The Taming of Capsaicin. Reversal of the Vanilloid Activity of *N*-Acylvanillamines by Aromatic Iodination

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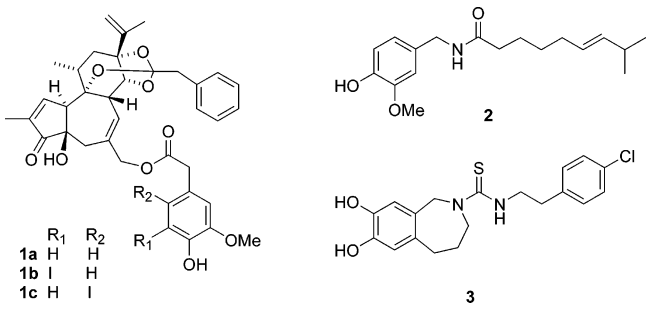
Aromatic iodination *ortho* to the phenolic hydroxyl reverts the activity of the ultrapotent vanilloid agonist resiniferatoxin (RTX, **1a**), generating the ultrapotent antagonist 5′-iodoRTX (**1b**). To better understand the role of iodine in this remarkable switch of activity, a systematic investigation on the halogenation of vanillamides, a class of compounds structurally simpler than resiniferonoids, was carried out. The results showed that (a) the antagonistic activity depends on the site of halogenation and is maximal at C-6′, (b) iodine is more efficient than chlorine and bromine at reverting the agonistic activity, and (c) iodine−carbon exchange decreases antagonist activity. Iodine-induced reversal of vanilloid activity was also observed in vanillamides more powerful than capsaicin, but a poor correlation was found between agonistic and antagonistic potencies, suggesting that differences exist in the way vanillamides and their 6′-iodo derivatives bind to TRPV1.″

Introduction

The heat-sensitive vanilloid receptor TRPV1 plays a central role in inflammatory pain and is a well recognized target for the discovery of new analgesic drugs aimed at the treatment of neuropathic pain.[1] This debilitating chronic condition is characterized by spontaneous pain, allodynia, and hyperalgesia, and develops when nerves are damaged through surgery, bone compression, diabetes, or infection. Furthermore, TRPV1 has also been implicated in the pathogenesis of a host of other conditions, including inflammatory bowel disease, cough, and bladder hyperreflexia, highlighting the pleiotropic potential of its manipulation.[2] TRPV1 activity is fine-tuned through a number of regulatory mechanisms that include endogenous ligands (endovanilloids, PIP_2), pH, and phosphorylation/dephophorylation by protein kinases (e.g. PKC, PKA) and phosphatases.[3] All these regulatory mechanisms provide the opportunity for intervention, but since some of them rely on ubiquitous cellular components (PIP_2, PKC, PKA, calcineurin), desensitization with agonists and block with antagonists have been the strategies of choice to selectively damp down TRPV1 activity and decrease sensitivity to nociceptive inputs.[4,5] Neither approach has so far produced a commercial drug, but several vanilloid agonists and antagonists are currently under clinical trial and might therefore reach the market in the next few years.[4] TRPV1 desensitization and antagonism have both relative advantages and disadvantages,[5] but current industrial research is overwhelmingly biased toward the discovery of vanilloid antagonists, since these compounds are devoid of the initial aversive and often dose-limiting side-effects of vanilloid agonists such as capsaicin (**2**).[5] While natural products have provided a host of lead structures to inspire the synthesis of vanilloid agonists,[4] the search for specific antagonists has long remained elusive. Thus, since the discovery of the weak antagonist capsazepine (**3**) in 1992,[6] no further advance was reported until 2001, when the powerful vanilloid antagonism of 5′-iodoresiniferatoxin (**1b**) was serendipitously observed during attempts to prepare a radioactive ligand for TRPV1.[7] 6′-Iodoresiniferatoxin (**1c**) was next reported as a partial agonist,[8] soon followed by a spate of entirely synthetic compounds discovered by random screening of chemical libraries and that therefore bear little resemblance with the archetypal vanilloid ligands capsaicin (CPS, **2**) and resiniferatoxin (RTX, **1a**).[4]



RTX has successfully served as a template to design structurally simpler and powerful vanilloid antagonists,[9] but the vanillamide motif of CPS has so far been largely overlooked, despite its structural simplicity and the observation that, when compared to RTX, CPS

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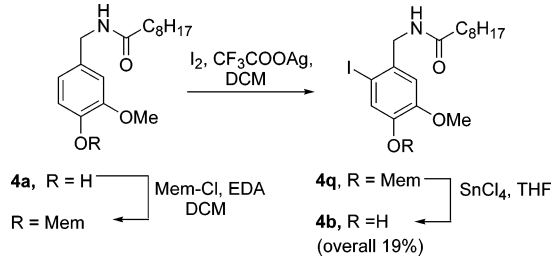
Scheme 1. Synthesis of 6′-Iodononivamide (**4b**) from Nonivamide (**4a**)



shows a certain selectivity for the human isoform of TRPV1.[10] Capsaicin is less potent than RTX and shows a pro-quinoid structure that might contribute to metabolic vulnerability.[11,12] However, these unfavorable features can in principle be addressed by changes in the acyl moiety and in the aromatic ring, since the vanillamides of certain fatty acids rival in potency with RTX,[13] and the stability of pro-quinoid structures can be increased by the introduction of substituents.[14]

