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DESIGN AND SYNTHESIS OF SOME NOVEL FUSED TRIHETEROCYCLIC THIAZOLOPYRIMIDINE DERIVATIVES INCORPORATING A BENZOQUINOLINE MOIETY

Hisham Abdallah A. Yosef[b] Nadia Ali Ahmed Elkanzi [a,c*] and Nesrin Mahmoud M. Mohamed[b,c]

[a]*Chemistry Department, Faculty of Science, Aswan University, Aswan, 81528, Egypt.*
[b]*Organometallic and Organometalloid Chemistry Department, National Research Centre, El -Buhouth St, Dokki, Giza, Egypt, PO 12622.*
[c]*Chemistry Department, Faculty of Science, Aljouf University, Al Jouf, 2014, Kingdom of Saudi Arabia.*
Corresponding author (N.A.A.Elkanzi):E−mail: kanzi20@yahoo.com

Abstract:
Knoevenagel condensation of 7-(4-amino-3-cyano-5,10-dioxo-1,5,10,10a-tetrahydrobenzo [*g*] quinolin-2-yl)-3,5-dioxo-3,5-dihydro-2*H*-thiazolo[3,2-*a*]pyrimidine-6-carbonitrile **(1)** with aldehydes **2a-c** afforded the respective 7-(4-amino-3-cyano-5,10-dioxo-1,5, 10,10a-tetrahydrobenzo[*g*]quinolin-2-yl)-2-arylidene-3,5-dioxo-3,5-dihydro-2*H*-thiazolo[3,2-*a*]-pyrimidine-6-carbonitrile derivatives **3a-c**. A number of interesting fused heterocyclic derivatives were prepared through heterocyclization reactions of compounds **3a-c** with some selected bidentate nitrogen nucleophiles, namely, hydrazine hydrate in acetic acid, phenyl-hydrazine, hydroxylamine hydrochloride, urea and thiourea to afford the polycondensed ring systems of *N*-acetylpyrazolothiazolopyrimidines **4a–c**, *N*-phenylpyrazolothiazolopyrimidines **5a–c**, isoxazolothiazolopyrimidines **6a-c,** oxopyrimidothiazolopyramidines **7a-c** and thioxopyrimidothiazolopyrimidines **8a-c,** respectively. Structures of the new products were elucidated by elemental analyses as well as spectroscopic measurements (IR, ^{1}H-NMR and MS).

Keywords: Benzoquinolines, *Knoevenagel* condensation, heterocyclization, thiazolopyrimidines and spectroscopic measurements.

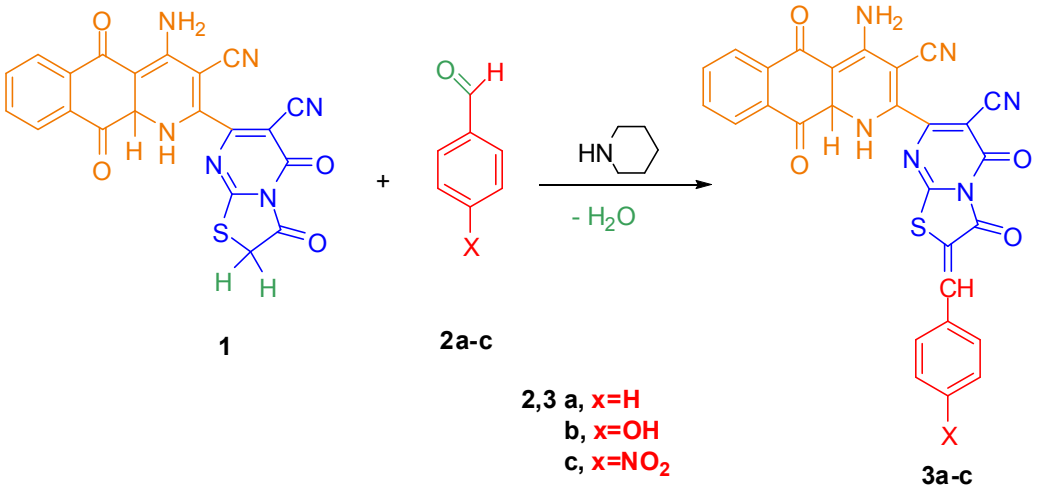
Introduction:

One of the most important heterocycles exhibiting remarkable biological activities and therapeutic applications is the pyrimidine nucleus. The presence of a pyrimidine base in thymine, cytosine, adenine, guanine and uracil, which are the essential building blocks of nucleic acids,

deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), is one of the possible reasons which make pyrimidine derivatives exhibiting a wide spectrum of pharmacophore. [I-VII] In addition, it has been observed over the years that the thiazole ring possesses different biological activities[VIII–XII] where it is a crucial part of many drugs like epothilones [XIII] which are used for treatment of cancer. Thus, due to the great potential of both moieties, thiazolopyrimidines have acquired a growing importance where their biological and synthetic significances place this scaffold at a prestigious position in medicinal chemistry research. Thiazolo[3,2-*a*]-pyrimidines are of pharmacological interest due to their anti-inflammatory,[XIV] psychopharmacological,[XV] antibacterial [XVI] and antiviral activity as inhibitors of HIV-1 reverse transcriptase.[XVII] Moreover, thiazolo[4,5-*d*]pyrimidine derivatives, which can be considered as thia-analogues of the natural purine bases such as adenine and guanine, have also acquired a growing importance in the field of medicinal chemistry because of their biological activities.[XVIII-XX] Considering all of the aforementioned pharmacological potentials, we herein continue our work [XXI] in designing and synthesis of novel heterocyclic derivatives with anticipated biological potency where some heterocyclic rings namely, pyrazole, isoxazole, oxopyrimidine and thioxopyrimidine, have been fused to a thiazolopyrimidine skeleton substituted with a benzoquinoline moiety which also possess diverse pharmacological activities.[XXII–XXV]

