Naphthalene-based bis-\(N\)-salicylidene aniline dyes: Crystal structures, Hirshfeld surface analysis, computational study and molecular docking with the SARS-CoV-2 proteins

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Abstract
In this work, we report structural and computational studies of a series of naphthalene-based bis-\(N\)-salicylidene aniline dyes, namely \(N,N'\)-bis-salicylidene-1,5-diaminonaphthalene (1), \(N,N'\)-bis(3-hydroxysalicylidene)-1,5-diaminonaphthalene (2) and \(N,N'\)-bis(3-methoxysalicylidene)-1,5-diaminonaphthalene (3). For 3, two polymorphs are known, namely 3\(\text{red}\) and 3\(\text{yellow}\). Both polymorphs of 3 were analyzed and discussed. All the molecules adopt an enol-imine tautomer, stabilized by two intramolecular O–H⋯N hydrogen bonds. The structure of 2 is further stabilized by a couple of additional O–H⋯O hydrogen bonds and by intermolecular O–H⋯O interactions, yielding a 1D zig-zag supramolecular chain. Molecules of 2, 3\(\text{red}\) and 3\(\text{yellow}\) are interlinked through intermolecular C–H⋯\(\pi\) interactions, while the crystal packing of 1 and 2 is also described by intermolecular \(\pi\)⋯\(\pi\) interactions. More than 90\% of the total Hirshfeld surface area for all the discussed molecules is occupied by H⋯H, H⋯C, H⋯O and C⋯C contacts. The polymorphs 3\(\text{red}\) and 3\(\text{yellow}\), despite being chemically the same, differ geometrically, thus yielding remarkably different Hirshfeld surfaces. The Hirshfeld surface of 3\(\text{yellow}\) is very similar to that of 2. All structures are mainly characterized by the dispersion energy framework followed by the less significant electrostatic energy framework contribution. Molecular docking studies were employed to inspect the effect of 1–3 on the SARS-CoV-2 protein targets. The docking analysis revealed that the dye 2 showed the best binding energies toward Papain-like protease (PLpro, \(-10.40\ \text{kcal/mol}\)), nonstructural protein 14 (nsp14 (N7-MTase), \(-10.10\ \text{kcal/mol}\)), RdRp-RTP (\(-9.70\ \text{kcal/mol}\)) and nonstructural protein 3 (nsp3\_range 207-379-MES, \(-9.30\ \text{kcal/mol}\)). The obtained results can give an insight into chemical and biological activities of the studied molecules that could aid in designing of potent reagents SARS-CoV-2.

Keywords \(N\)-salicylidene aniline dye · Crystal structure · Hirshfeld surface analysis · Molecular docking · SARS-CoV-2 proteins

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Introduction

Since Schiff bases $R^1R^2C=NR^3$ ($R^3 \neq H$) were first discovered more than one and a half century ago [1], this type of compounds has, most likely, become the most widely used ligands in chemistry. Schiff bases are readily obtained through condensation of the NH$_2$ group (primary amine) with the C(H)=O group (aldehyde), yielding secondary aldimes $R^1R^2C=NR$ ($R^1$ or $R^2 = H$, $R^3 \neq H$), or the $R^1R^2C=O$ group (ketone), yielding secondary ketimines $R^1R^2C=NR^3$ ($R^3 \neq H$). The former type is also known as azomethines.

One of the most famous class of Schiff bases is the so-called anils ($N$-phenyl imines), which are produced from aniline or its derivatives [2, 3]. Notably, salicylaldehyde-derived Schiff bases, due to the ortho-situated OH group, is one of the most fascinating family. This OH group dictates the possible tautomerization between the enol-imine and keto-enamine isomers, of which the latter one can exhibit either the cis- or trans-isomers (Scheme 1) [4–13]. Furthermore, this type of Schiff bases is well recognized for their broad color panel, varying from colorless through yellow to red, which is caused by the mentioned isomers (Scheme 1). The formation of a certain isomer, thus yielding different colors, can be dictated by stimuli such as irradiation, temperature and solvent. [4–13]. Nowadays, this feature becomes of great importance for optical devices [14] and molecular switches displaying (ir)reversible stimuli-induced color change in solid state [15]. In this regard, the salicylaldehyde-derived Schiff bases play a pivotal role due to their ease of synthesis, modification and a rich variety of optical properties, also in the solid state.

