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Biological Activities Of Schiff's Bases Synthesized From 1,3,4-Thiadiazole: A Computational Investigation

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Conflict of Interest

The authors declare that they have no conflict of interest.

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Abstract

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The research aims to investigate Schiff bases with a 1,3,4-thiadiazole nucleus to their potential therapeutic applications, particularly in cancer treatment. The computational studies have explained their binding attractions to protein targets and potential biological effects, highlighting their promise as novel therapeutic agents.

Keywords: Thiadiazole nucleus, biological effects, Schiff bases, Aldehyde/Ketone, Coumarin

INTRODUCTION

Thiadiazoles are five-membered heterocyclic aromatic compounds with two nitrogen and one sulfur atom.. Thiadiazole isomers, especially 1, 3, 4-thiadiazole, exhibit diverse biological activities. Thiadiazole derivatives are known for their therapeutic properties. A comprehensive overview of biological activity involving the thiadiazole fraction was published.

Schiff bases, synthesized from amines and carbonyls, are important in medical chemistry. Cancer research explores targeted therapies against oncogenic proteins. Schiff bases with a 1,3,4-thiadizole moiety are studied for their potential in drug discovery.

Thiadiazole compounds, exhibiting kinase inhibitory activity, hold significant promise in the field of cancer therapy. Enhancing their specificity for vascular endothelial growth factor receptor-2 (VEGFR-2) and other kinases is paramount in advancing oncology research. Schiff bases' binding affinities and interactions with oncology proteins were studied. Molecular docking and computational analyses suggest potential therapeutic efficacy.

The biological activity of Schiff bases with a 1,3,4-thiadizole moiety was examined in silico. "In silico biological activity" uses modelling, docking, and simulations as well as other computational techniques to forecast molecular effects. It is often used to assess how chemicals affect biological systems in drug discovery. A key technique in structural biology and computer-aided drug discovery, molecular docking predicts a ligand's main binding mechanism given a known protein structure. Effective docking techniques use scoring functions to rate possible dockings and navigate high-dimensional areas.

Research conducted investigated the binding affinities and molecular interactions of Schiff bases with oncology-related proteins. Molecular docking and computational analyses elucidated their potential therapeutic efficacy.

RESULT AND DISCUSSION

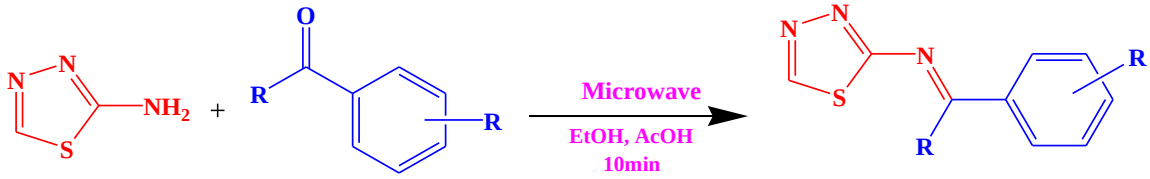
Synthesis of Schiff's Bases

All microwave-irradiated reactions were completed in 10 min with 42- 88% yield, whereas comparable conventional heating (refluxed) procedures yielded unsatisfactory yields with considerably lengthy reaction time periods of 3 hrs. For the production of compound 1a-8a and 1b-2b, the effects of microwave irradiation and conventional heating have been examined.

Experimental Section

0.005 moles of 1,3,4-thiadiazole of aldehyde/ ketone both are dissolved separately in ethyl alcohol (in minimum Quantity). Both are mixed together with constant stirring for 5-10min. catalytic amount that is 1-2 drops of glacial acetic acid was added in the same. The reaction mixture was microwaved for 10-15 min. The resultant mixture was tested in cold bath. The obtained precipitate was confirmed by TLC.

