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Full Length Article

Synthesis, Spectral Analysis, DFT and Molecular docking studies of Some Novel Oxime Derivatives

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ABSTRACT

A series of novel Di-tert-butyl(E)-4-hydroxy-6-(hydroxyimino)-4-methyl-2-arylcyclohexane-1,3-dicarboxylate derivatives were synthesized in two steps with excellent yields. In the First step, tert-butylacetoacetate and substituted benzaldehyde were directly condensed using methylamine catalyst in ethanol as a solvent to create substituted 1,3-bis(tert-butoxycarbonyl)-cyclohexanone. A second stage involved synthesizing BHMAC (Ar = pH and Ar = *p*-$OCH_3C_6H_4$) by treating the respective ketones in an ethanol medium with hydroxylamine hydrochloride and sodium acetate trihydrate. NMR, IR, and mass spectroscopy were used to confirm the oxime derivatives. Density functional theory calculations at the DFT/B3LYP level using 6–31G++ (d, p) have been performed to reproduce the structure and geometry in order to understand the electrical behavior of synthesized compounds. Using bovine serum albumin, a protein denaturation test is used to assess anti-inflammatory efficacy. BHMAC demonstrates conventional pharmacological molecules in its notable anti-inflammatory action and has effects that are dependent on concentration. Utilizing the phosphomolybdenum technique, the total antioxidant activity of the 2,4-bis(tert-butoxycarbonyl)-cyclohexanone oxime (2 a and 2 b) was assessed standard Vitamin C medications .The results revealed that 2 a & 2 b possess significant antioxidant activity Molecular docking experiments indicate that the chemical may interact with anti-inflammatory and antioxidant causing enzymes. Strong binding energies and inhibition constants with cyclooxygenase (PDB: 1PGG) are demonstrated by BHMAC, suggesting that it is a suitable material for investigations pertaining to anti-inflammatory. BHMAC's remarkable anti-inflammatory and antioxidant properties, together with its synthesis and characterization, highlight its potential as a viable candidate for more biomedical research and therapeutic development.

1. Introduction

The most popular and well-recognized nitrogen-containing biological motif, oximes have a wide range of biological and pharmaceutical uses. Numerous review publications in the field of oxime chemistry have demonstrated the ongoing interest in various aspects of the field [1–3]. In organic synthesis, oximes have been employed to preserve and refine carbonyl compounds [4]. Furthermore, these hydroxyl imine derivatives are recognized for their antibacterial, antioxidant, antiviral, anticancer, antitumor, antitumor, and anticonvulsant qualities [5–12]. Our continued focus on the development of improved methods for organic synthesis and the dearth of knowledge regarding the oximation of carbonyl compounds in the presence of oxalic acid [13–15]. Hydroxylamine is treated with aldehyde or ketone in the traditional oxime production process. Oximes can also be produced from non-carbonyl compounds; the most practical way to produce aldoximes and ketoximes is to reduce nitroalkenes [16]. The rationale behind the cyclohexanone oximes documented mutagenicity in Salmonella typhimurium strain TA1535 when hamster liver S9 is present [17]. Organic chemists have recently become interested in amidoximes in addition to oximes, oxime ethers, and esters because of their capacity to produce a wide range of heterocyclic compounds that are highly interesting from a biological and pharmacological standpoint [18].

The most effective method for figuring out an organic compounds stereochemistry and structure is NMR spectroscopy [19–22]. Eight t (3)-aryl-r(2),c(4)-dicarbalkoxy-c(5)-hydroxy-t

