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Molecular Docking Study of 2,3,4-trisubstituted-2,3,4,9-Tetrahydrothiopyrano[2,3-*b*]indole Derivatives with TRPV channels: Possible New Analgesics

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***Abstract*- In order to find the new possible analgesic drugs, the molecular docking analysis of several 2,3,4-trisubstituted-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole derivatives with TRPV channels is studied thoroughly in this article. The *in-silico* binding score of 2,3,4-trisubstituted-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole derivatives revealed that among all the derivatives one compound has the maximum binding energy of -7.0 kcal/mol target against protein TRPV1 (Transient receptor potential channels, of the vanilloid subtype 1). The initial finding suggests that this class of indole-based derivatives has significant and potential analgesic efficacy. The reason behind selecting this class of compounds is that the core tetrahydrothiopyrano[2,3-*b*]indoles shows considerable analgesic activities. In the context of this research, more investigation is still required into this mixture of derivatives for developing better analgesic medicines.**

***Keywords*- Indole, Heterocycle, Analgesic and Molecular Docking**

I. INTRODUCTION

Analgesics are painkilling drugs that work by blocking pain signals without causing the user to lose control. Pain relief medications affect both peripheral nerve methods in various ways. Pain relief medicines are available in a multitude of forms, including artificial pharmaceuticals.[1] Morphine, its equivalents, analgesics, and paracetamol are some of the most widely used and effective pain relievers.[2] Diagnosis and management of pharmaceutical pain control in older adults is typically inadequate, varying from neglect to utilize painkillers for patient in considerable pain to introducing older adults to possibly deadly toxicity, overdosing, or pharmaceutical combinations. Although there are models for effective and safe techniques to managing pain in elderly people, therapies must still be tailored to the needs of each person.[3] Pain killers[4][5][6] are reported to create gastrointestinal damage, especially in the stomach, which is manifested medically as peptic ulcers and inflammatory processes, and experimental studies suggest that NSAID use may raise the risk of anastomotic leak in patients undergoing colon cancer.[7][8] Diarrhea, dizziness, drowsiness, sleep disturbances, and respiratory arrest are among well-known morphine adverse effects.[9] Medicine could cause drug dependency, and if administered for a long period of time, the therapeutic range shrinks.[10] Because of all these serious adverse effects, it's critical to find ways to limit analgesic use, such as providing alternative painkillers with minimal side effects or creating medications that block the effects, such as periphery pain killers' receptors antagonists.[11][12][13][14][15] This was just studied with the conclusion that analgesic drug has a considerable relaxing influence prior to surgery.[16] Analgesic drug effect, on the other hand, remained disputed, since five research found opiate effects or decreased pain scores.[17]

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In the world of pharmacy, the indole core has been discovered to be a very active core since various natural compounds with indole as their fundamental ring have been discovered to be therapeutic drugs. Indole derivatives have been discovered to have antimicrobial,[18] antibiotic,[19] anti-inflammatory, [20] analgesics,[21] antiviral,[22] antimalarial, [23] chemotherapeutic,[24] anti-fungal,[25] and anti-TB (tuberculosis),[26] as well as antioxidant properties. [27] The compounds also show agonistic effects on a variety of receptors, including the Liver receptor and the 5-HT1D receptors [5-hydroxytryptamine (serotonin) receptor 1D]. Indoles can be found in a variety of bioactive alkaloids as well as agrochemicals and medicines. **Fig 1** shows some analgesic based pharmaceutical drug which are used generally in market such as Diclofenac, Ibufenac, Ketorolac, Flurbiprofen, Naproxen, Aspirin, etc.

