American Research Journal of
Chemical Engineering

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Research Article

Design, Structural Characterization, and *In Vivo* Disposition Analysis of Newly Developed Therapeutic Molecules

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Publication Information: Accepted: Aug 14, 2026, **Published:** Aug 21, 2026.

Citation: Kuipers L, et al. Design, Structural Characterization, and In Vivo Disposition Analysis of Newly Developed Therapeutic Molecules. American Research Journal of Chemical Engineering, Vol 1, no. 1, 2026: 1-8.

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Abstract

The development of structurally diverse organic molecules remains an important area of medicinal and pharmaceutical chemistry. Thiosemicarbazone derivatives have attracted research interest because their molecular frameworks can be modified through the introduction of different aromatic substituents, allowing changes in their electronic and physicochemical characteristics. The present investigation describes the preparation and structural examination of four substituted thiosemicarbazone compounds derived from diphenyl ketone and its halogenated and nitro-substituted analogues. The synthetic procedure involved condensation reactions under alcoholic reflux conditions, followed by crystallization and purification. Product structures were examined using proton and carbon nuclear magnetic resonance spectroscopy and mass spectrometry. Isolated yields ranged from 65% to 82%, with the unsubstituted derivative providing the highest recovery. Computational assessment included molecular weight, lipophilicity, hydrogen-bonding characteristics, and molecular surface descriptors. The calculated molecular weights ranged between 331.43 and 400.32 g/mol. Differences in aromatic substitution produced noticeable variations in partition coefficients and molecular surface characteristics. The findings demonstrate the value of combining controlled organic synthesis, spectroscopic verification, and preliminary molecular-property assessment when selecting compounds for subsequent pharmaceutical investigation.

Keywords: Thiosemicarbazone Derivatives; Organic Synthesis; Nuclear Magnetic Resonance; Spectroscopic Characterization; Molecular Lipophilicity; Drug-Likeness; Computational Chemistry; Molecular Surface Analysis; Physicochemical Properties; Medicinal Chemistry.

INTRODUCTION

The preparation of structurally modified organic compounds is an established approach in medicinal chemistry, where relatively small changes in molecular architecture can influence chemical reactivity, intermolecular interactions, and physicochemical behaviour. Nitrogen- and sulfur-containing organic molecules are of interest because these heteroatoms contribute to hydrogen bonding, electronic delocalization, and coordination interactions. Among these chemical families, thiosemicarbazone derivatives provide an adaptable framework for investigating relationships between aromatic substitution and molecular properties [1]. Thiosemicarbazones are generally obtained through condensation between carbonyl-containing compounds and thiosemicarbazide derivatives. Their characteristic azomethine linkage, together with the thiocarbonyl group, provides a combination of nitrogen and sulfur donor sites. Changes in the substituents attached to the carbonyl-derived portion can modify the electronic distribution and steric environment of the resulting molecule. These structural features have contributed to their extensive investigation in synthetic, coordination, and medicinal chemistry [2].

The chemistry of thiosemicarbazones has also been examined in relation to metal coordination, where ligand structure influences bonding arrangements, coordination geometry, and the properties of the resulting complexes. Aromatic substituents, halogen atoms, and electron-withdrawing groups can affect these interactions by changing the electronic environment of the ligand [3]. Reviews of heterocyclic thiosemicarbazone compounds have further documented the relationship between molecular structure, coordination behaviour, and reported biological activities [4]. The preparation of substituted derivatives therefore provides an opportunity to examine how modifications in aromatic rings influence molecular characteristics. Chlorine substitution can alter electron distribution and increase molecular hydrophobicity, whereas nitro substitution introduces additional oxygen atoms and changes the polar character of the structure. Such modifications may affect molecular partitioning, solubility, and interactions with biological environments. Earlier investigations of thiosemicarbazone chemistry have demonstrated the importance of examining these structural variations through complementary analytical approaches [5]. Nuclear magnetic resonance spectroscopy is particularly useful for confirming the structural changes associated with condensation reactions. Proton and carbon-13 spectra provide information about hydrogen environments, aromatic carbon atoms, imine formation, and thiocarbonyl-containing groups. The disappearance of signals associated with starting-material functional groups and the appearance of new resonances provide evidence supporting the proposed molecular structures [6].

