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New sulfonamide hybrids: synthesis, in vitro antimicrobial activity and docking study of some novel sulfonamide derivatives bearing carbamate/acyl-thiourea scaffolds

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Abstract: In this study, the novel hybrids sulfonamide carbamates were synthesized by treatment of *N*-substituted 4-isothiocyanatophenyl sulfonamides with ethyl carbamate in dry 1,4-dioxane at reflux temperature in the presence of triethylamine. Also, treatment of Phenylacetylisothiocyanate with sulfanilamide in refluxing acetonitrile afforded the corresponding hybrid sulfonamide acylthiourea derivatives. The anti-microbial activities of the synthesized compounds were evaluated. Ethyl ({4-[(5-methyl-1,2-oxazol-3-yl)sulfamoyl)-phenyl]carbamothioyl)-carbamate and 2-Phenyl-N-((4-(N-thiazol-2-yl)sulfamoyl)-phenyl)carbamothioyl)-acetamide exhibited the best activity against tested bacteria. Molecular docking studies for the final compounds were performed using the Open Eye docking suite. Moreover, Ligand efficiency (LE) and lipophilic ligand efficiency (LLE) parameters for Ethyl ({4-[(5-methyl-1,2-oxazol-3-yl)sulfamoyl)phenyl]carbamothioyl)-carbamate and 2-Phenyl-N-((4-(N-thiazol-2-yl)sulfamoyl)phenyl)carb-amothioyl)acetamide were evaluated. Quantum chemical calculations based on density functional theory (DFT) have been performed.

Keywords: Thiourea; carbamate; isothiocyanate; sulfonamide and Molecular docking.

Introduction

The synthesis of hybrid molecules and their evaluation as diverse range of pharmacological agents and as potent drugs has been under constant escalation for the last two decades [1]. The hybrid molecules, obtained by the combination of structural features of two differently active fragments, are the most popular chemical entities to work upon for developing modified scaffolds with many improved and amazing properties in the area of biology as well as medicinal science [2]. Sulfonamides drugs are very common compounds present in literature with massive activities [3-5]. Some important sulfonamide derivatives are used as carbonic anhydrase inhibitors of commercial importance [6]. Over 30 drugs containing this functionality are in clinical use, including anti-hypertensive agent bosentan [7], anti-bacterial [8], anti-protozoal [9], anti-fungal [10], anti-inflammatory [11], non-peptide vasopressin receptor antagonists [12] and translation initiation inhibitors [13]. They are also effective for the treatment of urinary, intestine, and ophthalmic infections, scalds, ulcerative colitis [14] rheumatoid arthritis [15], male erectile dysfunction as the phosphodiesterase-5 inhibitor sildenafil [16], obesity [17], and more recently as anticancer agents [18].

Prodrug sulfonamides are very important in the current medicinal protocol for sulfonamide therapy. For example, sulfonyl succinyl acts as a prodrug of sulfathiazole. It used in gut infections as it ionized in the alkaline conditions of the intestine and slowly hydrolysed by enzymes in the gut. Amide group lowers the polarity of the sulfonamide and increases the hydrophobic character. It allows the drug to crosses the gut wall more easilyandmetabolised by enzymes

(e.g. peptidases) *in vivo* to generate the primary amine. Primary amine ionizes and can form ionic interactions ionized primary amine also acts as a strong hydrogen bond (HB) [19].

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The carbamate group is a key structural motif in many approved drugs and prodrugs [20]. There is increasing use of carbamates in medicinal chemistry, and many derivatives are specifically designed to make drug target interactions through their carbamate moiety [21,22]. The carbamates emerging role in medicinal chemistry is also due to its chemical stability and its capability to increase permeability across cellular membranes. These attributes of organic carbamates have been exploited in drug design [23].

In recent years, several reports have indicated that carbamate linkage present in between the active pharmacophores of various structurally diverse molecules increases manifold biological activities of semi-synthetic/synthetic, natural/synthetic molecules. Furthermore, the role of carbamate linkage have been extensively studied in structurally diverse natural/semi-synthetic molecules against various disease such as anti-cancer, anti-bacterial, anti-fungal, anti-malarial, anti-viral, anti-HIV, anti-estrogenic, anti-progestational, anti-osteoporosis, anti-inflammatory, anti-filarial, anti-tubercular, ant-diabetic, anti-obesity, anti-convulsant, antihelminthics and Alzheimer disease [23-25].

Other uses of carbamates are well known. Particularly, the employment of carbamates in various industries as agrochemicals, in the polymer industry, and also in peptide synthesis [26,27]. Also, among the various amine protecting groups, carbamates are commonly used to enhance their chemical stability toward acids, bases, and hydrogenation [28].

Thiourea derivatives and thiourea hybrid with other functionality are useful compounds as precursors for the synthesis of different classes of acyclic and heterocyclic compounds [29]. They have been employed as an anti-inflammatory, antimicrobial [30] , antimalarial [31], pesticidal [32], and anticancer agents [33,34]. The derivatives of thiourea represent one of the most promising classes of anticancer agents with a wide range of activities against various leukaemia and solid tumors [35-37]. Thiocarlide is a pharmacologically important thiourea drug that is used as a therapeutic agent in the treatment of tuberculosis [38] and Phenethylthiazoylthiourea (PETT) derivatives (LY73497 and trovirdine HCl) [39,40] have been discovered as potent inhibitors of HIV type 1. The development of microbial resistance to presently available antibiotics led the search for new antimicrobial agents [41]. Due to the problem of microbial resistance to antibiotics, attention is given toward biologically active components isolated from natural products, as they may offer a new source of antimicrobial activities [42] found predictive rules that help in discovery and development of small molecules as antibiotics. In this interesting result, small molecules should contain some requirements as an amine group, be an amphiphilic and rigid, and have low globularity. Such information will assist us to design our compounds. It is important to examine the something that correlates between the activity of the compounds and their structures it is the quantum chemical calculation.

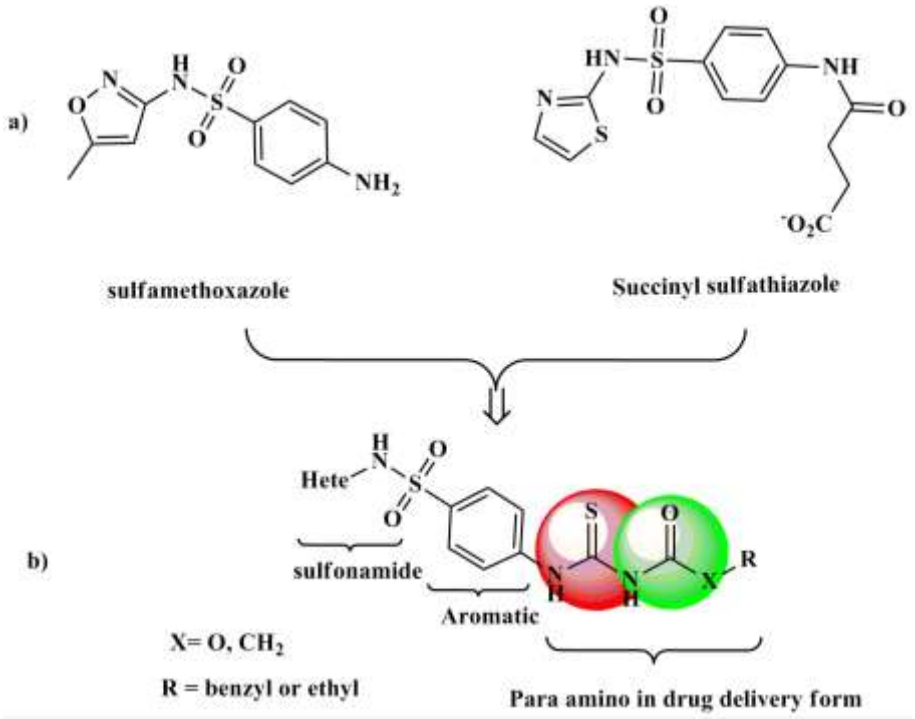


Figure 1: a) reported drugs contain sulfonamide prodrug as antimicrobial;
b) general formula of our designed compounds**.**

In general, the HOMO possesses an antibonding character between the consecutive subunits, whereas the LUMO generally shows a bonding character between the subunits. No direct correlation between HOMO or LUMO energies and antibacterial activities is highlighted. The gap in energy between the HOMO and LUMO is an important stability index [43]. Generally, the high stability indicates low chemical reactivity and small gap indicates high chemical reactivity. Softness (S) may be a property of a molecule that measures the extent of chemical reactivity. The chemical hardness (η) was related with the resistance towards the deformation of deformation cloud of chemical systems below little perturbation occurred. A small hardness means the compound features high polarizability. Polarizability (α) measures the pliability of electrons in an exceedingly} very molecule to maneuver merely as a result of data. The softer a molecule is, the upper is its average polarizability.

