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Synthesis of New Isolated Pyrazolo, Isoxazolo Derivatives Incorporating Pyrido[1,2]thiazinoquinoline

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Acetylation of 7,14-diamino-5,5a,12,12a-tetrahydro-[1,2]thiazino[4',5':5,6]pyrido[2,3-g][1,2]thiazino[5,4-b]quinoline-1,6,8,13(2H,4H,9H,11H)-tetraone (**1**) with acetic anhydride and glacial acetic acid gave 2,9-diacetyl-7,14-diamino-5,5a,6a,7,12,12a-hexahydro-[1,2]thiazino[4',5':5,6]pyrido[2,3-g][1,2]thiazino[5,4-b]quinoline-1,6,8,13(2H,4H,9H,11H)-tetraone (**2**) The one-pot reaction of compound (**2**) with the aromatic aldehydes (**3a-c**) in the presence of catalytic amount of piperidine gave the corresponding arylidene derivatives(**4a-c**). Reaction of the arylidene derivatives (**4a-c**) with an equimolar amount of hydrazine hydrate and/or phenylhydrazine in the presence of a base gave N-acetylpyrazolo-derivatives (**5a-c**) and N-phenylpyrazolo derivatives (6**a-c**). Similarly, the isooxazolo pyrimidine derivatives (**7a-c**) were obtained through the reaction of arylidene derivatives (**4a-c**) with an equimolar amount of hydroxylamine hydrochloride in ethanol in the presence of sodium hydroxide as a catalyst. The structures of the new compounds were elucidated by compatible analytical and spectroscopic measurements.

Keywords: Synthesis, N-acetylpyrazolo, N-phenylpyrazolo, Arylidene, Aromatic aldehydes.

INTRODUCTION

Pyrazoles are five member ring heterocyclic compounds, have some structural features with two nitrogen atoms in adjacent position and are also called as azoles[1]. Recently, pyrazole derivatives have been found in nature[1], β-[1-pyrazolyl]-alanine was isolated from the seeds of water melons [citurllus lanatus]. The best described property of almost every group of pyrazoles is in the treatment of inflammation and inflammation associated disorders, such as arthritis[2]. Pyrazole derivatives are the subject of many research studies due to their wide spread potential biological activities such as antimicrobial[3], antiviral[4], antitumor[5,6], antihistaminic[7], antidepressant[8], insecticides[9] and fungicides[9]. Several pyrazole derivatives have been found to possess significant activities such as 5-α-red-uctase inhibitor[10], ant proliferative[11], ant parasitic[12], herbicides[13]. A good number of pyrazoles have also been reported to have interesting biological activities like antiinflammatory[14] and antiprotozoal[15-16] which render them valuable active ingredients of medicine and plant protecting agents. Further, current literature indicates 1,2-pyrazole derivatives to possess various biological activities[17]. Isoxazoles possess interesting medicinal[18] properties and have some industrial utility[19]. Many biologically active isoxazoles and reduced isoxazole derivatives have been reported, *viz.*, the naturally occurring ant tuberculosis, antibiotic cycloserine, the mono amine oxidase inhibitor: isocarboxazid, useful in psychotherapy and isoxazole steroids show anabolic activity, *e.g.*, denazole[20]. The CNS active isoxazoles, ibotenic acid, muscimol and muscazone are isolated from amanita muscaria and other amanita species. Isoxazole derivatives were used as inhibitors for ulcers [21], lipoxygenase[22], acetyl choline esterase[23]. 3-Substituted 5-methylthio isoxazoles were found to exhibit anthelmintic activity[24]. Spiro isoxazolines[25] and benzofuro-isoxazoles[26] were used as anti-convergents. 5-Amino-3-methyl-4-ureidoisox-azoles were found to exhibitanti leukemic activity[27]. Some new 2-isoxazole derivatives prepared from α,β-dibromochalcones showed mild antibacterial activity[28]. A group of 4,5-diphenyl isoxazoles, 3,4-diphenyl-5-trifluoro methyl isoxazoles and 4,5-diphenyl-3-methyl sulfonoamido isoxazole possessing a variety of substitutions (H, F, MeS, MeSO, $MeSO_2$) at the *para* position of one of the phenyl rings were used as analgesic and selective COX-2 inhibitory and antiinflammatory agents[29]. Isoxazolyl naphthoquinones act as potential trypanocidal and antibacterial agents[30]. In the chemistry of polyfunctional heterocycles with enhanced biological potency, it is very interesting to synthesize new compounds which accommodate the biologically active quinoline, isolated pyrazole and/or isolated isoxazole moieties, in the same structure.

