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Synthesis of some new spirocyclic β-lactam and spirocyclic thiazolidin-4-one derivatives

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ABSTRACT

Selective oxidation of 4-amino-2-methyl-5,10-dioxo-1,5,10,10a-tetrahydrobenzo[g]-quinoline-3-carbonitrile (1) with selenium dioxide provided, 4-amino-2-formyl-5,10-dioxo-1,5,10,10a-tetrahydrobenzo[g]quinoline-3-carbonitrile (2). The one-pot reaction of compound 2 with ethyl cyanoacetate and thiourea in ethanol yielded 4-amino-2-(5-cyano-6-oxo-2-thioxo-1,2,3,6-tetrahydropyrimidin-4-yl)-5,10-dioxo-1,5,10,10a-tetrahydrobenzo[g]-quinoline-3-carbonitrile (3). The cycloaddition reaction of chloroacetic acid with compound 3 yielded 7-(4-amino-3-cyano-5,10-dioxo-1,5,10,10a-tetrahydrobenzo-[g]quinolin-2-yl)-3,5-dioxo-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carbonitrile (4). Moreover, Ehrlich-Sachs condensation reaction of compound 4 with the aromatic nitroso compounds 5a-c gave the corresponding new Schiff bases 6a-c. Staudinger's ketene-imine cycloaddition reaction of compounds 6a-c with chloroacetyl chloride afforded the corresponding spiro [chloroazetidinethiazolopyrimidine] derivatives, 7a-c. On the otherhand, cycoladdition reaction of thioglycolic acid with Schiff bases 6a-c yielded the corresponding spiro[thiazolidinethiazolopyrimidine] derivatives, 8a-c. Structures of the new compounds were elucidated by compatible analytical and spectroscopic (IR, ^{1}H NMR and MS) measurements. Moreover, the reaction mechanisms that account for formation of the synthesized compounds have been discussed.

1. Introduction

β-Lactam as synthetic intermediate has been widely recognized in organic synthesis because it is an active moiety present in most widely used antibiotics such as penicillin, cephalosporins, carbapenems, nocardicins and monobactams [1]. In addition to their use as antibiotics, β-lactams are increasingly being used as synthons for other biologically important molecules [2]. β-Lactams, particularly spirocyclic derivatives have been found to act as cholesterol absorption inhibitors (CAI) [3], making them potentially useful compounds for development of drugs for lowering the high level of cholesterol.

More recently the enzymatic cleavage of the amyloid precursor protein responsible for the pathogenesis of Alzheimer's disease has also been shown to coupled with cholesterol regulation [4]. β-Lactams act also as inhibitors for thrombin [5], human cytomegalovirus protease (HCMV) [6] (a β-herpes virus) which is a serious pathogen in immune-compromised individuals [7], matrix metalloprotease [8], cysteine protease [9] and human leukocyte elastase (HLE) [10]. Spirocyclic β-lactams have attracted attention as they have been shown to be β-turn mimetics [11] and precursors for α,α-disubstituted β-amino acids [12]. It has been found also that spiro-β-lactams act as poliovirus and human rhinovirus 3C-proteinases inhibitors [13]. Some other biological activities such as antiviral [13], antibacterial [14], anti-tumor [15], anti-HIV [16] and anti-inflammatory [17] have been discovered to be associated with β-lactams.

Moreover, thiazolidin-4-ones and their derivatives are an important class of compounds in organic and medicinal chemistry. The thiazolidin-4-one ring system is a core structure in various synthetic pharmaceutical agents, displaying a broad spectrum of biological activities such as, antitubercular [18], antibacterial [19], anti-HIV [20], anti-inflammatory [21], anti-histaminic [22], antifungal [23], anticancer [24] and analgesic [25].

On the other hand, quinolines and their annelated derivatives are of particular importance by virtue of their occurrence in numerous natural products along with their wide ranging pharmaceuticals applications, including antimicrobial [26], antimalarial [27], antiviral [28] antitumor [29], immunomodulatory [30], local anesthetic [31], antiarrhythmic [31] and anti-inflammatory activities [32]. Considering all of these benefits and in pursuance to our interest [33-35] in the chemistry of polyfunctional heterocycles with enhanced biological potency, it is very interesting to synthesize new compounds which accommodate the biologically active quinoline, spirocyclic β-lactam and/or spirocyclic thiazolidin-4-one moieties, in the same structure.

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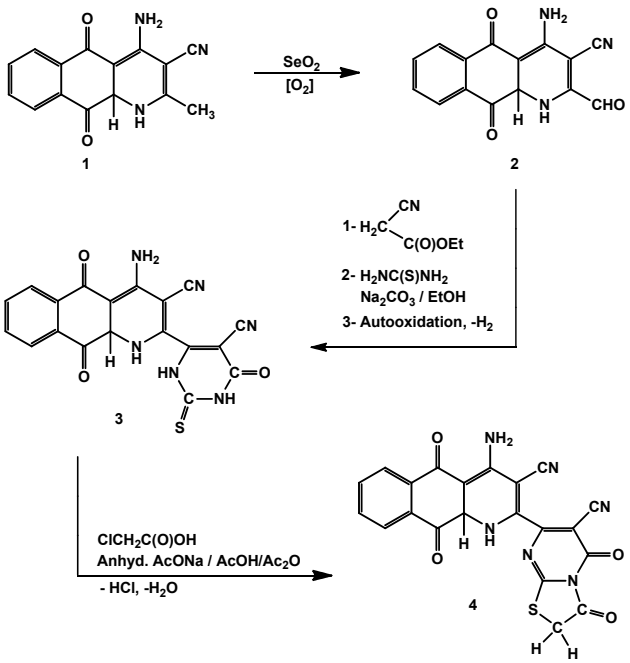


Scheme 1

2. Experimental

2.1. Instrumentation

Solvents were purified and dried according to usual procedures. Melting points were uncorrected and recorded on Gallenkamp electrothermal melting point apparatus. The reactions were monitored and the purity of products was controlled by Thin Layer Chromatography (TLC) using silica gel aluminum sheets $60F_{254}$ (Merck, Germany). The IR spectra were obtained from KBr disks using Perkin Elmer 1650 FT-IR Spectrophotometer (USA). ^{1}H NMR spectra were recorded on Bruker AMX-250 spectrometer (Germany) at 250 MHz. Mass spectra were recorded on Hewlett Packard MS 5988 Spectrometer (USA). Elemental microanalyses were carried out on CE 440 Elemental Analyzer-Automatic Injector (Exeter Analytical, Inc., USA) at Cairo University, Cairo, Egypt.

