*Available online www.jsaer.com*

***Journal of Scientific and Engineering Research*, 2022, 9(12):68-72**

**Research Article**

**ISSN: 2394-2630**
**CODEN(USA): JSERBR**

# Cyclohexylphenylketone Thiosemicarbazones: Synthesis in the Green Chemistry Condition and Spectral Characterization

**Bienvenu GLINMA[1*], Bénédicta KPADONOU [1], Mirhane HAOUTHAOU[3], Hyacinthe F. AGNIMONHAN[1], Jacques H. POUPAERT[2], Fernand A. GBAGUIDI[1]**

[1]Laboratoire de Chimie Organique Physique et de Synthèse (LaCOPS), Faculté des Sciences et Techniques, Université d'Abomey-Calavi, 01 BP 526 Cotonou, Benin.
[2]Louvain Drug Research Institute (LDRI), School of Pharmacy, Université Catholique de Louvain, B1 7203 Avenue Emmanuel Mounier 72, B-1200 Brussels, Belgique.
[3]Département de Chimie,, Centre universitaire de Patsy, Université de Comores, BP 9811396 Anjouan, Comores.
Corresponding authors: bienvenu.glinma@fast.uac.bj ; +229 97542805

**Abstract** Thiosemicarbazones and their derivatives have a significant awareness in the organic field, pharmacology, and biology; appreciations to their various applications. Their interest in medicinal chemistry has stimulated word researchers the development of new methods for their synthesis, respecting also the fundamental principles of green chemistry. In this paper, we reporte the synthesis of cyclohexylphenylketone thiosemicarbazone **P1** and cyclohexylphenylketone 4-phenyl-3-thiosemicarbazone **P2** with goods yields (81% and 85% respectively) and their pharmacokinetic properties determined theoretically. According to the results of the theoretical studies, it can be said that the bioavailability and bioactivity of compounds may be high. The evolution of the reaction is followed by TLC which allowed us to determine their frontal ratio Rf. Compounds structures have been characterised with the spectrometrical analysis methods (FT-IR, SM and specially $^{1}H$ and $^{13}C$ NMR). The results in the field of physical chemistry are more significant compared to the literature. Our synthesis conditions could explane the improvement of the reaction yield.

**Keywords** cyclohexylphenylketone, thiosemicarbazones, green chemistry, characterization

## 1. Introduction

Thiosemicarbazones are synthesized by the use of simple and economical methods through the condensation reaction of thiosemicarbazides with various aldehydes and ketones [1]. They are a type of N, S-donor ligands, possessing an important position in therapeutic chemistry research because of their structural assortment, modifiable synthesis, and valuable donating ability [2]. Both the thiosemicarbazones and their coordination compounds are well known to exhibit a broad spectrum of medicinal and agrochemical activities [3]. They have a significant awareness in the organic field, pharmacology, and biology; appreciations to their various applications [4,5]. In particular, the Schiff base compounds involving the substitution of these nitrogen and sulfur bidentate ligands at their N1 position with heteroatom rings have been widely investigated as anticancer agents and their anticancer effects are mainly associated with the inhibition of the essential enzyme "ribonucleoside diphosphate reductase" that is involved in converting the ribonucleotides into deoxyribonucleotides amid DNA syntheses [6]. Recently, TSCs were rediscovered for their potent copper-dependent activity against multiple microbes [7,8]. Their interest in medicinal chemistry has stimulated in research the development of new methods for their synthesis.

In this study, we synthesized two thiosemicarbazone compounds from a well-developed protocol that allowed us to synthesize bioactive molecules under conditions respecting the principles of green chemistry by using non- or less hazardous reagents and solvents in order to improve reaction yields.

