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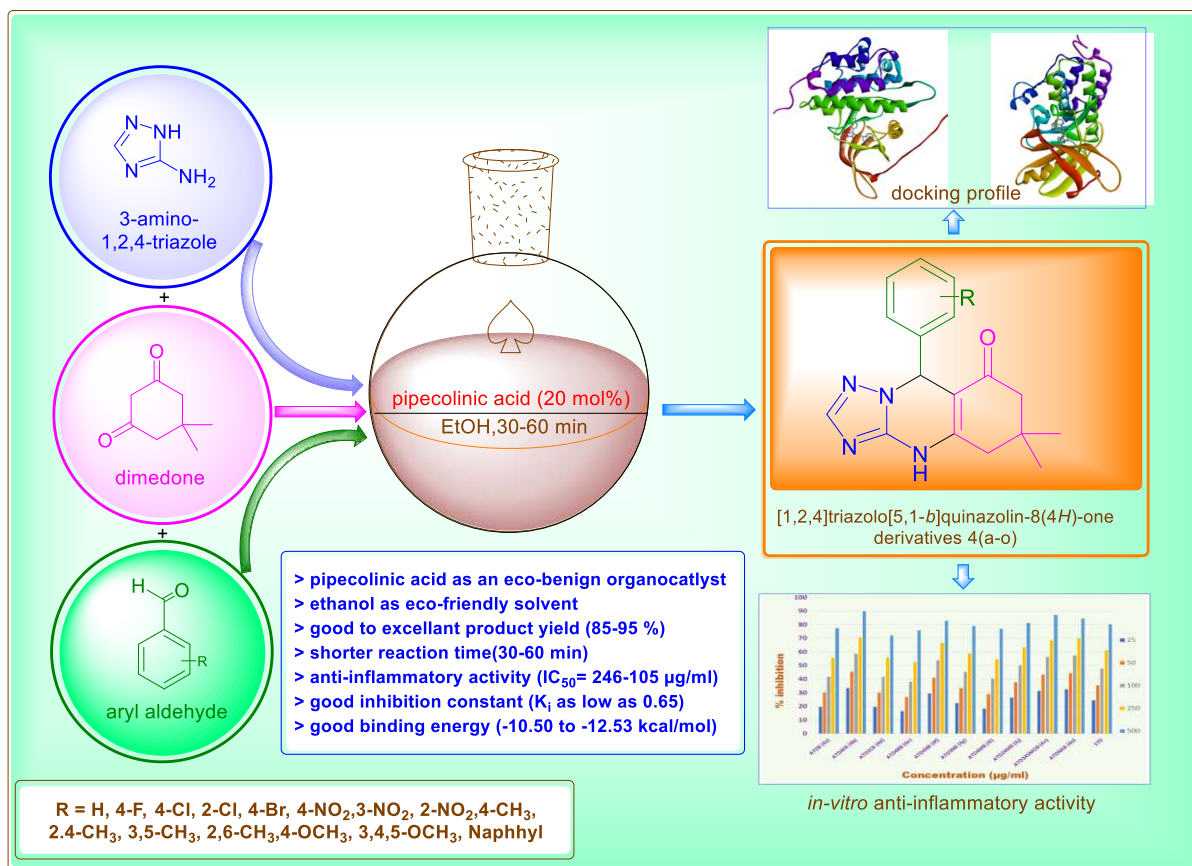
Non-Proteinogenic Amino Acid Catalyzed Green Synthesis of Triazolo[5,1-*b*]quinazolinone Scaffolds with Promising Anti-inflammatory Activity

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Graphical Abstract



Abstract

A series of 6,6-dimethyl-9-phenyl-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-*b*]quinazolin-8(4*H*)-one derivatives were synthesized *via* a one-pot multicomponent reaction of aromatic aldehydes, dimesone, and 3-amino-1,2,4-triazole (1:1:1 molar ratio) in ethanol at reflux temperature, employing pipecolic acid (20 mol%) as an organocatalyst. A library of 15 derivatives was obtained in good to high yields (up to 85-95%) within 30-60 min. The products were isolated by filtration, recrystallized, and fully characterized by IR, ¹H NMR, ¹³C NMR, ¹⁹F NMR and ESI-MS spectroscopy. This protocol offers a green, operationally simple, and efficient approach to triazolo-quinazolinone scaffolds using ethanol as solvent under reflux conditions. The anti-inflammatory activity of synthesized triazolo-quinazolines was evaluated *in-vitro* anti-inflammatory efficacy using the bovine serum albumin (BSA) denaturation assay, revealing that the substituents on benzaldehyde significantly influence protein stabilization. Among the tested compounds, the para-fluorophenyl derivative ATD4FB (4b) and the 2-naphthyl

analogue ATDNAB (4o) emerged as potent leads, exhibiting IC_{50} values of 93.99 $\mu\text{g/ml}$ and 105.61 $\mu\text{g/ml}$, respectively; and significantly outperforming the standard Diclofenac Sodium (IC_{50} =186.56 $\mu\text{g/ml}$). Mechanistically, the efficiency of para-fluorophenyl derivative ATD4FB (4b) is attributed to strong ring polarization and hydrogen bonding, while 2-naphthyl analogue ATDNAB (4o) leverages extensive π - π stacking and hydrophobic anchoring. In contrast, the bulky para-bromophenyl derivative ATD4BB (4e) was the least active (IC_{50} =255.39 $\mu\text{g/ml}$) due to severe steric hindrance. These findings highlight 4b and 4o as highly promising scaffolds for anti-inflammatory drug development.

Keywords: quinazolinone, triazole, molecular hybrid, pipecolinic acid, anti-inflammatory, bovine serum albumin

1. INTRODUCTION

Multicomponent reactions (MCRs) have become a basis of modern synthesis, offering a remarkably efficient route for synthesis of bioactive heterocycles and complex natural products. By reducing multiple steps into a single, green operation, these reactions maximize atom economy while reducing waste and purification hurdles.¹ This efficiency makes them indispensable in drug discovery. Today, the real breakthrough lies in pairing MCRs with organocatalysis; this synergy enables highly stereoselective cascades that produce the enantiomerically pure compounds essential for advanced chemical biology.²

Triazole-derived pharmaceuticals have emerged as a significant motif in modern therapy, largely due to their unique physicochemical profile.³ 1,2,4-triazole ring is a planar, π -excessive aromatic system whose electron-donating character helps in binding with target protein or enzyme through a captivating network of π - π stacking, hydrogen bonding, and non-covalent forces.⁴ Further, the polar nature of 1,2,4-triazole ring (marked by a low $\log P$) significantly enhances its solubility in physiological medium, and thereby results in improved absorption.⁵ Triazole-based drugs possess medicinal properties such as anti-convulsant,⁶ anti-tumour,⁷ anthelmintic,⁸ anti-inflammatory, anti-microbial,^{9,10} anti-bacterial,¹¹ antileishmanial,¹² anti-tubercular,¹¹ anti-Alzheimer,¹³ anti-fungal,¹⁴ trypanocidal,¹⁵ anti-cancer,¹⁶ anti-viral¹⁷ and anti-diabetic¹⁸ properties. Notably, compounds with triazole core have been identified as dipeptidyl peptidase IV (DPP-IV) inhibitors¹⁹ α -amylase inhibitor^{20,21} and α -glucosidase inhibitor^{21,22} for type 2 diabetes treatment. **Figure 1.** illustrates representative medicinally bioactive pharmaceuticals containing the 1,2,4-triazole core.

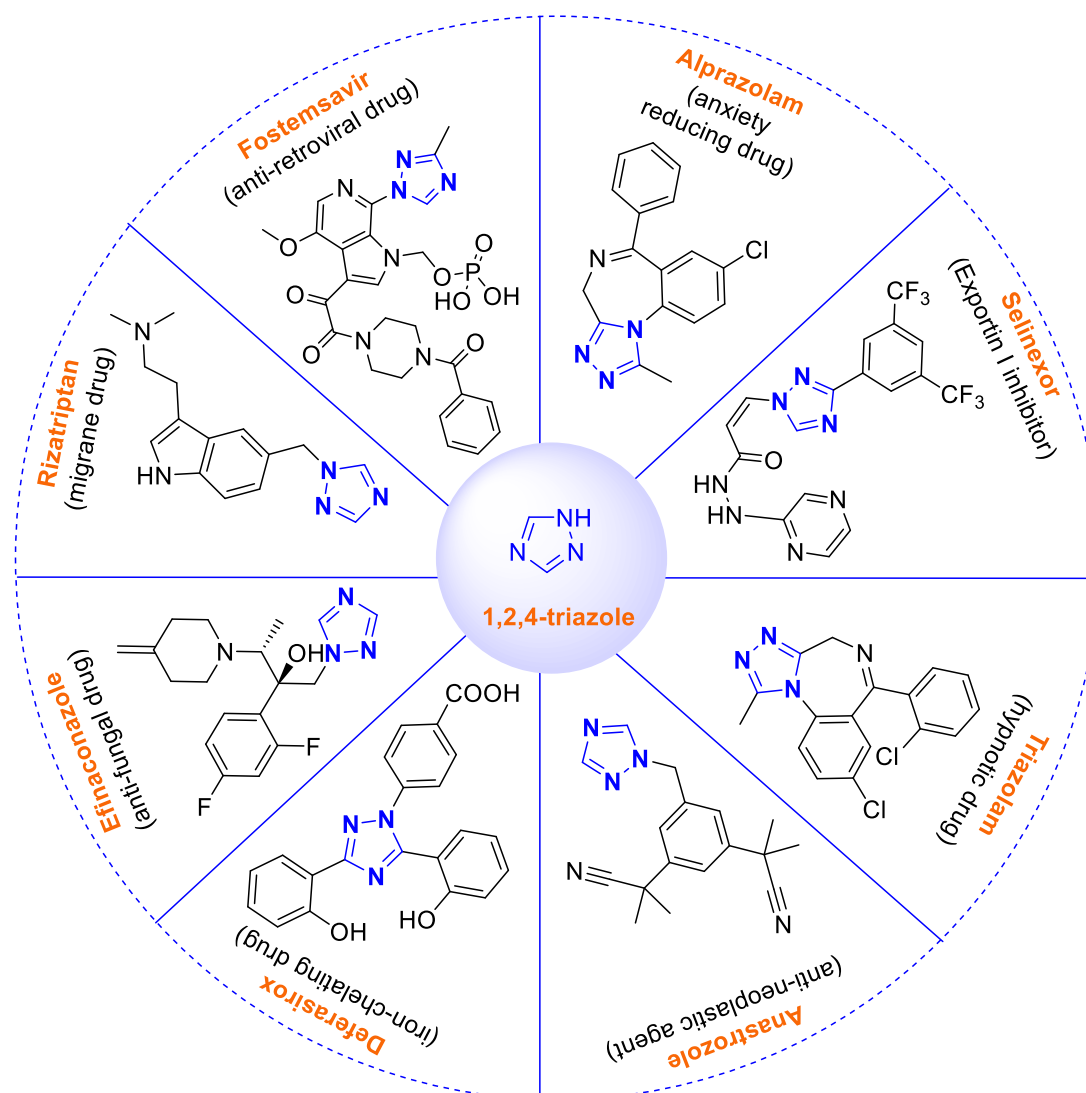


Figure 1: Commercial drugs containing triazole scaffolds

Quinazolinones are becoming important candidates in medicine because they can treat many different health conditions. In fact, several of them are already being tested on humans in clinical trials, including gefitinib, erlotinib, lapatinib, and afatinib (EGFR kinase inhibitors in oncology), *methaqualone* (sedative-hypnotic), and *prazosin* (antihypertensive).^{23–25} These compounds were pronounced for their wide range of pharmacological activities such as anti-cancer,²⁵ anti-convulsant,²⁶ anti-malarial,²⁷ anti-fungal,²⁸ anti-bacterial,²⁹ anti-inflammatory³⁰ and anti-diabetes activity.³¹ These findings indicates the importance of installing quinazolinone moiety into another heterocyclic systems to develop novel therapeutic agents.

