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Research Article

Development of novel substituted indole molecules as potential NAV1.7 inhibitors

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ABSTRACT

Pain is often defined as a single form of the nervous system for abnormal things in the human body. Neuropathic pain is a type of pain that is a consequence of nerve damage and usually, it is a chronic type. Sodium Channel 1.7 (Nav 1.7) is an upcoming target for neuropathic pain management. Several heterocyclic compounds are reported for potentials against neuropathic pain. 24 different heterocyclic derivatives from substituted indole class were synthesized and virtually analyzed against Nav 1.7 for inhibition potential. The developed substituted indole was confirmed via spectral analysis and showed excellent binding ability with Nav 1.7, which can be further explored for biological activity for the development of potential Nav 1.7 inhibitors with excellent activity against Neuropathic pain.

Keywords: Pain, Neuropathic pain, Indole, Docking.

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INTRODUCTION

Heterocyclic compounds are compounds with one or more heteroatoms in their structure. Heterocyclic compounds are known for their biological potentials. Heterocyclic systems like Indole are known for their biological activities. Numerous activities like anticancer, neuroprotective agent, antioxidant, anti-rheumatoid, aldose reeducates inhibitor, and anti-HIV agents are shown by substituted indole compounds. Neuropathic pain is one of the types of pain which involves nerve damages or injury to the nerve ending. This type of pain is often chronic one which can be caused by alcoholism, diabetes, AIDS, and chronic nerve disorders[1-6]. Neuropathic pain is often treated with antiseizure drugs like Gabapentin, Pregabalin, Topiramate, Carbamazepine, and certain antidepressant agents like Amitriptyline, Nortriptyline, and Venlafaxine. The development of selective and specific molecules targeting neuropathic pain needs time. Sodium Channel 1.7 (Nav 1.7) is one of the upcoming targets for the development of molecules against neuropathic pain. Nav1.7 is a channel that is encoded by the SCN9A gene normally it is found to be present in the high levels in nociceptive (pain) neurons in the dorsal root ganglion and trigeminal ganglion and sympathetic ganglion neurons which is a component of the ANS. Sodium channel NaV1.7 plays an important role in the maintenance of the threshold for the action potential in the primary sensory neurons, due to this reason Nav 1.7 is the main research area for many researchers[7-9] . For treatment of Neuropathic pain (NP), it is a need develop new non-steroidal anti-inflammatory drugs with antioxidative properties. In this process Sodium ion channel blocker is the one of the specific action ways of the drug to act in treatment of NP. Lacosamide is one of the drugs which is shows the similar action in treatment of NP. In similar way Potassium channel opener is another way in treatment of NP. Sodium channel blockage or potassium channel opening is the promising way for drug which act against neuropathic pain. Pregabalin and gabapentin is the effective drug which exert their biological action by which is act by inhibiting α2δ accessory subunit of voltage gated Ca channel as a result block the calcium channel and shows effective biological action. Phenytoin was first introduced in 1938 as an anti-epileptic. Recently we surprisingly found that there is no difference in the amount of evidence to support carbamazepine and phenytoin in the treatment of neuralgia [10-14]. Already as early as 1942, three patients were reported suffering from trigeminal neuralgia; 200-300 mg phenytoin daily was effective in a reducing pain. This drug is effective by showing Na channel blocking agent.

Molecular docking is one of the key techniques utilized for molecular scrutiny before the synthesis. Docking analysis is also called the molecular interaction analysis in which the interaction between the macromolecule and macromolecule is analyzed. The docking analysis can give an insight into the molecular behavior in the biological system and which will be helpful to analyze the

toxicity, metabolism, and off-target effects associated with the designed set of molecules. In this research paper, we are reporting the synthesis of the 10 different heterocyclic molecules and their *in-silico* analysis for potential activity against the Sodium channel NaV1.7.

