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New Cyclic Imides and Quinazolin-2,4-diones Based on 1,2,3,6-Tetrahydrophthalic anhydride: Synthesis, Semiempirical Study and *in vitro* Evaluation

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Abstract

1,2,3,6-Tetrahydrophthalic anhydride (**1**) was used as a precursor for the synthesis of new cyclic imides by reacting with several reagents such as 2-aminothiazole, 4-aminopyridine, 2-aminobenzothiazole, cyanoacetic acid hydrazide, amino guanidine, 2,2-diaminomalononitrile, hexamethylenediamine or 2-(amino-ethyldisulfanyl)-ethylamine where the corresponding cyclic imides **2-9** were obtained respectively. Similarly, a series of tetrahydroquinazolin-2,4-diones **11-20** have been synthesized from the reaction of 2-phenylsulphonyloxy-3a,4,7,7a-tetrahydroisoindol-1,3-dione **10** with different amino compounds as hetero-amines, amino acids and diamines. The proposed structures of the synthesized compounds were supported by their elemental and spectral analyses as well as their semiempirical **MOPAC** calculations. Semiempirical **MOPAC** calculations have been also performed to uncover the fundamental reaction pathway of the anhydride **1** with 4-aminopyridine as a model reaction and compound **10** with different amino compounds. The in vitro study of some selected imides and quinazolin-2,4-dinoes against two strains of bacteria possesses a high inhibition effect.

Keywords: Cyclic imides, anhydride, quinazolinones, semiempirical, diamines, bisamide.

1. Introduction

Bisamide linkages in cyclic imides with a general structure of [-CO-N(R)-CO-], are essential building blocks for the synthesis of heterocyclic compounds that have distinct pharmacophores and possess privileged biological properties such as antibacterial, antifungal, antiviral [1-3], anticancer [4,5], antinociceptive [6], analgesic [7], anti-inflammatory [8], anxiolytic activities [9]. Many quinazolinone derivatives possess a wide range of bioactivities such as antibacterial [10,11], anti-inflammatory [12], anticancer [13], anticonvulsant [14] and antiviral [15] activities. Also, various quinazoline derivatives such as an Alfuzosin, which consider as an α-adrenergic blocker for benign prostatic hyperplasia treatment, a chemotherapy drug Raltitrexed (Tomudex®) used to treat bowel cancer and dacomitinib which is used in the treatment of metastatic non-small cell lung cancer.

The semiempirical calculations provided good accuracy for the computation of molecular structure, energies and vibrational frequencies of chemical reactions [16-19]. Besides the total electronic energies (E), the highest occupied molecule orbital (HOMO), the lowest unoccupied molecule orbital (LUMO), gap energy difference between E_{HOMO} and E_{LUMO} (ΔE_{gap}), dipole moments (μ) chemical hardness (η) and softness (σ) [20,21]. Thus, the newly synthesized cyclic imide and quinazolin-2,4-dione derivatives starting from 1,2,3,6-tetrahydrophthalic anhydride **1** aim in increasing the biological activity materials for further development, considering the fact that small modifications of the chemical structure of a molecule can lead to the improvement the biological activity. Moreover, modeling techniques were performed for the synthesized compounds to understand their reactivity and stability and to investigate the mechanism of these reactions.

2. Experimental Section

2.1 Chemistry

Experimental Instrumentation

The starting material **1**, reagents and solvents were purchased from Across organics and used without further purification. Melting points (uncorrected) were recorded on an Electrothermal melting apparatus. The IR spectra were recorded on (Shimadzu 408 spectrometer using KBr pellet technique). The ^{1}H-NMR and ^{13}C-NMR spectra were

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determined in *DMSO-d_6* on a Varian AVANCE-III 400 MHz High-Performance FT-NMR Spectrum BRUKER, Bios pen International AG-Switzerland. Chemical shifts are reported in parts per million and are given in δ units. Electron impact mass spectra were obtained at 70 eV using (HP Model, MS 5988 JEOL JMS600, and AmD 402/3 mass spectrometers at ionization energy 70 eV). Elemental analyses were carried out at the microanalytical Center at Cairo University.

Reaction of 1,2,3,6-tetrahydrophthalic anhydride (1) with different amines: General procedure.

A mixture of 1,2,3,6-tetrahydrophthalic anhydride **1** (1.52 g, 10 mmol) and appropriate amines, namely, 2-aminothiazole, 4-aminopyridine, 2-aminobenzothiazole cyanoacetic acid hydrazide(10 mmol) and/or aminoguanidine (5 mmol) in glacial acetic acid (50 mL) was refluxed for 3 h. After cooling, the solid formed was filtered off and crystallized from ethanol to give the corresponding products **2-6**, respectively.

6-(Thiazol-2-ylcarbamoyl)cyclohex-3-ene-1-carboxylic acid (2). Yield 70%, yellow crystals (Acetic acid), mp 116–118°C; IR (KBr) v/cm^{-1}: 1680 (C=O's), 2970, 2910, 2850 (CH_2), 3250 (NH), 3300 (COOH). ^{1}H NMR (400 MHz), DMSO-*d_6*, δ (ppm): 2.12-2.30 (m, 2H, 2CH), 2.45-2.57 (m, 2H, 2CH), 2.79-2.94 (m, 2H, 2CH), 5.68 (t, 2H, CH=CH), 7.15 (d, 1H, SCH), 7.45 (d, 1H, NCH), 8.99 (s, 1H, NH, D_2O, exchangeable), 12.12 (s, 1H, COOH). Mass spectrum (EI, 70 eV), *m/z*: 252 [M]$^+$, 207, 100, 79, 45. Anal. calcd. for $C_{11}H_{12}N_2O_3S$: C 52.37; H 4.79; N 11.10; S 12.71. Found: C, 52.59; H 4.77; N 10.95; S 12.67.

2-Pyridin-4-yl-3a,4,7,7a-tetrahydroisoindol-1,3-dione (3). Yield 87%, pale brown crystals (Methanol), mp 180–182°C; IR (KBr) v/cm^{-1}: 1730 (C=O's), 2900, 2830 (CH_2). ^{1}H NMR (400 MHz), DMSO-*d_6*, δ (ppm): 2.19-2.31 (m, 2H, 2CH), 2.47-2.55 (m, 2H, 2CH), 3.35-2.45 (m, 2H, 2CH), 5.95 (t, 2H, CH=CH), 7.37 (d, 2H, Py-H), 7.70 (d, 2H, Py-H). ^{13}C NMR (100 MHz), DMSO-*d_6*, δ(ppm): 23.02 ($2CH_2$), 38.94 (2CH), 120.78, 139.71, 150.63 (pyridine-C), 127.73 (CH=CH), 178.63 (2C=O). Anal. calcd. for $C_{13}H_{12}N_2O_2$: C 68.41; H 5.30; N 12.27. Found: C 68.76; H 5.27; N 11.95.

2-Benzothiazol-2-*yl*-3a,4,7,7a-tetrahydroisoindole-1,3-dione (4). Yield 91 %, white crystals (Petroleum ether 60-80), mp 278–280°C. IR (KBr) v/cm^{-1}: 1720 (C=O's), 2995, 2950 (CH_2). ^{1}H NMR (400 MHz), DMSO-*d_6*, δ (ppm): 2.33-3.39 (m, 2H, 2CH), 2.44-2.61 (m, 2H, 2CH), 3.06-3.17 (m, 2H, 2CH), 5.68 (t, 2H, CH=CH), 7.27-7.95 (m, 4H, arom-H). Anal. calcd. for $C_{15}H_{12}N_2O_2S$: C 63.36; H 4.25; N 9.85; S 11.28. Found: C 63.16; H 4.32; N 9.83; S 11.44.

2-Cyano-*N*-(1,3-dioxo-1,3,3a,4,7,7a-hexahydroisoindol-2-*yl*)-acetamide (5). Yield 68%, yellow crystals (Acetic acid), mp 230–232°C. IR (KBr) v/cm^{-1}: 3270 (NH), 2980,2800 (CH_2), 2250 (CN), 1670 (C=O's). ^{1}H NMR (400 MHz), DMSO-*d_6*, δ (ppm): 2.26-2.30 (m, 2H, 2CH), 2.35-2.44 (m, 2H, 2CH), 3.29-3.42 (m, 2H, 2CH), 3.91 (s, 2H, CH_2), 5.89 (t, 2H, 2CH=CH), 11.91 (s, H, NH, D_2O, exchangeable). Mass spectrum (EI, 70 eV), *m/z*:233 [M]$^+$, 207, 150, 108, 79. Anal. calcd. for $C_{11}H_{11}N_3O_3$: C 56.65; H 4.75; N 18.02. Found: C 56.58; H 4.94; N 17.87.