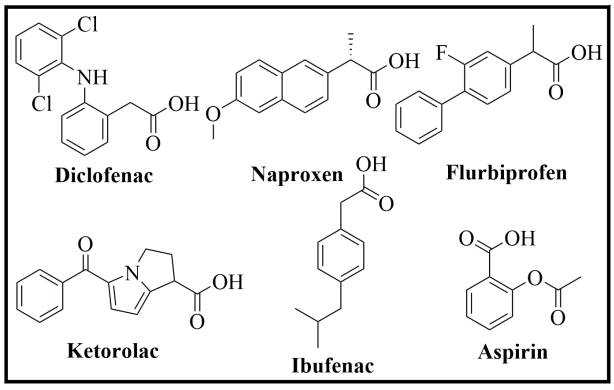


Fig 1. Some potent pharmaceutical drugs having analgesic properties.

Some common analgesic drug, for example Codeine, Fentanyl, Hydrocodone, Meperidine, Methadone, Naloxone, & naltrexone are also well-known drug **Fig 2**. [28][29][30]

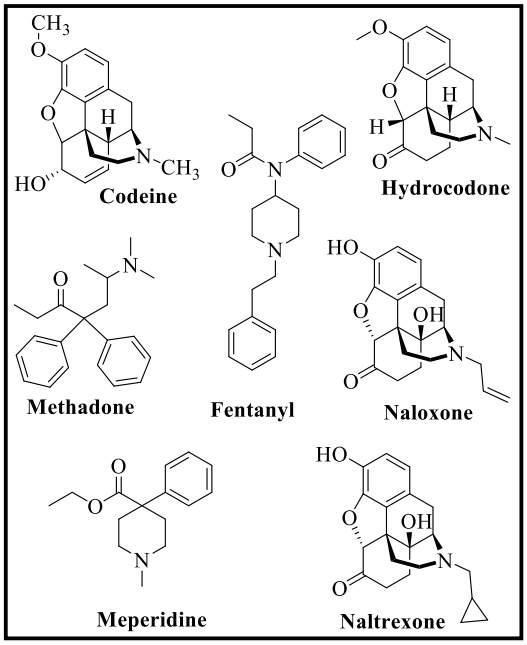
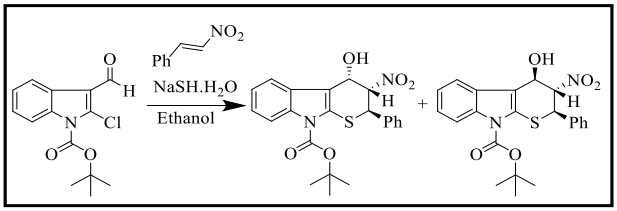


Fig 2. Useful potential analgesic drugs.

II. CHEMISTRY

Previously a simple, green and effective one-pot three-component method for the formation of trisubsituted-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole compounds in excellent yield were reported (**Scheme 1**).[31] The compounds were synthesized using *N*-protected-2-chloro-3-formylindoles, sodium hydrosulfide hydrate and trans β-nitrostyrenes at room temperature in ethanol with DABCO (1,4-diazabicyclo[2.2.2]octane) catalyst.



Scheme 1. Synthesis of tetrahydrothiopyrano[2,3-*b*]indole analogues.

Among different synthesized derivatives, we have chosen eight trisubstituted-2,3,4,9-tetrahydrothio-pyrano[2,3-*b*]indoles (**1**-**8**) for analgesic activities as shown in **Fig 3**.[32][33] We studied the interaction of protein with

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different analogues of trisubsituted-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole by the changing of different substituents.

