Synthesis, Structural Characterizations, and Quantum Chemical Investigations on 1-(3-Methoxy-phenyl)-3-naphthalen-1-yl-propenone

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ABSTRACT: In the present study, 1-(3-methoxy-phenyl)-3-naphthalen-1-yl-propenone (MPNP) is synthesized and characterized by several experimental techniques such as Fourier transform-infrared spectroscopy (FT-IR), FT-Raman, NMR and UV−vis spectral methods. The similar techniques are also investigated by the computational method using Gaussian software. The density functional theory (DFT) method is used to obtain the optimized structure using the B3LYP/6-311+ +G(d,p) basis set. This optimization procedure of the molecule gives the minimum energy confirmation of the structure. The computed geometrical parameters are compared with experimental data. The experimental FT-IR and FT-Raman spectra of MPNP are obtained in the regions 4000−400 and 4000−50 cm−1 respectively. The detailed vibrational assignments of the molecule are obtained with the support of potential energy distribution. The theoretical NMR (1H and 13C) analysis is conducted by the GIAO method for its structural characterization and compared with experimental chemical shifts. The experimental UV−vis spectrum is obtained in the dimethyl sulfoxide solvent and compared with the theoretically computed spectrum by the time-dependent DFT method. In addition to these studies, other analyses such as nonlinear optical, natural bonds orbital, frontier molecular orbital, molecular electrostatic potential, and NCI have been conducted to understand the nature of the molecule. The title molecule is docked and also the drug-likeness, ADMET studies were carried out. The RBD domain bound to the ACE2 receptor during the fusion makes spike glycoprotein an elusive therapeutic target in SARS-CoV-2 infection.

1. INTRODUCTION

In the recent past, the chemistry of chalcones has attracted the attention of the organic chemists due to the open-chain model and the characteristic of skeletal alteration to produce a new class of organic compounds, namely, azachalcones,1 isoxazoles,2 pyrazoles,3 and indole-grounded chalcones.4 Chalcone derivatives are structurally one of the most diverse group of flavonoids and straightforwardly allow to cyclize the forming flavonoid structure, which is an isomeric key step for the skeletal change of chalcones. They are resourceful molecules, which have been regarded as a biogenetic precursor for flavonoids and isoflavonoids, and are abundant in edible plants. Chalcones have a privileged structure composed of two aromatic (phenyl) rings, which are linked through the aethylenic bridge of the conjugated double bond with the three carbon-α,β-unsaturated carbonyl system, that is, 1,3-diphenyl-2-propen-1-one derivative. Hence, the core structure of the chalcones will be in the form of 1,3-diphenyl-2-propen-1-one (ph−CO−CH=CH-ph). They demonstrate a wide range of therapeutic activities such as anticancer, antioxidants,6 anti-inflammatory,11 antihypertensive,12 antimalarial,13 antitulcer,13 antiviral,10 antiprotozoal,11 cardiovascular activity,12 and mutagenic properties.13 In addition, chalcones have extensive use in medicinal and pharmaceutical areas such as antifungal, antifungal,6 anticarboxic anhydrase inhibitor, and anti-HIV activity, and so forth.14−16 Stereochemically, chalcone can exist in both trans (E) and cis (Z) isomers, but the Z conformer is most unstable due to steric hindrance. In chalcones, two aromatic rings and the electrophilic α,β-unsaturated carbonyl systems are in continuous conjugation. It may be the reason for their low redox potential, stability, electron transfer reactions, and more importantly for its promising biological activities.17 Thus, chalcones are an innovative class of compounds with significant therapeutic potential against various diseases.18 Several chalcone molecules also exhibit a nonlinear optical (NLO) nature, and they have gained the attention of

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researchers due to their enormous applications in the field of data storage, optical communication, and harmonic generators.\textsuperscript{19−22} In organic molecules, the chalcone and its derivatives exhibit significant NLO properties due to their excellent characteristics such as second harmonic generation efficiency, noncentrosymmetric structure and good optical limiting nature with the nanosecond laser pulse.\textsuperscript{23−25} Therefore, their NLO properties can be boosted by substituting appropriate electron donor groups at one end and electron acceptor groups at the end of the ethylenic bridge.

The above mentioned applications have motivated us to carry out the research work on chalcone derivatives. Hence, we have synthesized and conducted several analyses on 1-(3-methoxy-phenyl)-3-naphthalen-1-yl-propenone (MPNP). As per the literature survey, there have been no spectroscopic, electronic, and NLO studies conducted on the molecule. Hence, this report focuses on the structural, vibrational and electronic nature of the molecule by the experimental and computational methods. The experimental analyses such as FT-Raman, Fourier transform-infrared spectroscopy (FT-IR), NMR, and UV−vis studies are conducted and at the meantime, the quantum chemical calculations are performed using Gaussian software. The complete vibrational studies (FT-IR and FT-Raman) are conducted, and potential energy distribution (PED) is used to establish detailed vibrational assignments from VEDA4 program. The NMR chemical shifts have been obtained from the density functional theory (DFT)/B3LYP/6-311++G(d,p) basis set and compared with experimental \textsuperscript{1}H and \textsuperscript{13}C NMR spectral data. The experimentally obtained UV−vis spectrum in dimethyl sulfoxide (DMSO) solvent is compared with the theoretically obtained spectrum from the time-dependent DFT (TD-DFT) method. The charge transfer characteristics of the molecules have been understood with the help of highest occupied molecular orbital−lowest unoccupied molecular orbital (HOMO−LUMO). The molecular electrostatic potential (MEP) map is obtained on the optimized structure of the molecule. The natural bond orbital (NBO) and NLO properties are also studied. Furthermore, the title molecule is docked and the drug-likeness, ADMET studies were carried out for the property of receptor binding domain (RBD) to bind ACE2 receptor during the fusion, which makes spike glycoprotein an elusive therapeutic target in SARS-CoV-2 infection.