2.2. Synthesis of 4-Amino-2-methyl-5,10-dioxo-1,5,10,10a-tetrahydrobenzo[g]quinoline-3-carbonitrile (1)

This compound was prepared according to a reported method [33]. M.p.: 271-272 ^{o}C (EtOH) (Lit: 270 ^{o}C [33], EtOH), Yield: 75 %.

2.3. Synthesis of 4-Amino-2-formyl-5,10-dioxo-1,5,10,10a-tetrahydrobenzo[g]quinoline-3-carbonitrile (2)

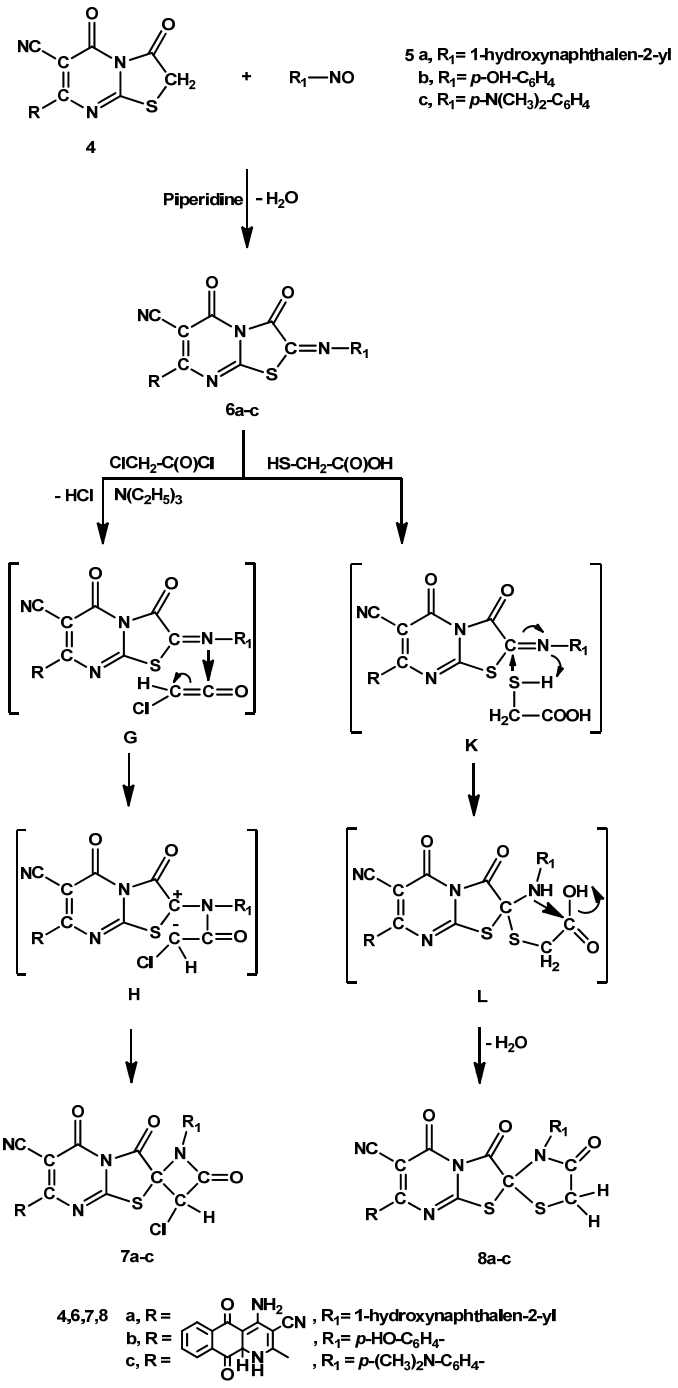
A mixture of compound **1** (2.65 g, 0.01 mol) and freshly sublimed SeO_2 (1.11 g, 0.01 mol) was heated under reflux in dry 1,4-dioxane (50 mL) for 24 h. The reaction mixture was filtered while hot and the filtrate was cooled to room temperature. The precipitate was filtered off, dried and recrystallized from methanol to give compound **2** (Scheme 1). Color: Brown crystals. M.p.: > 300 ^{o}C. Yield: 76 % (MeOH). IR (KBr, ν, cm^{-1}): 3387, 3331, 3286 (NH_2, NH), 3043 (C-H, aromatic), 2892 (C-H, saturated methine), 2785 (C-H, aldehyde), 2216 (C≡N), 1710 (HC=O), 1675 (C=O), 1602 (C=C, aromatic). ^{1}H NMR (250 MHz, DMSO-d_6, δ ppm): 3.62 (s, 1H, O=C-C*H*-NH), 6.55 (s, 2H, NH_2, D_2O-exchangeable), 7.42-8.09 (m, 4H, Ar-*H*), 9.98 (s, 1H, C*H*O) and 10.25 (s, 1H, N*H*, D_2O-exchangeable). MS (*m/z*, (%)): 279 (25) [M$^+$]. Anal. calcd. for $C_{15}H_9N_3O_3$ (279.25): C, 64.52; H, 3.25; N, 15.05. Found: C, 64.59; H, 3.22; N, 15.01%.