The remarkable effect of aromatic iodination on the activity of RTX, and the potential beneficial effects in terms of drug-likeness associated to the introduction of substituents on the vanillyl moiety, prompted us to carry out a systematic investigation on the aromatic iodination of capsaicinoids. Our aim was to assess if reversal of vanilloid activity was also possible in the vanillamide framework, identifying the optimal regiochemistry of substitution and establishing if other halogen atoms, or even alkyl groups, could share the functional reversing properties of iodine. Unsaturation and branching on the side chain of CPS are redundant for vanilloid activity.[15] Thus, since most protocols of aromatic halogenation are incompatible with the presence of double bonds, we selected nonivamide (**4a**), a minor constituent of *Capsicum* oleoresin having a linear saturated acyl moiety,[16] as lead structure. Nonivamide has the same biological profile of capsaicin[15] and is commonly referred to as "synthetic capsaicin" because synthesis predated its isolation.[16]

Chemistry. Nonivamide was unreactive, or was totally degraded, under a series of aromatic iodination conditions,[17] but, after MEM (methoxyethoxymethyl) protection of the phenolic hydroxyl, a clean reaction was observed with the iodine−silver trifluoracetate protocol.[18] Iodination took place selectively at C-6, that is *ortho* to the benzylic carbon and *para* to the methoxy group, and, after deprotection, 6′-iodononivamide (6′-iodonordihydrocapsaicin, **4b**) was obtained in overall 19% yield from nonivamide (**4a**) (Scheme 1).

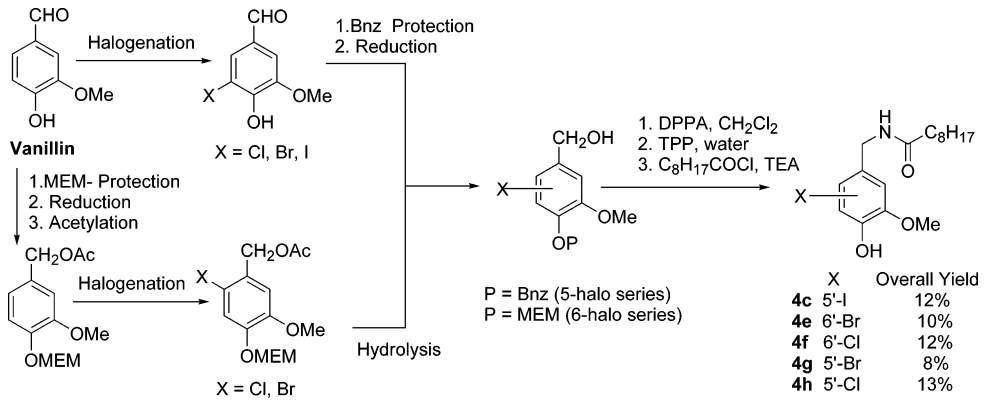
The other 5′- and 6′-halogenated nonivamides (**4c,e**−**h**) were prepared from the corresponding *O*-MEM (benzyl)-protected halovanillins, since the secondary amide function of nonivamide could not resist conditions of aromatic halogenation different from those employed for the synthesis of **4b**. All halovanillins required are known, but we often had to modify their original preparation or to resort to more recent halogenation protocols[19] to get compounds free (^{1}H NMR analysis) from isomeric products, as detailed in the Experimental Section. The presence of a free phenolic hydroxyl-directed halogenation to the *ortho* carbon (C-5), while protection as a MEM ether switched the regiochemistry of halogenation from C-5′ to C-6′ (Scheme 2). Conversion to the corresponding nonivamides was next carried out in a sequence of steps involving, after phenolic protection for the 5′-halo derivatives, aldehyde reduction, azidation, tandem Staudinger reduction−acylation, and deprotection (Scheme 2).

2-Iodo-4-*O*-MEM-vanillol (**6**) was prepared from 2-nitrovanillin acetate (**5**) by nitro-to-amine reduction, amine-to-iodine replacement via a diazonium salt,[20] protection, and borohydride reduction. 2-Iodo-(**6**) and 2-nitro-4-*O*-MEMvanillols (**7**) were converted to the corresponding nonivamides (**4d** and **4o**, respectively) in the usual way (Scheme 3). Reduction of 2-nitro-*O*-MEM-nonivamide (**8**) gave the corresponding amine, from which 2′-acetamidononivamide (**4p**) and the cyclic urea **9** were obtained by treatment with Ac_2O and BOC_2O, respectively, and deprotection (Scheme 3).

