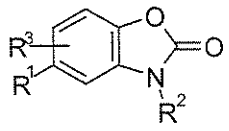
Summary of ~~the Invention~~Disclosure

The objects as mentioned above have surprisingly been solved in accordance with the present ~~invention~~disclosure. Thus, the present invention relates to specific 1,3-benzoxazol-2(3H)-ones according to formula (1) below.



formula (1)

The compounds according to formula (1) are alternative solutions to the same problem and have not been obvious for the skilled person.

In formula (1) the residue R^1 is selected from the group consisting of $-(CH_2)_nN(R^4)C(O)R^5$ and $-C(O)NR^4R^6$. Preferably R^1 is $-(CH_2)_nN(R^4)C(O)R^5$.

In formula (1) the residue R^2 is selected from the group consisting of hydrogen; $-C_{1-6}$alkyl, optionally substituted with one or more substituents selected from halogen, OH, OC_{1-6}alkyl, OC_{3-7}cycloalkyl; $-C_{3-7}$cycloalkyl, optionally substituted with one or more substituents selected from halogen, OH, OC_{1-6}alkyl, OC_{3-7}cycloalkyl; $-(C_{3-7}$cycloalkyl$)-C_{1-6}$-alkyl, optionally substituted with one or more substituents selected from halogen, OH, OC_{1-6}alkyl, OC_{3-7}cycloalkyl. While the above mentioned optional substituents are preferable according to the present ~~invention~~disclosure, other substituents as mentioned below in the description are suitable according to the present ~~invention~~ disclosure as well.

In formula (1) the residue R^3 is selected from the group consisting of hydrogen, halogen, hydroxy, methoxy or –CN.

In formula (1) the residue R^4 is selected from the group consisting of hydrogen or C_{1-6}-alkyl.

In formula (1) the residue R^5 is selected from the group consisting of C_{8-15}alkyl, C_{8-15}alkenyl, C_{8-15}alkinyl, (C_{6-10}aryl)-C_{6-10}alkyl, (C_{6-10}aryl)-C_{6-10}alkenyl, and (C_{6-10}aryl)-C_{6-10}alkinyl. In all of these aryl containing groups aryl may be substituted by one or more of the substituents as mentioned below in the present description.

In formula (1) the residue R^6 is selected from the group consisting of C_{9-16}alkyl, C_{9-16}alkenyl, C_{9-16}alkinyl, (C_{6-10}aryl)-C_{7-11}alkyl, (C_{6-10}aryl)-C_{7-11}alkenyl, and (C_{6-10}aryl)-C_{7-11}alkinyl. In all of these aryl containing groups aryl may be substituted by one or more of the substituents as mentioned below in the present description.

In formula (1) n is 0, 1, or 2, preferably 0 or 1, more preferably 0.

Preferably, the compounds according to the present ~~invention~~ disclosure are those, wherein in formula (1) R^1 is $-(CH_2)_nN(R^4)C(O)R^5$ with n being 0 or 1, preferably 0; R^2 is hydrogen or C_{1-6}alkyl, optionally substituted with one or more substituents selected from halogen, OH, OC_{1-6}alkyl, OC_{3-7}cycloalkyl; R^3 is hydrogen or halogen, preferably hydrogen; R^4 is hydrogen; and R^5 is selected from C_{8-15}alkyl, C_{8-15}alkenyl, (C_{6-10}aryl)-C_{6-10}alkyl, and (C_{6-10}aryl)-C_{6-10}alkenyl. In these definitions aryl is optionally substituted with one or more substituents as mentioned hereinbelow.

Preferably, the compounds according to the present ~~invention~~ disclosure are those, wherein in formula (1) R^1 is $-C(O)NR^4R^6$; R^2 is hydrogen or C_{1-6}alkyl, optionally substituted with one or more substituents selected from halogen, OH, OC_{1-6}alkyl, OC_{3-7}cycloalkyl; R^3 is hydrogen or halogen, preferably hydrogen; R^4 is hydrogen; and R^6 is selected from C_{9-16}alkyl, C_{9-16}alkenyl, (C_{6-10}aryl)-C_{7-11}alkyl, and (C_{6-10}aryl)-C_{7-11}alkenyl, wherein aryl is optionally substituted with one or more substituents as mentioned hereinbelow.

More preferably, the compounds according to the present ~~invention~~ disclosure are those, wherein in formula (1) R^1 is $-(CH_2)_nN(R^4)C(O)R^5$ with n being 0; R^2 is hydrogen or methyl; R^3 is hydrogen; R^4 is hydrogen; and R^5 is selected from C_{8-15}alkyl, C_{8-15}alkenyl (wherein alkenyl contains 1, 2, or 3 double bonds), (C_{6-10}aryl)-C_{6-10}alkyl, and (C_{6-10}aryl)-C_{6-10}alkenyl (wherein alkenyl contains 1 or 2 double bonds).

Even preferably, the compounds according to the present ~~invention~~ disclosure are those, wherein in formula (1) R^1 is $-C(O)NR^4R^6$; R^2 is hydrogen or methyl; R^3 is hydrogen; R^4 is hydrogen; and

R^6 is selected from C_{9-16}alkyl, C_{9-16}alkenyl (wherein alkenyl contains 1, 2, or 3 double bonds), $(C_{6-10}aryl)$-C_{7-11}alkyl, and $(C_{6-10}aryl)$-C_{7-11}alkenyl (wherein alkenyl contains 1 or 2 double bonds).

