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THIOSEMICARBAZIDES, POTENT REAGENTS FOR SYNTHESIS OF SOME NEW 1,4-DIPHENYLBENZO[*g*]QUINOXALINE-5,10-DIONE BASED HETEROCYCLES

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Abstract – 2-(5,10-Dioxo-1,4-diphenyl-3,4-dihydrobenzo[*g*]quinoxalin-2(1*H*,5*H*,10*H*)-ylidene)hydrazinecarbothioamide (**4**) and 2-((4-oxothiazolidin-2-ylidene)-hydrazono)-1,4-diphenyl-1,2,3,4-tetrahydrobenzo[*g*]quinoxaline-5,10-dione (**5**), were prepared and utilized as versatile building blocks, *via* incorporating in series of conversions including cyclocondensation reactions to afford a series of four and five–pharmacophoric–motif conjugates **10**, **13**, **18**, **20**, **21**, **25**, **30**, **31**, **32**, **33** and **34** in fair yields.

In continuation of our research work[1–12] aiming at merging of chemical architectures of significant pharmacophoric activities for developing verifications of impressive therapeutic potentials, in particular against profound diseases; we initiated a program aiming at merging of *p*-quinone, azole and thiazole moieties in single architectures.

Conjugates with the quinoid structure establish one of the most delightful classes of compounds in organic chemistry. Their syntheses as well as their assorted chemical and physical properties have been collected in the two volumes of Patai's series the chemistry of functional groups.[13] The chemistry of

quinones are broadly dependent on the derivatives being either on the quinonic or on adjacent rings. This is reflected in their chemical reactivity.[14]

Various heterocycles were synthesized *via* nucleophilic substitution on the halogenated *p*-quinones, 2,3-dichloro-1,4-naphthoquinone undergo substitution of one or two chlorine atoms by primary amines.[15–17] In the reactions of 2,3-dichloro-1,4-naphthoquinone, with pyrazoles,[18-20] imidazoles[18] and triazoles[18, 21–23] the two chlorine atoms are replaced by the heterocyclic moiety. Amides and thioamides were also added to 2,3-dichloro-1,4-naphthoquinone to yield two related heterocyclic dione series in excellent yield.[24-27] Cyclocondensation of thiosemicarbazide derivatives with benzo- and naphthoquinones as well as *α*-haloketones, was a successful tactic to anuulate the thiadiazine and thiadiazoles,[19,20] oxathiadiazole and pyrazolophthalazinol derivatives.[28]

Several anticancer conjugates are found to be containing the quinoid moiety in their structures. Due to the existence of this electro-active unit, these compounds can underwent a biochemical reduction by one or two electrons that are catalyzed by flavoenzymes in the organism using nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) as an electron donor. This process leads to semiquinone radical intermediates and sequent reactions with oxygen, all of which are believed to be responsible for most of the drug activity.[29-31] Among the wide variety of *N*-heterocyclic quinones with anticancer activity there are examples of naturally occurring aminoquinones containing the isoquinolinequinone scaffold such as cribrostatin 3,[32] caulibugulone A[33] and mansouramycin C (**Figure 1**).[34]

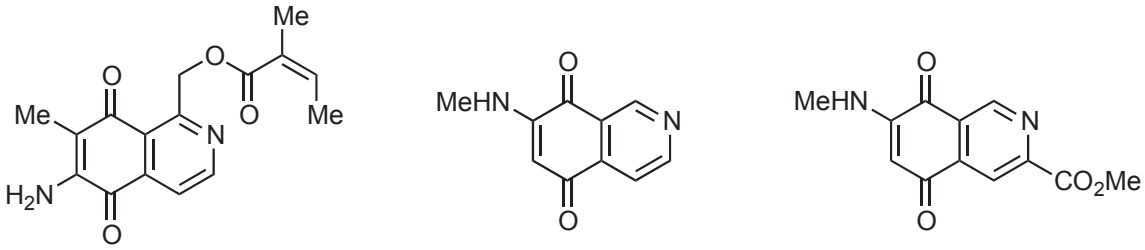


Figure **1**. Structures of naturally occurring isoquinolinequinones with antitumor activity