In the frame of previous data [44-48], we thought to design new derivatives of prodrug sulfonamides. Our strategy was designed base on linking the amino group with more labile pharmacophore than reported amide, (Figure 1).

We finally decided to install the interesting hybrid functionality from thiourea and carbamate. The thiourea was tethered with ethyl carbamate or acyl benzyl to examine the effect of the aliphatic or aromatic side chain. On the other site at sulfonamide head, we studied varieties of heterocyclic rings. Herein is verified a direct correlation between compound structures and their biological activities based on different parameters.

Experimental

Materials and methods

All analyses were done at the Microanalytical Center, Cairo University, Cairo (Egypt). Melting points (uncorrected) were determined in open capillaries on a Gallenkamp melting point apparatus (Sanyo Gallenkamp, Southborough, UK).IR spectra (KBr discs) were recorded using Schimadzu FT-IR 8400S spectrophotometer (Shimadzu, Kyoto, Japan), NMR Spectra were recorded on a Bruker spectrophotometer (Bruker, Karlsruhe, Germany). ^{1}H spectrum was run at 300 MHz, and the ^{13}C spectrum was run at 100 MHz in deuterated dimethylsulfoxide (DMSO-d_6). Chemical shifts (δ) are reported relative to MS as an internal standard. Mass spectral data were given by a GCMS-QP1000 EX-spectrometer (Shimadzu, Kyoto, Japan) at 70 eV. Elemental analyses were done on a model 2400 CHNSO instrument (Perkin Elmer, Waltham, MA, USA). All reagents used were of the Analytical grade.

General Procedure for Synthesis of carbamates 3a-e

Method A: A mixture of ethyl carbamate (0.01 mol) and isothiocyanate**2** (0.01 mol) and triethyl amine (0.01 mol) in 1,4-dioxane (10 mL) was refluxed for 3 h. The reaction mixture was left to cool at room temperature. The solid product, so formed, was collected by filtration and recrystallized from an appropriate solvent.

Method B: A mixture of 1 (0.01 mol), ethoxycarbonylisothiocyanate (0.01 mol) [prepared by adding ammonium thiocyanate (0.01 mol) to a solution of ethyl chloroformate (0.01 mol) in 1,4-dioxane (10 mL) and heat for 1/2 h followed by isolation of the byproduct, ammonium chloride] and triethylamine (0.01 mol) was refluxed for 1 h. The resulting solid product was collected by filtration and recrystallized to give **3**.

Ethyl[(4-sulfamoylphenyl)carbamothioyl]-carbamate 3a.

White crystals (ethanol), Yield: (meth. A = 82 %, meth. B = 78 %), m.p. 203-204ºC;
IR (KBr, cm^{-1}): 2959 (CH-aliph), 1711 (C=O), 1537 (C=S), 1371, 1162 (SO_2);
^{1}HNMR (DMSO-d_6): 1.27 (t, 3H, CH_3), 4.17 (q, 2H, CH_2),7.17 (s, 2H, SO_2NH_2, exchangeable with D_2O),7.42–7.83 (2d, 4H, Ar - H),11.32,11.68 (2s,2H,2NH, exchangeable with D_2O);
^{13}CNMR (DMSO-d_6,):14.56 (CH_3), 60.9 (CH_2), 118.11, 124.74, 127.18, 131.39 (aromatic C), 153.9 (C=O) and 179.38 (C=S);
Anal. Calcd.for$C_{10}H_{13}N_3O_4S_2$: C, 39.59; H, 4.32; N, 13.85; S,21.14. Found: C, 39.50; H, 4.30; N, 13.70, S, 21.10.

Ethyl{[(4-carbamidoimidoylsulfamoyl)phenyl]-carbamothioyl]carbamate 3b.

White crystals (ethanol),Yield: (meth. A = 80 %, meth. B = 76 %), m.p.113–114ºC;
IR(KBr,cm-1): 3431(NH_2),3220, 3160 (NH) ,3040 (CH-arom), 2950 (CH-aliph),1712(C=O), 1620 (C=N), 1526 (C=S), 1330, 1150 (SO_2);
^{1}HNMR (DMSO-d_6): 1.24(t, 2H, CH_3), 4.15(q, 2H, CH_2), 5.65(s,1H, NH, exchangeable with D_2O), 6.52, 6.63(2s, 4H, $2NH_2$, exchangeable with D_2O), 7.42–7.83(m, 4H, Ar-H), 9.90, 11.31, 11.64(s, 3H, 3NH, exchangeable with D_2O); MS: 345(M^+; 3.38%), 344(M-1; 1%), 321(1%), 316(163%), 268(12.68%), 241(1.55%), 168(1%), 165(1%), 127(1.12%), 119(1.52%), 109(2.46%), 101(3.29%), 97(13.6%), 85(21.68%), 83(30.29%), 77(3.38%), 72(37%), 71(57%), 69(55%), 57(100%).
Anal.Calcd.for $C_{11}H_{15}N_5O_4S_2$: C,38.25; H, 4.38; N, 20.28; S, 18.57. Found: C, 38.20; H, 4.40; N, 20.20; S, 18.60.

Ethyl({4-[(1,3-thiazol-2-yl)sulfamoyl)phenyl]-carbamothioyl)carbamate 3c.

White crystals (ethanol), Yield: (meth. A = 74 %, meth. B = 72 %), m.p.250–251ºC;
IR(KBr, cm-1): 3350, 3150 (2NH), 3034 (CH-arom), 2909 (CH-aliph), 1728 (C=O), 1537 (C=S), 1319, 1147 (SO_2);
^{1}HNMR (DMSO-d_6):1.24 (t, 2H, CH_3), 4.12 (q, 2H, CH_2), 6.79, 7.21 (2d, 2H, thiazole-H), 7.57, 7.7 (2d, 2H, Aromatic-H), 11.33, 11.66 (2s, 2H, 2NH, exchangeable with D_2O), 12.80 (hump, 1H, 1NH, exchangeable with D_2O);
^{13}CNMR (DMSO-d_6):14.5 (CH_3), 60.96 (CH_2), 118.1, 124.7, 126.77, 136.23 (aromatic C), 108.39, 127.65, 143.06 (thiazole C), 153.87 (C=O) and 169 (C=S);
MS: 386(M^+; 2.06%), 344(M-1; 1%), 322 (3.81%), 297(44 %), 233 (58.45%), 175(1.09%), 163(1.58%), 134(100%), 92(45%), 84(4.75%), 75(10.04%).
Anal. Calcd. For $C_{13}H_{14}N_4O_4S_3$: C, 40.40; H, 3.65; N, 14.50; S, 24.89. Found: C, 40.50; H, 3.60; N, 14.40; S, 24.80.

Ethyl({4-[(5-methyl-1,2-oxazol-3-yl)sulfamoyl)-phenyl]carbamothioyl)carbamate 3d.

White crystals (ethanol), Yield: (meth. A = 78 %, meth. B = 75 %), m.p.110–111ºC;
IR(KBr, cm-1):3350, 3222 (2NH),3034 (CH-arom), 2930 (CH-aliph), 1736(C=O), 1620 (C=N), 1593 (C=S), 1311, 1158 (SO_2);
^{1}HNMR (DMSO-d_6): 1.30 (t, 3H, CH_3), 2.26 (s, 3H, CH_3), 4.20 (q, 2H, CH_2), 6,07 (s, 1H, oxazole-H), 6.56, 7.74 (2d, 2H, Aromatic-H), 6.08, 7.80, 10.88 (3s, 3H, 3NH, exchangeable with D_2O);
MS: 384 (M^+; 46%), 385 (M+1; 15%), 383 (M-1; 3.81%), 368 (10%), 355 (8%), 339 (10%), 325 (6.64%), 313 (23%), 293 (29%), 277 (25%), 250 (14%), 108 (20%), 97 (22%), 91(16%), 84(20%), 76(10%),77(7.8%), 71(59%), 69(74%), 67(40%), 65(86%), 59(46%), 57(100%).
Anal.Calcd.for $C_{14}H_{16}N_4O_5S_2$: C,43.74; H, 4.20; N, 14.57; S,16.68. Found: C, 43.70; H, 4.30; N, 14.50; S, 16.60.

