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Synthesis of a New Family of *N*-Aryl Lactams Active on Chemesthesis and Taste

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A new class of synthetic compounds with chemesthetic activity has been identified. They have been designed ex-novo by structural similarity with known cooling compounds such as menthol, icilin and cyclic ketoenamines. 19 new derivatives have been obtained easily and in high yields by Goldberg arylation or lactam ring closure on the appropriate phenol or benzoic acid derivative. The synthetic procedures are suitable for gram-scale preparation, and the products are stable and easy to purify. 17 new compounds were submitted to preliminary sensory evaluation, and 3 of them showed cooling activity and, in some cases, tingling sensation in the oral cavity. These *N*-aryl lactams seem to be an interesting class of compounds to be enlarged in order to derive structure-activity relationships.

The term chemesthesis describes the sensitivity to some chemicals which generate pleasant or irritating stimuli. These stimuli mimic thermic or mechanical sensations on the skin and/or in the oral cavity. In the field of taste chemistry the phenomenon is very well known, and it is usually generated by hot, cooling and tingling compounds found in many spices. (–)-Menthol (**1**) is the lead of natural cooling compounds, which are used to generate a fresh sensation in some foods and beverages. Cooling compounds have also several important applications in the pharmaceutical and cosmetic industry as components of ointments, collutories, detergents, etc. Most information on structure–activity relationships (SAR) of cooling compounds is related to menthol and its analogues.[1,2] Sensory evaluation data of menthol and more than 1200 derivatives have been submitted to SAR, which allows one to derive some indications on the structural requirements needed to generate the cooling activity: a hydrogen bonding group, a compact hydrocarbon skeleton, a correct hydrophilic/hydrophobic balance ($1 < \log P < 5$), and a molecular weight in the range 150–350 g/mol. To date, the most active cooling compound is the synthetic derivative AG-3–5 or icilin **2**,[3] used in pharmacology as a drug to induce artificial "shaking" in animal experiments. Many tetrahydropyrimidine-2-one analogues have been recently synthesised and patented both for their cooling activity[4] and other applications.[5] In 2001, a new interesting class of cooling compounds was isolated from aqueous roast malt extracts[6] and studied for its taste properties. They are cyclic α-ketoenamines formed during a Maillard reaction, and they represent a new class of natural compounds from which to derive structure-activity relationships.[7] Both icilin and the cyclic ketoenamines suffer some limitations in their practical application: icilin has low solubility, and ketoenamines are chemically unstable, probably due to oxidation processes of the reactive enamino group.

Though hot compounds, such as capsaicin and its derivatives, and the function of the vanilloid receptor have been known for a long time, the understanding of the mechanism of action of cooling compounds is much more recent. Lately, a cold and menthol-sensitive receptor has been identified and cloned:[8] this receptor, TRPM8 (previously called CMR1), is sensitive both to thermic stimulation and to chemicals with cooling activity, such as menthol and icilin. TRPM8 belongs to the family of TRP ion channels,[9] the same family of thermoreceptors which binds the vanilloids, VR1, responsible for the hot sensation. A second receptor, TRPA1 (or ANKTM1),[10] is now known to be activated by cold, tetrahydrocannabinoids and other chemesthetic compounds, such as mustard oils. There seems to exist a connection between these receptors and some types of cancer, therefore the interest in the pharmacological properties of compounds able to bind to these receptors is very high.[11,12] In particular, the cold–menthol receptor, TRPM8, is normally expressed in testis and prostate tissues as well as the nervous system, and the reason for this localisation is still unknown. TRPM8 expression increases remarkably in some types of prostate cancer; therefore it was first described as a tumour-associated protein overexpressed in prostate cancer cells. Recently, it has also been shown that the menthol receptor is overexpressed in cancer cells following androgen stimulation.[13] Therefore, the study of cooling compounds

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and the mechanism of cooling perception are of interest both for the food industry, where they are used as menthol substitutes, and for the pharmaceutical industry.

Considering the lack of detailed information about the pharmacophores responsible for the cooling effect and the lack of fine structure-activity relationships, our approach to the discovery of new cooling compounds was the rational design of "hybrid" derivatives containing some of the structural features of known cooling compounds. This paper describes the synthesis of these new compounds and the results of the sensory evaluation of some of them.

Results and Discussion

In designing new compounds, we started from the observation of the molecular features of representative leads, three of which are shown in Figure 1: (–)-menthol (**1**), icilin (**2**), and one cyclic ketoenamine, 3-methyl-2-(1-pyrrolidinyl)-2-cyclopentenone (3-MPC, **3**).

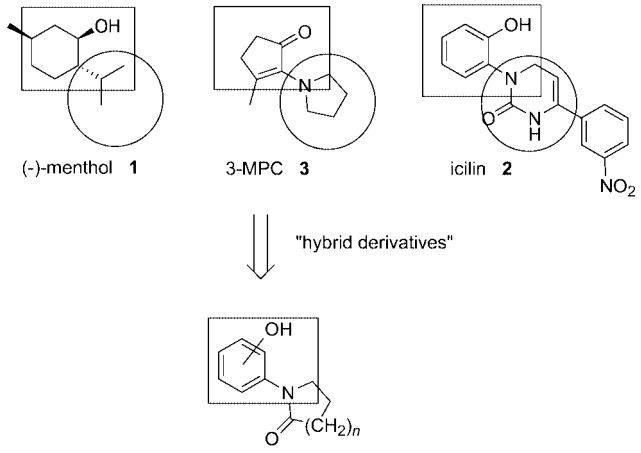
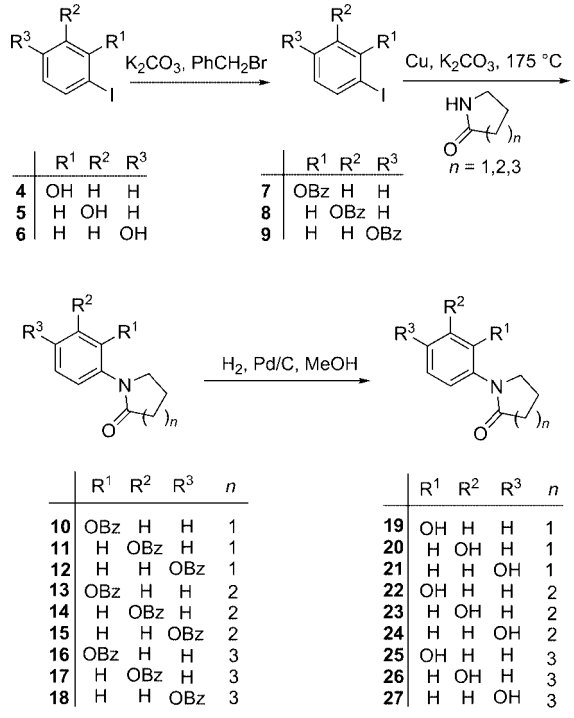


Figure 1. The rational design of new cooling derivatives from known active compounds such as menthol, 3-MPC and icilin. Block 1 (rectangle) contains an oxygenated function and block 2 (circle) an alkyl or nitrogenous ring.

