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# Synthesis of Hydrazone Derivatives and In-silico docking studies against JNK protein to assess anticonvulsant activity of synthesized derivatives

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**Abstract**

In the past few years, Scientific studies across the globe have led to the crucial insights about Hydrazone and Hydrazide derivatives. Hydrazone compounds and their derivatives have been known to possess antimicrobial, anti fungal, anti tumorous, anti inflammatory and anti convulsant activity. We had synthesized following chemical entities in our work: 2-(3,4-Dichloro-benzoyl)-benzoic acid (2-nitro-benzylidene)-hydrazide ;2-(3,4-Dichloro-benzoyl)-benzoic acid (4-chloro-benzylidene)-hydrazide and 2-(3,4-Dichloro-benzoyl)-benzoic acid (4-fluoro-benzylidene)-hydrazide .Chemical process adopted for synthesizing these derivatives was using phthalic anhydride and Dichlorobenzene dissolved in Nitro benzene in the presence of Aluminum trichloride to obtain 2-(3,4-Dichloro-benzoyl)-benzoic acid as a starting compound and further derivatizing this molecule to design aldehyde derivatives .The structure of synthesized compounds were confirmed by physical, analytical and elemental analysis. $^{1}$ H NMR Spectra of these compounds was studied to confirm their properties. Epilepsy is a chronic neurological disorder which is ranked in top ten neurological complicated disorders globally. Promiscuous symptoms which characterize the condition of Epilepsy includes recurrent spontaneous seizures and additional comorbid complications. Elevated expression level of JNK signalling pathways have been observed in epileptic cases. JNK hyperactivation has been substantially correlated with the pathogenesis of chronic epilepsy. Current scientific reports lead to implicit findings about novel identification of JNK phosphorylation signaling as a potential antiepileptic target in temporal lobe epilepsy and the possibility that with more complete inhibition of JNK activity, a more substantial antiepileptic effect might be achieved. Concurrent with the suggestive findings, Insilico strategies using Auto Dock 4.0 were applied where we have docked the newly synthesized derivatives against JNK protein and have calculated the binding affinities of these compounds to suggest their anti-convulsant activity. This research work leads to conclusion Hydrazone derivative, 2-(3,4-Dichloro-benzoyl)-benzoic acid (4-fluoro-benzylidene)-hydrazide has highest binding affinity for JNK-3 protein (Binding energy estimated to be -9.5 kcal/mol) and key amino acid residues involved in the interaction are Lysine, Methionine and Serine. Based on our work, We suggest to use , 2-(3,4-Dichloro-benzoyl)-benzoic acid (4-fluoro-benzylidene)-hydrazide as a potential lead compound to develop anti-epileptic drug therapies.

**Keywords:** Hydrazone derivatives, JNK signalling, Aluminium Trichloride, Binding affinity, NMR spectra, Docking

## 1. INTRODUCTION

Hydrazines and their derivatives constitute a crucial class of compounds that has been applied extensively in organic synthesis (1). Traditionally, hydrazines have been deployed as reagents for the derivatization and characterization of carbonyl compounds. In scientific investigations conducted in the recent years, the predominant N-N linkage has been exploited as a key structural conserved motif in various bioactive agents (2). Especially,an accelerated numbers of N-N bond-containing heterocycles and peptidomimetics have made their way into commercial applications such as reagents used in pharmaceutical and agricultural industries . Recently, hydrazide-hydrazones have gained great importance due to their diverse biological properties and have multifarious beneficial effects which includes their antibacterial (3,19), antifungal, anticonvulsant (4), anti-inflammatory (5), antimalarial, antituberculosis and anti cancerous activities (6,7,8, 9).

Epilepsy is a chronic neurological disorder which is ranked in top ten neurological complicated disorders globally. Promiscuous symptoms which characterize the condition of Epilepsy includes recurrent spontaneous seizures and additional comorbid complications. Many systemic factors like hypotension, hypoxia, and acidosis further add up to strengthen the neurologic complications of Epilepsy (10) .In recent years, the screening of newly designed compounds with anticonvulsant activity has focused on potential drugs beneficial against refractory epilepsy, suppression or retardation of epileptogenesis, disease progression as well as comorbid psychiatric complications. In this context, the following approaches are used: (i) screening of newly synthetized substances with different structures and unknown mechanism of action; (ii) structure modification of known targets and (iii) selectively synthesizing the compounds which will retrograde the progress of epileptogenic factors (11). While investigating the potential drug molecules, those lead molecules are preferred which have the tendency to raise the seizure threshold and prevent recurrent seizures. Many chemically synthesized Hydrazone derivatives have been shown to have anticonvulsant effect and prevent epileptic attacks (12).

A significant conclusion obtained from introspecting the metabolic dysfunctionalities causing epilepsy have led to the point of inhibition of brain p38 MAPK activity and it has been shown to produce a significant increase in seizure frequency, validating the role of this signaling pathway in modulating seizure activity (13,14). Further, it has been observed that expression level of protein JAK is elevated two fold in epileptic conditions. When the drug molecule like anisomycin is injected in patients having this neurological disorder, partial inhibition of JNK activity was recorded and a substantial, dose-dependent

antiepileptic effect was seen without causing any behavioral abnormalities (15,16). Deciphering enhanced levels of JNK expression and resultant activity in chronically epileptic animals has supported the notion that JNK hyperactivation may be relevant to the pathogenesis of chronic epilepsy. These results represent the novel identification of JNK phosphorylation signaling as a potential antiepileptic target in temporal lobe epilepsy. This raises the possibility that with more complete inhibition of JNK activity, a more substantial antiepileptic effect might be achieved (17,18).

In concurrence with the verified hypothesis of role of Hydrazine-Hydrazone derivatives to act as anticonvulsants, We have synthesized various aldehyde derivatives of Hydrazone using 2-(3,4-Dichloro-benzoyl)-benzoic acid as starting compound and have used insilico strategies to estimate the efficacy of these novel derivatives against JNK-3 protein targets. Binding residues and binding energies of newly synthesized derivatives were compared with the positive control molecules which were known to be existing in co-crystallized form with JNK-3 protein structure to establish the effects of these derivatives.

