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Research Article

Novel Analgesics Targeting TRPV1 an Insight into the Mechanism

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Abstract

The strategies for the development of new analgesic drugs enable the semi-conduction of the propagation of action potential in nerves targeting neurotransmitters or synapsis. An alternative strategy could be the interaction and inactivation of the receptors for chronic pain and inflammation. Transient Receptor Potential Channels (TRPV) are a family of conserved integral membrane ion channels that mediate the transmembrane cationic flux down. The changes in the electrochemical gradient result in an increase in intracellular calcium and sodium ion concentration which plays an important role in depolarization cells propagation of neural action potential and muscle contraction. The role of nociceptive signals due to chemical stimuli needs to be made more effective. In search of a more effective molecule, we selected 20 capsaicin derivatives which included both known molecules and newly designed molecules. Molecules were selected considering their drug-likeness. The improved efficacy of a novel capsaicin derivative MS-3 ((IUPAC name: (6E) -N'-(4-hydroxy-3-methoxyphenyl) -8-methylnon-6- enehydrazide)) is reported in this work. MS-3 was compared against capsaicin and already marketed drugs zucapsaicin and nonivamide and improved binding was registered. In addition, evidence was obtained for drug-likeness and was better than others in most of the attributes of ADMET.

Transient receptor potential channels (TRP channels) are a family of evolutionary conserved integral membrane ion channels found in a variety of animal cells ranging from worms [1], fruit flies [2], and zebrafish [3] to mice and humans [4]. TRP channels were first discovered in the fly eye, where light-activated rhodopsin stimulates phospholipase C (PLC) to hydrolyse the minor plasma membrane lipid, phosphatidyl-inositol bisphosphate (PIP2) [5-10]. This, in turn, promotes the gating of TRP channels to depolarize the photoreceptor cell. TRP channels mediate the transmembrane flux of cations down their electrochemical gradients, thereby raising intracellular Ca^{2+} and Na^{+} concentrations and depolarizing the cell. Changes in transmembrane voltage (Vm) underlie neuronal action potential propagation and muscle contraction [5]. Voltage also plays a crucial role in non-excitable cells both by directing the driving force for calcium entry through plasma membrane channels and by controlling the gating of voltage-dependent Ca^{2+}, K^{+}, and Cl^{-} channels. Calcium entry through plasma membrane channels is recognized as a cellular signalling event per se: Effector proteins sensitive to elevated Ca^{2+} ion control a plethora of cellular events from transcriptional regulation to migration and proliferation [9].

Structurally TRPV1 is made up of four identical subunits and each subunit has an N-terminus and transmembrane region and a C-terminus region as shown in Figure 1 [10]. The N-terminus region consists of six ankyrin repeats forming six A helix connected by finger loops. The transmembrane region comprises 6 helical segments (S1–S6) where S1–S4 makes the voltage-sensing domain, and S5–S6 contributes to the pore formation. S1-S4 are connected to S5-S6 by a small linker segment and act as a foundation that allows the linker segment to move and contribute towards pore opening and activation of TRPV1. The transmembrane region also contains binding sites for capsaicin. The C-terminus consists of a TRP Domain (TRP-D) which interacts with pre-S1 suggesting some structural significance. Following this, are several Protein Kinase A (PKA) and Protein Kinase C (PKC)

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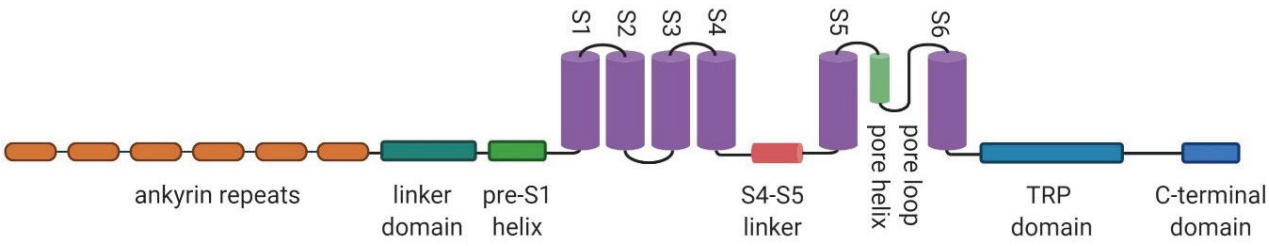

Figure 1: Linear diagram depicting major structural domains in a TRPV1 subunit.

phosphorylation sites, and sites for binding calmodulin and phosphatidylinositol-4,5-bisphosphate (PIP2).