Mass spectrometry offers complementary molecular-mass information and can assist in evaluating the identity of synthesized products. When combined with elemental and spectroscopic measurements, these techniques provide a more complete basis for structural assignment [7]. The interpretation of NMR data also requires consideration of solvent effects, chemical shifts, signal multiplicity, and possible geometrical isomerism [8]. Computational physicochemical assessment has become an established preliminary stage in pharmaceutical research. Molecular weight, hydrogen-bond donor and acceptor counts, and lipophilicity are frequently examined to identify compounds whose properties fall within commonly used drug-likeness ranges. These descriptors provide an initial indication of whether a molecular structure may possess suitable characteristics for further investigation [9].

The present study examines four thiosemicarbazone derivatives prepared using diphenyl ketone, bis(4-chlorophenyl)ketone,(3,4-dichlorophenyl)(phenyl)ketone, and (4-nitrophenyl)(phenyl) ketone. Their structures were examined through spectroscopic techniques, while calculated molecular properties and surface descriptors were used to compare the effects of aromatic substitution. The investigation focuses on the relationship between synthetic yield, structural confirmation, and preliminary physicochemical characteristics.

MATERIALS AND METHODS

Chemicals and Reagents

The starting materials and solvents were obtained from commercial chemical suppliers and used without additional purification. The principal reagents included diphenyl ketone, hydrazine hydrate, phenyl isothiocyanate, bis(4-chlorophenyl) ketone, (4-nitrophenyl)(phenyl) ketone, and (3,4-dichlorophenyl)(phenyl) ketone. Glacial acetic acid was employed during condensation reactions. Technical-grade ethanol and absolute ethanol were used as reaction and recrystallization solvents, respectively.

Preparation of the Thiosemicarbazide Intermediate

N(4)-Phenyl-3-thiosemicarbazide was prepared by reacting hydrazine hydrate with phenyl isothiocyanate in an alcoholic medium. The reaction was conducted according to the established synthetic procedure described in the source manuscript. The resulting intermediate served as the common precursor for preparing the four substituted derivatives.

Synthesis of Substituted Thiosemicarbazones

The intermediate was separately reacted with four aromatic ketones to obtain the corresponding thiosemicarbazone derivatives. Ethanol was used as the reaction medium, with absolute ethanol selected when necessary to improve the homogeneity of mixtures containing poorly soluble ketones. Glacial acetic acid was introduced to facilitate the condensation process (Figure 1).

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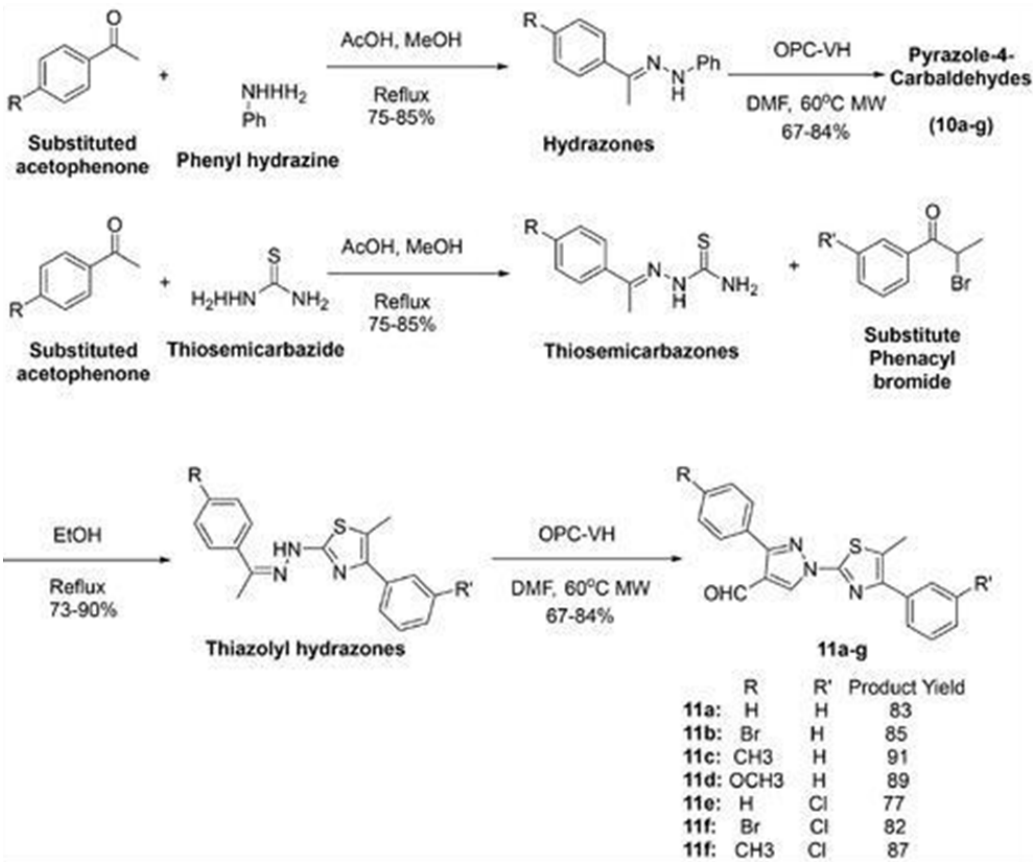


