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Synthesis, Antimicrobial Activity and Quantum Calculations of Novel Sulphonamide Derivatives

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THE reactivity of 2-bromo-*N*-(phenylsulfonyl)acetamide derivatives **3a-c** towards some nitrogen-based nucleophiles was studied in this investigation and gave the corresponding aminothiazole **6a-c**, aminooxazole **7a-c,** quinazoline-2-yl **10a-c**; respectively. Furthermore, the reaction of acetamide derivatives **3a-c** with aminopyridine gave pyridine-4-ylamino **12a-c.** Reaction of acetamide derivatives **3a-c** with benzo-2-thiol derivatives afforded benzo [*d*] thiazol-2-ylthio **14a-c** and 1*H*-benzo[*d*]imidazol-2-yl)thio derivatives **16a-c**; respectively. The synthesized compounds displayed good antimicrobial activity. Additionally, compounds **12a** and **14a** exhibited high activity towards most of the strains. The computational calculations for **12a** and **14a** were carried out *via* HF/6-31G(d) and DFT B3LYP/6-31G(d) basis sets and the corresponding results of HOMO–LUMO energy gap and Mulliken atomic charges were tabulated. This correlation between experimental and theoretical calculations provided a good confirmation for anticipated new compounds.

Keywords: Sulfonamide derivatives, Antimicrobial activity, Computational calculation.

Introduction

Heterocyclic compounds bearing sulfonamide moieties have a wide spectrum of biological actions, for instance, a monoamine oxidase inhibitory [1,2], anticonvulsant [3], antimicrobial [4], hypotensive [5,6], antipyretic [7,8], anti-inflammatory [9], and anthelmintic activities [10,11]. Furthermore, the target nucleus signifies the core unit in a variety of drugs, for example, Sulfafurazole (I), Chlorpropamide (II), Ethoxzolamide (III) and Sulfamethoxypyridazine (IV) as displayed in Fig. 1.

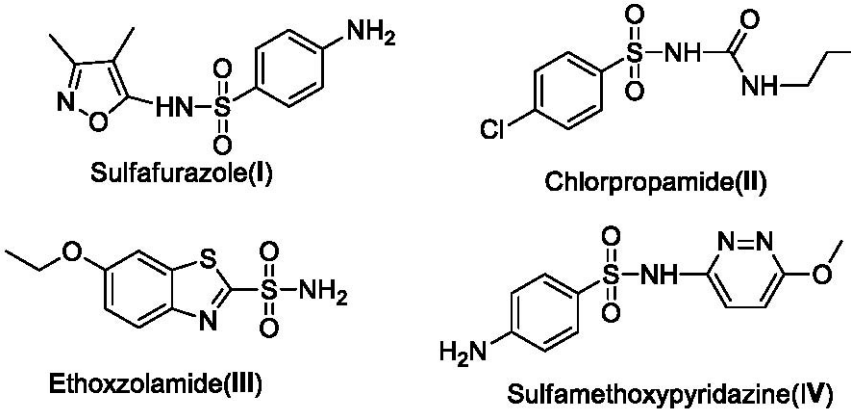

Fig. 1. Some drugs incorporating sulfonamide ring.

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Sulphonamides are one of the greatest generally used veterinary drugs and consequently, their residues are regularly found in the environment [12-15]. Consequently, there is a vital need to give more care to modernize and transform drug leads from the point of view of medicinal chemistry and drug design to achieve the most potent and effective drugs [16-18]. The foremost area of the research described here was to synthesize and characterize sulphonamide compounds and to estimate the energies of these molecules which are very important for chemical reactivity [19-22]. In this context, we report the synthesis of new sulphonamide derivatives. DFT calculations of designated examples of the synthesized sulphonamide derivatives **12a** and **14a** have also been carried out [23-25].

Experimental

General procedure

All melting points were measured on a Gallenkamp melting point apparatus. IR spectra were recorded on Shimadzu FT-IR 8101 PC infrared spectrophotometer. The ^{1}H-NMR and ^{13}C-NMR spectra were determined in DMSO-d_6 at 300 MHz on a Varian Mercury VX 300 NMR spectrometer (^{1}H at300 MHz,^{13}C at 75MHz) using TMS as an internal standard. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University, Giza, Egypt.

Materials and reagents

4-Chlorosulfonyl chloride, 4-methyl sulphonyl chloride, benzene sulphonyl chloride, 2-bromoacetamide, thiourea, urea, ammonium hydroxide, 2-aminophenol, 2-aminobenzothiazole, o-phenylenediamine, 4-aminopyridine, benzo[*d*] thiazole-2-ole and benzo[*d*]-imidazole-2-thiole were purchased from Aldrich Chemical CO.

*Synthesis of 2-Bromo-N-(phenylsulfonyl) acetamide derivatives (**3a-c**)*

A mixture of the benzene sulfonyl chloride derivatives **1** (3.01 g, 0.015 m), 2-bromoacetamide (**2**) (1.35 g, 0.01 m) in ethanol (25 ml) and pyridine (5.0 ml) was refluxed for 4h. The mixture was poured onto crush ice, filtered and washed with water. The isolated products were crystallized from (EtOH/H_2O) to afford 2-bromo-*N*-(phenylsulfonyl) acetamides **3a-c** [26]**:**

2-Bromo-*N*-((4-chlorophenyl)sulfonyl)acetamide (**3a**): yellow crystals, in 80% yield, m.p.=150-152^{o}C, $C_8H_7BrClNO_3S$ (312.57), Analysis% Calcd (Found): C: 30.74(30.70), H: 2.26(2.30), Br: 25.56(25.52), Cl: 11.34(11.30), N: 4.48(4.50), S: 10.26 (10.30), IR (KBr) $_{max}$/cm^{-1}: 3332 (NH), 1295 (S=O). ^{1}H NMR (DMSO-d_6): δ 3.54(s, 2H, H_2C), 7.69(d, 2H, *H*C aromatic, *J*= 3.2Hz), 8.02(d, 2H, *H*C aromatic, *J*= 1.2Hz), 9.40 (s, 1H, *H*N-D_2O exchangeable), ^{13}C NMR (DMSO-*d6*):δ 28.3(CH_2), 128.2(*C*H), 137.5(*C*H), 137.8(*C*H), 172.3(*C*=O), MS (*m*/*z*, r.i.%): 312(M^+,100%), 314 (M^{+2}, 97%), 176(52%).

2-Bromo-*N*-tosyl acetamide (**3b**): white crystals, in 77% yield, m.p. =114-116 ^{o}C, $C_9H_{10}BrNO_3S$ (292.1), Analysis% Calcd (Found): C: 37.0(37.52), H: 3.45(3.49), Br: 27.35(27.40), N: 4.79(4.68), S: 10.98 (11.01). IR (KBr) $_{max}$/cm^{-1}: 3300 (NH), 1300(S=O).^{1}H NMR (DMSO-d_6): δ 2.45(s, 3H, H_3C), 3.54(s, 2H, H_2C), 7.63(d, 2H, *H*C aromatic, *J*= 7.5Hz), 8.02(d, 2H, *H*C aromatic, *J*= 1.2Hz), 9.40 (s, 1H, *H*N D_2O exchangeable), MS (*m*/*z*, r.i. %): 292(M^+, 96%), 294(M^{+2}, 92%), 176(46%).