Solid-state optical properties (chromic properties) of the salicylaldehyde-derived Schiff bases are, obviously, dictated by their crystal structure, viz. geometry of a molecule, crystal packing, available free space around the switching unit, flexibility of the nearby environment, etc. [4–13]; thus, the so-called non-covalent interactions formed by this type of molecules become of great importance and therefore are worth to be studied in detail. This becomes even more important for the salicylaldehyde-derived Schiff bases with two or more functional fragments, i.e., obtained from polyamines and/or polyaldehydes.

In this work, in continuation of our ongoing interest to the salicylaldehyde-derived Schiff bases [16–26], we have directed our attention to an extremely rare family of naphthalene-based bis-$N$-salicylidene aniline dyes. Particularly, three dyes, namely $N,N'$-bis-salicylidene-1,5-diaminonaphthalene (1) [27], $N,N'$-bis(3-hydroxysalicylidene)-1,5-diaminonaphthalene (2) [28] and $N,N'$-bis(3-methoxysalicylidene)-1,5-diaminonaphthalene (3) (Fig. 1) [23, 28], which CIF files were subtracted from the Cambridge Structural Database (CSD; CCDC numbers 834421 for 1, 847259 for 2, 881637 for 3red and 881638 for 3yellow) [29], were subjected for an in-depth structural analysis. Notably, a comprehensive search in the CSD yielded one more crystal structure of the naphthalene-based bis-$N$-salicylidene aniline dye, fabricated from 3,5-di-tert-butylsalicyaldehyde [30]. However, the crystal structure of this compound was obtained as an acetone–dimethyl sulfoxide solvate with highly disordered solvent molecules, and thus, it was not considered herein. Recently, some of us have also established that the as-synthesized Schiff base 3 forms red crystals (3red), recrystallization of which from acetone produces yellow
crystals (3yellow). This solvent-induced interconversion is reversible and reproducible, yielding different photophysical properties [23]. Thus, both polymorphs of the Schiff base 3 were analyzed and discussed.

In this work, we focused on detailed studies of crystal structures of 1, 2, 3red and 3yellow using Hirshfeld surface analysis with the aim to shed more light on non-covalent interactions. Furthermore, energy frameworks have been calculated to analyze the overall crystal packing of these compounds. Besides the above studies, molecular docking studies, which are driven by intermolecular non-covalent interactions, were used to explore the binding modes and interactions of the compounds 1–3 with binding sites of the SARS-CoV-2 proteins as targets at the atomic level. It should be noted that the salicylaldehyde-derived Schiff bases were found to be of interest as antiviral agents against coronavirus [31].

**Experimental**

**Hirshfeld surface analysis**

The Hirshfeld molecular surfaces [32] and their associated 2D fingerprint plots [33] were generated using the Crystal-Explorer 17 software [34] on the basis of crystal structures. The $d_{\text{norm}}$ (normalized contact distance) surface and the breakdown of the 2D fingerprint plots were used for decoding and quantifying the intermolecular interactions in the crystal lattice. The $d_{\text{norm}}$ is a symmetric function of distances to the surface from the nuclei inside ($d_i$) and outside ($d_o$) the Hirshfeld surface, relative to their respective van der Waals radii. 2D fingerprint plots were generated using $d_i$ and $d_o$ in the translated 0.4–3.0 Å range and including reciprocal contacts as a pair of coordinates in 2D plots. A color gradient in the fingerprint plots ranging from blue to red is used to visualize the proportional contribution of contact pairs in the global surface.

**Enrichment ratio**

The enrichment ratio ($E$) [35] of a pair of elements ($X,Y$) is the ratio between the proportion of actual contacts in the crystal and the theoretical proportion of random contacts. $E$ is larger than unity for pairs of elements which have a high propensity to form contacts in crystals, while pairs which tend to avoid contacts with each other yield an $E$ value lower than unity. $E$ values are calculated from the percentage of contacts, which, in turn, are given by the CrystalExplorer 17 software [34], between one type or two types of chemical elements in a crystal packing.

