Synthesis, Characterization, DFT Calculations and Anticoagulant Activity of Symmetrical and Unsymmetrical N-Aryl Thiourea Derivatives

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Summary: The present study reports a methodology for the synthesis of symmetrical and unsymmetrical thiourea derivatives 1-9, which have been prepared in good overall yields from condensation reactions between phenylisothiocyanate and different primary amines. The structures of all products were confirmed by the spectroscopic analysis (UV, IR, and NMR). These derivatives were tested for anticoagulant activity using PT and APTT reagents, and those reagents are considered also a controller, the results showed that the theN-aryl thiourea derivatives have very high anticoagulant activity. Theoretical calculations based on DFT/B3LYP method have been performed in order to get insights into the molecular geometry and chemical reactivity of the studied compounds.

Keywords: Thiourea, Phenylisothiocyanate, Anticoagulant Activity, PT reagent, APTT reagent.

Introduction

In 1873 [1], Nencki have synthesized for the first time an emerging class of those compounds Due to its unique reactivity, Thiourea derivatives are used widely for the synthesis of natural products and biologically active compounds. Owing to the sulfur atom contained in these derivatives, they are widely described in literature [2-4], and synthesized commonly with different methods for example: Clara G.M de Oliveira et al, have proposed the synthesis of thiourea derivatives using Benzoyle Chloride added to a solution of ammonium [5], while Zainab Ngaini et al have prepared Hexasubstituted thiourea via a condensation of isothiocyanate cyclophosphazen intermediates with a series of aromatic amine and amino acid in one pot reaction system [6]. MoroverNongnit et al have synthesized thiourea by using ethanamine and isothiocyanatonaphtalene in the Chloroform (CHCl3) solution [7]. Whereas Sanna et al have prepared thiourea derivatives using ethanamine in anhydrous acétonitrile with an appropriate isothiocyanate and the mixture was refluxed for 8 hours [8]. Furthermore I.V.Kulakov et al have synthesized thiourea derivatives using an isothiocyante prepared added to anabasine under mild condition [9]. In another case Cheng Yinan et al have proposed the synthesis of new thiourea derivatives via cyclo-addition reaction of 3-mercaptobutan-2-one and methyl 3-substitutedsilyl propiolate, selective hydrolysis of ester, isothiocyanatation and amination [10]. Likewise, Alexandra Kowalczyk et al have prepared thiourea derivatives using anazidines in reaction with isothiocyanate [11]. In addition, Jian Wu et al have propounded a synthesis of thiourea derivatives from acylisothiocyanate and a suitable fluorinated aromatic amine [12]. While Jonna stefanska et al have prepared the thiourea derivatives from a solution of amine derivatives in acétonitrile in reaction with appropriate isothiocyanate [13]. Otherwise Azim Ziyaei et al have synthesized thiourea derivatives via primary amines and carbon disulfide in 1-butyl-3-methylimidazolium chloride [14]. Whilst Najmedin Azizi et al have synthesized symmetrical thiourea derivatives by reacting primary amines with carbon disulfide in biocompatible basic choline hydroxide [15]. Via rational modification of thiourea derivative structures, it is possible to obtain a wide range of compounds with high pharmacological activity and low side effects. Over the last two centuries, the synthesis and properties of thiourea derivatives have been widely studied, especially for their biological activities [16-19], the thiourea moiety is a significant synthon responsible for a large number of biological activities, citing for example: antistaphylococcal activity, corrosion inhibitor for carbon steel [5]; antimicrobial activity [8,20-24]; anti-tubercular, antithyroid [25]; antiviral activity [8,25-27];

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antibacterial [11, 20, 28]; antifungal [8, 12, 21, 25, 29, 30]; cytotoxic effects [11,31]; plant growth regulating [32]; herbicidal [32, 33]; antioxidant activities [34]; analgesic [32-34]; antitumor agents [23, 35-37]; antiaggregant [38]; anti arrhythmic drug [39]; local anesthetic [40]; antihyperlipidemic activities [41]; some thiourea derivatives are effective anticancer [42, 43];and found to inhibit HIV reverse transcriptase [8, 37]; lardivicidal activities [44]; antileishmanial activity [45]. The synthesis of new thiourea derivatives was achieved by reacting different amines and phenylisothiocyanate (Usually used as a creative intermediate in the synthesis of thiourea derivatives). The aim of this work is to indicate a new anticoagulant activity of these newderivatives as was the case in our previous works [46-53].

Experimental

Materials and Methods

Reagents and solvents

- Phenylisothiocyanate was purchased from FlukaChemika.
- The primary amines used were: Ethylamine, O-Toluidine, O-Anisidine, 4-Chloroaniline, 2-Chloroaniline, Aniline, Triethylamine, Nitro-2-Aniline, and Tert-butylamine, all of which were purchased from Sigma-Aldrich.

Apparatuses

- UV spectra were obtained in several solvents with UNI- CAM UV300 spectrophotometer assisted to desktop computer.
- IR-Spectra were recorded with an AGILENT Cary 630 FTIR spectrophotometer with a diamond ATR accessory for solid and liquid samples, requiring no sample preparation; wavenumbers are given in cm-1.
- NMR analysis were recorded with superconducting electromagnet made by the brand Bruker actively armored of 400MHz frequency monitored by AVANCE III HD console, corresponding to 9.4 Tesla magnetic field, and an exploitation software TOPSPIN 3.5 PL6.
- Melting points were determined by Büchi® melting point apparatus Model B-545 with capillary tubes, temperature range up to 400 °C.

