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SYNTHESIS, STRUCTURAL STUDY (GEOMETRIC ISOMERS) AND ANTIPARASITIC ACTIVITY OF THIOSEMICARBAZONES

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ABSTRACT

Geometric isomerism is the phenomenon of organic chemistry characterized by the asymmetry arising from at least two different substituents, linked to two atoms engaged with each other by a double bond. Molecules comprising the C=N double bond in their chain have been studied a lot because of the many properties of this functional unit both in terms of acid-base and redox, and even photochemical properties. Thiosemicarbazones, semicarbazones and their derivatives are the major subgroups of hydrazones (C=N-N-), alongside thioaroylhydrazones ... Here, we have synthesized six thiosemicarbazones from acetophenone (P_{1-3}) and propiophenone (P_{4-6}) with good yields. A structural study of the products based on their IR and ^{1}H and ^{13}C NMR spectra was made. Biological activity of products was evaluated on parasite *Trypanosoma brucei brucei*. It was remarked that the different structural elements of propiophenone thiosemicarbazones (P_{4-6}) exhibited two chemical shifts in NMR as well as two absorption bands in IR ; they appeared in their spectrum as two isomers *cis* and *trans* in the 2:3 ratio while molecules (P_{1-3}) with only a single chemical shift for its elements were present more under the anti configuration, which is more predominant. Several electronic and steric factors contributed to the adoption of this observed arrangement. For all

products, thiosemicarbazones (P_{4-6}) with their IC_{50} ranging from 7 to 210 µM and SI = 1 and 119 for P_5 and P_6 respectively were more actives and selectives on the parasite than their corresponding (P_{1-3}). Products could open opportunity to the treatment of trypanosomiasis.

KEYWORDS: Synthesis, thiosemicarbazones, *isomers cis* and *trans*, selectivity.

INTRODUCTION

In recent years, great progress has been made in the methods of studying chiral structures. These are important because they are involved in many biological processes. The majority of molecules of biological interest are chiral (polypeptides, enzymes, steroids, proteins, sugars, DNA, metabolites, etc.); therefore if we want to design molecules interfering with biological processes in order to correct a pathological situation, it is necessary to take into account this phenomenon of chirality.[1] Geometric isomerism is the phenomenon of organic chemistry characterized by the asymmetry arising from at least two different substituents, linked to two atoms engaged with each other by a double bond, e.g. the carbon-carbon double bond. As well, pharmaceutical analysis is a branch of practical chemistry that involves a series of processes for identification, determination, quantification and purification of a substance, separation of the components of a solution or mixture, or determination of structure of chemical compounds.[2] Compounds containing nitrogen and phosphorus atoms are of considerable interest because of their biological.[3-5] pharmacological: anti-inflammatory and analgesic,[6] anticancer[7] and in agriculture: pesticides[8] activities, insecticides,[9] herbicides.[10] The geometric isomers determined by the carbon-nitrogen double bond ($R_1R_2C=N-R_3$) and the substituents R_1, R_2, R_3 are called Z (syn) and E (anti). In the older chemical literature, these stereoisomers were designated as syn and anti forms, but these names are really no better than *cis* and *trans*. These isomers can exist in pairs in the ratio 1/1 or in a different ratio depending on the energy required for their formation, depending on their stability. It is well-known that oximes can be present as syn and anti (Z and E) isomers and they can undergo isomerization.[11] Only one can exist. Semicarbazones, thiosemicarbazones and their derivatives are the major subgroups of hydrazones (-C=N-N-) alongside thioaroylhydrazones and oxyaroylhydrazones. Thiosemicarbazones are a class of compounds with a broad spectrum of biological or therapeutic applications. Thus, they have been studied for their antitumor, antiviral (including against HIV), antibacterial, antimalarial, antifungal, anti-inflammatory properties.[12-15] Several studies have been carried out on its compounds, but less work discusses the cases of mixtures of isomers obtained in their

synthesis. In this study, we synthesized thiosemicarbazones of acetophenone and propiophenone and discussed their geometric structure, and then their antiparasitic activity on *Trypanosoma brucei brucei*.

MATERIALS AND METHODS

Chemistry

Theoretical study based on the design, pharmacokinetics and drug availability properties rules[16-17] was explored before the synthesis of compounds.