## 2. Material and methods

### *2.1. Apparatus*

Perkin-Elmer 457 spectrometer using KBr pellets was used for recording the IR spectra with frequences expressing in $cm^{-1}$. $^{1}H$- and $^{13}C$-NMR spectrum was recorded on a Brucker Avance 400MHz spectrometer at ambient temperature. The processing parameters are at 400.1300109 MHz for $^{1}H$-NMR, and for $^{13}C$-NMR, at 100.1316005 MHz. Compounds were dissolved in chloroform $CDCl_3$. Chemical shifts are given in parts per million (ppm) relative to tetramethylsilane as internal standard. Multiplicity is designated as singlet (s) and multiplet (m). Mass spectrometry (MS) data were reported using a LCQ advantage mass spectrometer with a source at atmospheric pressure chemical ionization (APCI), mode [$MH^+$]. All compounds were homogenous under TLC conditions.

### *2.2. Reagents*

The 4-phenyl-3-thiosemicarbazide was synthesised from reaction of hydrazine and phenylisothiocyanate on our laboratory and used on cyclohexylphenylketone purchased from Sigma Aldrich, Janssen Chimica and Fluka AG-Buchs SG. The glacial acetic acid (AAG), hexane and ethylacetate used in the reactions were obtained from PROLABO and Sigma Aldrich. We used technical ethanol as solvent at the reaction. All reagents were used without other purifying. Compounds were synthesized via the following synthesis route (scheme 1).

### *2.3. Methods*

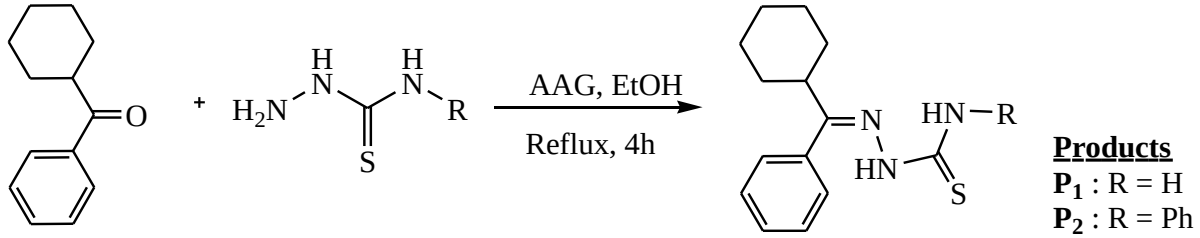
***Preparation of the 4-phenyl-3-thiosemicarbazide*** [9,10]

*In a 100 mL round-bottomed flask, place 3.5 g of hydrazine hydrate in 40 mL of ethanol. Prepare a solution of phenylisothiocyanate (7.5 g) in 30 mL of ethanol and transfer it to a dropping funnel. Place the "flask and ampoule" system in an ice bath and keep it stirred while adding the phenylisothiocyanate solution dropwise. Leave to stir for a further hour, filter off the precipitate obtained and recrystallize it from technical ethanol.*

***Synthesis of compounds***

Thiosemicarbazone (**$P_1$**) and 4-phenyl-3-thiosemicarbazone (**$P_2$**) of cyclohexylphenylketone were synthesised using the protocol described in our last publications [9,11].

*An equimolar mixture (0.01 mol) of thiosemicarbazide or 4-phenyl-3-thiosemicarbazide dissolved in 10-20 mL of ethanol (EtOH 96°) was added slowly to a solution (0.01 mol) of cyclohexylphenylketone dissolved in 20 mL of EtOH in presence of glacial acetic acid (GAA, 1.5 mL). The mixture was heated at reflux (80°C) for 4 hours with stirring. The progress of the reaction is followed by TLC using a mixture of eluent consisting of hexane and ethyl acetate in various proportions. After cooling, the precipitate was filtered, washed with cold distilled water until neutrality, dried and then recrystallized in technical ethanol and dried.*




*Scheme 1: Synthetic route of compounds*

## 3. Results and Discussion

Products were synthetisised with goods yieds ($P_1$ : 81% ; $P_2$ : 85%). These synthesised yields were hight than that obtenaid by Kassehin et *al*. (2013), 76%, when they used an aniline and a concentrated hydrochloric acid in

methanol [12]. In our study, we used solvents respecting the fundamental principles of green chemistry. Indeed, methanol, aniline and hydrochloric acid that others have used are more dangerous reagents than those that we have used. We have not only improved the yields of reactions but we have also respected the conditions of Designing synthesis routes less dangerous for both Humans and the environment, Favouring the use of non-polluting solvents or even the absence of solvent when it is possible [13-15].