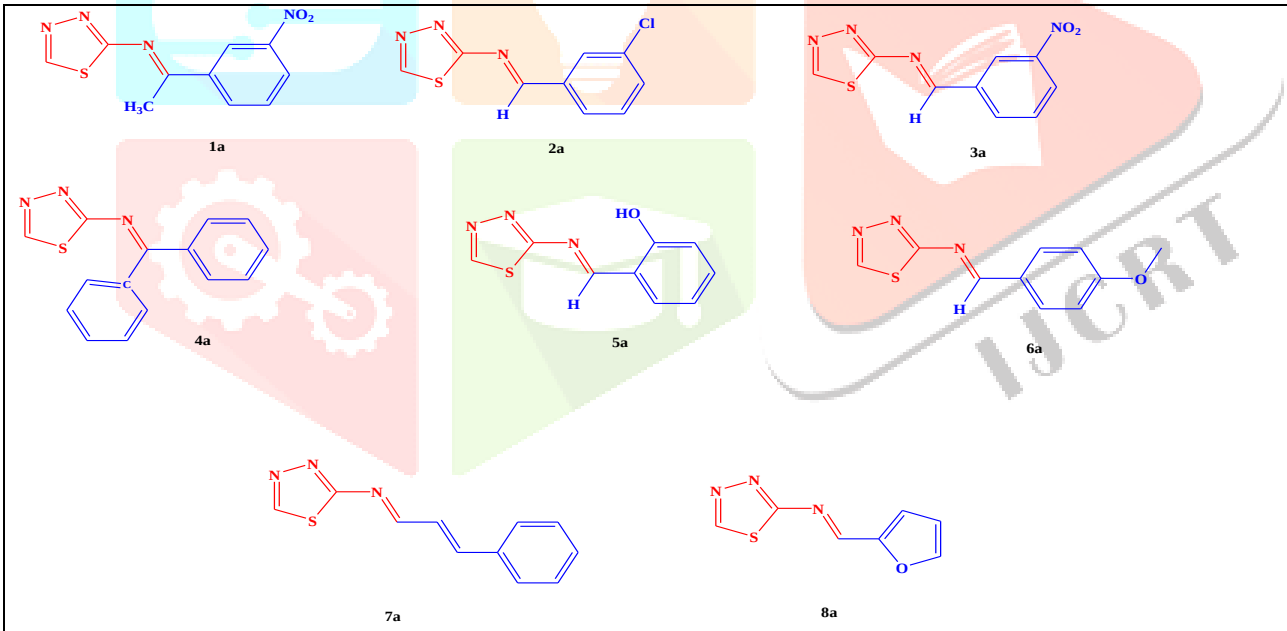
Scheme 1- Synthesis of Schiff's Bases by using 1,3,4-thiadiazole and aldehyde/ketone



1a-8a

Different substituents on the benzaldehyde and ketone were found to have no discernible impact on the reaction's outcome (Table 1, entries 1a–8a). These reaction conditions allowed for polar and halide substitution. Bulkier aldehyde doesn't have any reactivity problems either. The final product was produced via heterocyclic aldehydes without sacrificing yield.

table 1- substrate scope



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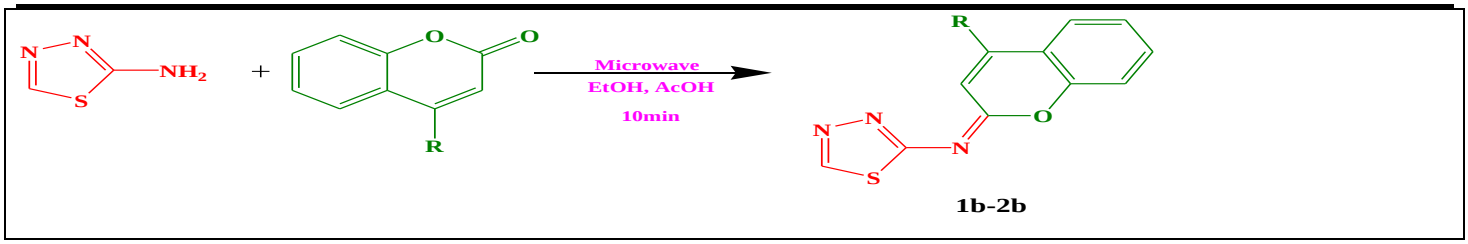
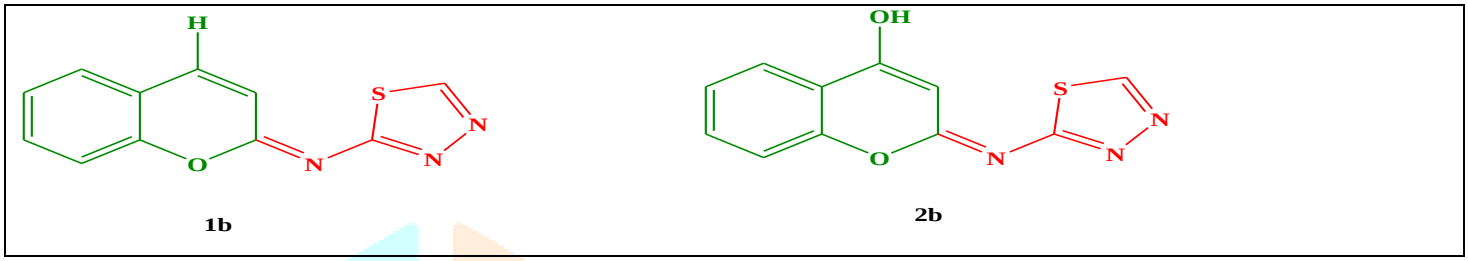
The structural scaffold of the Schiff bases obtained from the thiodiazole and coumarin molecule is shown in scheme 2, and the efficacy of the employed strategy is highlighted in table 2, which lists the derivatives and the corresponding reaction yields.



