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Molecular structure, NBO analysis of the hydrogen-bonded interactions, spectroscopic (FT–IR, FT–Raman), drug likeness and molecular docking of the novel anti COVID-2 molecule (2E)-N-methyl-2-[(4-oxo-4H-chromen-3-yl)methylidene]-hydrazinecarbothioamide (Dimer) - quantum chemical approach

S.J. Jenepha Mary a,1, Sayantan Pradhan b, C. James a,⇑

a Department of Physics and Research Centre, Scott Christian College (Autonomous), Nagercoil 629003, Tamil Nadu, Affiliated to Manonmaniam Sundarnar University, Abishekappatt, Tirunelveli 627012, India
b Department of Chemistry, Jadavpur University, Kolkata 700 032, West Bengal, India

Highlights
- N–H···O intermolecular interactions elucidates the effect of hyperconjugation.
- C–H···O intermolecular interactions elucidates the effect of rehybridization.
- FT-IR and FT-Raman spectral analysis substantiates the red shift and blue shift in stretching frequencies.
- Drug likeness and ADMET analysis reveals pharmacokinetic properties.
- Molecular docking shows the interaction of MCMH with SARS-CoV-2 protease.

Graphical abstract

Abstract
Prospective antiviral molecule (2E)-N-methyl-2-[(4-oxo-4H-chromen-3-yl)methylidene]-hydrazinecarbothioamide has been probed using Fourier transform infrared (FTIR), FT-Raman and quantum chemical computations. The geometry equilibrium and natural bond orbital analysis have been carried out with density functional theory employing Becke, 3-parameter, Lee-Yang-Parr method with the 6-311G**(d, p) basis set. The vibrational assignments pertaining to different modes of vibrations have been augmented by normal coordinate analysis, force constant and potential energy distributions. Drug likeness and oral activity have been carried out based on Lipinski’s rule of five. The inhibiting potency of 2(2E)-methyl-2-[(4-oxo-4H-chromen-3-yl)methylidene]-hydrazinecarbothioamide has been investigated by docking simulation against SARS-CoV-2 protein.

The optimized geometry shows a planar structure between the chromone and the side chain. Differences in the geometries due to the substitution of the electronegative atom and intermolecular contacts due to the chromone and hydrazinecarbothioamide were analyzed. NBO analysis confirms the presence of two strong stable hydrogen bonded N–H···O intermolecular interactions and two weak hydrogen bonded C–H···O interactions. The red shift in N–H stretching frequency exposed from IR substantiates the formation of N–H···O intermolecular hydrogen bond and the blue shift in C–H stretching frequency.

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1. Introduction

Recently, the emergence of new viruses and the re-emergence of existing viruses have become a great threat to the global population due to the outbreak of infections such as severe acute respiratory syndrome-associated corona virus, which gained the attention of current researchers in the development of new compounds possessing antiviral activity. In search of promising compounds, the title molecule (2E)-N-methyl-2-[(4-oxo-4H-chromen-3-yl)methylidene]-hydrazine carbothioamide (MCMH) has been selected. In the present study, the prime focus is on the investigation of the molecular structure, charge transfer interactions, vibrational spectra, drug likeness and molecular docking of MCMH, with the anticipation that the results of the present investigation may be decisive in the prognosis of its mechanism of biological activity.

Chromones, compounds widely distributed in nature, especially in the plant kingdom play a prominent role in the field of medicine owing to its multifarious pharmacological activity against influenza virus [1], hepatitis B virus [2], human rhino virus (HRV) [11] and neuro degenerative diseases [3]. Chromones have been reported to show anti-bacterial, anti-fungal [4,5], anti-cancer [6], anti-oxidant [7], anti-HIV [8] and immune-stimulatory [9] activity. Also, 4-oxo-4H-chromen has been used to treat cystic fibrosis by activating the transmembrane conductance regulator [10]. The title compound, which has the chromone moiety, shows antimutagenic property [11] and the ability to inhibit electron transport through nicotinamide adenine dinucleotide (NAD) + hydrogen (H) [12,13]. The NNS tridentate ligand system of thiosemicarbazone accounts for the anticancer activity molecule and has the capability to act against adenovirus, herpes virus rhinovirus and RNA tumor virus [14,15]. In the title compound, the presence of the substituent in the 3-position of the chromone acts as hMAO-B inhibitors, which plays an essential role in the expression of toxicity of the Parkinsonism-producing neurotoxin [16]. Also, the attachment of the thiosemicarbazone to the heterocyclic ring has the ability to inhibit ribonucleotide reductase, in mammalian cells, which acts as a key enzyme in the synthesis of DNA precursors [17]. The presence of the methyl group in the title molecule has the capability to lower plasma cholesterol levels [18]. The presence of hydrazine unit in thiosemicarbazide of MCMH has the capability to inhibit cholinesterase to treating Alzheimer’s and Parkinson’s disease [19,20].

