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Research Article

Design, Synthesis, And Molecular Docking Study of Novel Diclofenac Hybridized Heterocyclic -1,2,4-Triazol Derivative as Potent Anti-Inflammatory Anti-Cancer Agent

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ABSTRACT

Cancer and inflammation are closely associated pathological conditions in which chronic inflammatory processes contribute significantly to tumor initiation, progression, and metastasis. Non-steroidal anti-inflammatory drugs (NSAIDs), particularly diclofenac, have demonstrated promising anti-inflammatory and anticancer activities through inhibition of cyclooxygenase (COX) enzymes. However, the long-term use of diclofenac is associated with adverse effects such as gastrointestinal toxicity and limited selectivity. To overcome these limitations, the present research focuses on the design and synthesis of novel diclofenac hybridized heterocyclic 1,2,4-triazole derivatives with improved therapeutic potential. The study involves the synthesis of diclofenac-based 1,2,4-triazole derivatives through a multi-step synthetic pathway including esterification, hydrazide formation, and cyclization reactions using suitable substituted aldehydes. The synthesized compounds were characterized by various spectroscopic techniques such as FT-IR, ^{1}H NMR, Mass spectroscopy, and UV-visible spectroscopy to confirm their chemical structures. Furthermore, molecular docking studies were carried out using selected anticancer and anti-inflammatory protein targets to evaluate the binding affinity, interaction patterns, and possible mechanism of action of the synthesized compounds. The docking results indicated favorable interactions of the hybrid molecules with the active sites of target proteins, suggesting their potential as multifunctional therapeutic agents. The incorporation of the 1,2,4-triazole moiety into the diclofenac framework is expected to enhance biological activity, improve target binding, and provide better pharmacological properties. Overall, the present work highlights the significance of diclofenac-triazole hybridization as a promising strategy for the development of novel anti-inflammatory and anticancer agents.

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INTRODUCTION

Inflammation and cancer are among the most significant health challenges worldwide. Chronic inflammation has been recognized as a major factor in the initiation, progression, and metastasis of various cancers. Persistent inflammatory responses lead to the production of cytokines, reactive oxygen species (ROS), and other mediators that contribute to DNA damage, uncontrolled cell proliferation, angiogenesis, and inhibition of apoptosis. Therefore, the development of novel therapeutic agents possessing both anti-inflammatory and anticancer activities has become an important area of pharmaceutical research [2,6].

Diclofenac is a widely used non-steroidal anti-inflammatory drug (NSAID) that exerts its pharmacological action primarily through inhibition of cyclooxygenase (COX) enzymes, thereby reducing the synthesis of prostaglandins responsible for pain and inflammation. Recent studies have demonstrated that diclofenac and its derivatives possess additional biological activities, including anticancer properties, making it an attractive scaffold for the development of multifunctional therapeutic agents [1,2]. Structural modification of diclofenac has been extensively investigated to improve its efficacy, selectivity, and safety profile while exploring new therapeutic applications [2].

Heterocyclic compounds occupy a prominent position in medicinal chemistry due to their diverse biological activities and favorable pharmacokinetic properties. Among them, 1,2,4-triazole derivatives have attracted considerable attention because of their broad spectrum of pharmacological activities, including anti-inflammatory, antimicrobial, antioxidant, anticonvulsant, and anticancer effects [6,8,9]. The 1,2,4-triazole ring system is considered a privileged scaffold in drug design owing to its ability to form hydrogen bonds and other molecular interactions with biological targets, thereby enhancing biological activity [10,11].

Several studies have reported the successful synthesis and biological evaluation of novel 1,2,4-triazole derivatives exhibiting significant anticancer activity against various cancer cell lines [7,10]. Furthermore, triazole-containing compounds have demonstrated promising anti-inflammatory potential through modulation of inflammatory mediators and enzyme inhibition pathways [6]. These findings suggest that incorporation of the triazole pharmacophore into existing drug molecules may lead to the development of more potent therapeutic agents.

The concept of molecular hybridization has emerged as an effective strategy in modern drug discovery. Molecular hybridization involves the combination of two or more pharmacologically active moieties within a single molecular framework to produce compounds with enhanced biological activity, improved selectivity, and reduced adverse effects. Hybrid molecules often exhibit synergistic effects arising from the combined pharmacological properties of the parent structures [2,4]. Therefore, the hybridization of diclofenac with a biologically active 1,2,4-triazole nucleus represents a promising approach for the development of novel anti-inflammatory and anticancer agents.

Advances in synthetic organic chemistry have facilitated the efficient synthesis of heterocyclic compounds through environmentally friendly and sustainable methodologies. Green chemistry approaches, including one-pot synthesis, multicomponent reactions, catalytic processes, and solid-supported synthesis, have gained significant importance in medicinal chemistry research due to their reduced environmental impact and improved synthetic efficiency [14–20]. These strategies contribute to the development of economically

viable and environmentally sustainable pharmaceutical compounds.

In recent years, molecular docking has become an indispensable computational tool in drug discovery and development. Molecular docking enables the prediction of binding modes, interaction patterns, and binding affinities of synthesized compounds with specific biological targets, thereby facilitating the identification of potential lead molecules before extensive biological evaluation [12]. The integration of molecular docking studies with synthetic and biological investigations provides valuable insights into structure-activity relationships and mechanisms of action.

Based on these considerations, the present research work focuses on the design, synthesis, characterization, and molecular docking evaluation of novel diclofenac hybridized heterocyclic-1,2,4-triazole derivatives. The synthesized compounds are expected to exhibit enhanced anti-inflammatory and anticancer activities through the synergistic contribution of both diclofenac and triazole pharmacophores. The study aims to explore the therapeutic potential of these hybrid molecules and establish their structure-activity relationships through computational and experimental investigations.

Structure of Diclofenac Sodium

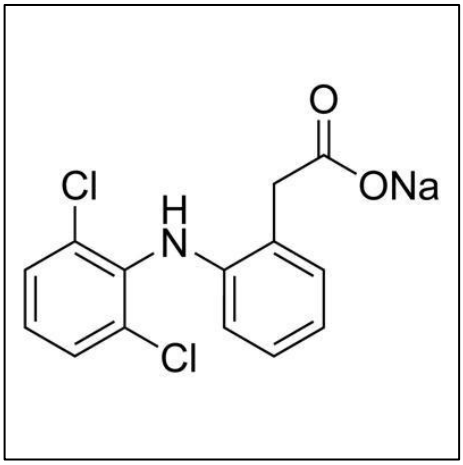


Figure. Structure of Sodium [2-(2,6-dichloroanilino) phenyl] acetate

General Information Diclofenac Sodium

Table No 1. General Information of drug

Parameter	Details
Generic Name	Diclofenac Sodium
Chemical Name	Sodium [2-(2,6-dichloroanilino) phenyl] acetate
Molecular Formula	$C_{14}H_{10}Cl_2NNaO_2$
Molecular Weight	318.13 g/mol
Drug Category	Non-Steroidal Anti-Inflammatory Drug (NSAID)

IUPAC Name	Sodium 2-[2-(2,6-dichloroanilino) phenyl] acetate
Appearance	White to slightly yellow crystalline powder
Solubility	Soluble in methanol and ethanol; sparingly soluble in water
Melting Point	Approximately 283–285°C

2. METERIAL & METHODS:

2.1 Experimental part:

All chemical reagents and solvents are purchased from commercial suppliers (HIMIDIA) and were without further purification. Melting points were determination on a capillary melting point apparatus and are uncorrected.

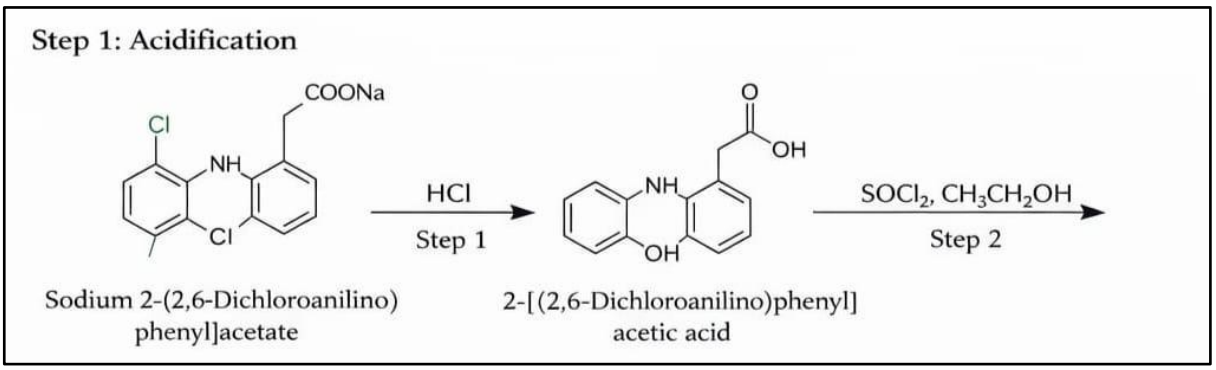
The identification and characterization of the synthesized compounds were carried out by the following procedure to ascertain that all the compounds were of parent compound.

- Melting Point
- Thin Layer Chromatography (TLC)
- FT-Infrared Spectroscopy (FTIR)
- Proton Nuclear Magnetic Resonance Spectroscopy (1H-NMR)
- UV Spectroscopy
- Mass Spectroscopy

2.1.1Synthetic Scheme

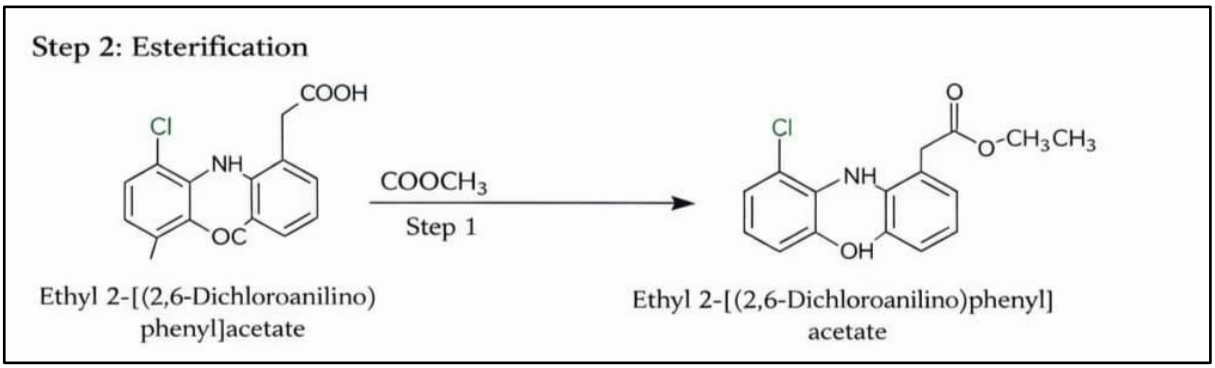
Procedure:

Step 1: Preparation of Diclofenac Free Acid



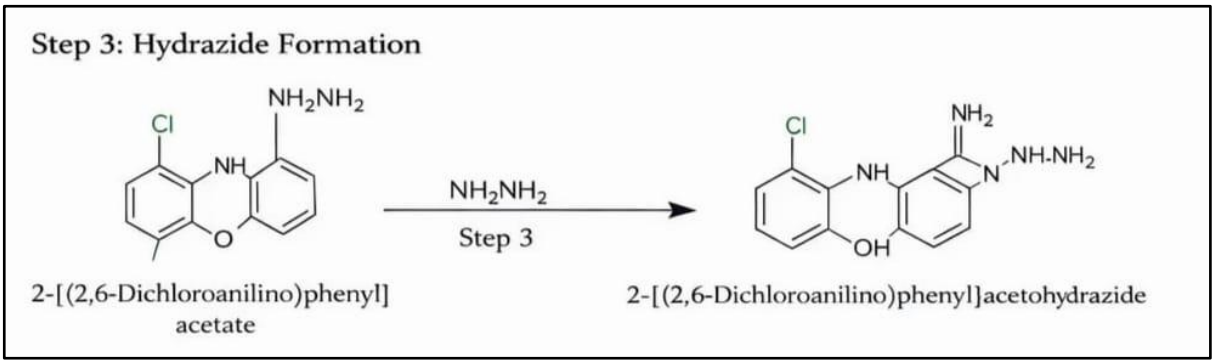
- Diclofenac sodium (3.18 g, 0.01 mol) was dissolved in 50 mL of distilled water with continuous stirring. Dilute hydrochloric acid was added dropwise until the pH of the solution reached approximately 2.
- A white precipitate formed immediately indicating the formation of diclofenac free acid.
- The precipitate was filtered under vacuum and washed with cold distilled water to remove traces of hydrochloric acid.
- The product was dried in a desiccator.
- Yield 88 % Melting Point 165-167°C