Moreover, researchers are focused on developing quinazolinone-triazole molecular hybrids because of their critical therapeutic and pharmacological applications. These compounds exhibit diverse biological activities, including anti-tubercular,³² anti-mycotic,³³ anti-fouling,³⁴ anti-fungal³² properties, Driven by the remarkable biological profiles of quinazolines and quinazolinones, various catalysts such as γ -Fe₂O₃@Ph-PMO-NaHSO₄,³⁵ silica gel,³⁶ [(DABCO)₂C₃H₅OH]·2Cl,³⁷ anthranilic acid,³⁸ I₂,³⁹ NH₂SO₃H,⁴⁰ @HAp@KIT-6),⁴¹ NGPU: glucose/pregabalin/urea,⁴² Nafion-H,⁴³ [RHA-[bip]-NH₂⁺HSO₄⁻],⁴⁴ Fe₃O₄@COF-SO₃H,⁴⁵ have been used for the synthesis of [1,2,4]triazolo[5,1-b]quinazolin-8(4H)-one derivatives. Although these methods expand chemical

synthesis options, they require metal-based or highly complex catalysts. The tedious laboratory work needed to prepare these catalysts limits their practical use, especially in the pharmaceutical industry.

However, organocatalysis, speeding up chemical reactions using small, metal-free organic molecules as catalysts — has emerged as a template in synthetic chemistry.⁴⁶ Organocatalysts are superior to metal catalysts because they are safer, cheaper, and easier to use. Being completely metal-free, they eliminate the risk of toxic contamination, and thereby bypass regulatory concerns. They are also highly cost-effective, readily available, cheap, durable, easy to handle.⁴⁷ Finally, they are incredibly precise, using specific activation pathways to build the exact molecular structures required for modern medicine.⁴⁸

Amino acids are remarkable source of organocatalysts, for example, L-proline and its structural congeners were extensively employed as organocatalyst in organic transformations.⁴⁹ Extending this logic beyond proline, pipercolinic acid – a naturally occurring, non-protein six membered cyclic α -amino acid - a structural analogous to five membered L-proline, differing only in the ring size, serves as a versatile organocatalyst in organic synthesis.⁵⁰ The larger ring of pipercolinic acid imparts greater conformational flexibility, steric nature, and enhanced availability of the nitrogen lone pair. This property increases the reactivity and selectivity patterns compared to proline.⁵¹ Its bifunctional nature allows it to act as both a Lewis base (through the nitrogen) and a Brønsted acid (through the carboxylic acid), enabling it to activate both nucleophiles and electrophiles simultaneously. This dual activation capability makes pipercolinic acid a good catalyst.^{52,53}

There are limited reports on utilizing pipercolinic acid as an organocatalyst for the synthesis of triazolo[5,1-*b*]quinazolinone derivatives. Furthermore, while existing green catalysis involves use of nano-catalysts or deep eutectic systems, which requires tedious laboratory work.^{41,42} This means that there is a need for simpler organo-catalyst alternatives. The pipercolinic acid has flexible ring geometry and bifunctional groups and use of it as an organocatalyst for organic synthesis of triazolo[5,1-*b*]quinazolinone derivatives remains unexplored field of study. Despite the fact that separate triazole and quinazolinone compounds are known to exhibit anti-inflammatory properties,^{19,31} the exploration of the combined triazolo-quinazolinone scaffold—specifically with the 6,6-dimethyl-9-phenyl substitution—for targeted anti-inflammatory activity remains entirely unexplored. Thus, in addition to our previous work on the viable design of heterocyclic compounds,^{54–60} herein, we report pipercolinic acid promoted green synthesis and anti-inflammatory study of 6,6-dimethyl-9-phenyl-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-*b*]quinazolin-8(4H)-one derivatives.

2. RESULTS AND DISCUSSION

To establish the most efficient protocol for synthesizing the target 6,6-dimethyl-9-phenyl-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-*b*]quinazolin-8(4H)-one derivatives, a systematic optimization study was conducted using anisaldehyde, dimedone, and 3-amino-1,2,4-triazole as model substrates using 5 mol% of pipercolinic acid as catalyst at reflux temperature. The reaction parameters—including the necessity of the catalyst, solvent screening, and catalyst loading—were evaluated to maximize product yield while minimizing reaction time. (**Table 1**)

When the cyclocondensation reaction of anisaldehyde, dimedone, and 3-amino-1,2,4-triazole was carried out in ethanol (EtOH) at reflux temperature for 6 hours without any catalyst, only a trace amount of the desired product, namely, 9-(4-methoxyphenyl)-6,6-dimethyl-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-*b*]quinazolin-8(4H)-

one (4m) was detected, (Entry 1). This implies that the presence of a catalyst is necessary for this multicomponent condensation.

The choice of solvent also has an influence on product yield. Both polar and non-polar solvents were screened for their efficiency in promoting this reaction. Non-polar solvents such as hexane yielded virtually no product (2%, Entry 2). Similarly, highly polar solvents like ethyl acetate (20%, Entry 6), water (26%, Entry 8), and acetonitrile (34%, Entry 5) resulted in poor conversions even after 5 to 6 hours. Performing the reaction in solvent-free conditions gave a low yield of 26% after 6 hours (Entry 13). We have employed ethanol and methanol as solvent, we have observed that methanol (MeOH) gave a moderate 55% yield in 4 hours (Entry 4), ethanol (EtOH) resulted in 75% yield in a shorter time of 3 hours (Entry 3). Its protic nature likely assists in hydrogen-bonding networks that stabilize transition states during the reaction.

To investigate the influence of the loading of the pipecolinic acid catalyst on reaction rate, catalyst amount was varied to optimize the reaction efficiency, we have achieved 75% of yield with catalyst load of 5 mol% pipecolinic acid after 3 hours (Entry 3). When the catalyst load was increased from 10 mol% to 15 mol%, the reaction time decreased and yield increased up to 81% and 85% respectively (Entries 9 & 10). Further raising the catalyst loading to 20 mol% yielded the most dramatic kinetic improvement, slashing the reaction time to just 30 minutes (0.5 h) and boosting the isolated yield to 89% (Entry 11). 25 mol%: Increasing the load even further to 25 mol% offered a negligible return, changing the yield by a mere 1% (90% yield, Entry 12) while consuming more catalyst. Thus, employing 20 mol% of pipecolinic acid in ethanol was needed to ensure an excellent yield (89%).

Table 1: optimization of reaction conditions ^s				
S.No	Catalyst	Solvent	Time (h)	% Yield
1	-	EtOH	6	Trace
2	Pipecolinic acid	hexane	6	2
3	Pipecolinic acid	EtOH	3	75
4	Pipecolinic acid	MeOH	4	55
5	Pipecolinic acid	acetonitrile	6	34
6	Pipecolinic acid	Ethyl acetate	5	20
7	Pipecolinic acid	Dichloromethane	6	42
8	Pipecolinic acid	Water	6	26
9	Pipecolinic acid ^a	EtOH	1	81
10	Pipecolinic acid ^b	EtOH	1	85
11	Pipecolinic acid ^c	EtOH	0.5	89
12	Pipecolinic acid ^d	EtOH	0.5	90
13	Pipecolinic acid ^c	-	4	36
^s anisaldehyde (5 mmol), dimedone (5 mmol), 3-Amino-1,2,4-triazole (5 mmol), Catalyst load = 5 mol%, room temperature, solvent volume=10 ml. ^a catalyst load=10 mol%; ^b catalyst load=15 mol%; ^c catalyst load=20 mol%; ^d catalyst load=25 mol%;				

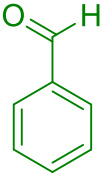
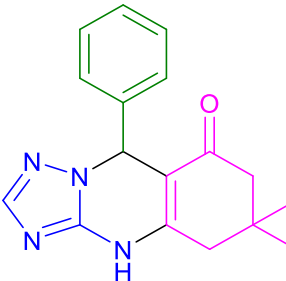
To evaluate the substrate scope of the pipecolinic acid-catalyzed multicomponent condensation, a diverse panel of aryl aldehydes bearing electronically and sterically varied substituents was subjected to reaction with

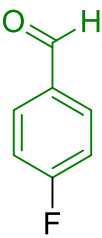
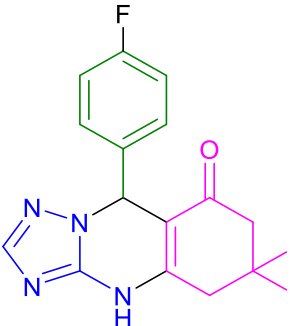
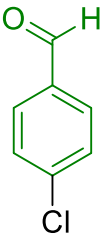
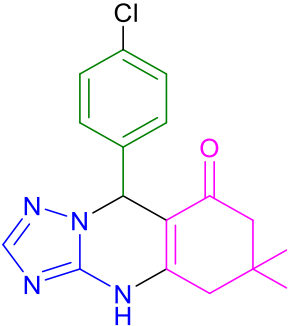
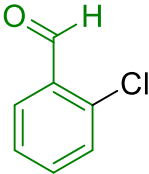
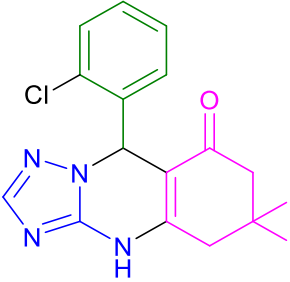
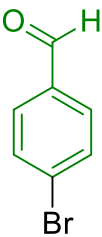
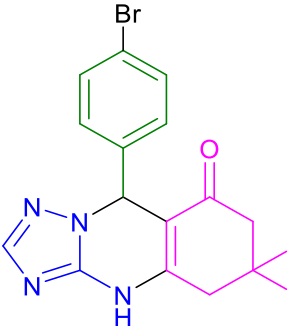
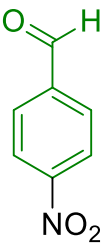
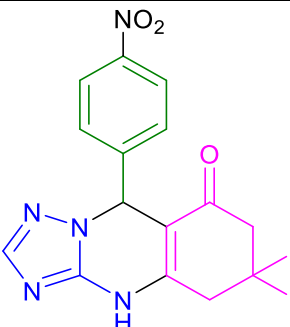
dimedone and 3-amino-1,2,4-triazole in ethanol at room temperature. The results, summarized in Table 2, reveal a consistent pattern wherein both the electronic nature and the positional disposition of substituents on the aromatic ring exert a discernible influence on reaction efficiency, as reflected in the isolated yields and reaction times. (Table 2)

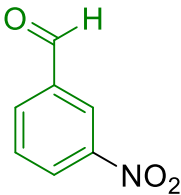
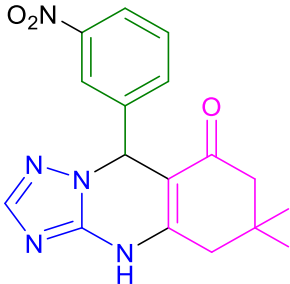
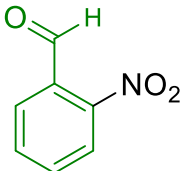
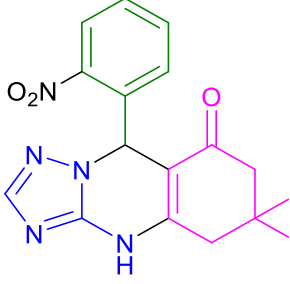
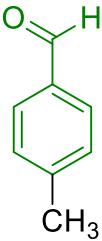
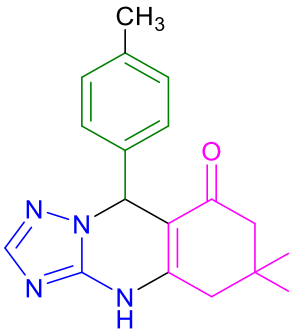
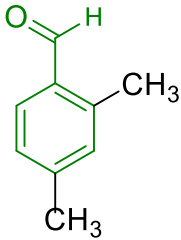
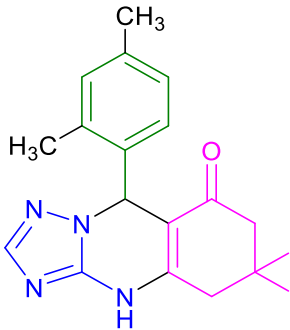
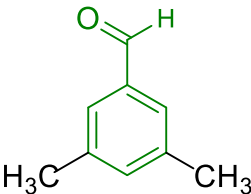
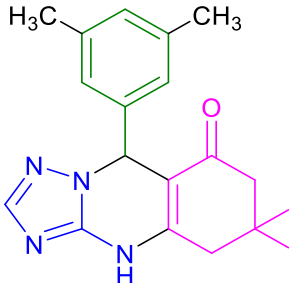
Unsubstituted benzaldehyde (entry **a**) afforded the triazoloquinazolinone product **4a** in 81% yield over 45 min, establishing a reliable baseline for comparative analysis. Introduction of substituents onto the aromatic ring produced notable and interpretable deviations from this benchmark, underscoring the electronic sensitivity of the catalytic manifold.