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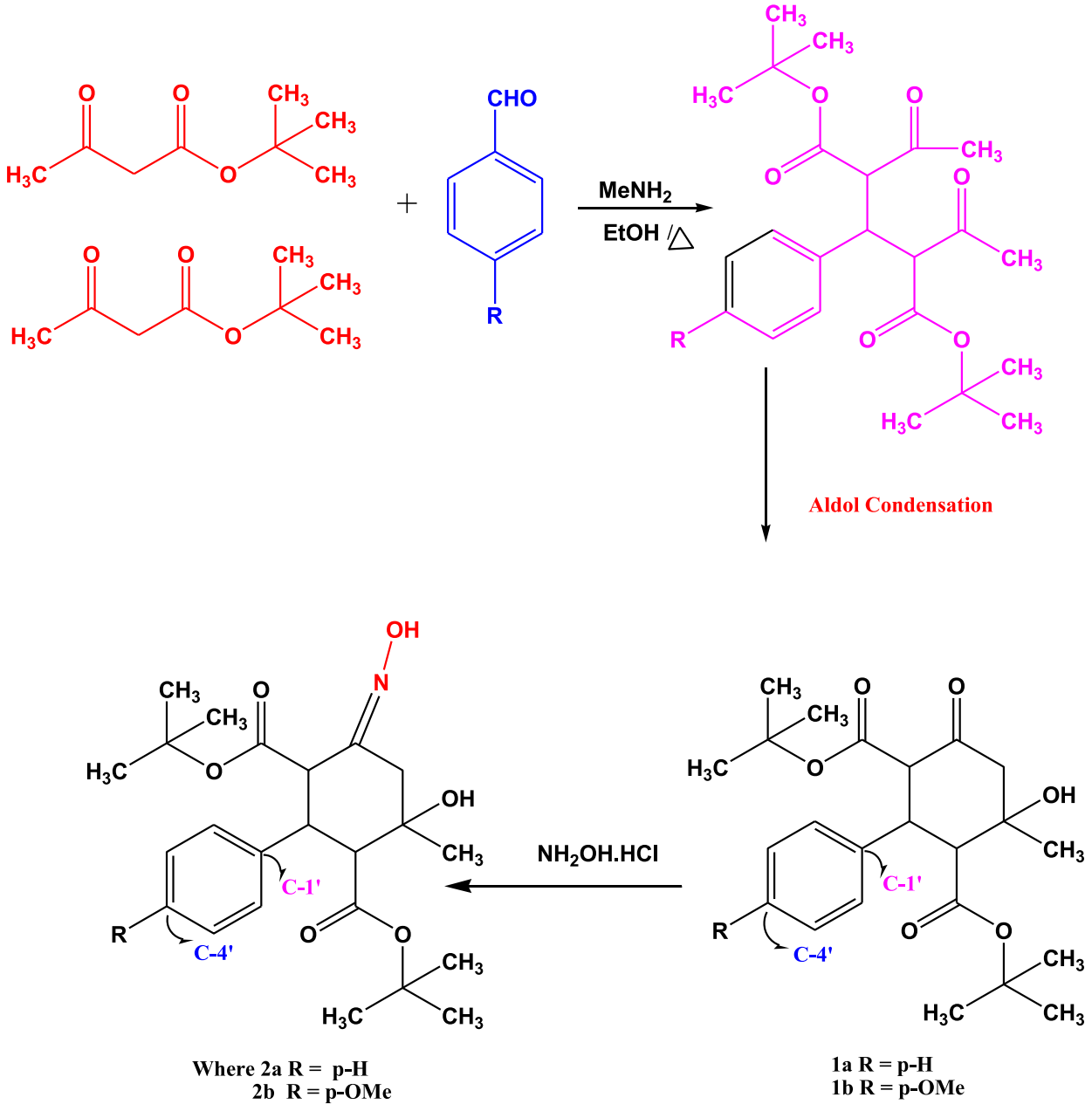
(5)-methylcyclohexanone oximes have been studied spectrally in ^{1}H and ^{13}C, according to Sabapathymohan et al. [23]. As we proceed, we present the results of our investigation of the products that are produced when 1,3-bis(tert-butoxycarbonyl)-cyclohexanone reacts with hydroxylamine hydrochloride in the presence of sodium acetate trihydrate, as indicated in Scheme 1. It has been demonstrated that these compounds take on chair conformations, where the OH group is oriented axially and the other substituents are oriented equatorially. More exact measurements have been made of the impacts of hydroxyl imine resting on the different element shifts and couple constants.

Configuration and conformation of oximes are assigned using the 1D and 2D NMR chemical shifts, which are also described. In the previous and current centuries, a great deal of study has been done on the synthesis of novel organic compounds and the examination of their biological applications. First, molecular electrostatic potential calculations, geometry optimisations, energy minimizations, and density functional theory (DFT) calculations were done on the compounds under investigation. The goal of the current study project was to synthesise oxime derivatives by adding the ketone moiety, taking into consideration the vast pharmacological potential of the oxime nucleus. An investigation of the function of the carbonyl, phenyl, and hydroxyl groups in the antibacterial properties of oximes was conducted by a molecular docking study involving the BHMAC molecule against a primary cyclooxygenase protein (1pgg.pdb). There is a good agreement between the geometric bond length, bond angle, and torsional angles optimized by density functional theory and the actual results. The antioxidant activity of synthesized oxime derivatives BHMAC was carried out to ascertain the potential of these derivatives to decrease oxidative stress. In vivo anti-inflammatory activity of the prepared Oxime derivatives was also determined, and results were compared with standard diclofenac sodium



Scheme 1. Synthetic route of BHMAC.

2. Experimental section

2.1. Materials and methods

Melting point was found using uncorrected unlocking finished capillary technique analogue melting point instrument. KBr pellets IR spectra were captured using an AVATAR 330FT-IR Thermo Nicolet spectrometer. At 400 MHz, the BRUKER DRX 400 NMR Spectrometer recorded 1D, HSQC, and HMBC spectra. Using a JEOL DX-303 mass spectrometer, the mass spectrum of sample **2a** was captured. A Perkin-Elmer CHNS/O analyzer was used to carry out the elemental analysis.

Acquiring and identifying substances

2.2. Synthetic procedure of di- tert- butyl-4-hydroxy-4-methyl-6-oxo-2-arylcyclohexane-1,3- dicarboxylates (1a & 1b)

Heat a solution of methylamine (50 mmol), substituted aldehyde (50 mmol), and tertiarybutyl acetoacetate (100 mmol) in 50 ml of ethanol to sweltering. Overnight, the reaction mixture was maintained at room temperature. Thin-layer chromatography (TLC) is used to track the reaction's progress and stops it when it's finished. After the isolated solid was filtered, it was purified via recrystallization from ethanol [24,25].