Ethyl({4-[(pyrimidin-2-yl)sulfamoyl)phenyl]-carbamothioyl)carbamate 3e.

White crystals (ethanol), Yield: (meth. A = 73 %, meth. B = 70 %), m.p. 220–221ºC;
IR(KBr, cm-1): 3428, 3358 (2NH), 3039 (CH-arom), 2950 (CH-aliph), 1716 (C=O), 1579 (C=S), 1326, 1154 (SO_2); ^{1}HNMR(DMSO-d_6): 1.25 (t, 2H, CH_3), 4.12 (q, 2H, CH_2), 5.96 (s, 1H, 1NH, exchangeable with D_2O), 6.57, 6.66 (2d, 2H, Aromatic-H), 7.36-7.86 (m, 3H, pyrimidine-H), 8.20, 9.80 (2s, 2H, 2NH, exchangeable with D_2O);
^{13}CNMR (DMSO-d_6): 14.8 (CH_3), 61.08 (CH_2), 115.94, 124.17, 125.78, 130.22 (aromatic C), 112.71, 157.78, 158.61 (pyrimidine C), 153.44 (C=O) and 179.17 (C=S);
Anal. Calcd.for $C_{14}H_{15}N_5O_4S_2$: C,44.08; H, 3.96; N, 18.36; S, 16.81. Found: C, 44.00; H, 3.90; N, 18.40; S, 16.78.

General procedure for the synthesis of acylthioureas 7a-e

A solution of phenylacetyl chloride **5** (0.01 mol) and ammonium thiocyanate (0.01 mol) in acetonitrile (10 mL) was heated under reflux for 10-20 min. After the reaction mixture was cooled to room temperature and the formed precipitate (NH_4Cl) was filtered off. To the freshly prepared solution of Phenylacetylisothiocyanate **6**, sulfanilamide **1** (0.01 mol) was added, and the mixture was refluxed for 2 h. Upon completion of reaction (checked by TLC), the resulting precipitate was collected by filtration and recrystallized to give the product **7**.

2-Phenyl-N-((4-sulfamoylphenyl)carbamothioyl)-acetamide 7a.

Yellow crystals (ethanol),Yield:84%,m.p.220-221ºC [Lit.220] [49];
IR(KBr,cm-1):3376, 3269, 3173, 3030(CH-arom), 1693(C=O), 1591(C=S), 1331, 1156 (SO_2);
^{1}HNMR (DMSO-d_6): 3.80 (s, 2H, CH_2), 7.31–7.81(m, 7H, Ar-H+NH_2), 7.31–7.81(s, 4H, Ar-H), 11.76, 12.5(2s, 2H, 2NH, exchangeable with D_2O); MS: 349(M^+; 38.68%), 214 (8.49%), 177(2.06%), 172(7.72%), 149(1.02%), 156(8.06%), 135(5.34%), 134(10.15%), 107 (3.85%), 119(14.30%), 118(91.48%), 105(0.8%), 93(2.79%), 91(100%).
Anal.Calcd.for $C_{15}H_{15}N_3O_3S_2$: C, 51.56; H, 4.33; N, 12.03; S, 18.35. Found: C, 51.42; H, 4.22; N, 11.95; S, 18.23.

2-Phenyl-N-((4-(N-thiazol-2-yl)sulfamoyl)phenyl)-carbamothioyl)acetamide7b.

Yellow crystals (ethanol), Yield:85%, m.p.210-211ºC;
IR(KBr,cm-1): 3150, 3118 (2NH), 3020 (CH-arom), 1701(C=O), 1537(C=S), 1288,1155 (SO_2);
^{1}HNMR (DMSO-d_6): 3.81(s, 2H, CH_2), 6.81, 7.26(2d, 2H, thiazole-H), 7.32(s, 5H, Aromatic-H), 7.80(s, 4H, Aromatic-H), 11.77, 12.52, 12.60(3s, 3H, 3NH, exchangeable with D_2O).
Anal.Calcd.for $C_{18}H_{16}N_4O_3S_3$: C,49.98; H, 3.73; N, 12.95; S,22.24. Found: C, 49.82; H, 3.84; N, 12.78; S, 22.12.

N-((4-(N-(5-methylisoxazol-3-yl)sulfamoyl)phenyl)-carbamothioyl)-2-Phenyl acetamide 7c.

Yellow crystals (ethanol),Yield:89%,m.p.110-111ºC;
IR(KBr,cm-1):3153, 3100(2NH), 3853(CH-aliph), 1695(C=O), 1614(C=N), 1529(C=S), 1344, 1162 (SO_2);
^{1}HNMR (DMSO-d_6): 2.28(s, 3H, CH_3), 3.81(s, 2H, CH_2), 6.14(s, 1H, isoxazole-H), 7.34(s, 5H, Aromatic-H), 7.82-7.92(m,4H,Aromatic-H), 11.43, 11.80, 12.57(3s, 3H, 3NH, exchangeable with D_2O).MS: 430 (M^+;0.6%), 371(1.48%), 307(1.19%), 295(7.06%), 274(2.35%), 255(1.67%), 216(1.18%), 204(1,88%), 198(1.92%), 189(3,33%), 174(5.36%), 162(7.56%),

92(62%), 91 (100%), 77(1.67%), 67(1.79%).
Anal.Calcd.for $C_{19}H_{18}N_4O_4S_2$: C, 53.01; H, 4.21; N, 13.01; S, 14.90. Found: C, 53.23; H, 4.34; N, 13.23; S, 14.72.

N-((4-(N-(4,5-dimethyloxazol-2-yl)sulfamoyl)-phenyl)carbamothioyl)-2-Phenyl acetamide 7d.

Yellow crystals (ethanol),Yield:80%,m.p.128-129ºC; IR(KBr,cm-1):3466, 3260(2NH), 3979(CH-aliph), 1691(C=O), 1604(C=N), 1559(C=S), 1342, 1144(SO_2); ^{1}HNMR(DMSO-d_6): 1.93, 2.04(2s, 6H, 2CH_3), 3.81(s, 2H, CH_2), 7.33(s, 5H, Aromatic-H), 7.60-7.82(m, 4H, Aromatic-H), 11.43(br., 2H, 2NH, exchangeablewithD_2O), 12.51(s, 1H, 1NH, exchangeable with D_2O).
MS:444 (M^+;1%), 425(0.84%), 385(1.08%), 369(1.27%), 348(1.06%), 329(1.07%), 329(1.10%), 293(3.51%), 245(1.03%), 149(1.96%), 115 (1.12%), 105(1.32%), 97(10.57%), 91(100%), 83(26.03%), 77(1.72%), 72(27.5%), 67(20.17%), 57(100%).
Anal.Calcd.for $C_{20}H_{20}N_4O_4S_2$: C, 54.04; H, 4.53; N, 12.60; S,14.43. Found: C, 54.15; H, 4.50 N, 12.74; S, 14.62.

2-Phenyl-N-((4-(N-(pyrimidin-2-yl)sulfamoyl)-phenyl)carbamothioyl)acetamide 7e.

Yellow crystals (ethanol),Yield:86%,m.p.208-209ºC; IR (KBr,cm-1): 3400, 3355 (NH), 3034 (CH-arom), 2870 (CH-aliph),1713 (C=O), 1600(C=N), 1581(C=S), 1341, 1159 (SO_2);
^{1}HNMR (DMSO-d_6): 3.81(s, 2H, CH_2), 6.55, 7.60(2d, 2H, Aromatic-H), 7.34-7.63(m, 6H, Aromatic-H+NH), 6,99(m, 2H, pyrimidine-H), 8.50(d, 2H, pyrimidine-H), 11.70, 12.51(2s, 2H, 2NH, exchangeable with D_2O).
Anal.Calcd.for $C_{19}H_{17}N_5O_3S_2$:C,53.38; H, 4.01; N, 16.38; S,15.00. Found: C, 53.45; H, 4.22; N, 16.40; S, 14.82.