## 2. METHODOLOGY

### 2.1 Synthesis of Novel Derivatives of of 2-(3,4-Dichloro-benzoyl)-benzoic acid

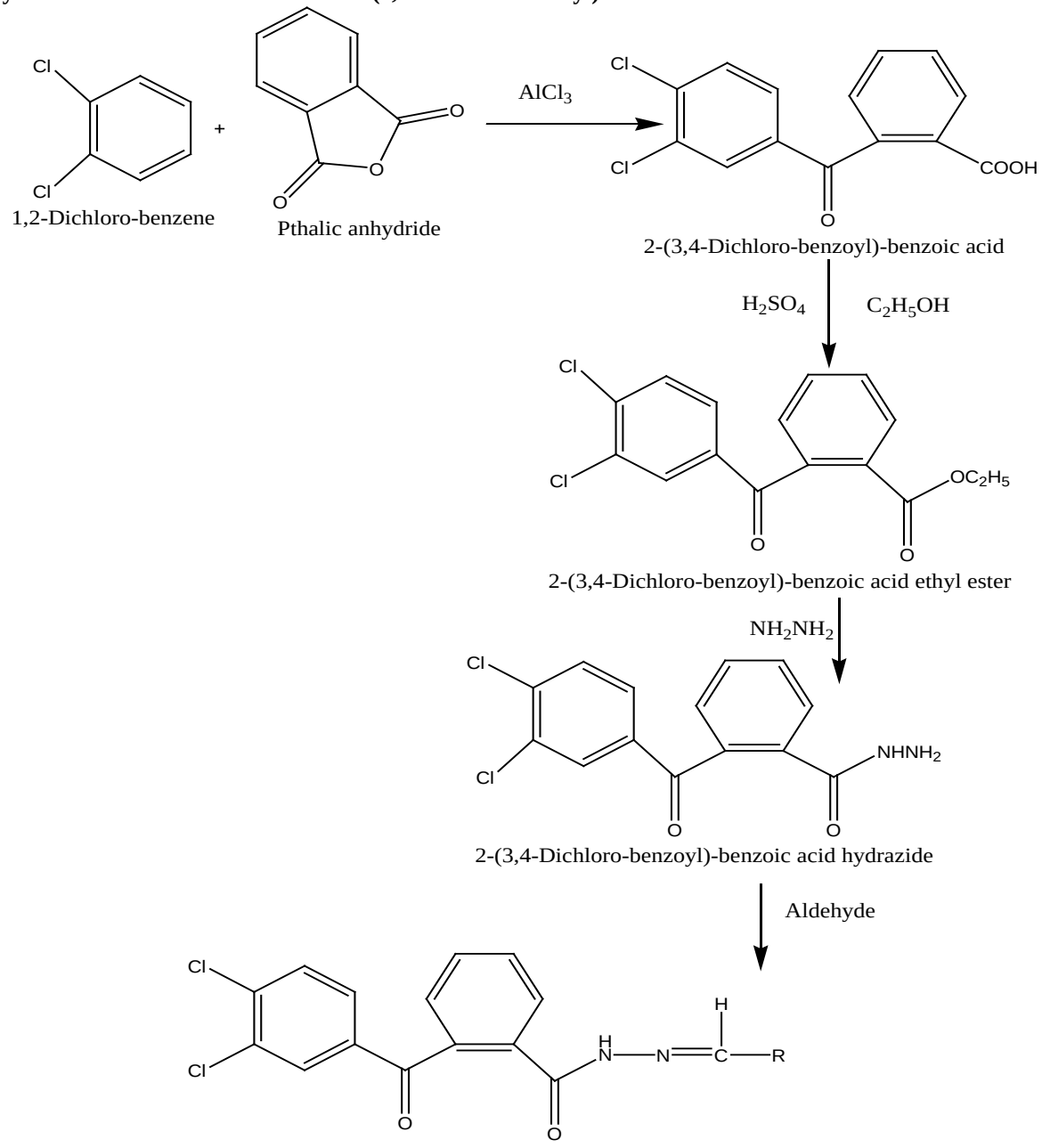
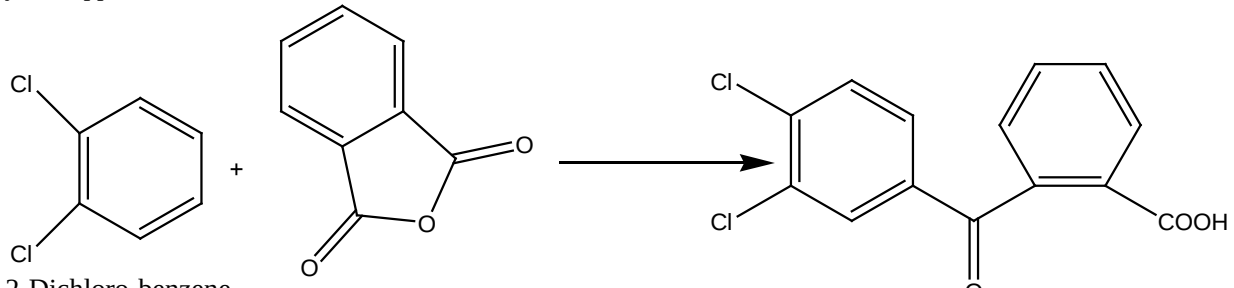



Fig 1: Scheme for Synthesis of 2-(3,4-Dicholoro-benzoyl)-benzoic acid (4-methyl-benzylidene) substituted Hydrazide