2.3. Synthetic procedure of di- tert- butyl(E)−4-hydroxy-6-(hydroxyimino)−4-methyl-2-arylcyclohexane-1,3-dicarboxylate (2a &2b)

Boiling ethanol was used to dissolve the appropriate amounts of bis (tert-butoxycarbonyl)-cyclohexanone (1a & 1b) (50 mmol) and sodium acetate trihydrate (150 mmol). Then, 60 mmol of hydroxylamine hydrochloride was added. The response mixture was heated beneath reflux for 30 min subsequent to the precipitated NaCl was removed by filtration. The ice was filled with the solution. *Re*-crystallization of the divided di-tert-butyl(E)−4-hydroxy-6-(hydroxyimino)−4-methyl-2-arylcyclohexane-1,3-dicarboxylates (**2a & 2b**) from ethanol was achieved. On TLC, their uniformity was examined. Table 1 provides the physical data for BHMAC compounds **2a** and **2b**.

2.4. Biological studies

2.4.1. Anti-inflammatory activities

Technique for BSA denaturation

The anti-inflammatory activity of the synthesised compound and standard diclofenac sodium was assessed using a slightly modified inhibition of albumin denaturation technique. In every solution comprising the reference drug and chemical, less than 2.5 percent of the minimal quantity of Dimethyl formamide was dissolved. One millilitre of a 1 nM bovine serum albumin solution in phosphate buffer was mixed with a test solution (2.5 mL) containing different drug doses, and the mixture was incubated for 10 min at 37 °C in an incubator. After cooling, the turbidity was measured at 660 nm. The percentage of denaturation inhibition was calculated using the formula below.

% of Inhibition = 100 x[Ac-At /Ac]; At: Absorbance of test; Ac: Absorbance of control.

2.4.2. Anti-oxidant activity

The total antioxidant activity of the samples was recorded. About 3 millilitres of antioxidant reagent (0.6 M H_2SO_4, 28 mM Na_3PO_4, and 4 mM ammonium molybdate) were added to the test samples in different amounts. The test mixture was then incubated in a water bath at 95 °C for 90 min to achieve adequate diffusion with the phosphomolybdenum reagent. The extracts with total antioxidant activity and standard Vitamin C medications were assessed using a spectrophotometer, and their absorbance at 695 nm was determined. The total antioxidant activities were then calculated using the given formula.

$$TOA = [(A_t A_c)/A_t.$$

2.5. Study of molecular docking

The Auto-Dock program (version 4.2) was used to molecularly dock synthesized compounds into the bacterial enzymeCOX-1 [26,27]. Gaussian 09 W software was used to optimize the three-dimensional structures of synthesized derivatives (for the ligand). The Protein Data Bank provided the crystal structures of the bacterial enzymes cyclooxygenase (1pgg.pdb), which was downloaded. All bound water and ligand were eliminated from the protein and polar hydrogen was added. Moreover all docking, a grid box size of 60 × 60 × 60 points in X, Y and Z direction. A grid spacing of 0.375 Å and ten runs were generated by using Lamarckian genetic algorithm searches.

2.6. Computational work

All computational calculations, including the DFT-based representation of HOMO and LUMO in the checkpoint files, were developed using the Gaussian 09 W programme [28]. To optimise the BHMAC, the basis set B3LYP/6–311+*G*(d,p) was employed. The Gauss view was used to visualise the computed structures, including the Frontier Molecular Orbital and MEP representation.

3. Results and discussion

3.1. Combination and description

Oximes have attracted a lot of attention in the field of organic chemistry [29] and they are simple to synthesise from carbonyl compounds and convert readily into amines, nitro compounds, nitriles, and other heterocyclic compounds Furthermore, they are widely used as intermediates in the Beckmann rearrangement, which is necessary to synthesise significant β-lactam derivatives, and as protective groups for carbonyl compounds [30]. Oximes are used in many different industrial applications. One well-known example of their importance is the massive annual production of caprolactam, a precursor to nylon-6, which is produced in excess of five million tonnes [31]. Hydroxylamine is treated with aldehydes or ketones in the traditional oxime production process. Oximes may also be produced from non-carbonyl compounds; the most practical way to produce aldoximes and ketoximes is to reduce nitroalkenes [32]. In this study, the corresponding ketones (**1a** and **1b**) were treated through hydroxylamine hydrochloride and sodium acetate trihydrate in an ethanol intermediate to create the oxime derivative of di-tert-butyl-4-hydroxy-4-methyl-6-oxo-2-arylcyclohexane-1,3-dicarboxylates (**2a** & **2b**). By using elemental analysis, infrared spectra, mass spectra, ^{1}H, ^{13}C, 2D NMR spectra, and biological studies, the structures of compounds **2a** and **2b** were verified.

Table 1
Physical statistics for BHMAC for 2a and 2b.