2.4. Synthesis of 4-Amino-2-(5-cyano-6-oxo-2-thioxo-1,2,3,6-tetrahydropyrimidin-4-yl)-5,10-dioxo-1,5,10,10a-tetrahydrobenzo[g]quinoline-3-carbonitrile (3)

A mixture of compound **2** (2.79 g, 0.01 mol), ethylcyanoacetate (1.13 g, 1.11 mL, 0.01 mol), thiourea (0.76 g, 0.01 mol) and sodium carbonate (2.2 g, 0.02 mol) was refluxed in ethanol (50 mL) for 24 h. The reaction mixture was cooled then neutralized with glacial acetic acid. The precipitate that formed was collected, filtered off and recrystallized from ethanol to give a brown crystalline product which is proved to be compound **3** (Scheme 1). Color: Brown crystals. M.p.: 280-282 ^{o}C. Yield: 71 % (EtOH). IR (KBr, ν, cm^{-1}): 3379, 3329, 3280 (NH_2, NH), 3038 (C-H, aromatic), 2895 (C-H, saturated methine), 2238, 2213 (C≡N), 1685, 1666 (C=O), 1605 (C=C, aromatic), 1165 (C=S). ^{1}H NMR (250 MHz, DMSO-d_6, δ ppm): 3.61 (s, 1H, O=C-C*H*-NH), 6.65 (s, 2H, NH_2, D_2O-exchangeable), 7.46 - 8.10 (m, 4H, Ar-*H*), 9.23 (s, 1H, N*H*, D_2O-exchangeable), 9.80 (s, 1H, N*H*, D_2O-exchangeable) and 10.15 (s, 1H, N*H*, D_2O-exchangeable). MS (*m/z*, (%)): 402 (30) [M$^+$]. Anal. calcd. for $C_{19}H_{10}N_6O_3S$ (402.39): C, 56.71; H, 2.50; N, 20.89; S, 7.97. Found: C, 56.76; H, 2.48; N, 20.85; S, 7.94%.

2.5. Synthesis of 7-(4-Amino-3-cyano-5,10-dioxo-1,5,10,10a-tetrahydrobenzo[g]quinolin-2-yl)-3,5-dioxo-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carbonitrile (4)

A mixture of compound **3** (4.02 g, 0.01 mol), chloroacetic acid (0.95 g, 0.01 mol) and fused sodium acetate (2 g) was refluxed for 16 h in a reaction medium of acetic acid and acetic anhydride (40 mL, 1:1, *v*:*v*). The reaction mixture was cooled, shaked well with cold water (50 mL) and allowed to stand for 1 h at room temperature. The solid product was filtered and recrystallized from methanol to give compound **4** (Scheme 1). Color: Reddish brown crystals. M.p.: > 300 ^{o}C.



Scheme 2

Yield: 80 % (MeOH). IR (KBr, ν, cm^{-1}): 3385, 3328, 3278 (NH_2, NH), 3036 (C-H, aromatic), 2940, 2893 (C-H, aliphatic), 2235, 2210 (C≡N), 1719, 1680 (C=O), 1604 (C=C, aromatic), 1574 (C=N, cyclic). ^{1}H NMR (250 MHz, DMSO-d_6, δ ppm): 3.60 (s, 1H, O=C-C*H*-NH), 3.74 and 4.00 (two douplets, each with $^{1,2}J_{HH}$ = 15.8 Hz, 2H, cyclic methylenes S-CH_2-CO], 6.69 (s, 2H, NH_2, D_2O-exchangeable), 7.43-8.11 (m, 4H, Ar-*H*) and 9.96 (s, 1H, N*H*, D_2O-exchangeable). MS (*m/z*, (%)): 442 (15) [$M^{+\cdot}$]. Anal. calcd. for $C_{21}H_{10}N_6O_4S$ (442.41): C, 57.01; H, 2.28; N, 19.00; S, 7.25. Found: C, 56.96; H, 2.31; N, 19.05; S, 7.22%.

2.6. General Procedure for the Synthesis of Schiff Base derivatives (6a-c)

A mixture of compound **4** (4.42 g, 0.01 mol) and the appropriate aromatic nitroso compound **5a-c** (0.01 mol) was refluxed in absolute ethanol for 10-12 h in the presence of a few drops of piperidine. The reaction mixture was filtered while hot and the filtrate was concentrated and cooled. The solid product was filtered off and recrystallized from ethanol to give the Schiff base derivatives **6a-c** (Scheme 2).

7-(4-Amino-3-cyano-5,10-dioxo-1,5,10,10a-tetrahydrobenzo [g]quinolin-2-yl)-2-(1-hydroxynaphthalen-2-ylimino)-3,5-dioxo-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carbonitrile (**6a**): Color: Purple crystals. M.P.: > 300 °C. Yield: 79 % (EtOH). IR (KBr, ν, cm^{-1}): 3445-3260 (OH, NH_2, NH), 3066, 3032 (C-H, aromatic), 2890 (C-H, saturated methine), 2235, 2212 (C≡N), 1715, 1680 (C=O), 1645 (C=N, exocylic), 1608 (C=C, aromatic), 1572 (C=N, cyclic). ^{1}H NMR (250 MHz, DMSO-d_6, δ ppm): 3.61 (s, 1H, O=C-C*H*-NH), 6.79 (s, 2H, NH_2, D_2O-exchangeable), 7.25-8.11 (m, 11H, Ar-*H* and O*H*) and 10.23 (s, 1H, N*H*, D_2O-exchangeable). MS (*m/z*, (%)): 597 (16) [M^+]. Anal. calcd. for $C_{31}H_{15}N_7O_5S$ (597.56): C, 62.31; H, 2.53; N, 16.41; S, 5.37. Found: C, 62.26; H, 2.55; N, 16.37; S, 5.34%.

7-(4-Amino-3-cyano-5,10-dioxo-1,5,10,10a-tetrahydrobenzo [g]quinolin-2-yl)-2-(4-hydroxy-phenylimino)-3,5-dioxo-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carbonitrile (**6b**): Color: Reddish brown crystals. M.p.: > 300 °C. Yield: 81 % (EtOH). IR (KBr, ν, cm^{-1}): 3435-3250 (OH, NH_2, NH), 3062, 3025 (C-H, aromatic), 2890 (C-H, saturated methine), 2238, 2216 (C≡N), 1713, 1682 (C=O), 1645 (C=N, exocylic), 1605 (C=C, aromatic), 1570 (C=N, cyclic). ^{1}H NMR (250 MHz, DMSO-d_6, δ ppm): 3.62 (s, 1H, O=C-C*H*-NH), 6.77 (s, 2H, NH_2, D_2O-exchangeable), 7.04-8.14 (m, 9H, Ar-*H* and O*H*), 10.25 (s, 1H, N*H*, D_2O-exchangeable). MS (*m/z*, (%)): 547 (20) [M^+]. Anal. calcd. for $C_{27}H_{13}N_7O_5S$ (547.50): C, 59.23; H, 2.39; N, 17.91; S, 5.86. Found: C, 59.19; H, 2.41; N, 17.87; S, 5.88%.