EXPERIMENTAL

All materials were obtained from commercial suppliers (Aldrich and Merck) and used without further purification. Melting points were uncorrected and recorded on Gallenkamp electro thermal 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). Elemental analytical data (in accordance with the calculated values) were calculated at the micro analytical unit of Cairo University. The IR spectra were obtained from KBr disks using Perkin Elmer 1650 ET-IR Spectrophotometer (USA). The ^{1}H NMR and ^{13}C-NMR spectra were recorded on an FT-NMR JNM-LA spectrometer (300 MHZ) in $CDCl_3$ or DMSO-d_6 as solvent, using TMS as an internal standard.

Synthesis of 7,14-diamino-5,5a,12,12a-tetrahydro-[1,2]thiazino[4',5':5,6]pyrido[2,3-g][1,2]thiazino[5,4-b]quinoline-1,6,8,13(2H,4H,9H,11H)-tetraone (1): This compound was prepared according to the reported method[31].

2,9-Diacetyl-7,14-diamino-5,5a,12,12a-tetrahydro-[1,2]thiazino[4',5':5,6]pyrido[2,3-g][1,2]thiazino[5,4-b]quinoline-1,6,8,13(2H,4H,9H,11H)-tetraone (2): A solution of compound **1** (4.30, 0.01 mol) in a mixture of acetic anhydride and acetic acid (1:1 molar ratio) was refluxed for about 9 h. The reaction mixture was filtred, dried and collected. On crystallization from the ethanol it gives compound **2**. This compound was obtained as brown crystals. m.p.: 296 °C, Yield: 68 % (EtOH). IR (KBr, ν_{max}, cm^{-1}): 3400-3100 (NH, NH_2), 3048 (C-H, aromatic) 1685 (2CO), 1660-1640 (4CO). ^{1}H NMR (DMSO-d_6, δ ppm): δ 1.66 (S, 6H, $2CH_3$), δ 6.76 (brs, 4H, $2NH_2$), δ 7.01-8.01 (m, 6 Ar-H), δ 11.12 (brs, 2H, 2NH). ^{13}C NMR δ (ppm):169.08 (C=O of acetyl, group), 161.07 (C=O of 1,2-thiazino ring), 36.89 (CH_2 of 1,2-thiazino ring), 19.02 (CH_3 for acetyl group). MS (*m/z*, (%)): 502 (25) [M$^+$]. Anal. (%) Calcd. for $C_{20}H_{18}N_6O_6S_2$ (502.52): C, 47.80; H, 3.61; N, 16.72; S, 12.76. Found: C, 47.79; H, 3.59; N, 16.71; S, 12.74.

Synthesis of arylidino derivatives (4a-c): A solution of compound **2** (5.14 g, 0.01 mol) and aromatic aldehydes (**3a-c**) (1.06, 1.22 and 1.51 g, 0.01 mol, respectively) in a mixture of ethanol and dimethyl formamide in presence of piperidine (0.5 mL) as catalyst was refluxed for 8-9 h. The mixture was concentrated and then left to cool and pour onto ice water acidified by concentrated hydrochloric acid. The solid product so formed was collected by filtration and recrystallized from the ethanol and dimethyl formamide to give arylidino derivatives (**4a-c**).

2-Acetyl-7,14-diamino-9-cinnamoyl-5,5a,12,12a-tetrahydro-[1,2]thiazino[4',5':5,6]pyrido[2,3-g][1,2]thiazino[5,4-b]quinoline-1,6,8,13(2H,4H,9H,11H)-tetraone (4a): This compound was obtained as reddish brown crystals. m.p.: >300 ºC, Yield: 60 % (EtOH/DMF). IR (KBr, ν_{max}, cm^{-1}): 3400-3150 (NH, NH_2), 3046 (C-H, aromatic) 1660 (2CO), 1658-1640 (4CO). ^{1}H NMR (DMSO-d_6, δ ppm): δ 1.66 (S, 3H, CH_3), δ 6.68 (brs, 4H, $2NH_2$), 7.01-8.01 (m, 13 Ar), 10.48 (brs, 2H, 2NH). ^{13}C NMR δ (ppm): 169.09 (C=O of acetyl group), 165.85 (C=O attached to chalcon), 118.02, 140.97 (CH=CH) 161.08 (C=O of 1,2-thiazino ring), 36.88 (CH_2 of 1,2-thiazino ring), 19.02 (CH_3 for acetyl group). MS (*m/z*, (%)): 590 (20) [M$^+$]. Anal. (%) Calcd. for $C_{27}H_{22}N_6O_6S_2$ (590.63): C, 54.91; H, 3.75; N, 14.23; S, 10.86. Found: C, 54.89; H, 3.73; N, 14.22; S, 10.85.