Structural and spectral investigation of 2-[(2-aminopyridin-3-yl)methylene]-N-ethylhydrazinecarbothioamide responsible for the antitumour activity [21], vibrational spectroscopic studies on ethylpyridine-4-carbothioamide and the NMR chemical shift has been reported [22]. FT-IR and FT-Raman studies pertaining to different modes of vibrations have been carried out on 9-methoxy-2H-furo[3,2-g]chromen-2-one [23]. The hydrogen bonding profile of the aniviral molecule valacyclovir with the target protein through hydrogen bonded interaction has been reported [24]. Literature screening reveals the crystal structure of (2E)-N-methyl-2-[(4-oxo-4H-chromen-3-yl)methylidene]-hydrazinecarbothioamide has been reported and no other studies has been reported so far on MCMH. MCMH has been probed using Density functional theory, vibrational spectroscopic techniques and docking simulation to elucidate the structure-activity relationship. Quantum chemical computations aided by density functional theory and vibrational spectroscopic methods have been used as an efficient method to determine the normal modes of vibration and the type of bonding in molecules. A detailed study of the intermolecular interactions has been done by NBO analysis. Drug likeness and the toxicity of the molecule have been done using ADMET (Adsorption, Distribution, Metabolism, Excretion and Toxicity) analysis. The antiviral potency of the title molecule has been probed by molecular docking simulations.

2. Experimental details

Synthesis of (2E)-N-methyl-2-[(4-oxo-4H-chromen-3-yl)methylidene]-hydrazinecarbothioamide

MCMH has been prepared by dissolving 1.05 g of N-methylhydrazinecarbothioamide in 20 ml of hot ethanol. To this 1.74 g of 4-oxo-4H-Chromene-3-carbaldehydein 10 ml of ethanol was added and stirred continuously for a period of 10 min. The reaction mixture was refluxed for 2 h and the completion of the reaction is monitored by thin layered chromatography (TLC). The resultant mixture was cooled, filtered, washed with ethanol and dried in vacuum. The compound has been recrystallized from hot ethanol yielding colourless block crystals [27].

2.1. Instrumentation for recording spectra

FT-IR spectrum of MCMH has been recorded using Perkin Elmer spectrum-I spectrometer in the spectral range of 4000–400 cm⁻¹ with a resolution of 1 cm⁻¹ and the FT-Raman spectrum of MCMH has been recorded using Bruker RS 277 Raman spectrometer in the spectral range of 4000–50 cm⁻¹. The neodymium doped yttrium aluminium (Nd:YAG) garnet acts as the laser source with an excitation of 1064 nm.

3. Computational details

The equilibrium geometry and the geometric optimization has been carried out using Gaussian 09 W [28] at the B3LYP/6-311G+(d,p) level of theory. In order to understand the interactions that take place between the filled and vacant orbitals, natural bonding orbitals (NBO) calculations [29] have been carried out using NBO3.1 program as implemented in the Gaussian 09 package. The normal coordinate analysis (NCA) and the normal modes of vibrations have been performed using MOLVIB 7.0 program [30,31]. The input required for the MOLVIB program has been employed as suggested by Pulay [32]. Molecular docking simulation has been carried out and the ligand-protein interactions have

substantiates the formation of C=H · O intermolecular hydrogen bond. Drug likeness, absorption, distribution, metabolism, excretion and toxicity property gives an idea about the pharmacokinetic properties of the title molecule. The binding energy of the nonbonding interaction with Histidine 41 and Cysteine 145, present a clear view that 2(2E)-methyl-2-[(4-oxo-4H-chromen-3-yl)methylidene]-hydrazinecarbothioamide can irreversibly interact with SARS-CoV-2 protease.
been studied using Auto Dock 4.2.6 software package [33]. The binding sites of the ligand-protein have been visualized using PYMOL graphic software [34].

4. Result and discussions

4.1. Optimized structural geometry

The optimized structural parameters of the monomer and dimer form of MCMH have been performed using Gaussian 09 W program package and the optimized molecular structure has been visualized using Gauss View 5.0.9. The optimized monomer and dimer structure of the MCMH is depicted in Figs. 1(a) and 1(b).

The optimized bond length of MCMH involved in intermolecular hydrogen bonding is given in Table 1. The optimized bond angle and dihedral angle of MCMH have been shown in supplementary Table S2 and S3.

The crystallographic information of MCMH [C12H11N3O2S] has been taken from Cambridge Crystallographic Data Center (CCDC 1027156). The molecular structure of MCMH has been visualised as consisting of a 4H-chromen-4-one ring and a methyl hydrazinecarbothioamide moiety substituted in the 3-position of the chromone ring. The calculated geometric parameters are in good agreement with the experimental data with small discrepancies. From the optimized geometry the global minimum energy of MCMH monomer and dimer are found to be $-1176$ Hartree and $-2353.64$ Hartree with the dipole moment of 0 Debye and 7.7226 Debye. The substitution of the carbonyl at the C5 position leads to an elongation in the C5–C6 bond angle by 0.004 Å and C5–C6–C11 bond angle by $1^\circ$. A considerable increase in the C22–S23 bond length by 0.007 Å is noticed. Also, there is an increase in the N20–C22–S23 bond angle by $1^\circ$. This is due to the presence of the electronegative nitrogen atom on either side of the C22 carbon atom. The attachment of the oxygen atom in the chromone ring causes a distortion from the regular hexagon structure. This is well reflected by the decrease in the C6–C11–C12 endoangle by $5^\circ$ [Table S1]. MCMH on dimerization leads to the formation of two N–H⋯O hydrogen bonded intermolecular interactions and two C–H⋯O hydrogen bonded inter-

![Fig. 1a. Optimized molecular structure of MCMH monomer at Becke three Lee–Yang–Parr /6-311++G (d,p) level of theory representing the most stable structure with minimum energy.](image1)

![Fig. 1b. Optimized molecular structure of MCMH dimer at Becke three Lee–Yang–Parr /6-311++G (d,p) level of theory representing the most stable structure with minimum energy.](image2)
molecular interactions, adding stability to the system. The formation of four hydrogen bonded interactions results in substantial changes which leads to an increase in the C11–O15 bond length by 0.009 Å, decrease in C46–H47 and C17–H18 bond lengths by 0.005 Å and an increase in N20–H21 and N49–H50 bond lengths by 0.007 Å. Owing to the formation of intermolecular hydrogen bonded interactions the N–H···O and C–H···O bond angles have been twisted by 22° and 39° with respect to the chromone plane. The elongation and contraction in bond length is due to the orbital interactions and charge distributions that take place within the molecule [35].

