



- (51) **International Patent Classification:**
A01N 43/84 (2006.01) *C07D 265/30* (2006.01)
- (21) **International Application Number:**
PCT/IN2012/000003
- (22) **International Filing Date:**
3 January 2012 (03.01.2012)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
204/DEL/2011 28 January 2011 (28.01.2011) IN
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(81) **Designated States** (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

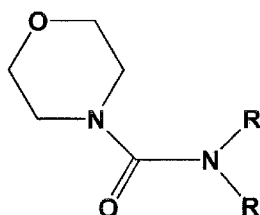
Declarations under Rule 4.17:

— of inventorship (Rule 4.17(iv))

Published:

— with international search report (Art. 21(3))

(54) **Title:** N, N- DIALKYL -MORPHOLIN- 4 - CARBOXAMIDE COMPOUNDS AS INSECT REPELLING AGENTS AND A PROCESS FOR THEIR PREPARATION



(I)

(57) **Abstract:** "An insect repelling compound and a process for preparation thereof. The present invention discloses a compound of formula I and a process for preparation thereof. The compound exhibits insect repellent properties. The invention also discloses pharmaceutical composition comprising the said compound. — N R O R Formula I which R is (CH₂)_n CH₃, or a pharmaceutically acceptable salts thereof, wherein

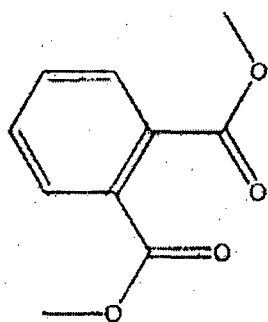
N,N-DIALKYL-MORPHOLIN-4-CARBOXAMIDE COMPOUNDS AS INSECT REPELLING
AGENTS AND A PROCESS FOR THEIR PREPARATION

FIELD OF INVENTION

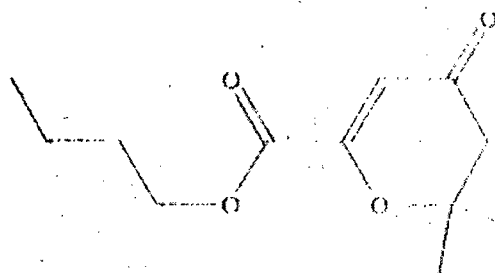
The present invention discloses a compound of the formula I or a pharmaceutically acceptable salts thereof and process for preparation thereof. The compound of formula I exhibits insect repellent properties. The invention discloses the pharmaceutical compositions comprising the compound of formula I along with pharmaceutical acceptable carrier.

PRIOR ART

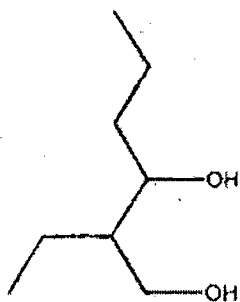
Before Second World War, there were only four principal repellents in use namely (i) oil of citronella oil, (ii) dimethyl phthalate, discovered in 1929, (iii) n-butyl 6, 6-dimethyl-5,6-dihydro-1, 4-pyrone-2-carboxylate (Indalone), which was patented in 1937 and (iv) 2-ethyl-1,3-hexanediol (Rutgers 612), which became available in 1939.



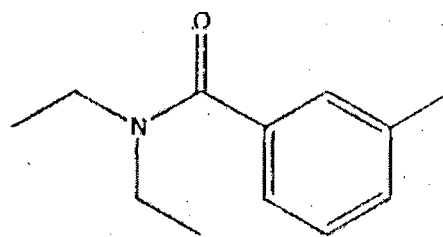
Dimethyl phthalate



6,6-Dimethyl-4-oxo-5,6-dihydro-4H-pyran-2-carboxylic acid butyl ester
(Indalone)



