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SYNTHESIS, BIOLOGICAL EVALUATION AND DOCKING STUDIES OF NEW 5-(4-ISOPROPYL PHENYL)-1,3,4-THIADIAZOL-2-AMINE DERIVATIVES

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ABSTRACT

A straightforward synthetic pathway has been developed to prepare N-acylated derivatives of 5-(4-isopropyl phenyl)-1,3,4-thiadiazol-2-yl)amines **3(a-j)** by reacting 5-(4-isopropyl phenyl)-1,3,4-thiadiazol-2-amine (**2**) with various symmetrical acid anhydrides in pyridine solvent under refluxing conditions with good yields. This study involves simple, easy, cheap, inexpensive, and benign processes. Molecular docking investigations were done using an auto dock and found that **3i, 3h**, and **3a** had good binding energies with PDB ID: 5JZX. The antibacterial efficacy of compounds 3(a-j) was investigated against *S. aureus* and *E. coli*. Among all the compounds **3c, 3h & 3j** showed good strength towards gram-positive and compounds **3e, 3i & 3j** showed good strength on gram-negative bacteria. Further antifungal activity is done against *Candida albicans.* Most of the prepared compounds **3(a-j)** showed good activity against tested microorganisms.

Keywords: Thiadiazol-Amides, Anti-Bacterial Strength, Anti-Fungal Activity, Docking Study.

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INTRODUCTION

Microbial infections severely harm the living world. Due to the rapid development of medication resistance by microorganisms, it is essential to suggest innovative antibiotics bearing new frameworks with mechanisms to stop the spread of microbial infections.[1-2] Heterocyclic ring systems have emerged as effective scaffolds for numerous biological analyses in this context. These compounds are important in the development and identification of novel pharmacologically active molecules[3-4]. Thiadiazoles are a significant family of heterocyclic systems, that contain two nitrogen atoms[5] and one sulfur atom. Among them, 1,3,4-thiadiazoles have received significant focus in medicinal chemistry due to their recognized biological-activity[6] which includes antimicrobial[7], antifungal activity[8-10], anticancer[11-13], anti-tuberculosis[14], anti-oxidant[15], anticonvulsants[16], antidepressant and anxiolytic[17-19], antihypertensive.[20] 1,3,4-thiadiazole scaffolds are thermally and chemically stable, highly aromatic, and have extremely weak bases. 1,3,4-thiadiazole moieties are extensively used in materials chemistry, agriculture[21], and pharmaceuticals[22]. Acetazolamide, methazolamide, and megazole are well-known 1,3,4-thiadiazole compounds. 4-Isopropylbenzoic acid hydrazide (1) is a fine white powder that is widely used in organic synthesis and pharmaceutical development. It can be used as a reagent in the synthesis of 2-(4-isopropylphenyl) propanoic acid, which is used to treat Alzheimer's disease. Hence, based on the biological significance and applications of the 1,3,4-thiadiazoles, we decided to synthesize a library of new compounds **3(a-j)** to develop antimicrobial agents with increased potency.

EXPERIMENTAL

All reagents as well as solvents are of the A.R. grade. Electrothermal melting point meters are utilized to document the melting temperatures. For CHNS analysis, a "PerkinElmer 2400 CHNS Organic Elemental Analyzer" was used. We employed analytical TLC to monitor the progress of the reaction. ^{1}H spectra on JEOL 400 and ^{13}C NMR spectra on JEOL 100 MHz. IR spectral data was recorded using a Bruker spectrometer. To capture the mass spectra, ESI-MS was employed.

General Procedure

Preparation of 5-(4-Isopropyl phenyl)-1,3,4-Thiadiazol-2-Amine (2)

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4-isopropyl benzo-2-carbohydrazides (1) (0.02 moles), ammonium thiocyanate (0.06 moles), and con. HCl (7 ml) mixture was taken in ethanol (45 ml) and refluxed for about 20 hrs to acquire Acyl thiosemicarbazide. The pure thiosemicarbazide (0.05mmol) sample was heated with sulfuric acid (10 ml) in a water bath and then neutralized with ammonia, resulting in the production of compound (2).