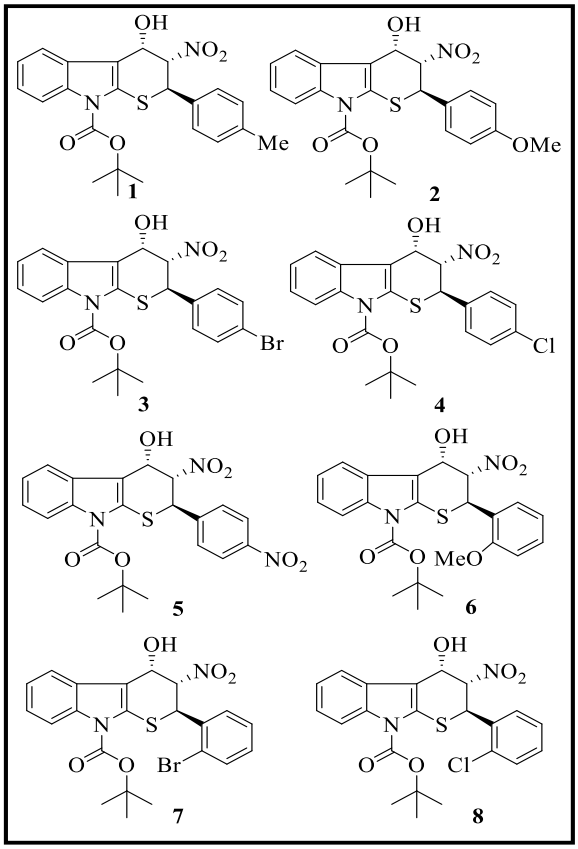

Fig 3. Analogues of trisubsituted-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indoles.

III. Molecular Docking Study

TRPV1 (Transient receptor potential channels, of the vanilloid subtype 1) is important in noxious stimuli because it is triggered by hot, low pH, and ligand like capsaicin, resulting in a searing pain feeling. [34][35] The structure of TRPV1's cytosolic ARD is characterized, and a multiligand-binding site important for receptor responsiveness modulation is found within the TRPV1-ARD. (Transient receptor potential channels, of the vanilloid subtype 1-Ankyrin repeat domain) A target protein for nucleotide nucleotides like ATP (Adenosine triphosphate) is shown in the protein structure.

The vanilloid family of TRP receptors (TRPV) in animals is implicated in perceptual and pain sensation as well as calcium homeostasis. TRPV1, a non-specific ion channels found in periphery nociceptive sensing neurons, is involved in the detection of painful temperature and the transfer of chronic pain receptors.[36] TRPV1 is triggered at the cellular scale by unpleasant heat, lower extracellular pH,[37] and a range of compounds, including vanilloids like capsaicin and resiniferatoxin.

TRP receptors (Transient receptor potential channel) may allow human cells to effectively detect in their immediate surroundings. Many TRP channels are signal integrators that are stimulated by a broad variety of stimuli. The TRP superfamily is divided into 7 subfamilies: TRPC, TRPV, TRPM, TRPN, as well as TRPA adhere to group 1, and TRPP as well as TRPML relate to group 2. TRP receptors are essential for human health because sickness is characterized by abnormalities in at least 4 TRP pathways. Express cloned has been used to identify the first mammal TRPV in a hunt for receptors stimulated by the inflammation vanilloid molecule capsaicin. TRPV1 is a sensory integrator which may transmit and receive signals elicited by a variety of pain. TRPV2, TRPV3, and TRPV4 are all capable of being stimulated by heat. Capsaicin and its variations in pH do not activate TRPV2, although unpleasant temperature does. TRPV1 as well as TRPV2 are defined in various diameters of sensory nerve ganglia neuron, providing signal accuracy in relation to different temperatures. At hot conditions, TRPV3 and TRPV4 are activated.

When activated by protons, TRPV1 experiences 2 kinds of de-sensitization: short-term de-sensitization and tachyphylaxis, or reduction of tolerance to successive sensory input.[38] TRPV1 de-sensitization can cause peripheral neurons to adapt to pain sensation in a biological manner.

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In Molecular Docking evaluation:

In general, Integration as well as retainment in the cell membrane controls various TRPV (Transient receptor potential), of the vanilloid subtype 1) channel activities. TRPV1 interactions with subunits of the SNARE (Soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor)-dependent exocytic process, which enhances TRPV1 transportation to the cell membrane.[39] Inner vesicles route implantation into the cell membrane, generated by the treatment of insulin-like protein called in cell cultures, may also modulate TRPV2 activation.[40] TRPV4 receptor expression is induced by glycosyl in the pores looping [41] and interactions with protein known as PACSINs (Protein kinase C and casein kinase substrate in neurons protein 1).[42] Insertion of TRPV5 and TRPV6 into the plasma membrane regulates their activity as well.[43] Retention of TRPV5 in the plasma membrane is promoted by the β-glucuronidase Klotho through hydrolysis of extracellular sugar residues on the channel.[44]