Synthesis of symmetrical and unsymmetrical N-aryl thiourea derivatives

Phenylisothiocyanate (5mmol) and the appropriate primary amine (5mmol) were mixed in Ethanol solution (5ml), the mixture was putted in ice bath (0°C) for 20 minutes. After that it was evaporated at 25°C for 48 hours, and a crystallized product was obtained.

Spectroscopic data

1-ethyl-3-phenylthiourea, $C_9H_{12}N_2S$ (**1**), this compound was obtained as a crystallized white solid, yield 82% , MP: 90°C, UVmax (MeOH, nm): 295.6 (Band I); 300.1 (Band II), IR (KBr, cm-1): 3300 (NH, medium), 3056.4 (C-H aromatic, medium), 2970 (C-H, strong) 2113.4 (R-N=C=S), 1591.6 (C=C aromatic, variable), 1390 (C-H (CH3), strong), 1200.2 (CN, medium); 1025.0 (C-O, strong), 745.5 (C-H aromatic, strong). 1H NMR (400 MHz, DMSO, ppm): 9.40 (s, 2H, H-7, H-10.); 7.06 – 7, 40 (m, 6H, H-1, H-2, H-3, H-4, H-6, H-10,); 3.48 (m, 2H, H-11); 1.11 (t, 3H, H-12). 13C NMR (101 MHz, DMSO, ppm):180.61 (C=S); 139.77 (C-1); 124.52 (C-2, C-6); 129.06 (C-3, C-5); 123.61 (C-4); 39.16 (C-N); 14, 66 (CH_3).

1-phenyl-3-(o-tolyl)thiourea, $C_{14}H_{14}N_2S$ (**2**), this compound was obtained as a crystallized white solid, yield 90%, MP: 141°C, UVmax (MeOH, nm): 290.3 (Band I); 300.2 (Band II), IR (KBr, cm^{-1}): 3332.2 (NH, medium), 3123.5 (C-H aromatic, medium), 2944.6 (C-H, strong), 2109.7 (R-N=C=S), 1595.3 (C=C aromatic, variable), 1349.3 (C-H (CH3), strong), 1207.7 (CN, medium), 1110.7 (C-O, strong), 760.4 (C-H aromatic, strong). ^{1}H NMR (400 MHz, DMSO, ppm): 9.64 (s, 3H, H-7); 9.29 (s, 1H,H-10); 7.49 (m, 1H, H-4, H-6); 7.10 – 7.34 (m, 1H, H-1, H-2, H-3, H-13, H-14, H-15, H-16); 2.25 (s, 2H, H-17). ^{13}C NMR (100 MHz, DMSO, ppm): 180.92 (C=S); 140, (C-1); 138,27 (C-1'); 135.27 (C-2); 130.80 (C-3); 126.92 (C-6); 128.89 (C-3', C-5'); 128.47 (C-5); 126.56 (C-4); 124.87 (C-6', C-2'); 18.35 (CH_3).

1-(2-methoxyphenyl)-3-phenylthiourea, $C_{14}H_{14}N_2OS$ (**3**), this compound was obtained as a crystallized white solid, yield 92% , MP: 127.1°C, UVmax (MeOH, nm): 288.6 (Band I); 300.6 (Band II), IR (KBr, cm-1) : 3358.3 (NH, medium), 3000.5 (C-H aromatic, medium), 2113.4 (R-N=C=S), 1591 (C=C aromatic, variable), 1370 (Ctet-H (CH3), strong), 1241.2 (C-O, strong), 1200.2 (C-O, strong), 745 (C-H aromatic Mono-substituted, strong), 689.6 (C-H aromatic Mono-substituted, strong). ^{1}H NMR (400 MHz, DMSO, ppm): 9.14 (s, 1H, H-7, H-10); 7.94 (d, 1H, H-16); 7.53 (d, 1H, H-4, H-6); 7.34 (m, 1H, H-1, H-3); 7,14 (m, 1H, H-2); 7.05 (dd, 1H, H-14); 6.92 (td, 1H, H-15); 3.31 (dd, 1H, H-13); 2.08 (s, 3H, H-18).^{13}C NMR (101 MHz, DMSO, ppm): 179.82 (C=S); 152.21 (C-2); 139.79 (C-1'); 128.91 (C-1); 128.16 (C-3', C-5');

126.21 (C-6', C-2'); 126.09 (C-6); 125 (C-4'); 124.18 (C-4); 120.26 (C-5); 111.92 (C-3); 56.19 (O-CH_3).

1-(4-chlorophenyl)-3-phenylthiourea, $C_{13}H_{11}ClN_2S$ (4), this compound was obtained as a crystallized white solid, yield 64% , MP: 150°C, UVmax (MeOH, nm): 288.4 (Band I); 300.9 (Band II), IR (KBr, cm^{-1}): 3343.3 (NH, medium), 3026.6 (C-H aromatic, medium), 2109 (R-N=C=S), 1599 (C=C aromatic, variable), 1084.7 (CN, medium), 708.2 (C-Cl, medium). ^{1}H NMR (400 MHz, DMSO, ppm): 10.5 (s, 1H, H-7, H-10); 9.84 (d, 1H, H-12, H-16); 7.52 (d, 1H, H-4, H-6); 7.46 (d, 1H, H-13, H-15); 7.34 (m, 1H, H-1, H-3); 7.13 (dd, 1H, H-2). ^{13}C NMR (100 MHz, DMSO, ppm):180.19 (C=S); 139.76 (C-1'); 138.98 (C-1); 128.96 (C-3', C-5'); 128.74 (C-3, C-5); 128.71 (C-4); 125.73 (C-2, C-6); 125.05 (C-6', C-2'); 124.18 (C-4').