**Molecular docking**

Docking applications were exerted with AutoDock Vina [36] to estimate the interaction mechanisms of the compounds 1–3 as ligands with a series of COVID-19 proteins as targets. Crystal structures of the applied proteins were extracted from the RCSB Protein Data Bank [37]. The ligands and proteins were prepared by using suitable protocols of Discovery Studio 3.5 [38] for molecular docking studies as described previously [39]. The active region of the molecular docking site contains the related proteins with an active region size of 40×40×40 with 0.375 Å grid spacing. Lamarckian genetic algorithm was used to fully search for the possible conformations and binding sites. Other docking parameters were set to the software’s default values. The lowest binding energy conformers along with the lowest RMSD were captured of 100 diversified conformers from the docking genetic algorithm runs. The docked poses were analyzed and visualized in Discovery Studio 3.5.

**Results and discussion**

The bis-N-salicylidene aniline dyes 1–3 (Fig. 1) are readily obtained by the condensation reaction of 1,5-diaminonaphthalene with salicylaldehyde [27], 3-hydroxysalicylaldehyde [28] and 3-methoxysalicylaldehyde [23, 28], respectively.

According to single-crystal X-ray diffraction, 1 and 3red crystallize in monoclinic space group $P2_1/c$, while 2 and 3yellow crystallize in triclinic $P$–1 and monoclinic $P2_1/n$ space groups, respectively [23, 27, 28]. The molecule in each structure lies on a crystallographic two-fold axis; thus, the asymmetric unit comprises one half-molecule (Fig. 2).

Notably, molecules in all the structures were found in the enol-imine form (Fig. 2). Particularly, the bond lengths of C–O, with respect to the moieties marked in bold in Fig. 1, are about 1.35 Å and those of C–C are about 1.45 Å (Table 1), which indicates single bonds, while a double bond of about 1.28 Å is revealed for C=N (Table 1). The enol-imine isomer formation is further supported by the sp$^2$-hybridization of both the carbon and the nitrogen atoms of the imine fragment as evidenced from the corresponding C–C=N and C=N–C bond angles, which vary from 119.64(11)$^{\circ}$ to 123.1(3)$^{\circ}$ (Table 1).

The overall shape of the discussed molecules is dictated by the corresponding dihedral angle between the least-square planes formed by the benzene and naphthalene rings. Particularly, this angle is similar in the structures of 1, 2 and 3yellow, which vary from 43.62(13)$^{\circ}$ to 56.37(5)$^{\circ}$ (Table 1) and is remarkably less in the structure of 3red, 21.31(8)$^{\circ}$. Thus, the molecule of the latter compound is much planar (Fig. 2).
The crystal structures of all molecules are stabilized by intramolecular O–H⋯N hydrogen bonds (Fig. 2, Table 2), yielding two six-membered hydrogen bonded pseudo-aromatic rings, which are almost perfectly planar in the structures of 1, 2 and 3yellow, and significantly deviated in the structure of 3red as evidenced from the corresponding dihedral angles (Table 1). This ring is constructed from five covalent bonds and one non-covalent bond (Fig. 2), which is accompanied by certain conjugation effects and has a certain degree of covalency [40]. This is the case of the resonance-assisted hydrogen bonding (RAHB), where the donor and acceptor are connected by a π-conjugated system [41]. The aromaticity index of this pseudo-aromatic ring was found to be 0.774, 0.721, 0.747 and 0.763 for 1, 2, 3red and 3yellow, respectively, as evidenced from the Harmonic Oscillator Model of Aromaticity for Heterocycle Electron Delocalization (HOMHED) [42]. Using the same approach, the aromaticity index for the benzene rings was found to be in the range of 0.977–0.989, while the aromaticity index for the C₆H₅ rings of the naphthalene fragments was found to be 0.917–0.949, respectively. Thus, the benzene, naphthalene and, remarkably, the hydrogen bonded six-membered heterocycles are aromatic for all the discussed structures. The crystal structure of 2 is additionally stabilized by intramolecular O–H⋯O hydrogen bonds (Fig. 2, Table 2), yielding two five-membered hydrogen bonded heterocycles, and by intermolecular O–H⋯O hydrogen bonds, formed between the OH groups of adjacent molecules, yielding a 1D zig-zag supramolecular chain, comprising $R_2^2$(10) H-bonded cycles.

