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Novel 4-Thiazolidinone derivatives act as potential Voltage Sensitive Sodium Channel Inhibitors

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A B S T R A C T

The objective of the present work was the synthesis of N-[2-(4-substituted phenyl)-4-oxo-1,3-thiazolidine-3-yl]-2-(naphthalene-2-yloxy)acetamide and evaluation of *in-vitro* anticonvulsant activity by Molecular Docking against Voltage Sensitive Sodium Channel (VSSC) and the best dock pose was selected based on the interaction study analysis. Based on this a new series of compound had been planned to synthesize by reacting β-naphthol, ethyl chloroacetate, hydrazine monohydrate, ethyl alcohol and various aromatic aldehydes in presence of anhydrous potassium carbonate. The synthesized compounds were characterized by IR, NMR, and Mass spectroscopy. In silico.molecular docking studies displayed the following binding energies of the synthesized compounds (A1-A10): -5.32, -5.67, -5.20, -4.44, -4.54, -5.07, -4.77, -5.92, -6.23, -5.21 and -6.03 k.cal/mol of standard drug phenytoin, which indicated that the compounds had high binding affinity towards the VSSC protein and inhibit the sodium channel when compared with standard drug phenytoin. *In vitro* molecular docking also displayed the estimated inhibition constant of the synthesized compounds as: 125.26, 69.70, 155.24, 557.10, 466.77, 192.21, 318.48, 45.77, 27.29, and 150.74 uM (A1-A10) and 37.83 uM (Phenytoin).

Keywords: Thiazolidinone, Anticonvulsant activity, IR, NMR, Molecular docking, Binding energy

A R T I C L E I N F O

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1. Introduction

4-thiazolidinones are the derivatives of thiazolidine with a carbonyl group at the 4 position. Several methods for the synthesis are available. The synthesis of 2-amino 4-thiazolidinones-4-C has been reported by using thiourea and sodium salt of labeled monochloroacetic acid [1]. Another method of synthesis of 4-thiazolidinones is by using of thiocyanate, alkylisothiocyanate with hydrazide /acetamide followed by the treatment with ethylchloro or ethylbromo acetate and sodium acetate [2]. The literature survey revealed that 4-thiazolidinone and their derivatives were possessed a wide range of pharmacological activities such as anti-inflammatory, analgesic, anticonvulsant, antimicrobial, local and spinal anesthetics, CNS stimulants, hypnotics, anti HIV, anti diabetic, anticancer, FSH receptor antagonist and CFTR inhibitor etc[3-4]**.** The objective of the present work is the synthesis of N-[2-(4-substituted phenyl)-4-oxo-1, 3-thiazolidine-3-yl]-2-(naphthalene-2-yloxy) acetamide and evaluation of anti inflammatory activity. Based on this a new series of compound have been planned to synthesize by reacting β-napthol, ethyl chloroacetate, hydrazine monohydrate, ethyl alcohol and various aromatic aldehydes in the presence of anhydrous potassium carbonate.

2. Materials and Methods

The all chemicals used for the synthesis were of laboratory grade and analytical grade. The melting points of newly synthesized thiazolidinone compounds were determined by open capillary method. The IR spectra of synthesized compounds were recorded by ABB Bomen FT-IR spectrometer MB 104 IR spectra recorder with KBr pellets**.** The H^1-NMR spectra of synthesized compounds were recorded by BRUKER NMR spectrometer in DMSO. The Mass spectra of synthesized compounds were recorded by JEOL GCmate. The purification of newly synthesiszed compounds were done by TLC method.TLC plates are pre-coated silica gel(HF254-200 mesh) aluminium plate using ethyl acetate and n-hexane as an solvent system and spots were visualized under U.V chamber. The IR, H^1-NMR and Mass spectra were assigned to elucidate the structure of synthesized compounds (A1-A10).

Steps involved in the synthesis of target compound [5]

Preparation of ethyl-2-naphthalene -6-yloxy acetate:

2-napthol (1.44gm, 10mmol), anhydrous potassium carbonate (1gm) and ethylchloroactate (1.67gm, 10mmol) in 50ml of anhydrous acetone were refluxed on oil bath for 6 hours. The reaction mixure was filtered and the excess solvent was removed by distillation under pressure.