(E)-2-Acetyl-7,14-diamino-9-(3-(4-aminophenyl)acryloyl)-5,5a,12,12a-tetrahydro-[1,2]thiazino[4',5':5,6]pyrido[2,3-g][1,2]thiazino[5,4-b]quinoline-1,6,8,13(2H,4H,9H,11H)-tetraone (4b): This compound was obtained as brown crystals. m.p.: >300 ºC, Yield: 63 % (EtOH/DMF). IR (KBr, ν_{max}, cm^{-1}): 3400-3150 (NH, NH_2), 3044 (C-H, aromatic), 1685 (2CO), 1675-1640 (4CO). ^{1}H NMR (DMSO-d_6, δ ppm): δ 1.16 (s, 3H, CH_3), δ 6.72 (brs, 4H, $2NH_2$), 7.01-8.01 (m, 14Ar-H), 10.52 (brs, 2H, 2NH). MS (*m/z*, (%)): 605 (16) [M$^+$]. Anal. (%) Calcd. for $C_{27}H_{23}N_7O_6S_2$ (605.64): C, 53.54; H, 3.83; N, 16.19; S, 10.59. Found: C, 53.53; H, 3.81; N, 16.18; S, 10.57.

(E)-2-Acetyl-7,14-diamino-9-(3-(4-hydroxyphenyl) acryloyl)-5,5a,12,12a-tetrahydro-[1,2]thiazino[4',5':5,6] pyrido[2,3-g][1,2]thiazino[5,4-b]quinoline-1,6,8,13 (2H,4H,9H,11H)-tetraone (4c): This compound was obtained as reddish violet crystals. m.p.: > 300 ºC Yield: 62 % (EtOH/DMF). IR (KBr, ν_{max}, cm^{-1}): 3400-3150 (NH, NH_2, OH), 3044 (C-H, aromatic), 1680 (2CO), 1670-1640 (4CO). ^{1}H NMR (DMSO-d_6, δ ppm): δ 1.09 (s, 3H, CH_3), δ 6.66 (brs, 4H, $2NH_2$), 7.01-8.01 (m, 13H), 10.49 (brs, 2H, 2NH). MS (*m/z*, (%)): 606 (20) [M$^+$]. Anal. (%) Calcd. for $C_{27}H_{22}N_6O_7S_2$ (606.63): C, 53.46; H, 3.66; N, 13.85; S, 10. 57. Found: C, 53.45; H, 3.64; N, 13.84; S, 10.55.

Synthesis of N-acetyl pyrazolino derivatives (5a-c): To a solution of arylidino (**4a-c**) (6.02, 6.47 and 6.18 g, 0.01 mol, respectively) in ethanol (30 mL) as solvent, hydrazine hydrate (0.5 g, 0.01 mol) was added followed by glacial acetic acid (10 mL). The reaction mixture was refluxed for 11 h. The reaction mixture was concentrated and filtred. These materials were triturated with water and the precipitates were separated, filtred, washed several times with water, dried, collected and recrystallized from the ethanol solvent to give pyrazolino derivatives (**5a-c**).

2-Acetyl-9-(1-acetyl-4-phenyl-1H-pyrazole-3-carbonyl)-7,14-diamino-5,5a,12,12a-tetrahydro-[1,2]-thiazino[4',5':5,6]pyrido[2,3-g][1,2]thiazino[5,4-b]quinoline-1,6,8,13(2H,4H,9H,11H)-tetraone (5a): This compound was obtained as violet crystals. m.p.: >300 ºC, Yield: 61 % (EtOH). IR (KBr, ν_{max}, cm^{-1}): 3400-3100 (NH, NH_2), 1665 (2CO), 1660-1640 (4CO), 3044 (C-H, aromatic). ^{1}H NMR (DMSO-d_6, δ ppm): δ 1.02 (s, 3H, CH_3), δ 1.5 (s, 3H, CH_3), δ 6.54 (brs, 4H, $2NH_2$), 7.01-8.01 (m, 12H), 10.39 (brs, 2H 2NH). ^{13}C NMR δ (ppm): 169.09 (C=O of acetyl group), 167.07 (C=O attached to pyrazole ring), 105.92, 139.89, 143.89 (carbon of pyrazole ring). 161.08 (C=O of 1,2-thiazino ring), 36.89 (CH_2 of 1,2-thiazino ring), 19.01 (CH_3 for acetyl group). MS (*m/z*, (%)): 672 (30) [M$^+$]. Anal. (%) Calcd. for $C_{30}H_{24}N_8O_7S_2$ (672.12): C, 53.56; H, 3.60; N, 16.66; S, 9.53. Found: C, 53.55; H, 3.58; N, 16.65; S, 9.52.

2-Acetyl-9-[1-acetyl-4-(4-aminophenyl)-1H-pyrazole-3-carbonyl]-7,14-diamino-5,5a,12,12a-tetrahydro-[1,2]thiazino[4',5':5,6]pyrido[2,3-g][1,2]thiazino[5,4-b]quinoline-1,6,8,13(2H,4H,9H,11H)-tetraone(5b): This compound was obtained as deep violet crystals. m.p.: > 300 ºC, Yield: 62 % (EtOH). IR (KBr, ν_{max}, cm^{-1}): 3400-3150 (NH, NH_2), 3044 (C-H, aromatic), 1688 (2CO), 1665-1640 (4CO).

