DFT and molecular docking investigations of oxicam derivatives

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ABSTRACT

The organic molecule tenoxicam and similar derivatives, piroxicam and isoxicam have been studied by quantum chemical theory (DFT), FT-Raman and FT-IR. By FMOs energies the charge transfer inside the molecules are obtained. The UV-Vis spectra of the compounds are simulated to study the electronic transition in the target molecules. By using natural bond orbital (NBO), charge delocalization analyzes arising from hyper conjugative interactions and the stability of the molecules are obtained. First order hyperpolarizability of piroxicam is higher than that of isoxicam and tenoxicam. The reactive areas are thoroughly studied by MEP. Prediction of Activity Spectra gives activities, anti-inflammatory, CYP2C9 substrate and gout treatment. Docked ligands form a stable complex with the receptors.

1. Introduction

Oxicams are enolcarboxamides that exhibit number of pharmacological properties and effective for postoperative pain, arthritis, degenerative joint diseases and osteoarthritis [1]. Tenoxicam is a nonsteroidal anti-inflammatory drug that is a part of the oxicam family and it can be used as an effective analgesic and antipyretic agent [2]. Piroxicam possess multifunctional activity including chemoprevention and its photochemical properties are sensitive to medium [3, 4]. Tamasi et al. [5] reported the synthesis and DFT studies of oxicam complexes. By giving the mol files of tenoxicam, piroxicam and isoxicam in the software it predicts different biological activities. Literature survey shows that there is no detailed study done on the molecules both quantum chemical and experimental spectroscopic studies which are very essential for micro level function of any organic compounds. The structural and physio-chemical properties of the compounds can be found out by spectroscopic and quantum computational tools like Density Functional Theory. These structural and physio-chemical properties can be used to establish relationships between these properties and biological activity of the compound [6]. Due to a large number of applications of NLO materials in optoelectronic technology, the molecules have been analyzed for their hyperpolarizability [7]. Several properties like highest occupied molecular orbital, lowest unoccupied molecular orbital energies, various chemical descriptors, molecular electrostatic potential analysis are carried out to provide information about charge transfer within the molecules. The spectral analysis of tenoxicam, piroxicam and isoxicam are performed and compared with theoretical values. The redistribution of electron density are investigated.

2. Calculation

All calculations are performed using the Gaussian09 software package [8]. DFT method was employed using B3LYP functional and cc-pVDZ (5D, 7F) basis set. Results from frequency calculations after scaling were used to get the IR spectral data, which is compared with the experimental spectral vibrations [9]. By using the TD-DFT method the electronic properties of the molecules (Fig. 1) determined using CAM-B3LYP functional and cc-pVDZ basis set. The spectral data are obtained from Bio-Rad Laboratories, Inc. SpectraBase [10].

3. Results and discussions

3.1. Natural bond orbital analysis

NBO analysis provides information about various hyper conjugative interactions and intermolecular charge transfer between bonding and antibonding orbitals. In the current work the analysis has been done using DFT method at B3LYP/cc-pVDZ (5D, 7F) level. The stabilization energy forms an important characteristic in this analysis and higher this energy, greater will be the interaction between the electron donors and hence greater the extent of conjugation. Intra molecular interactions are very much important in predicting the stability and reactivity of the...
target molecules [11]. To study intra and inter-molecular non-bonded interactions the NBO is the efficient method for organic and bio-molecular compounds [12]. Based on the second order perturbation theory the important donor-acceptor interactions are calculated. The important interactions are: For tenoxicam: The strong interactions are N8→π*(O6-C16), N8→π*(C18-C19), O6→σ*(N8-C16), O5→σ*(S1-C10), O5→σ*(S1-O4), C18-C19→π*(C20-C22), C18-C19→π*(O6-C16) with energies 79.05, 38.52, 21.56, 48.55, 22.48, 16.29, 20.19, 17.93, 21.35, 26.13, 22.73, 17.71, 26.08 kcal/mol. For piroxicam: N7→π*(O5-C16), N7→π*(C19-C20), O5→σ*(N7-C16), O4→π*(C11-C12), O3→σ*(S1-N6), O3→σ*(S1-C9), O2→σ*(S1-N6), O2→σ*(S1-C9), C19-C20→π*(N8-C22), C19-C20→π*(C21-C23), C11-C12→π*(O5-C16) with energies, 79.26, 38.71, 21.48, 48.24, 34.03, 19.38, 33.32, 22.57, 17.71, 22.81, 25.94 kcal/mol and for isoxicam: N8→π*(O5-C17), N8→π*(N9-C20), O6→π*(C12-C13), O6→π*(C12-C13), O5→π*(N8-C17), O5→π*(C11-C13), O3→π*(S1-N6), O2→σ*(S1-N7), O2→σ*(S1-O3), O2→σ*(S1-C9), C21-C22→π*(O6-C16) with energies, 74.85, 46.86, 16.12, 35.11, 22.01, 48.41, 33.52, 34.25, 18.74, 19.44, 28.36, 26.52, 19.66 kcal/mol. The delocalization energies are very high and hence the molecules are stable enough to show desired medicinal properties.

