SYNTHESIS AND STRUCTURAL INVESTIGATION OF 3-{-[(2 HYDROXYPHENYL)METHYLIDENE]AMINO}-5-(2-METHYLPROPYL)-2-SULFANILYDENEIMIDAZOLIDIN-4-ONE

SINTEZA ȘI INVESTIGAȚIA STRUCTURALĂ A 3-{-[(2-HIDROXIFENIL)METILIDEN]AMINO}-5-(2-METILPROPIL)-2-SULFANILIDENIMIDAZOLIDIN-4-ONEI

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Aliona PÎNTEA
ORCID: 0009-0008-1713-9195
E-mail: pintea.aliona@usm.md
Moldova State University, Chisinau, Republic of Moldova

Roman RUSNAC
ORCID: 0000-0002-5713-5251
e-mail: roman.rusnac@usm.md
Moldova State University, Chisinau, Republic of Moldova

Sergiu SHOVA
ORCID: 0000-0002-1222-4373
E-mail: shova@icmpp.ro
Romanian Academy, Iași, Romania

Aurelian GULEA
ORCID: 0000-0003-2010-7959
E-mail: aurelian.gulea@usm.md
Moldova State University, Chisinau, Republic of Moldova

Sumar. *Cancerul este a doua cea mai frecventă cauză de deces. Niciun medicament cunoscut nu satisface 100% nevoile industriei medicale. Din aceste motive, mulți cercetători încearcă să sintetizeze noi molecule cu proprietăți anticancerigene. O clasă de compuși organici numiți tiosemicarbazone prezintă un spectru larg de activități biologice utile, inclusiv anticancerigene și antimicrobiene. Acest articol prezintă metodele de sinteză și analiză fizico-chimică a compusului 3-{(E)-[(2-hidroxifenil)metiliden]amino}-5-(2-metilpropil)-2-sulfanilideneimidazolidin-4-onă. Ligandul a fost sintetizat în două etape folosind metode clasice, care au fost ulterior optimizate. În prima etapă, pornind de la 2-amino-4-metilpentanoat de metil-clorură de hidrogen, s-a obținut 3-amino-5-(2-metilpropil)-2-sulfanilideneimidazolidin-4-onă. Compușii sintetizați au fost caracterizați folosind tehnici moderne, cum ar fi spectroscopia FTIR, analiza elementară și difracția de raze X pe monocristal. Evaluarea activității biologice a compusului este în curs de desfășurare.*

Cuvinte-cheie*: sulfanil idena, imidazolidin-4-onă, tiohidantoină, baze Schiff.*

INTRODUCTION

Hydantoins are chemical compounds containing a hydantoin nucleus, an imidazole derivative, with the general formula $C_3H_4N_2O_2$.They have been studied mainly for their pharmacological activity and applicability in medicine, especially in the treatment of epilepsy. Here are some general characteristics of hydantoins. Hydantoins have a structure based on a heterocyclic system containing nitrogen (N), carbon (C) and oxygen (O). The hydantoin nucleus is made up of a 5-membered ring, in which 2 of the carbon atoms are replaced by nitrogen, and 1 oxygen atom completes the structure. Hydantoins are famous in medicine for their use as anticonvulsants [1]. For example, *Phenytoin* is used for the treatment of epilepsy, having stabilizing effects on the electrical activity of the brain. These compounds regulate neuronal activity by inhibiting sodium channels. Hydantoins are most commonly used as antiepileptic drugs. Some hydantoin derivatives can also be used to treat conditions related to anxiety or insomnia, and more recently they also have cardiological effects, being used for treatments against arrhythmia. Although their effectiveness is proven, the use of hydantoins can be accompanied by side effects, such as [3]: dizziness, gastrointestinal problems, skin rashes, and chronic toxicity in case of prolonged use.

Thiosemicarbazides are a class of chemical compounds containing the thiosemicarbazide functional group (-NH-NH-C=S), being derivatives of semicarbazides by replacing the oxygen atom with a sulfur atom. They are important from a pharmacological, biological and chemical point of view due to their multiple properties and applications [4]. Thiosemicarbazides have been studied extensively for their biological and pharmacological activities. Some of their properties are antimicrobial activity numerous studies have demonstrated that thiosemicarbazides and their derivatives exhibit antimicrobial activity against some microorganisms, including bacteria and fungi. Antitumor activity: Certain thiosemicarbazides have been investigated for anticancer properties, due to their ability to inhibit cell proliferation and induce apoptosis in tumor cells [5]. Antiviral properties: Thiosemicarbazides have shown antiviral activity against some viruses, being studied in the development of antiviral drugs. Anti-inflammatory and analgesic activity: Some studies suggest that thiosemicarbazides may also have anti-inflammatory and analgesic effects, being useful in the treatment of inflammatory conditions.