Molecules of 2, 3red and 3yellow are interlinked through intermolecular C–H⋯π interactions (Table 2). Interestingly, in the former two structures these interactions are formed

![Fig. 2 Crystal structures of 1–3. Color code: H = black, C = gold, N = blue, O = red; O–H⋯N hydrogen bond = dashed cyan line](image)

| Table 1 Selected bond lengths (Å) and angles (°) in the structures of 1–3 |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| **Bond lengths**                | 1               | 2               | 3red            | 3yellow         |
| C=N                             | 1.28(3)         | 1.282(17)       | 1.287(3)        | 1.284(2)        |
| C–N                             | 1.419(4)        | 1.4190(15)      | 1.417(3)        | 1.4152(18)      |
| C–O                             | 1.350(4)        | 1.3600(15)      | 1.353(3)        | 1.3493(18)      |
| C–C                             | 1.443(4)        | 1.4515(17)      | 1.454(3)        | 1.4486(19)      |
| **Bond angles**                 |                 |                 |                 |                 |
| C–C=N                           | 123.1(3)        | 121.82(12)      | 121.7(2)        | 121.90(13)      |
| C=N–C                           | 120.2(3)        | 119.64(11)      | 121.24(19)      | 121.02(13)      |
| **Dihedral angles**             |                 |                 |                 |                 |
| H–O–C–C                         | 0               | –4              | –32             | –1              |
| O–C–C–C                         | 0.8(5)          | 3.21(17)        | 3.3(3)          | 1.7(2)          |
| C–C–C=N                         | –0.5(5)         | –4.68(18)       | –5.3(3)         | 2.6(2)          |
| C–C=N–H                         | 0               | –4.5            | –15.7           | –4.3            |
| C=N–H–O                         | –0.9            | 8.4             | 54.4            | 6.7             |
| N–H–O–C                         | 0.8             | –7.3            | –56.6           | –3.4            |
| $C_{8\text{benzene}}$–$C_{8\text{naphthalene}}$ | 43.62(13)       | 56.37(5)        | 21.31(8)        | 47.04(6)        |

*Least-square planes, formed by the carbon atoms of the benzene and naphthalene rings*
with the benzene rings, while in the latter one both naphthalene six-membered rings are involved. Furthermore, the crystal packing of 1 and 2 is also described by intermolecular π⋯π interactions (Table 3). These interactions are formed exclusively between the benzene rings in the structure of 2, whereas both the benzene and naphthalene rings are involved in the structure of 1.

Crystal packing of 1, 2, 3red and 3yellow was further studied by a Hirshfeld surface analysis [32], also reflected in a set of corresponding 2D fingerprint plots [33], which were generated using CrystalExplorer 17 [34]. Additionally, the enrichment ratios (E) [35] of the intermolecular contacts were also calculated to estimate the propensity of two chemical species to be in contact. It was found that the Hirshfeld surfaces of 1, 2 and 3red, calculated over dnorm, each contain two symmetrical pairs of bright red spots, corresponding to donors and acceptors of the C–H⋯C (in 1), O–H⋯O (in 2), C–H⋯C and C–H⋯C (in 3red) intermolecular interactions (Fig. 3). The same surface of 3yellow contains ten symmetrical pairs of bright red spots, corresponding to donors and acceptors of the C–H⋯O, C⋯C and C–H⋯C intermolecular interactions (Fig. 3). The donors and the acceptors of these interactions can be evidenced as blue and red regions around the participating atoms on the Hirshfeld surface mapped over shape index (Fig. 3). Moreover, flat regions were observed over both sides of the benzene and naphthalene rings on the Hirshfeld surface of 1, mapped over curvedness, testifying to the reasonable π⋯π interactions (Fig. 3). Similar flat regions were found over one side of the benzene rings on the Hirshfeld surface of 2, also testifying to the reasonable π⋯π interactions (Fig. 3).

It was further found that more than 90% of the total Hirshfeld surface are for all the discussed molecules is occupied by H⋯H, H⋯C, H⋯O and C⋯C contacts (Table 4). However, the distribution of these contacts within each molecule differs significantly, which is, obviously, due to the presence of additional OH and MeO groups in the structures of 2, 3red and 3yellow, respectively. At the same time, we herein discuss two polymorphs 3red and 3yellow, which are chemically the same but differ geometrically (Fig. 2, Tables 1 and 2), thus yielding remarkably different Hirshfeld surfaces.

