

DETERMINING THE ANTI-INFLAMMATORY AND ANTIOXIDANT POTENTIALS OF 4(3*H*)-QUINAZOLINONES THROUGH COMPUTATIONAL AND EXPERIMENTAL APPROACHES

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ABSTRACT

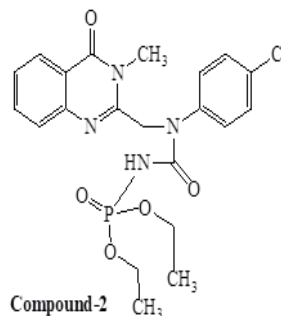
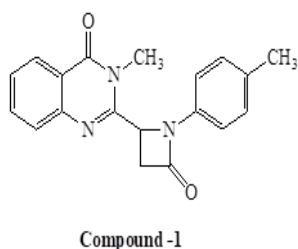
2-Heteryl and heteroalkyl substituted 4(3*H*)-quinazolinones have a captivating chemical structure with a group of pharmacological activities. In the current investigation, we have undertaken the anti-inflammatory activity (*in silico*, *in vitro* and *in vivo*) followed by antioxidant studies of 1-(4-methylphenyl)-4-(3-methyl-4(3*H*)-quinazolinone-2-yl)-2-azetidinone (Compound-1) and *N*-(diethoxyphosphorylaminoacetyl)-*N*-(4-chlorophenyl)aminomethyl-3-methyl-4(3*H*)-quinazolinone (Compound-2). Docking studies of both compounds for anti-inflammatory activity was analysed *in silico* using the docking server software. The Griess assay was executed to estimate the inflammatory response of the compounds that inhibit the nitric oxide production. Both compounds showed low-to-moderate antioxidant activity. Compound-2 showed the highest anti-inflammatory activity and is comparable to Ibuprofen.

Keywords: 4(3*H*)-quinazolinone, Anti-inflammatory, Antioxidant, *In vitro*, *In vivo*, *In silico*, Docking Studies.

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INTRODUCTION

2-Heteryl and heteroalkyl substituted-4(3*H*)-quinazolinones showed biological activities such as anti-proliferative¹, anti-inflammatory^{2,3}, phosphodiesterase 10A^{4,5}, antiosteoarthritis⁶, dual PI3K/HDAC inhibitors⁷, PI3Kδ inhibitor⁸, AChE inhibitors⁹, PARP-1 inhibitors^{10,11}, tyrosine kinase inhibitor¹², antimicrobial¹³, anticancer^{14,15,16}, anti-tubercular agents¹⁷, MurA inhibitors^{18,19}, phosphoinositide 3-kinase delta (PI3Kd) inhibitors²⁰, CYP1B1 inhibitors²¹, cytotoxic^{22,23}, adipogenesis/lipogenesis inhibitors²⁴, antiviral²⁵, cytostatic²⁵, anti-influenza²⁶, antiangiogenic²⁷, apoptotic effect²⁷, promoting osteogenesis²⁸, antibacterial²⁹, radiation induced oxidative stress³⁰ and against solid tumors.³¹ Non-steroidal anti-inflammatory drugs (NSAIDs) reduce swelling, get rid of pain and bring down a high temperature. Antioxidants are capable of interacting with free radicals and preventing their chain reactions before damage to vital molecules. Our laboratory has been engaged in the design and synthesis of new 2-heteryl-4(3*H*)-quinazolinones, including compound-1³² and compound-2³³, and has published several articles, including two reviews.^{34,35} In this context, in search of ‘drug candidates’, we have undertaken the anti-inflammatory activity and antioxidant studies of compound-1 and compound-2.



EXPERIMENTAL

Anti-inflammatory Activity

In silico Anti-Inflammatory Activity

Anti-inflammatory activity of compounds was analyzed by docking studies using the docking server software.³⁶ The docked molecule was 5COX, a cyclooxygenase enzyme that plays a significant role in inflammation.