Step 2: Synthesis of Ethyl-2-(2,6-dichloroanilino) phenylacetate



- Diclofenac acid (2.96 g, 0.01 mol) was refluxed with thionyl chloride (5 mL) for about two hours in a round bottom flask fitted with a reflux condenser.
- The reaction mixture was then cooled and excess thionyl chloride was removed by evaporation under reduced pressure.
- The resulting acid chloride intermediate was dissolved in absolute ethanol (30 mL) and refluxed for three hours.
- After completion of the reaction, the mixture was poured into ice-cold water which resulted in the formation of a solid ester product.
- The crude product was filtered and recrystallized using ethanol.
- Yield: 82 % Melting Point**:** 118-120°C

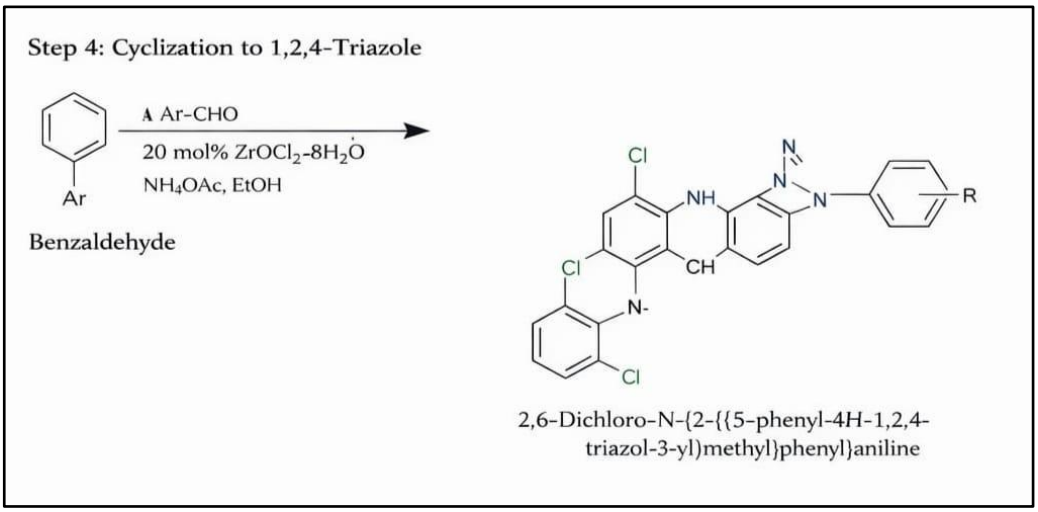
Step 3: Synthesis of Diclofenac Acetohydrazide



The ester derivative (3.24 g, 0.01 mol) was dissolved in ethanol (25 mL).

- Hydrazine hydrate (5 mL) was added slowly with constant stirring.
- The mixture was refluxed for 4 hours.
- Reaction progress was monitored using TLC.
- After completion, the reaction mixture was cooled and poured into ice water.
- A solid precipitate formed which was filtered and recrystallized from ethanol.
- Yield 78 % Melting Point 178-180°C

Step 4: Synthesis of Diclofenac-1,2,4-Triazole Derivatives

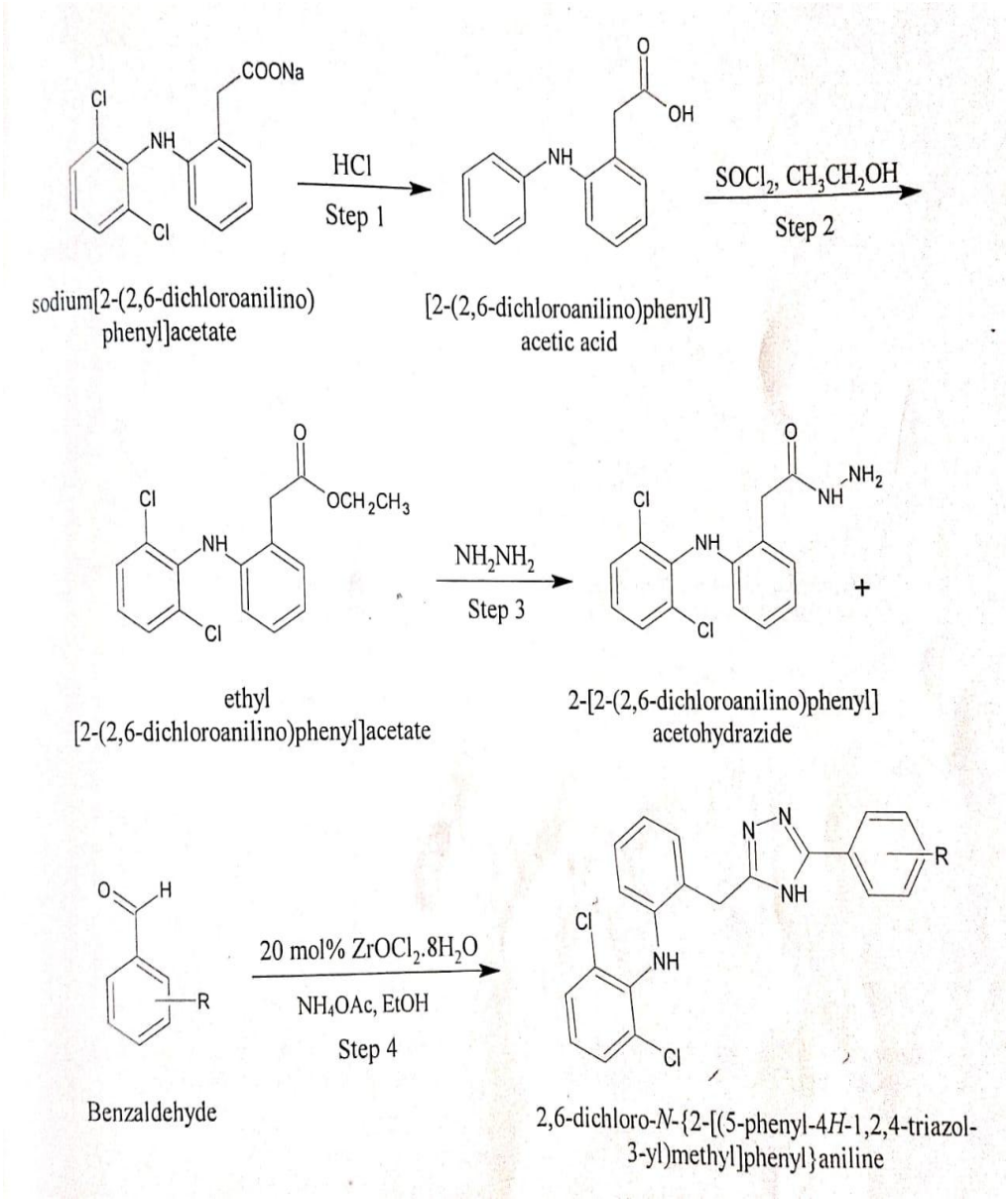


- Acetohydrazide (2.82 g, 0.01 mol) was dissolved in ethanol (30 mL).
- Substituted benzaldehyde (0.01 mol) was added to the solution followed by ammonium acetate (0.77 g) and zirconyl oxychloride octahydrate catalyst.
- The reaction mixture was refluxed for 5-6 hours.
- Reaction progress was monitored using TLC.
- After completion, the mixture was poured into ice-cold water.
- The solid product obtained was filtered and recrystallized from ethanol.
- Yield 65-75 %

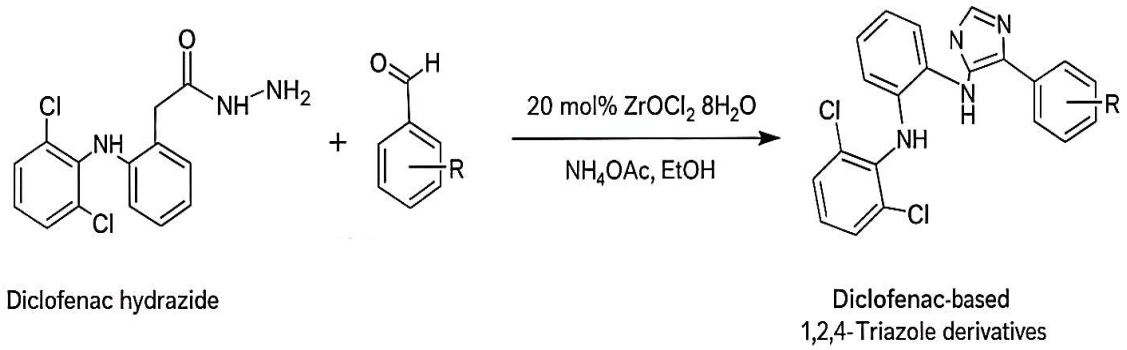
2.2 THE IUPAC NAMES OF SYNTHESIZED COMPOUNDS ARE AS FOLLOWS:

1. 2,6-dichloro-*N*-(2-{[5-(4-nitrophenyl)-4*H*-1,2,4-triazol-3-yl]methyl}phenyl)aniline
2. 2,6-dichloro-*N*-(2-{[5-(4-methoxyphenyl)-4*H*-1,2,4-triazol-3-yl]methyl}phenyl)aniline
3. 2,6-dichloro-*N*-(2-{[5-(4-fluorophenyl)-4*H*-1,2,4-triazol-3-yl]methyl}phenyl)aniline

2.3 METHOD:

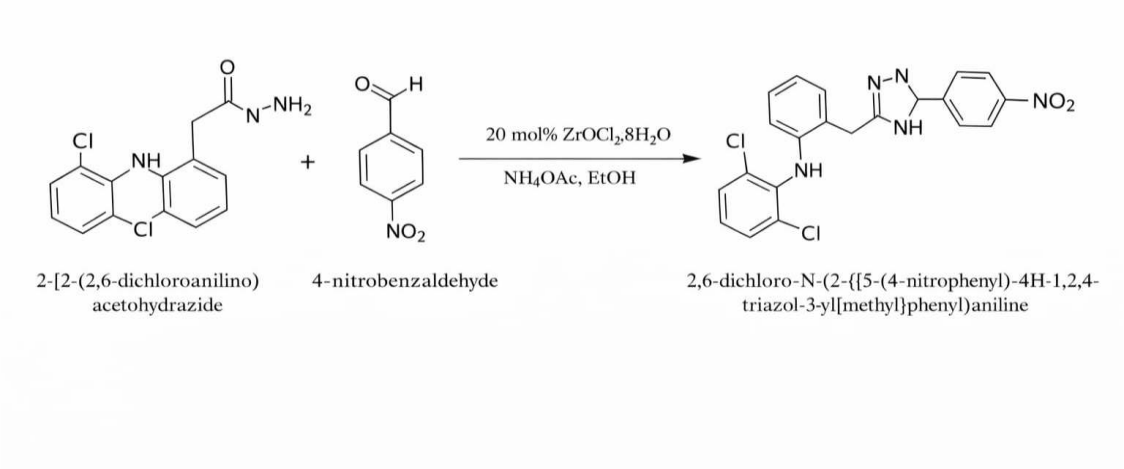

COONa
Cl
NH
Cl
HCl
Step 1
O
OH
NH
SOCl2, CH3CH2OH
Step 2
sodium[2-(2,6-dichloroanilino) phenyl]acetate
[2-(2,6-dichloroanilino)phenyl] acetic acid
O
OCH2CH3
Cl
NH
Cl
NH2NH2
Step 3
O
NH
NH2
Cl
NH
Cl
+
ethyl [2-(2,6-dichloroanilino)phenyl]acetate
2-[2-(2,6-dichloroanilino)phenyl] acetohydrazide
O
H
R
20 mol% ZrOCl2.8H2O
NH4OAc, EtOH
Step 4
N
N
NH
R
Cl
NH
Cl
Benzaldehyde
2,6-dichloro-N-{2-[(5-phenyl-4H-1,2,4-triazol-3-yl)methyl]phenyl}aniline