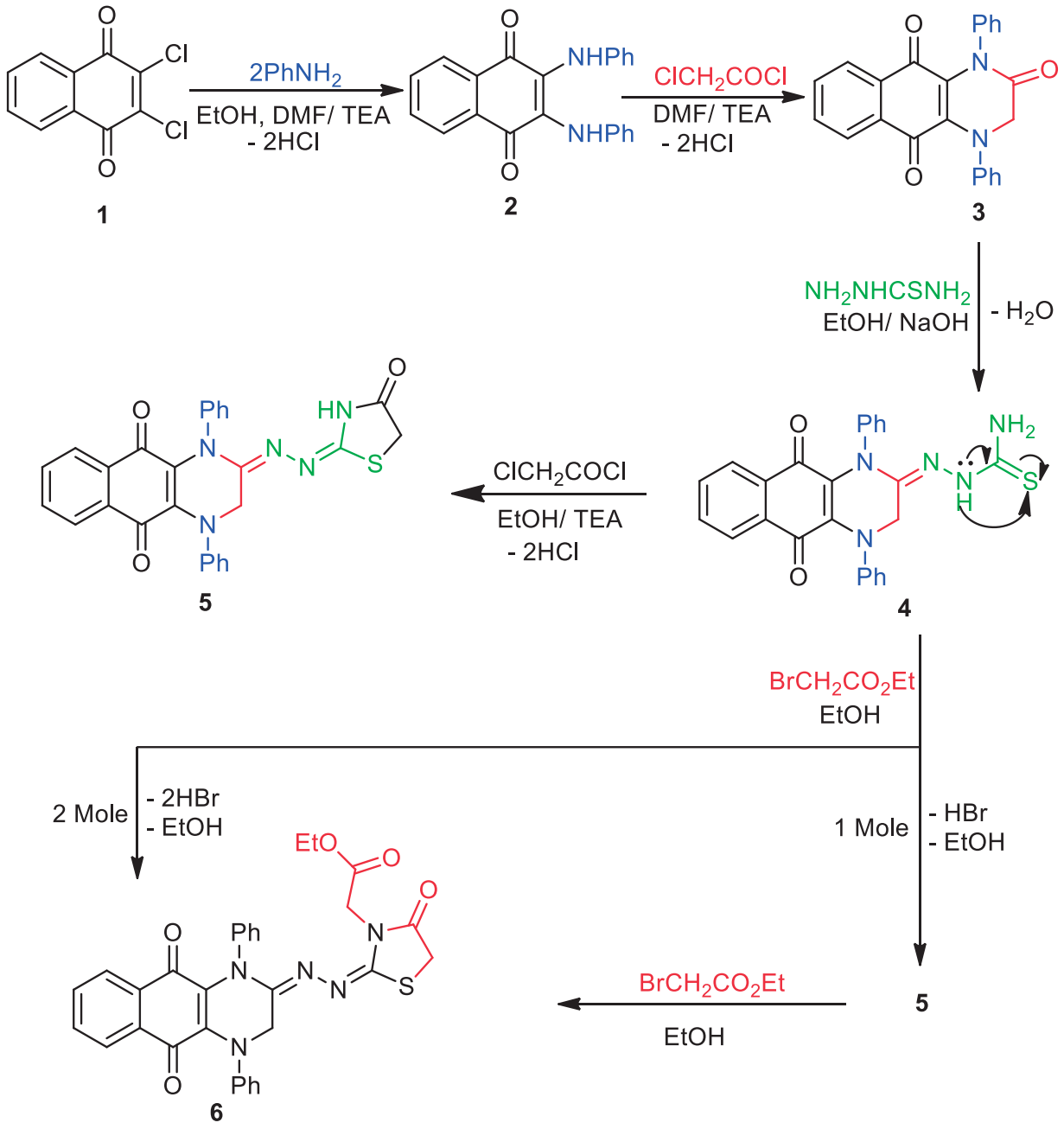
On other hand, a survey of literature declared that several conjugates of thiazole moiety are essential in the structure of various bioactive compounds. Thiazoles are found to be correlated with various biological activities such as antihypertensive,[35] antiviral,[36] anti-HIV,[37] antimicrobial,[38] anti-inflammatory,[39] antifungal,[40] anticancer,[41] anticoagulant and antiarrhythmic,[42] antidiabetic,[43] and antidepressant.[44]

Based on these aforesaid chemistry and biological significance of quinones and thiazoles, and as a part of our research interest towards developing new routes for the synthesis of a variety of heterocyclic systems promising biological and pharmacological activities.[1-12] Herein, we describe the synthesis and the utility

of 2-(5,10-dioxo-1,4-diphenyl-3,4-dihydrobenzo[*g*]quinoxalin-2(1*H*,5*H*,10*H*)-ylidene)hydrazinecarbothioamide (**4**), 2-((4-oxothiazolidin-2-ylidene)hydrazono)-1,4-diphenyl-1,2,3,4-tetrahydrobenzo[*g*]quinoxaline-5,10-dione (**5**) as reactive intermediates, for the synthesis of the 1,3-thiazole heterocycles based on 1,4-diphenyl-1,2,3,4-tetrahydrobenzo[*g*]quinoxaline-5,10-dione moiety of potential biological activity.