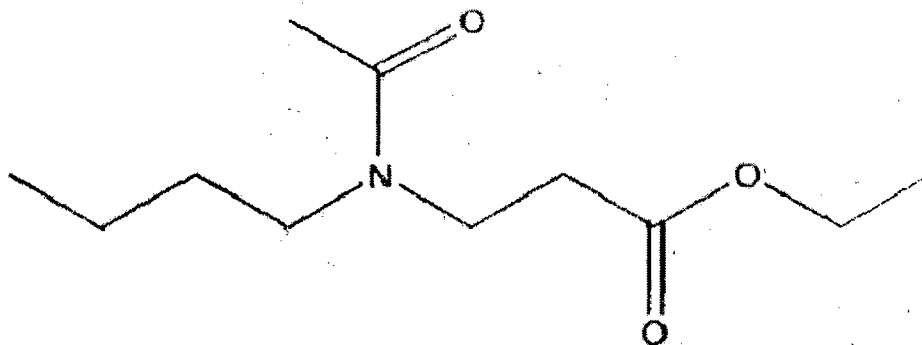
2-Ethyl-1,3-hexanediol (Rutgers 612)



N,N-Diethyl-3-methyl-benzamide (DEET)

In 1953, the insect repellent properties of *N,N*-diethyl-*m*-toluamide (DEET) were discovered and DEET remains the principal, and still generally considered, the most effective repellent in use today more than 50 years after its discovery. DEET is a broad spectrum repellent that is highly effective against all mosquitoes; other insects of medical importance repelled by DEET include sand flies, black flies, chiggers, hard and soft ticks, bedbugs, and fleas. It is therefore now used as the “gold-standard” repellent against which other substances are compared in laboratory and field trials.

Another Insect repellent, 3-(*N*-acetyl-*N*-butyl) aminopropionic acid ethyl ester, also known as IR 3535 or MERCK 3535 was developed in 1975 by Merck, and has been on the market in Europe for the past twenty years. It has low toxicity, although it is irritating to the eyes and sometimes the skin. It became available in the USA in 1999 after being approved by the Environmental Protection Agency. Efficacy data IR 3535 is in general comparable with DEET. Further World Health Organisation has approved it as an insect repellent for application to human skin and clothing in public health applications, to repel biting arthropods such as mosquitoes, flies and ticks and there is not a single recorded incidence of an adverse reaction to this compound.



3-(*N*-Acetyl, *N*-butyl-amino)-propionic acid ethyl ester
(IR3535)

Several piperidine-based compounds have been reported as effective repellents against mosquito (McGovern TP, Schreck CE Alicyclic piperidine derivatives as insect

repellents. US Patent 4,291,041, 1981). This interest in finding DEET alternatives has been motivated by the controversy around the safety of DEET, its low user acceptability and its plasticizing effect.

1-piperidine carboxylic acid, 2(2-hydroxyethyl)-1-methylpropyl ester was developed by Bayer using molecular modeling in 1980. It has several synonyms: Picaridin, the common name; I caridin used by WHO, Bayrepel and KBR 3023. This compound, the most recent piperidine derivative, is registered in many European, South American, Asian and African countries as well as Japan, Canada and USA. It does not have a significant plasticizing effect, which is a major drawback of DEET. Cosmetically, it is superior to DEET as it is colourless, odourless and has a pleasant feel on the skin. In addition, efficacy of picaridin is excellent, and it is generally superior to DEET in terms of long protection period because it evaporates at a slower rate than DEET.

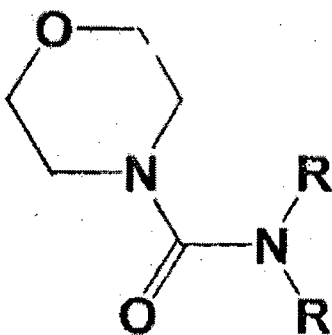
The piperidine compounds namely, 1-[3-cyclohexen-1-ylcarbonyl] piperidine called AI3-35765 and 1-[3-cyclohexan-1-ylcarbonyl]-2-methylpiperidine known as AI3-37220 were first synthesized in 1978. The latest addition in piperidine-based repellents is (1S, 2S)-2-methylpiperidinyl-3-cyclohexan-1-carboxamide, known as SS220 but its advantage lies in the fact that it is a single stereoisomer which is active, and therefore production cost will be more.