In the absence of more detailed information, a common feature that can be found in these molecules, and in many congeners, is the presence of two blocks. Block 1 (shown in the rectangle) is a ring containing an oxygenated function: an alcohol in menthol, an unsaturated ketone in 3-MPC, and phenol in icilin. In the ketoenamines of this family a certain degree of enolisation is expected, and we in fact detected it experimentally by NMR spectroscopy; therefore it could be hypothesised that the enolic function in compound **3** could act as a pharmacophore similar to the alcoholic group in menthol and the phenolic function in icilin. Block 2 (shown in the circle) corresponds to a hydrophobic substituent in an adjacent position, which is isopropyl in menthol, a simple nitrogenous ring in ketoenamines and the ureidic ring in icilin.

For the synthesis of new hybrid compounds, the choice of a phenolic ring for block 1 has several advantages, since the synthesis of the corresponding aliphatic compounds involves control of the stereogenic centres. Moreover, icilin is more active than menthol, and therefore the phenolic substituent seems to be a good pharmacophore candidate. As a second building block we decided to keep a nitrogenous ring. Nevertheless, we did not use simple cyclic amines as in 3-MPC and analogues. In fact, in our hands the chemical stability of these compounds at room temperature and in the presence of air was very low, probably due to the reactive enamino group. Similar instability to oxidation is observed for simple aminophenols. Therefore, we decided to introduce an amido or ureidic group in order to make the derivatives more stable and also to mimic the icilin ring. The amido group is indeed very often present in cooling and other chemesthetic compounds, such as the commercial derivative menthyl carboxyamide (WS-3). Compared to menthol, WS-3 is more active and also has the advantage of no mint flavour and a much lower volatility.

The first group of new derivatives are therefore 5–7-membered ring lactams *N*-arylated with a phenol, whose synthesis is shown in Scheme 1.



	R1	R2	R3
4	OH	H	H
5	H	OH	H
6	H	H	OH

	R1	R2	R3
7	OBz	H	H
8	H	OBz	H
9	H	H	OBz

	R1	R2	R3	n
10	OBz	H	H	1
11	H	OBz	H	1
12	H	H	OBz	1
13	OBz	H	H	2
14	H	OBz	H	2
15	H	H	OBz	2
16	OBz	H	H	3
17	H	OBz	H	3
18	H	H	OBz	3

	R1	R2	R3	n
19	OH	H	H	1
20	H	OH	H	1
21	H	H	OH	1
22	OH	H	H	2
23	H	OH	H	2
24	H	H	OH	2
25	OH	H	H	3
26	H	OH	H	3
27	H	H	OH	3

Scheme 1. Synthesis of phenolic derivatives **19**–**27**.

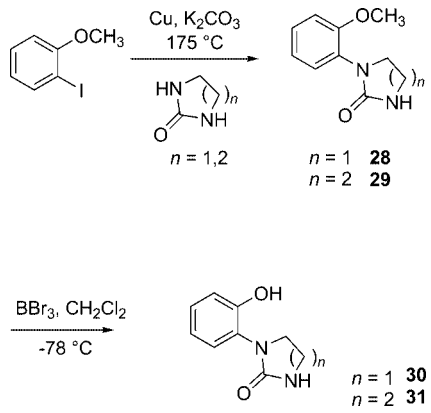
The intermediate *N*-arylated lactams were synthesized by a Goldberg reaction, i.e. the Cu-promoted *N*-arylation between a benzyl-protected iodophenol and a five-, six- or seven-membered ring lactam.[14] The yields of this step are between 57 and 91%. The title compounds **19**–**27** were obtained after the removal of the protecting group by catalytic hydrogenation, with yields between 80 and 96%. All compounds were purified by flash chromatography, and their purity was checked by HPLC and ^{1}H NMR before sensory evaluation. To assess the cooling activity, a sensory evaluation procedure was followed. An informed panel of 4–6 people from our lab underwent training to detect the cooling sensation, using WS-3 as a standard. The same com-

pounds were also tasted by a second external panel of trained people, which confirmed the results previously obtained. The compounds were tasted in water solutions with 3% ethanol. The results of the preliminary sensory analysis by the restricted panel are reported in Table 1.

Table 1. Preliminary sensory evaluation of phenolic *N*-aryl lactams in water/3% ethanol solution.

cpd	Concentration (10^{-3} M)	Sensory characteristics
19	4.67	cooling, persistent fresh sensation, slightly burning, slightly tingling
20	4.60	unpleasant
21	4.60	plastic like
22	4.60	cooling, slight bitter aftertaste, slightly tingling
23	4.18	bitter, slightly tingling
24	4.18	unpleasant
25	4.60	unpleasant
26	3.80	unpleasant
27	4.60	bitter, unpleasant aftertaste

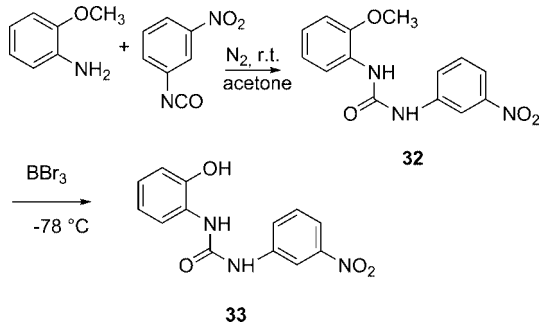
These results encouraged us to synthesise further derivatives. In particular, we decided to introduce a ureidic group in the second building block in order to mimic the icilin structure. The two cyclic ureas **30** and **31** were obtained by coupling of 2-iodoanisole with 2-imidazolidone or tetrahydro-2-pyrimidone (Scheme 2).