According to the Hirshfeld surface analysis of 1, the intermolecular H⋯H, H⋯C, H⋯O and C⋯C contacts comprise about 52%, 18%, 10% and 14% of the total number of contacts (Table 4). Incorporation of two additional OH groups in a molecule, yielding the structure of 2, significantly decreases proportions of the H⋯H (~38%) and C⋯C (~5%) contacts simultaneously increasing proportions of the H⋯C (~35%) and H⋯O (~18%) contacts (Table 4). This can be explained by the formation of O–H⋯O intermolecular hydrogen bonds (Table 2) in the crystal structure of 2 together with a superior propensity of 1 to produce π⋯π intermolecular interactions (Table 3). Substitution of two meta-OH groups by two MeO groups, yielding the structure of 3red, increases a proportion of the intermolecular H⋯H contacts (~46%) on the Hirshfeld surface area, which is now compatible with 1 (~52%), accompanied with a dramatic decreasing of a proportion of the H⋯C contacts (~24%).
Table 3  π−π distances (Å) and angles (°) for 1 and 2

|   | Cg(I)  | Cg(J)  | d[Cg(I)−Cg(J)] | α    | β    | γ    | Slippage | Symmetry operation |
|---|--------|--------|----------------|------|------|------|----------|--------------------|
| 1 | C6H4   | C6H4   | 3.851(2)       | 0.02(16) | 26.5 | 26.5 | 1.719 | −1 + x, y, z       |
|   | C6H4   | C6H4   | 3.851(2)       | 0.02(16) | 26.5 | 26.5 | 1.719 | 1 + x, y, z       |
|   | C6H3   | C6H3   | 3.851(2)       | 0.00(14) | 27.3 | 27.3 | 1.766 | −1 + x, y, z       |
|   | C6H4   | C6H3   | 3.851(2)       | 0.00(14) | 27.3 | 27.3 | 1.766 | 1 + x, y, z       |
|   | C6H3   | C6H3   | 3.647(2)       | 0.00(14) | 20.2 | 20.2 | 1.258 | 1 − x, 1 − y, − z  |
|   | C6H3   | C6H3   | 3.647(2)       | 0.00(14) | 20.2 | 20.2 | 1.258 | 1 + x, y, z       |
|   | C6H3   | C6H3   | 3.851(2)       | 0.00(14) | 27.3 | 27.3 | 1.766 | −1 − x, 1 − y, − z |
|   | C6H3   | C6H3   | 3.851(2)       | 0.00(14) | 27.3 | 27.3 | 1.766 | 1 − x, 1 − y, − z |
| 2 | C6H3(benzene) | C6H3(benzene) | 4.0348(8) | 0.00(6) | 34.6 | 34.6 | 2.290 | −x, 1 − y, 1 − z  |

aCg(I)−Cg(J): distance between ring centroids; α: dihedral angle between planes Cg(I) and Cg(J); β: angle Cg(I)−Cg(J) vector and normal to plane I; γ: angle Cg(I)−Cg(J) vector and normal to plane J; slippage: distance between Cg(I) and perpendicular projection of Cg(J) on ring I.

Fig. 3 Molecular Hirshfeld surfaces of 1–3 (top, middle and bottom denote normalized distance dnorm, shape index and curvedness, respectively)
Intramolecular O–H pairs of sharp spikes (Fig. 4) due to the formation of strong hydrogen bonds (Table 2). Further, the characteristic area on the diagonal at \(d_x = d_y \approx 1.7–2.2 \text{ Å}\) (Fig. 4) and correspond \(\pi \cdot \pi\) interactions.

Notably, while proportions of the H⋯O (~17%) and C⋯C (~7%) contacts in the structure of 3red are very similar to those in the structure of 2, a new type of intermolecular contacts, namely C⋯N contacts (5%), also comes to the fore on the Hirshfeld surface of 3red (Table 4). This can be explained by a much more planar structure of 3red in comparison with the other discussed molecules (Fig. 2, Table 1). Interestingly, the intermolecular H⋯H, H⋯C and H⋯O contacts in the Hirshfeld surface of 3yellow each comprise similar proportions as in the surface of 2 (Table 4). It should also be noted that proportions of the H⋯H and H⋯C contacts in 2 and 3yellow are not only pairwise similar but also very similar within each structure, varying from ~35 to ~39% (Table 4).