In vitro Anti-Inflammatory Activity

Dulbecco's modified Eagle medium (DMEM) was used to culture Murine macrophage RAW 264.7 cells with 10% fetal bovine serum (FBS), supplemented with penicillin and streptomycin at 50 U/mL and 50 mg/mL (Sigma-Aldrich), respectively and incubated at 37°C in 5% CO₂ incubator. The Griess assay was done to estimate the inflammatory response of the compounds inhibiting the nitric oxide synthesis. The culture of RAW264.7 macrophage cells was done in a 96-well culture plate (density of 2×10⁵ cells/well) and incubated for 3-4 hr at 37°C. Later, they were treated with lipopolysaccharides (1 mg/mL) to stimulate NO synthesis. Further, the cells were incubated (5% CO₂ at 37°C) for 20 hr. An equal part of the cells was treated with RAW 264.7 cells, and the cell culture medium of the control was added. Griess reagent was added to an equal part of the control and treated cultured cells, and read absorbance was read at 540 nm. The stimulation of the cells was attained with lipopolysaccharides in 1 hour, and treatment with the DMSO solution of the sample at various non-cytotoxic concentrations (5–100 µg/mL). The nitric oxide (NO) inhibition in percentage was calculated with Formula-1.

$$\frac{[(\text{NO level of control} - \text{NO level of compounds treated cell}) / (\text{NO level of control cells})] \times 100}{\text{Formula-1}}$$

In vivo Anti-Inflammatory Activity

The anti-inflammatory activity was assessed using male Swiss albino mice (24±10 grams). Each cohort contained a minimum of six animals. Before the experiment, all of the mice were kept in the workplace for three days to acclimatise to the lab conditions. Approvals were obtained from the Animal Ethics Committee at Jeeva Life Science, Uppal Industrial Area, Hyderabad, Telangana state, India, by following the CPCSEA norms (Reg No:1757/PO/RcBiBt/S/14) to carry out all pharmacological activities.

Acute toxicity: The animals were monitored for 24 hr. in the inflammatory experiments, and each group animal's mortality was recorded till the end by below Formula-2.

$$\frac{\text{Percentage of Inhibition} = [(\text{NO level of control} - \text{NO level of compounds treated cell}) / (\text{NO level of control cells})] \times 100}{\text{Formula-2}}$$

The anti-inflammatory activity was calculated as the percentage increase in paw oedema size in the treated animals. Results were carried as the mean ±SE, and various groups were connected using one-way analysis of variance (ANOVA) followed by Dunnett's test for numerous comparisons, and considered significant difference is $p < 0.01$. The test samples (50 mg/kg) were diluted in the suspension of a 0.5% mixture of carboxymethylcellulose (CMC) and double-purified water, and the experimental animals were administered intraperitoneally. The control group animals were also administered with similar volumes of the suspension without the test samples (drugs). Anti-inflammatory drug Ibuprofen (10 mg/kg) was used as a reference. With the stable radical DPPH, the synthesised molecules' free radical scavenging activity was assessed regarding their capacity to donate hydrogen or to scavenge radicals.³⁷ All the test samples (25, 50, 75 and 100 µL) were diluted with DPPH (1.0mL) solution, and a total volume of four mL was made by adding methanol. The resulting solution's absorbance was read at 517 nm. In this analysis, the control was ascorbic acid. The ensuing Formula-3 was used to calculate radical scavenging activity.

$$\% \text{ inhibition} = ((A_0 - A_t) \times 100)$$

Formula-3 The control tube absorbance is indicated as A₀ (blank), and absorbance in the presence of the test samples is indicated with A_t. All tests were executed, and the results were shown as mean ± S.D.

RESULTS AND DISCUSSION

Anti-Inflammatory Activity

In Silico Anti-Inflammatory Activity

The anti-inflammatory potency of two compounds was studied by docking with the 5COX enzyme to explore the binding pattern. Cyclooxygenase PDB (ID: 5COX) with 1.80 Å resolution was obtained from the PDB database. In this study, residues including SER38, PRO35, TYR55 and VAL165 were accountable for hydrophobic interactions and may be present in the active site of the receptor. ARG197 was showing a substantial H-bond within the binding pocket. Docking of compound-1 showed an H-bond with SER38 (Fig.-1a). The free binding energy was -4.85 kcal/mol. The docking of compound-2 with 5COX showed that residues including SER38, GLN42, THR70, GLU465, LYS166 and ASP499 were set up to be in the active site of the receptor, responsible for hydrophobic interactions (Fig.-1b). ARG197 was showing a significant H-bond within the binding pocket. The free energy of binding was -2.77 kcal/mol. Compound-1 has shown better binding to the cyclooxygenase enzyme when compared with compound-2 and is superior to Ibuprofen (Fig.-1c). According to the findings, compound-1 demonstrates a suitable positioning within the enzyme COX-2 binding region, with a better docking score and can be investigated further as a novel anti-inflammatory agent (Table-1).