7-(4-Amino-3-cyano-5,10-dioxo-1,5,10,10a-tetrahydrobenzo [g]quinolin-2-yl)-2-(4-(dimethylamino)phenylimino)-3,5-dioxo-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carbonitrile (**6c**): Color: Brown crystals. M.p.: > 300 °C.Yield: 84 % (EtOH). IR (KBr, ν, cm^{-1}): 3374, 3319, 3277 (NH_2, NH), 3062, 3025 (C-H, aromatic), 2890, 2860, 2810 (C-H, aliphatic), 2237, 2213 (C≡N), 1710, 1680 (C=O), 1644 (C=N, exocylic), 1605 (C=C, aromatic), 1573 (C=N, cyclic). ^{1}H NMR (250 MHz, DMSO-d_6, δ ppm): 2.84 (s, 6H, -N(CH_3)$_2$), 3.62 (s, 1H, O=C-C*H*-NH), 6.73 (s, 2H, NH_2, D_2O-exchangeable), 6.91-8.15 (m, 8H, Ar-*H*), 10.19 (s, 1H, N*H*, D_2O-exchangeable). MS (*m/z*, (%)): 574 (25) [M^+]. Anal. calcd. for $C_{29}H_{18}N_8O_4S$ (574.57): C, 60.62; H, 3.16; N, 19.50; S, 5.58. Found: C, 60.65; H, 3.15; N, 19.48; S, 5.57%.

2.7. General procedure for synthesis of the spiro[chloro azetidinethiazolopyrimidine] derivatives (7a-c)

To a mixture of the appropriate Schiff base derivative **6a-c** (0.01 mol) and triethylamine (1.4 mL, 0.01 mol) in dry 1,4-dioxane (40 mL), chloroacetyl chloride (1.13 g, 0.8 mL, 0.01 mol) was added drop wise at room temperature. After completion of addition, the reaction mixture was stirred for further 48 h. The formed triethylamine hydrochloride was removed by filtration and washed well with dioxane. After removal of the volatile materials from the filtrate in vacuum, a mixture of ice-cold water was added to the residue. The formed solid product was filtered off, washed thoroughly with water and recrystallized from the appropriate solvent to give finally the spiro[chloroazetidinethiazolopyrimidine] derivatives **7a-c** (Scheme 2).

7′-(4-Amino-3-cyano-5,10-dioxo-1,5,10,10a-tetrahydrobenzo [g]quinolin-2-yl)-3-chloro-1-(1-hydroxynaphthalen-2-yl)-3′,4,5′-trioxo-3′,5′-dihydrospiro[azetidine-2,2′-thiazolo[3,2-a] pyrimidine]-6′-carbonitrile (**7a**): Color: Brown crystals. M.p.: > 300 °C (EtOH). Yield: 78 %. IR (KBr, ν, cm^{-1}): 3440-3250 (OH, NH_2, NH), 3062, 3025 (C-H, aromatic), 2930, 2890 (C-H, saturated methine), 2235, 2207 (C≡N), 1713, 1685 (C=O), 1609 (C=C, aromatic), 1577 (C=N, cyclic), 627 (C-Cl, aliphatic). ^{1}H NMR (250 MHz, DMSO-d_6, δ ppm): 3.61 (s, 1H, O=C-C*H*-NH), 5.46 (s, 1H, Cl-C*H*), 6.66 (s, 2H, NH_2, D_2O-exchangeable), 7.02-8.13 (m, 11H, Ar-*H* and O*H*), 10.21 (s, 1H, N*H*, D_2O-exchangeable). MS (*m/z*, (%)): 673 (30) [M^+, ^{35}Cl], 675 (9) [M^+, ^{37}Cl]. Anal. calcd. for $C_{33}H_{16}ClN_7O_6S$ (674.05): C, 58.80; H, 2.39; N, 14.55; S, 4.76. Found: C, 58.78; H, 2.40; N, 14.52; S, 4.78%.

7′-(4-Amino-3-cyano-5,10-dioxo-1,5,10,10a-tetrahydrobenzo [g]quinolin-2-yl)-3-chloro-1-(4-hydroxyphenyl)-3′,4,5′-trioxo-3′,5′-dihydrospiro[azetidine-2,2′-thiazolo[3,2-a] pyrimidine]-6′-carbonitrile (**7b**): Color: Reddish brown crystals. M.p.: 279-280 °C. Yield: 82 % (MeOH). IR (KBr, ν, cm^{-1}): 3430-3250 (OH, NH_2, NH), 3062, 3025 (C-H, aromatic), 2930, 2890 (C-H, saturated methine), 2237, 2209 (C≡N), 1710, 1680 (C=O), 1607 (C=C, aromatic) and 1575 (C=N, cyclic), 629 (C-Cl, aliphatic). ^{1}H NMR (250 MHz, DMSO-d_6, δ ppm): 3.60 (s, 1H, O=C-C*H*-NH), 5.44 (s, 1H, Cl-C*H*), 6.68 (s, 2H, NH_2, D_2O-exchangeable), 7.01-8.13 (m, 9H, Ar-*H* and O*H*), 10.18 (s, 1H, N*H*, D_2O-exchangeable). MS (*m/z*, (%)): 623 (25) [M^+, ^{35}Cl], 625 (7) [M^+, ^{37}Cl]. Anal. calcd. for $C_{29}H_{14}ClN_7O_6S$ (623.99): C, 55.82; H, 2.26; N, 15.71; S, 5.14. Found: C, 55.87; H, 2.23; N, 15.68; S, 5.12%.

