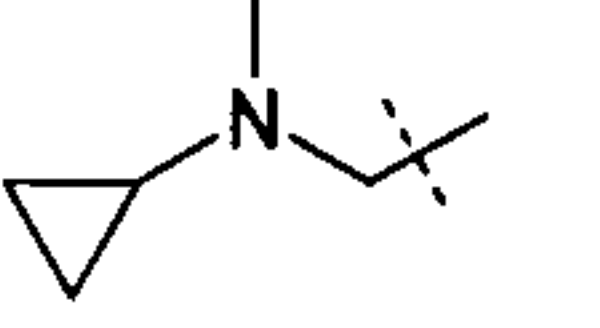
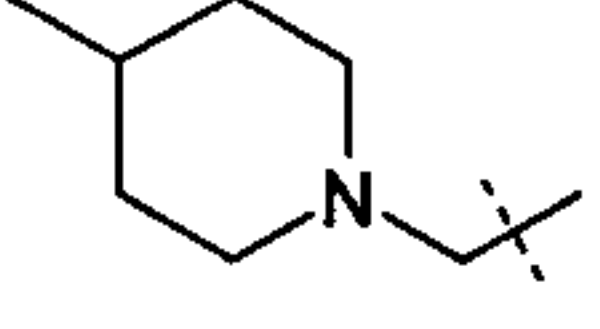


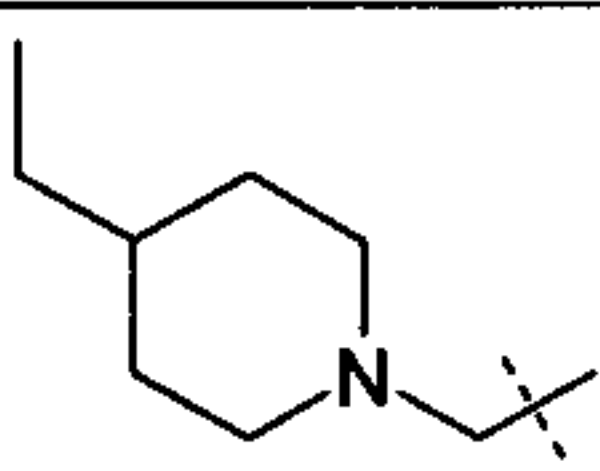
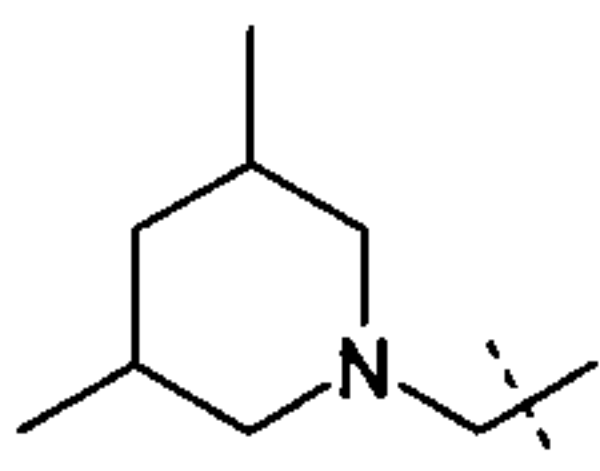
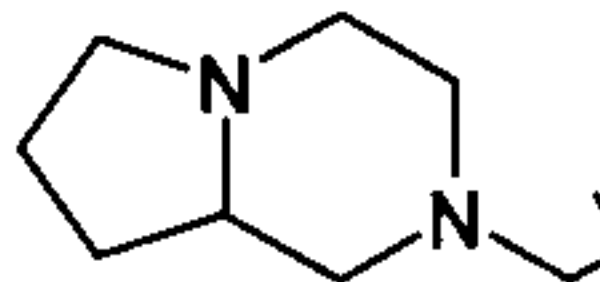
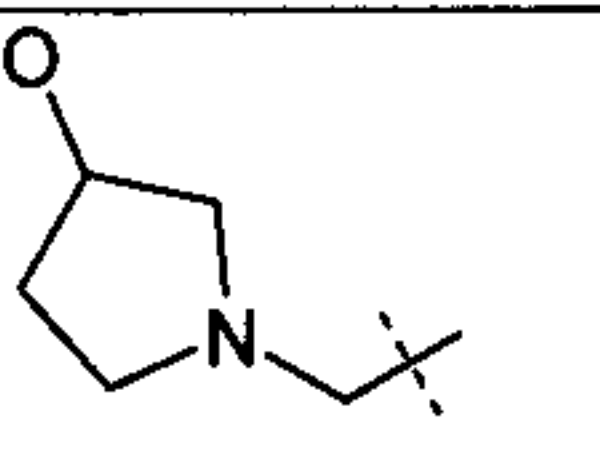
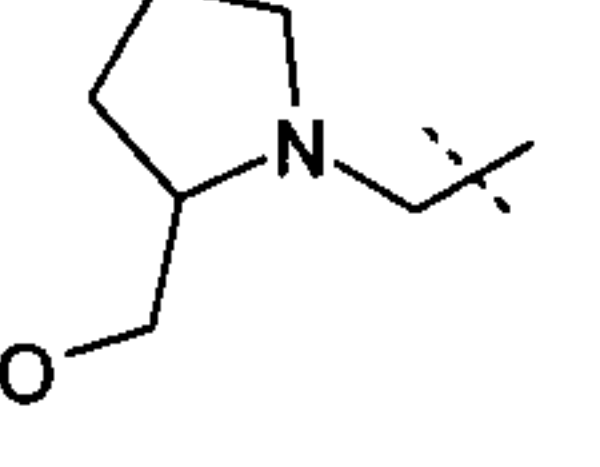
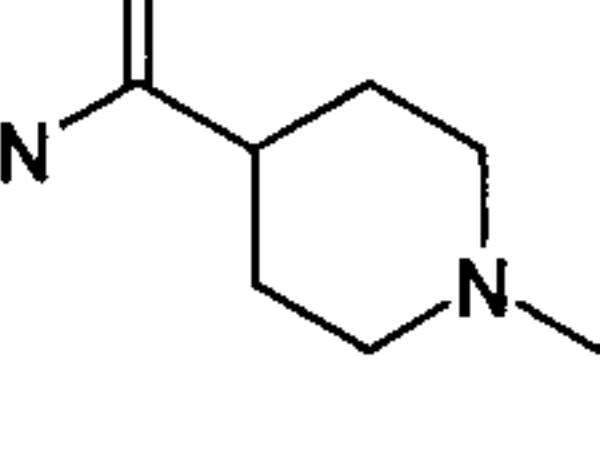
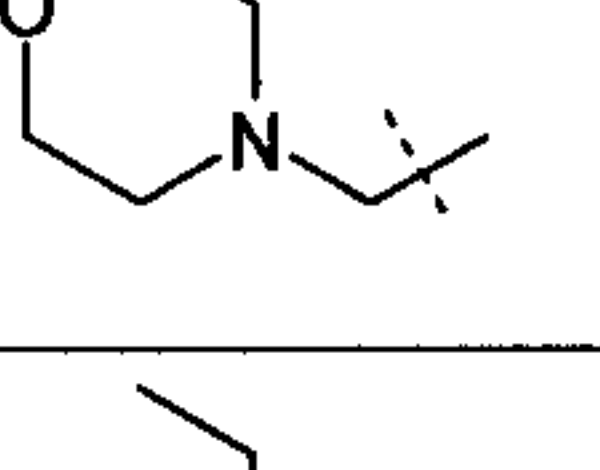
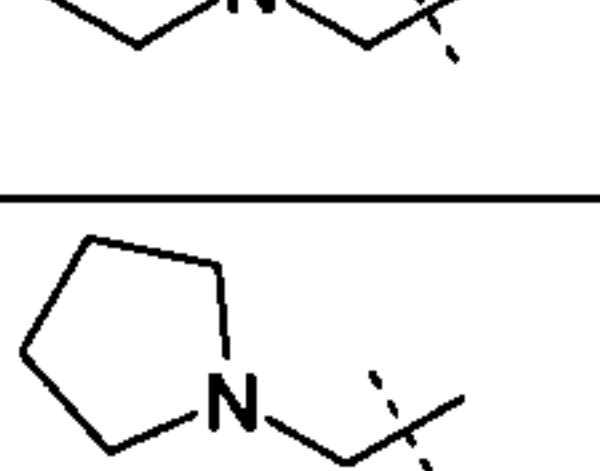
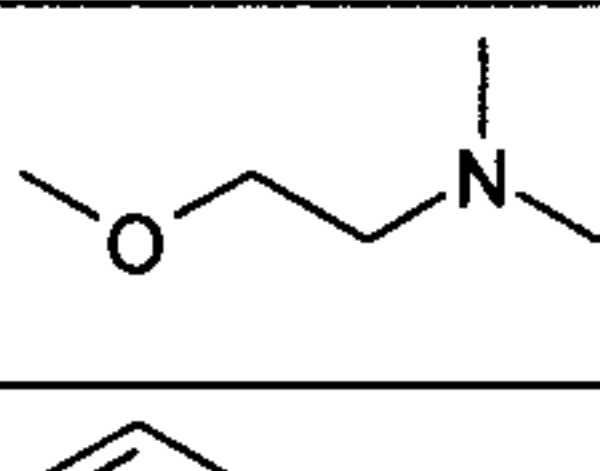
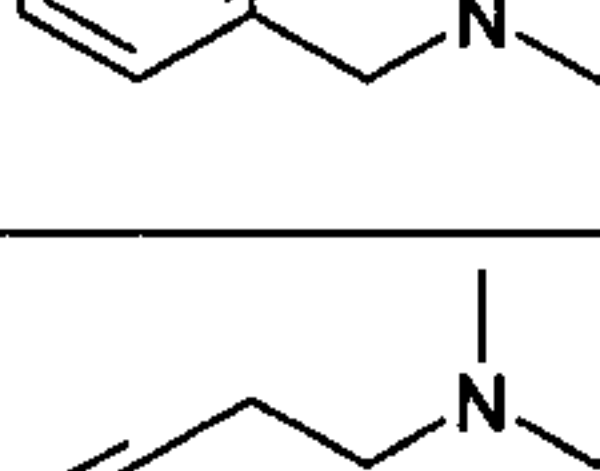
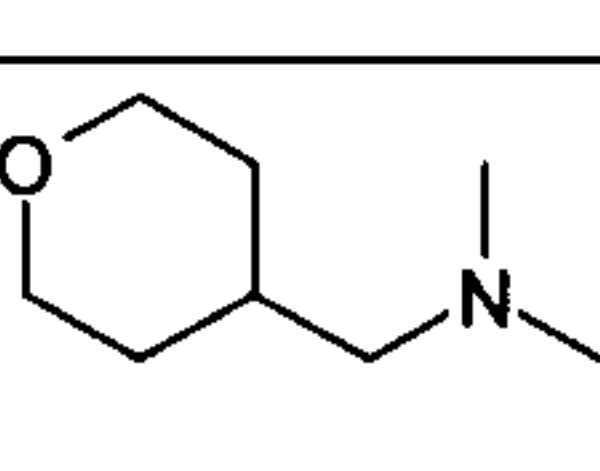
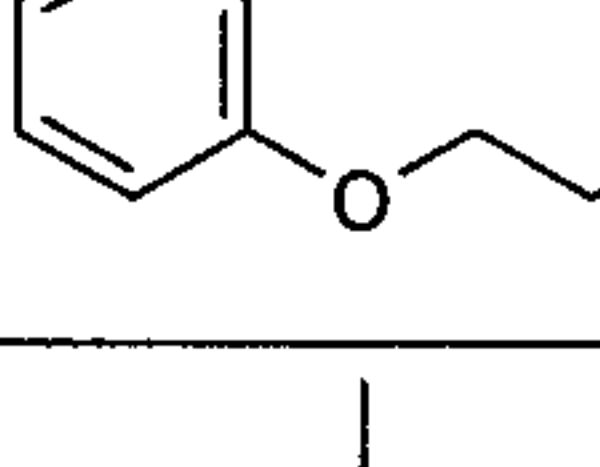
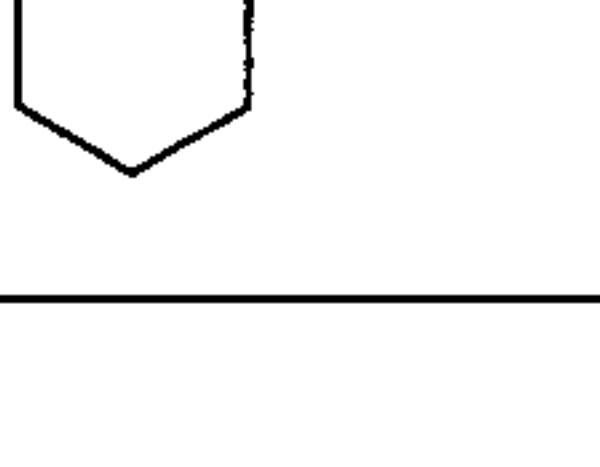
Example	R ₁ R ₂ N-X	L ₁	L ₂
1.158		H	Me
1.159		H	Me
1.160		H	Me
1.161		H	Me
1.162		H	Me

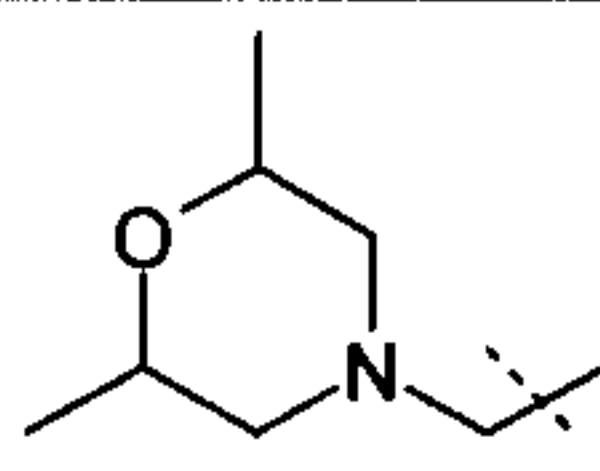
1.163		H	Me
1.164		H	Me
1.165		H	Me
1.166		H	Me
1.167		H	Me
1.168		H	Me
1.169		H	Me
1.170		H	Me
1.171		H	Me
1.172		H	Me
1.173		H	Me
1.174		H	Me
1.175		H	Me
1.176		H	Me
1.177		H	Me
1.178		H	Me

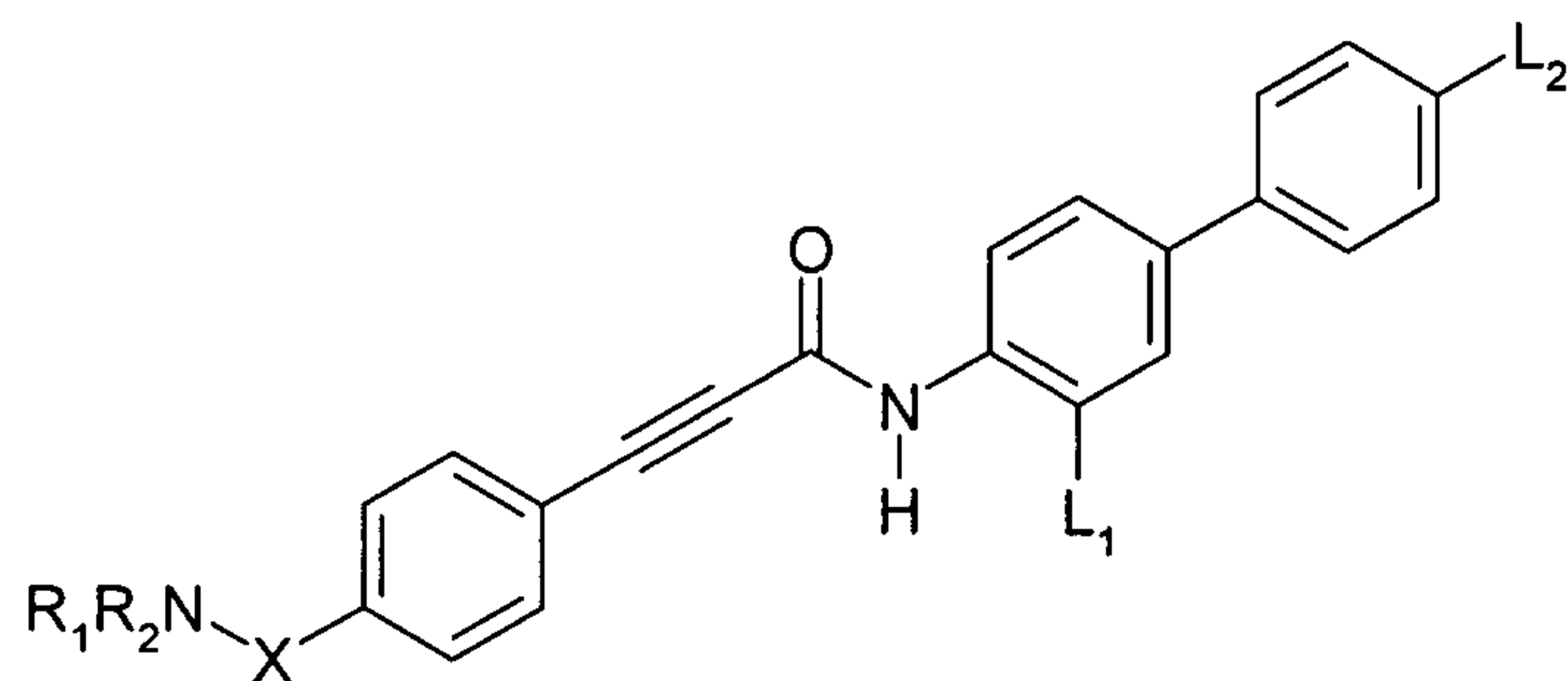
1.179		H	Me
1.180		H	Me
1.181		H	Me

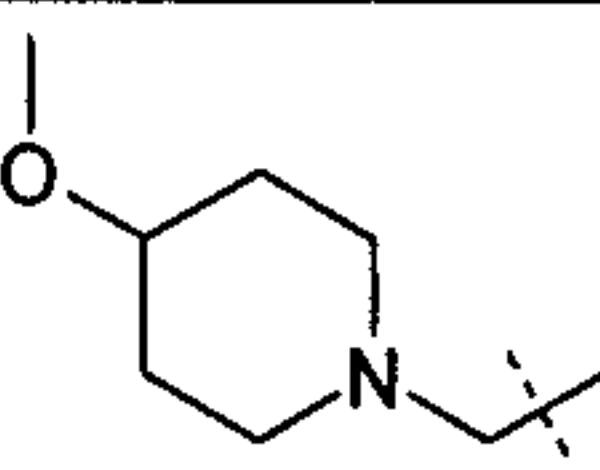
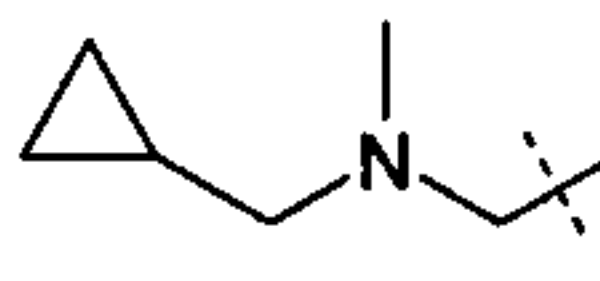
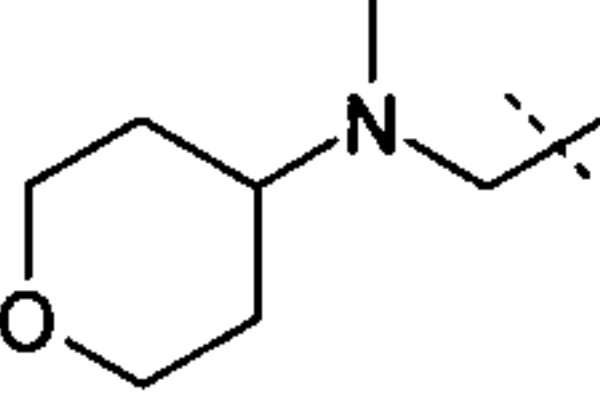
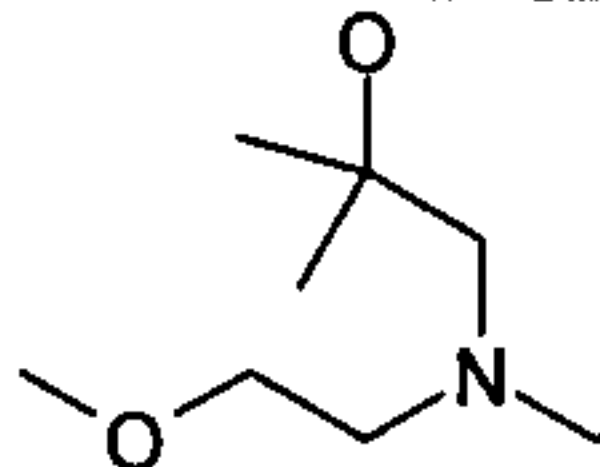
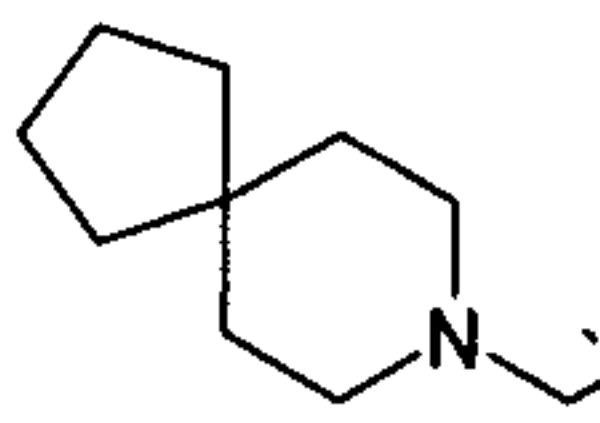
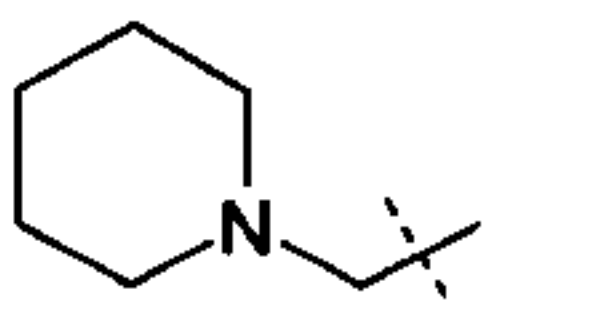
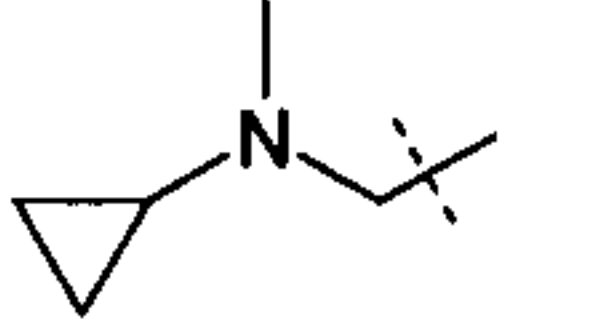
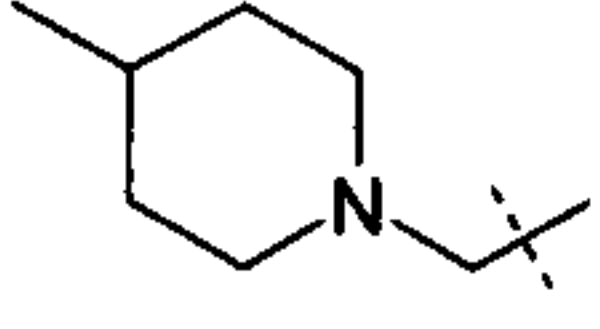
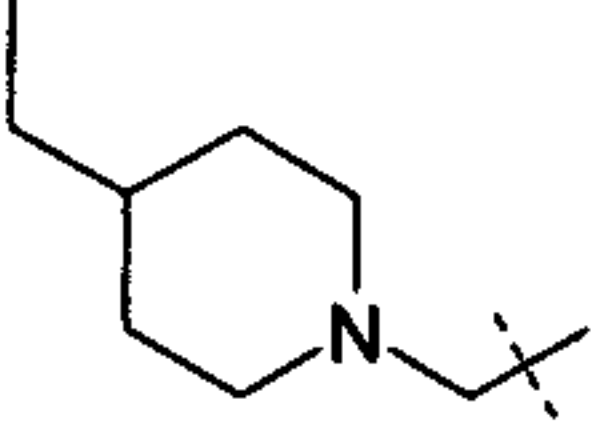


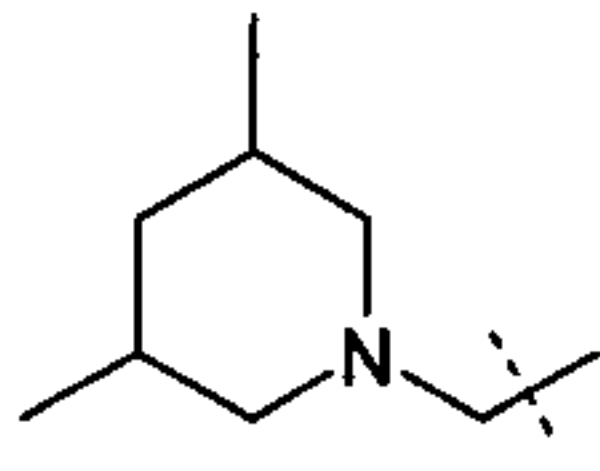
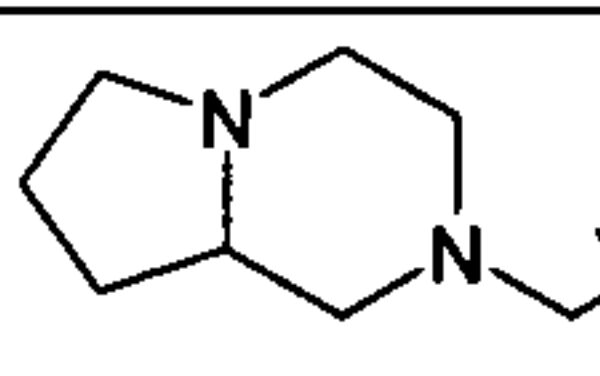
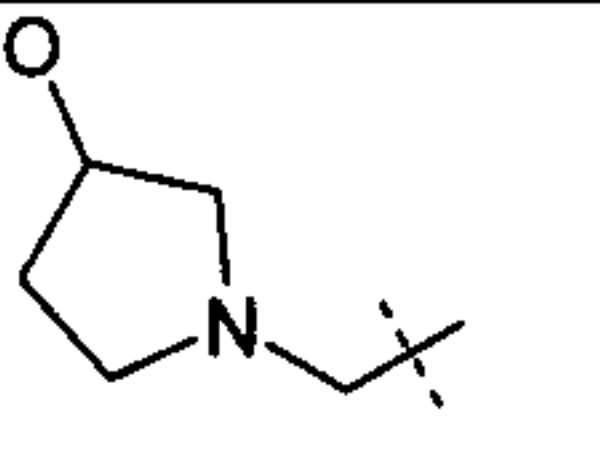
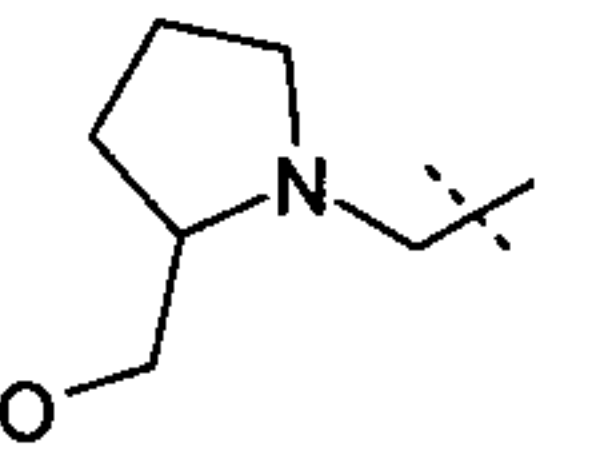
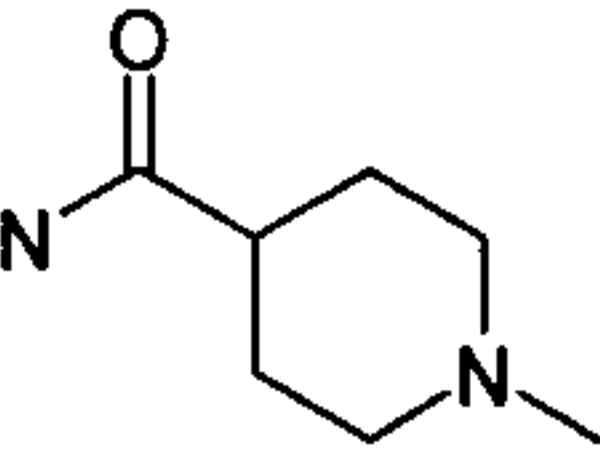
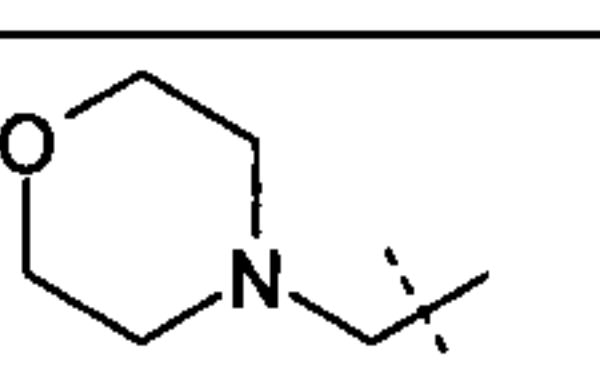
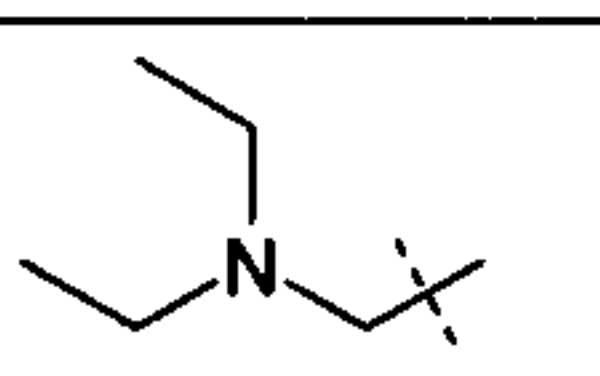
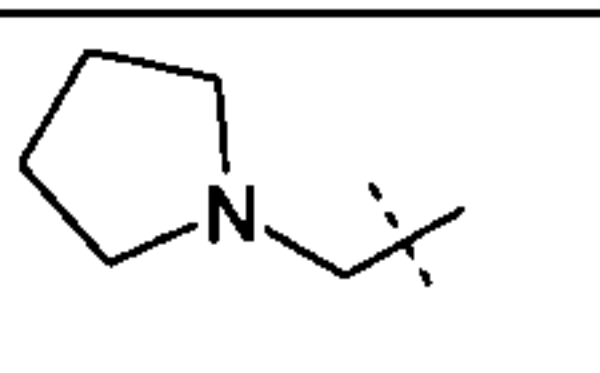
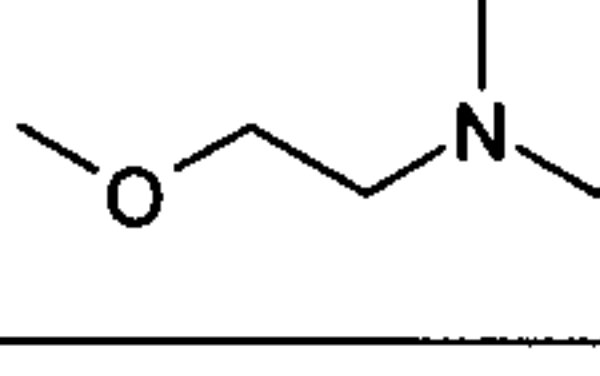
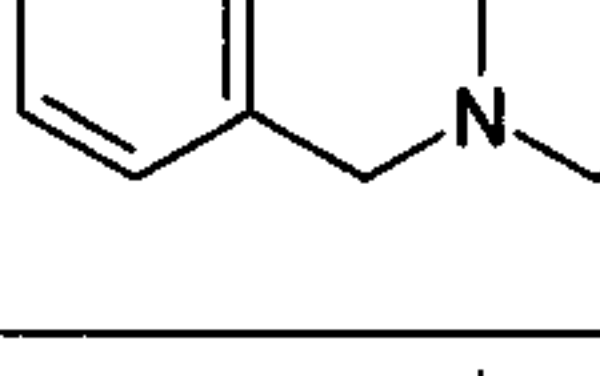
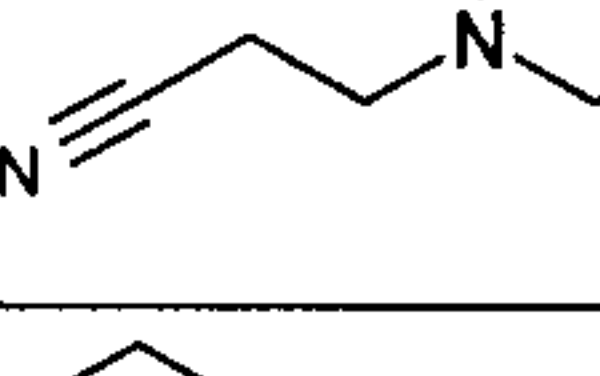
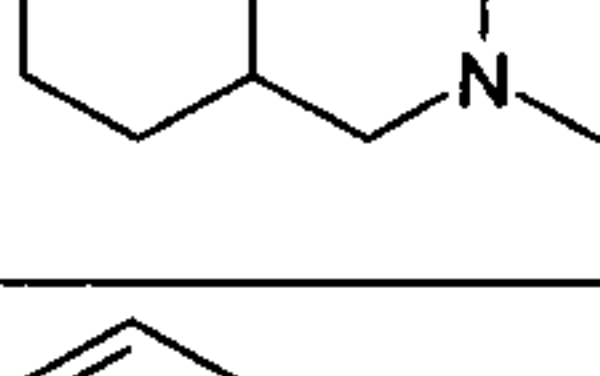
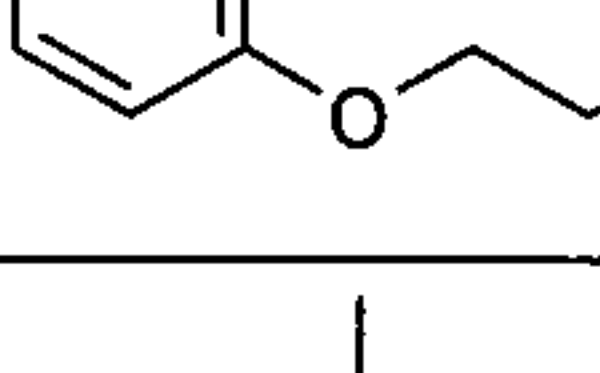
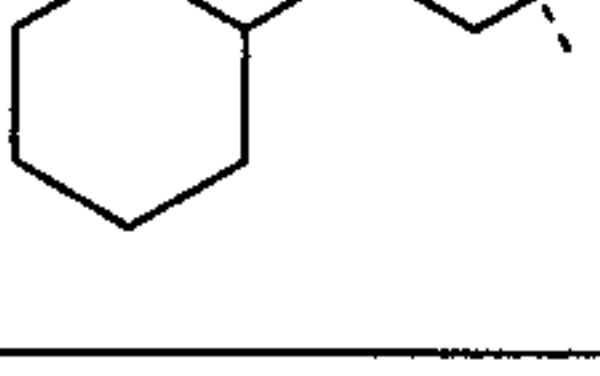
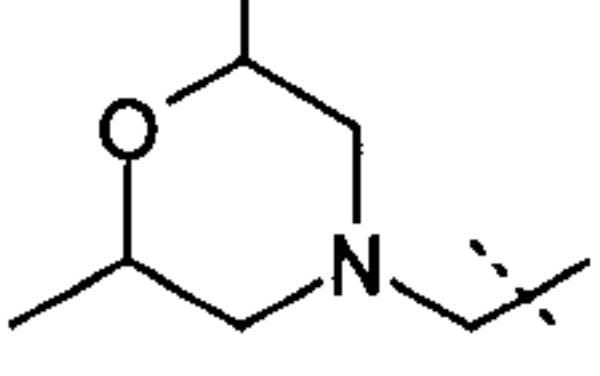
Example	$\text{R}_1\text{R}_2\text{N-X}$	L_1	L_2
1.182		H	F
1.183		H	F
1.184		H	F
1.185		H	F
1.186		H	F
1.187		H	F
1.188		H	F
1.189		H	F

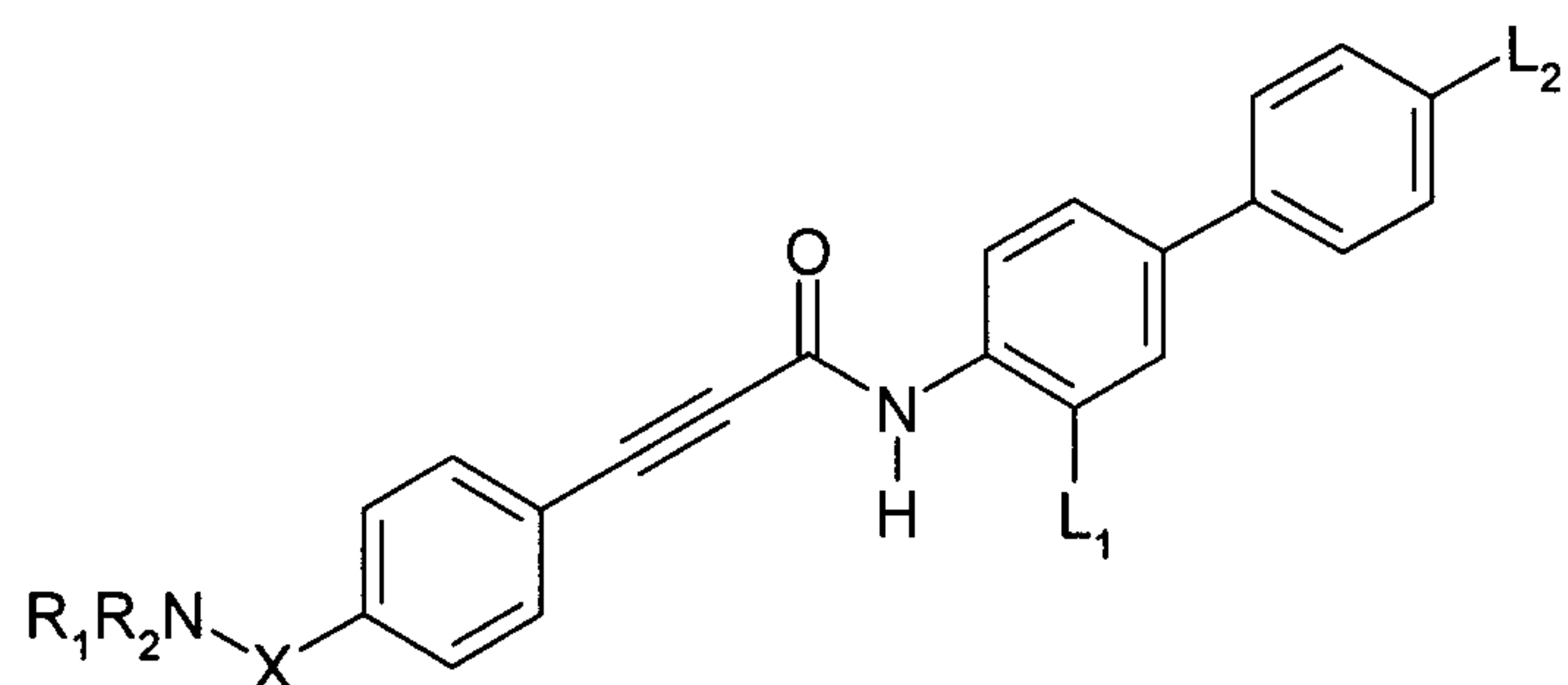
1.190		H	F
1.191		H	F
1.192		H	F
1.193		H	F
1.194		H	F
1.195		H	F
1.196		H	F
1.197		H	F
1.198		H	F
1.199		H	F
1.200		H	F
1.201		H	F
1.202		H	F
1.203		H	F
1.204		H	F

1.205		H	F

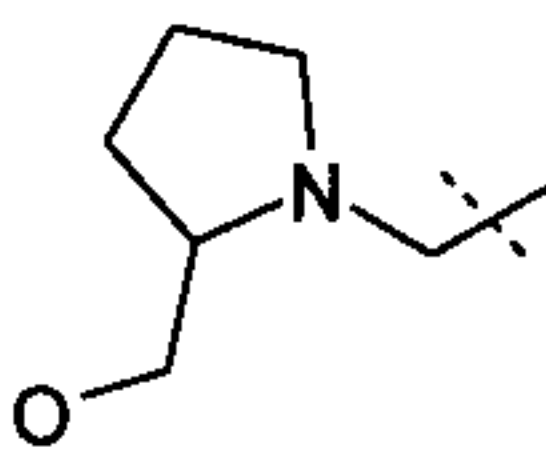
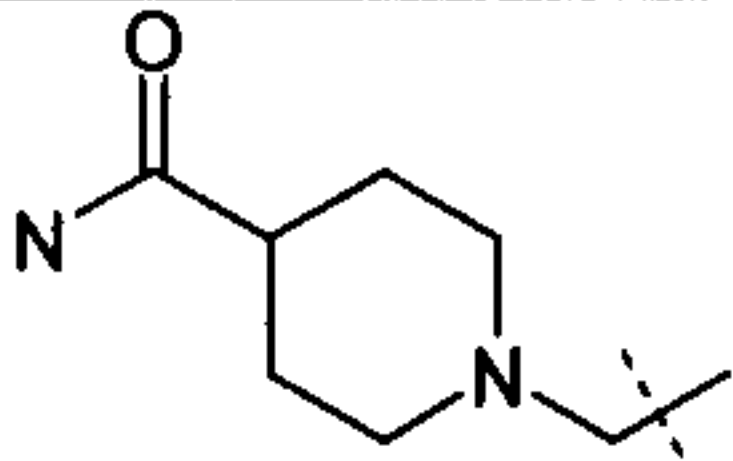
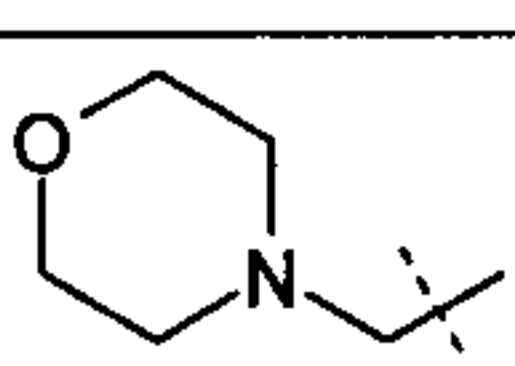
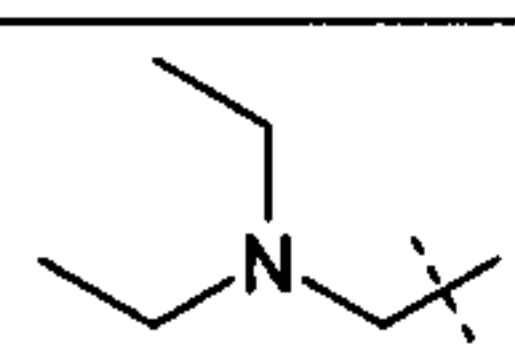
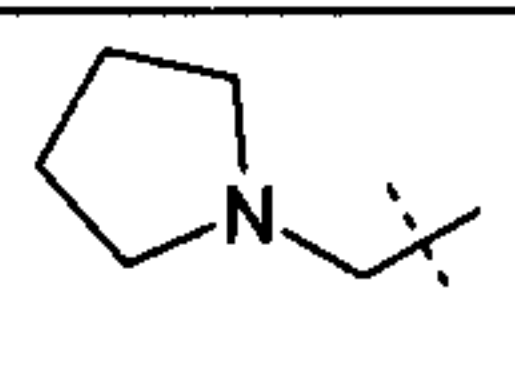
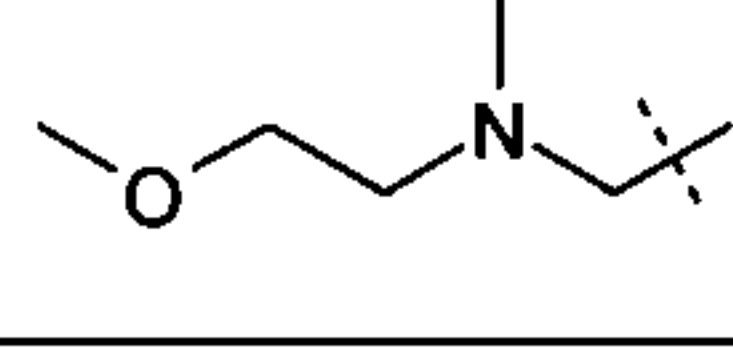
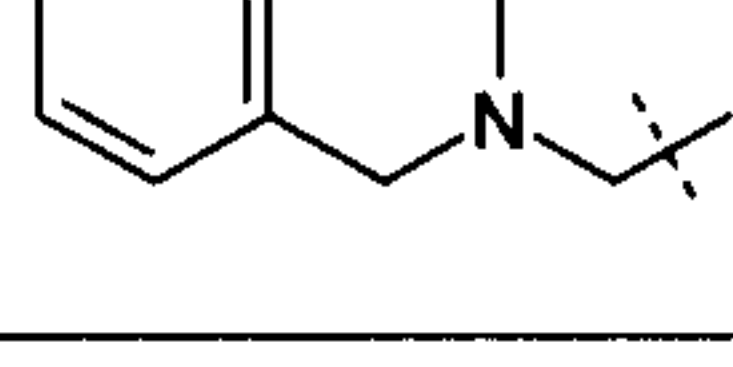
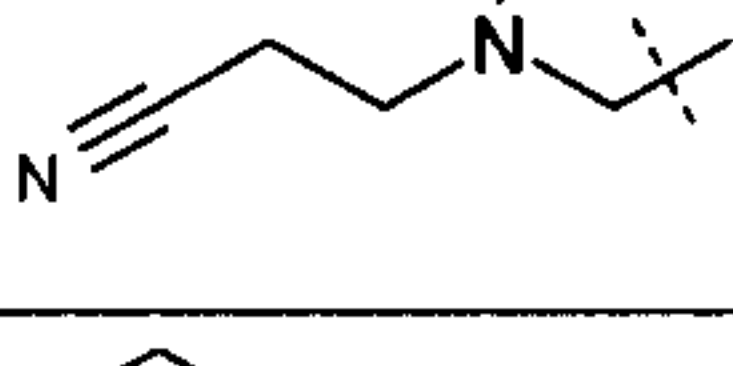
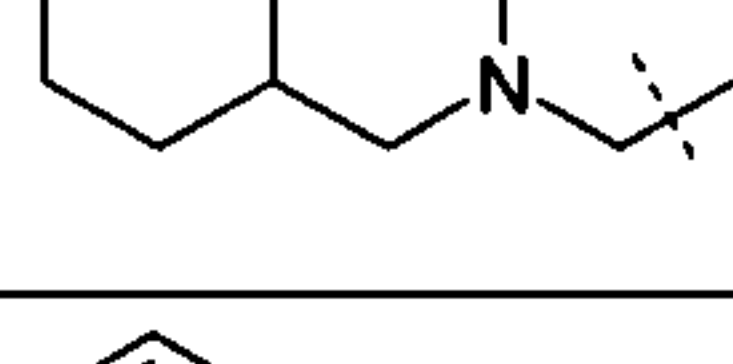
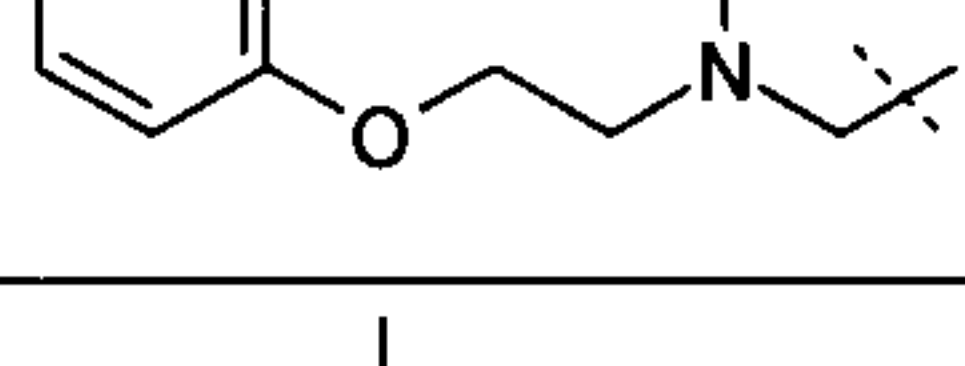
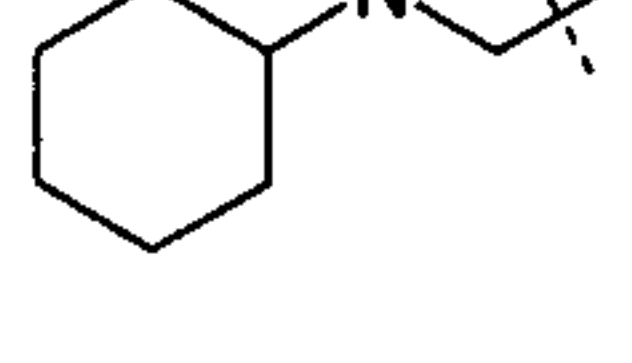
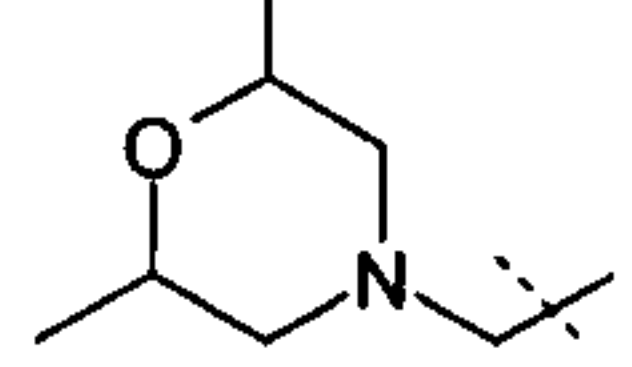


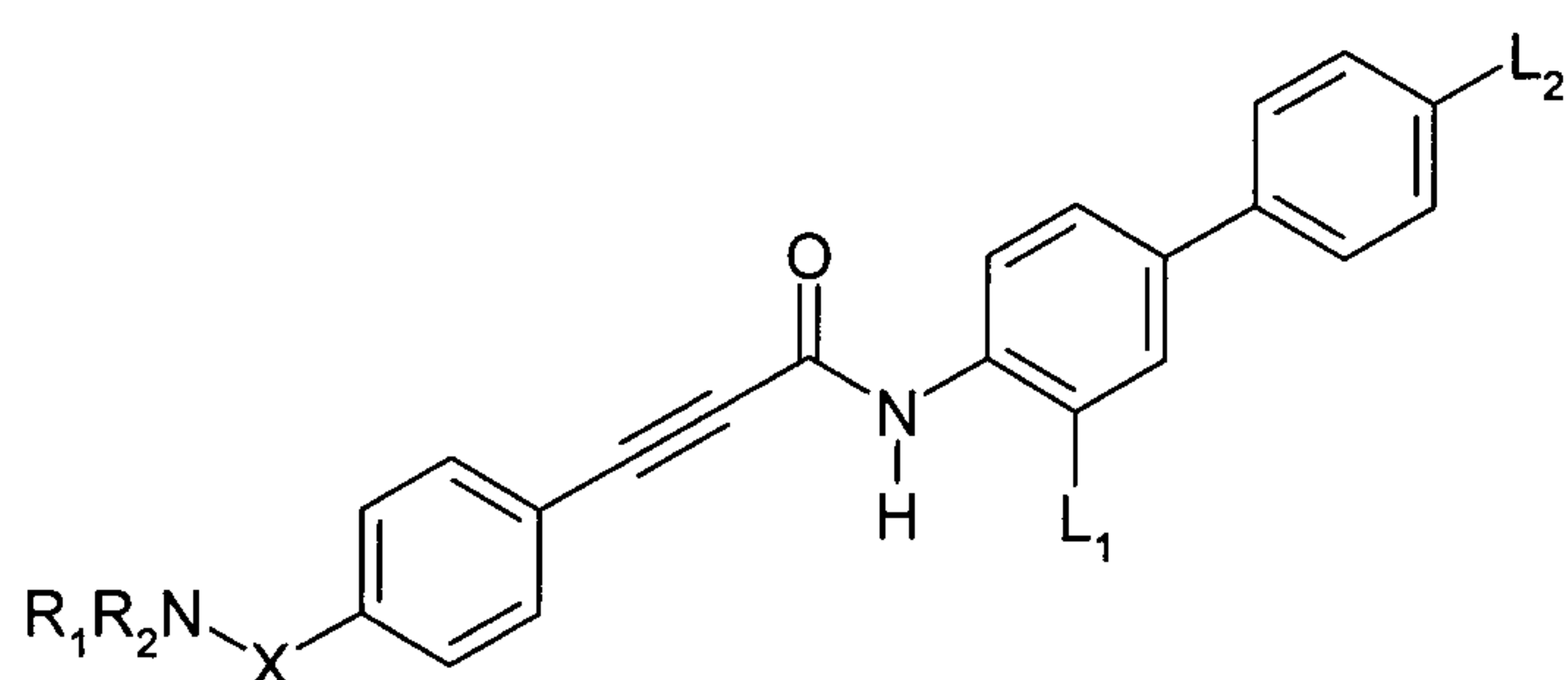
Example	R ₁ R ₂ N-X	L ₁	L ₂
1.206		F	CF ₃
1.207		F	CF ₃
1.208		F	CF ₃
1.209		F	CF ₃
1.210		F	CF ₃
1.211		F	CF ₃
1.212		F	CF ₃
1.213		F	CF ₃
1.214		F	CF ₃

1.215		F	CF ₃
1.216		F	CF ₃
1.217		F	CF ₃
1.218		F	CF ₃
1.219		F	CF ₃
1.220		F	CF ₃
1.221		F	CF ₃
1.222		F	CF ₃
1.223		F	CF ₃
1.224		F	CF ₃
1.225		F	CF ₃
1.226		F	CF ₃
1.227		F	CF ₃
1.228		F	CF ₃
1.229		F	CF ₃

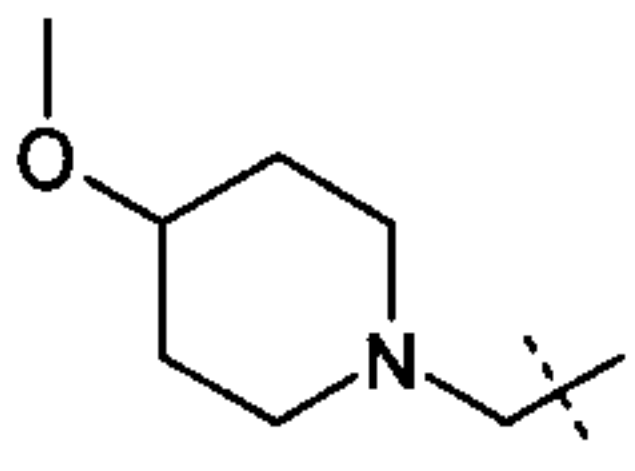
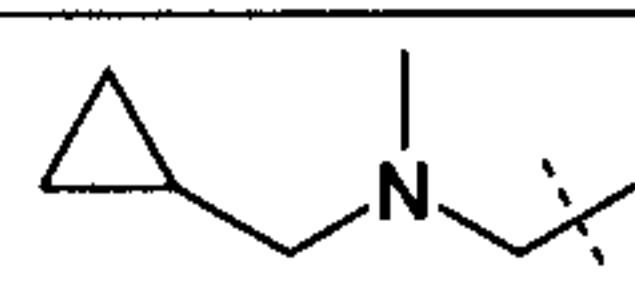
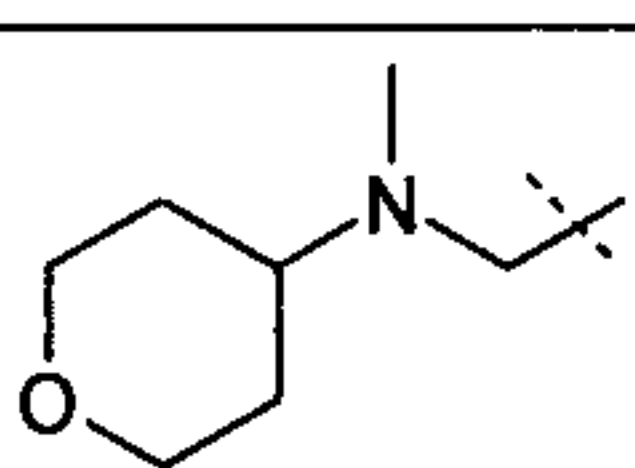
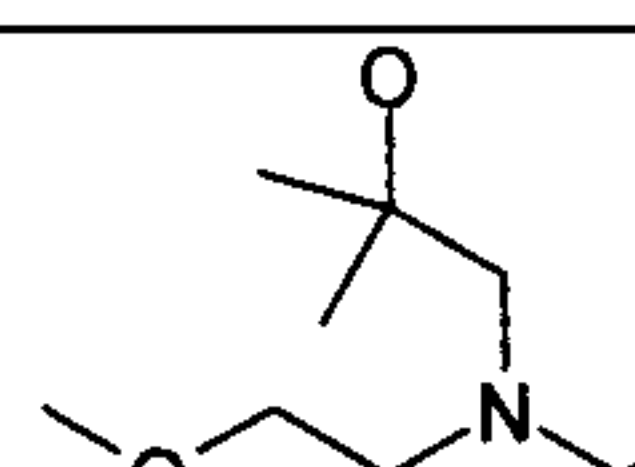
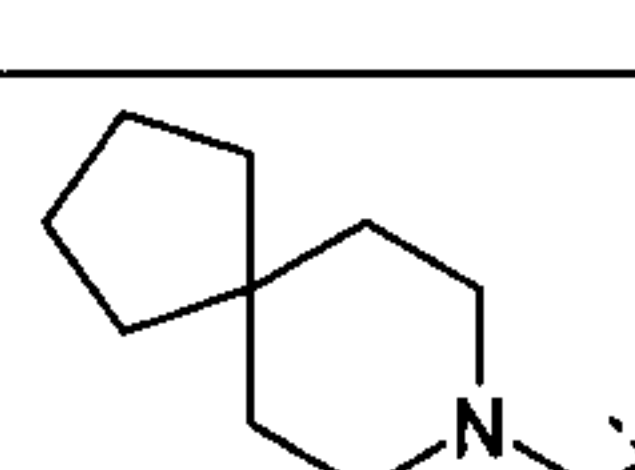
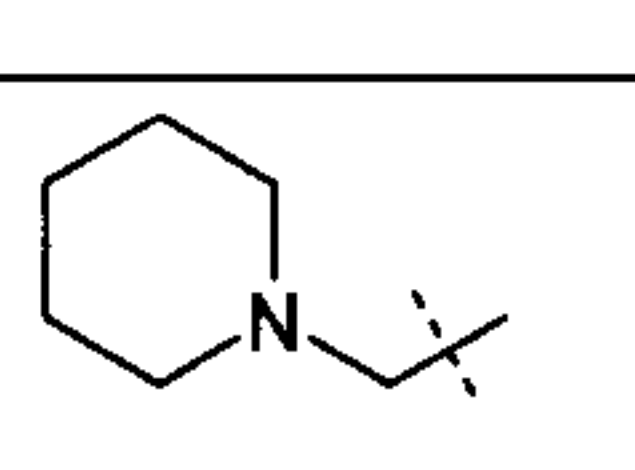
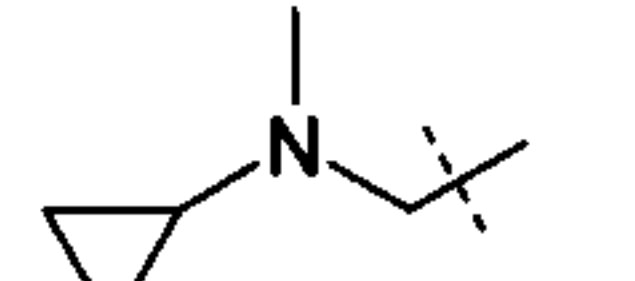
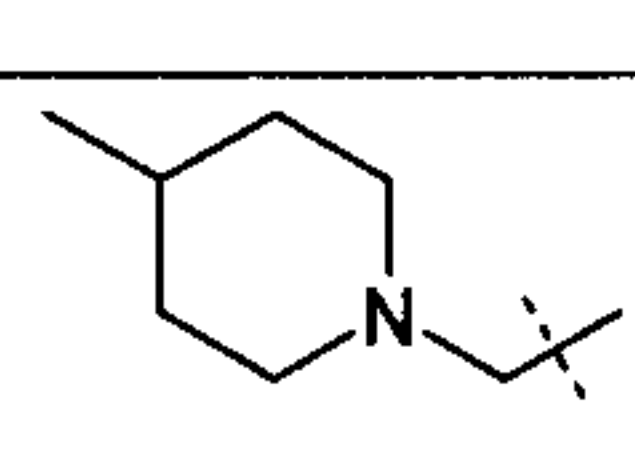
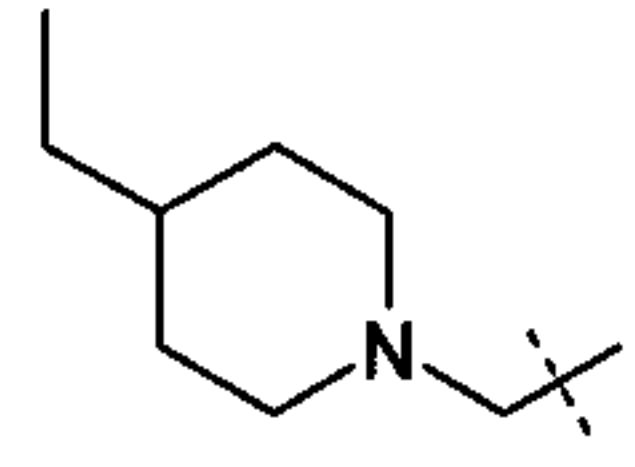
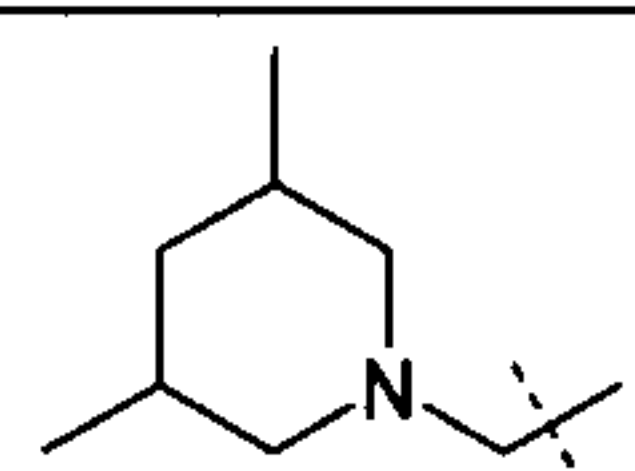
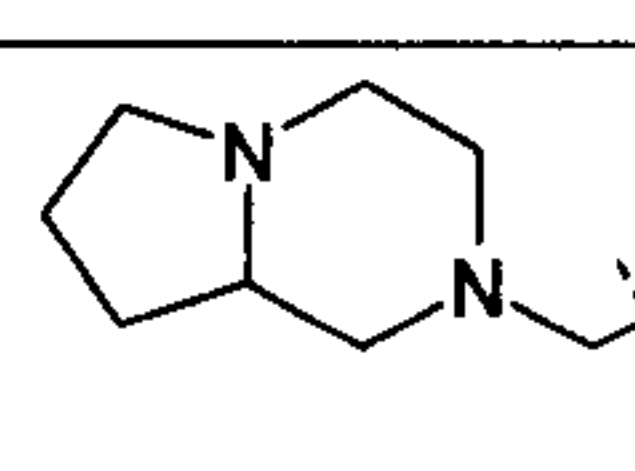
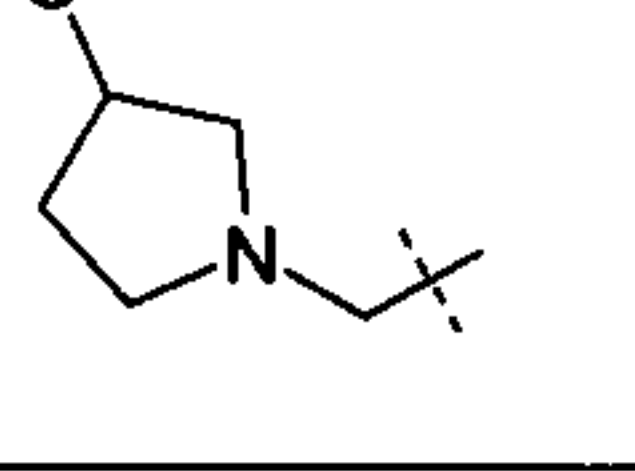
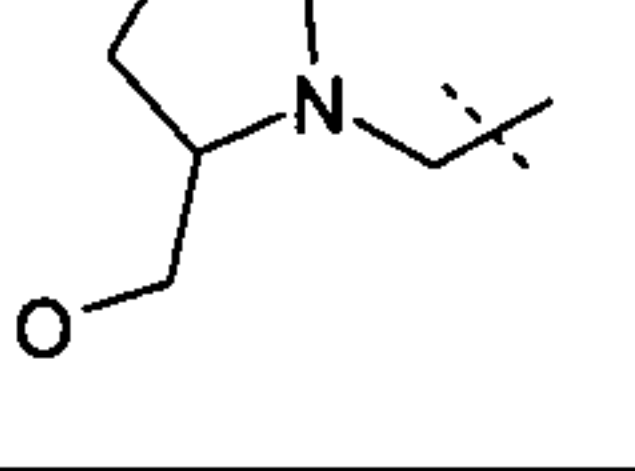
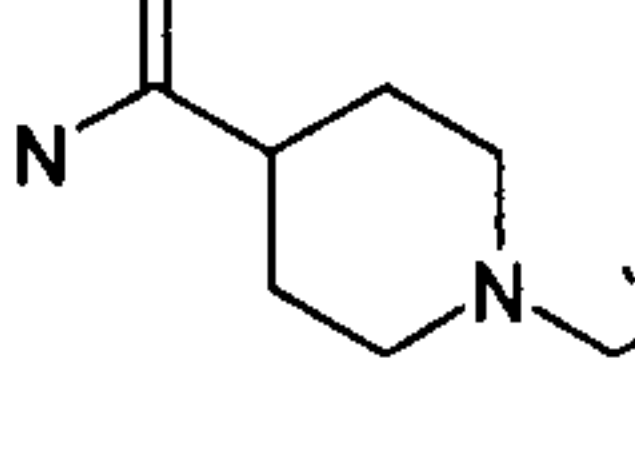
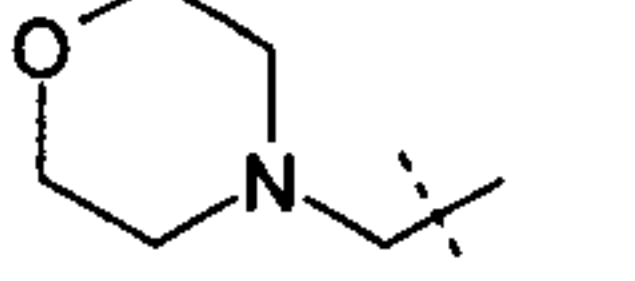


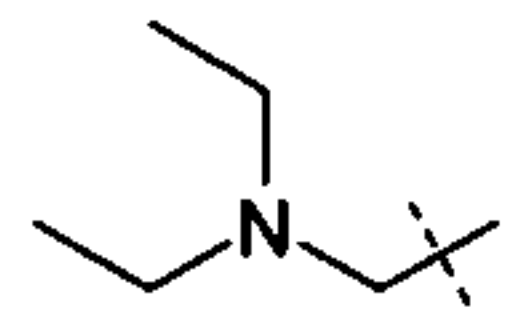
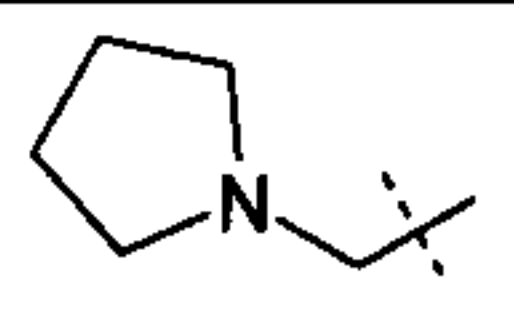
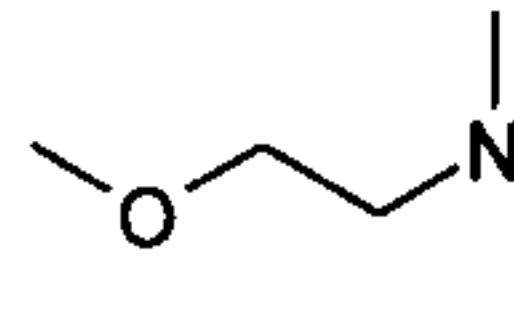
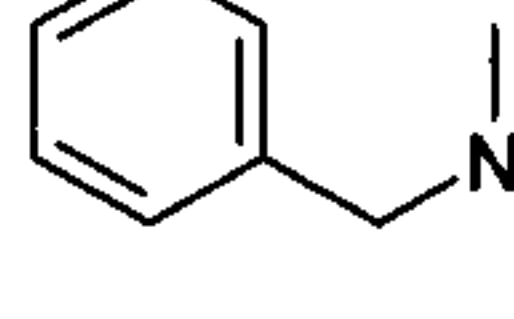
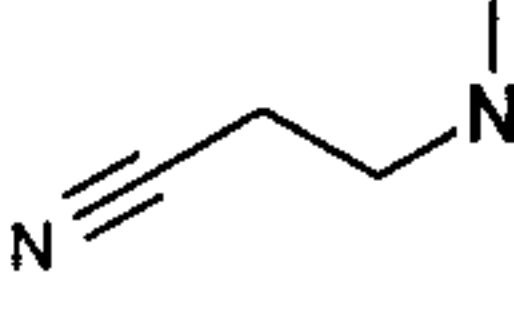
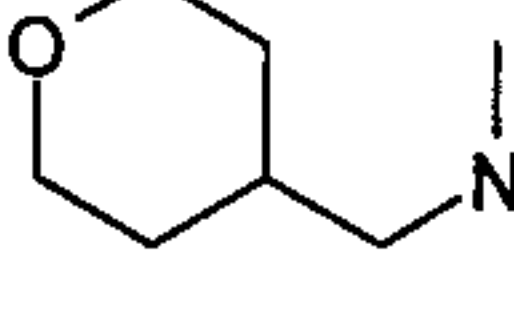
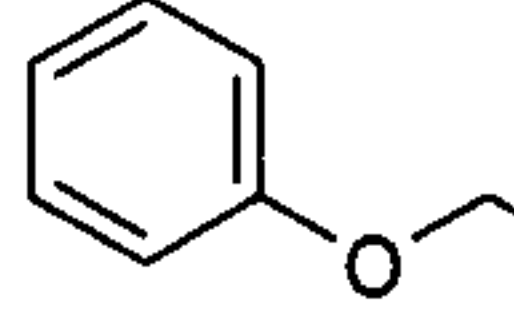
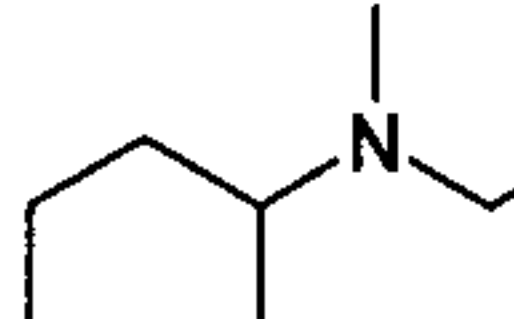
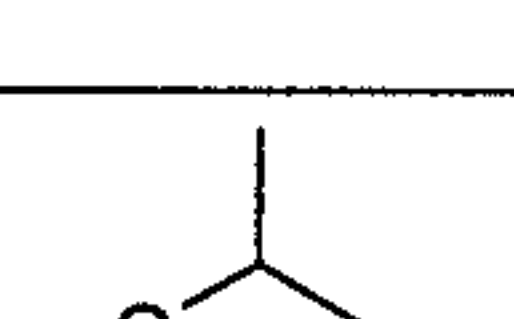
Example	R ₁ R ₂ N-X	L ₁	L ₂
1.230		F	Me
1.231		F	Me
1.232		F	Me
1.233		F	Me
1.234		F	Me
1.235		F	Me
1.236		F	Me
1.237		F	Me
1.238		F	Me
1.239		F	Me
1.240		F	Me
1.241		F	Me

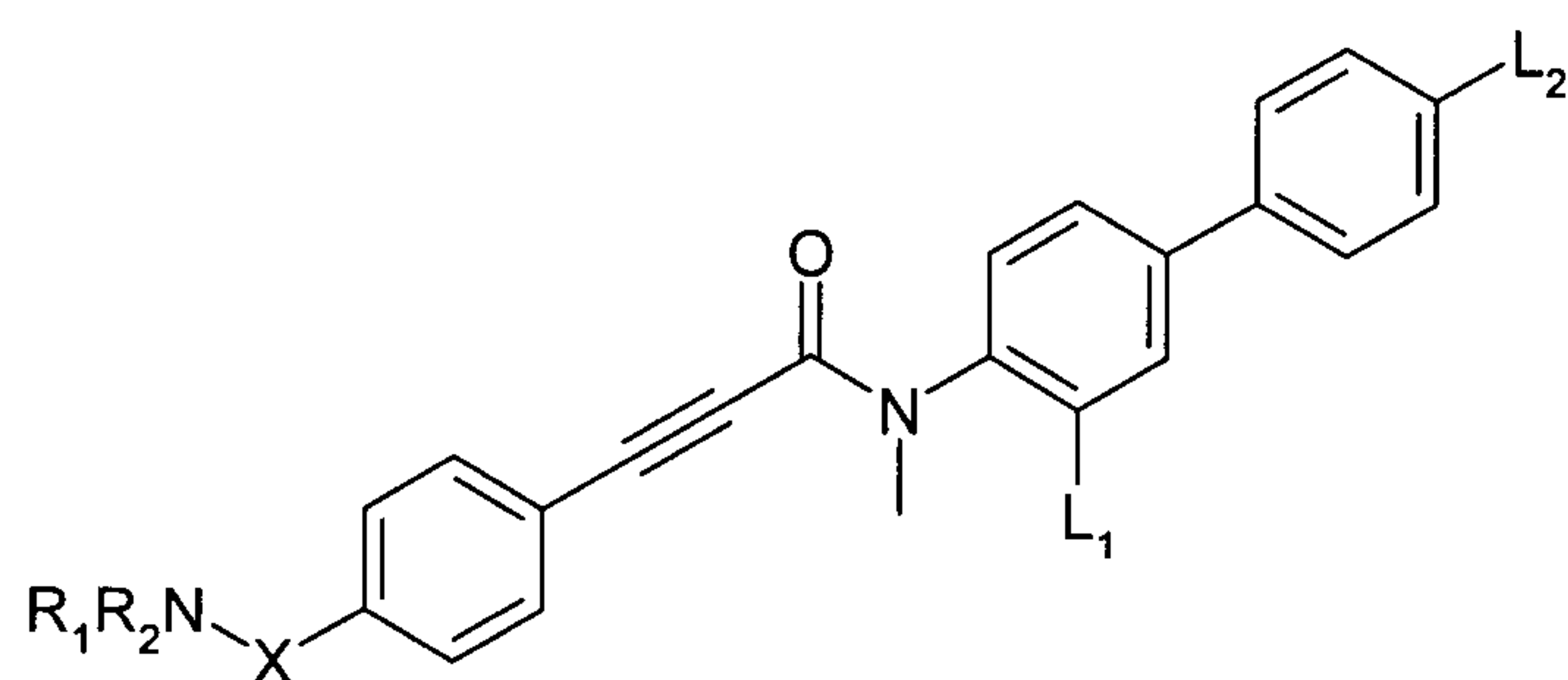
1.242		F	Me
1.243		F	Me
1.244		F	Me
1.245		F	Me
1.246		F	Me
1.247		F	Me
1.248		F	Me
1.249		F	Me
1.250		F	Me
1.251		F	Me
1.252		F	Me
1.253		F	Me

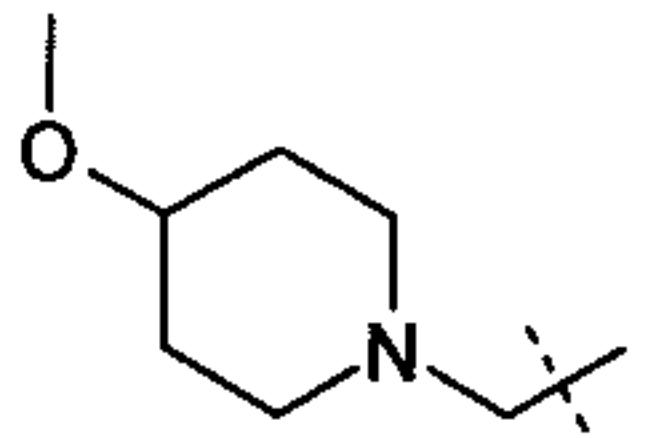
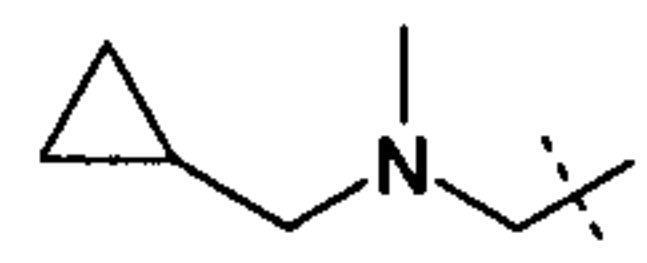
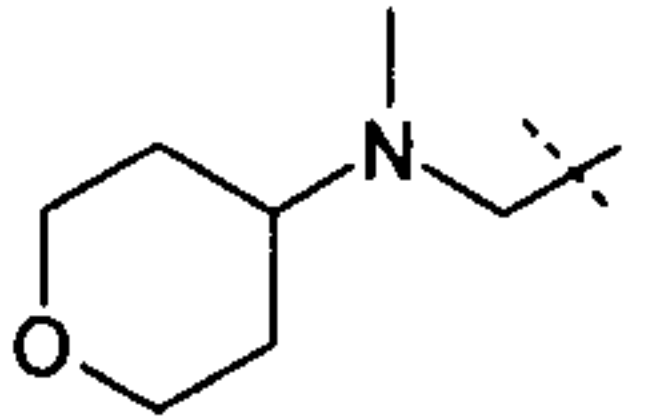


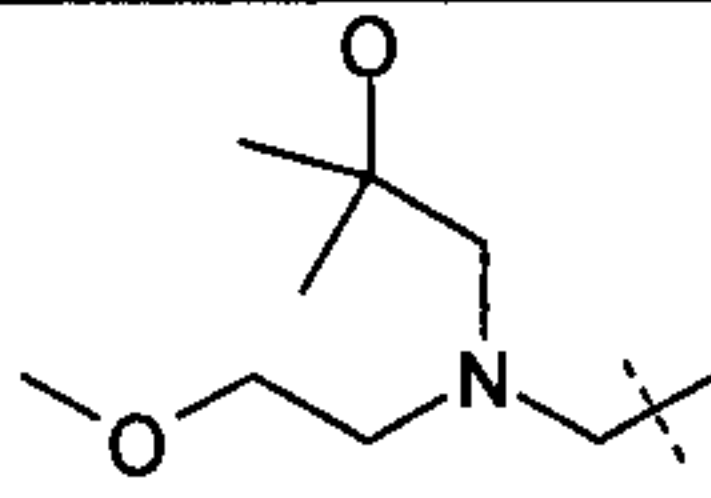
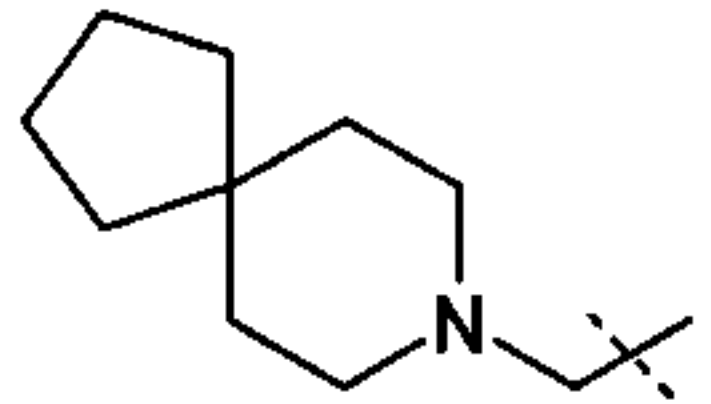
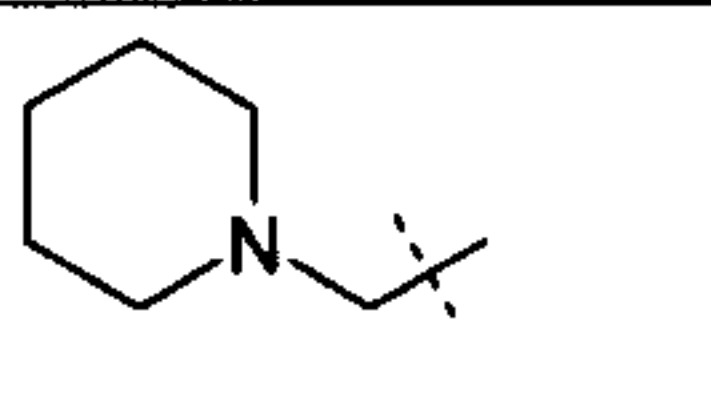
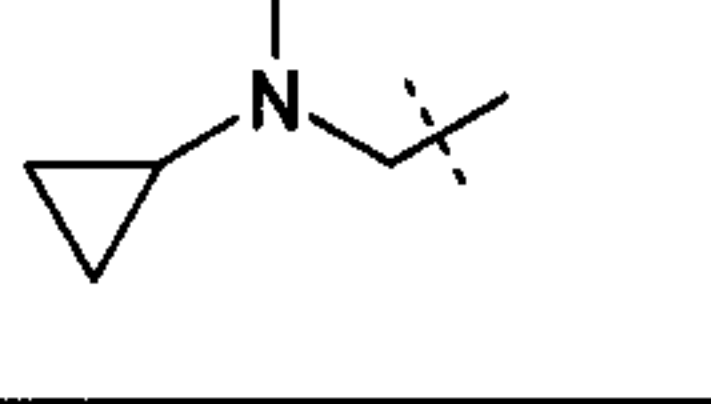
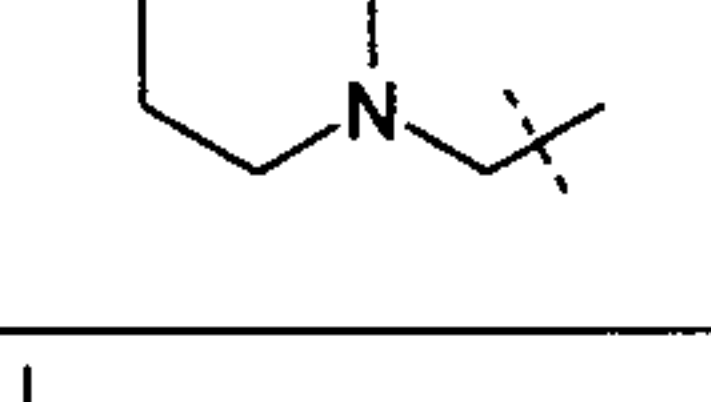
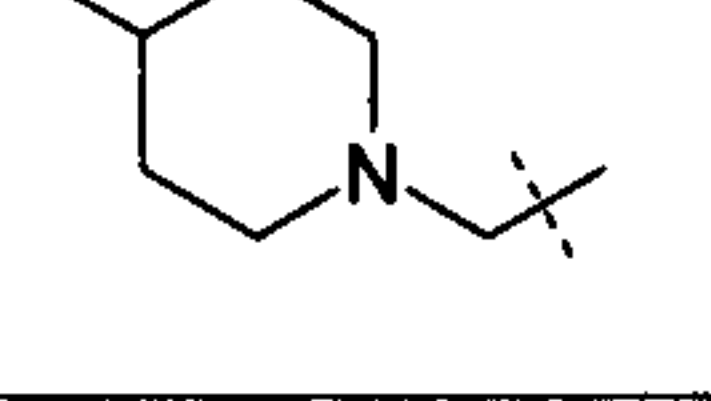
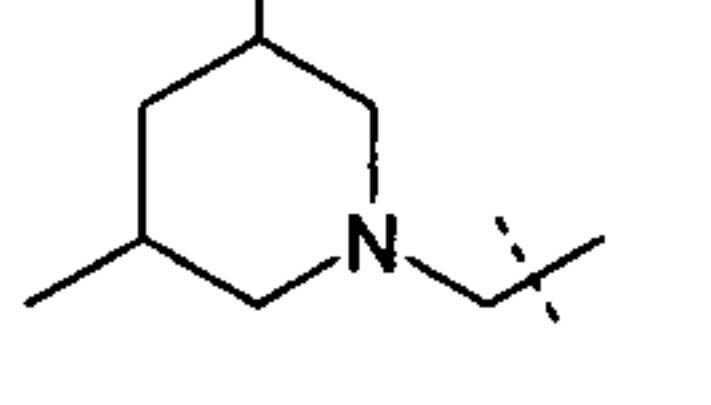
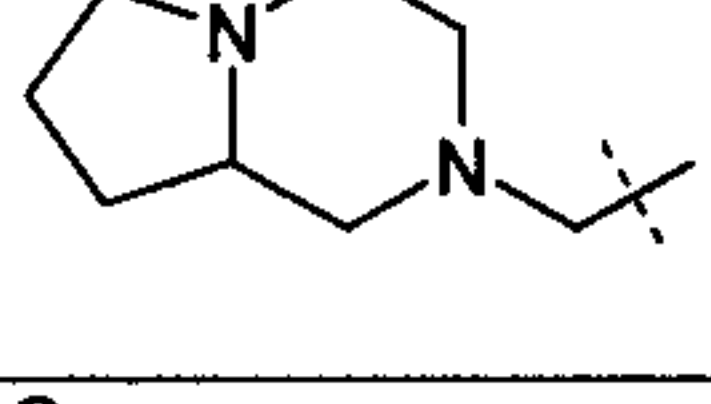
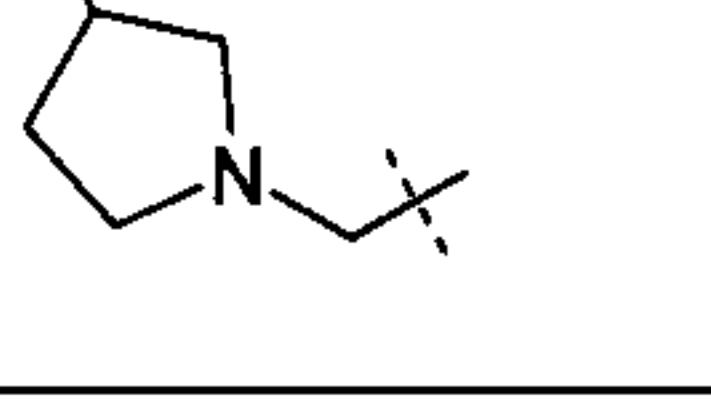
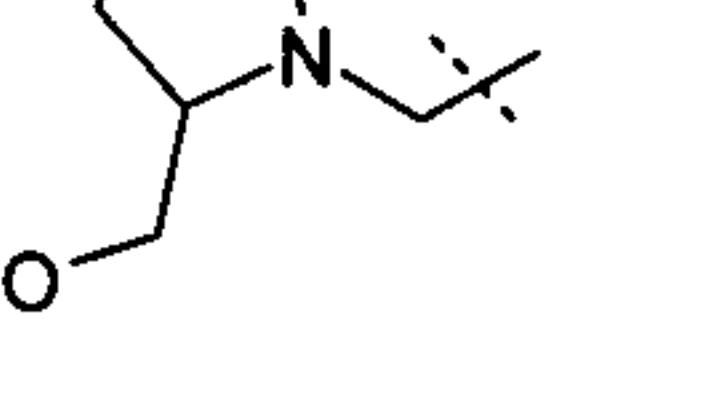
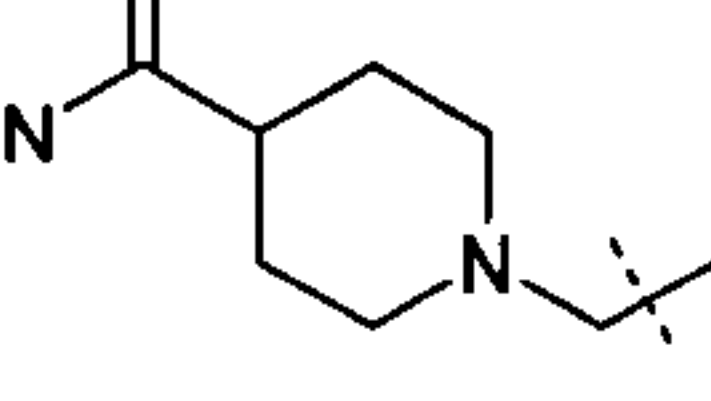
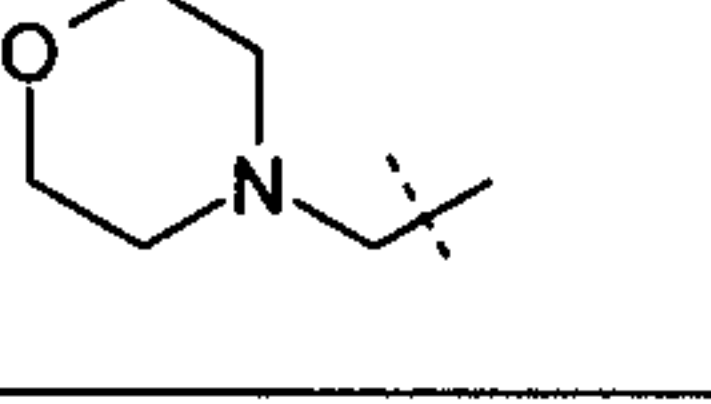
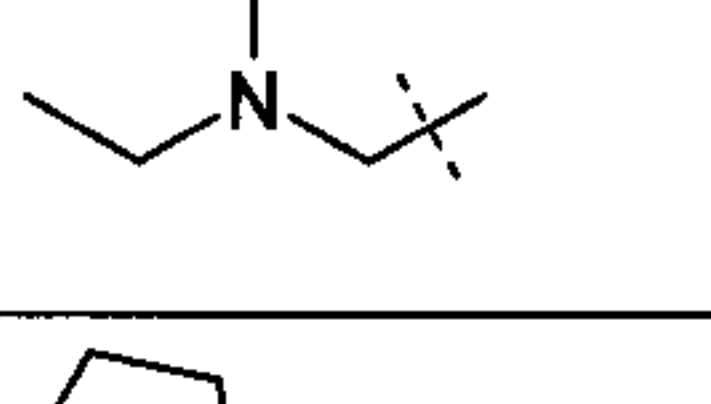
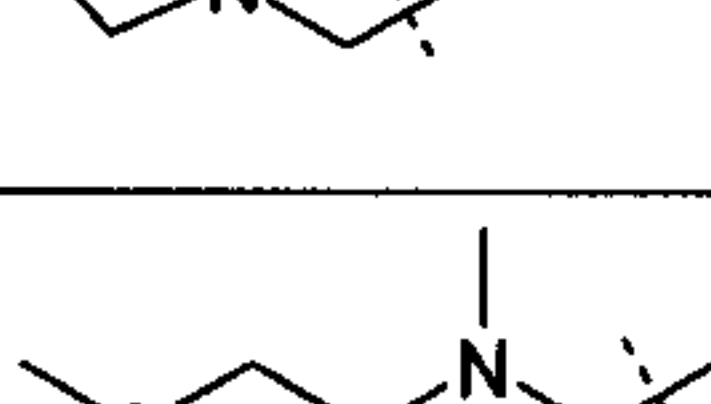
Example	R ₁ R ₂ N-X	L ₁	L ₂

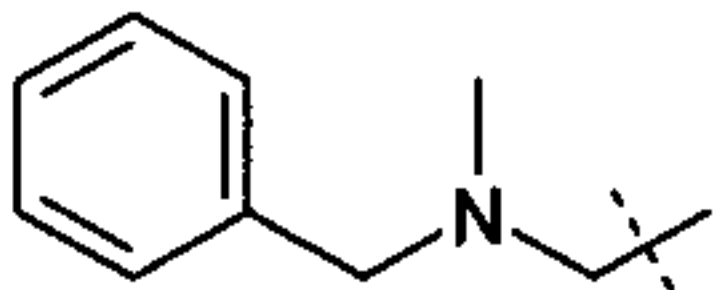
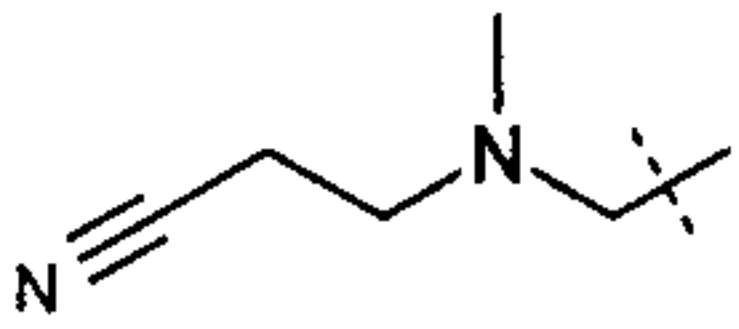
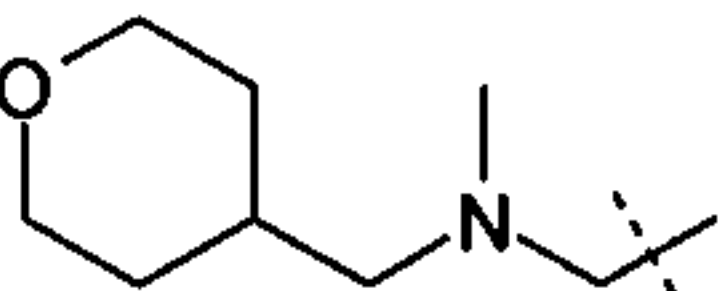
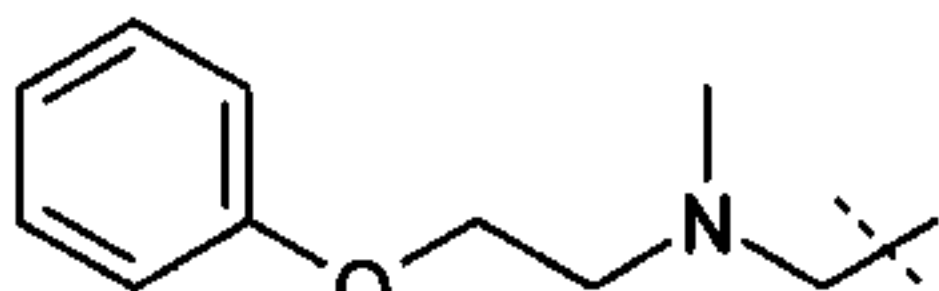
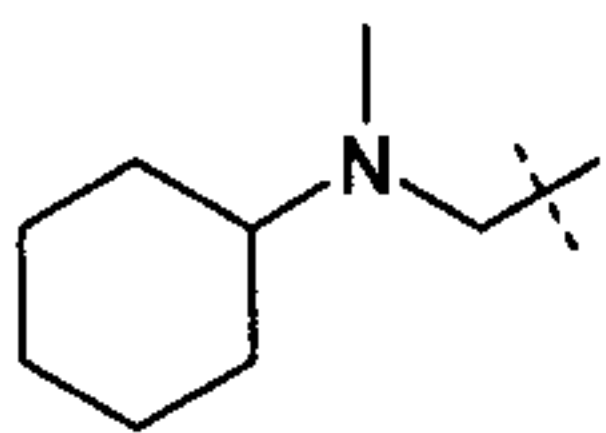
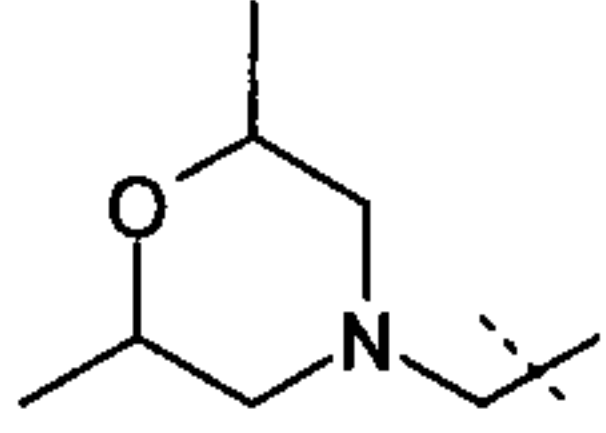
1.254		F	F
1.255		F	F
1.256		F	F
1.257		F	F
1.258		F	F
1.259		F	F
1.260		F	F
1.261		F	F
1.262		F	F
1.263		F	F
1.264		F	F
1.265		F	F
1.266		F	F
1.267		F	F
1.268		F	F

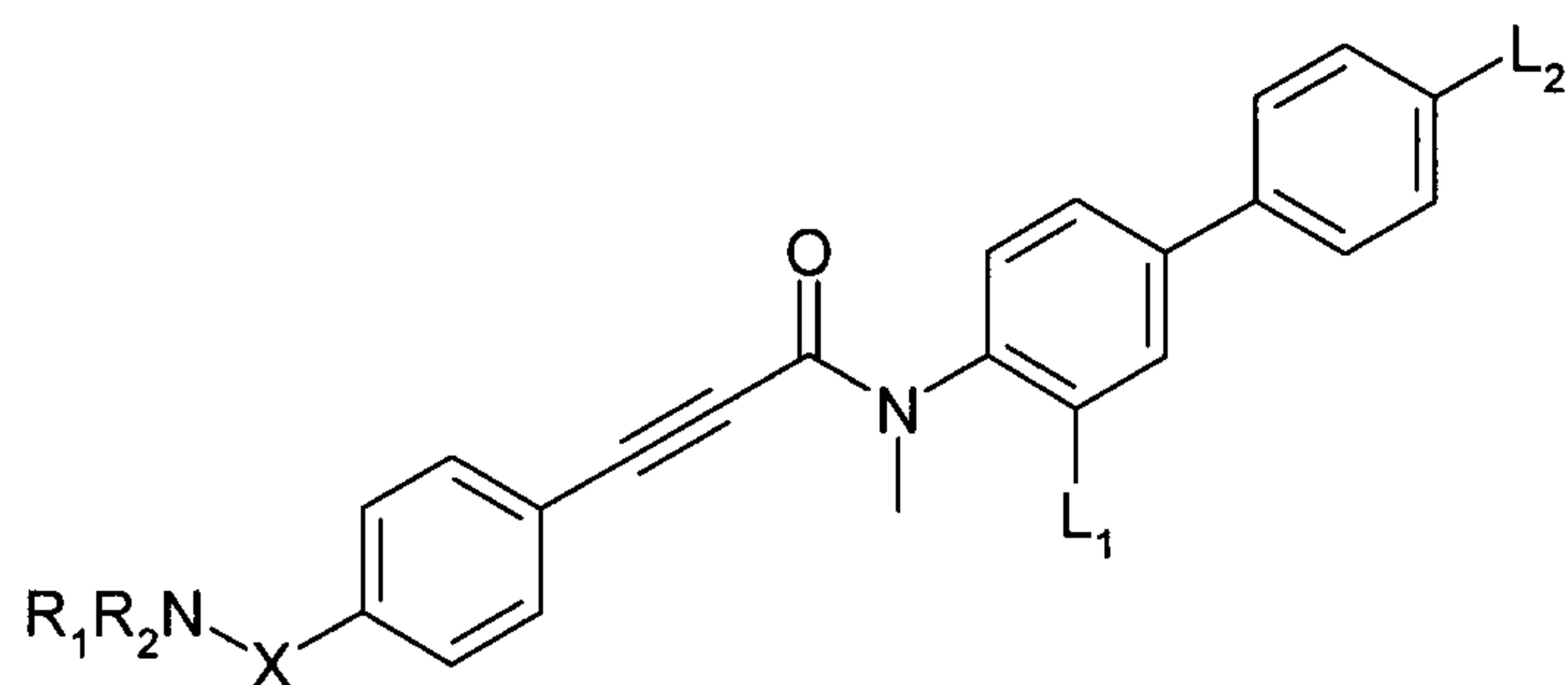
1.269		F	F
1.270		F	F
1.271		F	F
1.272		F	F
1.273		F	F
1.274		F	F
1.275		F	F
1.276		F	F
1.277		F	F

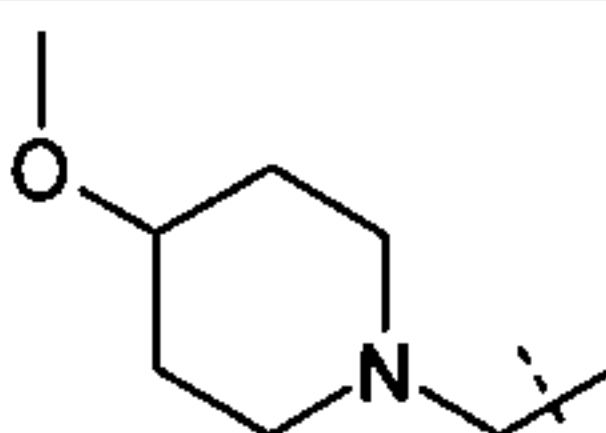
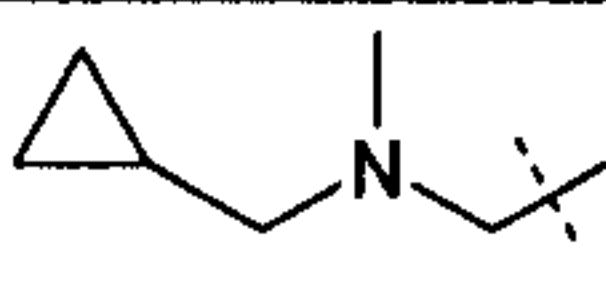
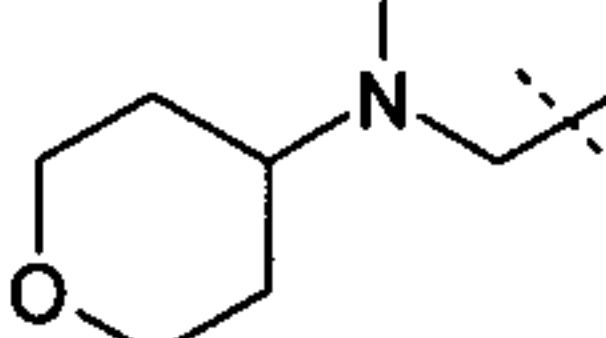
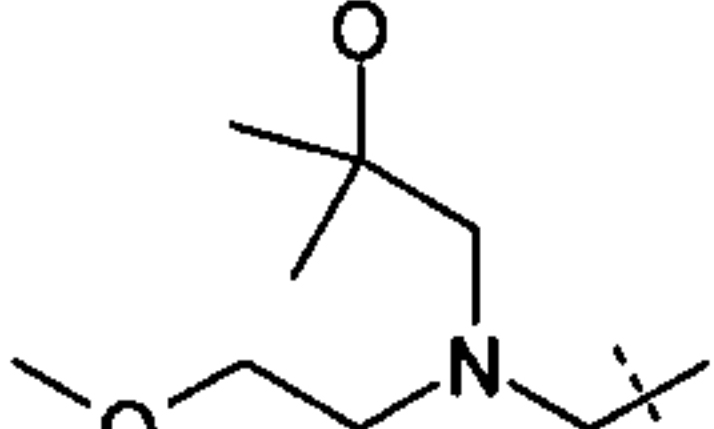
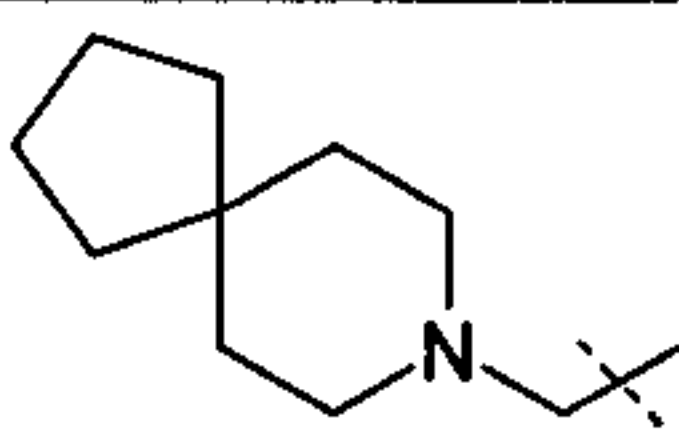


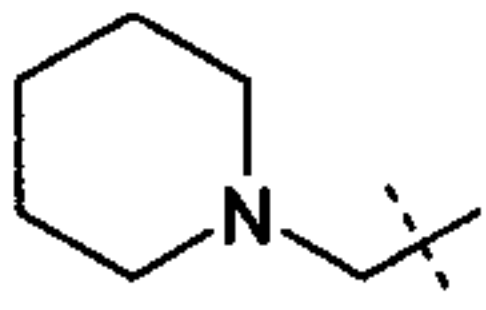
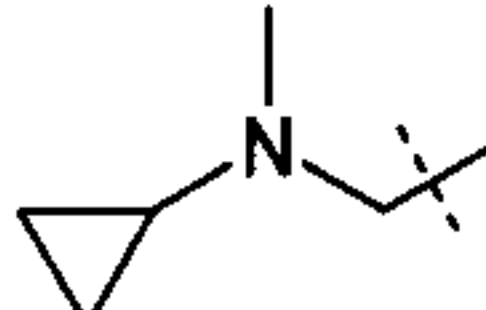
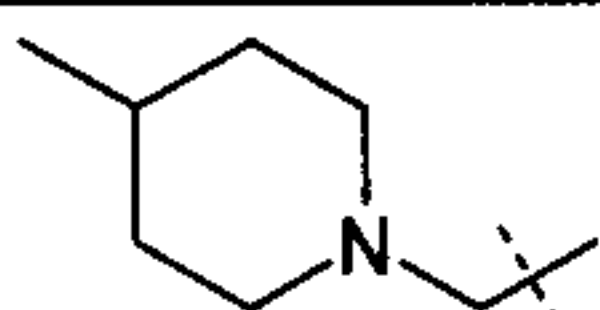
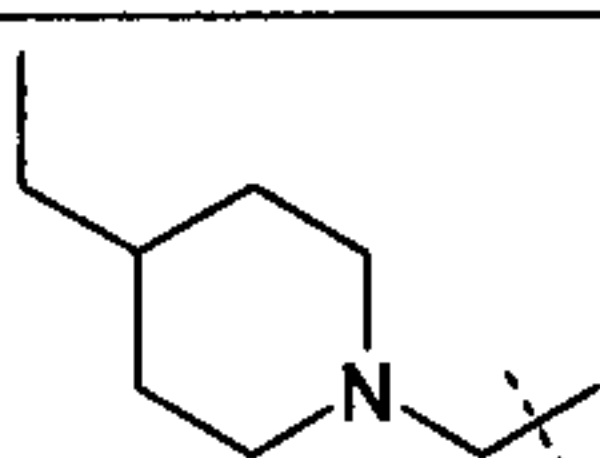
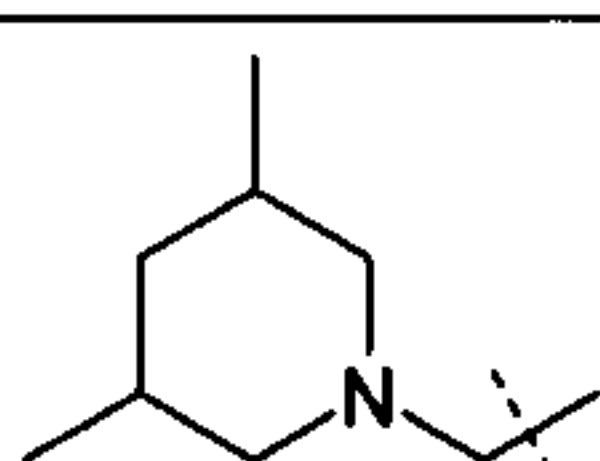
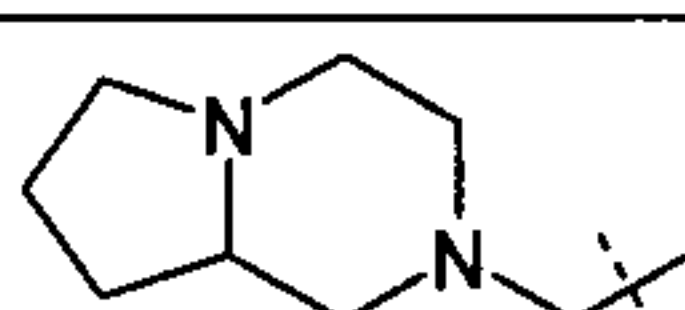
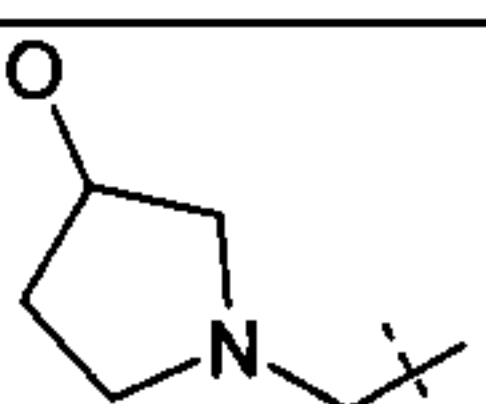
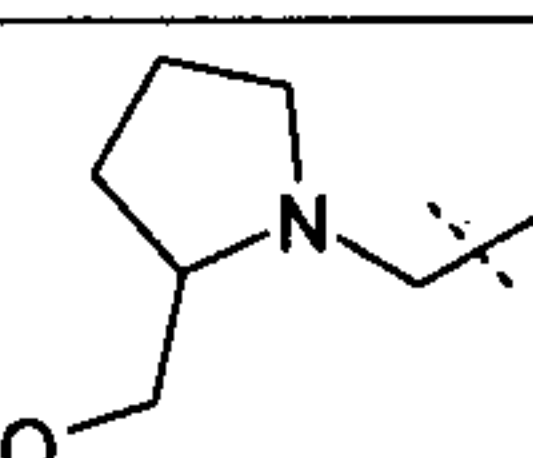
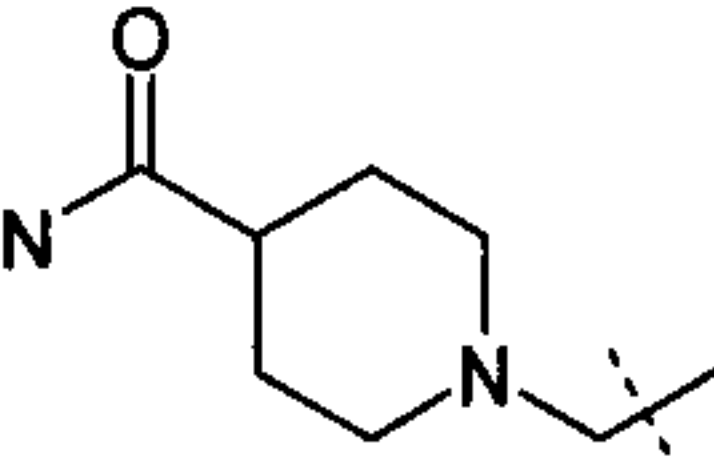
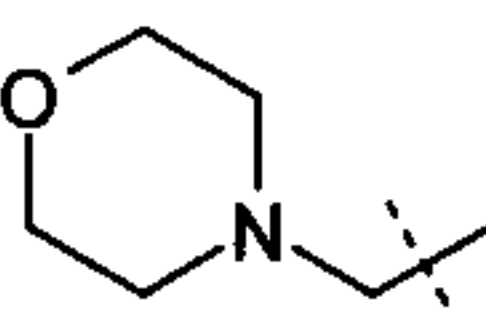
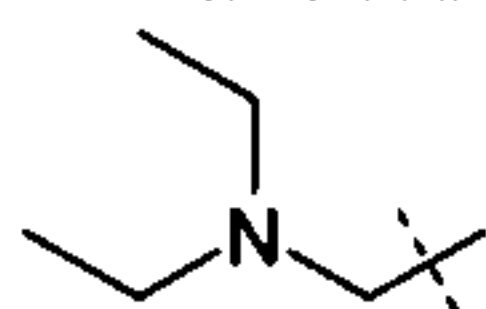
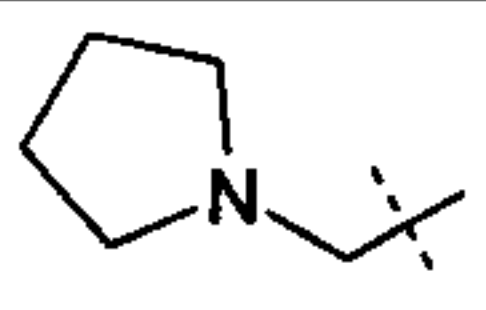
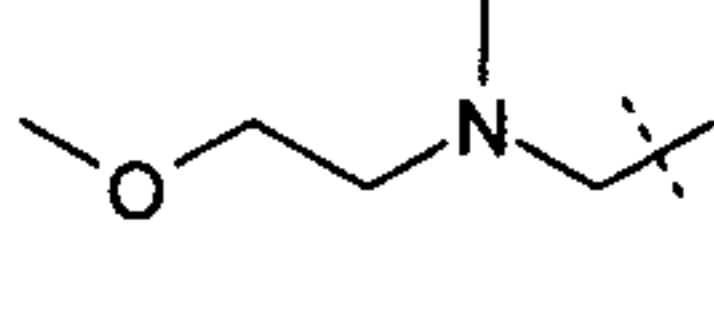
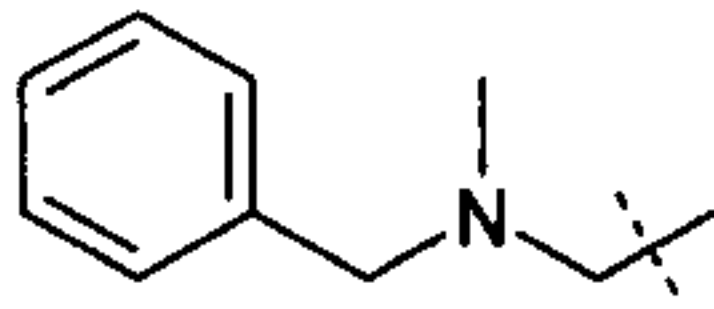
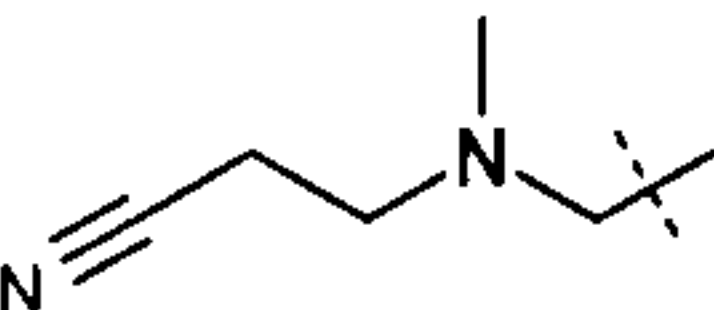
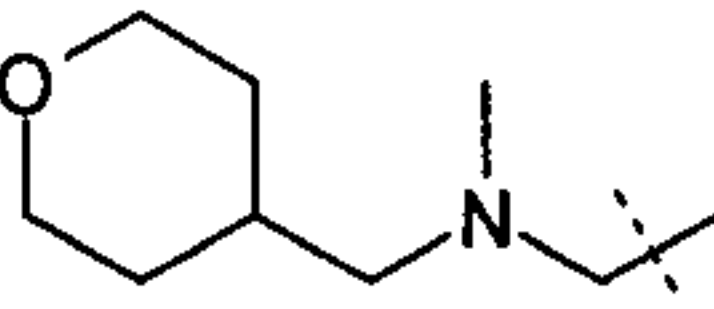
Example	R ₁ R ₂ N-X	L ₁	L ₂
1.278		H	CF ₃
1.279		H	CF ₃
1.280		H	CF ₃

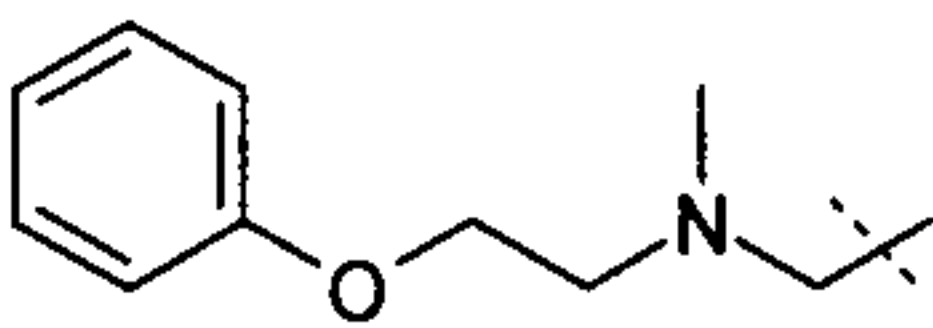
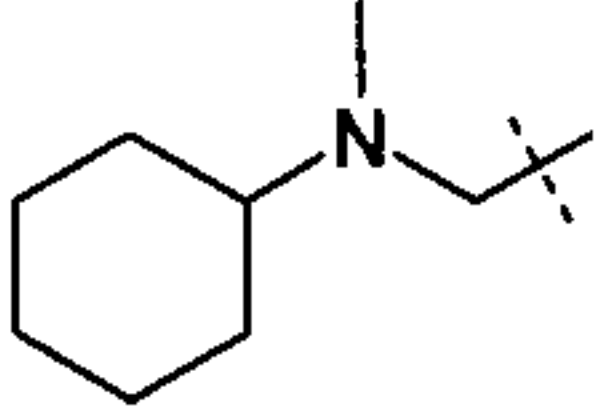
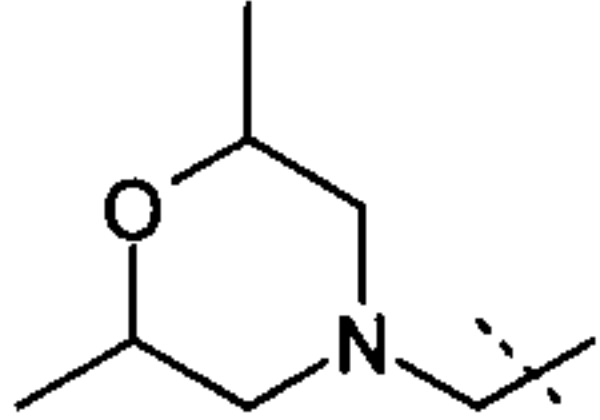
1.281		H	CF ₃
1.282		H	CF ₃
1.283		H	CF ₃
1.284		H	CF ₃
1.285		H	CF ₃
1.286		H	CF ₃
1.287		H	CF ₃
1.288		H	CF ₃
1.289		H	CF ₃
1.290		H	CF ₃
1.291		H	CF ₃
1.292		H	CF ₃
1.293		H	CF ₃
1.294		H	CF ₃
1.295		H	CF ₃

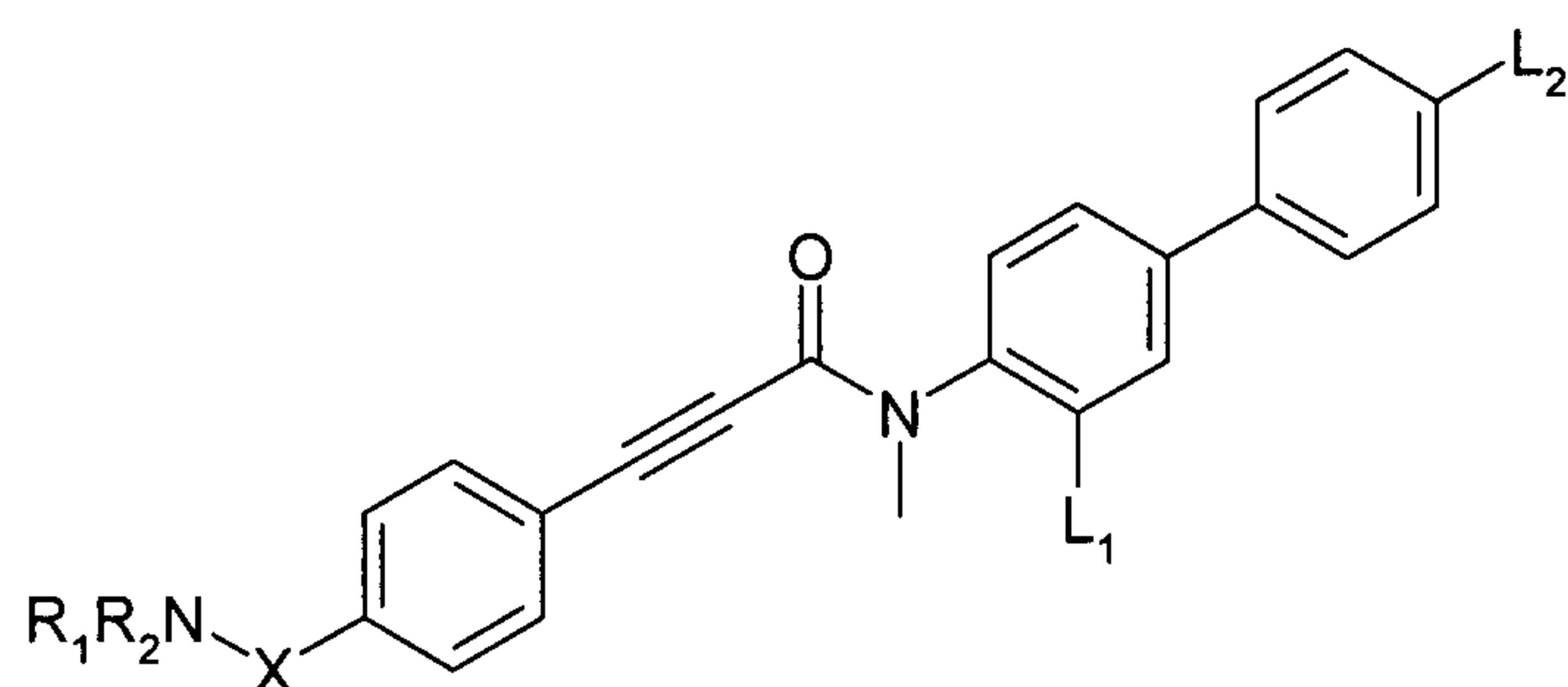
1.296		H	CF ₃
1.297		H	CF ₃
1.298		H	CF ₃
1.299		H	CF ₃
1.300		H	CF ₃
1.301		H	CF ₃

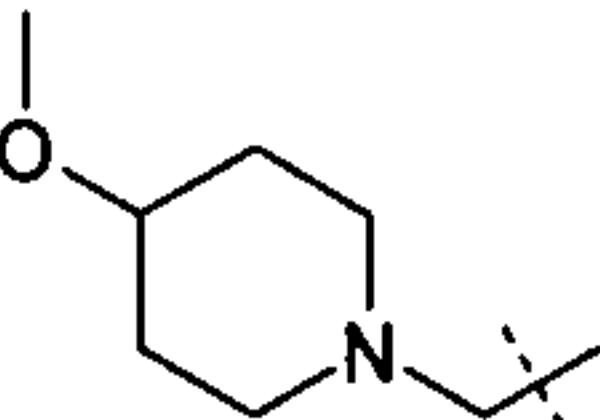
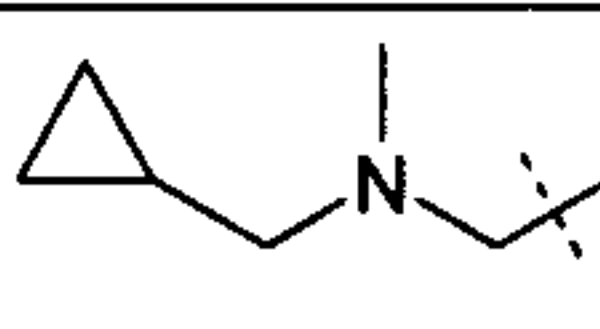
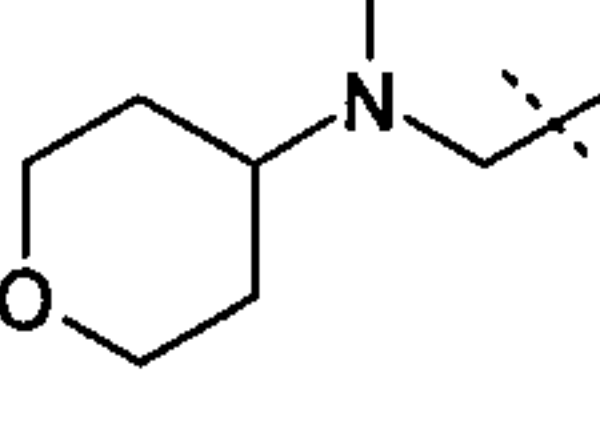
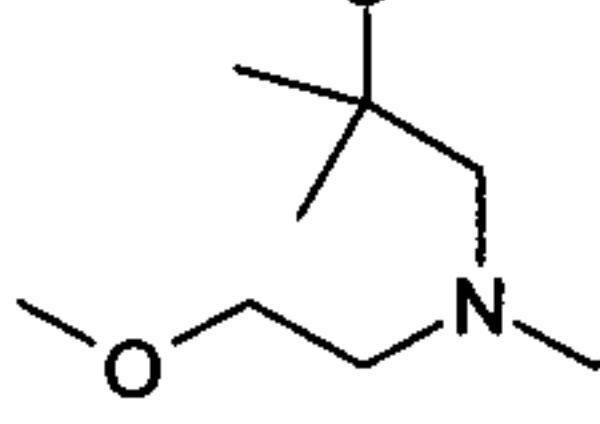
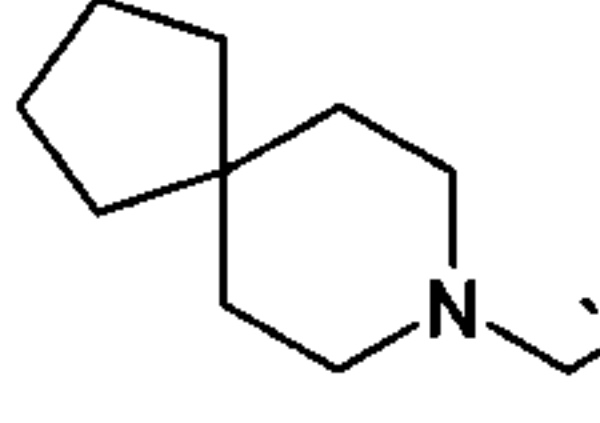
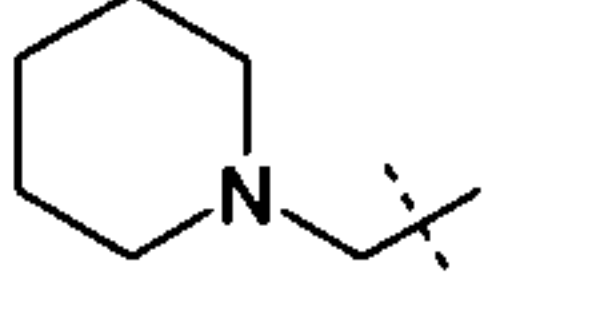
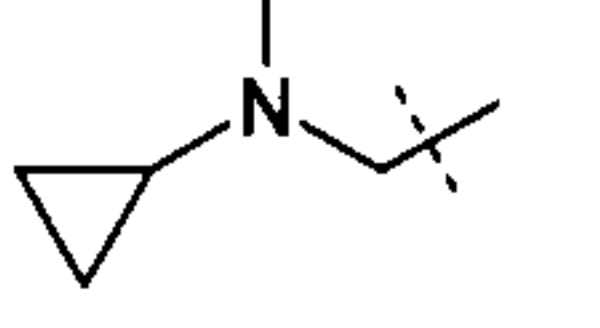
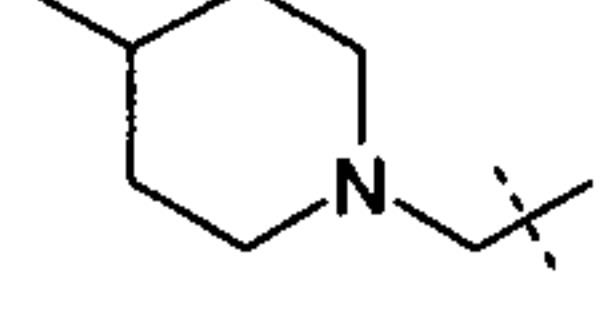


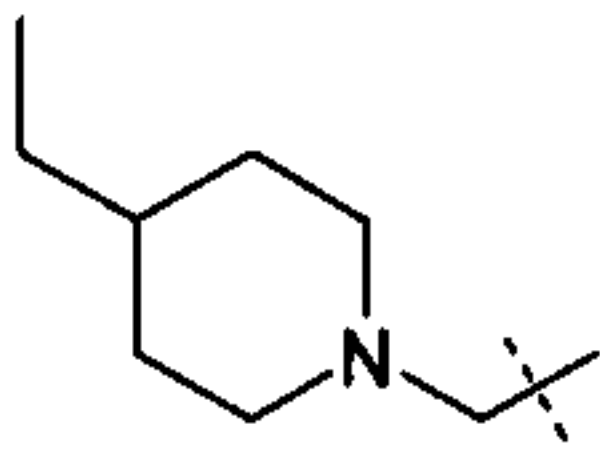
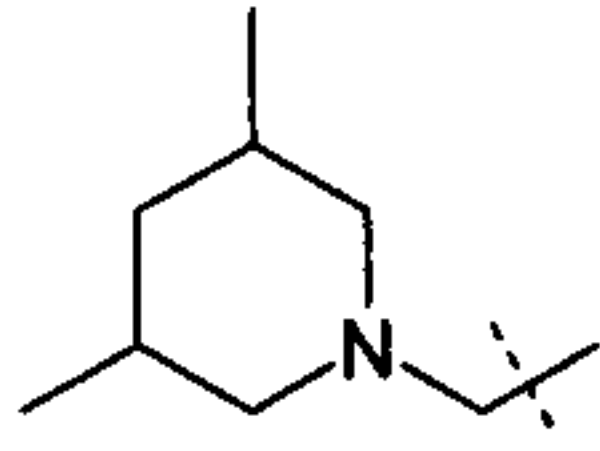
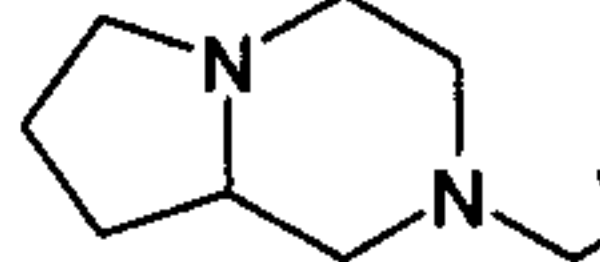
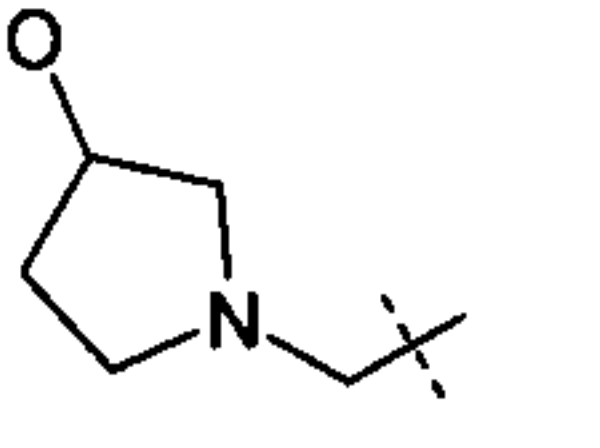
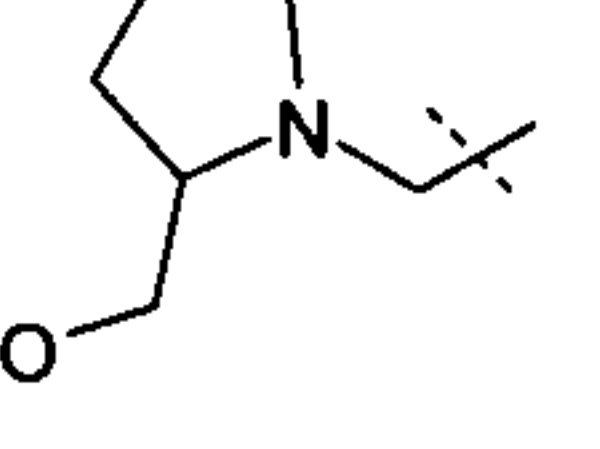
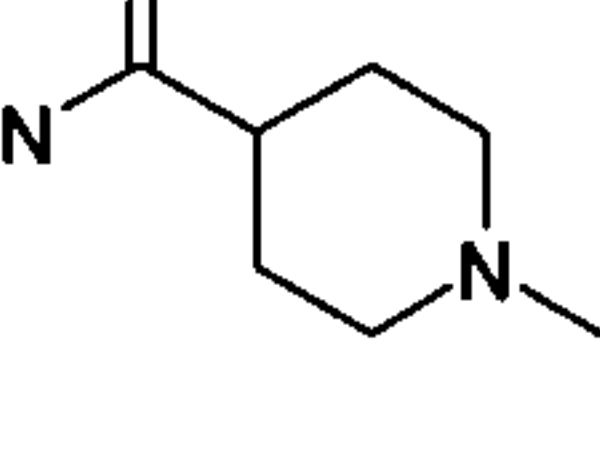
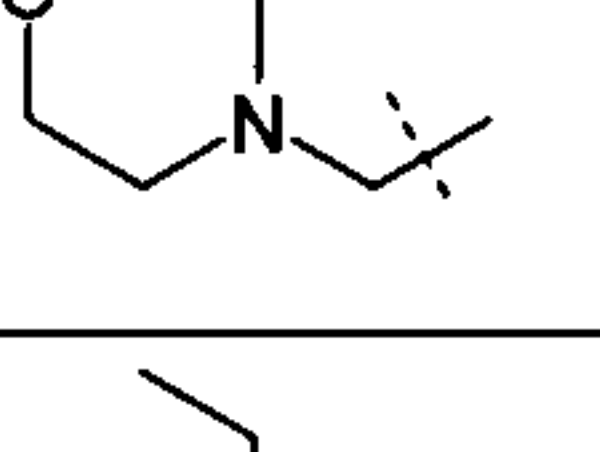
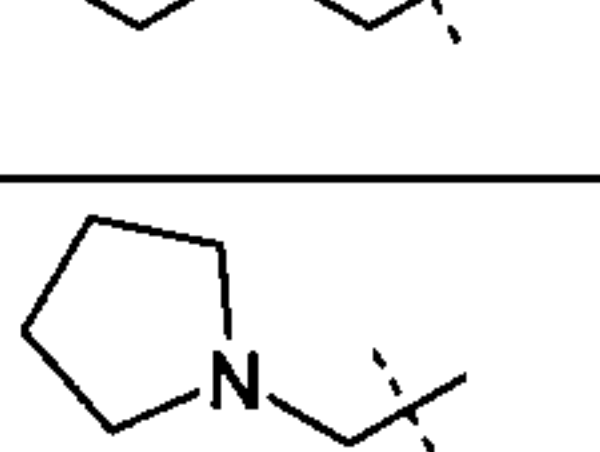
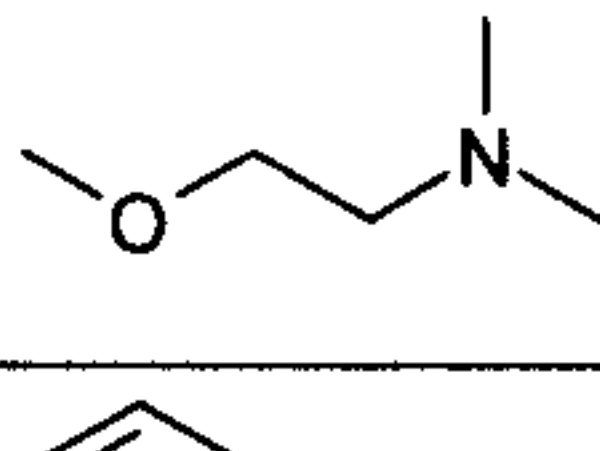
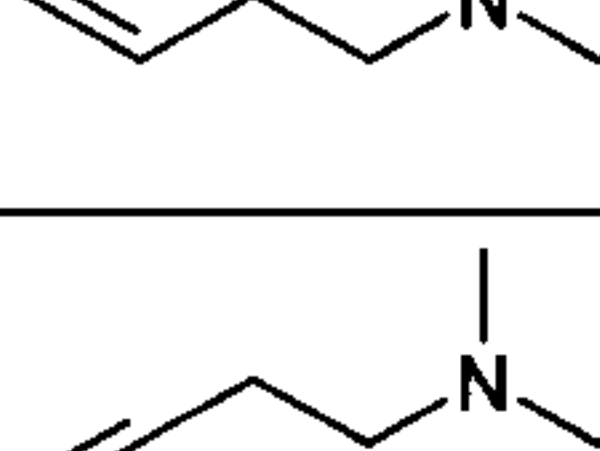
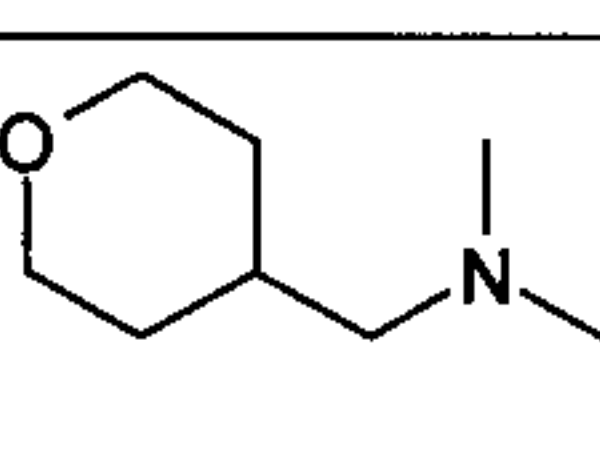
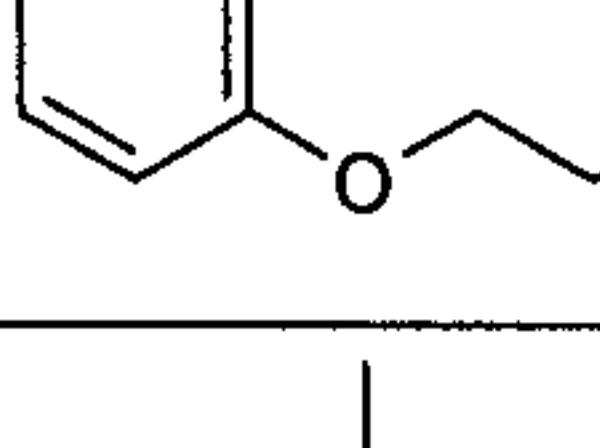
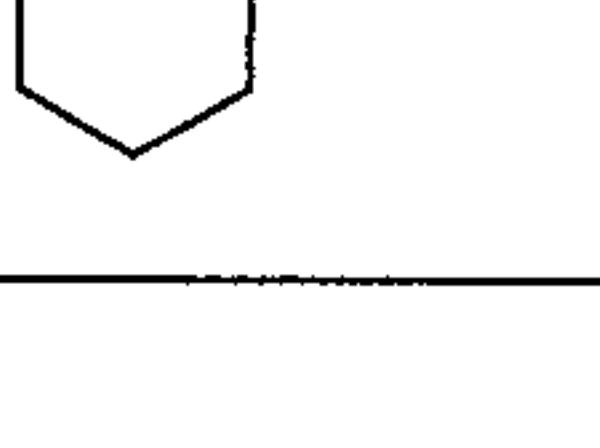
Example	R ₁ R ₂ N-X	L ₁	L ₂
1.302		H	Me
1.303		H	Me
1.304		H	Me
1.305		H	Me
1.306		H	Me

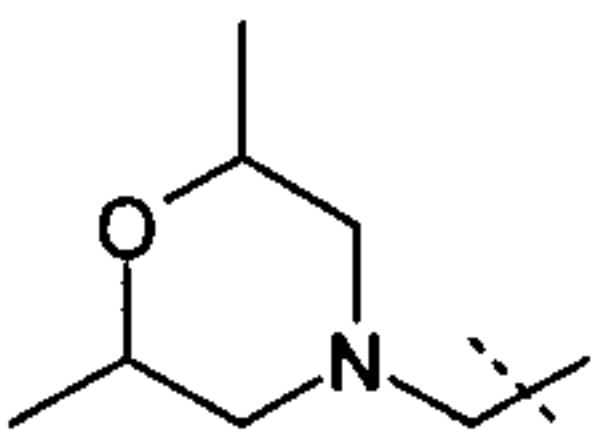
1.307		H	Me
1.308		H	Me
1.309		H	Me
1.310		H	Me
1.311		H	Me
1.312		H	Me
1.313		H	Me
1.314		H	Me
1.315		H	Me
1.316		H	Me
1.317		H	Me
1.318		H	Me
1.319		H	Me
1.320		H	Me
1.321		H	Me
1.322		H	Me

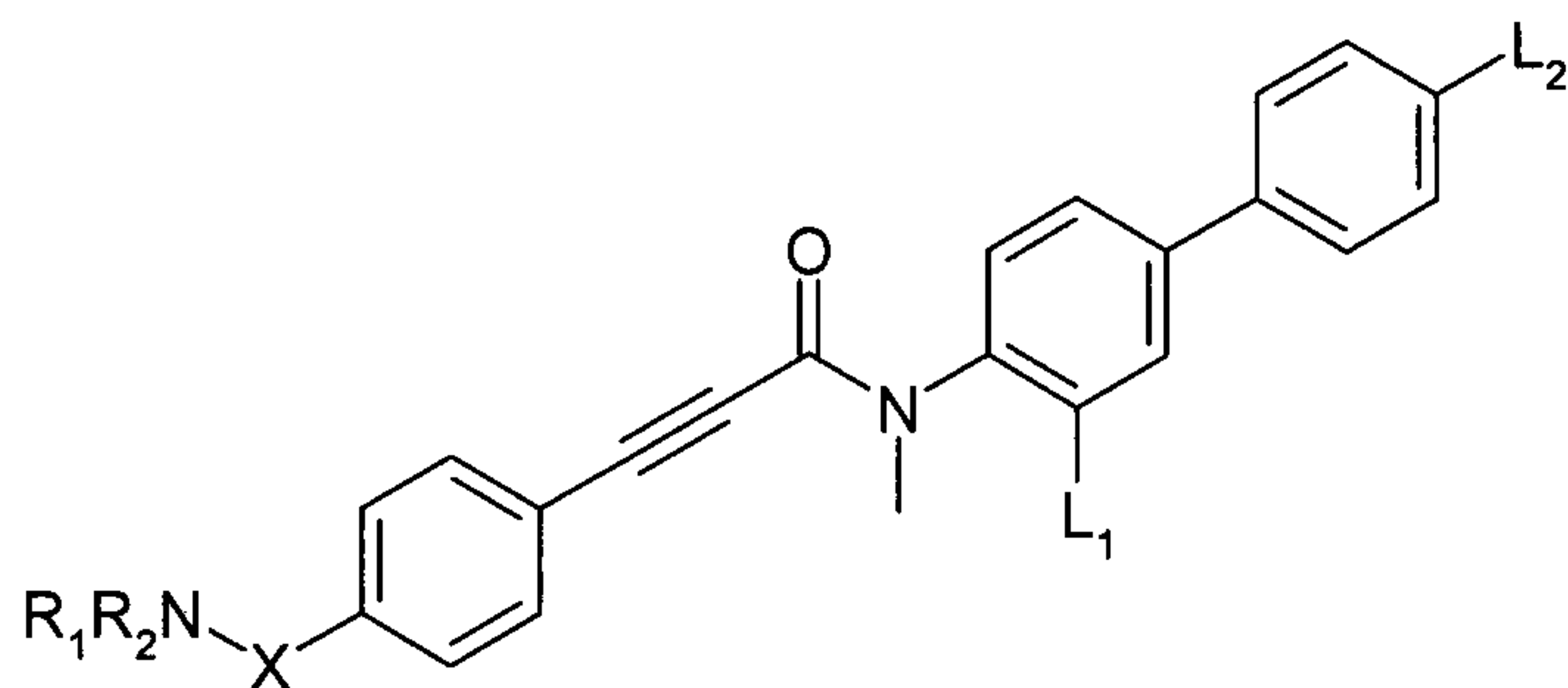
1.323		H	Me
1.324		H	Me
1.325		H	Me

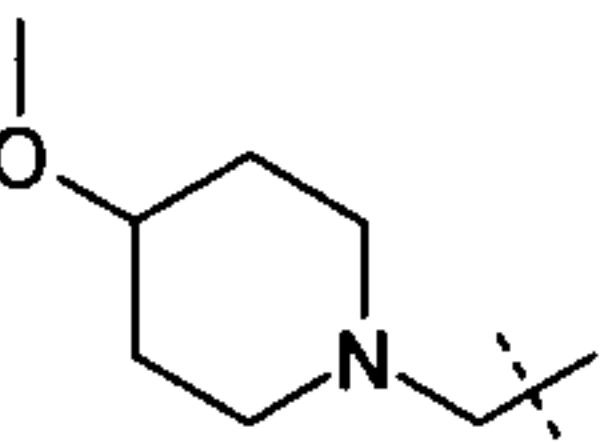
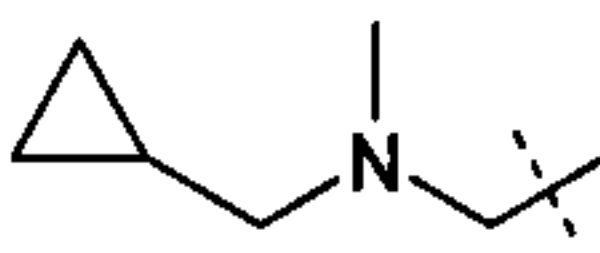
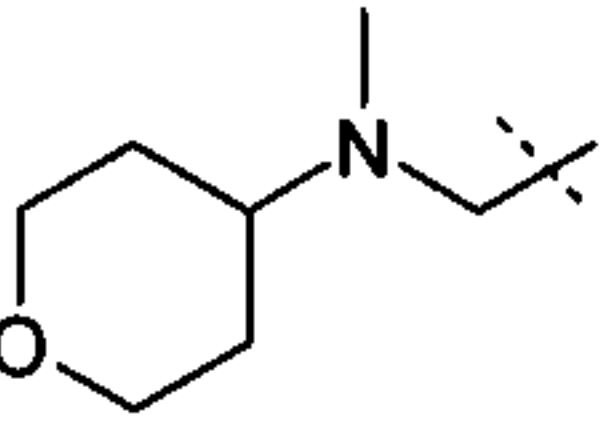
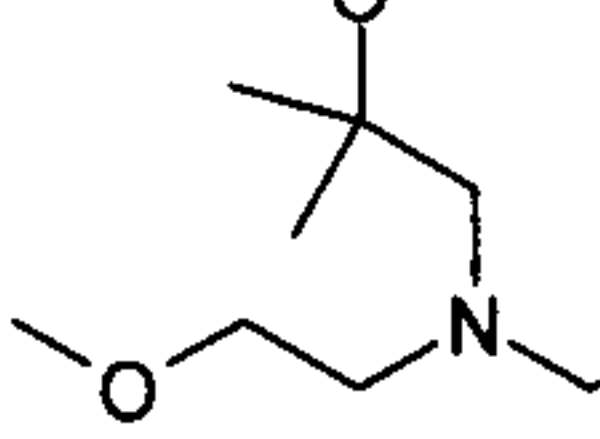
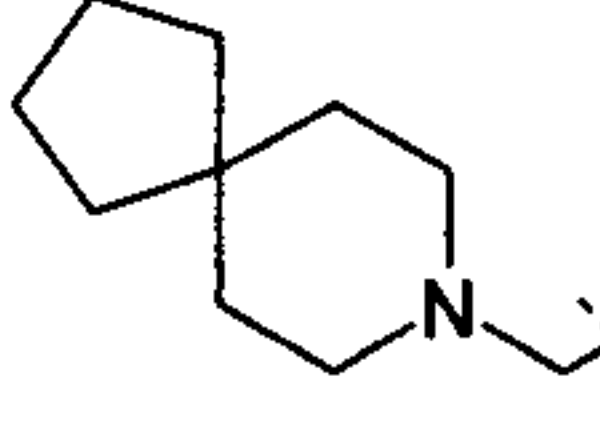
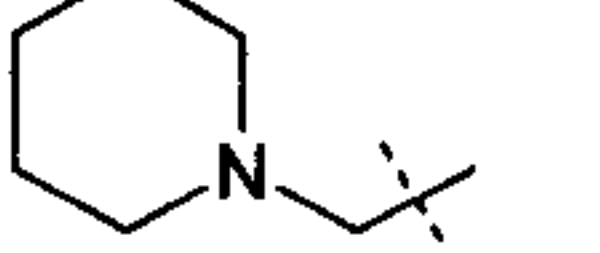
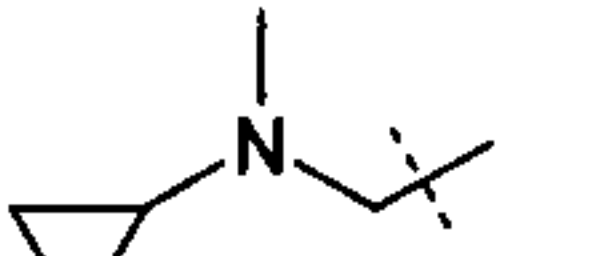
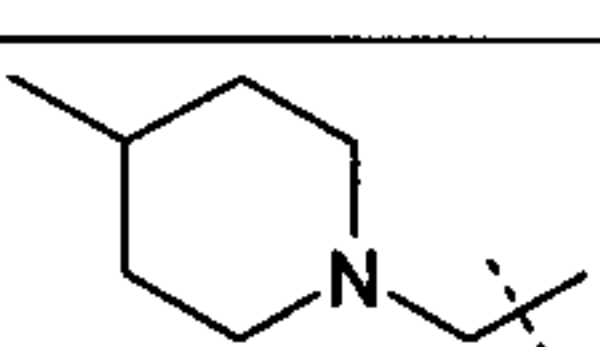
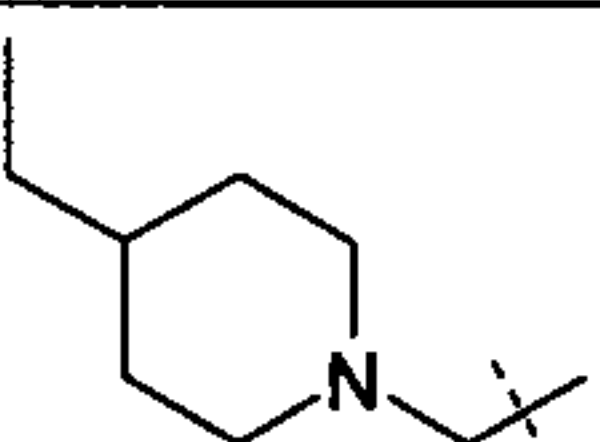


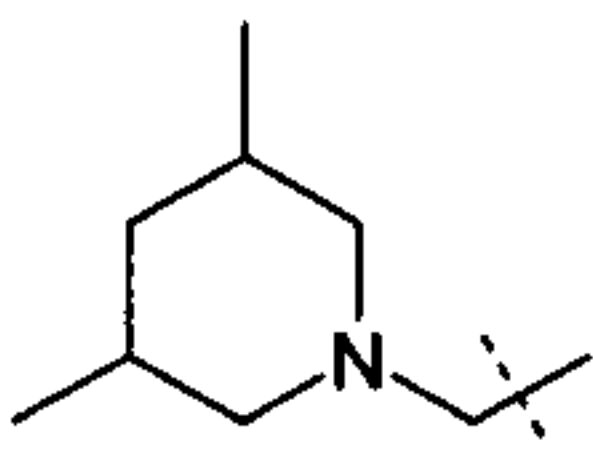
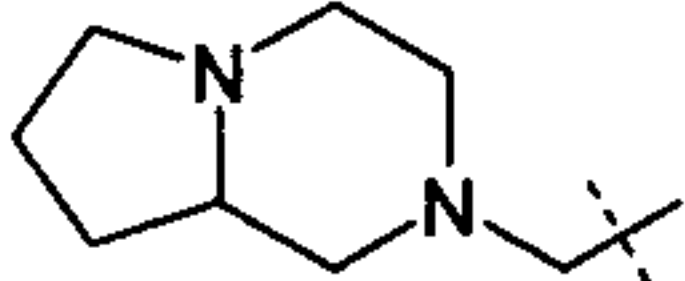
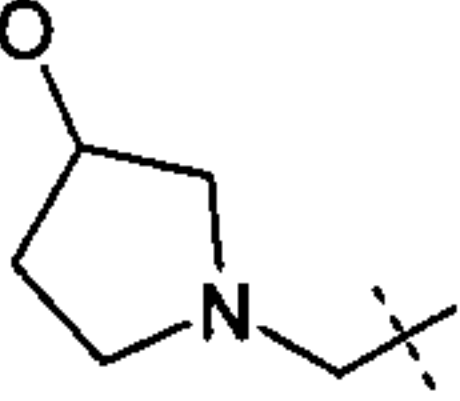
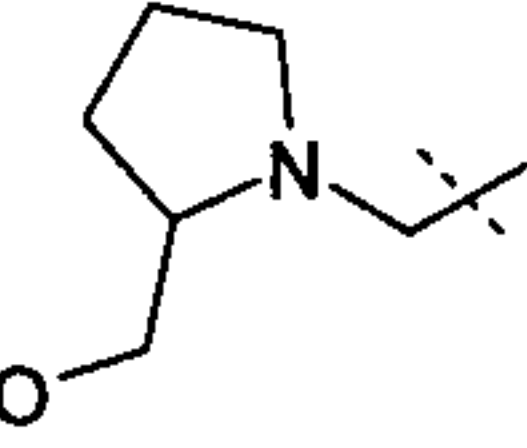
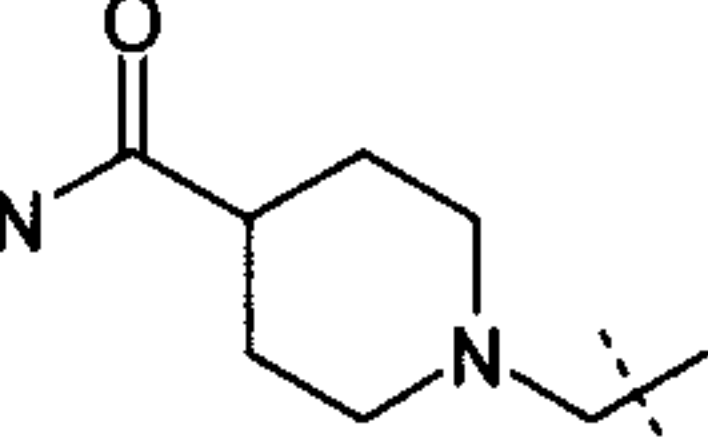
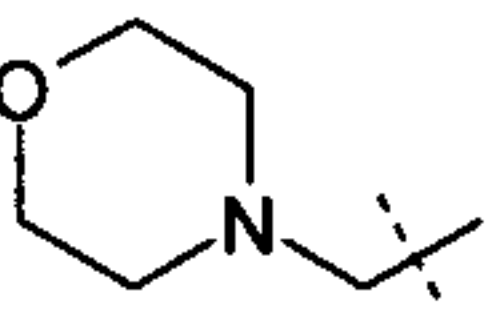
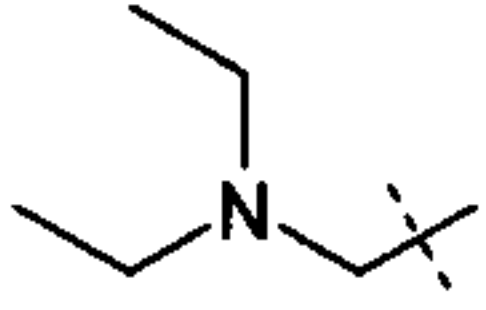
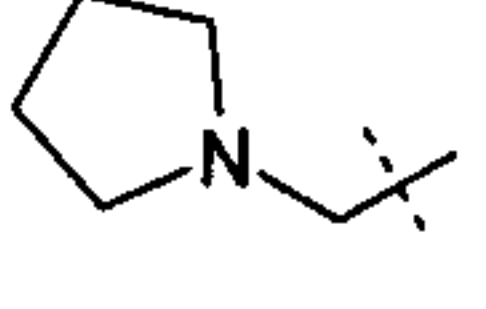
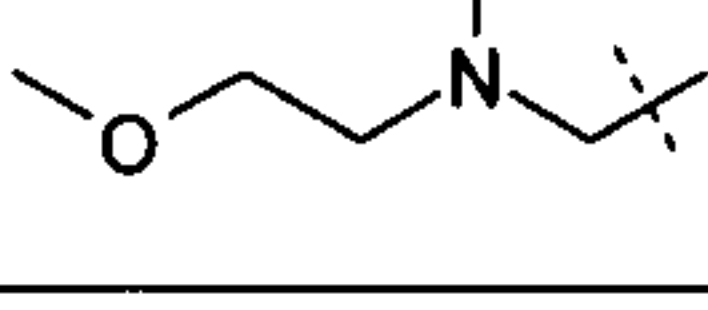
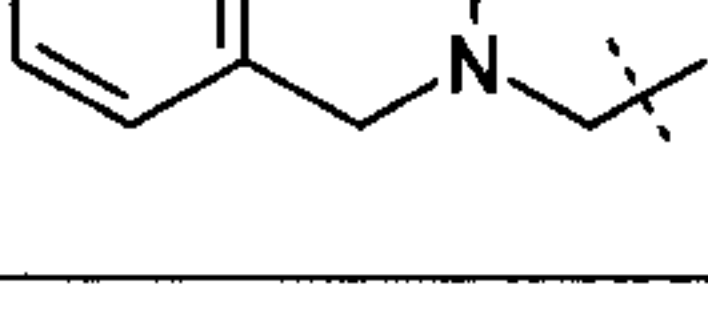
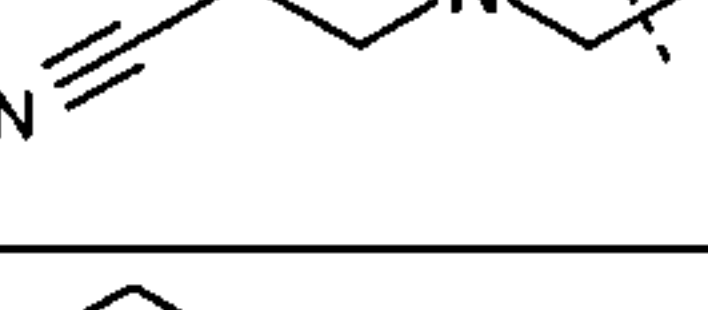
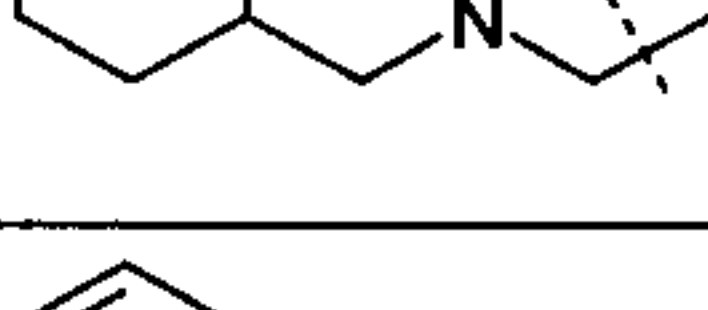
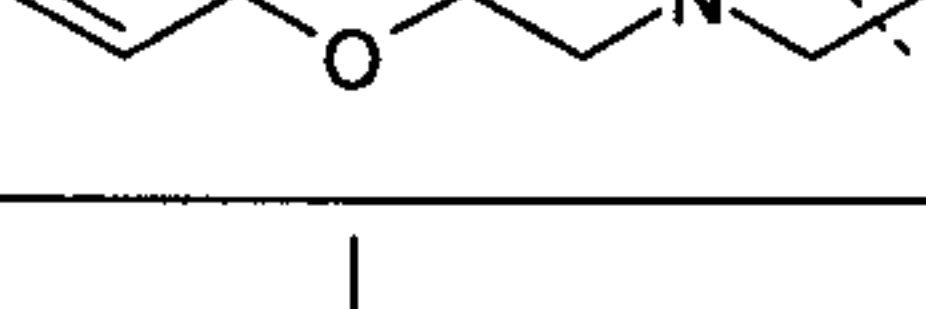
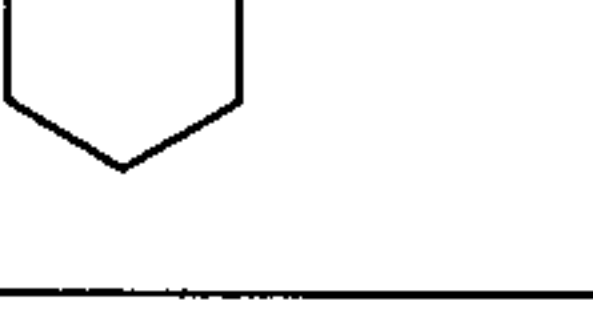
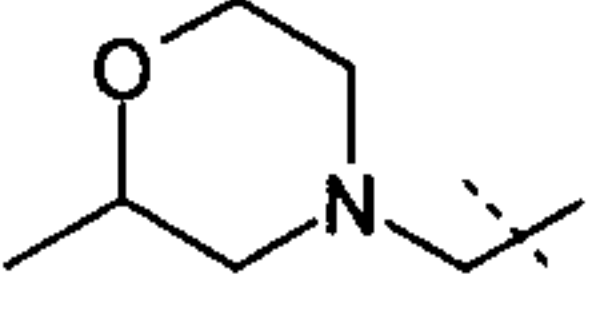
Example	R_1R_2N-X	L_1	L_2
1.326		H	F
1.327		H	F
1.328		H	F
1.329		H	F
1.330		H	F
1.331		H	F
1.332		H	F
1.333		H	F

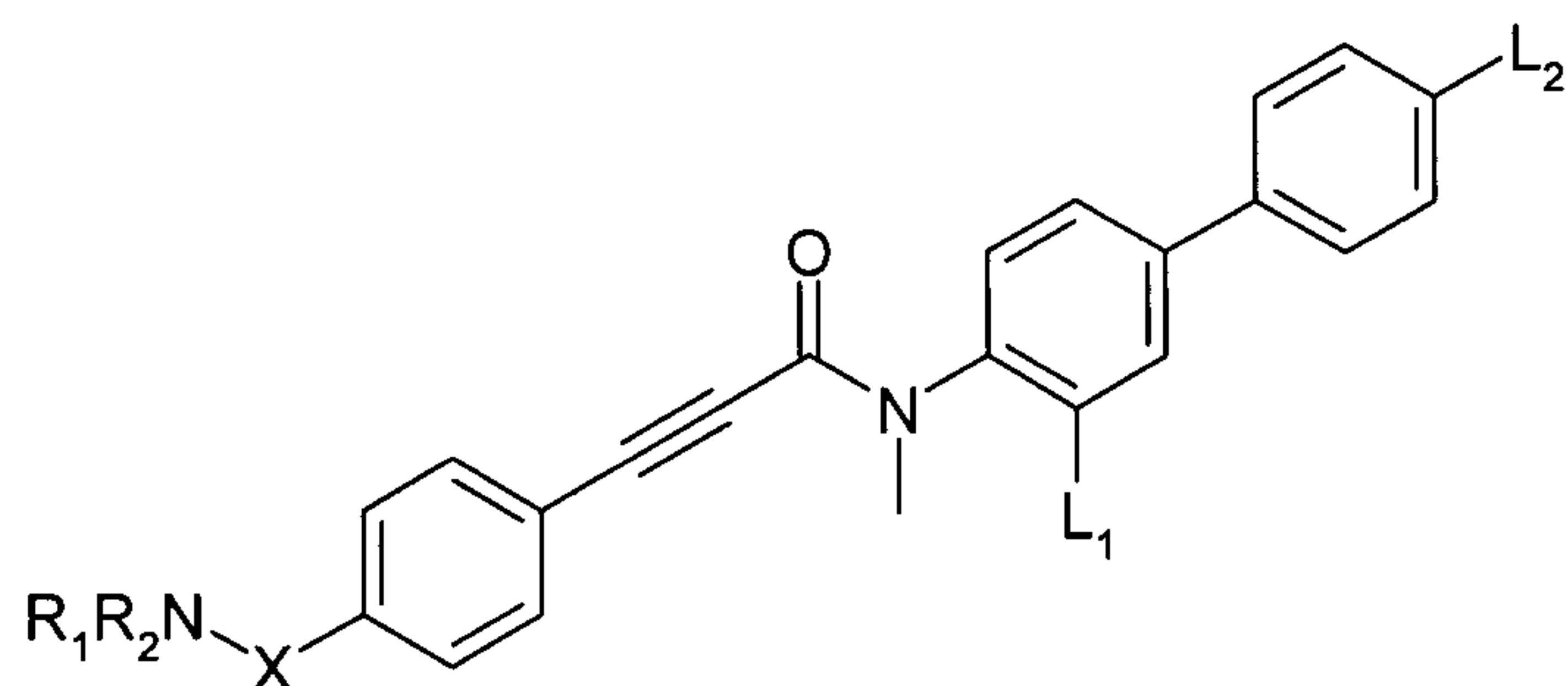
1.334		H	F
1.335		H	F
1.336		H	F
1.337		H	F
1.338		H	F
1.339		H	F
1.340		H	F
1.341		H	F
1.342		H	F
1.343		H	F
1.344		H	F
1.345		H	F
1.346		H	F
1.347		H	F
1.348		H	F

1.349		H	F

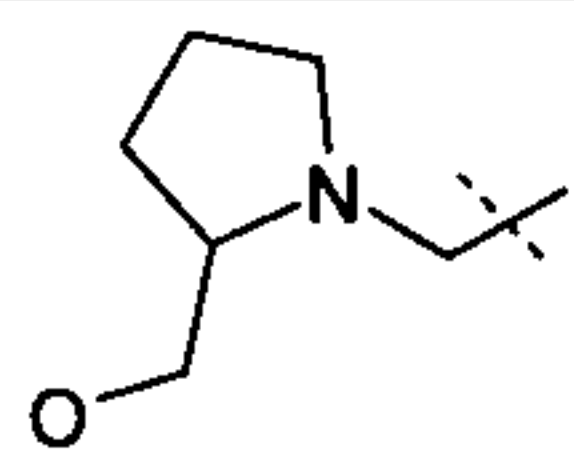
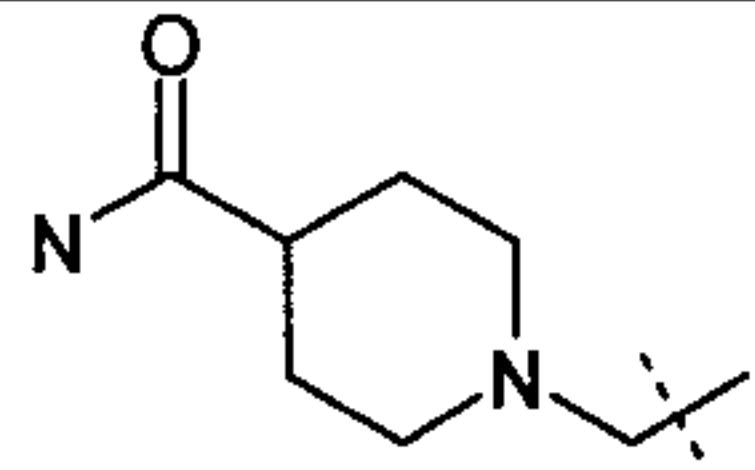
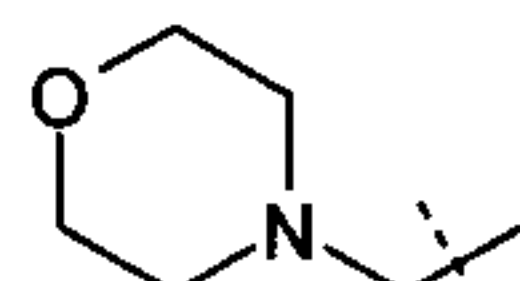
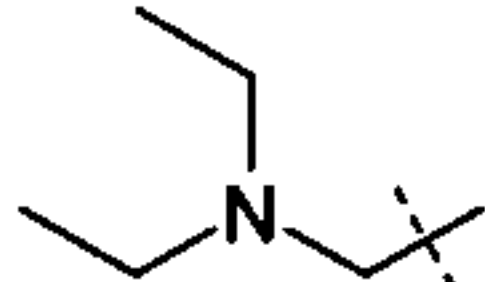
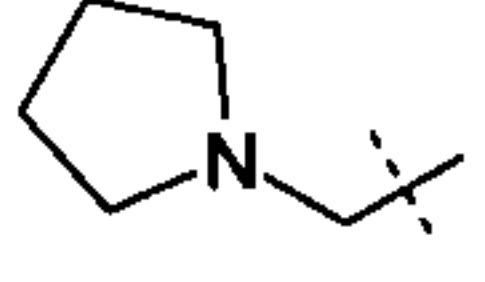
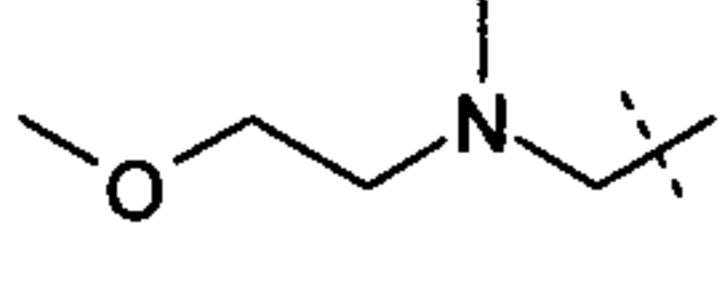
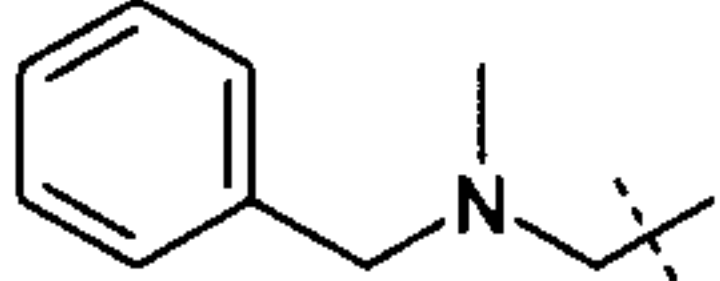
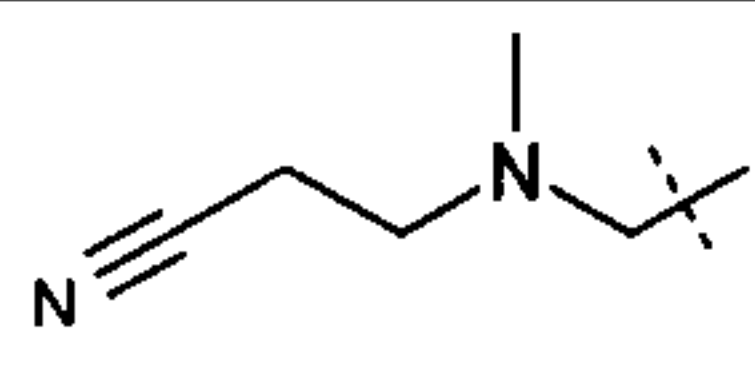
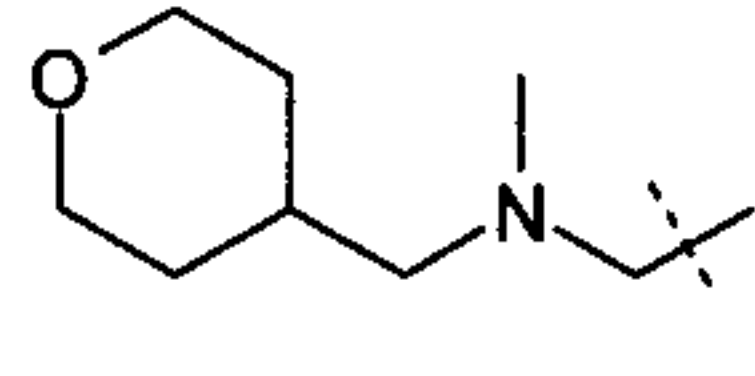
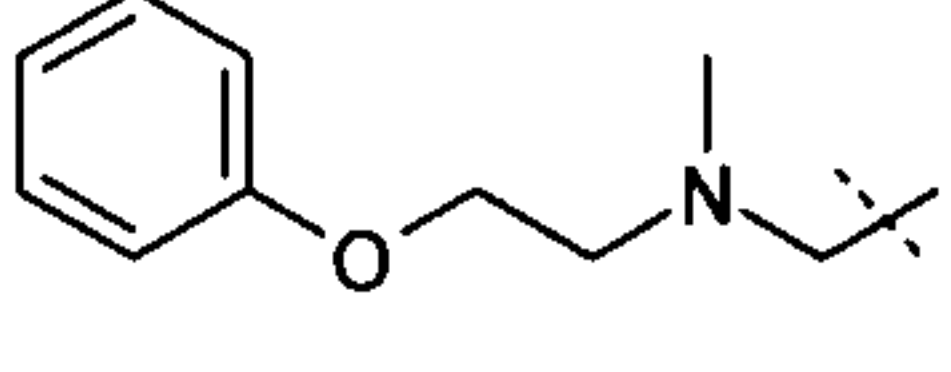
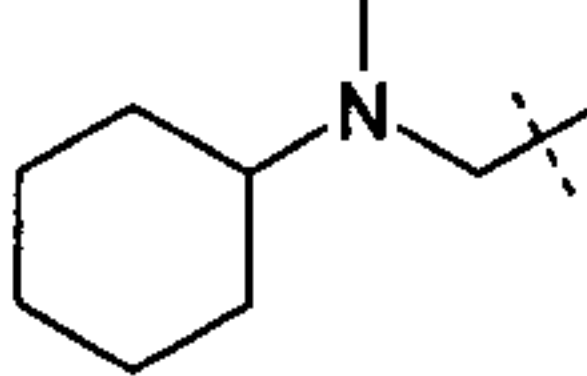
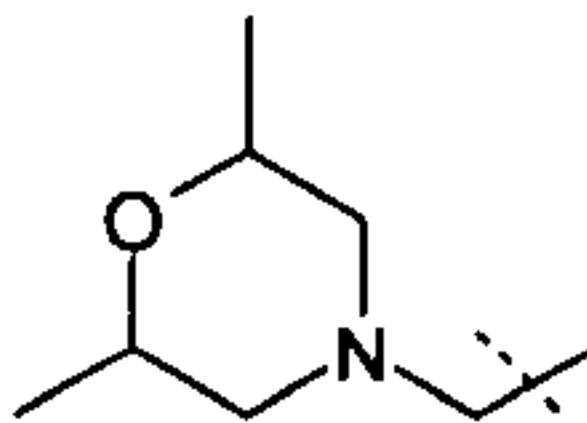


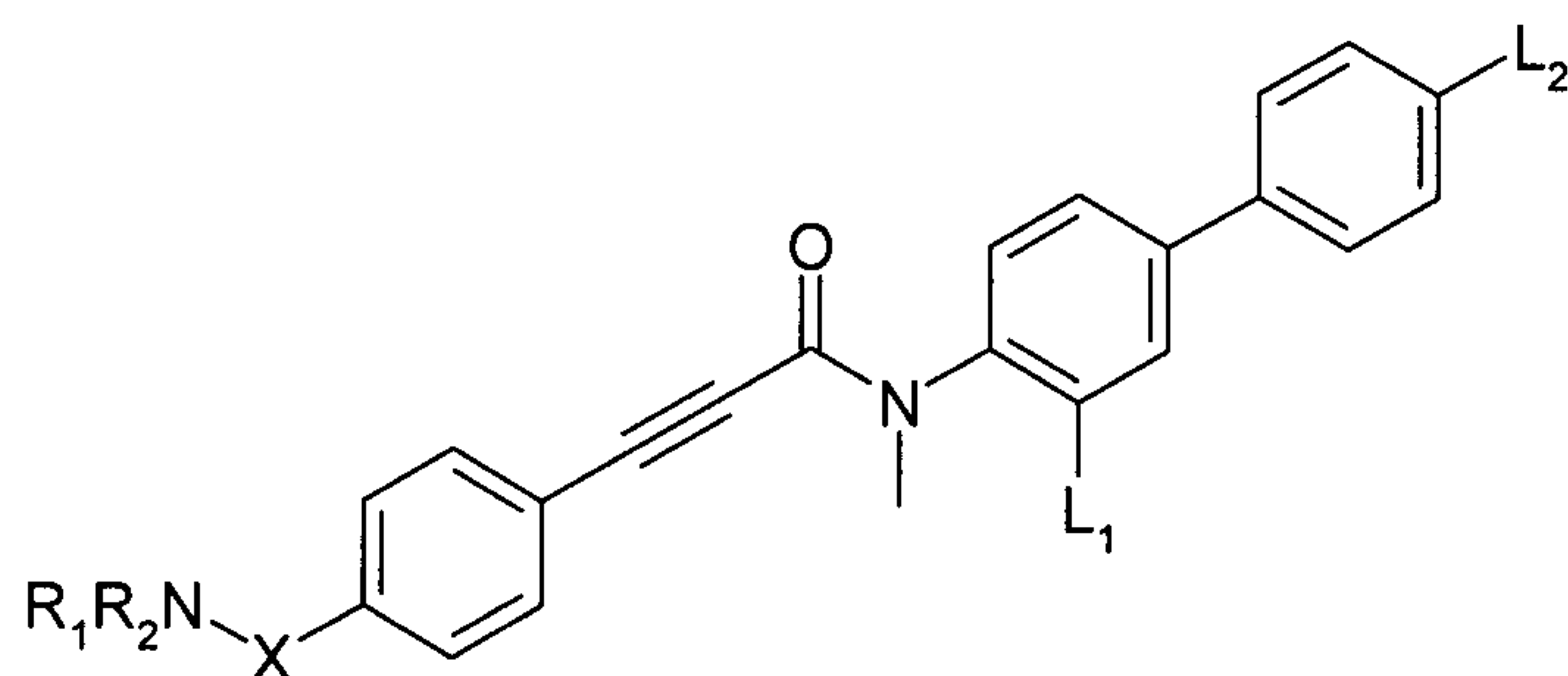
Example	$\text{R}_1\text{R}_2\text{N-X}$	L_1	L_2
1.350		F	CF_3
1.351		F	CF_3
1.352		F	CF_3
1.353		F	CF_3
1.354		F	CF_3
1.355		F	CF_3
1.356		F	CF_3
1.357		F	CF_3
1.358		F	CF_3

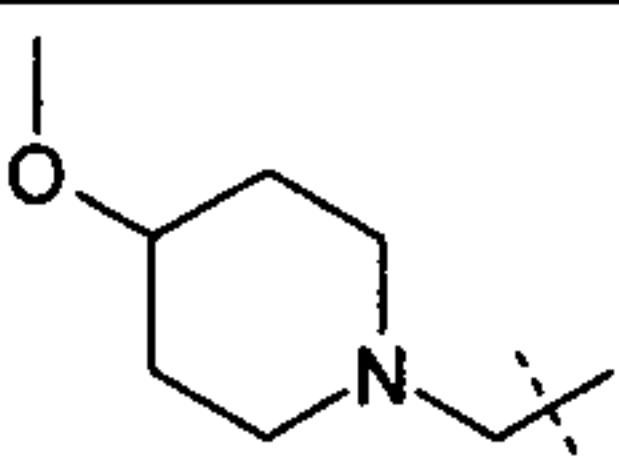
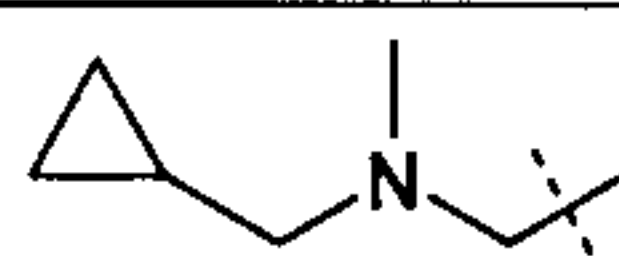
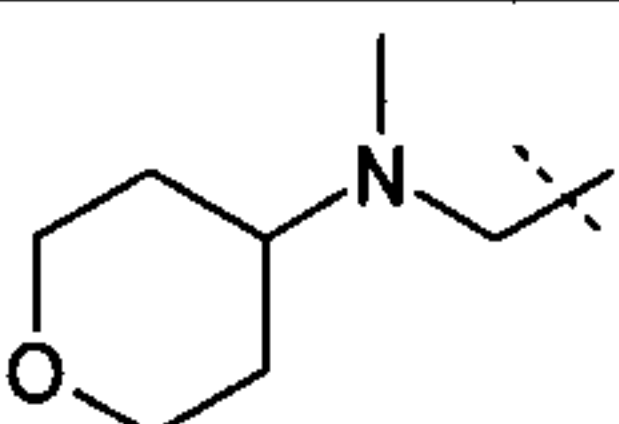
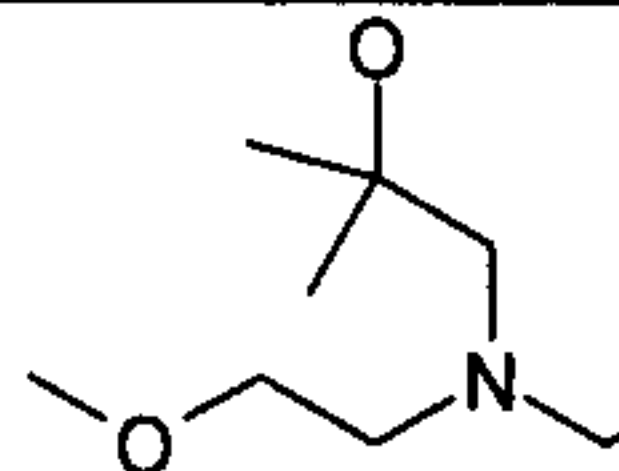
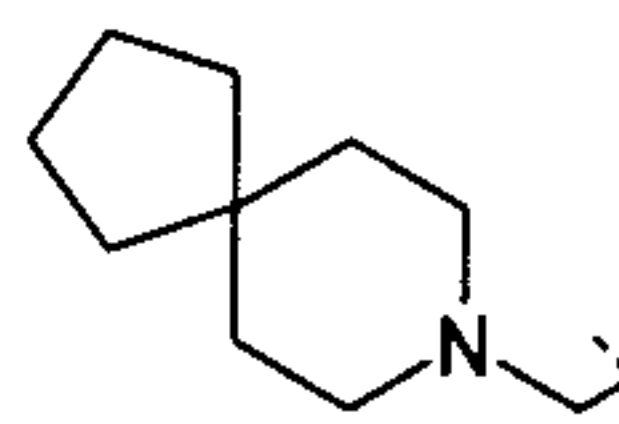
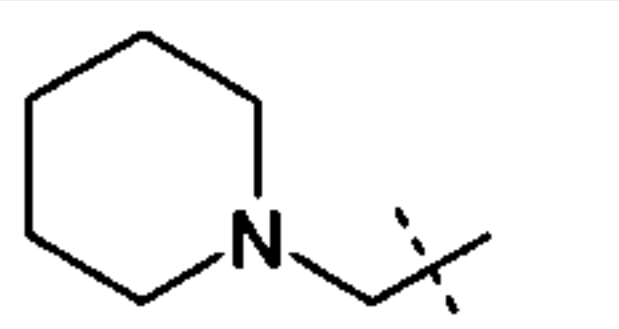
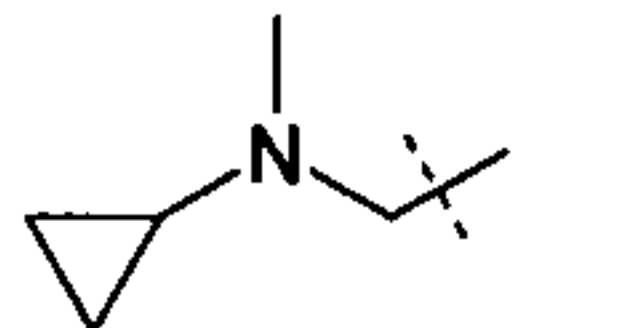
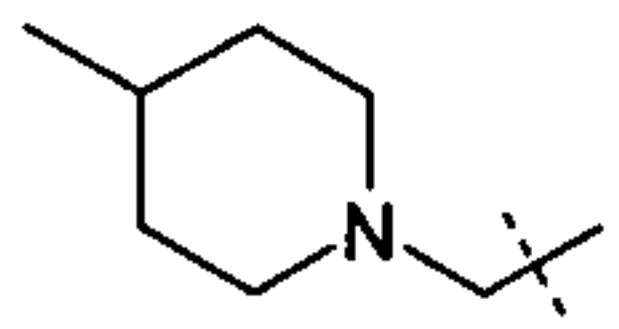
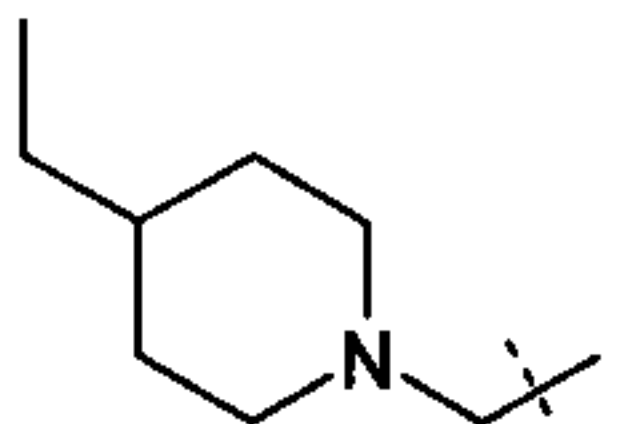
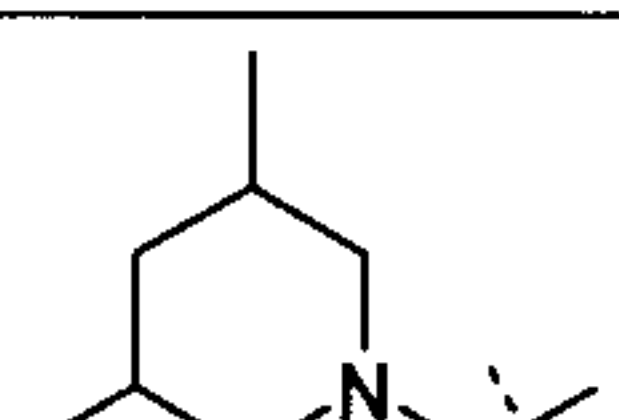
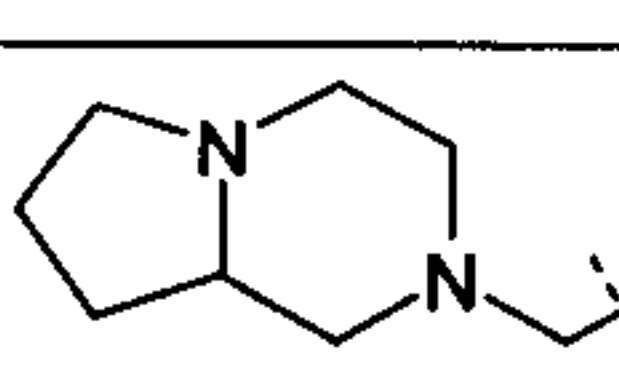
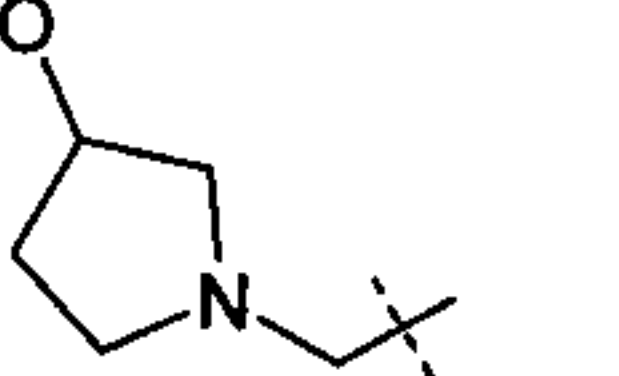
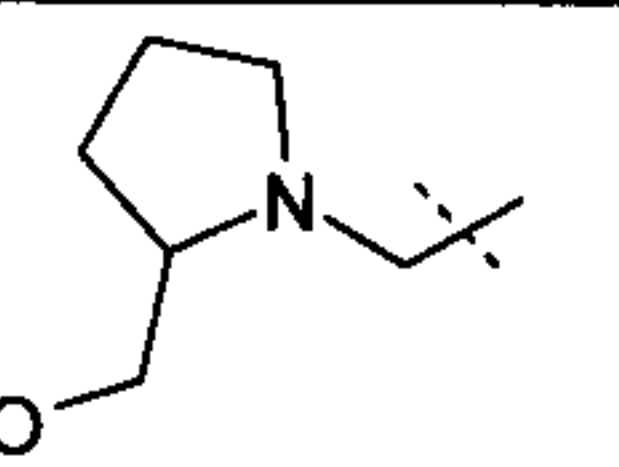
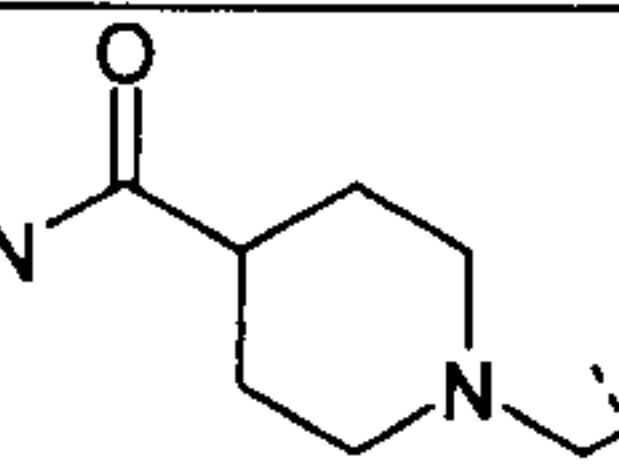
1.359		F	CF ₃
1.360		F	CF ₃
1.361		F	CF ₃
1.362		F	CF ₃
1.363		F	CF ₃
1.364		F	CF ₃
1.365		F	CF ₃
1.366		F	CF ₃
1.367		F	CF ₃
1.368		F	CF ₃
1.369		F	CF ₃
1.370		F	CF ₃
1.371		F	CF ₃
1.372		F	CF ₃
1.373		F	CF ₃

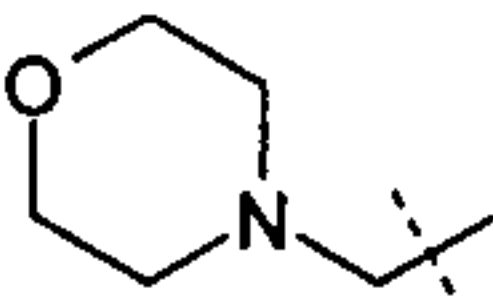
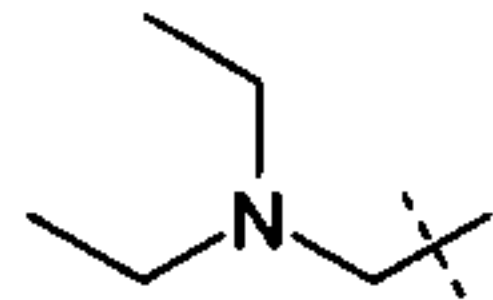
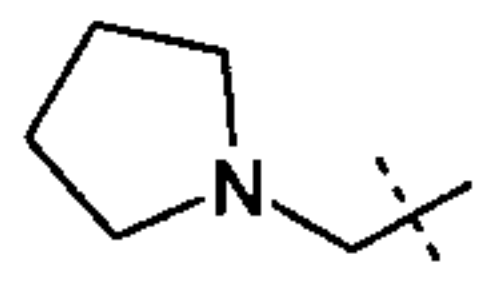
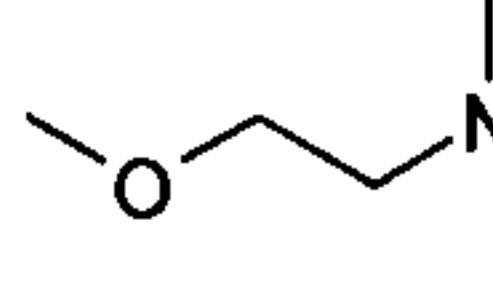
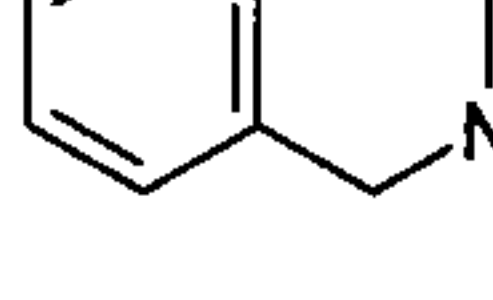
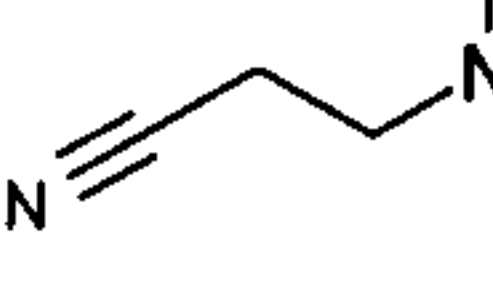
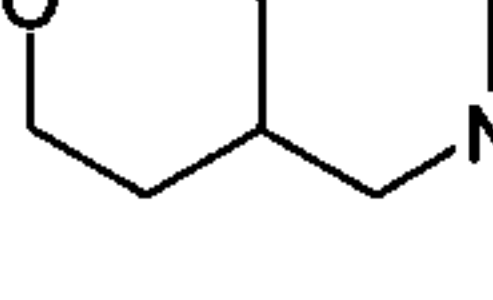
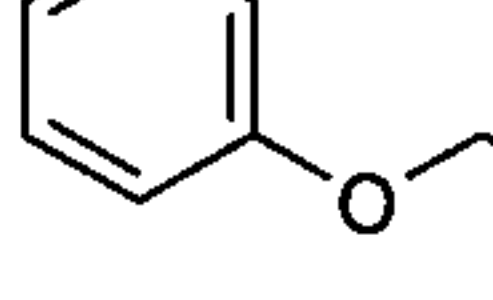
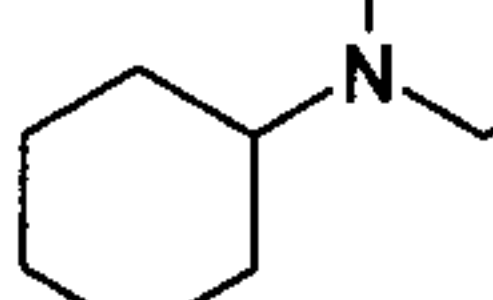
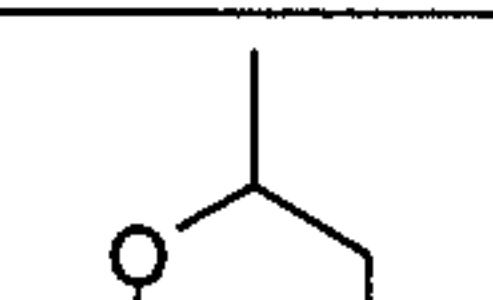


Example	$\text{R}_1\text{R}_2\text{N-X}$	L_1	L_2
1.374		F	Me
1.375		F	Me
1.376		F	Me
1.377		F	Me
1.378		F	Me
1.379		F	Me
1.380		F	Me
1.381		F	Me
1.382		F	Me
1.383		F	Me
1.384		F	Me
1.385		F	Me

1.386		F	Me
1.387		F	Me
1.388		F	Me
1.389		F	Me
1.390		F	Me
1.391		F	Me
1.392		F	Me
1.393		F	Me
1.394		F	Me
1.395		F	Me
1.396		F	Me
1.397		F	Me

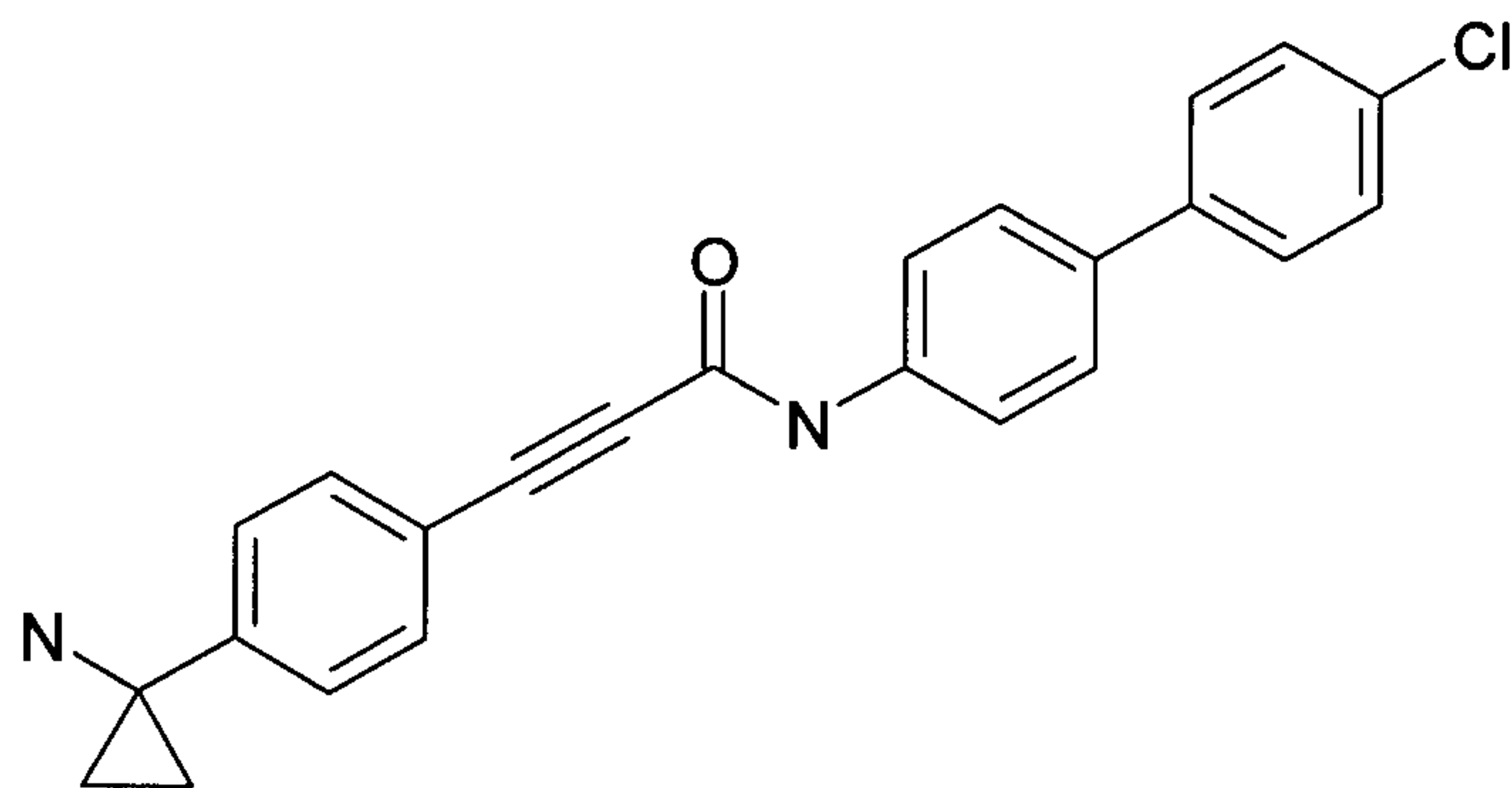


Example	R ₁ R ₂ N-X	L ₁	L ₂
1.398		F	F
1.399		F	F
1.400		F	F
1.401		F	F
1.402		F	F
1.403		F	F
1.404		F	F
1.405		F	F
1.406		F	F
1.407		F	F
1.408		F	F
1.409		F	F
1.410		F	F
1.411		F	F

1.412		F	F
1.413		F	F
1.414		F	F
1.415		F	F
1.416		F	F
1.417		F	F
1.418		F	F
1.419		F	F
1.420		F	F
1.421		F	F

Example 1.422:

3-[4-(1-amino-cyclopropyl)-phenyl]-propynoic acid-(4'-chloro-biphenyl-4-yl)-amide
5 trifluoroacetate



1.422.a: tert-butyl 1-(4-bromo-phenyl)-cyclopropyl]carbamate

10 g (29.04 mmol) 1-(4-bromobenzene)1-cyclopropanecarboxylic acid and 6.07 ml (43.55 mmol) triethylamine are dissolved in 63 ml *tert*-butanol. At RT 9.68 ml (43.55 mmol) diphenylphosphorylazide (DPPA) are added dropwise and refluxed for 15 h. Then 14.69 g (65.27 mmol) di-*tert*. butyl pyrocarbonate are added and the mixture is
5 refluxed for another 15 h. The solvent is distilled off and the residue is taken up in ethyl acetate, washed successively with 5% citric acid, saturated sodium hydrogen carbonate solution and saturated sodium chloride solution. The organic phase is dried with magnesium sulphate, filtered and the solvent is distilled off.

Yield: 6.00 g (66 % of theoretical)

10 $C_{14}H_{18}BrNO_2$ (M= 312.20)

Calc.: Molecular ion peak (M+H)⁺: 312/14 (Br) Found: Molecular ion peak (M+H)⁺: 312/14 (Br)

R_f value: 0.8 (silica gel, dichloromethane/ ethanol = 20:1)

15 1.422.b. *tert*-butyl [1-(4-iodo-phenyl)-cyclopropyl]carbamate

0.43 ml (4 mmol) N,N'-dimethylethylenediamine are added to a reaction mixture of 0.4 g (2 mmol) copper(I)iodide, 6.2 g (19.86 mmol) *tert*-butyl [1-(4-bromo-phenyl)-cyclopropyl]carbamate and 6 g (40 mmol) sodium iodide in 15 ml 1,4-dioxane and refluxed for 24 h under nitrogen. Then the cooled suspension is combined with 30%
20 ammonia solution, poured onto dist. water and extracted with dichloromethane. The organic phase is dried over sodium sulphate, filtered and the solvent is distilled off.

Yield: 6.60 g (93 % of theoretical)

$C_{14}H_{18}INO_2$ (M= 359.20)

Calc.: Molecular ion peak (M+H)⁺: 360 Found: Molecular ion peak (M+H)⁺:
25 360

R_f value: 0.8 (silica gel, dichloromethane/ ethanol = 50:1)

1.422.c. 3-[4-(1-*tert*-butoxycarbonyl-amino-cyclopropyl)-phenyl]-propynoic acid-(4'-chloro-biphenyl-4-yl)amide

30 1.4 g (4.2 mmol) caesium carbonate and 0.5 g (1.4 mmol) *tert*-butyl [1-(4-iodo-phenyl)-cyclopropyl]carbamate are placed in 20 ml THF and cooled to -15°C in the ice/methanol bath, rinsed with argon and degassed. To this reaction mixture are added successively 160 mg (0.14 mmol) tetrakis(triphenylphosphine) palladium and 30

mg (0.158 mmol) copper(I)iodide and the mixture is again degassed. 0.5 g (1.4 mmol) propynoic acid-(4'-chloro-biphenyl-4-yl)amide are finally added. The mixture is stirred for 24 hours at ambient temperature and the reaction mixture is then evaporated down. The residue is triturated with water and ethyl acetate, suction filtered, washed
5 with ethyl acetate and dried in the air.

Yield: 0.4 g (59 % of theoretical)

$C_{29}H_{27}ClN_2O_3$ (M= 486.99)

Calc.: Molecular ion peak (M+H)⁺: 487/89 (Cl)
(M+H)⁺: 487/89 (Cl)

Found: Molecular ion peak

10 R_f value: 0.62 (silica gel, cyclohexane/ethyl acetate 1:1)

1.422.d. 3-[4-(1-amino-cyclopropyl)phenyl]propynoic acid-(4'-chloro-biphenyl-4-yl)-amide trifluoroacetate

1 ml (12.92 mmol) trifluoroacetic acid are added to a solution of 0.24 g (0.49 mmol) 3-
15 [4-(1-*tert*-butoxycarbonyl-amino-cyclopropyl)-phenyl]-propynoic acid-(4'-chloro-biphenyl-4-yl)amide in 20 ml dichloromethane and stirred for 24 h. Then the solvent is eliminated by rotary evaporation and the residue is combined with toluene and again subjected to rotary evaporation. This residue is then triturated with dichloromethane, suction filtered and dried in the air.

20 Yield: 0.22 g (89 % of theoretical)

$C_{24}H_{19}ClN_2O \cdot C_2HF_3O_2$ (M=500.90)

Calc.: Molecular ion peak (M+H)⁺: 387 (Cl)

Found: Molecular ion

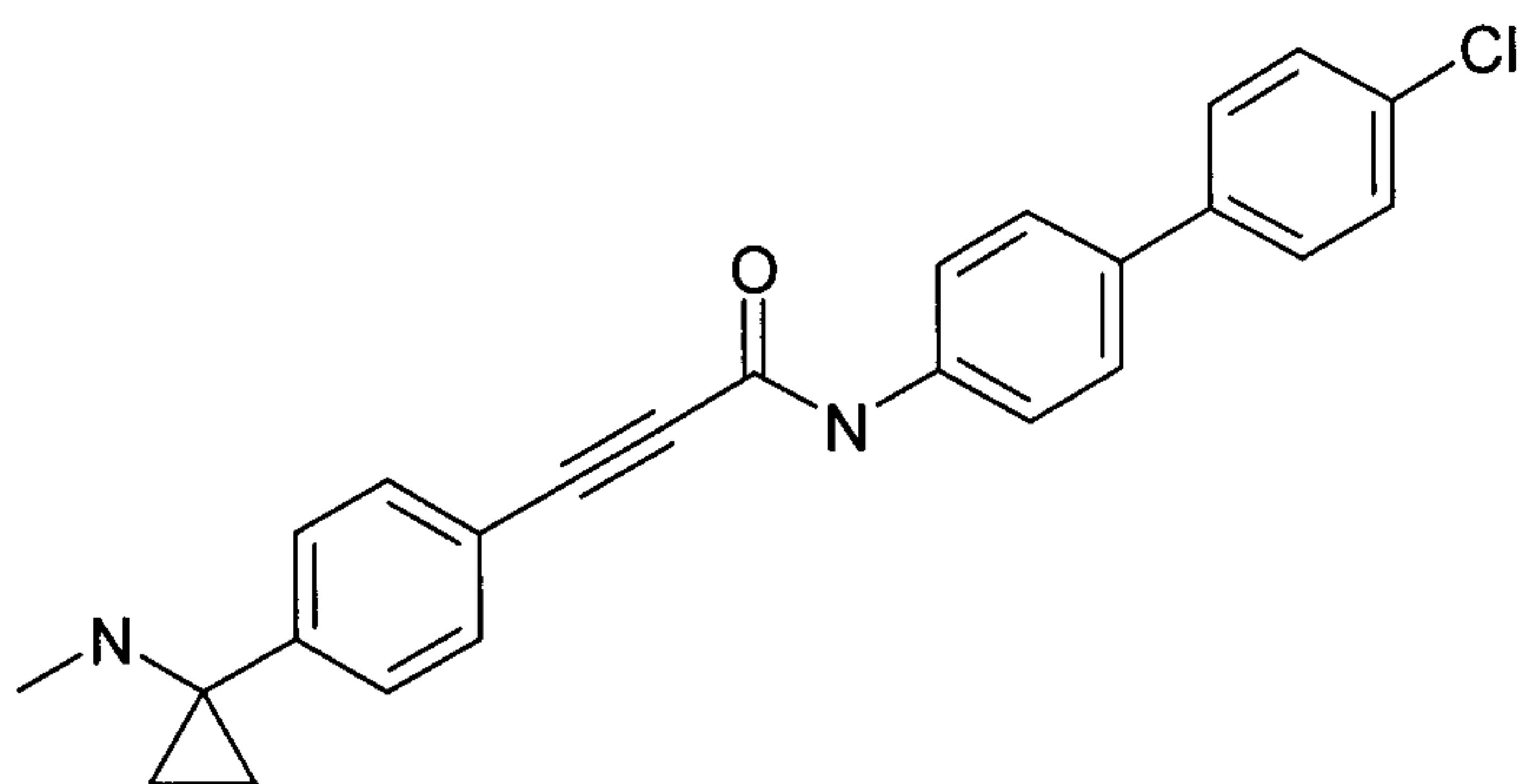
peak (M+H)⁺: 387 (Cl)

mp=160-164 °C

25

Example 1.423:

3-[4-(1-methylamino-cyclopropyl)phenyl]propynoic acid-(4'-chloro-biphenyl-4-yl)-amide trifluoroacetate



1.423.a: tert-butyl [1-(4-iodo-phenyl)-cyclopropyl]methyl-carbamate

131 mg (3 mmol) sodium hydride (55%) are added at RT to a solution of 1 g (2.78
5 mmol) tert-butyl [1-(4-iodo-phenyl)-cyclopropyl]carbamate in 20 ml DMF and the
mixture is stirred for 30 min at RT. Then 0.287 ml (4.4 mmol) methyl iodide are added
dropwise and the mixture is stirred for 24 hours. The solvent is eliminated by rotary
evaporation. The residue is extracted between water and ethyl acetate and the
organic phase is dried over sodium sulphate. The solvent is again eliminated by
10 rotary evaporation.

Yield: 1 g (96 % of theoretical)

C₁₅H₂₀INO₂ (M= 373.23)

Calc.: Molecular ion peak (M+H)⁺: 374

Found: Molecular ion peak

(M+H)⁺: 374

15 R_f value: 0.68 (silica gel, cyclohexane/ ethyl acetate 3:1)

1.423.b: 3-[4-(1-*tert*-butoxycarbonyl-methyl-amino-cyclopropyl)-phenyl]-propynoic
acid-(4'-chloro-biphenyl-4-yl)amide

2.28 g (7 mmol) caesium carbonate and 1 g (2.68 mmol) tert-butyl [1-(4-iodo-phenyl)-
20 cyclopropyl]-methylcarbamate are placed in 20 ml THF and cooled to -15°C in the
ice/methanol bath, rinsed with argon and degassed. To this reaction mixture are
added successively 180 mg (0.16 mmol) tetrakis(triphenylphosphine) palladium and 50
mg (0.263 mmol) copper(I)iodide and the mixture is again degassed. 0.75 g (2.9
mmol) propynoic acid-(4'-chloro-biphenyl-4-yl)amide are finally added. The mixture is
25 stirred for 24 hours at ambient temperature and the reaction mixture is then
evaporated down. The residue is extracted between water and ethyl acetate, the
organic phase is dried with sodium sulphate and the solvent is eliminated by rotary
evaporation. The purification is carried out by column chromatography on silica gel

(eluant: cyclohexane/ethyl acetate 2:1).

Yield: 0.75 g (56 % of theoretical)

C₃₀H₂₉ClN₂O₃ (M= 501.02)

Calc.: Molecular ion peak (M+H)⁺: 501/3 (Cl)

Found: Molecular ion

5 peak (M+H)⁺: 501/3 (Cl)

R_f value: 0.75 (silica gel, cyclohexane/ethyl acetate 1:1)

1.423.c: 3-[4-(1-methylamino-cyclopropyl)phenyl]propynoic acid-(4'-chloro-biphenyl-4-yl)-amide

10 Prepared analogously to Example 1.422.d from 3-[4-(1-*tert*-butoxycarbonyl-methyl-amino-cyclopropyl)-phenyl]-propynoic acid-(4'-chloro-biphenyl-4-yl)amide

Yield: 0.43 g (56 % of theoretical)

C₂₅H₂₁ClN₂O* C₂HF₃O₂ (M= 514.92)

Calc.: Molecular ion peak (M+H)⁺: 401/3 (Cl)

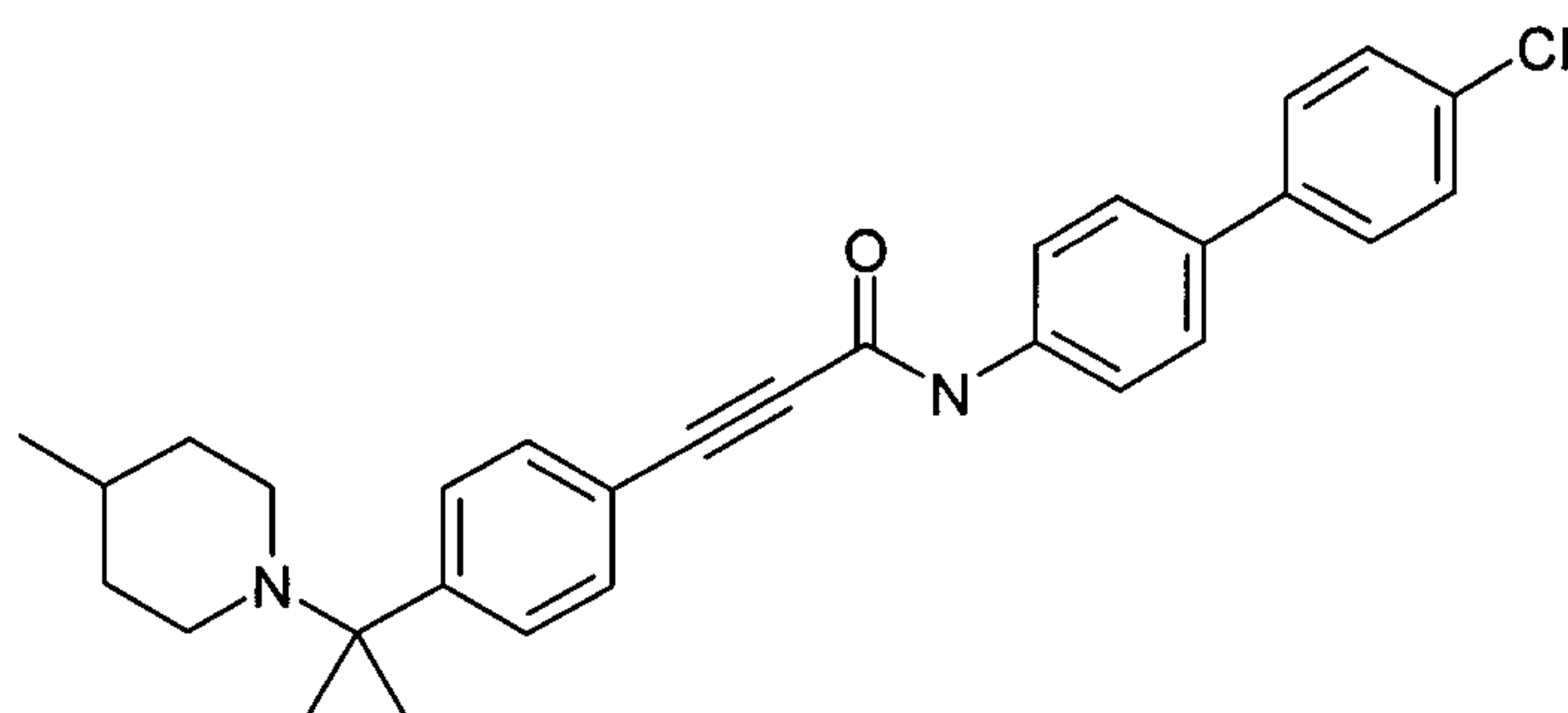
Found: Molecular ion

15 peak (M+H)⁺: 401/3 (Cl)

mp=217.3 °C

Example 1.424:

20 3-{4-[1-(4-methyl-piperidin-1-yl)-cyclopropyl]-phenyl}-propynoic acid(4'-chloro-biphenyl-4-yl)amide



25 1.424.a: 1-(4-iodo-phenyl)-cyclopropylamine

3 ml (38.76 mmol) trifluoroacetic acid are added to a solution of 1 g (2.78 mmol) *tert*-butyl [1-(4-iodo-phenyl)-cyclopropyl]carbamate in 40 ml dichloromethane and stirred for 24 h. Then the solvent is eliminated by rotary evaporation and the residue is

combined with toluene and then again eliminated by rotary evaporation. This residue is then added to a solution of 0.39 g (2.8 mmol) potassium carbonate in 20 ml of water and stirred for 30 min at RT. The aqueous phase is extracted with dichloromethane, the organic phase is dried with sodium sulphate and the solvent is eliminated by rotary evaporation.