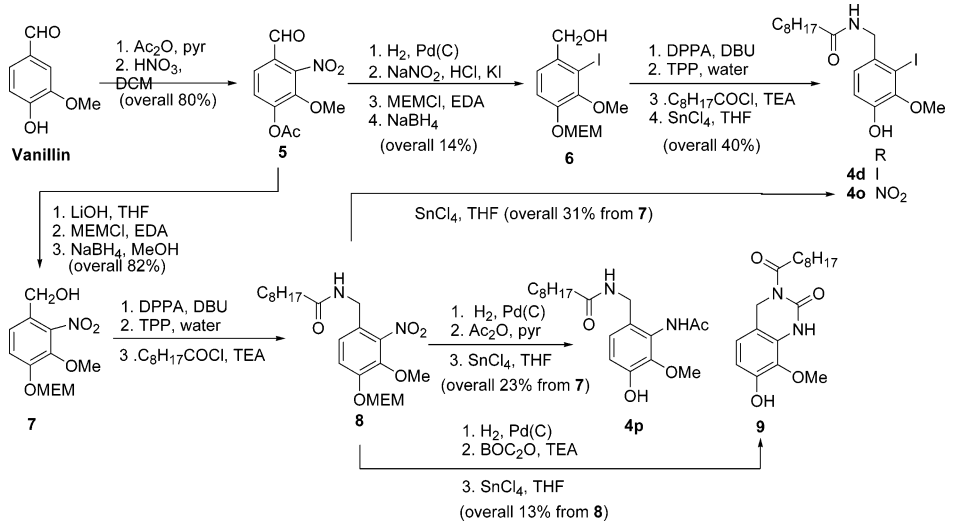
Palladium-catalyzed iodine-to-carbon exchange was carried out using a Suzuki coupling for the synthesis of 6′-phenylnonivamide (**4i**), and a Sonogashira coupling for the synthesis of 6-ethynylnonivamide (**4j**) (Scheme 4). Semireduction, reduction, and hydration of the ethinyl group afforded the 6′-ethenyl. 6′-ethyl, and 6′-acetyl analogues (compounds **4k**−**m**), while the vanillyl acrylate **4n** was prepared by Heck reaction of 6′-iodo-*O*-MEMnonivamide with methyl acrylate. A ferricyanide-mediated phenol coupling was used for the preparation of the 5,5-dimeric nonivamide **10**.[21]

The 6′-iodo derivatives of olvanil (**12b**),[15a] arvanil (**12c**),[22] and retvanil (**12d**)[23] could not be prepared from the parent vanillamides, since the side chain-unsaturated system was attacked by the couple iodine−silver

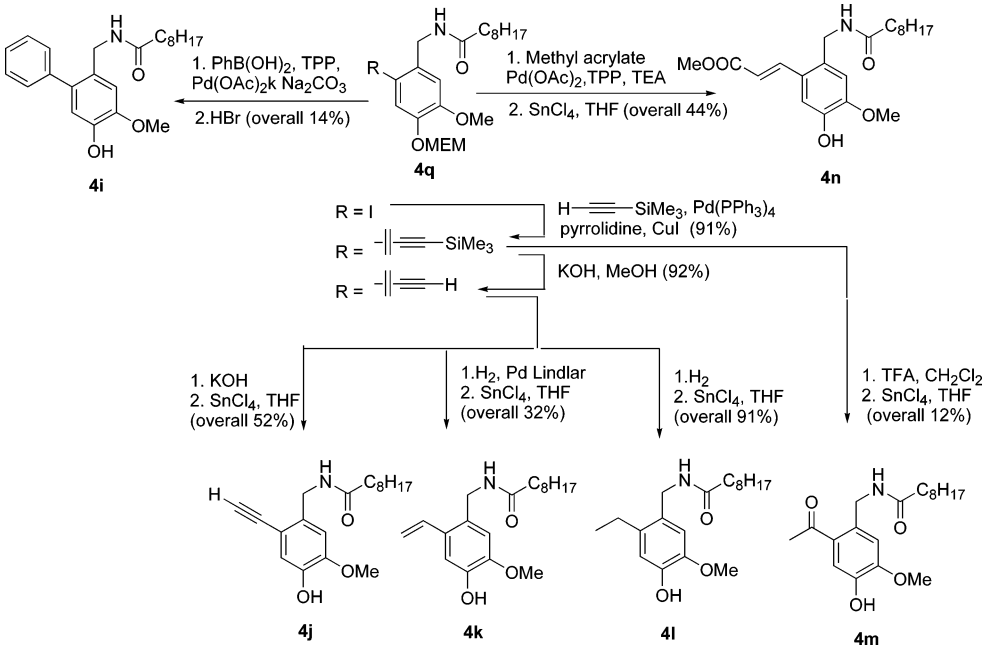
Scheme 2. General Synthetic Strategy for the Synthesis of the 5′-Halo- and 6′-Halononivamides **4c**, **4e**, **4f**, **4g**, **4h**, from Vanillin (for details, see Supporting Information)