**Step-1 Synthesis of 2-(3,4-Dichloro-benzoyl)-benzoic acid**

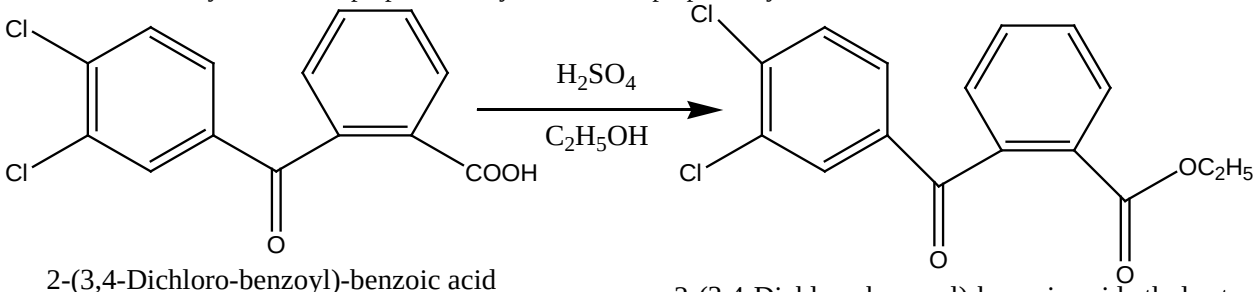
2-(3,4-Dichloro-benzoyl)-benzoic acid was synthesized from respective pthelic anhydride dissolve in nitro benzene with heat and continuous stirring on magnetic stirrer followed by adding Dichlorobenzene. Further, Aluminum trichloride was added by continuous stirring till removal of HCL fumes occurred. Then added water and took it for distillation to ensure removal of nitro benzene, followed by adding diluted HCL. The reddish shiny 2-(3,4-Dichloro-benzoyl)-benzoic acid crystals appeared.




1,2-Dichloro-benzene Pthalic anhydride 2-(3,4-Dichloro-benzoyl)-benzoic acid

**Step-2 Synthesis of 2 2-(3,4-Dichloro-benzoyl)-benzoic acid ethyl ester**

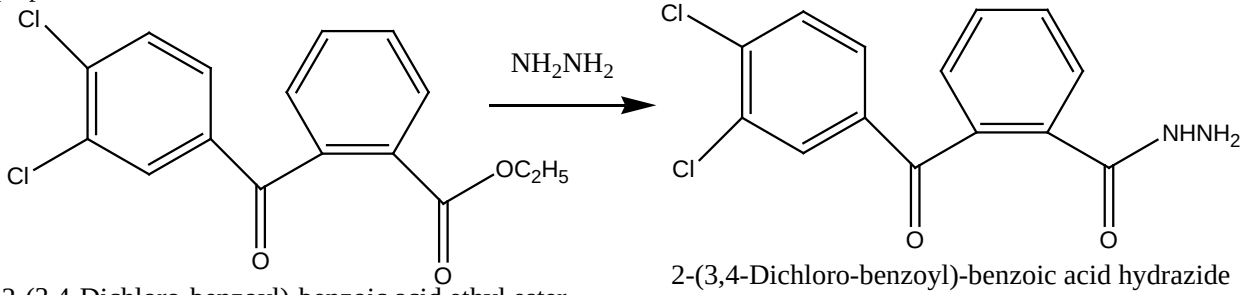
2 2-(3,4-Dichloro-benzoyl)-benzoic acid ethyl ester was synthesized from their respective 2 2-(3,4-Dichloro-benzoyl)-benzoic acid, using excess of dry ethanol in the presence of $H_2SO_4$ under reflux for 20-24 hours. The reddish semisolid solutions with fruity smell were prepared. *Dry ethanol was prepared by distillation method.




2-(3,4-Dichloro-benzoyl)-benzoic acid 2-(3,4-Dichloro-benzoyl)-benzoic acid ethyl ester

**Step-3 Synthesis of 2-(3,4-Dichloro-benzoyl)-benzoic acid hydrazide**

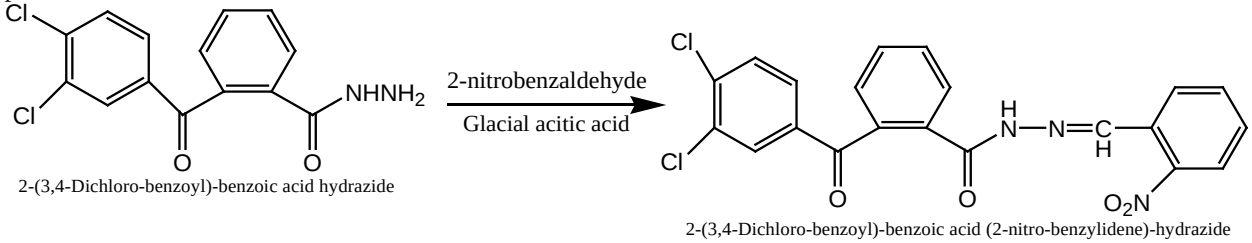
Synthesis of 2-(3,4-Dichloro-benzoyl)-benzoic acid hydrazide from 2 2-(3,4-Dichloro-benzoyl)-benzoic acid ethyl ester with Hydrazine hydrate in 99% pure ethanol under reflux was done for 20-24 hours. The reddish semisolid solution was prepared.




2-(3,4-Dichloro-benzoyl)-benzoic acid ethyl ester 2-(3,4-Dichloro-benzoyl)-benzoic acid hydrazide

**Step-4 synthesis of hydrazones derivatives (PS-1)**

Synthesis of hydrazone derivatives from 2-(3,4-Dichloro-benzoyl)-benzoic acid hydrazide was done by adding 2-nitrobenzaldehyde in 15ml ethanol and 15ml glacial acetic acid followed by R.B.F refluxing for 45 min. Identification was done by using TLC in every 20 min by applying chloroform and ethanol as solvents. The yellow color solid product was collected by filtration under suction. The product was re-crystallized in chloroform. The yellowish crystals are produced.