4.2. Natural bond orbital analysis

NBO analysis is proved to be an efficient method to elucidate the most possible natural Lewis structure picture of orbitals. MCMH has been subjected to NBO analysis to elucidate the intra and intermolecular interactions between the filled and vacant orbital, which is a measure of hyperconjugation or intramolecular delocalization. Intermolecular interactions arises due to the hyperconjugation and electron density transfer (EDT) from filed lone pair electrons of the n(\(\pi^v\)) of the “Lewis base” Y into the unfilled antibond \(\sigma^*(X\cdots Y)\) of the “Lewis acid” in X–H···Y have been recorded [36]. The calculated stabilization energy E(2) associated with the interaction between the filled orbital \(i\) and the vacant orbital \(j\) have been tabulated in (Table 2).

In MCMH, significant interactions have been noticed due to the interaction of lone pair electrons with the antibonding orbitals \(n_2(O14)\rightarrow \pi^*(C1–C6), n_2(O14)\rightarrow \pi^*(C12–C13), n_1(O15)\rightarrow \sigma^*(C6–C11), n_2(O15)\rightarrow \sigma^*(C11–C12), n_1(N20)\rightarrow \pi^*(C17–N19)\) and \(n_2(S23)\rightarrow \sigma^*(C22–N24)\) with the stabilization energy of 27.48 kcal/mol, 34.880 kcal/mol, 17.11 kcal/mol, 19.230, 31.03 kcal/l/mol and 11.16 kcal/mol respectively. The second order perturbation energies associated with the hyperconjugative interactions in NBO basis confirms the presence of intermolecular interactions. Bonding orbital analysis of MCMH monomer and dimer manifests the formation of four hydrogen bonded intermolecular interactions, of which two are C–H···O, observed between the oxygen lone pair electrons n1(O15) \(\rightarrow \sigma^*(C46–H47)\) and n1(O44) \(\rightarrow \sigma^*(C17–H18)\) with the stabilization energy of 1.860 kcal/mol interactions and 1.8 kcal/mol. As a consequence, the length of the C–H bond involved in intermolecular interaction is shortened by 0.005 Å. The C–H···O interaction energies are found to vary from 0.5 and 2 kcal/mol [37], which are weaker than conventional hydrogen bonds play a prominent role in molecular and protein conformation.

The other two N–H···O hydrogen bonded interactions are observed between the oxygen lone pair electrons n1(O15) \(\rightarrow \sigma^*(N49–H50)\) and n1(O44) \(\rightarrow \sigma^*(N20–H21)\) with the stabilization energy of 7.810 kcal/mol and 7.810 kcal/mol respectively. As a result, the N–H bond involved in intermolecular interactions shows an elongation in the N–H bond length by 0.007 Å. The occupancies and their corresponding energies of the interacting bonding orbitals have been represented in Table 3.

The quantity of charge transferred from lone pairs of n(O15) \(\rightarrow \sigma^* (N49–H50)\) and n(O44) \(\rightarrow \sigma^* (N20–H21)\) of the hydrogen
bonded atoms into the antibonds have been increased by 0.0146 upon dimerization provides clear evidence about the weakening of bond, elongation and a concomitant red shift in N–H stretching frequency.
Similarly upon dimerization, the amount of charge transferred from lone pairs of n(O15) → σ*(C46–H47) and n(O44) → σ*(C17–H18) of the hydrogen bonded atoms into the antibonds has been increased by 0.0031 with the stabilization energy of 1.860 kcal/mol and 1.800 kcal/mol. The observed low energy (<3 kcal/mol) shows the presence of improper hydrogen bonding [38].

Therefore rehybridization plays an important role in C–H bond. From Table 4 it has been seen that the s-character of the C17–H18 hybrid orbitals increases (0.97%) from sp2.28 to sp1.90 that leads to the strengthening of C17–H18 bond and its contraction. This has been well reflected in the geometry as bond C17–H18 contracts by 0.005 Å with respect to monomer. The contraction and elongation of C–H is due to the effect of rehybridization and hyperconjugation. However, rehybridization dominates and overshadow the hyperconjugative interaction resulting in the contraction of C–H bond (0.005 Å) and a concomitant blue shift (∼50) in stretching frequency. In case of N-Heteromolecular hydrogen bonding the hyperconjugative effect dominates rehybridization resulting in the elongation of N–H bond (0.007 Å) and a concomitant red shift (∼55) in stretching frequency.