Transient Receptor Potential Channel 1 (TRPV1) is one of the most extensively studied members of the TRP family. It is a non-specific cation channel expression in various tissues throughout the body, which include the soma of Dorsal Root Ganglia (DRG) and nodose ganglia in the peripheral nervous system, non-neuronal cells like mast cells, glial cells, keratinocytes as well as in various regions of the brain. These are transducers of heat (> 42 ºC) or chemical stimuli like vanilloid compounds (Ex. capsaicin) [8]. Once activated, TRPV1 allows the entry of monovalent and divalent cations like Na^{+}, Mg^{2+}, and Ca^{2+} [9]. Initial activation causes a burning sensation followed by a long-lasting refractory state when the neurons are desensitized during which the neurons are unresponsive to other stimuli [10]. Here we will be discussing a novel capsaicin derivative that can serve as a potential therapeutic agent for the management of chronic and neuropathic pain.

Methodology

Homology modelling of TRPV1

The amino acid sequence of human TRPV1 was retrieved from the UniProt database (UniProt ID: Q8NER1). The sequence length of a single chain was 839 amino acids. The 3D model was prepared by two rounds of homology modelling using a Swiss-Model server (www.swissmodel.expasy.org/) against rat TRPV1 protein (PDB ID: 3J5P.A) as a template.

The structure of Capsaicin (PubChem ID:1548943) Figure 2A, Zucapsaicin (PubChem ID: 1548942) Figure 2B, Nonivamide (PubChem ID: 2998) Figure 2C was retrieved from NCBI PubChem database in .sdf format. An online Simplified Molecular Input Line Entry System (SMILES) translator web server (www.cactus.nci.nih.gov/translate/) was used to convert this file to .pdb format as an input to AutoDock Vina.

The 3D model of the novel molecule named MS-3 (IUPAC name: (6E) -N'-(4-hydroxy-3-methoxyphenyl) -8-methylnon-6-enehydrazide) was designed using Marvin Sketch (v. 19.23.0) Figure 2D.

Validation of the crystal structure

The quality of the crystal structure was validated using several methods. 91.23% of the amino acids were found to

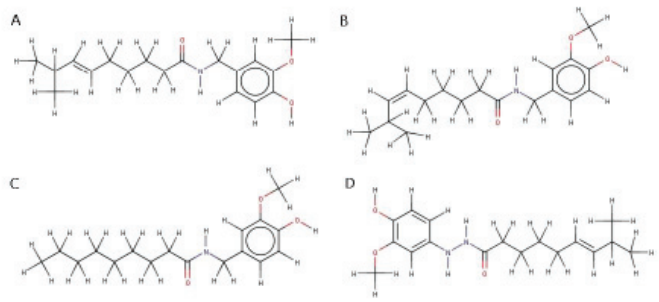

Figure 2: (A)Capsaicin (B)Zucapsaicin (C)Nonivamide (D)MS-3.

be Ramachandran favoured [11] and 2.06% were found to be Ramachandran outliers Figure 3A. The structure was also checked on the ERRAT server (www.servicesn.mbi.ucla.edu/ERRAT/) and the overall quality factor was recorded to be 93.761 Figure 3D. Additionally, the overall quality of the model was evaluated using the Protein Structure Analysis (ProSA) tool (www.prosa.services.came.sbg.ac.at/prosa.php) which provides a quality score, Z-score as compared to all known protein structures present in PDB database [12]. The obtained Z-score value was -8.06, which indicates a good quality of the model compared to known protein structures Figure 3B. The local quality of the model was also calculated and is presented in Figure 3C.

