

EUROPEAN QUALIFYING EXAMINATION 2013

Paper B(Ch)

Chemistry

This paper comprises:

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| * Description of the application | 2013/B(Ch)/EN/1-4 |
| * Claims | 2013/B(Ch)/EN/5-6 |
| * Communication | 2013/B(Ch)/EN/7-8 |
| * Document D1 | 2013/B(Ch)/EN/9-12 |
| * Document D2 | 2013/B(Ch)/EN/13-14 |
| * Letter from the applicant
(including new set of claims) | 2013/B(Ch)/EN/15-16 |

Description of the applicationUrea derivatives and their use as repellents

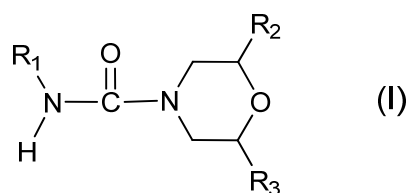
[001] The invention relates to new urea derivatives, to processes for their preparation, and to their use as agents for repelling insects (such as mosquitoes) and arachnids (such as mites or ticks).

[002] There is a constant search for repellents which exhibit high activity and essentially no toxicity towards animals and humans.

[003] One particularly well-known and long-used agent is DEET. Urea derivatives which have an insect-repelling effect are also known.

[004] A major deficiency of known repellents is that their effect is too weak or relatively short, lasting only a few hours.

[005] Now, new morpholine ring-containing urea derivatives of formula (I)



have been found, wherein

R_1 , R_2 , R_3 each independently stand for optionally substituted alkyl, as well as their pharmaceutically acceptable salts.

[006] The preferred compounds are those wherein

R_1 stands for lower alkyl and

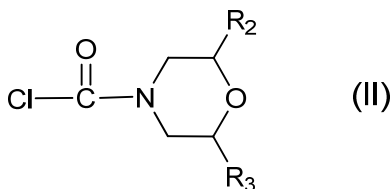
R_2, R_3 each independently stand for lower alkyl substituted by Cl, F, OH or CN.

[007] The preferred substituents for the R_2 and R_3 groups are CN or F. CN is particularly preferred.

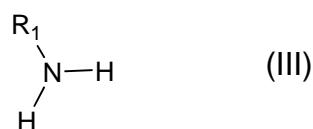
[008] "Alkyl" is taken to mean a saturated hydrocarbon group containing only C and H atoms. "Lower alkyl" is taken to mean an alkyl group containing from 1 to 4 C atoms (C_1 - C_4 alkyl). Examples are CH_3 (methyl) and C_2H_5 (ethyl).

[009] It has also been found that compounds of formula (I), wherein residues R_1 to R_3 have the meanings stated above, can be prepared as follows:

Morpholine compounds of formula (II)



are reacted with compounds of formula (III)



in a solvent in the presence of a base to form compounds of formula (I). The yields may be increased by performing the reaction in the presence of a crown ether as phase-transfer catalyst.

[010] Compounds of formula (I) have a strong insect- and mite-repelling effect.



Examples

[011] Example 1: A compound of formula (I) wherein $R_1 = R_2 = R_3 = C_2H_5$.

50 ml of ethylamine and the same amount of toluene are mixed with 3 g of 2,6-diethyl-4-chlorocarbonyl-morpholine, under cooling with ice/NaCl at approx. $-10^\circ C$. Then 0.5 g of dibenzo-18-crown-6 is added as phase-transfer catalyst. The reaction mixture is stirred for six hours at approx. $-5^\circ C$, filtered and washed with ample toluene.

The filtrate is purified by column chromatography (the eluent being toluene: chloroform = 8 : 2). The solvent is removed in a rotary evaporator, and the oily residue is recrystallised from ethanol. 2.4 g of a pale yellow solid are obtained.

Melting point: $162-164^\circ C$.

[012] Examples 2 - 5: Compounds of formula (I) corresponding to examples 2 to 5 of table 1 (see below) were prepared analogously.

Repellent effect against yellow fever mosquitoes

[013] The strength of the repellent effect against yellow fever mosquitoes of the compounds according to the invention was determined using the method described in *Progress in Parasitology*, 1976, vol. 33, No. 6, pp. 223-225. The repellent coefficients C_R thus calculated are expressed as a percentage (%). A high value (max. 100) indicates a stronger repellent effect and a lower value (min. zero) indicates a weaker repellent effect (see table 1). The repellent effect is good if C_R is at least 70 and very good if C_R is at least 90.

