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Synthesis and Caracterizations of New Thiosemicarbazone and Thiazole Derivatives From Polycyclic Chiral 1,5-Diketones

Hayreddin Gezegen*[a]

Thiosemicarbazone derivatives have a wide spectrum of biological activity as well as various application areas such as forming complexes with metals, using as intermediates in the synthesis of heterocyclic bioactive compounds. Thiazole derivatives can be easily synthesized from thiosemicarbazones and are among the important compounds in demand in terms of biological activity. In this study, 14 new thiosemicarbazone derivatives were synthesized starting from polycyclic 1,5-diketone derivatives with five stereocenters, and 14 thiazole derivatives were synthesized from the reaction of the obtained thiosemicarbazones with 2-bromoacetophenone and their structure determinations were carried out using spectroscopic methods (^{1}H-NMR, ^{13}C-NMR, 2D-NMR, FT-IR and Q-TOF LC/MS). This synthesis route from polycyclic chiral 1,5-diketones may contribute to the design of new drug-like molecules, which are important in medicinal chemistry.

Introduction

The synthesis and application areas of compounds containing heteroatoms such as N and S in their structure are among the current and worth topics researching for organic chemists.[1] Because the compounds containing heteroatom have been high bioactive potential and they are widely used in drug design and development.[2] Thiosemicarbazones readily obtained from the reaction of thiosemicarbazide with an aldehyde or a ketone, are an important class of nitrogen- and sulfur-containing ligands, and their coordination chemistry was first discovered in the early sixties.[3] Due to the presence of C=N and C=S bonds, these compounds can easily form complexes with metals and interact with biological molecules that are vital for living things. This situation allows having a broad spectrum of biological activity and they are widely used as a pharmacophore group in the synthesis of new compounds.[4] When look at the literature, it is seen that there are many studies on thiosemicarbazones and the scope of these studies is generally on the synthesis, biochemistry, structural properties, biological activities and analytical applications of thiosemicarbazones.[5–8] In the literature, it is seen that various thiosemicarbazone derivatives with antimicrobial,[9] antituberculosis,[10] anti-HIV,[11] anticonvulsant,[12] analgesic,[13] antitumor,[14] and antifungal[15] activities have been reported. In addition, there are many studies on ionophore properties of thiosemicarbazones.[16]

Thiosemicarbazone derivatives are good polyfunctional intermediates used in the synthesis and design of important heterocyclic compounds same time.[17–19] The synthesis of heterocyclic compounds, which are different from each other and have a large number of molecular diversity, can be carried out via thiosemicarbazones using appropriate reagents.[20] To give an example; thiazole, thiazoline, thiazolidine, pyrrolidine, pyrazole, indazole, oxoindenopyrazole, thiadiazole, oxadiazole, triazole, pyridazine, benzophthalazine, thiazine and triazine derivatives can be obtained from thiosemicarbazones.[19]

Thiazoles, which are among these compounds, are very valuable compounds in terms of biological activity and there are various derivatives used as medicine.[21,22] Can be given as an example of these are Sulfathiazole used as antimicrobial agent,[23] Ritonavir used in the treatment of HIV/AIDS[24] and Abafungin used as antifungal agent in dermatology[25] (Figure 1). There are also various thiazole derivatives with different biological activities.[26,27]

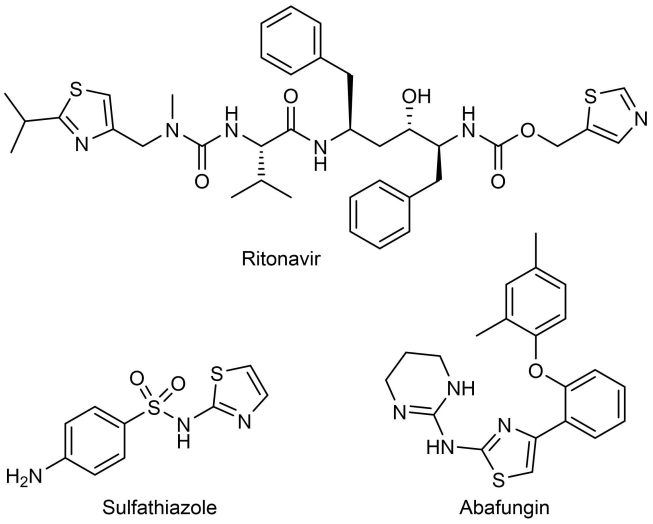

Figure 1. Examples of thiazole derivatives used as pharmaceutical agents.