Preparation of 2-(naphthalene-6-yloxy) acetohydrazide:

The residue and 1gm hydrazine monohydrate (20 mmol) were dissolved in 50 ml of absolute ethanol and refluxed on a steam bath for 1 hour. The solute must was filtered and dried and recrystalized from ethanol.

Preparation of substituted benzaldehyde derivatives:

0.01mol of substituted benzaldehyde and 0.01mol of substance and 2-3 drops of glacial acetic acid and 20ml of ethanol were taken in round bottom flask and reflux for 6 hours on water bath. After cooling add ice cold water to the mixture to give solid white mass. Filtered and dried. Recrystallized from chloroform-methanol mixture.

General method of synthesis of thiazolidinone derivatives: A mixture of Schiff base (0.001mmol) and Thioglycolic acid (0.001mol) dissolved in 1,4-dioxane (20ml), anhydrous zinc chloride (0.5mg) was added and refluxed for 8 hours. The reaction was then cooled to 30°C and the resulting solid was washed with sodium bicarbonate solution. The final compound recrystallized from absolute ethanol.

Compound A1:

N-[2-(4-hydroxyphenyl]-4-oxo-1,3-thiazolidin-3-yl-2-(naphthalene-2-yloxylacetamide. M.F- $C_{21}H_{18}N_2O_4S$, M.W 394.44, M.P-180^{O}c, R_f-0.55, Yield-62.1%, IR (KBr) ν (cm^{-1}):1624.11cm^{-1}(Ar-C=C), 3177.12cm^{-1}(aliph-N-H), 1026. 57cm^{-1}(N-N),747.42cm^{-1}(C-S),3610.57cm^{-1}(O-H phe), 1689.24cm^{-1}(C=O),1269.54cm^{-1}(C-N),1728.62cm^{-1}(C=O-thiazolidine), ^{1}H-NMR δ (ppm): 8.0(1H,-NH-),6.8-7.9(11H,Ar-H),5.92(1H,-N-CH-S-),5.21(1H,Ar-OH), 5.0 (2H,-O-CH_2-CO-),3.8(2H,-S-CH_2), Mass (m/e value): 394.5 (30%) (M^+), 395.4(25%)(M+1), 377.1(50%), 301.0(70%), 274.0(38%), 228.1(58%), 200.7(67%), 185.1(24%), 157.1(48%), 127.1(73%), 102.0(44%), 100.4(100%)B

Compound A2:

N-[2(4-chlorophenyl-4-oxo-1,3-thiazolidin-3-yl]-2-(naphthalene-2-yloxy)acetamide.M.F: $C_{21}H_{17}ClN_2O_3S$, MW-412.89, M.P-172^{0}c, R_f- 0.46, Yield-65.2%, IR (KBr) ν (cm^{-1}): 1611.20cm^{-1} (Ar-C=C) ,3186.99cm^{-1} (Aliph-N-H), 1086.99cm^{-1} (N-N) ,695.56cm^{-1} (C-S) ,1668.87cm^{-1}(C=O), 1267.68cm^{-1} (C-N) ,750.35cm^{-1} (Ar-C-Cl) ,1716.32cm^{-1} (C=O- thiazolidine), ^{1}H-NMR δ (ppm): 8.3 (1H,-NH-) ,6.8-7.9 (11H,Ar-H) ,5.80 (1H,-N-CH-S-) ,5.0 (2H,-O-CH_2-CO-), 3.3(2H,-S-CH_2), Mass (m/e value): 412.9(24%)(M^+), 413.8(20%)(M+1), 377.1(50%), 301.0(70%), 274.0(38%), 228.1(58%), 200.7(67%), 185.1(24%), 157.1(48%), 127.1(73%), 102.0(44%),100.4(100%)B.

