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Experimental and computational study of naphthalimide derivatives: Synthesis, optical, nonlinear optical and antiviral properties

Santosh Kumar a, b, Shabbir Muhammad c, Saleh S. Alarfaji d, Sanghyun Yoon b, Minse Kim b, Keechul Youm b, Muhammad Khalid e, Aijaz Rasool Chaudhry f, g, Joonseok Koh a, b, *  

a Division of Chemical Engineering, Konkuk University, Seoul 05029, Republic of Korea  
b Department of Organic and Nano System Engineering, Konkuk University, Seoul 05029, Republic of Korea  
c Department of Physics, College of Science, King Khalid University, P.O. Box 9004, Abha 61413, Saudi Arabia  
d Department of Chemistry, College of Science, King Khalid University, P.O. Box 9004, Abha 61413, Saudi Arabia  
e Department of Chemistry, Khwaja Fareed University of Engineering & Information Technology, Rahim Yar Khan 64200, Pakistan  
f Deanship of Scientific Research, University of Bisha, P.O. Box 551, Bisha 61922, Saudi Arabia  
g Department of Physics, College of Science, University of Bisha, P.O. Box 551, Bisha 61922, Saudi Arabia

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ABSTRACT

The nonlinear optical (NLO) and antiviral properties of naphthalimide Schiff base compounds (5a–c) were experimentally and computationally investigated. The synthesized compounds (5a–c) were successfully characterized via UV–Vis, FTIR, 1H NMR, fluorescence spectroscopy, and elemental analysis. The calculated average third-order NLO polarizabilities (˂γ˃) of 5a, 5b, and 5c were found to be 5, 9, and 21 times greater than the ˂γ˃ amplitude of p-NA, respectively. The computed results revealed the potential of the synthesized compounds for NLO applications. Additionally, molecular docking studies of the synthesized compounds with two crucial SARS-CoV-2 proteins were performed to examine their biochemical properties. Compound 5c exhibited a higher binding affinity with the spike protein compared to that with MPα+O. The results obtained herein indicate the potential of the synthesized naphthalimide derivatives for optoelectronic and drug design applications.

1. Introduction

The organic class of materials with their optical and nonlinear optical (NLO) response properties are the front runner candidates for laser frequency conversion, telecommunications and digital data storage [1]. In addition to optical and NLO applications, the naphthalimides are an important class of organic molecules that can be employed as fundamental scaffolds, for example, in anti-protozoal, anti-inflammatory, antiviral, and antitumor agents [2]. The naphthalimide class possesses a tricyclic planar ring system, which plays a crucial role in its intercalation with DNA to perturb cellular events; the substitution pattern of the molecule leads to numerous other applications as well [2]. The naphthalimide derivatives (5a–c) designed in the present study not only possess a
tricyclic planar ring system but also contain oxygen atoms of a dione for possible H-bond acceptors. Therefore, the antiviral activity of these compounds against SARS-CoV-2, which is currently devastating the communities globally, was examined. Recent investigations on docking have proved its effectiveness in discovering several therapeutic drug targets. The SARS-CoV-2 virus, which causes COVID-19, has devastated the global economy, and there is a dire need to discover a therapeutic drug. Unlike the conventional drug discovery techniques, molecular docking is an important technique for designing, evaluating, and comparing novel drugs and also for determining the factors that are critical in vital pharmacological interactions [3].

In connection with our research on the naphthalimide moiety [4,5], Schiff bases have been considered by our group for facilitating electro-optical and biomolecular applications. Therefore, 2-((4-hydroxybenzylidene)amino)–1H-benzo[de]isoquinoline-1,3(2H)-dione (5a), 2-((4-(dimethylamino)benzylidene)amino)–1H-benzo[de]isoquinoline-1,3(2H)-dione (5b), and 2-((4-(diphenylamino)benzylidene)amino)–1H-benzo[de]isoquinoline-1,3(2H)-dione (5c) were synthesized and evaluated for electro-optical and biomolecular applications herein. The present study designed to not only synthesize the naphthalimide derivatives (5a-c) but also to apply state-of-the-art computational techniques including quantum chemical and molecular docking techniques to investigate their optical, NLO and antiviral properties. It is expected through the use of dual approach consisting of experimental and computational techniques.