A various kind of Heterocyclic compounds are reach sources of scaffold for dealing with various chronic diseases. In this Indole class of heterocyclic compounds has important therapeutical agents in pharmaceutical chemistry. These indole class of drug shows potent biological activity against anticancer, antioxidant, anti-HIV agent, analgesic and neurological diseases such as Alzheimer, epilepsy and Parkinson diseases. Indole compound also very efficient in antioxidant activity, protect protein and lipid form peroxidation it impacts in antioxidant efficacy in biological activity.

MATERIAL AND METHOD

Material

The chemical structure of the synthesized compounds was established on the basis of physical, chemical and analytical data, melting point of synthesized compound is determined in one capillary tube and is uncorrected.

Synthesis:

Figure 1. Scheme for synthesis of Indole Derivatives

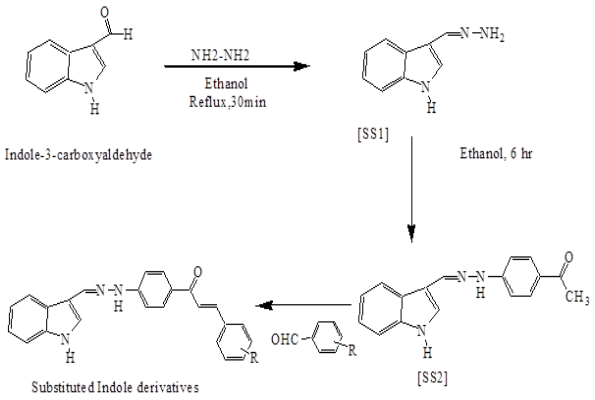


Table 1: Substituent's and physicochemical data of synthesized derivatives

Compound Code	R-Group	Molecular formula	Melting point in ºC	Rf value
SS3	4-NO_2	$C_{24}H_{18}N_4O_3$	148	0.65
SS4	4-OCH_3	$C_{25}H_{21}N_3O_2$	235	0.52
SS5	3-Cl	$C_{24}H_{18}ClN_3O$	116	0.56
SS6	H	$C_{24}H_{19}N_3O$	142	0.62
SS7	2-OH	$C_{24}H_{19}N_3O_2$	165	0.50
SS8	3-OH	$C_{24}H_{19}N_3O_2$	249	0.47
SS9	4-OH	$C_{24}H_{19}N_3O_2$	204	0.53
SS10	2-Cl	$C_{24}H_{18}ClN_3O$	106	0.58
SS11	4-Cl	$C_{24}H_{18}ClN_3O$	114	0.65
SS12	2-CH_3	$C_{25}H_{21}N_3O$	182	0.65
SS13	3- CH_3	$C_{25}H_{21}N_3O$	189	0.49
SS14	4-CH_3	$C_{25}H_{21}N_3O$	172	0.59
SS15	2-Br	$C_{24}H_{18}BrN_3O$	162	0.57
SS16	3-Br	$C_{24}H_{18}BrN_3O$	169	0.69
SS17	4-Br	$C_{24}H_{18}BrN_3O$	163	0.55
SS18	2-NH_2	$C_{24}H_{20}N_4O$	108	0.43
SS19	3-NH_2	$C_{24}H_{20}N_4O$	133	0.57
SS20	4-NH_2	$C_{24}H_{20}N_4O$	148	0.65
SS21	3-COOH	$C_{25}H_{19}N_3O_3$	182	0.61
SS22	4-COOH	$C_{25}H_{19}N_3O_3$	203	0.67
SS23	2-OH,3-Cl	$C_{24}H_{18}ClN_3O_2$	226	0.69
SS24	2-OH,4-Cl	$C_{24}H_{18}ClN_3O_2$	199	0.72
SS25	2-OH, 3,5-Br	$C_{24}H_{17}Br_2N_3O_2$	232	0.85
SS26	2-OH, 3,5-I	$C_{24}H_{17}I_2N_3O_2$	205	0.73