| Compound   | HOMO     | LUMO     | 1=EHOMO  | A=ELUMO  | Gap     | η=(I-A)/2 | μ=(I+A)/2 | ω=μ²/2η |
|------------|----------|----------|----------|----------|---------|-----------|-----------|---------|
| Tenoxicam  | -7.837   | -4.931   | 7.837    | 4.931    | 2.908   | 1.454     | -6.384    | 14.015  |
| Piroxicam  | -8.004   | -5.315   | 8.004    | 5.315    | 2.689   | 1.345     | -6.660    | 16.489  |
| Isoxicam   | -7.867   | -5.268   | 7.867    | 5.268    | 2.599   | 1.300     | -6.568    | 16.592  |

Fig. 1. Optimized geometry of (a) tenoxicam, (b) piroxicam and (c) isoxicam.

Fig. 2. HOMO-LUMO plots of (a) tenoxicam, (b) piroxicam and (c) isoxicam.

Fig. 3. MEP plots of (a) tenoxicam, (b) piroxicam and (c) isoxicam.
Table 2

2.1: Tenoxacan

| B3LYP-CC-pVdZ (5D, 7F) | IR | Raman | Assignments* |
|-------------------------|----|-------|--------------|
| v(cm⁻¹) | IRI | RA | v(cm⁻¹) | v(cm⁻¹) | - |
| 3411 | 61.99 | 188.9 | 3390 | - | νNH |
| 3132 | 4.19 | 49.90 | 3145 | 3140 | νCH |
| 3109 | 3.52 | 82.61 | 3105 | 3110 | νCH |
| 3084 | 16.36 | 311.8 | 3088 | 3085 | νCH |
| 2990 | 13.91 | 62.94 | 3000 | - | νCN |
| 2902 | 31.62 | 73.61 | 2915 | 2920 | νCH |
| 1614 | 137.20 | 371.6 | 2955 | 3160 | νC-O |
| 1566 | 142.5 | 303.6 | 1563 | - | νRIngII |
| 1501 | 105.7 | 1950.4 | - | 1500 | νC-RingII |
| 1499 | 368.0 | 34.34 | 1495 | - | 9πH |
| 1422 | 18.88 | 562.4 | 1424 | 1424 | νC-RingII |
| 1406 | 2.99 | 12.86 | - | 1404 | 8πCH |
| 1381 | 20.5 | 241.3 | - | 1380 | 8πCH |
| 1364 | 6.11 | 127.2 | 1370 | - | 8πCH |
| 1344 | 152.0 | 627.7 | 1345 | 1347 | νRIngII |
| 1315 | 78.31 | 80.18 | 1320 | 1290 | νRIng |
| 1292 | 92.89 | 74.80 | 1296 | 1290 | νRIng |
| 1253 | 176.2 | 5.3 | 1251 | - | νSO2 |
| 1247 | 27.41 | 126.2 | - | 1249 | νCN |
| 1201 | 58.53 | 299.0 | 1200 | 1200 | νCN |
| 1186 | 79.13 | 141.0 | - | 1188 | νC-O |
| 1186 | 79.13 | 141.0 | - | 1188 | νC-O |
| 1141 | 31.75 | 18.56 | 1147 | 1147 | νCN |
| 1130 | 26.31 | 47.27 | 1138 | - | 8πCH |
| 1102 | 9.25 | 72.35 | 1100 | 1100 | νC-O |
| 1082 | 7.35 | 5.65 | 1085 | - | νC-O |
| 1046 | 15.54 | 49.88 | 1048 | 1050 | νC-O |
| 1009 | 30.54 | 3.04 | 995 | 1005 | νC-O |
| 978 | 0.28 | 0.56 | 976 | - | γCH |
| 905 | 83.51 | 0.71 | 903 | - | γOH |
| 895 | 14.22 | 2.80 | - | 893 | νC-O |
| 870 | 6.93 | 27.68 | - | 871 | γCH |
| 839 | 2.01 | 23.58 | - | 838 | γCH |
| 803 | 10.64 | 11.24 | 840 | 840 | νRIng |
| 781 | 19.41 | 43.3 | 785 | - | νC-S |
| 769 | 38.51 | 0.77 | - | 770 | νRIngI |
| 763 | 16.96 | 14.04 | 760 | 755 | νC-O |
| 753 | 40.39 | 8.93 | 750 | - | νRIng |
| 703 | 38.57 | 2.00 | 703 | 700 | νCN |
| 662 | 11.20 | 6.26 | - | 668 | νC-S |
| 656 | 7.09 | 18.92 | 653 | 645 | νC-O |
| 589 | 79.05 | 7.45 | 590 | 580 | νRIng |
| 531 | 16.05 | 3.06 | 535 | 536 | νSO2 |
| 513 | 35.12 | 6.20 | - | 508 | γCH |
| 480 | 17.16 | 1.48 | 478 | 478 | νRIngII |
| 455 | 3.03 | 1.97 | 448 | 452 | νRIngII |
| 406 | 2.37 | 0.78 | 403 | 404 | νRIngII |
| 305 | 2.51 | 11.22 | - | 303 | νRIngII |
| 246 | 1.65 | 0.96 | - | 250 | νRIngII |
| 171 | 2.90 | 2.94 | - | 173 | νRIngI |