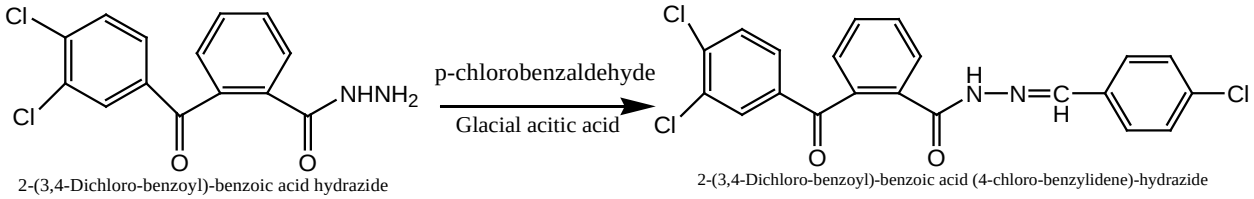



2-(3,4-Dichloro-benzoyl)-benzoic acid hydrazide

2-(3,4-Dichloro-benzoyl)-benzoic acid (2-nitro-benzylidene)-hydrazide

**Step-5 synthesis of hydrazones derivatives (PS-2)**

Synthesis of hydrazone derivatives from 2-(3,4-Dichloro-benzoyl)-benzoic acid hydrazide was done by adding p-chlorobenzaldehyde in 15ml ethanol and 15ml glacial acetic acid followed by R.B.F refluxing for 45 min. Identification was done by using TLC in every 20 min.The pink color solid product was collected by filtration under suction. The product was re-crystallized in chloroform. The pinkish crystals were produced.

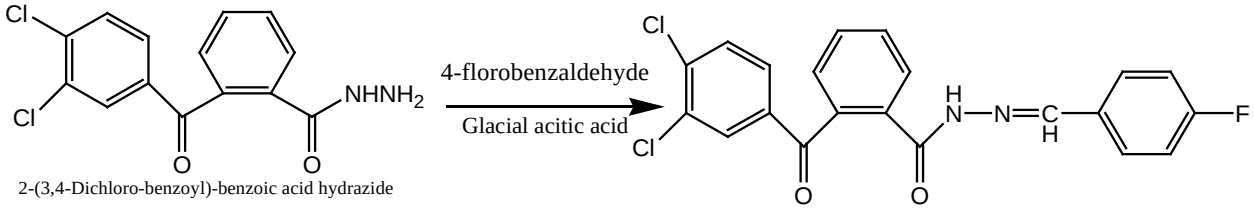



2-(3,4-Dichloro-benzoyl)-benzoic acid hydrazide

2-(3,4-Dichloro-benzoyl)-benzoic acid (4-chloro-benzylidene)-hydrazide

**Step-6 Synthesis of hydrazones derivatives (PS-3)**

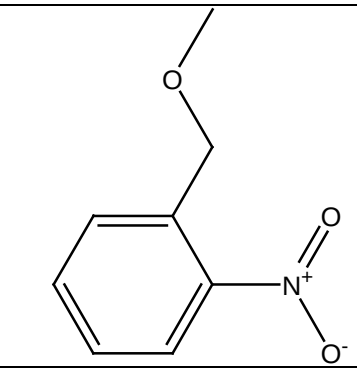
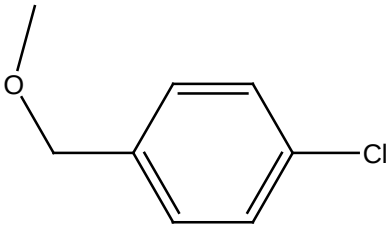
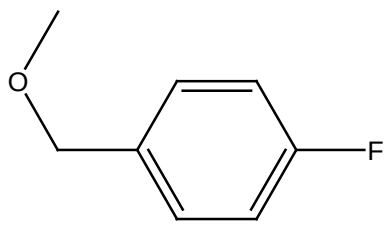
Synthesis of hydrazone derivatives from 2-(3,4-Dichloro-benzoyl)-benzoic acid hydrazide with adding p-chlorobenzaldehyde in 15ml ethanol and 15ml glacial acetic acid followed by R.B.F refluxing for 50 min. Identified by TLC in every 20 min. Poured in ice- cold water. The cream color solid product was collected by filtration under suction. The product was re-crystallized in chloroform. The ceramist crystals are produced.




2-(3,4-Dichloro-benzoyl)-benzoic acid hydrazide

2-(3,4-Dichloro-benzoyl)-benzoic acid (4-fluoro-benzylidene)-hydrazide

**Table -1 Physical properties of the Synthesized Hydrazone Derivatives (PS-Series)**

| Compounds | R | MP ($^{O}$C) | $R_f$ C:E (4:1) | Yield (%) | Mol. Formula (MW) |
|---|---|---|---|---|---|
| **PS-1** |  | 143-145$^{O}$C | 0.60 | 58 | $C_{21}H_{13}Cl_2N_3O_4$ (442.25) |
| **PS-2** |  | 127-130$^{O}$C | 0.59 | 62 | $C_{21}H_{13}Cl_3N_2O_2$ (441.70) |
| **PS-3** |  | 151-154$^{O}$C | 0.66 | 52 | $C_{21}H_{13}Cl_2FN_2O_2$ (415.24) |

### 2.2. Docking studies of PS-series compounds for Determining anti-convulsant activity

For docking study, we took chemical structures of synthesized Hydrazone derivates (PS-1,PS-2 and PS-3) as ligand molecules against the target protein structures, JNK-3 (c-Jun N-terminal kinase) which was downloaded from PDB database. 2ZDT, 2WAJ were the pdb structures of JNK-3 which were used to study the docking of PS series compounds against them.

#### 2.2.1 Generation of 3D structure of ligand molecules

Two dimensional (2D) structures of molecules, PS-1,PS-2 and PS-3 were drawn at ChemDraw/ChemSketch editor. These 2D structures were saved in .mol file format. The 2D structures were further converted to 3D structure and their structural geometry was optimized to lowest energy state. Finally, stable 3D structures were saved in .pdb format.