2-Bromo-*N*-(phenylsulfonyl)acetamide (**3c**): Buff powder in 77% yield, m.p.=122-124^{o}C, $C_8H_8BrNO_3S$ (276.12), Analysis% Calcd (Found): C: 34.55(34.58), H: 2.90(2.95), Br: 28.73 (28.78), N: 5.04(5.01), S: 11.53 (11.49); IR (KBr) $_{max}$/cm^{-1}: 3312(NH), 1303 (S=O). ^{1}H NMR (DMSO-d_6): δ 3.54 (s, 2H, H_2C), 7.78-7.82 (m, 5H, *H*-Ars), 9.25 (s, 1H, *H*N-D_2O exchangeable), ^{13}C NMR (DMSO-d_6): δ 27.2(CH_2), 127.3(*C*H), 131.2(*C*H), 172.3(*C*=O), MS (*m*/*z*, r.i.%): 276(M^+,100%), 278(M^{+2}, 98%), 176(55%).

Reaction of 2-Bromo-N-(phenylsulfonyl) acetamides (3a-c) with urea derivatives

An ethanolic solution of the 2-bromo-*N*-(phenylsulfonyl)acetamide derivative **3a-c** (3.88 g, 10mmol) with the appropriate urea derivatives was refluxed for 4 hours then allowed to cool and treated with ammonium hydroxide solution till it became alkaline at pH=9. The solid that formed was filtered off, washed with water, dried and finally crystallized from the proper solvent.

N-(2-aminothiazol-4-yl)-4-chlorobenzenesulfonamide (**6a**): Brown powder, recrystallized from (DMF/EtOH), in 72% yield, m.p.=185-187°C, $C_9H_8ClN_3O_2S_2$ (288.97), Analysis% Calcd (Found): C: 37.31(37.32), H: 2.78(2.80), Cl: 12.24(12.26), N: 14.50(14.53), S: 22.13 (22.15), IR $(KBr)_{max}$/cm^{-1}: 3350 (NH), 3010(NH_2), 1302 (S=O). ^{1}H NMR (DMSO-d_6): δ 6.60(s, 1H, *H*C, thiazole ring), 7.25 (s, 2H, H_2N-D_2O

exchangeable), 7.69(d, 2H, *H*C aromatic, *J*= 7.5Hz), 8.02 (d, 2H, *H*C aromatic, *J*= 3.2Hz), 10.23 (s,1H, *H*N-D_2O exchangeable),^{13}C NMR (DMSO-d_6): δ 112(*C*H), 128.2(*C*H), 137.8(*C*H), 140(*C*H), 169(*C*H), MS (*m*/*z*, r.i.%): 288 (M^+,100%), 290(M^{+2}, 32%), 95(23%).

N-(2-aminothiazol-4-yl)-4-methylbenzenesulfonamide (**6b**): Yellow solid, recrystallized from (DMF/EtOH) in 72% yield, m.p.=134-136°C, $C_{10}H_{11}N_3O_2S_2$(269.34), Analysis% Calcd (Found): C: 44.59(44.60), H: 4.12(4.19), N: 15.60(15.63), S: 23.79(23.49). IR (KBr) $_{max}$/cm^{-1}: 3215(NH), 3100-3025(NH_2), 1289 (S=O).^{1}H NMR (DMSO-d_6): δ 2.43(s, 3H, H_3C), 4.65(s, 2H, H_2N-D_2O exchangeable), 6.56(s, 1H, *H*C, thiazole), 7.25(d, 2H, *H*C aromatic, *J*= 3.2Hz), 7.73(d, 2H, *H*C aromatic, *J*=8.5Hz), 10.29(s, 1H, *H*N D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ 19.2 (CH_3), 112(*C*H), 128.2(*C*H), 129.3(*C*H), 137.8(*C*H), 140(*C*H), 169(*C*H), MS (*m*/*z*, r.i.%): 269(M^+,88%), 170(55%), 114(29%).

N-(2-aminothiazol-4-yl)benzenesulfonamide (**6c**): Reddish brown, recrystallized from (DMF/EtOH), in 70% yield, $C_9H_9N_3O_2S_2$ (255.32), m.p.=136-138°C, Analysis% Calcd (Found): C: 42.34(42.40), H: 3.55(3.58), N: 16.46(16.49), S: 25.11 (25.15). IR (KBr) $_{max}$/cm^{-1}: 3215(NH), 3100-3025(NH_2), 1289 (S=O). ^{1}H NMR (DMSO-d_6): δ 6.58(s, 1H, *H*C thiazole proton), 7.17(s, 2H, H_2N-D_2O exchangeable), 7.78-7.82(m, 5H, *H*Ars), 10.33(s, 1H, *H*N -D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ 110(*C*H), 129.3(*C*H), 131(*C*H), 137(*C*H), 140(*C*H), 170(*C*H), MS (*m*/*z*, r.i.%): 255 (M^+,100%), 156(10%), 114(25%)**.**

N-(2-aminooxazol-4-yl)-4-chlorobenzenesulfonamide (**7a**): Off white powder recrystallized from (EtOH/H_2O) in 62% yield, m.p.=166-168°C, $C_9H_8ClN_3O_3S$, (273.70), Analysis% Calcd (Found): C: 39.50(39.53), H: 2.95(2.98), Cl: 12.95(12.93), N: 15.35(15.40), S: 11.71(11.76). IR (KBr) $_{max}$/cm^{-1}: 3403(NH), 3230-3125(NH_2), 1310(S=O).^{1}H NMR (DMSO-d_6): δ 6.23(s, 2H, H_2N D_2O exchangeable), 7.12(s, 1H, *H*C oxazole), 7.69(d, 2H, *H*C aromatic, *J*= 1.5Hz), 8.02(d, 2H, *H*C aromatic, *J*= 7.5Hz), 10.25(s, 1H, *H*N D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ 126(*C*H), 128(*C*H), 137(*C*H), 165(*C*H), MS (*m*/*z*, r.i.%): 273(M^+,100%), 275(M^{+2}, 33%), 189(32%), 98 (25%).

N-(2-aminooxazol-4-yl)-4-methylbenzenesulfonamide (**7b**): White solid recrystallized from (EtOH/H_2O), in 64% yield, m.p.=141-143°C, $C_{10}H_{11}N_3O_3S$(253.28), Analysis% Calcd (Found): C: 47.42(47.40), H: 4.38(4.40), N: 16.59(16.57), S:12.66(12.69), IR (KBr)$_{max}$/cm^{-1}: 3403(NH), 3230-3125 (NH_2), 1310 (S=O). ^{1}H NMR (DMSO-d_6): δ 2.42(s, 3H, H_3C), 6.50 (s, 2H, H_2N D_2O exchangeable), 7.12(s, 1H, *H*C oxazole), 7.63(d, 2H, *H*C aromatic, *J*= 3.2Hz), 8.02(d, 2H, *H*C aromatic, *J*= 7.5Hz), 10.29(s, 1H, *H*N- D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ 19.2(CH_3), 125.4(*C*H), 129(*C*H), 138(*C*H), 164(*C*H), MS (*m*/*z*, r.i. %): 253(M^+, 100%), 170(7%), 98(21%).

N-(2-aminooxazol-4-yl)benzenesulfonamide (**7c**): Brown solid recrystallized from (EtOH/H_2O) in 64% yield, m.p.=133-135°C $C_9H_9N_3O_3S$ (239.25), Analysis% Calcd (Found): C: 45.18(45.20), H: 3.79(3.80), N: 17.56(17.55), S: 13.40 (13.42), IR (KBr) $_{max}$/cm^{-1}: 3403(NH), 3230-3125(NH_2), 1310 (S=O). ^{1}HNMR (DMSO-d_6): δ 6.53(s, 2H, H_2N D_2O exchangeable), 7.10(s, 1H, *H*C oxazole), 7.75-7.83(m, 5H, *H*Ars), 10.29(s, 1H, *H*N- D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ 125.4(*C*H), 127(*C*H), 129(*C*H), 131(*C*H), 138(*C*H), 163(*C*H), MS (*m*/*z*, r.i.%): 239(M^+, 100%), 156(12%), 98(25%).