Docking studies

Crystallographic structure for dihydropteroate synthase (DHPS) (ID: 3TZF) [57] contains the standard sulfamethoxazole co-crystalized inside the receptor was chosen for docking. A library of our designed sulfonamides linked thiourea-carbamate including standard drugs was designed, and energy minimized using MMFF94 force field calculations the catalytic domain of DHPS which was obtained from protein data bank (PDB code 3TZF)) and was prepared for docking using Open Eye [58-60] software. Omega application was used to prepare conformers for docking, and FRED application was selected to generate a physical property (ΔG) reflecting the predicted energy profile of the ligand-receptor complex

Quantum chemical calculations

The Quantum chemical calculations were performed using B3LYP that includes a mixture of Hartree– Fock with DFT exchange terms associated with the gradient-corrected exchange-correlation functional of Lee, Yang and Parr (LYP). It has fewer convergence problems than those found in the pure DFT methods. Thus, B3LYP has been used in this paper to carry out quantum calculations. Full geometry optimizations of all additives were carried out with the standard B3LYP/6- 311G++ (d, p) basis set using Gaussian 09.

Results and discussion

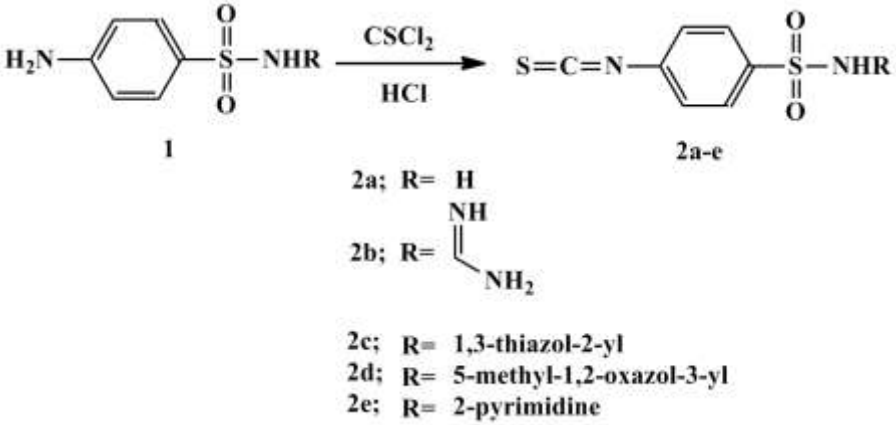
Chemistry

Isothiocyanates are useful and widely used building blocks in the synthesis of nitrogen, sulfur and oxygen heterocyclic and organometallic compounds of academic, pharmaceutical and industrial interest [50]. The high electrophilicity and nucleophilicity related to the carbon and sulfur atoms, severally, of the isothiocyanates and their extended π electron system, create them distinctive precursors of an outsized type of target molecules. Consequently, many classes of five and six-membered nitrogen and sulfur heterocyclic, either carrying various substituents or fused with benzo or non-benzo nuclei to interesting poly heterocyclic, have been synthesized from isothiocyanates which are undoubtedly a landmark in organ sulfur chemistry [51]. The intermediate, *N*-substituted 4-isothiocyanatophenyl sulfonamides **2** used for the preparation of target compounds have been synthesized in high yield *via* thiophosgenation of sulfonamides **1** at room temperature in the presence of dilute hydrochloric acid, according to literature procedure [52] (Scheme 1). The synthetic route designed for the carbamates **3a-e** containing sulfonamide moiety is outlined in (Scheme 2).

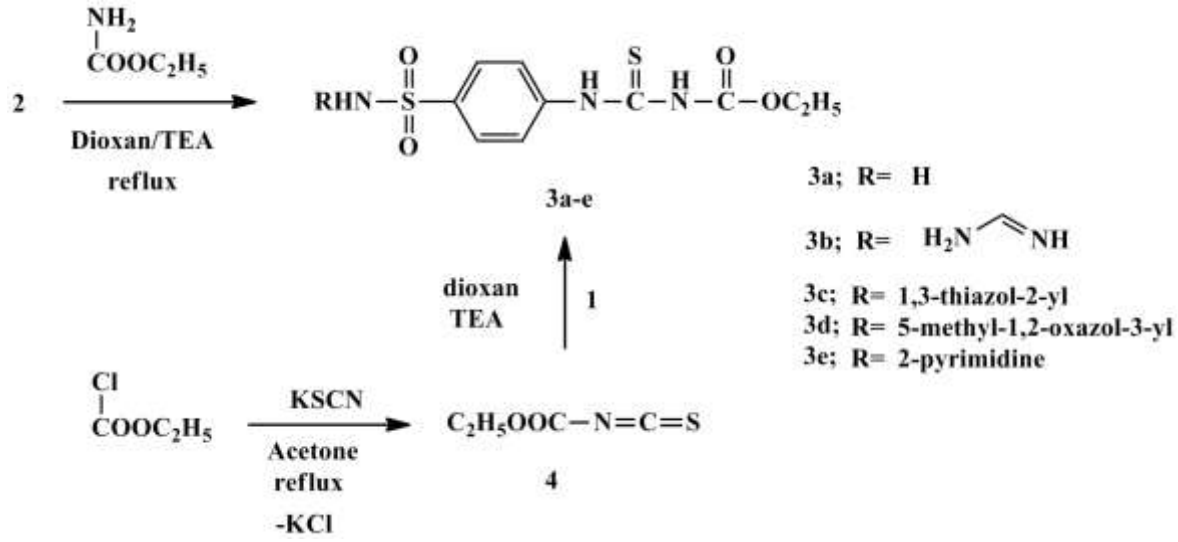
The treatment of *N*-substituted 4-isothiocyanatophenyl sulfonamides **2a-e** with ethyl carbamate in dry 1,4-dioxane at reflux temperature in the presence of triethylamine afforded the novel hybrid carbamates **3a-e**.

The structure of all newly synthesized carbamate derivatives **3a-e** was determined by analytical and spectroscopic analysis, which were consistent with the proposed structure. Carbamates **3a**–**e** were confirmed by the absence of characteristic infrared absorption peak at 2000–2200 cm^{-1} (N=C=S group). Also, the infrared spectra of the isolated compounds **3a-e** contained absorption bands 3349-3150 cm^{-1} due to stretching vibrations of the NH group and at 1736-1711 cm^{-1} for the carbonyl group in addition to the presence of sulfamoyl and thiocarbonyl groups. For example, the ^{1}H NMR spectrum of compound **3a** (DMSO-d_6) revealed a triplet signal at δ_H 1.27 ppm and a quartet at δ_H 4.17 ppm assigned to the ethyl group and a broad singlet at δ_H 7.41 ppm assigned for the NH_2 and two doublet signals at δ_H 7.42-7.83 ppm assigned to the aromatic protons. Also, in the ^{1}H NMR spectrums; two N–H protons at δ_H 11.32 and 11.68 ppm appeared as singlet signals. These are the most deshielded signals because of intramolecular hydrogen bonding that results in shifting the signals

towards higher ppm value, thus justify the presence of thio core in thiourea [53]. In the ^{13}C-NMR spectral data of compounds **3a, c, e** the thiocarbonyl group of thiourea moiety was also observed at around δ_C 169-179.38 ppm and carbonyl carbon appeared at around δ_C 153.4–153.9 ppm. Moreover, the mass spectral data of compounds **3b-d** were fully consistent with the assigned structures. The molecular ion peaks of synthesized compounds **3b**, **3c** and **3d** were observed at m/z 345(3.38%), 386(2.06%) and 384(46%) which compatible with its molecular weights, respectively. The molecular ion peak of compound **3c** underwent fragmentation to produce a peak at m/z 297 (44%), corresponding to the molecular ion of *N*-(2-thiazolyl)-4-isothiocyanato phenyl sulfonamides. It underwent further loss of SO_2, phenyl isothiocyanate and 2-thiazolyl sulfamoyl yielded peaks at m/z 233(58.45%),163(1.58%) and 134 (100%: base peak), respectively.