They expressed in degree centigrade.The compound synthesized was characterized by Infrared spectroscopy, Nuclear magnatic spectroscopy and Mass spectral data. This spectral data collected from Vishnu chemicals, Hyderabad. Chemicals required for synthesis such as indole-3-carboxyaldehyde, hydrazine sulphate,4-chloro acetophenone, ammonium hydroxide and substituted benzaldehydepurchesed from Himedia, Mumbai**.**

Synthesis of 3-(Hydrazonomethyl)-1H-indole (SS1) (I)

Equimolar concentration of Indole-3-carboxaldehyde (0.01M) and hydrazine sulphate (0.01M) were refluxed in 25 ml ethanol for 6 hours in water bath. After completion of reaction the mixture poured in crushed ice and recrystallize by using ethanol. Melting point -164ºC, R^f Value-0.58

Synthesis of 1-(4-2-(1H-indol-3yl) methylene) hydrazinyl) phenyl) ethenone (SS2) (II)

A mixture of 0.01M 3-(Hydrazonomethyl)-1H-indole (I) and p-chloroacetophenone and 3-5 drops of glacial acetic acid was refluxed with ethanol for 27 hrs. After completion of the reaction mixture was cooled and poured in crushed ice. The solid formed was filtered off and washed with 10% ammonium hydroxide recrystallized from ethanol. Melting point:-142ºc, R^f Value- 0.74

Synthesis of 1-(4-2-(1H-indol-3yl) methylene)hydrazinyl)phenyl)-3phenylprop-2-en-1-one

A mixture of 1-(4-2-(1H-indol-3yl) methylene) hydrazinyl) phenyl) -3phenylprop-2-en -1-one (II), the appropriate aromatic aldehyde (0.01M), 20% sodium hydroxide and rectified spirit taken in round bottom flask and stir the mixture for 3-4 hrs . Maintaining the temperature 25-30ºc.and then kept overnight in refrigerator, obtain product filter and wash with cold water and cold alcohol. Recrystallize the crude product in Ethanol.

Molecular Docking

Molecular docking was performed to assess the binding ability of the designed derivatives with Sodium Channel NAV 1.7. Structure of the Sodium Channel NAV 1.7(5EK0).was downloaded from the free protein databank www.rcsb.org and utilized for docking analysis. Grip-based docking analysis was performed [10-12].

RESULTAND DISCUSSION

Synthesis

All the targeted derivatives are synthesized in a very good yield and their physicochemical constants were recorded for the initial confirmation of the synthesis as shown in table no 1. Synthesized derivatives were further confirmed via various spectral techniques like Infrared spectroscopy, nuclear magnetic spectroscopy, and Mass to confirm the synthesized compounds. The results of the spectral analysis are given below.

Compound [SS1]: IR (KBr) cm^{-1} 3200.07(NH stretching of NH_2), 3113.59(NH stretching), 1631.97 (C=N stretching); ^1H NMR : ([D,]DMSO): δ 7.19(d,2H -NH_2), 7.23-7.21-7.23 (d, 2H, Ar-H),

8.10-8.28(d, 2H, Ar-H), 8.08 (s, 1H,-CH), 8.92 (s, 1H,-CH), 9.93(s, 1H,NH), ^{13}C NMR([D,]DMSO): δ = 112-137 (Ar-C),138-154(=CH), EIMS (M/z + 1): Molecular weight correspond to 160 (M+1) peak.

Compound [SS2] IR (KBr) cm^{-i}- 3230.20(NH stretching), 2917.63 (Aromatic C-H stretching),1630.14(C=O Stretching) 1612.48(aromatic C=N stretching); ^{1}H NMR **:**([D,]DMSO): δ 2.80 (s, 1H,-CH3), 7.19-7.23 (q, Ar-H), 7.24-7.26(d, Ar-H), 8.10 (s, 1H,-CH), 8.28 (s, 1H,-CH), 9.00(s, 1H,NH),9.93(s, 1H,NHIndole); ^{13}C NMR([D,]DMSO): δ27.13(-CH_3), 112.39-138.38 (Ar-C),155.04(=CH) 184.92 (C=O); EIMS (M/z) : Molecular weight correspond to 278.4 (M+1) peak.