2.2: Piroxicam

| B3LYP-CC-pVdZ (5D, 7F) | IR | Raman | Assignments* |
|-------------------------|----|-------|--------------|
| v(cm⁻¹) | IRI | RA | v(cm⁻¹) | v(cm⁻¹) | - |
| 3409 | 68.10 | 200.6 | 3400 | - | νNH |
| 3098 | 2.69 | 157.6 | - | 3100 | νRIngIII |
| 3084 | 16.55 | 311.8 | 3084 | - | νRIngII |
| 3062 | 9.34 | 120.9 | - | 3061 | νRIngII |
| 3036 | 23.86 | 151.6 | 3030 | 3038 | νRIngII |
| 2988 | 14.68 | 69.53 | 2950 | 2965 | νC=O |
| 2990 | 31.75 | 72.08 | 2900 | - | νC-O |
| 1617 | 107.8 | 141.0 | 1640 | 1615 | νC-O |
| 1598 | 76.25 | 596.6 | 1600 | 1600 | νC-O |
| 1579 | 57.84 | 599.6 | 1578 | 1585 | νRIng |
| 1566 | 89.17 | 119.3 | - | 1563 | νRIngII |
| 1545 | 45.92 | 131.4 | 1540 | 1547 | νRIngII |
| 1501 | 13.91 | 149.2 | - | 1498 | νCN |
| 1445 | 23.91 | 114.6 | 1447 | 1443 | νRIngII |
| 1409 | 299.2 | 2.94 | 1410 | - | νC-O |
| 1406 | 2.74 | 31.88 | - | 1405 | νC=O |