2.3.1 SCHEME:


O
NH
NH2
Cl
NH
Cl
+
O
H
R
20 mol% ZrOCl2 8H2O
NH4OAc, EtOH
N
N
N
H
R
Cl
NH
Cl
Diclofenac hydrazide
Diclofenac-based 1,2,4-Triazole derivatives

DERIVATIVES:

1. 2,6-dichloro-*N*-(2-{[5-(4-nitrophenyl)-4*H*-1,2,4-triazol-3-yl]methyl}phenyl)aniline

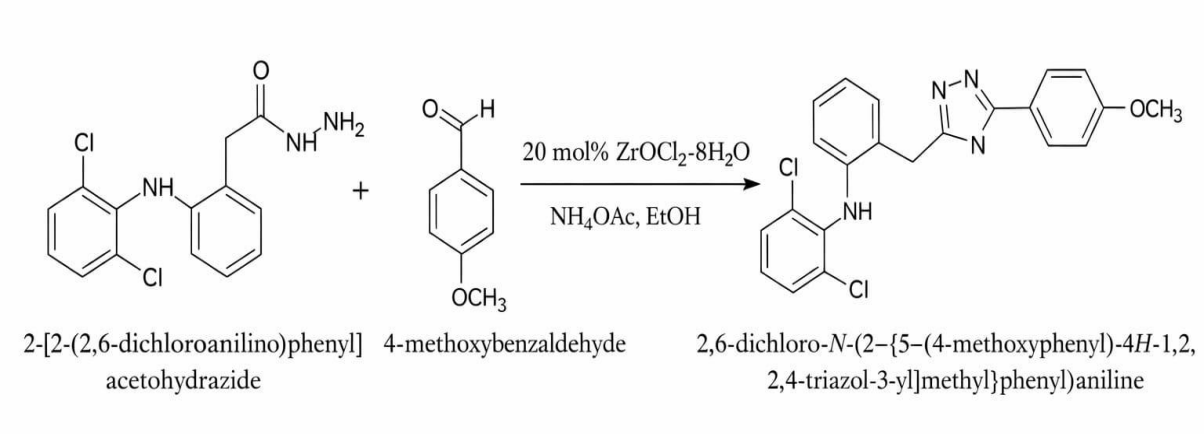


2-[2-(2,6-dichloroanilino) acetohydrazide | 4-nitrobenzaldehyde | 2,6-dichloro-N-(2-{[5-(4-nitrophenyl)-4H-1,2,4-triazol-3-yl[methyl}phenyl)aniline

Physical Properties

- Molecular formula: C21H15Cl2N5O2
- Molecular weight: 440.284
- Appearance: Pale yellow crystalline solid
- Melting Point: 205–210 °C
- Yield: 72–88%
- Solubility: Soluble in DMSO, DMF; sparingly soluble in ethanol

2. 2,6-dichloro-*N*-(2-{[5-(4-methoxyphenyl)-4*H*-1,2,4-triazol-3-yl]methyl}phenyl) aniline

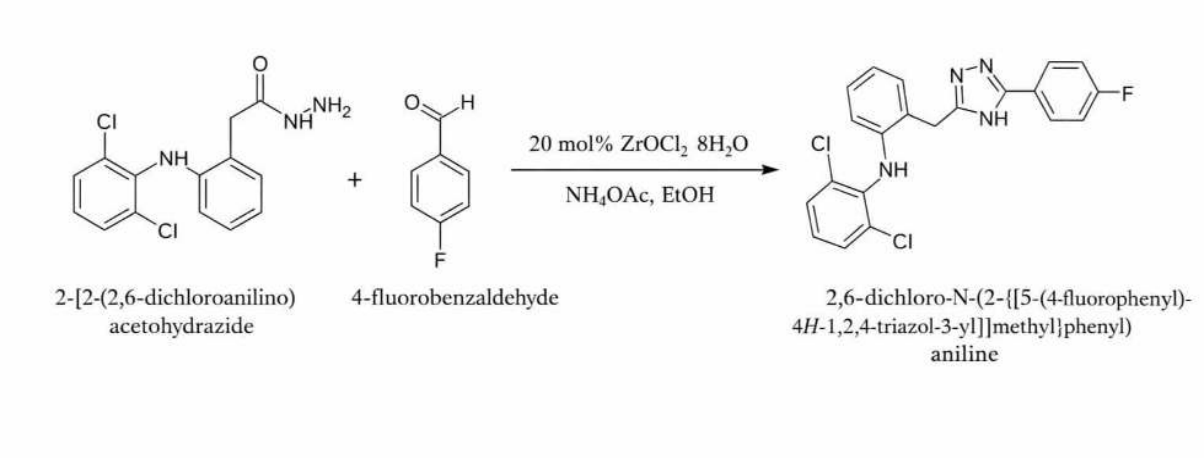


2-[2-(2,6-dichloroanilino)phenyl] acetohydrazide | 4-methoxybenzaldehyde | 2,6-dichloro-*N*-(2−{5−(4-methoxyphenyl)-4*H*-1,2,4-triazol-3-yl]methyl}phenyl)aniline

Physical Properties

- Appearance: Pale yellow crystalline solid
- Yield: 72–80 %
- Melting Poit : 198–204 °C
- Solubility: Soluble in DMSO, DMF; slightly soluble in ethanol
- Molecular Formula: $C_{22}H_{18}Cl_2N_4O$
- Molecular Weight: ~425.31 g/mol

3. 2,6-dichloro-*N*-(2-{[5-(4-fluorophenyl)-4*H*-1,2,4-triazol-3-yl]methyl}phenyl) aniline



2-[2-(2,6-dichloroanilino) acetohydrazide

4-fluorobenzaldehyde

2,6-dichloro-N-(2-{[5-(4-fluorophenyl)-4*H*-1,2,4-triazol-3-yl]]methyl}phenyl) aniline

Physical Properties

- Appearance: Pale yellow crystalline solid
- Melting Point: 205–210 °C
- Yield: 72–88%
- Solubility: Soluble in DMSO, DMF; sparingly soluble in ethanol
- Molecular Formula::
- Molecular Weight::

2.4 DOCKING STUDIES:

Structure Based Drug Design:

When the structure of the target is known (available), usually from X-ray crystallography, the most commonly used virtual screening method is molecular docking. Molecular docking can also be used to test possible hypotheses before conducting costly laboratory experiments. Molecular docking programs try to predict how a drug candidate binds to a protein target without performing a laboratory experiment. X-ray crystallographic techniques have been applied in medicinal chemistry to perform structural elucidation of large complex molecules. NMR techniques have also been used in the determination of the structure of proteins and enzymes. The basic assumption in SBDD is that good inhibitors must possess significant structural and chemical complementarity to their target receptor.

2.5 ADME PREDICTION:

The Qikprop Tool of Schrodinger_2015 (Maestro 10.2 version) is a quick, accurate, and easyto-use Absorption, Distribution, Metabolism, and Excretion (ADME) prediction program designed by Professor William L. Jorgensen. It predicts physically significant descriptors and pharmaceutically relevant properties of organic molecules, either individually or in batches. In addition to predicting molecular properties, QikProp provides ranges for comparing particular molecules' properties with those of 95% of known drugs.

3. RESULTS AND DISCUSSION

1. 2,6-dichloro-N-(2-{[5-(4-nitrophenyl)-4H-1,2,4-triazol-3-yl]methyl}phenyl)aniline

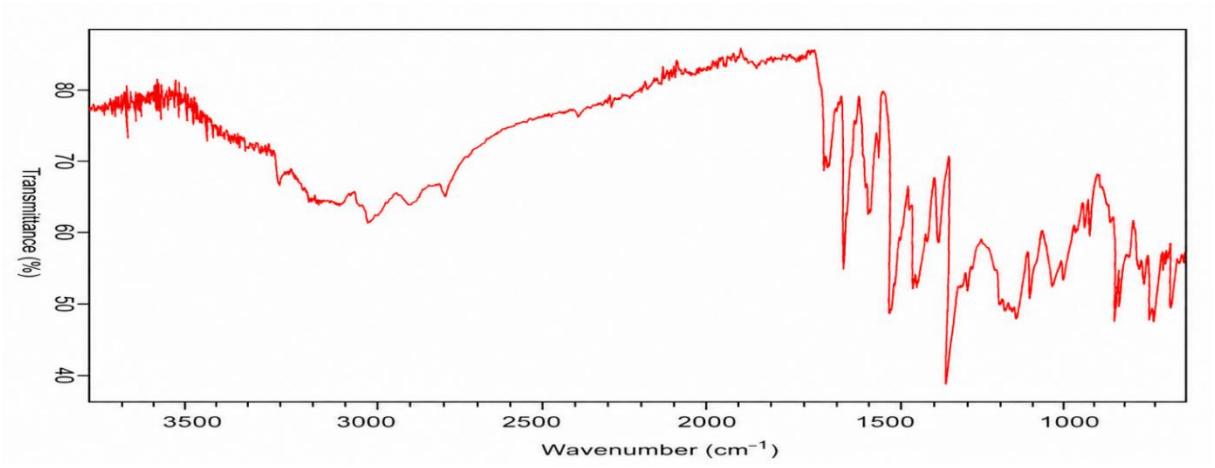


Fig.No.1 IR Spectrum of 2,6-dichloro-N-(2-{[5-(4-nitrophenyl)-4H-1,2,4-triazol-3-yl]methyl}phenyl)aniline

Observation Table for FTIR Spectrum

Table no.2. Observation table of IR Spectrum of 2,6-dichloro-N-(2-{[5-(4-nitrophenyl)-4H-1,2,4-triazol-3-yl]methyl}phenyl)aniline

Sr. No	Observed Frequency (cm^{-1})	Standard Frequency (cm^{-1})	Functional Group / Assignment
1	3290-3385	3200-3400	O-H/N-H stretching vibration
2	2955-3005	2850-3000	C-H stretching (Alkanes/Aromatic)
3	1645	1600-1650	C=N/C=O stretching vibration
4	1515-1560	1500-1600	C=C stretching (Aromatic ring)
5	1400-1475	1400-1450	C-H binding vibration
6	1270-1320	1250-1350	C-N/ C-O stretching vibration
7	1185-1210	1150-1250	C-O stretching (Alcohols/ethers)
8	1025-1075	1000-1100	C-O stretching (primary alcohol)
9	705-700	700-900	Aromatic C-H bending vibration
10	1728	1700-1750	C=O stretching (Carbonyl group)

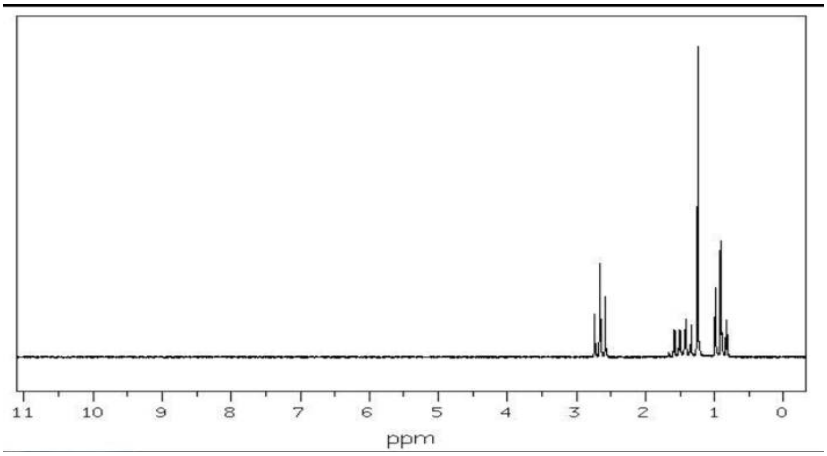


Fig No. 2 ^{1}H NMR Spectrum of 2,6-dichloro-N-(2-{[5-(4-nitrophenyl)-4H-1,2,4-triazol-3-yl]methyl}phenyl)aniline

Table no. 3 Observation table of ^{1}H NMR Spectrum of 2,6-dichloro-N-(2-{[5-(4-nitrophenyl)-4H-1,2,4-triazol-3-yl]methyl}phenyl)aniline