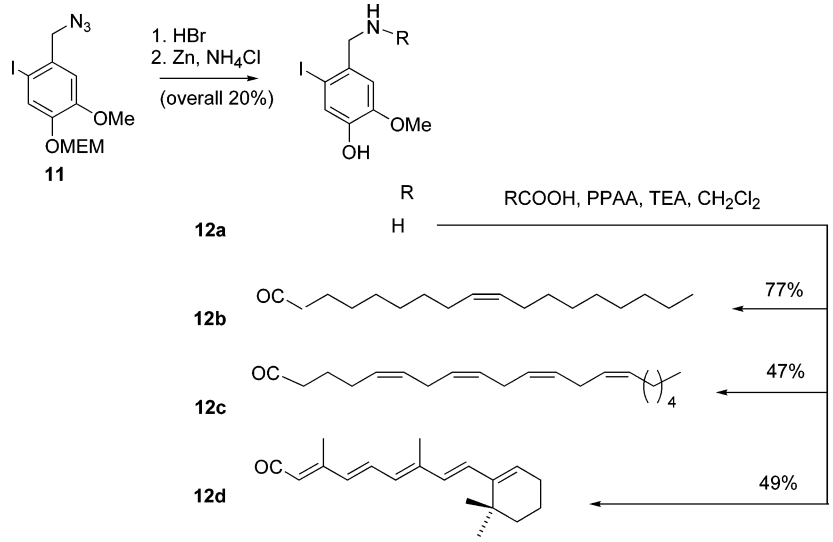
Scheme 3. Synthesis of the 2′-Substituted Nonivamides **4d**, **4o**, **4p**, and **9**



Scheme 4. Synthesis of the C-6′ C-Substituted Nonivamides **4i**−**n**



Scheme 5. Synthesis of the 6′-Iodo derivatives of Olvanil (**12b**), Arvanil (**12c**), and Retvanil (**12d**)

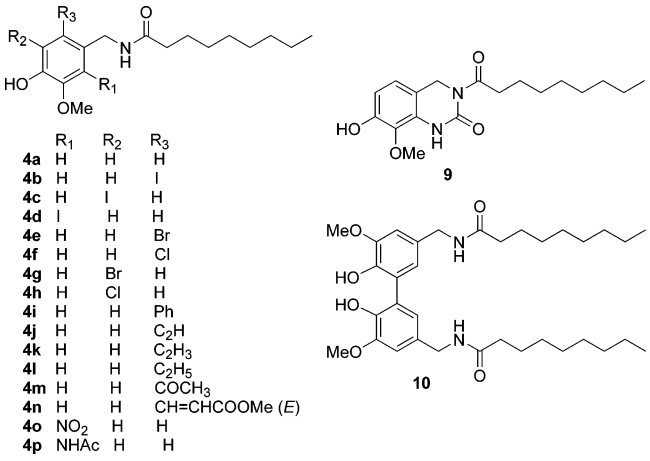


trifluoroacetate. An alternative and general synthesis based on the PPAA (propylphosphonic acid anhydride)-mediated acylation of 6′-iodovanillamine (**12a**) was employed.[23] 6-Iodovanillamine was in turn prepared (Scheme 5) by deprotection (HBr) and reduction (Zn−NH_4Cl) of the corresponding *O*-MEM azide (**11**), prepared from vanilline according to Scheme 2, as detailed in the Supporting Information.

Biological Evaluation. Vanilloid agonistic and antagonistic activities were evaluated in human embryonic kidney (HEK) 293 cells overexpressing human TRPV1. Experiments were carried out by measuring cell fluorescence at 25 °C (λ_{EX} = 488 nm, λ_{EM} = 540 nm) before and after the addition of the test compounds at various concentrations. In antagonism experiments, varying doses of the compounds were added 10 min prior to capsaicin (100 nM). Data were expressed as the concentration exerting a half-maximal inhibition (IC_{50}) calculated by GraphPad.

Results and Discussion

Several classes of structurally unrelated TRPV1 antagonists have recently discovered by random screening of synthetic libraries of small molecules.[4] Despite the wealth of activators that have emerged from the treasure trove of plant extracts.[4] natural products have substantially lagged behind synthetic compounds in providing TRPV1 antagonist leads.[24] The defense role of secondary metabolites might provide an evolutionary explanation for this observation, but the serendipitous discovery that iodination of the ultrapotent agonist resiniferatoxin (RTX) reverses its vanilloid activity[7] has provided new opportunities to exploit the pool of natural products to discover TRPV1-antagonists.



	R_1	R_2	R_3
4a	H	H	H
4b	H	H	I
4c	H	I	H
4d	I	H	H
4e	H	H	Br
4f	H	H	Cl
4g	H	Br	H
4h	H	Cl	H
4i	H	H	Ph
4j	H	H	C_2H
4k	H	H	C_2H_3
4l	H	H	C_2H_5
4m	H	H	$COCH_3$
4n	H	H	CH=CHCOOMe (*E*)
4o	NO_2	H	H
4p	NHAc	H	H

9

10

Modulation of activity by halogenation of aromatic amino acids has been reported in the realm of opioids,[25] but the effect of iodination on the activity of RTX is nevertheless quite remarkable and prompted us to assess the biological effect of aromatic halogenation on nonivamide (**4a**), the so-called "synthetic capsaicin". To this purpose, all three possible iodo-nonivamides (**4b**−**d**) were prepared and evaluated for vanilloid activity using HEK-293 cells transfected with the human recombinant TRPV1. None of these compounds activated TRPV1-mediated Ca^{2+} responses up to a 10 μM concentration. Both the 6′- and the 5′-iodo derivatives (**4b** and **4c**, respectively) behaved as powerful antagonists against the TRPV1 agonist capsaicin,[26] while 2′-iodononivamide (**4d**) showed only marginal antagonist potency (Table 1).