The synthetic strategies adopted to obtain the target compounds are depicted in Schemes 1-7. The thiosemicarbazide and thiazolidinone tagged intermediates **4** and **5** were prepared from **1** on three steps (**Scheme 1**). Thus, compound **1** was treated with two moles of $PhNH_2$ in refluxing abs. EtOH/ dry DMF (30 mL (2:1)) mixture containing catalytic amount of triethylamine to afford the *bis*-phenylamine derivative **2** in 85% yield. Compound **2** cyclocondensed with chloroacetyl chloride in worming DMF gave 1,4-diphenyl-3,4-dihydrobenzo[*g*]quinoxaline-2,5,10(1*H*)-trione (**3**) in 65% yield. Subsequent condensation of **3** with thiosemicarbazide in refluxing EtOH in the presence of catalytic amount of NaOH afforded thiosemicarbazone derivative **4** in 70% yield (**Scheme 1**). The structure of compound **4** was confirmed from it spectral data, where, the mass spectra recorded molecular ion peak ($C_{25}H_{19}N_5O_2S$) at *m/z* 453.00, while, the IR spectra showed characteristic absorption bands at 3410-3230, 1672 1620, and 1331 cm^{-1} due to N-$H_{str.}$, $NH_{2str.}$, C=$O_{str.}$, C=$N_{str.}$ and C=$S_{str.}$ groups, respectively. Also, the ^{1}H NMR spectrum displayed two broad singlets at 8.21 and 10.21 ppm for the NH_2 and N-H groups, respectively. Further, cyclocondensation of **4** with chloroacetyl chloride in worm EtOH afforded 2-((4-oxothiazolidin-2-ylidene)hydrazono)-1,4-diphenyl-1,2,3,4-tetrahydrobenzo[*g*]quinoxaline-5,10-dione (**5**) in 75% yield (**Scheme 1**). The signal of the thioureido moiety, protons originally observed in **4** (^{1}H NMR) at 8.21 and 10.21 ppm were disappeared, the most characteristic signals of compound **5** in ^{1}H NMR spectrum belong to thiazolidinone methylene protons and the exchangeable (N-H) proton, were observed at 3.82 and 11.41 ppm respectively. The mass spectrum of **5** showed a peak at *m/z* 493.00 corresponding to the molecular formula $C_{27}H_{19}N_5O_3S$. While, the IR spectrum showed strong stretching vibration bands at 1620-1625, 1672, 1689 and 3211 cm^{-1} corresponding to the two C=$N_{str.}$, three C=$O_{str.}$ and N–$H_{str.}$ groups, respectively.

For further confirmation, compound **4** was treated with an equimolar ratio of ethyl bromoacetate in EtOH. This digestion afforded again compound **5** but in better yield, while, treatment of the thioureido derivative **4** with two moles of ethyl bromoacetate gave *N*-ethoxycarbonylmethylthiazolidin-4-one derivative **6**. The structure of **6** was further confirmed unequivocally by an independent synthesis from **5** and ethyl bromoacetate under the same conditions (**Scheme 1**).