### Table 4

| NBO | Monomer | Dimer | ANBO |
|-----|---------|-------|------|
| sp2(C17–H18) | sp2.28 | sp1.90 | s |
| % s-char | 32.84 | 33.81 | 0.97 |
| pol. N30% | 37.92 | 37.17 | −0.75 |
| pol. H31% | 62.08 | 62.83 | 0.75 |
| (C17)/e | 0.6158 | 0.6996 | −0.0062 |
| (H18)/e | −0.7879 | −0.7927 | −0.0048 |
| sp2(C17–N19) | sp2.28 | sp1.90 | s |
| % s-char | 32.63 | 32.24 | −0.39 |
| pol. C17% | 60.31 | 60.28 | −0.03 |
| pol. N19% | 39.69 | 39.72 | 0.03 |
| (C17)/e | 0.7766 | 0.7764 | −0.0002 |
| (H18)/e | −0.63 | −0.6302 | −0.0002 |
| sp2(N20–H21) | sp2.28 | sp1.90 | s |
| % s-char | 30.5 | 32.62 | 2.12 |
| pol. N20% | 27.4 | 25.51 | −1.89 |
| pol. H21% | 72.6 | 74.49 | 1.89 |
| (N20)/e | 0.5324 | 0.505 | −0.0184 |
| (H21)/e | −0.8521 | −0.8631 | −0.011 |
| sp2(C17–O15) | sp2.28 | sp1.90 | s |
| % s-char | 31.12 | 30.36 | −0.76 |
| pol. C11% | 64.96 | 65.57 | 0.61 |
| pol. O15% | 35.04 | 34.43 | −0.61 |
| (C17)/e | 0.8059 | 0.8098 | 0.0039 |
| (O15)/e | −0.592 | −0.5868 | −0.0052 |

4.3. Vibrational analysis

MCMH dimer consists of 58 atoms and hence there are 168 modes of vibrations. The fundamental modes of vibration have been carried out using normal coordinate analysis following force field calculation with the *ab initio* method. The scaling has been carried out using multiple scaling factors. The calculated and the experimental wavenumbers of MCMH with their normal modes are 168 and 418, respectively. The corresponding potential energy distribution (PED) are represented in Table 5. Experimental spectra and simulated spectra of MCMH have been depicted in Fig. 2 and Fig. 3.

#### 4.3.1. C–H and C–C vibrations of the chromone ring

The normal modes of vibrations of the substituted phenyl rings have been assigned according to Wilson’s numbering convention [39,40]. Generally the allowed C–H stretching modes for phenyl ring are 2, 7b, 20a and 20b are expected in the range 3120–3010 cm⁻¹ [39]. The C–H stretching mode of the phenyl ring is observed at 3052 cm⁻¹ in IR spectra with weak intensity and in Raman it is observed at 3057 cm⁻¹ with medium intensity. The five C–C stretching vibrational modes are 8a, 8b, 19a, 19b, and 14, which depend more on the substituent. The degenerate mode 8a of di-substituted ring is expected to be in the range 1609–1565 cm⁻¹ and 8b extends from 1625 to 1586 cm⁻¹, with 8a smaller than 8b. The vibrational mode 8b of phenyl ring is observed as a very strong band in the Raman spectrum at 1592 cm⁻¹ and as a medium band at 1610 cm⁻¹ in the IR spectrum. The bands observed at 1318 cm⁻¹ with medium intensity in IR and at 1314 cm⁻¹ in Raman spectra have been has been assigned to normal mode 14. The normal mode 19a has been observed in the Raman spectrum at 1566 cm⁻¹. The enhanced intensity clearly shows the conjugation in the phenyl ring. Also, the bands observed at 1538 cm⁻¹ and 1537 cm⁻¹ in IR and Raman spectra have been assigned to mode 19a of the pyran ring. Due to the hyperconjugative interaction between the lone pair n1(O15) → σ*(C6–C11) predicted by the NBO analysis is well reflected in IR spectra at 1314 cm⁻¹ and in Raman spectra at 1318 cm⁻¹ showing a red shift in C–C stretching frequency.

The C–H in-plane bending modes are 3, 9a, 15, 18a, and 18b for the mono-substituted ring and modes 3, 15, 18b, and 9b for the di-substituted phenyl ring. The band observed at 1253 cm⁻¹ in IR spectra with medium intensity and a weak band observed at 1260 cm⁻¹ in Raman spectra have been assigned to C–H in-plane bending mode 3 of phenyl ring. Mode 15 coupled with oxygen shows enhanced intensity in IR spectrum at 1163 cm⁻¹. The vibrational modes are 11, 5, 17a, and 17b, which are usually observed in the region 1000–675 cm⁻¹ have been assigned to C–H out-plane bending vibrations. These modes have been identified as medium IR band at 953 cm⁻¹ (5), weak IR band at 904 cm⁻¹ (17b), weak IR band at 847 cm⁻¹ (10a), and the weak bands observed at 849 cm⁻¹ (10a) and 757 cm⁻¹ (11) in Raman spectra have been assigned to C–H out-of-plane bending vibration. In flavone derivatives, the C–C stretching vibrations are expected around 1619 cm⁻¹ [41–43]. In the IR spectra, an intense band has been observed at 1628 cm⁻¹ are predominantly localised on the C12–C13 atom of the chromone part, which is coupled with carbonyl stretching.

#### 4.3.2. C=O vibrations of the chromone ring

The most characteristic bands of the IR and Raman spectra are the carbonyl bands [44,45]. The intensity of C=O stretching frequency increases due to conjugation or due to the formation of hydrogen bonds, which leads to the intensification of Raman and IR bands[46]. In MCMH, the C=O bond is in conjugation with the pyrone ring. The carbonyl stretching frequency of flavones is observed in the range 1712–1675 cm⁻¹ [41]. The C=O stretching vibrations give rise to the characteristics in IR and Raman spectra, and the intensity of these bands may increase owing to the formation of hydrogen bonds[47]. The intense band observed at 1628 cm⁻¹ in the IR spectrum and the band at 1624 cm⁻¹ in Raman have been assigned to the C=O stretching mode. This decrease in stretching frequency is due to an increase in the p-conjugation between the ring and pyrone part. Also, the constraints induced by the intermolecular interactions results in a stronger p-electron delocalisation [48,49] resulting in the lowering of the carbonyl stretching mode, which is justified by DFT calculations. In case of pyran ring the C=O stretching frequency is expected to be in the region of 1200 cm⁻¹. From the IR spectra, the bands observed at 1218 cm⁻¹ and 1193 cm⁻¹ have been assigned to C=O stretching.