The theoretical study (rules of Lipinsky et *al*.) based on the structure of the products showed the pharmacokinetic properties [16] mentioned in the table.

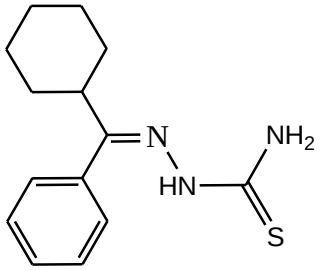
**Table 1:** Theoretical pharmacokinetic and drug availability study

| Compounds | Molecular weight (g.mol$^{-1}$) | *C logP (lipophilicity)* | Number of H-bond donors | Number of H-bond acceptors | Number of criteria met |
|---|---|---|---|---|---|
| **Rules** | **< 500** | **< 5** | **≤ 5** | **< 10** | **at least 3** |
| **$P_1$** | 261.39 | 4.432 | 3 | 4 | all |
| **$P_2$** | 337.48 | 6.102 | 2 | 4 | 3 |

Compounds were characterized by spectrometrical analysis methods.

***Characterization***

**Cyclohexylphenylketone thiosemicarbazone (P$_1$)**




White crystal : 81%. TLC : **R$_f$** (AcOEt/Hex, 7/3) = 0.61

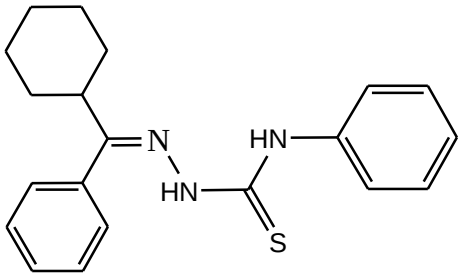
**IR** (KBr, ν in cm$^{-1}$) : 3357, 3243 ($NH_2$); 3145 (NH); 1624 (C=N); 1113, 1036, 857 (N-CS-N).

**$^1$H NMR** *($CDCl_3$, δ in ppm)* : 9.1 (s, 1H, NH) ; 8.35 (s, 2H, $NH_2$) ; 7.2-7.6 (m, 5H, H-Ar), 1.51-1.87 (m, 10H, H-cyclohexyl).

**$^{13}$C NMR** *($CDCl_3$, δ in ppm)* : 179.67 (C=S) ; 156.37 (C=N) ; 133.12, 129.87, 128.85, 127.59 (C-Ar) ; 43.95, 31.47, 26.01, 25.97 (C-cyclohexyl).

**MS** (m/z of [M-H$^+$]) = 262.17. ***Formula*** : $C_{14}H_{19}N_3S$.

**Cyclohexylphenylketone 4-phenyl-3-thiosemicarbazone (P$_2$)**




White crystal : 85%. TLC : **R$_f$** (AcOEt/Hex, 7/3) = 0.53

**IR** (KBr, ν in cm$^{-1}$) : 3388, 3178 (NH); 1597 (C=N); 1127, 1061, 897 (N-CS-N).

**$^1$H NMR** *($CDCl_3$, δ in ppm)* : 9.4 (s, 1H, NH) ; 8.5 (s, 1H, NH) ; 7.1-7.7 (m, 10H, H-Ar), 1.5-1.85 (m, 10H, H-cyclohexyl).

**$^{13}$C NMR** *($CDCl_3$, δ in ppm)* : 176.03 (C=S) ; 157.74 (C=N) ; 138.03, 132.72, 129.87, 129.70, 128.75, 127.09, 125.96, 124.22 (C-Ar) ; 45.88, 30.44, 26.02, 25.98 (C-cyclohexyl).

