

Research Article

Synthesis and Pharmacokinetic Evaluation of Novel Bioactive Organic Compounds

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Abstract

The integration of medicinal chemistry with modern computational and *in silico* approaches enables the scientific re-evaluation of traditional knowledge, particularly highlighting the role of organic bioactives products. This study describes the synthesis and pharmacokinetic profiling of a series of organic compounds of pharmaceutical interest that were designed to act as potential bioactive agents. Synthesis strategies were optimized to improve reaction yields. Comprehensive spectroscopic analyses, including nuclear magnetic resonance analysis of protons and carbon-13 (¹H and ¹³C) and mass spectrometry, were employed to verify the molecular structures and evaluate the purity of the synthesized compounds. The synthesized products were then theoretically evaluated for their pharmacokinetics using standard drug-type tests. The results revealed that products were obtained in the best yields (65-82%) using our validated protocols of synthesis and characterized for their structure. For the theoretical study on their pharmaceuticals assessments, most of the compounds exhibited favorable pharmacokinetic profiles (that satisfied the key criteria of Lipinski, and the Connolly parameters (solubility and stability)), as well as demonstrating a good safety profile. This study highlights the importance of combining optimized synthesis methodologies with computational pharmacokinetic screening as an effective method for the initial design and evaluation of new molecules.

Keywords

Synthesis, Spectroscopic Characterization, *In Silico* Pharmacokinetics, Lipinski-compliant Drug-likeness

1. Introduction

Recent advances in medicinal chemistry have intensified the search for new biologically active molecules exhibiting chemical stability, structural diversity, and good pharmacokinetic potential. Among these, Schiff bases, hydrazones,

semicarbazones, and thiosemicarbazones are of particular interest due to their ease of synthesis, functional adaptability, and numerous biological applications, notably antimicrobial, antioxidant, and anticancer properties [1, 2]. Schiff base metal

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complexes are widely used in medicine for treating multiple viral diseases due to their transition metal complexes, which play a key role in several areas, including antibacterial, anti-fungal, anticancer and anti-inflammatory activities [3-5]. These organometallic materials have also been used as catalysts in many reactions, such as the Aldol reaction, polymerization reaction and oxidation reaction [6-9]. These compounds result from the condensation of a carbonyl derivative with a primary amine, a hydrazine, or a (thio) semicarbazide, forming an azomethine bond ($-\text{CH}=\text{N}-$) responsible for numerous electronic and biological properties [10]. Their spectroscopic characterization-notably by IR, $^1\text{H}/^{13}\text{C}$ NMR and UV-Visible - makes it possible to confirm the formation of the $\text{C}=\text{N}$ double bond and to study the effect of substituents on electronic behavior [11]. The *in-silico* evaluation of drug-likeness parameters, based on Lipinski's rule [12], is an essential tool for predicting the oral bioavailability and membrane permeability of molecules. Recent approaches combine experimental spectroscopic analyses with calculations of physicochemical parameters (*Log P*, molecular weight, H-bond donors/acceptors "only N and O") to identify promising compounds [13]. In this context, the present study aims at the synthesis, spectroscopic characterization, and Lipinski parameter evaluation of new bioactive molecules, in order to correlate their structural and electronic properties with their pharmacological potential. Our work involved synthesizing a series of compounds, studying the effect of substituents based on a simple structure, and then examining their pharmacokinetic properties.

2. Material and Methods

2.1. Chemical Products

The reactants were used as obtained from Sigma-Aldrich, BDH AnalaR, AnalaR NORMAPUR[®] analytical reagent, Fisher Scientific, Ataman Chemicals, Thermo Scientific Chemicals, Acros Organic, etc. without further purification: diphenylketone (99%), hydrazine hydrate (100%), phenylisothiocyanate (97%), Bis (4-chlorophenyl) ketone (99.50%), (4-nitrophenyl)(phenyl) ketone (99%), (3, 4-dichlorophenyl)(phenyl) ketone (98%), glacial acetic acid ($\geq 99\%$), technical ethanol (EtOH, 96°), ethanol absolute (EtOH, 99.7-100%).