The shortest H⋯H, H⋯C and H⋯O contacts are shown in the corresponding fingerprint plots at \(d_x + d_y \approx 2.1–2.4, 2.7–2.9\) and 2.0–2.7 Å, respectively (Fig. 4). A subtle feature is evident in the fingerprint plots of 2 and 3red, namely a splitting of the short H⋯H fingerprint (Fig. 4). This splitting occurs when the shortest contact is between three atoms, rather than for a direct two-atom contact [32]. Notably, in the fingerprint plots of 2, 3red and 3yellow the H⋯C contacts are shown in the form of “wings” (Fig. 4) and are recognized as characteristic of C–H⋯\(\pi\) nature [33], while the H⋯O contacts in the fingerprint plot of 2 are shown as a pair of sharp spikes (Fig. 4) due to the formation of strong intermolecular O–H⋯O hydrogen bonds (Table 2). Furthermore, the H⋯C contacts are shown in the fingerprint plots as

| Contacts (C, %) | 1 | 2 | 3red | 3yellow |
|----------------|---|---|------|---------|
| H              | 51.8 | 18.1 | 37.6 | 37.9 |
| C              | 14.4 | 35.3 | 6.7  | 4.9 |
| N              | 1.3 | 2.0  | 0.0  | 0.6 |
| O              | 10.4 | 1.1  | 0.0  | 0.6 |

| Surface (S, %) | 66.7 | 25.1 | 2.0  | 6.2 |
|----------------|------|------|------|-----|
| Random contacts (R, %) | 65.1 | 24.1 | 0.9  | 10.2 |

| Enrichment (E) | 1.16 | 0.54 | 0.48 | 1.25 |

| Values were obtained from CrystalExplorer 17 [34] |

The “enrichment ratios” were not computed when the “random contacts” were lower than 0.9%, as they are not meaningful [35].
We have also calculated energy frameworks [43] using CrystalExplorer 17 [34] to further analyze the crystal packing of 1, 2, 3red and 3yellow (Table 5, Fig. 6). The overall topology of the energy distributions in the discussed crystal structures was studied through the energy framework. It was established that the structures are mainly characterized by the dispersion energy framework followed by the less significant electrostatic energy framework contribution (Fig. 7).

We have also examined evaluation of the biological efficacy of 1–3 against a series of the SARS-CoV-2 proteins (Table 6) using the molecular docking approach. Note that we used the structure of 3red as a general representative of both polymorphs of 3.

It was established that the predicted binding energies of 1–3 show high binding affinity with the four proteins, namely Papain-like protease (PLpro), nonstructural protein 3 (nsp3_range 207–379-MES), RdRp-RTR and Nsp14 (N7-MTase) (marked by bold in Table 6). Both 1 and 3 exhibit the best interaction with the latter protein, while 2 is more efficient toward the first protein.

These findings are explained by different sets of intermolecular interactions formed between 1 and 3 and corresponding proteins revealed from the molecular docking studies. Particularly, the main interactions between 1 and Nsp14 (N7-MTase) are one conventional hydrogen bond with ASP352, one carbon hydrogen bond with Asn386, one S⋯π-system interaction with Cys387, two π⋯π interactions with Ph3367 and Phe426, and three alkyl⋯π-system interactions with Val290 and Ala353, respectively (Fig. 8, Table S1 in the Supplementary Information).

The interaction of 2 with PLpro is described by two conventional hydrogen bonds with Asp164 and Thr301, one carbon hydrogen bond with Glu161, one cation⋯π-system interaction with Lys157, one anion⋯π-system interaction with Glu161, two π⋯π interactions with Tyr264 and Tyr207, and two alkyl⋯π-system interactions with Leu162 and Pro248 (Fig. 9, Table S1 in the Supplementary Information).