Molecular docking

A computational molecular docking approach was used to analyse structural complexes of the TRPV1 (receptor) with our four ligands viz. nonivamide, zucapsaicin, capsaicin, and MS-3 in order to understand the pattern of their interactions. Ligands were prepared using the Open Babel module in PyRx (v0.8). Molecular screening was carried out by PyRx, AutoDock Vina [13] option based on scoring functions. Docking was carried out at pH 7.4 and the rest of the parameters were kept by default. The best molecule was selected on the basis of binding energy.

Visualization

All the visualization of the structure files was done using the PyMol molecular graphics system (v2.3.3) and Schrödinger Maestro (v11.8).

In-silico ADMET study

PreADMET server (https://preadmet.bmdrc.kr/) [14] was

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used to predict various pharmacological parameters like Drug-likeness and ADMET properties. Ligands in SMILES format were entered in the online PreADME web tool. The server calculated drug-likeness based on rules like the CMC(Chemistry Manufacturing and Controls) -like rule, Lipinski's rule, MDDR (MACCS-II Drug Data Report) -like rule, and WDI (World Drug Index) -like rule (Table 1). Various ADMET properties such as human intestinal absorption, cellular permeability Caco-2 in vitro, cell permeability Maden Darby Canine Kidney (MDCK), skin permeability, plasma protein binding, and penetration of the blood-brain barrier (Table 2), carcinogenicity and mutagenicity were also calculated (Table 3).

Discussion

Noxious stimuli are transmitted by the peripheral nociceptors; these are known to transmit the signals of tissue damage to pain-processing centres in the brain. TRPV1 is involved in both afferent (sensation of pain) as well as efferent (release of neurotransmitters) functions which are experienced along with the burning sensation followed by vasodilation and sweating upon consumption of capsaicin. Thus, TRPV1 can mediate both pain and inflammation making it a very potent target for analgesics [15-17]. We have designed a molecule derived from the main chain of capsaicin and making changes to make it bind more efficiently to the TRPV1 receptor. In this

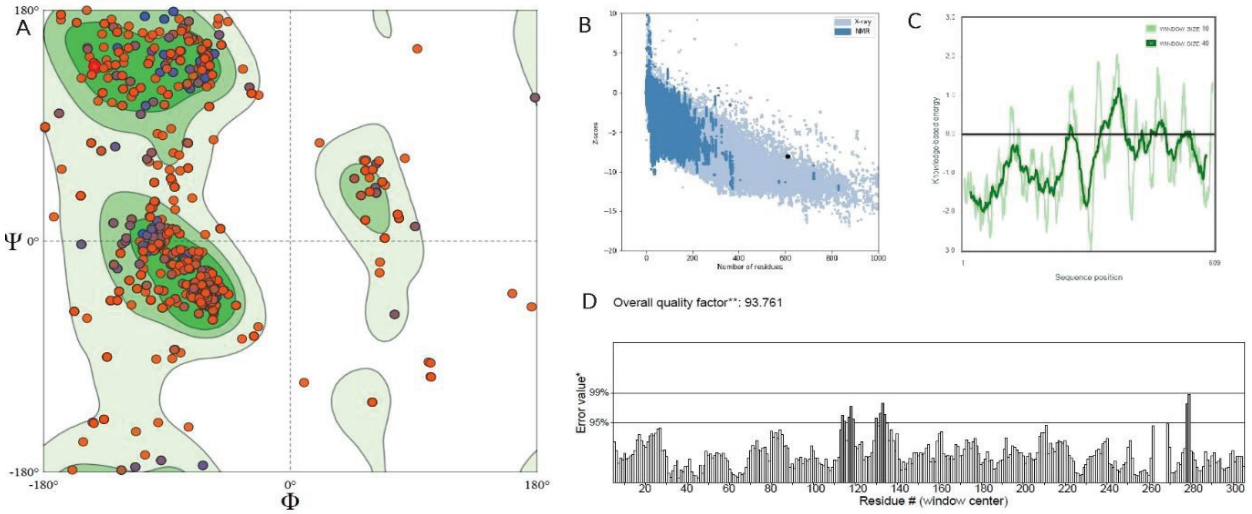

Figure 3: (A) Validation of modelled TRPV1 by Ramachandran plot. (B) ProSa Z-score plot of TRPV1 is indicated with a red arrow. (C) The local quality of the model is shown in a plot of energy as a function of amino acid sequence position. (D) ERRAT overall quality plot.