Formula	Compounds	Yield (%)	MP (°C)	Found			Calculated		
				C(%)	H(%)	N(%)	C(%)	H(%)	N(%)
$C_{23}H_{33}O_6N$	2a	92 %	192	65.81	7.92	3.32	65.85	7.93	3.34
$C_{24}H_{35}O_7N$	2b	90 %	164	64.10	7.82	3.10	64.12	7.84	3.12

3.2. IR spectrum

A first indication of the synthesised product has been confirmed by the FTIR spectra of compound **2a**. Compound **1** infrared spectrum revealed a medium band at 3491 cm^{-1} as a result of OH stretching. Because there were three different types of carbonyl groups, there were three distinct bands at 1701, 1711, and 1729 cm^{-1}. The keto carbonyl group should be the cause of the band at 1701 cm^{-1}. Because of their hydrogen bonding with OH, the two ester carbonyl groups at C-4 should contain a reduced stretching frequency. Because of the ester -CO group at C-4, there is a band at 1711 cm^{-1}.

It is evident from the FTIR that all of the raw ingredients that were used to create the product were fully used, as indicated by oxime **2a** absence of a peak at the carbonyl frequency. Furthermore, in compound **2a**, the corresponding peaks for the aromatic [33]C—H, C = N, C = C, -OH, and =*N*—OH stretching vibrations are 3489, 3303, 2973, 1721, 1690, 1613, and 1249 cm^{-1}, respectively. The creation of the product has also been supported by all of these stretching and bending peaks. Compound **2a** concern mass agrees well with both the computed value (419.52 *m/z*) and the measured value (420 *m/z*).

3.3. NMR spectral analysis

The methyl proton at C-4 is responsible for the sharp singlet at 1.34 ppm in the ^{1}H NMR spectra of BHMAC compounds (**2a** & **2b**), which corresponds to three protons. Two doublets for H-1 and H-3 are seen, as predicted, with nearly equal coupling constants. Therefore, for H-2, a triplet rather than a doublet of doublet is observed. At 3.66–3.71 ppm, there is a triplet, which represents one proton. The benzylic proton H-2a is thought to be the cause of this. H_{5a} & H_{5e} are given to the two doublets with coupling constants about around 15 Hz. One signal for oximino carbon, four signals for ipso carbons, one signal for methane carbon, and two signals for tert- Butyl carbons can be found in the ^{13}C NMR spectra of the BHMAC compounds (**2a** & **2b**).Two-dimensional NMR data validates each of the H_{1a}, H_{3a}, H_{5a}, and H_{5e} assignments separately. Table 2 presents the correlations derived from the HMBC and HSQC spectra.

The HSQC spectrum observed correlations are used to assign the signals for carbon-containing hydrogen. Signals that do not exhibit any correlation are caused by carbonyl carbon, which is proton-free. One band correlation exists in HSQC between ^{13}C resonance 36.0 ppm and the two methylene protons H_{5a} and H_{5e} (36.0/1.76, 36.0/3.64 ppm). The ^{13}C resonance 36.0 ppm is therefore attributed to C-5. By comparing the chemical shifts of the parent compound, the two doublets at 3.29 and 2.66 ppm are designated as H_{1a} and H_{3a}. With a total integral equivalent to nine protons of *tert* Butyl groups at C-1 and C-3, there are two singlets at 1.07 and 1.18 ppm.

Table 2
Relationships between HSQC, HMBC spectra of 2a.

Chemical shift of ^{13}C (ppm)	Relationships within the HSQC Range	Relationships inside the HMBC Sphere
173.5	None	H_{3a}
168.2	None	H_{2a}
154.8	None	H_{1a},H_{5a},H_{5e}
138.8	None	H_{2a}
127.4, 128.7	Aromatic protons	Aromatic protons
82.1, 81.2	None	Methyl protons at COOt-Bu at C-1 and C-3H_{5e}
71.0	None	CH_3 at C-4, H_{3a}
57.5	H_{3a}	None
55.2	H_{1a}	H_{1a},H_{3a}
45.5	H_{2a}	CH_3 at C-4
36.0	H_{5a}, H_{5e}	None
29.7	CH_3 protons at C-4	CH_3 at C-4
28.6	CH_3 Protons of COOt-Bu at C-3	None
27.7	CH_3 Protons of COOt-Bu at C-1	

The two tert-Butyl methyl carbons have ^{13}C signals at 82.1 and 81.2 ppm, according to the HMBC spectra of **2a**, because it is correlated with the methyl protons at C-1 and C-3 of tert-butyl group. Resonance in C-1, C-2, and C-3 is verified by HMBC and HSQC correlations. After assigning H_{1a}, HSQC correlation (3.35/55.2 ppm) yields C-1. Therefore, 57.5 ppm is identified as the C-3 resonance. Given that H-2 produces a triplet on its own, the C-2 resonance is determined to be 45.5 ppm from the HSQC cross peak (3.71/45.5 ppm). Table 3 lists the proton chemical shifts for BHMAC compounds **2a** and **2b**. Aromatic carbon signals are allocated according to known substituent effects and intensities. Compounds **2a** and **2b,** the ^{13}C chemical shifts are listed in Table 4.