Scheme 2. Synthesis of ureidic derivatives **30** and **31**.

The yields of these reactions are limited since the desired product is obtained in a mixture with the bis-*N*-substituted derivative, which must be separated by chromatography; moreover, the demethylation of the methoxy group was quite difficult using BBr_3 in dichloromethane and the yield of about 50% could not be improved using other demethylation methods such as $AlCl_3$ in dichloromethane, methionine and methanesulfonic acid, HBr-acetic acid or LiCl in DMF.

An acyclic analogue **33** was also prepared following the procedure shown in Scheme 3. This compound has an icilin-like structure but has a linear asymmetrically disubstituted ureidic group instead of the cycle. The new derivatives with ureidic structure were submitted to preliminary tasting trials as described above; none of them had cooling or other chemesthetic activities.



Scheme 3. Synthesis of ureidic derivative **33**.

A third group of derivatives was prepared with a carboxylic group instead of the phenol group in block 1. The idea of introducing a carboxylic function comes from the fact that the two groups possess a similar capability to act as ligands toward a potential binding site through the formation of hydrogen bonds or chelation. Moreover, we decided to mimic another class of natural compounds containing the 2-aminobenzoic moiety, the anthranilamides, which we recently discovered to have very interesting properties as chemesthetic compounds and taste modifiers[15] (Figure 2).

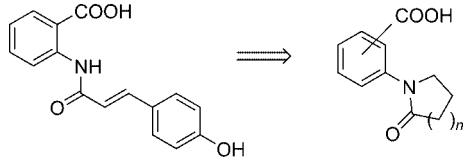
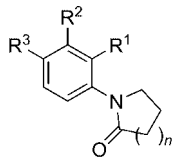


Figure 2. The design of carboxy derivatives by comparison with the avenanthramides skeleton (in the Figure avenanthramide A is shown).

For the synthesis of these new derivatives (compounds **34**–**40**, Figure 3), different approaches have been used. The reported one-pot synthesis of 4-(2-oxopyrrolydin-1-yl)benzoic acid (**36**), starting from 4-aminobenzoic acid and ethyl 4-bromobutyrate,[16] suffers from low yields and was not suitable for preparing the corresponding 2- and 3-carboxy derivatives. Some of them (**35**, **36** and **37**) were obtained by the Goldberg arylation starting from the corresponding 2- or 3- iodo carboxylic acids (or methylesters), but the yields were quite low (less than 60%).

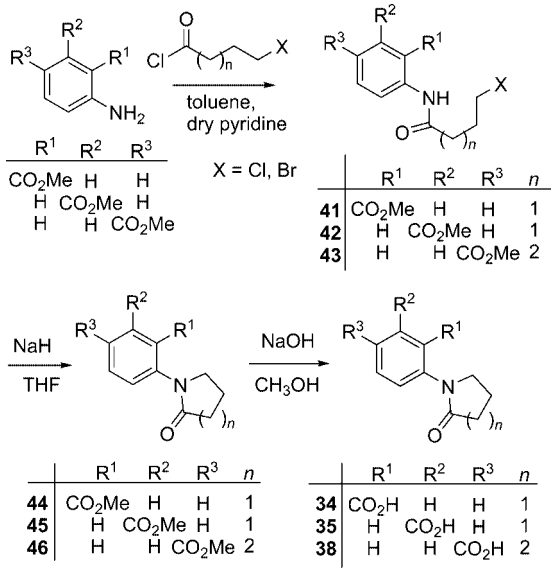
A more general alternative method with higher yields is shown in Scheme 4. In this case, we started from an aminobenzoate and the lactam ring was built by acylation and then closure of a suitable halogenated amide.

A similar procedure was described previously to prepare compound **34**,[17] but in that case the intermediate halogenated amide ester **41** was hydrolysed with phosphoric acid before the cyclisation step. The procedure reported in Scheme 4 was successfully applied to the synthesis of compounds **34**, **35** and **38**. This set of compounds was exten-



	R^1	R^2	R^3	*n*
34	CO_2H	H	H	1
35	H	CO_2H	H	1
36	H	H	CO_2H	1
37	CO_2H	H	H	2
38	H	H	CO_2H	2
39	CO_2H	H	H	3
40	H	CO_2H	H	3

Figure 3. The structures of carboxy lactam derivatives synthesised in this paper.



	R^1	R^2	R^3	*n*
41	CO_2Me	H	H	1
42	H	CO_2Me	H	1
43	H	H	CO_2Me	2

	R^1	R^2	R^3	*n*
44	CO_2Me	H	H	1
45	H	CO_2Me	H	1
46	H	H	CO_2Me	2

	R^1	R^2	R^3	*n*
34	CO_2H	H	H	1
35	H	CO_2H	H	1
38	H	H	CO_2H	2

Scheme 4. Synthesis of carboxy derivatives **34**, **35** and **38**.

sively purified by crystallisation. Five of them were obtained in sufficient amount and high purity and were submitted to preliminary sensory evaluation (Table 2).

Table 2. Preliminary sensory evaluation of carboxy *N*-aryl lactams in water-3% ethanol solution.

Compound	Concentration [10^{-3} M]	Sensory characteristics
34	4.90	slightly cooling
35	3.90	unpleasant
36	3.90	not cooling
37	4.60	not cooling
40	4.28	not cooling

Some cooling activity is retained in the 2-carboxy derivative **34**, but the cooling sensation is less strong than in the corresponding phenolic analogues.