Sr. No.	Chemical Shift (δ, ppm)	Proton Assignment	Multiplicity	Interpretation
1	7.5 – 8.3	Aromatic protons adjacent to nitro group	Multiplet	Deshielded aromatic protons of nitrophenyl ring
2	6.8 – 7.5	Aromatic protons (Ar–H)	Multiplet	Dichlorophenyl and substituted phenyl ring protons
3	2.7 – 3.1	–CH2 bridge protons	Singlet	Methylene group attached to triazole nucleus
4	1.2 – 1.8	Aliphatic/trace impurity signals	Broad peak	Residual solvent or impurity peaks
5	~7.0	NH proton	Broad singlet	Secondary amine proton of aniline group

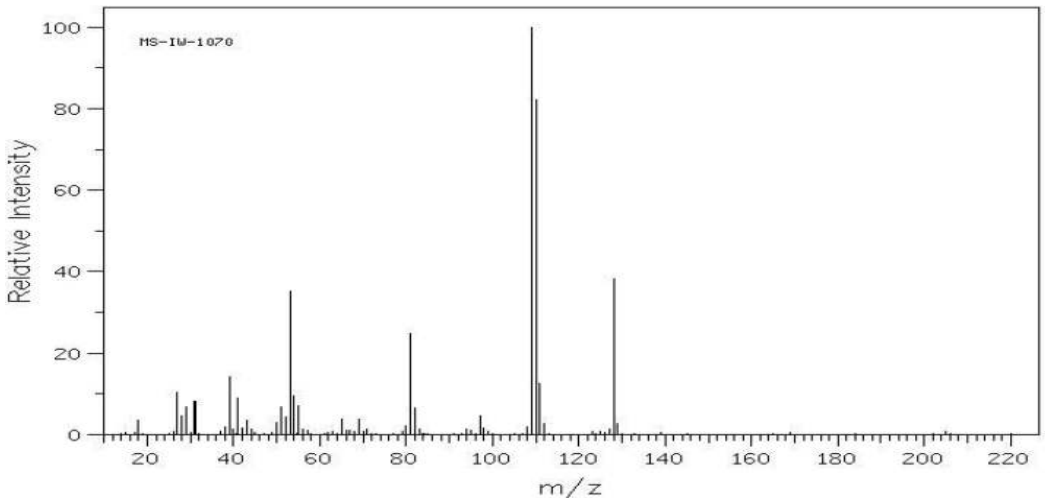


Fig No. 4. Mass Spectrum of 2,6-dichloro-N-(2-{[5-(4-nitrophenyl)-4H-1,2,4-triazol-3-yl]methyl}phenyl)aniline

Table no.5. Observation table of Mass Spectrum of 2,6-dichloro-N-(2-{[5-(4-nitrophenyl)-4H-1,2,4-triazol-3-yl]methyl}phenyl)aniline

Sr. No.	m/z Value (Observed)	Relative Intensity (%)	Probable Fragment / Assignment
1	18–20	Low	Small fragment ions
2	39–43	Moderate	Aromatic ring fragment
3	63–65	Moderate	Chlorophenyl fragment
4	77–79	Low to moderate	Phenyl ring cleavage fragment
5	91–93	Moderate	Benzyl/triazole fragment
6	103–105	Moderate	Methoxy substituted aromatic fragment
7	116–120	Moderate	Triazole-containing fragment ion
8	128–130	Base Peak (100%)	Stable methoxyphenyl-triazole fragment
9	144–147	High	Chlorinated aromatic fragment
10	160–162	Moderate	Dichloro substituted fragment
11	205–207	Weak molecular ion region	Molecular ion peak

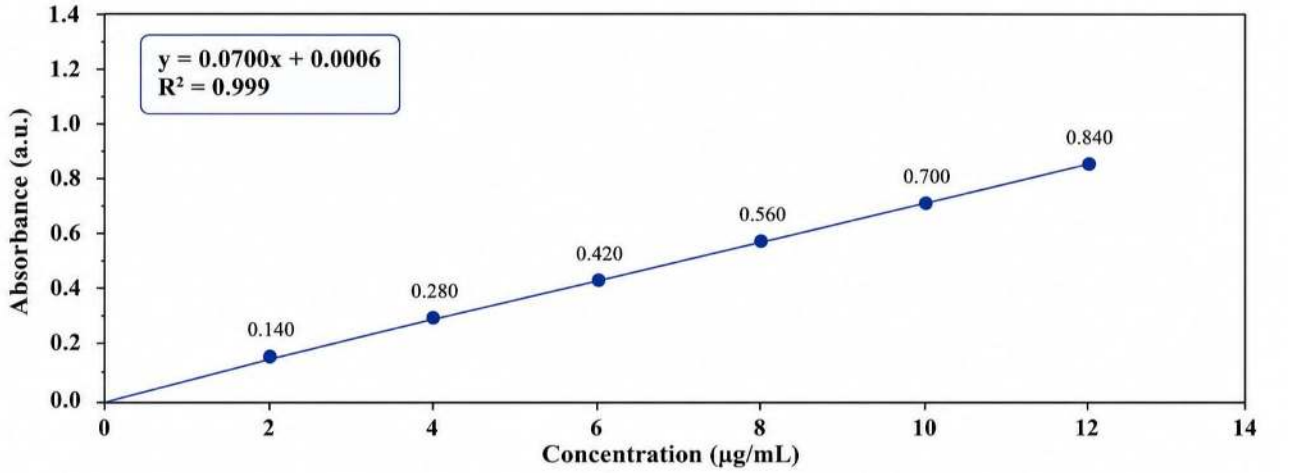


Fig No.5 Calibration of 2,6-dichloro-N-(2-{[5-(4-nitrophenyl)-4H-1,2,4-triazol-3-yl]methyl}phenyl)aniline

Table no.6 Observation table of Calibration of 2,6-dichloro-N-(2-{[5-(4-nitrophenyl)-4H-1,2,4-triazol-3-yl]methyl}phenyl)aniline

Sr. No	Concentration	Absorbance at Λmax (320)
1	2	0.140
2	4	0.280
3	6	0.420
4	8	0.560
5	10	0.700
6	12	0.840

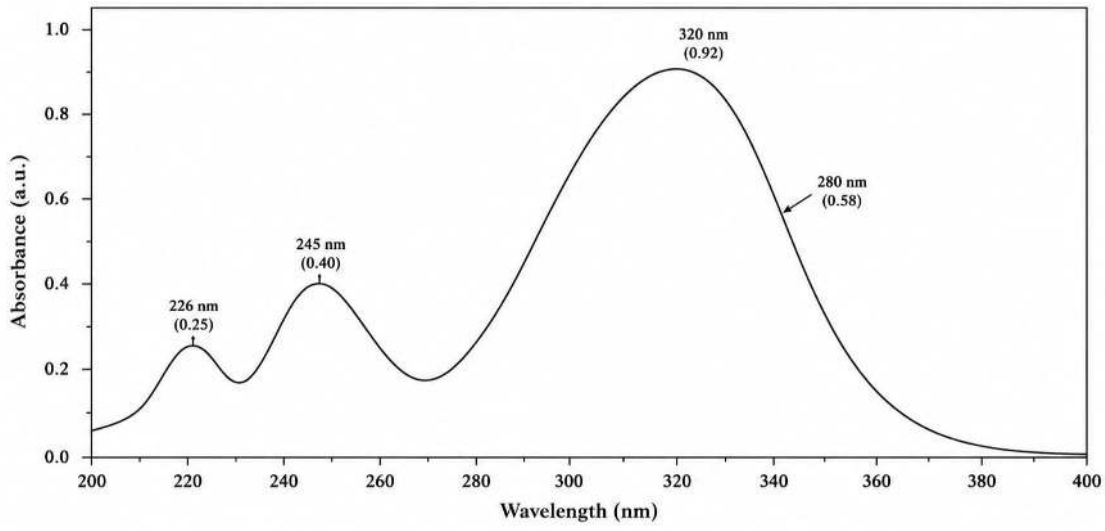


Fig No.6 UV–Visible Spectrum of 2,6-dichloro-N-(2-{[5-(4-nitrophenyl)-4H-1,2,4-triazol-3-yl]methyl}phenyl)aniline

Table no.7 Observation table of UV–Visible Spectrum of 2,6-dichloro-N-(2-{[5-(4-nitrophenyl)-4H-1,2,4-triazol-3-yl]methyl}phenyl)aniline

Sr. No	Amax (nm)	Absorbance (a.u.)
1	226	0.25
2	245	0.40
3	280	0.58
4	320	0.92

2. 2,6-dichloro-*N*-(2-{[5-(4-methoxyphenyl)-4*H*-1,2,4-triazol-3-yl]methyl}phenyl) aniline

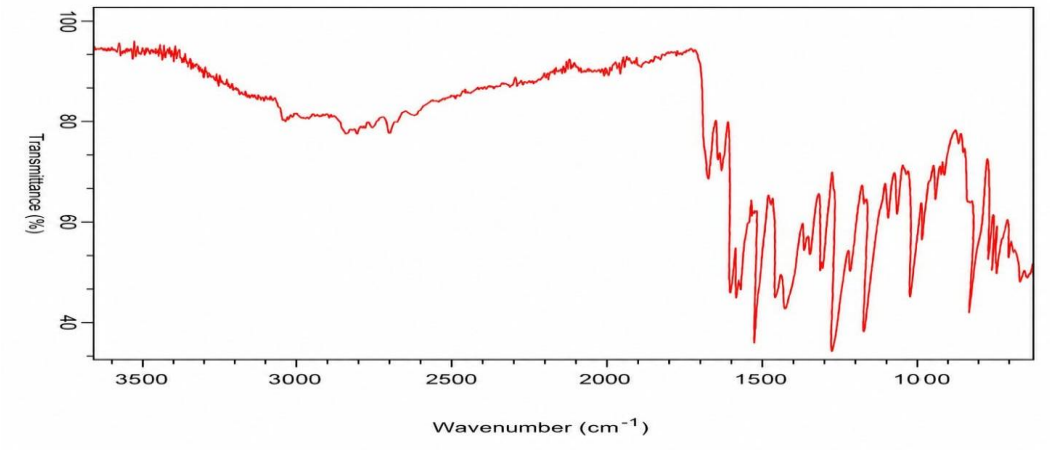


Fig No.7 IR Spectrum of 2,6-dichloro-*N*-(2-{[5-(4-methoxyphenyl)-4*H*-1,2,4-triazol-3-yl]methyl}phenyl) aniline

Table no.8 Observation table of IR Spectrum of 2,6-dichloro-*N*-(2-{[5-(4-methoxyphenyl)-4*H*-1,2,4-triazol-3-yl]methyl}phenyl) aniline

Sr. No.	Observed Frequency (cm^{-1})	Standard Frequency (cm^{-1})	Functional Group / Assignment
1	3320–3400	3200–3400	O–H / N–H stretching vibration
2	2920–3010	2850–3000	C–H stretching vibration (Alkanes/Aromatic)
3	1710–1730	1700–1750	C=O stretching vibration (Carbonyl group)
4	1600–1655	1600–1650	C=N / C=C stretching vibration
5	1500–1560	1500–1600	Aromatic C=C stretching vibration
6	1400–1470	1400–1450	C–H bending vibration
7	1260–1325	1250–1350	C–N / C–O stretching vibration

8	1160–1215	1150–1250	C–O stretching vibration (Alcohols/Ethers)
9	1020–1080	1000–1100	C–O stretching vibration (Primary alcohol)
10	700–760	700–900	Aromatic C–H bending vibration