Table 1: Comparative drug like-ness of Zucapsaicin, Nonivamide, Capsaicin and MS-3.

Test	Description	Zucapsaicin	Nonivamide	Capsaicin	MS-3
CMC like Rule	CMC like rule: qualified / not qualified	Qualified	Qualified	Qualified	Qualified
CMC like Rule Violation Fields	CMC like Rule Violation Fields	NA	NA	NA	NA
CMC like Rule Violations	CMC like Rule Violations	0	0	0	0
Lead like Rule Violation Fields	Lead-like Rule Violation Fields	AlopP98_value	AlopP98_value	AlopP98_value	AlopP98_value
Lead like Rule	Lead like Rule	Violated	Violated	Violated	Violated
Lead like Rule Violations	Lead like Rule Violations	1	1	1	1
MDDR like Rule	MDDR-like rule: nondrug-like / drug-like / mid-structure	Mid-structure	Mid-structure	Mid-structure	Mid-structure
MDDR like Rule Violation Fields	MDDR like Rule Violation Fields	Number of Rings	Number of Rings	Number of Rings	Number of Rings
MDDR like Rule Violations	MDDR like Rule Violations	1	1	1	1
Rule of Five	Lipinski's Rule, so called (Rule of Five)	Suitable	Suitable	Suitable	Suitable
Rule of Five Violation Fields	The number of violation fields for Lipinski's Rule	NA	NA	NA	NA
Rule of Five Violations	Rule of Five Violations	0	0	0	0
WDI like Rule	WDI-like rule: in 90% cut-off / out of 90% cut-off	Out of 90% cut-off	Out of 90% cut-off	Out of 90% cut-off	Out of 90% cut-off
WDI like Rule Violation Fields	WDI like Rule Violation Fields	Kier flexibility, Kier_alpha_03	Kier flexibility, Kier_alpha_03	Kier flexibility, Kier_alpha_03	Kier flexibility, Kier_alpha_03
WDI like Rule Violations	WDI like Rule Violations	2	2	2	2

CMD: Chemistry Manufacturing and Control; MDDR: MACCS-II Drug Data Repository; WDI: World Drug Index

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Table 2: Comparison of ADME properties of Zucapsaicin, Nonivamide, Capsaicin and MS-3.

Test	Description	Zucapsaicin	Nonivamide	Capsaicin	MS-3
Blood brain barrier penetration	In vivo blood-brain barrier penetration (C.brain/C.blood)	4.09871	4.46694	4.09871	3.53777
Caco2	In vitro Caco2 cell permeability (Human colorectal carcinoma)	37.371	37.0748	37.371	23.8474
CYP_2C19_inhibition	In vitro Cytochrome P450 2C19 inhibition	Non	Non	Non	Non
CYP_2C9_inhibition	In vitro Cytochrome P450 2C9 inhibition	Non	Non	Non	Non
CYP_2D6_inhibition	In vitro Cytochrome P450 2D6 inhibition	Non	Non	Non	Non
CYP_2D6_substrate	In vitro Cytochrome P450 2D6 substrate	Non	Non	Non	Non
CYP_3A4_inhibition	In vitro Cytochrome P450 3A4 inhibition	Non	Non	Non	Non
CYP_3A4_substrate	In vitro Cytochrome P450 3A4 substrate	Non	Non	Non	Non
HIA	Human intestinal absorption (HIA, %)	92.484626	91.847202	92.484626	88.08207
MDCK	In vitro MDCK cell permeability (Mandin Darby Canine Kidney)	95.025	75.3309	95.025	122.165
Pgp inhibition	In vitro P-glycoprotein inhibition	Non	Non	Non	Non
Plasma Protein Binding	In vitro plasma protein binding (%)	92.856444	93.940697	92.856444	96.74374
Pure water solubility (mg/L)	Calculated water solubility in pure water by SK atomic types (mg/L)	15.5047	12.0822	15.5047	24.8883
Skin Permeability	In vitro skin permeability (logKp, cm/hour) (transdermal delivery)	-1.88998	-1.49333	-1.88998	-2.63456
SKlogD value	Calculated logD by SK atomic types in pH 7.4	4.1105	4.23011	4.1105	4.38878