(continued on next page)
Table 2 (continued)

| BS3LYP/CC-pVDZ (5D, 7F) | IR | Raman Assignments* |
|-------------------------|----|-------------------|
| υ (cm⁻¹) | IR | RA | υ (cm⁻¹) | IR |
| 1011 | 11.88 | 5.75 | 1010 | - | υRingII |
| 1001 | 7.32 | 11.65 | - | 1000 | υCH3 |
| 983 | 3.01 | 14.98 | - | 985 | υCH3 |
| 966 | 0.48 | 1.93 | 960 | - | υRingI |
| 949 | 0.73 | 0.59 | 946 | - | υCHRingII |
| 908 | 76.85 | 0.99 | 910 | 910 | γOH |
| 894 | 51.44 | 2.41 | 893 | 892 | νNO |
| 813 | 11.99 | 6.31 | 812 | 816 | υCH2 |
| 795 | 21.01 | 0.87 | 793 | 793 | γCHRingII |
| 775 | 15.58 | 2.02 | - | 778 | γCHRingII |
| 753 | 30.39 | 8.11 | 752 | 752 | γCHRingII |
| 740 | 16.42 | 4.18 | 740 | - | γRingIII |
| 722 | 14.50 | 1.23 | - | 723 | γRingIII |
| 694 | 55.72 | 4.92 | 703 | 700 | - |
| 655 | 48.79 | 1.50 | 653 | 658 | γNH |
| 641 | 1.35 | 3.49 | - | 640 | νCS |
| 633 | 5.02 | 4.30 | 632 | - | νCS |
| 563 | 1.47 | 6.70 | 558 | - | υRingI |
| 545 | 32.26 | 1.47 | 544 | - | υRingII |
| 523 | 41.26 | 6.16 | 515 | 525 | ηSO2 |
| 441 | 7.86 | 1.31 | 447 | 440 | γRingII |
| 422 | 4.05 | 5.81 | 425 | 423 | γRingII |
| 397 | 5.00 | 8.06 | 400 | 400 | γRingII |
| 370 | 11.34 | 2.96 | - | 372 | γRingII |
| 353 | 4.66 | 4.21 | - | 348 | γRingII |
| 306 | 4.54 | 3.99 | - | 304 | γRingII |
| 276 | 5.02 | 1.30 | - | 275 | γRingII |
| 264 | 1.30 | 3.02 | - | 247 | γRingII |
| 203 | 0.08 | 0.79 | - | 200 | γRingII |
| 177 | 2.88 | 2.65 | - | 175 | γRingII |

* v-stretching; δ-in-plane deformation; γ-out-of-plane deformation; τ-torsion; IR-IR intensity(KM/Mole); RA-Raman activity(Raman activity(KM/Mole)); RingII-Ring having SO2; RingIII-Phenyl ring. RingII-Ring having SO2; RingIII-Five member ring. RingII-Ring having SO2; RingIII-pyridine ring. RingII-Ring having SO2; RingIII-Five member ring.

Table 3

PASS prediction for the activity spectrum. Pa represents probability to be active and Pi represents probability to be inactive.

| Pa | Fi | Activity |
|----|----|----------|
| 0.934 | 0.004 | Antiinflammatory |
| 0.904 | 0.004 | CYP2C9 substrate |
| 0.898 | 0.002 | Gout treatment |
| 0.862 | 0.005 | Analgesic |
| 0.853 | 0.005 | Antiinflammatory agent |
| 0.794 | 0.010 | CYP2C9 substrate |
| 0.774 | 0.004 | Non-steroidal antiinflammatory agent |
| 0.759 | 0.003 | Peroxidase substrate |
| 0.729 | 0.005 | Analgesic, non-opioid |
| 0.708 | 0.004 | CYP2C9 inhibitor |