Reaction of 2-bromo-N-(phenylsulfonyl) acetamide derivatives (3a-c) with amino heterocyclic derivatives

General procedure: 2-Bromo-*N*-(phenylsulfonyl) acetamide derivative (**3a-c**) (0.33 g, 2 mmol), the appropriate o-phenylenediamine (0.216, 2 mmol)(**8**) in ethanol (10 ml) and H_2SO_4(5ml) were refluxed for 6-8 hours The reaction mixture was evaporated *in vacuo* and the residual solid was collected by filtration, washed with ethanol, dried and finally recrystallized from the suitable solvent to afford the corresponding heterocyclic derivatives **10a-c**. The synthesized compounds together with their physical and spectral data are given below:

4-Chloro-*N*-(quinoxalin-2-yl)benzenesulfonamide (**10a**): Brown solid recrystallized from (EtOH/H_2O), in 71% yield, m.p.= 184-185°C, $C_{14}H_{10}ClN_3O_2S$ (319.76), Analysis% Calcd (Found): C: 52.59(52.60), H: 3.15(3.19), Cl: 11.09(11.12), N: 13.14(13.11), S:10.03(10.05). IR (KBr) $_{max}$/cm^{-1}: 3310(NH), 1302 (S=O). ^{1}H NMR (DMSO-d_6): δ 7.60(s, 2H, H_2C aromatic, *J*= 7.5Hz), 7.63(dd, 1H, *H*C aromatic, *J*=1.8Hz), 7.69 (d, 2H, *H*C aromatic, *J*= 7.5Hz), 7.84(dd, 2H, *H*C aromatic, *J*= 1.2Hz), 8.01(d, 1H, *H*C aromatic , *J*= 6.2Hz), 9.50(s, 1H, *H*C quinazoline), 11.35 (s, 1H, *H*N-D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ

119.3(*C*H), 122.2(*C*H), 125.1(*C*H), 128.3(*C*H), 131(*C*H), 156(*C*H), 178(*C*H), MS (*m*/*z*, r.i.%): 319(M^+,100%), 321(M^{+2},33%), 190(21%).

4-Methyl-*N*-(quinoxalin-2-yl)benzenesulfonamide (**10b**): Dark brown solid recrystallized from (EtOH/H_2O), in 69% yield, m.p.=164-165°C, $C_{15}H_{13}N_3O_2S$ (299.35), Analysis% Calcd (Found): C: 60.18(60.22), H: 4.38(4.40), N: 14.04(14.10), S: 10.71(10.73). IR (KBr) $_{max}$/cm^{-1}: 3310(NH), 1302 (S=O).^{1}H NMR (DMSO-d_6): δ 2.42(s, 3H, H_3C), 7.35(d, 2H, *H*C aromatic, *J*=3.2Hz), 7.45(dd, 1H, *H*C aromatic, *J*=2.4Hz), 7.70(d, 2H, *H*C aromatic, *J*=12Hz), 7.80(dd, 2H, *H*C aromatic, *J*=7.8Hz), 8.01(d, 1H, *H*C aromatic , *J*= 6Hz), 9.48(s, 1H, *H*C quinazolin), 11.49(s, 1H, *H*N -D_2O exchangeable), ^{13}C NMR (DMSO-d_6): δ 19.2(*C*H_3), 118.2(*C*H), 121.8(*C*H), 125.3(*C*H), 129.3(*C*H), 134(*C*H), 158(*C*H), 177.3(*C*H), MS (*m*/*z*,r.i.%): 299(M^+,100%), 144(39%), 170(43%).

N-(Quinoxalin-2-yl)benzenesulfonamide (**10c**): Brown solid recrystallized from (EtOH/H_2O), in 66% yield, m.p.=162-164°C, $C_{14}H_{11}N_3O_2S$ (285.32), Analysis% Calcd(Found): C:58.93(58.95), H: 3.89(3.90), N:14.73(14.78), S: 11.24 (11.26). IR (KBr) $_{max}$/cm^{-1}: 3310(NH), 1302 (S=O). ^{1}H NMR (DMSO-d_6): δ 7.25(d, 2H, *H*C aromatic , *J*=12Hz), 7.33(dd, 1H, *H*C aromatic, *J*= 2.5Hz), 7.55-7.68 (m, 5H, *H*Ars), 8.00(d, 1H, *H*C aromatic , *J*= 7.2Hz), 9.13(s, 1H, *H*C quinazolin), 11.52(s, 1H, *H*N- D_2O exchangeable), MS (*m*/*z*, r.i.%): 285(M^+, 100%), 156(45%), 144(25%).

*Reaction of 2-bromo-N-(phenylsulfonyl) acetamide derivatives (**3a-c**) with pyridin-4-aminebenzo[d] thiazole-2-thiol and 1H-benzo[d]imidazole-2-thiol*

A mixture of the 2-bromo-*N*-(phenylsulfonyl) acetamide derivative (**3a-c**) (0.33 g, 2 mmol), and the pyridin-4-amine(**11**), benzo [d]thiazole-2-thiol (**13**) ,or 1H-benzo[d]imidazole-2-thiol(**15**) (2 mmol) in ethanol (10 ml) and a few drops of piperidine were refluxed for 10 hours. The reaction mixture was evaporated in vacuo and the residual solid was collected via filtration, washed with ethanol, dried and finally recrystallized from the suitable solvent to afford the corresponding heterocyclic derivatives **12a-c**, **14a-c** and **16a-c**. The synthesized compounds together with their physical and spectral data are listed below:

N-(4-Chlorophenylsulfonyl)-2-(pyridin-4-ylamino) acetamide (**12a**): Orange solid recrystallized from (DMF/H_2O), in 77% yield, m.p.= 166-167°C, $C_{13}H_{12}ClN_3O_3S$ (325.77), Analysis% Calcd (Found):C: 47.93(47.95), H:3.71(3.76), Cl: 10.88(10.89), N: 12.90(12.88), S: 9.84 (9.86). IR (KBr) $_{max}$/cm^{-1}: 3425(NH), 3326 (NH), 1632(C=O), 1325 (S=O). ^{1}H NMR (DMSO-d_6): δ3.25(s, 2H, H_2C), 4.53(s, 1H, *H*N D_2O exchangeable), 6.9(d, 2H, *H*C pyridyl, *J*= 6.3Hz), 7.68(d, 2H, *H*C aromatic, *J*= 1.2Hz), 7.70 (d, 2H, *H*C aromatic, *J*= 7.8Hz), 8.53(d, 2H, *H*C pyridyl, *J*= 6.1Hz), 11.4(s, 1H, *H*N- D_2O exchangeable).^{13}C NMR (DMSO-d_6): δ 56(*C*H_2), 107.3(*C*H), 129(*C*H), 138(*C*H), 149(*C*H), 156(*C*H), 173(*C*H), MS (*m*/*z*, r.i.%): 325(M^+, 100%), 327(M^{+2}, 32%), 150 (56%), 113(21%).

