ijlpr 2023; doi 10.22376/ijlpr.2023.13.6.P127-P140

International Journal of Life science and Pharma Research

ISSN 2250-0480

Research Article

Quinoline On Hypertension, Inflammation and Docking Studies

Eco-Friendly Synthesis of Pyrrolo[1,2-A] Quinoline Derivatives and Evaluating Their Effects On Hypertension, Inflammation, And Docking Studies

Pramod Patil[1], Basavaraj Padmashal[1*], Vijayakumar Uppar[2], Pavankumar H[3]

[1,1]Department of Chemistry, Rani Channamma University, Belagavi, Karnataka, India- 591156.*

[2]Honeychem Pharma Research Pvt. LTD., Peenya Industrial Estate, Bangalore, Karnataka, India- 560058.

[3]Department of Chemistry, KLE's P.C. Jabin Science College, Hubballi-580031, Karnataka, India.

Abstract: Chronic inflammation diseases are a major cause of death worldwide, including heart diseases, kidney diseases, and liver diseases. Researchers are working on developing effective anti-inflammatory drugs. COX-2 inhibitors like coxibs were developed to reduce gastrointestinal side effects but were later withdrawn due to cardiovascular events. The need for safer coxibs and a better understanding of COX-1 and COX-2 in cardiovascular diseases and stroke is necessary. Chronic inflammation can last for months or years, and its effects vary depending on the underlying cause and the body's ability to repair damage. On the other hand, hypertension is a major cause of global mortality, mortality for 12.8% of annual deaths. The number of adults with hypertension has almost doubled to 1.28 billion, with the greatest increase in low- and middle-income countries, particularly sub-Saharan Africa, where 120 million people may have hypertension. This poses a significant challenge for the region in therapeutic development. In this study, by an eco-friendly method, we have synthesized pyrrolo[1,2-*a*]quinoline derivatives for anti-inflammatory activity along with its molecular docking and anti-hypertension activity. Green chemistry in organic synthesis has become a major focus in recent decades, to develop more environmentally friendly methods. Green chemistry has a significant focus in organic synthesis over the past few decades. Two key principles are "safer solvents" and "energy efficiency" reducing hazardous solvents, and minimizing energy consumption. The synthesis of pyrrolo[1,2-*a*]quinoline derivatives was obtained by a one-pot reaction in which 4-methylquinoline was treated with substituent phenacyl bromides and two different alkynes respectively, in the presence of TEA (triethylamine) with the addition of a minimal amount of acetonitrile as a solvent. The moieties 2a, 3b, and 3a showed the highest inhibitory capacity against reference standard ibuprofen in anti-inflammatory activity, along with their molecular docking study of these compounds displayed better (-3.5) to good (-9.2) docking score within the binding pocket towards crystal structure derivative. Derivative 3b has shown significant inhibition at 100 µg in anti-hypertensive activity.

Keywords- Anti-inflammatory, Chronic inflammation, Coxibs, Rofecoxib, Eco-friendly method, Gastrointestinal.

***Corresponding Author**

Basavaraj Padmashal , Department of Chemistry, Rani Channamma University, Belagavi, Karnataka, India- 591156.

Received On 28 April, 2023

Revised On 20 July, 2023

Accepted On 3 August, 2023

Published On 1 November, 2023

Funding This research did not receive any specific grant from any funding agencies in the public, commercial or not for profit sectors.

Citation Pramod Patil, Basavaraj Padmashal, Vijayakumar Uppar and Pavankumar H , Eco-Friendly Synthesis of Pyrrolo[1,2-A] Quinoline Derivatives and Evaluating Their Effects On Hypertension, Inflammation, and Docking Studies.(2023).Int. J. Life Sci. Pharma Res.13(6), P127-P140 http://dx.doi.org/10.22376/ijlpr.2023.13.6.P127-P140

1. INTRODUCTION

Beneath several decades, organic synthesis by green chemistry has been seized/clinched with scientific discipline[1,2]. In present scenario, the inquisitors in both savants and industry are continually encouraged to move on with environmentally benign methods for procreating desired opportune molecules. Green chemistry has gained significance as a field of study over the past few decades, focusing on an environmentally conscious approach to organic synthesis. Its primary objective is to develop methodologies that minimize environmental harm, while effectively producing desired molecules[3-5]. To advance green chemistry, researchers and industry professionals continually explore novel technologies and techniques[6,7]. Their collective aim is to adopt environmentally friendly methods for generating valuable compounds[8]. Among the numerous principles of green chemistry two key, ones deserves special mention the utilization of "safer solvents" and the prioritization of "energy efficiency" in synthetic processes[9-12]. These principles actively seek to diminish the environmental impact caused by chemical reactions. By embracing these principles, scientists and industry experts contribute to developing greener and more sustainable chemical processes[13-16]. On the other phase, for many chemical processes, a predominant effect on nature by heating or cooling methods to master this adversity. Herein, we have approached with an efficient method, i.e., by microwave irradiation which is proven to be 100 times faster than with conventional method (oil bath, etc.) and ease the chemical reaction[17-19]. Gedye and co-workers first synthesized it in 1986[20-22]. Microwaves generally depend on the endowment of the reaction mixture to intuitively consume microwave energy, taking advantage of "microwave dielectric heating" phenomena such as dipolar polarization or ionic conduction mechanisms[20,21]. The dominance of this method over conventional methods is the lower solvent consumption, reaction time, purity, high yield, efficiency, reduction of by-product formation, and minimal impact on the environment and human health. On the other hand, inflammation is being as the complex and essential biological response, which may also lead to chronic inflammation and various chronic pathologies such as rheumatoid arthritis, inflammatory bowel diseases, Alzheimer's or Parkinson's diseases, cancer-cell, and degeneration, representing a major core in biomedical research[22-28]. Reports suggested that only a few anti-inflammatory drugs, such as amfenac, echinocandins, and aspirins, are in demand to treat anti-inflammatory drug infections and have substantial side effects[29-31]. It is necessary to synthesize novel stimulants to reduce chronic inflammation without harming the physiologic inflammatory response. Researchers have focused on the discovery of anti-inflammatory agents and are in pursuit of developing novel anti-inflammatory agents. Reports suggest that a non-steroidal anti-inflammatory drug (NSAID) which was discovered as a metabolite of 7-benzoylindoline, possesses an N-heterocyclic compound with a pyrrole ring. In recent reports, it has been noticed that pyrrolo[1,2-a] quinolone is very attractive amid heterocyclic compounds[32]. In addition, , hypertension is a widespread issue affecting the global population. It is a problem that is being faced by people all around. Hypertension is a common disease that is a major risk factor for coronary and stroke and is typically treated with long-term medication. Recently, researchers have developed and tested several compounds that combine heterocyclic rings. Some of them have shown significant hypersensitive activity such as 3-substituted -1-[4-(2-indol-3-ylethyl) piperzinyl], pyridinylidinearylureas, (2-aminoethyl) thiourea derivatives, 2,4-diamino-6,7-dimethoxyquinoline derivatives, and 4-(substituted-carbonylamino)-2H-1-benzopyrans. To expand upon these findings, a new series of derivatives incorporated with heterocyclic rings were synthesized and evaluated for their anti-hypertensive effects[33-36.] The recent publication from Padmashali et al. (2020) also shows that pyrrolo[1,2-a] quinolone possesses very good activity for diseases such as cancer[37], malaria[38], inflammation[39], and Alzheimer's disease[40]. Owing to the increasing importance in medicinal chemistry and synthetic organic, they represent substructures often encountered in numerous bioactive natural isolates, pharmaceutically important compounds[41-43], and several marine alkaloids. (Figure 1).