The design of new hybrid compounds gave the expected results. The synthesis of the new derivatives is quite easy and the compounds are all obtained as white solids with low vapour pressure and are easy to purify by chromatography or crystallisation. Ease of purification is an important feature in compounds that have a possible application as food additives, as well as the high stability and solubility. Icilin is very insoluble in water and organic solvents, and in the paper by Wei and co-workers it has been tasted in water-DMSO mixtures.[3] This procedure is of no practical interest in sensory evaluation experiments both for toxicological reasons and for the fact that DMSO tastes and smells bad. Low solubility is probably one of the reasons why icilin has no practical application in food. Even if the new lactams are not completely soluble in water, it has been possible to taste some of them in water at concentrations as low as 100 ppm. The chemical stability of a food additive is also very important, especially during food processing. For instance, the cyclic α-ketoenamines with cooling activity are quite labile: in our hands, some of them [in particular 3-MPC and the analogous 2,5-dimethyl-4-(1-pyrrolidinyl)furan-3(2*H*)-one (DMPF)] quickly decomposed in the presence of air at room temperature, probably due to oxidation processes of the reactive enamino group. In this respect, the new lactam derivatives are much more stable, since the enamino group has been converted in the amide function. This functional group seems to be an important pharmacophore in many other chemesthetically active compounds , such as the cooling compounds icilin, WS-3 and the avenanthramides, the tingling natural compound sanshool and its derivatives, and also in capsaicin and many other pungent derivatives. The role of the oxygenated function in block 1 is not clear, but certainly the fact that most of the active compounds, including the carboxy derivatives, have this substituent in the 2-position, i.e. adjacent to the nitrogenous ring, suggests some specificity in the interaction with a putative receptor. As expected, none of the new compounds elicits any mint flavour, therefore their sensory characteristics are completely different from those of menthol. Nevertheless, a direct comparison with other known cooling compounds is not straightforward. An extensive study on the sensory properties of icilin is lacking; we were not able to taste commercial icilin due to its insolubility, and comparative data are not easy to obtain even for the ketoenamines. Qualitatively, all the new compounds are less active than WS-3; nevertheless, some panelists detected cooling activity for derivative **19** at concentrations as low as 2 ppm, whereas the threshold for cooling activity of WS-3 in water with our sensory panel was about 8 ppm.[18]

Knowledge of the mechanism of chemesthesis is still slight, although rapidly improving; therefore it is difficult to derive structure-activity relationships of general validity. For the same reason, it is necessary to understand which compounds activate a single receptor at molecular level in order to make a targeted drug design. Some of the lactam derivatives described in this paper (compounds **19**, **22**, **27**, **34**, **40**) have been also tested in vitro on the cloned TRPM8 (CMR1) receptor, showing no activity. Since TRPA1 is also involved in the cold sensation, it is not unreasonable to assume that these compounds might interact with this or other thermoreceptors, or that the cooling activity could be generated through a different mechanism that still needs to be elucidated.

Conclusion

By examining the known structures of cooling compounds it has been possible to design nineteen new derivatives, some of them having cooling activity. They contain two rings, one with an oxygenated function in the 2-position, and the other is a lactam ring. They have been obtained easily and in high yields by Goldberg arylation or lactam ring closure on the appropriate phenol or benzoic acid derivative. The synthetic procedures are suitable for gram-scale preparation, and the products are stable and easy to purify. In the preliminary sensory evaluation, some of them showed cooling activity, and in some cases tingling sensation in the oral cavity, even if at concentrations much higher than that of menthol. Owing to their simple structures, these compounds seem to be suitable for further studies of structure-activity relationships, which could give an insight into the molecular features needed to generate the chemesthetic sensation of cooling.

Experimental Section

Reagents were of commercial grade purity and solvents were dried using standard procedures. Melting points are uncorrected. Chromatography was carried out on 220–240 mesh silica gel using the flash methodology; thin-layer chromatography was performed on Merck precoated silica gel 60 F_{254} plates and the spots were visualised by UV at 254 nm. HPLC analyses were recorded with a Varian Prostar liquid chromatograph. IR spectra were recorded with a Perkin–Elmer 1310 infrared spectrophotometer. NMR spectra were recorded with a Bruker AMX-300 instrument, using TMS as an internal standard; *J* values are given in Hertz. Mass spectra were determined on a Finnigan 4021 spectrometer. HRMS were recorded with a Bruker Daltonics APEX II ICR-FTMS instrument, using the ESI ionisation mode. Compounds **7**, 1-(benzyloxy)-2-iodobenzene (142523-69-1), compound **19**,[19] 1-(2-hydroxyphenyl)-2-pyrrolidinone (19734-02-2) and compound **36**[15] (36151-44-7) were prepared following the literature method. Compounds **34** (41790-73-2) and **35** (515813-05-5) were identical to those described in the literature.

Syntheses of Phenolic Derivatives

General Procedure for Benzylation: Protection of halogenophenols as benzyl ethers was done by refluxing an appropriate halophenol (1 equiv.) with benzyl bromide (1 equiv.) and K_2CO_3 (2.6 equiv.) in acetone (0.1 M). After 4 h, the mixture was cooled, filtered and the solvent removed under reduced pressure. The crude product was purified by chromatography to give the title compounds.

General Procedure for Arylation: The aryl halide (1 equiv.) was heated at 175°C under nitrogen with the appropriate lactam (3 equiv.), Cu (2 equiv.) and K_2CO_3 (1 equiv.). After 6 h the mixture was cooled to room temperature, dissolved in methanol and filtered through celite. The solvent was evaporated, and the resulting mixture was purified by chromatography to give the title compound.

Compound 10: 3311.8 mg, 84%, white solid, m.p. 90–91 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.15 (quint, *J* = 7.1, 2 H, CH_2), 2.55 (t, *J* = 7.1, 2 H, CH_2CO), 3.78 (t, *J* = 7.1, 2 H, CH_2N), 5.12 (s, 2 H, CH_2OPh), 6.98–7.48 (m, 9 H, Ar) ppm.

Compound 11: 332.1 mg, 71%, pale yellow solid, m.p. 87–88 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.15 (quint, *J* = 7.0, 2 H, CH_2), 2.52 (t, *J* = 7.0, 2 H, CH_2CO), 3.84 (t, *J* = 7.0, 2 H, CH_2), 5.10 (s, 2 H, CH_2OPh), 6.78 (dd, *J* = 7.90, 1.1, 1 H, Ar), 7.11–7.48 (m, 8 H, Ar) ppm. HRMS (ESI): *m*/*z* = 557.24041 $(2M + Na)^+$, 290.11476 $[M + Na]^+$.