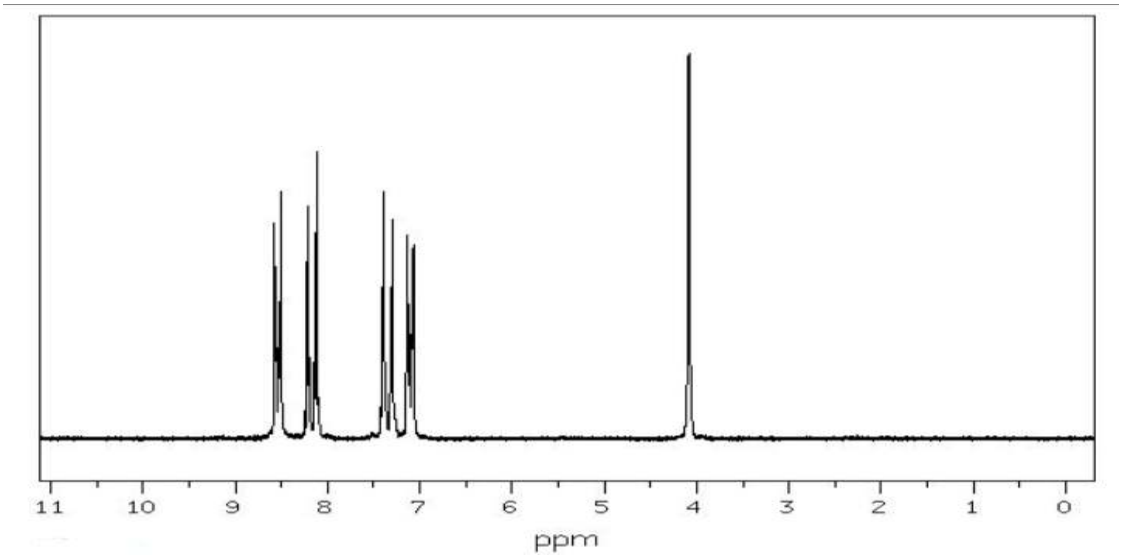


Fig No.8 ^{1}H NMR Spectrum of 2,6-dichloro-*N*-(2-{[5-(4-methoxyphenyl)-4*H*-1,2,4-triazol-3-yl]methyl}phenyl) aniline

Table no.9 Observation table of ^{1}H NMR Spectrum of 2,6-dichloro-*N*-(2-{[5-(4-methoxyphenyl)-4*H*-1,2,4-triazol-3-yl]methyl}phenyl) aniline

Sr. No.	Chemical Shift (δ, ppm)	Proton Assignment	Multiplicity	Interpretation
1	8.0 – 8.5	Triazole-associated aromatic protons	Multiplet	Protons attached near heterocyclic triazole ring
2	7.0 – 7.8	Aromatic protons (Ar–H)	Multiplet	Phenyl ring protons of dichlorophenyl and methoxyphenyl groups
3	4.0 – 4.2	–OCH3 protons	Singlet	Methoxy group attached to aromatic ring
4	3.8 – 4.0	–CH2 bridge protons	Singlet	Methylene group linking triazole and phenyl ring
5	~7.2	NH proton	Broad singlet	Secondary amine proton of aniline moiety

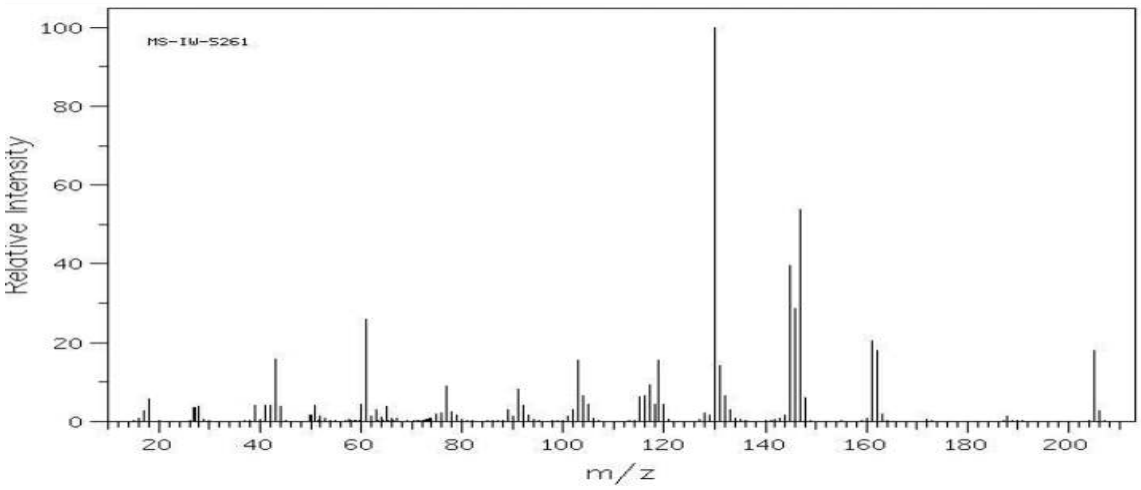


Fig No.9 Mass Spectrum of 2,6-dichloro-*N*-(2-{[5-(4-methoxyphenyl)-4*H*-1,2,4-triazol-3-yl]methyl}phenyl) aniline

Table no. 10 Observation table of Mass Spectrum of 2,6-dichloro-*N*-(2-{[5-(4-methoxyphenyl)-4*H*-1,2,4-triazol-3-yl]methyl}phenyl) aniline

Sr. No.	m/z Value (Observed)	Relative Intensity (%)	Probable Fragment / Assignment
1	18–20	Low	Small fragment ions
2	39–43	Moderate	Aromatic ring fragment
3	63–65	Moderate	Chlorophenyl fragment
4	77–79	Low to moderate	Phenyl ring cleavage fragment
5	91–93	Moderate	Benzyl/triazole fragment
6	103–105	Moderate	Methoxy substituted aromatic fragment
7	116–120	Moderate	Triazole-containing fragment ion
8	128–130	Base Peak (100%)	Stable methoxyphenyl-triazole fragment
9	144–147	High	Chlorinated aromatic fragment
10	160–162	Moderate	Dichloro substituted fragment
11	205–207	Weak molecular ion region	Molecular ion peak

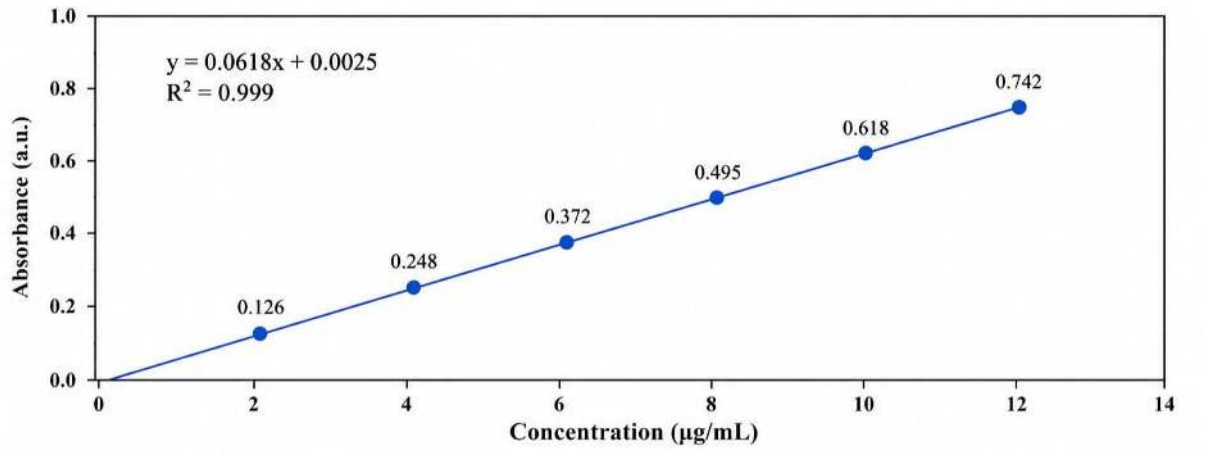


Fig No.10 Calibration of 2,6-dichloro-*N*-(2-{[5-(4-methoxyphenyl)-4*H*-1,2,4-triazol-3-yl]methyl}phenyl) aniline

Table no. 11 Observation table of Calibration of 2,6-dichloro-*N*-(2-{[5-(4-methoxyphenyl)-4*H*-1,2,4-triazol-3-yl]methyl}phenyl) aniline

Sr. No	Concentration	Absorbance at Λmax (320)
1	2	0.126
2	4	0.248
3	6	0.372
4	8	0.495
5	10	0.618
6	12	0.742

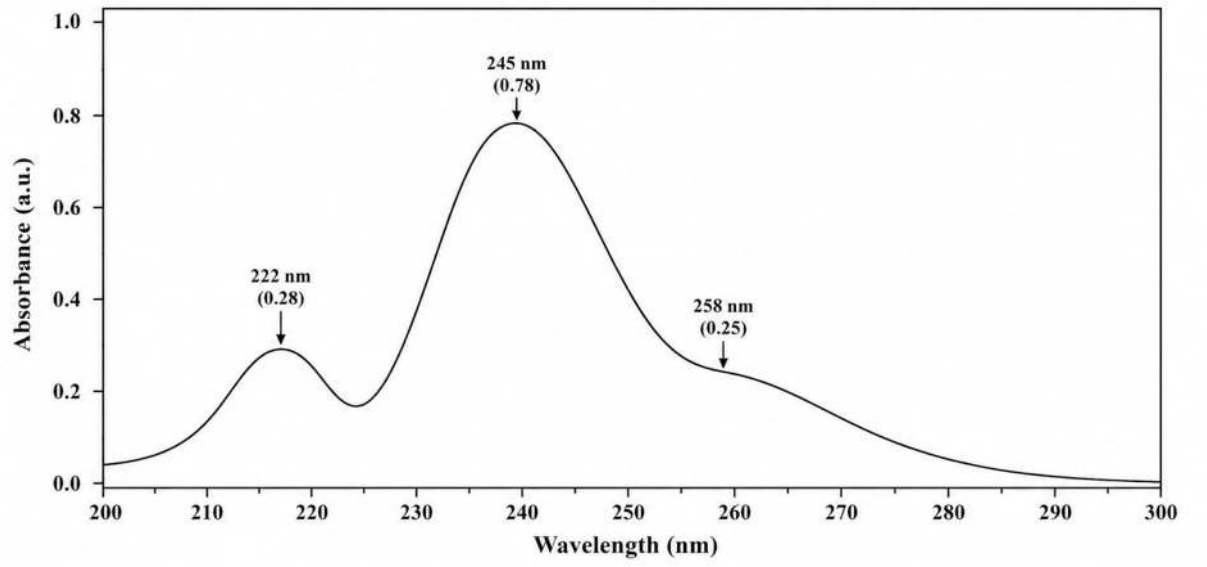


Fig No.11 UV Visible Spectrum of 2,6-dichloro-*N*-(2-{[5-(4-methoxyphenyl)-4*H*-1,2,4-triazol-3-yl]methyl}phenyl) aniline

Table no. 12 Observation table of UV Visible Spectrum of 2,6-dichloro-*N*-(2-{[5-(4-methoxyphenyl)-4*H*-1,2,4-triazol-3-yl]methyl}phenyl) aniline

Sr. No	Amax (nm)	Absorbance (a.u.)
1	222	0.28
2	245	0.78
3	258	0.25

3. 2,6-dichloro-*N*-(2-{[5-(4-fluorophenyl)-4*H*-1,2,4-triazol-3-yl]methyl}phenyl) aniline

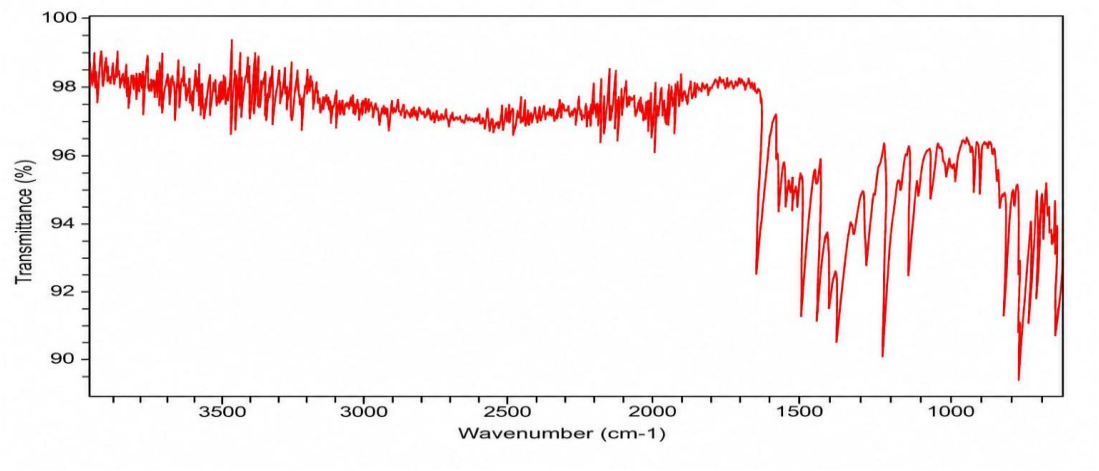


Fig No. 12 IR Spectrum of 2,6-dichloro-*N*-(2-{[5-(4-fluorophenyl)-4*H*-1,2,4-triazol-3-yl]methyl}phenyl) aniline

