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ADVANCED REVIEW OPEN ACCESS

Density Functional Theory in Forensic Science: Applications and Challenges

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ABSTRACT

Forensic science is evolving to tackle increasingly complex criminal investigations, where traditional methods may fall short. This review examines how computational chemistry enhances forensic techniques by providing detailed insights into molecular interactions, reaction mechanisms, and spectroscopic properties. A particular focus is placed on density functional theory (DFT), which has emerged as a powerful, cost-effective tool that balances computational efficiency and accuracy, making it ideal for studying a wide range of forensic compounds without the need for physical samples. Applications discussed include the analysis of new psychoactive substances (NPS), detection of food adulterants, development of chemical sensors, and forensic examination of luminol for blood detection, fingerprint visualization, and the analysis of explosives. Key advances in various DFT functionals are highlighted, along with prospects for integrating DFT with machine learning and sustainable practices to further expand its impact in forensic science.

1 | Introduction

Forensic science faces numerous challenges as it continuously evolves to address the complexity of modern criminal investigations. The demand for accurate, reliable, and rapid methods to detect and analyze evidence is greater than ever, especially as new forms of crimes and more sophisticated methods of concealment emerge. Traditional techniques, while valuable, often fall short in addressing the increasingly intricate nature of forensic problems, such as the detection of new psychoactive substances (NPS), food adulteration, and explosive residues. These

challenges call for the incorporation of modern approaches from chemistry to enhance forensic investigations.

One such approach is the integration of in silico methods, specifically computational chemistry, which offers significant advantages in forensic analysis. They allow for the study of molecular interactions, reaction mechanisms, and structural and spectroscopic properties of forensically relevant molecular compounds without the need for extensive laboratory experimentation. These methods are cost-effective, can handle a wide range of complex systems, and are ideal for scenarios where physical

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samples are limited, controlled, or contaminated. Computational methods are also crucial for developing predictive models, simulating spectra, and interpreting results that would be difficult or impossible to obtain through experimental techniques alone.

Among the most powerful *in silico* tools for forensic applications is density functional theory (DFT). DFT offers an efficient balance between computational cost and accuracy, making it a preferred choice for studying the molecular properties of compounds relevant to forensics. From analyzing drugs and substances of abuse at the molecular level to investigating chemical adulterants and optimizing materials for trace evidence detection, DFT has emerged as a versatile tool that can provide insights into chemical phenomena that directly impact forensic science. Its ability to handle large systems has made it an indispensable tool in fields ranging from materials science to biochemistry. As the development of more sophisticated DFT functionals continues, along with advancements in computational power, DFT's applicability will likely expand, addressing some of its current limitations and enabling new possibilities in molecular simulations. In this review, we highlight its growing applications in forensic science, particularly in areas such as the detection of NPS, food adulteration, and forensic materials, showcasing how DFT is pushing the boundaries of forensic investigations.

2 | Density Functional Theory

In this section, we provide a brief overview of the main features of DFT, including its historical development and general classifications, aimed at a broader audience. For those seeking more in-depth information, the specialized literature offers extensive coverage of this powerful computational methodology. Notable examples include the topical review of Mardirossian and Head-Gordon (2017), *Thirty years of density functional theory in computational chemistry*, which explores DFT's evolution and applications. Another essential reference is Grimme's *Best-practice DFT protocols for basic molecular computational chemistry* (Bursch et al. 2022), which outlines practical guidelines for utilizing DFT. Additionally, for a comprehensive review of the development and application of DFT and wavefunction-based approaches in both ground and excited states, with a special focus on organometallic systems, readers may consult the recent work of Souza and Fantuzzi (2024).

Traditionally, quantum chemistry courses begin by introducing computational approaches based on the wavefunction. These methods, starting with Hartree–Fock (HF) theory and progressing through various post-Hartree–Fock methods, such as configuration interaction, coupled cluster, and Møller–Plesset perturbation theory, aim to solve the many-electron Schrödinger equation. Wavefunction-based methods, while accurate, are computationally demanding due to the sheer complexity of dealing with the wavefunction, which depends on $3N$ coordinates for an N -electron system. This becomes prohibitively expensive as system size increases, making these approaches less feasible for larger molecules.

Unlike these wavefunction-based methods, DFT simplifies the problem by shifting the focus to the electron density, $\rho(r)$, rather than the full wavefunction. The electron density depends only

on three spatial coordinates, regardless of the number of electrons, making DFT computationally more efficient. This reduction in complexity allows DFT to provide a more practical balance between accuracy and computational cost, especially for large molecular systems. However, it is important to note that these computational costs are based upon today's technology, and future advancements, such as quantum computing (Motta and Rice 2022) and developments in machine learning (Kulik et al. 2022), could dramatically transform the computational time needed for electronic structure calculations.

DFT is grounded in the Hohenberg–Kohn theorems (Hohenberg and Kohn 1964), which state that the ground-state energy of a many-electron system is a unique functional of its electron density and can be obtained through the variational principle. A functional is a mathematical relationship that maps a function (in this case, the electron density) to a single value (the energy). However, in its simplest form, DFT faces challenges in accurately describing the kinetic energy of electrons. The Kohn–Sham (KS) formalism (Kohn and Sham 1965) addresses this by reintroducing orbitals similar to those in HF theory, allowing for a more accurate treatment of the kinetic energy. Furthermore, KS-DFT also refines the treatment of electron–electron interactions by incorporating an exchange–correlation (XC) functional. Though the exact form of the XC functional remains unknown, numerous approximations have been developed, each with its own balance between accuracy and computational cost. While the reintroduction of orbitals increases computational demands compared with orbital-free DFT, KS-DFT remains significantly more efficient than post-HF methods, with costs comparable to those of HF.

The simplest approximation within DFT is the local density approximation (LDA), which assumes that the XC energy at each point in space depends only on the local electron density. Although LDA works well for uniform electron gases, it is less accurate for systems where the electron density varies significantly. This limitation led to the development of the generalized gradient approximation (GGA), which incorporates the gradient of the electron density, improving the description of molecular systems where the electron density changes rapidly, such as at bond regions.

Beyond GGA, more sophisticated functionals, such as meta-GGA functionals, include higher-order terms like the Laplacian of the electron density to further refine predictions. Hybrid functionals, such as the widely used B3LYP (Becke 1993; Lee, Yang, and Parr 1988; Stephens et al. 1994; Vosko, Wilk, and Nusair 1980), mix a portion of exact exchange from HF theory with the approximate exchange–correlation functional, providing a significant boost in accuracy for many molecular systems.

Despite its many advantages, DFT is not without limitations. It struggles with accurately describing long-range dispersion interactions, charge transfer excitations, and contains the self-interaction error, where an electron erroneously interacts with itself. Various correction schemes, like Grimme's D3 dispersion correction (Grimme et al. 2010) and range-separated hybrid functionals, for example, CAM-B3LYP (Yanai, Tew, and Handy 2004) and ω B97X-D (Chai and Head-Gordon 2008), have been developed to address these issues, improving the accuracy

of DFT in systems where these effects are important. Another powerful approach to enhance DFT accuracy is the use of double hybrid functionals (Goerigk and Grimme 2014), which combine exact HF exchange with second-order Møller–Plesset perturbation theory (MP2), providing a more comprehensive treatment of electron correlation effects. These functionals are most effective in systems with strong electron correlation and, when coupled with an appropriate empirical dispersion correction, significantly improve the description of non-covalent interactions, particularly long-range dispersion forces (Schwabe and Grimme 2007). Double hybrids, such as B2PLYP (Grimme 2006) and PWPB95 (Goerigk and Grimme 2011), typically outperform traditional hybrid functionals in terms of accuracy, though they come with a higher computational cost. However, for many challenging systems, such as those involving reaction barriers, weak interactions, or multireference character, the improved accuracy of double hybrids makes them a valuable tool in modern computational chemistry, including forensic applications where precise molecular modeling is crucial.

In addition to ground-state properties, time-dependent DFT (TD-DFT) extends the utility of DFT to the study of excited states. TD-DFT is widely used for calculating excitation energies, UV–Vis spectra, and other properties related to electronic transitions, although it also faces challenges in systems with charge transfer or multireference character.

In the following sections, we explore the diverse applications of DFT in forensic science. Through selected case studies, we illustrate how DFT is transforming investigative techniques, offering innovative solutions to complex forensic problems.