Yield: 0.7 g (97 % of theoretical)

$C_9H_{10}IN$ (M= 259.09)

Calc.: Molecular ion peak $(M+H)^+$: 260

Found: Molecular ion peak

$(M+H)^+$: 260

1.424.b: 1[1-1-(4-iodo-phenyl)cyclopropyl]-4-methylpiperidine

0.55 g (4 mmol) potassium carbonate are added to a reaction mixture of 0.5 g (1.93 mmol) 1-(4-iodo-phenyl)-cyclopropylamine and 0.89 g (2 mmol) of 1,5-dibromo-3-methylpentane in 20 ml N,N-dimethylformamide and stirred at 80 °C for 24 h. Then the solvent is evaporated down and the residue is extracted between ethyl acetate and water. The organic phase is dried over sodium sulphate. The purification is carried out by column chromatography (eluant: cyclohexane/ethyl acetate 3:1).

Yield: 0.065 g (10 % of theoretical)

$C_{15}H_{20}IN$ (M= 341.23)

Calc.: Molecular ion peak $(M+H)^+$: 342

Found: Molecular ion peak

$(M+H)^+$: 342

R_f value: 0.65 (silica gel, cyclohexane/ethyl acetate 3:1)

1.424.c: 3-{4-[1-(4-methyl-piperidin-1-yl)-cyclopropyl]-phenyl}-propynoic acid(4'-chloro-biphenyl-4-yl)amide

Prepared analogously to Example 1.424.b from 1[1-1-(4-iodo-phenyl)cyclopropyl]-4-methylpiperidine and propynoic acid-(4'-chloro-biphenyl-4-yl)amide

Yield: 20 mg (24 % of theoretical)

$C_{30}H_{29}ClN_2O$ (M= 469.02)

Calc.: Molecular ion peak $(M+H)^+$: 469/71 (Cl)

Found: Molecular ion peak

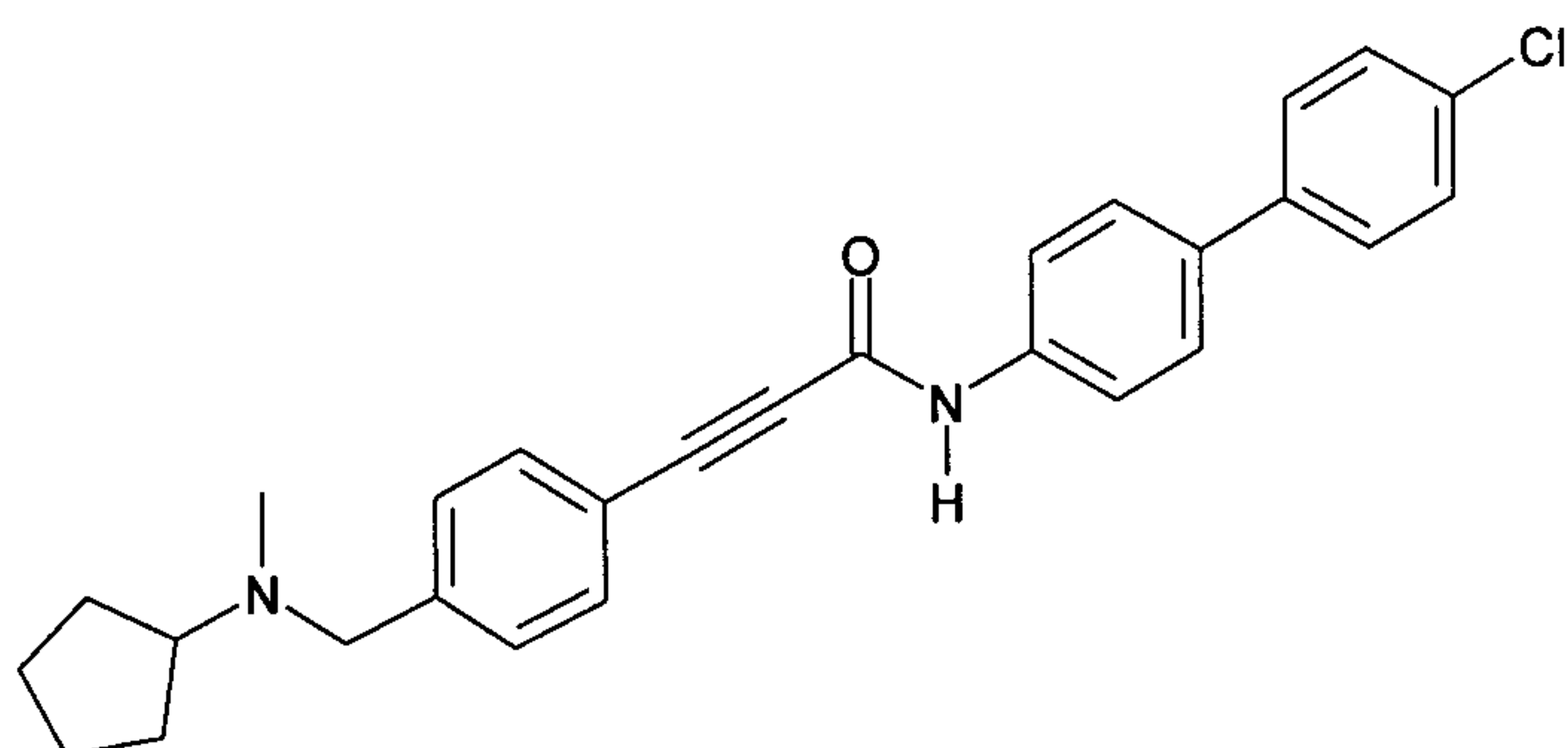
$(M+H)^+$: 469/71 (Cl)

R_f value: 0.3 (silica gel, cyclohexane/ethyl acetate 3:1)

mp=128-129 °C

Example 1.425:

3-{4-[cyclopentyl-methyl-amino)-methyl]-phenyl}-propynoic acid-(4'-chloro-biphenyl-4-yl)-amide



Prepared analogously to Example 1.40 d from 3-(4-chloromethyl-phenyl)-propynoic acid-(4'-chloro-biphenyl-4-yl)-amide and methyl-cyclopentylamine.

Yield: 10 mg (316 % of theoretical)

Melting point: 217-219°C

C₂₈H₂₇ClN₂O (M= 442.98)

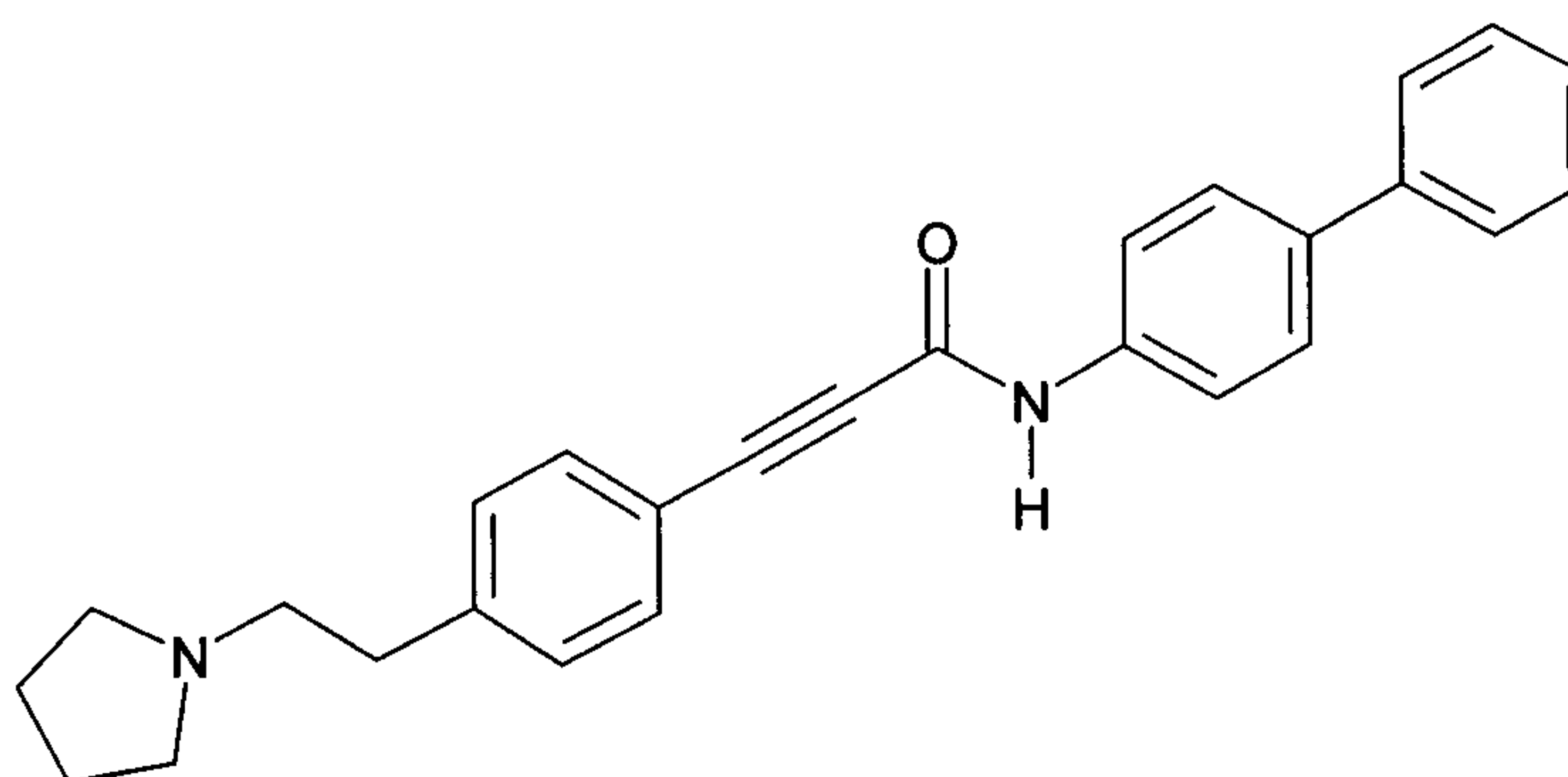
Calc.: Molecular ion peak (M+H)⁺: 443/45(Cl)

Found: Molecular ion peak

(M+H)⁺: 443/45(Cl)

Example 2.1.:

3-[4-(2-pyrrolidin-1-yl-ethyl)-phenyl]-propynoic acid-biphenyl-4-ylamide



2.1.a. 2-(4-iodo-phenyl)-ethanol

0.474 g (2.48 mmol) copper(I)iodide, 5 g (24.86 mmol) 2-(4-bromo-phenyl)-ethanol

and 7.45 g (49.73 mmol) sodium iodide are successively added to a flask under an

argon atmosphere. Then 0.438 g (4.97 mmol) dimethylenediamine and 25 ml dioxane are added and the reaction mixture is refluxed for 14 hours. Then the reaction mixture is combined with 20 ml concentrated ammonia solution at ambient temperature, with 100 ml of water diluted and extracted with dichloromethane. The organic phase is
 5 extracted three times with water and dried over sodium sulphate.

Yield: 5.4 g (87.5 % of theoretical)

C_8H_9IO (M= 248.06)

Calc.: Molecular ion peak (M)⁺: 248
 248

Found: Molecular ion peak (M)⁺:

10 R_f value: 0.6 (silica gel, dichloromethane/ ethanol = 10:1)

2.1.b. 2-(4-iodo-phenyl)-ethyl methanesulphonate

Prepared analogously to Example 1.2.b from 2-(4-iodo-phenyl)-ethanol and methanesulphonic acid chloride.

15 Yield: 5.7 g (77.4 % of theoretical)

$C_9H_{11}IO_3S$ (M= 326.15)

Calc.: Molecular ion peak (M)⁺: 326
 326

Found: Molecular ion peak (M)⁺:

20 2.1.c. 1-[2-(4-iodo-phenyl)-ethyl]-pyrrolidine

1 ml (12.26 mmol) pyrrolidine are added to a solution of 2 g (6.13 mmol) 2-(4-iodo-phenyl)-ethyl methanesulphonate in 30 ml DMF and the reaction solution is stirred for six hours at 70°C. The reaction mixture is poured onto water and extracted with ethyl acetate. The organic phase is extracted three times with water and dried over sodium
 25 sulphate. The sodium sulphate is separated off and the solvent removed.

Yield: 1.28 g (69.3 % of theoretical)

$C_{12}H_{16}IN$ (M= 301.17)

Calc.: Molecular ion peak (M+H)⁺: 302
 (M+H)⁺: 302

Found: Molecular ion peak

30 R_f value: 0.4 (silica gel, dichloromethane/ methanol = 10:1)

2.1.d. propynoic acid-biphenyl-4-ylamide

9.38 g (45.5 mmol) DCC are added batchwise to a solution of 2.89 g (41.36 mmol) propynoic acid in 100 ml dichloromethane at -15°C and stirred for one hour. Then a solution of 7 g (41.36 mmol) biphenyl-4-ylamine -15°C is added dropwise to 30 ml dichloromethane and stirred for two hours. After this time the cooling bath is removed and the reaction mixture is allowed to come up to ambient temperature. 20 g Celite are added to the reaction mixture and it is then filtered. The filtrate is evaporated down in vacuo. The residue is combined with acetonitrile and stirred. The suspension is filtered, the filtrate is evaporated down and the residue is stirred with petroleum ether and pentane. The solid is isolated by filtration.

10 Yield: 5.5 g (60.1 % of theoretical)

$\text{C}_{15}\text{H}_{11}\text{NO}$ (M= 221.26)

Calc.: Molecular ion peak $(\text{M}+\text{H})^{+}$: 222
 $(\text{M}+\text{H})^{+}$: 222

Found: Molecular ion peak

R_f value: 0.7 (silica gel, dichloromethane/ methanol = 10:1)

15

2.1.e. 3-[4-(2-pyrrolidin-1-yl-ethyl)-phenyl]-propynoic acid-biphenyl-4-ylamide
25 ml THF are degassed and combined with 0.25 g (0.83 mmol) 1-[2-(4-iodo-phenyl)-ethyl]-pyrrolidine, 0.81 g (2.49 mmol) caesium carbonate, 16 mg (0.083 mmol) copper(I)iodide and 38 mg (0.033 mmol) tetrakis(triphenyl)phosphine palladium. Then the mixture is again degassed, and 184 mg (0.83 mmol) propynoic acid-biphenyl-4-ylamide are added. The reaction mixture is stirred for 3 hours at ambient temperature, poured onto water and extracted with ethyl acetate. The organic phase is extracted three times with water and dried over sodium sulphate. The purification is carried out by column chromatography on silica gel (dichloromethane/ methanol/ ammonia =

20

25 10:1:0.1)

Yield: 90 mg (27.5 % of theoretical)

Melting point: $180-189^{\circ}\text{C}$

$\text{C}_{27}\text{H}_{26}\text{N}_2\text{O}$ (M= 394.52)

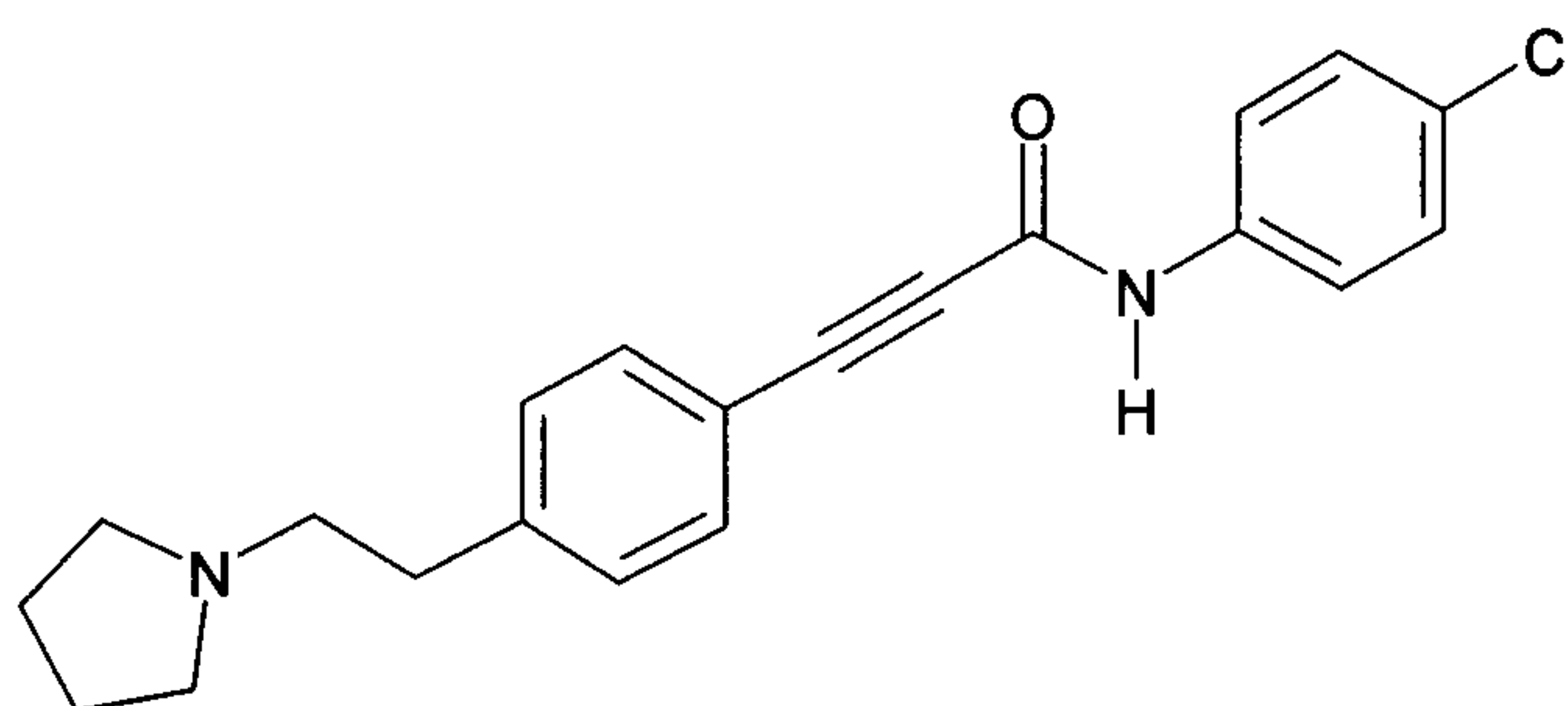
Calc.: Molecular ion peak $(\text{M}+\text{H})^{+}$: 395

Found: Molecular ion peak

30 $(\text{M}+\text{H})^{+}$: 395

Example 2.2.:

3-[4-(2-pyrrolidin-1-yl-ethyl)-phenyl]-propynoic acid-4-chloro-phenylamide



2.2.a. propynoic acid-(4-chloro-phenyl)-amide

Prepared analogously to Example 1.1.b from propynoic acid and 4-chloro-aniline.

5 Yield: 0.56 g (31.2 % of theoretical)

C_9H_6ClNO (M= 179.60)

Calc.: Molecular ion peak (M-H)⁻: 178/180

Found: Molecular ion

peak (M-H)⁻: 178/180

R_f value: 0.53 (silica gel, dichloromethane/ methanol/ammonia = 90:10:1)

10

2.2.b. 3-[4-(2-pyrrolidin-1-yl-ethyl)-phenyl]-propynoic acid-4-chloro-phenylamide

Prepared analogously to Example 2.1.e from propynoic acid-(4-chloro-phenyl)-amide and 1-[2-(4-iodo-phenyl)-ethyl]-pyrrolidine.

Yield: 80 mg (34.1 % of theoretical)

15 Melting point: 153-154⁰C

$C_{21}H_{21}ClN_2O$ (M= 352.86)

Calc.: Molecular ion peak (M+H)⁺: 353/355

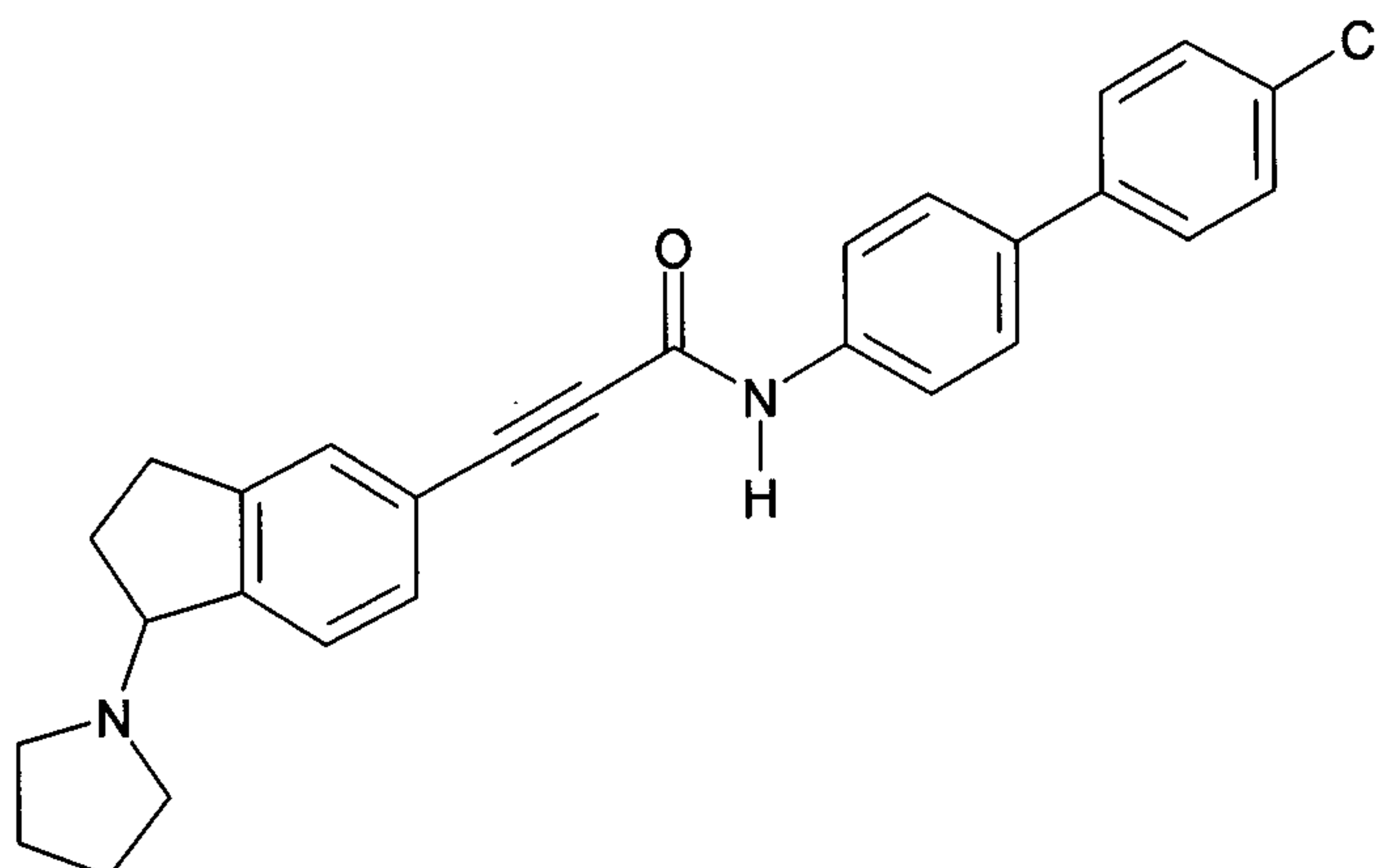
Found: Molecular ion

peak (M+H)⁺: 353/355

20

Example 2.3.:

3-(1-pyrrolidin-1-yl-indan-5-yl)-propynoic acid-(4'-chloro-biphenyl-4-yl)-amide



2.3.a. 5-bromo-indan-1-ol

0.987 g (23 mmol) sodium borohydride are added to a solution of 5 g (22.98 mmol) 5-bromo-1-indanone in 100 ml isopropanol at ambient temperature and the reaction mixture is stirred for five hours. Then an acidic pH is obtained by the careful addition of potassium hydrogen sulphate solution and the reaction mixture is extracted with tert.butylmethylether. The organic phase is extracted with saturated sodium chloride solution and then dried with magnesium sulphate. The filtrate is evaporated down in vacuo after removal of the magnesium sulphate. The residue is dissolved in tert.butylmethylether and extracted successively with dilute sodium hydrogen carbonate solution and water. Then it is dried over magnesium sulphate and filtered through activated charcoal. The filtrate is evaporated down *in vacuo*.

Yield: 3.6 g (73.5 % of theoretical)

C_9H_9BrO (M= 213.07)

R_f value: 0.6 (silica gel, petroleum ether/ethyl acetate = 6:4)

2.3.b. 5-bromo-1-chloro-indane

3.09 ml (37.45 mmol) thionyl chloride, dissolved in cooled dichloromethane, are added dropwise at $-10^{\circ}C$ to a solution of 3.8 g (17.83 mmol) 5-bromo-indan-1-ol in 200 ml dichloromethane. The reaction mixture is allowed to come up slowly to ambient temperature and stirred for 14 hours at ambient temperature. Then ice and 100 ml of dilute sodium hydrogen carbonate solution are added successively. The organic phase is extracted twice with 50 ml of water. The combined organic phases are dried over magnesium sulphate, filtered and the solvent is distilled off.

Yield: 3.7 g (90 % of theoretical)

C_9H_8BrCl (M= 231.52)

R_f value: 0.91 (silica gel, petroleum ether/ethyl acetate = 6:4)

2.3.c. 1-(5-bromo-indan-1-yl)-pyrrolidine

7 ml (85.23 mmol) pyrrolidine are added at 0°C to a solution of 3.71 g (16.92 mmol) 5-bromo-1-chloro-indane in 250 ml dichloromethane. The reaction mixture is allowed to come up to ambient temperature and stirred for 24 hours. Then it is extracted once with water and the organic phase is extracted with potassium hydrogen sulphate solution. The aqueous phase is extracted once with dichloromethane. Then the aqueous phase is made basic with sodium carbonate solution, in order to liberate the product. This solution is extracted with dichloromethane, the organic phase is extracted with water and dried over magnesium sulphate.

Yield: 1.81 g (42.4 % of theoretical)

C₁₃H₁₆BrN (M= 266.18)

Calc.: Molecular ion peak (M+H)⁺: 266/268
Found: Molecular ion peak (M+H)⁺: 266/268

2.3.d. 1-(5-iodo-indan-1-yl)-pyrrolidine

Prepared analogously to Example 2.1.a from 1-(5-bromo-indan-1-yl)-pyrrolidine.

Yield: 1.42 g (83.5 % of theoretical)

C₁₃H₁₆IN (M= 313.18)

Calc.: Molecular ion peak (M+H)⁺: 314
Found: Molecular ion peak (M+H)⁺: 314

2.3.e. (1-pyrrolidin-1-yl-indan-5-yl)-propynoic acid

Under an argon atmosphere at 0°C, 0.5 g (1.59 mmol) 1-(5-iodo-indan-1-yl)-pyrrolidine and 123 microlitres (2 mmol) propynoic acid are dissolved in 25 ml acetonitrile. 0.66 ml (4.79 mmol) triethylamine, 30 mg (0.16 mmol) copper(I)iodide and 80 mg (0.11 mmol) ditriphenylphosphine palladium dichloride are added to this solution and the mixture is stirred for two hours, while the solution is allowed to come up to ambient temperature. The purification is carried out by preparative HPLC (eluant: dichloromethane/methanol/ammonia = 8:2:0.2)

Yield 0.1 g (24.5 % of theoretical)

$C_{16}H_{17}NO_2$ (M= 255.31)

Calc.: Molecular ion peak $(M+H)^+$: 256

Found: Molecular ion peak

$(M+H)^+$: 256

5

2.3.f. 3-(1-pyrrolidin-1-yl-indan-5-yl)-propynoic acid-(4'-chloro-biphenyl-4-yl)-amide

A solution of 0.1 g (0.39 mmol) (1-pyrrolidin-1-yl-indan-5-yl)-propynoic acid and 47 microlitres (0.43 mmol) N-methylmorpholine in 5 ml absolute THF is combined with 56 microlitres (0.43 mmol) isobutyl chloroformate at $-15^{\circ}C$ and stirred for ten minutes.

10 Then 87 mg (0.43 mmol) 4'-chloro-biphenyl-4-ylamine are added at ambient temperature and the reaction mixture is stirred for 14 hours. Then 3 ml of dichloromethane are added to the reaction mixture and this is stirred for 48 hours. Then the reaction mixture is filtered, the filtrate is evaporated down, combined with water and extracted with dichloromethane. The organic phase is evaporated down.

15 The purification is carried out by preparative HPLC (eluant: dichloromethane / methanol/ammonia = 8:2:0.2)

Yield: 9 mg (5.7 % of theoretical)

$C_{28}H_{25}ClN_2O$ (M= 440.97)

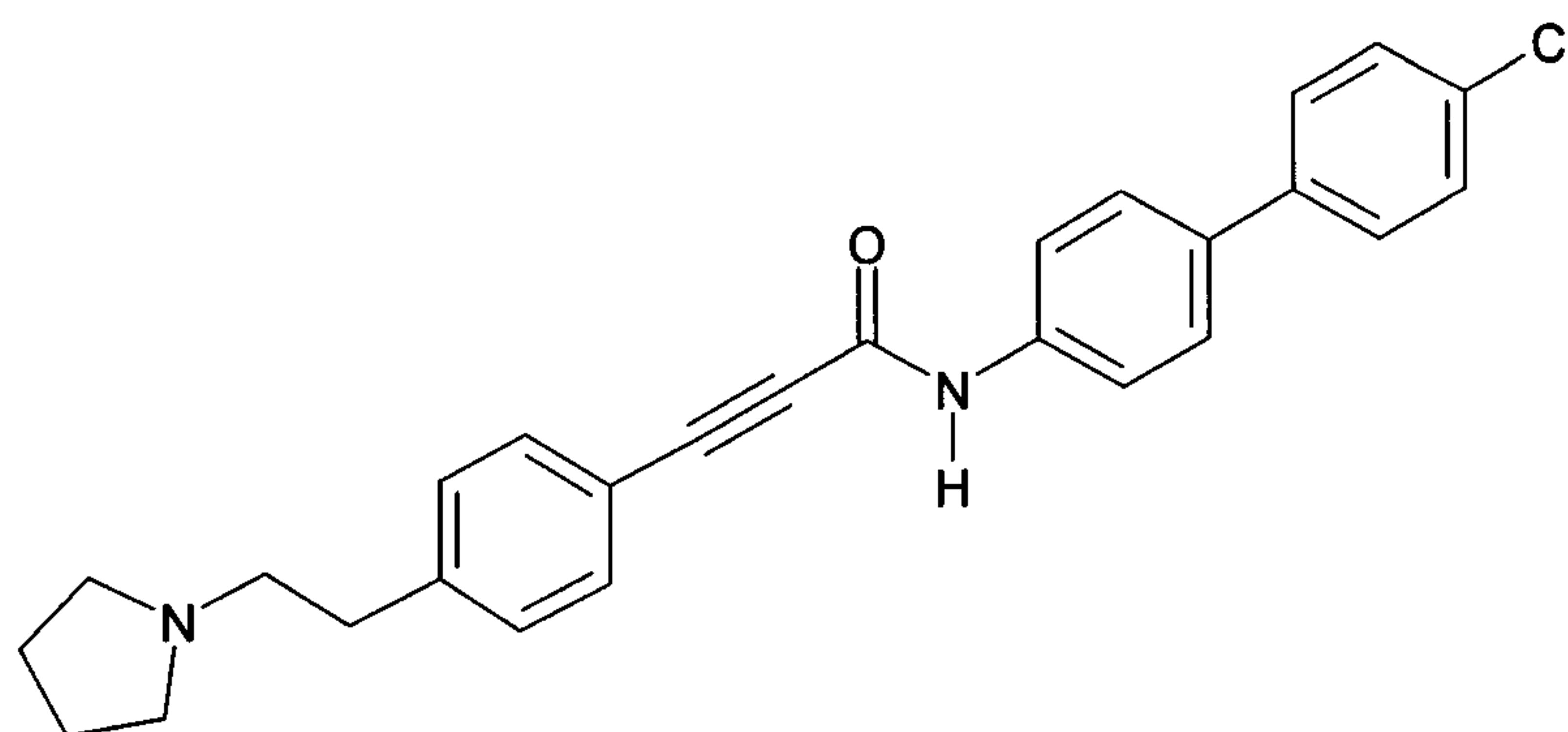
Calc.: Molecular ion peak $(M+H)^+$: 441/443

Found: Molecular ion

20 peak $(M+H)^+$: 441/443

Example 2.4.:

3-[4-(2-pyrrolidin-1-yl-ethyl)-phenyl]-propynoic acid-(4'-chloro-biphenyl-4-yl)-amide



25

2.3.a. 3-[4-(2-pyrrolidin-1-yl-ethyl)-phenyl]-propynoic acid-(4'-chloro-biphenyl-4-yl)-amide

Prepared analogously to Example 2.1.e from propynoic acid-(4'-chloro-biphenyl-4-yl)-amide and 1-[2-(4-iodo-phenyl)-ethyl]-pyrrolidine.

Yield: 70 mg (32.8 % of theoretical)

Melting point: 217-218 C

5 C₂₇H₂₅ClN₂O (M= 428.96)

Calc.: Molecular ion peak (M+H)⁺: 429/431

Found: Molecular ion

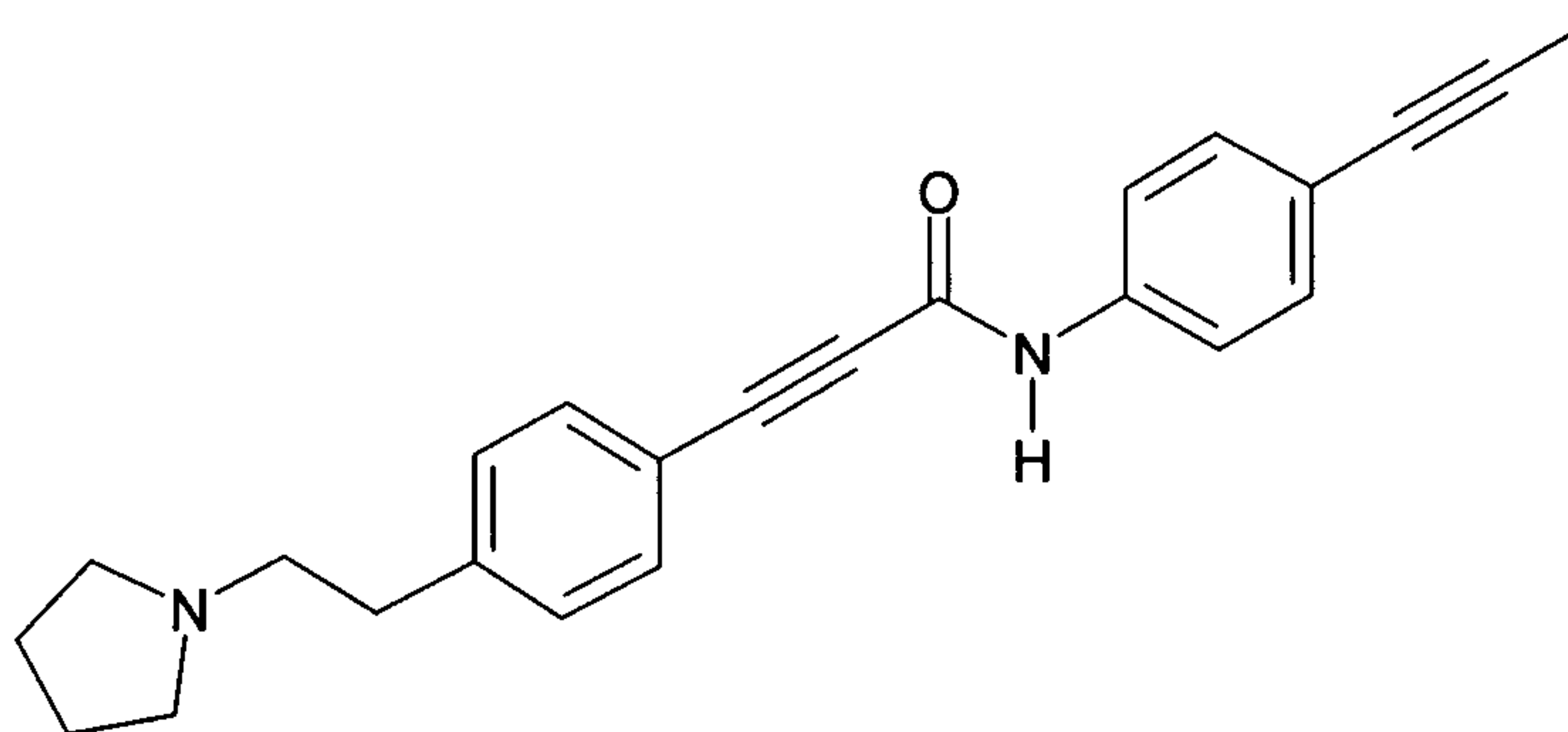
peak (M+H)⁺: 429/431

R_f value: 0.3 (silica gel, dichloromethane/ methanol=10:1)

10

Example 2.5.:

3-[4-(2-pyrrolidin-1-yl-ethyl)-phenyl]-propynoic acid-(4-prop-1-ynyl-phenyl)-amide



15 2.4.a. 3-[4-(2-pyrrolidin-1-yl-ethyl)-phenyl]-propynoic acid-(4-prop-1-ynyl-phenyl)-amide

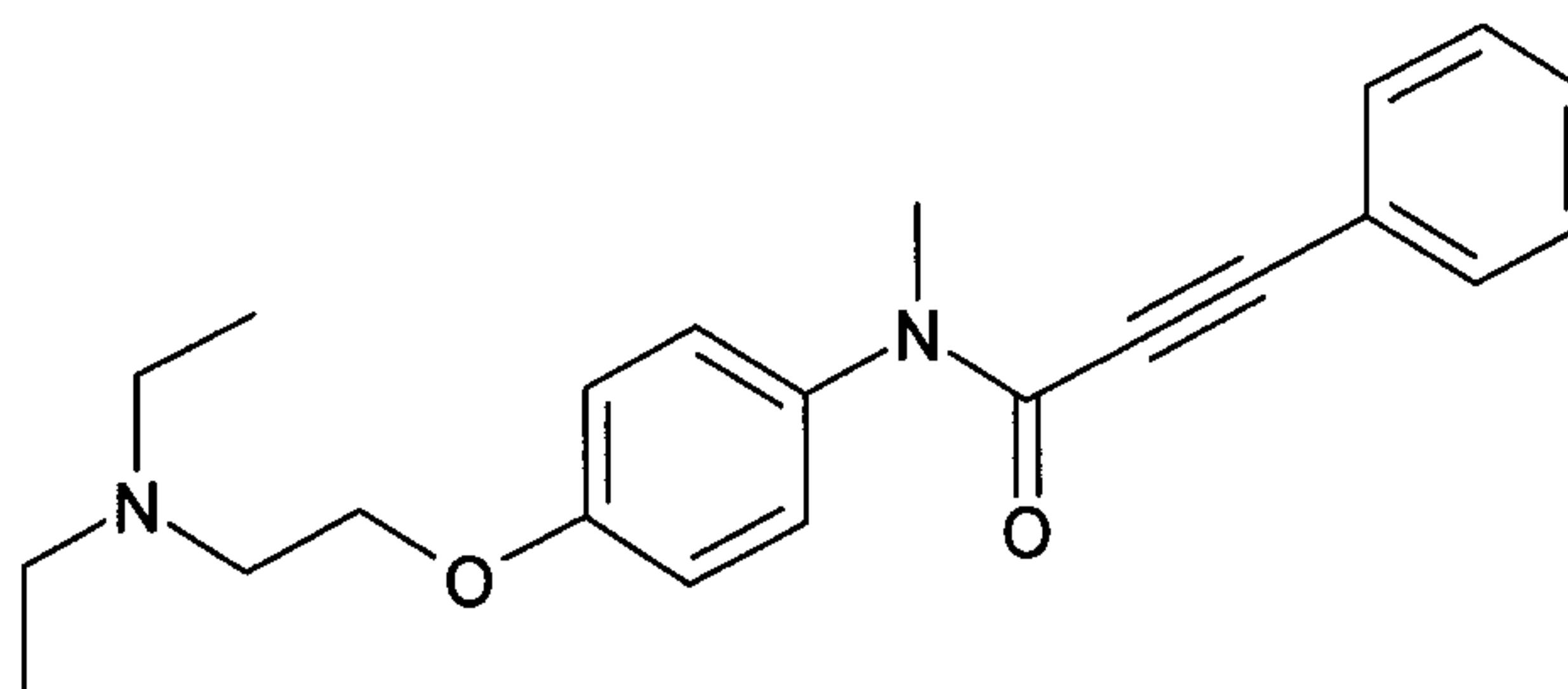
Prepared analogously to Example 2.1.e from propynoic acid- (4-prop-1-ynyl-phenyl)-amide and 1-[2-(4-iodo-phenyl)-ethyl]-pyrrolidine.

Yield: 20 mg (11 % of theoretical)

20 Melting point: 198-199 C

C₂₄H₂₄N₂O (M= 356.47)

R_f value: 0.1 (silica gel, dichloromethane/ methanol=10:1)

Example 3.1.:**3-phenyl-propynoic acid-[4-(2-diethylamino-ethoxy)-phenyl]-methyl-amide****3.1.a. diethyl-[2-(4-nitro-phenoxy)-ethyl]-amine**

- 5 88.7 g (515.41 mmol) (2-chloro-ethyl)-diethyl-amine-hydrochloride are added at ambient temperature to a suspension of 71.7 g (515.41 mmol) p-nitrophenol and 284.94 g (2.061 mol) potassium carbonate in 600 ml DMF and the reaction mixture is heated to 80°C for eight hours. The reaction mixture is evaporated down and the residue poured onto water and extracted with ethyl acetate. The organic phase is
- 10 extracted three times with water and dried over sodium sulphate. The desiccant is filtered off and the filtrate is evaporated down.

Yield: 110.52 g (90 % of theoretical)

C₁₂H₁₈N₂O₃ (M= 238.28)

R_f value: 0.52 (silica gel, dichloromethane/ methanol = 10:1)

15

3.1.b. 4-(2-diethylamino-ethoxy)-phenylamine

A reaction mixture of 110.52 g (0.464 mol) diethyl-[2-(4-nitro-phenoxy)-ethyl]-amine and 17 g Raney nickel in 700 ml of methanol is hydrogenated for 30 hours at 20°C and 3 bar hydrogen. The catalyst is filtered off and the filtrate is evaporated down.

- 20 Yield: 93 g (96.2 % of theoretical)

C₁₂H₂₀N₂O (M= 208.30)

Calc.: Molecular ion peak (M)⁺: 209

Found: Molecular ion peak (M)⁺:

209

- 25 3.1.c. methyl [4-(2-diethylamino-ethoxy)-phenyl]-carbamate

76.38 g (366.66 mmol) 4-(2-diethylamino-ethoxy)-phenylamine and 101.65 ml (733.33 mmol) triethylamine are dissolved in 400 ml THF. A solution of 49.16 g (366.66 mmol) dimethylpyrocarbonate in 200 ml THF is added dropwise to this solution within 45 minutes at 25°C and the mixture is stirred for two hours at ambient temperature.

The reaction mixture is evaporated down, the residue is added to water and extracted with ethyl acetate. The combined organic phases are extracted twice with water. The organic phase is evaporated down, during which time a precipitate forms, which is filtered off. The filtrate is evaporated down further. The purification is carried out by column chromatography on aluminium oxide (eluant: ethyl acetate/ petroleum ether= 3:1).

Yield: 63.3 g (64.8 % of theoretical)

$C_{14}H_{22}N_2O_3$ (M= 266.34)

Calc.: Molecular ion peak (M+H)⁺: 267

Found: Molecular ion peak

(M+H)⁺: 267

R_f value: 0.62 (aluminium oxide, ethyl acetate/ petroleum ether = 3:1)

3.1.d. [4-(2-diethylamino-ethoxy)-phenyl]-methyl-amine

30 g (112.63 mmol) methyl [4-(2-diethylamino-ethoxy)-phenyl]-carbamate, dissolved

in 300 ml absolute THF, are slowly added dropwise to a suspension of 10.68 g

(281.59 mmol) lithium aluminium hydride in 600 ml absolute THF while cooling with

ice under a nitrogen atmosphere. Then the mixture is stirred for 14 hours, while the

reaction mixture is allowed to come up to ambient temperature. Then after the

reaction has been monitored 7 g lithium aluminium hydride are added and the mixture

is stirred for 14 hours. The reaction is stopped by the addition of 60 ml 20% sodium

hydroxide solution. The precipitate is filtered off and rinsed with diisopropylether. The

filtrate is dried over sodium sulphate and the solvent is distilled off.

Yield: 24.7 g (98.6 % of theoretical)

$C_{13}H_{22}N_2O$ (M= 222.33)

Calc.: Molecular ion peak (M+H)⁺: 223

Found: Molecular ion peak

(M+H)⁺: 223

R_f value: 0.44 (silica gel, dichloromethane/ methanol/ammonia = 10:1)

3.1.e. 3-phenyl-propynoic acid-[4-(2-diethylamino-ethoxy)-phenyl]-methyl-amide

A solution of 0.29 g (2 mmol) phenyl-propynoic acid, 0.44 g (2 mmol) [4-(2-

diethylamino-ethoxy)-phenyl]-methyl-amine, 0.7 g (2.2 mmol) TBTU 0.29 g (2.2 mmol)

HOBt and 0.51 ml (3 mmol) Hünig base in 30 ml THF and 2 ml DMF is stirred for 14

hours at ambient temperature. The reaction mixture is evaporated down. The

purification is carried out by column chromatography on silica gel (dichloromethane/ methanol = 80:20)

Yield: 130 mg (18.5 % of theoretical)

C₂₂H₂₆N₂O₂ (M= 350.46)

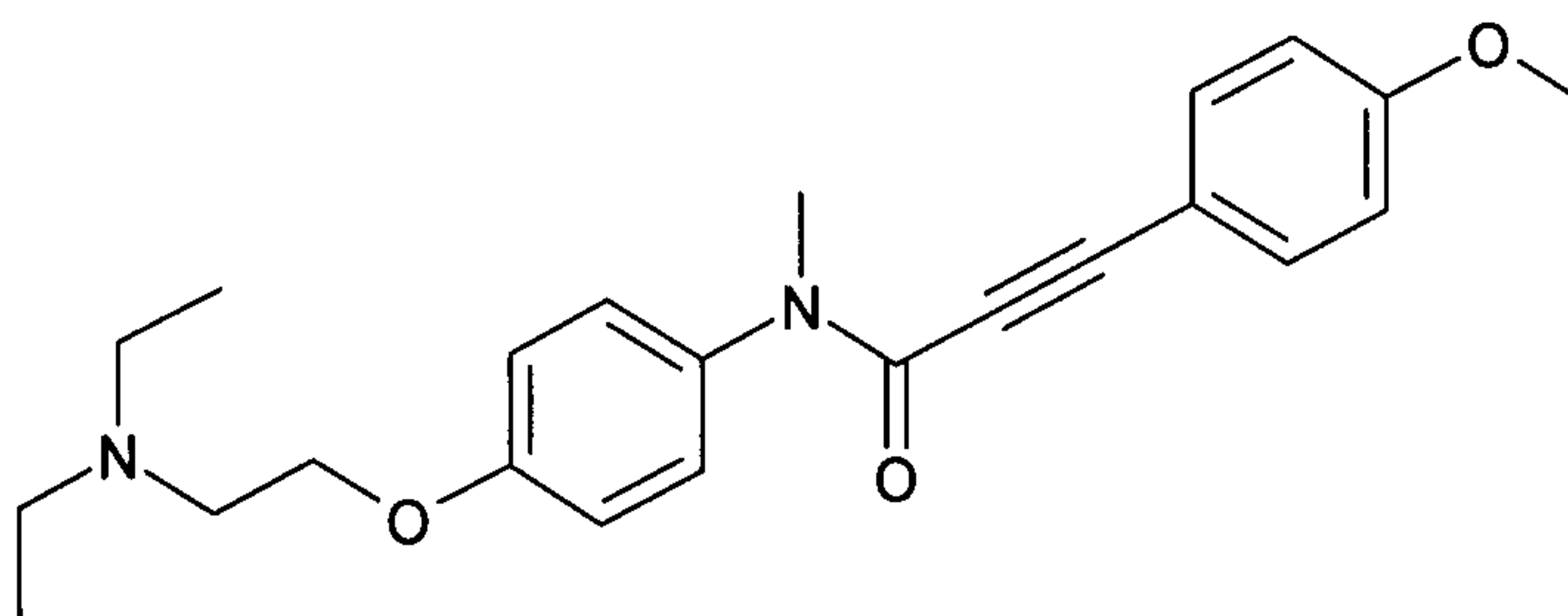
5 Calc.: Molecular ion peak (M+H)⁺: 351
(M+H)⁺: 351

Found: Molecular ion peak

R_f value: 0.39 (silica gel, dichloromethane/ methanol = 80:20)

10 **Example 3.2.:**

3-(4-methoxy-phenyl)-propynoic acid-[4-(2-diethylamino-ethoxy)-phenyl]-methyl-
amide



3.2.a. 3-(4-methoxy-phenyl)-propynoic acid-[4-(2-diethylamino-ethoxy)-phenyl]-
15 methyl-amide

Prepared analogously to Example 3.1.e from [4-(2-diethylamino-ethoxy)-phenyl]-
methyl-amine and (4-methoxy-phenyl)-propynoic acid in dichloromethane as solvent.

Yield: 300 mg (46.3 % of theoretical)

C₂₃H₂₈N₂O₃ (M= 380.49)

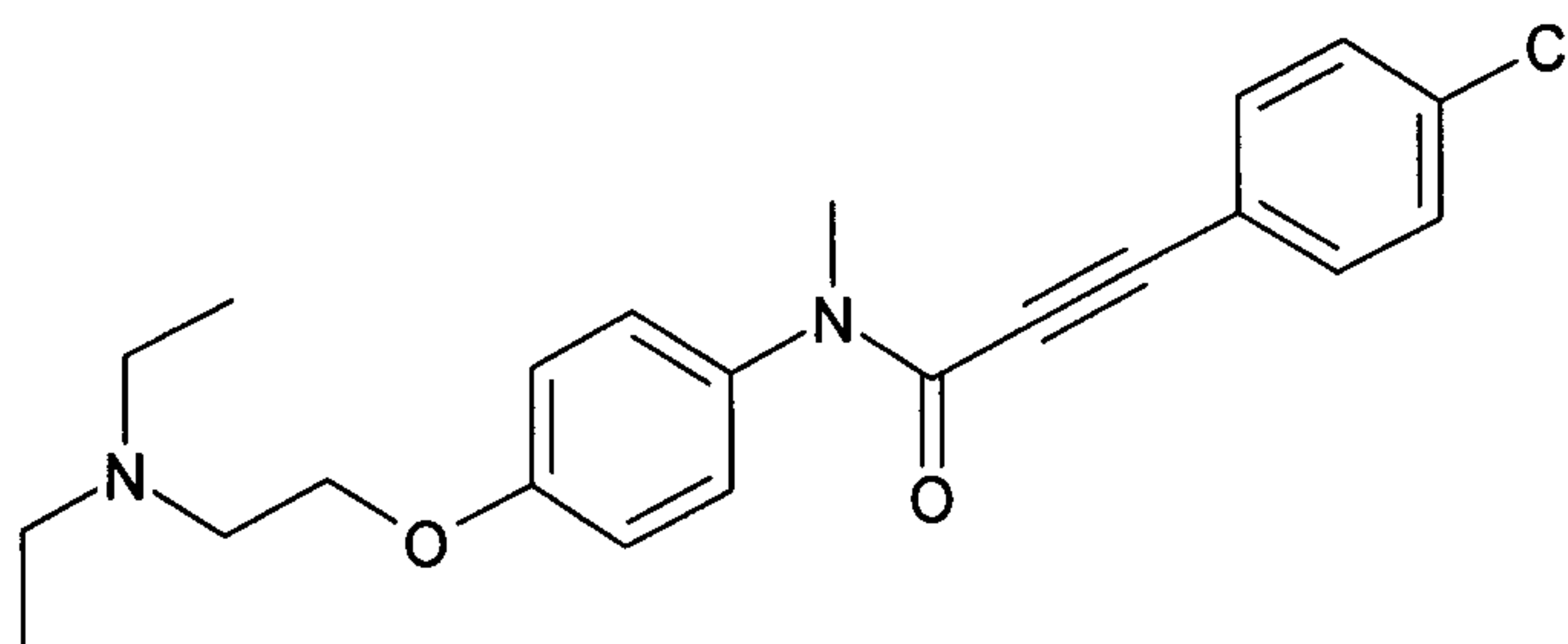
20 Calc.: Molecular ion peak (M+H)⁺: 381
(M+H)⁺: 381

Found: Molecular ion peak

R_f value: 0.42 (silica gel, dichloromethane/ methanol = 80:20)

Example 3.3:

25 3-(4-chloro-phenyl)-propynoic acid-[4-(2-diethylamino-ethoxy)-phenyl]-methyl-amide



3.3.a. 3-(4-chloro-phenyl)-propynoic acid-[4-(2-diethylamino-ethoxy)-phenyl]-methyl-amide

Prepared analogously to Example 3.1.e from [4-(2-diethylamino-ethoxy)-phenyl]-methyl-amine and (4-chloro-phenyl)-propynoic acid in dichloromethane as solvent.

Yield: 36 mg (5 % of theoretical)

C₂₂H₂₅ClN₂O₂ (M= 384.91)

Calc.: Molecular ion peak (M+H)⁺: 385/387

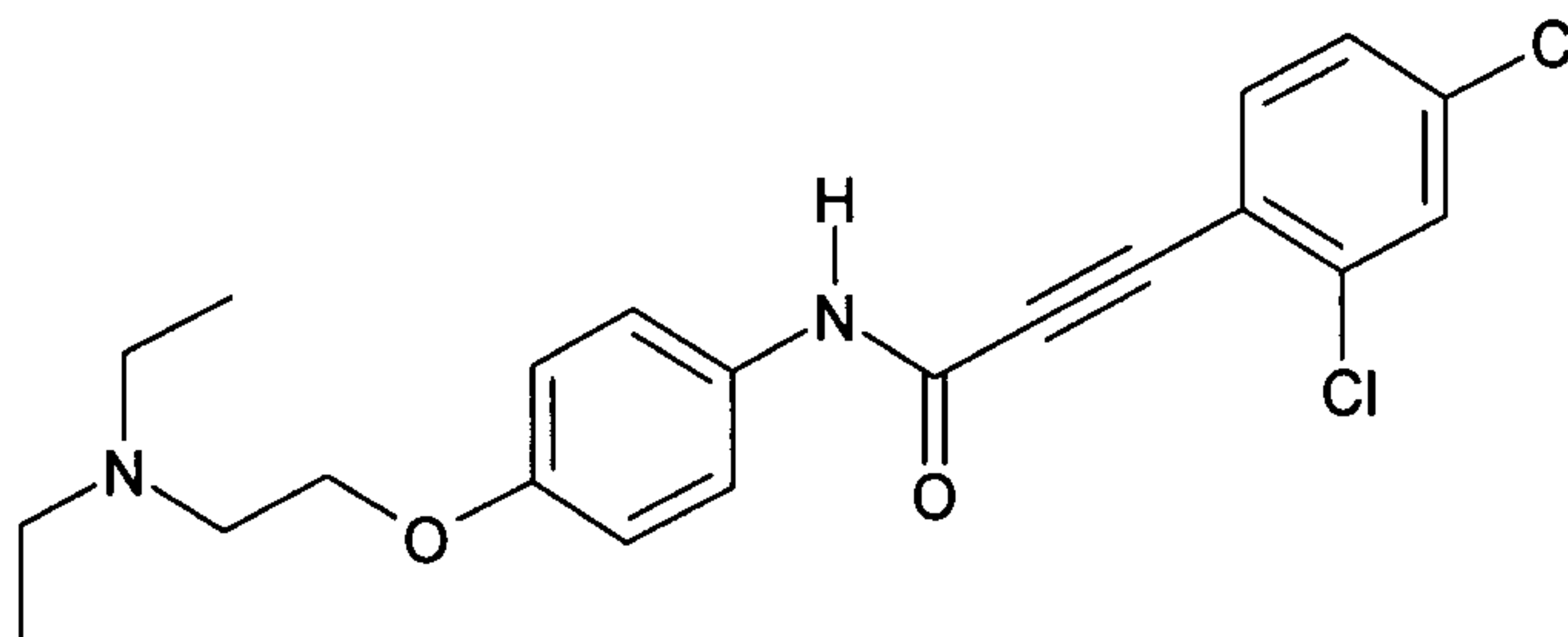
Found: Molecular ion

peak (M+H)⁺: 385/387

R_f value: 0.4 (silica gel, dichloromethane/ methanol/ammonia = 90:10:1)

Example 3.4:

3-(2,4-dichloro-phenyl)-propynoic acid-[4-(2-diethylamino-ethoxy)-phenyl]-amide



3.4.a. 2,3-dibromo-3-(2,4-dichloro-phenyl)-propanecarboxylic acid

9.45 g (59.14 mmol) bromine, dissolved in 20 ml carbon tetrachloride, are added dropwise at 0°C to a suspension of 11.67 g (53.76 mmol) 2,6-dichlorocinnamic acid in 500 ml carbon tetrachloride and the mixture is stirred for three hours at ambient temperature. Then the solvent is distilled off and the residue is combined with petroleum ether. The solid is filtered off and dried in the circulating air dryer at 50°C.

Yield: 19.22 g (94.9 % of theoretical)

Melting point: 184-185°C

C₉H₆Br₂Cl₂O₂ (M= 376.86)

3.4.b. (2,4-dichloro-phenyl)-propynoic acid

A solution of 19.2 g (50.94 mmol) 2,3-dibromo-3-(2,4-dichloro-phenyl)-propanecarboxylic acid in 130 ml tert-butanol is combined batchwise with a total of 22.86 (203.78 mmol) potassium tert. butoxide, so that the temperature does not exceed 40°C. Then the mixture is stirred for another 90 min at this temperature. The reaction mixture is poured into 2N hydrochloric acid and the precipitate is taken up in ethyl acetate. The organic phase is extracted three times with water and dried over sodium sulphate. The desiccant is filtered off and the solvent is distilled off. The residue is dried in the circulating air dryer at 80°C.

Yield: 9.73 g (88.8 % of theoretical)

Melting point: 168-171°C

C₉H₄Cl₂O₂ (M= 215.03)

R_f value: 0.5 (silica gel, dichloromethane/ ethanol/glacial acetic acid = 10:1:0.1)

3.4.c. 3-(2,4-dichloro-phenyl)-propynoic acid-[4-(2-diethylamino-ethoxy)-phenyl]-amide

Prepared analogously to Example 2.3.f from 4-(2-diethylamino-ethoxy)-phenylamine and (2,4-dichloro-phenyl)-propynoic acid.

Yield: 0.62 g (85 % of theoretical)

Melting point: 107-109°C

C₂₁H₂₂Cl₂N₂O₂ (M= 405.32)

Calc.: Molecular ion peak (M+H)⁺: 405/407/409

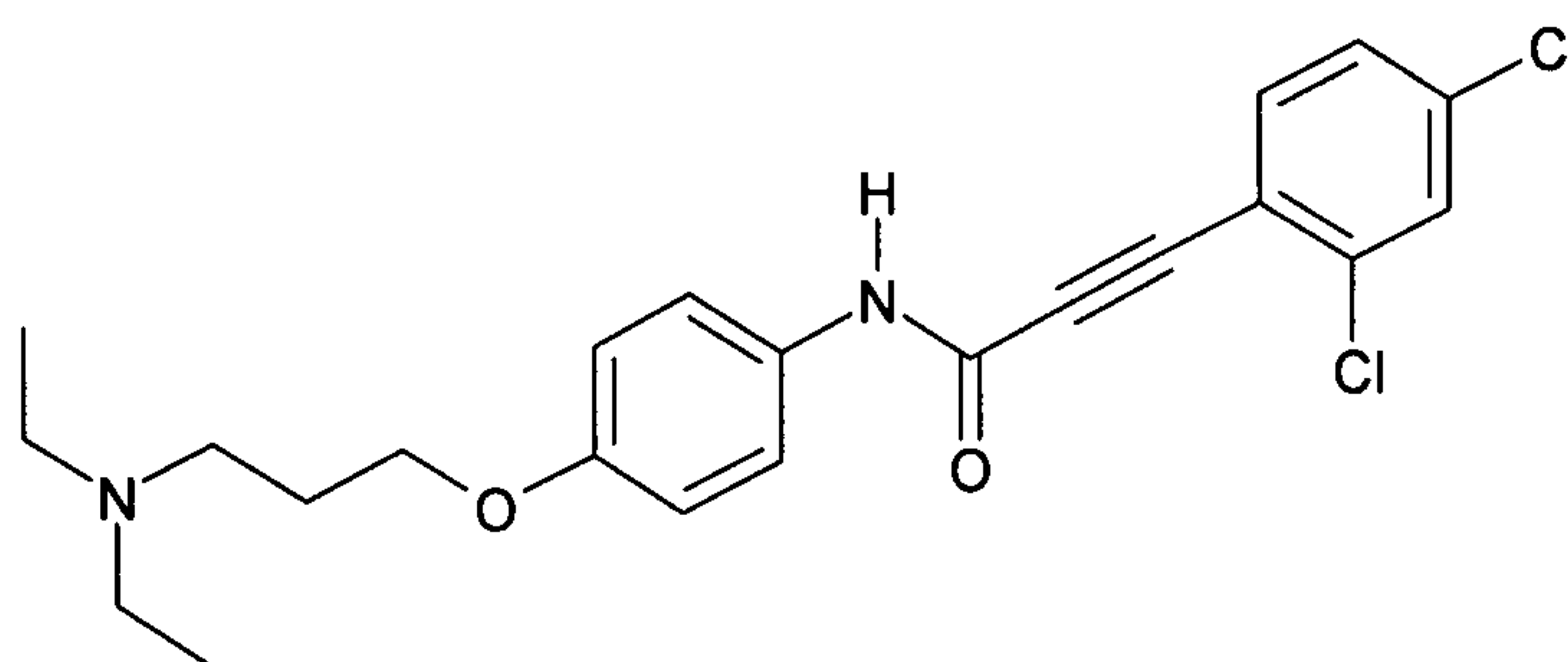
Found: Molecular ion

peak (M+H)⁺: 405/407/409

R_f value: 0.6 (silica gel, dichloromethane/ methanol/ammonia = 5:1:0.1)

Example 3.5:

3-(2,4-dichloro-phenyl)-propynoic acid-[4-(2-diethylamino-propoxy)-phenyl]-amide



3.5.a. 3-(2,4-dichloro-phenyl)-propynoic acid-[4-(2-diethylamino-propoxy)-phenyl]-amide

Prepared analogously to Example 3.4.c from 4-(2-diethylamino-propoxy)-phenylamine and (2,4-dichloro-phenyl)-propynoic acid.

Yield: 0.41 g (65.2 % of theoretical)

Melting point: 70-72°C

C₂₂H₂₄Cl₂N₂O₂ (M= 419.35)

Calc.: Molecular ion peak (M+H)⁺: 419/421/423

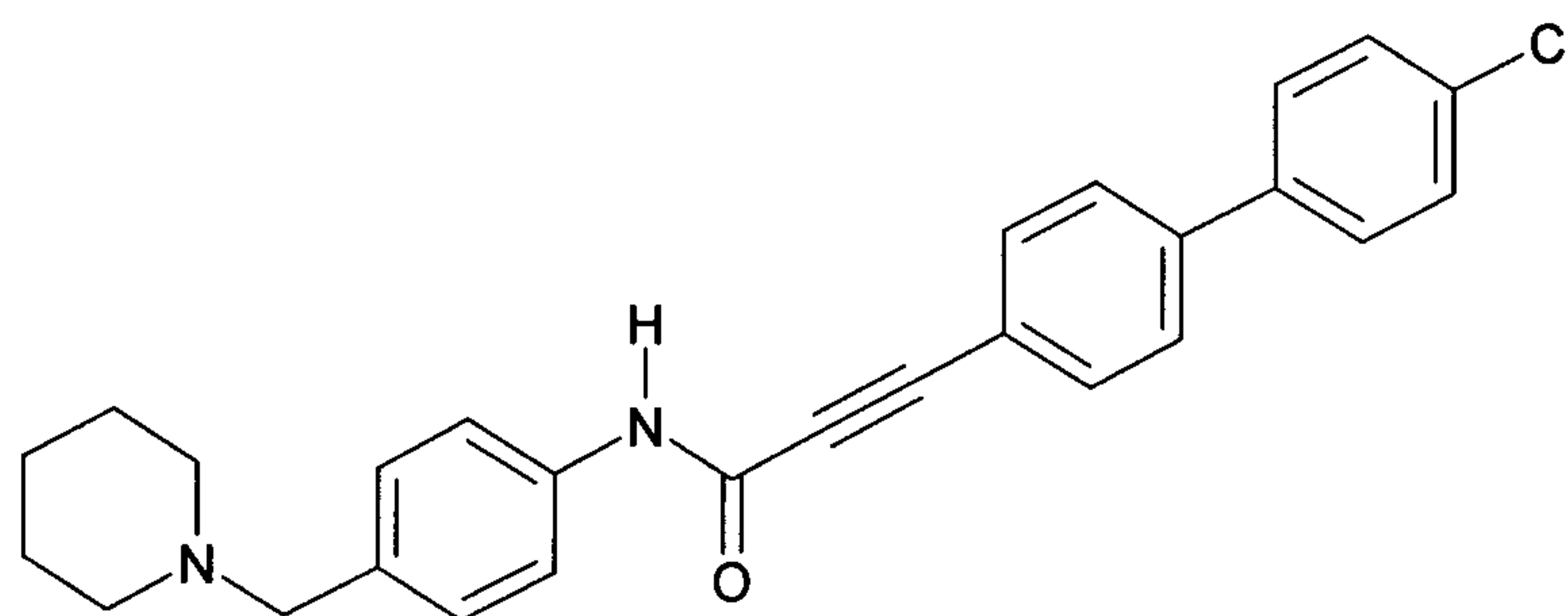
Found: Molecular ion

peak (M+H)⁺: 419/421/423

R_f value: 0.4 (silica gel, dichloromethane/ ethanol/ammonia = 5:1:0.01)

Example 3.6:

3-(4'-chloro-biphenyl-4-yl)-propynoic acid-(4-piperidin-1-ylmethyl-phenyl)-amide



3.6.a. ethyl (E)-3-(4'-chloro-biphenyl-4-yl)-acrylate

173 mg (0.15 mmol) tetrakis(triphenyl)phosphine palladium and 4.4 ml (8.8 mmol) of a

2M sodium carbonate solution are added at ambient temperature to a solution of

1.124 g (4.04 mmol) ethyl (E)-3-(4-bromo-phenyl)-acrylate in 50 ml dioxane. 0.689 g

(4.404 mmol) 4-chloro-phenylboric acid dissolved in 10 ml of methanol are added to

this reaction mixture and refluxed for five hours. The reaction mixture is evaporated

down, the residue is taken up in dichloromethane and extracted with water. The

organic phase is dried over sodium sulphate. The purification is carried out by column chromatography on silica gel (eluant: petroleum ether/ ethyl acetate= 9:1).

Yield: 0.94 g (74.4 % of theoretical)

$C_{17}H_{15}ClO_2$ (M= 286.76)

5 Calc.: Molecular ion peak $(M+H)^+$: 287/289 Found: Molecular ion
peak $(M+H)^+$: 287/289

R_f value: 0.44 (silica gel, petroleum ether/ ethyl acetate = 40:10)

3.6.b. [(E)-3-(4'-chloro-biphenyl-4-yl)-acrylic acid

10 6.27 ml of a 1M sodium hydroxide solution are added to a solution of 0.9 g (3.13
mmol) ethyl (E)-3-(4'-chloro-biphenyl-4-yl)-acrylate in 30 ml of ethanol and stirred for
three hours at ambient temperature. The reaction is stopped by the addition of 6.27
ml of 1N hydrochloric acid and the reaction mixture is stirred for two hours. Then the
15 mixture is evaporated down, the residue is combined with water and the precipitate is
filtered off. The precipitate is repeatedly rinsed with water and dried at 80°C in the
vacuum drying chamber.

Yield: 0.68 g (67 % of theoretical)

$C_{15}H_{11}ClO_2$ (M= 258.70)

Calc.: Molecular ion peak $(M-H)^-$: 257/259 Found: Molecular ion
20 peak $(M-H)^-$: 257/259

R_f value: 0.5 (silica gel, dichloromethane/methanol = 90:10)

3.6.c. (E)-3-(4'-chloro-biphenyl-4-yl)-N-(4-piperidin-1-ylmethyl-phenyl)-acrylamide

Prepared analogously to Example 3.1.e from [(E)-3-(4'-chloro-biphenyl-4-yl)-acrylic
25 acid and 4-piperidin-1-ylmethyl-phenylamine.

Yield: 0.57 g (62.9 % of theoretical)

Melting point: 265-270°C

$C_{27}H_{27}ClN_2O$ (M= 430.98)

Calc.: Molecular ion peak $(M+H)^+$: 431/433 Found: Molecular ion
30 peak $(M+H)^+$: 431/433

R_f value: 0.31 (silica gel, dichloromethane/methanol = 90:10)

3.6.d. 2,3-dibromo-3-(4'-chloro-biphenyl-4-yl)-*N*-(4-piperidin-1-ylmethyl-phenyl)-propionamide

A suspension of 150 mg (0.348 mmol) (E)-3-(4'-chloro-biphenyl-4-yl)-*N*-(4-piperidin-1-ylmethyl-phenyl)-acrylamide in 15 ml dichloromethane is combined with 0.02 ml (0.383 mmol) bromine and stirred for three hours at ambient temperature. Then the reaction mixture is evaporated down, the residue is recrystallised from petroleum ether and dried at 70°C in the vacuum drying chamber.

Yield: 0.19 g (92.4 % of theoretical)

10 Melting point: 145-150°C

$C_{27}H_{27}Br_2ClN_2O$ I (M= 590.79)

Calc.: Molecular ion peak (M+H)⁺: 589/591/593/595

Found: Molecular ion peak (M+H)⁺: 589/591/593/595

R_f value: 0.47 (silica gel, dichloromethane/methanol/ammonia = 90:10:1)

15

3.6.e. 3-(4'-chloro-biphenyl-4-yl)-propynoic acid-(4-piperidin-1-ylmethyl-phenyl)-amide
Prepared analogously to Example 3.4.b from 2,3-dibromo-3-(4'-chloro-biphenyl-4-yl)-*N*-(4-piperidin-1-ylmethyl-phenyl)-propionamide.

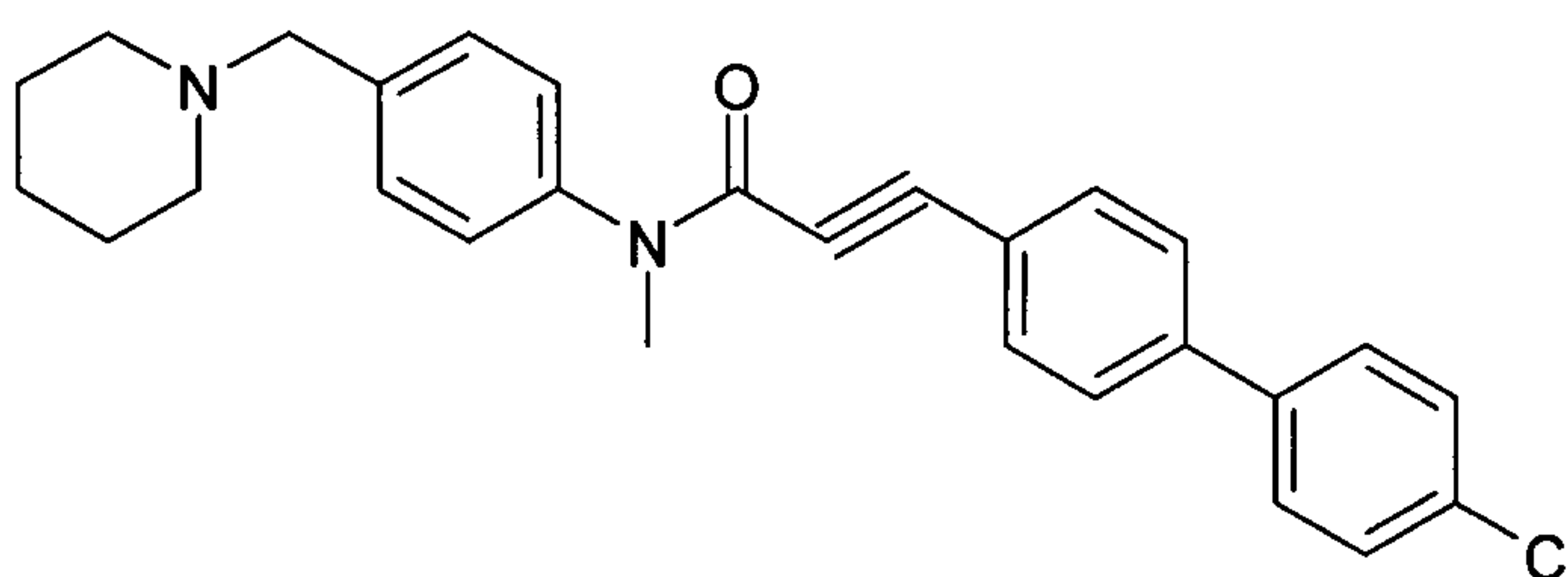
Yield: 26 mg (23.9 % of theoretical)

20 $C_{27}H_{25}ClN_2O$ I (M= 428.96)

Calc.: Molecular ion peak (M+H)⁺: 429/431 Found: Molecular ion peak (M+H)⁺: 429/431

R_f value: 0.42 (silica gel, dichloromethane/methanol/ammonia = 90:10:1)

25 **Example 3.7:** 3-(4'-chloro-biphenyl-4-yl)-propynoic acid-(4-piperidin-1-ylmethyl-phenyl)-methyl-amide



30 3.7.a. 2,3 dibromo-3-(4'-chloro-biphenyl-4-yl) propynoic acid

3.3 ml (64.22 mmol) bromine are added dropwise at ambient temperature to a suspension of 15 g (58 mmol) 3-(4'-chloro-biphenyl-4-yl) acrylic acid in 370 ml carbon tetrachloride and stirred for three hours at ambient temperature. The precipitate obtained is suction filtered, washed with petroleum ether and dried in the circulating
5 air dryer at 70°C.

Yield: 24 g (99 % of theoretical)

Melting point: 230-234 °C

$C_{15}H_{11}Br_2ClO_2$ (M= 418.51)

R_f value: 0. 2 (silica gel, dichloromethane/methanol= 90:10)

10

3.7.b. (4'-chloro-biphenyl-4-yl)-propynoic acid

A solution of 24 g (57.35 mmol) 2,3 dibromo-3-(4'-chloro-biphenyl-4-yl) propynoic acid in 270 ml THF is combined batchwise with 25.74 g (229.39 mmol) potassium tert. butoxide, so that the temperature does not exceed 40 °C. Then the mixture is stirred
15 for another 3.5 hours at this temperature. The reaction mixture is poured onto ice water/conc. hydrochloric acid and the precipitate is taken up in ethyl acetate. The organic phase is washed with water and dried over sodium sulphate. The desiccant is filtered off and the solvent is distilled off. The residue is stirred with petroleum ether and suction filtered.

20 Yield: 14.2 g (97 % of theoretical)

$C_{15}H_9ClO_2$ (M= 256.68)

R_f value: 0. 45 (silica gel, dichloromethane/methanol/glacial acetic acid= 90:10:0.1)

25

3.7.c. 3-(4'-chloro-biphenyl-4-yl)-propynoic acid-(4-piperidin-1-ylmethyl-phenyl)-methyl-amide

A solution of 0.26 g (1 mmol) (4'-chloro-biphenyl-4-yl)-propynoic acid and 0.12 ml (1.1 mmol) N-methylmorpholine in 20 ml absolute THF is combined at -15°C with 0.14 ml (1.1 mmol) isobutyl chloroformate and stirred for ten minutes. Then 0.225 g (1.1 mmol) methyl-(4-piperidin-1-ylmethyl-phenyl)-amine dissolved in 10 ml THF are
30 added and the reaction mixture is stirred for two hours until it reaches ambient temperature. The reaction mixture is evaporated down and the residue is dissolved in dichloromethane. The organic phase is washed twice with water and then dried over sodium sulphate. The desiccant is filtered off and the solvent is distilled off. The

residue is triturated with ether, suction filtered and dried at 80°C in the vacuum drying chamber.

Yield: 220 mg (50 % of theoretical)

Melting point: 237-239 °C

5 $C_{28}H_{27}ClN_2O$ (M= 442.98)

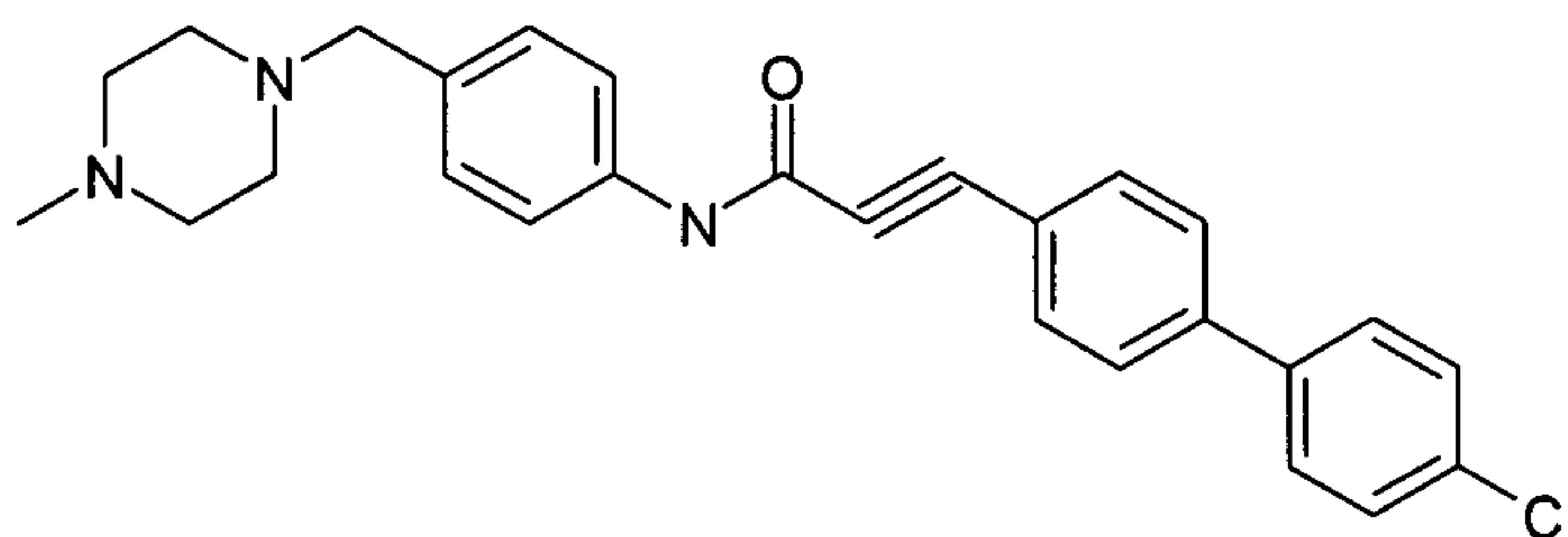
Calc.: Molecular ion peak (M+H)⁺: 443/445 (Cl)

Found: Molecular ion

peak (M+H)⁺: 443/445 (Cl)

R_f value: 0. 5 (silica gel, dichloromethane/methanol = 90:10)

10 **Example 3.8:** 3-(4'-chloro-biphenyl-4-yl)-propynoic acid-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-amide



A solution of 0.26 g (1 mmol) (4'-chloro-biphenyl-4- yl)-propynoic acid and 0.12 ml
15 (1.1 mmol) N-methylmorpholine in 20 ml absolute THF is combined at -15°C with 0.14
ml (1.1 mmol) isobutyl chloroformate and stirred for ten minutes. Then 0.226 g (1.1
mmol) 4-(4-methyl-piperazin-1-ylmethyl)-phenylamine, dissolved in 7 ml THF are
added and the reaction mixture is stirred for two hours until ambient temperature is
reached. The reaction mixture is evaporated down and the residue is dissolved in
20 dichloromethane. The organic phase is washed twice with water and then dried over
sodium sulphate. The desiccant is filtered off and the solvent is distilled off. The
residue is triturated with ether and suction filtered. The purification is carried out by
column chromatography on silica gel (dichloromethane/methanol/ammonia=
90/10/0.1)

25 Yield: 60 mg (14 % of theoretical)

Melting point: 182-185 °C

$C_{27}H_{26}ClN_3O$ (M= 443.97)

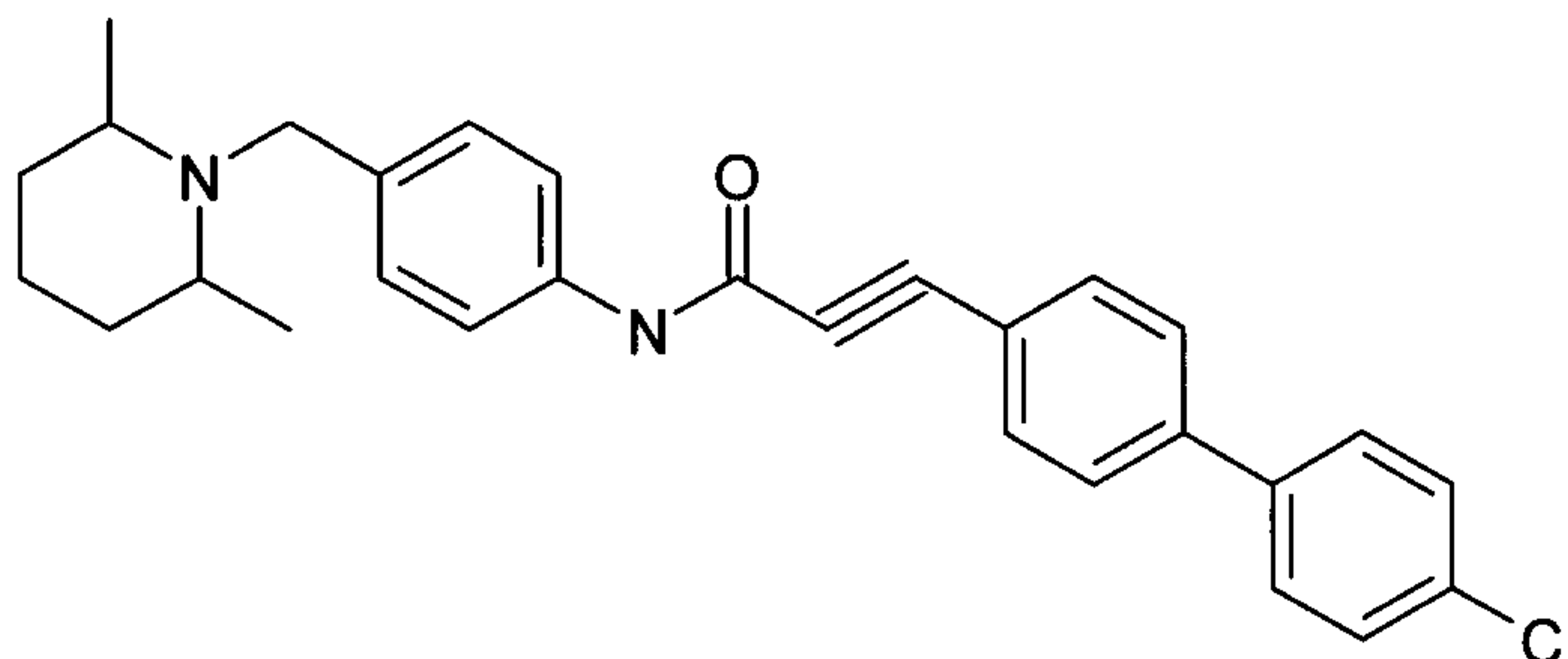
Calc.: Molecular ion peak (M+H)⁺: 444/446 (Cl)

Found: Molecular ion

peak (M+H)⁺: 444/446 (Cl)

30 R_f value: 0. 4 (silica gel, dichloromethane/methanolic ammonia = 90:10:0.1)

Example 3.9. 3-(4'-chloro-biphenyl-4-yl)-propynoic acid-[4-(2,6-dimethyl-piperidin-1-ylmethyl)-phenyl]-amide



5

Prepared analogously to Example 3.8. from (4'-chloro-biphenyl-4-yl)-propynoic acid and 4-(2,6-dimethyl-piperidin-1-ylmethyl)-phenylamine.

Yield: 100 mg (22 % of theoretical)

Melting point: 158-163 °C

10 C₂₉H₂₉ClN₂O (M= 457.01)

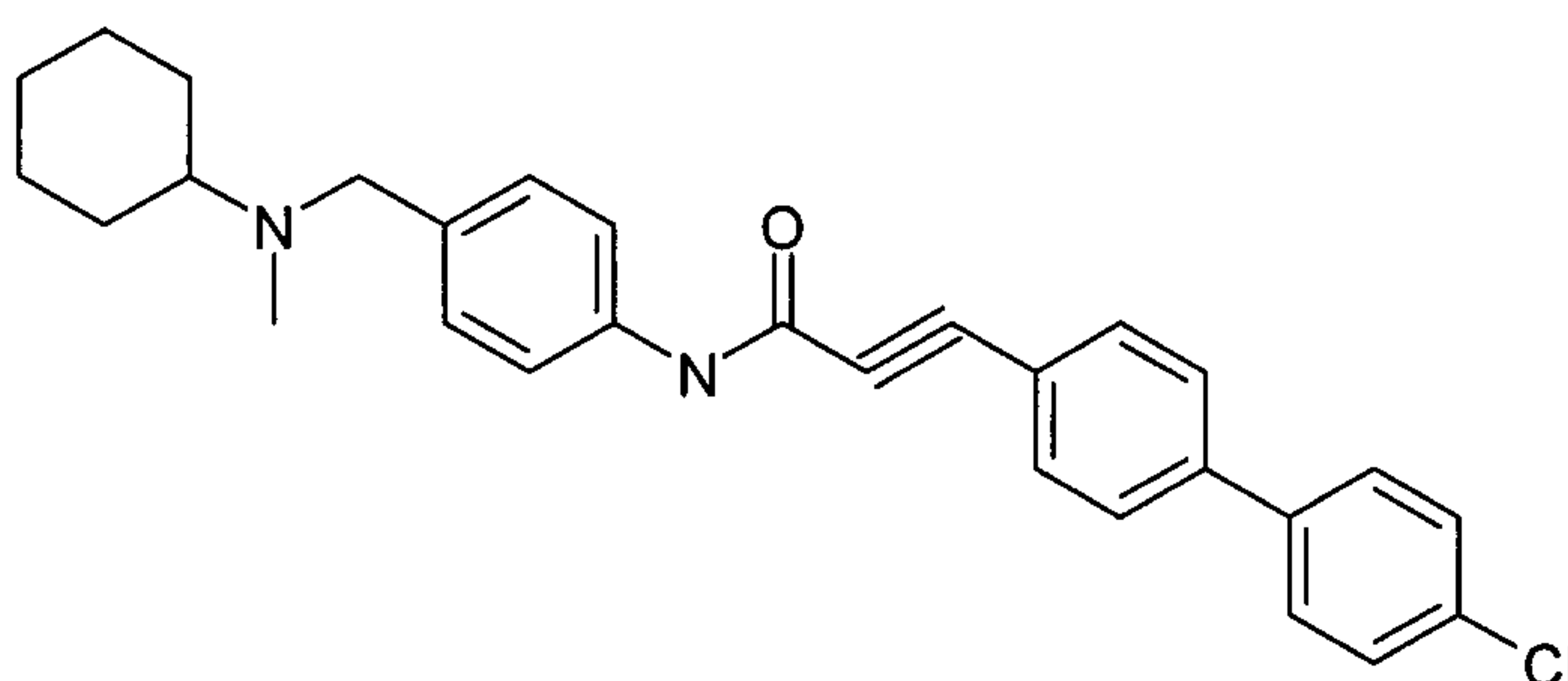
Calc.: Molecular ion peak (M+H)⁺: 458/460 (Cl)

Found: Molecular ion

peak (M+H)⁺: 458/460 (Cl)

R_f value: 0.50 (silica gel, dichloromethane/methanolic ammonia = 90:10:0.1)

15 **Example 3.10:** 3-(4'-chloro-biphenyl-4-yl)-propynoic acid-{4-[(cyclohexyl-methyl-amino)-methyl]-phenyl}-amide



Prepared analogously to Example 3.8. from (4'-chloro-biphenyl-4-yl)-propynoic acid and 4-[(cyclohexyl-methyl-amino)-methyl]-phenylamine hydrochloride

20 Yield: 60 mg (13 % of theoretical)

Melting point: 205-210 °C

C₂₉H₂₉ClN₂O (M= 457.01)

Calc.: Molecular ion peak (M+H)⁺: 457/459 (Cl)

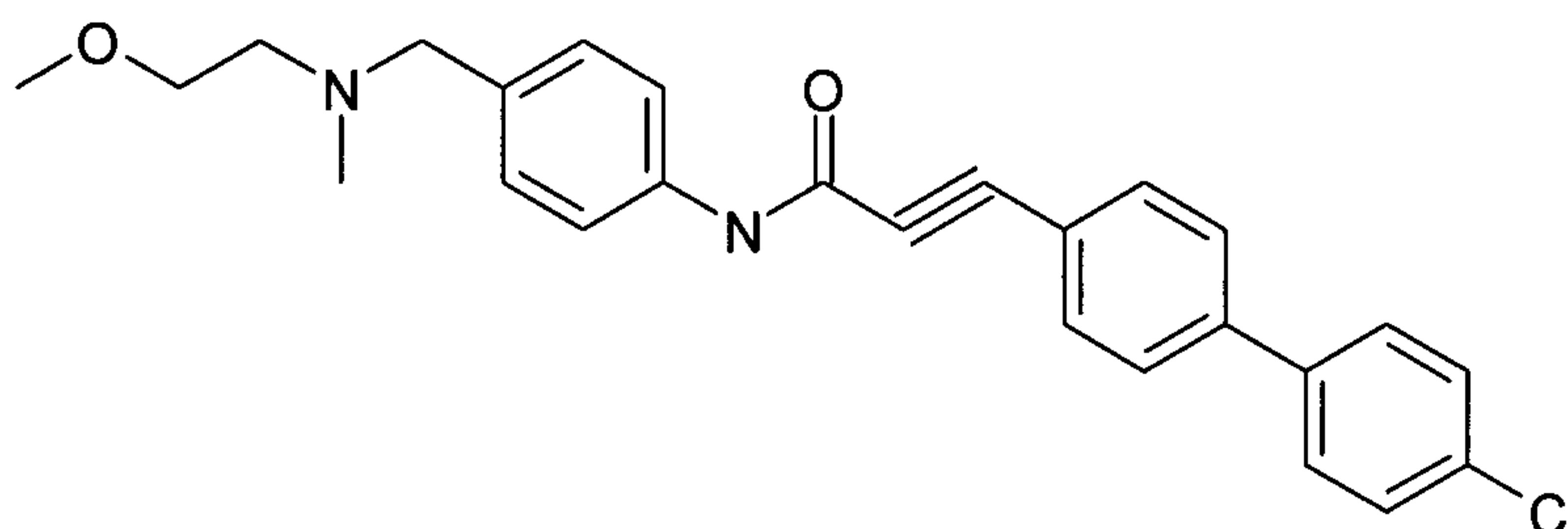
Found: Molecular ion

peak (M+H)⁺: 457/459 (Cl)

R_f value: 0. 60 (silica gel, dichloromethane/methanol = 90:10)

Example 3.11: BI00017862

3-(4'-chloro-biphenyl-4-yl)propynoic acid-(4-[[2-methoxy-ethyl)-methyl-amino]-
5 methyl}-phenyl)-amide



Prepared analogously to Example 3.8. from (4'-chloro-biphenyl-4-yl)-propynoic acid
and 4-[[2-methoxy-ethyl)-methyl-amino]-methyl}-phenylamine.

10 Yield: 150 mg (35 % of theoretical)

Melting point: 130-133 °C

C₂₆H₂₅ClN₂O₂ (M= 432.94)

Calc.: Molecular ion peak (M+H)⁺: 433/435 (Cl)

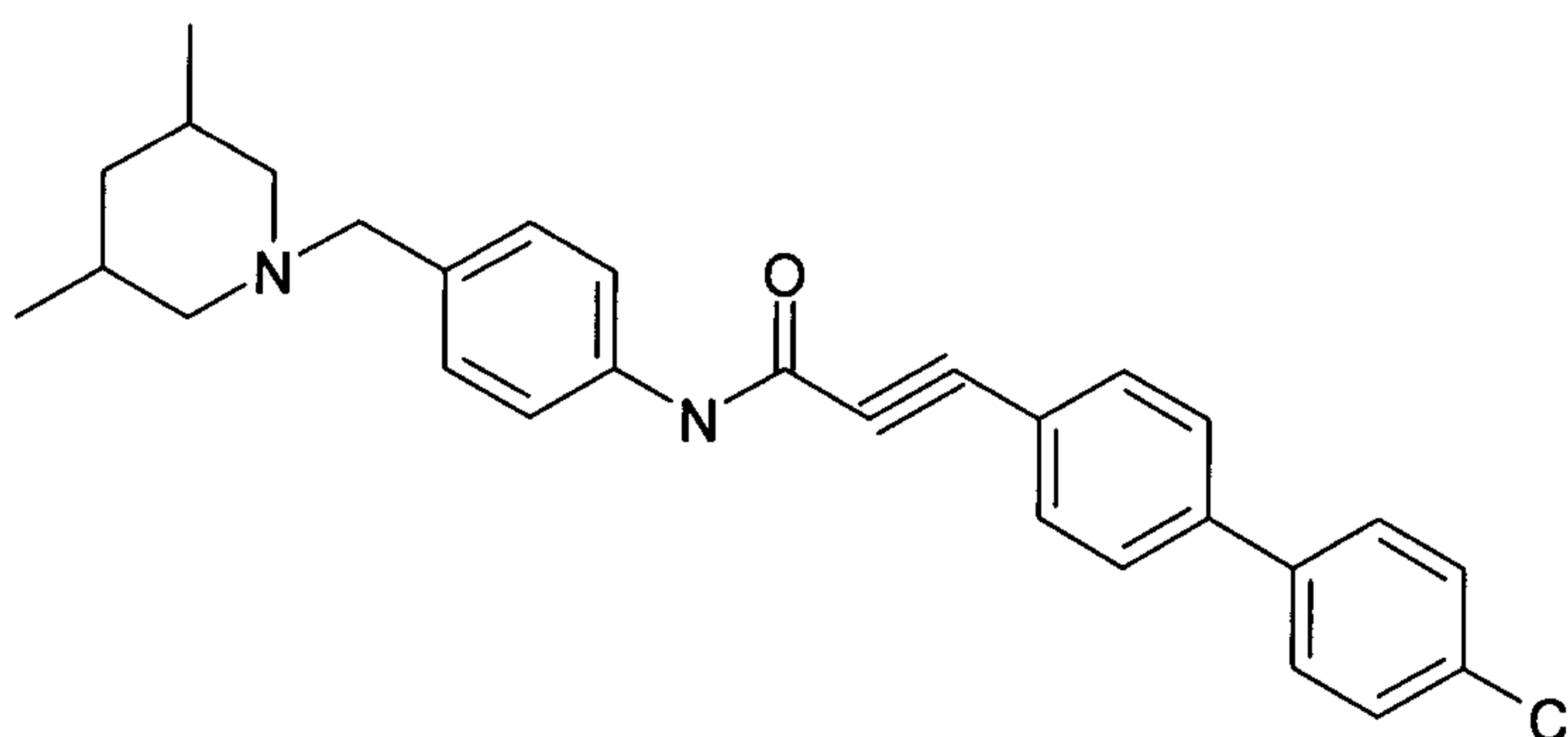
Found: Molecular ion

peak (M+H)⁺: 433/435 (Cl)

15 R_f value: 0. 50 (silica gel, dichloromethane/methanol/ammonia = 90:10:1)

Example 3.12:

3-(4'-chloro-biphenyl-4-yl)-propynoic acid-[4-(3,5-dimethyl-piperidin-1-ylmethyl)-
20 phenyl]-amide



A solution of 0.26 g (1 mmol) (4'-chloro-biphenyl-4-yl)-propynoic acid and 0.12 ml (1.1 mmol) N-methylmorpholine in 20 ml absolute THF is combined with 0.14 ml (1.1 mmol) isobutyl chloroformate at -15°C and stirred for ten minutes. Then 0.240 mg

(1.1 mmol) 4-[(3,5-dimethyl-cyclohexylamino)-methyl]-phenylamine, dissolved in 7 ml THF are added and the reaction mixture is stirred for 16 hours. The reaction mixture is evaporated down. The purification is carried out by column chromatography on silica gel (dichloromethane/methanol = 90/10).

5 Yield: 300 mg (66 % of theoretical)

Melting point: 209-214 °C

C₂₉H₂₉ClN₂O (M= 457.01)

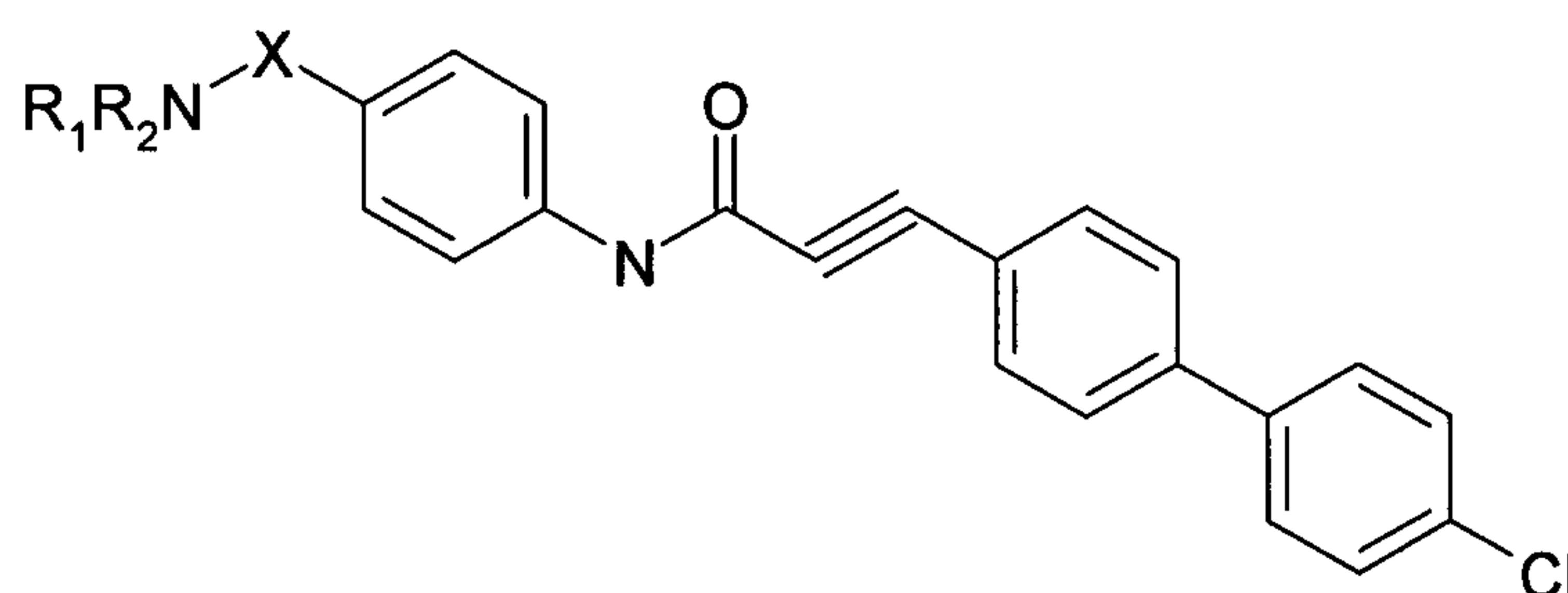
Calc.: Molecular ion peak (M+H)⁺: 457/459 (Cl)

Found: Molecular ion

peak (M+H)⁺: 457/459 (Cl)

10 R_f value: 0. 60 (silica gel, dichloromethane/methanol = 90:10)

The following compounds are prepared analogously to Example 3.12.:



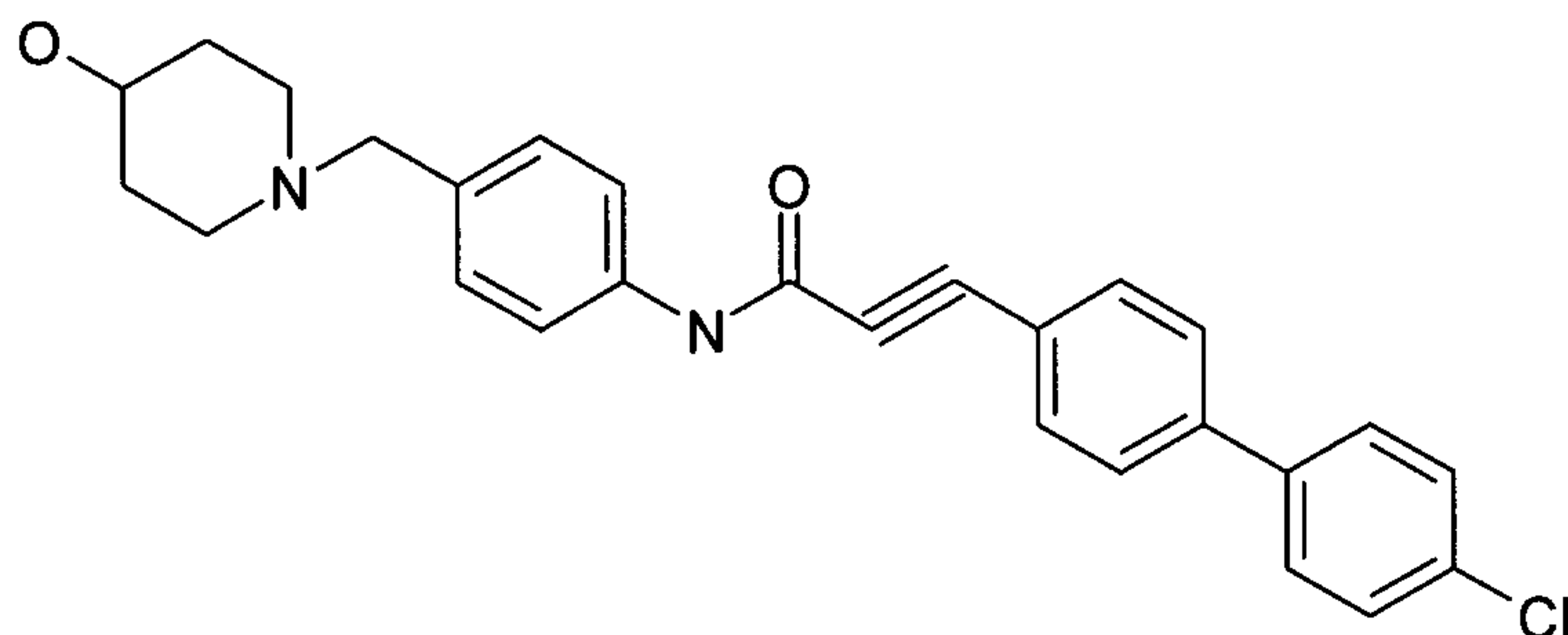
15

Example	R ₁ R ₂ N-X	educt	empirical formula	mass spectrum	mp [°C]	R _f value
3.13		3.7.b	C ₂₈ H ₂₇ ClN ₂ O ₂	459/461 (Cl) [M+H] ⁺	227- 234	0.6 (B)
3.14		3.7.b	C ₂₈ H ₂₇ ClN ₂ O	443/445 (Cl) [M+H] ⁺	263- 268	0.5 (B)
3.15		3.7.b	C ₂₇ H ₂₅ ClN ₂ O	429/431 (Cl) [M+H] ⁺	164- 167	0.5 (A)
3.16		3.7.b	C ₂₆ H ₂₃ ClN ₂ O ₂	431/433 (Cl) [M+H] ⁺	180- 184	0.4 (B)
3.17		3.7.b	C ₂₈ H ₂₄ Cl F ₃ N ₂ O ₂	513/515 (Cl) [M+H] ⁺	194- 200	0.5 (B)

R_f value: A= (silica gel, dichloromethane/methanol/ammonia 90:10:0.1)

B= (silica gel, dichloromethane/methanol 90:10)

5 **Example 3.18:** 3-(4'-chloro-biphenyl-4-yl)-propynoic acid-[4-(4-hydroxy-piperidin-1-ylmethyl)-phenyl]-amide



3.18.a 4-(4-nitro-benzyl)-piperidin-4-ol

137 ml (0.983 mol) triethylamine are added to a solution of 41.5 g (0.410 mol) 4-hydroxypiperidine in 500 ml dichloromethane. Then 56.28 g (0.328 mol) 4-nitrobenzylchloride are slowly added. The reaction mixture is boiled for 12 hours. The solid formed is suction filtered, the filtrate is washed twice with water and dried over magnesium sulphate. The solvent is evaporated down.

Yield: 66.45 g (86 % of theoretical)

15 $C_{12}H_{16}N_2O_3$ (M= 236.27)

Calc.: Molecular ion peak (M+H)⁺: 237
237

Found: Molecular ion peak (M+H)⁺:

20 3.18.b. 4-(4-amino-benzyl)-piperidin-4-ol

6.6 g Raney nickel are added to a solution of 66.45 g (0.281 mol) 4-(4-nitro-benzyl)-piperidin-4-ol in 660 ml of methanol. The reaction mixture is hydrogenated for 13 hours at ambient temperature and 3 bar hydrogen. The catalyst is filtered off and the filtrate is evaporated down.

25 Yield: 64.5 g (111 % of theoretical)

$C_{12}H_{18}N_2O$ (M= 206.28)

Calc.: Molecular ion peak (M+H)⁺: 207
207

Found: Molecular ion peak (M+H)⁺:

3.18.c. 4-[4-(*tert*-butyl-dimethyl-silanyloxy)-piperidin-1-ylmethyl]-phenylamine

3.3 g (22 mmol) *tert*. butyldimethylchlorosilane are added to a solution of 4.13 g (20 mmol) 4-(4-amino-benzyl)-piperidin-4-ol and 3.4 g (50 mmol) imidazole in 30 ml of dimethylformamide. The reaction mixture is stirred for 16 hours at ambient temperature. Then the solvent is evaporated down and extracted between ether and water. The organic phase is dried over sodium sulphate and evaporated down. The purification is carried out by column chromatography on aluminium oxide (eluant: petroleum ether/ethyl acetate 90:10).

Yield: 1.65 g (26 % of theoretical)

$C_{18}H_{32}N_2OSi$ (M= 320.55)

Calc.: Molecular ion peak (M+H)⁺: 321

Found: Molecular ion peak (M+H)⁺: 321

R_f value: 0.80 (aluminium oxide, petroleum ether/ethyl acetate = 1:1)

3.18.d. 3-(4'-chloro-biphenyl-4-yl)propynoic acid-{4-[(4-hydroxy-cyclohexylamine)-methyl]-phenyl}-amide

A solution of 0.26 g (1 mmol) (4'-chloro-biphenyl-4-yl)-propynoic acid and 0.12 ml (1.1 mmol) N-methylmorpholine in 20 ml absolute THF is combined with 0.14 ml (1.1 mmol) isobutyl chloroformate at -15°C and stirred for ten minutes. Then 0.350 g (1.1 mmol) 4-[4-(*tert*-butyl-dimethyl-silanyloxy)-piperidin-1-ylmethyl]-phenylamine, dissolved in 7 ml THF are added and the reaction mixture is stirred for four hours. The reaction mixture is evaporated down. The residue is dissolved in 30 ml of tetrahydrofuran and combined with 0.95 g (3 mmol) tetrabutylammonium fluoride hydrate. The reaction mixture is stirred for 16 h at ambient temperature. Then another 0.5 g (1.5 mmol) tetrabutylammonium fluoride hydrate are added and the mixture is stirred for another 16 h at ambient temperature. The last step is repeated twice more. Then the solvent is evaporated down and the residue is extracted between dichloromethane and water. The organic phase is dried over sodium sulphate, the desiccant is filtered off and the filtrate is evaporated down. The purification is carried out by column chromatography on silica gel (dichloromethane/methanol = 90/10)

Yield: 100 mg (23 % of theoretical)

Melting point: 243-247 °C

$C_{27}H_{25}ClN_2O_2$ (M= 444.95)

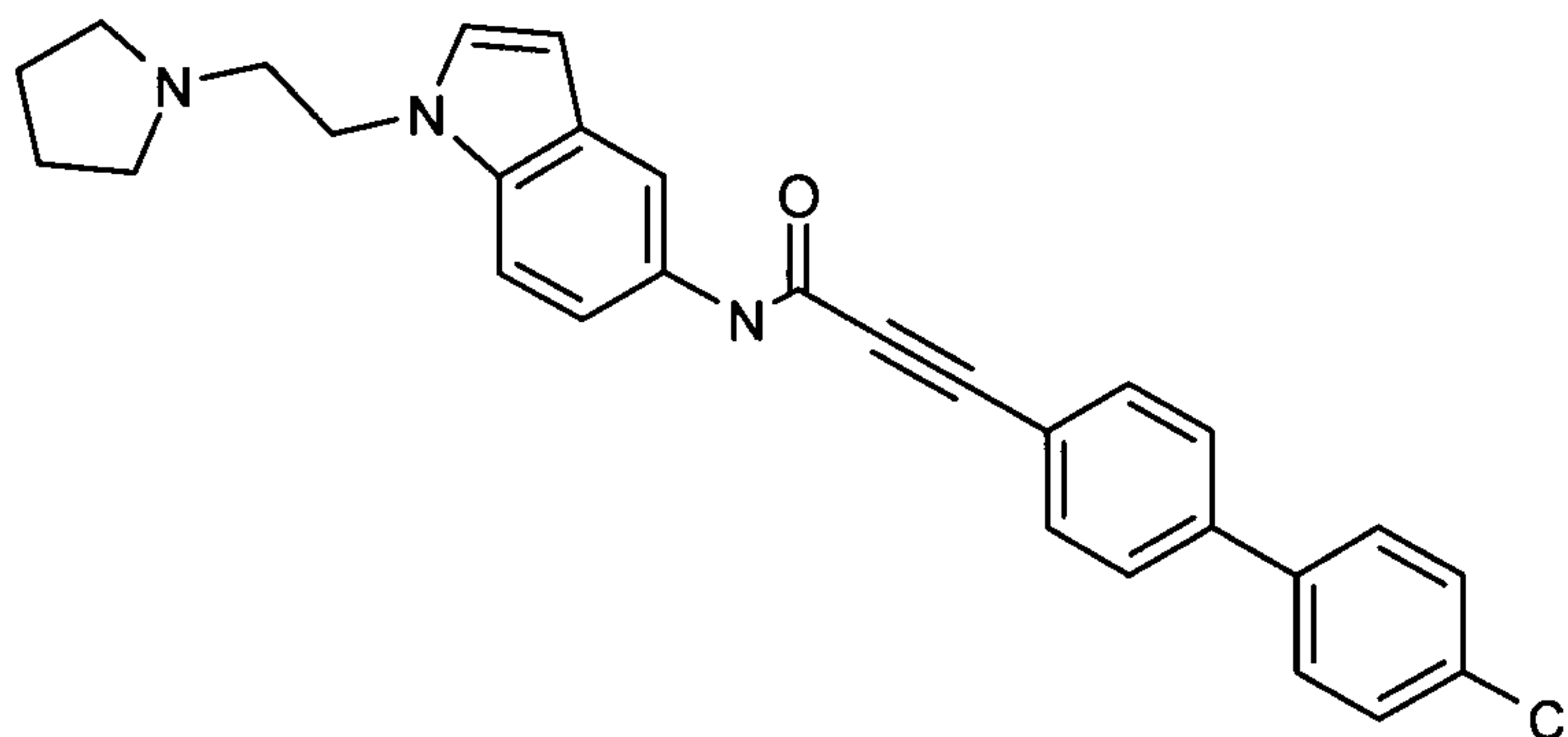
Calc.: Molecular ion peak (M+H)⁺: 445/447 (Cl)

Found: Molecular ion

peak (M+H)⁺: 445/447 (Cl)

R_f value: 0.40 (silica gel, dichloromethane/methanol/ammonia = 90:10:1)

5 **Example 3.19:** 3-(4'-chloro-biphenyl-4-yl)propynoic acid-[1-(2-pyrrolidin-1-yl-ethyl)-1*H*-indol-5-yl]-amide



3.19.a. 5-nitro-1-(2-pyrrolidin-1-yl-ethyl)-1*H*-indole

10 A reaction mixture of 16.22 g (0.1 mol) 5-nitroindole, 35 g (0.205 mol) 1-(2-chloro-ethyl)-pyrrolidine-hydrochloride and 51 g (0.369 mol) potassium carbonate in 500 ml DMF is stirred for 48 hours at ambient temperature and then filtered. The filtrate is evaporated down, the residue dissolved in dichloromethane and dried over sodium sulphate. The desiccant is filtered off and the filtrate is evaporated down.

Yield: 25 g (96.3 % of theoretical)

15 C₁₄H₁₇N₃O₂ (M= 259.31)

Calc.: Molecular ion peak (M+H)⁺: 260

Found: Molecular ion peak

(M+H)⁺: 260

R_f value: 0.65 (silica gel, dichloromethane/ methanol/ammonia = 90:10:1)

20

3.19.b. 5-amino-1-(2-pyrrolidin-1-yl-ethyl)-1*H*-indole

Prepared analogously to Example 3.1.b from 5-nitro-1-(2-pyrrolidin-1-yl-ethyl)-1*H*-indole in THF as solvent.

Yield: 0.83 g (93.9 % of theoretical)

25 C₁₄H₁₉N₃ (M= 229.32)

Calc.: Molecular ion peak (M+H)⁺: 230

Found: Molecular ion peak

(M+H)⁺: 230

R_f value: 0.37 (silica gel, dichloromethane/ methanol/ammonia = 90:10:1)

3.19.c. 3-(4'-chloro-biphenyl-4-yl)propynoic acid-[1-(2-pyrrolidin-1-yl-ethyl)-1*H*-indol-5-yl]-amide

Prepared analogously to Example 3.7.c. from 5-amino-1-(2-pyrrolidin-1-yl-ethyl)-1*H*-indole and (4'-chloro-biphenyl-4-yl)-propynoic acid in THF as solvent.

Yield: 230 mg (49 % of theoretical)

C₂₉H₂₆ClN₃O (M= 467.99)

Melting point: 224-227°C

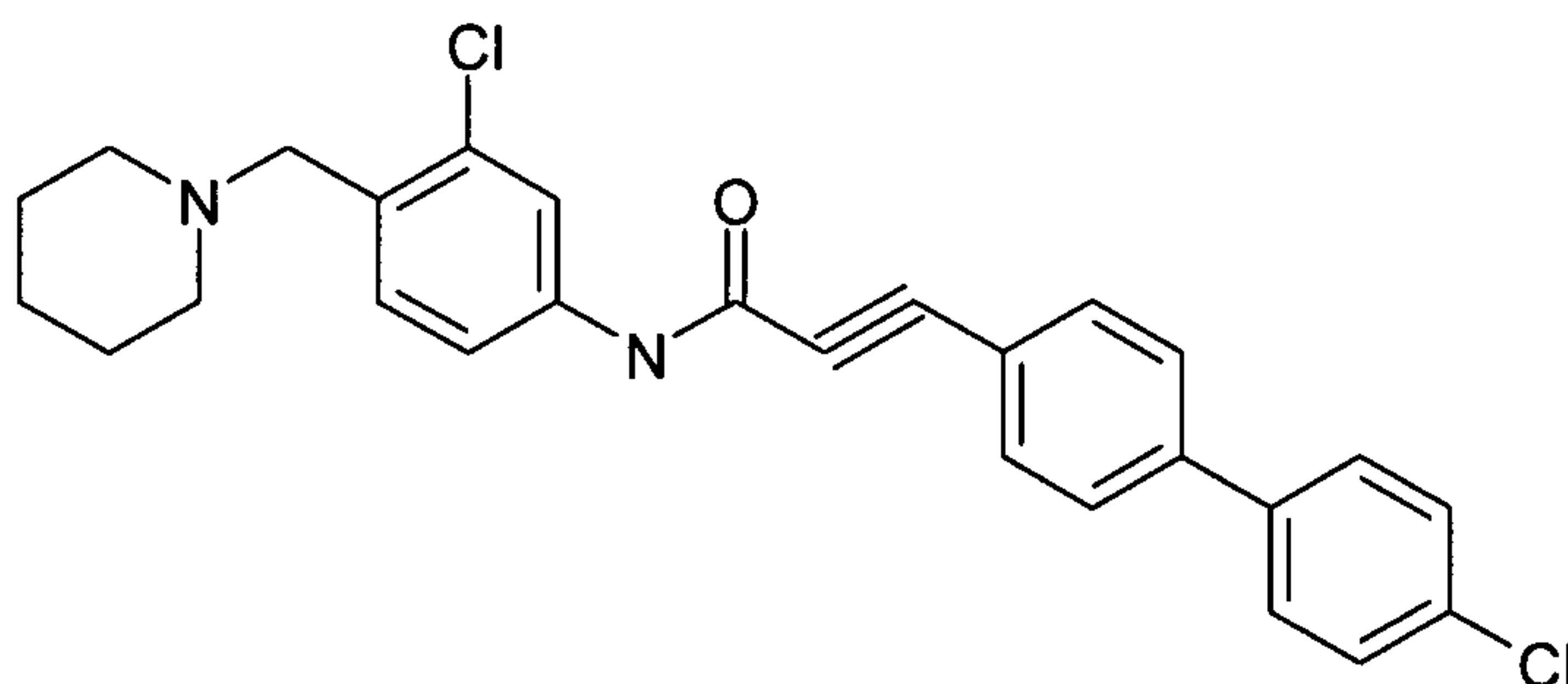
Calc.: Molecular ion peak (M+H)⁺: 468/470 (Cl)

Found: Molecular ion

peak (M+H)⁺: 468/470 (Cl)

R_f value: 0.4 (silica gel, dichloromethane/ methanol = 90:10)

Example 3.20: 3-(4'-chloro-biphenyl-4-yl)-propynoic acid-(3-chloro-4-piperidin-1-ylmethyl-phenyl)-amide



3.20.a: (2-chloro-4-nitro-phenyl)-methanol

35.9 g (0.22 mol) 1,1'-carbonyldiimidazole are slowly added to a solution of 41.1 g (0.2 mol) 2-chloro-4-nitrobenzoic acid in 400 ml of tetrahydrofuran. The reaction

mixture is stirred for 1.5 h at 35 °C. Then the green reaction mixture is cooled down

using ice and at max. 20 °C combined dropwise with a solution of 26.5 g (0.7 mol)

sodium borohydride in 400 ml of water. After 1.5 hours stirring the reaction mixture is diluted with 200 ml of water and then neutralised with 250 ml semiconcentrated

hydrochloric acid. It is stirred for one hour, then extracted twice with ethyl acetate and the organic phase is dried over sodium sulphate. The desiccant is filtered off and the solvent is evaporated down. The residue is crystallised with petroleum ether, suction filtered and dried at 50 °C in the drying chamber.

Yield: 37.66 g (100 % of theoretical)

Melting point: 62-64 °C

C₇H₆ClNO₃ (M= 187.58)

Calc.: Molecular ion peak (M+H)⁺: 187/189 (Cl)

Found: Molecular ion

peak (M+H)⁺: 187/189 (Cl)

R_f value: 0. 70 (silica gel, dichloromethane/methanol = 90:10)

5 3.20.b. 2-chloro-1-chloromethyl-4-nitro-benzene

11.6 ml (160 mmol) thionyl chloride and 1 ml of dimethylformamide are added to a solution of 15 g (80 mmol) 2-chloro-4-nitro-phenyl)-methanol in 300 ml dichloromethane and the whole lot is refluxed for 2 hours. Then the solvent is evaporated down and the residue is dissolved in ethyl acetate and washed with water.
10 The organic phase is dried over sodium sulphate, the desiccant is filtered off and the filtrate is evaporated down. Oily product.

Yield: 16.8 g (102 % of theoretical)

C₇H₅Cl₂NO₂ (M= 206.03)

Calc.: Molecular ion peak (M+H)⁺: 205/7/9 (Cl₂)

Found: Molecular ion

15 peak (M+H)⁺: 205/7/9 (Cl₂)

R_f value: 0. 90 (silica gel, dichloromethane/methanol = 90:10)

3.20.c. 1-(2-chloro-4-nitro-benzyl)-piperidine

2g (9.71 mmol) 2-chloro-1-chloromethyl-4-nitro-benzene are slowly added to 4 ml
20 (40.04 mmol) piperidine at ambient temperature. After 15 min the reaction mixture is combined with ethyl acetate and washed twice with water. The organic phase is dried over sodium sulphate, the desiccant is filtered off and the filtrate is evaporated down. Oily product.

Yield: 2.39 g (97 % of theoretical)

25 C₁₂H₁₅ClN₂O₂ (M= 254.71)

R_f value: 0. 30 (silica gel, petroleum ether/ ethyl acetate = 6:1)

3.20.d 3-chloro-4-piperidin-1-ylmethyl-phenylamine

0.4 g Raney nickel are added to a solution of 2.37 g (9.31 mmol) 1-(2-chloro-4-nitro-benzyl)-piperidine in 100 ml of tetrahydrofuran and hydrogenated at ambient
30 temperature and 3 bar hydrogen. After hydrogen uptake has ended the catalyst is filtered off and the filtrate is evaporated down.

Yield: 1.88 g (90 % of theoretical)

$C_{12}H_{17}ClN_2$ (M= 224.73)

Calc.: Molecular ion peak $(M+H)^+$: 255/7 (Cl)

Found: Molecular ion peak

$(M+H)^+$: 255/7 (Cl)

R_f value: 0. 20 (silica gel, dichloromethane/methanol = 90:10)

5

3.20.e 3-(4'-chloro-biphenyl-4-yl)-propynoic acid(3-chloro-4-piperidin-1-ylmethyl-phenyl)-amide

Prepared analogously to Example 3.7.c from (4'-chloro-biphenyl-4-yl)-propynoic acid and 3-chloro-4-piperidin-1-ylmethyl-phenylamine.

10 Yield: 0.1 g (22 % of theoretical)

Melting point: 277-281 °C

$C_{27}H_{24}Cl_2N_2O$ (M= 463.4)

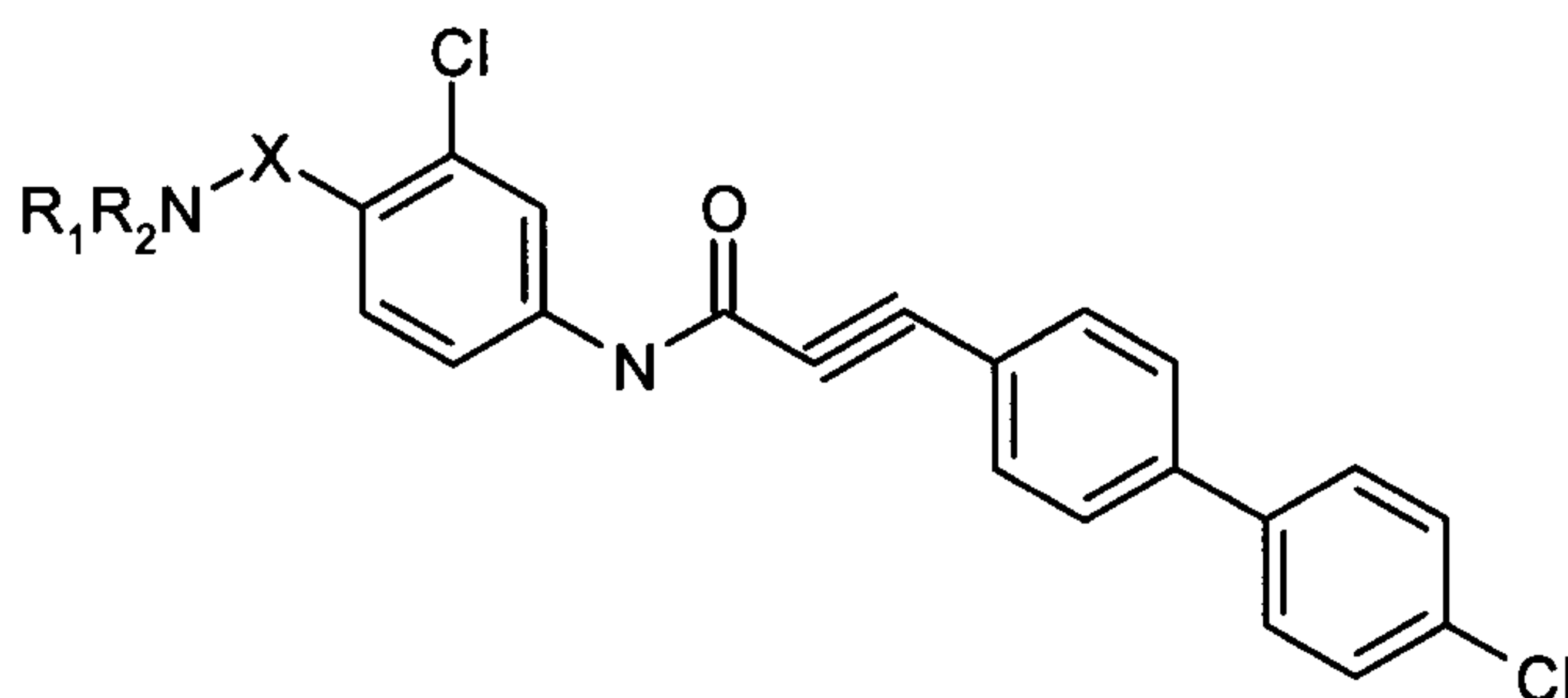
Calc.: Molecular ion peak $(M+H)^+$: 463/5/7 (Cl₂)

Found: Molecular ion

peak $(M+H)^+$: 463/5/7 (Cl₂)

15 R_f value: 0. 50 (silica gel, dichloromethane/methanol = 90:10)

The following compounds are prepared analogously to Example 3.20:

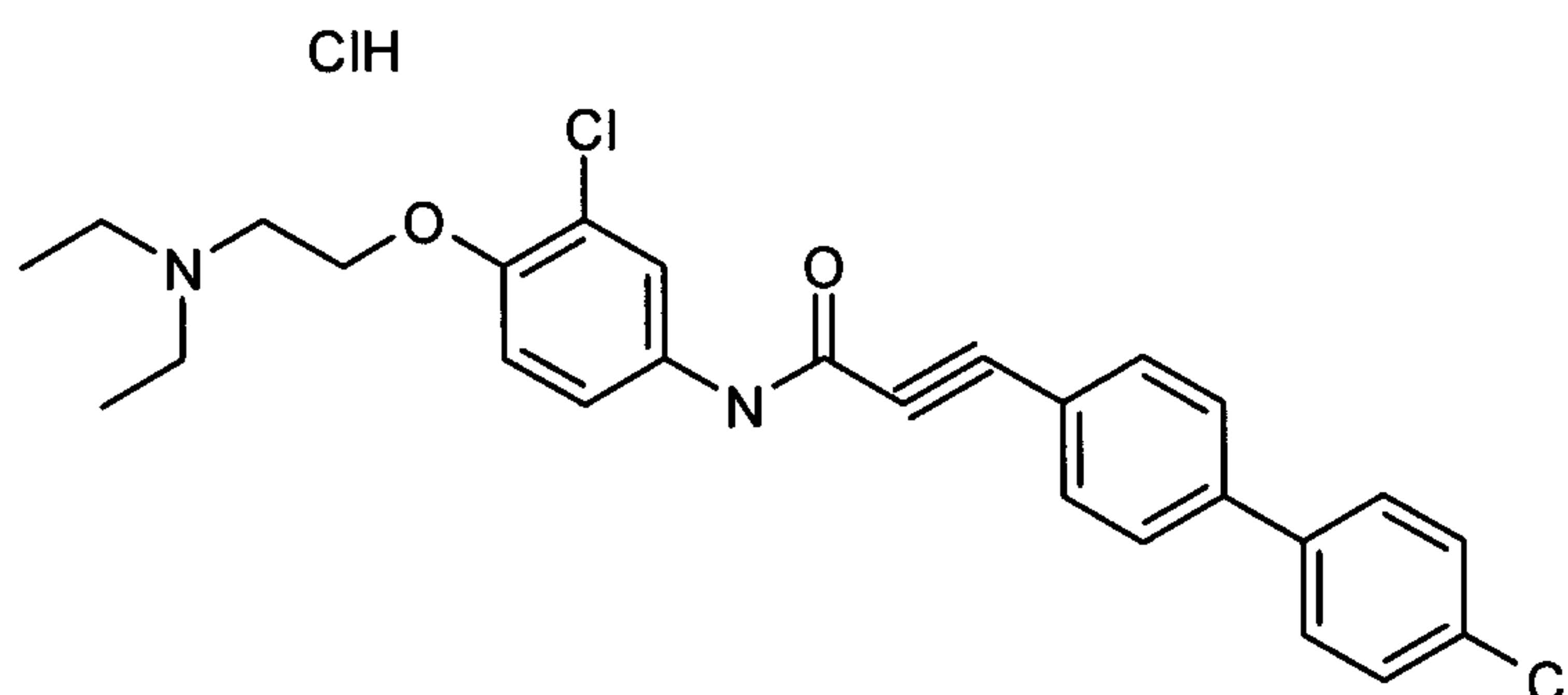


Example	R_1R_2N-X	educt	empirical formula	mass spectrum	mp [°C]	R_f value
3.21		3.7.b	$C_{29}H_{28}Cl_2N_2O$	491/3/5 (Cl ₂) [M+H] ⁺	282- 286	0.5 (A)
3.22		3.7.b	$C_{27}H_{24}Cl_2N_2O_2$	479/81/83 (Cl ₂) [M+H] ⁺	197- 203	0.5 (B)
3.23		3.7.b	$C_{27}H_{24}Cl_2N_2O_2$	479/81/83 (Cl ₂) [M+H] ⁺	204- 209	0.45 (B)

R_f value: A= (silica gel, dichloromethane/methanol 90:10)

B= (silica gel, dichloromethane/methanol/ammonia 90:10:0.1)

Example 3.24: 3-(4'-chloro-biphenyl-4-yl)-propynoic acid-[3-chloro-4-(2-dimethylamino-ethoxy)-phenyl]-amide hydrochloride



5

Prepared analogously to Example 3.7.c from (4'-chloro-biphenyl-4-yl)-propynoic acid and 3-chloro-4-(2-diethylamino-ethoxy)-phenylamine.

Yield: 0.28 g (58 % of theoretical)

Melting point: 226-233 °C

10 $C_{27}H_{26}Cl_2N_2O_2$ (M= 481.41)*HCl

Calc.: Molecular ion peak (M+H)⁺: 481/3/5 (Cl₂)

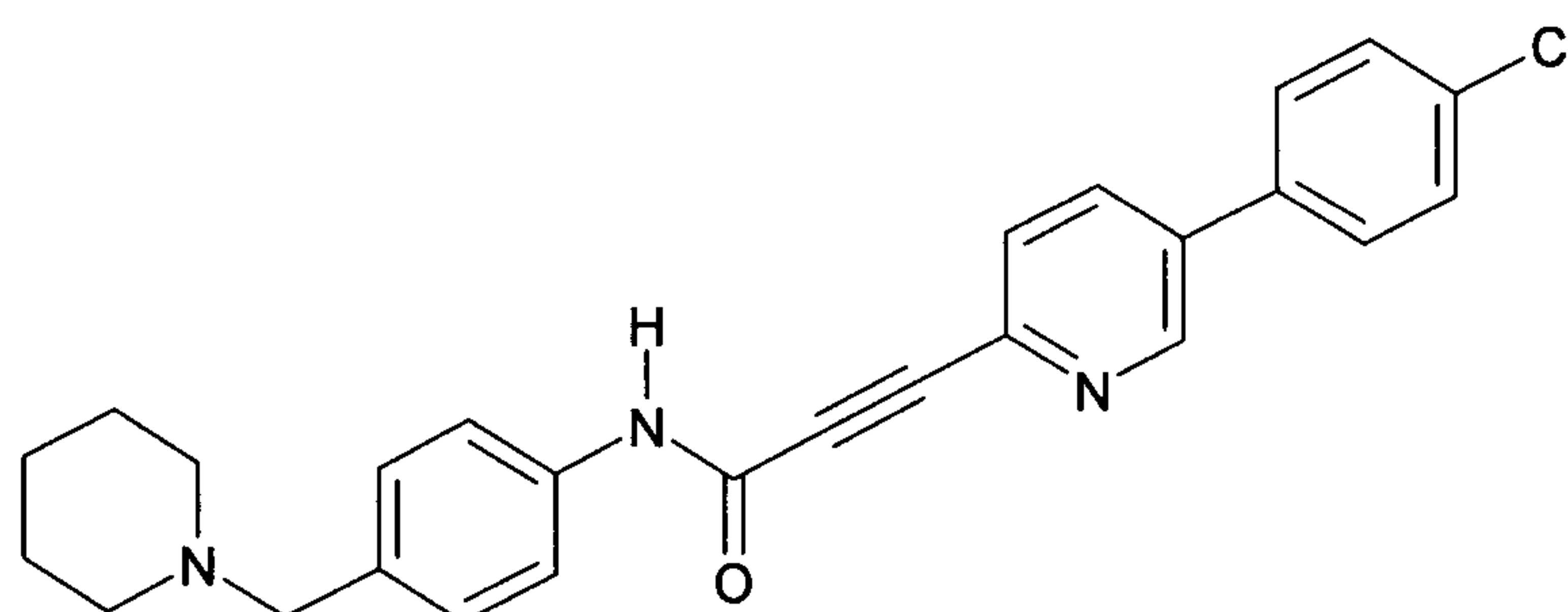
Found: Molecular ion

peak (M+H)⁺: 481/3/5 (Cl₂)

R_f value: 0. 45 (silica gel, dichloromethane/methanol = 90:10)

15 **Example 3.25:**

3-[5-(4-chloro-phenyl)-pyridin-2-yl]-propynoic acid-(4-piperidin-1-ylmethyl-phenyl)-amide



20 3.25.a. 5-bromo-2-trimethylsilanylethynyl-pyridine

1.15 g (1.63 mmol) tetrakis(triphenyl)phosphine palladium, 0.311 g (1.63 mmol)

copper(I)iodide and 50 ml triethylamine are added to a solution of 20 g (81.89 mmol)

2,5-dibromopyridine in 250 ml absolute THF under an argon atmosphere. At 17 °C a

solution of 13 ml (90.14 mmol) trimethylsilylacetylene in 20 ml THF is immediately

added dropwise to this reaction mixture. After ten minutes the cooling is removed. After 20 minutes the temperature is 30° C. The mixture is then cooled to 20°C and briefly stirred. The reaction mixture is evaporated down, the residue is taken up in ethyl acetate and extracted twice with sodium hydrogen carbonate solution. The combined organic phases are dried over magnesium sulphate. The purification is carried out by column chromatography on silica gel (eluant: petroleum ether).

Yield: 20.4 g (98 % of theoretical)

$C_{10}H_{12}BrNSi$ (M= 254.20)

Calc.: Molecular ion peak (M+H)⁺: 254/256

Found: Molecular ion

peak (M+H)⁺: 254/256

R_f value: 0.72 (silica gel, petroleum ether)

3.25.b. 5-(4-chloro-phenyl)-2-trimethylsilanylethynyl-pyridine

In an argon atmosphere 6.93 g (6 mmol) tetrakis(triphenylphosphine) palladium and 17 ml of a 2M sodium carbonate solution are added to a solution of 20.4 g (80.25 mmol) 5-bromo-2-trimethylsilanylethynyl-pyridine and 26.33 g (160 mmol) 4-chlorophenylboric acid in 350 ml dioxane and the reaction mixture is stirred for five hours at 90 C, while every 30 minutes 7 ml of 2M sodium carbonate solution are added. Then at ambient temperature 1000 ml of ethyl acetate are added, and the mixture is extracted twice with 400 ml sodium hydrogen carbonate solution. The organic phase is dried over magnesium sulphate. The purification is carried out by column chromatography on silica gel (eluant: petroleum ether to petroleum ether/ ethyl acetate= 9:1).

Yield: 7.9 g (34.4 % of theoretical)

$C_{16}H_{16}ClNSi$ (M= 285.85)

Calc.: Molecular ion peak (M-H)⁻: 286/288

Found: Molecular ion

peak (M-H)⁻: 286/288

R_f value: 0.6 (silica gel, petroleum ether/ ethyl acetate = 8:2)

3.25.c. 5-(4-chloro-phenyl)-2-ethynyl-pyridine

A reaction mixture of 7.4 g (25.88 mmol) 5-(4-chloro-phenyl)-2-trimethylsilanylethynyl-pyridine and 7.18 g (52 mmol) potassium carbonate in 80 ml of methanol is stirred for 30 minutes at ambient temperature. 500 ml dichloromethane are added and the reaction mixture is extracted with water and sodium hydrogen carbonate solution. The combined organic phases are dried over magnesium sulphate. The purification is

carried out by column chromatography on silica gel (eluant: petroleum ether to petroleum ether/ ethyl acetate= 8:2).

Yield: 2 g (36.2 % of theoretical)

$C_{13}H_8ClN$ (M= 213.66)

5 Calc.: Molecular ion peak (M+H)⁺: 214/216 Found: Molecular ion
peak (M+H)⁺: 214/216

3.25.d. [5-(4-chloro-phenyl)-pyridin-2-yl]-propynoic acid

1.6 ml (2.46 mmol) butyllithium solution (1.6M in hexane) are added dropwise at -10 C
10 to a solution of 0.5 g (2.34 mmol) 5-(4-chloro-phenyl)-2-ethynyl-pyridine in 30 ml
absolute THF and the mixture is stirred for five minutes at -8°C stirred. The reaction
mixture is combined with dry ice batchwise at -70° C, stirred for one hour at ambient
temperature and evaporated down. The residue is suspended in 5 ml of water and
combined with 1.6 ml 1N hydrochloric acid, whereupon a precipitate is formed. Then
15 ethyl acetate is added and the suspension is filtered. The solid is dried in the vacuum
drying chamber at 70 °C.

Yield: 0.25 g (41.5 % of theoretical)

Melting point: 210°C

$C_{14}H_8ClNO_2$ I (M= 257.67)

20 Calc.: Molecular ion peak (M+H)⁺: 258/260
Found: Molecular ion peak (M+H)⁺: 258/260

3.25.e. 3-[5-(4-chloro-phenyl)-pyridin-2-yl]-propynoic acid-(4-piperidin-1-ylmethyl-phenyl)-amide

25 Prepared analogously to Example 2.3.f from [5-(4-chloro-phenyl)-pyridin-2-yl]-
propynoic acid and 4-piperidin-1-ylmethyl-phenylamine.

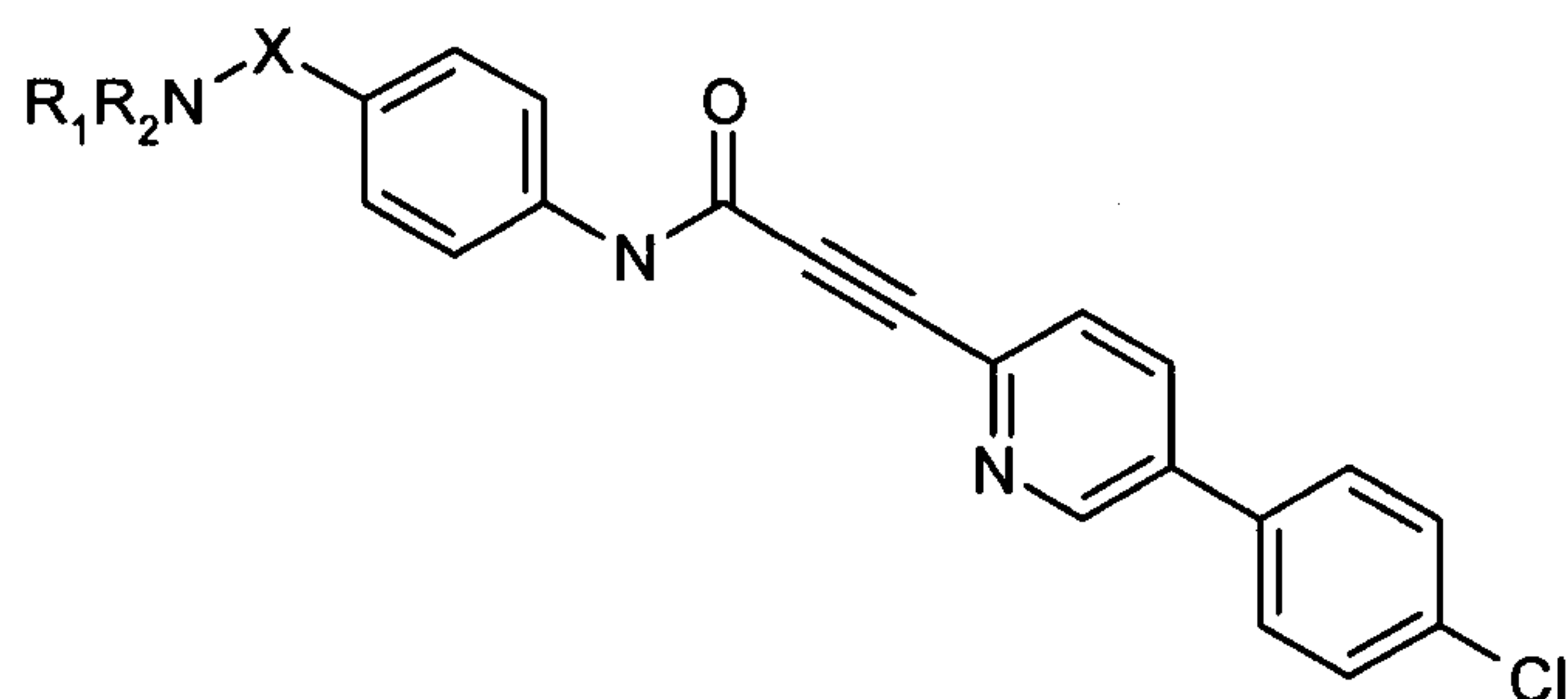
Yield: 0.2 g (48 % of theoretical)

$C_{26}H_{24}ClN_3O$ I (M= 429.95)

30 Calc.: Molecular ion peak (M+H)⁺: 430/432 Found: Molecular ion
peak (M+H)⁺: 430/432

R_f value: 0.4 (silica gel, dichloromethane/methanol/ammonia = 90:10:0.1)

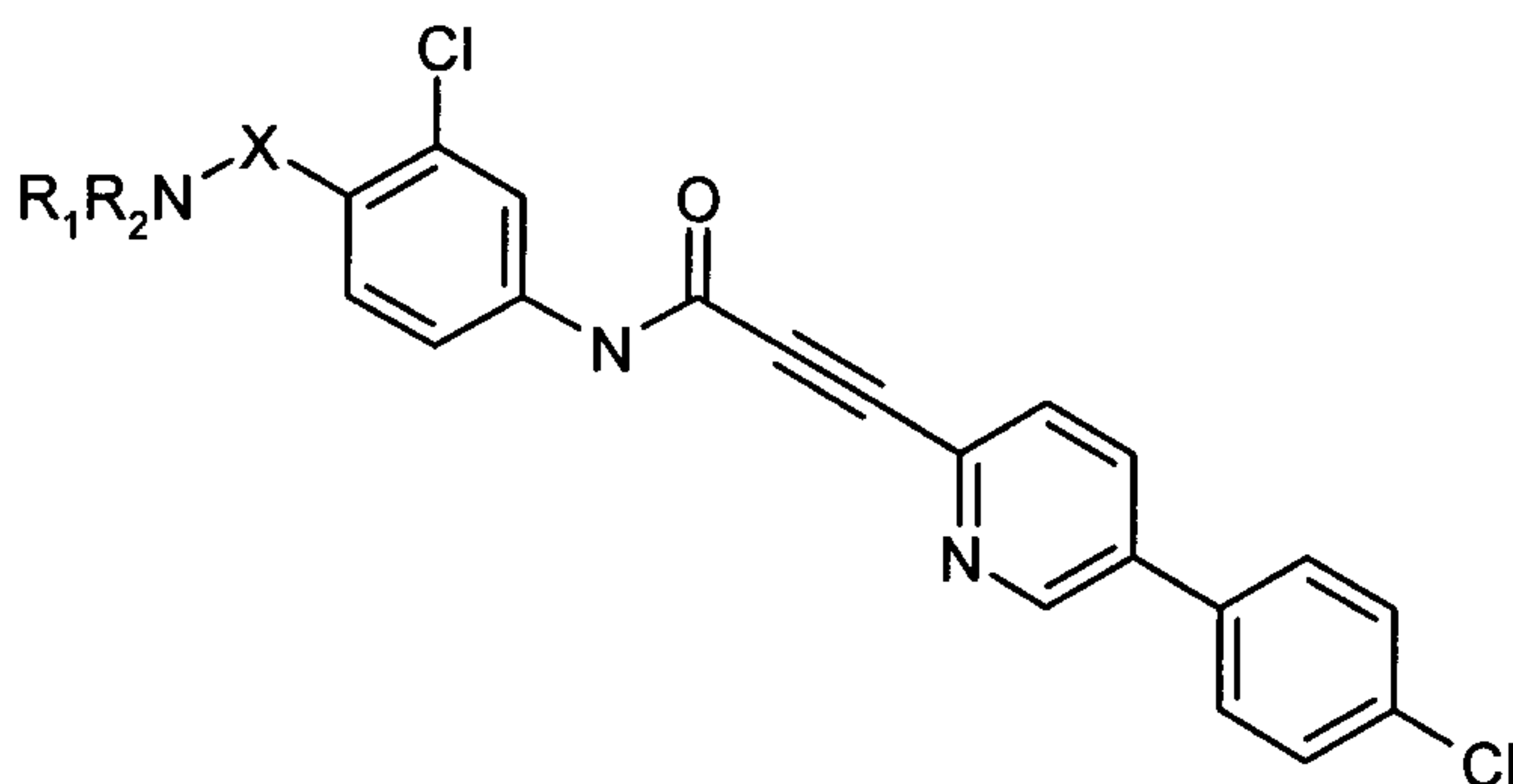
The following compounds are prepared analogously to Example 3.25:



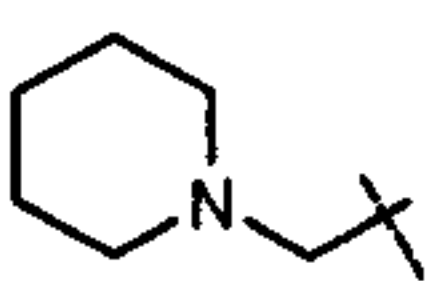
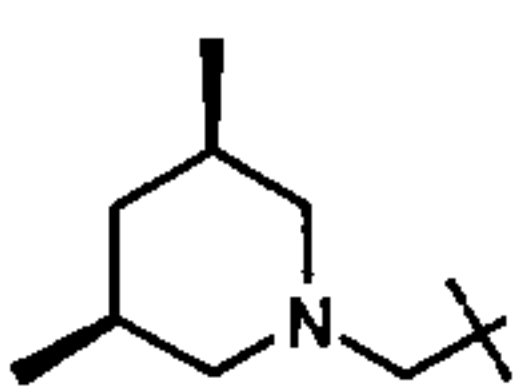
Example	R ₁ R ₂ N-X	educt	empirical formula	mass spectrum	mp [°C]	R _f value
3.26		3.24.d	C ₂₇ H ₂₆ ClN ₃ O ₂	460/462 (Cl) [M+H] ⁺	155- 159	0.6 (A)
3.27		3.24.d	C ₂₇ H ₂₆ ClN ₃ O	444/446 (Cl) [M+H] ⁺	183- 185	0.7 (B)
3.28		3.24.d	C ₂₆ H ₂₄ ClN ₃ O	430/432 (Cl) [M+H] ⁺	158- 161	0.6 (B)
3.29		3.24.d	C ₂₈ H ₂₈ ClN ₃ O	458/460 (Cl) [M+H] ⁺	195- 197	0.7 (B)

- 5 **R_f value:** A= (silica gel, dichloromethane/methanol 90:10)
 B= (silica gel, dichloromethane/methanol/ammonia 90:10:0.1)

The following compounds are prepared analogously to Example 3.25:

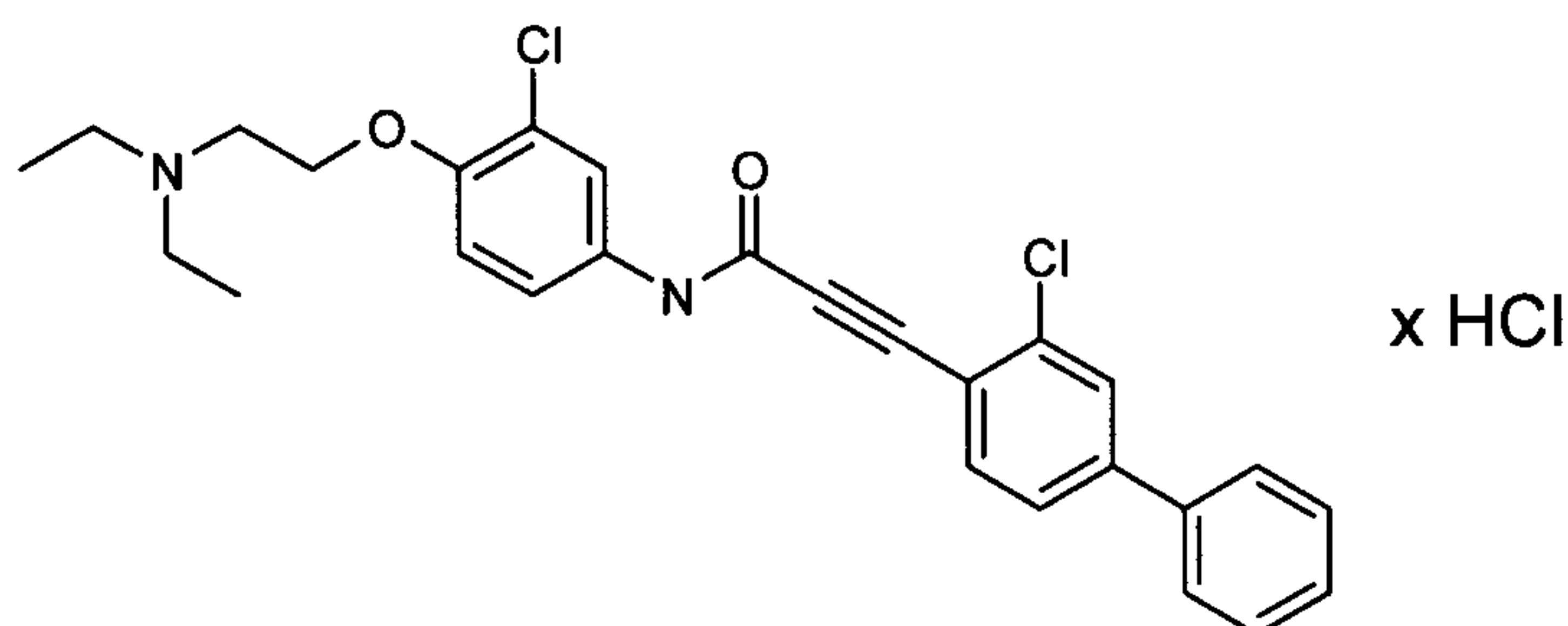


Example	R ₁ R ₂ N-X	educt	empirical formula	mass	mp	R _f value

				spectrum	[°C]	
3.30		3.24.d	C ₂₆ H ₂₃ Cl ₂ N ₃ O	464/66/68 (Cl ₂) [M+H] ⁺	150- 153	0.6 (A)
3.31		3.24.d	C ₂₈ H ₂₇ Cl ₂ N ₃ O	492/94/96 (Cl ₂) [M+H] ⁺	180- 185	0.8 (A)

R_f value: A= (silica gel, dichloromethane/methanol/ammonia 90:10:0.1)

Example 3.32: 3-(3-chloro-biphenyl-4-yl)-propynoic acid-[3-chloro-4-(2-diethylaminoethoxy)phenyl]-amide hydrochloride



3.32.a. trifluoro-methanesulphonic acid 3-chloro-biphenyl-4-yl ester

6.7 ml (40.32 mmol) trifluoromethanesulphonic acid anhydride, dissolved in 5 ml dichloromethane, are added dropwise between -10 to -5°C to a solution of 7.5 g (36.65 mmol) 3-chloro-biphenyl-4-ol and 6.1 ml (44 mmol) triethylamine in 100 ml dichloromethane. Then the mixture is stirred for 30 minutes. The reaction solution is then extracted with water, the organic phase is separated off and filtered through an alox frit. The filtrate is concentrated by evaporation.

Yield: 12 g (97 % of theoretical)

15 C₁₃H₈ClF₃O₃ S (M= 336.72)

Calc.: Molecular ion peak (M+H)⁺: 336/338 (Cl)
(M+H)⁺: 336/338 (Cl)

Found: Molecular ion peak

R_f value: 0.7 (silica gel, petroleum ether/ethyl acetate = 5:1)

20 3.32.b. tert-butyl-(3-chloro-biphenyl-4-ylethynyl)-dimethyl-silane

0.84 g (1.2 mmol) bis-(triphenylphosphine)-palladium(II)-chloride, 0.23 g (1.2 mmol) copper(I)iodide and 6.28 ml (33.6 mmol) (*tert*-butyldimethylsilyl)acetylene are added under an argon atmosphere to a solution of 8.1 g (24 mmol) 3-chloro-biphenyl-4-yl

trifluoro-methanesulphonate in 50 ml absolute dimethylformamide and 13.31 ml (96 mmol) triethylamine. At ambient temperature the reaction mixture is stirred for 24 hours. Then the reaction mixture is evaporated down, the residue is taken up in ethyl acetate and extracted with water. The organic phase is dried. The purification is carried out by column chromatography on silica gel (eluant: petroleum ether/ethyl acetate 4:1).

Yield: 8.4 g (107 % of theoretical)

$C_{20}H_{23}ClSi$ (M= 326.94)

Calc.: Molecular ion peak (M+H)⁺: 327/329 (CI)

Found: Molecular ion

peak (M+H)⁺: 327/329 (CI)

R_f value: 0.7 (silica gel, petroleum ether/toluene 9:1)

3.32.c. 3-chloro-4-ethynyl-biphenyl

7.85 g (24 mmol) tert-butyl-(3-chloro-biphenyl-4-ylethynyl)-dimethyl-silane are dissolved in 150 ml absolute tetrahydrofuran and at 5°C combined batchwise with 11.4 g (36 mmol) tetrabutylammonium fluoride*3H₂O. The reaction mixture reaches ambient temperature after 30 minutes. Then the solvent is evaporated down and the residue is extracted between ether and water. The organic phase is dried, combined with activated charcoal and filtered through Celite. The filtrate is evaporated down.

The purification is carried out by column chromatography on silica gel (eluant: petroleum ether/ethyl acetate 20:1)

Yield: 4.7 g (92 % of theoretical)

$C_{14}H_9Cl$ (M= 212.67)

R_f value: 0.6 (silica gel, petroleum ether/toluene 5:1)

3.32.d. (3-chloro-biphenyl-4-yl)-propynoic acid

13.8 ml (22.1 mmol) butyllithium solution (1.6M in hexane) are added dropwise to a solution of 4.7 g (22.1 mmol) 3-chloro-4-ethynyl-biphenyl in 100 ml absolute tetrahydrofuran at -10 to -20°C and after five minutes cooled to -60°C. At this

temperature dry ice is added batchwise to the reaction mixture and it is slowly allowed to come up to ambient temperature. Then the solvent is evaporated down and the residue is extracted between ethyl acetate and 1 M hydrochloric acid. The organic phase is dried, the desiccant filtered off and the solvent concentrated by evaporation.

The residue is stirred with petroleum ether, suction filtered and dried at 80°C in the circulating air dryer.

Yield: 4.8 g (85 % of theoretical)

$C_{15}H_9ClO_2$ (M= 256.68)

- 5 Calc.: Molecular ion peak (M+H)⁺: 257/259 (Cl) Found: Molecular ion peak (M+H)⁺: 257/259 (Cl)

R_f value: 0.2 (silica gel, dichloromethane/methanol/glacial acetic acid 90:10:0.1)

- 10 3.32.e. 3-(3-chloro-biphenyl-4-yl)-propynoic acid-[3-chloro-4-(2-diethylamino-ethoxy)phenyl]-amide hydrochloride

Prepared analogously to Example 3.8.a from (3-chloro-biphenyl-4-yl)-propynoic acid and 3-chloro-4-(2-diethylamino-ethoxy)-phenylamine.

Yield: 0.35 g (68 % of theoretical)

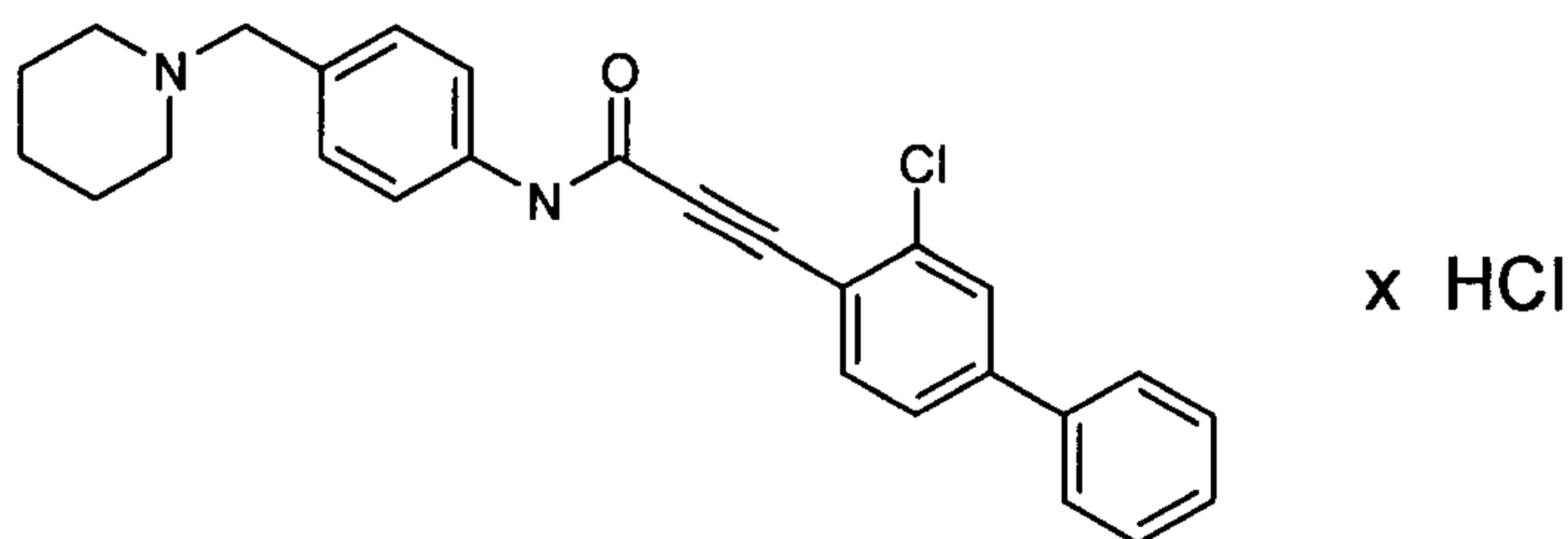
Melting point: 195-200 °C

- 15 $C_{27}H_{26}Cl_2N_2 O_2 \cdot HCl$ (M= 517.87)

Calc.: Molecular ion peak (M+H)⁺: 481/3/5 (Cl₂) Found: Molecular ion peak (M+H)⁺: 481/3/5 (Cl₂)

R_f value: 0.6 (silica gel, dichloromethane/methanol/ammonia = 90:10:0.1)

- 20 **Example 3.33:** 3-(3-chloro-biphenyl-4-yl)-propynoic acid-(4-piperidin-1-ylmethyl-phenyl)-amide hydrochloride



- 25 Prepared analogously to Example 3.8. from (3-chloro-biphenyl-4-yl)-propynoic acid and 4-piperidin-1-ylmethyl-phenylamine.

Yield: 0.35 g (75 % of theoretical)

Melting point: 260-265 °C

$C_{27}H_{25}ClN_2 O \cdot HCl$ (M= 465.41)

Calc.: Molecular ion peak (M+H)⁺: 429/31 (Cl)
(M+H)⁺: 429/31 (Cl)

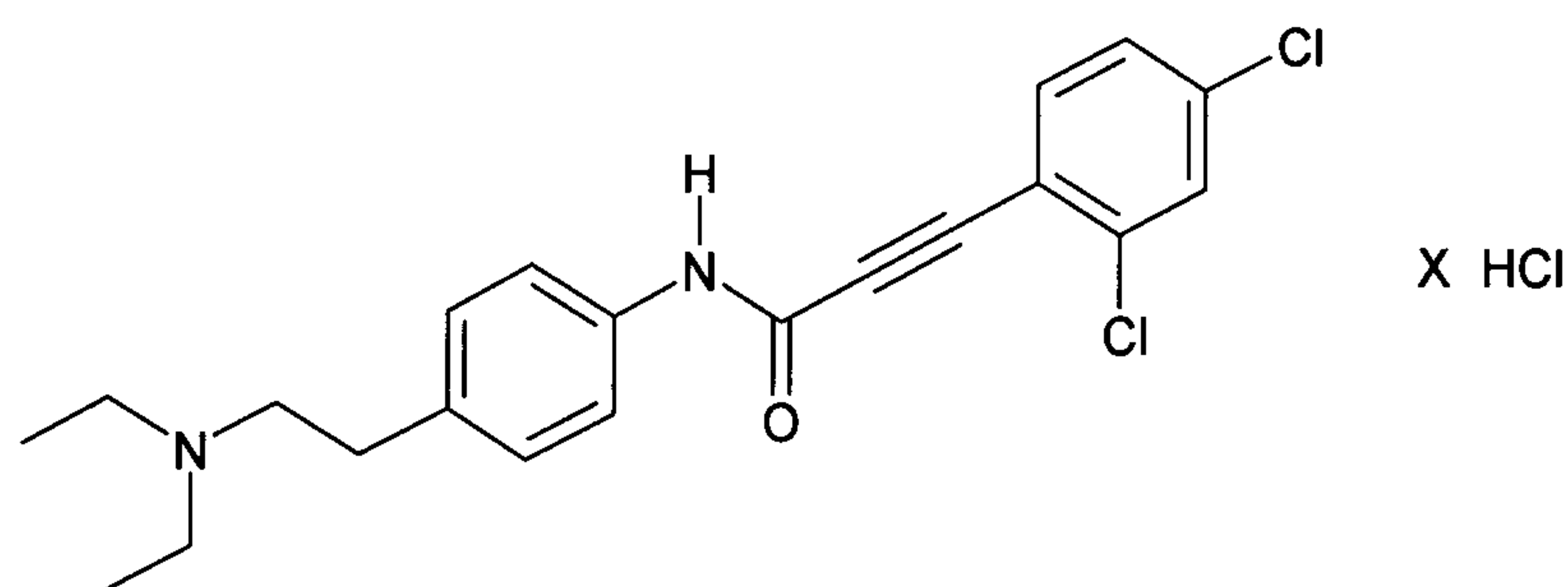
Found: Molecular ion peak

R_f value: 0.6 (silica gel, dichloromethane/methanol/ammonia = 90:10:0.1)

5

Example 3.34:

3-(2,4-dichloro-phenyl)-propynoic acid-[4-(2-diethylamino-ethyl)-phenyl]-amide-hydrochloride



10

3.34.a. 3-(2,4-dichloro-phenyl)-propynoic acid-[4-(2-diethylamino-ethyl)-phenyl]-amide-hydrochloride

Prepared analogously to Example 2.3.f from 4-(2-diethylamino-ethyl)-phenylamine and (2,4-dichloro-phenyl)-propynoic acid.

15 Yield: 0.3 g (47 % of theoretical)

Melting point: 204-208⁰C

C₂₁H₂₂Cl₂N₂O (M= 425.78)

Calc.: Molecular ion peak (M+H)⁺: 389/391/393

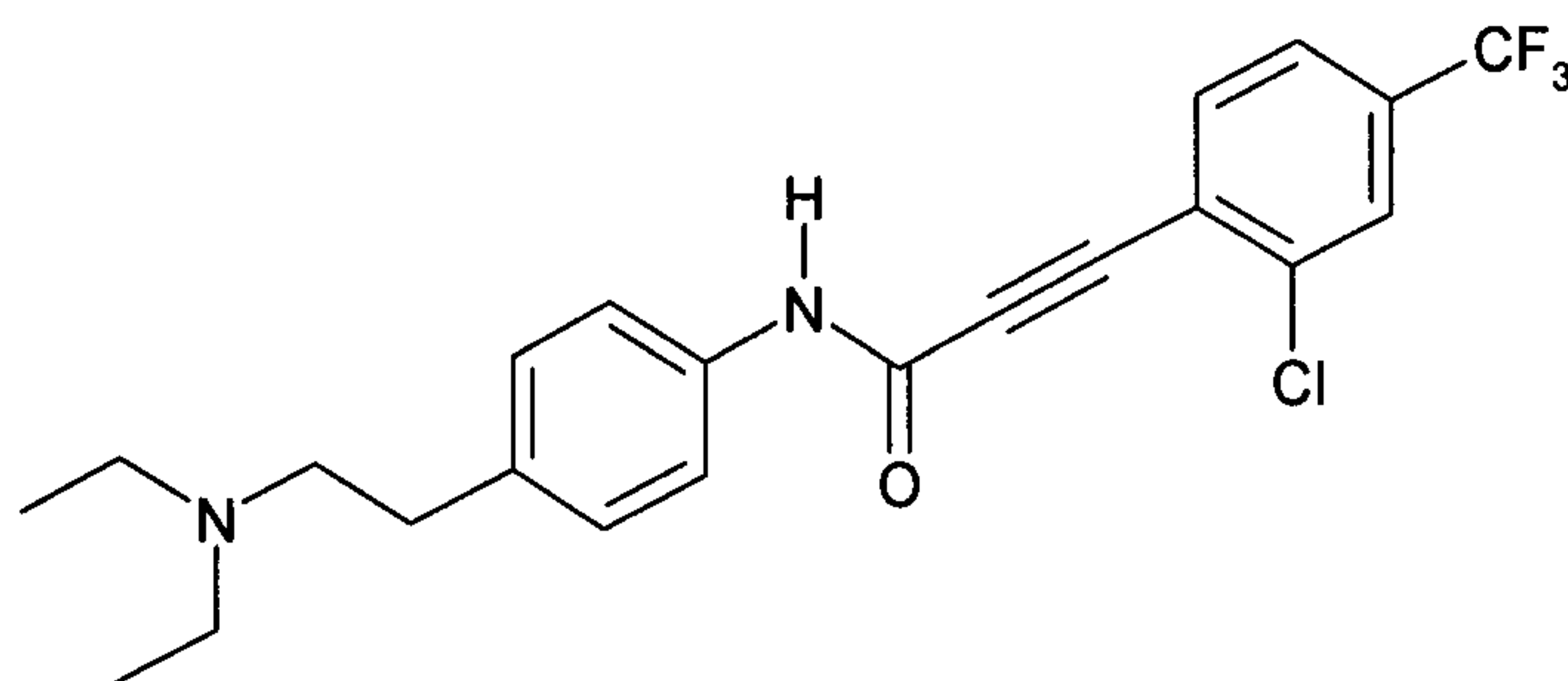
Found: Molecular ion

peak (M+H)⁺: 389/391/393

20 R_f value: 0.6 (silica gel, dichloromethane/ ethanol/ammonia = 5:1:0.01)

Example 3.35.

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[4-(2-diethylamino-ethyl)-phenyl]-amide



Prepared analogously to Example 2.3.f from 90 mg (0.44 mmol) 4-(2-diethylamino-ethyl)-phenylamine and 99 mg (0.40 mmol) 2-chloro-4-trifluoromethyl-phenyl)-propynoic acid.

Yield: 71 mg (42 % of theory)

Melting point: 145-150 C

$C_{22}H_{22}ClF_3N_2O$ (M= 422.88)

Calc.: Molecular ion peak (M+H)⁺: 423/425

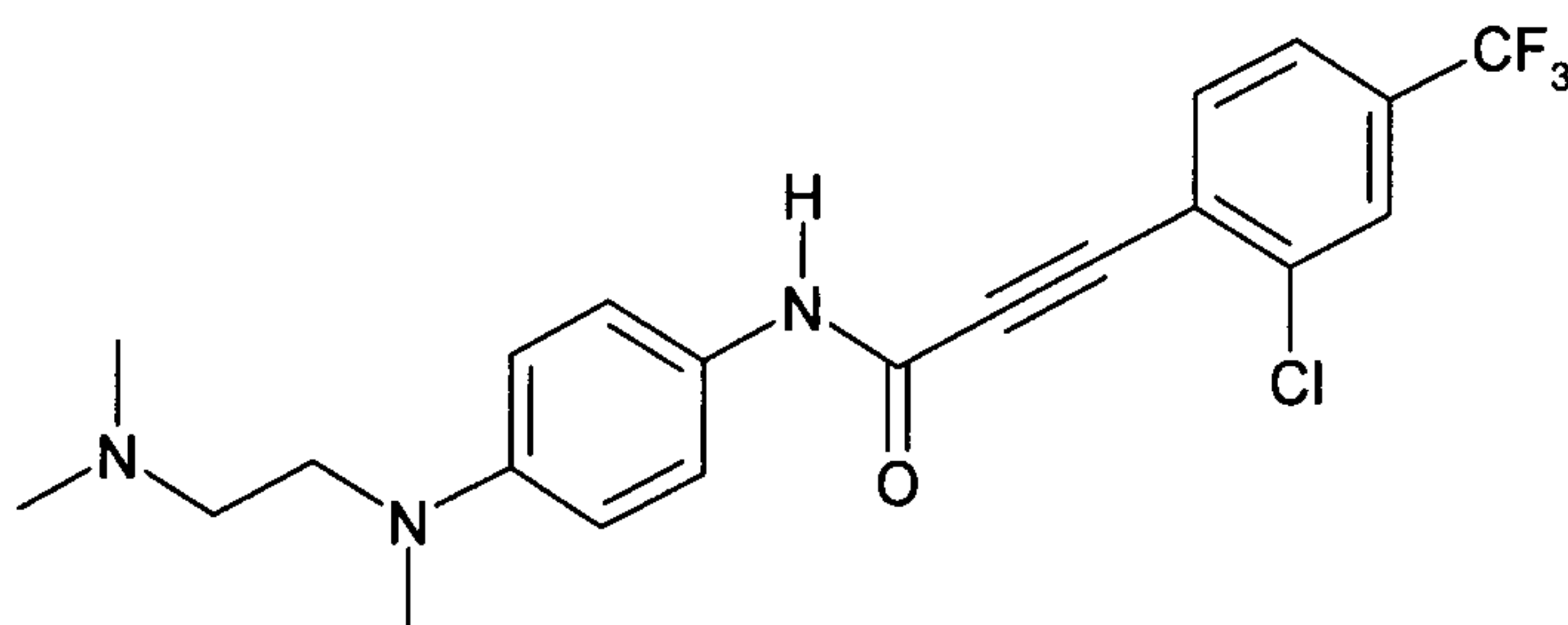
Found: Molecular ion peak

(M+H)⁺: 423/425

R_f value: 0.30 (silica gel, dichloromethane/methanol = 9:1)

Example 3.36

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-{4-[N-(2-dimethylamino-ethyl)-methylamino]-phenyl}-amide-formate



Prepared analogously to Example 2.3.f. from 90 mg (0.44 mmol) 4-[N-(2-dimethylamino-ethyl)-methylamino]-phenylamine (for preparation see International Patent Application WO 01/27081) and 99 mg (0.40 mmol) 2-chloro-4-trifluoromethyl-phenyl)-propynoic acid.

Yield: 64 mg (38 % of theory)

$C_{21}H_{21}ClF_3N_3O \times CH_2O_2$ (M= 469.89)

Calc.: Molecular ion peak (M+H)⁺: 424/426

Found: Molecular ion peak

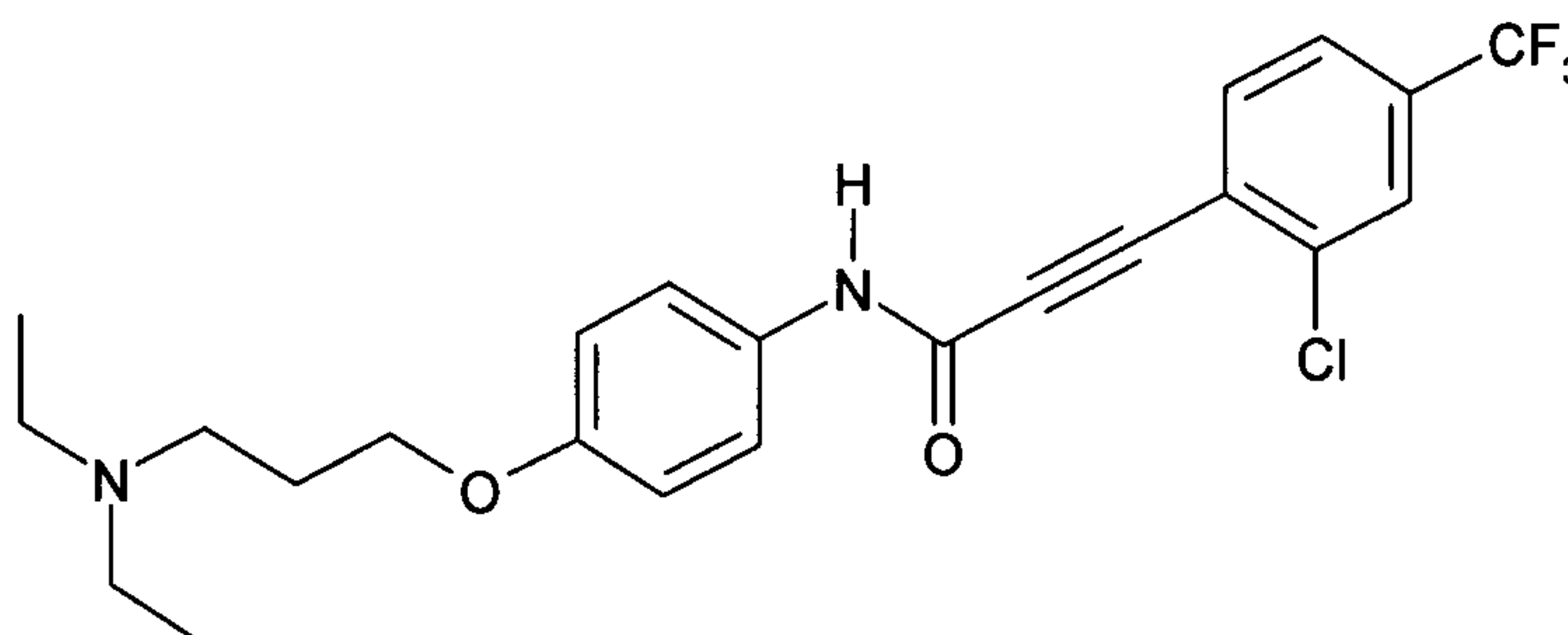
(M+H)⁺: 424/426

R_f value: 0.35 (silica gel, dichloromethane/methanol = 9:1)

5

Example 3.37

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[4-(2-diethylamino-propoxy)-phenyl]-amide



- 10 Prepared analogously to Example 2.3.f. from 67 mg (0.3 mmol) 4-(2-diethylamino-propoxy)-phenylamine and 75 mg (0.3 mmol) (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid.

Yield: 71 mg (52 % of theory)

Melting point: 172-176 C

- 15 C₂₃H₂₄ClF₃N₂O₂ (M= 452.90)

Calc.: Molecular ion peak (M+H)⁺: 453/455

Found: Molecular ion peak

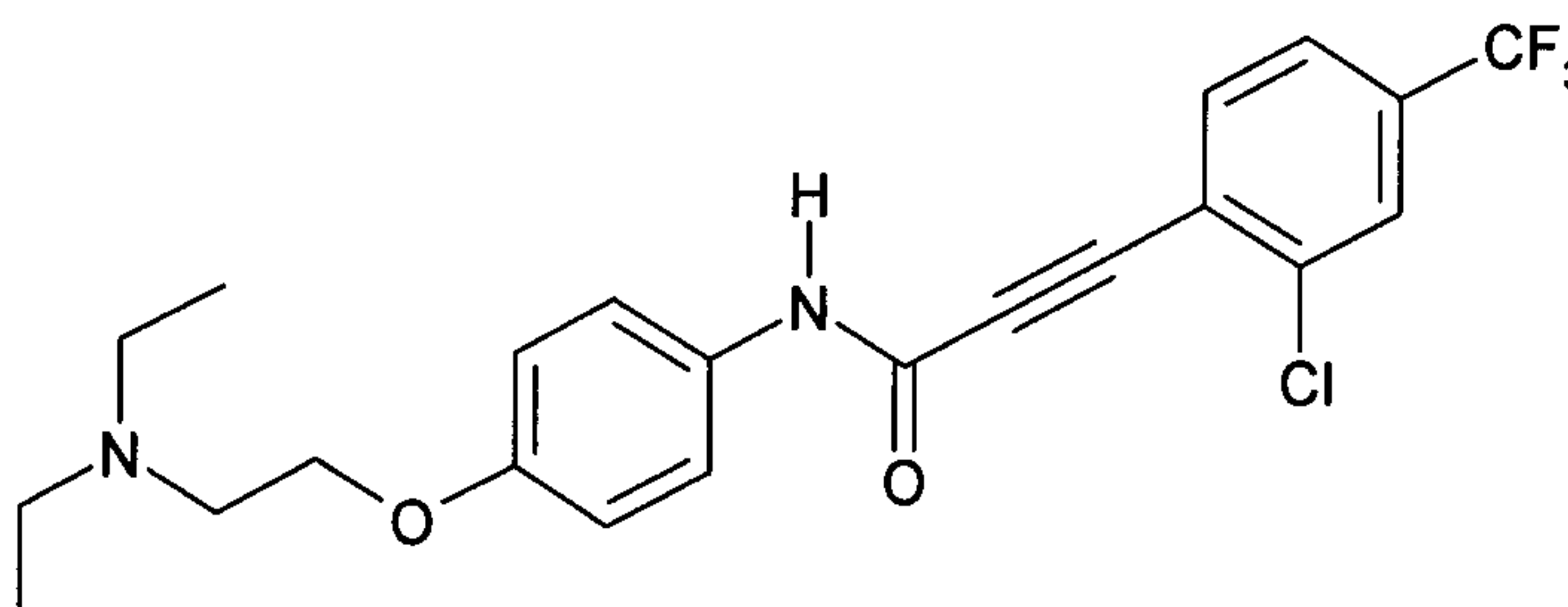
(M+H)⁺: 453/455

R_f value: 0.30 (silica gel, dichloromethane/methanol = 9:1)

20

Example 3.38

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[4-(2-diethylamino-ethoxy)-phenyl]-amide



25

Prepared analogously to Example 2.3.f from 69 mg (0.33 mmol) 4-(2-diethylamino-ethoxy)-phenylamine and 75 mg (0.30 mmol) (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid.

Yield: 70 mg (53 % of theory)

5 Melting point: 194-197 °C

$C_{22}H_{22}ClF_3N_2O_2$ (M= 438.88)

Calc.: Molecular ion peak (M+H)⁺: 439/441

Found: Molecular ion peak

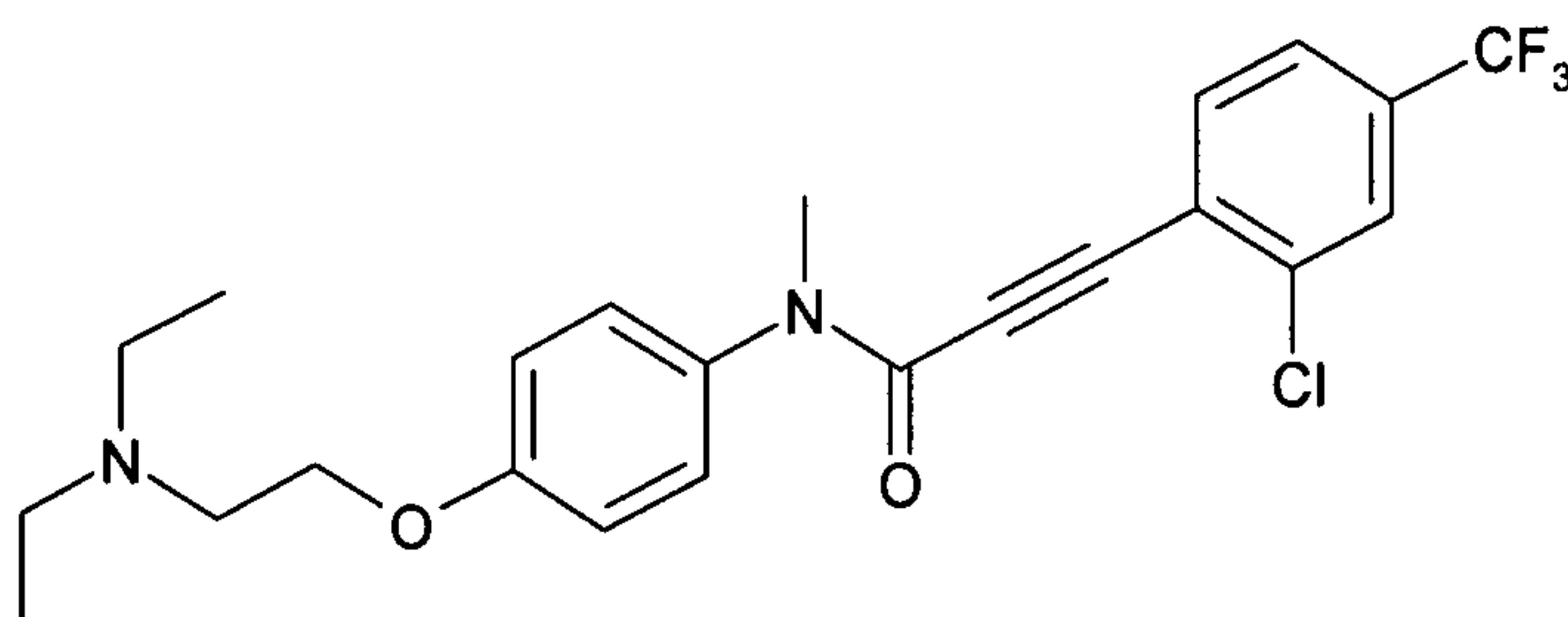
(M+H)⁺: 439/441

R_f value: 0.35 (silica gel, dichloromethane/methanol = 9:1)

10

Example 3.39

3-(2-chloro-4-methyl-phenyl)-propynoic acid-[4-(2-diethylamino-ethoxy)-phenyl]-methyl-amide



15

Prepared analogously to Example 2.3.f from [4-(2-diethylamino-ethoxy)-phenyl]-methyl-amine and (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid.

Yield: 60 mg (22 % of theory)

20 Melting point: 135-138 °C

$C_{23}H_{24}ClF_3N_2O_2$ (M= 452.90)

Calc.: Molecular ion peak (M+H)⁺: 453/455

Found: Molecular ion peak

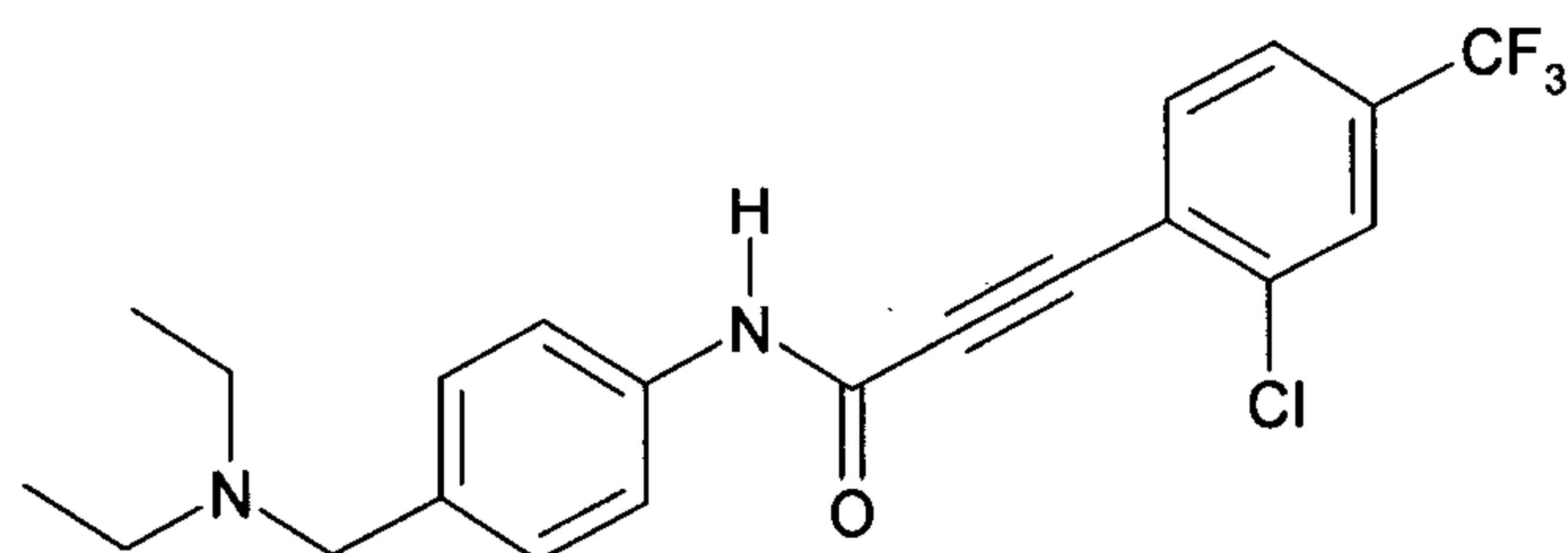
(M+H)⁺: 453/455

R_f value: 0.4 (silica gel, dichloromethane/methanol = 9:1)

25

Example 3.40

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-(4-diethylaminomethyl-phenyl)-amide



Prepared analogously to Example 2.3.f from 4-diethylaminomethyl-phenylamine and (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid.

Yield: 72 mg (59 % of theory)

5 $C_{21}H_{20}ClF_3N_2O$ (M= 408.85)

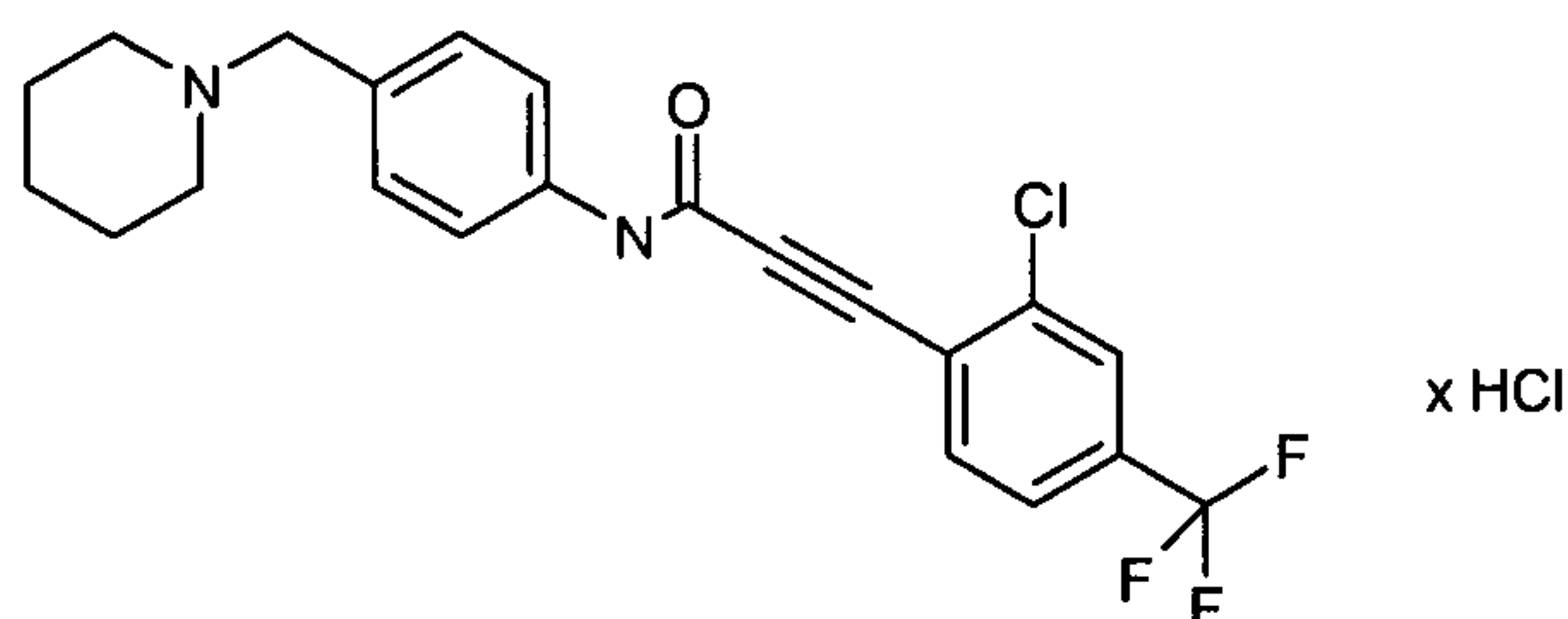
Calc.: Molecular ion peak (M+H)⁺: 409/411

Found: Molecular ion peak

(M+H)⁺: 409/411

R_f value: 0.35 (silica gel, dichloromethane/methanol = 9:1)

10 **Example 3.41** 3-(2-chloro-4-trifluoromethyl-phenyl)propynoic acid(4-piperidin-1-ylmethyl-phenyl)-amide hydrochloride



Prepared analogously to Example 2.3.f from 4-piperidin-1-ylmethyl-phenylamine and (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid.

15 Yield: 170 mg (40 % of theory)

$C_{22}H_{20}ClF_3N_2O$ (M= 420.86)

Melting point: 193-195 °C

Calc.: Molecular ion peak (M-H)⁻: 419/421(Cl)

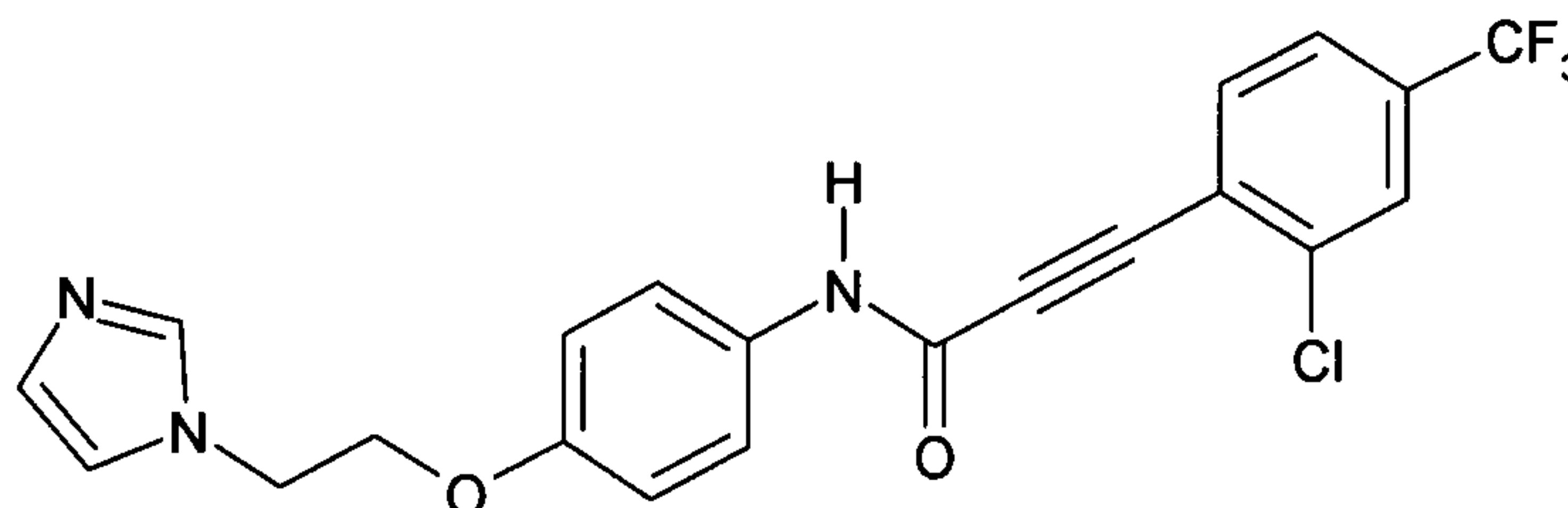
Found: Molecular ion peak (M-

H)⁻: 419/421 (Cl)

20 R_f value: 0.5(silica gel, dichloromethane/methanol = 9:1)

Example 3.42

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[4-(2-imidazol-1-yl-ethoxy)-phenyl]-amide



5

Prepared analogously to Example 2.3.f from 4-(2-imidazol-1-yl-ethoxy)-phenylamine and (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid.

Yield: 78 mg (60 % of theory)

Melting point: 182-186 °C

10 $C_{21}H_{15}ClF_3N_3O_2$ (M= 433.82)

Calc.: Molecular ion peak (M+H)⁺: 434/436

Found: Molecular ion peak

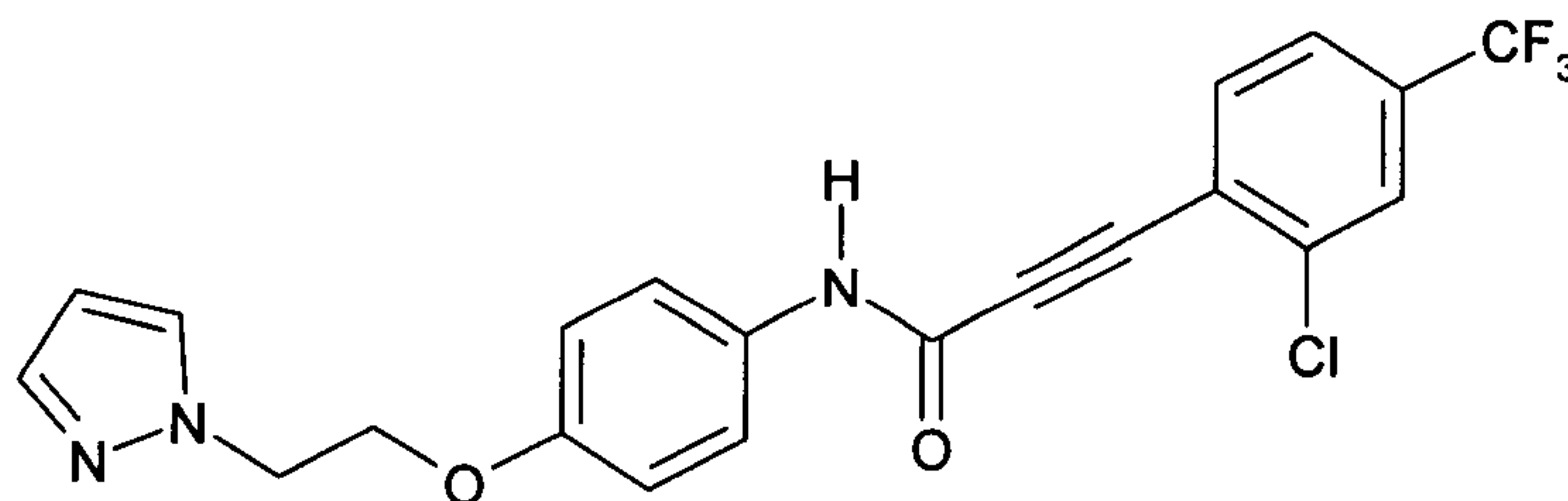
(M+H)⁺: 434/436

R_f value: 0.33 (silica gel, dichloromethane/methanol = 9:1)

15

Example 3.43

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[4-(2-pyrazol-1-yl-ethoxy)-phenyl]-amide



20

Prepared analogously to Example 2.3.f from 4-(2-pyrazol-1-yl-ethoxy)-phenylamine and (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid.

Yield: 56 mg (43 % of theory)

Melting point: 120-125 °C

25 $C_{21}H_{15}ClF_3N_3O_2$ (M= 433.82)

Calc.: Molecular ion peak (M+H)⁺: 434/436
(M+H)⁺: 434/436

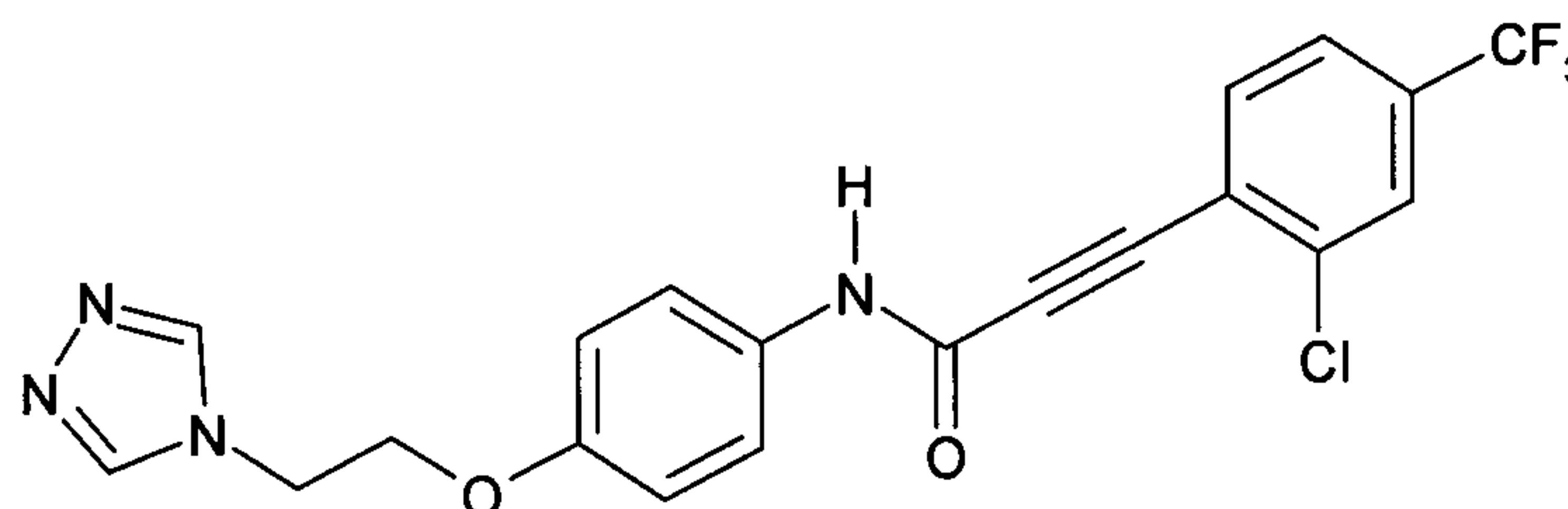
Found: Molecular ion peak

R_f value: 0.6 (silica gel, dichloromethane/methanol = 9:1)

5

Example 3.44

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[4-(2-[1,2,4]triazol-4-yl-ethoxy)-phenyl]-amide



10

Prepared analogously to Example 2.3.f from 4-(2-[1,2,4]triazol-4-yl-ethoxy)-phenylamine and (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid.

Yield: 51 mg (39.4 % of theory)

Melting point: 223-227 °C

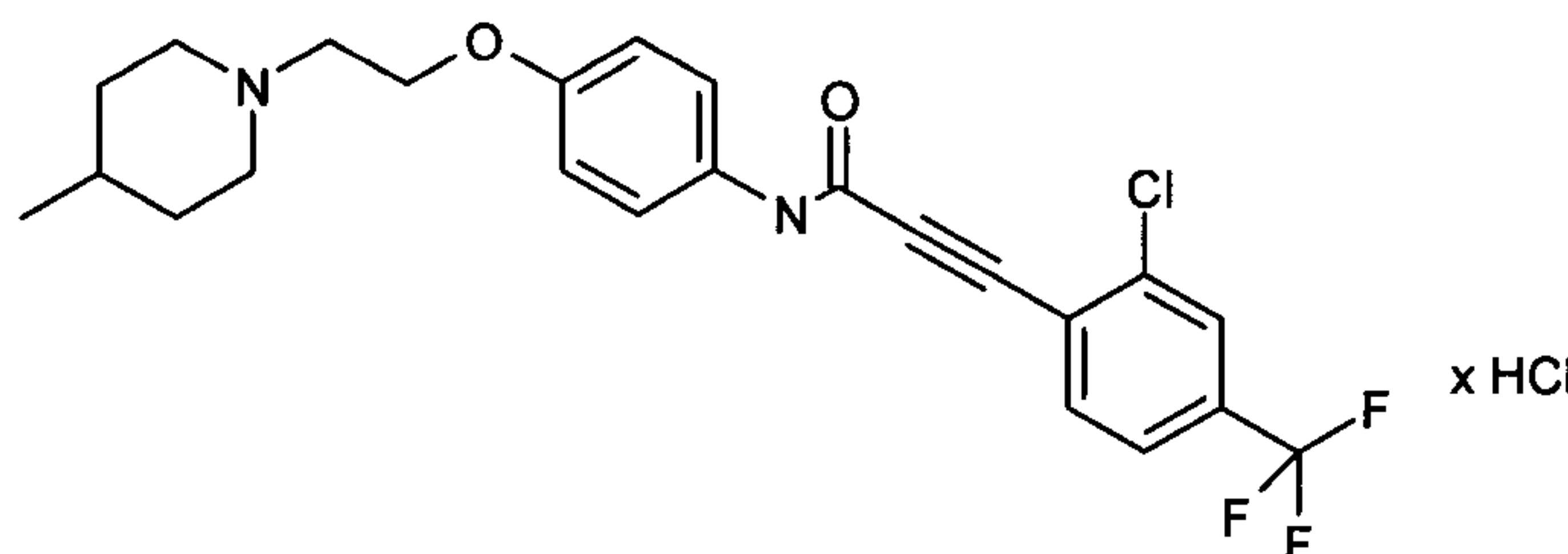
15 C₂₀H₁₄ClF₃N₄O₂ (M= 434.80)

Calc.: Molecular ion peak (M+H)⁺: 435/437
(M+H)⁺: 435/437

Found: Molecular ion peak

R_f value: 0.31 (silica gel, dichloromethane/methanol = 9:1)

20 **Example 3.45** 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid {4-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenyl}-amide hydrochloride



3.45.a. 4-methyl-1-[2-(4-nitro-phenoxy)-ethyl]-piperidine

200 mg (4.2 mmol) sodium hydride (55%) are added at 0°C to a solution of 0.54 g

25 (3.83 mmol) 1-fluoro-4-nitrobenzene and 0.6 g (4.2 mmol) 2-(4-methyl-piperidin-1-yl)-ethanol in 10 ml of dimethylformamide under an argon atmosphere. The reaction

mixture is stirred for two hours at 0°C and then stirred for a further 1.5 hours at ambient temperature. The reaction mixture is evaporated down and the residue is extracted between water and ethyl acetate. The organic phase is dried, the desiccant is filtered off and the filtrate is evaporated down. The purification is carried out by column chromatography on silica gel (eluant: dichloromethane/methanol 9:1)

Yield: 700 mg (69 % of theory)

$C_{14}H_{20}N_2O_3$ (M= 264.32)

Calc.: Molecular ion peak (M+H)⁺: 265

Found: Molecular ion peak (M+H)⁺:

265

R_f value: 0.7 (silica gel, dichloromethane/methanol = 9:1)

3.45.b. 4-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenylamine

A reaction mixture of 680 mg (2.57 mmol) 4-methyl-1-[2-(4-nitro-phenoxy)-ethyl]-

piperidine and 80 mg palladium (10% on charcoal) in 10 ml of methanol is

hydrogenated at ambient temperature and 3 bar hydrogen for 4.5 hours. The catalyst is suction filtered and the filtrate is evaporated down.

Yield: 540 mg (90 % of theory)

$C_{14}H_{22}N_2O$ (M= 234.34)

Calc.: Molecular ion peak (M+H)⁺: 235

Found: Molecular ion peak (M+H)⁺:

235

R_f value: 0.33 (silica gel, dichloromethane/methanol/ammonia = 90:10:0.1)

3.45.c. 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid {4-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenyl}-amide hydrochloride

Prepared analogously to Example 3.7.c. from 4-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenylamine and (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid.