2. Experimental details

2.1. Materials and method

1,8-Naphthalic anhydride, 4-hydroxybenzaldehyde, 4-dimethylaminobenzaldehyde, 4-(diphenylamine)benzaldehyde, glacial acetic acid, and ethanol were purchased from Sigma-Aldrich. All the chemicals were used without further purification. 1H nuclear magnetic resonance (NMR) spectra were recorded using a Bruker Avance (600 MHz) Fourier transform NMR spectrometer with tetramethylsilane as an internal reference and DMSO-d6. Mass spectroscopy was performed using a Bruker amazon SL setup with the ion trap method. Elemental analyses were performed using an EA 2000 apparatus (Thermo Finnigan). Melting points were measured using a BUCHI setup (Switzerland). Fourier transform infrared (FTIR) spectra were obtained using a JASCO FTIR 4100 spectrophotometer equipped with an attenuated total reflection-infrared spectroscope. UV–vis absorption and fluorescence spectra were recorded using an Agilent 8453 spectrophotometer (USA) and a SCINCO FS-2 fluorescence spectrometer, respectively.

2.2. Synthesis

2.2.1. Synthesis of 2-amino-1H-benzo[de]isoquinoline-1,3(2H)-dione (compound 3)

A mixture of 9 mmol of 1,8-naphthalic anhydride (1), 18 mmol of hydrazine hydrate (2), and 30 mL of dimethylformamide (DMF) was added to a 100-mL round-bottomed flask and refluxed for 20 h. The reaction mixture was mixed by a magnetic stirrer. The resulting product was cooled overnight in a refrigerator. Subsequently, the solid product was filtered and dried. Yield 68%. M.P. = 262–267 °C. Elemental analysis: Calculated for C12H18N2O2 (mol wt. = 236.31) C= 72.15, H= 3.86. The resulting solid was filtered and washed with ethanol. The solid compound was dried at room temperature for 1 d. Yield 80%. M.P. = 236–239 °C. Elemental analysis: Calculated for C10H12N2O3 (mol wt. = 316.31) C= 72.15, H= 3.82, N= 8.66. The reaction mixture was mixed by a magnetic stirrer. The resulting solid was filtered and washed with ethanol. The solid compound was dried at room temperature for 1 d. Yield 84%. M.P. = 234–236 °C. Elemental analysis: Calculated for C12H17N2O2 (mol wt. = 243.38) C= 73.45, H= 4.99, N= 12.24. The reaction mixture was mixed by a magnetic stirrer. The resulting solid was filtered and washed with ethanol. The solid compound was dried at room temperature for 1 d. Yield 86%. M.P. = 234–237 °C. Elemental analysis: calculated for C13H17N2O2 (mol wt. = 245.32).
1119, 1071, 839, 766, 693; $^1$H NMR (500 MHz, DMSO-d$_6$) $\delta$ 9.73 (s, N = CH, 1 H), 8.53–8.49 (d, 1H, aromatic), 7.88 (d, 1H, aromatic), 7.75 (d, 1H, aromatic), 7.38 (d, 1H, aromatic), 7.19 (d, 1H, aromatic), 7.15 (m, 1H, aromatic), 6.85 (d, 1H, aromatic), 6.83 (m, 1H, aromatic).

2.3. Computational details

In the present study, Gaussian 16 suite of programs [7] was used for the quantum chemical calculations while a grid-based method through AutoDock Vina [8] is applied for docking of the flexible ligands over rigid proteins. The geometric structures of compounds 5a, 5b, and 5c were optimized using the M06 method and the 6–311 G** basis set. The reliability of M06 functional was already tested in our previous studies [9,10]. Frequency calculations were performed to investigate possible local minima of potential energy surfaces. The absence of a negative frequency indicated the presence of optimized structures with the lowest energy for compounds 5a, 5b, and 5c. Further details about quantum chemical methodology is seen from our previous reports [11,12] while the working equations used in the above-mentioned calculations are provided in the supporting information.

Fig. 1. Synthesis of the naphthalimide derivatives, 5a–c.
For molecular docking analysis of synthesized ligands with SARS-CoV-2, its X-ray crystal structures of the spike [PDB ID: 7JVA] and main protease (MPR®) [PDB ID: 6LU7] proteins were retrieved from a free online protein data bank [www.rcsb.org]. The details about protein preparation methodology along with grid dimensions are provided in Supporting information.