1-(2-chlorophenyl)-3-phenylthiourea, C13H11ClN2S (5) , this compound was obtained as a crystallized white solid, yield 92% , MP: 157.8°C, UVmax (MeOH, nm): 289,7 (Band I); 300,6 (Band II), IR (KBr, cm^{-1}): 3302.4 (NH, medium), 3034.1 (C-H aromatic, medium), 2109.7 (R-N=C=S), 1591 (C=C aromatic, variable), 1028.7 (CN, medium), 745.5 (C-Cl, medium). ^{1}H NMR (400 MHz, DMSO, ppm): 9.76 (s, 1H, H-7, H-10); 7.50 (d, 1H, H-16); 7.48 (d, 1H, H-4, H-6); 7,30 -7.35 (m, 1H, H-1, H-3, H-13, H-15); 7.10-7.14 (m, 1H, H-2, H-14). ^{13}C NMR (100 MHz, DMSO, ppm): 180.14 (C=S); 139.94 (C-1'); 130,38 (C-1); 129.27 (C-3); 129.19 (C-5); 128.91 (C-3', C-5'); 126.40 (C-2); 124.90 (C-6); 124.13 (C-2', C-6'); 123.79 (C-4); 114,37 (C-4').

1,3-diphenylthiourea, C13H12N2S (6), this compound was obtained as a crystallized white solid, yield 90% , MP: 152°C, UVmax (MeOH, nm): 284,6 (Band I); 300,3 (Band II), IR (KBr, cm-1): 3300 (NH, medium), 3034.1 (C-H aromatic, medium), 2113.4 (R-N=C=S), 1595 (C=C aromatic, variable), 1069.7 (CN, medium), 685.8 (Ctri-H of -HC=CH-, strong). ^{1}H NMR (400 MHz, DMSO, ppm): 8.2 (s, 1H, H-7, H-10); 7.57 (m, 1H, H-4, H-6, H-12, H-16); 7.36 (m, 1H, H-1, H-3, H-13, H-15); 7, 16 (m, 1H, H-2, H-14). 13C NMR (101 MHz, DMSO, ppm): 179.51 (C=S); 139, 39 (C-1, C-1'); 128 (C-3, C-5, C-5', C-3'); 125,38 (C-2, C-6); 123,91 (C-4, C-4').

1-(2-nitrophenyl)-3-phenylthiourea, $C_{13}H_{11}N_3O_2S$ (7) , this compound was obtained as a crystallized white solid, yield 86% , MP: 52°C, UVmax (MeOH, nm): 288.4 (Band I); 300.6 (Band II), IR (KBr, cm^{-1}): 3343.4 (NH, medium), 3049 (C-H aromatic, medium), 2113.4 (R-N=C=S), 1543 (C=C aromatic, variable), 1520.8 (N=O, strong), 1543.1 (N-O, strong), 1200 (C-N, medium), 738 (Ctri-H aromatic Mono-substituted, strong), 685.8 (C-H aromatic Mono-substituted, strong). ^{1}H NMR (400 MHz, DMSO, ppm): 9.4 (s, 1H, H-7, H-10); 8.29 (dd, 1H, H-13); 8.05 (dd, 1H, H-16); 7.65 (td, 1H, H-15); 7.57 (m, 1H, H-4, H-6); 7.40 (m, 1H, H-14); 7.36 (m, 1H, H-1, H-3); 7,16 (m, 1H, H-2). ^{13}C NMR (100 MHz, DMSO, ppm): 176.69 (C=S); 137.04 (C-2); 136.92 (C-1'); 136.70 (C-1); 134.48 (C-5); 128.48 (C-3', C-5'); 126.63 (C-3), 125.38 (C-6', C-2'); 125.34 (C-6); 123.91 (C-4'), 118.93 (C-4).

1-(tert-butyl)-3-phenylthiourea, $C_{11}H_{16}N_2S$ (**8**), this compound was obtained as a crystallized yellow solid, yield 91% , MP:121°C,UVmax (MeOH, nm): 286 (Band I); 300.6 (Band II), IR (KBr, cm^{-1}): 3380.7 (NH, medium), 3019 (C-H aromatic, medium), 2959.5 (C-H, strong), 2109.7 (R-N=C=S), 1520 (C=C aromatic, variable), 1203 (C-O, strong), 1155.5 (C-N, medium), 711 (C-H of -HC=CH-, strong). ^{1}H NMR (400 MHz, DMSO, ppm): 10,40 (s, 1H, H-7, H-10); 9,91 (s, 1H, H-10); 7,97 (dd, 1H, H-4, H-6); 7,03 (dd, 1H, H-1, H-3); 6,62 (m, 1H, H-2); 2,09 (s, 3H, H-12, H-13, H-14). 13C NMR (101 MHz, DMSO, ppm): 180,71 (C=S); 146,66 (C-1); 136,13 (C-3, C-5); 125,66 (C-6, C-2); 123,99 (C-4); 115,86 (C-N); 14,38 (CH_3).