#### 2.2.2 Docking Studies

After preparation of '.pdb' files of ligand compounds as well as protein structures, we processed the docking studies. Docking studies were performed with Auto Dock Vina software (Trott and Olson, 2010), which simulates the molecular nteraction studies of ligand and protein, through Lamarckian genetic algorithm. Auto Dock Vina has higher accuracy as well as computational performance over traditional Auto Dock software. Whole protein structure was considered for docking. For each docking study, best generated pose was used for analysis. Each docking study resulted into negative binding affinity values containing unit of kilo-calorie per mol (kcal/mol). Total 25 docking studies were performed.

## 3. RESULTS

We had used 46C as a control for studying the docking of PS-1 with the target file 2ZDT and SNB as a control for studying the docking of PS-2 and PS-3 against the target file 2WAJ. Basis for considering these compounds as our control compounds is that 46C is found to be occurring as co-crystallized structure bound to 2ZDT and SNB is found to be occurring as co-crystallized structure bound to 2WAJ.

### 3.1. Docking results of PS-1 against JNK-3

PS-1 was docked with JNK3 protein (PDB 2ZDT) for anti-convulsant activity. PDB 2ZDT structure co-crystallized with ligand '46C' was used as control. PS-1 was compared with control molecule,46C for determining the residues which are bound at active site of JNK3.. As result, control compound was found to be Hydrogen-bonded with MET, while PS-1 was found to bind with residues ALA and GLY. Control and PS-1 showed binding affinity of -10.4 & -9.8 kcal/mol respectively. On the basis of these observations we can say that PS-1 did not showed molecular interaction similarity with control (Figure 2).

### 3.2. Docking results of PS-2 against JNK-3

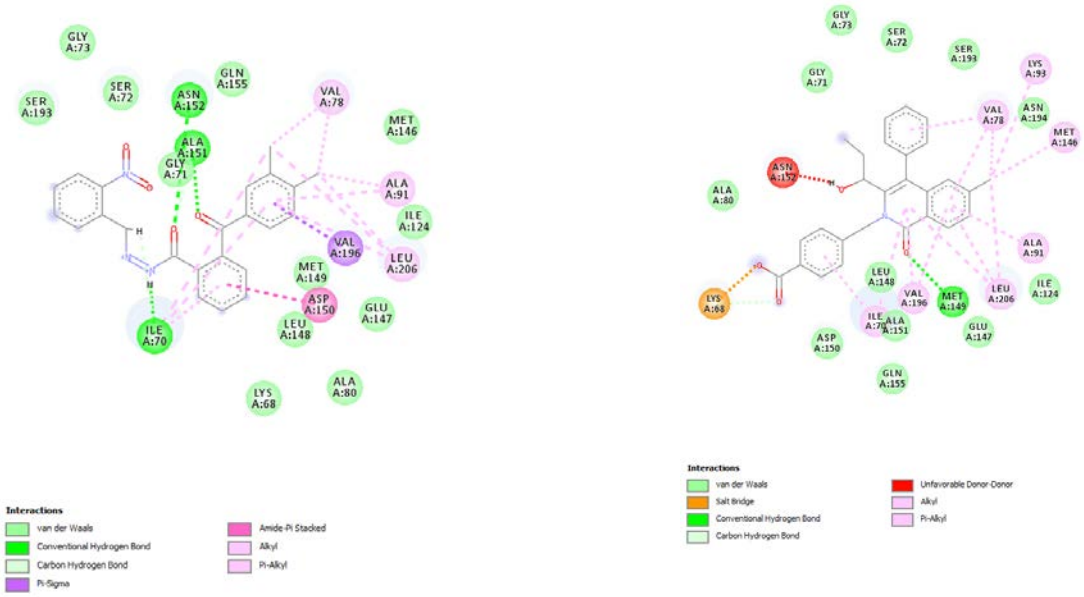
PS-2 was docked with JNK3 protein (PDB 2WAJ) for anti-convulsant activity. PDB 2WAJ co-crystallized ligand 'SNB' was used as control. PS-2 was compared with SNB for checking its residues involved in binding with active site of JNK3. Control compound was found to have Pi-pi ntercation with LYS, similarly PS-2 was also found to bind with LYS through pi-pi interaction. Componds SNB and PS-2 showed binding affinity of -9.6 & -9.4 kcal/mol respectively. On the basis of these observations, it can be said that PS-2 showed similar kind of molecular interaction as the control molecule, SNB.(Fig 3)

### 3.3. Docking results of PS-3 against JNK-3

PS-3 was docked with JNK3 protein (PDB 2WAJ) for checking anti-convulsant activity. PDB 2WAJ co-crystallized ligand 'SNB' was used as control. PS-3 was compared with control compound to assess the residues involved in binding of PS-3 and SNB with target site in 2WAJ. Control compound was found to have Pi-pi ntercation with LYS, similarly PS-3 was also found to bind with LYS & MET through pi-pi interaction as well as with SER amino acid through H-bonding. Control and PS-3 showed binding affinity of -9.6 & -9.5 kcal/mol respectively. On the basis of these observations, it can be said that PS-3 showed molecular interaction similarity with control compound, SNB.(Fig 4)