N,N-diethylphenylacetamide (DEPA) was developed by DRDE, Gwalior to use as multi-insect repellent in India. It is also commercially available in various formulations in India. It has similar cosmetic properties to DEET, similar dermal absorption and excretion, plus the symptoms of acute poisoning with DEPA are similar to DEET (S.S. Rao et al, Toxicologic studies of an insect repellent, N,N-diethylphenylacetamide, Indian J Med Res, 1987, 85, 626). Many of its analogs were also synthesized and evaluated for possible use as insect repellents.

A large number of repellents of plants origin are reported in the literature (Cox, C. Plant-based mosquito repellents: making a careful choice, Journal of pesticide reform, 2005, Vol.25, No.3, page 6-7). Plant-derived substances that repel mosquitoes include citronella; eucalyptus, cedar, verbena, pennyroyal, geranium, lavender, pine, cajuput, cinnamon, rosemary, basil, thyme, allspice, garlic, and peppermint. However, these products only provide temporary protection. Many formulations based on these natural oils viz Buzz Away® containing citronella, cajuput, lavender, safrole-free sassafras, peppermint, bergaptene-free bergamot, calendula, soy, and tea tree oils are available commercially for repellency against mosquitoes. In general, citronella, geraniol, p-menthane-3,8-diol, soyabean oil are some of the compounds used successfully in many commercial repellent formulations along with DEET.

SUMMARY OF THE INVENTION

The present disclosure provides a compound of Formula I which is as follows:-



Formula I

wherein R = $(\text{CH}_2)_n\text{CH}_3$ and n ranges between 1-9.

The present invention also discloses a process for preparation of compound of Formula I.

The process for preparation of said compound comprises the following steps:

- a) addition of 4-morpholinecarbonyl chloride to an organic solvent,
- b) addition of dialkyl amine followed by treatment with a solution having pH between 6 and 10

Embodiments of the present invention disclose the compounds of formula I and salts thereof wherein the said salts include Oxalic acid hydrochloride, citric acid hydrochloride, malonic acid hydrochloride, adipic acid hydrochloride etc.

Embodiments of the invention provide the compounds of formula I which exhibit insect repelling properties against disease-transmitting insects which repels the insects effectively i.e. longer protection time.

Embodiments of the invention provide the compounds of formula I which exhibit insect repelling properties against disease-transmitting insects that is safe for living organisms.

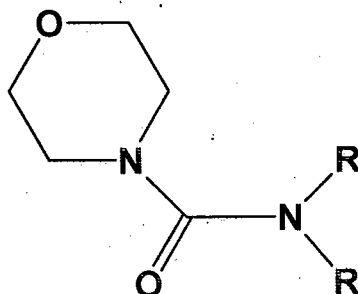
Embodiments of the invention provide the compounds of formula I which do not irritate the skin or mucous membranes.

Embodiments of the invention provide the compounds of formula I which are not greasy in nature.

Embodiments of the invention provide a pharmaceutical composition comprising the compound of formula I along with pharmaceutical acceptable carriers.

DETAILED DESCRIPTION OF INVENTION

The present invention provides a compound of Formula I given herein below:-



Formula I

wherein $R = (CH_2)_nCH_3$ and n ranges between 1-9.

The compounds of formula I are useful as free base and also as salts. The salts of the compound are derived from mineral acids such as hydrochloric acid, sulfuric acid, nitric acid and organic acids such as ethanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid etc.

The compounds of formula I wherein the said compound may be prepared by a process wherein the said process comprises following steps:

- a) addition of 4-morpholinecarbonyl chloride to an organic solvents,
- b) addition of dialkyl amine followed by treatment with a solution having pH between 6 and 10

The acid salts of the compound are prepared either by dissolving the free base, in aqueous or aqueous alcohol or other suitable solvents containing the appropriate acid and isolating the salt by evaporating the solution or by reacting the free base and acid in an organic solvent. The salt separates directly or can be obtained by concentration of the solution.

The process for preparing a compound of formula I wherein the solvents include one or more selected from the group of dichloromethane, acetone, diethyl ether, chloroform, tetrahydrofuran, dichloroethane solvent system etc.

The process for preparing a compound of formula I wherein the basic solution is prepared by dissolving a suitable base in an aqueous solvent system.

The process for preparing a compound of formula I wherein the suitable base compound includes one or more selected from the group of sodium bicarbonate or potassium bicarbonate.