3 | New Psychoactive Substances

3.1 | An Overview of NPS

NPS have emerged as a significant challenge in global drug control, cleverly evading existing legal frameworks (Berretta et al. 2022; Zapata et al. 2021). Contrary to what the term might suggest, these substances are not necessarily new or recently synthesized. In fact, the majority were developed in the last century for therapeutic purposes. However, due to their potential for abuse, research and testing were eventually discontinued. Defined by the United Nations Office on Drugs and Crime (UNODC) as substances not regulated by the 1961 and/or 1971 conventions, NPS continuously evolve in response to legislative measures. These substances are used because they mimic the effects of prohibited drugs while staying one step ahead of regulations (Mariotto, Rodrigues, and Bruni 2024; Rodrigues et al. 2023).

NPS encompass a wide variety of molecules, many of which are derived from or mimic classic psychoactive substances. Substances like tetrahydrocannabinol (THC), cocaine, lysergic acid diethylamide (LSD), 3,4-methylenedioxymphetamine (MDA), and 3,4-methylenedioxymphetamine (MDMA) represent examples of foundational compounds that serve as references for many NPS (Figure 1A). For example, synthetic cannabinoids (Figure 1B), such as HU-210 (1,1-dimethylheptyl-11-hydroxy-tetrahydrocannabinol), JWH-018 (1-pentyl-3-(1-naphthoyl)indole),

and MDMB-4en-PINACA (methyl (S)-3,3-dimethyl-2-(1-(pent-4-en-1-yl)-1H-indazole-3-carboxamido)butanoate), mimic the effects of THC by interacting with cannabinoid receptors (Le Boisselier et al. 2017; Mills, Yepes, and Nugent 2015; Roque-Bravo et al. 2023; Spaderna, Addy, and D'Souza 2013). Similarly, synthetic cathinones like 4-methylmethcathinone (4-MMC), 3,4-methylenedioxy-N-methylcathinone (MDMC), and pentedrone (α -methylaminovalerophenone), shown in Figure 1C, produce stimulant effects reminiscent of cocaine and MDMA (Karila et al. 2015; Kuropka, Zawadzki, and Szpot 2023; Prosser and Nelson 2012). Hallucinogens also have their NPS counterparts. Tryptamines (Figure 1D), such as 4-AcO-DMT (4-acetoxy-N, N-dimethyltryptamine), DPT (N,N-dipropyltryptamine), and 4-HO-MPT (4-hydroxy-N-methyl-N-propyltryptamine), act on 5-HT_{2A} receptors (Araújo et al. 2015; Tittarelli et al. 2015), similar to their substituted phenethylamine counterparts (Figure 1E) (Adams and Gallahue 2024; Dean et al. 2013; King 2014), which include compounds like 2C-B (4-bromo-2,5-dimethoxyphenylamine), 25C-NBOMe (2-(4-chloro-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethan-1-amine), and 25I-NBOH (2-((2-(4-iodo-2,5-dimethoxyphenyl)ethylamino)methyl)phenol). Both classes share mechanisms of action with classic hallucinogens like LSD, which also targets 5-HT_{2A} receptors. In contrast, piperazines, including meta-chlorophenylpiperazine (mCPP), 3-trifluoromethylphenylpiperazine (TFMPP), and para-fluorophenylpiperazine (pFPP) (Figure 1F), function as potent psychostimulants, elevating levels of serotonin, norepinephrine, and dopamine (Arbo, Bastos, and Carmo 2012; Welz and Koba 2020). Finally, benzofurans—depicted in Figure 1G with 6-APB (6-(2-aminopropyl)benzofuran), 5-MAPB (1-(benzofuran-5-yl)-N-methylpropan-2-amine), and 6-MAPB (1-(benzofuran-6-yl)-N-methylpropan-2-amine)—are structurally similar to MDMA, exhibiting both stimulant effects and producing MDA-like metabolites (Rickli et al. 2015; Roque Bravo et al. 2019, 2022).

When these substances are seized, they automatically become critical pieces of evidence in criminal cases. To ensure the investigation progresses efficiently and leads to a reliable outcome, robust scientific analysis is essential. However, in the case of NPS, the continuous emergence of new compounds with modified structures poses a significant challenge, as they often bypass existing legislation. This rapid evolution outpaces traditional methods of study—both in situ, in vivo, and postmortem—which require substantial time and financial resources. As a result, comprehensive analyses of these substances, including their identification and toxicity, struggle to keep up with the fast-moving nature of NPS development (Bruni et al. 2018; Shaker et al. 2021).

The international guidelines for the identification of illicit drugs are provided by the Scientific Working Group for the Analysis of Seized Drugs (SWGDRUG, swgdrug.org), which classifies identification methods into three categories: A, B, and C. Category A tests are the most accurate, as they identify substances based on their structural characteristics. For sample identity confirmation, a Category A test must be paired with another test from any other category. Category B tests focus on specific chemical and physical properties, providing more substance-specific identification. If a Category A test is not possible, two Category B tests, along with a third Category C test, must be conducted. Category

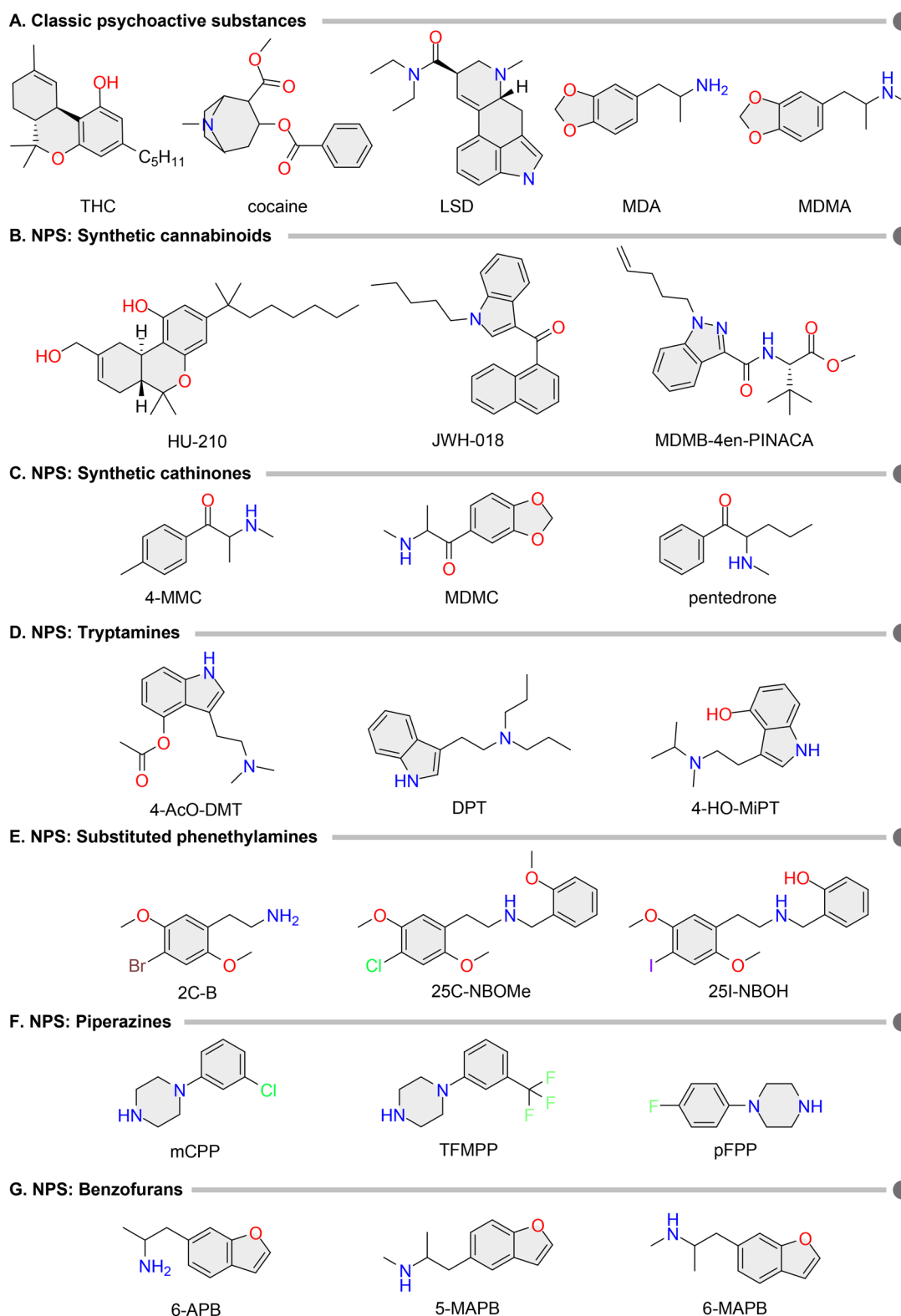


FIGURE 1 | Classic psychoactive substances alongside examples of various classes of NPS, including synthetic cannabinoids, synthetic cathinones, tryptamines, substituted phenethylamines, piperazines, and benzofurans.