Compound [SS3] IR (KBr) cm^{-} - 3225.42(NH stretching), 1620.38(C=O Stretching) 1586.94(aromatic C=C stretching);1517.13(aromatic C=N stretching),1243.60 (C=C in CH=CH); ^{1}H NMR: ([D,]DMSO): 7.21-7.27 (q, Ar-H), 7.30-7.58(q, Ar-H), 7.60-7.82(q, Ar-H), 8.10 (s, 1H,-CH), 8.52 (s, 1H,-CH), 8.90(s, 1H,NH),9.93(s, 1H,NHIndole); ^{13}C NMR ([D,]DMSO): δ = 112.50-138.54 (Ar-C),141.09-14.55(=CH) 184.88 (C=O); EIMS (M/z): Molecular weight correspond to 412.2 (M+1) peak.

Compound [SS4] IR (KBr) cm^{-1} 3178.25(NH stretching**),** 2916.11(Aromatic C-H stretching), 1649.56(C=O Stretching) 1610.60(aromatic C=C stretching);1575.89(aromatic C=N stretching),1242.66 (C=C in CH=CH); ^{1}H NMR: ([D,]DMSO): δ 3.88 (s, 1H,-CH3), 7.32-7.33 (q, Ar-H), 7.34-7.45(q, Ar-H), 7.46-7.86(q, Ar-H), 8.32 (s, 1H,-CH), 8.34 (s, 1H,-CH), 8.72 (s, 1H,-CH), 5.41(s, 1H,NH),10.07(s, 1H,NHIndole); EIMS (M/z): Molecular weight Correspond to 396.2 (M+1) peak.

Compound [SS5] IR (KBr) cm^{-1} 3110.07(NH stretching),2916.91(Aromatic C-H stretching) 1648.98(C=O Stretching) 1624.93(aromatic C=C stretching);1586.66(aromatic C=N stretching),761.79(Ar-Cl); ^{1}H NMR**:** ([D,]DMSO): 7.31-7.86 (q,, Ar-H), 8.31(s, 1H,-CH), 8.35 (s, 1H,-CH), 8.34 (s, 1H,-CH), 8.84(s, 1H,NH),10.07(s, 1H,NHIndole); EIMS (M/z): Molecular weight correspond to 401.6 (M+1) peak.

Compound [SS6] IR (KBr) cm^{-1} 3267.56 (NH stretching), 1661.08(C=O Stretching) 1604.34(aromatic C=C stretching); 1586(aromatic C=N stretching), 1218.43 (C=C in CH=CH).

Compound [SS7] IR (KBr) cm^{-1} 3165.69 (NH stretching), 1631.32(C=O Stretching), 1611.40(aromatic C=C stretching); 1576.32(aromatic C=N stretching), 1242.02 (C=C in CH=CH).

Compound [SS8] IR (KBr) cm^{-1} 3179.35(NH stretching), 2916.45 (Aromatic C-H stretching), 1612.18(C=O stretching); 1576.59(aromatic C=N stretching), 1243.49 (C=C in CH=CH).

Compound [SS9] IR (KBr) cm^{-1} 3164.38(NH stretching), 2916.86 (Aromatic C-H stretching), 1611.85(C=O stretching); 1576.32(aromatic C=N stretching), 1242.70 (C=C in CH=CH).

Compound [SS10] IR (KBr) cm^{-1} 3196.38(NH stretching), 2916.63 (Aromatic C-H stretching), 1675.91(C=O Stretching), 1618.43(aromatic C=C stretching); 1587.99(aromatic C=N stretching), 1245.80 (C=C in CH=CH), 745.59 (Ar-Cl).