2. RESULTS AND DISCUSSION

2.1. Molecular Geometry. The optimized molecular structure of the present molecule is obtained from DFT the method with the B3LYP/6-311++G(d,p) basis set, and the 3D picture is presented in Figure 1. The geometrical parameters such as bond length, angles, and dihedral angles are calculated from the optimized geometrical structure and given in Table S1. There are no experimental geometrical parameters available for this molecule. Hence, we have considered the similar reported molecule’s experimental geometrical parameters for the comparison study. The theoretically computed bond angles, dihedral angles, and bond lengths are compared with the reported X-ray diffraction (XRD) data.\textsuperscript{26} From the calculated values, it is found that most of the optimized molecular bond lengths are slightly higher than the experimental values due to the fact that the experimental XRD results were carried out in the solid state and theoretical calculations were carried out in the gas phase.\textsuperscript{27} This title molecule has 21 C−C bond lengths, 17 C−H bond lengths, and 2 C−O bond lengths. In MPNP, the bond length C15=O18 in the ethylenic bridge is 1.226 Å in DFT and 1.222 Å in XRD. The C−C bond lengths in the benzene ring, ethylenic bridge, and naphthalene ring lie in the range of 1.395−1.395, 1.349, and 1.461−1.373 Å, respectively. The ethylenic bridge acts as the connector between benzene...
and naphthalene rings, and hence, bond lengths and dihedral angle of this ethylene bridge are important. The C−C bond angles (DFT/XRD) in the ethylenic bridge are C16−C15−O18 (122.4984/121.73), C16−C15−C27 (126.584/118.620), C15−C16−C17 (119.929/120.620), and C6−C17−C16 (126.287/127.990). The important dihedral angle (DFT/XRD) in the ethylenic bridge is 178.213/170.480 for C27−C15−C16−C17 and 178.892/175.213 for C15−C16−C17−C6. The abovementioned geometrical parameters are in good agreement with each other. The remaining parameters such as bond length, bond angle, and dihedral angle are mentioned in Table S1.

2.2. Vibrational Assignment. The MPNP molecule is subjected to vibrational studies (FT-IR, FT-Raman characterization). The experimentally obtained spectra are compared with theoretically computed spectra. The present molecule is made up of 38 atoms, which undergo 108 fundamental modes of vibrations. Figures 2 and 3 display the FT-IR and FT-Raman spectra obtained by experimental and theoretical approaches. Table S2 contains the experimental FT-IR and FT-Raman wavenumbers, theoretically computed vibrational (unscaled and scaled) wavenumbers, and all the fundamental vibrational modes along with the assignments (PED %). The small variation between theoretical and experimental frequencies is due to the fact that theoretical values are obtained in the gas phase and experimental values in the solid phase. Hence, the scaling factor of 0.9614 is used to reduce the differences.

2.2.1. Ethylenic Bridge. The carbonyl group present in the ethylenic bridge plays a vital role in charge transfer. The identification of C=O stretching modes in IR and Raman spectra is quite simpler because of their increased polarization, high degree of conjugation, and strength. The conjugation of the π bond between oxygen and carbon is responsible for C=O formation. The unequal distribution of bonding electrons takes place due to the difference in the electronegativity of carbon and oxygen. The polar nature carbonyl group is due to the existence of a lone pair of electrons on the oxygen atom. As per the literature, high intense peaks representing C=O stretching occur in the IR spectrum in the span 1600−1850 cm\(^{-1}\)\(^{25,26}\). In the present molecule, C=O stretching modes have been identified as a strong peak at 1654 cm\(^{-1}\) in FT-IR and weak peak at 1657 cm\(^{-1}\) in FT-Raman. The theoretically calculated wavenumbers appear at 1649 cm\(^{-1}\).

The strong peak indicating C16=C17 stretching is observed at 1576 cm\(^{-1}\) in FT-Raman. The computations based on PED results predict the C16=C17 stretching mode at 1574 cm\(^{-1}\). The peak appeared at 3067 cm\(^{-1}\) in the FT-IR spectrum, and the theoretically computed wavenumbers at 3068 and 3040 cm\(^{-1}\) were assigned to the C−H stretching mode. C−H in plane bending generally occurs in the range of 1300−1000 cm\(^{-1}\). In the present molecule, CH in-plane bending is observed at 1304, 1279, and 1237 cm\(^{-1}\) in FT-IR and 1308 and 1240 cm\(^{-1}\) in FT-Raman and theoretically computed at 1306, 1300, 1282, and 1234 cm\(^{-1}\). The peak C−H out of plane bending is observed at 992 cm\(^{-1}\) in FT-Raman and is compared with the computed wavenumber at 975 cm\(^{-1}\). These vibrations are in good agreement with the literature.

2.2.2. Naphthalene Ring Vibrations. In the naphthalene ring, the C−H stretching vibrations occur in the range of 3100−3000 cm\(^{-1}\).\(^{27,28}\) In the present molecule, C−H stretching vibrations are computed at 3078, 3063, 3053, 3049, 3041, and 3037 cm\(^{-1}\), and the IR and Raman peaks are recognized at 3038 and 3071 cm\(^{-1}\), respectively. C−H in plane bending peaks are observed at 1369, 1142 and 1368, 1146 cm\(^{-1}\) in IR and Raman, respectively, and the theoretical values are estimated at 1412, 1370, 1151, 1144, and 1124 cm\(^{-1}\). The out of plane C−H bending modes are computed at 950 and 884 cm\(^{-1}\), and the FT-IR peak is obtained at 887 cm\(^{-1}\). The C−C vibrations are noticed at 1595, 1563, 1545, 1336, and 1021 cm\(^{-1}\) in DFT and observed at 1567, 1516, 1345, and 1016 cm\(^{-1}\) in FT-Raman and is compared with the theoretical values at 1576, 1347, and 1017 cm\(^{-1}\) in Raman. The other vibrations of the naphthalene ring are mentioned in Table S2. These vibrations are in good agreement with the literature.

2.2.3. Phenyl Ring. The C−H stretching vibrations of the phenyl ring occur in the region of 3100−3000 cm\(^{-1}\).\(^{29,30}\) In the present molecule, the C−H stretching vibrations are computed at 3085, 3081, and 3049 cm\(^{-1}\) and recognized at 3050 cm\(^{-1}\) in FT-Raman. C−H in plane bending vibrations slightly mixed with C−C stretching vibrations, and the medium strong peaks appear in the span of 1500−1000 cm\(^{-1}\).\(^{31}\) The C−H bending is observed at 953, 879, 861, and 855 cm\(^{-1}\), and the experimental FT-Raman values are observed at 870 and 852 cm\(^{-1}\). In the present molecule, the C−C in-plane bending vibrations occur in the span of 774−381 cm\(^{-1}\).