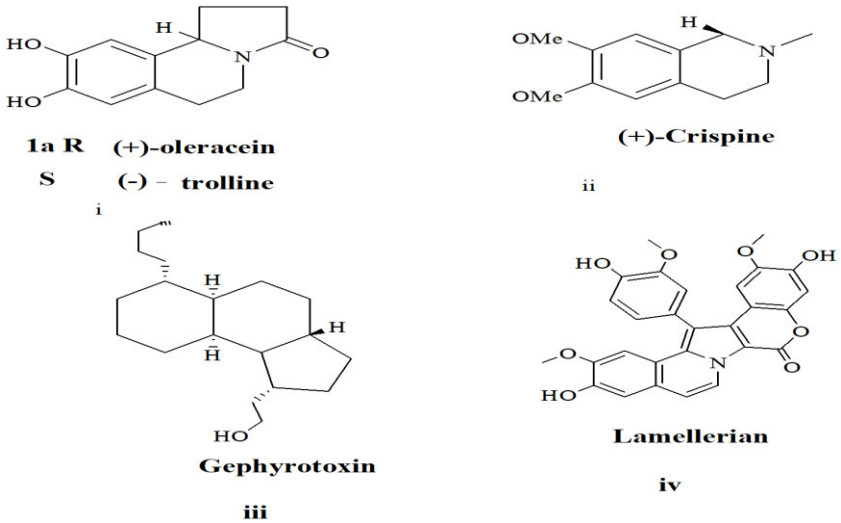


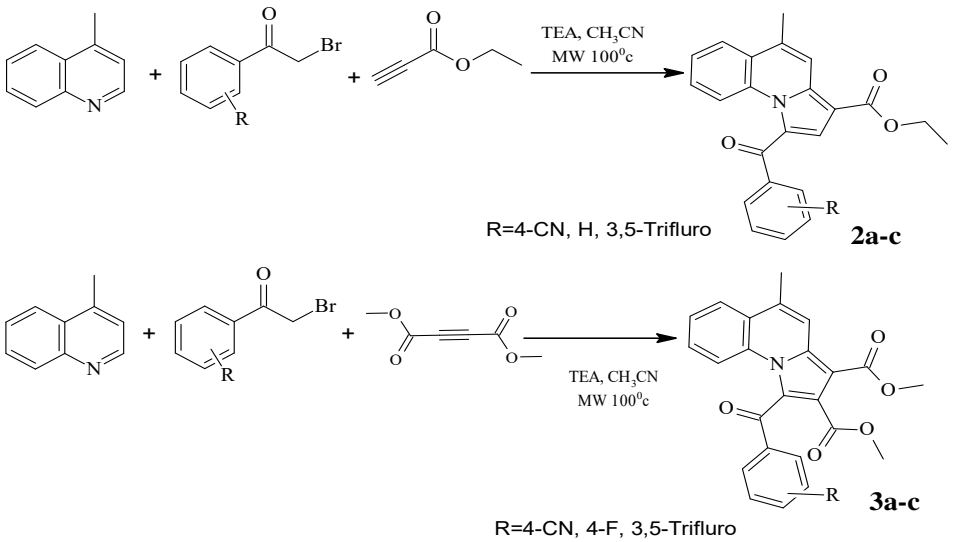
Fig1: A few derivatives of pyrrolo[1,2-*a*] quinolines contain bioactive natural isolates, pharmaceutically important compounds, and several marine alkaloids. For example, i) (+)-oleraceini (-)-trolline ii) (+)-crispine iii) gephyrotoxin iv) Lamellerlian.

Most of the pyrrolo[1,2-*a*]quinolines and pyrrolo[2,1-*a*]isoquinolines are the structural basis of alkaloids exhibiting remarkable antitumor, antibacterial and antiviral [44,45], antidepressant[46], and cardiovascular [47]properties. Owing to the inquisitiveness in various biological activities and the synthetic value of this pyrrolo[1,2-*a*]quinoline moieties, Herein, the aim focus of the study is to develop one of the facile and fascinating powerful tools for the synthesis, that is, by green synthesis method, with low consumption of solvent provides with declined time limit for the synthesis of pyrrolo[1,2-*a*]quinoline derivatives by the 1,3 dipolar cycloaddition reaction of 4-methylquinoline with alkynes such as dimethyl acetylene dicarboxylate, and ethyl propiolate respectively.

2. MATERIALS AND METHODS

The starting materials were purchased from Sigma Aldrich and TCI Chemicals, and satisfying the purity percentage, the reaction proceeded without purification. Microwave-assisted synthesis was carried out using mono mode CEM-Discover microwave apparatus. The melting point was recorded in an open capillary tube. FT-IR was recorded on a KBr disk on a Shimadzu FTIR. ^{1}H and ^{13}C-NMR spectra were recorded on a 400MHz solution-state JEOL instrument. The anti-inflammatory study of pyrrolo[1,2-*a*]quinoline was performed by inhibiting bovine serum albumin denaturation method using ibuprofen as a standard.

Scheme-01



Scheme 1: Synthetic scheme for the preparation of ethyl-1-(substituted benzoyl)-5-methylpyrrolo[1,2-*a*] quinoline-3-carboxylate 2(a-c) and ethyl-1-(substitutedbenzoyl)-5-methylpyrrolo[1,2-*a*] quinoline-2,3-dicarboxylate 3(a-c)

3. EXPERIMENTAL

3.1.1. General procedure for the preparation of ethyl-1-(4-cyanobenzoyl)-5-methylpyrrolo[1,2-a] quinoline-3-carboxylate 2a-c

The reaction was carried out in a single pot in which three components, namely, 4-methylquinoline with 4-cyano phenacyl bromide, ethyl propiolate in presence of trimethylamine as a base in 10mL of acetonitrile solvent taken in a 50mL round bottom flask and was irradiated under microwave oven at 100°C for 6 minutes in which microwave oven was provided with reflux condenser at top. The reaction was monitored by TLC using ethyl acetate and hexane as an eluent. The product formed was poured into crushed ice, then extracted with ethyl acetate, and washed two times with brine solution. The organic layer formed was then treated with anhydrous Na_2SO_4, the solvent was placed for evaporation, and the yield obtained of 2a was 81%. The compounds 2b-c have also been synthesized with the same protocol.

3.1.2. General procedure for the preparation of dimethyl 1-(4-cyanobenzoyl)-5-methylpyrrolo[1,2-a] quinoline-2,3-dicarboxylate 3a-c

The reaction was carried out in a single pot in which three components, namely, 4-methylquinoline with 4-cyano phenacyl bromide, dimethyl acetylene dicarboxylate in the presence of triethylamine as a base in 10mL of acetonitrile solvent taken in a 50mL round bottom flask and was irradiated under microwave oven at 100°C for 6 minutes which is provided with reflux condenser at top. The reaction was monitored by TLC using ethyl acetate and hexane as an eluent. [3:7]. The product formed was poured into crushed ice, then extracted with ethyl acetate two times (2x20ml) and washed with brine solution. The organic layer formed was treated with anhydrous Na_2SO_4, and the solvent was placed for evaporation. It was purified by column chromatography using 60-12 column mesh silica gel using ethyl acetate and hexane as eluent. After purification, the yield obtained for 3a was 83%, 3b, 3c, 76%, and 78%, respectively. The compounds 3b-c have also been synthesized similarly.

3.2. Biological activity

3.2.1. In-vitro anti-inflammatory assay

The newly synthesized compounds were screened for *in-vitro*

anti-inflammatory activity by inhibiting bovine serum albumin denaturation method. The test compounds were dissolved in a minimum dimethyl sulphoxide (DMSO) and diluted with phosphate buffer (0.2M, pH 7.4). The final concentration of DMF in all solutions was less than 2.5%. Test solution (1 ml) containing different drug concentrations was mixed with 1 ml of 1 mm albumin solution in phosphate buffer and incubated at 27-37°C ±10 °C for 15 min. Denaturation was induced by keeping the reaction mixture at 60 °C ±10 °C in a water bath for 10 min. After cooling, the turbidity was measured at 210-660 nm. (Shimadzu Spectrometer). Percentage inhibition of denaturation was calculated from control where no drug was added. Each experiment was done in triplicate, and the average was taken. The percentage of inhibition is calculated from the following formula. The standard solution was also prepared similarly to that of the test solution. Ibuprofen was used as a standard[48].

% Inhibition = 100(1 - Vt/Vc)

Where Vt = Drug absorbance of triplicate average
Vc = Control absorbance of triplicate average

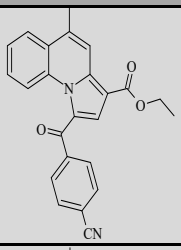
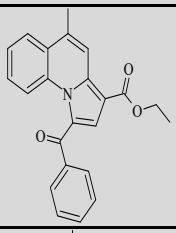
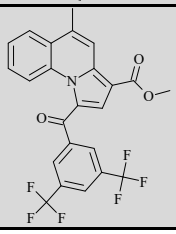
3.2.2. Molecular Docking

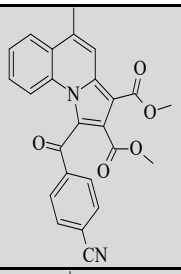
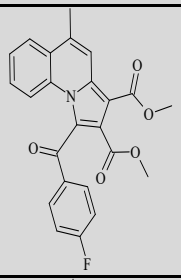
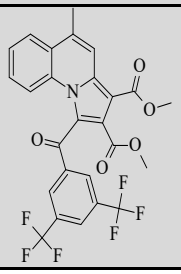
In-silico investigations have been conducted to pinpoint the structural characteristics that may have antimicrobial potential and interact with the protein's active site. We next used molecular docking studies to expand SAR investigations to investigate how these synthesized molecules interact. The findings of the in vitro activities are similarly supported by this research. The 3D crystallographic structure of the protein (PDB ID: 1CX2) was retrieved from Protein Data Bank [49] Auto Dock Vina together with the Auto Dock Tools[50] was employed to set up and perform docking calculations of ligand binding to 1CX2. The ligand and the receptor input files were prepared using Discovery Studio 2021[51], Open Babel GUI[52], and Auto dock tools. The outputs of the studies were visualized using Discovery Studio 2021 Claint Visualizer. Docked pose visualization is performed using PyMol Molecule Viewer[53-57] and Discovery Studio 2021 program. Depending on the extent of docking, the scores were produced (docking score), determining the best-fitted ligand to target protein.