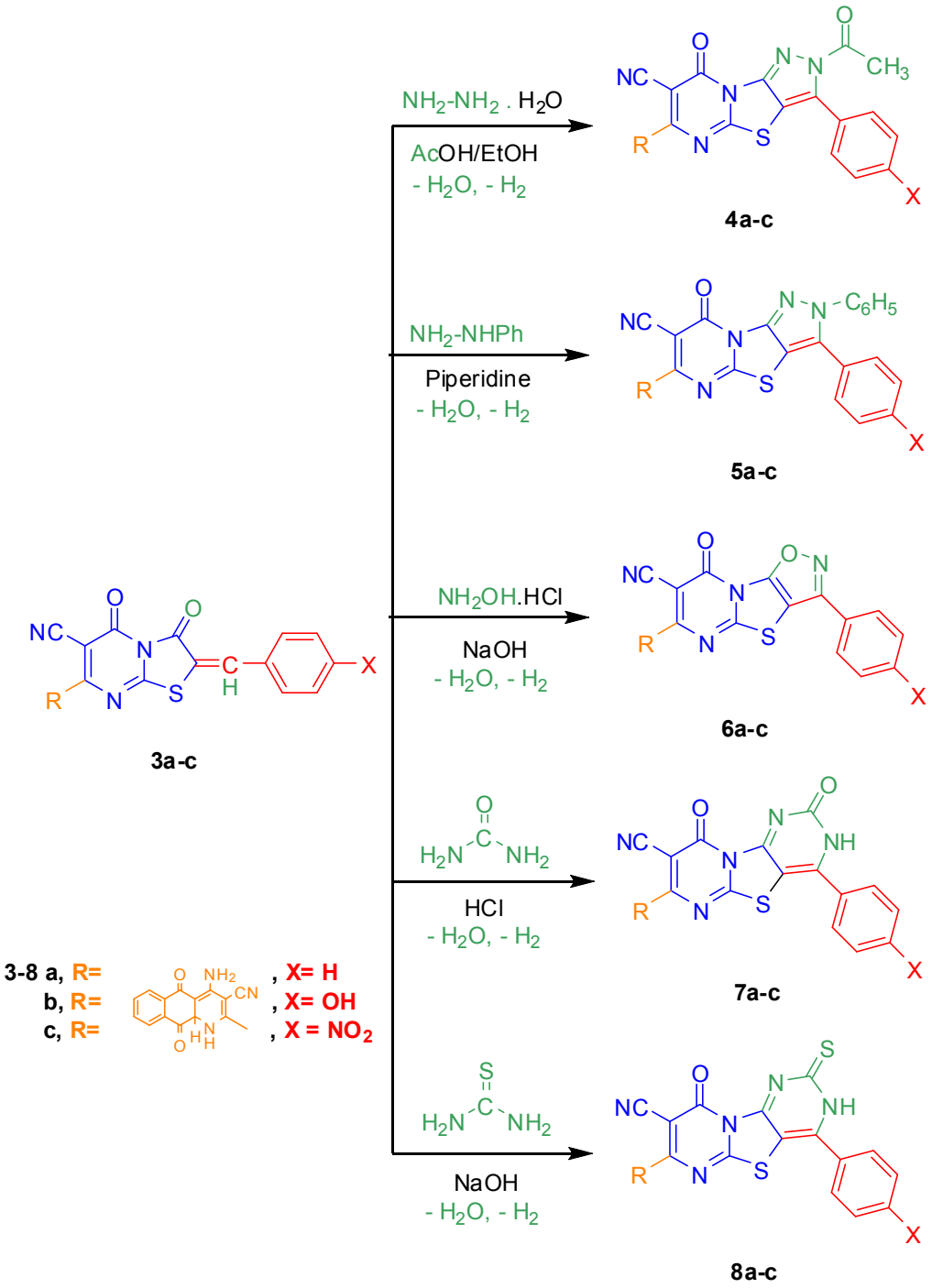
Results and Discussion

We have now found that 7-(4-amino-3-cyano-5,10-dioxo-1,5,10,10a-tetrahydrobenzo[*g*]quinolin-2-yl)-3,5-dioxo-3,5-dihydro-2*H*-thiazolo [3,2-*a*]pyrimidine-6-carbonitrile **(1)**[XXI] undergoes *Knoevenagel* condensation [XXVI] with the freshly distilled and/or crystallized aromatic aldehydes **2a-c,** namely benzaldehyde **(2a),** *p*-hydroxybenzaldehyde **(2b)** and *p*-nirtobenzaldehyde **(2c),** in presence of a catalytic amount of piperdine in ethanol at reflux to give the respective 7-(4-amino-3-cyano-5,10-dioxo-1,5,10,10a-tetrahydrobenzo[*g*]quinolin-2-yl)-2-arylidene-3,5-dioxo-3,5-dihydro-2*H*-thiazolo[3,2-*a*]pyrimidine-6-carbonitrile derivatives **3a-c** (Scheme 1) as brown crystals and in relatively good yields (up to 71 %).



Scheme 1. *Knoevenagel* condensation of compound **1** with aldehydes **2a-c**.

The structures of compounds **3a-c** have been confirmed though their elemental analysis and spectroscopic data (*cf*. Experimental). For example, 7-(4-amino-3-cyano-5,10-dioxo-1,5,10,10a-tetrahydrobenzo[*g*]quinolin-2-yl)-2-(4-nitrobenzylidene)-3,5-dioxo-3,5-dihydro-2*H*-thiazolo[3,2-*a*]pyrimidine-6-carbonitrile **(3c)** was given the assigned structure due to the following reasons:
a) Correct elemental microanalysis of compound **3c** corresponded to a molecular formula of $C_{28}H_{13}N_7O_6S$ (575.51).
b) Its mass spectrum (MS) recorded the molecular ion peak [M^+] at m/z 575 (16 %).
c) The IR spectrum (KBr, ν_{max}, cm^{-1}) of **3c** showed strong bands at 1638 and 1533 cm^{-1} due to the absorption of the exocyclic C=C and NO_2 groups,[XXVII] respectively. The spectrum revealed also the presence of bands at 3380, 3329, 3290 (NH_2, N−H), 3077, 3023 (aromatic and olefinic C−H), 2900 (saturated methine C−H), 2233, 2210 (C≡N), 1722, 1678 (C=O), 1600 (aromatic C=C), 1575 (cyclic C=N).
d) The ^{1}H NMR spectrum of compound **3c** (250 MHz, DMSO-d_6, δ_H ppm) revealed the absence of absorption due to the two geminal methylene protons which appeared as two doublets at δ_H = 3.74 ppm and δ_H = 4.00 ppm in the ^{1}H NMR spectrum of compound **1.**[XXI] However, the spectrum showed a multiplet in the 7.41– 8.22 ppm region corresponding to nine protons and could be attributed to the aromatic protons (8H) in addition to the methine proton of the exocyclic olefinic bond. The ^{1}H NMR spectrum of **3c** showed also a singlet at 3.66 ppm due to the proton on the sp^3 carbon atom of the benzoquinoline moiety (-(O)C-C***H***-NH-). The absorption due to the D_2O exchangeable protons of N***H***$_2$ and N***H*** groups appeared as two singlet signals at δ_H = 6.75 and 10.23 ppm, respectively.
The newly synthesized arylidene derivatives **3a-c,** as *Michael* receptors, have been now investigated as key molecules for building new fused heterocyclic rings through the addition on their α,β−unsaturated carbonyl system with different *Michael* donors, namely hydrazine hydrate, phenylhydrazine, hydroxylamine hydrochloride, urea and thiourea to give compounds **4**, **5**, **6**, **7** and **8**, respectively (Scheme 2).