Copound A3:

N[2-(4-fluorophenyl)-4-oxo-1,3-thiazolidin-3-yl]-2-(naphthalene)acetamide. M.F- $C_{21}H_{17}FN_2O_3S$, MW-396.43, M.P-175^{0}c, R_f- 0.48, Yield- 55.7%, IR (KBr) ν (cm^{-1}):1609.09cm^{-1}(Ar-C=C),3194.42cm^{-1}(Aliph-N-H), 1026. 76cm^{-1} (N-N) 1256.34cm^{-1}(C-N), 705.10cm^{-1}(C-S), 1662. 09cm^{-1}(C=O),1000.62cm^{-1}(Ar-C-F),1721.94cm^{-1}(C=O-thiazolidin), ^{1}H-NMR δ (ppm): 8.20(1H,-NH-),6.8-7.9(11H, Ar-H),6.0(1H,-N-CH-S-),4.90(2H,-O-CH_2-CO-),3.5(2H,-S-CH_2-), Mass (m/e value): 396.5(13%)(M^+), 397.4 (11%) (M+1), 377.1(50%), 301.0(70%), 274.0(38%), 228.1(58%), 200.7 (67%), 185.1(24%), 157.1(48%), 127.1(73%), 102.0(44%), 100.4(100%)B

Compound A4

N-[2-(4-bromophenyl)-4-oxo-1,3-thiazolidin-3-yl]-2-(naphthalene-2-yloxy)acetamide. M.F- $C_{21}H_{17}BrN_2O_3S$, M.W-457.34, M.P- 178^{0}c, R_f- 0.51, Yield- 64.96%, IR (KBr) ν (cm^{-1}): 1621.73cm^{-1}(Ar-C=C), 3198.97 cm^{-1}(Aliph-

N-H), 1031.38 cm^{-1}(N-N), 758.36 cm^{-1}(C-S), 1681.77 cm^{-1}(C=O), 1530.18 cm^{-1}(Ar-C-Br), 1721.46 cm^{-1}(C=O-thiazolidine), ^{1}H-NMR δ (ppm): 8.0(1H,-NH-), 6.8-7.9(11H,Ar-H), 5.9(1H,-N-CH-S-), 5.2(2H,-O-CH_2-CO-), & 3.3(2H,-S-CH_2-), Mass (m/e value): 457.4(10%)(M^+), 458.3(9%)(M+1), 377.1(50%), 301.0(70%), 274.0(38%), 228.1(58%), 200.7(67%), 185.1(24%), 157.1(48%), 127.1(73%), 102.0(44%),100.4(100%)B.

Compound A5:

2-(naphthalene-2-yloxy)-N-[2-(4-nitrophenyl)-4-oxo-1,3-thiazolidin-3-yl]acetamide. M.F- $C_{21}H_{17}N_3O_5S$, M.W-423.44, M.P- 160^{0}c, R_f- 0.71,Yield- 68.2%, IR (KBr) ν (cm^{-1}): 1605.0cm^{-1}(Ar-C=C), 3181.81 cm^{-1},(Aliph-N-H), 1050.57 cm^{-1}(N-N), 1248.07 cm^{-1}(C-N), 752.45 cm^{-1}(C-S), 1685.27 cm^{-1}(C=O), 1521.57 cm^{-1}(Ar-NO_2), 1721.09 cm^{-1}(C=O-thiazolidine), ^{1}H-NMR δ (ppm): 8.2(1H,-NH-), 6.8-7.9(11H, Ar-H), 5.8(1H,-N-CH-S-), 5.1(2H, -O=CH_2-CO-), & 3.4(2H, -S-CH_2-), Mass (m/e value) **:** 423.5(11%)(M^+), 424.4(9%)(M+1), 377.1(50%), 301.0(70%), 274.0(38%), 228.1(58%), 200.7(67%), 185.1(24%), 157.1(48%), 127.1(73%), 102.0(44%),100.4(100%)B.