During the works, we have used reactifs and solvents purchased from Sigma-Aldrich, Janssen Chimica and Riedel-de Haen. Substrates, reagents, catalysts and solvents were used directly for syntheses without any further purification. There are thiosemicarbazide, 4-methyl-3-thiosemicarbazide and 4-phenyl-3-thiosemicarbazide, acetophenone, propiophenone, glacial acetic acid (AAG), ethanol (EtOH, 95°). Melting points (m.p.) were determined on a *fusionometer* of the type *electrothermal 1A 9000* and were not corrected. The Infra-Red spectrum of each compound were recorded with a Perkin-Elmer FTIR 286 apparatus. The solid sample is mixed with sodium chloride powder or potassium bromide flakes and squeezed to obtain a disc which will be introduced into the IR spectrophotometer for analysis. The wavenumbers are expressed per centimeter. Compounds were also characterized by Nuclear Magnetic Resonance spectra using Bruker Avance 400 UltraSheild with dimethylsufoxide (DMSO)-d_6 or chloroform $CDCl_3$. The frequencies for ^{1}H and ^{13}C are 400.130 and 100.612 MHz respectively. Chemical shifts are given in parts per million (ppm) relative to tetramethylsilane as internal standard. Multiplicity was designated as singlet (s), singlet dedouble (sd), doublet (d), doublet dedouble (dd), triplet (t), triplet dedouble (td), quadruplet (q), quadruplet dedouble (qd) and multiplet (m).

Biology

We have used the bloodstream form of the strain 427 of *Trypanosoma brucei brucei and the* larvae of brine shrimp (*Artemia salina* Leach) as the biological material.

Methods

Synthesis of the compound ($P_{1\text{-}6}$)

An equimolar mixture (0.01 mol) thiosemicarbazide dissolved in 10 mL ethanol (EtOH 95°) was added slowly to a solution (0.01 mol) of ketone dissolved in 20-30 mL of EtOH in presence of a few drops of glacial acetic acid (GAA). Each mixture was heated at reflux for

2-4 hours with stirring. After cooling, the precipitate was filtered, washed with cold distilled water until neutrality, dried and then recrystallized in ethanol to give corresponding thiosemicarbazones.

Biological activity

Anti-trypanosomal test

The assessment is performed according to the «LILIT Alamar Blue^{TM}» method.[18-19] The stock solutions of each product have been prepared from an initial concentration of 10 mg/mL in dimethylsufoxide (DMSO). The trypanosomes are grown in a medium containing 10% of heat inactivated fetal calf serum and bloodstream form supporting factor. The trypanosome suspensions were adjusted to 5×10^4 tryp/mL. In each well, 50 µL of different dilutions of the stock solution were added to 50 µL of suspension of trypanosomes. The plates were then incubated at 37°C for 72 hours in an atmosphere with 5% CO_2. 10 µL of dye "Alamar BlueTM" is added to each well and then incubated for 4 hours. The dye "Alamar BlueTM" is a reagent for detecting enzymatic activity. The wells in which the concentration of compound is insufficient to inhibit the proliferation of trypanosomes are stained. The half inhibitory concentration (IC_{50}) is the concentration of unstained wells in which there is the lowest amount of compound and it is expressed in micromolar. The plate reading is made in comparison with control wells on a fluorescence plate reader using an excitation wavelength of 530 nm and an emission wavelength 590 nm.

We carried out the test in triplicate for each compound. All data were expressed as means ± standard deviation of triplicate measurements.

Toxicity screen

This test was performed according to the method of Sleet and Brendel (1983).[20] *Artemia salina* eggs were incubated in seawater until hatching of young larvae (48 hours). Then, series of solutions of test compound at varying concentrations were prepared in DMSO/seawater. A defined number of larvae were introduced into each solution and incubated under rocking condition for 24 hours. To evaluate the toxicity of the solution, counting of larvae viability was performed under microscope by determining the number of dead larvae in each solution. In the case where there was death in the control medium, the data was corrected by Abbott's formula:

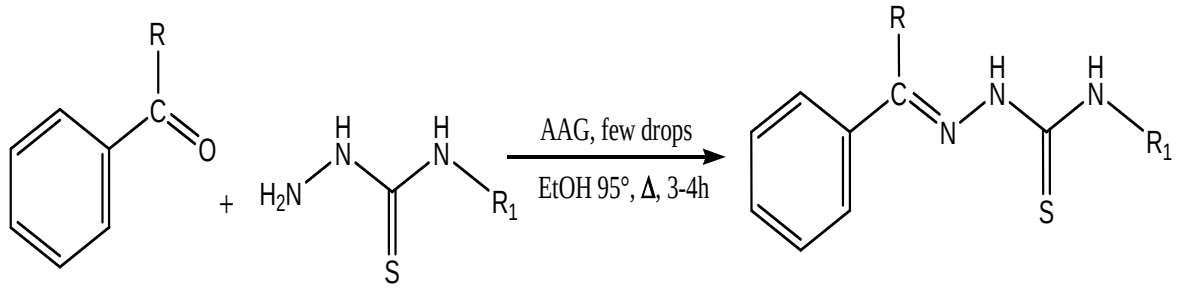
% death = [(nd test - nd control) / nd control)] x 100 with nd = number of dead larvae [21].

Data (dose-response) were transformed by logarithm and the half-lethal concentration LC_{50} was determined by linear regression[22] and, then, expressed in micromolar. Tests were carried out in triplicates. All data were expressed as mean ± standard deviation of triplicate measurements.

RESULTS

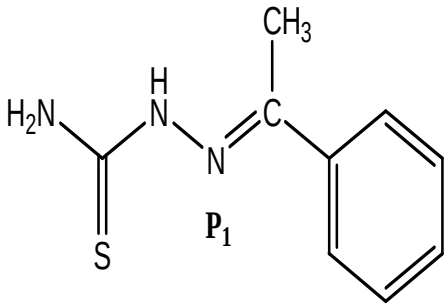
Chemistry

Six compounds have been synthesized (Figure 1, Table 1). Physico-chemical properties as yield, chemical formula (C.F) and melting point (m.p), and then the structural characterisation of products were studied.

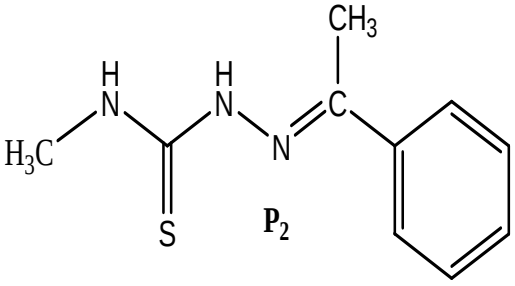


P1 : R = CH_3, R_1 = H ; **P2** : R = CH_3, R1 = CH_3 ; **P3** : R = CH3, R1 = Ph

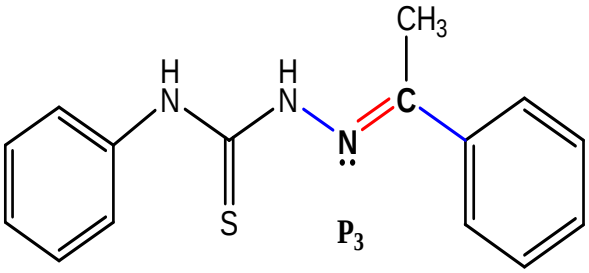
P4 : R = CH_2CH_3, R1 = H ; **P5** : R = CH_2CH_3, R_1 = CH_3 ; **P6** : R = CH_2CH_3, R_1 = Ph



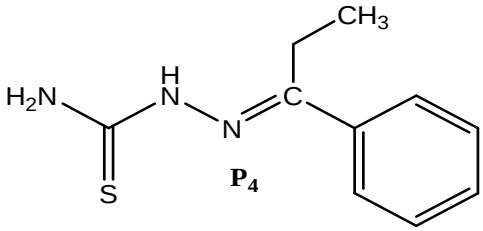
acetophenone thiosemicarbazone ;



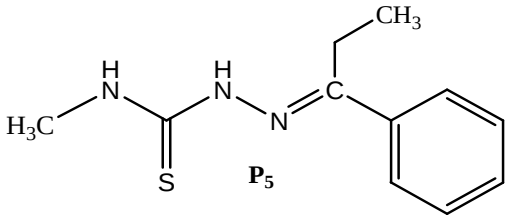
acetophenone 4-methyl-3-thiosemicarbazone ;