Schiff bases are a class of organic compounds characterized by the presence of an azomethine group (–C=N–)**,** formed by the condensation of a primary amine with an aldehyde or ketone**:**

$$R\text{-}NH_2+R\text{-}CHO\rightarrow R\text{-}N=CH\text{-}R+H_2O$$

Structural and Chemical Propertiesof sff bases :the C=N (azomethine) bond is central to the reactivity and functionality of Schiff bases.These compounds often contain additional donor atoms such as oxygen (O), nitrogen (N), or sulfur (S), which enables them to act as chelating ligands in coordination chemistry.Schiff bases derived from salicylaldehyde or thiosemicarbazide contain additional functional groups (e.g., –OH or

–C=S), enhancing their chelating ability and biological activity.Chemical Reactivity of schiff bases are generally unstable in acidic media, where they can undergo hydrolysis back to the parent amine and aldehyde.They are reducible to secondary amines.Due to their donor atoms (N, O, S), they form stable coordination complexes with many transition metals.

Applications of sff bases is various medicinal chemistry: Schiff bases show antibacterial, antifungal, anticancer, and antiviral activities Coordination Chemistry: Serve as bidentate or tridentate ligands in transition metal complexes.Analytical Chemistry: Useful as colorimetric sensors or metal ion indicators.Catalysis: Used in organic synthesis, including oxidation, condensation, and polymerization reactions.

Methods for the synthesis of Schiff base HL with a thiohydantoin fragment

To obtain thiohydantoin compound II (according to figure 1), the following method is used: leucine is dissolved in a solution of $NaHCO_3$.The reaction proceeds in the cooling system that involves stirring in an ice-water bath and salt, and to the solution in the stirring vessel, $CSCl_2$ is added dropwise where the color changes. After approximately 6 hours of stirring, the appearance of an oily layer representing the isothiocyanate is observed, and it is confirmed by FTIR and chromatographically in relation to the initial amine to confirm its consumption.

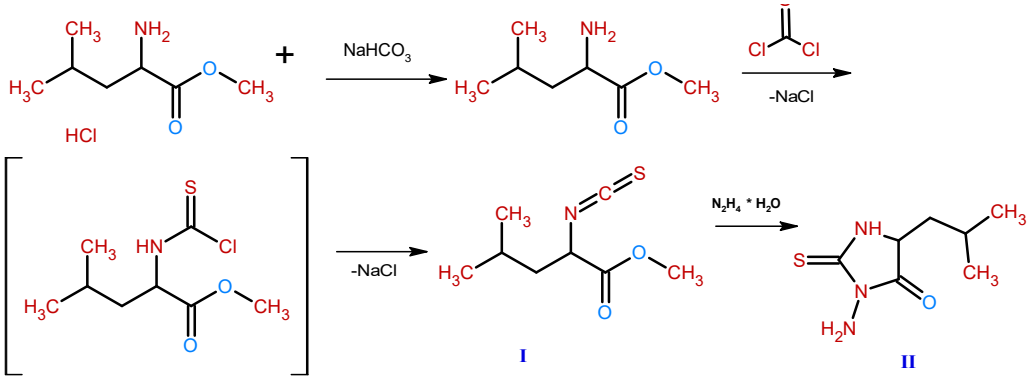


Figure 1. Scheme of synthesis of 3-amino-5-(2-methylpropyl)-2-sulfanilideneimidazolidin-4-one (II)

After separating the organic layer and drying it, hydrazine monohydrate reacts with isothiocyanate. To the alcoholic solution of isothiocyanate (I), hydrazine monohydrate is added drop by drop in a 1:1 ratio and stirred for about 2 hours, during which a white solid forms. This solid is then filtered and dried. Next, it is mixed with salicylaldehyde while stirring and heating in ethanol, which results in the creation of a Schiff base (HL). To the alcoholic solution of isothiocyanate (I), hydrazine monohydrate is added drop by drop in equal amounts, and the mixture is stirred for about 2 hours, during which a white solid forms that is then filtered and dried. The precipitate is further subjected to condensation

with salicylaldehyde under stirring, temperature, and reflux conditions in ethanol, which subsequently leads to the formation of a Schiff base (HL).