Table-1: Docking Scores of Compound-1, Compound-2 and Ibuprofen against 5COX

Compound	Dock Score (Kcal/mole)
1	-4.85
2	-2.77
Ibuprofen	-3.38

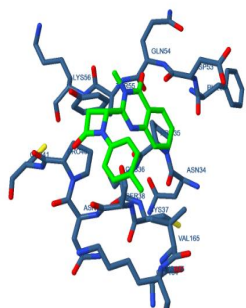


Fig.-1a: Docking Pose of Compound-1 to 5COX Protein

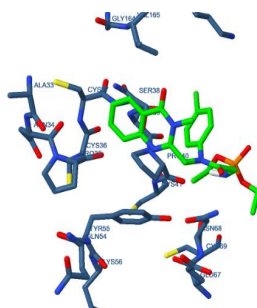


Fig.-1b: Docking Pose of Compound-2 to 5COX Protein

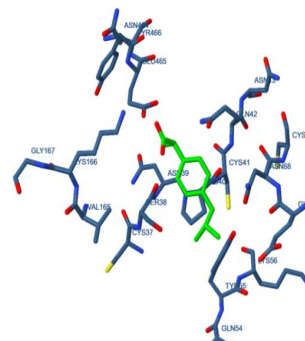


Fig.-1c: Docking Pose of Ibuprofen to 5COX Protein

In vitro Anti-Inflammatory Activity:

The Griess reagent was used to assess the *in vitro* anti-inflammatory efficacy of substances by inhibiting NO production against the control Lipopolysaccharide (1µg/mL). In both the compounds at a concentration of 100µg/mL, Compound-1 showed an NO inhibition of 59.84% (Table-2), and Compound-2 showed an NO inhibition of 66.19% (Table-2) with ascorbic acid as a standard.

Table-2: Percentage of NO Inhibition

Concentration (µg/ml)	Compound-1 % NO Inhibition	Compound-2 % NO Inhibition
Control LPS (1µg/ml)	100±0	100±0
5	2.89±0.201	3.18±0.172
10	6.23±0.217	7.41±0.261
25	15.46±0.443	18.57±0.335
50	32.69±0.427	33.64±0.367
75	49.28±0.526	52.36±0.416
100	59.84±0.605	66.19±0.484

In vivo anti-Inflammatory Activity

The two compounds were tested for their *in vivo* anti-inflammatory efficacy as per the reported method.³⁸ The obtained results were shown as increased paw volume with time compared to the initial levels. The volume increase was estimated as a percentage by differentiation between the initial paw sizes and the paw sizes obtained after the carrageenan agent was injected. The paw edema volume was measured three, six, nine and twenty-four hours after inflammation was induced. The results of two compounds and Ibuprofen are presented in Table-3, as inhibition percentage in Table-4 and Fig.-2 as the mean $\pm$ SE. Variance one-way analysis (ANOVA) and Dunnett's test for several comparisons were used to check the variation among treatments and controls. The data in Table-3 reveal that the compounds synthesised meaningfully ($P < 0.01$) reduced the rat paw edema size within 3 hr after carrageenan administration. After 12 hr, compound-1 significantly reduced paw edema volume in mice. The data in Table-4 reveals, anti-inflammatory activity of compound-1 with 19.19 %, 14.21%, and 21.36% inhibition at 12 hr and 28.83 %, 23.61% and 32.20% inhibition at 24 hr. At 24 hr, an increase in the inhibition of inflammation was time-dependent when compared to Ibuprofen at 24hr (Fig.-2). After 12 hr of evaluation, compound-1 demonstrated more significant activity than compound-2. The foot of rat paw edema following carrageen injection was deemed 0 h after 3 h, as indicated in Table-3.