2.2.4. O−CH\(_3\) Vibrations. In the present molecule, the methoxy group is attached to the phenyl ring. The presence of an oxygen atom affects the reduction of the stretching wavenumbers of the CH\(_3\) vibrations.\(^{32,33}\) Generally, in O−CH\(_3\), the symmetric and asymmetric (CH\(_3\)) stretching vibrations occur in the span of 2870−2825 and 2985 ± 80 cm\(^{-1}\), respectively. In the present molecule, the computed wavenumbers 2888 (91%), 2945 (99%), and 3013 (92%) cm\(^{-1}\)
represent the symmetric and asymmetric \((\text{CH}_3)\) stretching vibrations. The related FT-Raman and FT-IR peaks observed at 2833, 2945, 3014, 297, and 3012 cm\(^{-1}\). For asymmetric and symmetric bending vibrations, the computed values appeared at 1435 and 1421 cm\(^{-1}\), respectively. The related FT-Raman peak for asymmetric bending is observed at 1439 cm\(^{-1}\). The \(O-\text{CH}_3\) stretching modes commonly occur in the span of 1100–1000 cm\(^{-1}\). In present molecule, the \(O-\text{CH}_3\) stretching mode is computed at 1035 cm\(^{-1}\). The bending mode of \(O-\text{CH}_3\) is expected in the region of 670–300 cm\(^{-1}\). In the MPNP, \(O-\text{CH}_3\) bending modes are observed at 566, 303, and 562 cm\(^{-1}\) in FT-Raman and FT-IR. The corresponding computed values are 559 and 302 cm\(^{-1}\). In the MPNP, the \(\text{CH}_3\) in-plane and out-of-plane rocking modes are estimated at 1123 and 1168 cm\(^{-1}\), respectively. For the out-of-plane rocking mode, the Raman peak is observed at 1195 cm\(^{-1}\). The \(\text{CH}_3\) torsion mode is observed at 211 cm\(^{-1}\).

Table 1. Experimental and Theoretical\(^{13}\)C and \(^1\)H NMR Chemical Shifts [with Respect to TMS, All Values in ppm] of MPNP

| C-atom | experimental | CAM-B3LYP | B3LYP | H-atom | experimental | CAM-B3LYP | B3LYP |
|--------|--------------|-----------|-------|--------|--------------|-----------|-------|
| 15-C   | 190.07       | 190.27    | 193.01| 20-H   | 8.7          | 9.47      | 9.41  |
| 29-C   | 159.97       | 163.83    | 166.76| 11-H   | 8.66         | 8.58      | 8.70  |
| 17-C   | 141.8        | 150.76    | 151.04| 13-H   | 8.28         | 8.25      | 8.37  |
| 27-C   | 139.55       | 143.58    | 144.93| 22-H   | 8.26         | 8.14      | 8.35  |
| 4-C    | 133.75       | 137.89    | 138.54| 23-H   | 7.95         | 8.09      | 8.25  |
| 6-C    | 132.36       | 137.06    | 138.38| 32-H   | 7.93         | 8.09      | 8.04  |
| 5-C    | 131.78       | 135.89    | 137.68| 19-H   | 7.91         | 7.85      | 8.03  |
| 3-C    | 130.87       | 134.19    | 137.46| 12-H   | 7.9          | 7.84      | 7.97  |
| 25-C   | 129.67       | 132.82    | 134.82| 21-H   | 7.68         | 7.78      | 7.88  |
| 7-C    | 128.8        | 131.99    | 133.95| 33-H   | 7.66         | 7.73      | 7.87  |
| 9-C    | 127.02       | 129.93    | 132.25| 14-H   | 7.64         | 7.70      | 7.87  |
| 8-C    | 126.35       | 129.21    | 131.36| 31-H   | 7.6          | 7.61      | 7.74  |
| 1-C    | 125.49       | 128.04    | 130.66| 30-H   | 7.26         | 6.95      | 7.28  |
| 2-C    | 125.2        | 127.86    | 130.37| 37-H   | 3.9          | 4.08      | 4.16  |
| 10-C   | 124.73       | 127.17    | 127.72| 36-H   | 3.9          | 3.63      | 3.83  |
| 16-C   | 123.53       | 124.47    | 126.35| 35-H   | 3.9          | 3.58      | 3.77  |
| 26-C   | 121.19       | 124.38    | 124.43|        |              |           |       |
| 28-C   | 119.48       | 120.69    | 122.67|        |              |           |       |
| 24-C   | 112.9        | 113.26    | 118.16|        |              |           |       |
| 34-C   | 55.64        | 50.43     | 55.45 |        |              |           |       |

Figure 4. UV–vis spectrum of MPNP (experimental and theoretical).
These vibrations are in good agreement with the literature.26−38

2.3. NMR Spectral Calculations. The chemical shift values of the MPNP are executed by the optimized geometry of the molecule with the help of the GIAO method along with two different hybrid exchange−correlation functionals such as B3LYP and CAM-B3LYP along with the same basis level 6-311++G(d,p), and the experimental values are achieved in DMSO-\(d_6\) solvent. Both data are tabulated in Table 1. The \(^1\)H and \(^{13}\)C experimental and computational spectra are mentioned in Figures S1 and S2. The C15 atom present in the carbonyl group has the signal at 190.27 ppm in CAM-B3LYP, 193.01 ppm in B3LYP, and 190.07 ppm in the experimental spectrum. These values are in good agreement with the literature.10 The chemical shifts of aromatic carbons of the compound generally occurred in the range of 175−100 ppm.40,41 The chemical shifts of the carbon atoms present in the phenyl ring are found around 166.76 to 118.159 ppm. The carbon C29 atom has a highly deshielded signal in \(^{13}\)C NMR, and it has experimentally occurred at 159.97 ppm and theoretically found at 163.83 and 166.76 ppm in CAM-B3LYP and B3LYP, respectively, because it is present along with the oxygen atom. Theoretically obtained values of chemical shift of C34 atom are at 50.43 ppm in CAM-B3LYP and 55.45 ppm in B3LYP respectively whereas experimental value is at 55.64 ppm which is mainly due to more number of hydrogen atoms present around C34 atom. Therefore, the most shielded and deshielded signals are

| \(\lambda_{\text{max}}\) (nm) | band gap (eV) | \(\lambda_{\text{cal}}\) (nm) | energy (\(\text{cm}^{-1}\)) | band gap (eV) | \(f\) (O.S) | \(\lambda_{\text{cal}}\) (nm) | energy (\(\text{cm}^{-1}\)) | band gap (eV) | \(f\) (O.S) | in solvent major contribution |
|--------------------------|---------------|--------------------------|-----------------|---------------|-------------|--------------------------|-----------------|---------------|-------------|-------------------------------|
| 268                      | 4.63          | 299                      | 33480.88        | 4.15          | 0.0371      | 406                      | 24654.8         | 3.06          | 0.4381      | HOMO → LUMO (96%)             |
| 360                      | 3.45          | 348                      | 28711.72        | 3.57          | 0.4689      | 359                      | 27820.5         | 3.44          | 0.0138      | H − 3 → LUMO (71%)            |