1-(2-ethoxyphenyl)-3-phenylthiourea, $C_{15}H_{16}N_2OS$ (**9**), this compound was obtained as a crystallized orange solid, yield 93% , MP: 139,8°C, UVmax (MeOH, nm): 287.2 (Band I); 300.3 (Band II), IR (KBr, cm^{-1}) : 3309.9 (NH, medium), 3168.2 (C-H aromatic, medium), 2981.9 (Ctet-H, strong), 2113.4 (R-N=C=S), 1591 (C=C aromatic), 1233.7 (C-O, strong), 1155 (C-N, medium), 1114.5 (C-O, strong), 738 (C-H of -HC=CH-). ^{1}H NMR (400 MHz, DMSO, ppm): 9.0 (s, 1H, H-7, H-10); 8.03 (dd, 1H, H-16); 7.53 (d, 1H, H-4, H-6); 7.36 (m, 1H, H-1, H-3); 7.16 (tt, 1H, H-2); 7.01- 7.12 (m, 1H, H-14, H-15); 6.92 (m, 1H, H-13); 4.07 (q, 2H, H-18); 1.32 (t, 3H, H-19). ^{13}C NMR (100 MHz, DMSO, ppm): 179.48 (C=S); 151.17 (C-2); 139.50 (C-1'); 129.12 (C-1); 128.36 (C-3', C-5'); 126.03 (C-6', C-2'); 125.57 (C-4'); 125.28 (C-4), 124.43 (C-6), 120.21 (C-5), 112.83 (C-3), 64.42 (O-CH_2), 15.16 (CH_3).

Anticoagulant activity

To achieve the goal of this work which is the anticoagulant activity; we chose 100 healthy people (without chronic diseases, Non-smokers...), by specifying the age group (20-40 years) with equal distribution (Male/Female) to avoid the external factors as much as possible. Also that, Activated partial thromboplastin time (APTT), and Prothrombin time (PT) coagulation tests were performed using normal human plasma. Coagulation was expressed as clotting time (unit in second). We prepared the synthesized

products in four increasing concentrations (C1=20µg/mL, C2=40 µg/mL, C3=80 µg/mL, C4=100µg/mL), firstly, in a dry tube, 90 µl of citrated serum was added to 10 µl of the sample and incubated in a water bath for 3 minutes, then 200 µl of PT reagent (which were placed in a dry tube and incubated at 37°C water bath to activate it) was added and mixed with the reactor, when the fibrin (coagulation) is obtained the timer is stopped and the time recorded corresponds to the appropriate percentage of coagulation. While for the APTT assay, the citrated human plasma (90 µl) was mixed with the sample (10 µl), and the APT reagent (100 µl), the reactor was incubated for three minutes at 37°C. The coagulation time was recorded when the fibrin appears, by a timer.

Computational details

Gaussian09 software [55] has been used for all density functional theory (DFT) calculations of this study. The B3LYP functional [56, 57] and the 6-311G (d,p) basis set have been used for all calculations. This approach has been used successfully by several research groups and good agreement between theory and experiment was found [58, 59]. All the ground states were confirmed by vibrational frequency analysis (no imaginary frequency).

Results and Discussion

Synthesis of N-aryl thiourea derivatives

The synthesis of N-aryl thiourea derivatives (compounds 1- 9) was achieved directly from phenylisothiocyanate, which was treated with various primary amines dissolved in Ethanol, in an ice bath (0°C), without addition of any catalyst as shown in Fig 2. The reaction yields ranged 60% to 93% as shown in Table 1. The structures of the synthesized compounds were confirmed by the analysis of their spectral data, including UV, IR, 1H NMR and 13C NMR; our synthesis procedure showed a better range of yields than that presented by Muhammad Taha et al [54], who performed the same synthetic route using dichloromethane as the solution and leave the reaction for 1-1.5 hours. Although our procedure may be simpler and faster than the one used by Muhammad Taha et al [54], we have seen good results in terms of yield of thiourea derivatives.

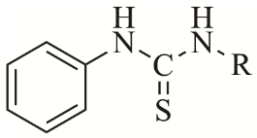
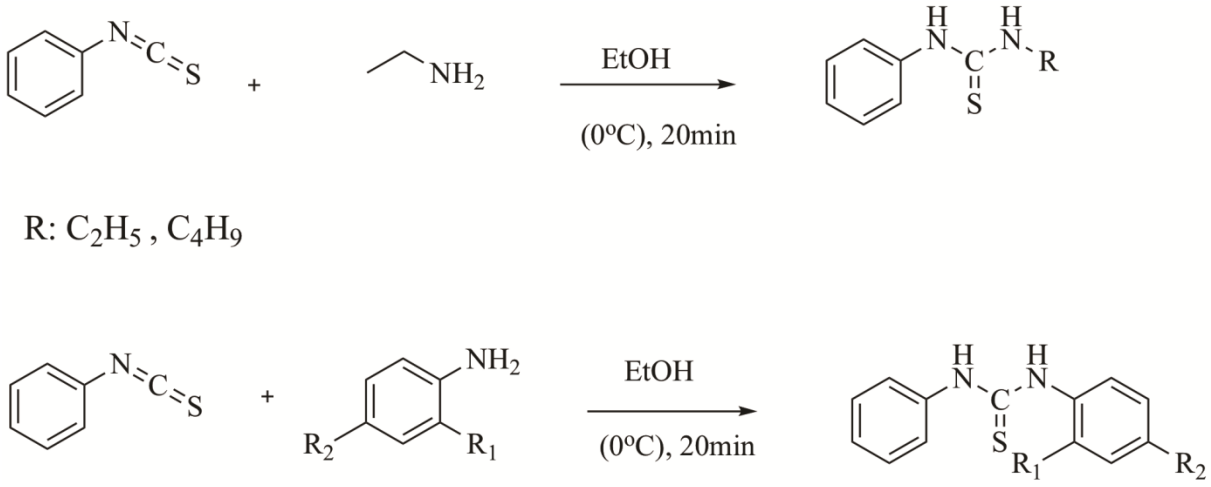


Fig 1: Structure of Thiourea derivatives.