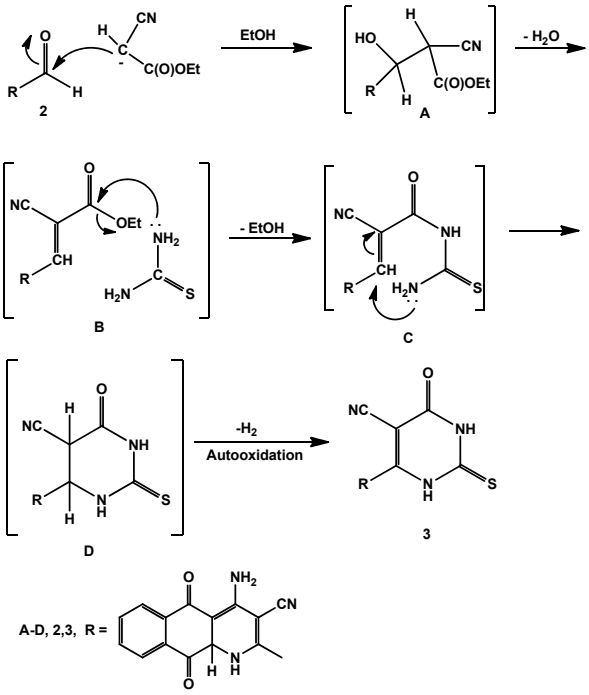
7′-(4-Amino-3-cyano-5,10-dioxo-1,5,10,10a-tetrahydrobenzo [g]quinolin-2-yl)-3-chloro-1-(4-(dimethylamino)phenyl)-3′,4,5′-trioxo-3′,5′-dihydrospiro[azetidine-2,2′-thiazolo[3,2-a] pyrimidine]-6′-carbonitrile (**7c**): Color: Green crystals. M.p.: > 300 °C. Yield: 79 % (MeOH). IR (KBr, ν, cm^{-1}): 3381, 3329, 3277 (NH_2, NH), 3062, 3025 (C-H, aromatic), 2930, 2890, 2860, 2810 (C-H, aliphatic), 2238, 2210 (C≡N), 1706, 1675 (C=O), 1607 (C=C, aromatic), 1575 (C=N, cyclic), 624 (C-Cl, aliphatic). ^{1}H NMR (250 MHz, DMSO-d_6, δ ppm): 2.82 (s, 6H, -N(CH_3)$_2$), 3.60 (s, 1H, O=C-C*H*-NH), 5.50 (s, 1H, Cl-C*H*), 6.65 (s, 2H, NH_2, D_2O-exchangeable), 6.94-8.14 (m, 8H, Ar-*H*), 10.13 (s, 1H, N*H*, D_2O-exchangeable). MS (*m/z*, (%)): 650 (20) [M^+, ^{35}Cl] and 652 (6) [M^+, ^{37}Cl]. Anal. calcd. for $C_{31}H_{19}ClN_8O_5S$ (651.06): C, 57.19; H, 2.94; N, 17.21; S, 4.92. Found: C, 57.15; H, 2.96; N, 17.18; S, 4.94%.

2.8. General Procedure for synthesis of the spiro[thiazolidine thiazolopyrimidine] derivatives (8a-c)

A mixture of the appropriate Schiff base derivative **6a-c** (0.01 mol) and thioglycolic acid (0.92 g, 0.01 mol) was refluxed in dry benzene (50 mL) for 24 h. After removal of the volatile materials under reduced pressure, an ice -cold water mixture was added to the residue. The formed solid product was filtered off, washed thoroughly with water, dried and recrystallized from the appropriate solvent to give the spiro[thiazolidinethiazolopyrimidine] derivatives **8a-c** (Scheme 2).

7′-(4-Amino-3-cyano-5,10-dioxo-1,5,10,10a-tetrahydrobenzo [g]quinolin-2-yl)-3-(1-hydroxynaphthalen-2-yl)-3′,4,5′-trioxo-3′,5′-dihydrospiro[thiazolidine-2,2′-thiazolo[3,2-a]pyrimidine]-6′-carbonitrile (**8a**): Color: Brown crystals. M.p.: > 300 °C. Yield: 80 % (EtOH). IR (KBr, ν, cm^{-1}): 3430-3240 (OH, NH_2, NH), 3062, 3025 (C-H, aromatic), 2940, 2893 (C-H, aliphatic), 2239, 2214 (C≡N), 1717, 1680 (C=O), 1610 (C=C, aromatic), 1571 (C=N, cyclic). ^{1}H NMR (250 MHz, DMSO-d_6, δ ppm): 3.61 (s, 1H, O=C-C*H*-NH), 3.76 and 4.02 (two doublets each with $^{1,2}J_{HH}$ = 16.2 Hz, 2H, cyclic methylenes, S-CH_2-C=O), 6.74 (s, 2H, NH_2, D_2O-exchangeable), 7.01-8.14 (m, 11H, Ar-*H* and O*H*), 10.19 (s, 1H, N*H*, D_2O-exchangeable). MS (*m/z*, (%)): 671 (15) [M^+]. Anal. calcd. for $C_{33}H_{17}N_7O_6S_2$ (671.66): C, 59.01; H, 2.55; N, 14.60; S, 9.55. Found: C, 59.07; H, 2.53; N, 14.57; S, 9.52%.

7′-(4-Amino-3-cyano-5,10-dioxo-1,5,10,10a-tetrahydrobenzo [g]quinolin-2-yl)-3-(4-hydroxyphenyl)-3′,4,5′-trioxo-3′,5′-dihydro spiro[thiazolidine-2,2′-thiazolo[3,2-a]pyrimidine]-6′-carbonitrile (**8b**): Color: Reddish brown crystals. M.p.: > 300 °C. Yield: 78 % (MeOH). IR (KBr, ν, cm^{-1}): 3440-3240 (OH, NH_2, NH), 3057, 3025 (C-H, aromatic), 2940, 2893 (C-H, aliphatic), 2234, 2210 (C≡N), 1710, 1680 (C=O), 1608 (C=C, aromatic), 1572 (C=N, cyclic). ^{1}H NMR (250 MHz, DMSO-d_6, δ ppm): 3.61 (s, 1H, O=C-C*H*-NH), 3.76 and 4.03 (two doublets each with $^{1,2}J_{HH}$ = 16.0 Hz, 2H, cyclic methylenes *S*-CH_2-C=O), 6.70 (s, 2H, NH_2, D_2O-exchangeable), 7.01-8.14 (m, 9H, Ar-*H* and O*H*), 10.15 (s, 1H, N*H*, D_2O exchangeable). MS (*m/z*, (%)): 621 (20) [M^+]. Anal. calcd. for $C_{29}H_{15}N_7O_6S_2$ (621.60): C, 56.04; H, 2.43; N, 15.77; S, 10.32. Found: C, 55.98; H, 2.44; N, 15.80; S, 10.35%.