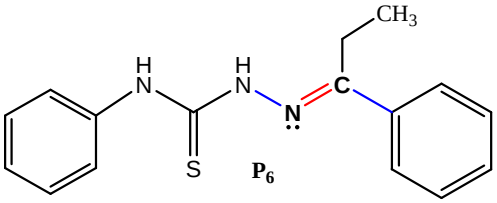
(*anti*) acetophenone 4-phenyl-3-thiosemicarbazone



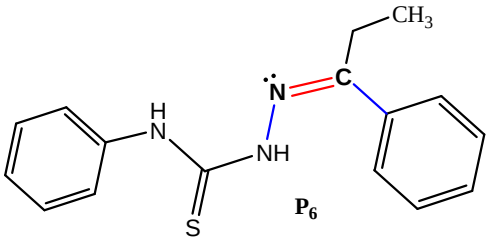
propiophenone thiosemicarbazone ;



propiophenone 4-methyl-3-thiosemicarbazone ;



(*anti*) propiophenone 4-phenyl-3-thiosemicarbazone ;



(syn) propiophenone 4-phenyl-3-thiosemicarbazone

Figure 1: Synthetisis reaction and structure of products.

***Acetophenone thiosemicarbazone* (P_1)**

Yield : 85% ; m.p : 120-121°C ; IR ν(NaCl, cm^{-1}): 3408, wide band 3300, 3233 (NH_2); 3145 (NH); 1587 (C=N); 1074, 964, 845, (N-CS-N). ^{13}C NMR δ (DMSO-d_6, ppm): 177.41 (C=S); 146.19 (C=N); 135.07; 128.55; 127.13; 123.05 (C-Ar); 12.28 (CH_3). ^{1}H NMR δ (DMSO-d_6, ppm): 8.90 (s, 1H, C=N–NH−); 7.70-7.20 (m, 5H, H-Ar); 6.50 (band, 2H, CS-NH_2); 2.30 (s, 3H, CH_3). C.F : $C_9H_{11}N_3S$.

***Acetophenone 4-methyl-3-thiosemicarbazone* (P_2)**

Yield : 73% ; m.p : 132-133°C ; IR ν(KBr, cm^{-1}): 3444, 3335 (NH); 1544 (C=N); 1065, 1045, 831 (N-CS-N). ^{13}C NMR δ ($CDCl_3$, ppm) : 178.94 (C=S); 146.79 (C=N); 137.47; 129.96; 128.58; 126.53 (C-Ar); 31.28 (N-CH_3); 13.60 (CH_3). ^{1}H NMR δ ($CDCl_3$, ppm) : 8.70 (s, 1H, C=N–NH–); 7.25 (q, 1H, CS-NH-CH_3); 7.70-7.30 (m, 5H, H-Ar); 3.25 (s, 3H, N-CH_3); 2.30 (s, 3H, CH_3). C.F : $C_{10}H_{13}N_3S$.

***Acetophenone 4-phenyl-3-thiosemicarbazone* (P_3)**

Yield : 86% ; m.p : 191-192°C ; IR ν(NaCl, cm^{-1}): 3302, 3248 (NH); 1588 (C=N); 1100, 1026, 847 (N-CS-N). ^{13}C NMR δ (DMSO-d_6, ppm): 176.33 (C=S); 147.29 (C=N); 137.92; 137.28; 130.18; 129.88; 128.82; 128.72; 126.57; 124.22 (C-Ar); 13.85 (CH_3). ^{1}H NMR δ ($CDCl_3$, ppm): 9.40 (s, 1H, C=N–NH−); 8.80 (s, 1H, CS–NH-Ph); 7.80-7.20 (m, 10H, H-Ar); 2.35 (s, 3H, CH_3). C.F : $C_{15}H_{15}N_3S$.