The process for preparing a compound of formula I wherein the temperature of the process is maintained between 20-40 °C.

The process for preparing a compound of formula I wherein the compounds obtained exhibits more than 99% purity and characterized by spectroscopy techniques. GC-FID, IR, GCMS, NMR.

The compounds of formula I are useful as free base form and as salts. The salt form of the compound of formula I are derived from mineral acids such as hydrochloric acid, sulfuric acid, nitric acid and organic acids such as ethanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid etc.

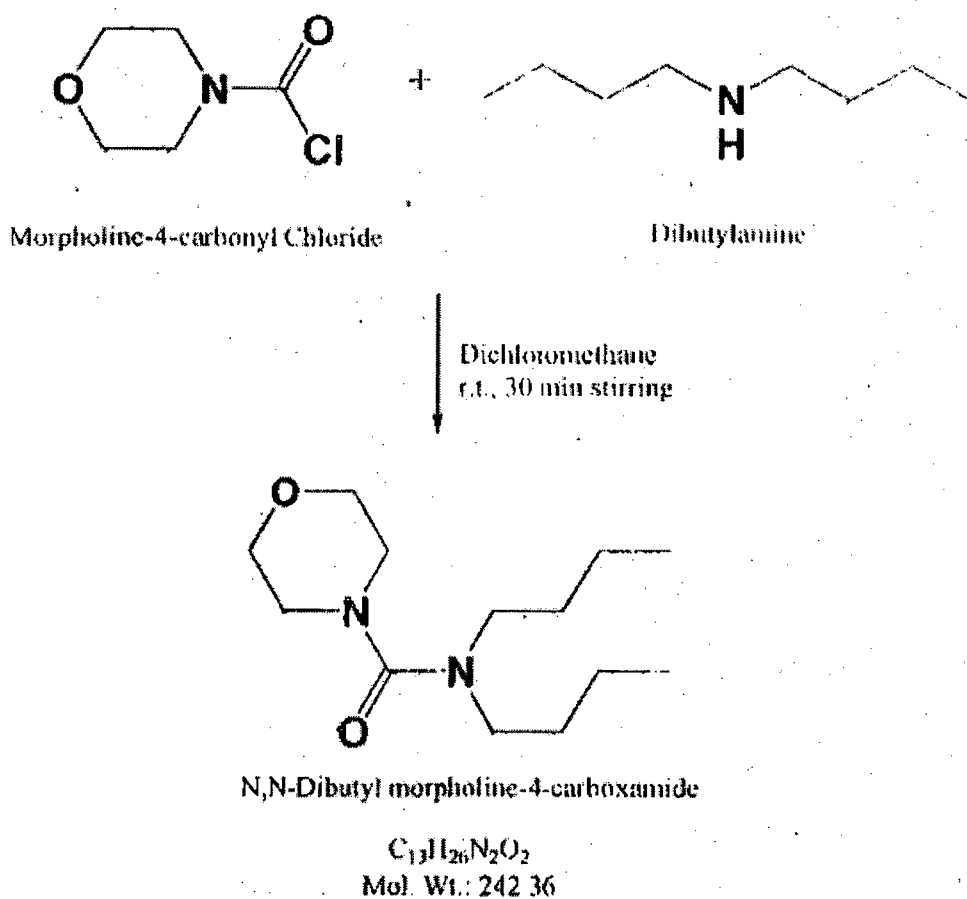
The acid salts of the compound of formula I are prepared either by dissolving the free base in aqueous or aqueous alcohol or other suitable solvents containing the appropriate acid and isolating the salts by evaporating the solution or by reacting the free base and acid in an organic solvent, in which case salt separates directly or can be obtained by concentration of the solution.

Embodiments of the present invention is a compound of formula I wherein $n=1$ i.e. N,N-Diethyl morpholine-4-carboxamide.

Embodiments of the present invention is a compound of formula I wherein $n=2$ i.e. N,N-Dipropyl morpholine-4-carboxamide or N,N-Diisopropyl morpholine-4-carboxamide.