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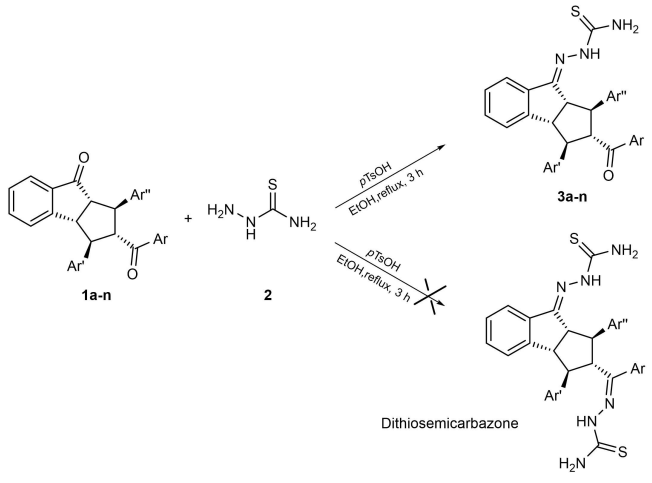
In the light of this information, it is seen that the synthesis of new thiosemicarbazone derivatives allow the synthesis of new bioactive and polyfunctional compounds and plays a key role. In this respect, in this study, aimed to synthesis and characterization of new thiosemicarbazone (**3 a**–**n**) (Table 1) and thiazole derivatives (**5 a**–**n**) (Table 2) from polycyclic 1,5-diketone derivatives with five stereocenters, which we synthesized in our previous study (**1 a**–**n**).[28]

Results and Discussion

In this study, it was reported the synthesis and characterization of a series of novel thiosemicarbazone and thiazole derivatives with high yields (Table 1 and Table 2). The synthesis of new thiosemicarbazone derivatives was carried out by refluxing of **1 a**–**n** with thiosemicarbazide (**2**) in ethanol for 3 hours in the presence of *p*-TsOH. According to the information obtained from the spectral analyzes at the end of the reaction, it was understood that the thiosemicarbazide was substituted to the carbonyl carbone located on the five membered ring in the structure. The same study was repeated using ethanol, toluene and ethanol-toluene mixture to obtain 1,5-dithiosemicarbazone derivatives from the reaction of polycyclic chiral 1,5 diketones with thiosemicarbazide at 1 : 2 and 1 : 4 ratios, but this product was not formed. (Scheme 1). Considering the three-dimensional structure of polycyclic chiral compounds (**1 a**–**n**), it is understood that the indanone unit in the structure folds inward and sterically blocks the related ketone unit.[28]

The obtained thiosemicarbazone derivatives were tried to be converted into thiazole derivatives (**3 a**–**n**) by reacting with 2-bromo acetophenone (**4**) in ethanol, but it was observed that the solubility of thiosemicarbazones (**3 a**–**n**) in ethanol was low and the reaction was not completed. Thereupon, the reaction was carried out by refluxing in EtOH-toluene (1 : 1) mixture for 2 hours, thiazole derivatives (**5 a**–**n**) were obtained at the end of the reaction.



Scheme 1. Synthesis of thiosemicarbazones and structure of 1,5-dithiosemicarbazone.