***N*-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2H-isoindol-2-*yl*)-1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindole-2-carboximidamide (6).** Yield 81%, reddish brown crystals (Acetic acid), mp 126–128°C. IR (KBr) v/cm^{-1}: 3390 (NH's), 3000, 2890 (CH_2), 1690 (C=O's). ^{1}H NMR (400 MHz), DMSO-*d_6*, δ (ppm): 2.05-2.14 (m, 4H, 4CH), 2.22-2.37 (m, 4H, 4CH), 3.08-3.18 (m, 4H, 4CH), 5.88 (t, 4H, 2CH=CH), 11.03 (s, 2H, 2NH, D_2O, exchangable). Mass spectrum (EI, 70 eV), *m/z*: 342 [M]$^+$, 326, 309, 279, 185. Anal. calcd. for $C_{17}H_{18}N_4O_4$: C 59.64; H 5.30; N 16.37. Found: C 59.55; H 5.18; N 16.58.

Reaction of 1,2,3,6-tetrahydrophthalic anhydride (1) with different diamines: General procedure.

A mixture of the anhydride **1** (1.52 g, 10 mmol) and appropriate diamines, namely, 2,2-diaminomalononitrile, hexamethylenediamine, and/or 2-(amino-ethyldisulfanyl)-ethylamine (20 mmol) in glacial acetic acid (50 mL) was refluxed for 3 h. After cooling, the solid formed was filtered off and crystallized from ethanol to give the corresponding products **7-9**, respectively.

2-Amino-2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydroisoindol-2-*yl*)-malononitrile (7). Yield 70%, white crystals (Ethanol), mp 202–204°C. IR (KBr) v/cm^{-1}: 3290,3200 (NH_2), 2990, 2800 (CH_2), 2220 (CN), 1720, 1700 (C=O's). ^{1}H NMR (400 MHz), DMSO-*d_6*, δ (ppm): 2.12-2.28 (m, 2H, 2CH), 2.39-2.43 (m, 2H, 2CH), 2.73-2.88 (m, 2H, 2CH), 4.40 (s, 2H, NH_2, D_2O, exchangeable), 5.62 (t, 2H, 2CH=CH). Anal. calcd. for $C_{11}H_{10}N_4O_2$: C 57.39; H 4.38; N 24.34. Found: C 57.36; H 4.57; N 24.17.

1,6-Bis(2-hexyl)-3a,47,7a-tetrahydroisoindole-1,3-dione (8). Yield 75%, yellow crystals (Acetic acid), mp 138–140°C. IR (KBr) v/cm^{-1}: 2920, 2870 (CH_2), 1680, 1660 (C=O's). ^{1}H NMR (400 MHz), DMSO-*d_6*, δ (ppm): 1.15-1.25 (m, 4H, $2CH_2$), 1.38-1.46 (m, 4H, $2CH_2$), 2.05-2.16 (m, 4H, 4CH), 2.37-2.48 (m, 4H, 4CH), 3.04-3.12 (m, 4H, 4CH), 3.31 (m, 4H, $2CH_2$), 5.85 (t, 4H, 2CH=CH). ^{13}C NMR (100 MHz), DMSO, δ(ppm): 23.18, 25.46, 26.91, 38.48 (10CH2), 37.87 (4CH), 127.75 (2CH=CH), 180.08 (4C=O). Mass spectrum (EI, 70 eV), m/z:384 [M]$^+$, 239, 210,

122, 66. Anal. calcd. for $C_{22}H_{28}N_2O_4$: C 68.73; H 7.34; N 7.29. Found: C 68.59; H 7.32; N 7.40.

2,2-Bis(2-ethyldisulfanylethyl)-3a,4,7,7a-tetrahydroisoindol 1,3-dione (9). Yield 69%, white crystals (Benzene), mp over 300°C. IR (KBr) v/cm^{-1}: 3050,3000, 2880 (CH_2), 1680, 1670 (C=O's). ^{1}H NMR (400 MHz), DMSO-*d*$_6$, δ (ppm): 2.09-2.19 (m, 4H, 4CH), 2.31-2.40 (m, 4H, 4CH), 2.70-2.85 (m, 4H, 2SCH$_2$), 3.04-3.13 (m, 4H, 4CH), 3.64-3.76 (m, 4H, 2NCH$_2$), 5.86 (t, 4H, 2CH=CH). ^{13}C NMR (100 MHz), DMSO-*d*$_6$, δ(ppm): 19.00 (4CH2), 34.55 (2CH2S), 37.22 (2CH2-N), 38.47 (4CH), 127.64 (2CH=CH), 179.83 (4C=O). Mass spectrum (EI, 70 eV), *m/z*: 420 [M]$^+$, 312, 362, 178, 105. Anal. calcd. for $C_{20}H_{24}N_2O_4S_2$: C 57.12; H 5.75; N 6.66; S 15.25. Found: C 57.17; H 5.76; N 6.81; S 15.04.

2-Phenylsulphonyloxy-3a,4,7,7a-tetrahydroisoindol-1,3-dione (10).

2-phenylsulphonyloxy-3a,4,7,7a-tetrahydroisoindol-1,3-dione **(10)** was prepared from 1,2,3,6-tetrahydrophthalic anhydride (**1**) according to N. F. Aly *et al* method [22,23].

Reaction of 2-phenylsulphonyloxy-3a,4,7,7a-tetrahydroisoindol-1,3-dione (10) with hetero-amines: General procedure.

A mixture of 2-phenylsulphonyloxy-3a,4,7,7a-tetrahydroisoindol-1,3-dione **(10)** (1.53 g, 5 mmol) and appropriate hetero-amine namely 4-aminopyridine and/or 2-aminobenzothiazole (5 mmol) in dry toluene 50 ml was refluxed for 6 h. After cooling, the solid formed was filtered off and crystallized from toluene to give tetrahydroquinazolines **11** and/or **12** as white crystals, respectively.

4-Hydroxy-3-pyridin-4-yl-3,4,5,8-tetrahydro-1*H*-quinazolin-2-one (11). Yield 75%, white crystals, mp 180–182°C. IR (KBr) v/cm^{-1}: 3230 (NH), 2960, 2820 (CH_2), 1700 (C=O's) cm^{-1} .^{1}H NMR (400 MHz), DMSO-*d*$_6$, δ (ppm): 2.89 (s, 4H, 2CH$_2$), 5.68-5.80 (two dd, 2H, CH=CH), 6.92 (s, 1H, CH), 7.56 (d, 2H, Py-H), 8.44 (d, 2H, Py-H), 10.53 (s, 1H, NH, D_2O, exchangeable), 10.90 (s, 1H, NH). ^{13}C NMR (100 MHz), DMSO-*d*$_6$, δ(ppm): 24.31, 26.49 (2CH$_2$), 113.79, 150.44, 169.22 (pyridine-C), 122.42, 123.80 (CH=CH), 128.37, 129.00 (CH=CH), 144.66, 151.22, (2C=O). Anal. calcd. for $C_{13}H_{13}N_3O_2$: C 64.19; H 5.39; N 17.27. Found: C 64.08; H 5.59; N 17.18.

3-Benzothiazol-2-yl-4-hydroxy-3,4,5,8-tetrahydro-1*H*-quinazolin-2-one (12). Yield 80%, white crystals, mp 250–252°C. IR (KBr) v/cm^{-1}: 3300 (NH), 2950, 2900 (CH_2), 1690 (C=O's). ^{1}H NMR (400 MHz), DMSO-*d*$_6$, δ (ppm): 2.92 (s, 4H, 2CH$_2$), 5.69-5.82 (two dd, 2H, CH=CH), 6.97 (s, 1H, CH), 7.31-7.79 (m, 4H, arom-H), 10.96 (s, 1H, NH, D_2O, exchangeable), 11.98 (s, 1H, OH). ^{13}C NMR (100 MHz), DMSO-*d*$_6$, δ(ppm): 24.29, 26.53 (2CH$_2$), 120.68, 121.7, 122.35, 123.68 (2CH=CH), 126.26, 128.70, 129.01, 131.84, 136.01, 148.75 (Ar-c), 151.09 (C=N), 157.28, 169.35 (2C=O). Mass spectrum (EI, 70 eV), *m/z*: 299 [M]$^+$, 177, 150, 105, 77. Anal. calcd. for $C_{15}H_{13}N_3O_2S$: C 60.19; H 4.38; N 14.04; S 10.71. Found: C 60.28; H 4.36; N 13.88; S 10.79.

Reaction of 2-phenylsulphonyloxy-3a,4,7,7a-tetrahydroisoindol-1,3-dione (10) with 1,4-diaminopiprazine hydrochloride: Synthesis of 1,4-bis[3-piperazin-1-yl-4a,5,8,8a-tetrahydro-1H-quinazoline-2,4-dione] (13).