Figure 1: Synthetic pathway for the preparation of substituted thiosemicarbazone derivatives.

The reaction mixtures were maintained under reflux for approximately 2–4 hours, depending on the substrate. After completion, the mixtures were allowed to cool to room temperature. The crystalline products were collected by filtration, washed until neutral, and dried. Further purification was carried out through recrystallization using 96% ethanol.

Four compounds were obtained:

1. DPMPT – 1-(Diphenylmethylene)-N(4)-phenyl-3-thiosemicarbazide.
2. B4CPMPT – 1-[Bis(4-chlorophenyl)methylene]-N(4)-phenyl-3-thiosemicarbazide.
3. DCPPMPT – 1-[(3,4-Dichlorophenyl)(phenyl) methylene]-N(4)-phenyl-3-thiosemicarbazide.
4. NPPMPT – 1-[(4-Nitrophenyl)(phenyl)methylene]-N(4)-phenyl-3-thiosemicarbazide.

Spectroscopic Characterization

The synthesized products were examined using elemental analysis, proton nuclear magnetic resonance, carbon-13 nuclear magnetic resonance, and mass spectrometry. NMR measurements were recorded using a Bruker Avance 400 UltraShield instrument. Dimethyl sulfoxide-d6 and deuterated chloroform were employed as solvents according to sample requirements. The proton and carbon-13 resonance frequencies were 400.130 MHz and 100.613 MHz, respectively. Chemical shifts were reported in parts per million relative to tetramethylsilane. Proton signals were described according to their observed multiplicity, including singlet, doublet-like singlet, and multiplet patterns. Mass spectra were acquired in positive atmospheric-pressure chemical ionization mode. The mass-to-charge values were reported as provided in the original analytical dataset.

Computational Physicochemical Assessment

The molecular characteristics of the four compounds were evaluated using calculated physicochemical descriptors. Molecular weight, Log P, calculated Log P, hydrogen-bond donor count, and hydrogen-bond acceptor count were

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considered when comparing the structures. The assessment was based on commonly applied drug-likeness criteria, including the molecular-property thresholds proposed in the Rule of Five framework [10]. These parameters were used for preliminary screening rather than as direct measurements of gastrointestinal absorption or biological activity.

Molecular Surface Descriptor Analysis

Molecular surface characteristics were examined through Connolly accessible surface area, molecular surface area, and solvent-excluded volume. These descriptors provide information about molecular geometry, surface accessibility, and spatial dimensions. The underlying surface calculation approach was developed to represent molecular boundaries and calculate associated surface and volume characteristics [11]. The calculated descriptors were compared among the four compounds to identify variations associated with chlorine and nitro substitution. These measurements were treated as geometric descriptors and were not considered direct experimental determinations of aqueous solubility, chemical stability, or pharmacokinetic performance.