Compound 12: 351.0 mg, 78%, white solid, m.p. 146–148 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.18 (quint, *J* = 6.9, 2 H, CH_2), 2.58 (t, *J* = 6.9, 2 H, CH_2CO), 3.84 (t, *J* = 6.9, 2 H, CH_2), 5.08 (s, 2 H, CH_2OPh), 6.98 (d, *J* = 8.0, 2 H, H-3 and H-5), 7.32–7.42 (m, 5 H, Ar), 7.52 (d, *J* = 8.0, 2 H, H-2 and H-6) ppm. HRMS (ESI): *m*/*z* = 557.24041 $(2M + Na)^+$, 290.11473 $[M + Na]^+$.

Compound 13: 1173.5 mg, 85%, white solid, m.p. 89–90 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.89 (2 s, 4 H, 2 CH_2), 2.52 (br., 2 H, CH_2CO), 3.52 (br., 2 H, CH_2N), 5.10 (s, 2 H, CH_2OPh), 6.95–7.10 (m, 2 H, Ar), 7.12–7.48 (m, 7 H, Ar) ppm. MS: *m*/*z* (%) = 281 (60) $[M^+]$, , 190 (30), 174 (60), 162 (38), 91 (100).

Compound 14: 339.2 mg, 73%, oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.93 (2 s, 4 H, 2 CH_2), 2.59 (br., 2 H, CH_2CO), 3.64 (br., 2 H, CH_2N), 5.06 (s, 2 H, CH_2OPh), 6.81–6.99 (m, 3 H, Ar), 7.23–7.50 (m, 6 H, Ar). MS: *m*/*z* (%) = 281 (60) $[M^+]$, 264 (10), 190 (40), 91 (100).

Compound 15: 583.7 mg, 89%, pale yellow solid, m.p. 152–153 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.92 (br., 4 H, 2 CH_2), 2.05 (br., 2 H, CH_2CO), 3.58 (br., 2 H, CH_2N), 5.07 (s, 2 H, CH_2OPh), 6.99 (d, *J* = 8.0, 2 H, H-2 and H-6), 7.13 (d, *J* = 8.0, 2 H, H-3 and H-5), 7.32–7.48 (m, 5 H, Ar) ppm. MS: *m*/*z* (%) = 281 (100) $[M^+]$, 190 (90), 162 (10), 147 (10), 91 (80).

Compound 16: 1200.3 mg, 90%, oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.72 (s, 6 H, 3 CH_2), 2.65 (br., 2 H, CH_2CO), 3.62 (br., 2 H, CH_2N), 5.08 (s, 2 H, CH_2OPh), 6.92–7.48 (m, 9 H, Ar) ppm. MS: *m*/*z* (%) = 295 (62) $[M^+]$, 204 (40), 188 (85), 176 (40), 120 (45), 91 (100).

Compound 17: 318.0 mg, 57%, oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.82 (br., 6 H, 3 CH_2), 2.73 (br., 2 H, CH_2CO), 3.67 (br., 2 H, CH_2N), 5.08 (s, 2 H, CH_2OPh), 6.88–7.50 (m, 9 H, Ar) ppm. MS: *m*/*z* (%) = 296 (15) $[M + 1]^+$, 295 (40) $[M^+]$, 204 (20), 91 (100).

Compound 18: 688.3 mg, 70%, white solid, m.p. 118–120 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.81 (br., 6 H, 3 CH_2), 2.71 (br., 2 H, CH_2CO), 3.72 (br., 2 H, CH_2N), 5.07 (s, 2 H, CH_2OPh), 6.99 (d, *J* = 8.0, 2 H, H-2 and H-6), 7.13 (d, *J* = 8.0, 2 H, H-3 and H-5), 7.32–7.50 (m, 5 H, Ar) ppm. MS: *m*/*z* (%) = 295 (100) $[M^+]$, 204 (100), 176 (10), 96 (15), 91 (25).

General Procedure for Debenzylation: The protecting benzyl group was removed by standard procedures with H_2-Pd/C in methanol.

Compound **19** is identical to the substance described in ref.[18]; yield 2020.0 mg, 94%.

Compound 20: 280.7 mg, 94%, white solid, m.p. 210–211 °C. ^{1}H NMR (300 MHz, [D_6]acetone): δ = 2.11 (quint, *J* = 7.5, 2 H, CH_2), 2.45 (t, *J* = 7.5, 2 H, CH_2CO), 3.80 (t, *J* = 7.5, 2 H, CH_2), 6.51–6.62 (m, 1 H, Ar), 7.00–7.20 (m, 2 H, Ar), 7.34–7.45 (m, 1 H, Ar), 8.27–8.39 (m, 1 H, Ar) ppm. ^{13}C NMR ([D_6]acetone): δ = 17.5, 32.4, 48,1, 106.4, 110.0, 110.5, 129.1, 141.3, 157.4, 173.4 ppm. MS: *m*/*z* (%) = 178 (20) $[M + 1]^+$, 177 (75) $[M^+]$, 148 (10), 122 (100), 120 (10), 93 (15).

Compound 21: 297.4 mg, 93%, white solid, m.p. 167 °C. ^{1}H NMR (300 MHz, [D_6]acetone): δ = 2.12 (quint, *J* = 7.5, 2 H, CH_2), 2.43 (t, *J* = 7.5, 2 H, CH_2CO), 3.82 (t, *J* = 7.5, 2 H, CH_2N), 6.79 (d, *J* = 7.5, 2 H, H-2 and H-6), 7.50 (d, *J* = 7.5, 2 H, H-3 and H-5) ppm. ^{13}C NMR ([D_6]acetone): δ = 18.5, 32.9, 49.4, 115.8 (two signals overlapping), 122.0 (two signals overlapping), 133.3, 154.7, 173.8 ppm. MS: *m*/*z* (%) = 177 (40) $[M^+]$, 122 (100).

Compound 22: 1332.3 mg, 96%, white solid, m.p. 138 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.98 (m, 4 H, 2 CH_2), 2.68 (m, 2 H, CH_2CO), 3.75 (m, 2 H, CH_2N), 6.90–7.75 (m, 4 H, Ar) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.7, 23.1, 32.3, 51.7, 119.7, 120.8, 124.9, 128.3, 131.7, 151.3, 171.8 ppm. HRMS (ESI): *m*/*z* = 214.08366 [M + Na]$^+$, 192.10194 [M + 1]$^+$.

