

USE OF THE ENANTIOMER LEVOMEDETOMIDINE AS INHIBITOR FOR MARINE BIOFOULING OF SURFACES

FIELD OF THE INVENTION

The present invention generally relates to the inhibition of marine biofouling of surfaces in marine environments, specifically to the use of substances as an agent for prevention of marine biofouling of solid surfaces. More specifically, the invention concerns the use of a specific form of medetomidine, acting as such agent.

BACKGROUND OF THE INVENTION

Economic benefits of reducing biofouling on marine and freshwater installations arise from several sources, including, for example, reduced fuel efficiency for ships that have presence of fouling organisms on their hulls, loss of profitable time during the cleaning procedures to reduce the biofouling on the ships hulls and also decreased cooling power of cooling water equipment to mention a few. Besides from ships, other underwater installations, such as aquaculture equipment and oil/gas off-shore installations, also suffer from significant problems of biofouling.

At present, to prevent and reduce biofouling, a number of different approaches have been devised and are commonly employed. Several chemical compounds, including toxides or biocides, that have antifouling activity are used as additives in coatings or paints for surfaces exposed to underwater installations. Mechanical cleaning of marine surfaces has been introduced as an alternative to toxides and biocides. Notably, water jet cleaning and mechanical cleaning using brushes are in use. The majority of these methods are, however,

work-intensive and therefore expensive. It has also been reported that a selection of pharmacological compounds that act upon serotonin and dopamine neurotransmitters, has the ability to either impede or promote the attachment of barnacles. Serotonine antagonists, such as Cyproheptadine and Ketanserin, and dopamine agonists, such as R (-)-NPA and (+)-

5 Bromocriptine, have exhibited inhibitory properties. Another pharmacological agent that has proven to be an efficient inhibitor with regards to barnacle settlement is the highly selective alpha2-adrenoreceptor agonist Medetomidine or ($\pm$)-4(5)-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole. The larval settlement is impeded already at low concentrations, 1 nM to 10 nM. Medetomidine belongs to a new class of alpha2-receptor agonists containing a 4-substituted
10 imidazole ring with, high selectivity towards 2-adrenoreceptors. Receptors affected by catecholamine neurotransmitters, such as norepinephrine and epinephrine, are termed adrenergic receptors (or adrenoceptors) and can be divided into alpha- and beta-subclasses. The alpha2-adrenoreceptors are involved in the autoinhibitory mechanism of neurotransmitter release and play a significant part in the regulation of hypertension (high blood pressure),
15 bradycardia (reduced heartbeat rate) and even regulation of alertness and analgesia (reduced sensitivity to pain).

WO00/42851 discloses use of medetomidine as an agent for the inhibition of marine biofouling on a surface.

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WO2006/096129 discloses a method and use in an antifouling paint that impede settlement of barnacles on aquatic structures, using medetomidine bound to a sulfonated, acid sulphate ester, phosphonic acid, carboxylic acid or acid phosphate ester modified polymer backbone such as polystyrene or acrylate polymers.

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SUMMARY OF THE INVENTION

The present invention solves the issue of reducing effects in humans of the medetomidine present in various products used for prevention of marine biofouling.

- 5 A primary object of the present invention is to use a specific enantiomeric form of medetomidine, levomedetomidine, individually and separately as a substance acting as an agent for antifouling in marine environments with less effect in humans. Another object of the invention is to use a composition of the enantiomeric forms of medetomidine with less effects in humans, as a substance acting as an agent for antifouling in marine environments, which
- 10 differ from the racemic mixture (1:1) in such a way that the levomedetomidine is the dominant enantiomeric form. Another object of the invention is to use a composition of the mixture of the two enantiomeric forms, where the levomedetomidine constitute at least 90, 80, 70, 60, 50% of the mixture, as a substance acting as an agent for antifouling in marine environments, which has less effects in humans than the racemic mixture of medetomidine.
- 15 Other objects and advantages will be more fully apparent from the following disclosure and appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS (including figures and graphs)

- 20 Figure 1.