Among electron-withdrawing substituents, *para*-fluorobenzaldehyde (entry **b**, 82%, 30 min) and *para*-chlorobenzaldehyde (entry **c**, 85%, 30 min) delivered improved yields relative to the parent aldehyde, with a concurrent reduction in reaction time. This trend reached its most pronounced expression with *ortho*-chlorobenzaldehyde (entry **d**), which furnished the product in an exceptional 96% yield in merely 15 min — the highest yield and shortest reaction time across the entire substrate series. The markedly superior performance of the *ortho*-chloro derivative may be attributed to a combination of the strong inductive withdrawal of the halogen and a possible steric-electronic synergism arising from its proximal disposition relative to the carbonyl, which further polarizes the aldehyde carbon and renders it more susceptible to nucleophilic attack in the initial Knoevenagel-type condensation step. Similarly, *para*-bromobenzaldehyde (entry **e**, 84%, 15 min) proved highly reactive, consistent with the strong -I effect of the bromo substituent.

Nitro-substituted aldehydes, being among the most potent electron-withdrawing groups, further corroborated this electronic trend. The *para*-nitrobenzaldehyde (entry **f**) delivered 94% yield in 30 min, while the *meta*-nitro isomer (entry **g**) gave 88% yield in 20 min, and the *ortho*-nitro counterpart (entry **h**) afforded 91% yield in 30 min. The slightly diminished yield of the *meta*-nitro derivative relative to the *para* isomer is consistent with the meta-directing, purely inductively withdrawing character of the nitro group at this position, which activates the carbonyl through field effects but to a somewhat lesser degree than at the para position. Collectively, the halo- and nitro-bearing aldehydes confirm that electron withdrawal from the aromatic ring activates the aldehyde toward condensation and accelerates product formation under these mild catalytic conditions.

Table 2: Substrate scope for synthesis of 6,6-Dimethyl-9-phenyl-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1 b]quinazolin-8(4H)-one derivatives [#]				
Entry	Aldehyde (3)	Product (4)	Time (h)	Yield (%)
a			45	81

b			30	82
c			30	85
d			15	96
e			15	84
f			30	94

g			20	88
h			30	91
i			30	85
j			30	95
k			25	85

l			15	87
m			20	89
n			15	95
o			60	88
#Aromatic aldehyde (5 mmol), dimedone (5 mmol), 3-Amino-1,2,4-triazole (5 mmol), Catalyst= pipecolinic acid; Catalyst load = 20 mol%, reflux temperature, solvent=EtOH, solvent volume=10 ml.				

A contrasting, yet equally informative, trend emerged with electron-donating substituents. Methyl-substituted aldehydes (entries **i-l**) consistently produced good yields in the range of 85–95%, though reaction times were modestly longer than those of the more reactive electron-withdrawing analogues. The *para*-methylbenzaldehyde (entry **i**, 85%, 30 min) provided a moderate improvement over benzaldehyde, while the 2,4-dimethyl (entry **j**, 95%, 30 min) and 3,5-dimethyl (entry **k**, 85%, 25 min) derivatives demonstrated that additional methyl substitution does not attenuate reactivity. Notably, the 2,6-dimethylbenzaldehyde (entry **l**, 87%, 15 min) gave a shortened reaction time despite flanking steric bulk, suggesting that the cumulative electron donation

through hyperconjugation and inductive effects from two *ortho*-methyl groups sufficiently activates the aldehyde to compensate for any steric retardation. The *para*-methoxybenzaldehyde (entry **m**, 89%, 20 min) and the 3,4,5-trimethoxybenzaldehyde (entry **n**, 95%, 15 min) likewise performed admirably; the latter, bearing three methoxy groups, achieved the highest yield among the electron-rich substrates and a surprisingly short reaction time, which may reflect the cumulative electron-donating and coordination-facilitating effect of the polyoxygenated ring amplifying substrate–catalyst interactions in a favorable manner. These results indicate that electron donation, while generally moderating electrophilicity, does not substantially inhibit the reaction under the organocatalytic conditions employed, likely because pipercolinic acid activates the carbonyl sufficiently through iminium or hydrogen-bonding intermediacy to override modest reductions in intrinsic aldehyde electrophilicity.

Finally, 1-naphthaldehyde (entry **o**), a heteroaromatic/polycyclic substrate with extended conjugation, produced the product in 88% yield, albeit requiring a prolonged reaction time of 60 min. The extended π -system delocalizes electron density from the carbonyl, reducing its electrophilicity, while the peri-hydrogen of the naphthalene ring may also impose a degree of steric hindrance. The combination of these factors is reflected in the noticeably longer reaction times relative to monoaromatic substrates of comparable electronic character. Taken together, the substrate scope data establish that this pipercolinic acid-catalyzed three-component protocol is broadly tolerant of electronic and steric variations. Electron-withdrawing substituents, particularly halogens at the *ortho* and *para* positions and nitro groups, generally enhance both yield and reaction rate by increasing the electrophilicity of the aldehyde carbonyl. Electron-donating groups permit the reaction to proceed with good efficiency, reflecting the robustness of the organocatalytic activation mode. The reaction is thus well-suited for the rapid and efficient construction of structurally diverse 6,6-dimethyl-9-aryl-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-*b*]quinazolin-8(4H)-one derivatives under operationally simple, ambient conditions.

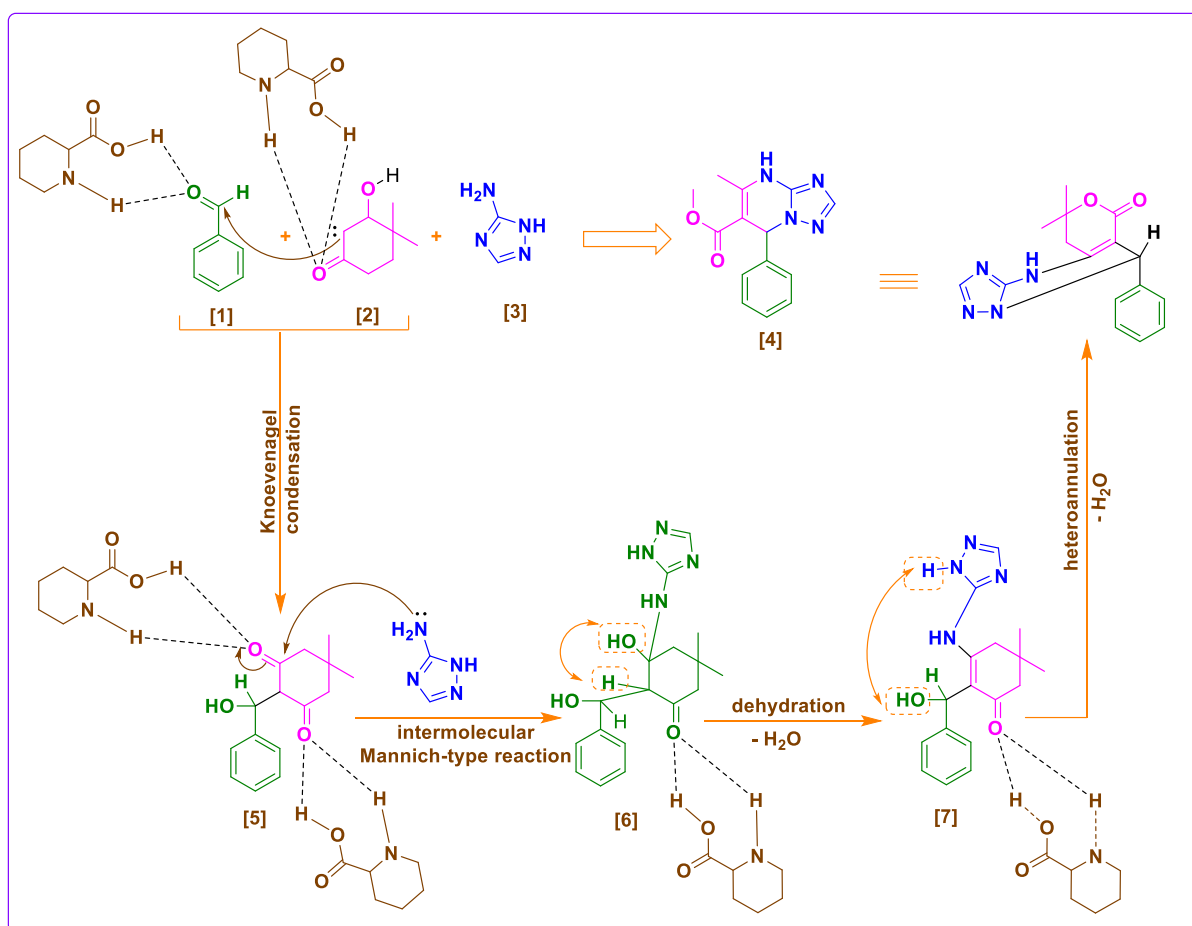
All the synthesized compounds were characterized by analytical techniques like IR, ^1H NMR, ^{13}C NMR and mass spectroscopy. For example, the synthesized compound (**4o**) was identified as 6,6-dimethyl-9-(naphthalen-1-yl)-5,6,7,9-tetrahydro-triazolo[5,1-*b*]quinazolin-8(4H)-one on the basis of IR, ^1H NMR, ^{13}C NMR and mass spectral data. The IR spectrum showed a strong absorption band at 1639 cm^{-1} corresponding to the C=O stretching of the quinazolin-8-one lactam carbonyl, along with aromatic C–H stretching at 3075 cm^{-1} and aliphatic C–H bands at 2959 and 2805 cm^{-1} , indicating the presence of both aromatic and saturated aliphatic moieties. The ^1H NMR spectrum (400 MHz, DMSO- d_6) displayed a singlet at 11.21 ppm attributable to a deshielded N-H proton, a multiplet region between 8.15–7.09 ppm corresponding to aromatic protons of the naphthalene and fused benzene rings, a signal at around 3.35 ppm assigned to a benzylic/N-CH proton, a series of signals between 2.63–2.04 ppm due to the tetrahydro ring CH_2/CH protons, and a signal at 1.12 ppm due to the 6,6-dimethyl protons. The ^{13}C NMR spectrum (100 MHz, DMSO- d_6) exhibited a downfield signal at 193.6 ppm for the lactam carbonyl carbon, signals in the range 151–147 ppm for C=N and quaternary aromatic carbons of the triazoloquinazoline system, multiple aromatic carbons between 138.8–124.3 ppm, a heteroaromatic carbon at 106.6 ppm, N-CH/benzylic carbons at 56.5–50.3 ppm, and several saturated ring carbons around 40–33 ppm, and two methyl carbons at 28.9 and 27.6 ppm consistent with the 6,6-dimethyl substitution. The positive-ion mass spectrum showed a prominent molecular ion peak in the region of m/z 346–347, which is in agreement with the expected $[\text{M}+\text{H}]^+$ of the proposed structure, along with characteristic fragment ions at 217.1 supporting the presence of a naphthalene substituent and a fused heterocyclic core. Taken together, the IR, NMR and mass spectrometric

features are mutually consistent and unambiguously support the structure of 6,6-dimethyl-9-(naphthalen-1-yl)-5,6,7,9-tetrahydro-triazolo[5,1-b]quinazolin-8(4H)-one.

Plausible mechanism

The multicomponent condensation proceeds through a well-orchestrated sequence of elementary steps — Knoevenagel condensation, intermolecular Mannich-type reaction, and terminal heteroannulation — each facilitated by the pipercolinic acid organocatalyst. The catalytic cycle is initiated by the activation of dimedone **[2]** through enamine formation with the secondary amine functionality of pipercolinic acid. The resulting nucleophilic enamine intermediate engages the aryl aldehyde **[1]** in a Knoevenagel condensation, generating the α,β -unsaturated adduct **[5]** — a classic arylidene-dimedone Knoevenagel product — with concomitant regeneration of water. This step establishes the electrophilic alkene that serves as the linchpin for the subsequent carbon–nitrogen bond-forming event. The role of pipercolinic acid here is dual: its secondary amine condenses with the active methylene of dimedone to generate the reactive enamine, while its carboxylate provides proton shuttle assistance, collectively lowering the activation barrier for C–C bond formation.