^{1}H NMR (DMSO-d_6, δ ppm): δ 1.08 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), δ 6.61 (brs, 4H, $2NH_2$), 7.01-8.01 (m, 13H, Ar-H), 10.56 (brs, 2H, 2NH). MS (*m/z*, (%)): 687 (15) [M^+]. Anal. (%) Calcd. for $C_{30}H_{25}N_9O_7S_2$ (687.71): C, 52.39; H, 3.66; N, 18.33; S, 9.33. Found: C, 52.38; H, 3.64; N, 18.31; S,9.32.

2-Acetyl-9-[1-acetyl-4-(4-hydroxyphenyl)-1H-pyrazole-3-carbonyl]-7,14-diamino-5,5a,12,12a-tetrahydro-[1,2]thiazino[4',5':5,6]pyrido[2,3-g][1,2]thiazino[5,4-b]quinoline-1,6,8,13(2H,4H,9H,11H)-tetraone (5c): This compound was obtained as green violet crystals. m.p.: >300 ºC, Yield: 63 % (EtOH). IR (KBr, ν_{max}, cm^{-1}): 3450-3100 (NH, NH_2, OH), 3042 (C-H, aromatic), 1670 (2CO), 1665-1640 (4CO). ^{1}H NMR (DMSO-d_6, δ ppm): δ 1.04 (s, 3H, CH_3), δ 1.52 (s, 3H, CH_3), δ 6.63 (brs, 4H, $2NH_2$), 7.01-8.01 (m, 12H, Ar-H), 10.42 (brs, 2H, 2NH). MS (*m/z*, (%)): 688 (25) [M^+]. Anal. (%) Calcd. for $C_{30}H_{24}N_8O_8S_2$ (688.69): C, 52.32; H, 3.51; N, 16.27; S, 9.31. Found: C, 52.31; H, 3.50; N, 16.25; S,9.30.

Synthesis of N-phenyl pyrazolino derivatives (6a-c): To a solution of arylidino derivatives (**4a-c**) (6.02 g, 6.47 g, 6.18 g, 0.0l mol, respectively) in ethanol as solvent, added phenylhydrazine (1.08 g, 0.01 mol) in the presence of piperidine (0.5 mL) as catalyst. The reaction mixture was refluxed for 12 h. The reaction mixture was concentrated, cooled, poured onto ice water acidified by concentrated hydrochloric acid. The solid products were collected by filtration, washed with water for several times and crystallized from the ethanol solvent to yield the corresponding **6a-c**.

2-Acetyl-7,14-diamino-9-(1,4-diphenyl-1H-pyrazole-3-carbonyl)-5,5a,12,12a-tetrahydro-[1,2]thiazino[4',5':5,6] pyrido[2,3-g][1,2]thiazino[5,4-b]quinoline-1,6,8,13(2H, 4H,9H,11H)-tetraone (6a): This compound was obtained as green violet crystals. m.p.: >300 ºC, Yield: 63 % (EtOH). IR (KBr, ν_{max}, cm^{-1}): 3400-3100 (NH, NH_2), 3044 (C-H, aromatic), 1668 (2CO), 1660-1640 (3CO). ^{1}H NMR (DMSO-d_6, δ ppm): δ 1.07 (s, 3H, CH_3), δ 6.65 (brs, 4H, $2NH_2$), 7.01-8.01 (m, 17H, Ar-H), 10.46 (brs, 2H, 2NH). ^{13}C NMR δ (ppm): 169.09 (C=O of acetyl group), 167.02 (C=O attached to phenyl pyrazole ring), 107.92, 141.99, 143.02 (carbon of pyrazole ring). 161.08 (C=O of 1,2-thiazino ring), 36.89 (CH_2 of 1,2-thiazino ring), 19.01 (CH_3 for acetyl group). MS (*m/z*, (%)): 706 (30) [M^+]. Anal. (%) Calcd. for $C_{34}H_{26}N_8O_6S_2$ (706.14): C, 57.78; H, 3.71; N, 15.85; S, 9.07. Found: C, 57.77; H, 3.70; N, 15.84; S, 9.06.