Figure 5. HOMO−LUMO orbitals of MPNP.
present around C15 and C34 atoms, respectively. The chemical shift values for hydrogen atoms are found in the region of 9.47 to 3.58 ppm in the computational section and 8.7 to 3.9 ppm in the experimental section. Both of these regions coincide with one another.

2.4. UV–Vis Spectral Studies. The UV–vis spectrum is the basic tool to understand the charge transfer concepts in the molecule. The experimental UV–vis spectrum of the title molecule is measured in DMSO solvent. From a recent literature, it is understood that TD-DFT is the suitable computational tool to study the static and dynamic characteristics of the molecule in the excited state. The theoretical excitation energy, absorption maximum (\( \lambda_{\text{max}} \)), and oscillator strength (\( f \)) of the title molecule are obtained by the TD-DFT method in DMSO solvent along with two different hybrid exchange–correlation functionals such as CAM-B3LYP and B3LYP along with the same basis level 6-311++G(d,p) in DMSO solvent (IEFPCM model). The experimental and theoretical (CAM-B3LYP and B3LYP) spectrum is presented in Figure 5. The absorption wavelengths (\( \lambda \)), oscillator strengths (\( f \)), and excitation energies (\( E \)) and major contributions to the electronic transition are presented in Table 2.

In the title molecule, the experimental absorption peaks are observed at 360 and 268 nm. The related theoretical peaks are observed at 348, 330, and 299 nm in the CAM-B3LYP method and 406, 376, and 359 nm in the B3LYP method. The comparison study between both theoretical wavelengths shows that the CAM-B3LYP results are good correlation with the experimental observed peaks. Hence, finally, we have considered the comparison study between experimental and CAM-B3LYP results. The experimental maximum absorption peak is 360 nm, and the theoretical corresponding maximum absorption peak is 348.29 nm in CAM-B3LYP and 405 nm in B3LYP. The related oscillator strength is 0.4689 and major contribution at a particular maximum wavelength is H

The 3D MEP surface map of the title molecule having several regions for nucleophilic and electrophilic attacks is observed and shown in Figure 6. The positive electrostatic potential region partially shaded on all the hydrogen atoms present in the molecule, but the highest electropositive region is situated around the oxygen atom of the CH3 group because the carbon atom of the CH3 group is bonded with the most electronegative oxygen atom. The small portion of the electronegative region is present around the oxygen atom in the methoxy group. The highest electronegative region is situated around the oxygen atom of the C=O group present in the ethylenic bridge.

| parameters                           | DFT (B3LYP) (eV) |
|--------------------------------------|------------------|
| \( E_{\text{HOMO}} \)               | −6.12            |
| \( E_{\text{LUMO}} \)               | −2.49            |
| ionization potential                | 6.12             |
| electron affinity                   | 2.49             |
| energy gap                           | 3.63             |
| electronegativity                    | 4.305            |
| chemical potential                  | −4.305           |
| chemical hardness                   | 1.815            |
| chemical softness                   | 0.55096 (eV)^−1 |
| electrophilicity index              | 5.1055           |

Table 3. Calculated Energy Values of the MPNP Molecule by the DFT/B3LYP/6-311++G(d,p) Method

indicates that the molecule is soft and reactive. The energy gap of the MPNP is 3.63 a.u. Hence, the molecule is soft and reactive. According to Figure 5, in the case of HOMO, charges are distributed over the ethylenic bridge and naphthalene ring, while comparing HOMO and LUMO, the negative and positive charges are not equally distributed. HOMO is split up into the ethylenic bridge and naphthalene ring, which shows that almost all the atoms in the naphthalene ring and ethylenic bridge carry positive and negative charges. However, in LUMO, charges are localized on all the carbon atoms of the naphthalene ring most negative charges are located on the oxygen atom in the ethylenic bridge, and charges are also located on the phenyl ring. The HOMO–LUMO transition implies an electron density transfer of the ethylenic bridge and naphthalene ring to the phenyl ring region, and this is predicted as (\( \pi-\pi^* \)) transition in NBO analysis. The HOMO – 1–LUMO + 1 transition implies an electron density transfer of methoxy-phenyl to the ethylenic bridge and naphthalene ring, and this is also predicted as (\( \pi-\pi^* \)) transition in NBO analysis.

2.6. MEP Surface Analysis. MEP surface mapping is the most helpful analysis to characterize the molecular structure with the relationship between the physicochemical properties of the molecule. MEP surface mapping is helpful in analyzing the hydrogen bonding interactions through the sites of electrophilic and nucleophilic regions. The MEP map gives the valuable information about the shape, size, and charge region present in the molecule and also provides the net electrostatic effect caused by the total charge distribution. The MEP map is plotted using the optimized structure of the title molecule. The color coding of the surface takes place based on the electrostatic potential (more electron-rich region represented by red color and more electron-poor region represented by blue color). The increasing order of electrostatic potential as per the color code is red < orange < yellow < green < blue. The 3D MEP surface map of the title molecule having several sites for nucleophilic and electrophilic attacks is observed and shown in Figure 6.