The Knoevenagel adduct **[5]** next undergoes conjugate addition with 3-amino-1,2,4-triazole **[3]**, wherein the exocyclic amino group acts as the nucleophile and attacks the activated β -carbon of the arylidene double bond in a Michael/Mannich-type fashion. This step forges the critical C–N bond that tethers the triazole fragment to the dimedone-derived scaffold, yielding the open-chain adduct **[6]** bearing a free hydroxyl group and a pendant aminotriazole unit poised for ring closure. The catalyst is retained in this intermediate as a non-covalent ion-pair or hydrogen-bonding complex, maintaining activation and directing the molecular geometry toward productive cyclization. Intermediate **[6]**, upon intramolecular nucleophilic attack, undergoes heteroannulation: the ring nitrogen of the triazole condenses with the carbonyl/hemiketal functionality of the dimedone ring system, closing the dihydroquinazolinone ring with expulsion of water ($-\text{H}_2\text{O}$, **7** $\rightarrow$ **4**). This dehydration step is thermodynamically favorable and is facilitated by the acidic conditions provided by the pipercolinic acid catalyst, which protonates the departing hydroxyl and stabilizes the developing iminium ion in the transition state. The net outcome is the aromatization-driven formation of the fused triazoloquinazolinone ring system **[4]**, releasing the pipercolinic acid catalyst to re-enter the cycle. (**Scheme 1**)



Scheme 1 Proposed plausible mechanism

The elegance of this mechanism lies in the cascade nature of the three steps — each product serves as the substrate for the next transformation without isolation. The pipercolinic acid catalyst threads through the entire sequence not merely as a proton donor, but as an active enamine-forming organocatalyst in the first step and as a Brønsted acid facilitator in the latter two. The thermodynamic driving force for the overall transformation is the release of two equivalents of water and the concomitant gain in aromatic/conjugative stabilization upon formation of the bicyclic heteroaromatic product. This cascade design is precisely why the reaction proceeds efficiently at room temperature in ethanol within remarkably short reaction times — the successive steps are kinetically coupled, preventing accumulation of any single intermediate and driving the equilibrium decisively toward the fused heterocyclic product.

Anti-inflammatory activity (BSA denaturation method)

Protein denaturation is implicated in inflammation, a process characterized by redness, pain, heat, swelling, and loss of function in injured living tissues. This denaturation involves the disruption of electrostatic, hydrogen, hydrophobic, and disulfide bonds within the protein structure. Furthermore, a complex cascade of enzyme activation, mediator release, cell migration, tissue breakdown, and repair mechanisms ensues, leading to the loss of protein molecular conformation and function. Consequently, compounds capable of preventing these structural changes and inhibiting thermally induced protein denaturation possess potential therapeutic value as anti-inflammatory agents. The Bovine Serum Albumin (BSA) denaturation method is an *in vitro* assay used to screen compounds for anti-inflammatory properties. It evaluates a substance's ability to prevent proteins from losing their structural shape when exposed to heat, which is a known mechanism of action for common NSAIDs.

The synthesized compound and standard diclofenac sodium were screened for anti-inflammatory activity by using the inhibition of albumin denaturation technique with minor modification. The standard drug and compound were dissolved in minimum quantity of Dimethyl formamide (DMF) and diluted with phosphate buffer (0.2 M, PH 7.4). The final concentration of DMF in all solutions was less than 2.5%. Test Solution (2.5 mL) containing different concentrations of the drug was mixed with 1 mL of 1 mM Bovine serum albumin solution in phosphate buffer and incubated at 37 °C in an incubator for 10 min. Denaturation was induced by keeping the reaction mixture at 70°C in a water bath for 10 min. After cooling, the turbidity was measured at 660 nm. Percentage of inhibition of denaturation was calculated from the control where no drug was added. The percentage inhibition of denaturation was calculated by using the following formula:

$$\% \text{ of inhibition} = 100 \times \left(\frac{A_c - A_t}{A_c} \right)$$

where, A_t = Absorbance of test; A_c = Absorbance of control.

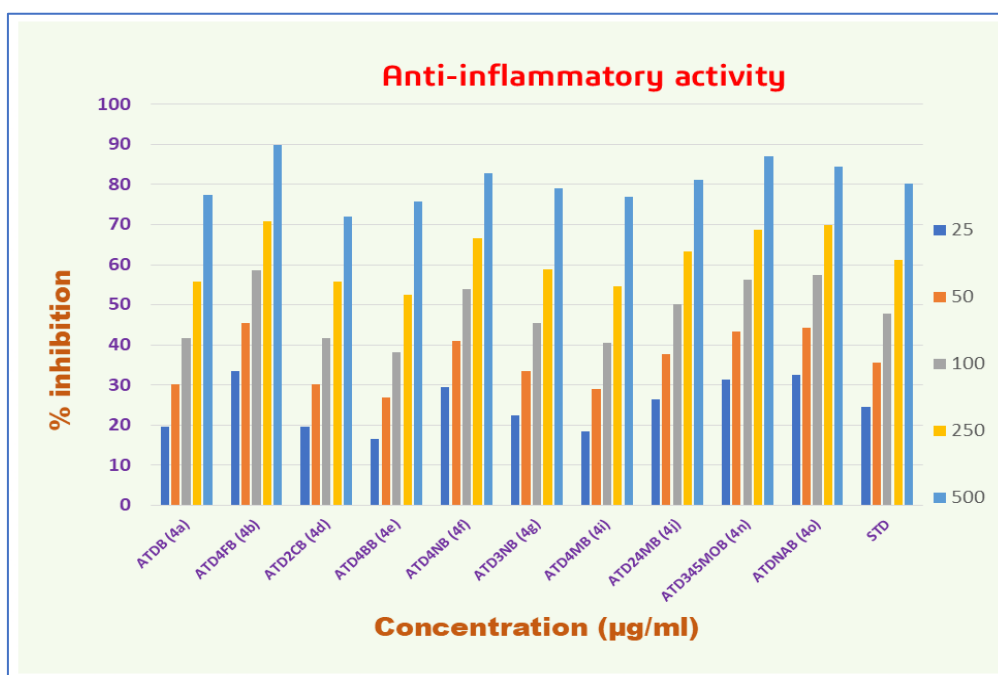


Figure 2 Anti-inflammatory activity by BSA denaturation method

Across all tested compounds and the standard (diclofenac sodium), there is a clear dose-dependent increase in anti-inflammatory activity. As the concentration scales up from 25 µg/ml to 500 µg/ml. The bars on the graph steadily rise. The percentage inhibition values increased significantly. For instance, compound 4b jumps from 33.46% inhibition at 25 µg/ml to an impressive 89.89% inhibition at 500 µg/ml. The bottom row of your table shows the IC_{50} value (µg/ml). IC_{50} is the concentration of a compound required to inhibit protein denaturation by exactly 50%. In pharmacology, a lower IC_{50} value means a compound is more potent because it requires a smaller dose to achieve a 50% therapeutic effect. By ranking the compounds according to their IC_{50} values, we can determine which synthesized drugs outperform the standard and which are less effective. (Figure 2, Table 3)

Table 3. Anti-inflammatory activity of 6,6-dimethyl-9-phenyl-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-b]quinazolin-8(4H)-one derivatives

Conc ($\mu\text{g}/\text{ml}$)	ATDB (4a)	ATD4 FB (4b)	ATD2 CB (4d)	ATD4 BB (4e)	ATD4 NB (4f)	ATD3 NB (4g)	ATD4 MB (4i)	ATD24 MB (4j)	ATD345M OB (4n)	ATD NAB (4o)	STD (Diclofena c)
25	19.48	33.46	19.48	16.43	29.44	22.45	18.44	26.47	31.45	32.49	24.46
50	30.11	45.50	30.11	26.77	41.04	33.38	29.00	37.77	43.27	44.39	35.58
100	41.78	58.66	41.78	38.14	53.83	45.35	40.52	50.26	56.28	57.47	47.81
250	55.69	70.93	55.69	52.42	66.62	58.96	54.65	63.35	68.77	69.89	61.16
500	77.40	89.89	71.97	75.76	82.83	79.03	76.88	81.19	86.99	84.46	80.12
IC ₅₀	230.61	93.99	246.48	255.39	137.96	204.86	239.02	167.67	114.98	105.61	186.56

While the standard reference drug (diclofenac sodium) exhibited an IC₅₀ value of 186.56 $\mu\text{g}/\text{ml}$, four of the synthesized compounds demonstrated significantly higher anti-inflammatory potency by achieving 50% inhibition at much lower concentrations. Leading the series as the most potent candidate was **ATD4FB (4b)** with an IC₅₀ of 93.99 $\mu\text{g}/\text{ml}$ —requiring nearly half the dose of the standard drug to achieve the same protective effect—closely followed by **ATDNAB (4o)** at 105.61 $\mu\text{g}/\text{ml}$, which displayed excellent activity that closely resembled compound 4b. The highly electronegative *para*-fluorophenyl group of **ATD4FB (4b)** compound exerts a strong negative inductive effect (*-I*), polarizing the ring to enhance electrostatic interactions with Bovine Serum Albumin (BSA). Furthermore, the fluorine atom acts as an effective hydrogen bond acceptor, binding with exposed polar side chains (*-NH* or *-OH*) of the denaturing protein to lock its native conformation. The exceptional potency of **ATDNAB (4o)** compound stems from the bulky, bicyclic 2-naphthyl ring system. It provides an expanded hydrophobic surface area and participates in robust π - π stacking interactions with aromatic residues (phenylalanine, tyrosine, tryptophan) in BSA. This acts as a hydrophobic anchor, protecting the albumin core against thermal breakdown.

Furthermore, **ATD345MOB (4n)** also proved highly effective compared to the standard with an IC₅₀ of 114.98 $\mu\text{g}/\text{ml}$, while **ATD4NB (4f)** rounded out this superior group with a value of 137.96 $\mu\text{g}/\text{ml}$, remaining considerably more potent than the reference standard. The tri-methoxy derivative **ATD345MOB (4n)** showed strong activity due to the electron-donating resonance (*+M*), but its high steric bulk slightly limited optimal pocket fit. The nitro group in **ATD4NB (4f)** provided good electron withdrawal, but its polar bulk decreased geometric fit compared to the compact fluorine atom. In contrast to the top-performing derivatives, **ATD24MB (4j)** emerged as a comparable performer with an IC₅₀ value of 167.67 $\mu\text{g}/\text{ml}$, showing slightly better activity than the standard drug and marking it as a viable candidate for further study. Conversely, the remaining derivatives ATDB (4a), **ATD2CB (4d)**, ATD3NB (4g), ATD4MB (4i) required concentrations exceeding 200 $\mu\text{g}/\text{ml}$ to achieve 50% inhibition, making them less active anti-inflammatory agents than Diclofenac Sodium. Weakly activating methyl (4i) and unsubstituted phenyl (4a) groups failed to establish strong electrostatic or hydrophobic bonds, resulting in poor protection and high IC₅₀ value. **ATD4BB (4e)** exhibited the highest IC₅₀ value at 255.39 $\mu\text{g}/\text{ml}$, ultimately identifying it as the least effective candidate within the studied series. The exceptionally low potency of **ATD4BB (4e)** stems from the detrimental steric and electronic traits of its *para*-bromophenyl group. Compared to the highly potent, compact fluorine in **4b**, bromine possesses a much larger atomic radius (114 pm vs. 64 pm), creating severe steric hindrance that obstructs the molecule from penetrating the narrow active pockets of BSA. Additionally, its lower electronegativity (2.96 vs. 3.98) and diffuse electron cloud make it a poor hydrogen bond acceptor,

preventing it from forming stabilizing intermolecular bonds with exposed polar side chains (-NH or -OH) during thermal unfolding. Unlike the bulky yet planar 2-naphthyl ring in **4o** that benefits from extensive π - π stacking, the spherical bromine atom adds localized spatial bulk without offering the broad hydrophobic surface area needed to anchor within the albumin core, making **4e** the least effective candidate. Thus, the compound, 9-(4-fluorophenyl)-6,6-dimethyl-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-b]quinazolin-8(4H)-one, **ATD4FB (4b)** and 6,6-dimethyl-9-(naphthalen-2-yl)-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-b]quinazolin-8(4H)-one, **ATDNAB (4o)** show exceptional promise as anti-inflammatory agents because they stabilize proteins against thermal degradation at much lower concentrations than the commercially available standard drug, indomethacin.