2-(Pyridin-4-ylamino)-*N*-tosylacetamide (**12b**): Dark orange powder recrystallized from (DMF/H_2O), in 76% yield, m.p.=130-132°C, $C_{14}H_{15}N_3O_3S$ (305.08), Analysis% Calcd (Found): C: 55.07(55.10), H: 4.95(4.96), N: 13.76(13.78), S: 10.50 (10.52). IR (KBr) $_{max}$/cm^{-1}: 3416(NH), 3307 (NH), 1621(C=O), 1300 (S=O).^{1}H NMR (DMSO-d_6):δ 2.21 (s, 3H, H_3C), 3.35(s, 2H, H_2C), 5.02(s, 1H, *H*N D_2O exchangeable), 7.01(d,2H, *H*C pyridyl, *J*= 6.3Hz), 7.53(d, 2H, *H*C aromatic, *J*= 1.2Hz), 7.69 (d, 2H, *H*C aromatic, *J*= 3.2Hz), 8.61(d, 2H, *H*C pyridyl, *J*= 6.1Hz), 12.03(s, 1H, *H*N- D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ 20.2(*C*H_3), 54.3(*C*H_2), 107.3(*C*H), 129(*C*H), 137.2(*C*H), 149(*C*H), 154(*C*H), 170(*C*H), MS(*m*/*z*, r.i.%): 305(M^+,100%), 236(23%), 170(52%), 150(21%).

N-(Phenylsulfonyl)-2-(pyridin-4-ylamino) acetamide (**12c**): Orange solid recrystallized from (DMF/H_2O), in 74% yield, m.p.=152-154°C, $C_{13}H_{13}N_3O_3S$ (291.33), Analysis% Calcd (Found): C: 53.60(53.58), H:4.50(4.48), N: 14.42(14.46), S: 11.00(10.89). IR (KBr) $_{max}$/cm^{-1}: 3400(NH), 3310(NH), 1633(C=O), 1289(S=O). ^{1}H NMR (DMSO-d_6): δ 3.31(s, 2H, H_2C), 5.01(s, 1H, *H*N D_2O exchangeable), 7.01(d, 2H, *H*C pyridyl, *J*= 6.3Hz), 7.68(d, 2H, *H*C aromatic, *J*= 7.8Hz), 7.70 (d, 2H, *H*C aromatic, *J*= 3.2Hz), 8.60(d, 2H, *H*C pyridyl, *J*= 6.1Hz), 12.01(s, 1H, *H*N- D_2O exchangeable). MS (*m*/*z*, r.i.%): 291 (M^+, 100%), 213(55%), 156(12%).

2-(Benzo[*d*]thiazol-2-ylthio)-*N*-(4-chlorophenylsulfonyl)acetamide (**14a**): Yellow solid recrystallized from (DMF/EtOH), in 64% yield, m.p.=204-205°C, $C_{15}H_{11}ClN_2O_3S_3$ (398.91), Analysis% Calcd (Found): C: 45.16(45.20), H: 2.78(2.81), Cl: 8.89(8.90), N: 7.02(7.05), S: 24.11 (24.08), IR(KBr) $_{max}$/cm^{-1}: 3215(NH), 1611(C=O), 1305 (S=O). ^{1}H NMR (DMSO-d_6): δ 4.51(s, 2H, H_2C), 7.50(d, 2H, H_2C aromatic , *J*=6.1Hz), 7.63(d, 2H, *H*C aromatic, *J*=6.2Hz), 7.78(d, 2H, *H*C

aromatic, *J*= 7.5Hz), 7.85(d,1H, *H*C aromatic, *J* = 3.2Hz), 7.9(d, 1H, *H*C aromatic, *J*=1.2Hz), 12.3(s, 1H, *H*N- D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ 38.2(*C*H_2), 123(*C*H), 124(*C*H), 136.2(*C*H), 154(*C*H), 164(*C*H), 176(*C*=O), MS (*m*/*z*, r.i.%): 398(M^+, 100%), 400(M^{+2}, 31%), 223(56%), 189(7%), 179(21%).

2-(Benzo[*d*]thiazol-2-ylthio)-*N*-tosylacetamide (**14b**): Brown solid recrystallized from (DMF/EtOH) in 62% yield, m.p. =208-210°C, $C_{16}H_{14}N_2O_3S_3$ (378.49), Analysis% Calcd (Found): C: 50.78(50.80), H: 3.73(3.75), N: 7.40(7.38), S: 25.41 (25.42). IR (KBr) $_{max}$/cm^{-1}: 3303(NH), 1609(C=O), 1310 (S=O). ^1H NMR (DMSO-d_6): δ 2.37(s, 3H, H_3C), 4.49(s, 2H, H_2C), 7.39(d, 2H, H_2C aromatic , *J*= 6.1Hz), 7.63(d, 2H, *H*C aromatic, *J*=3.2Hz), 7.72(d, 2H, *H*C aromatic, *J*= 7.5Hz), 7.85(d,1H, *H*C aromatic , *J*=3.2Hz), 7.92(d, 1H, *H*C aromatic , *J*=1.2Hz), 11.89(s, 1H, *H*N- D_2O exchangeable), MS (*m*/*z*,r.i.%): 378(M^+, 100%), 223 (48%), 189(5%).

2-(Benzo[*d*]thiazol-2-ylthio)-*N*-(phenylsulfonyl) acetamide (**14c**): Reddish brown recrystallized from (EtOH/H_2O), in 59% yield, m.p.=225-226°C, $C_{15}H_{12}N_2O_3S_3$ (364.46), Analysis% Calcd (Found): C: 49.43(49.45), H: 3.32(3.30), N: 7.69(7.65), S: 26.39 (26.42). IR (KBr) $_{max}$/cm^{-1}: 3303(NH), 1609(C=O), 1310 (S=O). ^1H NMR (DMSO-d_6): δ 4.59(s, 2H, H_2C), 7.39(d, 2H, H_2C aromatic, *J*=6.1Hz), 7.55-7.68 (m, 5H, Ars*H*), 7.85(d, 1H, *H*C aromatic , *J*=1.2Hz), 7.9 (d,1H, *H*C aromatic , *J*=3.2Hz), 12.5 (s, 1H, *H*N- D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ 37.2(*C*H_2), 123 (*C*H), 124(*C*H), 136.2(*C*H), 155(*C*H), 168(*C*H), 171(*C*=O), MS (*m*/*z*,r.i.%): 364(M^+,100%), 223 (43%), 189(12%).

2-(1*H*-Benzo[*d*]imidazol-2-ylthio)-*N*-(4-chlorophenylsulfonyl)acetamide (**16a**): Yellow solid recrystallized from (EtOH/H_2O) in 61% yield, m.p.=160-161°C, $C_{15}H_{12}ClN_3O_3S_2$ (381.86), Analysis% Calcd (Found): C: 47.18(47.20), H: 3.17(3.18), Cl: 9.28(9.30), N: 11.00(10.98), S: 16.79 (16.77). IR (KBr)$_{max}$/cm^{-1}: 3350(NH), 3210 (NH), 1637(C=O), 1310 (S=O). ^1H NMR (DMSO-d_6): δ 4.53(s, 2H, H_2C), 7.11(d, 2H, *H*C aromatic, *J*=3.2Hz), 7.39(d, 2H, *H*C aromatic, *J*=7.8Hz), 7.63(d, 2H, *H*C aromatic, *J*= 7.5Hz), 7.74(d, 2H, *H*C, aromatic , *J*=7.8Hz), 11.8(s, 1H, *H*N -D_2O exchangeable), 12.2(s, 1H, *H*N imidazole D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ 38.1(*C*H_2), 115.2(*C*H), 123(*C*H), 138(*C*H), 148 (*C*H), 170 (*C*H), MS (*m*/*z*, r.i.%): 381(M^+, 100%), 383 (M^{+2}, 33%), 206 (10%), 189 (24%).