Table 1. Vanilloid Antagonistic Activity of Aryl-Substituted Vanillamides[a]

compd	name	IC_{50} (nM)
1b	5′-iodoresiniferatoxin	0.4 ± 0.1
3	capsazepine	56.2 ± 5.1
4b	6′-iodononivamide	10.0 ± 2.1
4c	5′-iodononivamide	126.2 ± 15.4
4d	2′-iodononivamide	3383.0 ± 350.3
4e	6′-bromononivamide	16.1 ± 2.7
4f	6′-chlorononivamide	50.3 ± 3.9
4g	5′-bromononivamide	251.6 ± 22.2
4h	5′-chlorononivamide	631 ± 45.5
4i	6′-phenylnonivamide	>20000[b]
4j	6′-ethynylnonivamide	2740 ± 281.0
4k	6′-ethenylnonivamide	389.6 ± 43.2
4l	6′-ethylnonivamide	355.3 ± 37.8
4m	6′-acetylnonivamide	10380.0 ± 780.9
4n	6′-(*E*-2-methoxycarbonylethenyl)-nonivamide	3932.0 ± 278.5
4o	2′-nitrononivamide	10970.0 ± 930.7
4p	2′-acetamidononivamide	9544.0 ± 889.1
9	*N*,*N*′-carbonyl-2′-aminononivamide	3402.0 ± 444.2
10	5′,5″-dinonivamide	>20000[b]
12b	6′-iodoolvanil	35.0 ± 1.2
12c	6′-iodoarvanil	51.0 ± 2.3
12d	6′-iodoretvanil	17490 ± 985.7

[a] Data are reported as IC_{50} (nM) against the effect of capsaicin 100 nM on intracellular Ca^{2+} concentration in HEK293 cells overexpressing the human recombinant TRPV1. Unless otherwise indicated, all compounds had no appreciable effect per se on intracellular Ca^{2+} concentration up to 10 μM. [b] Weak agonist activity (<35% of the effect of 4 μM ionomycin) at 10 μM.

In striking contrast with the observation reported for RTX,[8] the 6′-iodo derivative (**4b**) was not only a full antagonist, but was also more potent than the 5′-iodo derivative **4c** (Table 1). 2′-Nitro- (**4o**) and 2′-acetamido (**4p**) nonivamides were even less potent than their corresponding iodo derivative (**4d**), while no significant change of activity was observed between **4d** and its cyclic acylurea **9**. Substitution at C-2′ seems therefore detrimental for TRPV1 binding, prompting us focus on the functionalization of C-5′ and C-6′. The chlorine and bromine analogues of **4b** and **4c** were next prepared (**4e**−**h**). In both regioisomeric series, the order of antagonistic potency was iodine > bromine > chlorine (Table 1). 6′-Iodononivamide was identified as the most potent compound in this series and was next subjected to palladium-mediated halogen-to-carbon exchange, replacing the iodine atom with a phenyl (**4i**) and ethynyl group (**4j**). The 6′-ethynyl group was in turn further elaborated into ethenyl, ethyl, and acetyl substituents by semireduction, hydrogenation, and hydration, respectively (**4k**−**m**). None of these carbon-substituted compounds (**4i**−**m**) showed activity comparable to that of the parent 6′-iodo derivative, but all compounds still behaved as antagonists, with the exception of the 6′-phenyl derivative (**4i**), which lacked significant affinity for TRPV1. The possibility that an oxygen function on the C-6′ substituent is detrimental for activity was further supported by the very low potency of the 6′-acrylate **4n**. Capsaicinoids readily dimerize under biomimetic oxidative conditions,[21] and compounds of this type occur naturally in chili pepper.[27] It was therefore interesting to evaluate the effect of the oxidative dimerization on vanilloid activity. The dimer **10**,

prepared by ferricyanate-induced phenol coupling,[21] showed only very modest vanilloid agonistic activity and was inactive as an antagonist, suggesting that dimerization by phenol coupling is detrimental for the vanilloid activity of capsaicinoids. A comparison of the activity data on 6′-halo and the 6′-alkylnonivamides shows that, within each series, the size and the polarity of the substituent are important for the reversal of vanilloid activity, with bulky and less polar groups performing better than their smaller and more polar counterparts (I ≥ Br > Cl; ethyl ≥ vinyl > ethynyl). The reversal of activity seems therefore essentially due to a steric effect, that leads to an unproductive binding within the receptor cavity.