3.3. Anti-hypertensive assay

The compound of interest is tested at three concentrations, 1, 5, 10, 15, 20, and 25µg, dissolved in assay buffer (10mM HEPES buffer containing 0.3M NaCl and 10µM Zinc Sulphate) containing 20µl kidney cortex plasma membranes (ACE enzyme source) and 1mM Hippuryl-His-Leu as substrate. Briefly, the compounds are incubated with the enzyme for 10 minutes at 37°C. Then the substrate is added, making final reaction volume of 50µl and incubating for 45 min at 37°C. The addition of 1M HCl terminates the reaction. The yellow colour is developed by adding 100µl of pyridine and 50µl of benzenesulphonylchloride. The yellow colour that formed is measured at 410 nm in an ELISA Plate Reader (iMARK, BIORAD). Compounds with an inhibitory potential block and substrate availability to the enzyme and thereby cause enzyme inhibition leading to no formation of yellow colour. The inhibition is represented in the form of percentage over control. Captopril, a known ACE inhibitor, is tested in this assay as a standard compound [58,59].

Table1: Physicochemical characteristics of substituted pyrrolo[1,2-*a*]quinoline derivatives (2a-c) and (3a-c)

Code	Structure	Molecular Formulae/ Molecular Weight	Yield Reported by conventional method	Yield % Obtained	Melting Point Reported by conventional method	Melting Point Obtained
2a		$C_{24}H_{18}N_2O_3$ (382.4)	50.5%	81%	179-180	180
2b		$C_{23}H_{19}NO_3$ (357.4)	58.9%	76%	154-156	154
2c		$C_{25}H_{17}F_6NO_3$ (493.4)	53.7%	72%	174-175	174

3a		$C_{25}H_{18}N_2O_5$ (426.4)	66.7%	83%	184-185	185
3b		$C_{24}H_{18}FNO_5$ (419.4)	63.9%	76%	196-197	196
3c		$C_{26}H_{17}F_6NO_5$ (537.4)	66.5%	78%	188-189	188

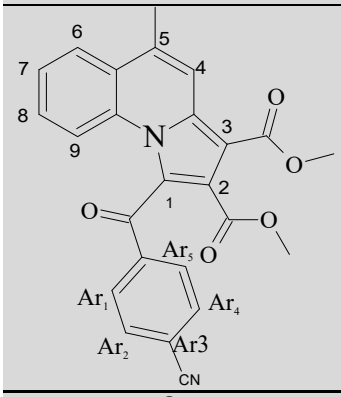
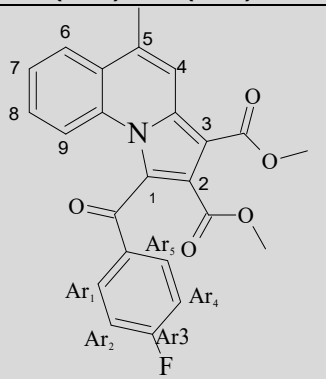
- Spectral and physical data characterized synthesized compounds.
- The yield was determined after column chromatography purification and confirmation.

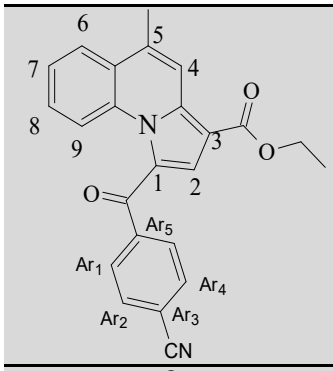
3.4.1. ^{1}H NMR studies of (2a-c) and (3a-c)

Aromatic protons of this compound were seen at δ 8.51-7.54 ppm, and singlet peak at δ 2.79 indicating methyl group, and a peak at δ1.41-1.37 ppm indicating CH_2CH_3 in its ^{1}H NMR spectrum.

^{1}H NMR studies of (2a-c) and (3a-c)

Table 2.^{1}H NMR studies of (2a-c) and (3a-c)

	
3a	**3b**
(8.2-7.4) aromatic protons, 3.906(3H, s, OCH_3), 3.475(3H, s, OCH_3) 2.7(3H, s, CH3). **^{13}C δ (ppm)** 52.435 (OCH_3), 51.797 (OCH_3) 19.556 (CH_3).	(8.0-7.13 aromatic protons, 3.902(3H, s, OCH_3), 3.501(3H, s, OCH_3), 2.680(3H, s, CH_3) **^{13}C δ (ppm)** 52.329 (OCH_3), 51.682 (OCH_3), 19.513 (CH_3)



2a

(8.5-7.9) aromatic protons
4.8-4.3(2H, q, CH_2),
2.79(3H, s, CH_3)
1.41-1.37(3H, t, CH_2CH_3).
^{13}C δ (ppm)
60.326 (CH_2),
19.604 (CH_3),
14.439(CH_3).

3.4.2. FT-IR studies

The IR spectrum of compound 2a shows absorption bands at 2212 cm $^{-1}$, 1701 cm $^{-1}$, and 1626 cm $^{-1}$, indicating the presence of aromatic C-H, ester, and C=O groups.

Table-3. IR-data of pyrrolo[1,2-a]quinoline derivatives (2a-c) and (3a-c)

CODE	(Ar-C-H)	Ester group	C=O
2a	2957	1728	1701
3a	2857	1747	1730
3b	2854	1725	1709

3.5. Pharmacological Studies

3.5.1. Anti-inflammatory activity

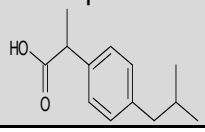
Table-4. *Anti-inflammatory* activity of the synthesized pyrrolo[1,2-*a*] quinoline substituted derivatives (2a-c) and (3a-c)

Comp code	% Inhibition		
	10 µgm	20 µgm	Average
2a	56.21	56.80	56.50
2b	55.67	58.96	57.31
2c	52.97	55.72	54.34
3a	56.75	57.88	*57.31*
3b	55.13	57.88	*56.50*
3c	54.59	56.26	*55.42*
IBUPROFEN	82.70	84.88	83.75

The bovine serum albumin denaturation method was used for the anti-inflammatory activity of various derivatives *in-vitro.* The results, presented in Table 4, indicated that 2a and 3a demonstrated significant anti-inflammatory activity, while the remaining derivative exhibited moderate activity.

Table 5-Molecular docking of studies synthesized pyrrolo[1,2-*a*] quinolone molecules with 1CX2 protein.

Entry	Binding affinity (kcal/mole)	H-bond interactions with Amino acid residues	σ -π interactions	Hydrophobic residual π-Alkyl interactions
2a	-8.2	NF	Ala-527, Ser-353, Val-523,	Gly-526, Ile-345, Leu-359, Leu-531, Met-113, Val-349
2b	-9.2	Arg-120	Ala-527, Ser-353, Val-349, Val-523	Gly-526, Leu-352, Lue-231
2c	-7.6	Arg-120, Tyr-355	Leu-349, Val-349	His-90, Ile-345, Leu-531, Leu-352, Leu-359, Lys-526, Met-522, Ile-345, Val-115, Val-523

3a	-5.1	Tyr-355	Ala-522, Lue-352	Arg-120, Arg-513, Lue-351, Lue-534, Val-349, Val-523
3b	-6.1	Arg-120, His -90, Tyr-355	Ala-527, Ser-353, Val-349, Val-523 Ser-353[a], Leu-352[a]	Ala-527, Leu-531, Leu-352, Leu-359, Val-349
3c	-3.5	Arg-120, Tyr-355	Ala-527, Val-349	Ile-345, Leu-531, Leu-352, Leu-359, Met-113,Trp-387, Tyr-348, Val-116
Ibuprofen 	-6.9	Arg-120, Tyr-355	NF	Leu-352, Leu-352, Tyr-385, Val-349

The binding affinity of the synthetic compounds and their bonding interactions with ligands 3c, 3a, 3b, 2a, and 2b are summarized in Table 5. The maximum negative value of the docking score with the 1CX2 protein ranges from -3.5 to -9.2 kcal/mol. All the synthesized compounds have shown similar residual amino acids binding interactions with Ala-527, Arg-120, His-90, Ile-345, Leu-531, Leu-352, Leu-359, Lys-526, Met-522, Ile-345, Tyr-355, Val-115, Val-523 (Hydrophobic) and Arg-12b0, Tyr-355, His-90 (Hydrogen bonds). Compound 2a has a docking score -of 8.2 kcal/mol without hydrogen bond and residual interactions with Gly-526, Ile-345, Leu-359, Leu-531, Met-113, and Val-349 in the binding pocket. The compound 3c is of t docking score -7.2 kcal/mol with Arg-120, Tyr-355 hydrogen bonds and residual interactions with His-90, Ile-345, Leu-531, Leu-352, Leu-359, Lys-526, Met-522, Ile-345, Val-115, and Val-523 when compared to standard inhibitor like Ibuprofen, docking score -6.9 kcal/mol with Arg-120, Tyr-355 hydrogen bonds, Leu-352, Leu-352, Tyr-385, Val-349 residual interaction. The compound 3b formed additional residual interaction with residual amino acids Ala-527, Leu-531, Leu-and 352, Leu-359, Val-349 and hydrogen bond with Arg-120, His -90, Tyr-355 with docking score -6.1 kcal/mol. Compounds 3c and 3a have hydrogen bond interaction in the binding pocket (Arg-120, Tyr-355) also residual interaction His-90, Ile-345, Leu-531, Leu-352, Leu-359, Met-113, Trp 387, Tyr-348, Val-116 with docking score -3.5 kcal/mol and -5.1 kcal/mol. The Molecular docking study of these compounds displayed moderate (-3.5) to better (-9.2) docking score within the binding pocket toward the crystal structure of cyclooxygenase-2 (1CX2). Compound 2b showed residual interactions and a docking score similar to those of Ibuprofen among the studied drugs. Therefore, compound 2b is a better anti-inflammatory agent than the other compounds in this study. The binding affinity, H-bonds, and residual amino acid interactions of the four compounds are summarized in Table 5, and their binding interactions are shown in Figure.3- …2D, 3D structure of cyclooxygenase-2 with compounds. Hydrogen bonds between compounds and amino acids are shown as green dashed lines, while hydrophobic interaction is shown as pink lines.