The synthesis of 3-{-[(2-hydroxyphenyl)methylidene]amino}-5-(2-methylpropyl)-2-sulfanilideneimidazolidin-4-one (HL) (figure 2) was carried out according to the classical methods of condensation of the corresponding amine (3-amino-5-(2-methylpropyl)-2-sulfanylideneimidazolidin-4-one (II)) with carbonyl compounds (salicylaldehyde) according to the synthesis schemes (figure 2).

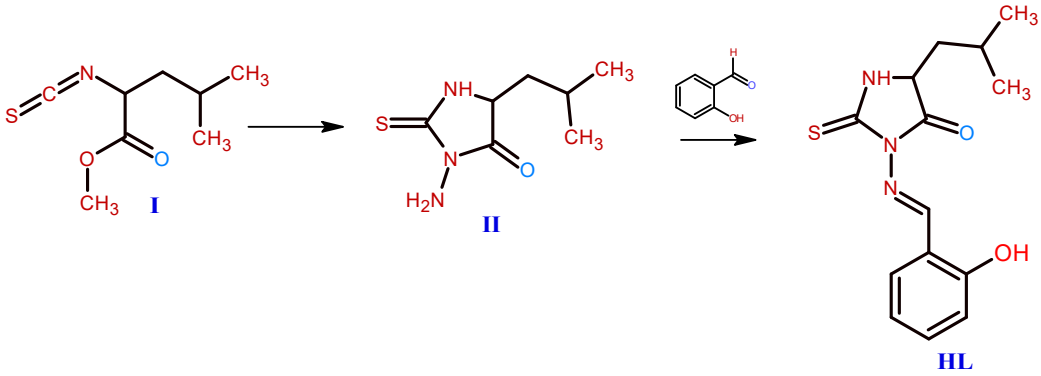


Figure 2. Synthesis scheme of 3-{-[(2-hydroxyphenyl)methylidene]amino}-5-(2-methylpropyl)-2-sulfanilideneimidazolidin-4-one (HL)

RESULTS AND DISCUSSION

The syntheses yielded leucine-amine isothiocyanate, which was subsequently subjected to interaction with hydrazine monohydrate, which, following the heterocyclization reaction, leads to the formation of a new organic compound, characteristic of the class of compounds called thiohydantoins.

The results obtained were confirmed by IR spectroscopy, where the appearance of characteristic bands of both the classes of thiohydantoin compounds and thiosemicarbazones was observed. The characteristic bands are C=N stretch (imine): ~1600–1640 cm^{-1}, C=O (lactam): ~1690–1740 cm^{-1}**,** O–H (phenol): ~3200–3600 cm^{-1} (broad), and N–H: ~3300–3400 cm^{-1}. With ^{1}H-NMR, the characteristic peaks are imine proton (HC=N): ~8.0–8.5 ppm, aromatic protons (phenyl ring): ~6.8–7.6 ppm, OH (phenol): ~9–10 ppm (exchangeable, broad), aliphatic chain (isobutyl): ~0.9–2.5 ppm, and CH–N and CH (from ring): ~3–5 ppm. Characteristic peaks with ^{13}C-NMR C=N (imine group): ~160–170 ppm, C=O (lactam carbonyl): ~170–180 ppm, aromatic carbons: ~110–150 ppm, aliphatic CH, CH_2, CH_3: ~10–40 ppm. UV-Vis spectroscopy demonstrates that the substance obtained has the following characteristics: π→π* and n→π* transitions are due to the conjugated imine system, aromatic ring, and phenol group; absorption is expected around 250–350 nm**.** A physicochemical property of substances is solubility: likely soluble in ethanol**,** DMSO, and DMF and partially soluble in water.

CONCLUSION

The synthetic pathway shown above describes how to efficiently make the Schiff base ligand 3-{[(2-hydroxyphenyl)methylidene]amino}-5-(2-methylpropyl)-2-sulfanilideneimidazolidin-4-one (HL) through a series of steps. The synthesis begins with the cyclization to form the 2-sulfanylideneimidazolidin-4-one (compound I) and condensation of compound I with salicylaldehyde, the formation of compound II. This intermediate is an important building block for further modification through a reaction with 2-hydroxybenzaldehyde, which produces the final Schiff base HL. The resulting compound has several atoms that can donate electrons (N, O, S), which means it could act as a tridentate ligand useful in coordination chemistry. The presence of the imine bond (C=N), phenolic OH group, and thiocarbonyl group (C=S) suggests the compound may also exhibit intriguing biological or chelating properties. The overall process to make it is simple and effective, allowing for the creation of different types of ligands based on the imidazolidinone structure. This synthetic approach demonstrates the versatility of novel Schiff base ligands with potential applications in medicinal chemistry.

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