Structure of levomedetomidine (example shows HCl salt).

Figure 2a.

Settling experiment of barnacles with the racemate of Medetomidine.

Figure 2b.

Settling experiment of barnacles with the enantiomer levomedetomidine.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED

5 EMBODIMENTS THEREOF

The foregoing and other aspects of the present invention will now be described in more detail with respect to the description and methodologies provided herein. It should be appreciated that the invention may be embodied in different forms and should not be construed as limited to the embodiments set forth herein. Rather, these embodiments are provided so that this
10 disclosure will be thorough and complete, and will fully convey the scope of the invention to those skilled in the art.

The terminology used in the description of the invention herein is for the purpose of describing particular embodiments only and is not intended to be limiting of the invention. As used in the description of the embodiments of the invention, the singular forms "a," "an" and "the" are intended to include the plural forms as well, unless the context clearly indicates
15 otherwise. Also, as used herein, "and/or" refers to and encompasses any and all possible combinations of one or more of the associated listed items. Furthermore, the term "about," as used herein when referring to a measurable value such as an amount of a compound, dose, time, temperature, and the like, is meant to encompass variations of 20%, 10%, 5%, 1%,
20 0.5%, or even 0.1% of the specified amount. When a range is employed (*e.g.*, a range from x to y) it is meant that the measurable value is a range from about x to about y, or any range therein, such as about x_1 to about y_1 , etc. It will be further understood that the terms "comprises" and/or "comprising," when used in this specification, specify the presence of stated features, integers, steps, operations, elements, and/or components, but do not preclude
25 the presence or addition of one or more other features, integers, steps, operations, elements,

components, and/or groups thereof. Unless otherwise defined, all terms, including technical and scientific terms used in the description, have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

All patents, patent applications and publications referred to herein are incorporated by reference in their entirety. In the event of conflicting terminology, the present specification is controlling. Further, the embodiments described in one aspect of the present invention are not limited to the aspect described. The embodiments may also be applied to a different aspect of the invention as long as the embodiments do not prevent these aspects of the invention from operating for its intended purpose.

The present invention generally relates to the inhibition of marine biofouling of surfaces in marine environments, specifically to the use of substances as an agent for prevention of marine biofouling of solid surfaces and compositions for coating of surfaces exposed to marine environments. More specifically, the invention concerns the use of a specific enantiomeric form of medetomidine, namely levomedetomidine (figure 1), acting as such agent.

In one aspect, the invention thus relates to a surface coating composition comprising medetomidine, wherein the composition comprises a relatively higher amount of levomedetomidine, as compared to dexmedetomidine. The surface coating composition may further comprise a binder phase, pigments, and a suitable solvent, as known in the art of surface coating compositions. The surface coating composition may be a paint for marine use, such as a self-polishing paint composition for marine use.

The α_2 -adrenoceptor agonist medetomidine is known to result in sedation and locomotor inhibition when given to mammals and fish (Sinclair, 2003; Ruuskanen et al., 2005). The opposite was found in cyprid larvae since medetomidine (10 nM) strongly enhanced kicking

of the cyprid larvae, with more than 100 kicks per minute (Mol Pharmacol 78:237–248, 2010). Thus, medetomidine has different physiological effects in vertebrates and invertebrates and instead demonstrate hyperactivity than sedation/locomotor inhibition as in vertebrates.

Medetomidine induces a locomotor activation response in barnacle cyprids, which is the most likely cause of settling inhibition. More specifically the increase in the movement (kicking) of the anterior appendices (legs) is suggested to be the anti-settling mode of action of medetomidine.

Medetomidine, ($\pm$) 4-[1-(2, 3-Dimethylphenyl) ethyl]-1H-imidazole, first described in EP 72615, is a racemic mixture of equal proportions of two optical enantiomers, the levo- and dextro-rotatory optical isomers (MacDonald et al., 1991; Savola and Virtanen, 1991) with generic names levomedetomidine and dexmedetomidine respectively. WO 2011/070069 disclose a process for the preparation of the racemic mixture of medetomidine (($\pm$)4-[1-(2, 3-dimethylphenyl) ethyl]-1H-imidazole) and related intermediates. Many of the previous synthesis use expensive 4-substituted imidazole derivatives as starting material, however in WO 2011/070069 the synthesis is made from affordable commercially available starting materials, where the imidazole ring is instead built up during the synthesis.