Embodiments of the present invention is a compound of formula I wherein $n=3$ i.e. N,N-Dibutyl morpholine-4-carboxamide (Formula II) or N,N-Diisobutyl morpholine-4-carboxamide.

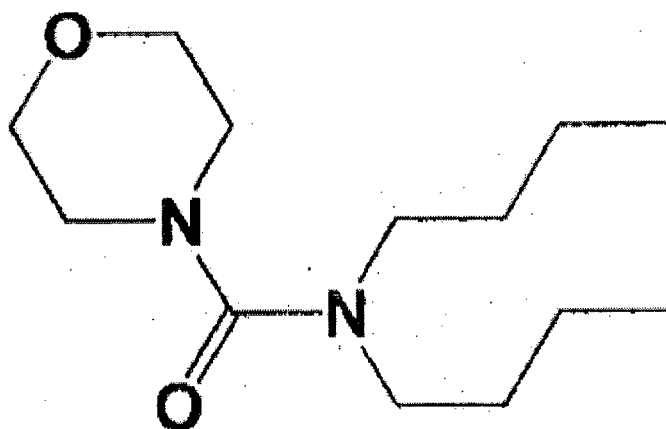
Embodiments of the present invention is a compound of formula I wherein $n=5$ i.e. N,N-Dihexyl morpholine-4-carboxamide.



Scheme I

The present invention discloses N,N-Dibutyl morpholine-4-carboxamide a mosquito repellent synthetic molecule as an potent insect repellent agent.

The molecular formula of the compound of formula II is $C_{13}H_{26}N_2O_2$; molecular weight is 242.



Formula II: N,N-Dibutyl morpholine-4-carboxamide ($C_{13}H_{26}N_2O_2$),

The compounds of formula I may be prepared by a process as described exhibit more than 99% purity and characterized by spectroscopy techniques.

The compounds of formula I showed insect repellent property against the insects.

The compounds of formula I showed insect repellency property against the insects wherein the insects includes mosquitoes, moths, *Aedes aegypti*.

Embodiments of the invention provide a pharmaceutical composition comprising the compounds of formula I along with pharmaceutically acceptable carrier.

The pharmaceutical composition comprising the compounds of formula I along with pharmaceutically acceptable carrier may further comprises additional insect repellants as active ingredient or a combination with insect repellent molecules.

The pharmaceutical composition comprising the compounds of formula I along with pharmaceutically acceptable carrier may be formulated in a suitable dosage form.

The pharmaceutical composition comprising the compounds of formula I along with pharmaceutically acceptable carrier wherein the dosage form may comprise solution, powder, sachet, tablets, implants, capsules, ointment, aerosol spray, creams, etc.

The pharmaceutical composition comprising the compounds of formula I along with pharmaceutically acceptable carrier wherein the pharmaceutically acceptable carrier includes solvents, diluents, polymers, lubricants, plasticizers, pH modifying agent, polymeric matrix, polymeric reservoir etc.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

WORKING EXAMPLES

Example 1: Preparation of N,N-Dibutyl morpholine-4-carboxamide:

150 g of 4-Morpholinecarbonyl chloride and 250 ml of dichloromethane are taken in a 1 litre two-necked round-bottom flask fitted water condenser and a calcium chloride guard tube. This is placed over a magnetic stirrer cum hot plate. To this, 130 g of dibutyl amine is added slowly using a pressure-equalizing funnel fitted in the side neck of the round bottom flask at room temperature. After complete addition, the reaction mixture is stirred constantly for 30 minutes. The temperature is maintained by the reflux of dichloromethane. The reaction mixture is then treated with 500 ml of 20% sodium bicarbonate solution and the dichloromethane layer is separated. The solvent is removed by distillation and pure N,N-Dibutyl morpholine-4-carboxamide is obtained by distillation under vacuum.

The purity of the compound was analyzed using GC-MS (>99.5%).