3.5.2. Docking Images

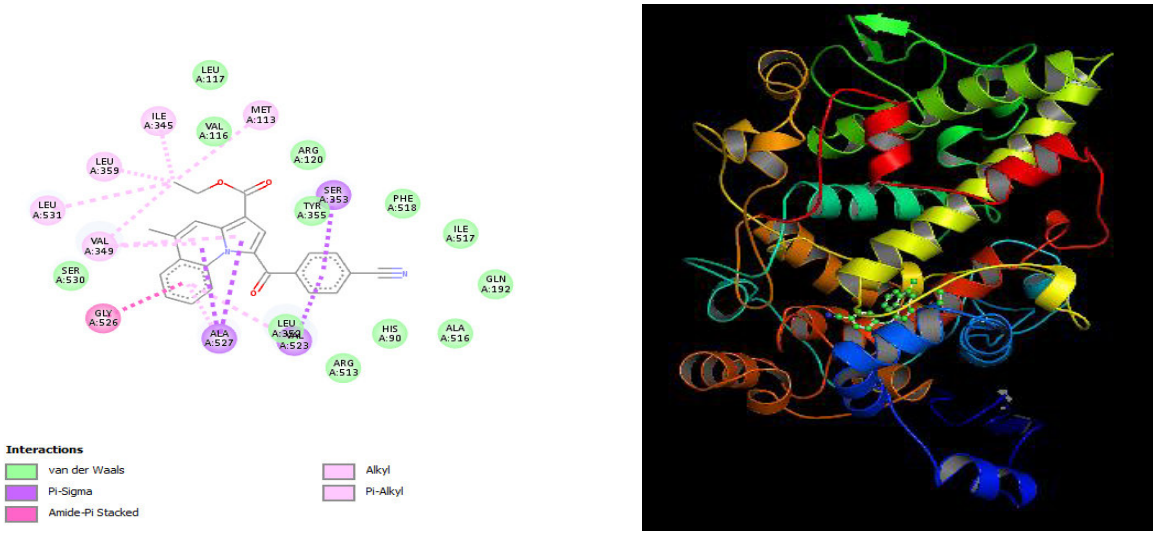


Fig 2: 2D &3D diagram of derivatives of 2a with 1CX2 protein.

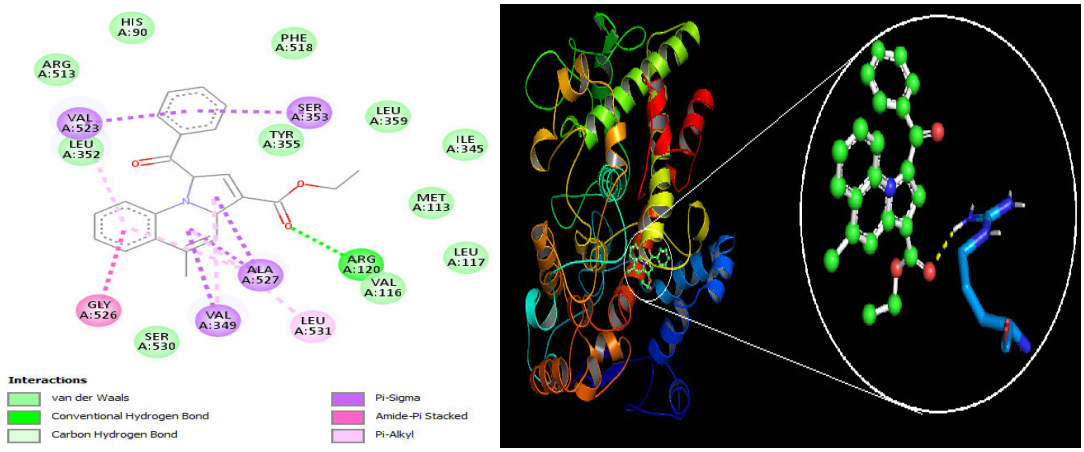


Fig 3: 2D &3D diagrams of derivatives of 2b with 1CX2 protein.

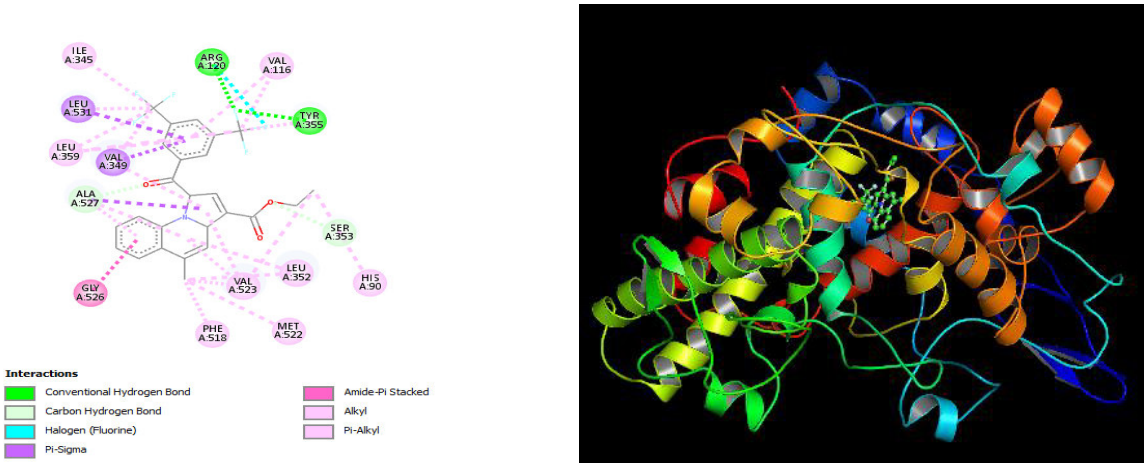


Fig 4: 2D &3D diagrams of derivatives of 2c with 1CX2 protein.

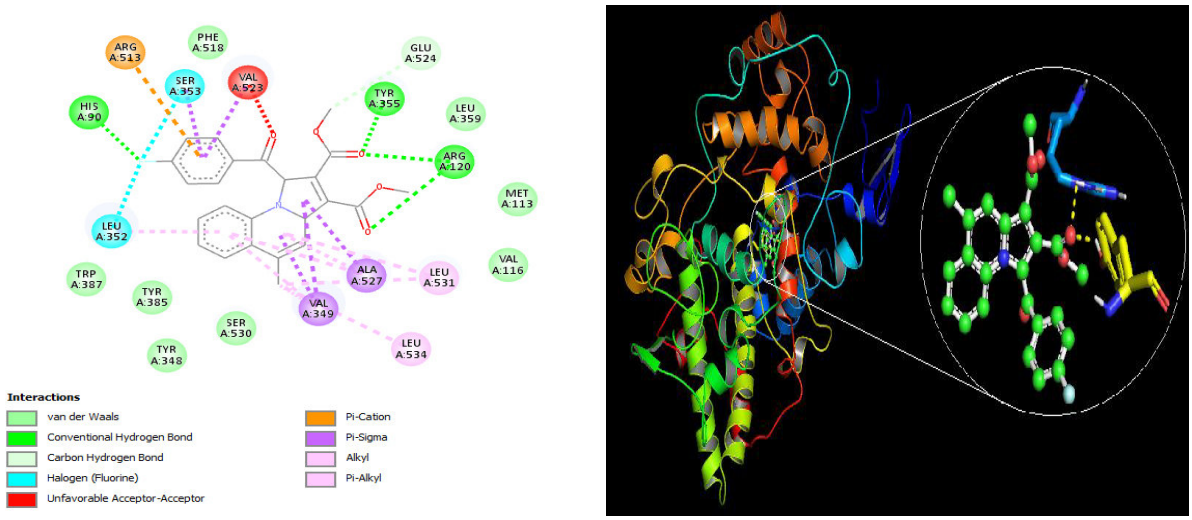
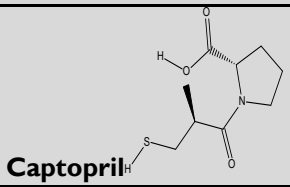


Fig 5: 2D &3D diagram of derivatives of 3b with 1CX2 protein.[49,50]

3.6. Anti-hypertension activity

Table-6 Anti-hypertension activity of the synthesized pyrrolo[1,2-*a*]quinoline substituted derivatives (2a-c) and (3a-c)

Code	% hypertensive activity		
	10 µg	50 µg	100 µg
2a	0.00	0.00	19.03
2b	0.00	0.00	47.35

2c	0.00	0.00	19.05
3a	0.00	0.00	33.03
3b	0.00	0.00	24.08
3c	0.00	0.00	28.65
 Captopril	25.22	53.54	86.28

Derivative 2b has shown significant inhibition at 100 µg, but no activity was found at lower concentrations. At the same time, all derivatives have not shown any inhibition at 10 µg and 50 µg concentrations. Captopril, a standard ACE inhibitor, inhibited over at its IC_{50} concentration of 15 nM.