2.2. Methods

Theoretical analysis: Pharmacokinetic profiles determined with standard drug-likeness tests using key Lipinski criteria [12, 14].

Preparation: N (4)-Phenyl-3-thiosemicarbazide was prepared from hydrazine hydrate and phenyl isothiocyanate in the presence of technical ethanol according to our synthesis method described in our previous work [15, 16]. This product, in turn, reacted with ketone differences in 96° ethanol or absolute ethanol in the presence of glacial acetic acid to produce synthetic products. For the synthesis of products, we explored the methods validated and described in our previous works (Scheme), varying the reaction catalysts [16-19].

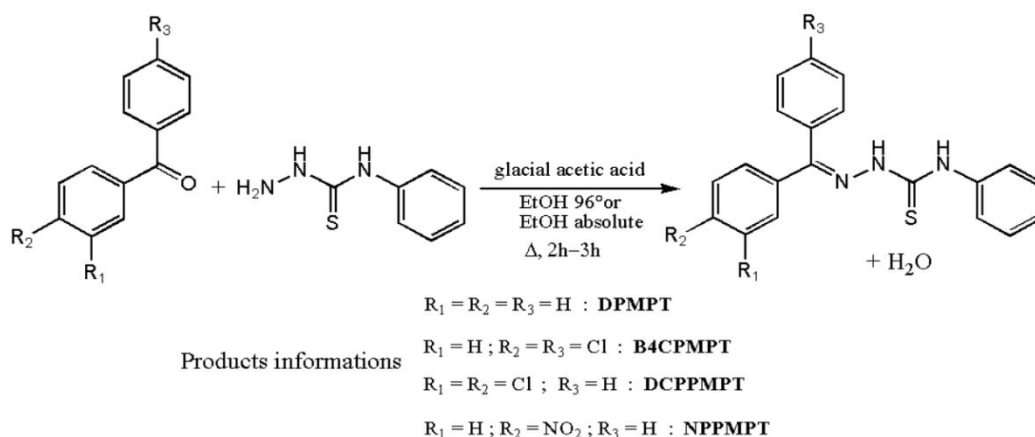


Figure 1. Synthesis route of products.

After their synthesis, the products were submitted to structural analysis methods.

Apparatus: The synthesis products were characterized by elemental analysis. Proton (^1H) and carbon-13 (^{13}C) NMR spectra were recorded on a Bruker Avance 400 UltraShield apparatus with DMSO- d_6 and CDCl_3 as the solvent, when the instrument was calibrated to frequencies of 400.130 MHz and 100.613 MHz for protons and carbon-13, respectively.

Chemical shifts (δ) are expressed in parts per million (ppm) relative to the reference tetramethylsilane (TMS). The multiplicity of ^1H NMR signals was classified as follows: singlet (s), doubled singlet (sd), multiple or massive (m), etc. (ii) Mass spectra were recorded in positive mode by atmospheric pressure chemical ionization (APCI) ($[\text{M}-\text{H}]^+$) and masses are given in m/z .

3. Results and Discussion

Each reaction had its own specific characteristics, with reflux times varying from 2 to 4 hours depending on the substrate used. Carbazone synthesis is generally carried out in the presence of acids (HCl, H₂SO₄, etc.) with alcoholic solvents. In our study, we used optimal synthesis conditions. Certain ketones do not produce a homogeneous mixture in an aqueous medium when dissolved, such as diphenylketone for example. We therefore used absolute ethanol as the solvent. As the acids mentioned above are not anhydrous, we opted for glacial acetic acid, which allowed us to obtain a homogeneous reaction mixture throughout the reflux reactions. After cooling to room temperature, we obtained crystals that we filtered and washed to neutrality and then dried. We then recrystallized all the crude reaction products in ethanol 96°. The electronic effects at the level of each ketone explained the different yields obtained for each synthesis, as the reagent was the same.

Four molecules were synthesized in this study.