3. Results and discussion

Compounds 5a, 5b, and 5c were synthesized by the Schiff-base condensation reaction (Fig. 1). The formation of the synthesized Schiff bases was confirmed through spectral analyses, such as FTIR NMR spectroscopy, mass spectroscopy, and CHN analysis. All the Schiff-base synthesized compounds exhibited FTIR absorption bands corresponding to amide C–O stretching and C–N stretching in the ranges of 1661–1773 cm⁻¹ and 1575–1584 cm⁻¹, respectively. The ¹H NMR (600 MHz, DMSO-d₆) spectra of the Schiff-base synthesized compounds showed chemical shift values of δ ppm 9.6 (s, N = CH, 1H).

3.1. Optical properties

3.1.1. UV–vis spectroscopy

The UV–vis absorption spectra of 5a, 5b, and 5c in ethanol are shown in Fig. 2(a). The absorption peaks of the UV–vis spectra of 5a and 5b in ethanol are visible at 339 nm and 341 nm, respectively, whereas that of 5c in ethanol appears at 353 nm because of the electron-donating diphenylamine group (Fig. 2a). The UV–vis spectra of 5a, 5b, and 5c were computationally evaluated using the TD-M06/6-311G** level of theory, as shown in Fig. 2(b). The evaluated maximum absorption wavelengths of 5a, 5b, and 5c correspond to approximately 334, 337, and 373 nm, respectively. The computationally calculated wavelengths are slightly smaller than the corresponding experimental values, possibly because of the lack of electron correlation and long-range corrections in hybrid functionals, especially in transitions that involve π–π* transitions [4,13,14]. However, the calculated UV–vis spectra of 5a, 5b, and 5c are in reasonable agreement with those of their experimental counterparts. A comparison of the absorption spectra of 5a, 5b, and 5c shows a

![Fig. 2](image-url)

(a) Experimental

(b) Calculated

Fig. 2. (a) UV–vis spectra of the synthesized naphthalimide derivatives (5a, 5b, and 5c) obtained via experiments in ethanol and (b) calculations using the TD-M06/6–311G** method.
red shift among the absorption wavelengths, which is due to the greater donor effect of the N(CH$_3$)$_2$ and N(C$_6$H$_5$)$_2$ groups in 5b and 5c, respectively.

3.1.2. Fluorescent properties

The fluorescence emission spectra of the naphthalimide derivatives (5a–c) in ethanol at an excitation wavelength of 320 nm are shown in Fig. 3(a). The fluorescence emission spectra of 5a, 5b, and 5c in ethanol appear to peak at 381, 389, and 420 nm, respectively. The fluorescence spectrum of 5c is red-shifted compared to that of 5a and 5b [15]. Furthermore, the fluorescence emission spectra of 5a, 5b, and 5c were calculated by optimizing the geometries at their respective excited states using the TD-M06/6-311G** method and are shown in Fig. 3(b). The computationally calculated absorption spectra of 5a, 5b, and 5c appear to peak at approximately 364, 380, and 400 nm, respectively, which are also in reasonable agreement with their respective experimental values. The close resemblance of both the absorption and emission spectra of the investigated compounds was encouraging in terms of employing the adopted methodology for further optical and NLO calculations.

3.2. Linear and NLO polarizabilities

3.2.1. Linear polarizability ($\alpha$)

The characteristic linear response of molecules can be described by linear polarizability. Consequently, determining the effect of structural modification on linear polarizability is crucial. The isotropic ($\alpha_{\text{iso}}$) and anisotropic ($\alpha_{\text{aniso}}$) polarizabilities along with their individual tensor components are listed in Table 1. A comparison between the isotropic ($\alpha_{\text{iso}}$) and anisotropic ($\alpha_{\text{aniso}}$) polarizabilities of all the compounds is depicted in Fig. 4. A careful analysis of Fig. 4 suggest that a small difference can be observed between the isotropic and anisotropic linear polarizabilities of 5a and 5b, which indicates that the direction of the applied electric field is not important for these two compounds. However, this difference is significant for 5c (~16.97 × 10$^{-24}$ esu), which indicates that the direction of the

![Fig. 3. Fluorescence emission spectra of the synthesized naphthalimide derivatives (5a, 5b, and 5c) obtained via (a) experiments at an excitation wavelength of 320 nm and (b) computation using the TD-M06/6-311G** method.](image-url)
applied field is significant for the linear polarizability of $5c$.