**MS** (m/z of [M-H$^+$]) = 338.29. ***Formula*** : $C_{20}H_{23}N_3S$.

The analysis of the data in the table showed that products respected criteria of pharmacocinetic properties met and then could be able to have biological activities (**P$_1$**, all criteria and **P$_2$**, 3 criteria and more lipophilic). Compounds

have physical properties compatible with reasonable pharmacokinetics and drug availability. The scaffold (scheme 1) has some advantageous properties: low molecular weight, reasonable *C.logP*, good hydrogen bond donating and accepting capabilities (Table), easy and economical synthetic routes [16].

Spectrometrical data showed the signicant results. IR gave the frequency of fonctional groups in each products, especially the C = N fonction which is formed during reaction (1624 $cm^{-1}$ for **$P_1$** and 1594 $cm^{-1}$ for **$P_2$**). These results are consistent with our previously works [9-11]. The pics of C-imine function (C=N) of products appeared at 156.37 and 157.74 ppm respectively in $^{13}C$ NMR. We noted the disparition of the pic of C=O in the ketone compound which is at 202 ppm. This result confirms the obtaining of the reaction products. $^{1}H$ NMR specta analysis presented characteristic proton which appeared, especially the H-N in molecules' structure. These results confirm the previously works in the littérature [17,18]. The analysis these spectral data confirms generaly the structure of each molecule synthesized.

## 4. Conclusion

We have synthesised two molecules such as cyclohexylphenylketone thiosemicarbazone (**$P_1$**) and cyclohexylphenylketone 4-phenyl-3-thiosemicarbazone (**$P_2$**) in the green chemistry condition with the improvement reaction yield. All products showed physical properties compatible with reasonable pharmacokinetics and drug availability and will be subjected to biological properties in the futur.

## Acknowledgement

We thank the collaboration of the staff and the material of the LDRI laboratory at the Université Catholique de Louvain, Bruxelles, Belgium.

## References

[1]. Matsa, R., Makam, P., Kaushik, M., Hoti, SL. & Kannan, T. (2019) Thiosemicarbazone derivatives: Design, synthesis and *in vitro* antimalarial activity studies. *European Journal of Pharmaceutical Sciences*, 137: 104986. doi: 10.1016/j.ejps.2019.10498

[2]. Prajapati, N. P. & Patel, H. D. (2019). Novel thiosemicarbazone derivatives and their metal complexes: Recent development. *Synthetic Communications*, 49(21): 2767–2804

[3]. Fathy, A., Ibrahim, A. B. M., Abd Elkhalik, S., Meurer, F., Bodensteiner, M., Abbas S. M. (2022) Thiosemicarbazones and Derived Antimony Complexes: Synthesis, Structural Analysis, and In Vitro Evaluation against Bacterial, Fungal, and Cancer Cells. *Inorganics*, 10(10): 172. https://doi.org/10.3390/inorganics10100172

[4]. Arooj, M., Zahra, M., Islam, M., Ahmed, N., Waseem, A., Shafiq, Z. (2021). Coumarin based thiosemicarbazones as effective chemosensors for fluoride ion detection. *Spectrochimica Acta Part A Molecular and Biomolecular Spectroscopy*, 261: 120011.

[5]. Hashmi, S., Khan, S., Shafiq, Z., Taslimi, P., Ishaq, M., Sadeghian, N., Karaman, H. S., Akhtar, N., Islam, M., Asari, A., Mohamad, H., Gulçin, İ. (2021). Probing 4-(diethylamino)-salicylaldehyde-based thiosemicarbazones as multi-target directed ligands against cholinesterases, carbonic anhydrases and α-glycosidase enzymes. *Bioorganic Chemistry*, 107: 104554.

[6]. Gojo, I., Tidwell, M. L., Greer, J., Takebe, N., Seiter, K., Pochron, M. F., Johnson, B., Sznol, M., Karp, J. E. (2007). Phase I and pharmacokinetic study of Triapine®, a potent ribonucleotide reductase inhibitor, in adults with advanced hematologic malignancies. *Leukemia Research*, 31: 1165-1173.