Table 3: Comparison of toxicological properties of Zucapsaicin, Nonivamide, Capsaicin and MS-3.

Test	Description	Zucapsaicin	Nonivamide	Capsaicin	MS-3
Algae at	Acute algae toxicity	0.0120402	0.00968043	0.0120402	0.010969
Ames test	Ames test	mutagen	mutagen	mutagen	mutagen
Carcino Mouse	2 years carcinogenicity bioassay in mouse	negative	negative	negative	negative
Carcino Rat	2 years carcinogenicity bioassay in rat	negative	negative	negative	positive
Daphnia at	Acute Daphnia toxicity	0.0560175	0.0426779	0.0560175	0.056218
hERG inhibition	in vitro Human ether-a-go-go related gene channel inhibition	Medium risk	Low risk	Medium risk	Medium risk
Medaka at	Acute fish toxicity (medaka)	0.00499673	0.00285709	0.00499673	0.00512572
Minnow at	Acute fish toxicity (minnow)	0.00515298	0.00320217	0.00515298	0.00483084
TA100_10RLI	in vitro Ames test result in TA100 strain (Metabolic activation by rat liver homogenate)	negative	negative	negative	negative
TA100_NA	in vitro Ames test result in TA100 strain (No metabolic activation)	negative	negative	negative	negative
TA1535_10RLI	in vitro Ames test result in TA1535 strain (Metabolic activation by rat liver homogenate)	negative	negative	negative	negative
TA1535_NA	in vitro Ames test result in TA1535 strain (No metabolic activation)	negative	negative	negative	Negative

study, we compared our molecule with capsaicin and similar established drugs like nonivamide, and zucapsaicin for binding efficiency and ADMET properties (Table 2,3).

In our studies, our molecule MS-3 reported the highest binding energy of -8.1 followed by zucapsaicin which was -7.1 then capsaicin (-6.3) and nonivamide (-6.1) (Figure 4). The binding pockets of all four interactions were compared and were found to be similar. Capsaicin was found to form stable interactions with polar uncharged amino acids like serine and threonine however interactions with charged amino acids like aspartic acid and arginine were also reported. In the case of nonivamide and zucapsaicin, a H-bond was formed between the OH group of the amide bond of capsaicin and Thr 439 of TRPV1. In the case of capsaicin and MS-3, one H-bond was reported between the OH- group on ring and Ser 401. Another H- bond in capsaicin formed between the amide nitrogen and Asp 398. In MS-3 another H-bond formed between 11th nitrogen and Arg 380 (Figure 5).

Capsaicin is known to activate TRPV1 by binding to a pocket formed by the channel's transmembrane segments, where it takes a "tail-up, head-down" configuration as was found in our study Figure 5. Binding is found to be mediated by both H-bonds and van der Waals interactions. Upon binding, capsaicin interacts with the S4-S5 linker region and stabilizes the open state of the TRPV1 channel by the 'pull and contact' mechanism [18-21]. As for all molecules binding to the almost same pocket (Figure 6), they are supposed to activate TRPV1 with the same mechanism and bring about a similar physiological effect. With greater binding efficiency, MS-3 is expected to perform better than already existing drugs like zucapsaicin and nonivamide.