Example 2: Repellent Test on Human Volunteers

The insect repellent property of these compounds is evaluated against mosquitoes. For this, 200 µl of each compound enlisted in table 1 is dissolved in 800 µl of isopropanol (20 % w/v) and used to determine the protection time (repellency effect) against mosquitoes. 200 µl solution is applied on the external surface of the fist of human hand over an area of about 1.50 cm². The treated surface is exposed to 200 non-blood fed female (5-7 days old) *Aedes aegypti* mosquitoes in a 75 x 60 x 60 cm³ test chamber for 5 min at intervals of 30 min. Less than 5 bites in 5 min is considered to be indicative of repellency (Rao et al., 1991 and Sikder et al., 1994). All the tests are carried out with two different human volunteers and different cages. For compounds which showed repellency more than 4 hrs are repeated on different days. In case of N, N-Dibutyl morpholine-4-carboxamide, which gives protection time of > 6.5 hrs, the test is conducted with 15 different human volunteers on different days to confirm the repellent property. The volunteers include both male and female gender categories, of age group varying 25 to 60 years.

The insect repellency of known repellents such as N,N-diethylbenzamide, N,N-diethyl toluamide and N,N-diethyl phenylacetamide respectively is studied under similar experimental conditions. The results are given herein in Table 1.

Compound Name	Protection Time (Hrs)
N,N-Diethyl morpholine-4-carboxamide	1.5 (maximum)
N,N-Dipropyl morpholine-4-carboxamide	2.0 (maximum)
N,N-Diisopropyl morpholine-4-carboxamide	1.5 (maximum)
N,N-Dibutyl morpholine-4-carboxamide	> 6.5 (minimum)
N,N-Diisobutyl morpholine-4-carboxamide	3.5 (maximum)
N,N-Dihexyl morpholine-4-carboxamide	0.5 (maximum)
N,N-diethylbenzamide (DEB)	1.6 (maximum)
N,N-diethyl toluamide (DEET)	6.0 (maximum)
N,N-diethyl phenylacetamide (DEPA)	5.0 (maximum)

Table 1: insect repellency of various compound and the compounds of present invention

The oral LD50 data of the above new compound, N,N-Dibutyl morpholine-4-carboxamide along with known repellents is given below:

Compound Name	LD50 (oral, mouse)
N,N-Dibutyl morpholine-4-carboxamide	4525 mg/kg
N,N-diethylbenzamide (DEB)	449 mg/kg
N,N-diethyl toluamide (DEET)	1131 mg/kg
N,N-diethyl phenylacetamide (DEPA)	500 mg/kg (in cream formulation)

Example 3: A solution of N, N-Dibutyl morpholine-4-carboxamide (20% w/w) in isopropanol is made by dissolving N, N-Dibutyl morpholine-4-carboxamide in isopropanol.

Example 4: A solution of N, N-Dibutyl morpholine-4-carboxamide (20% w/w), stearic acid 13%, stearyl alcohol 1%, cetyl alcohol 1% glycerine 5%, glycerine 5%, methyl paraben 0.05%, propyl paraben 0.05%, potassium hydroxide 0.9% and pure water was prepared. This cream can be applied on the exposed area of the skin to protect from disease-transmitting mosquito bites.

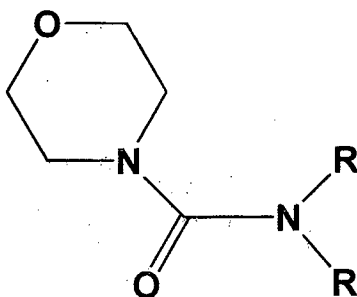
Example 5: A solution of N, N-Dibutyl morpholine-4-carboxamide (10% v/v), and N,N-diethyl-2-phenylacetamide (10% v/v) in plant origin oil like coconut oil, soyabean oil.

Example 6: A solution of N, N-Dibutyl morpholine-4-carboxamide (15% v/v) along with any other natural repellents like eucalyptus oil, Cedar oil, Chrysanthemum oil, Citronella oil, Clove oil, Lavender oil, Lemongrass oil, Neem oil, Peppermint oil (10% v/v) and Isopropanol (75% v/v) can be used as mosquito repellent formulation.