Scheme 2. Cycloaddition reactions of selected nitrogen nucleophiles with arylidenes **3a-c.**

Pyrazole and isoxazole derivatives have attracted much attention due to their versatile chemotherapeutic importance and biological activities.[XXVIII-XXXII] In addition, a number of pyrazoles and isoxazoles can act as agrochemical herbicides, soil fungicides, pesticides and insecticides.[XXXIII] Furthermore, pyrazoles and isoxazoles are useful synthetic intermediates capable of undergoing various transformations and transition-metal catalyzed cross-coupling

reactions, such as Heck, Stille, Suzuki, Sonogashira, and Negishi couplings.[XXXIV] These facts substantiate a significant amount of research effort to be focused on the syntheses of these two nuclei.[XXVIII, XXXV] Thus, in this investigation compounds **3a-c** were reacted with hydrazine hydrate and acetic acid in ethanol at reflux, to give the respective *N*-acetylpyrazolothiazolo-pyrimidine derivatives **4a-c** as exclusive products (Scheme 2). It is assumed that, under acidic conditions,[XXXVI] the reaction follows via hydrazone intermediate formation, intramolecular *Michael type* addition [XXXVII] by the amino group on the β-carbon of the exocylic olefinic bond, cyclization and autoxidation [XXXV,XXXVIII,XXXIX] sequence to give the *N*-acetyl pyrazole ring. Compound **4c**, taken as a representative example, was formulated as 2-acetyl-6-(4-amino -3-cyano-5,10-dioxo-1,5,10,10a-tetrahydro- benzo[*g*] quinolin-2-yl)-3-(4-nitrophenyl)-8-oxo-2*H*,8*H*-pyrazolo[3',4':4,5][1,3] thiazolo[3,2-*a*]pyrimidine-7-carbonitrile due to the following reasons:

a) Compatible elementary and molecular weight determination of **4c** (MS: m/z 629, 14 %) corresponded to a molecular formula of $C_{30}H_{15}N_9O_6S$ (629.56).

b) Its IR spectrum revealed the absence of absorption due to the exocyclic C=C group which appeared in the spectrum of **3c** around 1638 cm^{-1} as a result of the involvement of this bond in the addition and formation of the pyrazole ring. Moreover, the spectrum disclosed the presence of bands at 1718, 1693, 1675 cm^{-1} due to the three carbonyl groups. The C≡N groups appeared as weak bands at 2235 and 2212 cm^{-1}. The spectrum showed also bands at 3384, 3332, 3279 (NH_2, N–H), 3092, 3028 (aromatic C–H), 2942, 2878 (aliphatic C–H), 1605 (aromatic C=C), 1578 (cyclic conjugated C=N) and 1538, 1350 (NO_2).

c) The ^{1}H NMR spectrum of **4c** showed a singlet at δ_H = 2.18 ppm due to methyl protons of the acetyl group. The methine proton (-C(O)-C***H***-NH) of the benzoquinoline moiety appeared as a singlet at δ_H = 3.60 ppm. No other signals due to protons on saturated carbon atoms have been detected in the spectrum. These data confirm the pyrazolyl structure and exclude the pyrazolinyl form from consideration. The aromatic protons (8H) appeared as a multiplet in 7.41- 8.28 ppm region. The spectrum showed also signals at δ_H = 6.65, 10.25 ppm due to (N***H***$_2$) and (N***H***) protons.

Moreover, refluxing of compounds **3a-c** with phenylhydrazine in ethanol with the presence of piperdine gave *N*-phenylpyrazolothiazolopyrimidine derivatives **5a-c**, respectively, as exclusive products in a reddish brown crystalline form (Scheme 2). Apparently, in presence of a base,[XXXV] a *Michael* type addition [XXXVII] by the NHPh group on the β-carbon of the exocyclic olefinic bond followed by an intramolecular heterocyclization with subsequent spontaneous oxidative dehydrogenation [XXXV, XXXVIII, XXXIX] gave compounds **5a-c**. The IR spectrum of compound **5b** exhibited a broad band at 3440 cm^{-1} due to the absorption of O–H group. The spectrum disclosed the absence of absorption due to the exocyclic C=C group that appeared around 1625 cm^{-1} for compound **3b**. The ^{1}H-NMR spectrum of **5b** showed three singlets at δ_H = 6.75, 8.26, 10.24 ppm due to the protons of N***H***$_2$ (2H), O***H*** (1H), N***H*** (1H) groups, respectively**.** The methine proton (-C(O)-C***H***-NH) of the benzoquinoline moiety appeared as a singlet at δ_H = 3.59 ppm. The spectrum showed the absence of any other signals due to protons on sp^3 carbon atoms which reveal the dehydrogenation occurance and formation of the pyrazolyl structure. The aromatic protons (13H) appeared as a multiplet in δ_H 6.81 – 8.18 ppm region. A compatible elemental analysis and molecular weight determination for **5b** (MS: m/z 634, 16 %) corresponded to a molecular formula of $C_{34}H_{18}N_8O_4S$ (*cf*. Experimental).

The isoxazole ring could be also fused to the investigated arylidenes **3a-c** by their refluxing with hydroxylamine hydrochloride in ethanol to give the isoxazolothiazolopyrimidine derivatives **6a-c** (Scheme 2).

The mass spectrum of compound **6c**, as an example, recorded the molecular ion peak [M^+] at 588 (30 %) which corresponded to a molecular formula of $C_{28}H_{12}N_8O_6S$ (588.51). The IR spectrum of **6c** recorded absorption bands at 1580 cm^{-1} and 1532 cm^{-1} due to cyclic C=N and NO_2 groups, respectively. It showed also bands at 3380, 3315, 3265 (NH_2, N−H), 3085, 3033 (aromatic C–H), 2900 (saturated C–H), 2239, 2212 (C≡N), 1713, 1675 (C=O) and 1607 (C=C, aromatic). Moreover, the spectrum does not exhibit the absorption band of the exocyclic olefinic bond that appeared around 1638 cm^{-1} for compound **3c.** The ^{1}H NMR spectrum showed a signlet at δ_H = 3.66 ppm due to –(O)C-C***H***-NH- proton of the benzoquinoline moiety. The spectrum has not recorded any other signals due to protons on saturated carbon atoms. The aromatic protons (8H) appeared in δ_H 7.41− 8.30 ppm region. The spectrum revealed also the presence of two singlets at δ_H = 6.69 and 10.16 ppm due to the D_2O exchangeable protons of N***H***$_2$ and N***H*** groups, respectively.

On the other hand, six membered heterocyclic rings could also be condensed to the arylidene derivatives **3a-c** through their heterocyclization with 1,3−binucleophiles like urea and thiourea to form the 2-oxoprymidine and 2-thioxoprymidine rings, respectively. Derivatives of the two latter rings are structurally related to nucleic acids and they are well known of their pharmacological properties. Anti-inflammatory,[XL] anticonvulsant,[XLI] antidiabetic,[XLII] antiviral [XLIII] and antihypertensive [XLIV] activities are observed for some oxopyrimidine and thioxopyrimidine derivatives.