Compound A6

2-(naphthalene-2-yloxy)-N-[2-nitrophenyl)-4-oxo-1,3-thiazolidin-3-yl]acetamide. M.F- $C_{21}H_{17}N_3O_5S$, M.W-423.44, M.P- 165^{0}c, R_f- 0.69, Yield- 68.2%, IR (KBr) ν (cm^{-1}): 1613.0cm-1(Ar-C=C), 3211.27 cm-1(Aliph-N-H), 1061.45 cm-1(N-N), 1248.01 cm-1(C-N), 774.86 cm-1(C-S),1681.31 cm-1(C=O),1516.23 cm-1(NO_2), 1717.68 cm-1(C=O-thiazolidine), ^{1}H-NMR δ (ppm): 8.2(1H, -NH-), 6.8-7.9(11-H, Ar-H), 5.8(1H,-N-CH-S-), 5.2(2H,-O-CH_2-CO-),3.4(2H, -S-CH_2-), Mass (m/e value): 423.5(9%)(M^+), 424.4(8%)(M+1), 377.1(50%), 301.0(70%), 274.0(38%), 228.1(58%), 200.7(67%), 185.1(24%), 157.1(48%), 127.1 (73%), 102.0(44%),100.4(100%)B.

Compound A7

N-[2-(3,4-dimethoxyphenyl)-4-oxo-thiazolidin-3-yl]-2-(naphthalene-2-yloxy)acetamide.M.F- $C_{23}H_{22}N_2O_5S$,M.W-438.12, M.P-185^{0}c, R_f-0.66, Yield-58.6%, IR (KBr) ν (cm^{-1}): 1619.0cm-1(Ar-C=C), 3202.17cm-1(Aliph-N-H), 1026. 57cm-1(N-N), 1265.59cm-1(C-N), 747.42cm-1(C-S), 1663. 99cm-1(C=O), 1126.82cm-1(-C-O-C-), 1723.15cm-1(C=O-thiazolidine), ^{1}H-NMR δ (ppm): 8.2(1H, -NH-), 6.8-7.9(11H, Ar-H), 6.1(1H, -N-CH-S-), 5.3(2H, -O-CH_2-CO-), 3.8(6H, -O-CH_3), 3.4(2H,-S-CH_2-), Mass (m/e value): 438.1(6%) (M^+), 439.1(5%)(M+1), 377.1(50%), 301.0 (70%), 274.0(38%), 228.1(58%), 200.7(67%), 185.1(24%), 157.1(48%), 127.1(73%), 102.0(44%), 100.4 (100%)B.

Compound A8

N-[2-(2-chlorophenyl)-4-oxo-1, 3-thiazolidin-3-yl]-2-(naphthalene- 2-yloxy) acetamide. M.F- $C_{21}H_{17}ClN_2O_3S$, M.W- 412.89, M.P- 198^{0}C, R_f – 0.44, Yield-71.2%, IR (KBr) ν(cm^{-1}): 1614.07cm-1(Ar-C=C), 3188.27cm-1(Aliph-N-H), 1048.26cm-1(N-N), 1267.13cm-1(C-N), 774.55cm-1(C-S), 1685.07cm-1(C=O), 700.46cm-1(Ar-C-Cl), 1721. 07cm-1 (C=O-thiazolidine), ^{1}H-NMR δ (ppm): 8.4(1H, -NH-), 6.8-7.9(11H, Ar-H), 6.2(1H, -N-CH-S-), 5.2(2H, -O-CH_2-CO-), 3.7(2H, -S-CH_2-), Mass (m/e value): 412.9 (14%) (M^+), 413.8(13%)(M+1), 377.1(50%), 301.0(70%), 274.0(38%), 228.1(58%), 200.7(67%), 185.1(24%), 157.1(48%), 127.1(73%), 102.0(44%), 100.4 (100%)B.