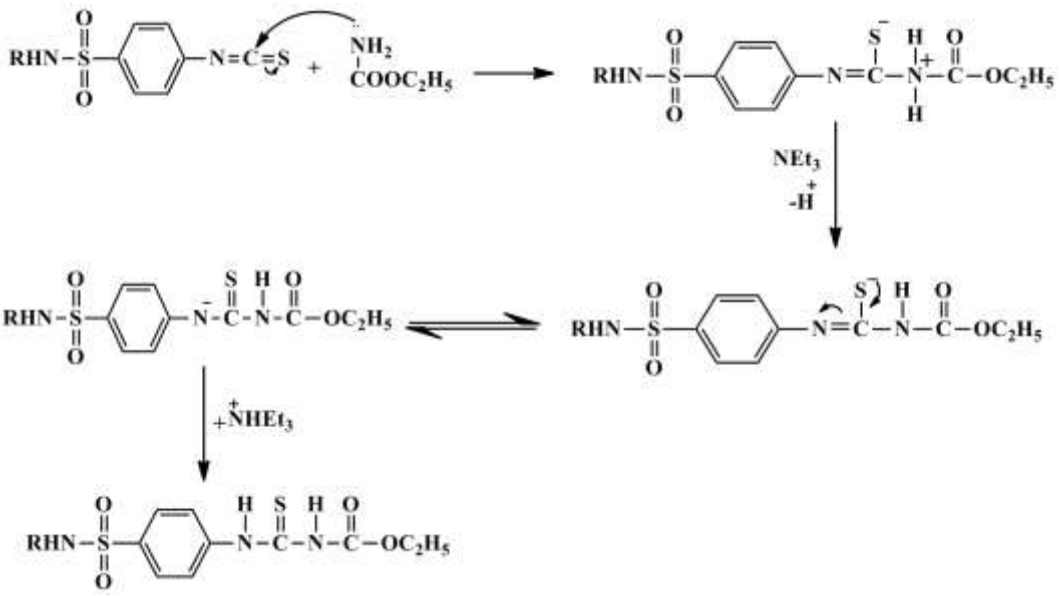


Scheme 1. synthesis of p-substituted sulfamoylphenylisothiocyanate **2a-e**

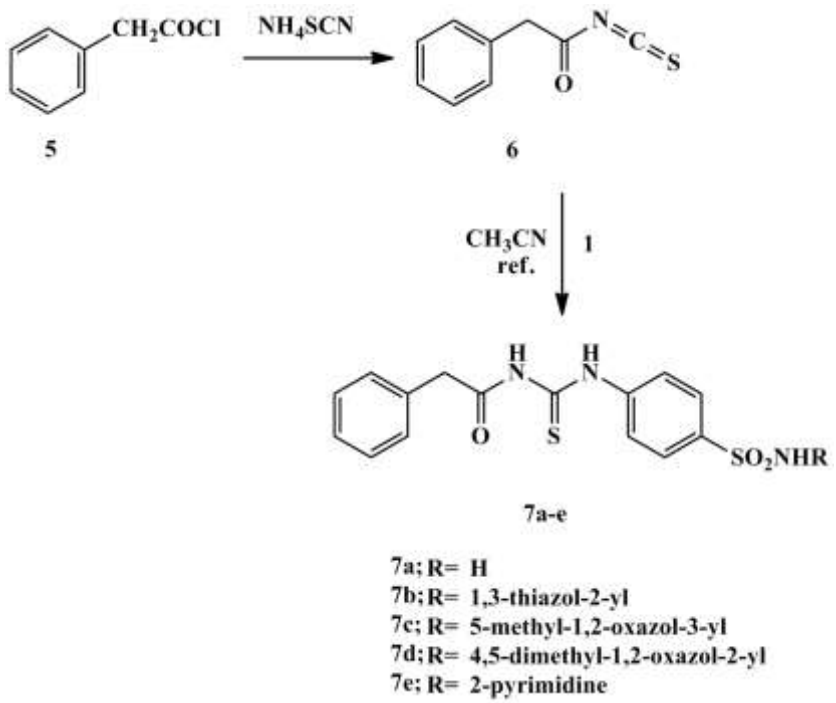


Scheme 2. synthesis of carbamates **3a-e** containing sulfonamide moiety

The formation of carbamate **3** can be explained by the reaction pathway depicted in (Scheme 3). The formation of **3** is assumed to proceed *via* the nucleophilic attack of the amino group of the ethyl carbamate on thiocarbonyl group of isothiocyanate to form the intermediate (**A**), followed by deprotonation and protonation to yield the carbamate skeleton [45]. A further evidence for the formation of carbamate **3** was obtained by an independent synthesis of compound **3a** *via* treatment of sulfanilamide **1** with ethoxycarbonylisothiocyanate **4** in 1,4-dioxane in the presence of a catalytic amount of triethylamine to yield a product identical in all respect (mp. TLC and spectra) with that obtained previously from reaction of **2a** with ethyl carbamate (Scheme 2). The physical properties, spectral information, and mass analysis of all the synthesized compounds **3a-e** are illustrated in the experimental section.



Scheme 3. the proposed mechanism for the formation of carbamates **3a-e**



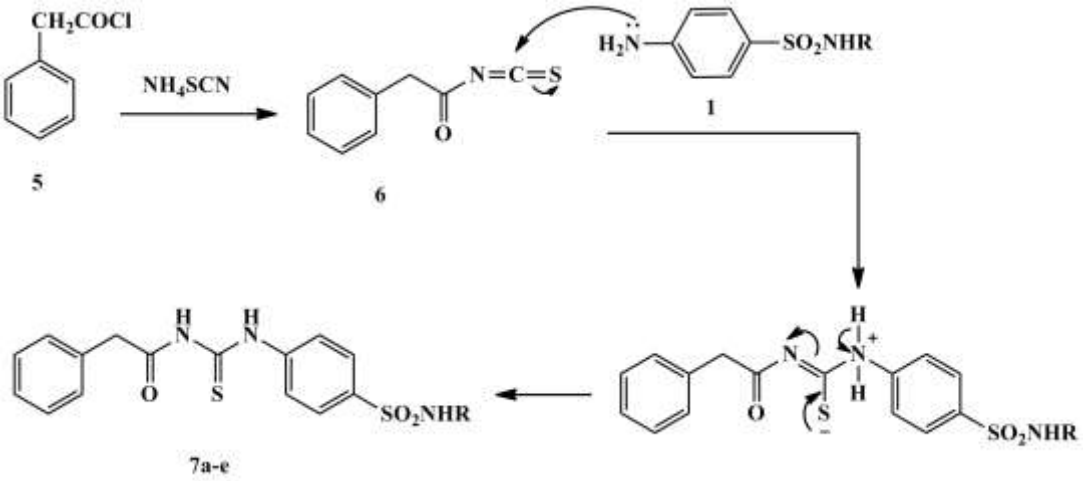
Scheme 4. synthesis of acetamides**7a-e** containing sulfonamide moiety

The chemistry of acyl isothiocyanates is very rich and diverse and has been employed in the synthesis of some biologically important organic compounds [54]. In recent years,1-(acyl/aroyl)-3-(substituted)thioureas have been seen increasing importance in organic chemistry with privileged structures. They have been the subject of extensive study in coordination chemistry, and are also known to play a promising role in the fields of material sciences, molecular electronics, molecular recognition, agriculture, biological activities and pharmaceuticals [55]. Phenylacetylisothiocyanate **6** was prepared *in situ* by reaction of Phenylacetyl chloride **5** with an equimolar quantity of ammonium thiocyanate in dry acetonitrile. Treatment of Phenylacetylisothiocyanate **6** with sulfanilamide **1** in refluxing acetonitrile afforded the corresponding acylthiourea derivatives **7a-e**, (Scheme 4).

The structures of acylthiourea derivatives **7a-e** were established by their elemental analysis and spectral data. The infrared spectra of compounds **7**

indicated the characteristic absorption bands at 1690-1713 cm^{-1} for the C=O group in addition to the presence of NH, C=S and SO_2 groups. The ^{1}HNMR spectral data were also consistent with the assigned structures. For example, the ^{1}H NMR spectrum of compound **7c** (DMSO-d_6) showed a singlet signal at δ_H 2.28 ppm assigned to the methyl protons, a singlet signal at δ_H = 3.81 ppm assigned to the methylene protons, a singlet signal at δ_H 6.14 ppm due to proton of isoxazole ring in addition to the presence of aromatic protons. Also, in ^{1}H NMR the characteristic broad signals at δ_H 11.43 and 12.57 ppm for protons of N_1 and N_3, respectively. In the mass spectrum of compound **7a**, **7c** and **7d** molecular ion peaks were observed at m/z 349 (38.68%), m/z 430 (0.5%) and m/z 444 (1%) which compatible with its molecular weights.