Yield: 230 mg (49 % of theoretical)

$C_{24}H_{24}ClF_3N_2O_2$ (M= 464.91)*HCl

Melting point: 240-245°C

Calc.: Molecular ion peak (M+H)⁺: 465/467 (Cl)

Found: Molecular ion

peak (M+H)⁺: 465/467 (Cl)

R_f value: 0.6 (silica gel, dichloromethane/methanol = 9:1)

The following compounds are prepared analogously to the Examples mentioned
5 above:

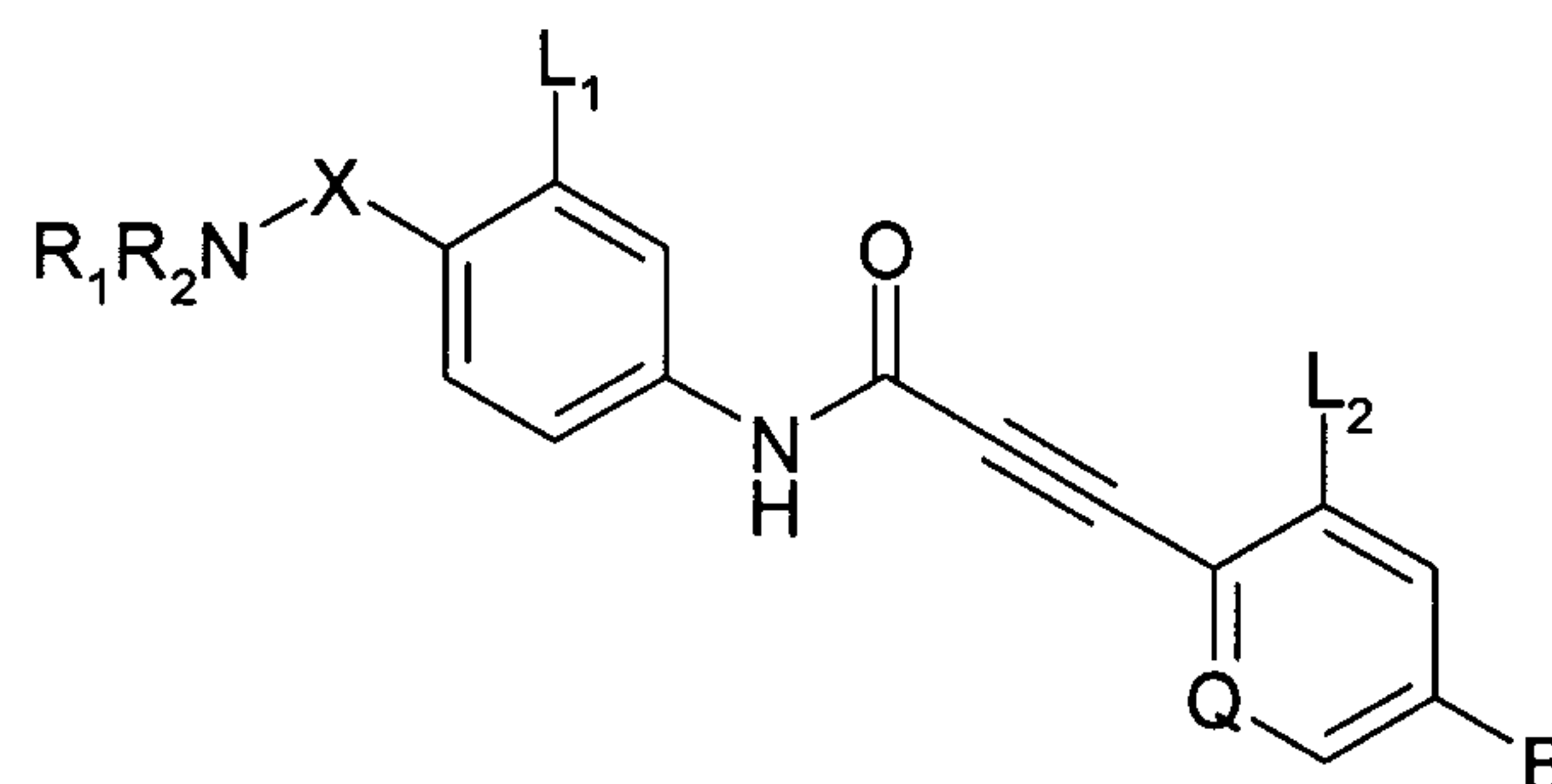
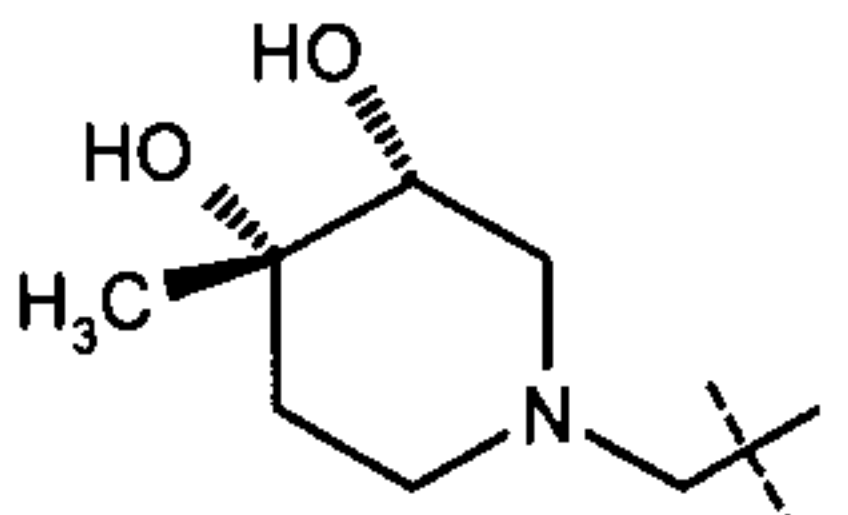
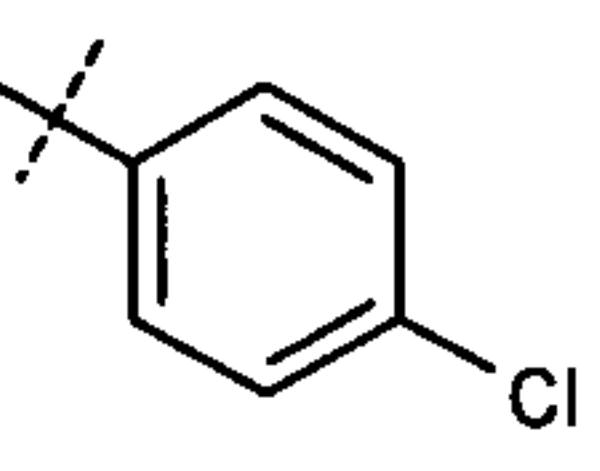
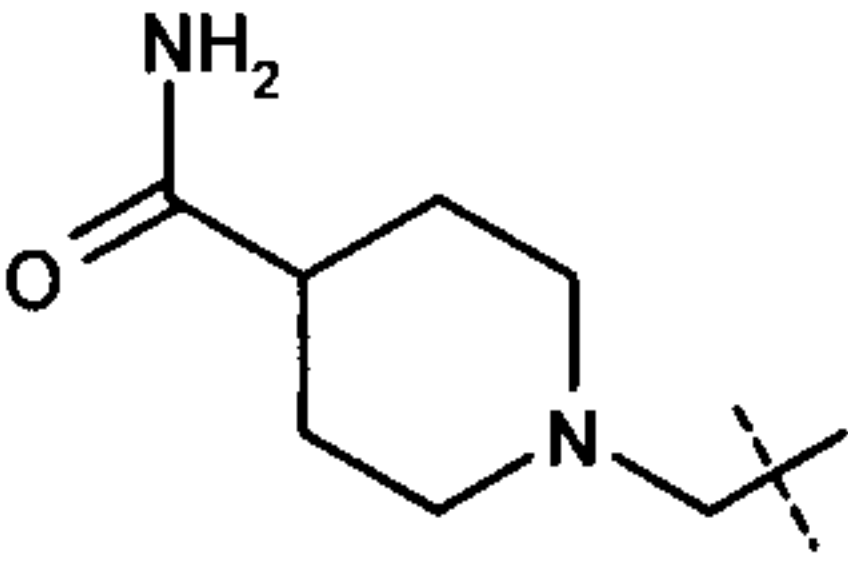
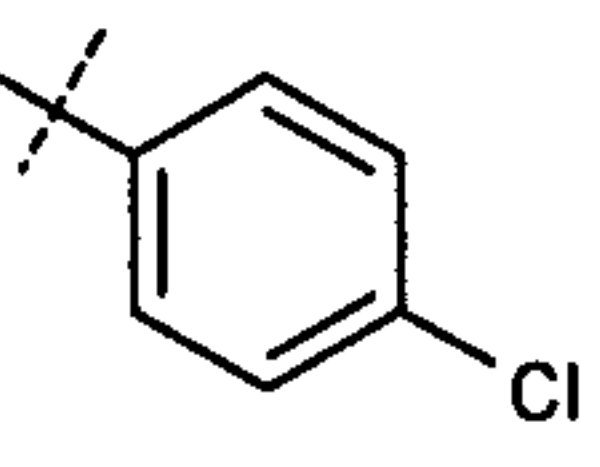
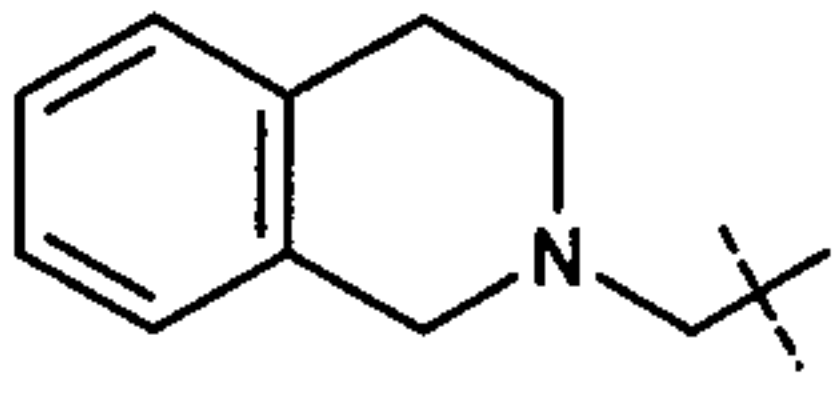
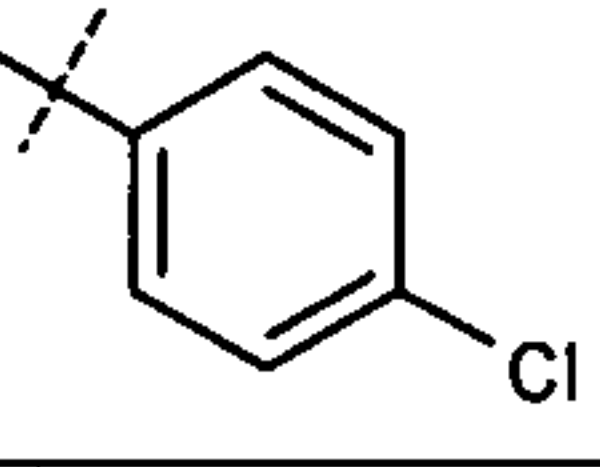
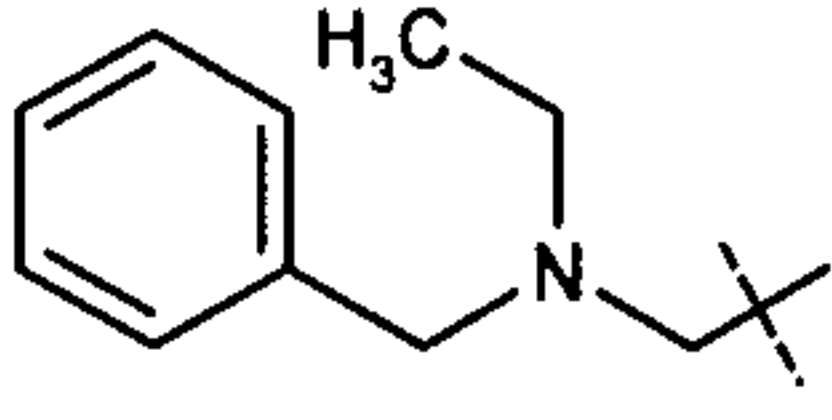
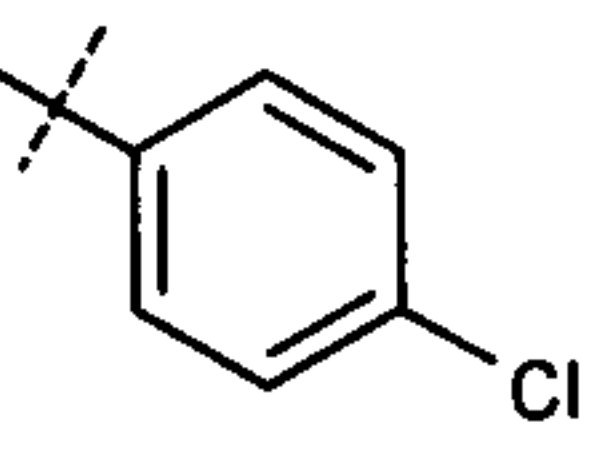
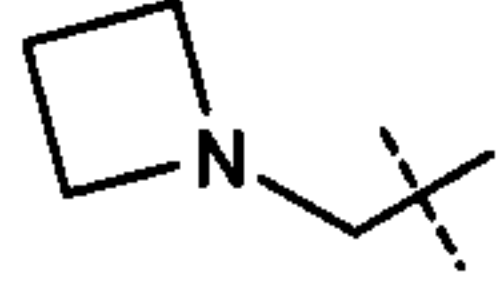
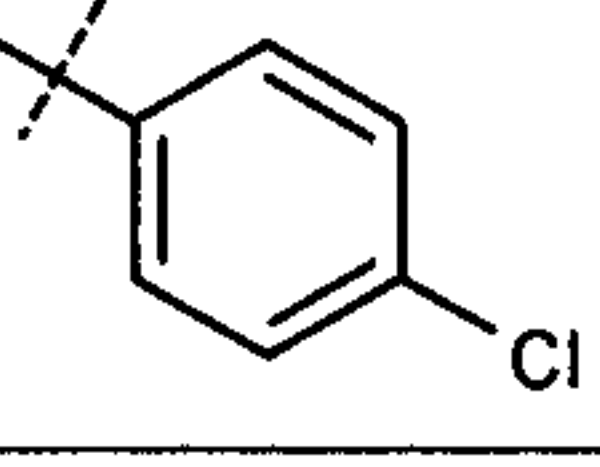
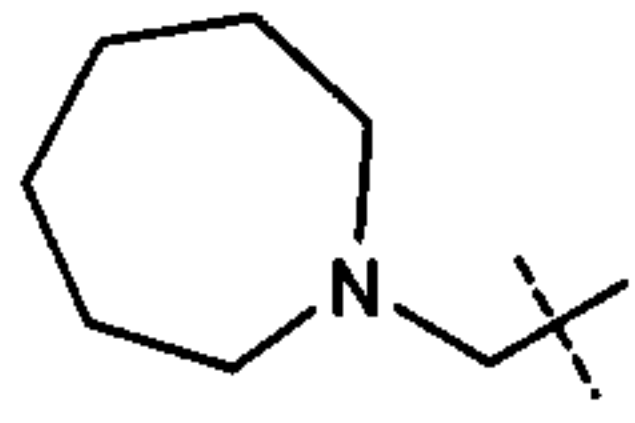
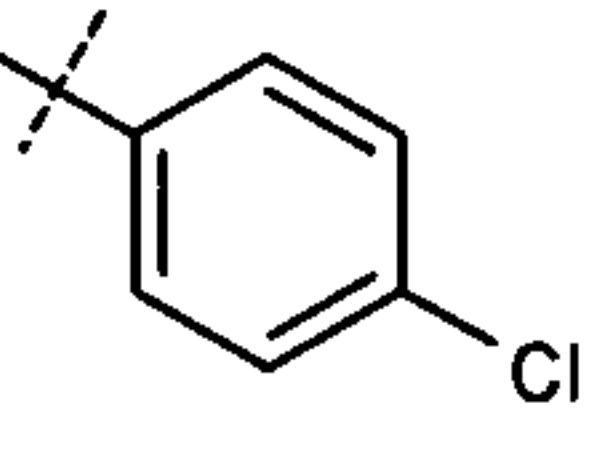
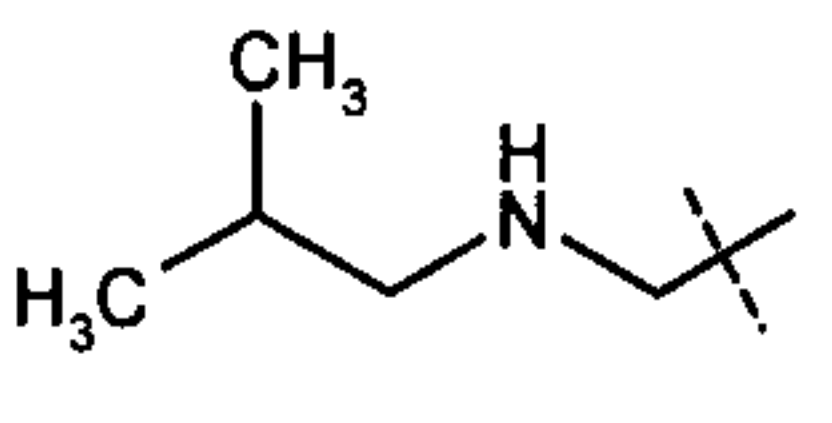
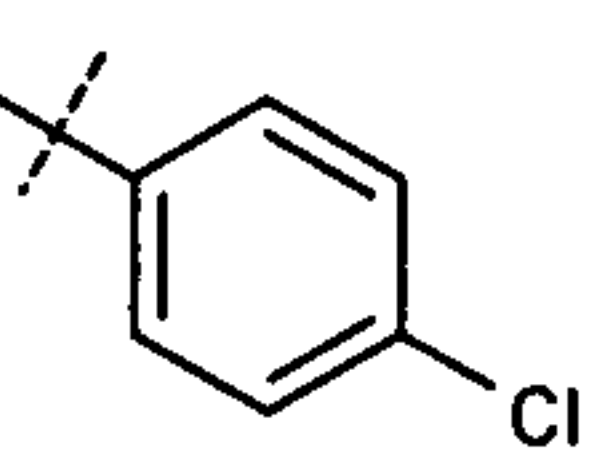
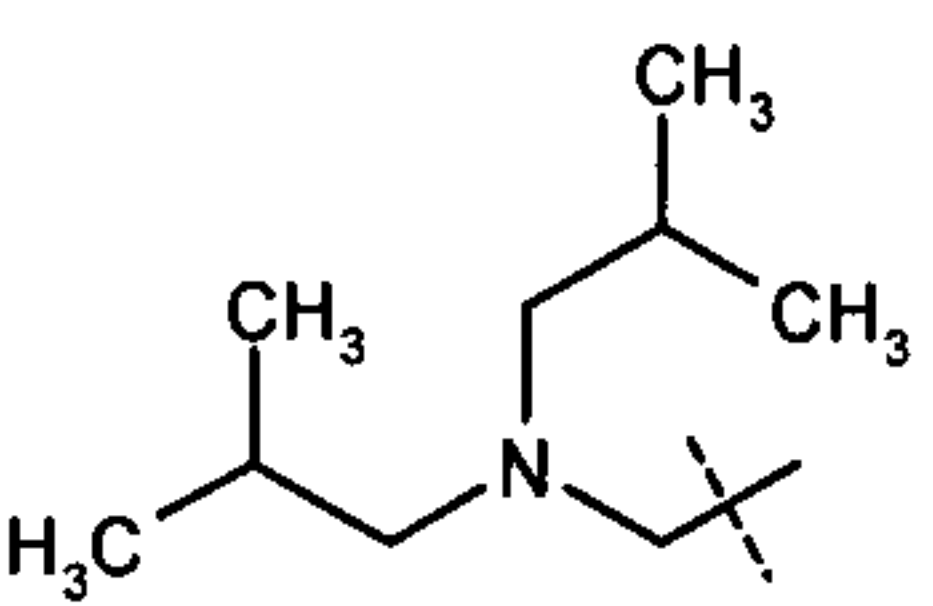
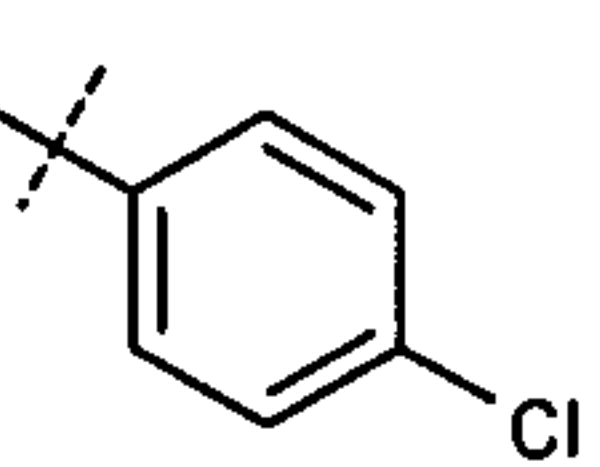
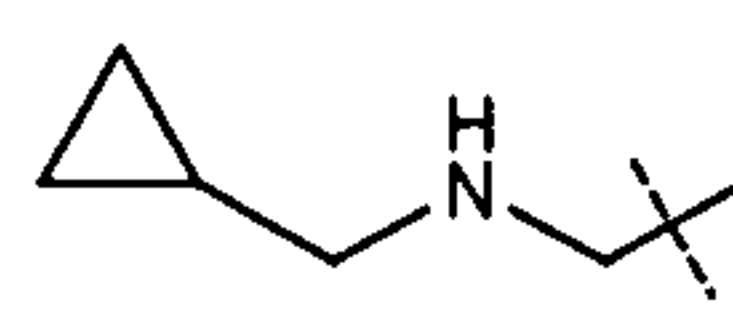
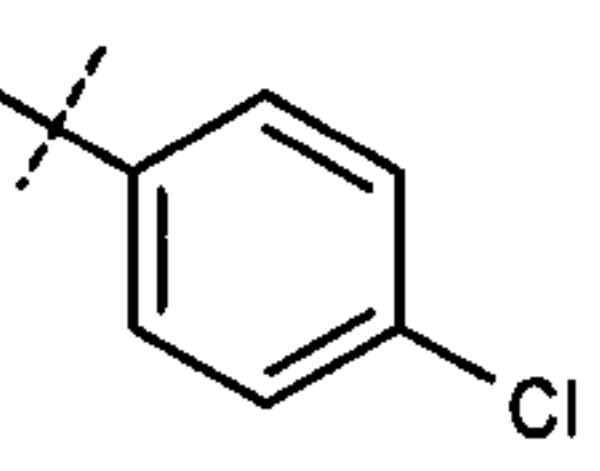
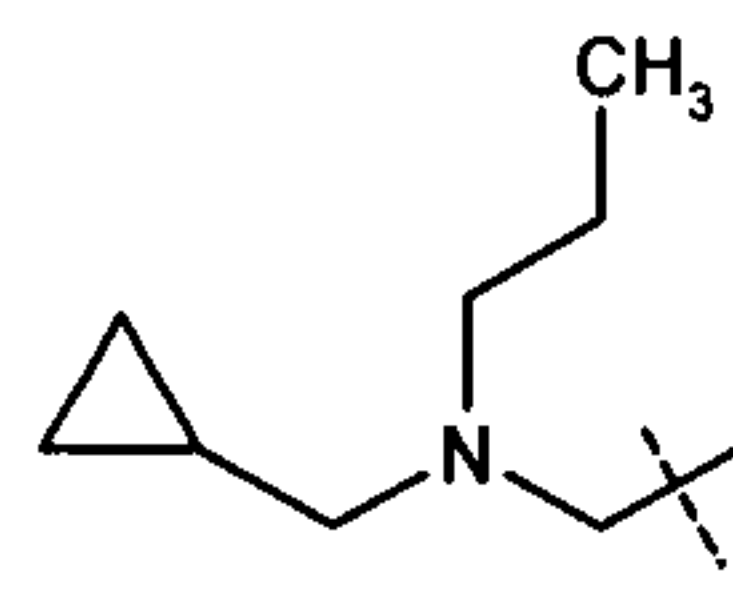
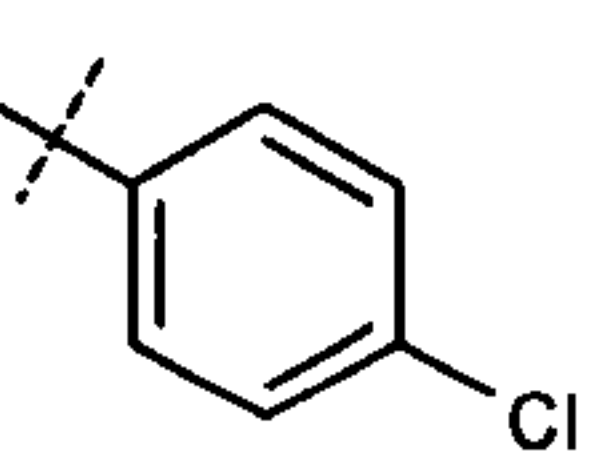
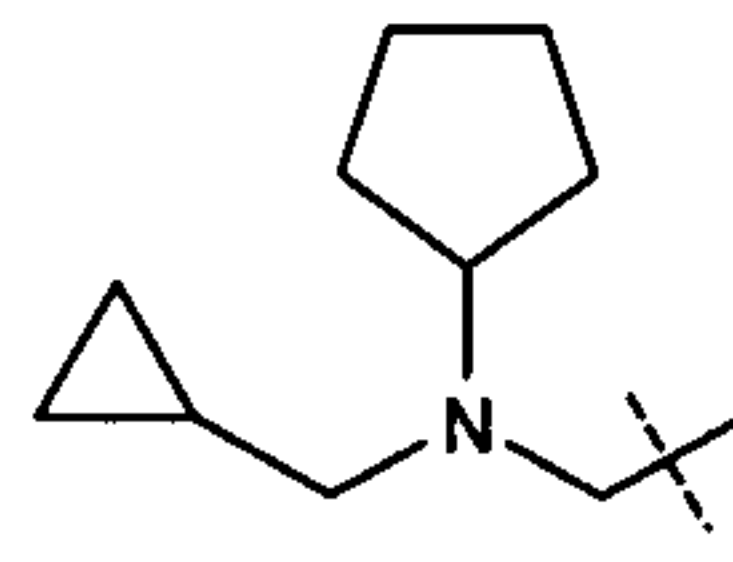
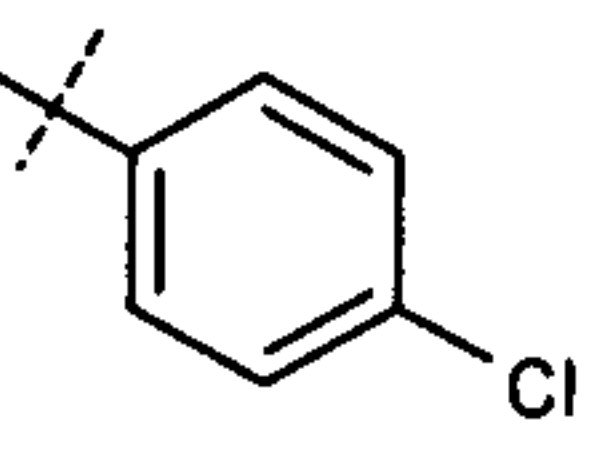
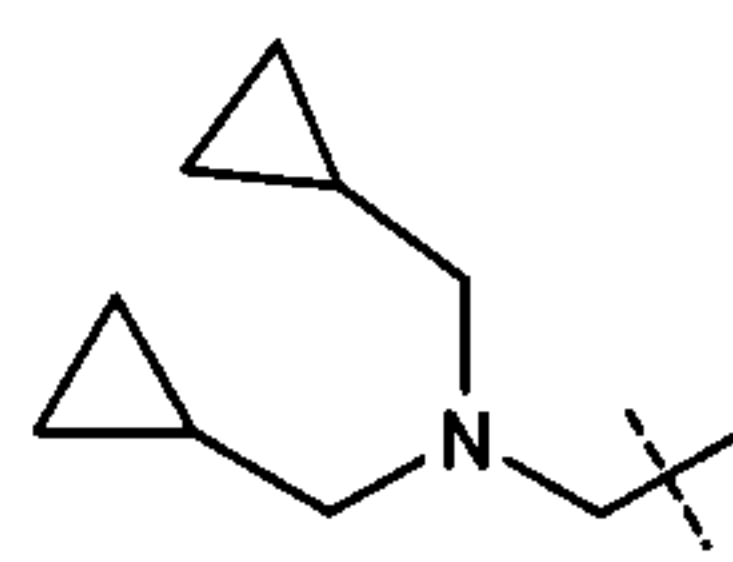
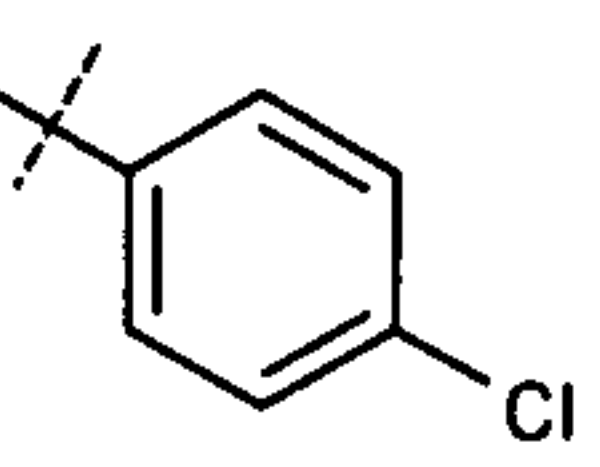
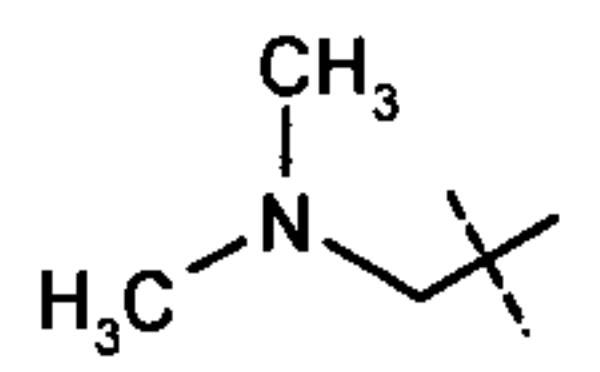
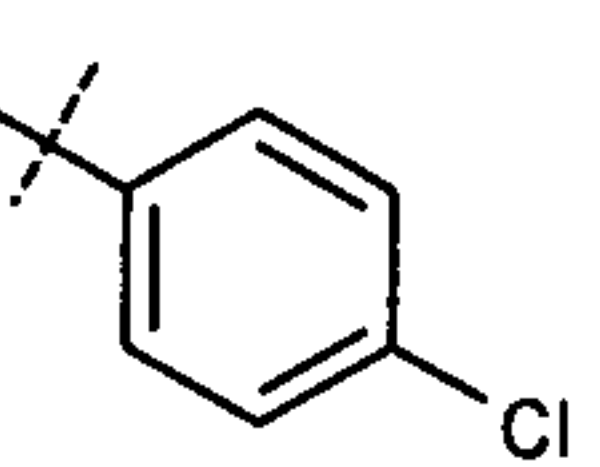
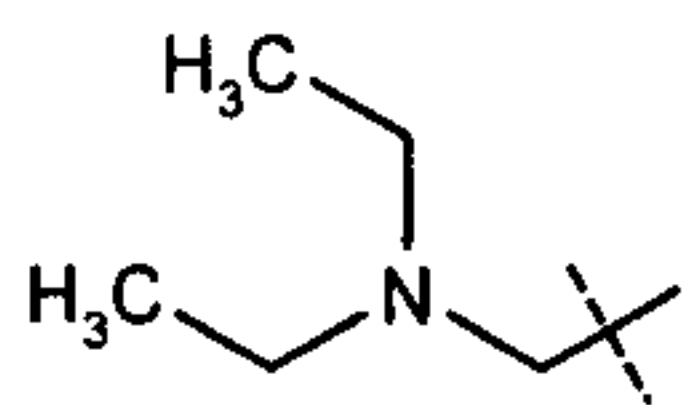
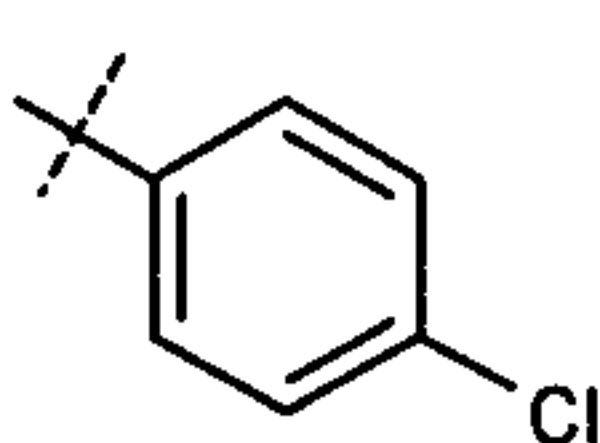
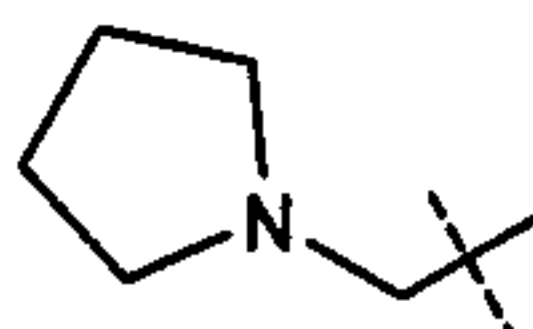
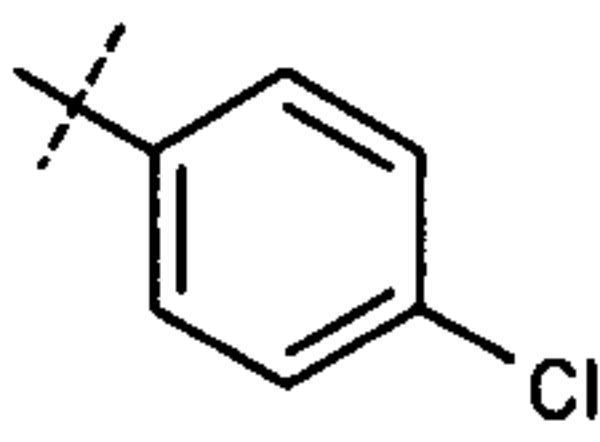
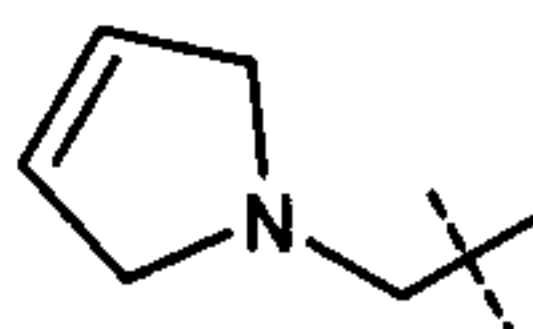
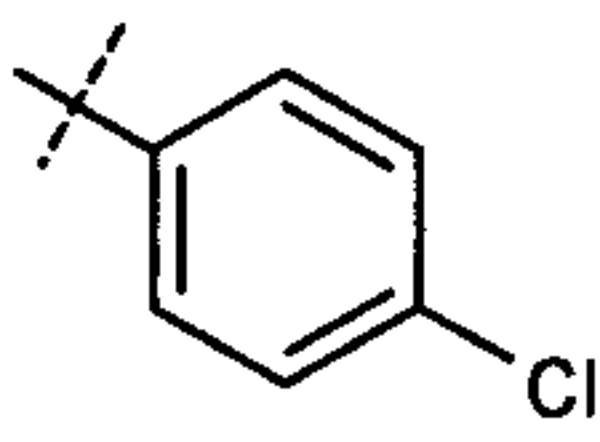
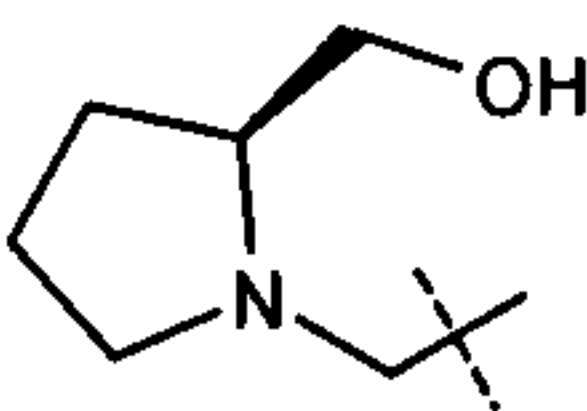
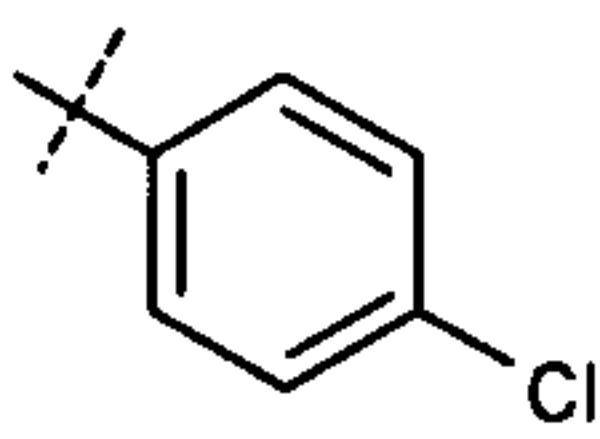
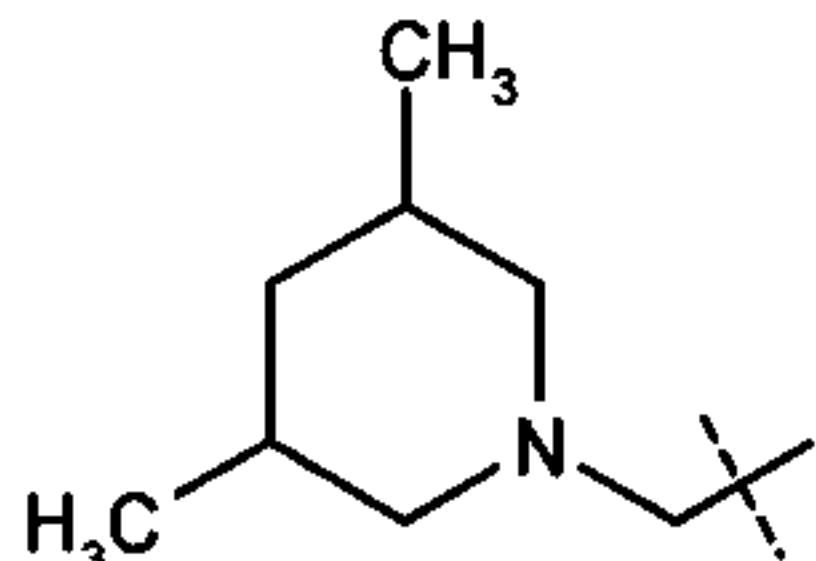
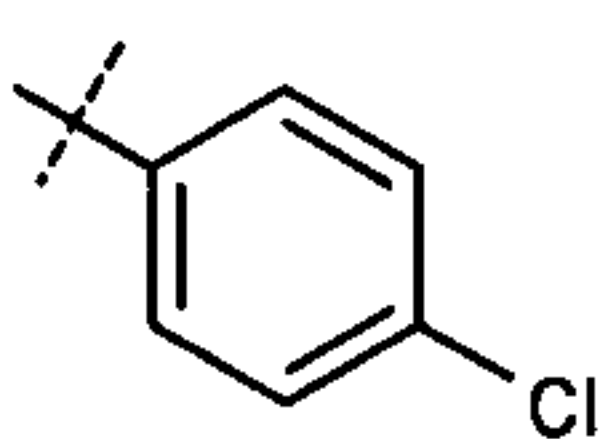
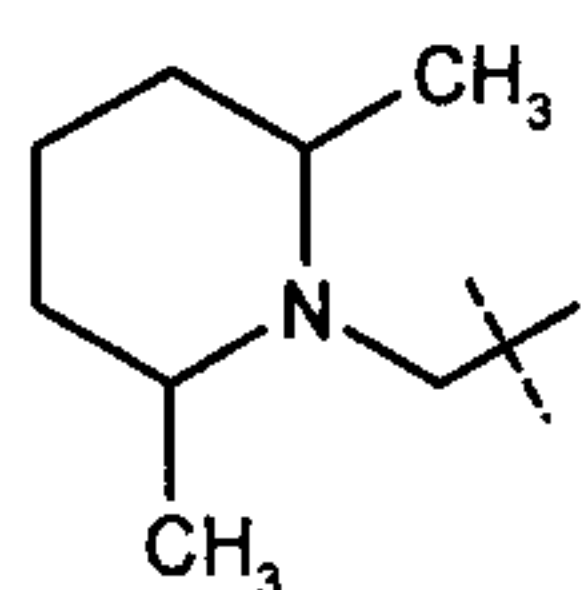
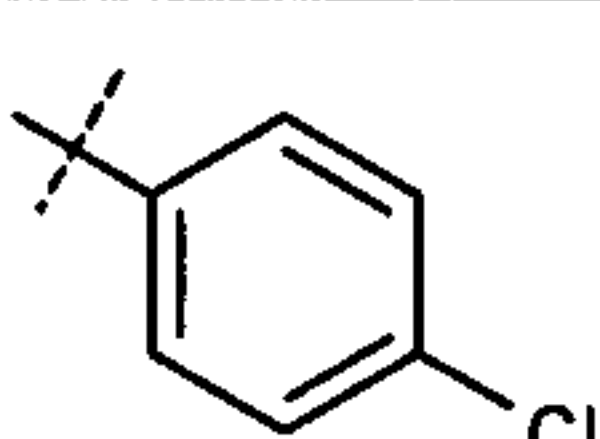
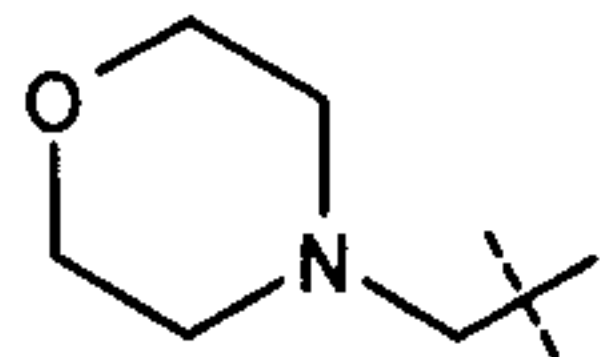
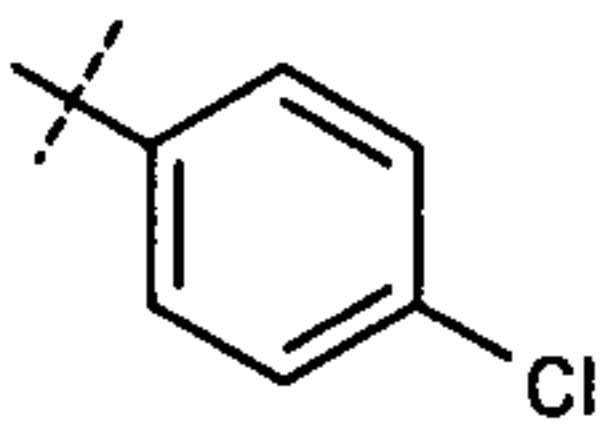
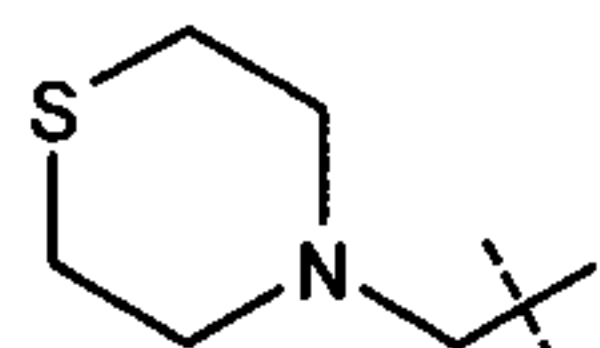
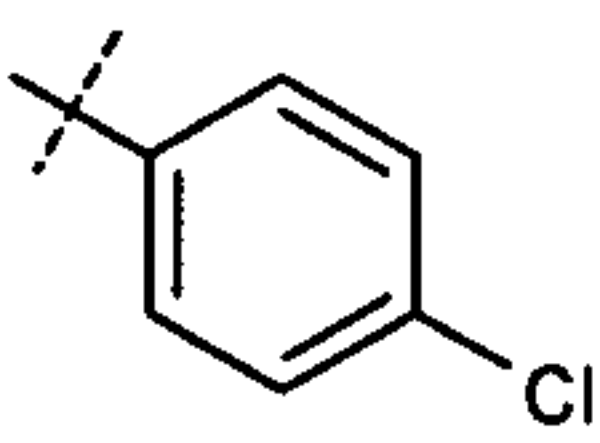
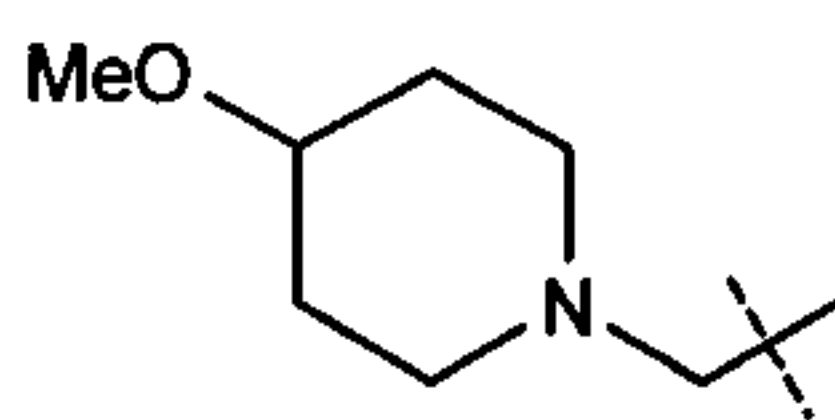
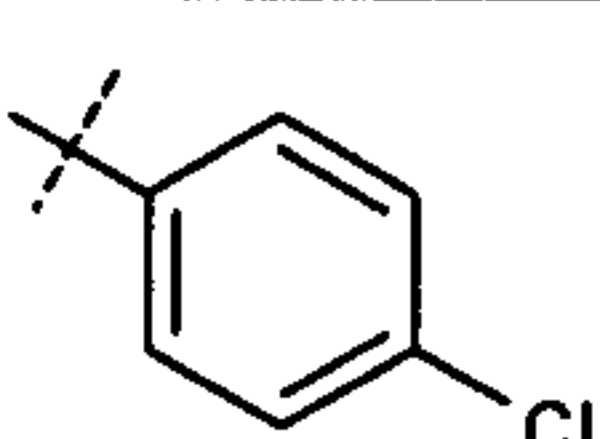
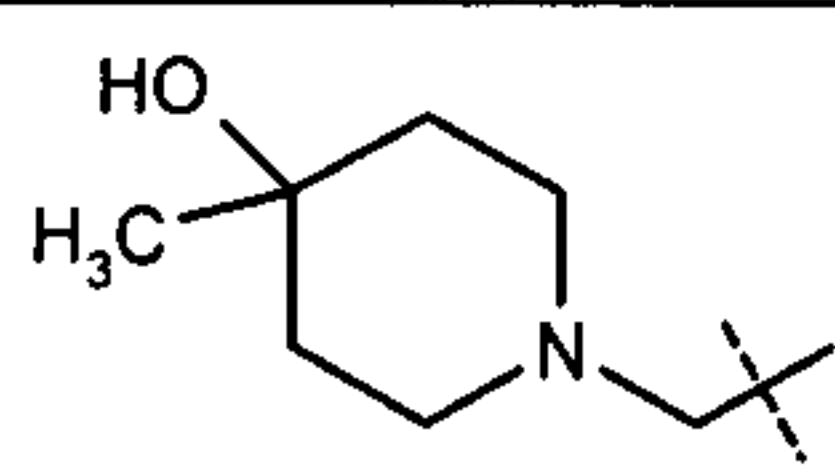
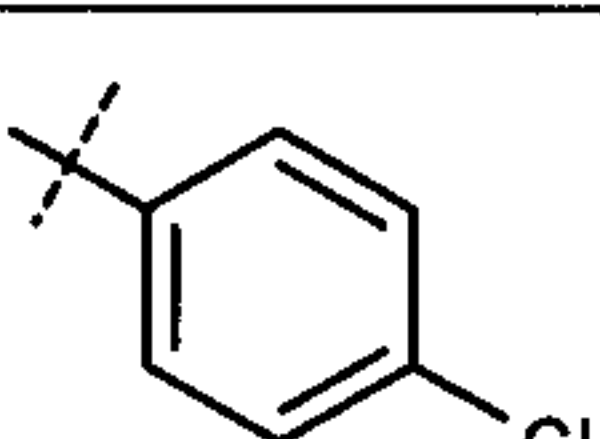
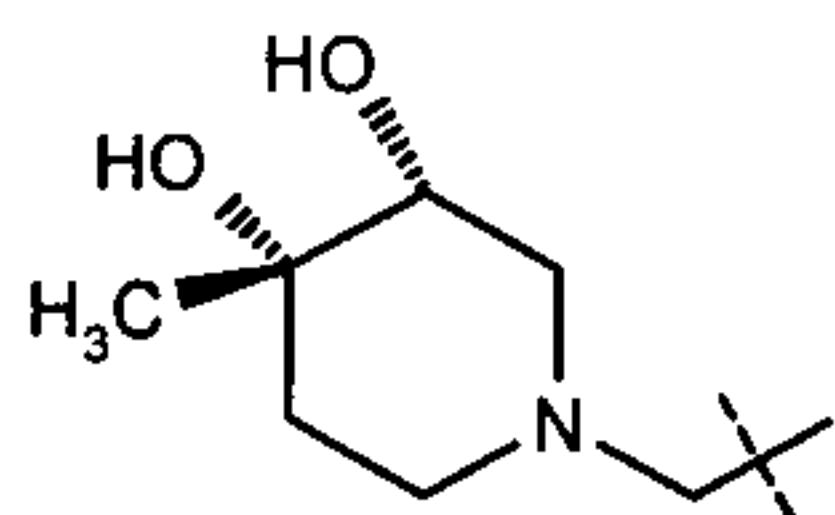
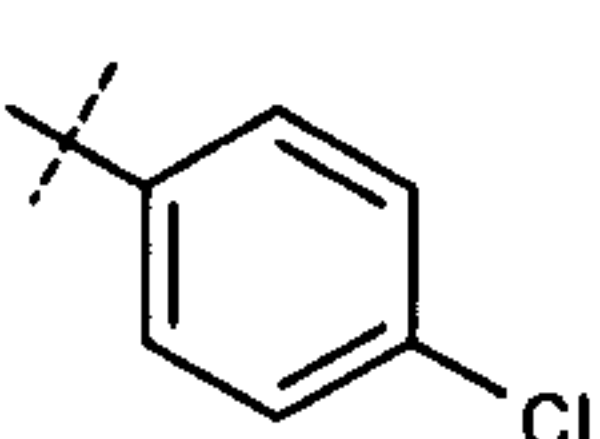
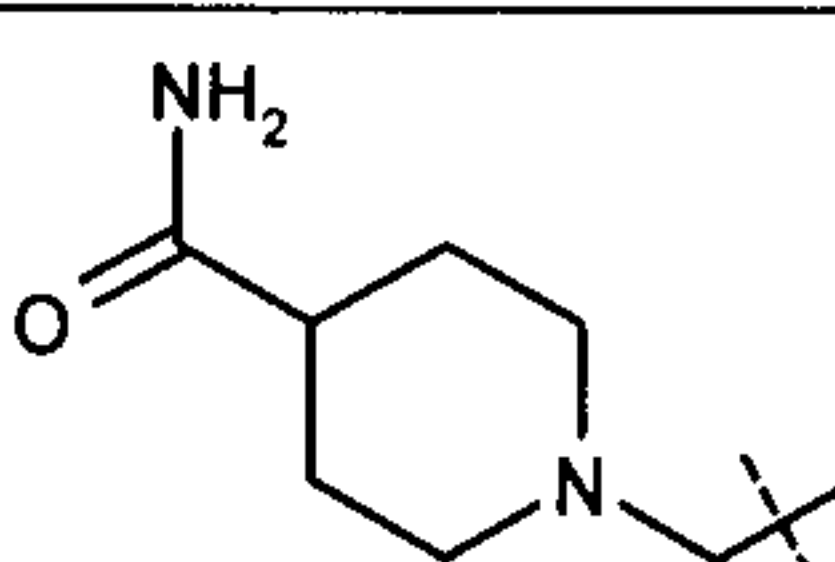
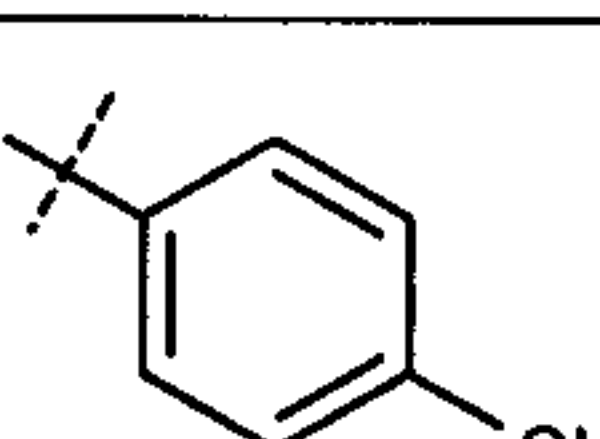
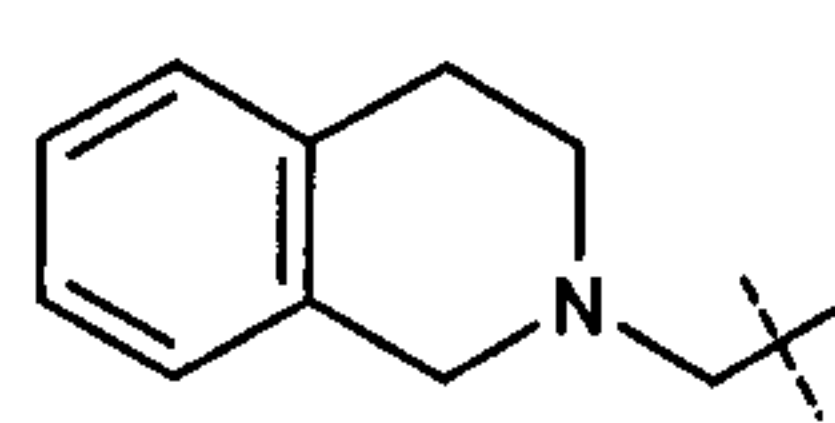
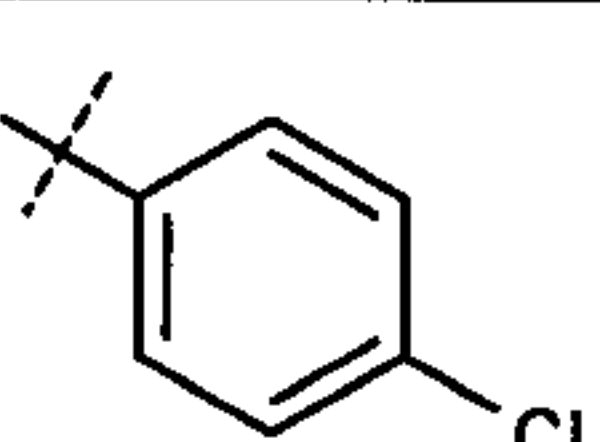
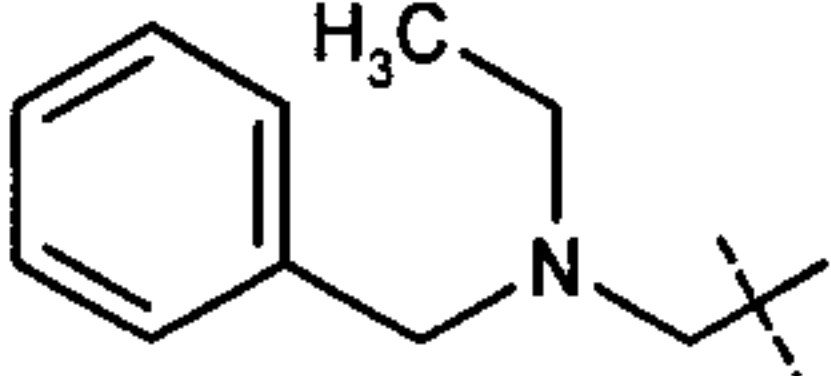
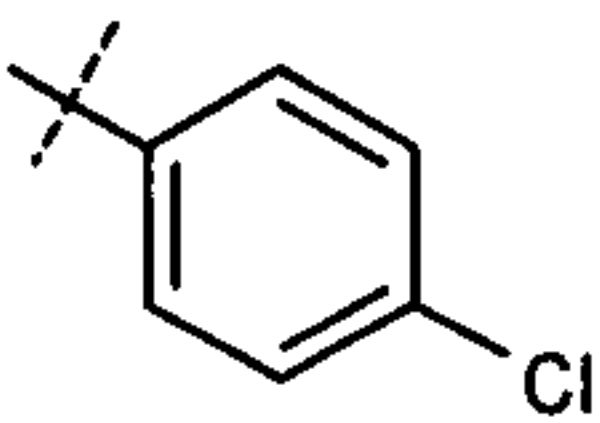
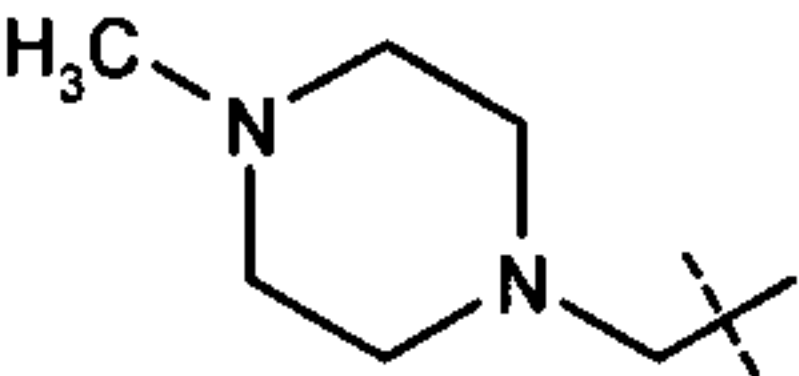
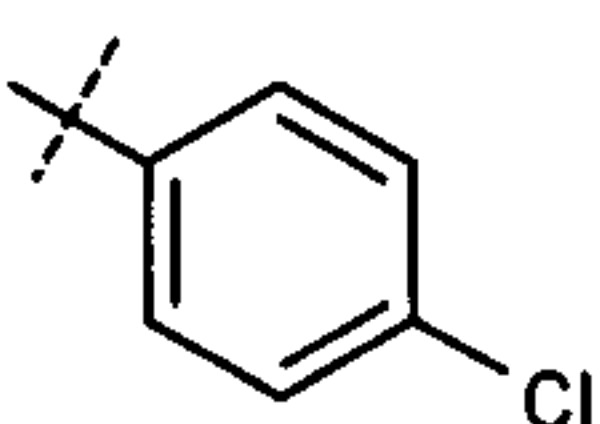
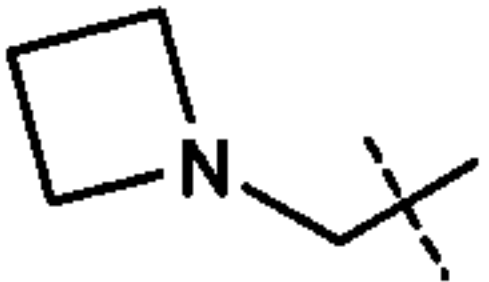
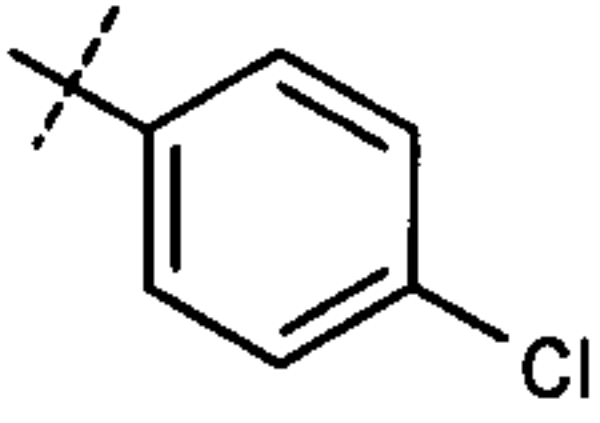
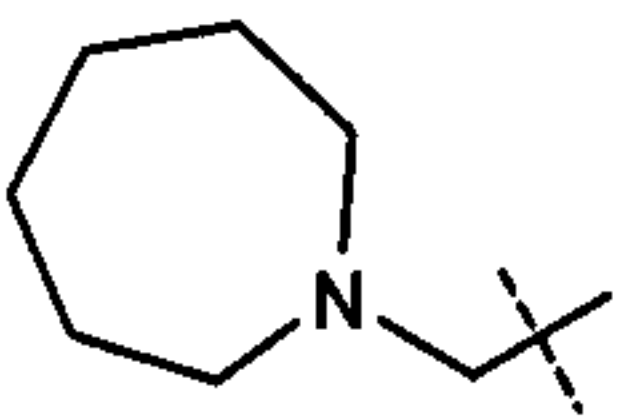
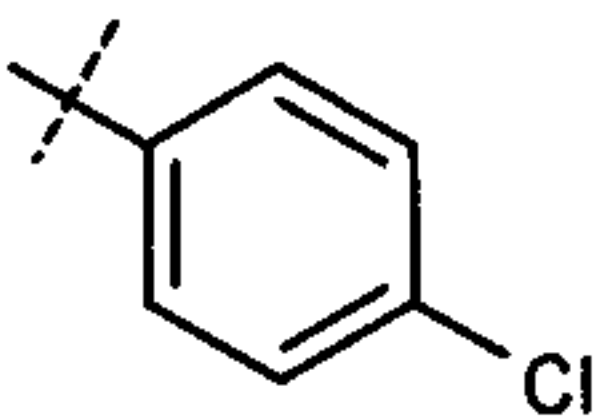
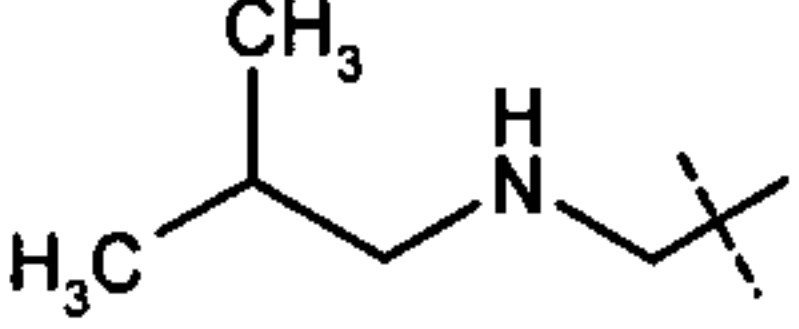
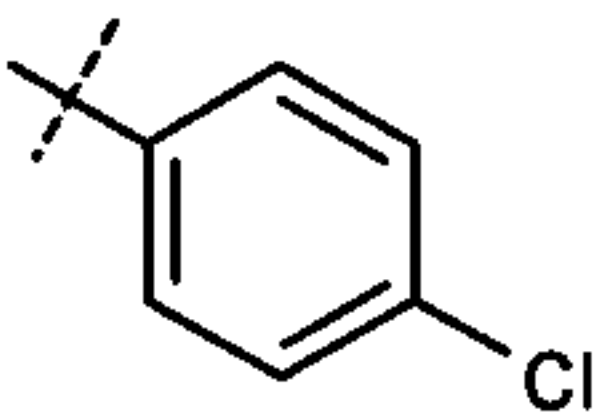
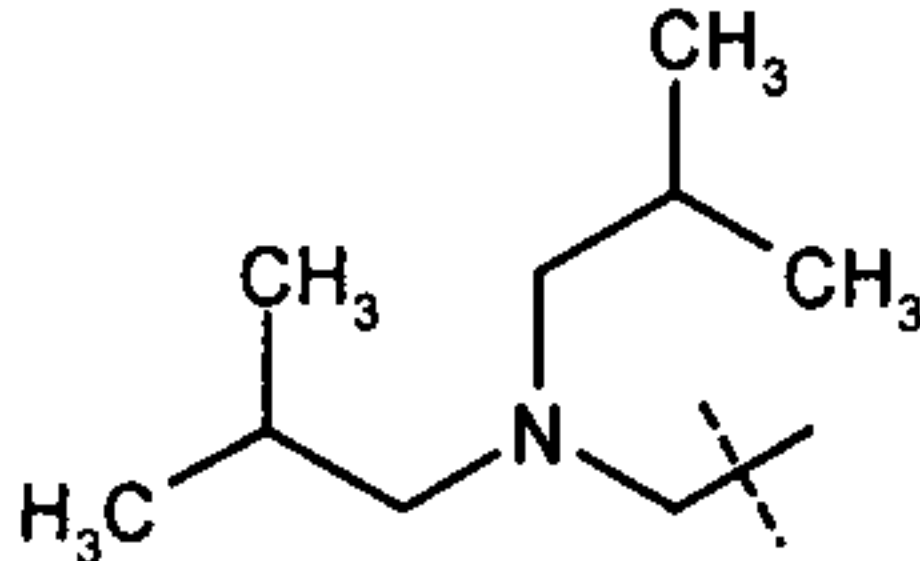
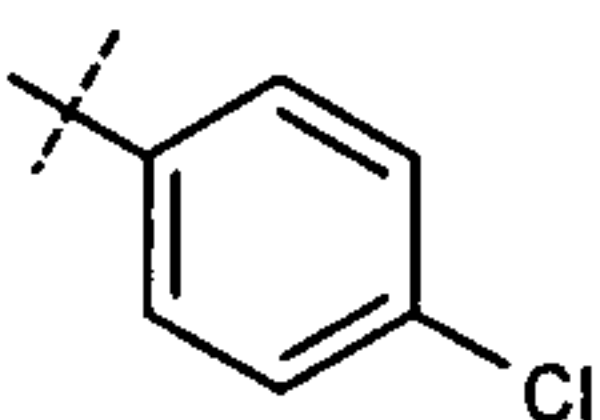
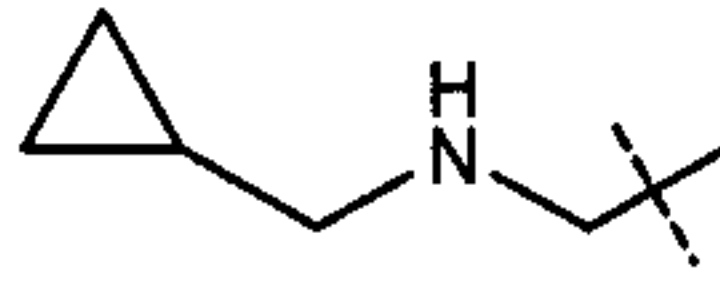
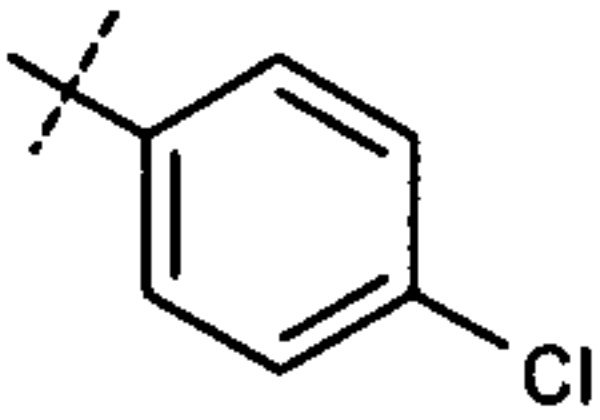
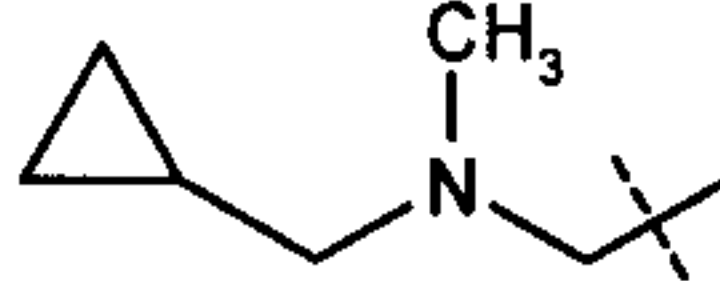
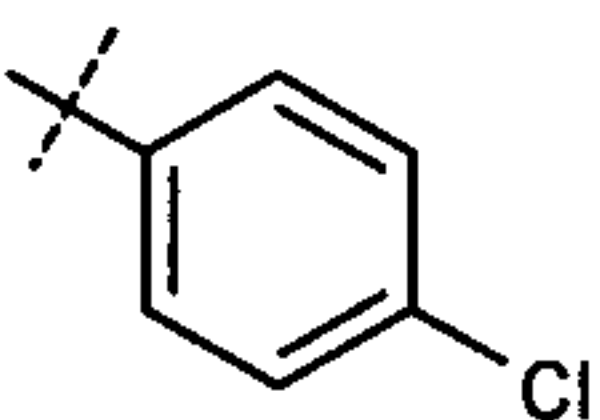
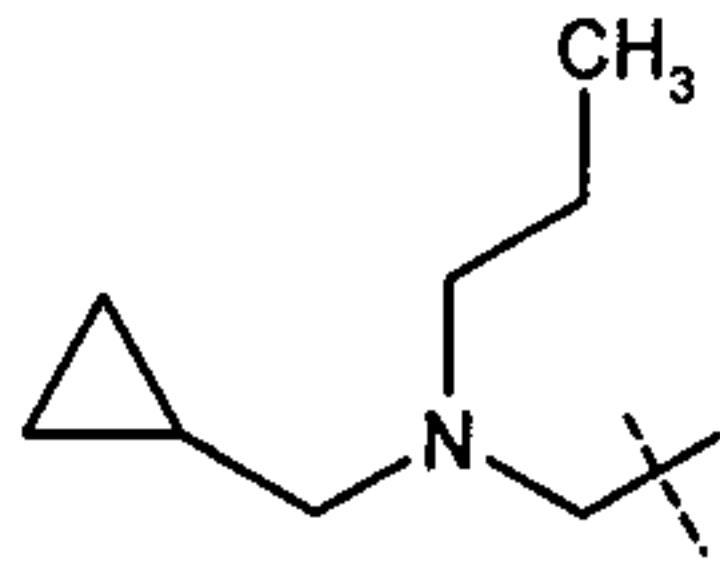
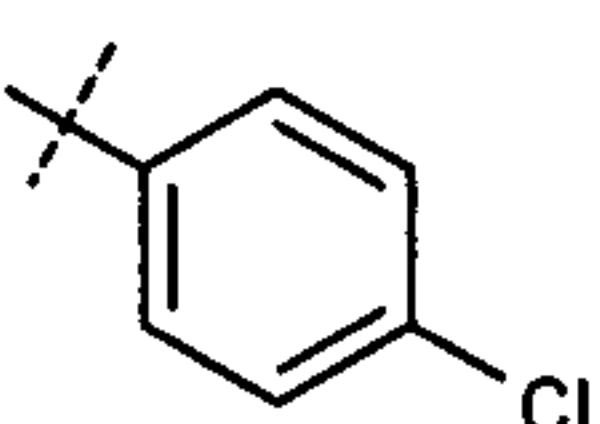
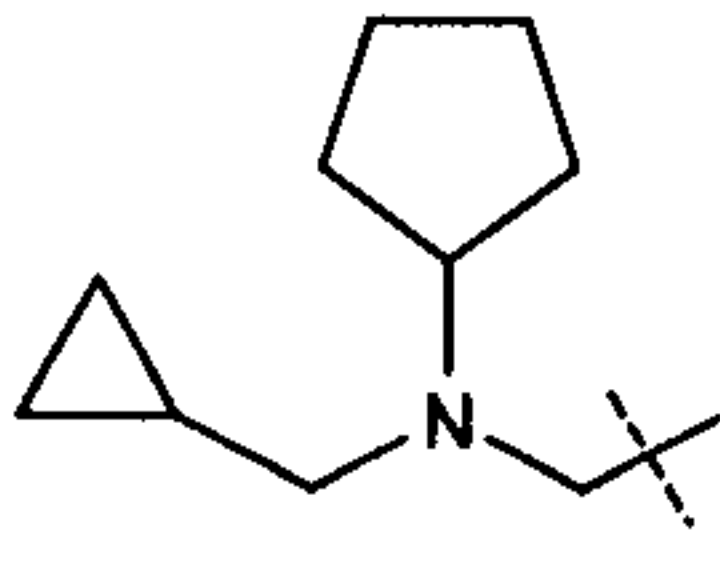
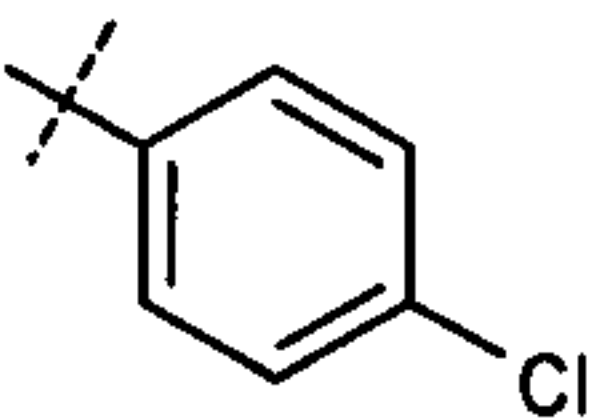
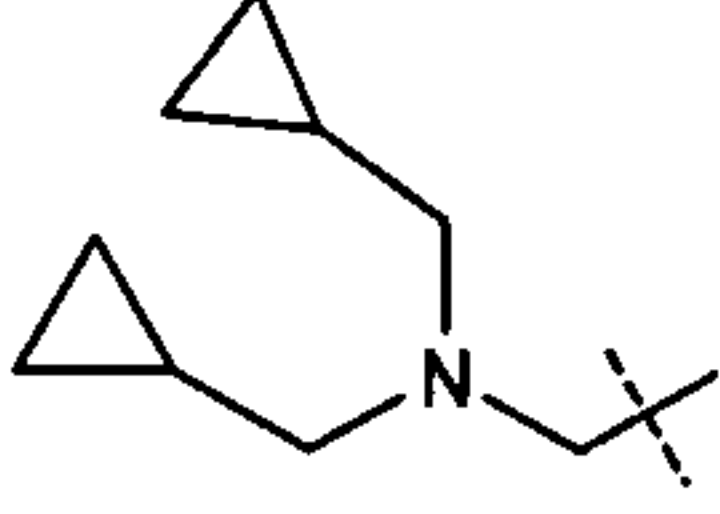
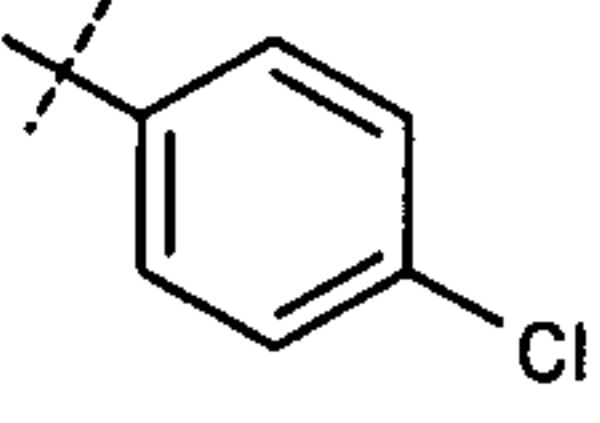
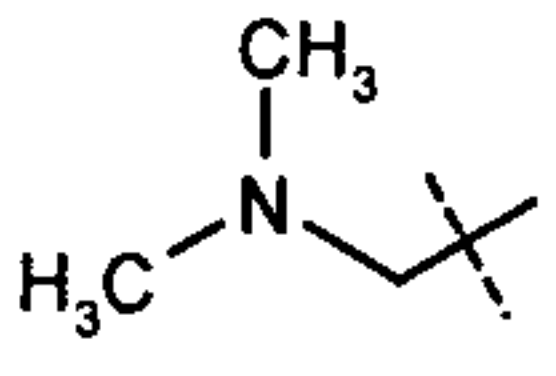
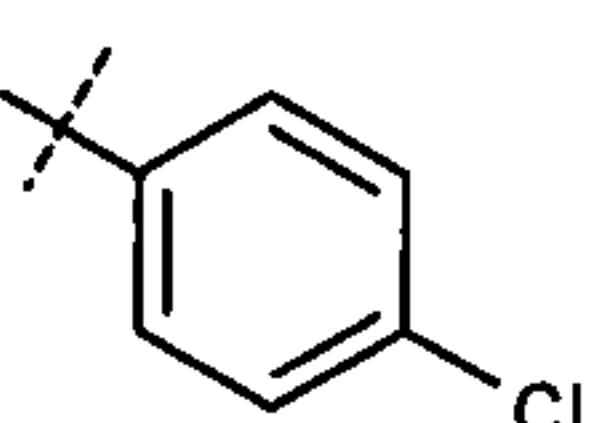
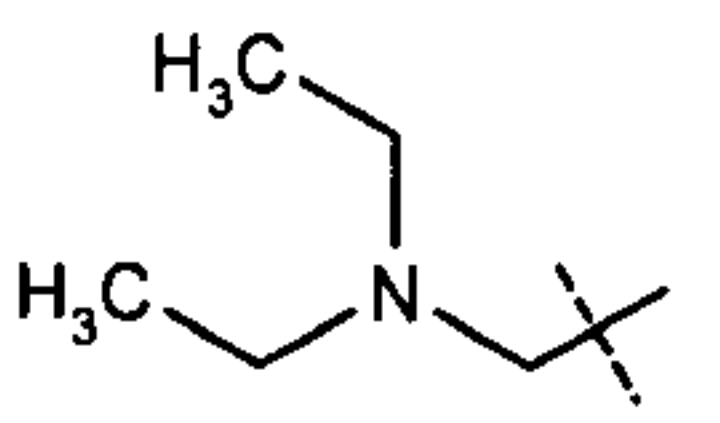
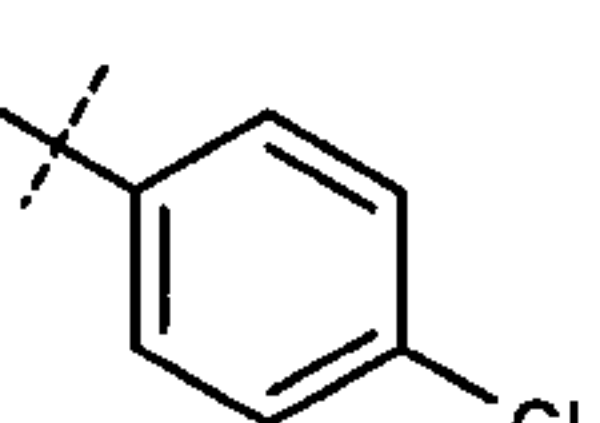


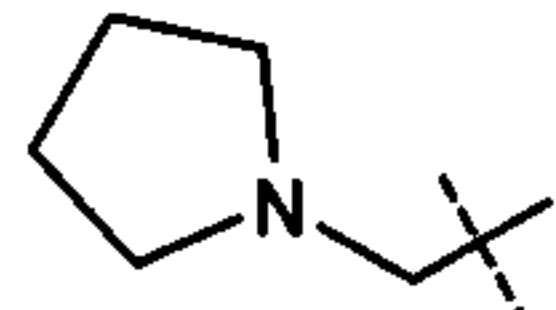
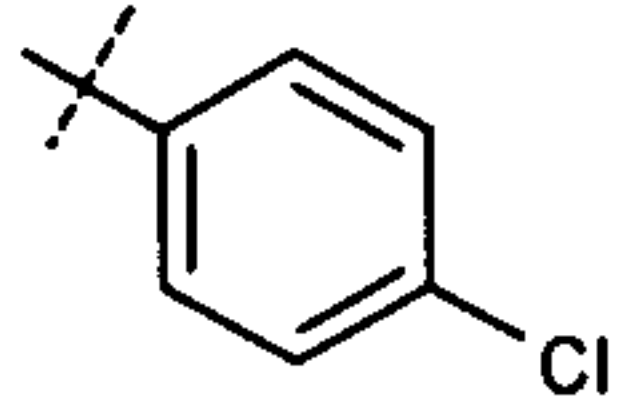
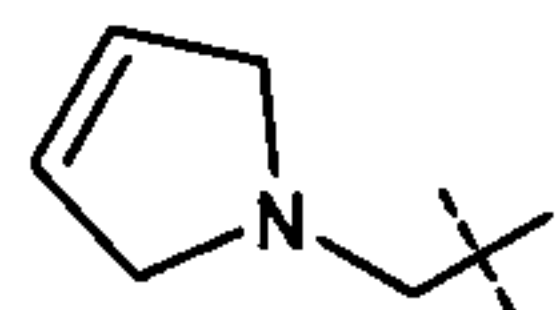
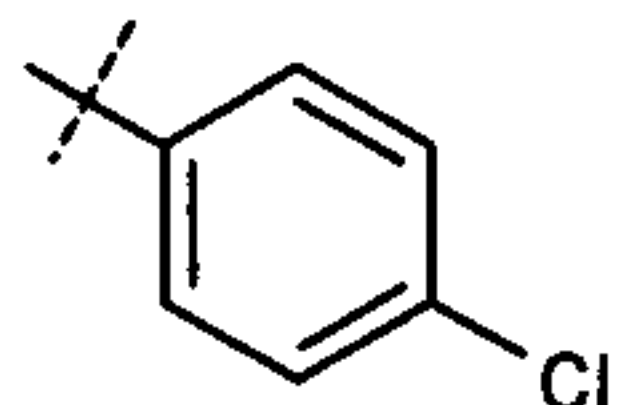
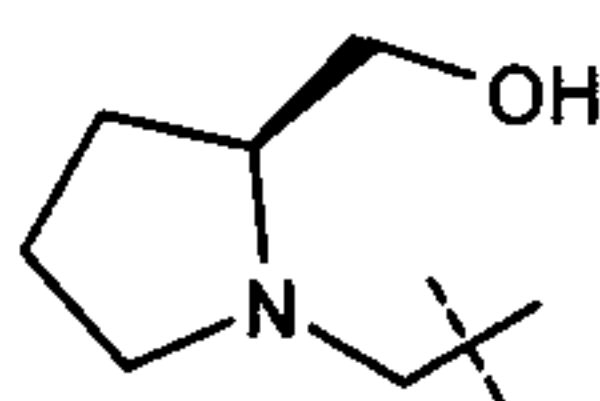
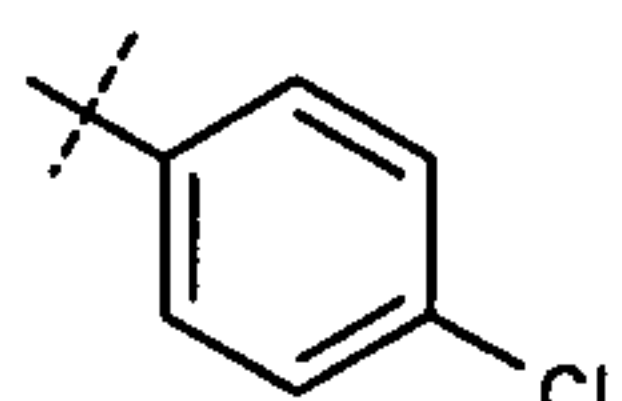
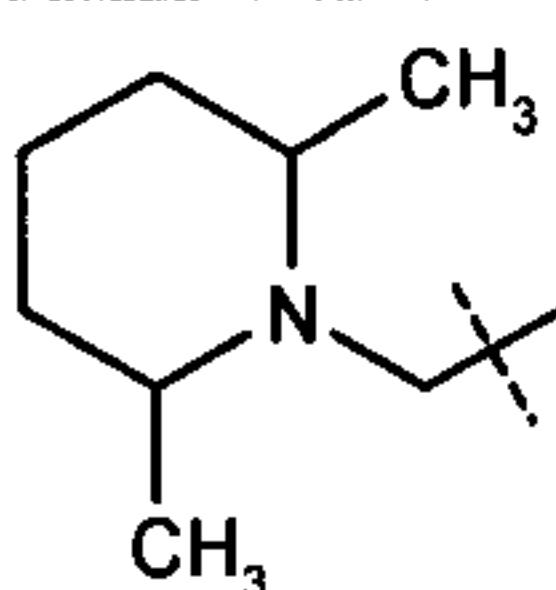
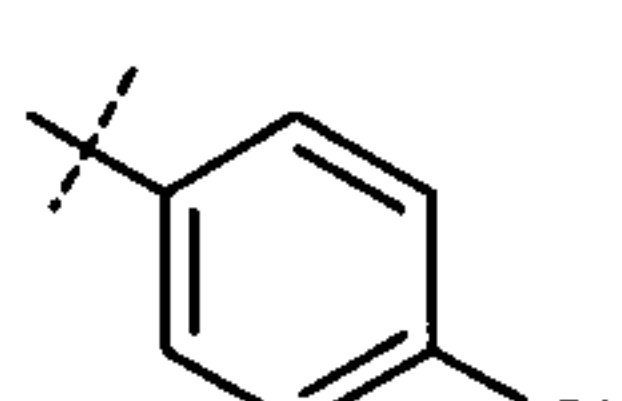
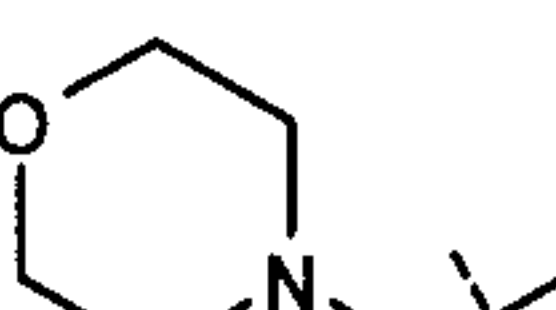
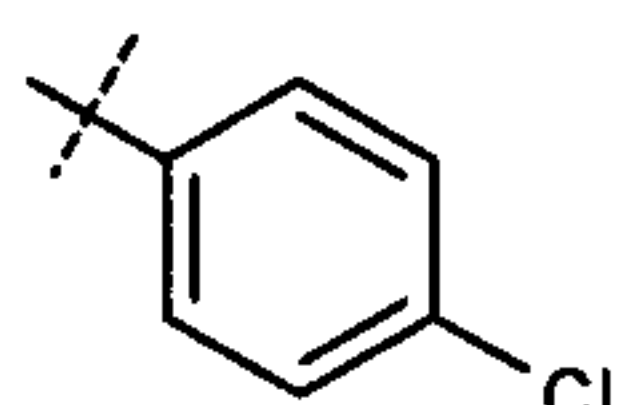
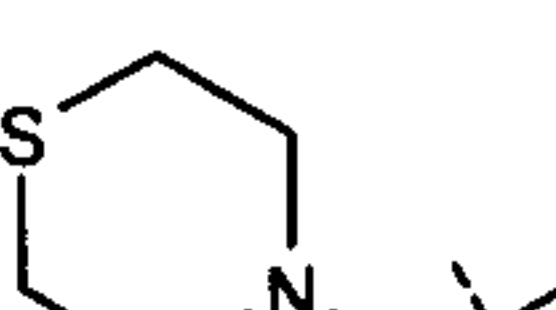
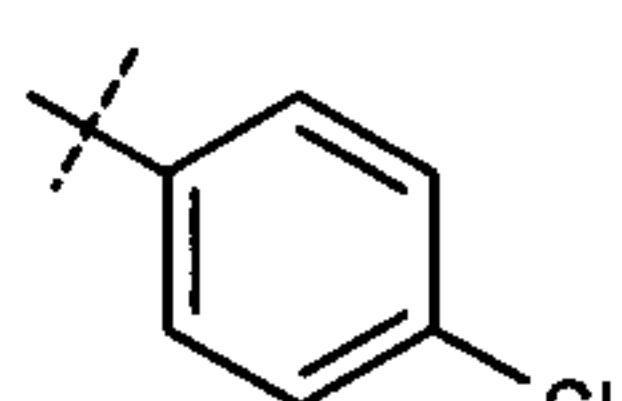
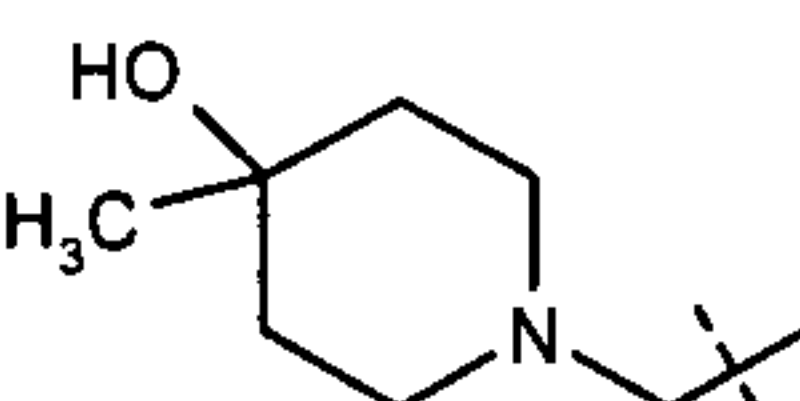
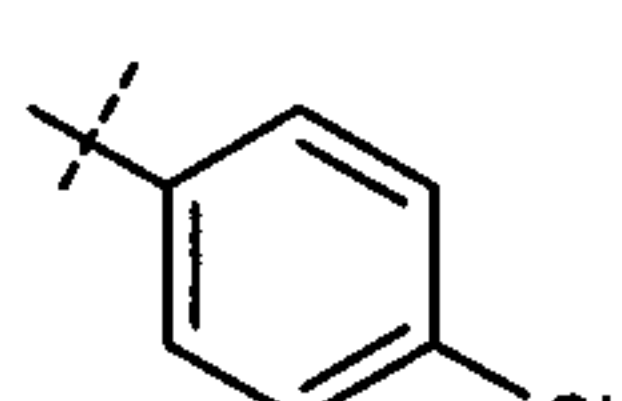
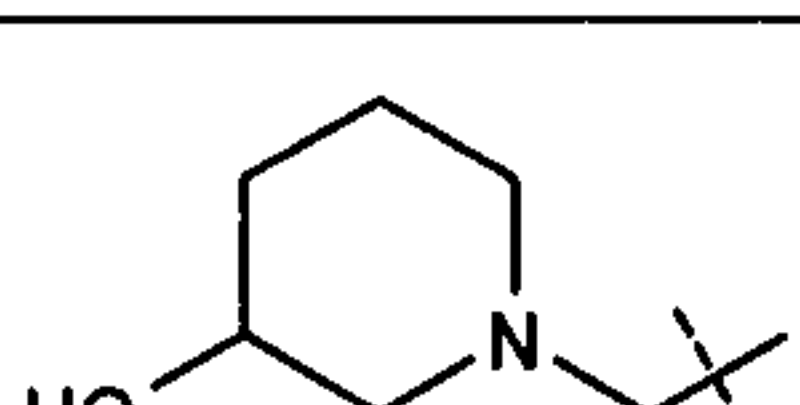
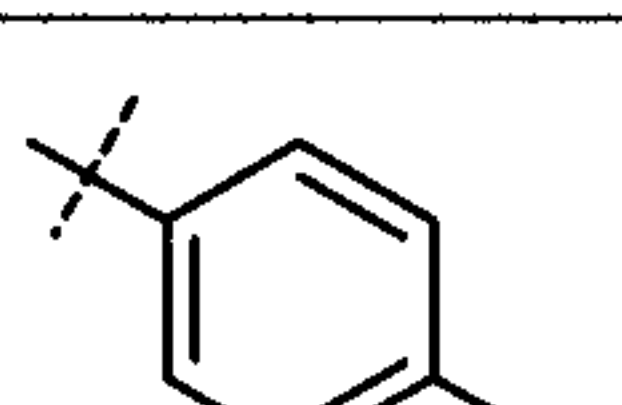
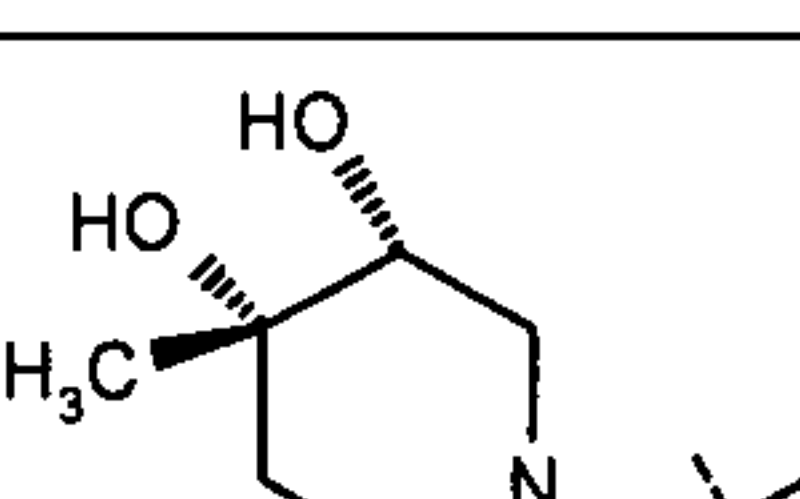
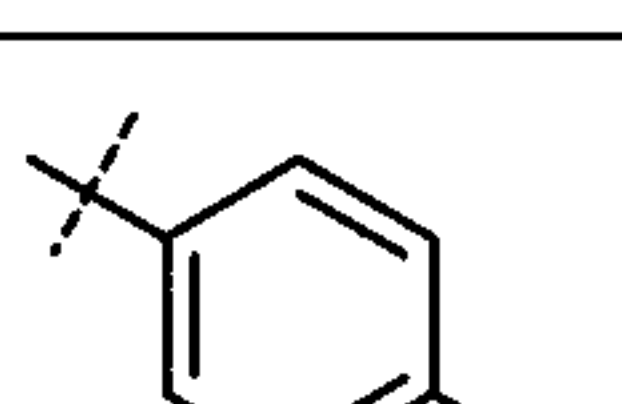
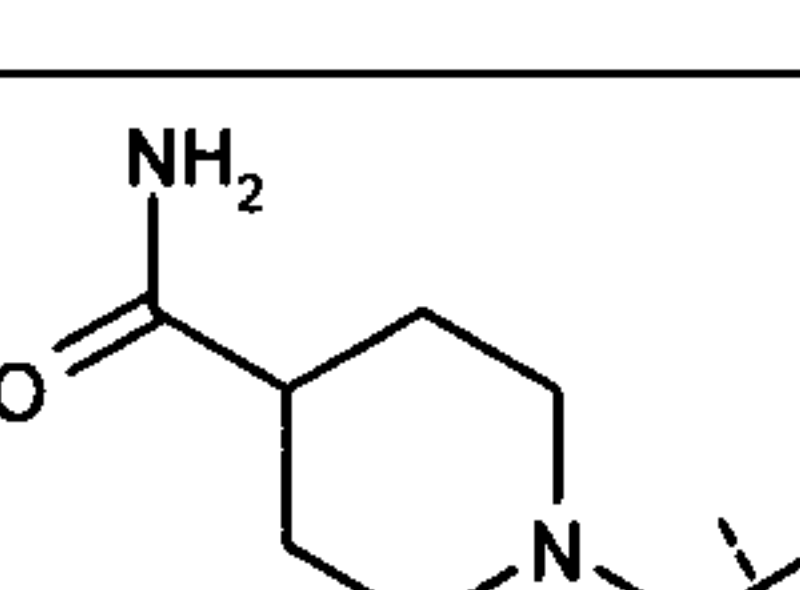
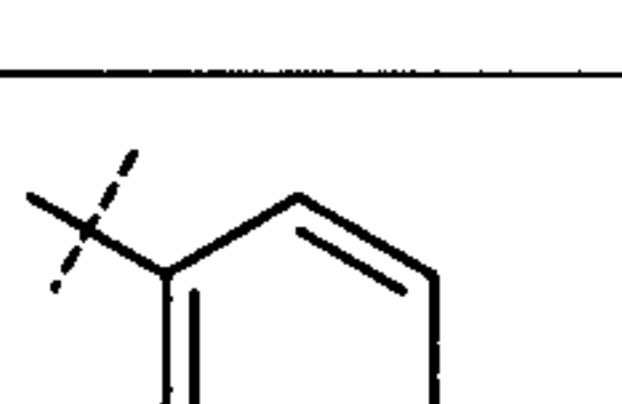
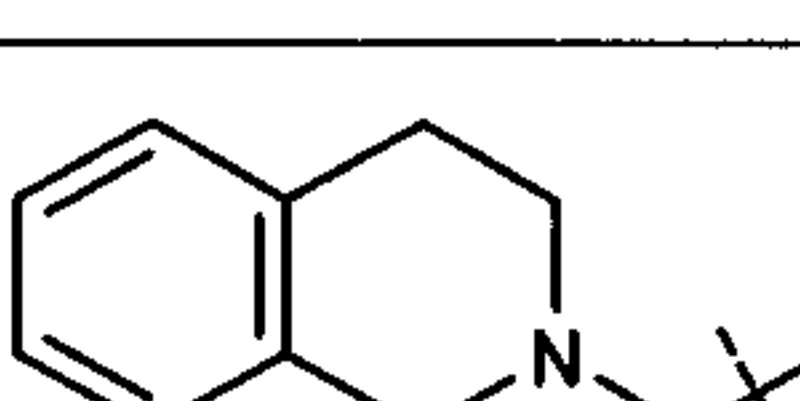
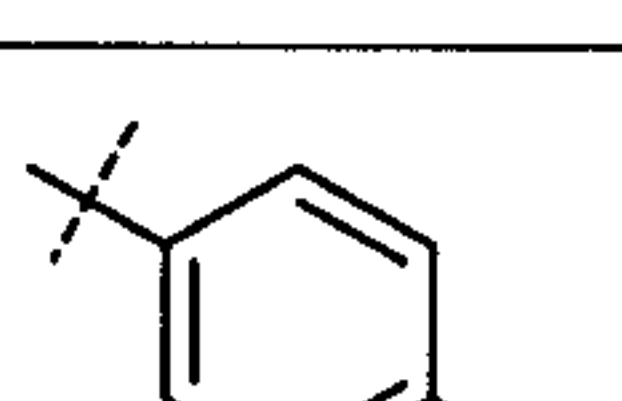
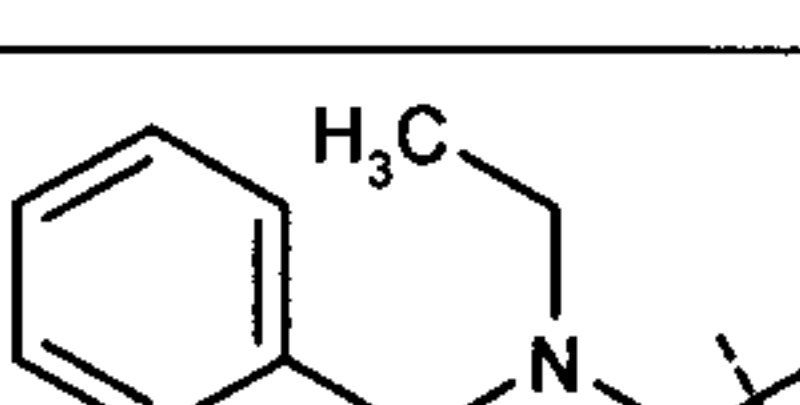
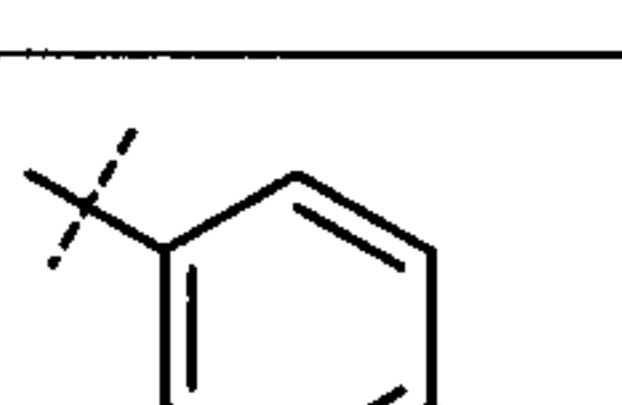
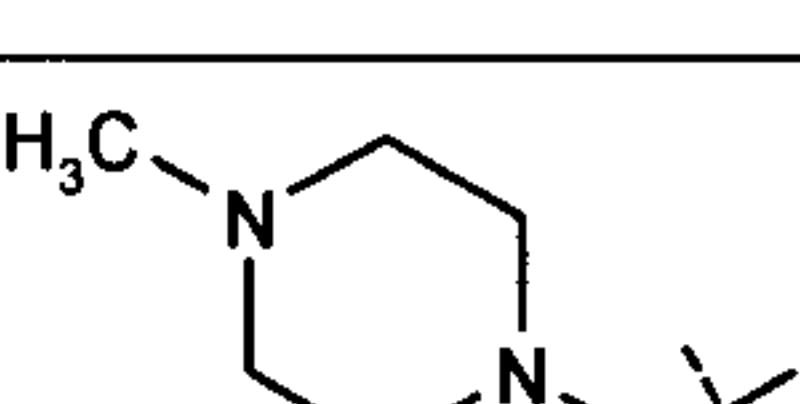
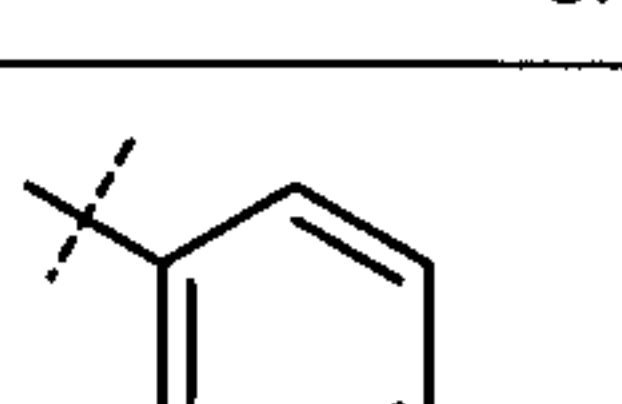
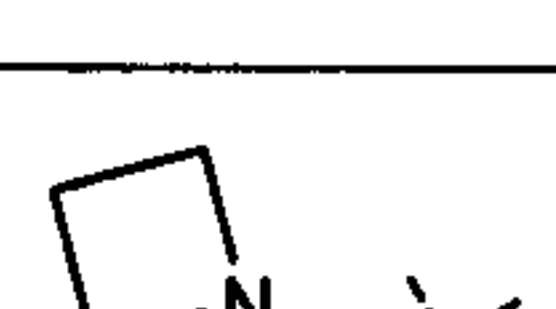
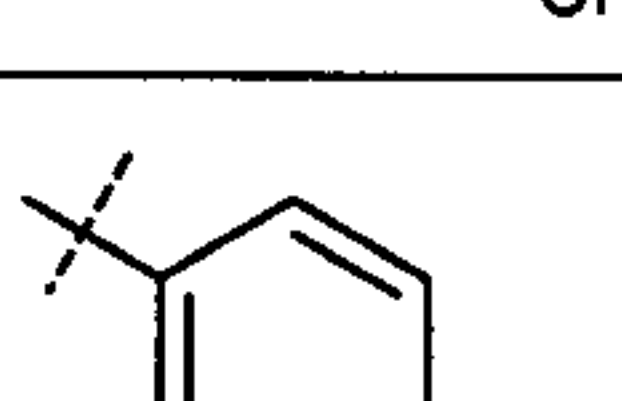
Table 1

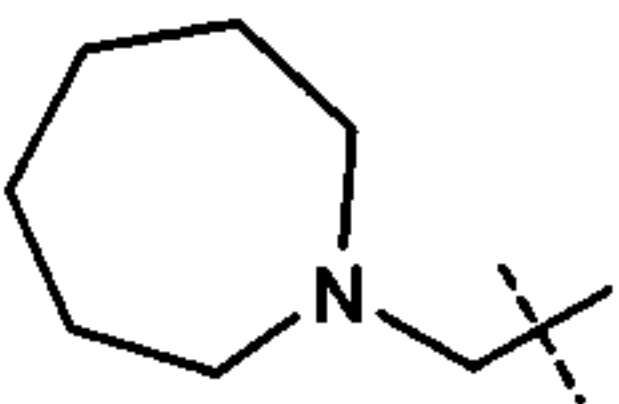
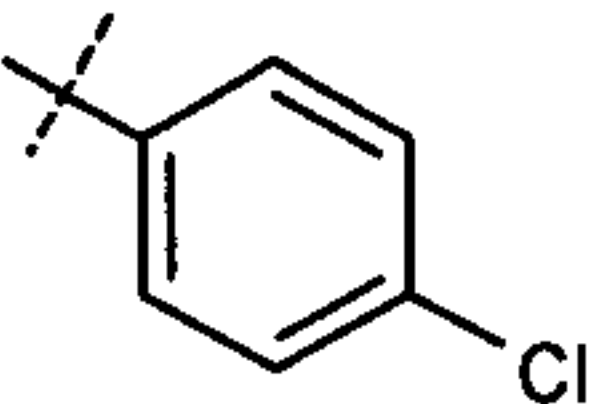
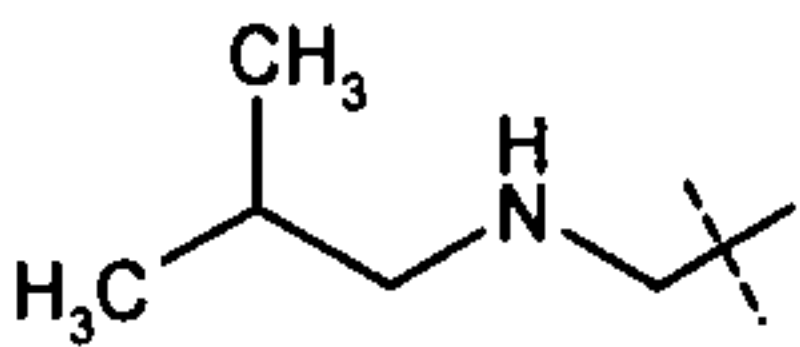
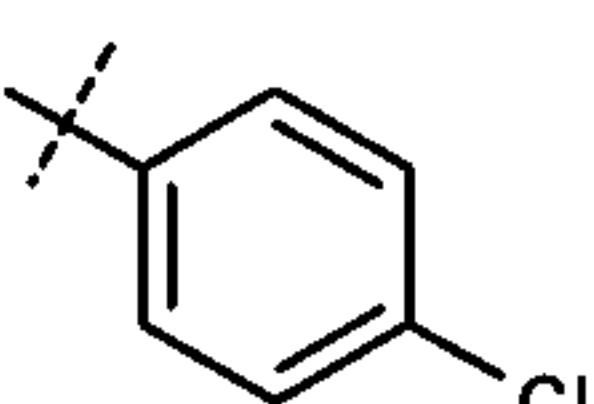
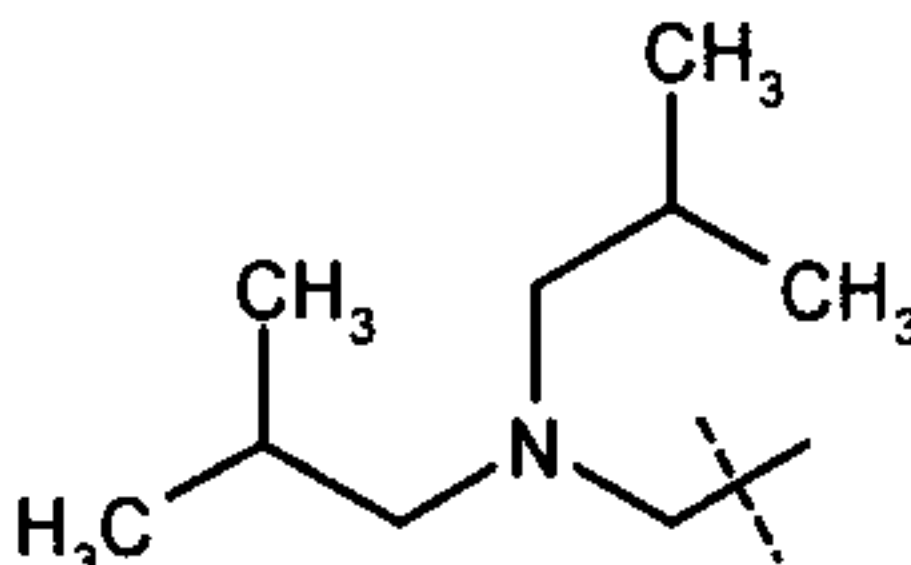
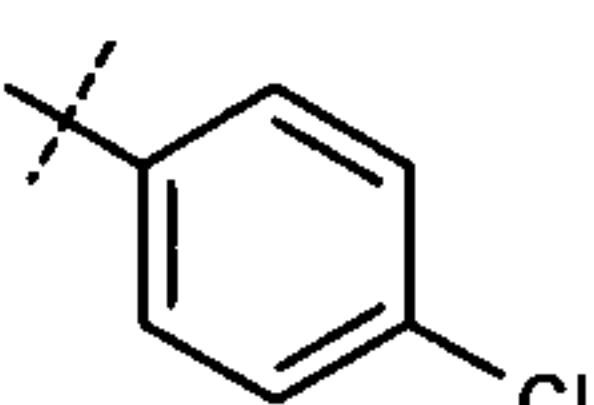
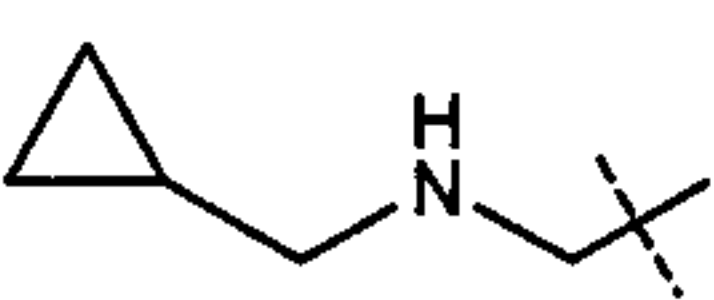
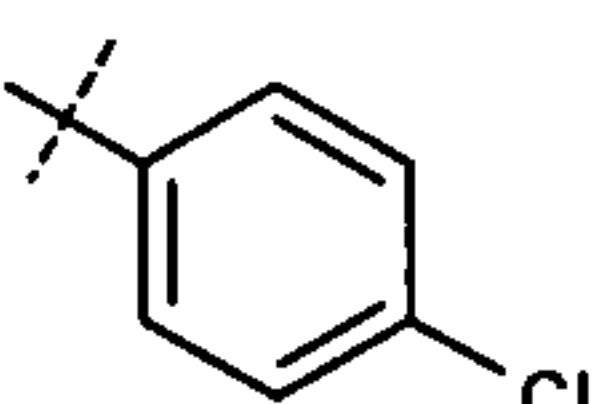
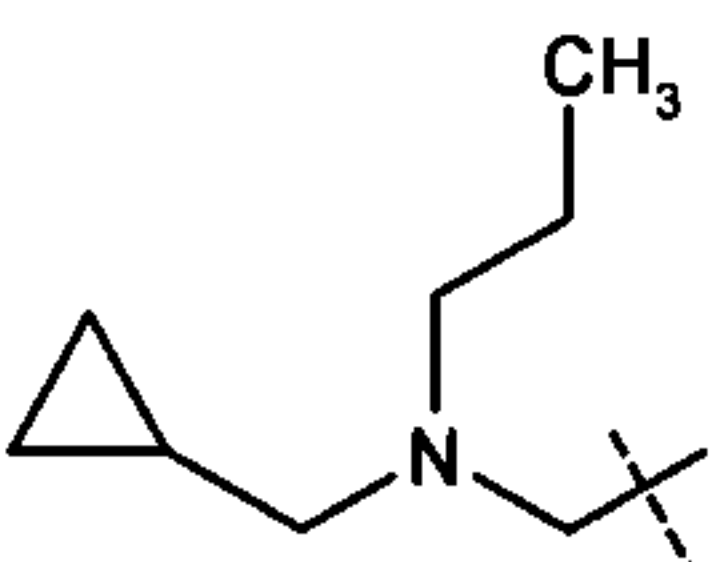
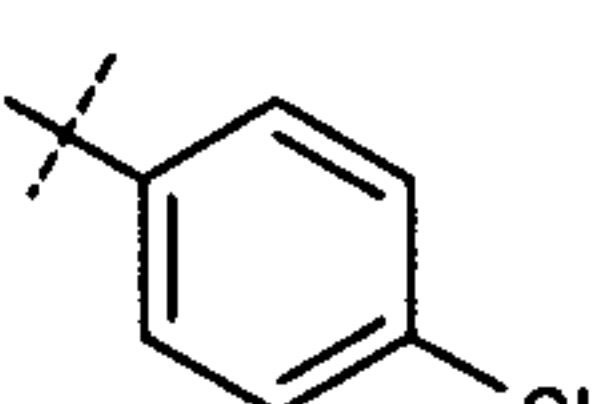
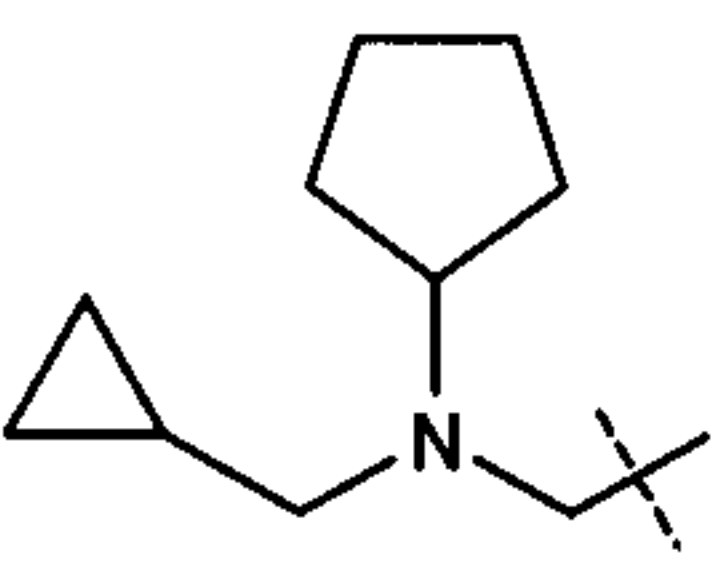
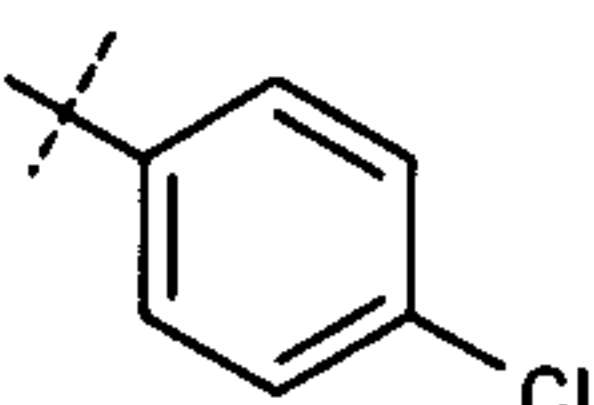
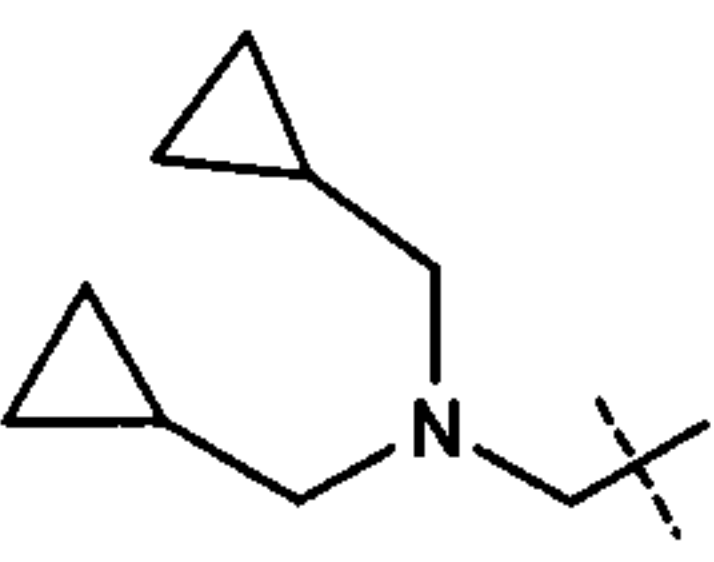
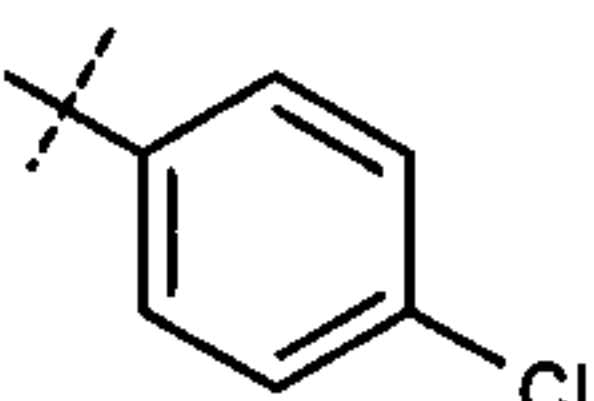
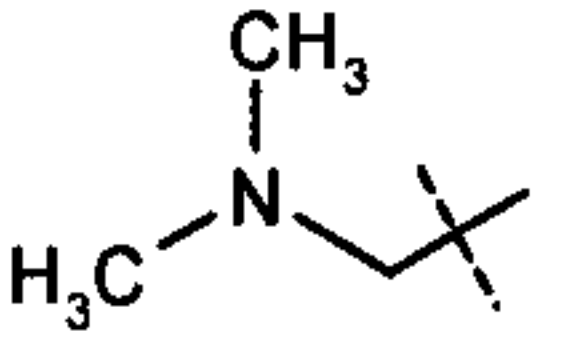
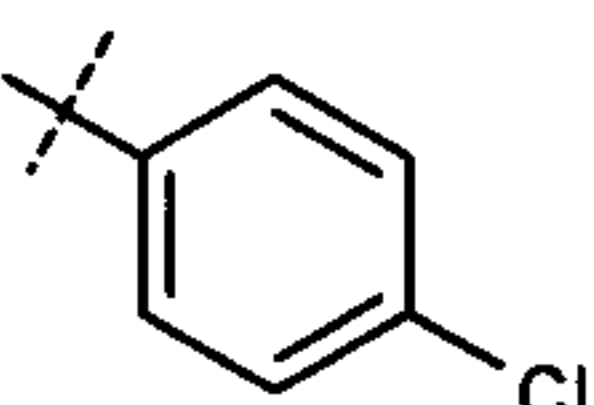
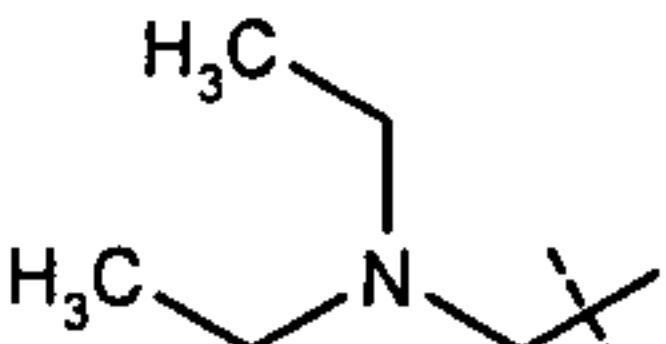
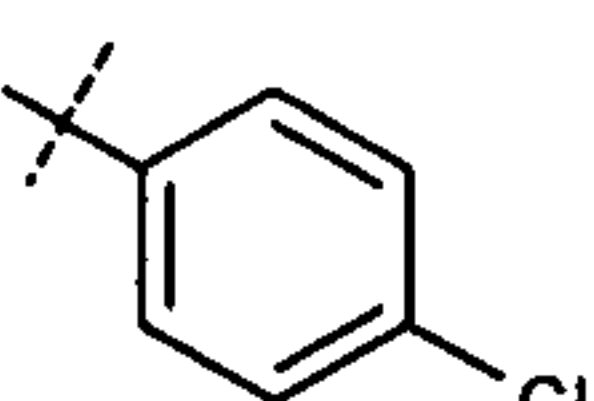
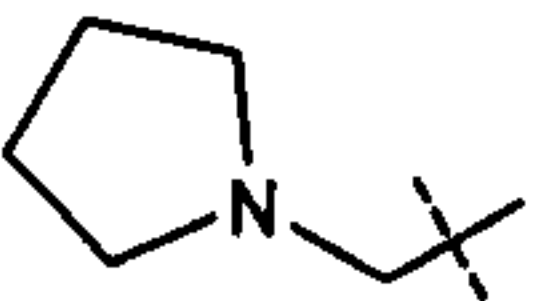
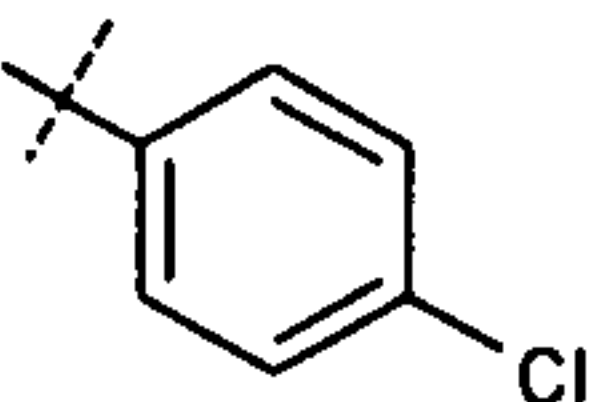
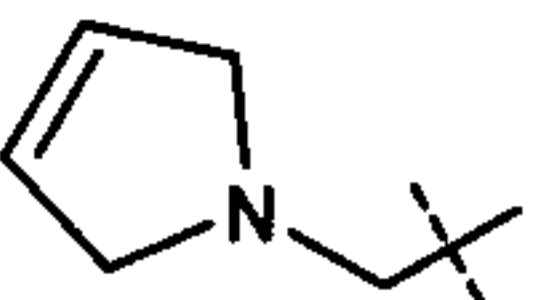
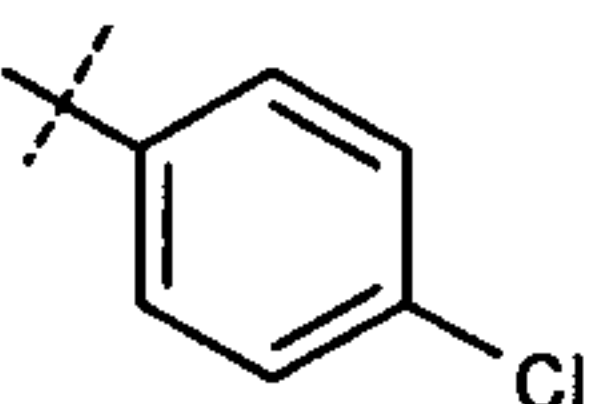
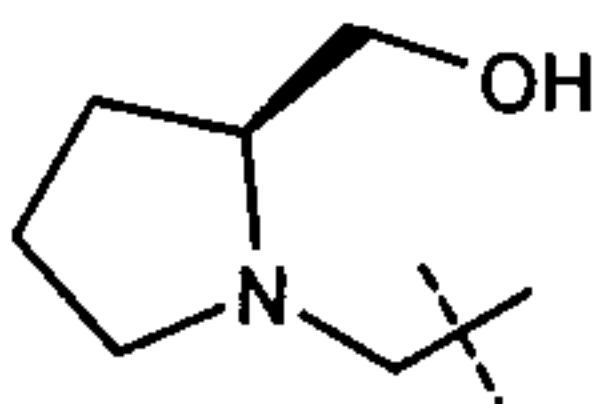
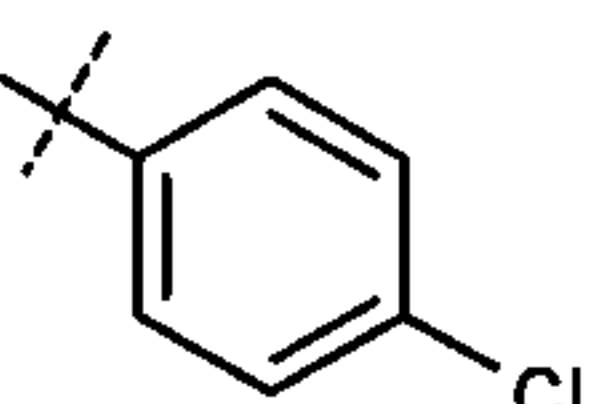
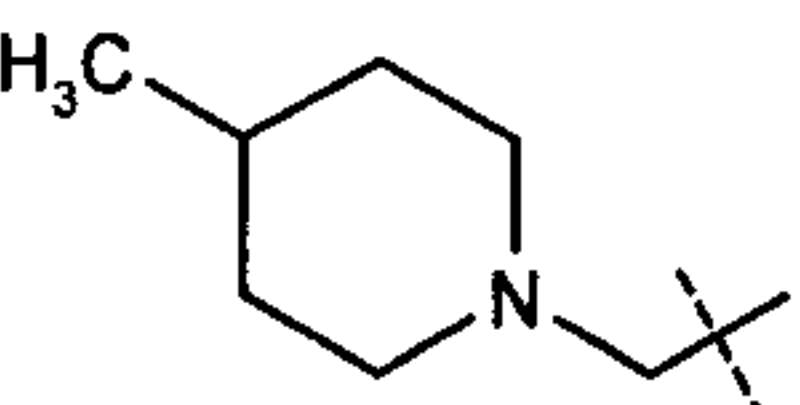
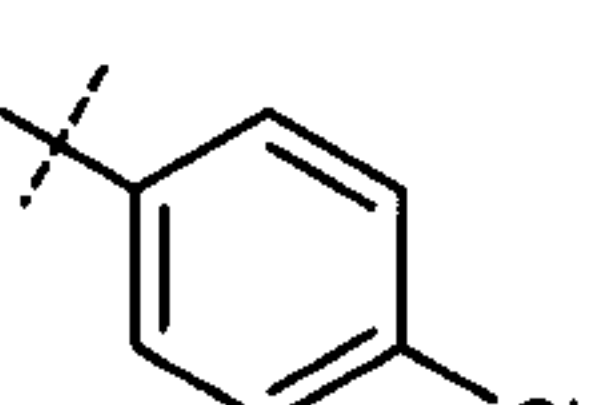
Example	R_1R_2N-X	L1	L2	B	Q
3.52		-H	-H		CH
3.53		-H	-H		CH
3.54		-H	-H		CH
3.55		-H	-H		CH
3.56		-H	-H		CH
3.57		-H	-H		CH
3.58		-H	-H		CH
3.59		-H	-H		CH

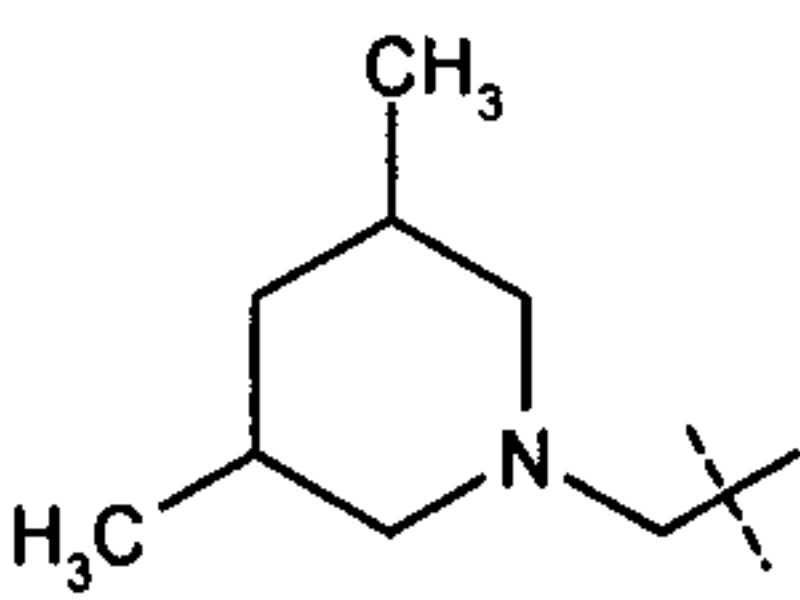
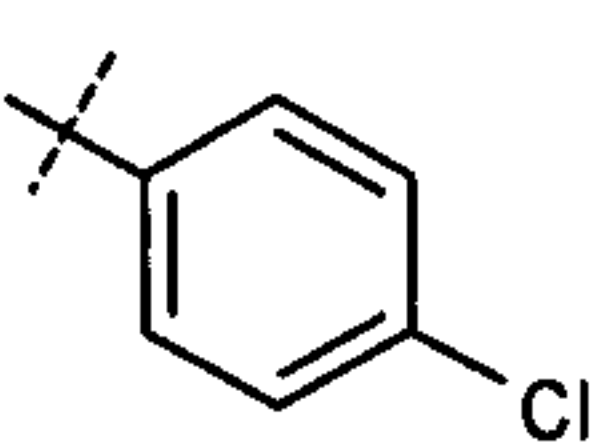
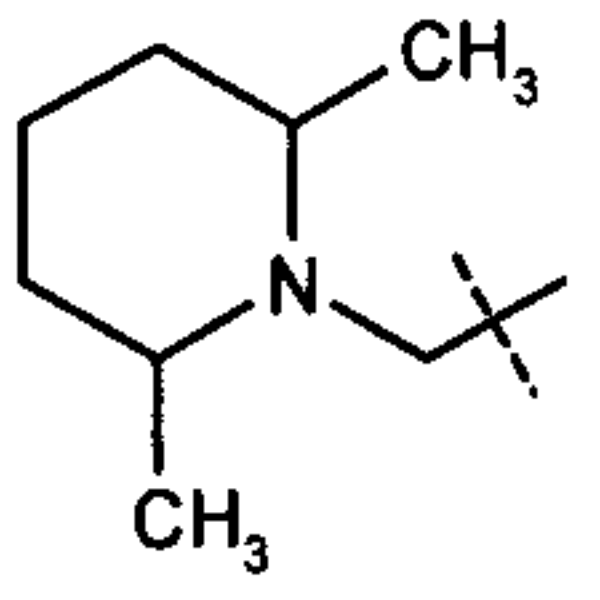
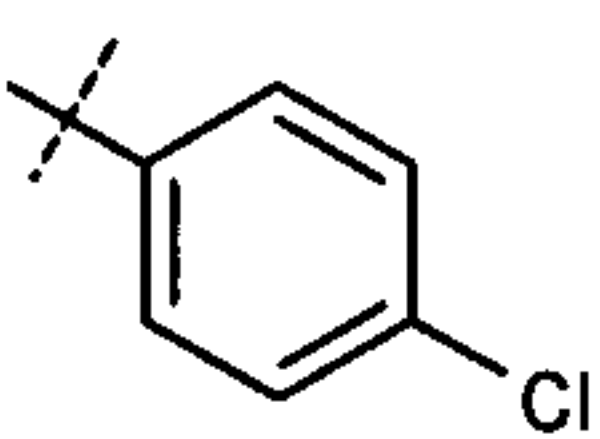
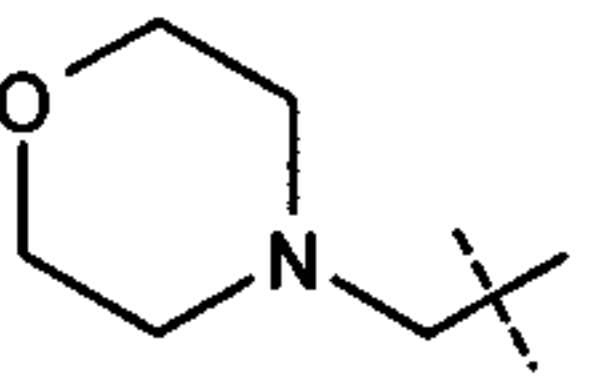
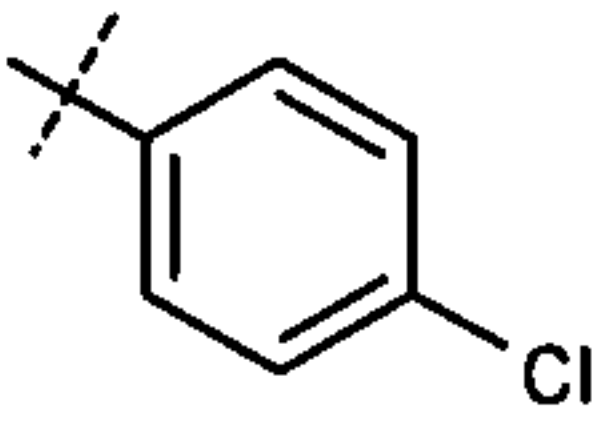
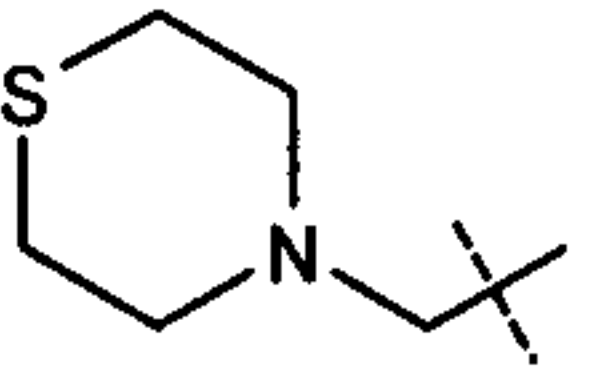
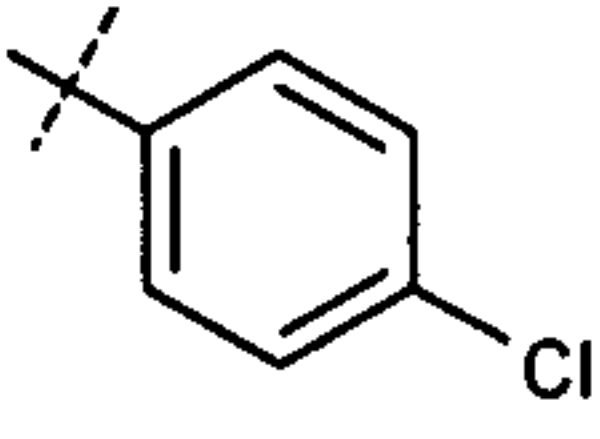
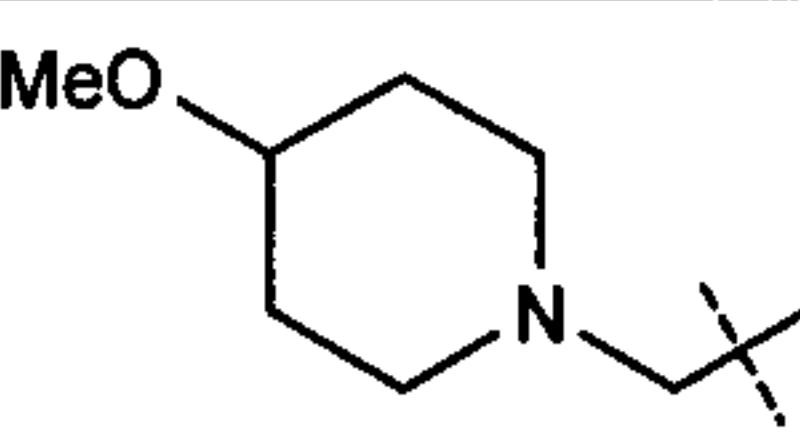
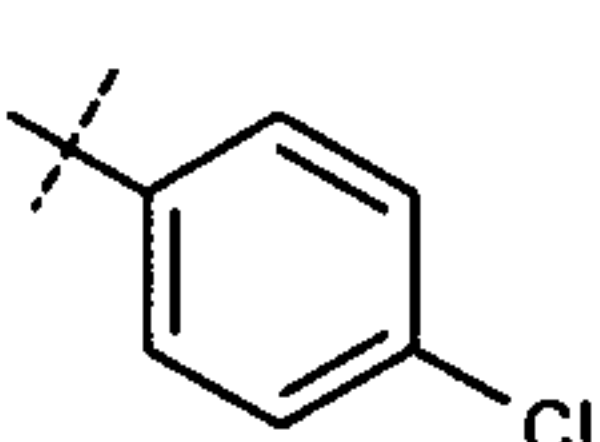
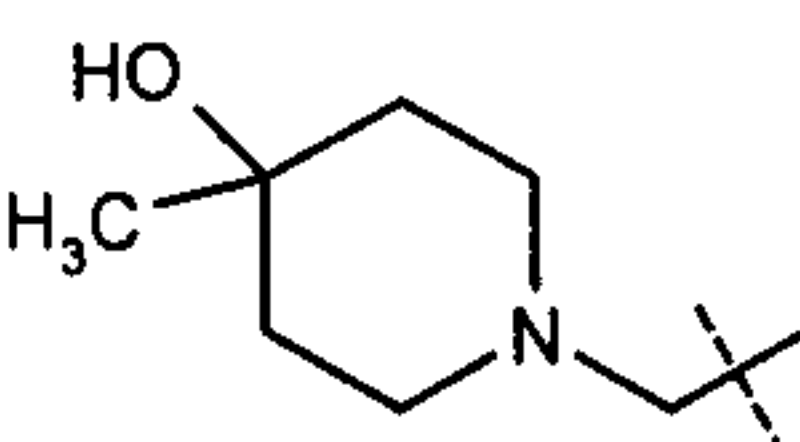
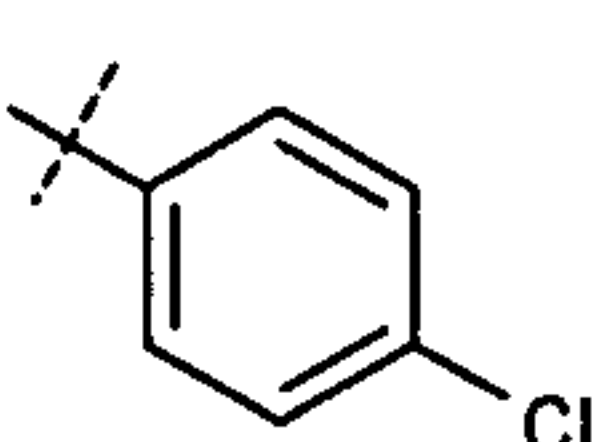
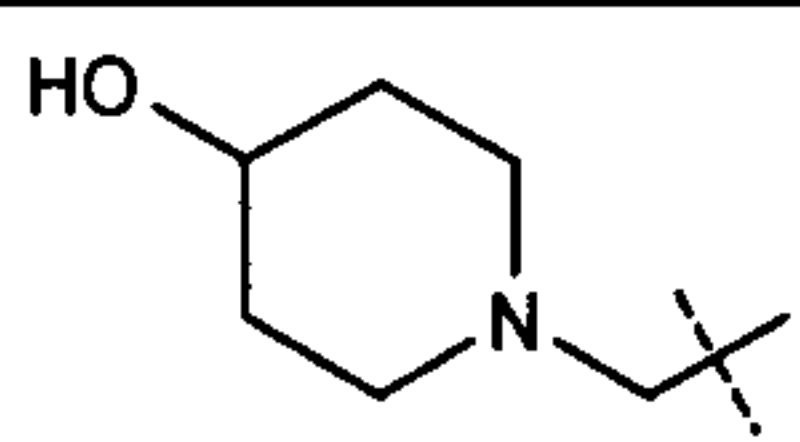
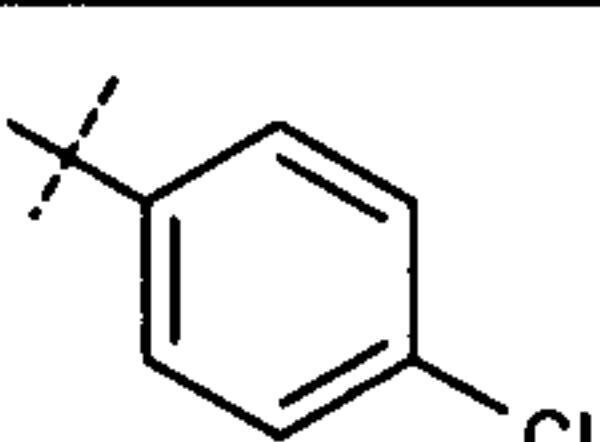
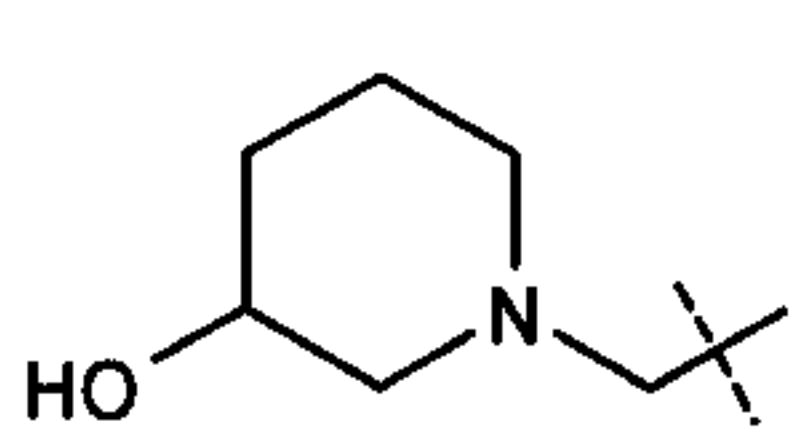
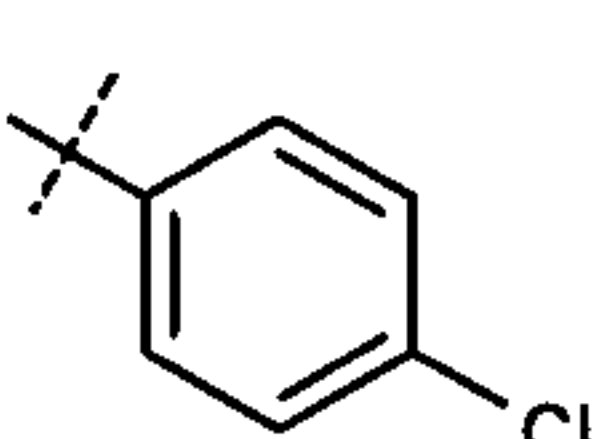
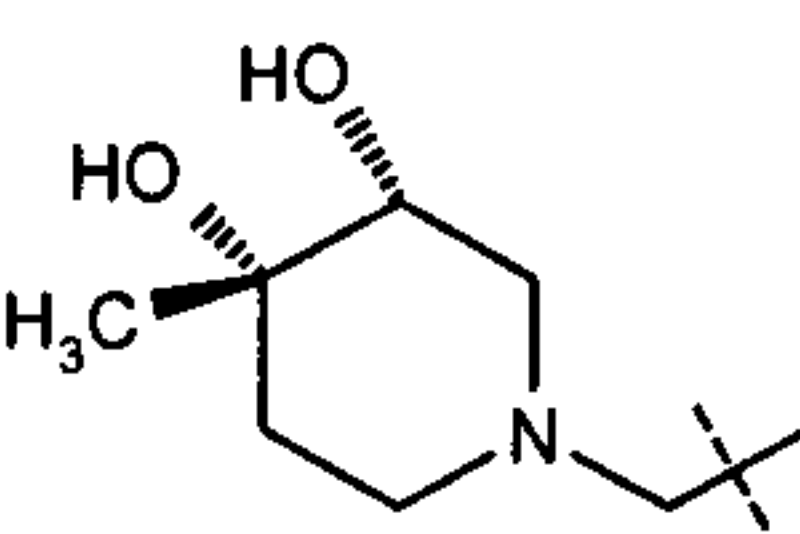
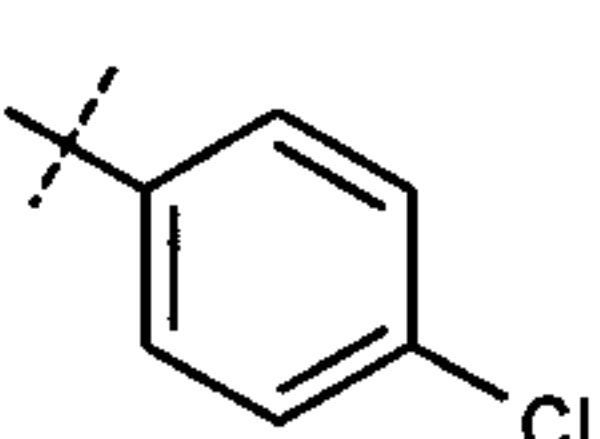
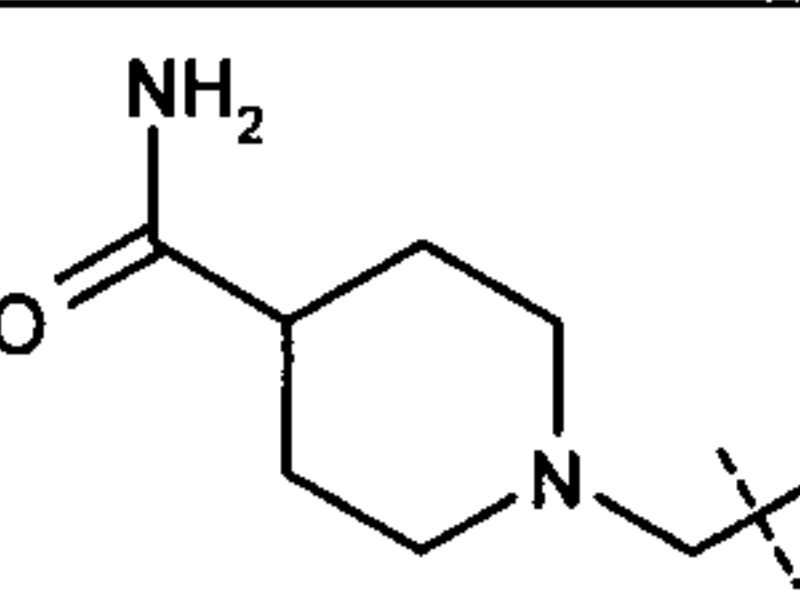
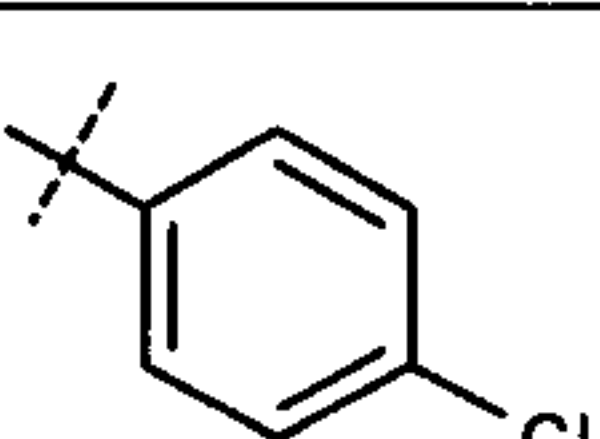
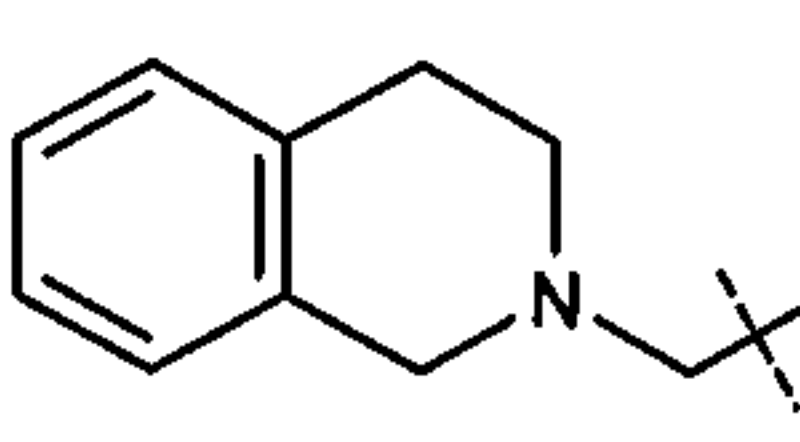
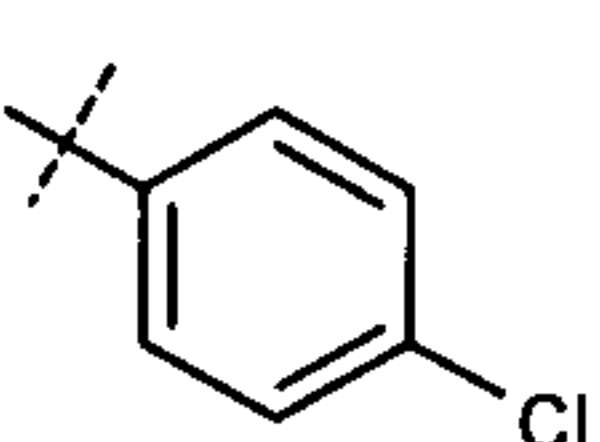
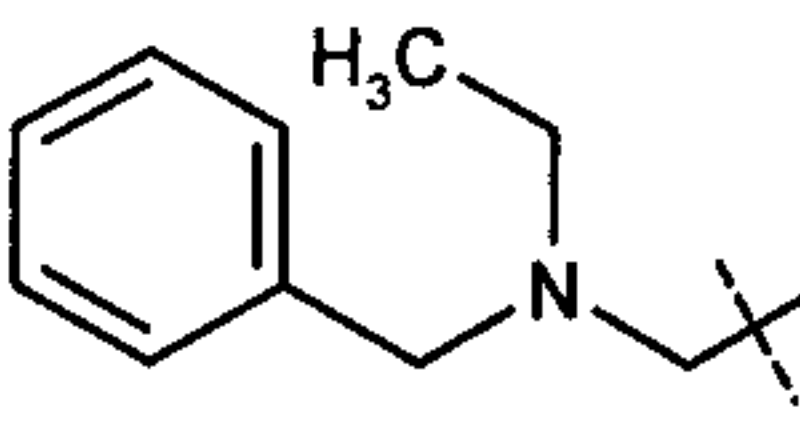
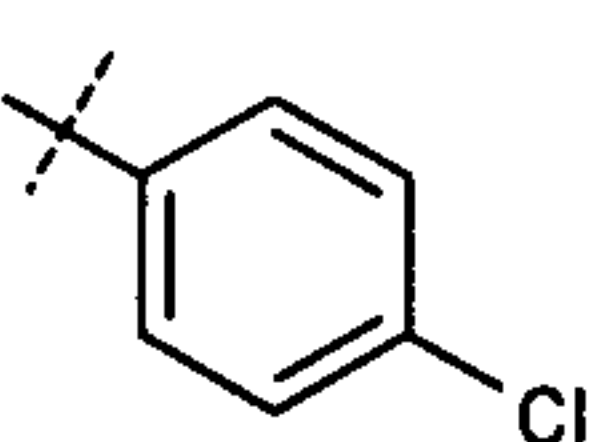
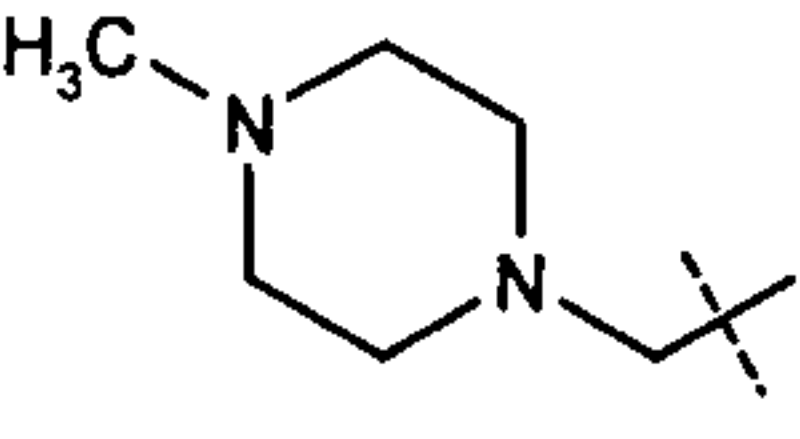
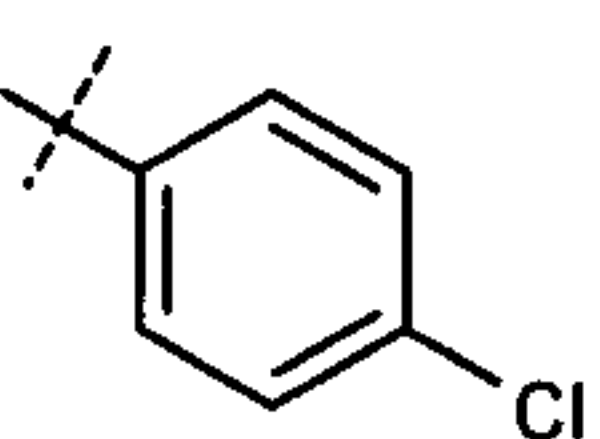
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3.61		-H	-H		CH
3.62		-H	-H		CH
3.63		-H	-H		CH
3.64		-H	-H		CH
3.65		-H	-H		CH
3.66		-H	-H		CH
3.67		-H	-H		CH
3.68		-H	-H		CH
3.69		-H	-H		CH
3.70		-H	-H		CH
3.71		-H	-H		CH
3.72		-Cl	-H		CH

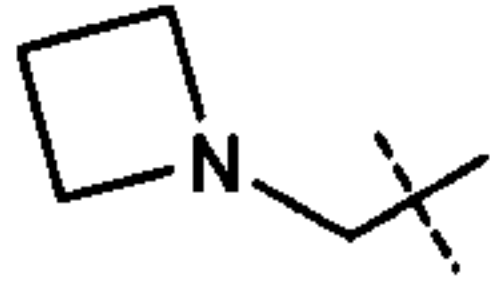
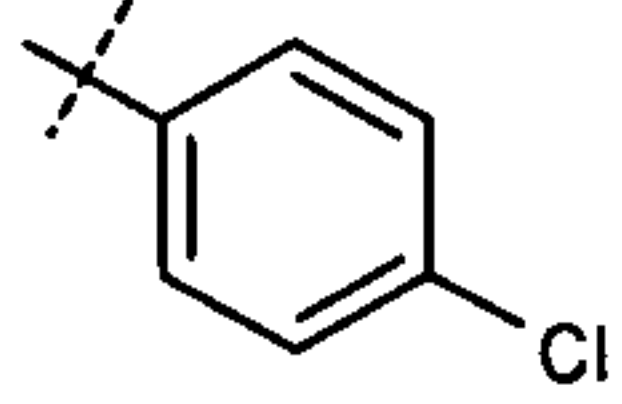
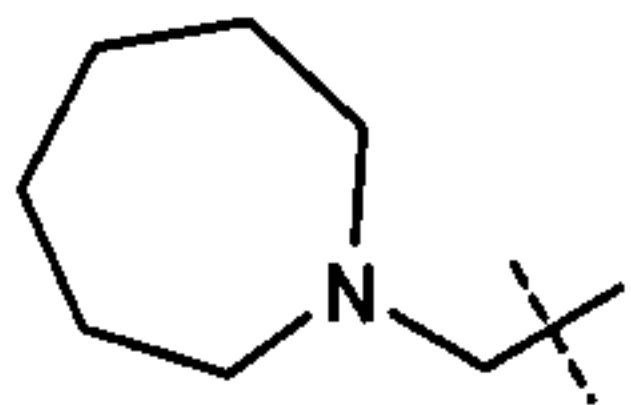
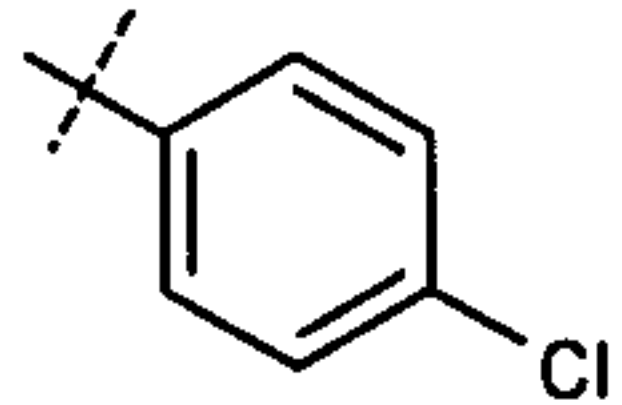
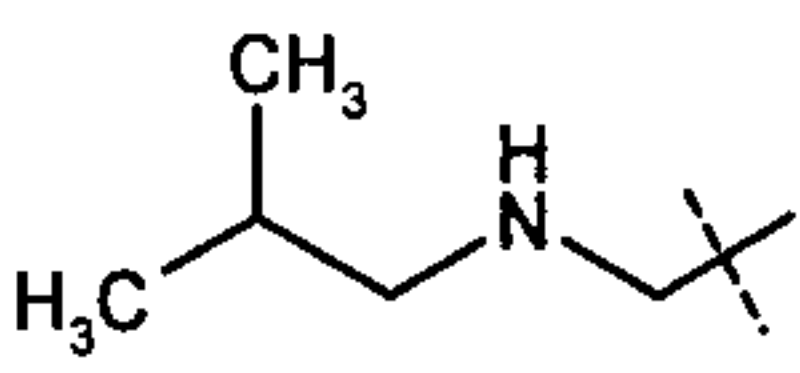
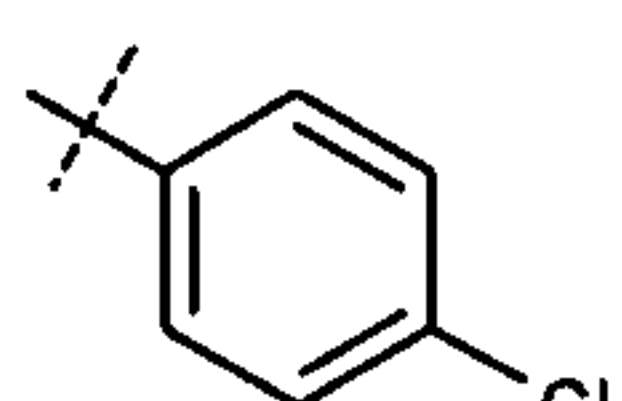
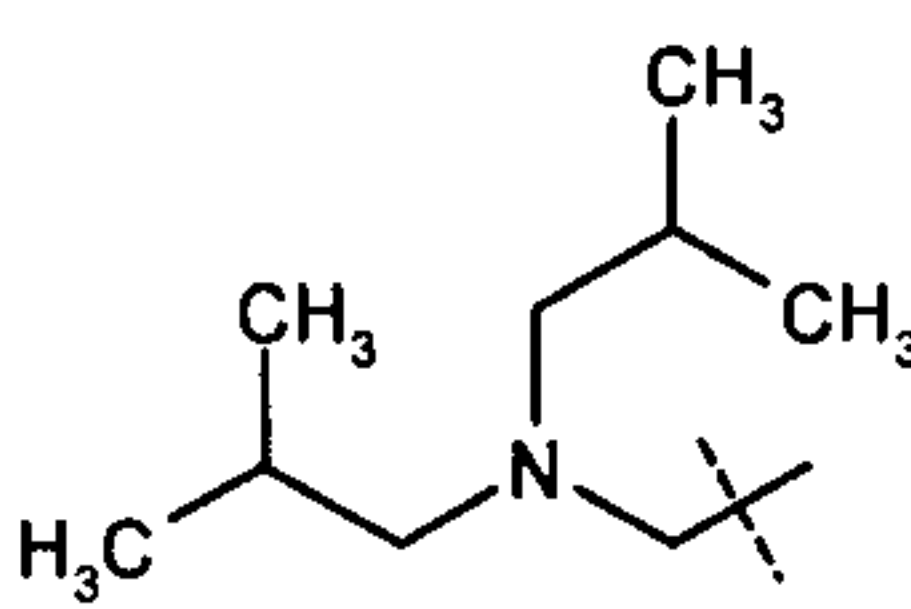
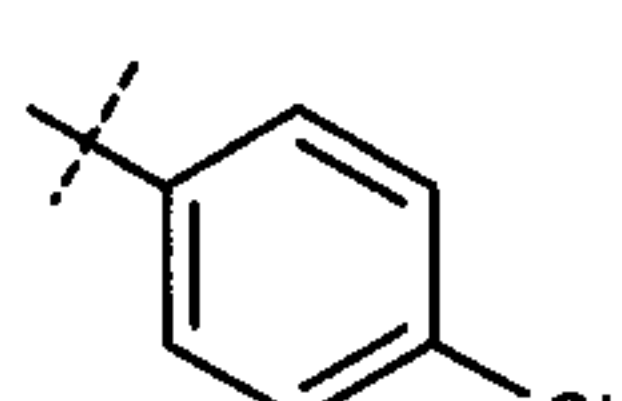
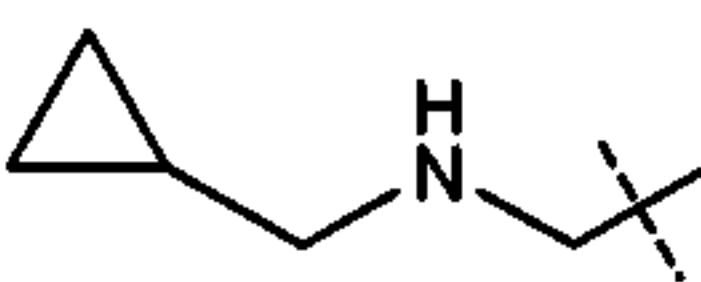
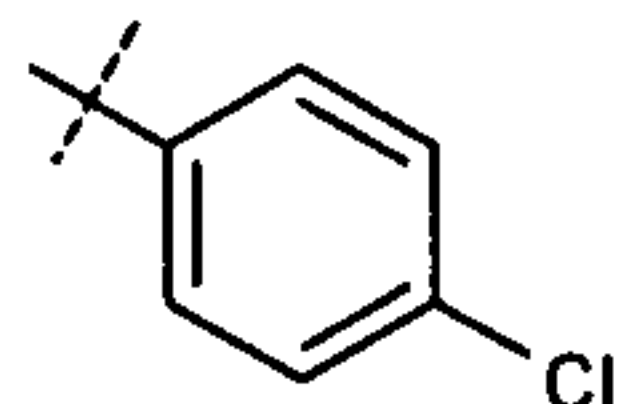
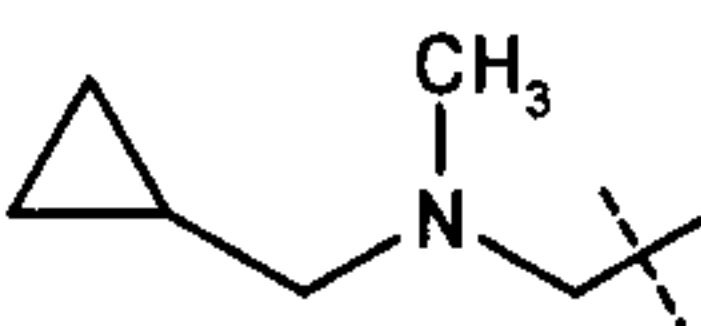
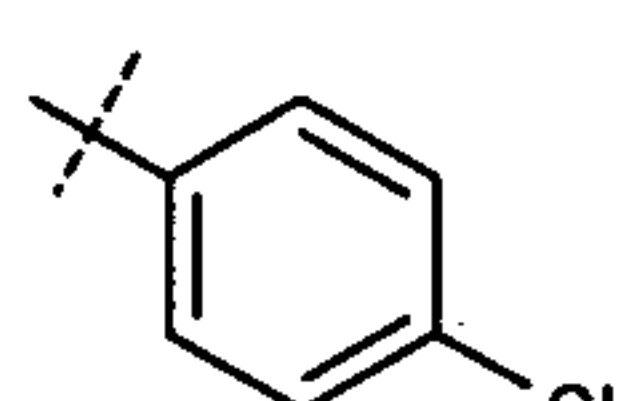
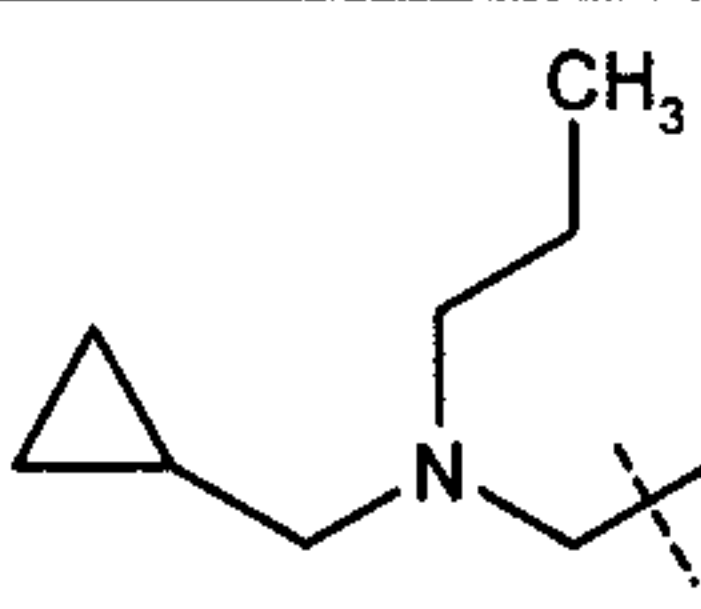
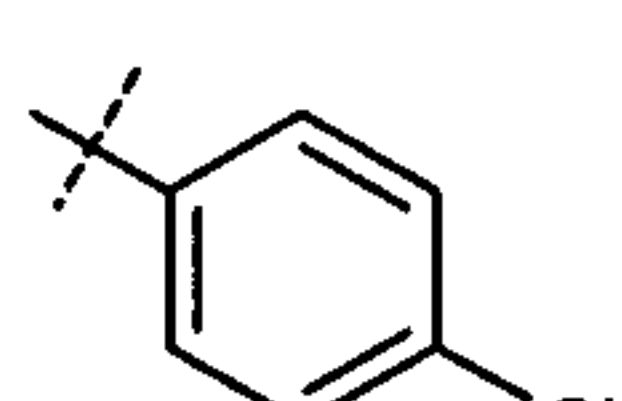
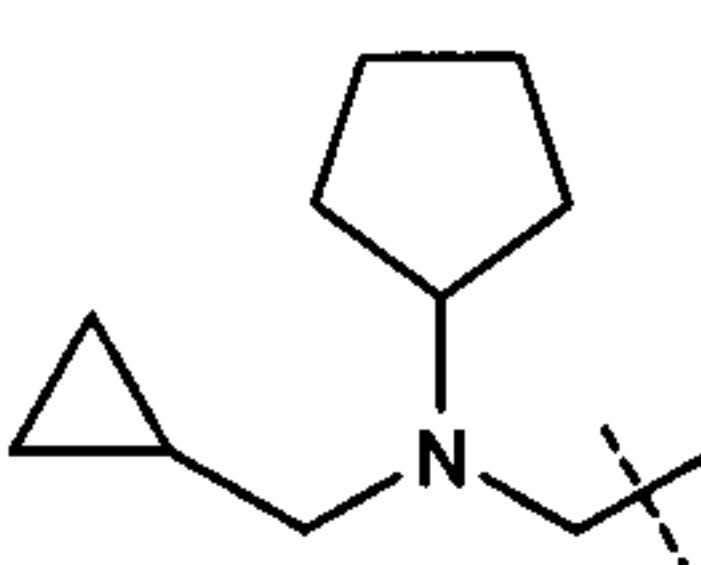
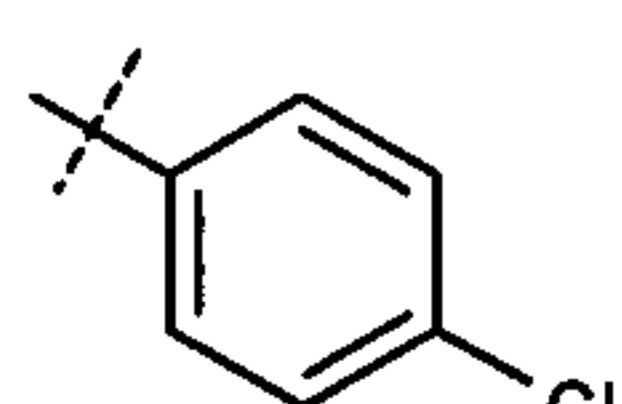
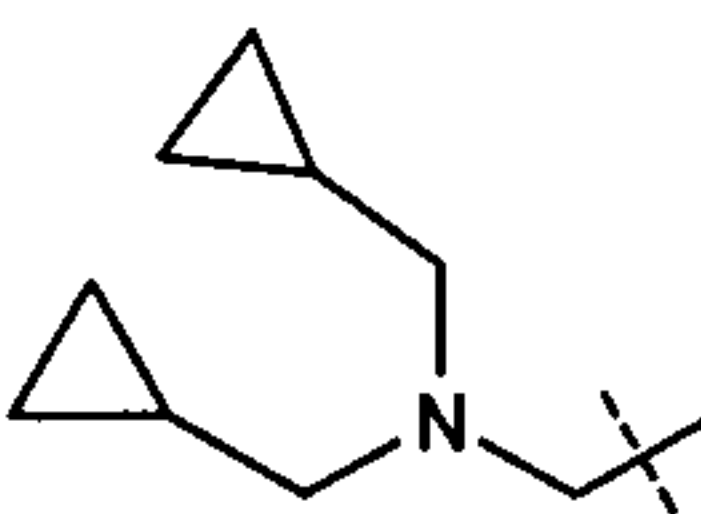
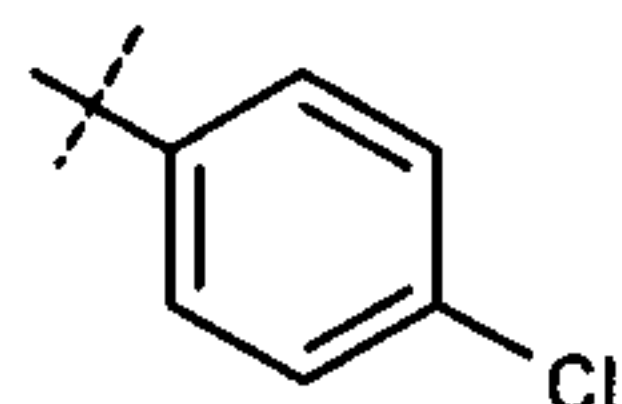
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3.74		-Cl	-H		CH
3.75		-Cl	-H		CH
3.76		-Cl	-H		CH
3.78		-Cl	-H		CH
3.79		-Cl	-H		CH
3.80		-Cl	-H		CH
3.81		-Cl	-H		CH
3.82		-Cl	-H		CH
3.83		-Cl	-H		CH
3.84		-Cl	-H		CH
3.85		-Cl	-H		CH
3.86		-Cl	-H		CH

3.87		-Cl	-H		CH
3.88		-Cl	-H		CH
3.89		-Cl	-H		CH
3.90		-Cl	-H		CH
3.91		-Cl	-H		CH
3.92		-Cl	-H		CH
3.93		-Cl	-H		CH
3.94		-Cl	-H		CH
3.95		-Cl	-H		CH
3.96		-Cl	-H		CH
3.97		-Cl	-H		CH
3.98		-H	-H		N
3.99		-H	-H		N

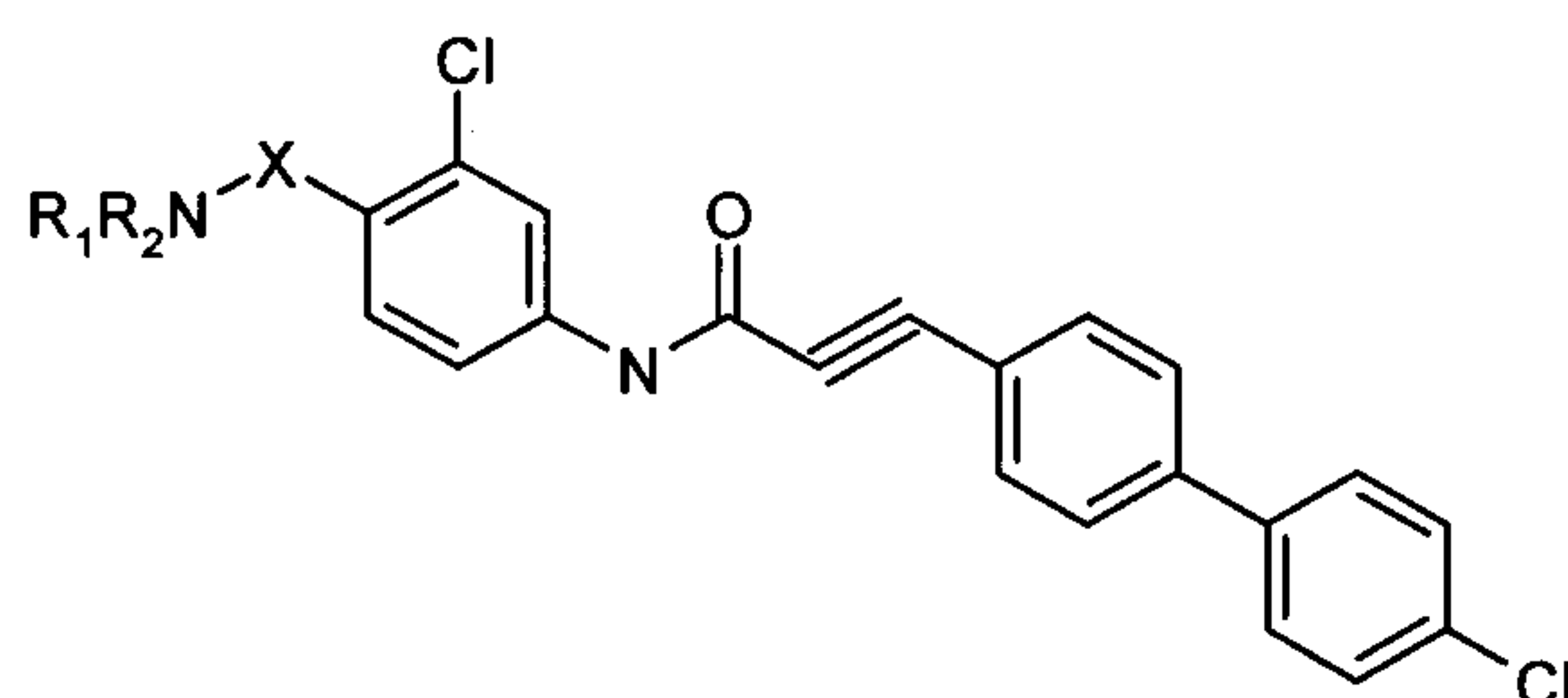
3.100		-H	-H		N
3.101		-H	-H		N
3.102		-H	-H		N
3.103		-H	-H		N
3.104		-H	-H		N
3.105		-H	-H		N
3.106		-H	-H		N
3.108		-H	-H		N
3.109		-H	-H		N
3.110		-H	-H		N
3.111		-H	-H		N
3.112		-H	-H		N
3.113		-H	-H		N
3.114		-H	-H		N

3.115		-H	-H		N
3.116		-H	-H		N
3.117		-H	-H		N
3.118		-H	-H		N
3.119		-H	-H		N
3.120		-H	-H		N
3.121		-H	-H		N
3.122		-Cl	-H		N
3.123		-Cl	-H		N
3.124		-Cl	-H		N
3.125		-Cl	-H		N
3.126		-Cl	-H		N
3.127		-Cl	-H		N

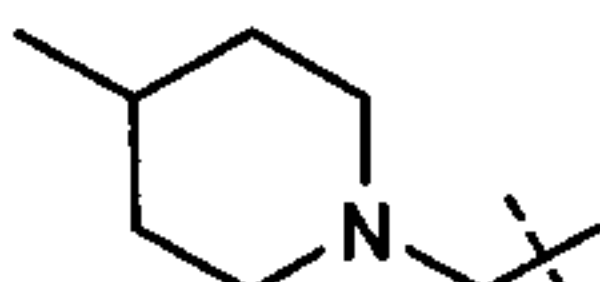
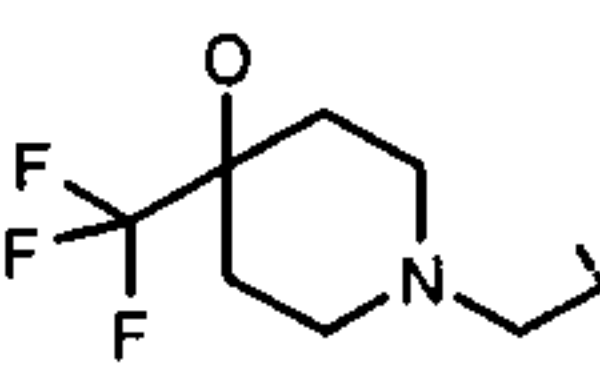
3.128		-Cl	-H		N
3.129		-Cl	-H		N
3.130		-Cl	-H		N
3.131		-Cl	-H		N
3.132		-Cl	-H		N
3.133		-Cl	-H		N
3.134		-Cl	-H		N
3.135		-Cl	-H		N
3.136		-Cl	-H		N
3.137		-Cl	-H		N
3.138		-Cl	-H		N
3.139		-Cl	-H		N
3.140		-Cl	-H		N

3.141		-Cl	-H		N
3.142		-Cl	-H		N
3.143		-Cl	-H		N
3.144		-Cl	-H		N
3.145		-Cl	-H		N
3.146		-Cl	-H		N
3.147		-Cl	-H		N
3.148		-Cl	-H		N
3.149		-Cl	-H		N

The following compounds are prepared analogously to Example 3.20:



Example	R ₁ R ₂ N-X	educt	empirical formula	mass spectrum	mp [°C]	R _f value

3.166		3.7.b	$C_{28}H_{26}Cl_2N_2O$	477/79/81 (Cl ₂) [M+H] ⁺	160- 164	0.8 (B)
3.167		3.7.b	$C_{28}H_{23}Cl_2F_3N_2$ O ₂	547/49/51 (Cl ₂) [M+H] ⁺	128- 132	0.5 (A)

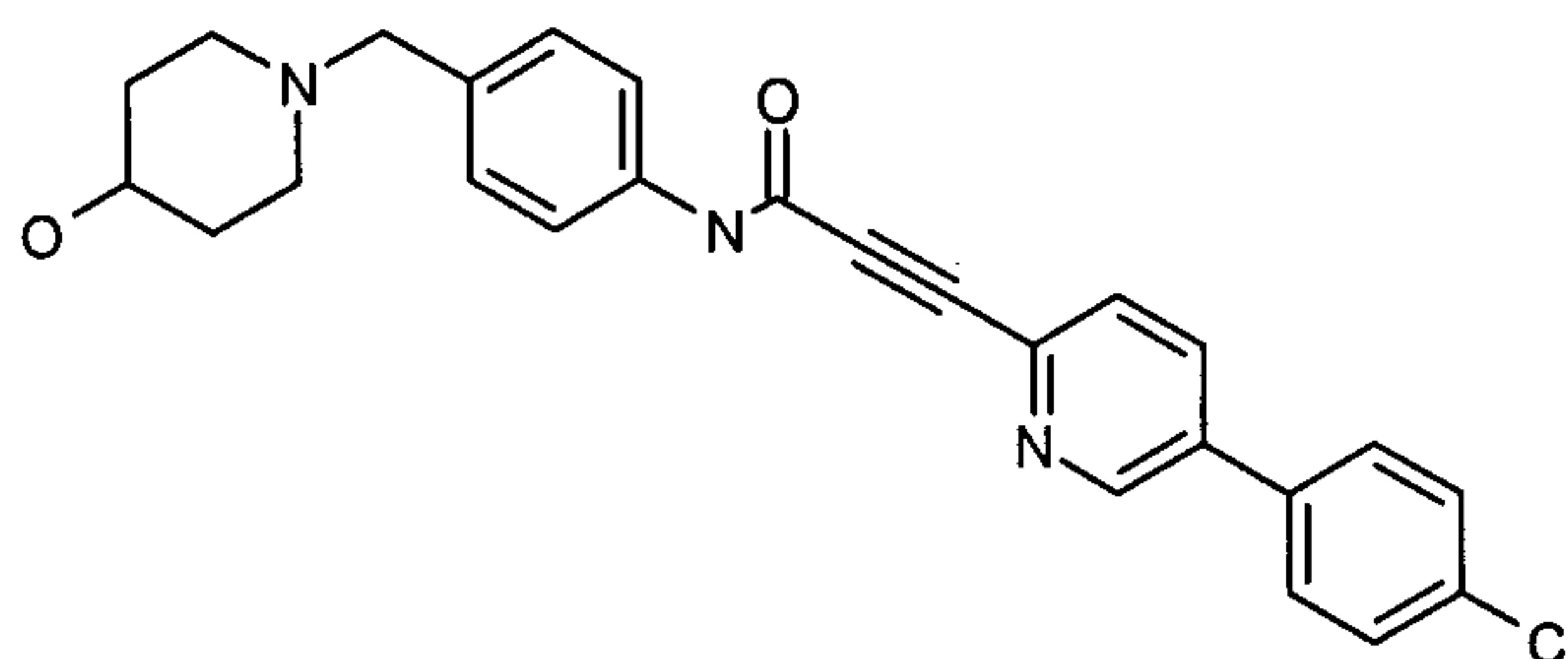
R_f value: A= (silica gel, dichloromethane/methanol 90:10)

B= (silica gel, dichloromethane/methanol/ammonia 90:10:0.1)

5

Example 3.168:

3-[5-(4-chloro-phenyl)-pyridin-2-yl]-propynoic acid-[4-(4-hydroxy-piperidin-1-ylmethyl)-phenyl]-amide



10

Prepared analogously to Example 2.3.f from [5-(4-chloro-phenyl)-pyridin-2-yl]-propynoic acid and 4-[4-(*tert*-butyl-dimethyl-silanyloxy)-piperidin-1-ylmethyl]-phenylamine. The cleaving of the silyl group is carried out by adding
15 tetrabutylammonium fluoride to a solution of the silylether in THF.

Yield: 0.25 g (43 % of theoretical)

Melting point: 186-190 °C

$C_{26}H_{24}ClN_3O_2$ (M= 445.94)

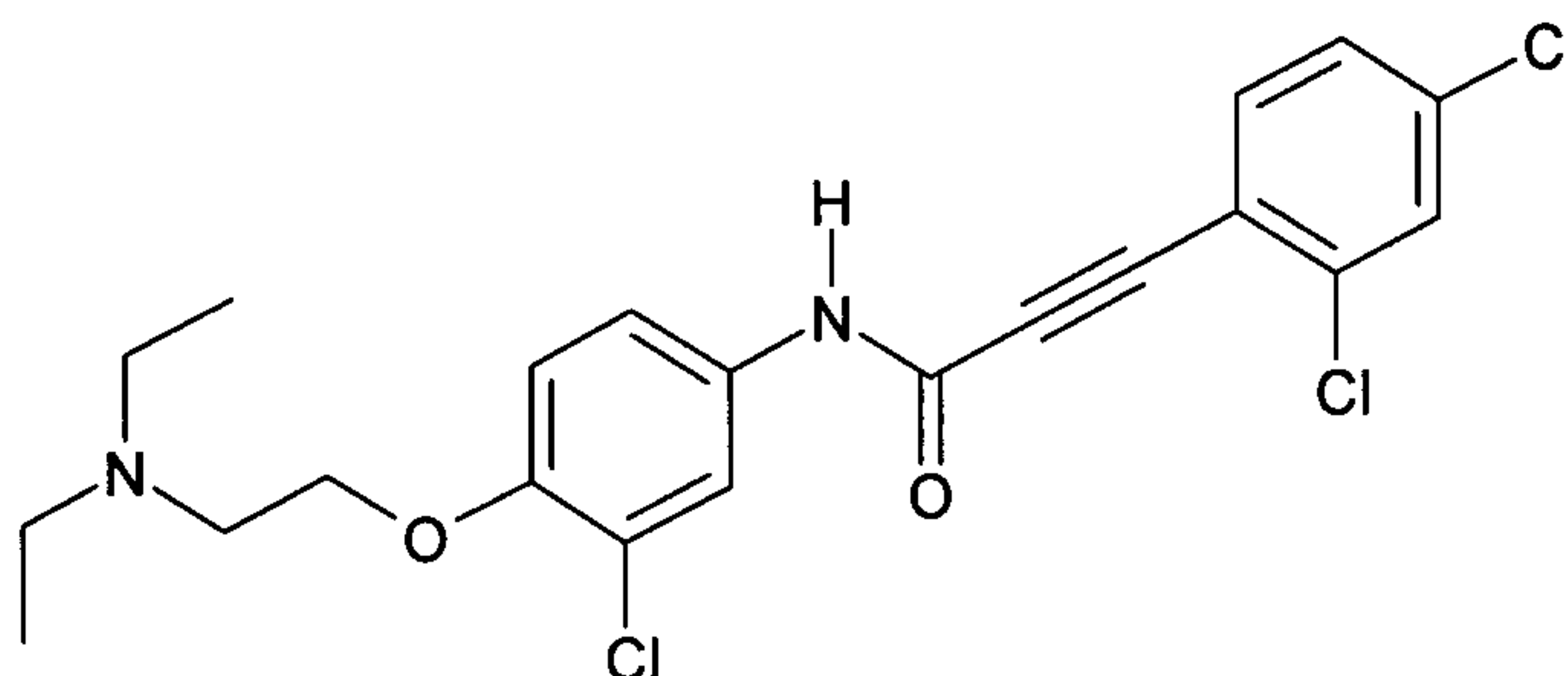
20 Calc.: Molecular ion peak (M+H)⁺: 446/448
peak (M+H)⁺: 446/448

Found: Molecular ion

R_f value: 0.6 (silica gel, dichloromethane/methanol/ammonia = 90:10:0.1)

Example 4.1:

3-(2,4-dichloro-phenyl)-propynoic acid-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-amide



5

4.1.a. [2-(2-chloro-4-nitro-phenoxy)-ethyl]-diethyl-amine

112 g (0.81 mol) potassium carbonate are added to a solution of 35 g (0.202 mol) 2-chloro-4-nitro-phenol in 350 ml DMF. Then the reaction mixture is combined with 35 g (0.203 mol) (2-chloro-ethyl)-diethyl-amine hydrochloride and stirred for three hours at 80° C and 14 hours at ambient temperature. The reaction mixture is evaporated down and the residue is poured onto 1000 ml of water and this mixture is extracted three times with ethyl acetate. The combined organic phases are dried over sodium sulphate, the desiccant is filtered off and the filtrate is evaporated down.

Yield: 49.6 g (90 % of theoretical)

15 $C_{12}H_{17}ClN_2O_3$ (M= 272.73)

Calc.: Molecular ion peak (M+H)⁺: 273

Found: Molecular ion peak

(M+H)⁺: 273

R_f value: 0.36 (silica gel, dichloromethane/methanol = 90:10)

20 4.1.b. [2-(2-chloro-4-amino-phenoxy)-ethyl]-diethyl-amine

Prepared analogously to Example 3.1.b from [2-(2-chloro-4-nitro-phenoxy)-ethyl]-diethyl-amine in methanol in a reaction time of 4.5 hours.

Yield: 36.12 g (81.8 % of theoretical)

$C_{12}H_{19}ClN_2O$ (M= 242.75)

25 Calc.: Molecular ion peak (M+H)⁺: 243/245

Found: Molecular ion

peak (M+H)⁺: 243/245

R_f value: 0.36 (silica gel, dichloromethane/methanol = 90:10)

4.1.c. (2,4-dichloro-phenyl)-propynoic acid chloride

A reaction mixture of 0.34 g (1.58 mmol) (2,4-dichloro-phenyl)-propynoic acid and 0.14 ml (1.9 mmol) thionyl chloride in 15 ml absolute toluene is stirred for three hours at 70 °C and then evaporated down. The residue is taken up in absolute toluene and the solution is evaporated to dryness. This procedure is then repeated once more and the residue is further reacted in its crude state.

4.1.d. 3-(2,4-dichloro-phenyl)-propynoic acid-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-amide

0.37 g (1.58 mmol) (2,4-dichloro-phenyl)-propynoic acid chloride are dissolved in 15 ml absolute toluene and while cooling with ice combined with 0.77 g (3.16 mmol) [2-(2-chloro-4-amino-phenoxy)-ethyl]-diethyl-amine, dissolved in 10 ml absolute toluene, and stirred for four hours at ambient temperature. Then the reaction mixture is extracted with ethyl acetate and dilute aqueous ammonia solution. The organic phase is extracted with water and dried over sodium sulphate. The purification is carried out by column chromatography on silica gel (eluant: dichloromethane/methanol= 9:1). The product obtained is recrystallised from petroleum ether and dried in the vacuum drying chamber at 50° C.

Yield: 0.21 g (30.2 % of theoretical)

Melting point: 98-100°C

$C_{21}H_{21}Cl_3N_2O_2$ (M= 439.77)

Calc.: Molecular ion peak (M+H)⁺: 439/441/443

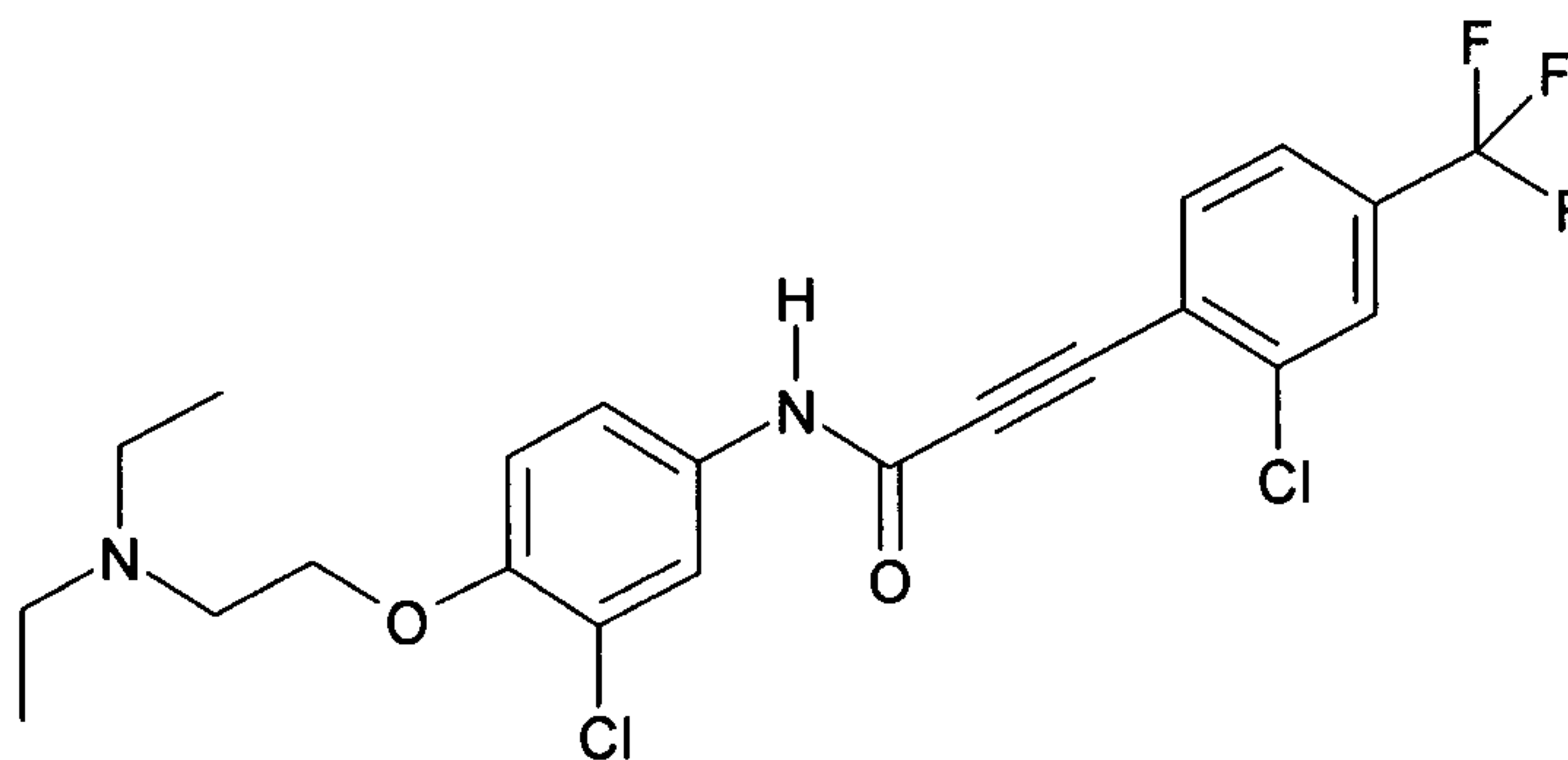
Found: Molecular ion

peak (M+H)⁺: 439/441/443

R_f value: 0.5 (silica gel, dichloromethane/ methanol/ammonia = 9:1:0.1)

Example 4.2:

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-amide



4.2.a. (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid chloride

Prepared analogously to Example 4.1.c from (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid. The compound is further reacted in its crude state.

4.2.b. 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-amide

Prepared analogously to Example 4.1.d from (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid chloride and [2-(2-chloro-4-amino-phenoxy)-ethyl]-diethyl-amine.

Yield: 0.26 g (27.5 % of theoretical)

$C_{22}H_{21}Cl_2F_3N_2O_2$ (M= 473.32)

Calc.: Molecular ion peak (M+H)⁺: 473/475

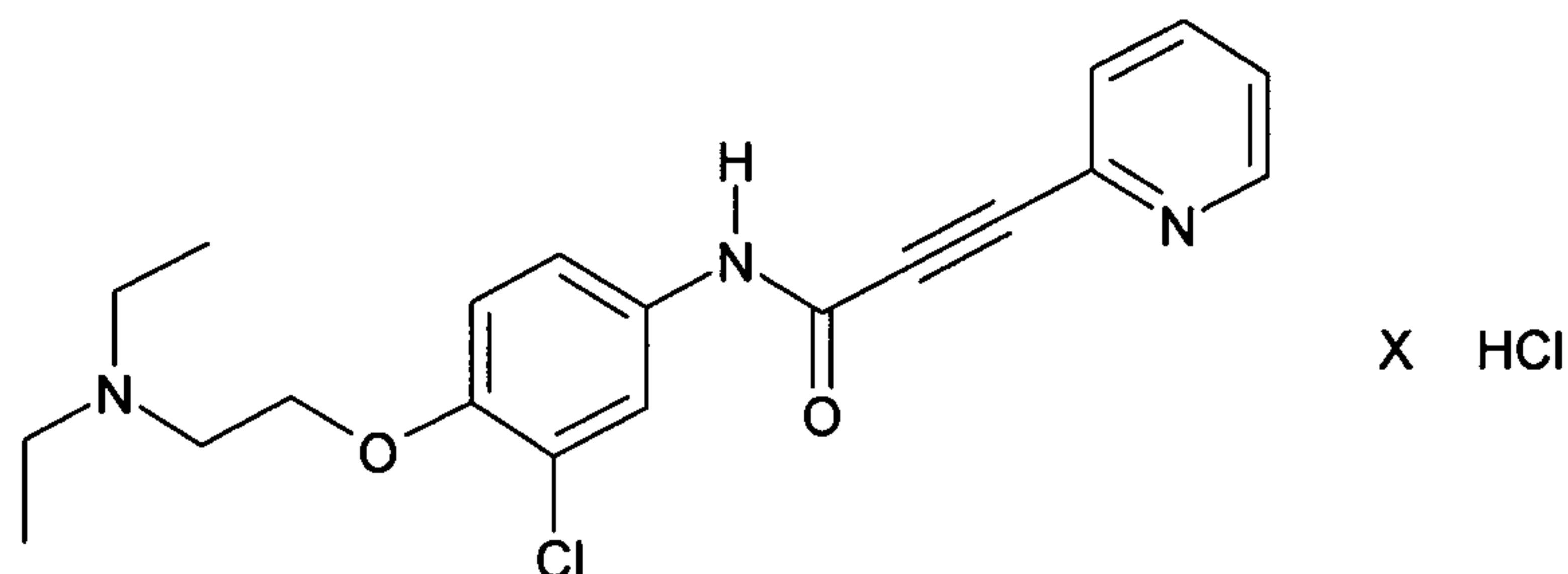
Found: Molecular ion peak

(M+H)⁺: 473/475

R_f value: 0.5 (silica gel, dichloromethane/ methanol/ammonia = 9:1:0.1)

Example 4.3:

3-pyridin-2-yl-propynoic acid-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-amide-hydrochloride



4.3.a. pyridin-2-yl-propynoic acid

6.3 ml n-butyllithium solution (1.6 M in hexane) are added dropwise at -10°C to a solution of 1 g (9.7 mmol) 2-ethynylpyridine in 30 ml absolute THF and stirred for 30

minutes. At -78 C dry ice is added batchwise and the reaction mixture is allowed to heat up to ambient temperature. After about one hour the reaction mixture is evaporated down and the residue is taken up in 10 ml 1N hydrochloric acid while cooling with ice. The precipitate is filtered off, rinsed with isopropanol and diethyl ether and dried in the vacuum drying chamber at 70°C.

Yield: 0.6 g (42 % of theoretical)

Melting point: 130°C

C₈H₅NO₂ (M= 147.13)

Calc.: Molecular ion peak (M+H)⁺: 148

Found: Molecular ion peak (M+H)⁺:

148

4.3.b. 3-pyridin-2-yl-propynoic acid-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-amide-hydrochloride

Prepared analogously to Example 2.3.f from pyridin-2-yl-propynoic acid and [2-(2-chloro-4-amino-phenoxy)-ethyl]-diethyl-amine.

Yield: 0.37 g (53.3 % of theoretical)

C₂₀H₂₂ClN₃O₂ X HCl (M= 408.33)

Calc.: Molecular ion peak (M+H)⁺: 372/374

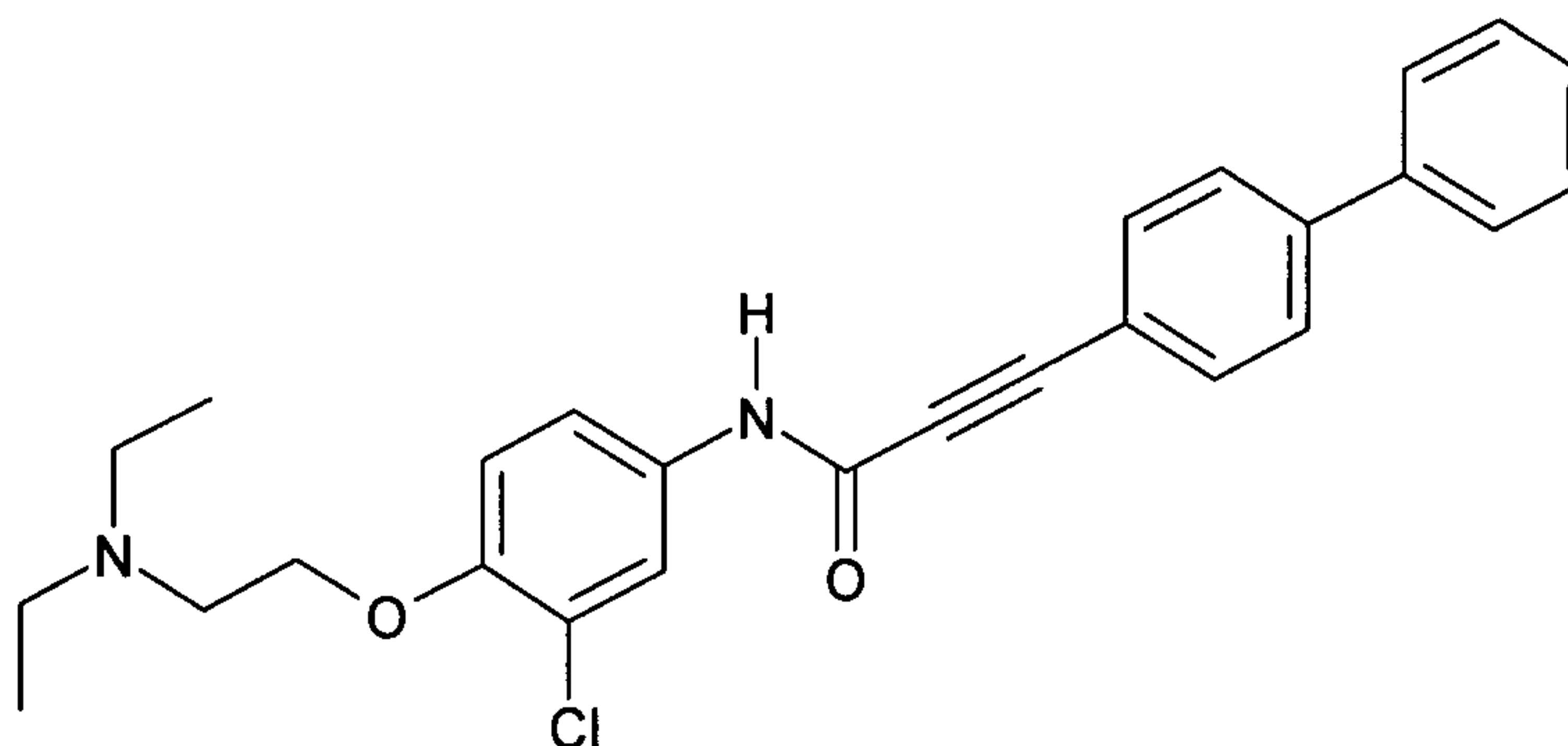
Found: Molecular ion peak

(M+H)⁺: 372/374

R_f value: 0.5 (silica gel, dichloromethane/ methanol/ammonia = 9:1:0.1)

Example 4.4:

3-biphenyl-4-yl-propynoic acid-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-amide



4.4.a. 3-biphenyl-4-yl-2,3-dibromo-propanecarboxylic acid

Prepared analogously to Example 3.4.a from 3-biphenyl-4-yl-acrylic acid.

Yield: 5 g (91.2 % of theoretical)

Melting point: 200-203⁰C

C₁₅H₁₂Br₂O₂ (M= 384.07)

R_f value: 0.4 (silica gel, dichloromethane/methanol/acetic acid = 90:10:1)

5

4.4.b. biphenyl-4-yl-propynoic acid

Prepared analogously to Example 3.4.b from 3-biphenyl-4-yl-2.3-dibromopropanecarboxylic acid.

Yield: 2.8 g (96.8 % of theoretical)

10 C₁₅H₁₀O₂ (M= 222.24)

Melting point: 170⁰C

Calc.: Molecular ion peak (M+H)⁺: 223

Found: Molecular ion peak

(M+H)⁺: 223

R_f value: 0.4 (silica gel, dichloromethane/methanol/acetic acid = 90:10:1)

15

4.4.c. biphenyl-4-yl-propynoic acid chloride

Prepared analogously to Example 4.1.c from biphenyl-4-yl-propynoic acid. The compound is further reacted in its crude state.

20 4.4.d. 3-biphenyl-4-yl-propynoic acid-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-amide

Prepared analogously to Example 4.1.d from biphenyl-4-yl-propynoic acid chloride and [2-(2-chloro-4-amino-phenoxy)-ethyl]-diethyl-amine.

Yield: 0.28 g (31.3 % of theoretical)

25 Melting point: 105-108⁰C

C₂₇H₂₇ClN₂O₂ (M= 446.98)

Calc.: Molecular ion peak (M+H)⁺: 447/449

Found: Molecular ion

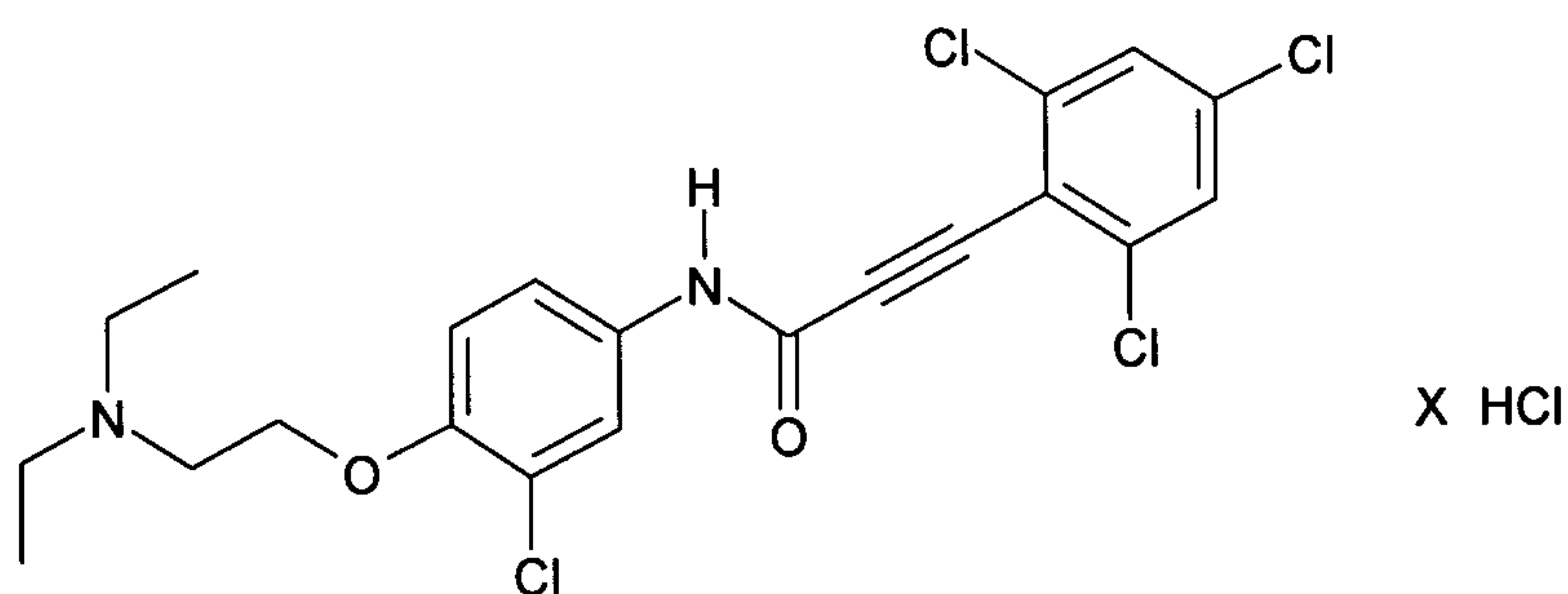
peak (M+H)⁺: 447/449

R_f value: 0.5 (silica gel, dichloromethane/ methanol/ammonia = 9:1:0.1)

30

Example 4.5:

3-(2,4,6-trichloro-phenyl)-propynoic acid-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-amide-hydrochloride



5

4.5.a. triphenyl-(2,4,6-trichloro-phenylethynyl)-silane

In an argon atmosphere 9 g (34.6 mmol) 1-bromo-2,4,6-trichlorobenzene, 9.8 g (34.45 mmol) triphenylsilylacetylene and 15 ml triethylamine are dissolved in 100 ml absolute dioxane and at 90 °C combined with 0.2 g (1.04 mmol) copper(I)iodide and 1.2 g (1.04 mmol) tetrakis(triphenylphosphine) palladium and stirred for 20 hours. The reaction mixture is filtered through Celite and the filtrate is evaporated down. The residue is taken up in ethyl acetate and extracted with water. The organic phase is dried over sodium sulphate. The purification is carried out by column chromatography on silica gel (eluant: petroleum ether/ toluene= 5:1). The product is recrystallised from petroleum ether and dried in the vacuum drying chamber at 70 °C.

Yield: 6.9 g (43 % of theoretical)

Melting point: 115-120°C

C₂₆H₁₇Cl₃Si (M= 463.87)

Calc.: Molecular ion peak (M+H)⁺: 463/465/467/469

Found: Molecular ion peak (M+H)⁺: 463/465/467/469

R_f value: 0.6 (silica gel, petroleum ether/ toluene= 4:1)

4.5.b. 1,3,5-trichloro-2-ethynyl-benzene

A reaction mixture of 5 g (10.8 mmol) triphenyl-(2,4,6-trichloro-phenylethynyl)-silane and 4.2 g (16.2 mmol) tetrabutylammonium fluoride in 50 ml absolute THF is stirred for half an hour at ambient temperature and then evaporated down. The residue is taken up in diethyl ether and water and extracted. The organic phase is dried over sodium sulphate. The purification is carried out by column chromatography on silica gel (eluant: petroleum ether/ toluene= 9:1).

Yield: 0.46 g (20.7 % of theoretical)

R_f value: 0.6 (silica gel, petroleum ether/ toluene= 9:1)

4.5.c. (2,4,6-trichloro-phenyl)-propynoic acid

- 5 Prepared analogously to Example 4.3.a from triphenyl-(2,4,6-trichloro-phenylethynyl)-silane and dry ice.

Yield: 3.3 g (77.7 % of theoretical)

Melting point: 170-175°C

C₉H₃Cl₃O₂ (M= 249.48)

- 10 Calc.: Molecular ion peak (M+H)⁺: 249/251/253 Found: Molecular ion peak (M+H)⁺: 249/251/253

R_f value: 0.4 (silica gel, dichloromethane/methanol/acetic acid = 50:10:1)

4.5.d. 3-(2,4,6-trichloro-phenyl)-propynoic acid-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-amide-hydrochloride

- 15

Prepared analogously to Example 2.3.f from (2,4,6-trichloro-phenyl)-propynoic acid and [2-(2-chloro-4-amino-phenoxy)-ethyl]-diethyl-amine.

Yield: 0.72 g (82.9 % of theoretical)

Melting point: 188-191°C

- 20 C₂₁H₂₀Cl₄N₂O₂ X HCl (M= 510.67)

Calc.: Molecular ion peak (M+H)⁺: 473/475/477/479/481

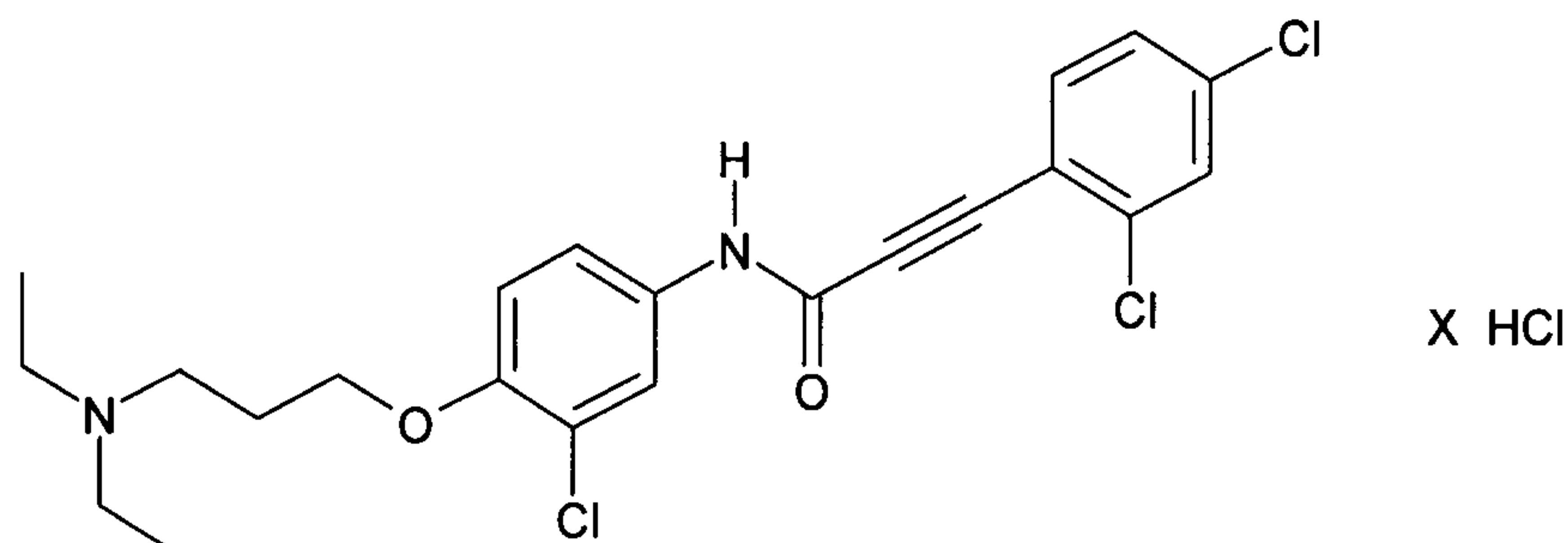
Found: Molecular ion peak (M+H)⁺: 473/475/477/479/481

R_f value: 0.4 (silica gel, dichloromethane/methanol/ammonia= 90:10:0.1)

25

Example 4.6:

3-(2,4-dichloro-phenyl)-propynoic acid-[3-chloro-4-(2-diethylamino-propoxy)-phenyl]-amide-hydrochloride



4.6.a. [2-(2-chloro-4-nitro-phenoxy)-propyl]-diethyl-amine

1.6 g (33 mmol) sodium hydride (50% in oil) are added at 0°C to a solution of 5.3 g (30 mmol) 3-chloro-4-fluoro-nitrobenzene and 4.3 g (33 mmol) 3-diethylaminopropan-1-ol in 50 ml DMF and stirred for two hours. Then the mixture is heated to ambient temperature and stirred for one hour. The reaction mixture is evaporated down, combined with water and extracted with ethyl acetate. The organic phase is dried over sodium sulphate. The purification is carried out by column chromatography on silica gel (eluant: dichloromethane/methanol/ammonia= 9:1:0.1).

Yield: 8 g (93 % of theoretical)

$C_{13}H_{19}ClN_2O_3$ (M= 286.76)

R_f value: 0.3 (silica gel, dichloromethane/methanol/ammonia = 90:10:0.1)

4.6.b. [2-(2-chloro-4-amino-phenoxy)-propyl]-diethyl-amine

Prepared analogously to Example 3.1.b from [2-(2-chloro-4-nitro-phenoxy)-propyl]-diethyl-amine in methanol in a reaction time of 8 hours.

Yield: 6.7 g (93.5 % of theoretical)

$C_{13}H_{21}ClN_2O$ (M= 256.77)

Calc.: Molecular ion peak (M+H)⁺: 257/259

Found: Molecular ion

peak (M+H)⁺: 257/259

R_f value: 0.4 (silica gel, dichloromethane/methanol/ammonia = 50:10:0.1)

4.6.c. 3-(2,4-dichloro-phenyl)-propynoic acid-[3-chloro-4-(2-diethylamino-propoxy)-phenyl]-amide-hydrochloride

Prepared analogously to Example 3.4.c from [2-(2-chloro-4-amino-phenoxy)-propyl]-diethyl-amine and (2,4-dichloro-phenyl)-propynoic acid

Yield: 0.62 g (84.3 % of theoretical)

Melting point: 180-185°C

$C_{22}H_{23}Cl_3N_2O_2 \times HCl$ (M= 490.26)

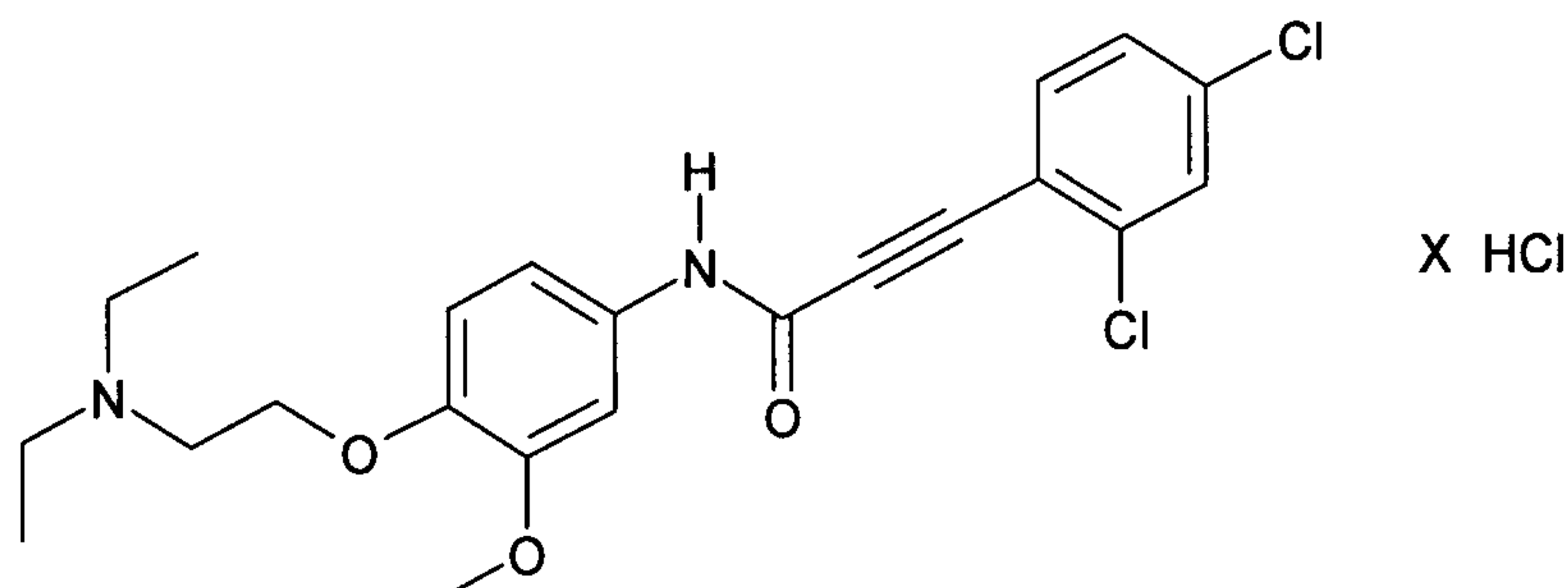
Calc.: Molecular ion peak (M+H)⁺: 453/455/457/459

Found: Molecular ion peak (M+H)⁺: 453/455/457/459

R_f value: 0.7 (silica gel, dichloromethane/ methanol/ammonia = 50:10:0.1)

Example 4.7:

3-(2,4-dichloro-phenyl)-propynoic acid-[3-methoxy-4-(2-diethylamino-ethoxy)-phenyl]-amide-hydrochloride



5

4.7.a. 3-(2,4-dichloro-phenyl)-propynoic acid-[3-methoxy-4-(2-diethylamino-ethoxy)-phenyl]-amide-hydrochloride

Prepared analogously to Example 2.3.f from (2,4-dichloro-phenyl)-propynoic acid chloride and [2-(2-methoxy-4-amino-phenoxy)-ethyl]-diethyl-amine.

10 Yield: 0.25 g (31.2 % of theoretical)

Melting point: 205-207°C

$C_{22}H_{24}Cl_2N_2O_3 \times HCl$ (M= 471.81)

Calc.: Molecular ion peak (M+H)⁺: 435/437/439

Found: Molecular ion

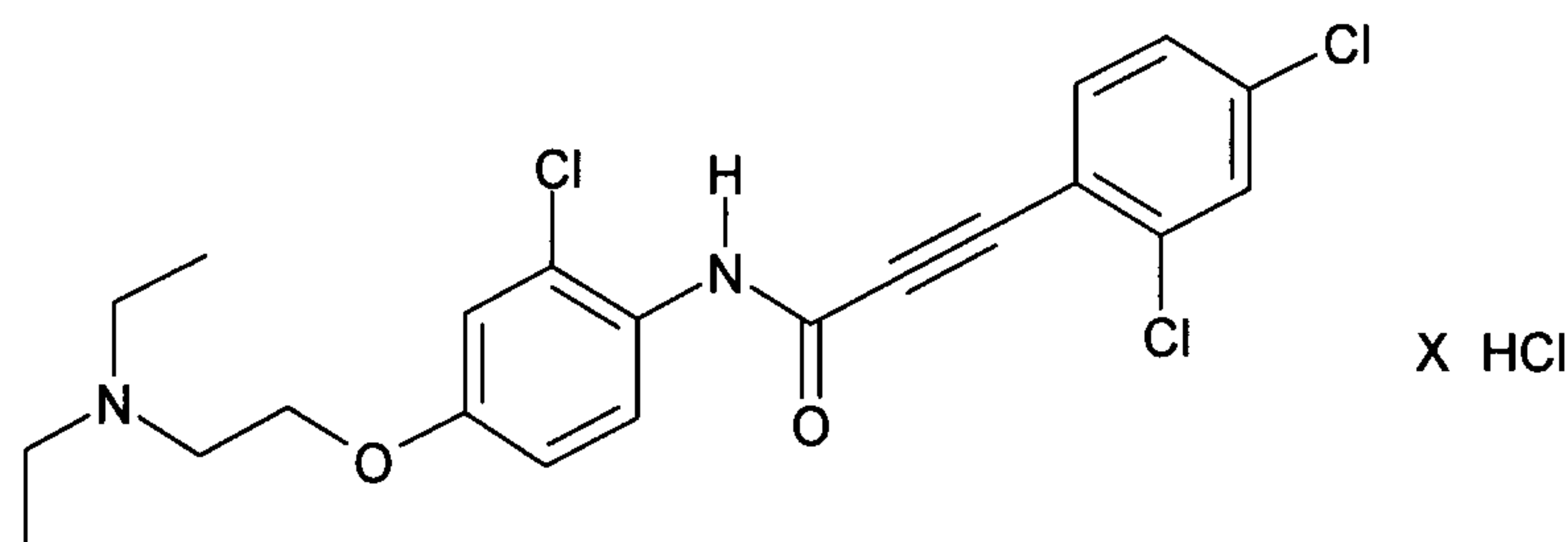
peak (M+H)⁺: 435/437/439

15 R_f value: 0.6 (silica gel, dichloromethane/ methanol/ammonia = 50:10:0.1)

Example 4.8:

3-(2,4-dichloro-phenyl)-propynoic acid-[2-chloro-4-(2-diethylamino-ethoxy)-phenyl]-amide

20



4.8.a. [2-(3-chloro-4-nitro-phenoxy)-ethyl]-diethyl-amine

Prepared analogously to Example 4.1.a from 3-chloro-4-nitro-phenol and (2-chloro-ethyl)-diethyl-amine hydrochloride.

25

Yield: 1.25 g (79.5 % of theoretical)

$C_{12}H_{17}ClN_2O_3$ (M= 272.73)

Calc.: Molecular ion peak (M+H)⁺: 273/275
peak (M+H)⁺: 273/275

Found: Molecular ion

5 R_f value: 0.44 (silica gel, dichloromethane/methanol = 90:10)

4.8.b. [2-(3-chloro-4-amino-phenoxy)-ethyl]-diethyl-amine

Prepared analogously to Example 3.1.b from [2-(3-chloro-4-nitro-phenoxy)-ethyl]-diethyl-amine in ethyl acetate.

10 Yield: 1.05 g (95.4 % of theoretical)

$C_{12}H_{19}ClN_2O$ (M= 242.75)

Calc.: Molecular ion peak (M+H)⁺: 243/245
peak (M+H)⁺: 243/245

Found: Molecular ion

R_f value: 0.41 (silica gel, dichloromethane/methanol = 90:10)

15

4.8.c. 3-(2,4-dichloro-phenyl)-propynoic acid-[2-chloro-4-(2-diethylamino-ethoxy)-phenyl]-amide-hydrochloride

Prepared analogously to Example 2.3.f from (2,4-dichloro-phenyl)-propynoic acid chloride and [2-(3-chloro-4-amino-phenoxy)-ethyl]-diethyl-amine.