Table no. 13 Observation table of IR Spectrum of 2,6-dichloro-*N*-(2-{[5-(4-fluorophenyl)-4*H*-1,2,4-triazol-3-yl]methyl}phenyl) aniline

Sr. No.	Observed Frequency (cm^{-1})	Standard Frequency (cm^{-1})	Functional Group / Assignment
1	3300–3380	3200–3400	O–H / N–H stretching vibration
2	2920–3000	2850–3000	C–H stretching vibration (Alkanes/Aromatic)
3	1720–1730	1700–1750	C=O stretching vibration (Carbonyl group)
4	1600–1650	1600–1650	C=N / C=C stretching vibration
5	1500–1560	1500–1600	Aromatic C=C stretching vibration
6	1400–1470	1400–1450	C–H bending vibration
7	1260–1320	1250–1350	C–N / C–O stretching vibration

8	1150–1210	1150–1250	C–O stretching vibration (Alcohols/Ethers)
9	1020–1070	1000–1100	C–O stretching vibration (Primary alcohol)
10	700–760	700–900	Aromatic C–H bending vibration

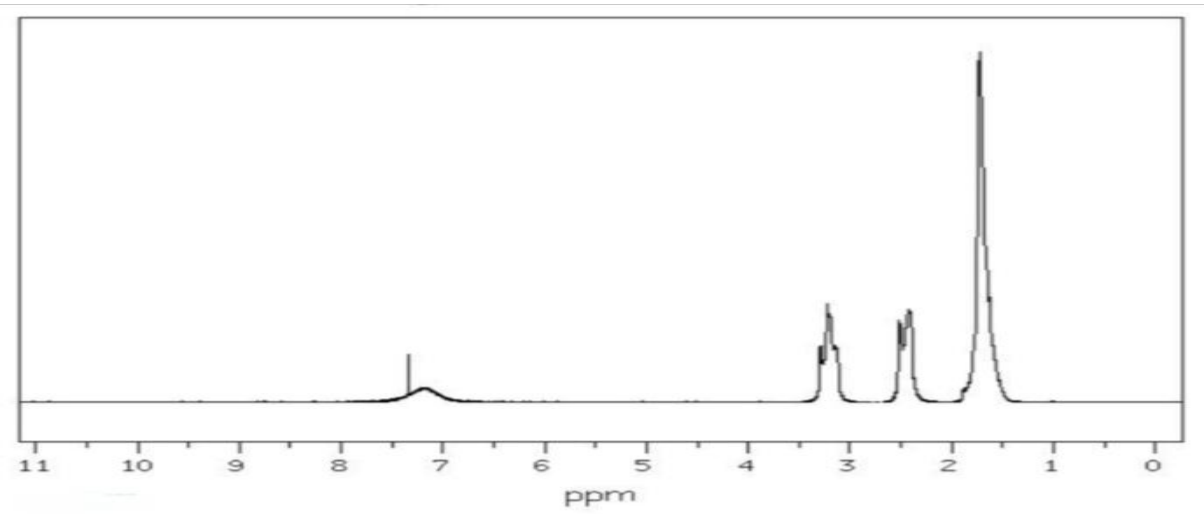


Fig No.13 ^{1}H NMR Spectrum of 2,6-dichloro-*N*-(2-{[5-(4-fluorophenyl)-4*H*-1,2,4-triazol-3-yl]methyl}phenyl) aniline

Table no. 14 Observation table of ^{1}H NMR Spectrum of 2,6-dichloro-*N*-(2-{[5-(4-fluorophenyl)-4*H*-1,2,4-triazol-3-yl]methyl}phenyl) aniline

Sr. No.	Chemical Shift (δ, ppm)	Proton Type / Assignment	Multiplicity	Possible Proton Environment
1	7.0 – 7.5	Aromatic protons (Ar–H)	Multiplet	Phenyl ring protons attached to triazole and dichlorophenyl group
2	3.1 – 3.3	–CH2 group	Singlet / Multiplet	Methylene proton attached to triazole ring
3	2.3 – 2.5	Aromatic substituted proton	Multiplet	Proton near electron-withdrawing substituent
4	1.4 – 1.7	Residual solvent / aliphatic impurity peak	Broad / Singlet	Trace solvent or impurity signal
5	~7.2	NH proton (aniline NH)	Broad singlet	Secondary amine proton

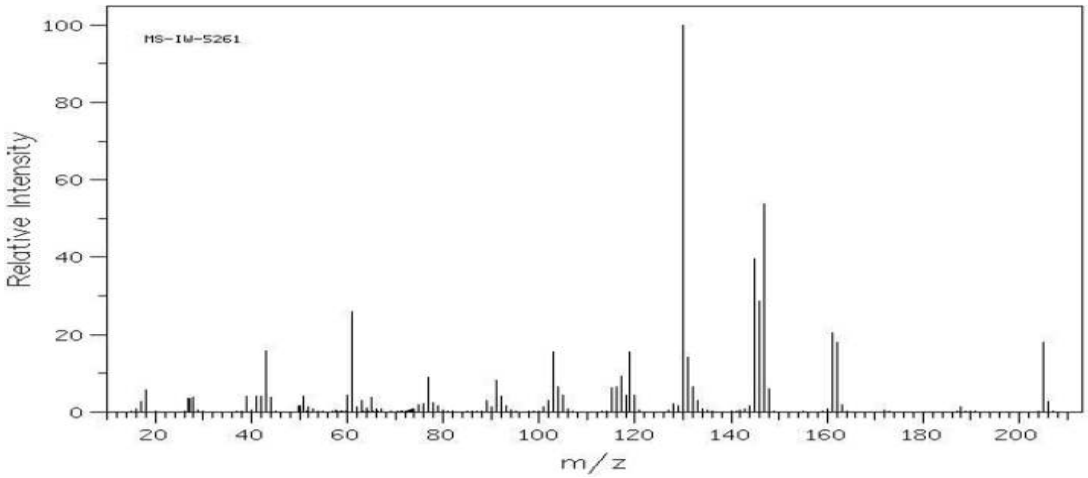


Fig No. 14 Mass Spectrum of 2,6-dichloro-*N*-(2-{[5-(4-fluorophenyl)-4*H*-1,2,4-triazol-3-yl]methyl}phenyl) aniline

Table no. 15 Observation table of Mass Spectrum of 2,6-dichloro-*N*-(2-{[5-(4-fluorophenyl)-4*H*-1,2,4-triazol-3-yl]methyl}phenyl) aniline

Sr. No.	m/z Value (Observed)	Relative Intensity (%)	Possible Fragment / Assignment
1	43	15	Alkyl fragment ion
2	63	25	Aromatic substituted fragment
3	77	10	Phenyl cation fragment
4	91	8	Benzyl/tropylium ion
5	103	15	Aromatic ring cleavage fragment
6	117	12	Triazole substituted fragment
7	130	100 (Base Peak)	Stable major fragment ion
8	145	38	Fluorophenyl-triazole fragment
9	147	52	Molecular fragment ion
10	160	20	Higher molecular fragment
11	205	18	Molecular ion peak (M^+)

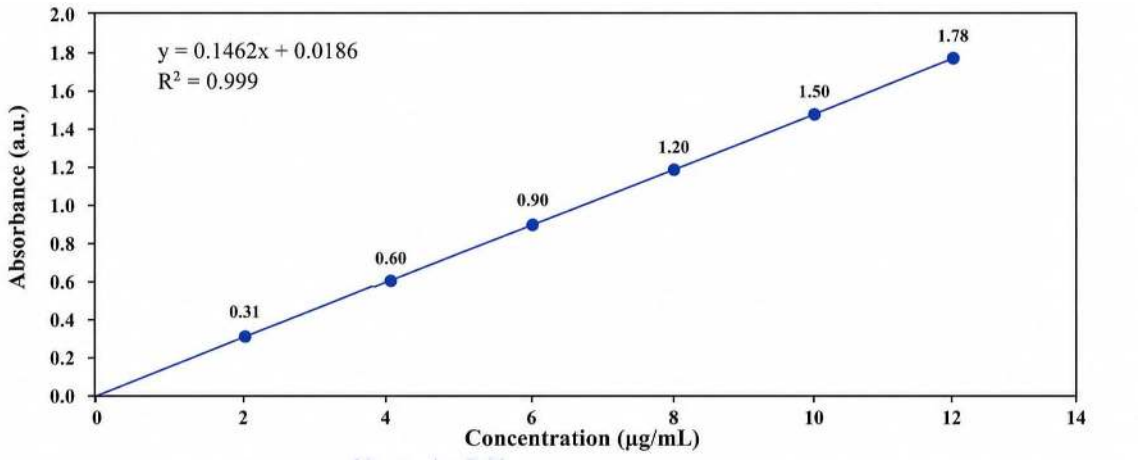


Fig No. 15 Calibration of 2,6-dichloro-*N*-(2-{[5-(4-fluorophenyl)-4*H*-1,2,4-triazol-3-yl]methyl}phenyl) aniline

Table no. 16 Observation table of Calibration of 2,6-dichloro-*N*-(2-{[5-(4-fluorophenyl)-4*H*-1,2,4-triazol-3-yl]methyl}phenyl) aniline

Sr. No	Concentration	Absorbance at Λmax (320)
1	2	0.31
2	4	0.60
3	6	0.90
4	8	1.20
5	10	1.50
6	12	1.78

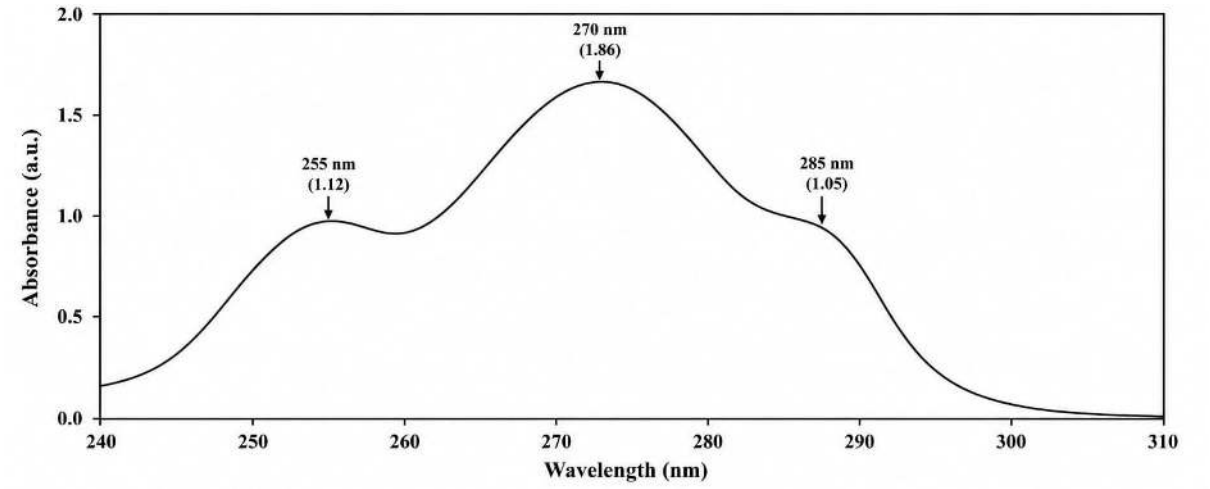


Fig No. 16 UV Visible spectrum of 2,6-dichloro-*N*-(2-{[5-(4-fluorophenyl)-4*H*-1,2,4-triazol-3-yl]methyl}phenyl) aniline

Table no. 17 Observation table of UV Visible spectrum of 2,6-dichloro-*N*-(2-{[5-(4-fluorophenyl)-4*H*-1,2,4-triazol-3-yl]methyl}phenyl) aniline