Molecular Docking Studies

To rationalize the *in-vitro* anti-inflammatory activity of the synthesized 6,6-dimethyl-9-phenyl-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-b]quinazolin-8(4H)-one derivatives, molecular docking studies were performed against the target *Bovine Serum Albumin* protein (PDB:4F5S), and the resulting binding energies, inhibition constants (K_i), and key interacting residues are summarized in **Table 4**. The binding energies of the 14 derivatives (4a-4o) ranged from -10.50 to -12.53 kcal/mol, indicating overall favourable and energetically stable interactions within the active site across the series.

Table 4. <i>In vitro</i> anti-inflammatory and molecular docking studies of triazolo-quinazolinone derivatives						
Compound	Binding energy (kcal/mol)	Inhibition constant (nm)	Docking interaction			
			H- bonding	Pi-sigma	Pi-sulphur	Alkyl/Pi-alkyl
4a/B	-11.65	2.91	-	LEU B:574 THR B:578	-	ALA B:527 LEU B:531 LEU B:528 VAL B:575
4b/4FB	-10.54	18.96	TYR B:137	ILE B:141	-	PRO B:117 LEU B:115 VAL B:188 ARG B:185 ILE B:181 MET B:184
4c/4CB	-10.83	11.55	TYR A:137	-	MET A:184	ILE A:141 HIS A:145 LEU A:189 ARG A:185 VAL A:188 LEU A:115
4d/2CB	-10.58	17.44	-	-	MET A:184	ARG A:185 VAL A:188 PRO A:117 LEU A:115 ILE A:181

						ILE A:141 LEU A:189 HIS A:145
4e/4BB						
4f/4NB	-11.79	2.28	TYR A:137	-	MET A:184	AGR A:185 VAL A:188 LEU A:115 ILE A:141 HIS A:145 LEU A:189
4g/3NB	-11.69	2.70	TYR A:137	LEU A:115	MET A:184	ARG A:185 VAL A:188 PRO A:117 ILE A:141 HIS A:145
4h/2NB	-11.78	2.33	TYR A:137 TYR A:160	LEU A:115	MET A:184	ARG A:185 VAL A:188 ILE A:141 LEU A:189 HIS A:145
4i/4MB	-10.64	15.78	-	-	MET A:184	ARG A:185 VAL A:188 LEU A:115 ILE A:141 HIS A:145 LEU A:189
4j/24MB	-11.08	7.60	-	-	MET A:184	ARG A:185 VAL A:188 PRO A:117 LEU A:115 ILE A:141 HIS A:145 LEU A:189
4k/35MB	-10.97	9.03	TRY A:137	LEU A:115	MET A:184	ARG A:185 VAL A:188 ILE A:141 LEU A:122 PRO A:117 LEU A:189 HIS A:145

4l/26MB	-10.50	20.12	TRY A:137	-	MET A:184	ARG A:185 VAL A:188 ILE A:181 PRO A:117 LEU A:115 ILE A:141 HIS A:145 ARG A:144
4m/4MOB	-11.62	8.37	-	-	MET A:184	ARG A:185 VAL A:188 LEU A:115 LYS A:136 ILE A:141 HIS A:145 LEU A:189
4n/345MOB	-12.53	0.652	TYR A:137	LEU A:115	MET A:184	ARG A:185 VAL A:188 LEU A:122 PRO A:117 ILE A:141 HIS A:145
4o/NAB	-11.64	2.94	TYR A:137	-	MET A:184	ARG A:185 VAL A:188 LEU A:115 PRO A:117 HIS A:145

Among the tested derivatives, compound **4n/345MOB** emerged as the strongest binder, exhibiting the lowest inhibition constant (K_i) = 0.652 nM) and the most negative binding energy (-12.53 kcal/mol) in the series. This superior potency likely stems from two electron-withdrawing meta-methoxy (-OCH₃) groups on the phenyl ring, which allow the compound to engage TYR A:137 via hydrogen bonding and LEU A:115 via π -sigma interactions, alongside the conserved MET A:184/ARG A:185/VAL A:188 cluster.

The nitro substituted compounds **4f/4NB** (-11.79 kcal/mol, K_i = 2.28 nM), **4h/2NB** (-11.78 kcal/mol, K_i = 2.33 nM), and **4g/3NB** (-11.69 kcal/mol, K_i = 2.70 nM) have emerged as the stronger binders, exhibiting the lower inhibition constants in the series, The enhanced binding energies of these compounds are due to the presence of a hydrogen bond with TYR A:137, reinforced by π -sigma interactions with LEU A:115 and a conserved hydrophobic contact with MET A:184. This pattern suggests that electron-withdrawing nitro substituents favourably orient the aryl ring for both H-bonding and π -type interactions within the binding pocket.

In contrast, derivatives bearing electron-donating methoxy/methyl substituents (**4i/4MB**, **4j/24MB**, **4m/4MOB**) generally displayed weaker binding affinities and an absence of TYR A:137-mediated hydrogen

bonding, relying instead on nonspecific alkyl/ π -alkyl contacts with ARG A:185, VAL A:188, and LEU A:115. This is consistent with reduced π -electron availability at the aryl ring for directional interactions, resulting in comparatively higher K_i values (7.60–15.78 nM) relative to the nitro-substituted analogs.

A recurring structural feature across nearly all derivatives is the involvement of MET A:184 as an alkyl-type anchor residue and ARG A:185/VAL A:188/ILE A:141 as a conserved hydrophobic cluster, indicating that this region of the binding pocket accommodates the core triazolo-quinazolinone scaffold irrespective of peripheral substitution. The 2D molecular docking interaction triazolo-quinazolinones derivatives (compound 4n, 4f, 4g and 4h) with bovine serum albumin receptor (PBD:4F5S) were given in **Figure 3**. The 2D molecular docking interaction other triazolo-quinazolinones derivatives with bovine serum albumin receptor (PBD:4F5S) were given in supporting information file.

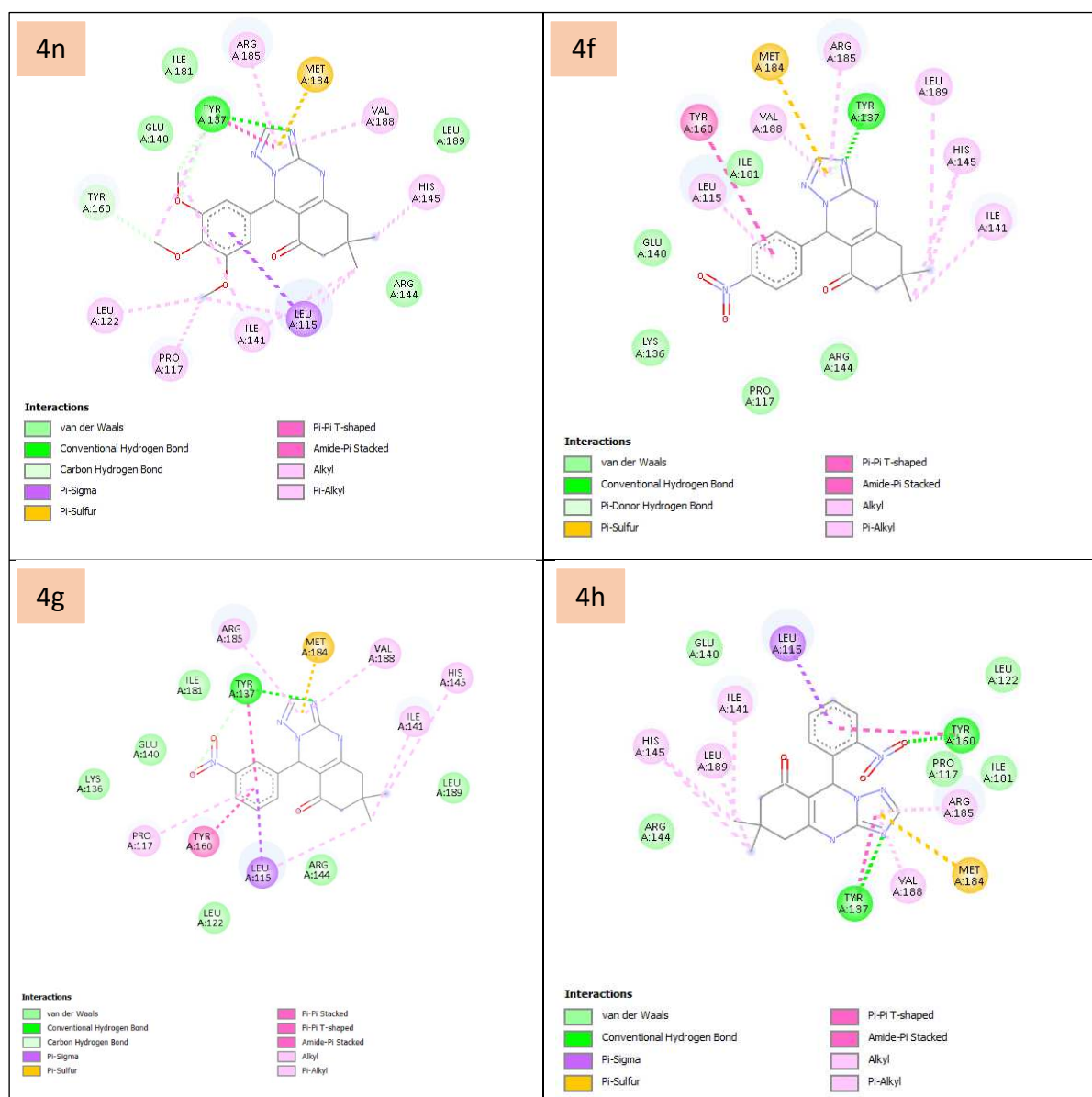


Figure 3: 2D molecular docking interaction diagram of triazolo-quinazolinones derivatives (compound 4n, 4f, 4g and 4h) with bovine serum albumin receptor (PBD:4F5S)

The visual presentation of the molecular docking poses of the synthesized tryptamine-tethered quinazolinone derivatives 4n, 4f, 4g, 4h within the active binding pocket of the MCF-7 breast cancer cell line receptor (PDB ID: 1M17) is depicted in **Figure 4**. The molecular docking poses of the other tryptamine-tethered quinazolinone derivatives were given in supporting information file.