Synthesis of Acylated N-(5-(4-Isopropyl phenyl)-1,3,4-Thiadiazol-2-yl) Amine Derivatives 3 (a-j):
Compound-2 (10 mol) was taken in 10 ml of pyridine and then anhydrides (10 moles) were added and refluxed for 12 hrs. Then the resulting residue was dried with a saturated $NaHCO_3$ solution (10 ml) to acquire the corresponding pure-titled products with a good yield (3a).

Table-1: Thermophysical Data of New Compounds 2 and 3(a-j)

S. No	Compounds	Molecular Formula	Molecular Weight	M.P./ B.P. (^{0}C)	Yield (%)
1	2	$C_{11}H_{13}N_3S$	219.30	369.3°C	68%
2	3a	$C_{14}H_{17}N_3OS$	275.37	203-205°C	71%
3	3b	$C_{15}H_{19}N_3OS$	289.40	218-220°C	72%
4	3c	$C_{16}H_{21}N_3OS$	303.42	196-198°C	66%
5	3d	$C_{16}H_{21}N_3OS$	303.42	213-215°C	79%
6	3e	$C_{17}H_{23}N_3OS$	317.45	188-190°C	80%
7	3f	$C_{18}H_{25}N_3OS$	331.48	172-174°C	67%
8	3g	$C_{19}H_{27}N_3OS$	345.50	174-176°C	70%
10	3h	$C_{20}H_{29}N_3OS$	359.53	173-175°C	77%
11	3i	$C_{21}H_{31}N_3OS$	373.56	162-164°C	80%
12	3j	$C_{23}H_{35}N_3OS$	401.61	153-155° C	55%

Characterization

Compound-2

IR (KBr, ν cm−1): 3270.84, 3092.47 (-NH_2-stretching), 2959.41 (aromatic C-H-stretching), 2870.87, 2771.40, 1630.18 (C=N, Stretching, thiadiazol ring), 1567.43,1468.70 (C=C, aromatic ring), 1055.51(C-S-C, stretching, thiadiazol ring); proton-NMR(400 MHz, *Dimethyl sulfoxide-D_6*): δ1.26 (d, 6H, methyl), 2. 96 (m, 1H, -CH), 7.32 (d, 2H, (-CH-)$_2$) 7.50 (brs, 2H, -NH_2, D_2O-Exchangeable), 7.64 (dd, 2H, (-CH-)$_2$); ^{13}CNMR 400MHz (DMSO-d_6, δ, ppm): 23.79, 23.94, 33.64, 38.87, 39.29, 126.78, 127.46, 128.80, 150.71, 157.25 (C_2- thiadiazol ring), 168.56 (C_5- thiadiazol ring); LCMS (m/z): 220.3 $[M+H]^+$; Elemental Analysis: Found % (Calculated %): C, 60.24 (60.29); H, 5.97 (6.10); N, 19.16 (19.22); S, 14.62 (14.70).

N(5-(4-isopropylphenyl)-1,3,4-thiadiazol-2-yl)propionamide-3(a)

IR (KBr, υ cm^{-1}): 3150.66 (-NH-stretching), 3015.25, 2938.31(aromatic C-H, stretching), 1608.80 (C=N, thiadiazol ring), 1460.59 (-C=C- stretching, aromatic ring), 1058.06 (C-S-C, stretching, thiadiazol ring); ^{1}H NMR (400 MHz, *Dimethyl sulfoxide-D_6*): δ1.09 (t, 3H, methyl), 1.24(d, 6H, (methyl), 2.54 (q, 2H, methylene), 2.97 (m, 1H), 7.40 (d, 2H), 07.84 (dd, 2H), 12.58 (brs, 1H, -NH-, D_2O Exchang); ^{13}C-NMR 400 MHz: δ 9.13, 23.71, 28.33, 33.46, 38.87, 39.08, 40.12, 127.07, 127.43, 127.97, 151.33, 158.14 (C_2-thiadiazol ring), 161.83 (C_5- thiadiazol ring) 172.38 (C=O amide carbon); LCMS (m/z): 276.5$[M+H]^+$; Elemental Analysis: Found % (Calculated %): C-61.06 (61.17); H-6.22 (6.33); N-15.26 (15.31); O-5.81 (5.89); S-11.64 (11.71).