In our previous work, we performed diastereoselective synthesis and structure determination of polycyclic chiral 1,5-diketone derivatives.[28] Here, the structure determination of new thiosemicarbazone and thiazole derivatives is discussed. When the ^{1}H-NMR spectrum of the compound **3 a** is examined, it is seen that the –NH proton on the thiosemicarbazone unit gives a singlet at 8.30 ppm, one of the $-NH_2$ protons in the structure gives a singlet at 8.00 ppm, and the other one gives multiplets between 7.69–7.62 ppm by overlapping with aromatic protons in the *ortho* position with respect to the ketone group in the 4-chlorophenylethanone unit in the structure. The H–Cb proton and the H–Ce proton on the indanone unit give multiplets between 7.98–7.90 ppm and 6.89–6.83 ppm respectively. Signals from other aromatic protons are seen in the spectrum as doublet at 7.58 (J = 8.3 Hz) and 7.53 (J = 8.5 Hz) ppm, and as multiplet between 7.43–7.29 ppm. Among the aliphatic protons in the structure, H–C2 gives a triplet (J = 11.2 Hz) at 4.92 ppm, while H–C4 and H–C5 give multiplet between 4.38–4.21 ppm, H–C1 gives multiplet between 3.34–3.26 ppm. In addition, H–C3 proton is resonated giving a doublet of doublet (J = 11.1, 8.3 Hz) at 3.21 ppm.

In the ^{13}C-NMR spectrum of **3 a**, the peak at 199.3 ppm is the signal of the carbonyl carbon (CB). The thioamide carbon in the structure gives signal at δ 178.31 ppm characteristically, while the imine carbon at 155.0 ppm. Quaternary carbons (Cf and Ca) in the indanone unit resonate at 149.57 and 139.91 ppm, respectively. Other carbons in the indanone unit give signal at 131.61 (Cc), 128.42 (Cd), 124.38 (Ce) and 123.36 (Cb) ppm, respectively. Other aromatic carbon signals are also in harmony with the structure. The carbon atoms in the aliphatic region C1, C2, C3, C4 and C5 resonate at 54.1, 63.6, 58.0, 55.6 and 52.6 ppm, respectively.

The 2D-NMR spectra of **3 a** are given in the supporting information and appear to confirm the proposed structure. When the NOESY spectrum of the compound is examined, it is seen that there is no interaction between the -NH proton and the H–Cb proton in the structure. This indicates that the compound is in the form of the *E*-isomer. If the compound were in *Z* form, this interaction should be seen clearly (Figure 2).

The singlet, located at 8.34 ppm in the lowest area in the ^{1}H-NMR spectrum of **5 a**, comes from the -NH- group in the

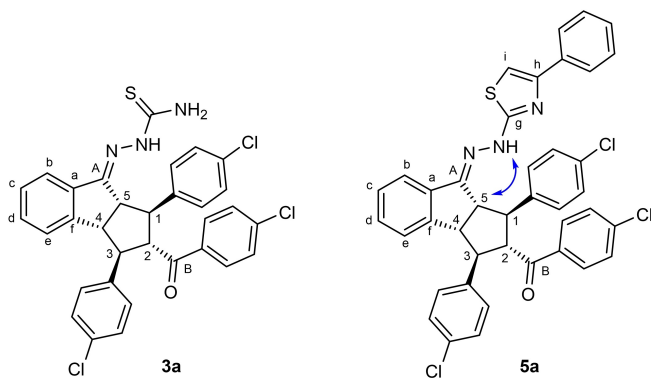
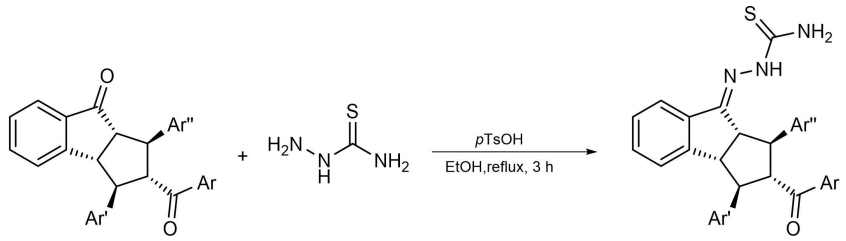
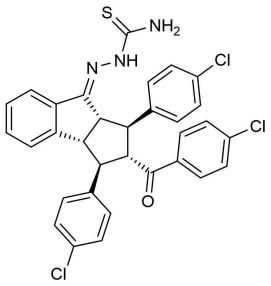


Figure 2. Structures of **3 a** and **5 a** compounds, ^{1}H-1H interactions obtained from the NOESY spectrum of **5 a**.