A plausible mechanism for the synthesis of acyl thioureas **7a-e** is depicted in (Scheme 5).



Scheme 5. The proposed mechanism for the synthesis of acyl thioureas **7a-e**

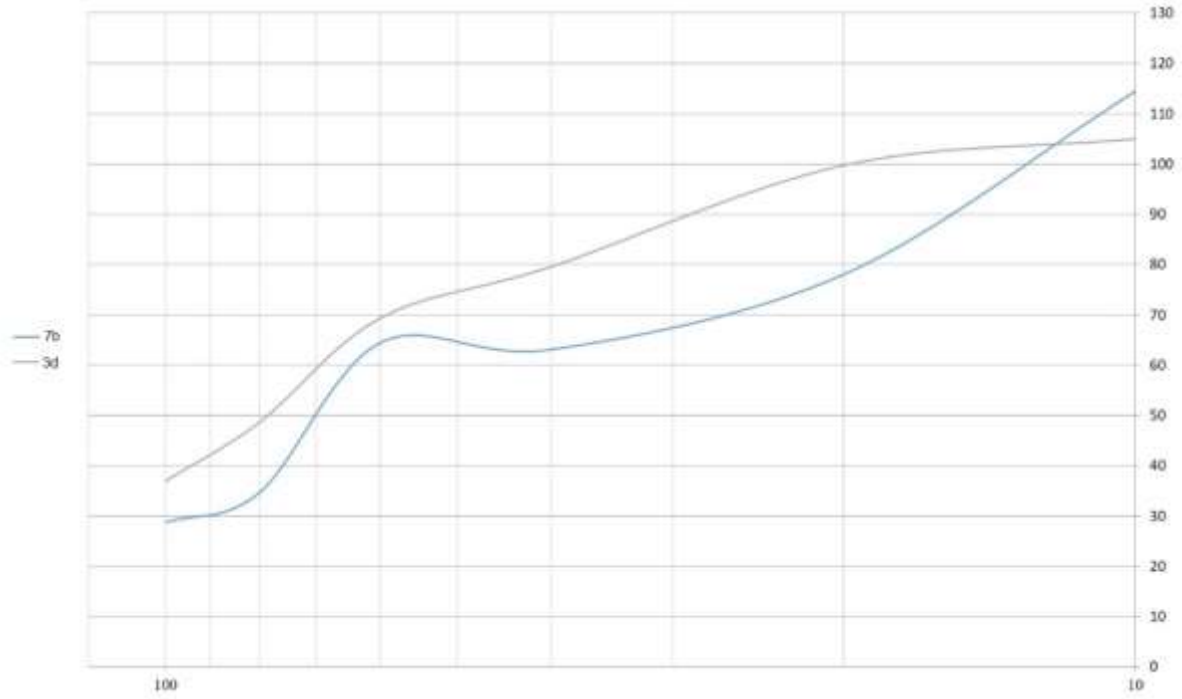


Figure 2. The minimum inhibitory concentration of **7b** and **3d** on *Bacillus subtilis*

Antimicrobial activity

The in vitro antimicrobial activities of the synthesized compounds were evaluated for four Gram-positive bacteria viz. *Staphylococcus aureus*, *Methicillin-Resistant Staphylococcus aureus* (*MRSA*), *Bacillus subtillis*, *Streptococcus pyogenes*, and three Gram-negative organisms viz. *Escherichia coli*, *Proteus vulgaris*, *Erwiniacarotovora*, as well as one fungi viz. *Candida Albicans* by agar well diffusion method [56]. Ampicillin and penicillin were used as standards. The antibacterial and antifungal data were depicted in Table 1. Compounds **7b** and **3d** exhibited

appreciable broad spectrum (87.5%) against both Gram-positive bacteria and Gram-negative bacteria (Figure 3), followed by **2e** (37.5%, each) then **7a**, **7c**, and **3e** (25%). The pathogen *S. aureus* was the most sensitive bacteria in case of **7a** (1.4 mm diameter of inhibition zone), whereas, *Proteus vulgaris* was the most sensitive in case of **3d** (1.3 mm diameter). Compounds **7b** and **3d** were selected for determination of MIC as the highest for inhibition the growth of *Bacillus subtilis*. The minimum inhibitory concentration of **7b** and **3d** on *Bacillus subtilis* were 70 and 80 μ/ml, respectively, (Figure 2).

Table 1. The antibacterial and antifungal data of prepared compounds.

Tested Microorganisms		Activated Chemicals								Standard Antibiotics	
		3b	**3d**	**3e**	**7a**	**7b**	**7c**	**7d**	**7e**	**Ampicillin**	**Penicillin**
G +ve bacteria	*Staphylococcus aureus*	0	20	27	30	14	0	0	0	16	18
	MRSA	0	29	13	0	28	20	0	18	0	0
	Bacillus subtillis	0	30	0	0	35	0	12	0	0	0
	Streptococcus pyogenes	0	20	22	25	20	0	20	0	25	0
G -ve bacteria	*Escherichia coli*	0	23	0	0	15	0	0	0	10	8
	Proteus vulgaris	20	13	0	0	15	27	0	21	14	16
	Erwiniacarotovora	0	25	0	0	15	0	0	0	0	0
Fungi	*Candida albicans*	0	0	0	0	0	0	0	0	0	0

Docking Study

Sulfonamides drugs are reported to inhibit bacterial dihydropteroate synthase (DHPS) which has an important role in the biosynthesis of the tetrahydrofolate cofactor which is crucial to pyrimidine and DNA biosynthesis.

Crystallographic structure for dihydropteroate synthase (DHPS) (ID: 3TZF) [57] illustrated that the active site region contains the standard sulfamethoxazole co-crystalized inside the receptor with the formation of hydrogen bonding (HB) with amino acids Lys 221 AA, Ser 222 AA, and Ther 62 AA through its sulfonamide and para-amino group. Also, benzene ring form π-π bonding interactions with amino acids Arg 63, Pro 64 [57]. The docking of our target compounds with (DHPS) represents consensuses scores and binding modes correlated with their biological activity as antimicrobial. A library of our designed sulfonamides linked thiourea-carbamate including standard drugs was designed. The catalytic domain of DHPS which was obtained from protein data bank (PDB code 3TZF)) was prepared for docking using Open Eye [58-60] software. To validate our docking, the study commenced with docking with standard sulfamethoxazole and another standard which showed docking pose and a mode similar to co-crystalized pose [57]. The active compound **3d** (sulfamethoxazole linked thiourea-ethyl carbamate) lays in the active sit with the formation of four HBs; two HBs with Ser 222 AA through both sulfonamide and nitrogen of isoxazole ring (acceptor). Also forms HB with Arg 225 AA through the thiourea part (acceptor). The carbonyl of ethyl carbamate group interacts with Thr 62 though the formation of HB (acceptor), (Figure 3).

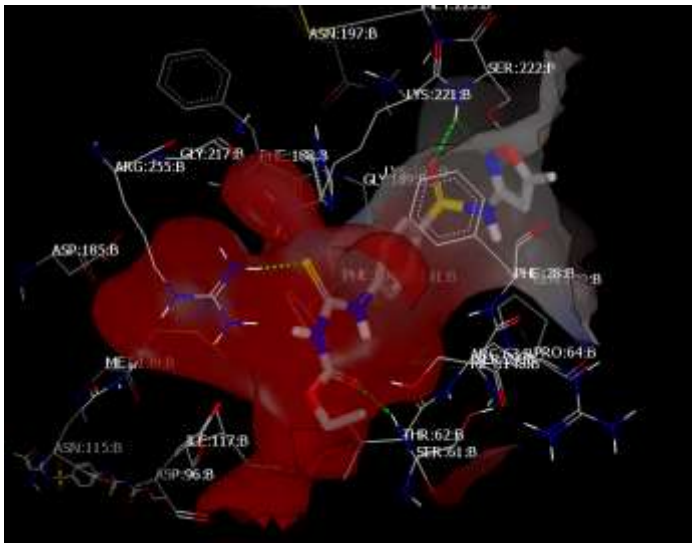


Figure 3. A visual representation for **3d** docked with PDB: 3TZF showing three HBs interaction towards the binding site

Compound **7c** (sulfamethoxazole linked thiourea-benzyl carbamate) forms one HB (in comparison **3d**) with Ser 222 AA through the sulfur of thiourea. Sulfonamide and oxygen of isoxazole form HB with Arg 255 AA. The nitrogen of isoxazole forms HB with Lys 221 AA, (Figure 4).