3.4. Oximation effect

In saturated six-membered cyclic ketones, the equatorial α-proton on the syn side shows a greater chemical shift (0.9–1.0 ppm) than on the anti-side. The effects of oximation on BHMAC ^{13}C and proton chemical shifts (2a & 2b) and related ketones (1a & 1b). All but H_{6e} of the protons in the cyclohexanone ring are shielded by oxidation. The effects shown in methoxy and ethoxy oximes [20] are comparable to those seen in oximes 2a and 2b. Table 5 shows the impact of oximation on the proton chemical shifts of BHMAC (2a & 2b). When the ^{13}C chemical shifts of cyclohexanone (1a & 1b) and their corresponding oximes (2a & 2b) are compared, it can be observed that both syn α and anti α-carbon are shielded. The shielding of syn α-carbon is between 15 and 17 ppm, while the shielding of anti-carbon is between 8 and 10 ppm. Compared to anti-β-carbon, syn-β-carbon offers more protection. Table 6 shows the impact of oximation on the ^{13}C chemical shifts BHMAC (2a & 2b).

3.5. Conformations

Depending on the orientation of the groups surrounding the C = N bond, oxides typically occur as inter convertible E and Z stereoisomers [34]. These isomers can be easily separated using chromatography or recrystallization procedures, and they may have distinct physical characteristics. Studies have shown that E-isomers are more stable and prevalent than Z-isomers, and that oxide stereoisomers have significant pharmacological effects. Only E oximes are produced when cyclohexanone (**1a** & **1b**) is Oximation. Z-oximes other isomer does not form. With the hydroxyl group at position C-4 oriented axially and the other substituents oriented equatorially, all two oximes (**2a** & **2b**) adopt chair conformation. In $CDCl_3$, the proton of the parent cyclohexanones (**1a** & **1b**) likes to opposed to the C(4)-C(5) bond. On the other hand, a long-range interaction among the OH proton and H_{5a} was noted. The arrangement seen in Fig. 1 is preferred by the –OH proton.

In $CDCl_3$, the oximes (**2a** & **2b**) –OH seeks to be opposed to the C(3)–C(4) link as depicted in Fig. 2. This is due to the fact that the extended array coupling between the -OH proton and H_{5a} in these compound spectra was not seen. A technique is suggested to determine the oximes configuration by contrasting the α-carbons chemical shift in the BHMAC compounds with the parent ketones.

Table 3
BHMAC (2a and 2b) proton chemical shifts (ppm).

Compds.	Chemical shifts δ(ppm)						Others
	H-1a	H-2a	H-3a	OH at C-4	H-5a	H-5e	
2a	3.35	3.71	2.69	3.85	1.77	3.66	7.26 [a], 1.18 [b], 1.07 [c], 1.34[d]
2b	3.29	3.67	2.66	3.79	1.76	3.64	6.81 (2^1,6^1)[a] 7.16 (3^1,5^1)[a] 1.10 [b],1.20[b]

[a] Aromatic; the numbers in the parentheses gives the position of the protons
[b] Protons of the $COCH_3$ group at C-1
[c] Protons of the $COCH_3$ group at C-3.
[d] Methyl protons at C-4; [e]OMe protons at C-4′.

Table 4
^{13}C Chemical shifts (ppm) of BHMAC (2a and 2b).

Compds.	Chemical shifts δ (ppm)									
	C-6 (C = N)	C-1	C-2	C-3	C-4	C-5	CO, ipso and Methyl group of COOt-Bu at C-1	CO,ipso and Methyl group of COOt-Bu at C-3	CH_3 at C-4	Aryl ring
2a	154.8	55.2	45.5	57.5	71.0	36.0	168.2, 82.1,28.6	173.4, 81.2,27.7	28.6	127.3, 128.7 138.8 (C-1^1) 129.9(2′,6′) 113.5(3′,5′) 130.9(1′), 158.9(4′) 55.4 (OCH_3 at C-4^1)
2b	154.7	55.4	44.5	57.7	70.9	36.0	168.4, 82.0, 27.8	173.5, 81.2, 28.6	29.7	

Table 5
Effect of oximaton on 1H chemical shifts.

Oxime	Ketone	δ $_{Oxime}$ - δ $_{Ketone}$ (ppm)						
		H_{1a}	H_{2a}	H_{3a}	H_{5a}	H_{5e}	CH_3 at C-4	OH at C-4
2a	1a	−0.14	−0.25	−0.25	−0.68	+0.99	−0.01	−0.18
2b	1b	−0.17	−0.17	−0.25	−0.67	+1.01	+0.01	−0.05

Table 6
Impact of oximation on ^{13}C chemical transitions.

Oxime	Ketone	δ $_{Oxime}$ - δ $_{Ketone}$ (ppm)					
		α-Carbon		β-Carbon		γ-Carbon	
		Syn C-5	Anti C-1	Syn C-4	Anti C-2	C-3	CH_3 at C-4
2a	1a	−16.9	−8.5	−2.1	0.0	−1.3	+1.2
2b	1b	−16.9	−8.0	−2.2	−0.8	+0.9	+1.2

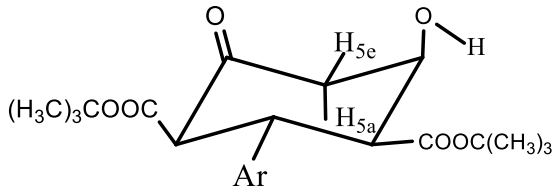


Fig. 1. Conformation -OH group in cyclohexanones (1a & 1b).