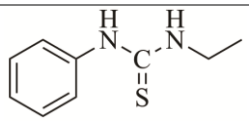
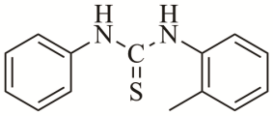
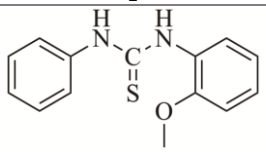
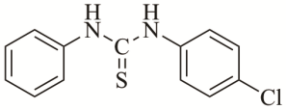
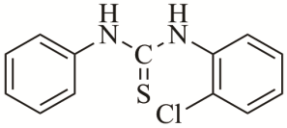
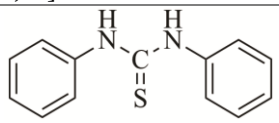
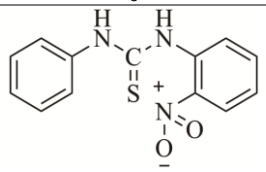
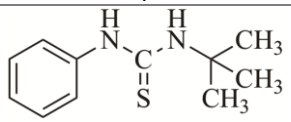
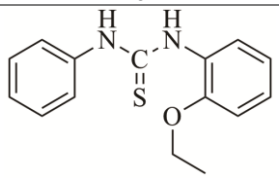


R_1 : CH_3 , OCH_3, H, Cl, H, NO_2, OC_2H_5 .

R_2 : H, H, Cl, H, H, H, H .

Fig. 2: Synthesis of Thiourea derivatives.

Table-1: The characteristics of the synthesized products [64,65].

Product	Yield %	MP
 1	82%	90°C
 2	90%	141°C
 3	92%	127.1°C
 4	64%	150°C
 5	92%	157.8°C
 6	90%	152°C
 7	86%	152
 8	91%	121°C
 9	93%	139.8°C

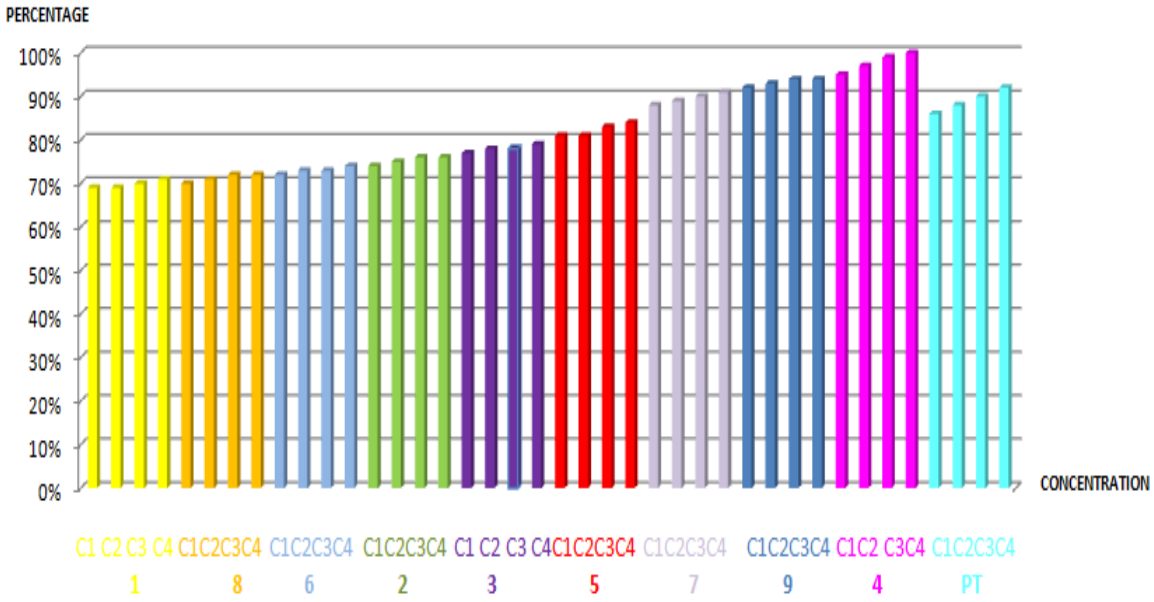


Fig. 3: Percentage of anticoagulant effect in terms of concentration using PT reagent.

Anticoagulant activity

Our synthesized products were estimated for the anticoagulant activity, employing PT and APTT tests which have been reacted with our samples and human plasma citrated; also, that the clotting time which was calculated by a timer show the appropriate percentage of coagulation. Since the comparison was made with the PT and APTT reagents, the results gotten which are presented in the Fig 3 and Fig 4 indicate that the N-aryl thiourea derivatives have a high anticoagulant activity.