Upon heating the appropriate arylidene derivative **3a-c** with urea in conc. HCl at 100 ºC the respective oxopyrimidothiazolopyrimidine derivatives **7a-c** have been formed (Scheme 2). The elementary microanalysis and mass spectrometry measurement of 7-(4-Amino-3-cyano-5,10-dioxo-1,5,10,10a-tetrahydrobenzo[*g*]quinolin-2-yl)-4-(4-hydroxyphenyl)-2,9-dioxo-2,3-dihydro-9*H*-pyrimido[4',5':4,5] [1,3]thiazolo- [3,2-*a*]pyrimidine-8-carbonitrile **(7b),** as an example, corresponded to a molecular formula of $C_{29}H_{14}N_8O_5S$ (586.54). Its IR spectrum showed a broad band in the region 3460 – 3220 cm^{-1} and was attributed to the absorption of O–H, NH_2 and N–H bonds. The spectrum showed also bands at 3077, 3025 (aromatic C–H), 2892 (aliphatic C–H), 2238, 2216 (C≡N), 1719, 1668 (C=O), 1590 (aromatic C=C and cyclic conjugated C=N). The ^{1}H NMR spectrum of **7b** exhibited three signals due to D_2O exchangeable protons at δ_H = 8.28 (O***H***), 9.16 (N***H***, 2-prymidinone moiety) and 10.22 (N***H***, benzoquinoline moiety). The multiplet that appeared in 6.62 – 8.20 ppm region is attributed to the aromatic protons (8H) in addition to NH_2 group protons (2H). Similarly, the thioxopyrimidothiazolopyrimidine derivatives **8a-c** were obtained as green crystals by refluxing an ethanolic solution of the appropriate arylidene derivative **3a-c** with thiourea in the presence of sodium hydroxide (Scheme 2). The IR spectrum of compound **8c** showed strong absorption bands at 1538 and 1178 cm^{-1} due to NO_2 and C=S groups, respectively. The ^{1}H NMR spectrum of compound **8c** showed three signals due to D_2O exchangeable protons on nitrogen at δ_H = 6.78 ppm (N***H***$_2$), 9.23 ppm (N***H***) and 10.26 ppm (N***H***). The multiplet that appeared in the region 7.43 – 8.21 ppm was attributed to the aromatic protons (8H). The methine proton of the benzoquinoline moiety (-(O)C-C***H***-NH-) appeared as a singlet at δ_H = 3.68 ppm. No other signals due to protons on sp^3 carbon atoms have been detected.

Conclusion

In conclusion, this investigation describes our continuing interest in the development of new polyfunctionalized heterocycles of anticipated biological activity. The new arylidenes **3a−c** have been utilized successfully to fuse heterocylic rings, namely pyrazole, isoxazole, oxopyrimidine and/or thioxopyrimidine to a thiazolopyrimidine scaffold which is substituted with a benzoquinoline moiety. The resulted new compounds incorporate various heterocyclic moieties of known pharmaceutical activities in one and the same structure and might be able to work as potential new drugs. The mild reaction conditions, simple workup and good yields are the most significant advantages of the synthetic procedures described in this study.

Experimental Section

Solvents were purified and dried according to usual procedures. The reacting aldehydes **2a-c** were purified directly before use by distillation and/or recrystallization. Melting points were uncorrected and recorded on Gallenkamp electrothermal melting point apparatus (UK). 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 ET-IR Spectrophotometer (USA). ^{1}H-NMR spectra were recorded on Bruker AMX-250 spectrometer (Germany) at 250 MHz. Chemical shifts are indicated in parts per million (ppm) with respect to TMS as an internal standard. Mass spectra were recorded on Hewlett Packard Ms 5988 Spectrometer (USA). The microanalytical data were determined with CE 440 Elemental Analyzer-Automatic Injector (Exeter Analytical, Inc., USA) at Cairo University, Cairo, Egypt.

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

This compound has been prepared according to a reported method [XXI] m.p. > 300 ºC (MeOH) (Lit: [XXI] mp > 300 ºC, MeOH), yield 79 %.

General procedure for the synthesis of the arylidene derivatives 3a-c

A mixture of compound **1** (0.04 mol, 18.0 g), the appropriate aromatic aldehyde **2a-c** (0.04 mol) and a catalytic amount of piperidine in absolute ethanol (200 ml) was refluxed for 16-20 h (TLC). The reaction mixture was concentrated, cooled and the precipitated solid was filtered off and recrystallized from DMF/EtOH to afford the respective arylidene derivatives **3a–c.**

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

Brown crystals, yield 71 % (15.0 g); mp > 300 ºC; IR (KBr, ν_{max}, cm^{-1}): 3389, 3323, 3277 (NH_2, N−H), 3086, 3022 (C−H, aromatic and olefinic), 2885 (C−H, saturated methine), 2235, 2213 (C≡N), 1718, 1682 (C=O), 1630 (C=C, exocyclic), 1605 (C=C, aromatic), 1575 (C=N, cyclic conjugated); ^{1}H NMR (250 MHz, DMSO-d_6): δ_H 10.12 (s, 1H, N***H***, D_2O exchangeable), 8.16 − 7.24 (m, 10H, Ar-***H*** and olefinic methine C=C***H***), 6.71 (s, 2H, N$\boldsymbol{H}_2$, D_2O exchangeable), 3.64 (s, 1H, CO-C***H***-NH); MS: m/z (%) 530 (15) [M^+]. Anal. calcd for $C_{28}H_{14}N_6O_4S$ (530.51): C, 63.39; H, 2.66; N, 15.84; S, 6.04 %. Found: C, 63.30; H, 2.69; N, 15.79; S, 6.07 %.

7-(4-Amino-3-cyano-5,10-dioxo-1,5,10,10a-tetrahydrobenzo[*g*]quinolin-2-yl)-2-(4-hydroxybenzylidene)-3,5-dioxo-3,5-dihydro-2*H*-thiazolo[3,2-*a*]pyrimidine-6-carbonitrile (3b)

Dark brown crystals, yield 69 % (15.0 g), mp > 300 ºC; IR (KBr, ν_{max}, cm^{-1}): 3460 (O−H), 3380, 3270 (NH_2, N−H), 3088, 3022 (C−H, aromatic and olefinic), 2888 (C−H, saturated methine), 2236, 2211 (C≡N), 1720, 1680 (C=O), 1625 (C=C, exocyclic), 1590 (C=C, aromatic and C=N, cyclic conjugated); ^{1}H NMR (250 MHz, DMSO-d_6): δ_H 9.99 (s, 1H, N***H***, D_2O exchangeable), 8.19 − 6.71 (m, 10H, Ar-***H***, olefinic methine C=C***H*** and O***H***), 6.67 (s, 2H, N***H***$_2$, D_2O exchangeable), 3.60 (s, 1H, CO-C***H***-NH); MS: m/z (%) 546 (14) [M^+]. Anal. Calcd for $C_{28}H_{14}N_6O_5S$ (546.51): C, 61.54; H, 2.58; N, 15.38; S, 5.87 %. Found: C, 61.61; H, 2.55; N, 15.32; S, 5.90 %.