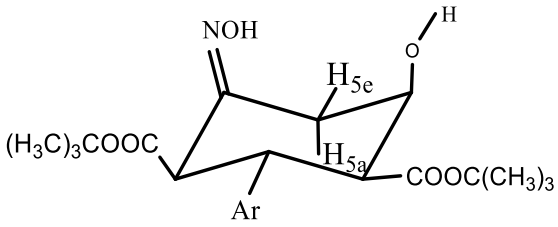


Fig. 2. Conformation OH group in BHMAC (2a & 2b).

3.6. In vitro anti-inflammatory activity

BSA denaturation technique

Employing protein denaturation procedures, Compounds **2a** and **2b** were evaluated intended for in vitro anti-inflammatory efficacy. Two distinct protein methods, such as those involving bovine serum albumin (BSA), were examined. Through the use of UV–visible spectrophotometric methods, the absorbance variations at 660 nm were determined in these activities. Diclofenac sodium is employed as a benchmark medication. The outcomes were contrasted at different concentrations (20, 40, 80, 200, and 800 μm) with the reference medication. In the BSA experiments, compound **2a** and compound **2b** at different concentrations had stronger anti-inflammatory effects than the conventional medication diclofenac sodium. Compounds with electron-donating groups, such as the methoxy and phenyl units (**2a** & **2b**) in this series, exhibited more activity. The percentage inhibition of both denaturation processes was calculated using the following formula, and the resultant percentage inhibition is displayed in Fig. 3.

3.7. In vitro antioxidant activity

Utilizing the phosphomolybdenum technique, the total antioxidant activity of the 2,4-bis(tert-butoxycarbonyl)-cyclohexanone oxime (**2a** and **2b**) was assessed in accordance with the protocol outlined by Prieto et al. [35]. Compounds **2a, 2b**, and the reference were tested for total antioxidant activity at various concentrations (10–400 μm). The test outcomes are shown in Fig. 4. The test for phosphomolybdenum also revealed the closest performance to the reference medication. These findings suggested that the antioxidant activity of BHMAC (**2a** & **2b**) is good. The control and test results were used to compute the percentage inhibition.s

3.8. Molecular docking study with cyclooxygenase

Inflammation in the biological system is caused by the enzyme cyclooxygenase. Thus, cyclooxygenase (COX-1) suppression will lessen inflammation and pain. Here are the results of employing molecular docking techniques to dock the synthesised chemicals with COX-1 enzymes. The interaction between the synthesised compounds and the COX-1 enzyme (1PGG.pdb) was investigated. In addition to standard hydrogen bonding interactions, compound **2a** hydroxyl, estercarbonyl, and phenyl rings displayed pi-donar interactions with amino acid residues. In addition, the amino acid residues and the functional groups (hydroxyl and ketone) are forming a hydrogen bond.

In particular, molecule **2b** methoxy group has been seen to form hydrogen bonds with ILE523, GLY526. Better ligand binding energies are also found in proteins. Compared to compound **2a**, and **2b** displayed a higher binding energy. Furthermore, compound **2a** exhibited a higher inhibition constant than the compounds with methoxy substituents. The docking data, including hydrogen bond interactions, inhibition constant, and binding energy, are shown in Table 7. Figs. 5 show the interaction of BHMAC with cyclooxygenase with one HNY.

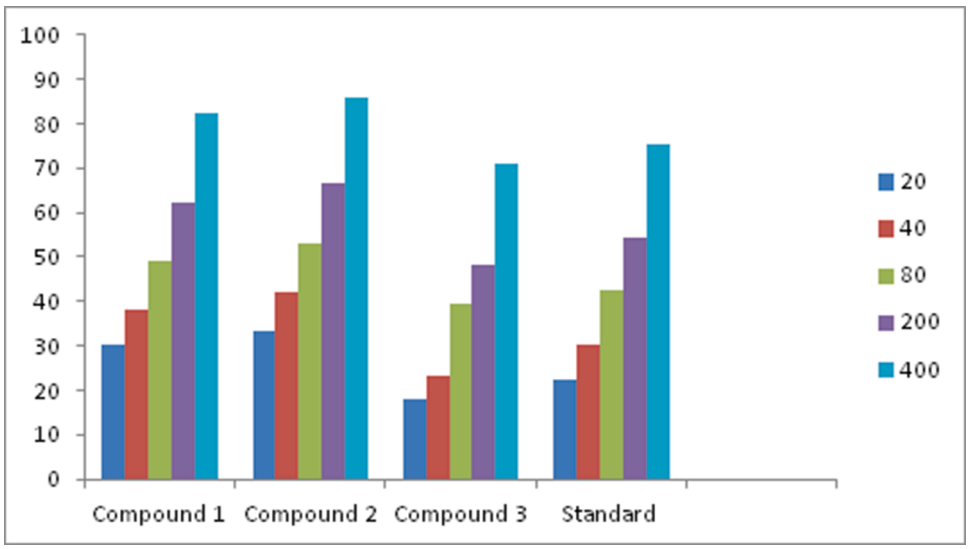


Fig. 3. Anti-inflammatory activity of compound 2a & 2b.