2-Acetyl-7,14-diamino-9-[4-(4-aminophenyl)-1-phenyl-1H-pyrazole-3-carbonyl]-5,5a,12,12a-tetrahydro-[1,2]thiazino[4',5':5,6]pyrido[2,3-g][1,2]thiazino[5,4-b]quinoline-1,6,8,13(2H,4H,9H,11H)-tetraone (6b): This compound was obtained as blue violet crystals. m.p.: >300 ºC, Yield: 57 % (EtOH). IR (KBr, ν_{max}, cm^{-1}): 3400-3150 (NH, NH2), 3041 (C-H, aromatic), 1663 (2CO), 1657-1645 (3CO). ^{1}H NMR (DMSO-d_6, δ ppm): δ 1.15 (s, 3H, CH_3), δ 6.69 (brs, 4H, $2NH_2$), 7.01-8.01 (m, 18H, Ar-H), 10.44 (brs, 2H, 2NH). MS (*m/z*, (%)): 721 (25) [M^+]. Anal. (%) Calcd. for $C_{34}H_{27}O_6N_9S_2$ (721.76): C, 56.58; H, 3.77; N, 17.47; S, 8.89. Found: C, 56.56; H, 3.75; N, 17.46; S, 8.88.

2-Acetyl-7,14-diamino-9-[4-(4-hydroxyphenyl)-1-phenyl-1H-pyrazole-3-carbonyl]-5,5a,12,12a-tetrahydro-[1,2]thiazino[4',5':5,6]pyrido[2,3-g][1,2]thiazino[5,4-b]quinoline-1,6,8,13(2H,4H,9H,11H)-tetraone (6c): This compound was obtained as violet crystals. m.p.: >300 ºC Yield 60 % (EtOH). IR (KBr, ν_{max}, cm^{-1}): 3400-3310 (NH, NH_2, OH), 3041 (C-H, aromatic), 1660 (2CO), 1655-1640 (3CO). ^{1}H NMR (DMSO-d_6, δ ppm): δ 1.11 (s, 3H, CH_3), δ 6.67 (brs, 4H, $2NH_2$), 7.01-8.01 (m, 17H, Ar-H), 10.40 (brs, 2H, 2NH). MS (*m/z*, (%)): 722 (15) [M^+]. Anal. (%) Calcd. for $C_{34}H_{26}N_8O_7S_2$ (722.75): C, 56.50; H, 3.63; N, 15.50; S, 8.87. Found: C, 56.48; H, 3.61; N, 15.49; S,8.86.

Synthesis of arylisooxazolo derivatives (7a-c): A solution of arylidino derivatives (**4a-c**) (6.20 g, 6.47 g, 6.18 g, 0.01 mol, respectively) was refluxed with hydroxylamine hydrochloride (0.69 g, 0.01 mol) in presence of sodium hydroxide as catalyst and ethanol as solvent for 9 h. The reaction mixture was filtred hot, the filtrate was concentrated and poured onto ice water where the products were separated, filtred, washed several times with water and crystallized from the methanol solvent to yield the corresponding **7a-c**.

2-Acetyl-7,14-diamino-9-(4-phenylisoxazole-3-carbonyl)-5,5a,12,12a-tetrahydro-[1,2]thiazino[4',5':5,6]pyrido[2,3-g][1,2]thiazino[5,4-b]quinoline-1,6,8,13(2H,4H,9H,11H)-tetraone (7a): This compound was obtained as reddish brown crystals. m.p.: >300 ºC, Yield: 58 % (MeOH). IR (KBr, ν_{max}, cm^{-1}): 3400-3100 (NH, NH_2), 3044 (C-H, aromatic),1670 (2CO), 1660-1640 (3CO). ^{1}H NMR (DMSO-d_6, δ ppm): δ 1.06 (s, 3H, CH_3), δ 6.56 (brs, 4H, $2NH_2$), 7.01-8.01 (m, 12H, Ar-H), 10.29 (brs, 2H, 2NH). ^{13}C NMR δ (ppm): 169.09 (C=O of acetyl group), 166.87 (C=O attached to oxazole ring), 99.02, 149.87, 168.79 (carbon of oxazole ring). 161.08 (C=O of 1,2-thiazino ring), 36.89 (CH_2 of 1,2-thiazino ring), 19.01 (CH_3 for acetyl group). MS (*m/z*, (%)): 631 (20) [M^+]. Anal. (%) Calcd. for $C_{28}H_{21}N_7O_7S_2$ (631.64): C, 53.24; H, 3.35; N, 15.52; S, 10.15. Found: C, 53.22; H, 3.32; N, 15.49; S, 10.13.