#### 4.3.3. Methylidene hydrazinecarbothioamide vibrations

In MCMH, the skeletal vibrations have been defined by C–H vibrations, C=N vibration, N–N vibrations, N–H vibrations, thioamide group vibrations and methyl group vibrations.
Vibrational assignments of MCMH dimer by normal coordinate analysis.

| ʋIR cm⁻¹ | ʋRaman cm⁻¹ | ʋ(scaled) cm⁻¹ | allIR | bIRaman | Assignments of modes with PED ≥ 10% |
|----------|--------------|----------------|-------|---------|-----------------------------------|
| 3352(w)  | –            | 3311           | 48    | 68      | vNH(99)                           |
| 3305(m)  | 3310(vw)     | 3311           | 48    | 68      | vNH(99)                           |
| –        | 3270         | 1107           | 2     | 3       | v(ops)(NH(51)) + v(ops)(NH(43))  |
| 3225(m)  | –            | 3265           | 2     | 1294    | v(ops)(NH(51)) + v(ops)(NH(43))  |
| 3146(w)  | –            | 3087           | 3     | 54      | vCH(mol1)(48) + vCH(mol1)(42)     |
| –        | 3087         | 2              | 59    | 0       | vCH(mol1)(36) + vCH(mol1)(32)     |
| 3057(m)  | –            | 3064           | 6     | 130     | vCH(mol2)(99)                      |
| –        | 3064         | 8              | 108   | 0       | vCH(mol1)(99)                      |
| 3052(w)  | –            | 3053           | 0     | 208     | vCH(mol1)(48) + vCH(mol1)(42)     |
| 3005(w)  | –            | 3048           | 1     | 204     | vCH(mol1)(86)                      |
| –        | 3048         | 1              | 258   | 0       | vCH(mol2)(98)                      |
| 3000(w)  | –            | 2993           | 19    | 84      | vMe(ops)(73) + vMe(ops)(26)        |
| –        | 2993         | 19              | 82    | 0       | vMe(ops)(73) + vMe(ops)(26)        |
| 2915(w)  | –            | 2966           | 14    | 65      | vMe(ops)(73) + vMe(ops)(26)        |
| 2848(w)  | –            | 2908           | 23    | 345     | vC(15) + vNH(13) + vCN(12)        |
| 1628(s)  | –            | 1633           | 617   | 68      | vCO(mol1)(58)                      |
| –        | 1624(m)      | 1625           | 170   | 287     | vCO(mol2)(60) + vCC(mol2)(10)      |
| –        | 1592(vs)     | 1583           | 55    | 5       | vCC(mol1)(61) + vCC(mol2)(17)      |
| 1560(s)  | –            | 1539           | 50    | 2014    | vCC(mol3)(32) + vCN(mol3)(32)      |
| 1538(s)  | –            | 1547           | 18    | 1589    | vCC(mol4)(45) + vCC(mol5)(13) + | |
| –        | 1512         | 107            | 140   | 0       | vNH(46) + vOH(hb)(26)              |
| 1510(s)  | –            | 1501           | 55    | 84      | Rad(hb)(18) + pMe(11)              |
| 1495(s)  | –            | 1479           | 31    | 61      | Rad(hb)(34) + pNH2(22) + vCN(15)   |
| 1459(s)  | –            | 1457           | 8     | 20      | vCN(15) + vCN(13) + vCN(12)       |
| 1399(m)  | –            | 1390           | 46    | 13      | pH(15) + pCH(13) + vOH(10)         |
| 1375(m)  | –            | 1372           | 111   | 2       | vCC(mol1)(45) + vCH(17) + vCN(16)  |
| 1314(s)  | –            | 1224           | 162   | 26      | vCC(mol2)(50) + vCC(mol3)(15) + vCH(mol4)(13) |
| 1253(s)  | –            | 1253           | 13    | 64      | vCC(mol3)(55) + vCH(11) + vCH(10) |
| 1233     | –            | 1235           | 156   | 2       | vCC(mol4)(17) + vCC(mol5)(11)      |
| 1223(m)  | –            | 1230           | 0     | 57      | vCO(12) + vCO(11)                  |
| 1218(s)  | –            | 1202           | 727   | 3       | vCO(16) + vCO(13)                  |
| 1193(s)  | –            | 1197           | 6     | 447     | vCO(14)                           |
| 1163(s)  | –            | 1165           | 2     | 16      | vCO(14)(31) + vCO(20) + vCC(mol2)(20) |
| –        | 1090(m)      | 1094           | 37    | 42      | vNN(37) + vCH(12)(12) + vCC(mol3)(11) |
| 1085(s)  | –            | 1075           | 160   | 177     | vNN(13) + vCC(mol1)(10)           |
| 1038(s)  | –            | 1031           | 2     | 30      | vCN(13) + vCN(mol1)(10)           |
| 1030(m)  | –            | 1030           | 145   | 2       | vCN(15) + vCN(11) + vCH(mol1)(11) |
| 953(m)   | –            | 952            | 1     | 1       | oCH(mol2)(93)                      |
| 903(m)   | –            | 906            | 2     | 1       | oCH(mol2)(69)                      |
| 849(m)   | –            | 873            | 0     | 1       | oCH(mol2)(90)                      |
| 847(m)   | –            | 865            | 0     | 1       | oCH(mol2)(74)                      |
| –        | 824(w)       | 833            | 0     | 1       | oCH(mol2)(50)                      |
| 757(s)   | –            | 757(w)         | 741   | 51      | oCH(mol2)(84)                      |
| –        | 745(m)       | 737            | 30    | 113     | vCH(mol1)(28) + vCN(12) + vCC(mol3)(10) |
| 692(m)   | –            | 666            | 31    | 1       | t OH(34)(48) + t OH(40)(31)       |
| 628(s)   | –            | 633            | 17    | 23      | t OH(34)(45) + tOC(mol1)(11)      |
| 590(m)   | –            | 562            | 19    | 1       | oCS(55) + tOH(18)(18) + t OH(34)(15) |
| 557(m)   | –            | 558            | 3     | 0       | (12)                               |
| –        | 419(w)       | 441            | 3     | 6       | oCHN(17) + oCH(12) + 2CSO(11)     |
| –        | 263(w)       | 252            | 11    | 0       | t CC(16) + tOH(12) + t OH(10)     |
| –        | 115(w)       | 85             | 2     | 0       | t CH(37)(37) + oNH(18)            |
| –        | 90(m)        | 85             | 2     | 0       | oNH(18)                           |
| –        | 66(m)        | 65             | 5     | 5       | oNH(18)(18) + t CH(15) + t NH(mol2)(12) |