They are: 1-(diphenylmethylene) N-(4-phenyl-3-thiosemicarbazide (*DPMPT*); 1-[bis(4-chlorophenyl)methylene] N-(4-phenyl-3-thiosemicarbazide (*B4CPMPT*); 1-[(3,4-dichlorophenyl)(phenyl)methylene] N-(4-phenyl-3-thiosemicarbazide (*DCPPMPT*) and 1-[(4-nitrophenyl)(phenyl)methylene] N-(4-phenyl-3-thiosemicarbazide (*NPPMPT*).

After their synthesis, products were submitted to structural characterization.

Product 1: *DPMPT*

Yield: 82%; ¹³C NMR δ (DMSO-d₆, ppm): 175.47 (C=S); 149.22 (C=N); 137.11; 135.73; 130.49; 129.65; 129.15; 128.02; 127.75; 125.38 (C-Ar). ¹H NMR δ (CDCl₃, ppm): 9.45 (s, 1H, C=NNH-); 8.75 (s, 1H, CSNH-Ph); 7.60-7.25 (m, 15H, H-Ar). MS (m/z) [M-H]⁺: 332.02.

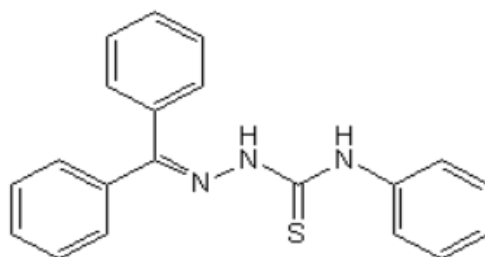


Figure 2. 1-(diphenylmethylene) N-(4-phenyl-3-thiosemicarbazide (*DPMPT*).

Product 2: *B4CPMPT*

Yield: 73%; ¹³C NMR δ (CDCl₃, ppm): 179.03 (C=S); 148.57 (C=N); 139.19; 137.03; 136.68; 135.51; 134.59;

131.35; 130.50; 128.95 (C-Ar). ¹H NMR δ (CDCl₃, ppm): 9.45 (s, 1H, C=NNH-); 8.75 (s, 1H, CSNH-Ph); 7.60-7.25, 6.49 (m, 13H, H-Ar). MS (m/z) [M-H]⁺: 401.27.

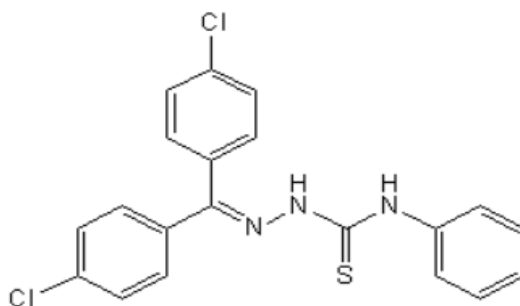


Figure 3. 1-[bis(4-chlorophenyl)methylene] N-(4-phenyl-3-thiosemicarbazide (*B4CPMPT*).

Product 3: *DCPPMPT*

Yield: 69%; ¹³C NMR δ (CDCl₃, ppm): 176.06 (C=S); 147.59 (C=N); 137.69; 136.57; 134.40; 133.09; 132.15; 131.07; 130.66; 130.29; 129.30; 128.92; 128.44; 127.87;

127.68; 126.88; 126.48; 124.59 (C-Ar). ¹H NMR δ (CDCl₃, ppm): 9.35 (sd, 1H, C=NNH-); 8.75 (sd, 1H, CSNH-Ph); 7.75-7.25 (m, 13H, H-Ar). MS (m/z) [M-H]⁺: 401.31.

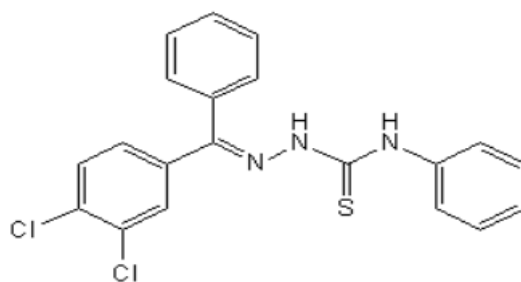


Figure 4. 1-[(3,4-dichlorophenyl)(phenyl)methylene] N-(4)-phenyl-3-thiosemicarbazide (DCPPMPT).