C tests, which have the lowest discriminatory power, provide more general information and classify substances broadly (Abrahamsson et al. 2020).

Spectroscopic methods such as infrared spectroscopy, Raman spectroscopy, and nuclear magnetic resonance (NMR) are

classified as Category A tests, offering high discriminatory power for drug identification. Spectroscopy is a widely used analytical technique in scientific research, particularly for substance identification, as it measures the interaction between electromagnetic radiation and matter. This makes it a powerful tool for studying atomic and molecular structures. These methods

are fast, accurate, provide results in graphical form, and require only small sample amounts. However, when it comes to NPS, they are not always sufficient for proper identification. Due to the rapid emergence of new NPS compounds, consolidated analytical protocols and reference standards are often lacking, making accurate identification more challenging (Bruni et al. 2021; Rodrigues, Leite, and Bruni 2021).

3.2 | DFT Characterization of NPS

As an alternative to traditional methods, *in silico* approaches are gaining prominence when it comes to studies of NPS. These methods offer faster and more cost-effective results compared with conventional techniques, and they do not require a physical sample of the substance or regulatory approvals (de Melo et al. 2020). DFT calculations, in particular, have emerged as a valuable tool for the study of NPS. DFT is well-suited for the simulation of larger molecules, making it an ideal choice for determining the structures and properties of complex NPS compounds (Tandon, Chakraborty, and Suhag 2019). DFT enables the simulation of chemical profiles across various spectroscopic techniques, facilitating the identification of seized substances, even for novel compounds lacking experimental reference data. This capability allows for rapid analysis, making DFT invaluable in the timely investigation of emerging NPS.

DFT often offers good accuracy and allows for the consideration of solvent effects. Through the careful selection of appropriate keywords at the start of the calculation to match the molecular characteristics and the application of scaling factors to account for systematic errors such as anharmonicity (Merrick, Moran, and Radom 2007), highly satisfactory spectra can be obtained that can be used to identify the compounds in seized NPS samples. Moreover, the generated spectra represent pure samples, which is particularly beneficial, as seized substances often contain contaminants that can complicate traditional analyses. However, for accurate identification in real-world samples, it is important to account for the presence of contaminants. In these cases, DFT's ability to predict the spectra of pure compounds can serve as a reference point, but additional methods may be needed to disentangle the target substance from impurities during analysis (Castaing-Cordier et al. 2021; Mariotto, Rodrigues, and Bruni 2024; Rodrigues, De Mascarenhas, and Bruni 2022).

The outputs of DFT calculations offer extensive data on simulated spectra, including vibrational frequencies, oscillator strengths, and intensities. These parameters are critical for plotting the spectra and enable detailed comparison with experimental spectra. Vibrational frequencies provide insights into molecular motions, while oscillator strengths represent transition probabilities, both of which are essential for accurately matching simulated and experimental data. To ensure a thorough and reliable comparison, advanced data analysis techniques, such as chemometric methods, can be applied to extract the maximum amount of information from the calculated spectra and identify subtle differences or correlations between theoretical and experimental results.

Given the richness of this data, some studies integrate chemometric techniques with DFT-simulated spectra to develop robust *in silico* approaches, particularly for applications in forensic intelligence. These simulated spectra are typically validated by comparing them with experimental spectra from established databases, such as SWGDRUG and DWG-ENFSI (Drugs Working Group of the European Network of Forensic Science Institutes). The most common comparison methods involve point-by-point evaluations of discrete peak values and their corresponding intensities. When statistical analyses are applied, they often rely on univariate and bivariate metrics, including Pearson's correlation coefficients, Spearman's rank correlation coefficients, and Tanimoto's similarity coefficients, to quantify the degree of alignment between theoretical and experimental results (Bruni et al. 2018; Džodić et al. 2023; Graf et al. 2020; Kolodziejczyk et al. 2016; Mariotto, Rodrigues, and Bruni 2024; Milhazes et al. 2007; Minaeva et al. 2021; Rodrigues, De Mascarenhas, and Bruni 2022).

To illustrate the use of quantum chemical calculations combined with statistical analysis, Figure 2 presents theoretical and experimental results in the infrared region for two molecules: 2C-H and 25I-NBOMe. The theoretical spectra were obtained from Mariotto, Rodrigues, and Bruni 2024, while the experimental data, comprising six spectra for 2C-H (Figure 2A) and five for 25I-NBOMe (Figure 2B), were sourced from the SWGDRUG database. Each experimental spectrum is identified by its database ID and most indicate whether it was measured as the pure hydrochloride salt or the free base. Visual inspection suggests that for both compounds, the spectra of different samples qualitatively match well, both among themselves and with the computed spectra.

Figure 2C,D displays the Pearson's correlation coefficients calculated for the entire dataset, using wavenumbers from Mariotto, Rodrigues, and Bruni (2024) and the SWGDRUG database as variables. While the profiles of the substances (Figure 2A,B) appear visually similar, this similarity is not supported by the correlation analysis. Most data show weak correlations (coefficients between 0.20 and 0.49) or no significant correlation (coefficients below 0.20), not only between the experimental and theoretical spectra but also among the different experimental spectra themselves. These discrepancies may arise from variations in the spectra caused by factors such as adulterants, contaminants, or differences in the equipment and experimental conditions used during the analyses.

These results underscore the limitations of relying solely on univariate or bivariate metrics, such as Pearson's correlation coefficients, for the classification of NPS spectra. The complexity and variability in such datasets emphasize the need for more advanced statistical approaches to enhance the robustness and accuracy of spectral classification.

On the other hand, several studies employing multivariate analyses stand out, highlighting the potential of advanced data processing and analysis techniques. Fundamentally, these approaches can be divided into two major groups: unsupervised and supervised machine learning methods. Unsupervised methods do not require prior information about the system, such as class labels or discrete values. Commonly