Scheme 3

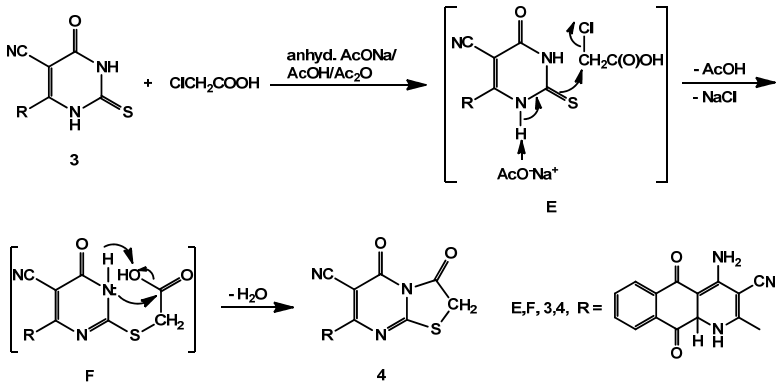
7'-(4-Amino-3-cyano-5,10-dioxo-1,5,10,10a-tetrahydrobenzo [g]quinolin-2-yl)-3-(4-(dimethylamino)phenyl)-3',4,5'-trioxo-3', 5'-dihydrospiro[thiazolidine-2,2'-thiazolo[3,2-a] pyrimidine]-6'-carbonitrile (**8c**): Color: Brown crystals. M.p.: > 300 °C. Yield: 87 % (EtOH). IR (KBr, ν, cm^{-1}): 3373, 3333, 3275 (NH_2, NH), 3059, 3027 (C-H, aromatic), 2940, 2893, 2860, 2810 (C-H, aliphatic), 2237, 2210 (C≡N), 1705, 1675 (C=O), 1608 (C=C, aromatic) and 1572 (C=N, cyclic). ^{1}H NMR (250 MHz, DMSO-d_6, δ ppm): 2.82 (s, 6H, -N(CH_3)$_2$), 3.61 (s, 1H, O=C-C*H*-NH), 3.75 and 4.01 (two doublets each with $^{1,2}J_{HH}$ = 16.1 Hz, 2H, cyclic methylenes S-CH_2-C=O), 6.64 (s, 2H, NH_2, D_2O-exchangeable), 6.89-8.12 (m, 8H, Ar-*H*), 10.11 (s, 1H, N*H*, D_2O-exchangeable). MS (*m/z*, (%)): 648 (18) [M^+]. Anal. calcd. for $C_{31}H_{20}N_8O_5S_2$ (648.67): C, 57.40; H, 3.11; N, 17.27; S, 9.88. Found: C, 57.46; H, 3.09; N, 17.25; S, 9.92%.

3. Results and discussion

It has been now found that selective oxidation [36] of 4-amino-2-methyl-5,10-dioxo-1,5,10,10a-tetrahydrobenz[g] quinoline-3-carbonitrile (**1**) [33] with freshly sublimed selenium dioxide in dry 1,4-dioxane gave 4-amino-2-formyl-5,10-dioxo-1,5,10,10a-tetrahydrobenz[g]-quinoline-3-carbo-nitrile (**2**) as brown crystals in yield of 76% (Scheme 1). Correct elementary and molecular weight determination (MS) for compound **2** corresponded to $C_{15}H_9N_3O_3$ (MS: [M^+] at *m/z* 279). Its IR spectrum showed strong absorption bands at 2785 and 1710 cm^{-1} due to C–H and C=O bonds, respectively, of the formed aldehyde group. The IR spectrum showed also absorption bands at 3387, 3331, 3286 (NH_2 and NH), 3043 (C–H, aromatic), 2892 (C-H, saturated methine), 2216 (C≡N) and 1675 (C=O). The ^{1}H NMR spectrum of compound **2** lacked any absorption due to methyl group protons which appeared around δ 2.43 ppm in the ^{1}H NMR spectrum of compound **1** [33]. On the other hand, the ^{1}H NMR spectrum of compound **2** showed a singlet at 9.98 ppm which is attributed to the proton of the aldehyde group [37]. Moreover, the singlet that appeared at 3.62 ppm is attributed to the methine proton O=C-C*H*-NH on the saturated sp^3 carbon atom in the benzoquinoline moiety. The spectrum showed also signals at 6.55 (s, 2H, NH_2, D_2O-exchangeable), 7.42-8.09 (m, 4H, aromatic) and 10.25 (s, 1H, N*H*, D_2O-exchangeable).

The one–pot reaction of compound **2** with ethylcyanoacetate and thiourea in ethanol with the presence of sodium carbonate gave 4-amino-2-(5-cyano-6-oxo-2-thioxo-1,2,3,6-tetrahydro-pyrimidin-4-yl)-5,10-dioxo-1,5,10,10a-tetrahydrobenzo[g]- quinoline-3-carbonitrile (**3**) where a new substituted tetrahydropyrimidine ring has been formed (Schemes 1 and 3). A postulated reaction mechanism that accounts for the formation of compound **3** is represented in Scheme 3. The carbanion which is generated from ethylcyano acetate, in presence of sodium carbonate, undergoes a nucleophilic attack on the aldehydic carbon atom of compound **2** to give an intermediate like **A** with subsequent dehydration process to eliminate a water molecule (Scheme 3). Such addition-elimination processes resulted in the formation of the cyanoacrylate intermediate **B** (Scheme 3). A second nucleophilic attack by the NH_2 group of thiourea on the carbonyl ester group followed by an elimination of an alcohol molecule gave the intermediate **C** (Scheme 3). An intramolecular heterocyclization of **C** gave intermediate **D** which undergoes a spontaneous auto oxidation process [38,39] with an elimination of a hydrogen molecule to give finally 4-amino-2-(5-cyano-6-oxo-2-thioxo-1,2,3,6-tetrahydropyrimidin-4-yl)-5,10-dioxo-1,5,10,10a-tetrahydrobenzo[g]quinoline-3-carbonitrile (**3**) (Schemes 1 and 3).