Table-3: Anti-Inflammatory Activity of the Tested Compounds

Mean paw volume $\pm$ SEM (% of inhibition)							
S. No.	Compound code	Zero hr	3hr	6hr	9hr	12hr	24hr
1	Compound-1	0.423 $\pm$ 0.004	0.437 $\pm$ 0.003	0.386 $\pm$ 0.007	0.358 $\pm$ 0.010	0.322 $\pm$ 0.002	0.266 $\pm$ 0.011
2	Compound-2	0.440 $\pm$ 0.001	0.472 $\pm$ 0.004	0.414 $\pm$ 0.019	0.371 $\pm$ 0.003	0.3423 $\pm$ 0.002	0.286 $\pm$ 0.052
3	Paw edema mice (Normal)	0.244 $\pm$ 0.003	0.237 $\pm$ 0.006	0.244 $\pm$ 0.002	0.241 $\pm$ 0.001	0.243 $\pm$ 0.002	0.244 $\pm$ 0.003
4	Ibuprofen (10mg/kg)	0.467 $\pm$ 0.005	0.470 $\pm$ 0.008	0.415 $\pm$ 0.003	0.361 $\pm$ 0.003	0.314 $\pm$ 0.003	0.254 $\pm$ 0.065
5	Carrageenan (Control)	0.492 $\pm$ 0.002	0.485 $\pm$ 0.003	0.431 $\pm$ 0.004	0.406 $\pm$ 0.004	0.397 $\pm$ 0.003	0.372 $\pm$ 0.070

Table-4: Inhibition of Inflammation (%) of Tested Compounds

S.No.	Compound code	3hr	6hr	9hr	12hr	24hr
1	Compound-1	10.438	11.561	12.229	19.199	28.833**
2	Compound-2	3.103	4.443	8.953	14.241	23.618*
3	Ibuprofen (10mg/kg) (Control)	3.577	4.218	11.409	21.364	32.203

** The mean difference is significant ($P < 0.01$ level). Analysis of data was done by one-way. ANOVA and Dunnett's test.

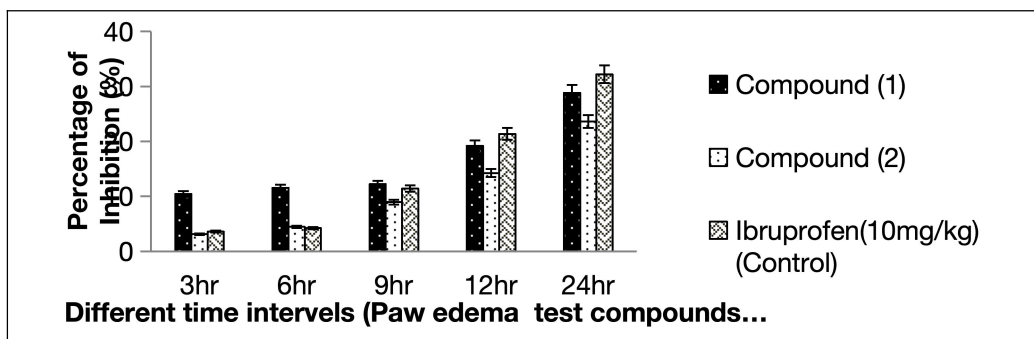


Fig.-2: Inhibition of Inflammation (%)

Antioxidant Activity of the Tested Compounds:

Compounds-1 and 2 antioxidant activity *in vitro* was measured spectroscopically using DPPH radicals, and the findings are shown in Table-5. DPPH radicals' capability reduction was measured by a decrease in absorbance at 517 nm. Tested compounds 1 and 2 showed similar or slightly lower activity than the ascorbic acid (Table-6). However, it is widely proven that organic compounds comprising electron-

donating groups (amine, hydroxyl and methoxy) can operate as free radical trapping agents and withstand oxidative stress.