Structure-activity relationship

By performing the anticoagulant activity, and comparing with the results obtained with the PT and APTT reagents, there were different positives results that depend on the different structures of compounds synthesized. (Fig 5, Fig 6). While for unsymmetrical thiourea derivatives the presence of the three Methyl groups (Product 8) slightly affects the anticoagulant activity. For symmetrical thiourea derivatives there is difference in the electronegative effect of the substituent that exist at the "meta" position, it has a great influence on the anticoagulant activity; which means that the product 9 has a better activity compared to the rest in this range. Lastly, the product 4 exhibits the excellent anticoagulant activity in comparison with all the preceding products due to the presence of the chlorine molecule at the "meta" position, which has increased the electronegative effect leading to a development of the anticoagulant activity. Finally, regarding the anticoagulant activity, the thiourea derivatives showed a good activity, due to the electronegative substituent

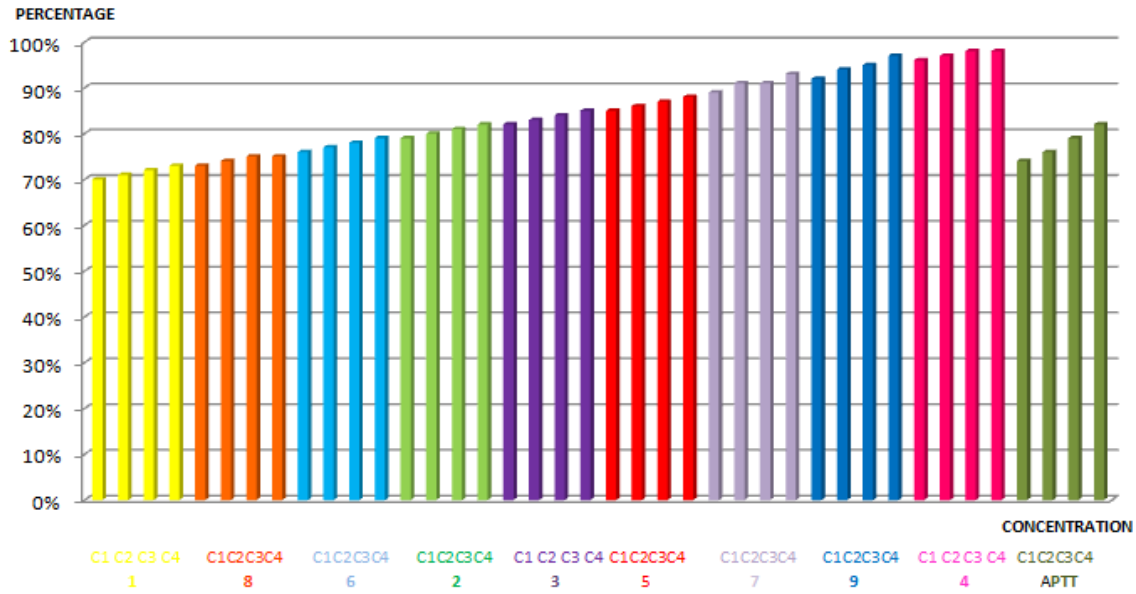


Fig. 4: Percentage of anticoagulant effect in terms of concentration using APTT reagent.

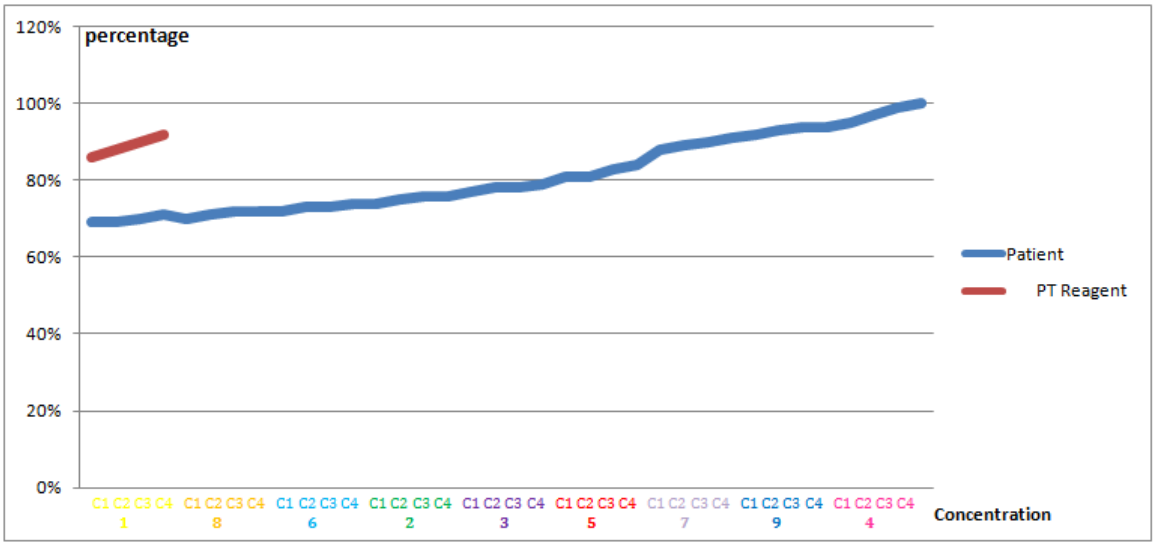


Fig. 5: Curve represents Percentage changes of anticoagulant effect in terms of concentration using PT reagent.