Sr. No	Amax (nm)	Absorbance (a.u.)
1	255	1.12
2	270	1.86
3	285	1.05

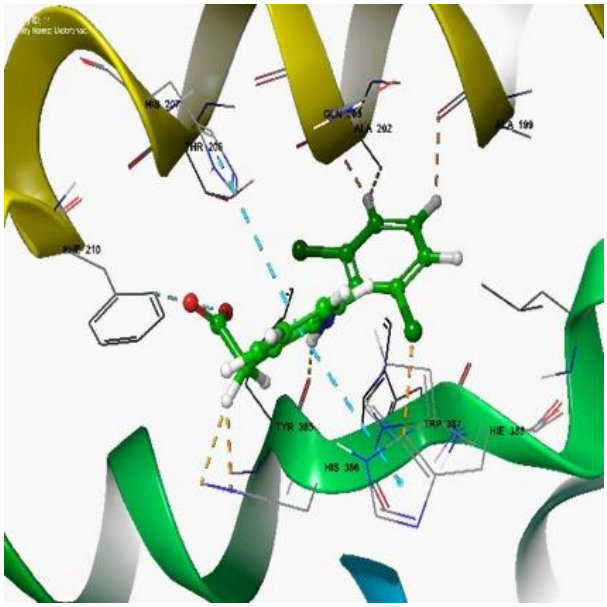
Molecular Docking:

Table No. 18. Structures, scores and key interactions of 12 selected compounds along with standard Diclofenac & Dacomitinib

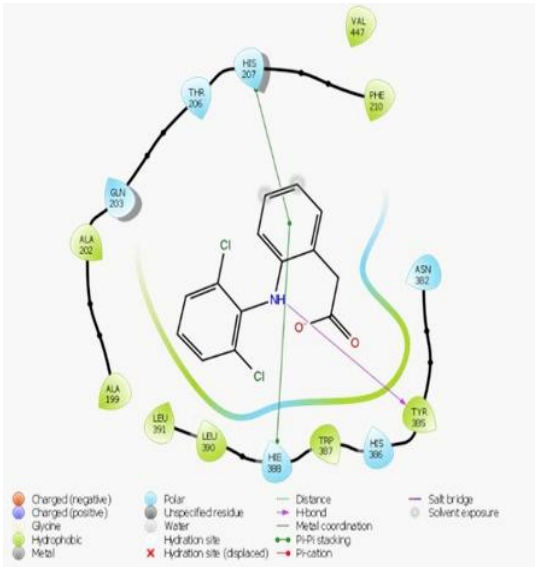
Sr. No.	Comp. Code	Docking Score (PDB: 5F19)	Glide emodel	Interacting residues	Docking Score (PDB: 4I23)	Glide emodel	Interacting residues
1	**Diclofenac**	-6.504	-45.654	HIS207, HIE388, TYR385	-	-	-
2	**Dacomitinib**	-	-	-	-9.050	-78.565	MET793, CYS797, ASP800
3	**S1**	-6.279	-70.788	HIS207	-5.670	-69.112	MET793, GLU762, LYS745, ASP855
4	**S2**	-6.604	-76.933	HIS207, GLN203	-5.892	-71.098	MET793

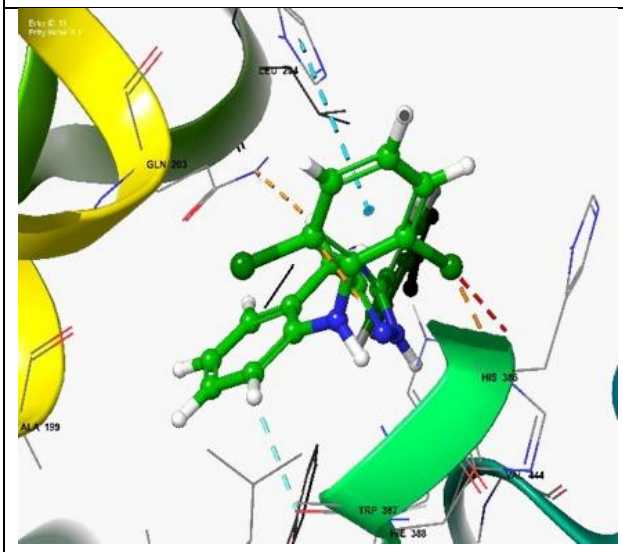
5	**S3**	**-7.152**	-69.764	HIS207	**-7.280**	-69.836	GLN791, MET793

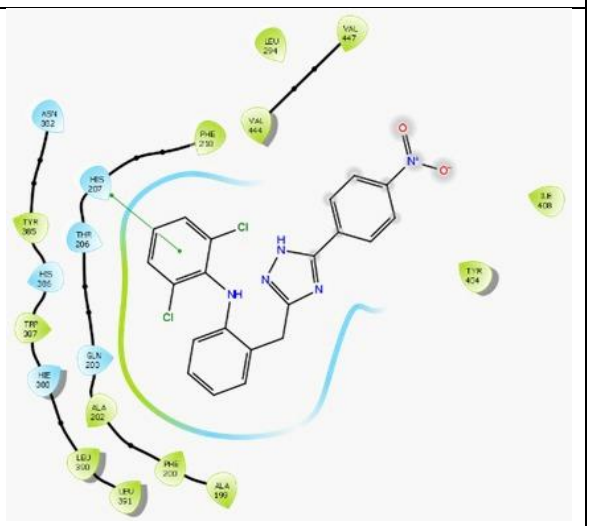
a) 3D Interaction (Standard)



b) 2D interactions (Standard)







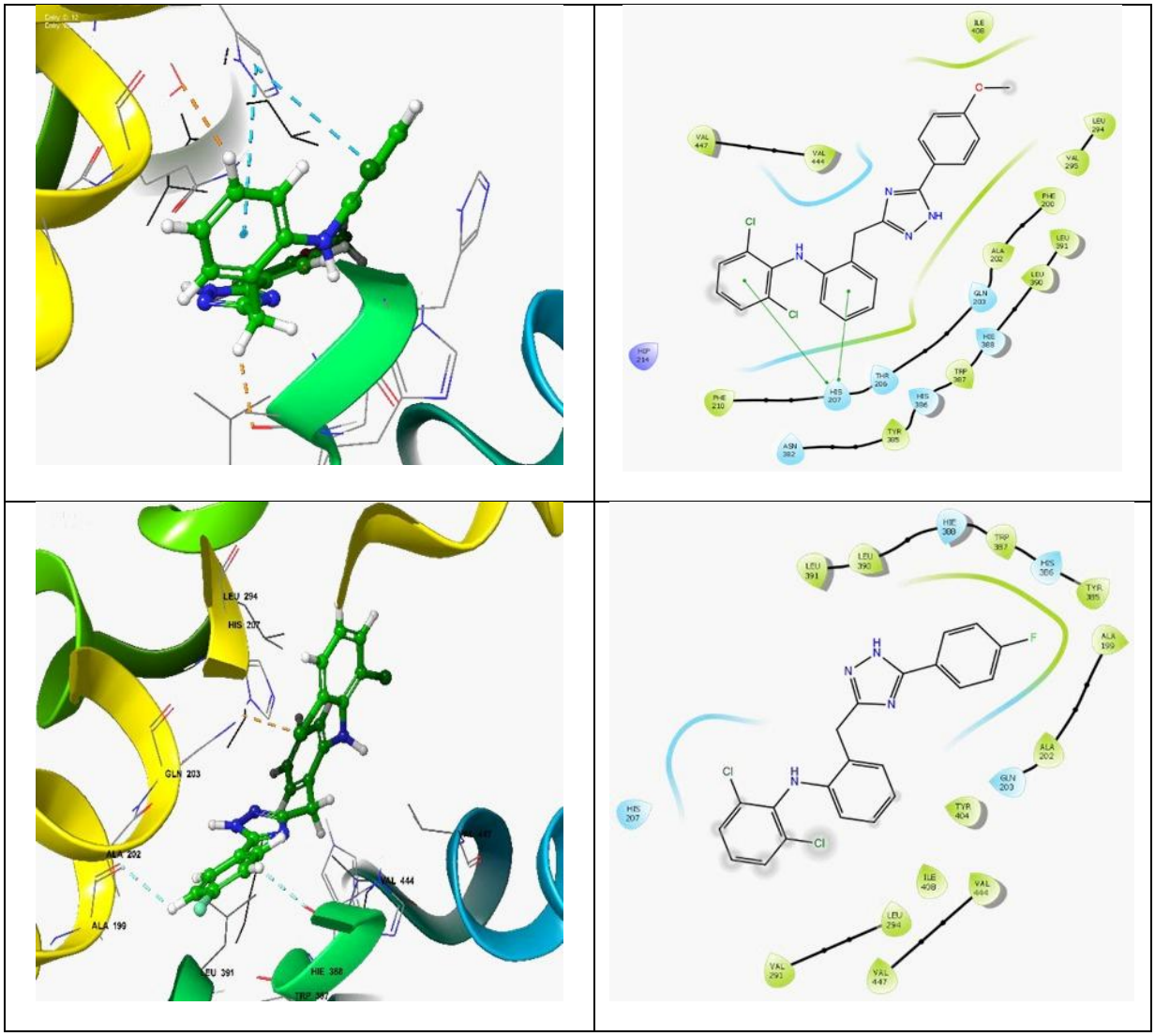
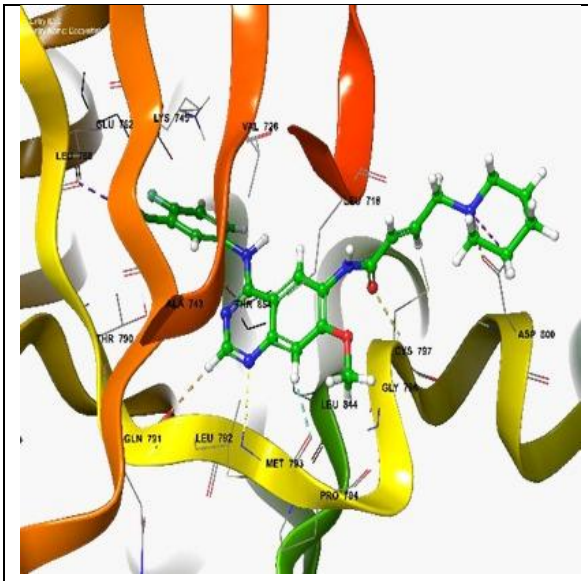