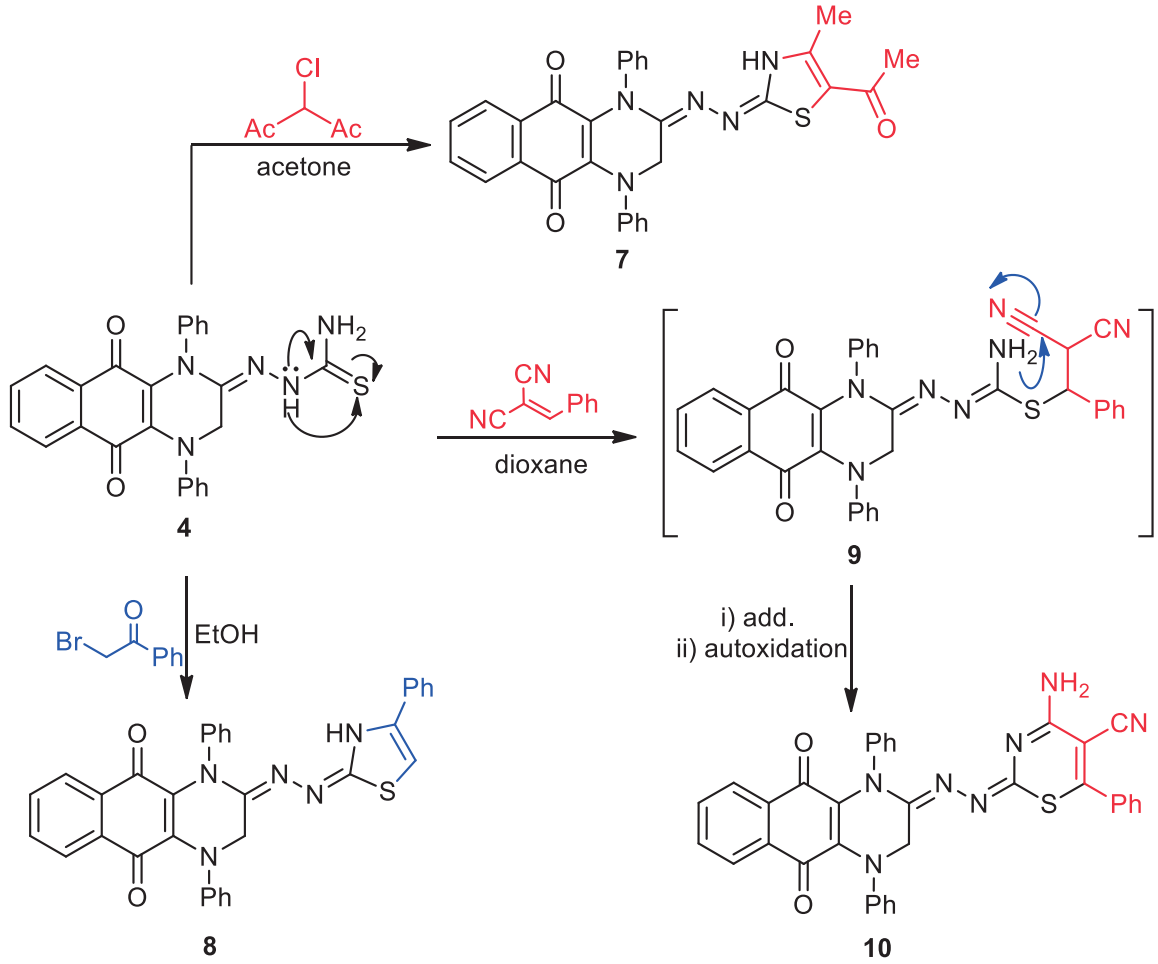


Scheme **1**. Synthesis of thiazolidinone derivaives **5** and **6**

Then, the thioureido derivative **4** was incorporated in a set of investigations aiming at exploiting the reactivity of its thioureido moiety to build up the target four–motive architectures. Thus, compound **4** was treated with 3-chloropentane-2,4-dione in refluxing acetone afforded 2-substituted 4-methyl-5-acetylthiazole derivative **7**, (**Scheme 2**). Also, compound **4** was cyclized in another investigation into the thiazole derivative **8** in 75% yield by condensation with phenacyl bromide in absolute EtOH.

In a similar manner, compound **4** was converted to the thiazine derivative, thus, compound **4** treated with benzylidenemalononitrile in boiling dioxane containing catalytic amount of triethylamine to yield