A mixture of 2-phenylsulphonyloxy-3a,4,7,7a-tetrahydroisoindol-1,3-dione **(10)** (1.53 g, 5 mmol) and 1,4-diaminopiprazine hydrochloride (0.38 gm, 2.5 mmol) in pyridine 10 ml was refluxed for 2 h. After cooling the reaction mixture was poured onto dilute hydrochloric acid. The precipitate was formed, filtered off and crystallized from ethanol to give **13**. Yield 68%, pale brown crystals, mp 270-272°C. IR (KBr) v/cm^{-1}: 3250 (NH), 2900, 2850 (CH_2), 1710, 1695 (C=O's). ^{1}H NMR (400 MHz), DMSO-*d*$_6$, δ (ppm): 2.23-3.23 (m, 8H, 4CH$_2$), 3.32 (m, 2H, 2H), 3.80 (m, 2H, 2H), 5.77– 5.85 (two dd, 4H, 2CH=CH), 7.46 (m, 4H, 4H$_{axial}$), 8.05 (m, 4H, 4H$_{equatorial}$), 8.20 (s, 2H, 2NH, D_2O, exchangeable). Mass spectrum (EI, 70 eV), *m/z*: 414 [M]$^+$, 271, 231, 177, 140. Anal. calcd. for $C_{20}H_{26}N_6O_4$: C 57.96; H 6.32; N 20.28. Found: C 57.89; H 6.42; N 20.25.

Reaction of 2-phenylsulphonyloxy-3a,4,7,7a-tetrahydroisoindol-1,3-dione (10) with glycine and *DL*-Alanine: General procedure.

A mixture of 2-phenylsulphonyloxy **(10)** (1.53 g, 5 mmol) and an amino acid such as glycine and/or *DL*-Alanine (5 mmol) in glacial acetic acid 30 ml in presence of anhydrous sodium acetate (0.41 gm, 5 mmol) was refluxed for 4 h. After cooling, the solid formed was filtered off and crystallized from petroleum ether 60-80 to give **14** and/or **15**, respectively.

(4-Hydroxy-2-oxo-1,4,5,8-tetrahydro-2*H*-quinazolin-3-yl)-acetic acid (14). Yield 74%, white crystals, mp 240–242°C. IR (KBr) v/cm^{-1}: 3350 (COOH), 3300 (NH), 3200, 2800 (CH_2), 1750, 1690 (C=O's). ^{1}H NMR (400 MHz), DMSO-*d*$_6$, δ (ppm): 2.91 (s, 4H, 2CH$_2$), 3.91 (s, 2H, NCH$_2$), 5.67-5.79 (two dd, 2H, CH=CH), 6.89 (s, 1H, CH), 8.79 (s, 1H, NH, D_2O, exchangeable), 10.19 (s, 1H, NH), 12.61 (s, 1H, COOH). ^{13}C NMR (100 MHz), DMSO-*d*$_6$, δ(ppm): 24.00, 26.00 (2CH$_2$), 41.43 (N-CH$_2$), 122.49, 123.91 (C=C), 129.26, 133.96 (CH=CH), 153.78, 168.79 (2C=O), 171.23 (COOH). Anal. calcd. For $C_{10}H_{12}N_2O_4$: C 53.57; H 5.38; N 12.49. Found: C 53.73; H 5.36; N 12.30:

2-(4-Hydroxy-2-oxo-1,4,5,8-tetrahydro-2H-quinazolin-3-yl) propanoic acid (15). Yield 88%,

pale red crystals (ethanol), mp 250–252°C. IR (KBr) v/cm^{-1}: 3300 (COOH), 3250 (NH), 2950, 2900(CH_3, CH_2), 1790, 1710 cm^{-1} for (C=O's). ^{1}H NMR (400 MHz), DMSO-d_6, δ (ppm): 2.85 (s, 4H, $2CH_2$), 4.33 (q, 1H, CH), 5.66-5.78 (two dd, 2H, CH=CH), 6.82 (s, 1H, CH), 8.91 (s, 1H, NH, D_2O, exchangable), 10.09 (s, 1H, OH), 12.78 (s, 1H, COOH). Anal. calcd. for $C_{11}H_{14}N_2O_4$: C 55.45; 5.92; N 11.76. Found: C 55.23; H 5.95; N, 11.96.

Reaction of 2-phenylsulphonyloxy-3a,4,7,7a-tetrahydroisoindol-1,3-dione (10) with aliphatic diamines: General procedure.

A mixture of compound **10** (1.53 g, 5 mmol) and aliphatic diamine such as hexamethylenediamine and/or 2-(amino-ethyldisulfanyl)-ethylamine (2.5 mmol) in dry toluene was refluxed for 5-6 h. After cooling, the solid formed was crystallized from benzene to give the product **16** and/or **17** as pale yellow crystals, respectively.

1,6-Bis(3-hexyl-4-hydroxy-3,4,5,8-tetrahydro-1*H*-quinazoline-2-one (16). Yield 76%, yellow crystals, mp 174–176°C. IR (KBr) v/cm^{-1}: 3330 (NH), 2980, 2910 (CH_2), 1695 (C=O's). ^{1}H NMR (400 MHz), DMSO-d_6, δ (ppm): 1.27-1.50 (m, 8H, $4CH_2$), 2.84 (s, 8H, $4CH_2$), 3.19-3.27 (m, 4H, $2CH_2$), 5.65-5.77 (two dd, 4H, 2CH=CH), 6.79 (s, 2H, 2CH), 8.50 (s, 2H, 2NH, D_2O, exchangeable), 9.88 (s, 2H, 2OH). Anal. calcd. for $C_{22}H_{30}N_4O_4$: C, 63.75; H 7.30; N 13.52. Found: C 63.55; H 7.44; N 13.57.

2,2-Bis[3-(2-ethyldisulfanylethyl)-4-hydroxy-3,4,5,8-tetrahydro-1*H*-quinazoline-2-one] (17). Yield 72 **%,** white crystals, mp 108–110°C. IR (KBr) v/cm^{-1}: 3250 (NH), 2950, 2850 (CH_2), 1720 (C=O's). ^{1}H NMR (400 MHz), DMSO-d_6, δ (ppm): 2.61 (s, 8H, $4CH_2$), 2.87 (t, 4H, $2SCH_2$), 3.28 (t, 4H, $2NCH_2$), 5.61-5.78 (two dd, 4H, 2CH=CH), 6.90 (s, 2H, 2CH), 7.97 (s, 2H, 2NH, D_2O, exchangable), 8.65 (s, 2H, 2OH). Anal. calcd. for $C_{20}H_{26}N_4O_4S_2$: C 53.33; H 5.82; N 12.44; S 14.24. Found: C 53.31; H 5.76; N 12.41; S 14.23.

Reaction of 2-phenylsulphonyloxy-3a,4,7,7a-tetrahydroisoindol-1,3-dione (10) with diaminomalononitrile and 3,4-diaminobenzoic acid: General procedure.

A mixture of compound **10** (1.53 g, 5 mmole) and a proper diamine such as diaminomalononitrile and/or 3,4-diaminobenzoic acid (2.5 mmol) in glacial acetic acid 30 ml in presence of anhydrous sodium acetate (0.41 gm, 5 mmol) was refluxed for 4 h. After cooling, the solid formed was crystallized from acetic acid to give **18** and/or **19**, respectively.

synthesis of new imides and tetrahydroquinazoline derivatives starting with 1,2,3,6-tetrahydrophthalic anhydride (**1**) and 2-phenylsulphonyloxy-3a,4,7,7a-tetrahydro-isoindol-1,3-dione (**10**). Condensation of

3-Amino-2-imino-5-oxo-2,3,6,7,10,10b-hexahydro-5*H*-oxazolo[3,2-c]quinazoline-3-carbonitrile (18). Yield 79%, white crystals, mp 274–276°C. IR (KBr) v/cm^{-1}: 3400-3200 (NH's), 2850 (CH_2), 2230 (CN), 1740 (C=O). ^{1}H NMR (400 MHz), DMSO-d_6, δ (ppm): 2.91 (s, 4H, $2CH_2$), 5.69-5.82 (two dd, 2H, CH=CH), 6.90 (s, 2H, NH_2, D_2O, exchangeable), 7.58 (s, 1H, CH), 8.61 (s, 1H, NH, D_2O, exchangeable), 9.11 (s, 1H, NH, D_2O, exchangeable). Mass spectrum (EI, 70 eV), *m*/*z*: 245 [M]$^+$, 219, 203, 177, 121. Anal. calcd. for $C_{11}H_{11}N_5O_2$: C 53.87; H 4.52; N 28.56. Found: C, 53.89; H, 4.51; N, 28.55.

12-Oxo-1,4,4a,6,12,12a-hexahydrobenzo[4,5]imidazo[2,1-b]quinazoline-9-carboxylic acid (19). Yield 81%**,** yellow crystals, mp over 300°C. IR (KBr) v/cm^{-1}: 3250 (COOH), 3220 (NH), 1710 (C=O's). ^{1}H NMR (400 MHz), DMSO-d_6, δ (ppm): 2.21-2.90 (m, 4H, $2CH_2$), 3.25-3.41 (m, 1H, H), 3.66-3.80 (m, 1H, H), 5.76 – 5.81 (two dd, 2H, CH=CH), 7.73-8.51 (m, 3H, arom-H), 8.67 (s, 1H, NH, D_2O, exchangeable), 12.72-12.82 (broad band, 1H, COOH). ^{13}C NMR (100 MHz), DMSO-d_6, δ(ppm): 26.09 (CH_2), 30.19 (CH_2), 35.04 (CH), 49.82 (CH), 115.53, 118.84 (CH=CH), 124.19, 124.87, 125.45, 126.26, 131.58, 145.92(Ar-C), 149.15 (C=N), 157.24 (COOH), 167.48 (N-C=O). Mass spectrum (EI, 70 eV), *m*/*z*: 283 [M]$^+$, 238, 198, 169, 105. Anal. calcd. for $C_{15}H_{13}N_3O_3$: C 63.60; H 4.63; N 14.83. Found: C, 63.45; H 4.64; N 14.97.