Having identified a 6′-iodo-group as the best reversal agent, the 6′-iodo derivatives of vanillamides more potent than capsaicin and nonivamide as TRPV1 agonists were synthesized, preparing the 6′-iodo analogues of olvanil (**12b**),[15] arvanil (**12c**),[22] and retvanil (**12d**).[23] Iodination caused a reversal of vanilloid activity in all cases, but 6′-iodoretvanil (**12d**) exhibited only marginal activity. Overall, a poor correlation was found between the potency of vanillamides as a TRPV1 agonist and that of their corresponding 6′-iodo derivatives as antagonists. Thus, olvanil, arvanil, and retvanil are at least 1 order of magnitude more potent than nonivamide and capsaicin as TRPV1 activators,[15,22,23] but their corresponding 6′-iodo derivatives were less potent than 6′-iodononivamide or almost inactive, suggesting that the activity switch caused by aromatic iodination upsets also the structure−activity relationships of the acyl moiety.

An even more striking discrepancy exists, however, between the effect of iodination on the vanilloid activity of CPS and RTX, resulting in different structure−activity relationships for the reversal of activity, that is maximal upon iodination at C-5 in RTX and upon iodination at C-6 in capsaicinoids. This observation supports the view that capsaicin and RTX, while interacting with the same binding site of TRPV1, establish contacts with different, and only partly overlapping, subsets of residues within the ligand pocket, generating distinct structure−activity relationships.[1] This view is in accordance with docking and site-directed mutagenesis experiments, that suggest that different pharmacophores of CPS and RTX interact with critical tyrosine residues (tyr-511 and tyr-555, respectively) in the vanilloid binding pocket.[28] Given the promiscuous binding behavior of TRPV1, the existence of a common pharmacophore for its structurally diverse natural products ligands seems therefore unlikely.

A few general considerations can be made also on the TRPV1 antagonist activity of the iodinated compounds described here. First, all the antagonists are very likely to behave as competitive antagonists against capsaicin, since such a behavior was demonstrated for 6′-iodononivamide (**4b**),[26] 6′-iodoarvanil (**12c**),[31] and 6′-iodoolvanil (**12b**).[31] Additionally, the antagonists appear to be also efficacious against endogenous agonists of TRPV1, such as anandamide and *N*-arachidonoyldopamine.[32] In fact, although we did not test 6′-nordihydrocapsaicin,[26] we did find that 6-iodoarvanil (**12c**) and 6′-iodoolvanil (**12b**) antagonize the effect of EC_{80} concentrations of these two "endovanilloids" (i.e., 1 μM and 300 nM, respectively, for intracellular Ca^{2+} elevation in HEK cells transfected with the human TRPV1) with IC_{50} values similar to, or slightly lower than, those reported in Table 1 against 100 nM capsaicin.[31] However, we have not studied the possibility that these iodinated antagonists are less efficacious at antagonizing TRPV1-mediated responses when TRPV1 is sensitized, for example, following activation of protein kinase C. Finally, it is also possible, although unlikely given the structural similarities among the compounds tested here, that the potency of the antagonists is influenced by their different cell membrane permeability and, hence, lipophilicity.[33] However, a 10 min incubation, which is what we used here with the antagonists prior to treatment of cells with capsaicin, has been shown to be sufficient for vanillylamides and anandamide to exert maximal agonist effect and, hence, to penetrate the cell membrane and bind to TRPV1 intracellular binding site.[33]

Conclusions

The TRPV1 antagonist activity of halovanillamides depends on (1) the site of halogenation, the effect being maximal at C-6′, and (2) the nature of the halogen substituent, with iodine being more efficient than bromine or chlorine in reverting the agonistic activity. In a series of iodinated vanillamides, the antagonistic potency did not correlate with the agonist potency of the parent compounds, while alkyl and acyl substituents at C-6′ of the vanillyl moiety were inferior surrogates of a iodine atom. The structure−activity relationships for the reversal of biological activity by iodination are different in capsaicinoids and resiniferonoids, supporting the view that these compounds, while sharing the same binding pocket of TRPV1, interact with distinct groups of its sensor region and exhibit distinct structure−activity properties.

Capsaicin is the archetypal obnoxious compound, as testified by its controversial use as an antiriot agent[29] and the pungency of chili pepper, its only natural source.[30] The discovery that the introduction of a iodine atom nullifies or reverses its aversive properties is noteworthy and should spur investigations aimed at translating these findings, and those reported for the iodination of RTX, in terms of binding modes to TRPV1.

Experimental Section

Materials. Column chromatography: Merck Silica Gel. IR: Shimadzu DR 8001 spectrophotometer. NMR: JEOL Eclipse (300 and 75 MHz for ^1H and ^{13}C, respectively). For ^1H NMR, $CDCl_3$ as solvent, $CHCl_3$ at $\delta = 7.26$ as reference. For ^{13}C NMR, $CDCl_3$ as solvent, $CDCl_3$ at $\delta = 77.0$ as reference. CH_2Cl_2 and toluene were dried by distillation from CaH_2, and THF by distillation from Na/benzophenone. Reactions were monitored by TLC on Merck 60 F_{254} (0.25 mm) plates, that were visualized by UV inspection and/or staining with 5% H_2SO_4 in ethanol and heating. Organic phases were dried with Na_2SO_4 before evaporation. Satisfactory elemental analyses were obtained for all the final compounds (±0.4% of the theoretical value).