Table 1: Yellow fever mosquitoes-repelling effect

Example No.	R_1	R_2	R_3	C_R
1	C_2H_5	C_2H_5	C_2H_5	72
2	CH_3	CH_3	CH_3	68
3	CH_3	CH_2CN	CH_2CN	98
4	CH_3	CH_2F	CH_2F	84
5	C_2H_5	CF_3	CF_3	85



Repellent effect against mites

[014] Each test compound was dissolved in acetone. Strips of paper 2.5 cm² in size were first impregnated with the solution, such that the test compounds were present in an amount of 10 µg per cm², and were then dried. Paper strips impregnated only with acetone acted as controls. A defined number of mites and a strip of impregnated paper were placed in a plastic container, which was then closed. After 15 minutes a count was made of the number of mites that had climbed up the front and back of the paper strip. The procedure was repeated three times. The resultant average value was compared with that of the control group.

The repellence rate was calculated using the following equation:

$$\text{repellence rate} = [(A - B) / A] \times 100 (\%)$$

where A is the number of mites that had climbed up in the control group and B is the number of mites that had climbed up in the treated group. Thus a higher value means higher repellent effectiveness (see table 2). It is considered that there is a mite-repelling effect if the repellence rate is at least 20.

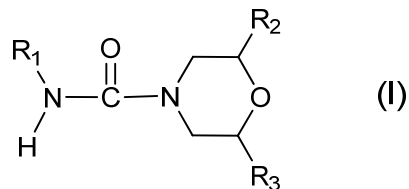
Table 2: Mite-repelling effect

Example No.	Compounds of formula (I)			Repellence rate
	R ₁	R ₂	R ₃	
1	C ₂ H ₅	C ₂ H ₅	C ₂ H ₅	52
2	CH ₃	CH ₃	CH ₃	14
3	CH ₃	CH ₂ CN	CH ₂ CN	81
4	CH ₃	CH ₂ F	CH ₂ F	80
5	C ₂ H ₅	CF ₃	CF ₃	82



Claims

1. Compounds of formula (I),



wherein

R_1 , R_2 , R_3 each independently stand for optionally substituted alkyl, as well as their pharmaceutically acceptable salts.

2. Compounds of formula (I) according to claim 1, wherein

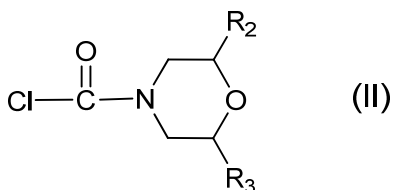
R_1 stands for lower alkyl and

R_2 , R_3 each independently stand for lower alkyl substituted by Cl, F, OH or CN,

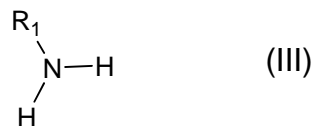
as well as their pharmaceutically acceptable salts.



3. Process for the preparation of compounds of formula (I) according to claim 1 characterised in that morpholine compounds of formula (II)



are reacted with compounds of formula (III)



in a solvent in the presence of a base.

4. Insect- and mite-repelling agents characterised in that they contain at least one compound of formula (I) according to claim 1.



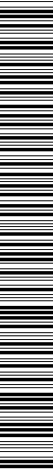
Communication

1. This communication is based on the application as originally filed. Attached documents D1 and D2 are prior art according to Article 54(2) EPC.
2. Document D1 discloses morpholine ring-containing urea derivatives corresponding to formula (I) of the application. The compounds in D1 are also insect repellents. The subject-matter of the present claim 1 is not novel in view of claims 1 and 2 of D1. Moreover, D1 discloses an individual compound which corresponds to formula (I) of the application (see example 3 in the table in D1). This compound is novelty-destroying for the subject-matter of claims 1 and 2. The subject-matter of claim 4 is not novel over claim 3 of D1.
3. Document D2 discloses a compound which is prejudicial to the novelty of the subject-matter of claims 1 and 2. D2 also destroys the novelty of claims 3 and 4.
4. The subject-matter of claim 2 lacks clarity (Article 84 EPC) in respect of the term "lower alkyl" as the claim does not define the number of possible C atoms.
5. If the applicant wishes to maintain the application, amended claims taking the above objections into account should be filed. These amended claims would need to satisfy the EPC's requirements with respect to novelty, inventive step, clarity and, where appropriate, unity of invention. They should also not feature any amendments which cause the subject-matter to extend beyond the content of the application as originally filed (Article 123(2) EPC).