RESULTS

Formation and Recovery of the Synthesized Compounds

The condensation reactions produced four crystalline thiosemicarbazone derivatives. The reflux period varied between two and four hours according to the aromatic ketone used. Differences in the physical behaviour of the starting materials influenced the selection of the reaction solvent. Absolute ethanol was used when the ketone did not form a sufficiently homogeneous mixture in the initial alcoholic medium.

The addition of glacial acetic acid helped maintain suitable reaction conditions during reflux. After cooling, the products separated as crystalline materials and were recovered through filtration, washing, drying, and recrystallization. The isolated yields were different for the four derivatives. DPMPT produced the highest yield of 82%, followed by B4CPMPT at 73%, DCPPMPT at 69%, and NPPMPT at 65%. The variation indicates that the identity of the aromatic substituent was associated with differences in product recovery under the employed synthetic conditions.

Structural Confirmation Through Nuclear Magnetic Resonance

The carbon-13 NMR measurements showed characteristic resonances assigned to the thiocarbonyl and imine carbon atoms. The C=S signals occurred between 173.70 and 179.03 ppm, whereas the C=N resonances were observed between 146.02 and 149.22 ppm. The presence of these signals supported the formation of the expected thiosemicarbazone framework. The observed imine-carbon resonances were consistent with the structural transformation expected from condensation of the carbonyl-containing starting materials with the thiosemicarbazide intermediate (Figure 2).

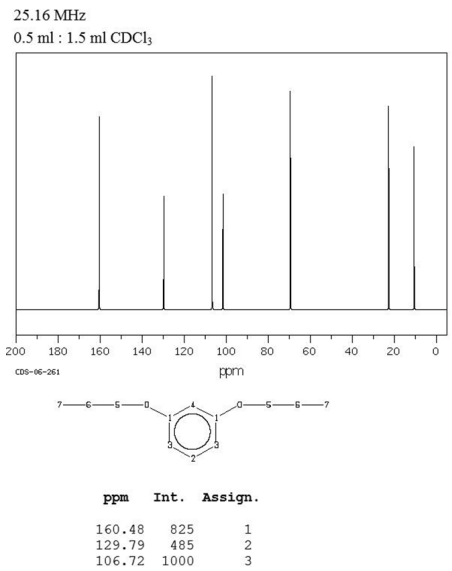


Figure 2: Representative spectroscopic features supporting the structural assignment of the prepared compounds.

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The proton NMR spectra contained signals associated with the two nitrogen-bound hydrogen environments and the aromatic protons. The disappearance of the terminal amino proton signals associated with the starting hydrazine-containing intermediate provided additional evidence of condensation. Aromatic proton resonances were distributed mainly across the 7.25–7.85 ppm region. These observations are consistent with the established use of NMR spectroscopy for distinguishing thiosemicarbazone structures and examining geometrical isomerism [12].

Individual Spectral Characteristics of the Compounds

DPMPT: The unsubstituted derivative was isolated with an 82% yield. Its carbon-13 NMR spectrum showed resonances at 175.47 ppm for C=S and 149.22 ppm for C=N. Proton signals appeared at 9.45 ppm and 8.75 ppm, corresponding to the two nitrogen-associated hydrogen environments. Aromatic proton signals were recorded between 7.25 and 7.60 ppm. The reported mass-to-charge value was 332.02.

B4CPMPT: The bis-chlorinated derivative provided a 73% yield. Its carbon-13 spectrum contained characteristic signals at 179.03 ppm and 148.57 ppm for the thiocarbonyl and imine carbons, respectively. The proton spectrum showed resonances at 9.45 ppm and 8.75 ppm, together with aromatic signals extending through the reported 6.49–7.60 ppm region. The reported mass-to-charge value was 401.27.

DCPPMPT: The derivative containing two chlorine atoms on one aromatic ring was obtained with a 69% yield. Its carbon-13 NMR spectrum showed C=S and C=N signals at 176.06 ppm and 147.59 ppm, respectively. Proton resonances were observed at 9.35 ppm and 8.75 ppm, while aromatic signals appeared between 7.25 and 7.75 ppm. The reported mass-to-charge value was 401.31.