Because of its excellent selectivity, TRPV1 can be a successful analgesic drug. TRPV1>TRPV4> TRPV5>TRPV3. It is the order of analgesic activity against the pain or inflammation.[45] Therefore, compound interacts with protein TRPV1 (PDB ID: 2NYJ), it is analgesic peptides derived from Ankyrin Repeats domains as found by Auto Dock 4.[46] The synthesized compound (**1-8**) was found the binding energy (**-6.4 to -7.0**) in (**Table-1**) with the best result found at one compounds **1** (**-7.0 kcal/mol**). The hydrogen bond, residual interaction, hydrogen bond, pi-pi interaction of all these eight compounds were summarized in (**Table-1**).

Compound **1** shows a hydrogen bond, residual interaction, hydrophobic interaction, pi-pi interaction which were summarized in **Fig. 4**. The compounds show amino acid residues ASN-301, PHE-304, VAL-294, THR-258. It shows additional hydrogen bonding GLU-210, LEU-158, ARG-211, PHE-304, VAL-294 and salt bridges shows LYS-160, and hydrophobic interaction shows PHE-304, VAL-294. PHE-304 residue shows pi-interaction. The *in-silico* interaction results match the docking analysis of the synthesized compounds showed against the structure of TPRV1, a novel analgesic peptide derived from Ankyrin Repeats domains in which compound **1** shows high affinity value **-7.0 kcal/mol**.

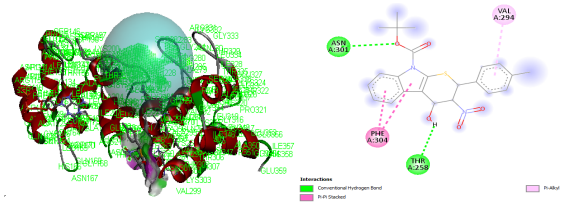

Fig 4. The binding interaction of 4-Methyl-hydrothiopyrano[2,3-*b*]indole against TRPV1 (PDB ID: 2NYJ).

Compound **2** shows a hydrogen bond, residual interaction, hydrophobic interaction, pi-cation, alkyl, pi-sigma, carbon hydrogen bond, Pi-Pi T shaped, as well as conventional hydrogen bond, unfavorable donor-donor which were summarized in **Fig. 5**. The compounds show amino acid residues ASN-301, PHE-304, VAL-294, ASN-259.

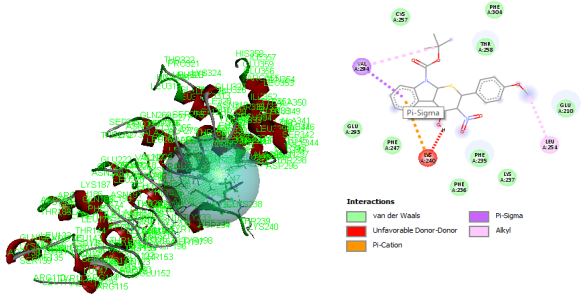

Fig 5. The binding interaction of 4-methoxy-hydrothiopyrano[2,3-*b*]indole against TRPV1 (PDB ID: 2NYJ).

It shows additional hydrogen bonding LEU-

158, THR-218, ILE-312, PHE-304, VAL-294, in hydrophobic interaction they have some residues are PHE-304, VAL-294 and salt bridges show LYS-160. ASN-259 shows carbon hydrogen bond. The conventional hydrogen bond is shown by two residues, ASN-259 and VAL-294. Residue ASN-259 shows carbon hydrogen bond. Residue PHE-304 shows a Pi-Pi T shaped. The *in-silico* interaction results match the docking analysis of the synthesized compounds showed against the structure of TPRV1, a novel analgesic peptide derived from Ankyrin Repeats domains in which compound **2** shows low affinity as comparison to other compounds value **-6.4 kcal/mol**.