Finally, 3, similar to 1, exhibits the best interaction with Nsp14 (N7-MTase), however with 0.2 kcal/mol lower
Table 5 Interaction energies (kJ/mol) calculated at the B3LYP/6-31G(d,p) theory level for the crystal structures of 1–3. *Values in parenthesis are obtained after normalizing to 100% the sum of the attractive energy contributions

|   | N    | symmetry operation | $E_{\text{ele}}$ | $E_{\text{pol}}$ | $E_{\text{disp}}$ | $E_{\text{rep}}$ | $E_{\text{tot}}$ |
|---|------|--------------------|-----------------|-----------------|------------------|-----------------|----------------|
| 1 | 4    | $-x, y + 1/2, -z + 1/2$ | 11.35 | -3.7 (12.1) | -1.5 (4.9) | -25.3 (83.0) | 15.7 | -17.3 |
|   | 2    | $x, y, z$           | 19.77 | 0.0 (0.0) | -0.3 (3.8) | -7.5 (96.2) | 4.9 | -3.8 |
|   | 2    | $x, y, z$           | 3.85  | -6.1 (4.5) | -3.2 (2.4) | -126.6 (93.1) | 70.6 | -75.5 |
|   | 4    | $-x, y + 1/2, -z + 1/2$ | 11.79 | -6.1 (25.2) | -1.4 (5.8) | -16.7 (69.0) | 12.1 | -14.7 |
|   | 4    | $-x, y + 1/2, -z + 1/2$ | 12.18 | -0.7 (8.1) | -0.2 (2.3) | -7.7 (89.6) | 4.1 | -5.1 |
|   | 2    | $x, y, z$           | 20.87 | -0.1 (6.3) | 0.0 (0.0) | -1.5 (93.7) | 0.0 | -1.4 |
| 2 | 2    | $x, y, z$           | 6.28  | -11.2 (18.0) | -1.9 (3.1) | -49.1 (78.9) | 30.3 | -37.3 |
| 3red | 2   | $x, y, z$           | 8.65  | -9.0 (16.2) | -1.5 (2.7) | -44.9 (81.1) | 33.2 | -29.2 |
| 2  | 2    | $x, y, z$           | 8.75  | -6.2 (11.8) | -1.2 (2.3) | -45.3 (85.9) | 23.7 | -32.3 |
| 2  | 2    | $x, y, z$           | 12.61 | -14.9 (19.0) | -2.9 (3.7) | -60.5 (77.3) | 42.2 | -44.5 |
| 2  | 2    | $x, y, z$           | 18.86 | -6.5 (34.6) | -1.6 (8.5) | -10.7 (56.9) | 11.1 | -10.5 |
| 2  | 2    | $x, y, z$           | 19.60 | -0.8 (10.3) | 0.0 (0.0) | -7.0 (89.7) | 3.9 | -4.6 |
| 2  | 2    | $x, y, z$           | 13.10 | -38.0 (68.7) | -1.9 (3.4) | -15.4 (27.9) | 42.5 | -28.8 |
| 3red | 2   | $-x, y + 1/2, -z + 1/2$ | 7.79  | -4.0 (18.7) | -1.6 (7.5) | -15.8 (73.8) | 6.4 | -15.3 |
| 2  | 2    | $-x, y + 1/2, -z + 1/2$ | 10.58 | -9.0 (30.1) | -2.3 (7.7) | -18.6 (62.2) | 12.6 | -19.7 |
| 2  | 2    | $x, y, z$           | 5.07  | -11.3 (9.4) | -2.4 (2.0) | -106.4 (88.6) | 50.9 | -74.9 |
| 2  | 2    | $-x, y + 1/2, -z + 1/2$ | 14.95 | -4.4 (12.8) | -4.4 (12.8) | -25.7 (74.4) | 18.6 | -18.8 |
| 2  | 2    | $x, y, z$           | 17.31 | -1.6 (15.0) | 0.0 (0.0) | -9.1 (85.0) | 4.9 | -6.6 |
| 2  | 2    | $x, y, z$           | 21.18 | -0.7 (28.0) | -0.1 (4.0) | -1.7 (68.0) | 0.1 | -2.2 |
| 2  | 2    | $-x, y + 1/2, -z + 1/2$ | 14.65 | -1.6 (12.5) | -0.5 (3.9) | -10.7 (83.6) | 13.2 | -3.2 |
| 2  | 2    | $x, y, z$           | 20.69 | 0.5 | 0.0 (0.0) | -0.9 (100.0) | 0.0 | -0.3 |
| 3yellow | 2   | $x, y, z$           | 7.58  | -9.6 (13.5) | -6.6 (9.3) | -54.7 (77.2) | 22.9 | -48.5 |
| 2  | 2    | $x, y, z$           | 6.74  | -5.0 (8.2) | -5.1 (8.4) | -50.7 (83.4) | 33.3 | -32.7 |
| 2  | 2    | $x, y, z$           | 6.87  | -15.4 (16.0) | -1.6 (1.7) | -79.5 (82.3) | 56.6 | -51.7 |
| 3yellow | 2   | $-x + 1/2, y + 1/2, -z + 1/2$ | 12.68 | -11.2 (35.2) | -0.3 (0.9) | -20.3 (63.9) | 19.8 | -17.4 |
| 3yellow | 2   | $-x + 1/2, y + 1/2, -z + 1/2$ | 13.36 | -3.3 (18.8) | -0.1 (0.6) | -14.2 (80.6) | 10.1 | -9.8 |