More preferably, the compounds according to the present ~~invention~~ disclosure are those, wherein in formula (1) R^1 is $-(CH_2)_nN(R^4)C(O)R^5$ with n being 0; R^2 is hydrogen or methyl; R^3 is hydrogen; R^4 is hydrogen; and R^5 is selected from C_{8-12}alkyl, C_{8-12}alkenyl (wherein alkenyl contains 2 double bonds), $(C_{6-10}aryl)$-C_{6-8}alkyl, and $(C_{6-10}aryl)$-C_{6-8}alkenyl (wherein alkenyl contains 2 double bonds).

In a particularly preferred embodiment of the present ~~invention~~ disclosure the compound according to formula (1) contains R^1 being $-(CH_2)_nN(R^4)C(O)R^5$ with n being 0, R^2 being hydrogen or methyl, and R^3 being hydrogen. In the definition of R^1 herein, R^4 is hydrogen and R^5 is selected from C_{8-12}alkyl, C_{8-12}alkenyl containing a (*2E,4E*)-diene moiety as the unsaturation, $(C_{6-10}aryl)$-C_{6-8}alkyl, and $(C_{6-10}aryl)$-C_{6-8}alkenyl containing a (*2E,4E*)-diene moiety as the unsaturation in the alkenyl group thereof.

Also preferably, the compounds according to the present ~~invention~~ disclosure are those, wherein in formula (1) R^1 is $-C(O)NR^4R^6$; R^2 is hydrogen or methyl; R^3 is hydrogen; R^4 is hydrogen; and

R^6 is selected from C_{9-13}alkyl, C_{9-13}alkenyl (wherein alkenyl contains 2 double bonds), $(C_{6-10}aryl)$-C_{7-9}alkyl, and $(C_{6-10}aryl)$-C_{7-9}alkenyl (wherein alkenyl contains 2 double bonds).

In another particularly preferred embodiment of the present ~~invention~~ disclosure the compound according to formula (1) contains R^1 being $-C(O)NR^4R^6$, R^2 being hydrogen or methyl, and R^3 being hydrogen. In the definition of R^1 herein, R^4 is hydrogen and R^6 is selected from C_{9-13}alkyl, C_{9-13}alkenyl containing a (*2E,4E*)-diene moiety as the unsaturation, $(C_{6-10}aryl)$-C_{7-9}alkyl, and $(C_{6-10}aryl)$-C_{7-9}alkenyl containing a (*2E,4E*)-diene moiety as the unsaturation in the alkenyl group thereof.

Moreover, the present ~~invention~~ disclosure relates to the use of these compounds as a medicament, preferably a dermatologic agent, and as a cosmetic. The compounds are effective in the treatment and/or prevention of inflammation, irritation, itching, pruritus, pain, oedema, and/or pro-allergic or allergic conditions, particularly of the skin and mucosa of a mammal. Further conditions include hair growth (e.g. forms of alopecia, effluvium) and sebaceous gland disorders (e.g. acne, seborrhea), benign and malignant skin tumors, hyperproliferative skin diseases (e.g. psoriasis), excessive hair growth (e.g. hirsutism), different forms of dermatitis, dry skin conditions, and systemic sclerosis (scleroderma).

In one embodiment, there is provided a non-therapeutic use of the compound as disclosed herein as a cosmetic, preferably for the cosmetic treatment of the skin and/or mucosa of a mammal.

In one embodiment, there is provided a composition comprising the compound as disclosed herein and a pharmaceutically and/or cosmetically acceptable carrier, preferably an apolar carrier, wherein the composition preferably is a liniment, skin cream, gel, or lotion.

Detailed Description of the Invention

In accordance with the present invention the applicant has developed the new 1,3-benzoxazol-2(3H)-ones as defined in formula (1) and has surprisingly found out that these compounds can effectively be used as a medicament, preferably as a dermatologic agent, and as a cosmetic due to their lipophilic nature. The conditions and diseases to be treated are particularly inflammation, itching, pruritus, irritation, pain, oedema, and/or pro-allergic or allergic conditions. The compounds turned out to be effective not only in the treatment but also in the prevention of the above mentioned conditions. The conditions also comprise inflammatory reactions and irritation of skin and mucosa of a mammal, preferably of a human, e.g. caused by environmental stress and influences, such as UV irradiation, toxic substances, and allergens in general. Thus, the compounds have shown to effectively reduce several kinds of skin and mucosa discomforts as mentioned above. In particular, they have shown to provide for analgesic and anti-pruritic properties.

Without intending to be bound by any theory the applicant believes that the reason for the activity of the 1,3-benzoxazol-2(3H)-ones of the present invention is based on their function as modulators of the endocannabinoid system. In this respect it is known that the endocannabinoids *N*-arachidonoylethanolamide (Anandamide, AEA) and 2-arachidonoylglycerol (2-AG) bind to G-protein-coupled CB_1 and CB_2 cannabinoid receptors. The CB_1 receptor is primarily (but not exclusively) expressed in neurons, the CB_2 receptor is mainly present in immunocytes, such as monocytes (splenocytes), macrophages, B cells, but also in astroglial cells. In the skin, CB receptors, in particular the CB_2 receptor, are expressed in keratinocytes and fibroblasts. Upon CB receptor activation, endocannabinoids are actively