4.3.3.1. C–H vibrations. In methyleneidene molecules, the most interesting and informative parameter is the C–H stretching frequency. In general, the C–H stretching modes are expected to occur in the range 3120–3010 cm⁻¹ [39]. The C–H stretching frequency in methyleneidene is found to be higher than the normal C–H stretching frequencies. The bands with weak intensity observed at 3146 cm⁻¹ in IR spectra and at 3130 cm⁻¹ in Raman spectra have been assigned to C–H stretching mode. The blue shift in wavenumber (~35 cm⁻¹) shows the spectral evidence about the intermolecular interactions that take place between n1 (O44) → σ*(C17–H18)
and n1 (O15) → σ*(C49–H50) with the stabilization energy of 1.860 kcal/mol. The presence of C–H⋯O bond bound to the cationic nitrogen atom (N+–C–H) plays an important role in molecular recognition and drug binding [50-53].

4.3.3.2. C=N vibrations. In compounds, the presence of C=N group has been characterized by the C=N stretching band in IR and Raman spectra. The C=N stretching frequency is expected to occur in the region 1680–1640 cm⁻¹ [54]. In MCMH, the C=N stretching frequencies coupled with C–C bands have been observed at 1538 cm⁻¹ in IR spectra and at 1566 cm⁻¹ in Raman with medium intensity. A significant shift in frequency is pronounced due to the phase sensitivity of the C=N group due to hydrogen-bond interactions of the neighbouring atom [55].

4.3.3.3. N–N Vibrations. In compounds containing N–N bond, the N–N stretching frequency is expected to occur as a very strong polarized band in Raman at 1111 cm⁻¹ [56]. In MCMH, the band observed with medium intensity at 1090 cm⁻¹ in Raman spectra has been assigned to N–N stretching mode. The in-plane and out-plane bending vibrations associated with N–N have been observed in the IR spectra at 557 cm⁻¹ with medium intensity and in Raman spectra at 559 cm⁻¹ with very weak intensity. These modes are found to be coupled with other modes.

4.3.3.4. N–H vibrations. The N–H stretching frequency is expected to occur in the region 3320–3280 cm⁻¹ [45]. In the IR spectra of MCMH, a broadened band has been observed at 3225 cm⁻¹ with medium intensity. This widened band with
intermolecular charge transfer interactions between n1(O15) has been evinced by the redshift in stretching frequency have been evinced by the results obtained from the optimized geometry by an increase in intermolecular interactions. This shift has been evinced from the Drug likeness properties of MCMH.

A red shift in stretching frequency (A/C0 noticed at 3352 cm-1) has been assigned to N24 H21 bond length by 0.007 Å over the isolated molecule. Also, the redshift in stretching frequency have been evinced by the intermolecular charge transfer interactions between n1(O15) → σ* (N49–H50) and n1(044) → σ* (N20–H21) in NBO basis with the stabilization energy of 7.810 kcal/mol.

4.3.3.6. Methyl vibrations. The asymmetric stretching and symmetric stretching modes of methyl group attached nitrogen atom are usually downshifted due to electronic effects and are expected near 2820 cm-1 and 2810 cm-1 for asymmetric and symmetric stretching vibrations. Also, the low force constant of the methyl group attached with amine nitrogen leads to the lowering of C–H stretching frequency in methyl group [44]. The C–S stretching mode is usually exhibited as a strong band in Raman spectra in the region of 750–500 cm-1 [60]. In the title molecule, the delocalization of the C–S bond and the vibrational coupling effect caused by the attachment of the adjacent nitrogen atom leads to the band with medium intensity at 745 cm-1 in Raman spectra, which has been assigned to C–S stretching vibration. The out-plane C–N–S bending (CNS wagging) and the in-plane bending mode(CNS rocking) coupled with other modes have been observed as a weak band at 563 cm-1 in Raman spectra and as an intense band at 558 cm-1 in IR spectra has been assigned to these modes respectively.