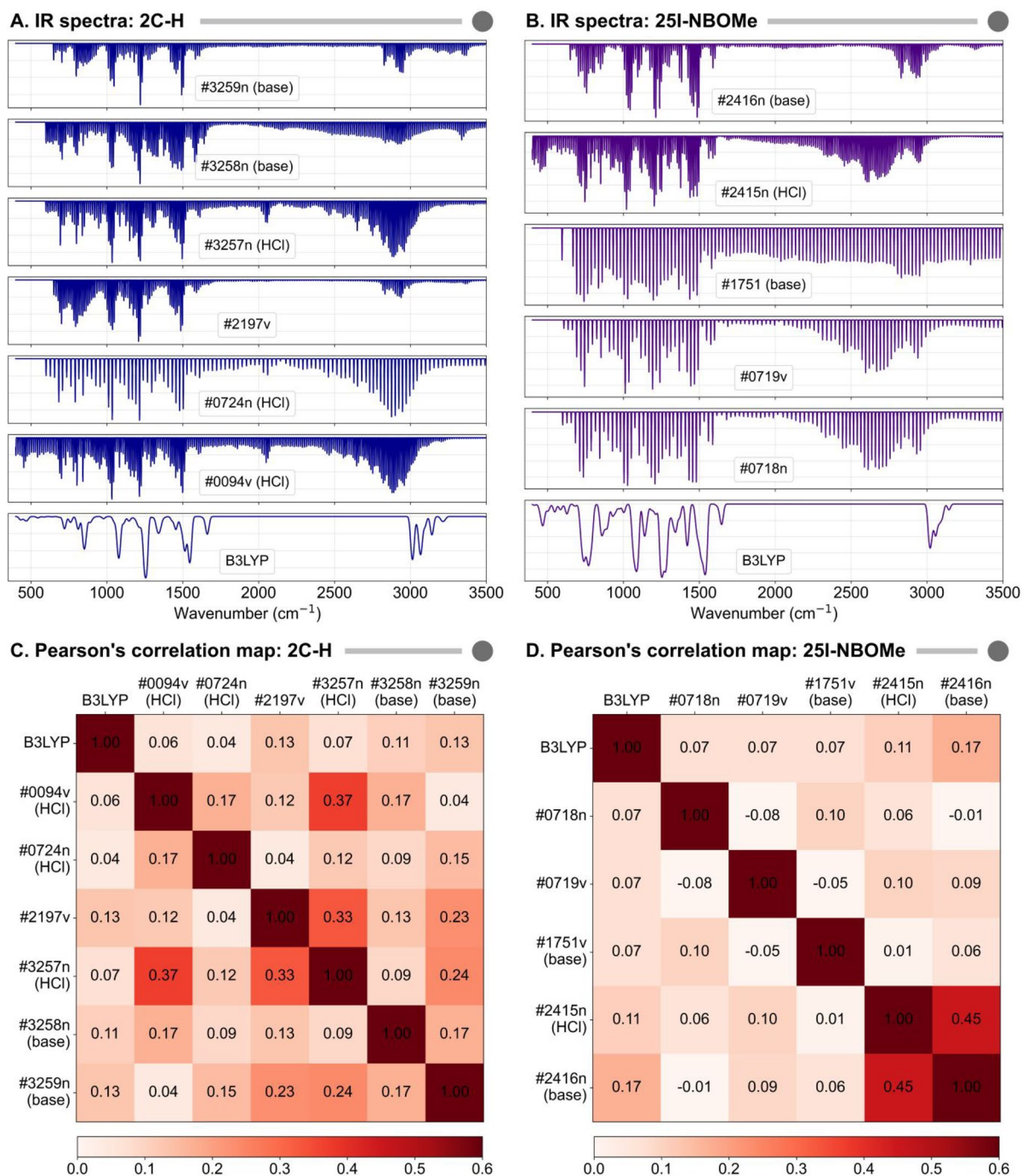


FIGURE 2 | Comparison of theoretical and experimental infrared spectra for (A) 2C-H and (B) 25I-NBOMe. Theoretical spectra were derived from Mariotto, Rodrigues, and Bruni (2024), while experimental data were obtained from the SWGDRUG database. Each experimental spectrum is labeled with its database ID, and most specify whether it was measured as the pure hydrochloride salt or the free base. Pearson's correlation coefficients, shown in (C) and (D), were used to quantify the agreement between the theoretical and experimental spectra.

used unsupervised methods include hierarchical cluster analysis (HCA) (Köhn and Hubert 2015; Zloh et al. 2017) and principal component analysis (PCA) (Abdi and Williams 2010; Calvo-Castro et al. 2018). HCA groups components into clusters based on their similarity by comparing key characteristics, while PCA reduces data dimensionality without significant information loss, transforming multivariate data into a new coordinate system using linear combinations. These

techniques are often referred to as exploratory methods because they are typically employed as a first step in analyzing large datasets to guide subsequent decision-making.

Tcharkhetian, Bruni, and Rodrigues (2021) used PCA to reduce the complexity of their dataset and identify the optimal combination of simulation parameters for DFT-based infrared spectra. This study focused on α -pyrrolidinopentiophenone, a synthetic

cathinone. Similarly, Sinhorini et al. (2021) employed PCA to organize and visualize the infrared spectra of 46 fentanyl analogs simulated by DFT. This analysis allowed the authors to define five classes, which were subsequently used to develop a supervised model using the SIMCA technique (see below) to classify experimental results.

Further exploring the characteristics of fentanyl analogs, Dogruer Erkok et al. (2024) examined the natural grouping of structures derived from DFT simulations. Their work revealed that cyclic compounds tended to cluster naturally, with the most intense spectral peaks serving as decisive factors for group formation.

For supervised analysis, soft independent modeling by class analogy (SIMCA) is a widely applied technique (Balabin, Safieva, and Lomakina 2011; Wold and Sjöström 1977). As a supervised classification method, SIMCA enables predictions of new data classifications based on a training set model. If a classification cannot be made, the method flags the data, allowing the analyst to investigate further or interpret the samples as outliers. Additionally, SIMCA offers graphical representations that aid in result interpretation and in assessing similarities between simulated and experimental spectra. This visualization capability has been effectively demonstrated in studies such as those by Bruni et al. (2018), de Castro, Rodrigues, and Bruni (2020), dos Santos and Bruni (2024), e Silva et al. (2008), Kumar et al. (2014), and Tcharkhetian, Bruni, and Rodrigues (2021).

Bruni et al. (2018) showed that the SIMCA technique could successfully classify the spectroscopic data of amphetamines and their homologous cathinones using only three principal components. Similarly, de Castro, Rodrigues, and Bruni (2020) achieved the correct classification of 41 synthetic cannabinoids into five classes with a SIMCA model using just two principal components. Both studies utilized models constructed from data obtained through DFT simulations, showcasing the power of SIMCA in effectively classifying complex spectroscopic datasets with minimal input dimensions.

3.3 | DFT in NPS Sensing Development

Beyond spectral analysis, DFT calculations also find applications in the development of chemical sensors for detecting NPS. These sensors interact with the molecular structure of NPS to generate analytical signals that can be interpreted both qualitatively and quantitatively. DFT aids in optimizing these interactions, improving sensor performance for accurate detection and analysis (Stetter, Penrose, and Yao 2003).

The literature reports various types of sensors, often based on host-guest chemistry, where a sensor molecule complexes with the target drug. These systems operate through mechanisms such as fluorescent response, photoluminescence, energy adsorption differentials, as well as potentiometric and electrochemical detection (Couto et al. 2018; Hosseini et al. 2017; Pang et al. 2023; Qu and Lin 2020; Razavipanah et al. 2018; Yen et al. 2022). Some examples are shown in Figure 3. DFT calculations are frequently employed to predict absorption and fluorescence spectra, assisting in the design of sensors that rely on colorimetric phenomena. For example, Pang et al. (2023)

developed a practical and cost-effective probe for the detection of tryptamines. The probe operates through π - π stacking and hydrogen bonding interactions, generating both colorimetric and fluorescent responses. DFT calculations were employed to predict the absorption spectra of 4-mercapto-1,8-naphthalic anhydride (MNA) before and after its complexation with tryptamine, a noncontrolled model molecule, providing information into the probe's sensing mechanism for tryptamines (Figure 3A).

For sensors based on adsorption mechanisms, where the chemical substance must adsorb onto the sensor material's surface, DFT calculations can be used to estimate adsorption energies. This is especially valuable when employing nanomaterials, as demonstrated by Hosseini et al. (2017), who predicted the adsorption energy of aluminum nitride nanostructures (nanosheets, nanotubes, and nanocages) with benzoylethanamine (Figure 3C). These calculations provide a key understanding of sensor-substance interactions, playing a vital role in optimizing the engineering and design of sensors.

In the case of photoluminescence-based sensors, TD-DFT can predict both electronic absorption and emission spectra by simulating the transitions between high-lying occupied molecular orbitals, such as the highest occupied molecular orbital (HOMO), and low-lying unoccupied molecular orbitals, including the lowest unoccupied molecular orbital (LUMO). These calculations account for vertical transitions, which occur instantaneously upon photon absorption and adhere to the Franck-Condon principle, as well as adiabatic transitions, where nuclear relaxation in both excited and ground states is considered.

Vibronic effects, which result from the interaction between electronic and vibrational states, can also be integrated into DFT calculations to more accurately capture detailed spectral features. In addition, Herzberg-Teller effects, which account for intensity borrowing due to vibronic coupling between electronic states, can be included to provide a more nuanced understanding of transition intensities. This comprehensive approach not only enhances the prediction of spectra but also facilitates the optimization of sensor design for improved photoluminescent performance. For example, Rodríguez-Nuévalos et al. (2022) developed colorimetric and fluorescent hydrazone-BODIPY (boron dipyrromethene) probes, BODIPY-1 and BODIPY-2, for the detection of γ -hydroxybutyric acid (GHB) and cathinones, including ephedrone (methcathinone), MPHP (4'-methyl- α -pyrrolidinohexiophenone), cathinone (β -keto-amphetamine), MDMC, and 3,4-MDPHP (3',4'-methylenedioxy- α -pyrrolidino hexiophenone) (Figure 3D). The electronic transitions responsible for the UV-Vis spectra, including the vertical excitation energies, were computed using TD-DFT calculations to provide insights into the probe's optical properties. In turn, Yen et al. (2022) employed DFT to explore the sensing mechanism of hydrophobic 1-dodecanethiol-stabilized gold nanoclusters for detecting synthetic cannabinoids. Their calculations revealed that the analyte induces photoluminescence quenching via an electron transfer process. The synthetic cannabinoids investigated include UR-144 ((1-pentylindol-3-yl)-(2,2,3,3-tetramethylcyclopropyl)methanone) and AB-PINACA (*N*-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-1-pentyl-1H-indazole-3-carboxamide) (Figure 3B).