Compound 23: 202.1 mg, 88%, white solid, m.p. 172–173 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.97 (m, 4 H, 2 CH_2), 2.62 (m, 2 H, CH_2CO), 3.62 (m, 2 H, CH_2N), 6.91 (m, 3 H, Ar), 7.21 (t, *J* = 7.90, 1 H, H-5) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.9, 23.1, 32.3, 52.0, 114.5, 115.2, 116.0, 130.0, 143.1, 157.8, 171.1 ppm. MS: *m*/*z* (%) = 191 (100) [M$^+$], 162 (15), 135 (70), 122 (62), 120 (15).

Compound 24: 315.8 mg, 80%, white solid, m.p. 241–242 °C. ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 1.79 (m, 4 H, 2 CH_2), 2.30 (m, 2 H, CH_2CO), 3.46 (m, 2 H, CH_2N), 6.69 (d, 2 H, *J* = 8.0, H-2 and H-6), 7.00 (d, 2 H, *J* = 8.0, H-3 and H-5), 9.39 (s, 1 H, OH) ppm. ^{13}C NMR ([D_6]DMSO): δ = 21.2, 23.3, 32.7, 51.5, 115.4 (two signals overlapping), 127.6 (two signals overlapping), 135.3, 155.7, 168.8 ppm. MS: *m*/*z* (%) = 191 (100) [M$^+$], 162 (90), 135 (60), 122 (75), 120 (20), 107 (10), 93 (15).

Compound 25: 716.3 mg, 86%, white solid, m.p. 154–155 °C. ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 1.68 (br., 6 H, 3 CH_2), 2.52 (m, 2 H, CH_2CO), 3.48 (m, 2 H, CH_2N), 6.73 (dt, *J* = 8.0, 0.9, 1 H, H-5), 6.84 (dd, *J* = 8.0, 0.9, 1 H, H-3), 6.98 (dd, *J* = 8.0, 0.9, 1 H, H-6), 7.04 (dt, *J* = 8.0, 0.9, 1 H, H-4), 9.32 (s, 1 H, OH) ppm. ^{13}C NMR ([D_6]DMSO): δ = 23.2, 28.9, 29.5, 37.6, 54.3, 120.1, 121.1, 124.3, 127.9, 133.4, 150.9, 177.2 ppm. MS: *m*/*z* (%) = 205 (100) [M$^+$], 188 (20), 177 (20), 162 (5), 148 (35), 122 (90), 120 (60), 109 (40).

Compound 26: 186.8 mg, 88%, white solid, m.p. 136–137 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.82 (br., 4 H, 3 CH_2), 2.72 (m, 2 H, CH_2CO), 3.73 (m, 2 H, CH_2N), 6.65 (m, 3 H, Ar), 7.18 (t, *J* = 7.9, 1 H, H-5) ppm. ^{13}C NMR ($CDCl_3$): δ = 23.3, 28.5, 29.8, 37.4, 53.5, 114.5, 114.8, 116.1, 130.0, 144.5, 157.7, 176.7 ppm. MS: *m*/*z* (%) = 205 [M$^+$, 90], 177 (20), 148 (50), 135 (25), 122 (100), 109 (18).

Compound 27: 649.6 mg, 81%, white solid, m.p. 167–168 °C. ^{1}H NMR (300 MHz, [D_6]acetone): δ = 1.72 (br., 6 H, 3 CH_2), 2.57 (m, 2 H, CH_2CO), 3.62 (m, 2 H, CH_2N), 6.88 (d, *J* = 8.0, 2 H, H-3 and H-5), 6.99 (d, *J* = 8.0, 2 H, H-2 and H-6) ppm. ^{13}C NMR ([D_6]acetone): δ = 24.3, 38.1, 53.6, 115.9 (two signals overlapping), 128.3 (two signals overlapping), 138.2, 156.1, 175.1 ppm. MS: *m*/*z* (%) = 205 (100) [M$^+$], 177 (5), 148 (18), 135 (20), 122 (90), 120 (18), 109 (3), 96 (5). HRMS (ESI): *m*/*z* = 228.09951 [M + Na]$^+$.

Synthesis of Ureidic Derivatives: The arylation of iodophenols was performed under the same conditions described above for lactams by using 2-imidazolidinone or tetrahydropyrimidin-2-one. The resulting methyl ethers **28** and **29** were deprotected with BBr_3 at –78°C to give the title compounds.

Compound 28: 640.0 mg, 29%, white solid, m.p. 158–161 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.58 (t, *J* = 7.35, 2 H, CH_2), 3.85 (s, 3 H, OCH_3), 3.90 (t, *J* = 7.35, 2 H, CH_2), 6.90–7.50 (m, 4 H, Ar) ppm. MS: *m*/*z* (%) = 192 (100) [M$^+$], 136 (10), 121 (18). IR $\tilde{\nu}$ = 1500, 1595, 1695, 3220 cm^{-1}.

Compound 29: 30.0 mg, 11%, white solid, m.p. 174–178 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.10 (m, 2 H, H-5), 2.60 (br. s, 1 H, NH), 3.42 (m, 2 H, CH_2) 3.83 (s, 3 H, OCH_3), 6.90–7.34 (m, 4 H, Ar) ppm. MS: *m*/*z* (%) = 206 (60) [M$^+$], 175 (100), 147 (20), 136 (38), 120 (36), 106 (20), 92 (5), 77 (5), 65 (5).

Compound 30: 430.7 mg, 32%, white solid, m.p. 105 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.72 (m, 2 H, CH_2), 4.04 (m, 2 H, CH_2), 6.85–7.17 (m, 4 H, Ar) ppm. MS: *m*/*z* (%) = 179 (55) [M + 1]$^+$, 178 (100) [M$^+$], 149 (10), 122 (80), 120 (20), 106 (5), 95 (15), 77 (15), 65 (12), 52 (10).