Biological Evaluation. Human embryonic kidney (HEK) 293 cells overexpressing hTRPV1 were kindly donated by Dr. John Davis at GlaxoSmithKline. Cells were grown as monolayers in minimum essential medium supplemented with nonessential amino acids, 10% fetal calf serum, and 0.2 mM glutamine, and maintained under 95%/0/5% O_2/CO_2 at 37 °C. One day prior to experiments, cells were transferred into six-well dishes coated with poly-L-lysine (Sigma), and grown in

the culture medium described before. On the day of the experiment, the cells (50000−60000 per well) were loaded for 2 h at 25 °C with 4 μM Fluo-3-methylester (Molecular Probes) in DMSO containing 0.04% Pluoronic. After the loading, the cells were washed with Tyrode (pH = 7.4), trypsinized, resuspended in Tyrode, and transferred to the cuvette of the fluorescence detector (Perkin-Elmer LS50B) under continuous stirring. Experiments were carried out by measuring the fluorescence at 25 °C (λ_{EX} = 488 nm, λ_{EM} = 540 nm) before and after the addition of the test compounds at various concentrations. In antagonist experiments, varying doses of the compounds were added 10 min prior to capsaicin (100 nM). Data were expressed as the concentration exerting a half-maximal inhibition (IC_{50}) calculated by GraphPad.

Standard Synthetic Protocols. Acetylation of Phenol, Alcohols, and Amino Groups. To a solution of the phenol (alcohol, amine) in dry pyridine (ca. 3 mL/mmol) was added an excess Ac_2O (10 mol. equiv). After being stirred overnight, the excess Ac_2O was quenched with the addition of a few drops of methanol, and the reaction was worked up by dilution with 2 N H_2SO_4 and extraction with EtOAc. The organic phase was sequentially washed with sat. $NaHCO_3$ and brine, dried, and evaporated to afford a crude product, used as such for the next step unless specified otherwise.

MEM-Protection of the Phenolic 4-Hydroxyl of Vanillin and Derivatives. To a solution of the phenolic compound in toluene (ca. 3 mL/mmol) were added ethyldiisopropylamine (1.5 mol equiv) and MEM-chloride (1.5 mol equiv). After being stirred at room temp for 2−5 h, the reaction was worked up by dilution with EtOAc and washing with 2 N H_2SO_4. After being washed with brine, the organic phase was dried and evaporated. The residue was directly used for the next synthetic step unless specified otherwise.

Benzyl-Protection of the Phenolic 4-Hydroxyl of Vanillin and Derivatives. To a suspension of the phenolic compound in dry CH_2Cl_2 (ca. 2 mL/mmol) were added ethyldiisopropylamine (2 mol equiv) and benzyl bromide (2 mol. equiv), resulting in a clear solution. After being stirred 72 h at room temp, the reaction was worked up by addition of 2N H_2SO_4 and extraction with EtOAc. After being washed with brine, the organic phase was dried and evaporated. The residue was directly used for the next synthetic step unless specified otherwise.

6-Iodination of Vanillic Substrates. To a solution of the substrate in $CHCl_3$ (ca. 2 mL/mmol) was added silver trifluoroacetate (2 mol. equiv). To the stirred suspension, a solution of iodine (2 mol equiv) in $CHCl_3$ (ca. 0.5 mL/mmol iodine) was added dropwise. During the addition, a yellow precipitate of AgI was slowly formed, and the reaction was stirred at room temp for 3−8 h. In general, it was difficult to follow the course of the reaction by TLC, since the iodination product and the starting material had similar chromatographic behavior. The reaction was therefore monitored by ^{1}H NMR in this way: a few drops of the reaction mixture were filtered on a Pasteur pipet containing small bed of a of Celite, $Na_2S_2O_3$, and $NaHCO_3$ (1:1:1 in weight), evaporated, and dissolved in $CDCl_3$. When ^{1}H NMR analysis evidenced the disappearance of the starting material, the reaction was worked up by filtration on Celite. The filtrate was next washed sequentially with sat. $NaHCO_3$ and sat. $Na_2S_2O_3$, dried, and evaporated.

Conversion of 4-*O*-Protected Vanillols into *N*-Nonanoylvanillamides (Nonivamides). A solution of the 4-O-protected vanillol in toluene (ca. 4 mL/mmol of alcohol) was treated sequentially with diphenylphosphoryl azide (DPPA, 2 mol equiv) and 1,4-diazabicycloundecene (DBU, 2 mol equiv). After being stirred 2−4 h at room temp, the reaction was worked up by dilution with EtOAc and washing with sat. $NaHCO_3$. The organic phase was dried and evaporated. The residue was purified by filtration on silica gel using petroleum ether−EtOAc 8:2 to afford a crude azide (still containing variable amounts of unreacted DPPA). The azide was dissolved in THF (ca. 10 mL/mmol of starting alcohol) and treated with triphenylphosphine (TPP, 1.5 mol equiv) and water (4 mol equiv). After being stirred at 65 °C (oil bath) for 1−5 h, the reaction was cooled to room temp, and nonanoyl chloride (1.2 equiv) and triethylamine (1.2 equiv) were added. The reaction was next worked up by dilution with EtOAc and washing with 2 N H_2SO_4. The crude product, still containing triphenylphosphine oxide, was used as such for the deprotection step.

