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

Hisham Abdallah Abd El-Monem Yosef, Nadia Ali Ahmed Elkanzi and Nesrin Mahmoud Morsy Mohamed

*Department of Organometallic and Organometalloid Chemistry, National Research Centre, Dokki, 12622, Cairo, Egypt
+ Chemistry Department, Aswan-Faculty of Science, Aswan University, Aswan, 81528, Egypt
† Chemistry Department, Faculty of Science, Al Jouf University, Al Jouf, 2014, Kingdom of Saudi Arabia

*Corresponding author at: Chemistry Department, Faculty of Science, Al Jouf University, Al Jouf, 2014 Kingdom of Saudi Arabia.
Tel: +966.04.6242271; fax: +966.04.6247183. E-mail address: naadil@nau.edu (N.A.A. Elkanzi).

Article information

Received: 19 March 2013
Received in revised form: 19 April 2013
Accepted: 19 April 2013
Online: 30 September 2013

Keywords:
Schiff Bases
Benzoquinolines
Spirocyclic β-lactams
Reaction mechanisms
Spirocyclic thiazolidin-4-ones
Spectroscopic measurements

Abstract

Selective oxidation of 4-amino-2-methyl-5,10-dioxo-1,5,10a-tetrahydrobenzo[g]-quinoline-3-carbonitrile (1) with selenium dioxide provided, 4-amino-2-formyl-5,10-dioxo-1,5,10a-tetrahydrobenzo[g]-quinoline-3-carbonitrile (2). The one-pot reaction of compound 2 with ethyl cyanocetate and thiourea in ethanol yielded 4-amino-2-[5-cyano-6-oxo-2-thioxo-1,2,3,6-tetrahydropyrimidin-4-yl]-5,10-dioxo-1,5,10a-tetrahydrobenzo[g]-quinoline-3-carbonitrile (3). The cycloaddition reaction of chloroacetic acid with compound 3 yielded 7-(4-amino-3-cyano-5,10-dioxo-1,5,10a-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. Sauerbringer’s ketene-imine cyclodaddition reaction of compounds 6a-c with chloroacetyl chloride afforded the corresponding spiro[chloroazetidinethiazolopyrimidine] derivatives, 7a-c. On the otherhand, cyclodaddition reaction of thiglycolic 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, 'H NMR and MS) measurements. Moreover, the reaction mechanisms that account for formation of the synthesized compounds have been discussed.

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, carbenapens, nocardidins 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 ααdisubstituted 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 aneledated 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 polynuclear 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.
2. Experimental

2.1. Instrumentation

Solvents were purified and dried according to usual procedures. Melting points were uncorrected and recorded on Gallenkamp electrotropical melting point apparatus. The reactions were monitored and the purity of products was controlled by Thin Layer Chromatography (TLC) using silica gel aluminum sheets 60F254 (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 Varian Gemini 2000 (USA) at Cairo University, Cairo, Egypt.

Analytical procedures.

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

This compound was prepared according to a reported method [63]. M.p.: 271-272 °C (EtOH) (Lit: 270 °C [63], EtOH), Yield: 75%.

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

A mixture of compound 1 (2.65 g, 0.01 mol) and freshly sublimed SeO2 (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 °C. Yield: 76% (MeOH).

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

A mixture of compound 2 (2.79 g, 0.01 mol), ethylcyanoacetate (1.13 g, 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 °C. Yield: 71% (EtOH). IR (KBr, v, cm-1): 3379, 3329, 3280 (N-H, aromatic), 2985 (C-H, saturated methine), 2238, 2213 (C=O, 1685, 1666 (C=O), 1605 (C=C, aromatic), 1165 (C=S). 1H NMR (250 MHz, DMSO-d6, δ ppm): 2.61 (s, 1H, O=CH-NH), 6.65 (s, 2H, N-H, D=O-exchangeable), 7.46 - 8.10 (m, 4H, Ar-H), 9.23 (s, 1H, NH, D=O-exchangeable) and 10.15 (s, 1H, NH, D=O-exchangeable). MS (m/z, [%]): 402 (30) [M+]. Anal calcd. for C19H10N6O3S: 56.71; H, 2.48; N, 20.85; S, 7.94%.