Table-5: DPPH Assay for % Radical Scavenging Activity Measurement of the Two Compounds and IC₅₀ Values

Concentration of (μg/μl) compounds	Blank +DPPH	Compound-1			Compound-2		
		O.D. Values at 517 nm	% RSA	IC ₅₀ Values	O.D. Values at 517 nm	% RSA	IC ₅₀ Values
25μg/ 25μl	0.781	0.724	7.298	5.059	0.656	16.00512164	7.02
50μg/ 50μl	0.781	0.621	20.486		0.613	21.51088348	
75μg/ 75μl	0.781	0.584	25.224		0.572	26.76056338	
100μg/ 100μl	0.781	0.486	37.772		0.522	33.16261204	

Table-6: DPPH Assay for % Radical Scavenging Activity Measurement of Ascorbic Acid and IC₅₀ Values

Ascorbic Acid (1mg/ML)	%RSA	IC ₅₀
10μg / 10μl	25.152	3.197
20μg /20 μl	43.890	
40μg /40 μl	56.109	
60μg/ 60μl	57.637	
80μg / 80μl	64.663	
100μg /100 μl	66.598	

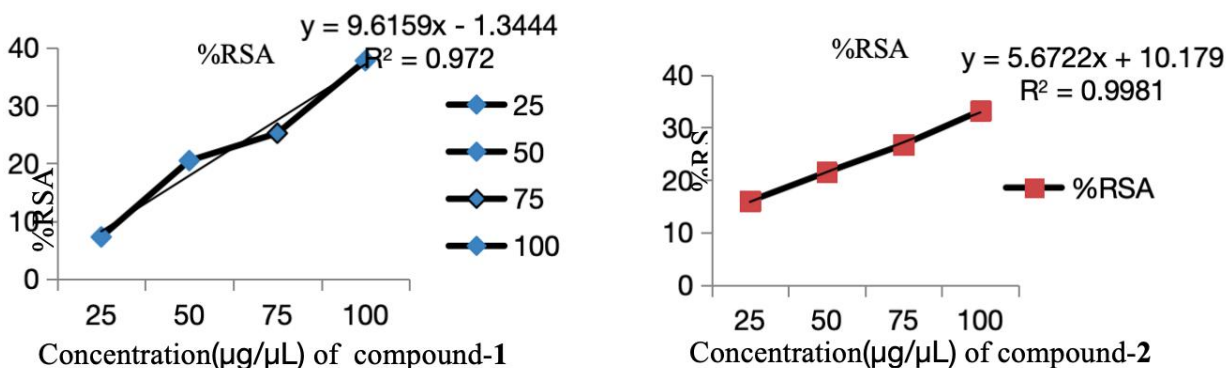


Fig.-3: DPPH Assay for % Radical Scavenging Activity Measurement of Two Compounds

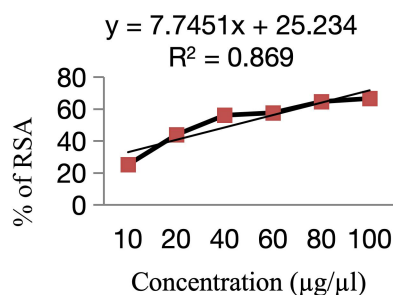


Fig.-4: DPPH Assay for % Radical Scavenging Activity Measurement of Ascorbic Acid

Compound-1 bearing a methyl group (electron-donating group) at the para position showed the best DPPH activity with IC₅₀ values at 5.059 μg/μL. Chlorine (electronegative atom) at the para position in compound-2 further dominates activity with an IC₅₀ value of 7.02 μg/μL. In summary, the pharmacological potential of 2-heteryl and heteroalkyl substituted -4(3*H*)-quinazolinones is vast and encompasses a wide range of therapeutic activities. This potential includes but is not limited to cardioprotective, antioxidant, anti-inflammatory, neuroprotective and antimicrobial effects.

CONCLUSION

Computational analysis through molecular docking of compound-1 showed hydrogen bond interactions with SER38 with an estimated free binding energy of -4.85 kcal/mol. The docking of compound-2 with 5COX exhibited a significant hydrogen bond within the binding pocket by ARG197 as the hotspot residue. Docking of compound-2 with 5COX showed that ARG197 is the hotspot residue with a hydrogen bond inside the binding pocket. The estimated free energy of binding was -2.77kcal/mol. The biological activities of the compounds have been evaluated, and both compounds were found to show significant anti-inflammatory and antioxidant activities. Compound-1 showed an NO inhibition of 59.84 % while compound-2 showed an NO inhibition of 66.19 %. Compounds and 2 showed IC₅₀ values of 5.059 µg/ µL and 7.02 µg/ µL, respectively. The compound-2 showed the highest anti-inflammatory activity than Ibuprofen.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

The present work is related to *SDG-3: Good Health and Well-being*. All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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