7-(4-Amino-3-cyano-5,10-dioxo-1,5,10,10a-tetrahydrobenzo[*g*]quinolin-2-yl)-2-(4-nitro-benzylidene)-3,5-dioxo-3,5-dihydro-2*H*-thiazolo[3,2-*a*]pyrimidine-6-carbonitrile (3c)

Brown crystals, yield 71 % (16.5 g); mp > 300 ºC; IR (KBr, ν_{max}, cm^{-1}): 3380, 3329, 3290 (NH_2, N−H), 3077, 3023 (C−H, aromatic and olefinic), 2900 (C−H, saturated methine), 2233, 2210 (C≡N), 1722, 1678 (C=O), 1638 (C=C, exocyclic), 1600 (C=C, aromatic), 1575 (C=N, cyclic conjugated), 1533 (NO_2); ^{1}H NMR (250 MHz, DMSO-d_6): δ_H 10.23 (s, 1H, N***H***, D_2O exchangeable), 8.22 −7.41 (m, 9H, Ar-***H*** and olefinic methine C=C***H***), 6.75 (s, 2H, N***H***$_2$, D_2O exchangeable), 3.66 (s, 1H, CO-C***H***-NH); MS: m/z (%) 575 (16) [M^+]. Anal. Calcd for $C_{28}H_{13}N_7O_6S$ (575.51): C, 58.43; H, 2.28; N, 17.04; S, 5.57 %. Found: C, 58.37; H, 2.30; N, 16.96; S, 5.53 %.

General procedure for the synthesis of *N*-acetylpyrazolothiazolpyrimidines 4a-c

Hydrazine hydrate (99%, 0.02 mol, 1.0 g) was added to a mixture of the appropriate compound of **3a-c** (0.004 mol) and acetic acid (0.02 mole, 1.2 ml) in ethanol (50 ml) at r. t. The reaction mixture was refluxed for 18-24 h (TLC) and then was concentrated in *vacu*e. After cooling the reaction mixture to r. t., the separated resinous materials were washed with petroleum ether 60–80 °C (3 × 20 ml) then with water (3 × 20 ml). The solid products were filtered off, washed with water, dried and recrystallized from ethanol to give the respective *N*-acetylpyrazolothiazolopyrimidine derivatives **4a–c**.

2-Acetyl-6-(4-amino-3-cyano-5,10-dioxo-1,5,10,10a-tetrahydrobenzo [*g*] quinolin-2-yl)-8-oxo-3-phenyl-2*H*,8*H*-pyrazolo[3',4':4,5][1,3]thiazolo[3,2-*a*] pyrimidine-7-carbonitrile (4a)

Green crystals; yield 59 % (1.4 g); mp > 300 ºC; IR (KBr, ν_{max}, cm^{-1}): 3374, 3312, 3275 (NH_2, N−H), 3080, 3030 (C−H, aromatic), 2948, 2887 (C−H, aliphatic), 2233, 2210 (C≡N), 1716, 1690, 1676 (C=O), 1590 (C=C, aromatic and C=N, cyclic conjugated); ^{1}H NMR (250 MHz, DMSO-d_6): δ_H 10.22 (s, 1H, N***H***, D_2O exchangeable), 8.17 − 7.39 (m, 9H, Ar-***H***), 6.63 (s, 2H, N***H***$_2$, D_2O exchangeable), 3.55 (s, 1H, O=C-C***H***-NH), 2.14 (s, 3H, O=C-C***H***$_3$); MS: m/z (%) 542 (18) [M^+ - O=C=CH_2]. Anal. Calcd for $C_{30}H_{16}N_8O_4S$ (584.56): C, 61.64; H, 2.76; N, 19.17; S, 5.49 %. Found: C, 61.69; H, 2.73; N, 19.11; S, 5.46 %.

2-Acetyl-6-(4-amino-3-cyano-5,10-dioxo-1,5,10,10a-tetrahydrobenzo [*g*] quinolin-2-yl)-3-(4-hydroxyphenyl)-8-oxo-2*H*,8*H*-pyrazolo[3',4':4,5][1,3]thiazolo[3,2-*a*]pyrimidine-7-carbonitrile (4b)

Green crystals; yield 62 % (1.5 g); mp > 300 ºC; IR (KBr, ν_{max}, cm^{-1}): 3443 – 3274 (O−H, NH_2, N−H), 3088, 3028 (C−H, aromatic), 2938, 2877 (C−H, aliphatic), 2236, 2210 (C≡N), 1718, 1690, 1675 (C=O), 1595 (C=C, aromatic), 1565 (C=N, cyclic conjugated); ^{1}H NMR (250 MHz, DMSO-d_6): δ_H 10.15 (s, 1H, N***H***, D_2O exchangeable), 8.20 − 6.82 (m, 9H, Ar-***H*** and O***H***), 6.58 (s, 2H, N$\boldsymbol{H}_2$, D_2O exchangeable), 3.59 (s, 1H, O=C-C***H***-NH), 2.12 (s, 3H, O=C-C$\boldsymbol{H}_3$); MS: m/z (%) 557 (17) [M^+- O=C-CH_3]. Anal. Calcd for $C_{30}H_{16}N_8O_5S$ (600.56): C, 60.00; H, 2.69; N, 18.66; S, 5.34 %. Found: C, 59.91; H 2.73; N, 18.70; S 5.31 %.

2-Acetyl-6-(4-amino-3-cyano-5,10-dioxo-1,5,10,10a-tetrahydrobenzo[*g*]- quinolin-2-yl)-3-(4-nitrophenyl)-8-oxo-2*H*,8*H*-pyrazolo[3',4':4,5][1,3]thiazolo[3,2-*a*]pyrimidine-7-carbonitrile (4c)

Dark green crystals; yield 64 % (1.6 g); mp > 300 ºC; IR (KBr, ν_{max}, cm^{-1}): 3384, 3332, 3279 (NH_2, N−H), 3092, 3028 (C−H, aromatic), 2942, 2878 (C−H, aliphatic), 2235, 2212 (C≡N), 1718, 1693, 1675 (C=O), 1605 (C=C, aromatic), 1578 (C=N, cyclic conjugated), 1538, 1350 (NO_2); ^{1}H NMR (250 MHz, DMSO-d_6): δ_H 10.25 (s, 1H, N***H***, D_2O exchangeable), 8.28 − 7.41 (m, 8H, Ar-***H***), 6.65 (s, 2H, N$\boldsymbol{H}_2$, D_2O exchangeable), 3.60 (s, 1H, O=C-C***H***-NH), 2.18 (s, 3H, O=C-C$\boldsymbol{H}_3$); MS: m/z (%) 629 (14) [M^+]. Anal. Calcd for $C_{30}H_{15}N_9O_6S$ (629.56): C, 57.23; H, 2.40; N, 20.02; S, 5.09 %. Found: C, 57.32; H, 2.38; N, 19.96; S, 5.13 %.