Compound A9:

2-(naphthalene-2-yloxy)-N-[2-(3-nitrophenyl)-4-oxo-1,3-thiazolidin-3-yl]acetamide. M.F- $C_{21}H_{17}N_3O_5S$, M.W-423.44, M.P-166^{0}c, R_f - 0.68, Yield-71.5%, IR(KBr) ν (cm^{-1}): 1612.32cm-1(Ar-C=C), 3217.42cm-1(Aliph-N-H), 1050.57cm-1(N-N), 1237.20cm-1(C-N), 703.59cm-1(C-S), 1682.57cm-1(C=O), 1507.14cm-1(Ar-NO_2), 1721.38cm-1(C=O-thiazolidine), ^{1}H-NMR δ (ppm): 8.2(1H, -NH-), 6.8-7.9(11H, Ar-H), 6.1(1H, -N-CH-S-), 5.1(2H, -O-CH_2-CO-), 3.6(2H, -S-CH_2-), Mass (m/e value): 423.5(9%)(M^+), 424.4(M+1), 377.1(50%), 301.0(70%), 274.0(38%), 228.1 (58%), 200.7(67%), 185.1(24%), 157.1(48%), 127.1 (73%), 102.0(44%),100.4(100%)B.

Compound A10: N-[2-(3-hydroxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-2-(naphthalene-2-yloxy)- acetamide. M.F-$C_{21}H_{18}N_2O_4S$, M.W-394.44, M.P- 187^{0}c, R_f-0.58, Yield-62.3%, IR (KBr) ν (cm^{-1}): 1603.86cm-1(Ar- C=C), 3210.68cm-1(Aliph-N-H), 1048.26cm-1(N-N), 1258.95cm-1(C-N), 703.47cm-1(C-S), 1686.85cm-1(C=O),3610.93cm-1(O-H-Ph), 1721. 63 cm-1(C=O-thiazolidine), ^{1}H-NMR δ (ppm): 8.3(1H, -NH-), 6.8-7.9(11H, Ar-H), 6.1(1H, -N-CH-S-), 5.2(2H, -O-CH_2-CO-), 4.9(1H, Ar-OH), 3.3(2H, -S-CH_2-), Mass (m/e value): 394.5(26%)(M^+), 395.4 (25%) (M+1), 377.1(50%), 301.0(70%), 274.0(38%), 228.1(58%), 200.7(67%), 185.1 (24%), 157.1(48%), 127.1(73%), 102.0 (44%), 100.4 (100%) B.

Molecular docking [6]

Molecular docking is defined as an optimization problem, which would describe the "best-fit" orientation of a ligand that binds to a particular protein of interest. During the course of the process, the ligand and the protein adjust their conformation to achieve an overall "best-fit" and this kind of conformational adjustment resulting in the overall binding is referred to as "induced fit". It is done to achieve an optimized conformation for both the protein and the ligand and relative orientation between protein and ligand such that free energy of overall system is minimized.

Docking approaches [7]:

There are several well defined and generalized methodologies for docking, namely: interactive graphics, docking by superimposition, energy based docking programmes, builders, growers and linkers, flexible docking and fragmentation approach. Here we have done energy based docking programmes which have included various physicochemical parameters are involved in the evaluation of pharmacological activity of the synthesized compounds **(Table-1)**. It involved essentially make use of a particular energy grid with an assumption that body ligand and target molecule happen to be absolutely rigid in nature. Importantly, the energy based docking programmes many afford two important functionalities to the ligand, namely: (a) conformational flexibility and (b) motional flexibility.

3. Results and Discussion

Chemistry

The synthesis of target compounds (A1-A10) N-[2-(4-substituted phenyl)-4-oxo-1, 3-thiazolidine-3-yl]-2-(naphthalene-2-yloxy) acetamide was carried out by reacting β-napthol, ethylchloroacetate, hydrazine monohydrate, ethyl alcohol and various aromatic aldehydes

in the presence of anhydrous potassium carbonate. The progress of the reaction was monitored by TLC using solvent systems of different polarities. TLC plates are pre-coated silica gel (HF254-200 mesh) aluminium and spots were visualized under U.V chamber. The synthesized compounds were characterized by IR, NMR, and Mass spectroscopy. All the synthesized compounds having the following solubility profile: Insoluble in water, slightly soluble in chloroform, ethanol, and freely soluble in DMF, DMSO. The molecular properties of all the synthesized compounds were significantly differ from each other.