Compound [SS11] IR (KBr) cm^{-1} 3156.48(NH stretching), 2917.09 (Aromatic C-H stretching) 1649.09(C=O Stretching), 1586.40 (aromatic C=C stretching) 1561.71(aromatic C=N stretching), 1189.91 (C=C in CH=CH), 761.93 (Ar-Cl).

Compound [SS12] IR (KBr) cm^{-1} 3167.24(NH stretching), 2916.78 (Aromatic C-H stretching) 1630.57(C=O Stretching), 1575.53 (aromatic C=C stretching) 1519.91(aromatic C=N stretching), 1123.83 (C=C in CH=CH).

Compound [SS13] IR (KBr) cm^{-1} 3187.23(NH stretching), 2916.52 (Aromatic C-H stretching) 1611.99(C=O Stretching), 1575.88 (aromatic C=C stretching) 1519.58(aromatic C=N stretching), 1120.83 (C=C in CH=CH).

Compound [SS14] IR (KBr) cm^{-1} 3189.38(NH stretching), 2916.31 (Aromatic C-H stretching) 1613.90(C=O Stretching); 1561.29 (aromatic C=N stretching), 1128.53 (C=C in CH=CH).

Compound [SS15] IR (KBr) cm^{-1} 3125.56(NH stretching), 2916.84 (Aromatic C-H stretching) 1649.32(C=O Stretching); 1583.16 (aromatic C=N stretching), 1191.79 (C=C in CH=CH), 742.02 (Ar-Br).

Compound [SS16] IR (KBr) cm^{-1} 3187.25(NH stretching), 2916.95 (Aromatic C-H stretching) 1649.52(C=O Stretching); 1583.25 (aromatic C=N stretching), 1191.94 (C=C in CH=CH), 742.02 (Ar-Br).

Compound [SS17] IR (KBr) cm^{-1} 3138.56(NH stretching), 2916.25 (Aromatic C-H stretching) 1640.82(C=O Stretching); 1584.37 (aromatic C=N stretching), 1121.94 (C=C in CH=CH), 741.01 (Ar-Br).

Compound [SS18] IR (KBr) cm^{-1} 3114.26(NH stretching), 2920.29 (Aromatic C-H stretching) 1630.79(C=O Stretching); 1580.45 (aromatic C=N stretching), 1118.97 (C=C in CH=CH).

Compound [SS19] IR (KBr) cm^{-1} 3455(NH stretching),2933.47 (Aromatic C-H stretching)1683.24(C=O Stretching);1586.58 (aromatic C=N stretching),1059.51 (C=C in CH=CH).

Compound [SS20] IR (KBr) cm^{-1} 3148.27(NH stretching), 2917.28 (Aromatic C-H stretching) 1632.18(C=O Stretching); 1520.09 (aromatic C=N stretching), 1118.76 (C=C in CH=CH).

Compound [SS21] IR (KBr) cm^{-1} 3113(NH stretching), 2935.68 (Aromatic C-H stretching) 1630.86(C=O Stretching); 1576.84 (aromatic C=N stretching), 1124.42 (C=C in CH=CH).

Compound [SS22] IR (KBr) cm^{-1} 3156.89(NH stretching), 2919.96 (Aromatic C-H stretching) 1629.71(C=O Stretching); 1575.67

(aromatic C=N stretching), 1122.63 (C=C in CH=CH).

Compound [SS23] IR (KBr) cm^{-1} 3164.28(NH stretching), 2919.01 (Aromatic C-H stretching) 1610.34(C=O Stretching); 1575.91 (aromatic C=N stretching), 1153.24 (C=C in CH=CH), 740.78 (Ar-Cl).

Compound [SS24] IR (KBr) cm^{-1} 3238.50 (NH stretching), 2945.74 (Aromatic C-H stretching) 1637.70(C=O Stretching); 1590.30(aromatic C=N stretching), 1171.41.24 (C=C in CH=CH), 749.39 (Ar-Cl).