### 3.2.2. First hyperpolarizability ($\beta$)

The first and second hyperpolarizabilities define the NLO response of materials. The average static NLO first-hyperpolarizabilities ($\beta_{//}$) of all the compounds with their individual tensor components computed at the M06/6-311G** level of theory is listed in Table 2. An increasing trend of the first hyperpolarizability ($5a < 5b < 5c$) is observed, with corresponding $\beta_{//}$ amplitudes of $15.72 \times 10^{-24}$, $43.53 \times 10^{-24}$, and $65.11 \times 10^{-24}$ esu, respectively. Among all the compounds, $5c$ exhibits a higher amplitude compared to that of $5a$ and $5b$; the $\beta_{//}$ amplitude of $5c$ appears to be ~4 and ~2 times higher than that of $5a$ and $5b$, respectively. The considerable improvement in $\beta_{//}$ of $5c$ can be attributed to the increased electron-donating strength of the donor moiety and the suitable configuration of donor–acceptor fragments. Furthermore, Table 2 indicates that the diagonal component ($\beta_{zz}$) has a higher value of the first hyperpolarizability than the other components. The higher amplitude of $\beta_{//}$ along the $z$-axis indicates that it is the

![Isotropic and anisotropic polarizability ($\alpha$) of compounds $5a$, $5b$, and $5c$ at the M06/6-311G** level of theory.](image)

| Component of $\alpha$        | $5a$     | $5b$     | $5c$     |
|------------------------------|----------|----------|----------|
| $\alpha_{xx}$                | 43.44    | 56.17    | 79.51    |
| $\alpha_{xy}$                | –15.83   | –23.41   | –24.94   |
| $\alpha_{yz}$                | 48.95    | 48.19    | 78.65    |
| $\alpha_{zz}$                | 19.09    | 16.91    | –27.14   |
| $\alpha_{xx}$                | –2.07    | –0.08    | –5.15    |
| $\alpha_{xy}$                | 56.68    | 70.30    | 87.99    |
| $\alpha_{xz}$                | 49.69    | 58.22    | 82.05    |
| $\alpha_{yz}$                | 44.62    | 53.66    | 65.08    |

| $\beta$                      | $5a$     | $5b$     | $5c$     |
|------------------------------|----------|----------|----------|
| $\beta_{xxx}$                | 1.90     | –22.75   | –24.41   |
| $\beta_{xy}$                 | –0.10    | 20.38    | 12.96    |
| $\beta_{yy}$                 | 5.15     | –22.06   | –9.62    |
| $\beta_{yy}$                 | –13.87   | 32.68    | 6.90     |
| $\beta_{zz}$                 | 5.77     | –11.19   | 36.39    |
| $\beta_{zx}$                 | –1.70    | 7.15     | 18.18    |
| $\beta_{xy}$                 | 4.62     | –2.40    | 12.08    |
| $\beta_{xz}$                 | 6.18     | –3.21    | 35.88    |
| $\beta_{yz}$                 | –1.13    | –0.17    | 18.52    |
| $\beta_{xz}$                 | 6.44     | 0.95     | 25.13    |
| $\beta_{yy}$                 | 15.72    | 43.53    | 65.11    |
| $\beta_{zz}$                 | 16.64    | 60.54    | 128.3    |

* Wavelength, $\omega = 1064$ nm; * Average static ($\beta_{//}$) amplitude of para-nitroaniline (para-NA) = $6.38 \times 10^{-30}$ esu (calculated at the M06/6-311G** level of theory).
principal axis of charge transfer, which implies that the designed molecules are of the push–pull type. The first hyperpolarizability of para-nitroaniline (p-NA), a prototype push–pull NLO molecule, was also computed herein using the M06 functional and 6-113G** basis set for comparison. A comparison of the amplitude of first hyperpolarizability of p-NA (6.38 $\times$ 10$^{-30}$ esu) with that of the synthesized compounds indicates that 5a, 5b, and 5c exhibit higher values of first hyperpolarizabilities (−2, −7, and −10 times higher than that of p-NA, respectively); this result hints at the potential of the designed molecules for second-order NLO applications. Furthermore, the frequency-dependent first hyperpolarizability values for second-harmonic generation, $\beta$ (−2ω060,60), are also listed in Table 2. The $\beta$ (−2ω060,60) amplitudes are slightly larger than the static amplitudes and are free of any abnormal resonance enhancement effects.