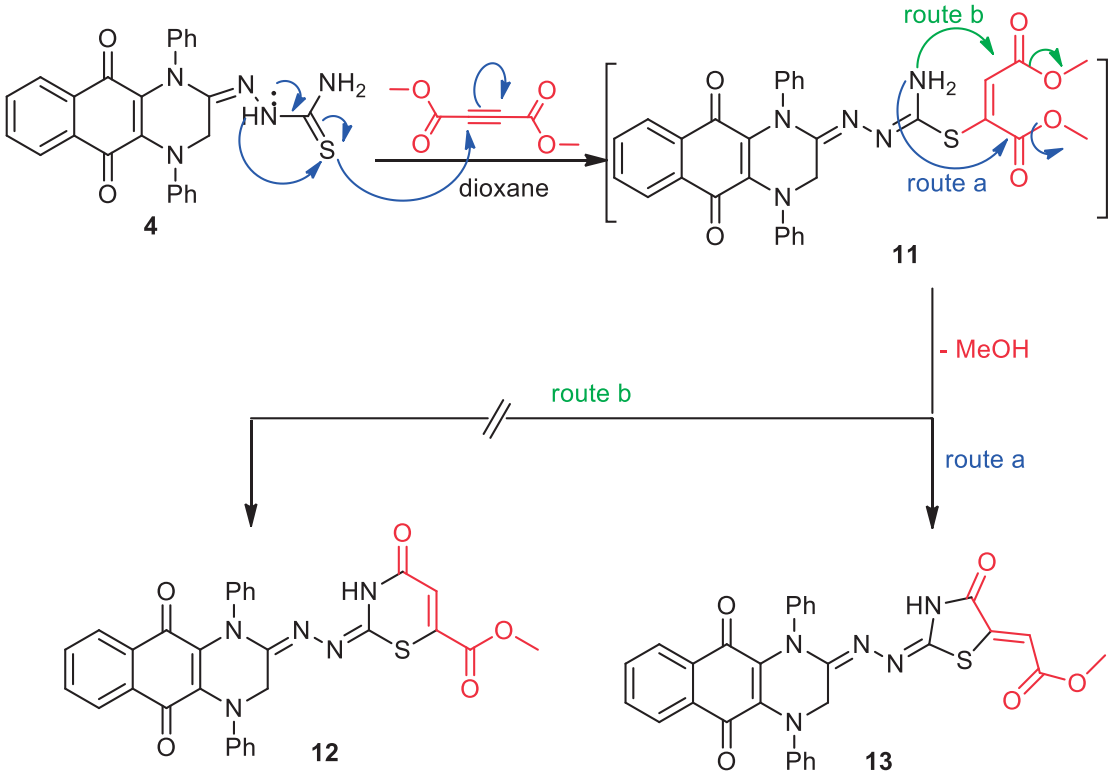
4-amino-2-((5,10-dioxo-1,4-diphenyl-3,4-dihydrobenzo[*g*]quinoxalin-2(1*H*,5*H*,10*H*)-ylidene)hydrazono)-6-phenyl-2*H*-1,3-thiazine-5-carbonitrile (**10**) in 69% yield, (**Scheme 2**). The structure of the latter product was confirmed on the basis of its elemental and spectral data. The mass spectrum displayed an intense peak at *m/z* 605.00 corresponding to the molecular formula $C_{35}H_{23}N_7O_2S$. Its, IR spectrum revealed the presence of (NH_2) stretching band at 3452 cm^{-1}, (C≡N) stretching band at 2215 cm^{-1} and two equivalent (C=O) stretching bands at 1672 cm^{-1}.



Scheme **2**. Synthesis of thiazole and thiazine derivatives **7**, **8** and **10**