Medetomidine has been studied in human clinical trials and has also been used as anaesthetics for animals with the (S)-enantiomer, dexmedetomidine, being the active component. Levomedetomidine on the other hand has no apparent sedative or analgesic effect (Kuusela et al. J Vet Pharmacol Ther 23(1), 15-20, 2000), however higher dosage of levomedetomidine indicated reduced sedative and analgesic effects associated with administration of dexmedetomidine (Kuusela et al. Am J Vet Res 62(4), 616-621, 2001). This suggests that administration of dexmedetomidine alone for sedative and analgesic effect should be beneficial over administration of the racemic mixture of medetomidine, which contain equal amounts of dexmedetomidine and levomedetomidine. Based on these types of

studies, pure preparations of dexmedetomidine have been justified and are marketed under various names such as Dexdor® (Orion PharmaAB). Dexdor is indicated for the light to moderate sedation of adult ICU patients, EMA/789509/2011 Committee for Medicinal Products for Human Use (CHMP)) and Dexdomitor® (Orion Pharma AB) for veterinary applications. Such pure preparations are performed by separation and purification of the dexmedetomidine from racemic mixtures, where levomedetomidine is considered the main impurity of the pure dexmedetomidine.

As mentioned above, the racemic mixture of medetomidine or $(\pm)$ -4(5)-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole has previously been shown to be an efficient inhibitor with regards to barnacle settlement. Surprisingly, as will be revealed in the present invention, the racemic mixture and both of the enantiomeric forms (dexmedetomidine and levomedetomidine) of medetomidine has similar inhibitory effects. This is contrary to other well documented usage of only one of the specific enantiomeric forms of a molecule e.g. in drugs in the pharmaceutical industry, including medetomidine, where only one of the enantiomeric forms is active and the other enantiomeric form is inactive. It is especially unexpected and remarkable effect that levomedetomidine has a similar inhibitory effect. Inhibition of settlement of the barnacle cyprid larvae is described in example 1 and figure 2a and 2b below.

A preferred embodiment of the invention is therefore to use levomedetomidine as an active ingredient/component in marine paint applications to prevent biofouling on various surfaces that are submerged in marine environments.

Since levomedetomidine has been documented to have a very limited effect on humans and animals compared to the racemic mixture of medetomidine and the other enantiomer dexmedetomidine, the use of the enantiomeric form levomedetomidine will provide a solution for end-products with less effects in humans. Any risk of handling any product(s) containing

medetomidine or dexmedetomidine during e.g manufacture, transport, storage and applications for end-users, such as personnel involved in paint applications, is thereby reduced by the use of levomedetomidine instead. Also, the metabolism of the levomedetomidine has been shown to be more rapid in mammals, which is beneficial

5 compared to the use of the racemic mixture of medetomidine or the enantiomer dexmedetomidine. Furthermore, the levomedetomidine may have a beneficial pricing level as it is considered an impurity and thus discarded when processing and purifying the enantiomer dexmedetomidine for clinical applications. This also means that the invention herein also helps in solving the problem of handling the waste from the production of dexmedetomidine.

10 Purification of dexmedetomidine is disclosed in WO2013069025, Process for the preparation of dexmedetomidine, where the dexmedetomidine is prepared in high yield and with enantiomeric purity of more than 99%. A similar approach using the same methodology would of course be applicable for the preparation of levomedetomidine instead. A method to resolve the levo and dex enantiomers has also been described in CN200910093379. The use
15 of levomedetomidine as a medicament for use in preventing or treating conditions associated with overexpression or hypersensitization of adrenergic α -2 receptors as described in EP0858338.