scheme 2- synthesis of Schiff's Bases by using 1,3,4-thiadiazole and Coumarin

table 2- Substrate scope



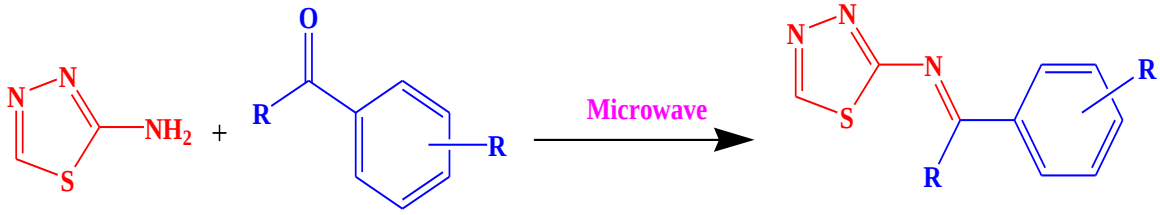
Substituted aldehydes and Acetophenone yielded 50-82% under ideal conditions, with less sensitivity to substrate structure.

table 2: Derivatives of thiadiazole were designed to get the Schiff's bases

Sr.No	R1	R2	Temperature	Time	Reaction Yield
1a	CH_3	m NO_2	70^0C	10 min	82%
2a	H	m Cl	70^0C	10 min	81%
3a	H	NO_2	70^0C	10 min	82%
4a	Ph	H	70^0C	10 min	54%
5a	H	OH	70^0C	10 min	50%
6a	H	OCH_3	70^0C	10 min	48%
7a	H	CH=CHPh	70^0C	10min	50%
8a	H	Furan	70^0C	10min	60%
1b	H	-	70^0C	15 min	76%
2b	OH	-	70^0C	15 min	88%

Optimization of synthesis of 1a-8a

It was also observed that in in different solvent, the reaction gives different performance therefore we studied a series of Solvent for the current protocol and results are incorporated in Table 2. (Table 2 entry 5).



1a-7a

Table 3-Different solvent study

Sr No.	Solvent	Time (Min)	Yield
1	Acetone	7	10%
2	Acetone	10	10%
3	Water	10	--
4	Methanol	10	15%
5	Methanol	1	15%
6	Methanol+ Chloroform	10	--
7	Ethanol	10	55%
8	Ethanol	15	80%

Spectral Analysis-

Laboratory-grade chemicals were used to synthesize Schiff bases, confirmed by TLC and spectral analyses. Microwave reactions in a closed glass vessel system confirmed the compounds' structures.

1a. 1−(3−nitrophenyl)−N−(1,3,4−thiadiazol−2−yl)ethan−1−imine.

Molecular formula: $C_{10}H_8N_4SO_2$. Molecular weight: 248 gm

FTIR: 3090 cm^{-1}(aromatic ring CH), 1682 cm^{-1}(−C=N),1338 cm^{-1}(−NO_2)

1525 cm^{-1}(C=C aromatic ring), 800 cm^{-1}(meta coupling),652 cm^{-1}(C−S−C),1400 cm^{-1}(thiadiazole ring)

C^{13}NMR:(125 MHz, $CdCl_3$,δin ppm)167.3(−C=N),134, 132.8, 132.4, 129.6, 129.5, 127.8 (C=C), 39.72 (C − C)

H^1 NMR: (500 MHz CdCl3, δin ppm) 8.38 (1H, S), 8.34 (1H, S), 8.3 (dd, 1H, J=8Hz, 3Hz)

2a. 1−(3−chlorophenyl) −N−(1,3,4−thiadiazol−2−yl) methanimine.