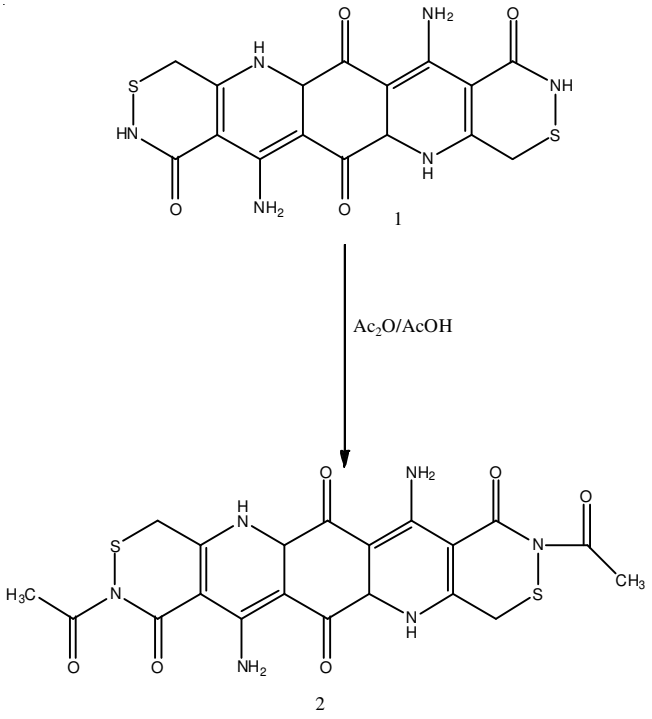
2-Acetyl-7,14-diamino-9-(4-(4-aminophenyl)isoxazole-3-carbonyl)-5,5a,12,12a-tetrahydro-[1,2]thiazino[4',5':5,6] pyrido[2,3-g][1,2]thiazino[5,4-b]quinoline-1,6,8,13(2H,4H, 9H,11H)-tetraone (7b): This compound was obtained as brown crystals. m.p.: > 300 ºC, Yield: 57 % (MeOH). IR (KBr, ν_{max}, cm^{-1}): 3450-3100 (NH, NH_2), 3044 (C-H, aromatic), 1678 (2CO), 1665-1640 (3CO). ^{1}H NMR (DMSO-d_6, δ ppm): δ 1.13 (s, 3H, CH_3), δ 6.60 (brs, 4H, $2NH_2$), 7.01-8.01 (m, 13H, Ar-H), 10.34 (brs, 2H, 2NH). MS (*m/z*, (%)): 646 (18) [M^+]. Anal. (%) Calcd. for $C_{28}H_{22}N_8O_7S_2$ (646.65): C, 52.01; H, 3.43; N, 17.33; S, 9.92. Found: C, 52; H, 3.41; N, 17.30; S, 9.90.

2-Acetyl-7,14-diamino-9-(4-(4-hydroxyphenyl)isoxazole-3-carbonyl)-5,5a,12,12a-tetrahydro-[1,2]thiazino[4',5': 5,6]pyrido[2,3-g][1,2]thiazino[5,4-b]quinoline-1,6,8,13 (2H,4H,9H,11H)-tetraone(7c): This compound was obtained as reddish violet crystals. m.p.: >300 ºC, Yield 55 %. (MeOH). IR (KBr, ν_{max}, cm^{-1}): 3100-3450 (NH, NH_2, OH), 3044 (C-H, aromatic)1673 (2CO), 1640-1660 (3CO). ^{1}H NMR (DMSO-d_6, δ ppm): δ 1.09 (s, 3H, CH_3), δ 6.58 (brs, 4H, $2NH_2$), 7.01-8.01 (m, 12H, Ar-H), 10.36 (brs, 2H, 2NH). MS (*m/z*, (%)): 631 (15) [M^+]. Anal. (%) Calcd. for $C_{28}H_{21}N_7O_8S_2$ (647.64): C, 51.93; H, 3.27; N, 15.14;S, 9.90. Found: C, 51.91; H, 3.26; N, 15.13; S, 9.87.

RESULTS AND DISCUSSION

Compound **2** was prepared by the reaction of compound **1**[31] with a mixture of acetic anhydride and glacial acetic acid

which was heated together under reflux for 12 h (**Scheme-I**). The IR spectra revealed the presence of band at 1685 (2CO) for two carbonyl groups of acetyl, ^{1}H NMR spectra revealed the presence of singlet at δ 1.66 (d, S, 6H, 2CH_3), for two methyl group. The structure of compound **2** was also confirmed by elemental analysis, IR spectra ^{1}H NMR, ^{13}C NMR and mass spectra as follow: (a) Compatible elementary and molecular weight determination (MS: *m/z* 502, 25 %) corresponded to $C_{20}H_{18}N_6O_6S_2$ (502.52); (b) Its IR spectrum (KBr, ν_{max}, cm^{-1}) showed strong absorption bands at 3048 (C-H, aromatic) 1685 (2CO), 1660-1640 (4CO); (c) The ^{1}H NMR spectrum (DMSO-d_6, δ ppm) showed singlet due to two methyl protons which appeared in the spectrum of compound **2** around 1.66 ppm, δ 1.66 (S, 6H, 2CH_3); (d) ^{13}C NMR δ (ppm): 169.08 (C=O of acetyl, group), 161.07 (C=O of 1,2-thiazino ring), 36.89 (CH_2 of 1,2-thiazino ring), 19.02 (CH_3 for acetyl group).