[7]. Dalecki, A. G., Cameron, L. C., Wolschendorf, F. (2017). Copper and Antibiotics: Discovery, Modes of Action, and Opportunities for Medicinal Applications. *Advances in Microbial Physiology*, 70: 193-260. DOI:10.1016/bs.ampbs.2017.01.007

[8]. Dalecki, A. G., Malalasekera, A. P., Schaaf, K., Kutsch, O., Bossmann, S. H., Wolschendorf, F. (2016). Combinatorial phenotypic screen uncovers unrecognized family of extended thiourea inhibitors with copper-dependent anti-staphylococcal activity. *Metallomics*, 8(4): 412–421, https://doi.org/10.1039/c6mt00003g.

[9]. Glinma, B, Medegan, S., Yayi, E., Agnimonhan, F. H., Kpoviessi, D. S. S., Quetin-Leclercq, J., Accrombessi, C. G., Kotchoni, O. S., Poupaert, H. J., Gbaguidi, A. F. (2019). Lipophilic And Structure Activity Relationships Study Of Thiosemicarbazones And Derivatives. *International Journal of Advanced Research*, 7(11): 29-40. http://www.journalijar.com/uploads/670_IJAR-29066.pdf

[10]. Glinma, B., Agnimonhan, H., Medegan, S., Ahoussi Akanni, L., Kpoviessi, S., Quetin-Leclercq, J., Poupaert, J., Gbaguidi, F. (2020a). Study of benzoin 4-phenyl-3-thiosemicarbazone and benzil Bis(4-phenyl-3-thiosemicarbazone) : Synthesis and their Antiparasitic activity on trypanosome. *Journal of Chemical, Biological and Physical Sciences*, 10(4): 408-418. http://www.jcbsc.org/issuechem.php?volume=10&issue=4

[11]. Glinma, B., Medegan, S., Yayi, E., Kpoviessi, S., Bero, J., Quetin-Leclercq, J., Poupaert, J., Accrombessi, G., Gbaguidi, F. (2020b). Benzaldehyde and Derivatives N(4)-Phenyl-3-Thiosemicarbazones: Synthesis, Characterization and Biological Activity. *The Pharmaceutical and Chemical Journal*, 7(1): 10-15. http://tpcj.org/download/vol-7-iss-1-2020/TPCJ2020-07-01-10-15.pdf

[12]. Kassehin, U. C., Gbaguidi, F., Kapanda, C., Mccurdy, C., Bigot, A., Poupaert, J. (2013). Electronic and steric effects in the control of the Anilinium chloride catalyzed condensation reaction between Aldones and 4-Phenylthiosemicarbazide. *African Journal of Pure and Applied Chemistry*, 7(9): 325-329.

[13]. Ducamp C. (2011). Chimie verte: approche nouvelle et responsable face aux problèmes issus des activités chimiques. Développement durable et autres questions d'actualité-Questions socialement vives dans l'enseignement et la formation, educagri,. ffhal-01905726f.

[14]. Michael, A., Irene, A. (2004). Synapse Handbook of Green Chemicals. Information Resources Inc; Édition : 2nd.

[15]. Anastas, P. T., Warner, J. C. (2001). Green Chemistry: Theory and Practice. Oxford University Press.

[16]. Lipinski, C. A., Lombardo, F., Dominy, D. W., Feeney, P. J. (2001). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Advanced Drug Delivery Reviews*, 46(1-3): 3-26.

[17]. dos Reis, C. M., Pereira, D. S., de Oliveira, P. R., Kneipp, L. F., Echevarria, A. (2011). Microwave-Assisted Synthesis of New N1,N4-Substituted Thiosemicarbazones. *Molecules*, 16: 10668-10684.

[18]. Hernández, W., Paz, J., Carrasco, F., Vaisberg, A., Spodine, E., Manzur, J., Hennig, L., Sieler, J., Blaurock, S., Beyer, L. (2013). Synthesis and characterization of new palladium(II) thiosemicarbazone complexes and their cytotoxic activity against various human tumor cell lines, *Bioinorganic Chemistry and Applications*, 2013: 12.