Figure No.17 1a & b Docked images of 3 compounds (PDB: 5F19).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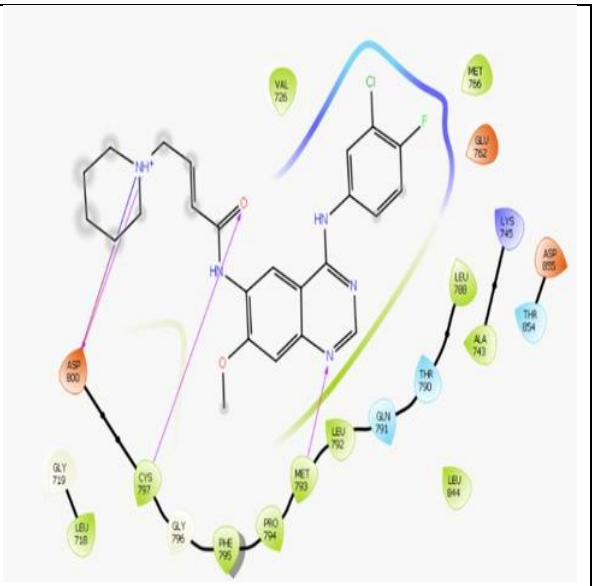
LYS 745
VAL 726
LEU 718
ALA 743
THR 854
THR 790
CYS 797
ASP 800
GLY 719
LEU 844
GLN 791
LEU 792
MET 793
PRO 794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LYS 745
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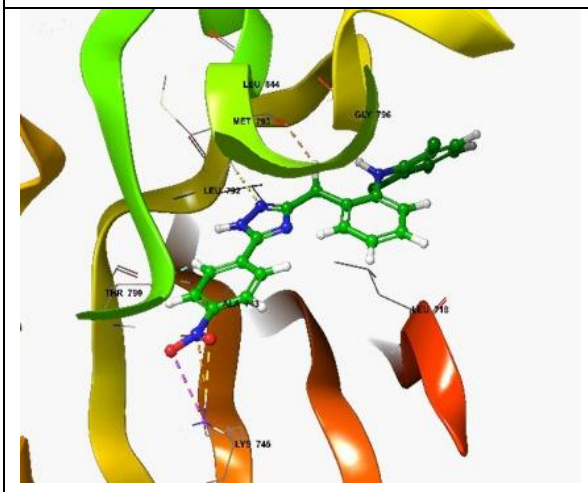
PHE 795
PRO 794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GLY 796
LEU 792
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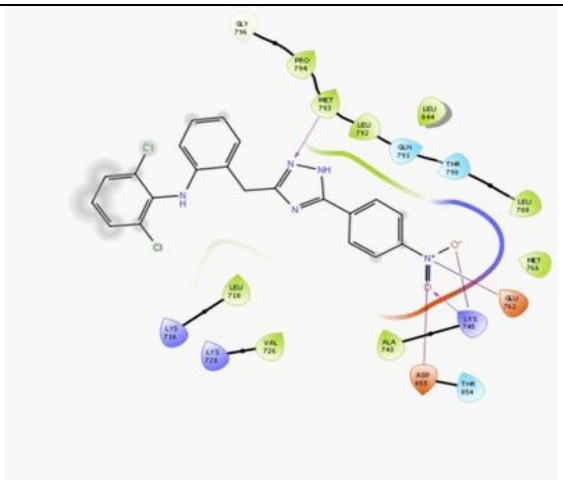
LYS 745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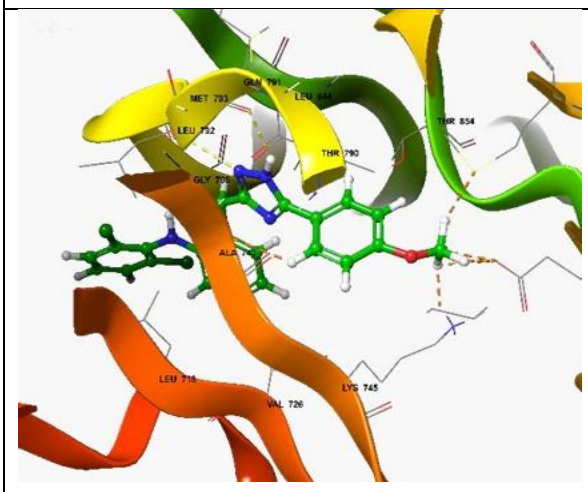
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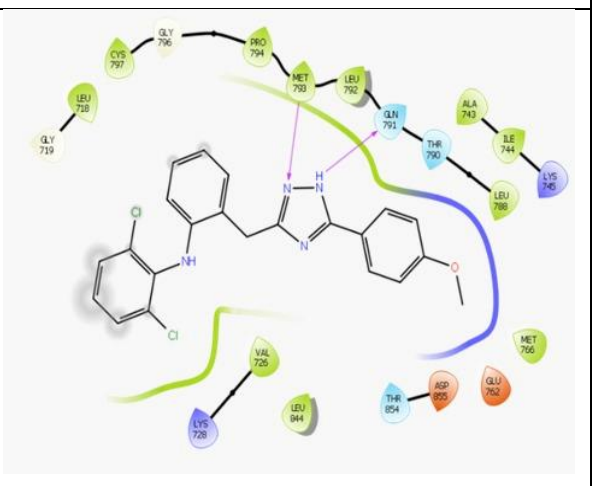
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LYS 728

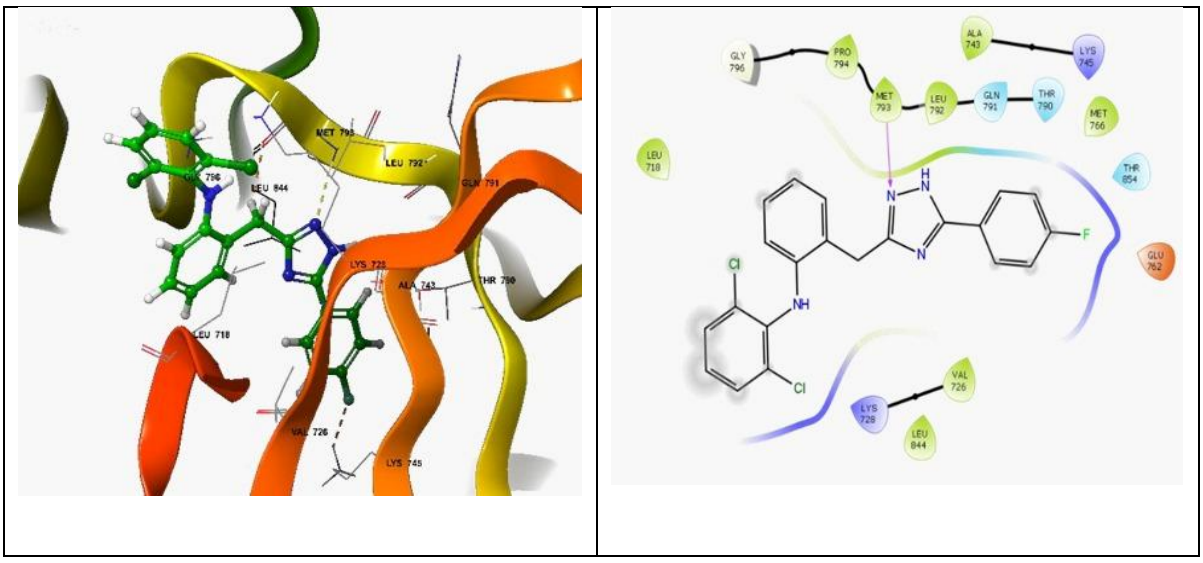

Figure No. 18 1a & b Docked images of 3 compounds over EGFR (PDB: 4I23).

ADME PREDICTION:

Table No. 19. Structures, scores and key interactions of 12 selected compounds along with standard Diclofenac & Dacomitinib

Comp. No.	Mol. MW	Donor HB	Acceptor HB	# Rotor	CNS	Q PlogS	Q PlogKhsa	PSA	QPlogPo /w	Percent Human Oral Absorption
Diclofenac (Standard drug)	296.152	2	2.5	4	-1	-5.323	0.039	57.948	4.501	100
Gefitinib (Standard drug)	446.908	1	7.7	8	1	-4.386	0.312	60.338	4.169	100
1	440.288	2	4	5	-1	-6.84	0.901	92.385	5.03	91.25
2	425.31	2	3.75	5	0	-6.32	0.89	55.17	5.54	100
3	413.28	2	3	4	1	-6.68	0.936	47.81	5.68	100

4. SUMMARY AND CONCLUSION

The present study focused on the design, synthesis, characterization, and molecular docking evaluation of novel diclofenac-based heterocyclic 1,2,4-triazole derivatives as potential anti-inflammatory and anticancer agents. The synthesized compounds containing different substituents such as chloro, nitro, methoxy, and fluoro groups were successfully prepared through a systematic synthetic approach.

Structural characterization was carried out using FTIR, UV-Visible, ^1H NMR, and Mass spectroscopy. FTIR analysis confirmed the presence of characteristic functional groups including N–H, C=N, aromatic C=C, and substituent-specific vibrations. UV-Visible spectroscopy revealed electronic transitions and demonstrated the influence of electron-donating and electron-withdrawing groups on the molecular framework. The ^1H NMR spectra confirmed the proton environment and validated the proposed structures, while mass spectral analysis verified the molecular weights and fragmentation patterns of the synthesized compounds. Collectively, the spectral data confirmed the successful synthesis of the target 1,2,4-triazole derivatives.

Molecular docking studies were performed against target proteins PDB ID: 5F19 and PDB ID: 4I23 to evaluate the anti-inflammatory and anticancer potential of the synthesized compounds. The docking results indicated that all compounds exhibited favorable binding affinities and interaction profiles with the selected targets. Among the synthesized derivatives, compound S3 demonstrated the most promising activity, showing the lowest docking scores and stable interactions with key amino acid residues such as HIS207 and MET793. The observed interactions suggest that these compounds may possess significant biological activity comparable to standard drugs.

Structure–activity relationship analysis revealed that the presence of the triazole ring along with suitable substituents enhanced ligand–protein interactions and improved binding stability. Drug-likeness evaluation showed that all synthesized compounds complied with Lipinski's Rule of Five and exhibited good predicted oral absorption, indicating favorable pharmacokinetic properties. However, their relatively high lipophilicity and low aqueous solubility suggest the need for further optimization.

In conclusion, the synthesized diclofenac hybridized 1,2,4-triazole derivatives represent promising lead molecules for the development of new anti-inflammatory and anticancer agents. Among them, compound S3 emerged as the most potent candidate based on docking performance and drug-likeness characteristics. Although the findings are encouraging, further in vitro and in vivo investigations are required to validate their biological efficacy, safety, and therapeutic potential. This work provides a valuable foundation for the future development of novel heterocyclic compounds with improved pharmacological activity and clinical relevance.

REFERENCES:

1. Chem. Yaseen YS, Farha MS, Salih SJ. Synthesis and evaluation of new diclofenac acid having 2-azetidinone. Der Pharma Chemica. 2017;9(20):44–49.
2. Galisteo A, Jannus F, García-García A, Aheget H, Rojas S, Lupiáñez JA, et al. Diclofenac N-derivatives as therapeutic agents with anti-inflammatory and anti-cancer effect. Int J Mol Sci. 2021;22:5067. doi:10.3390/ijms22105067.
3. Al-Tamimi MBW, Al-Majidi SMH. Synthesis, identification of some new 1,2,4-triazole derivatives from 6-amino-1,3-dimethyluracil and evaluation of their molecular docking, antioxidant and experimental activities. Int J

Health Sci. 2022;6(S6):7185–7203. doi:10.53730/ijhs.v6nS6.12019.
4. Thakkar K, Thakur S, Ray M, Doshi H. Synthesis, characterization and in silico designing of diethyl-3-methyl-5-(6-methyl-2-thioxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamido) thiophene-2,4-dicarboxylate derivative as antiproliferative and antimicrobial agents. Bioorg Chem. 2016;68:265–274.
5. Mason PR, Sinha BK. Biotransformation of hydrazine derivatives in the mechanism of toxicity. J Drug Metab Toxicol. 2014;5(2):1–5.
6. Kumari M, Tahlan S, Narasimhan B, Ramasamy K, Lim SM, Shah SAA, et al. Synthesis and biological evaluation of heterocyclic 1,2,4-triazole scaffolds as promising pharmacological agents. BMC Chem. 2021;15:5. doi:10.1186/s13065-020-00717-y.
7. Ahsan MJ, Gautam K, Ali A, Altamimi ASA, Salahuddin, Alossaimi MA, et al. Synthesis, anticancer activity, and in silico studies of 5-(3-bromophenyl)-N-aryl-4H-1,2,4-triazol-3-amine analogs. Molecules. 2023;28:6936.
8. Singhal N, Sharma PK, Dudhe R, Kumar N. Recent advancement of triazole derivatives and their biological significance. J Chem Pharm Res. 2011;3(2):126–133.
9. Matin MM, et al. Triazoles and their derivatives: chemistry, synthesis, and therapeutic applications. Front Mol Biosci. 2022;9:864286.
10. Emami L, et al. Design, synthesis and evaluation of novel 1,2,4-triazole derivatives as promising anticancer agents. BMC Chem. 2022;16:91.
11. Dai J, et al. Synthesis methods of 1,2,3-/1,2,4-triazoles: a review. Front Chem. 2022;10:891484.
12. Tange PR, et al. Molecular docking. JIPPR. 2023;28(4):28–40.
13. Bala S, et al. 1,3,4-Oxadiazole derivatives: synthesis, characterization, antimicrobial potential, and computational studies. Biomed Res Int. 2014.
14. Anastas PT, Warner JC. Green chemistry: theory and practice. Chem Rev. 2022;123(5):4567–4592.
15. Smith AR, Johnson BL. Advances in region- and stereo-selective synthetic procedures for complex molecule synthesis. J Org Chem. 2023;88(5):123–135.
16. Brown CD, White EF. Recent developments in one-pot, multicomponent, and domino reactions in organic synthesis. Org Lett. 2023;24(3):210–225.
17. Wang L, Li X. Recent advances in acid-base catalysis, transition metal catalysis, and enzymatic catalysis in green chemistry. Green Chem. 2023;30(2):359–372.
18. Garcia RS, Patel SK. Inter-phase catalysis: recent developments in phase transfer catalysis and micellar catalysis. J Catal. 2023;127(4):45–58.
19. Lee J, Kim H. Synthetic applications of supported catalysts and auxiliaries for easy separation, regeneration, and reusing in green chemistry. J Green Chem. 2022;9(1):310–325.
20. Zhang Q, Wang Y. Recent trends in solid-supported and combinatorial synthesis: applications in green chemistry. Chem Commun. 2024;41(8):780–793.
21. Li S, Li H, Yao S. Synthesis of polycarbonates from diphenyl carbonate: a green alternative to phosgene and methylene chloride. Green 2024;25(3):123–135.

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