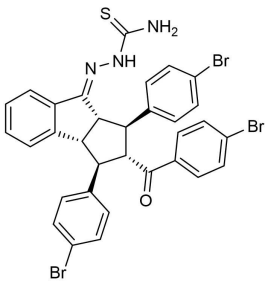
Table 1. Synthesis of new thiosemicarbazone derivatives from chiral polycyclic 1,5-diketone derivatives.[a]



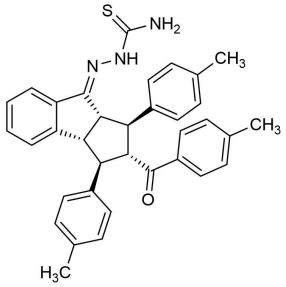
1 a–n **2** **3 a–n**



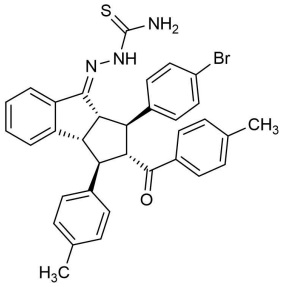
3 a, 84 %[b]



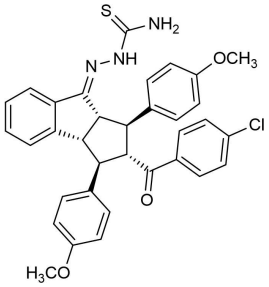
3 b, 70 %



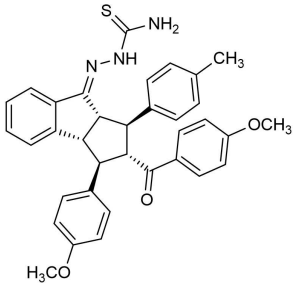
3 c, 86 %



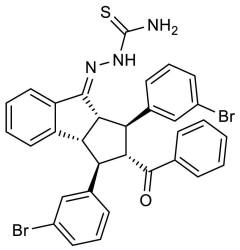
3 d, 80 %



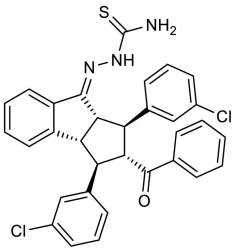
3 e, 86 %



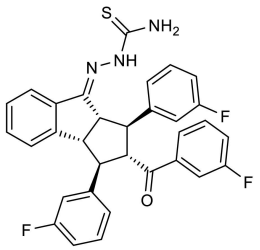
3 f, 88 %



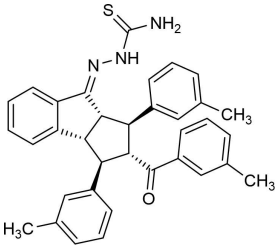
3 g, 94 %



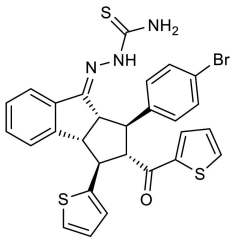
3 h, 87 %



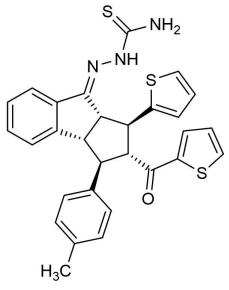
3 i, 89 %



3 j, 82 %

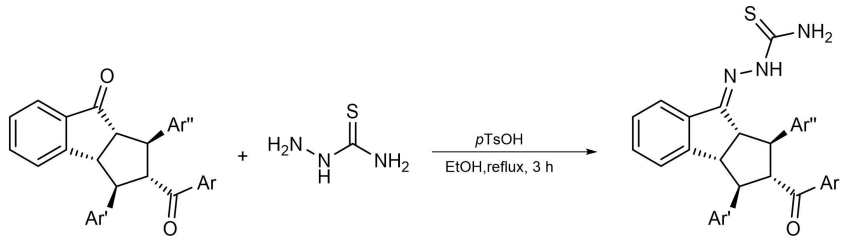


3 k, 92 %

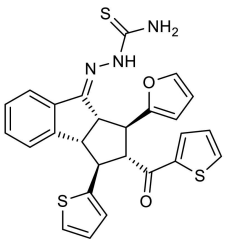


3 l, 83 %

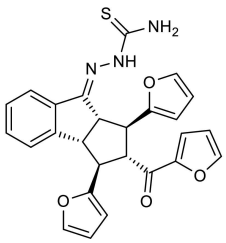
Table 1. continued



1 a–n **2** **3 a–n**



3 m, 95 %



3 n, 70 %

[a] Reactions were performed using polycyclic chiral 1,5-diketone (**1 a–n**) (1.0 mmol), thiosemicarbazide (**2**) (1.2 mmol), *p*-TsOH (0.25 mmol) in 50 mL EtOH. [b] Isolated yields.

structure. The aromatic protons in the *ortho* position with respect to the ketone group in the 4-chlorophenylethanone unit give a doublet ($J = 7.8$ Hz) at 7.79 ppm, while the H–Ce proton and the two protons in the 4-chlorophenyl rings overlap and give a multiplet between δ 7.73–7.64 ppm. The H–Cb proton resonates giving a doublet ($J = 7.4$ Hz) at 6.87 ppm. Other aromatic protons in the structure resonate by giving a triplet ($J = 8.5$ Hz, 4H) at 7.59 ppm and a multiplet (12H) between 7.42–7.26 ppm. Aliphatic protons on the structure give signal in the spectrum, as follows: H–C2 triplet at 5.02 ppm ($J = 11.2$ Hz), H–C5 triplet at 4.43 ppm ($J = 9.3$ Hz), H–C4 triplet at 4.32 ppm ($J = 8.9$ Hz), H–C1 triplet at 3.39 ppm ($J = 10.3$ Hz) and H–C3 doublet at 3.24 ppm ($J = 11.2, 8.9$ Hz).