Compound **3** shows a hydrogen bond, residual interaction, hydrophobic interaction, pi-alkyl, pi-sigma, carbon hydrogen bond, Pi-Pi T shaped which were summarized in **Fig. 6**. The compounds show amino acid residues ASP-296, PHE-304, ASN-301, VAL-294.

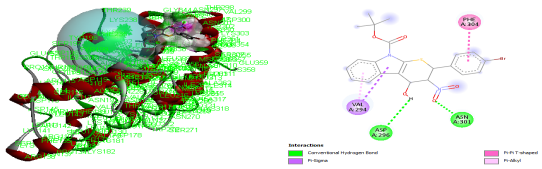

Fig 6. The binding interaction of 4-Bromo-hydrothiopyrano[2,3-*b*]indole against TRPV1 (PDB ID: 2NYJ).

It shows additional hydrogen bonding ASN-164, TYR-194, GLU-210, ASN-301, ASP-296, in the hydrophobic interaction show a residue that is VAL-294, PHE-304 and salt bridges shows LYS-160, ASP-296. The PHE-304 residue shows Pi-Pi T shaped and VAL-294 residue shows pi-sigma bond. The conventional hydrogen bonding is shown by these two residues are ASN-301 and ASP-296. The *in-silico* interaction results match the docking analysis of the synthesized compounds showed against the structure of TPRV1, a novel analgesic peptide derived from Ankyrin Repeats domains in which compound **3** shows affinity value **-6.5 kcal/mol**.

Compound **4** shows a hydrogen bond, residual interaction, hydrophobic interaction, pi-alkyl, pi-sigma summarized in **Fig. 7**. The compound 4 shows only one amino acid residue LEU-254. LEU-254 shows pi-sigma interaction.

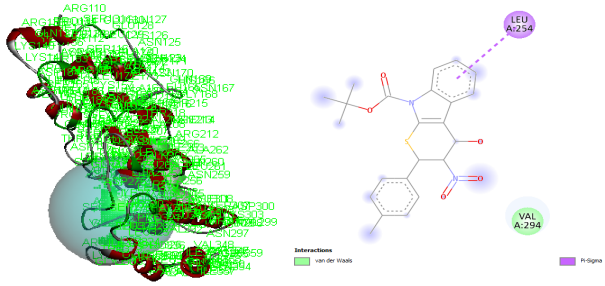

Fig 7. The binding interaction of 4-Chloro-hydrothiopyrano[2,3-*b*]indole against TRPV1 (PDB ID: 2NYJ).

In addition to this, LEU-291 shows hydrophobic interaction, and for hydrogen bonding residues are LEU-158, GLY-248, VAL 294. The *in-silico* interaction results match the docking analysis of the synthesized compounds showed against the structure of TPRV1, a novel analgesic peptide derived from Ankyrin Repeats domains in which compound **4** shows affinity value **-6.6 kcal/mol**.

Compound **5** shows a hydrogen bond, residual interaction, hydrophobic interaction, pi-cation, alkyl, pi-sigma, carbon hydrogen bond which were summarized in **Fig. 8**. The compounds show amino acid residues VAL-294, LYS-240, PHE-236, GLU-210, LYS-238.

In additional, hydrogen bonding ASN-164, VAL-217, GLU-210, LYS-240, PHE-236, in hydrophobic interaction it shows PHE-304, LYS-240, LYS-238 residue shows a salt bridge

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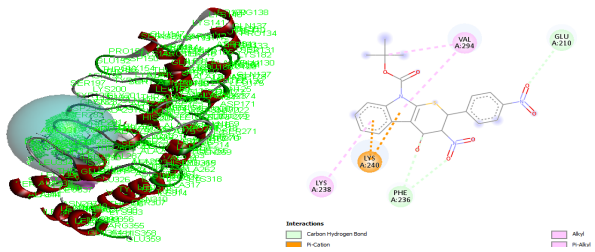

Fig 8. The binding interaction of 4-Nitro-hydrothiopyrano[2,3-*b*]indole against TRPV1 (PDB ID: 2NYJ).