20 Yield: 0.53 g (65.5 % of theoretical)

Melting point: 128-130°C

$C_{21}H_{21}Cl_3N_2O_2 \times HCl$ (M= 476.23)

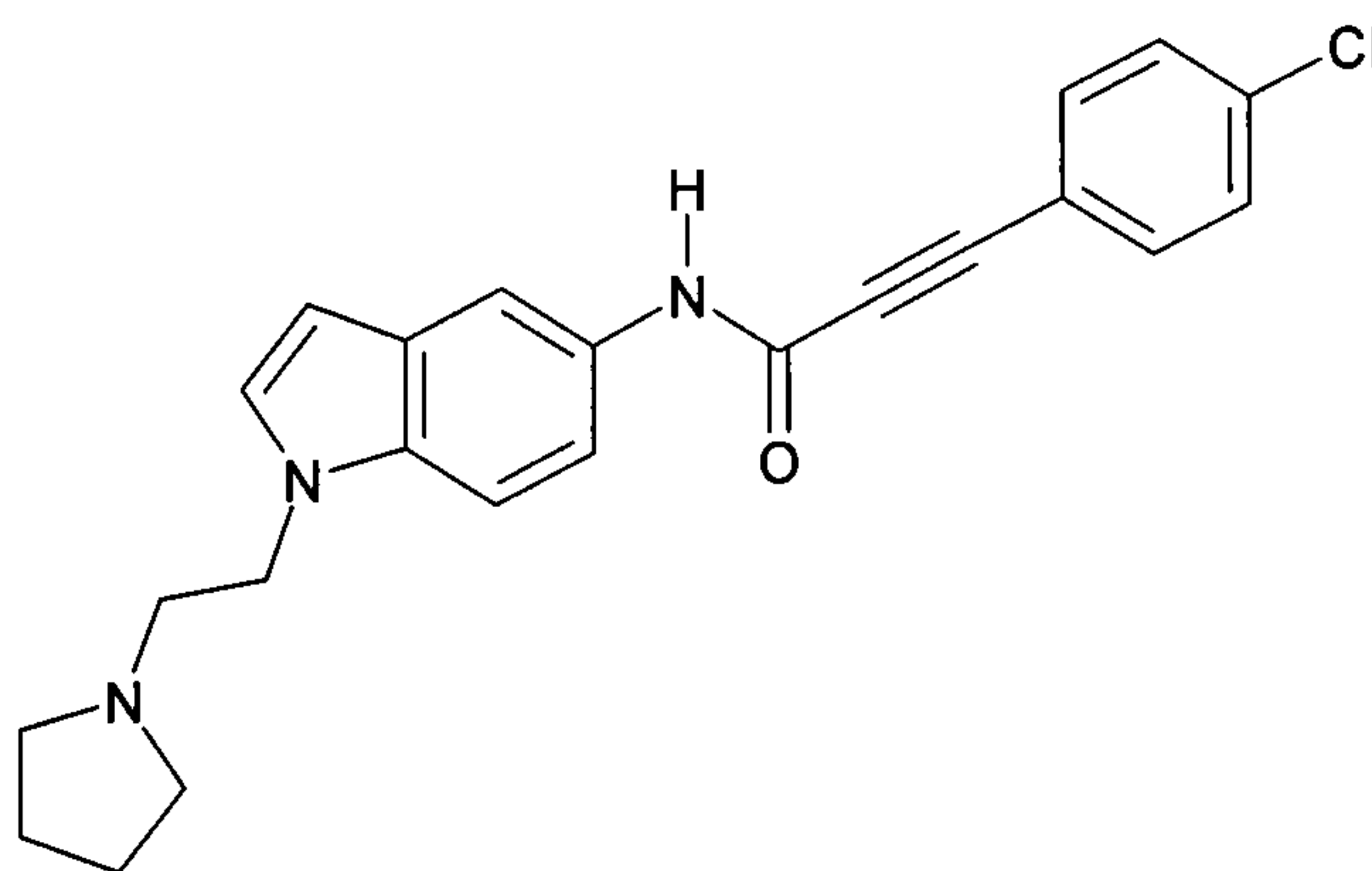
Calc.: Molecular ion peak (M+H)⁺: 439/441/443
peak (M+H)⁺: 439/441/443

Found: Molecular ion

25 R_f value: 0.7 (silica gel, dichloromethane/ methanol/ammonia = 50:10:0.1)

Example 4.9:

3-(4-chloro-phenyl)-propynoic acid-[1-(2-pyrrolidin-1-yl-ethyl)-1*H*-indol-5-yl]-amide



4.9.a. 5-nitro-1-(2-pyrrolidin-1-yl-ethyl)-1*H*-indole

A reaction mixture of 16.22 g (0.1 mol) 5-nitroindole, 35 g (0.205 mol) 1-(2-chloro-ethyl)-pyrrolidine-hydrochloride and 51 g (0.369 mol) potassium carbonate in 500 ml DMF is stirred for 48 hours at ambient temperature and then filtered. The filtrate is evaporated down, the residue dissolved in dichloromethane and dried over sodium sulphate. The desiccant is filtered off and the filtrate is evaporated down.

Yield: 25 g (96.3 % of theoretical)

$C_{14}H_{17}N_3O_2$ (M= 259.31)

10 Calc.: Molecular ion peak (M+H)⁺: 260 Found: Molecular ion peak (M+H)⁺: 260

R_f value: 0.65 (silica gel, dichloromethane/ methanol/ammonia = 90:10:1)

15 4.9.b. 5-amino-1-(2-pyrrolidin-1-yl-ethyl)-1*H*-indole

Prepared analogously to Example 3.1.b from 5-nitro-1-(2-pyrrolidin-1-yl-ethyl)-1*H*-indole in THF as solvent.

Yield: 0.83 g (93.9 % of theoretical)

$C_{14}H_{19}N_3$ (M= 229.32)

20 Calc.: Molecular ion peak (M+H)⁺: 230 Found: Molecular ion peak (M+H)⁺: 230

R_f value: 0.37 (silica gel, dichloromethane/ methanol/ammonia = 90:10:1)

25 4.9.c. 3-(4-chloro-phenyl)-propynoic acid-[1-(2-pyrrolidin-1-yl-ethyl)-1*H*-indol-5-yl]-amide

Prepared analogously to Example 3.1.e from 5-amino-1-(2-pyrrolidin-1-yl-ethyl)-1*H*-indole and (4-chloro-phenyl)-propynoic acid in THF as solvent.

Yield: 186 mg (47.5 % of theoretical)

C₂₃H₂₂ClN₃O (M= 391.90)

Melting point: 135-144⁰C

Calc.: Molecular ion peak (M+H)⁺: 393/394

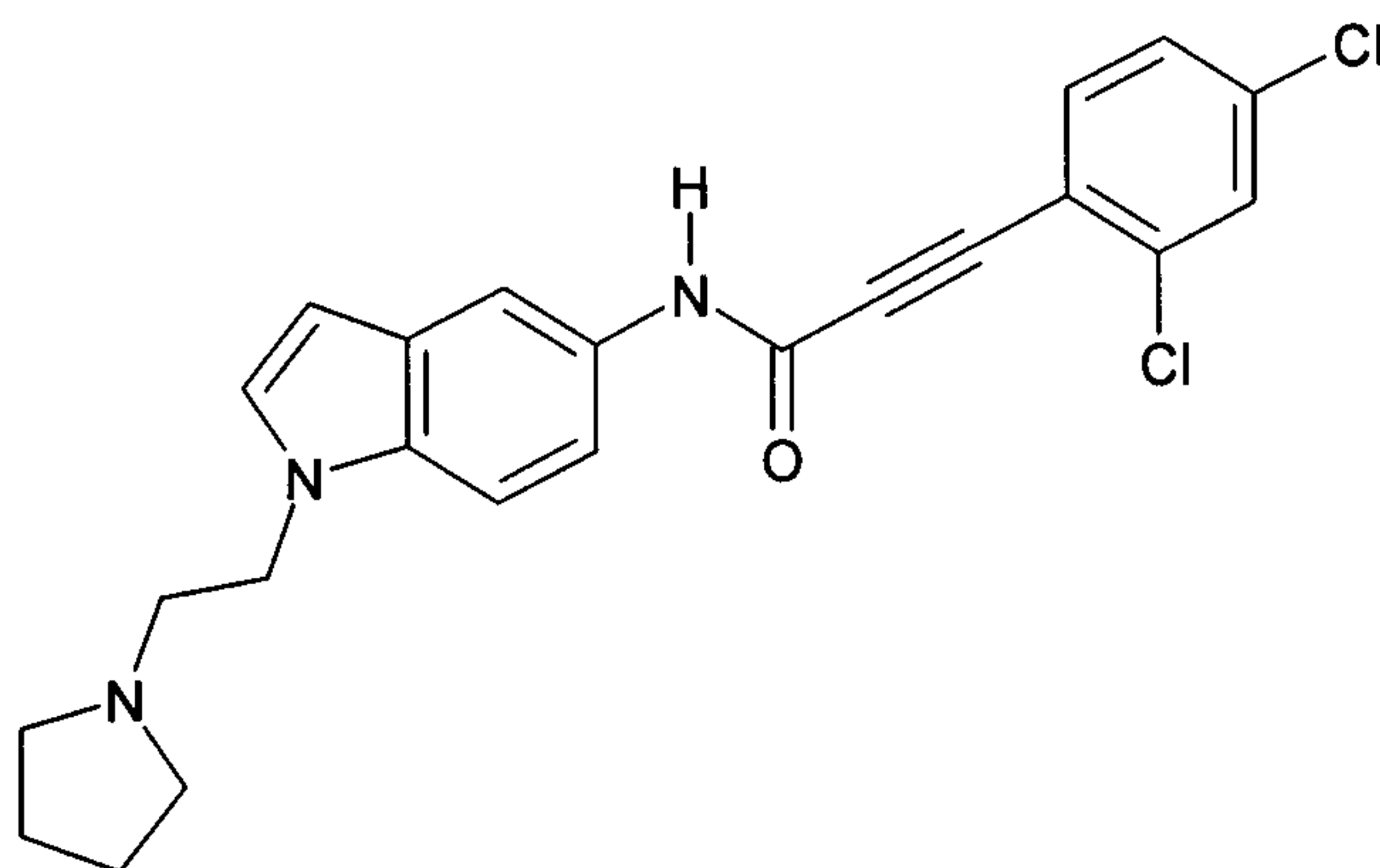
Found: Molecular ion

5 peak (M+H)⁺: 393/394

R_f value: 0.4 (silica gel, dichloromethane/ methanol/ammonia = 90:10:1)

Example 4.10:

10 3-(4-chloro-phenyl)-propynoic acid-[1-(2-pyrrolidin-1-yl-ethyl)-1*H*-indol-5-yl]-amide



Prepared analogously to Example 3.1.e from 5-amino-1-(2-pyrrolidin-1-yl-ethyl)-1*H*-indole and (2,4-dichloro-phenyl)-propynoic acid in THF as solvent.

Yield: 133 mg (31.2 % of theoretical)

15 C₂₃H₂₁Cl₂N₃O (M= 426.34)

Melting point: 127-129⁰C

Calc.: Molecular ion peak (M+H)⁺: 426/428/430

Found: Molecular ion

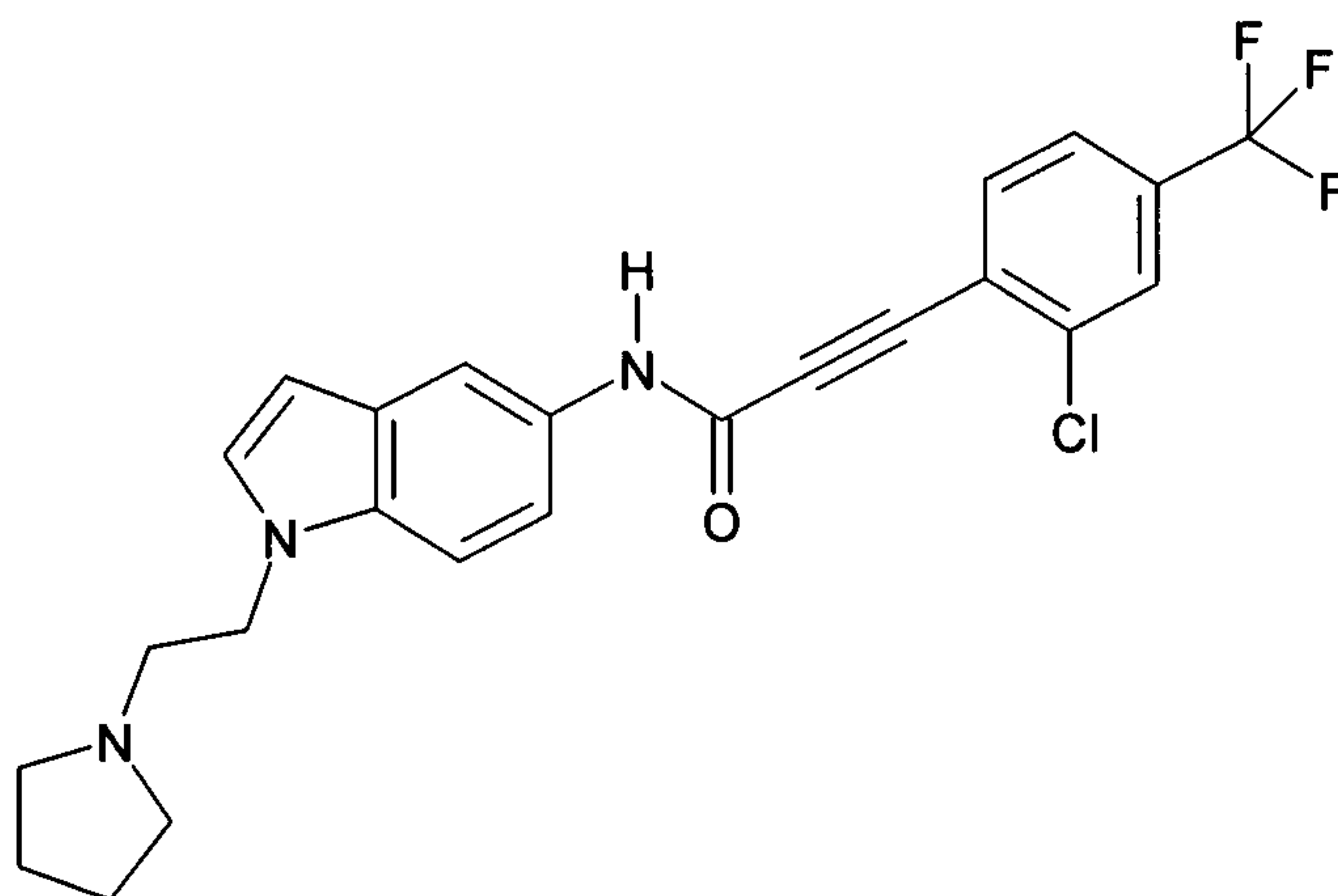
peak (M+H)⁺: 426/428/430

R_f value: 0.4 (silica gel, dichloromethane/ methanol/ammonia = 90:10:1)

20

Example 4.11:

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[1-(2-pyrrolidin-1-yl-ethyl)-1*H*-indol-5-yl]-amide



4.11.a. ethyl (2-chloro-4-trifluoromethyl-phenyl)-propynoate

A reaction mixture of 0.556 ml (5.42 mmol) ethyl propynoate, 875 mg (2.8 mmol) 3-chloro-4-iodo-benzotrifluoride, 214 mg (0.3 mmol) bistriphenylphosphine palladium dichloride, 57.1 mg (0.3 mmol) copper(I)iodide and 1.17 g (3.6 mmol) caesium carbonate in 50 ml THF is degassed and stirred for 24 hours at ambient temperature under an argon atmosphere. The reaction mixture is combined with a saturated sodium hydrogen carbonate solution and twice extracted with ethyl acetate. The combined organic phases are extracted with saturated sodium chloride solution and dried over sodium sulphate.

Yield: 0.65 g (43.3 % of theoretical)

$C_{12}H_8ClF_3O_2$ (M= 276.64)

Calc.: Molecular ion peak (M+H)⁺: 277/279
peak (M+H)⁺: 277/279

Found: Molecular ion

4.11.b. (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid

0.65 g (1.175 mmol) ethyl (2-chloro-4-trifluoromethyl-phenyl)-propynoate are dissolved in 20 ml of ethanol, combined with 2 ml 2M sodium hydroxide solution and stirred for three hours at ambient temperature. The reaction mixture is evaporated down, the residue is taken up in water and extracted with ethyl acetate. The aqueous phase is combined with 2 ml 1M hydrochloric acid and stirred for one hour at ambient temperature. Then it is extracted three times with ethyl acetate. The combined organic phases are dried over sodium sulphate.

Yield: 0.14 g (48 % of theoretical)

$C_{10}H_4ClF_3O_2$ (M= 248.59)

Calc.: Molecular ion peak (M-H)⁻: 247/249

Found: Molecular ion

peak (M-H)⁻: 247/249

R_f value: 0.09 (silica gel, petroleum ether/ethyl acetate= 4:1)

5 4.11.c. 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[1-(2-pyrrolidin-1-yl-ethyl)-1*H*-indol-5-yl]-amide

Prepared analogously to Example 2.3.f from 5-amino-1-(2-pyrrolidin-1-yl-ethyl)-1*H*-indole and (2-chloro-4-trifluorophenyl)-propynoic acid.

Yield: 160 mg (66.5 % of theoretical)

10 C₂₄H₂₁ClF₃N₃O (M= 459.90)

Melting point: 200-205°C

Calc.: Molecular ion peak (M+H)⁺: 460/462

Found: Molecular ion

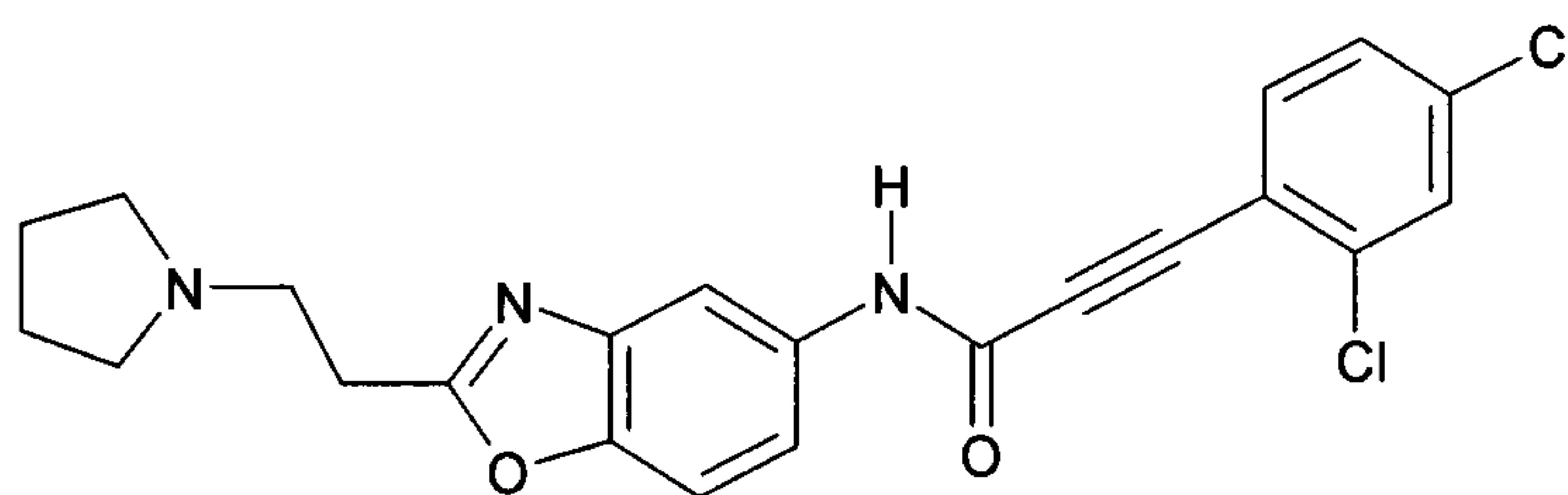
peak (M+H)⁺: 460/462

R_f value: 0.45 (silica gel, dichloromethane/ methanol= 90:10:)

15

Example 4.12:

3-(2,4-dichloro-phenyl)-propynoic acid-[2-(2-pyrrolidin-1-yl-ethyl)-benzoxazol-5-yl]-amide



20

4.12.a. 5-nitro-2-vinyl-benzoxazole

A reaction mixture of 1.54 g (10 mmol) 2-amino-4-nitrophenol, 1.36 g (10 mmol) ethyl 3-chloropropionate and 20 g polyphosphoric acid is stirred for two hours at 170°C.

Then the mixture is neutralised by the addition of saturated sodium hydrogen

25 carbonate solution at ambient temperature. The aqueous phase is extracted with dichloromethane. The organic phase is dried over sodium sulphate. The purification is carried out by column chromatography on silica gel (eluant: dichloromethane/ethanol = 20:1).

Yield: 0.3 g (15.8 % of theoretical)

30 C₉H₆N₂O₃ (M= 190.16)

Calc.: Molecular ion peak (M+H)⁺: 191

Found: Molecular ion peak

(M+H)⁺: 191

R_f value: 0.8 (silica gel, dichloromethane/ethanol = 20:1)

5 4.12.b. 5-nitro-2-(2-pyrrolidin-1-yl-ethyl)-benzoxazole

A solution of 1 g (5.25 mmol) 5-nitro-2-vinyl-benzoxazole and 0.66 ml (8 mmol) pyrrolidine in 8 ml of ethanol is stirred for two hours at ambient temperature. Then the reaction solution is evaporated down. The purification is carried out by column chromatography on silica gel (eluant: dichloromethane/ethanol/ammonia = 20:1:0.1).

10 Yield: 0.74 g (53.9 % of theoretical)

C₁₃H₁₅N₃O₃ (M= 261.28)

Calc.: Molecular ion peak (M+H)⁺: 262

Found: Molecular ion peak

(M+H)⁺: 262

R_f value: 0.2 (silica gel, dichloromethane/ethanol/ammonia = 20:1:0.1)

15

4.12.c. 5-amino-2-(2-pyrrolidin-1-yl-ethyl)-benzoxazole

A reaction mixture of 0.74 g (2.83 mmol) 5-nitro-2-(2-pyrrolidin-1-yl-ethyl)-benzoxazole and 0.1 g palladium (10% on activated charcoal) in 20 ml of ethanol is hydrogenated for three hours at 3 bar and 20°C. The catalyst is filtered off and the filtrate is evaporated down.

20

Yield: 0.6 g (91.6 % of theoretical)

C₁₃H₁₇N₃O (M= 231.30)

Calc.: Molecular ion peak (M+H)⁺: 232

Found: Molecular ion peak

25 (M+H)⁺: 232

R_f value: 0.3 (silica gel, dichloromethane/ethanol/ammonia = 20:1:0.1)

4.12.d. 3-(2,4-dichloro-phenyl)-propynoic acid-[2-(2-pyrrolidin-1-yl-ethyl)-benzoxazol-5-yl]-amide

30

Prepared analogously to Example 3.1.e from 5-amino-2-(2-pyrrolidin-1-yl-ethyl)-benzoxazole

and (2,4-dichlorophenyl)-propynoic acid.

Yield: 43 mg (33.1 % of theoretical)

$C_{22}H_{19}Cl_2N_3O_2$ (M= 428.32)

Melting point: 130°C

Calc.: Molecular ion peak (M+H)⁺: 428/430/432

Found: Molecular ion

peak (M+H)⁺: 428/430/432

5 $C_{13}H_{17}N_3O$ (M= 231.30)

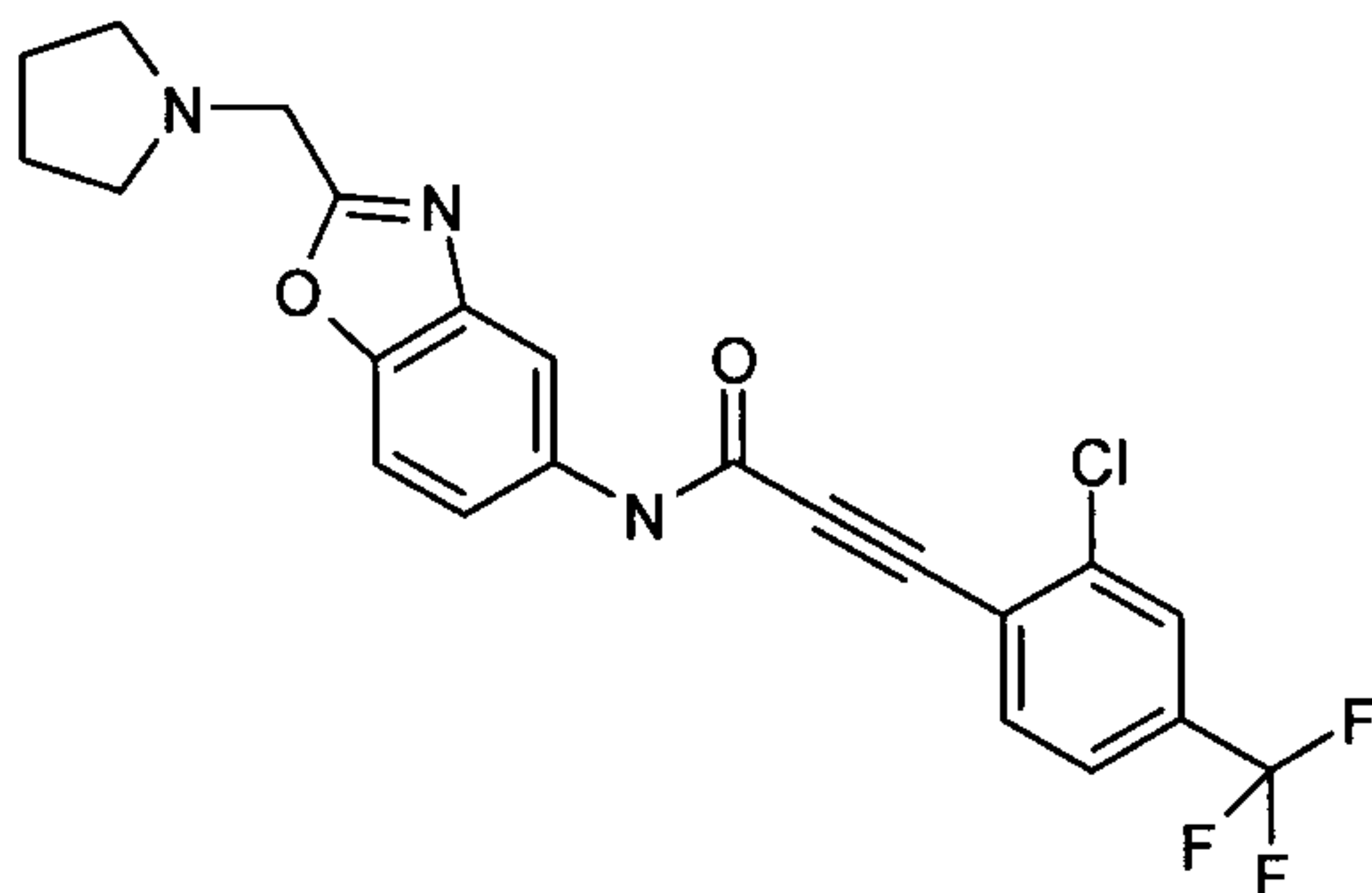
Calc.: Molecular ion peak (M+H)⁺: 232

Found: Molecular ion peak

(M+H)⁺: 232

R_f value: 0.21 (silica gel, dichloromethane/methanol/ammonia = 10:1:0.1)

10 **Example: 4.13** 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-(2-pyrrolidin-1-ylmethyl-benzoxazol-5-yl)-amide



4.13.a 2-chloromethyl-5-nitro-benzoxazole

10.5 ml (77.87 mmol) 2-chloro-orthoacetic acid are added to a solution of 12 g (77.86 mmol) 2-amino-4-nitrophenol in 110 ml of ethanol and the whole lot is heated for 3 h at 80 °C. Then the reaction mixture is poured onto water, the precipitate formed is suction filtered and washed several times with water. The product is dried at 80°C in the circulating air dryer.

Yield: 14.2 g (86 % of theoretical)

20 $C_8H_5ClN_2O_3$ (M= 212.59)

Calc.: Molecular ion peak (M+H)⁺: 213/215 (Cl)

Found: Molecular ion

peak (M+H)⁺: 213/215 (Cl)

4.13.b. 5-nitro-2-pyrrolidin-1-ylmethyl-benzoxazole

25 A reaction mixture of 3 g (14.11 mmol) 2-chloromethyl-5-nitro-benzoxazole, 1.5 ml (17.97 mmol) pyrrolidine and 3.9 g (28.22 mmol) potassium carbonate in 30 ml of dimethylformamide is stirred for 4 h at 50 °C. Then the reaction mixture is diluted with

water and covered with diisopropylether. The precipitated yellow solid is suction filtered, washed again and dried in the circulating air dryer at 60 °C.

Yield: 1.8 g (52 % of theoretical)

$C_{12}H_{13}N_3O_3$ (M= 247.25)

5 Calc.: Molecular ion peak (M+H)⁺: 248 Found: Molecular ion peak (M+H)⁺: 248

R_f value: 0.4 (silica gel, dichloromethane/ethanol = 20:1)

4.13.c. 2-pyrrolidin-1-ylmethyl-benzoxazol-5-ylamine

10 Prepared analogously to Example 4.12.c from 5-nitro-2-pyrrolidin-1-ylmethyl-benzoxazole.

Yield: 1.1 g (70 % of theoretical)

$C_{12}H_{15}N_3O$ (M= 217.27)

15 Calc.: Molecular ion peak (M+H)⁺: 218 Found: Molecular ion peak (M+H)⁺: 218

R_f value: 0.6 (aluminium oxide, dichloromethane/ethanol = 20:1)

4.13.d. 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid (2-pyrrolidin-1-ylmethyl-benzoxazol-5-yl)-amide

20 Prepared analogously to Example 2.3.f from 0.2 g (0.92 mmol) 2-pyrrolidin-1-ylmethyl-benzoxazol-5-ylamine and 0.2 g (0.8 mmol) (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid.

Yield: 290 mg (81 % of theoretical)

$C_{22}H_{17}ClF_3N_3O_2$ (M= 447.84)

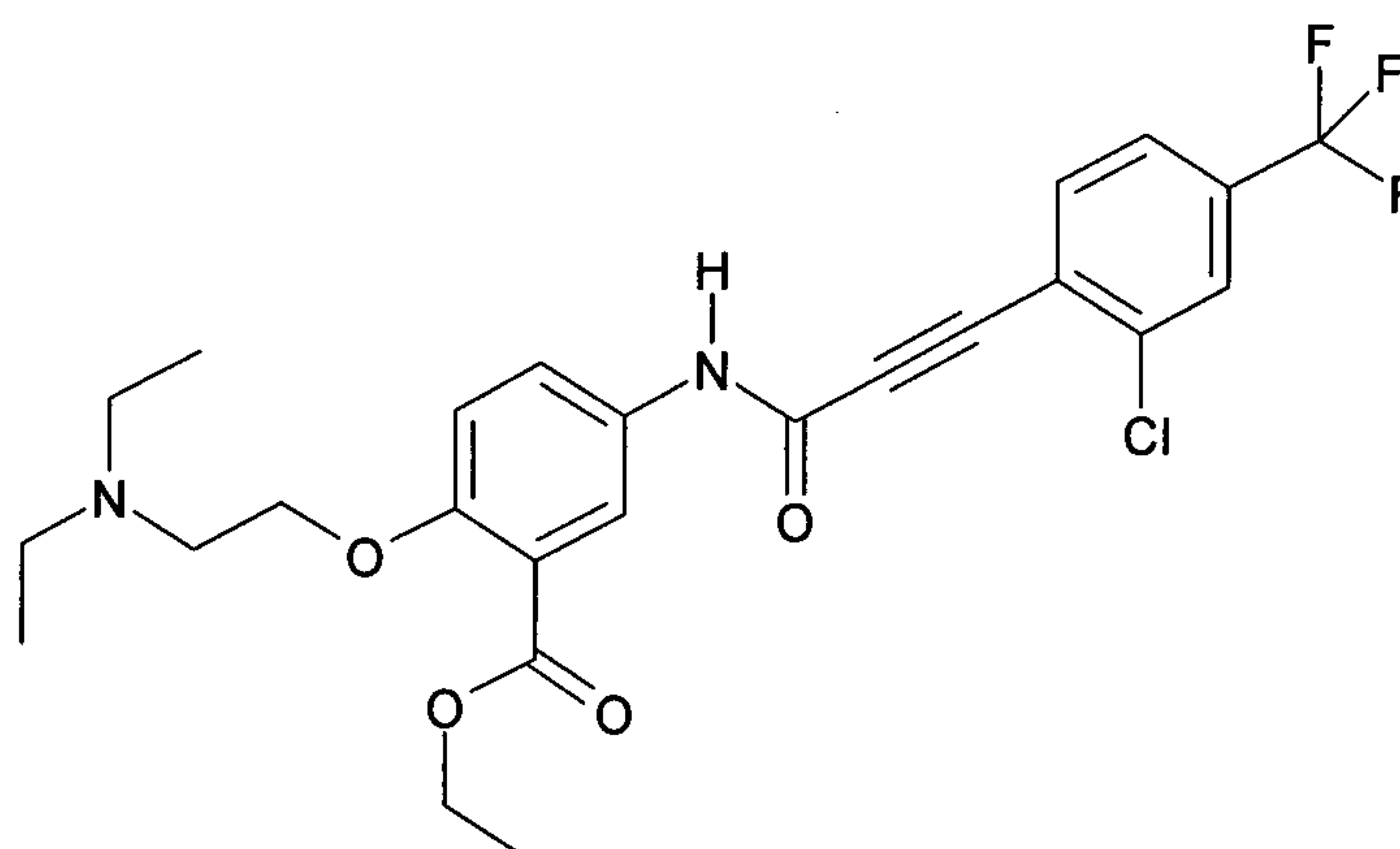
25 Melting point: 218-223 °C

Calc.: Molecular ion peak (M+H)⁺: 448/450 (Cl) Found: Molecular ion peak (M+H)⁺: 448/450 (Cl)

R_f value: 0.33 (silica gel, dichloromethane/methanol = 19:1)

30 **Example 4.14**

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[3-ethoxycarbonyl-4-(2-diethylamino-ethoxy)-phenyl]-amide



4.14.a. ethyl 2-(2-diethylamino-ethoxy)-5-nitro-benzoate

1.06 g (5.00 mmol) ethyl 2-fluoro-5-nitro-benzoate and 0.58 ml (5.00 mmol) 2-diethylaminoethanol are dissolved in 20 ml of dimethylformamide and at 0 °C 0.36 g (7.45 mmol) sodium hydride (50%) is added. The mixture is stirred for 45 minutes at 0°C, poured onto ice water and finally extracted three times with ethyl acetate. The organic phase is dried over sodium sulphate, the solvent is eliminated and the residue is purified through a silica gel column with petroleum ether/ethyl acetate 4:1 as eluant.

Yield: 0.30 g (19 % of theory)

$C_{15}H_{22}N_2O_5$ (M= 310.35)

Calc.: Molecular ion peak (M+H)⁺: 311
(M+H)⁺: 311

Found: Molecular ion peak

R_f value: 0.1 (silica gel, petroleum ether/ethyl acetate 4:1)

4.14.b. ethyl 5-amino-2-(2-diethylamino-ethoxy)-benzoate

Prepared analogously to Example 3.1.b. from 0.30 g ethyl 2-(2-diethylamino-ethoxy)-5-nitro-benzoate in ethyl acetate.

Yield: 0.27 g (100 % of theory)

$C_{15}H_{24}N_2O_3$ (M= 280.37)

Calc.: Molecular ion peak (M+H)⁺: 281
(M+H)⁺: 281

Found: Molecular ion peak

R_f value: 0.40 (silica gel, dichloromethane/methanol/ammonia = 39:1:0.1)

4.14.c. 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[3-ethoxycarbonyl-4-(2-diethylamino-ethoxy)-phenyl]-amide

Prepared analogously to Example 2.3.f. from 99 mg (0.40 mmol) (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid and 120 mg (0.44 mmol) ethyl 5-amino-2-(2-diethylamino-ethoxy)-benzoate.

Yield: 44 mg (22 % of theory)

5 $C_{25}H_{26}ClF_3N_2O_4$ (M= 510.94)

Calc.: Molecular ion peak (M+H)⁺: 511/513

Found: Molecular ion peak

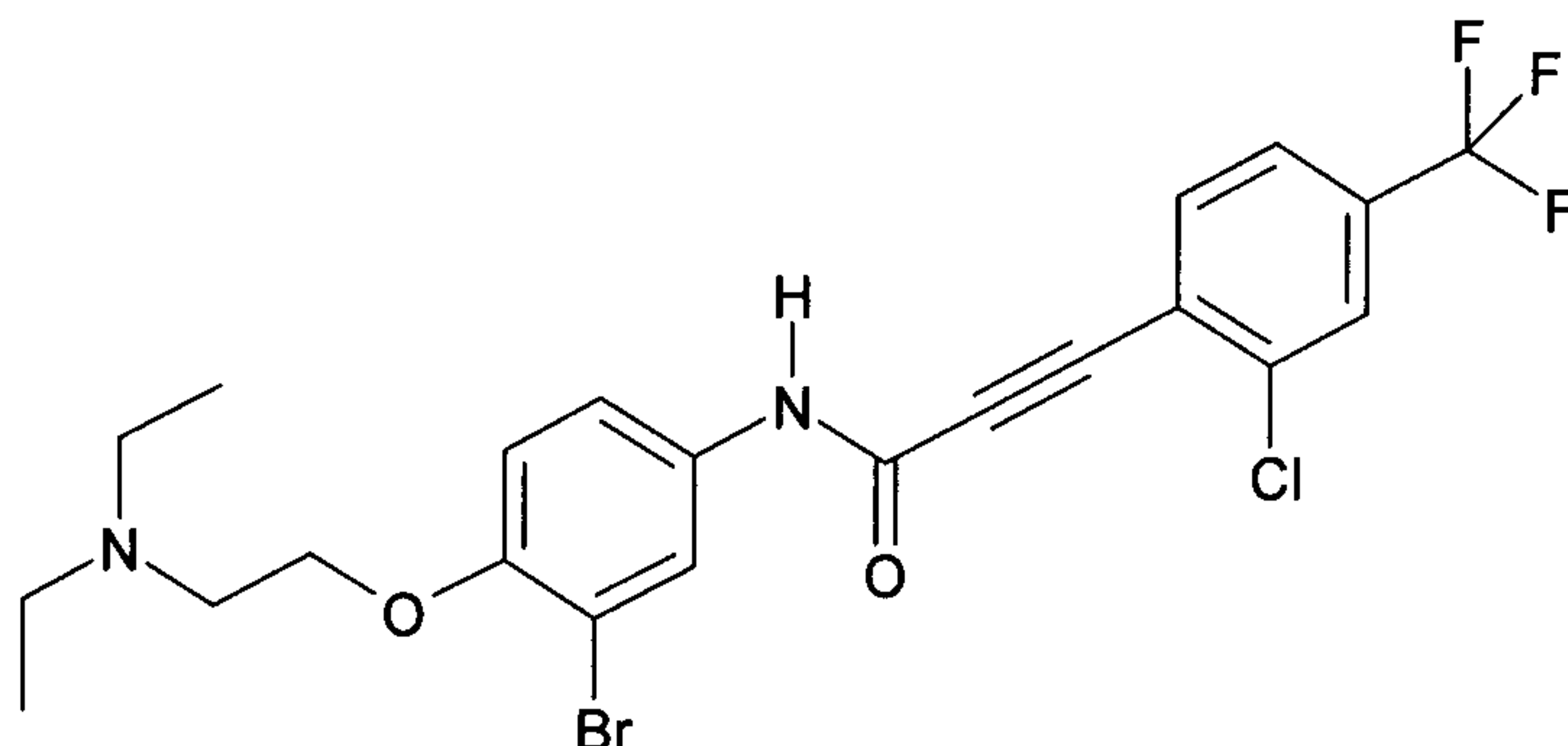
(M+H)⁺: 511/513

R_f value: 0.35 (silica gel, dichloromethane/methanol = 9:1)

10

Example 4.15

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[3-bromo-4-(2-diethylamino-ethoxy)-phenyl]-amide



15

4.15.a. [2-(2-bromo-4-nitro-phenoxy)-ethyl]-diethyl-amine

Prepared analogously to method 4.13.a. starting from 0.66 g (2.00 mmol) 2-bromo-1-fluoro-4-nitro-benzene and 0.40 ml (3.00 mmol) 2-diethylamino-ethanol.

Yield: 0.95 g (100 % of theory)

20 $C_{12}H_{17}BrN_2O_3$ (M= 317.185)

Calc.: Molecular ion peak (M+H)⁺: 317/319

Found: Molecular ion peak

(M+H)⁺: 317/319

R_f value: 0.50 (silica gel, dichloromethane /methanol 9:1).

25 4.15.b. 3-bromo-4-(2-diethylamino-ethoxy)-phenylamine

Prepared analogously to Example 3.1.b. from 1.10 g (3.47 mmol) [2-(2-bromo-4-nitro-phenoxy)-ethyl]-diethyl-amine in ethyl acetate.

Yield: 0.58 g (58 % of theory)

$C_{12}H_{19}BrN_2O$ (M= 287.202)

Calc.: Molecular ion peak (M+H)⁺: 287/289

Found: Molecular ion

peak (M+H)⁺: 287/289

R_f value: 0.30 (silica gel, dichloromethane /methanol 9:1).

5

4.15.c. 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[3-bromo-4-(2-diethylamino-ethoxy)-phenyl]-amide

Prepared analogously to Example 2.3.f. from 450 mg (1.80 mmol) (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid and 550 mg (1.92 mmol) 3-bromo-4-(2-diethylamino-ethoxy)-phenylamine.

10

Yield: 370 mg (40 % of theory)

$C_{22}H_{21}BrClF_3N_2O_2$ (M= 517.77)

Calc.: Molecular ion peak (M+H)⁺: 517/519/521

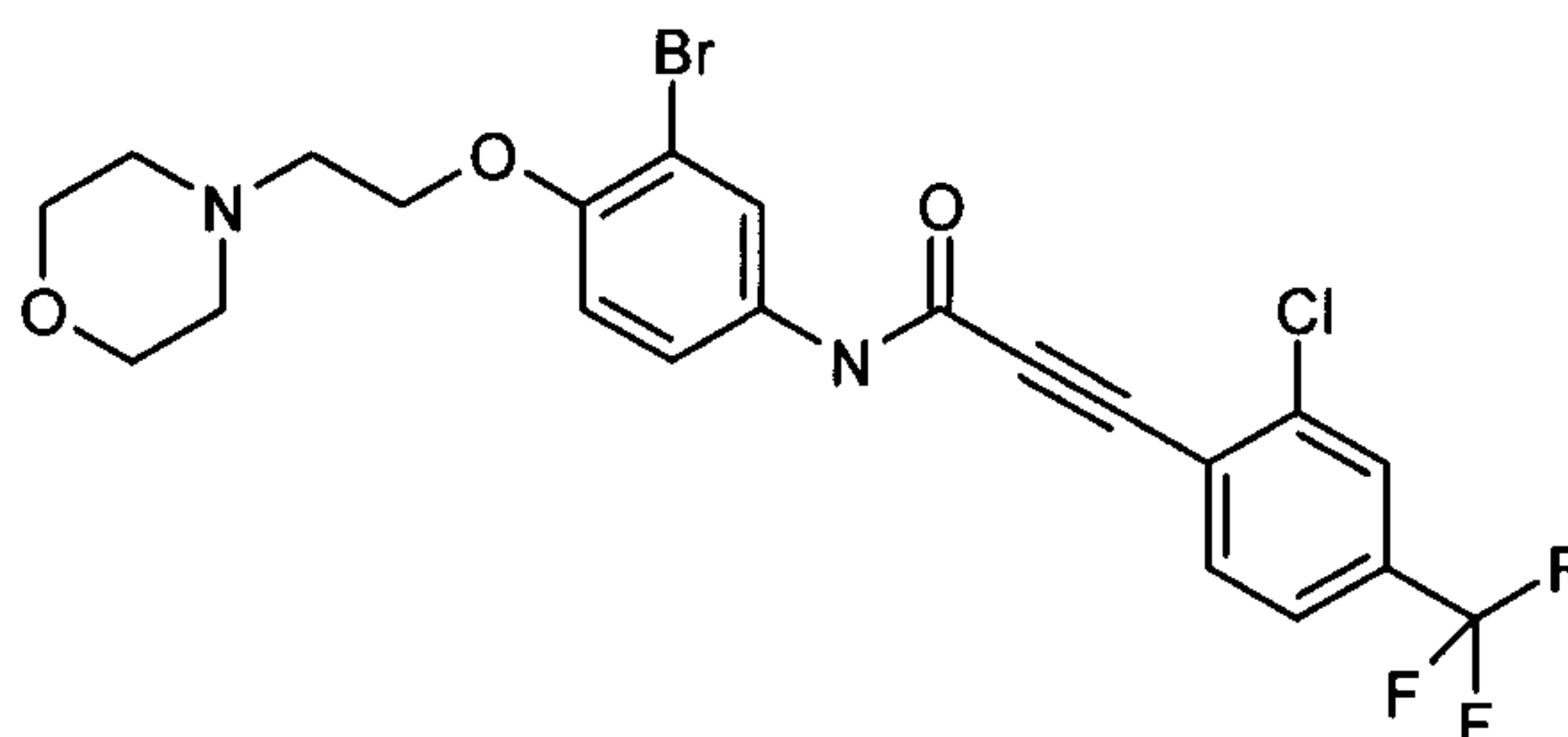
Found: Molecular ion

peak (M+H)⁺: 517/519/521

15

R_f value: 0.45 (silica gel, dichloromethane/methanol = 19:1)

Example 4.16 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[3-bromo-4-(2-morpholin-4-yl-ethoxy)-phenyl]-amide



20 4.16.a. 4-[2-(2-bromo-4-nitro-phenoxy)-ethyl]-morpholine

92 mg (1.9 mmol) sodium hydride (55%) are added at 0°C to a solution of 0.3 g (1.27 mmol) 3-bromo-4-chloro-nitrobenzene and 0.15 ml (1.27 mmol) in 20 ml of dimethylformamide under an argon atmosphere. The reaction mixture is stirred for two hours at 0°C and then poured onto ice water. The aqueous phase is extracted three times with ethyl acetate. The organic phase is dried, the desiccant is filtered off and the filtrate is evaporated down. The purification is carried out by column chromatography on silica gel (eluant: dichloromethane/methanol 19:1)

25

Yield: 230 mg (55 % of theory)

$C_{12}H_{15}BrN_2O_4$ (M= 331.16)

Calc.: Molecular ion peak (M+H)⁺: 331/333 (Br)
peak (M+H)⁺: 331/333 (Br)

Found: Molecular ion

4.16.b. 3-bromo-4-(2-morpholin-4-yl-ethoxy)-phenylamine

- 5 A reaction mixture of 220 mg (0.66 mmol) 4-[2-(2-bromo-4-nitro-phenoxy)-ethyl]-morpholine and 100 mg Raney nickel in 50 ml of ethyl acetate is hydrogenated at ambient temperature and 3 bar hydrogen. The catalyst is suction filtered and the filtrate is evaporated down. The purification is carried out by column chromatography on aluminium oxide (eluant: petroleum ether/ethyl acetate 1:1).

- 10 Yield: 100 mg (50 % of theory)

C₁₂H₁₇BrN₂O₂ (M= 301.18)

Calc.: Molecular ion peak (M+H)⁺: 301/303 (Br)
peak (M+H)⁺: 301/303 (Br)

Found: Molecular ion

- 15 4.16.c. 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[3-bromo-4-(2-morpholin-4-yl-ethoxy)-phenyl]-amide

Prepared analogously to Example 2.3.f from 100 mg (0.33 mmol) 3-bromo-4-(2-morpholin-4-yl-ethoxy)-phenylamine and 75 mg (0.3 mmol) (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid.

- 20 Yield: 130 mg (82 % of theoretical)

C₂₂H₁₉BrClF₃N₂O₃ (M= 531.75)

Calc.: Molecular ion peak (M+H)⁺: 529/531/533 (Br, Cl)

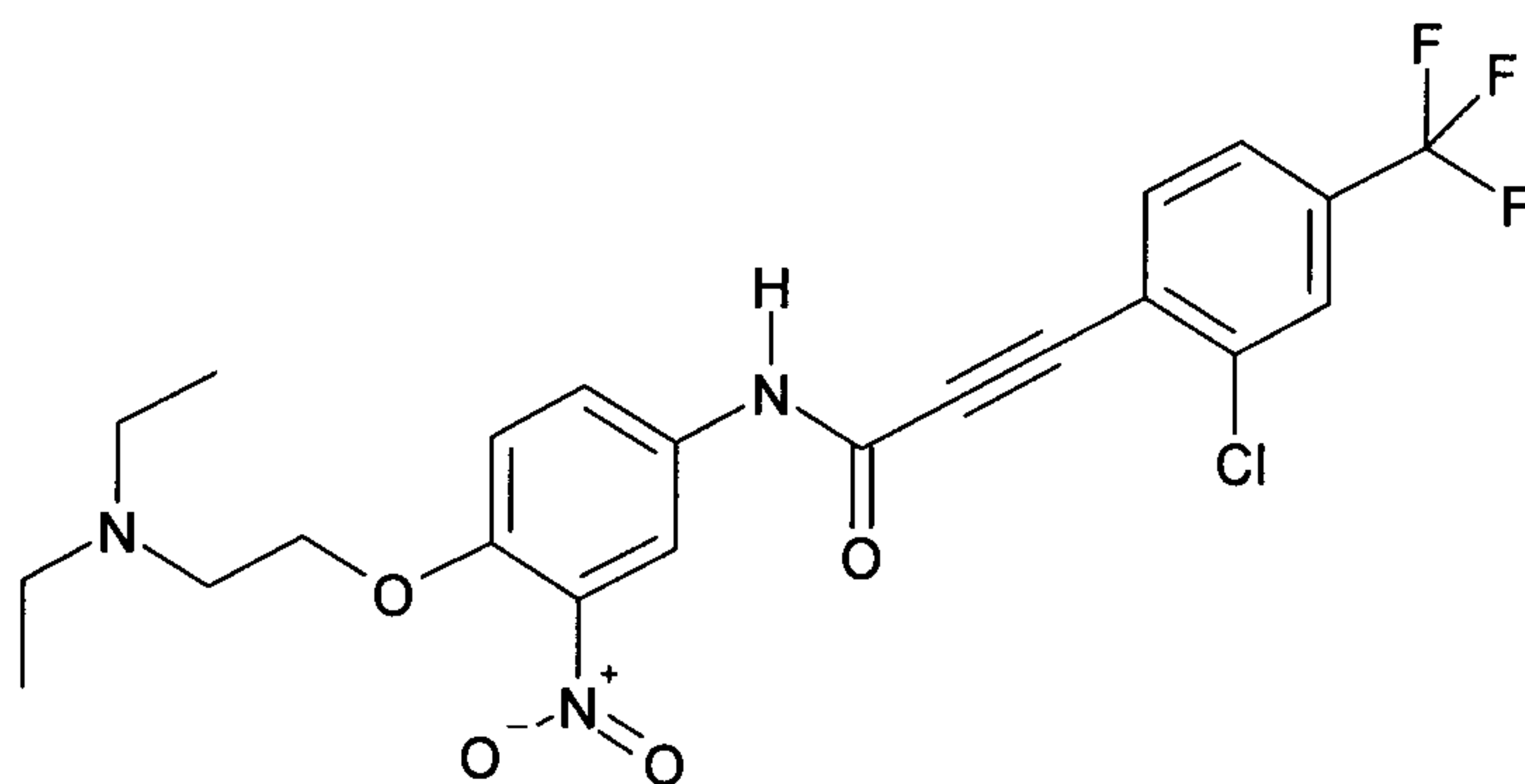
Found: Molecular ion peak (M+H)⁺: 529/531/533 (Br, Cl)

R_f value: 0.33 (aluminium oxide, petroleum ether/ethyl acetate = 1:1)

25

Example 4.17

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[3-nitro-4-(2-diethylamino-ethoxy)-phenyl]-amide



4.17.a. N-[4-(2-diethylamino-ethoxy)-3-nitro-phenyl]-acetamide

- 5 0.74 g (7.29 mmol) potassium nitrate are added batchwise at -10 °C to a solution of 1.52 g (6.07 mmol) N-[4-(2-diethylamino-ethoxy)-phenyl]-acetamide in 25 mL conc. sulphuric acid and the mixture is stirred for 1 hour at -10 °C. The reaction mixture is poured onto a mixture of ice and concentrated aqueous ammonia and the aqueous phase is exhaustively extracted with ethyl acetate. The combined organic phases are
- 10 dried over sodium sulphate and evaporated down.

Yield: 1.8 g (100 % of theory)

$C_{14}H_{21}N_3O_4$ (M= 295.34)

Calc.: Molecular ion peak (M+H)⁺: 296

Found: Molecular ion peak (M+H)⁺:

296

- 15 R_f value: 0.50 (Alox, dichloromethane/methanol 39:1).

4.17.b. 4-(2-diethylamino-ethoxy)-3-nitro-phenylamine

- A solution of 1.85 g (6.26 mmol) N-[4-(2-diethylamino-ethoxy)-3-nitro-phenyl]-acetamide in semiconcentrated aqueous hydrochloric acid is stirred for 2 hours at
- 20 100°C, cooled to ambient temperature, made basic with ice and concentrated aqueous ammonia and the aqueous phase is exhaustively extracted with ethyl acetate. The combined organic phases are washed with water and dried over sodium sulphate.

Yield: 1.38 g (87% of theory)

- 25 $C_{12}H_{19}N_3O_3$ (M= 253.30)

Calc.: Molecular ion peak (M+H)⁺: 254

Found: Molecular ion peak (M+H)⁺:

254

R_f value: 0.68 (Alox, dichloromethane/methanol 39:1).

4.17.c. 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[3-nitro-4-(2-diethylamino-ethoxy)-phenyl]-amide

Prepared analogously to Example 2.3.f. from 450 mg (1.80 mmol) (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid and 500 mg (1.98 mmol) 4-(2-diethylamino-ethoxy)-3-nitro-phenylamine.

Yield: 590 mg (68 % of theory)

$C_{22}H_{21}ClF_3N_3O_4$ (M= 483.87)

Calc.: Molecular ion peak (M+H)⁺: 484/486

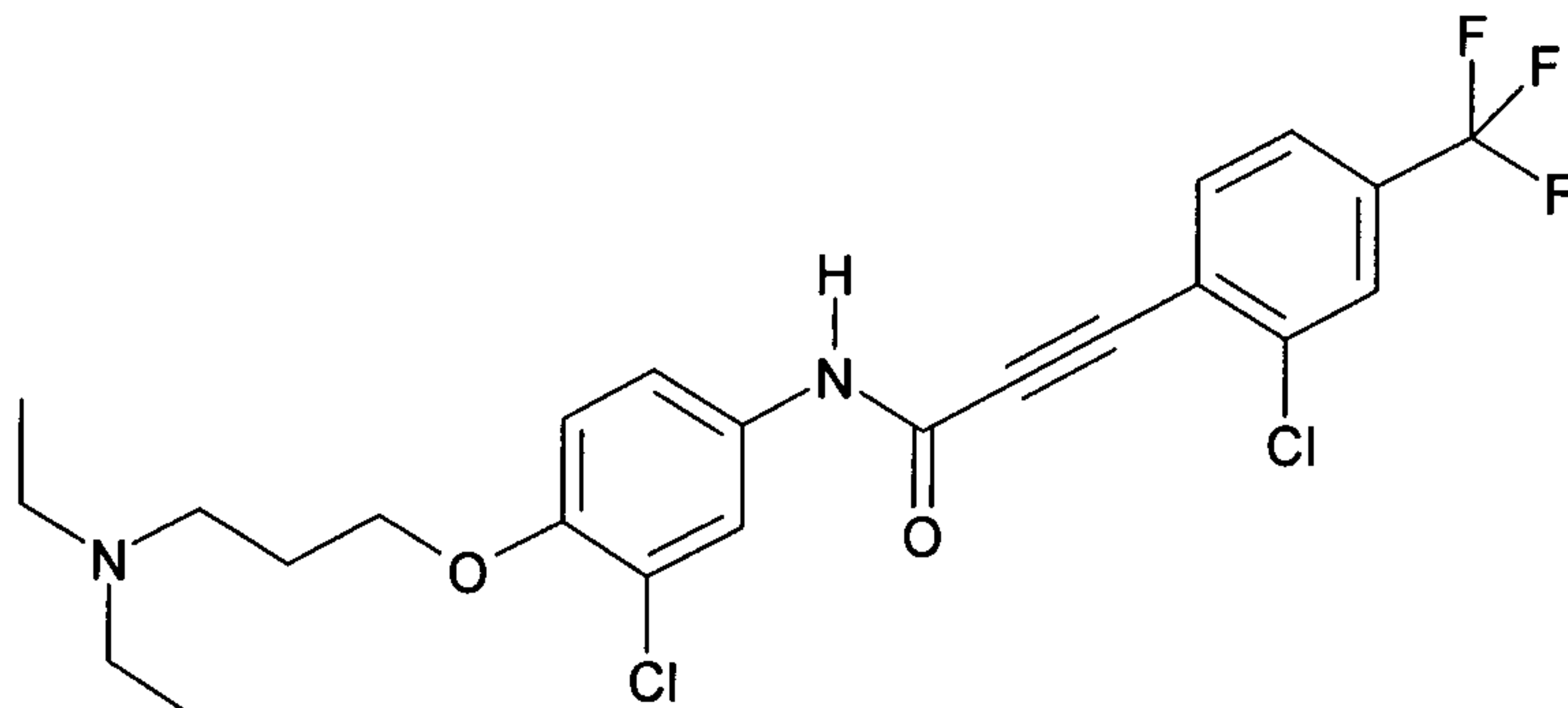
Found: Molecular ion peak

(M+H)⁺: 484/486

R_f value: 0.40 (silica gel, dichloromethane/methanol = 9:1)

Example 4.18:

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[3-chloro-4-(3-diethylamino-propoxy)-phenyl]-amide-formate



Prepared analogously to Example 2.3.f. from 99 mg (0.40 mmol) (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid and 110 mg (0.44 mmol) [2-(2-chloro-4-amino-phenoxy)-propyl]-diethyl-amine.

Yield: 49 mg (25 % of theory)

Melting point: 112-116 °C

$C_{23}H_{22}Cl_2F_3N_2O_2 \times CH_2O_2$ (M= 533.37)

Calc.: Molecular ion peak (M+H)⁺: 487/489/491

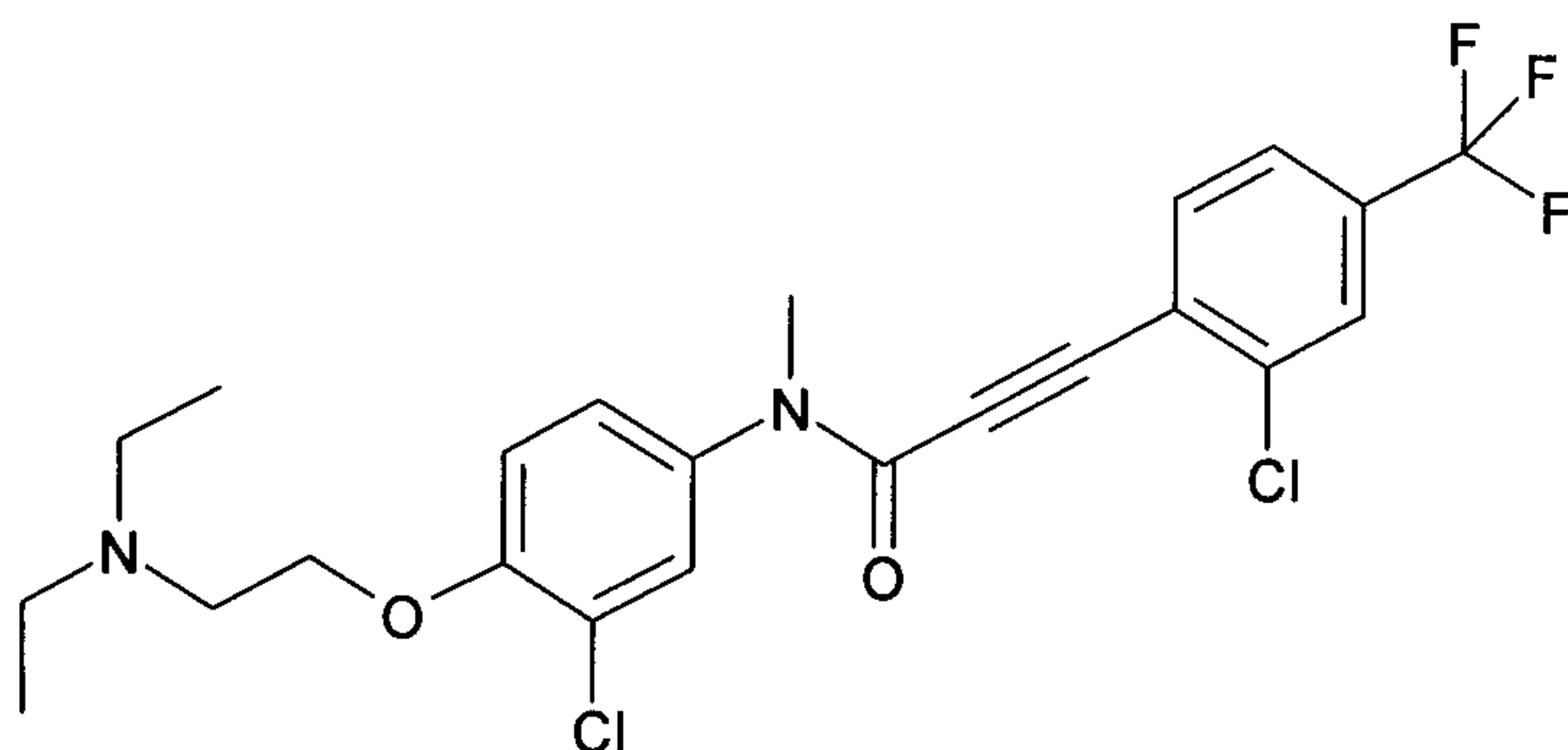
Found: Molecular ion

peak (M+H)⁺: 487/489/491

R_f value: 0.35 (silica gel, dichloromethane/methanol = 9:1)

Example 4.19:

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-methyl-amide



4.19.a. tert. butyl [3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-carbamate

Prepared analogously to Method 3.1.c. starting from 3.00 g (12.4 mmol) 3-chloro-4-(2-diethylamino-ethoxy)-phenylamine and 2.97 g (13.6 mmol) di-tert-butyl-pyrocarbonate in dichloromethane.

Yield: 2.85 g (67 % of theory)

C₁₇H₂₇ClN₂O₃ (M= 342.86)

Calc.: Molecular ion peak (M+H)⁺: 343/345
(M+H)⁺: 343/345

Found: Molecular ion peak

4.19.b. [3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-methylamine

Prepared analogously to Example 3.1.d. from 2.85 g (8.31 mmol) tert.butyl [3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-carbamate with 10.63 ml (24.9 mmol) 10% lithium aluminium hydride solution in tetrahydrofuran.

Yield: 0.72 g (34 % of theory)

C₁₃H₂₁ClN₂O (M= 256.77)

Calc.: Molecular ion peak (M+H)⁺: 257/259
peak (M+H)⁺: 257/259

Found: Molecular ion

R_f value: 0.80 (silica gel, ethyl acetate/methanol/ammonia 9:1:0.1).

4.19.c. 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-methylamide

Prepared analogously to Example 2.3.f. from 99 mg (0.40 mmol) (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid and 110 mg (0.44 mmol) [3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-methylamine.

Yield: 54 mg (28 % of theory)

5 Melting point: 97-100° C

$C_{23}H_{23}Cl_2F_3N_2O_2$ (M= 487.35)

Calc.: Molecular ion peak (M+H)⁺: 487/489/491

Found: Molecular ion

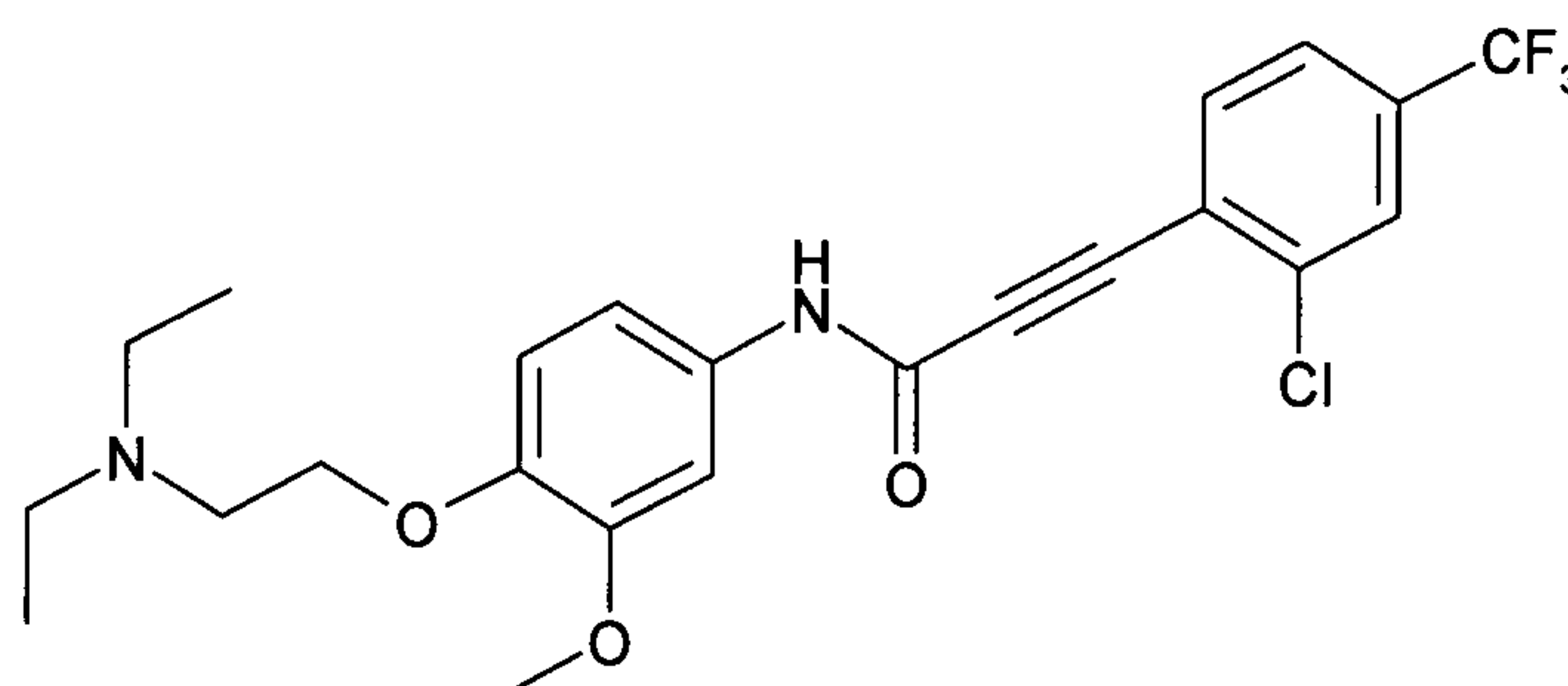
peak (M+H)⁺: 487/489/491

R_f value: 0.35 (silica gel, dichloromethane/methanol = 9:1)

10

Example 4.20:

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[3-methoxy-4-(2-diethylamino-ethoxy)-phenyl]-amide-hydrochloride



15

Prepared analogously to Example 2.3.f. from 75 mg (0.30 mmol) (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid and 79 mg (0.33 mmol) [2-(2-methoxy-4-amino-phenoxy)-ethyl]-diethyl-amine.

20 Yield: 14 mg (10 % of theory)

$C_{23}H_{24}ClF_3N_2O_3$ (M= 468.90)

Calc.: Molecular ion peak (M+H)⁺: 469/471

Found: Molecular ion peak

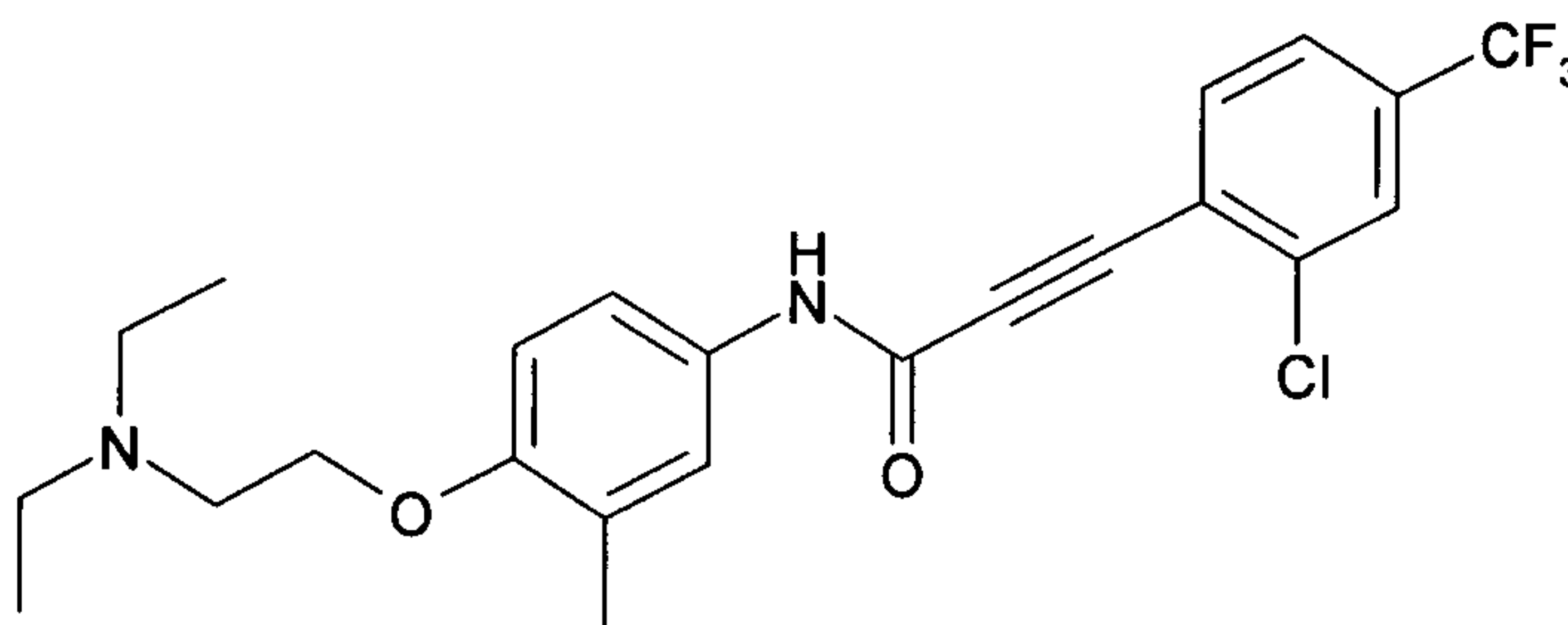
(M+H)⁺: 469/471

R_f value: 0.35 (silica gel, dichloromethane/methanol = 9:1)

25

Example 4.21:

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[3-methyl-4-(2-diethylamino-ethoxy)-phenyl]-amide



4.21.a. diethyl-[2-(2-methyl-4-nitro-phenoxy)-ethyl]-amine

0.92 g (19.2 mmol) sodium hydride (50% in oil) are added at 0 °C under an argon atmosphere to a solution of 2.70 g (17.4 mmol) 2-fluoro-5-nitro-toluene and 2.54 ml (19.2 mmol) 2-diethylaminoethanol in 50 mL DMF and the mixture is stirred for 2 hours at 0 °C and for 1 hour at ambient temperature. The solvent is removed, the residue is taken up in ethyl acetate and extracted with water. The organic phase is dried over sodium sulphate and evaporated down i. vac. . Then it is purified by silica gel column chromatography with dichloromethane/methanol 9:1 as eluant.

Yield: 3.1 g (71% of theory)

 $C_{13}H_{20}N_2O_3$ (M= 252.31)Calc.: Molecular ion peak (M+H)⁺: 253Found: Molecular ion peak (M+H)⁺:

253

R_f value: 0.60 (silica gel, dichloromethane/methanol 9:1)

4.21.b. 4-(2-diethylamino-ethoxy)-3-methyl-phenylamine

3.10 g (12.3 mmol) diethyl-[2-(2-methyl-4-nitro-phenoxy)-ethyl]-amine are dissolved in 250 mL ethyl acetate, 0.55 g Raney nickel are added and the mixture is hydrogenated for 36 hours at 50 psi and ambient temperature. The catalyst is filtered off and the filtrate is evaporated down i. vac. .

Yield: 2.70 g (99% of theory)

 $C_{13}H_{22}N_2O$ (M= 222.33)Calc.: Molecular ion peak (M+H)⁺: 223Found: Molecular ion peak (M+H)⁺:

223

R_f value: 0.35 (silica gel, dichloromethane/methanol 9:1)

4.21.c. 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[3-methyl-4-(2-diethylamino-ethoxy)-phenyl]-amide

Prepared analogously to Example 2.3.f. from 75 mg (0.30 mmol) (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid and 73 mg (0.33 mmol) 4-(2-diethylamino-ethoxy)-3-methyl-phenylamine.

Yield: 134 mg (99 % of theory)

5 $C_{23}H_{24}ClF_3N_2O_2$ (M= 452.90)

Calc.: Molecular ion peak (M+H)⁺: 453/455

Found: Molecular ion peak

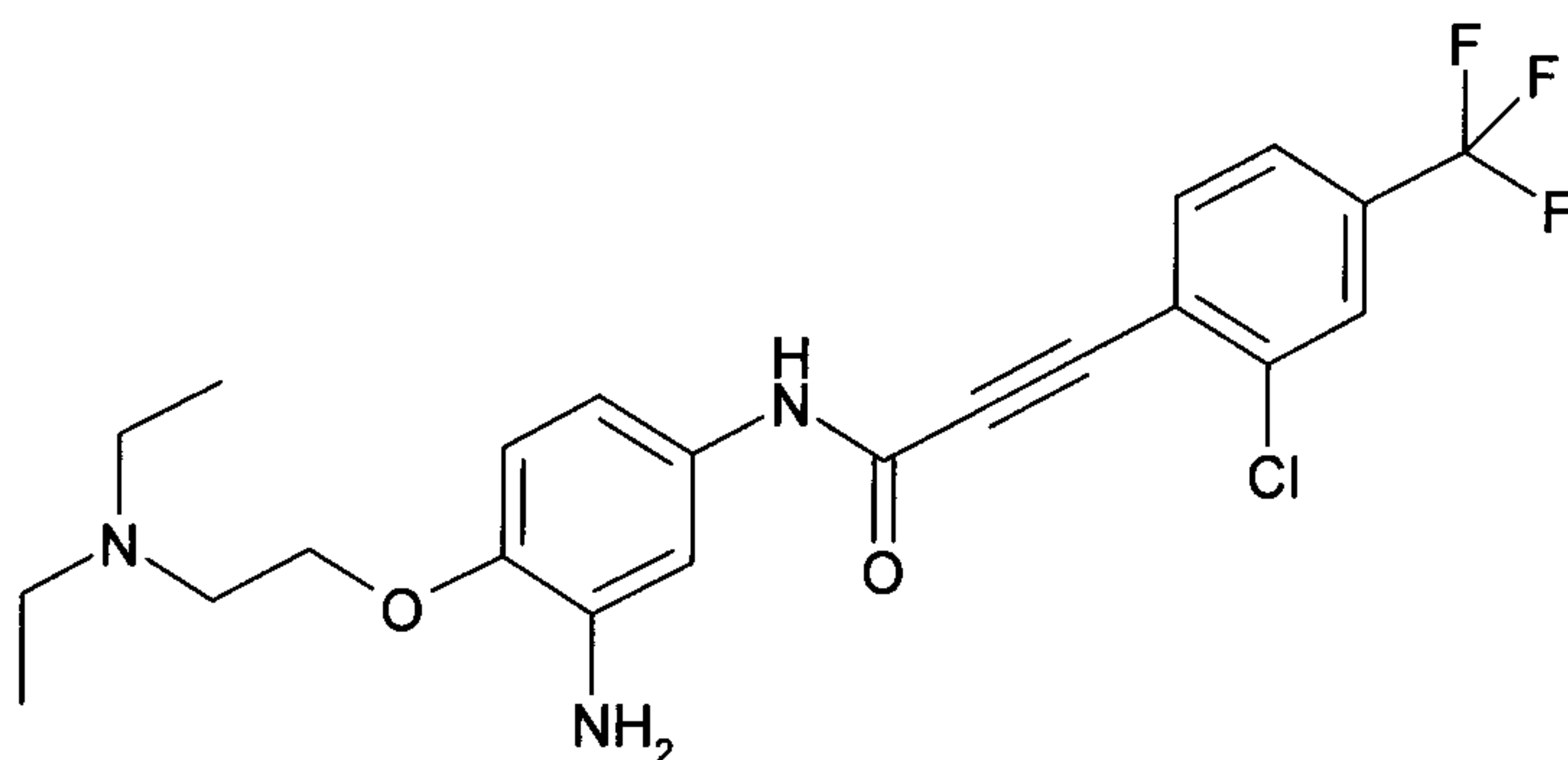
(M+H)⁺: 453/455

R_f value: 0.40 (silica gel, dichloromethane/methanol = 9:1)

10

Example 4.22

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[3-amino-4-(2-diethylamino-ethoxy)-phenyl]-amide



15

870 mg (10.3 mmol) sodium hydrogen carbonate and 1.17 g (5.17 mmol) tin-(II)-chloride-dihydrate are added at ambient temperature to a solution of 250 mg (0.52 mmol) 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[3-nitro-4-(2-diethylamino-ethoxy)-phenyl]-amide in 50 ml of ethyl acetate. The mixture is refluxed for twelve hours. After cooling water is added and the organic phase is separated off. The aqueous phase is extracted twice more with ethyl acetate. The combined organic phases are dried over sodium sulphate and the solvent is eliminated. The purification of the residue is carried out by column chromatography on Alox (eluant: dichloromethane/methanol = 39:1).

20

25 Yield: 100 mg (43 % of theory)

Melting point: 127-130 °C

$C_{22}H_{23}ClF_3N_3O_2$ (M= 453.89)

Calc.: Molecular ion peak (M+H)⁺: 454/456

Found: Molecular ion

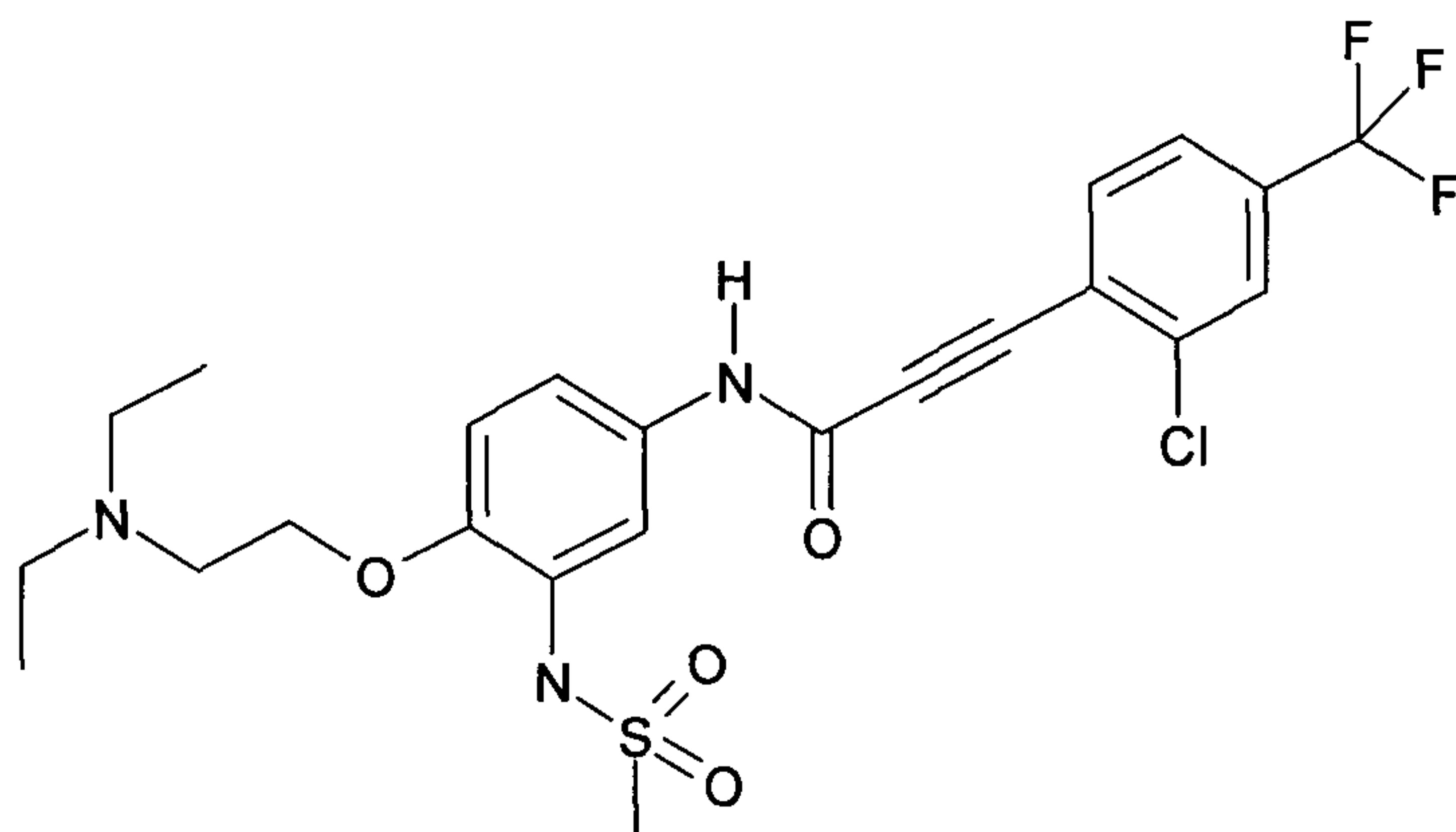
peak (M+H)⁺: 454/456

R_f value: 0.60 (Alox, dichloromethane/methanol = 39:1)

5

Example 4.23:

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[4-(3-diethylamino-ethoxy)-3-methanesulphonylamino-phenyl]-amide



10 0.019 ml (0.242 mmol) methanesulphonic acid chloride are added dropwise at 0° C to a solution of 0.1 g (0.22 mmol) 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[3-amino-4-(2-diethylamino-ethoxy)-phenyl]-amide in 5 ml of pyridine. The reaction mixture is slowly heated to ambient temperature and stirred for three hours. Then the reaction mixture is poured into ice water and extracted three times with ethyl acetate.

15 The combined organic phases are dried over sodium sulphate and the solvent is distilled off. The residue is freeze-dried.

Yield: 101 mg (86.3 % of theory)

Melting point: 57-60 °C

C₂₃H₂₅ClF₃N₃O₄S (M= 531.98)

20 Calc.: Molecular ion peak (M+H)⁺: 532/534

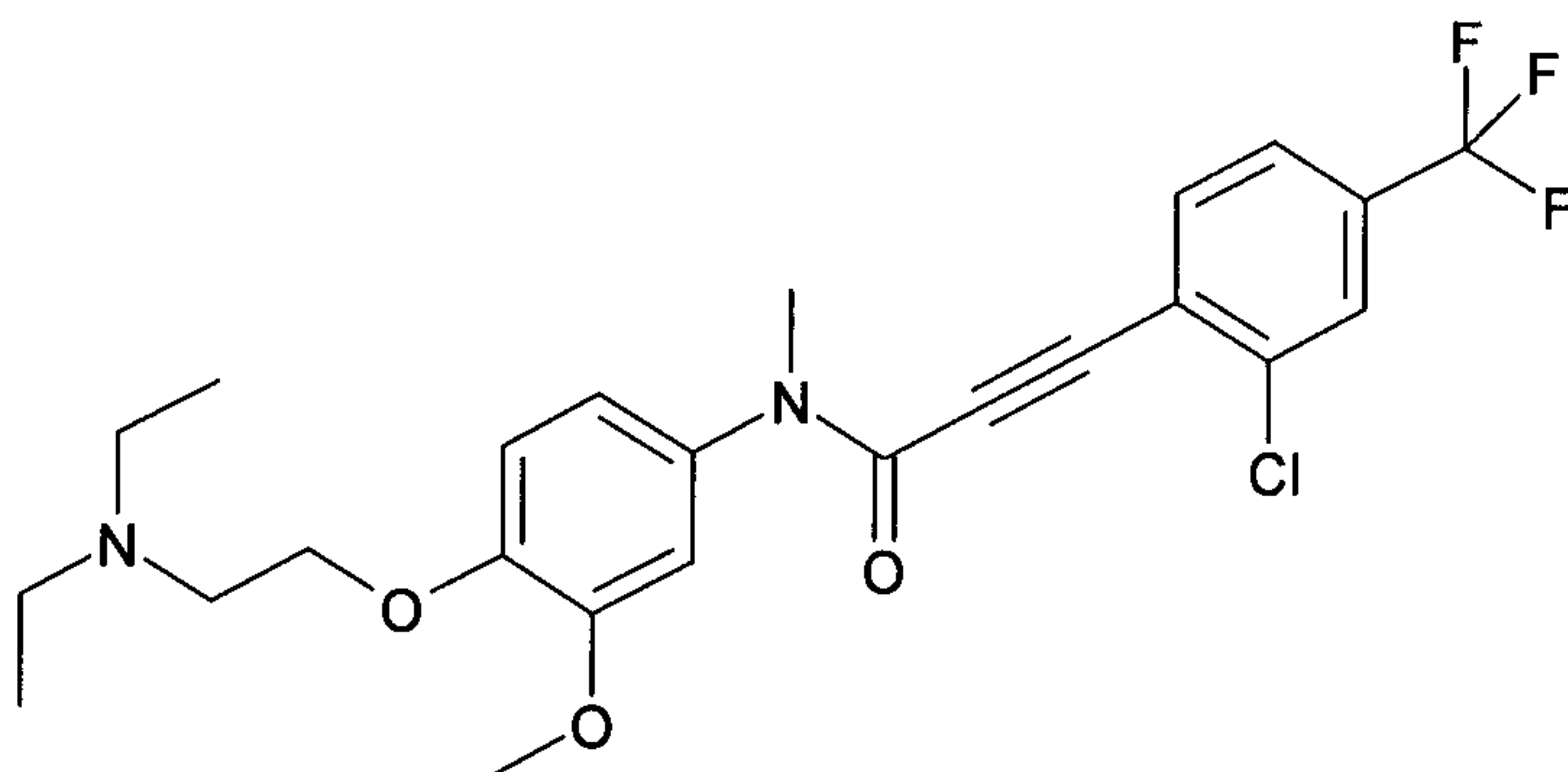
Found: Molecular ion peak

(M+H)⁺: 532/534

R_f value: 0.32 (silica gel, dichloromethane/methanol = 9:1)

25 **Example 4.24:**

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[4-(3-diethylamino-ethoxy)-3-methoxy-phenyl]-methyl-amide



4.24.a. tert.butyl [4-(3-diethylamino-ethoxy)-3-methoxy-phenyl]-carbamate

Prepared analogously to 3.1.c from 4-(3-diethylamino-ethoxy)-3-methoxy-phenylamine.

5 Yield: 0.26 g (91.6 % of theory)

$C_{18}H_{30}N_2O_4$ (M= 338.45)

Calc.: Molecular ion peak (M+H)⁺: 339

Found: Molecular ion peak (M+H)⁺: 339

R_f value: 0.45 (silica gel, dichloromethane/methanol/ammonia = 9:1:0.1)

10

4.24.b. [4-(3-diethylamino-ethoxy)-3-methoxy-phenyl]-methyl-amine

Prepared analogously to 3.1.d from tert.butyl [4-(3-diethylamino-propoxy)-3-methoxy-phenyl]-carbamate.

Yield: 0.08 g (44.7 % of theory)

15 $C_{14}H_{24}N_2O_2$ (M= 252.36)

Calc.: Molecular ion peak (M+H)⁺: 253

Found: Molecular ion peak (M+H)⁺: 253

4.24.c. 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[4-(3-diethylamino-ethoxy)-3-methoxy-phenyl]-methyl-amide

20

Prepared analogously to Example 2.3.f. from (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid and [4-(3-diethylamino-propoxy)-3-methoxy-phenyl]-methyl-amine.

Yield: 33 mg (30 % of theory)

$C_{24}H_{26}ClF_3N_2O_3$ (M= 482.93)

25 Calc.: Molecular ion peak (M+H)⁺: 483/485

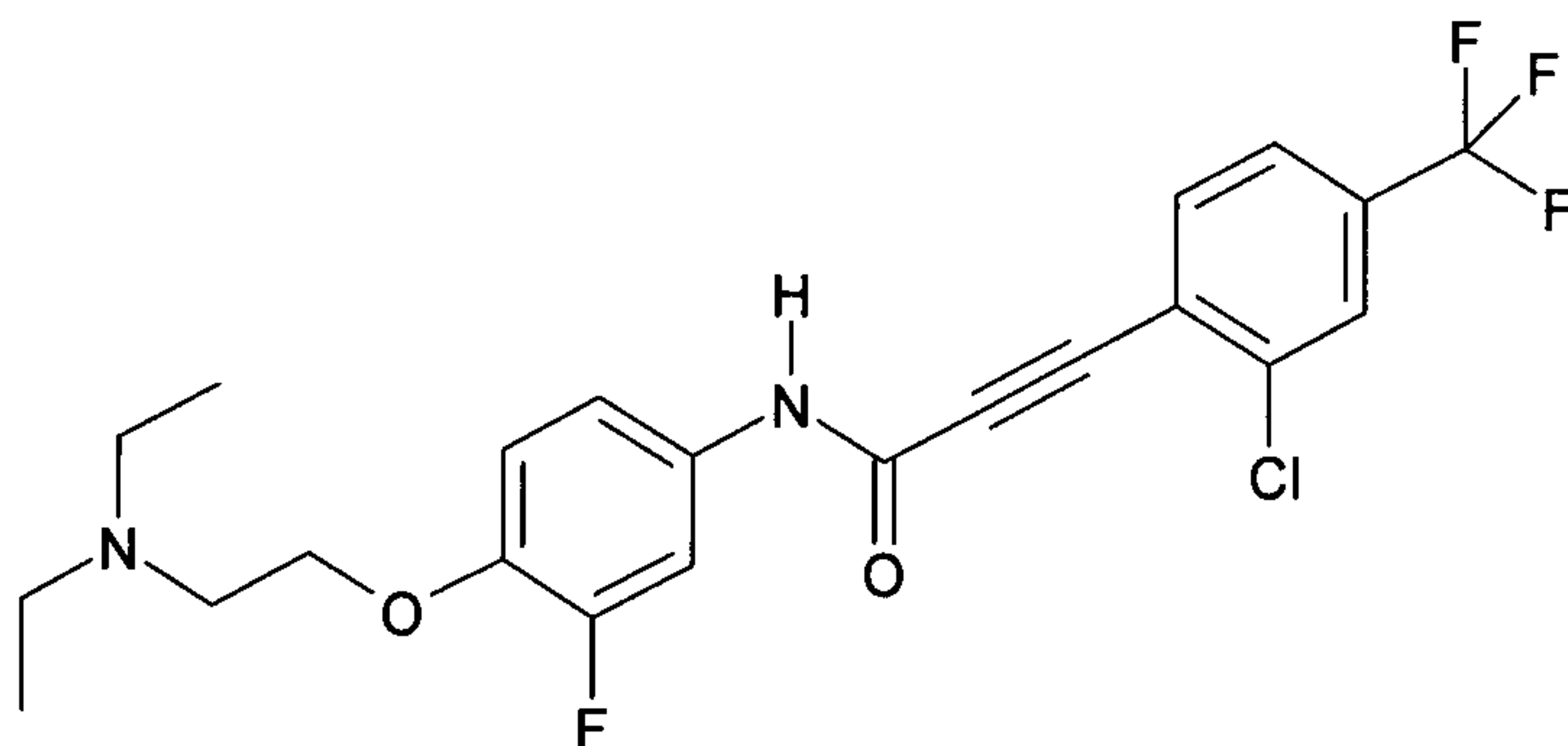
Found: Molecular ion peak

(M+H)⁺: 483/485

R_f value: 0.43 (silica gel, dichloromethane/methanol = 9:1)

Example 4.25:

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[4-(3-diethylamino-ethoxy)-3-fluoro-phenyl]-amide



4.25.a. [diethyl-[3-(2-fluoro-4-nitro-phenoxy)-ethyl]-amine

Prepared analogously to 4.6.a from 3,4-difluoro-nitrobenzene and 2-diethylaminoethanol.

Yield: 6.94 g (87.4 % of theory)

10 $C_{12}H_{17}FN_2O_3$ (M= 256.27)

Calc.: Molecular ion peak (M+H)⁺: 257

Found: Molecular ion peak (M+H)⁺:

257

R_f value: 0.46 (silica gel, dichloromethane/methanol/ammonia = 9:1:0.1)

15 4.25.b. 4-(3-diethylamino-ethoxy)-3-fluoro-phenylamine

Prepared analogously to 3.1.b from [diethyl-[3-(2-fluoro-4-nitro-phenoxy)-ethyl]-amine.

Yield: 5.93 g (97.1 % of theory)

$C_{12}H_{19}FN_2O$ (M= 226.29)

Calc.: Molecular ion peak (M+H)⁺: 229

Found: Molecular ion peak (M+H)⁺:

20 227

R_f value: 0.33 (silica gel, dichloromethane/methanol/ammonia = 9:1:0.1)

4.25.c. 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[4-(3-diethylamino-ethoxy)-3-fluoro-phenyl]-amide

25 Prepared analogously to Example 2.3.f. from (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid and 4-(3-diethylamino-ethoxy)-3-fluoro-phenylamine.

Yield: 0.14 g (33.5 % of theory)

Melting point: 85-88 C

$C_{22}H_{21}ClF_4N_2O_2$ (M= 456.87)

Calc.: Molecular ion peak (M+H)⁺: 455/457

Found: Molecular ion peak

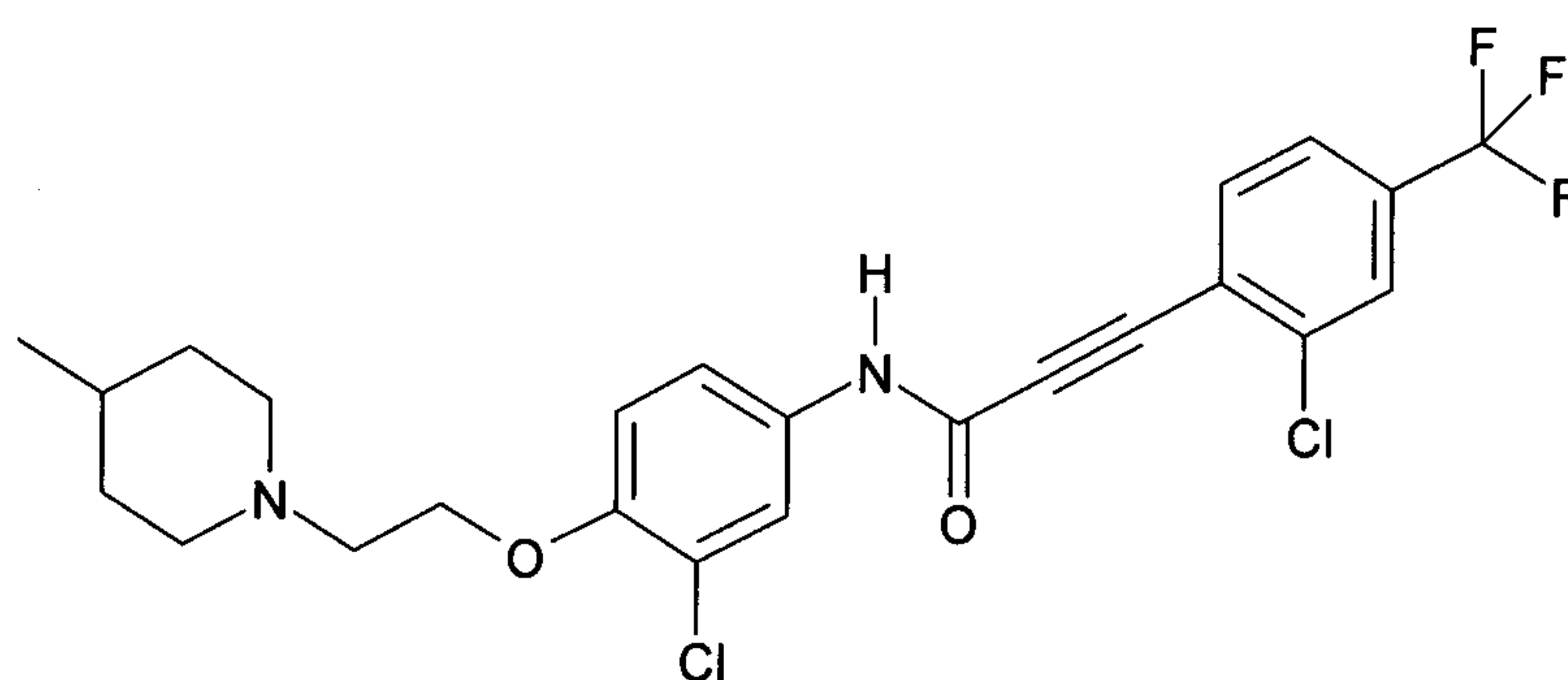
(M+H)⁺: 455/457

R_f value: 0.35 (silica gel, dichloromethane/methanol = 9:1)

5

Example 4.26:

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-{3-chloro-4-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenyl}-amide



4.26.a. 1-[2-(2-chloro-4-nitro-phenoxy)-ethyl]-4-methyl-piperidine

A reaction mixture of 7.8 g (27.81 mmol) 1-(2-bromo-ethoxy)-2-chloro-4-nitro-benzene and 10.14 ml (84 mmol) 4-methylpiperidine in 100 ml dichloromethane is stirred for 18 hours at ambient temperature. Then the solution is purified by column

15 chromatography on 400 g Alox act. II-III (eluant: dichloromethane/methanol=49:1).

Yield: 6.9 g (83 % of theory)

$C_{14}H_{19}ClN_2O_3$ (M= 298.77)

Calc.: Molecular ion peak (M+H)⁺: 209/301

Found: Molecular ion peak

(M+H)⁺: 209/301

20 R_f value: 0.48 (Alox, petroleum ether/ethyl acetate = 3:1)

4.26.b. 3-chloro-4-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenylamine

Prepared analogously to 3.1.b from 1-[2-(2-chloro-4-nitro-phenoxy)-ethyl]-4-methyl-piperidine.

25 Yield: 3.66 g (59 % of theory)

$C_{14}H_{21}ClN_2O$ (M= 268.78)

Calc.: Molecular ion peak (M+H)⁺: 269/271

Found: Molecular ion peak

(M+H)⁺: 269/271

R_f value: 0.52 (silica gel, dichloromethane/methanol = 9:1)

4.26.c. 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-{3-chloro-4-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenyl}-amide

5 Prepared analogously to Example 2.3.f. from (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid and 3-chloro-4-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenylamine.

Yield: 0.33 g (66 % of theory)

C₂₄H₂₃Cl₂F₃N₂O₂ (M= 499.36)

Calc.: Molecular ion peak (M+H)⁺: 499/501/503

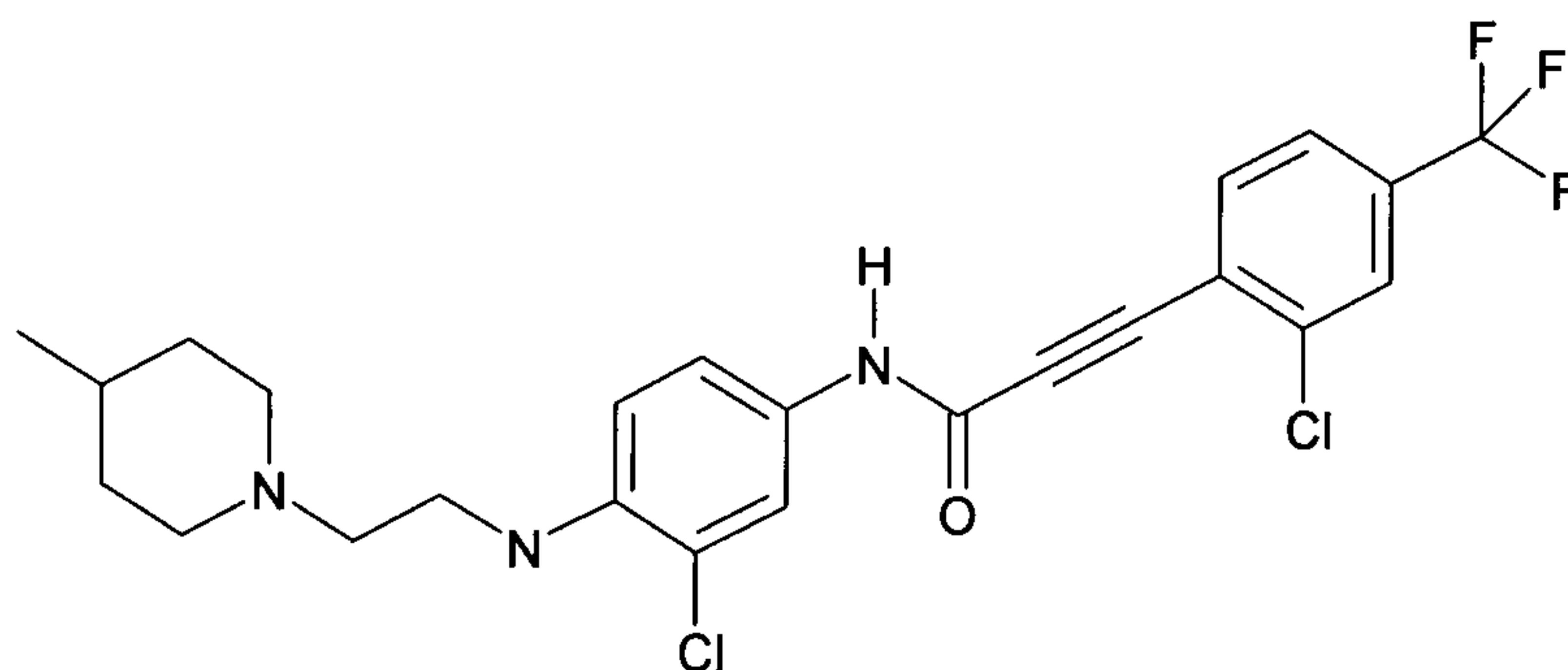
Found: Molecular ion

10 peak (M+H)⁺: 499/501/503

R_f value: 0.68 (Alox, dichloromethane/methanol = 49:1)

Example 4.27:

15 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-{3-chloro-4-[2-(4-methyl-piperidin-1-yl)-ethylamino]-phenyl}-amide



4.27.a. (2-chloro-4-nitro-phenyl)-[2-(4-methyl-piperidin-1-yl)-ethyl]-amine

A solution of 12.02 g (32.45 mmol) 2-(4-methyl-piperidin-1-yl)-ethylamine in 100 ml

20 DMF is combined with 17.94 g (64.82 mmol) potassium carbonate and stirred for 15 minutes at ambient temperature. Then 5.81 g (32.45 mmol) 3-chloro-4-fluoro-nitrobenzene are added and the reaction mixture is stirred for 18 hours. Then the reaction mixture is poured into ice water and the crystalline residue is filtered off.

Yield: 8.85 g (91.6 % of theory)

25 C₁₄H₂₀ClN₃O₂ (M= 297.78)

Calc.: Molecular ion peak (M+H)⁺: 298/300

Found: Molecular ion peak

(M+H)⁺: 298/300

4.27.b. 2-chloro-*N*¹-[2-(4-methyl-piperidin-1-yl)-ethyl]-benzene-1,4-diamine

Prepared analogously to 3.1.b from (2-chloro-4-nitro-phenyl)-[2-(4-methyl-piperidin-1-yl)-ethyl]-amine.

Yield: 7 g (89.3 % of theory)

5 C₁₄H₂₂ClN₃ (M= 267.80)

Calc.: Molecular ion peak (M+H)⁺: 268/270

Found: Molecular ion peak

(M+H)⁺: 268/270

R_f value: 0.6 (Alox, dichloromethane/methanol = 49:1)

10 4.27.c. 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-{3-chloro-4-[2-(4-methyl-piperidin-1-yl)-ethylamino]-phenyl}-amide

Prepared analogously to Example 2.3.f. from (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid and 2-chloro-*N*¹-[2-(4-methyl-piperidin-1-yl)-ethyl]-benzene-1,4-diamine.

15 Yield: 0.35 g (70.2 % of theory)

C₂₄H₂₄Cl₂F₃N₃O (M= 498.38)

Calc.: Molecular ion peak (M+H)⁺: 455/457

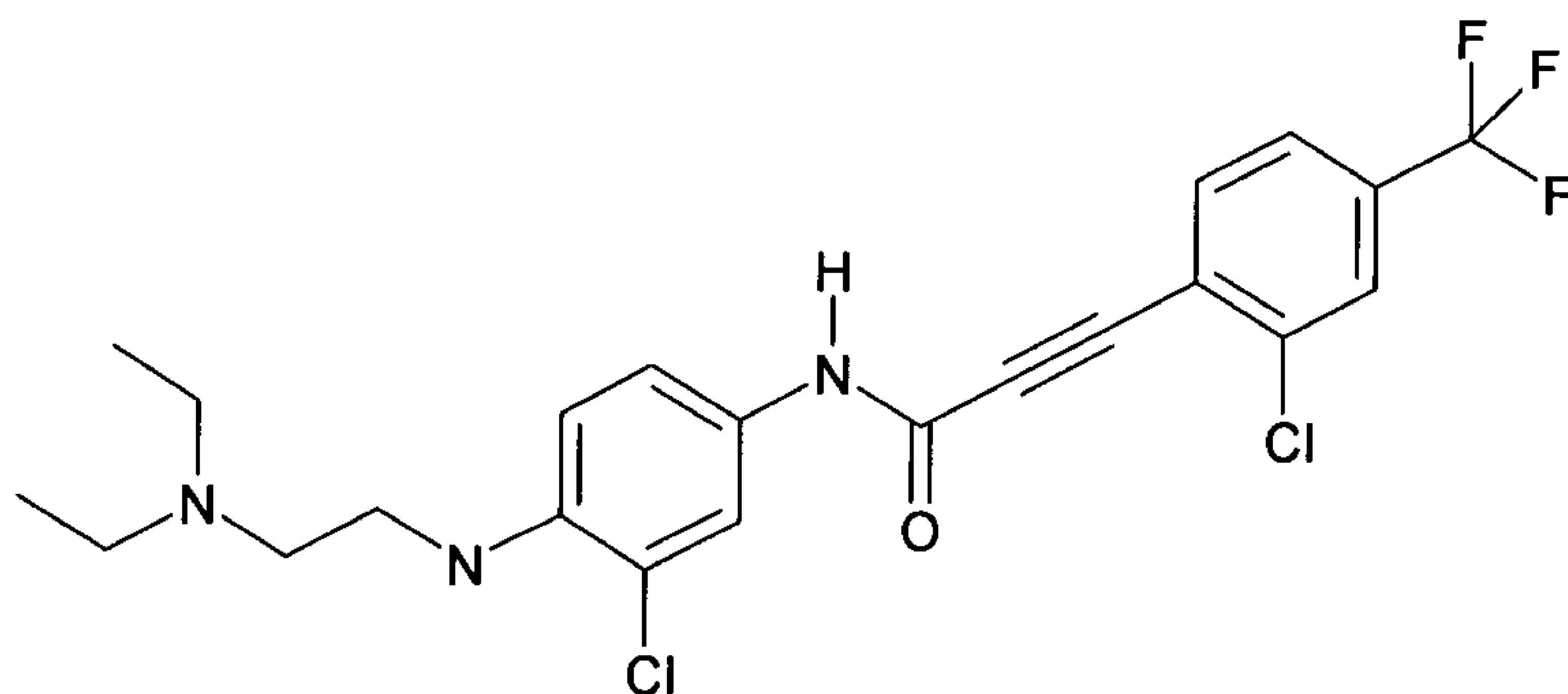
Found: Molecular ion peak

(M+H)⁺: 455/457

20

Example 4.28:

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[3-chloro-4-(2-diethylamino-ethylamino)-phenyl]-amide-formate

25 4.28.a. *N*'-(2-chloro-4-nitro-phenyl)-*N,N*-diethyl-ethane-1,2-diamine

Prepared analogously to 4.25.a from *N*¹,*N*¹-diethyl-ethane-1,2-diamine and 3-chloro-4-fluoro-nitrobenzene.

Yield: 9.2 g (99.1 % of theory)

$C_{12}H_{18}ClN_3O_2$ (M= 271.74)

Calc.: Molecular ion peak (M+H)⁺: 272/274

Found: Molecular ion peak

(M+H)⁺: 272/274

R_f value: 0.72 (Alox, dichloromethane/methanol = 49:1)

5

4.28.b. 2-chloro-*N*¹-(2-diethylamino-ethyl)-benzene-1,4-diamine

Prepared analogously to 3.1.b from *N*'-(2-chloro-4-nitro-phenyl)-*N,N*-diethyl-ethane-1,2-diamine.

Yield: 6.15 g (78 % of theory)

10 $C_{12}H_{20}ClN_3$ (M= 241.76)

Calc.: Molecular ion peak (M+H)⁺: 242/244

Found: Molecular ion peak

(M+H)⁺: 242/244

R_f value: 0.62 (Alox, dichloromethane/methanol = 49:1)

15 4.28.c. 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[3-chloro-4-(2-diethylamino-ethylamino)-phenyl]-amide

Prepared analogously to Example 2.3.f. from (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid and 2-chloro-*N*¹-(2-diethylamino-ethyl)-benzene-1,4-diamine.

Yield: 0.17 g (32.8 % of theory)

20 $C_{22}H_{22}Cl_2F_3N_3O \times HCOOH$ (M= 518.36)

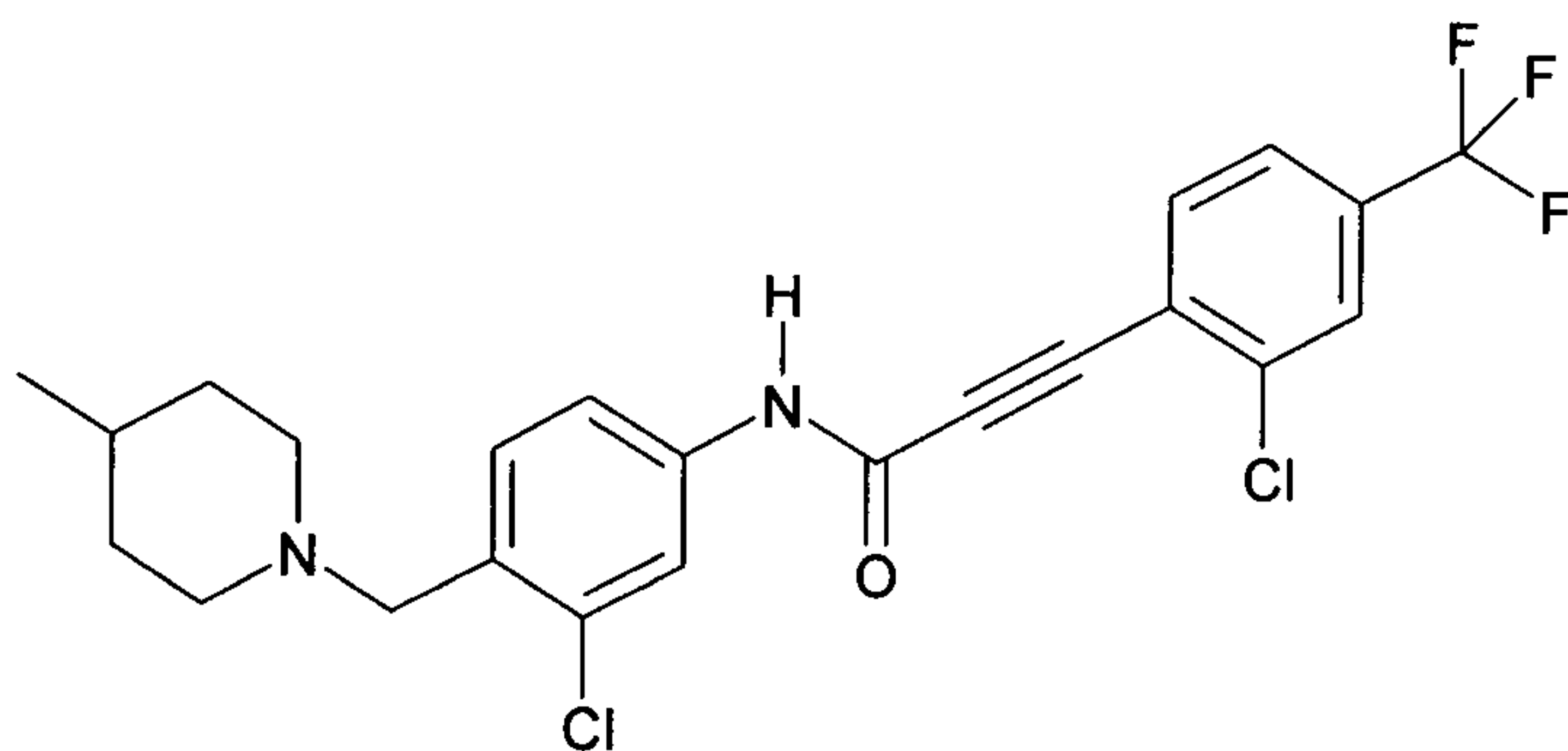
Calc.: Molecular ion peak (M+H)⁺: 472/474/476

Found: Molecular ion

peak (M+H)⁺: 472/474/476

25 **Example 4.29:**

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[3-chloro-4-(4-methyl-piperidin-1-ylmethyl)-phenyl]-amide



4.29.a. 1-(2-chloro-4-nitro-benzyl)-4-methyl-piperidine

1 g (4.85 mmol) 2-chloro-4-nitrobenzylchloride is slowly added dropwise to 2 ml (16.22 mmol) 4-methylpiperidine at ambient temperature and the mixture is stirred for 15 minutes. The reaction mixture is diluted with ethyl acetate and extracted twice with water. The organic phase is dried over sodium sulphate and evaporated down.

Yield: 1.3 g (99.7 % of theory)

$C_{13}H_{17}ClN_2O_2$ (M= 268.74)

Calc.: Molecular ion peak (M+H)⁺: 269/271

Found: Molecular ion peak

(M+H)⁺: 269/271

10 R_f value: 0.4 (Alox, petroleum ether)

4.29.b. 3-chloro-4-(4-methyl-piperidin-1-ylmethyl)-phenylamine

Prepared analogously to 3.1.b from 1-(2-chloro-4-nitro-benzyl)-4-methyl-piperidine.

Yield: 0.93 g (80 % of theory)

15 $C_{12}H_{20}ClN_3$ (M= 241.76)

Calc.: Molecular ion peak (M+H)⁺: 242/244

Found: Molecular ion peak

(M+H)⁺: 242/244

R_f value: 0.59 (Alox, petroleum ether/ethyl acetate = 3:1)

20 **4.29.c. 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[3-chloro-4-(4-methyl-piperidin-1-ylmethyl)-phenyl]-amide**

Prepared analogously to Example 2.3.f. from (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid and 3-chloro-4-(4-methyl-piperidin-1-ylmethyl)-phenylamine.

Yield: 25 mg (5.3 % of theory)

25 $C_{23}H_{21}Cl_2F_3N_2O$ (M= 469.33)

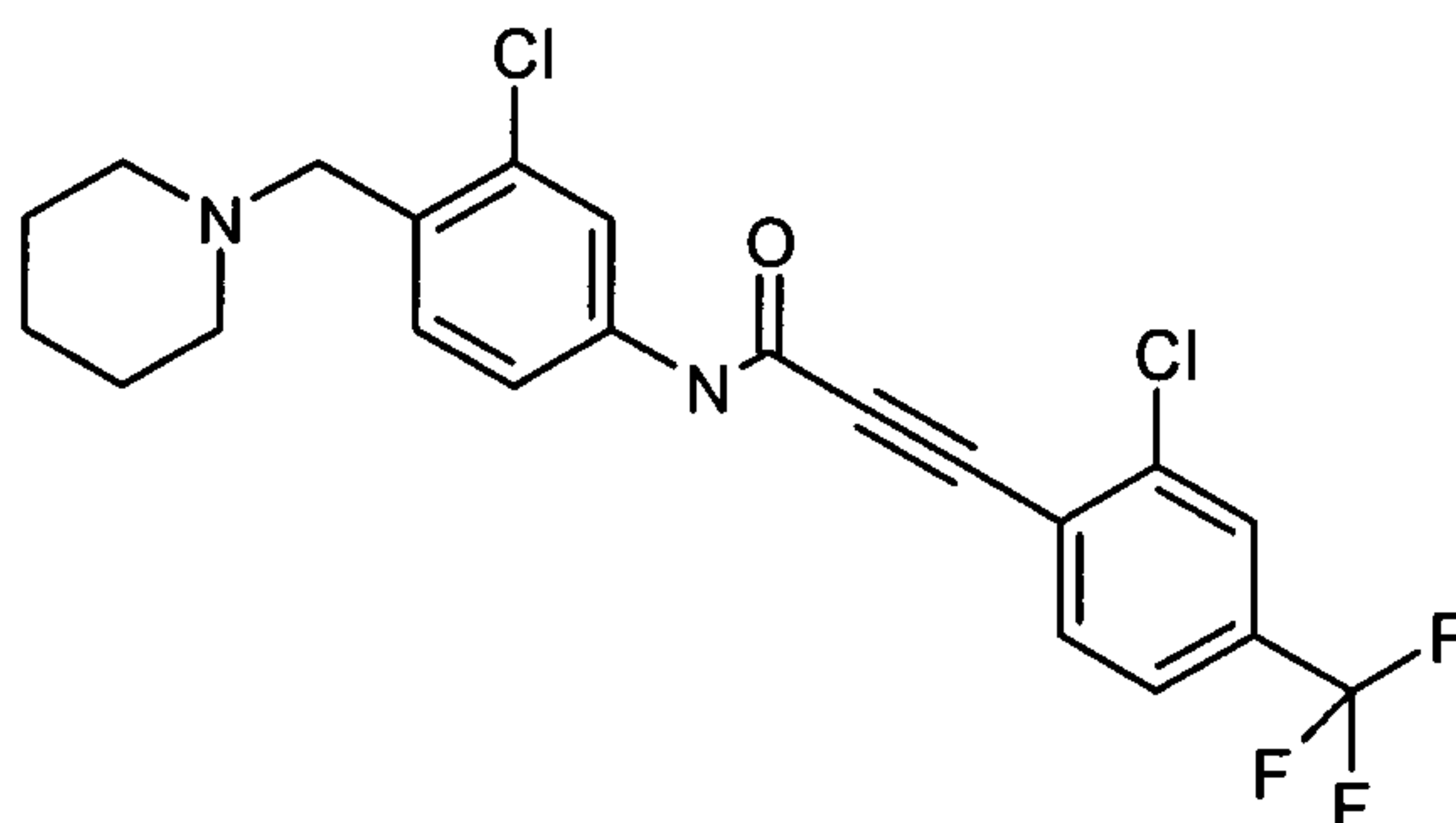
Calc.: Molecular ion peak (M+H)⁺: 469/471/473

Found: Molecular ion

peak (M+H)⁺: 469/471/473

R_f value: 0.59 (Alox, petroleum ether/ethyl acetate = 3:1)

30 **Example 4.30: 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-(3-chloro-4-piperidin-1-ylmethyl-phenyl)amide**



4.30.a. 1-(2-chloro-4-nitro-benzyl)-piperidin

Prepared analogously to Example 4.29.a. from 4 ml (40 mmol) piperidine and 2 g (9.71 mmol) 2-chloro-4-nitrobenzylchloride.

5 Yield: 2.39 g (97 % of theory)

$C_{12}H_{15}ClN_2O_2$ (M= 254.71)

Calc.: Molecular ion peak (M+H)⁺: 255/257 (Cl)

Found: Molecular ion

peak (M+H)⁺: 255/257 (Cl)

R_f value: 0.32 (silica gel, petroleum ether/ethyl acetate = 6:1)

10

4.30.b. 3-chloro-4-piperidin-1-ylmethyl-phenylamine

Prepared analogously to Example 3.1.b from 1-(2-chloro-4-nitro-benzyl)-piperidine.

Yield: 1.88 g (90 % of theory)

$C_{12}H_{17}ClN_2$ (M= 224.73)

15 Calc.: Molecular ion peak (M+H)⁺: 225/227 (Cl)

Found: Molecular ion

peak (M+H)⁺: 225/227 (Cl)

R_f value: 0.2 (silica gel, dichloromethane/methanol = 9:1)

20 4.30.c. 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-(3-chloro-4-piperidin-1-ylmethyl-phenyl)amide

Prepared analogously to Example 2.3.f. from (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid and 3-chloro-4-piperidin-1-ylmethyl-phenylamine.

Yield: 200 mg (44 % of theory)

$C_{22}H_{19}Cl_2F_3N_2O$ (M= 455.3) x HCl

25 Calc.: Molecular ion peak (M+H)⁺: 455/457/459 (Cl)

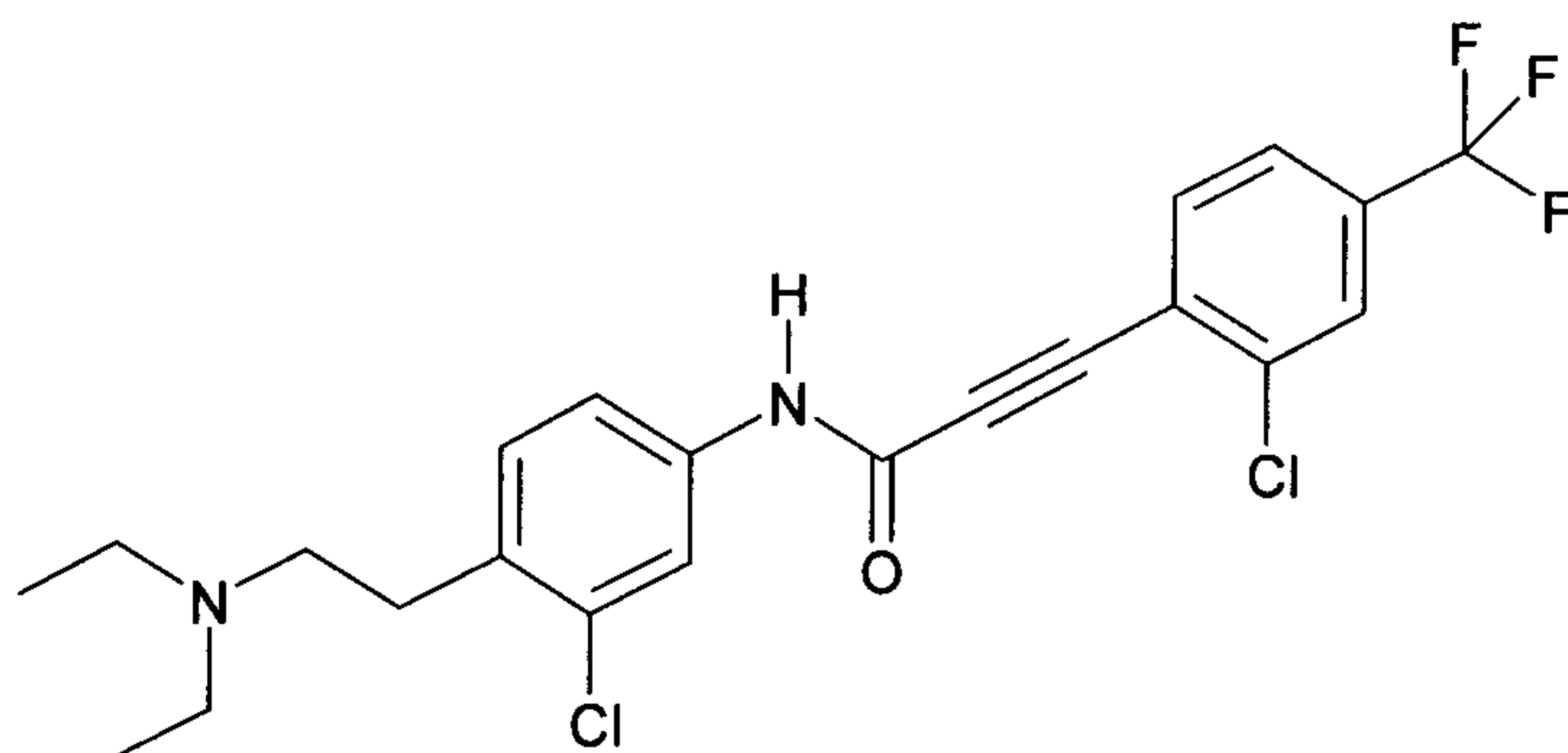
Found: Molecular ion peak

(M+H)⁺: 455/457/459 (Cl)

R_f value: 0.49 (silica gel, dichloromethane/methanol = 9:1)

Example 4.31:

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[3-chloro-4-(2-diethylamino-ethyl)-phenyl]-amide

**4.31.a. (2-chloro-4-nitro-phenyl)-acetic acid chloride**

Prepared analogously to 4.1.c from (2-chloro-4-nitro-phenyl)-acetic acid. The product is used in other reactions without further purification.

Yield: 8.8 g (100 % of theory)

$C_8H_5Cl_2NO_3$ (M= 234.04)

4.31.b. 2-(2-chloro-4-nitro-phenyl)-N,N-diethyl-acetamide

Prepared analogously to 4.1.d from (2-chloro-4-nitro-phenyl)-acetic acid chloride and diethylamine in ethyl acetate.

Yield: 3.7 g (100 % of theory)

$C_{12}H_{15}ClN_2O_3$ (M= 270.71)

Calc.: Molecular ion peak (M+H)⁺: 271/273

Found: Molecular ion peak

(M+H)⁺: 271/273

R_f value: 0.45 (silica gel, petroleum ether/ethyl acetate = 1:1)

4.31.c. [2-(2-chloro-4-nitro-phenyl)-ethyl]-diethyl-amine

65 ml (65 mmol) of a 1M borane-THF solution are added dropwise to a solution of 3.7 g (13.67 mmol) 2-(2-chloro-4-nitro-phenyl)-N,N-diethyl-acetamide in 130 ml THF at ambient temperature and stirred for four hours. Then the reaction mixture is evaporated down and the residue is combined with 15 ml of methanol and 15 ml dilute hydrochloric acid. The mixture is then stirred for 15 minutes at 100 °C, cooled and diluted with water. Then the mixture is made alkaline with sodium carbonate

solution and extracted twice with ethyl acetate. The combined organic phases are extracted twice with water and once with saturated saline solution and dried over sodium sulphate. The purification is carried out by column chromatography on Alox, neutral, act.II-III (eluant: petroleum ether/ ethyl acetate= 4:1).

5 Yield: 2.1 g (59.8 % of theory)

$C_{12}H_{17}ClN_2O_2$ (M= 256.73)

R_f value: 0.63 (Alox, petroleum ether/ ethyl acetate= 3:1)

10 4.31.d. 3-chloro-4-(2-diethylamino-ethyl)-phenylamine

Prepared analogously to 3.1.b from [2-(2-chloro-4-nitro-phenyl)-ethyl]-diethyl-amine.

Yield: 1.8 g (100 % of theory)

$C_{12}H_{19}ClN_2$ (M= 226.75)

Calc.: Molecular ion peak (M+H)⁺: 227/229

Found: Molecular ion peak

15 (M+H)⁺: 227/229

R_f value: 0.63 (Alox, petroleum ether/ ethyl acetate= 1:1)

4.31.e. 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[3-chloro-4-(2-diethylamino-ethyl)-phenyl]-amide

20 Prepared analogously to Example 2.3.f. from (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid and chloro-4-(2-diethylamino-ethyl)-phenylamine.

Yield: 0.21 g (46.8 % of theory)

$C_{22}H_{21}Cl_2F_3N_2O$ (M= 457.32)

Calc.: Molecular ion peak (M+H)⁺: 457/459/461

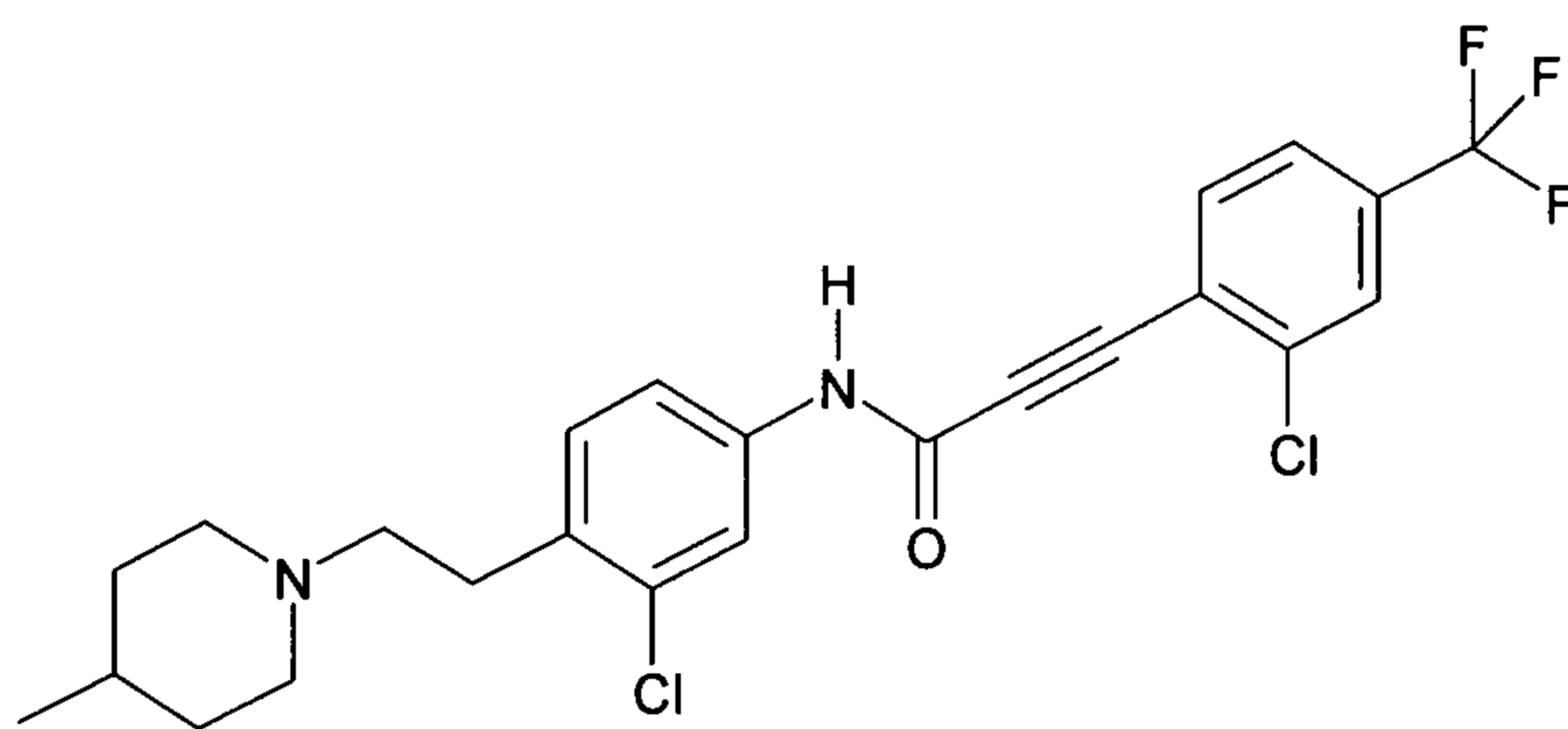
Found: Molecular ion

25 peak (M+H)⁺: 457/459/461

R_f value: 0.63 (Alox, petroleum ether/ ethyl acetate= 1:1)

Example 4.32:

30 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-{3-chloro-4-[2-(4-methyl-piperidin-1-yl)-ethyl]-phenyl}-amide



4.32.a. 3-chloro-4-[2-(4-methyl-piperidin-1-yl)-ethyl]-phenylamine

Prepared analogously to 4.28.a to c from (2-chloro-4-nitro-phenyl)-acetic acid chloride.

5 Yield: 0.71 g (99.3 % of theory)

$C_{14}H_{21}ClN_2$ (M= 252.79)

Calc.: Molecular ion peak (M+H)⁺: 253/255
(M+H)⁺: 253/255

Found: Molecular ion peak

10 4.32.b. 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-{3-chloro-4-[2-(4-methyl-piperidin-1-yl)-ethyl]-phenyl}-amide

Prepared analogously to Example 2.3.f. from (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid and 3-chloro-4-[2-(4-methyl-piperidin-1-yl)-ethyl]-phenylamine.

Yield: 0.21 g (45.3 % of theory)

15 $C_{24}H_{23}Cl_2F_3N_2O$ (M= 483.36)

Calc.: Molecular ion peak (M+H)⁺: 483/485/487
peak (M+H)⁺: 483/485/487

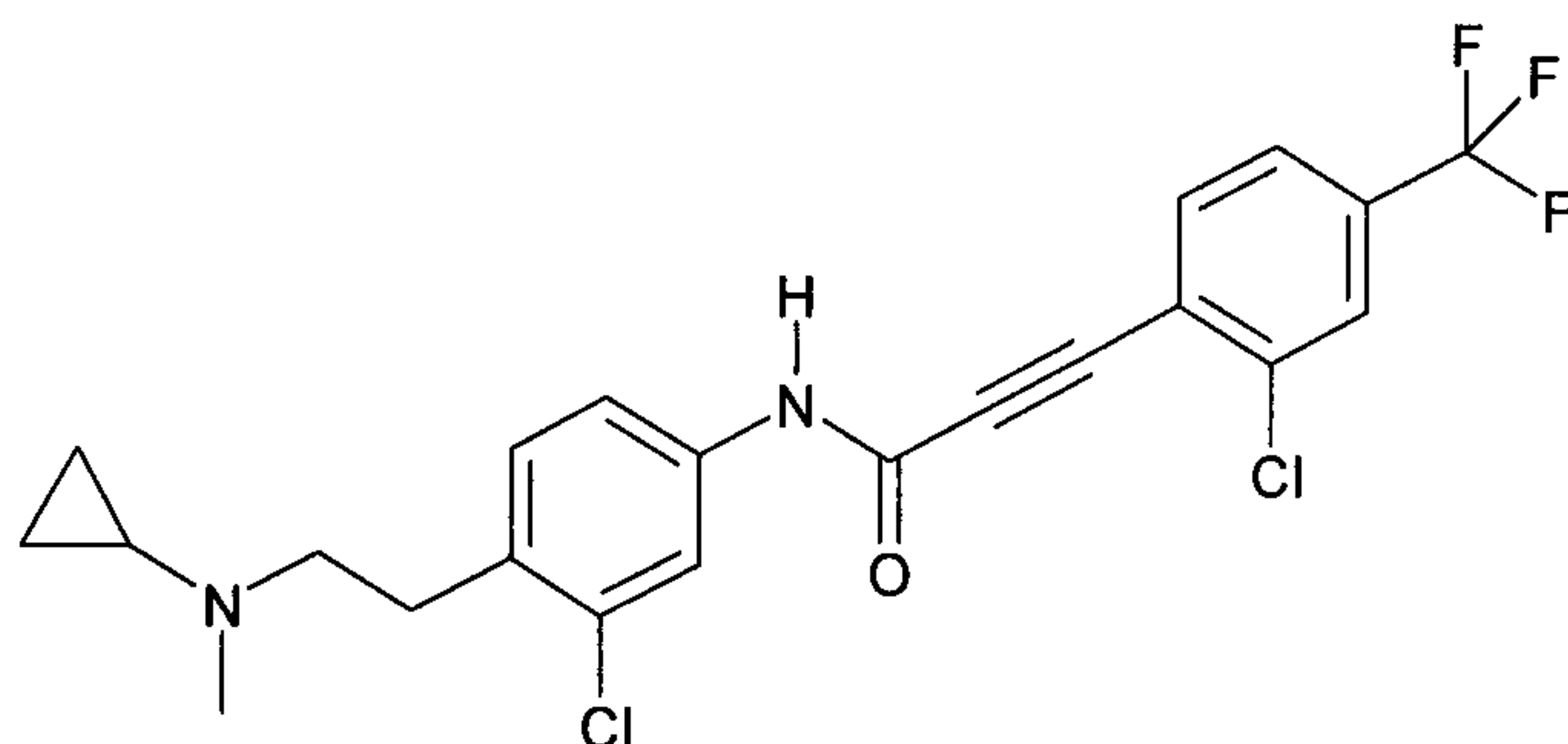
Found: Molecular ion

R_f value: 0.65 (Alox, petroleum ether/ ethyl acetate= 1:1)

20

Example 4.33:

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-{3-chloro-4-[2-(cyclopropyl-methyl-amino)-ethyl]-phenyl}-amide



4.33.a. [(E)-2-(2-chloro-4-nitro-phenyl)-vinyl]-dimethyl-amine

A reaction mixture of 8.49 g (48 mmol) 2-chloro-4-nitrotoluene and 15.03 ml (72.8 mmol) tert.butoxybis(dimethylamino)methane in 200 ml THF is refluxed for eight

- 5 hours. The reaction solution is evaporated down and the residue is combined with petroleum ether. The precipitate is filtered off, rinsed with petroleum ether and dried at ambient temperature under a high vacuum. The product is used in other reactions without further purification.

Yield: 11g

10 $C_{10}H_{11}ClN_2O_2$ (M= 226.66)

Calc.: Molecular ion peak (M+H)⁺: 227/229

Found: Molecular ion peak

(M+H)⁺: 227/229

R_f value: 0.55 (silica gel, petroleum ether/ethyl acetate = 3:1)

15 4.33.b. (2-chloro-4-nitro-phenyl)-acetaldehyde

50 ml 1N hydrochloric acid are added dropwise to a solution of 10 g (30.88 mmol)

[(E)-2-(2-chloro-4-nitro-phenyl)-vinyl]-dimethyl-amine in 200 ml of ethanol and the

reaction mixture is then refluxed for one hour. Then the reaction mixture is evaporated

down, diluted with water and twice extracted with ethyl acetate. The combined organic

- 20 phases are dried over sodium sulphate. The purification is carried out by column chromatography on silica gel (eluant: petroleum ether/ ethyl acetate= 3:1).

Yield: 4.5 g (73 % of theory)

$C_8H_6ClNO_3$ (M= 199.59)

R_f value: 0.62 (silica gel, petroleum ether/ethyl acetate = 1:1)

25

4.33.c. [2-(2-chloro-4-nitro-phenyl)-ethyl]-cyclopropyl-methyl-amine

1.07 g (10 mmol) N-methyl-cyclopropylamine is added to a solution of 1 g (5.01 mmol)

(2-chloro-4-nitro-phenyl)-acetaldehyde in 50 ml THF and then 4.46 g (20 mmol)

sodiumtriacetoxymethylborohydride (95 %) are added. The reaction mixture is stirred for 120

hours at ambient temperature and then poured into a saturated sodium hydrogen carbonate solution and twice extracted with ethyl acetate. The combined organic phases are dried over sodium sulphate. The purification is carried out by column chromatography on Alox, neutral, act.II-III (eluant: petroleum ether/ ethyl acetate= 5:1).

Yield: 0.75 g (58.8 % of theory)

$C_{12}H_{15}ClN_2O_2$ (M= 254.71)

Calc.: Molecular ion peak (M+H)⁺: 255/257

Found: Molecular ion peak

(M+H)⁺: 255/257

10 R_f value: 0.61 (Alox, petroleum ether/ ethyl acetate= 5:1)

4.33.d. 3-chloro-4-[2-(cyclopropyl-methyl-amino)-ethyl]-phenylamine

Prepared analogously to 3.1.b from [2-(2-chloro-4-nitro-phenyl)-ethyl]-cyclopropyl-methyl-amine.

15 Yield: 0.6 g (100 % of theory)

$C_{12}H_{17}ClN_2$ (M= 224.73)

Calc.: Molecular ion peak (M+H)⁺: 225/227

Found: Molecular ion peak

(M+H)⁺: 225/227

R_f value: 0.57 (Alox, petroleum ether/ ethyl acetate= 1:1)

20

4.33.e. 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-{3-chloro-4-[2-(cyclopropyl-methyl-amino)-ethyl]-phenyl}-amide

Prepared analogously to Example 2.3.f. from (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid and 3-chloro-4-[2-(cyclopropyl-methyl-amino)-ethyl]-phenylamine.

25 Yield: 15 mg (3.4 % of theory)

$C_{22}H_{19}Cl_2F_3N_2O$ (M= 455.31)

Calc.: Molecular ion peak (M+H)⁺: 455/457/459

Found: Molecular ion

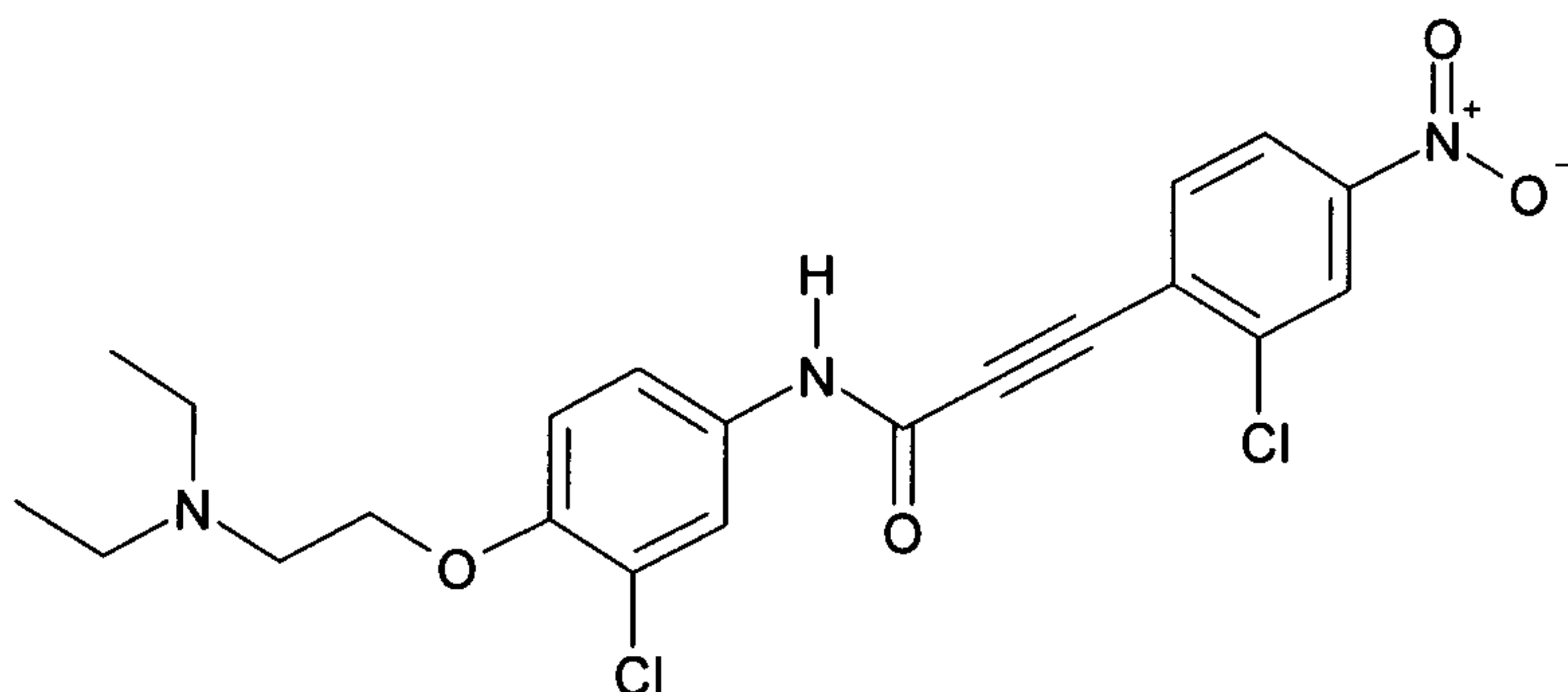
peak (M+H)⁺: 455/457/459

R_f value: 0.3 (Alox, petroleum ether/ ethyl acetate= 3:1)

30

Example 4.34:

3-(2-chloro-4-nitro-phenyl)-propynoic acid-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-amide



5 4.34.a. ethyl (2-chloro-4-nitro-phenyl)-propynoate

Prepared analogously to 4.11.a from 3-chloro-4-iodo-nitrobenzene and ethyl propynoate

Yield: 1.6 g (46.5 % of theory)

$C_{11}H_8ClNO_4$ (M= 253.64)

10 Calc.: Molecular ion peak (M+H)⁺: 254/256

Found: Molecular ion peak

(M+H)⁺: 254/256

R_f value: 0.6 (silica gel, petroleum ether/ethyl acetate = 6:1)

4.34.b. (2-chloro-4-nitro-phenyl)-propynoic acid

15 Prepared analogously to 4.11.b from ethyl (2-chloro-4-nitro-phenyl)-propynoate.

Yield: 0.76 g (66.8 % of theory)

$C_9H_4ClNO_4$ (M= 225.59)

Calc.: Molecular ion peak (M+H)⁺: 225/227

Found: Molecular ion peak

(M+H)⁺: 225/227

20

4.34.c. 3-(2-chloro-4-nitro-phenyl)-propynoic acid-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-amide

Prepared analogously to Example 2.3.f. from (2-chloro-4-nitro-phenyl)-propynoic acid and 3-chloro-4-(2-diethylamino-ethoxy)-phenylamine.

25 Yield: 0.49 g (54.4 % of theory)

$C_{21}H_{21}Cl_2N_3O_4$ (M= 450.32)

Calc.: Molecular ion peak (M+H)⁺: 448/450/452

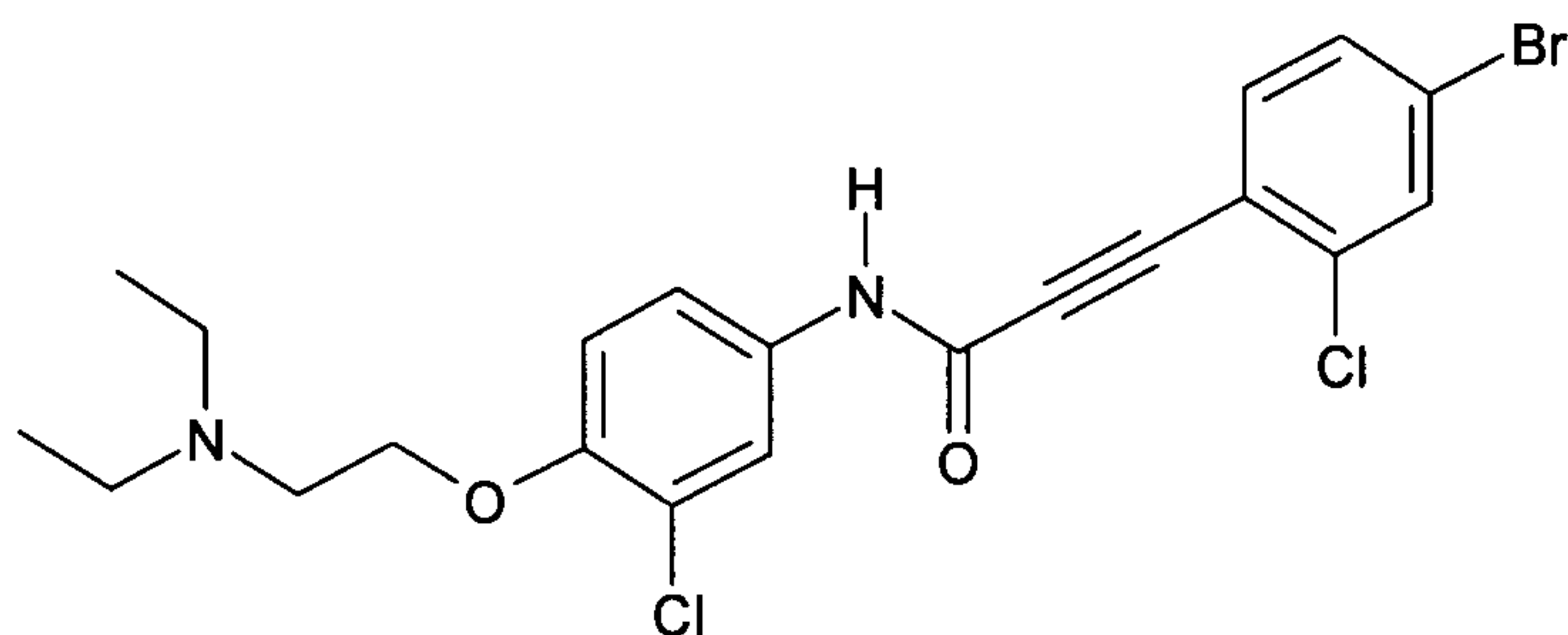
Found: Molecular ion

peak (M+H)⁺: 448/450/452

R_f value: 0.36 (silica gel, dichloromethane/methanol = 9:1)

Example 4.35:

5 3-(4-bromo-2-chloro-phenyl)-propynoic acid-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-amide



4.35.a. ethyl (4-bromo-2-chloro-phenyl)-propynoate

Prepared analogously to 4.11.a from 3-chloro-4-iodo-bromobenzene and ethyl
10 propynoate

Yield: 0.97 g (48.2 % of theory)

C₁₁H₈BrClO₂ (M= 287.54)

Calc.: Molecular ion peak (M+H)⁺: 287/289/291
peak (M+H)⁺: 287/289/291

Found: Molecular ion

15 R_f value: 0.62 (silica gel, petroleum ether/ethyl acetate = 6:1)

4.35.b. (4-bromo-2-chloro-phenyl)-propynoic acid

Prepared analogously to 4.11.b from ethyl (4-bromo-2-chloro-phenyl)-propynoate.

Yield: 0.8 g (93.4 % of theory)

20 C₉H₄BrClO₂ (M= 259.48)

Calc.: Molecular ion peak (M+H)⁺: 258/260/262
peak (M+H)⁺: 258/260/262

Found: Molecular ion

25 4.35.c. 3-(4-bromo-2-chloro-phenyl)-propynoic acid-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-amide

Prepared analogously to Example 2.3.f. from (4-bromo-2-chloro-phenyl)-propynoic acid and 3-chloro-4-(2-diethylamino-ethoxy)-phenylamine.

Yield: 0.25 g (64.5 % of theory)

C₂₁H₂₁BrCl₂N₂O₂ (M= 484.22)

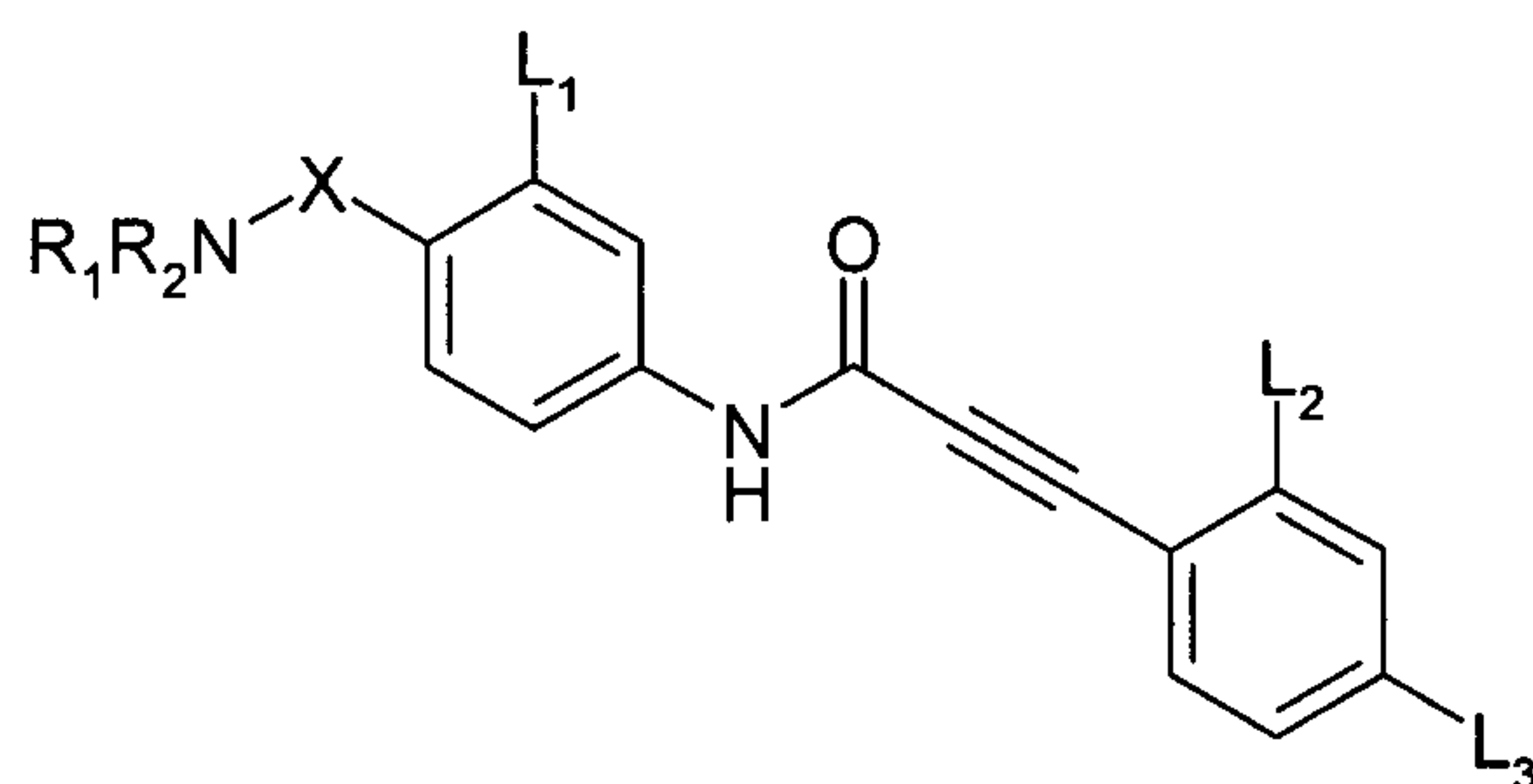
Calc.: Molecular ion peak (M+H)⁺: 483/485/487/489

Found: Molecular ion peak (M+H)⁺: 483/485/487/489

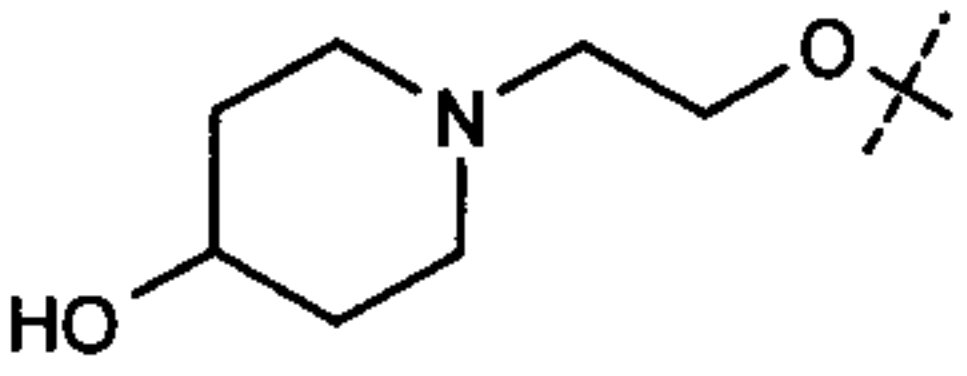
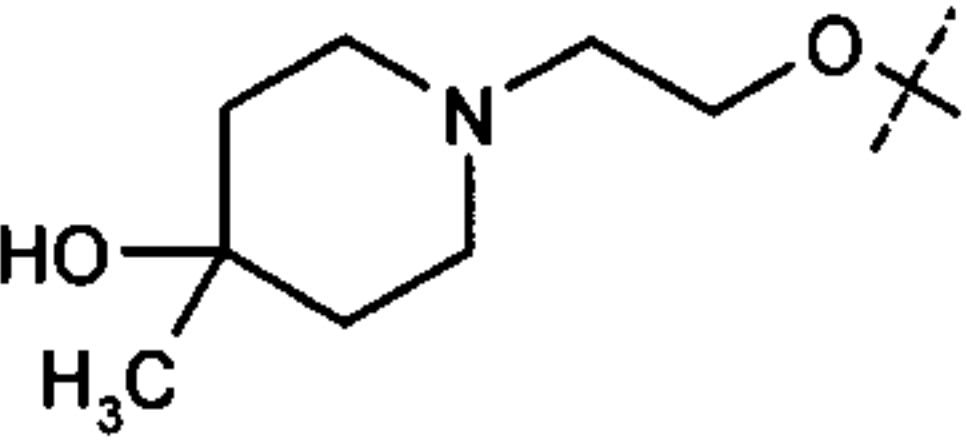
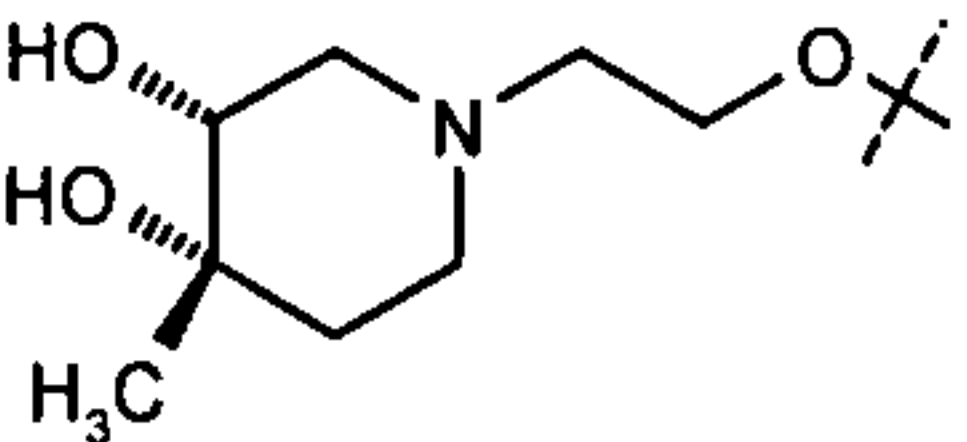
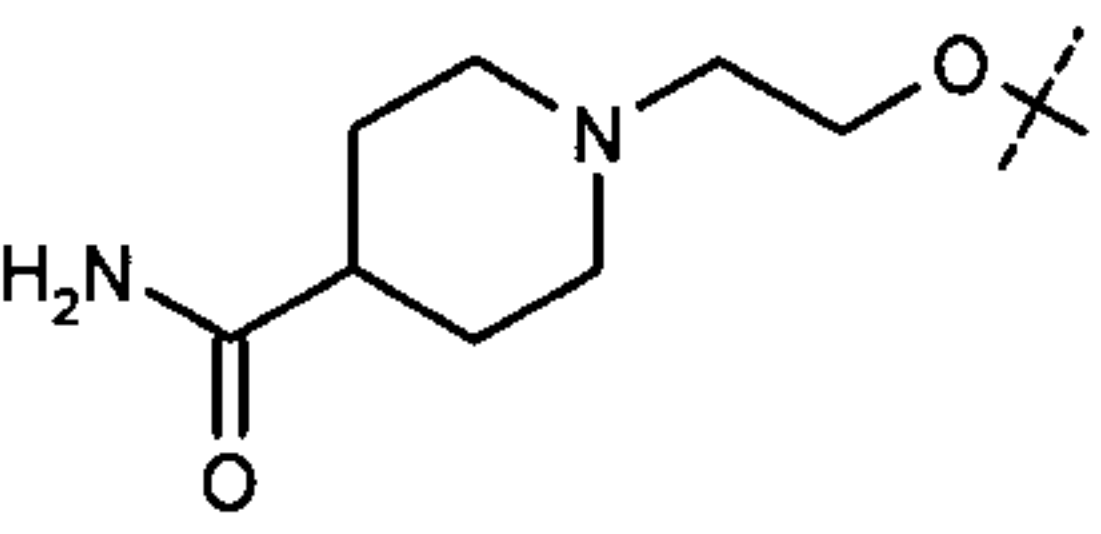
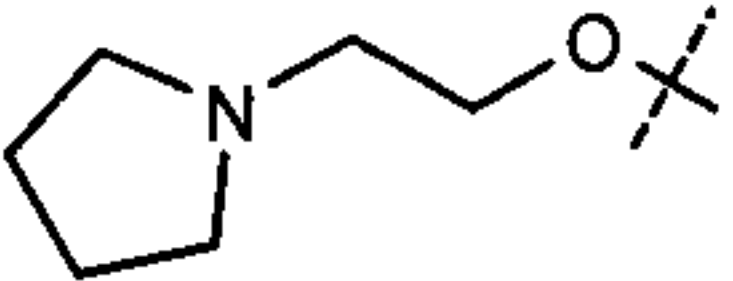
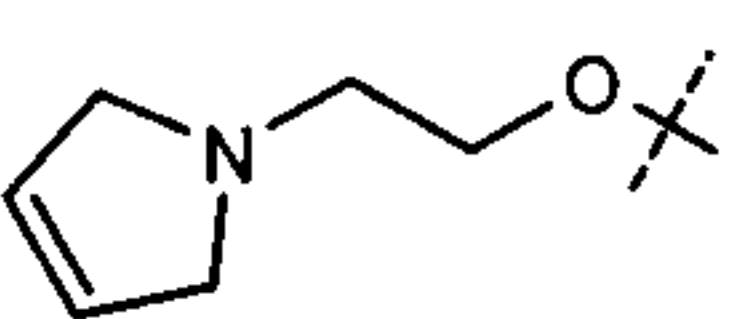
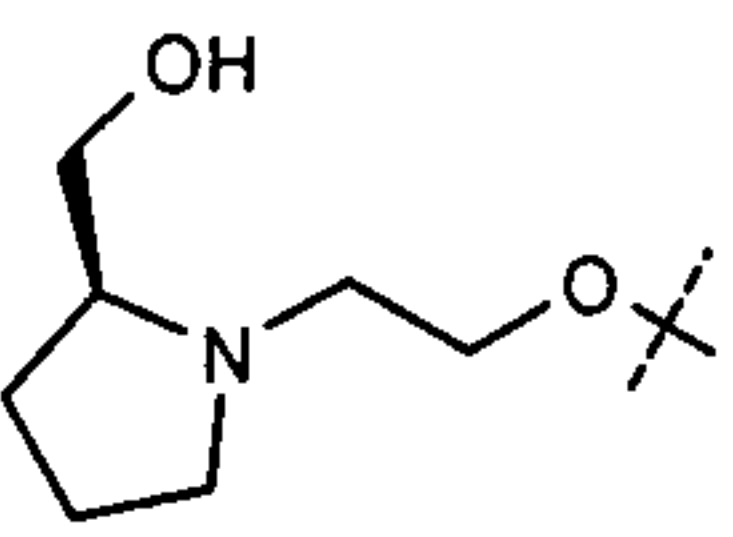
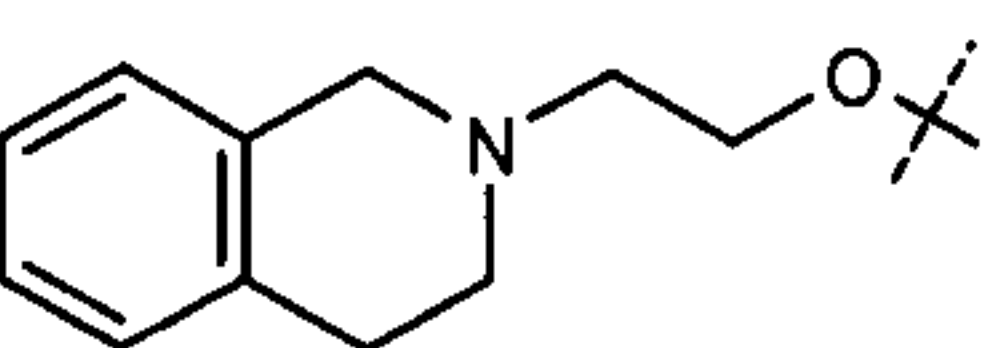
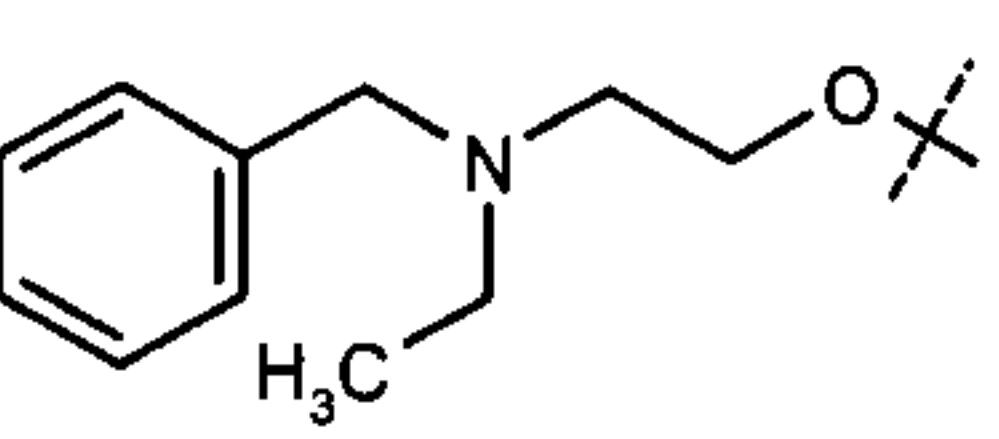
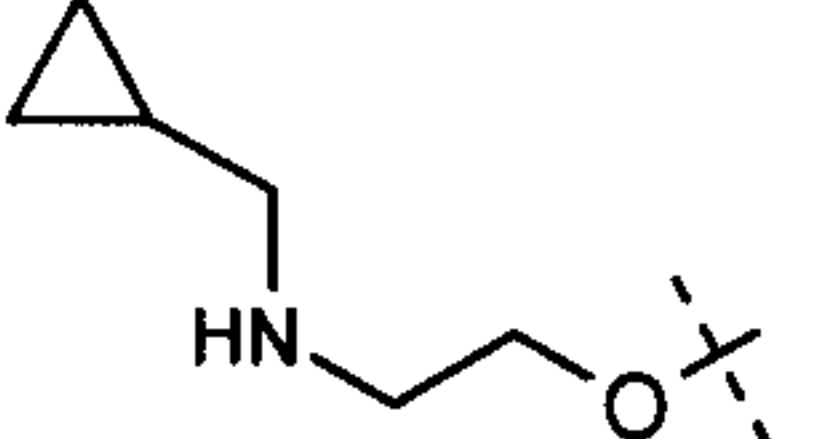
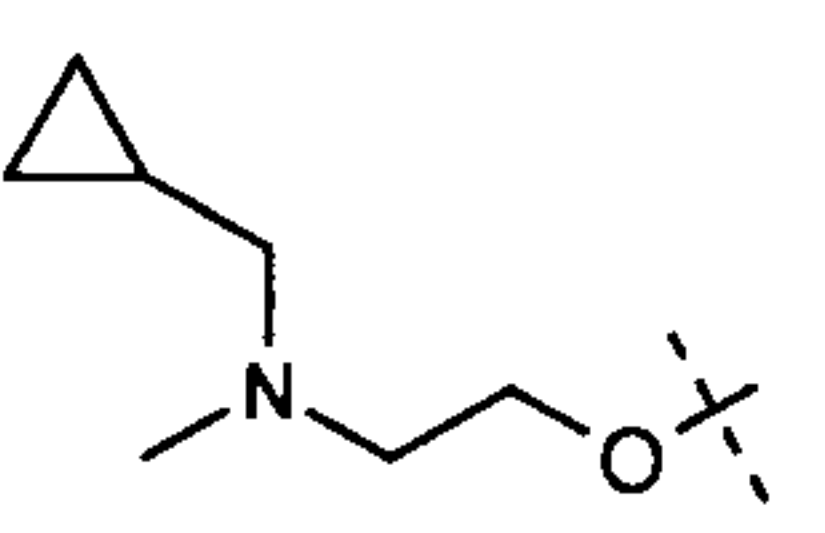
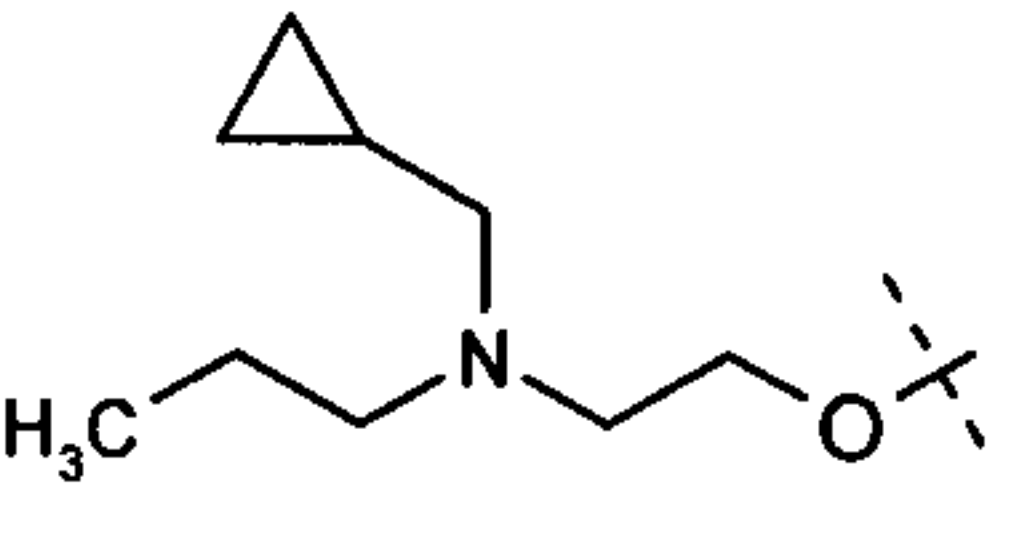
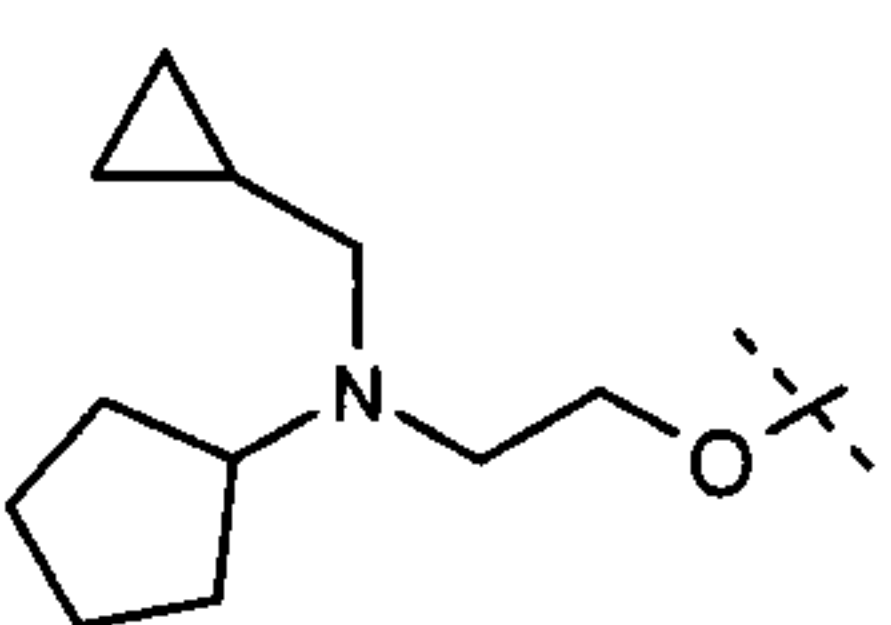
R_f value: 0.86 (silica gel, dichloromethane/methanol = 49:1)

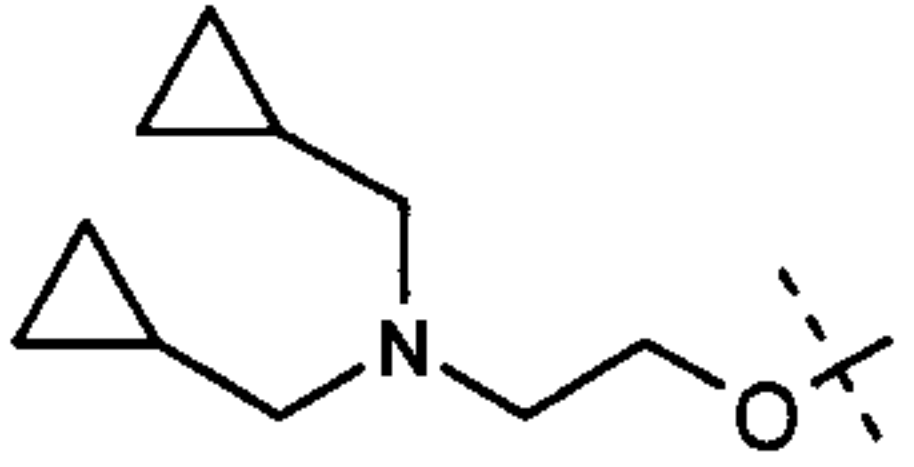
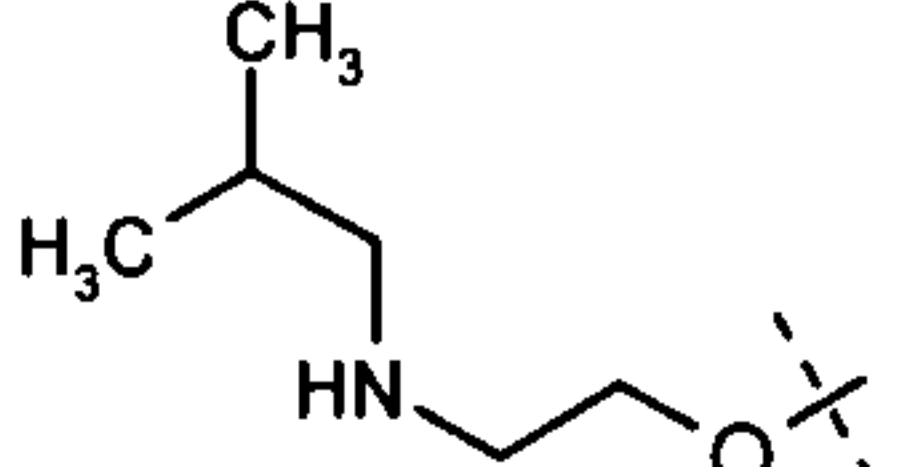
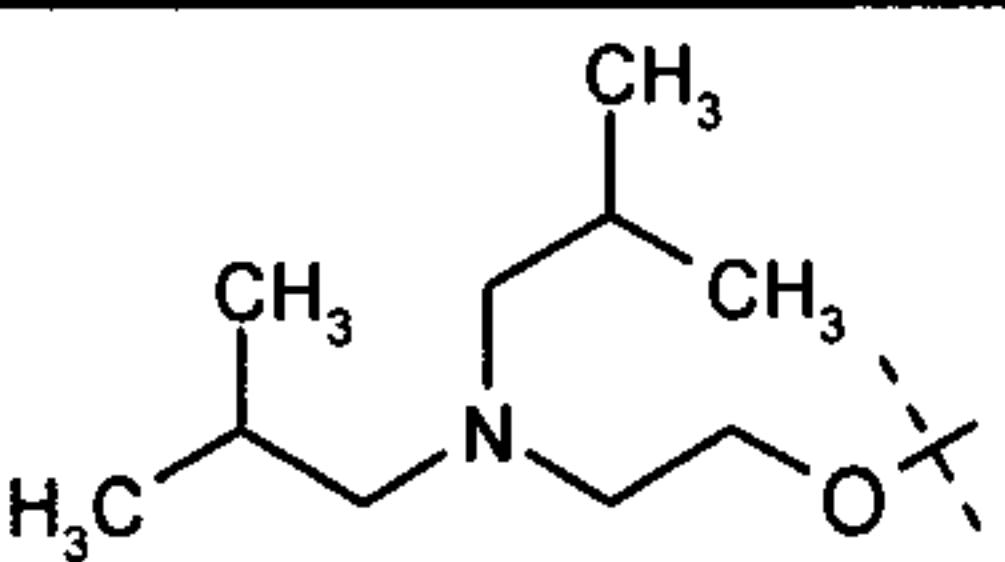
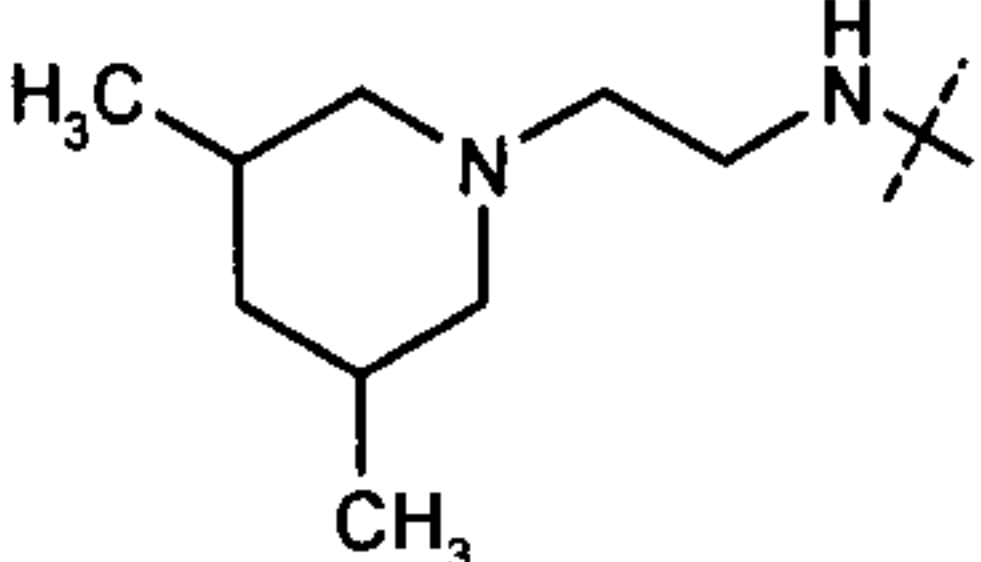
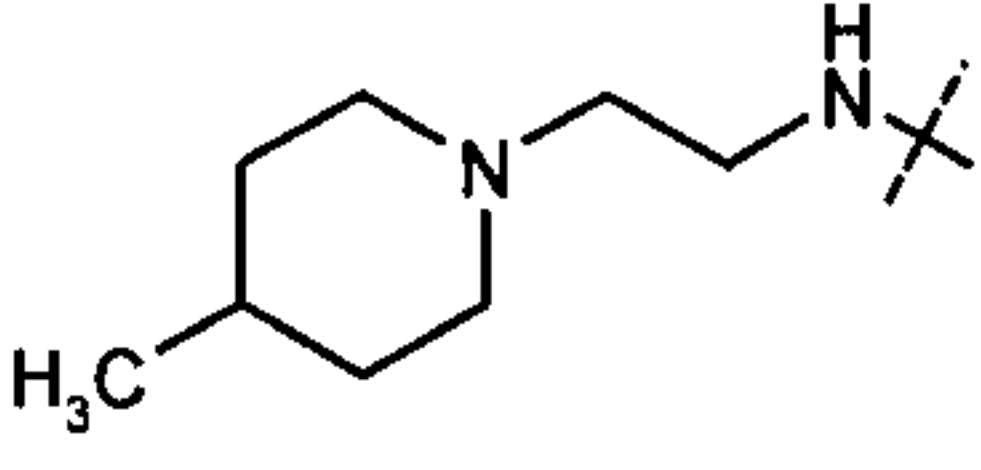
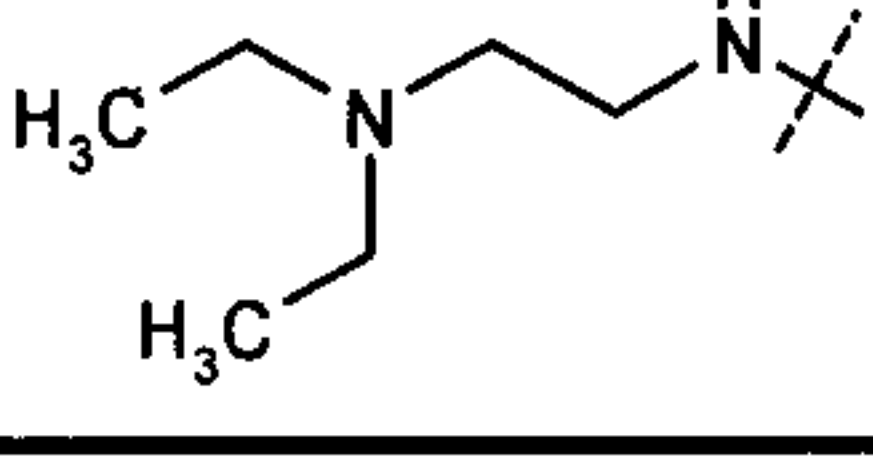
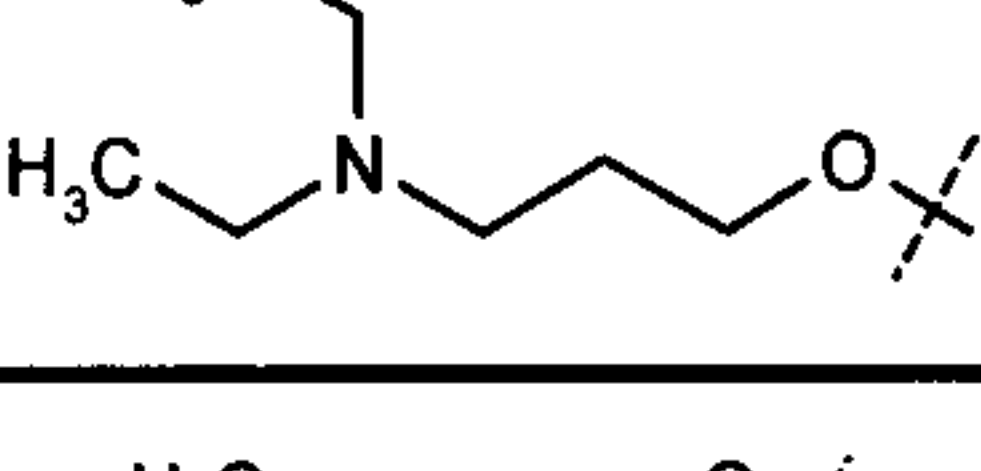
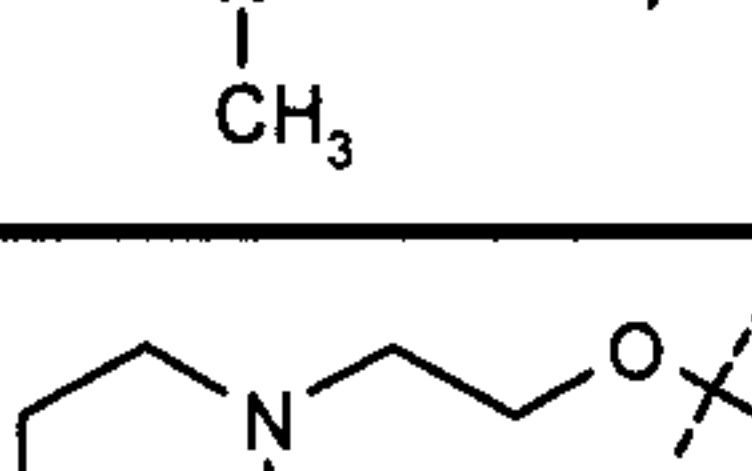
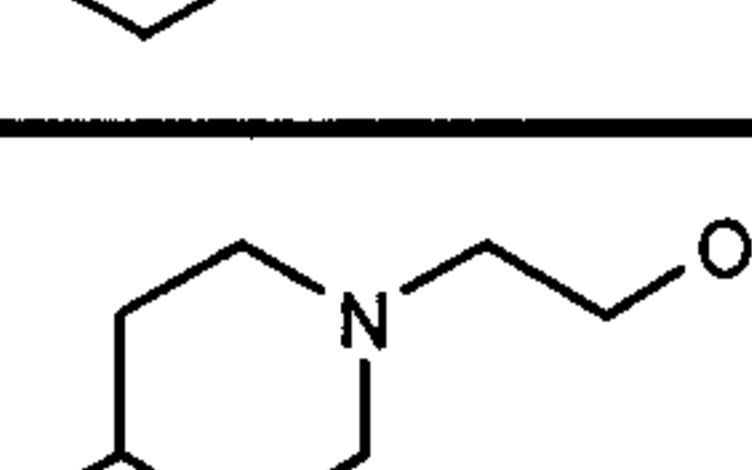
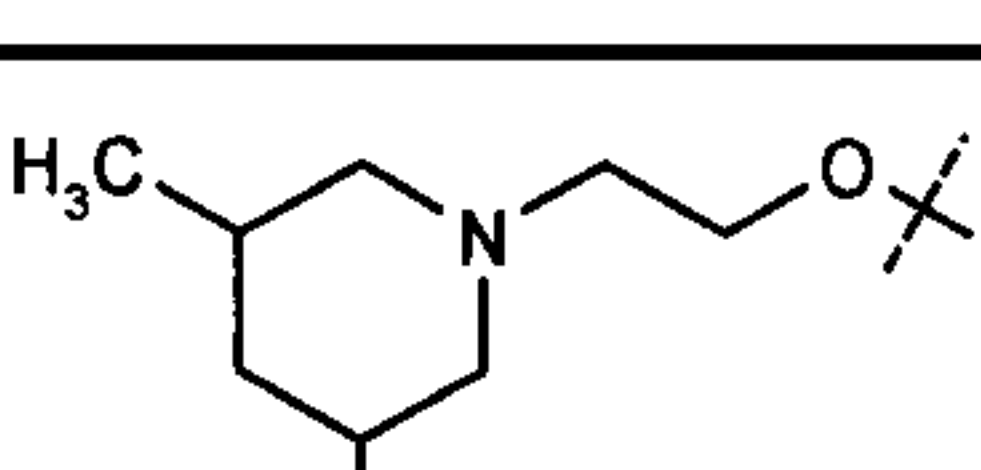
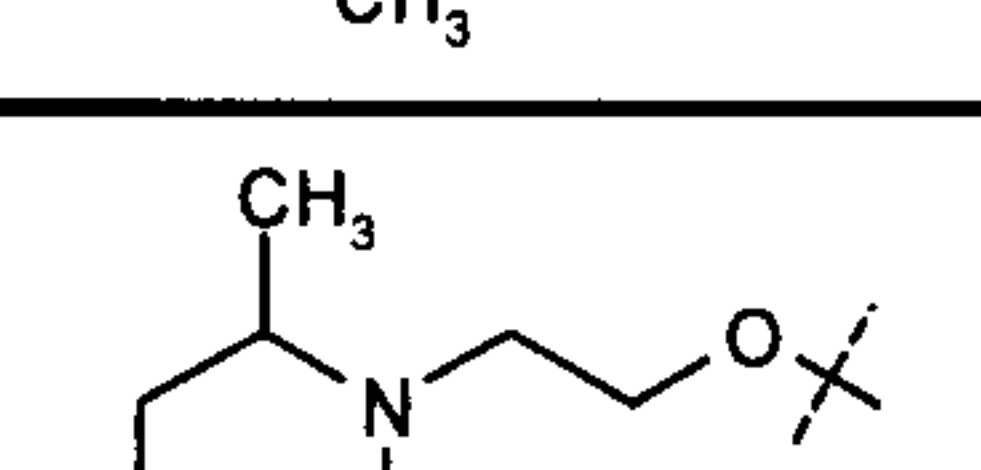
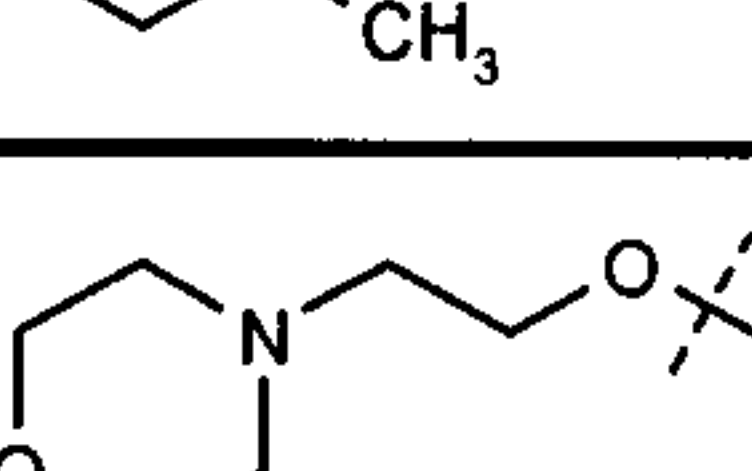
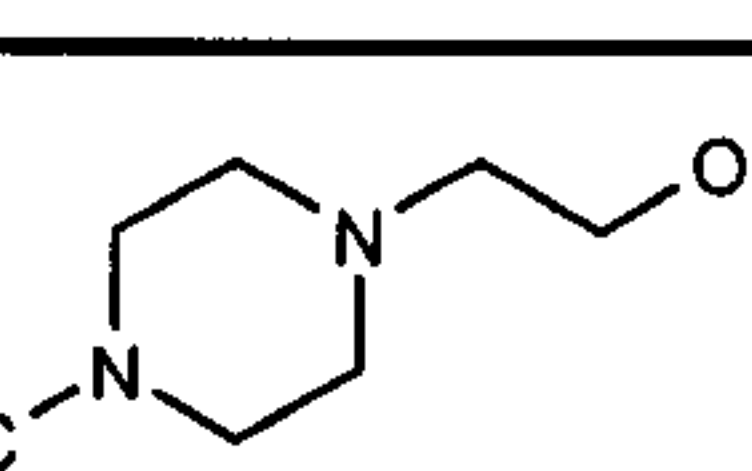
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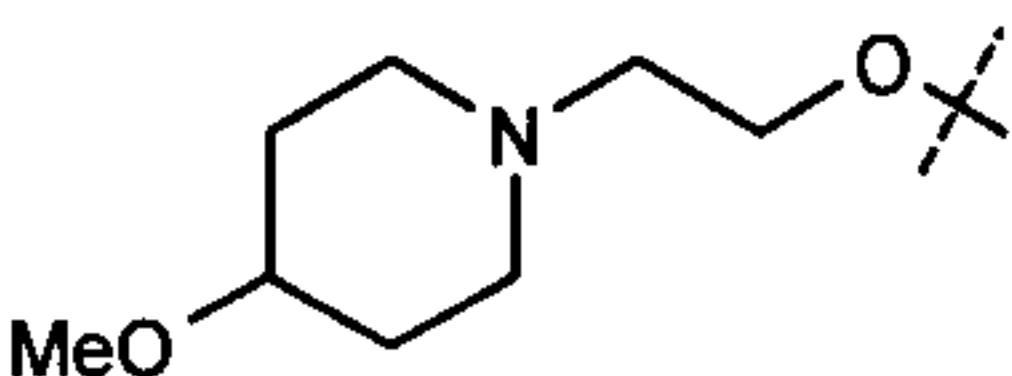
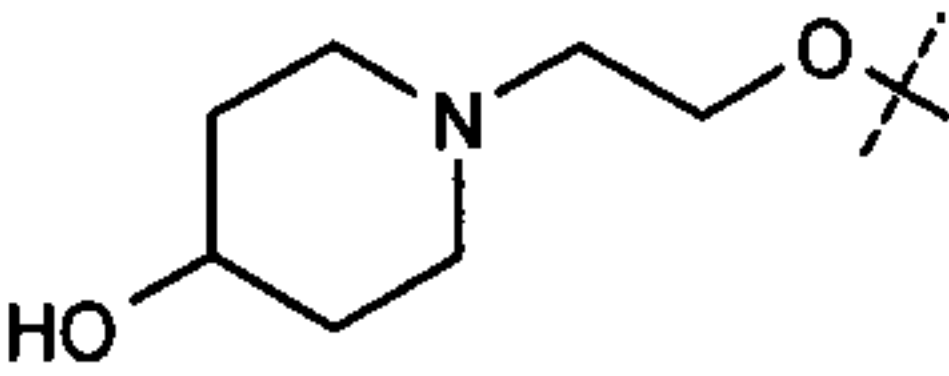
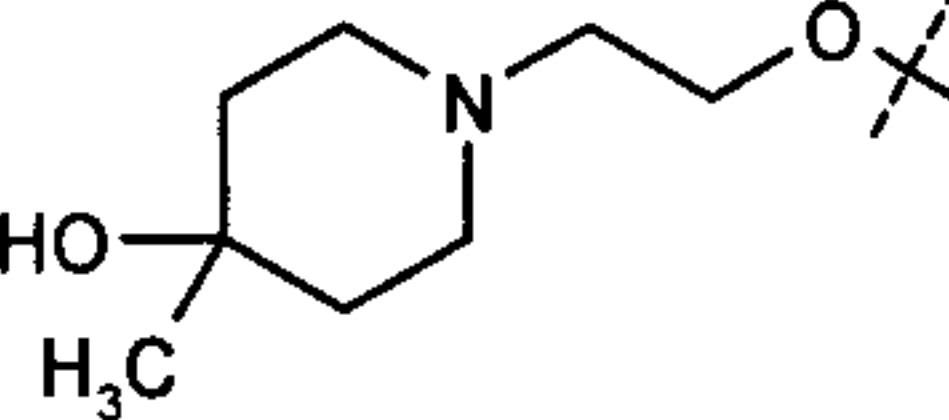
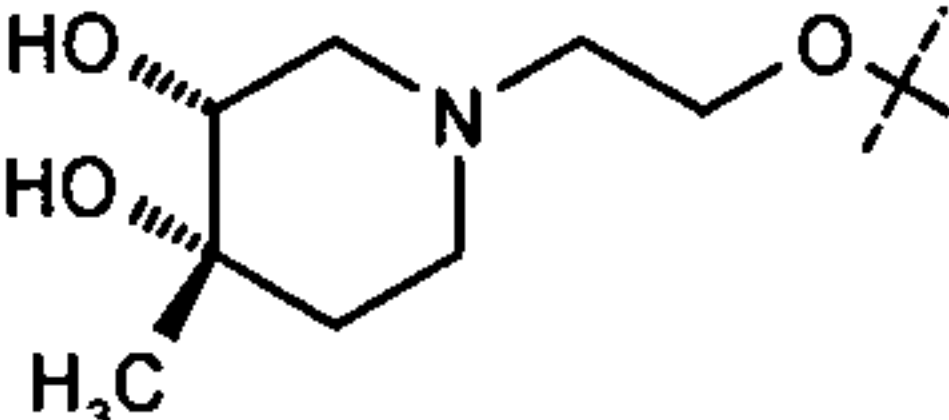
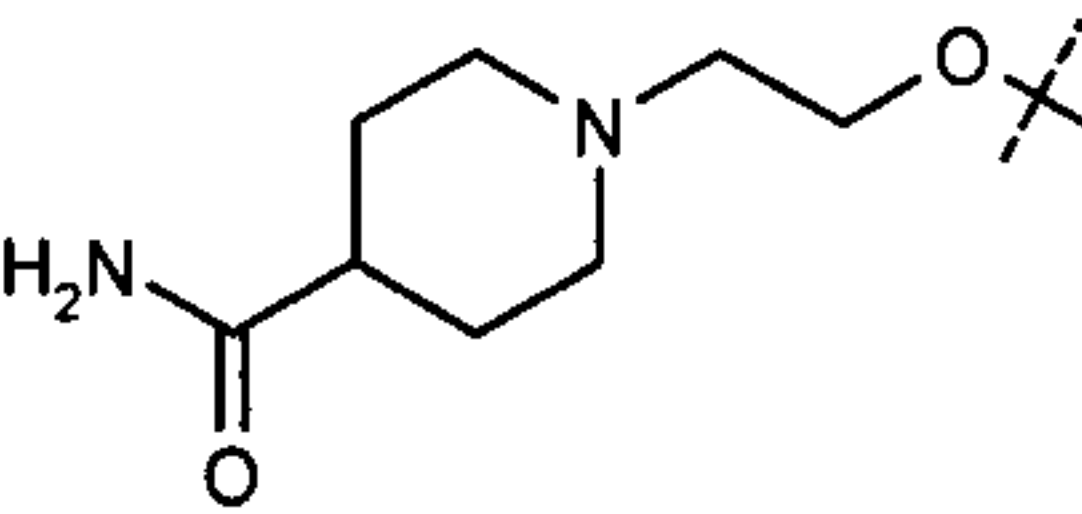
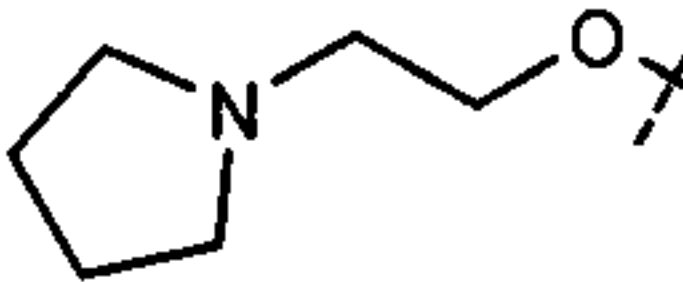
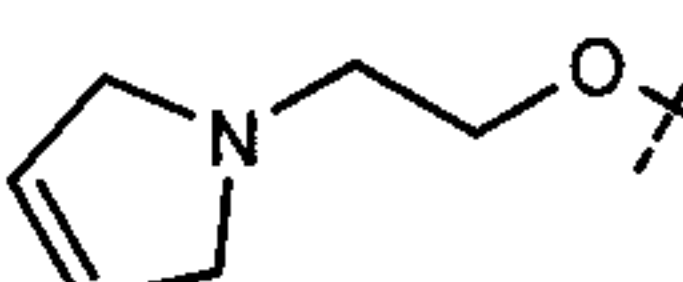
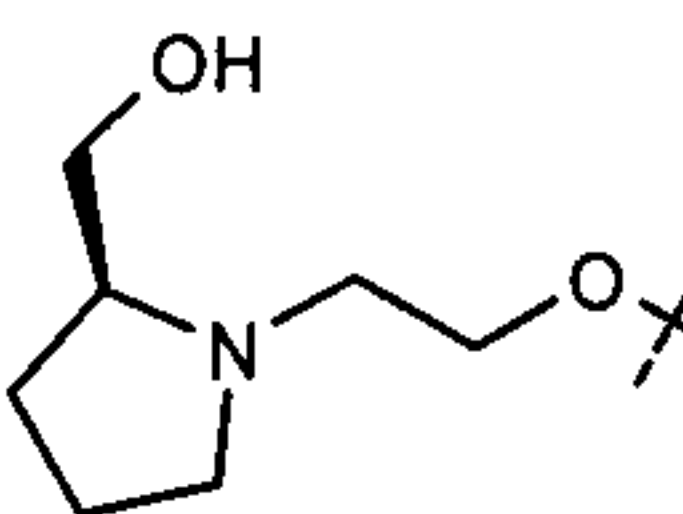
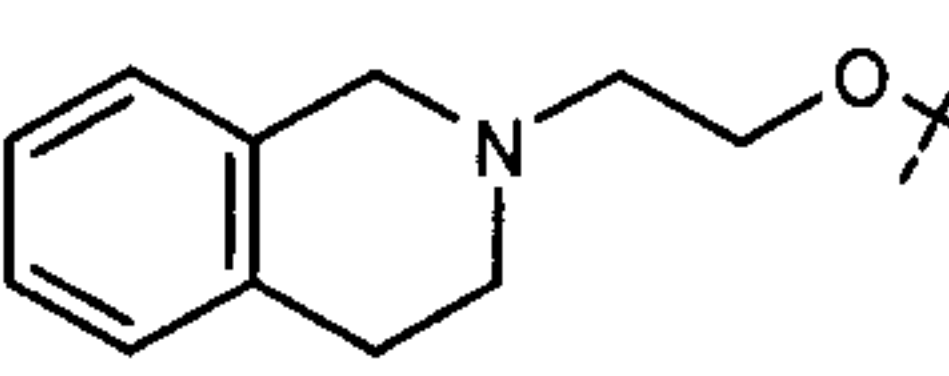
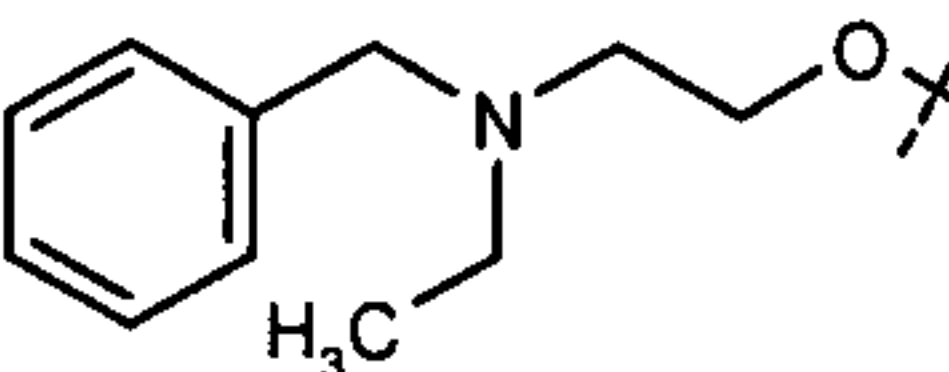
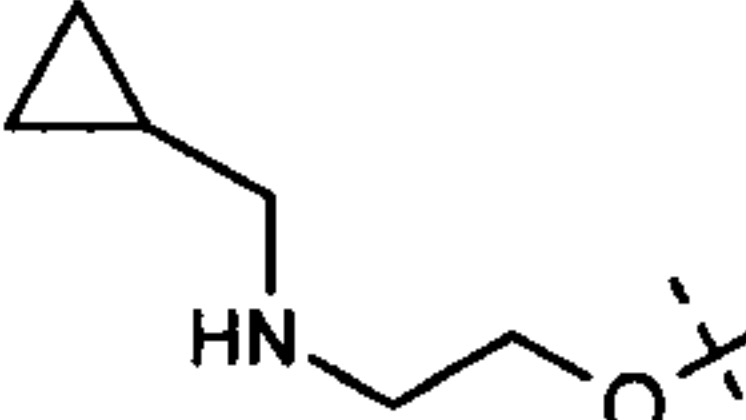
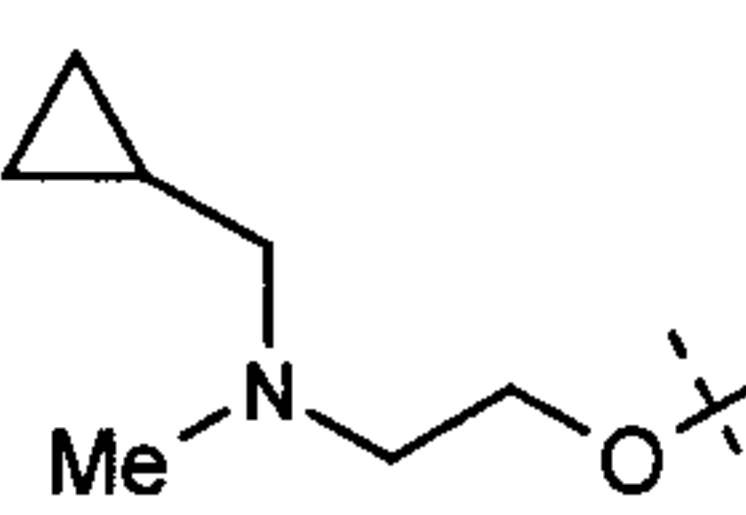
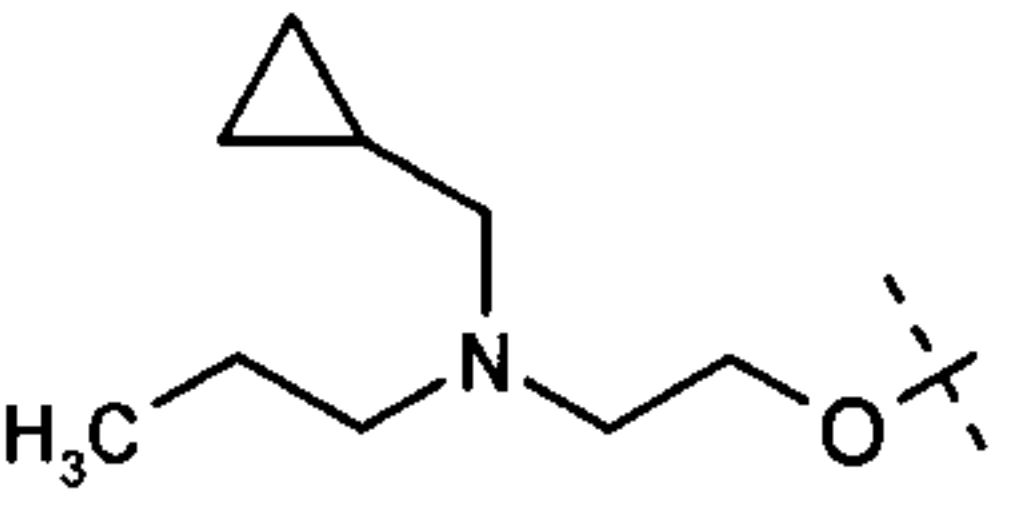
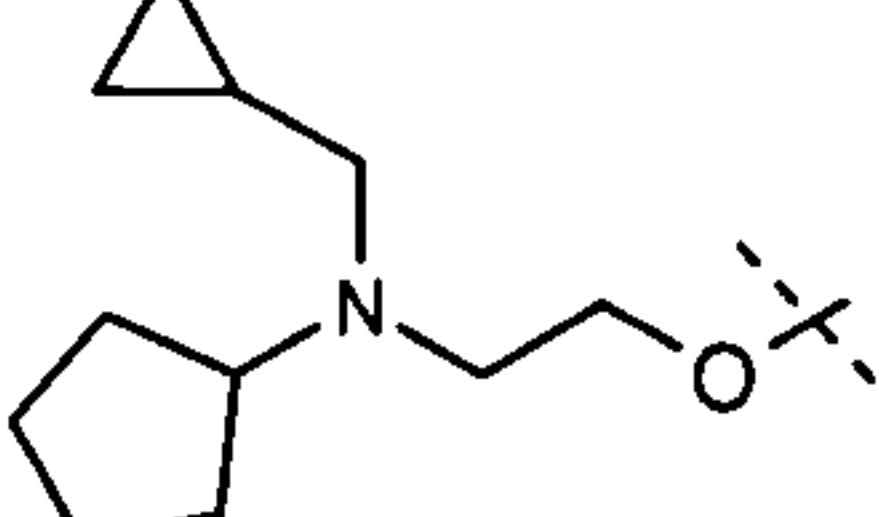
The following compounds are prepared analogously to the above-mentioned Examples:

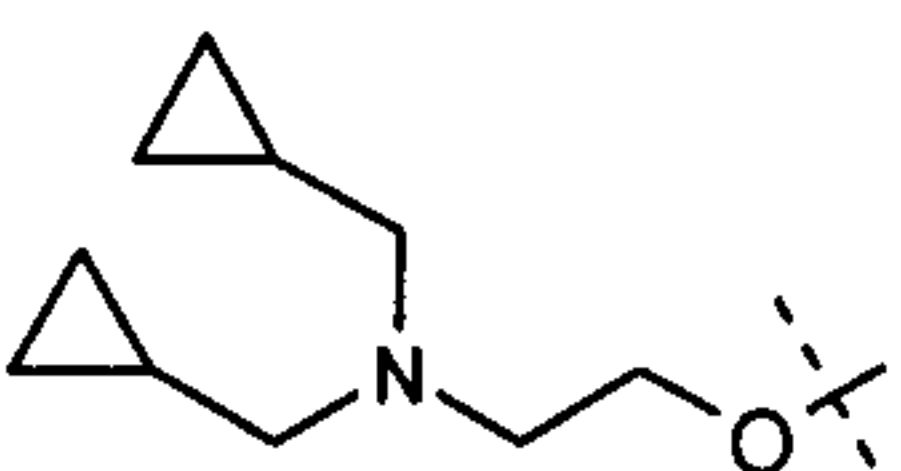
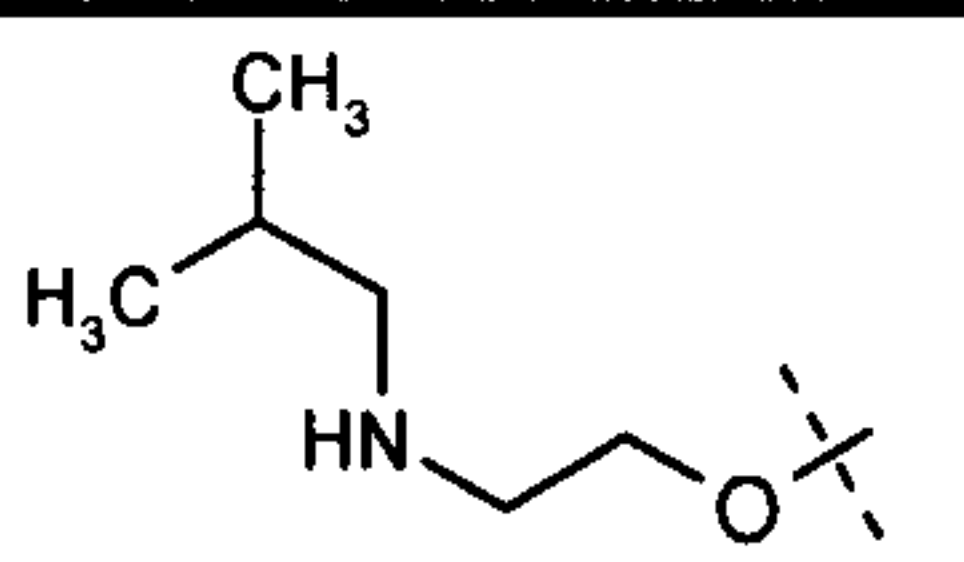
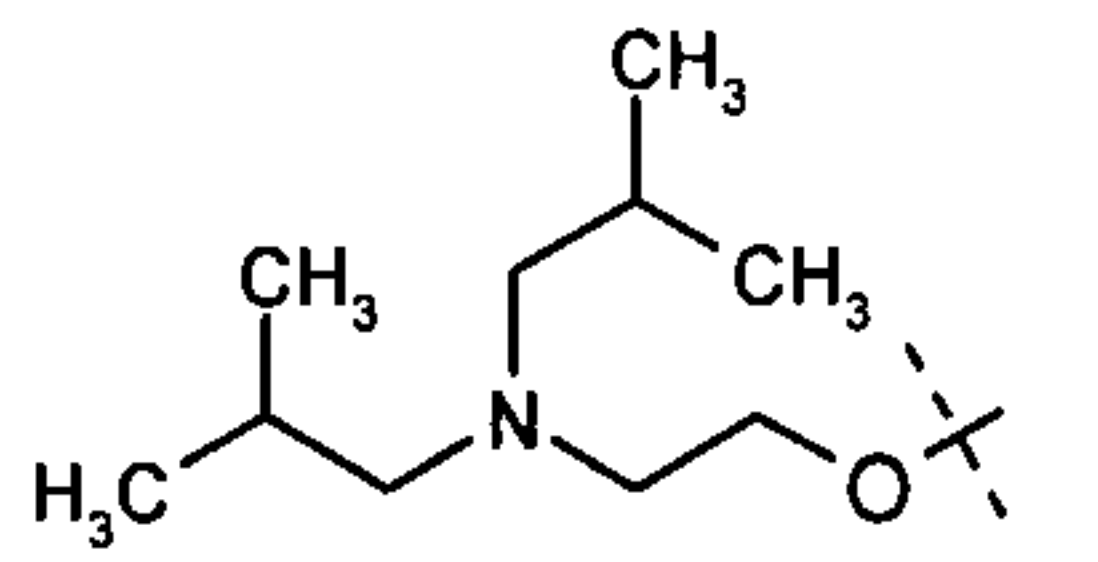
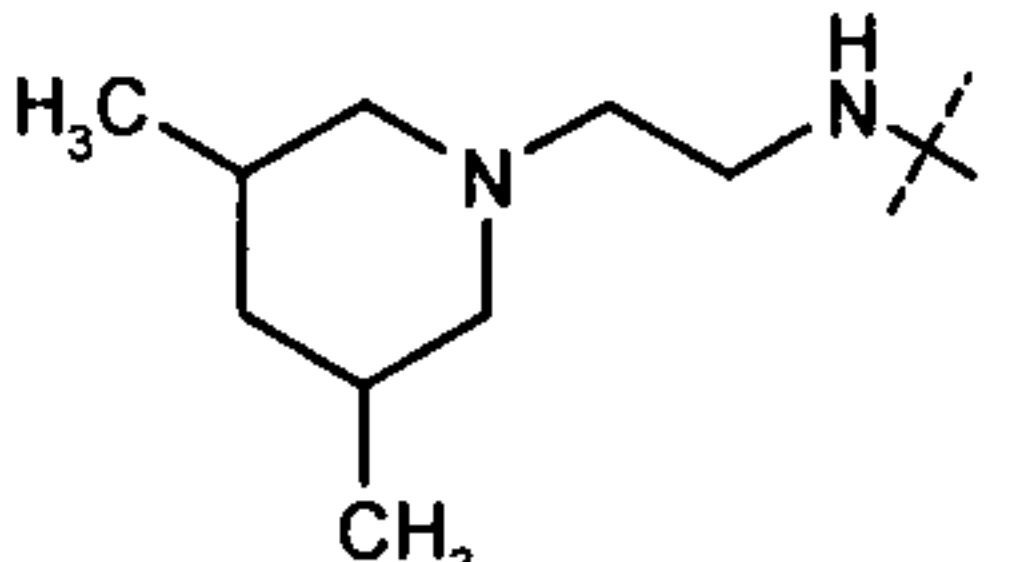
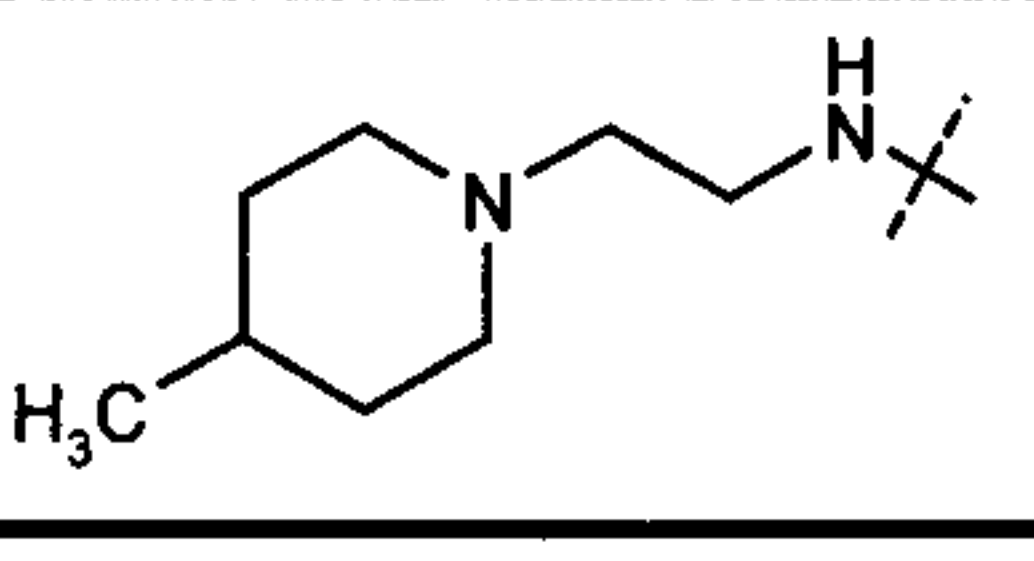
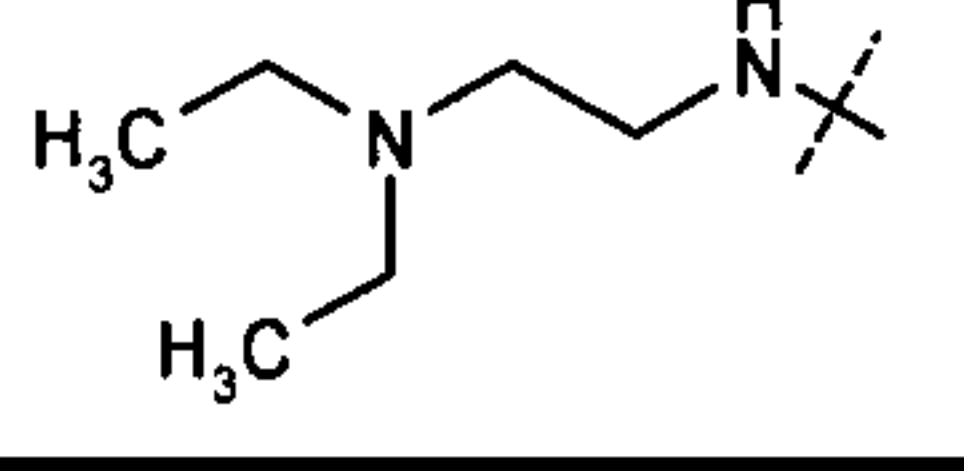
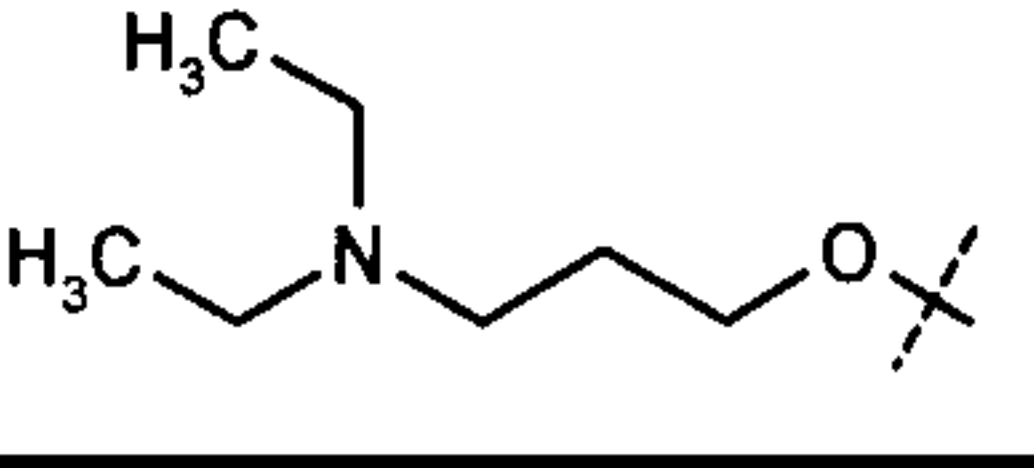
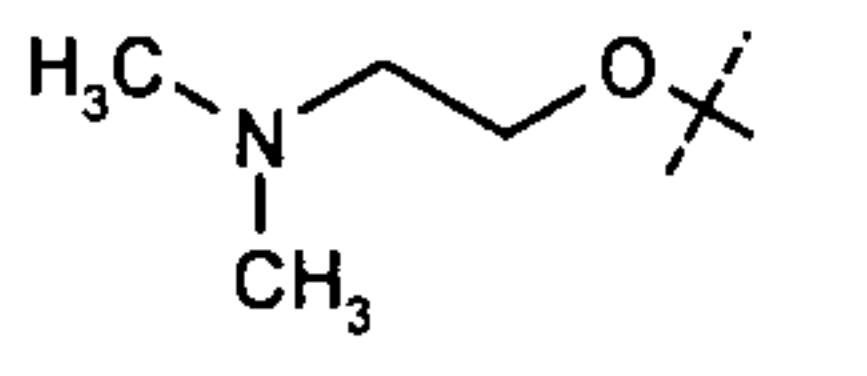
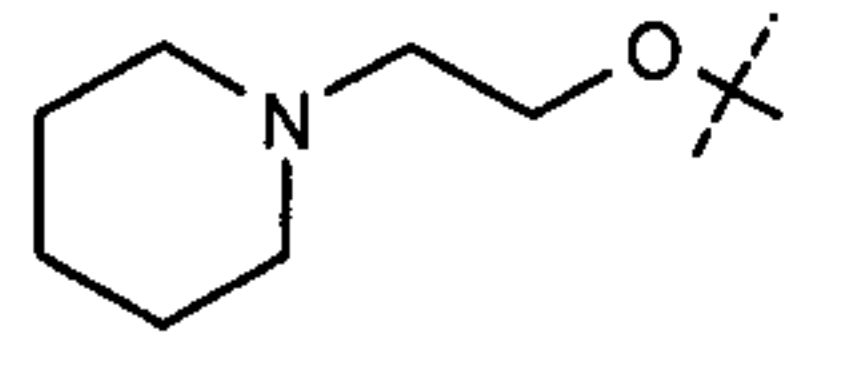
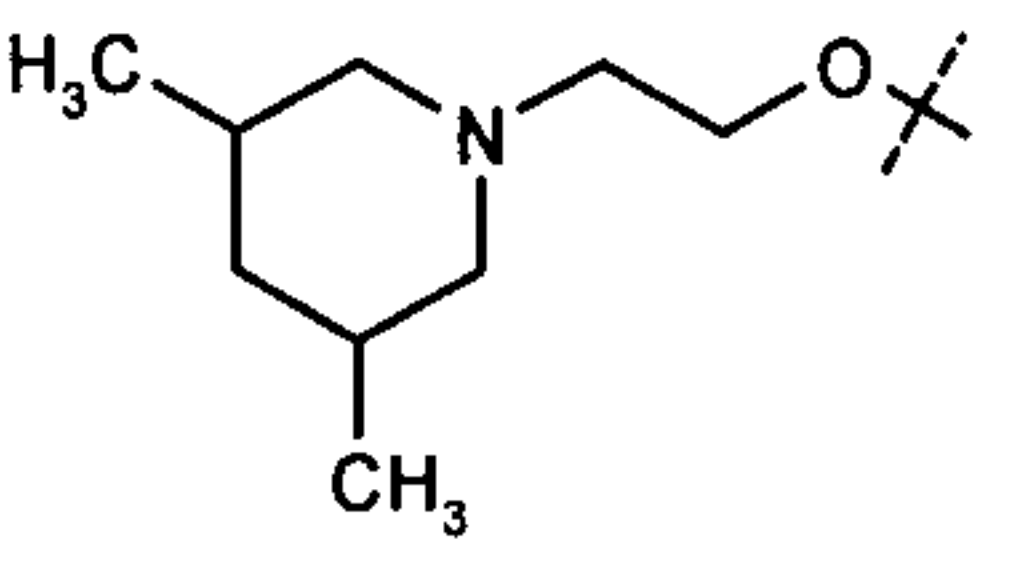
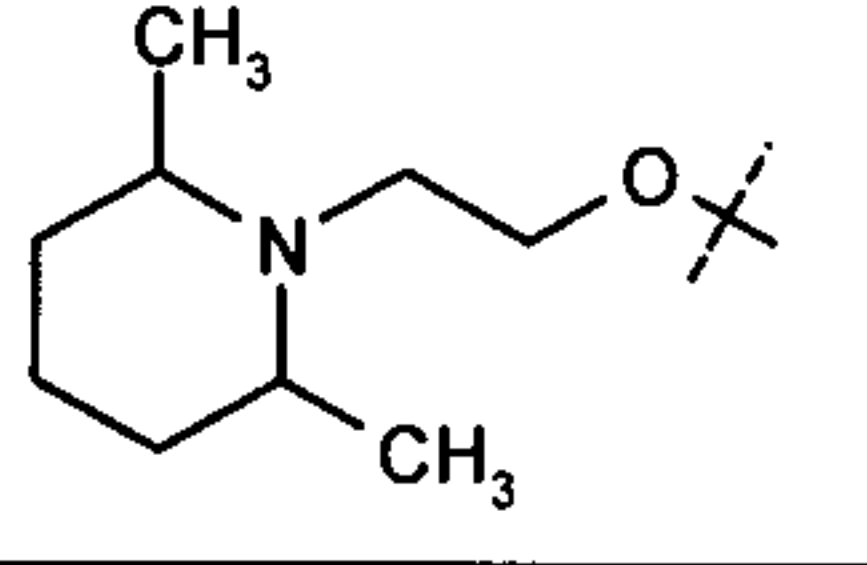
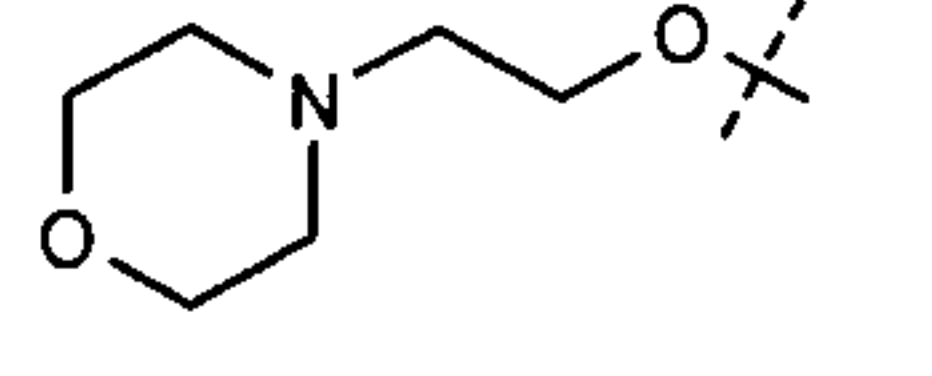
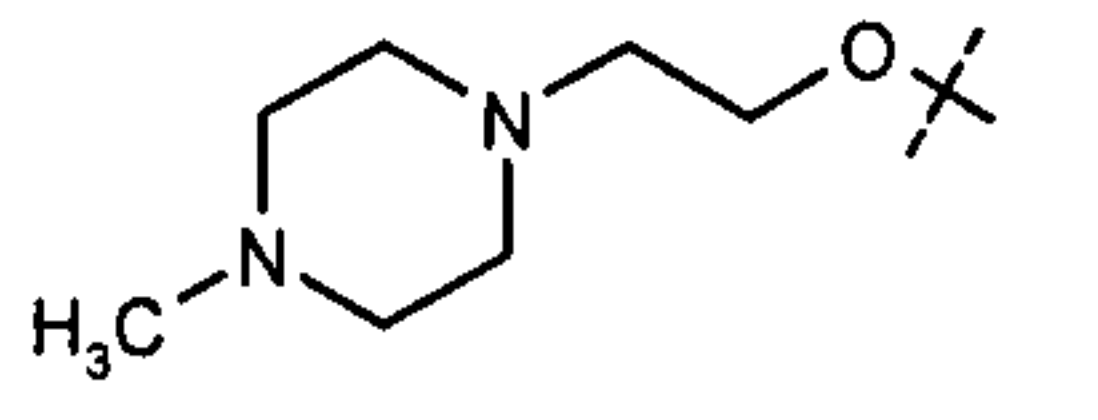
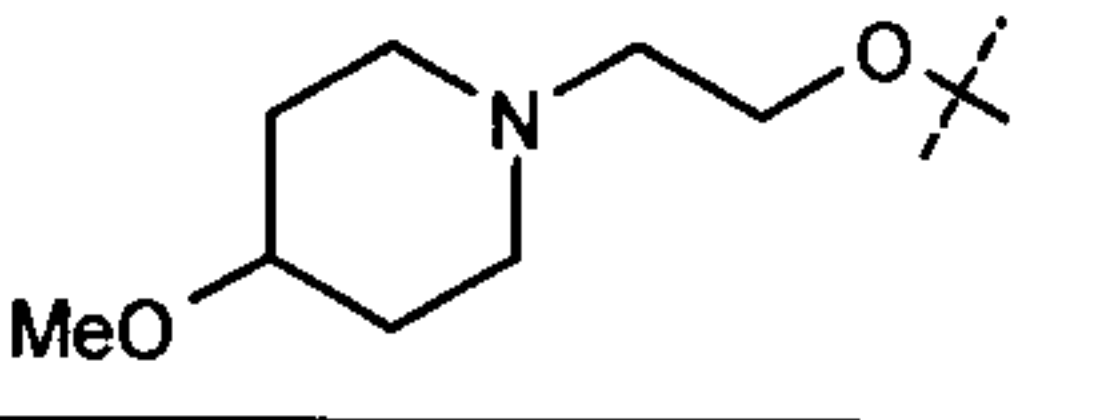


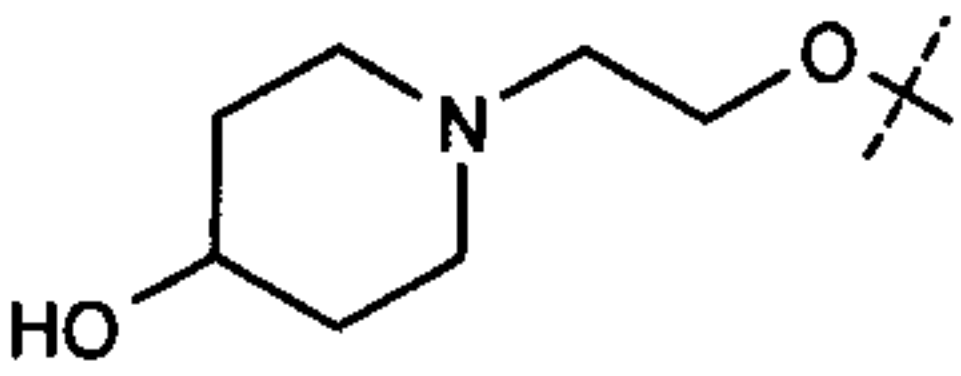
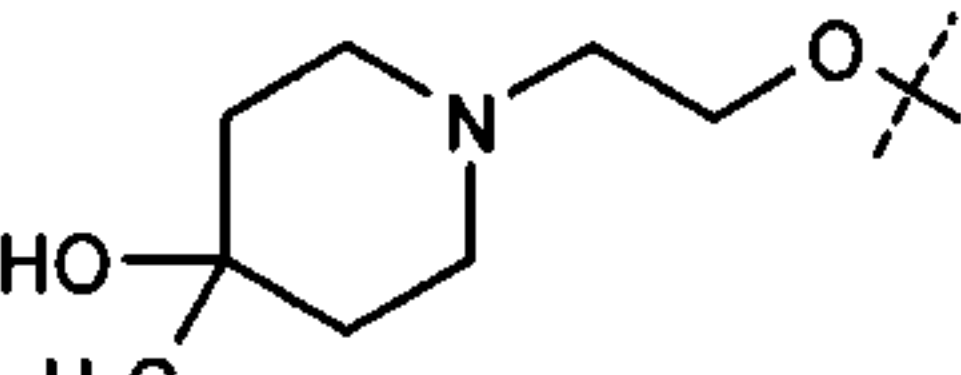
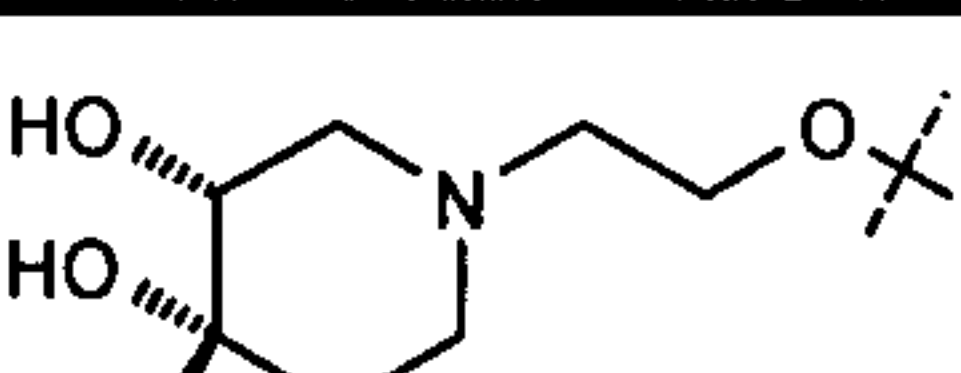
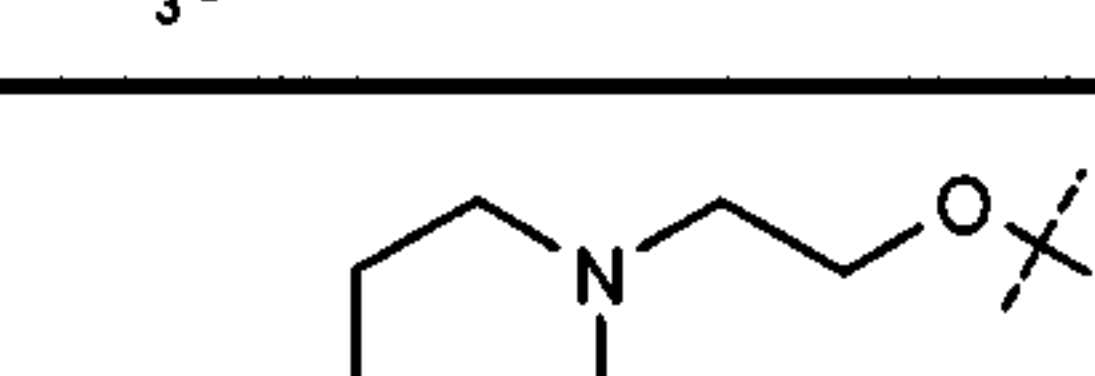
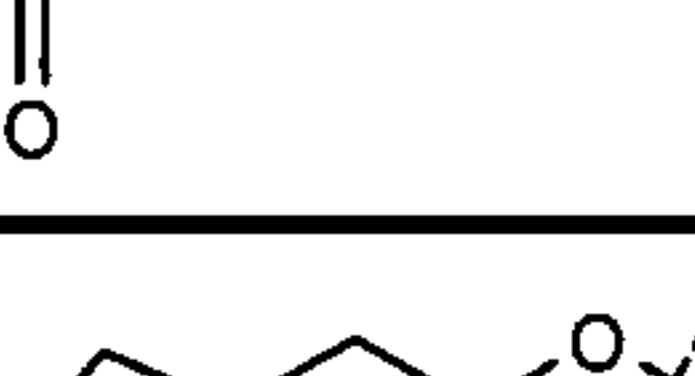
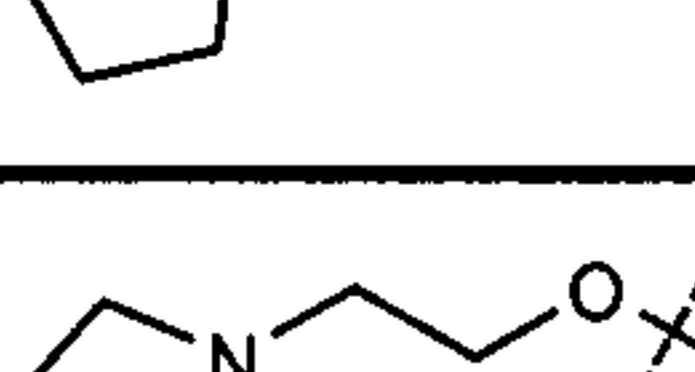
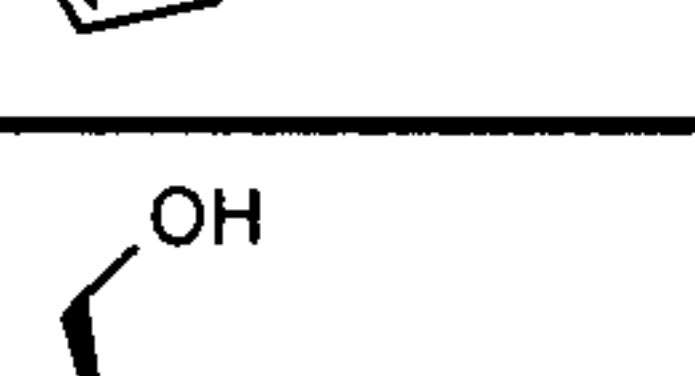
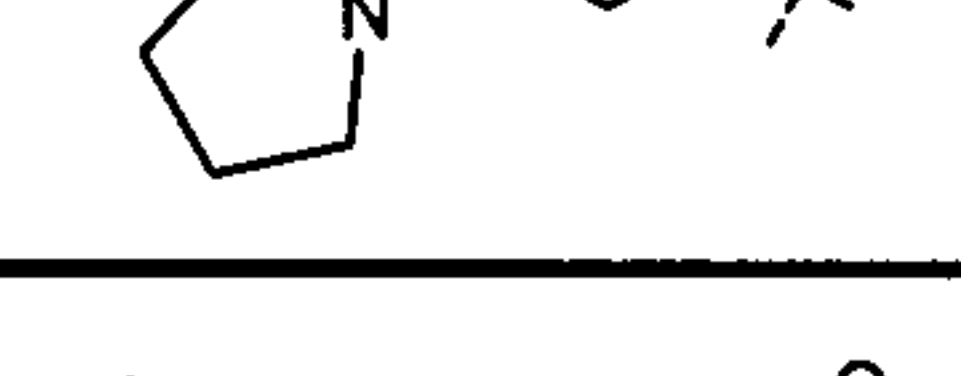
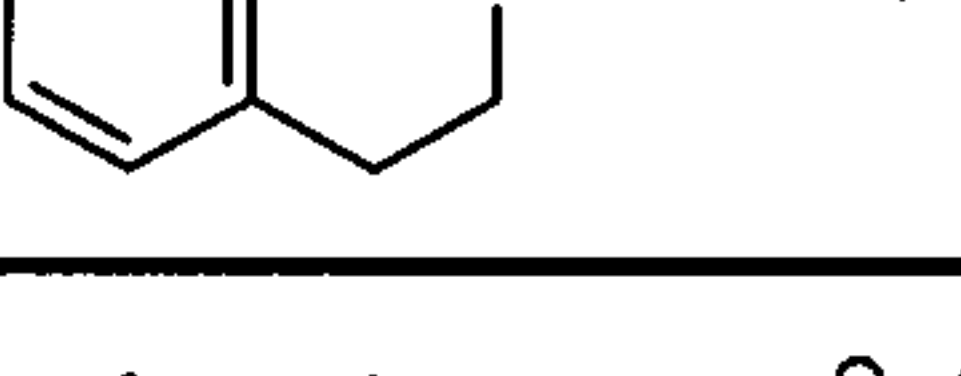
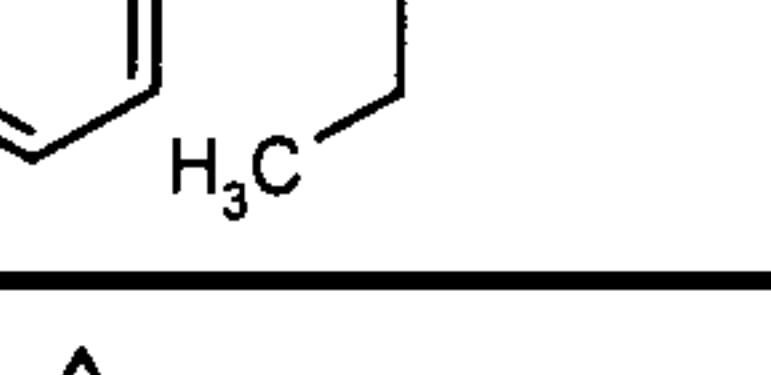
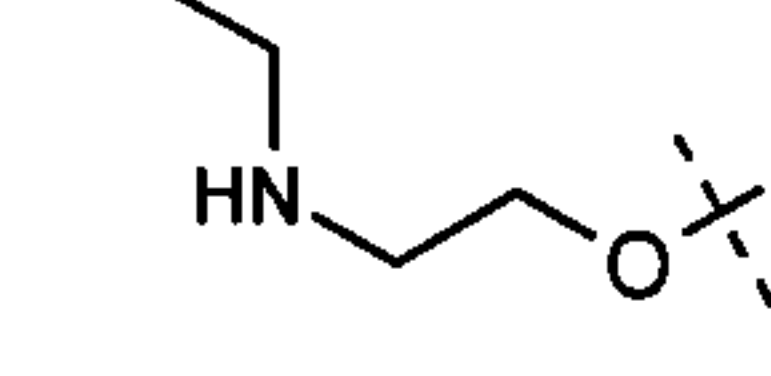
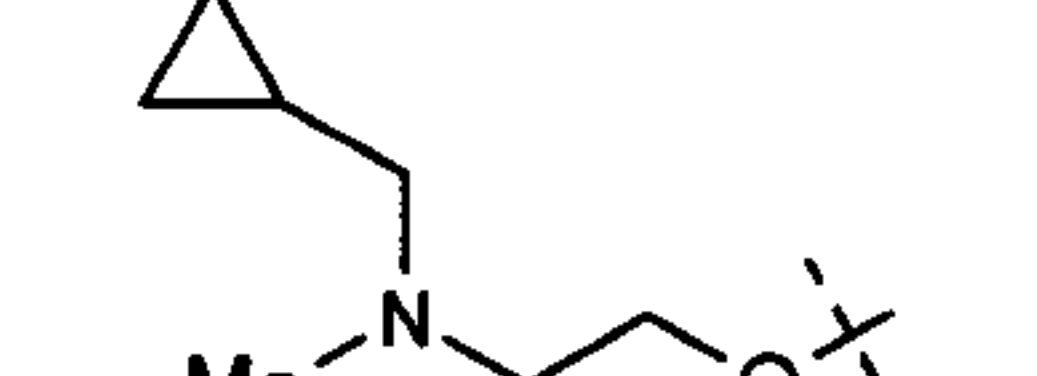
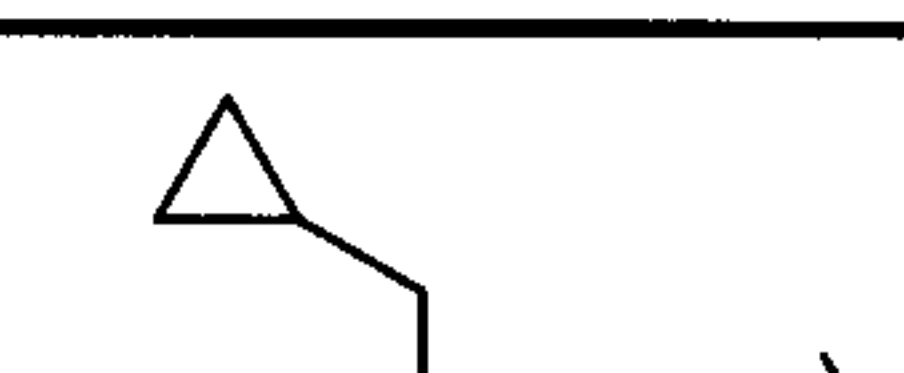
	R ₁ R ₂ N-X	L ₁	L ₂	L ₃
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4.37		-Br	-Cl	-CF ₃
4.38		-Br	-Cl	-CF ₃
4.39		-Br	-Cl	-CF ₃
4.40		-Br	-Cl	-CF ₃
4.41		-Br	-Cl	-CF ₃
4.43		-Br	-Cl	-CF ₃
4.44		-Br	-Cl	-CF ₃

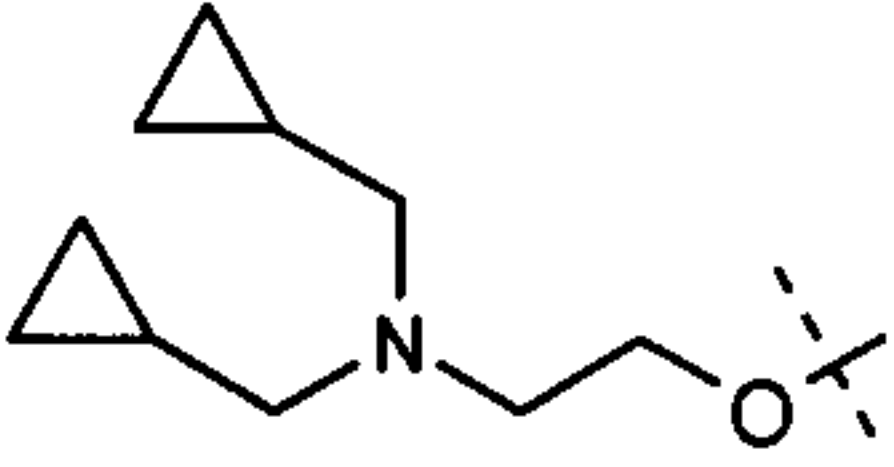
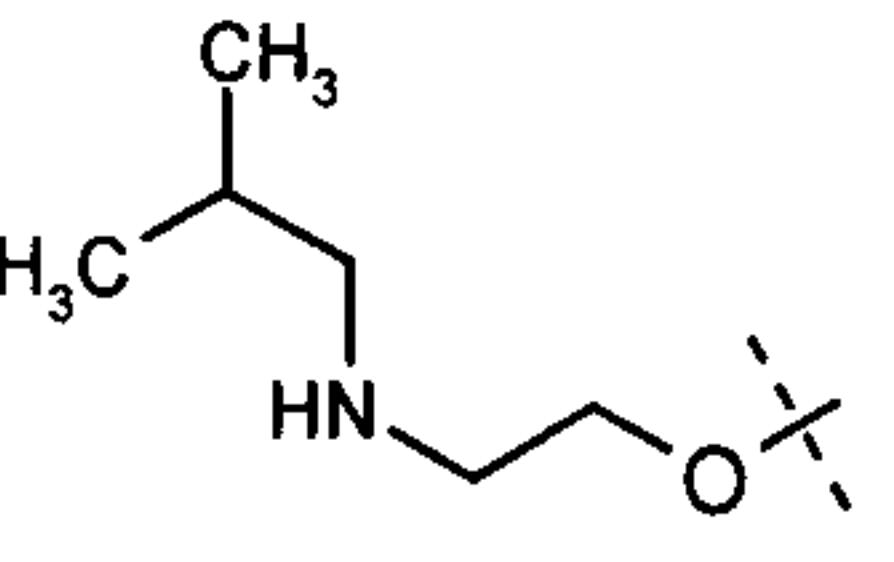
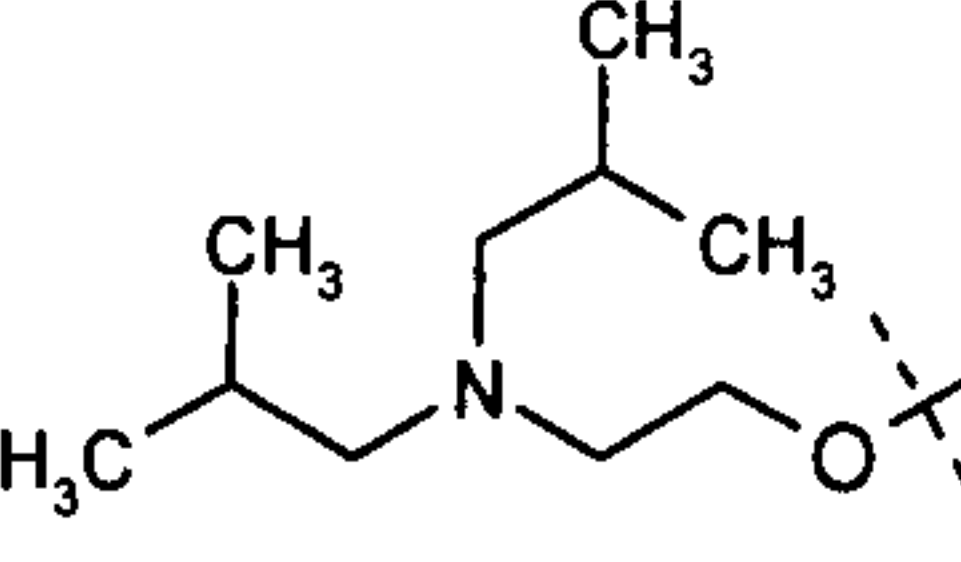
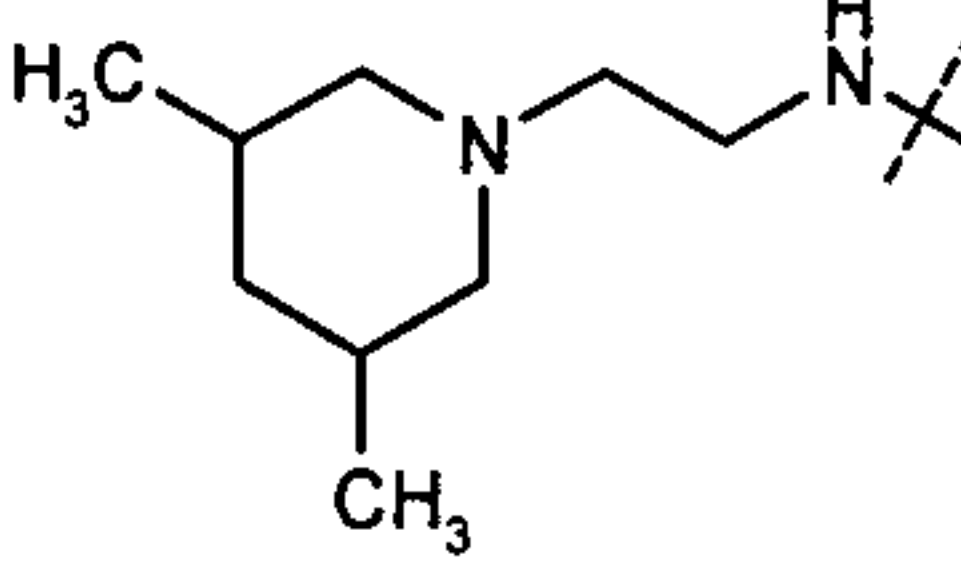
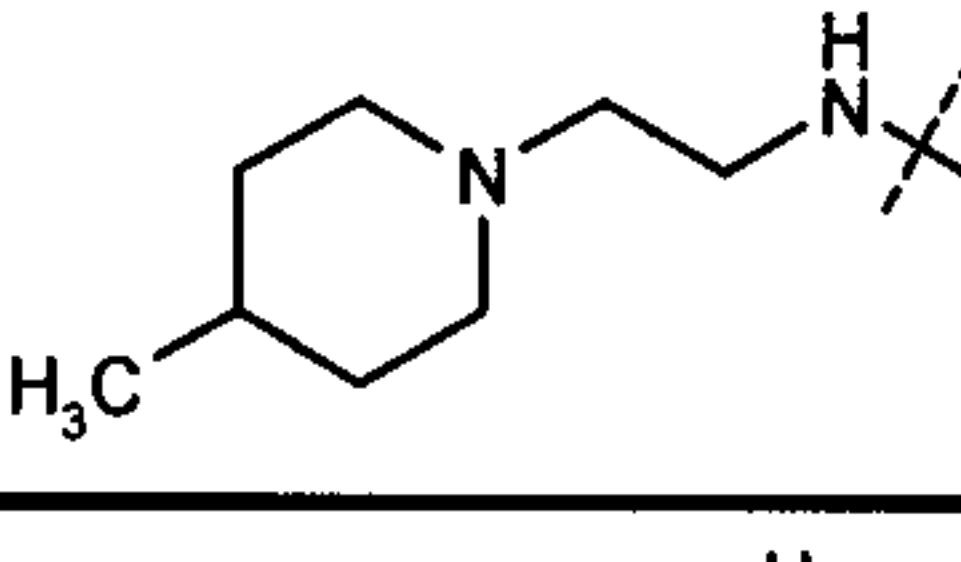
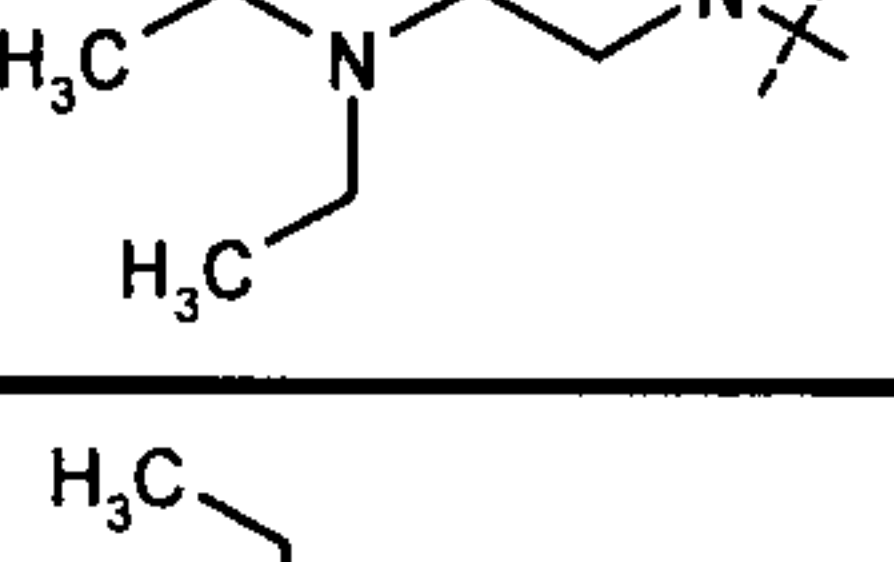
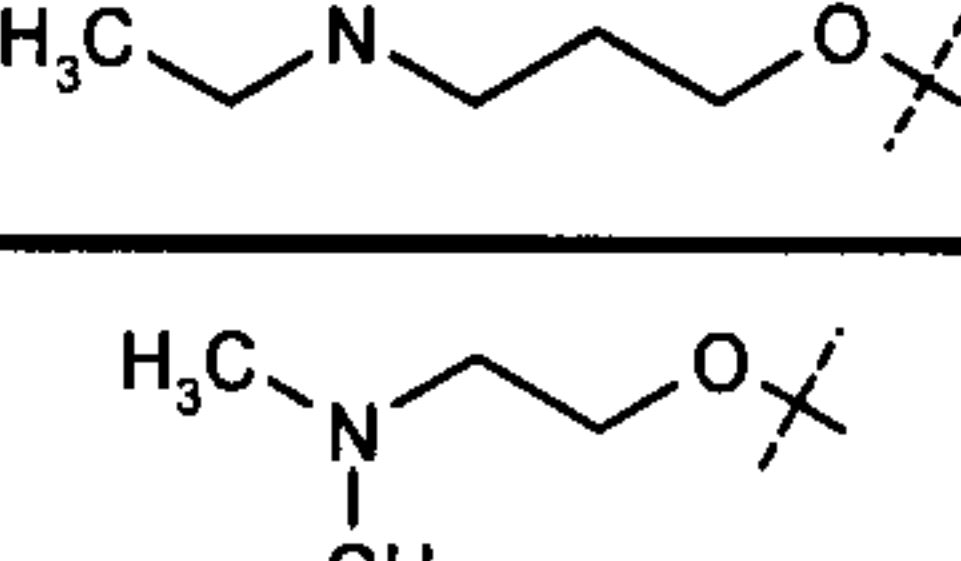
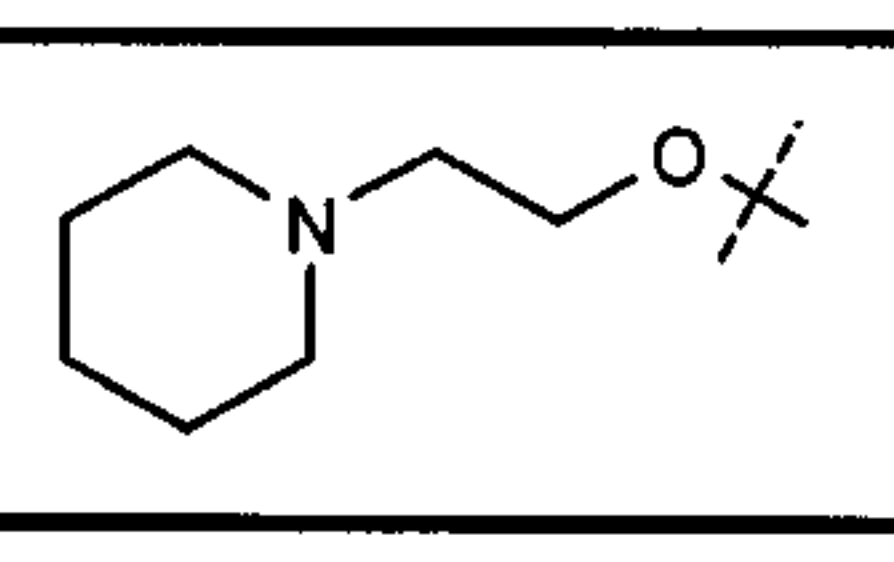
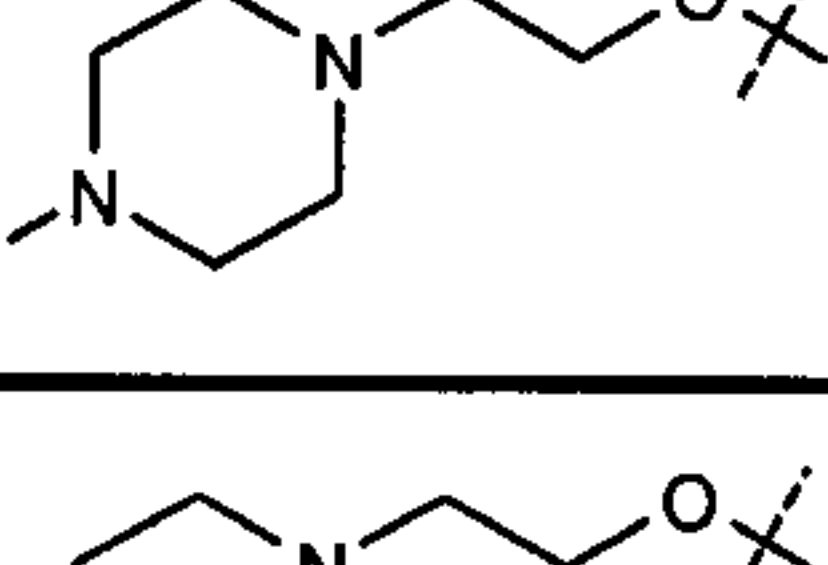
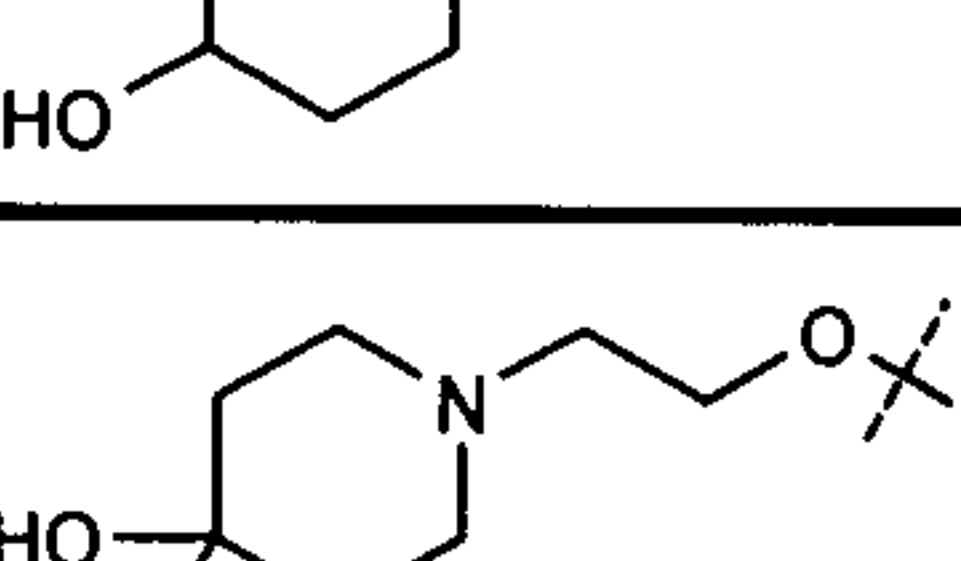
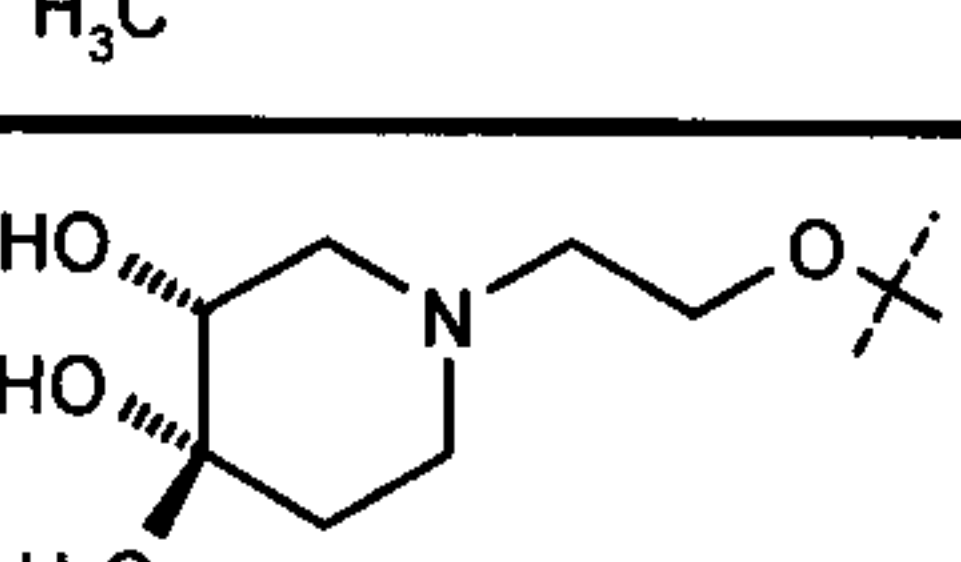
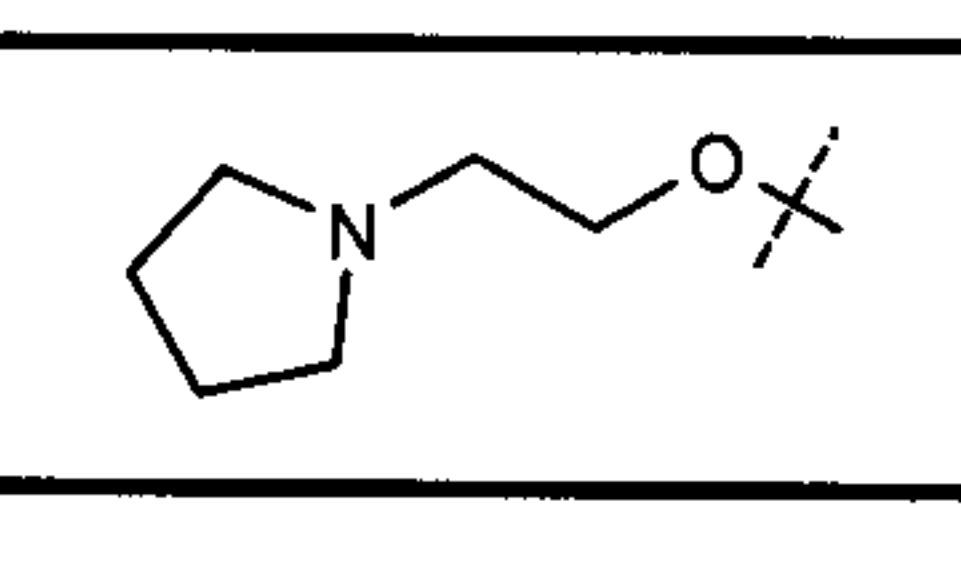
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4.46		-Br	-Cl	-CF ₃
4.47		-Br	-Cl	-CF ₃
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4.49		-Br	-Cl	-CF ₃
4.50		-Br	-Cl	-CF ₃
4.51		-Br	-Cl	-CF ₃
4.52		-Br	-Cl	-CF ₃
4.53		-Br	-Cl	-CF ₃
4.54		-Br	-Cl	-CF ₃
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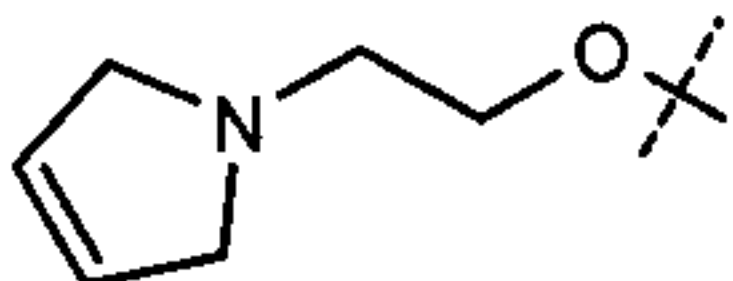
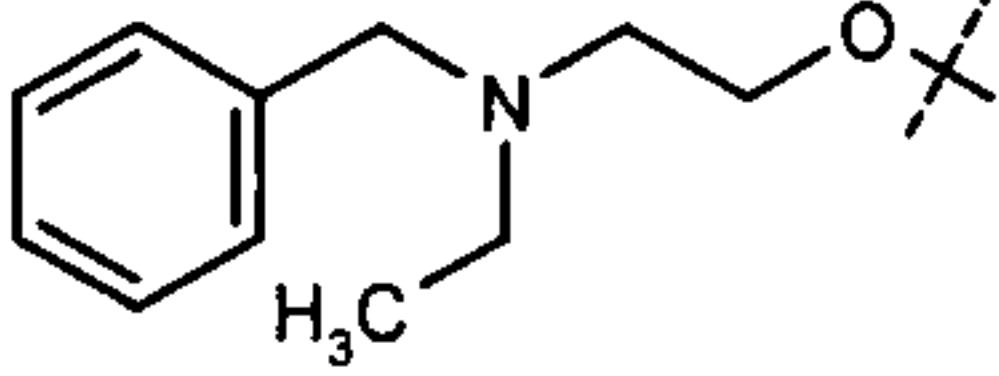
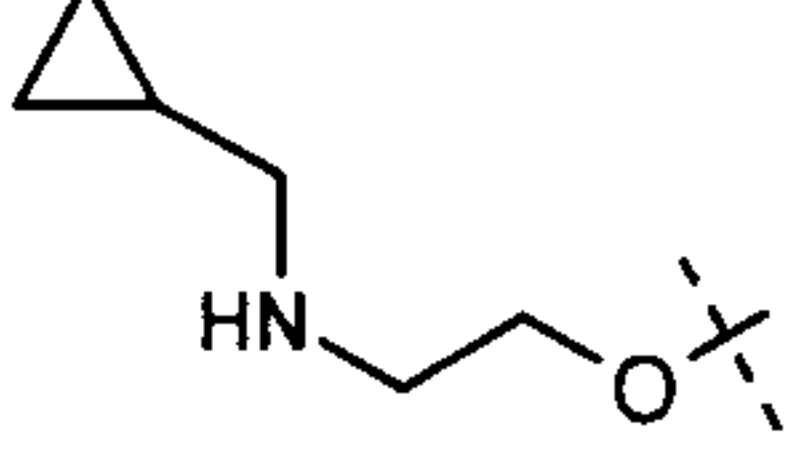
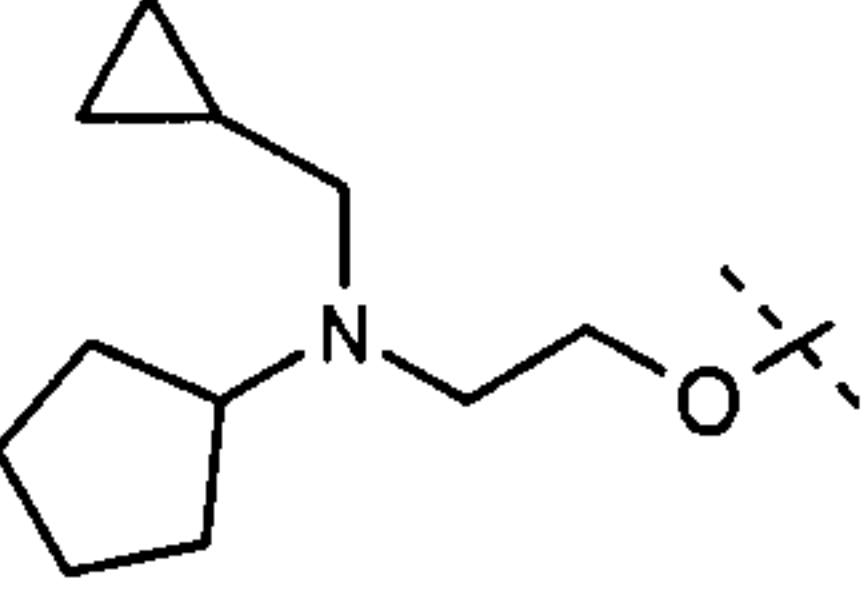
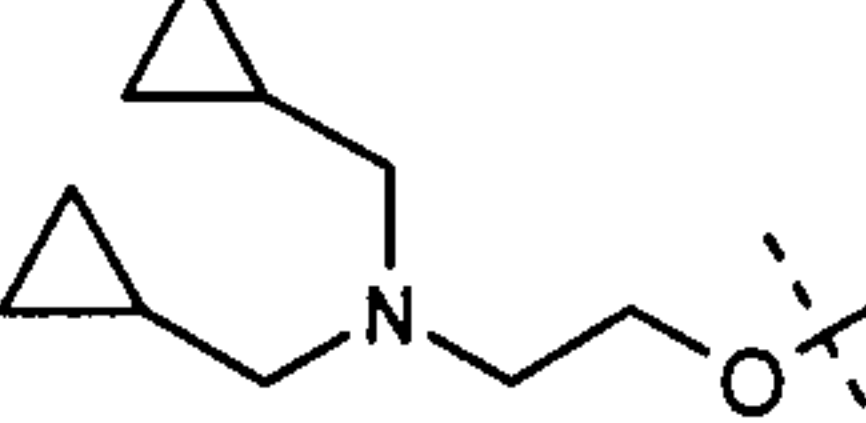
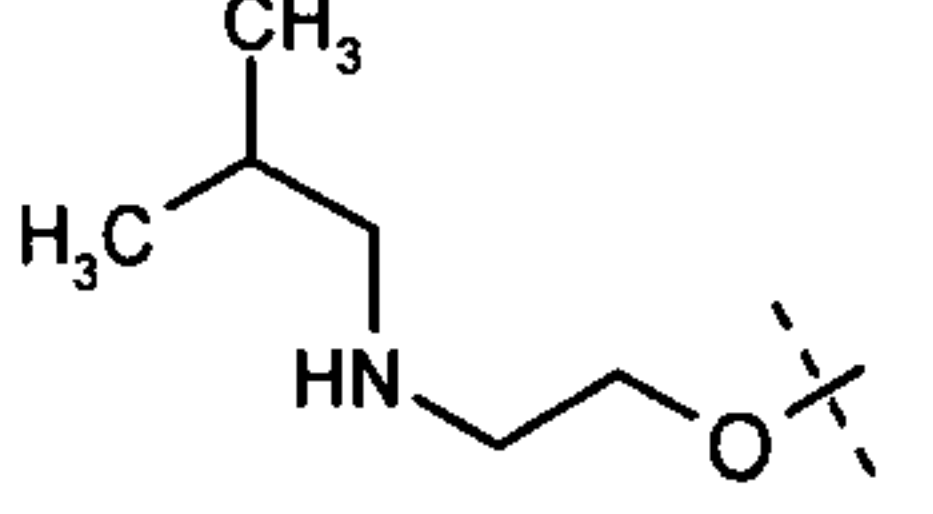
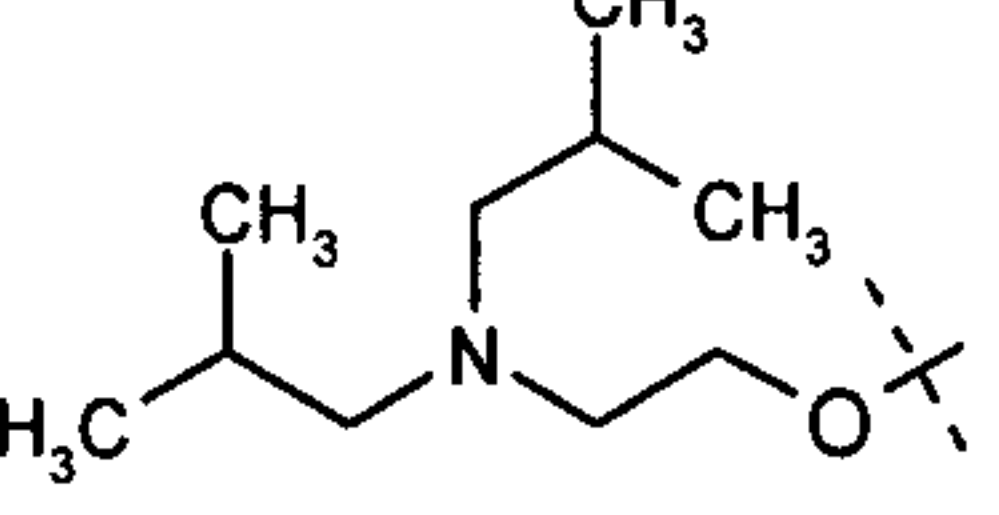
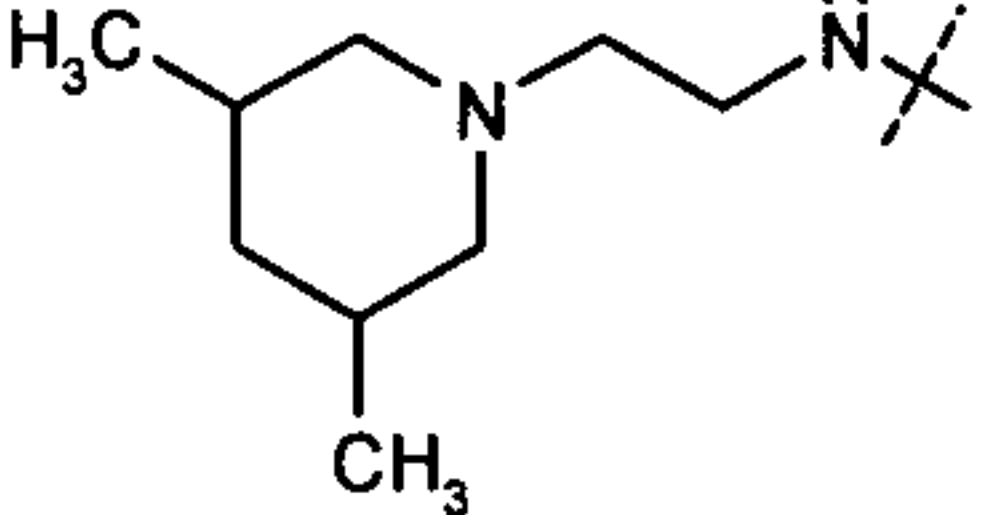
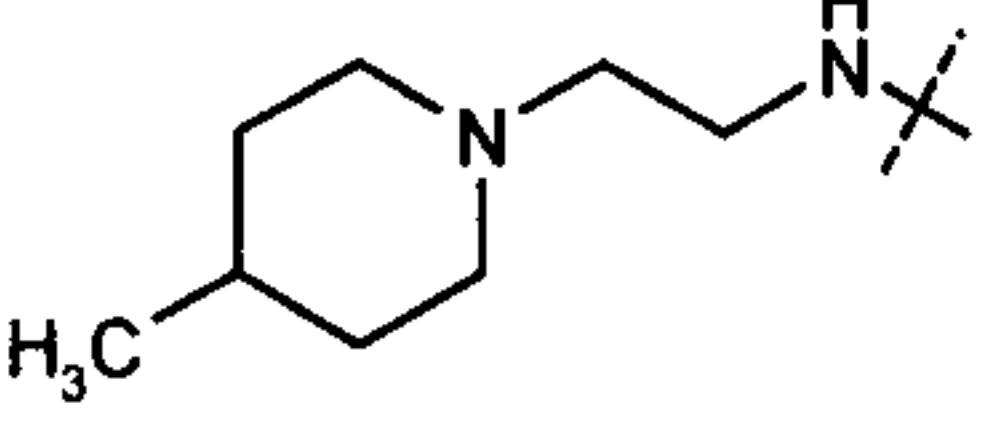
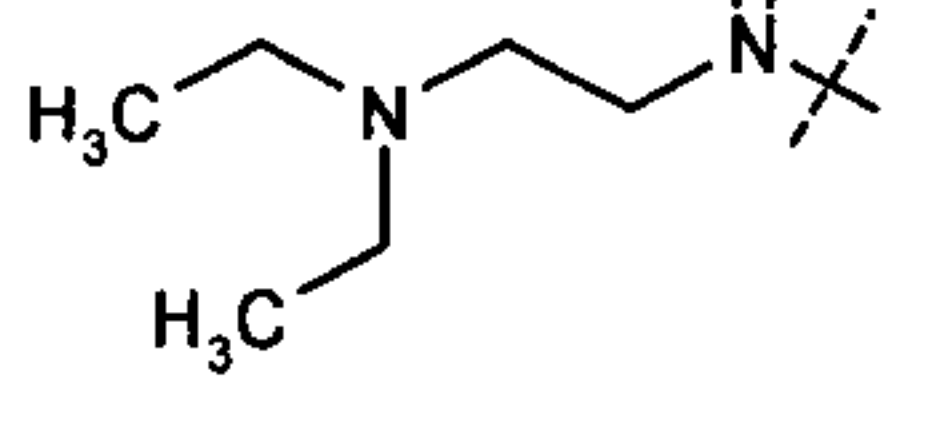
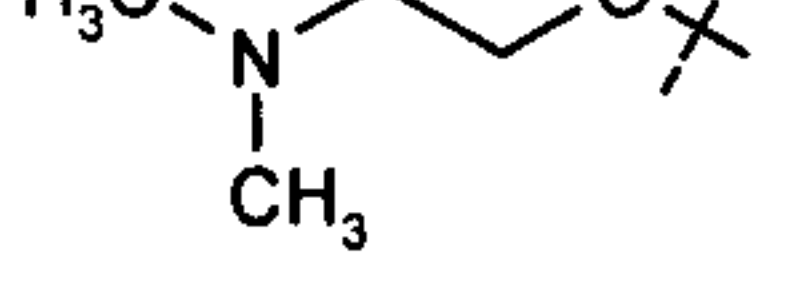
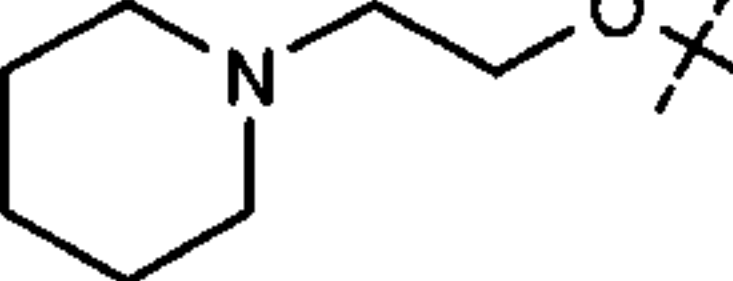
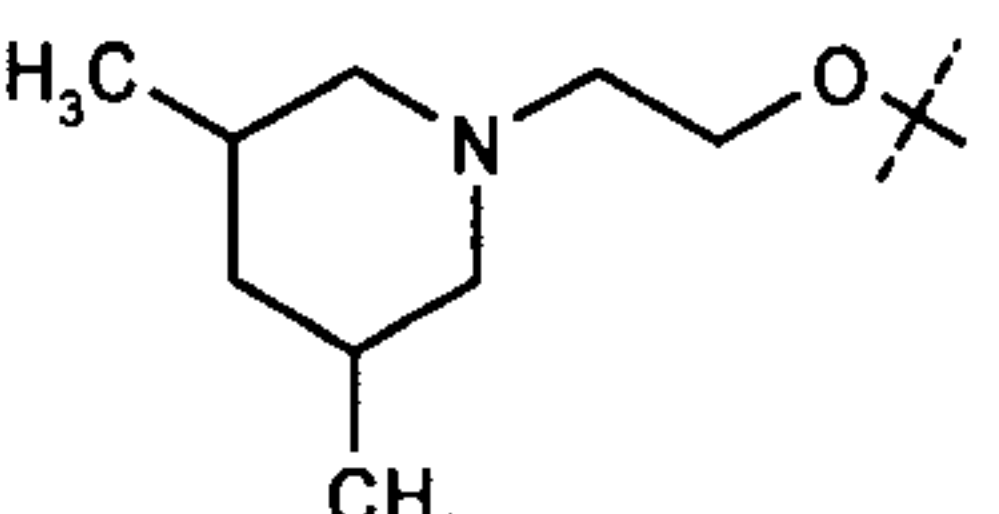
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4.59		-Br	-Cl	-CF ₃
4.60		-Br	-Cl	-CF ₃
4.61		-Br	-Cl	-CF ₃
4.62		-Br	-Cl	-CF ₃
4.63		-Br	-Cl	-CF ₃
4.64		-CH ₃	-Cl	-CF ₃
4.65		-CH ₃	-Cl	-CF ₃
4.66		-CH ₃	-Cl	-CF ₃
4.67		-CH ₃	-Cl	-CF ₃
4.68		-CH ₃	-Cl	-CF ₃
4.69		-CH ₃	-Cl	-CF ₃
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4.71		-CH ₃	-Cl	-CF ₃

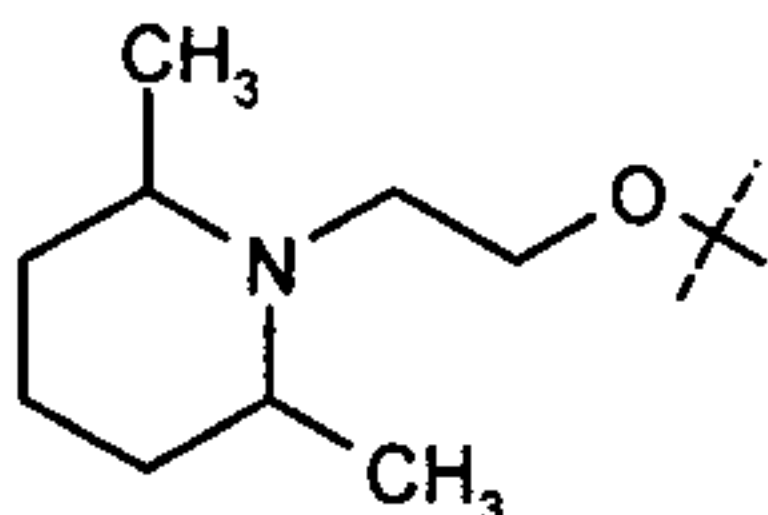
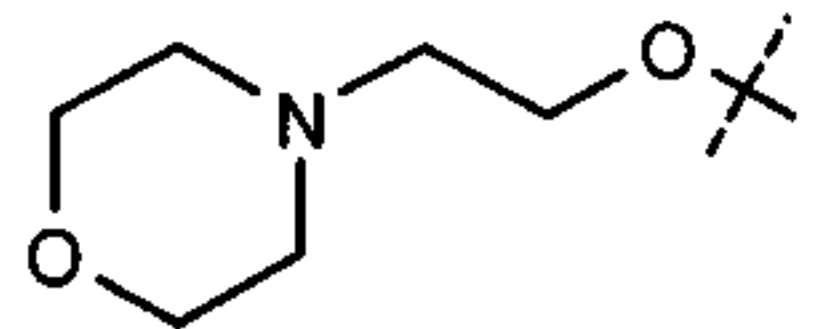
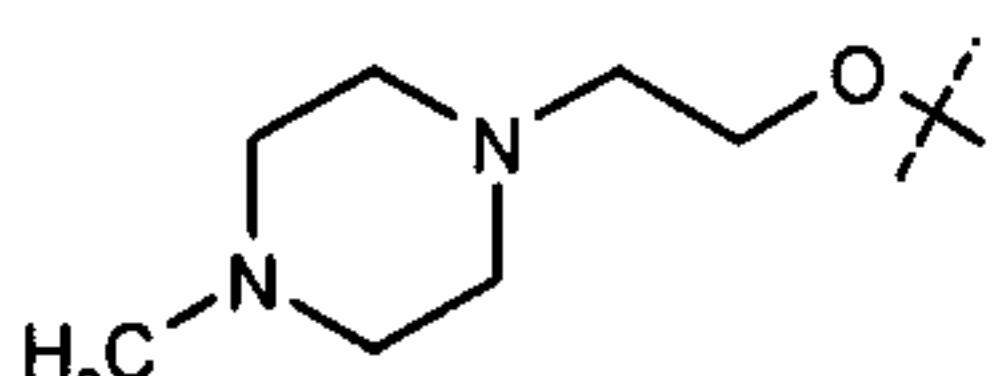
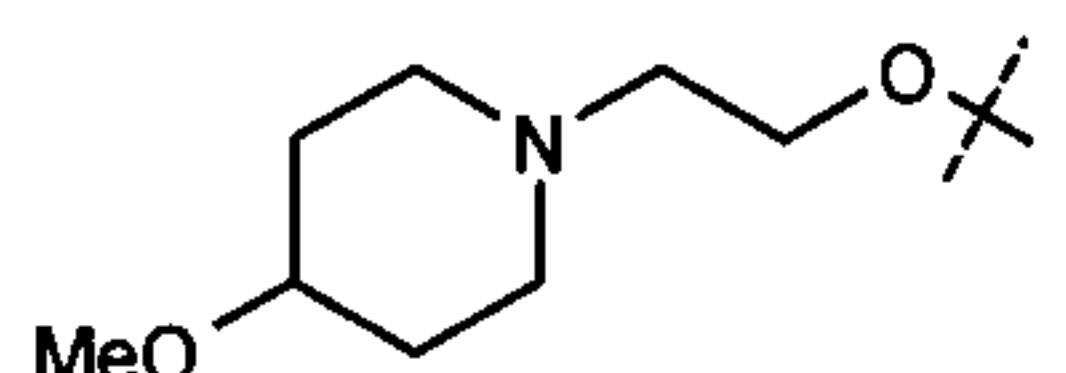
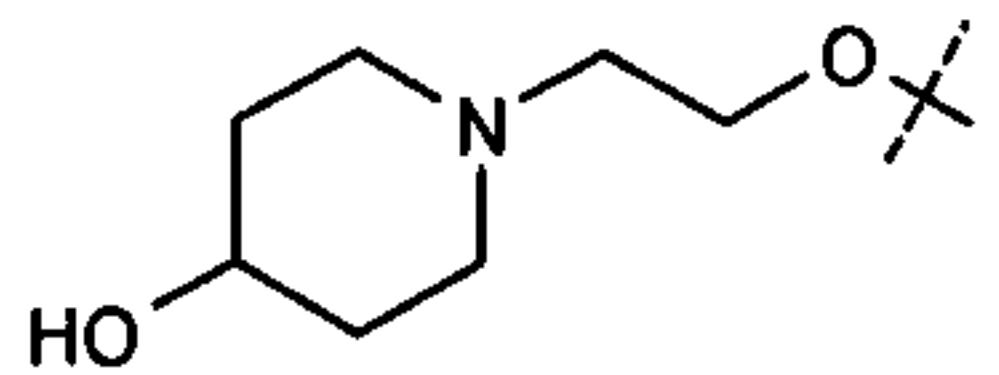
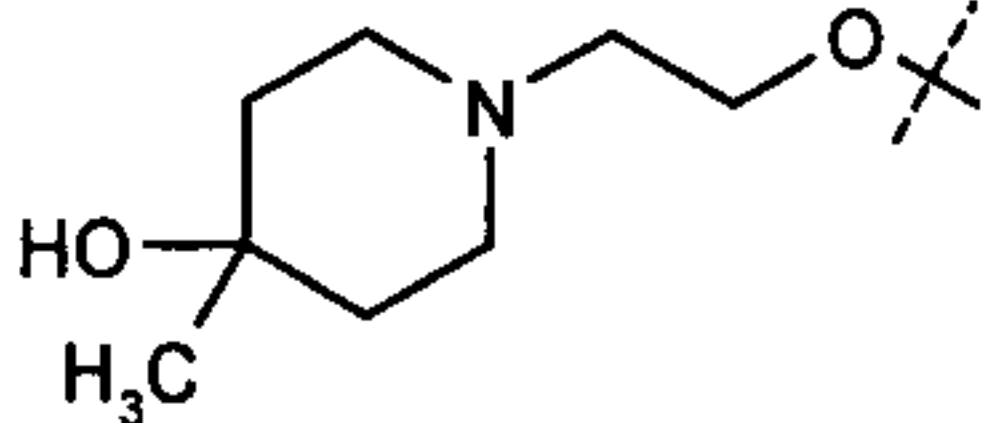
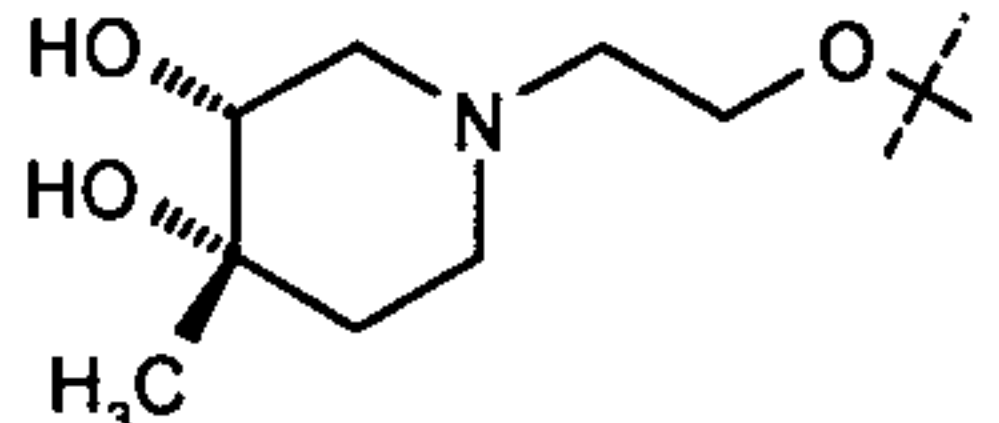
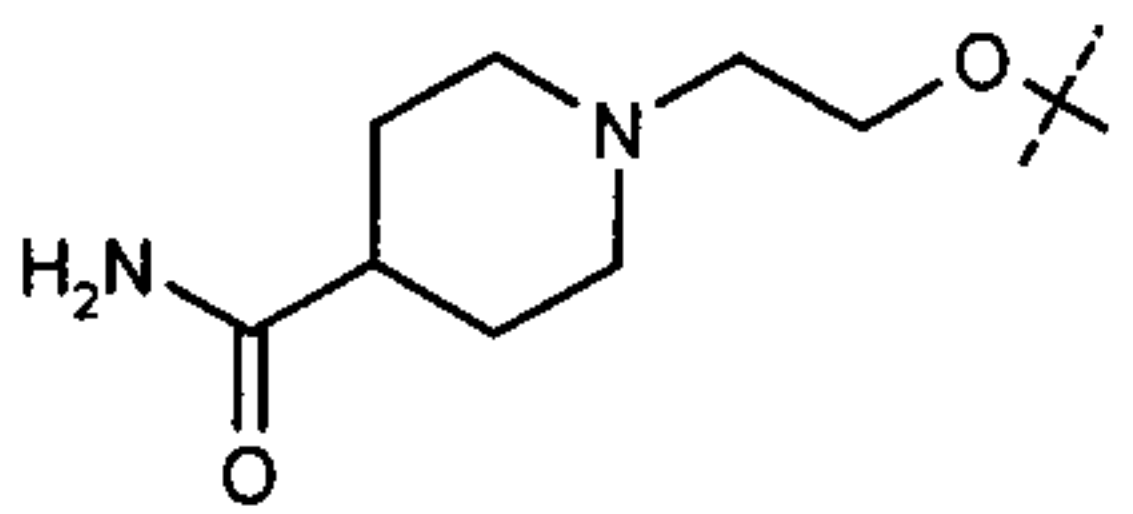
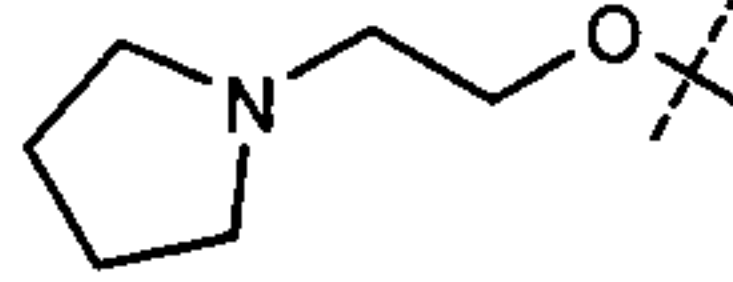
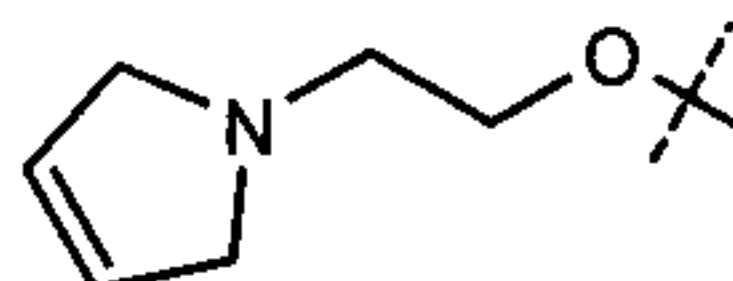
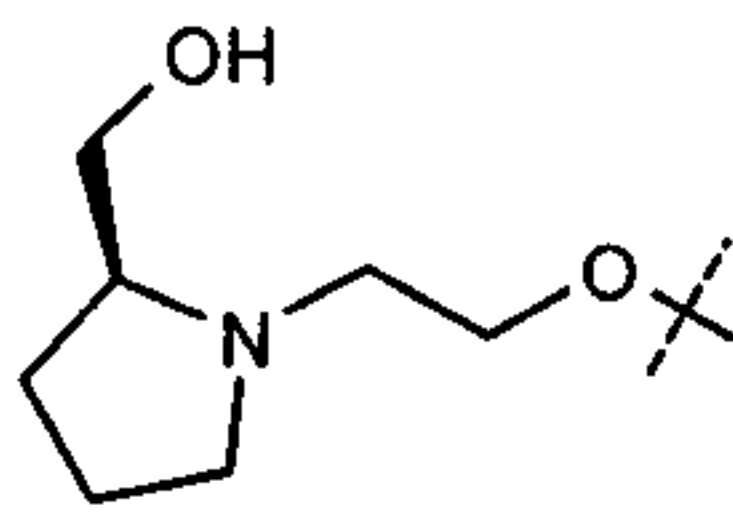
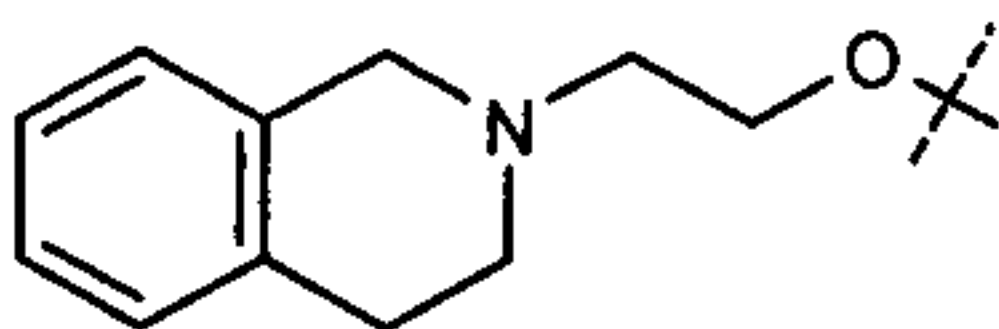
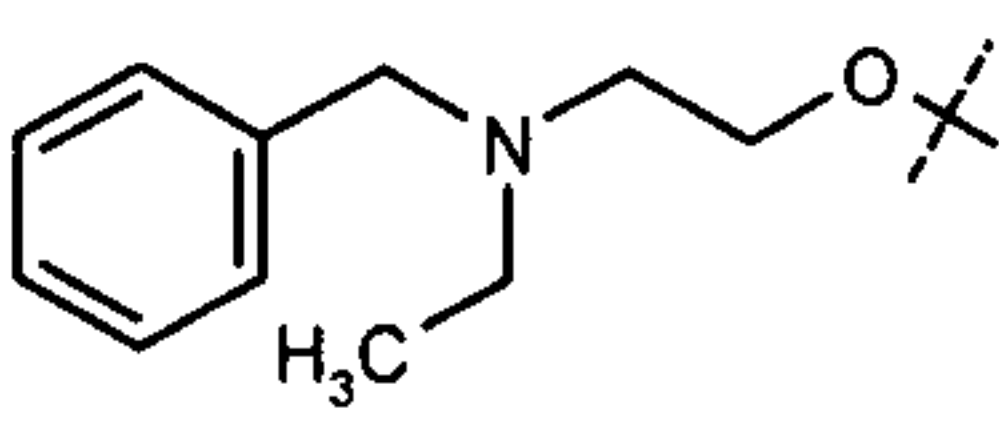
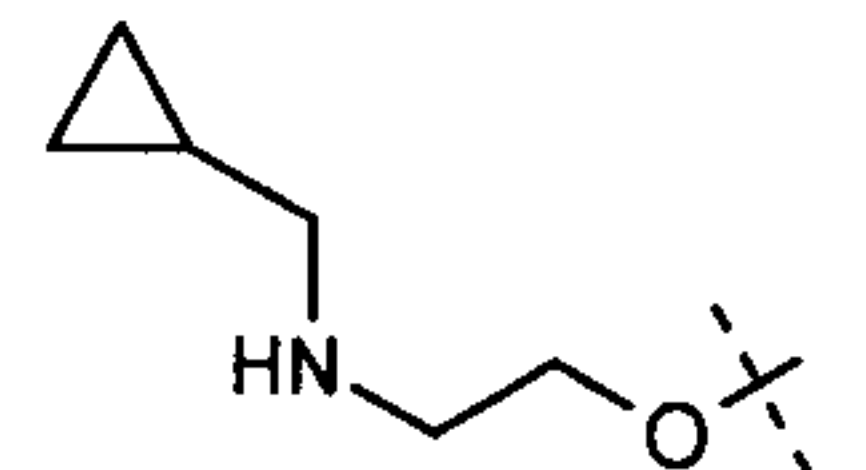
4.72		-CH ₃	-Cl	-CF ₃
4.73		-CH ₃	-Cl	-CF ₃
4.74		-CH ₃	-Cl	-CF ₃
4.75		-CH ₃	-Cl	-CF ₃
4.76		-CH ₃	-Cl	-CF ₃
4.77		-CH ₃	-Cl	-CF ₃
4.78		-CH ₃	-Cl	-CF ₃
4.79		-CH ₃	-Cl	-CF ₃
4.80		-CH ₃	-Cl	-CF ₃
4.81		-CH ₃	-Cl	-CF ₃
4.82		-CH ₃	-Cl	-CF ₃
4.83		-CH ₃	-Cl	-CF ₃
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4.85		-CH ₃	-Cl	-CF ₃

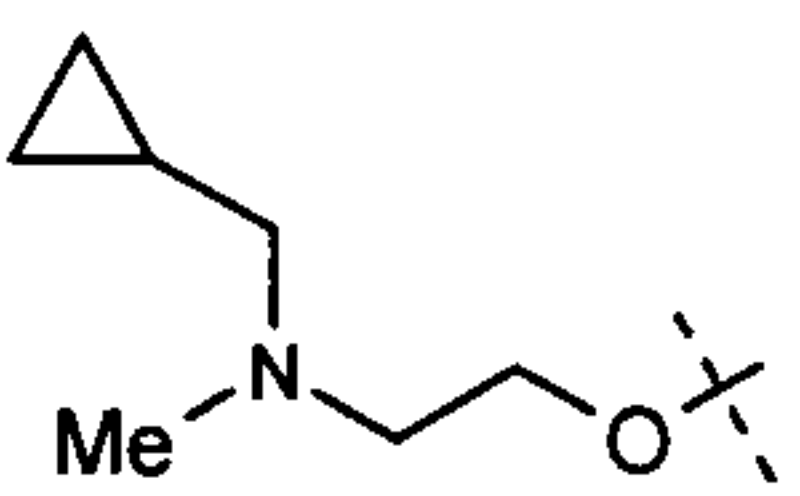
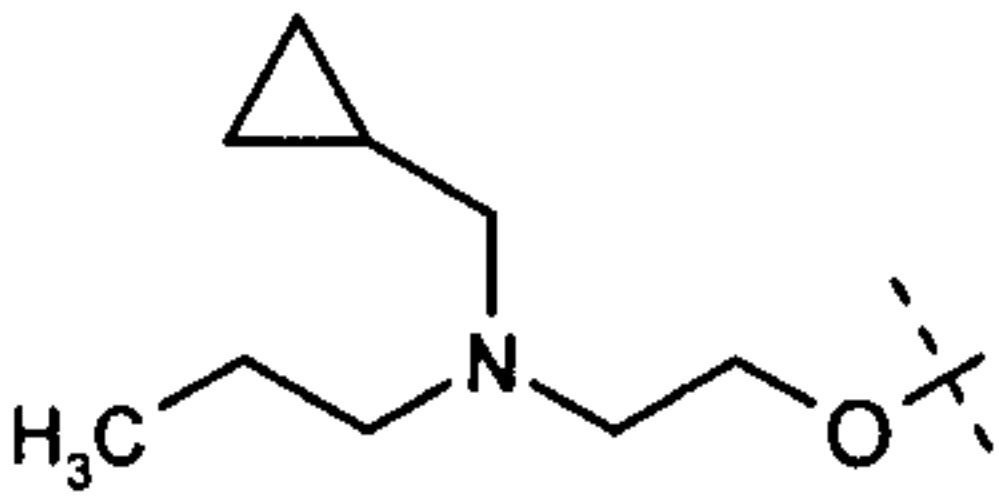
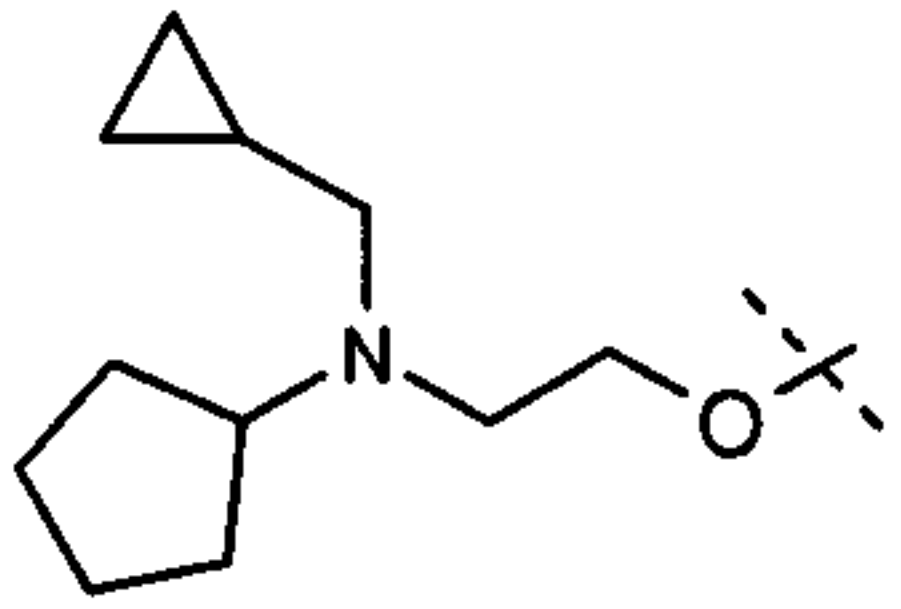
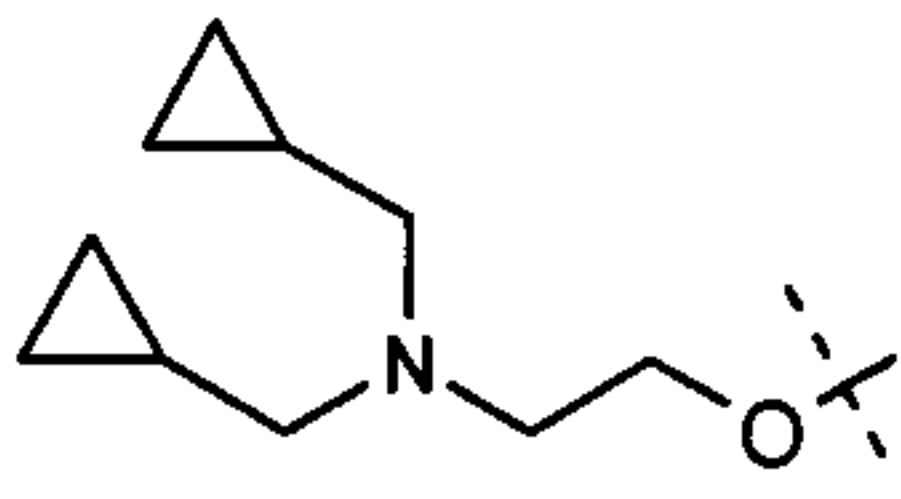
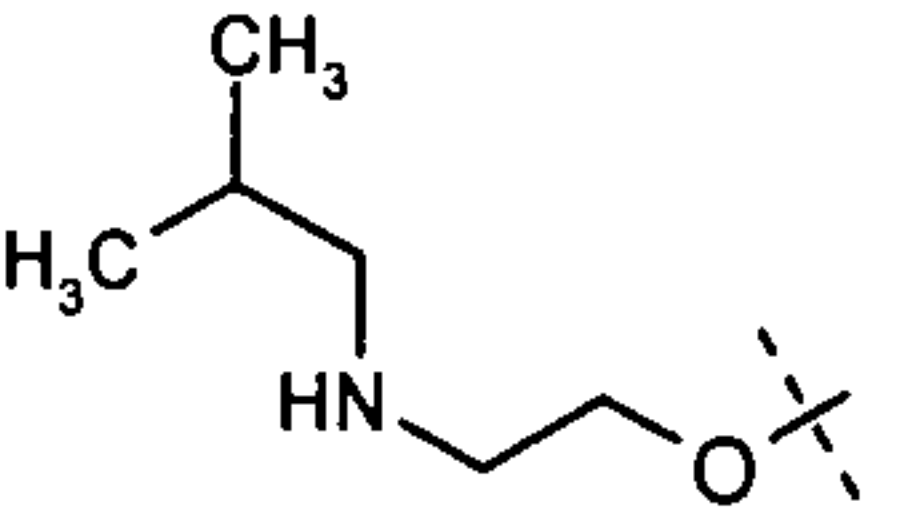
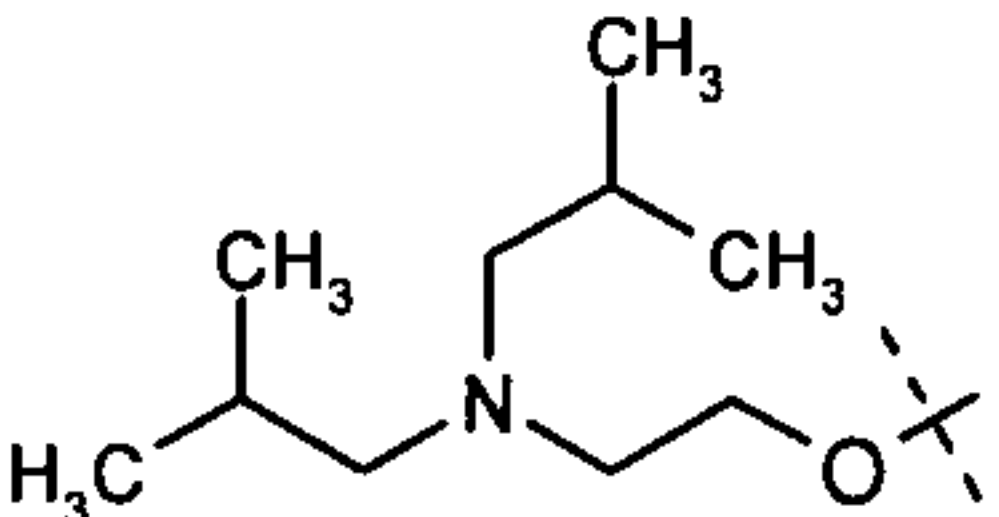
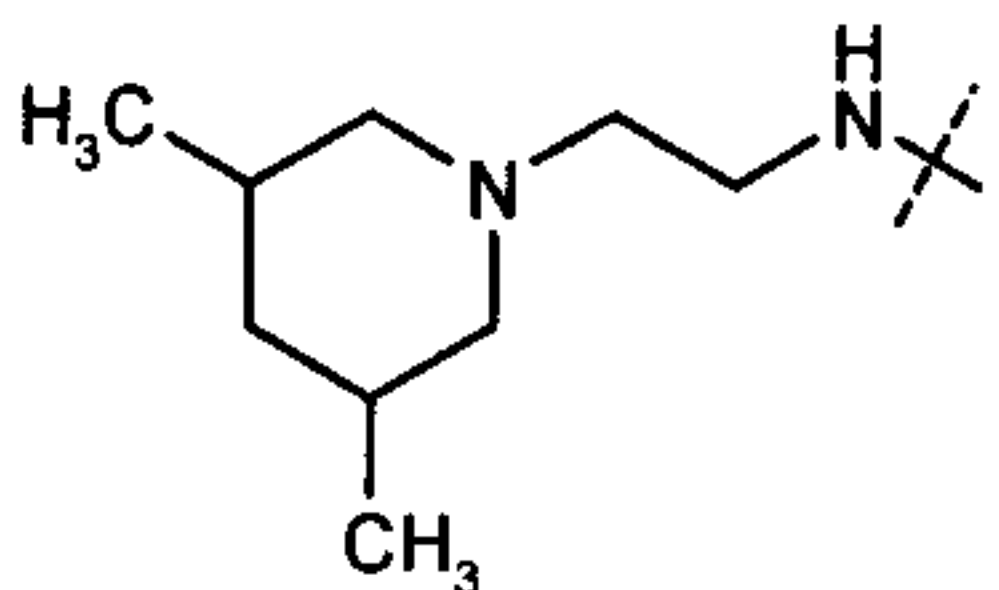
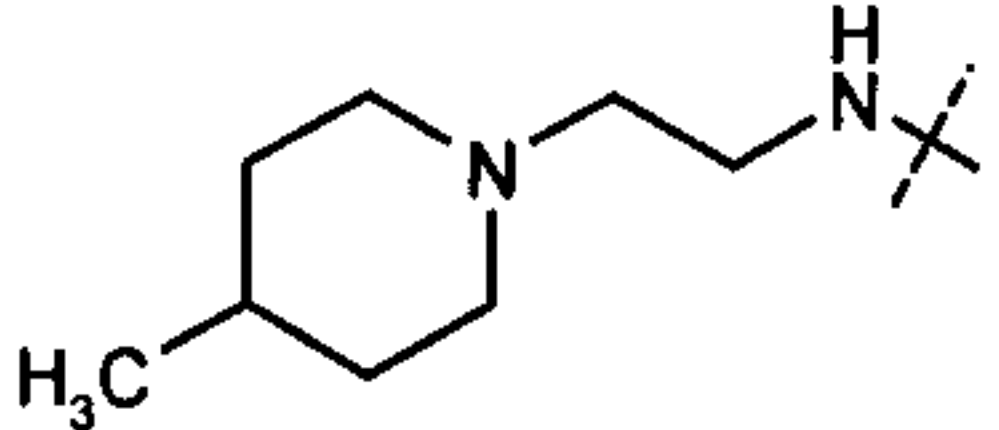
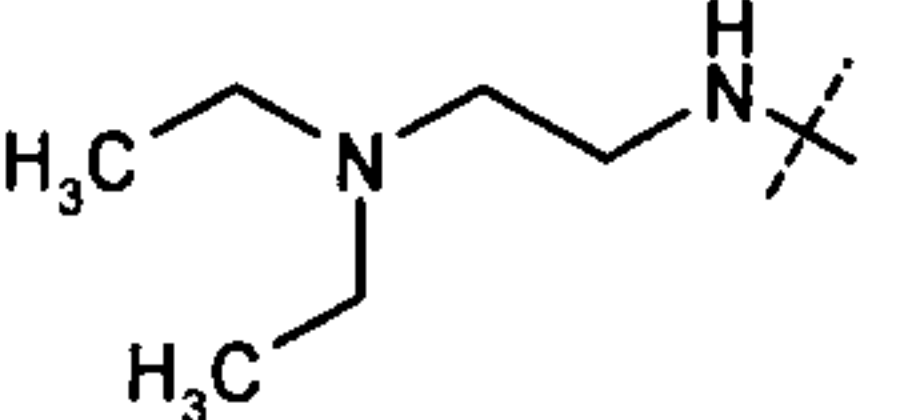
4.86		-CH ₃	-Cl	-CF ₃
4.87		-CH ₃	-Cl	-CF ₃
4.88		-CH ₃	-Cl	-CF ₃
4.89		-CH ₃	-Cl	-CF ₃
4.90		-CH ₃	-Cl	-CF ₃
4.91		-CH ₃	-Cl	-CF ₃
4.92		-H	-Cl	-CF ₃
4.93		-H	-Cl	-CF ₃
4.94		-H	-Cl	-CF ₃
4.96		-H	-Cl	-CF ₃
4.97		-H	-Cl	-CF ₃
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4.100		-H	-Cl	-CF ₃

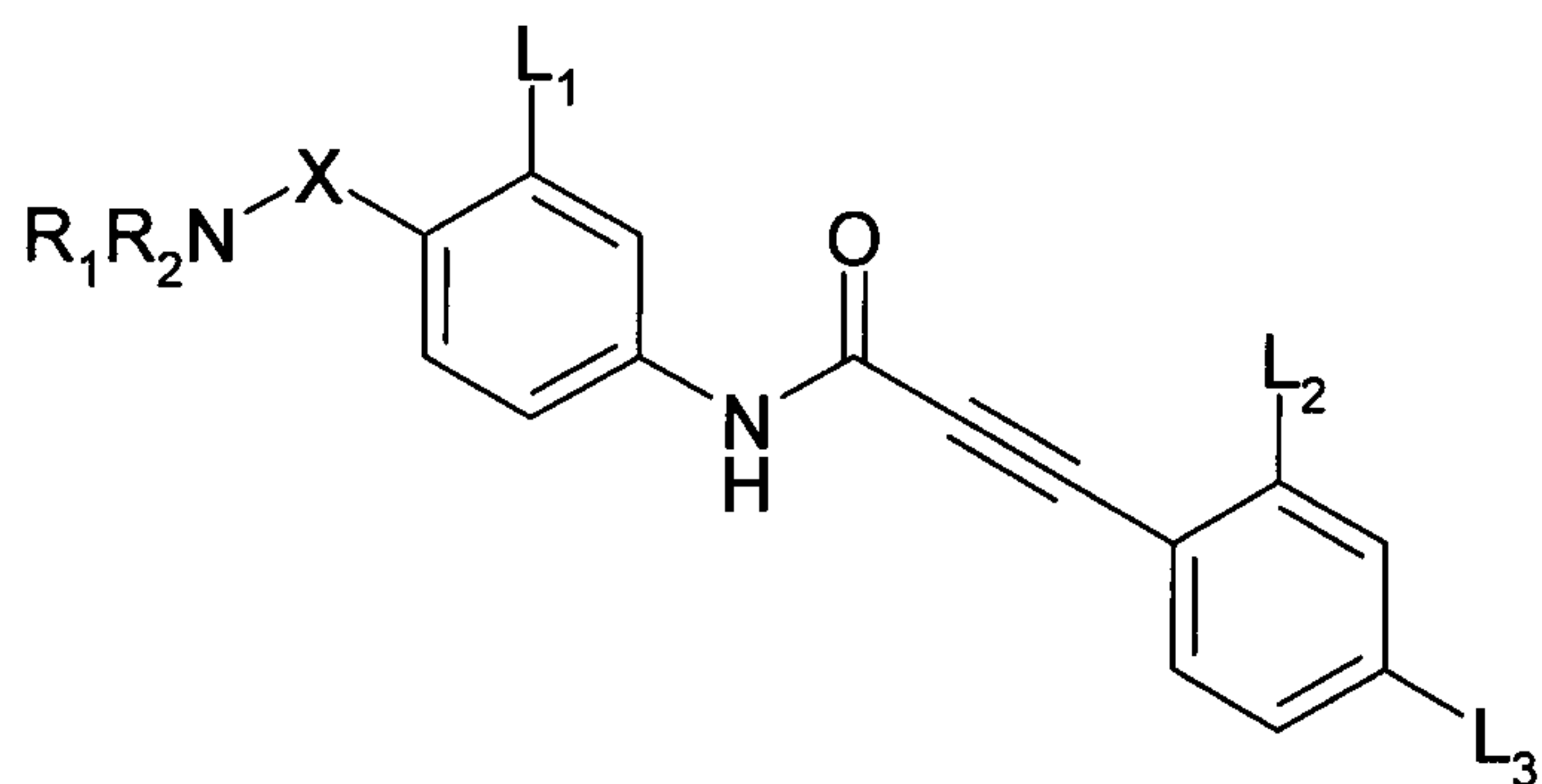
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4.102		-H	-Cl	-CF ₃
4.103		-H	-Cl	-CF ₃
4.104		-H	-Cl	-CF ₃
4.105		-H	-Cl	-CF ₃
4.106		-H	-Cl	-CF ₃
4.107		-H	-Cl	-CF ₃
4.108		-H	-Cl	-CF ₃
4.109		-H	-Cl	-CF ₃
4.110		-H	-Cl	-CF ₃
4.111		-H	-Cl	-CF ₃
4.112		-H	-Cl	-CF ₃
4.113		-H	-Cl	-CF ₃

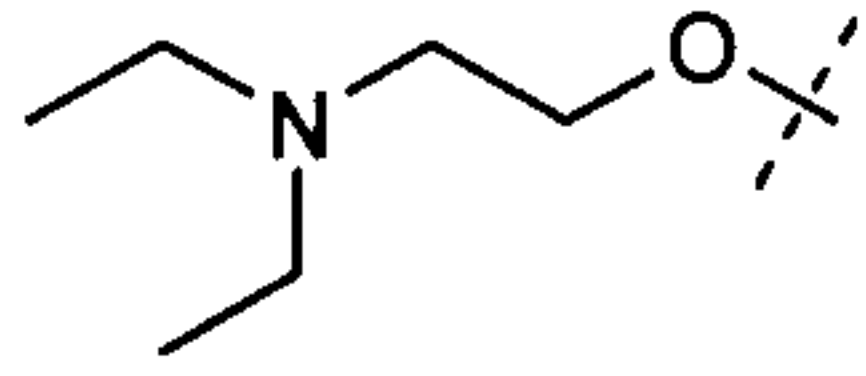
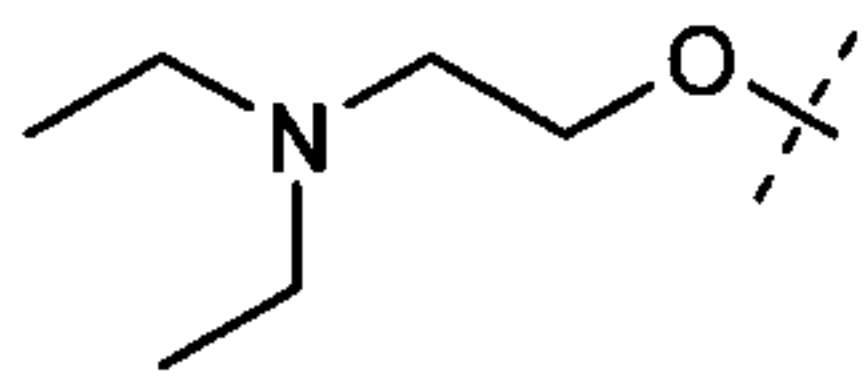
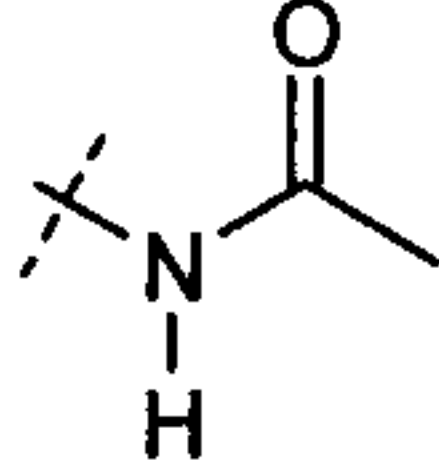
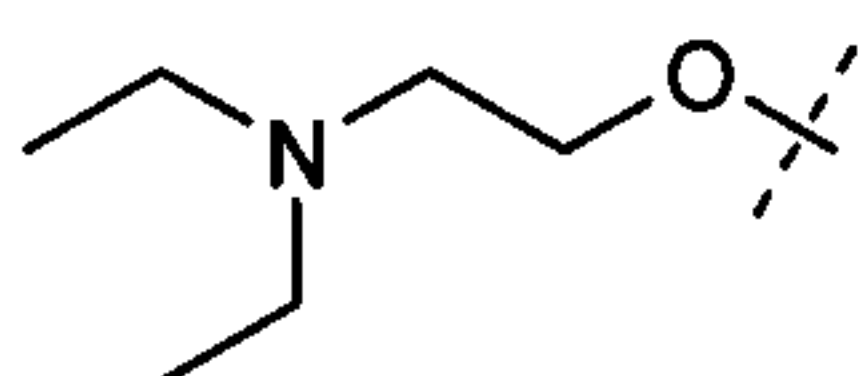
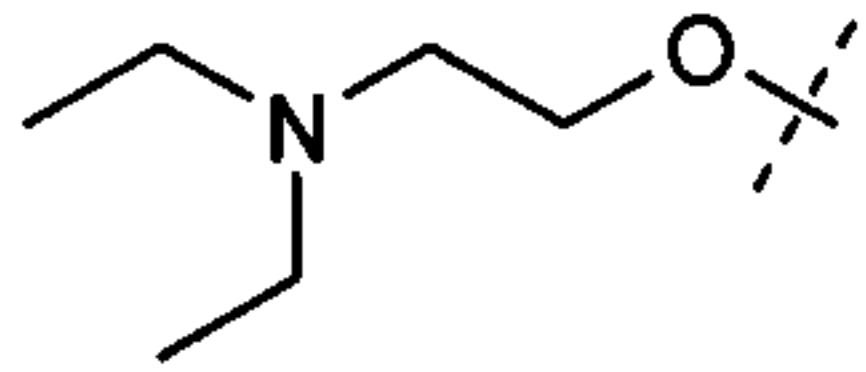
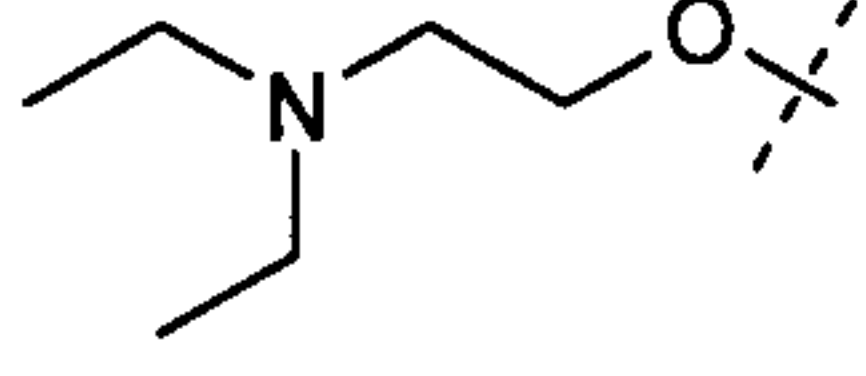
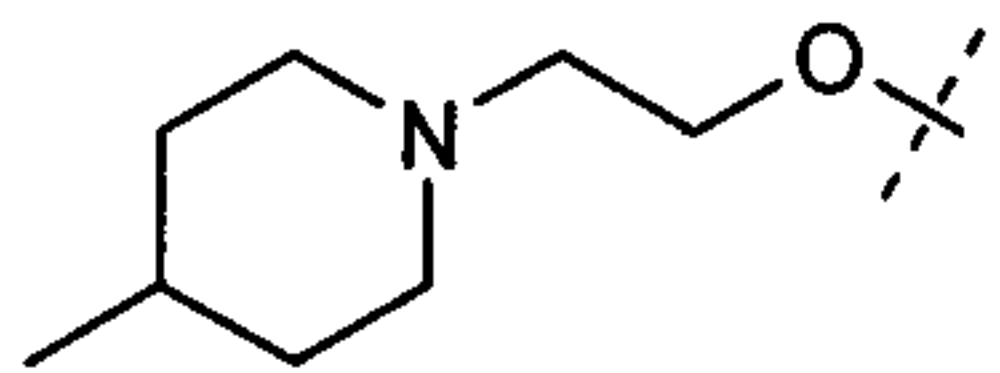
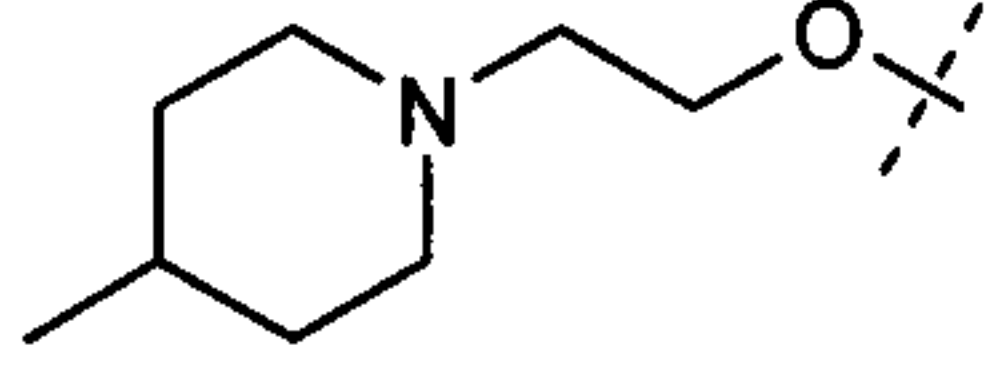
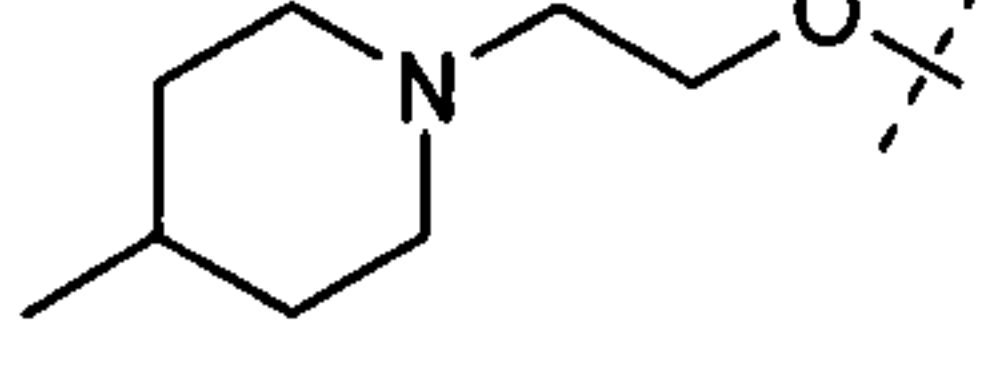
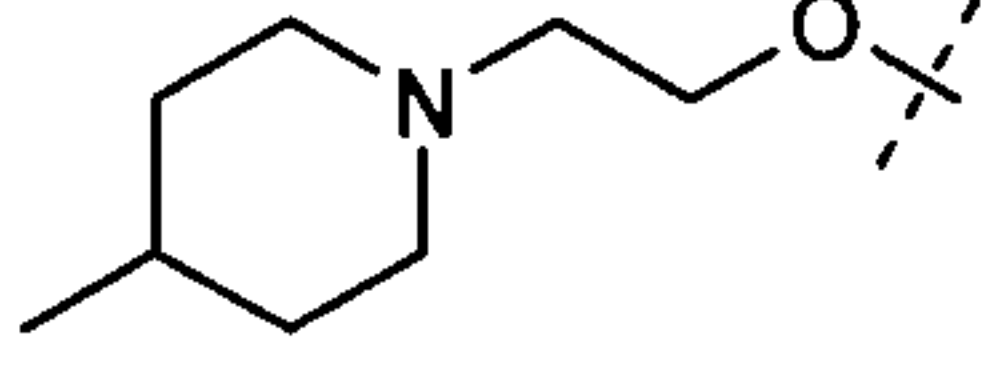
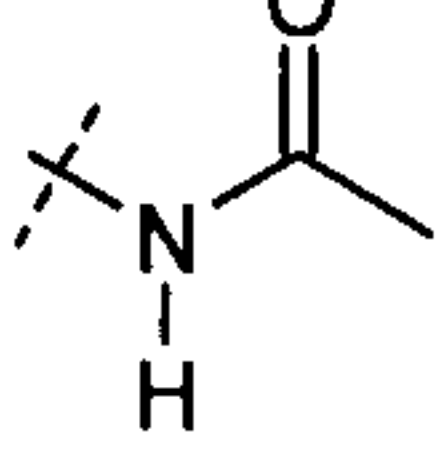
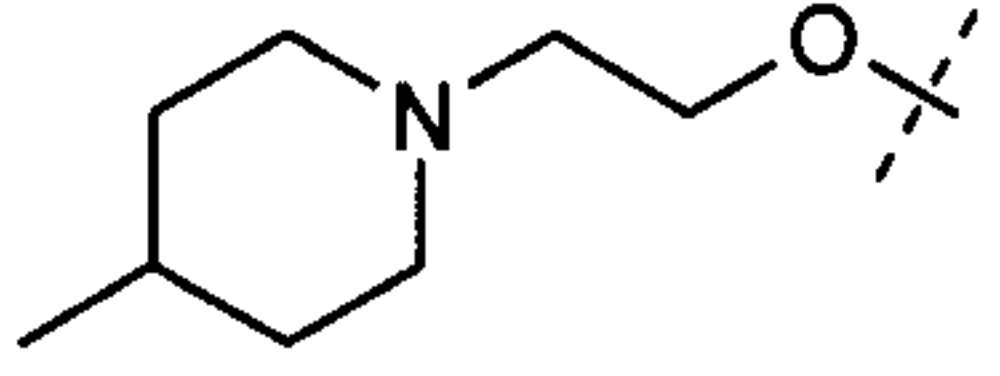
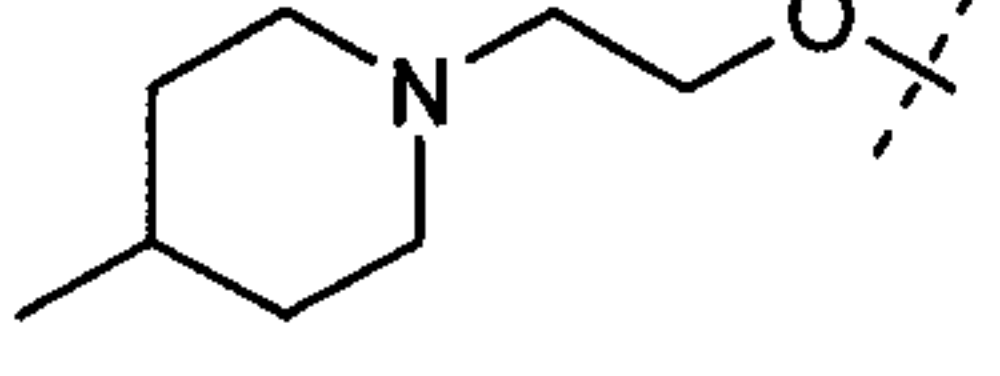
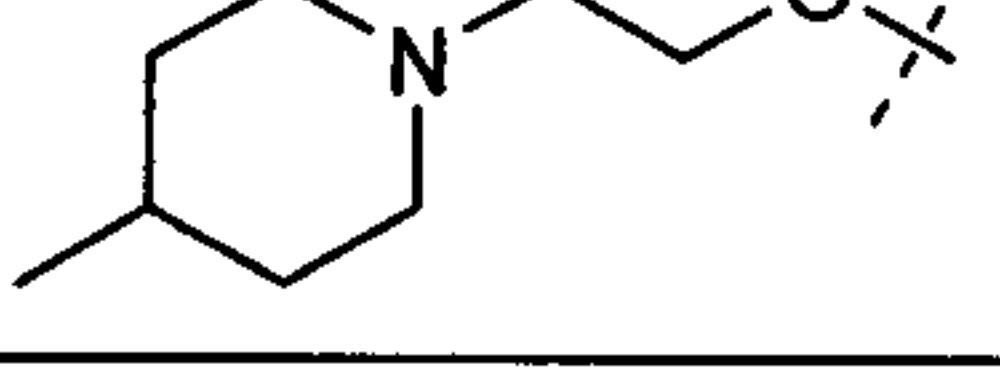
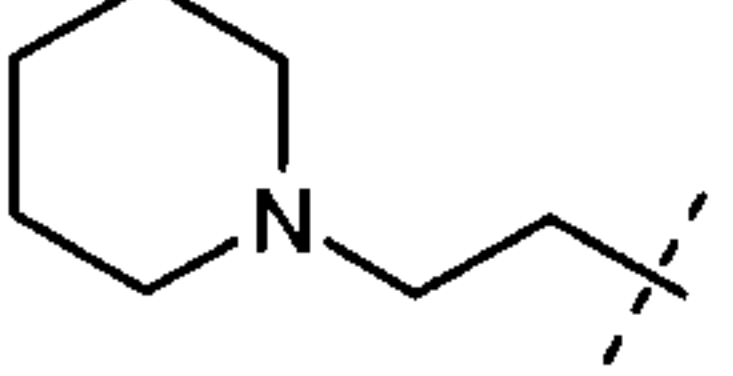
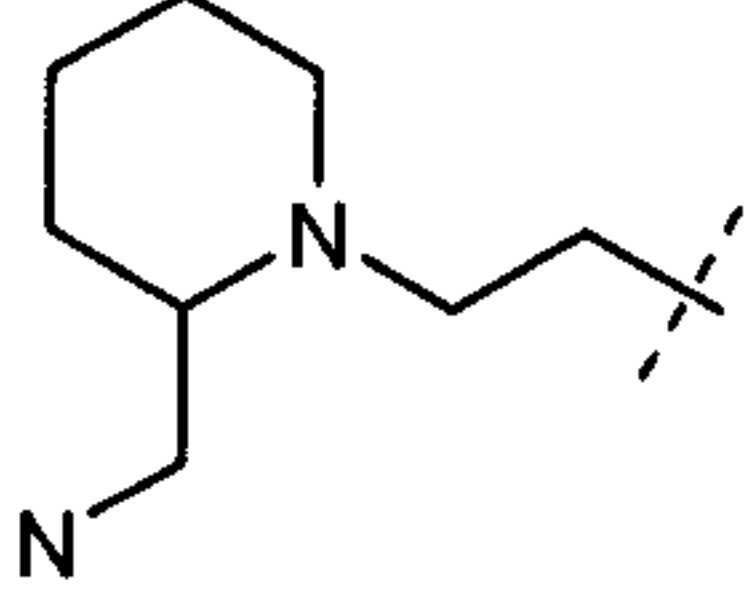
4.114		-H	-Cl	-CF ₃
4.115		-H	-Cl	-CF ₃
4.116		-H	-Cl	-CF ₃
4.117		-H	-Cl	-CF ₃
4.118		-H	-Cl	-CF ₃
4.119		-H	-Cl	-CF ₃
4.120		-OCH ₃	-Cl	-CF ₃
4.121		-OCH ₃	-Cl	-CF ₃
4.122		-OCH ₃	-Cl	-CF ₃
4.123		-OCH ₃	-Cl	-CF ₃
4.124		-OCH ₃	-Cl	-CF ₃
4.125		-OCH ₃	-Cl	-CF ₃
4.126		-OCH ₃	-Cl	-CF ₃
4.127		-OCH ₃	-Cl	-CF ₃

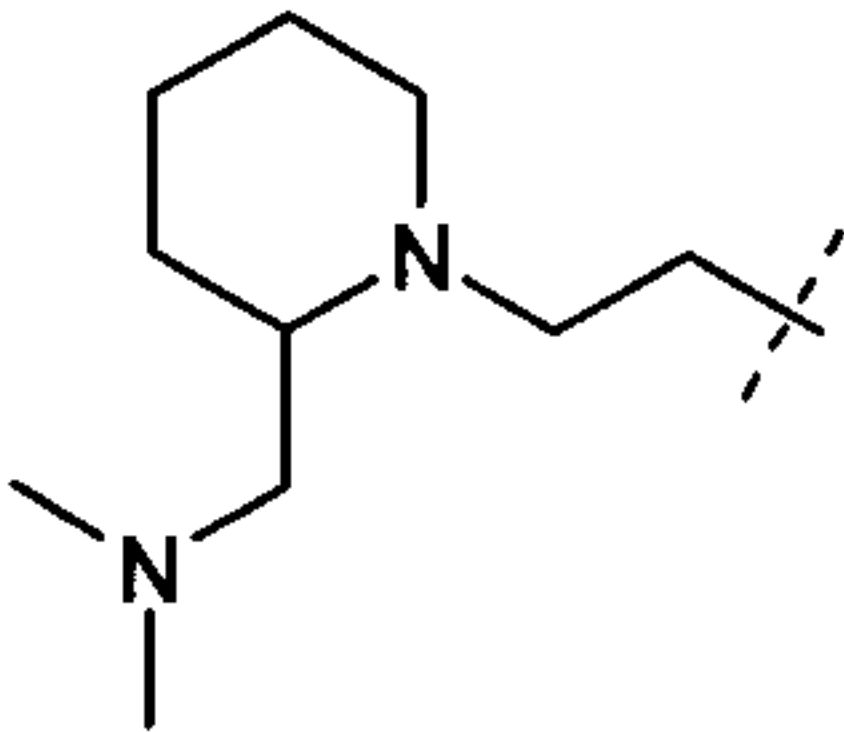
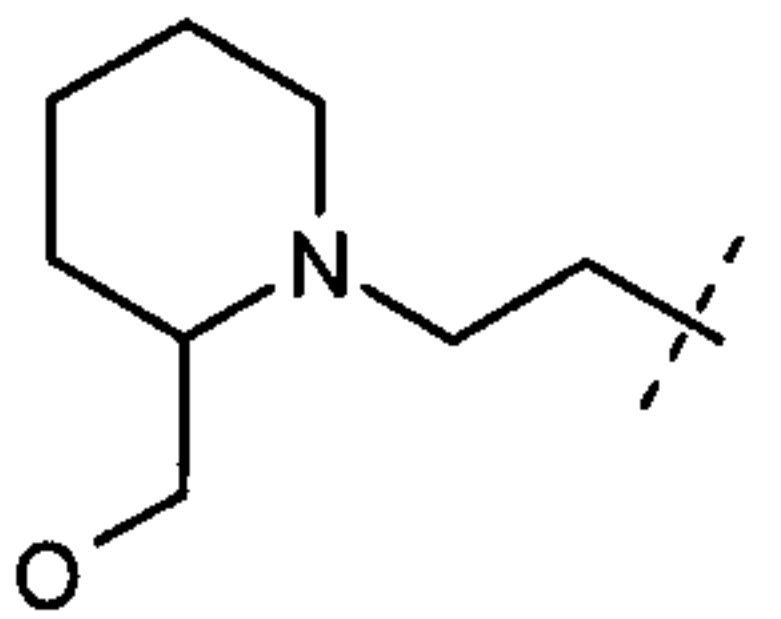
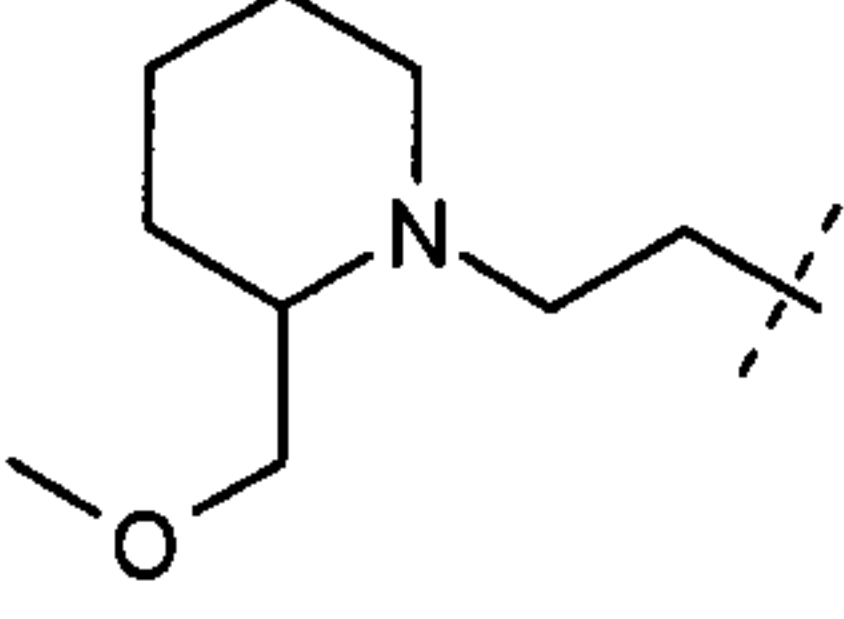
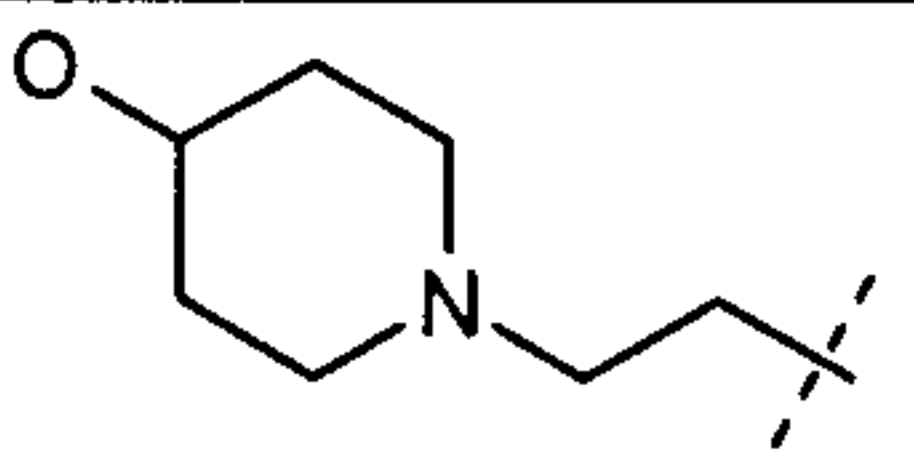
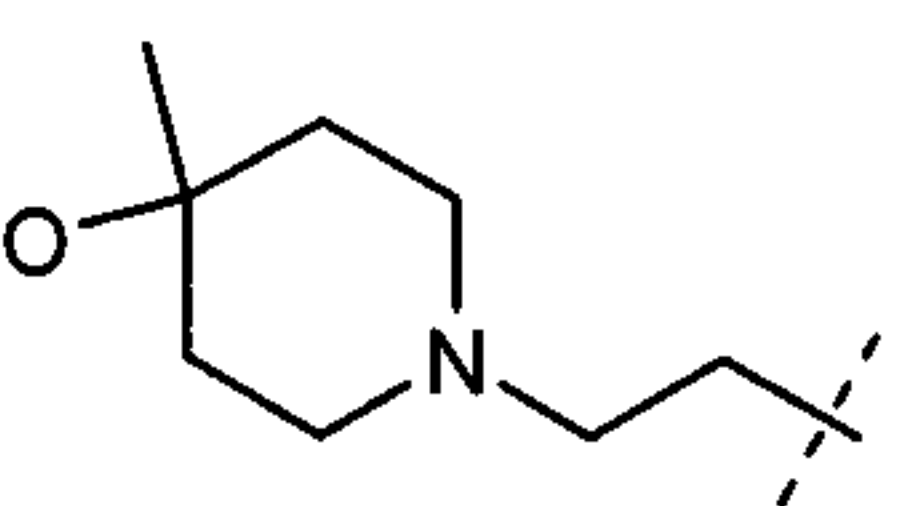
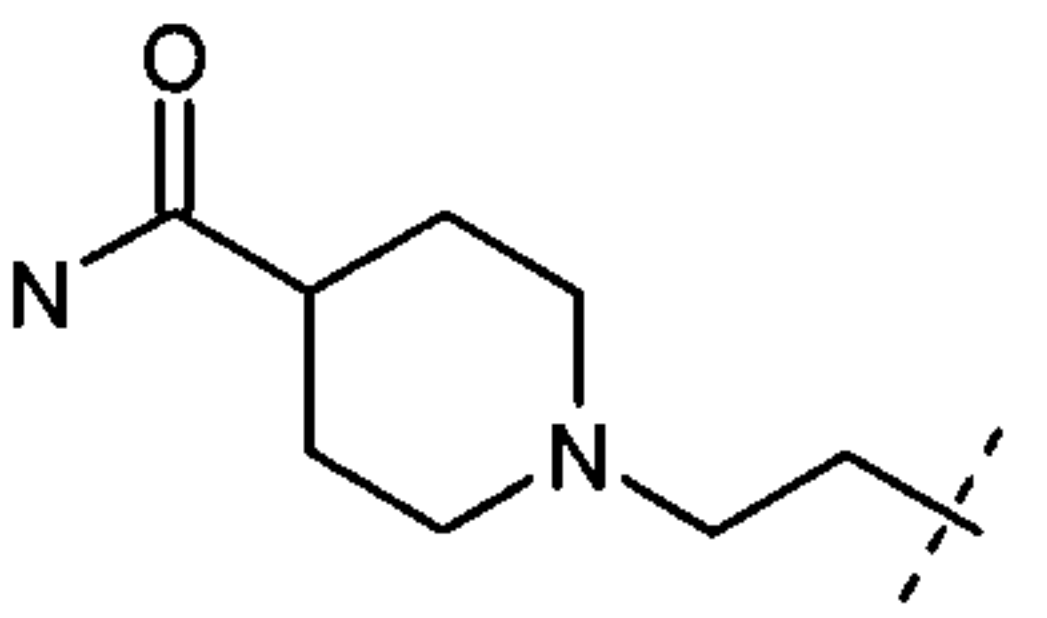
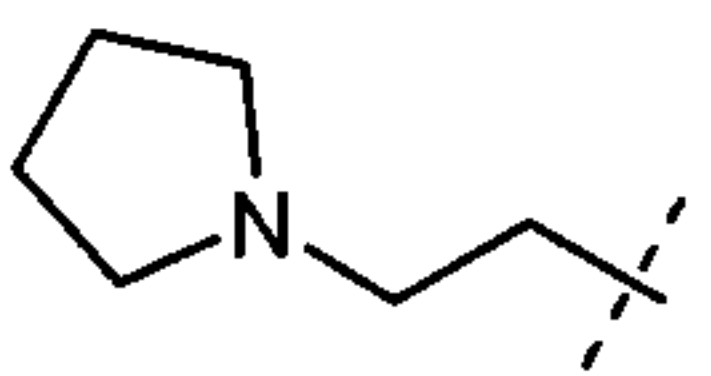
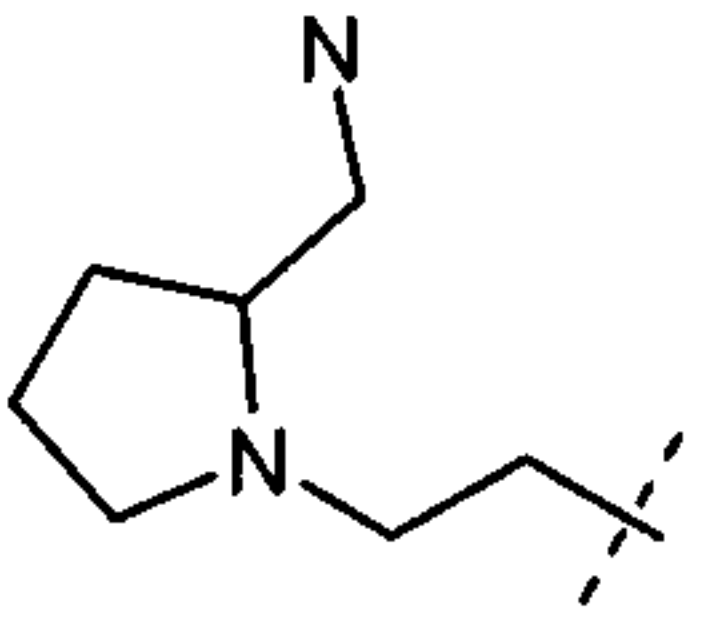
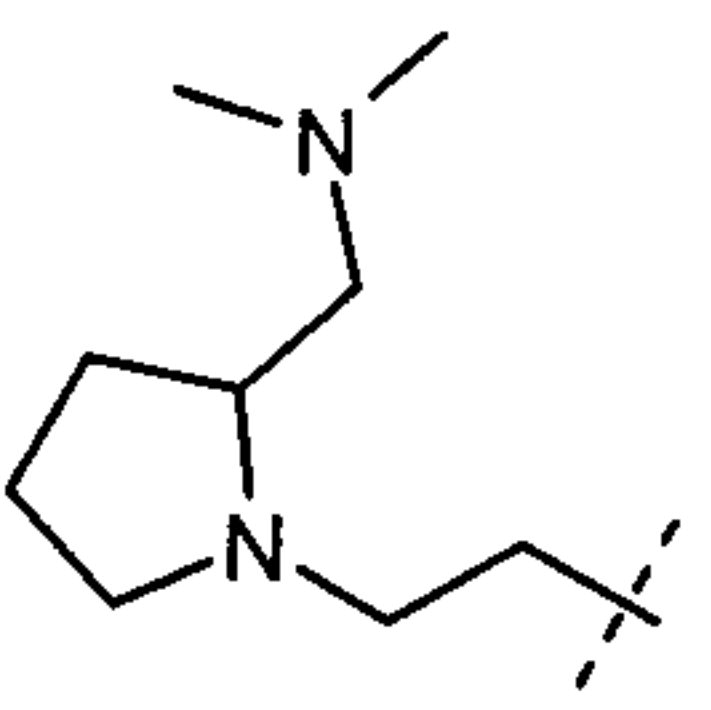
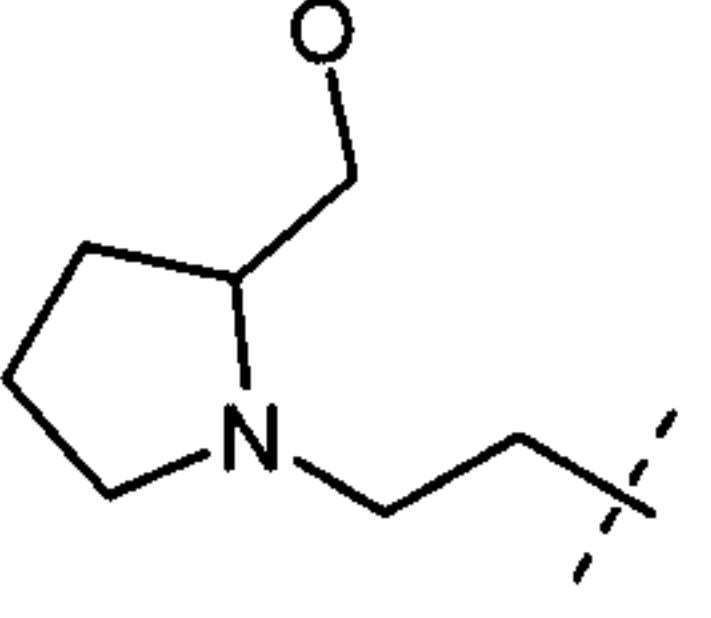
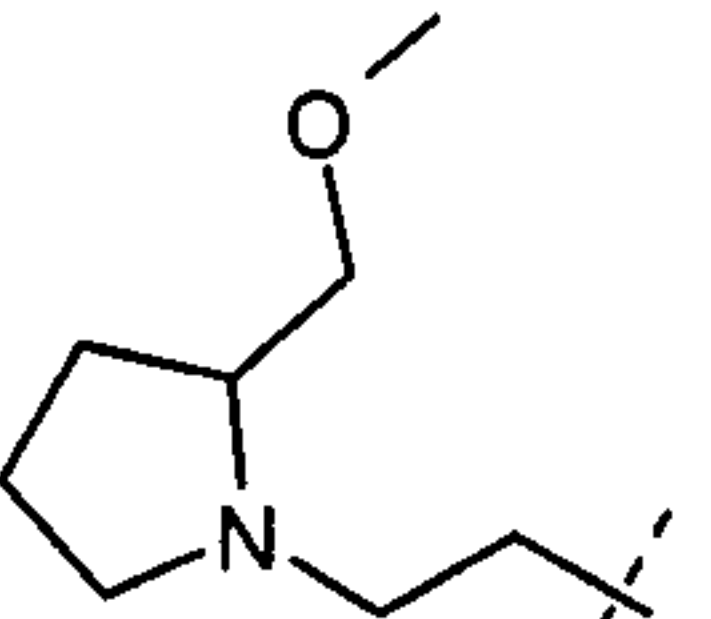
4.128		-OCH ₃	-Cl	-CF ₃
4.129		-OCH ₃	-Cl	-CF ₃
4.130		-OCH ₃	-Cl	-CF ₃
4.131		-OCH ₃	-Cl	-CF ₃
4.132		-OCH ₃	-Cl	-CF ₃
4.133		-OCH ₃	-Cl	-CF ₃
4.134		-OCH ₃	-Cl	-CF ₃
4.135		-OCH ₃	-Cl	-CF ₃
4.136		-OCH ₃	-Cl	-CF ₃
4.137		-OCH ₃	-Cl	-CF ₃
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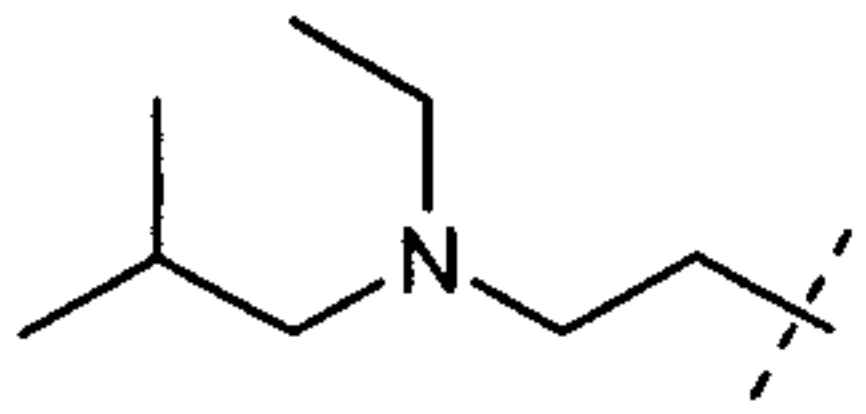
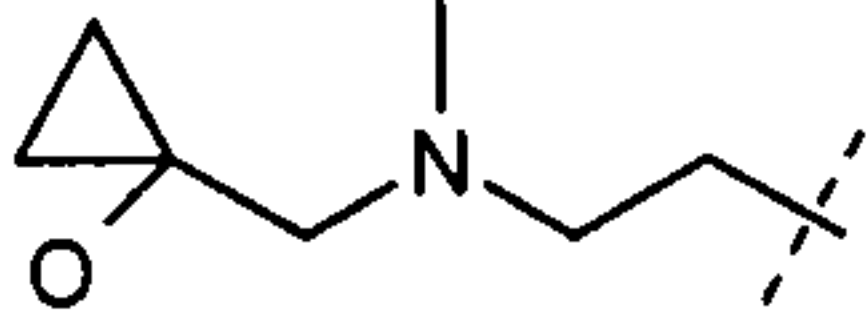
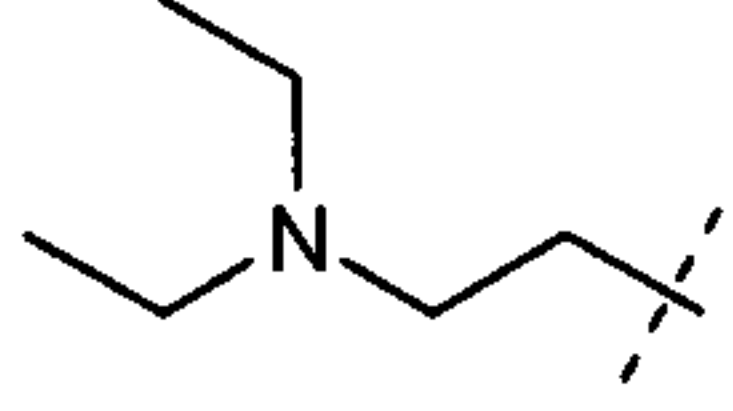
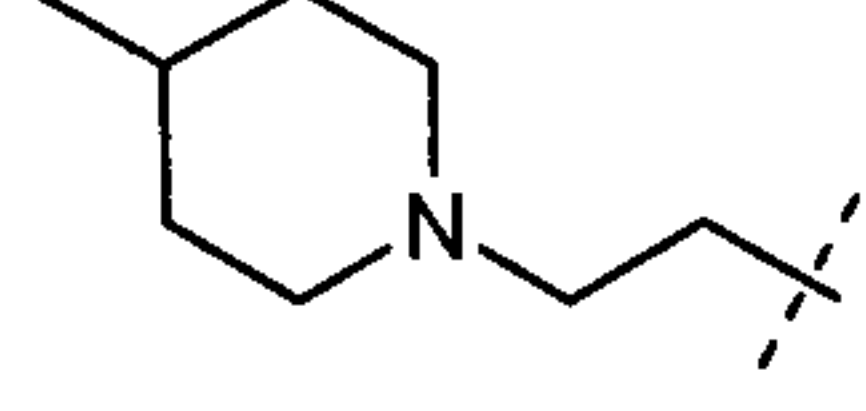
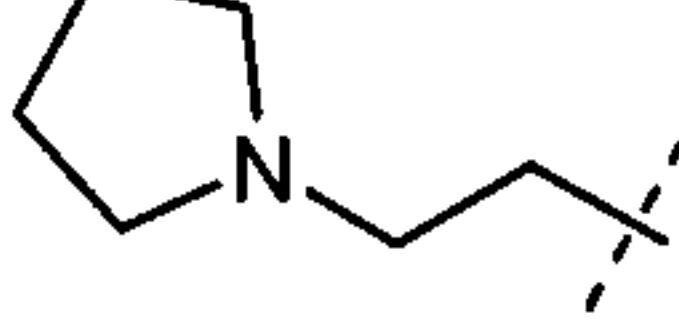
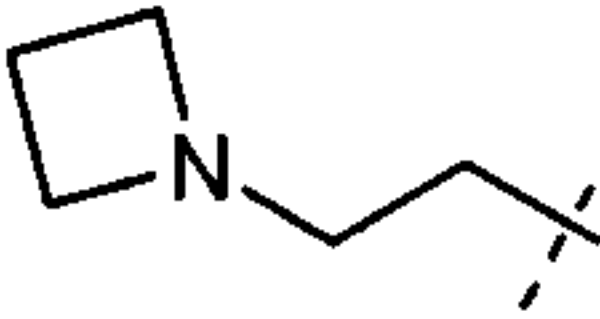
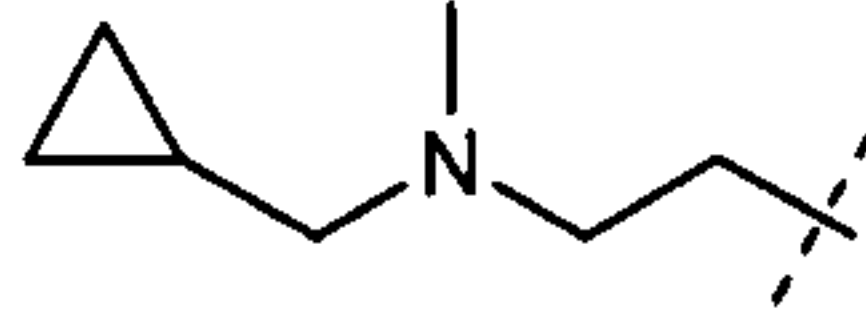
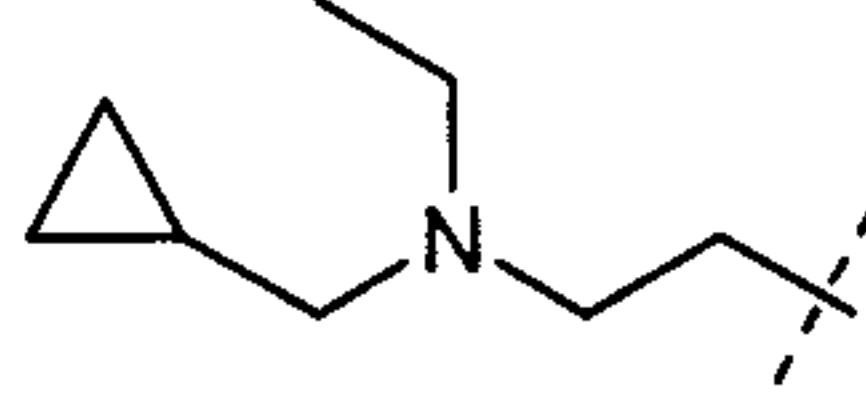
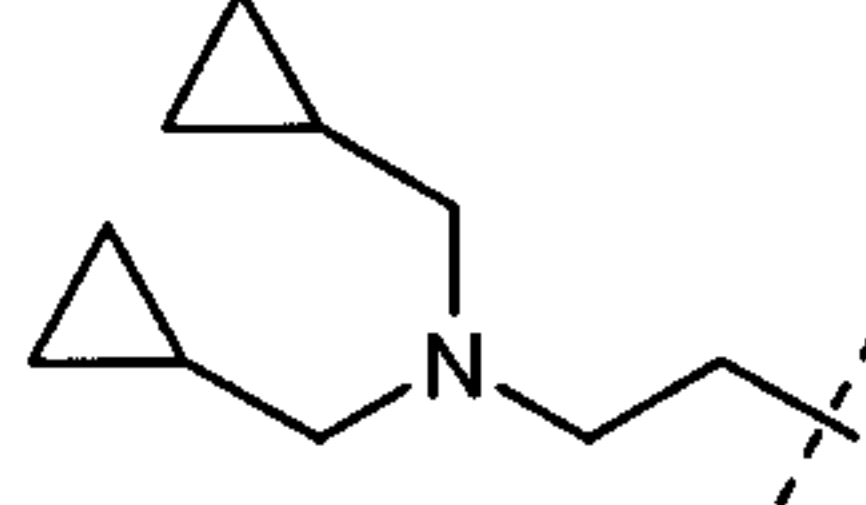
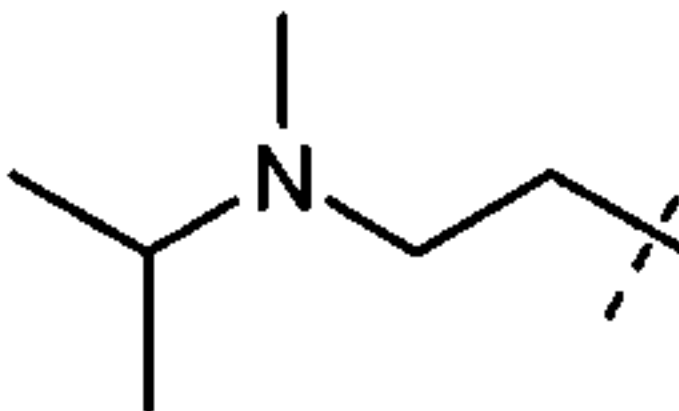
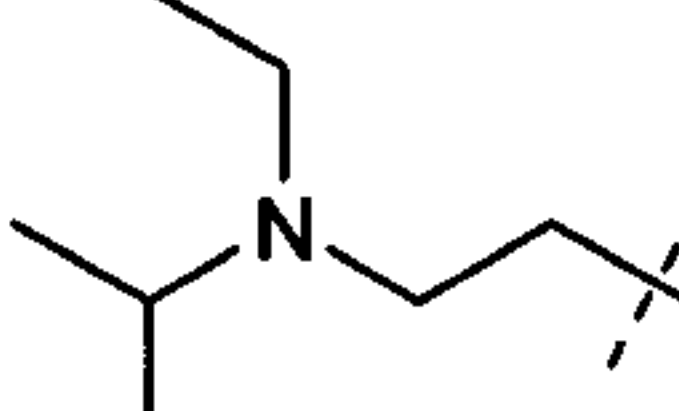
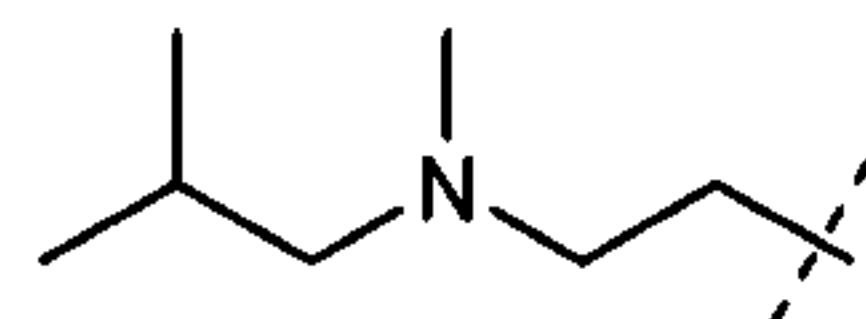
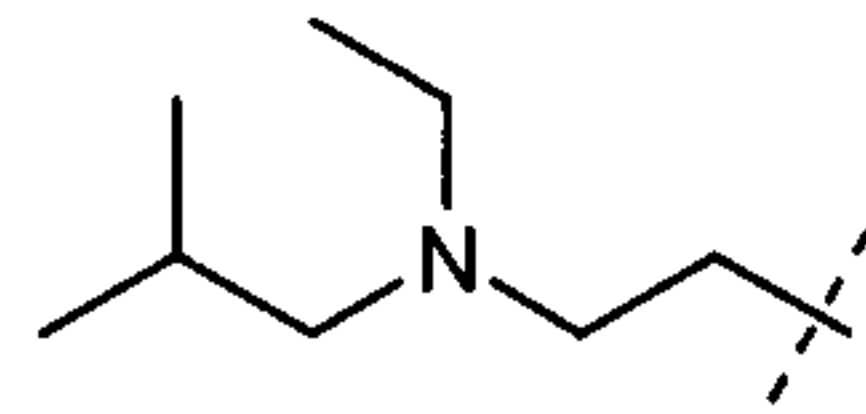
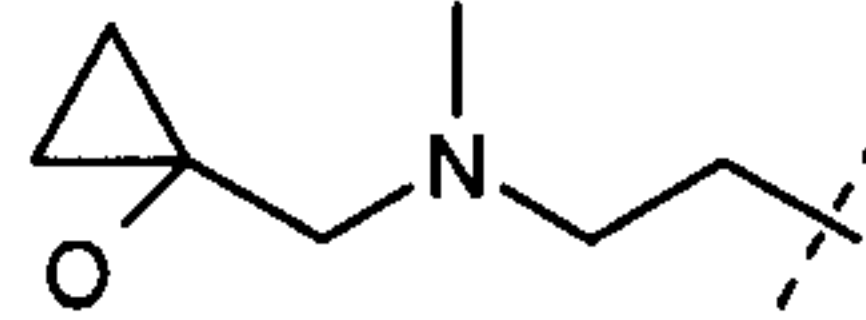
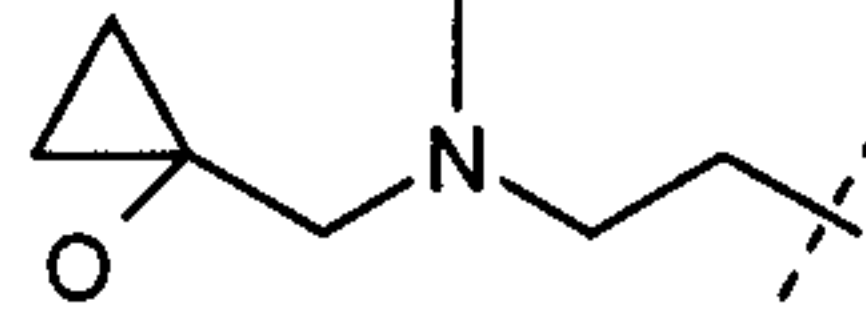
4.141		-Cl	-Cl	-CF ₃
4.142		-Cl	-Cl	-CF ₃
4.143		-Cl	-Cl	-CF ₃
4.144		-Cl	-Cl	-CF ₃
4.145		-Cl	-Cl	-CF ₃
4.146		-Cl	-Cl	-CF ₃
4.147		-Cl	-Cl	-CF ₃
4.148		-Cl	-Cl	-CF ₃
4.149		-Cl	-Cl	-CF ₃
4.150		-Cl	-Cl	-CF ₃
4.151		-Cl	-Cl	-CF ₃
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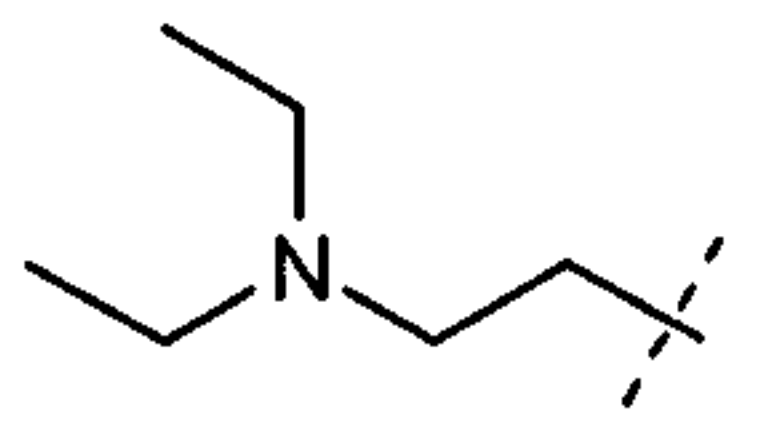
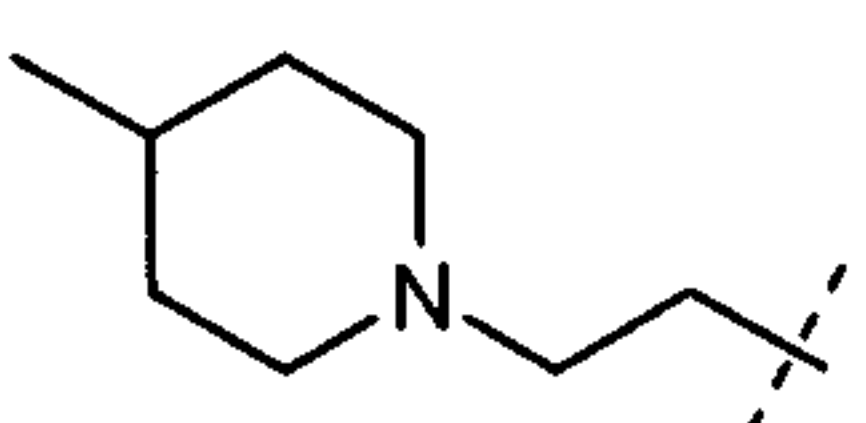
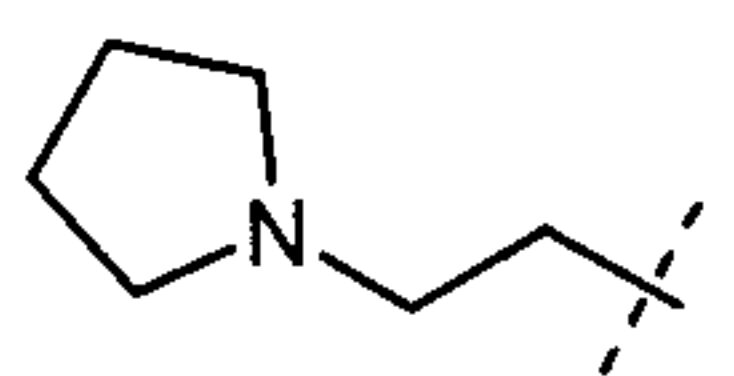
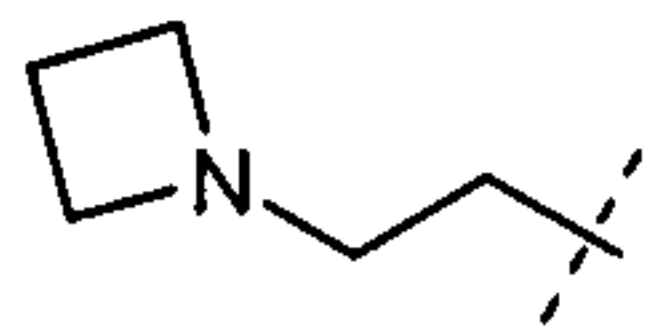
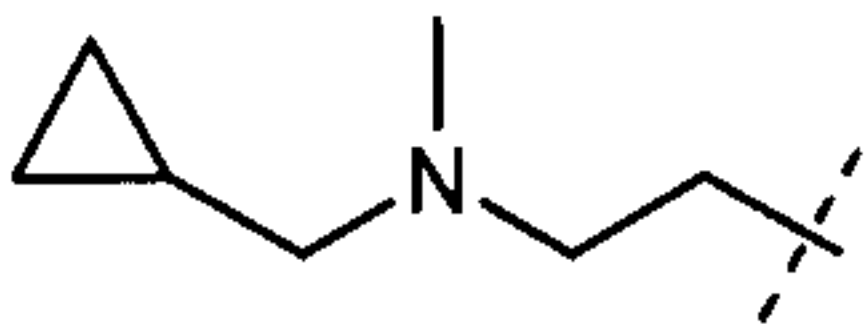
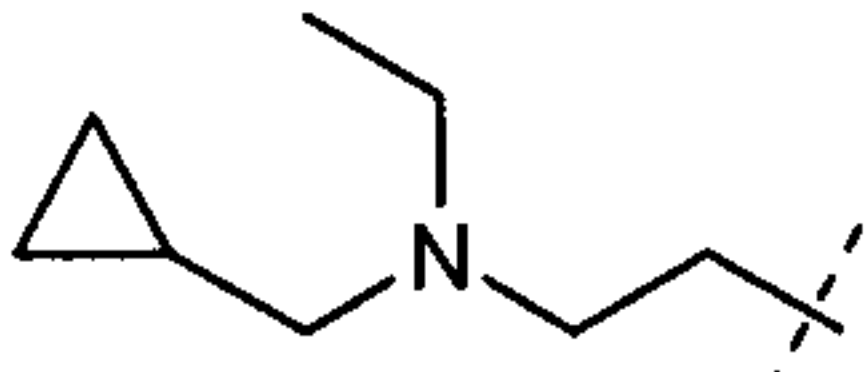
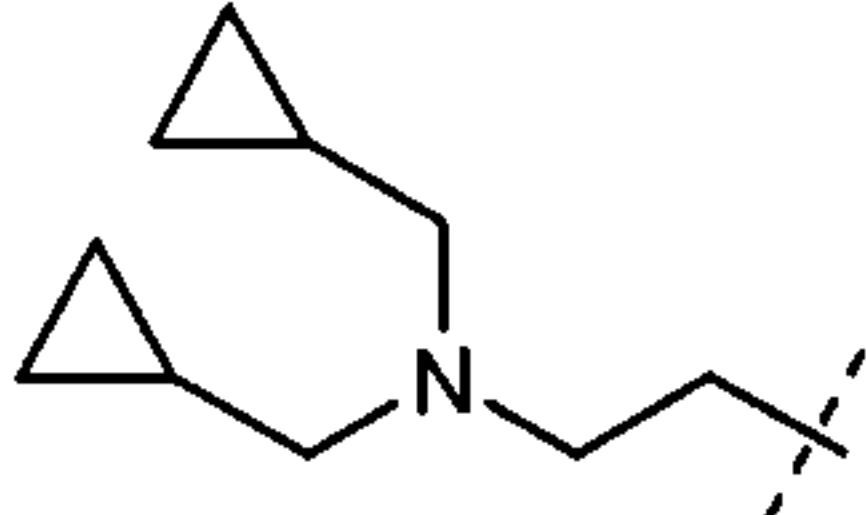
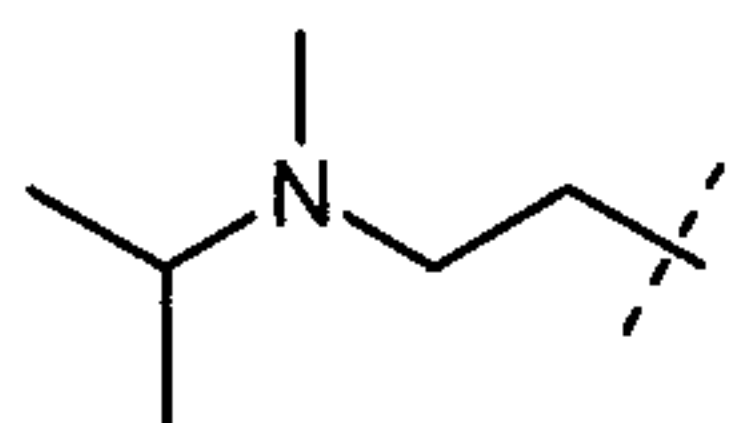
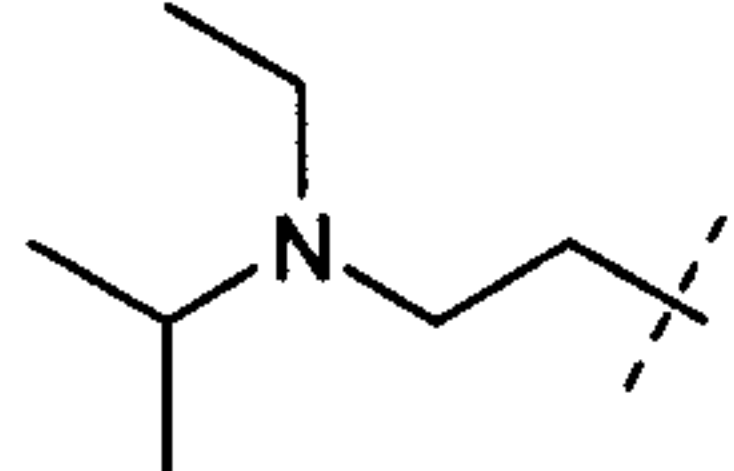
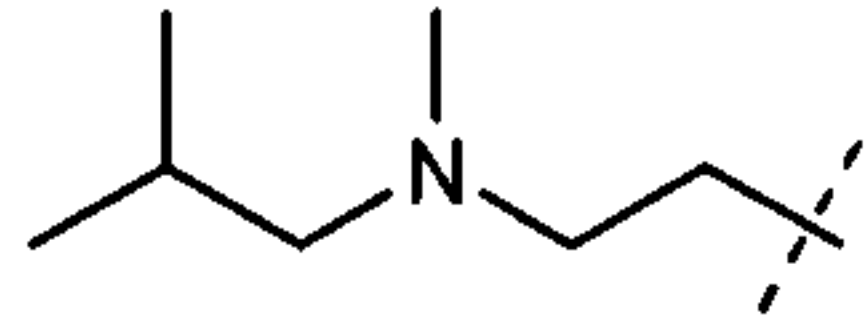
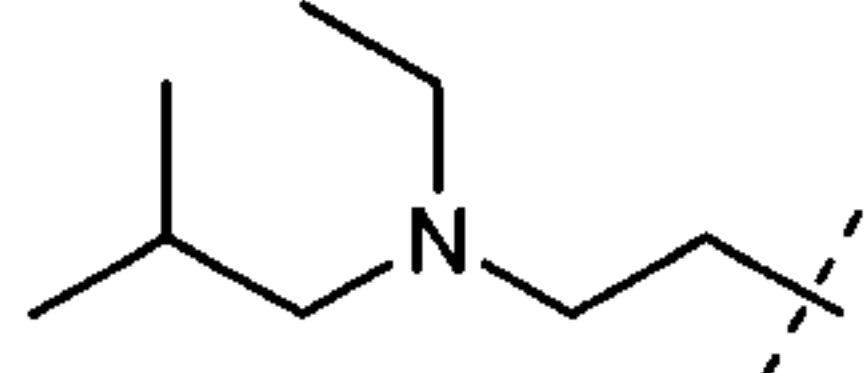
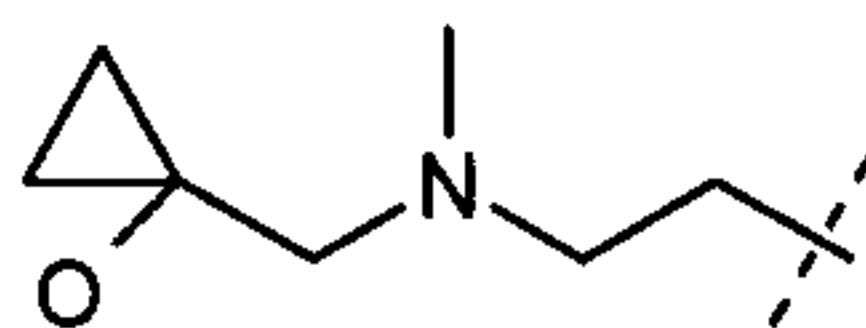
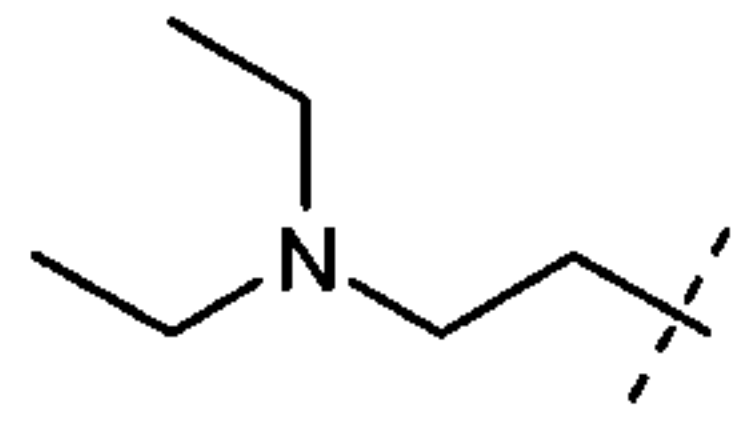
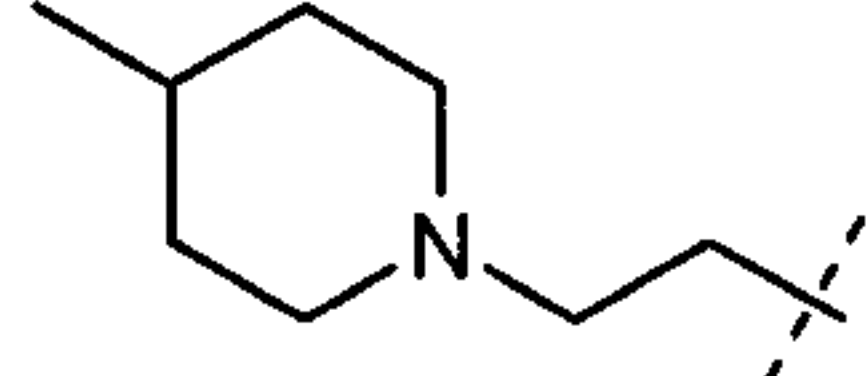
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4.159		-Cl	-Cl	-CF ₃
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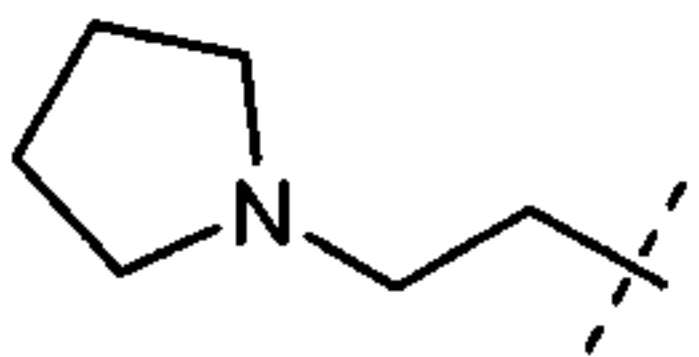
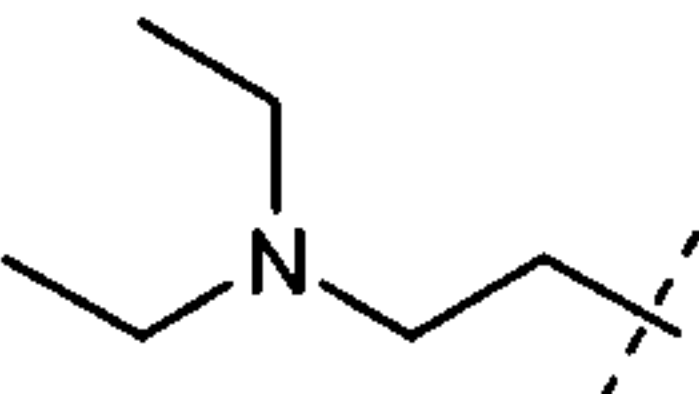
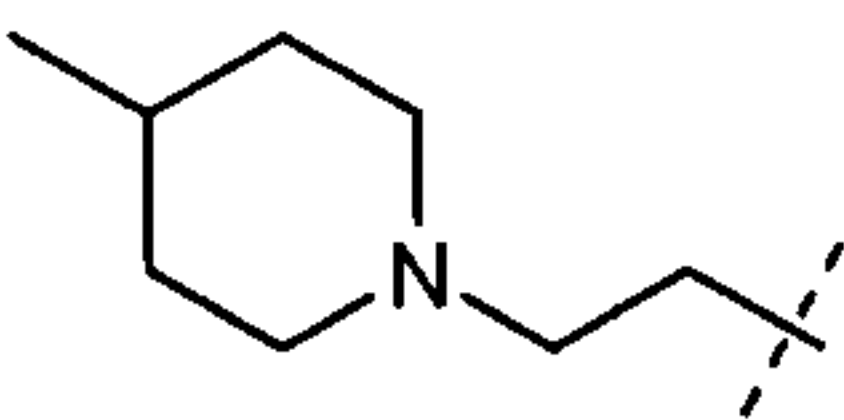
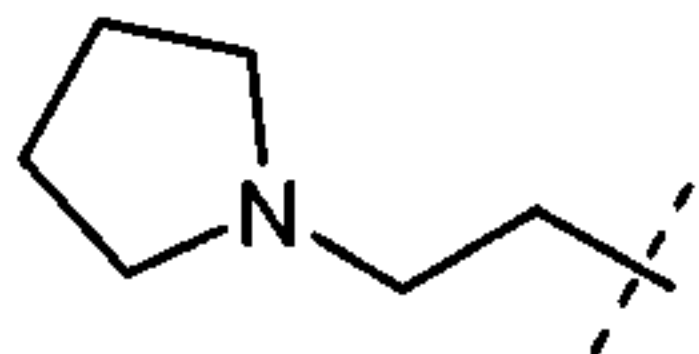
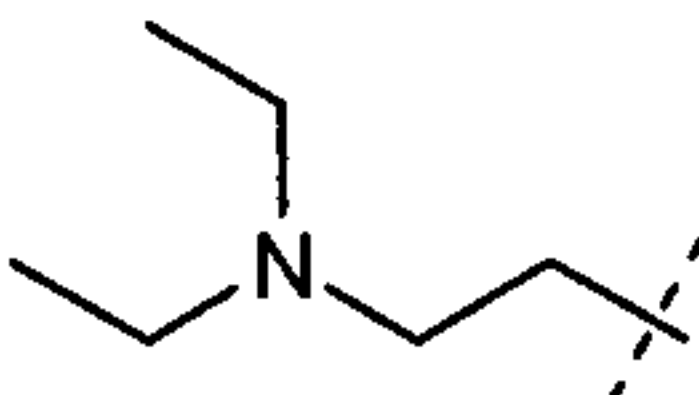
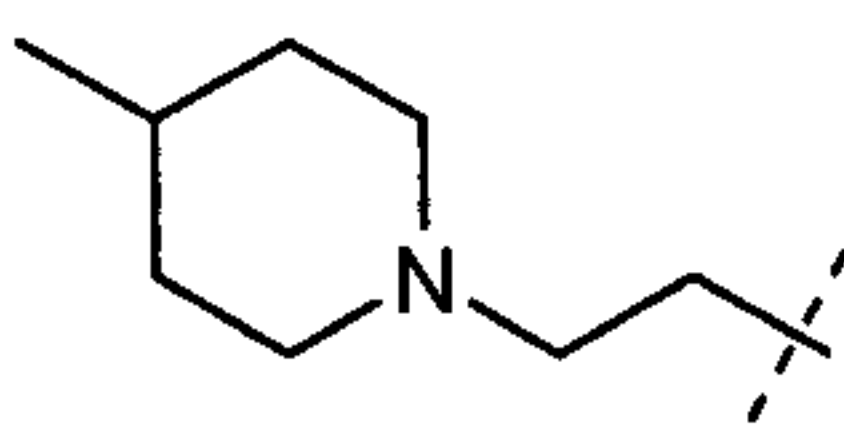
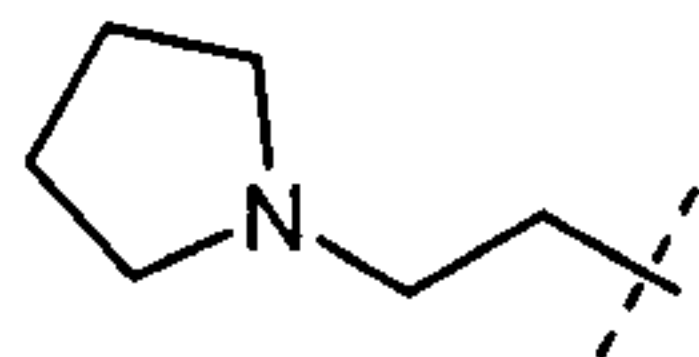
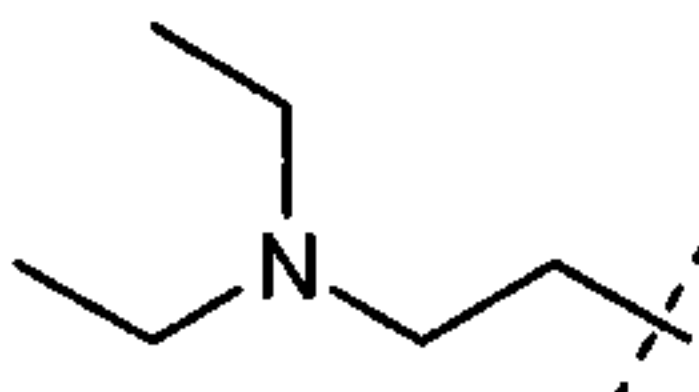
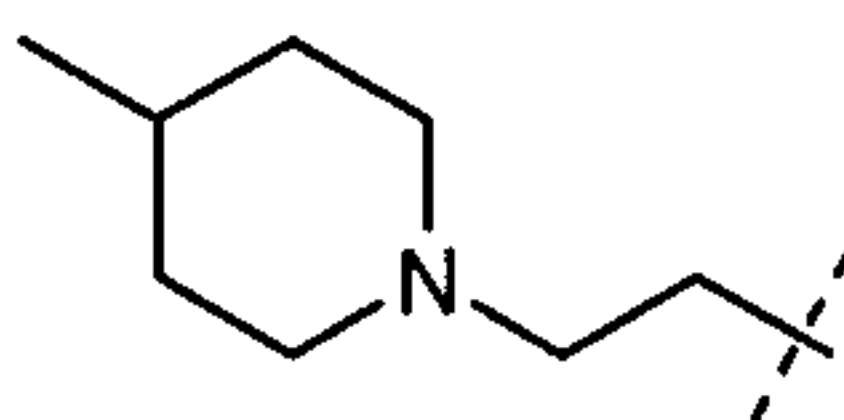
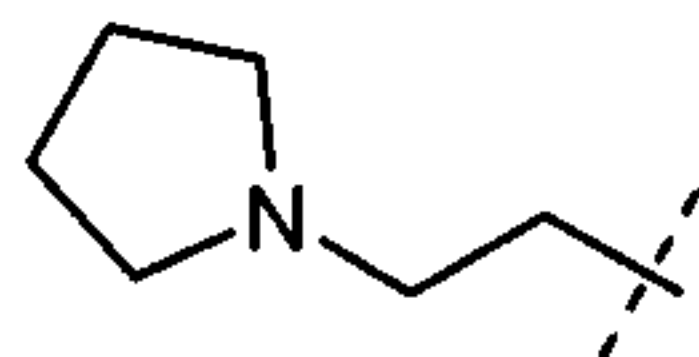
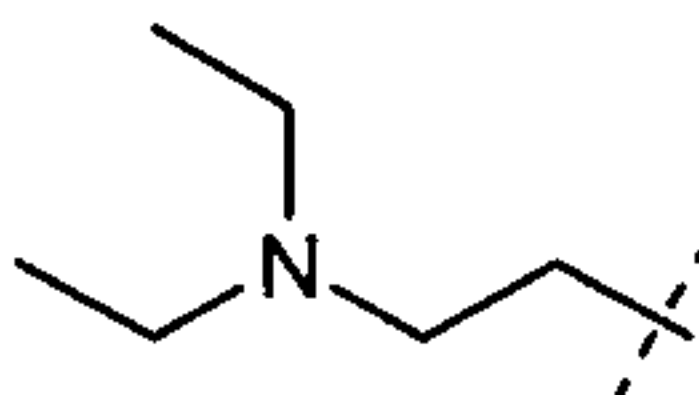
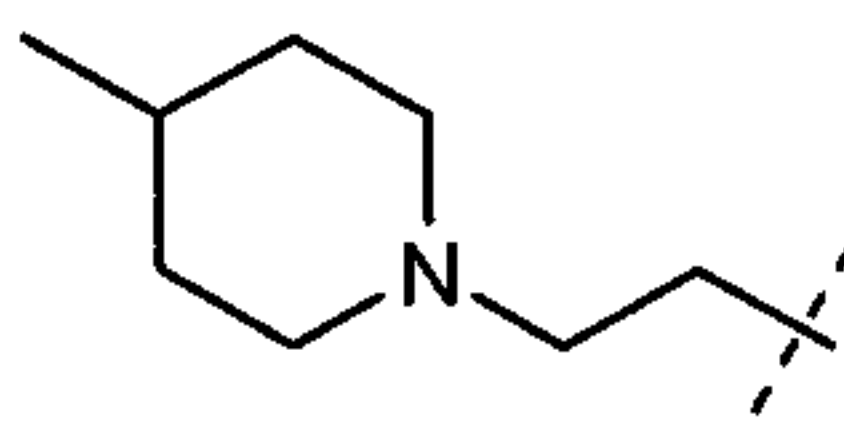
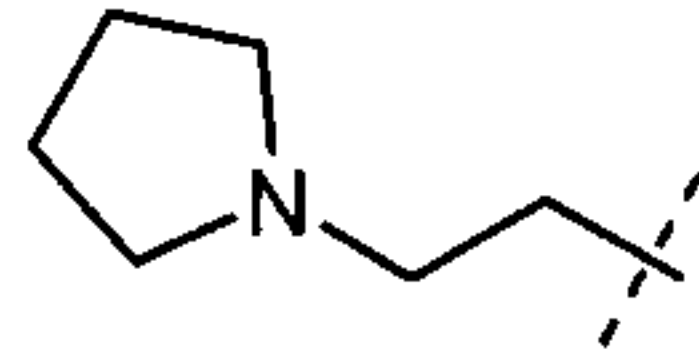
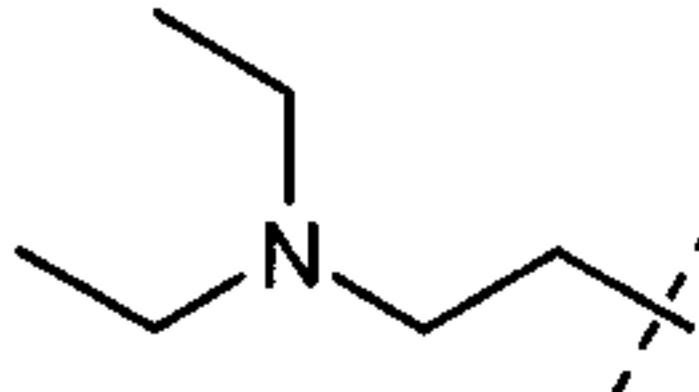


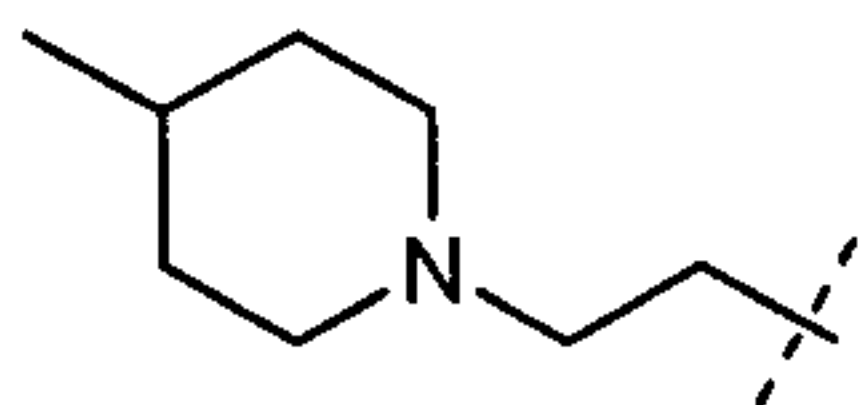
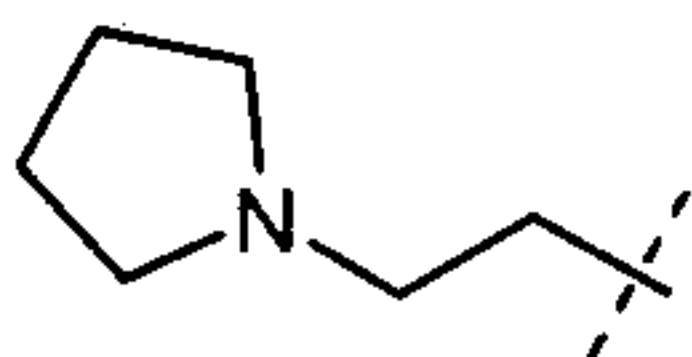
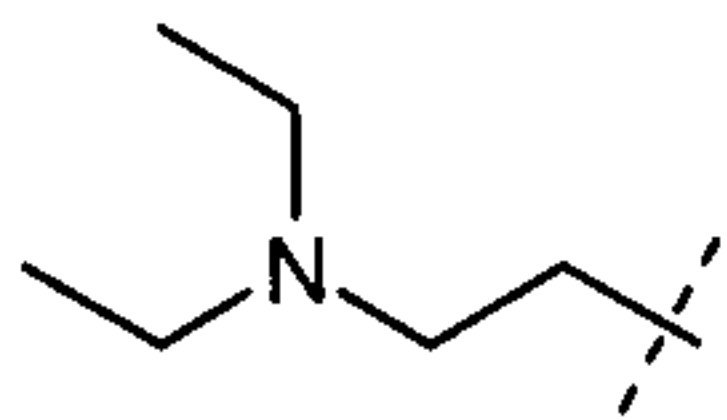
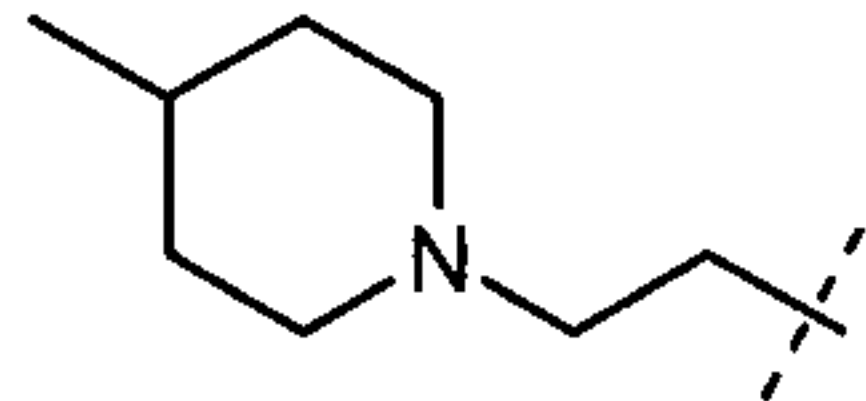
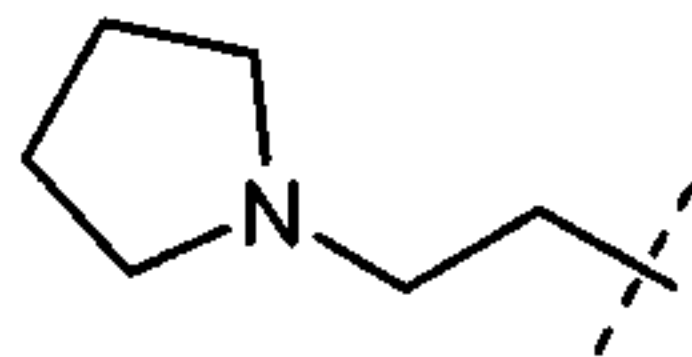
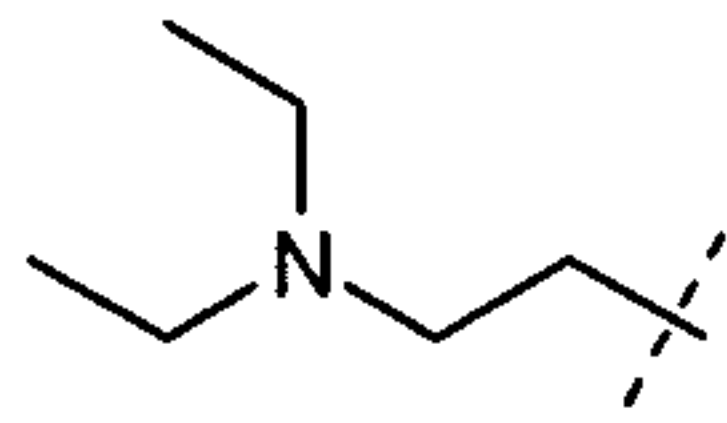
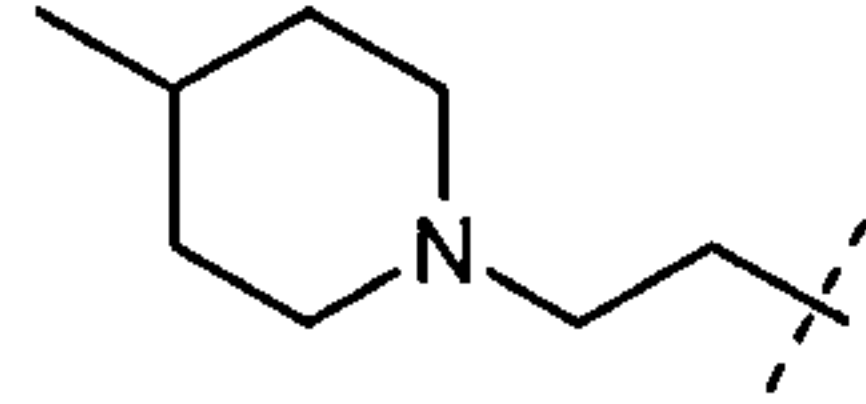
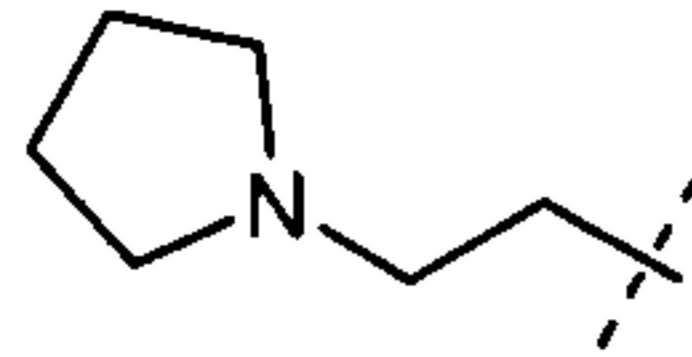
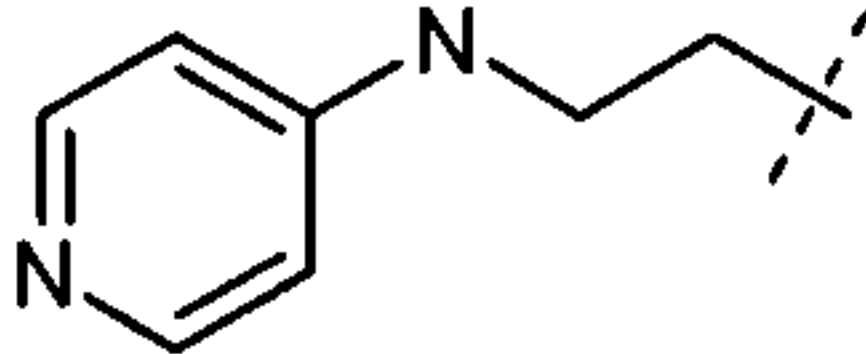
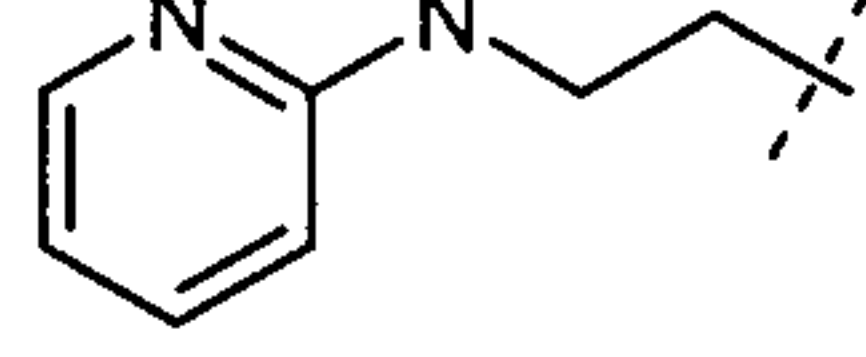
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4.167		-Cl	-Cl	-OMe
4.168		-Cl	-Cl	-Me
4.169		-Cl	-Cl	-Br
4.170		-Cl	-Cl	-NO ₂
4.171		-Cl	-Cl	-NH ₂
4.172		-Cl	-Cl	
4.173		-Cl	-Cl	
4.174		-Cl	-Cl	-OMe
4.175		-Cl	-Cl	-Me
4.176		-Cl	-Cl	-CF ₃
4.177		-Cl	-Cl	-CF ₃

4.178		-Cl	-Cl	-CF ₃
4.179		-Cl	-Cl	-CF ₃
4.180		-Cl	-Cl	-CF ₃
4.181		-Cl	-Cl	-CF ₃
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4.183		-Cl	-Cl	-CF ₃
4.184		-Cl	-Cl	-CF ₃
4.185		-Cl	-Cl	-CF ₃
4.186		-Cl	-Cl	-CF ₃
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4.188		-Cl	-Cl	-CF ₃

4.217		-Me	-Cl	-CF ₃
4.218		-Br	-Cl	-CF ₃
4.219		-Br	-Cl	-CF ₃
4.220		-Br	-Cl	-CF ₃
4.221		-Br	-Cl	-CF ₃
4.222		-Br	-Cl	-CF ₃
4.223		-Br	-Cl	-CF ₃
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4.225		-Br	-Cl	-CF ₃
4.226		-Br	-Cl	-CF ₃
4.227		-Br	-Cl	-CF ₃
4.228		-Br	-Cl	-CF ₃
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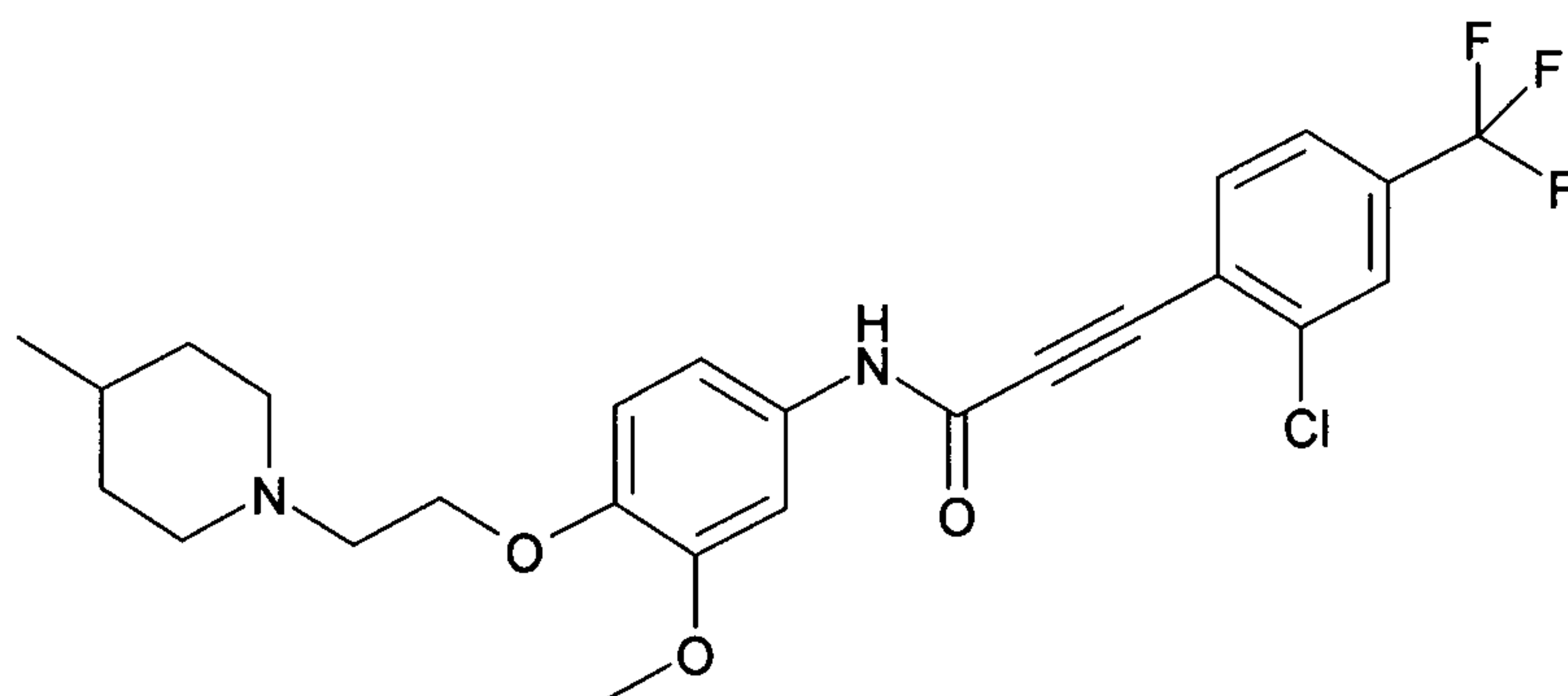
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4.236		-OMe	-Cl	-CF ₃
4.237		-OMe	-Cl	-CF ₃
4.238		-OMe	-Cl	-CF ₃
4.239		-OMe	-Cl	-CF ₃
4.240		-OMe	-Cl	-CF ₃
4.241		-OMe	-Cl	-CF ₃
4.242		-OMe	-Cl	-CF ₃
4.243		-OMe	-Cl	-CF ₃
4.244		-Cl	-Cl	-Cl
4.245		-Cl	-Cl	-Cl

4.246		-Cl	-Cl	-Cl
4.247		-Cl	-Cl	-Me
4.248		-Cl	-Cl	-Me
4.249		-Cl	-Cl	-Me
4.250		-Cl	-Cl	-OMe
4.251		-Cl	-Cl	-OMe
4.252		-Cl	-Cl	-OMe
4.253		-Cl	-Cl	
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4.255		-Cl	-Cl	
4.256		-Cl	-Br	-CF ₃
4.257		-Cl	-Br	-CF ₃
4.258		-Cl	-Br	-CF ₃
4.259		-Cl	-Me	-CF ₃

4.260		-Cl	-Me	-CF ₃
4.261		-Cl	-Me	-CF ₃
4.262		-Cl	-OMe	-CF ₃
4.263		-Cl	-OMe	-CF ₃
4.264		-Cl	-OMe	-CF ₃
4.265		-Cl	-F	-CF ₃
4.266		-Cl	-F	-CF ₃
4.267		-Cl	-F	-CF ₃
4.268		-Cl	-Cl	-CF ₃
4.269		-Cl	-Cl	-CF ₃

Example 4.270:

3-(2-chloro-4-(trifluoromethyl)phenyl)-propynoic acid-{3-methoxy-4-[2-(4-methylpiperidin-1-yl)-ethoxy]-phenyl}-amide



4.270.a. 1-[2-(2-methoxy-4-nitro-phenoxy)-ethyl]-4-methyl-piperidine

Prepared analogously to Method 1.1.c from 1-(2-bromo-ethoxy)-2-methoxy-4-nitro-benzene and 4-methylpiperidine.

Yield: 0.7 g (88.2 % of theory)

5 $C_{15}H_{22}N_2O_4$ (M= 294.35)

Calc.: Molecular ion peak (M+H)⁺: 295

Found: Molecular ion peak (M+H)⁺:

295

R_f value: 0.5 (silica gel, dichloromethane/methanol 9:1).

10 4.270.b. 3-methoxy-4-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenylamine

Prepared analogously to Example 3.1.b. from 1-[2-(2-methoxy-4-nitro-phenoxy)-ethyl]-4-methyl-piperidine.

Yield: 0.51 g (81.1 % of theory)

$C_{15}H_{24}N_2O_2$ (M= 264.37)

15 Calc.: Molecular ion peak (M+H)⁺: 265

Found: Molecular ion peak

(M+H)⁺: 265

R_f value: 0.3 (silica gel, dichloromethane/methanol 9:1).

20 4.270.c. 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-{3-methoxy-4-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenyl}-amide

Prepared analogously to Example 2.3.f. from (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid and 3-methoxy-4-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenylamine.

Yield: 70 mg (23.5 % of theory)

Melting point: 207-209 C

25 $C_{25}H_{26}ClF_3N_2O_3$ (M= 494.94)

Calc.: Molecular ion peak (M+H)⁺: 495/497

Found: Molecular ion peak

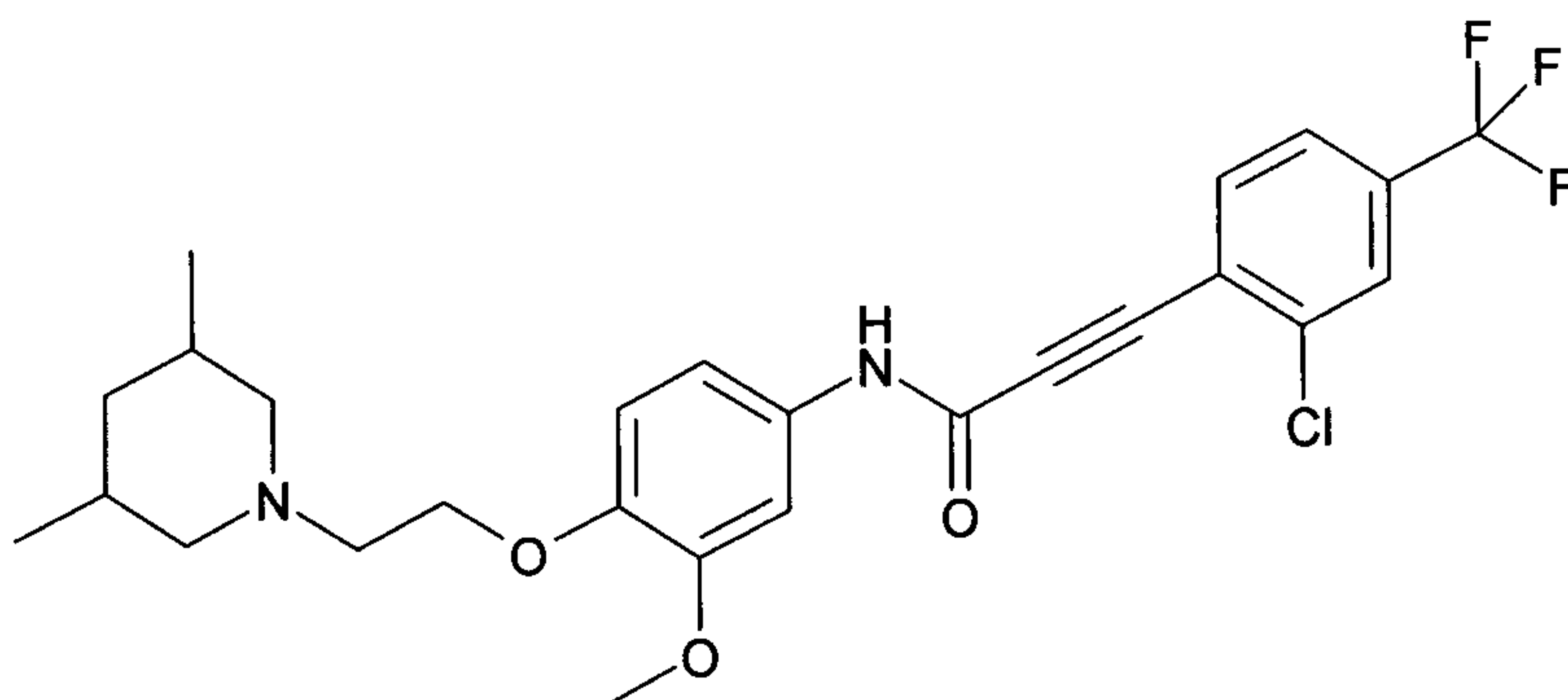
(M+H)⁺: 495/497

R_f value: 0.45 (silica gel, dichloromethane/methanol = 9:1)

30

Example 4.271:

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-{4-[2-(3,5-dimethyl-piperidin-1-yl)-ethoxy]-3-methoxy-phenyl}-amide



4.271.a. 1-[2-(2-methoxy-4-nitro-phenoxy)-ethyl]-3,5-dimethyl-piperidine

Prepared analogously to Method 1.1.c from 1-(2-bromo-ethoxy)-2-methoxy-4-nitro-benzene and 3,5-dimethylpiperidine.

Yield: 0.4 g (48.1 % of theory)

$C_{16}H_{24}N_2O_4$ (M= 308.38)

Calc.: Molecular ion peak (M+H)⁺: 309

Found: Molecular ion peak (M+H)⁺:

309

10 R_f value: 0.5 (silica gel, dichloromethane/methanol 9:1).

4.271.b. 4-[2-(3,5-dimethyl-piperidin-1-yl)-ethoxy]-3-methoxy-phenylamine

Prepared analogously to Example 3.1.b. from 1-[2-(2-methoxy-4-nitro-phenoxy)-ethyl]-3,5-dimethyl-piperidine.

15 Yield: 0.35 g (96.9 % of theory)

$C_{15}H_{24}N_2O_2$ (M= 264.37)

Calc.: Molecular ion peak (M+H)⁺: 279

Found: Molecular ion peak

(M+H)⁺: 279

R_f value: 0.3 (silica gel, dichloromethane/methanol 9:1).

20

4.271.c. 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-{4-[2-(3,5-dimethyl-piperidin-1-yl)-ethoxy]-3-methoxy-phenyl}-amide

Prepared analogously to Example 2.3.f. from (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid and 4-[2-(3,5-dimethyl-piperidin-1-yl)-ethoxy]-3-methoxy-phenylamine.

25 Yield: 160 mg (52.1 % of theory)

Melting point: 196-201 °C

$C_{26}H_{28}ClF_3N_2O_3$ (M= 508.97)

Calc.: Molecular ion peak (M+H)⁺: 509/511

Found: Molecular ion peak

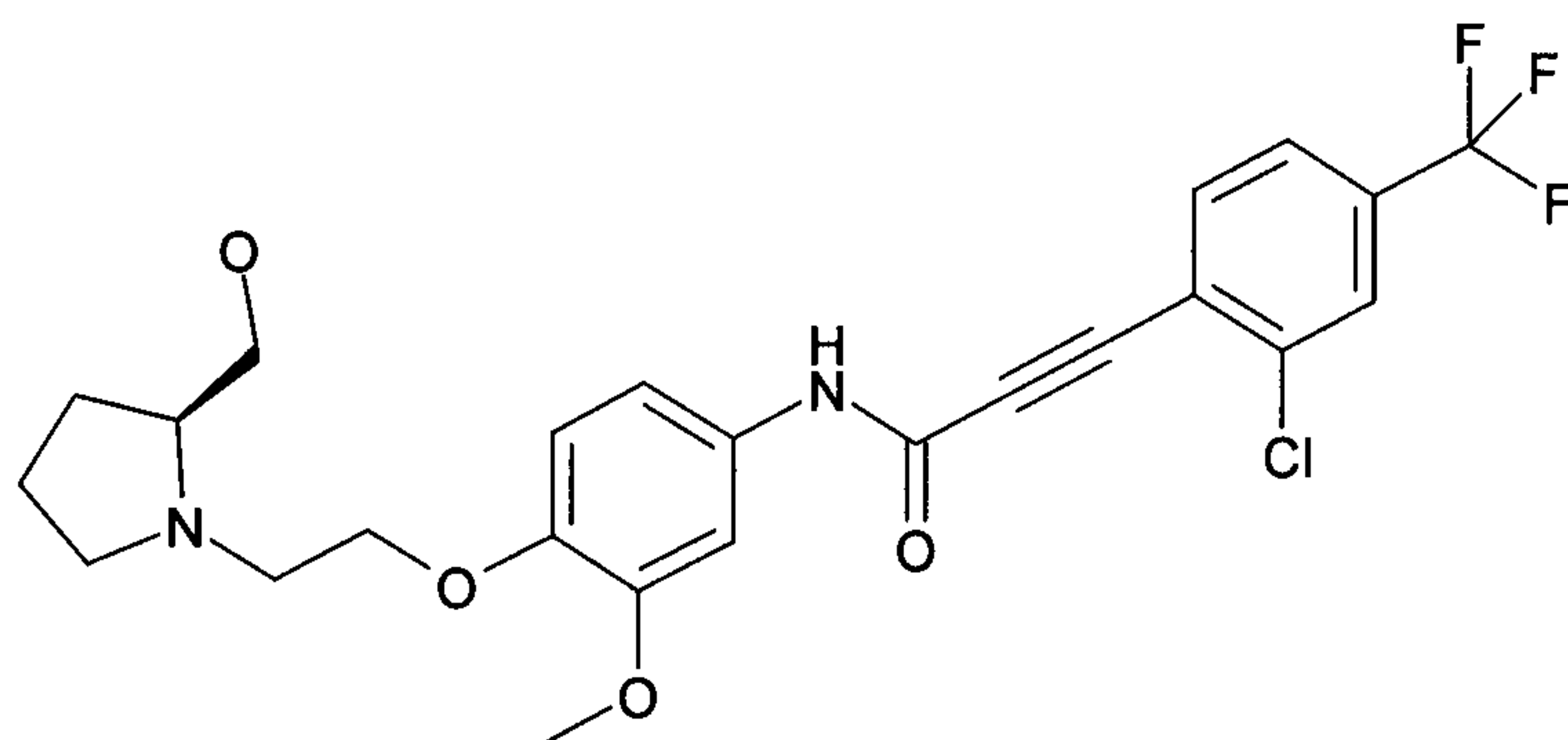
(M+H)⁺: 509/511

R_f value: 0.5 (silica gel, dichloromethane/methanol = 9:1)

5

Example 4.272:

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-{4-[2-((S)-2-hydroxymethyl-pyrrolidin-1-yl)-ethoxy]-3-methoxy-phenyl}-amide



10

4.272.a. {(S)-1-[2-(2-methoxy-4-nitro-phenoxy)-ethyl]-pyrrolidin-2-yl}-methanol

Prepared analogously to Method 1.1.c from 1-(2-bromo-ethoxy)-2-methoxy-4-nitro-benzene and (S)-1-pyrrolidin-2-yl-methanol.

Yield: 0.2 g (25 % of theory)

15 C₁₄H₂₀N₂O₅ (M= 296.32)

Calc.: Molecular ion peak (M+H)⁺: 297

Found: Molecular ion peak (M+H)⁺:

297

R_f value: 0.55 (silica gel, dichloromethane/methanol 9:1).

20 4.272.b. {(S)-1-[2-(4-amino-2-methoxy-phenoxy)-ethyl]-pyrrolidin-2-yl}-methanol

Prepared analogously to Example 3.1.b. from {(S)-1-[2-(2-methoxy-4-nitro-phenoxy)-ethyl]-pyrrolidin-2-yl}-methanol.

Yield: 0.15 g (83.4 % of theory)

C₁₄H₂₂N₂O₃ (M= 266.34)

25 Calc.: Molecular ion peak (M+H)⁺: 267

Found: Molecular ion peak

(M+H)⁺: 267

R_f value: 0.15 (silica gel, dichloromethane/methanol 9:1).

4.272.c. 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-{4-[2-((S)-2-hydroxymethyl-pyrrolidin-1-yl)-ethoxy]-3-methoxy-phenyl}-amide

Prepared analogously to Example 2.3.f. from (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid and {(S)-1-[2-(4-amino-2-methoxy-phenoxy)-ethyl]-pyrrolidin-2-yl}-methanol.

Yield: 140 mg (58.9 % of theory)

Melting point: decomposition at 300 °C

C₂₄H₂₄ClF₃N₂O₄ (M= 496.91)

Calc.: Molecular ion peak (M+H)⁺: 497/499

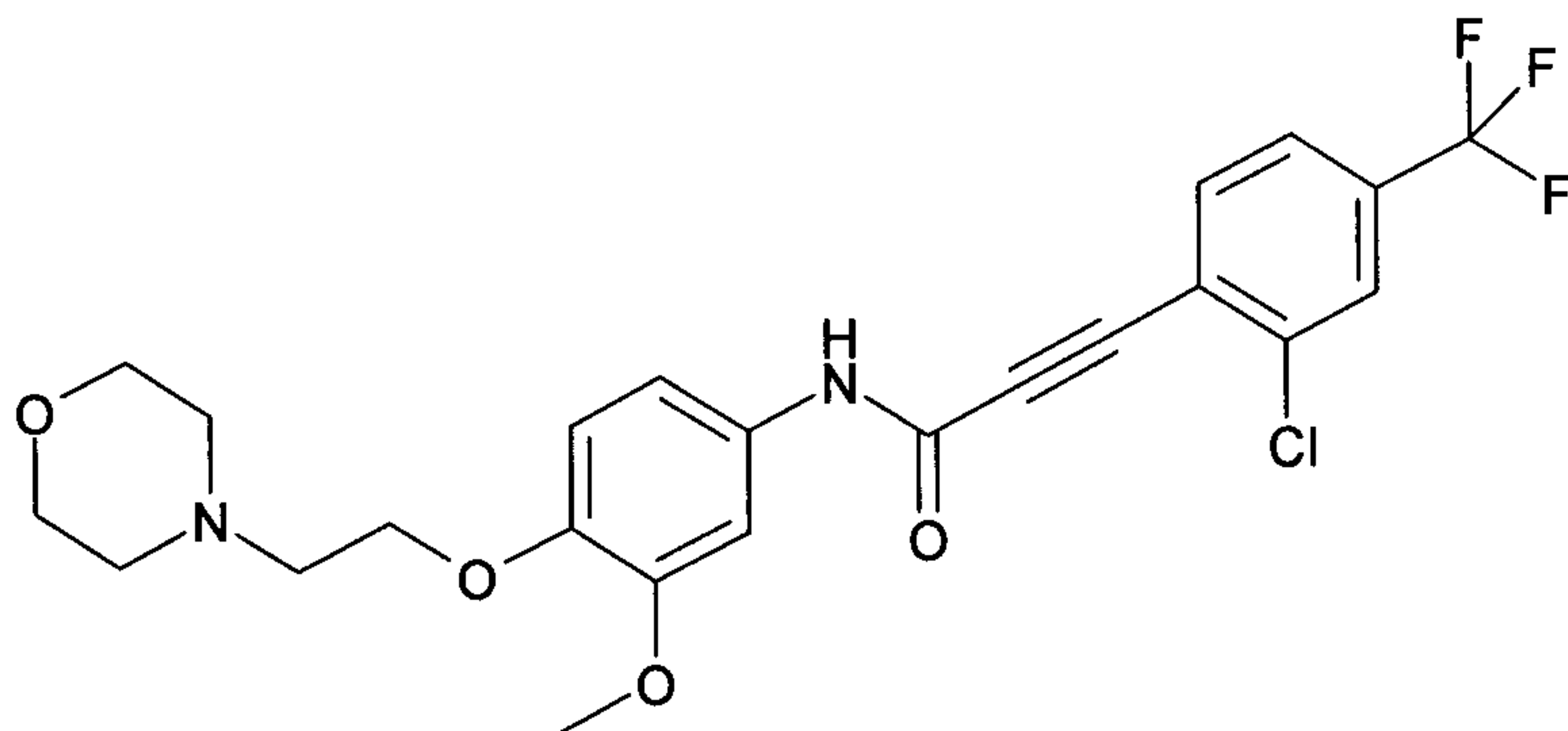
Found: Molecular ion peak

(M+H)⁺: 497/499

R_f value: 0.2 (silica gel, dichloromethane/methanol = 9:1)

Example 4.273:

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[3-methoxy-4-(2-morpholin-4-yl-ethoxy)-phenyl]-amide



4.273.a. 4-[2-(2-methoxy-4-nitro-phenoxy)-ethyl]-morpholine

Prepared analogously to Method 1.1.c from 1-(2-bromo-ethoxy)-2-methoxy-4-nitro-benzene and morpholine.

Yield: 0.3 g (39.4 % of theory)

C₁₃H₁₈N₂O₅ (M= 282.29)

Calc.: Molecular ion peak (M+H)⁺: 283

Found: Molecular ion peak (M+H)⁺:

283

R_f value: 0.6 (silica gel, dichloromethane/methanol 9:1).

4.273.b. 3-methoxy-4-(2-morpholin-4-yl-ethoxy)-phenylamine

Prepared analogously to Example 3.1.b. from 4-[2-(2-methoxy-4-nitro-phenoxy)-ethyl]-morpholine.

Yield: 0.23 g (85.8 % of theory)

C₁₃H₂₀N₂O₃ (M= 252.31)

5 Calc.: Molecular ion peak (M+H)⁺: 253
(M+H)⁺: 253

Found: Molecular ion peak

R_f value: 0.5 (silica gel, dichloromethane/methanol 9:1).

10 4.273.c. 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-[3-methoxy-4-(2-morpholin-4-yl-ethoxy)-phenyl]-amide

Prepared analogously to Example 2.3.f. from (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid and 3-methoxy-4-(2-morpholin-4-yl-ethoxy)-phenylamine.

Yield: 20 mg (6.9 % of theory)

Melting point: 209-211 C

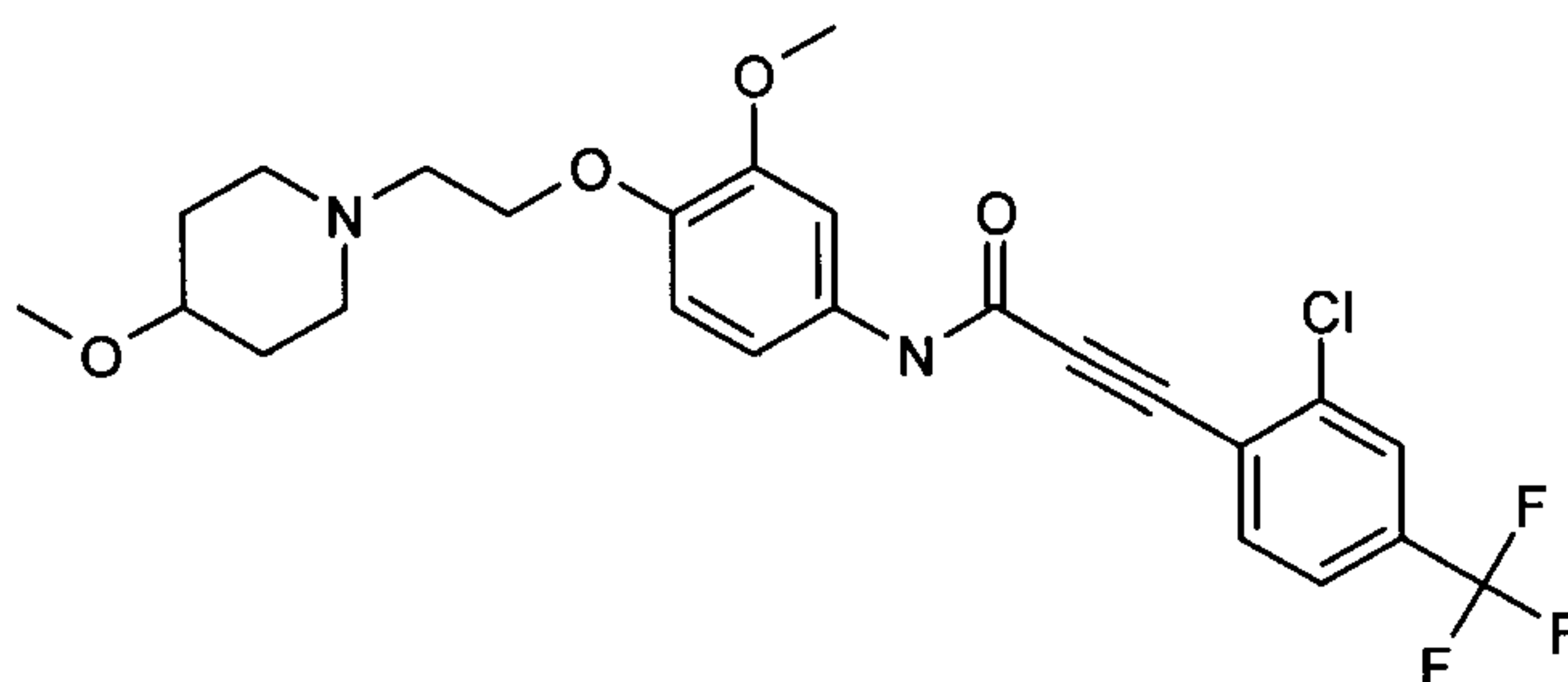
15 C₂₃H₂₂ClF₃N₂O₄ (M= 482.89)

Calc.: Molecular ion peak (M+H)⁺: 483/485
(M+H)⁺: 483/485

Found: Molecular ion peak

R_f value: 0.5 (silica gel, dichloromethane/methanol = 9:1)

20 **Example 4.274:** 3-(2-chloro-4-trifluoromethyl-phenyl)propynoic acid-{3-methoxy-4-[2-(4-methoxy-piperidin-1-yl)-ethoxy]-phenyl}amide



4.274.a. 4-methoxy-1-[2-(2-methoxy-4-nitro-phenoxy)-ethyl]-piperidine

25 Prepared analogously to Example 1.1.c from 1g (3.62 mmol) 1-(2-bromo-ethoxy)-2-methoxy-4-nitro-benzene and 1.25 g (10.87 mmol) 4-methoxypiperidine.