In the ^{13}C-NMR spectrum of **5 a**, the carbonyl carbon (CB) is seen at 199.4 ppm. The quaternary carbon (Cg) connecting the thiazole ring to the hydrazine unit signals at 167.7 ppm, and the imine carbon (CA) at 149.2 ppm. Ce and Cb carbons resonate at 124.6 and 122.0 ppm, respectively, while Cc and Cd carbons resonate at 131.2 and 128.6 ppm. The carbon on the thiazole ring (Ch) give signal at 139.9 ppm and the Ci carbon at 104.4 ppm. Other carbon signals in the aromatic region are in harmony with the structure. The carbon atoms on the quintuple ring resonate at δ 63.1 (C2), 58.2 (C3), 55.4 (C4), 54.6 (C1) and 53.3 (C5) ppm, respectively.

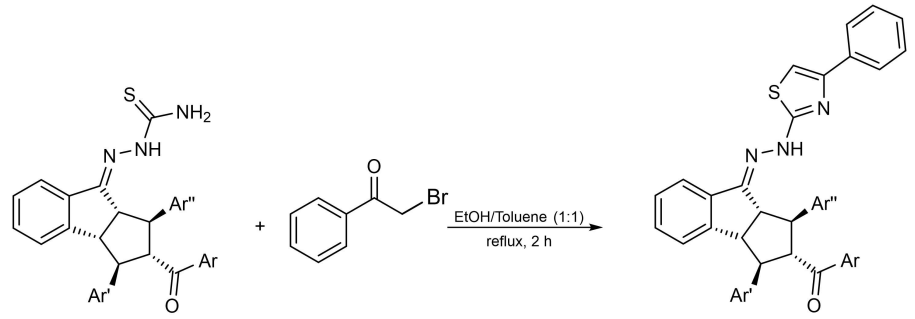
The interaction between the -NH- proton (8.34 ppm) and the H–C5 proton (4.43 ppm) in the NOESY spectrum is proof that the structure is the *E*-isomer. Otherwise, the -NH- proton would be expected to interact with the H–Cb proton (Figure 2).

Conclusions

Thiosemicarbazone and thiazole derivatives are among the important compounds with a wide biological activity potential. In addition, thiosemicarbazones have various application areas because they can easily form complexes with metals. In this respect, the synthesis of new thiosemicarbazone and thiazole derivatives is a current and important issue. Although the synthesis of various thiosemicarbazone and thiazole derivatives has been reported in the literature, there is no study on the synthesis of thiosemicarbazone and thiazole derivatives in which polycyclic 1,5-diketone derivatives with five stereocenters are substituted.