In the title molecule, the positive electrostatic potential region partially shaded on all the hydrogen atoms present in the molecule, but the highest electropositive region is present around the hydrogen atoms of the CH3 group because the carbon atom of the CH3 group is bonded with the most electronegative oxygen atom. The small portion of the electronegative region is present around the oxygen atom present in the methoxy group. The highest electronegative region is situated around the oxygen atom of the C=O group present in the ethylenic bridge.
2.7. NBO Analysis. The NBO analysis is fruitful for evaluating the molecular energy from the same geometry in the nonexistence of the electronic delocalization. This analysis is also helpful to evaluate the rehybridization, intramolecular, and delocalization of electron density in the molecule.\textsuperscript{51,52} To evaluate the several second-order interactions between the vacant orbital of one subsystem to the filled orbital of another subsystem, NBO 3.0\textsuperscript{53} is used for the DFT method with two different hybrid exchange–correlation functionals such as B3LYP and CAM-B3LYP along with the same basis level 6-311++G(d,p), and it deduces the hyperconjugation. The second-order perturbation method is used to predict the hyperconjugative interaction energy of the molecule. The hyperconjugation interaction provides the stabilizing effect of the molecule, and this effect is obtained by the overlap of the occupied orbital with the next electron lacking orbital. This interaction of noncovalent bonding can be clearly expressed from the NBO analysis in the form of second-order perturbation interaction energy $E(2)$. The higher the $E(2)$ value indicates the higher capability of the interaction between the electron acceptors and electron donors present in the molecule. The possible intensive interactions are given in Table 4.

In the title molecule, the stronger intramolecular hyperconjugative interaction between $(C27$–$C28) \rightarrow \Pi^* (C24$–$C29/C15$–$O18)$ (21.21/16.87 kJ/mol in DFT and 29.58/24.65 kJ/mol in CAM-DFT), $\Pi (C25$–$C26) \rightarrow \Pi^* (C27$–$C28/C24$–$C29)$ (20.66/18.7 kJ/mol in DFT, and 31.43/27.23 kJ/mol in CAM-DFT). Along with these interactions, some important oxygen lone pair interactions also mentioned in Table 4 such as $LP (2) O38 \rightarrow \sigma^* (C24$–$C29)$ (29.45 kJ/mol in DFT and 35.56 kJ/mol in CAM-DFT) and $LP (2) O18 \rightarrow \sigma^* (C15$–$C16/C15$–$C27)$ (18.69/18.69 kJ/mol in DFT and 21.98/22.14 kJ/mol in CAM-DFT) are also present. Among all these interactions, the lone pair oxygen present in the methoxyphenyl ring has the highest $E(2)$ value of 35.56 kJ/mol in CAM-DFT.

2.8. NLO Studies. A NLO study is one of the important concepts in the present era due to its significance in the field of optoelectronic. As per the literature data, no NLO studies (experimental and theoretical) have been conducted on the present molecule. Therefore, we concentrated on calculating the total static dipole moment ($\mu$), the mean polarizability ($\alpha$), and the mean first-order hyperpolarizability ($\beta$) of the molecule using the DFT/B3LYP/6-311++G(d,p) basis set, and the results are given in Table 5. The resulting values from the Gaussian output are in terms of atomic units (a.u.). The

![Figure 6. MEP surface of MPNP.](https://doi.org/10.1021/acsomega.1c02688)

Table 4. Selected Second-Order Perturbation Theory Analysis of the Fock Matrix in the NBO Basis of MPNP

| donor (i) | type of bond | occupancy | acceptor (j) | type of bond | occupancy | $E_i$ (kJ/mol)$^{ab}$ | $E(i) − E(j)$ (a.u.)$^b$ | $F(i,j)$ (a.u.)$^b$ | $E_i$ (kJ/mol)$^{ab}$ | $E(i) − E(j)$ (a.u.)$^b$ | $F(i,j)$ (a.u.)$^b$ |
|-----------|--------------|-----------|-------------|--------------|-----------|----------------------|------------------------|------------------------|----------------------|------------------------|------------------------|
| O18       | LP2          | 1.88825   | C15−C16    | $\sigma^*$   | 0.05839   | 18.69                | 0.7                    | 0.103                  | 21.98                | 0.83                    | 0.122                  |
| O38       | LP2          | 1.88825   | C15−C27    | $\sigma^*$   | 0.06485   | 18.69                | 0.69                   | 0.103                  | 22.14                | 0.82                    | 0.122                  |
| C1−C6     | $\pi$        | 1.6886    | C2−C1      | $\sigma^*$   | 0.26023   | 17.34                | 0.29                   | 0.064                  | 23.88                | 0.39                    | 0.087                  |
| C2−C3     | $\pi$        | 1.72081   | C1−C6      | $\sigma^*$   | 0.30134   | 16.13                | 0.29                   | 0.063                  | 21.56                | 0.37                    | 0.083                  |
| C4−C5     | $\pi$        | 1.53359   | C1−C6      | $\sigma^*$   | 0.30134   | 16.53                | 0.3                    | 0.067                  | 25.54                | 0.39                    | 0.090                  |
| C7−C8     | $\pi$        | 1.73908   | C4−C5      | $\sigma^*$   | 0.45926   | 16.2                 | 0.29                   | 0.064                  | 21.94                | 0.38                    | 0.085                  |
| C9−C10    | $\pi$        | 1.73412   | C4−C5      | $\sigma^*$   | 0.26023   | 16.96                | 0.27                   | 0.064                  | 22.51                | 0.36                    | 0.084                  |
| C16−C17   | $\pi$        | 1.84533   | C15−O18    | $\sigma^*$   | 0.24989   | 16.38                | 0.28                   | 0.064                  | 22.14                | 0.36                    | 0.084                  |
| C24−C29   | $\pi$        | 1.65717   | C25−C26    | $\sigma^*$   | 0.25181   | 16.51                | 0.28                   | 0.064                  | 22.27                | 0.36                    | 0.085                  |
| C25−C26   | $\pi$        | 1.67744   | C24−C29    | $\sigma^*$   | 0.37956   | 17.8                 | 0.27                   | 0.065                  | 27.23                | 0.35                    | 0.089                  |
| C27−C28   | $\pi$        | 1.67462   | C15−O18    | $\sigma^*$   | 0.3564    | 17.65                | 0.3                    | 0.065                  | 29.43                | 0.39                    | 0.097                  |
|           | $\pi$        | 1.67462   | C24−C29    | $\sigma^*$   | 0.37956   | 17.8                 | 0.28                   | 0.064                  | 29.58                | 0.39                    | 0.097                  |
|           | $\pi$        | 1.67462   | C25−C26    | $\sigma^*$   | 0.29461   | 17.37                | 0.29                   | 0.064                  | 24.65                | 0.38                    | 0.087                  |