N(5-(4-Isopropylphenyl) -1,3,4-Thiadiazol-2-yl) Butyramide -(3b)

1H-NMR(400 M. Hz, *Dimethyl sulfoxide-D6*): δ 0.92 (t, 3H, -methyl), 1.24 (d, 6H, methylene), 01.67 (m, 2H), 2.50 (t, 2H, methylene), 2.98 (m, 1H), 3.45 (br,1H, -NH-), 7.4 (dd, 2H), 7.85 (dd, 2H); LCMS (m/z): 290.5$[M+H]^+$; Elemental Analysis : Found % (Calculated %): C, 62.25 (62.31); H, 6.62 (6.71); N, 14.52 (14.59); O, 5.53 (5.61); S, 11.08 (11.16).

N(5-(4-Isopropylphenyl) -1,3,4-Thiadiazol-2-yl) Pentamide-(3c)

1H-NMR(400 M.Hz, *Dimethyl sulfoxide-D6*): δ 0.91 (t, 3H, methyl), 1.24 (d, 6H), 1.34 (m ,2H, methylene), 01.62 (pent, 2H), 2.50 (t, 2H), 02.97 (m, 1H), 3.37 (brs, 1H, -NH-),7.41 (dd, 2H), 7.86 (dd,

2H); LCMS (m/z): 304.5[M+H]$^+$; Anal. Calc. C, 63.33 (63.41); H, 6.98 (7.11); N, 13.85 (13.92); O, 5.27 (5.32); S, 10.57 (10.62).

N(5-(4-Isopropylphenyl) -1,3,4-Thiadiazol-2-yl) Pivalamide-(3d):
1H-NMR(400 M.Hz, *Dimethyl sulfoxide-D6*): δ 1.24 (d, 6H, methyl), 1.32 (s, 9H), 2.96 (m, 1H), 7.40 (dd, 2H), 07.85 (dd, 2H), 12.31 (brs, 1H, -NH-); LCMS (m/z): 304.5[M+H]$^+$; Anal. Calc. C, 63.33 (63.42); H, 6.98 (7.08); N, 13.85 (13.92); O, 5.27 (5.32); S, 10.57 (10.62).

N(5-(4-Isopropylphenyl) -1,3,4-Thiadiazol-2-yl) Hexanamide-(3e)
1H-NMR (400 M.Hz, *Dimethyl sulfoxide-D6*): δ 0.89 (t, 3H, methyl), 1.24 (d, 6H, 1.25- 1.33 (m, 4H), 01.66 (2H), 2.51 (t, 2H), 2.95 (m, 1H), 07.41 (dd, 2H), 07.86 (dd, 2H), 12.59 (brs, 1H, -NH-); LCMS (m/z): 318.4 [M+ H] $^+$, Anal. Calc. C, 64.32 (64.39); H, 7.30 (7.38); N, 13.24 (13.29); O, 5.04 (5.13); S, 10.10 (10.18).

N(5-(4-Isopropyl phenyl) -1,3,4-Thiadiazol-2-yl) Heptanamide-(3f)
1H-NMR(400 M.Hz, *Dimethyl sulfoxide-D6*): δ 0.88 (t, 3H, methyl), 1.22 (d, 6H), 01.27 (m, 6H), 01.63 (m, 2H), 2.52 (t, 2H), 02.99 (m, 1H), 7.41 (dd, 2H), 7.86 (dd, 2H), 12.62 (brs, 1H, -NH-); LCMS (m/z): 332.5[M+ H] $^+$, Analy. Calc. C, 65.22 (65.31); H, 7.60 (7.68); N, 12.68 (12.73); O, 4.83 (4.89); S, 9.67 (9.73).

N(5-(4-Isopropyl phenyl) -1,3,4-Thiadiazol-2-yl) Octanamide-(3g)
1H-NMR(400 M.Hz, *Dimethyl sulfoxide-D6*): δ 0.87 (t, 3H, methyl), 1.22 (d, 6H), 01.28 (m, 8H), 01.61 (m, 2H), 02.39 (t, 2H), 02.95 (m, 1H), 3.42 (brs, 1H, -NH-), 07.37 (dd, 2H), 07.82 (dd, 2H); LCMS (m/z): 346.6 [M+H]$^+$; Analy. Calc. C, 66.05 (66.11); H, 7.88 (7.93); N, 12.16 (12.21); O, 4.63 (4.69); S, 9.28 (9.32).