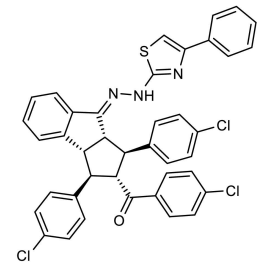
In this study, 14 new thiosemicarbazone derivatives (**3 a–n**) were obtained from the reaction of chiral polycyclic 1,5-diketone derivatives (**1 a–n**) with thiosemicarbazide (2), and 14 new thiazole derivatives (**5 a–n**) were obtained from the reaction of thiosemicarbazones (**3 a–n**) with 2-bromoacetophenone (4). The chemical structures of the synthesized compounds were determined by spectroscopic methods (^{1}H-NMR, ^{13}C-NMR, 2D-NMR, FT-IR and Q-TOF LC/MS). The spectral analyzes performed support the proposed configurations of the compounds. The conducted synthesis and caracterization study may be useful and applicable in the synthesis of new chiral compounds with high bioactive potential and polyfonctional. In this respect, it is thought that this study will make an important contribution to the literature.

Table 2. Synthesis of new thiazole derivatives from new thiosemicarbazones.[a]

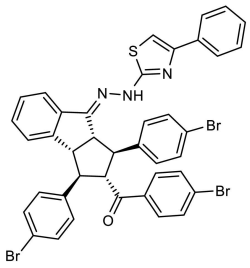


3a–n + **4** → **5a–n**

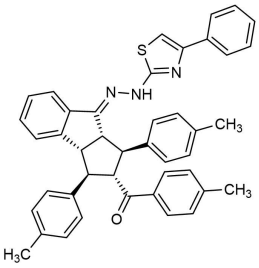
5a, 74%[b]