Product 4: *NPPMPT*

Yield: 65%; ^{13}C NMR δ (CDCl_3 , ppm): 173.70 (C=S); 146.02 (C=N); 144.81; 140.02; 135.14; 128.65; 127.98; 127.74; 127.69; 126.54; 126.28; 126.00; 124.16; 122.05;

121.91; 121.36 (C-Ar). ^1H NMR δ (CDCl_3 , ppm): 9.45 (s, 1H, C=NNH-); 8.85 (s, 1H, CSNH-Ph); 7.85-7.25 (m, 14H, H-Ar). MS (m/z) $[\text{M}-\text{H}]^+$: 377.26.

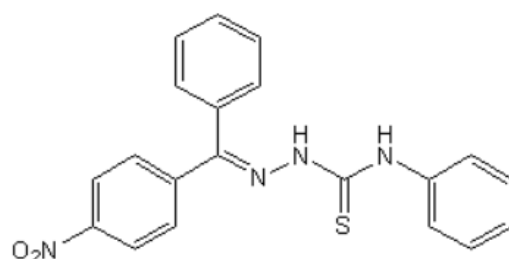


Figure 5. 1-[(4-nitrophenyl)(phenyl)methylene] N-(4)-phenyl-3-thiosemicarbazide (NPPMPT).

For structural characterization, we relied heavily on NMR analysis, especially with regard to the new imine function that forms at the end of the synthesis. Carbon-13 NMR proved the absence of carbonyl (C=O) after synthesis. The spectra show peaks with a different chemical shift from that of the carbonyls of the substrate ketones. We have peaks originating from the carbon in the main C=N function. We have peaks at δ = 149.22, 148.57, 147.59, and 146.02 ppm, which correspond well to the C in the imine of the synthetic molecules. In proton NMR, the two terminal H atoms of $\text{H}_2\text{N}-\text{NH}-$ disappear. No signal corresponding to these protons was found. These results are consistent with those in our previous work and those in the literature [16, 18, 19]. We observed the presence of Syn

and Anti isomers in the compound 1-[(3,4-dichlorophenyl)(phenyl)methylene] N-(4)-phenyl-3-thiosemicarbazide (DCPPMPT), even though the ratio is practically 1:1 [19].

One of the most important physicochemical factors in assessing the biological behavior of bioactive compounds is lipophilicity. The lipophilicity of drugs exerts a considerable influence on their pharmacokinetic and pharmacodynamic behavior, thus prompting the intensive search for methods to accurately assess this property [20-22].

In our study, we obtained *Log P* and *C Log P* values using ChemDraw Ultra 8.0 Application software (Table 1).

Table 1. Reasonable Pharmacokinetics and Drug Availability Parameters (Five Rules of Lipinski) of Synthesized Products.

Compound	Molecular weight (g.mol ⁻¹)	LogP	C LogP	Number of H bond donors	Number of H bond acceptors	Number of criteria met
Rules	< 500	< 5		≤ 5	< 10	at least 3
DPMPT	331.43	5.35	4.70	2	3	all
B4CPMPT	400.32	6.46	6.24	2	3	3
DCPPMPT	400.32	6.46	6.12	2	3	3
NPPMPT	376.43	4.23	4.62	2	6	all

Taking diphenylketone N-(4)-phenyl-3-thiosemicarbazide (DPMPT) as the reference compound ($\text{Log } P = 5.35$; $C \text{ Log } P = 4.70$), it can be seen that the addition of chlorine atoms to both aromatic rings of diphenylketone or to both atoms on the same ring caused an increase in the permeability and solubility parameters of the new compound ($\text{Log } P = 6.46$; $C \text{ Log } P \geq 6.12$). The substitution of a 4-H by the nitro group ($-\text{NO}_2$) led to a decrease in lipophilicity compared to the reference compound ($\text{Log } P = 4.23$; $C \text{ Log } P = 4.62$). This result therefore confirms previous work in the literature [18]. In drug development, lipophilicity is vital for predicting and improving the pharmacokinetic and toxicological profile of synthetic molecules. Controlling this is key to developing new, biologically active compounds with high therapeutic potential.