3.2. Electronic spectra and NLO properties

The 3D diagrams of HOMO and LUMO are shown in Fig. 2. HOMO represents the donating nature of an electron and LUMO represent accepting nature of electrons [13]. HOMO and LUMO energy are -7.837, -4.931 for tenoxicam, -8.004, -5.315 for piroxicam and -7.867, -5.268 for isoxicam. The band gap energy is 2.908 for tenoxicam, 2.689 for piroxicam and 2.599 for isoxicam explains the ultimate transfer of charge happening within the molecule and shows the biological activity. The values of chemical descriptors are given in Table 1. Due to the low value of HOMO-LUMO energy gap [14] these compounds have high softness nature. The low value of the electrophilicity index suggests the biological activity of the compounds. Nonlinear optical studies are an important part in the present world of researchers as NLO active materials find applications in telecommunication, potential applications in modern communication technology, optical signal processing and data storage [15]. Molecular based nonlinear optical behavior (NLO) materials have current attention and great importance because they involve new technical phenomena owing to the emerging application in electronic devices [16]. First order hyperpolarizability of piroxicam (9.232 × 10⁻⁶ esu) > isoxicam (9.112 × 10⁻⁶ esu) > tenoxicam (7.756 × 10⁻⁶ esu) which are 71, 60 and 70 times that of urea while the second order values are -18.132 × 10⁻⁷, -18.336 × 10⁻⁷ and -19.060 × 10⁻⁷ for tenoxicam, piroxicam and isoxicam [17]. These values show that the title compounds are an important class of compounds in the rank of NLO materials [18]. Electronic transitions in a molecule usually happen in the UV and Visible region of the electromagnetic spectra. Being a time dependent phenomenon, original DFT treatment could not explain this phenomenon which involves a change in the electric field of the radiations. For that time dependent density functional theory, known as TDDFT is used to simulate the electronic spectra of the compounds. Long range corrected density functional- CAM-B3LYP is used in this study with the generic 6-31G(d) basis set in methanol solvent cage as provided in the PCM solvation model [19]. In the case of tenoxicam, the DOS spectra show no unusual overlap in the frontier molecular orbitals. Simulated UV spectrum shows two strong excitations at 336.76 nm and 263.69 nm with oscillator strength 0.7602 and 0.103 respectively. The former may be due to the pi to antibonding orbital transitions and it is found that HOMO to LUMO transition contributes 75% to it followed by HOMO1 to LUMO (21%). The second transition can be attributed to the lone pair to antibonding orbital interactions, hence of low intensity. Data shows that this transition is due to HOMO-LUMO (14%), HOMO-1 to LUMO (60%) and HOMO-3 to LUMO (11%). For the compound piroxicam, the one dominant transition was at 310 nm with oscillator strength 0.8658 due to the HOMO-1 to LUMO (21%) and HOMO to LUMO (74%), which is due to the pi to pi antibonding transition. There are other two less intense transitions too at 265.48 and 253.00 nm originating from the antibonding orbitals. Isoxicam shows an intense peak at 304.81 nm with intensity 0.6978 and can be attributed to HOMO to LUMO (91%) and HOMO-1 to LUMO (4%). There is another low intense transition originating from the lone pairs at 262.10 nm with oscillator strength of 0.0262.

3.3. Molecular electrostatic potential

MEPs map of the title compounds are shown in Fig. 3 [20]. The various surfaces of the molecule are having different electrostatic potentials and are in different colors. The negative spots are represented by red, blue is the regions of the positive and the green gives zero potential. From the diagram we can see that the negative portions are near the oxygen atoms and the N atom in the ring for all the compounds. The positive areas are around the NH groups. In this molecule, the negative regions attract proton from the amino acids or protein. These active sites are evidence of the biological activity of the title molecules.

3.4. IR and Raman spectra

Bands (Table 2) at 3390 (IR), 3411 (DFT) for tenoxicam, 3400 (IR), 3409 (DFT) for piroxicam and 3290 (IR), 3300 (Raman), 3417 (DFT) for isoxicam are assigned as the NH stretching modes [21]. The νC=O is assigned at 1610 (IR), 1605 (Raman), 1614 (DFT) for tenoxicam, 1640 (IR), 1615 (Raman), 1617 (DFT) for piroxicam and 1630 (IR), 1624 (DFT) for isoxicam [21]. The downshift of these NH and C=O modes are due to strong hyper conjugative interactions as given by NBO analysis. The C=C stretching modes are assigned at 1422 (IR), 1500, 1429 (Raman), 1501, 1422 (DFT) for tenoxicam, 1600 (IR), 1600 (Raman), 1598 (DFT) for piroxicam and at 1608, 1600 (IR), 1603 (Raman), 1606,
The SO2 stretching modes are assigned nearly at around 1251 (IR) and 1250 (DFT) for all the three molecules [21]. The CS stretching mode are observed at 785, 653 (tenoxicam), 631 (piroxicam), 632 (isoxicam) in IR, 668, 645 (tenoxicam), 640 (piroxicam and isoxicam) in Raman spectrum [21]. All the experimentally observed bands are identified as assigned.