Yield: 1 g (89 % of theory)

C₁₅H₂₂N₂O₅ (M= 310.35)

Calc.: Molecular ion peak (M+H)⁺: 311

Found: Molecular ion peak (M+H)⁺:

311

R_f value: 0.5 (silica gel, dichloromethane/methanol 9:1).

5 4.274.b. 3-methoxy-4-[2-(4-methoxy-piperidin-1-yl)-ethoxy]-phenylamine

Prepared analogously to Example 3.1.b. from 1 g (3.22 mmol) 4-methoxy-1-[2-(2-methoxy-4-nitro-phenoxy)-ethyl]-piperidine.

Yield: 0.85 g (94 % of theory)

C₁₅H₂₄N₂O₃ (M= 280.36)

10 Calc.: Molecular ion peak (M+H)⁺: 281

Found: Molecular ion peak

(M+H)⁺: 281

R_f value: 0.6 (silica gel, dichloromethane/methanol 9:1)

15 4.274.c. 3-(2-chloro-4-trifluoromethyl-phenyl)propynoic acid-{3-methoxy-4-[2-(4-methoxy-piperidin-1-yl)-ethoxy]-phenyl}amide

Prepared analogously to Example 2.3.f. from 150 mg (0.6 mmol) (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid and 186 mg (0.66 mmol) 3-methoxy-4-[2-(4-methoxy-piperidin-1-yl)-ethoxy]-phenylamine.

Yield: 20 mg (7 % of theory)

20 Melting point: 195-197° C

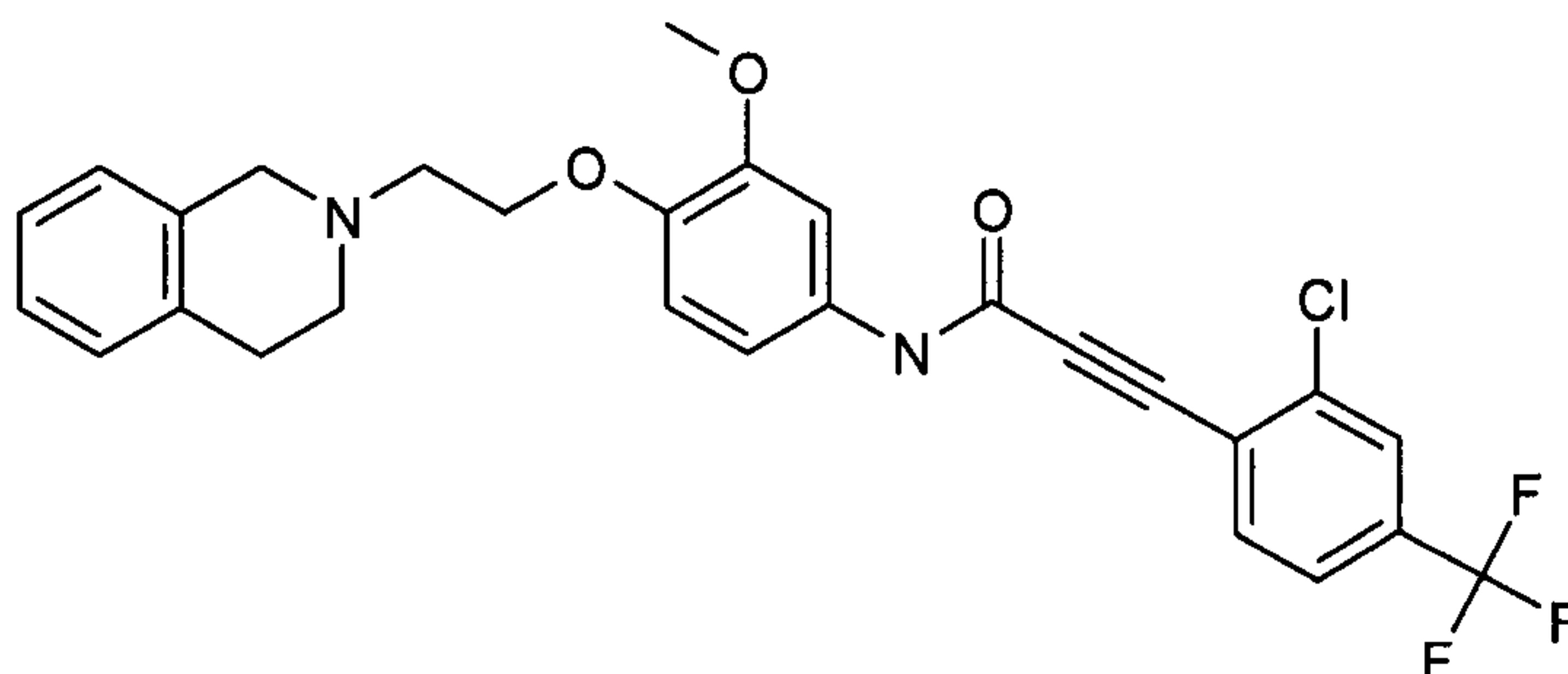
C₂₅H₂₆ClF₃N₂O₄ (M= 510.93)

Calc.: Molecular ion peak (M+H)⁺: 511/513 (Cl) Found: Molecular ion peak (M+H)⁺:
(M+H)⁺: 511/513 (Cl)

R_f value: 0.3 (silica gel, dichloromethane/methanol = 9:1)

25

Example 4.275: 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-{4-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-ethoxy]-3-methoxy-phenyl}-amide-formate



4.275.a. 2-[2-(2-methoxy-4-nitro-phenoxy)-ethyl]-1,2,3,4-tetrahydro-isoquinoline

Prepared analogously to Example 1.1.c from 1 g (3.622 mmol) 1-(2-bromo-ethoxy)-2-methoxy-4-nitro-benzene and 1.36 ml (10.87 mmol) 1,2,3,4-tetrahydro-isoquinoline.

Yield: 1.4 g (77 % of theory)

5 $C_{18}H_{20}N_2O_4$ (M= 328.36)

Calc.: Molecular ion peak (M+H)⁺: 329

Found: Molecular ion peak (M+H)⁺:

329

R_f value: 0.7 (silica gel, dichloromethane/methanol 9:1).

10 **4.275.b. 4-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-ethoxy]-3-methoxy-phenylamine**

Prepared analogously to Example 3.1.b. from 1.4 g (2.77 mmol) 2-[2-(2-methoxy-4-nitro-phenoxy)-ethyl]-1,2,3,4-tetrahydro-isoquinolin (65 %).

Yield: 1.2 g (94 % of theory)

$C_{18}H_{22}N_2O_2$ (M= 298.38)

15 Calc.: Molecular ion peak (M+H)⁺: 299

Found: Molecular ion peak

(M+H)⁺: 299

R_f value: 0.5 (silica gel, dichloromethane/methanol 9:1)

20 **4.275.c. 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-{4-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-ethoxy]-3-methoxy-phenyl}-amide-formate**

Prepared analogously to Example 2.3.f. from 150 mg (0.6 mmol) (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid and 304 mg (0.66 mmol) 4-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-ethoxy]-3-methoxy-phenylamine (65 %).

Yield: 17 mg (5 % of theory)

25 Melting point: 92-95 C

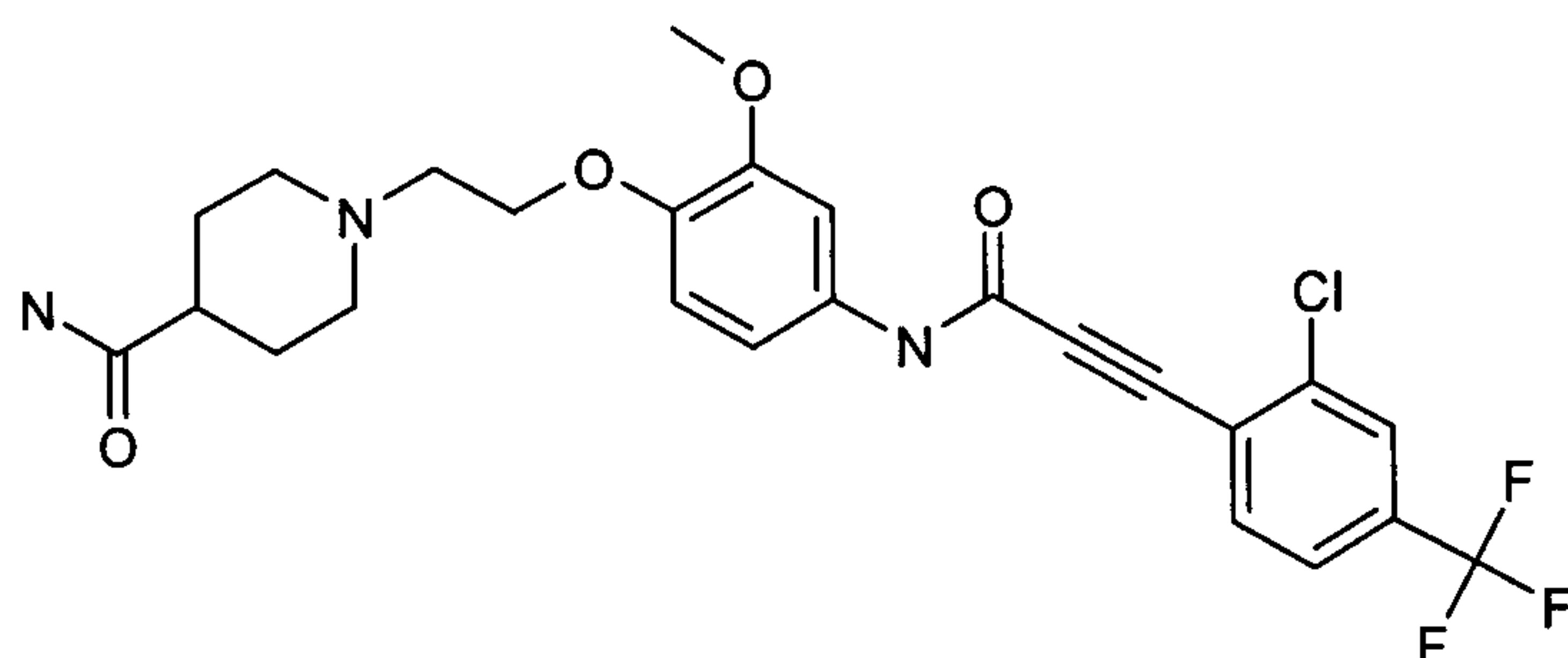
$C_{28}H_{24}ClF_3N_2O_3$ (M=528.96) *CH₂O₂

Calc.: Molecular ion peak (M+H)⁺: 529/531 (Cl) Found: Molecular ion peak (M+H)⁺: 529/531 (Cl)

R_f value: 0.55 (silica gel, dichloromethane/methanol = 9:1)

30

Example 4.276: 1-(2-{4- [3-(2-chloro-4-trifluoromethyl-phenyl)-propynoylamino]-2-methoxy-phenoxy}-ethyl)-piperidine-4-carboxylic acid amide



4.276.a. 1-[2-(2-methoxy-4-nitro-phenoxy)-ethyl]-piperidine-4-carboxylic acid amide

Prepared analogously to Example 1.1.c from 1 g (3.622 mmol) 1-(2-bromo-ethoxy)-2-methoxy-4-nitro-benzene and 1.4 g (10.87 mmol) piperidine-4-carboxylic acid amide.

5 Yield: 1.05 g (90 % of theory)

$C_{15}H_{21}N_3O_5$ (M= 323.34)

Calc.: Molecular ion peak (M+H)⁺: 324

Found: Molecular ion peak (M+H)⁺:

324

R_f value: 0.4 (silica gel, dichloromethane/methanol/ammonia 9:1:0.1).

10

4.276.b. 1-[2-(4-amino-2-methoxy-phenoxy)-ethyl]-piperidine-4-carboxylic acid amide

Prepared analogously to Example 3.1.b. from 1 g (3.1 mmol) 1-[2-(2-methoxy-4-nitro-phenoxy)-ethyl]-piperidine-4-carboxylic acid amide.

Yield: 0.8 g (88 % of theory)

15 $C_{15}H_{23}N_3O_3$ (M= 298.38)

Calc.: Molecular ion peak (M+H)⁺: 294

Found: Molecular ion peak

(M+H)⁺: 294

R_f value: 0.3 (silica gel, dichloromethane/methanol/ammonia 9:1:0.1)

20 4.276.c. 3-(1-(2-{4- [3-(2-chloro-4-trifluoromethyl-phenyl)-propinoylamino]-2-methoxy-phenoxy}-ethyl)-piperidine-4-carboxylic acid amide

Prepared analogously to Example 2.3.f. from 150 mg (0.6 mmol) (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid and 194 mg (0.66 mmol) 1-[2-(4-amino-2-methoxy-phenoxy)-ethyl]-piperidine-4-carboxylic acid amide.

25 Yield: 310 mg (98 % of theory)

Melting point: 150 °C

$C_{25}H_{25}ClF_3N_3O_4$ (M=523.93)

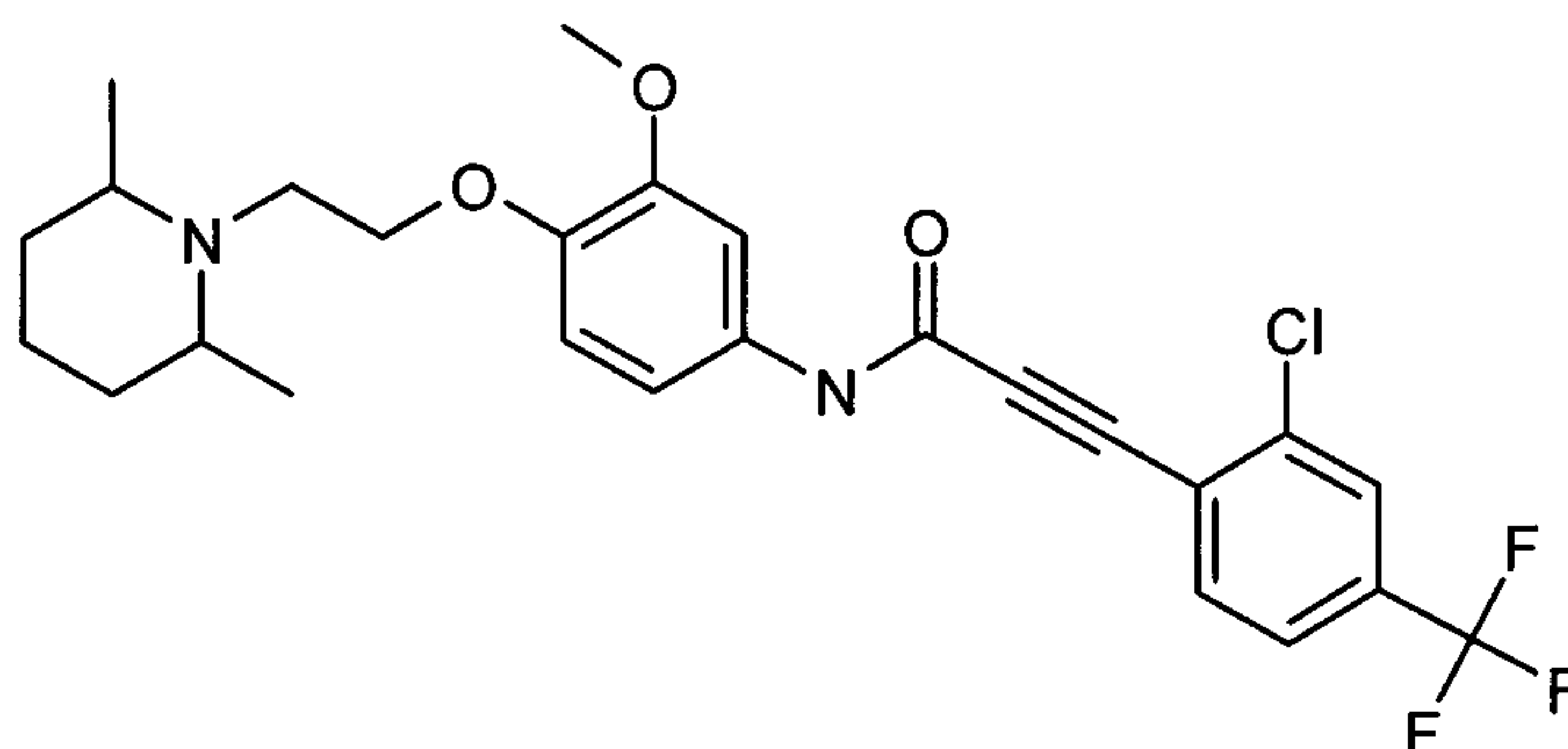
Calc.: Molecular ion peak (M+H)⁺: 524/526 (Cl)

Found: Molecular ion peak

(M+H)⁺: 524/526 (Cl)

R_f value: 0.4 (silica gel, dichloromethane/methanol/ammonia = 9:1:0.1)

Example 4.277: 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-{4-[2-(2,6-dimethyl-piperidin-1-yl)-ethoxy]-3-methoxy-phenyl}-amide



5

4.277.a. 1-[2-(2-methoxy-4-nitro-phenoxy)-ethyl]-2,6-dimethyl-piperidine Prepared analogously to Example 1.1.c from 1 g (3.622 mmol) 1-(2-bromo-ethoxy)-2-methoxy-4-nitro-benzene and 1.5 ml (10.87 mmol) 2,6-dimethyl-piperidine.

Yield: 0.85 g (76 % of theory)

10 C₁₆H₂₄N₂O₄ (M= 308.37)

Calc.: Molecular ion peak (M+H)⁺: 309

Found: Molecular ion peak (M+H)⁺:

309

R_f value: 0.55 (silica gel, dichloromethane/methanol 9:1).

15 4.277.b. 4-[2-(2,6-dimethyl-piperidin-1-yl)-ethoxy]-3-methoxy-phenylamine

Prepared analogously to Example 3.1.b. from 0.84 g (2.72 mmol) 1-[2-(2-methoxy-4-nitro-phenoxy)-ethyl]-2,6-dimethyl-piperidine.

Yield: 0.65 g (86 % of theory)

C₁₆H₂₆N₂O₂ (M= 278.39)

20 Calc.: Molecular ion peak (M+H)⁺: 279
(M+H)⁺: 279

Found: Molecular ion peak

R_f value: 0.1 (silica gel, dichloromethane/methanol 9:1)

4.277.c. 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-{4-[2-(2,6-dimethyl-piperidin-1-yl)-ethoxy]-3-methoxy-phenyl}-amide

25

Prepared analogously to Example 2.3.f. from 150 mg (0.6 mmol) (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid and 185 mg (0.663 mmol) 4-[2-(2,6-dimethyl-piperidin-1-yl)-ethoxy]-3-methoxy-phenylamine.

Yield: 150 mg (49 % of theory)

Melting point: 225-227° C

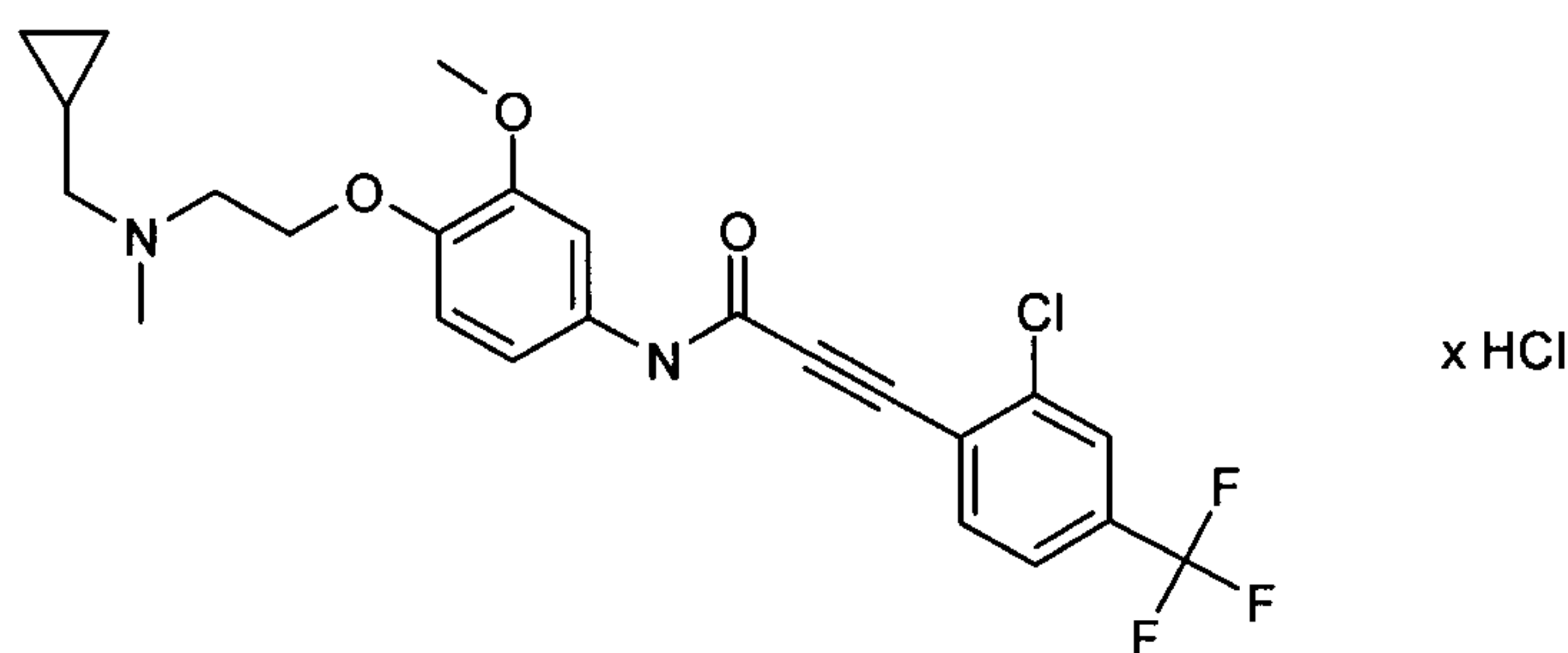
$C_{26}H_{28}ClF_3N_2O_3$ (M=508.96)

Calc.: Molecular ion peak (M+H)⁺: 509/511 (Cl) Found: Molecular ion peak (M+H)⁺:

5 509/511 (Cl)

R_f value: 0.2 (silica gel, dichloromethane/methanol 9:1)

Example 4.278: 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-{4-[2-(cyclopropylmethyl-methyl-amino)-ethoxy]-3-methoxy-phenyl}-amide-hydrochloride



10

cyclopropylmethyl-[2-(2-methoxy-4-nitro-phenoxy)-ethyl]-methyl-amine

Prepared analogously to Example 1.1.c from 1 g (3.62 mmol) 1-(2-bromo-ethoxy)-2-methoxy-4-nitro-benzene and 900 mg (10.57 mmol) cyclopropyl-methyl-amine.

Yield: 0.95 g (94 % of theory)

15 $C_{14}H_{20}N_2O_4$ (M= 280.32)

Calc.: Molecular ion peak (M+H)⁺: 281

Found: Molecular ion peak (M+H)⁺:

281

R_f value: 0.4 (silica gel, dichloromethane/methanol 9:1).

20 4.278.b. 4-[2-(cyclopropylmethyl-methyl-amine)-ethoxy]-3-methoxy-phenylamine

Prepared analogously to Example 3.1.b. from 950 mg (3.4 mmol) cyclopropylmethyl-[2-(2-methoxy-4-nitro-phenoxy)-ethyl]-methyl-amine.

Yield: 0.68 g (80 % of theory)

$C_{14}H_{22}N_2O_2$ (M= 250.34)

25 Calc.: Molecular ion peak (M+H)⁺: 251

Found: Molecular ion peak

(M+H)⁺: 251

R_f value: 0.35 (silica gel, dichloromethane/methanol/ammonia 9:1:0.1)

4.278.c. 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-{4-[2-(cyclopropylmethyl-methyl-amino)-ethoxy]-3-methoxy-phenyl}-amide-hydrochloride

Prepared analogously to Example 2.3.f. from 150 mg (0.6 mmol) (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid and 166 mg (0.66 mmol) 4-[2-(cyclopropylmethyl-methyl-amine)-ethoxy]-3-methoxy-phenylamine.

Yield: 130 mg (45 % of theory)

Melting point: 173-176 C

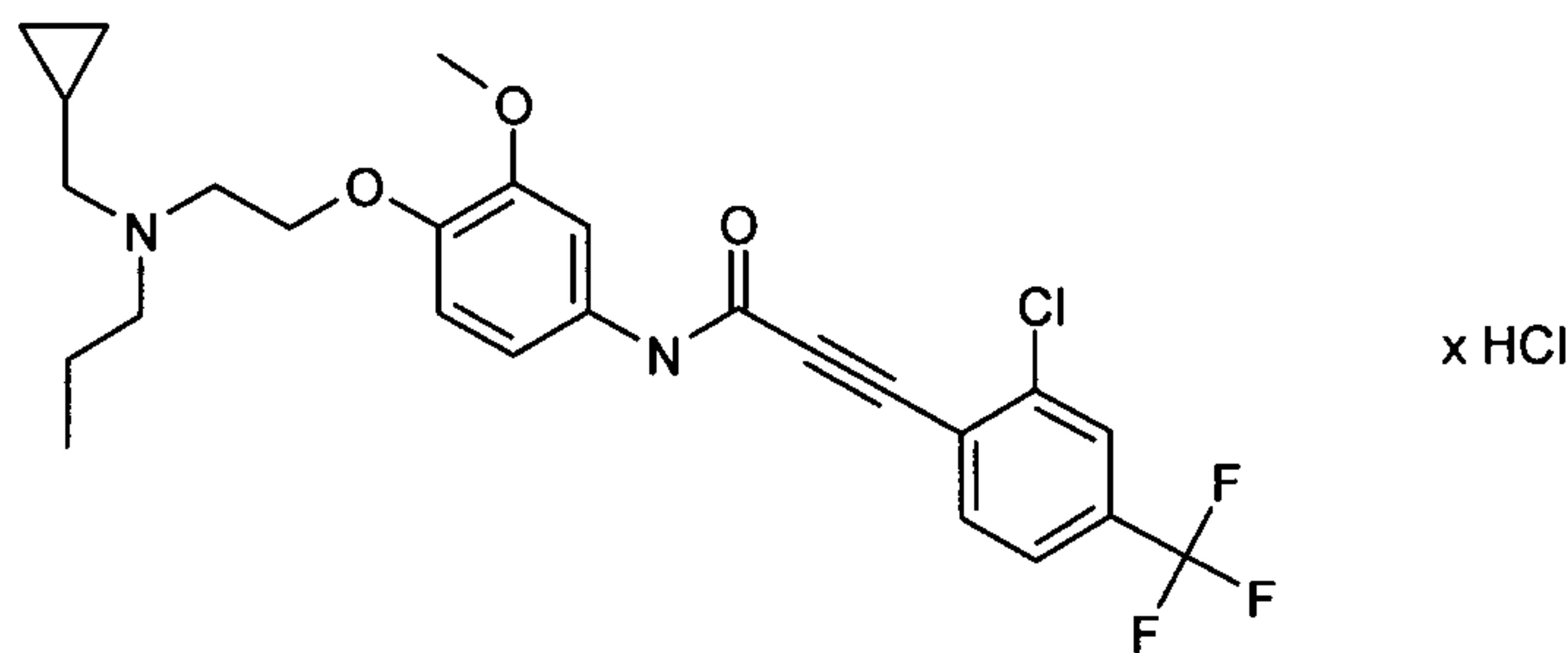
$C_{24}H_{24}ClF_3N_2O_3$ (M=480.91) *HCl

10 Calc.: Molecular ion peak (M+H)⁺: 481/483 (Cl) Found: Molecular ion peak (M+H)⁺: 481/483 (Cl)

R_f value: 0.2 (silica gel, dichloromethane/methanol 9:1)

Example 4.279: 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-{4-[2-(cyclopropylmethyl-propyl-amino)-ethoxy]-3-methoxy-phenyl}-amide-hydrochloride

15



cyclopropylmethyl-[2-(2-methoxy-4-nitro-phenoxy)-ethyl]-propyl-amine

Prepared analogously to Example 1.1.c from 1 g (3.62 mmol) 1-(2-bromo-ethoxy)-2-methoxy-4-nitro-benzene and 1.51 ml (10.57 mmol) cyclopropyl-methyl-propyl-amine.

20 Yield: 0.95 g (85 % of theory)

$C_{16}H_{24}N_2O_4$ (M= 308.37)

Calc.: Molecular ion peak (M+H)⁺: 309

Found: Molecular ion peak (M+H)⁺:

309

R_f value: 0.4 (silica gel, dichloromethane/methanol 9:1).

25

4.279.b. 4-[2-(cyclopropylmethyl-propyl-amino)-ethoxy]-3-methoxy-phenylamine

Prepared analogously to Example 3.1.b. from 950 mg (3.1 mmol) cyclopropylmethyl-[2-(2-methoxy-4-nitro-phenoxy)-ethyl]-propyl-amine.

Yield: 0.74 g (86 % of theory)

C₁₆H₂₆N₂O₂ (M= 278.39)

Calc.: Molecular ion peak (M+H)⁺: 279

Found: Molecular ion peak

(M+H)⁺: 279

R_f value: 0.4 (silica gel, dichloromethane/methanol/ammonia 9:1:0.1)

5

4.279.c. 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-{4-[2-(cyclopropylmethyl-propyl-amino)-ethoxy]-3-methoxy-phenyl}-amide-hydrochloride

Prepared analogously to Example 2.3.f. from 150 mg (0.6 mmol) (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid and 185 mg (0.66 mmol) 4-[2-

10 (cyclopropylmethyl-propyl-amino)-ethoxy]-3-methoxy-phenylamine.

Yield: 180 mg (59 % of theory)

Melting point: 185-188° C

C₂₆H₂₈ClF₃N₂O₃ (M=508.96) *HCl

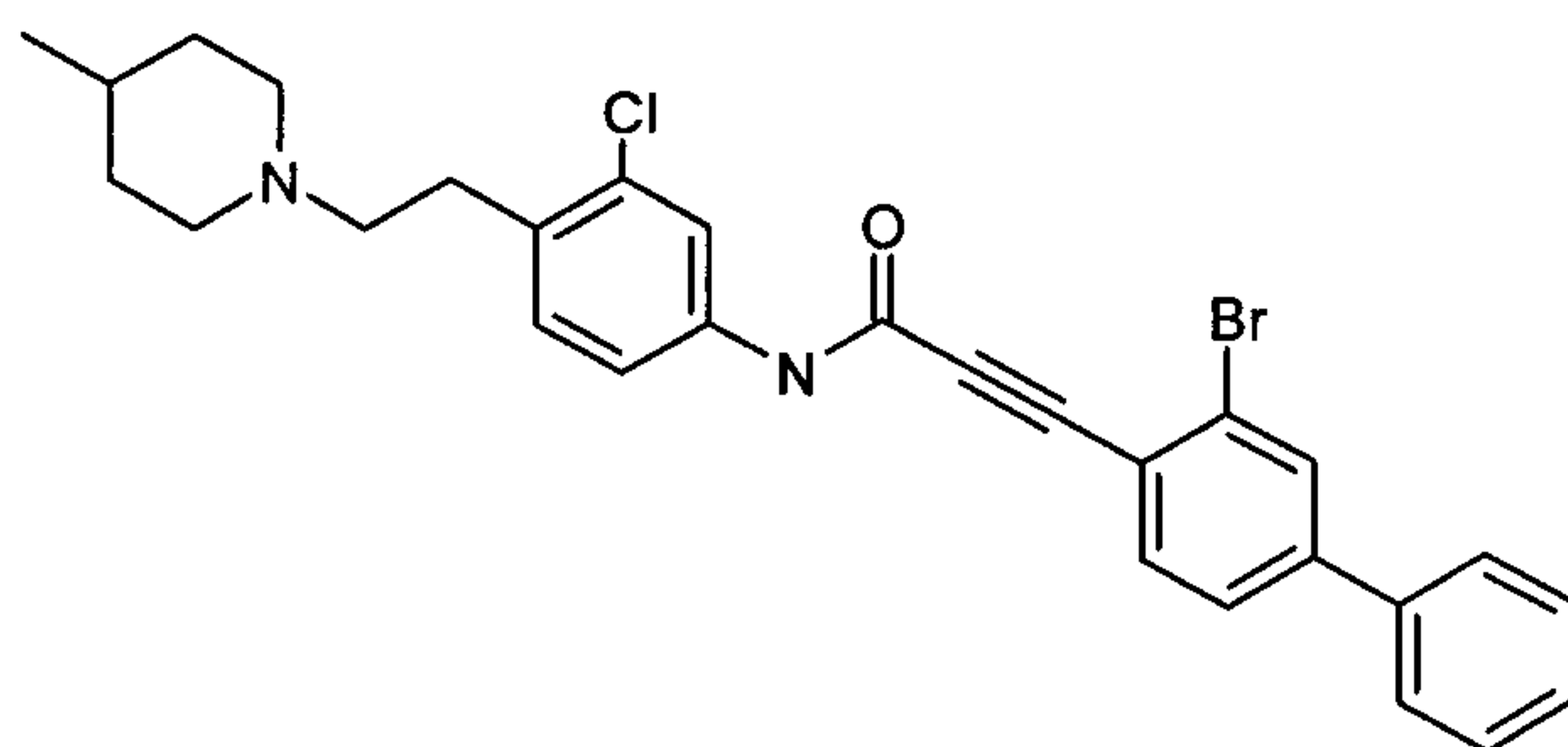
Calc.: Molecular ion peak (M+H)⁺: 509/511 (Cl) Found: Molecular ion peak (M+H)⁺:

15 509/511 (Cl)

R_f value: 0.35 (silica gel, dichloromethane/methanol 9:1)

20 **Example 4.281:**

3-(3-bromo-biphenyl-4-yl)-propynoic acid-{3-chloro-4-[2-(4-methyl-piperidin-1-yl)-ethyl]-phenyl}-amide



25 **4.281a. 3-bromo-biphenyl-4-ylamine**

8.7 ml (76.8 mmol) of a 48% hydrogen bromide solution are added dropwise to a solution of 13.008 g (76.8 mmol) biphenyl-4-ylamine in 60 ml DMSO at ambient temperature and the mixture is stirred for 14 hours. Then it is heated to 100 °C for one hour, the mixture is then cooled and poured onto water. By the addition of ammonia

solution the reaction mixture is made alkaline and the precipitate formed is filtered off and washed with water. The purification is carried out by column chromatography on silica gel (eluant: dichloromethane).

Yield: 11.3 g (60 % of theory)

5 $C_{12}H_{10}BrNO$ (M= 248.19)

Calc.: Molecular ion peak (M+H)⁺: 248/250 (Cl) Found: Molecular ion peak (M+H)⁺: 248/250 (Cl)

4.281b. 3-iodo-biphenyl-4-ylamine

10 A solution of 7.3 g (29.4 mmol) 3-bromo-biphenyl-4-ylamine in 120 ml acetic acid is mixed with 6 ml concentrated hydrochloric acid at ambient temperature, cooled to 15°C and stirred for 30 minutes. A solution of 2 g (28.9 mmol) sodium nitrite in 7 ml of water is slowly added dropwise to this reaction mixture at 15 °C and stirred for 30 minutes. Then at 5°C a solution of 5.4 g (32.5 mmol) potassium iodide in 28 ml of
15 water is slowly added dropwise and the mixture is stirred. After 30 minutes 2.95g sodium thiosulphate are added and the mixture is stirred for a further 30 minutes. Then the reaction mixture is evaporated down and combined with water/ethyl acetate. The aqueous phase is again extracted with ethyl acetate, the combined aqueous phases are extracted once with water and dried over sodium sulphate. The
20 purification is carried out by column chromatography on silica gel (eluant: petroleum ether).

Yield: 6.6 g (85 % of theory)

$C_{12}H_8BrI$ (M= 359.00)

Calc.: Molecular ion peak (M)⁺: 358/360 (Br) Found: Molecular ion peak (M)⁺:
25 358/360 (Br)

4.281c. (3-bromo-biphenyl-4-ylethynyl)-*tert*-butyl-dimethyl-silane

Prepared analogously to 1.1.d from 3-iodo-biphenyl-4-ylamine and *tert*-butyl-ethynyl-dimethyl-silane.

30 Yield: 0.52 g (72 % of theory)

$C_{20}H_{23}BrSi$ (M= 371.38)

Calc.: Molecular ion peak (M+H)⁺: 371/373 (Br) Found: Molecular ion peak (M+H)⁺: 371/373 (Br)

4.281.d 3-bromo-4-ethynyl-biphenyl

1.99 ml (1.99 mmol) of a 1 M tetrabutylammonium fluoride solution in THF are added batchwise at 5 °C to a solution of 495 mg (1.33 mmol) (3-bromo-biphenyl-4-ylethynyl)-
5 *tert*-butyl-dimethyl-silane in 8 ml anhydrous THF. The reaction mixture is stirred for another 30 minutes at ambient temperature and evaporated down. The residue is combined with diethyl ether and water and the organic phase is dried over sodium sulphate.

Yield: 0.34 g (99 % of theory)

10 $C_{14}H_9Br$ (M= 257.12)

Calc.: Molecular ion peak (M-H)⁻: 255/257 (Br) Found: Molecular ion peak (M-H)⁻: 255/257 (Br)

15 4.281e. (3-bromo-biphenyl-4-yl)-propynoic acid

Prepared analogously to 4.3.a from 3-bromo-4-ethynyl-biphenyl and carbon dioxide.

Yield: 2.5 g (89% of theory)

$C_{15}H_9BrO_2$ (M= 301.13)

Calc.: Molecular ion peak (M+H)⁺: 301/303 (Br) Found: Molecular ion peak
20 (M+H)⁺: 301/303 (Br)

R_f value: 0.3 (silica gel, dichloromethane/methanol 90:10)

25 4.281.f. 3-(3-bromo-biphenyl-4-yl)-propynoic acid-{3-chloro-4-[2-(4-methyl-piperidin-1-yl)-ethyl]-phenyl}-amide

Prepared analogously to Example 2.3.f. from (3-bromo-biphenyl-4-yl)-propynoic acid and 3-chloro-4-[2-(4-methyl-piperidin-1-yl)-ethyl]-phenylamine.

Yield: 0.24 g (50% of theory)

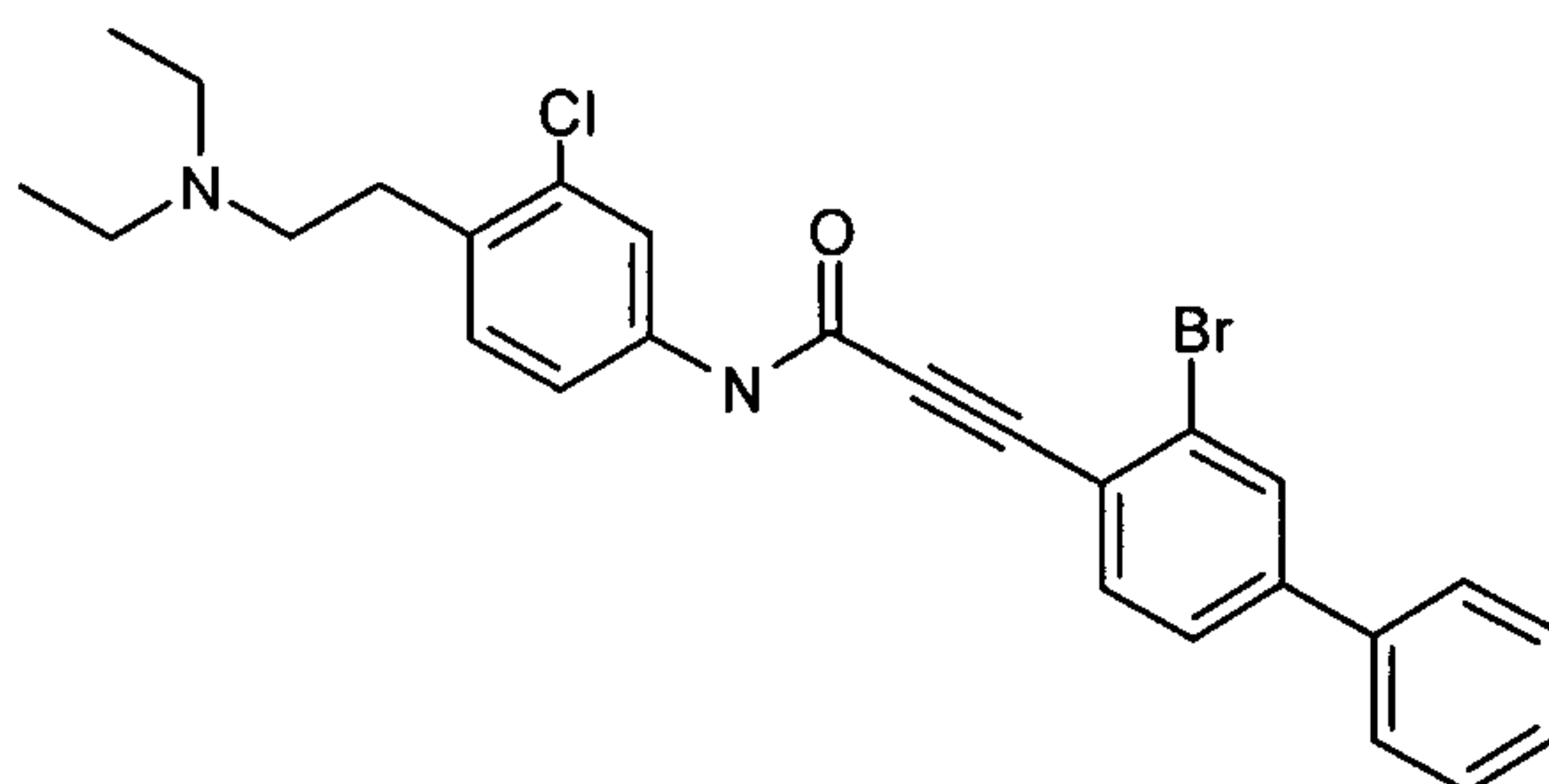
$C_{29}H_{28}BrClN_2O$ (M= 535.90)

30 Calc.: Molecular ion peak (M+H)⁺: 535/37/39 Found: Molecular ion peak (M+H)⁺: 535/37/39

R_f value: 0.48 (silica gel, dichloromethane/methanol 90:10)

Example 4.282:

3-(3-bromo-biphenyl-4-yl)-propynoic acid-[3-chloro-4-(2-diethylamino-ethyl)-phenyl]-amide-hydrochloride



5

Prepared analogously to Example 2.3.f. from (3-bromo-biphenyl-4-yl)-propynoic acid and 3-chloro-4-(2-diethylamino-ethyl)-phenylamine.

Yield: 95 mg (23.8% of theory)

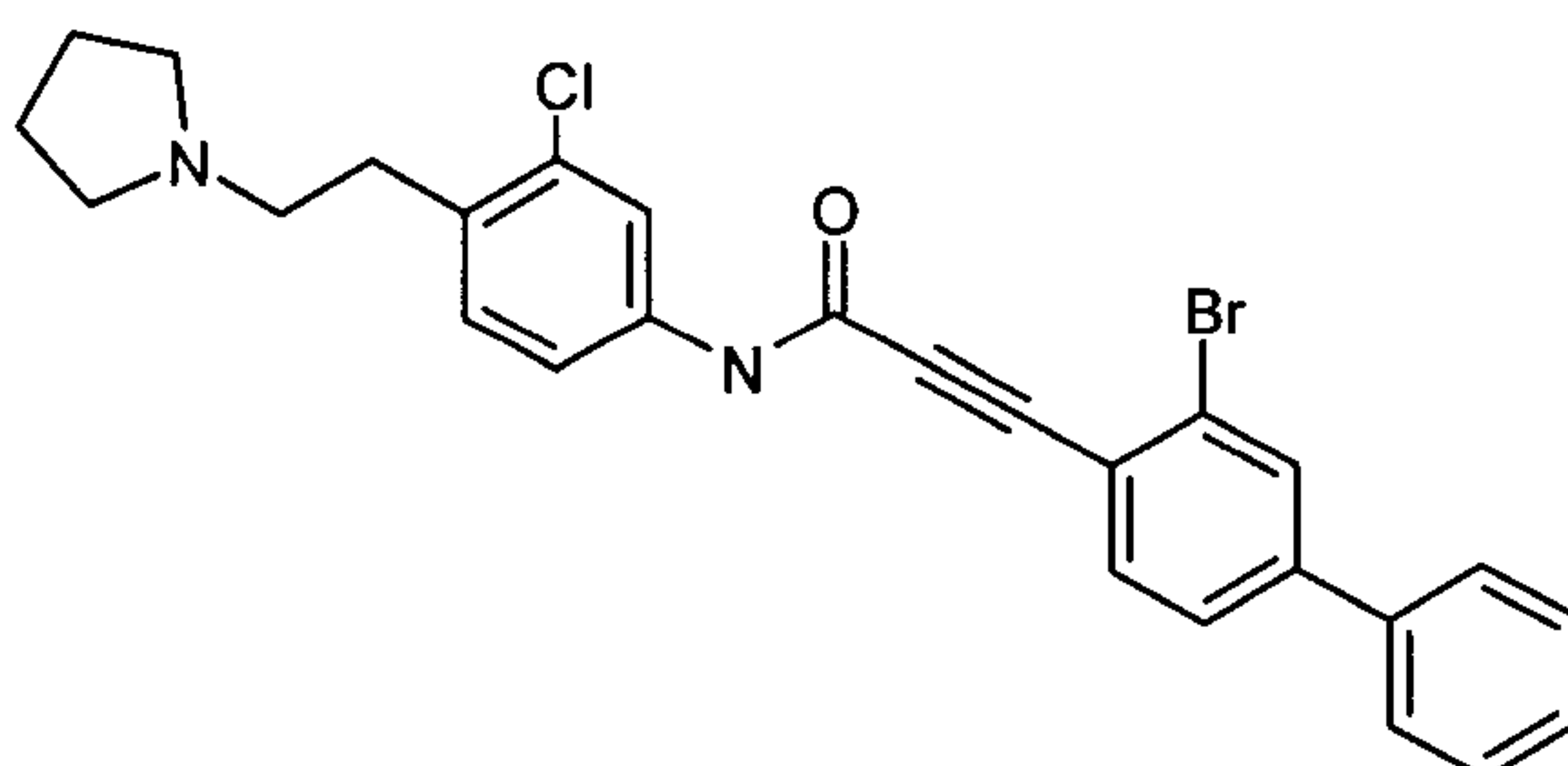
$C_{27}H_{26}BrClN_2O \cdot HCl$ (M= 546.32)

10 Calc.: Molecular ion peak $(M+H)^+$: 509/11/13 Found: Molecular ion peak $(M+H)^+$: 509/11/13

R_f value: 0.3 (silica gel, dichloromethane/methanol 90:10)

15 **Example 4.283:**

3-(3-bromo-biphenyl-4-yl)-propynoic acid-[3-chloro-4-(2-pyrrolidin-1-yl-ethyl)-phenyl]-amide



20 Prepared analogously to Example 2.3.f. from (3-bromo-biphenyl-4-yl)-propynoic acid and 3-chloro-4-(2-pyrrolidin-1-yl-ethyl)-phenylamine.

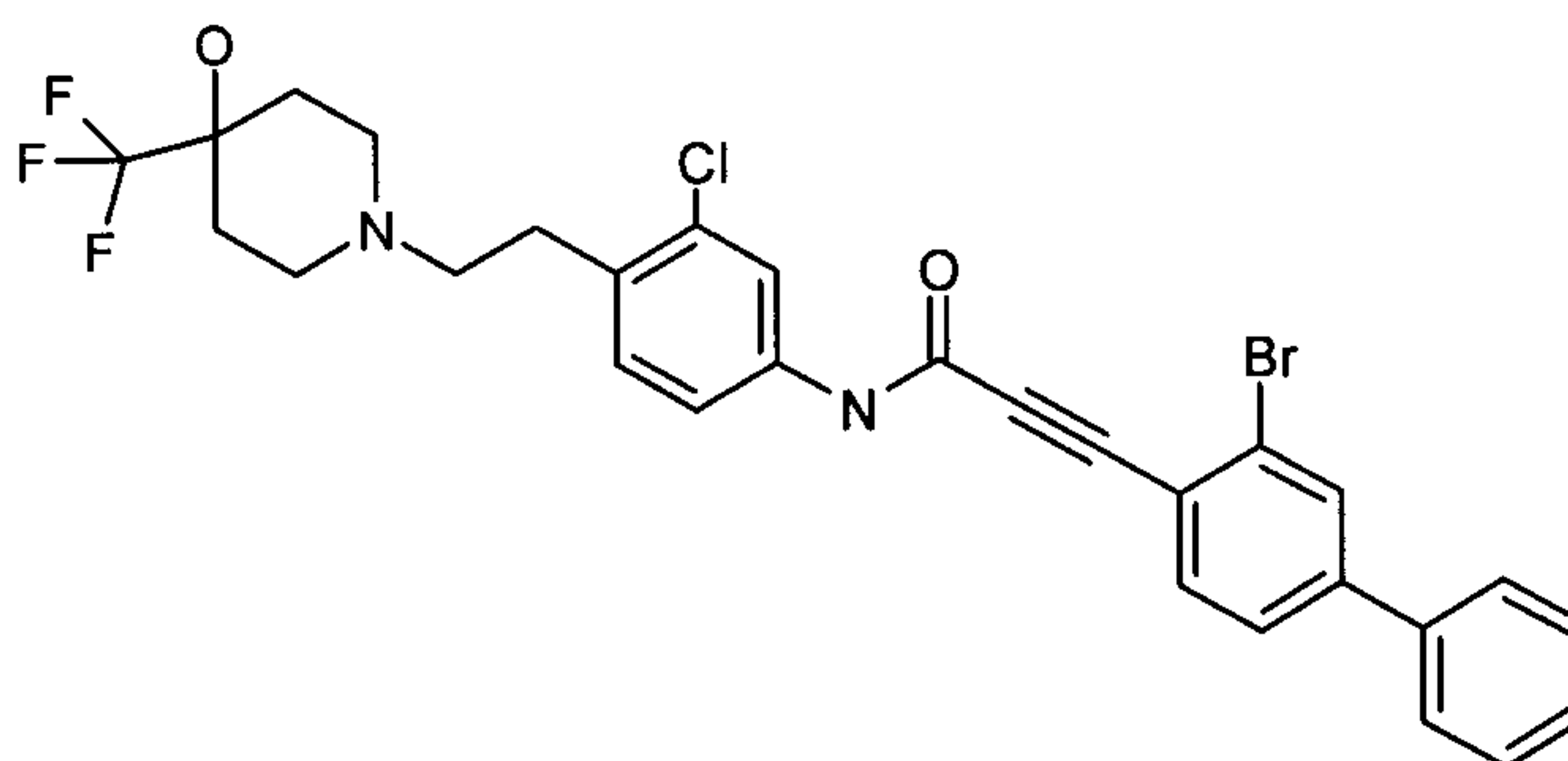
Yield: 140 mg (27.2% of theory)

$C_{27}H_{24}BrClN_2O$ (M= 507.84)

Calc.: Molecular ion peak $(M+H)^+$: 507/09/11 Found: Molecular ion peak $(M+H)^+$: 507/09/11

Example 4.284:

3-(3-bromo-biphenyl-4-yl)-propynoic acid-{3-chloro-4-[2-(4-hydroxy-4-trifluoromethyl-
5 piperidin-1-yl)-ethyl]-phenyl}-amide



Prepared analogously to Example 2.3.f. from (3-bromo-biphenyl-4-yl)-propynoic acid and 1-[2-(4-amino-2-chloro-phenyl)-ethyl]-4-trifluoromethyl-piperidin-4-ol.

Yield: 36 mg (10.5% of theory)

10 $C_{29}H_{25}BrClF_3N_2O_2$ (M= 605.87)

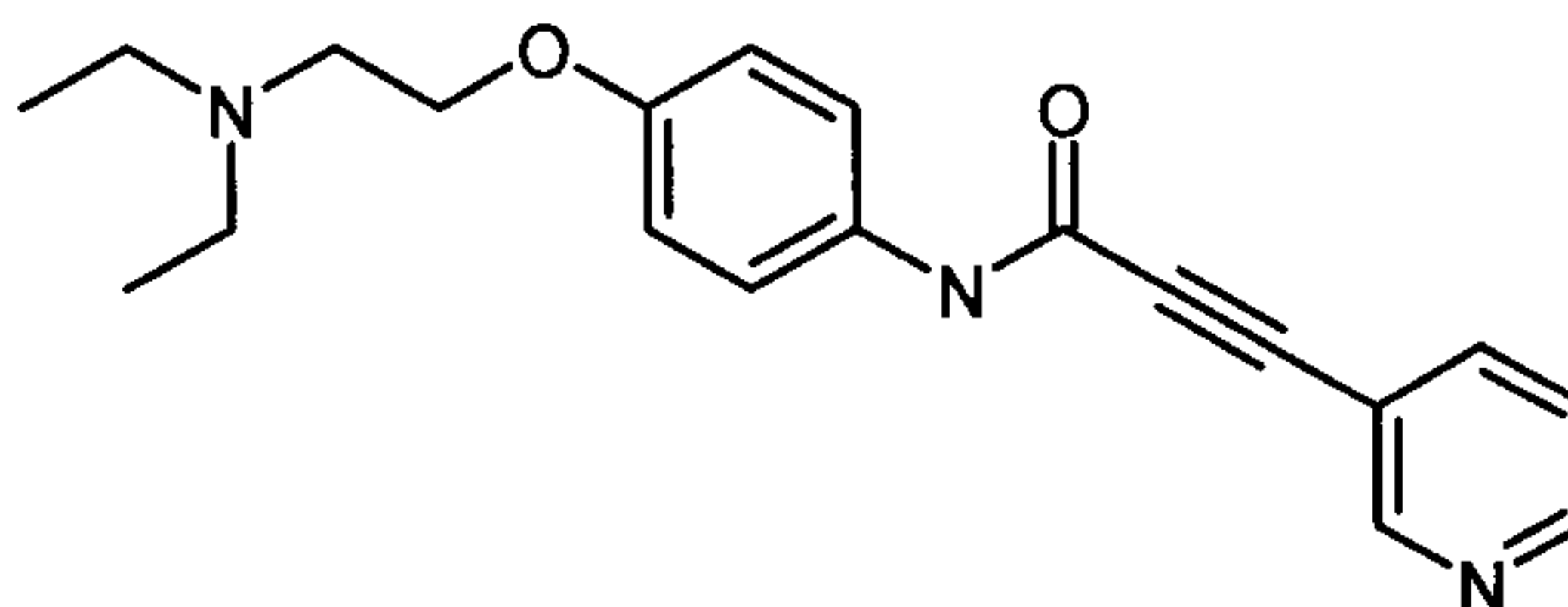
Calc.: Molecular ion peak (M+H)⁺: 605/07/09

Found: Molecular ion peak

(M+H)⁺: 605/07/09

15 **Example 4.285:**

3-pyridin-3-yl-propynoic acid-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-amide



Prepared analogously to Example 2.3.f from pyridin-3-yl-propynoic acid and [2-(2-chloro-4-amino-phenoxy)-ethyl]-diethyl-amine.

20 Yield: 0.42 g (66.4 % of theoretical)

Melting point: 118-120°C

$C_{20}H_{22}ClN_3O_2$ (M= 371.86)

Calc.: Molecular ion peak (M+H)⁺: 372/374

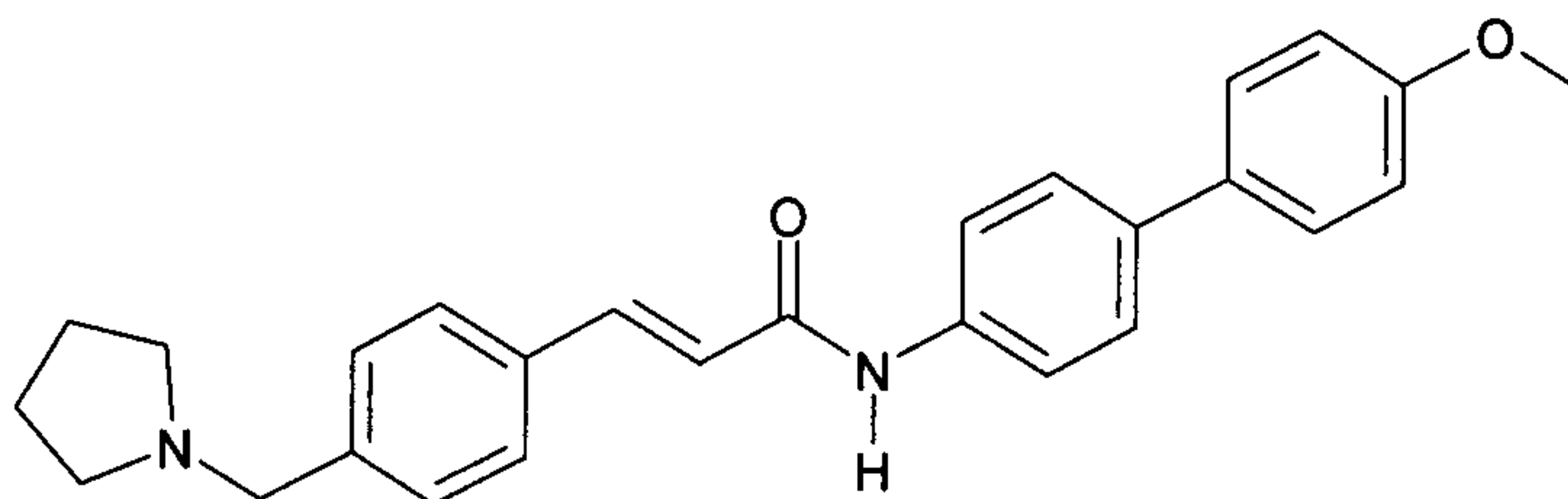
Found: Molecular ion peak

(M+H)⁺: 372/374

25 R_f value: 0.4 (silica gel, dichloromethane/ methanol/ammonia = 9:1:0.1)

Example 5.1:

(E)-N-(4'-methoxy-biphenyl-4-yl)-3-(4-pyrrolidin-1-ylmethyl-phenyl)-acrylamide



5.1.a. ethyl (E)-3-(4-pyrrolidin-1-ylmethyl-phenyl)-acrylate

2 g (7.43 mmol) ethyl (E)-3-(4-bromomethyl-phenyl)-acrylate are added to a suspension of 0.69 ml (8.2 mmol) pyrrolidine and 2.05 g (14.86 mmol) potassium

carbonate in 40 ml DMF and stirred for 18 hours at ambient temperature. The reaction mixture is evaporated down and the residue is extracted with water and ethyl acetate. The organic phase is dried over sodium sulphate, evaporated down and the residue is purified by column chromatography on silica gel (eluant: dichloromethane/methanol/ammonia = 90:10:1).

Yield: 0.3 g (15.6 % of theoretical)

$C_{16}H_{21}NO_2$ (M= 259.35)

Calc.: Molecular ion peak $(M+H)^+$: 260

Found: Molecular ion peak

$(M+H)^+$: 260

R_f value: 0.5 (silica gel, dichloromethane/methanol/ammonia 90:10:1)

5.1.b. (E)-3-(4-pyrrolidin-1-ylmethyl-phenyl)-acrylic acid

A reaction mixture of 0.3 g (1.15 mmol) ethyl (E)-3-(4-pyrrolidin-1-ylmethyl-phenyl)-acrylate and 0.4 g (9.53 mmol) lithium hydroxide-monohydrate in 20 ml of a 1:1 mixture of methanol, THF and water is stirred for 48 hours at ambient temperature.

Then the reaction mixture is evaporated down, the residue is diluted with water and acidified with hydrochloric acid. The mixture is evaporated down, combined with methanol and dichloromethane, filtered and the filtrate is evaporated to dryness.

Yield: 0.27 g

$C_{14}H_{17}NO_2$ (M= 231.29)

Calc.: Molecular ion peak (M+H)⁺: 232
(M+H)⁺: 232

Found: Molecular ion peak

R_f value: Starting spot (silica gel, dichloromethane/methanol/ammonia 90:10:1)

- 5 5.1.c. (E)-N-(4'-methoxy-biphenyl-4-yl)-3-(4-pyrrolidin-1-ylmethyl-phenyl)-acrylamide
Prepared analogously to 3.1.e from (E)-3-(4-pyrrolidin-1-ylmethyl-phenyl)-acrylic acid
and 4'-methoxy-biphenyl-4-yl-amine.

Yield: 74 mg (15.4 % of theoretical)

Melting point: 199-200° C

- 10 C₂₇H₂₈N₂O₂ (M= 412.53)

Calc.: Molecular ion peak (M+H)⁺: 413
(M+H)⁺: 413

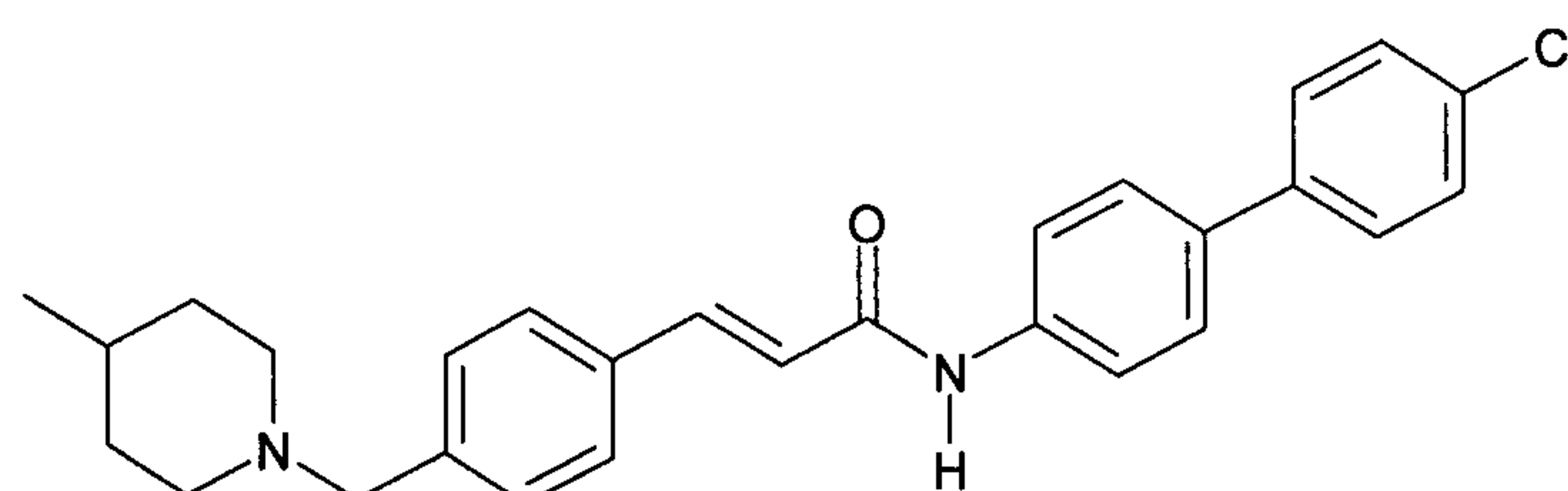
Found: Molecular ion peak

R_f value: 0.77 (silica gel, dichloromethane/ methanol/ ammonia = 80:20:1)

15

Example 5.2:

(E)-N-(4'-chloro-biphenyl-4-yl)-3-[4-(4-methyl-piperidin-1-ylmethyl)-phenyl]-acrylamide



- 20 5.2.a. (E)-3-(4-dimethoxymethyl-phenyl)-acrylic acid

38.81 ml (0.354 mmol) trimethylorthoformate are added to a suspension of 25 g (0.141 mol) (E)-3-(4-formyl-phenyl)-acrylic acid in 350 ml of methanol and the mixture is refluxed for 48 hours. After cooling the reaction mixture is filtered and the filtrate is evaporated down. The residue is taken up in 500 ml dichloromethane and filtered through Celite . The filtrate is evaporated down to 150 ml and cooled to 0°C. The precipitate formed is filtered off, washed with dichloromethane/petroleum ether (1:1) and dried at 60 °C in the circulating air dryer.

Yield: 12.05 g (31.5 % of theoretical)

C₁₂H₁₄O₄ (M= 222.24)

Calc.: Molecular ion peak (M+H)⁺: 245

Found: Molecular ion peak

(M+H)⁺: 245

R_f value: 0.6 (silica gel, petroleum ether/ethyl acetate = 1:1)

5 5.2.b. (E)-N-(4'-chloro-biphenyl-4-yl)-3-(4-dimethoxymethyl-phenyl)-acrylamide

Prepared analogously to 3.1.e from (E)-3-(4-dimethoxymethyl-phenyl)-acrylic acid and 4'-chloro-biphenyl-4-yl-amine.

Yield: 9.8 g

C₂₄H₂₂ClNO₃ (M= 407.90)

10 Calc.: Molecular ion peak (M+H)⁺: 408/410

Found: Molecular ion

peak (M+H)⁺: 408/410

R_f value: 0.3 (silica gel, dichloromethane/ethanol 20:1)

5.2.c. (E)-N-(4'-chloro-biphenyl-4-yl)-3-(4-formyl-phenyl)-acrylamide

15 70 ml of water and 21 ml trifluoroacetic acid are added to a suspension of 9.8 g (24.02 mmol) (E)-N-(4'-chloro-biphenyl-4-yl)-3-(4-dimethoxymethyl-phenyl)-acrylamide in 280 ml chloroform and the reaction mixture is stirred for eight hours at ambient temperature. It is diluted with chloroform and water, the organic phase is separated off and extracted with water. The organic phase is dried, filtered through
20 silica gel and the solvent is distilled off.

Yield: 5.5 g

C₂₂H₁₆ClNO₂ (M= 361.83)

Calc.: Molecular ion peak (M+H)⁺: 362/364

Found: Molecular ion

peak (M+H)⁺: 362/364

25 R_f value: 0.6 (silica gel, cyclohexane/ethyl acetate 1:1)

5.2.d. (E)-N-(4'-chloro-biphenyl-4-yl)-3-[4-(4-methyl-piperidin-1-ylmethyl)-phenyl]-acrylamide

Prepared analogously to 4.30.c from (E)-N-(4'-chloro-biphenyl-4-yl)-3-(4-formyl-phenyl)-acrylamide and 4-methyl-piperidine.

Yield: 80 mg (21.7 % of theoretical)

Melting point: 207-208 °C

C₂₈H₂₉ClN₂O (M= 445.00)

Calc.: Molecular ion peak (M+H)⁺: 445/447

Found: Molecular ion

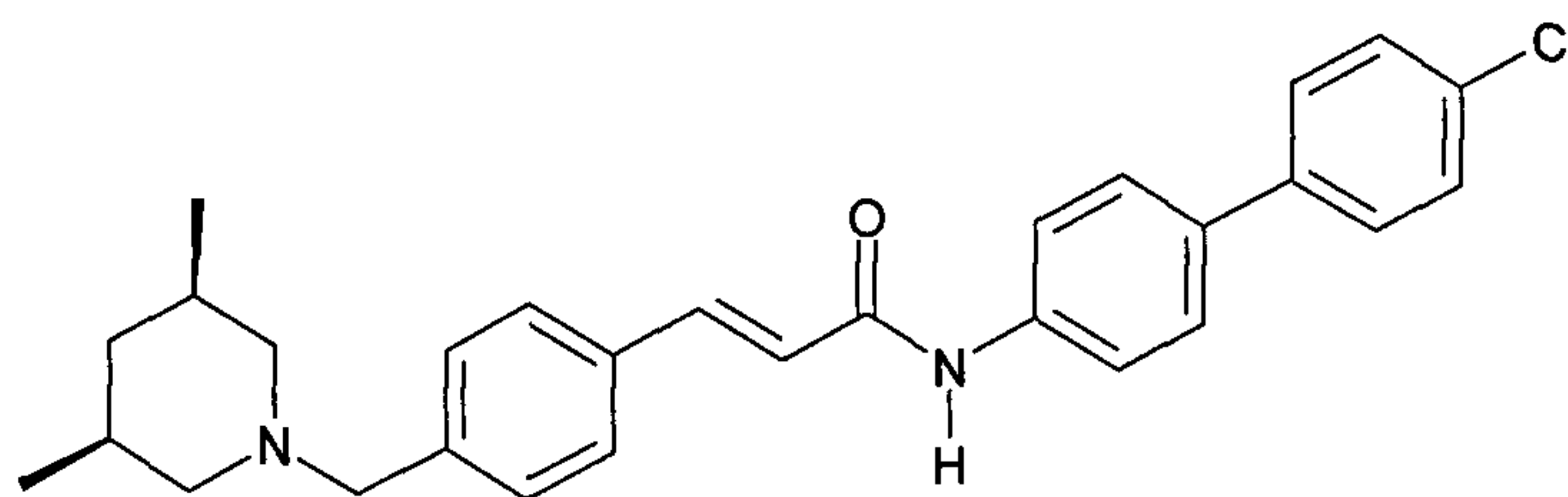
peak (M+H)⁺: 445/447

R_f value: 0.76 (silica gel, dichloromethane/ methanol = 10:1)

5

Example 5.3:

(E)-N-(4'-chloro-biphenyl-4-yl)-3-[4-(cis-3,5-dimethyl-piperidin-1-ylmethyl)-phenyl]-acrylamide



10

5.3.a. (E)-N-(4'-chloro-biphenyl-4-yl)-3-(4-hydroxymethyl-phenyl)-acrylamide

A solution of 4.4 g (12.16 mmol) (E)-N-(4'-chloro-biphenyl-4-yl)-3-(4-formyl-phenyl)-acrylamide in 200 ml THF is adjusted with glacial acetic acid to a pH of three, combined with 8.14 g (36.48 mmol) sodium triacetoxyborohydride and stirred for 18

15

hours at ambient temperature. Then the reaction mixture is poured into water and the precipitate is filtered off. The filtrate is extracted with ethyl acetate, washed with water and dried over sodium sulphate. The solvent is removed and the residue is combined with the solid which has been filtered off. The purification is carried out by column chromatography on silica gel (eluant: dichloromethane/ethanol/ammonia= 30:1:0.1).

20

Yield: 3.2 g (72.4 % of theoretical)

C₂₂H₁₈ClNO₂ (M= 363.84)

Calc.: Molecular ion peak (M+H)⁺: 364/366

Found: Molecular ion

peak (M+H)⁺: 364/366

R_f value: 0.2 (silica gel, dichloromethane/ethanol = 20:1)

25

5.3.b. (E)-N-(4'-chloro-biphenyl-4-yl)-3-(4-chloromethyl-phenyl)-acrylamide

A suspension of 2.1 g (5.77 mmol) (E)-N-(4'-chloro-biphenyl-4-yl)-3-(4-hydroxymethyl-phenyl)-acrylamide in 100 ml dichloromethane is with 1.7 ml (12.19 mmol) triethylamine and then combined with 0.46 ml (5.88 mmol) methanesulphonic acid

30

chloride. The reaction mixture is stirred for three hours at ambient temperature,

diluted with water and extracted several times with dichloromethane. The combined organic phases are dried over sodium sulphate, filtered through silica gel and the filtrate is evaporated down.

Yield: 0.4 g (18.1 % of theoretical)

5 C₂₂H₁₇Cl₂NO (M= 382.29)

Calc.: Molecular ion peak (M+H)⁺: 381/383/385
peak (M+H)⁺: 381/383/385

Found: Molecular ion

10 5.3.c. (E)-N-(4'-chloro-biphenyl-4-yl)-3-[4-(cis-3,5-dimethyl-piperidin-1-ylmethyl)-phenyl]-acrylamide

Prepared analogously to 1.2.c from (E)-N-(4'-chloro-biphenyl-4-yl)-3-(4-chloromethyl-phenyl)-acrylamide and cis-3,5-dimethylpiperidine.

Yield: 30 mg (30 % of theoretical)

Melting point: 217-218 C

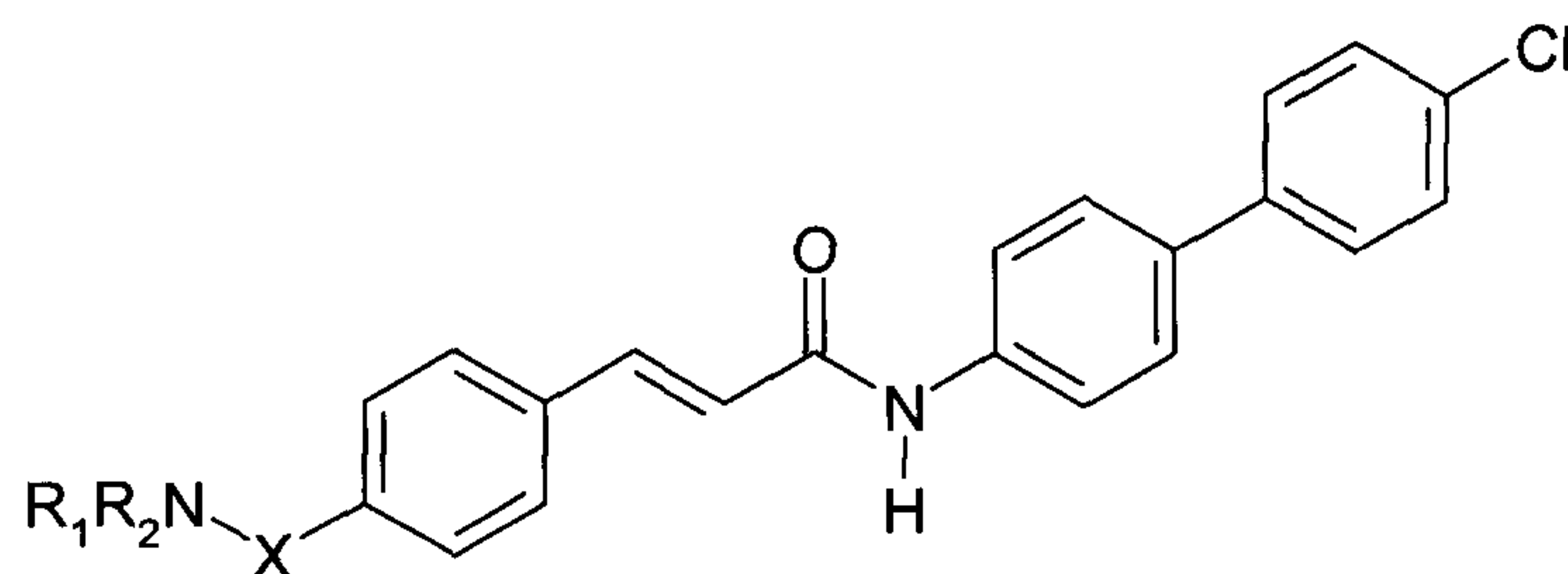
15 C₂₉H₃₁ClN₂O (M= 459.03)

Calc.: Molecular ion peak (M+H)⁺: 459/461
peak (M+H)⁺: 459/461

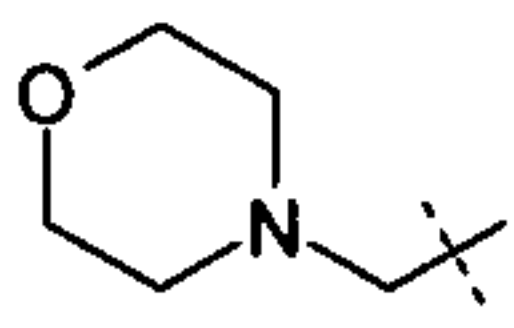
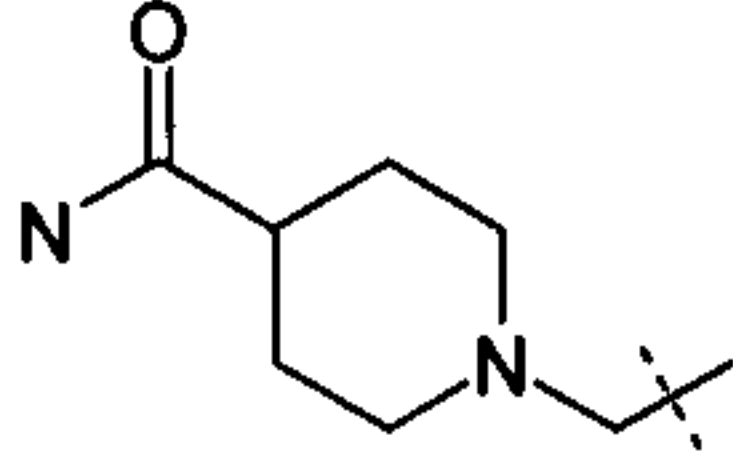
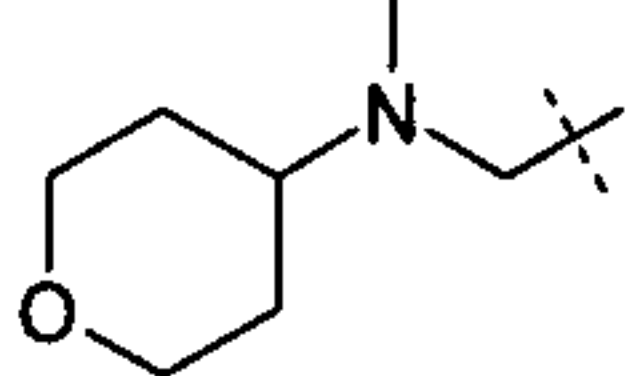
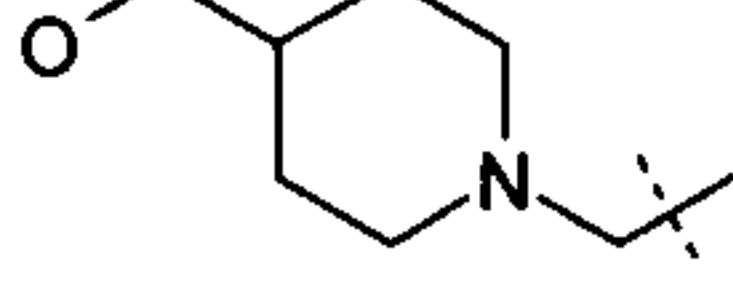
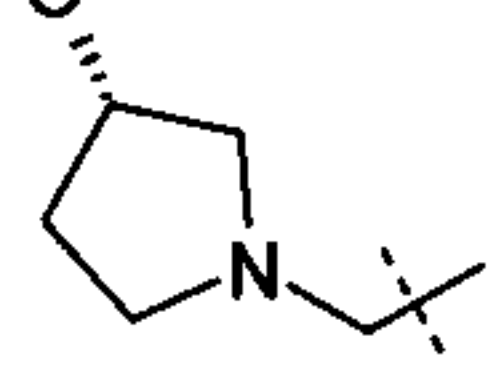
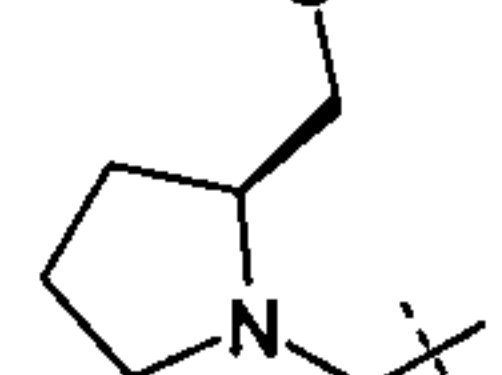
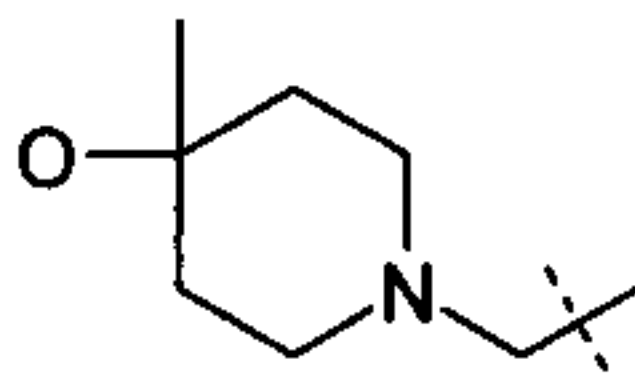
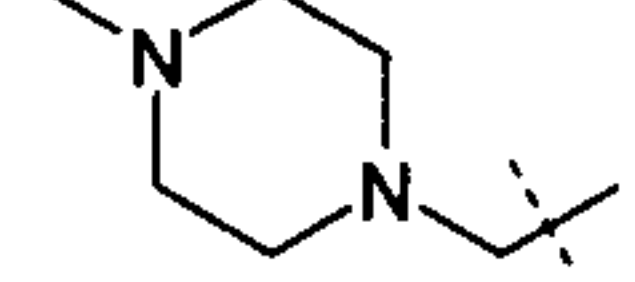
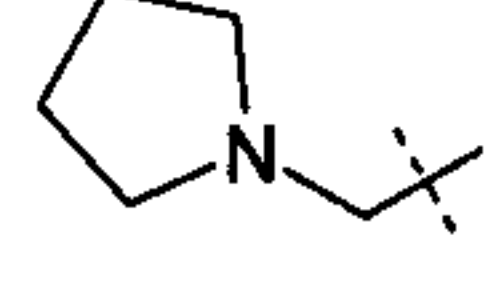
Found: Molecular ion

The following compounds are prepared analogously to Example 5.3.c:

20



Example	R ₁ R ₂ N-X	educt	empirical formula	mass spectrum	mp [°C]	R _f value
5.4		5.3.b	C ₂₈ H ₂₉ ClN ₂ O ₂	461/463 [M+H] ⁺	205- 206	0.4 (A)

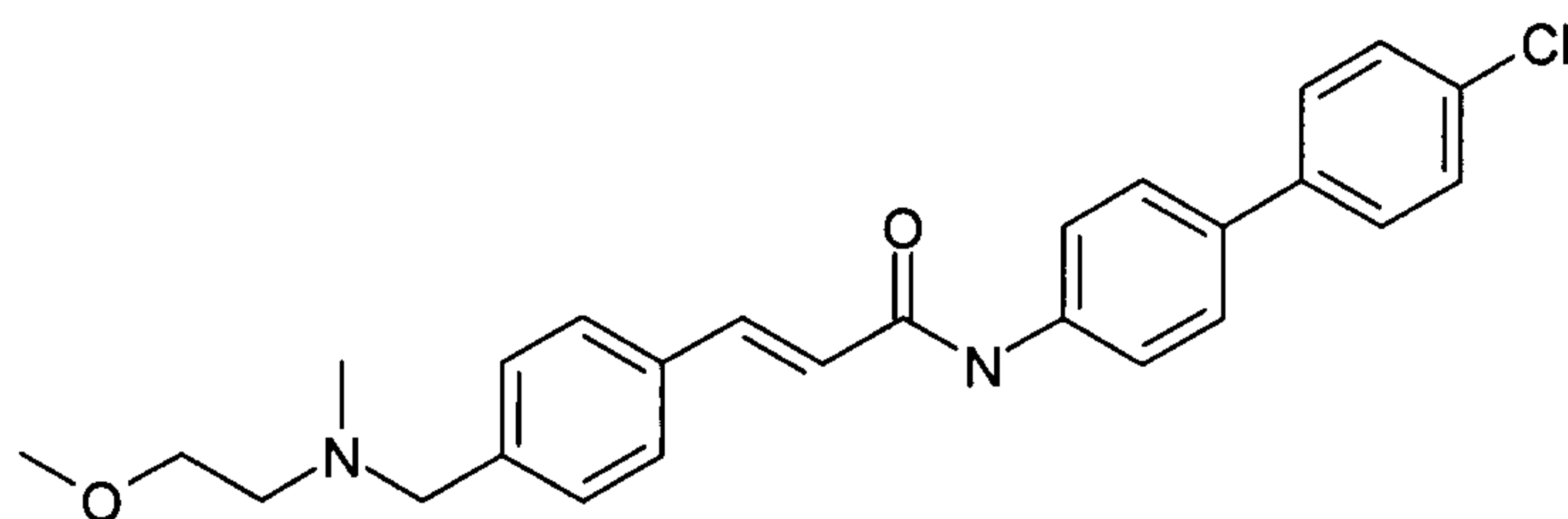
5.5		5.3.b	C ₂₆ H ₂₅ ClN ₂ O ₂	432/435 [M+H] ⁺	184- 185	0.6 (A)
5.6		5.3.b	C ₂₈ H ₂₈ ClN ₃ O ₂	474/476 [M+H] ⁺	254- 255	0.05 (A)
5.7		5.3.b	C ₂₈ H ₂₉ ClN ₂ O ₂	461/463 [M+H] ⁺	196- 197	0.2 (A)
5.8		5.3.b	C ₂₈ H ₂₉ ClN ₂ O ₂	461/463 [M+H] ⁺	190- 191	0.1 (A)
5.9		5.3.b	C ₂₆ H ₂₅ ClN ₂ O ₂	433/435 [M+H] ⁺	178- 179	0.14 (A)
5.10		5.3.b	C ₂₇ H ₂₇ ClN ₂ O ₂	447/449 [M+H] ⁺	192- 193	0.2 (A)
5.11		5.3.b	C ₂₈ H ₂₉ ClN ₂ O ₂	461/463 [M+H] ⁺	212	0.25 (B)
5.12		5.3.b	C ₂₇ H ₂₈ ClN ₃ O	446/448 [M+H] ⁺	216	0.2 (B)
5.13		5.3.b	C ₂₆ H ₂₅ ClN ₂ O	417/419 [M+H] ⁺	219	0.25 (B)

R_f value: A= (silica gel, dichloromethane/methanol (10:1))

B= (silica gel, dichloromethane/methanol/ammonia (10:1:0.1))

5 Example 5.14.

(E)-N-(4'-chloro-biphenyl-4-yl)-3-(4-cyclopropylaminomethyl-phenyl)-acrylamide



A reaction mixture of 100 mg (0.26 mmol) (E)-N-(4'-chloro-biphenyl-4-yl)-3-(4-chloromethyl-phenyl)-acrylamide, 70 mg (0.77 mmol) 2-methoxy-ethylmethanamine and 140 mg (1 mmol) potassium carbonate in 10 ml acetone is agitated for 24 hours at reflux temperature. The reaction mixture is evaporated down. The residue is

5 purified by column chromatography on silica gel (eluant:

dichloromethane/ethanol/ammonia 20/1/0.1)

Yield: 92 mg (81 % of theoretical)

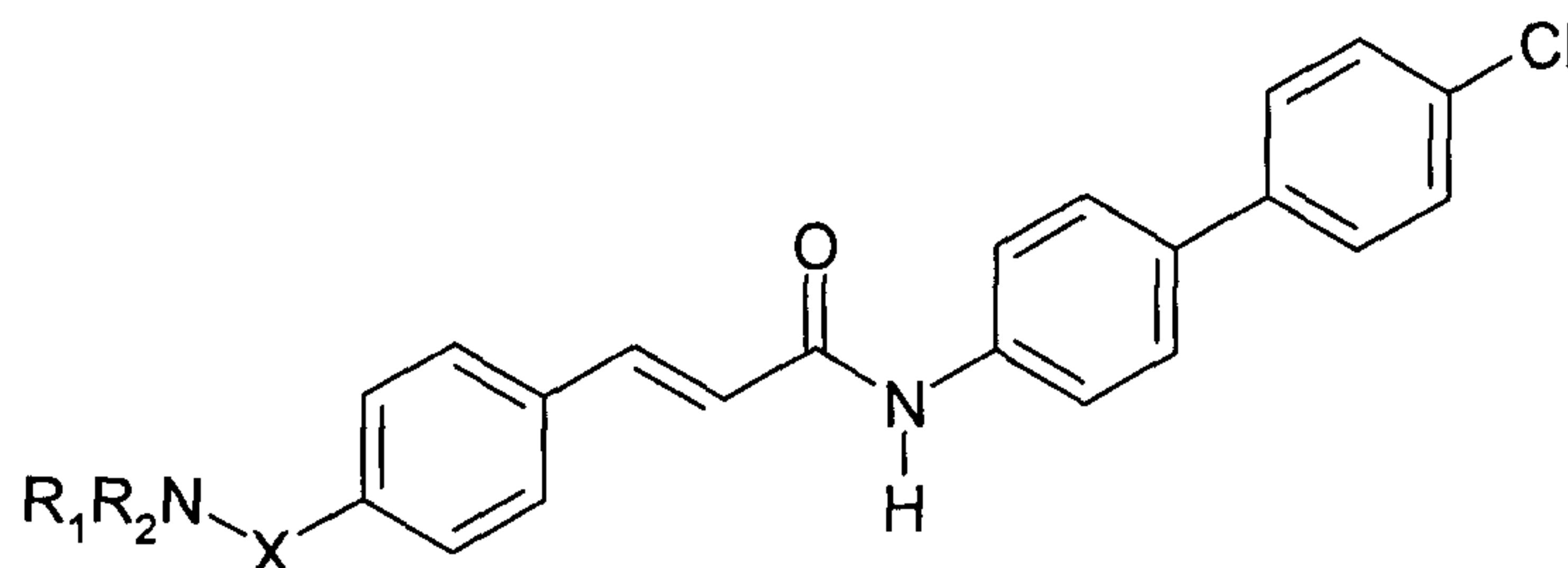
Melting point: 222-223°C

C₂₆H₂₇ClN₂O₂ (M= 434.96)

10 Calc.: Molecular ion peak (M+H)⁺: 435/37(Cl) Found: Molecular ion peak (M+H)⁺: 435/37(Cl)

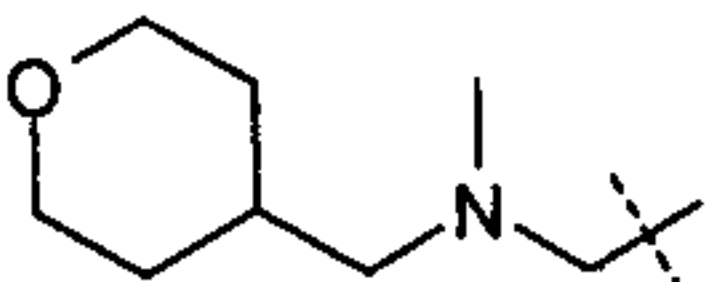
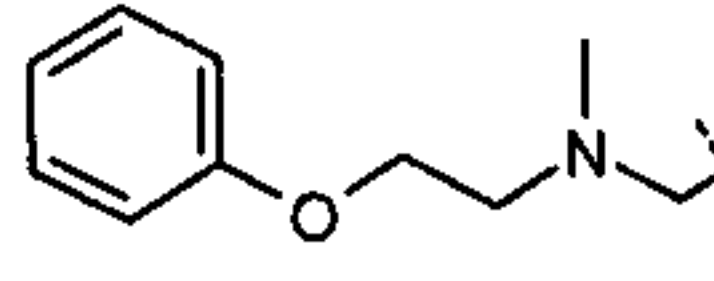
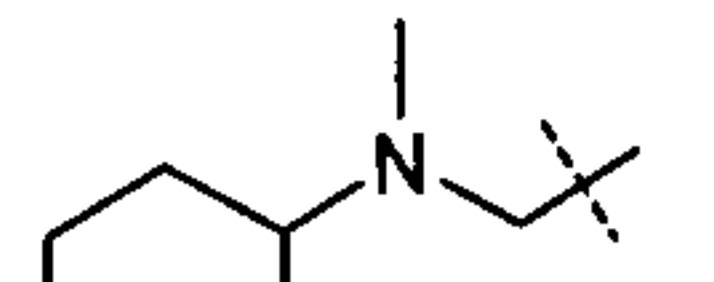
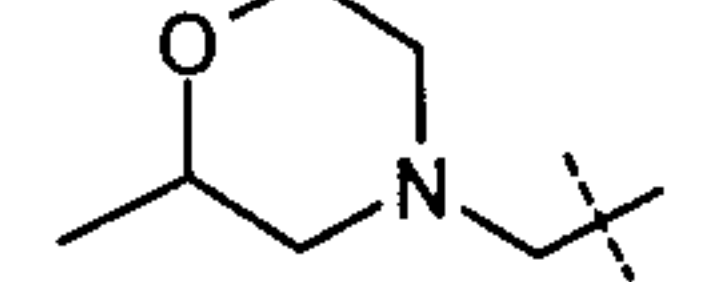
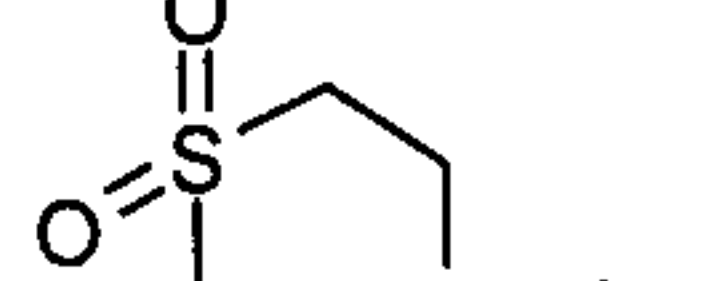
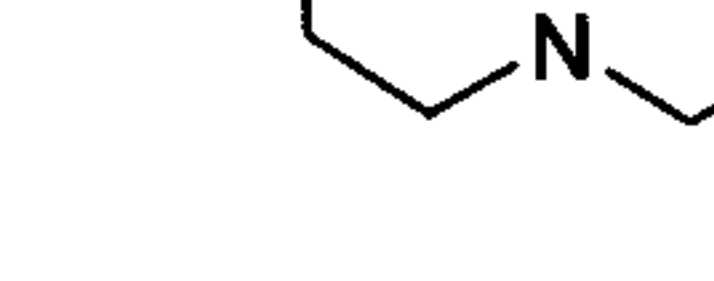
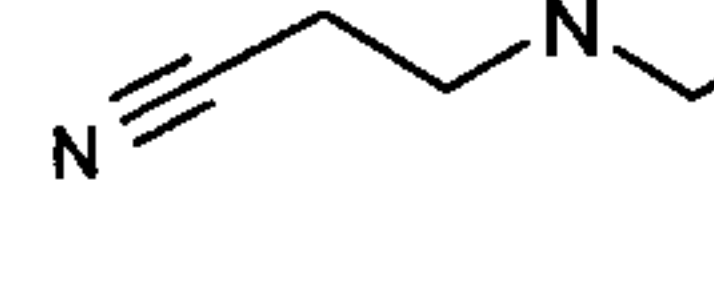
R_f value: 0.4 (silica gel, dichloromethane/methanol/ammonia = 20:1:0.1)

The following compounds are prepared analogously to Example 5.14:



15

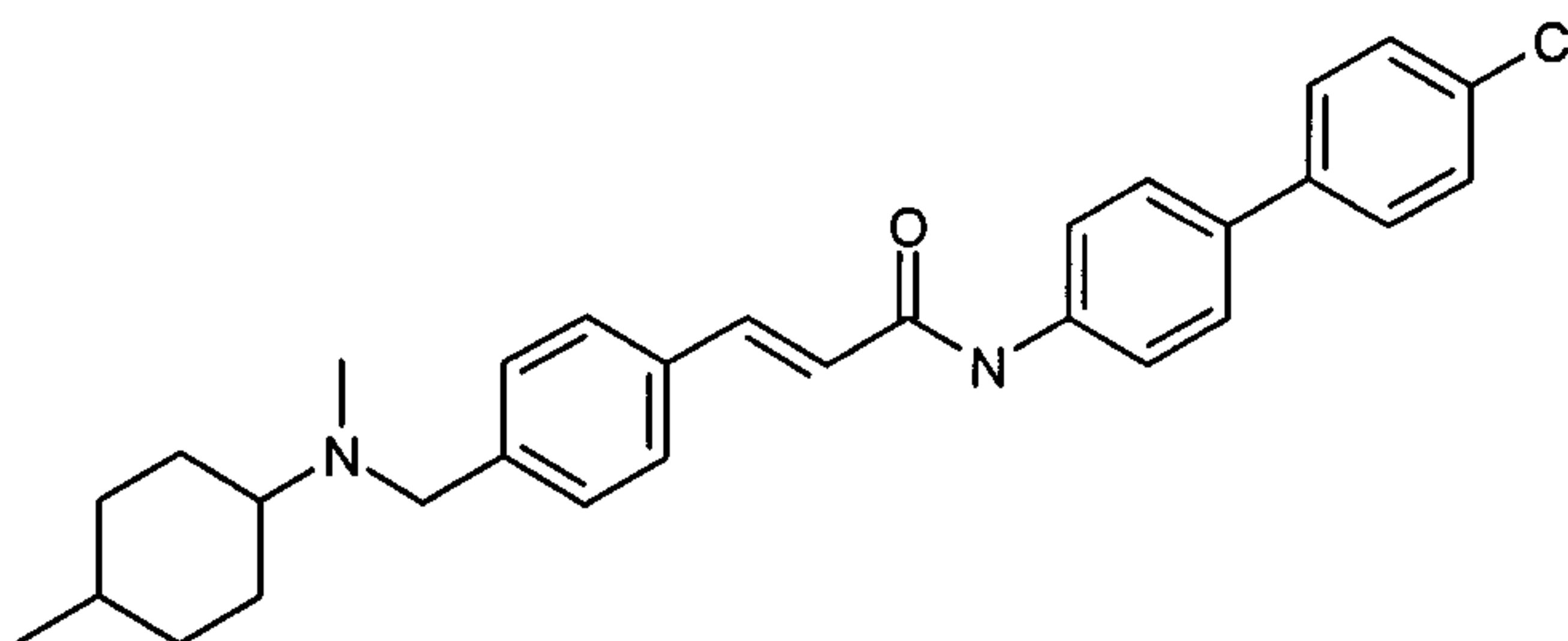
Example	R ₁ R ₂ N-X	educt	empirical formula	mass spectrum	mp [°C]	R _f value
5.15		5.3.b	C ₂₈ H ₂₈ ClN ₃ O	458/460 [M+H] ⁺	206- 207	0.1 (B)
5.16		5.3.b	C ₂₉ H ₃₀ ClN ₃ O	472/474 [M+H] ⁺	223- 224	0.2 (A)
5.17		5.3.b	C ₂₇ H ₂₇ ClN ₂ O	431/433 [M+H] ⁺	246- 247	0.4 (B)
5.18		5.3.b	C ₃₀ H ₂₇ ClN ₂ O	467/469 [M+H] ⁺	210- 212	0.6 (A)

5.19		5.3.b	C ₂₉ H ₃₁ ClN ₂ O ₂	475/477 [M+H] ⁺	181	0.35 (A)
5.20		5.3.b	C ₃₁ H ₂₉ ClN ₂ O ₂	497 [M+H] ⁺	188- 189	0.35 (A)
5.21		5.3.b	C ₂₉ H ₃₁ ClN ₂ O	459/461 [M+H] ⁺	262- 263	0.4 (A)
5.22		5.3.b	C ₂₆ H ₂₅ ClN ₂ O	417/419 [M+H] ⁺	238- 239	0.5 (B)
5.23		5.3.b	C ₂₈ H ₂₉ ClN ₂ O ₂	461/463 [M+H] ⁺	212- 213	0.45 (A)
5.24		5.3.b	C ₂₆ H ₂₅ ClN ₂ O ₃ S	481/83 [M+H] ⁺	264- 266	0.45 (B)
5.25		5.3.b	C ₃₁ H ₃₃ ClN ₂ O	485/87 [M+H] ⁺	250	0.35 (B)
5.26		5.3.b	C ₂₆ H ₂₄ ClN ₃ O	430/32 [M+H] ⁺	160- 161	0.45 (B)
5.27		5.3.b	C ₂₉ H ₃₃ ClN ₂ O ₃	493/95 [M+H] ⁺	125- 126	0.4 (A)
5.28		5.3.b	C ₃₁ H ₃₄ ClN ₃ O	500/02 [M+H] ⁺	209- 210	0.15 (A)

R_f value: A= (silica gel, dichloromethane/ethanol/ammonia (20:1:0.1))

B= (silica gel, dichloromethane/methanol/ammonia (10:1:0.1))

5 **Example 5.29:** (E)-N-(4'-chloro-biphenyl-4-yl)-3-(4-([methyl-(4-methyl-cyclohexyl)amino]-methyl)-phenyl)-acrylamide



5.29.a. 4-[(E)-2-(4'-chloro-biphenyl-4-ylcarbamoyl)-vinyl]-benzyl methanesulphonate

A suspension of 2.3 g (6.3 mmol) (E)-N-(4'-chloro-biphenyl-4-yl)-3-(4-hydroxymethyl-phenyl)-acrylamide in 200 ml dichloromethane is combined with 1.94 ml (13.9 mmol) triethylamine and then with 0.54 ml (6.92 mmol) methanesulphonic acid chloride. The reaction mixture is stirred for 18 hours at ambient temperature, diluted with water and extracted several times with dichloromethane. The combined organic phases are dried over sodium sulphate, filtered through silica gel and the filtrate is evaporated down.

Yield: 1.85 g (67 % of theoretical)

$C_{23}H_{20}ClNO_4S$ (M= 441.93)

Calc.: Molecular ion peak (M+H)⁺: 442/444 (Cl)
peak (M+H)⁺: 442/444 (Cl)

Found: Molecular ion

R_f value: 0.73 (silica gel, dichloromethane/methanol/ammonia = 90:10: 1)

5.29.b. (E)-N-(4'-chloro-biphenyl-4-yl)-3-(4-[[methyl-(4-methyl-cyclohexyl)amino]-methyl]-phenyl)-acrylamide

A reaction mixture of 100 mg (0.226 mmol) 4-[(E)-2-(4'-chloro-biphenyl-4-ylcarbamoyl)-vinyl]-benzyl methanesulphonate, 37.34 mg (0.29 mmol) methyl-(4-methyl-cyclohexyl)-amine and 0.1 ml triethylamine in 10 ml dichloromethane is stirred for 18 hours at ambient temperature. Then the reaction mixture is extracted between water and dichloromethane, the organic phase is separated off, dried and evaporated down. The residue is purified by column chromatography on silica gel (eluant: dichloromethane/methanol/ammonia 90:10:1).

Yield: 52 mg (49 % of theoretical)

$C_{30}H_{33}ClN_2O$ (M= 473.05)

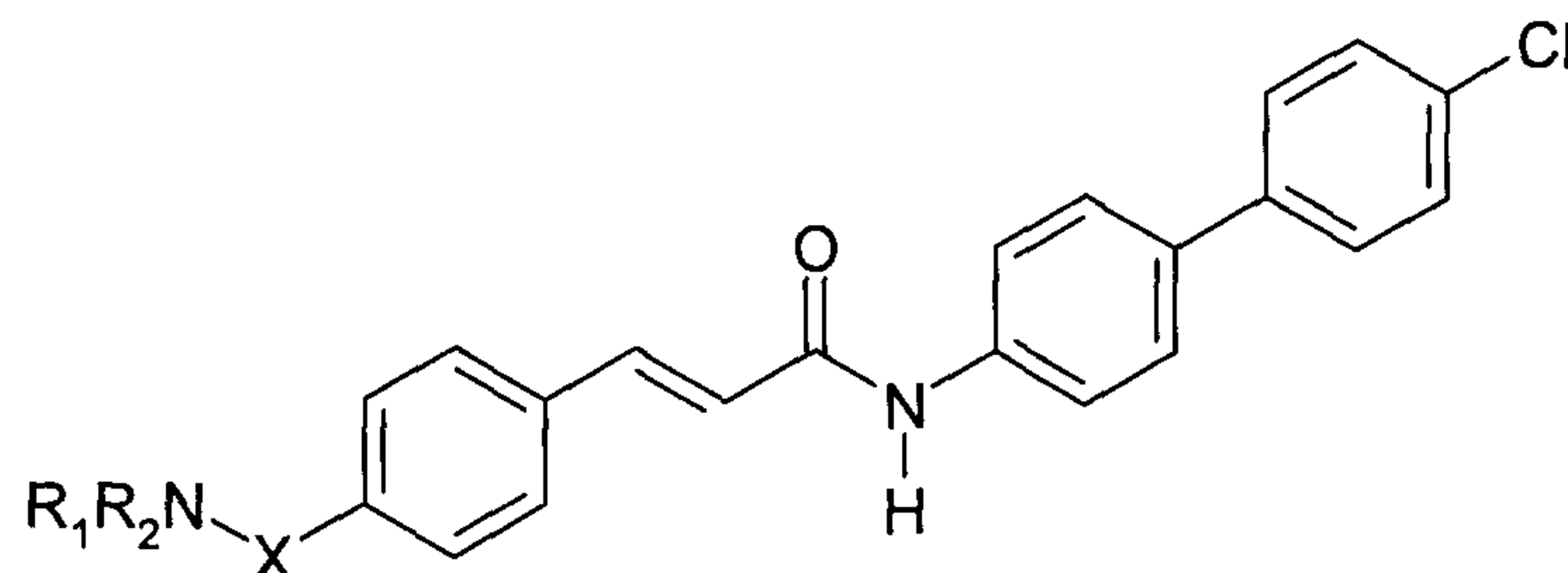
Melting point: 227-258°C

Calc.: Molecular ion peak (M+H)⁺: 473/475 (Cl)
peak (M+H)⁺: 473/475 (Cl)

Found: Molecular ion

R_f value: 0.48 (silica gel, dichloromethane/methanol/ammonia = 90:10:1)

The following compounds are prepared analogously to Example 5.29.b:

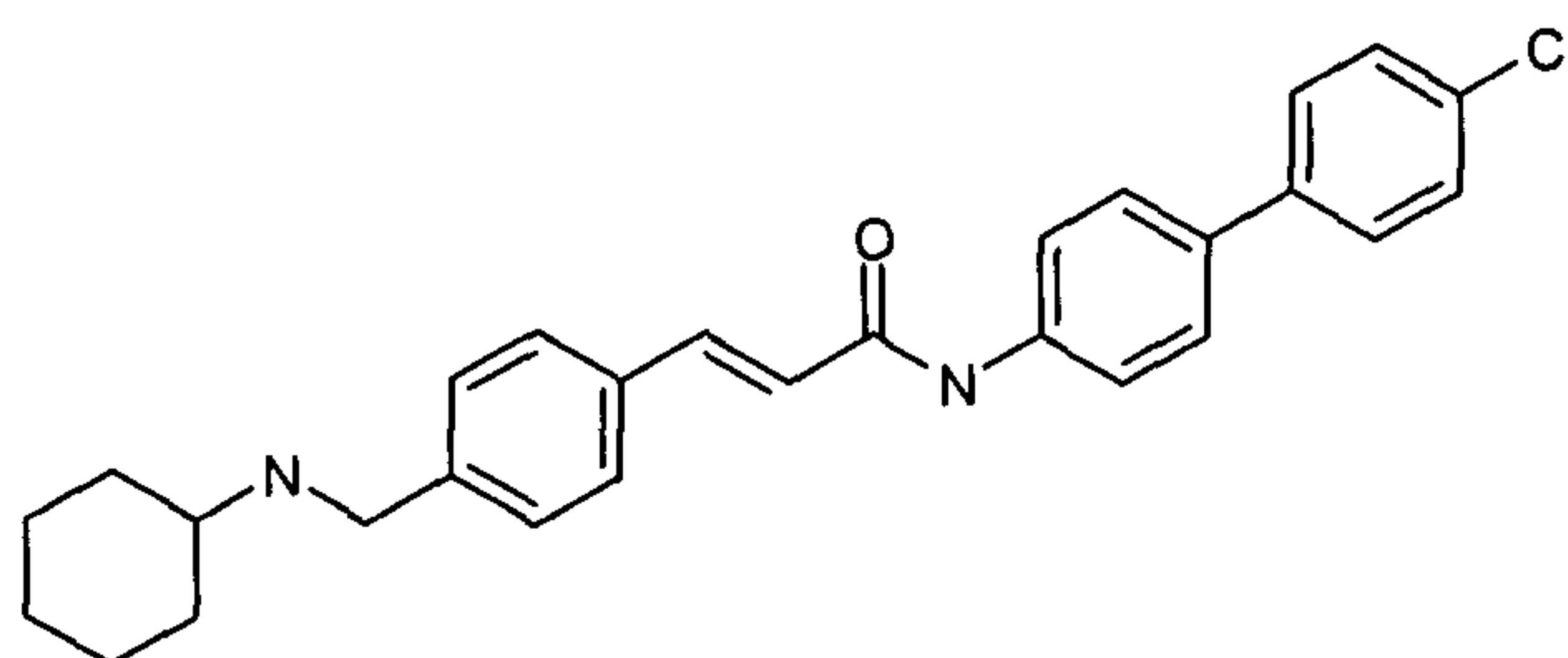


5

Example	R_1R_2N-X	educt	empirical formula	mass spectrum	mp [$^{\circ}C$]	R_f value
5.30		5.29.a	$C_{29}H_{31}ClN_2O_2$	475/477 (Cl) [M+H] ⁺	225- 265	0.37 (A)
5.31		5.29.a	$C_{29}H_{32}ClN_3O$	474/476 (Cl) [M+H] ⁺	226- 254	0.6 (A)
5.32		5.29.a	$C_{30}H_{33}ClN_2O$	473/475 (Cl) [M+H] ⁺	205- 210	0.42 (A)

R_f value: A= (silica gel, dichloromethane/methanol/ammonia (90:10:1))

10 **Example 5.33:**
(E)-N-(4'-chloro-biphenyl-4-yl)-3-(4-cyclohexylaminomethyl-phenyl)-acrylamide



0.082 ml (0.72 mmol) cyclohexylamine are added to a suspension of 150 mg (0.39 mmol) (E)-N-(4'-chloro-biphenyl-4-yl)-3-(4-chloromethyl-phenyl)-acrylamide in 5 ml of tetrahydrofuran and the mixture is refluxed for 18 h. Then the reaction mixture is
5 poured onto water and the precipitate formed is suction filtered. Further purification is carried out by column chromatography on silica gel (eluant: dichloromethane/methanol 95:5 – 50:50).

Yield: 70 mg (40 % of theoretical)

C₂₈H₂₉ClN₂O (M= 444.99)

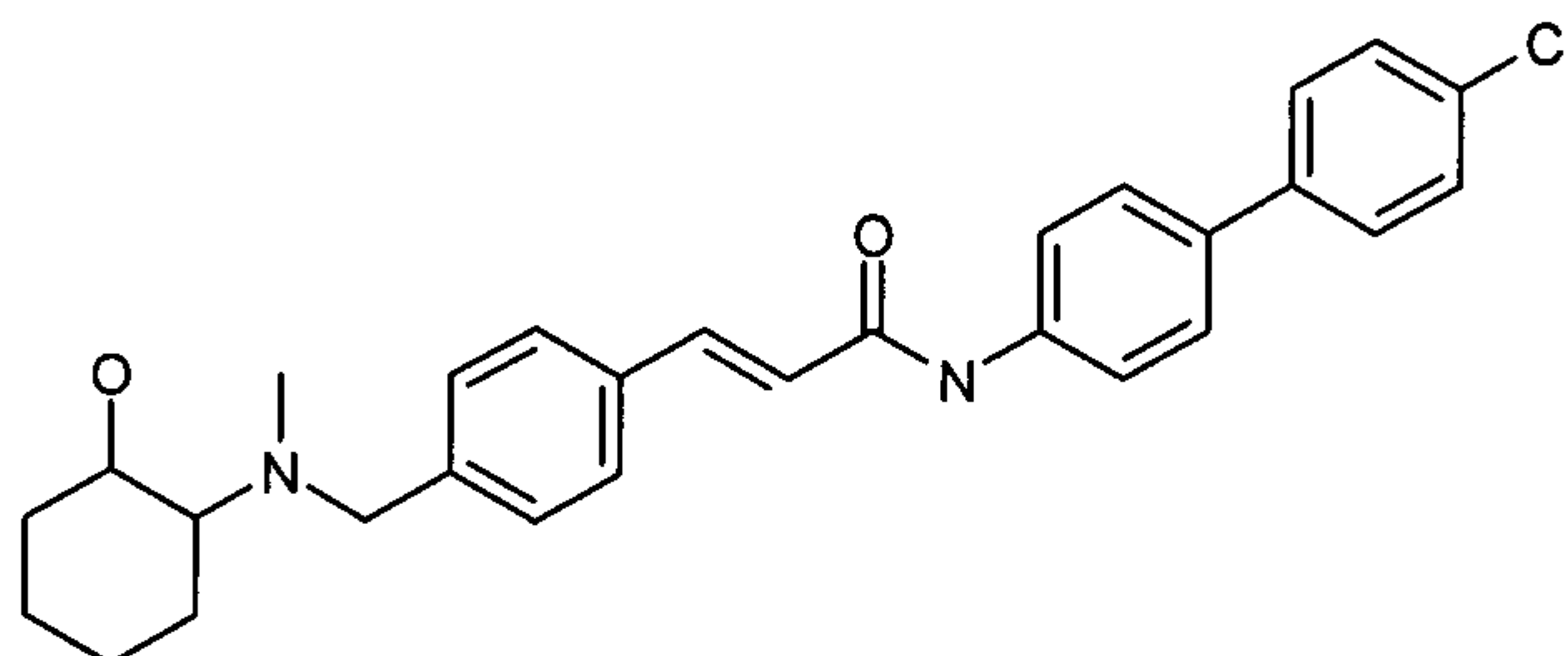
10 Melting point: 247-248°C

Calc.: Molecular ion peak (M+H)⁺: 445/447 (Cl)

Found: Molecular ion

peak (M+H)⁺: 445/447 (Cl)

Example 5.34: (E)-N-(4'-chloro-biphenyl-4-yl)-3-(4-[(2-hydroxy-cyclohexyl)-methyl-
15 amino]-methyl)-phenyl)-acrylamide



Prepared analogously to Example 5.33. from (E)-N-(4'-chloro-biphenyl-4-yl)-3-(4-chloromethyl-phenyl)-acrylamide and 2-methylamino-cyclohexanol.

Yield: 90 mg (48 % of theoretical)

20 C₂₉H₃₁ClN₂O₂ (M= 475.02)

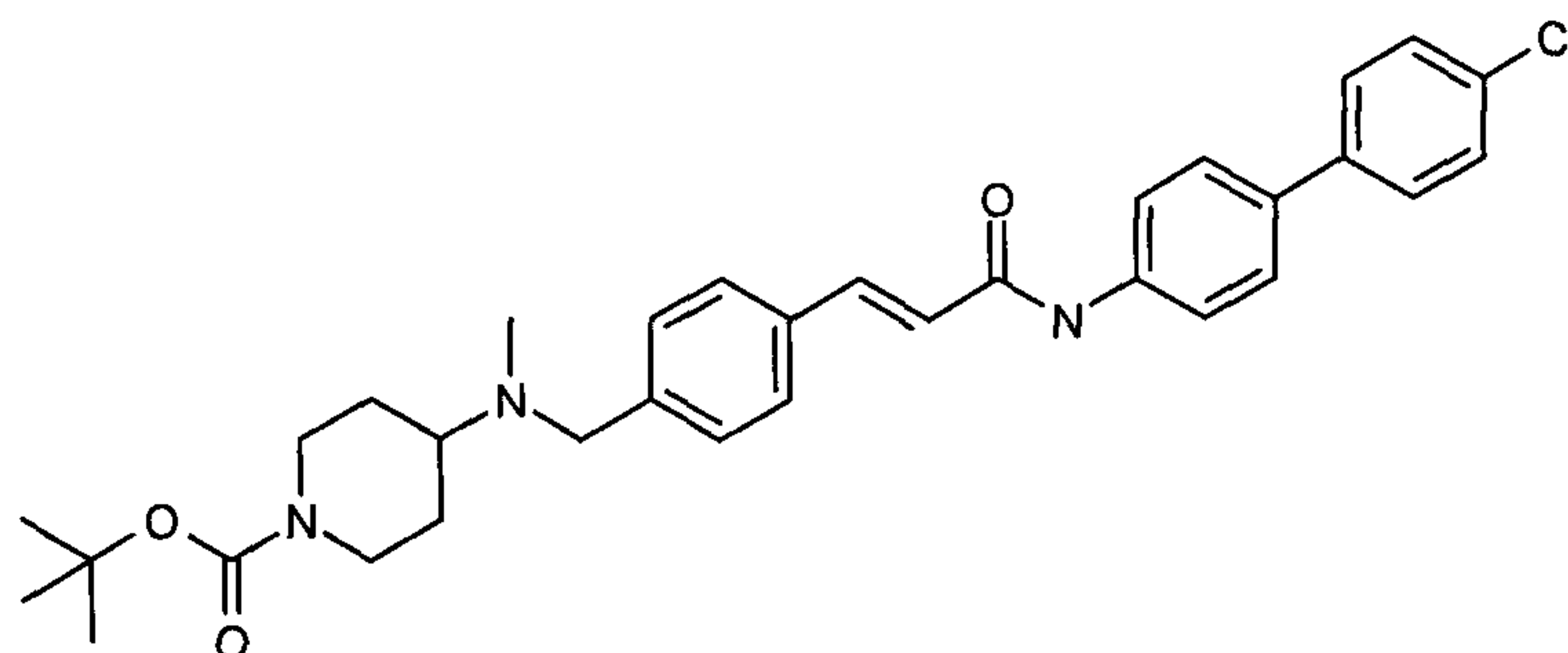
Melting point: 210-211°C

Calc.: Molecular ion peak (M+H)⁺: 475/477 (Cl)

Found: Molecular ion

peak (M+H)⁺: 475/477 (Cl)

25 **Example 5.35:** *tert*-butyl 4-({-[(E)-2-(4'-chloro-biphenyl-4-yl)carbamoyl]-vinyl}-benzyl)-methyl-amino)-piperidine-1-carboxylate



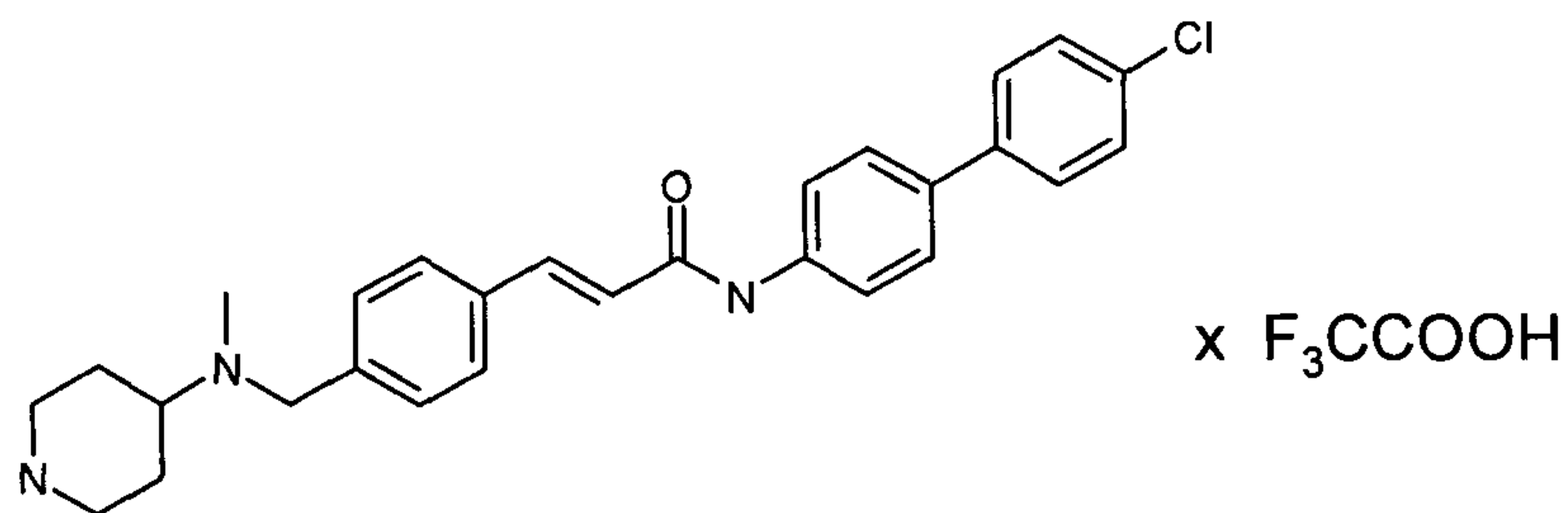
0.5 g (2.34 mmol) *tert*-butyl 4-methylamino-piperidine-1-carboxylate are added to a suspension of 300 mg (0.79 mmol) (E)-*N*-(4'-chloro-biphenyl-4-yl)-3-(4-chloromethyl-phenyl)-acrylamide in 5 ml of dimethylformamide and the mixture is stirred for 18 h at 80 °C. Then the reaction mixture is poured onto water and the precipitate formed is suction filtered. Further purification is carried out by stirring out from a little methanol. Yield: 200 mg (45 % of theoretical)

$C_{33}H_{38}ClN_3O_3$ (M= 560.13)

Melting point: 168-169°C

10 Calc.: Molecular ion peak (M+H)⁺: 560/562 (Cl) Found: Molecular ion peak (M+H)⁺: 560/562 (Cl)

Example 5.36: (E)-*N*-(4'-chloro-biphenyl-4-yl)-3-{4[(methyl-piperidin-4-yl-amino)-methyl]-phenyl}-acrylamide x trifluoroacetic acid acetate



15 1 ml trifluoroacetic acid are added to a suspension of 170 mg (0.3 mmol) *tert*-butyl 4-({-[(E)-2-(4'-chloro-biphenyl-4-ylcarbamoyl)-vinyl]-benzyl}-methyl-amino)-piperidine-1-carboxylate (Example 5.35) in 25 ml dichloromethane and the mixture is stirred for 18 h at ambient temperature. Then the solvent is evaporated down and the residue is crystallised from ethyl acetate/diisopropylether 1:1. The precipitated solid is suction filtered and dried at 60°C in the circulating air dryer.

Yield: 70 mg (40 % of theoretical)

$C_{28}H_{30}ClN_3O$ (M= 460.02)* trifluoroacetic acid acetate

Melting point: 207-208°C

Calc.: Molecular ion peak (M+H)⁺: 460/462 (Cl)

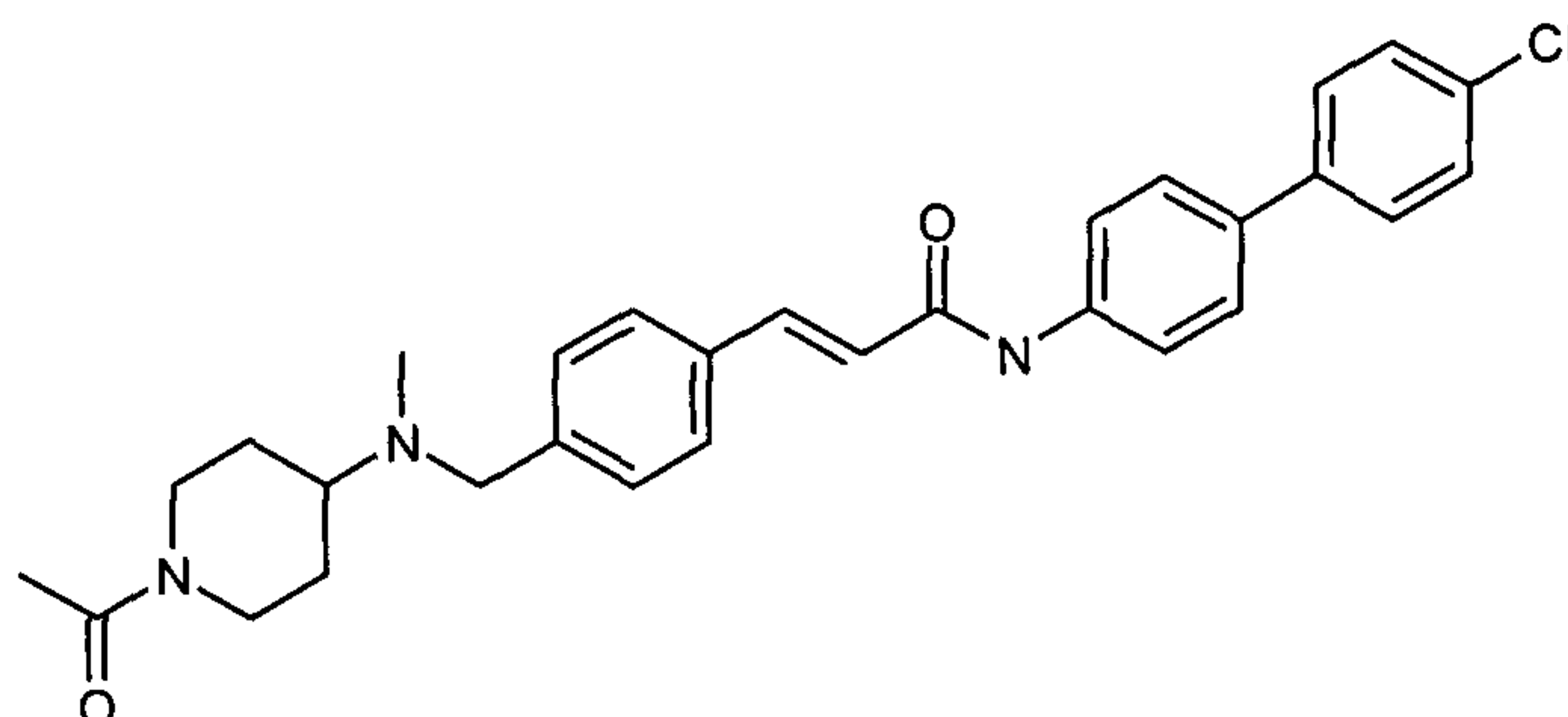
Found: Molecular ion

peak (M+H)⁺: 460/462 (Cl)

Example 5.37:

(E)-3-(4-[[[(1-acetyl-piperidin-4-yl)-methyl-amino]-methyl]-phenyl]-N-(4'-chloro-

5 biphenyl-4-yl)-acrylamide



0.017 ml (0.18 mmol) acetic anhydride are added to a solution of 50 mg (0.087 mmol) (E)-N-(4'-chloro-biphenyl-4-yl)-3-{4[(methyl-piperidin-4-yl-amino)-methyl]-phenyl}-acrylamide x trifluoroacetic acid acetate in 4 ml acetic acid and the mixture is stirred
10 for 18 hours at ambient temperature. Then the reaction mixture is poured onto water and made basic with ammonia. The precipitate formed is suction filtered and washed with water. The product is dried at 60 °C in the circulating air dryer.

Yield: 20 mg (46 % of theoretical)

C₃₀H₃₂ClN₃O₂ (M= 502.05)

15 Melting point: 225-226°C

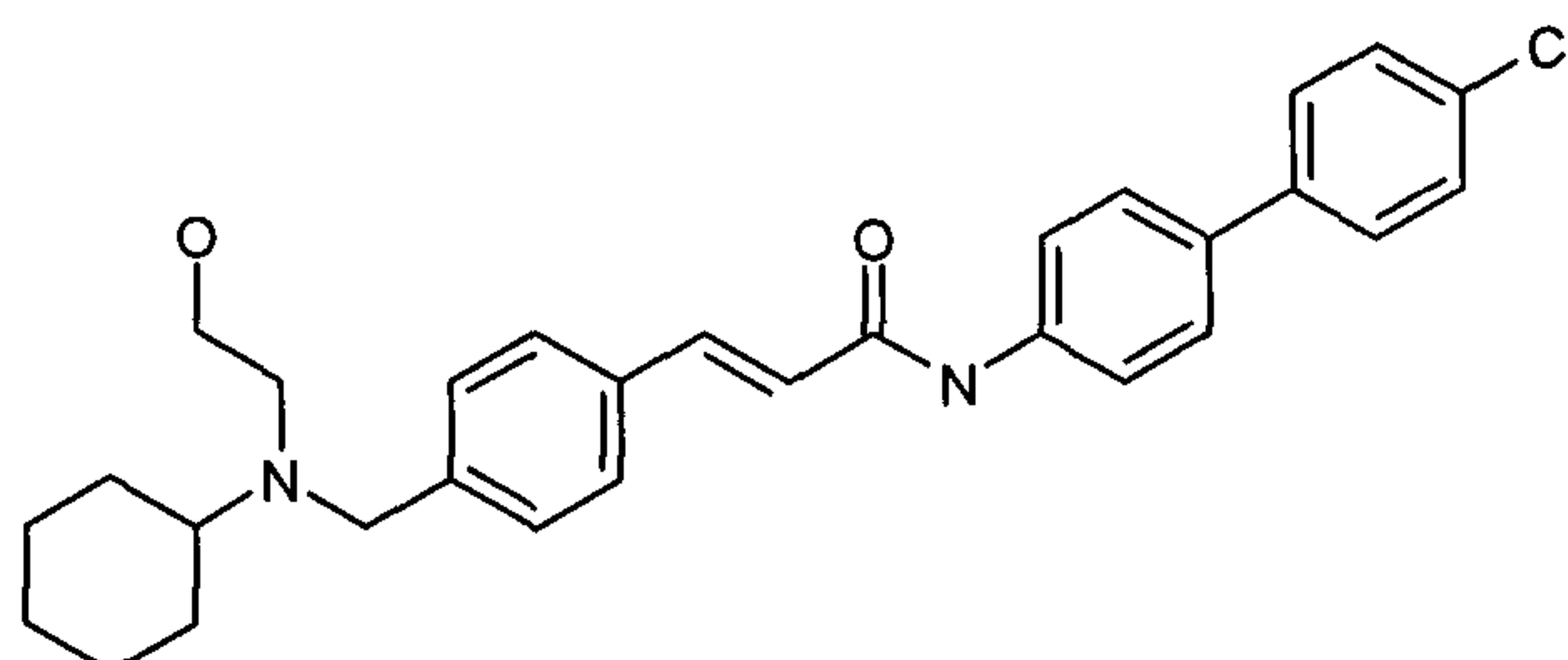
Calc.: Molecular ion peak (M+H)⁺: 502/504 (Cl)

Found: Molecular ion

peak (M+H)⁺: 502/504 (Cl)

Example 5.38:

20 (E)-N-(4'-chloro-biphenyl-4-yl)-3-(4-[[cyclohexyl-(2-hydroxy-ethyl)-amino]-methyl]-phenyl)-acrylamide



0.24 g (1.7 mmol) 2-cyclohexylamino-ethanol are added to a suspension of 130 mg (0.34 mmol) (E)-N-(4'-chloro-biphenyl-4-yl)-3-(4-chloromethyl-phenyl)-acrylamide in
25 10 ml of dimethylformamide and the mixture is stirred for 48 hours at 80 °C. Then the

reaction mixture is poured onto water and the precipitate formed is suction filtered and washed with water. The solid is dried in the circulating air dryer at 50°C .

Yield: 20 mg (10 % of theoretical)

C₃₀H₃₃ClN₂O₂ (M= 489.05)

5 Melting point: 178-179°C

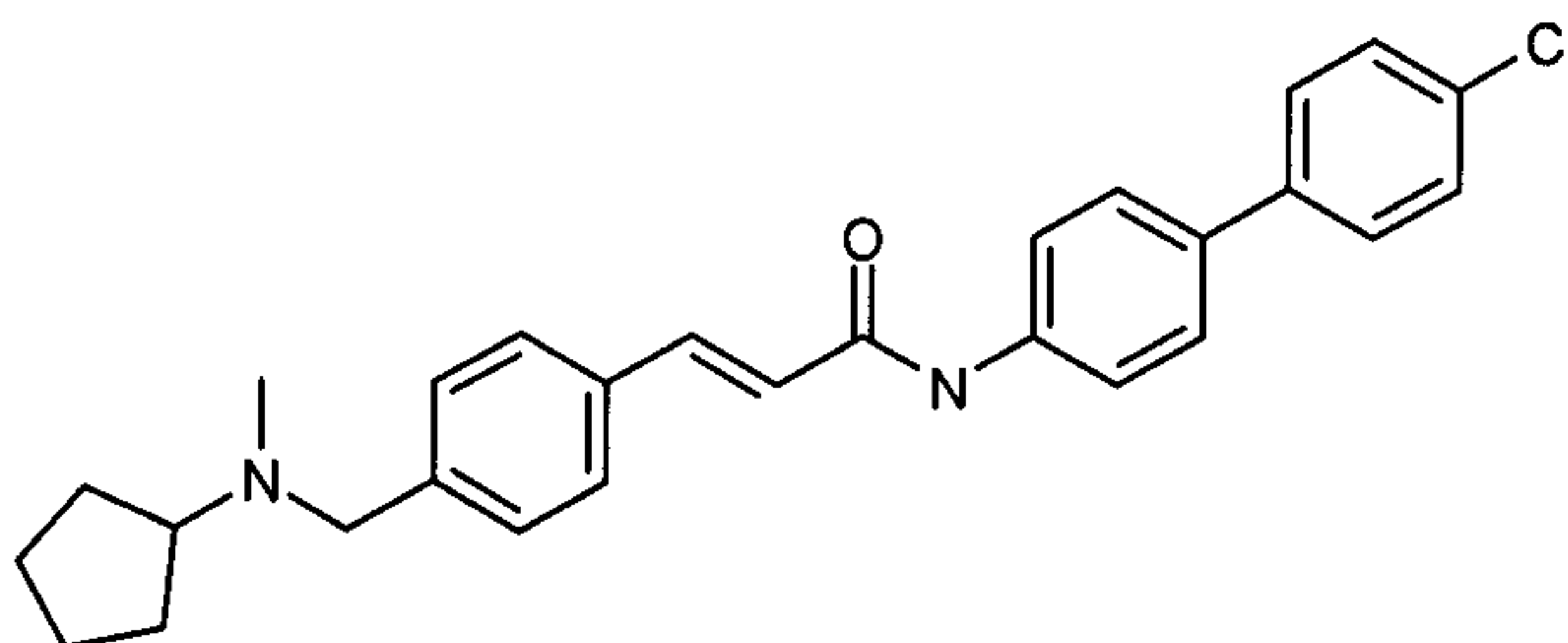
Calc.: Molecular ion peak (M+H)⁺: 489/491 (Cl)

Found: Molecular ion

peak (M+H)⁺: 489/491 (Cl)

Example 5.39:

10 (E)-N-(4'-chloro-biphenyl-4-yl)-3-{4-[(cyclopentyl-methyl-amino)-methyl]-phenyl}-acrylamide



A reaction mixture of 200 mg (0.523 mmol) (E)-N-(4'-chloro-biphenyl-4-yl)-3-(4-chloromethyl-phenyl)-acrylamide, 295 mg (1.56 mmol) cyclopentyl-methyl-amine

15 oxalic acid acetate and 0.44 ml (3.12 mmol) triethylamine in 5 ml of tetrahydrofuran is refluxed for 18 hours. Then the reaction mixture is poured onto water and the precipitate formed is suction filtered. Further purification is carried out by column chromatography on silica gel (eluant: dichloromethane/methanol 10:1).

Yield: 10 mg (4 % of theoretical)

20 C₂₈H₂₉ClN₂O (M= 445.0)

Melting point: 209-210°C

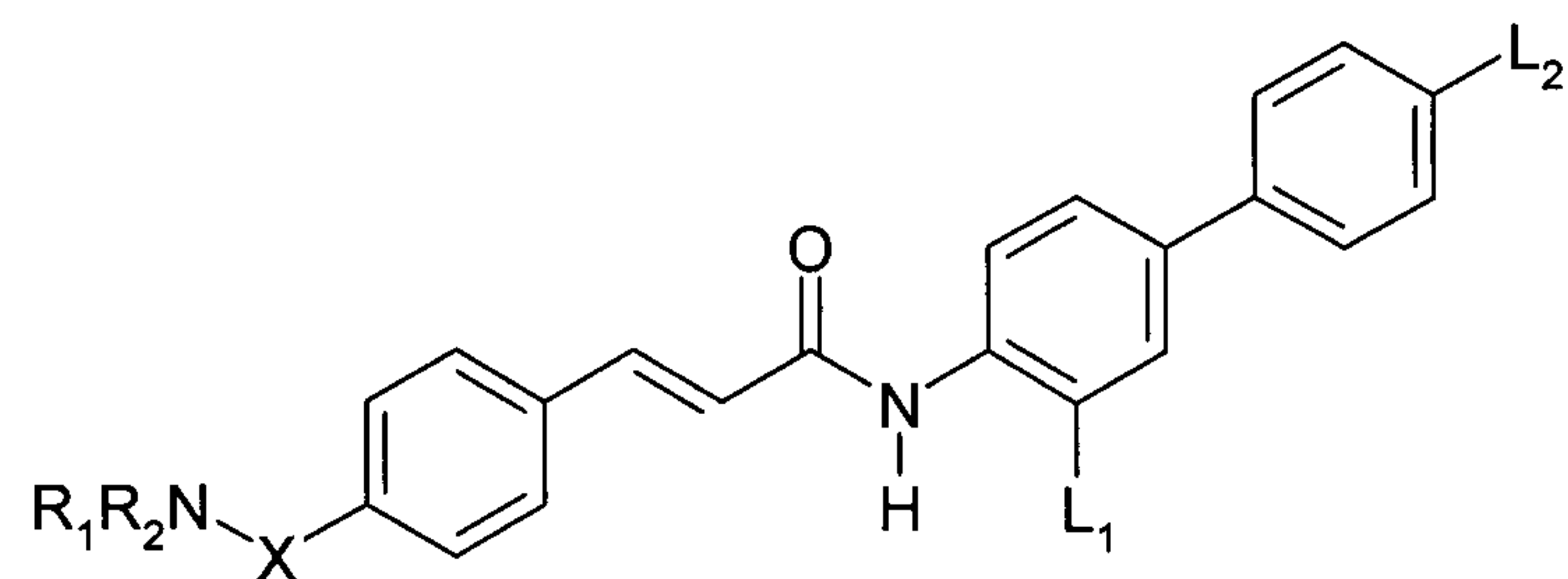
Calc.: Molecular ion peak (M+H)⁺: 445/447 (Cl)

Found: Molecular ion

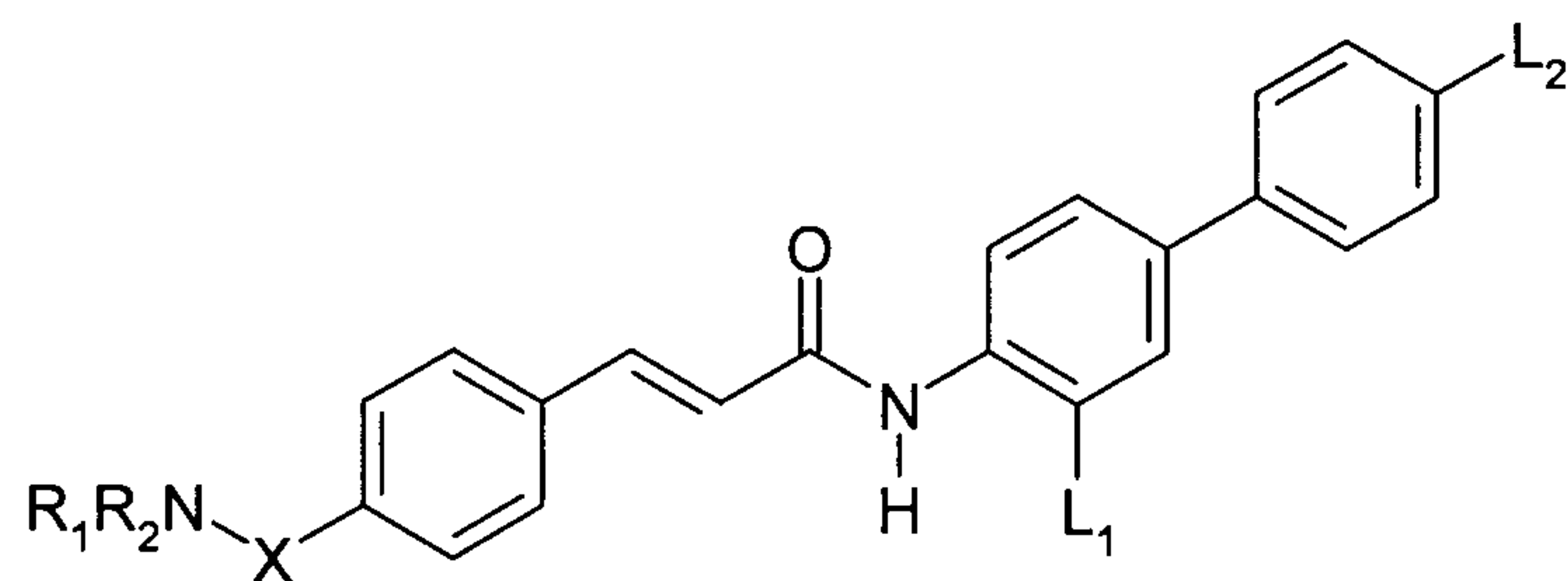
peak (M+H)⁺: 445/447 (Cl)

25

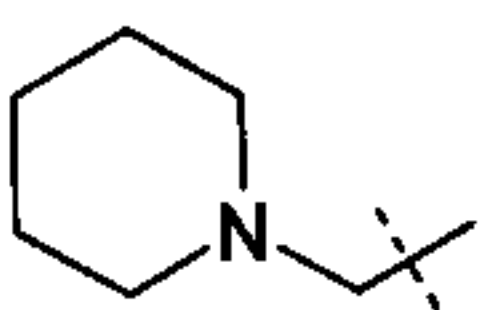
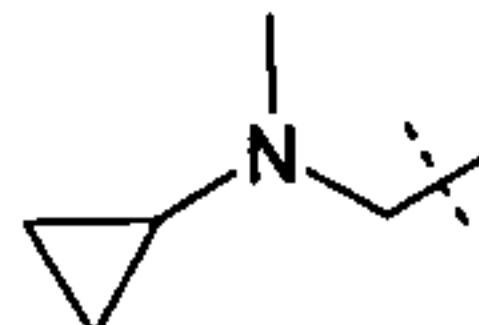
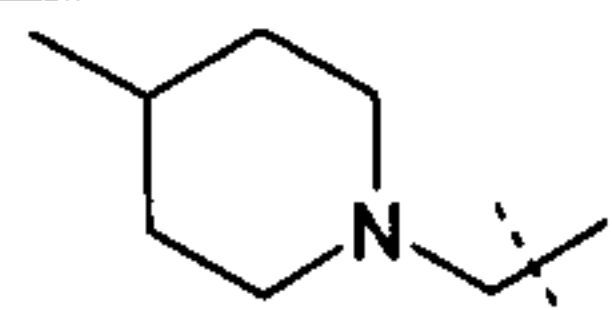
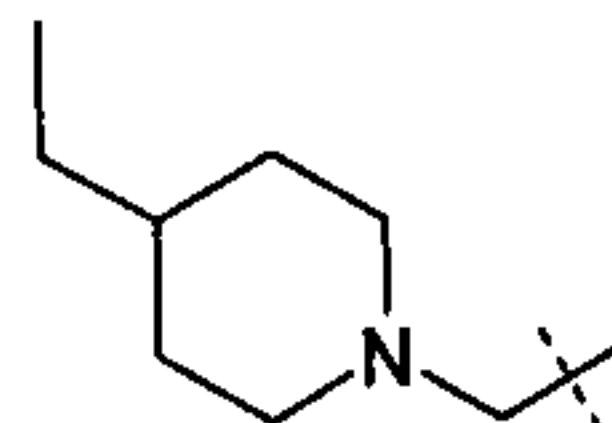
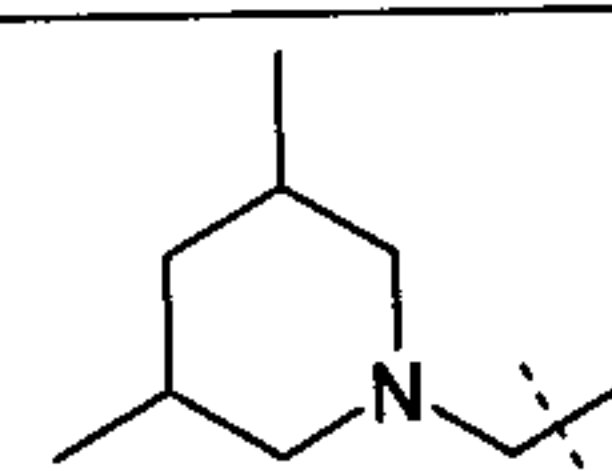
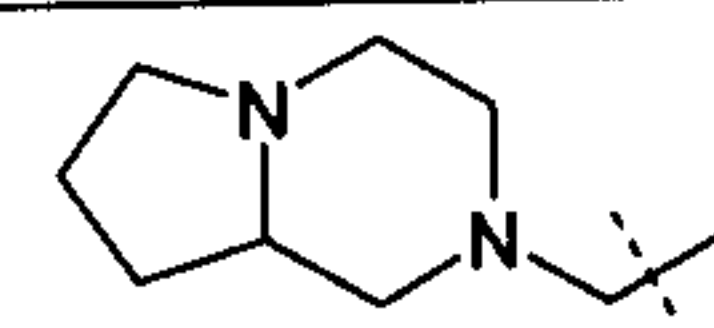
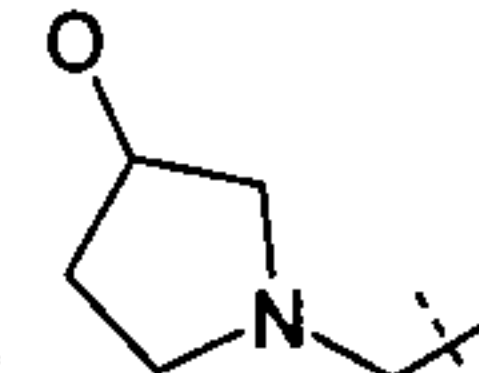
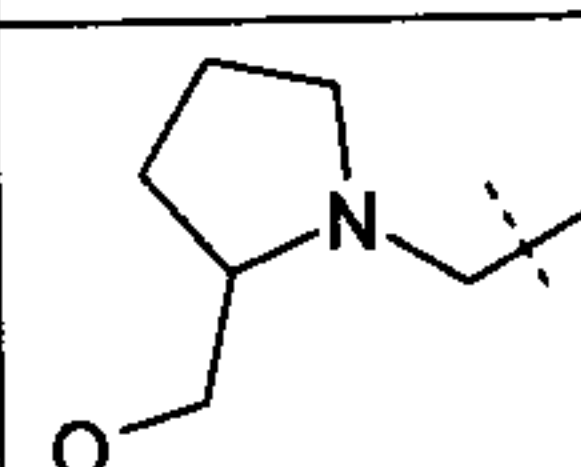
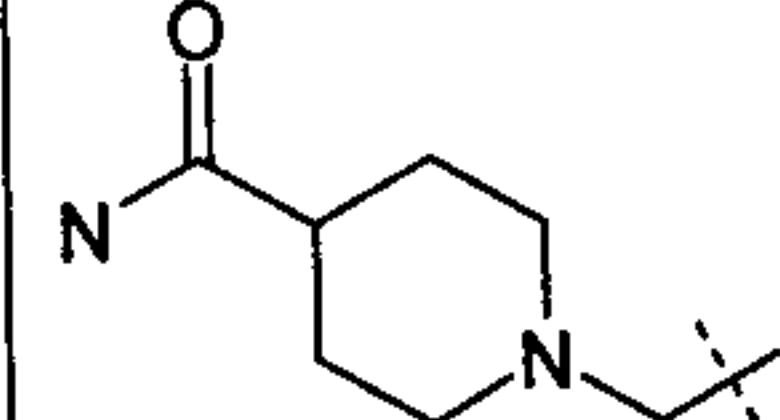
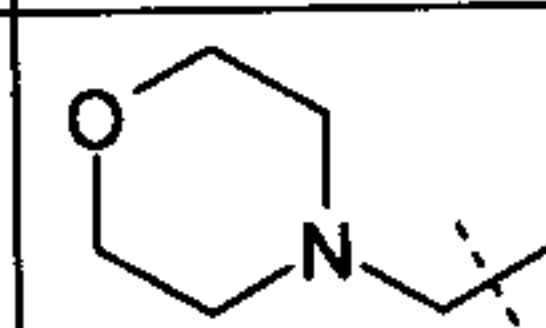
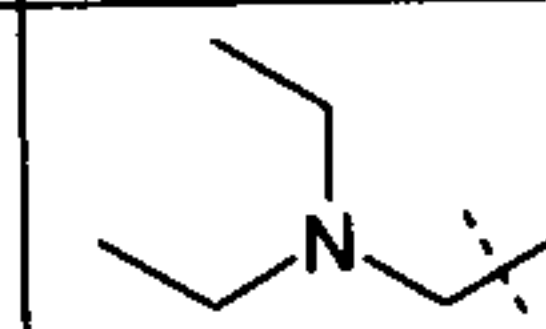
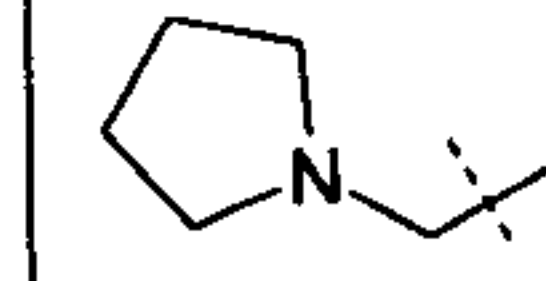
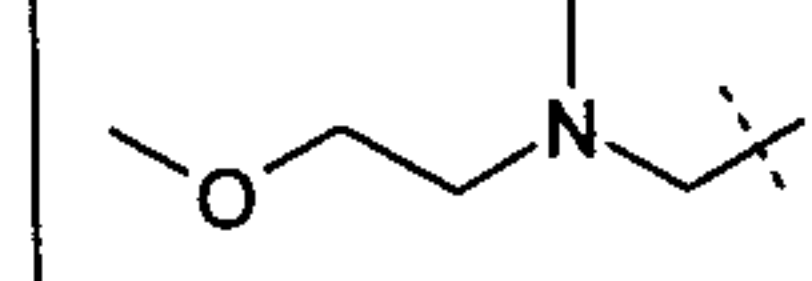
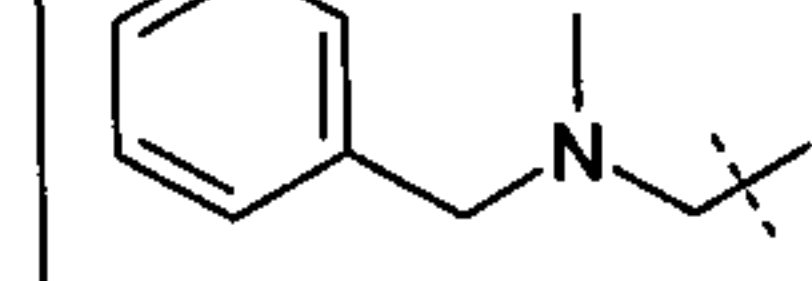
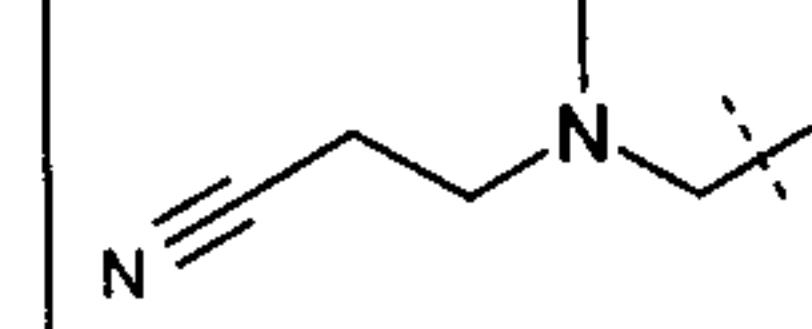
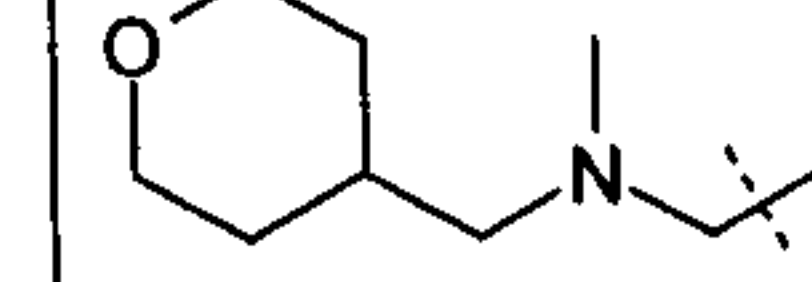
The following compounds are prepared analogously to Example 5.3.c:

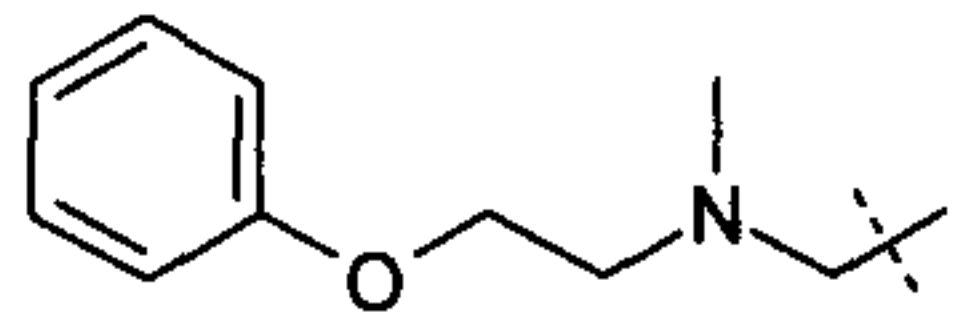
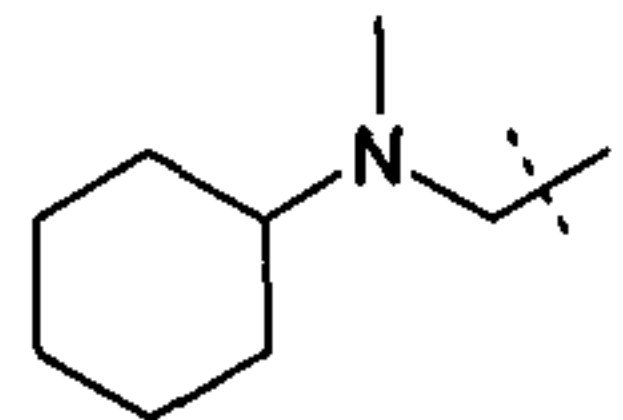
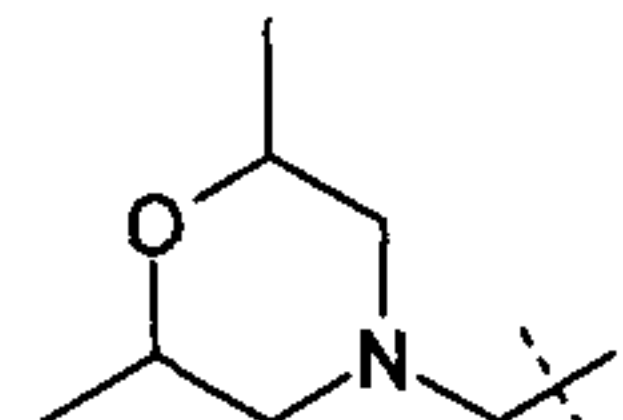


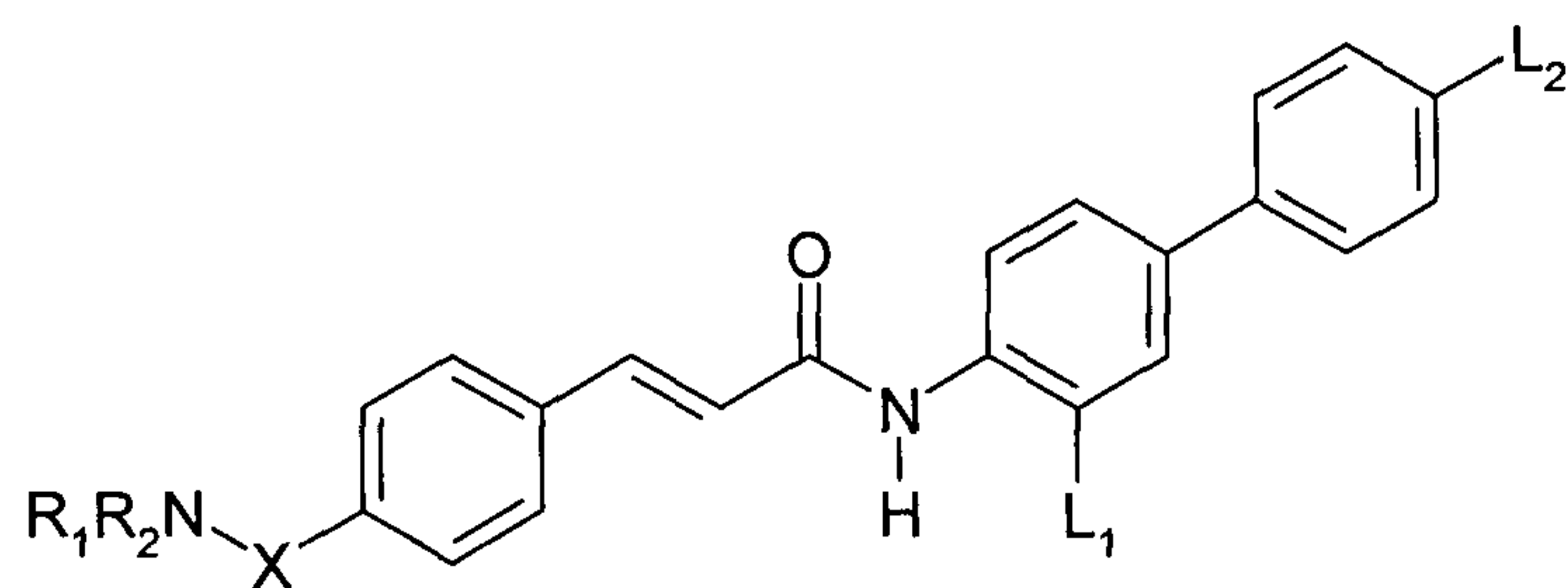
Example	R ₁ R ₂ N-X	L ₁	L ₂
5.40		H	Cl
5.41		H	Cl
5.42		H	Cl

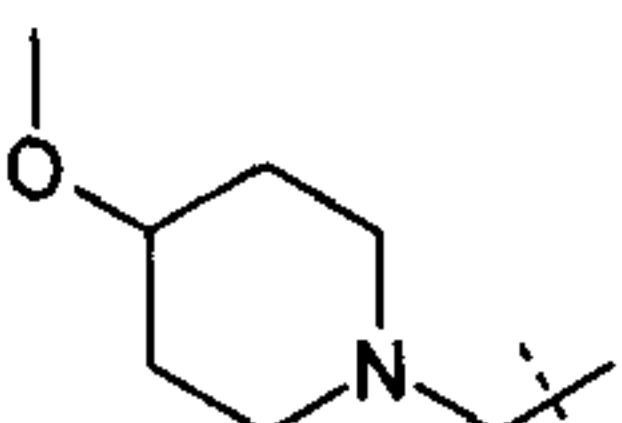
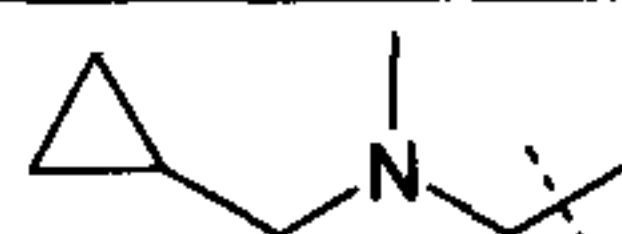
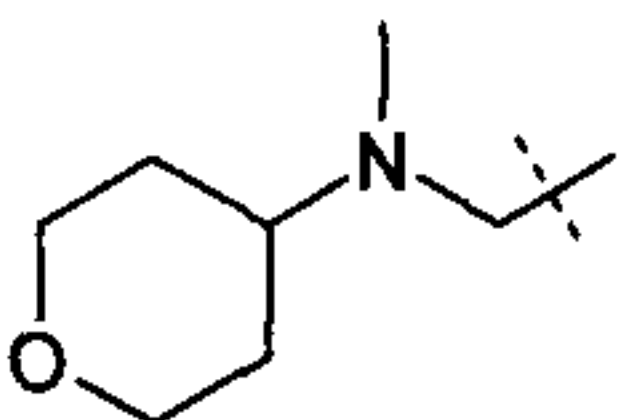
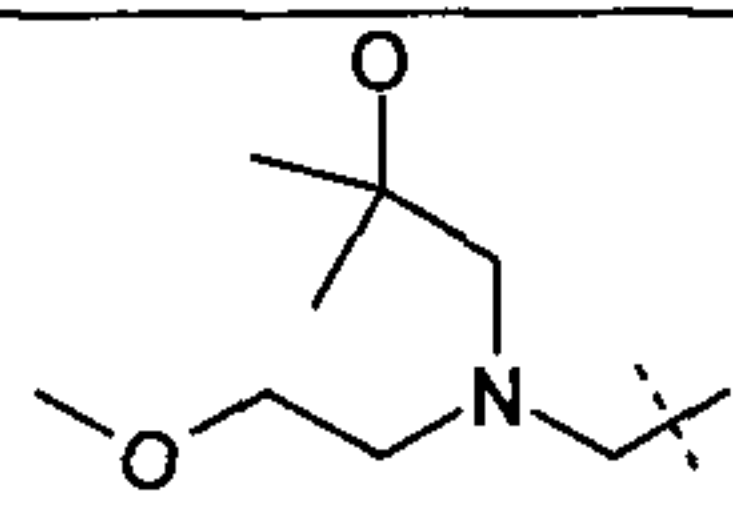
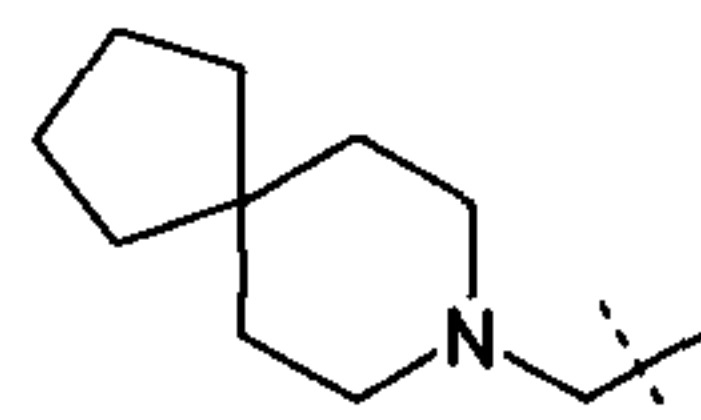
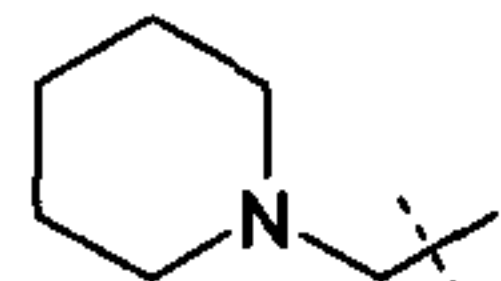
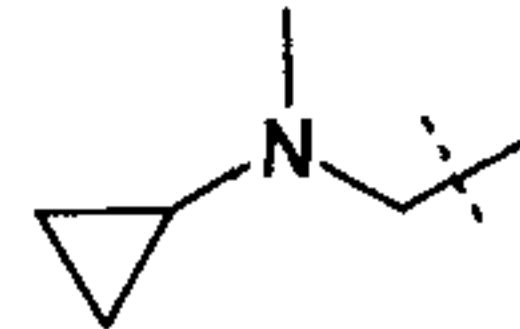
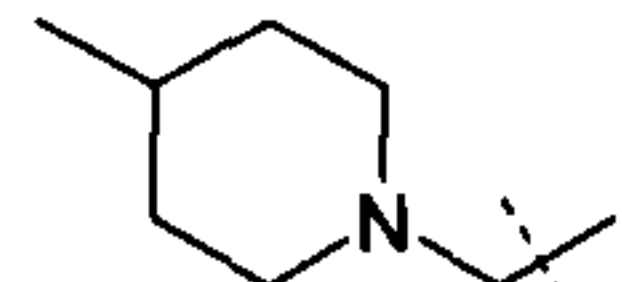


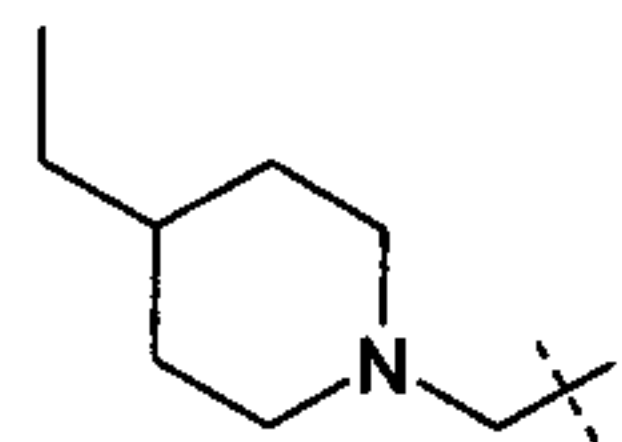
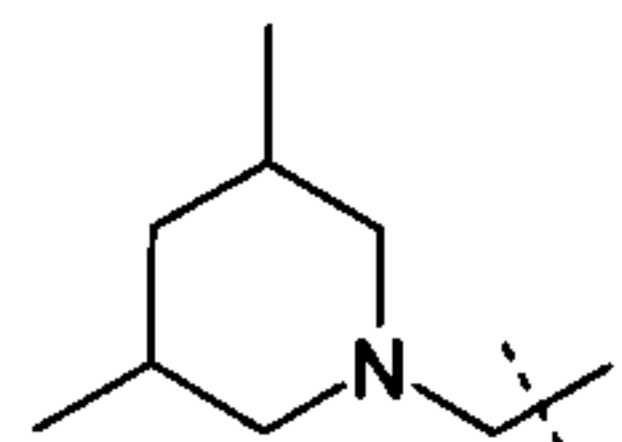
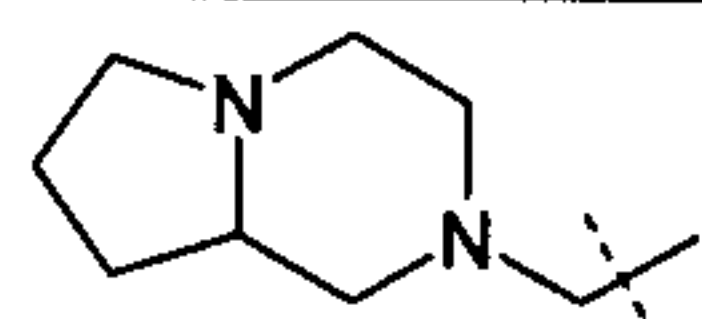
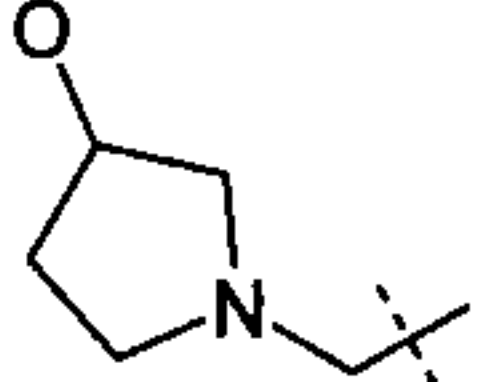
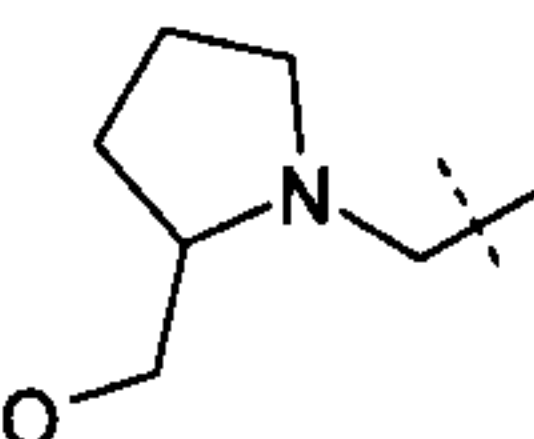
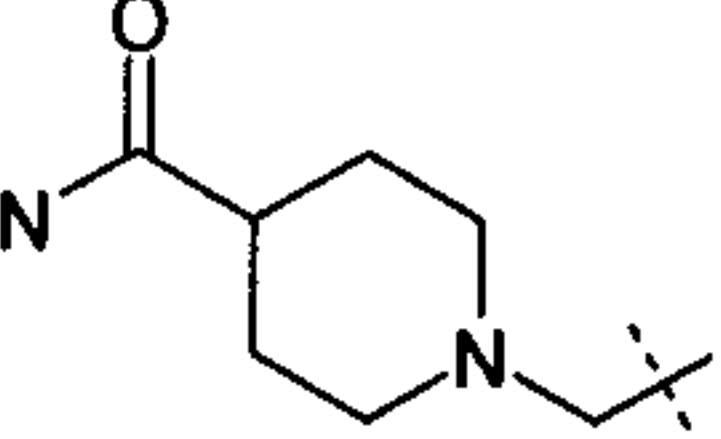
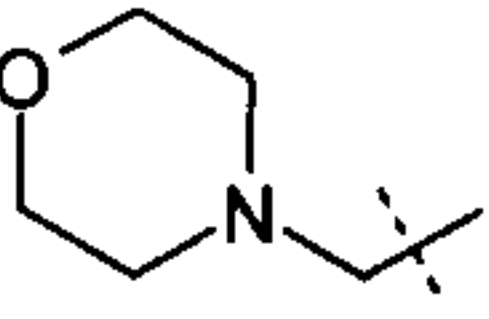
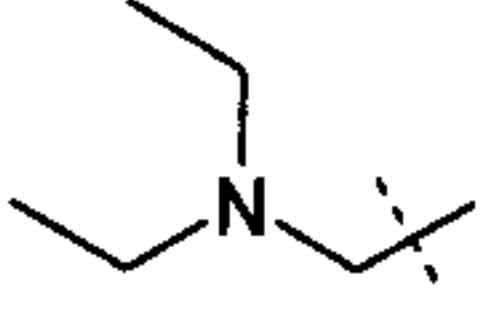
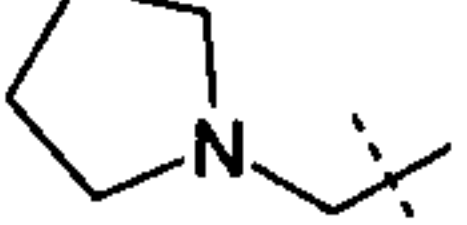
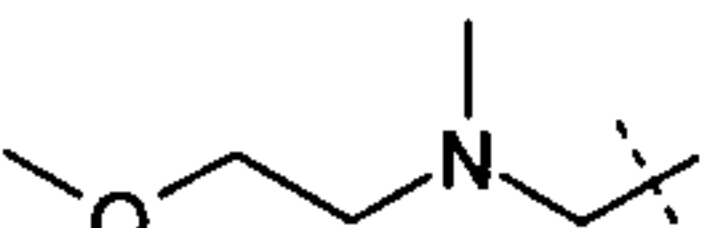
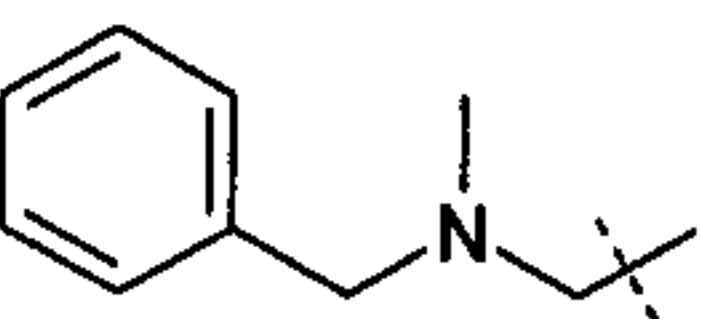
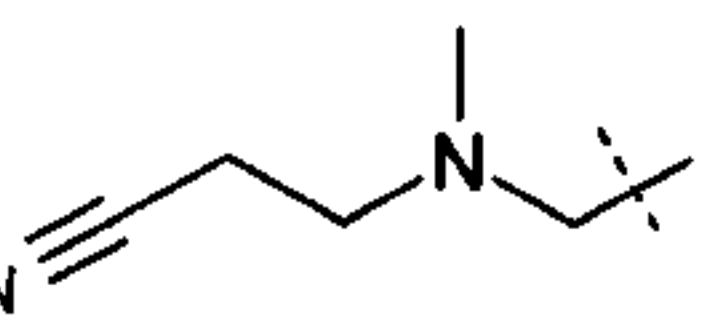
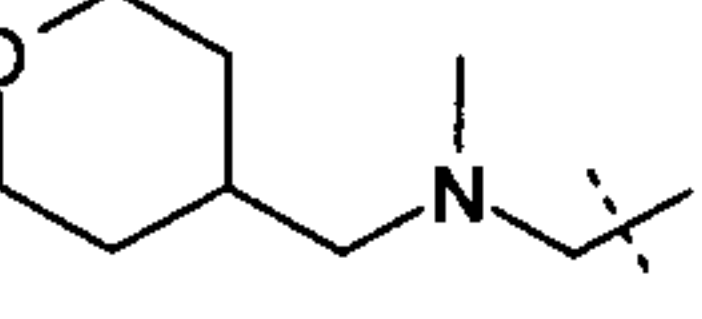
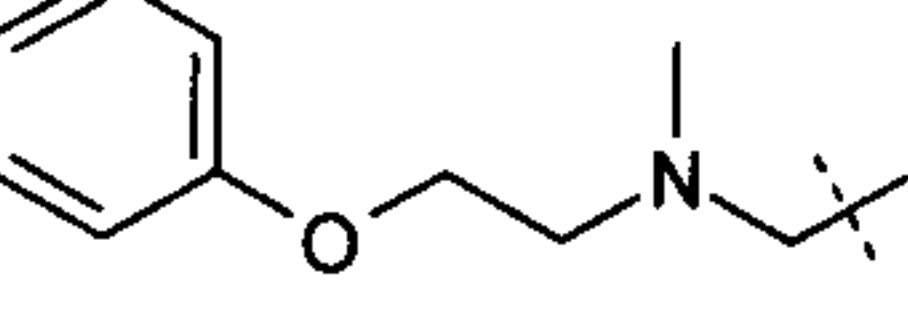
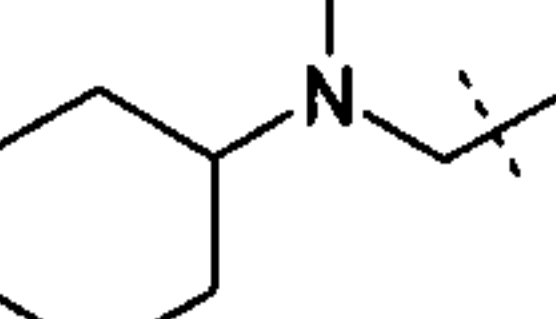
Example	R ₁ R ₂ N-X	L ₁	L ₂
5.43		F	Cl
5.44		F	Cl
5.45		F	Cl
5.46		F	Cl
5.47		F	Cl

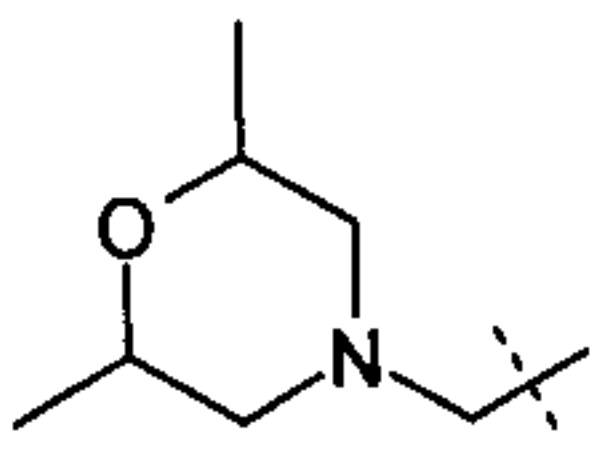
5.48		F	Cl
5.49		F	Cl
5.50		F	Cl
5.51		F	Cl
5.52		F	Cl
5.53		F	Cl
5.54		F	Cl
5.55		F	Cl
5.56		F	Cl
5.57		F	Cl
5.58		F	Cl
5.59		F	Cl
5.60		F	Cl
5.61		F	Cl
5.62		F	Cl
5.63		F	Cl

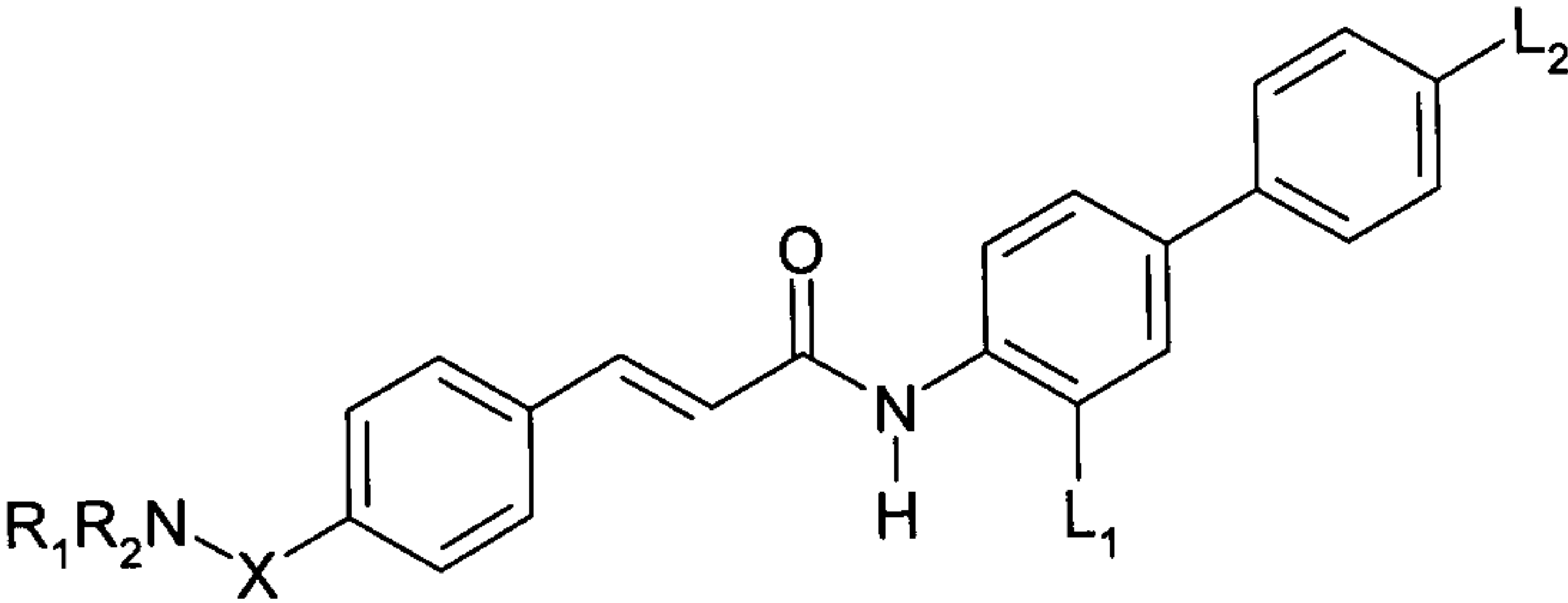
5.64		F	Cl
5.65		F	Cl
5.66		F	Cl

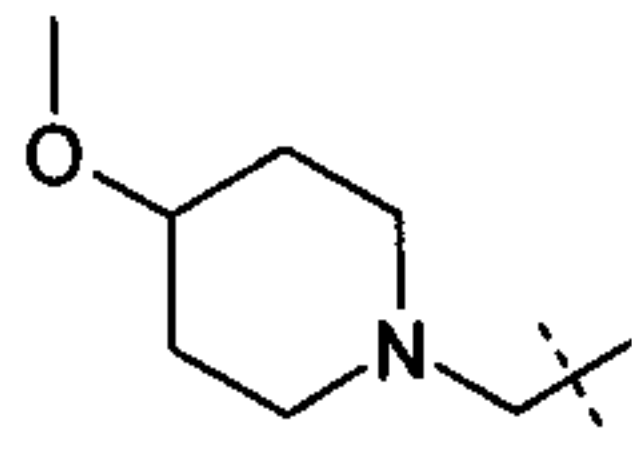
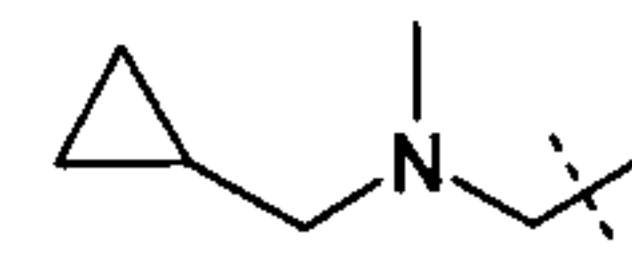
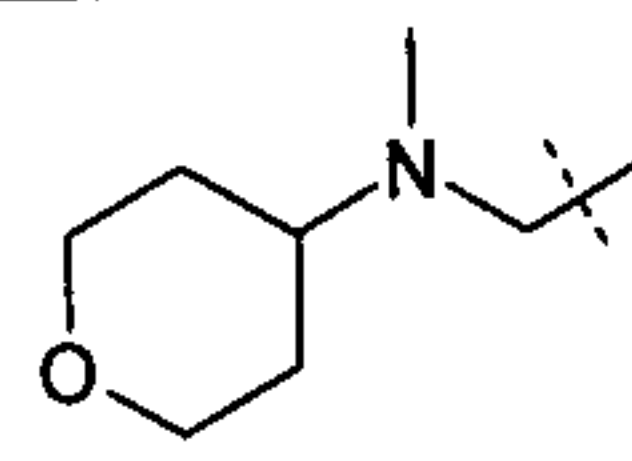
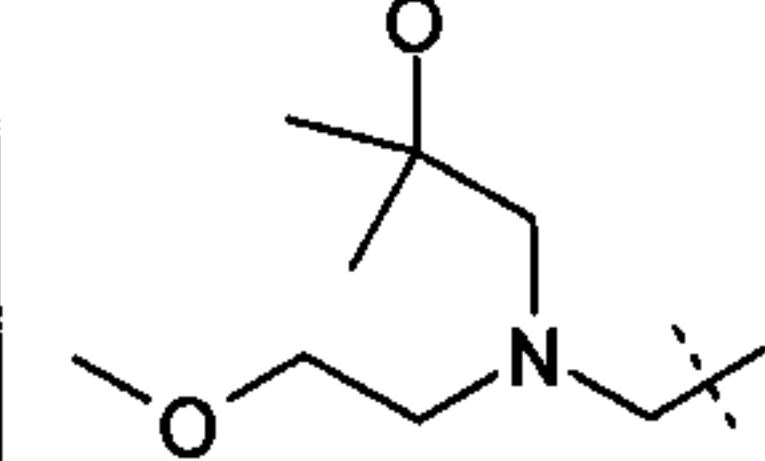
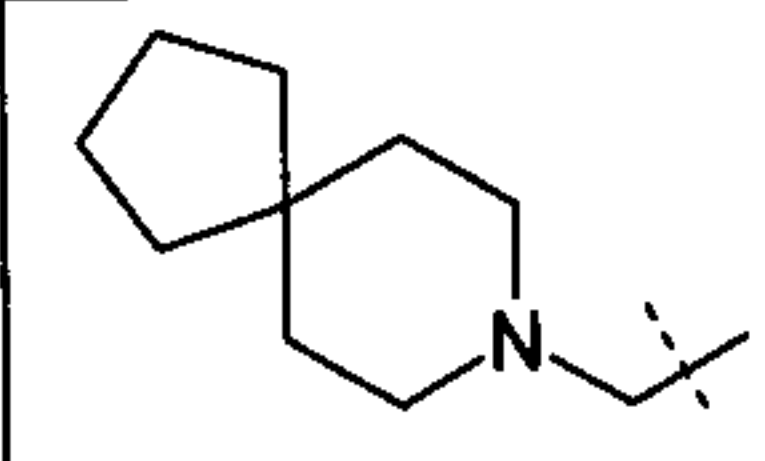
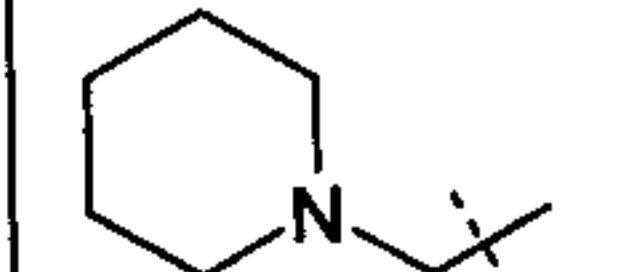
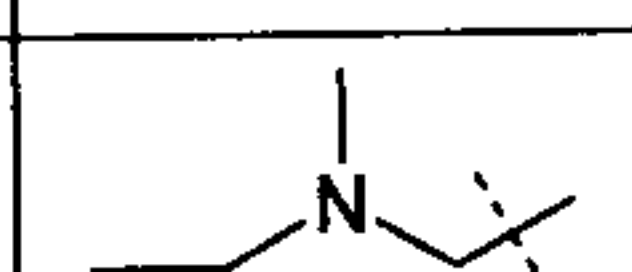
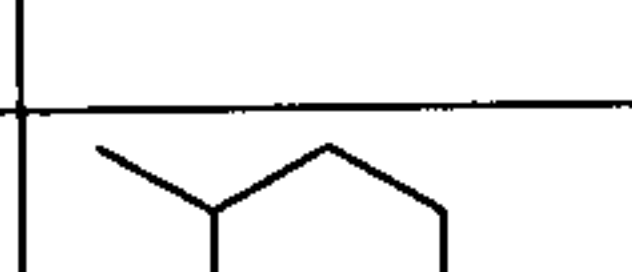
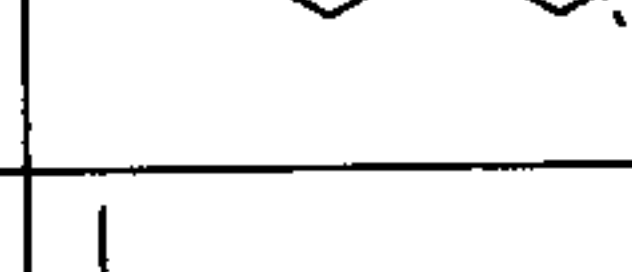
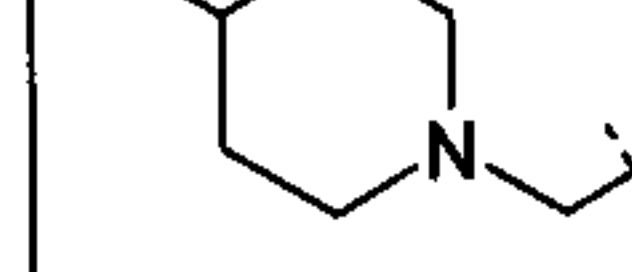


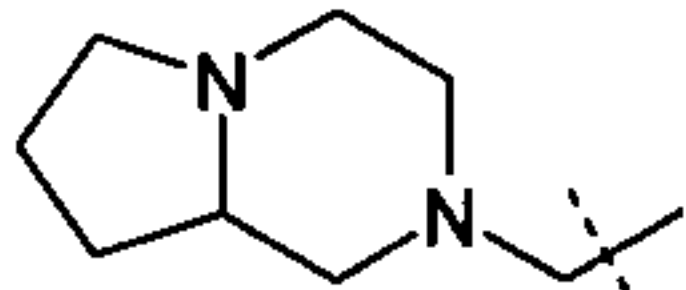
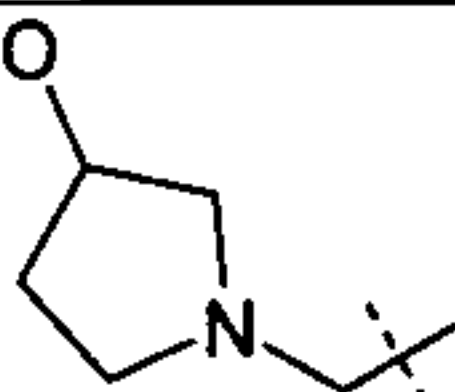
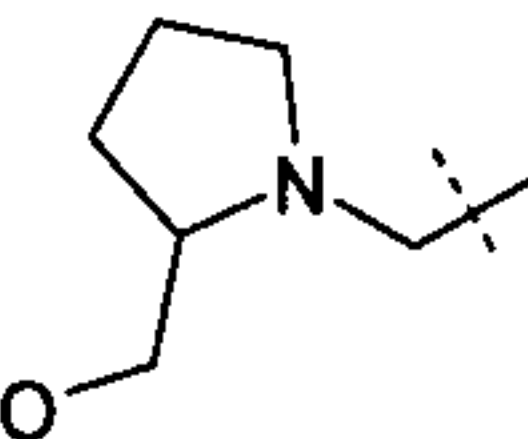
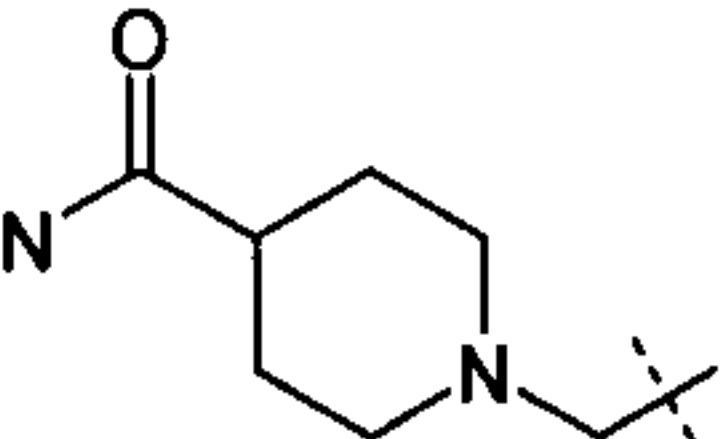
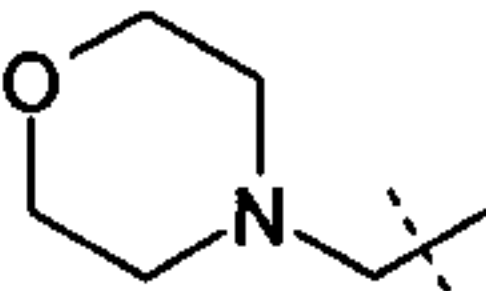
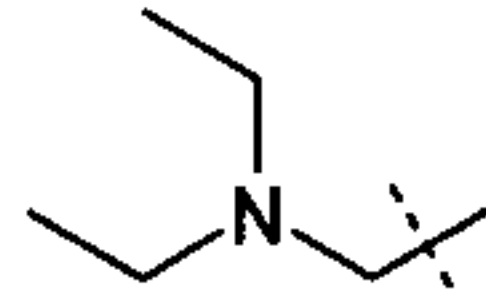
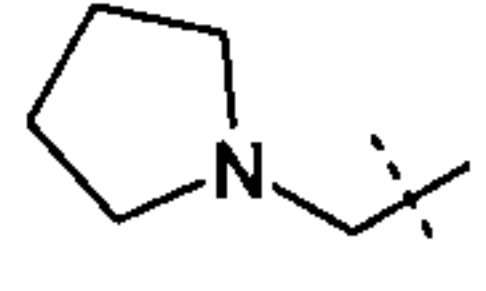
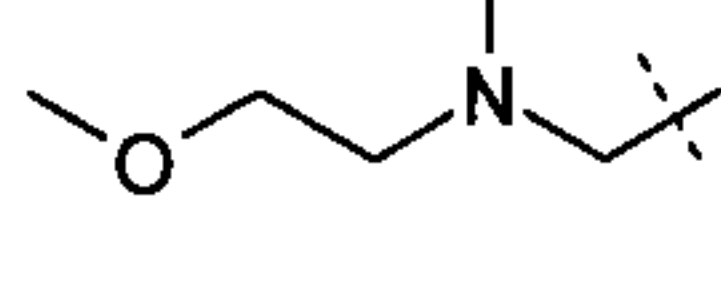
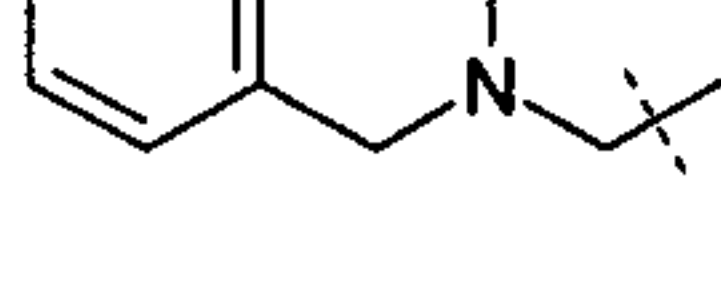
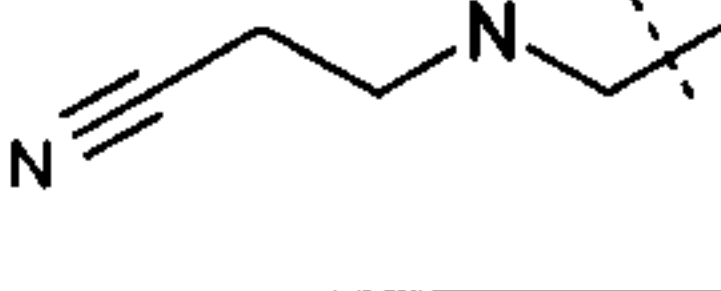
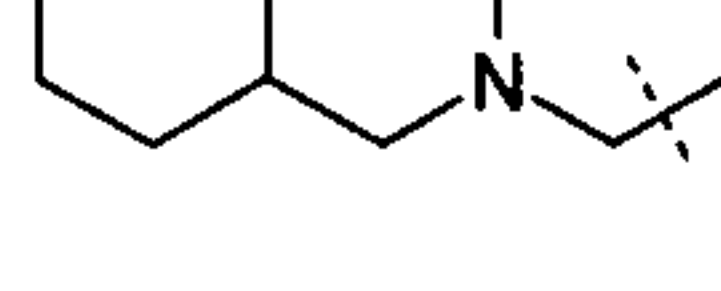
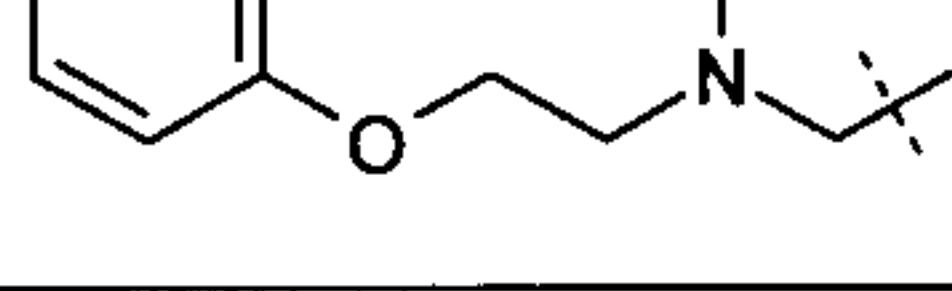
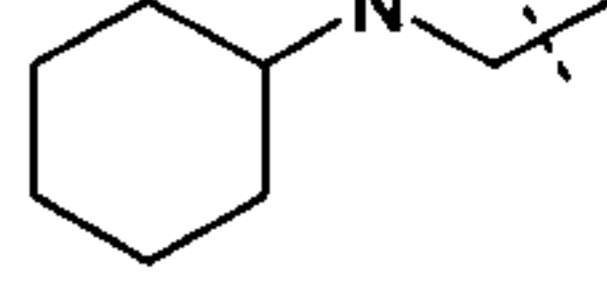
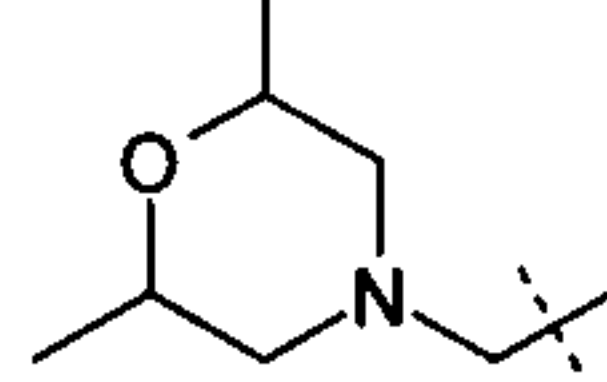
Example	R_1R_2N-X	L1	L2
5.67		H	CF ₃
5.68		H	CF ₃
5.69		H	CF ₃
5.70		H	CF ₃
5.71		H	CF ₃
5.72		H	CF ₃
5.73		H	CF ₃
5.74		H	CF ₃

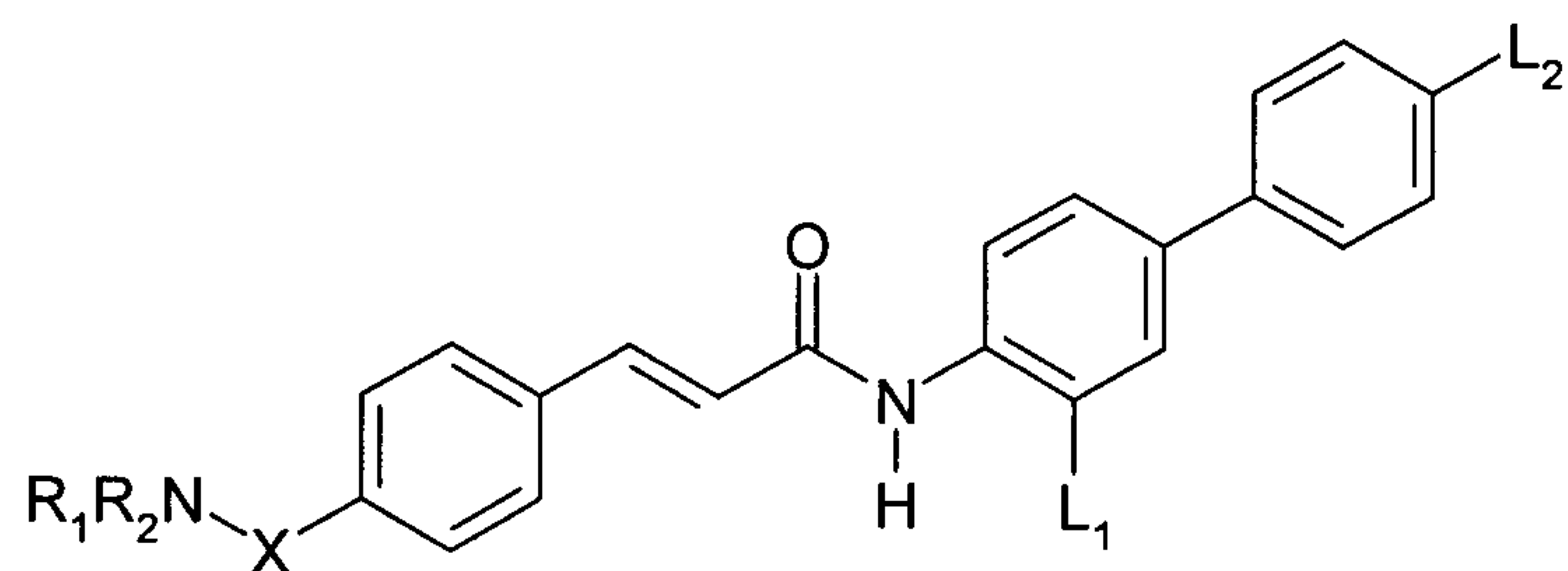
5.75		H	CF ₃
5.76		H	CF ₃
5.77		H	CF ₃
5.78		H	CF ₃
5.79		H	CF ₃
5.80		H	CF ₃
5.81		H	CF ₃
5.82		H	CF ₃
5.83		H	CF ₃
5.84		H	CF ₃
5.85		H	CF ₃
5.86		H	CF ₃
5.87		H	CF ₃
5.88		H	CF ₃
5.89		H	CF ₃

5.90		H	CF ₃

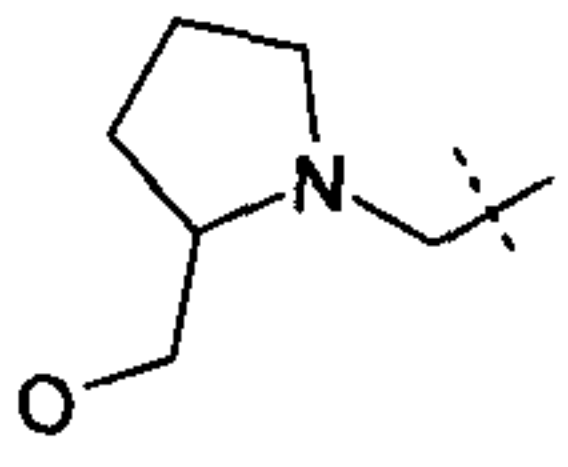
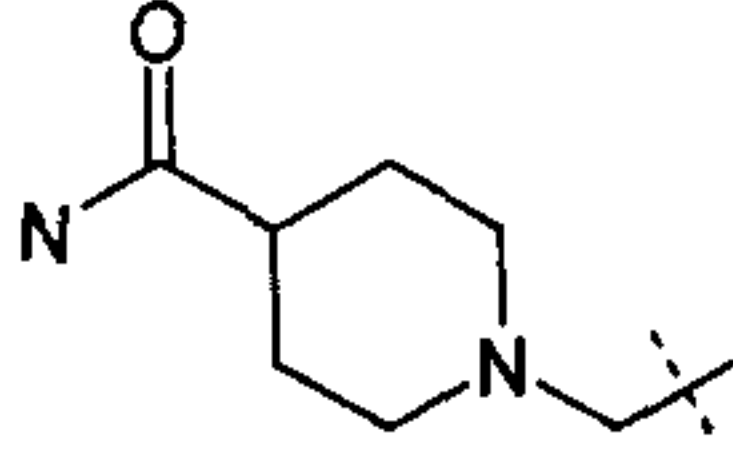
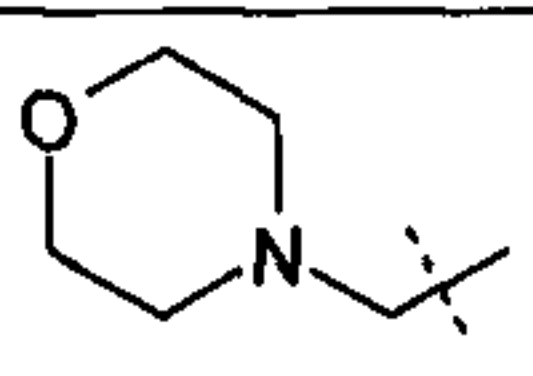
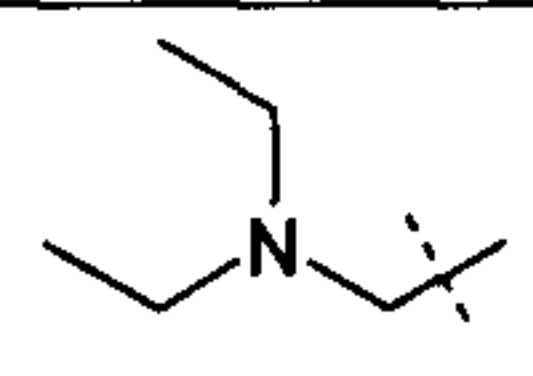
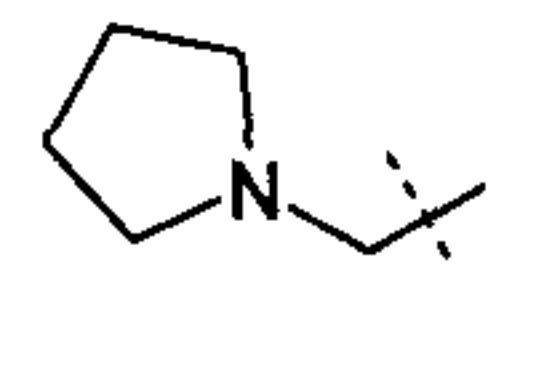
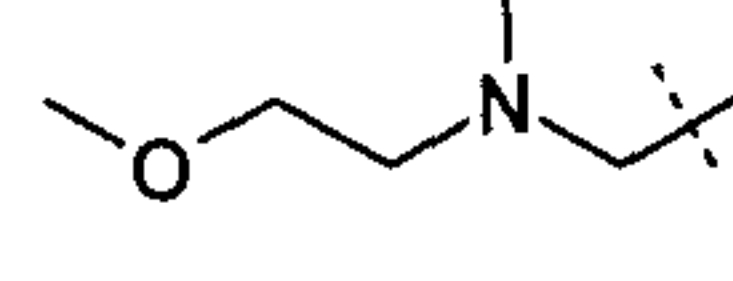
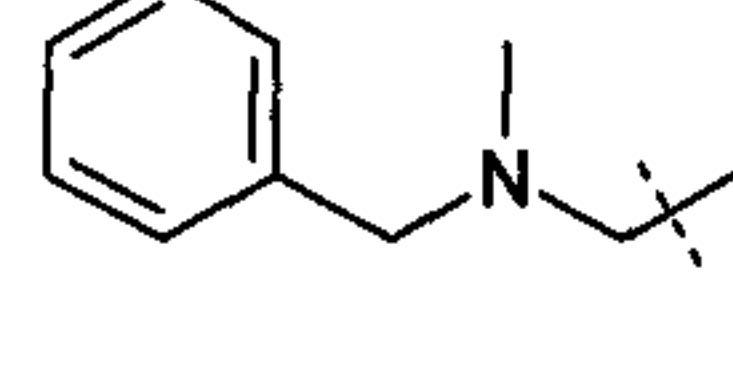
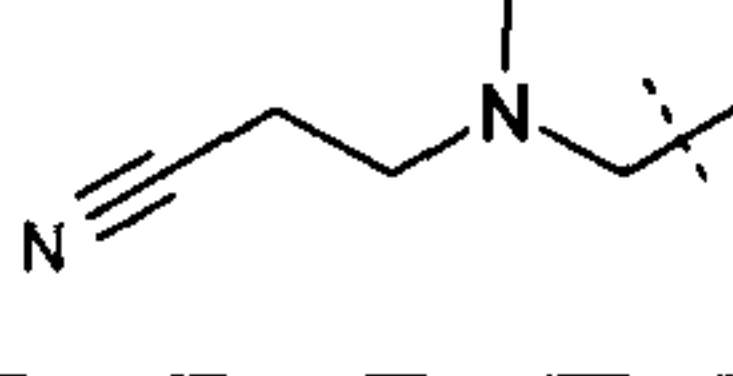
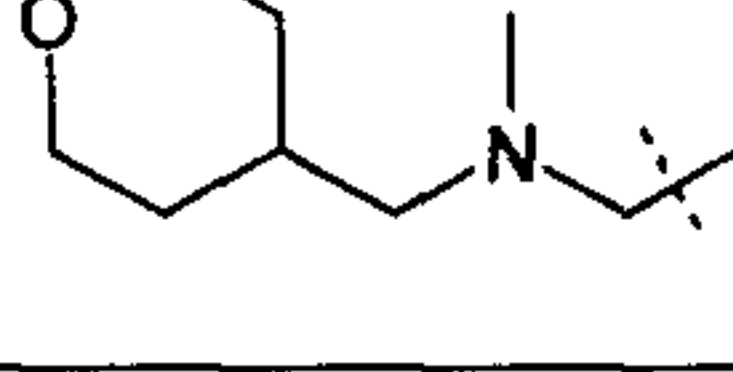
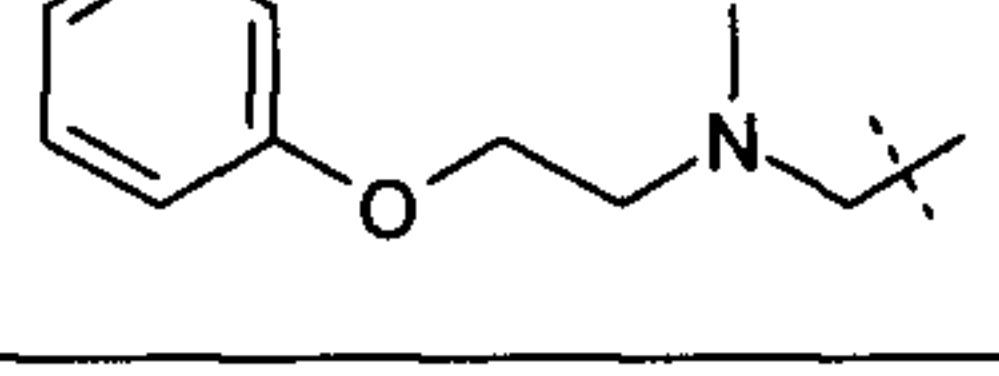
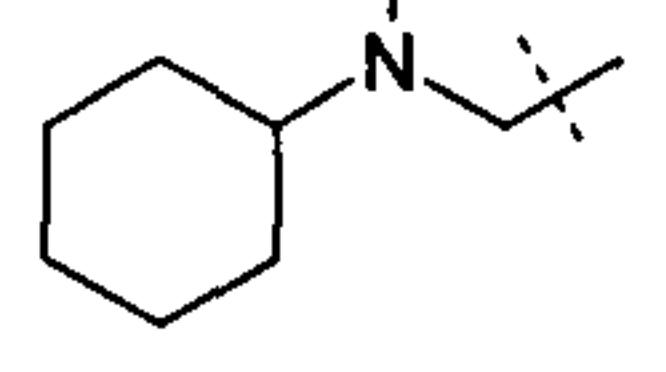
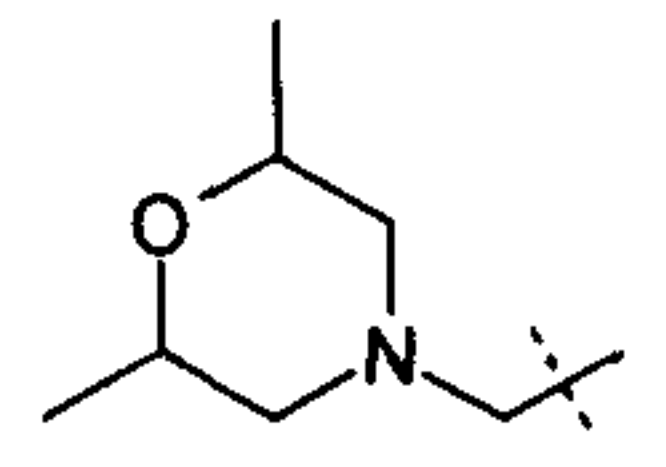


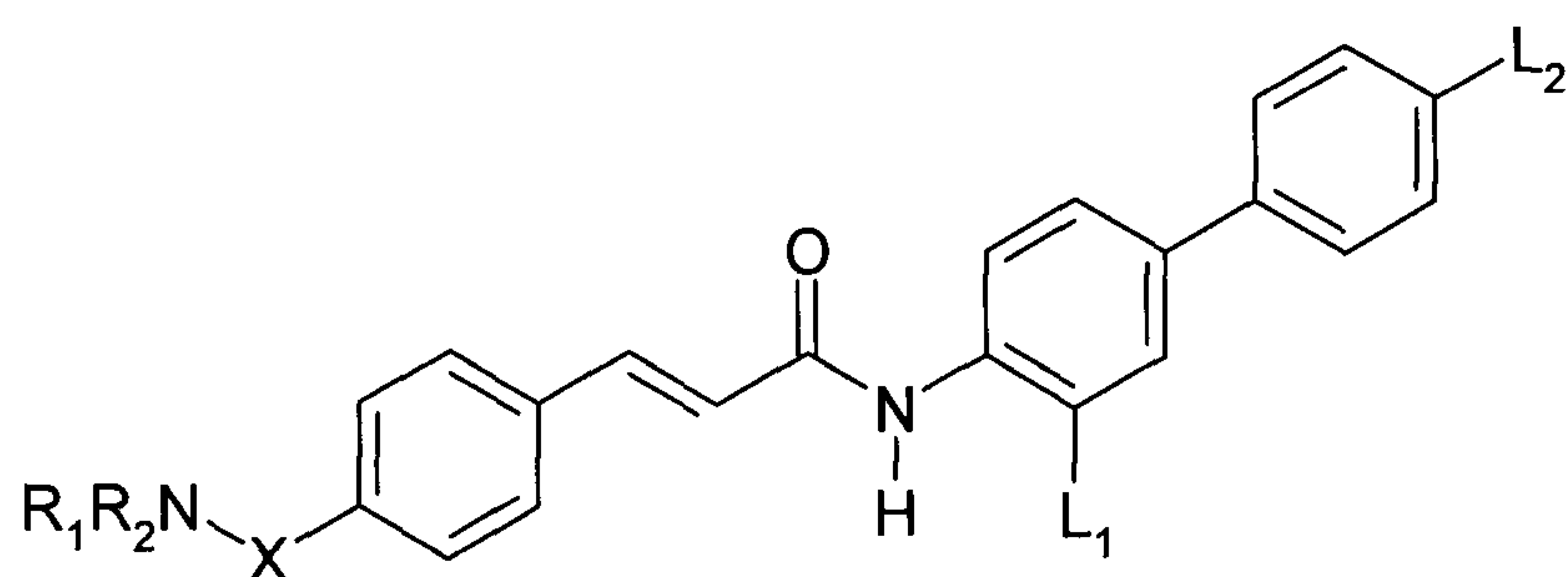
Example	R ₁ R ₂ N-X	L ₁	L ₂
5.91		H	Me
5.92		H	Me
5.93		H	Me
5.94		H	Me
5.95		H	Me
5.96		H	Me
5.97		H	Me
5.98		H	Me
5.99		H	Me
5.100		H	Me

5.101		H	Me
5.102		H	Me
5.103		H	Me
5.104		H	Me
5.105		H	Me
5.106		H	Me
5.107		H	Me
5.108		H	Me
5.109		H	Me
5.110		H	Me
5.111		H	Me
5.112		H	Me
5.113		H	Me
5.114		H	Me