$^aE_i$ means the energy of hyper conjugative interactions. $^b$Energy difference between the donor and acceptor i and j of NBO orbitals. $^cF(i,j)$ is the Fock matrix element between i and j NBO orbitals.
obtained values are expressed in standard units with help of relation $1 \text{ a.u.} = 2.5412 \times 10^{-24} \text{ esu}$, and $1 \text{ a.u.} = 8.6393 \times 10^{-33} \text{ esu}$ for $\mu$, $\alpha$, and $\beta$, respectively. For the investigation of NLO properties, the organic compound urea is considered as a reference molecule. Hence, urea is also computed with the basis set for the comparative study. The total dipole moment of the title molecule obtained by the computation method is found at 3.4408 D and it is compared with urea ($\mu = 3.8903$ D), and the first-order hyperpolarizability ($\beta$) of the title molecule is $21.6781 \times 10^{-30}$ esu and it is compared with urea $\beta_{\text{tot}} = 0.6218 \times 10^{-30}$ esu. Hence, hyperpolarizability of the studied molecule is 35 times larger compared to the reference material urea. Vinay Parol et al.\textsuperscript{54} reported the NLO properties of the similar derivative; $\beta_{\text{tot}}$ is $18.65 \times 10^{-30}$ esu and $\mu = 3.59$ D. Shruthi et al.\textsuperscript{55} also reported a similar kind of the molecule having $\beta_{\text{tot}} = 36.017 \times 10^{-30}$ esu and $\mu = 4.17$ D. The title molecule data are present in the reported data. Hence, we can conclude that the title molecule may be useful to study the detailed NLO properties in future.

2.9. Fukui Function. DFT is an effective method to inspect the reactivity and selectivity in an organic molecule. Fukui function is recognized as a highly recommendable local reactive factor. The Fukui function is carried out by using Multiwfn software.\textsuperscript{56} Fukui functions are prominent functions, which give idea related to the capacity of the molecule to donate or accept an electron, and therefore reveal information about an atom being electrophilic or nucleophilic. Generally, nucleophilic $f^-(r)$ and electrophilic $f^+(r)$ attacks are computed via Fukui function.

$$f^-(r) = \rho(N) - \rho(N - 1)$$

$$f^+(r) = \rho(N + 1) - \rho(N)$$

Dual descriptor $\Delta f(r)$ exposes the reactive sites\textsuperscript{57} more suitably. It is represented by

$$\Delta f(r) = f^+(r) - f^-(r)$$

$\Delta f(r)$ provides an effective distinction among nucleophilic and electrophilic attacks at the accurate region along their sign. If $\Delta f(r) < 0$, the site is favorable for electrophilic attack, and if $\Delta f(r) > 0$, the site is favorable for nucleophilic attack.

The pictorial depictions of the dual descriptor and Fukui function of MPNP are shown in the Figure 7a,b, and the complete values are mentioned in Table 6. In this analysis, the nucleophilic attacks lie in the manner of $18O > 38O > 26C > 15C > 1C > 3C > 24C > 22H > 27C > 14H > 21H > 31H > 30H > 19H > 20H > 23H > 12H > 16C > 28C > 7C > 13H >$.

Table 5. NLO Properties of the MPNP Molecule

| parameter | a.u. | esu ($\times 10^{-24}$) | parameter | a.u. | esu ($\times 10^{-30}$) |
|-----------|------|-------------------------|-----------|------|-------------------------|
| $\mu_x$   | $-0.4375$ | $-1.1117$ | $\beta_{xxx}$ | $-1839.6654$ | $-15.8934$ |
| $\mu_y$   | 1.2600  | 3.2019      | $\beta_{yy}$ | $-1221.0111$ | -10.5487  |
| $\mu_z$   | 0.2334  | 0.5932      | $\beta_{zz}$ | $-234.5846$  | 2.0266   |
| $\mu$     | 1.3540  | 3.4408      | $\beta_{yy}$ | $-153.4758$  | -1.3259  |
| $\alpha_{xx}$ | 413.0188 | 61.2094     | $\beta_{xx}$ | $-184.0428$  | -1.5900  |
| $\alpha_{yy}$ | 4.6741  | 0.6927      | $\beta_{yy}$ | 45.7209      | 0.3950   |
| $\alpha_{zz}$ | 255.7315 | 37.8994     | $\beta_{zz}$ | $-70.5314$   | -0.6093  |
| $\alpha_{xy}$ | 18.7176 | 2.7739      | $\beta_{xz}$ | 0.9679       | 0.0084   |
| $\alpha_{xz}$ | $-13.2507$ | $-1.9637$  | $\beta_{yz}$ | $-11.1361$   | -0.0962  |
| $\alpha_{yz}$ | 153.7840 | 22.7908     | $\beta_{zz}$ | $-24.4834$   | -0.2115  |
| $\alpha$   | 274.1781 | 40.6332     | $\beta_{o}$  | 2509.2475   | 21.6781  |
| $\Delta f$ | 226.2026 | 33.5232     | \ | \ | \ |

Figure 7. (a,b) $f^+$ & $f^-$ Fukui functions of MPNP.
Table 6. Condensed Fukui Function $fr$ for MPNP