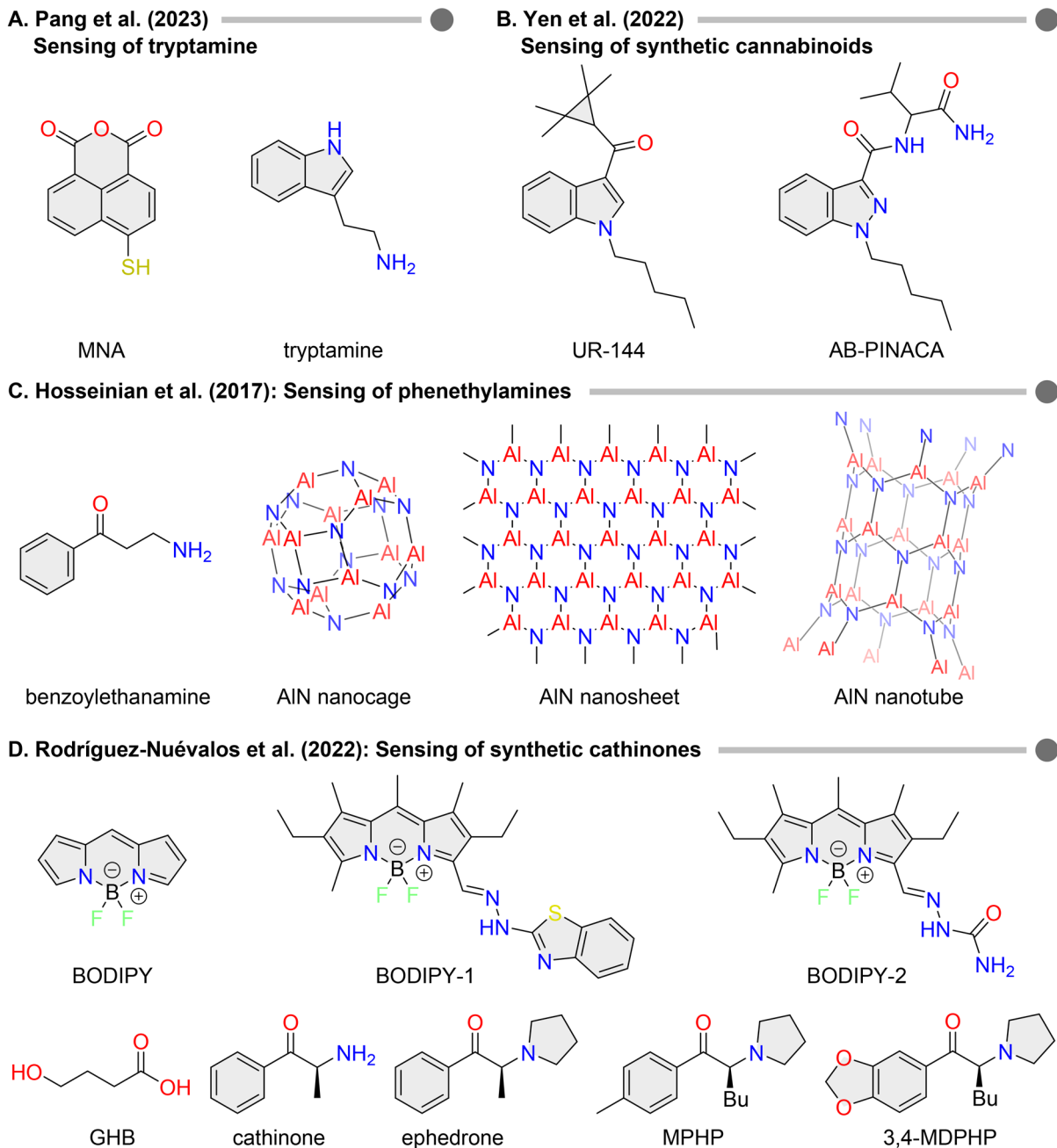


FIGURE 3 | Overview of selected sensors and NPS molecules discussed in Section 3.3. The molecular structure of MDMC is shown in Figure 1.

4 | Food Adulteration

4.1 | Principles of Food Adulteration

The importance of food laws has been evident throughout history, as records from various civilizations highlight the emphasis on honesty and integrity in combating food adulteration. This practice involves either the introduction of foreign substances into food or the depletion of its essential nutrients. The addition of foreign substances often includes chemical contaminants that have no place in food (Ayza and Belete 2015).

As urban populations expanded and processed food production increased during the 16th–18th centuries, opportunities for adulteration grew as well. In response, laws were introduced to

combat the practice, but they were largely ineffective due to the lack of reliable detection methods. However, the emergence of analytical chemistry in the early 1800s marked a turning point, as advancements in chemical analysis and the use of microscopes enabled the identification of foreign substances in food (Fortin 2023).

The issue of food adulteration has become increasingly widespread, prompting significant advancements in the establishment of international regulations. One of the most recommended global standards is the Codex Alimentarius ([fao.org/fao-who-codexalimentarius](https://www.fao.org/fao-who-codexalimentarius)), established in 1963 by the Food and Agriculture Organization (FAO) of the United Nations and the World Health Organization (WHO). In addition to international standards, many countries have national regulatory agencies

that enforce measures to prevent food adulteration and ensure compliance with safety regulations (Ayza and Belete 2015).

A notable case of intentional food adulteration is the 2008 Chinese milk scandal (Sharma and Paradakar 2010). Analysis of milk and dairy products from various companies revealed the presence of melamine (Figure 4A), a compound added to falsify protein content tests. In China, around 300,000 infants fell ill, and six died due to melamine contamination (Sharma and Paradakar 2010; Wang, Wei, and Wang 2021).

Accidental contamination of food products can also pose serious risks to public health. In 1979, a rice oil contamination incident occurred in Taiwan, where the oil was inadvertently tainted with polychlorinated biphenyls (PCBs), highly carcinogenic compounds (Pérez-Lucas, Navarro, and Navarro 2024), during the deodorization and decolorization process (Leon Guo et al. 2003). PCB 118 (2,3',4,4',5-pentachlorobiphenyl, Figure 4A) is a particularly toxic variant within the PCB family.

As a result of this accident, ~2000 individuals were poisoned, exhibiting symptoms such as hyperpigmentation of the skin and nails, severe acne, and excessive secretion from the Meibomian glands (Leon Guo et al. 2003).

When the identity of adulterants is unknown, detection becomes particularly challenging, as distinguishing between intentional and accidental adulteration is necessary for legal enforcement. While numerous chemical methods have been developed to detect adulterants, *in silico* approaches are increasingly utilized as complementary tools to enhance detection capabilities.

4.2 | DFT and Food Adulterants

Numerous studies have explored the intersection of food adulteration and the application of DFT calculations, focusing on various types of substances present in contaminated samples. These works (see Figure 4A–F) cover a range of