4.4. ADMET property analysis of MCMH

In recent years, the development of assays and computer-based (in silico) models to assess absorption, distribution, metabolism, excretion and toxicity (ADMET) properties has greatly abridged drug development time. The ability to predict these properties quickly and reliably facilitate the exclusion of compounds with potential ADMET problems, and hence help investigators prioritize which compounds to synthesize and evaluate. There is an overall of 26 constraints in ADMET statistics, which has been taken from the full text of peer-reviewed scientific journals through weekly PubMed and Google Scholar searches from 2002 to 2018 [61]. ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) results show that MCMH (+) in human intestinal

| Table 6 | Absorption, Distribution, Metabolism, Excretion, Toxicity (ADMET) properties of MCMH. |
|---------|--------------------------------------------------------------------------------------------|
| Model   | Result | Probability |
| Blood-Brain Barrier | BBB+ | 0.6848 |
| Human Intestinal Absorption | MIA+ | 0.9467 |
| Caco-2 Permeability | Caco2- | 0.5212 |
| P-glycoprotein Substrate | Non-substrate | 0.5276 |
| P-glycoprotein Inhibitor | Inhibitor | 0.5312 |
| Renal Organic Cation Transporter | Non-inhibitor | 0.9707 |
| Distribution | Subcellular localization | Mitochondria | 0.7474 |
| Metabolism | CY450 2C9 Substrate | Non-substrate | 0.6888 |
| | CY450 2D6 Substrate | Non-substrate | 0.7930 |
| | CY450 2A4 Substrate | Non-substrate | 0.6131 |
| | CY450 1A2 Inhibitor | Inhibitor | 0.9284 |
| | CY450 2C9 Inhibitor | Inhibitor | 0.5322 |
| | CY450 2D6 Inhibitor | Non-inhibitor | 0.7092 |
| | CY450 2C19 Inhibitor | Inhibitor | 0.6732 |
| | CY450 3A4 Inhibitor | Inhibitor | 0.7602 |
| | CYP Inhibitory Promiscuity | High CYP Inhibitory Promiscuity | 0.6030 |
| Excretion | Toxicity | Human Ether-a-go-related Gene Inhibition | Weak inhibitor | 0.6478 |
| | | Non-inhibitor | 0.8486 |
| | | AMES Toxicity | Non AMES toxic | 0.5460 |
| | | Carcinogens | Non-carcinogens | 0.8349 |
| | | Fish Toxicity | High FHMT | 0.9876 |
| | | Tetrahymena Pyriformis Toxicity | High TPT | 0.9980 |
| | | Honey Bee Toxicity | Low HBT | 0.5065 |
| | | Biodegradation | Not ready biodegradable | 1.0000 |
| | | Acute Oral Toxicity | III | 0.5237 |
| | | Carcinogenicity (Three-class) | Non-required | 0.5724 |

| Table 7 | Drug likeness properties of MCMH. |
|---------|----------------------------------|
| Lipinski’s rule | Drug likeness properties of MCMH | Lipinski’s rule Satisfied (Yes/No) |
| Molecular weight(<500 g/mol) | 275.41 g/mol | Yes |
| Number of HB acceptors (<10) | 5 | Yes |
| Number of HB donors (<5) | 4 | Yes |
| Lipophilicity Log P (<5) | 0.91 | Yes |
| Molar refractivity (40–130) | 74.15 | Yes |

medium intensity has been assigned to N20–H21 stretching mode. A red shift in stretching frequency (~55 cm-1) has been observed, which proves the spectral evidence of the formation of N–H · · · O intermolecular interactions. This shift has been evinced from the results obtained from the optimized geometry by an increase in N20–H21 bond length by 0.007 Å over the isolated molecule. Also, the redshift in stretching frequency have been evinced by the intermolecular charge transfer interactions between n1(O15) → σ* (N49–H50) and n1(044) → σ* (N20–H21) in NBO basis with the stabilization energy of 7.810 kcal/mol.
absorption and blood-brain barrier permeability, which suggests that the molecule is well absorbed in the human body (Table 7). Inhibition and initiation of P-glycoprotein have been described as the causes of drug-drug interactions. [62]. It has been observed that MCMH has P-glycoprotein non-inhibitor, which shows the non interacting activity of MCMH with other drugs. ADMET data show MCMH is in permissible limit [63,64]. Organic cation transporters are accountable for drug absorption and disposition in the kidney, liver, and intestine [63]. ADMET result of MCMH shows that it has been a non-inhibitor of renal organic cation transporter. The human cytochromes P450 (CYPs) are responsible for about 90% oxidative metabolic reactions. Inhibition of CYP enzymes will lead to inductive or inhibitory failure of drug metabolism [65]. A non-inhibitor and non-substrate property of MCMH supports the fact it is safe to the human liver. The Ames test is employed to test the mutagenic activity of chemical compounds. It is usually carried out to test bacteria and viruses to whether a given chemical can cause cancer [66,67]. ADMET result of MCMH is shown in Table 6 ADMET property analysis result shows MCMH has been non-ames toxic and non-carcinogenic. Human Ether-à-go-go-Related Gene (hERG) is a gene delicate to drug binding [68]. ADMET results shows MCMH have been weak inhibitor and non-inhibitor of hERG inhibition (predictor I and II). That means the MCMH molecules will well bind with SARS-CoV-2 main protease [69]. Analyzing the ADMET properties, together with their attributes and prediction, has given an idea about the pharmacokinetic properties of MCMH.