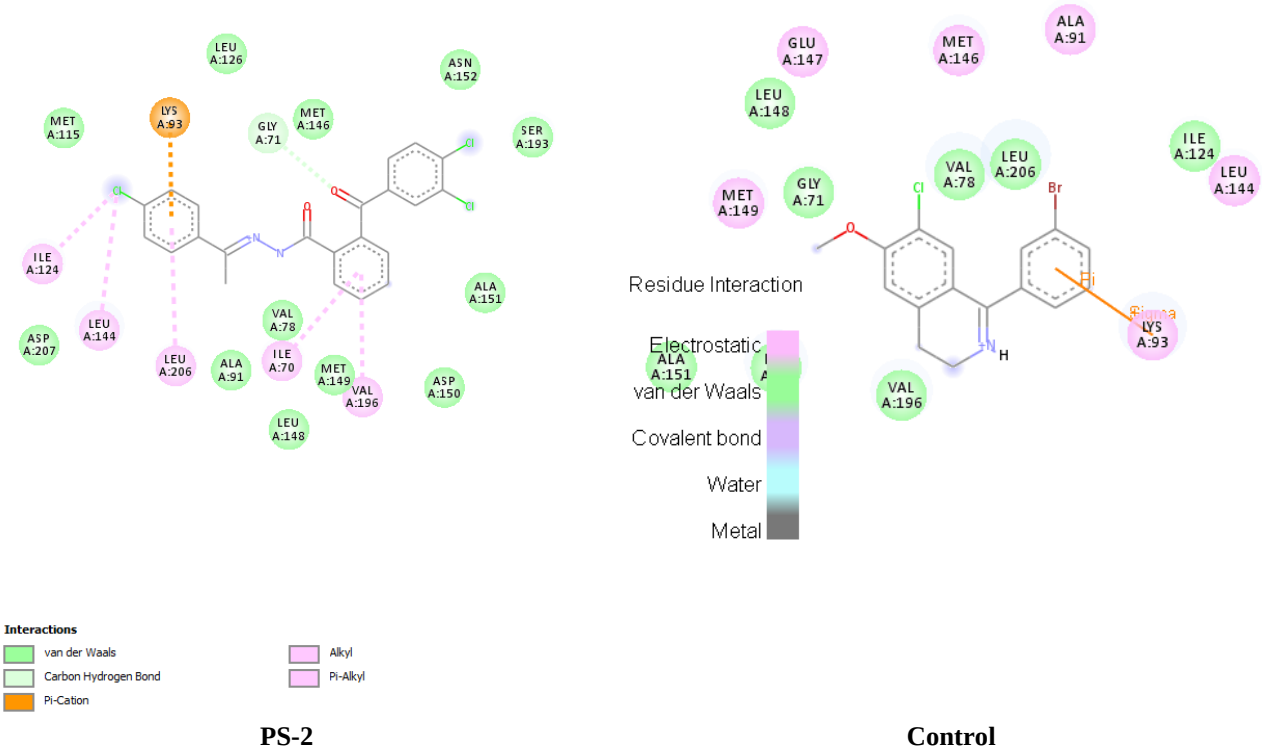
**Table 2. Ligands and Proteins used in anti-convulsant docking studies**

| Ligands to dock | PDB file used to dock | Target Name | Control used for docking studies (Co-crystallized ligand) |
|---|---|---|---|
| **PS-1** | 2ZDT | JNK3 | 46C |
| **PS-2** | 2WAJ | JNK3 | SNB |
| **PS-3** | 2WAJ | JNK3 | SNB |




**PS-1** **Control**

**Figure 2.** Molecular interaction of JNK3 with compound PS-1 and control compound,46C




**PS-2** **Control**

**Figure 3**. Molecular interaction of JNK3 with compound PS-2 and Control compound-SNB

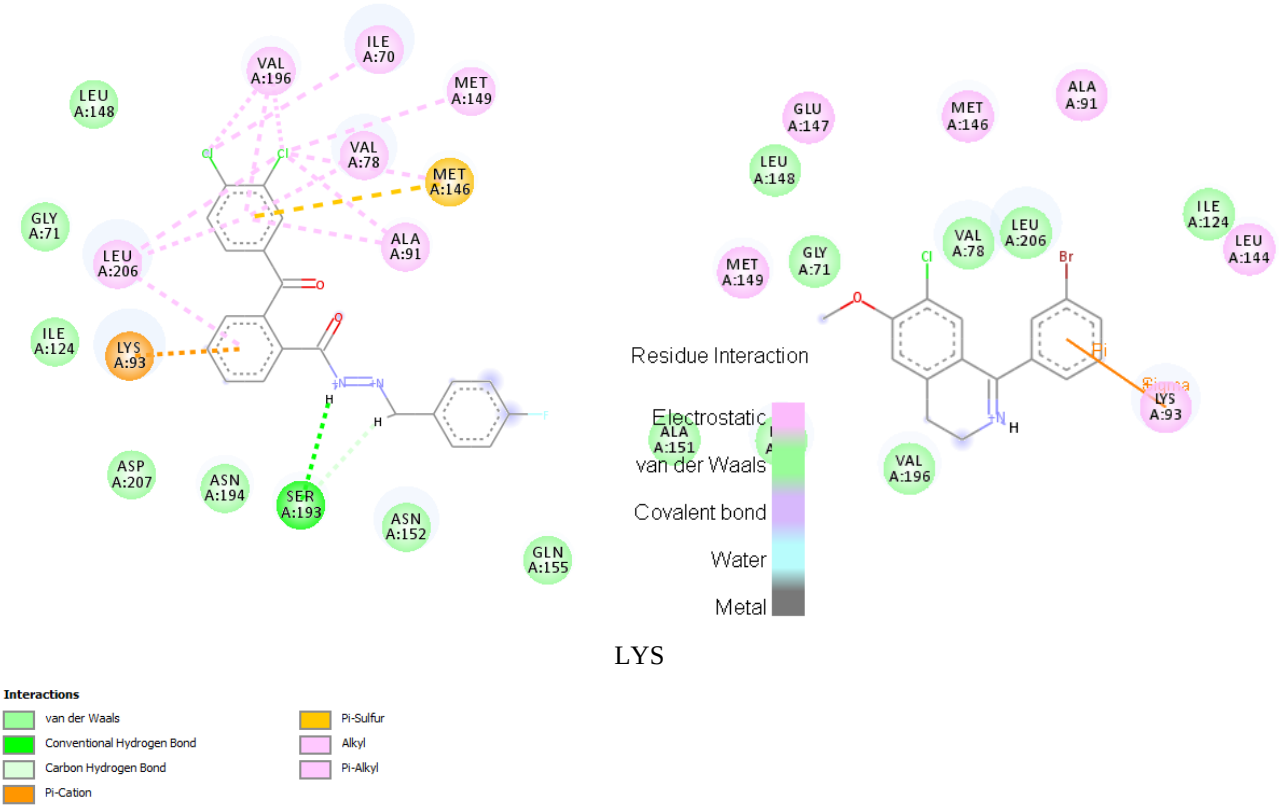
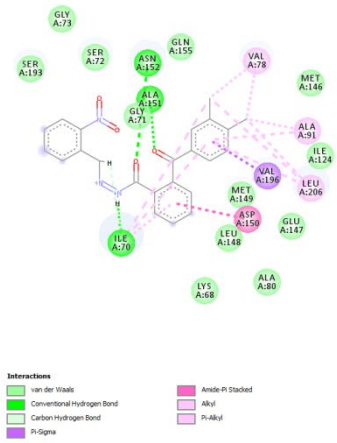
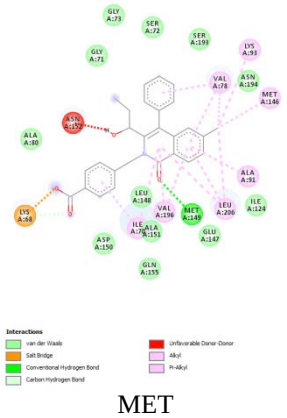