N(5-(4-Isopropyl phenyl) -1,3,4-Thiadiazol-2-yl) Nonanamide-(3h)
1H-NMR (400 M.Hz, *Dimethyl sulfoxide-D6*): δ0.87 (t, 3H, methyl), 01.22 (d, 6H), 1.23-1.27 (m, 10H), 1.62 (m, 2H), 2.46 (t, 2H), 02.92-2.98 (m, 1H), 03.45 (brs, 1H, -NH-), 7.40 (dd, 2H), 7.85 (dd, 2H); LCMS (m/z): 360.6 [M+H]$^+$; Anal. Calc. C, 66.81 (66.89); H, 8.13 (8.19); N, 11.69 (11.73); O, 4.45 (4.51); S, 8.92 (8.99).

N(5-(4-Isopropyl phenyl) -1,3,4-Thiadiazol-2-yl) Decanamide-(3i)
1H-NMR(400 M.Hz, *Dimethyl sulfoxide-D6*): δ 0.86 (t, 3H, methyl), 01.24 (d, 6H), 1.23-01.59 (m, 12H), 1.62 (m, 2H), 02.48 (t, 2H), 2.91-2.98 (m, 1H), 03.34 (brs, 1H, -NH-), 7.41 (dd, 2H), 7.86 (dd, 2H); LCMS (m/z): 374.6 [M+H]$^+$; Anal. Calc. C, 67.52 (67.59); H, 8.36 (8.41); N, 11.25 (11.35); O, 4.28 (4.33); S, 8.58 (8.63).

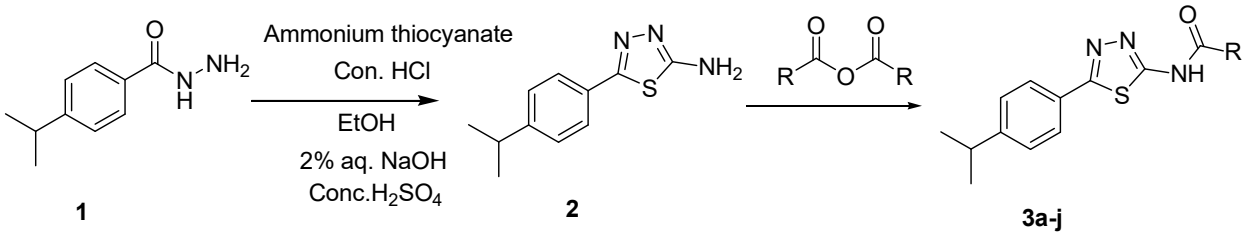
N(5-(4-isopropylphenyl) -1,3,4-thiadiazol-2-yl) dodecanamide-(3j)
1H-NMR (400 M.Hz, *Dimethyl sulfoxide-D6*): δ 0.82-0.86 (t, 3H, methyl), 1.21-1.26 (m, 16H), 01.59-1.62 (m, 6H), 02.44-2.50 (m, 4H), 02.91-2.99 (m, 1H), 3.20 (brs, 1H, -NH-), 7.40 (dd, 2H), 7.84 (dd, 2H); LCMS (m/z): 402.39 [M+H]$^+$; Anal. Calc. C, 68.78 (68.82); H, 8.78 (8.83); N, 10.46 (10.49); O, 3.98; S, 7.98 (8.04).

RESULTS AND DISCUSSION

All the titled new compounds were synthesized **3(a-j)** from the compound-**2** reaction with various symmetrical acid anhydrides (R=a-j) in the presence of pyridine under reflux conditions. The structure of compound **3(a-j)** was verified by spectral data.