Molecular Docking

Most of the scoring functions in molecular docking are physics-based molecular mechanics force fields that estimate the energy of the binding pose; a low (negative) energy indicates a stable system and thus a likely binding interaction. Molecular docking is performed to find out the binding affinity or molecular interaction energy (kcal/mol) of docked compounds. Lowest (negative value) energy of docked molecule indicates high binding affinity with the target protein/compound and the best dock pose was selected based on the interaction study analysis. In silico.molecular docking studies displayed the binding energies (Table:1 and Fig:1-4) : -5.32, -5.67, -5.20, -4.44, -4.54, -5.07, -4.77, -5.92, -6.23, -5.21 of the synthesized compounds (A1-A10) and -6.03 k.cal/mol of standard drug phenytoin, which indicated that the compounds had high binding affinity towards the VSSC protein and inhibit the sodium channel when compared with standard drug phenytoin. *In vitro* molecular docking also displayed the estimated inhibition constant of the synthesized compounds as: 125.26, 69.70, 155.24, 557.10, 466.77, 192.21, 318.48, 45.77, 27.29, and 150.74 uM (A1-A10) and 37.83 uM (Phenytoin).

Table 1: For the final docking results of synthesized compounds (A1-A10) and phenytoin (as a standard drug) against VSSC

Compounds	EFEB (K.cal/mol)	EIC (Ki) uM	V+ Hb + DE (K.cal/mol)	EE (K.cal/mol)	TIME (K.cal/mol)	Fr	IS
S	-6.03	37.83	-6.03	-0.00	-6.03	50%	413.685
A1	-5.32	125.26	-6.55	+0.04	-6.51	50%	733.296
A2	-5.67	69.70	-6.62	+0.07	-6.55	50%	716.922
A3	-5.20	155.24	-6.05	-0.00	-6.05	50%	707.495
A4	-4.44	557.10	-5.25	-0.02	-5.26	50%	657.145
A5	-4.54	466.77	-5.17	-0.04	-5.21	50%	681.112
A6	-5.07	192.21	-6.64	+0.02	-6.61	50%	637.822
A7	-4.77	318.48	-5.63	-0.11	-5.73	50%	702.672
A8	-5.92	45.77	-6.17	-0.14	-6.31	50%	664.868
A9	-6.23	27.29	-6.95	-0.15	-7.10	50%	693.019
A10	-5.21	150.74	-6.25	+0.31	-5.94	50%	654.229

S = Standard drug phenytoin, EFEB = Estimated Free Energy Binding., EIC = Estimated Inhibition constant (Ki), V+Hb +DE = Vdw + H-bonding+Dissolve Energy, EE=Electrostatic Energy, TIME = Total Intermolecular Energy, Fr = Frequency and IS = Interacting surface.