NPPMPT: The nitro-substituted compound was obtained with a 65% yield. Its carbon-13 NMR spectrum displayed characteristic resonances at 173.70 ppm for C=S and 146.02 ppm for C=N. Proton signals appeared at 9.45 ppm and 8.85 ppm, with aromatic resonances between 7.25 and 7.85 ppm. The reported mass-to-charge value was 377.26.

DISCUSSION

Comparative Spectroscopic and Synthetic Data

The spectroscopic results demonstrate that the four compounds retained the expected thiosemicarbazone functional groups despite differences in aromatic substitution. The variation in chemical shifts suggests changes in the electronic environment surrounding the imine and thiocarbonyl carbons. These differences are consistent with the influence of substituent electronic effects on molecular structure (Table 1).

Table 1: **Isolated Yields and Principal Spectroscopic Characteristics of the Prepared Derivatives.**

Compound	Yield (%)	C=S (ppm)	C=N (ppm)	Reported Mass-to-Charge Value
DPMPT	82	175.47	149.22	332.02
B4CPMPT	73	179.03	148.57	401.27
DCPPMPT	69	176.06	147.59	401.31
NPPMPT	65	173.70	146.02	377.26

The formation of geometrical isomers in DCPPMPT also demonstrates that structural variation can influence the conformational behaviour of substituted thiosemicarbazones. Similar syn–anti behaviour has been investigated through combined NMR and computational studies [13].

Lipophilicity and Drug-Likeness Assessment

Lipophilicity is a significant physicochemical descriptor because it influences the distribution of organic molecules between aqueous and non-aqueous environments. The octanol–water partition coefficient is frequently employed to describe this behaviour and to compare structurally related molecules [14]. The molecular-property results showed noticeable differences between the unsubstituted, chlorinated, and nitro-containing derivatives. DPMPT displayed a Log P value of 5.35 and a calculated Log P value of 4.70. The two chlorinated compounds showed higher reported values, with Log P of 6.46 and calculated values of 6.24 and 6.12. NPPMPT exhibited lower lipophilicity, with Log P of 4.23 and calculated Log P of 4.62.

The higher values associated with the chlorinated derivatives suggest an increase in hydrophobic character following chlorine substitution. In contrast, the nitro group introduces additional oxygen-containing functionality and changes the distribution of polar character within the molecule. Substituent effects on molecular physicochemical

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properties have long been examined through quantitative structure–property relationships [15]. The molecular-property screening results are summarized in Table 2. Molecular weights ranged from 331.43 to 400.32 g/mol, while the hydrogen-bond donor count remained at two for all compounds. The acceptor count varied between three and six (Table 2).

Table 2: Calculated Molecular Descriptors and Preliminary Drug-Likeness Assessment.

Compound	Molecular Weight (g/mol)	Log P	Calculated Log P	H-Bond Donors	H-Bond Acceptors	Reported Criteria Met
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

The unsubstituted and nitro-containing derivatives were reported to satisfy all assessed criteria, whereas the chlorinated compounds met three. This difference was mainly associated with their higher calculated lipophilicity values.The Rule of Five provides a useful initial framework for identifying molecular structures that may possess suitable properties for oral drug development [16]. However, compliance with these criteria does not establish actual absorption, distribution, metabolism, excretion, or therapeutic effectiveness. Other molecular descriptors and experimental measurements are also required when evaluating potential pharmaceutical candidates [17].

Additional classification approaches have been developed to distinguish compounds according to molecular size, polarity, hydrogen-bonding properties, and other structural characteristics [18]. Multivariate models have also been used to investigate the relationship between molecular descriptors and intestinal absorption behaviour [19].

Molecular Surface Area and Volume Characteristics

The Connolly descriptors provided an additional basis for comparing the geometrical characteristics of the synthesized compounds. The accessible surface area, molecular surface area, and solvent-excluded volume differed according to the aromatic substitution pattern (Table 3).

Table 3: Molecular Surface Geometry and Solvent-Excluded Volume of the Synthesized Compounds at 298 K.