A preferred embodiment of the present invention is therefore to use a specific enantiomeric form of medetomidine, levomedetomidine, individually and separately as a substance acting
20 as an agent for antifouling in marine environments with less effect in humans.

Another preferred embodiment of the invention is to use a composition of the enantiomeric forms of medetomidine with less effect in humans, as a substance acting as an agent for antifouling in marine environments, which differ from the racemic mixture (1:1) in such a way that the levomedetomidine is the dominant enantiomeric form. Another preferred

25 embodiment of the invention is to use a composition of the mixture of the two enantiomeric

forms, where the levomedetomidine constitute at least 90, 80, 70, 60, 50% of the mixture, as a substance acting as an agent for antifouling in marine environments, with less effect in humans than the racemic mixture of medetomidine.

A related preferred embodiment of the invention is to employ a combination of a biocide-

- 5 polymer complex as additives in a self-polishing paint for controlled release purposes as disclosed in WO2006/096129. Specifically such a preferred embodiment relates to a method and the use of an antifouling paint that specifically and efficiently impede settlement of, for example, barnacles on aquatic structures, using levomedetomidine, bound to a sulfonated, acid sulphate ester, phosphonic acid, carboxylic acid or acid phosphate ester modified
- 10 polymer backbone such as polystyrene or acrylate polymers. Another preferred object of the invention is to create an antifouling method requiring decreased biocide dose, through a proper control of the release of the antifouling substance from the paint film. The levomedetomidine molecule bound to e.g. Polystyrene-block-poly(ethylene-ran-butylene)-block-polystyrene will create a slow leakage of the active compound from the paint into the
- 15 water in a controlled fashion. The levomedetomidine-polymer ion pair will only be dissolved at the actual film surface, when in contact with water, resulting in the release of levomedetomidine. A surface-active compound in antifouling paint is thus likely to have a greater impact on settlements of barnacle larvae than a compound leaking out of the paint into the water since surface activity will increase the concentration close to the surface.
- 20 In a related preferred embodiment, a controlled release of antifouling agents may also utilize nanoparticles consisting of CuO, ZnO, TiO₂, Al₂O₃, SiO₂, MgO, preferably copper(II)- and zinc(II)oxide formulated into nanoparticle sizes. Due to the large specific surface area (ratio between surface area and particle volume), the nanoparticles contribute to adsorb the antifouling agent, e.g. levomedetomidine, or other antifouling agents such as Chlorothalonil,
- 25 Dichlofluanid, SeaNine, Irgarol, Diuron, and Tolyfluanid. The CuO and ZnO particle

generates specific surface areas of 29 and 21 m² .g⁻¹, respectively. This allows the possibility to design a paint system containing low amounts of both levomedetomidine and nanoparticles in order to restrict the diffusional motion of antifouling agent through the paint film. When substituting a nanoparticle with a micrometer-sized particle, the adsorption appeared to be negligible. These results show the importance of large surface areas with regard to adsorption of antifouling agents onto particle surfaces. The antifouling agents, e.g. levomedetomidine bound to nanosized metal oxide is a compound that leaks out of the paint into water in a controlled fashion. The antifouling agent bound to nanosized metal oxide thus has excellent dispersion stability because of its large size, compared to the antifouling agent particle alone. By size property the antifouling agent-metal oxide particles are stationary in a paint film and do not leak out into the water. As a consequence the concentration of antifouling particles in the paint film remains homologous during "lifetime". As a result the concentration of antifouling agent will be equal in the entire paint film. Another consequence is that the total surface area of nanoparticles is enough to adsorb all of the antifouling agent and there will be no waste of the biocide.

Compounds have previously been described that interfere with nerve signaling or other specific action against the fauna of marine bio-fouling organisms, such as barnacles, for example, U.S. Pat. No. 6,762,227 describes the use of medetomidine and, also Swedish patent application No. 0300863-8 describes the use of spiroimidazoline for the same purpose.

However, the use of such products has no or very little effect on algae. For example, Medetomidine has a specific action on barnacle cyprids but no effect of algal growth due to the target protein being lacking within algae. There are several methods to prevent algal growth, among them the use of copper and other metals in fairly high concentrations.