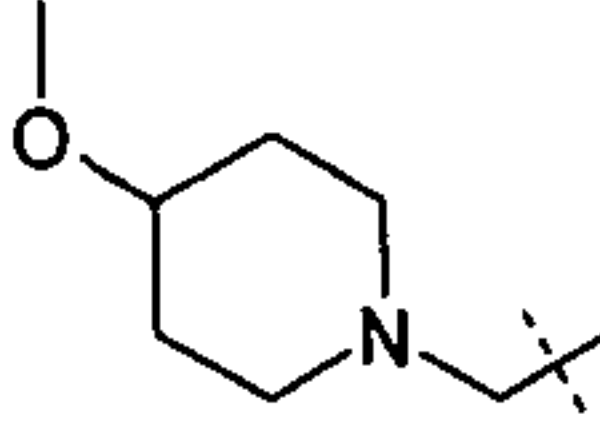
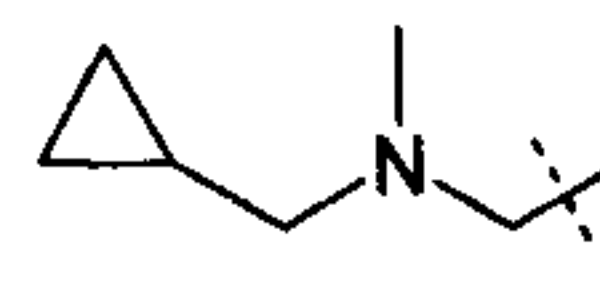
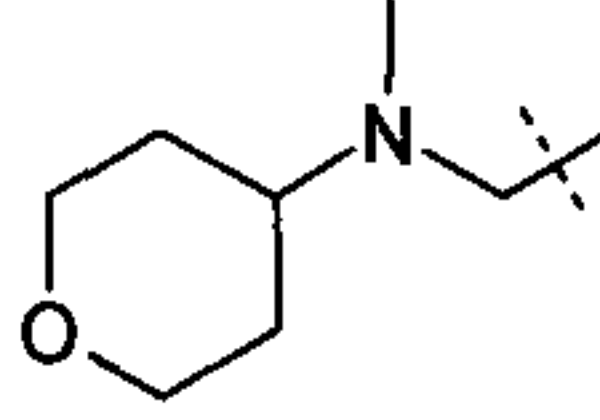
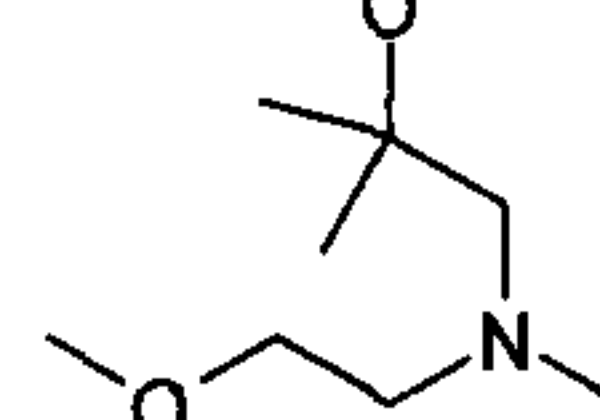
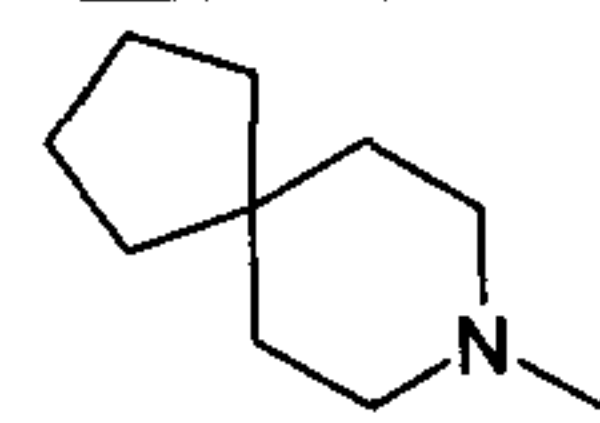
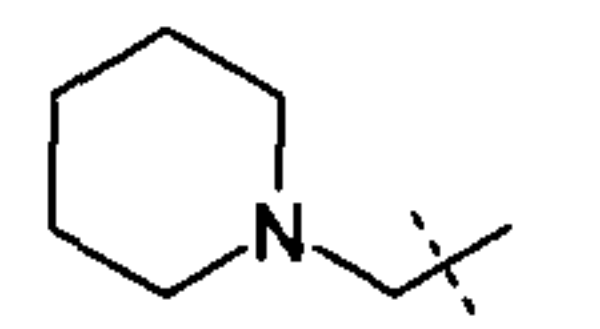
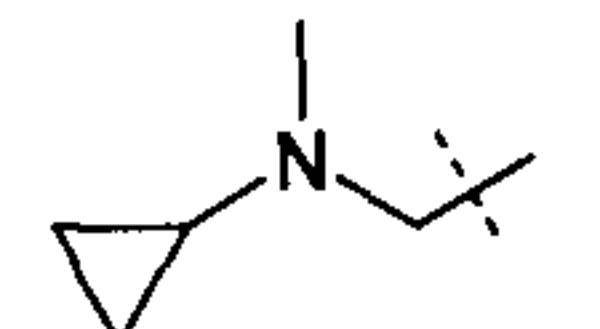
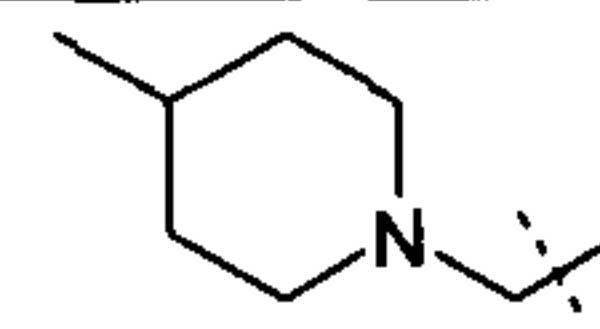
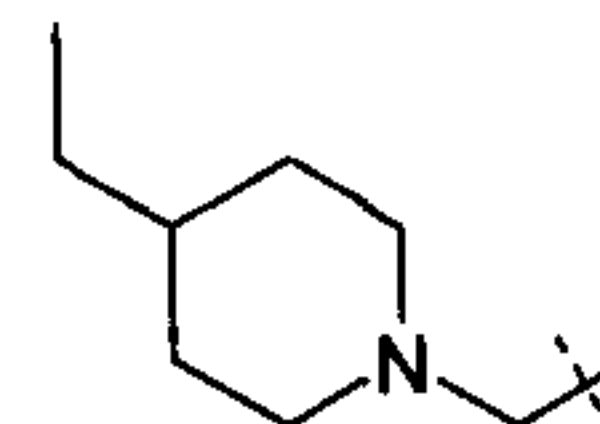
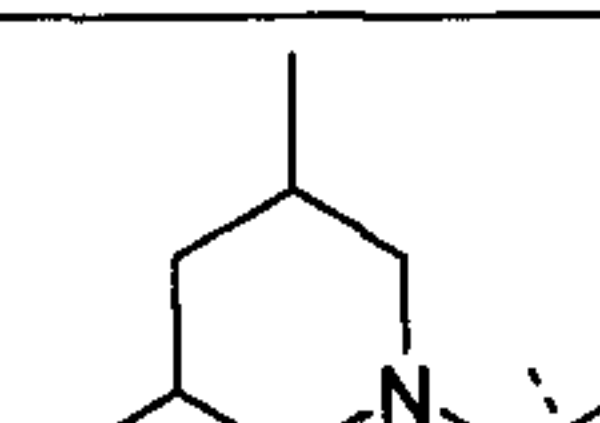
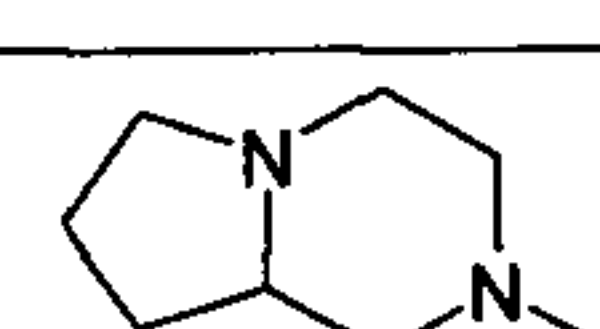
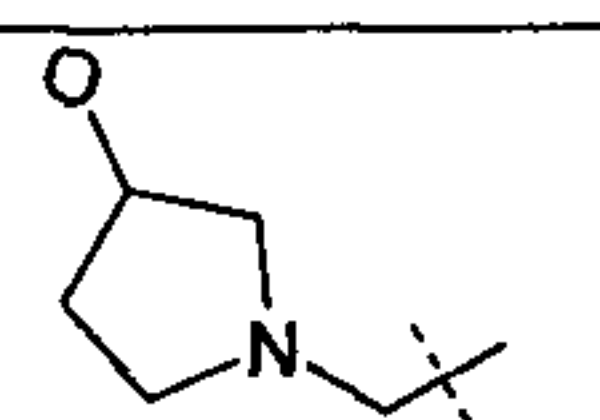
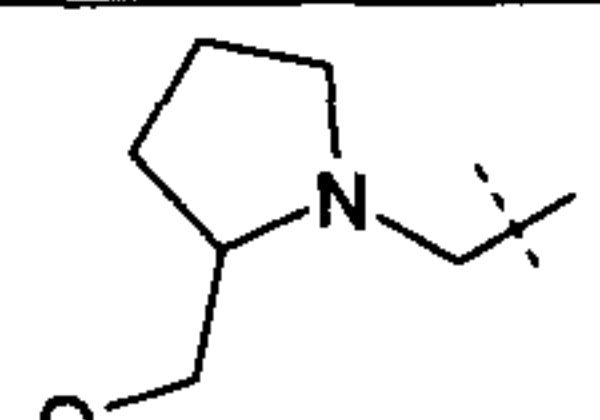
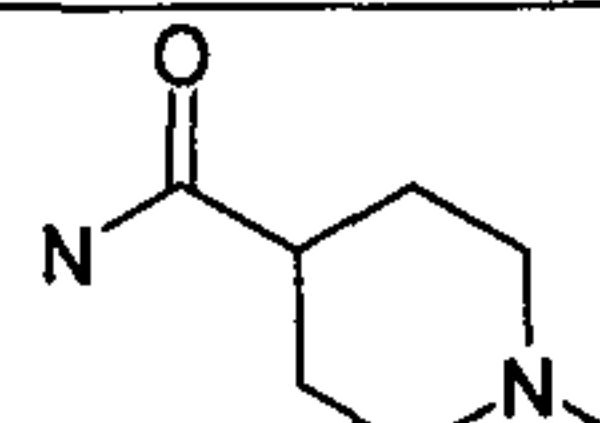
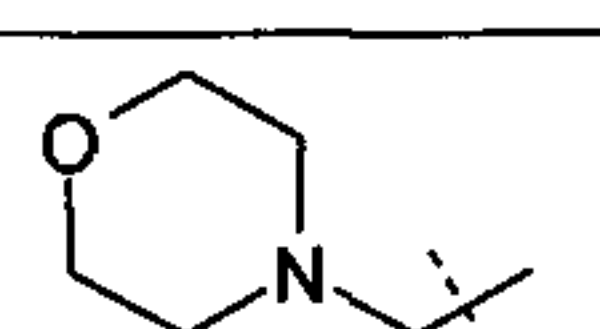


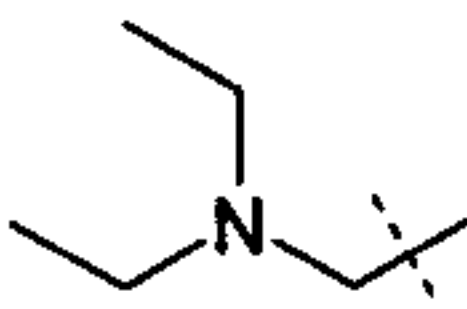
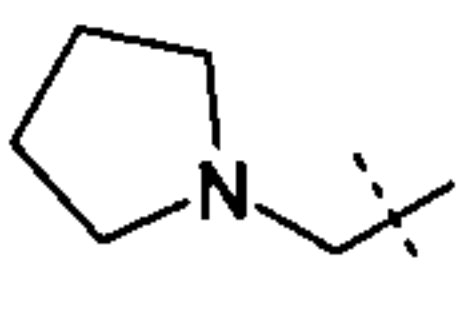
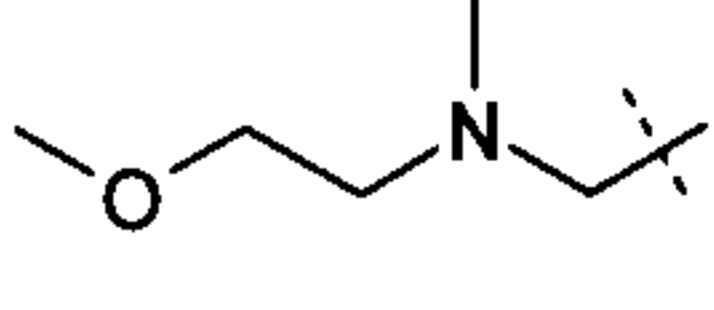
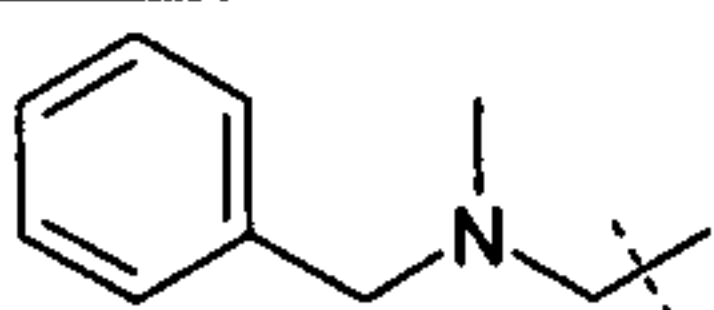
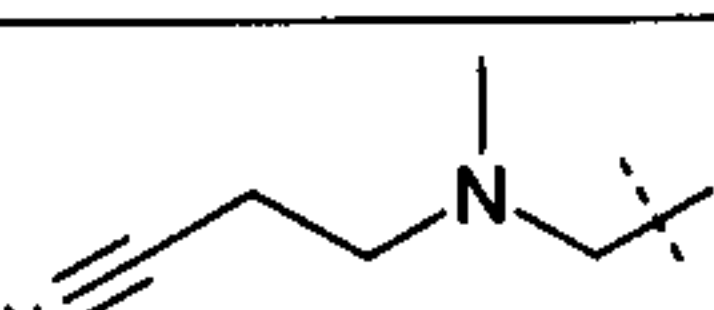
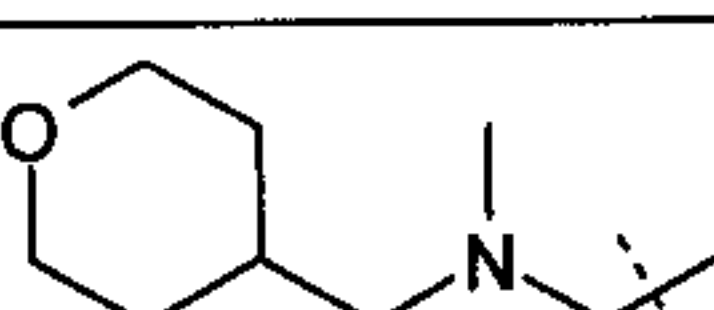
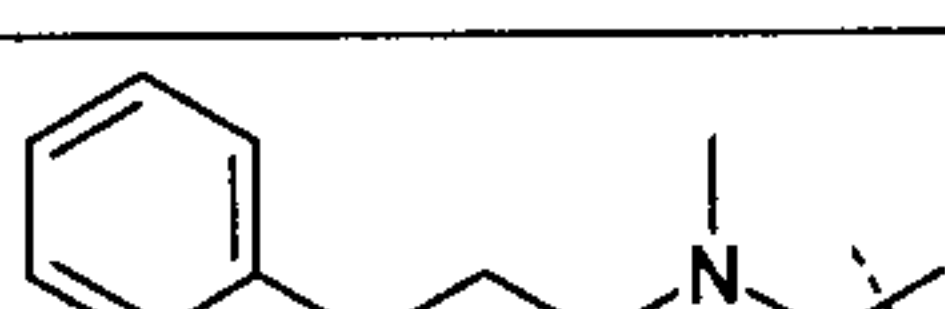
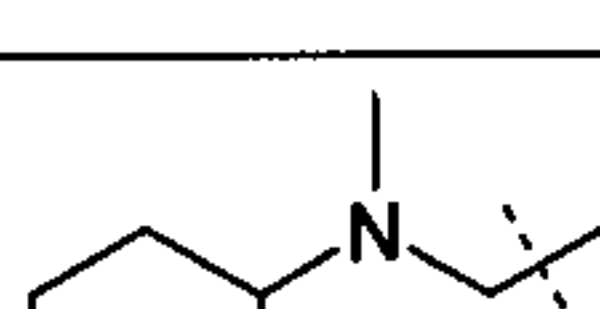
Example	R_1R_2N-X	L_1	L_2
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5.116		H	F
5.117		H	F
5.118		H	F
5.119		H	F
5.120		H	F
5.121		H	F
5.122		H	F
5.123		H	F
5.124		H	F
5.125		H	F
5.126		H	F

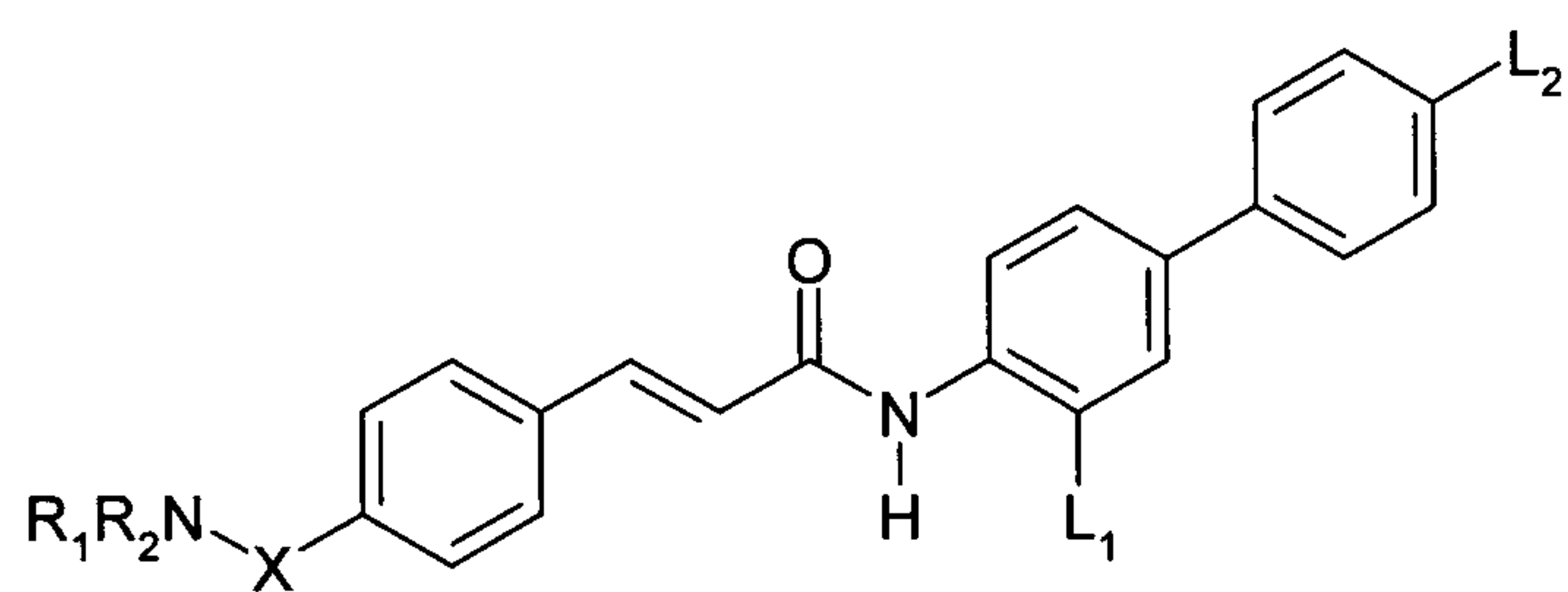
5.127		H	F
5.128		H	F
5.129		H	F
5.130		H	F
5.131		H	F
5.132		H	F
5.133		H	F
5.134		H	F
5.135		H	F
5.136		H	F
5.137		H	F
5.138		H	F

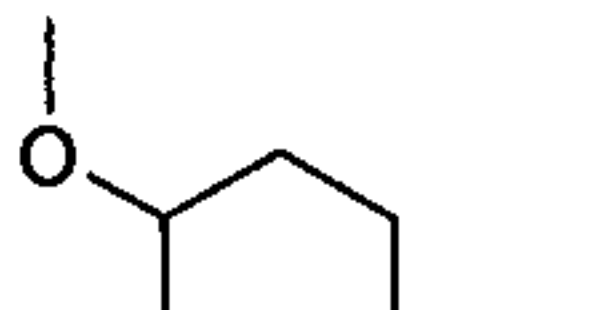
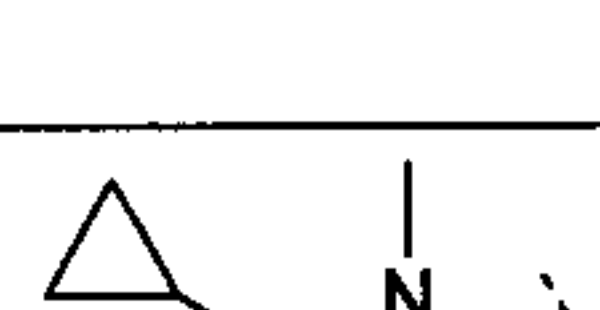
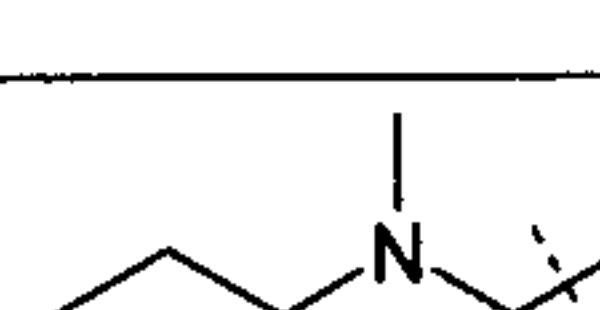


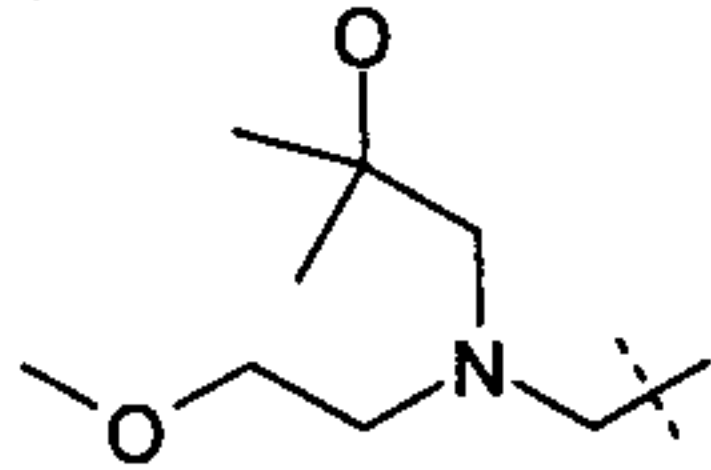
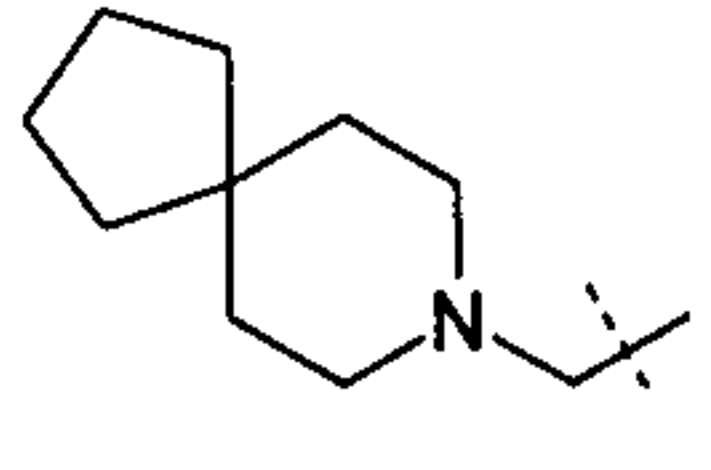
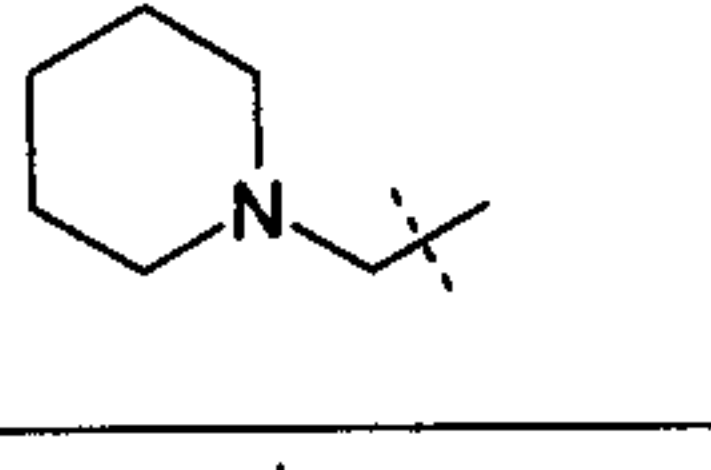
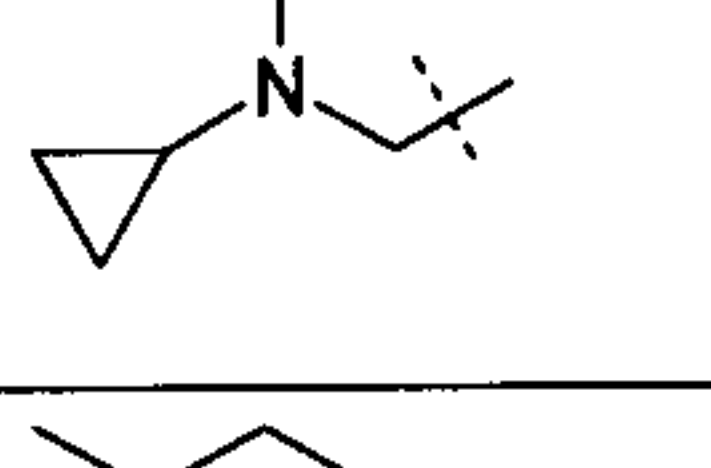
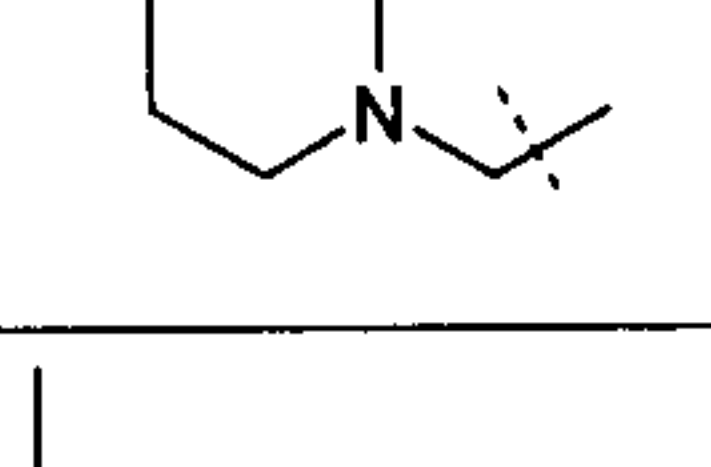
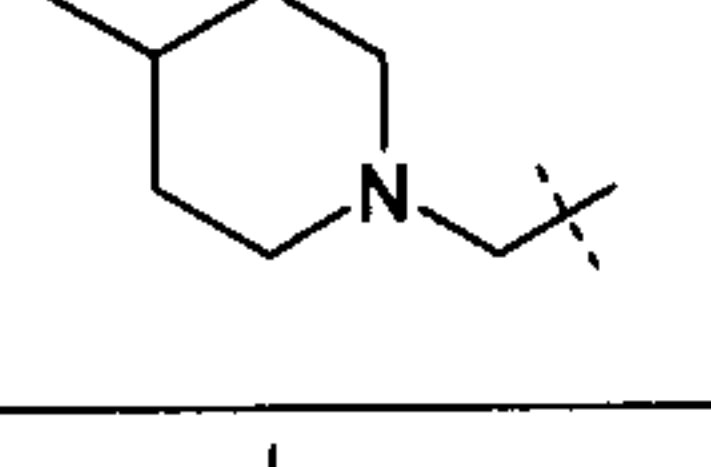
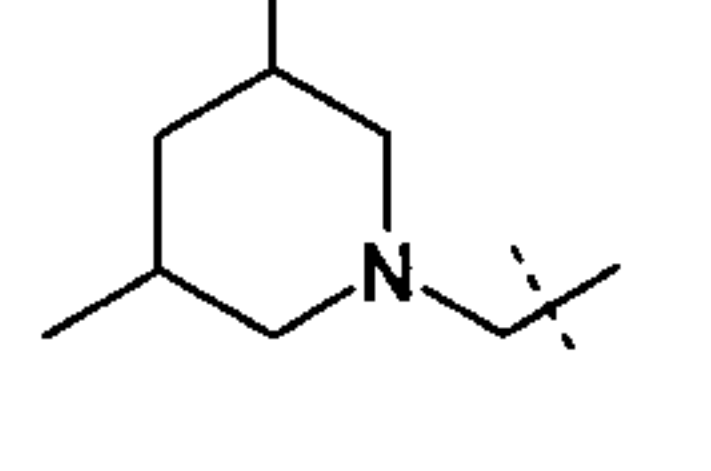
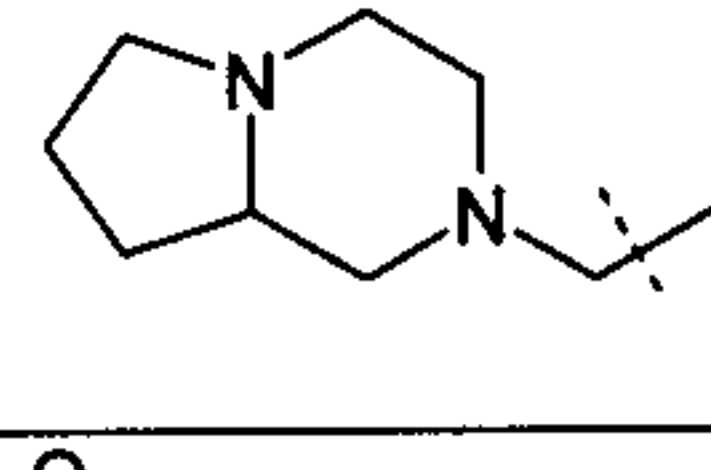
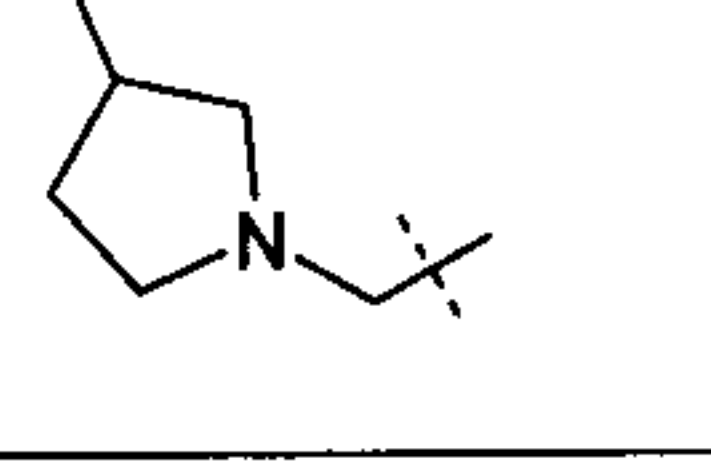
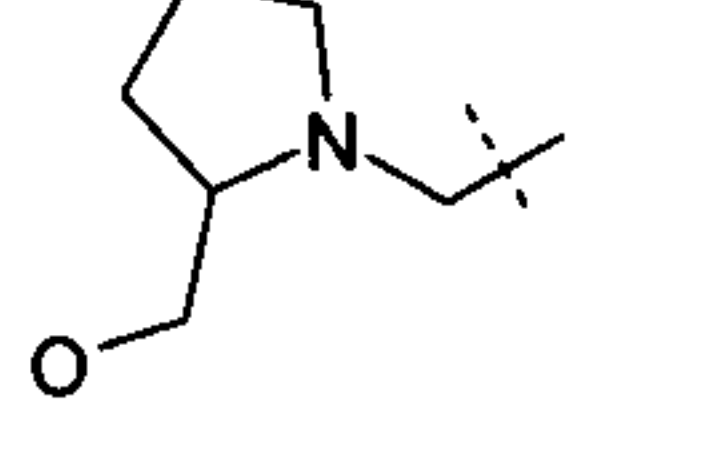
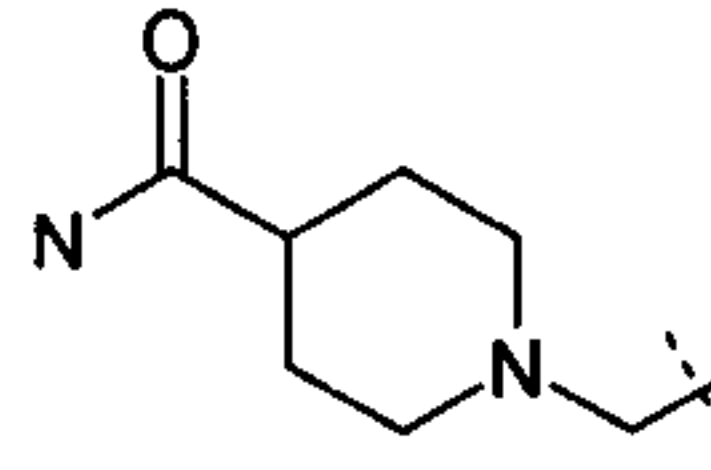
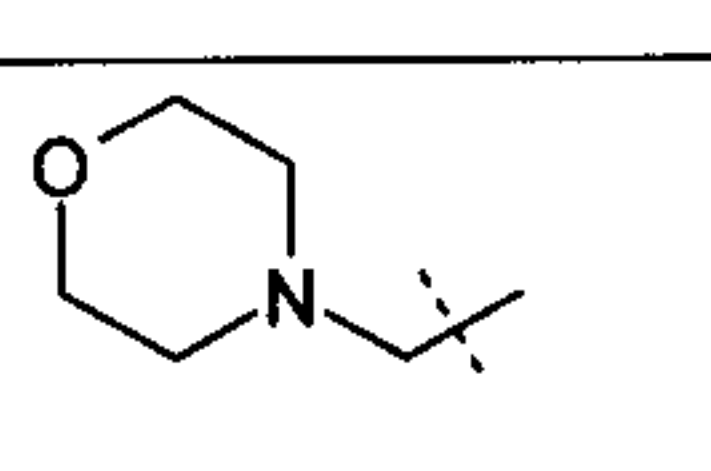
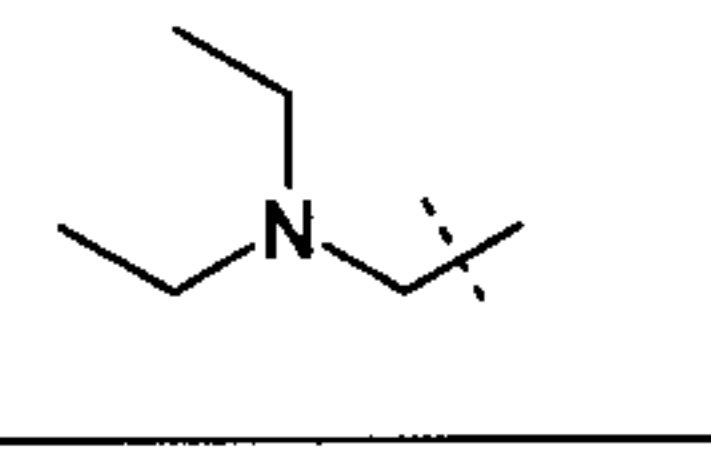
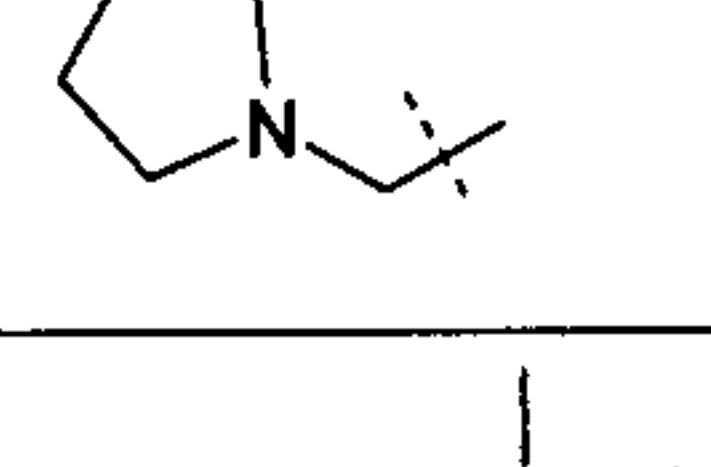
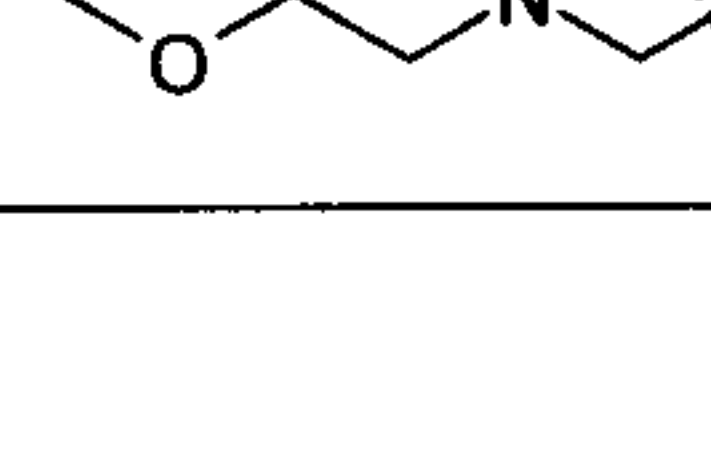
Example	R_1R_2N-X	L_1	L_2

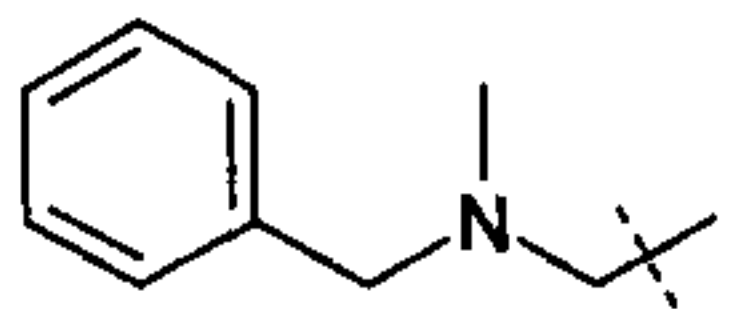
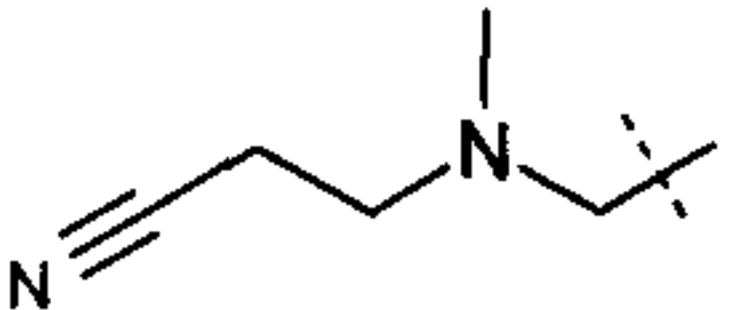
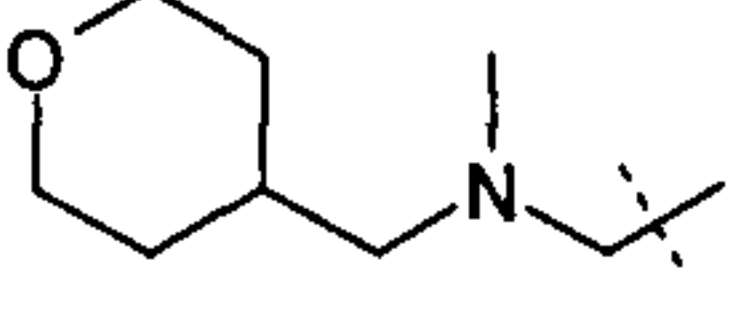
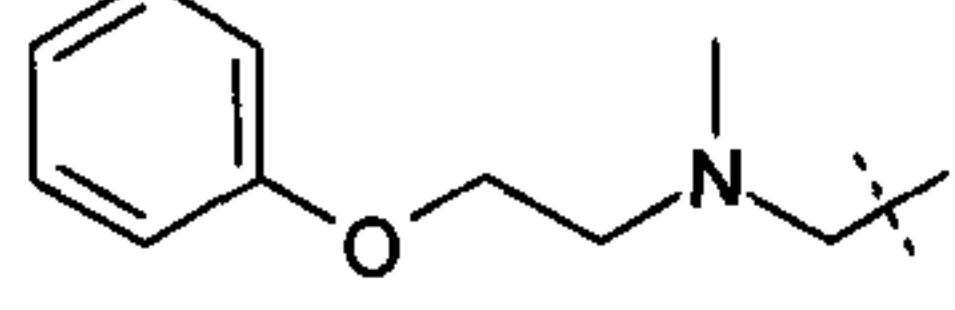
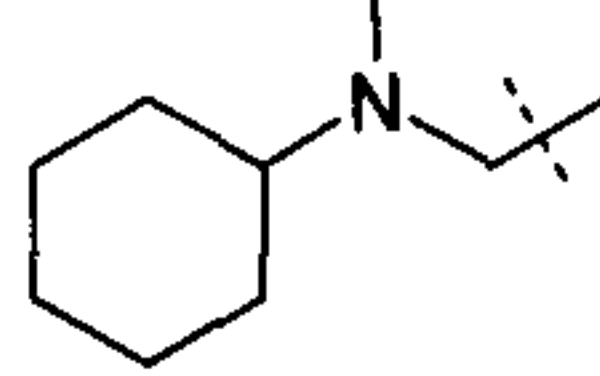
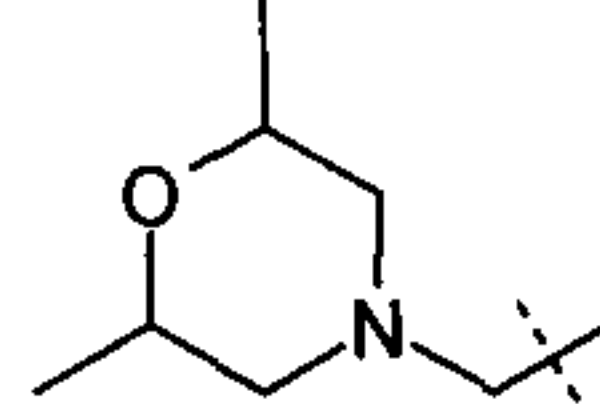
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5.140		F	CF ₃
5.141		F	CF ₃
5.142		F	CF ₃
5.143		F	CF ₃
5.144		F	CF ₃
5.145		F	CF ₃
5.146		F	CF ₃
5.147		F	CF ₃
5.148		F	CF ₃
5.149		F	CF ₃
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5.152		F	CF ₃
5.153		F	CF ₃

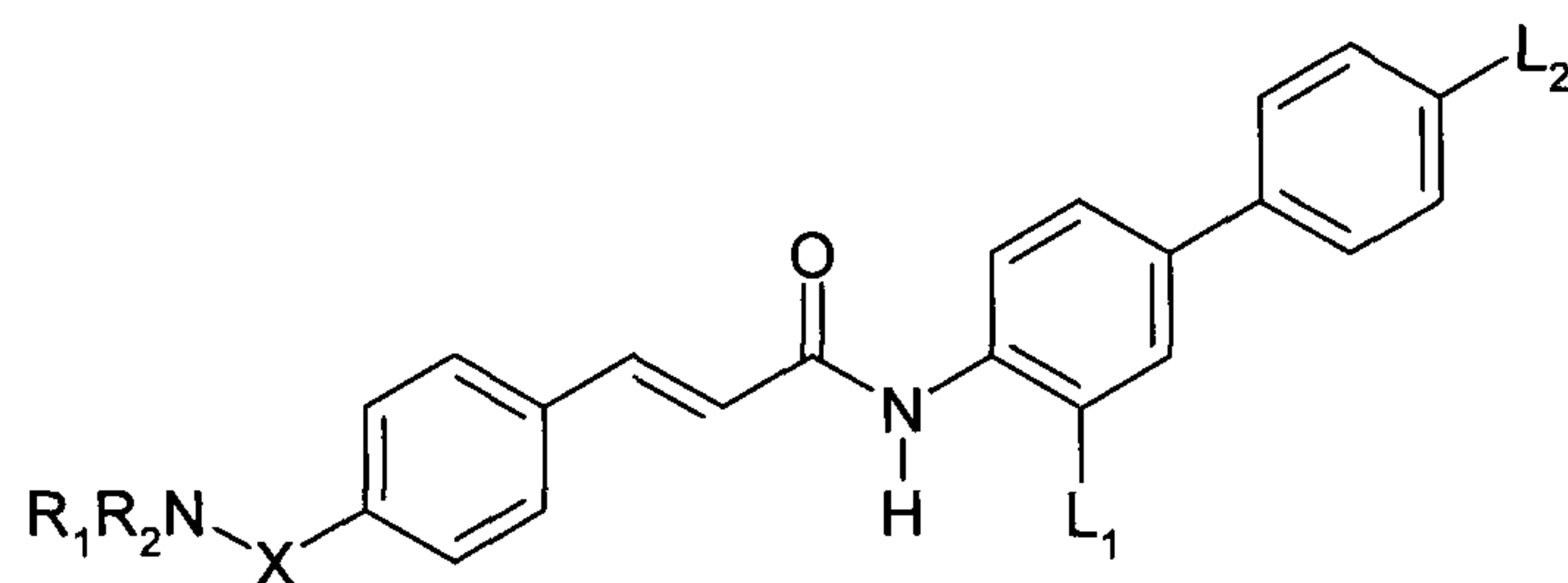
5.154		F	CF ₃
5.155		F	CF ₃
5.156		F	CF ₃
5.157		F	CF ₃
5.158		F	CF ₃
5.159		F	CF ₃
5.160		F	CF ₃
5.161		F	CF ₃
5.162		F	CF ₃

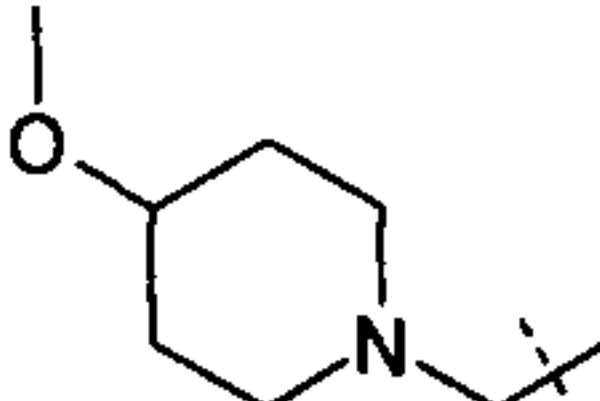
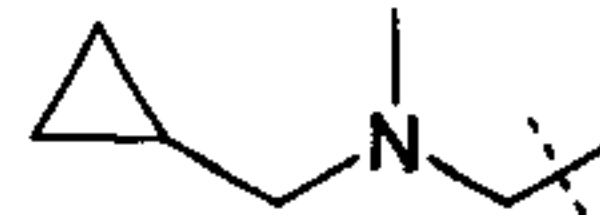
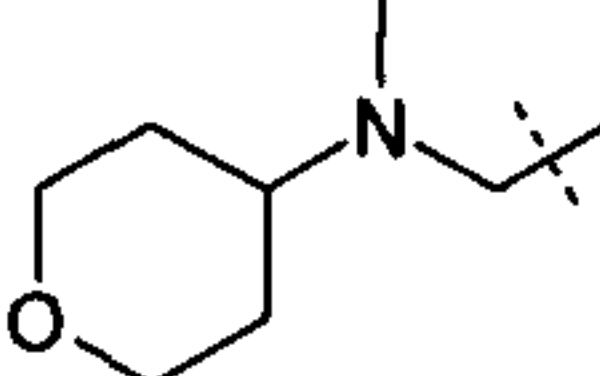
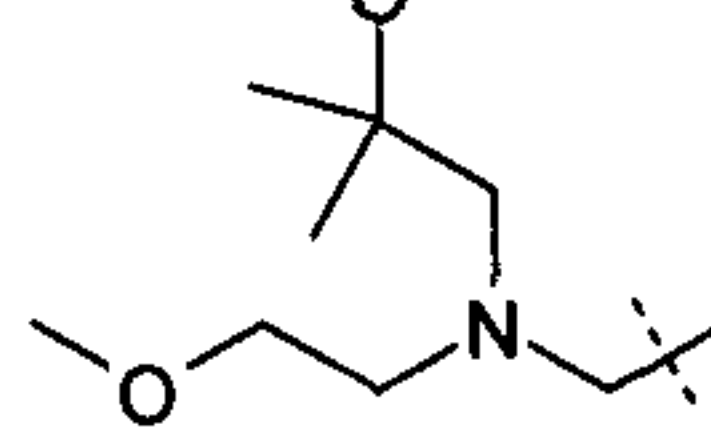
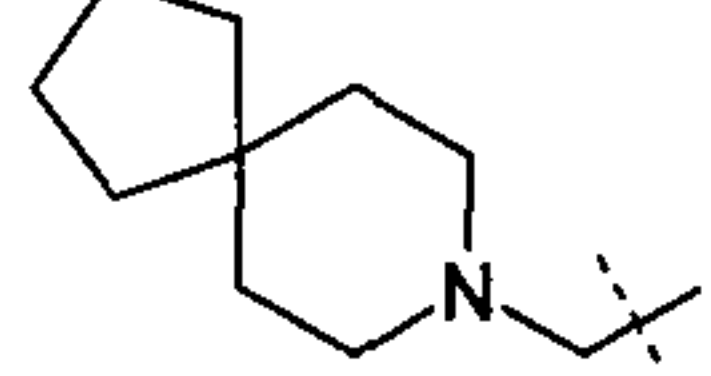


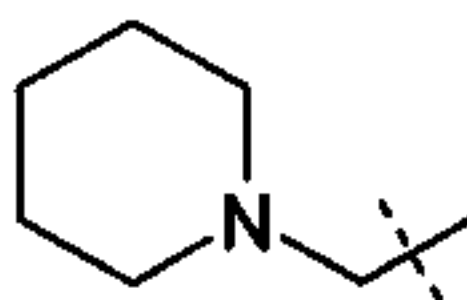
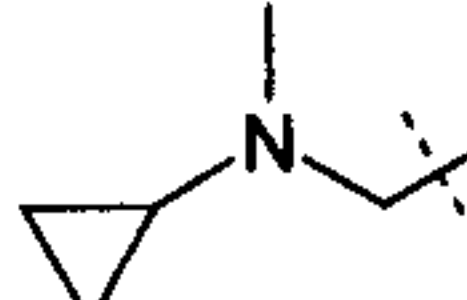
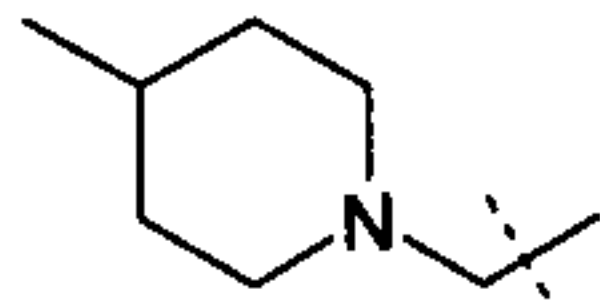
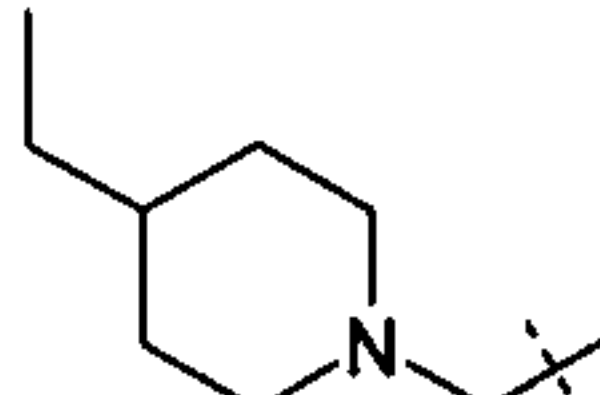
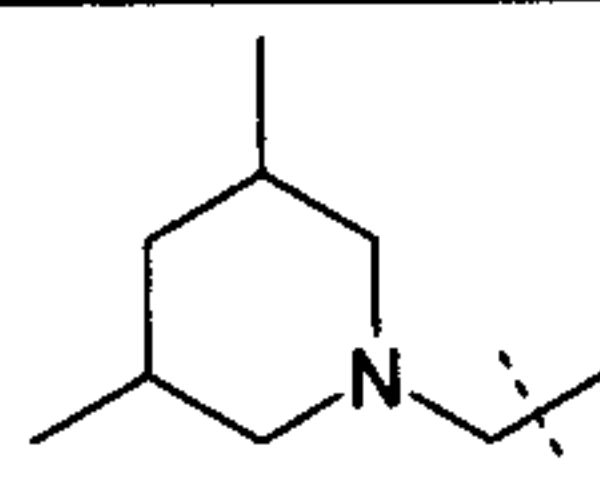
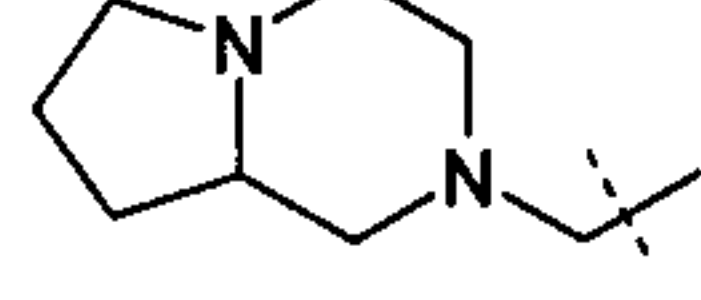
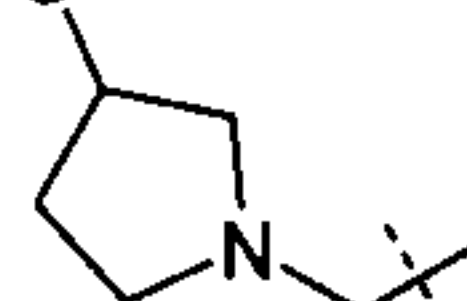
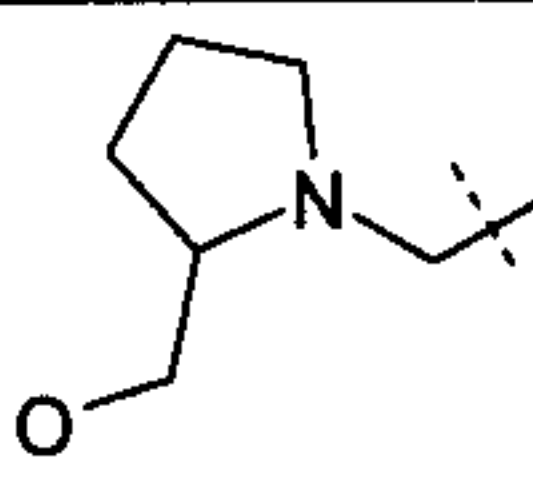
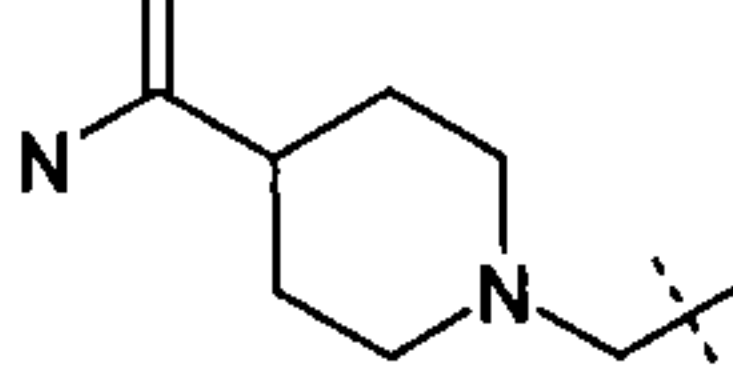
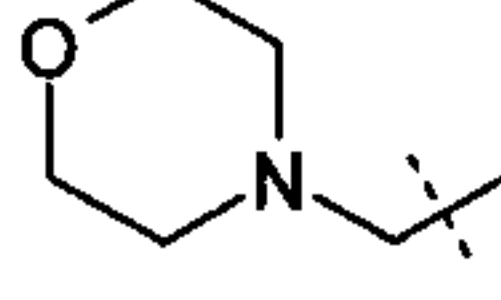
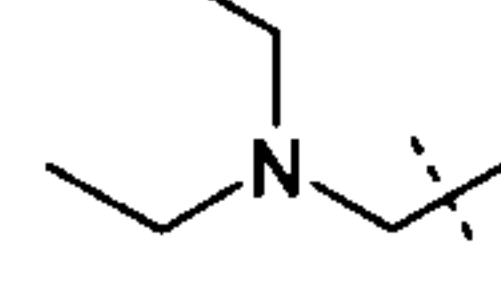
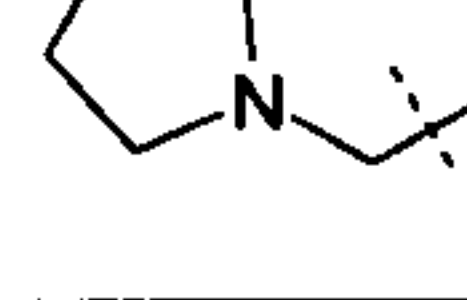
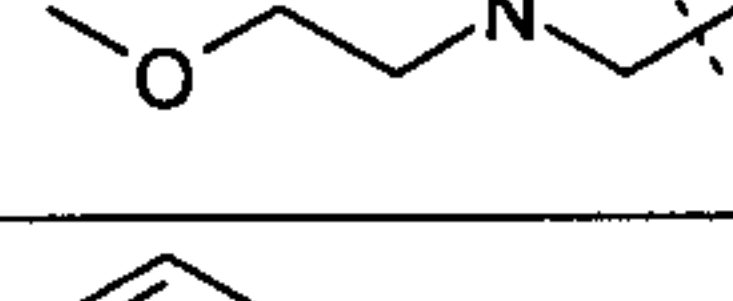
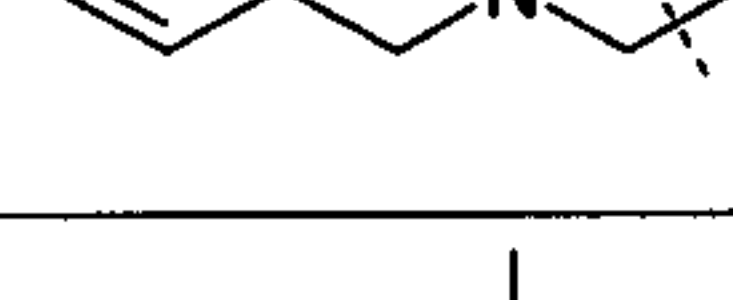
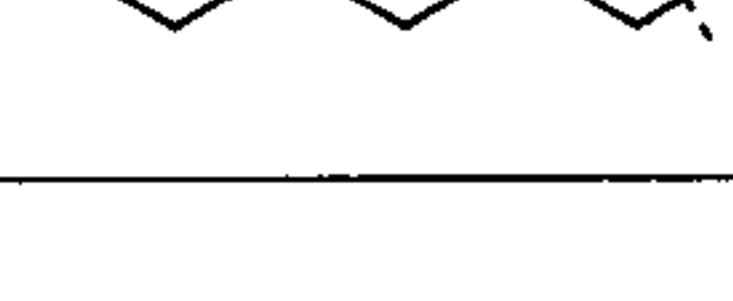
Example	R_1R_2N-X	L_1	L_2
5.163		F	Me
5.164		F	Me
5.165		F	Me

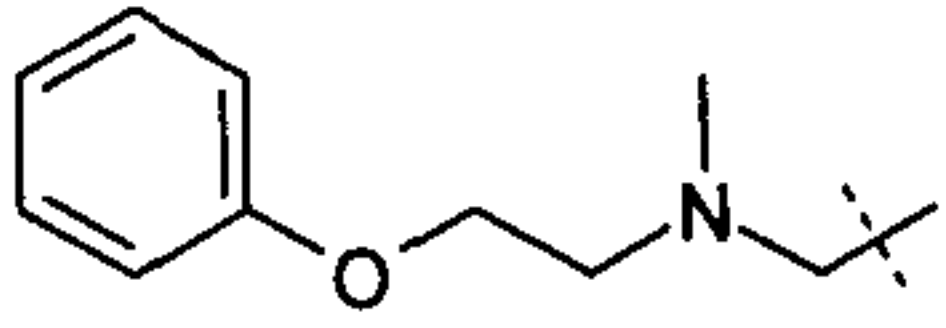
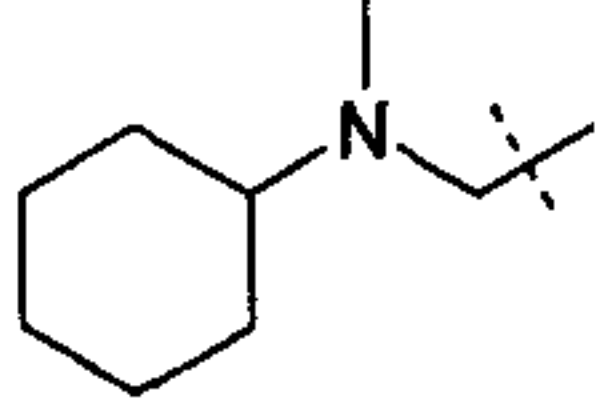
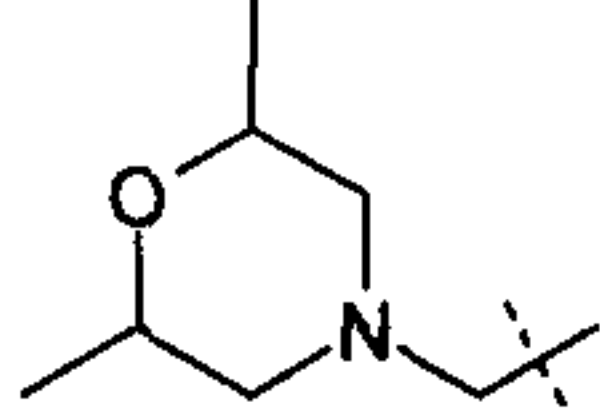
5.166		F	Me
5.167		F	Me
5.168		F	Me
5.169		F	Me
5.170		F	Me
5.171		F	Me
5.172		F	Me
5.173		F	Me
5.174		F	Me
5.175		F	Me
5.176		F	Me
5.177		F	Me
5.178		F	Me
5.179		F	Me
5.180		F	Me

5.181		F	Me
5.182		F	Me
5.183		F	Me
5.184		F	Me
5.185		F	Me
5.186		F	Me



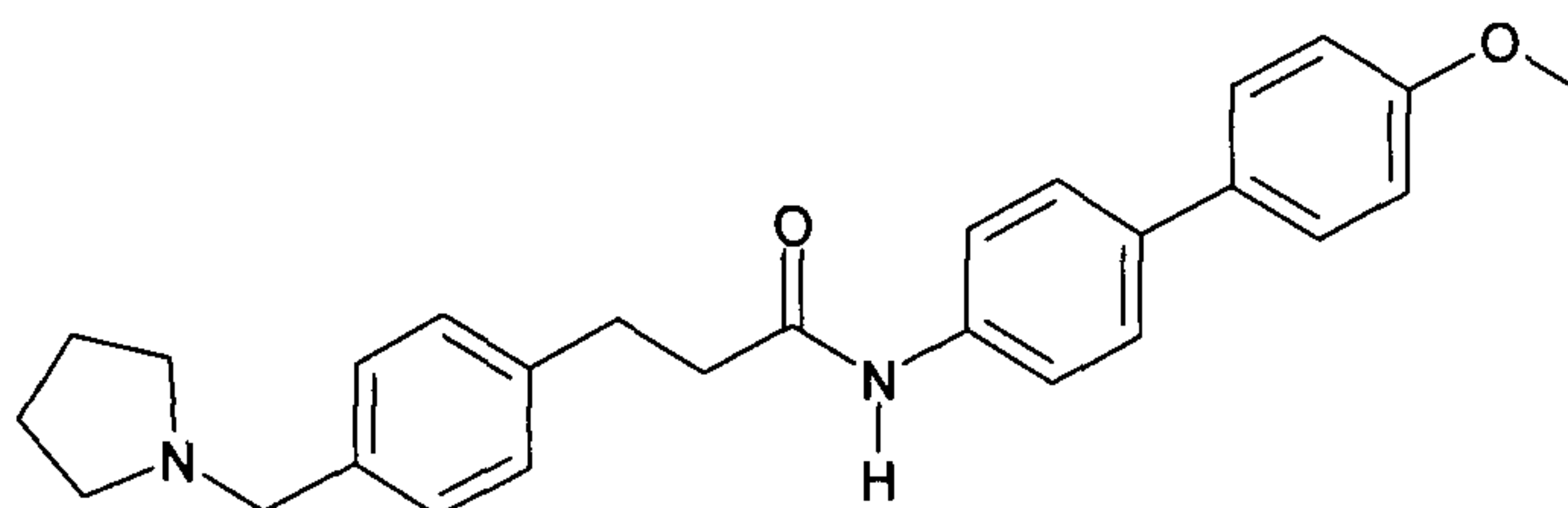
Example	R_1R_2N-X	L_1	L_2
5.187		F	F
5.188		F	F
5.189		F	F
5.190		F	F
5.191		F	F

5.192		F	F
5.193		F	F
5.194		F	F
5.195		F	F
5.196		F	F
5.197		F	F
5.198		F	F
5.199		F	F
5.200		F	F
5.201		F	F
5.202		F	F
5.203		F	F
5.204		F	F
5.205		F	F
5.206		F	F
5.207		F	F

5.208		F	F
5.209		F	F
5.210		F	F

Example 6.1:

N-(4'-methoxy-biphenyl-4-yl)-3-(4-pyrrolidin-1-ylmethyl-phenyl)-propionamide



5

A reaction mixture of 60 mg (0.14 mmol) (E)-*N*-(4'-methoxy-biphenyl-4-yl)-3-(4-pyrrolidin-1-ylmethyl-phenyl)-acrylamide and 10 mg Raney nickel in 30 ml of methanol is hydrogenated for four hours. The catalyst is filtered off and the filtrate is evaporated to dryness.

10 Yield: 56 mg (93.2% of theoretical)

Melting point: 185-188 °C

$C_{27}H_{30}N_2O_2$ (M= 414.55)

Calc.: Molecular ion peak (M+H)⁺: 415

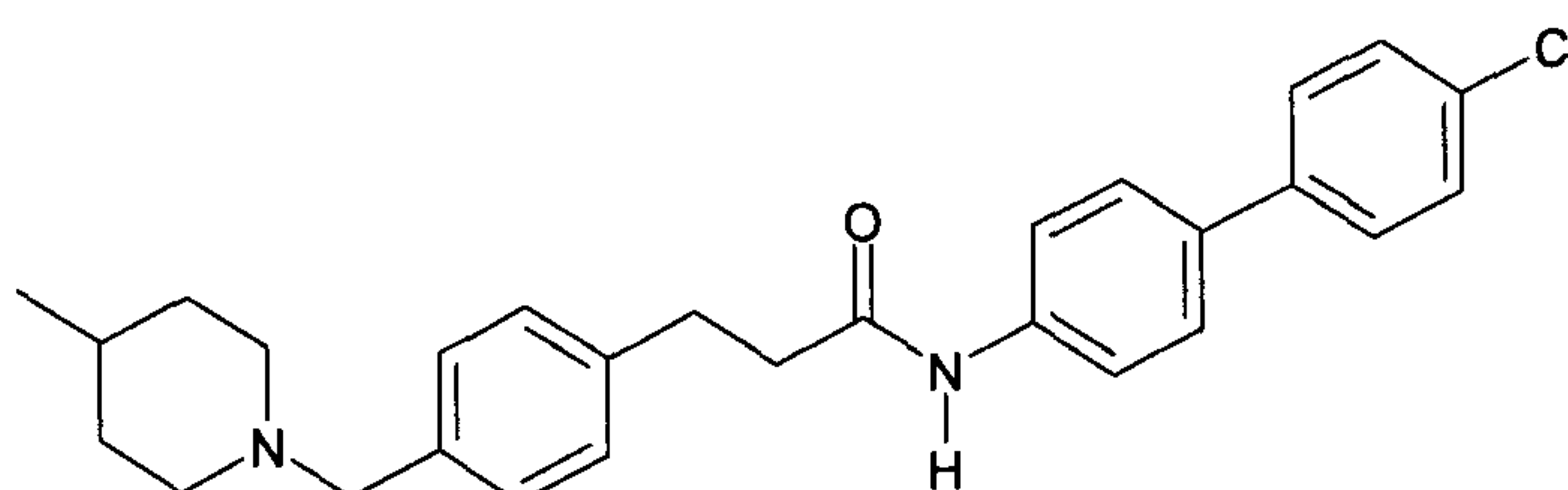
Found: Molecular ion peak

(M+H)⁺: 415

15 R_f value: 0.29 (silica gel, dichloromethane/methanol/ammonia = 90:10:1)

Example 6.2:

N-(4'-chloro-biphenyl-4-yl)-3-[4-(4-methyl-piperidin-1-ylmethyl)-phenyl]-propionamide



20

A reaction mixture of 80 mg (0.18 mmol) (E)-N-(4'-chloro-biphenyl-4-yl)-3-[4-(4-methyl-piperidin-1-ylmethyl)-phenyl]-acrylamide and 20 mg Raney nickel in 15 ml of ethyl acetate and 15 ml of methanol is hydrogenated for one hour at 50 psi and ambient temperature. The catalyst is filtered off, the filtrate is evaporated to dryness and stirred with diisopropylether.

Yield: 40 mg (49.7 % of theoretical)

Melting point: 150-151° C

C₂₈H₃₁ClN₂O (M= 447.02)

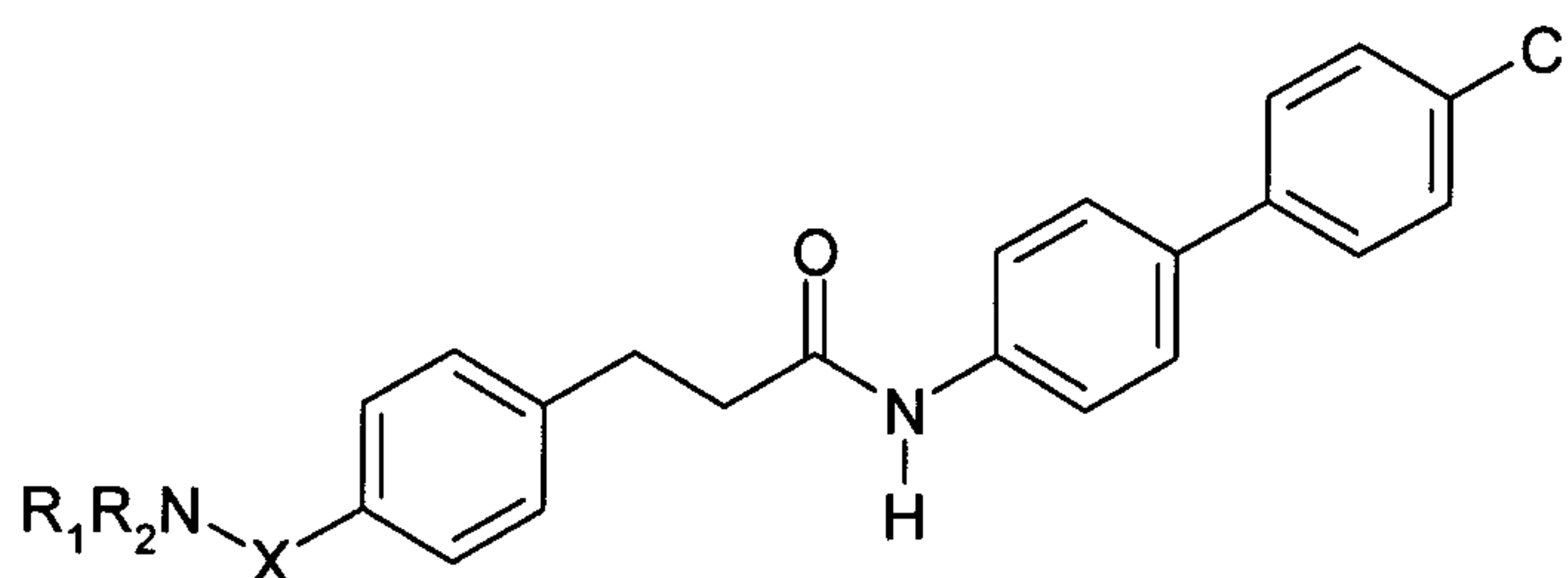
Calc.: Molecular ion peak (M+H)⁺: 447/449

Found: Molecular ion

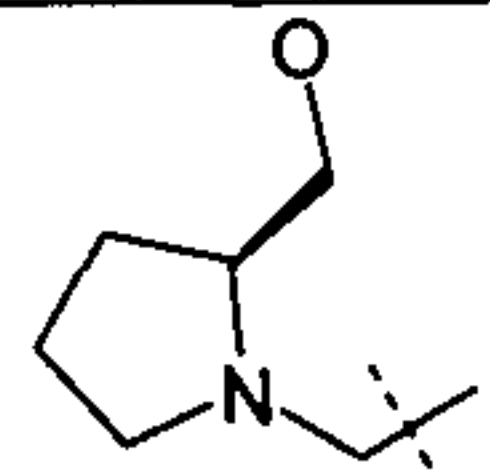
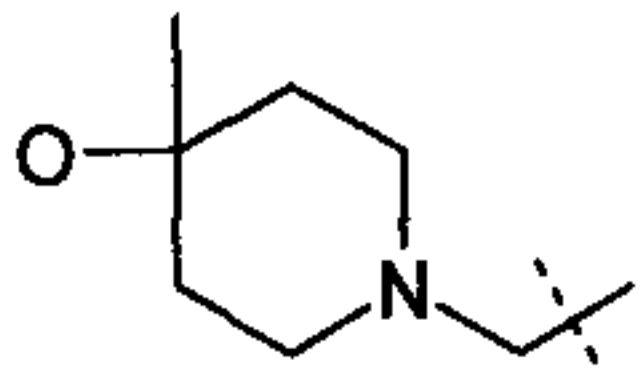
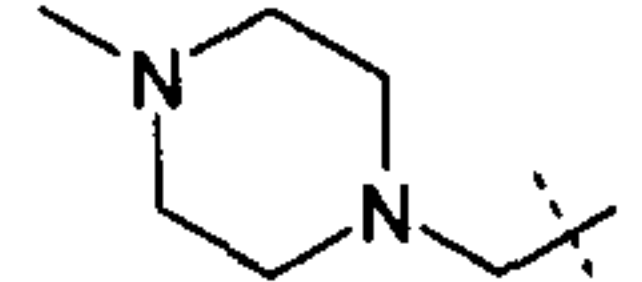
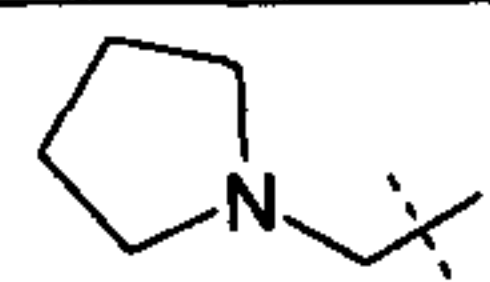
peak (M+H)⁺: 447/449

R_f value: 0.5 (silica gel, dichloromethane/methanol = 10:1)

The following compounds are prepared analogously to Example 6.2.:



Ex.	R ₁ R ₂ N-X	educt	empirical formula	mass spectrum	mp [°C]	R _f value
6.3		5.4	C ₂₈ H ₃₁ ClN ₂ O ₂	463/465 [M+H] ⁺	143-144	0.4 (A)
6.4		5.5	C ₂₆ H ₂₇ ClN ₂ O ₂	435/437 [M+H] ⁺	193-194	
6.5		5.6	C ₂₈ H ₃₀ ClN ₃ O ₂	476/478 [M+H] ⁺	240-241	
6.6		5.8	C ₂₈ H ₃₁ ClN ₂ O ₂	463/465 [M+H] ⁺	185-186	0.1 (A)
6.7		5.9	C ₂₆ H ₂₇ ClN ₂ O ₂	435/437 [M+H] ⁺	171-172	0.14 (A)

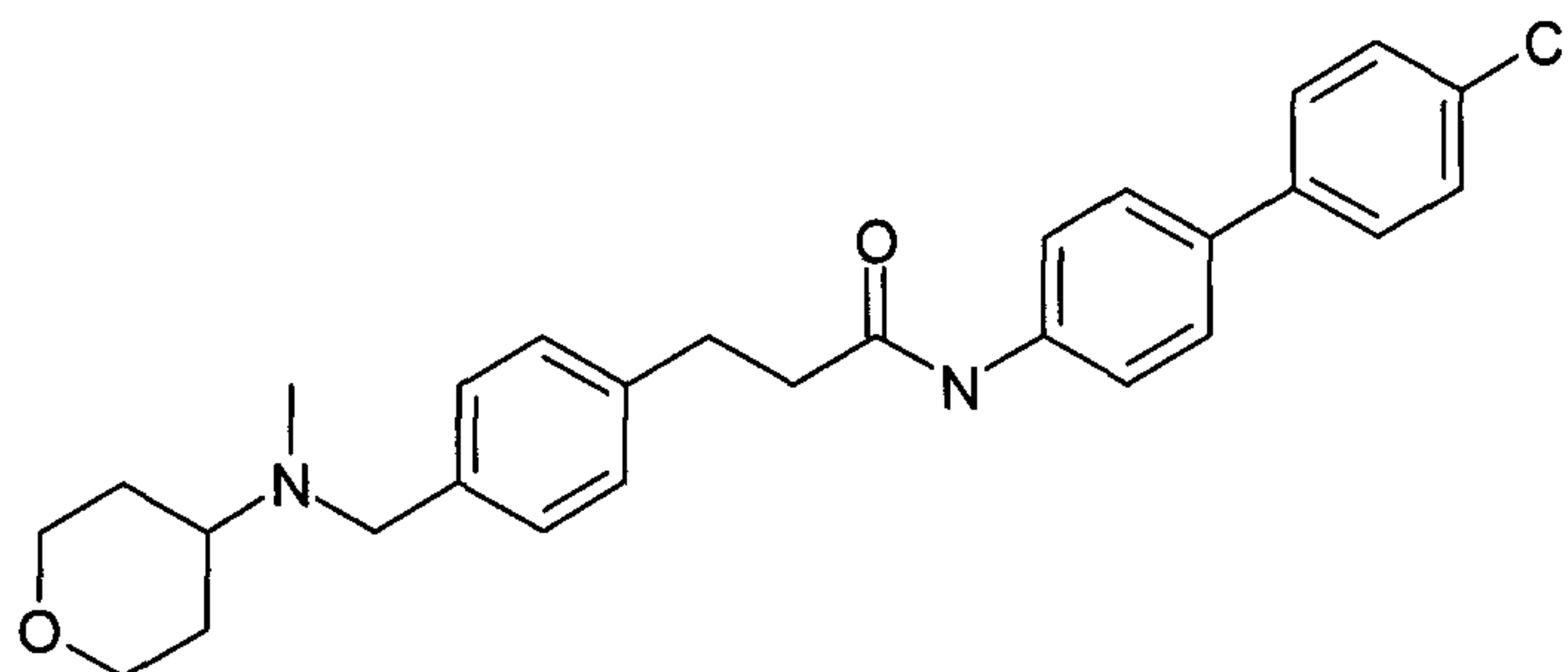
6.8		5.10	$C_{27}H_{29}ClN_2O_2$	449/451 [M+H] ⁺	156- 157	0.2 (A)
6.9		5.11	$C_{28}H_{31}ClN_2O_2$	463/465 [M+H] ⁺	192	0.25 (B)
6.10		5.12	$C_{27}H_{30}ClN_3O$	448/450 [M+H] ⁺	172	0.2 (B)
6.11		5.13	$C_{26}H_{27}ClN_2O$	419 [M+H] ⁺	183- 184	0.25 (B)

R_f value: A, B as specified hereinbefore

C= (silica gel, dichloromethane/ethanol/ammonia 20/1/0.1)

5 Example 6.12:

N-(4'-chloro-biphenyl-4-yl)-3-(4-([methyl-(tetrahydro-pyran-4-yl)-amino]-methyl)-phenyl)-propionamide



A reaction mixture of 60 mg (0.13 mmol) (E)-*N*-(4'-chloro-biphenyl-4-yl)-3-(4-([methyl-(tetrahydro-pyran-4-yl)-amino]-methyl)-phenyl)-acrylamide and 20 mg Raney nickel in 10 ml *N,N*-dimethylformamide is hydrogenated for three hours at 50 psi and ambient temperature. The catalyst is filtered off and the filtrate is evaporated to dryness. The purification is carried out by column chromatography on silica gel (eluant: dichloromethane/methanol/ammonia 20/1/0.1)

15 Yield: 22 mg (29 % of theoretical)

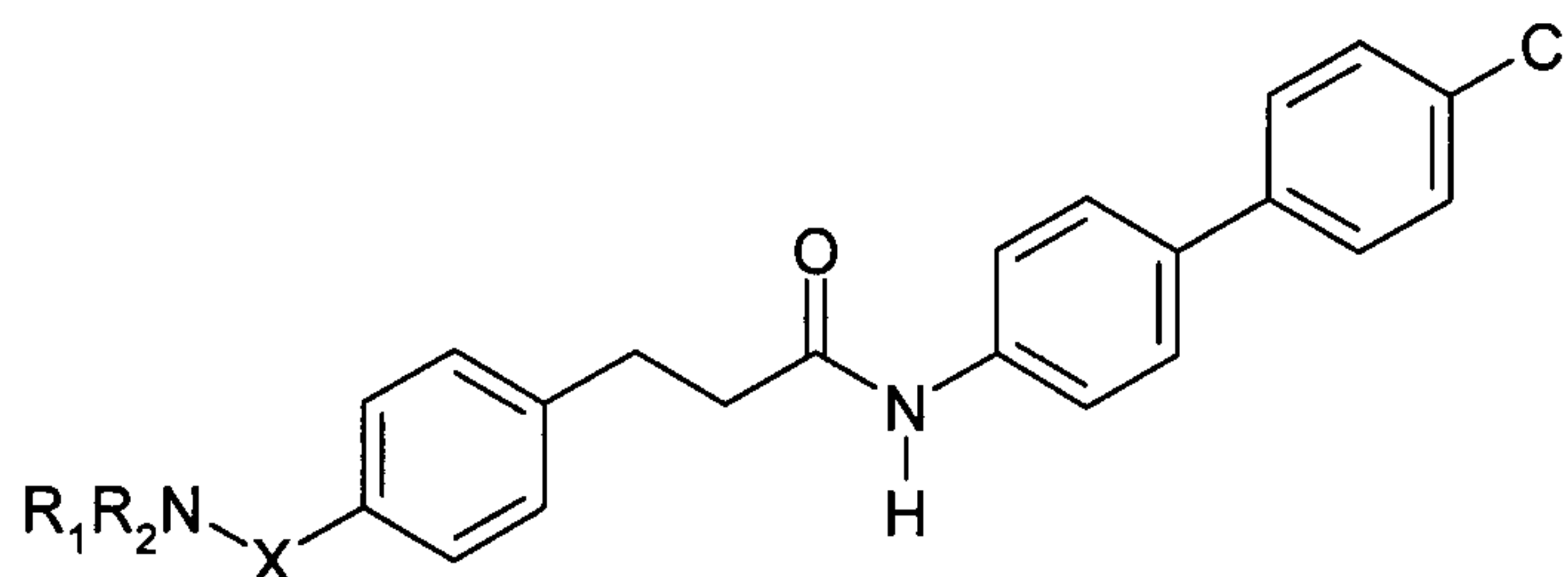
Melting point: 167-173 C

$C_{28}H_{31}ClN_2O_2$ (M= 463.01)

Calc.: Molecular ion peak (M+H)⁺: 463/65 (Cl)
(M+H)⁺: 463/65 (Cl)

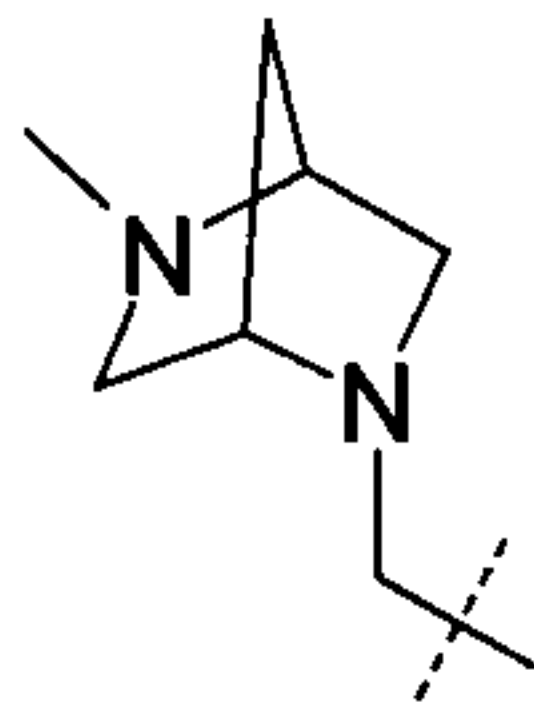
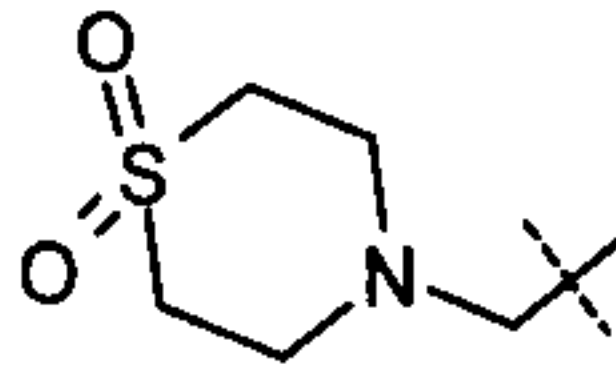
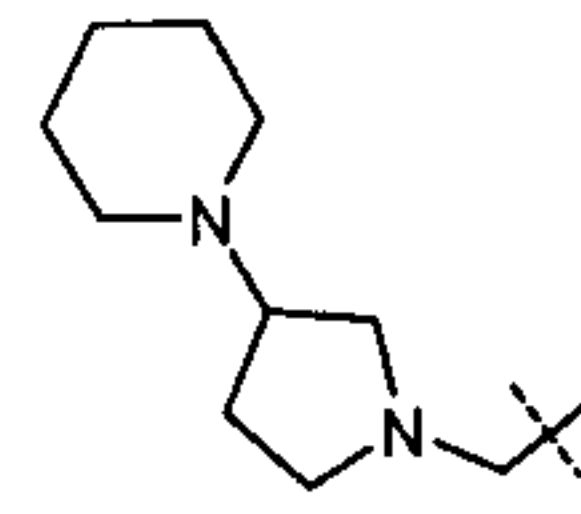
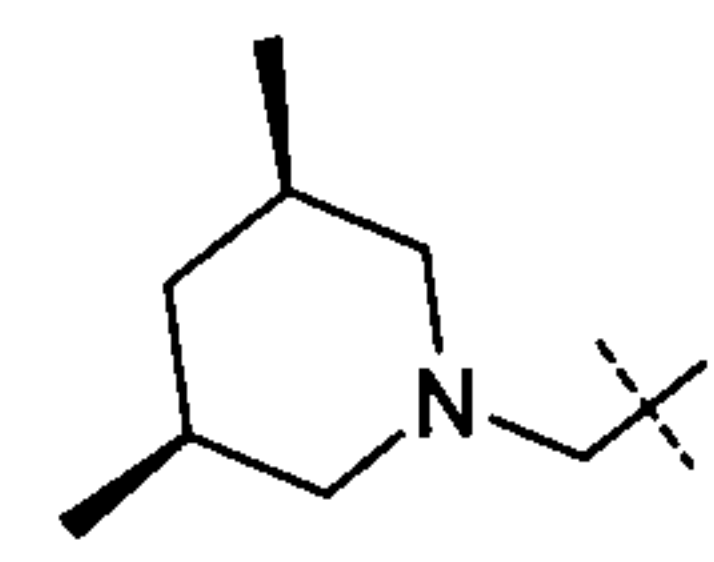
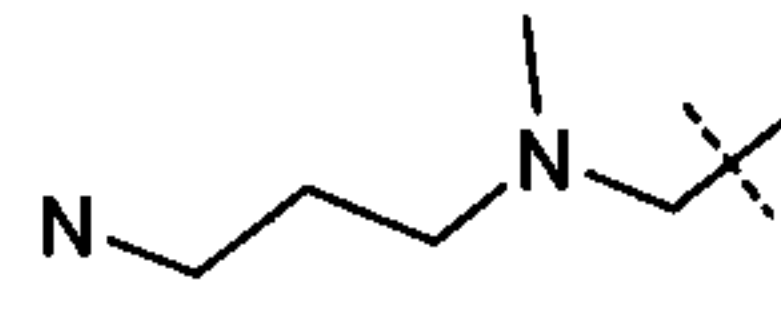
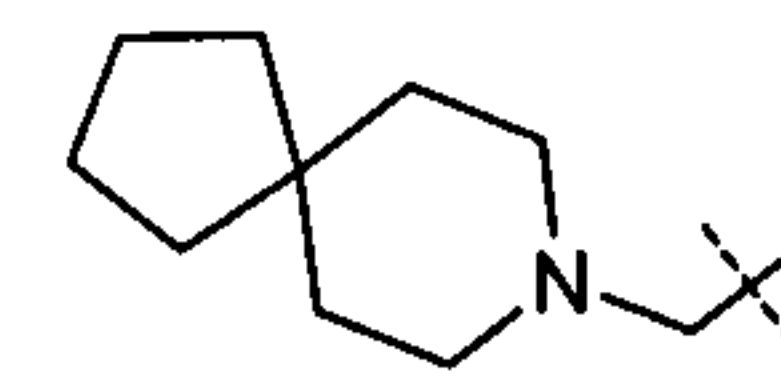
Found: Molecular ion peak

The following compounds are prepared analogously to Example 6.12.:



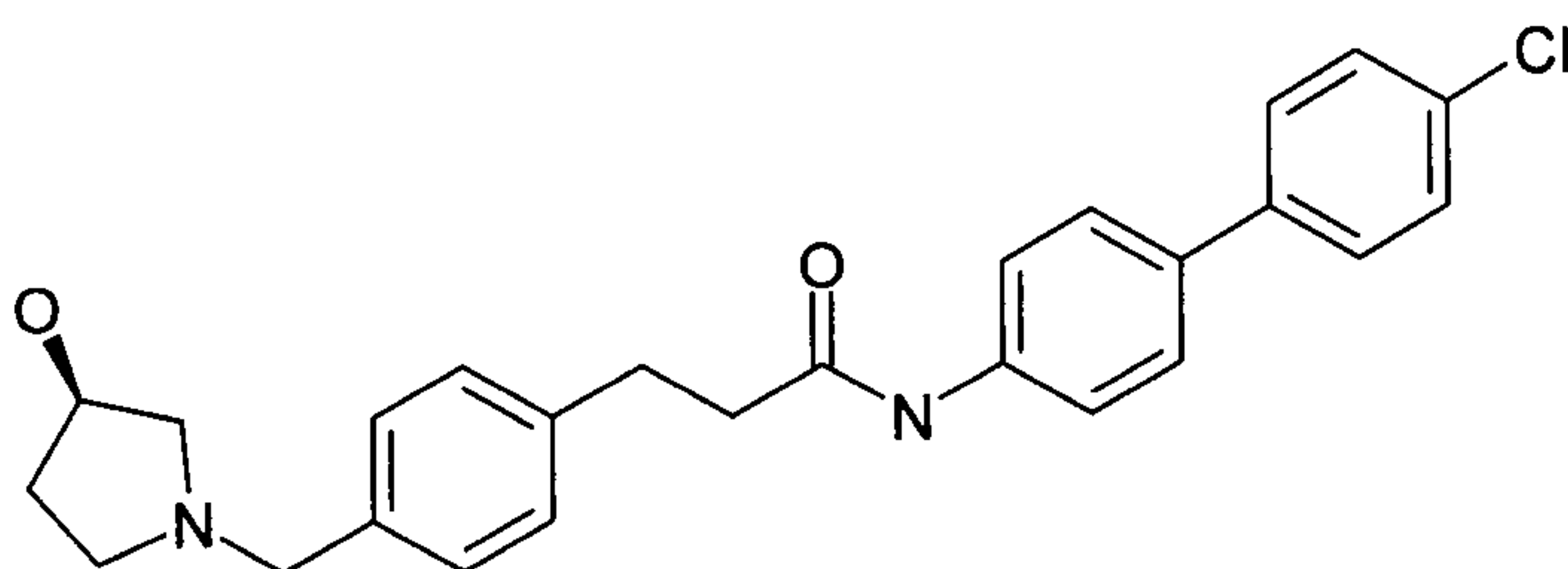
5

Example	R ₁ R ₂ N-X	educt	empirical formula	mass spectrum	mp [°C]
6.13		5.17	C ₂₇ H ₂₉ ClN ₂ O	433/35 (Cl) [M+H] ⁺	156
6.14		5.27	C ₂₉ H ₃₅ ClN ₂ O ₃	495/97 (Cl) [M+H] ⁺	108-109
6.15		5.22	C ₂₆ H ₂₇ ClN ₂ O	418/20 (Cl) [M+H] ⁺	191-192
6.16		5.16	C ₂₉ H ₃₂ ClN ₃ O	474/76 (Cl) [M+H] ⁺	177
6.17		5.14	C ₂₆ H ₂₉ ClN ₂ O ₂	437/39 (Cl) [M+H] ⁺	138
6.18		5.18	C ₃₀ H ₂₉ ClN ₂ O	469/71 (Cl) [M+H] ⁺	174-175
6.19		5.19	C ₂₉ H ₃₃ ClN ₂ O ₂	477/79 (Cl) [M+H] ⁺	162-163
6.20		5.20	C ₃₁ H ₃₁ ClN ₂ O ₂	499/501 (Cl) [M+H] ⁺	122-124
6.21		5.23	C ₂₈ H ₃₁ ClN ₂ O ₂	463/65 (Cl) [M+H] ⁺	158.5-160.5
6.22		5.21	C ₂₉ H ₃₃ ClN ₂ O	461/63 (Cl) [M+H] ⁺	201-204

6.23		5.15	$C_{28}H_{30}ClN_3O$	460/62 (Cl) [M+H] ⁺	143- 144
6.24		5.24	$C_{26}H_{27}ClN_2O_3S$	483/85 (Cl) [M+H] ⁺	198- 201
6.25		5.28	$C_{31}H_{36}ClN_3O$	502/04 (Cl) [M+H] ⁺	168.8
6.26		5.3.c	$C_{29}H_{33}ClN_2O$	461/63 (Cl) [M+H] ⁺	164- 169
6.27		5.26	$C_{26}H_{30}ClN_3O$	436/38 (Cl) [M+H] ⁺	165
6.28		5.25	$C_{31}H_{35}ClN_2O$	487/89 (Cl) [M+H] ⁺	201.5

Example 6.29

- 5 N-(4'-chloro-biphenyl-4-yl)-3-[4-(R)-3-hydroxy-pyrrolidin-1-ylmethyl]-phenyl]-propionamide



- 10 A reaction mixture of 40 mg (0.09 mmol) 3-[4-((R)-3-hydroxy-pyrrolidin-1-ylmethyl)-phenyl]-propynoic acid(4'-chloro-biphenyl-4-yl)amide and 10 mg Raney nickel in 10 ml N,N-dimethylformamide is hydrogenated for three hours at 50 psi and ambient temperature. The catalyst is filtered off and the filtrate is evaporated to dryness. The

purification is carried out by column chromatography on silica gel (eluant: dichloromethane/methanol/ammonia 15/1/0.1)

Yield: 20 mg (50 % of theoretical)

Melting point: 169-170 C

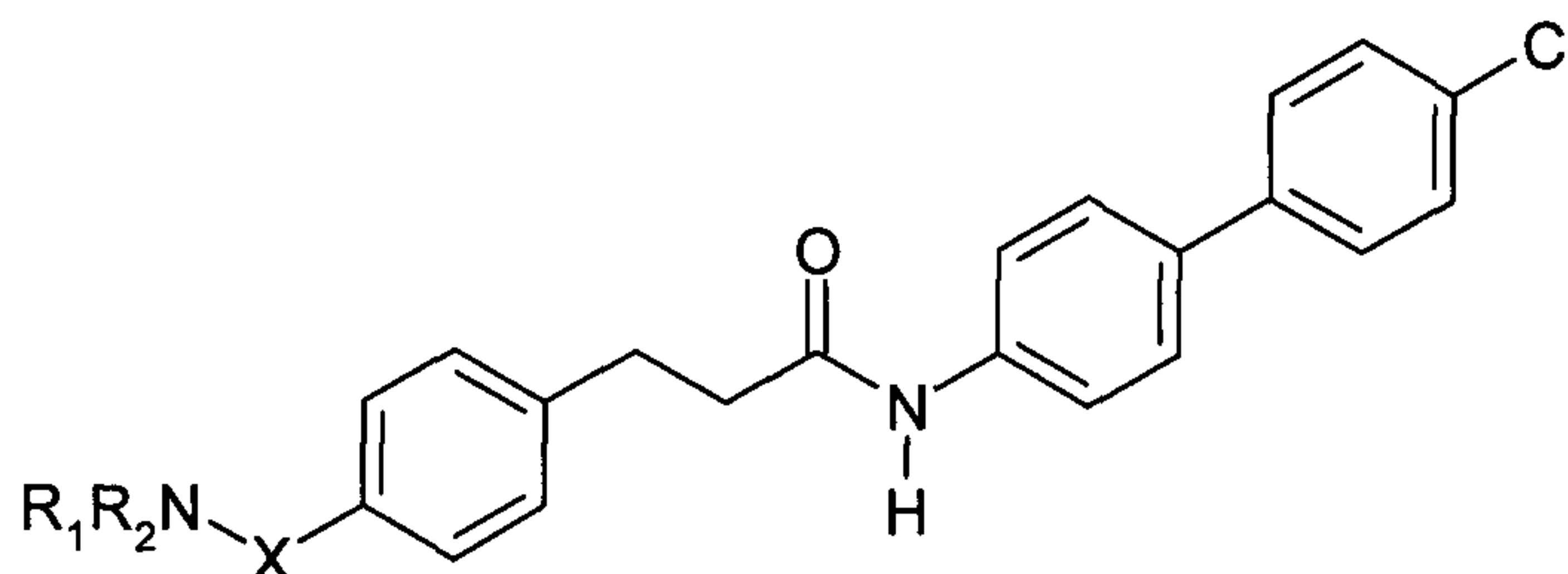
5 $C_{26}H_{27}ClN_2O_2$ (M= 434.96)

Calc.: Molecular ion peak (M+H)⁺: 435/37 (Cl)
(M+H)⁺: 435/37 (Cl)

Found: Molecular ion peak

The following compounds are prepared analogously to Example 6.29.:

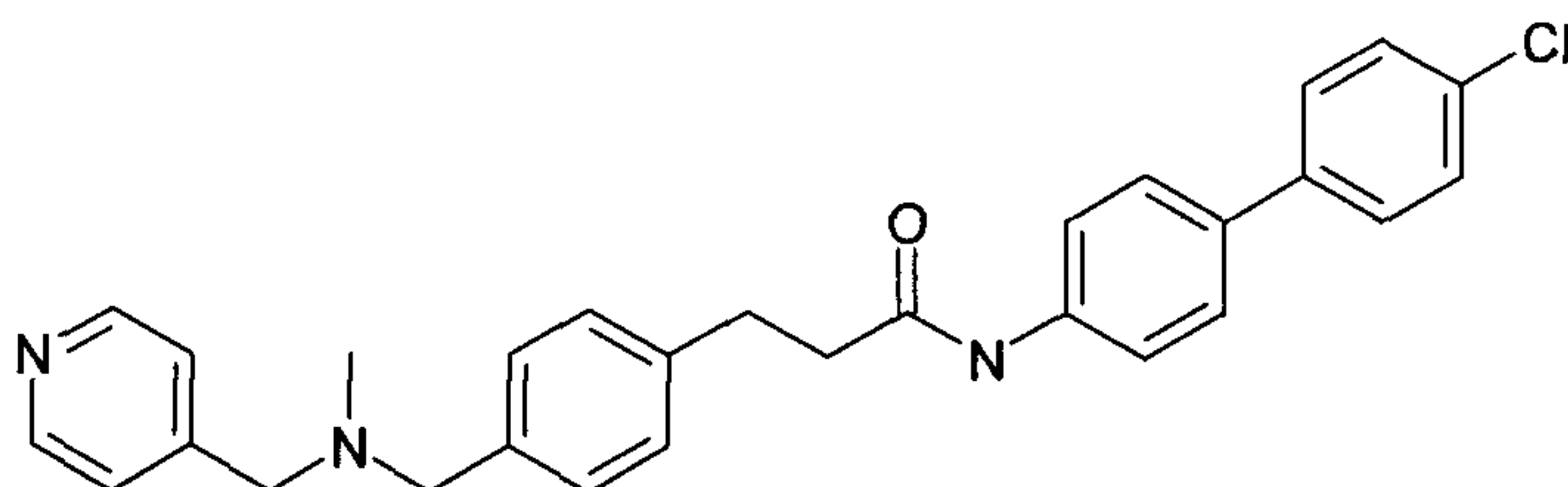
10



Example	R ₁ R ₂ N-X	educt	empirical formula	mass spectrum	mp [°C]
6.30		1.47	C ₃₁ H ₃₁ ClN ₂ O	483/85 (Cl) [M+H] ⁺	137- 138
6.31		1.48	C ₃₁ H ₃₁ ClN ₂ O	483/85 (Cl) [M+H] ⁺	133- 136

Example 6.32:

15 *N*-(4'-chloro-biphenyl-4-yl)-3-{4-[(methyl-pyridin-4-ylmethyl-amino)-methyl]-phenyl}-propionamide



6.32.a *N*-(4'-chloro-biphenyl-4-yl)-3-(4-cyano-phenyl)-propionamide

6 ml (43.04 mmol) triethylamine and 13.73 g (42.75 mmol) TBTU are added to a reaction mixture of 7.5 g (42.81 mmol) 4-cyano-phenylpropionic acid in 150 ml N,N-dimethylformamide and the mixture is stirred for 30 min at RT. Then a further 6 ml (43.04 mmol) triethylamine and 8.72 g (42.83 mmol) 4'-chloro-biphenyl-4-ylamine are added and the mixture is stirred for 24 h at RT. The solution is mixed with plenty of water and the precipitated *N*-(4'-chloro-biphenyl-4-yl)-3-(4-cyano-phenyl)-propionamide is suction filtered, washed with water and finally with diisopropylether. The yellow solid is dried for 6 h at 50°C and 20 mbar in the vacuum drying chamber. Yield: 14.22 g (92 % of theoretical)

10 $C_{22}H_{17}ClN_2O$ (M= 360.84)

Calc.: Molecular ion peak (M+H)⁺: 361/63 (Cl) Found: Molecular ion peak (M+H)⁺: 361/63 (Cl)

R_f value: 0.5 (silica gel, dichloromethane/ethanol = 20:1)

15

6.32.b *N*-(4'-chloro-biphenyl-4-yl)-3-(4-formyl-phenyl)-propionamide

100 ml formic acid are added to a reaction mixture of 3 g Raney nickel moistened with water and 14.22 g (39.41 mmol) *N*-(4'-chloro-biphenyl-4-yl)-3-(4-cyano-phenyl)-propionamide and refluxed for 20 h. Then the catalyst is suction filtered and the filtrate is diluted with plenty of water. The precipitated *N*-(4'-chloro-biphenyl-4-yl)-3-(4-formyl-phenyl)-propionamide is suction filtered and dissolved in ethyl acetate. The organic phase is washed first of all with 2 molar sodium hydroxide solution, then with water and finally with saturated sodium chloride solution, dried over sodium sulphate and activated charcoal and freed from solvent by rotary evaporation.

25 Yield: 11.7 g (57 % of theoretical)

$C_{22}H_{18}ClNO_2$ (M= 363.84)

Calc.: Molecular ion peak (M+H)⁺: 364/66 (Cl) Found: Molecular ion peak (M+H)⁺: 364/66 (Cl)

R_f value: 0.5 (silica gel, cyclohexane/ethyl acetate = 1:1)

30

6.32.c *N*-(4'-chloro-biphenyl-4-yl)-3-(4-hydroxymethyl-phenyl)-propionamide

First of all 8 ml glacial acetic acid are added to a reaction solution of 11.7 g (22.51 mmol) *N*-(4'-chloro-biphenyl-4-yl)-3-(4-formyl-phenyl)-propionamide in 200 ml of

tetrahydrofuran and then 15.1 g (67.53 mmol) sodium triacetoxymethylborohydride are added and the mixture is stirred for 20 h at RT. The reaction mixture is poured onto plenty of water and the precipitate formed is suction filtered. This is purified by column chromatography on silica gel. (eluant: dichloromethane/acetone 15/1 to 10/1)

5 Yield: 5.46 g (66 % of theoretical)

$C_{22}H_{20}ClNO_2$ (M= 365.85)

Calc.: Molecular ion peak $(M+H)^+$: 366/68 (Cl) Found: Molecular ion peak $(M+H)^+$: 366/68 (Cl)

R_f value: 0.35 (silica gel, dichloromethane/acetone = 10:1)

10

6.32.d *N*-(4'-chloro-biphenyl-4-yl)-3-(4-chloromethyl-phenyl)-propionamide

0.43 ml (5.6 mmol) methanesulphonic acid chloride are slowly added dropwise at ambient temperature to a solution of 2 g (5.47 mmol) *N*-(4'-chloro-biphenyl-4-yl)-3-(4-hydroxymethyl-phenyl)-propionamide and 1.56 ml (11.2 mmol) triethylamine in 50 ml

15 dichloromethane and the reaction mixture is stirred for 24 hours at ambient temperature. It is extracted with water and the organic phase is dried over sodium sulphate. The solvent is distilled off and the residue is stirred with diisopropylether and suction filtered.

Yield: 1.45 g (69 % of theoretical)

20 $C_{22}H_{19}Cl_2NO$ (M= 384.3)

Calc.: Molecular ion peak $(M+H)^+$: 384/86/88 (Cl₂) Found: Molecular ion peak $(M+H)^+$: 384/86/88 (Cl₂)

R_f value: 0.45 (silica gel, dichloromethane/ ethanol = 50:1)

25 6.32.e *N*-(4'-chloro-biphenyl-4-yl)-3-{4-[(methyl-pyridin-4-ylmethyl-amino)-methyl]-phenyl}-propionamide

A reaction mixture of 70 mg (0.18 mmol) *N*-(4'-chloro-biphenyl-4-yl)-3-(4-chloromethyl-phenyl)-propionamide, 18 mg (0.15 mmol) methylpyridin-4-ylmethylamine and 41 mg (0.3 mmol) potassium carbonate in 5 ml acetone is agitated
30 for 24 hours at reflux temperature. The reaction mixture is evaporated down. The residue is triturated with water and diisopropylether, suction filtered and dried in the air.

Yield: 52 mg (87 % of theoretical)

Melting point: 102°C

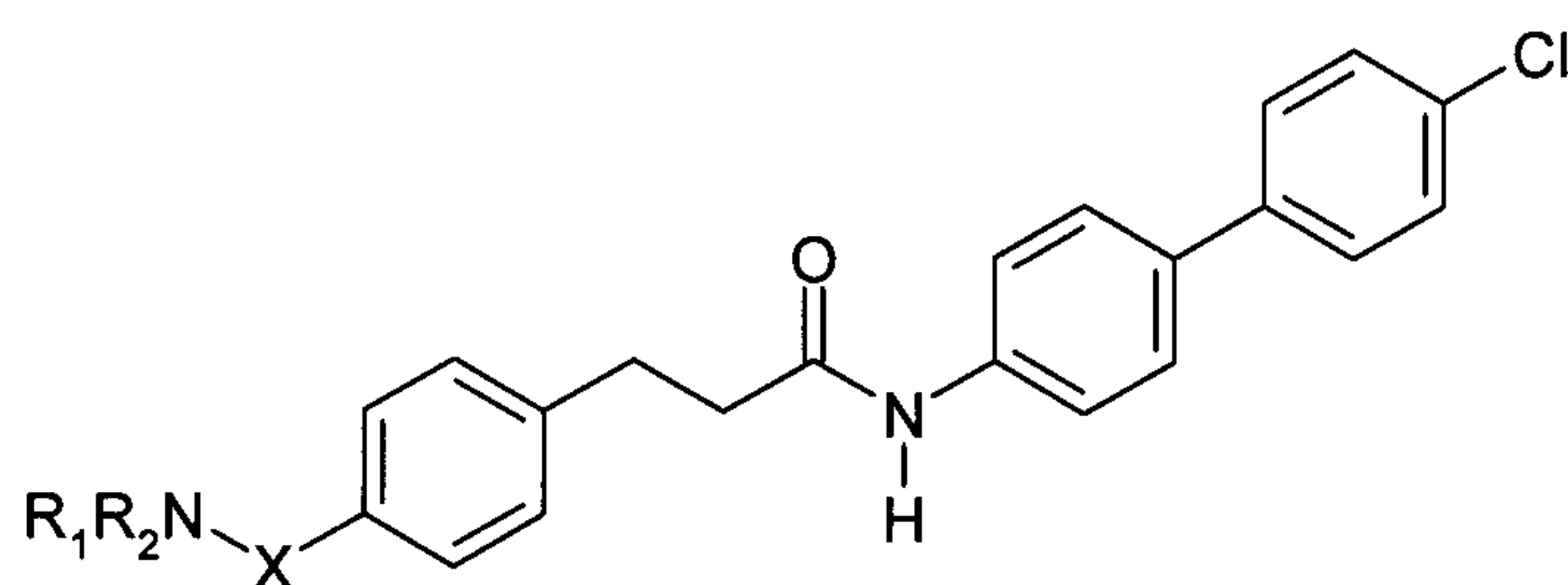
C₂₉H₂₈ClN₃O (M= 470.01)

Calc.: Molecular ion peak (M+H)⁺: 470/72(Cl)

Found: Molecular ion peak

(M+H)⁺: 470/72(Cl)

5



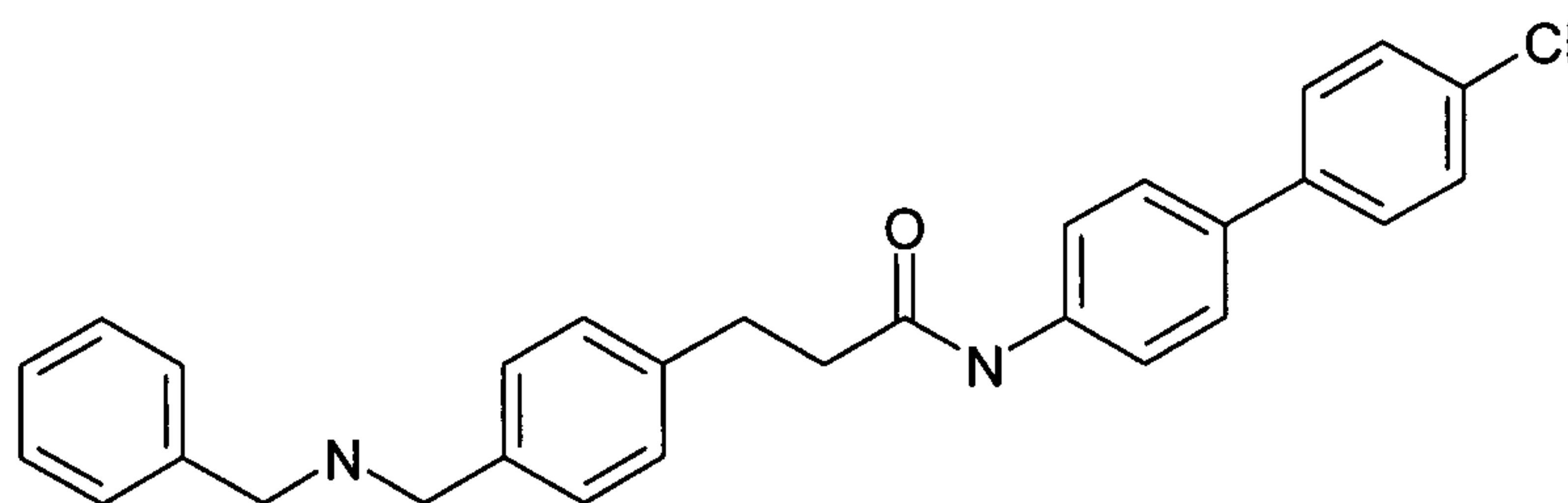
The following compounds are prepared analogously to Example 6.32.e:

Example	R ₁ R ₂ N-X	educt	empirical formula	mass spectrum	mp [°C]
6.33		6.32.d	C ₂₉ H ₂₈ ClN ₃ O	470/72 (Cl) [M+H] ⁺	168- 169
6.34		6.32.d	C ₂₉ H ₂₈ ClN ₃ O	470/72 (Cl) [M+H] ⁺	144- 145
6.35		6.32.d	C ₃₀ H ₃₅ ClN ₂ O	475/77 (Cl) [M+H] ⁺	149- 150.5
6.36		6.32.d	C ₂₈ H ₂₈ ClF ₃ N ₂ O ₂	517/19 (Cl) [M+H] ⁺	193
6.37		6.32.d	C ₂₈ H ₃₁ ClN ₂ O	447/49 (Cl) [M+H] ⁺	182,5- 184

10

Example 6.38.

3-[4-(benzylamino-methyl)-phenyl]-N-(4'-chloro-biphenyl-4-yl)-propionamide



A reaction mixture of 70 mg (0.18 mmol) *N*-(4'-chloro-biphenyl-4-yl)-3-(4-chloromethyl-phenyl)-propionamide, 16 mg (0.15 mmol) benzylamine and 41 mg (0.3 mmol) potassium carbonate in 5 ml acetone is agitated for 24 hours at reflux temperature. The reaction mixture is evaporated down. The residue is triturated with water and diisopropylether, suction filtered and dried in the air. The residue is purified by column chromatography on silica gel (eluant: dichloromethane/ethanol/ammonia 30/1/0.1)

Yield: 23 mg (40 % of theoretical)

10 Melting point: 176°C

$C_{29}H_{27}ClN_2O$ (M= 454.99)

Calc.: Molecular ion peak $(M+H)^+$: 455/57(Cl)
 $(M+H)^+$: 455/57(Cl)

Found: Molecular ion peak

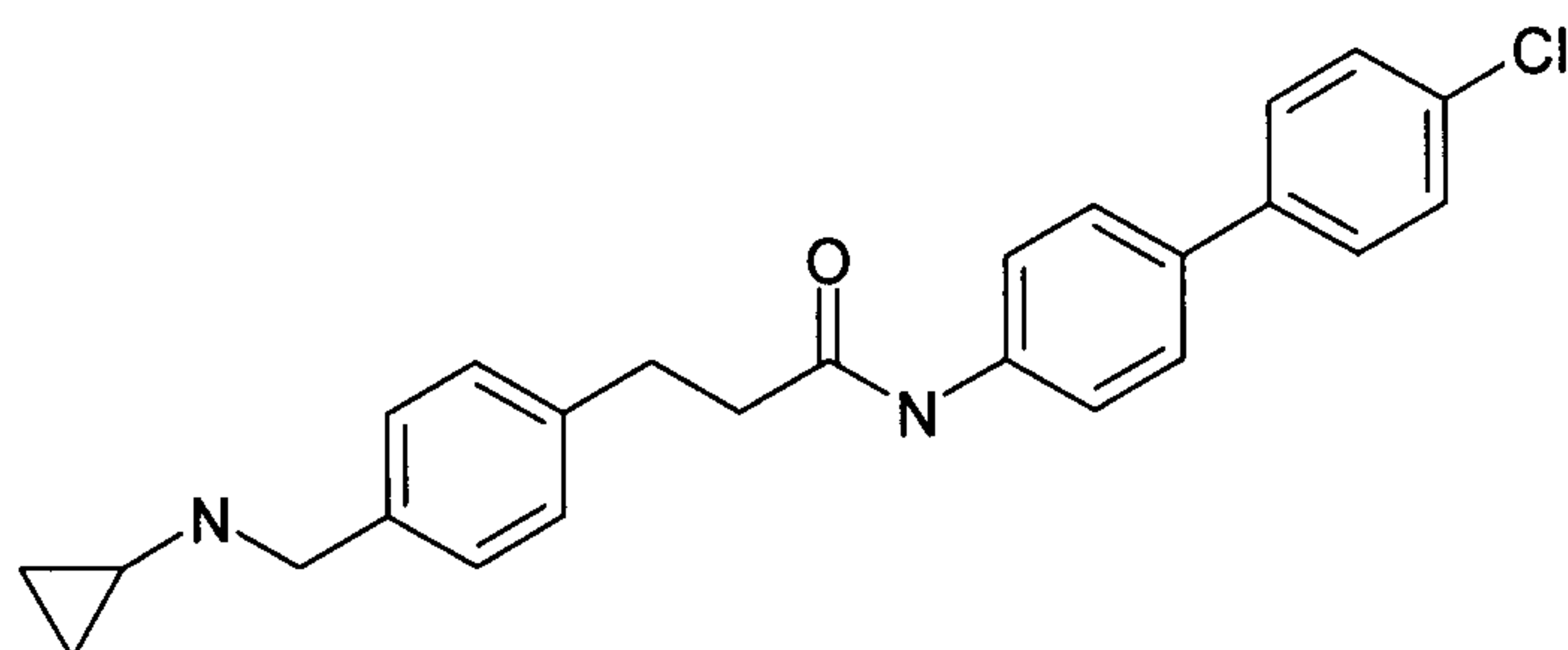
15 The following compounds are prepared analogously to Example 6.38:

Example	R_1R_2N-X	educt	empirical formula	mass spectrum	mp [°C]	R_f value
6.39		6.32.d	$C_{28}H_{31}ClN_2O$	447/49 (Cl) $[M+H]^+$	208	
6.40		6.32.d	$C_{31}H_{37}ClN_2O$	489/91 (Cl) $[M+H]^+$	165	
6.41		6.32.d	$C_{27}H_{29}ClN_2O$	432/34 (Cl) $[M+H]^+$	196- 197	
6.42		6.32.d	$C_{28}H_{33}ClN_2O_2$	465/67 (Cl) $[M+H]^+$	135	0.3 (A)

R_f value: A= (silica gel, dichloromethane/ethanol/ammonia 20:1:0.1)

Example 6.43.

- 5 *N*-(4'-chloro-biphenyl-4-yl)-3-(4-cyclopropylaminomethyl-phenyl)-propionamide trifluoroacetate



- A reaction mixture of 70 mg (0.18 mmol) *N*-(4'-chloro-biphenyl-4-yl)-3-(4-chloromethyl-phenyl)-propionamide, 16 mg (0.15 mmol) cyclopropylamine and 41 mg
 10 (0.3 mmol) potassium carbonate in 5 ml acetone is shaken for 24 hours at reflux temperature. The reaction mixture is evaporated down. The residue is triturated with water and diisopropylether, suction filtered and dried in the air. The residue is purified by column chromatography on silica gel (eluant: dichloromethane/ethanol/ammonia 30/1/0.1) and then by column chromatography on RP-18 (eluant: water + 0.1%
 15 trifluoroacetic acid/acetonitrile + 0.1 % trifluoroacetic acid 100/0 to 50/50)
 Yield: 24 mg (36 % of theoretical)

Melting point: 208°C

$C_{25}H_{25}ClN_2O \cdot C_2HF_3O_2$ (M= 518.96)

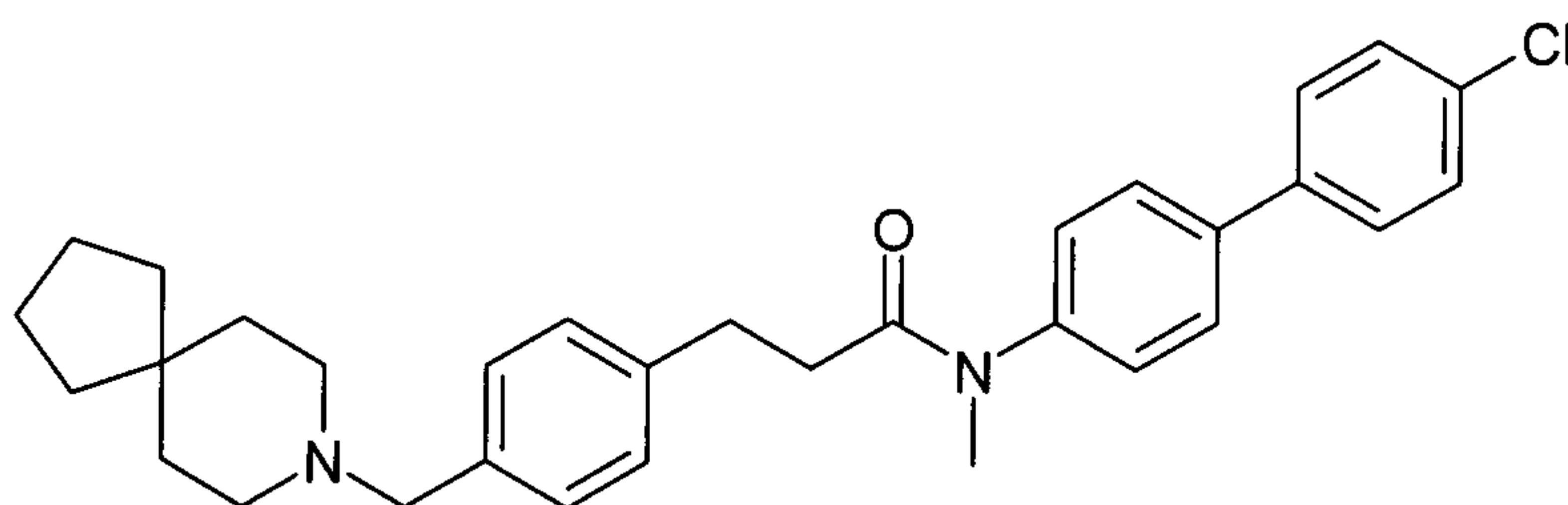
- Calc.: Molecular ion peak (M+H)⁺: 405/07(Cl) Found: Molecular ion peak
 20 (M+H)⁺: 405/07(Cl)

The following compound is prepared analogously to Example 6.43:

Example	R ₁ R ₂ N-X	educt	empirical formula	mass spectrum	mp [°C]
6.44		6.32.d	$C_{26}H_{26}ClN_3O$	432/34 (Cl) [M+H] ⁺	148- 149

Example: 6.45

3-[4-(8-aza-spiro[4.5]dec-8-ylmethyl)-phenyl]-*N*-(4'-chloro-biphenyl-4-yl)-*N*-methyl-propionamide



5

Prepared analogously to Example 6.29 from 3-[4-(8-aza-spiro[4.5]dec-8-ylmethyl)-phenyl]-propynoic acid(4'-chloro-biphenyl-4-yl)methyl-amide.

10 Yield: 43 mg (86 % of theoretical)

Melting point: 119°C

C₃₂H₃₇ClN₂O (M= 501.10)

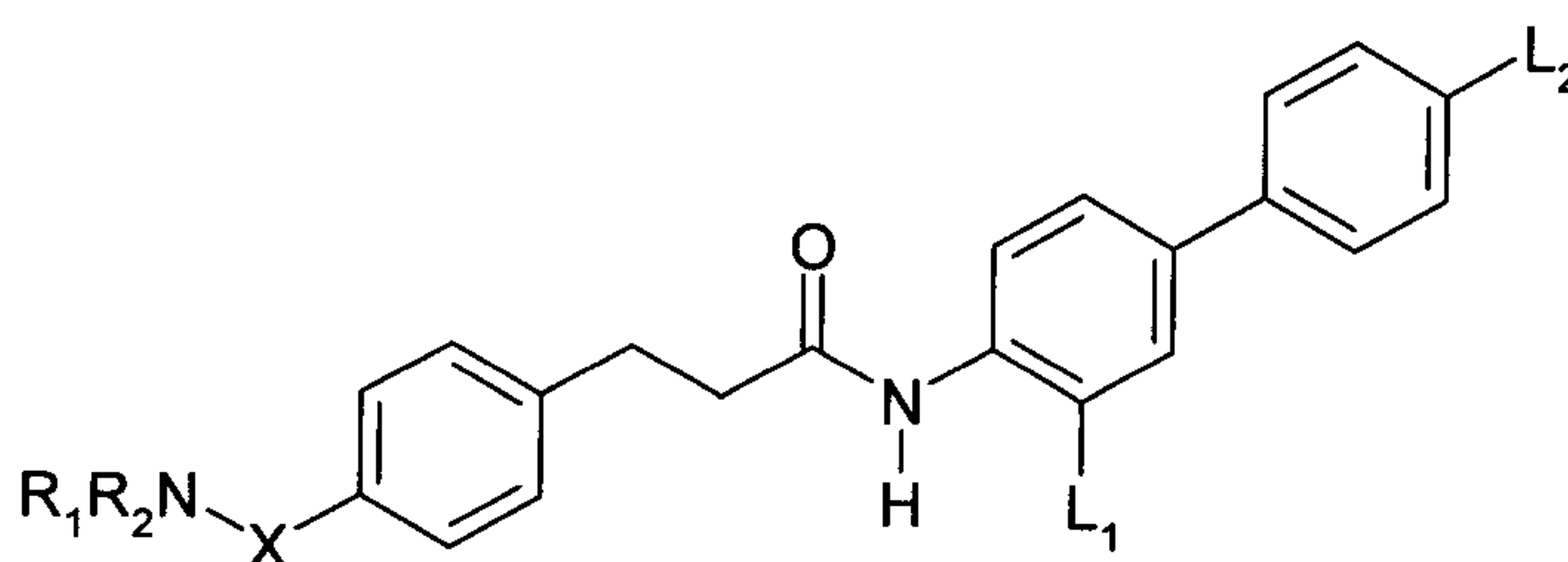
Calc.: Molecular ion peak (M+H)⁺: 501/07(Cl)

Found: Molecular ion peak

(M+H)⁺: 501/03(Cl)

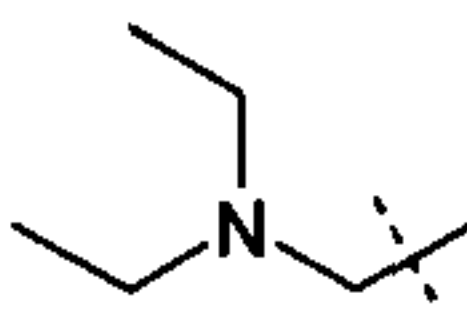
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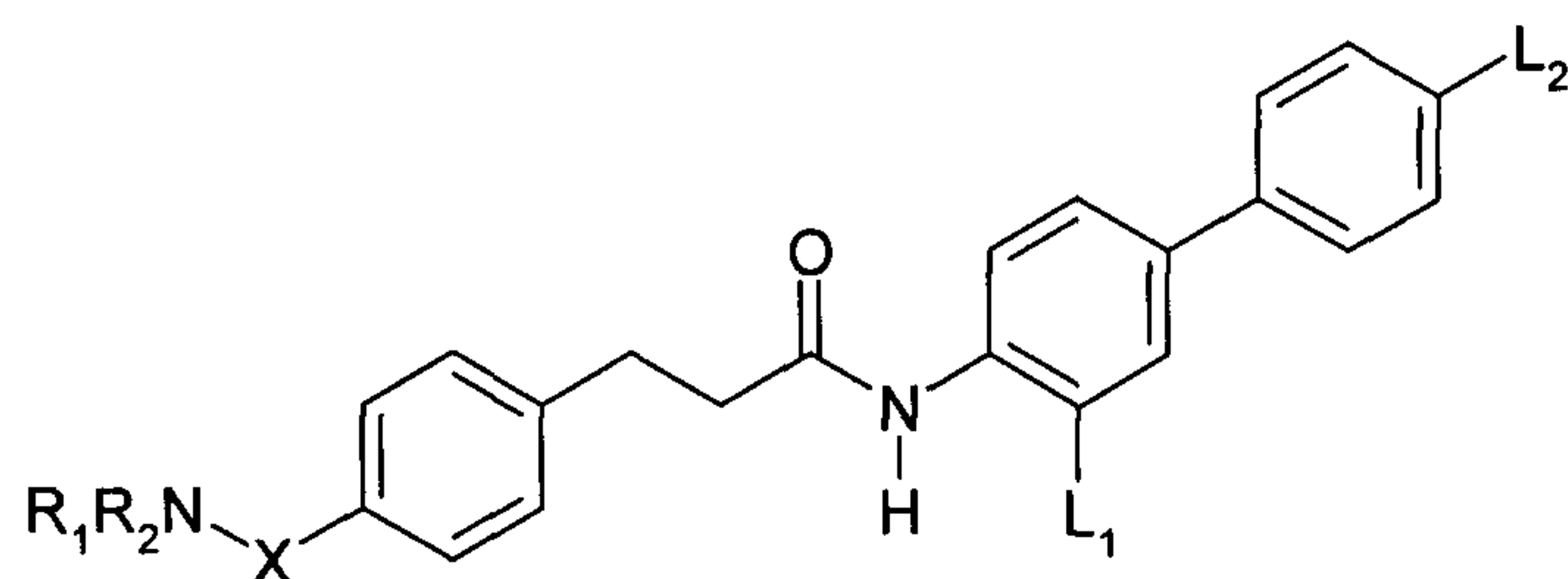
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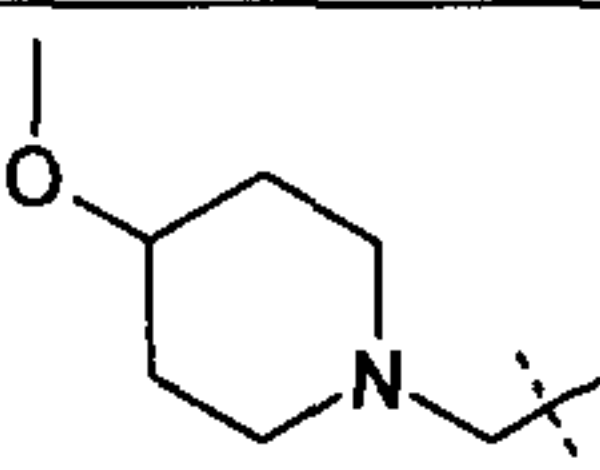
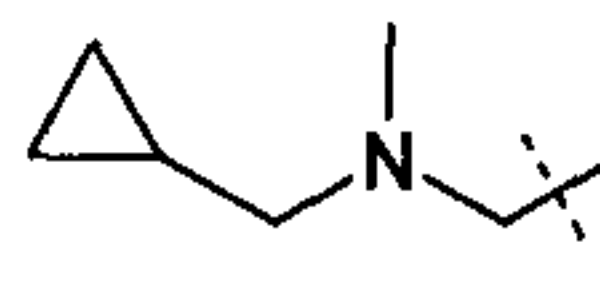
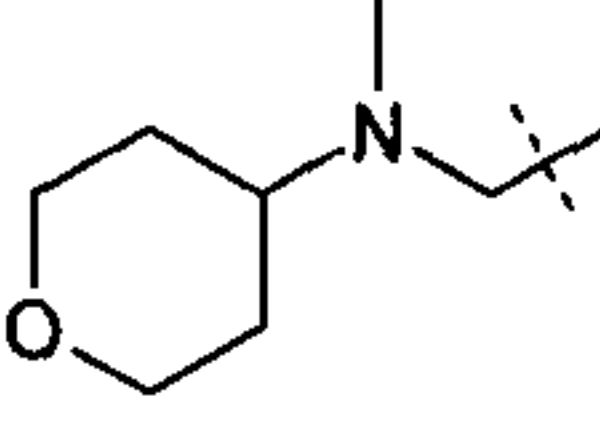
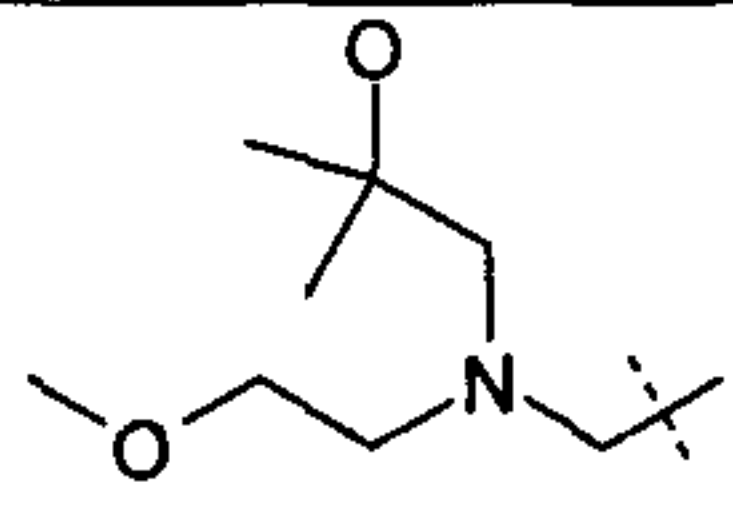
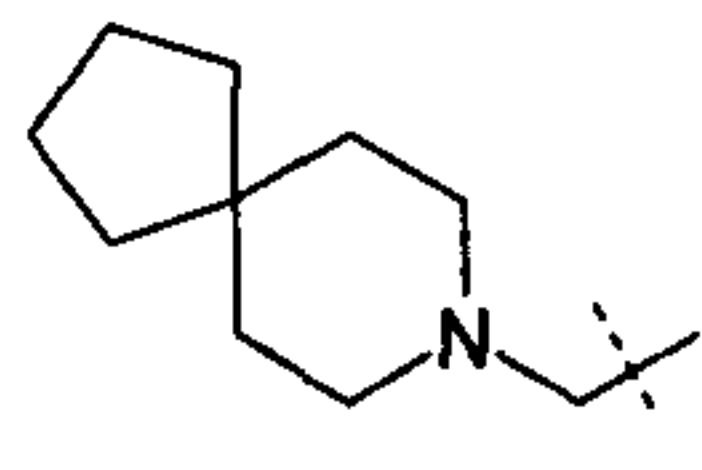
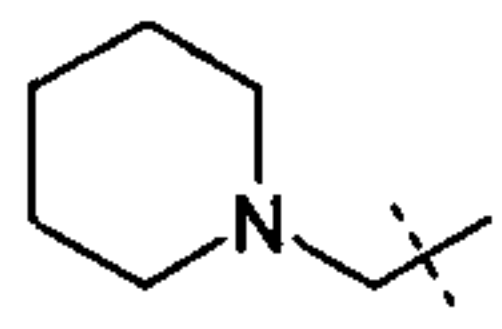
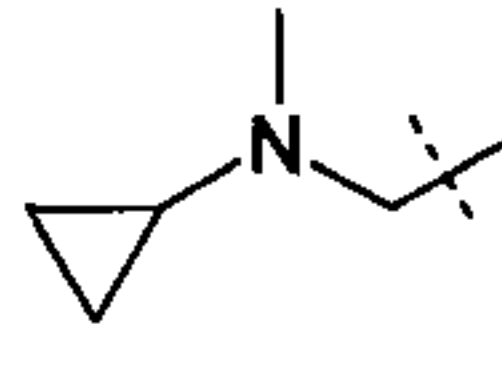
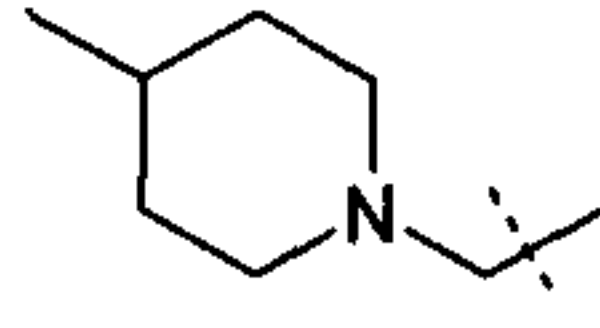
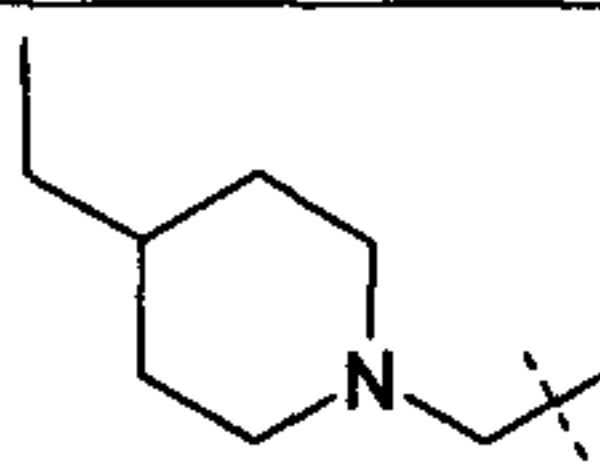
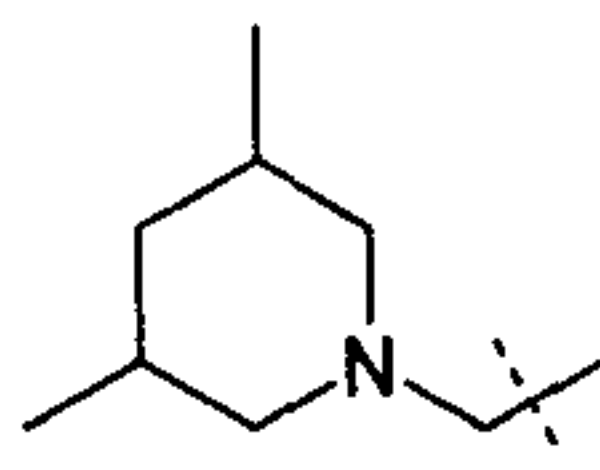


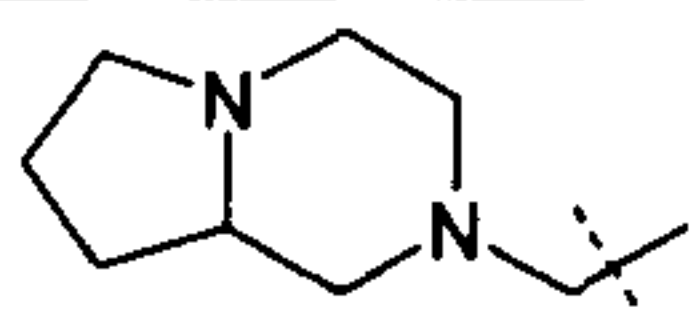
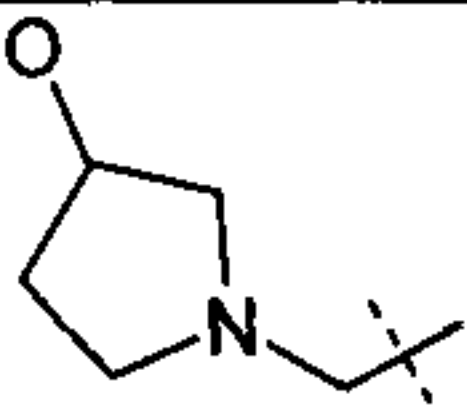
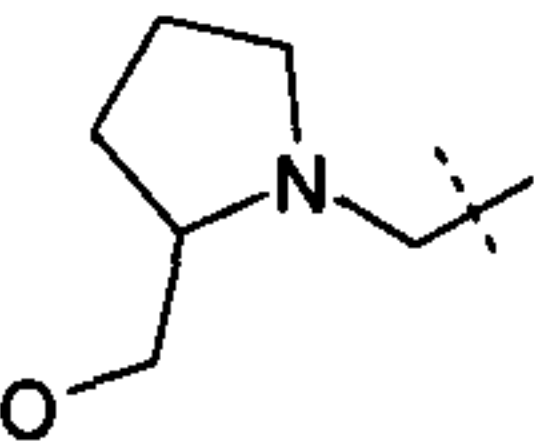
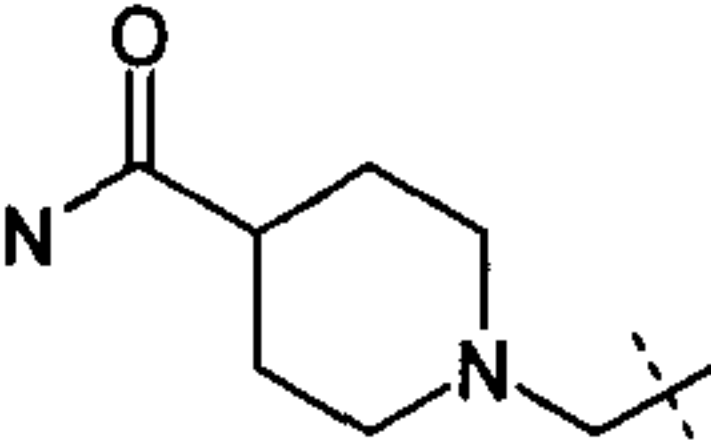
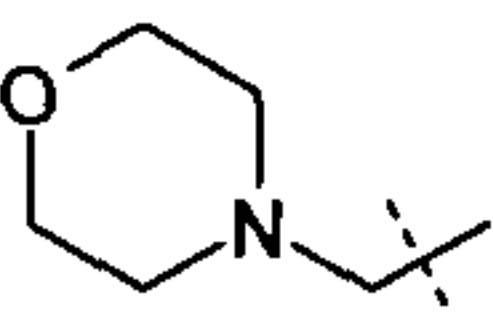
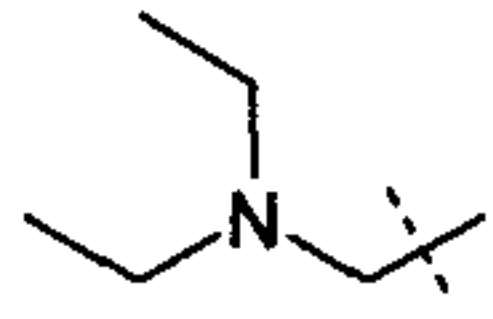
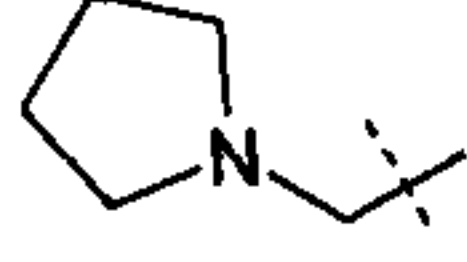
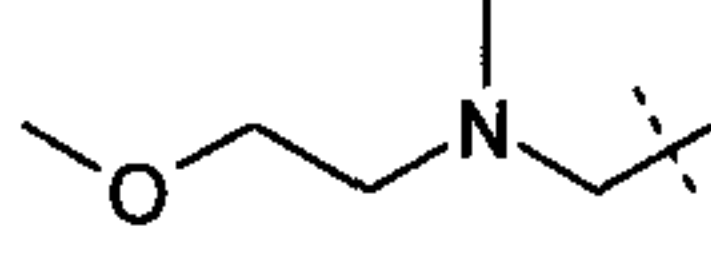
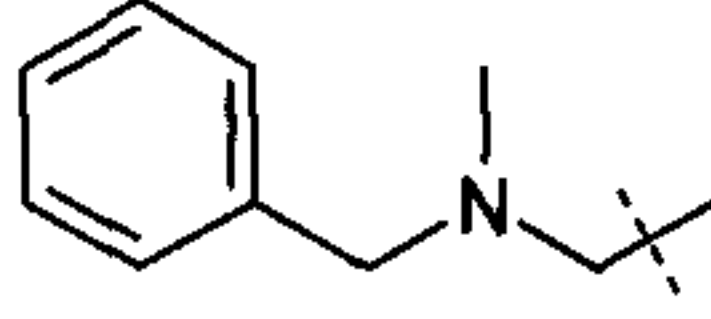
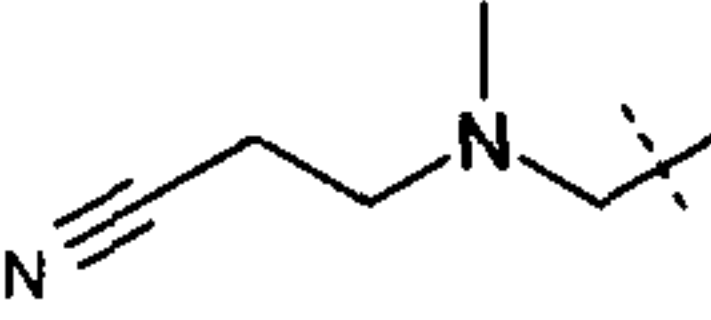
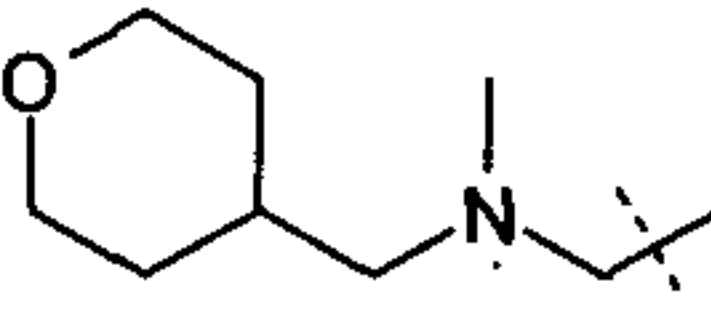
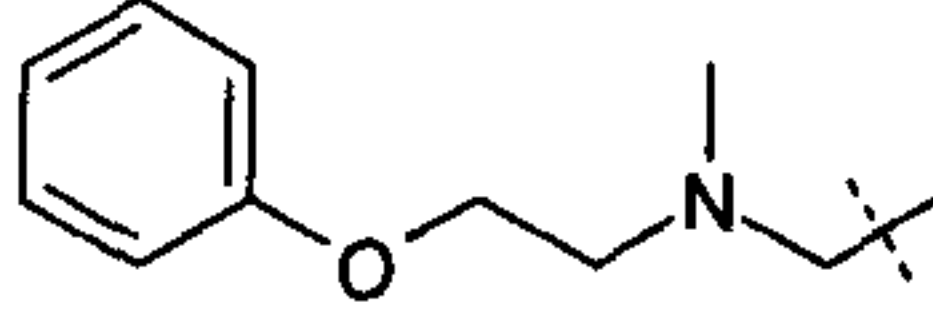
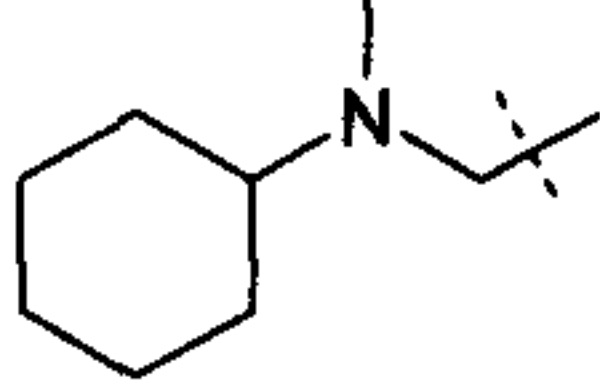
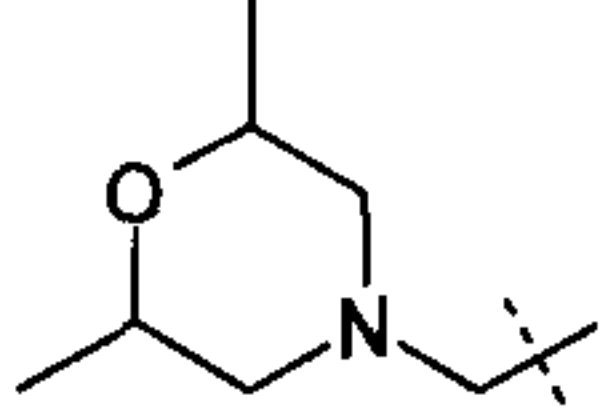
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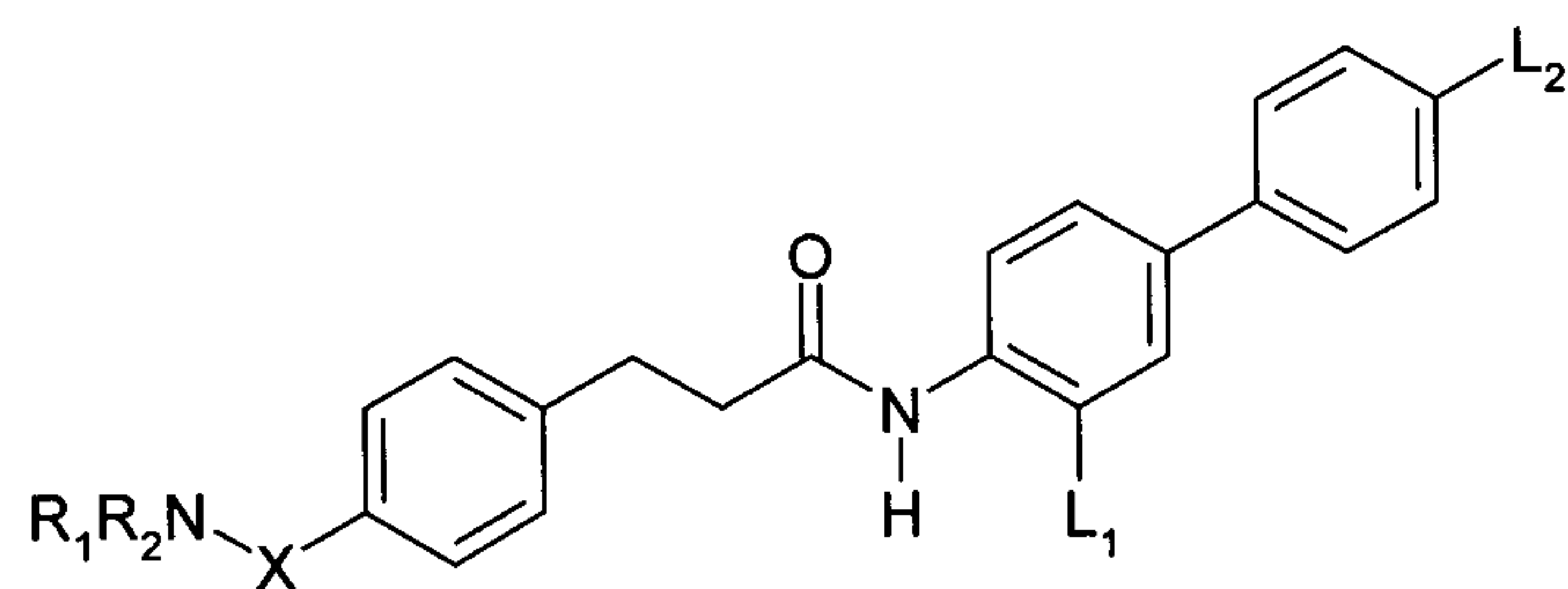
Example	R ₁ R ₂ N-X	L ₁	L ₂
6.46		H	Cl
6.47		H	Cl

6.48		H	Cl

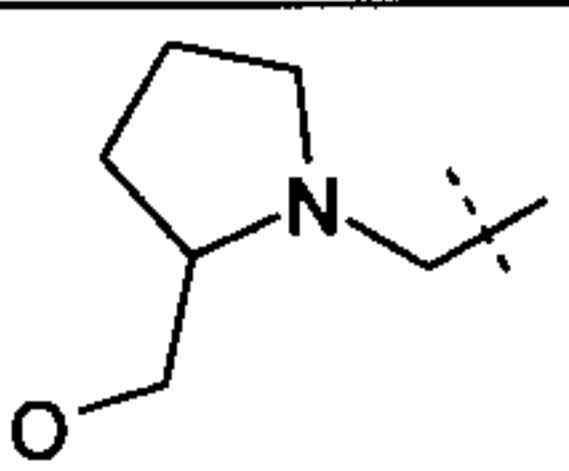
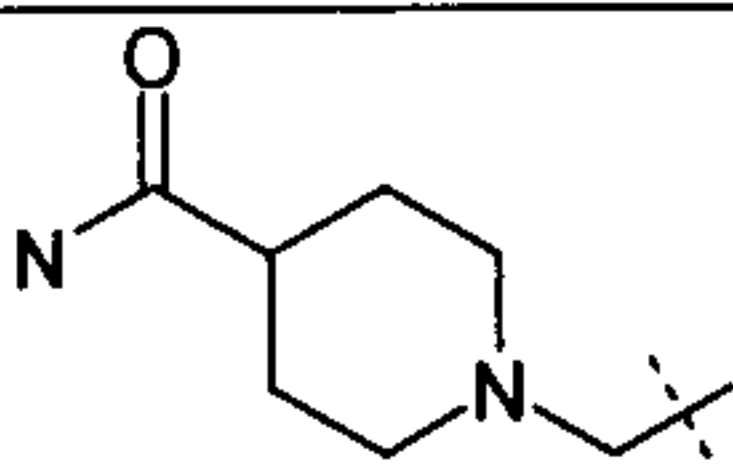
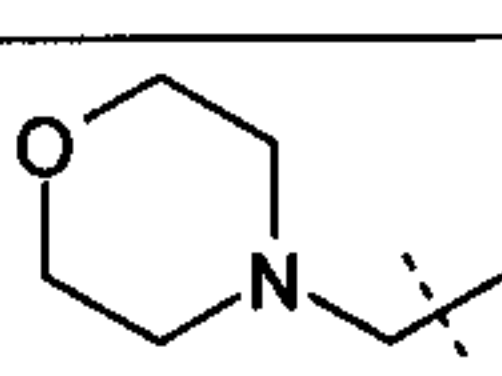
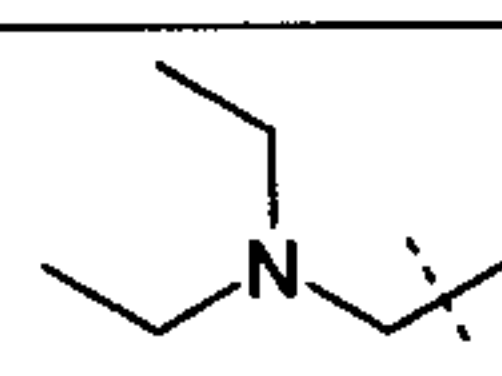
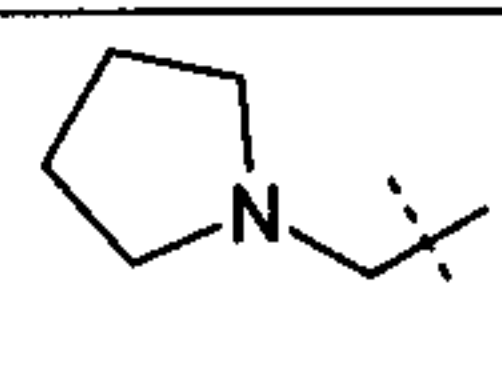
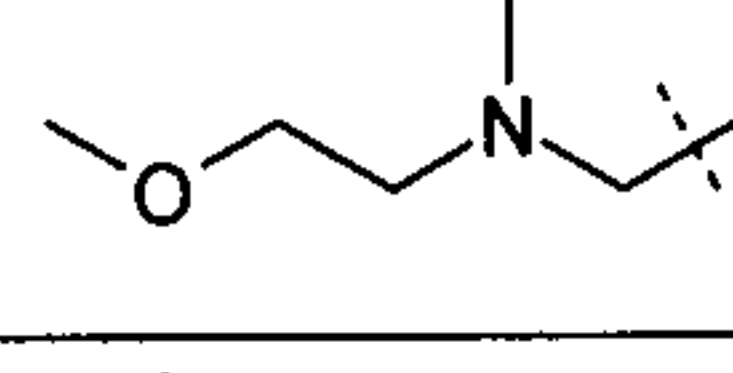
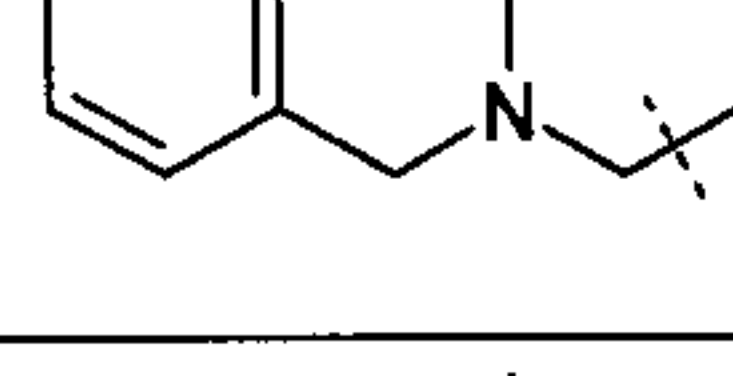
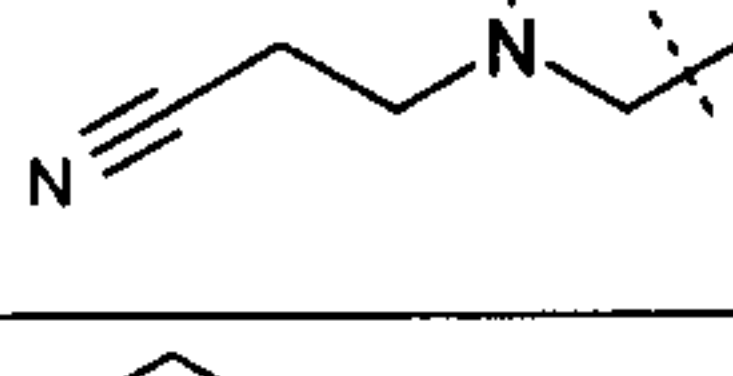
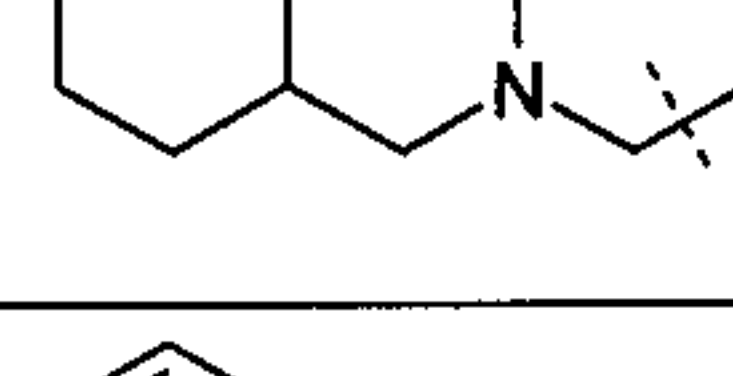
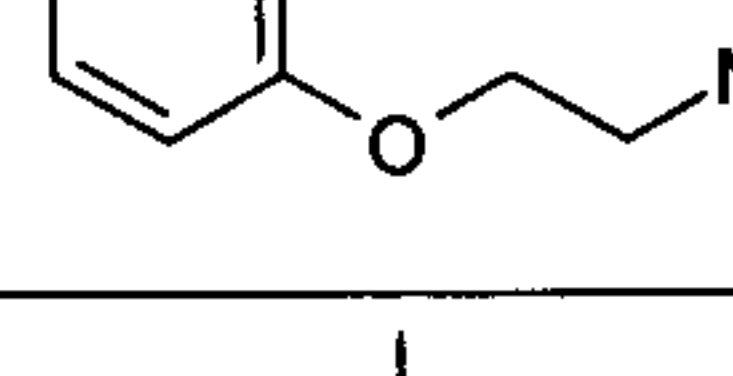
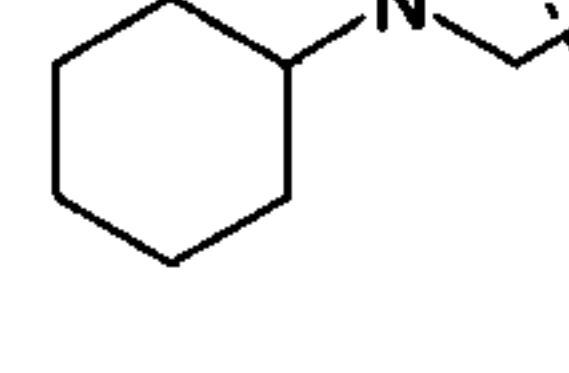
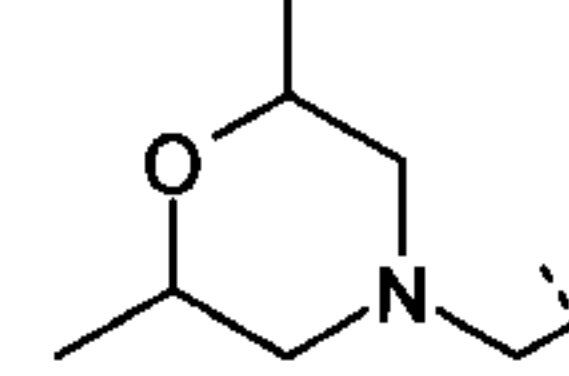


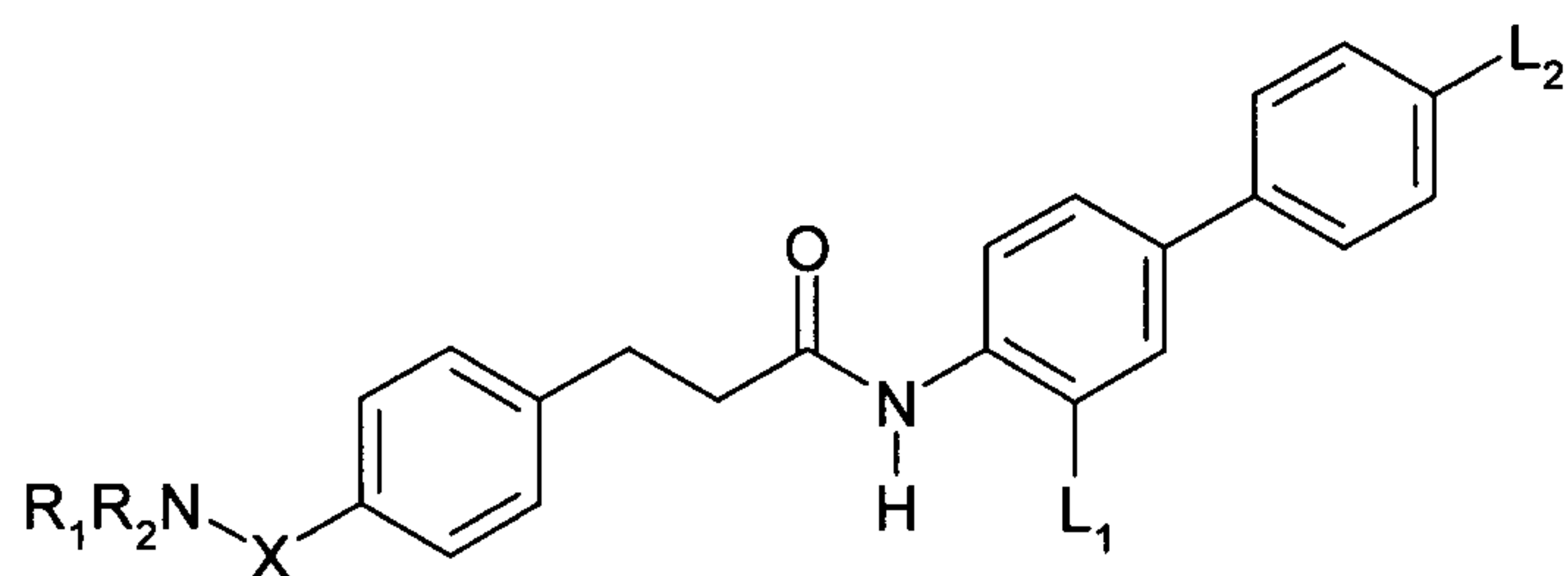
Example	R ₁ R ₂ N-X	L ₁	L ₂
6.49		F	Cl
6.50		F	Cl
6.51		F	Cl
6.52		F	Cl
6.53		F	Cl
6.54		F	Cl
6.55		F	Cl
6.56		F	Cl
6.57		F	Cl
6.58		F	Cl

6.59		F	Cl
6.60		F	Cl
6.61		F	Cl
6.62		F	Cl
6.63		F	Cl
6.64		F	Cl
6.65		F	Cl
6.66		F	Cl
6.67		F	Cl
6.68		F	Cl
6.69		F	Cl
6.70		F	Cl
6.71		F	Cl
6.72		F	Cl

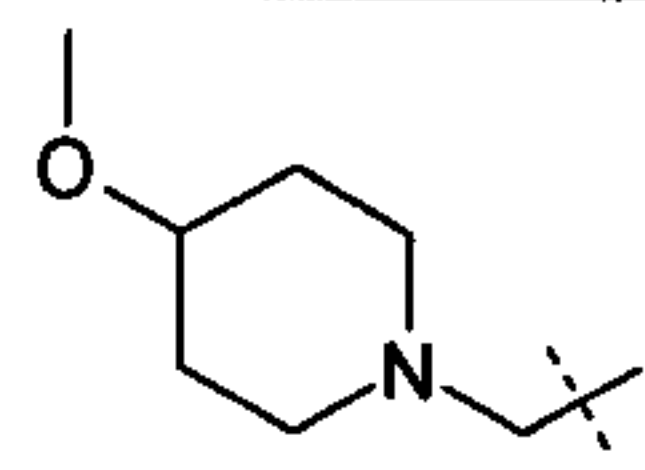
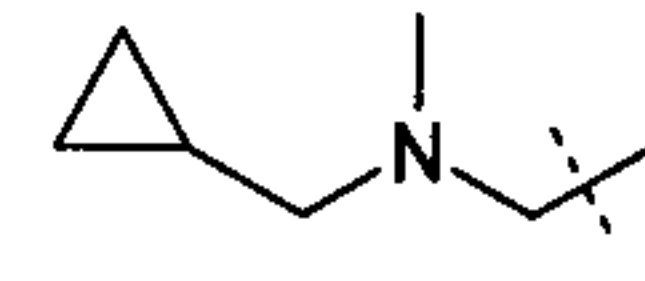
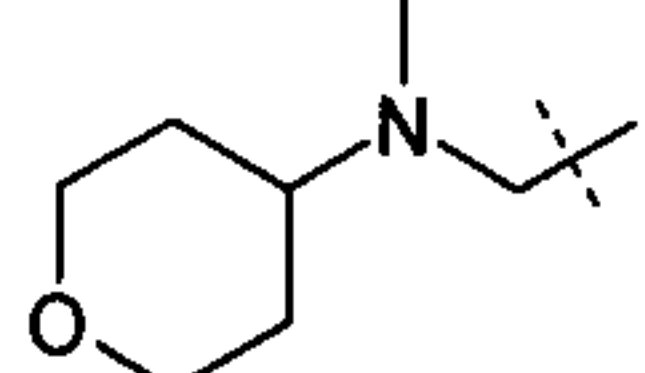
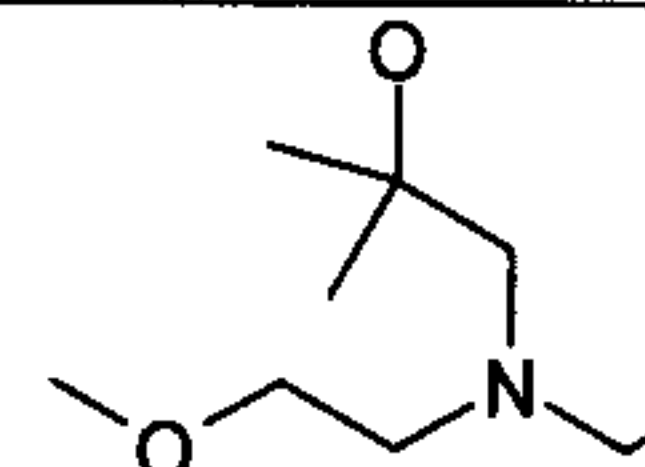
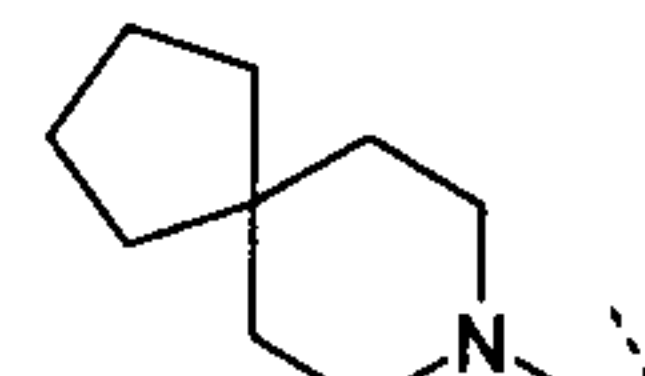
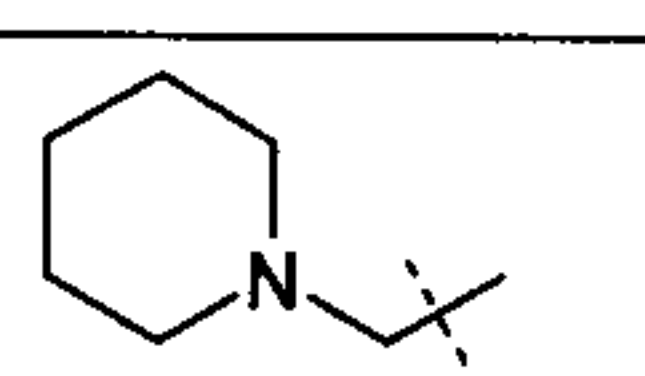
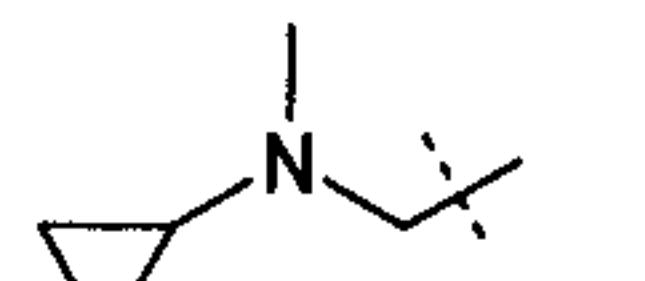
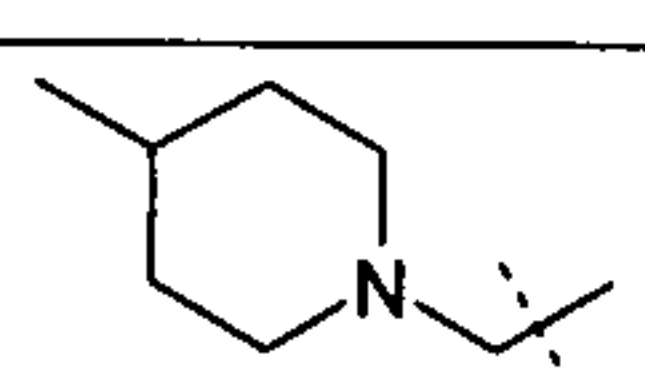
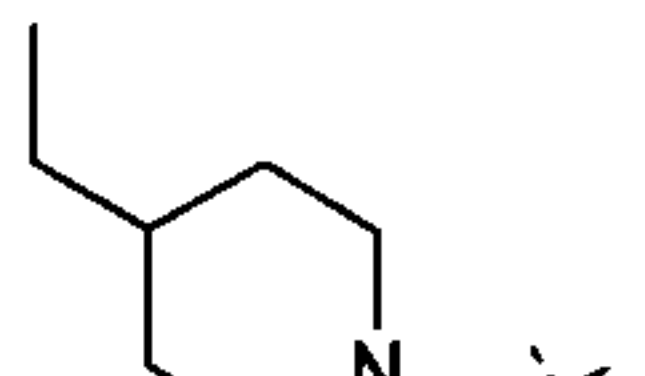
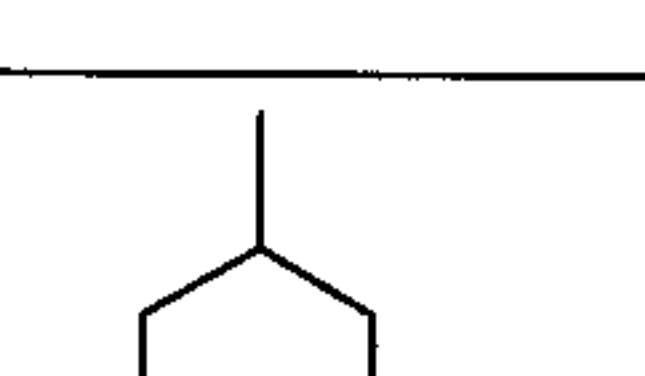
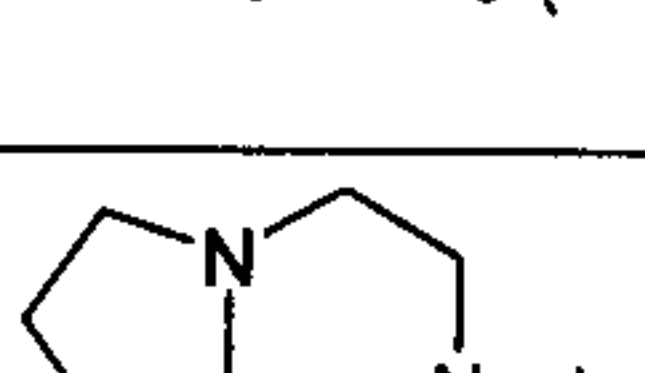
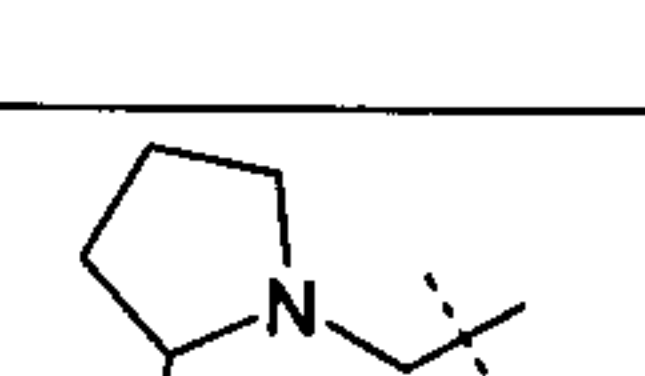
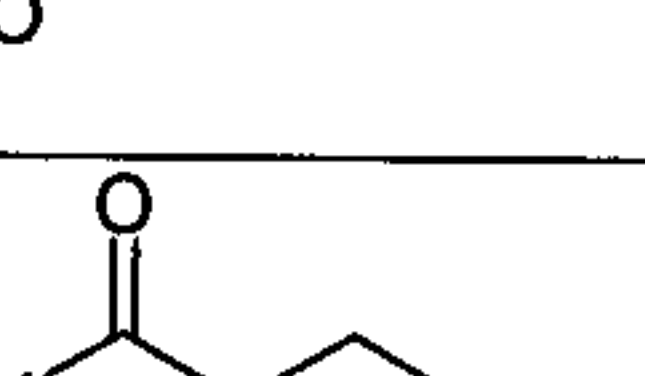
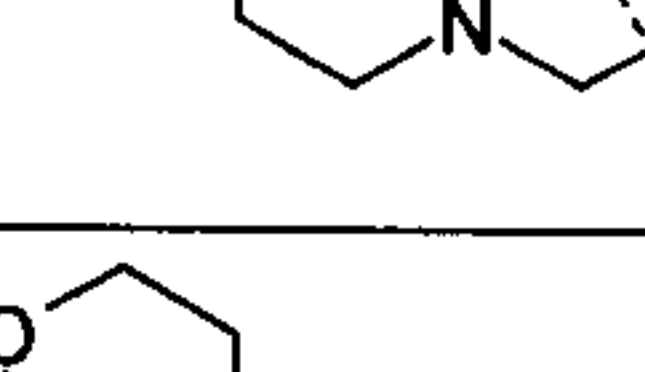


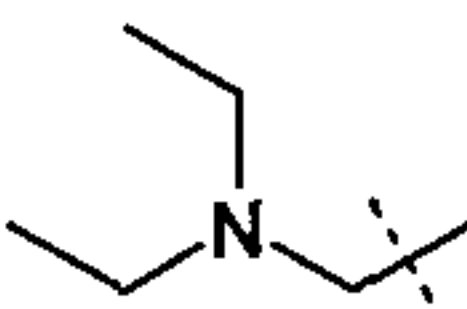
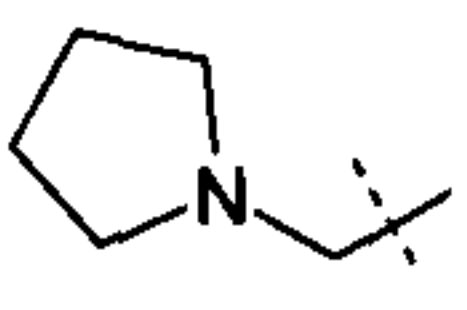
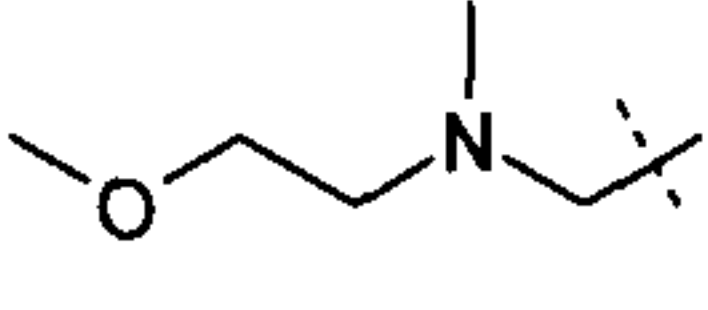
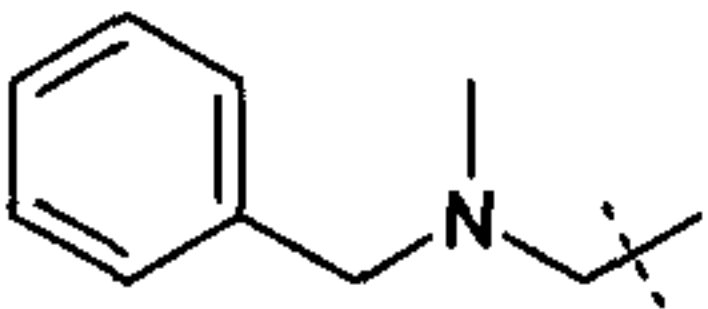
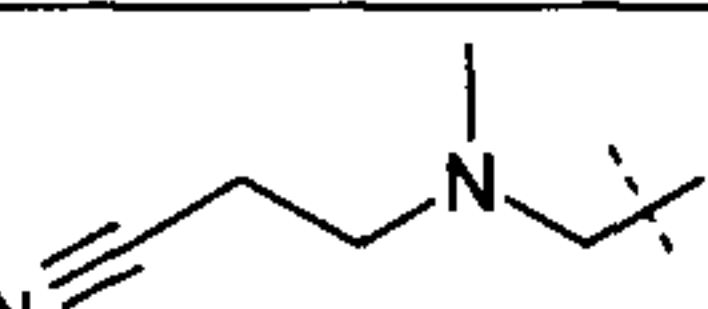
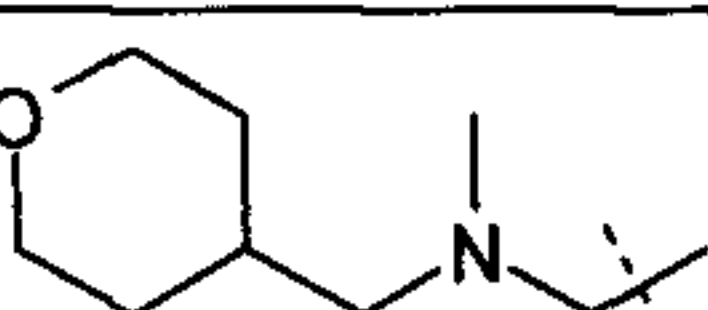
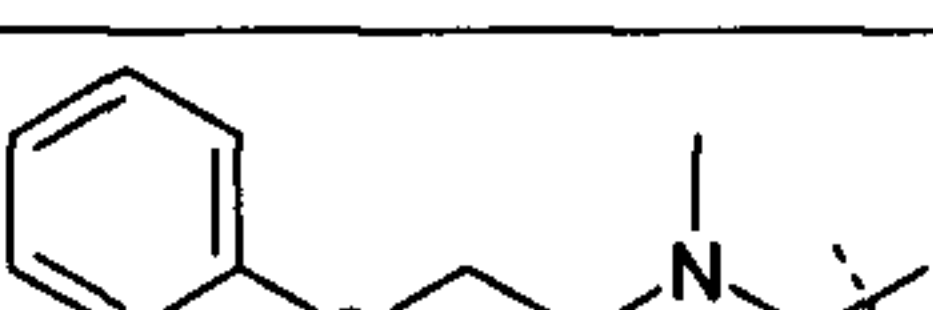
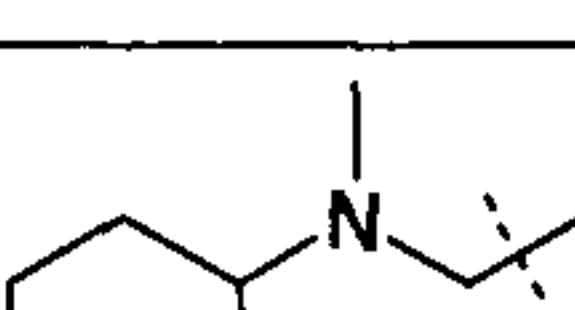
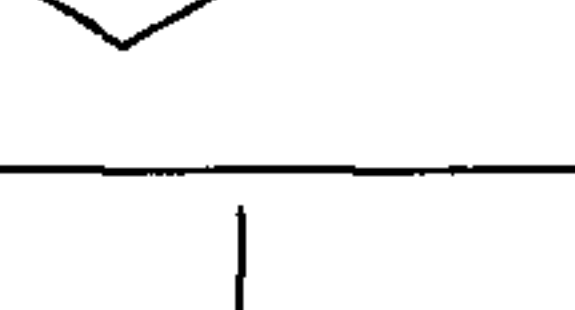
Example	R ₁ R ₂ N-X	L ₁	L ₂
6.73		H	CF ₃
6.74		H	CF ₃
6.75		H	CF ₃
6.76		H	CF ₃
6.77		H	CF ₃
6.78		H	CF ₃
6.79		H	CF ₃
6.80		H	CF ₃
6.81		H	CF ₃
6.82		H	CF ₃
6.83		H	CF ₃
6.84		H	CF ₃

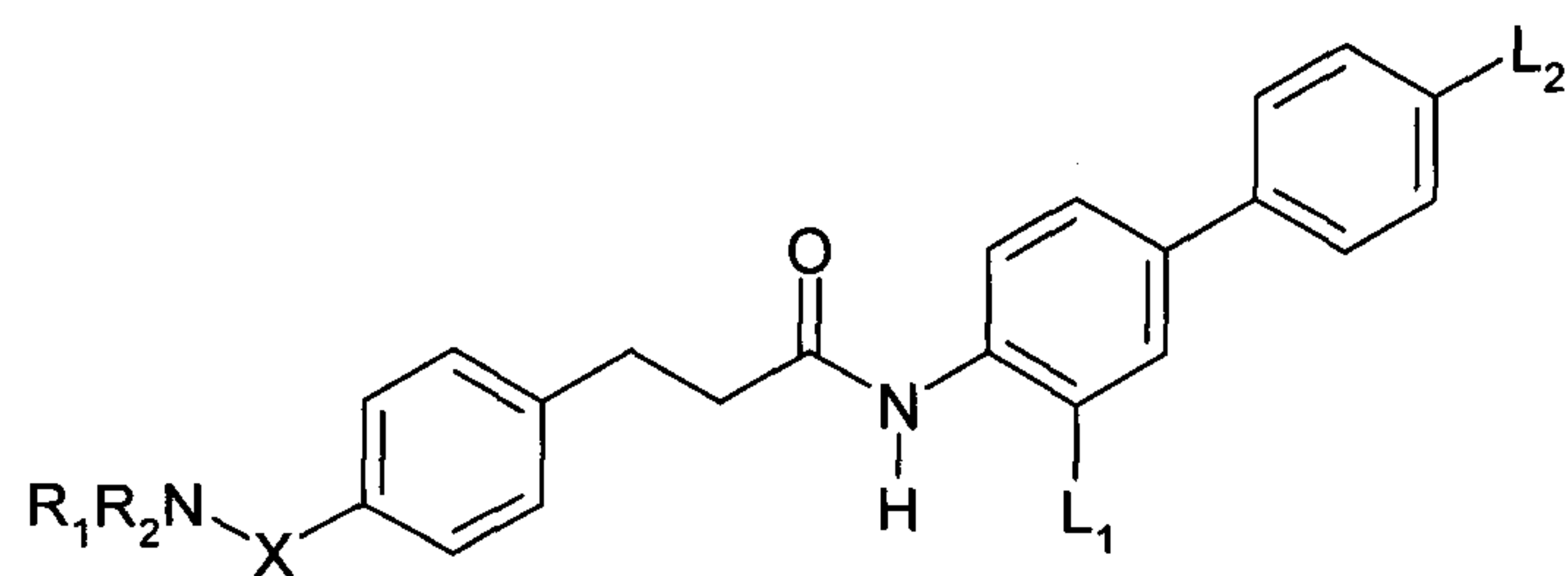
6.85		H	CF ₃
6.86		H	CF ₃
6.87		H	CF ₃
6.88		H	CF ₃
6.89		H	CF ₃
6.90		H	CF ₃
6.91		H	CF ₃
6.92		H	CF ₃
6.93		H	CF ₃
6.94		H	CF ₃
6.95		H	CF ₃
6.96		H	CF ₃

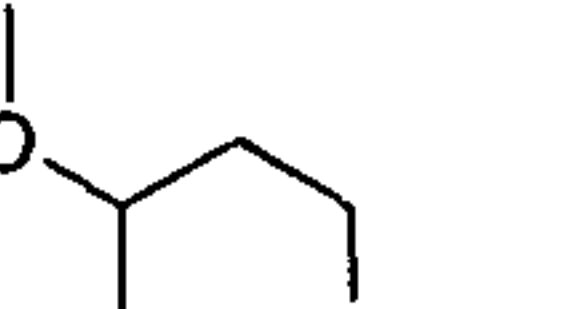
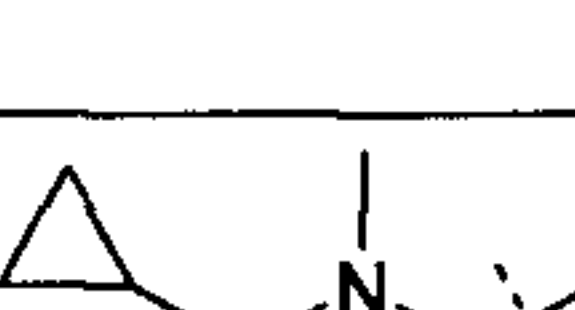
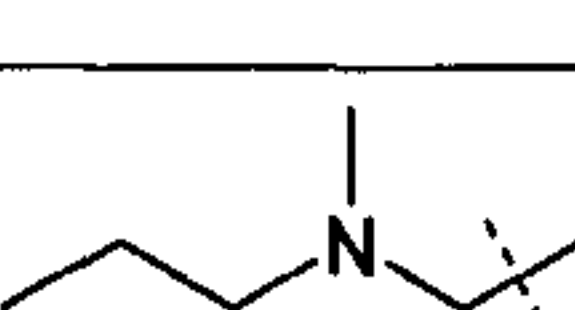


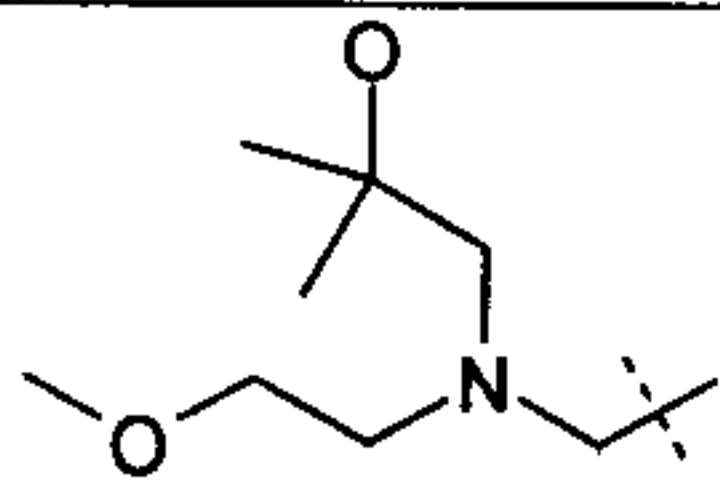
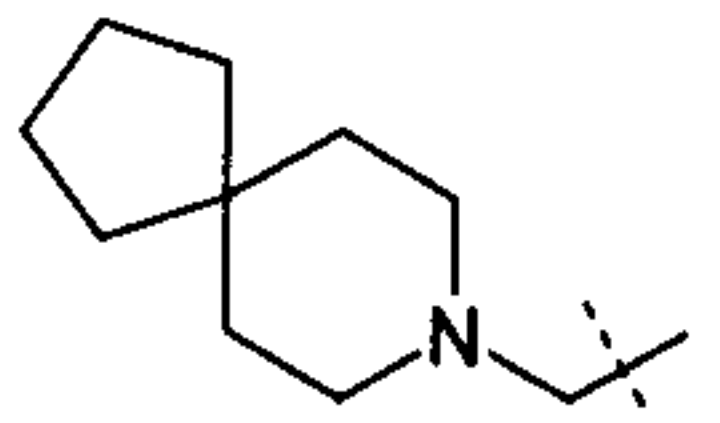
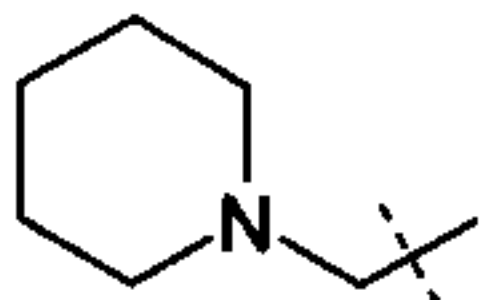
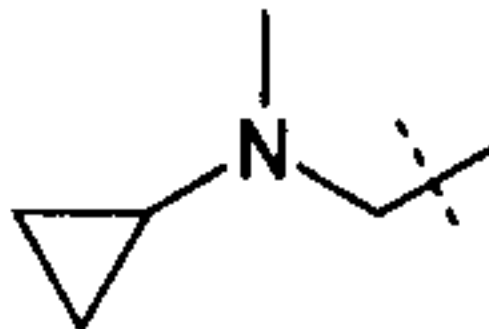
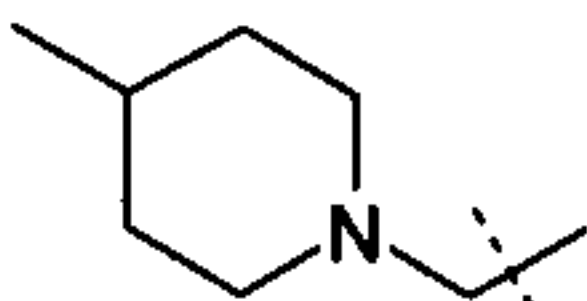
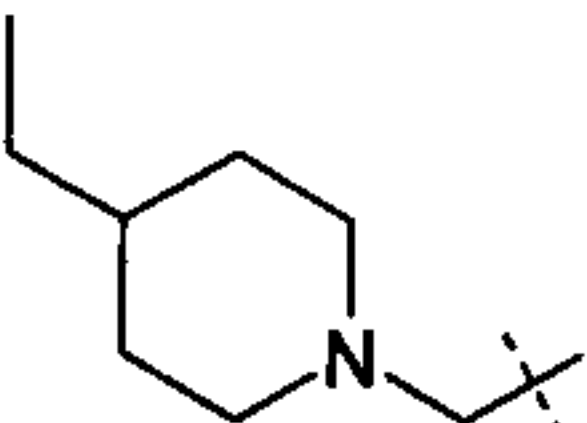
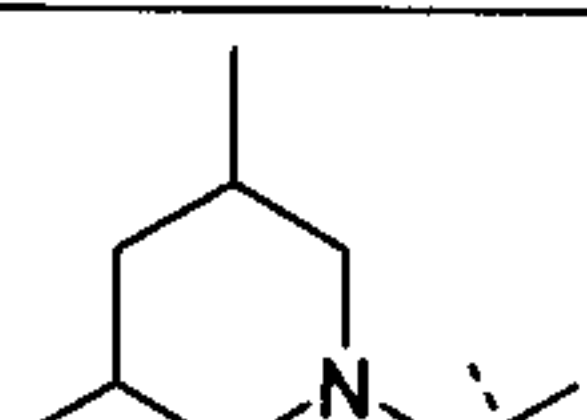
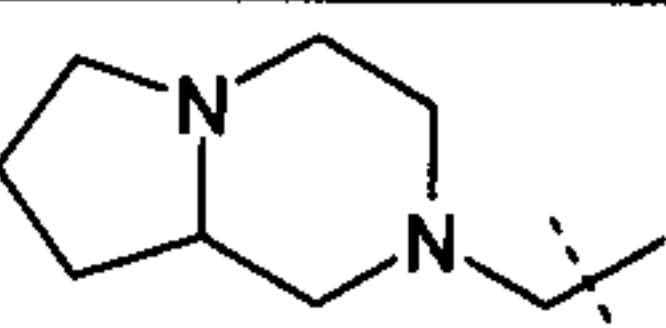
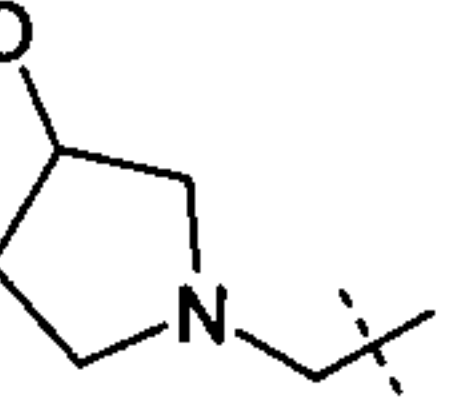
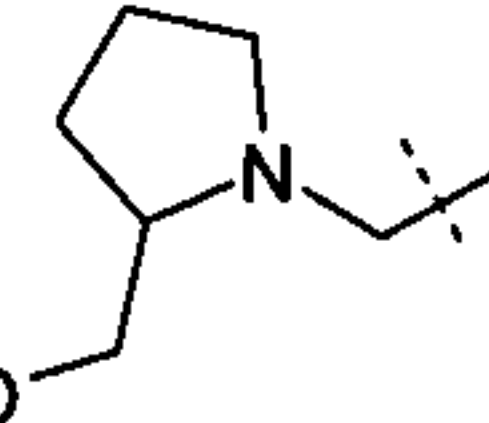
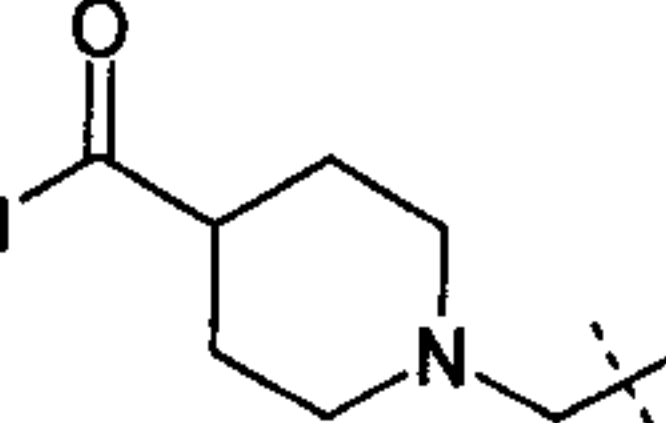
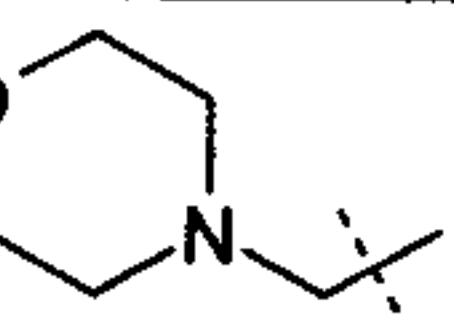
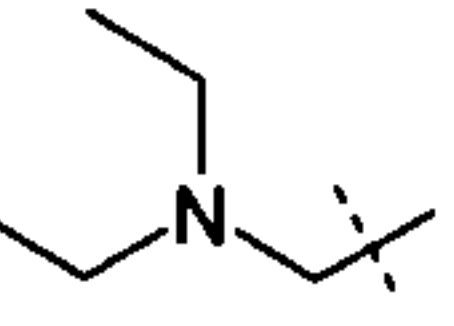
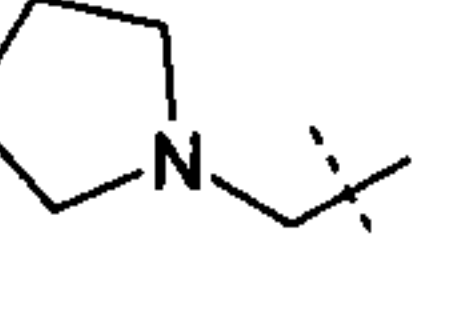
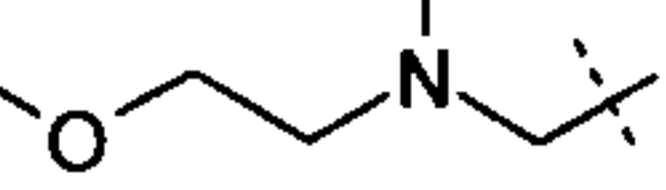
Example	R ₁ R ₂ N-X	L ₁	L ₂

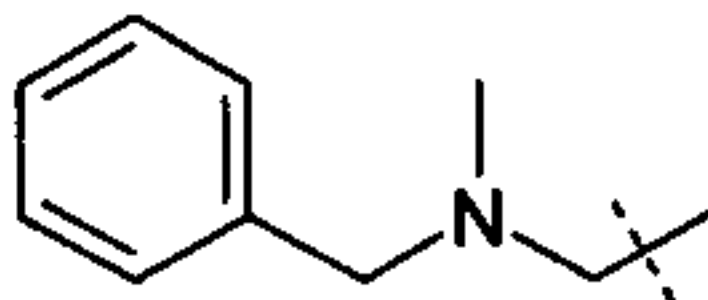
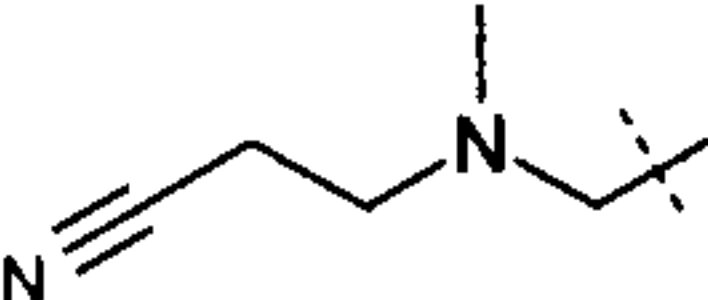
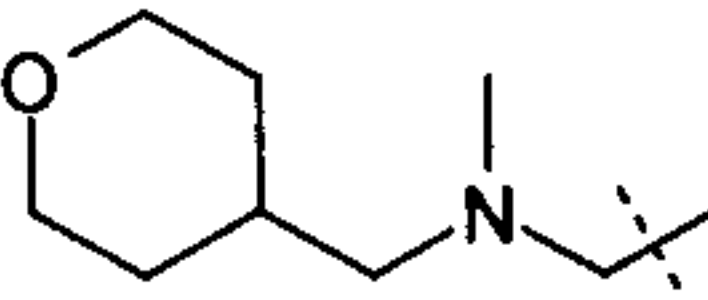
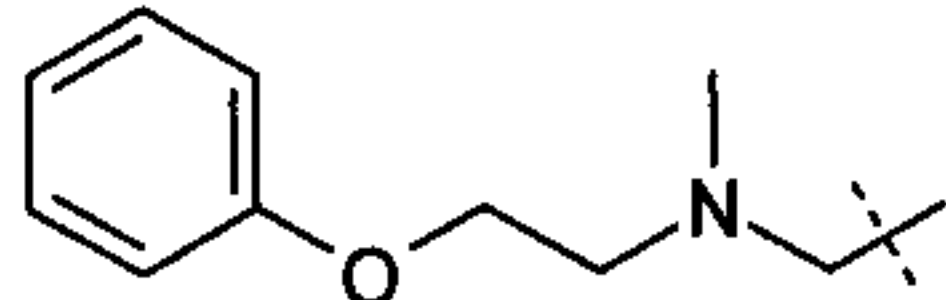
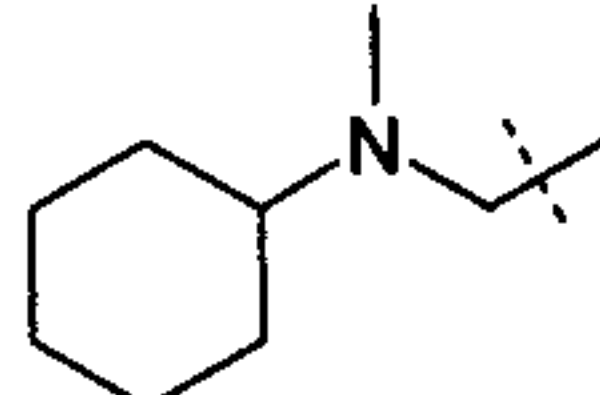
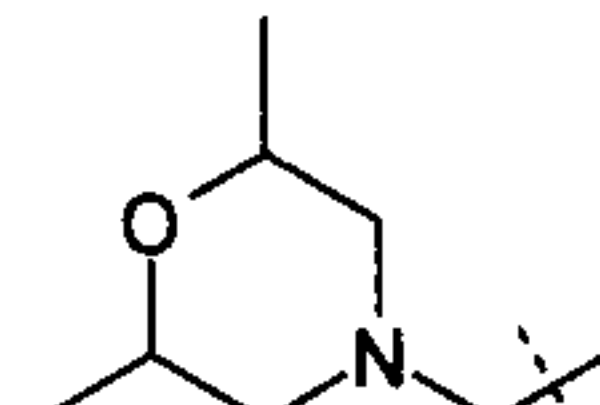
6.97		H	Me
6.98		H	Me
6.99		H	Me
6.100		H	Me
6.101		H	Me
6.102		H	Me
6.103		H	Me
6.104		H	Me
6.105		H	Me
6.106		H	Me
6.107		H	Me
6.108		H	Me
6.109		H	Me
6.110		H	Me
6.111		H	Me

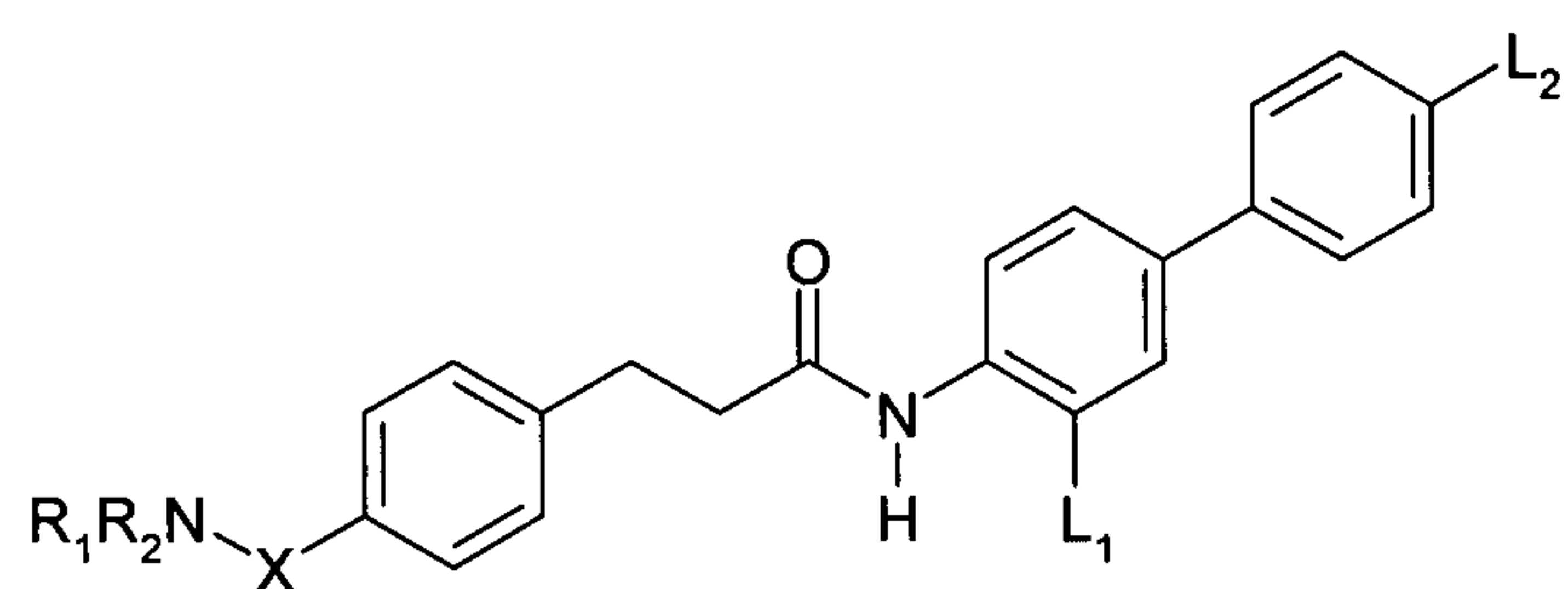
6.112		H	Me
6.113		H	Me
6.114		H	Me
6.115		H	Me
6.116		H	Me
6.117		H	Me
6.118		H	Me
6.119		H	Me
6.120		H	Me

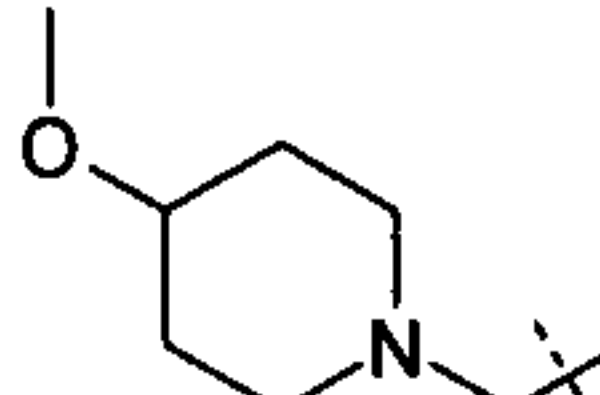
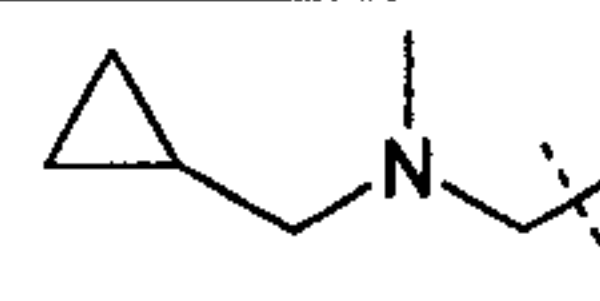
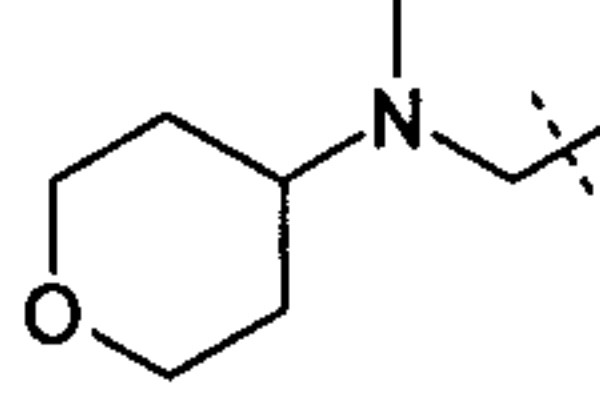
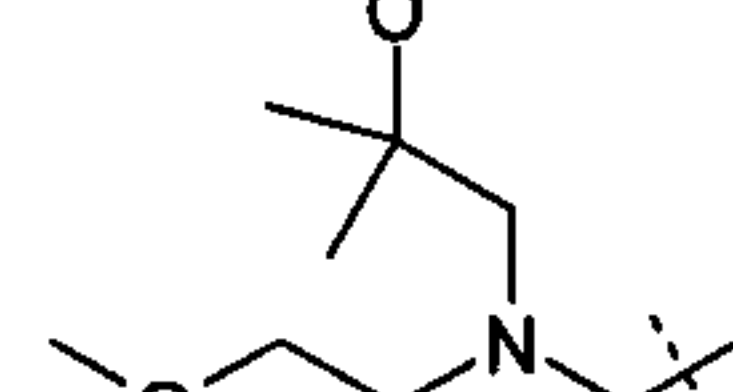
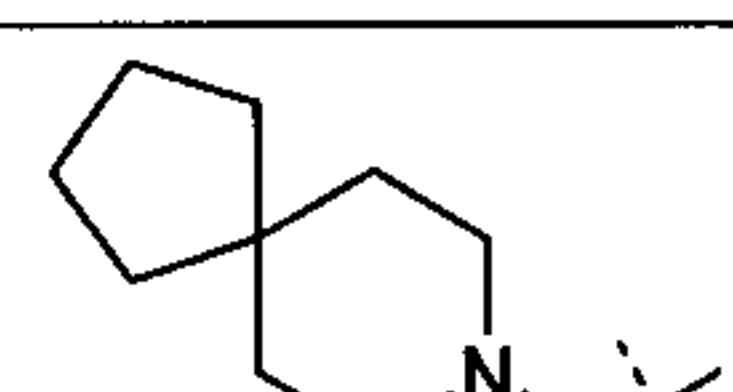


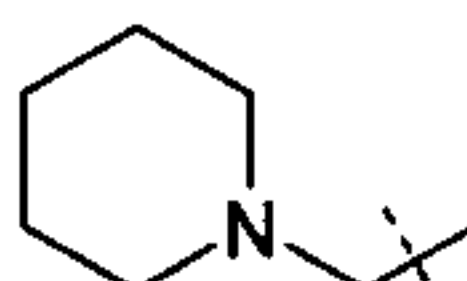
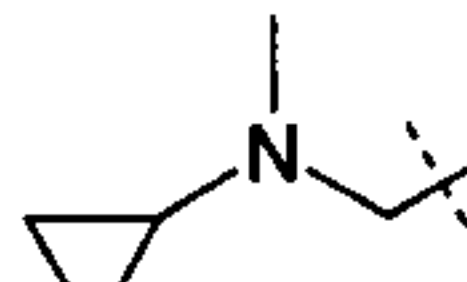
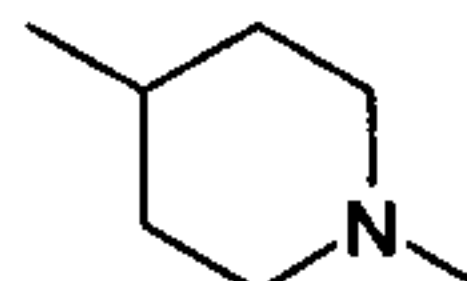
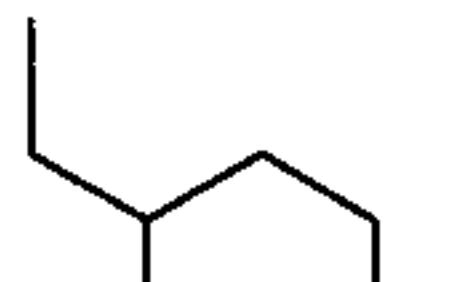
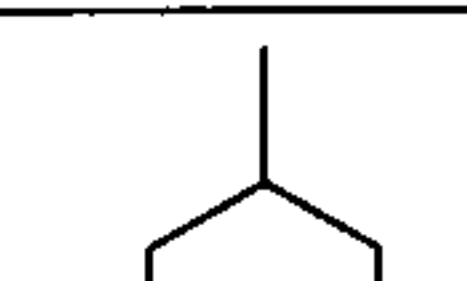
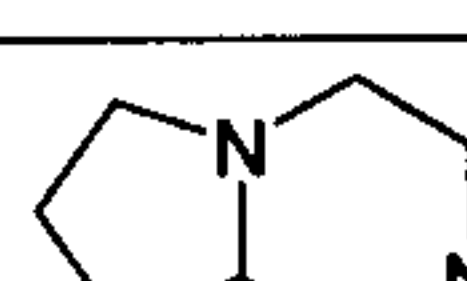
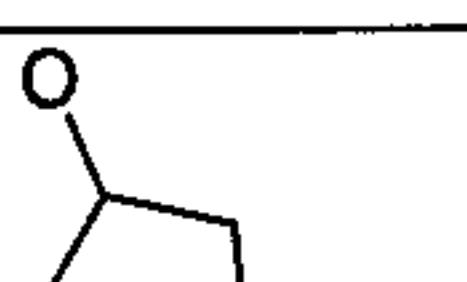
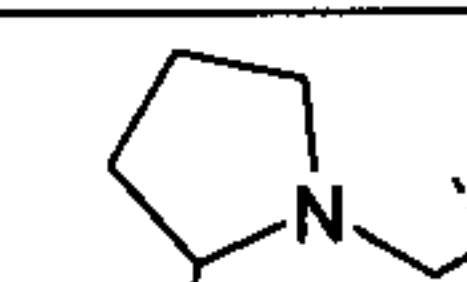
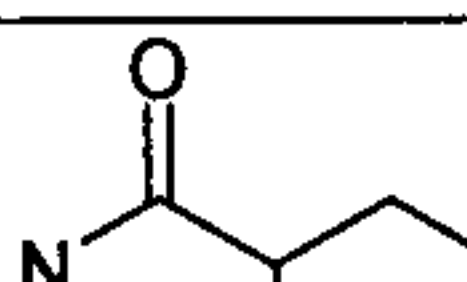
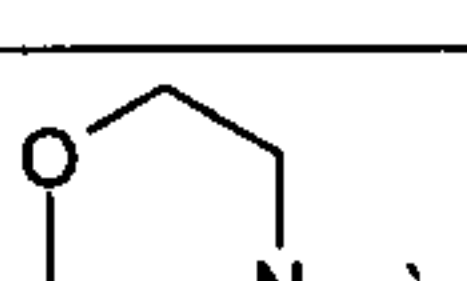
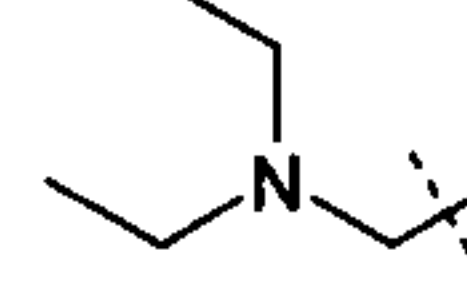
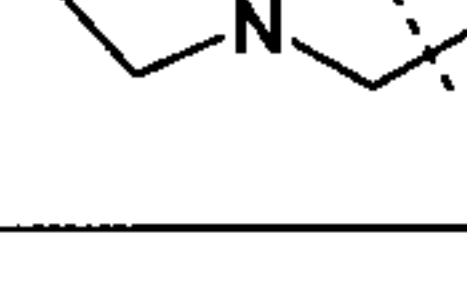
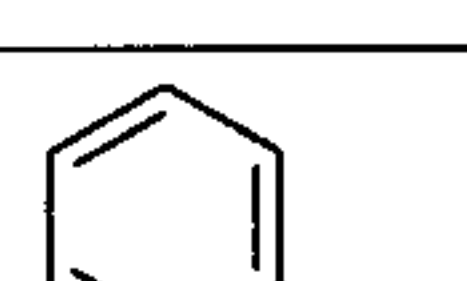
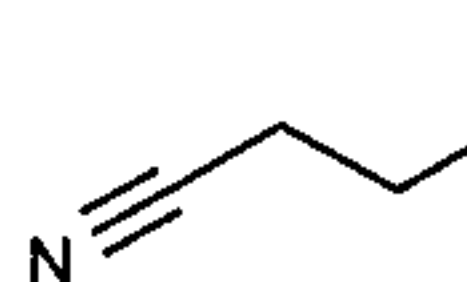
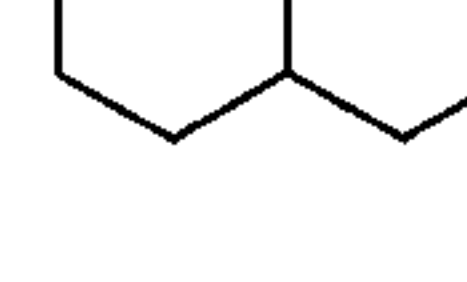
Example	R ₁ R ₂ N-X	L ₁	L ₂
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6.122		H	F
6.123		H	F