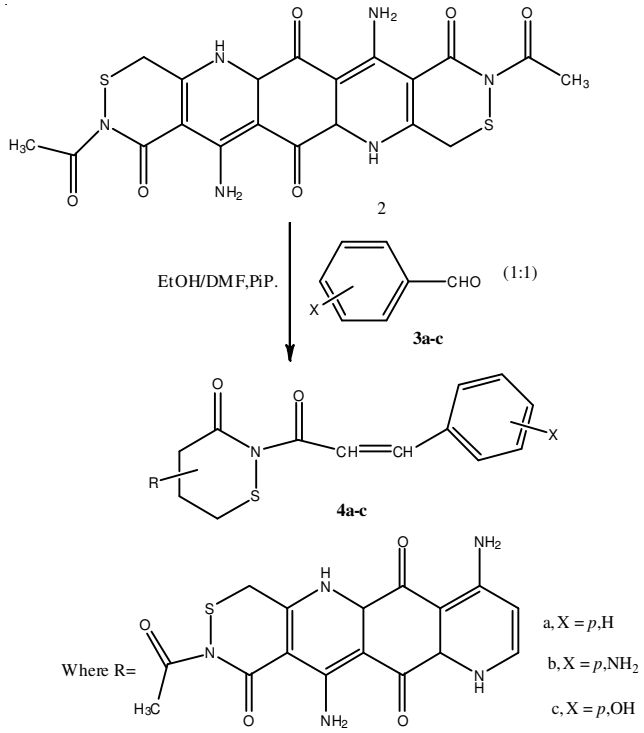


Scheme-I

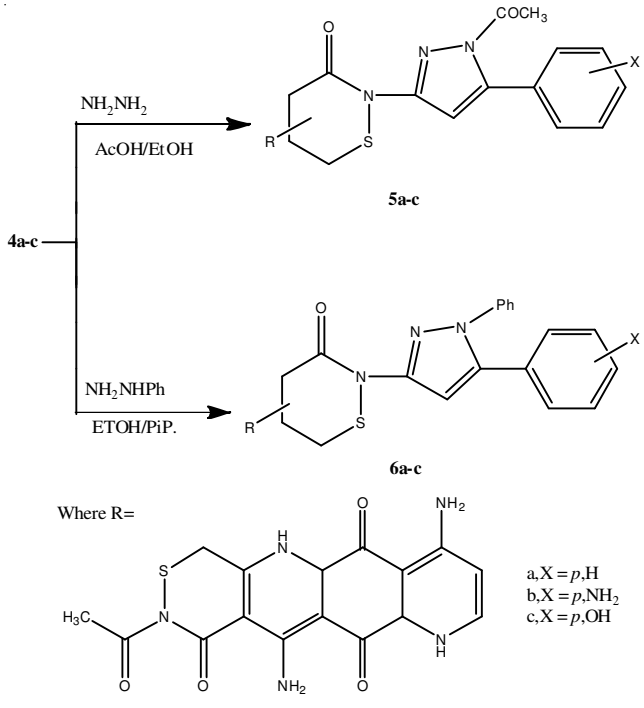
Reaction of compound **2** with the aromatic aldehydes (**3a-c**) in the presence of catalytic amount of piperidine gave the corresponding arylidene derivatives (**4a-c**). The reaction passed through the condensation of the methyl protons of compound **2** with the aldehydic carbonyl group of (**3a-c**).

Structural reasonings for 4a, taken as a representative example are: (a) Compatible elementary and molecular weight determination (MS: *m/z* 590, 20 %) corresponded to $C_{27}H_{22}N_6O_6S_2$ (590.63); (b) Its IR spectrum (KBr, ν_{max}, cm^{-1}) showed strong absorption bands at 3046 (C-H, aromatic) 1660 (2CO), 1640-1658 (4CO); (c) The ^{1}H NMR spectrum (DMSO-d_6, δ ppm) showed one singlet due to methyl protons which appeared in the spectrum of compound **2** around 1.66 ppm; (d) ^{13}C NMR δ (ppm): 169.09 (C=O of one acetyl group), 165.85 (C=O attached to chalcon), 118.02, 140.97 (CH=CH) 161.08 (C=O of 1,2-thiazino ring), 36.88 (CH_2 of 1,2-thiazino ring), 19.02 (CH_3 for one acetyl group).

Moreover, reaction of the arylidene derivatives (**4a-c**) with an equimolar amount of hydrazine hydrate and/or phenylhydrazine in the presence of a base (**Scheme-II**) gave N-acetylpyrazolo derivatives **5a-c** and N-phenylpyrazolo derivatives (**6a-c**), respectively (**Scheme-III**).