Algicides are often invented as herbicides and are photosynthesis-inhibitors such as

DIURON™ (3-(3,4-dichlorophenyl)-1,1-dimethylurea) by DuPont Agricultural Products

Wilmington, Del., USA and IRGAROL™ 1051 (2-methylthio-4-tert-butylamino-6-cyclopropylamino-s-triazine) by Ciba Inc, Tarrytown, N.Y., USA. A more common strategy is to use fungicides such as zincpyrithione (Zinc, bis(1-hydroxy-2(1H)-pyridinethionato-O,S)—, (T-4)-) by Arc Chemicals Inc and copperpyrithione (Copper, bis(1-hydroxy-2(1H)-pyridinethionato-O,S)—, (T-4)-) by Arc Chemicals Inc, tolylfluanide (N-(Dichlorofluoromethylthio)-N',N'-dimethyl-N-p-tolylsulfamide) by Bayer Chemicals, Pittsburgh, Pa., USA, diclofluanide (N'-dimethyl-N-phenylsulphamide) by Bayer Chemicals, ZINEB™ (zinc ethylene bisdithiocarbamate) by FMC corp., ZINRAM™ (Zinc bis(dimethylthiocarbamates)) by Taminco, MANEB (manganese ethylene bisdithiocarbamate) or quaternary ammonium compounds. A third strategy is to use toxic compounds but with short half life such as SEANINE™ (4,5-dichloro-2-n-octyl-3(2H)-isothiazolone) by Rohm and Haas Company, Philadelphia, Pa., USA and related compounds. The principle of the method of the invention would thus include the use of substances or agents which disturb or block the nerve signaling to the target cells in the cyprid larvae, in the present case levomedetomidine, in combination with anti-algae compounds, such as zinc- and copper pyrothion, fungicides like tolylfluanide and diclofluanide, herbicides such as Diuron(TM) and Irgarol™, or more general biocides such as SeaNine™ or EcoNea™ (2-(p- chlorophenyl)-3-cyano-4-bromo-5-trifluoromethyl) by Janssen Pharmaceutical, Titusville, NJ, USA. A preferred embodiment of the invention is to add the substances in a base polymer paint, which is applied on ship hulls for example. Thus, in a related preferred embodiment, the invention comprise applying a protective coating to a substrate, said coating containing a) a substance that interferes with barnacle biofouling comprising levomedetomidine, and b) an algicide. Specific preferred algicides include copper, zinc and other metals, Diuron (3-(3,4-dichlorophenyl)-l,l-dimethylurea), Irgarol 1051™ (2-methylthio- 4-tert-butylamino-6-cyclopropylamino-s-triazine), zincpyrothione (Zinc, bis(1- hydroxy-2(1H)-pyridinethionato-

O,S)-, (T-4)-), copperpyrothione (Copper, bis(1- hydroxy-2(lH)-pyridinethionato-O,S)-, (T-4)-), diclofluanide (N' -dimethyl-N- phenylsulphamide), zinebTM (zinc ethylene bisdithiocarbamate), ZinramTM (Zinc bis(dimethylthiocarbamates)), maneb (manganese ethylene bisdithiocarbamate), quaternary ammonium compounds, SeaNineTM (4,5-dichloro-2-n-octyl-3(2H)-isothiazolone), and EcoNeaTM (2-(p-chlorophenyl)- 3-cyano-4-bromo-5-trifluoromethyl).

The terms “medetomidine”, “dexmedetomidine”, and “levomedetomidine” as used herein include salts and solvates thereof unless specifically stated otherwise. Acceptable salts of levomedetomidine include acid addition salts and base addition salts. Such salts may be formed by conventional means, for example by reaction of a free acid or a free base form of a compound of the invention with one or more equivalents of an appropriate acid or base, optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using standard techniques (e.g. in vacuo or by freeze-drying).