Propiophenone thiosemicarbazone (P$_4$)

Yield : 74% ; m.p : 116-117°C ; IR ν(KBr, cm^{-1}): 3406, 3301, 3203 (NH); shoulder at 3200 (NH_2); 1600 (C=N); 1074, 1053, 840 (N-CS-N). ^{13}C NMR δ (DMSO-d_6, ppm): 179.13 & 178.76 (C=S); 155.81 & 152.97 (C=N); 136.14; 132.92; 130.03; 129.96; 129.81; 128.69; 126.76; 126.46 (C-Ar); 31.54 & 20.30 (–CH_2–); 10.73 & 10 65 (CH_3). ^{1}H NMR δ ($CDCl_3$, ppm): 8.85 & 8.65 (sd, 1H, C=N–NH−); 7.70-7.20 (m, 10H, H-Ar); 6.70 & 6.55 (sd, 2H, CS-NH_2); 2.83 & 2.61 (qd, 2H, –CH_2–); 1.23 & 1.11 (td, 3H, CH_3). C.F : $C_{10}H_{13}N_3S$.

Propiophenone 4-methyl-3-thiosemicarbazone (P$_5$)

Yield : 67% ; m.p : 98-99°C ; IR ν(KBr, cm^{-1}): 3414, 3290 (NH); 1544 (C = N); 1062, 1033, 845 (N-CS-N). ^{13}C NMR δ ($CDCl_3$, ppm): 178.99 & 178.62 (C=S); 154.50 & 151.50 (C=N); 136.39; 133.17; 129.85; 129.72; 129.69; 128.85; 126.79; 126.35 (C-Ar); 31.44 & 31.30 (N-CH_3); 31.09 & 20.18 (–CH_2–); 10.85 & 10.55 (CH_3). ^{1}H NMR δ ($CDCl_3$, ppm): 8.80 & 8.50 (sd, 1H, C=N–NH–); 7.17 (q, 1H, CS–NH-CH_3); 7.80-7.30 (m, 5H, H-Ar); 3.30 & 3.20 (sd, 3H, N-CH_3); 2.70 & 2.50 (qd, 2H, –CH_2–); 1.20 & 1.10 (td, 3H, CH_3). C.F : $C_{11}H_{15}N_3S$.

Propiophenone 4-phenyl-3-thiosemicarbazone (P$_6$)

Yield : 80% ; m.p : 113-114°C ; IR ν(NaCl, cm^{-1}) : band 3450, 3294 (NH); 1598, 1588 (C=N); 1114, 1055, 920 (N-CS-N). ^{13}C NMR δ (DMSO-d_6, ppm): 176.35 & 176.01 (C=S); 154.79 & 152.02 (C=N); 138.05; 137.96; 136.21; 133.06; 130.08; 129.99; 129.85; 128.81; 126.83; 126.46; 126.13; 125.05; 124.21 (C-Ar); 31.54 & 20.45 (–CH_2–); 10.83 & 10.67 (CH_3). ^{1}H NMR δ ($CDCl_3$, ppm): 9.40 (s, 1H, C=N–NH−); 8.90 & 8.60 (sd, 1H, CS–NH–Ph); 7.85-7.15 (m, 10H, H-Ar); 2.80 & 2.65 (qd, 2H, –CH_2–); 1.30 & 1.15 (td, 3H, CH_3). C.F : $C_{16}H_{17}N_3S$.

Table 1: Theoretical pharmacokinetic and drug availability study.

Compounds	Molecular weight (g.mol^{-1})	*C logP*	Number of H-bond donors	Number of H-bond acceptors	Number of criteria met
Rules	< 500	< 5	≤ 5	< 10	at least 3
P_1	193.27	2.401	3	4	all
P_2	207.30	2.287	2	4	all
P_3	269.36	4.071	2	4	all
P_4	207.30	2.930	3	4	all
P_5	221.32	2.816	2	4	all
P_6	283.39	4.600	2	4	all

Biology

Thiosemicarbazones, semicarbazones and their complexes have a wide spectrum of biological and / or therapeutic applications. Thus, they have been studied for their antiparasitic properties. The various results obtained from the biological tests are shown in Table 2. From these results, we also determined the selectivity of the active compounds on the parasite *T. b. brucei*.

Table 2: Trypanocidal, Toxicity and Selectivity of synthesized compounds.