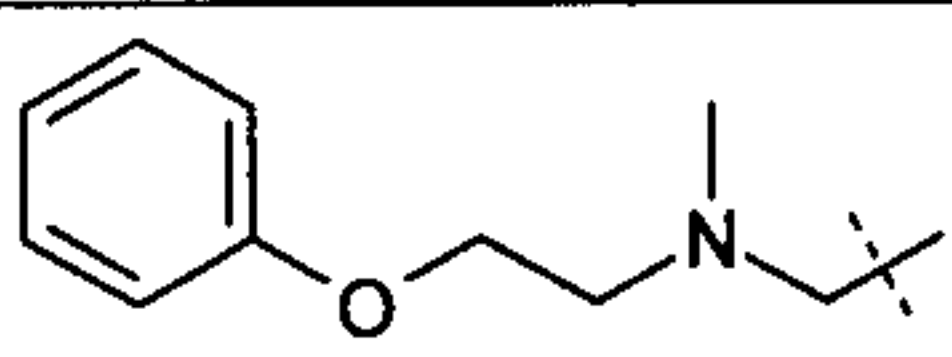
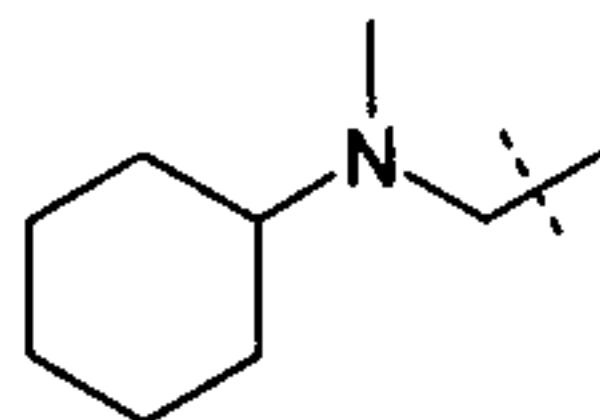
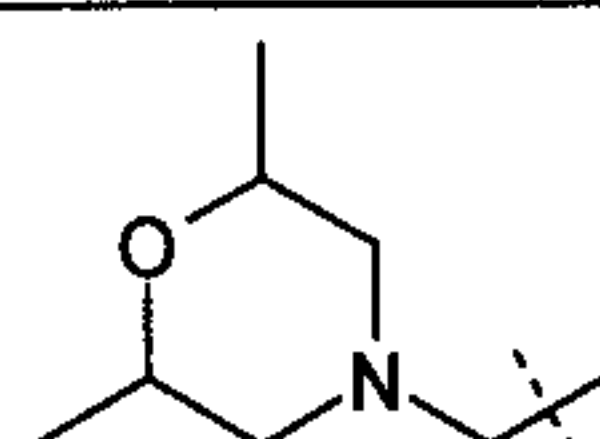
6.124		H	F
6.125		H	F
6.126		H	F
6.127		H	F
6.128		H	F
6.129		H	F
6.130		H	F
6.131		H	F
6.132		H	F
6.133		H	F
6.134		H	F
6.135		H	F
6.136		H	F
6.137		H	F
6.138		H	F

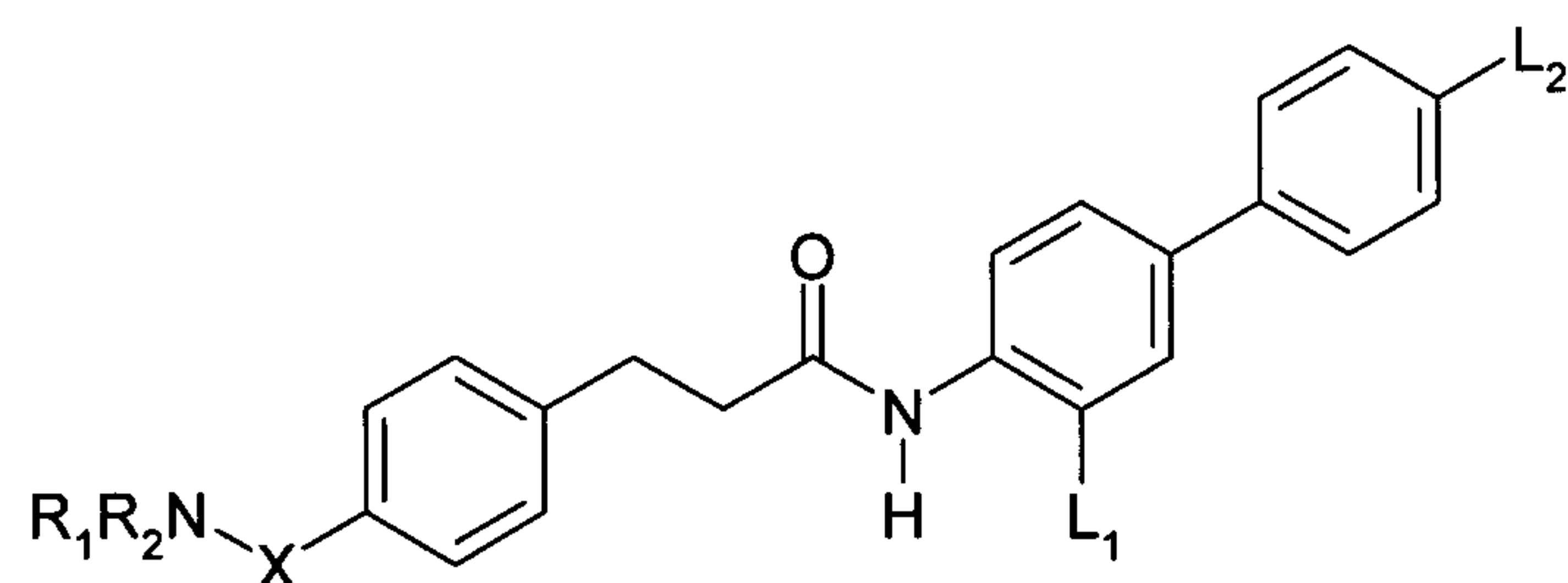
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6.140		H	F
6.141		H	F
6.142		H	F
6.143		H	F
6.144		H	F

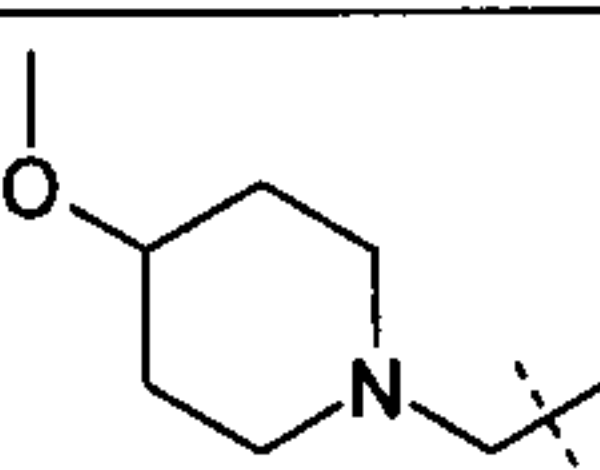
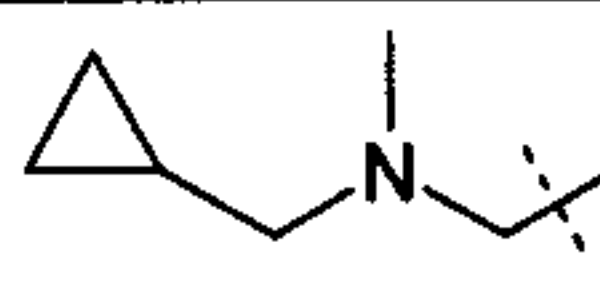
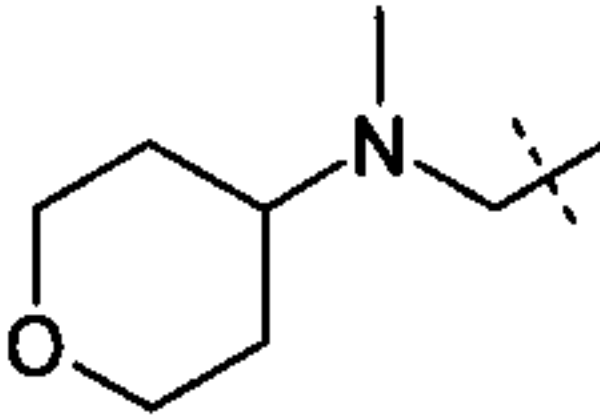
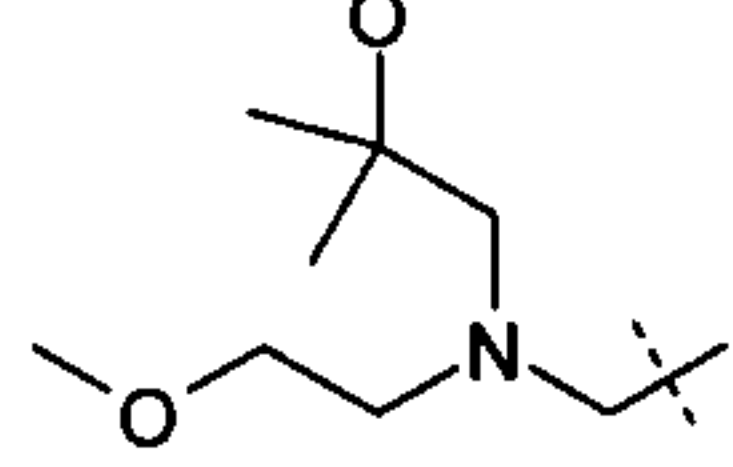
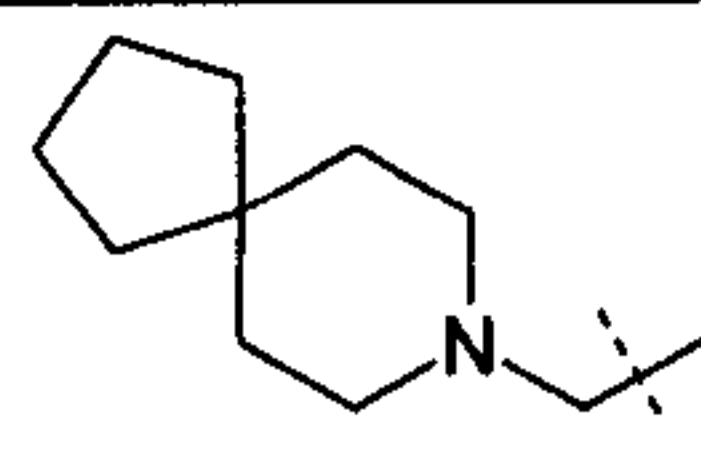
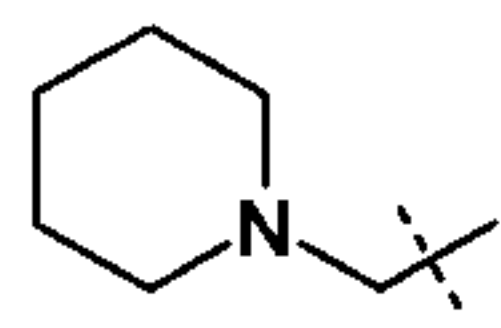
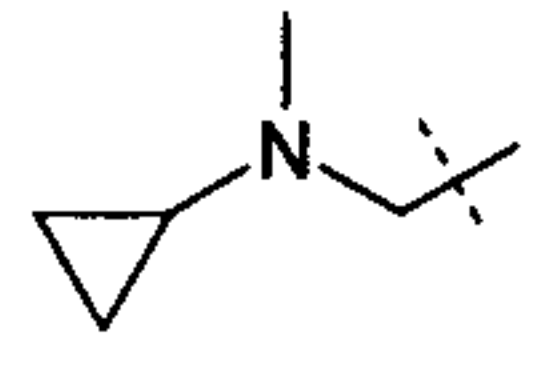
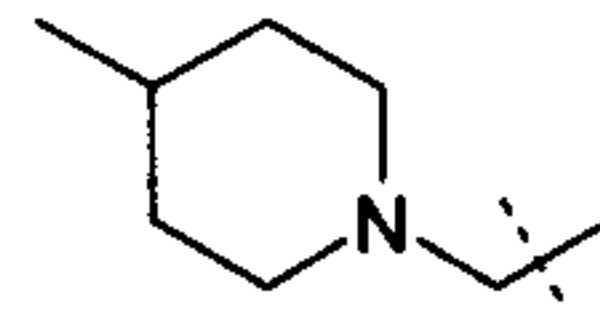


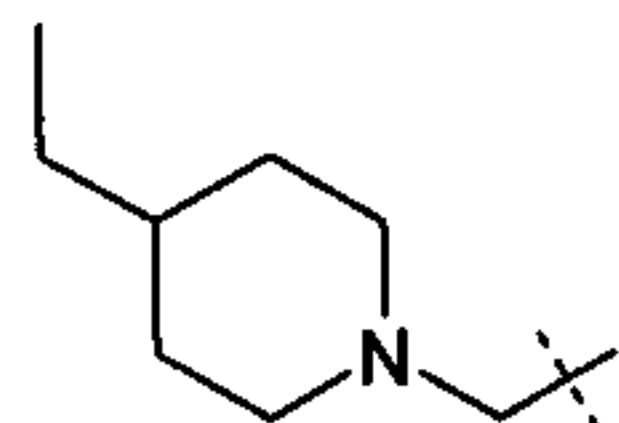
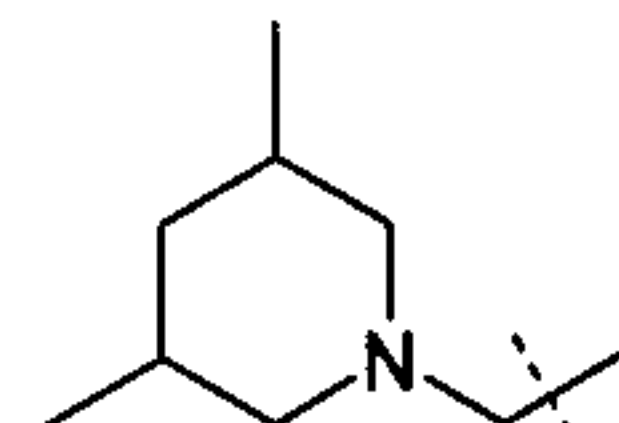
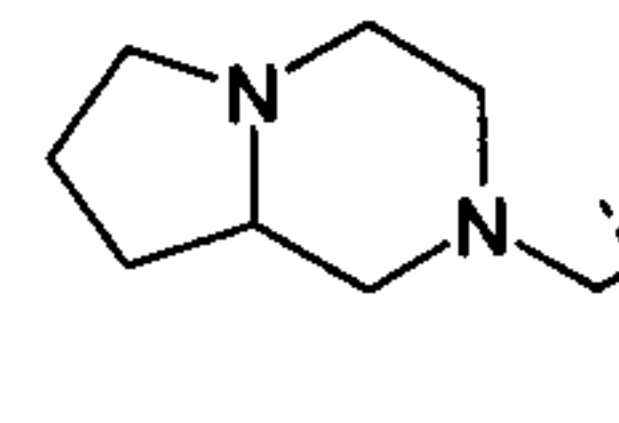
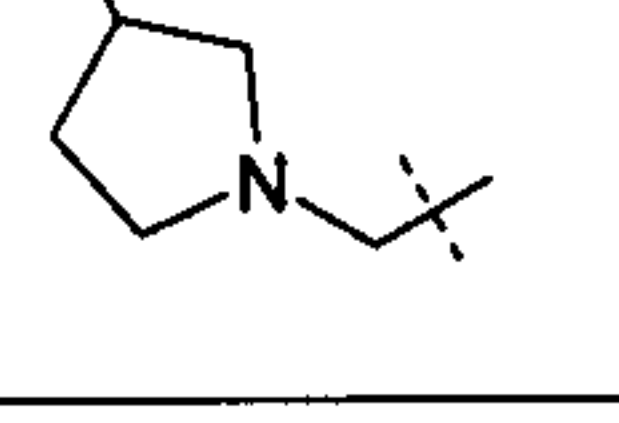
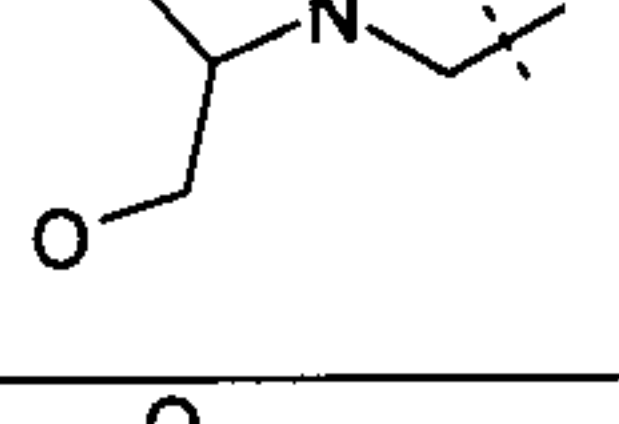
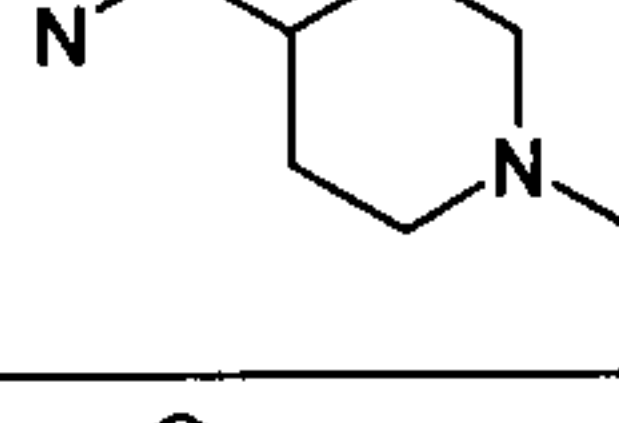
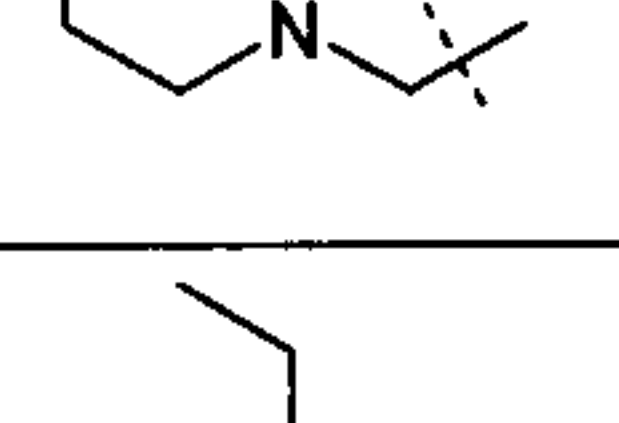
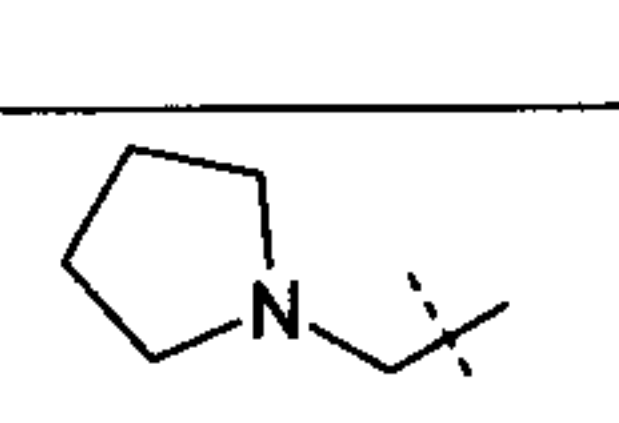
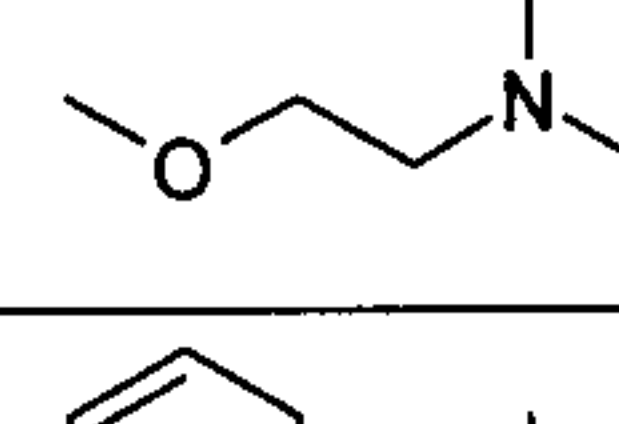
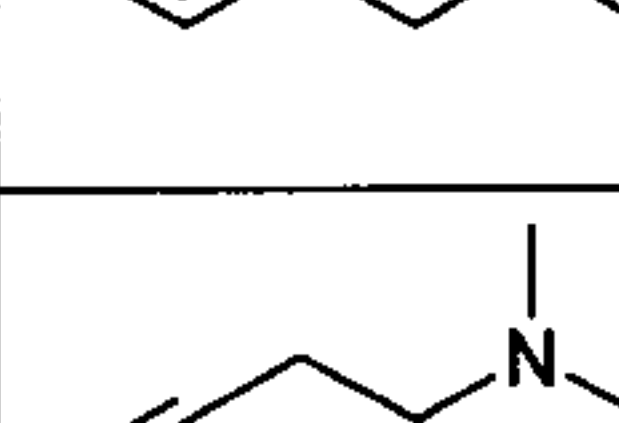
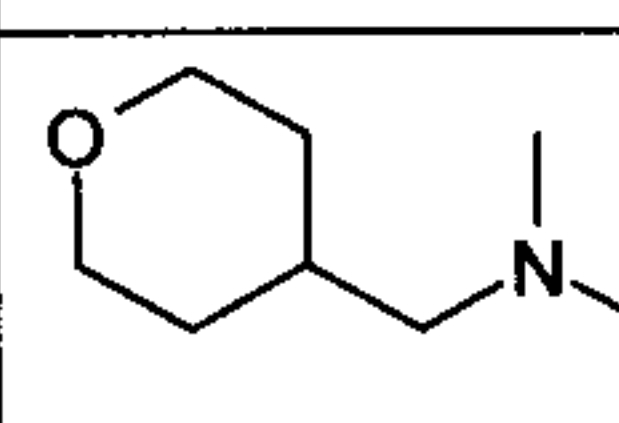
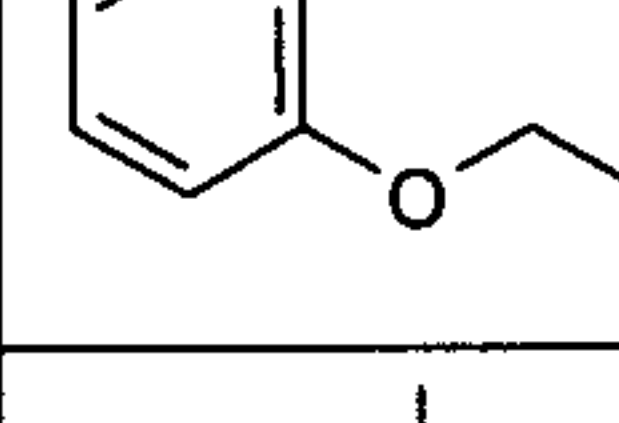
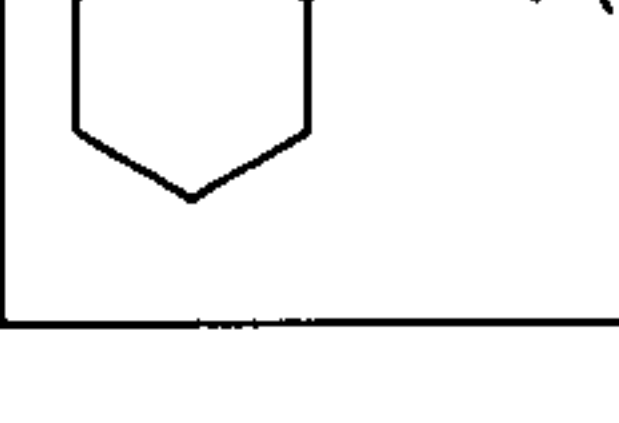
Example	R ₁ R ₂ N-X	L ₁	L ₂
6.145		F	CF ₃
6.146		F	CF ₃
6.147		F	CF ₃
6.148		F	CF ₃
6.149		F	CF ₃

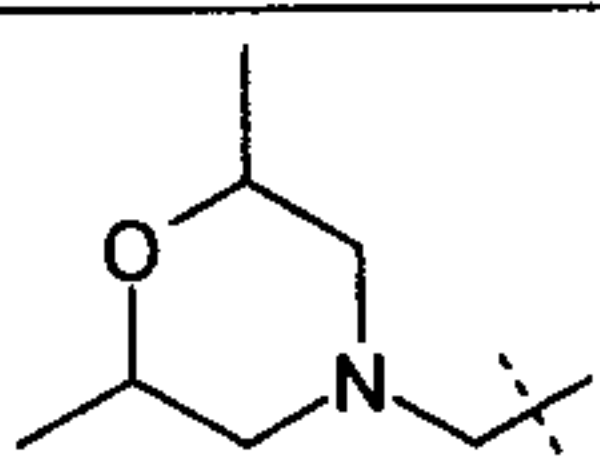
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6.151		F	CF ₃
6.152		F	CF ₃
6.153		F	CF ₃
6.154		F	CF ₃
6.155		F	CF ₃
6.156		F	CF ₃
6.157		F	CF ₃
6.158		F	CF ₃
6.159		F	CF ₃
6.160		F	CF ₃
6.161		F	CF ₃
6.162		F	CF ₃
6.163		F	CF ₃
6.164		F	CF ₃
6.165		F	CF ₃

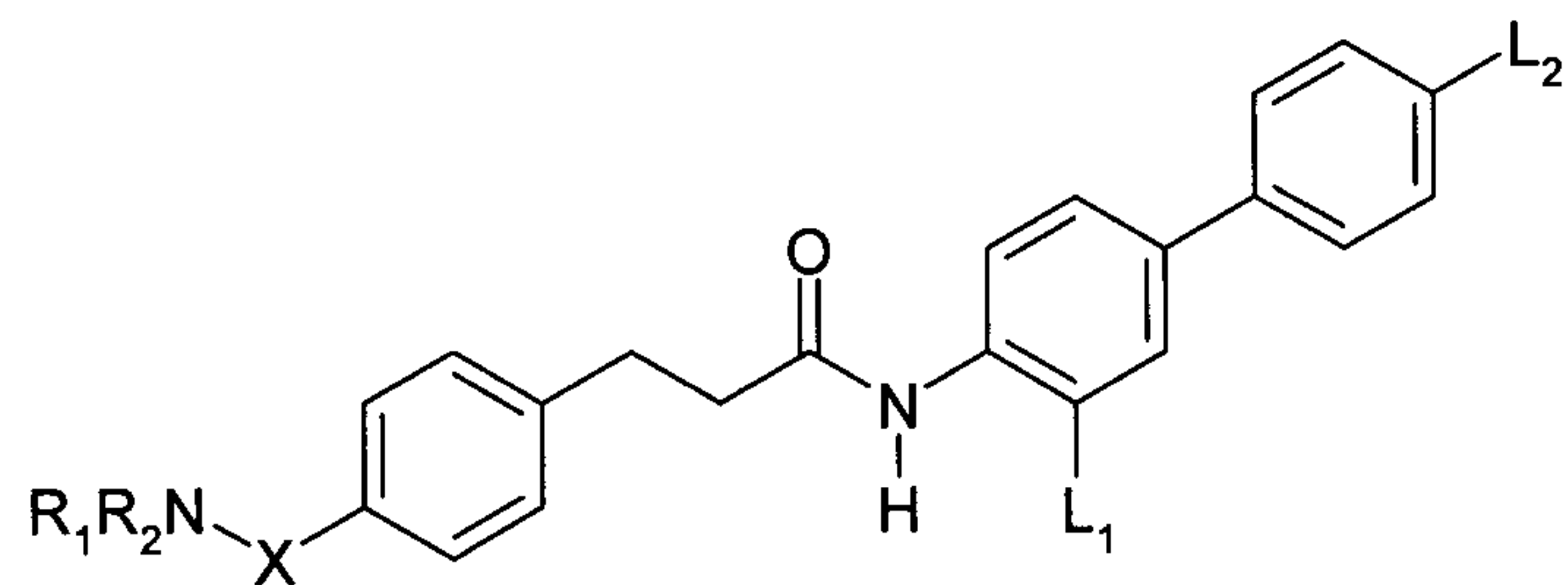
6.166		F	CF ₃
6.167		F	CF ₃
6.168		F	CF ₃

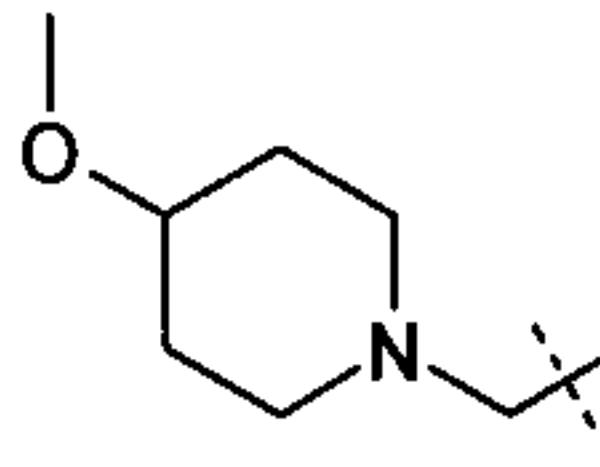
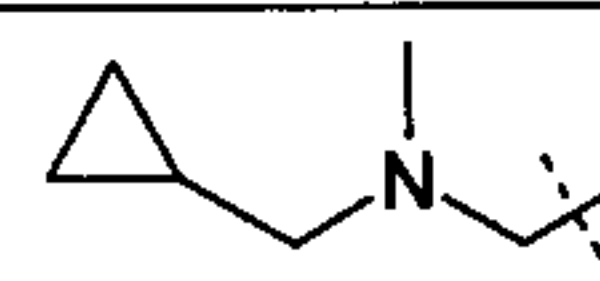
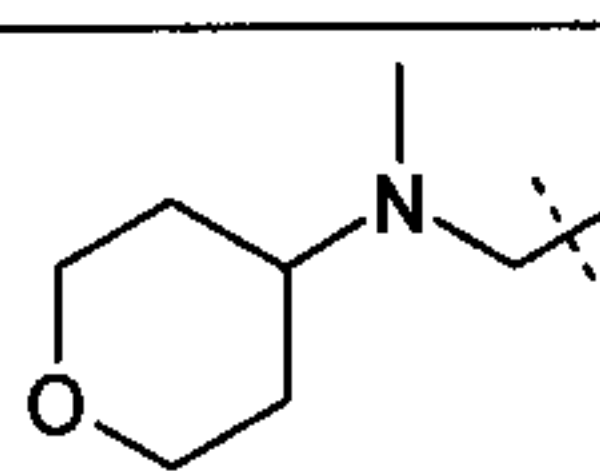
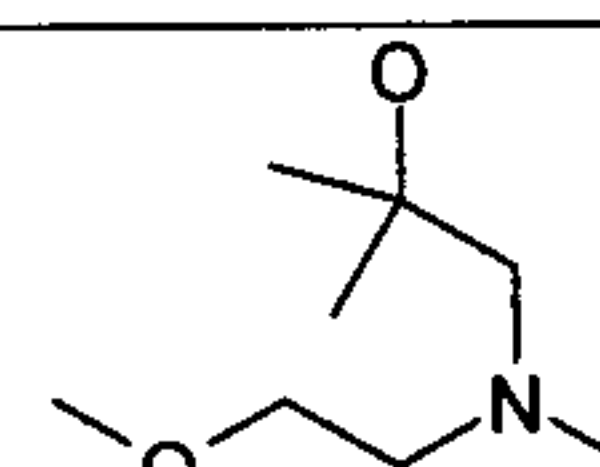
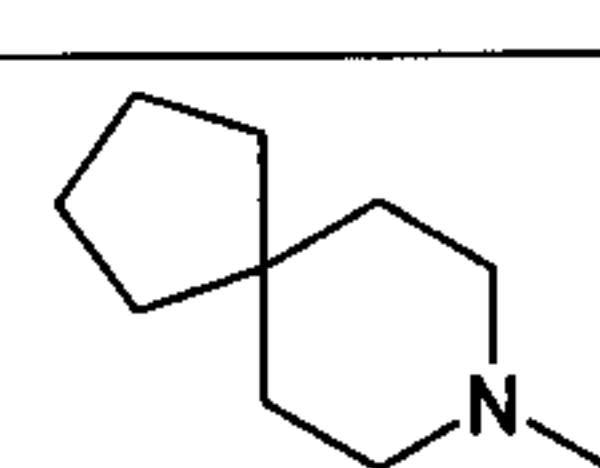
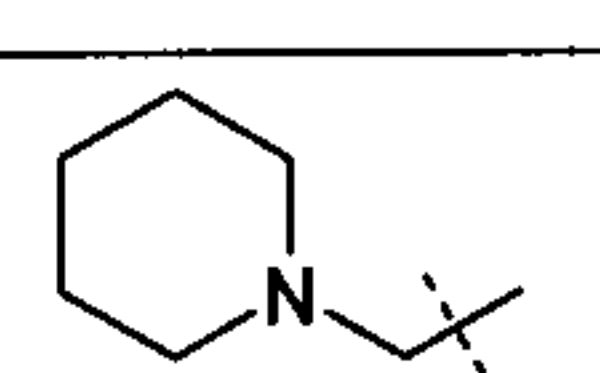
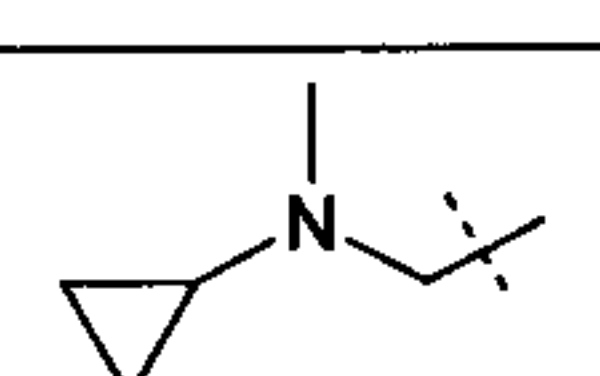
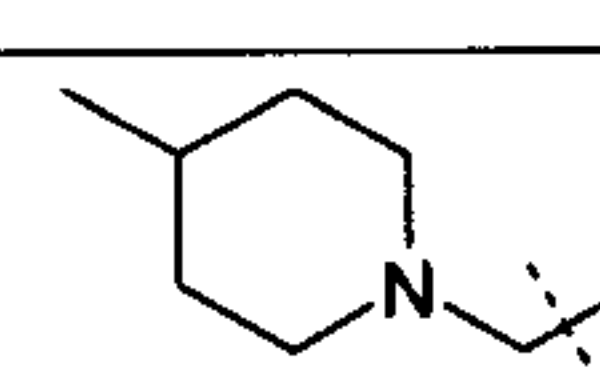
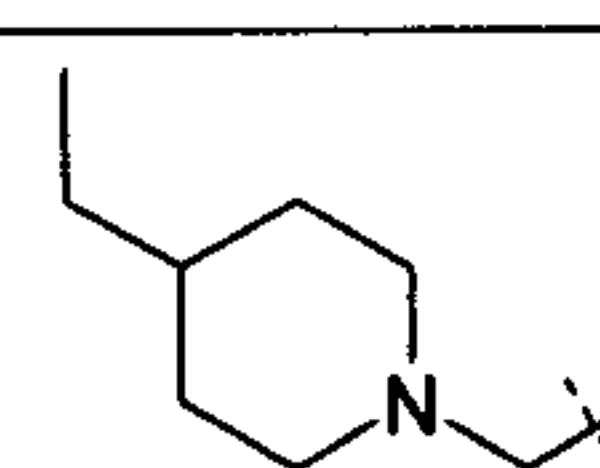
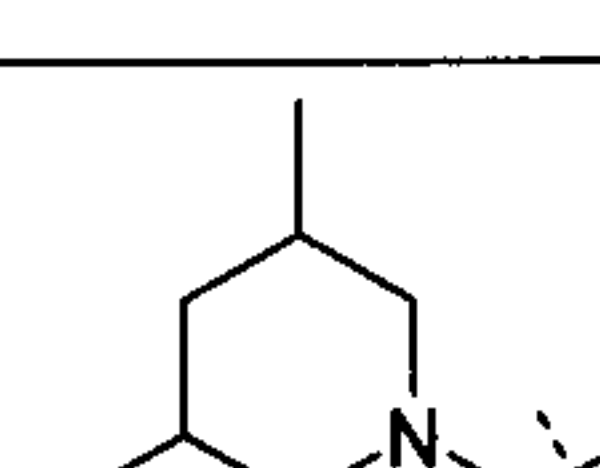


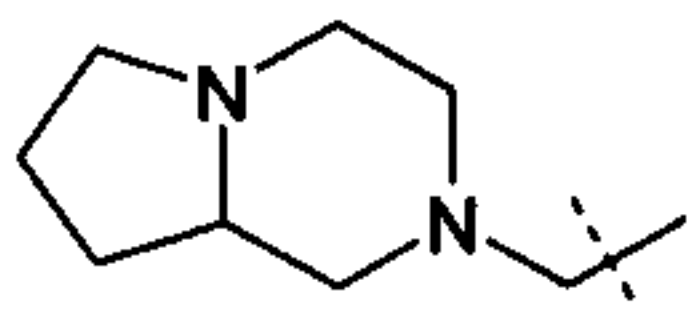
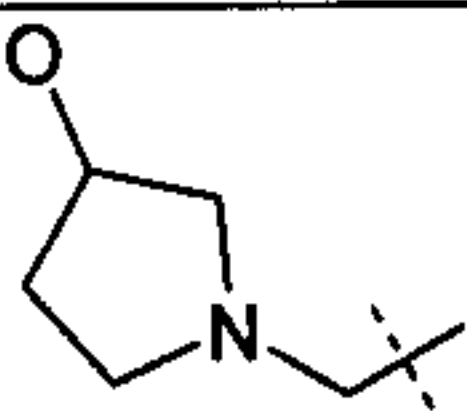
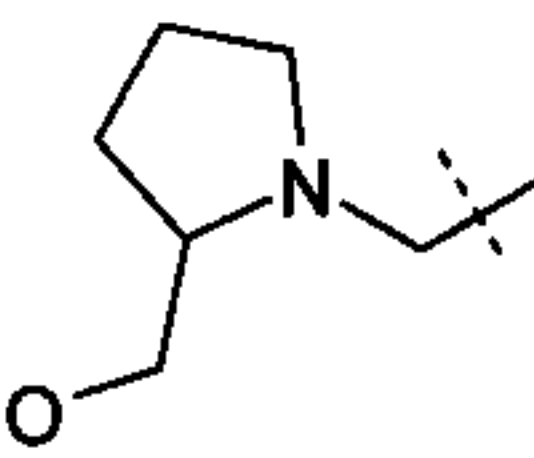
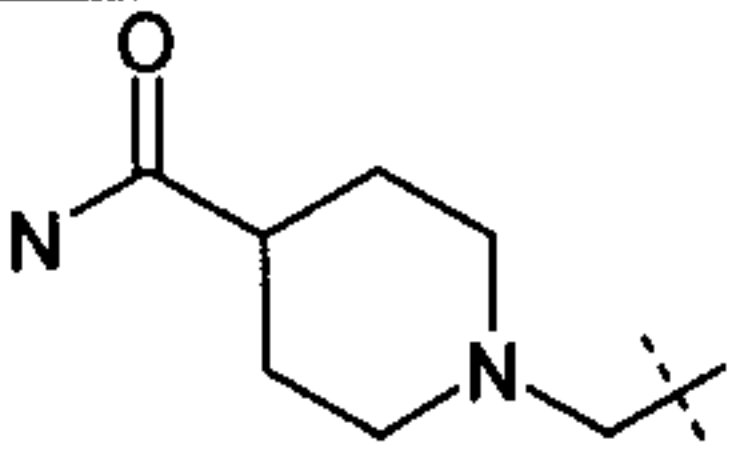
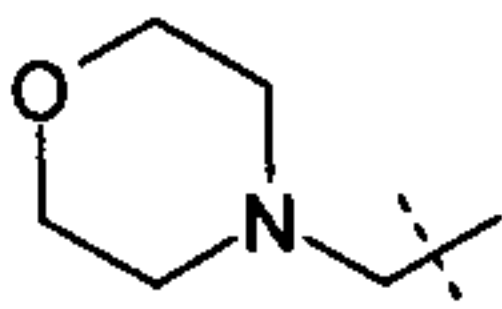
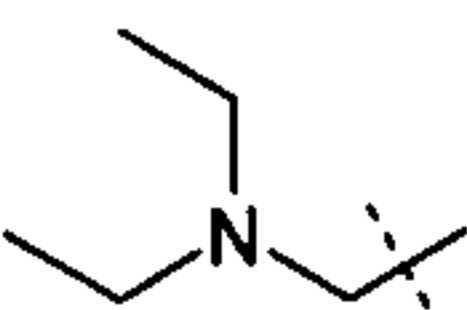
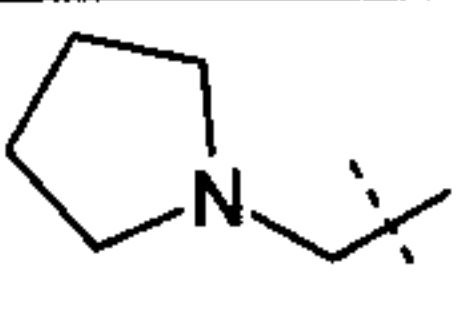
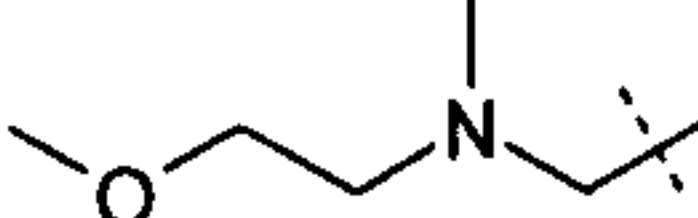
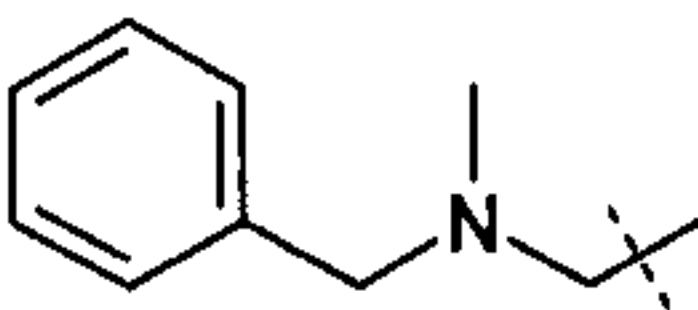
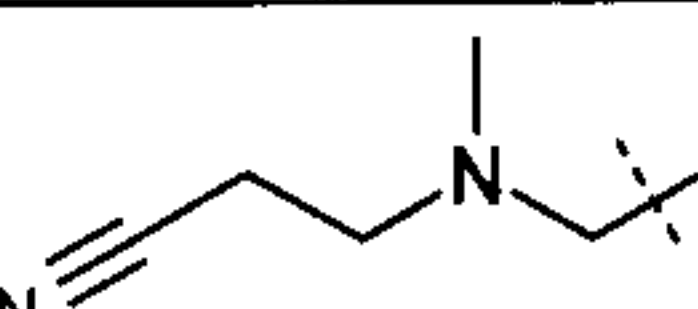
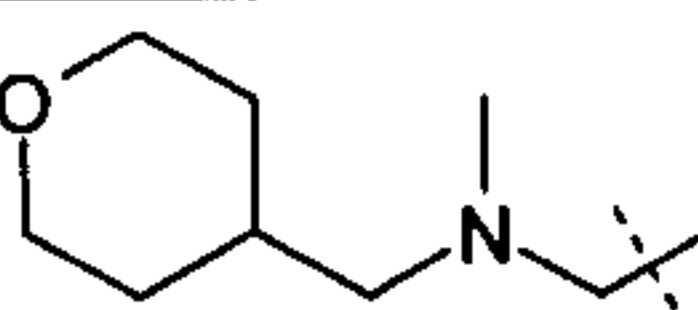
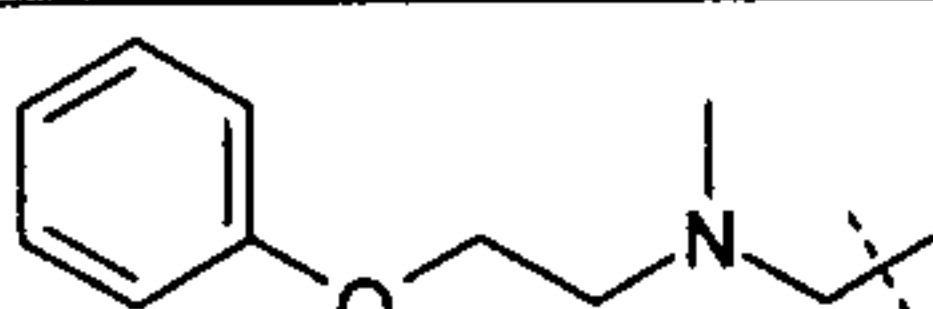
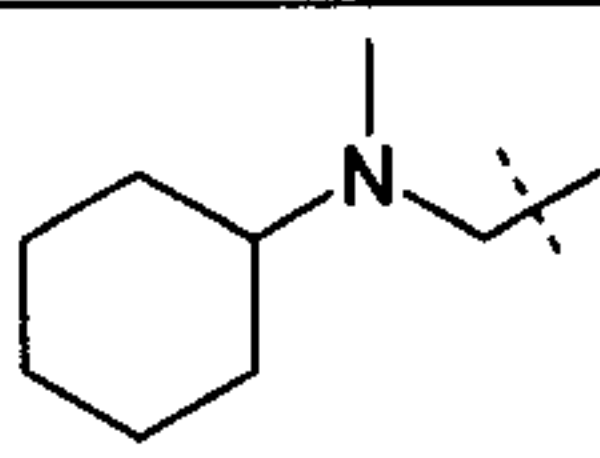
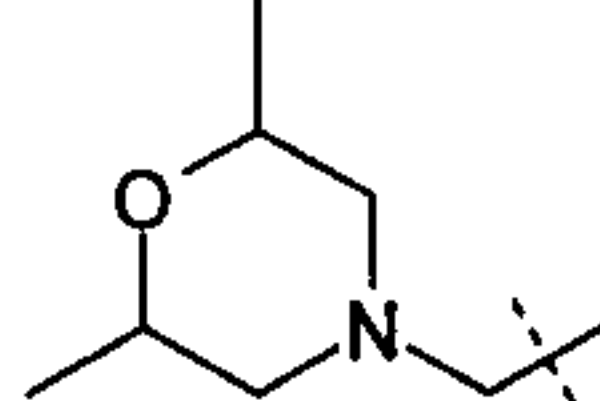
Example	R ₁ R ₂ N-X	L ₁	L ₂
6.169		F	Me
6.170		F	Me
6.171		F	Me
6.172		F	Me
6.173		F	Me
6.174		F	Me
6.175		F	Me
6.176		F	Me

6.177		F	Me
6.178		F	Me
6.179		F	Me
6.180		F	Me
6.181		F	Me
6.182		F	Me
6.183		F	Me
6.184		F	Me
6.185		F	Me
6.186		F	Me
6.187		F	Me
6.188		F	Me
6.189		F	Me
6.190		F	Me
6.191		F	Me

6.192		F	Me

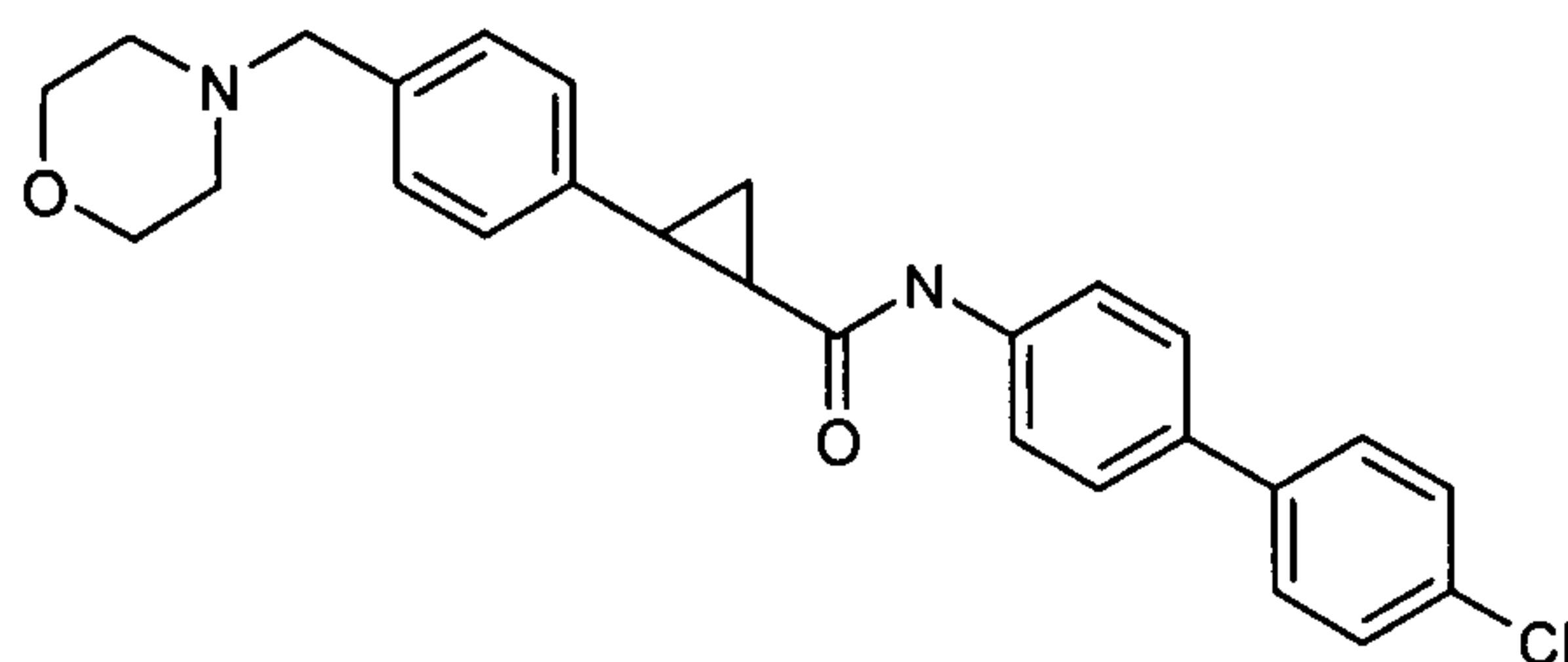


Example	R_1R_2N-X	L_1	L_2
6.193		F	F
6.194		F	F
6.195		F	F
6.196		F	F
6.197		F	F
6.198		F	F
6.199		F	F
6.200		F	F
6.201		F	F
6.202		F	F

6.203		F	F
6.204		F	F
6.205		F	F
6.206		F	F
6.207		F	F
6.208		F	F
6.209		F	F
6.210		F	F
6.211		F	F
6.212		F	F
6.213		F	F
6.214		F	F
6.215		F	F
6.216		F	F

Example 6.217:

2-(4-morpholin-4-ylmethyl-phenyl)-cyclopropanecarboxylic acid (4'-chloro-biphenyl-4-yl)-amide



Preparation of diazomethane: 0.15 g (1.48 mmol) N-nitroso-N-methylurea are added
5 with manual shaking to 10 ml diethyl ether, over a lower layer of 3 ml of 40%
potassium hydroxide solution, at 5 to 0°C. The reaction mixture is left to stand for ten
minutes and then the yellow ether solution is decanted off and dried over potassium
hydroxide.

The yellow diazomethane solution prepared is slowly added dropwise at 0°C to a
10 suspension of 80 mg (0.19 mmol) (E)-N-(4'-chloro-biphenyl-4-yl)-3-(4-morpholin-4-
ylmethyl-phenyl)-acrylamide (for preparation see 6.4) and 202 mg (0.001 mmol)
palladium(II)acetate in 20 ml diethyl ether. The dark reaction mixture is stirred for 30
min. Then the reaction mixture is mixed twice with double the amount of a
diazomethane solution. After the reaction has ended 10 ml glacial acetic acid are
15 added dropwise to the suspension and extracted several times with a sodium
hydrogen carbonate solution. The organic phase is dried over sodium sulphate, the
desiccant is filtered off and the filtrate is evaporated down. Further purification is
carried out by column chromatography on silica gel (eluant:
dichloromethane/ethanol/ammonia 30:1:0.1)

20 Yield: 32 mg (82.6 % of theoretical)

$C_{27}H_{27}ClN_2O_2$ (M= 446.97)

Melting point: 187-188°C

Calc.: Molecular ion peak (M+H)⁺: 447/449 (Cl)

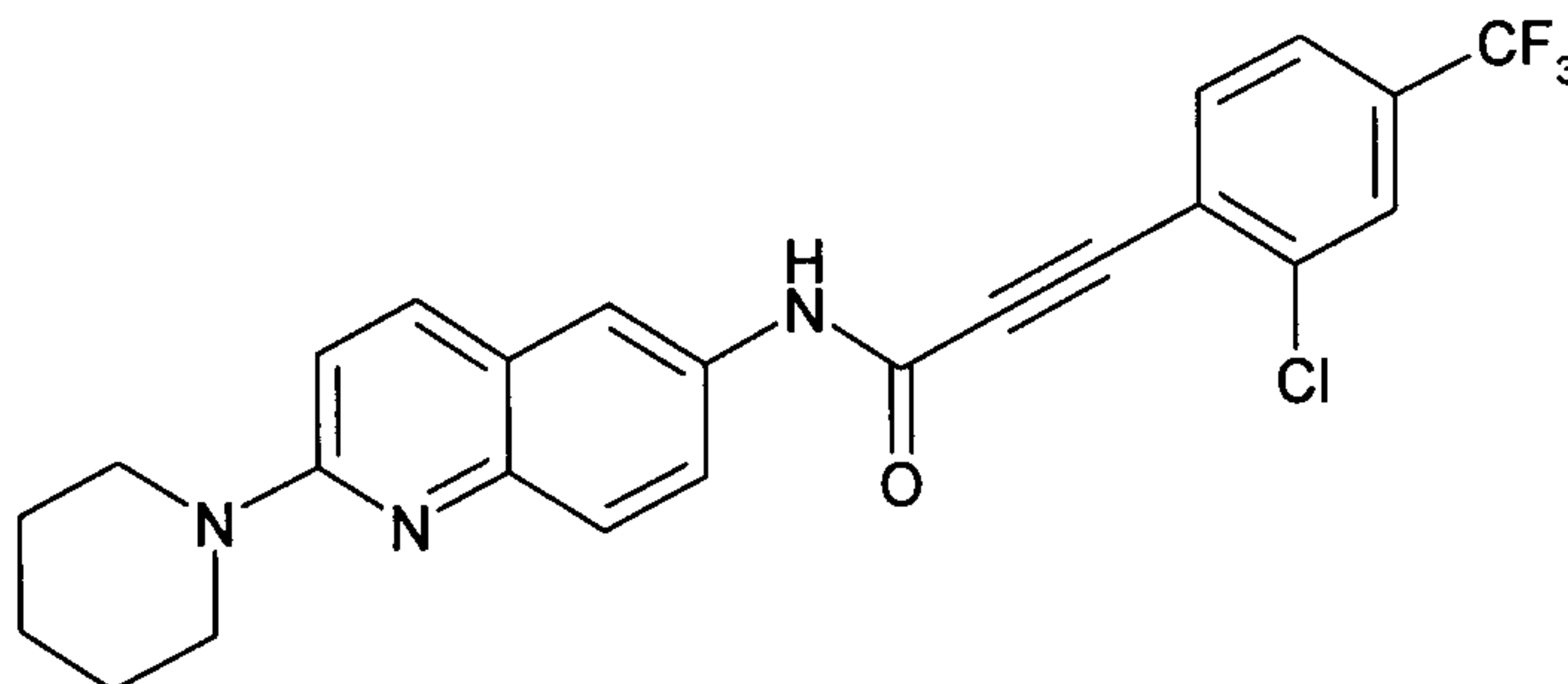
Found: Molecular ion

peak (M+H)⁺: 447/449 (Cl)

25 R_f value: 0.3 (silica gel, dichloromethane/ethanol/ammonia = 20:1:0.1)

Example 7.1:

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-(2-piperidin-1-yl-quinolin-6-yl)-amide



5 7.1.a. 6-amino-2-piperidin-2-yl-quinoline

Prepared analogously to 3.1.b from 6-nitro-2-piperidin-2-yl-quinoline.

Yield: 0.79 g (59.6% of theory)

$C_{14}H_{17}N_3$ (M= 227.31)

Calc.: Molecular ion peak (M+H)⁺: 228

Found: Molecular ion peak (M+H)⁺:

10 228

R_f value: 0.37 (silica gel, dichloromethane/methanol 19:1)

7.1.b. 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-(2-piperidin-1-yl-quinolin-6-yl)-amide

15 Prepared analogously to Example 2.3.f. from (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid and 6-amino-2-piperidin-2-yl-quinoline.

Yield: 170 mg (37.1 % of theory)

Melting point: 176-179°C

$C_{24}H_{19}ClF_3N_3O$ (M= 457.88)

20 Calc.: Molecular ion peak (M+H)⁺: 456/458

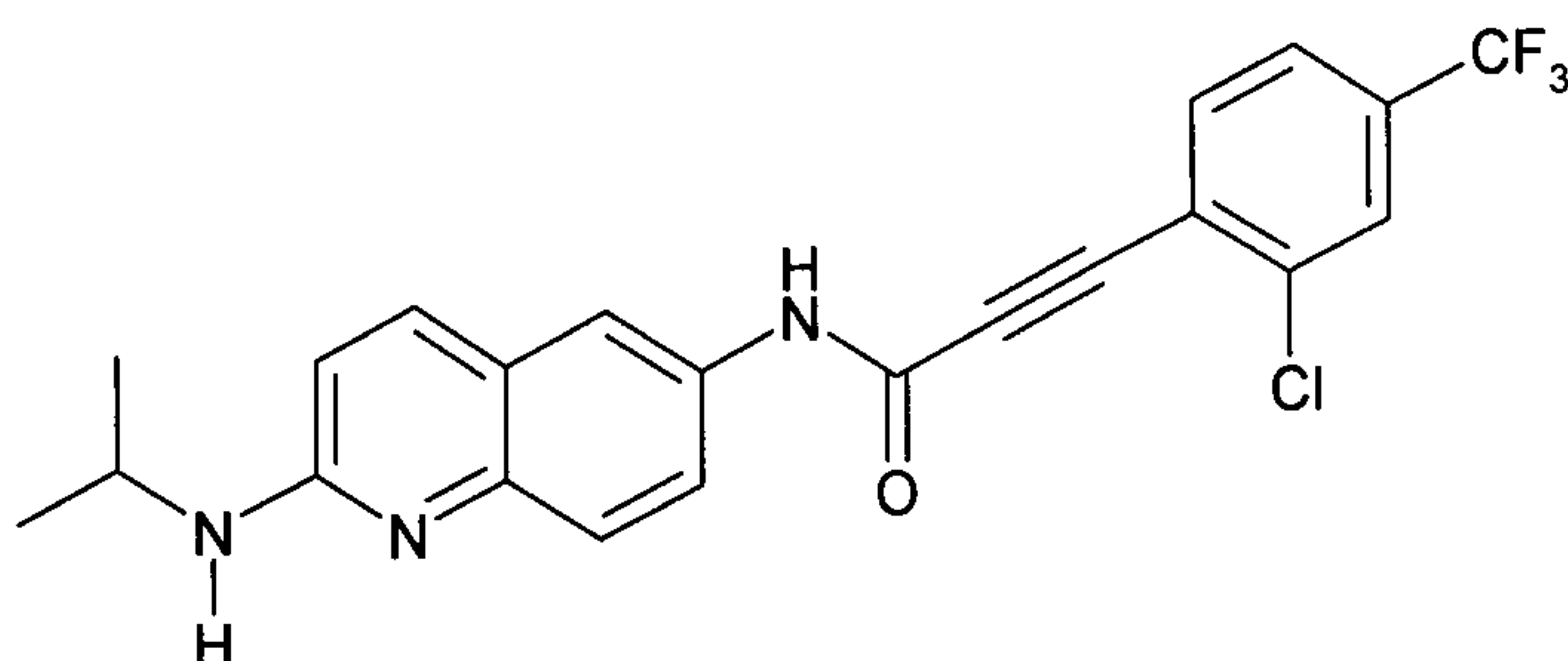
Found: Molecular ion peak

(M+H)⁺: 456/458

R_f value: 0.62 (silica gel, dichloromethane/methanol = 19:1)

25 **Example 7.2:**

3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-(2-isopropylamino-quinolin-6-yl)-amide



7.2.a. isopropyl-(6-nitro-quinolin-2-yl)-amine

2.55 ml (29.96 mmol) isopropylamine are added to a solution of 1.25 g (5.99 mmol) 2-chloro-6-nitro-quinoline in 50 ml of ethanol and the mixture is stirred for 18 hours at ambient temperature. Then the reaction mixture is heated to 65°C in the microwave for two hours. The reaction mixture is then evaporated down, the residue is taken up in 20 ml DMF, combined with 2.55 ml (29.96 mmol) isopropylamine and stirred for 18 hours at ambient temperature. The reaction mixture is evaporated down and the residue is combined with ethyl acetate and water. The organic phase is extracted twice with water. The aqueous phases are extracted twice with ethyl acetate. The combined organic phases are dried over sodium sulphate and the solvent is then removed.

Yield: 0.75 g (54.1% of theory)

$C_{12}H_{13}N_3O_2$ (M= 221.25)

Calc.: Molecular ion peak (M+H)⁺: 232 Found: Molecular ion peak (M+H)⁺: 232

R_f value: 0.48 (silica gel, petroleum ether/ethyl acetate 2:1)

7.2.b. N²-isopropyl-quinoline-2,6-diamine

Prepared analogously to 3.1.b from isopropyl-(6-nitro-quinolin-2-yl)-amine.

Yield: 0.51 g (78.1 % of theory)

$C_{12}H_{15}N_3$ (M= 201.27)

Calc.: Molecular ion peak (M+H)⁺: 202 Found: Molecular ion peak (M+H)⁺: 202

R_f value: 0.25 (silica gel, dichloromethane/methanol 19:1)

7.2.c. 3-(2-chloro-4-trifluoromethyl-phenyl)-propynoic acid-(2-isopropylamino-quinolin-6-yl)-amide

Prepared analogously to Example 2.3.f. from (2-chloro-4-trifluoromethyl-phenyl)-propynoic acid and *N*²-isopropyl-quinoline-2,6-diamine.

Yield: 140 mg (46.3 % of theory)

Melting point: 57-60°C

5 C₂₂H₁₇ClF₃N₃O (M= 431.84)

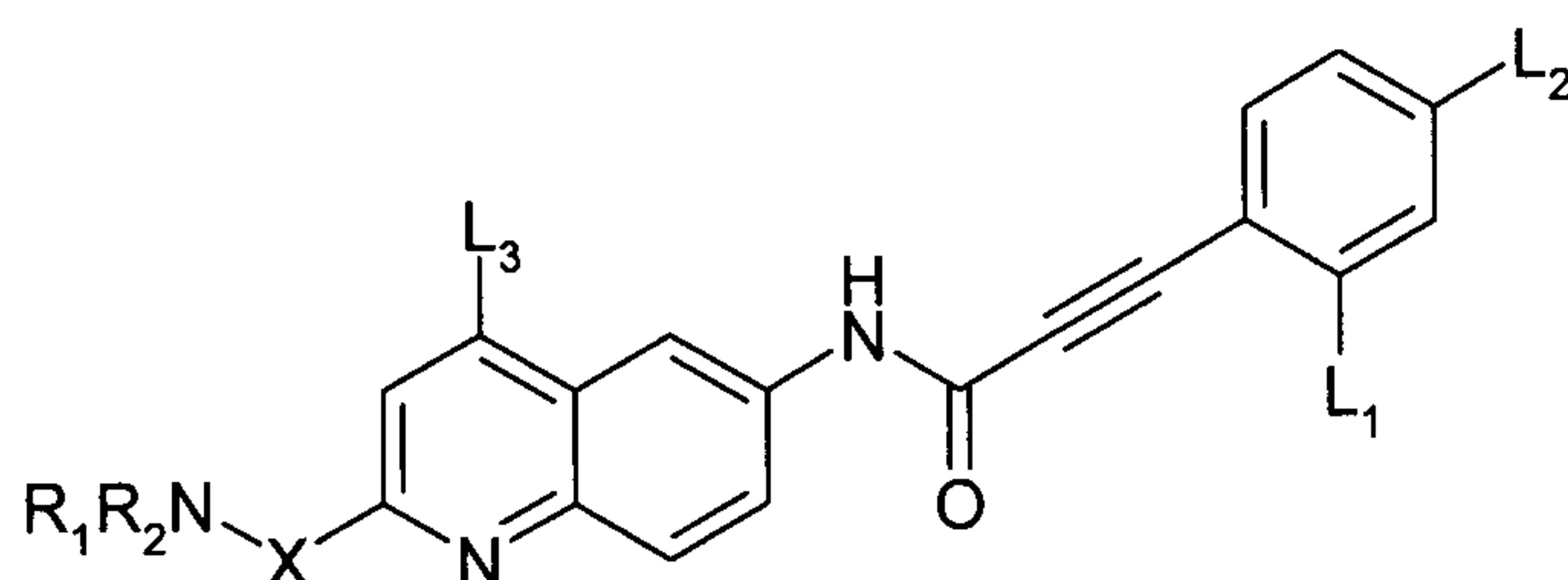
Calc.: Molecular ion peak (M+H)⁺: 432/434

Found: Molecular ion peak

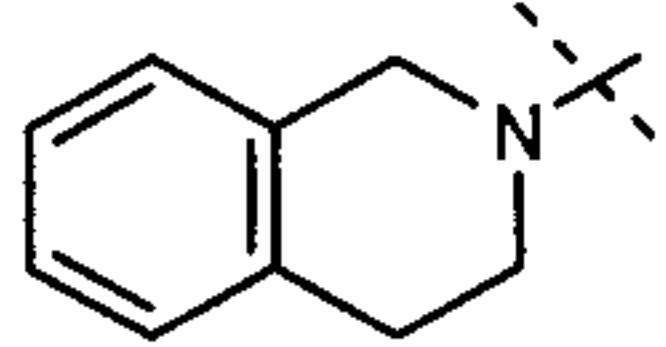
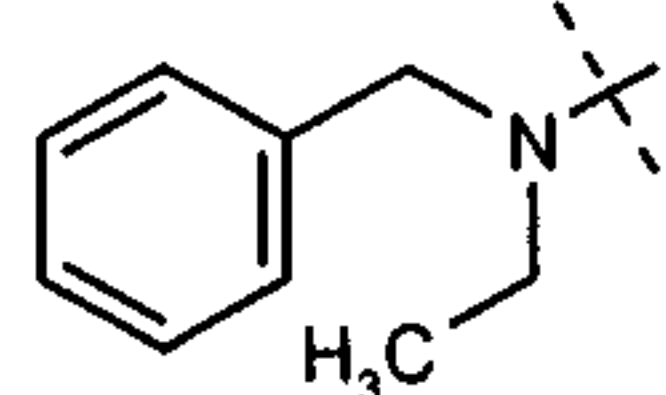
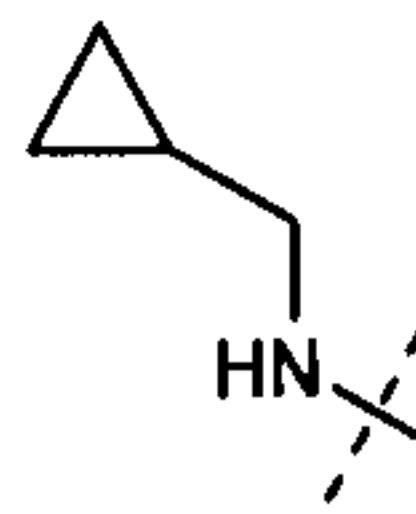
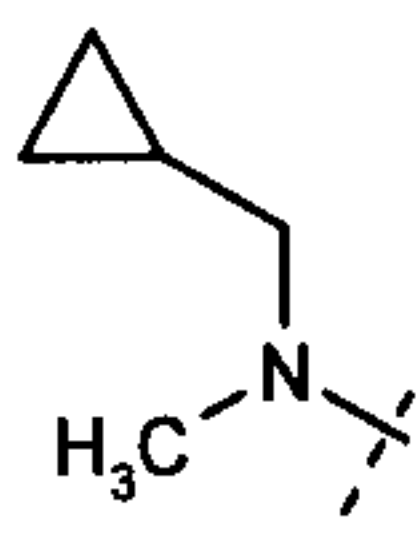
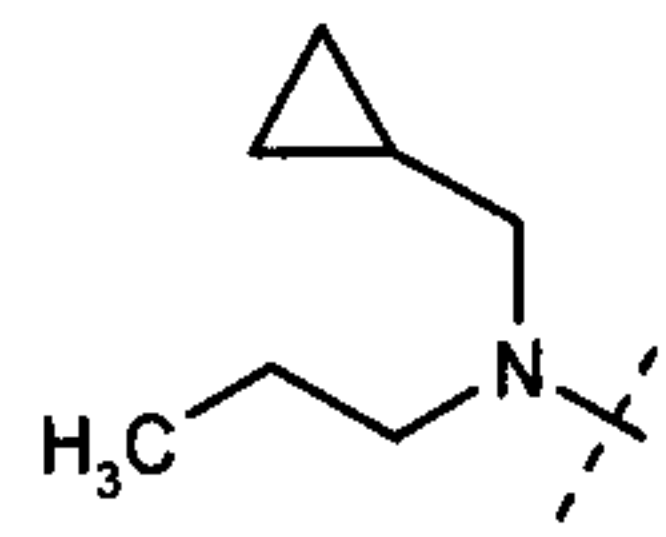
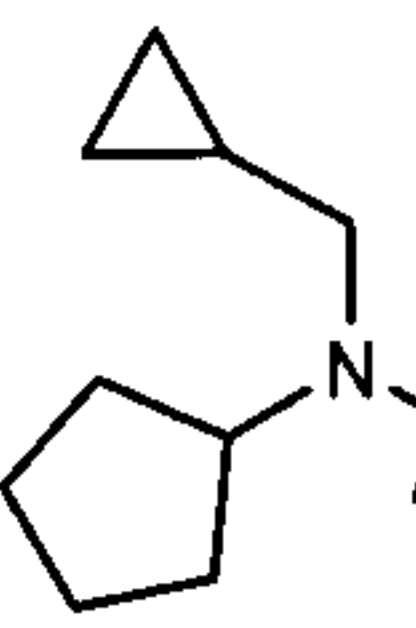
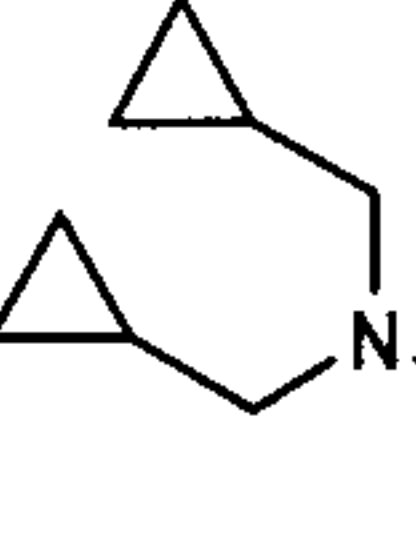
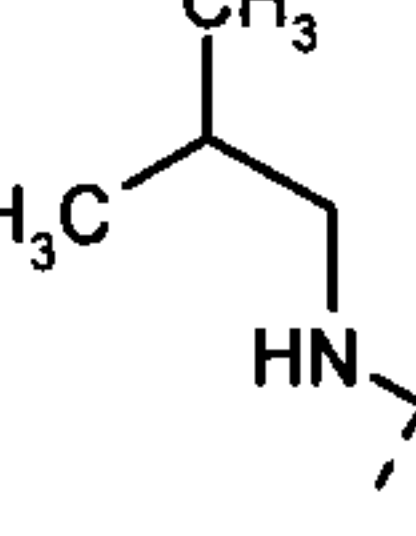
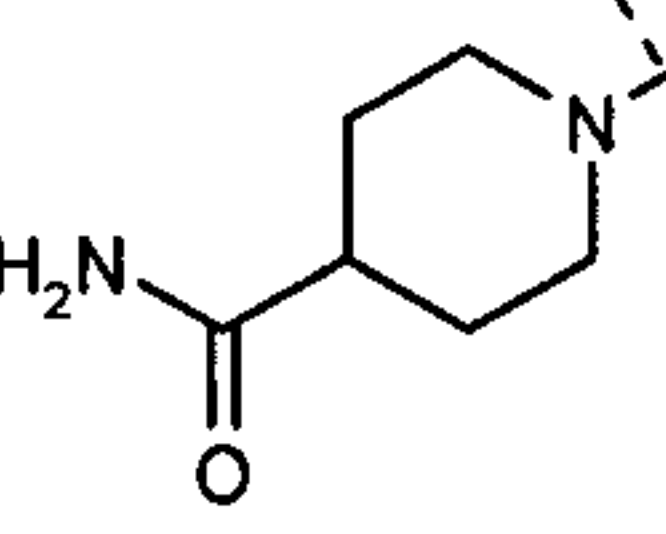
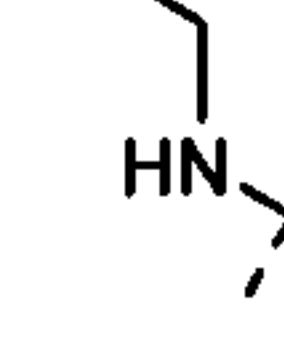
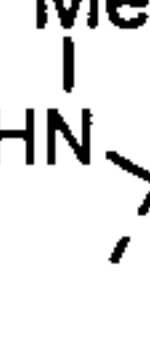
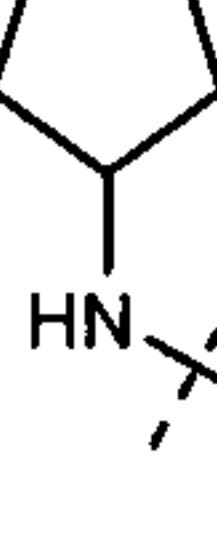
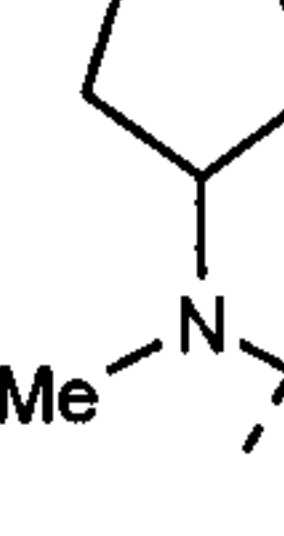
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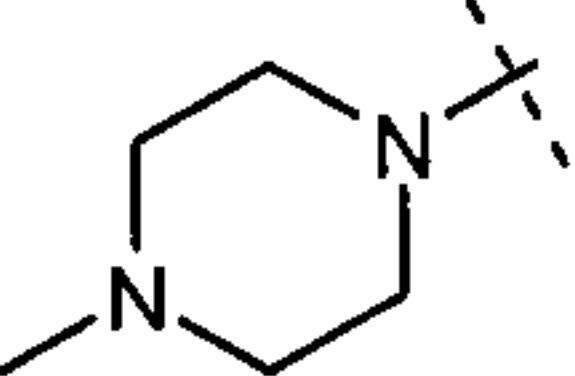
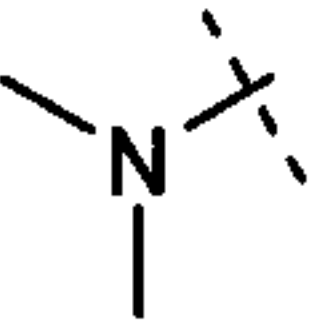
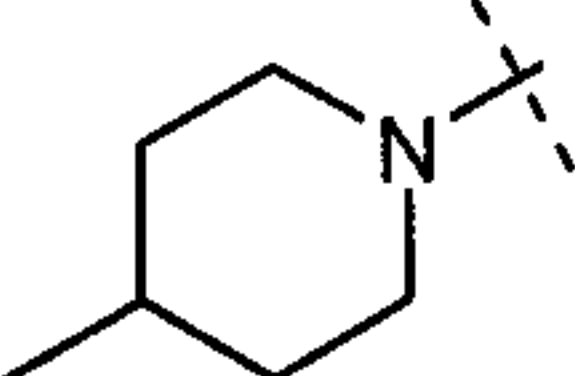
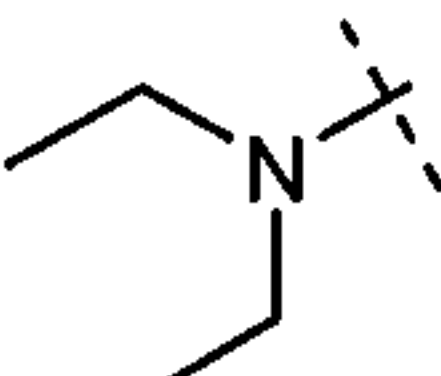
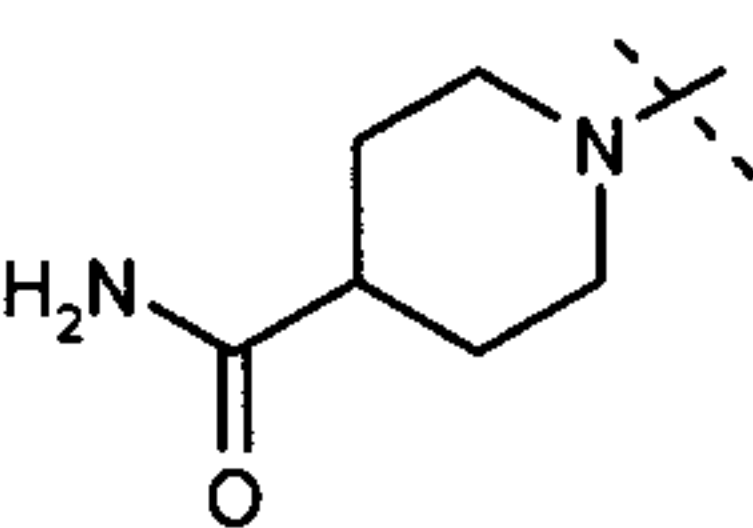
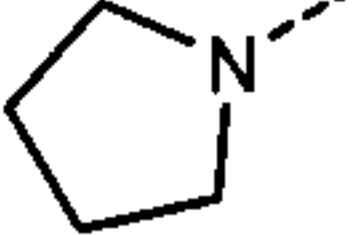
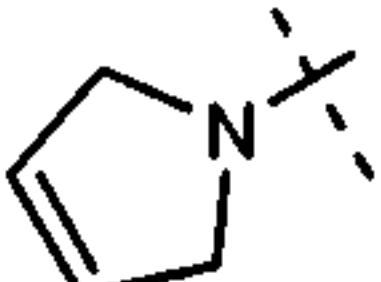
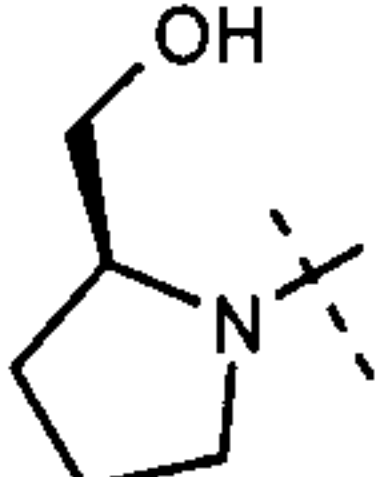
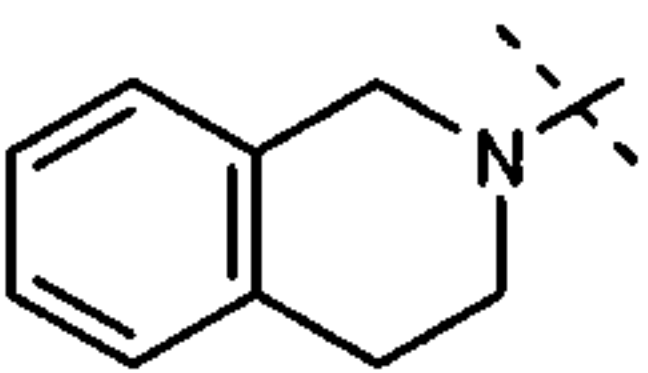
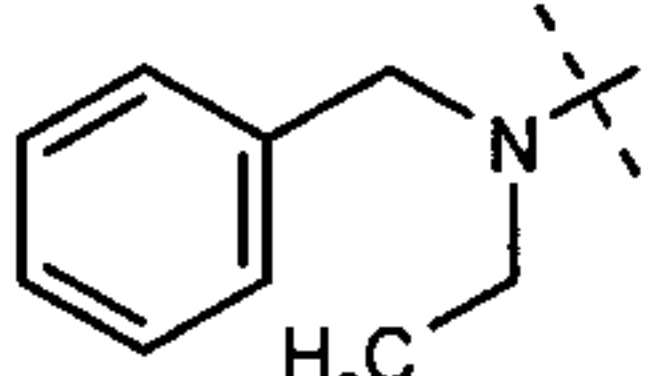
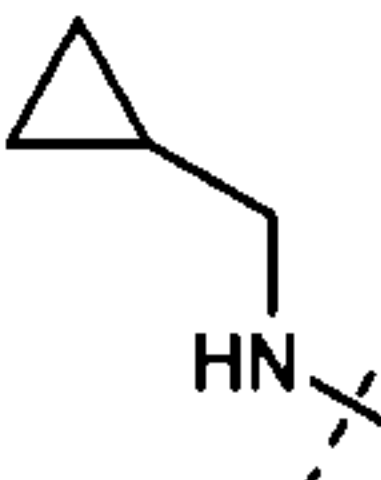
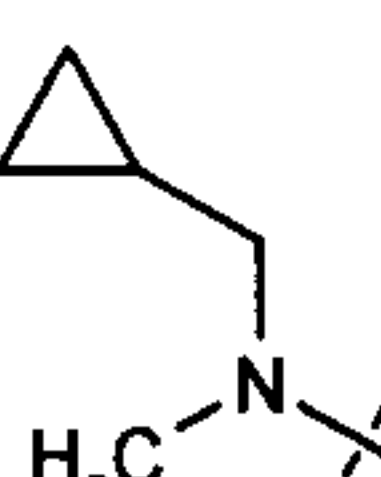
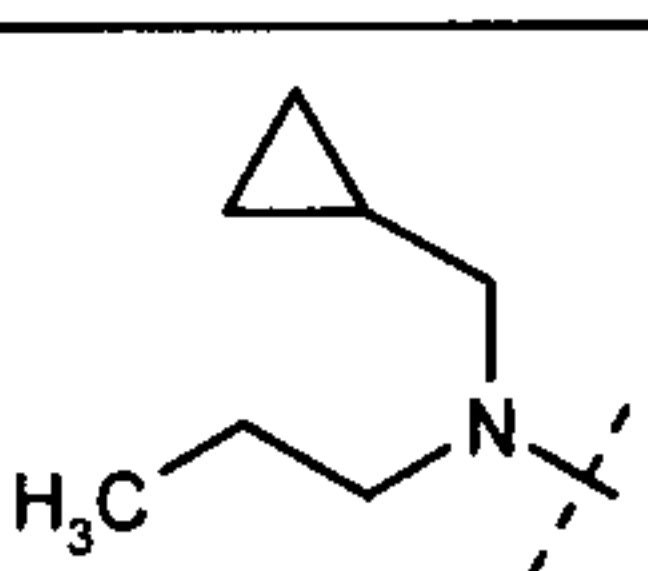
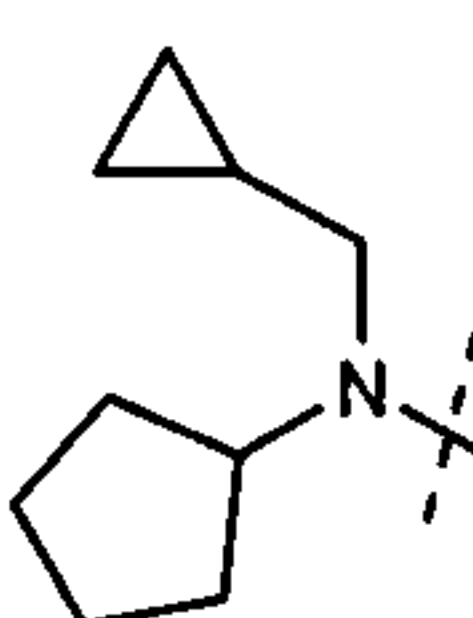
R_f value: 0.49 (silica gel, petroleum ether/ethyl acetate 2:1)

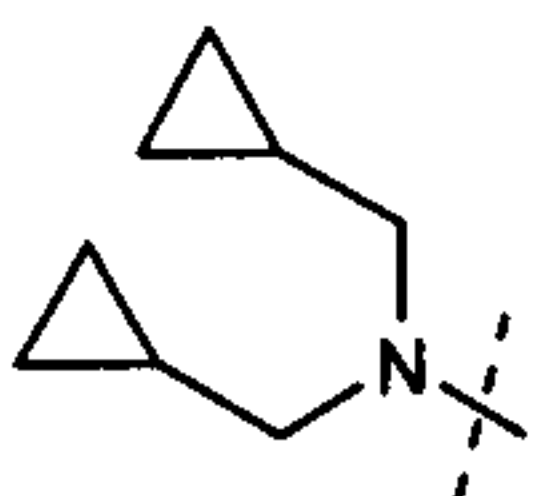
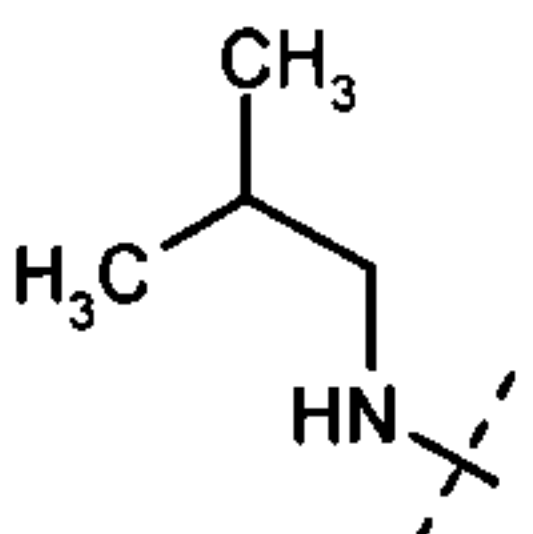
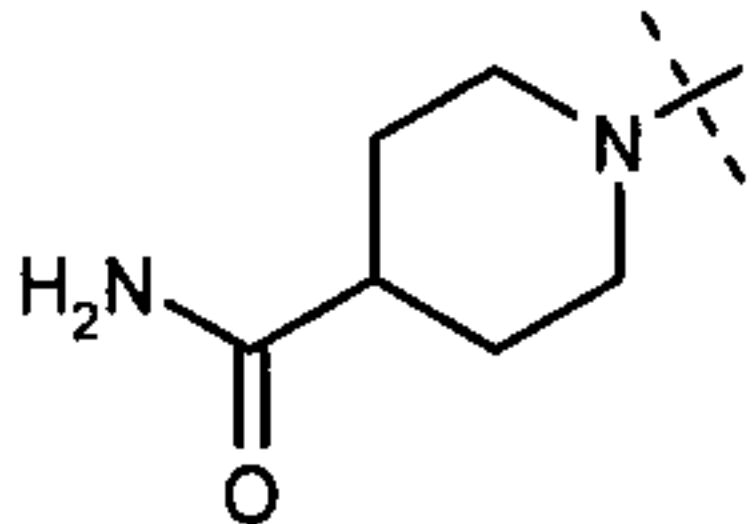
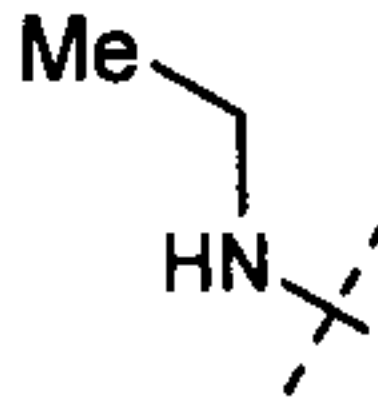
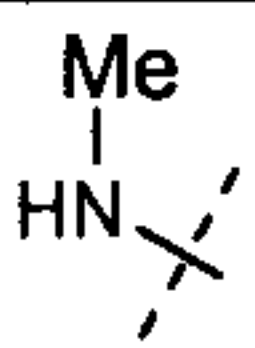
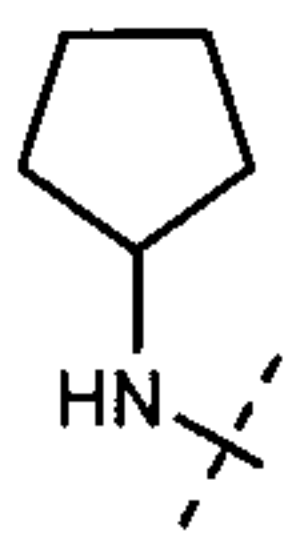
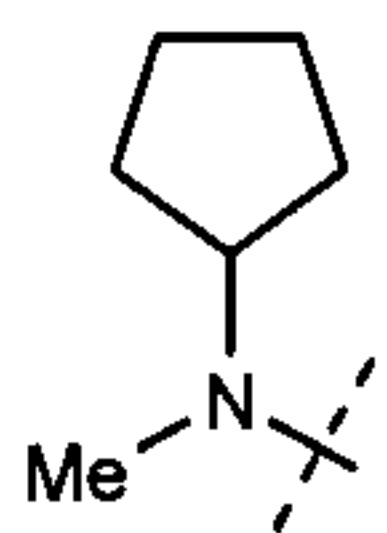
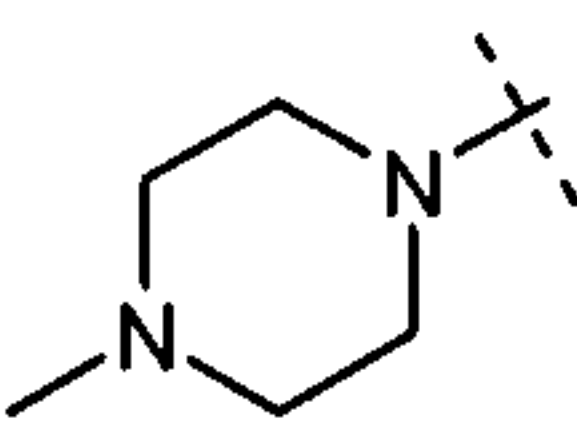
10 The following compounds are prepared analogously to Example 7.1:



Example	R ₁ R ₂ N-X-	L ₁	L ₂	L ₃
7.3		-Cl	-CF ₃	-H
7.4		-Cl	-CF ₃	-H
7.5		-Cl	-CF ₃	-H
7.6		-Cl	-CF ₃	-H
7.7		-Cl	-CF ₃	-H
7.8		-Cl	-CF ₃	-H
7.9		-Cl	-CF ₃	-H

7.10		-Cl	-CF ₃	-H
7.11		-Cl	-CF ₃	-H
7.12		-Cl	-CF ₃	-H
7.13		-Cl	-CF ₃	-H
7.14		-Cl	-CF ₃	-H
7.15		-Cl	-CF ₃	-H
7.16		-Cl	-CF ₃	-H
7.17		-Cl	-CF ₃	-H
7.18		-Cl	-CF ₃	-H
7.19		-Cl	-CF ₃	-H
7.20		-Cl	-CF ₃	-H
7.21		-Cl	-CF ₃	-H
7.22		-Cl	-CF ₃	-H

7.23		-Cl	-CF ₃	-H
7.24		-Cl	-CF ₃	-Me
7.25		-Cl	-CF ₃	-Me
7.26		-Cl	-CF ₃	-Me
7.27		-Cl	-CF ₃	-Me
7.28		-Cl	-CF ₃	-Me
7.29		-Cl	-CF ₃	-Me
7.30		-Cl	-CF ₃	-Me
7.31		-Cl	-CF ₃	-Me
7.32		-Cl	-CF ₃	-Me
7.33		-Cl	-CF ₃	-Me
7.34		-Cl	-CF ₃	-Me
7.35		-Cl	-CF ₃	-Me
7.36		-Cl	-CF ₃	-Me

7.37		-Cl	-CF ₃	-Me
7.38		-Cl	-CF ₃	-Me
7.39		-Cl	-CF ₃	-Me
7.19		-Cl	-CF ₃	-Me
7.20		-Cl	-CF ₃	-Me
7.21		-Cl	-CF ₃	-Me
7.21		-Cl	-CF ₃	-Me
7.22		-Cl	-CF ₃	-Me

Some test methods for determining an MCH-receptor antagonistic activity will now be described. In addition, other test methods known to the skilled man may be used, e.g. by inhibiting the MCH-receptor-mediated inhibition of cAMP production, as described
5 by Hoogduijn M et al. in "Melanin-concentrating hormone and its receptor are expressed and functional in human skin", Biochem. Biophys. Res Commun. 296 (2002) 698-701 and by biosensory measurement of the binding of MCH to the MCH receptor in the presence of antagonistic substances by plasmon resonance, as described by Karlsson OP and Lofas S. in "Flow-Mediated On-Surface Reconstitution
10 of G-Protein Coupled Receptors for Applications in Surface Plasmon Resonance Biosensors", Anal. Biochem. 300 (2002), 132-138. Other methods of testing antagonistic activity to MCH receptors are contained in the references and patent documents mentioned hereinbefore, and the description of the test methods used is hereby incorporated in this application.

MCH-1 receptor binding test

Method: MCH binding to hMCH-1R transfected cells

Species: Human

Test cell: hMCH-1R stably transfected into CHO/Galpha16 cells

20 Results: IC50 values

Membranes from CHO/Galpha16 cells stably transfected with human hMCH-1R are resuspended using a syringe (needle 0.6 x 25 mm) and diluted in test buffer (50 mM HEPES, 10 mM MgCl₂, 2 mM EGTA, pH 7.00; 0.1 % bovine serum albumin (protease-free), 0.021 % bacitracin, 1 µg/ml aprotinin, 1 µg/ml leupeptin and 1 µM
25 phosphoramidone) to a concentration of 5 to 15 µg/ml.

200 microlitres of this membrane fraction (contains 1 to 3 µg of protein) are incubated for 60 minutes at ambient temperature with 100 pM of ¹²⁵I-tyrosyl melanin concentrating hormone (¹²⁵I-MCH commercially obtainable from NEN) and increasing concentrations of the test compound in a final volume of 250 microlitres. After the
30 incubation the reaction is filtered using a cell harvester through 0.5% PEI treated fibreglass filters (GF/B, Unifilter Packard). The membrane-bound radioactivity retained on the filter is then determined after the addition of scintillator substance (Packard Microscint 20) in a measuring device (TopCount of Packard).

The non-specific binding is defined as bound radioactivity in the presence of 1 micromolar MCH during the incubation period.

The analysis of the concentration binding curve is carried out on the assumption of one receptor binding site.

5 Standard:

Non-labelled MCH competes with labelled ^{125}I -MCH for the receptor binding with an IC50 value of between 0.06 and 0.15 nM.

The KD value of the radioligand is 0.156 nM.

10

MCH-1 receptor-coupled Ca^{2+} mobilisation test

Method: Calcium mobilisation test with human MCH (FLIPR³⁸⁴)

15 Species: Human

Test cells: CHO/ Galpha 16 cells stably transfected with hMCH-R1

Results: 1st measurement: % stimulation of the reference (MCH 10^{-6}M)
 2nd measurement: pKB value

Reagents:	HBSS (10x)	(GIBCO)
	HEPES buffer (1M)	(GIBCO)
	Pluronic F-127	(Molecular Probes)
	Fluo-4	(Molecular Probes)
	Probenecid	(Sigma)
	MCH	(Bachem)
	bovine serum albumin (protease-free)	(Serva)
	DMSO	(Serva)
	Ham's F12	(BioWhittaker)
	FCS	(BioWhittaker)
	L-Glutamine	(GIBCO)
	Hygromycin B	(GIBCO)
	PENStrep	(BioWhittaker)
	Zeocin	(Invitrogen)

20

Clonal CHO/Galpha16 hMCH-R1 cells are cultivated in Ham's F12 cell culture medium (with L-glutamine; BioWhittaker; Cat.No.: BE12-615F). This contains per 500

ml 10% FCS, 1% PENStrep, 5 ml L-glutamine (200 mM stock solution), 3 ml hygromycin B (50 mg/ml in PBS) and 1.25 ml zeocin (100 µg/ml stock solution). One day before the experiment the cells are plated on a 384-well microtitre plate (black-walled with a transparent base, made by Costar) in a density of 2500 cells per cavity and cultivated in the above medium overnight at 37°C, 5% CO₂ and 95% relative humidity. On the day of the experiment the cells are incubated with cell culture medium to which 2 mM Fluo-4 and 4.6 mM Probenicid have been added, at 37°C for 45 minutes. After charging with fluorescent dye the cells are washed four times with Hanks buffer solution (1 x HBSS, 20 mM HEPES), which has been combined with 0.07% Probenicid. The test substances are diluted in Hanks buffer solution, combined with 2.5% DMSO. The background fluorescence of non-stimulated cells is measured in the presence of substance in the 384-well microtitre plate five minutes after the last washing step in the FLIPR³⁸⁴ apparatus (Molecular Devices; excitation wavelength: 488 nm; emission wavelength: bandpass 510 to 570 nm). To stimulate the cells MCH is diluted in Hanks buffer with 0.1% BSA, pipetted into the 384-well cell culture plate 35 minutes after the last washing step and the MCH-stimulated fluorescence is then measured in the FLIPR³⁸⁴ apparatus.

Data analysis:

1st measurement: The cellular Ca²⁺ mobilisation is measured as the peak of the relative fluorescence minus the background and is expressed as the percentage of the maximum signal of the reference (MCH 10⁻⁶M). This measurement serves to identify any possible agonistic effect of a test substance.

2nd measurement: The cellular Ca²⁺ mobilisation is measured as the peak of the relative fluorescence minus the background and is expressed as the percentage of the maximum signal of the reference (MCH 10⁻⁶M, signal is standardised to 100%). The EC50 values of the MCH dosage activity curve with and without test substance (defined concentration) are determined graphically by the GraphPad Prism 2.01 curve program. MCH antagonists cause the MCH stimulation curve to shift to the right in the graph plotted.

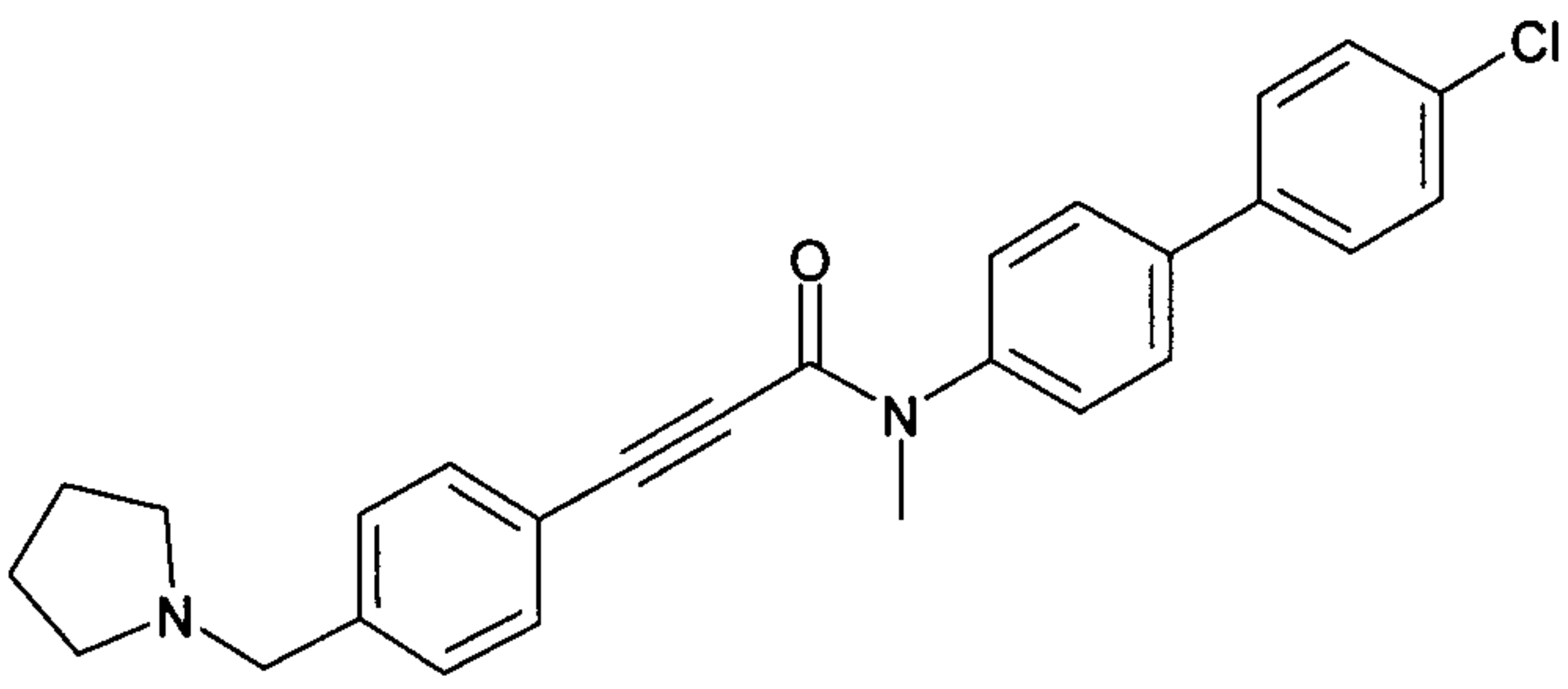
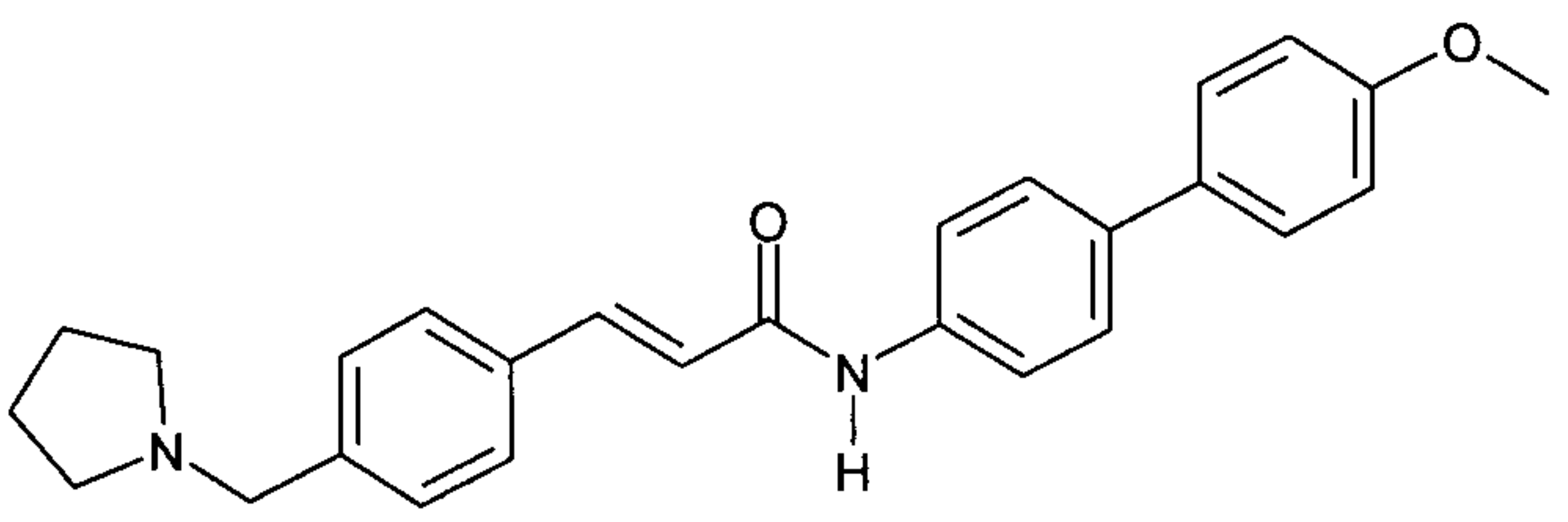
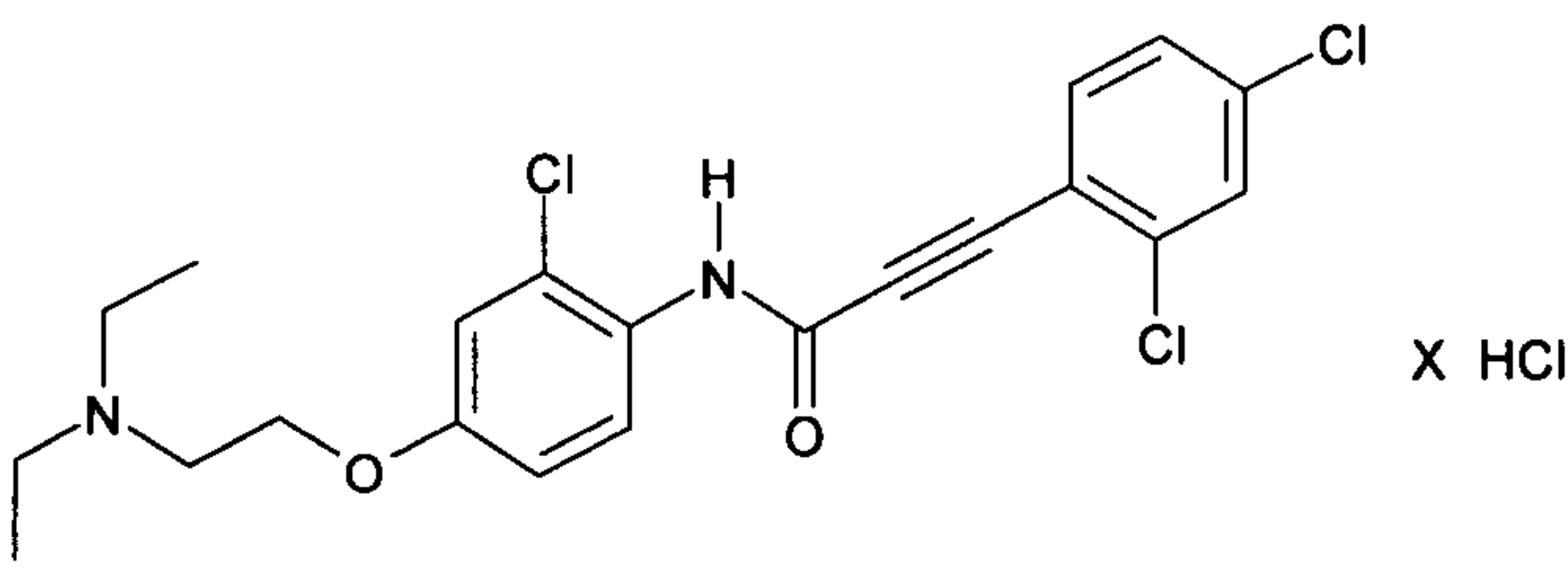
The inhibition is expressed as a pKB value:

$$\text{pKB} = \log(\text{EC}_{50}(\text{testsubstance} + \text{MCH}) / \text{EC}_{50}(\text{MCH}) - 1) - \log c(\text{testsubstance})$$

The compounds according to the invention, including their salts, exhibit an MCH-receptor antagonistic activity in the tests mentioned above. Using the MCH-1 receptor binding test described above an antagonistic activity is obtained in a dosage range from about 10^{-10} to 10^{-5} M, particularly from 10^{-9} to 10^{-6} M.

5

The following IC₅₀ values were determined using the MCH-1 receptor binding test described above:

Compound according to Example no.	Structure	IC ₅₀ value
1.23		7.5 nM
5.1		20 nM
4.8	 X HCl	50 nM

10 Some examples of formulations will be described hereinafter, wherein the term "active substance" denotes one or more compounds according to the invention, including their salts. In the case of one of the combinations with one or more active substances described, the term "active substance" also includes the additional active substances.

15

Example A

Capsules for powder inhalation containing 1 mg active substance

Composition:

1 capsule for powder inhalation contains:

5	active substance	1.0 mg
	lactose	20.0 mg
	hard gelatine capsules	<u>50.0 mg</u>
		71.0 mg

Method of preparation:

- 10 The active substance is ground to the particle size required for inhalation. The ground active substance is homogeneously mixed with the lactose. The mixture is packed into hard gelatine capsules.

Example B

15

Inhalable solution for Respimat[®] containing 1 mg active substance

Composition:

1 spray contains:

20	active substance	1.0	mg
	benzalkonium chloride	0.002	mg
	disodium edetate	0.0075	mg
	purified water ad	15.0	µl

- 25 Method of preparation:

The active substance and benzalkonium chloride are dissolved in water and packed into Respimat[®] cartridges.

- 30 Example C

Inhalable solution for nebulisers containing 1 mg active substance

Composition:

1 vial contains:

active substance	0.1 g
sodium chloride	0.18 g
benzalkonium chloride	0.002 g
purified water ad	20.0 ml

5

Method of preparation:

The active substance, sodium chloride and benzalkonium chloride are dissolved in water.

10 Example DPropellant type metered dose aerosol containing 1 mg active substance

Composition:

1 spray contains:

15	active substance	1.0 mg
	lecithin	0.1 %
	propellant gas ad	50.0 µl

Method of preparation:

- 20 The micronised active substance is homogeneously suspended in the mixture of lecithin and propellant gas. The suspension is transferred into a pressurised container with a metering valve.

Example E25 Nasal spray containing 1 mg active substance

Composition:

	active substance	1.0 mg
	sodium chloride	0.9 mg
30	benzalkonium chloride	0.025 mg
	disodium edetate	0.05 mg
	purified water ad	0.1 ml

Method of preparation:

The active substance and the excipients are dissolved in water and transferred into a corresponding container.

Example F

5 Injectable solution containing 5 mg of active substance per 5 ml

Composition:

	active substance	5 mg
	glucose	250 mg
10	human serum albumin	10 mg
	glycofurool	250 mg
	water for injections ad	5 ml

Preparation:

- 15 Glycofurool and glucose are dissolved in water for injections (Wfl); human serum albumin is added; active ingredient is dissolved with heating; made up to specified volume with Wfl; transferred into ampoules under nitrogen gas.

Example G

20

Injectable solution containing 100 mg of active substance per 20 ml

Composition:

	active substance	100 mg
25	monopotassium dihydrogen phosphate = KH_2PO_4	12 mg
	disodium hydrogen phosphate = $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$	2 mg
	sodium chloride	180 mg
30	human serum albumin	50 mg
	Polysorbate 80	20 mg
	water for injections ad	20 ml

Preparation:

Polysorbate 80, sodium chloride, monopotassium dihydrogen phosphate and disodium hydrogen phosphate are dissolved in water for injections (Wfl); human serum albumin is added; active ingredient is dissolved with heating; made up to specified volume with Wfl; transferred into ampoules.

Example HLyophilisate containing 10 mg of active substance

Composition:

Active substance	10 mg
Mannitol	300 mg
human serum albumin	20 mg

Preparation:

Mannitol is dissolved in water for injections (Wfl); human serum albumin is added; active ingredient is dissolved with heating; made up to specified volume with Wfl; transferred into vials; freeze-dried.

Solvent for lyophilisate:

Polysorbate 80 = Tween 80	20 mg
mannitol	200 mg
water for injections ad	10 ml

Preparation:

Polysorbate 80 and mannitol are dissolved in water for injections (Wfl); transferred into ampoules.

Example ITablets containing 20 mg of active substance

Composition:

	active substance	20 mg
	lactose	120 mg
	maize starch	40 mg
	magnesium stearate	2 mg
5	Povidone K 25	18 mg

Preparation:

Active substance, lactose and maize starch are homogeneously mixed; granulated with an aqueous solution of Povidone; mixed with magnesium stearate; compressed in a tablet press; weight of tablet 200 mg.

Example J

Capsules containing 20 mg active substance

15

Composition:

	active substance	20 mg
	maize starch	80 mg
	highly dispersed silica	5 mg
20	magnesium stearate	2.5 mg

Preparation:

Active substance, maize starch and silica are homogeneously mixed; mixed with magnesium stearate; the mixture is packed into size 3 hard gelatine capsules in a capsule filling machine.

Example K

Suppositories containing 50 mg of active substance

30

Composition:

active substance	50 mg
hard fat (Adeps solidus) q.s. ad	1700 mg

Preparation:

Hard fat is melted at about 38°C; ground active substance is homogeneously dispersed in the molten hard fat; after cooling to about 35°C it is poured into chilled moulds.

5

Example LInjectable solution containing 10 mg of active substance per 1 ml10 Composition:

active substance	10 mg
mannitol	50 mg
human serum albumin	10 mg
water for injections ad	1 ml

15

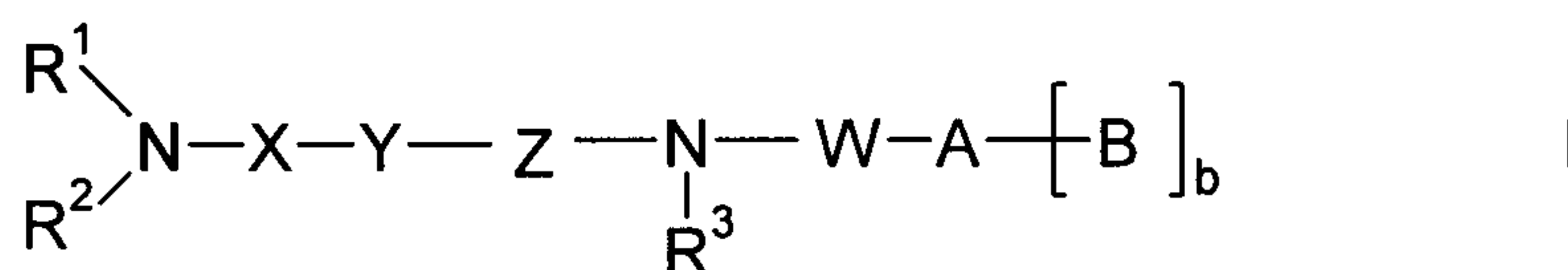
Preparation:

Mannitol is dissolved in water for injections (Wfi); human serum albumin is added; active ingredient is dissolved with heating; made up to specified volume with Wfi;

20 transferred into ampoules under nitrogen gas.

Patent Claims

1. Amide compounds of general formula I



wherein

R^1, R^2 independently of one another denote H, a C_{1-8} -alkyl or C_{3-7} -cycloalkyl group optionally mono- or polysubstituted by the group R^{11} , while a $-CH_2-$ group in position 3 or 4 of a 5-, 6- or 7-membered cycloalkyl group may be replaced by $-O-$, $-S-$ or $-NR^{13}-$, or a phenyl or pyridinyl group optionally mono- or polysubstituted by the group R^{12} and/or monosubstituted by nitro, or

R^1 and R^2 form a C_{2-8} -alkylene bridge, wherein

- one or two $-CH_2-$ groups independently of one another may be replaced by $-CH=N-$ or $-CH=CH-$ and/or
- one or two $-CH_2-$ groups independently of one another may be replaced by $-O-$, $-S-$, $-SO-$, $-(SO_2)-$, $-C=N-O-R^{18}-$, $-CO-$, $-C(=CH_2)-$ or $-NR^{13}-$ in such a way that heteroatoms are not directly joined together, and that a group $-C=N-O-R^{18}$ or $-CO-$ is not directly linked to the group R^1R^2N- ,

while in the alkylene bridge defined hereinbefore one or more H atoms may be replaced by R^{14} , and

the alkylene bridge defined hereinbefore may be substituted by one or two identical or different carbo- or heterocyclic groups Cy such that the bond between the alkylene bridge and the group Cy is made

- via a single or double bond,
- via a common C atom forming a spirocyclic ring system,

- via two common adjacent C and/or N atoms forming a fused bicyclic ring system or
- via three or more C and/or N atoms forming a bridged ring system,

5 R^3 denotes H, C_{1-6} -alkyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-4} -alkyl or phenyl- C_{1-3} -alkyl,

 X denotes a single bond or a C_{1-8} -alkylene bridge, wherein

- 10 - a $-CH_2-$ group which is not directly linked to the group R^1R^2N- may be replaced by $-CH=CH-$ or $-C\equiv C-$ and/or
- one or two non-adjacent $-CH_2-$ groups, which are not directly linked to the group R^1R^2N- , may be replaced independently of one another by $-O-$, $-S-$, $-(SO)-$, $-(SO_2)-$, $-CO-$ or $-NR^4-$ in such a way that in each case two O, S or N atoms or an O and an S atom are not directly joined
- 15 together,

 while the bridge X may be connected to R^1 including the N atom linked to R^1 and X, forming a heterocyclic group, while the bridge X may additionally also be connected to R^2 including the N atom connected to R^2 and X, forming a heterocyclic group, and

20

 while two C atoms or a C and an N atom of the alkylene bridge may be joined together by an additional C_{1-4} -alkylene bridge, and

25 a C atom may be substituted with R^{10} and/or one or two C atoms may be substituted in each case by one or two identical or different substituents selected from C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, C_{4-7} -cycloalkenyl and C_{4-7} -cycloalkenyl- C_{1-3} -alkyl, while two alkyl and/or alkenyl substituents may

30 be joined together, forming a carbocyclic ring system, and

 W denotes a single bond, while

Z denotes $-C\equiv C-C(=O)-$, $-CR^{7a}=CR^{7c}-C(=O)-$ or $-CR^{7a}R^{7b}-CR^{7c}R^{7d}-C(=O)-$, or

W denotes $-C(=O)-C\equiv C-$, while

5 Z denotes a single bond; and

Y has one of the meanings given for Cy,

10 while X may be connected to Y, forming a carbo- or heterocyclic group fused to Y, and/ or

optionally R^1 may be connected to Y, including the group X and the N atom connected to R^1 and X, forming a heterocyclic group fused to Y, and

15

A has one of the meanings given for Cy, while if the index b has the value 0, the group Cy does not have an amino group as substituent in the ortho position to the bridge W;

20 B has one of the meanings given for Cy,

b denotes the value 0 or 1,

25 Cy denotes a carbo- or heterocyclic group selected from one of the following meanings

- a saturated 3- to 7-membered carbocyclic group,
- a unsaturated 4- to 7-membered carbocyclic group,
- a phenyl group,
- a saturated 4- to 7-membered or unsaturated 5- to 7-membered heterocyclic group with an N, O or S atom as heteroatom,
- 30 - a saturated or unsaturated 5- to 7-membered heterocyclic group with two or more N atoms or with one or two N atoms and one O or S atom as heteroatoms,

- an aromatic heterocyclic 5- or 6-membered group with one or more identical or different heteroatoms selected from N, O and/or S,

while the above-mentioned 4, 5-, 6- or 7-membered groups may be fused to a phenyl or pyridine ring via two common adjacent C atoms, and

in the above-mentioned 5-, 6- or 7-membered groups one or two non-adjacent -CH₂- groups may independently of one another be replaced by a -CO-, -C(=CH₂)-, -(SO)- or -(SO₂)- group, and

the above-mentioned saturated 6- or 7-membered groups may also occur as bridged ring systems with an imino, N-(C₁₋₄-alkyl)-imino, methylene, C₁₋₄-alkyl-methylene or di-(C₁₋₄-alkyl)-methylene bridge, and

the above-mentioned cyclic groups may be mono- or polysubstituted by R²⁰ at one or more C atoms, in the case of a phenyl group may also additionally be monosubstituted by nitro, and/or one or more NH groups may be substituted by R²¹,

R⁴ has one of the meanings given for R¹⁷ or denotes C₂₋₆-alkenyl or C₃₋₆-alkynyl,

R^{7a}, R^{7c} denote H, F, Cl, C₁₋₄-alkyl or CF₃,

R^{7b}, R^{7d} denote H, F, C₁₋₄-alkyl, while R^{7b} and R^{7d} representing alkyl may be joined together to form a cyclopropyl group;

R¹⁰ denotes hydroxy, hydroxy-C₁₋₃-alkyl, C₁₋₄-alkoxy, C₁₋₄-alkoxy-C₁₋₃-alkyl, carboxy, C₁₋₄-alkoxycarbonyl, amino, C₁₋₄-alkyl-amino, di-(C₁₋₄-alkyl)-amino, cyclo-C₃₋₆-alkyleneimino, amino-C₁₋₃-alkyl, C₁₋₄-alkyl-amino-C₁₋₃-alkyl, di-(C₁₋₄-alkyl)-amino-C₁₋₃-alkyl, cyclo-C₃₋₆-alkyleneimino-C₁₋₃-alkyl, amino-C₁₋₃-alkoxy, C₁₋₄-alkyl-amino-C₁₋₃-alkoxy, di-(C₁₋₄-alkyl)-amino-C₁₋₃-alkoxy, cyclo-C₃₋₆-alkyleneimino-C₁₋₃-alkoxy, aminocarbonyl, C₁₋₄-alkyl-

aminocarbonyl, di-(C₁₋₄-alkyl)-aminocarbonyl or cyclo-C₃₋₆-alkyleneimino-carbonyl,

5 R¹¹ denotes C₂₋₆-alkenyl, C₂₋₆-alkynyl, R¹⁵-O-, R¹⁵-O-C₁₋₃-alkyl, R¹⁵-O-CO-, R¹⁵-CO-O-, R¹⁶R¹⁷N, cyano, R¹⁸R¹⁹N-CO- or Cy,

R¹² has one of the meanings given for R²⁰,

10 R¹³ has one of the meanings given for R¹⁷, with the exception of carboxy,

15 R¹⁴ denotes halogen, C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, R¹⁵-O, R¹⁵-O-CO, R¹⁵-CO, R¹⁵-CO-O, R¹⁶R¹⁷N, R¹⁸R¹⁹N-CO-, R¹⁵-O-C₁₋₃-alkyl, R¹⁵-O-CO-C₁₋₃-alkyl, R¹⁵-O-CO-NH, R¹⁵-SO₂-NH, R¹⁵-O-CO-NH-C₁₋₃-alkyl, R¹⁵-SO₂-NH-C₁₋₃-alkyl, R¹⁵-CO-C₁₋₃-alkyl, R¹⁵-CO-O-C₁₋₃-alkyl, R¹⁶R¹⁷N-C₁₋₃-alkyl, R¹⁸R¹⁹N-CO-C₁₋₃-alkyl or Cy-C₁₋₃-alkyl,

20 R¹⁵ denotes H, C₁₋₄-alkyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₃-alkyl, phenyl, phenyl-C₁₋₃-alkyl, pyridinyl or pyridinyl-C₁₋₃-alkyl,

25 R¹⁶ denotes H, C₁₋₆-alkyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₃-alkyl, C₄₋₇-cycloalkenyl, C₄₋₇-cycloalkenyl-C₁₋₃-alkyl, hydroxy-C₂₋₃-alkyl, C₁₋₄-alkoxy-C₂₋₃-alkyl, amino-C₂₋₆-alkyl, C₁₋₄-alkyl-amino-C₂₋₆-alkyl, di-(C₁₋₄-alkyl)-amino-C₂₋₆-alkyl or cyclo-C₃₋₆-alkyleneimino-C₂₋₆-alkyl,

30 R¹⁷ has one of the meanings given for R¹⁶ or denotes phenyl, phenyl-C₁₋₃-alkyl, pyridinyl, dioxolan-2-yl, -CHO, C₁₋₄-alkylcarbonyl, carboxy, hydroxycarbonyl-C₁₋₃-alkyl, C₁₋₄-alkoxycarbonyl, C₁₋₄-alkoxycarbonyl-C₁₋₃-alkyl, C₁₋₄-alkylcarbonylamino-C₂₋₃-alkyl, N-(C₁₋₄-alkylcarbonyl)-N-(C₁₋₄-alkyl)-amino-C₂₋₃-alkyl, C₁₋₄-alkylsulphonyl, C₁₋₄-alkylsulphonylamino-C₂₋₃-alkyl or N-(C₁₋₄-alkylsulphonyl)-N(C₁₋₄-alkyl)-amino-C₂₋₃-alkyl

R^{18} , R^{19} independently of one another denote H or C_{1-6} -alkyl,

R^{20} denotes halogen, hydroxy, cyano, C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, hydroxy- C_{1-4} -alkyl, R^{22} - C_{1-3} -alkyl or has one of the meanings given for R^{22} ,

R^{21} denotes C_{1-4} -alkyl, hydroxy- C_{2-3} -alkyl, C_{1-4} -alkoxy- C_{2-6} -alkyl, C_{1-4} -alkyl-amino- C_{2-6} -alkyl, di-(C_{1-4} -alkyl)-amino- C_{2-6} -alkyl, cyclo- C_{3-6} -alkyleneimino- C_{2-6} -alkyl, phenyl- C_{1-3} -alkyl, C_{1-4} -alkyl-carbonyl, C_{1-4} -alkoxy-carbonyl or C_{1-4} -alkylsulphonyl,

R^{22} denotes phenyl- C_{1-3} -alkoxy, cyclo- C_{3-6} -alkyleneimino- C_{2-4} -alkoxy, OHC-, HO-N=HC-, C_{1-4} -alkoxy-N=HC-, C_{1-4} -alkoxy, C_{1-4} -alkylthio, carboxy, C_{1-4} -alkylcarbonyl, C_{1-4} -alkoxycarbonyl, aminocarbonyl, C_{1-4} -alkylaminocarbonyl, di-(C_{1-4} -alkyl)-aminocarbonyl, cyclo- C_{3-6} -alkyl-amino-carbonyl, cyclo- C_{3-6} -alkyleneimino-carbonyl, cyclo- C_{3-6} -alkyleneimino- C_{2-4} -alkylaminocarbonyl, phenyl-amino-carbonyl, C_{1-4} -alkyl-sulphonyl, C_{1-4} -alkylsulphinyl, C_{1-4} -alkyl-sulphonylamino, amino, C_{1-4} -alkylamino, di-(C_{1-4} -alkyl)-amino, C_{1-4} -alkyl-carbonyl-amino, cyclo- C_{3-6} -alkyleneimino, phenyl- C_{1-3} -alkylamino, N-(C_{1-4} -alkyl)-phenyl- C_{1-3} -alkylamino, acetylamino, propionylamino, phenylcarbonylamino, phenylcarbonylmethylamino, hydroxyalkylaminocarbonyl, (4-morpholinyl)carbonyl, (1-pyrrolidinyl)carbonyl, (1-piperidinyl)carbonyl, (hexahydro-1-azepinyl)carbonyl, (4-methyl-1-piperazinyl)carbonyl, methylenedioxy, aminocarbonylamino or alkylaminocarbonylamino-,

while in the above-mentioned groups and radicals, particularly in A, B, W, X, Y, Z, R^1 to R^4 , R^{7a} , R^{7b} , R^{7c} , R^{7d} , R^{10} to R^{22} , in each case one or more C atoms may additionally be mono- or polysubstituted by F and/or in each case one or two C atoms independently of one another may additionally be monosubstituted by Cl or Br and/or in each case one or more phenyl rings may independently of one another additionally comprise one, two or three substituents selected from the group F, Cl, Br, I, C_{1-4} -alkyl, C_{1-4} -alkoxy, difluoromethyl, trifluoromethyl, hydroxy, amino, C_{1-3} -alkylamino, di-(C_{1-3} -alkyl)-amino, acetylamino, aminocarbonyl, cyano, difluoromethoxy,

trifluoromethoxy, amino-C₁₋₃-alkyl, C₁₋₃-alkylamino-C₁₋₃-alkyl and di-(C₁₋₃-alkyl)-amino-C₁₋₃-alkyl and/or may be monosubstituted by nitro, and

the H atom of a carboxy group present or an H atom bound to an N atom in each
5 case may be replaced by a group which can be cleaved in vivo,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof,

10 while the following compounds according to provisos (M1) to (M14) are not included:

(M1) N-[4-[[[(methylamino)sulphonyl]methyl]phenyl]-3-[2-(dimethylamino)-ethyl]-1-H-indole-5-propanamide oxalate,

15 (M2) 3-[2-[3-[3,6-dihydro-4-(2-naphthyl)-1(2H)-pyridinyl]-2-hydroxypropoxy]phenyl]-N-methyl-N-phenyl-2-propenamide,

(M3) 3-[2-[2-hydroxy-3-[4-(1-naphthyl)-1-piperidinyl]propoxy]phenyl]-N-methyl-N-phenyl-2-propenamide,

20

(M4) 3-[2-[2-hydroxy-3-[4-(2-naphthyl)-1-piperidinyl]propoxy]phenyl]-N-methyl-N-phenyl-2-propenamide,

25

(M5) 3-[2-[2-hydroxy-3-[4-(2-naphthalyl)-1-piperidinyl]propoxy]phenyl]-N-phenyl-2-propenamide,

(M6) N-[4-[1-(1H-imidazol-1-yl)-2-methylpropyl]phenyl]-3-phenyl-2-propinamide,

(M7) 2'-[[3-(dimethylamino)propyl]thio]-3-phenyl-propiolanilide,

30

(M8) 2-(methylthio)-5-[[3-[4-(octadecylamino)phenyl]-1-oxopropyl]amino]-benzoic acid, including the trifluoroacetate salt,

(M9) 4-amino-N-(4-hydroxy-3,5-dimethylphenyl)-benzenepropanamide,

(M10) 4-(dimethylamino)-N-(4-hydroxy-3,5-dimethylphenyl)-benzenepropanamide,

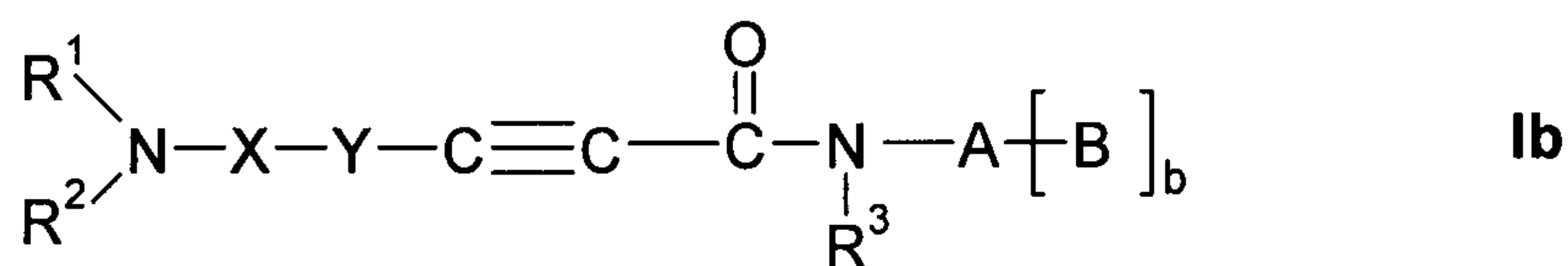
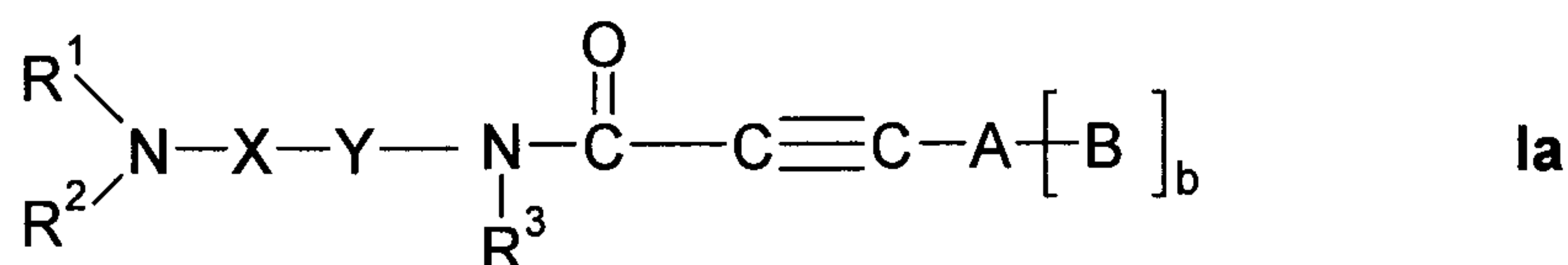
(M11) β -methyl-4-[[3-[2-[(2-methylphenyl)amino]-6-benzoxazolyl]-1-oxopropylamino]-benzenepropanoic acid,

(M12) 4-[3-[[1-oxo-3-[2-(phenylamino)-6-benzoxazolyl]-propyl]amino]phenoxy]-butanoic acid,

(M13) 2-chloro-5-[[1-oxo-3-[4-[(5-phenylpentyl)amino]phenyl]propyl]amino]-benzoic acid,

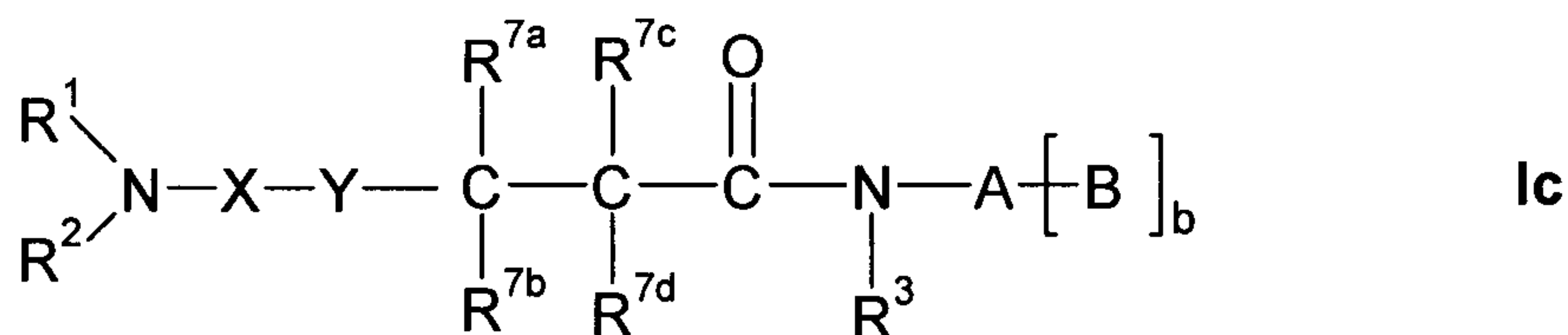
(M14) methyl 2-chloro-5-[[1-oxo-3-[4-[(5-phenylpentyl)amino]phenyl]propyl]amino]-benzoate.

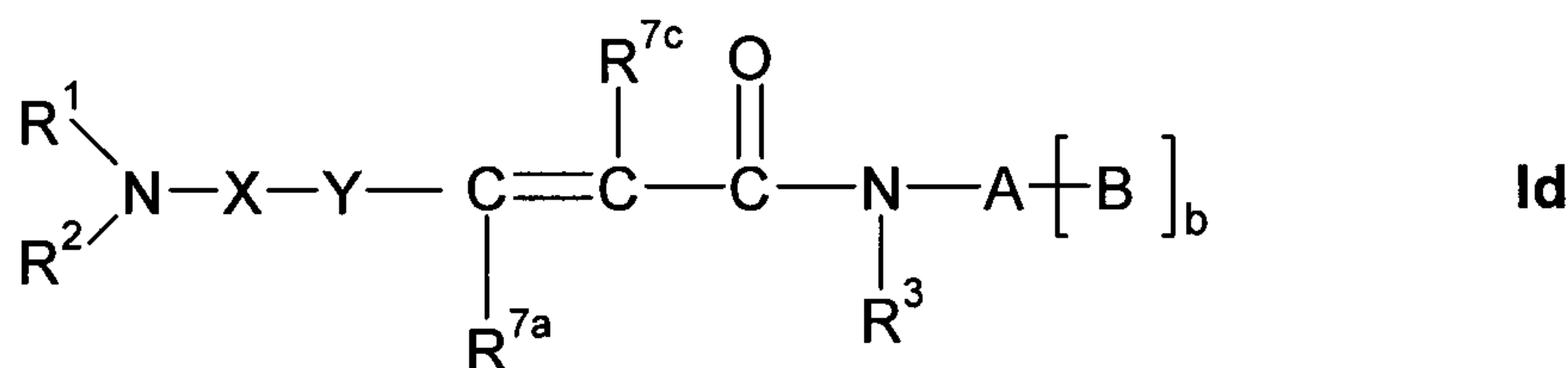
2. Amide compounds according to claim 1 characterised by formulae Ia or Ib



wherein R^1 , R^2 , R^3 , X, Y, A, B and b have the meanings given in claim 1.

3. Amide compounds according to claim 1, characterised by formulae Ic or Id





wherein R^1 , R^2 , R^3 , R^{7a} , R^{7b} , R^{7c} , R^{7d} , X, Y, A, B and b have the meanings given in claim 1.

4. Amide compounds according to one or more of the preceding claims,

5 characterised in that R^1 , R^2 independently of one another denote C_{1-6} -alkyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, hydroxy- C_{2-4} -alkyl, NC- C_{2-4} -alkyl, C_{1-4} -alkoxy- C_{2-4} -alkyl, C_{1-4} -alkoxy-carbonyl- C_{1-4} -alkyl, carboxyl- C_{1-4} -alkyl, amino- C_{2-4} -alkyl, C_{1-4} -alkyl-amino- C_{2-4} -alkyl, di- $(\text{C}_{1-4}$ -alkyl)-amino- C_{2-4} -alkyl, cyclo- C_{3-6} -alkyleneimino- C_{2-4} -alkyl, pyrrolidin-3-yl, while the NH group may
 10 be substituted by R^{13} , pyrrolidinyl- C_{1-3} -alkyl, while the NH group may be substituted by R^{13} , piperidin-3-yl or -4-yl, while the NH group may be substituted by R^{13} , piperidinyl- C_{1-3} -alkyl, while the NH group may be substituted by R^{13} , tetrahydropyran-3-yl or -4-yl, tetrahydropyranyl- C_{1-3} -alkyl, tetrahydrofuran-3-yl, tetrahydrofuranyl- C_{1-3} -alkyl, phenyl, phenyl- C_{1-3} -alkyl,
 15 pyridyl or pyridyl- C_{1-3} -alkyl,

while in the above-mentioned groups and radicals one or more C atoms may be mono- or polysubstituted by F and/or one or two C atoms, particularly one C atom may independently of one another be monosubstituted by Cl or Br,
 20 and

the phenyl or pyridyl group may be mono- or polysubstituted by the group R^{12} defined hereinbefore and/or may be monosubstituted by nitro, and

25 cycloalkyl rings may be mono- or polysubstituted by substituents selected from hydroxy, hydroxy- C_{1-3} -alkyl, C_{1-3} -alkyl or C_{1-3} -alkyloxy, and

C_{2-4} -alkyl bridges contained in hydroxy- C_{2-4} -alkyl- and C_{1-4} -alkoxy- C_{2-4} -alkyl- may additionally be monosubstituted by hydroxy, hydroxy- C_{1-3} -alkyl, C_{1-3} -alkyl

or C₁₋₃-alkyloxy, and

one of the groups R¹, R² may also represent H, and

5 R¹³ is defined as in claim 1.

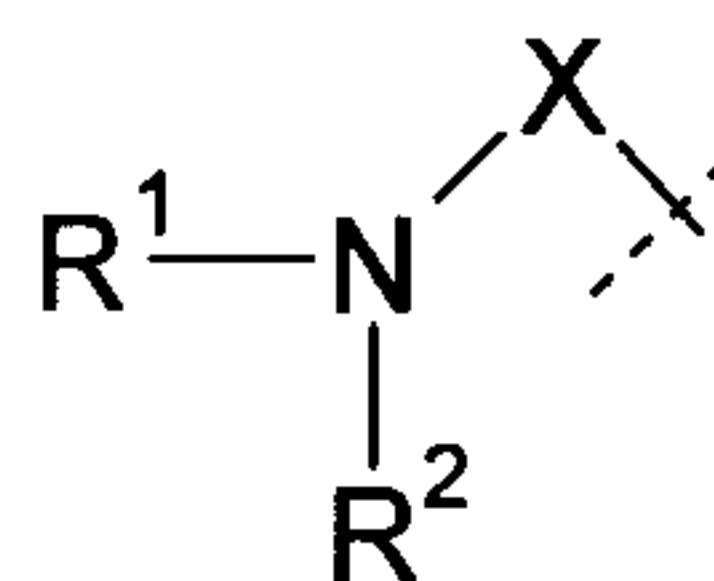
10 5. Amide compounds according to one or more of claims 1 to 3, characterised in that R¹ and R² form an alkylene bridge according to claim 1 such that R¹R²N- denotes a group selected from azetidine, pyrrolidine, piperidine, azepan, 2,5-dihydro-1H-pyrrole, 1,2,3,6-tetrahydro-pyridine, 2,3,4,7-tetrahydro-1H-azepine, 2,3,6,7-tetrahydro-1H-azepine, piperazine, wherein the free imine function is substituted by R¹³, piperidin-4-one-oxime, piperidin-4-one-O-C₁₋₄-alkyl-oxime, morpholine and thiomorpholine,

15 while according to claim 1 one or more H atoms may be replaced by R¹⁴, and/or may be substituted by one or two identical or different carbo- or heterocyclic groups Cy in the manner specified in claim 1,

20 while R¹³, R¹⁴ and Cy have the meaning given in claim 1.

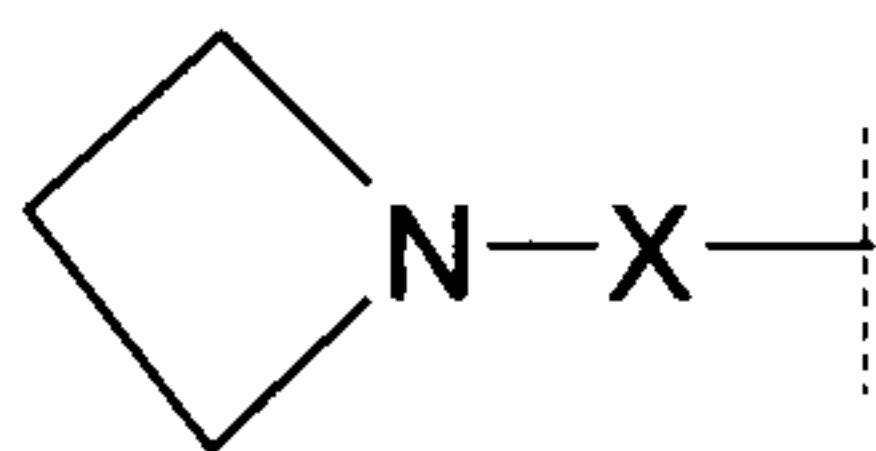
6. Amide compounds according to one or more of the preceding claims, characterised in that

the group

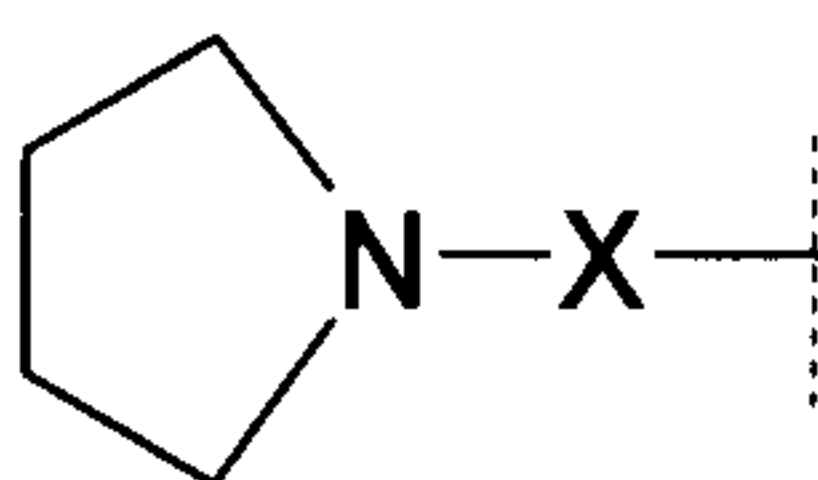


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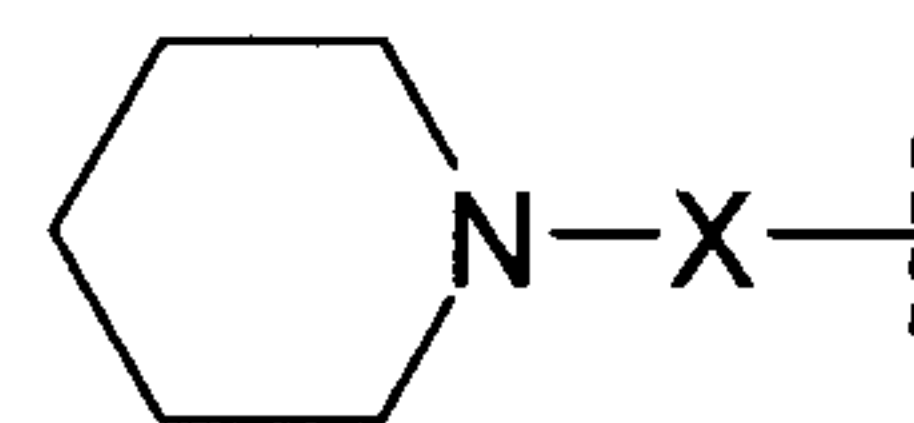
is defined according to one of the following partial formulae



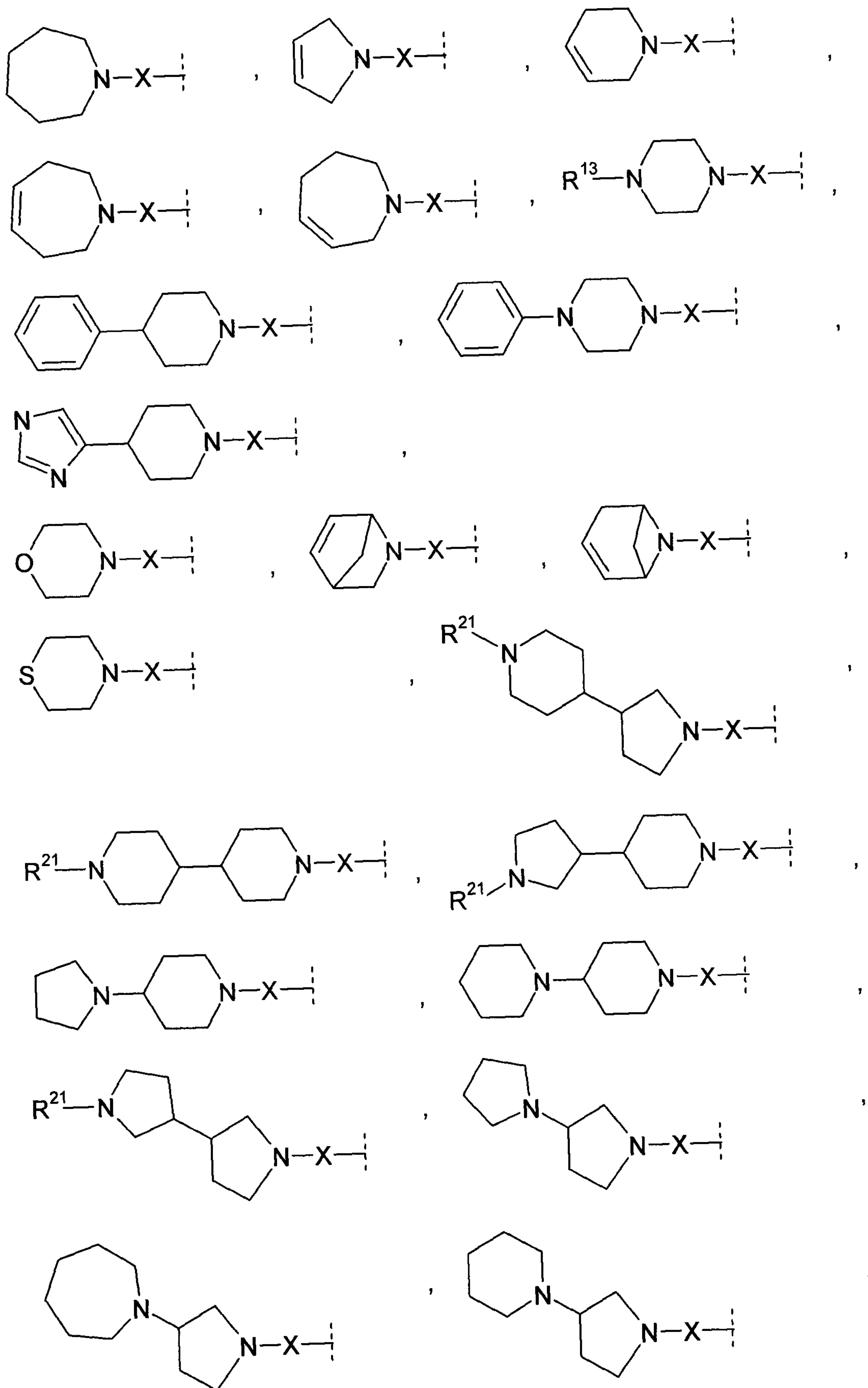
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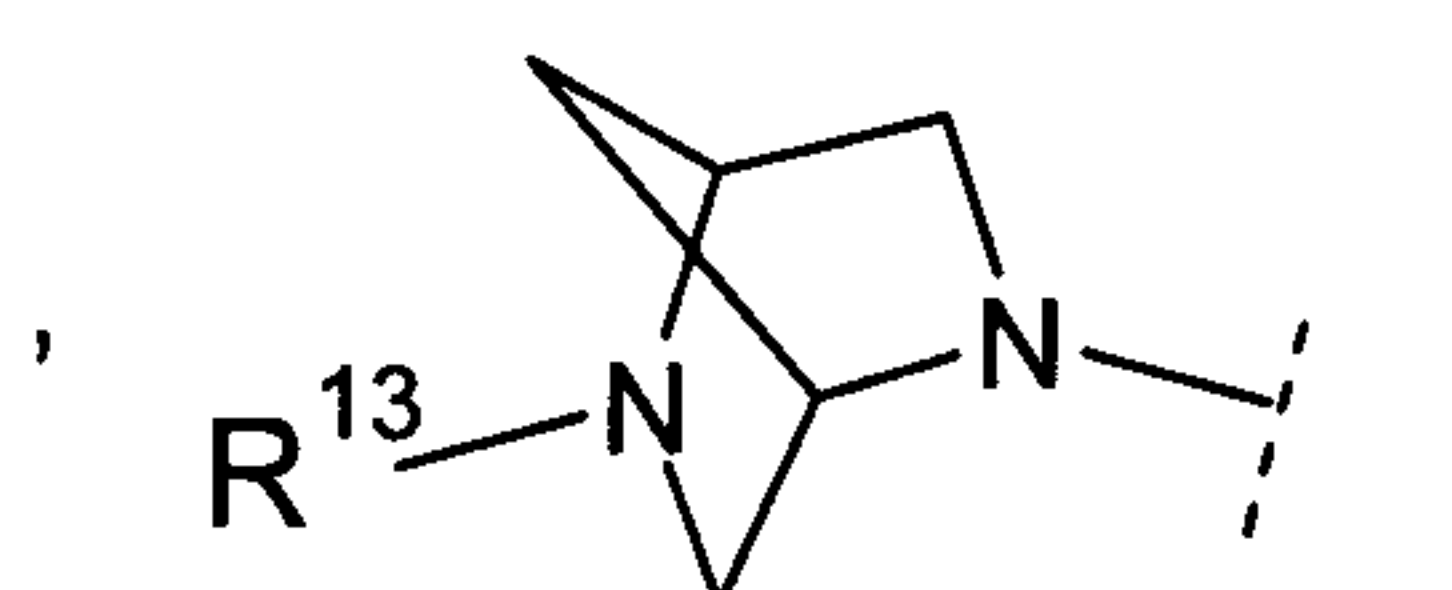
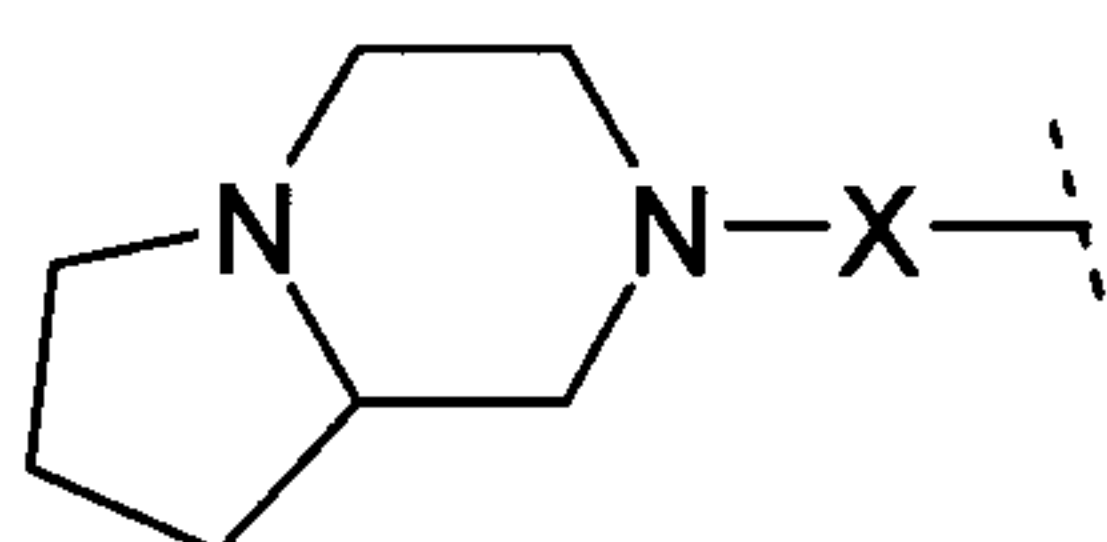
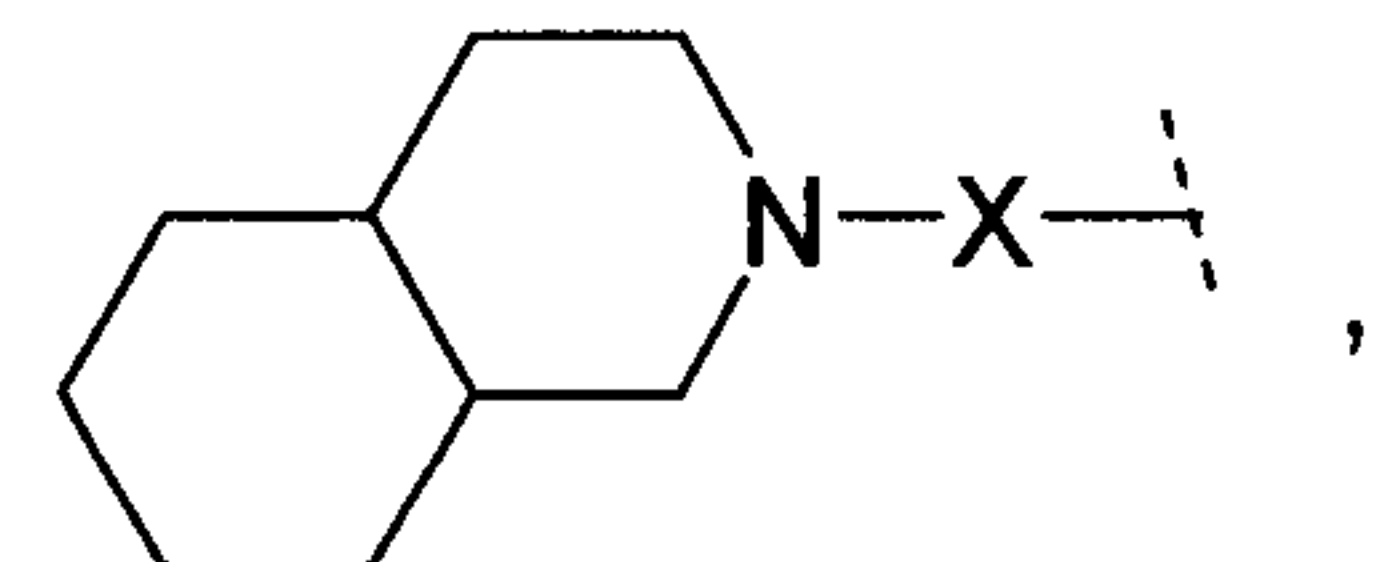
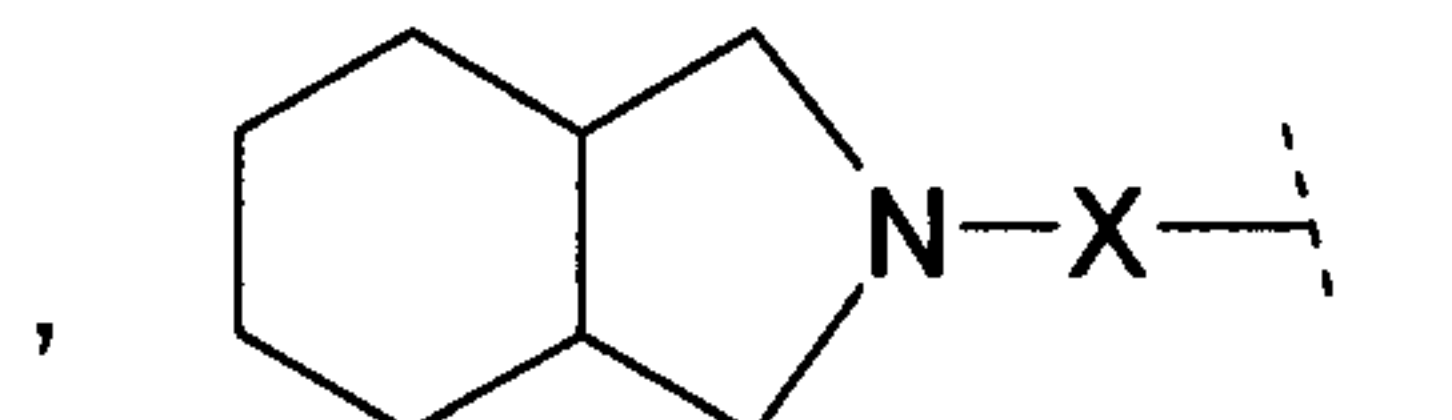
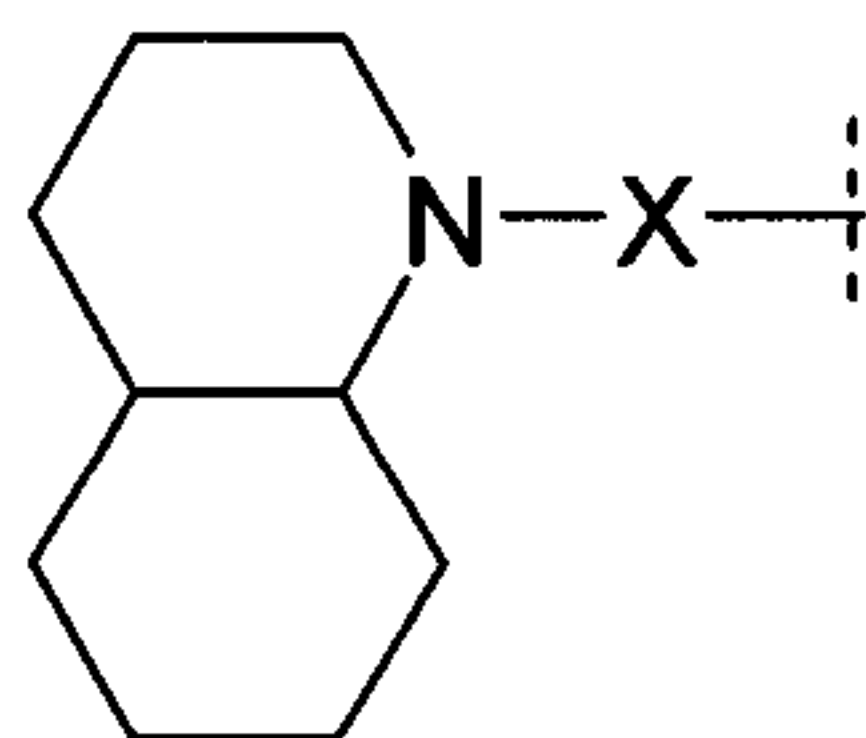
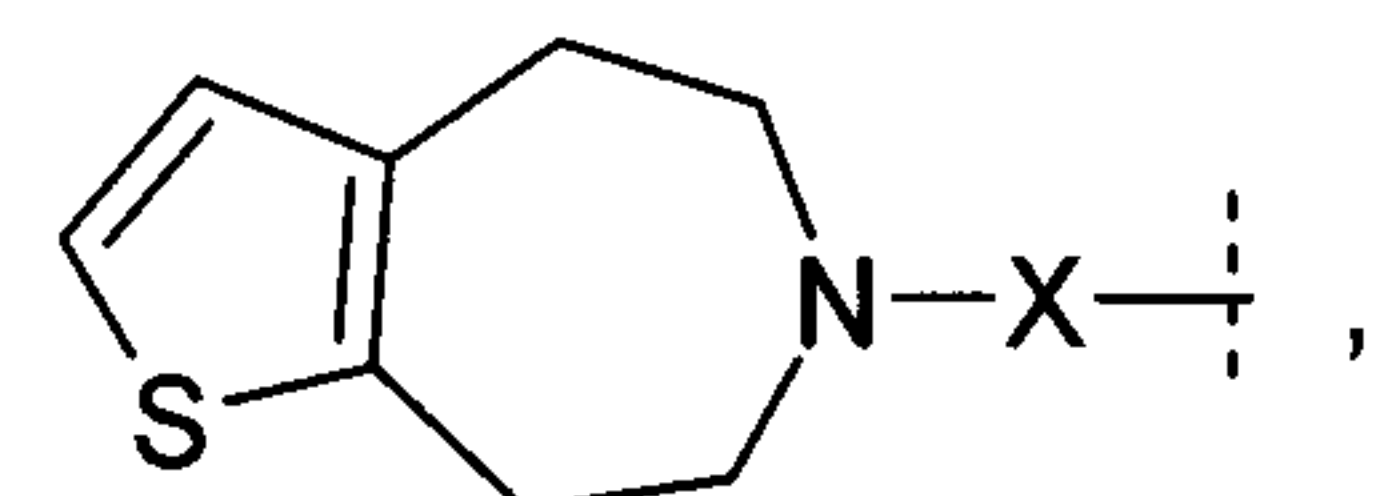
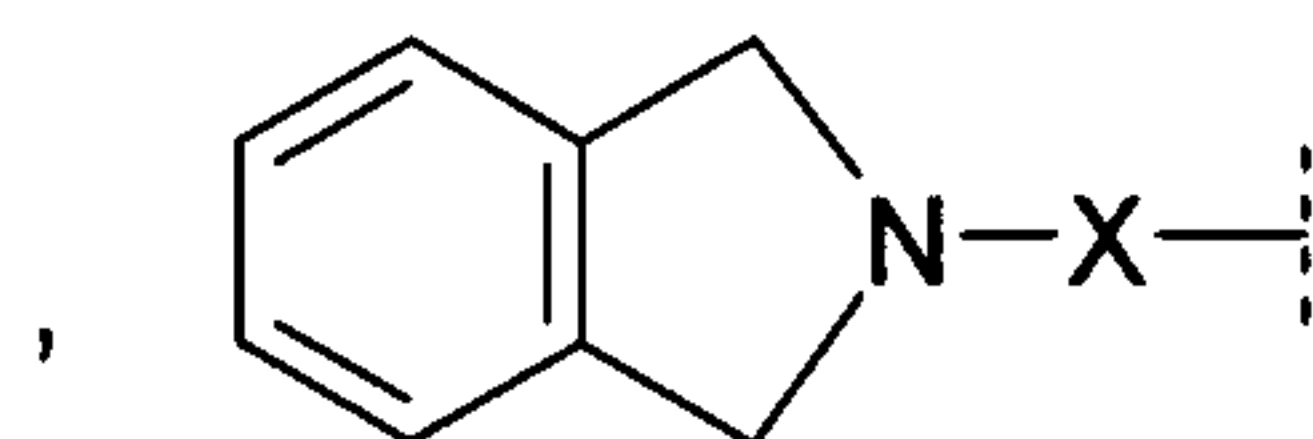
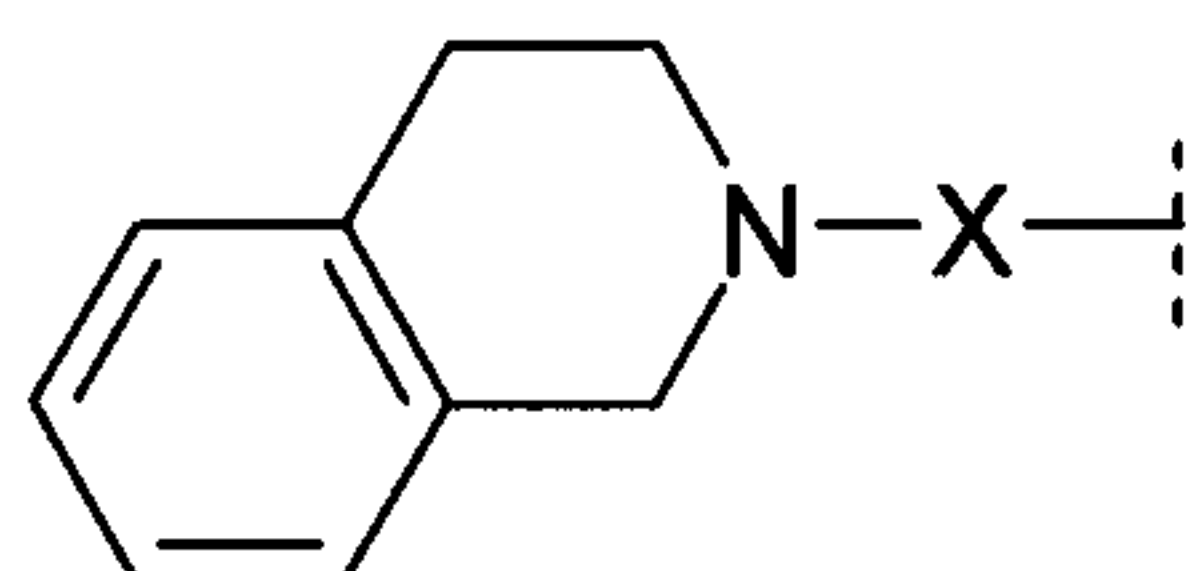
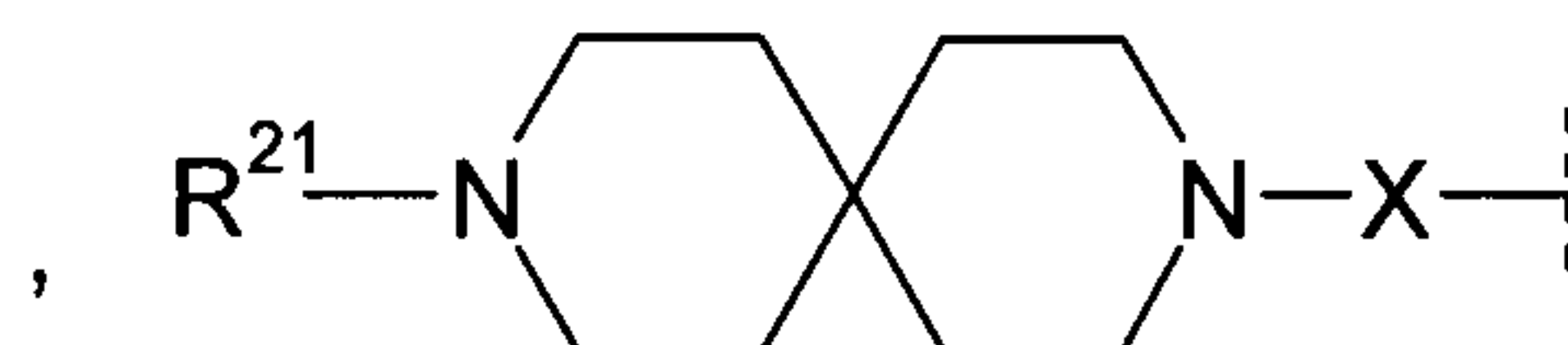
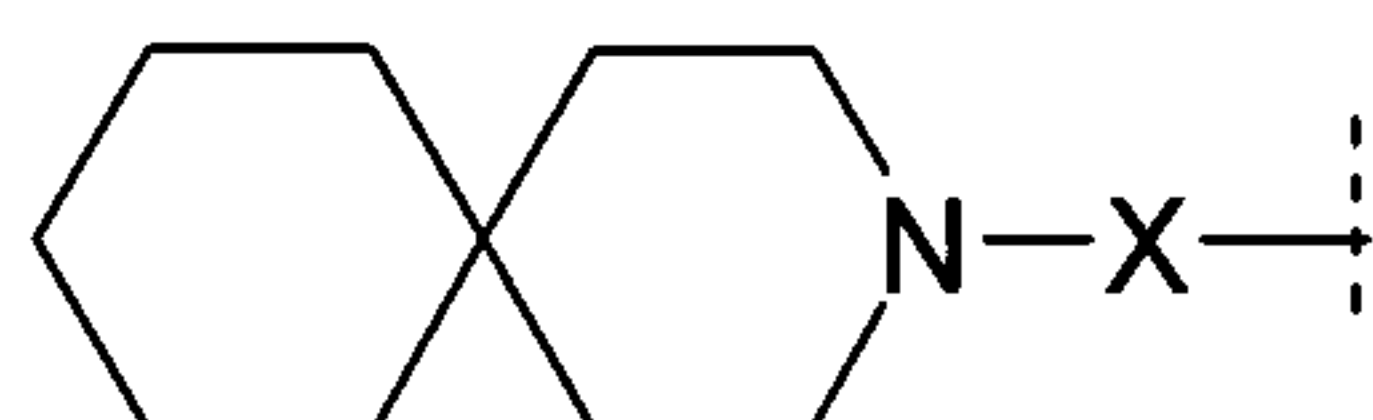
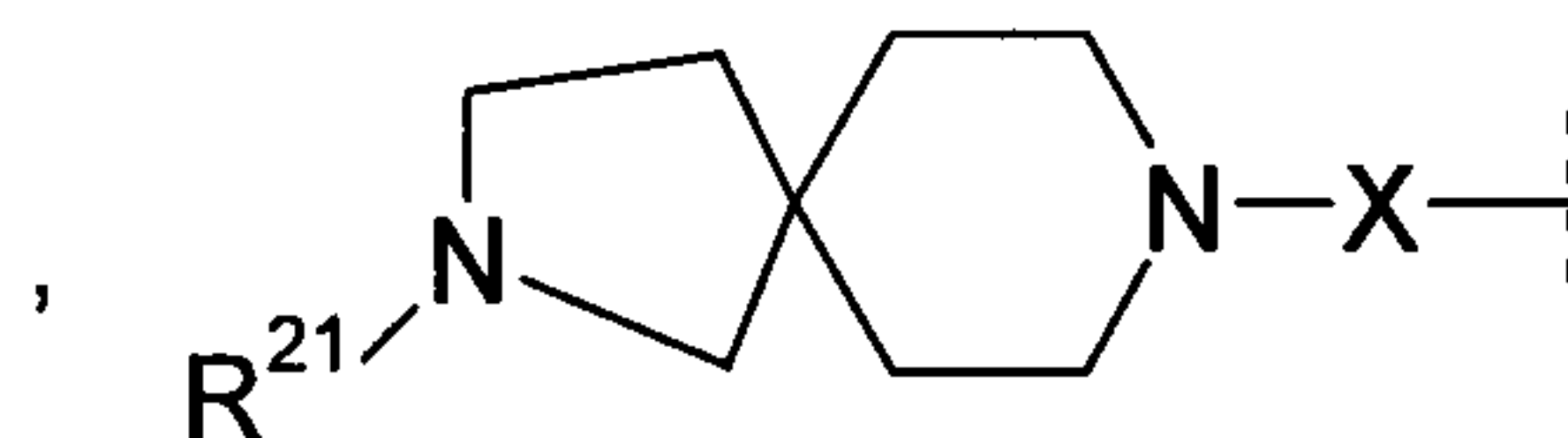
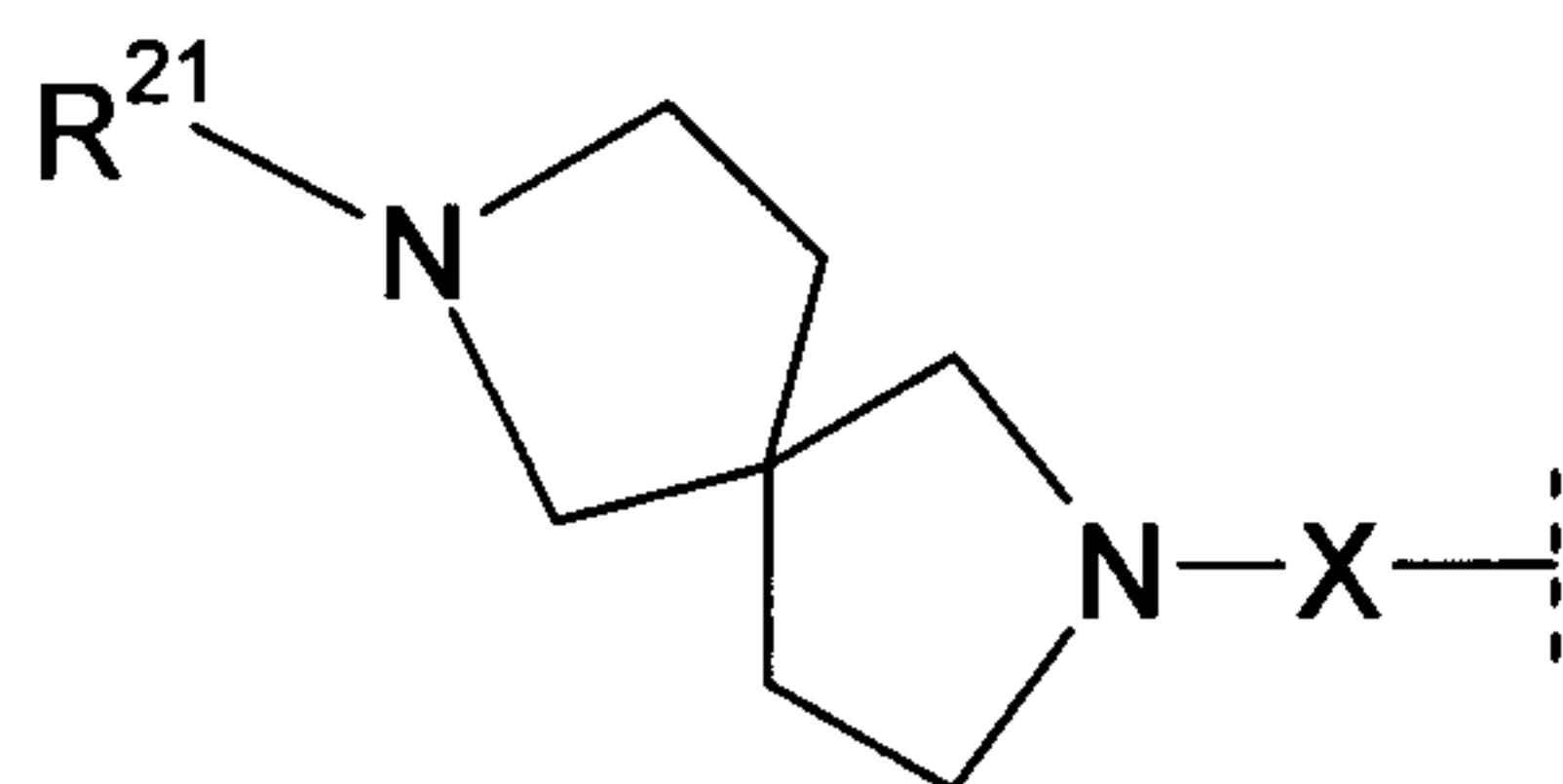
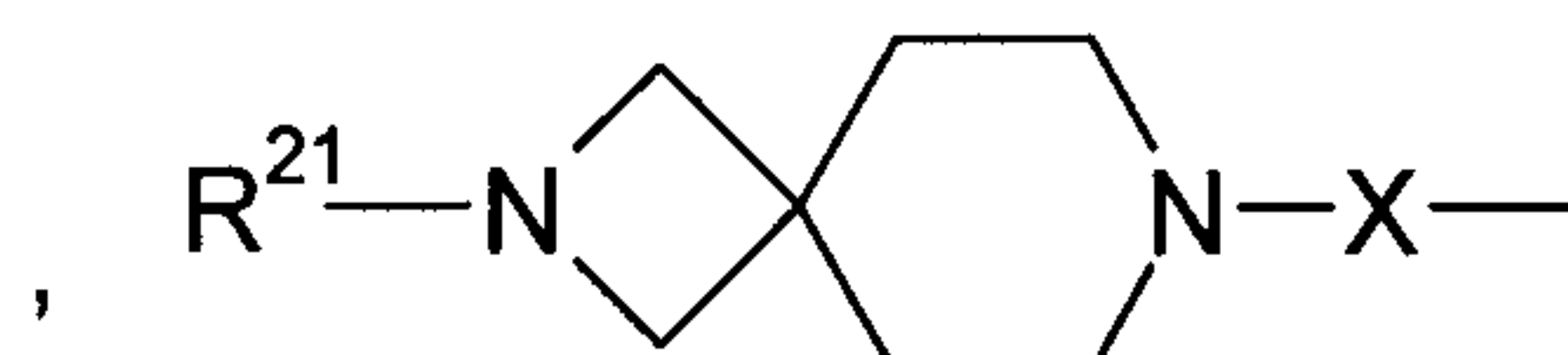
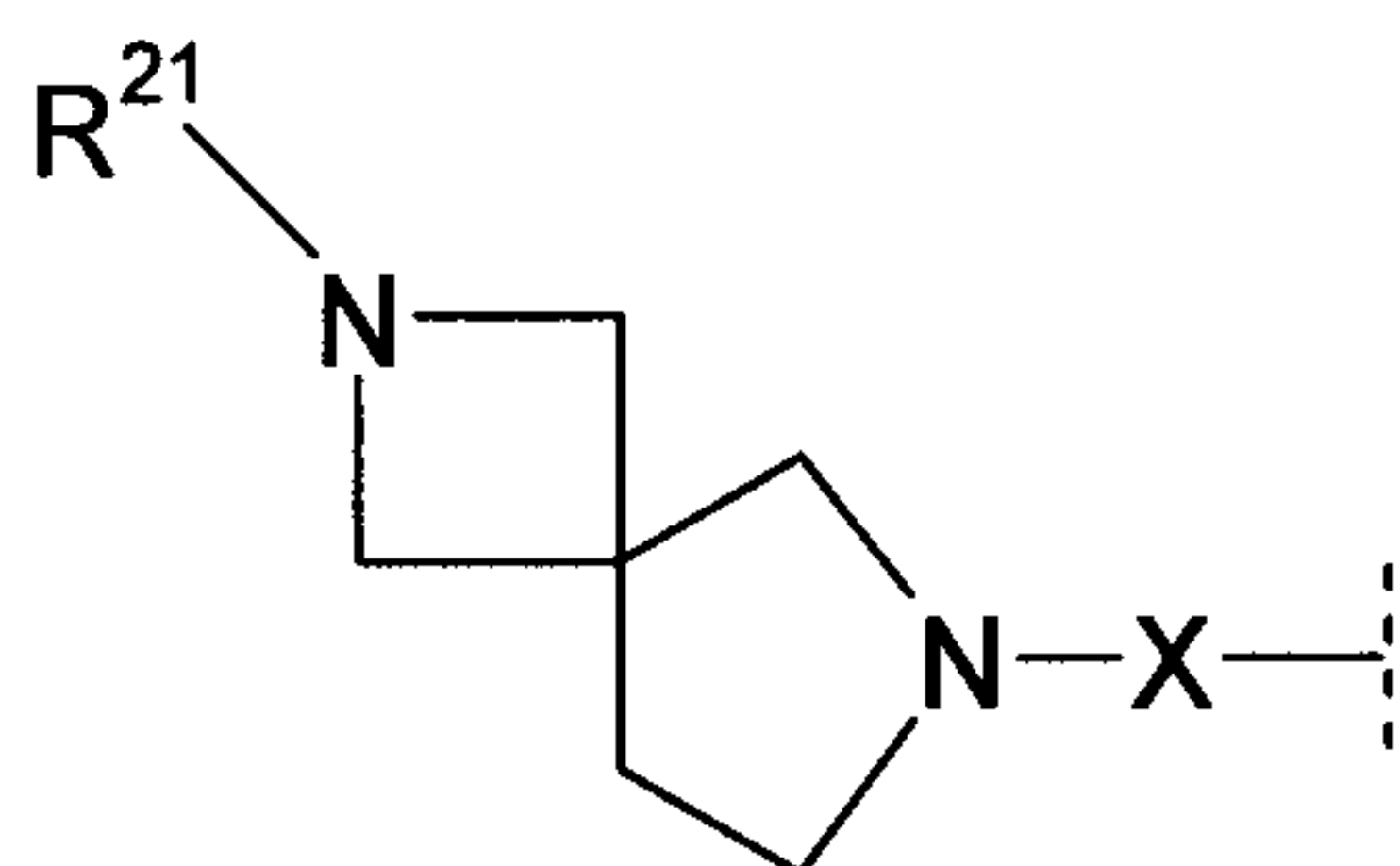
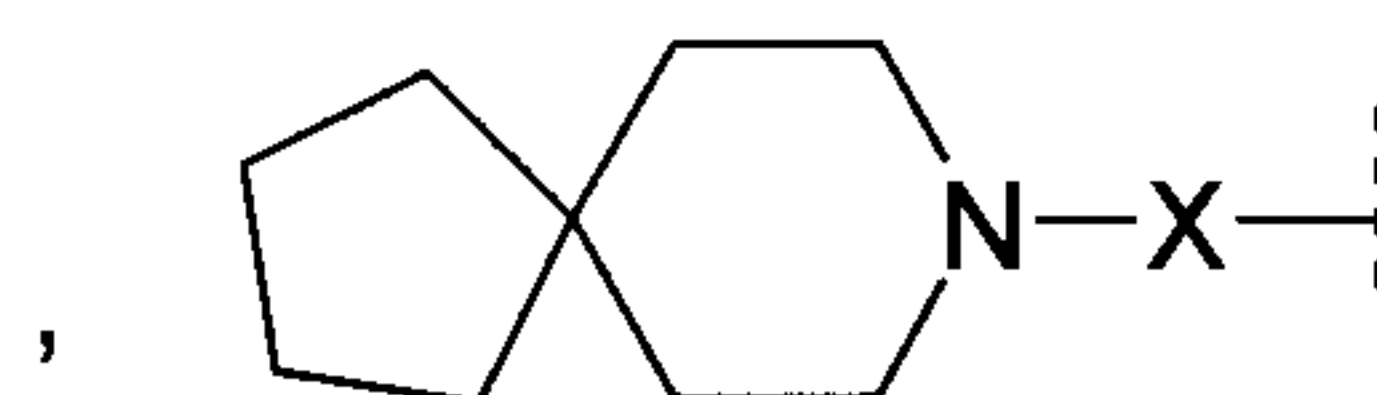
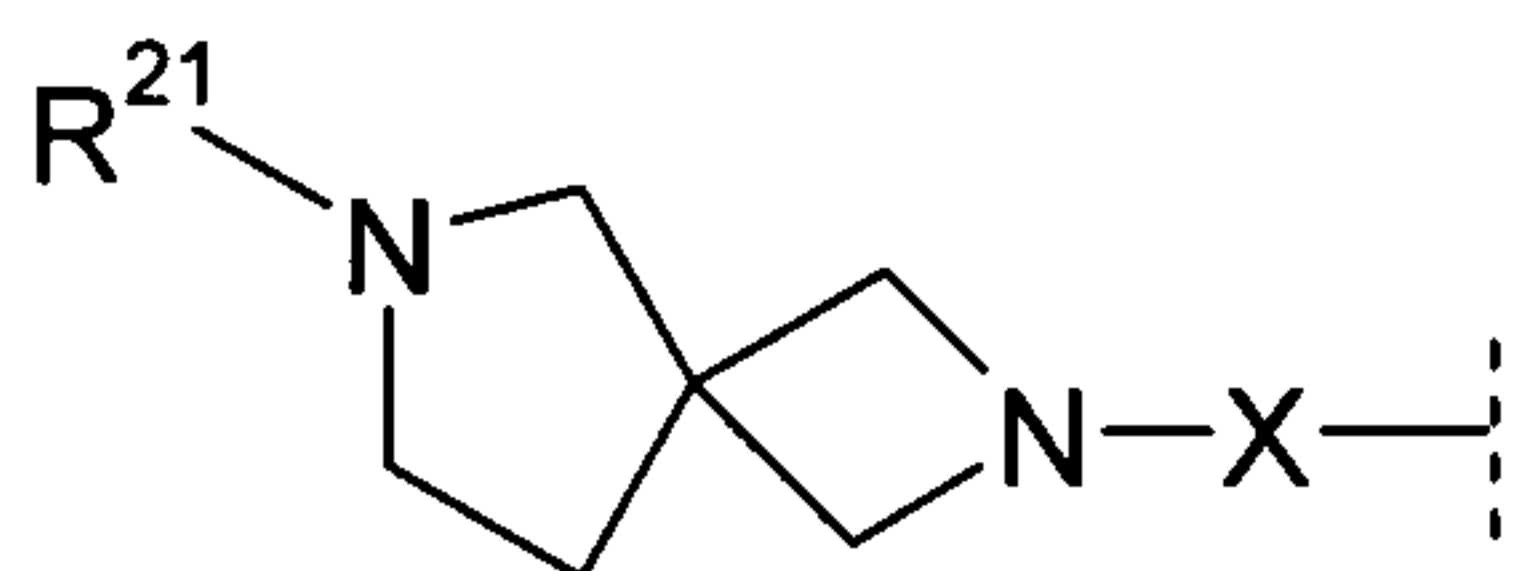
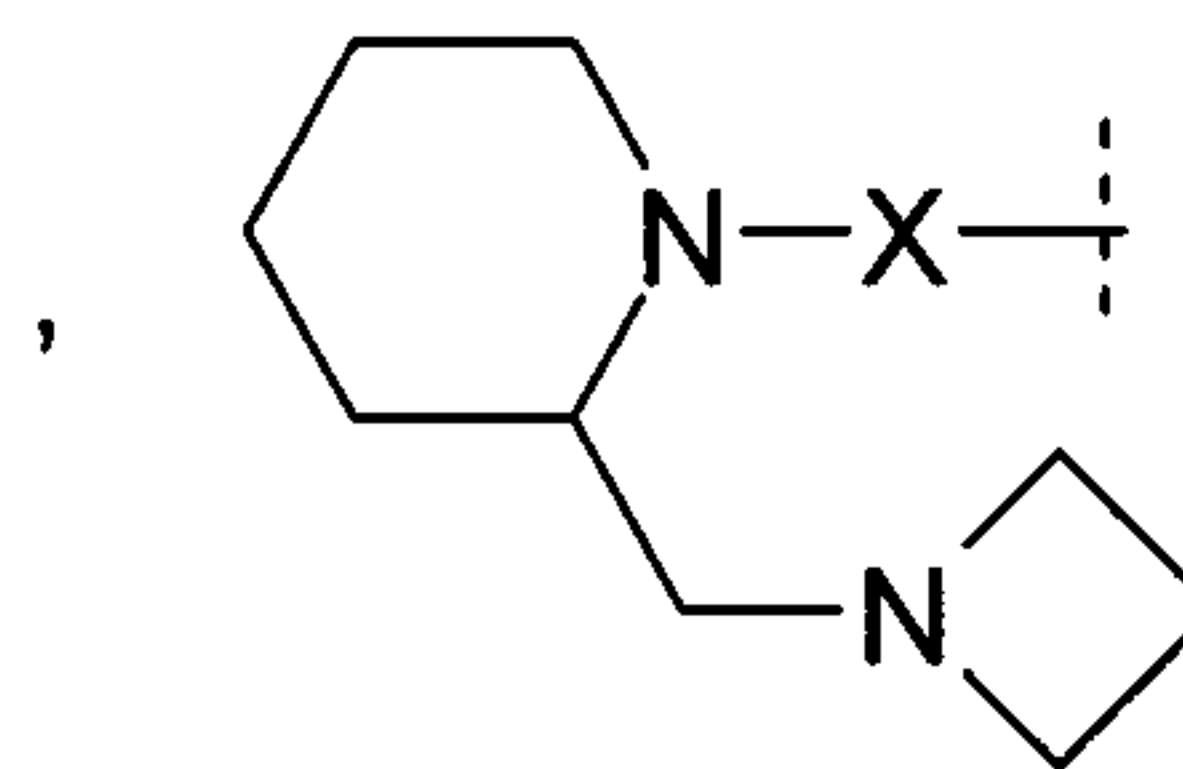
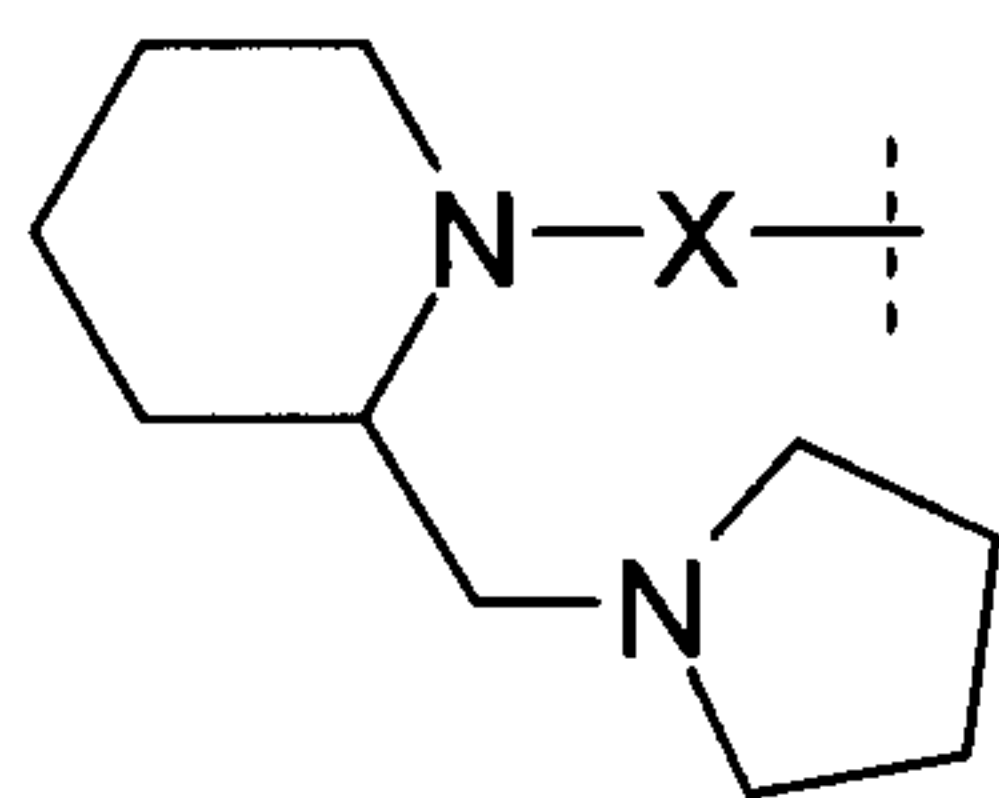


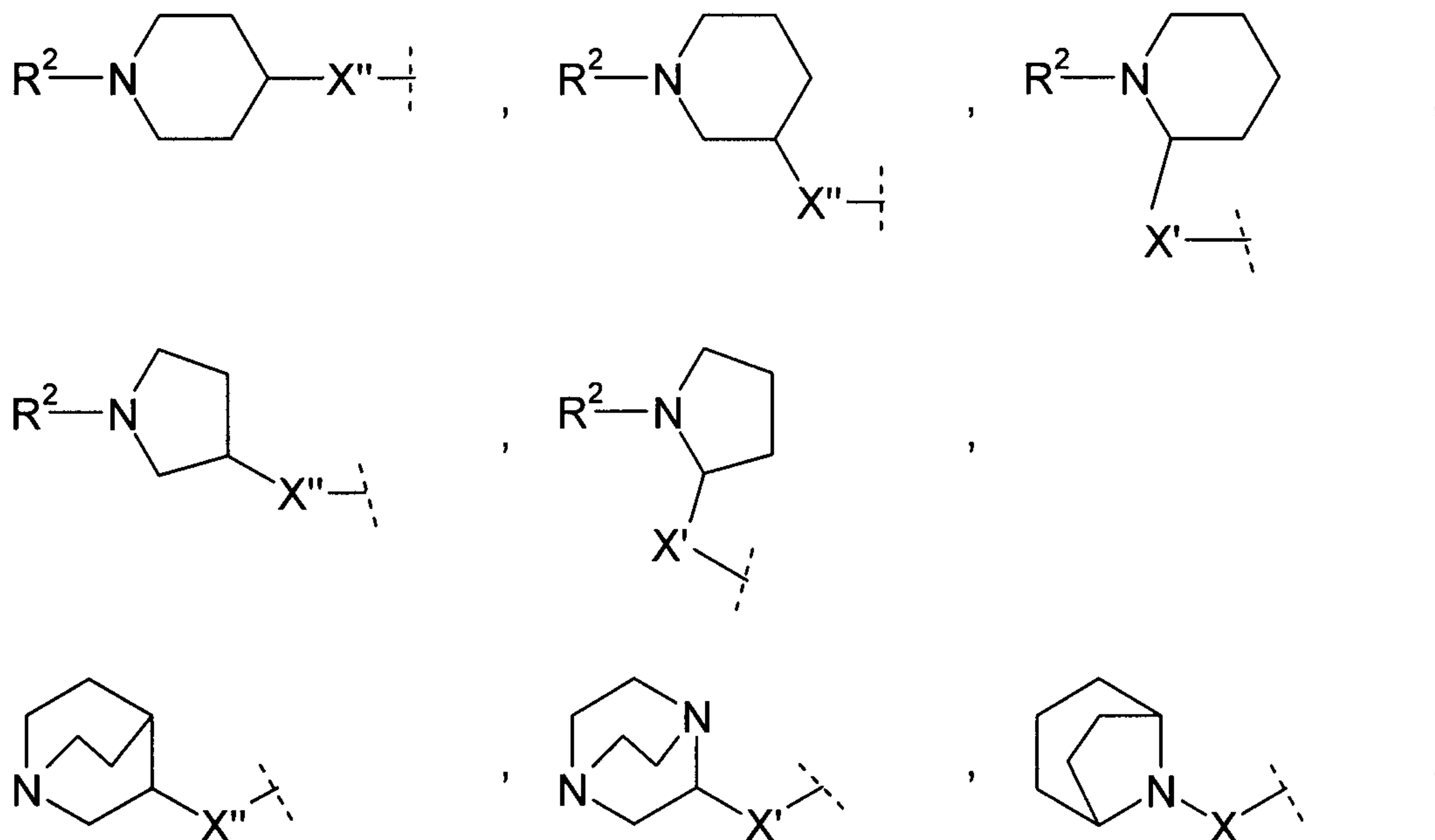
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while in the heterocycle formed by the group R^1R^2N - one or more H atoms may be replaced by R^{14} and/or a H atom may be substituted by Cy defined as C_{3-7} -cycloalkyl, which may be mono- or polysubstituted by R^{20} , and the ring connected to the

5 heterocycle formed by the group R^1R^2N - may be mono- or polysubstituted at one or more C atoms by R^{20} , and in the case of a phenyl ring may also additionally be monosubstituted by nitro, and

X' , X'' independently of one another denote a single bond or C_{1-3} -alkylene and

10 in the event that the group Y is linked to X' or X'' via a C atom, may also denote $-C_{1-3}$ -alkylene-O-, $-C_{1-3}$ -alkylene-NH- or $-C_{1-3}$ -alkylene-N(C_{1-3} -alkyl)-, and

15 X'' additionally also denotes $-O-C_{1-3}$ -alkylene-, $-NH-C_{1-3}$ -alkylene- or $-N(C_{1-3}$ -alkyl)- C_{1-3} -alkylene- and

in the event that the group Y is linked to X'' via a C atom, also denotes $-NH$ -, $-N(C_{1-3}$ -alkyl)- or $-O$ -,

20 while in the meanings given for X' , X'' hereinbefore in each case a C atom may be substituted by R^{10} , preferably by a hydroxy, ω -hydroxy- C_{1-3} -alkyl,

ω -(C₁₋₄-alkoxy)-C₁₋₃-alkyl and/or C₁₋₄-alkoxy group, and/or one or two C atoms in each case may be substituted by one or two identical or different substituents selected from C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₃-alkyl, C₄₋₇-cycloalkenyl and C₄₋₇-cycloalkenyl-C₁₋₃-alkyl, while two alkyl and/or alkenyl substituents may be joined together, forming a carbocyclic ring system, and

in X', X" independently of one another in each case one or more C atoms may be mono- or polysubstituted by F and/or in each case one or two C atoms independently of one another may be monosubstituted by Cl or Br and

wherein R², R¹⁰, R¹³, R¹⁴, R²⁰, R²¹ and X have the meanings given in claim 1.

7. Amide compounds according to one or more of the preceding claims, characterised in that X denotes an unbranched C₁₋₄-alkylene bridge and

in the event that the group Y is linked to X via a C atom, it also denotes a single bond, -CH₂-CH=CH-, -CH₂-C $\equiv$ C-, C₂₋₄-alkylenoxy or C₂₋₄-alkylene-NR⁴,

while the bridge X may be connected to R¹, including the N atom connected to R¹ and X, forming a heterocyclic group, and

in X a C atom may be substituted by R¹⁰ and/or one or two C atoms may each be substituted by one or two identical or different substituents selected from C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₃-alkyl, C₄₋₇-cycloalkenyl and C₄₋₇-cycloalkenyl-C₁₋₃-alkyl, while two alkyl and/or alkenyl substituents may be joined together, forming a carbocyclic ring system, and

in the above-mentioned groups and radicals one or more C atoms may be mono- or polysubstituted by F and/or one or two C atoms independently of one another may be monosubstituted by Cl or Br and

R¹, R⁴ and R¹⁰ are defined as in claim 1.

8. Amide compounds according to claim 7, characterised in that X denotes
-CH₂-, -CH₂-CH₂- or -CH₂-CH₂-CH₂- and

5

in the event that the group Y is linked to X via a C atom, it also denotes
a single bond, -CH₂-CH=CH-, -CH₂-C≡C-, -CH₂-CH₂-O-, -CH₂-CH₂-CH₂-O-,
-CH₂-CH₂-NR⁴- or -CH₂-CH₂-CH₂-NR⁴-,

- 10 while the bridge X may be connected to R¹, including the N atom linked to R¹
and X, forming a heterocyclic group, and

in X a C atom may be substituted by R¹⁰, preferably a hydroxy,
hydroxy-C₁₋₃-alkyl, C₁₋₄-alkoxy-C₁₋₃-alkyl and/or C₁₋₄-alkoxy group, and/or one
15 or two C atoms in each case may be substituted by one or two identical or
different substituents selected from C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₃₋₇-
cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₃-alkyl, C₄₋₇-cycloalkenyl and C₄₋₇-cycloalkenyl-
C₁₋₃-alkyl, while two alkyl and/or alkenyl substituents may be joined together,
forming a carbocyclic ring system, and

20

in each case one or more C atoms may be mono- or polysubstituted by F
and/or in each case one or two C atoms independently of one another may be
monosubstituted by Cl or Br and

- 25 wherein R¹, R⁴ and R¹⁰ have one of the meanings given in claim 1.

9. Amide compounds according to one or more of the preceding claims,
characterised in that the group Y is selected from among the bivalent cyclic
30 groups phenyl, pyridinyl, naphthyl, tetrahydronaphthyl, indolyl, dihydroindolyl,
quinolinyl, dihydroquinolinyl, tetrahydroquinolinyl, isoquinolinyl,
dihydroisoquinolinyl, tetrahydro-isoquinolinyl and benzoxazolinyll,

30

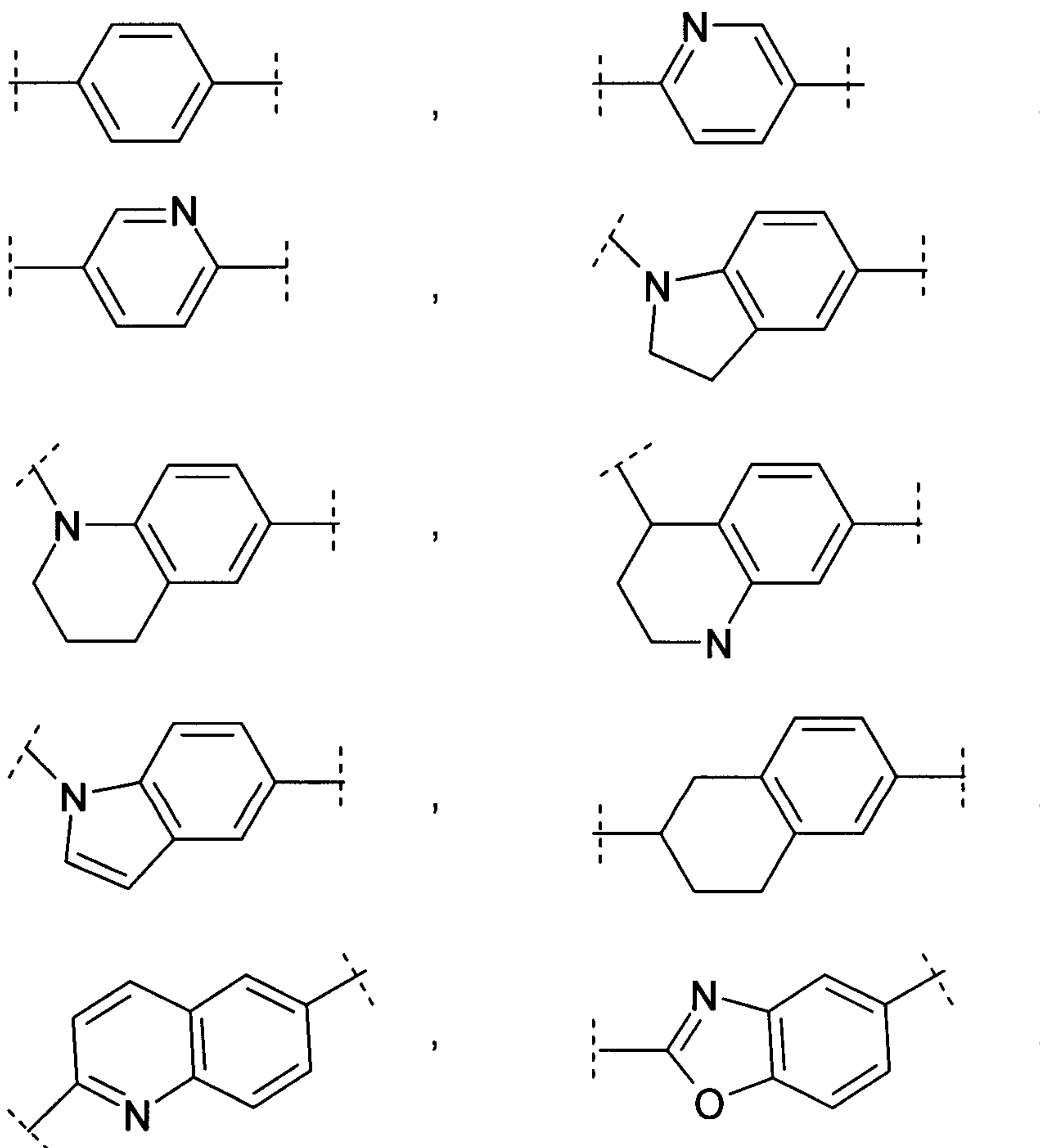
while the above-mentioned cyclic groups may be mono- or polysubstituted by

R^{20} at one or more C atoms, in the case of a phenyl group may also additionally be monosubstituted by nitro, and/or may be substituted by R^{21} at one or more N atoms,

5 while X may be connected to Y as in claim 1, and

X, R^{20} and R^{21} have the meanings given in claim 1.

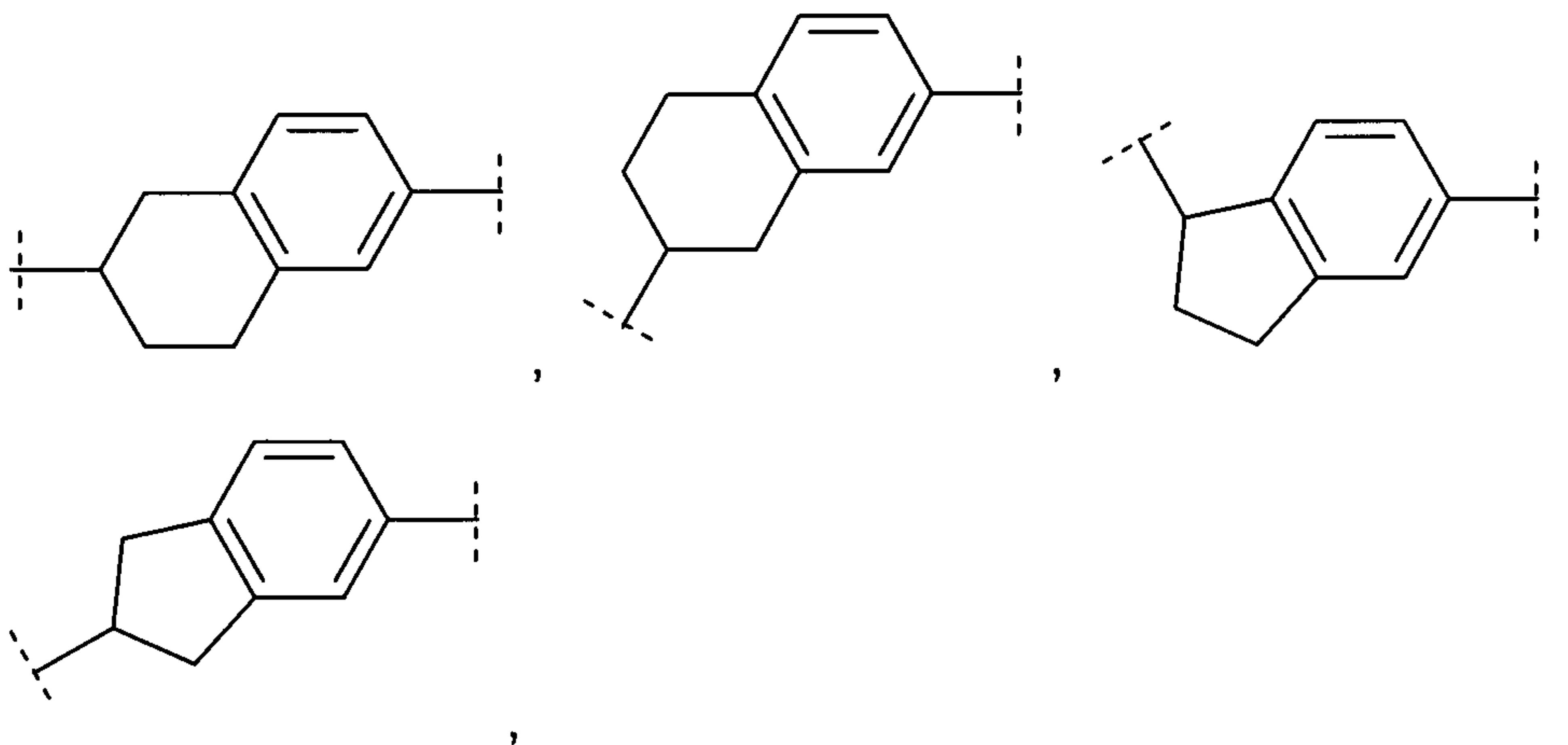
10 10. Amide compounds according to one or more of the preceding claims, characterised in that the group Y is selected from among the bivalent cyclic groups



15 while the above-mentioned cyclic groups may be mono- or polysubstituted by R^{20} at one or more C atoms, in the case of a phenyl group may also

additionally be monosubstituted by nitro, and/or one or more NH groups may be substituted by R^{21} , wherein R^{20} and R^{21} are defined as in claim 1.

- 5 11. Amide compounds according to one or more of the preceding claims, characterised in that the group Y is linked to the group X forming a carbocyclic group fused to Y, while the carbocyclic group -X-Y- formed is selected from



10 while in the above-mentioned bicyclic groups the phenyl ring may be mono- or polysubstituted by R^{20} or may also additionally be monosubstituted by nitro, and the saturated carbocyclic ring may be mono- or disubstituted by C_{1-3} -alkyl.

- 15 12. Amide compounds according to one or more of the preceding claims, characterised in that the group A denotes phenyl, pyridyl or naphthyl,

20 while the above-mentioned cyclic groups may be mono- or polysubstituted by R^{20} at one or more C atoms, and in the case of a phenyl ring may also additionally be monosubstituted by nitro, and/or one or more NH groups may be substituted by R^{21} , while if the index b has the value 0, the group A does not have an amino group as substituent in the ortho position to the bridge W, and

25

R^{20} and R^{21} have the meanings given in claim 1.

13. Amide compounds according to one or more of the preceding claims, characterised in that b has the value 0.

5

14. Amide compounds according to one or more of the preceding claims, characterised in that b has the value 1 and B has a meaning selected from the group consisting of phenyl, furanyl, thienyl and pyridyl,

10

while the above-mentioned cyclic groups may be mono- or polysubstituted by R^{20} at one or more C atoms, and in the case of a phenyl ring may also additionally be monosubstituted by nitro, and

R^{20} has the meaning given in claim 1.

15

15. Amide compounds according to one or more of the preceding claims, characterised in that

20

Y is defined according to claim 9 or 10 and 11,

A is defined according to claim 12,

B is defined according to claim 14 and

25

b denotes the value 0 or 1.

16. Amide compounds according to claim 15, characterised in that

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R^1, R^2 are defined as in claim 4 and 5 or 4 and 6,

X is defined as in claim 7 or 8,

W and Z are defined as in claim 2 or 3.

17. Amide compounds according to one or more of the preceding claims,
characterised in that

R^{20} denotes F, Cl, Br, I, OH, cyano, C₁₋₄-alkyl, C₁₋₄-alkoxy, difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethoxy, amino, C₁₋₃-alkyl-amino, di-C₁₋₃-alkyl-amino, carboxy or C₁₋₄-alkoxy-carbonyl, while substituents R^{20} occurring more than once may have the same or different meanings and in the case of a phenyl ring this may also additionally be monosubstituted by nitro.

18. Physiologically acceptable salts of the amide compounds according to one or more of claims 1 to 17.

19. Composition containing at least one amide compound according to one or more of claims 1 to 17 and/ or a salt according to claim 18 optionally together with one or more physiologically acceptable excipients.

20. Pharmaceutical compositions, containing at least one amide compound according to one or more of claims 1 to 17 and/ or a salt according to claim 18 optionally together with one or more inert carriers and/or diluents.

21. Use of at least one amide compound according to one or more of claims 1 to 17 and/ or a salt according to claim 18, including the compounds excluded by provisos (M1) to (M14) according to claim 1, for influencing the eating behaviour of a mammal.

22. Use of at least one amide compound according to one or more of claims 1 to 17 and/ or a salt according to claim 18, including the compounds excluded by

provisos (M1) to (M14) according to claim 1, for reducing the body weight and/ or for preventing an increase in the body weight of a mammal.

- 5 23. Use of at least one amide compound according to one or more of claims 1 to 17 and/ or a salt according to claim 18, including the compounds excluded by provisos (M1) to (M14) according to claim 1, for preparing a pharmaceutical composition with an MCH-receptor-antagonistic activity.
- 10 24. Use of at least one amide compound according to one or more of claims 1 to 17 and/ or a salt according to claim 18, including the compounds excluded by provisos (M1) to (M14) according to claim 1, for preparing a pharmaceutical composition, which is suitable for preventing and/or treating symptoms and/or diseases which are caused by MCH or are otherwise causally connected with MCH.
- 15
25. Use of at least one amide compound according to one or more of claims 1 to 17 and/ or a salt according to claim 18, including the compounds excluded by provisos (M1) to (M14) according to claim 1, for preparing a pharmaceutical composition, which is suitable for preventing and/or treating metabolic disorders and/or eating disorders, particularly obesity, bulimia, bulimia nervosa, cachexia, anorexia, anorexia nervosa and hyperphagia.
- 20
- 25 26. Use of at least one amide compound according to one or more of claims 1 to 17 and/ or a salt according to claim 18, including the compounds excluded by provisos (M1) to (M14) according to claim 1, for preparing a pharmaceutical composition, which is suitable for preventing and/or treating diseases and/or disorders associated with obesity, particularly diabetes, especially type II diabetes, complications of diabetes including diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, insulin resistance, pathological glucose tolerance, encephalorrhagia, cardiac insufficiency, cardiovascular diseases, particularly arteriosclerosis and high blood pressure, arthritis and gonitis.
- 30

27. Use of at least one amide compound according to one or more of claims 1 to 17 and/ or a salt according to claim 18, including the compounds excluded by provisos (M1) to (M14) according to claim 1, for preparing a pharmaceutical composition which is suitable for preventing and/or treating hyperlipidaemia, cellulitis, fat accumulation, malignant mastocytosis, systemic mastocytosis, emotional disorders, affective disorders, depression, anxiety, sleep disorders, reproductive disorders, sexual disorders, memory disorders, epilepsy, forms of dementia and hormonal disorders.
28. Use of at least one amide compound according to one or more of claims 1 to 17 and/ or a salt according to claim 18, including the compounds excluded by provisos (M1) to (M14) according to claim 1, for preparing a pharmaceutical composition which is suitable for preventing and/or treating micturition disorders, such as for example urinary incontinence, hyperactive urinary bladder, urgency, nycturia and enuresis.
29. Process for preparing a composition or a pharmaceutical composition according to one or more of claims 19 to 28, characterised in that at least one amide compound according to one or more of claims 1 to 17 and/ or a salt according to claim 18 is incorporated in one or more inert carriers and/or diluents by a non-chemical method.
30. Pharmaceutical compositions, containing
- a first active substance selected from the amide compounds according to one or more of claims 1 to 17 and/ or a salt according to claim 18, including the compounds excluded by provisos (M1) to (M14) according to claim 1, and
- a second active substance selected from the group consisting of active substances for the treatment of diabetes, active substances for the treatment of diabetic complications, active substances for the treatment of obesity, preferably other than MCH antagonists, active substances for the treatment of high blood pressure, active substances for the treatment of hyperlipidaemia, including arteriosclerosis, active substances for the treatment of arthritis, active

substances for the treatment of anxiety states and active substances for the treatment of depression,

optionally together with one or more inert carriers and/or diluents.

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