6. The letter of reply should set out the difference between the new claims and the prior art disclosed in documents D1 and D2 as well as its significance as regards inventive step. The technical problem underlying the invention compared with the closest prior art and the solution to that problem should emerge clearly from the applicant's arguments.

7. To make it easier to assess whether the amended claims comprise subject-matter which extends beyond the content of the application as filed, the applicant is urged to give an exact indication of the points in the application as filed to which the proposed amendments relate (Article 123(2) EPC).



Document D1

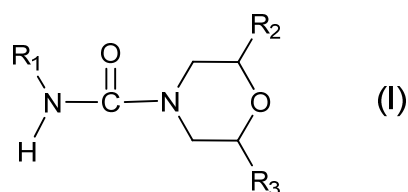
Insect-repelling agents

[001] The present invention relates to insect-repelling agents based on heterocyclic urea derivatives for use on human skin.

[002] Substances with a repellent effect against insects (e.g. mosquitoes, flies, fleas) and against arachnids (e.g. mites, ticks) are already known. DEET has long been in use as an insect repellent.

[003] A major deficiency of known repellents is that their effect is too weak or relatively short. A search has therefore been made for substances which have a better repellent effect, i.e. having a maximally prolonged effectiveness, or requiring a lower concentration for the same effectiveness.

[004] New repellents have now been found which contain heterocyclic urea derivatives of formula (I),

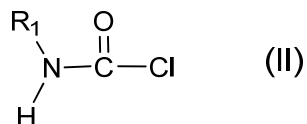


wherein

R₁, R₂, R₃ each independently stand for optionally substituted alkyl.

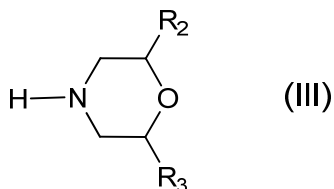
[005] Alkyl preferably has from 1 to 18 C atoms. Optionally, the alkyl radical may independently be substituted by one or more substituents from the group OH, OCH₃, OC₂H₅, NO₂ or NH₂.

[006] The new compounds of formula (I) can be prepared by reacting under suitable conditions carbamic acid derivatives of formula (II),



wherein R₁ has the meaning stated above,

with heterocyclic compounds of formula (III),



wherein R₂ and R₃ have the meanings stated above.

[007] The compounds of formula (I) numbered 1 to 5 in the table below were prepared using the described process.

[008] The new urea derivatives of formula (I) can be mixed with the usual extenders and/or surface-active agents to prepare repellents. They have a marked insect-repelling effect which is significantly better than that of the known repellent DEET. They are also assumed to have a mite-repelling effect.



Repellence test with fleas and yellow fever mosquitoes

[009] The compounds according to the invention were tested with fleas and yellow fever mosquitoes. The test method applied was described in *Progress in Parasitology*, 1976, vol. 33, No. 6, pp. 223-225.

[010] The table shows the results of the lab tests in the form of the calculated repellent coefficients (C_R) compared with the known repellent DEET.

Table:

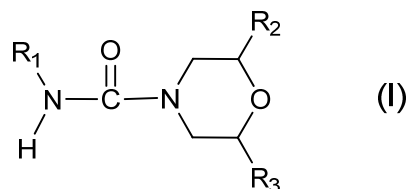
Example No.	R ₁	R ₂	R ₃	C _R (%) (fleas)	C _R (%) (yellow fever mosquitoes)
1	CH ₃	CH ₃	CH ₃	75	71
2	C ₂ H ₅	CH ₃	CH ₃	70	68
3	CH ₃	CH ₂ OH	CH ₂ OH	54	80
4	C ₂ H ₅	C ₂ H ₅	C ₂ H ₅	47	72
5	CH ₃	C ₂ H ₅	C ₂ H ₅	80	74
Reference substance: DEET				45	62

[011] The higher the value of C_R , the stronger the repellent effect. All tested compounds according to the invention have a repellent effect greater than that of the reference substance DEET.



Claims

1. Heterocyclic urea derivatives of formula (I)



wherein

R_1 , R_2 , R_3 each independently stand for optionally substituted alkyl, as well as their pharmaceutically acceptable salts.

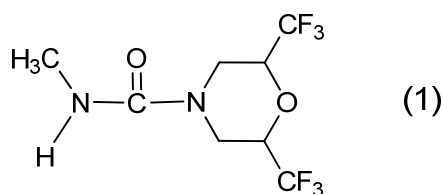
2. Heterocyclic urea derivatives of formula (I) according to claim 1 wherein the optionally present substituents are selected from the group OH, OCH₃, OC₂H₅, NO₂ or NH₂, as well as their pharmaceutically acceptable salts.
3. Insect-repelling agents characterised in that they contain at least one heterocyclic urea derivative of formula (I) according to claim 1.
4. Use of heterocyclic urea derivatives of formula (I) according to claim 1 to repel insects.