PHE-236 and GLU-210 both shows carbon hydrogen bond. VAL-217 and LYS-238 shows pi- alkyl interaction. And residue LYS-240 shows pi-cation. The *in-silico* interaction results match the docking analysis of the synthesized compounds showed against the structure of TPRV1, a novel analgesic peptide derived from Ankyrin Repeats domains in which compound 5 shows affinity value **-6.7 kcal/mol**.

Compound **6** shows a hydrogen bond, residual interaction, hydrophobic interaction, pi-cation, alkyl, pi-sigma or pi-cation, carbon hydrogen bond which were summarized in **Fig. 9**. The compounds show amino acid residues VAL-294, LYS-240, PHE-236, PHE-247.

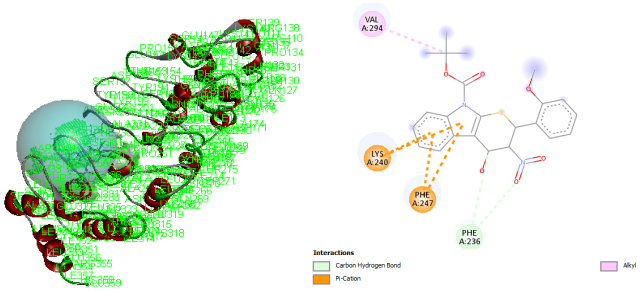

Fig 9. The binding interaction of 2-methoxy-hydrothiopyrano[2,3-*b*]indole against TRPV1 (PDB ID: 2NYJ).

LYS-240, PHE-247 residues show pi-cation interaction, the carbon hydrogen bond is showed by the PHE-236 residue as well as alkyl is showing a VAL-294 residue. In additional hydrogen bonding shows by these two residues PHE-236, PHE-247, GLU-210, and a salt bridge is show by residue LYS-240. Residue GLU-210 also shows a hydrophobic interaction. The *in-silico* interaction results match the docking analysis of the synthesized compounds showed against the structure of TPRV1, a novel analgesic peptide derived from Ankyrin Repeats domains in which compound **6** shows an affinity value **-6.5 kcal/mol**.

Compound **7** shows a hydrogen bond, residual interaction, hydrophobic interaction, pi-cation, alkyl, pi-sigma or pi-cation, carbon hydrogen bond which were summarized in **Fig. 10**. The compounds show amino acid residues VAL-294, LYS-240, PHE-236, PHE-247.

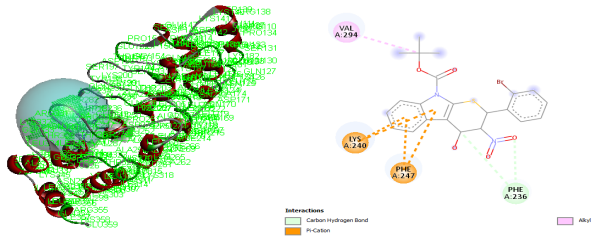

Fig 10. The binding interaction of 2-Bromo-hydrothiopyrano[2,3-*b*]indole against TRPV1 (PDB ID: 2NYJ).

The LYS-240, PHE-247 residues show pi-cation interaction, the carbon hydrogen bond is showed by the PHE-236 residue as well as alkyl is showing a VAL-294 residue. In additional, hydrogen bonding shows by these GLU-210, TYR-199, PHE-236, ASN-301 and LYS-240 shows salt bridge. And the hydrophobic interaction by GLU-210 and VAL-294 residues. The *in-silico* interaction results match the docking analysis of the synthesized compounds showed against the structure of TPRV1, a novel analgesic peptide

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derived from Ankyrin Repeats domains in which compound **7** shows an affinity value **-6.7 kcal/mol**.