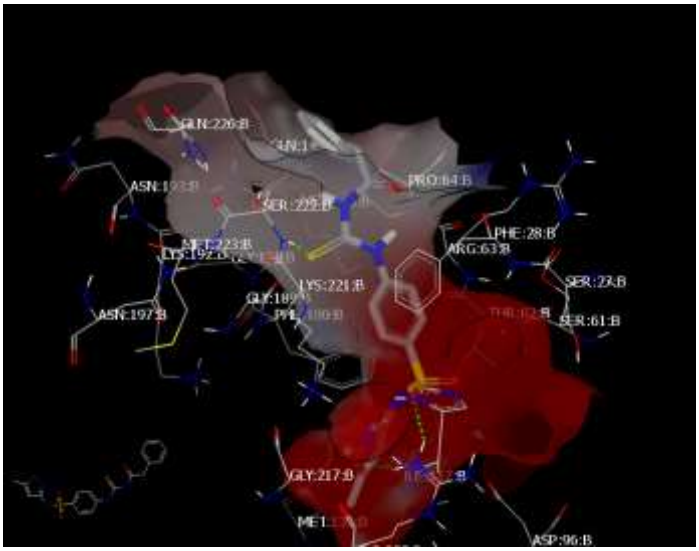


Figure 4. A visual representation for **7c** docked with PDB: 3TZF showing Two HBs interaction towards the binding site.

Judging from the docking study, both analogues **3d** and **7c** have different docking mode and pose. The R (ethyl or benzyl) group from carbamate part has a great effect, and this explains the difference in activity. Compound **7b** docked with the receptor with formations of different hydrogen bonding; with Ser 222 AA through it Sulfur and NH of thiourea as acceptor and donor, respectively. The sulfonamide forms HB with Arg 255 AA. The thiazole ring forms HB through its nitrogen atom with Lys 221 AA, (Figure 5).

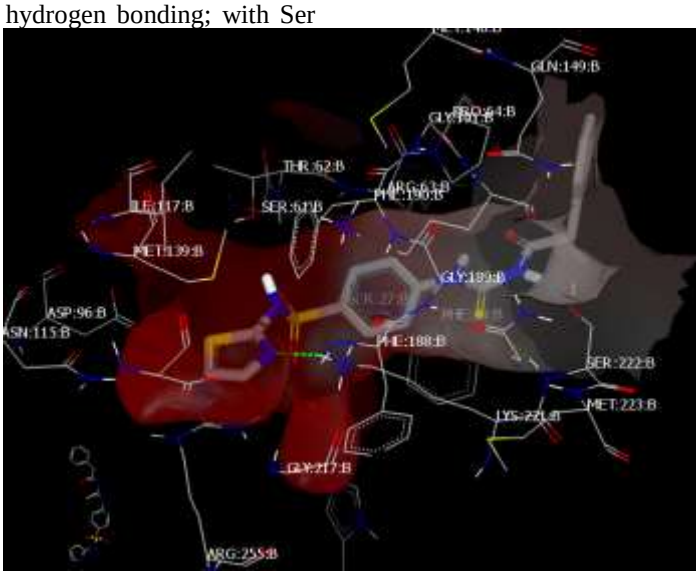


Figure 5. A visual representation for **7b** docked with PDB: 3TZF showing HB interaction towards the binding site

Among the synthesized compounds, the benzyl group forms hydrophobic-hydrophobic interaction while the ethyl group in ethyl carbamate facilitate the formation of HB interactions. In order to understand the effect of a heterocyclic ring, compounds **7d** and **7c** were examined. Unfortunately, both compounds differ in the docking pose and mode. Compound **7d** forms hydrophobic-hydrophobic interaction without formation of HB. Although both compounds **3d** and **3c** form HB with an essential amino acid for binding, both have different poses.

Calculation of Ligand efficiency (LE) and Ligand lipophilic efficiency (LLE) [61]

Ligand efficiency (LE) scores:

ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) properties are important in drug discovery and were calculated, with special

emphasis on the lipophilicity requirements. LE is used in fragment-based drug discovery [62] to lead compounds with optimal combinations of physicochemical properties and pharmacological properties. LE is used to estimate the efficiency of compounds and determine binding affinity about the number of heavy atoms in a molecule. This provides a way to compare the affinity of molecules corrected for their size.

***Ligand-lipophilicity efficiency* (LLE)** [62]

LLE describes how efficient a ligand exploits its lipophilicity. If lipophilicity is too high, the likelihood of a compound to bind to multiple targets increases. Moreover, affinity is often optimized through the introduction of lipophilic groups, as these contribute favorably to the hydrophobic effect without the need for specific interactions with the target. These contrast with polar groups, which need to establish very good interactions with the target to compensate for the desolvation penalty. For this reason, polar groups are often used to improve solubility rather than affinity.

LE = (pIC50 x 1.37) ÷ NHA

LLE = pIC50 – logP

IC50 = half-maximal inhibitory concentration (in term of molar concentration); NHA = non-hydrogen atom; log P = lipophilicity

pIC50 (**7b**) = 4.15; NHA (**7b)** = 28; log P = 2.29

pIC50 (**3d**) = 4.09; NHA (**3d**) = 24; log P = 1.40;

pIC50 (sulfamethoxazole) = 4.9 [63];

NHA = 17; log P = 0.61;

LE = 0.39; LLE = 8.03

Compounds **3d** exhibited LE similar to **7b** but it has LLE (2.6) higher than **7b** (1.86), Table 2. This results emphasize the hypothesis of ethyl carbamate is better than benzyl carbamate.

Table 2. Summary of ligand efficiency scores to be considered during fragment-based drug Discovery (FBDD**)**

Compound	Molecular weight	LE	LLE
7b	432.55	0.20	1.86
3d	384.44	0.23	2.6
Sulfamethoxazole	253.27	0.39	8.03

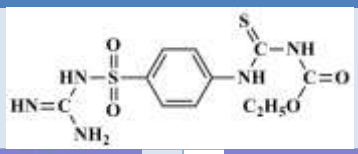
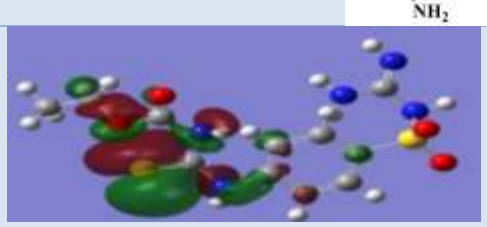
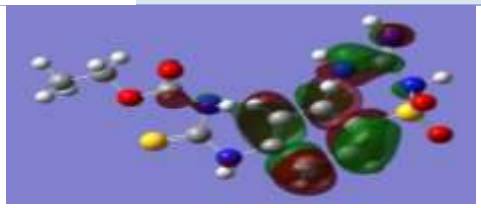
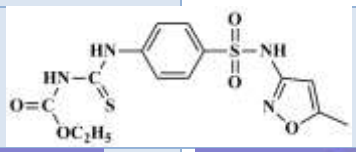
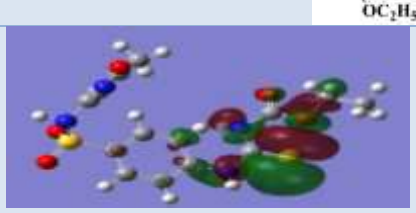
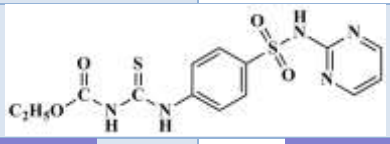
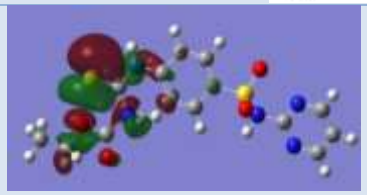
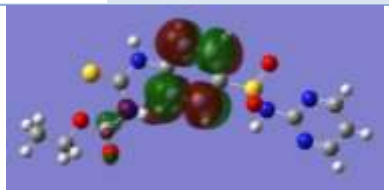
Quantum chemical calculations