General procedure for the synthesis of N-phenylpyrazolothiazolpyrimidines 5a-c

To a solution of the appropriate compound of **3a-c** (0.004 mol) in ethanol (50 ml), phenyl-hydrazine (0.005 mol, 0.55 g) was added in presence of a few drops of piperdine. The reaction mixture was refluxed for 18-24 h (TLC) then poured on a mixture of ice and HCl where a solid precipitate was separated. The solid product was filtered off, washed with water (3×50 ml), dried and recrystallized from DMF/EtOH to give the respective *N*-phenylpyrazolothiazolopyrimidine derivatives **5a-c** as radish brown crystals.

6-(4-Amino-3-cyano-5,10-dioxo-1,5,10,10a-tetrahydrobenzo[*g*]quinolin-2-yl)-8-oxo-2,3-diphenyl-2*H*,8*H*-pyrazolo[3',4':4,5][1,3]thiazolo[3,2-*a*]pyrimidine-7-carbonitrile (5a)

Yield 63 % (1.6 g); mp > 300 ºC; IR (KBr, ν_{max}, cm^{-1}): 3392, 3323, 3276 (NH_2, N−H), 3084 (C−H, aromatic), 2888 (C−H, saturated methine), 2233, 2210 (C≡N), 1722, 1676 (C=O), 1585 (C=C, aromatic and C=N, cyclic conjugated); ^{1}H NMR (250 MHz, DMSO-d_6): δ_H 10.24 (s, 1H, N***H***, D_2O exchangeable), 8.17 − 7.39 (m, 14H, Ar-***H***), 6.77 (s, 2H, N$\boldsymbol{H}_2$, D_2O exchangeable), 3.63 (s, 1H, CO-C***H***-NH); MS: m/z (%) 618 (20) [M^+]. Anal. Calcd for $C_{34}H_{18}N_8O_3S$ (618.62): C, 66.01; H, 2.93; N, 18.11; S, 5.18 %. Found: C, 66.11; H, 2.89; N, 18.07; S, 5.21 %.

6-(4-Amino-3-cyano-5,10-dioxo-1,5,10,10a-tetrahydrobenzo[*g*]quinolin-2-yl)-3-(4-hydroxy-phenyl)-8-oxo-2-phenyl-2*H*,8*H*-pyrazolo[3',4':4,5][1,3]thiazolo[3,2-*a*]pyramidine-7-carbonitrile (5b)

Yield 60 % (1.5 g); mp > 300 ºC; IR (KBr, ν_{max}, cm^{-1}): 3440 (O−H), 3325, 3274 (NH_2, NH), 3088, 3028 (C−H, aromatic), 2905 (C−H, saturated methine), 2236, 2210 (C≡N), 1723, 1678 (C=O), 1605 (C=C, aromatic), 1580 (C=N, cyclic conjugated); ^{1}H NMR (250 MHz, DMSO-d_6): δ_H 10.24 (s, 1H, N***H***, D_2O exchangeable), 8.26 (s, 1H, O***H***, D_2O exchangeable), 8.18 − 6.81 (m, 13H, Ar-***H***), 6.75 (s, 2H, N$\boldsymbol{H}_2$, D_2O exchangeable), 3.59 (s, 1H, CO-C***H***-NH); MS: m/z (%) 634

(16) [M^+]. Anal. Calcd for $C_{34}H_{18}N_8O_4S$ (634.62): C, 64.35; H, 2.86; N, 17.66; S, 5.05 %. Found: C, 64.44; H, 2.82; N, 17.61; S 5.49 %.

6-(4-Amino-3-cyano-5,10-dioxo-1,5,10,10a-tetrahydrobenzo[*g*]quinolin-2-yl)-3-(4-nitrophenyl)-8-oxo-2-phenyl-2*H*,8*H*-pyrazolo[3',4':4,5][1,3]thiazolo[3,2-*a*]pyrimidine-7-carbonitrile (5c)

Yield 57 % (1.5 g); mp > 300 ºC; IR (KBr, ν_{max}, cm^{-1}): 3380, 3325 (NH_2, N−H), 3085, 3025 (C–H, aromatic), 2904 (C–H, saturated methine), 2225 (C≡N), 1719, 1678 (C=O), 1604 (C=C, aromatic), 1577 (C=N, cyclic conjugated), 1538 (NO_2); ^{1}H NMR (250 MHz, DMSO-d_6): δ_H 10.29 (s, 1H, N***H***, D_2O exchangeable), 8.29 − 7.41 (m, 13H, Ar-***H***), 6.79 (s, 2H, N$\boldsymbol{H}_2$, D_2O exchangeable), 3.60 (s, 1H, CO-C***H***-NH); MS: m/z (%) 663 (18) [M^+]. Anal. Calcd for $C_{34}H_{17}N_9O_5S$ (663.62): C, 61.54; H, 2.58; N, 19.00; S, 4.83 %. Found: C, 61.47; H, 2.60; N, 19.09; S, 4.79 %.

General procedure for the synthesis of isoxazolothiazolpyrimidines 6a-c

A mixture of the appropriate arylidene derivative **3a-c** (0.004 mol), hydroxylamine hydrochloride (0.005 mol, 0.35 g) and a catalytic amount of sodium hydroxide (0.05 g) was refluxed in ethanol (50 ml) for 18-24 h (TLC). After removal of the solid materials by filtration, the filtrate was concentrated then poured on ice-HCl mixture. The precipitated solid was filtered off, washed with water, dried and recrystallized from the proper solvent to give the respective isoxazolothiazolopyrimidine derivatives **6a-c**.

6-(4-Amino-3-cyano-5,10-dioxo-1,5,10,10a-tetrahydrobenzo[*g*]quinolin-2-yl)-8-oxo-3-phenyl-8*H*-[1,2]oxazolo[5',4':4,5][1,3]thiazolo[3,2-*a*]pyrimidine-7-carbonitrile (6a)

Pale Green crystals from ethanol; yield 65 % (1.4 g); mp > 300 ºC; IR (KBr, ν_{max}, cm^{-1}): 3390 – 3237 (NH_2, N−H), 3089, 3033 (C–H, aromatic), 2895 (C–H, saturated methine) 2240, 2217 (C≡N), 1716, 1676 (C=O), 1595 (C=C, aromatic and C=N, cyclic conjugated); ^{1}H NMR (250 MHz, DMSO-d_6): δ_H 10.13 (s, 1H, N***H***, D_2O exchangeable); 8.16 − 7.40 (m, 9H, Ar-***H***), 6.66 (s, 2H, N$\boldsymbol{H}_2$, D_2O exchangeable), 3.62 (s, 1H, CO-C***H***-NH); MS: m/z (%): 543 (22) [M^+]. Anal. Calcd for $C_{28}H_{13}N_7O_4S$ (543.51): C, 61.88; H, 2.41; N, 18.04; S, 5.90 %. Found: C, 61.94; H, 2.39; N, 18.09; S, 5.86 %.