DFT Calculations

DFT calculations were performed for compound 1 and 6, as representative molecules, in order to get insights into the molecular geometry and chemical reactivity of the investigated compounds. First, a full geometry optimization of all possible tautomers and conformers of compounds 1 and 6 has been carried out at B3LYP/6-311G (d,p) level in the gas phase and the obtained results are shown in Fig 7 and 8. It was found that both compounds present six different molecular geometries with relative energies ranging from -4.38 to 17.36 kcal/mol for compound 1 and -4.39 to 11.94 kcal/mol for compound 6. In both cases, the thiocarbonyl form was found to be significantly stablethan the enolic forms. For example, the thiocarbonyl form of compound 1 is stable by 14.41 kcal/mol than its enolic form. These results suggest that the thiocarbonyl form is the dominant tautomer for both compound 1 and compound 6. The position of NH bonds has also been found to have a considerable effect on the stability of molecules. For the two compounds, the most stable geometry is obtained when the NH bonds are in the Anti-configuration.

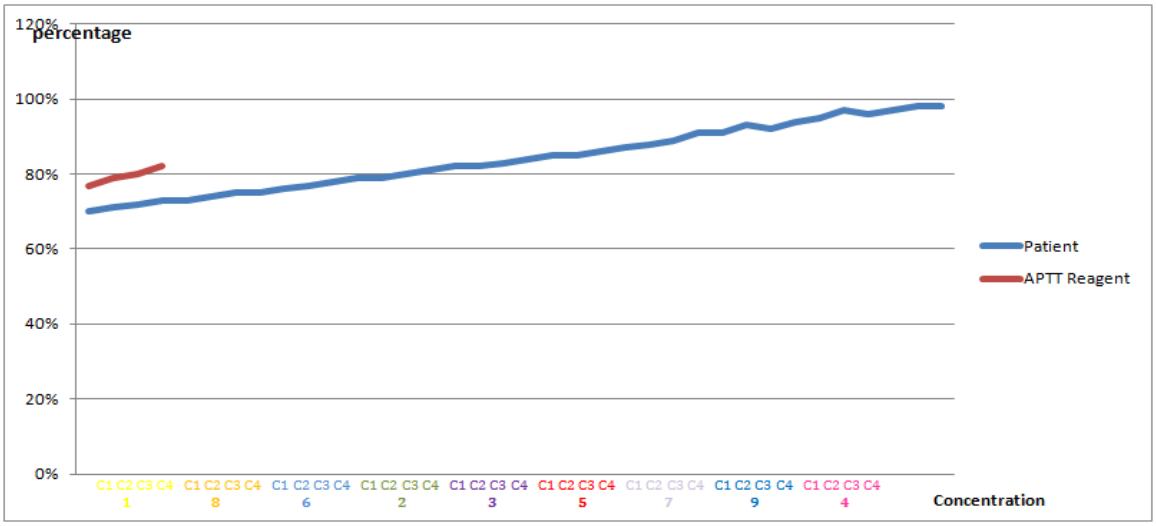


Fig. 6: Curve represents Percentage changes of anticoagulant effect in terms of concentration using APTT reagent.

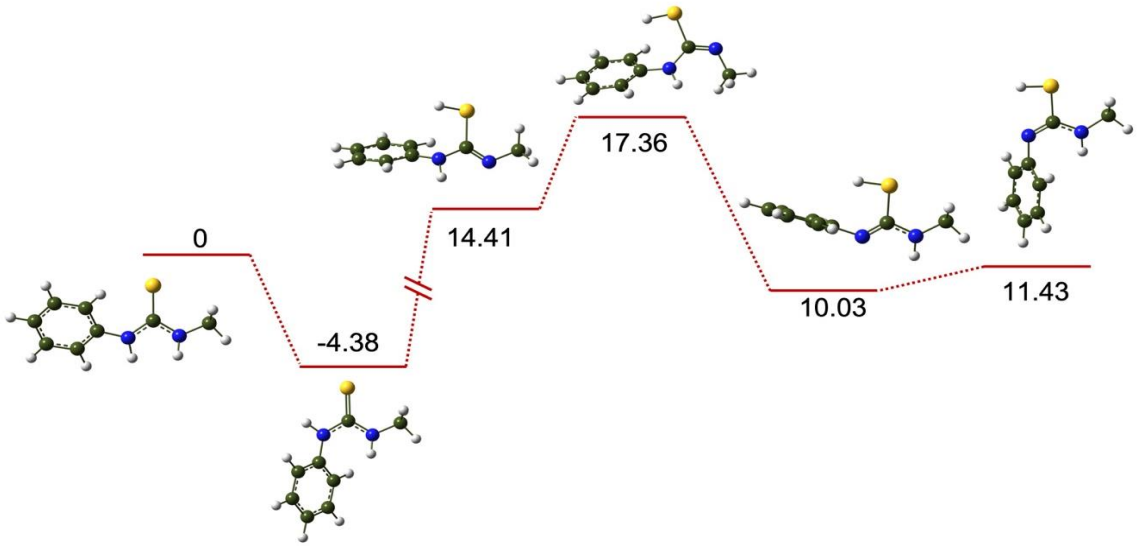


Fig 7. The most stable conformers of compound 1 and their relative energy in kcal/mol