Compound	Molecular Weight (g/mol)	Log P	Calculated Log P	H-Bond Donors	H-Bond Acceptors	Reported Criteria Met
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

B4CPMPT exhibited the highest values for all three descriptors, followed by DCPPMPT and NPPMPT. DPMPT showed the lowest accessible surface area, molecular surface area, and solvent-excluded volume. The increased dimensions of the chlorinated compounds are consistent with the additional atomic contributions introduced through substitution. Differences in molecular geometry can influence the accessible surface and spatial distribution of functional groups. The theoretical treatment of molecular surface area provides a mathematical basis for describing these characteristics [20].

The solvent-excluded volume is also useful for comparing molecular dimensions and enclosed spatial regions. It should not, however, be interpreted as a direct measure of aqueous solubility or degradation resistance [21].

Relationship Between Molecular Substitution and Physicochemical Characteristics

Comparison of the four compounds reveals that aromatic substitution influenced both calculated lipophilicity and molecular geometry. Chlorine incorporation was associated with higher partition coefficients and larger

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surface descriptors, whereas nitro substitution produced a different balance of molecular polarity and hydrophobicity. These differences demonstrate that changes in functional groups can influence several molecular descriptors simultaneously. The relationship between molecular structure and calculated physicochemical behaviour is an important consideration in early-stage medicinal chemistry research [22].

Computational prediction tools provide a convenient way to compare molecular properties before undertaking more extensive experimental investigations. Contemporary platforms combine molecular descriptors with prediction models to support preliminary evaluations of drug-likeness and pharmacokinetic characteristics [23]. The present findings should therefore be interpreted as an initial physicochemical comparison rather than evidence of established pharmacological performance. Experimental solubility measurements, permeability studies, metabolic stability testing, and biological assays would be needed to determine whether the observed structural differences translate into useful biological properties.

Scientific Implications and Study Limitations

The results demonstrate that a common thiosemicarbazide intermediate can be used to prepare several aromatic derivatives with different substituent patterns. The combination of condensation chemistry and spectroscopic analysis provided evidence supporting the formation of the intended molecular structures. The computational findings further showed that chlorine and nitro substitution produced distinguishable molecular-property profiles. These observations may assist in selecting compounds for additional characterization and comparative biological investigation.

Several limitations should be recognized. The available dataset does not provide experimental measurements of absorption, metabolic stability, biological potency, toxicity, or in vivo pharmacokinetics. The reported lipophilicity and molecular surface values are computational descriptors, and their predictive interpretation depends on the underlying calculation methods. Furthermore, the original experimental description does not provide complete reagent quantities, stoichiometric ratios, detailed catalyst concentrations, or the full computational software settings. These details should be supplied before independent laboratory reproduction or definitive comparison with other studies.

Additional Considerations for Molecular Property Prediction

Molecular polarity, surface accessibility, and lipophilicity provide complementary information when comparing candidate structures. Topological polar surface area can help characterize molecular transport-related properties [24]. However, calculated solubility estimates remain dependent on molecular structure, model selection, and environmental conditions, making experimental verification necessary [25].

CONCLUSION

The investigation resulted in the preparation of four substituted thiosemicarbazone derivatives through condensation reactions involving a common thiosemicarbazide intermediate. The isolated products showed yields between 65% and 82%, with the unsubstituted compound providing the highest recovery. Spectroscopic examination supported the formation of the expected imine and thiocarbonyl functionalities, while differences in aromatic substitution were reflected in their measured chemical shifts. Computational comparisons revealed variations in molecular weight, lipophilicity, hydrogen-bonding characteristics, and molecular surface dimensions. Chlorinated derivatives displayed higher calculated partition coefficients and larger surface descriptors, whereas the nitro-containing compound exhibited a different physicochemical profile. These findings establish a preliminary relationship between aromatic modification and calculated molecular characteristics within this compound series. Further investigation involving experimental solubility, permeability, metabolic stability, toxicity, and biological activity measurements is necessary to determine their pharmaceutical suitability. The combined synthetic and computational approach provides a useful foundation for subsequent structural optimization and biological evaluation.

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