$\text{Log } P$ is adjusted by adding polar groups ($-\text{OH}$, $-\text{NO}_2$, $-\text{NH}_2$) to decrease or halogenated or alkyl groups to increase [23-25]. We noticed in our study that all products also have a significant molecular weight ($331\text{--}400 \text{ g.mol}^{-1}$) and number of N and O atoms (3-6), which induce interesting pharmaceutical properties. The parameters of molecular weight and the sum of nitrogen and oxygen atoms are of great significance as described Lipinski [12, 14, 23].

Data on the solubility and degradation of organic compounds in green solvents is needed for environmental remediation, chemistry, chemical engineering and medicine. The solubility of organic compounds increases with water temperature (Table 2).

Table 2. Connolly Parameters (Solubility and Stability) of Products at 298°K [26-28].

Compound	Connolly Accessible Area ($\text{\AA}^2$)	Connolly Molecular Area ($\text{\AA}^2$)	Connolly Solvent-Excluded Volume ($\text{\AA}^3$)
DPMPT	496.925	308.464	251.135
B4CPMPT	540.261	338.449	279.285
DCPPMPT	536.881	336.963	279.029
NPPMPT	531.091	331.516	270.678

The lipophilicity obtained from theoretical calculations agrees well with the surface areas and exchange volumes. In our work, product more lipophilic (B4CPMPT) has the widest distribution of available surface area and volume, and therefore the greatest solubility. Studies have shown that a molecular dot surface consists of a smooth envelope of points on the molecular surface. The solubility of organic compounds affects the design and operation of process equipment. The free volume and distribution of the compound influence the transport properties of penetrants. Low-polarity organics are insoluble in water under ambient conditions but become soluble at higher temperatures [27, 28]. These parameters facilitate the quantification of molecules' geometry, dimensions, and accessibility, which are pivotal for optimizing their pharmacodynamic and pharmacokinetic properties. If a molecule is too large or difficult to mix with other substances, it may not dissolve well or bind strongly [29-32]. If a drug does not dissolve well in water, it may not be absorbed well in the gut. This is because the amount of drug that is absorbed is related to how much is in the gut [23].

Our products constitute a strategic structural database in medicinal chemistry, due to the synergy between the thiosemicarbazide pharmacophore and the substituted aryl groups, which gives them high bioactive potential, modifiable by electronic and steric effects. These various pharmacokinetic parameters are favorable for the development of new thera-

peutic candidates.

4. Conclusion

Our work has led to the synthesis of four molecules with good yields. These results demonstrate the value of combining the optimization of synthesis processes with pharmacokinetic modeling approaches in order to accelerate the identification of promising bioactive candidates. Pharmacokinetic predictions revealed general compliance with Lipinski's criteria and several key indicators of drug-likeness, suggesting favorable potential for oral bioavailability and limited toxic risk in the early stages of selection. This consistency between experimental properties and theoretical behaviors highlights the relevance of combining modeling and synthetic chemistry in the exploratory phase of drug discovery.

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Author Contributions

Bienvenu Glinma: Conceptualization, Methodology, Val-

idation, Formal Analysis, Writing – original draft, Writing – review & editing, Software.

Sedami Medegan Fagla: Methodology, Formal Analysis, Writing – original draft.

Hyacinthe Finagnon Agnimonhan: Formal Analysis, Investigation, Writing – original draft.

Benedicta Kpadonou-Kpoviessi: Data curation, Investigation.

Eleonore Yayi: Visualization, Formal Analysis, Writing – review & editing, Resources.

Joachim Gbenou: Visualization, Validation, Resources.

Jacques Poupaert: Conceptualization, Methodology, Resources, Writing – review & editing.

Fernand Gbaguidi: Methodology, Validation, Writing – original draft, Supervision.

Salome Kpoviessi: Resources, Visualization, Supervision, Investigation.

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Data Availability Statement

The data supporting the outcome of this research work has been reported in this manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

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