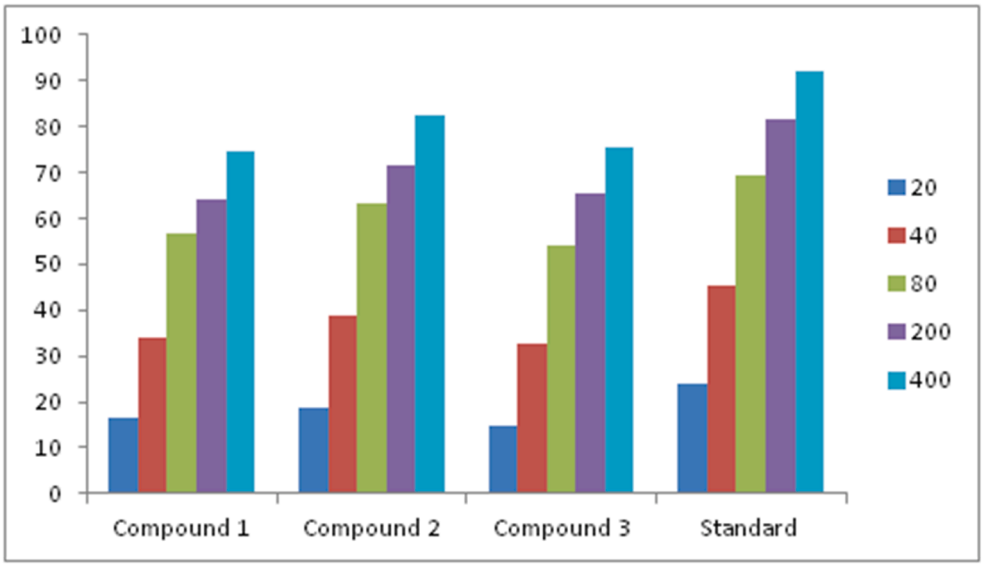


Fig. 4. Antioxidant activity of compound 2a & 2b.

Table 7
DFT parameters for 2a and 2b.

S.No.	Oxime	HOMO	LUMO	Band gap	Eletroneg-ativity	Chemical potential	Global hardness	Global softness	Electrophilicity index
1.	2a	−6.5602	−0.3107	6.249	3.4355	−3.4355	3.1247	0.1600	1.8885
2.	2b	−5.8992	−0.2536	5.645	3.0764	−3.0764	2.8228	0.1771	1.6764

3.9. Frontier molecular orbitals

As illustrated in Fig. 6, the band gap value of all β-cycloketol is larger, at 5.439 eV. Similar to this, characteristics like chemical softness, chemical hardness, and electophilicity index are determined by the band gap [36–38]. The stability and binding ability with biomolecules are explained by these factors. HOMO has energy of −6.5121 eV, while LUMO has energy of −1.0721 eV. One crucial component of the compounds stability is the energy dissimilarity between HOMO and LUMO orbitals. The compounds HOMO-LUMO energy hole of 5.439 eV verifies the stability of the molecules structure. The global softness, global hardness, and chemical potential ranges were 2.72, −3.79, and 0.18, respectively and are tabulated in Table 8.

3.10. Molecular electrostatic potential

The charge distribution of the three-dimensional molecules—positive and negative charge is categorised by the electrostatic potential. MEP can evaluate hydrogen bonds and ligand binding with the biomolecule. An electron with a varied charge can represent any hue. The red-colored negative potential is where the proton is drawn. Green denotes the zero potential, while blue, which has a proton-repulsion, symbolises the positive potential [39–41]. The excellent activity is attributed to the hydroxyl group unit, according to MEP and docking