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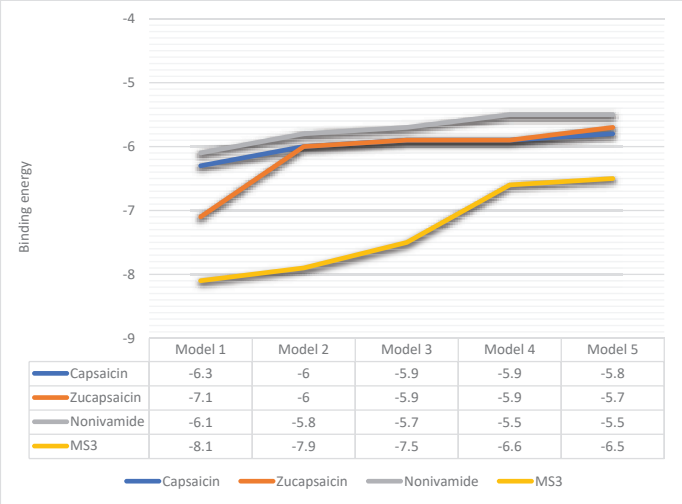
Further, we studied and compared these molecules for various pharmacological attributes. Starting with drug likeness similar results were seen for all four drugs. All of them qualified CMC-like rule and Lipinski's rule of five, but could not qualify for the MDDR rule as they have only one ring (Table 1). ADME of all four molecules showed almost similar results, MS-3 showed higher water solubility and plasma protein binding. It also reported lower permeability to colorectal cells but higher permeability to colorectal cells directing towards its easy excretion. Neither of them was found to substrate or inhibitor of cytochrome P450 and hence will probably be unaffected by first-pass metabolism (Table 2). We also checked for toxicity using on PreADME server and all four drugs showed similar results except for MS-3 found to be positive in two years carcinogenicity bioassay in rats (Table 3), but as is molecule is proposed as an analgesic such long-term continuous consumption is not expected. As the molecule is in the early stage of development further studies and optimization can lead us to a more potent non-opioid painkiller.



	Model 1	Model 2	Model 3	Model 4	Model 5
Capsaicin	-6.3	-6	-5.9	-5.9	-5.8
Zucapsaicin	-7.1	-6	-5.9	-5.9	-5.7
Nonivamide	-6.1	-5.8	-5.7	-5.5	-5.5
MS3	-8.1	-7.9	-7.5	-6.6	-6.5

Figure 4: Graph representing binding energy for predicted interaction models of ligands with TRPV1.

Conclusion

With these studies, we can conclude that MS-3 ((6E) -N'-(4-hydroxy-3-methoxyphenyl)-8-methylnon-6-enehydrazide) is 10% more potent than other similar drugs in the market. It targets TRPV1 (Arg 380 and Ser401) with high affinity. Based on our *in-silico* ADMET studies it was found to show no significant adverse effects. Further optimization of the molecule as a novel analgesic based on binding to the TRPV1 receptor (Arg 380, Ser401) by an alternative strategy of *in-silico* assessment followed by *in-vitro* and *in-vivo* studies can lead us to a novel highly effective analgesic drug.