**Figure 4.** Molecular interaction of JNK3 with compound PS-3 and respective control compound SNB

**Table 3. Docking results of PS-1,PS-2,PS-3 against JNK3**

| Ligands to dock | PDB file used to dock | Control used for docking studies (Co-crystallized ligand) | Ligand | Control |
|---|---|---|---|---|
| PS-1 | 2ZDT | 46C |  ALA, GLY |  MET |
| | | | -9.8 kcal/mol | -10.4 kcal/mol |

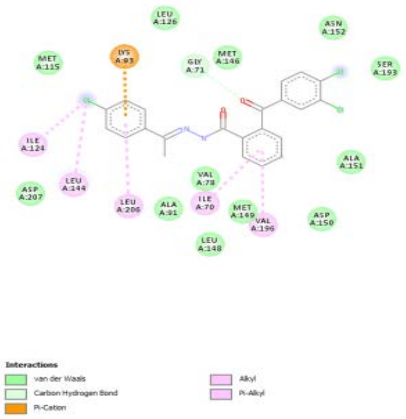
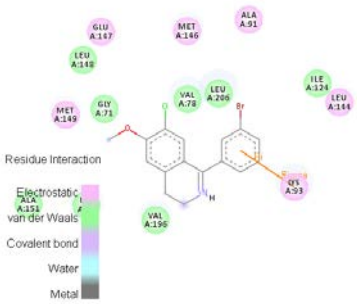
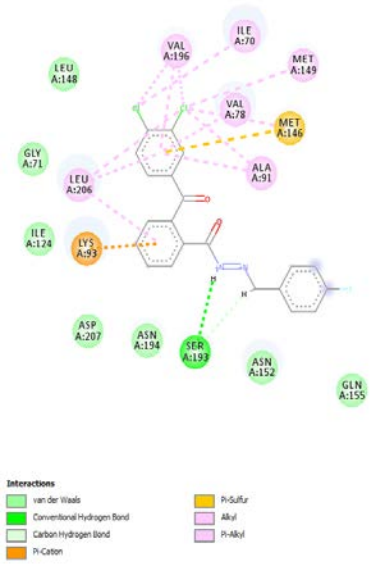
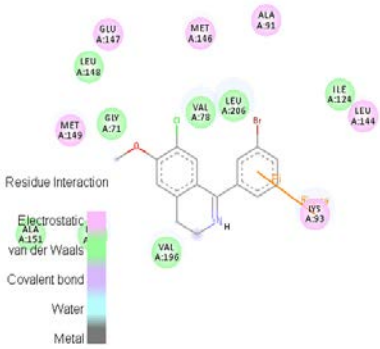
| Ligands to dock | PDB file used to dock | Control used for docking studies (Co-crystallized ligand) | Ligand | Control |
|---|---|---|---|---|
| PS-2 | 2WAJ | SNB |  LYS |  LYS |
| | | | -9.4 kcal/mol | -9.6 kcal/mol |
| PS-3 | 2WAJ | SNB |  LYS, MET, SER |  LYS |
| | | | -9.5 kcal/mol | -9.6 kcal/mol |

**Table 4. Type of interaction and Active site residues of ligands PS-1,PS-2,PS-3 involved in interaction with target sites in JNK3**

| Ligands to dock | PDB file used to dock | Control used for docking studies (Co-crystallized ligand) | Ligand (Binding residues) | Control (Binding residues) |
|---|---|---|---|---|
| **PS-1** | 2ZDT | 46C | H bond: ALA, GLY | H bond: MET |
| **PS-2** | 2WAJ | SNB | Pi-pi: LYS | Pi-pi: LYS |
| **PS-3** | 2WAJ | SNB | Pi-pi: LYS, MET, SER | Pi-pi: LYS |