Synthesis of 4-hydroxy-2-oxo-1,4,5,8-tetrahydro-2*H*-quinazolin-3-carboxylic acid amide (20):

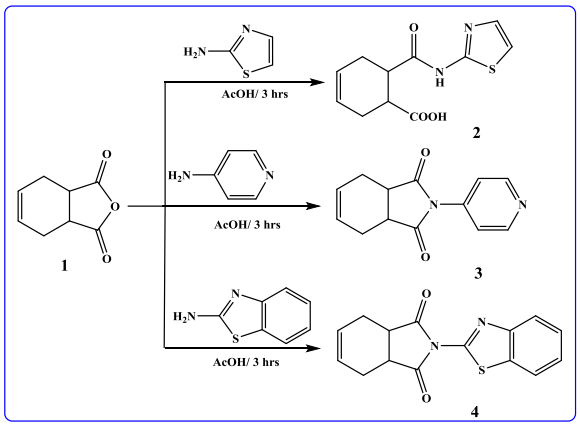
A mixture of the phenylsulphonyloxy **10** (1.53 gm, 5 mmol) and urea (0.3 g, 5 mmol) in dry toluene 10 ml was refluxed for 6 h**.** After cooling, the solid formed was crystallized from ethanol to give the product **20** as greenish white crystals. Yield 77%, white crystals, mp 184–186°C. IR (KBr) v/cm^{-1}: 3250-3150 (NH's), 2910 (CH_2), 1690, 1670 (C=O's). ^{1}H NMR (400 MHz), $CDCl_3$, δ (ppm): 2.81 (s, 4H, $2CH_2$), 5.52 (s, 2H, NH_2), 5.88-5.94 (two dd, 2H, CH=CH), 6.89 (s, 1H, CH), 8.13 (s, 1H, NH, D_2O, exchangeable), 9.23 (s, 1H, OH). Mass spectrum (EI, 70 eV), *m*/*z*: 209 [M]$^+$, 193, 165, 107, 77. Anal. calcd. for $C_9H_{11}N_3O_3$: C, 51.67; H, 5.30; N, 20.09. Found: C 51.77; H 5.28; N 20.01.

3. Results and Discussion

3.1 Chemistry

In continuation of our previous work in the synthesis of heterocyclic nitrogen compounds from anhydrides [24-26], we herein reported a detailed account for the the anhydride **1** with different heteroamines such as 2-aminothiazole, 4-aminopyridine and 2-aminobenzothiazole in acetic acid afforded the corresponding 6-(thiazol-2-ylcarbamoyl)cyclohex-3-

ene-1-carboxylic acid (**2)** and the tetrahydro-isoindol-1,3-dione derivatives **3** and/or **4**, respectively, **Scheme 1**.

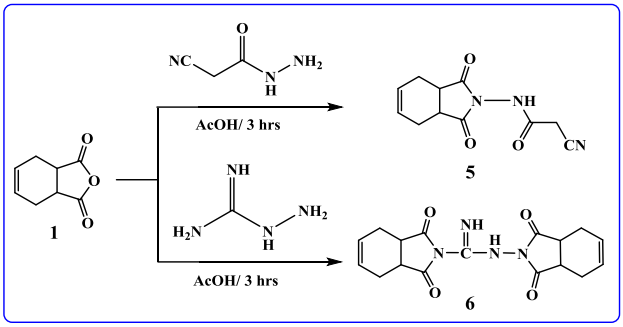


Scheme 1. The reaction of the anhydride 1 with different heteroamines.

Structures of compounds **2-4** were established on the basis of their elemental and spectral data. ^{1}H-NMR spectrum of the imide **2** indicates the presence of three multiplets at δ 2.12, 2.45 and δ 2.79 for 6 protons of the cyclohexene ring plus triplet at δ 5.68 (2H, CH=CH), doublet at δ 7.15 (1H, SCH), doublet at δ 7.45 (1H, NCH), δ 9.00 (1H, NH) and the carboxylic proton at δ12.12 ppm. The ^{13}C-NMR spectrum of **2** and **3** showed eleven and fourteen signals corresponding to their different carbons, respectively.

It's worth mentioning that the expected cyclic imide in the case of compound **2** was not formed as a result of the weak basic character of the secondary amine in the group of CONH thiazole due to the delocalization of the nitrogen electrons in this group.

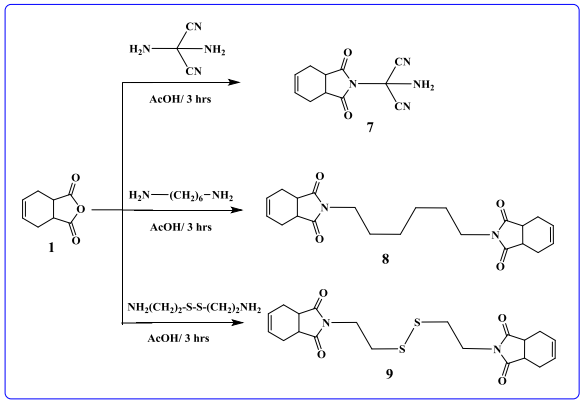
Moreover, the cyanoacetic acid hydrazide and/or the aminoguanidine were condensed with the anhydride **1** in hot glacial acetic acid to produce the corresponding 2-cyano-acetamide **5** and/or the carboxamidine **6,** respectively.



Scheme 2. The reaction of the anhydride 1 with hydrazino reagents

The mass spectra of **5** and **6** gave molecular ion peaks at 233 and 342 which correspond to their molecular formulae $C_{11}H_{11}N_3O_3$ and $C_{17}H_{18}N_4O_4$, respectively (**Scheme 2)**.

Additionally, under the above-mentioned experimental condition, different diamines named 2,2-diaminomalononitrile, hexamethylenediamine or 2-(amino-ethyldisulfanyl)-ethylamine were chosen to react with the target anhydride **1** in (2:1) molar ratio, the assigned imides **7-9** could be gained, respectively with good yields as shown in **Scheme 3**. The ^{1}H-NMR indicates the presence of a singlet at δ 4.40 for the NH_2 group for compound **7**; twelve protons of six methylene groups at δ 1.15, 1.38, and δ 3.31 ppm for compound **8,** and multiplet eight protons of four methylene groups at 2.70-2.85 (4H, $2SCH_2$) and 3.64-2.76 (4H, $2NCH_2$) for compound **9**. The mass spectra and the ^{13}C NMR of **8** and **9** give more evidence for the proposed structure (Experimental Section).

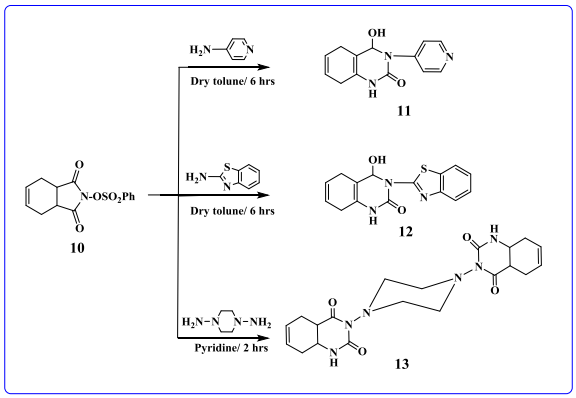


Scheme 3. The reaction of the anhydride 1 with different diamines

As it is clear that the reaction of diaminemalononitrile with compound **1** did not give a bis-product like the other diamino-compounds, this may be due to the presence of the two cyano groups in the structure of compound **7**, which are electron-withdrawing groups, which reduce the nucleophilicity of the second amino group and cause a steric hindrance that prevents the nucleophilic attack to any carbonyl of another anhydride molecule.

The high potency of quinazolinones as bioactive agents was our motivation to synthesize new derivatives of these rings in continuation with our previous work [26]. Thus, 2-phenylsulphonyloxy-3a,4,7,7a-tetrahydroisoindol-1,3-dione **(10)** was previously prepared according to the reported method [22,23] by condensation of the anhydride **1** with hydroxyl amine hydrochloride in pyridine followed by replacement reaction with benzene sulphonyl chloride. In the present work, compound **10** was used to react with different hetreoamines namely, 4-

aminopyridine and/or 2-aminobenzothiazole under reflux in dry toluene to give 3-pyridin-tetrahydro-quinazolin-2-one **11** and/or 3-benzothiazol-tetrahydro-1H-quinazolin-2-one **12**, respectively (**Scheme 4)**. The ^{1}HNMR spectra of compounds **11** and **12** give support for their structures which exhibited the presence of the pyridine protons at δ 7.56 and δ 8.44 ppm for the quinazoline **11**, and the aromatic protons at δ 7.31-7.79 ppm for **12**. Moreover, the ^{13}C-NMR gave additional verification to the structures of **11** and **12**, which showed twelve and fifteen different signals for twelve and fifteen different carbon atoms for **11** and **12,** respectively.