The IR absorption values of the compound (**2**) structure analysis based on IR absorptions of the NH2 primary amine group have a stretching vibration at 3270 cm^{-1}. IR absorptions of the -C-H (aromatic and aliphatic), -C=C- (stretching, aromatic), -C=N- (thiadiazol ring), and C-S-C functional groups vibration at 3092, 2959, 2870, 1630 and 829 cm^{-1} respectively. The IR absorption values of the compound (3a) structure analysis based on IR absorptions of the NH- secondary amine group have a stretching and bending vibration at 3150, and 1460 cm^{-1} respectively. IR absorptions of the -C-H (aromatic and aliphatic), -C=C- (stretching, aromatic), -C=N (thiadiazol ring), and C-S-C functional groups vibration at 3015, 2938, 2905, 1699, and 838 cm^{-1}, respectively. ^{1}HNMR Spectroscopy chemical shift values of

compound-2 structure values are the aromatic protons were detected between 7.3 to 7.6 ppm, the -NH_2 broad peak singlet located at 7.4 ppm (D_2O exchangeable), the isopropyl group -CH- group observed as multiple between 2.8 to 2.9 ppm and the remaining six protons of aliphatic methyl protons were located at 1.20 to 1.26 ppm.



R=

a. -CH_2-CH_3 (Propionic Anhydride)
b. -CH_2-CH_2-CH_3 (Butyric Anhydride)
c. -CH_2-$(CH_2)_2$-CH_3 (Pentanoic Anhydride)
d -C-$(CH_3)_3$ (Pivalic Anhydride)
e. -CH_2-$(CH_2)_3$-CH_3 (Hexanoic Anhydride)
f. -CH_2-$(CH_2)_4$-CH_3 (Heptanioc Anhydride)
g. -CH_2-$(CH_2)_5$-CH_3 (Octanoic Anhydride)
h. -CH_2-$(CH_2)_6$-CH_3 (Nonanoic Anhydride)
i. -CH_2-$(CH_2)_7$ -CH_3 (Decanoic Anhydride)
j. -CH_2-$(CH_2)_9$ -CH_3 (Dodecanoic Anhydride)

Scheme-1: Synthetic Process for Synthesis of New Amides 3(a-j)

^{1}HNMR Spectroscopy chemical shift values of the compound **(3a**) structure values are the aromatic protons were seen between 7.41 to 7.84 ppm, the -NH- broad peak singlet peak located at 12.58 ppm (D_2O exchangeable), the isopropyl group -CH- group observed as multiplate at 2.97 ppm, the methyl group of the side chain at 1.09 ppm, the -CH_2- group attached to carbonyl at 2.54 ppm and the remaining six protons of two methyl protons were observed at 1.24 ppm. ^{13}C NMR spectroscopy of the compound (**2**) signals C-2 and C-5 carbons observed at 157.25 (C_2- Thiadiazol ring), 168.56 (C_5- Thiadiazol ring) ppm. Compound (**3a**) signals of carbonyl carbon are seen at 172.38 ppm.

Antibacterial Activity

Luria-Bertani Agar (LBA) dilution method is employed to test the efficacy of synthetic compounds against bacteria. The antibacterial ability of new compounds was assessed using *Staphylococcus aureus*, and *E. coli* bacteria with ampicillin reference (**Table-2**). Compounds **3c, 3e, 3i, and 3j** showed better antibacterial strength at 100 µg/ml concentration on *E. coli* with the inhibition zones 11, 11, and 14 mm. Compounds **3c, 3j, and 3h** showed good antibacterial strength at 100 µg/ml concentration on *S. aureus,* with the zones of inhibition at 13,12 and 12 mm respectively.

Antifungal Activity

The spread plate approach is used to study the antifungal ability of the new derivatives with Candida albicans fungus. The analysis of antifungal data (**Table-2**) revealed that all the synthesized compounds **3 (a-j)** exhibited the most promising results against the tested fungus *Candida albicans*. The compounds **3c** and **3e** showed zones of **16 mm** of good antifungal activity at **100 µg/ml** while the compounds **3i** and **3h** showed zones of **17 mm** which is more effective than the standard compound Fluconazole.