Molecular formula: $C_9H_6N_3SCl$. Molecular weight: 223.5 gm

FTIR: 3000 cm^{-1}(aromatic ring CH),1679 cm^{-1}(−C=N), 730.4 cm^{-1} (C−S−C), 547 cm^{-1} (C−Cl),1564 cm^{-1}(C=C),1410 cm^{-1}(thiadiazole ring)

C^{13} NMR:190.3 (thiadiazole ring), 151.1(imine), 140, 144,130, 124.3

H^1NMR: 8.03(1H, S),8.33(1H, S), 7.9(d,1H, J=8Hz), 7.5(d,1H, J=8Hz), 7.3(t,1H, J=8Hz)

3a. 1−(4−nitrophenyl) −N−(1,3,4−thiadiazol−2−yl) methenamine.

Molecular formula: $C_9H_6N_4SO_2$. Molecular weight: 234gm

FTIR: 3100 cm^{-1}(aromatic ring CH),1600 cm^{-1}(−C=N), 1564 cm^{-1}(C=C),1410 cm^{-1}(thiadiazole ring) 1510 cm^{-1}(C=C aromatic ring), 1450 cm^{-1}(−C−NO_2)

C^{13}NMR: (125MHz, $CdCl_3$, δin ppm): 190.3 (−C=N thiadiazole ring),151.1(−C=N−),140(−C−NO_2), 130.4, 124.3, 124.2

H^1 NMR: (500 MHz CdC_{l3},δin ppm):10.12(−C=N− thiadiazole ring), 10.0 (−C=N−), 8.341(d,2H, J=8Hz),8.025(d,2H, J=8Hz)

1b.2−(1,3,4−thiadiazol−2−yl) imino)- 2H−chromen.

Molecular formula: $C_{11}H_6N_3SO$Molecular weight: 228gm

FTIR: 2700 cm^{-1}(C−H aromatic ring), 1591 cm^{-1}(C=N thiadiazole ring),1679 cm^{-1}(−C=N), 1535 cm^{-1}(C=C aromatic ring),1014 cm^{-1}(−C−O−C−), 930 cm^{-1}(C−S)

C^{13}NMR: (125 MHz, dmso ,δ ppm):162.1,154.3,150.4,133.1,124.3,123.6,116.7,116.2

H^1 NMR: (500 MHz,dmso,δin ppm):) 9.0(1H,S) 7.96(=CH),6.3(=CH), 7.49(m,1H,J=8Hz, 3Hz)7.31(m,1H,J=8Hz, 3Hz)

2b. 2−(1,3,4−thiadiazol−2−yl) imino) −2H−chromen−4−ol.

Molecular formula: $C_{11}H_7N_3SO_2$Molecular weight: 245gm

FTIR: 3343 cm^{-1}(− OH),2700 cm^{-1}(C−H aromatic ring), 1594 cm^{-1}(C=N thiadiazole ring),1679 cm^{-1}(−C=N), 1535 cm^{-1}(C=C aromatic ring),1014 cm^{-1}(−C−O−C−), 930 cm^{-1}(C−S)

C^{13}NMR: (125 MHz, dmso,δ ppm):166.1,162.3,153.9,133.1,124.3,123.6,116.7,116.2

H^1 NMR: (500 MHz, dmso, δin ppm): 12 (intramolecular H bonding), 5.6 (=CH) 7.64 (m, 1H, J=8Hz, 3Hz) 7.63 (m, 1H, J=8Hz, 3Hz)

Molecular Docking Analysis

Schiff bases and thiadiazole derivatives inhibit kinase enzymes, crucial for cell signaling and cancer progression.