Scheme 4. The reaction of the sulphonyloxy 10 with different heteroamines

The compound **10** and 1,4-diaminopiprazine hydrochloride in (2:1) molar ratio were refluxed in pyridine to give 1,4-bis[3-piperazin-1-yl-4a,5,8,8a-tetrahydro-1H-quinazoline-2,4-dione] (**13)**. The assigned and optimized structure of compound **13** was represented in **Figure 1**.

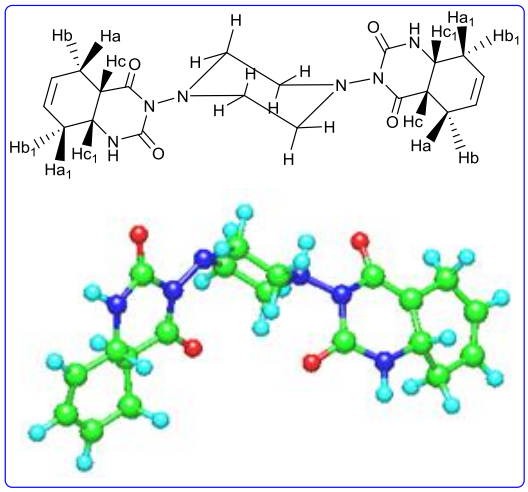
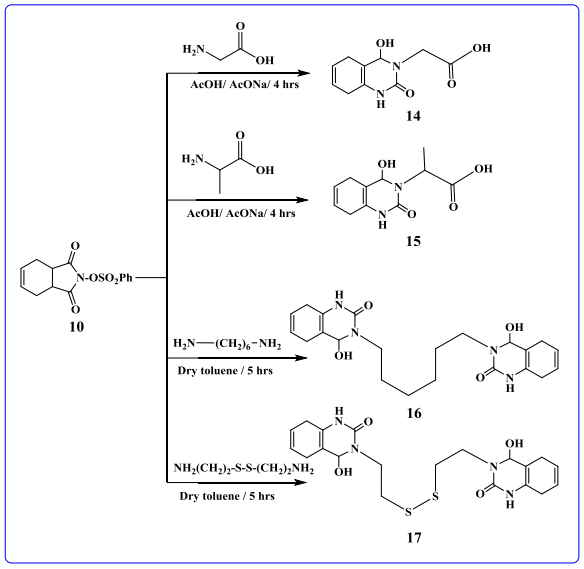


Fig. 1. The optimized structure of compound 13.

The chemical structure of compound **13** was confirmed based on its spectral data as follows, the ^{1}H-NMR spectrum indicates the presence of multiplet at δ 2.23-3.23 ppm (8H, $2H_a$+$2H_{a1}$+$2H_b$ +$2H_{b1}$), multiplet at δ 3.32 (2H, $2H_c$), multiplet at δ 3.80 (2H, $2H_{c1}$), two interfered doublets at δ 5.77–5.85 (4H, 2CH=CH), multiplet at δ 7.46 (4H, $4H_{axial}$), multiplet at δ 8.05 (4H, $4H_{equatorial}$) and a singlet at δ 8.20 ppm (2H, 2NH). From the structure of compound **13,** we note that four hydrogens of the piperazine ring are axial and the other four hydrogens are equatorial which is indicated by its ^{1}H-NMR spectrum. The mass spectrum gave additional verification to the structure of **13**, which showed a molecular ion peak at m/z = 414.

Similarly, the reaction of the phenylsulphonyloxy **10** and amino acids such as glycine and/or *DL*-Alanine in glacial acetic acid in presence of sodium acetate furnished the corresponding quinazoline-3-acetic acid derivatives **14** and/or **15,** and their structures were established by their elemental and spectral data (**Scheme 5**).

It is found that refluxing the diamines namely hexamethylenediamine and/or 2-(amino-ethyldisulfanyl)-ethylamine with **10** in (2:1) molar ratio in dry toluene yielded the corresponding 1,6-bis(3-hexyl-4-hydroxy-3,4,5,8-tetrahydro-1H-quinazoline-2-one (**16**) and/or 2,2-bis[3-(2-ethyldisulfanylethyl)-4-hydroxy-3,4,5,8-tetrahydro-1H-quinazoline-2-one] (**17**), respectively (**Scheme 5**) Structures conformation of compounds **14-17** was deduced from their elemental and spectral data (Experimental Section).



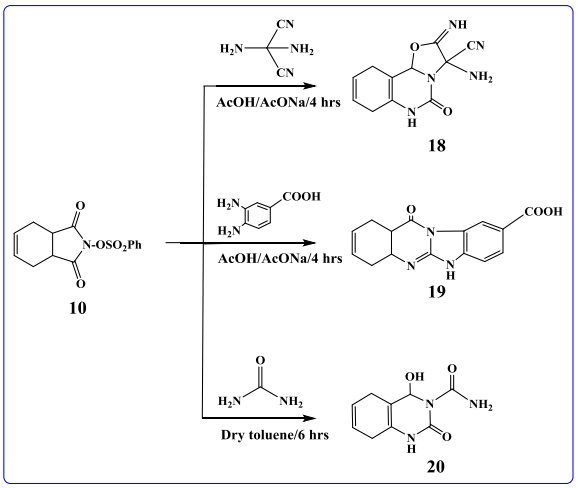
Scheme 5. The reaction of the sulphonyloxy 10 with different amino acids and diamines

Additional different diamines such as 2,2-diaminomalononitrile and/or 3,4-diaminobenzoic acid

were refluxed in acetic acid/sodium acetate mixture with the sulphonyloxy **10** in (2:1) molar ratio to give the corresponding malononitrile derivative **18** and/or benzo-imidazole-9-carboxylic acid derivative **19** (**Scheme 6**) The structures of **18** and **19** were confirmed by their IR spectra which showed bands at 3300,3250 cm^{-1} for (NH_2 and NH) groups, and 2210 cm^{-1} for (*ν*CN) for compound **18**, and characteristic bands at 3400 and 1720 cm^{-1} for the carboxylic acid group for **19**. Moreover, the ^{13}C NMR spectrum of compound **19** gave additional evidence for the proposed structure, which showed the presence of fifteen different signals for fifteen carbons.

Finally, the tetrahydro-2*H*-quinazolin-3-carboxylic acid amide **20** was synthesized with good yield by refluxing urea in dry toluene with the sulphonyloxy **10**. The assigned structure of **20** was supported by its elemental analysis and spectral data which were in agreement with its structure (Experimental Section).

Scheme 6. Reaction of the sulphonyloxy 10 with different diamines and urea.

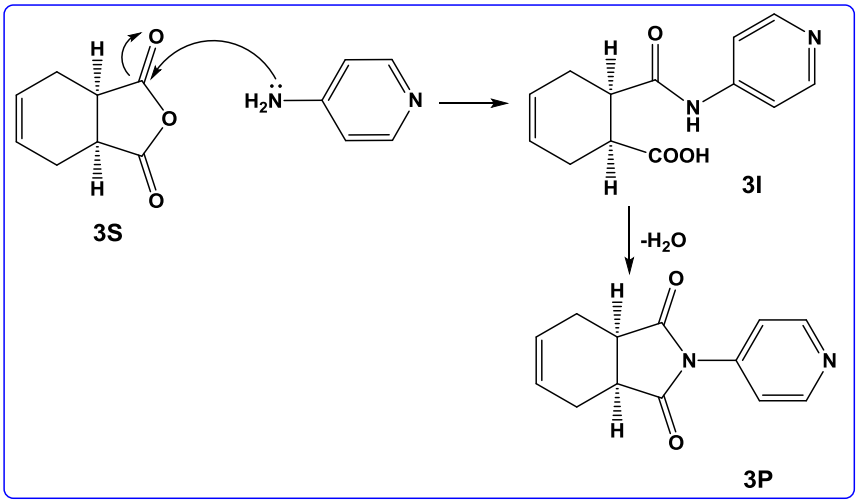


It appears clearly that compounds **11**, **12**, **14**, **15**, **16** and **17** prefer to stay more on the enol form than on the keto form, which was confirmed by their spectral analyses which showed the presence of the *sp*3 proton at~ δ 6.8 ppm, and the OH proton, also the disappearance of the two H*c* protons of the hexene ring. This may be due to the low energy of the enol form than the keto form as shown in the energy profile of the reaction of the sulphonyloxy **10** with amines, (**Figure 6**).

3.2 Molecular Modeling Study

Calculations were performed on PC (Pentium III, 733 MHz) using **MOPAC2000** [27] with **WinMOPAC 2.0** [28] as a graphic interface. In the beginning, the structure of the starting material was optimized with the eigenvector-following routine (**EF**) [29] using the semi-empirical **AM1** method [30]. The input file for the geometry optimization of the starting material should contain keywords that request an explanation of the electronic state of the chemical system, what kind of computational study should be performed (**Method-AM1**), and how we can deviate from the stationary point on the potential energy surface (**GNORM = 0.1**) and it is particularly good when the gradient is small [29].