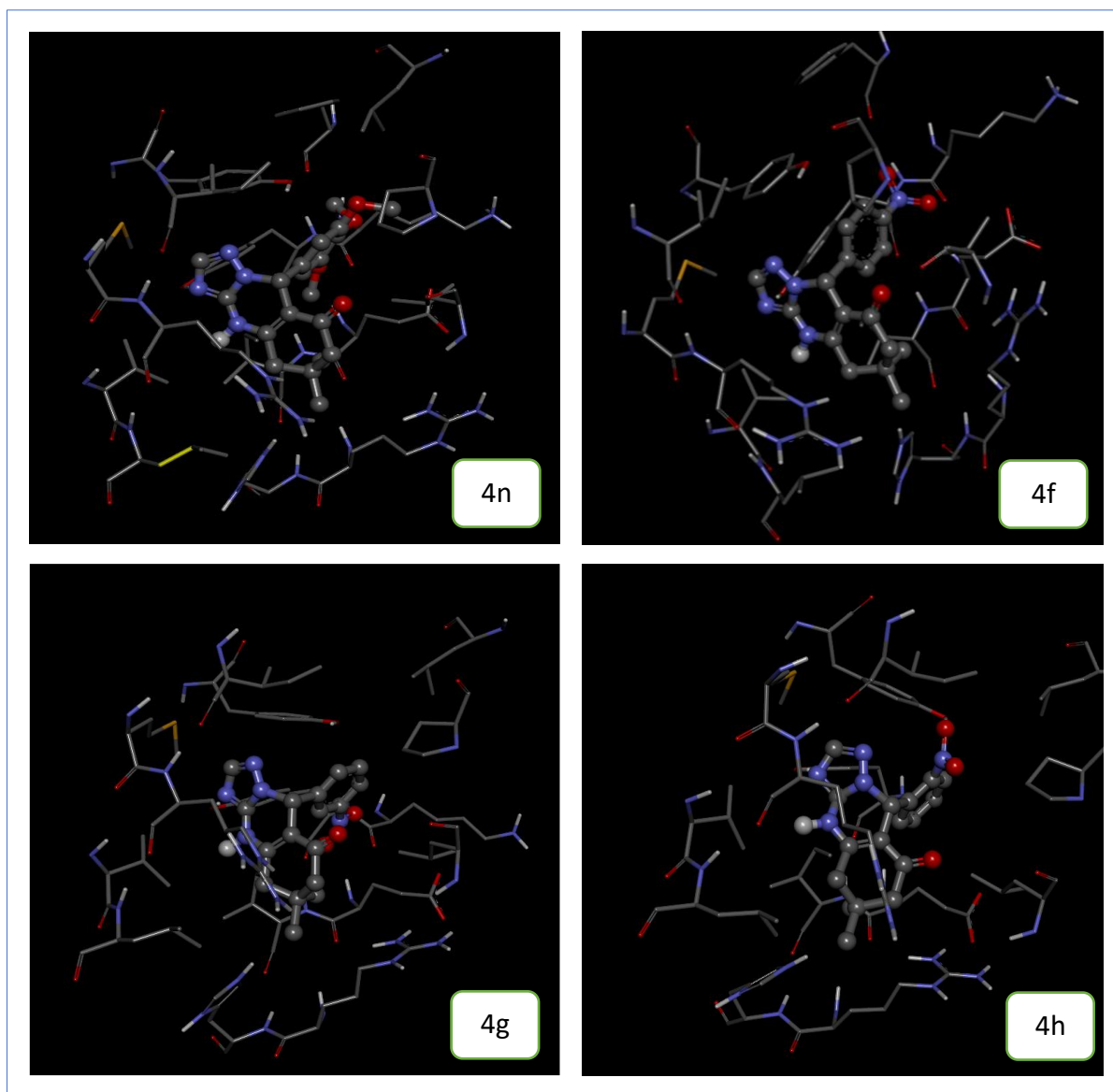


Figure 4 Molecular docking poses of the synthesized triazolo-quinazolinone derivatives (Compound 4n, 4f, 4g and 4h) within the active binding pocket of the Bovine Serum Albumin receptor (PDB ID: 4F5S)

Comparison of the computational binding parameters (**Table. 4**) with experimental IC_{50} values (Table 3) revealed a notable divergence between predicted and observed potency. **Compound 4f/4NB** was the only derivative where both analyses agreed — it ranked among the top three in silico binders (binding energy = -11.79 kcal/mol, K_i = 2.28 nM, stabilized by a TYR A:137 hydrogen bond and LEU A:115 π -sigma interaction) and also showed strong in vitro potency (IC_{50} = 137.96 μ g/mL), outperforming the diclofenac standard (IC_{50} = 186.56 μ g/mL). In contrast, **4b/4FB** was the most potent compound experimentally (IC_{50} = 93.99 μ g/mL), surpassing even the reference drug, despite showing the weakest predicted binding affinity in the entire docked panel (-10.54

kcal/mol, K_i = 18.96 nM). Similarly, **4n/345MOB** had the most favourable binding energy of any derivative (-12.53 kcal/mol) but did not translate this into the strongest experimental potency (IC_{50} = 114.98 μ g/mL, still better than standard); its docking-derived K_i (652.59 nM) was also anomalously low relative to its own binding energy and the rest of the series. Such discrepancies are unsurprising, as rigid-receptor docking evaluates a single static pose and ignores protein flexibility, solvation, and entropic effects, whereas the *in vitro* assay reflects the compound's overall functional behavior, including solubility and diffusion. The docking results are therefore best viewed as providing mechanistic insight into plausible binding orientations and key residues (TYR A:137, LEU A:115, MET A:184) rather than as a quantitative predictor of experimental potency across the series.

3. CONCLUSION

In summary, a library of fifteen novel 6,6-dimethyl-9-phenyl-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-b]quinazolin-8(4H)-one derivatives were successfully synthesized via an efficient, pipecolic acid-catalyzed, one-pot multicomponent reaction of aromatic aldehydes, dimedone, and 3-amino-1,2,4-triazole in refluxing ethanol. This clean organocatalytic protocol afforded the desired heterocycles in good to excellent yields (85–95%) within 30–60 minutes. All synthesized compounds were isolated easily through filtration and recrystallization, and their chemical structures were fully confirmed using IR, ^1H NMR, ^{13}C NMR, and ESI-MS spectroscopic techniques. The synthesized triazoloquinazoline derivatives were evaluated for *in vitro* anti-inflammatory activity using the BSA denaturation assay. Structure-activity relationship (SAR) analysis demonstrated that the electronic and steric properties of the C-9 substituent dictate the stabilization of the protein matrix. Notably, **ATD4FB (4b)** (IC_{50} = 93.99 μ g/ml) and **ATDNAB (4o)** (IC_{50} = 105.61 μ g/ml) emerged as highly potent leads, significantly outperforming the standard Diclofenac Sodium (IC_{50} = 186.56 μ g/ml). The superior efficacy of **4b** is attributed to ring polarization and targeted hydrogen bonding by its compact *para*-fluorophenyl group, whereas **4o** utilizes extensive π - π stacking and hydrophobic anchoring via its planar 2-naphthyl system. In contrast, the *para*-bromophenyl analogue **ATD4BB (4e)** was the least effective candidate (IC_{50} = 255.39 μ g/ml) due to severe steric clash and a diffuse electron cloud that hindered pocket entry and hydrogen bonding. Overall, **ATD4FB (4b)** and **ATDNAB (4o)** show exceptional promise as scaffolds for future anti-inflammatory drug design.

4. MATERIALS AND METHODS

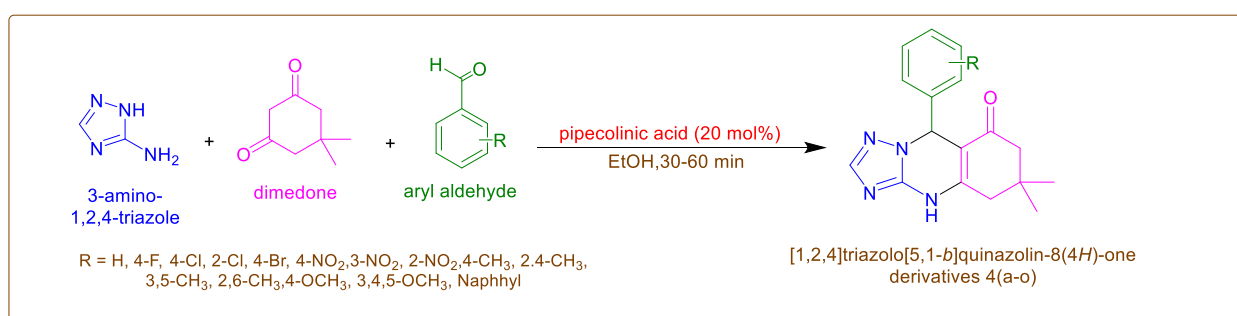
Materials and Methods

All starting materials and reagents, including pipecolinic acid, 3-amino-1,2,4-triazole, methyl acetoacetate, and various substituted benzaldehydes (e.g., benzaldehyde, 4-methylbenzaldehyde, and 3,4,5-trimethoxybenzaldehyde), were procured from TCI and BLD Pharmatech Co., Ltd. These chemicals were utilized directly in the synthetic procedures without further purification. Reaction progress and compound purity were monitored by thin-layer chromatography (TLC) using Merck silica gel 60 F₂₅₄ plates. Melting points of the synthesized compounds were determined in open capillary tubes using a SciLab melting point apparatus and are reported uncorrected in degrees Celsius. Fourier-transform infrared (FT-IR) spectra were recorded on a Bruker Alpha-P spectrophotometer, with absorption bands reported in wavenumbers (cm^{-1}). Nuclear magnetic resonance (^1H and ^{13}C NMR) spectra were acquired on a Bruker Avance spectrometer operating at 400 MHz and 100 MHz, respectively. Samples were dissolved in DMSO- d_6 , and chemical shifts (δ) are reported in parts per million (ppm).

relative to tetramethylsilane (TMS) as an internal standard. Mass spectrometric data were collected on a JEOL GC Mate II mass spectrometer to confirm molecular weights and fragmentation patterns.

General procedure for synthesis of 6,6-dimethyl-9-phenyl-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-b]quinazolin-8(4H)-one

To a round-bottom flask equipped with a magnetic stirrer, equimolar amounts (5 mmol each) of 3-amino-1,2,4-triazole, dimedone, and the appropriate aryl aldehyde are added, followed by the addition of pipecolic acid (20 mol%) as an organocatalyst in 10 ml of ethanol. The reaction mixture is stirred vigorously under reflux temperature for 30 to 60 minutes, with the reaction progress monitored by Thin-Layer Chromatography (TLC). Upon completion, the mixture is allowed to cool to room temperature, and the target [1,2,4]-triazolo[5,1-b]-quinazolin-8(4H)-one derivatives (4{a-o}) are isolated via filtration or solvent evaporation, followed by final purification through recrystallization. (**Scheme 2**)



Scheme 2 synthesis of 6,6-dimethyl-9-aryl-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-b]quinazolin-8(4H)-one derivatives

BSA denaturation technique

The synthesized compound and standard diclofenac sodium were screened for anti-inflammatory activity by using the inhibition of albumin denaturation technique with minor modification.^{61,62} The standard drug and compound were dissolved in minimum quantity of Dimethyl formamide (DMF) and diluted with phosphate buffer (0.2 M, PH 7.4). The final concentration of DMF in all solution was less than 2.5%. Test Solution (2.5 mL) containing different concentrations of the drug was mixed with 1 mL of 1 mM Bovine serum albumin solution in phosphate buffer and incubated at 37 °C in an incubator for 10 min. Denaturation was induced by keeping the reaction mixture at 70°C in a water bath for 10 min. After cooling, the turbidity was measured at 660 nm. Percentage of Inhibition of denaturation was calculated from control where no drug was added. The percentage inhibition of denaturation was calculated by using the following formula.

$$\% \text{ of Inhibition} = 100 \times [(\text{Ac}-\text{At}) / \text{Ac}]$$

At: Absorbance of test

Ac: Absorbance of control

IR, ¹H NMR, ¹³C NMR and Mass spectral data of synthesised triazolo[5,1-b]quinazolinone

6,6-dimethyl-9-phenyl-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-b]quinazolin-8(4H)-one (4a)

White solid; yield: %; mp: 254-255 °C (lit. 250-251 °C)⁴¹; FT-IR (ATR, $\nu_{\text{max}}/\text{cm}^{-1}$): 3028 (aromatic C–H stretch), 2958, 2873 (aliphatic C–H stretch), 1759 (C=O stretch), 1643 (C=N stretch), 1573, 1543 (aromatic C=C stretch), 1411 (C–N stretch), 883, 840 (C–H out-of-plane bending), 729, 694 (monosubstituted aromatic C–H bending); ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.12 (1H, s, N–H proton of triazole ring), 7.68 (1H, s, triazole C3–H proton), 7.30–7.18 (5H, m, aromatic C–H protons), 6.21 (1H, s, C9–H methine proton), 3.33 (2H, s, C5–CH₂ methylene proton), 2.24 (1H, d, *J* = 16.2 Hz, C7–CH₂ methylene proton), 2.06 (1H, d, *J* = 16.2 Hz, C7–CH₂ methylene proton), 1.05 (3H, s, CH₃ proton), 0.97 (3H, s, CH₃ proton); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 193.5, 150.9, 150.5, 147.4, 142.1, 128.7, 128.2, 127.4, 106.1, 58.4, 50.3, 35.2, 29.0, 27.3; HRMS (*m/z*): Calcd for C₁₆H₁₉N₄O [M+H]⁺: 295.1559, Found: 295.1488.