Table-2: The Antimicrobial Properties of Compounds 3(a-j)

Compounds	Inhibition of microorganisms (mm)											
	Anti-Bactrial Activity								Anti Fungal Activty			
	Staphylococcus aureus				*E. Coli*				*Candida albicans*			
	25µg	50µg	75µg	100µg	25µg	50µg	75µg	100µg	25µg	50µg	75µg	100µg
2	0	0	0	0	0	0	6	6	0	10	14	15
3a	0	0	0	6	0	0	0	0	0	0	0	14
3b	0	7	7	11	0	0	0	0	0	7	13	15
3c	0	0	11	13	0	0	0	0	0	0	10	16

3d	0	6	8	8	0	0	8	8	0	0	10	13
3e	6	6	6	8	6	8	8	11	0	0	9	16
3f	0	0	7	10	0	0	6	0	9	11	12	15
3g	0	0	0	8	0	0	0	8	0	0	0	15
3h	0	0	9	12	0	0	0	6	0	0	10	17
3i	0	0	0	0	0	0	0	11	0	0	14	17
3j	0	9	9	12	0	10	12	14	0	0	0	0
Ampicillin	17	19	23	20	16	18	20	26	-	-	-	-
Fluconazole	-	-	-	-	-	-	-	-	0	0	8	15

Docking Study

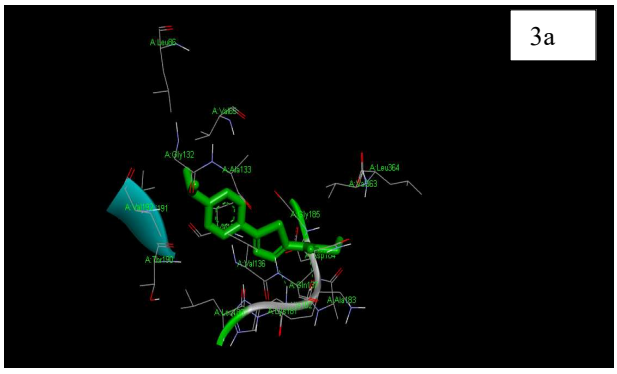
The Auto Dock Vina software[23] was utilized for the process of molecular docking. Applied protein crystal structures were retrieved from the 'RCSB Protein' DataBank.[24] All the synthesized amide derivatives are verified for their binding efficiency against the 'PDB ID-5JZX' protein. The computational studies of titled derivatives well accord with experimental results. Among all the synthesized compounds **3i, 3a,** and **3h** showed good binding energy against PDB ID-5JZX. Compounds **3i** (-8.67 kcal/mol), **3a** (-8.48 kcal/mol), and **3h** (-8.46 kcal/mol) demonstrated better binding affinity.

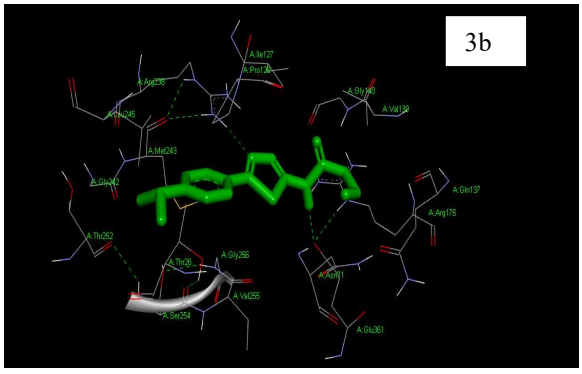
Table-3: Binding Energies of Titled Compounds 3(a-j) Against PDB ID: 5JZX

S. No.	Compounds	Binding Energies (Kcal/mol)		
		PDB ID-5JZX		
		Binding energy	No. of Hydrogen-Bonds	Protein interactions
1	2	-7.46	5	VAL65(2), GLY69(2), ALA67
2	3a	-8.48	3	GLN137, HIS182(2)
3	3b	-8.26	2	GLU361, ARG238
4	3c	-7.95	4	SER130(2), SER70(2), ASN71
5	3d	-8.07	3	SER130, SER70, GLY68
6	3e	-8.21	5	SER130(2), GLY68, ASN71, SER70
7	3f	-8.29	3	SER130(2), GLY68
8	3g	-7.93	3	ASN71, SER130, SER70
10	3h	-8.46	1	SER70
11	3i	-8.67	2	SER130, ASN71

CONCLUSION

In conclusion, we have successfully produced new N-acylated derivatives **3(a-j)**. The benefits of the current approach include easy work-up, mild reaction conditions, readily available, affordable reagents, and high yields. The antibacterial evaluation showed that compounds **3c, 3j, and 3h** performed good antibacterial strength on *S. aureus*, whereas compounds **3c, 3e, 3h, and 3i** showed good anti-fungal activity. Among the synthesized derivatives, compounds **3a**, **3i,** and **3h** are shown good docking scores.