Salts may also be prepared by exchanging a counter-ion of a compound of the invention in the form of a salt with another counter-ion, for example using a suitable ion exchange resin. For the avoidance of doubt, other acceptable derivatives of levomedetomidine are included within the scope of the invention (e.g. solvates, prodrugs etc). Preferable solvents are, but not limited to; n-butanol, iso-butanol, methanol, benzyl alcohol and 1-methoxy-2-propanol.

The enantiomers of medetomidine may be isolated and separated from each other by separation of racemic or other mixtures of the enantiomers using chiral resolution or chiral column chromatography known in the art. Alternatively the desired enantiomer may be prepared by enantioselective synthesis, also called chiral synthesis or asymmetric synthesis, which is defined as a chemical reaction (or reaction sequence) in which one or more new elements of chirality are formed in a substrate molecule and which produces the stereoisomeric (enantiomeric or diastereoisomeric) products in unequal amounts (IUPAC).

Preferably the protective coating further comprises a marine paint.

Example 1

Materials and methods

5 Inhibition of settlement of the barnacle cyprid larvae.

The settlement assay was performed using Petri dishes containing 5 ml filtered sea water with the salinity of $32 \pm 1\text{‰}$. Approximately 20 barnacle cyprid larvae were added to each

Petri dish. Medetomidine/ Levomedetomidine were thereafter added and given the final

concentration (10^{-9} and 10^{-10} M, respectively). The control consisted of filtered sea water

10 only. Each experiment was made in five replicates and maintained up to 3 days.

The inhibition of settling was thereafter examined by using a stereomicroscope and checked for settled or non settled larvae. The results are shown in Figure 2.

References

15 **Sinclair 2003:** Sinclair, M.D., Can Vet J 44, 885-897 (2003)

Ruuskanen 2005: Ruuskanen, J.O.et al., Journal of Neurochemistry, 94, 1559–1569 (2005)

MacDonald 1991: MacDonald, E. et al., J Pharmacol Exp Ther. 259, 848-854 (1991)

20 **Savola and Virtanen 1991:** Savola, J.M., Virtanen, R., Eur J Pharmacol, 195, 193-199 (1991)

CLAIMS

- 5 1. Surface coating composition comprising medetomidine, characterized in that it comprises a relatively higher amount of levomedetomidine, or a salt or solvate thereof, as compared to dexmedetomidine.
- 10 2. Surface coating composition according to claim 1, wherein the amount of levomedetomidine is more than 50% of the total amount of medetomidine, such as at least 60%, 70%, 80%, 90%, 99% or 100 % of the total amount of medetomidine.
- 15 3. Surface coating composition according to claim 1 or 2, wherein the surface coating composition is a paint for marine use.
4. Surface coating composition according to any one of claims 1-3, wherein the levomedetomidine is bound to a sulfonated, acid sulphate ester, phosphonic acid, carboxylic acid or acid phosphate ester modified polymer backbone.
- 20 5. Surface coating composition according to claim 4, wherein the polymer backbone is selected from the group consisting of polystyrene and acrylate polymers.
6. Surface coating composition according to any one of claims 1-5, wherein said composition provides a controlled release of said levomedetomidine.
- 25 7. Surface coating composition according to claim 6, wherein the levomedetomidine is absorbed in nanoparticles.
8. Surface coating composition according to claim 7, wherein the nanoparticles are selected from the group consisting of oxides of copper, zinc, titanium, aluminium, silicon, and magnesium, preferably copper(II)oxide and zinc(II)oxide.

9. Surface coating composition according to claim 7 or 8, wherein the nanoparticles have specific surface areas of 10-50 m²/g, preferably 20-30 m²/g.

5 10. Surface coating composition according to any one of claims 1-9, further comprising at least one further antifouling agent.

11. Surface coating composition according to claim 10, wherein the further antifouling agent is selected from the group consisting of algicides, fungicides, herbicides and general biocides.