Compound 31: 66.0 mg, 17%, grey solid, m.p. 188 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.12 (m, 2 H, CH_2), 3.44 (t, *J* = 5.8, 2 H, CH_2N), 3.78 (t, *J* = 5.5, 2 H, CH_2NHCO), 5.55 (br. s, 1 H, NH), 6.85–7.20 (m, 4 H, Ar) ppm. MS: *m*/*z* (%) 192 (60) [M$^+$], 175 (10), 135 (15), 122 (100), 120 (40), 109 (20), 95 (18), 80 (5), 65 (5). IR $\tilde{\nu}$ = 1530, 1620, 3400 cm^{-1}.

The acyclic urea **33** was obtained in two steps. 3-nitrophenyl isocyanate (2.67 g, 16.6 mmol) in acetone was added to 2-anisidine in acetone under N_2. The mixture was stirred for 3 hours and the precipitate filtered, washed with diethylether and crystallised with ethanol to give compound **32**. This was deprotected with BBr_3 at –78° in dichloromethane under N_2.

Compound 32: 1970.5 mg, 42%, solid, m.p. 187–189 °C. ^{1}H NMR ([D_6]DMSO): δ = 3.88 (s, 3 H, OCH_3), 6.85–7.10 (m, 3 H, Ar), 7.52–7.90 (m, 3 H, Ar), 8.13 (dd, *J* = 7.77, 1.39, 1 H, Ar), 8.31 (s, 1 H, NH), 8.58 (t, *J* = 2.21, 1 H, H-2), 9.91 (s, 1 H, NH) ppm. MS: *m*/*z* (%) = 287 (60) [M$^+$], 256 (10), 240 (10), 149 (28), 134 (20), 123 (75), 108 (100).

Compound 33: 560.0 mg, 47%, white solid, m.p. 215 °C. ^{1}H NMR ([D_6]DMSO): δ = 6.80–6.92 (m, 3 H, Ar), 7.51–8.12 (m, 4 H, Ar), 8.31 (s, 1 H, NH), 8.58 (t, *J* = 2.21, 1 H, H-2), 9.82 (s, 1 H, NH), 10.05 (br. s, 1 H, OH) ppm. MS: *m*/*z* (%) = 273 (18) [M$^+$], 135 (30), 109 (100), 92 (8), 80 (15), 65 (9).

Synthesis of Carboxy Derivatives: Compounds **37**, **39** and **40** were prepared following the Goldberg general procedure as described above.

Compound 37: 1252.0 mg, 59%, white solid, m.p. 140 °C. ^{1}H NMR ($CDCl_3$): δ = 1.92 (br., 4 H, 2 CH_2), 2.56 (br., 2 H, CH_2CO), 3.61 (br., 2 H, CH_2N), 7.18 (dd, *J* = 8.0, 0.7, 1 H, H-3), 7.48 (dt, *J* = 7.8, 0.7, 1 H, H-5), 7.54 (dt, *J* = 7.8, 0.7, 1 H, H-4), 7.98 (dd, *J* = 7.8, 0.7, 1 H, H-6) ppm. MS: *m*/*z* (%) 219 (60) [M$^+$], 174 (65), 163 (100), 145 (60), 132 (70), 119 (30), 105 (20), 90 (20), 77 (40), 70 (15), 65 (20).

Compound 39: 440.8 mg, 44%, white solid, m.p. 175–176 °C. ^{1}H NMR ([D_6]DMSO): δ = 1.72 (br., 6 H, 3 CH_2), 2.50 (br., 2 H, CH_2CO), 3.37 (br., 2 H, CH_2N), 7.22 (dd, *J* = 8.0, 0.7, 1 H, H-3), 7.33 (dt, *J* = 7.7, 0.8, 1 H, H-5), 7.55 (dt, *J* = 7.7, 1.1, 1 H, H-4), 7.75 (dd, *J* = 7.5, 1.4, 1 H, H-6) ppm. HRMS (ESI): 256.09410 [M + Na]$^+$.

Compound 40: 148.9 mg, 45%, beige solid, m.p. 190 °C. ^{1}H NMR ([D_6]acetone): δ = 1.81 (br., 6 H, 3 CH_2), 2.62 (br., 2 H, CH_2CO), 3.87 (br., 2 H, CH_2N), 7.39–7.95 (m, 4 H, Ar) ppm. MS: *m*/*z* (%) = 233 (100) [M$^+$], 176 (70), 150 (90).

Compounds **34**, **35** and **38** were synthesised following Scheme 4.

General Procedure: A solution of acyl chloride in toluene was added to a mixture of aminobenzoic acid (1 equiv) in pyridine at 0 °C. The mixture was stirred for 4–8 hours at 0 °C then allowed to reach room temperature, filtered, evaporated to dryness, diluted with water and extracted with ethyl acetate. The corresponding halogenated amide was purified by flash chromatography.

Compound 41: 1684.9 mg, 95%, colorless oil. ^{1}H NMR ($CDCl_3$): δ = 2.21 (m, 2 H, CH_2), 2.68 (t, *J* = 7.9, 2 H, CH_2CO), 3.54 (t, *J* = 7.9, 2 H, CH_2Br), 3.98 (s, 3 H, CO_2CH_3), 7.08 (dt, *J* = 7.8, 0.8, 1 H, H-5), 7.55 (dt, *J* = 7.8, 0.8, 1 H, H-4), 8.04 (dt, *J* = 7.8, 0.8, 1 H, H-3), 8.76 (dd, *J* = 7.8, 0.8, 1 H, H-6), 11.20 (br., 1 H, NH) ppm. MS: *m*/*z* (%) = 301 (25) [M + 1]$^+$, 193 (35).

Compound 42: 1320.0 mg, 93%, colorless oil. ^{1}H NMR ($CDCl_3$): δ = 2.30 (m, 2 H, CH_2), 2.60 (t, J = 6.9, 2 H, CH_2CO), 3.55 (t, J = 6.1, 2 H, CH_2Br), 3.92 (s, 3 H, CO_2CH_3), 7.33 (m, 1 H, H-5), 7.42 (t, J = 8.0, 1 H, H-4), 7.83 (m, 2 H, H-6 and H-2), 8.05 (s, 1 H, NH) ppm. MS: m/z (%) = 301 (20) $[M + 1]^+$, 299 (20), 270 (15), 268 (10).