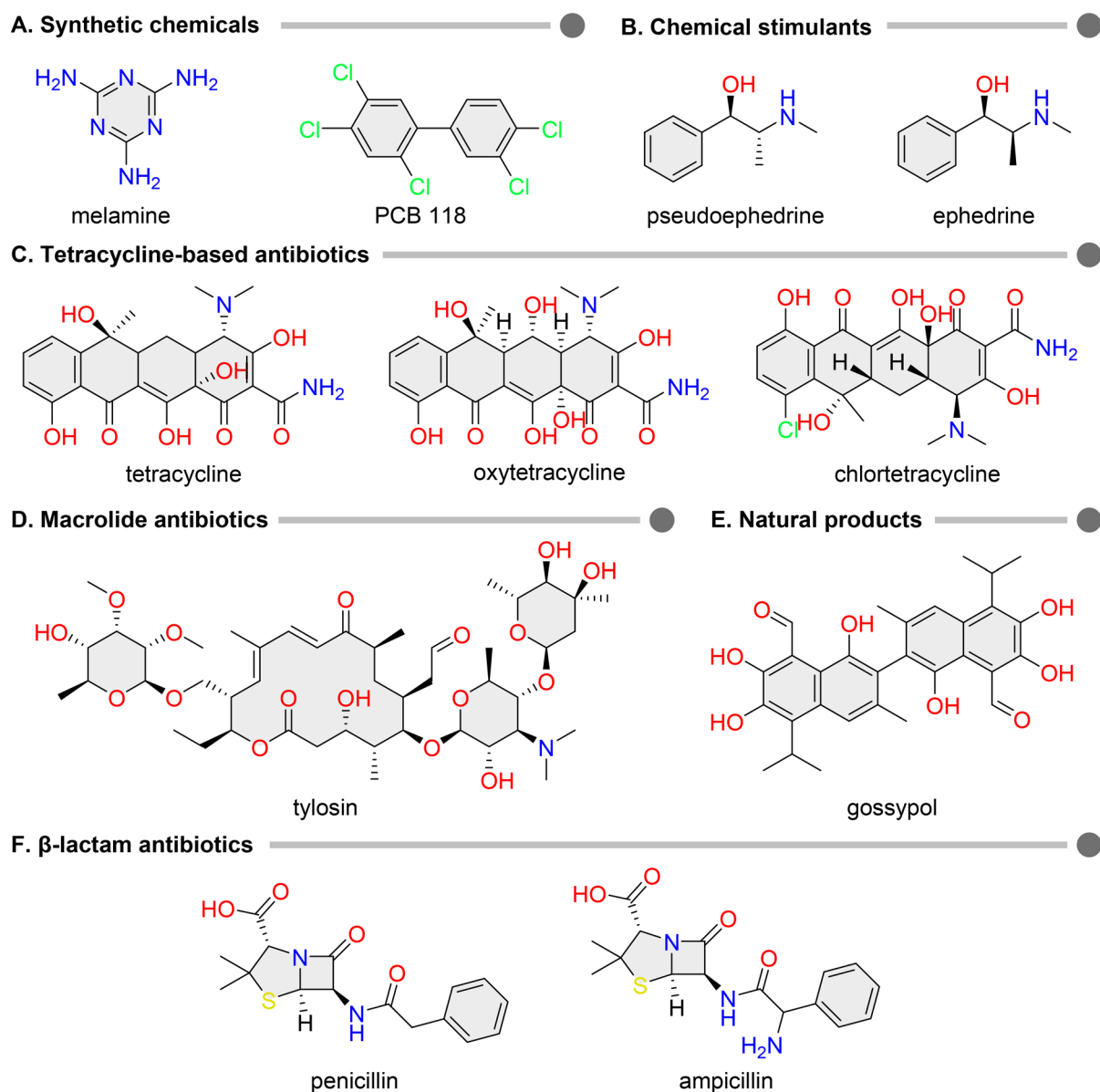


FIGURE 4 | Examples of food adulterants discussed in Section 3.3.

adulteration types, from the detection of veterinary drugs used during food production to diluents added to reduce manufacturing costs. For example, González Fá et al. (2019) investigated the detection of oxytetracycline (OTC) in honey using surface-enhanced Raman spectroscopy (SERS) with green-synthesized silver nanoparticles (Figure 4C). DFT calculations were employed to predict the vibrational frequencies of OTC and model its interaction with a silver cluster (Ag_3). Similarly, Teixeira et al. (2020) used DFT and vibrational spectroscopy to detect β -lactam antibiotics, such as penicillin and ampicillin (Figure 4F), in bovine milk. In their review, Ceniti et al. (2023) addressed the presence of other antibiotics in milk samples besides OTC, including tetracycline, chlortetracycline, and tylosin (Figure 4C,D).

DFT calculations were used to optimize the molecular structures and simulate IR and Raman spectra of these antibiotics, with solvent effects modeled using the polarizable continuum model (PCM). In this approach, the solvent is represented as a continuous medium that surrounds the solute, allowing the solvent's electrostatic influence to be accounted for without explicitly modeling individual solvent molecules. Theoretical spectra closely matched experimental data, helping establish spectroscopic patterns for antibiotics in milk, and providing a quick and accurate tool for detecting antibiotic residues in dairy products. Another recent example comes from the work of Pavlov et al. (2024), where they developed a 3D metal-organic framework, namely $\{[\text{Cd}_{16}(\text{tr2btd})_{10}(\text{dcdps})_{16}(\text{H}_2\text{O})_3(\text{EtOH})] \cdot 15\text{DMF}\}_n$ (**MOF-1**, $\text{tr2btd} = 4,7\text{-di}(1,2,4\text{-triazol-1-yl})\text{benzo-}2,1,3\text{-thiadiazole}$, $\text{H2dcdps} = 4,4'\text{-sulfonyldibenzoic acid}$) (**MOF-1**) with strong blue-green luminescence and a high quantum yield of 74%. **MOF-1** effectively detected gossypol (Figure 4E) in cottonseed oil, with a detection limit of $0.20\ \mu\text{M}$. Gossypol is a toxic polyphenolic compound found in cotton plants, known for its adverse effects on reproduction (Gadelha et al. 2014), making its detection in food products critical for safety. DFT calculations were employed to analyze the energy levels of the ligands in **MOF-1** and gossypol, showing that the LUMO levels of the tr2btd ligand and gossypol were close enough to enable a donor photo-induced electron transfer (d-PET) process. The X-ray structure of the asymmetric unit of **MOF-1** is shown in Figure 5. Finally, Miao et al. (2017) used two-dimensional correlation spectroscopy (2DCOS) to detect ephedrine and pseudoephedrine (Figure 4B) in illegally adulterated slimming herbal products (SHPs). By applying second derivative spectral pretreatment, they enhanced

the resolution and reduced the detection limit to below 1%. DFT calculations were employed to compute the IR spectra of both compounds, helping identify their distinct vibrational modes. The calculated spectra closely matched experimental results, confirming the effectiveness of this method for detecting adulterants in SHPs.

5 | Forensic Materials

The development of advanced tools for effective forensic investigation is crucial. Several studies incorporate DFT calculations to improve materials used in forensic investigations and to enhance the interpretation of trace evidence.

5.1 | Materials for Blood Detection: Luminol

One of the most iconic traces at a crime scene is the presence of blood. Luminol (5-amino-2,3-dihydro-1,4-phthalazine-dione, Figure 6A) has been a key substance for blood detection for over 40 years, due to its capacity to reveal blood traces even when they are invisible to the naked eye. Luminol reacts with oxidants, such as the iron in hemoglobin, producing a characteristic bluish luminescence (Barni et al. 2007). It is sensitive to both light and the presence of cations, typically remaining stable for 8–12 h. However, it is thermally unstable and must be protected from high temperatures to maintain its effectiveness (Barni et al. 2007).

DFT calculations have been playing a significant role in investigating the chemiluminescence mechanism of luminol, aiming to unravel the complex reaction pathways and identify key intermediates responsible for light emission. These studies focus on understanding the oxygenation of luminol, the chemiexcitation steps, and the formation of the light-emitting species. DFT provides atomistic and electronic insights into the structures, prototropic states, and behaviors of intermediates in various solvents, clarifying electron transfer processes and reaction pathways that are challenging to observe experimentally. Overall, *in silico* approaches continue to enhance our understanding of luminol's chemiluminescence, aiding not only in the interpretation of experimental data and improving forensic analysis but also in the design and development of new luminol-based compounds with improved sensitivity and performance for forensic applications

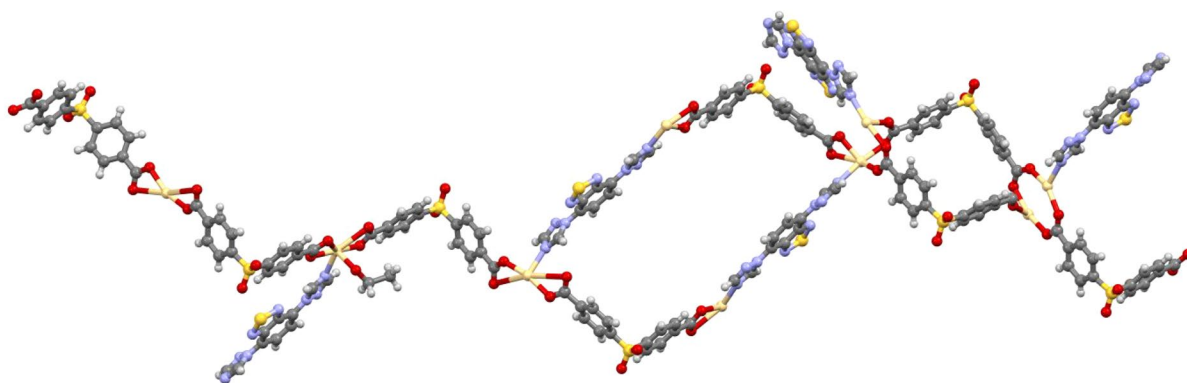


FIGURE 5 | X-ray structure of the asymmetric unit of **MOF-1**.