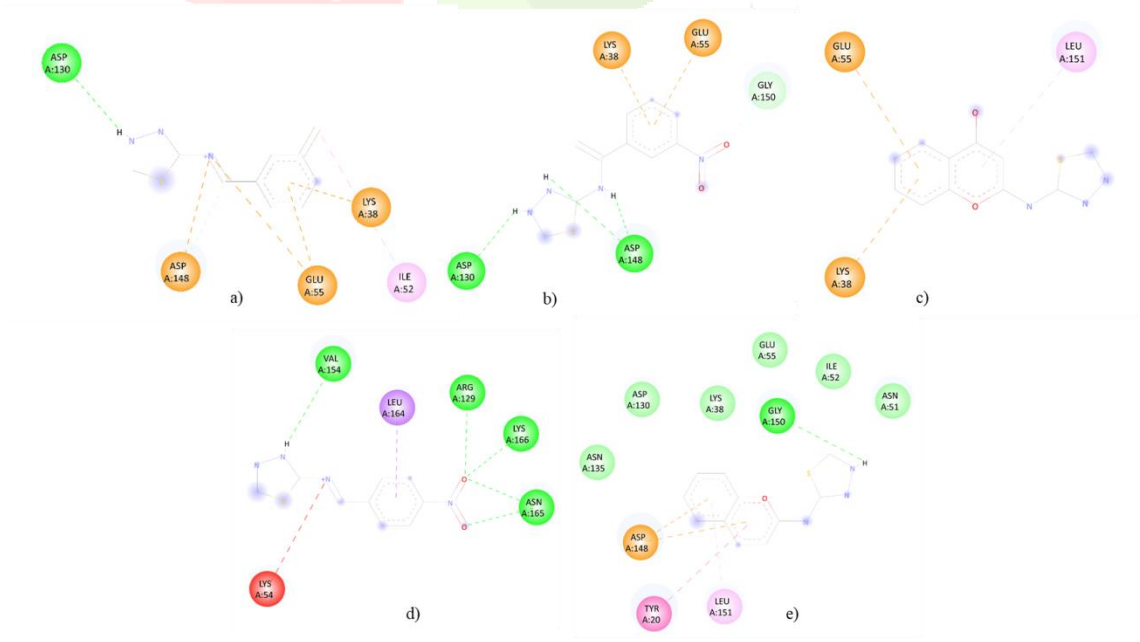


Figure 2: Pharmacophore of CHK1 and Schiff's bases nitro_acetophenone, c) 4-hydroxy_coumarin, d) 4-nitro_benzaldehyde, and e) coumarin

Table 2: Molecular docking studies of Schiff's bases with CHK1 (PDB Id- 1NVS) showing the binding affinity and pharmacophoric interactions depicted in Figure 2.

Sr No.	Ligands	Binding Affinity (kcal/mol)	Pharmacophore
a)	3-chlorobenzaldehyde	-5.1	Asp 130- conventional hydrogen bond; Ile 52- alkyl, and Lys 38, Glu 55, Asp 148- Pi- anion, cation and attractive charges
b)	3-nitroacetophenone	-5.6	Asp 130 and 148- conventional hydrogen bond; Gly 150- carbon hydrogen bond; and Lys 38, Glu 55- Pi- cation and anion bond.
c)	4-hydroxycoumarin	-5.7	Lue 151- Pi-alkyl; Lys 38, Glu 55- Pi-cation and Anion bond.
d)	4-nitrobenzaldehyde	-5.3	Arg 129, Val 154, Asn 165, Lys 166- conventional hydrogen bond; Lue 164- Pi- sigma; Lys 154- unfavored positive-positive interaction.
e)	Coumarin	-5.3	Gly 150- conventional hydrogen bond; Tyr 20- Pi- Pi T-shaped; Lue 151- Pi-alkyl; Asp 148- Pi- anion bond.