Compound 43: 1088.0 mg, 89%, pale yellow solid, m.p. 56–57 °C. ^{1}H NMR ($CDCl_3$): δ = 1.92 (m, 4 H, 2 CH_2), 2.50 (t, J = 6.8, 2 H, CH_2CO), 3.61 (t, J = 6.8, 2 H, CH_2Cl), 3.94 (s, 3 H, CO_2CH_3), 7.36 (br., 1 H, NH), 7.60 (d, J = 8.3, 2 H, H-3 and H-5), 8.01 (d, J = 8.3, 2 H, H-2 and H-6) ppm. MS: m/z (%) = 269 (25) $[M^+]$, 234 (25).

The halogenated amide of type **41**–**43** was dissolved in THF, and NaH (1 equiv.) was added. The solution was stirred for 4 h at room temperature, evaporated to dryness, diluted with water, and extracted with ethyl acetate. The corresponding lactams (**44**, **45** and **46**) were purified by flash chromatography.

Compound 44: 360.4 mg, 71%, colourless oil. ^{1}H NMR ($CDCl_3$): δ = 2.32 (m, 2 H, CH_2), 2.52 (t, J = 7.9, 2 H, CH_2CO), 3.82 (t, J = 6.9, 2 H, CH_2N), 3.88 (s, 3 H, CO_2CH_3), 7.22 (dd, J = 7.9, 0.8, 1 H, H-3), 7.35 (dt, J = 8.0, 0.8, 1 H, H-5), 7.54 (dt, J = 7.9, 0.9, 1 H, H-4), 7.93 (dd, J = 7.9, 0.9, 1 H, H-6) ppm. MS: m/z (%) 219 (60) $[M^+]$, 191 (30), 187 (40), 159 (50), 132 (100), 104 (20), 90 (18), 77 (50), 65 (18).

Compound 45: 910.0 mg, 56%, colourless oil. ^{1}H NMR ($CDCl_3$): δ = 2.19 (m, 2 H, CH_2), 2.67 (t, J = 8.0, 2 H, CH_2CO), 3.92 (t, J = 8.0, 2 H, CH_2N), 3.92 (s, 3 H, CO_2CH_3), 7.45 (t, J = 8.0, 1 H, H-5), 7.82 (dt, J = 7.7, 1.1, 1 H, H-4), 8.07 (m, 2 H, H-2 and H-6) ppm. MS: m/z (%) = 219 (85) $[M^+]$, 164 (100).

Compound 46: 153.5 mg, 66%, white solid, m.p. 120–121 °C. ^{1}H NMR ($CDCl_3$): δ = 1.98 (m, 4 H, 2 CH_2), 2.61 (t, J = 6.8, 2 H, CH_2CO), 3.72 (t, J = 6.8, 2 H, CH_2N), 3.98 (s, 3 H, CO_2CH_3), 7.37 (d, J = 8.0, 2 H, H-2 and H-6), 8.05 (d, J = 8.0, 2 H, H-3 and H-5) ppm. MS: m/z (%) = 233 (100) $[M^+]$, 202 (20), 190 (20), 177 (100), 146 (40), 118 (30), 104 (15), 90 (18), 77 (20), 70 (10), 55 (10).

The lactams of type **34**, **35**, **38** were obtained by hydrolysis of corresponding esters (**44**, **45** and **46**) (1 equiv) for 2 d with NaOH 0.25 N (3 equiv.) in MeOH under reflux. The reaction mixtures were evaporated, diluted with water, and acidified with diluted HCl and extracted with ethyl acetate. The corresponding lactams were purified by crystallisation from ethanol.

Compound 34: 240.8 mg, 85% white solid, m.p. 198–199 °C. ^{1}HNMR ($CDCl_3$): δ = 2.24 (quint, J = 7.3, 2 H, CH_2), 2.62 (t, J = 7.3, 2 H, CH_2CO), 3.87 (t, J = 7.3, 2 H, CH_2N), 7.26 (m, 1 H, H-3), 7.38 (dd, J = 7.4, 1, 1 H, H-5), 7.57 (dt, J = 7.4, 0.8, 1 H, H-4), 7.99 (dd, J = 7.6, 1, 1 H, H-6) ppm. MS: m/z (%) = 205 (65) $[M^+]$, 150 (100), 177 (10). HRMS (ESI): m/z = 250.04559 $(M - H + 2Na)^+$, 228.06359 $[M + Na]^+$.

Compound 35: 240.0 mg, 50%, white solid, m.p. 245–246 °C. ^{1}HNMR ([D_6]acetone): δ = 2.19 (m, 2 H, CH_2), 2.54 (t, J = 7,0 2 H, CH_2CO), 3.95 (t, J = 7.0, 2 H, CH_2N), 7.49 (t, J = 7.9, 1 H, H-5), 7.95 (dt, J = 7.9, 1.1, 1 H, H-4), 8.00 (ddd, J = 7.9, 2.0, 1.9, 1 H, H-6), 8.36 (t, J = 2.0, 1 H, H-2) ppm. MS: m/z (%) = 205 (65) $[M^+]$, 177 (10), 150 (100), 104 (10), 97 (30), 81 (40), 69 (60).

Compound 38: 181.2 mg, 57%, white solid, m.p. 127 °C. ^{1}HNMR ([D_6]acetone): δ = 1.69 (m, 2 H, CH_2), 2.33 (br., 2 H, CH_2CO), 3.72 (br., 2 H, CH_2N), 6.61 (d, J = 8.6, 2 H, H-2 and H-6), 7.73 (d, J = 8.6, 2 H, H-3 and H-5) ppm.

Sensory Evaluation Procedures: All the compounds were purified by chromatography and crystallisation until the purity was >98% (HPLC). Two standard toxicology tests used for episodic administration of oral drugs (determination of acute toxicity in mice and cytotoxicity on keratinocytes) were done on representative compounds **19** and **33**, which resulted negative to both tests. The compounds have been evaluated by two independent panels, each of 5–6 people. The panelists were previously trained to detect the cooling sensation in the oral cavity using WS-3 as a standard at the threshold concentration of 10 ppm, and were asked to individuate the cooling sensation and other relevant sensory properties in the new compounds. The compounds have been dissolved in water with 3% ethanol at room temperature and tested using the standard "sip and spit" procedure.

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