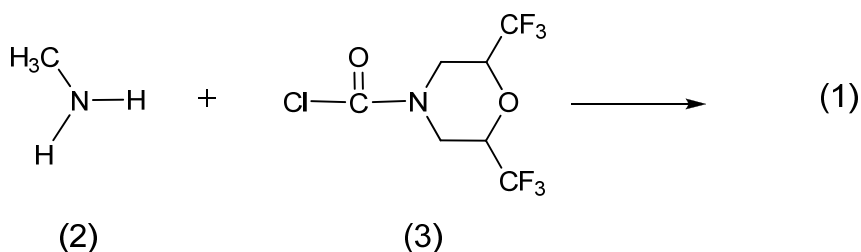
Document D2

Flavour AGInformation on compound F123456

Structural formula:

Molecular formula: $C_8H_{10}N_2O_2F_6$

Preparation:



Reaction conditions:

The compound of formula (2) is reacted with the compound of formula (3) in a solvent (such as benzene, toluene or 1,2-dichloroethane) in the presence of a base at temperatures between -10°C and $+30^{\circ}\text{C}$ to form a compound of formula (1).



Properties:

- easily soluble in organic solvents;
- colourless crystals, melting point: 78°C.

Use:

Compound (1) can be used as a highly effective insect repellent in scented candles or scented oils. Its use as an additive in apricot oil, coconut oil, St John's wort oil, sesame oil, sea buckthorn oil, almond oil, macadamia oil and jojoba oil causes no impairment or alteration of the scent of those oils. The insect-repelling effect is reinforced if compound (1) is combined with citronella oil.



Letter from the applicant

Dear Dr. Milbe,

You have informed us that documents prejudicial to novelty have been found in the course of grant proceedings for a European patent for our application entitled "Urea derivatives and their use as repellents". We should like you to make sure that we are granted a patent for our application, even if its scope is limited compared with the original claims.

We have thoroughly analysed the arguments raised in the European Patent Office's communication and in response have drafted an amended set of claims, which we enclose. We hope our new set of claims has essentially overcome the EPO's objections, but we leave it to you to make further amendments as necessary.

In the new claim 1, the contested term "lower alkyl" in the definitions of R_2 and R_3 has been replaced with "C₁-C₄ alkyl".

R_2 and R_3 have been amended such as to establish novelty vis-à-vis document D1.

In the new claim 1 we have added a disclaimer to establish novelty vis-à-vis D2.

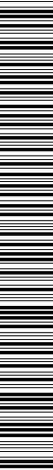
In the new claim 2 directed to the preparation process we have added the presence of a crown ether.

In our opinion an inventive step is involved.

Regards,

Dr. R. E. Pellent
Goaway GmbH

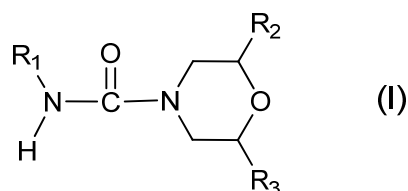
Attachment: New set of claims (claims 1-3)



Letter from the applicant

Attachment: New set of claims

1. Compounds of formula (I)



wherein

R_1 stands for C_1 - C_4 alkyl,

R_2 and R_3 each independently stand for C_1 - C_4 alkyl substituted by CN or F, as well as their pharmaceutically acceptable salts,

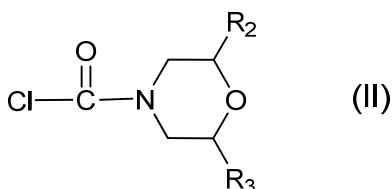
excluding the compound of formula (I)

wherein R_1 stands for CH_3 ,

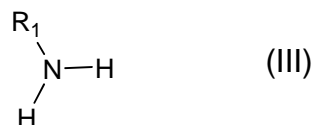
R_2 stands for CF_3 and

R_3 stands for CF_3 .

2. Process for the preparation of compounds of formula (I) according to claim 1 characterised in that morpholine compounds of formula (II)



are reacted with compounds of formula (III)



in a solvent in the presence of a base and in the presence of a crown ether.

3. Insect- and mite-repelling agents characterised in that they contain at least one compound of formula (I) according to claim 1.