* $N$ is the number of molecules with an $R$ molecular centroid-to-centroid distance (Å); color codes in the first column are referenced to Fig. 6

$E_{\text{ele}}$ is the electrostatic energy, $E_{\text{pol}}$ is the polarization energy, $E_{\text{disp}}$ is the dispersion energy, $E_{\text{rep}}$ is the exchange-repulsion energy; $k$ values are scale factors; $E_{\text{tot}} = E_{\text{ele}} + E_{\text{pol}} + E_{\text{disp}} + E_{\text{rep}}$ [43]

binding energy, which is most likely, due to steric effects (Fig. 10, Table 6). Compound 1 interacts with Nsp14 (N7-MTase) through three conventional hydrogen bonds with Arg310 and Ala353, five carbon bonds with Gly333, Asn386, Asn306 and Leu366, one $\pi-\pi$ interaction with Val290, one S$\cdots$S-system interaction with Cys387, two $\pi-\pi$ interactions with Phe367 and Phe426, and one alkyl-$\pi$-system interaction with Ala353 (Fig. 9, Table S1 in the Supplementary Information).

Conclusions

In summary, we report detailed structural studies of an extremely rare family of naphthalene-based bis-$N$-salicylidenes aniline dyes, namely $N,N'$-bis-salicylidene-1,5-diaminonaphthalene (1), $N,N'$-bis(3-hydroxysalicylidene)-1,5-diaminonaphthalene (2) and $N,N'$-bis(3-methoxysalicylidene)-1,5-diaminonaphthalene (3).
The Schiff base 3 exists as two polymorphs, herein named as 3red and 3yellow. Both polymorphs of 3 were analyzed and discussed.

Single-crystal X-ray diffraction revealed that all the discussed molecules lie on a crystallographic two-fold axis; thus, the asymmetric unit comprises one half-molecule exhibiting an enol-imine tautomer, stabilized by a couple of intramolecular O–H⋯N hydrogen bonds. The structure of 2 is further stabilized by a couple of additional O–H⋯O intramolecular hydrogen bonds and by intermolecular O–H⋯O interactions, yielding a 1D zig-zag supramolecular chain. Molecules of 2, 3red and 3yellow are interlinked through intermolecular C–H⋯π interactions, while the crystal
The packing of 1 and 2 is also described by intermolecular π⋯π interactions. It was established that more than 90% of the total Hirshfeld surface area for all the discussed molecules is occupied by H⋯H, H⋯C, H⋯O and C⋯C contacts. However, the distribution of these contacts within each molecule differs significantly, which is, obviously, due to the presence of additional OH and MeO groups in the structures of 2, and 3red and 3yellow, respectively. Notably, two polymorphs 3red and 3yellow, despite being chemically the same, differ geometrically, thus yielding remarkably different Hirshfeld surfaces. In general, the Hirshfeld surface of 3yellow is very similar to that of 2.

Energy frameworks have been calculated to additionally analyze the overall crystal packing. It was established that the all the structures are mainly characterized by the dispersion energy framework followed by the less significant electrostatic energy framework contribution.

The molecular docking studies were performed to elucidate the effects of 1–3 on to reveal the binding mechanisms of a series of the SARS-CoV-2 proteins. Docking results revealed that 1–3 show high binding affinity with Papain-like protease (PLpro), nonstructural protein 3 (nsp3_range 207–379-MES) and RdRp-RTR and Nsp14 (N7-MTase). Both 1 and 3 exhibit the best interaction with the latter protein, while 2 is more efficient toward the first protein.

Finally, we hope that the results reported herein will be of value for future design of potential chemicals against SARS-CoV-2.
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Declarations  

Conflict of interest  The authors declared that they have no conflicts of interest in this work.

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