Compound [SS25] IR (KBr) cm^{-1} 3178.27(NH stretching), 2916.21 (Aromatic C-H stretching) 1610.80(C=O Stretching); 1576.25(aromatic C=N stretching), 1153.31 (C=C in CH=CH), 740.93 (Ar-Br).

Compound [SS26] IR (KBr) cm^{-1} 3164.34(NH stretching), 2930.35 (Aromatic C-H stretching) 1630.39(C=O Stretching); 1526.08(aromatic C=N stretching), 1121.49 (C=C in CH=CH), 786.40 (Ar-Br).

Molecular Docking

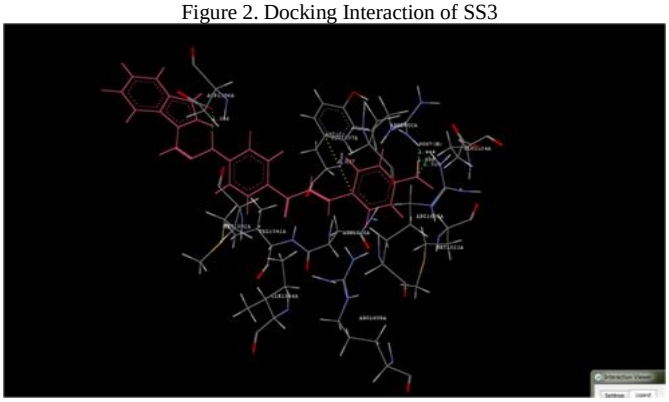
Molecular docking was performed to assess the binding ability of the designed derivatives with Sodium Channel NAV 1.7. Structure of the Sodium Channel NAV 1.7.was downloaded from the free protein databank www.rcsb.org and utilized for docking analysis. Grip based docking analysis was performed. Derivative SS6 was found to interacting via formation of hydrogen bond interaction with GLN1530 and aromatic interaction with TRP1538. Derivative SS6 was found showing hydrogen bond interaction with ARG1608 and aromatic interactions with TYR1537 TRP1538. Derivative SS8 was found showing hydrogen bond interaction with GLN1530 and aromatic interaction with TRP1538. SS9 interacted via hydrogen bond interaction with GLN1530 and aromatic interaction with TRP1538, while SS10 Showed hydrogen bond interaction with ASP1586 and three aromatic interactions with TYR1537, TRP1538, PHE1598. Derivative SS5 was found showing hydrogen bond interaction with ARG1608 and aromatic interactions with TYR1537 TRP1538. SS11 interacted with formation of single hydrogen bond interaction with GLN1530. Derivative SS12 was found showing hydrogen bond interaction with GLN1530 and aromatic interactions with PHE1592, TRP1538. Derivative SS13 was found showing hydrogen bond interaction with GLN1530 and aromatic interactions with TYR1537, PHE1598. Derivative SS14 was found showing hydrogen bond interaction with GLN1530 and aromatic interactions with TRP1538, PHE1592. Derivative SS4 was showed two hydrogen bond interactions with ASP1586 ARG1602 and aromatic interaction with TYR1537. SS15 interacted via formation of hydrogen bond interaction with GLN1530 and aromatic interaction with TYR1537 PHE1598, SS16 interacted via formation of hydrogen bond interaction with GLN1530 and aromatic interaction with TYR1537 PHE1598, ss17 interacted with formation of hydrogen bond interaction with TRP1538. SS18 interacted via formation of hydrogen bond interaction with ARG1605 and aromatic interaction with TYR1537 PHE1598, SS19 interacted via formation of hydrogen bond interaction with ASP1586 and aromatic interaction with TYR1537 TRP1538, SS20 interacted with formation of hydrogen bond interaction with GLN1530 and aromatic interactions with TYR1537. SS21 showed two hydrogen bond interactions with ASP1586, ARG1602 and aromatic interaction with TYR1537, SS22 showed hydrogen bond interaction with ASP1586 and two aromatic interactions with TYR1537, TRP1538. SS24 interacted via formation of hydrogen bond interaction with ASP1586 and aromatic interaction with TRP1538 PHE1592, SS25 interacted with formation of hydrogen bond interaction with GLN1530 and two aromatic interactions with TRP1538, PHE1592, SS26 interacted with formation of hydrogen bond interaction with GLN1530 and aromatic interaction with TRP1538, SS23 interacted with formation of hydrogen bond interaction with ARG1608 and two aromatic interaction with TYR1537, TRP1538.All the docking results are shown in table 2 and figures 2-3.