### 3.4 NMR Spectra for synthesized Derivatives PS-1,PS-2 and PS-3

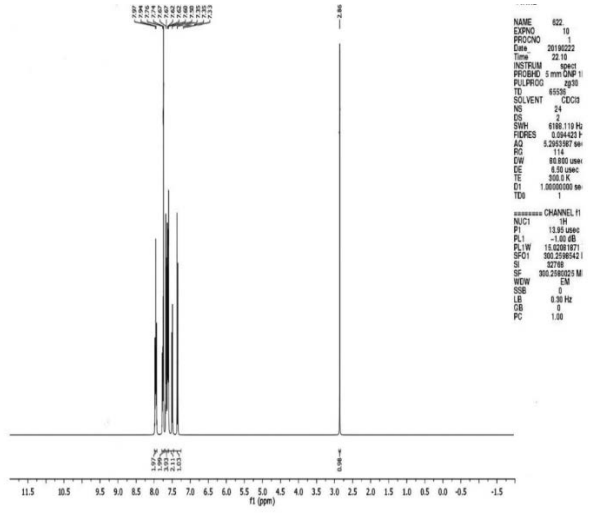


Figure 5: $^{1}$ H NMR Spectra of compound PS-1

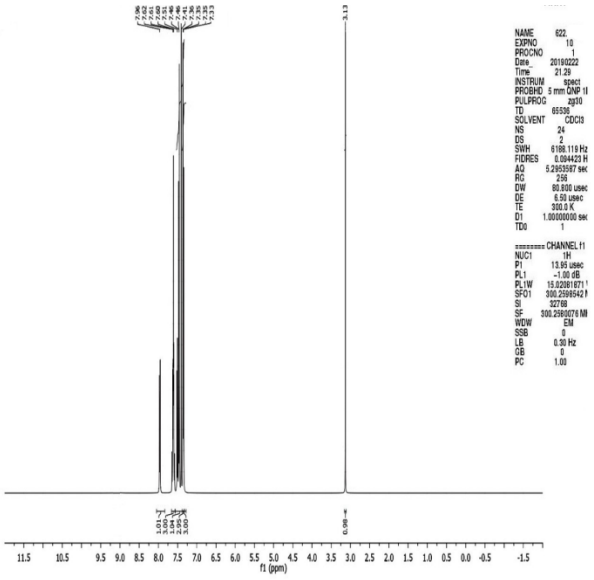


**Figure 6. $^{1}$ H NMR Spectra of compound PS-2**

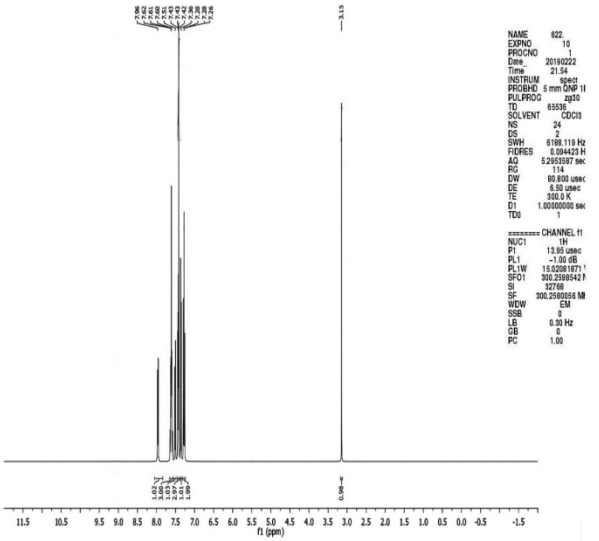


**Figure 7. $^{1}$ H NMR Spectra of compound PS-3**

## 4. CONCLUSION

A series of substituted hydrazones were synthesized, 2-(3,4-Dichloro-benzoyl)-benzoic acid (2-nitro-benzylidene)-hydrazide (PS-1),2-(3,4-Dichloro-benzoyl)-benzoic acid (4-chloro-benzylidene)-hydrazide (PS-2) and 2-(3,4-Dichloro-benzoyl)-benzoic acid (4-fluoro-benzylidene)-hydrazide (PS-3).Chemical process adopted for synthesizing these derivatives was using phthalic anhydride and Dichlorobenzene dissolved in Nitro benzene in the presence of Aluminum trichloride to obtain 2-(3,4-Dichloro-benzoyl)-benzoic acid as a starting compound. Further, Ethanol was added to treat this reaction followed by the addition of few drops of con. $H_2SO_4$ to obtain 2-(3,4-Dichloro-benzoyl)-benzoic acid ethyl ester. The ester was treated with hydrazine hydrate and ethanol. As a result, we obtained 2-(3,4-Dichloro-benzoyl)-benzoic acid hydrazide. The hydrazide was further treated with substituted Aldehyde in the presence of ethanol and glacial acetic acid to obtain the final compounds of PS series. The structure of synthesized compounds were confirmed by physical, analytical and elemental analysis. $^{1}$ H NMR Spectra of these compounds was studied to confirm their properties. Insilico analysis of Binding energy and affinity of PS-1,PS-2 and PS-3 have shown that binding energy of PS-3 i.e 2-(3,4-Dichloro-benzoyl)-benzoic acid (4-fluoro-benzylidene)-hydrazide is maximum for JNK protein (2WAJ ) and it is almost similar to the positive compound SNB which exists as co-crystallized ligand molecule with 2WAJ. Binding energy of PS-3 is -9.5 Kcal/mol which is quite close to binding energy of SNB as for SNB, binding energy is estimated to be -9.6 Kcal/mol. Our studies also signify that 2-(3,4-Dichloro-benzoyl)-benzoic acid (2-nitro-benzylidene)-hydrazide (PS-1) does not shows binding affinity for JNK-3 protein (2 ZDT) as for the positive control 46C, binding energy was -10.4 kcal/mole in contrast to -9.8 Kcal/mole observed for PS-1 compound. 2-(3,4-Dichloro-benzoyl)-benzoic acid (4-chloro-benzylidene)-hydrazide is also a potential lead molecule which has significant binding affinity towards JNK protein (2WAJ) as the binding energy for PS-2 was -9.4 Kcal/mole in comparison to -9.6 Kcal/mole observed for positive control, SNB. Our studies lead to conclusion that 2-(3,4-Dichloro-benzoyl)-benzoic acid (4-chloro-benzylidene)-hydrazide and 2-(3,4-Dichloro-benzoyl)-benzoic acid (4-fluoro-benzylidene)-hydrazide have a high potential to be considered as potent lead molecule to target JNK protein and can be considered to have anti-convulsant activity. These compounds can be used to decrease the hyperactive JNK signalling pathway and offer a potential treatment for epileptic patients.

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