First, the reaction of tetrahydrophthalic acid anhydride with 4-aminopyridine was selected as a model reaction **(Scheme 7).** The reaction pathway was suggested to proceed *via* a nucleophilic attack of the amino group onto the carbonyl group of compound **1**.



Scheme 7. The proposed mechanism for the reaction of 4-aminopyridine with tetrahydrophthalic anhydride 1.

As the geometry of the starting material (**3S**) has optimized, the reaction path was simulated and the energetic profile of the nucleophilic attack of 4-aminopyridine onto the tetrahydophthalic anhydride

was studied (also using **EF** procedures) by decreasing the atomic distance between atoms 7C and 11N from 4.042 Å to 1.54 Å at flag= -1 using reaction path calculations. This finished in obtaining local minima close to (**3I**) and a maximum close to (**TS**). This maximum which is a saddle point on the energy profile surface (**Figure 2**) was selected and then was optimized using TS procedures [28] at very low **GNORM** (geometry optimization termination criteria in both gradient and energy minimization).

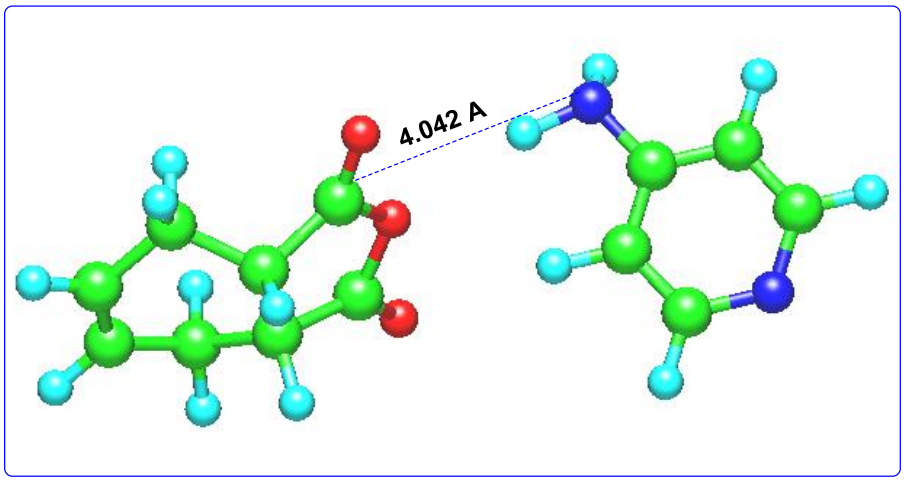


Fig. 2. The atomic distance between atoms 7C and 11N in the reacting molecules.

Another intramolecular nucleophilic attack of the NH group in the intermediate product (**3I**) onto the carboxylic carbonyl group and subsequent elimination of H_2O molecule affords the corresponding product (**3P**) (**Scheme 7**).

The structural and electronic properties of the compounds such as the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) energies, orbital coefficients, together with the FMO energy gap for geometries were calculated to gain insight about their relative stability (**Table 1**).

The semiempirical **MOPAC** calculations present the calculated values of the energy of the highest occupied and lowest unoccupied molecular orbital (HOMO and LUMO), energy gap ($\Delta E=E_{LUMO}-E_{HOMO}$), electronegativity ($\chi$), global hardness ($\eta$), softness ($\sigma$).

The structures of selected products **2, 3, 4, 16** and **17** were optimized and some results of compounds **2**-**7** were listed in **Table 1**, and the results of the calculations are found as supplementary materials attached to this article.

The value of HOMO energy (E_{HOMO}) is often associated with the electron-donating ability of the inhibitor molecule, which the higher values of E_{HOMO} are an indication of the greater ease of donating electrons to the unoccupied orbital or acceptor. On the other hand, it is important to examine the HOMO and LUMO energies for these compounds because the relative ordering of occupied and virtual orbitals provides a reasonable qualitative indication of electronic properties and the ability of electron transport, **Fig. 3** and **Fig. 4.**

Entry	ΔH Kcal/mol	Dipole Moment (D)	HOMO (ev)	LUMO (ev)	ΔE (ev)	Electronegativity χ	Hardness η	Softness σ
2	1.66992	2.359	-9.5215	-0.4557	9.0658	4.9886	4.5329	0.2206
3	-8.43318	4.890 D	-9.7365	-0.0283	9.7082	4.8824	4.8541	0.2060
4	18.04563	2.044	-8.9339	-0.6493	8.4646	4.7916	4.2323	0.2362
5	-25.5251	2.677	-10.221	0.0401	10.2608	5.0904	5.1304	0.1949
7	32.5803	4.394	-10.333	-0.0581	10.2754	5.1955	5.1377	0.1946

Table 1. Selected results of the AM1 calculations for the obtained compounds

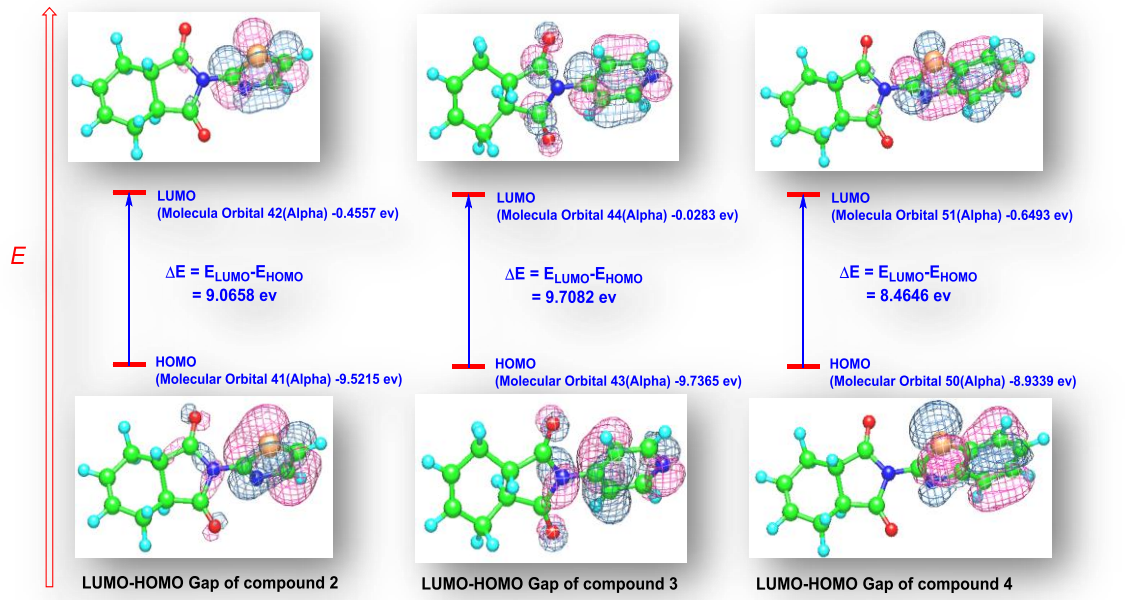


Fig. 3. Schematic representation of HOMO and LUMO coefficient distribution of compounds 2-4.