3.5. Molecular docking

PASS (Prediction of Activity Spectra) [22] gives (Table 3) activities, anti-inflammatory, CYP2C9 substrate and gout treatment (activity values 0.934, 0.904 and 0.898. Receptors, 3DY9, 4NZ2 and 2AYR were obtained from the protein data bank website. PatchDock Server is used for docking purpose [23, 24, 25, 26].

For the protein 3DY9: the amino acid interactions are: Amino acid His129 forms H-bond with methylene and OH while Phe13 has \( \pi \)-sulfur interaction with SO2 group. Lys132, Lys136 having \( \pi \)-alkyl interaction with pyridine ring and Trp37 shows two \( \pi \)-sulfur interaction with sulphur atom of the thiophene ring for tenoxicam; Lys149 forms H-bond with SO2 and Lys150, Ala275 having \( \pi \)-alkyl interaction with pyridine ring for piroxicam and Lys149, Gly130, His129 forms H-bond with carbonyl group, SO2 group, methyl group respectively while Tys139, Lys136, Lys132 shows \( \pi \)-\( \pi \)-T shaped, alkyl, \( \pi \)-alkyl interaction respectively with the ligand for isoxicam.

For the protein 4NZ2: The residues of Lys421 forms H-bond with methylene and OH while Asp349 shows \( \pi \)-anion interaction with pyridine ring. Lys420, Lys421, Lys423 having \( \pi \)-alkyl interaction with pyridine and phenyl ring whereas as Phe419 shows \( \pi \)-sulfur interaction with SO2 group for tenoxicam; Lys421 forms H-bond with SO2 and methyl group as well as \( \pi \)-alkyl interaction with pyridine ring. Lys150, Ala275 having \( \pi \)-alkyl interaction with phenyl ring. His353, Lys420 shows \( \pi \)-\( \pi \)-T shaped, \( \pi \)-alkyl interactions respectively with pyridine whereas Phe419 has a \( \pi \)-sulfur interaction with SO2 group for piroxicam and Amino acids Asp414, Asp349 forms \( \pi \)-anion interaction and Arg342 shows \( \pi \)-alkyl interaction with phenyl ring. Lys423, Lys421 shows \( \pi \)-alkyl interaction respectively with the isoxicam.

For the protein 2AYR: The residues of amino acid Gly390, Trp393 forms H-bond with C=O and OH while Glu323, Glu353 shows \( \pi \)-anion interaction with thiophene ring and pyridine. Trp393 forms \( \pi \)-sulfur interaction with sulphur atom and Pro324 having \( \pi \)-alkyl interaction with SO2 group for tenoxicam; Amino acids Ile326, Gly390, Trp393 forms H-bond with sulphur atom, C=O, OH group respectively while Glu323, Glu353 shows \( \pi \)-anion interaction with pyridine. Pro324, Met357 having \( \pi \)-alkyl interaction with pyridine ring whereas Ile326,
Fig. 5. The docked ligands (a) tenoxicam with 3DY9 (b) tenoxicam with 4NZ2 (c) tenoxicam with 2AYR (d) piroxicam with 3DY9 (e) piroxicam with 4NZ2 (f) piroxicam with 2AYR and (g) isoxicam with 3DY9 (h) isoxicam with 4NZ2 (i) isoxicam with 2AYR at the active sites of proteins.

Table 4
The top ten conformation of the complex candidate of ligands.

| No. | Global Energy | Attractive Energy | Repulsive Energy | Atomic Contact Energy |
|-----|---------------|-------------------|------------------|-----------------------|
| 1   | -24.54        | -1.31             | 4.74             | -10.59                |
| 2   | -23.13        | -9.64             | 3.26             | -9.97                 |
| 3   | -20.96        | -8.23             | 3.68             | -9.86                 |
| 4   | -19.95        | -8.81             | 3.95             | -8.85                 |
| 5   | -19.00        | -9.76             | 4.56             | -7.27                 |
| 6   | -18.42        | -8.52             | 3.30             | -6.46                 |
| 7   | -18.03        | -10.12            | 4.77             | -6.69                 |
| 8   | -17.80        | -8.15             | 1.05             | -5.16                 |
| 9   | -17.65        | -6.41             | 1.11             | -6.73                 |
| 10  | -16.05        | -11.04            | 6.24             | -4.37                 |