Scheme-II



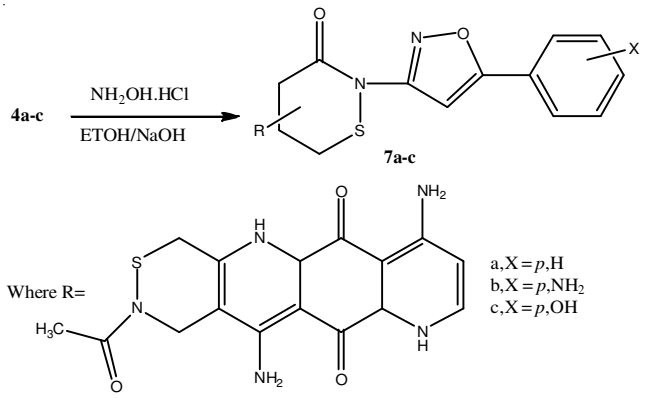
Scheme-III

Structural reasonings for **5a**, taken as a representative example for formation of acetyl pyrazole, are: (a) Compatible elementary and molecular weight determination (MS: *m/z* 672, 30 %) corresponded to $C_{30}H_{24}N_8O_7S_2$ (672.12); (b) IR (KBr,

ν_{max}, cm^{-1}): 3400-3100 (NH, NH_2), 1665 (2CO), 1660-1640 (4CO), 3044 (C-H, aromatic); (c) ^1H NMR (DMSO-d_6, δ ppm): δ 1.02 (s, 3H, CH_3), δ 1.5 (s, 3H, CH_3), δ 6.54 (brs, 4H, $2NH_2$), 7.01-8.01 (m, 12H, Ar-H), 10.39 (brs, 2H, 2NH); (d) ^{13}C NMR δ (ppm): 169.09 (C=O of acetyl group), 167.07 (C=O attached to pyrazole ring), 105.92, 139.89, 143.89 (carbon of pyrazole ring), 161.08 (C=O of 1,2-thiazino ring), 36.89 (CH_2 of 1,2-thiazino ring), 19.01 (CH_3 for acetyl group).

Structural reasonings for **6a**, taken as a representative example for formation of phenyl pyrazole, are: (a) Compatible elementary and molecular weight determination (MS: *m/z* 706, 30 %) corresponded to $C_{34}H_{26}N_8O_6S_2$ (706.14); (b) IR (KBr, ν_{max}, cm^{-1}): 3100-3400 (NH, NH_2), 3044 (C-H, aromatic), 1668 (2CO), 1640-1660 (3CO); (c) ^1H NMR (DMSO-d_6, δ ppm): δ 1.07 (s, 3H, CH_3), δ 6.65 (brs, 4H, $2NH_2$), 7.01-8.01 (m, 17H, Ar-H), 10.46 (brs, 2H, 2NH); (d) ^{13}C NMR δ (ppm): 169.09 (C=O of acetyl group), 167.02 (C=O attached to phenyl pyrazole ring), 107.92, 141.99, 143.02 (carbon of pyrazole ring), 161.08 (C=O of 1,2-thiazino ring), 36.89 (CH_2 of 1,2-thiazino ring), 19.01 (CH_3 for acetyl group).

Similarly, the isooxazolo pyrimidine derivatives (**7a-c**) were obtained through the reaction of arylidene derivatives (**4a-c**) with an equimolar amount of hydroxylamine hydrochloride in ethanol with the presence of sodium hydroxide as a catalyst (**Scheme-IV**).



Scheme-IV

Structural reasonings for **7a**, taken as a representative example for formation of Isoxazole , are: (a) Compatible elementary and molecular weight determination (MS: *m/z* 631, 20 %) corresponded to $C_{28}H_{21}N_7O_7S_2$ (631.64); (b) IR (KBr, ν_{max}, cm^{-1}): 3100-3400 (NH, NH_2), 3044 (C-H, aromatic), 1670 (2CO), 1640-1660 (3CO); (c) ^1H NMR (DMSO-d_6, δ ppm): δ 1.06 (s, 3H, CH_3), δ 6.56 (brs, 4H, $2NH_2$), 7.01-8.01 (m, 12H, Ar-H), 10.29 (brs, 2H, 2NH); (d) ^{13}C NMR δ (ppm): 169.09 (C=O of acetyl group), 166.87 (C=O attached to oxazole ring), 99.02, 149.87, 168.79 (carbon of oxazole ring), 161.08 (C=O of 1,2-thiazino ring), 36.89 (CH_2 of 1,2-thiazino ring), 19.01 (CH_3 for acetyl group).

Conclusion

In the present investigation, we have successfully synthesized some novel compounds which incorporate two and/or three heterocyclic moieties of anticipated biological activities in one and the same molecule. Thus, the molecule of compound **2** incorporates both of the quinoline moiety as well as the 1,2-thiazino moiety which is also known of its pharmaceutical activity[32]. In addition to the two latter moieties, compounds **5a-c** , **6a-c** and **7a-c** incorporate also the isolated pyrazole and the isolated isoxazole moieties, respectively, in their structures. 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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