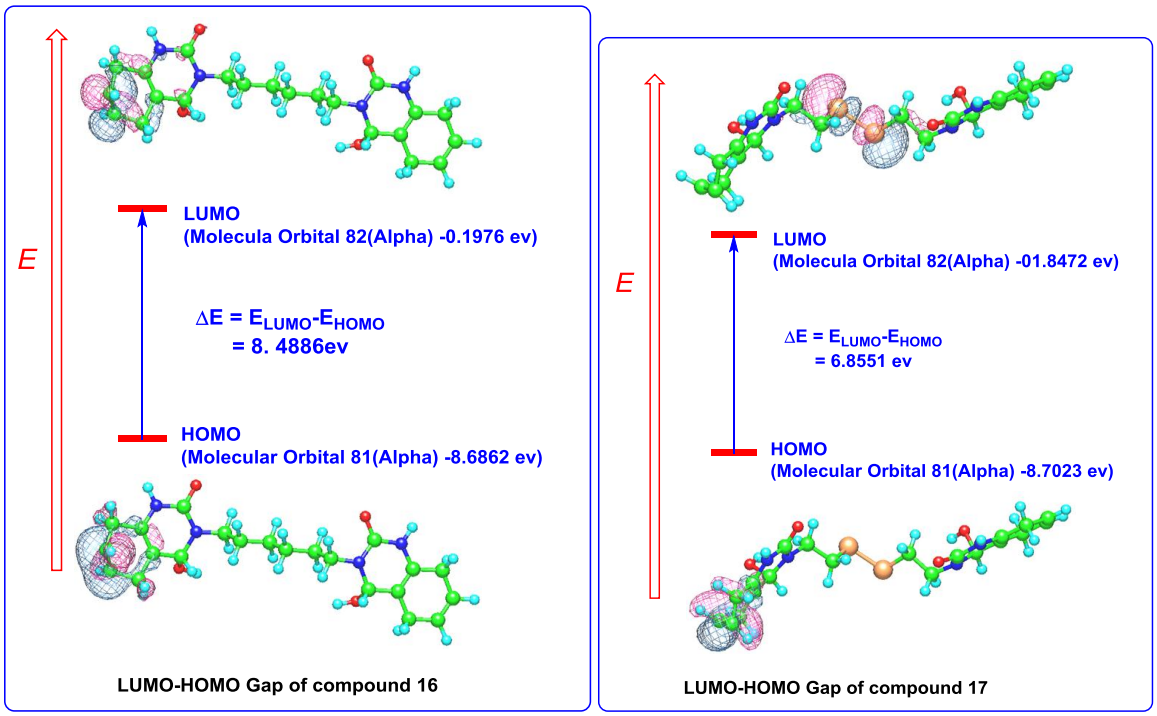


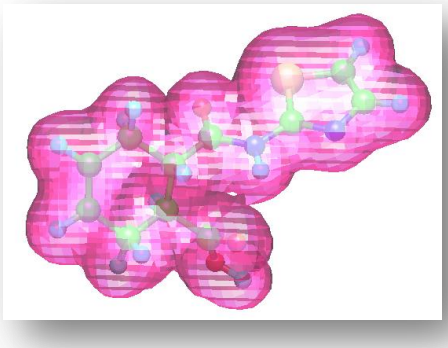
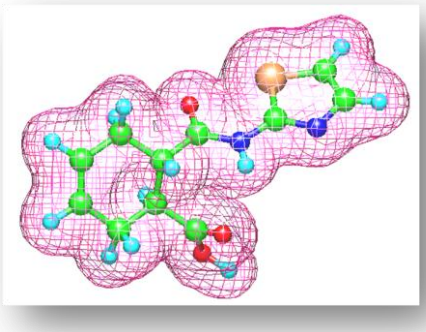
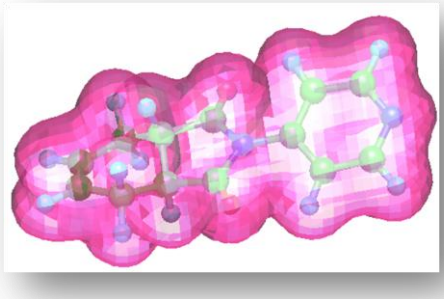
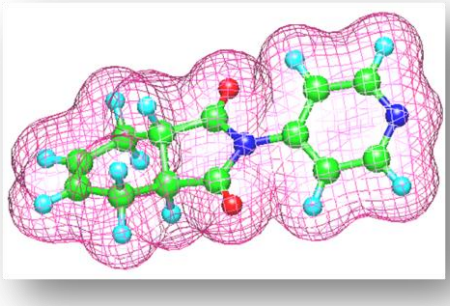
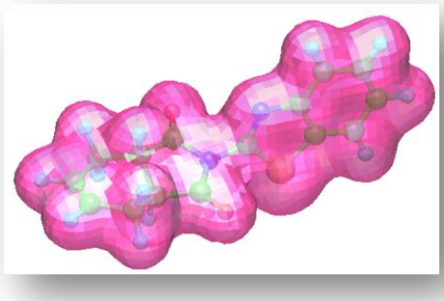
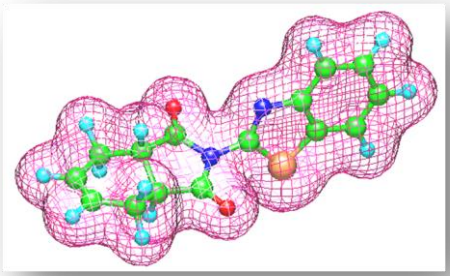
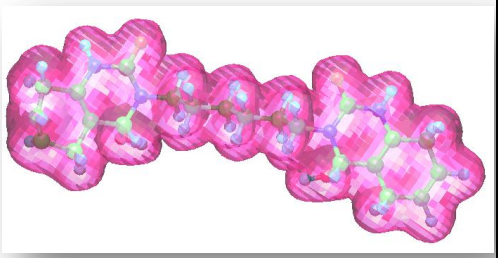
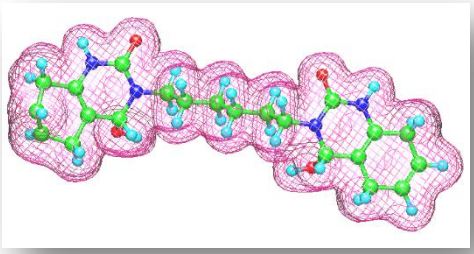
Fig. 4. Schematic representation of HOMO and LUMO coefficient distribution of compounds 16 and 17.

The energy differences of HOMO and LUMO (ΔE_{gap}) provide a measure of the stability of the formed compound. The lower value of ΔE is related to the higher stability of the formed compound. The overall analysis of HOMO and LUMO energy values revealed that the E_{HOMO} for the selected compounds **2, 3, 4, 16** and **17** varied from 8.4646 eV to 10.4277 eV and these results correlate with the values of antibacterial activity. Charges of atoms give important information about the electron density flow inside a chemical system and are thus related to the concept of electronegativity (**Fig. 5**).

Furthermore, the suggested mechanism for the other reaction of the sulponyloxy **10** with different amines is expected to proceed via *Lossen* rearrangement as shown in **Scheme 8**.

The reaction pathway of compound **10** with 4-aminopyridine was studied using **MOPAC200**, the starting material was optimized with the eigenvector-following routine (**EF**) [27,28] using the semi-empirical **AM1** method and each step was followed using reaction path calculations (**RPC**), also each step was confirmed by FORCE analysis and **TS** calculations, see supplementary material.

Fig. 6 illustrates the energy profile of the overall reaction.

Comp. No.	Solid surface	Wire frame
2		
3		
4		
16		

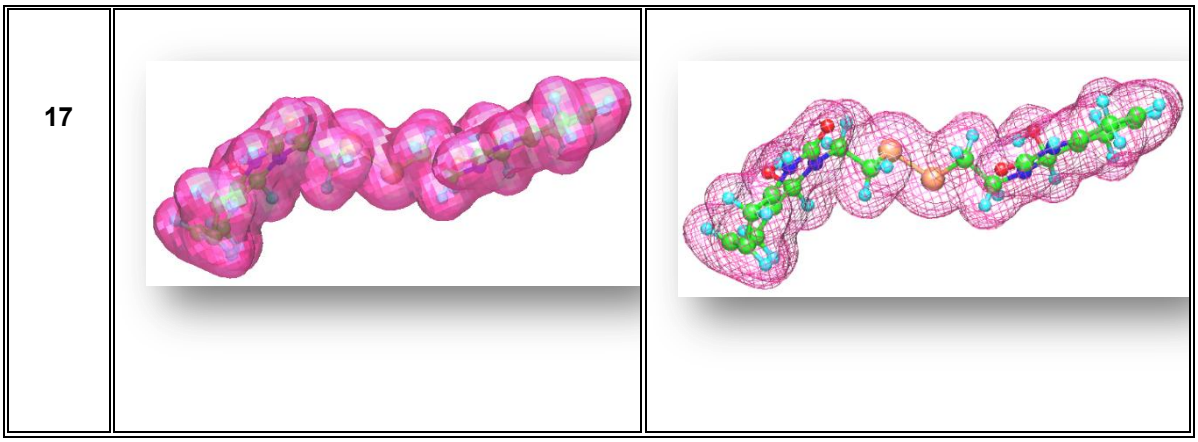
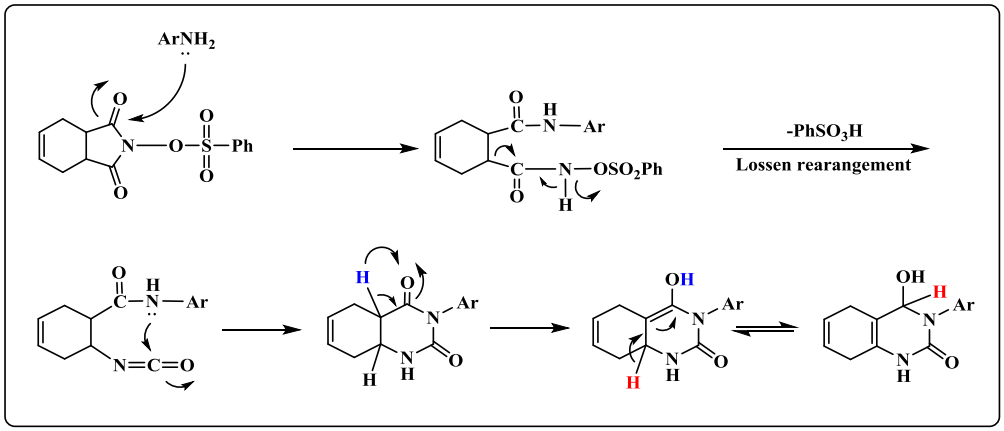


Fig. 5. The electron density of compounds 2, 3, 4, 16 and 17.



Scheme 8. The reaction mechanism of the sulphonyloxy 10 with amines via Lossen rearrangement.