3.2.3. Second hyperpolarizability ($\gamma$)

The second hyperpolarizability or third-order nonlinear polarizability is typically regarded as an infrequently observed NLO response and is also considered an indicator of the presence of two-photon absorption in materials. Unlike the first hyperpolarizability, the second hyperpolarizability is independent of crystallographic symmetry and practically easy to achieve. The second hyperpolarizability of all investigated compounds along with their tensor components are listed in Table 3, and the corresponding average $\langle\gamma\rangle$ amplitudes of compounds 5a–c are graphically depicted in Fig. 5. Table 3 indicates that among the tensor components, $\gamma_{zzzz}$ is relatively dominant and reasonably exhibits greater values in contrast to the other tensor components, possibly because of the considerable charge transfer along the $z$-axis. The $\gamma_{zzzz}$ amplitudes of 5a, 5b, and 5c are 107.9 $\times$ 10$^{-36}$, 360.7 $\times$ 10$^{-36}$, and 568.2 $\times$ 10$^{-36}$ esu, respectively. The $\gamma$ amplitude of second-order hyperpolarizability for the compounds conforms to the following trend: 5a < 5b < 5c. Similar to the linear and first-order hyperpolarizability, compound 5c also exhibits an enhanced $\gamma$ amplitude as compared to that of 5a and 5b. The $\gamma$ amplitude of 5c (568.2 $\times$ 10$^{-36}$ esu) is ~9 and ~18 times greater than that of 5a and 5b, respectively. This is due to the replacement of hydroxyl and dimethylamine moieties with diphenylamine groups in the donor fragment; the higher $\pi$-conjugation and greater electron donating strength in these groups enable a promising donor–acceptor molecular configuration in 5c. The $\gamma$ amplitude of all the studied compounds was compared with that of p-NA. The average third-order nonlinear polarizability, $\langle\gamma\rangle$, of p-NA is evaluated to be 25.45 $\times$ 10$^{-36}$ esu, which indicates that all the compounds synthesized herein exhibit larger $\gamma$ amplitudes compared to those of p-NA. Compounds 5a, 5b, and 5c exhibit $\gamma$ amplitudes of 122.0 $\times$ 10$^{-36}$, 225.7 $\times$ 10$^{-36}$, and 527.7 $\times$ 10$^{-36}$ esu, respectively, which are 5, 9, and 21 times greater than those of p-NA also calculated at the M06/6-113G** level of theory; this hints at the decent potential of the naphthalimide derivatives for NLO applications. The $\gamma$ amplitudes of compounds 5a–c are also found better than the $\langle\gamma\rangle$ amplitudes of our several previously calculated compounds [16,17].

3.2.4. The origin of NLO polarizabilities

Time-dependent density functional theory (TD-DFT) calculations can be used to trace the origin of the significant NLO response in the synthesized compounds. Simple three-state approximations based on the perturbative formula were considered, at least for the static longitudinal $\gamma_1$ ($\gamma_{zzzz}$) component, as follows:

$$\gamma_1 = 24 \left[ \frac{\mu_{zz}^4 \Delta E_{\text{zz}}}{\Delta E_{\text{zz}}} - \frac{\mu_{nn}^4 \Delta E_{\text{nn}}}{\Delta E_{\text{nn}}} + \sum_{m=n,m} \frac{\mu_{nm}^2 \mu_{mm}^2 \Delta E_{\text{mm}}}{\Delta E_{\text{nn}}} \right]$$

where $\mu_{gg}$, $\Delta E$, and $\Delta \mu$ represent the transition moment, transition energy, and changes in the dipole moment related to the transition from the ground ($|g\rangle$) to the crucial excited states ($|n\rangle$) along the ICT axis ($z$-axis), and $\mu_{nm}$ represents the transition moment between the $m$th and $n$th excited states. Spectroscopic variables were computed using the TD-DFT method with the M06 functional and 6-113G** basis set. The cubic transition-energy term in the denominator in equation indicates its significance in modulating the NLO response; a lower transition energy is expected to result in a higher $\gamma$ amplitude. The computed values of $\mu_{gg}$ and $\Delta E$ for all the compounds are listed in Table S1 of Supporting information. A comparison of the transition moments and transition energies of all the compounds suggests that 5c has a larger $\gamma_{zzzz}$ amplitude than that of 5a and 5b, presumably because of its low transition energy (3.325 eV) and high transition moment (3.51), as shown in Table S1 of Supporting information. A similar comparison between the first hyperpolarizability and transition energy is depicted in Fig. 5.