Table 1. Value of Molecular docking of the compounds against TRPV1 (PDB ID: 2NYJ)

Compound	Affinity (kcal/mol)	distance from best mode r.m.s.d l. b.	distance from best mode r.m.s.d u. b.	Receptor interaction	Distance	Hydrophobic interaction	Hydrogen bonds	Pi-cation	Salt bridges
1	-7	4.53	8.797	THR-258, PHE-304, ASN-301, VAL-294	1.88-5.12	ASN-259,VAL-294	VAL-294, PHE-304	PHE-304	
2	-6.4	3.553	6.399	PHE-304, ASN-301, VAL-294, ASP-297	2.80-5.22	PHE-236, VAL-294	VAL-294, PHE-304	PHE-304	LYS-160
3	-6.5	3.671	6.335	PHE-304, ASN-301, VAL-294, ASP-297	3.07-4.03	VAL-294, PHE-304	ASN-301, ASP-296	ASN-301, ASP-296	LYS-160
4	-6.6	3.626	6.318	LEU-254	1.88-4.90			LEU-294	
5	-6.7	5.175	7.804	VAL-294, LYS-240, PHE-236, GLU-210, LYS-238	1.88-5.72	VAL-294, PHE-304	GLU-210, LYS-240, PHE-236	PHE-304, LYS-240	LYS-238
6	-6.5	2.612	4.654	VAL-294, LYS-240, PHE-236, PHE-247	2.69-4.31	VAL-294	PHE-236, PHE-247	PHE-247	LYS-240
7	-6.7	2.418	3.689	VAL-294, LYS-240, PHE-236, PHE-247	3.07-4.03	VAL-295	PHE-236	LYS-240	LYS-240
8	-6.7	3.054	4.804	VAL-294, LYS-240, PHE-236, PHE-247	2.90-4.31	VAL-295	PHE-236	LYS-240	LYS-240

Compound **8** shows a hydrogen bond, residual interaction, hydrophobic interaction, pi-cation, alkyl, pi-sigma or pi-cation, carbon hydrogen bond which were summarized in **Fig. 11**. The compounds show amino acid residues VAL-294, LYS-240, PHE-236, PHE-247.

Both the residue LYS-240, PHE-247 shows pi-cation interaction, the carbon hydrogen bond is showed by the PHE-236 residue as well as alkyl is showing a VAL-294 residue.

In additional, hydrogen bonding shows by these GLU-210, TYR-199, PHE-236, ASN-301 and LYS-240 shows salt bridge. And the hydrophointeraction by GLU-210 and VAL-294 residues. The *in-silico* interaction results match the docking analysis of the synthesized compounds showed against the structure of TPRV1, a novel analgesic peptide derived from Ankyrin Repeats domains in which compound **8** shows an affinity value **-6.7 kcal/mol**.

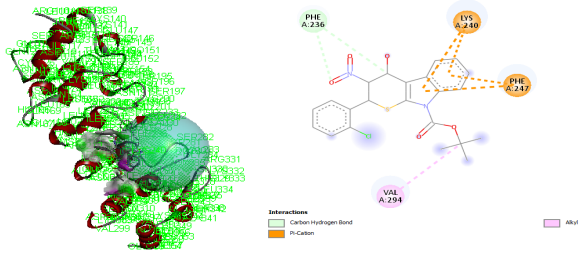

Fig 11. The binding interaction of 2-Chloro-hydrothiopyrano[2,3-*b*]indole against TRPV1 (PDB ID: 2NYJ).

IV. CONCLUSION

The tetrahydrothiopyrano[2,3-*b*]indole analogues interact with protein TRPV1 (Transient receptor potential channels, of the vanilloid subtype 1) (PDB ID: 2NYJ), an analgesic peptides derived from Ankyrin Repeats domains. The docking compound were synthesized *via* an organocatalyzed one-pot three-component process that yields a broad range of trisubstituted-2,3,4,9-tetrahydrothio-pyrano[2,3-*b*]indoles. The *in-silico* molecular docking studies revealed that the tetrahydrothiopyrano[2,3-*b*]indole analogues shows *in vivo* analgesic activity. The *in-silico* binding score revealed that compound **1** had the maximum binding energy of **-7.0 kcal/mol** target against protein TRPV1, suggesting that it has significant analgesic efficacy. In context of this research, more investigation must need into this mixture of drugs for better analgesic medicines.

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