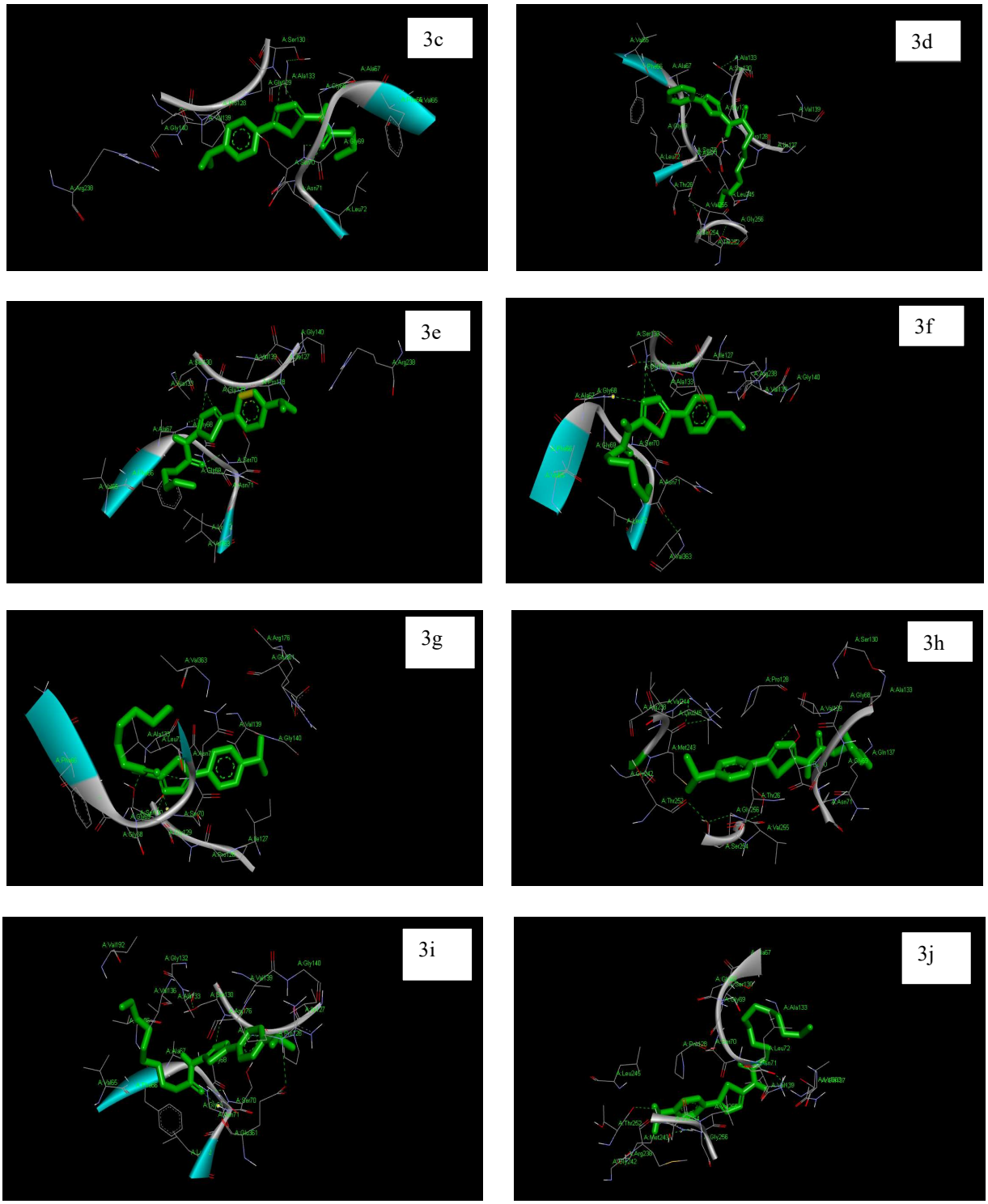


Fig.-1: Binding Poses and interactions of 3(a-j) to the Binding Sites of Target Proteins

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing, and approved the final draft for publication. The research profile of the authors can be verified from their ORCID IDs, given below:

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