6–(4-Amino-3-cyano-5,10-dioxo-1,5,10,10a-tetrahydrobenzo[*g*]quinolin-2-yl)-3-(4-hydroxyphenyl)-8-oxo-8*H*-[1,2]oxazolo[5',4':4,5][1,3]thiazolo[3,2-*a*]pyrimidine-7-carbonitrile (6b)

Green crystals from methanol; yield 71 % (1.6 g); mp > 300 ºC; IR (KBr, ν_{max}, cm^{-1}): 3544 - 3300 (OH, NH_2, N−H), 3077, 3019 (C–H, aromatic), 2895 (C–H, saturated methine), 2236, 2212 (C≡N), 1718, 1672 (C=O), 1598 (C=C, aromatic), 1575 (C=N, cyclic conjugated); ^{1}H NMR (250 MHz, DMSO-d_6): δ_H 10.09 (s, 1H, N***H***, D_2O exchangeable). 8.19 − 6.81 (m, 9H, Ar-***H*** and O***H***), 6.63 (s, 2H, N$\boldsymbol{H}_2$, D_2O exchangeable); 3.57 (s, 1H, CO-C***H***-NH); MS: m/z (%): 559 (25) [M^+]. Anal. Calcd for $C_{28}H_{13}N_7O_5S$ (559.51): C, 60.11; H, 2.34; N, 17.52; S, 5.73 %. Found: C, 60.18; H, 2.32; N, 17.47; S, 5.70 %.

6-(4-Amino-3-cyano-5,10-dioxo-1,5,10,10a-tetrahydrobenzo[*g*]quinolin-2-yl)-3-(4-nitro−phenyl)-8-oxo-8*H*-[1,2]oxazolo[5',4':4,5][1,3]thiazolo[3,2-*a*]pyrimidine-7-carbonitrile (6c)

Green crystals from methanol; yield 68 % (1.6 g); mp > 300 ºC; IR (KBr, ν_{max}, cm^{-1}): 3380, 3315, 3265 (NH_2, N−H), 3085, 3033 (C−H, aromatic), 2900 (C−H, saturated methine), 2239, 2212 (C≡N), 1713, 1675 (C=O), 1607 (C=C, aromatic), 1580 (C=N, cyclic conjugated), 1532 (NO_2); ^{1}H NMR (250 MHz, DMSO-d_6): δ_H 10.16 (s, 1H, N***H***, D_2O exchangeable); 8.30 − 7.41 (m, 8H, Ar-***H***), 6.69 (s, 2H, N***H***$_2$, D_2O exchangeable), 3.66 (s, 1H, CO-C***H***-NH); MS: *m/z* (%) 588 (30) [M^+]. Anal. Calcd for $C_{28}H_{12}N_8O_6S$ (588.51): C, 57.14; H, 2.06; N, 19.04; S, 5.45 %. Found: C, 57.09; H, 2.08; N, 19.08; S, 5.41 %.

General procedure for the synthesis of oxopyrimidothiazolpyrimidines 7a-c

A mixture of the appropriate arylidene derivative **3a-c** (0.004 mol) and urea (0.004 mol, 0.25 g) was heated in conc. HCl (20 ml) at 100 ºC for 16-20 h (TLC). After removal of the solid materials from the hot reaction mixture by filtration, the filtrate was cooled to r. t. and neutralized with 5 N NaOH. The precipitated solid materials were filtered, washed with water (5 × 25 ml), dried and recrystallized from a suitable solvent to give the respective oxopyrimidothiazolopyrimidine derivatives **7a-c**.

7–(4-Amino-3-cyano-5,10-dioxo-1,5,10,10a-tetrahydrobenzo[*g*]quinolin-2-yl)-2,9-dioxo-4-phenyl-2,3-dihydro-9*H*-pyrimido[4',5':4,5][1,3]thiazolo[3,2-*a*]pyrimidine-8-carbonitrile (7a)

Reddish brown crystals from ethanol; yield 70 % (1.6 g); mp > 300 ºC; IR (KBr, ν_{max}, cm^{-1}): 3362, 3314, 3255 (NH_2, N−H), 3082, 3035 (C−H, aromatic), 2895 (C−H, saturated methine), 2237, 2214 (C≡N), 1722, 1670 (C=O), 1605 (C=C, aromatic), 1578 (C=N, cyclic conjugated); ^{1}H NMR (250 MHz, DMSO-d_6): δ_H 10.25 (s, 1H, N***H***, D_2O exchangeable); 9.23 (s, 1H, N***H***, D_2O exchangeable), 8.16 − 7.26 (m, 9H, Ar-***H***), 6.73 (s, 2H, N***H***$_2$, D_2O exchangeable), 3.59 (s, 1H, CO-C***H***-NH); MS: *m/z* (%) 570 (20) [M^+]. Anal. Calcd for $C_{29}H_{14}N_8O_4S$ (570.54): C, 61.05; H, 2.47; N, 19.64; S, 5.62 %. Found: C, 61.13; H, 2.44; N, 19.68; S, 5.64 %.

7-(4-Amino-3-cyano-5,10-dioxo-1,5,10,10a-tetrahydrobenzo[*g*]quinolin-2-yl)-4-(4-hydroxyphenyl)-2,9-dioxo-2,3-dihydro-9*H*-pyrimido[4',5':4,5] [1,3]thiazolo- [3,2-*a*] pyrimidine-8-carbonitrile (7b)

Brown crystals from methanol; yield 67 % (1.6 g); mp > 300 ºC; IR (KBr, ν_{max}, cm^{-1}): 3460 - 3220 (O−H, NH_2, NH), 3077, 3025 (C−H, aromatic), 2892 (C−H, saturated methine), 2238, 2216 (C≡N), 1719, 1668 (C=O), 1590 (C=C, aromatic and C=N, cyclic conjugated); ^{1}H NMR (250 MHz, DMSO-d_6): δ_H 10.22 (s, 1H, N***H***, D_2O exchangeable); 9.16 (brs, 1H, N***H***, D_2O exchangeable), 8.28 (s, 1H, O***H***, D_2O exchangeable), 8.20 − 6.62 (m, 10H, Ar-***H*** and N***H***$_2$), 3.59 (s, 1H, CO-C***H***-NH); MS: *m/z* (%) 586 (15) [M^+]. Anal. Calcd for $C_{29}H_{14}N_8O_5S$ (586.54): C, 59.38; H, 2.41; N, 19.10; S, 5.47 %. Found: C, 59.30; H, 2.44; N, 19.07; S, 5.50 %.