Table 3: Docking Interactions of synthesized Molecules

Molecule No	Interactions	
	Amino acid anvloved in H bond Inteacion	Amino acid anvloved in Aromatic Interaction
SS3	ASP1586, ARG1602	TYR1537
SS4	ASP1586, ARG1602	TYR1537
SS5	ASP1586	TYR1537 TRP1538
SS6	GLN1530	TRP1538
SS7	ARG1608	TYR1537 TRP1538
SS8	GLN1530	TRP1538
SS9	GLN1530	TRP1538
SS10	ASP1586	TYR1537 TRP1538 PHE1598
SS11	GLN1530	NA
SS12	GLN1530	PHE1592 TRP1538
SS13	GLN1530	TYR1537 PHE1598
SS14	GLN1530	TRP1538 PHE1592
SS15	GLN1530	TYR1537 PHE1598
SS16	GLN1530	TYR1537 PHE1598
SS17	TRP1538	NA
SS18	ARG1605	TYR1537 TRP1538
SS19	ASP1586	TYR1537 TRP1538
SS20	GLN1530	TYR1537
SS21	GLN1530 ARG1602	TYR1537 PHE1598
SS22	ASP1586	TYR1537 TRP1538
SS23	ARG1608	TYR1537 TRP1538
SS24	GLN1530	TRP1538 PHE1592
SS25	ARG1608	TYR1537 TRP1538
SS26	GLN1530	TRP1538

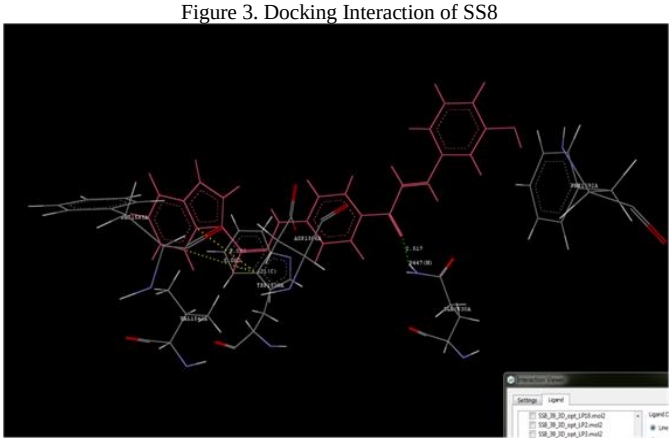
Docking of pose of most potent compound SS3 is shown in Figures 2.

Figure 2. Docking Interaction of SS3



Docking of pose of some least potent compound SS8 is shown in Figures 3.

Figure 3. Docking Interaction of SS8



CONCLUSION

Sodium Channel 1.7(Nav 1.7) is one of the promising biological targets for the development of the molecules against neuropathic pain. 24 different heterocyclic derivatives were prepared via the reaction of Indole 3 carboxy aldehyde. Molecules that are synthesized are characterized via spectral analysis. Virtual analysis of the synthesized derivatives was carried out to ascertain their potential against neuropathic pain. All the synthesized derivatives were found to be interacting with Nav 1.7 which indicated further biological optimization of these compounds may lead to potent Nav 1.7inhibitors.

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