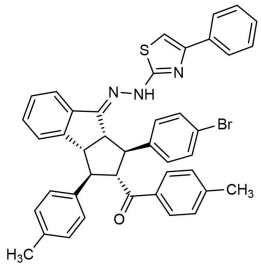
5b, 69%



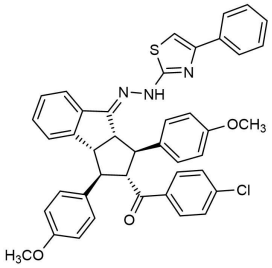
5c, 70%



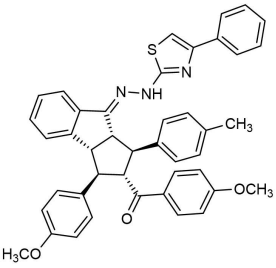
5d, 67%



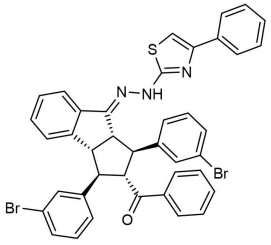
5e, 82%



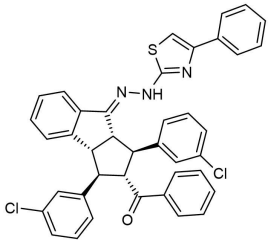
5f, 80%



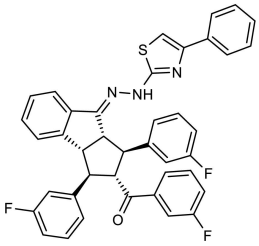
5g, 68%



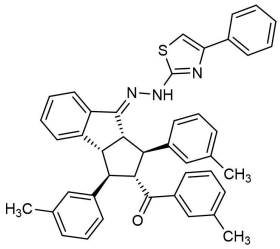
5h, 70%



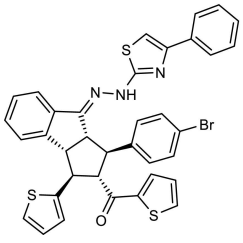
5i, 80%



5j, 71%



5k, 78%



5l, 71%

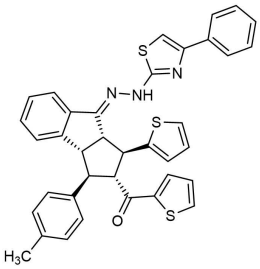
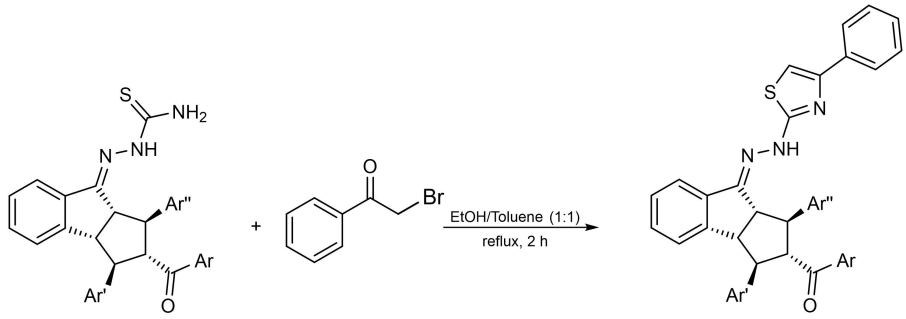
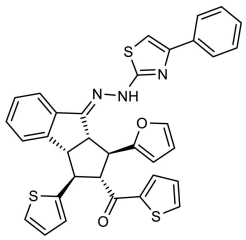


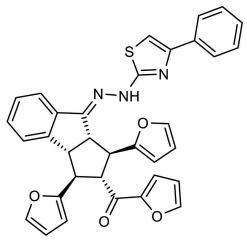
Table 2. continued



3a–n **4** **5a–n**



5m, 71%



5n, 60%

[a] Reactions were performed using thiosemicarbazone (**3a–n**) (1.0 mmol), 2-bromoacetophenone (**4**) (1.2 mmol), in 50 mL EtOH-Toluene (1:1). [b] Isolated yields.

Experimental Section

General information

Melting points were measured on an Electrothermal IA9100 apparatus. IR spectra (ATR) were recorded on a Bruker Tensor II FT-IR spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a JEOL (400 MHz) JNM-ECZ400S/L1 NMR instrument and 2D-NMR spectra were recorded on a Bruker Avance DPX-400 instrument in $CDCl_3$ at room temperature; δ in ppm relative to tetramethylsilane (TMS), with J in hertz (Hz). Agilent Technology Inc. of 1260 Infinity HPLC System was coupled with 6530 Q-TOF LC/MS detector and ZORBAX SB-C18 (2.1×50 mm, 1.8 μm) column. ^{1}H-NMR, ^{13}C-NMR, and Q-TOF LC/MS analyses of the compounds were carried out at the Advanced Technology Application and Research Center (CUTAM) of Sivas Cumhuriyet University and 2D-NMR analyses were carried out at the Advanced Technology Application and Research Center (GUBİTAM) of Tokat Gaziosmanpaşa University.

General procedure for the synthesis of thiosemicarbazone derivatives (3a–n)

The synthesized polycyclic chiral 1,5-diketone derivatives were reacted with thiosemicarbazide in the presence of *p*-toluene sulfonic acid in ethanol. The corresponding 1,5-diketone derivative (**1a–n**) (1.0 mmol) was taken into a reaction flask and dissolved in ethanol (50 mL) by adding thiosemicarbazide (**2**) (1.2 mmol) and *p*-TsOH (0.25 mmol). The reaction flask was placed on a heated magnetic stirrer and refluxed for 3 hours. At the end of the reaction, it was observed that white precipitates formed at the bottom of the flask. The mixture was taken into a separatory funnel and extracted with dichloromethane (3×15 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed from the evaporator. The remaining viscous fraction (**3a–n**) was crystallized from an ethanol-diethyl ether (1:1) mixture.

Supporting Information Summary

The full experimental section, including materials, details of procedures, characterization methods, and results, and the spectra of compounds, are given in the Supporting Information

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: 1,5-Diketone · Thiazole · Thiosemicarbazide · Thiosemicarbazone · Polycyclic compounds

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