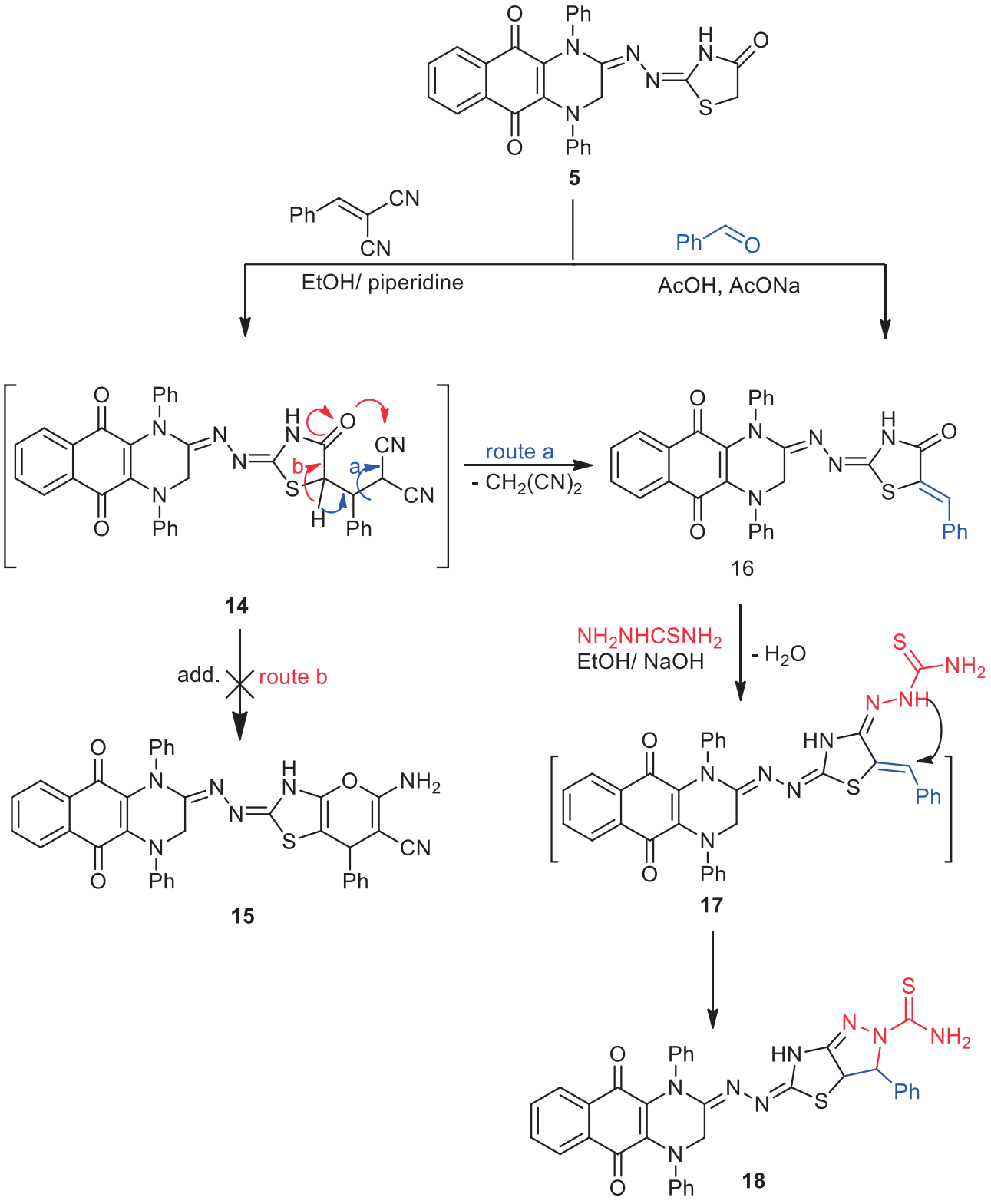
Further, investigation of the reactivity of the thioureido derivative **4** towards activated triple bond was achieved. Thus, compound **4** treated with DMAD in refluxing AcOH afforded methyl 2-(2-((5,10-dioxo-1,4-diphenyl-3,4-dihydrobenzo[*g*]quinoxalin-2(1*H*,5*H*,10*H*)-ylidene)hydrazono)-4-oxo-thiazolidin-5-ylidene)acetate (**13**), *via* the intermediate **11** which subsequently cyclized through elimination of MeOH molecule as shown in **Scheme 3**. Formation of compound **13** can be explained on the basis of initial Michael type addition of the thiol function[45,46] in thioureido moiety to the activated triple bond in DMAD to afford the non-isolable intermediate **11**. The latter intermediate undergoes intramolecular cyclization *via* loss of MeOH molecule (route a), to afford the final product **13**. The IR

spectrum of **13** showed absorption bands at 1620-1625, 1672, 1689, 1690 and 3214 cm^{-1} attributed to two $C{=}N_{str.}$, four carbonyls and $N\text{-}H_{str.}$ groups, respectively. Besides the most characteristic signal of compound **13** in its ^1H NMR spectrum belong to thiazolidinone exchangeable (N-H) proton at δ 11.41, two new singlets were observed at 3.51 and 6.72 ppm, attributed to the methyl and olefinic protons, respectively. The mass spectrum of **13** showed a peak at *m/z* 563.00 corresponding to the molecular $C_{30}H_{21}N_5O_5S$.