The chemical structure of compound **3** was confirmed through its elemental analysis and mass spectrometry measurement ([$M]^+$ at *m/z* 402), which corresponded to $C_{19}H_{10}N_6O_3S$. The IR spectrum of compound **3** showed an absorption band at 1165 cm^{-1} due to the exocyclic C=S bond [37]. The spectrum revealed the absence of the aldehyde carbonyl group absorption band that appeared in spectrum of compound **2** at 1710 cm^{-1}. However, it showed bands at 2238, 2213 and 1685, 1666 cm^{-1} due to the absorption of C≡N and C=O groups, respectively.



Scheme 4

The ^{1}H NMR spectrum of compound **3** revealed the presence of four signals at 6.65, 9.23, 9.80 and 10.15 ppm where all were found to be D_2O-exchangeable. These signals were attributed to the five protons bonded to the four nitrogen atoms in compound **3**. The singlet that appeared at 3.61 ppm is attributed to the methine proton O=C-C*H*-NH on the *sp*^{3} saturated carbon atom in the benzoquinoline moiety. Moreover, the spectrum lacked any other absorption bands due to protons on saturated carbon atoms.

Moreover, compound **3** reacted with chloroacetic acid in presence of fused sodium acetate and acetic acid to give 7-(4-amino-3-cyano-5,10-dioxo-1,5,10,10a-tetrahydrobenzo-[g] quinolin-2-yl)-3,5-dioxo-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carbonitrile (**4**) as reddish brown crystals in a yield of 80% (Schemes 1 and 4).

A suggested mechanism for formation of compound **4** is depicted in Scheme 4. Thus, the reaction apparently involves a nucleophilic attack by the sulphur atom of compound **3** on the chlorine-bearing carbon atom of chloroacetic acid to give an intermediate **F** through a transition state like **E** with elimination of acetic acid and sodium chloride molecules (Scheme 4). Intermediate **F** undergoes an intramolecular heterocyclization reaction with an elimination of a water molecule to give finally compound **4** (Schemes 1 and 4).

Compound **4** was given the assigned structure for the following reasons:

a) Molecular weight determination for compound **4** corresponds to $C_{21}H_{10}N_6O_4S$ (442.41).

b) Its mass spectrum showed the molecular ion peak [M$^+$] at *m/z* 442.

c) The IR spectrum of compound **4** showed absorption bands at 3385, 3328, 3278 cm^{-1} due to -NH_2 and NH groups. It showed also bands at 3036 (C-H, aromatic), 2940, 2893 (C-H, aliphatic), 2235, 2210 (C≡N), 1719, 1680 (C=O) and 1574 (C=N, cyclic). Moreover, absorption due to C=S group which appeared around 1165 cm^{-1} in the IR spectrum of **3** has disappeared in that of compound **4**.

d) The ^{1}H NMR spectrum revealed the presence of two doublets at δ 3.74 ppm and 4.00 ppm (each with $^{1,2}J_{HH}$ = 15.8 Hz) due to the geminal methylene protons in the formed fused thiazolidinone ring. These two protons are chemically equivalent but magnetically non-equivalent, therefore, they coupled with each other [37].

The spectrum showed only two signals due to absorption of protons on nitrogen at δ 6.69 ppm (s, 2H, N*H*$_2$, D_2O-exchangeable) and 9.96 ppm (s, 1H, N*H*, D_2O-exchangeable). The aromatic protons appeared as a multiplet in the region 7.43-8.11 ppm (4H).

Schiff bases represent a very important class of organic compounds because of their applications in many fields, including biological, inorganic and analytical chemistry [40]. They are usually prepared by condensing primary amines with aldehydes or ketones where one or both of the reactants is aromatic [40]. However, an alternative method for the synthesis of Schiff bases is Ehrlich-Sachs reaction [41,42] where the imino group is formed by nitrosation at a carbon bearing active methylene hydrogen atoms. Thus, compound **4** reacted with the aromatic nitroso derivatives **5a-c** in absolute ethanol under reflux with the presence of piperidine to give the corresponding new Schiff base derivatives **6a-c** (Scheme 2). Structural reasoning for 7-(4-amino-3-cyano-5,10-dioxo-1,5,10, 10a-tetrahydrobenzo[g] quinolin-2-yl)-2-(4-(dimethyl amino) phenylimino)-3,5-dioxo-3,5-dihydro-2H-thiazolo[3,2-a] pyrimidine-6-carbonitrile (**6c**), taken as a representative example, are:

a) Elemental analysis of compound **6c** corresponds to a molecular formula of $C_{29}H_{18}N_8O_4S$ (574.57).

b) Its mass spectrum recorded the molecular ion peak [M]$^+$ at *m/z* 574.

c) Its IR Spectrum showed absorption bands at 3374, 3319 and 3277 (NH_2, NH), 3062, 3025 (C-H, aromatic), 2890, 2860, 2810 (C-H, aliphatic), 2237, 2213 (C≡N), 1710, 1680 (C=O), 1644 (C=N, exocyclic), 1605 (C=C, aromatic) and 1573 (C=N, cyclic).

d) The ^{1}H NMR spectrum of compound **6c** lacked any signals due to the two methylene protons which appeared in that of compound **4** at 3.74 and 4.00 ppm. However, the spectrum showed a singlet at 2.84 ppm due to the six protons of two methyl groups on nitrogen. The spectrum revealed also the presence of signals at 3.62 (s, 1H, O=C-C*H*-NH), 6.73 (s, 2H, N*H*$_2$, D_2O-exchangeable), 6.91-8.15 (m, 8H, aromatic protons) and 10.19 (s, 1H, N*H*, D_2O-exchangeable).

Among the several methods for the synthesis of β-lactams, the cycloaddition reaction of Schiff bases with ketenes (Staudinger reaction) [43,44] is mostly applied. This method has been used for the synthesis of a large number of monocyclic, bicyclic, tricyclic and spirocyclic β-lactams [1]. The α-methylene protons in chloroacetyl chloride are activated due to the electron-withdrawing inductive effect (-*I*) effect exerted by the adjacent chlorine atom and the carbonyl group. Therefore, in presence of triethylamine, chloroacetyl chloride loses a hydrogen chloride molecule to give the ketene ClHC=C=O [45].