| $\gamma$ | 5a | 5b | 5c |
|---|---|---|---|
| $\gamma_{zzzz}$ | 77.20 | 183.3 | 484.0 |
| $\gamma_{yyyy}$ | 65.65 | 30.08 | 135.0 |
| $\gamma_{zzzz}$ | 107.9 | 360.7 | 568.2 |
| $\gamma_{yyyy}$ | 58.99 | 205.0 | 183.1 |
| $\gamma_{zzzz}$ | 69.43 | 40.34 | 419.7 |
| $\gamma_{yyyy}$ | 51.24 | 31.88 | 123.1 |
| $\langle\gamma\rangle$ | 122.0 | 225.7 | 527.7 |
| $\gamma_1$ (−2ω060,60,0)$^a$ | 150.3 | 360.9 | 1166 |

$^a$ Wavelength, $\omega = 1064$ nm; $^c$ Average static $\langle\gamma\rangle$ amplitude for para-nitroaniline (p-NA) = 25.45 $\times$ 10$^{-36}$ esu (calculated at the M06/6-311G** level of theory).
gastrointestinal (GI) absorption and blood can potentially act as decent drug candidates. Furthermore, a boiled-egg plot was constructed using the SwissADME tool to confirm the follow the rule of five without any violation, except for compound toxicity level, good absorption, and oral bioavailability. The drug likeness check of synthesized compounds, as potential drugs. Any compound that has two or fewer than two violations of the Lipinski

Nonetheless, they are based on rigorous literature and can provide a rough estimate for the real-time use of the synthesized compounds accessible tool [21]. It is important to note these toxicity and drug-likeness parameters are strictly theoretical and predictive.

3.3. The ADME properties and drug-likeness of the synthesized compounds 5a-c

Naphthalimides are an important class of organic molecules that are used for various biological activities. Therefore, it is crucial to examine their antiviral activity against SARS-CoV-2, which is devastating communities globally. Recent docking studies have proven to be effective in discovering several therapeutic drug targets [18]. Therefore, docking studies for the synthesized naphthalimide derivatives were performed herein along these lines. The main protease (M$^\text{PRO}$) and spike proteins of SARS-CoV-2, which are vital for replication and attachment of the virus in the human body, were selected for the docking studies. The docking results and inhibition constants of the compounds 5a, 5b, and 5c with both the M$^\text{PRO}$ and spike proteins are listed in Table 4.

A careful analysis of Table 4 reveals that all three compounds exhibit reasonable interaction energies, because a higher negative binding interaction energy implies a greater binding probability of the ligand with the protein. The binding interaction energies of 5a, 5b, and 5c are approximately $-7.9$, $-6.7$, and $-8.3$, which are reasonably good as compared with previous investigations with same methodology [19,20]. The intermolecular interactions of 5c with both proteins are shown in Fig. 7(a)–(c). The interactions of the optimally docked ligands based on binding affinity, that is, compound 5c with both proteins, are listed in Table 5, which includes H-bond interactions, electrostatic attraction, hydrophobic interactions, and other interactions and bond distances. The interactions of compound 5c with five residues of the spike protein, including one PHE515H-bond interaction, two electrostatic interactions, and two other hydrophobic interactions, are particularly noteworthy. Similarly, compound 5c reacts with nine residues of M$^\text{PRO}$, including four interactions with LYS137, ASP197, and H bonds, one electrostatic interaction, and four other hydrophobic interactions. The hydrophobic and H-bond interactions, which are exhibited by compound 5c, are considered important factors for potential inhibitory ligands. Additionally, the total density surfaces of both the M$^\text{PRO}$ and spike proteins with the docked compound 5c are shown in Fig. S1 and Fig. S2, respectively, in Supporting information. Three types of interactions, that is, hydrogen bonding, hydrophobicity, and ionizability, were considered on the density surfaces, which show the interactions and orientations of compound 5c with the respective sites of both the M$^\text{PRO}$ and spike proteins. For instance, Fig. S1 of Supporting information indicates that the isoquinolinodione moiety of 5c is more oriented toward hydrophilic residues, presumably owing to the presence of partial charges of carbonyl groups.