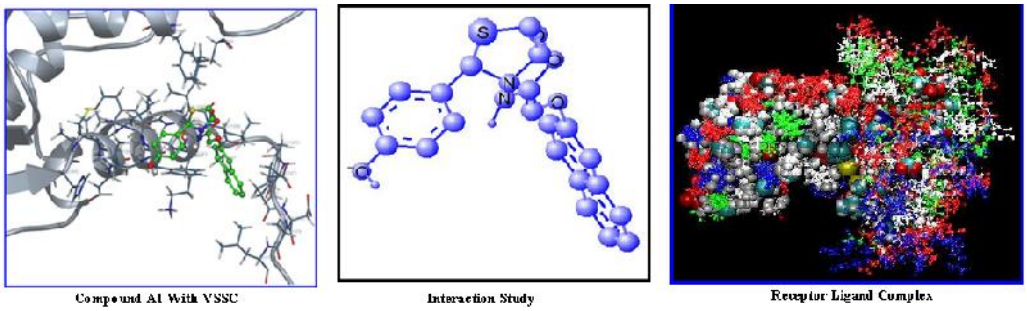

Figure 1: Molecular Docking of Compound A1 with VSSC

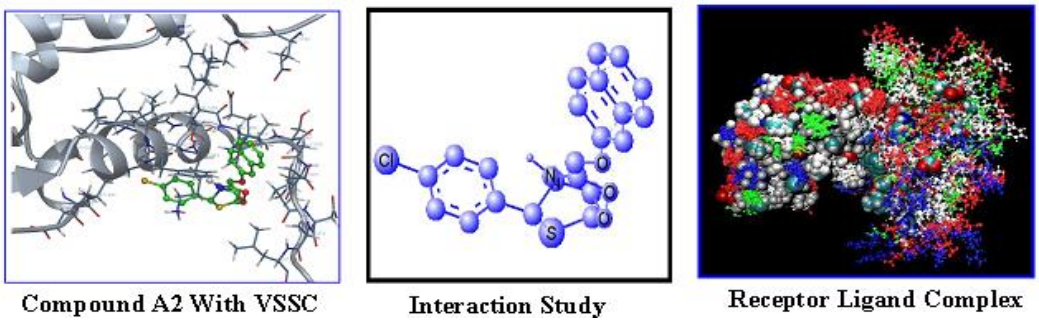

Figure 2: Molecular Docking of Compound A2 with VSSC

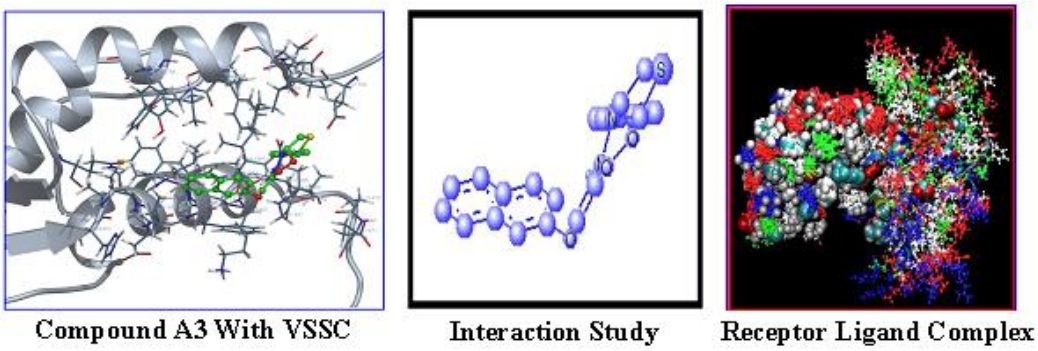

Figure 3: Molecular Docking of Compound A3 with VSSC

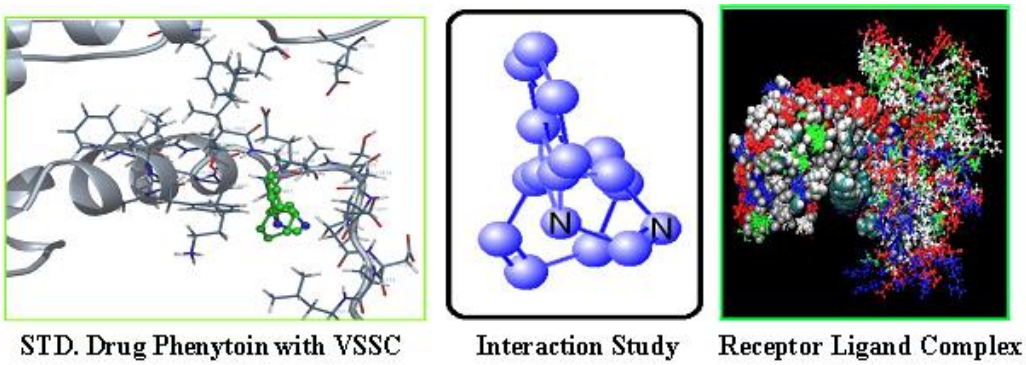

Figure 4: Molecular Docking of Std. drug Phenytoin with VSSC.

4. Conclusion

The above experimental data concluded that the synthesized compounds (A1-A10) had the potential anticonvulsant activity and all the synthesized compounds showed their potential anticonvulsant activity by blocking the voltage sensitive sodium channel proved by molecular docking studies. In silico.molecular docking studies of synthesized compounds were revealed comparable binding energies and similar docking poses on target proteins such as VSSC and known to be inhibitors of sodium channel.

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