***N*-(4-Hydroxy-6-iodo-3-methoxybenzyl)nonanamide (6′-Iodononivamide, 6′-Iodonordihydrocapsaicin 4b).** Mp 106 °C, Anal. ($C_{17}H_{26}INO_3$) C, H, N.

***N*-(4-Hydroxy-5-iodo-3-methoxybenzyl)nonanamide (5′-Iodononivamide, 4c).** Mp 182−184 °C, Anal. ($C_{17}H_{26}INO_3$) C, H, N.

***N*-(4-hydroxy-2-iodo-3-methoxybenzyl)nonanamide (2′-Iodononivamide, 4d).** Mp 73 °C, Anal. ($C_{17}H_{26}INO_3$) C, H, N.

***N*-(6-Bromo-4-hydroxy-3-methoxybenzyl)nonanamide (6′-Bromononivamide, 4e).** Mp 88 °C, Anal. ($C_{17}H_{26}BrNO_3$) C, H, N.

***N*-(6-Chloro-4-hydroxy-3-methoxybenzyl)nonanamide (6′-Chlorononivamide, 4f).** Mp 93 °C, Anal. ($C_{17}H_{26}ClNO_3$) C, H, N.

***N*-(5-Bromo-4-hydroxy-3-methoxybenzyl)nonanamide (5′-Bromononivamide, 4 g).** Mp 83 °C, Anal. ($C_{17}H_{26}BrNO_3$) C, H, N.

***N*-(5-Chloro-4-hydroxy-3-methoxybenzyl)nonanamide (5′-Chlorononivamide, 4h).** Mp 81 °C, Anal. ($C_{17}H_{26}ClNO_3$) C, H, N.

***N*-(6-Phenyl-4-hydroxy-3-methoxybenzyl)nonanamide (6′-phenylnonivamide, 4i).** Mp 88 °C, Anal. ($C_{23}H_{31}NO_3$) C, H, N.

***N*-(6-Ethynyl-4-hydroxy-3-methoxybenzyl)nonanamide (6′-ethynylnonivamide, 4j).** Mp 104 °C, Anal. ($C_{19}H_{27}NO_3$) C, H, N.

***N*-(6-Ethenyl-4-hydroxy-3-methoxybenzyl)nonanamide (6′-ethenylnonivamide, 4k).** Mp 91 °C, Anal. ($C_{19}H_{29}NO_3$) C, H, N.

***N*-(6-Ethyl-4-hydroxy-3-methoxybenzyl)nonanamide (6′-ethylnonivamide, 4l).** Mp 86 °C, Anal. ($C_{19}H_{31}NO_3$) C, H, N.

***N*-(6-Acetyl-4-hydroxy-3-methoxybenzyl)nonanamide (6′-acetylnonivamide, 4m).** Foam, Anal. ($C_{19}H_{29}NO_4$) C, H, N.

***N*-[4-hydroxy-3-methoxy-6-(*E*-2-Methoxycarbonylethenyl)benzyl)nonanamide (6′-methylacry- loylnonivamide, 4n).** Mp 157 °C, Anal. ($C_{21}H_{31}NO_3$) C, H, N.

***N*-(4-Hydroxy-3-methoxy-2-nitrobenzyl)nonanamide (2′-nitrononivamide, 4o).** Foam, Anal. ($C_{17}H_{26}N_2O_5$) C, H, N.

***N*-(2-Acetamido-4-hydroxy-3-methoxybenzyl)nonanamide (2′-acetamidononivamide, 4p).** Foam; Anal. ($C_{17}H_{30}N_2O_4$) C, H, N.

3-Nonanoyl-3,4-dihydro-7-hydroxy-8-methoxyquinazolin-2(1*H*)-one (N,N′Carbonyl-2′-amino-nonivamide, 9). Foam, Anal. ($C_{18}H_{26}N_2O_4$) C, H, N.

5,5′-bis-*N*-(4-hydroxy-3-methoxybenzyl)nonanamide (5′,5″-Dinonivamide, 10). Mp 165 °C; Anal. ($C_{34}H_{52}N_2O_6$) C, H, N.

***N*-(4-Hydroxy-6-iodo-3-methoxybenzyl)oleamide (6′--Iodoolvanil, 12b).** Foam; Anal. ($C_{26}H_{42}INO_3$) C, H, N.

***N*-(4-Hydroxy-6-iodo-3-methoxybenzyl)arachidonamide (6′-Iodoarvanil, 12c).** Foam; Anal. ($C_{28}H_{40}INO_3$) C, H, N.

***N*-(4-Hydroxy-6-iodo-3-methoxybenzyl)retinamide (6′-Iodoretvanill, 12d).** Foam; Anal. ($C_{28}H_{36}INO_3$) C, H, N.

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Supporting Information Available: Experimental procedures and characterization data (mp, IR, MS, and ^{1}H and

^{13}C NMR) of all target compounds and key intermediates. This material is available free of charge at http://pubs.acs.org.

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