Scheme **3**. Synthesis of thiazolidinone derivative **13**

On the other hand, the reactivity of the thiazolidinone tag in compound **5** was investigated *via* incorporating in a series of manipulations including cyclocondensation reactions aiming to annulate the target five–motive architectures. Thus, the thiazolidinone derivative **5** was treated with benzylidenemalononitrile containing 1 mL piperidine to give the expected pyranothaizole derivative **15** (**Scheme 4**). However, the *m/z* record at 581.00 of the isolated product ruled out this hypothesis and supported splitting of malononitrile moiety upon Michael addition yielding the benzylidene derivative **16** in 90% yield. For further confirmation, the same product **16** was obtained by its alternate synthesis through treating traditionally of compound **5** with benzaldehyde in glacial AcOH containing AcONa. The signal of the methylene protons originally observed in **5** (^1H NMR) at 3.82 ppm was disappeared, while the N–H signal was still observable at 11. 41 ppm and its stretching band (IR) was observed at 3211 cm^{-1}.



Scheme **4**. Synthesis of pyrazolo[3,4-*d*]thiazole-2-carbothioamide derivative **18**

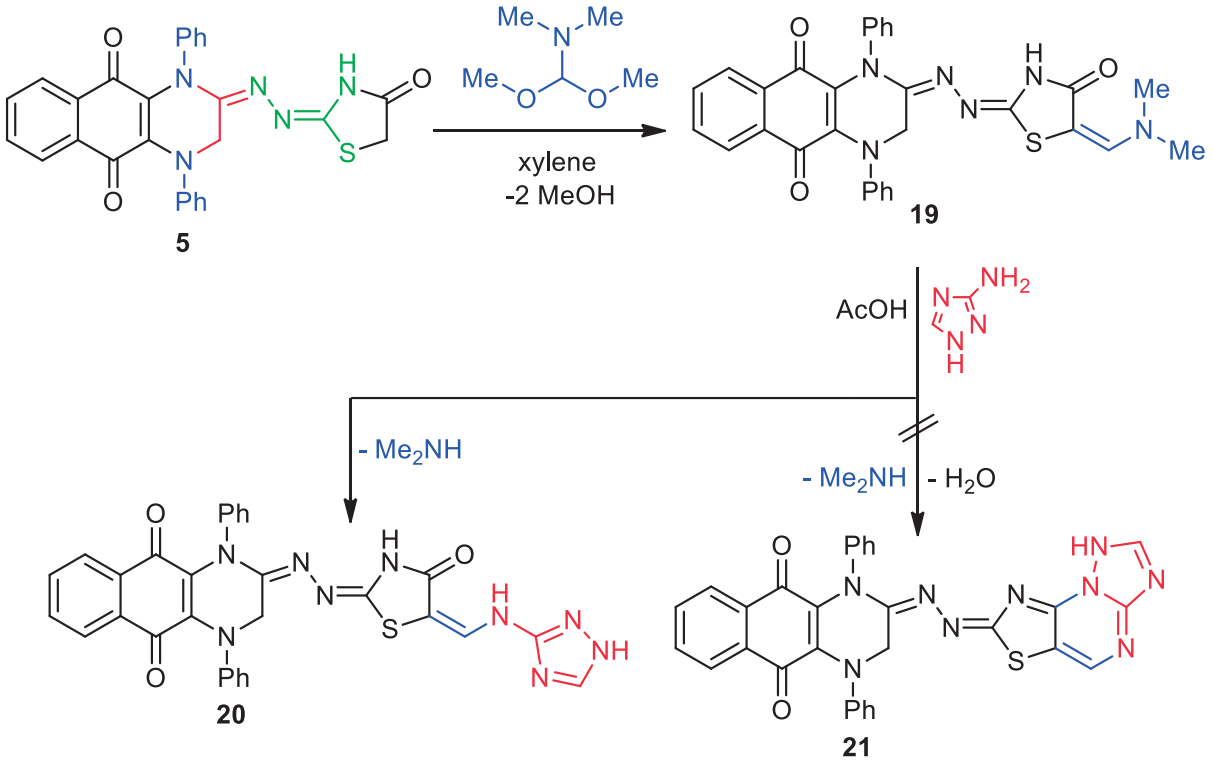
Neither the C≡N nor the NH_2 groups were observed in the IR spectra, while two C=N absorption bands at 1620-1625 cm^{-1}, and three C=O bands were observed at 1672 and 1710 cm^{-1} corresponding to the two

equivalent carbonyls of the qinone moiety, and the thiazolidinone carbonyl. The ^{1}H NMR spectrum of compound **16** displayed the olefinic proton as singlet at 6.87 ppm.