Figure 6 clearly illustrates the reaction profile of the reaction of sulphonyloxy **10** with 4-aminopyridine *via Lossen* rearrangement. In the studied reaction mechanism, there were several chemical processes such as a nucleophilic attack, rearrangement, and elimination to form quinazoline derivative **11** from compound **10**. Our calculated free energy barrier of 56.7 kcal mol^{-1} is reasonably close to the experimentally derived free energy barrier, suggesting that the mechanistic insights obtained from this computational study are reasonable.

The semiempirical calculations and molecular modeling study manifest that the compounds **2, 3, 4, 16** and **17** have an electron density spreading on the whole molecule with numerous bumps through the molecule surface leads to high polarity which encourages binding with bacteria or fungi enzyme wall and stops its action in microbial growth. Finally, HOMO and LUMO energy values show a clue about the biological activity profile of the obtained compounds.

3.3 Antibacterial activity

3.3.1 Bacterial source and culture conditions:

The used bacterial strains were gram-negative bacteria including *E. coli* (ATCC25922) and gram-positive bacteria *Enterococcus faecalis* (ATC29212). Nutrient agar was used as culture media (gl-1) PH=7.3±0.1.(1). The plates were incubated at 37ºC for 24-48 hours. Antibacterial activity was determined against the above strains by using the paper disc assay method [31,32]. Chloramphenicol 30 mg/disc was used. The diameter of the growth inhibition halos caused by the tried compounds was measured and expressed in millimeters. All the assays were carried out in triplicate. The zones of inhibitions were measured in mm and the data is introduced in **Table 2** and **Fig. 7**.

3.3.2 Structure-activity correlation

Nine compounds **2, 3, 4, 6, 11, 15, 16, 17,** and **20** were selected and evaluated *in-vitro* for antibacterial activity against two bacterial strains *E. Coli* and *Enterococcus faecalis*. Compounds **16** and **17** are the most active derivatives when compared to the standard chloramphenicol. Obviously, the greater inhibition of both compounds may be due to the long-chain carbon which connects the two quinazoline rings specially compound **17** which contains two sulfur atoms in its carbon chain. Compounds **2**, **11** and **15** exhibited a good inhibition effect, that may be attributed to the presence of thiazole and pyridine moieties of **2** and **11**, respectively, as well as, the binding of the carboxylic group of compound **2** with the amino group of the protein amino acid residue, in addition, the reactivity of compound **15** against both kinds of bacteria may be explained by the presence of the free carboxylic group. On the other hand, the remaining compounds **3**, **4, 6,** and **20** gave slightly lower reactivity than the previously mentioned compounds, where the reactivity of **3** and **4** may be due to

the presence of pyridine and benzothiazole moieties, while the reactivity of compound **20** may be attributed to the binding of the carboxylic group of the protein amino acid residue with their amide and imine groups. From **Table 1** and **Figure 2**, it can be observed that all the tested compounds have good biological activity against both bacterial species especially the derivatives **16** and **17** which possessed a stronger effect and may be considered as potential sources of bioactive compounds with further investigations.

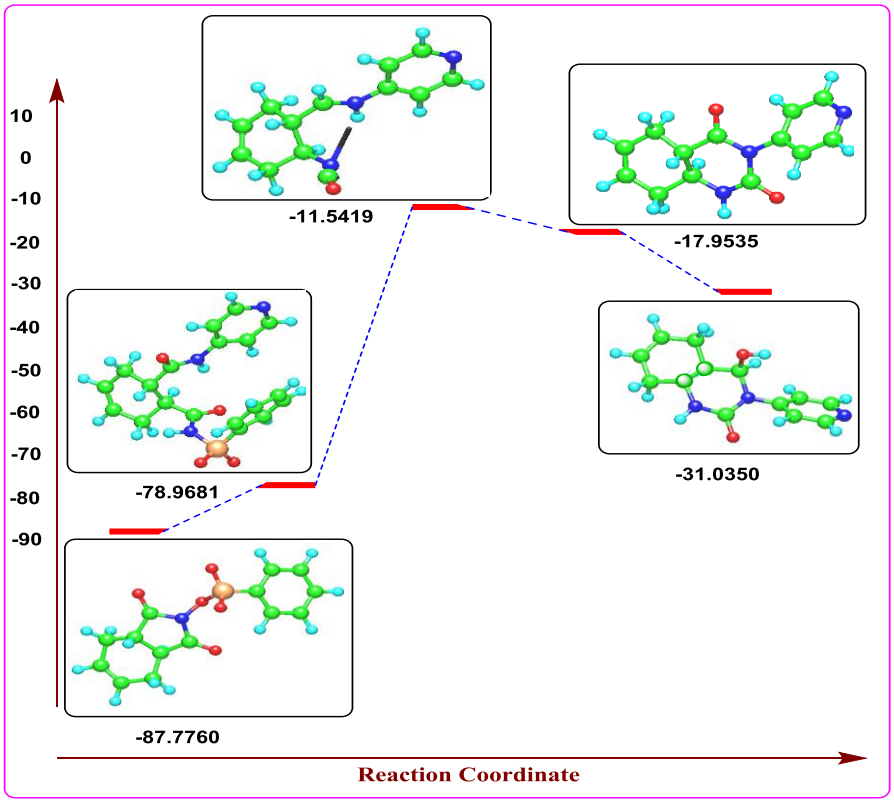


Fig. 6. The energy profile of the reaction of the sulphonyloxy 10 with amines via *Lossen* rearrangement.

Table 2. Effect of some selected synthesized compounds on bacterial growth

Sample	Bacterial growth inhibition zone diameter (mm)	
Bacteria	**Gram (-ve) bacteria *E.Coli***	**Gram (+ve) Bacteria *Enterococcus-faecalis***
2	**24 ± 0.5**	**21 ± 0.4**
3	**21± 0.4**	**17 ± 0.5**
4	**21 ± 0.3**	**18 ± 0.3**
6	**18±0.3**	**18±0.4**
11	**24±0.2**	**20±0.3**
15	**23±0.3**	**20±0.5**
16	**26±0.4**	**22±0.2**
17	**27±0.5**	**22±0.4**
20	**20±0.4**	**20 ±0.6**
Chloro-amphenicol (30mg)	**30**	**30**

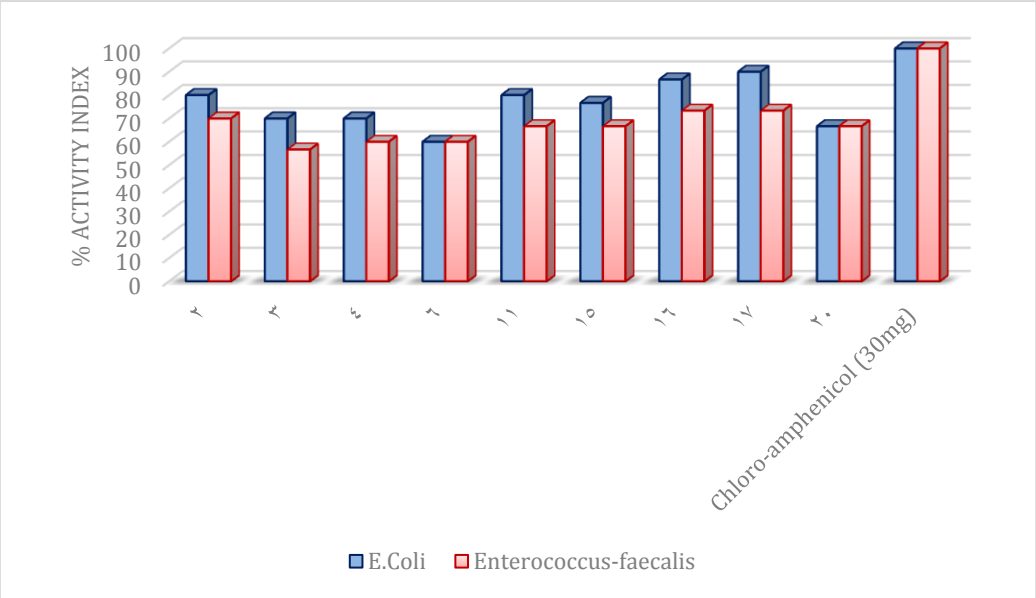


Fig. 7. The effectiveness of the tested compounds against the chosen bacteria.

4. Conclusion

New cyclic imides and quinazolin-2,4-diones **2-20** were synthesized by conventional methods. The structures of these products were proved by their spectral and elemental analyses. The *in vitro* study of some selected synthesized compounds **2, 3, 4, 6, 11, 15, 16, 17** and **20** was explained**.** Compounds **16** and **17** gave promising activity against the two types of bacteria tested this may be due to the electron density spreading on the whole of both molecules leads to high polarity which encourages binding with bacteria wall and stops its action in microbial growth, so it can be predicted that these compounds are effective antibacterial agents. **AM1 MOPAC2000** calculations were achieved to confirm the reaction mechanism and the relative stability of the obtained compounds. The obtained calculation results were agreed with the proposed mechanisms and the suggested structures.

Conflicts of Interest

"There are no conflicts to declare".

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