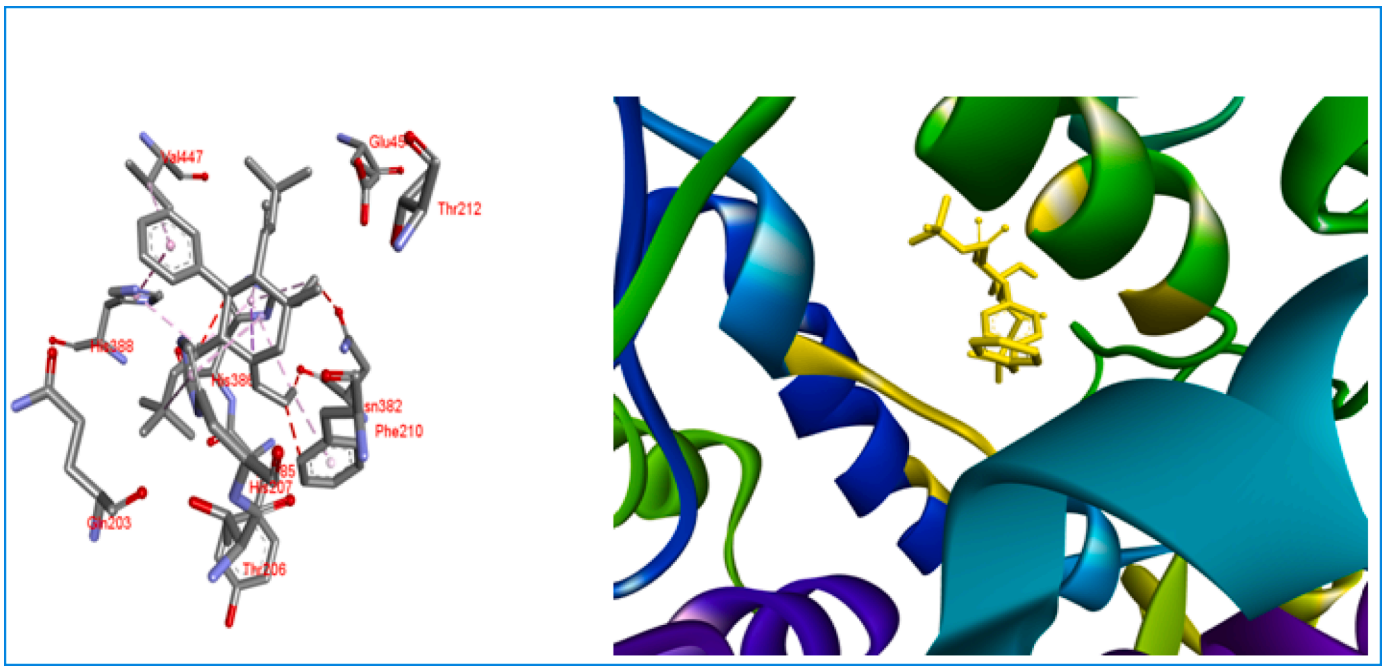


Fig. 5. β-cycloketol (2) binding interaction in the 1HNY active site.

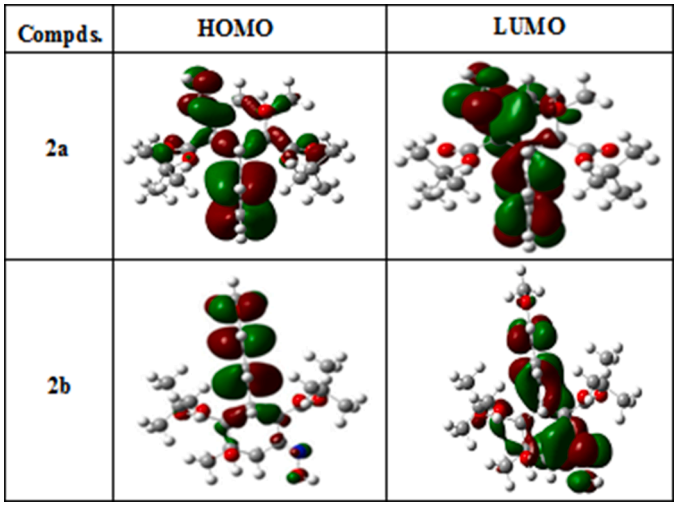


Fig. 6. HOMO-LUMOs with β-cycloketol energy (2a & 2b).

Table 8
BHMAC's molecular docking interaction (2a & 2b).

Compds.	Energy of binding (kcal/mol)	Inhibition constant	The quantity of hydrogen bonds	Residue of an amino acid hydrogen bonding
2a	−4.53 kcal/mol	475.9 μM	–	–
2b	−6.46 kcal/mol	18.27 μM	2	Interaction of carbon hydrogen bonds in ILE523(2.92 Å) GLY526(3.01 Å) interaction between hydrogen bonds in carbon

tests. As shown in Fig. 7, the findings of the molecular electrostatic potential will be a very useful observation to determine the molecules nucleophilic and electrophilic sites as well as MEP. Extraordinarily

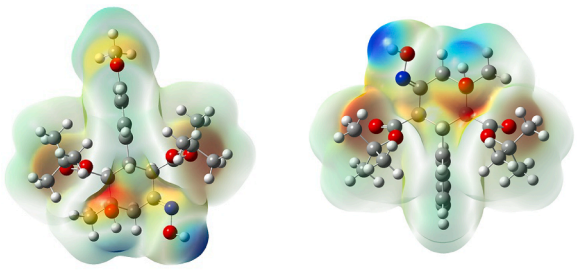


Fig. 7. MEP images of compounds 2a & 2b.

useful for estimating the reaction site of the chemical system [42].

4. Conclusion

The simplest method was used to synthesise the BHMAC (**2a** and **2b**), which was then characterised using several analytical techniques. The BHMAC has conducted studies on anti-inflammatory and anti-oxidant effects. The compound's in vitro activity has outperformed that of reference medication molecules. Theoretical investigations include molecule docking, DFT, and molecular electrostatic potential all contributed to the explanation of this behaviour. Cyclooxygenase contains hydrogen bonding contacts and was used to the majority of relative sites, according to the findings of the molecular docking and MEP studies. The BHMAC adopts a chair conformation with a hydrogen position at C-4 and an equatorial direction for each of its substituents. Regarding the C = N bond, the configuration is E. The aforementioned research findings support the compound's action, suggesting that it may be utilised as an anti-inflammatory and anti-oxidant medication in addition to complying with clinical analysis.

CRediT authorship contribution statement

T. Sumathi: Formal analysis, Investigation, Methodology. **R. Nithya:** Resources, Data curation, Formal analysis, Investigation, Methodology. **S. Kamatchi:** Conceptualization, Supervision, Validation,

Writing – original draft, Writing – review & editing. **P. Ramanathan:** Writing – review & editing, Validation, Data curation.

Declaration of competing interest

The authors declare no conflict of interest.

Data availability

Data will be made available on request.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.chphi.2024.100583.

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