| atoms | Mulliken atomic charges | Fukui functions |
|-------|-------------------------|-----------------|
|       | $N$ | $(N + 1)$ | $-1$, 2 | $(N - 1)$ | 1, 2 | $fr^+$ | $fr^-$ | $fr^0$ | $\Delta fr$ |
| 1C    | -0.4014 | -0.4659 | -0.3795 | -0.0645 | -0.0220 | -0.0432 | -0.0426 |
| 2C    | -0.3800 | -0.3734 | -0.3752 | 0.0066 | -0.0048 | 0.0009 | 0.0114 |
| 3C    | -0.3376 | -0.4003 | -0.2813 | -0.0627 | -0.0563 | -0.0595 | -0.0064 |
| 4C    | 0.4527 | 0.4734 | 0.4363 | -0.0205 | 0.0164 | 0.0186 | -0.0369 |
| 5C    | 0.7161 | 0.6975 | 0.7161 | -0.0185 | -0.0478 | -0.0093 | 0.0293 |
| 6C    | 0.7566 | 0.7645 | 0.7992 | -0.0136 | -0.0426 | -0.0173 | 0.0290 |
| 7C    | -0.1182 | -0.1462 | -0.0639 | -0.0280 | -0.0542 | -0.0411 | 0.0262 |
| 8C    | -0.3082 | -0.3140 | -0.2975 | -0.0059 | -0.0106 | -0.0082 | 0.0048 |
| 9C    | -0.5355 | -0.5522 | -0.5171 | -0.0167 | -0.0185 | -0.0176 | 0.0017 |
| 10C   | -0.4305 | -0.4289 | -0.3927 | 0.0016 | -0.0378 | -0.0181 | 0.0394 |
| 11H   | 0.0866 | 0.0792 | 0.1136 | -0.0074 | -0.0269 | -0.0172 | 0.0195 |
| 12H   | 0.1800 | 0.1432 | 0.2257 | -0.0368 | -0.0457 | -0.0413 | 0.0089 |
| 13H   | 0.1663 | 0.1433 | 0.1978 | -0.0231 | -0.0315 | -0.0273 | 0.0084 |
| 14H   | 0.1767 | 0.1322 | 0.2242 | -0.0445 | -0.0475 | -0.0460 | 0.0030 |
| 15C   | -0.3357 | -0.4063 | -0.3259 | -0.0706 | -0.0098 | -0.0402 | -0.0607 |
| 16C   | -0.2434 | -0.2762 | -0.2024 | -0.0328 | -0.0410 | -0.0369 | 0.0081 |
| 17C   | -0.1280 | -0.2138 | -0.1015 | -0.0054 | -0.0265 | -0.0562 | 0.0211 |
| 18O   | -0.2376 | -0.3481 | -0.1768 | -0.1105 | -0.0608 | -0.0856 | -0.0497 |
| 19H   | -0.1200 | -0.1580 | -0.1005 | -0.0380 | -0.0195 | -0.0288 | -0.0185 |
| 20H   | 0.1878 | 0.1502 | 0.2087 | -0.0376 | -0.0209 | -0.0292 | -0.0167 |
| 21H   | 0.1624 | 0.1211 | 0.2099 | -0.0414 | -0.0475 | -0.0444 | 0.0061 |
| 22H   | 0.1280 | 0.0780 | 0.1790 | -0.0050 | -0.0510 | -0.0505 | 0.0010 |
| 23H   | 0.1401 | 0.1032 | 0.1860 | -0.0369 | -0.0459 | -0.0416 | 0.0090 |
| 24C   | 0.4796 | 0.4256 | 0.5212 | -0.0539 | -0.0416 | -0.0478 | -0.0123 |
| 25C   | -0.6269 | -0.6181 | -0.6215 | -0.0015 | -0.0054 | 0.0017 | 0.0039 |
| 26C   | 0.6037 | 0.5316 | 0.6597 | -0.0721 | -0.0560 | -0.0641 | -0.0161 |
| 27C   | 1.5272 | 1.4800 | 1.5443 | -0.0472 | -0.0172 | -0.0322 | -0.0300 |
| 28C   | -1.8707 | -1.7943 | -1.8957 | -0.0146 | 0.0251 | 0.0507 | -0.0397 |
| 29C   | -0.4868 | -0.4553 | -0.5072 | 0.0079 | 0.0204 | 0.0260 | -0.0125 |
| 30H   | 0.1720 | 0.1335 | 0.2054 | -0.0386 | -0.0334 | -0.0360 | -0.0052 |
| 31H   | 0.1762 | 0.1357 | 0.2165 | -0.0405 | -0.0403 | -0.0404 | -0.0002 |
| 32H   | 0.1945 | 0.1737 | 0.2228 | -0.0208 | -0.0282 | -0.0245 | 0.0074 |
| 33H   | 0.2108 | 0.1978 | 0.2231 | -0.0131 | -0.0123 | -0.0127 | -0.0008 |
| 34C   | -0.2857 | -0.2852 | -0.2886 | 0.0088 | 0.0049 | 0.0017 | 0.0039 |
| 35H   | 0.1537 | 0.1391 | 0.1773 | 0.0763 | -0.0237 | -0.0191 | 0.1000 |
| 36H   | 0.1516 | 0.1380 | 0.1734 | 0.0315 | -0.0218 | -0.0177 | 0.0532 |
| 37O   | 0.1785 | 0.1580 | 0.2028 | 0.0207 | -0.0243 | -0.0224 | 0.0450 |
| 38O   | -0.1571 | -0.1625 | -0.1158 | -0.0858 | -0.0413 | -0.0233 | -0.0445 |

2.10. ADMET, Drug-Likeness and Molecular Docking Analysis. ADMET analysis (absorption, distribution, metabolism, excretion, and toxicity) is one of the most important steps involved in the drug discovery pipeline. There are two major aims of the ADMET analysis, one is at the compound designing stage where it helps in reducing risks of last-stage attrition of compounds and second is the optimization of the compound screening from the existing libraries. The important aspects to be looked in ADMET analysis are oral absorption, clearance, receptor toxicity, and brain penetration. The details of ADMET properties of the title compound MPNP are given in Table S3.

2.10.1. Spike Protein. Spike glycoprotein from SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) commonly known as a spike protein is a membrane protein, which binds to host cells. In humans, it has very strong affinity toward the ACE2 receptor. The spike protein has three major domains, namely, SP1, SP2, and SP2’. The SP1 domain plays a vital role in binding of the protein to host cells and hence known as a RBD, the SP2 domain mediates the process of membrane fusion, and SP2’ domain proliferation of viral particles into host cells by acting like a fusion peptide after the cleavage of the SP2 domain. The spike protein also has a property to downregulate host physical tethers like BST2 (bone marrow stromal cell antigen 2) by lysosomal degradation, which counters the antiviral activity of the tether. The property of the RBD domain to bind to the ACE2 receptor during the fusion makes spike glycoprotein an elusive therapeutic target in SARS-CoV-2 infection.

2.10.2. Molecular Docking. The RBD of the spike protein (PDB id: 7NEH) Figure 8 was docked with chalcone using AutoDock Vina with 100 exhaustiveness.
molecule was converted to pdbqt 3D format using AutoDock tools. The grid box for docking was assigned based on the literature. The first aspect, which was considered for assigning the binding site, is the ACE2 receptor binding sites on the spike protein and the second aspect considered was the antibody recognition sites on the RBD of the spike protein based on the co-crystallized structure of the spike protein with antibody fragments. The details of the binding sites considered for the construction of the grid are given in Table 7.

The best conformation of the protein–ligand complex was chosen based on binding energy and hydrogen bond interactions.