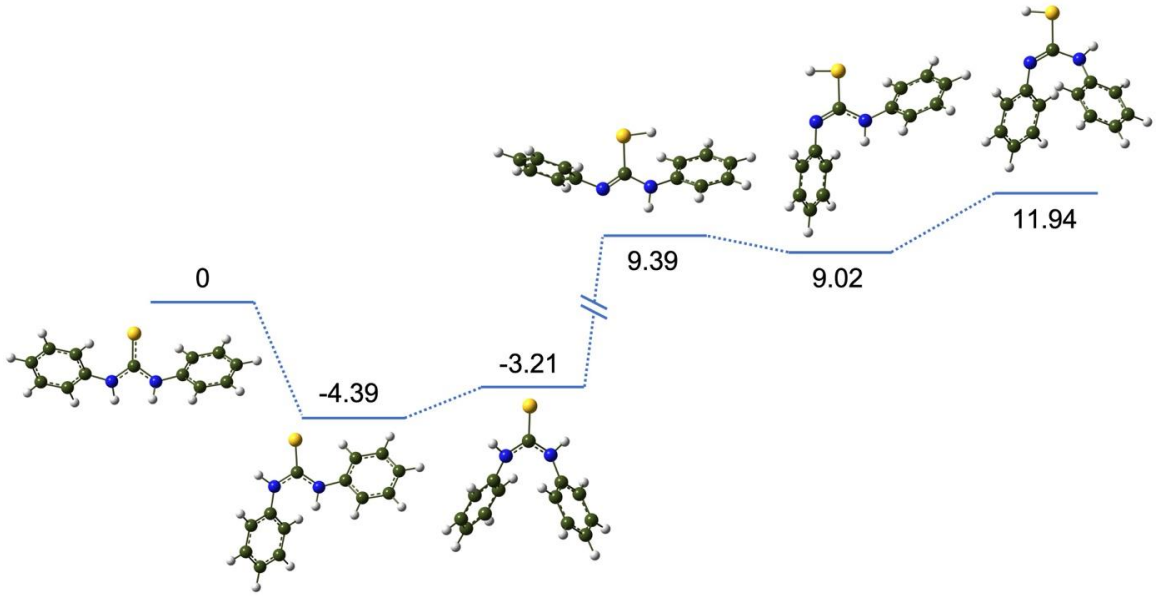


Fig. 8: The most stable conformers of compound 6 and their relative energy in kcal/mol [66].

After having determined the most stable geometry of molecules 1 and 6, we then investigated their chemical reactivity by computing their frontier molecular orbitals (FMOs). FMO represents the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO). These orbitals are important parameters that can be used to predict the chemical reactivity of the studied compounds [60-62]. The HOMO is the highest molecular orbital occupied by at leastone electron. The distribution of this orbital determines the sites for nucleophilic attacks and its energy is correlated with the electron-donating ability. LUMO is the lowest energy orbital unoccupied by an electron and determines the sites of electrophilic attacks. The computed FMOs energies and distributions of compounds 1 and 6are reported in Fig 9. As shown, the FMOs of both compounds present similar distributions. The HOMOs are mainly localized on the sulfur atom with very small contributions on the nitrogen atoms. Whereas the LUMOs are distributed over the entire molecule. This suggests that the sulfur atom is the most reactive site as a nucleophile, while the entire molecule can undergo electrophilic attack. The FMOs of both compounds have also comparable energies. The energies of HOMOs are -5.72 and -5.82 eV and those of LUMOs are -1.04 and -1.35 eV for compounds 1 and 6, respectively. Compared to recognized antioxidants, the HOMO energies of compounds 1 and 6 are comparable to those of BHT (-5.74 eV) and Trolox (-5.39 eV), but higher than that of ascorbic acid (-6.50 eV) [63]. This suggests that 1 and 6 may be good radical scavengers. The difference between HOMO and LUMO energy of compounds 1 and 6 is 4.68 and 4.47 eV, respectively. This small energy gap reflects the high chemical reactivity of the studied compounds.

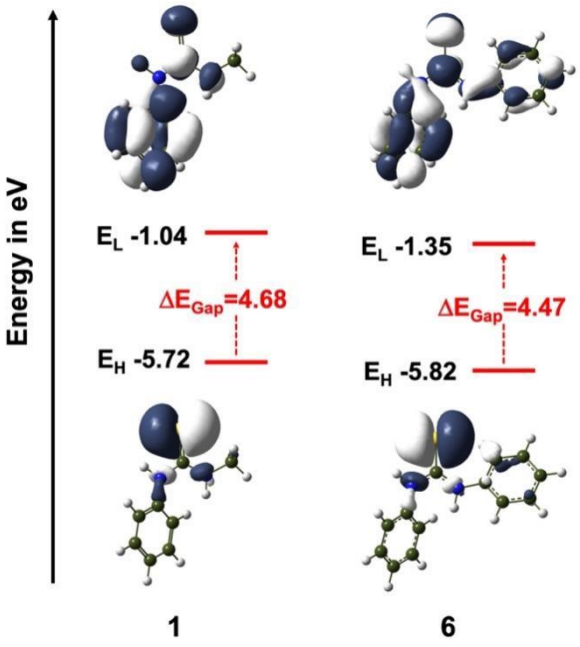


Fig. 9: HOMO and LUMO distributions and energies of compounds 1 and 6.

Conclusion

In summary, this study is based on our previous works. We have synthesized nine thiourea derived from phenyl-isothiocyanate. The nine compounds were obtained by the reaction of phenyl-isothiocyanate with various primary amines, which gave good yields. Their structures were confirmed by spectral analysis (UV, IR and NMR 1H, 13C). The anticoagulant activity has been realized using PT and APTT reagents, the results showed that the tested compounds exhibit a good anticoagulant activity. The synthetic benefits of the presented method are reflected in the operational simplicity, mild reaction conditions, short reaction time, high purity and the excellent yield of products.

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