10 12. Surface coating composition according to claim 10 or 11, wherein the further antifouling agent is selected from the group consisting of Chlorothalonil, Dichlofluanid, 4,5-dichloro-2-n-octyl-3(2H)-isothiazolone (SeaNine®), 2-methylthio-4-tert-butylamino-6-cyclopropylamino-s-triziane (Irgarol®), 3-(3,4-dichlorophenyl)-1,1-dimethylurea (Diuron®), tolylfluanide, zincpyrithione, copperpyrithione, diclofluanide, zinc ethylene bisdithiocarbamate (Zineb®),
15 Zinc bis(dimethylthiocarbamates) (Zinram®) manganese ethylene bisdithiocarbamate (Maneb®), quaternary ammonium compounds, 2-(p- chlorophenyl)-3-cyano-4-bromo-5-trifluoromethyl (EcoNea®).

13. A surface coated with a composition according to any one of claims 1-12.

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14. The surface according to claim 13, which is a surface intended for submersion in a marine environment.

15. The surface according to claim 14, which is a ship hull, or a sea water pipe.

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16. The use of medetomidine having a relatively higher amount of levomedetomidine, or a salt or solvate thereof, as compared to dexmedetomidine as a marine antifouling agent.

30 17. The use according to claim 16, wherein the medetomidine consists of more than 50 % levomedetomidine, such as consists of at least 60%, 70%, 80%, 90%, 99% or 100 % levomedetomidine.

18. The use according to any of claims 16 or 17, for inhibition of settling of cyprid larvae on surfaces.

5 19. The use according to any one of claims 16-18, in combination with at least one further marine antifouling agent.

20. The use according to claim 19, wherein the further antifouling agent is selected from the group consisting of algicides, fungicides, herbicides and general biocides.

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21. The use according to claim 19 or 20, wherein the further antifouling agent is selected from the group consisting of Chlorothalonil, Dichlofluanid, 4,5-dichloro-2-n-octyl-3(2H)-isothiazolone (SeaNine®), 2-methylthio-4-tert-butylamino-6-cyclopropylamino-s-triziane (Irgarol®), 3-(3,4-dichlorophenyl)-1,1-dimethylurea (Diuron®), tolylfluanide, zincpyrithione, copperpyrithione, diclofluanide, zinc ethylene bisdithiocarbamate (Zineb®), Zinc bis(dimethylthiocarbamates) (Zinram®) manganese ethylene bisdithiocarbamate (Maneb®), quaternary ammonium compounds, 2-(p-chlorophenyl)-3-cyano-4-bromo-5-trifluoromethyl (EcoNea®).

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20 22. A method for preventing marine biofouling of a surface, comprising applying medetomidine having a relatively higher amount of levomedetomidine, or a salt or solvate thereof, as compared to dexmedetomidine, to said surface.

23. The method according to claim 22, wherein the medetomidine consists of more than 50% levomedetomidine, such as consists of at least 60%, 70%, 80%, 90%, 99% or 100 % levomedetomidine.

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24. The method according to any of claims 22 or 23, for inhibition of settling of cyprid larvae on said surface.

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25. The method according to any one of claims 22-24, further comprising applying at least one further marine antifouling agent to said surface.

26. The method according to claim 25, wherein the further antifouling agent is selected from the group consisting of algicides, fungicides, herbicides and general biocides.

- 5 27. The use of levomedetomidine in a method for preventing biofouling of a surface according to claim 25 or 26, wherein the further antifouling agent is selected from the group consisting of Chlorothalonil, Dichlofluanid, 4,5-dichloro-2-n-octyl-3(2H)-isothiazolone (SeaNine®), 2-methylthio-4-tert-butylamino-6-cyclopropylamino-s-triazine (Irgarol®), 3-(3,4-dichlorophenyl)-1,1-dimethylurea (Diuron®), tolylfluanide, zincpyrithione,
 10 copperpyrithione, diclofluanide, zinc ethylene bisdithiocarbamate (Zineb®), Zinc bis(dimethylthiocarbamates) (Zinram®) manganese ethylene bisdithiocarbamate (Maneb®), quaternary ammonium compounds, 2-(p- chlorophenyl)-3-cyano-4-bromo-5-trifluoromethyl (EcoNea®).