Products	IC_{50} (µM)	Trypanocidal activity	LC_{50} (µM)	Toxicity on larvae	SI = LC_{50}/IC_{50}	Selectivity
P_1	212.15 ± 6.17	low	-	-	-	-
P_2	> 241	no	-	-	-	-
P_3	> 371	no	-	-	-	-
P_4	210.00 ± 20.67	low	-	-	-	-
P_5	87.15 ± 1.13	moderate	149.27 ± 0.17	toxic	1.71	selective
P_6	7.63 ± 1.27	trypanocidal	909.18 ± 0.17	no toxic	119.18	selective

DISCUSSION

The products having physical properties compatible with reasonable pharmacokinetics and drug availability were synthesized. The product (Figure 1) has advantageous properties : low molecular weight, reasonable *C logP* (lipophily), good hydrogen bond donating and accepting capabilities (Table 1), easy and economical synthetic routes.[16-17] They are therefore organic molecules of bioactive interest.

Thiosemicarbazones exhibit the phenomenon of tautomerism. In the solid state, they mainly exist in the thione form. The terminal amino group (NH_2) of compounds P_1 and P_4 has three different vibration frequencies : two NH which do not have the same chemical environment and one NH_2 frequency. Molecules P_2, P_3, P_5 and P_6 substituted on nitrogen N(4) did not show this vibrating frequency of NH_2. On each of the spectra we observe three types of vibrations of the thioamide group.[23] The proposed assignments are based on previous results[24-28] and pertinent references.[29-33]

The two nitrogenous protons ($CS–NH_2$) in thiosemicarbazones appear at chemical shifts 6.70-6.50 ppm in products P_1 and P_4. Since the chemical environment has not been the same, we have sometimes seen two distinct singlets for this type of proton. The non-equivalence of protons on the thioamide nitrogen atom is caused by the impeded rotation around the –CS–N bond due to the contribution of the resonance shape particulary in propiophenone

thiosemicarbazone P_4.[34,35] As for the thiosemicarbazones of propiophenone, they appear in the spectrum in the form of two isomers syn and anti. In fact, two different chemical shifts are observed for each proton or for each group of protons. For example, the spectrum of thiosemicarbazone propiophenone gives as chemical shifts of the proton of -NH- at δ = 8.65 ppm and δ = 8.85 ppm; the integral curve showing about 40% syn and 60% anti. The anti isomer is more screened than the syn isomer.[36] This result is not observed at the level of the spectra recorded on the thiosemicarbazones of acetophenone. This remark would be due to the small steric hindrance of the alkyl groups (methyle and phenyle) at the carbon level of the imine function in the thiosemicarbazone of acetophenone in comparising to the same carbon imine with phenyl and ethyl groups, more hindrance, in the thiosemicarbazones of propiophenone. In the literature, it is well known that the syn isomer is stable and appears in appreciable percentage only when it is a ketone for which the substituents of the carbonyl group are very different and bulky.[36] Whereas both syn- and anti-isomers of the thiosemicarbazones and carbomethoxymethyl hydrazones cyclize, only the syn-isomer of the semicarbazones can be converted to the corresponding azauracil.[37] It can therefore say that the thiosemicarbazones of acetophenone were present more under the anti configuration, which is more predominant.

The products submitted to their biological activity against parasite *T b. brucei* and toxicity on *Artemia salina* L, exhibited an interesting activities especially the propiophenone thiosemicarbazones which gave the low half inhibitory concentrations ranging from 7 to 210 µM. Almong them, propiophenone 4-phenyl-3-thiosemicarbazone P_6 (IC_{50} = 7.63 µM) was the most trypanocidal and selective on the parasite (IS = 119), and its 4-methyl-3-thiosemicarbazone P_5 (IC_{50} = 87.15 µM) exhibited a moderate antiparasitic activity on the trypanosome (table 2) according to the scale of antiparasitic activity and selectivity established in the littérature.[38-40]

CONCLUSION

We have synthesized and studied some physisco-chemical as well as structural properties of some thiosemicarbazones. The molecules obtained from the more bulky ketones have been found to occur in the two geometric isomers *Cis* and *Trans* in different ratios. The trypanocidal and toxic activities were evaluated and it is the N (4)alkylthiosemicarbazones of propiophenone which showed interesting activities and are selective on the parasite.

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Competing interests

The authors declare that they have no competing interests.

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