2-(1*H*-Benzo[*d*]imidazol-2-ylthio)-*N*-tosylacetamide (**16b**): Pale yellow recrystallized from (EtOH/H_2O), in 62% yield, m.p.=185-186°C, $C_{16}H_{15}N_3O_3S_2$(361.44), Analysis% Calcd (Found): C: 53.17(53.20), H: 4.18(4.15), N: 11.63(11.69), S: 17.74 (17.76). IR (KBr) $_{max}$/cm^{-1}: 3350 (NH), 3210 (NH), 1613(C=O), 1310 (S=O). ^1H NMR (DMSO-d_6): δ 2.39(s, 3H, H_3C), 7.13(d, 2H, *H*C aromatic, *J*=1.2Hz), 7.40(d, 2H, *H*C aromatic, *J*=6Hz), 7.52(d, 2H, *H*C aromatic, *J*= 6Hz), 7.68(d, 2H, *H*C aromatic, *J*= 7.8Hz), 11.8(s, 1H, *H*N- D_2O exchangeable), 12.2(s, 1H, *H*N imidazole D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ 21.3(*C*H_3), 38.2(*C*H_2), 115.2(*C*H), 123(*C*H), 138(*C*H), 148(*C*H), 170(*C*H), MS (*m*/*z*,r.i.%): 361(M^+, 100%), 206(23%), 170(6%).

2-(1H-Benzo[*d*]imidazol-2-ylthio)-*N*-(phenylsulfonyl)acetamide (**16c)**: yellow solid recrystallized from (EtOH/H_2O), in 59% yield, m.p.=187-188°C, $C_{15}H_{13}N_3O_3S_2$ (347.41), Analysis% Calcd (Found): C: 51.86(51.88), H: 3.77(3.78), N: 12.10(12.09), S: 18.46(18.49). IR (KBr) $_{max}$/cm^{-1}: 3350(NH), 3210 (NH), 1609(C=O), 1310 (S=O). ^1H NMR (DMSO-d_6): δ 4.53(s, 2H, H_2C), 7.09(d, 2H, *H*C aromatic, *J* =1.2Hz), 7.55-7.68 (m, 5H, Ars*H*), 7.74(d, 2H, *H*C, aromatic, *J* = 7.8Hz), 11.8(s, 1H, *H*N- D_2O exchangeable), 12.2(s, 1H, *H*N imidazole D_2O exchangeable). MS (*m*/*z*, r.i.%): 347(M^+, 100%), 206(33%), 156(6%).

Antimicrobial screening

Antibacterial and antifungal activities were performed at the Regional Center for Mycology and Biotechnology (RCMB), Al-Azhar University, Cairo, Egypt. Initially, the tested compounds and reference drugs were evaluated *in vitro* for their antimicrobial activity, using three fungi: A. fumigates (RCMB 02568), Syncephala strumracemosum (RCMB 05922) and Geotricum candidum (RCMB 05097), two Gram-positive bacteria: S. pneumonia (RCMB 010010) and B. subtitles (RCMB 010069), two Gram-negative bacteria: P. aeruginosa (RCMB 010043), and E. coli (RCMB 010052) and the results were

compared with respect to those of Amphotericin B, Ampicillin and Gentamicin as standard drugs. Suspension of the above-mentioned micro-organisms was prepared by inoculating fresh stock cultures into separate broth tubes, each containing 7 ml of nutrient broth (pepton, 0.3%) beef extract (0.3%). The inoculated tubes were incubated at 37 °C for 24 h. Solutions of the tested compounds and reference drugs were prepared by dissolving 0.5 mg of the compound in 10 ml DMF [27,28].

Computational method

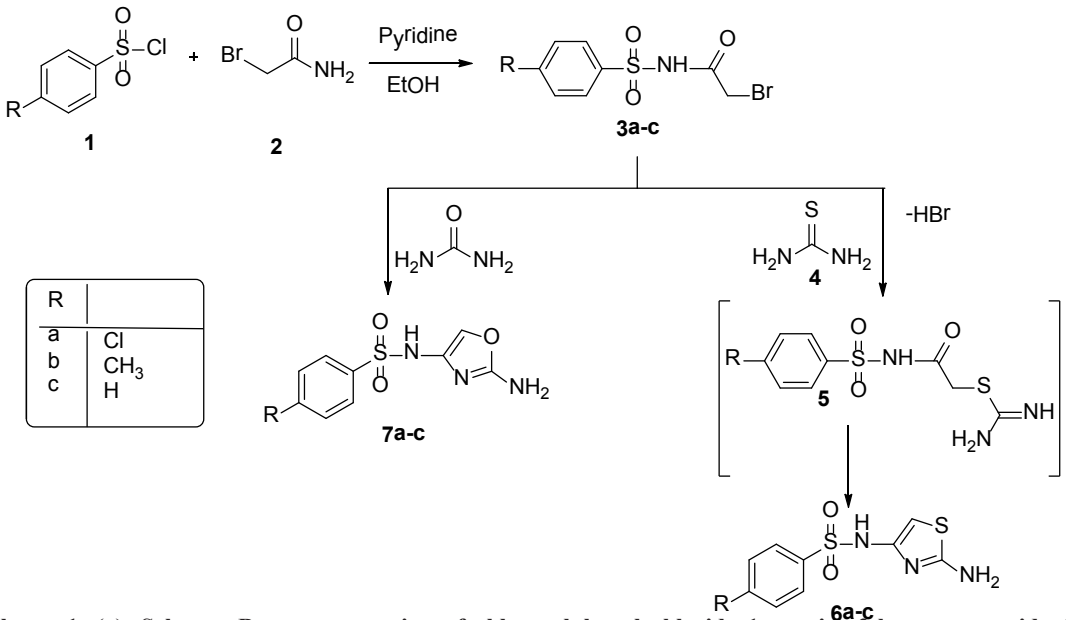
Calculations have been performed using KhoneSham's DFT and HF methods subjected to the gradient-corrected hybrid density functional B3LYP. This function is a combination of the Becke's three parameters non-local exchange potential with the non-local correlation functional of [29a-c] For each structure, a full geometry optimization was performed using this function and the 6-31G bases set as implemented by Gaussian 09 package [30]. All geometries were visualized either using Gauss View5.0.9 [31] and chemcraft1.6 53 [32]. No symmetry constrains were applied during the geometry optimization.

Results and Discussion

Chemistry

The Schotten-Baumann reaction is a method for the synthesis of amide derivatives from amines and acid chlorides [**33a,b**]. In this investigation, the reaction of benzene sulfonyl chloride derivatives **1a-c** with 2-bromoacetamide (**2)** was undertaken to afford the corresponding bromo-N-(phenylsulfonyl) acetamide derivatives **3a-c**.

The behavior of the acetamide derivatives **3a-c** towards urea derivatives was investigated. Thus, when an ethanolic solution of the bromoacetamide derivatives 3a-c was treated with the appropriate urea derivative it gave the corresponding aminothiazole derivatives **6a-c** and amino oxazole derivatives **7a-c**, respectively; (**Scheme 1**). The IR spectrum of compound **6b**, taken as a representative example; showed characteristic absorption bands at 3215 cm^{-1} due to NH function, at 3100-3025cm^{-1} due to an amino group and a strong stretching absorption band of the sulfoxide group at 1289 cm^{-1}. The ^1H NMR spectrum of the same compound revealed a singlet signal at δ 6.56 due to the thiazole proton, at δ 10.29 due to NH



Scheme 1. (a). Schotten-Baumann reaction of chlorosulphonyl chloride 1a-c with 2-bromoacetamide (2), (b) Reaction of bromo-N-(phenylsulfonyl)acetamide derivatives 3a-c with urea derivatives 4.