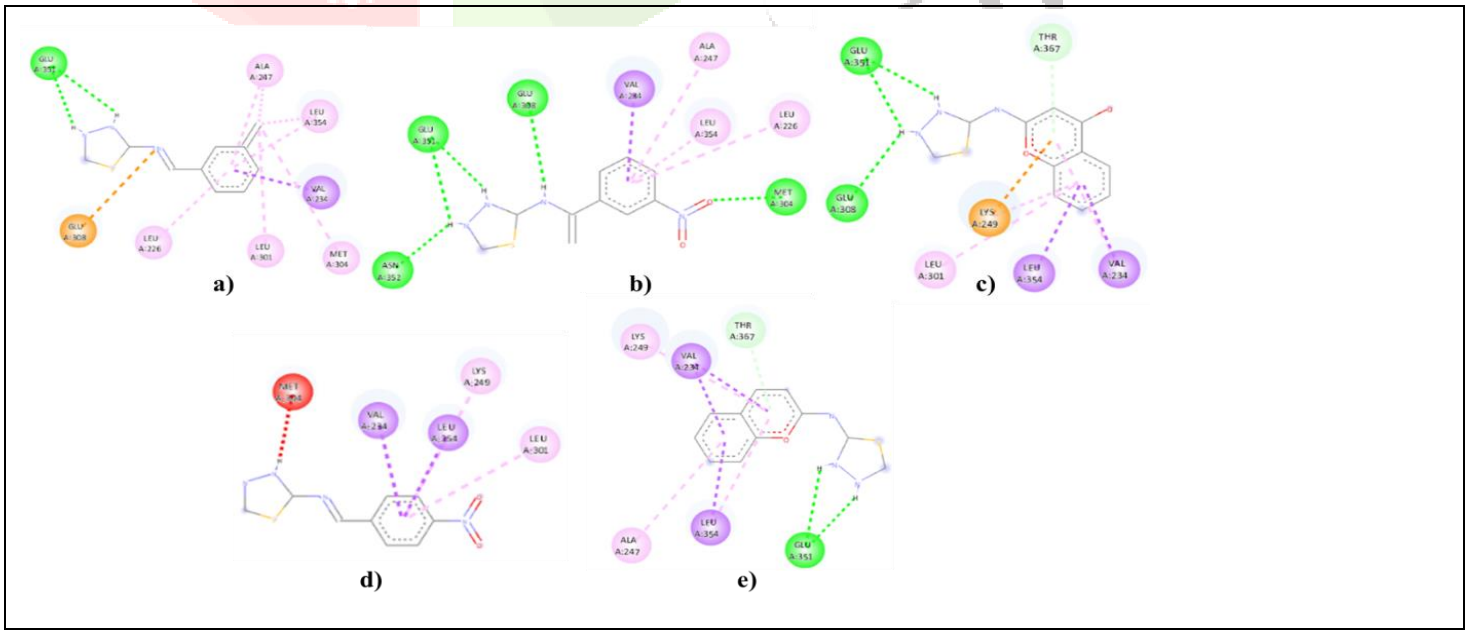
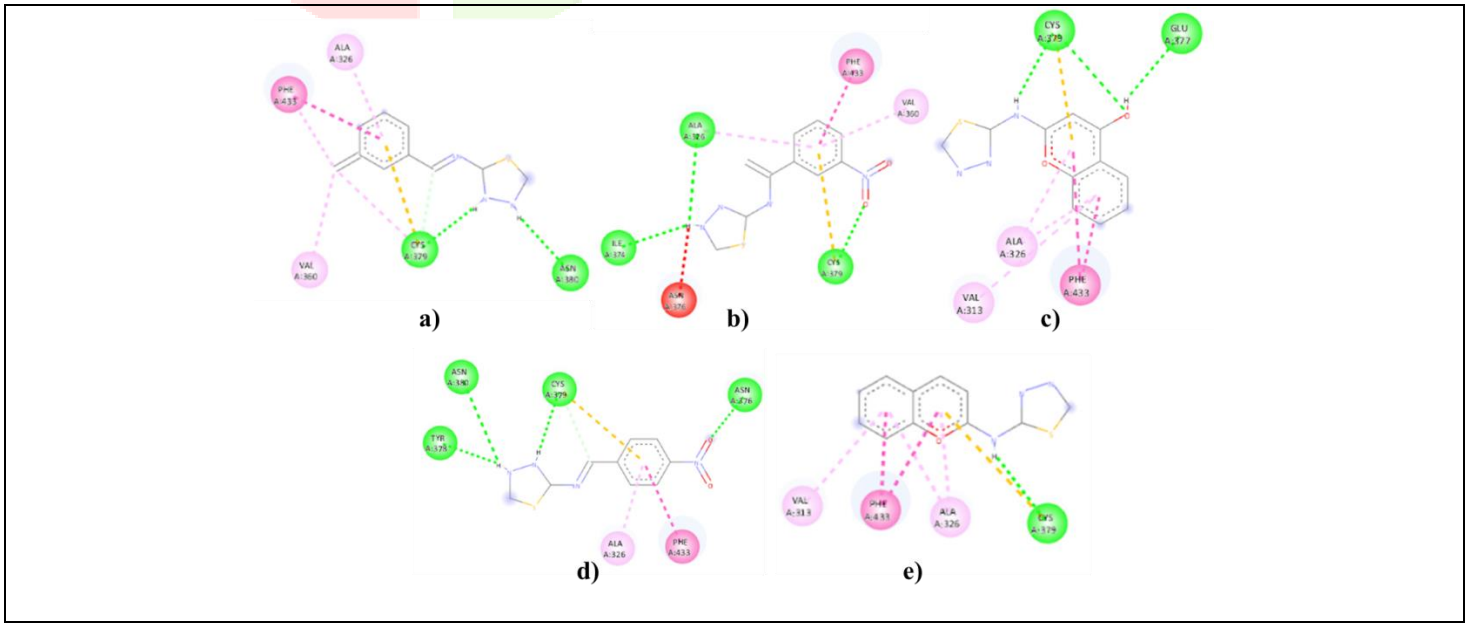