Fig. 4. Comprehensive perception of main protease and MCMH after docking, (a) secondary structure of Mpro represented by surface ribbon and MCMH is represented by ball and stick model (b) interactions of MCMH with Mpro amino acids. Bonds are in dots. MCMH (light blue) surrounding amino acids (pink) are in three letters code.
4.5. Drug likeness of MCMH

According to the rule of thumb, orally absorbed drugs should have the tendency to obey Lipinski’s rule of five. The rule was derived from an analysis of compounds from the World Drugs Index database aimed at identifying features that have been important in making a drug orally active. It has been found that the factors concerned involved numbers that are multiples of five: a molecular weight less than 500; no more than 5 hydrogen bond donor (HBD) groups; no more than 10 hydrogen bond acceptor groups; a calculated log P value less than +5 [70–75]. MCMH has been passed through Lipinski’s rule of five (Table 7) to overcome drug-likeness filter.

4.6. Docking study of MCMH with SARS-CoV-2 main protease

**In silico study**

Molecular docking has been used to acquire binding modes and binding affinities of the title molecule. Binding mode and affinity to SARS-CoV-2 main protease (Mpro) are essential for in silico drug design [76,77]. The protein structure of SARS-CoV-2 has been retrieved from protein data bank (PDB id: 5r80), which has 1.93 Å resolution. Mpro was co-crystallized with methyl 4-sulfamoylbenzoate inhibitor. The docking study has been performed by AutoDock Vina [33], which uses a Lamarckian genetic algorithm (GA) in combination with grid-based energy estimation, to check the docking accuracy of software we have performed re-docking to the co-crystal bound ligand. To find the effective inhibitors for Mpro, the 3D structure of MCMH from the Cambridge Crystallographic Data Centre (CCDC) database. The protein (Mpro) and ligand (MCMH) structures have been modified by Autodock Tools [78]. The chains of the main protease have been modified by removing water and bound ligand. Missing amino acids have been checked, and polar hydrogen has been added to the protein structure. Centre Grid box x:5.108, y:18.9177, z:-18.1863 and number of points in x,y,z dimensions are considered as 30x30x30 Å respectively and grid spacing has been taken as 0.3750 Å. Ligand has been prepared by adding Gasteiger charges, detecting root and choosing torsions from the torsion tree of Autodock Tools panel [79]. Docking procedure has been performed by using the Lamarckian genetic algorithm [80] and the results have been tabulated in Table 8.

MCMH bound to the active site of Mpro with good complementarity (Fig. 4) and formed three hydrogen bonds and four hydrophobic bonds with the Mpro. The binding energy of the nonbonding interaction is -8.8 kcal/mol. MCMH has been bound to the Cysteine-Histidine catalytic dyad (Cys-145 and His-41) by pi-sulphur interaction as well as significant interactions with the other amino acids, and the docking score (-8.8 kcal/mol) was relatively higher than most of the other inhibitor drugs targeting Mpro [81] and hence proves its ability to bind with the SARS-CoV-2 main protease. The pi-sulphur interaction taken place pi-electron cloud of aromatic ring of amino acid histidine 41, Cysteine145 acts as the aromatic pi-motif and interacted with lone pair of the electron cloud of Sulphur atom of MCMH (Fig. 4). The pi-sulphur interaction has been probed in biological and model systems and it has been estimated to contribute between 0.5 and 2 kcal/mol to binding stability [82]. All these results present a clear view that MCMH can irreversibly interact with Mpro. The catalytic dyad composed of Histidine 41 and Cysteine 145 is a set of amino acids that can be found in the active site of most SARS-CoV-2 main proteases, plays an essential role in drug binding [83]. MCMH bound both to Histidine 41 and Cysteine 145 (Fig. 4 and Table 8) claims to be an excellent antiviral drug.

5. Conclusion

The compound MCMH has been characterized by FT-IR, FT-Raman spectroscopic techniques at B3LYP/6-311++G(d,p) level using DFT method and the complete vibrational analysis has been carried out. The presence of the intermolecular and intramolecular hydrogen bonds has been analyzed using NBO analysis. The transfer of electrons from the lone pair oxygen to the antibonding orbital of N–H and C–H bond evinces the formation of two hydrogen bonds that brings about most interesting biological properties. The occurrence of N–H -O intermolecular interactions and the conspicuous red shifting in the wavenumber have been authenticated by the increase in N–H bond length and an increase in the electron density in the antibonding orbitals. Also, the presence of C–H -O intermolecular interactions and the blue shifting in the wavenumber have been authenticated by the decrease in C–H bond length and the occupancy of the interacting NBOs. The existence of N–H -O and C–H -O intermolecular hydrogen bonding plays an important role in imparting stability to protein structure. Drug likeness predicts the oral activity and ADMET property analysis gives an idea about the pharmacokinetic properties of the title molecule. The binding energy of -8.8 kcal/mol and the binding affinity of MCMH with Histidine 41 and Cysteine 145 with nonbonding interactions present a clear view that MCMH can irreversibly interact with SARS-CoV-2 protease and claims to be an excellent antiviral inhibitor.

Credit authorship contribution statement

S.J. Jenepha Mary: Conceptualization, Data curation, Investigation, Software, Validation. Sayantan Pradhan: Data curation. C. James: Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.saa.2020.119388.

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