2.5. Synthesis of 7-(4-Amino-3-cyano-5,10-dioxo-1,5,10a-tetrahydrobenzo[g]quinolin-2-yl)-3,5-dioxo-3,5-dihydro-2H-thiazolo[3,2-alpyrimidine-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 °C.
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-1,5,10a,10b-tetrahydrobenzo [g]quinolin-2-yl]-2-(4-hydroxyphenyl)-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, cm⁻¹): 3445-3260 (OH, NH, NH), 3066, 3032 (C=C, aromatic), 2980 (C-H, saturated methane), 2235, 2212 (C-N), 1715, 1680 (C=O), 1645 (C=N, exocyclic), 1608 (C=C, aromatic), 1572 (C=N, cyclic). 1H NMR (250 MHz, DMSO-d₆, δ ppm): 3.61 (s, 1H, O=C-CH₃), 6.79 (s, 2H, NH₂, D₂O-exchangeable), 7.25-8.11 (m, 11H, Ar-H and OH) and 10.23 (s, 1H, NH, D₂O-exchangeable). MS (m/z (%)): 597 (16) [M⁺]. Anal. calc. for C₃₂H₁₃N₇O₅S: C, 58.78; H, 2.39; N, 14.55; S, 4.76. Found: C, 58.78; H, 2.40; N, 14.52; S, 4.79%.

7-{4-Amino-3-cyano-5,10-dioxo-1,5,10a,10b-tetrahydrobenzo [g]quinolin-2-yl]-3-chloro-1-(4-hydroxyphenyl)-3,5-dioxo-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carbonitrile (7b): Color: Reddish brown crystals. M.p.: 279-280 °C. Yield: 82 % (MeOH). IR (KBr, cm⁻¹): 3430-3250 (OH, NH, NH), 3062, 3025 (C-H, aromatic), 2930, 2890 (C-H, saturated methane), 2237, 2209 (C=O), 1710, 1680 (C=O), 1607 (C=C, aromatic) and 1575 (C=N, cyclic), 629 (C-Cl, aliphatic). 1H NMR (250 MHz, DMSO-d₆, δ ppm): 3.60 (s, 1H, O=C-CH₃), 6.68 (s, 2H, NH₂, D₂O-exchangeable), 7.01-8.13 (m, 9H, Ar-H and OH), 10.18 (s, 1H, NH, D₂O-exchangeable). MS (m/z (%)): 623 (25) [M⁺], 621 (36) [M⁺-H₂O]. Anal. calc. for C₂₇H₁₃ClN₇O₅S: 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%.