4.2: Tenoxicam with 4NZ2

| No. | Global Energy | Attractive Energy | Repulsive Energy | Atomic Contact Energy |
|-----|---------------|-------------------|------------------|-----------------------|
| 1   | -34.66        | -16.32            | 12.43            | -13.55                |
| 2   | -31.94        | -17.60            | 9.76             | -8.63                 |
| 3   | -31.87        | -15.12            | 3.04             | -81.0                 |
| 4   | -31.68        | -14.01            | 4.05             | -10.74                |
| 5   | -31.34        | -15.29            | 7.15             | -10.20                |
| 6   | -31.01        | -13.51            | 2.10             | -8.87                 |
| 7   | -30.53        | -13.98            | 9.73             | -12.44                |
| 8   | -29.49        | -15.72            | 4.58             | -6.27                 |
| 9   | -29.32        | -12.55            | 2.09             | -9.18                 |
| 10  | -28.73        | -18.44            | 5.89             | -6.08                 |

4.3: Tenoxicam with 2AYR

| No. | Global Energy | Attractive Energy | Repulsive Energy | Atomic Contact Energy |
|-----|---------------|-------------------|------------------|-----------------------|
| 1   | -34.66        | -16.32            | 12.43            | -13.55                |
| 2   | -31.94        | -17.60            | 9.76             | -8.63                 |
| 3   | -31.34        | -15.29            | 7.15             | -10.20                |
| 4   | -31.01        | -13.51            | 2.10             | -8.87                 |
| 5   | -30.53        | -13.98            | 9.73             | -12.44                |
| 6   | -29.49        | -15.72            | 4.58             | -6.27                 |
| 7   | -29.32        | -12.55            | 2.09             | -9.18                 |
| 8   | -28.73        | -18.44            | 5.89             | -6.08                 |

Table 4 (continued)

| No. | Global Energy | Attractive Energy | Repulsive Energy | Atomic Contact Energy |
|-----|---------------|-------------------|------------------|-----------------------|
| 1   | -51.31        | -17.01            | 4.57             | -14.33                |
| 2   | -40.33        | -15.82            | 3.69             | -12.34                |
| 3   | -37.62        | -15.70            | 5.96             | -12.74                |
| 4   | -37.42        | -15.77            | 4.36             | -13.93                |
| 5   | -36.79        | -14.47            | 4.89             | -12.86                |
| 6   | -36.31        | -13.68            | 7.37             | -14.24                |
| 7   | -35.81        | -16.05            | 6.72             | -12.25                |
| 8   | -33.94        | -13.08            | 3.54             | -11.40                |
| 9   | -33.89        | -14.92            | 2.07             | -10.81                |
| 10  | -33.11        | -16.88            | 7.67             | -11.98                |

4.4: Piroxicam with 3DY9

| No. | Global Energy | Attractive Energy | Repulsive Energy | Atomic Contact Energy |
|-----|---------------|-------------------|------------------|-----------------------|
| 1   | -31.03        | -15.28            | 3.95             | -7.96                 |
| 2   | -30.98        | -12.00            | 1.99             | -9.53                 |

(continued on next page)
with methyl and Pro324 forms. The results show that the molecules have inhibitory activity against piroxicam and Amino acids Glu323 forms H-bond with OH while Arg394

Table 4 (continued)

|   | Global Attractive Repulsive Atomic Contact |
|---|-------------------------------------------|
|   | Energy VdW Energy VdW Energy               |
| 3 | -30.62 -15.97 2.88 -6.32                  |
| 4 | -30.06 -16.11 4.65 -5.50                  |
| 5 | -30.05 -16.21 8.99 -10.29                 |
| 6 | -29.95 -16.89 4.80 -5.55                  |
| 7 | -29.60 -13.91 2.61 -8.22                  |
| 8 | -29.33 -14.44 5.50 -9.38                  |
| 9 | -28.70 -16.15 3.84 -5.78                  |
| 10 | -28.66 -15.18 4.96 -7.65                 |