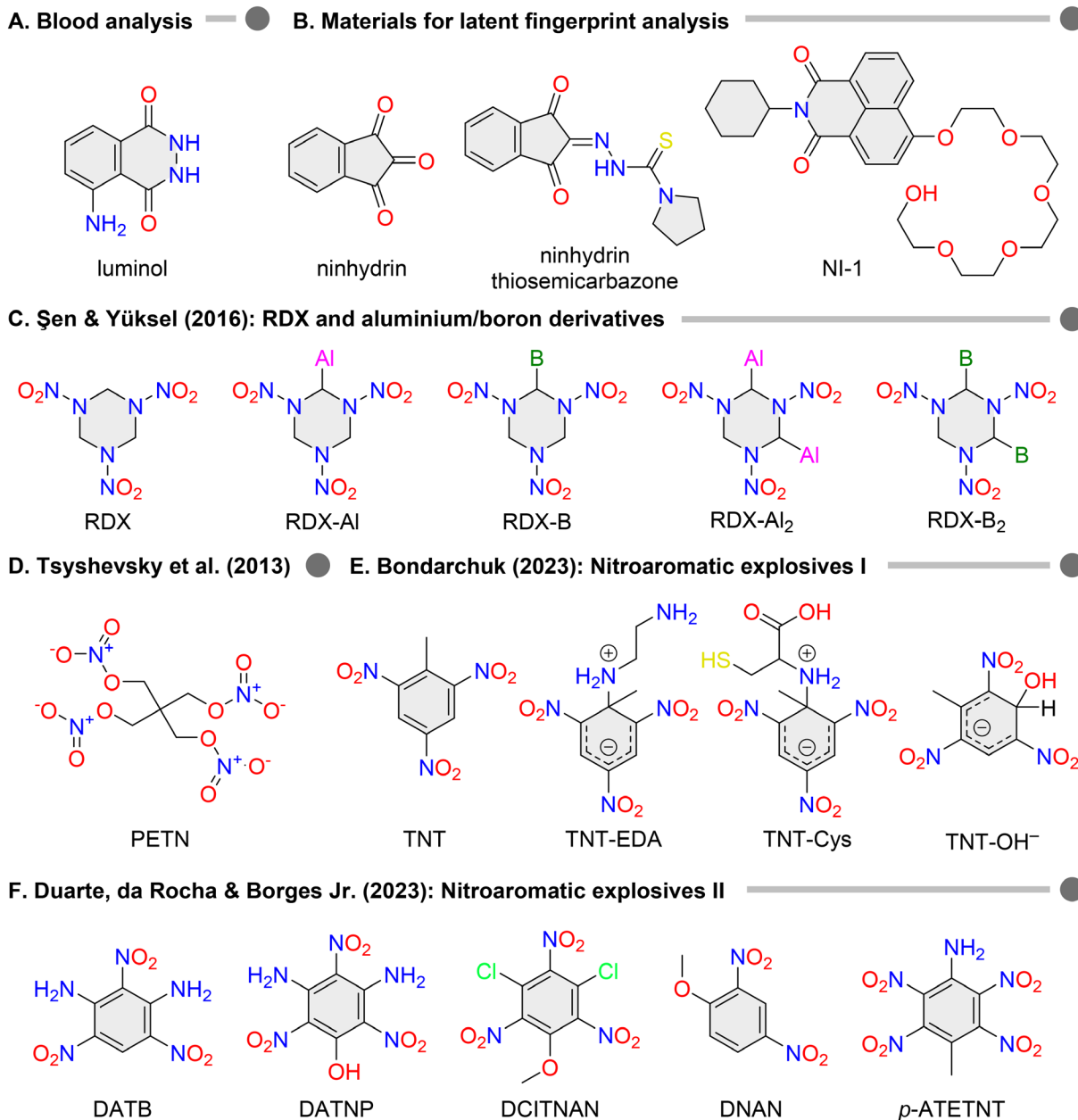


FIGURE 6 | Molecular structures of compounds used in (A) blood analysis, (B) latent fingerprint detection, and (C–F) explosives.

(Borrego-Sánchez et al. 2020; Cabello et al. 2023; Giussani et al. 2019; Mikroulis et al. 2021; Vacher et al. 2018; Yue and Liu 2019, 2020).

5.2 | Materials for Fingerprint Detection

Fingerprints are vital tools for human identification due to their unique patterns and have been used in crime investigation since 1892 (De Souza and Da Cunha Oliveira Neto 2021; Huynh and Halánek 2016; Yager and Amin 2004). They consist of ridges (raised portions) and furrows (lowered portions), which leave behind secretions that imprint the pattern onto surfaces (Yager and Amin 2004). At crime scenes, fingerprints are classified as latent, patent, or plastic. Latent fingerprints are invisible to the naked eye and require specialized visualization techniques. Patent fingerprints are visible,

often resulting from contact with substances like ink or blood, while plastic fingerprints are imprints found on soft, moldable surfaces (Gomes et al. 2023).

Recent studies have utilized DFT calculations to enhance tools for visualizing latent fingerprints. These tools often include fluorescent sensors, which make previously invisible fingerprints visible. DFT is used to improve the understanding of how these sensors interact with molecules, optimizing their design and effectiveness (Filipek et al. 2023; Jindal and Kaur 2023; Patel, Ashok Kumar, and Sahoo 2023; Tharmalingam et al. 2023; Zhu and Yan 2023).

For instance, DFT studies have examined the interaction of ninhydrin (Figure 6B), a reagent for revealing latent fingerprints, and its derivatives with various transition metals and naphthalimide-based fluorescent dyes. These calculations

help predict molecular interactions, including those with solvents, contributing to improve sensor efficacy for fingerprint analysis (Promkatkaew, Boonsri, and Hannongbua 2019; Rasin et al. 2023; Singh and Kumar 2023). Notably, Rasin et al. (2023) demonstrated that a ninhydrin-based thiosemicarbazone (Figure 6B) not only distinguishes Hg^{2+} and Zn^{2+} ions from other metal ions but also works for latent fingerprint detection, exhibiting strong adherence and clear ridge features without background stains, even on various surfaces. Additionally, Singh and Kumar (2023) showed that a naphthalimide-based fluorescent dye, **NI-1** (Figure 6B), doped in nanoporous silica powder, can visualize latent fingerprints up to levels 1–3. These levels include the detection of general ridge patterns (level 1), minutiae such as ridge endings and bifurcations (level 2), and finer details like sweat pores (level 3), on porous, non-porous, colored, stained, engraved, and aged surfaces.

Truccolo et al. (2020) carried out an extensive review involving the application of rare earths in several areas of forensic science. Their unique luminescent properties make them particularly valuable for applications such as fingerprint analysis and anti-counterfeiting technologies, including inks, labels, dopants, and resins. Several studies are currently applying DFT to investigate the electronic band structure of various rare earth compounds. These efforts aim to elucidate the mechanisms driving electron transfer from the valence band to the conduction band at specific points, enhancing understanding of how these processes affect, for example, fingerprint visibility (Ouyang et al. 2023; Vogiatzis et al. 2019).

Finally, sustainable approaches in latent fingerprint detection are becoming essential as forensic science aligns with the United Nations' sustainable development goals. In resource-constrained regions of the Global South, limited access to expensive reagents, advanced equipment, and training necessitates innovative, frugal alternatives. For instance, Bouzin et al. (2023) have explored the use of naturally occurring substances, such as genipin from *Genipa americana* L. and turmeric, to develop low-cost, environmentally friendly protocols for visualizing latent fingerprints. These alternatives, while potentially less effective than methods employed in the Global North, offer practical and sustainable solutions where resources are scarce. Moreover, they highlight opportunities for DFT calculations to investigate the fluorescence properties of natural materials, aiding the screening of candidates for sustainable fingerprint detection applications.

5.3 | Explosives

The use of explosives spans a wide range of activities, from lawful applications like mining and demolition to unlawful activities such as terrorist attacks. They are classified based on their chemical composition and are categorized as either single compounds or mixtures. Mixtures may consist of multiple explosive compounds or a combination of an explosive compound with fuels, binders, plasticizers, or oxidizer-fuel blends (Zapata and García-Ruiz 2020). Currently, there is an urgent need for effective trace detection of high explosives and the development of

methods that enable detection and identification of explosives at a standoff distance (Moore 2004).