Figure 3: Pharmacophore of CHK2 and Schiff's bases a) 3-chlorobenzaldehyde, b) 3-nitroacetophenone, c) 4-hydroxycoumarin, d) 4-nitrobenzaldehyde, and e) coumarin

Table 3: Molecular docking studies of Schiff's bases with CHK2 (PDB Id- 2XK9) showing the binding affinity and pharmacophoric interactions depicted in Figure 3.

Sr No.	Ligand	Binding Affinity (kcal/mol)	Pharmacophore
a)	3-chlorobenzaldehyde	-7.1	Glu 351- conventional hydrogen bond; Glu- attractive charges; Val 234- Pi-sigma; Leu 226, Ala 247, Leu 301, 354 Met 304- Pi-alkyl
b)	3-nitroacetophenone	-7.7	Met 304, Glu 308, 351, Asn 352- conventional hydrogen bond; Val 284- Pi-sigma; Leu 226, Ala 247, Leu 354- Pi-alkyl
c)	4-hydroxycoumarin	-7.7	Glu 308, 351- conventional hydrogen bond; Thr 367- Pi-donor hydrogen bond; Val 234, Leu 354- Pi-sigma; Lys 249- Pi-cation; Leu 301- Pi-alkyl
d)	4-nitrobenzaldehyde	-7.3	Lys 249, Lue 301- Pi-alkyl; Val 234, Leu 354- Pi-sigma; Met 304- unfavored donor-donor
e)	Coumarin	-7.9	Glu 351- conventional hydrogen bond; Thr 367- Pi-donor hydrogen bond; Leu-354, Val 234- Pi-sigma; Ala 247, Lys 249- Pi-alkyl



Schiff's bases were docked with WEE1, and their binding affinity and pharmacophoric interactions are presented in Figure 4 and Table 4.

Sr No.	Ligand	Binding Affinity (kcal/mol)	Pharmacophore
a)	3-chlorobenzaldehyde	-7.7	Cys 379, Asn 380- conventional hydrogen bond; Phe 433- Pi-Pi stacked; Ala 326, Val 360- Pi-alkyl
b)	3-nitroacetophenone	-7.6	Ala 326, Ile 374, Cys 379- conventional hydrogen bond; Phe 433- Pi-Pi stacked; Val 360- Pi-alkyl; Asn 376- unfavorable donor-donor
c)	4-hydroxycoumarin	-8.1	Glu 377, Cys 379- conventional hydrogen bond;Phe 433- Pi-Pi stacked;Ala 326, Val 313- Pi-alkyl
d)	4-nitrobenzaldehyde	-7.8	Asn 376,380, Tyr 378, Cys 379- conventional hydrogen bond; Phe 433- Pi-Pi stacked; Ala 326- Pi-alkyl
e)	Coumarin	-8.1	Cys 379- conventional hydrogen bond; Phe 433- Pi-Pi stacked; Ala 326, Val 313- Pi-alkyl

Schiff's base ligands, particularly 4-hydroxy coumarin and coumarin derivatives, show promise in cancer therapy due to their strong interactions with CHK1, CHK2, and WEE1 kinases.

Conclusion

Schiff bases with a 1,3,4-thiadiazole ring system exhibit promising potential as cancer therapeutics due to their potent binding affinity to checkpoint kinases, as evidenced by molecular docking simulations and green chemistry approaches. The findings underscore the versatility of Schiff bases as molecular scaffolds for drug discovery, particularly in oncology. The study provides a platform for ongoing exploration and optimization of these compounds, with the ultimate goal of advancing medicinal chemistry and developing effective cancer therapeutics.

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