2.10.3. Docking Results. After molecular docking, the binding energy between the target and compound was calculated in the order of $-6.7$ kcal/mol. The 2D and 3D diagrams of the spike protein RBD in complex with chalcone can be seen in Figures 9 and 10. From the 2D interaction diagram, it was seen that chalcone formed a stable hydrogen bonding with the chalcone molecule at a distance of 2.40 Å.

Table 7. Active Residues and the Co-ordinates of the Pocket Predicted Based on the Literature

| center X | center Y | center Z | residues |
|----------|----------|----------|----------|
| -1.86    | 60.53    | -1.38    | GLY339, PHE342, ASN343, LEU368, SER371, SER373, PHE374, TRP382, LEU391, ARG395, TYR396, ASP428, THR430, PHE445, SER445, PHE455, GLU458, LYS458, ARG463, TYR465, TYR495, GLY502, GLN498, ASN501 |

3. CONCLUSIONS

The MPNP molecule is successfully synthesized and characterized by the different spectroscopic studies. The computed geometrical parameter agreed with the experimental geometrical parameter as per the reference. The experimentally obtained FT-IR and FT-Raman spectral values are finely agreed with the computationally obtained spectral values by the DFT method. From NMR spectral analysis, the most shielded and deshielded signals are present around C15 and C34 atoms, respectively. The absorption wavelength and energy band gap values obtained from experimental UV–vis analysis in DMSO solvent are found to be nearly equal to the theoretically computed values in the DMSO phase. From FMO analysis, we found that the energy gap is 3.63 eV, which indicates that the title molecule has decent soft and reactive nature. From the MEP map, we observed that the highest electropositive region is present around the hydrogen atoms of the CH$_3$ group because the carbon atom of the CH$_3$ group is bonded with the most electronegative oxygen and the highest electronegative region is situated around the oxygen atom of the C=O group present in the ethylenic bridge. From NBO analysis, we found that L(2)O38 $\rightarrow$ $\sigma^*$ (C24–C29) 35.56 kJ/mol in CAM-DFT has highest stabilization energy compared to all the bonding and antibonding orbitals. First-order hyperpolarizability ($\beta$) of the title molecule obtained by the computational method is $21.6781 \times 10^{-30}$ esu. Hence, hyperpolarizability of the studied molecule is 35 times larger compared to the theoretically reported value of reference material urea. The title molecule is docked, and the drug-likeness and ADMET studies are also carried out. The property of the RBD to bind to the ACE2 receptor during the fusion makes spike glycoprotein an elusive therapeutic target in SARS-CoV-2 infection. Furthermore, it was seen that chalcone formed a stable hydrogen bonding with the chalcone molecule.
at a distance of 2.40 Å. With all the computational studies, it is concluded that chalcone MPNP can be used in the development of drugs for SARS-CoV-2 with the modification of the structure. The present study gives the avenue for further research to explore chalcones as potent SARS-CoV-2 drugs.

4. EXPERIMENTAL SECTION

4.1. Materials. The MPNP molecule is synthesized by the following procedure on the basis of the literature. Equimolar quantities of 3-methoxy acetophenone and 1-naphthaldehyde are dissolved in ethanol (20 mL). Aqueous sodium hydroxide solution (2 mL, 40%) is added dropwise with stirring for 10 min. The stirring is continued at room temperature for 5 h. The completion of reaction is confirmed by thin-layer chromatography (10% ethyl acetate in hexane). The reaction was quenched in ice, and the solid separated is filtered and dried and purified by recrystallization in a 10% ethyl acetate and hexane mixture to give yellow-colored crystals. The synthesized structural characterization is done by NMR and IR spectra. The synthetic route for MPNP is shown in Scheme 1.

4.2. Experimental Methods. In the present work, we have utilized four experimental spectroscopic methods such as FT-IR, FT-Raman, NMR, and UV–vis spectrometer. The FT-IR and FT-Raman spectra are used to determine the vibrational wavenumbers. The NMR (1H, 13C) analyses give information about the configuration and structure of the organic molecules in terms of chemical shift (ppm). The UV–vis spectrum offers information about electronic transitions in the molecule. The PerkinElmer spectrum FT-IR spectrometer model is employed to measure the FT-IR spectrum in the range of 4000–400 cm⁻¹ at room temperature. The 100 numbers of scans are used with the 2 cm⁻¹ optical resolution. The small amounts of solid samples are utilized with the help of the KBr pallet method. The BRUKER RFS 27: stand-alone FT-Raman spectrometer model is employed to measure the FT-Raman spectrum in the range of 4000–100 cm⁻¹. The 100 numbers of scans used with the 2 cm⁻¹ optical resolution are used to collect the signals at room temperature. The spectrometer includes 1064 nm wavelength of the Nd:YAG laser source with 200 mW power. The Agilent Technology’s Cary series UV–vis spectrometer model is employed to measure the ultraviolet–vis (UV–vis) spectrum in the range 900–100 nm. The JNM-ECZ400S FT-NMR spectrometer model is employed to measure the 1H and 13C NMR spectra at 500 MHz in DMSO-d₆ and TMS used as the standard reference.

4.3. Computational Methods. The entire computational studies are performed using Gaussian 09w software along with the DFT method and B3LYP/6-311++G(d,p) basis set. GaussView 5.0 software is used for visualization of the molecule. The optimization process gives the minimum energy confirmation of the structure. The title molecule is completely optimized by the DFT method with B3LYP and CAM-B3LYP along with the 6-311++G(d,p) basis level. The computed vibrational wavenumbers are commonly greater than the values obtained by experimental methods. So, the scaling factor of 0.9614 is used to scale the computed wavenumbers to establish the good comparison between both vibrational wavenumbers. The detailed vibrational assignments are assigned on the basis of PED (%) obtained from the VEDA 04 software tool. The chemical shift values of 1H and 13C NMR are obtained using the GIAO method with the same basis set. The TD-DFT method is employed to compute the UV–vis spectral parameters at the same basis level. The HOMO–LUMO, NLO, NBO, and MEP have been computed by the optimized structure along with appropriate methods present in the Gaussian tool.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c02688.

Details of geometrical parameters of MPNP by X-ray and DFT, detailed assignments of experimental and theoretical wavenumbers of MPNP with the 6-311+G(d,p) basis set, 1H and 13C experimental and computational B3LYP and CAM-B3LYP spectra, and the ADMET properties of the compound MPNP (PDF)

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Notes
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