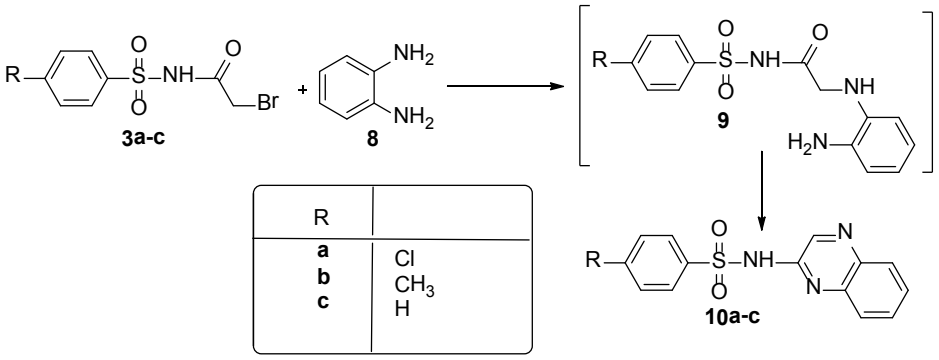
proton and at δ 4.65 (D_2O-exchangeable) due to NH_2 protons. Its mass spectrum revealed a peak at m/z 269 corresponding to its molecular ion. In the same manner; compound **7a** revealed a singlet signal at δ 7.12 due to the (oxazole-*H*C) and singlet signal at 10.25 due to NH proton. Its ^{13}C NMR spectrum showed a characteristic signal of δ CH at 126 ppm due to the oxazole ring, The IR spectrum of the same compound revealed the presence of two strong absorption bands at 3230-3125 cm^{-1} corresponding to an amino group.

Ring-forming reaction of bromo-*N*-(phenylsulfonyl) acetamide derivatives **3a-c** with nitrogen nucleophiles such as o-phenylenediamine (**8**), afforded quinazoline-2-yl derivatives **10a-c**, respectively. The reaction afforded in each case, only one isolable product as shown by TLC analysis and in different yields as depicted in **Scheme 2**.

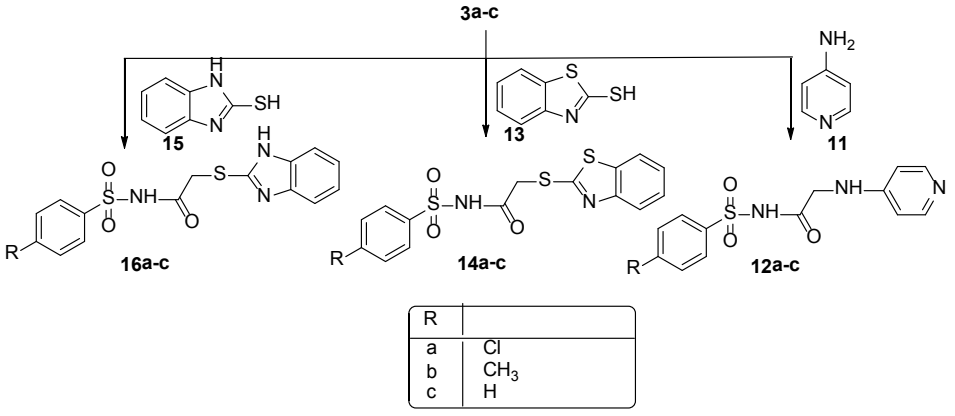
The ^1H NMR spectrum of compound **10b** displayed the singlet signal due to quinazoline ring at δ 9.48 and its mass spectrum revealed a peak at *m/z* 299 corresponding to its molecular ion (**Scheme 2**).

When compounds **3a-c** were allowed to react with 4-aminopyridine (**11**) in the presence of piperidine in ethanol they afforded the corresponding (sulfonyl)-2-(pyridine-4-acylamino)acetamide derivatives **12a-c**. The ^1H NMR spectrum of **12a** showed a signal due to the active methylene protons at δ 3.25 and signal appeared at 8.53 due to protons of pyridine moiety. Also, its ^{13}C NMR spectrum showed a signal at δ 56 due to methylene and δ 173 due to carbonyl carbon as displayed in **Scheme 3**.

The acetamide derivatives **3a-c** were reacted with benzo-2-thiol derivatives to afford the corresponding 2-(benzo[d]thiazol-2-ylthio)-N-(phenylsulfonyl)acetamide derivatives **14a-c** and 2-(1H-benzo[d]imidazol-2-ylthio)-N-(sulfonyl) acetamide **16a-c**, respectively; as shown in **Scheme 3**. For example, the IR spectrum of



Scheme 2. The reaction of bromo-N-(phenylsulfonyl)acetamide 3a-c with o-Phenylene diamine(8).



Scheme 3. The reaction of acetamides 3a-c with different nucleophiles.

compound **14c** revealed absorption bands due to NH and sulphoxide functions at 3303 (NH) and 1310 (S=O), respectively. Furthermore, its ^{1}H NMR spectrum revealed an aromatic multiplet in the region δ 7.55-7.69, in addition to singlet at δ 4.59 due to a methylene group (CH_2) and at δ12.5 ppm due to NH proton [*cf.* Experimental part] (**Scheme 3**).

Anti-Microbial Activity

The synthesized compounds were tested against inhibitory effects on the growth of *G+* and *G-* bacterial strain and three antifungal strains as displayed in **Table 1**. In this investigation, the effect of attaching different fused heterocyclic rings to the tested sulphonamide derivatives were gave antimicrobial activity. Some of the tested compounds showed higher and moderate antimicrobial activity where compare with the reference drug. It is worthy to mention that the synthesized compounds **10a**, **12a**, **14a**, and **16a** showed high activity against all types of strains due to the presence of an electron withdrawing group (Cl group). Also, the compounds **5a** and **6a** show moderate activity against all strains, Generally, sulphonamides **10a**, **12a**, **14a**, and **16a** showed better antibacterial activities due to presence the chlorine group rather than the other derivatives **10b**, **12b**, **14b** and **16b** which have methyl group (electron donating group), Also, incorporation of 2-(pyridin-4-ylamino) acetamide moiety in compound **12a** resulted in a good antibacterial activity against Gram-negative bacteria. Moreover, compound **12a** bearing substituted 2-(pyridin-4-ylamino) acetamide moiety emerged as the most active compound against Gram-positive *B. subtilis* (28.3±0.13 µg/ml $^{-1}$) and fungus *G. Candidum* (23.6±0.09 µg/ml^{-1}). On the other hand, 2-(benzo[*d*]thiazol-2-ylthio)-*N*-(4-chlorophenylsulfonyl)acetamide (**14a**) showed high activity against *S. peneumoniae* (21.3±0.26 µg/ml $^{-1}$) and *G. candidum* (23.9±0.1 µg/ml $^{-1}$).

Computational Studies

Molecular Orbital Calculations

The optimization of compound structures **12a** and **14a** utilizing Gaussian program 09[30] as displayed in (**Fig. 2**), and calculation their total energy E_T, energy of highest occupied E_{HOMO}, energy of lowest unoccupied E_{LUMO}, energy gap (E_g), dipole moment (μ), absolute electronegativities (χ), chemical potentials (Pi), absolute hardness,(η) absolute softness (σ), global electrophilicity (ω) , global softness (S), and additional electronic charge, (ΔN_{max}), were

TABLE 1. The antimicrobial activity screening of the prepared compounds at concentration 2mg/disc compared with Amphotericin B and Ampicillin and Gentamicin as reference drugs.