9-(4-fluorophenyl)-6,6-dimethyl-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-*b*]quinazolin-8(4H)-one (4b)

White solid; yield: %; mp: >300 °C (lit. 306–308 °C)³⁸; FT-IR (ATR, $\nu_{\text{max}}/\text{cm}^{-1}$): 3244 (N–H stretch), 3136 (aromatic C–H stretch), 2963, 2889 (aliphatic C–H stretch), 1643 (C=O stretch), 1547, 1504 (aromatic C=C stretch), 1412 (C–N stretch), 1215 (C–F stretch), 853, 829 (C–H out-of-plane bending); ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.15 (1H, s, N–H proton of dihydropyrimidine ring), 7.70 (1H, s, triazole C–H proton), 7.22–7.25 (2H, m, aromatic C–H proton), 7.09–7.13 (2H, m, aromatic C–H proton), 6.23 (1H, s, C–H methine proton), 2.54 (2H, m, –CH₂– methylene proton), 2.22 (1H, d, *J* = 16.2 Hz, –CH₂– methylene proton), 2.11 (1H, d, *J* = 16.2 Hz, –CH₂– methylene proton), 1.05 (3H, s, CH₃ proton), 0.97 (3H, s, CH₃ proton); ¹³C NMR (125 MHz, DMSO-*d*₆): δ 193.4, 162.9, 161.0, 150.9, 150.6, 147.2, 138.3, 129.5, 129.4, 115.6, 115.4, 105.8, 57.7, 50.2, 40.1, 32.6, 28.8, 27.3; HRMS (*m/z*): Calcd for C₁₇H₁₇FN₄O [M+H]⁺: 313.1464, Found: 313.1399.

9-(4-chlorophenyl)-6,6-dimethyl-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-*b*]quinazolin-8(4H)-one (4c)

White solid; yield: %; mp: 295-297 °C (lit. 292-295 °C)⁴¹; FT-IR (ATR, $\nu_{\text{max}}/\text{cm}^{-1}$): 3028 (aromatic C–H stretch), 2916, 2846 (aliphatic C–H stretch), 1762 (C=O stretch), 1643 (C=N stretch), 1573, 1546 (aromatic C=C stretch), 1411 (C–N stretch), 883, 837 (C–H out-of-plane bending), 725 (C–Cl stretch); ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.18 (1H, s, N–H proton of triazole ring), 7.71 (1H, s, triazole C3–H proton), 7.36 (2H, d, *J* = 8.4 Hz, aromatic C–H proton), 7.21 (2H, d, *J* = 8.4 Hz, aromatic C–H proton), 6.23 (1H, s, C9–H methine proton), 3.35 (2H, s, C5–CH₂ methylene proton), 2.24 (1H, d, *J* = 16.2 Hz, C7–CH₂ methylene proton), 2.09 (1H, d, *J* = 16.2 Hz, C7–CH₂ methylene proton), 1.05 (3H, s, CH₃ proton), 0.97 (3H, s, CH₃ proton); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 193.5, 151.1, 150.7, 147.3, 141.0, 132.8, 129.4, 128.8, 105.7, 57.9, 51.2, 27.9, 27.4, 22.9; HRMS (*m/z*): Calcd for C₁₆H₁₈ClN₄O [M+H]⁺: 329.1119, Found: 329.1097.

9-(2-chlorophenyl)-6,6-dimethyl-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-*b*]quinazolin-8(4H)-one (4d)

White solid; yield: %; mp: 282-285 °C (lit. > 300 °C)⁴¹; FT-IR (ATR, $\nu_{\text{max}}/\text{cm}^{-1}$): 3240 (N–H stretch), 3086 (aromatic C–H stretch), 2959, 2870 (aliphatic C–H stretch), 1639 (C=O stretch), 1574, 1547 (aromatic C=C stretch), 1416 (C–N stretch), 752 (C–Cl stretch); ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.21 (1H, s, N–H proton), 7.71 (1H, s, triazole C3–H proton), 7.25–7.38 (4H, m, aromatic C–H proton), 6.57 (1H, s, C9–H methine proton), 3.36 (2H, s, C5–CH₂ methylene proton), 2.59 (1H, d, *J* = 16.4 Hz, C7–CH₂ methylene proton), 2.22 (1H, d, *J* = 16.0 Hz, C7–CH₂ methylene proton), 1.06 (3H, s, CH₃ proton), 1.00 (3H, s, CH₃ proton); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 193.4, 151.6, 150.6, 147.4, 138.7, 132.7, 131.0, 130.1, 129.9, 127.6, 105.0, 56.8, 50.3, 32.6, 29.0, 27.3; HRMS (*m/z*): Calcd for C₁₇H₁₇ClN₄O [M+H]⁺: 329.1169, Found: 329.1103.

9-(4-bromophenyl)-6,6-dimethyl-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-*b*]quinazolin-8(4H)-one (4e)

White solid; yield: %; mp: 281-283 °C (lit. 282-284 °C)^{40,41}; FT-IR (ATR, $\nu_{\text{max}}/\text{cm}^{-1}$): 3089 (aromatic C–H stretch), 2958, 2916 (aliphatic C–H stretch), 1762 (C=O stretch), 1647 (C=N stretch), 1573, 1550 (aromatic C=C stretch), 1411 (C–N stretch), 883, 837 (C–H out-of-plane bending), 729 (C–Br stretch); ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.18 (1H, s, N–H proton of triazole ring), 7.71 (1H, s, triazole C3–H proton), 7.50 (2H, d, *J* = 8.4 Hz, aromatic C–H proton), 7.17 (2H, d, *J* = 8.0 Hz, aromatic C–H proton), 6.21 (1H, s, C9–H methine proton), 3.35 (2H, s, C5–CH₂ methylene proton), 2.24 (1H, d, *J* = 16.2 Hz, C7–CH₂ methylene proton), 2.07 (1H, d, *J* = 16.2 Hz, C7–CH₂ methylene proton), 1.04 (3H, s, CH₃ proton), 0.96 (3H, s, CH₃ proton); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 193.5, 151.1, 150.7, 147.3, 141.4, 131.7, 129.7, 121.4, 105.7, 58.0, 50.2, 32.7, 28.9, 27.4; HRMS (*m/z*): Calcd for C₁₆H₁₈BrN₄O [M+H]⁺: 373.0664, Found: 373.0597.

6,6-dimethyl-9-(4-nitrophenyl)-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-*b*]quinazolin-8(4H)-one (4f)

White solid; yield: %; mp: 295-297 °C (lit. 292-294 °C)⁴¹; FT-IR (ATR, $\nu_{\text{max}}/\text{cm}^{-1}$): 3024 (aromatic C–H stretch), 2963, 2886 (aliphatic C–H stretch), 1643 (C=O stretch), 1574, 1524 (aromatic C=C stretch), 1350 (NO₂ symmetric stretch), 1412 (C–N stretch), 891, 829 (C–H out-of-plane bending); ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.30 (1H, s, N–H proton), 8.16 (2H, d, *J* = 8.4 Hz, aromatic C–H proton), 7.74 (1H, s, triazole C3–H proton), 7.49 (2H, d, *J* = 8.4 Hz, aromatic C–H proton), 6.38 (1H, s, C9–H methine proton), 3.34 (2H, s, C5–CH₂ methylene proton), 2.23 (1H, d, *J* = 16.4 Hz, C7–CH₂ methylene proton), 2.09 (1H, d, *J* = 16.4 Hz, C7–CH₂ methylene proton), 1.05 (3H, s, CH₃ proton), 0.96 (3H, s, CH₃ proton); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 193.5, 151.5, 150.9, 148.9, 147.4, 147.3, 129.0, 124.1, 105.2, 58.0, 50.2, 32.7, 28.8, 27.5; HRMS (*m/z*): Calcd for C₁₇H₁₇N₅O₃ [M+H]⁺: 340.1410, Found: 340.1347.

6,6-dimethyl-9-(3-nitrophenyl)-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-*b*]quinazolin-8(4H)-one (4g)

White solid; yield: %; mp: 264-265 °C (lit. 266-268 °C)⁴¹; FT-IR (ATR, $\nu_{\text{max}}/\text{cm}^{-1}$): 3082 (aromatic C–H stretch), 2959, 2789 (aliphatic C–H stretch), 1643 (C=O stretch), 1578, 1551 (aromatic C=C stretch), 1528 (NO₂ asymmetric stretch), 1331 (NO₂ symmetric stretch), 1416 (C–N stretch), 899, 822 (C–H out-of-plane bending); ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.31 (1H, s, N–H proton), 8.12 (1H, d, *J* = 8.0 Hz, aromatic C–H proton), 8.07 (1H, s, aromatic C–H proton), 7.74 (1H, s, triazole C3–H proton), 7.67 (1H, d, *J* = 7.6 Hz, aromatic C–H proton), 7.62 (1H, t, *J* = 7.6 Hz, aromatic C–H proton), 6.43 (1H, s, C9–H methine proton), 3.34 (2H, s, C5–CH₂ methylene proton), 2.24 (1H, d, *J* = 16.4 Hz, C7–CH₂ methylene proton), 2.11 (1H, d, *J* = 16.0 Hz, C7–CH₂ methylene proton), 1.06 (3H, s, CH₃ proton), 0.99 (3H, s, CH₃ proton); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 193.6, 151.6, 150.9, 148.1, 147.3, 144.0, 134.2, 130.5, 123.3, 122.2, 105.1, 57.9, 50.2, 32.7, 28.8, 27.4; HRMS (*m/z*): Calcd for C₁₇H₁₇N₅O₃ [M+H]⁺: 340.1410, Found: 340.1355.

6,6-dimethyl-9-(2-nitrophenyl)-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-*b*]quinazolin-8(4H)-one (4h)

White solid; yield: %; mp: 287-289 °C (lit. 288-290 °C)⁴¹; FT-IR (ATR, $\nu_{\text{max}}/\text{cm}^{-1}$): 3090 (aromatic C–H stretch), 2870 (aliphatic C–H stretch), 1639 (C=O stretch), 1582, 1528 (aromatic C=C stretch / NO₂ asymmetric stretch), 1342 (NO₂ symmetric stretch), 1416 (C–N stretch), 860, 826 (C–H out-of-plane bending); ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.30 (1H, s, N–H proton), 7.87 (1H, d, *J* = 8.0 Hz, aromatic C–H proton), 7.74 (1H, s, triazole C3–H proton), 7.60 (1H, m, aromatic C–H proton), 7.47 (1H, m, aromatic C–H proton), 7.21 (1H, d, *J* = 7.6 Hz, aromatic C–H proton), 6.98 (1H, s, C9–H methine proton), 3.34 (2H, s, C5–CH₂ methylene proton), 2.20 (1H, d, *J* = 16.4 Hz, C7–CH₂ methylene proton), 2.06 (1H, d, *J* = 16.4 Hz, C7–CH₂ methylene proton), 1.03 (3H, s, CH₃ proton), 0.93 (3H, s, CH₃ proton); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 193.7, 151.5, 150.9, 148.9, 147.5, 135.7,

133.8, 129.6, 129.5, 124.5, 105.5, 53.4, 49.9, 32.7, 28.7, 27.5; HRMS (m/z): Calcd for $C_{17}H_{17}N_5O_3$ $[M+H]^+$: 340.1410, Found: 340.1332.

6,6-dimethyl-9-(4-methylphenyl)-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-b]quinazolin-8(4H)-one (4i)

White solid; yield: %; mp: 258-260 °C (lit. 260-263 °C)^{40,41}; FT-IR (ATR, $\nu_{\max}/\text{cm}^{-1}$): 3251 (N–H stretch), 3089 (aromatic C–H stretch), 2966 (aliphatic C–H stretch), 1647 (C=O stretch), 1577, 1546 (aromatic C=C stretch), 1411 (C–N stretch), 887, 848 (C–H out-of-plane bending), 729 (aromatic C–H bending); ^1H NMR (400 MHz, DMSO- d_6): δ 11.08 (1H, s, N–H proton of triazole ring), 7.67 (1H, s, triazole C3–H proton), 7.07 (4H, s, aromatic C–H protons), 6.16 (1H, s, C9–H methine proton), 3.34 (2H, s, C5–CH₂ methylene proton), 2.23 (1H, d, J = 16.2 Hz, C7–CH₂ methylene proton), 2.24 (3H, s, Ar–CH₃ proton), 2.09 (1H, d, J = 16.2 Hz, C7–CH₂ methylene proton), 1.05 (3H, s, CH₃ proton), 0.96 (3H, s, CH₃ proton); ^{13}C NMR (100 MHz, DMSO- d_6): δ 193.4, 150.7, 150.5, 147.4, 139.6, 134.3, 134.2, 127.5, 127.3, 106.2, 58.1, 50.3, 32.7, 29.0, 27.3, 21.1; HRMS (m/z): Calcd for $C_{17}H_{21}N_4O$ $[M+H]^+$: 309.1715, Found: 309.1653.