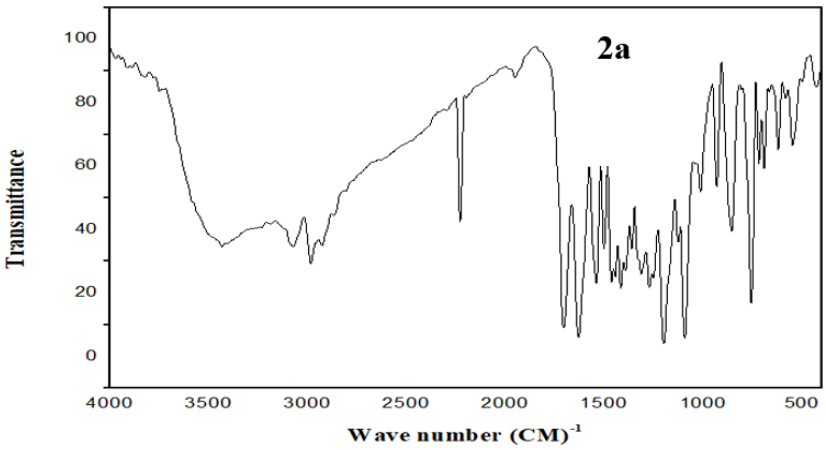


Fig 6: FT-IR of ethyl 1-(4-cyanobenzoyl)-5-methylpyrrolo[1,2-a]quinoline-3-carboxylate 2a

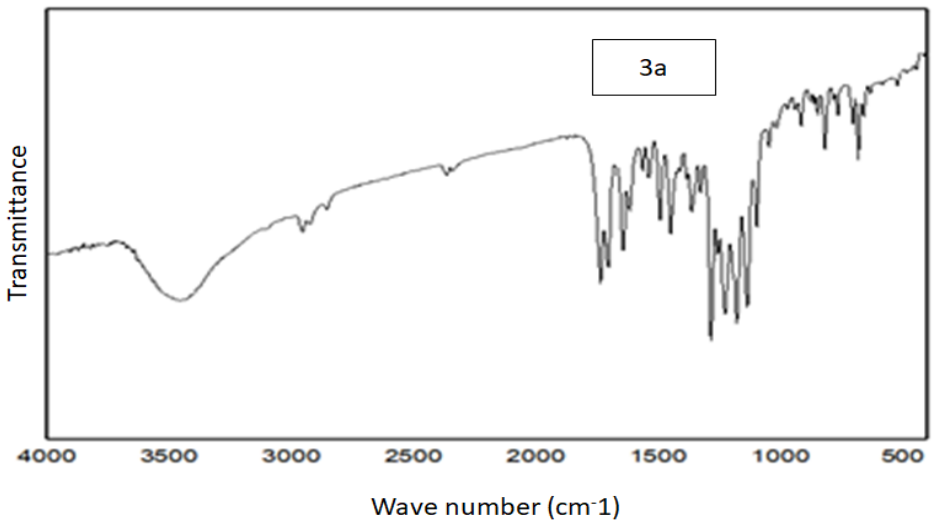


Fig 7: FT-IR of dimethyl 1-(4-cyanobenzoyl)-5-methylpyrrolo[1,2-a] quinoline-2,3-dicarboxylate 3a.

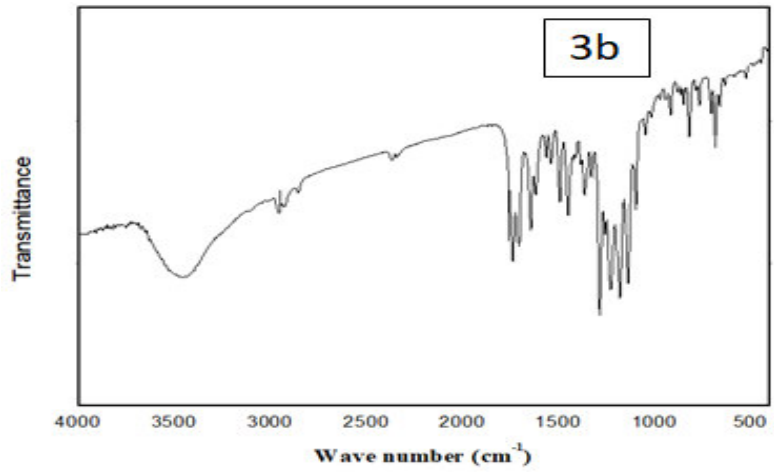


Fig 8: FT-IR of dimethyl-(4-fluorobenzoyl)-5-methylpyrrolo[1,2-*a*] quinoline-2,3-dicarboxylate 3b

4. DISCUSSION

Recent studies have highlighted the potential of N-benzo-fused homologous derivatives as a promising drug target for treating inflammatory infections. Our research article explores the potential of pyrrolo[1,2-*a*]quinoline derivatives to discover novel compounds with therapeutic applications. In particular, pyrrolo[1,2-*a*] pyrazine derivatives have shown moderate activity against inflammation, with MTT assay evaluating them *in-vitro* anti-inflammatory effects against lipopolysaccharide in RAW264.7 cells. These derivatives exhibited inhibition ranging from 43-59% at 50 μM[60]. Notably, compound 3-methyl -2,8-dixo-7,8-dihydro-2H-pyrrolo[1,2-a] [1,2,4] triazino[2,3-c] quinazoline-5a(6H) carboxylic acid, derivative 1a exhibited a significant suppressive effect on inflammation in both the carrageenan and formalin models, reducing it by 57.90% and 53.76% respectively[61].Another study reported that derivative 1b exhibited the strongest inhibitory activity against COX-2, with an IC_{50} value of 70nM and a selectivity index of 220, surpassing that of Zileuton. The active compounds also displayed considerable inhibitory activity against LOX *in-vitro* and demonstrated a favourable safety profile for the gastrointestinal tract (GIT) experimental animals that tolerated these derivatives well[62]. Additionally, derivatives of 7-alkoxy1-amino-4,5-dihydro [1,2,4]-triazole[4,3, -a]quinolines were synthesized and evaluated for *in-vivo* anti-inflammatory effect. Among them, compounds 1c and 1d demonstrated anti-inflammatory activity with ibuprofen as a reference drug[63].Based on the literature survey, it was found that N-benzo fused homologous derivatives possessed moderate potency in inhabiting ACE. Derivatives1a (3-Methyl-2,8-dioxo-7,8-dihydro-2H-pyrrolo[1,2-a] [1,2,4] triazino[2,3-c] quinazoline-5a(6H)carboxylic acid) and 1f(1-propyl-3-(pyridin-2-ylmethyl)urea) and 1f (1-propyl-3-(pyridin-2-ylmethyl)urea) have displayed note-worthy anti-hypertensive activity in DHR, while the other derivatives did not exhibit significant results. On the other hand, Centpyraquin has demonstrated considerable hypertensive and CNS depressant properties[64]. In one study, out of 18 compounds tested, 17 demonstrated notable anti-hypertensive effects in DHR, two of these compounds were specifically identified as 1-propyl-3-(pyridin-2-ylmethyl)urea and 1-(4-methoxyphenyl)-3-(pyridin-2-ylmethyl)urea[65,66]. Two new derivatives 12-methyl-6*H*-isoquino[2,1, a]quinazolin-6-one and 13*H*-Quinazolino[3, 4-a]quinazoline-13-one of quinazolines were synthesized, and subsequently assessed for their effectiveness in combating inflammation[67,68]. The *in-vivo* anti-inflammatory activity of compounds2-phenyl-3-(4-methylbenzothiazol-2-yl)quinazolin-4(3H)-one, 2-phenyl-3-(5-methylbenzothiazol-2-yl)quinazolin-4(3H)-one, and 2-Phenyl-3-(4-6-dimethylbenzothiazol-2-yl)quinazolin-4(3H)-one was found to be similar to that of indomethacin in rats with carrageenan-induced paw edema. Subsequently, these were subjected to further testing to determine their ability to inhibit COX-1 AND COX-2 enzymes using the procedure outlined by Wakini et.al[69,70]. The recently developed derivatives of quinazoline 1g (4-chloro-3-{2-[(*Z*)-2-(4-fluorophenyl)ethenyl]-4-oxoquinazolin-3(4*H*)-yl}benzoic acid)have exhibited efficacy at a dose of 200mg/kg, demonstrating activity that is on par with the widely used standard medication ibuprofen[71,72]**.** The anti-inflammatory properties of acridine and furo[2,3-b]quinoline derivatives were found to be attractive, to some extent, to their ability to suppress the release of chemical mediators from mast cells, neutrophils, and macrophages. These findings suggest that these compounds have the potential to serve as novel anti-inflammatory agents while exhibiting minimal toxicity[73].Compound(E)-4-methoxy-N-(tetrazolo[1,5-a] quinolin-4-ylmethylene) benzenamine exhibited 44.5% protection against inflammation. On the other hand, compounds (E)-3,4-dimethyl-N-(tetrazolo[1,5-a]quinolin-4-ylmethylene)benzenamineand **(**E)-2-methyl-N-(tetrazolo[1,5-a]quinolin-4-ylmethylene)benzenamin**e** displayed 32.0% and 28.9% protection, respectively, against carrageenan-induced inflammation when compared to indomethacin, which provided 78.9% protection against rat paw edema[74]The study findings demonstrated with derivatives (1a-g), that the presence of quinoline substitution on various nitrogenous heterocycles exhibited notable anti-inflammatory effects in a carrageenan-induced rat paw edema model. Among these compounds, compound N-(Ribosylhydrazon)-2-phenylquinolin-4- carboxamide emerged as a highly potential anti-inflammatory agent, displaying significant activity comparable to diclofenac sodium, a standard drug. Consequently, these derivative holds promise as a valuable lead compound for developing potent and selective anti-inflammatory agent[75] A series of quinoline-based hybrids incorporating 1,2 4-triazole/oxime moieties exhibited remarkable anti-inflammatory activity while demonstrating a low occurrence of gastric ulceration, comparable to the effects observed with indomethacin and celecoxib. Furthermore, many of the tested compounds showed strong inhibition of COX-1. Importantly, most tested compounds exhibited excellent safety potential, preserving the integrity of the stomach tissues [76].