4.6: Piroxicam with 2AYR

|   |                       |
|---|-----------------------|
| 1 | -37.85 -17.33 5.90 -12.41 |
| 2 | -36.08 -16.48 4.57 -10.83 |
| 3 | -35.96 -17.16 4.34 -11.19 |
| 4 | -34.04 -14.50 4.95 -11.94 |
| 5 | -33.99 -15.73 5.94 -12.53 |
| 6 | -33.99 -15.11 6.47 -11.55 |
| 7 | -33.51 -3.65 3.54 -11.09 |
| 8 | -33.12 -15.10 2.21 -7.97  |
| 9 | -31.94 -14.23 1.24 -7.53  |
| 10 | -31.02 -12.45 1.87 -10.00 |

4.7: Isoxicam with 3DY9

|   |                       |
|---|-----------------------|
| 1 | -26.00 -11.53 3.63 -10.59 |
| 2 | -25.72 -13.30 3.88 -8.13  |
| 3 | -23.43 -8.48 1.41 -8.64  |
| 4 | -19.41 -11.68 5.27 -5.59  |
| 5 | -19.35 -9.10 2.36 -7.89  |
| 6 | -19.18 -10.49 3.90 -6.91  |
| 7 | -19.07 -8.18 3.38 -7.26  |
| 8 | -18.81 -8.40 4.97 -8.39  |
| 9 | -18.60 -12.28 7.80 -5.68  |
| 10 | -18.36 -7.93 0.54 -7.12  |

4.8: Isoxicam with 4NZ2

|   |                       |
|---|-----------------------|
| 1 | -37.12 -16.16 2.35 -10.90 |
| 2 | -34.72 -13.37 2.18 -12.16 |
| 3 | -33.12 -12.59 0.90 -9.56  |
| 4 | -32.08 -15.24 5.98 -9.06  |
| 5 | -31.53 -15.55 4.47 -8.39  |
| 6 | -29.81 -16.07 2.44 -5.55  |
| 7 | -29.54 -13.01 0.78 -8.32  |
| 8 | -28.60 -16.09 8.45 -8.67  |
| 9 | -27.16 -14.20 5.24 -8.46  |
| 10 | -27.05 -12.26 2.32 -8.50  |

4.9: Isoxicam with 2AYR

|   |                       |
|---|-----------------------|
| 1 | -42.31 -19.70 5.02 -12.99 |
| 2 | -38.86 -16.62 2.34 -9.76  |
| 3 | -34.63 -14.96 2.06 -9.48  |
| 4 | -34.52 -15.48 3.75 -10.61 |
| 5 | -33.93 -14.41 1.86 -9.98  |
| 6 | -33.62 -15.16 3.42 -11.22 |
| 7 | -30.98 -14.96 7.86 -6.22  |
| 8 | -30.94 -12.87 5.08 -6.29  |
| 9 | -29.64 -11.61 3.41 -10.35 |
| 10 | -29.61 -15.41 4.42 -9.28  |

4. Conclusion

The spectroscopic analysis of tenoxicam, piroxicam and isoxicam are reported. The theoretical normal modes of vibrations based on DFT theory has been investigated and compared with the experimental values. NBO analysis was carried out on the molecule to find the interactions and found that these compounds are highly stable due to hyperconjugative interactions. Simulated electronic spectra show that there is an intense peak in red shift region due to π to anti-bonding π-electron transition and a weak peak due to lone pair to anti-bonding orbital transition. The lower value of HOMO and LUMO energy gap describes the stability and biological activity of the tenoxicam, piroxicam and isoxicam compounds. Reactive sites were obtained from MEP, which indicates that there are enough sites for nucleophilic and electrophilic interaction in the molecules, which is very important to show biological activities. Finally the molecular docking shows the ligands have good pharmacological properties with the proteins. From atomic contact energy and global energy values more stable complex are identified.

Declarations

Author contribution statement

Y. Shyma Mary, Y. Sheena Mary, K.S. Resmi, Renjith Thomas: Conceived and designed the analysis; Analyzed and interpreted the data; Wrote the paper.

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The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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