9-(2,4-dimethylphenyl)-6,6-dimethyl-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-b]quinazolin-8(4H)-one (4j)

White solid; yield: %; mp: 273-275 °C; FT-IR (ATR, $\nu_{\max}/\text{cm}^{-1}$): 3252 (N–H stretch), 3090 (aromatic C–H stretch), 2916 (aliphatic C–H stretch), 1647 (C=O stretch), 1578, 1551 (aromatic C=C stretch), 1412 (C–N stretch), 868, 818 (C–H out-of-plane bending); ^1H NMR (400 MHz, DMSO- d_6): δ 11.06 (1H, s, N–H proton of quinazolinone), 7.63 (1H, s, triazole C3–H proton), 6.94 (1H, s, aromatic C–H proton), 6.87 (2H, m, aromatic C–H proton), 6.40 (1H, s, C9–H methine proton), 3.36 (2H, s, C5–CH₂ methylene proton), 2.52 (3H, s, Ar–CH₃ proton), 2.23 (3H, s, Ar–CH₃ proton), 2.19 (1H, d, J = 16.4 Hz, C7–CH₂ methylene proton), 2.05 (1H, d, J = 16.4 Hz, C7–CH₂ methylene proton), 1.06 (3H, s, CH₃ proton), 1.00 (3H, s, CH₃ proton); ^{13}C NMR (125 MHz, DMSO- d_6): δ 193.5, 150.8, 150.3, 147.0, 138.0, 137.1, 135.8, 131.1, 127.2, 127.1, 106.7, 54.4, 50.2, 40.1, 32.7, 29.0, 27.3, 20.9, 19.3; HRMS (m/z): Calcd for $C_{19}H_{22}N_4O$ $[M+H]^+$: 323.1872, Found: 323.1816.

9-(3,5-dimethylphenyl)-6,6-dimethyl-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-b]quinazolin-8(4H)-one (4k)

Off-white solid; yield: %; mp: 282-284 °C; FT-IR (ATR, $\nu_{\max}/\text{cm}^{-1}$): 3210 (N–H stretch), 3013 (aromatic C–H stretch), 2920, 2870 (aliphatic C–H stretch), 1632 (C=O stretch), 1566, 1535 (aromatic C=C stretch), 1404 (C–N stretch), 895, 860 (C–H out-of-plane bending); ^1H NMR (400 MHz, DMSO- d_6): δ 11.07 (1H, s, N–H proton), 7.67 (1H, s, triazole C3–H proton), 6.85 (1H, s, aromatic C–H proton), 6.80 (2H, s, aromatic C–H proton), 6.12 (1H, s, C9–H methine proton), 3.37 (2H, s, C5–CH₂ methylene proton), 2.55 (1H, d, J = 16.4 Hz, C7–CH₂ methylene proton), 2.20 (1H, d, J = 16.4 Hz, C7–CH₂ methylene proton), 2.11 (6H, s, Ar–CH₃ proton), 1.05 (3H, s, CH₃ proton), 1.00 (3H, s, CH₃ proton); ^{13}C NMR (125 MHz, DMSO- d_6): δ 193.4, 150.8, 150.4, 147.1, 142.0, 137.6, 129.6, 125.2, 106.1, 58.3, 50.3, 40.1, 32.7, 29.0, 27.2, 21.3; HRMS (m/z): Calcd for $C_{19}H_{22}N_4O$ $[M+H]^+$: 323.1872, Found: 323.1807.

9-(2,6-dimethylphenyl)-6,6-dimethyl-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-b]quinazolin-8(4H)-one (4l)

Off-white solid; yield: %; mp: 266-268 °C; FT-IR (ATR, $\nu_{\max}/\text{cm}^{-1}$): 3132 (N–H stretch), 2959, 2874 (aliphatic C–H stretch), 1643 (C=O stretch), 1578, 1551 (aromatic C=C stretch), 1416 (C–N stretch), 883, 845 (C–H out-of-plane bending); ^1H NMR (400 MHz, DMSO- d_6): δ 11.13 (1H, s, N–H proton), 7.66 (1H, s, triazole C3–H proton), 7.01 (2H, d, J = 6.4 Hz, aromatic C–H proton), 6.85 (1H, m, aromatic C–H proton), 6.69 (1H, s, C9–H methine proton), 3.38 (2H, s, C5–CH₂ methylene proton), 2.67 (1H, d, J = 16.4 Hz, C7–CH₂ methylene proton), 2.49 (1H, d, J = 16.4 Hz, C7–CH₂ methylene proton), 2.13 (3H, s, Ar–CH₃ proton), 1.82 (3H, s, Ar–CH₃ proton), 1.04 (3H, s, CH₃ proton), 1.01 (3H, s, CH₃ proton); ^{13}C NMR (125 MHz, DMSO- d_6): δ 193.7, 150.9, 150.2, 147.5,

138.4, 136.8, 136.0, 130.3, 128.5, 127.6, 105.2, 54.7, 50.5, 40.1, 32.4, 28.3, 28.0, 21.2, 18.1; HRMS (m/z): Calcd for $C_{19}H_{22}N_4O$ $[M+H]^+$: 323.1872, Found: 323.1807.

9-(4-methoxyphenyl)-6,6-dimethyl-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-b]quinazolin-8(4H)-one (4m)

Pale yellow solid; yield: %; mp: > 300 °C (lit. 299-301 °C)⁴¹; FT-IR (ATR, $\nu_{\max}/\text{cm}^{-1}$): 3410 (N–H stretch), 3090 (aromatic C–H stretch), 2963, 2839 (aliphatic C–H stretch), 1647 (C=O stretch), 1574, 1551 (aromatic C=C stretch), 1412 (C–N stretch), 1246 (C–O stretch), 891, 849 (C–H out-of-plane bending); ^1H NMR (400 MHz, DMSO- d_6): δ 11.07 (1H, s, N–H proton), 7.67 (1H, s, triazole C3–H proton), 7.11 (2H, d, J = 8.4 Hz, aromatic C–H proton), 6.83 (2H, d, J = 8.4 Hz, aromatic C–H proton), 6.15 (1H, s, C9–H methine proton), 3.70 (3H, s, OCH₃ proton), 3.34 (2H, s, C5–CH₂ methylene proton), 2.20 (1H, d, J = 16.4 Hz, C7–CH₂ methylene proton), 2.07 (1H, d, J = 16.4 Hz, C7–CH₂ methylene proton), 1.03 (3H, s, CH₃ proton), 0.98 (3H, s, CH₃ proton); ^{13}C NMR (100 MHz, DMSO- d_6): δ 193.5, 159.2, 150.7, 150.4, 147.3, 134.3, 128.6, 114.1, 106.3, 57.8, 55.5, 50.3, 32.6, 29.0, 27.3; HRMS (m/z): Calcd for $C_{18}H_{20}N_4O_2$ $[M+H]^+$: 325.1664, Found: 325.1587.

6,6-dimethyl-9-(3,4,5-trimethoxyphenyl)-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-b]quinazolin-8(4H)-one (4n)

Pale yellow solid; yield: %; mp: 272-274 °C ; FT-IR (ATR, $\nu_{\max}/\text{cm}^{-1}$): 2932, 2832 (aliphatic C–H stretch), 1647 (C=O stretch), 1582, 1504 (aromatic C=C stretch), 1234, 1119 (C–O stretch), 895, 856 (C–H out-of-plane bending); ^1H NMR (400 MHz, DMSO- d_6): δ 11.11 (1H, s, N–H proton), 7.70 (1H, s, triazole C3–H proton), 6.50 (2H, s, aromatic C–H proton), 6.16 (1H, s, C9–H methine proton), 3.70 (6H, s, OCH₃ proton), 3.62 (3H, s, OCH₃ proton), 3.36 (2H, s, C5–CH₂ methylene proton), 2.26 (1H, d, J = 16.4 Hz, C7–CH₂ methylene proton), 2.13 (1H, d, J = 16.4 Hz, C7–CH₂ methylene proton), 1.07 (3H, s, CH₃ proton), 1.04 (3H, s, CH₃ proton); ^{13}C NMR (125 MHz, DMSO- d_6): δ 193.5, 153.1, 151.1, 150.4, 147.0, 137.6, 137.5, 105.7, 104.9, 60.3, 58.4, 56.2, 50.2, 40.1, 32.5, 29.2, 27.0; HRMS (m/z): Calcd for $C_{20}H_{24}N_4O_4$ $[M+H]^+$: 385.1875, Found: 385.1803.

6,6-dimethyl-9-(naphthalen-1-yl)-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-b]quinazolin-8(4H)-one (4o)

White solid; yield: %; mp: °C (lit. 287–290 °C)⁴⁰; FT-IR (ATR, $\nu_{\max}/\text{cm}^{-1}$): 3075 (aromatic C–H stretch), 2959, 2805 (aliphatic C–H stretch), 1639 (C=O stretch), 1551 (aromatic C=C stretch), 1416 (C–N stretch), 787, 768 (aromatic C–H out-of-plane bending); ^1H NMR (400 MHz, DMSO- d_6): δ 11.21 (1H, s, N–H proton), 8.53 (1H, d, J = 8.4 Hz, aromatic C–H proton), 7.92 (2H, m, aromatic C–H proton), 7.82 (2H, m, aromatic C–H proton), 7.61 (1H, m, aromatic C–H proton), 7.50–7.59 (2H, m, aromatic C–H proton), 7.42 (1H, m, aromatic C–H proton), 7.09 (1H, s, C9–H methine proton), 3.35 (2H, s, C5–CH₂ methylene proton), 2.21 (1H, d, J = 16.0 Hz, C7–CH₂ methylene proton), 2.06 (1H, d, J = 16.0 Hz, C7–CH₂ methylene proton), 1.07 (3H, s, CH₃ proton), 1.03 (3H, s, CH₃ proton); ^{13}C NMR (100 MHz, DMSO- d_6): δ 193.6, 151.2, 150.3, 147.0, 138.8, 133.7, 131.2, 128.9, 128.8, 126.7, 126.2, 125.9, 124.3, 106.6, 56.5, 54.1, 50.3, 32.7, 29.0, 27.6; HRMS (m/z): Calcd for $C_{17}H_{17}N_5O_3$ $[M+H]^+$: 345.1715, Found: 345.1660.

STATEMENTS & DECLARATIONS

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Author contributions

CRedit: **Dhamodharan Swathi**: Experimental investigation, Methodology, Data acquisition, Formal analysis; **Vimal Dinesh Vishwa**: Data acquisition, Formal analysis; **Peeli Kumar Anjali**: Data acquisition, Formal analysis; **Muniyan Ramasamy Kuppusamy**: Data validation, Date curation, Review and Editing; **Devendiran Parthiban**: Conceptualization, Resources, Supervision, Writing – Original, Review and Editing.

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Ethics approval

This manuscript does not include or involve the use of any data derived from animal or human subjects. All research conducted was performed in accordance with ethical guidelines and regulations, ensuring the exclusion of any involvement with animal or human participants in the study.

Consent to participate

Not applicable

Consent to publish

Not applicable

Open access

Not applicable

Conflict of interest

The authors declare that they have no competing interests that could potentially influence or bias the content of this article.

Data availability statement

The authors affirm that the data supporting the findings of this study are available within the manuscript and its Supplementary Information files. Further inquiries for additional information may be directed to the corresponding author via email.

Supporting Information

Full experimental details, IR, ¹H NMR, ¹³C NMR and Mass spectral data can be found via the “Supplementary Content” section of this article’s webpage.

Use of generative AI and AI-assisted technologies

During the preparation of this manuscript, AI-assisted tools were used only for language editing, readability improvement, and formatting support. The authors independently verified the scientific content, reference selection, interpretation, and conclusions, and take full responsibility for the final manuscript.

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