Various analytical techniques have been explored for this purpose, including electrochemical sensors, immunosensors, and biosensor systems (Singh 2007; Wang et al. 2024), all of which offer promising platforms for the application of computational methods. Luminescence-based methods (Meaney and McGuffin 2008), including fluorescence sensing (Li et al. 2023), offer rapid and sensitive detection, while electrochemical techniques (Wang 2007) are valued for their portability and ability to detect trace levels of explosives. Advances in these technologies, combined with increased portability and rapid analysis times, are essential for enhancing the ability to detect explosives in real-world scenarios, including in public security settings (Moore 2004). Future developments are expected to prioritize enhanced sensitivity, specificity, and standoff detection capabilities to address the escalating demands of explosive detection.

DFT calculations have been widely applied to the study of explosives, providing information about molecular geometry, thermodynamic properties, decomposition mechanisms, and binding processes, as well as the behavior of explosive isomers. For example, Şen and Yüksel (2016) used DFT methods to study the detonation performance and thermal stability of explosives based on RDX (1,3,5-trinitro-1,3,5-triazinane, commonly known as royal demolition explosive), with the incorporation of boron and aluminum atoms (Figure 6C). Tsyshevsky, Sharia, and Kuklja (2013) combined DFT with variational transition state theory and large-scale periodic supercell calculations to elucidate the thermal decomposition of pentaerythritol tetranitrate (PETN), a representative of nitroester explosive (Figure 6D).

As thoroughly highlighted before, DFT methods are very useful for simulating spectra from various techniques. In the context of explosives, Bondarchuk (2023) applied DFT to study the structure and UV-Vis spectra of colored complexes of nucleophiles with nitroaromatic energetic materials. Specifically, they examined Meisenheimer and charge-transfer complexes of TNT (2,4,6-trinitrotoluene) with nucleophiles such as ethylenediamine (EDA), cysteine (Cys), and hydroxyl groups (Figure 6E).

Another recent example is Duarte, da Rocha, and Borges (2023), who used DFT and machine learning to analyze the molecular properties of explosives, focusing on factors that affect sensitivity. Their study decomposed the charge densities of nitroaromatic molecules into electric multipoles, providing key information for the development of safer explosives. Investigated systems (Figure 6F) included DATB (1,3-diamino-2,4,6-trinitrobenzene), DATNP (3,5-diamino-2,4,6-trinitrophenol), DCITNAN (3,5-dichloro-2,4,6-trinitroanisole), DNAN (2,4-dinitroanisole), and *p*-ATETNT (4-aminotetranitrotoluene).

In addition to DFT, *ab initio* methods are frequently used to investigate decomposition mechanisms and thermal stability, as demonstrated in Zakai et al. (2019). Specific software like EXPLO5, which calculates detonation parameters, has also been utilized, as shown in Sućeska's (1999) work on evaluating the detonation energies of various explosives. These examples highlight the utility of *in silico* tools like DFT in advancing our

understanding of explosive materials, enriching studies, and aiding the development of safer and more efficient explosives.

5.4 | Other Applications

Advances in computational chemistry are driving progress across various branches of forensic science, a rapidly expanding and inherently interdisciplinary field. This section highlights a few notable examples of computational approaches applied to areas not covered in the previous sections.

DNA and RNA detection and sequencing are crucial in forensic science, with theoretical methods playing an increasingly prominent role. Nanostructured materials like silicon nanowires (SiNW), graphene, and hexagonal boron nitride (BN) are key to advancing these applications. Santana et al. (2023) used DFT simulations to show that Cu-functionalized SiNW effectively adsorbs adenine, cytosine, and guanine, while Au functionalization favors thymine and uracil. Rani and Ray (2021) explored graphene-BN heterostructures, demonstrating their potential as efficient, high-resolution, and cost-effective DNA/RNA sensors, particularly when integrated into single electron transistor (SET) devices. These studies exemplify the precision and innovation theoretical approaches bring to DNA/RNA research.

DFT has been widely applied to predict drug fragmentation profiles, aiding in the interpretation of mass spectra. Huxley et al. (2024) investigated this approach for synthetic cathinones, exploring the azirine species as a potential intermediate in the reaction mechanism. They concluded that while azirine formation is energetically favorable, it is likely a short-lived species, making it difficult to observe through NMR. Similarly, Denis et al. (2022) and Lau et al. (2021) used DFT to study the fragmentation of fentanyl and its analogues, identifying fragmentation patterns, ion formation mechanisms, and dissociation pathways. Furthermore, the simulation of mass spectra using a combination of semi-empirical methods, such as GFN2-xTB (Bannwarth, Ehlert, and Grimme 2019), molecular dynamics simulations, and DFT calculations, has become increasingly common. Softwares like QCxMS (Koopman and Grimme 2021; Schnegotzki et al. 2022) and MBN Explorer (Solovyov et al. 2012, 2024) are particularly effective for identifying fragmentation pathways and elucidating the structures of molecular ions in the mass spectra of organic molecules, showcasing significant potential for application in the analysis of, for example, drugs of abuse and trace evidence, including cosmetics (Bruce et al. 2024).

Finally, theoretical methods are increasingly applied to the analysis of works of art and historical artifacts. The forensic aspect lies in the precise identification and authentication of materials, uncovering degradation pathways, and developing strategies to preserve and restore artifacts of historical and cultural importance. Due to the fragility and cultural significance of these pieces, experimental analyses are often constrained. Cañamares, Mieites-Alonso, and Leona (2022) used DFT to study the vibrational modes of shikonin, a dye derived from *Lithospermum erythrorhizon* roots, in the 8th-century Japanese calligraphy *Fragment of the Flower Garland Sutra* (Kegonkyō),

aiding in the assignment of Raman and surface-enhanced Raman spectroscopy (SERS) bands for pigment identification. Lubani et al. (2022) investigated degradation pathways in oil paints, focusing on zinc oxide (ZnO), a common white pigment. Their DFT simulations investigated the adsorption and thermodynamics of metallic soaps (zinc-fatty acid complexes), offering guidance for artwork conservation. Similarly, Mayda et al. (2023) used DFT to examine charge transfer processes at the interface of CdS and Cd(OH)Cl in Edvard Munch's *The Scream*. Their study highlighted the role of Cd(OH)Cl as an oxidative catalyst for CdS in humid conditions, shedding lights into degradation mechanisms and conservation strategies for oil paintings, as well as offering a foundation for detecting art adulteration.

6 | Conclusion

DFT has become an indispensable tool in forensic science, providing detailed insights into molecular properties, decomposition mechanisms, and spectroscopic behavior of forensic materials. Its application spans various forensic disciplines, including the detection of NPS, food adulteration, and forensic materials such as luminol and explosives. Future perspectives for DFT in forensics include expanding its application to fields such as bone osteology, where it can provide deeper insights into bone composition and degradation, aiding investigations involving skeletal remains. In art adulteration, DFT shows promise in detecting modern forgeries by simulating the spectroscopic signatures of pigments and binders, contributing to artwork authentication. Additionally, DFT has potential in sustainable forensics, exploring natural products as environmentally friendly alternatives to reagents like ninhydrin for latent fingerprint detection, thereby reducing the ecological footprint of forensic analyses. Machine learning is another area of future development, where DFT outputs can be integrated with machine learning models to enhance predictive power, streamline forensic investigations, and improve the accuracy of identifying forensic materials. This synergy between computational methods and artificial intelligence will open new avenues for more efficient, scalable, and accurate forensic tools. Overall, the continued integration of DFT with machine learning will drive innovations in forensic science, offering sustainable, precise, and advanced solutions for emerging challenges.

Author Contributions

Livia Salviano Mariotto: conceptualization (equal), formal analysis (equal), investigation (equal), methodology (equal), project administration (equal), writing – original draft (equal), writing – review and editing (equal). **Caio Henrique Pinke Rodrigues:** conceptualization (equal), investigation (equal), methodology (equal), writing – review and editing (equal). **Nigel John Mason:** conceptualization (equal), funding acquisition (equal), investigation (equal), methodology (equal), project administration (equal), resources (equal), supervision (equal), writing – review and editing (equal). **Aline Thais Bruni:** conceptualization (equal), funding acquisition (equal), investigation (equal), methodology (equal), project administration (equal), resources (equal), writing – review and editing (equal). **Felipe Fantuzzi:** conceptualization (equal), funding acquisition (equal), investigation (equal), methodology (equal), project administration (equal), resources (equal), supervision (equal), validation (equal), writing – original draft (equal), writing – review and editing (equal).

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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