Sample ID	Bacillus subtitles(G+)Bs	Streptococcus peneumoniae (G+) Sp	Escherichia coli (G-)Ec	Pseudomonos aeruginosa (G-) Pa	Aspergllusflavus (Fungus) Af	Syncephalastrum racemosum (Sr)	Geotricum candidum (Gc)
6a	21.3±0.12	15.2±0.23	11.3±0.12	10.6±0.09	13.5±0.13	15.5±0.11	19.8±0.19
6b	17.2±0.26	10.2±0.29	10.02±0.11	8.9±0.12	11.4±0.14	13.6±0.13	17.6±0.21
7a	23.2±0.23	16.3±0.15	11.6±0.09	10.9±0.15	14.2±0.09	18.5±0.06	15.7±0.25
7b	15.2±0.33	12.3±0.12	9.8±0.08	9.8±0.17	11.3±0.08	11.2±0.08	12.4±0.19
10a	25.1±0.21	18.6±0.19	12.6±0.10	11.7±0.15	14.9±0.13	25.7±0.13	18.7±0.11
10b	23.2±0.19	13.2±0.11	9.63±0.09	8.1±0.19	11.3±0.14	18.2±0.11	15.6±0.19
12a	28.3±0.13	19.3±0.06	16.5±0.13	16.3±0.07	22.4 ±0.12	19.8±0.17	23.6±0.09
12b	20.23±0.18	14.6±0.12	14.3±0.16	11.8±0.09	18.7±0.14	15.3±0.19	19.7±0.04
14a	26.8±0.23	21.3±0.26	17.6±0.11	15.9±0.14	20.6±0.23	20.7±0.11	23.9±0.1
14b	20.23±0.13	13.6±0.14	13.7±0.14	10.6±0.10	15.6±0.28	19.3±0.10	20.6±0.15
16a	25.9±0.06	19.9±0.13	14.2±0.09	13.5±0.13	19.5±0.10	20.3±0.12	22.9±0.09
16b	23.3±0.18	15.6±0.10	12.5±0.04	12.8±0.11	17.3±0.11	22.5±0.15	19.2±0.15
Amphotericin B	-	-			23.7±0.1	28.7±0.2	25.4±0.1
Ampicillin	32.4±0.3	23.8±0.2	-	-	-	-	-
Gentamicin	-	-	19.9±0.3	17.3±0.1	-	-	-

The screening organisms, Mould: Gram-positive bacteria: *B. subtilis* (RCMB 010069, Bs) and *S. pneumonia* (RCMB 010010, Sp), two Gram-negative bacteria: *E. coli* (RCMB 010052, Ec) *and Neisseria gonorrhoea* (NCCP11945, Ng), Four fungi *A. fumigatus* (RCMB 02568, Af), *, Candida albicans*(RCMB 05036, Ca)*Syncephalastrumracemosum*(RCMB, 016001, *Sr*) *and Geotricum candidum*(RCMB,052006 , *Gc*),

scheduled in **Table 2** according to the following equations and optimized *via* DFT/B3LYP/6-31G(d) and HF/6-31G(d) [34]. The molecular structure of these compounds was not planar. The potential activities presented in the precursor compounds **12a** and **14a** due to an electron withdrawing group which increased their activity and gave them more stable rather than other compounds [35].

$$\Delta E = E_{LUMO} - E_{HOMO} \quad (1)$$

$$\chi = \frac{-(E_{HOMO} + E_{LUMO})}{2} \quad (2)$$

$$\eta = \frac{(E_{LUMO} - E_{HOMO})}{2} \quad (3)$$

$$\sigma = 1/\eta \quad (4)$$

$$Pi = -\chi \quad (5)$$

$$S = 1/2\,\eta \quad (6)$$

$$\omega = Pi^2/2\,\eta \quad (7)$$

$$\Delta N\ max = -Pi/\eta \quad (8)$$

From the results listed in Table **2** and Fig. **2, 3**; the following conclusions were inferred:

(1) The optimization of (sulfonyl)-2-(pyridin-4-ylamino)acetamide derivative **12a** and (4-chlorophenylsulfonyl)acetamide derivative **14a** utilizing Gaussian 09 program, indicated that the two compounds are non-planer and they are out of the plane as shown in **Figure 2.**

(2) The Energy gap (E_g) of (sulfonyl)-2-(pyridin-4-ylamino)acetamide **12a** was found to be more reactive in DFT than HF via -409.46 kcal/mol.

(3) Furthermore, the energy gap of (4-chlorophenylsulfonyl)acetamide **14a** in DFT was more stable than HF by -8.193 kcal/mol.

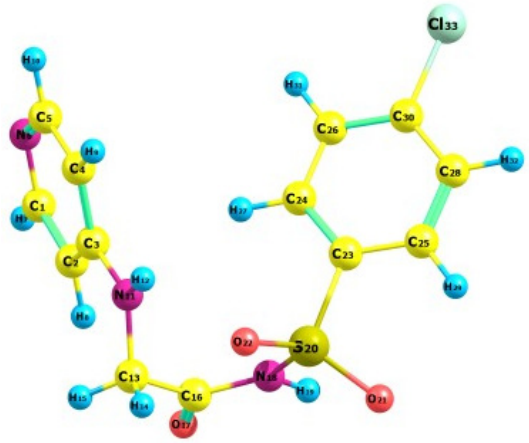
(4) The Dipole moment μ (polarity of charge) showed that the (sulfonyl)-2-(pyridin-4-ylamino)acetamide derivative **12a** is <(4-chlorophenylsulfonyl)acetamide derivative **14a** by 15.882D in DFTB3LYP/6-31G(d) function theory which indicates that dipole-dipole interaction of compound **14a** gave more strong intermolecular force for another bond.

(5) The HOMO-LUMO energy gap is considered as an important stability index which uses for explaining the structure and conformation barriers in many molecular systems. therfore (sulfonyl)-2-(pyridin-4-ylamino) acetamide **12a** and (4-chlorophenylsulfonyl) acetamide **14a** showed values ΔE_{gap}=3.53eV and 3.72934eV, respectively, utilizing DFT function theory which indicates the stability of these compounds.

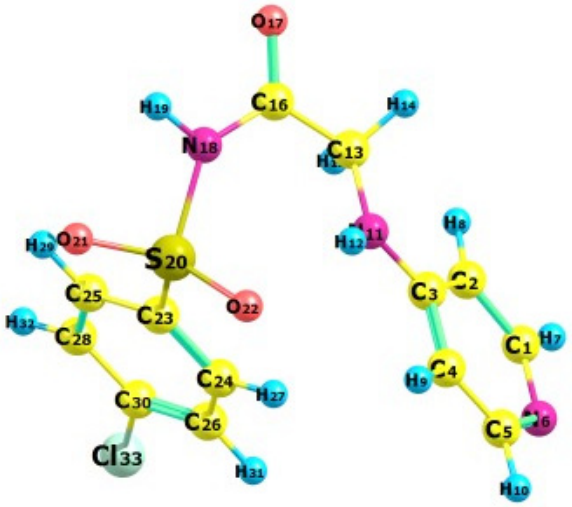
(6) Furthermore, the value of chemical potential (Pi) was negative, while the electrophilicity index (χ) had a positive value. These indicated that the sulphonamide might be the donor for electrons [36].