7-(4-Amino-3-cyano-5,10-dioxo-1,5,10,10a-tetrahydrobenzo[*g*]quinolin-2-yl)-4-(4-nitro-phenyl)-2,9-dioxo-2,3-dihydro-9*H*-pyrimido[4',5':4,5][1,3]thiazolo- [3,2-*a*] pyrimidine-8-carbonitrile (7c)

Reddish brown crystals from ethanol; yield 72 % (1.8 g); mp > 300 ºC; IR (KBr, ν_{max}, cm^{-1}): 3356, 3300 (NH_2, N−H), 3069, 3021 (C−H, aromatic), 2891 (C−H, saturated methine), 2232, 2210 (C≡N), 1718, 1670 (C=O), 1600 (C=C, aromatic), 1578 (C=N, cyclic conjugated) and 1525, 1365 (NO_2); ^{1}H NMR (250 MHz, DMSO-d_6): δ_H 10.32 (s, 1H, N***H***, D_2O exchangeable);

9.25 (brs, 1H, N***H***, D_2O exchangeable), 8.23 − 7.41 (m, 8H, Ar-***H***), 6.76 (s, 2H, N$\boldsymbol{H}_2$, D_2O exchangeable), 3.62 (s, 1H, CO-C***H***-NH); MS: *m/z* (%) 615 (22) [M^+]. Anal. Calcd for $C_{29}H_{13}N_9O_6S$ (615.54): C, 56.59; H, 2.13; N, 20.48; S, 5.21 %. Found: C, 56.66; H, 2.10; N, 20.43; S, 5.18 %.

General procedure for the synthesis of thioxopyrimidothiazolpyrimidines 8a-c

A solution of the appropreiate arylidene derivative **3a-c** (0.004 mol) in ethanol (50 ml) was refluxed for 16-20 h with thiourea (0.004 mol, 0.31 g) in the presence of a catalytic amount of sodium hydroxide (0.05 g). The reaction mixture was concentrated then poured into ice-HCl mixture. The precipitated solid was filtered off, washed with water (5 × 25 ml), dried and recrystallized from the appropriate solvent to give compounds **8a-c,** respectively, as green crystals.

7-(4-Amino-3-cyano-5,10-dioxo-1,5,10,10a-tetrahydrobenzo[*g*]quinolin-2-yl)–9-oxo-4-phenyl-2-thioxo-2,3-dihydro-9*H*-pyrimido[4',5':4,5][1,3]thiazolo[3,2-*a*]pyramidine-8-carbonitrile (8a)

Yield 64 % (1.5 g); mp > 300 ºC; IR (KBr, ν_{max}, cm^{-1}): 3365, 3328 (NH_2, N−H), 3068, 3022 (C−H, aromatic), 2894 (C−H, saturated methine), 2236, 2213 (C≡N), 1724, 1683 (C=O), 1605 (C=C aromatic) and 1580 (C=N, cyclic conjugated), 1165 (C=S); ^{1}H NMR (250 MHz, DMSO-d_6): δ_H 10.23 (s, 1H, N***H***, D_2O exchangeable), 9.22 (brs, 1H, N***H***, D_2O exchangeable), 8.14 − 7.27 (m, 9H, Ar-***H***), 6.72 (s, 2H, N$\boldsymbol{H}_2$, D_2O exchangeable), 3.63 (s, 1H, CO-C***H***-NH); MS: *m/z* (%) 586 (16) [M^+]. Anal. Calcd (%) for $C_{29}H_{14}N_8O_3S_2$ (586.60): C, 59.38; H, 2.41; N, 19.10; S, 10.93 %. Found: C, 59.32; H, 2.44; N, 19.07; S, 10.90 %.

7–(4-Amino-3-cyano-5,10-dioxo-1,5,10,10a-tetrahydrobenzo[*g*]quinolin-2-yl)-4-(4-hydroxyphenyl)-9-oxo-2-thioxo-2,3-dihydro-9*H*-pyrimido[4',5':4,5][1,3]thiazolo[3,2-*a*] pyrimidine-8-carbonitrile (8b)

Yield 61 % (1.5 g); mp > 300 ºC; IR (KBr, ν_{max}, cm^{-1}): 3465- 3244 (O−H, NH_2, N−H), 3055 (C–H, aromatic), 2894 (C–H, saturated methine), 2234 (C≡N), 1705, 1678 (C=O), 1595 (C=C, aromatic and C=N, cyclic conjugated), 1155 (C=S); ^{1}H NMR (250 MHz, DMSO-d_6): δ_H 10.09 (s, 1H, N***H***, D_2O exchangeable); 9.14 (s, 1H, N***H***, D_2O exchangeable), 8.21 − 6.88 (m, 9H, Ar-***H*** and O***H***), 6.70 (s, 2H, N$\boldsymbol{H}_2$, D_2O exchangeable), 3.63 (s, 1H, CO-C***H***-NH); MS: *m/z* (%) 602 (18) [M^+]. Anal. Calcd for $C_{29}H_{14}N_8O_4S_2$ (602.60): C, 57.80; H, 2.34; N, 18.59; S, 10.64 %. Found: C, 57.86; H, 2.31; N, 18.55; S, 10.61 %.

7-(4-Amino-3-cyano-5,10-dioxo-1,5,10,10a-tetrahydrobenzo[*g*]quinolin-2-yl)-4-(4-nitrophenyl)-9-oxo-2-thioxo-2,3-dihydro-9*H*-pyrimido[4',5':4,5][1,3]thiazolo[3,2-*a*] pyrimidine-8-carbonitrile (8c)

Yield 55 % (1.4 g); mp > 300 ºC; IR (KBr, ν_{max}, cm^{-1}): 3385, 3337, 3258 (NH_2, N−H), 3088, 3025 (C−H, aromatic), 2890 (C−H, saturated methine), 2240, 2212 (C≡N), 1726, 1690 (C=O), 1605 (C=C, aromatic), 1585 (C=N, cyclic conjugated), 1538 (NO_2), 1178 (C=S); ^{1}H NMR (250 MHz, DMSO-d_6): δ_H 10.26 (1H, s, N***H***, D_2O exchangeable); 9.23 (brs, 1H, N***H***, D_2O exchangeable), 8.21 − 7.43 (m, 8H, Ar-***H***), 6.78 (s, 2H, N$\boldsymbol{H}_2$, D_2O exchangeable), 3.68 (s, 1H, CO-C***H***-NH); MS: *m/z* (%) 631 (15) [M^+]. Anal. Calcd for $C_{29}H_{13}N_9O_5S_2$ (631.60): C, 55.15; H, 2.07; N, 19.96; S, 10.15 %. Found: C, 55.09; H, 2.10; N, 19.92; S, 10.11 %.

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