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-1,5,10a,10b-tetrahydrobenzo [g]quinolin-2-yl]-3-chloro-1-(4-hydroxyphenyl)-3,5-dioxo-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carbonitrile (8a): Color: Brown crystals. M.p.: > 300 °C. Yield: 80 % (EtOH). IR (KBr, cm⁻¹): 3430-3240 (OH, NH, NH), 3052 (C-H, aromatic), 2940, 2983 (C-H, aliphatic), 2229, 2214 (C=O), 1717, 1680 (C=O), 1610 (C=C, aromatic), 1571 (C=N, cyclic). 1H NMR (250 MHz, DMSO-d₆, δ ppm): 3.61 (s, 1H, O=C-CH₃), 6.73 (s, 2H, NH₂, D₂O-exchangeable), 6.91-8.15 (m, 8H, Ar-H), 10.19 (s, 1H, NH, D₂O-exchangeable). MS (m/z (%)): 671 (15) [M⁺]. Anal. calc. for C₂₇H₁₃ClN₇O₅S: 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-1,5,10a,10b-tetrahydrobenzo [g]quinolin-2-yl]-3-(1-hydroxynaphthalen-2-yl)-3',5'-dioxo-3,5'-dihydrospiroazetidine-2',2'-thiazolo[3,2-a]pyrimidine-6-carbonitrile (8b): Color: Reddish brown crystals. M.p.: > 300 °C. Yield: 78 % (MeOH). IR (KBr, cm⁻¹): 3440-3240 (OH, NH, NH), 3057, 3025 (C-H, aromatic), 2940, 2893 (C-H, aliphatic), 2224, 2210 (C=O), 1710, 1680 (C=O), 1608 (C=C, aromatic), 1572 (C=N, cyclic). 1H NMR (250 MHz, DMSO-d₆, δ ppm): 3.61 (s, 1H, O=C-CH₃), 6.76 (s, 2H, NH₂, D₂O-exchangeable), 7.02-8.14 (m, 11H, Ar-H and OH), 10.19 (s, 1H, NH, D₂O-exchangeable). MS (m/z (%)): 621 (20) [M⁺]. Anal. calc. for C₂₇H₁₃N₇O₅S: 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%.
7′-(4-Amino-3-cyano-5,10-dioxo-1,5,10,10a-tetrahydrobenzo[4]quinolin-2-yl)-3-(4-(dimethylamino)phenyl)-3′,4′,5′-trioxo-3′,5′-dihydrospiro[thiazolidine-2,2′-thiazolo][3,2-a] pyrimidine-6′-carbonitrile (Bc): Color: Brown crystals. M.p.: > 300 °C. Yield: 87 % (EtOH). IR (KBr, v, cm⁻¹): 3373, 3333, 3275 (NH₂, NH), 3059, 3027 (C-H, aromatic), 2940, 2893, 2860, 2810 (C-H, aliphatic), and 1710 cm⁻¹ due to C–H and C=O bonds, respectively, of the saturated sp³ carbon atom in the benzoquinoline moiety. The spectrum showed also signals at 6.55 (s, 2H, NH₂, D₂O-exchangeable), 7.42-8.09 (m, 4H, aromatic) and 10.25 (s, 1H, NH, D₂O-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-1,5,10a-tetrahydropyrimidin-3(2H)-quinoiline-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 carbocation which is generated from ethylcyanoacetate, in presence of sodium carbonate, undergoes a nuclophilic 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 nuclophilic attack by the NH₂ 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-1,5,10a-tetrahydropyrimidin-3(2H)-quinoiline-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 C₁₅H₁₀N₆O₃S. 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 2230, 2213 and 1685, 1666 cm⁻¹ due to the absorption of C=N and C=O groups, respectively.
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$_2$O-exchangeable. These signals were attributed to 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 $\text{O=C-CH-NH}$ 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 nucelophic 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$_{29}$H$_{18}$N$_8$O$_4$S (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=C, aromatic), 1719, 1680 (C=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 $\delta$ 3.74 ppm and 4.00 ppm (each with $^{13}$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 $\delta$ 6.69 ppm (s, 2H, NH$_2$, D$_2$O-exchangeable) and 9.96 ppm (s, 1H, NH, D$_2$O-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-dihy whole-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$_{30}$H$_{22}$N$_8$O$_4$S (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, NH, 3062, 3025 (C-H, aromatic), 2890, 2860, 2810 (C-H, aliphatic), 2237, 2213 (C=N), 1710, 1680 (C=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-CH-CH), 6.73 (s, 2H, NH$_2$, D$_2$O-exchangeable), 6.91-8.15 (m, 8H, aromatic protons) and 10.19 (s, 1H, NH$_2$, D$_2$O-exchangeable).

Among the several methods for the synthesis of $\beta$-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 $\beta$-lactams [1]. The $\alpha$-methylene protons in chloroacetyl chloride are activated due to the electron-withdrawing inductive effect ($\text{-I}$) 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 CHC=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$^3$ hybridized carbon of the ketene, which is formed in situ, to form a zwiterionic intermediate like H through the transition state G. In the second step, intra-
molecular cyclization of intermediate H forms the spiroazetidinone giving compound 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-tetrahydrobenzog][quinolin-2-yl]-3-(4-dimethylaminophenyl)-3',4,5'-trioxo-3',5'-dihydrospiro[azeidine-2,2'-thiazolo[3,2-a]pyrimidine]-6'-carbonitrile (7c), taken as a representative example, recorded the molecular ion peak \([M^+]/m/z 650\) based on \([C^37]O\) and \(m/z 652\) based on \([C^37]O\) which corresponds to \(C_{29}H_{15}N_7O_6S_2\). 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 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, 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 \(^1\)H NMR spectrum of compound 7c, the methine proton on the carbon-bearing chlorine appeared as a singlet at \(\delta 5.50\) 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\(^{+}\)) and 2.10 ppm (s, 3H, CH\(_3\)). The spectrum of 7c also shows a sharp signal at 7.28 ppm due to the aromatic protons.

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 [10,20]. Thus, when Schiff base derivatives 6a-c were refluxed in benzene with thioglycolic acid the corresponding 7a-c and 8a-c incorporate also the spiro-b-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.

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 thiazolopyrimidine 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-b-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.

Acknowledgements

We are thankful to the Department of Chemistry, Aswan-Faculty of Science, Aswan University for the facilities provided.

References