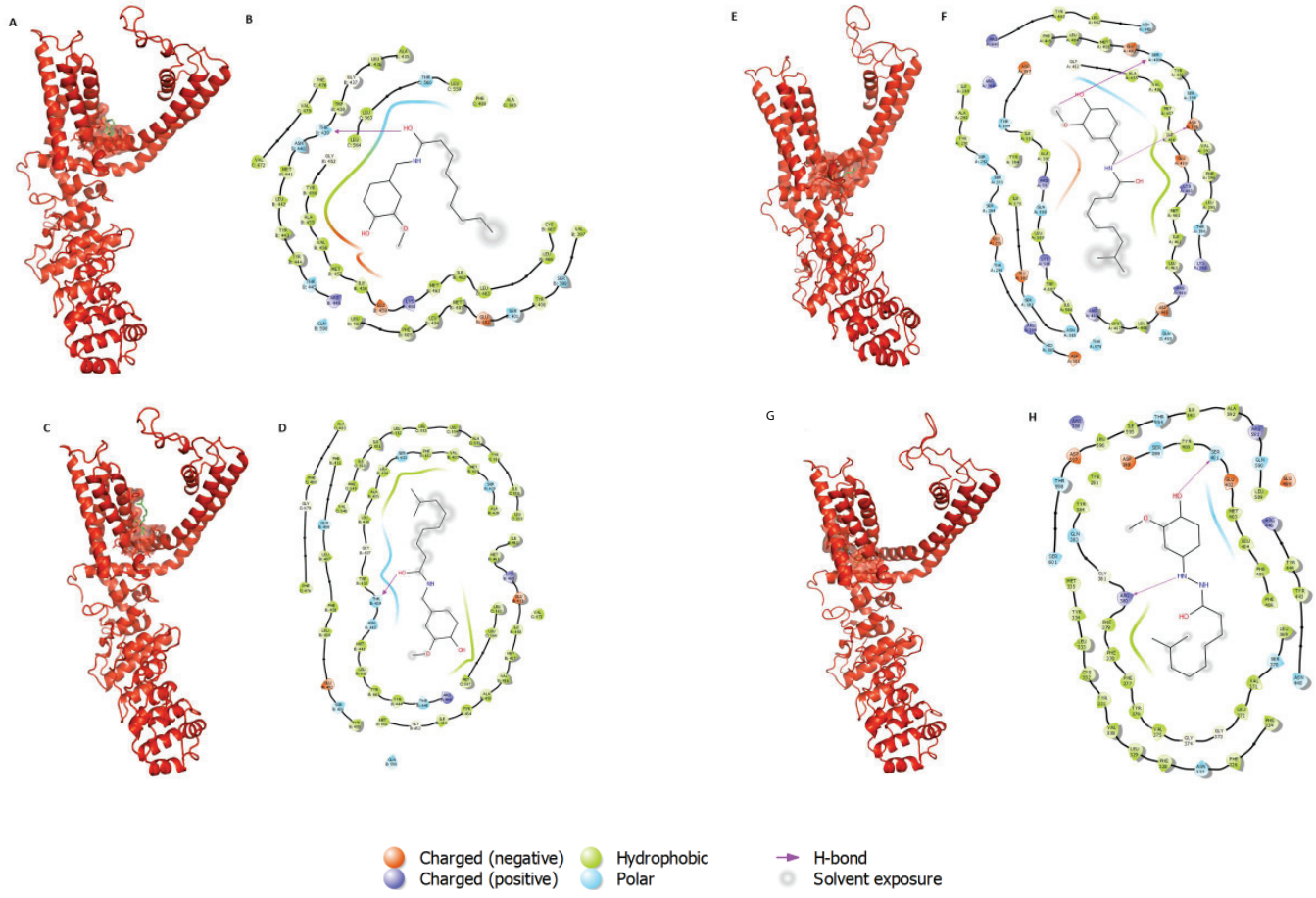


Figure 5: 2-D representation of binding sites (A,B) Nonivamide (C,D) Zucapsaicin (E,F) Capsaicin (G,H) MS-3.

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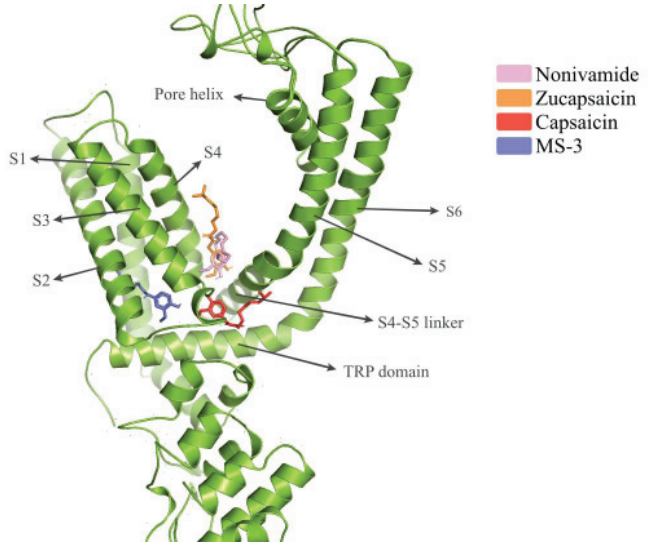

Figure 6: Ribbon diagram representing superimposed binding pockets.

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