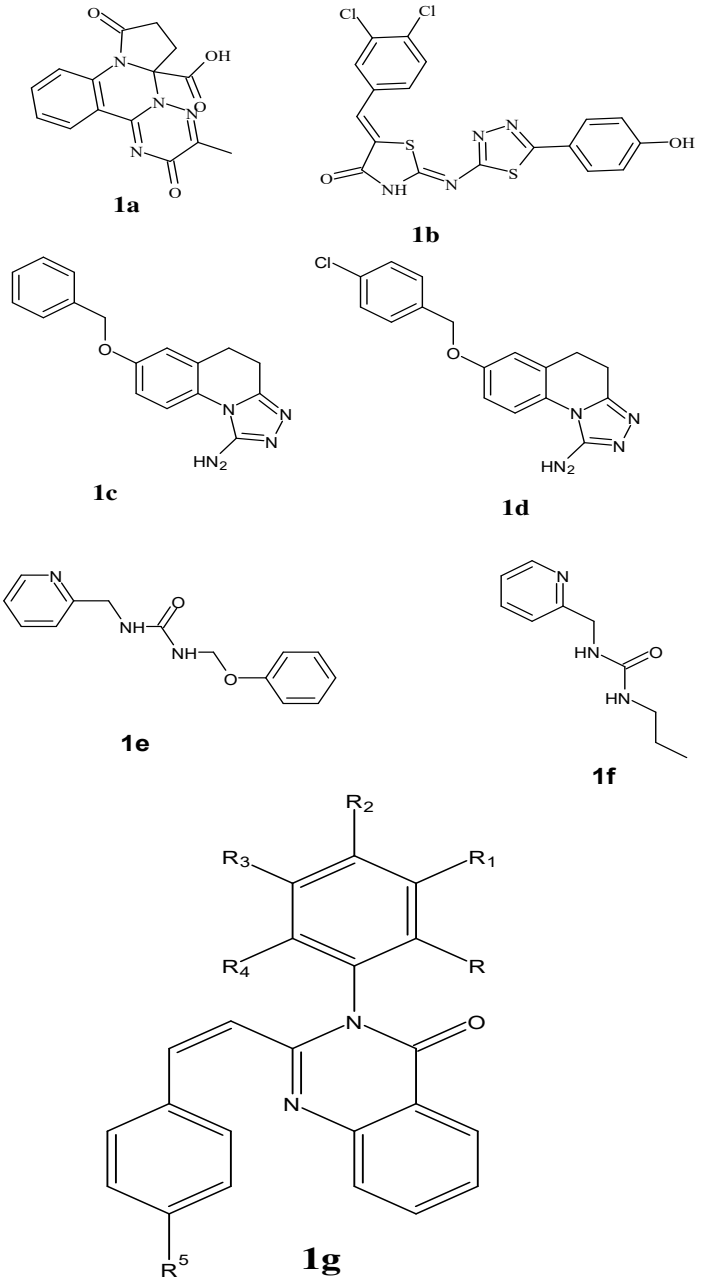


Fig 9: Analogues (1a-g) tested for anti-inflammatory for various reference standards, anti-hypertensive activity, inhibitory activity against ACE, and different values.

The synthesized compounds have demonstrated noteworthy effectiveness against anti-inflammatory and anti-hypertensive activity. This indicated that utilizing N-benzo fused homologous derivative skeleton can be a promising approach for developing potent and innovative therapeutic agents.

5. CONCLUSION

The current trend is towards environmentally friendly approaches, and we have successfully achieved targeted moieties using microwave irradiation. This method resulted in higher yields with minimal solvent usage and reduced reaction time, in a one-pot reaction followed by a 1,3-dipolar cycloaddition reaction. Spectral analyses such as IR, ^{1}H, and ^{13}C NMR confirmed the purity of the derivatives obtained. Our synthesized derivatives were evaluated for their anti-inflammatory activity; two of them, 2a and 3a, showed significant activity. The rest exhibited moderate activity. Docking studies revealed that compound 2b has a maximum negative value of the docking score with the 1CX2 protein, ranging from -3.5 to -9.2kcal/mol. Furthermore, compounds 2a, 2b, and 2c displayed residual interactions and a docking score similar to those of ibuprofen among the drugs examined, indicating that it is a better anti-inflammatory agent than the other derivatives. Compound 3b demonstrated significant inhibition at 100 µg in anti-hypertensive activity compared to other derivatives.

6. ACKNOWLEDGEMENT

We thank Rani Channamma University, Belagavi, for providing laboratory facilities.

7. AUTHORS CONTRIBUTION STATEMENT

Basavaraj Padmashali conceptualized the synthesis design, and Pavankumar H performed the molecular docking studies. Vijayakumar Uppar and Pramod Patil conducted the synthesis

and analyzed the data, and necessary inputs were given for designing the manuscript. All the authors discussed the methodology and contributed to the final manuscript.

8. CONFLICT OF INTEREST

Conflict of interest declared none.