TABLE 2. The various quantum chemical parameters of compounds 12a and 14a utilizing DFT/B3LYP/6-31G (d) and HF/6-31G (d):

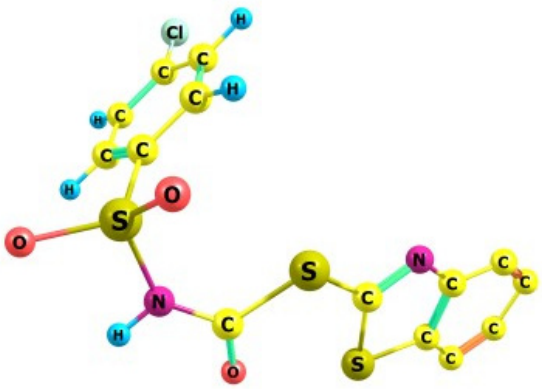
	HF/6-31G (d)	DFT B3LYP/6-31G(d)		HF/6-31G(d)	DFT B3LYP/6-31G (d)
Compound	**12a**			**14a**	
E_T (au)	-1734.91	-1750.416	E_T (au)	-2517.423	-2525.593
E_{HOMO}	-9.97433	-0.409531	E_{HOMO}	-9.962093	-0.49960
E_{LUMO}	-9.00561	-0.31619	E_{LUMO}	0.1983711	-0.374213
ΔE	0.96872	0.0343	ΔE	10.160539	3.72934
μ (Debye)	2.1261	3.0220	μ (Debye)	4.5621	4.0638
χ (eV)	9.48997	0.36286	χ (eV)	4.881861	0.8108
η(eV)	0.48436	0.046670	η(eV)	5.08026	1.86467
σ(eV)	2.064	21.4268	σ(eV)	0.19684032	0.536287
P_i(eV)	-9.48997	-0.36286	P_i(eV)	-4.8818610	--0.81083
S(eV)	1.0322	10.7134	S(eV)	0.098420	0.26814396
ω(eV)	-19.5928	1.41061	ω(eV)	606.4263	0.9323097
ΔN_{max}	19.592	7.77494	ΔN_{max}	-0.960935	0.434838



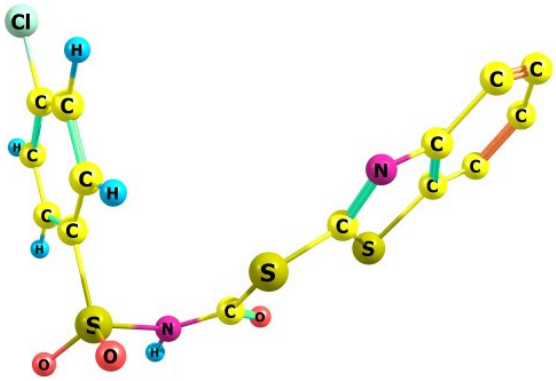
12a
HF/6-31G(d)



12 a
DFT B3LYP/6-31G(d)



14a
HF/6-31G (d)



14a
DFT B3LYP/6-31G (d)

Fig. 2. The optimized geometry, numbering system of Compound 12a and 14a in DFT/B3LYP/6-31G and HF/6-31G (d).

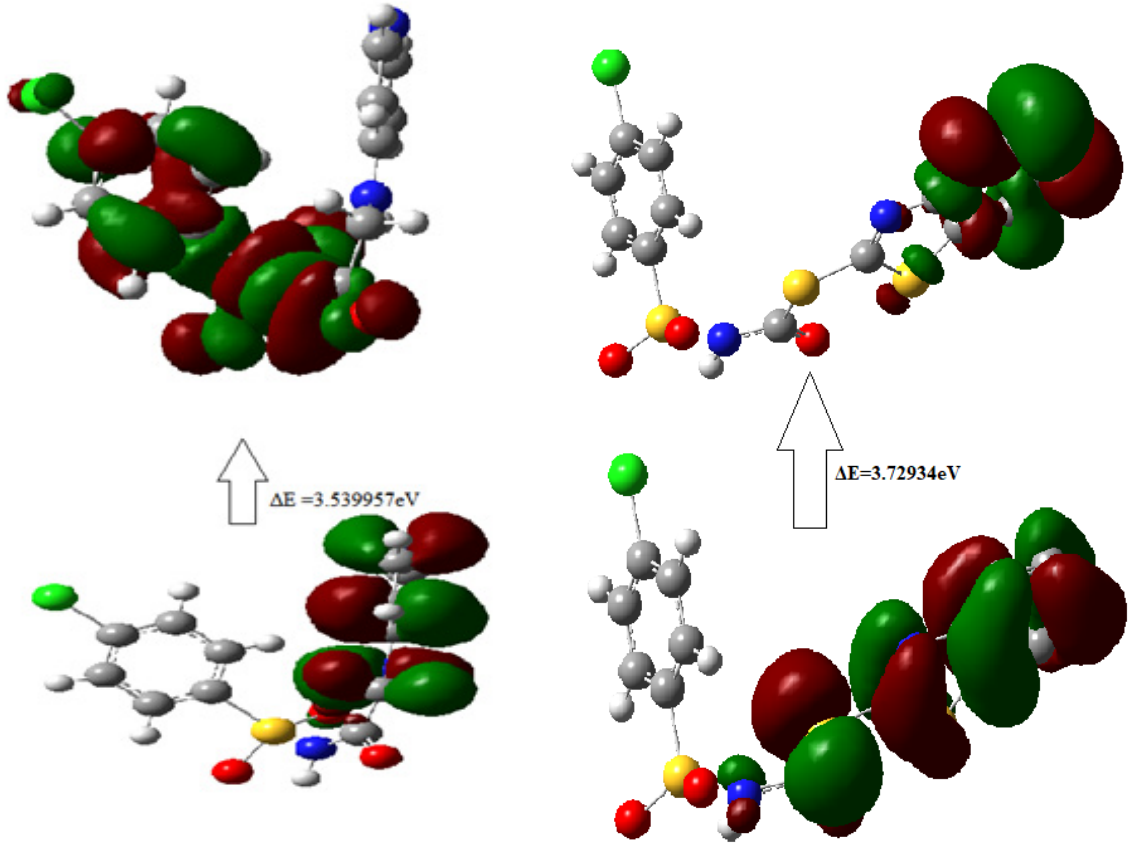


Fig. 3. Gap energy (HOMO-LUMO) (eV) calculated for compounds 12a and 14a using (TD-DFT).

Conclusion

A new series of heterocyclic compounds bearing sulfonamide moieties have been synthesized and examined for their antimicrobial activities against *G+* and *G-* bacterial strains and three antifungal strains. Particularly, the fused sulphonamides **12a** and **14a** showed high activity against most types of strains. Further studies are being conducted to acquire more information about quantitative structure-activity relationships (QSAR). Also, the characterization of compounds **12a** and **14a** using DFT/B3LYP/6-31G(d) and HF/6-31G(d) basis sets supported the stability of these compounds. The large HOMO-LUMO gap characterizes the high kinetic stability, the biological reactivity and the chemical reactivity for these compounds.

Acknowledgment

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التشييد والتقييم البيولوجى والدراسات الفيزيائية لمشتقات السلفونـاميد

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تم تحضير مشتقات السلفونـاميد الجديدة من تفاعل ٢ بروموفينيل سلفونيل أسيتاميد مع النيوكليوفيلات النيتروجينية وأدى ذلك الى العديد من المركبات العضوية غير متجانسة الحلقة مثل امينوثيازول ٤ بنزواوكسازين, امينو اوكسازول, بنزو ثيازول و بنزو ايمدازول .

بالاضافة إلى ما سبق فإنه قد تم إجـراء التقييم البيولوجي للمركبات المشـيدة الجـديدة كمضـادات للميكروبات حيث أبدت بعض المركبات نشاطا ملحوظا يقترب من فاعلية المركبات القياسية. كما أثبتت النتائج وجود علاقة بين التركيب الكيميائى للمركبات الجديدة وفاعليتها البيولوجية وقد اثبتت فعاليه هذه المركبات بدراسه الكيمياء الفيزيائيه باستخدام برنامج جاوسين لاثبات مدى فعاليتها وقدرتها على التفاعل وفرق الطاقه بين مستوياتها.