It is to be noted that the present invention is susceptible to modifications, adaptations and changes by those skilled in the art. Such variant embodiments employing the concepts and features of this invention are intended to be within the scope of the present invention, which is further set forth under the following claims:-

WE CLAIM:

1. A compound of the formula I

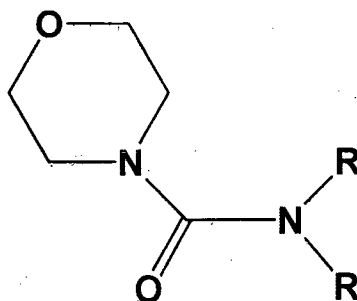


Formula I

in which R is $(\text{CH}_2)_n \text{CH}_3$, or a pharmaceutically acceptable salts thereof, wherein n is 1 to 9.

2. A process for preparing a compound of formula I wherein the said process comprises following steps:

- a) addition of 4-morpholinecarbonyl chloride to organic solvent,
- b) addition of dialkyl amine followed by treatment with a basic solution having pH between 6 and 10

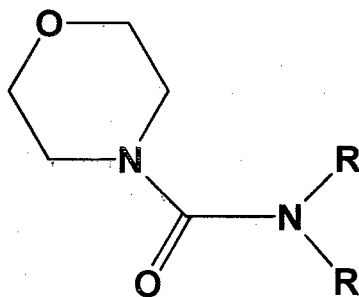


Formula I

in which R is $(\text{CH}_2)_n \text{CH}_3$, or a pharmaceutically acceptable salts thereof wherein n is 1 to 9.

3. The process as claimed in claim 2, wherein the dialkyl amine is such as diethyl amine, dipropyl amine, diisopropyl amine, dibutyl amine, diisobutyl amine, dipentyl amine, dihexyl amine and the like.

4. The process as claimed in claim 2, wherein the solvent is such as dichloromethane, acetone, diethyl ether, chloroform, tetrahydrofuran, dichloroethane.
5. The process as claimed in claim 2, wherein the basic solution is such as aqueous sodium bicarbonate, potassium bicarbonate of pH between 6 and 10.
6. A pharmaceutical composition comprising a compound of formula I and a pharmaceutical acceptable carrier wherein the said compound is as follows:-



Formula I

in which R is $(\text{CH}_2)_n \text{CH}_3$, or a pharmaceutically acceptable salts thereof wherein n is 1 to 9.

7. A pharmaceutical composition as claimed in claim 6, further comprises additional insect repelling agent.
8. A pharmaceutical composition as claimed in claim 6, wherein the carrier is one or more selected from a group comprising of solvents, diluents, polymers, lubricants, plasticizers, pH modifying agent, polymeric matrix, polymeric reservoir etc.
9. A pharmaceutical composition as claimed in claim 6, wherein the composition is provided in the form of solution powder, sachet, tablets, implants, capsules, ointment, aerosol spray and creams.
10. The compound of formula I exhibits insect repelling property.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2012/000003

A. CLASSIFICATION OF SUBJECT MATTER
INV. A01N43/84 C07D265/30
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A01N C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 218 002 A (STROECH KLAUS [DE] ET AL) 8 June 1993 (1993-06-08) columns 14-16; claims 2,3; example 1, -----	1-10
Y	WO 02/02088 A2 (BAYER AG [DE]; HARDER ACHIM [DE]; VON SAMSON HIMMELSTJERNA GEORG [DE];) 10 January 2002 (2002-01-10) claims 1-6 -----	1-10
X	S.N. KHATTAB, S.Y. HASSAN, E.A. HAMED, F. ALBERICIO, A.EL-FAHAM: "synthesis and aminolysis of N,N-Diethyl Carbamic Ester of HOBt Derivatives", BULLETIN KOREAN CHEMICAL SOCIETY, vol. 31, no. 1, 2010, pages 75-81, XP002674635, scheme 2 compound 19; ----- -/-	1-5



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

25 April 2012

Date of mailing of the international search report

11/05/2012

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Schuemacher, Anne

INTERNATIONAL SEARCH REPORT

International application No

PCT/IN2012/000003

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	FR 2 050 522 A5 (ARIES ROBERT) 2 April 1971 (1971-04-02) page 1, lines 19-21 page 4, lines 4-23 claims 7,8 -----	1-10
X	DE 22 06 366 A1 (CIBA-GEIGY AG, BASEL) 31 August 1972 (1972-08-31) page 9; claims 1,13 -----	1-5

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IN2012/000003

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