9. REFERENCES

1. Spargo P. Green chemistry, an introductory text by Mike Lancaster. Cambridge: Royal Society of Chemistry, ISBN 0-85404-620-8; 2002. p. 310.
2. Macquarrie DJ, Clark JH, editors. Handbook of green chemistry and technology. Blackwell Science; 2002.
3. Haswell SJ, Kingston HM. Microwave-enhanced chemistry: fundamentals, sample preparation, and applications. American Chemical Society; 1997.
4. Spargo P. Microwaves in organic synthesis Loupy A, editor. Vol. 159. Weinheim: Wiley-VCH Press; 2002. p. 499.
5. Hayes BL. Microwave synthesis: chemistry at the speed of light. Chem Corporation; 2002.
6. Tierney J, Lidström P, editors. Microwave assisted organic synthesis. John Wiley & Sons; 2009.
7. Kappe CO, Stadler A, Dallinger D. Microwaves in organic and medicinal chemistry. John Wiley & Sons; 2012.
8. Larhed M, Olofsson K, editors. Microwave methods in organic synthesis. Springer; 2006.
9. Kappe CO. Controlled microwave heating in modern organic synthesis. AngewChemInt Ed Engl. 2004;43(46):6250-84. doi: 10.1002/anie.200400655, PMID 15558676.
10. De la Hoz A, Díaz-Ortiz A, Moreno A. Microwaves in organic synthesis. Thermal and non-thermal microwave effects. ChemSoc Rev. 2005;34(2):164-78. doi: 10.1039/b411438h, PMID 15672180.
11. De la Hoz A, Díaz-Ortiz A, Moreno A. Microwaves in organic synthesis. Thermal and non-thermal microwave effects. ChemSoc Rev. 2005;34(2):164-78. doi: 10.1039/b411438h, PMID 15672180.
12. Loupy A, de la Hoz A, editors. Microwaves in organic synthesis. John Wiley & Sons; 2013. p. 26.
13. Kuhnert N. Microwave-assisted reactions in organic synthesis—are there any nonthermal microwave effects? AngewChemInt Ed Engl. 2002;41(11):1863-6. doi: 10.1002/1521-3773(20020603)41:11<1863::aid-anie1863>3.0.co;2-l, PMID 19750616.
14. Dallinger D, Kappe CO. Microwave-assisted synthesis in water as solvent. Chem Rev. 2007;107(6):2563-91. doi: 10.1021/cr0509410, PMID 17451275.
15. Mont N, Fernández-Megido L, Teixidó J, Kappe CO, Borrell JI. A Diversity-Oriented, Microwave-Assisted Synthesis of 4-oxo and 4-chloropyrido[2,3-d]pyrimidin-7(8 H)-ones. QSAR Comb Sci. 2004;23(10):836-49. doi: 10.1002/qsar.200420033.
16. Stadler A, Kappe CO. The effect of microwave irradiation on carbodiimide-mediated esterifications on solid support. Tetrahedron. 2001;57(18):3915-20. doi: 10.1016/S0040-4020(01)00260-5.
17. Benakki H, Colacino E, André C, Guenoun F, Martinez J, Lamaty F. Microwave-assisted multi-step synthesis of novel pyrrolo-[3, 2-c] quinoline derivatives. Tetrahedron. 2008;64(25):5949-55. doi: 10.1016/j.tet.2008.04.034.
18. Gedye R, Smith F, Westaway K, Ali H, Baldisera L, Laberge L et al. The use of microwave ovens for rapid organic synthesis. Tetrahedron Lett. 1986;27(3):279-82. doi: 10.1016/S0040-4039(00)83996-9.
19. Giguere RJ, Bray TL, Duncan SM, Majetich G. Application of commercial microwave ovens to organic synthesis. Tetrahedron Lett. 1986;27(41):4945-8. doi: 10.1016/S0040-4039(00)85103-5.
20. Gabriel C, Gabriel S, H. Grant E, H. Grant E, S. J. Halstead B, Michael P. Mingos D. Dielectric parameters relevant to microwave dielectric heating. ChemSoc Rev. 1998;27(3):213-24. doi: 10.1039/a827213z.
21. Georgescu E, Georgescu F, Dumitrascu F, Draghici C, Nicolescu A, Marinescu D et al. Microwave-assisted multicomponent synthesis of benzo[f]pyrrolo [1,2-a]quinoline derivatives. Rev RoumChim. 2020;65(1):91-102. doi: 10.33224/rrch/2020.65.1.11.
22. Artis D, Spits H. The biology of innate lymphoid cells. Nature. 2015;517(7534):293-301. doi: 10.1038/nature14189, PMID 25592534.
23. Isailovic N, Daigo K, Mantovani A, Selmi C. Interleukin-17 and innate immunity in infections and chronic inflammation. J Autoimmun. 2015;60:1-11. doi: 10.1016/j.jaut.2015.04.006, PMID 25998834.
24. Pedraza-Alva G, Pérez-Martínez L, Valdez-Hernández L, Meza-Sosa KF, Ando-Kuri M. Negative regulation of the inflammasome: keeping inflammation under control. Immunol Rev. 2015;265(1):231-57. doi: 10.1111/imr.12294, PMID 25879297.
25. Mauriz JL, Collado PS, Veneroso C, Reiter RJ, González-Gallego J. A review of the molecular aspects of melatonin's anti-inflammatory actions: recent insights and new perspectives. J Pineal Res. 2013;54(1):1-14. doi: 10.1111/j.1600-079X.2012.01014.x, PMID 22725668.
26. Azab A, Nassar A, Azab AN. Anti-inflammatory activity of natural products. Molecules. 2016;21(10):1321. doi: 10.3390/molecules21101321, PMID 27706084.
27. Muchowski JM, Unger SH, Ackrell J, Cheung P, Cooper GF, Cook J et al. Synthesis and antiinflammatory and analgesic activity of 5-aroyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acids and related compounds. J Med Chem. 1985;28(8):1037-49. doi: 10.1021/jm00146a011, PMID 4020827.
28. Welstead Jr WJ, Moran HW, Stauffer HF, Turnbull LB, Sancilio LF. Antiinflammatory agents. 1. Synthesis and antiinflammatory activity of 2-amino-3-benzoylphenylacetic acid. J Med Chem. 1979;22(9):1074-9. doi: 10.1021/jm00195a012, PMID 490552.
29. Walsh DA, Moran HW, Shamblee DA, Uwaydah IM, Welstead Jr WJ, Sancilio LF et al. Anti-inflammatory agents. 3. Synthesis and pharmacological evaluation of 2-amino-3-benzoylphenylacetic acid and analogs. J Med Chem. 1984;11:1379-88.
30. Ruiz J, López M, Milà J, Lozoya E, Lozano JJ, Pouplana R. QSAR and conformational analysis of the antiinflammatory agent amfenac and analogues. J Comput Aided Mol Des. 1993;7(2):183-98. doi: 10.1007/BF00126444, PMID 8320556.

31. Walsh DA, Moran HW, Shamblee DA, Welstead Jr WJ, Nolan JC, Sancilio LF et al. Anti-inflammatory agents. 4. Syntheses and biological evaluation of potential pro-drugs of 2-amino-3-benzoylbenzeneacetic acid and 2-amino-3-(4-chlorobenzoyl) benzeneacetic acid. J Med Chem. 1999;33(18):2296-304.
32. Uppar V, Chandrashekharappa S, Mohan MK, Basarikattia AI, Rachotimath BB, Chougala M et al. Synthesis and characterization of indolizine and 5,6-benzo-fused indolizine derivatives with their pharmacological applications. Chem Data Coll. 2020;29:100524. doi: 10.1016/j.cdc.2020.100524.
33. Glamkowski EJ, Reitano PA, Woodward DL. Synthesis and evaluation of 3-substituted 1-[4-(2-indol-3-ylethyl)piperazinyl]ureas as potential antihypertensive agents. J Pharm Sci. 1978;67(12):1773-4. doi: 10.1002/jps.2600671240, PMID 722502.
34. Ludden CT, Scriabine A, Ulm EH, Morgan G, Fisher MH, Ruyle WV. Antihypertensive activity of some novel pyridinylidenearylurea derivatives in spontaneously hypertensive rats. Experientia. 1979;35(6):799-801. doi: 10.1007/BF01968258, PMID 467597.
35. Tilley JW, Levitan P, Kierstead RW, Cohen M. Antihypertensive (2-aminoethyl)thiourea derivatives. 1. J Med Chem. 1980;23(12):1387-92. doi: 10.1021/jm00186a019, PMID 7452693.
36. Vajragupta O, Pathomsakul A, Matayatsuk C, Ruangreangyingyod L, Wongkrajang Y, Foye WO. Synthesis and antihypertensive activity of N-(alkyl/alkenyl/aryl)-N-heterocyclic ureas and thioureas. J Pharm Sci. 1996;85(3):258-61. doi: 10.1021/js930295x, PMID 8699324.
37. Sandeep C, Padmashali B, Kulkarni RS, Mallikarjuna SM, Siddesh MB, Nagesh HK et al. Synthesis of substituted 5-acetyl-3-benzoylindolizine-1-carboxylate from substituted 2-acetyl pyridinium bromides, Heterocycl. Lett. 2014;4:371-6.
38. Sandeep C, Padmashali B, Venugopala KN, Kulkarni RS, Venugopala R, Odhav B. Synthesis and Characterization of Ethyl 7-Acetyl-2-substituted 3-(substituted benzoyl)indolizine-1-carboxylates for in vitro Anticancer Activity. Asian J Chem. 2016;28(5):1043-8. doi: 10.14233/ajchem.2016.19582.
39. Venugopala KN, Uppar V, Chandrashekharappa S, Abdallah HH, Pillay M, Deb PK et al. Cytotoxicity and Antimycobacterial Properties of Pyrrolo[1,2-a]quinoline Derivatives: Molecular Target Identification and Molecular Docking Studies. Antibiotics (Basel). 2020;9(5):233. doi: 10.3390/antibiotics9050233, PMID 32392709.
40. Uppar V, Basarikatti AI, Padmashali B, Chandrashekharappa S, Chougala M, Mudnakudu-Nagaraju KK et al. Synthesis, anti-bacterial and Antioxidant Properties of ethyl 7-amino-3-benzoyl-2-methylindolizine-1-carboxylate derivatives. AIP Conf Proc. 2020, (Vol. 2274, No. 1, p. 050015). doi: 10.1063/5.0022905.
41. Dubé D, Blouin M, Brideau C, Chan CC, Desmarais S, Ethier D et al. Quinolines as potent 5-lipoxygenase inhibitors: synthesis and biological profile of L-746,530. Bioorg Med Chem Lett. 1998;8(10):1255-60. doi: 10.1016/s0960-894x(98)00201-7, PMID 9871745.
42. Testa ML, Lamartina L, Mingoia F. A new entry to the substituted pyrrolo[3,2-c]quinoline derivatives of biological interest by intramolecular heteroannulation of internal imines. Tetrahedron. 2004;60(28):5873-80. doi: 10.1016/j.tet.2004.05.047.
43. Martins C, Carreiras MC, León R, De Los Ríos C, Bartolini M, Andrisano V et al. Synthesis and biological assessment of diversely substituted furo[2,3-b]quinolin-4-amine and pyrrolo[2,3-b]quinolin-4-amine derivatives, as novel tacrine analogues. Eur J Med Chem. 2011;46(12):6119-30. doi: 10.1016/j.ejmech.2011.09.038, PMID 22000936.
44. Su B, Cai C, Deng M, Liang D, Wang L, Wang Q. Design, synthesis, antiviral activity, and SARs of 13a-substituted phenanthroindolizidine alkaloid derivatives. Bioorg Med Chem Lett. 2014;24(13):2881-4. doi: 10.1016/j.bmcl.2014.04.101, PMID 24835986.
45. Wang RF, Yang XW, Ma CM, Cai SQ, Li JN, Shoyama Y. A bioactive alkaloid from the flowers of Trolliuschinensis. Heterocycles-Sendai institute of heterocyclic chemistry. 2004;63(6):1443-8.
46. Maryanoff BE, Vaught JL, Shank RP, McComsey DF, Costanzo MJ, Nortey SO. Pyrroloisoquinoline antidepressants. 3. A focus on serotonin. J Med Chem. 1990;33(10):2793-7. doi: 10.1021/jm00172a018, PMID 2213832.
47. Martins C, Carreiras MC, León R, De Los Ríos C, Bartolini M, Andrisano V et al. Synthesis and biological assessment of diversely substituted furo[2,3-b]quinolin-4-amine and pyrrolo[2,3-b]quinolin-4-amine derivatives, as novel tacrine analogues. Eur J Med Chem. 2011;46(12):6119-30. doi: 10.1016/j.ejmech.2011.09.038, PMID 22000936.
48. Pandey AK, Kashyap PP, Kaur CD. Anti-inflammatory activity of novel Schiff bases by in vitro models. Bangladesh J Pharmacol. 2017;12(1):41-3. doi: 10.3329/bjp.v12i1.29675.
49. Narramore S, Stevenson CEM, Maxwell A, Lawson DM, Fishwick CWG. New insights into the binding mode of pyridine-3-carboxamide inhibitors of E. coli DNA gyrase. Bioorg Med Chem. 2019;27(16):3546-50. doi: 10.1016/j.bmc.2019.06.015, PMID 31257079.
50. Trott O, Olson AJ. AutoDockVina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. J Comput Chem. 2010;31(2):455-61. doi: 10.1002/jcc.21334, PMID 19499576.
51. Eberhardt J, Santos-Martins D, Tillack AF, Forli S. AutoDockVina 1.2.0: New docking methods, expanded force field, and python bindings. J ChemInf Model. 2021;61(8):3891-8. doi: 10.1021/acs.jcim.1c00203, PMID 34278794.
52. Ochieng PJ, Sumaryada T, Okun D. Molecular docking and pharmacokinetic prediction of herbal derivatives as maltase-glucoamylase inhibitor. Asian J Pharm Clin Res. 2017;10(9):392-98. doi: 10.22159/ajpcr.2017.v10i9.19337.
53. BIOVIA DS. BIOVIA Discovery Studio academic research suite. [San Diego, Dassaultsystèmes]; 2021.
54. O'Boyle NM, Banck M, James CA, Morley C, Vandermeersch T, Hutchison GR. Open Babel: an open chemical toolbox. J Cheminform. 2011;3:33. doi: 10.1186/1758-2946-3-33, PMID 21982300.
55. Sanner MF. Python: a programming language for software integration and development. J Mol Graph Model. 1999;17(1):57-61. PMID 10660911.
56. Palomer A, Cabré F, Pascual J, Campos J, Trujillo MA, Entrena A et al. Identification of novel