3.3.1. The ADME properties and drug-likeness of the synthesized compounds 5a–c

The toxicity and drug-likeness of the synthesized compounds were subsequently predicted using SwissADME a web-based freely accessible tool [21]. It is important to note these toxicity and drug-likeness parameters are strictly theoretical and predictive. Nonetheless, they are based on rigorous literature and can provide a rough estimate for the real-time use of the synthesized compounds as potential drugs. Any compound that has two or fewer than two violations of the Lipinski’s rule of five is considered to have a low toxicity level, good absorption, and oral bioavailability. The drug likeness check of synthesized compounds, 5a–c exhibits that all compounds possess low toxicity, good oral bioavailability, and absorption (see Table S2 of Supporting information). These compounds follow the rule of five without any violation, except for compound 5c, which exhibits one violation [22]. Therefore, these compounds can potentially act as decent drug candidates. Furthermore, a boiled-egg plot was constructed using the SwissADME tool to confirm the gastrointestinal (GI) absorption and blood–brain barrier (BBB) permeability of all three compounds as shown in Fig. S3 of Supporting
4. Conclusions

Naphthalimide derivatives were successfully synthesized via a condensation reaction. The formation of the synthesized Schiff-base compounds was confirmed by spectral analysis. The experimental and calculated UV–Vis and fluorescence spectra of compound 5c were red-shifted compared to those of compounds 5a and 5b. The computation of their nonlinear optical (NLO) properties especially third-order NLO response ($\gamma$) of 5a, 5b, and 5c were calculated to be $122.0 \times 10^{-36}$, $225.7 \times 10^{-36}$ and $527.7 \times 10^{-36}$ esu, respectively, which are reasonably large as compared with standard p-NA molecule. From the viewpoint of antiviral activity, the binding energies of compounds 5a, 5b, and 5c were estimated to be $-7.9$, $-6.7$, and $-8.3$, and $-7.4$, $-6.8$, and $-8.6$ kcal/mol with the M$^\text{PRO}$ and spike proteins of the SARS-CoV-2 virus, respectively. Compound 5c exhibited a higher binding affinity with the spike protein compared to that with M$^\text{PRO}$. The drug likeness was also predicted and all compounds are found good drug candidates. Therefore, the

| Compound | Protein | Interaction energy (kcal/mol) | Inhibition constant ($K_i$ (µM)) | Protein | Interaction energy (kcal/mol) | Inhibition constant ($K_i$ (µM)) |
|----------|---------|-----------------------------|---------------------------------|---------|-----------------------------|---------------------------------|
| 5a       | M$^\text{PRO}$ | $-7.9$                       | 1.54                            | Spike   | $-7.4$                       | 3.58                            |
| 5b       | M$^\text{PRO}$ | $-6.7$                       | 11.78                           | Spike   | $-6.8$                       | 9.94                            |
| 5c       | M$^\text{PRO}$ | $-8.3$                       | 0.78                            | Spike   | $-8.6$                       | 0.47                            |

Table 4
Bonding interaction energies and inhibition constants of synthesized compounds 5a, 5b, and 5c with respect to the M$^\text{PRO}$ and spike proteins of SARS-CoV-2.

Table 5
Details of intermolecular interactions including interaction distances (Å) and the interacting amino acid residues of the M$^\text{PRO}$ and spike proteins with 5c.

![Fig. 6](image-url) (a) Interactions of compound 5c with the M$^\text{PRO}$ whole protein shown via (b) a 3D structure focus box, and a (c) 2D interaction diagram.

information. This plot confirms that no compound is present beyond the limits of GI absorption and BBB permeability [22], which shows another factor to use the synthesized compounds as good drug candidates.
naphthalimide derivatives synthesized herein can incite scientific curiosity in the optical material and drug design areas.

CRediT authorship contribution statement

SK and SM conceptualized and wrote the original draft of the manuscript. SSA, SY, MK, KY, MK, and ARC supported the formal analysis. All authors have contributed to the interpretation of the results. JK resources reviewed and edited the manuscript draft, which was approved by all authors.

Declaration of Competing Interest

The author declares that there is no competitive or financial interest known to influence the work reported in this paper

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ijleo.2021.167748.

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