Although commonly described as a [2+2] cycloaddition, it is generally accepted that Staudinger reaction is in fact stepwise [46,47]. Thus, the cycloaddition reaction of compounds **6** with chloroacetyl chloride (Scheme 2) involves, in its first step, a nucleophilic attack by nitrogen atom of the polarized exocyclic imino group on the *sp*-hybridized carbon of the ketene, which is formed *in situ*, to form a zwitterionic intermediate like **H** through the transition state **G**. In the second step, intra-

molecular cyclization of intermediate **H** forms the spiro-azetidinone ring giving compounds **7a-c** (Scheme 2). The substituents present in the imines or the acid chlorides, the nature of bases/solvents, the reaction conditions and even the order of addition of the reagents have been found to affect the formation of the azetidinone ring as well as its stereochemistry [46,47].

The mass spectrum of 7'-(4-amino-3-cyano-5,10-dioxo-1,5,10,10a-tetrahydrobenzo[g]quinolin-2-yl)-3-chloro-1-(4-(dimethylamino)phenyl)-3',4,5'-trioxo-3',5'-dihydrospiro-[azetidine-2,2'-thiazolo[3,2-a]pyrimidine]-6'-carbonitrile (**7c**), taken as a representative example, recorded the molecular ion peak $[M]^+$ at *m/z* 650 (based on ^{35}Cl) and *m/z* 652 (based on ^{37}Cl) which corresponds to $C_{31}H_{19}ClN_8O_5S$. Its IR spectrum showed no absorption band due to the exocyclic C=N which appeared for compound **6c** at 1644 cm^{-1}. This indicates the saturation of such bond due to addition. Moreover, the spectrum showed strong bands at 2930, 2890, 2860, 2810 cm^{-1} due to the aliphatic C-H bonds and at 624 cm^{-1} due to C-Cl bond [37]. The spectrum showed also absorption bands at 3381, 3329, 3277 (NH_2, NH), 3062, 3025 (C-H, aromatic), 2238, 2210 (C≡N), 1706, 1675 (C=O), 1607 (C=C, aromatic) and 1575 (C=N, cyclic). In the ^1H NMR spectrum of compound **7c**, the methine proton on the carbon-bearing chlorine appeared as a singlet at δ 5.50 ppm. The singlet that appeared at 2.82 ppm was attributed to protons (6H) of the two methyl groups on nitrogen. The spectrum revealed also the presence of bands at 3.60 (s, 1H, O=C-C*H*-NH), 6.65 (s, 2H, NH_2, D_2O-exchangeable), 6.94-8.14 (m, 8H, aromatic protons) and 10.13 (s, 1H, N*H*, D_2O-exchangeable).

Moreover, the imino group of Schiff base derivatives **6a-c** could be utilized also to form a new thiazolidin-4-one ring. A conventional method for thiazolidin-4-one ring formation is the heterocyclization of imino groups with thioglycolic acid [18,20]. Thus, when Schiff base derivatives **6a-c** were refluxed in benzene with thioglycolic acid the corresponding 7'-(4-amino-3-cyano-5,10-dioxo-1,5,10,10a-tetrahydrobenzo[g] quinolin-2-yl)-3-(aryl)-3',4,5'-trioxo-3',5'-dihydrospiro [thiazolidine-2,2'-thiazolo[3,2-a]pyrimidine]-6'-carbonitriles **8a-c** have been obtained as crystalline products in yields up to 80% where a spiro-thiazolidin-4-one ring has been formed (Scheme 2). Apparently, the reaction involves a nucleophilic attack by sulpher atom of thioglycolic acid on the carbon atom of the imino group to give intermediate **L** through a transition state like **K**. Heterocyclization of **L** with an elimination of a water molecule gave compounds **8a-c** (Scheme 2).

The structures of compounds **8a-c** have been confirmed through their elemental analysis and spectroscopic data. For example, 7'-(4-amino-3-cyano-5,10-dioxo-1,5,10,10a-tetra hydro-benzo[g]quinolin-2-yl)-3-(4-hydroxyphenyl)-3',4,5'-trioxo-3',5'-dihydrospiro [thiazolidine-2,2'-thiazolo[3,2-a] pyrimidine]-6'-carbonitrile (**8b**) was given the assigned structure due to the following reasons:

a) Elemental microanalysis of compound **8b** corresponds to a molecular formula of $C_{29}H_{15}N_7O_6S_2$ (621.60).

b) The mass spectrum of compound **8b** recorded the molecular ion peak $[M]^+$ at *m/z* 621.

c) Its IR spectrum lacked any absorption due to the exocyclic C=N that appeared for **6b** at 1645 cm^{-1} as result of addition on that bond. The broad band appeared from 3440 to 3240 is attributed to the absorption of OH, NH_2 and NH groups. The spectrum revealed also the presence of bands at 3057, 3025 (aromatic C-H), 2940, 2893 (aliphatic C-H), 2234, 2210 (C≡N), 1710, 1680 (C=O), 1608 (aromatic C=C) and 1572 (cyclic C=N).

d) The ^1H NMR spectrum of **8b** revealed the presence of two doublets at δ 3.76 ppm and 4.03 ppm, each with $^{1,2}J_{HH}$ = 16.0 Hz, which are attributed to the two chemically but not magnetically equivalent geminal cyclic methylene protons in the N-substituted thiazolidin-4-one ring. The integration of the multiplet that appeared in region 7.01-8.14 ppm was found to correspond to nine protons. Such multiplet is due to absorption of the eight aromatic protons in addition to the hydroxyl group proton. The spectrum showed also bands at 3.61 (s, 1H, O=C-C*H*-NH), 6.70 (s, 2H, NH_2, D_2O-exchangeable) and 10.15 (s, 1H, N*H*, D_2O-exchangeable).

4. Conclusion

In the present investigation, we have successfully synthesized some novel compounds incorporating two and/or three heterocyclic moieties of anticipated biological activities in one and the same molecule. Thus, the molecule of compound **4** incorporates both of the quinoline moiety as well as the thiazoloprymidine moiety, which is also known of its pharmaceutical activity [48]. In addition to the two latter moieties, compounds **7a-c** and **8a-c** incorporate also the spiro-β-lactam and the spiro-thiazolidin-4-one moieties, respectively, in their structures. On the other hand, compounds **6a-c** also belong to the class of Schiff bases that are well known of their biological activities [40]. The feasibility of the synthetic procedures and the good yield of the prepared compounds are also advantages for the present study.

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