cyclooxygenase-2 selective inhibitors using pharmacophore models. J Med Chem. 2002;45(7):1402-11. doi: 10.1021/jm010458r, PMID 11906281.
57. Kumara HK, Suhas R, SuyogaVardhan DM, Shobha M, Channe Gowda D. A correlation study of biological activity and molecular docking of Asp and Glu linked bis-hydrazones of quinazolinones. RSC Adv. 2018;8(19):10644-53. doi: 10.1039/c8ra00531a, PMID 35540474.
58. Jimsheena VK, Gowda LR. Colorimetric, high-throughput assay for screening angiotensin I-converting enzyme inhibitors. Anal Chem. 2009;81(22):9388-94. doi: 10.1021/ac901775h, PMID 19839596.
59. Hooper NM, Turner AJ. Isolation of two differentially glycosylated forms of peptidyl-dipeptidase A (angiotensin converting enzyme) from pig brain: a re-evaluation of their role in neuropeptide metabolism. Biochem J. 1987;241(3):625-33. doi: 10.1042/bj2410625, PMID 2439065.
60. Zhou YM, Wei Y, Yang J, Li HH, Liu MD, Huang NY. Synthesis and In Vitro Anti-Inflammatory Activity of Pyrrolo[1,2-A]pyrazines via Pd-Catalyzed Intermolecular Cyclization Reaction, Trans Tech Publications Ltd. AMR. 2014;830:115-8. doi: 10.4028/www.scientific.net/AMR.830.115.
61. Stavytskyi V, Antypenko O, Nosulenko I, Berest G, Voskoboinik O, Kovalenko S. Substituted 3-R-2,8-dioxo-7,8-dihydro-2H-pyrrolo[1,2-a][1,2,4] triazino [2,3-c]quinazoline-5a(6H)carboxylic Acids and their Salts – a Promising Class of Anti-inflammatory Agents. AntiinflammAntiallergy Agents Med Chem (Formerly Current Medicinal Chemistry-Anti-Inflammatory and Anti-Allergy Agents). 2021;20(1):75-88. doi: 10.2174/1871523019666200505073232, PMID 32368980.
62. Omar YM, Abdu-Allah HHM, Abdel-Moty SG. Synthesis, biological evaluation and docking study of 1,3,4-thiadiazole-thiazolidinone hybrids as anti-inflammatory agents with dual inhibition of COX-2 and 15-LOX. Bioorg Chem. 2018;80:461-71. doi: 10.1016/j.bioorg.2018.06.036, PMID 29986191.
63. Sun XY, Wei CX, Chai KY, Piao HR, Quan ZS. Synthesis and anti-inflammatory Activity Evaluation of Novel 7-Alkoxy-1-amino-4, 5-dihydro [1, 2, 4] triazole [4, 3-a] quinolines, Archiv der Pharmazie an International. J Pharm Med Chem. 2008;341(5):288-93.
64. Tilley JW, Ramuz H, Hefti F, Gerold M. Antihypertensive (2-aminoethyl)thiourea derivatives. 2. J Med Chem. 1980;23(12):1438-9. doi: 10.1021/jm00186a027, PMID 6779010.
65. Vajragupta O, Pathomsakul A, Matayatsuk C, Ruangreangyingyod L, Wongkrajang Y, Foye WO. Synthesis and antihypertensive activity of N-(alkyl/alkenyl/aryl)-N-heterocyclic ureas and thioureas. J Pharm Sci. 1996;85(3):258-61. doi: 10.1021/js930295x, PMID 8699324.
66. Campbell SF, Hardstone JD, Palmer MJ. 2,4-Diamino-6,7-dimethoxyquinoline derivatives as alpha 1-adrenoceptor antagonists and antihypertensive agents. J Med Chem. 1988;31(5):1031-5. doi: 10.1021/jm00400a025, PMID 2896245.
67. Ozaki K, Yamada Y, Oine T. Studies on 4 (1H)-quinazolinones. IV. Convenient Synth of. 1984;32(6), 2160-4:12-Methyl-6H-isoquino [2, 1-a] quinazolin-6-one and 6-Methyl-13H-quinazolino [3, 4-a] quinazolin-13-one. Chemical and pharmaceutical bulletin.
68. Ashwood VA, Cassidy F, Coldwell MC, Evans JM, Hamilton TC, Howlett DR et al. Synthesis and antihypertensive activity of 4-(substituted-carbonylamino)-2H-1-benzopyrans. J Med Chem. 1990;33(9):2667-72. doi: 10.1021/jm00171a051, PMID 2391705.
69. Laddha SS, Wadodkar SG, Meghal SK. Studies on some biologically active substituted 4 (3H)-quinazolinones. Part 1. Synth Char Anti-Inflamm-Antimicrob Act of. 2006;6, 8-disubstituted 2-phenyl-3-[substituted-benzothiazol-2-yl]-4 (3H)-quinazolinones, Arkivoc:1, 11, 1-20.
70. Wakitani K, Nanayama T, Masaki M, Matsushita M. Profile of JTE-522 as a human cyclooxygenase-2 inhibitor. Jpn J Pharmacol. 1998;78(3):365-71. doi: 10.1254/jjp.78.365, PMID 9869271.
71. Jessy EM, Sambanthan AT, Alex J, Sridevi CH, Srinivasan KK. Synthesis and biological evaluation of some novel quinazolones. Indian J Pharm Sci. 2007;69(3):476. doi: 10.4103/0250-474X.34571.
72. Singh GB, Nityanand S, Srimal RC, Rao VA, Jain PC, Dhawan BN. Antihypertensive and central nervous system depressant properties of 3-(γ-p-fluorobenzoyl propyl). Experientia. 1973, 1529-30;2(3), 4, 4a, 5:6-hexahydro-1 (H)-pyrazino (1, 2-a) quinoline hydrochloride (compound 69-183, centpyraquin).
73. Chen YL, Chen IL, Lu CM, Tzeng CC, Tsao LT, Wang JP. Synthesis and anti-inflammatory evaluation of 9-phenoxyacridine and 4-phenoxyfuro[2,3-b]quinoline derivatives. Part 2. Bioorg Med Chem. 2003;11(18):3921-7. doi: 10.1016/s0968-0896(03)00439-5, PMID 12927852.
74. Bawa S, Kumar S. Synthesis of Schiff's bases of 8-methyl-tetrazolo [1, 5-a] quinoline as potential anti-inflammatory and antimicrobial agents. Indian J Chem. 2009;48B:142-5.
75. Khalifa NM, Al-Omar MA, AbdEl-Galil AA, Abd El-Reheem M. Anti-inflammatory and analgesic activities of some novel carboxamides derived from 2-phenyl quinoline candidates. Biomed Res. 2017;28(2):869-74.
76. Mohassab AM, Hassan HA, Abdelhamid D, Abdel-Aziz M, Dalby KN, Kaoud TS. Novel quinoline incorporating 1,2,4-triazole/oxime hybrids: Synthesis, molecular docking, anti-inflammatory, COX inhibition, ulceroginicity, and histopathological investigations. Bioorg Chem. 2017;75:242-59. doi: 10.1016/j.bioorg.2017.09.018, PMID 29032325.