The ultimate goal of the structure-activity relationship (SAR) studies is to correlate the biological activity of a series of compounds with their structures. Unconstrained geometry optimizations of prepared compounds (**3b,d,e and 7a-e**) were carried out at gradient corrected DFT using Becke's three parameters hybrid method and the Lee-Yang - Parr correlation functional (B3LYP) [63] combined with 6-31G(d) [64] basis set using Gaussian 09 in both gas and solvent (DMSO) media. Figure 6 shows HOMO and LUMO frontier orbital's obtained for the studied compounds. It is important to examine the HOMO and LUMO for these compounds because the relative ordering of occupied and virtual orbital provides a reasonable qualitative indication of electronic properties. Molecular electrostatic potential mapping is very useful in the investigation of the physicochemical properties of the studied compounds. Different values of the electrostatic potential at the surface are represented by different colors: red represents regions of most electro negative potential, blue represents regions of most positive electrostatic potential and green represents regions of zero potential. Herein, the three MESPs are very similar and revealed that the high electronic density suitable for the electrophilic attack is located on sulfonyl oxygen atoms in the red region.

The quantum chemical calculation of the prepared compound (**3b, d, e and 7a-e**) was tabulated in Table 3. These data proved the ΔHE is less value in compound 3d and 7b that indicate that the two compounds are more active than another compounds. As soon as the softness value showed the high value in the same compound 3d and 7b that indicate that the two compounds highly active. From the foregoing, we find that quantum calculated data is fully compatible with biological activities. The theoretical study implies that gap, softness and hardness tend to be the best chemical descriptors to identify compounds presenting an interesting antibacterial activity. The reaction of inhibition in question seems to be mainly directed by hard-hard interactions, for example, the transfer of a proton to a hard base. In that case, the reactions are mainly controlled by electrostatic relationships as modelled by Mulliken charges that can be also considered as important descriptors.

Table 3. The quantum chemical calculation of the prepared compounds.

File name	LUMO	HOMO	ΔHE	Softness	Hardness
3b	-0.16087	-0.224	0.06313	31.68066	1.173174
3d	-0.17807	-0.22393	0.04586	43.61099	1.761928
3e	-0.1507	-0.229	0.0783	25.54278	0.920639
7a	-0.16004	-0.21777	0.05773	34.64403	1.236276
7b	-0.17167	-0.21762	0.04595	43.52557	1.649039
7c	-0.15786	-0.22138	0.06352	31.48615	1.132108
7d	-0.15785	-0.22137	0.06352	31.48615	1.131988
7e	-0.16245	-0.21823	0.05578	35.85515	1.299007

Comp	HOMO	LUMO
3b	 	
3d	 	
3e	 	

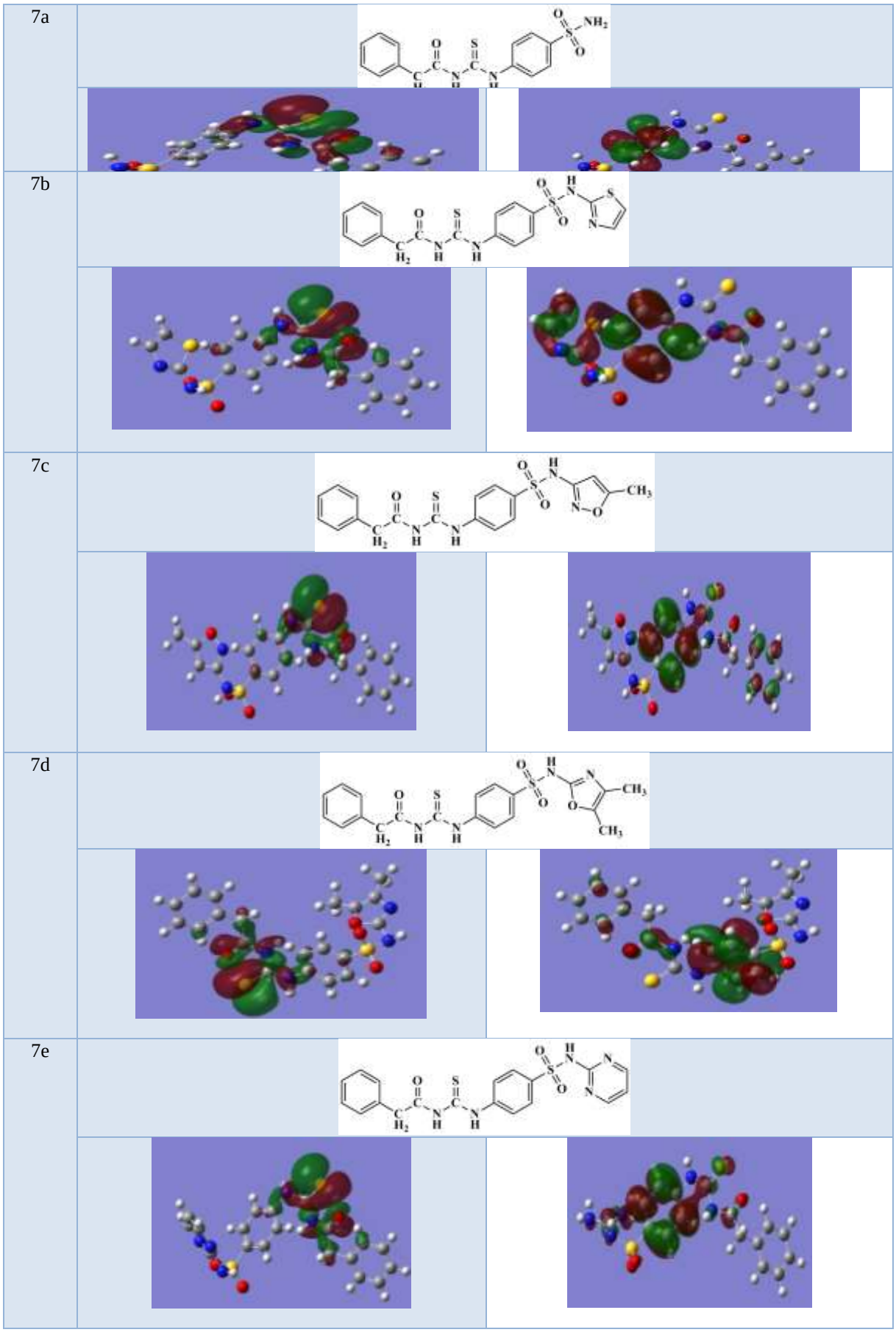


Figure 6. Quantum Homo and Lumo of prepared compounds

Conclusion

The present study describes the synthesis, structure elucidations, in-vitro anti-microbial activity assay and molecular docking of new sulfonamide hybrids. A series of new sulfonamide carbamates hybrids were synthesized by treatment of N-substituted 4-isothiocyanatophenyl sulfonamides with ethyl carbamate. Also, the novel hybrids sulfonamide-acylthiourea derivatives were obtained by treatment of Phenylacetylisothiocyanate with sulfanilamide. The structures of all the title products were elucidated by spectroscopic data, IR, NMR (1H and ^{13}C NMR) and mass and elemental analyses. The in vitro anti-microbial potential of all the synthesized compounds were investigated. It is evident that synthesized compounds Ethyl({4-[(5-methyl-1,2-oxazol-3-yl)sulfamoyl)-phenyl]carbamothioyl) carbamate and 2-Phenyl-N-((4-(N-thiazol-2-yl)sulfamoyl)-phenyl)-carbamothioyl)-acetamide have good antimicrobial activity. Molecular docking studies for the final compounds were performed using the Open Eye docking suite. Moreover, Ligand efficiency (LE) and lipophilic ligand efficiency (LLE) parameters for Ethyl({4-[(5-methyl-1,2-oxazol-3-yl)sulfamoyl)-phenyl]carbamothioyl)-carbamate and 2-Phenyl-N-((4-(N-thiazol-2-yl)sulfamoyl)phenyl)carb-amothioyl)acetamide were evaluated. Quantum chemical calculations based on density functional theory (DFT) have been explored.

Conflict of interest

The authors declare that they have no conflict of interest.

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