Furthermore, cyclocondensation of **16** with thiosemicarbazide proceeded smoothly in refluxing EtOH containing NaOH to afford pyrazolo[3,4-*d*]thiazole derivative **18** in 70% yield. The mass spectrum showed a molecular ion peak at *m/z* 654.00 corresponding to the molecular formula $C_{35}H_{26}N_8O_2S_2$. Its, IR spectrum showed intense absorption bands at 1332, 3235-3480 cm^{-1} due to C=S, NH and NH_2 groups, respectively, besides the originally observed bands due to the quinone carbonyls, while The ^{1}H NMR spectrum displayed two D_2O-exchangeable broad singlets at 7.01 and 11.01 ppm for the NH_2 and NH groups, respectively.

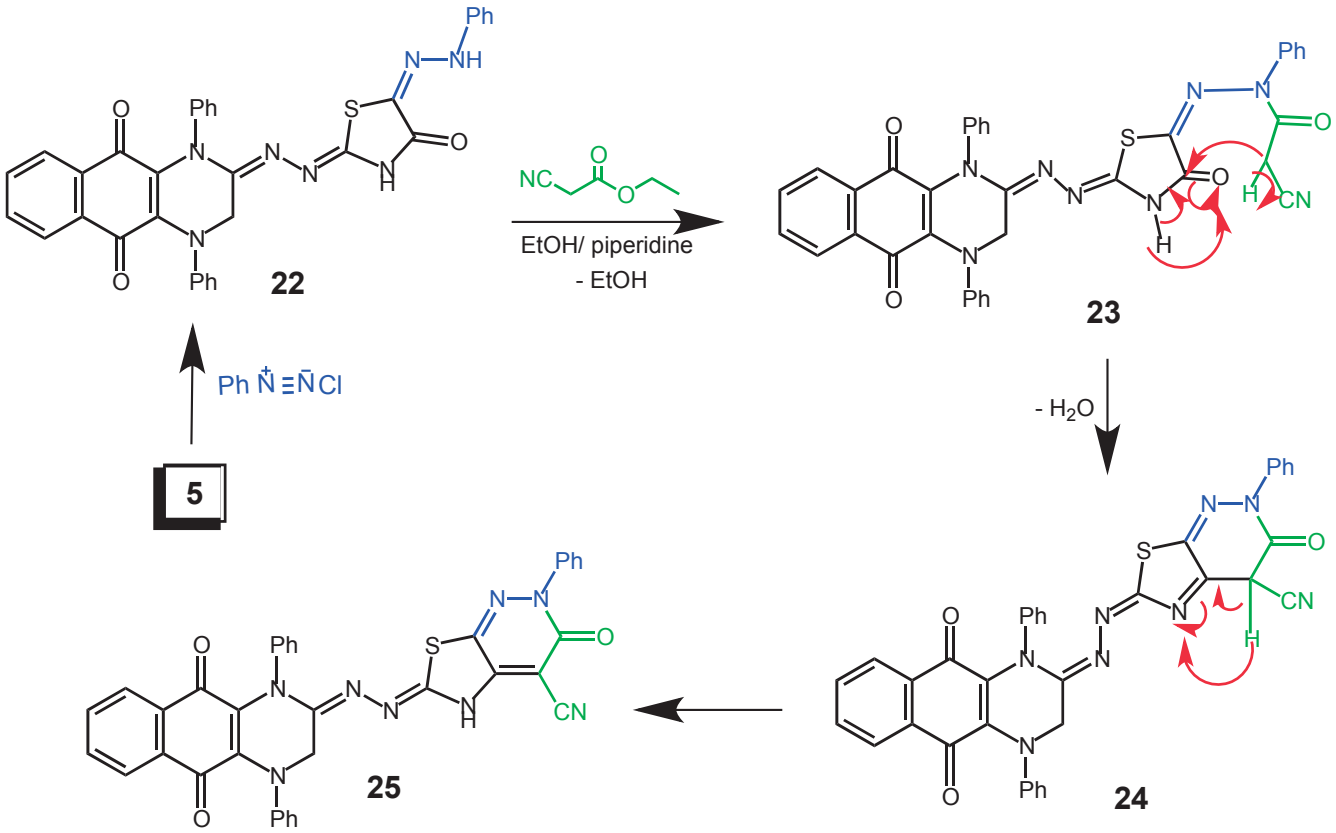
Furthermore, the thiazolidinone **5** was treated with dimethyformamide dimethyl acetal (DMF-DMA), in dry xylene, at reflux temperature, to afford the active enamine derivative **19** as a yellow crystalline product in 79% yield (**Scheme 5**). Structure of compound **19** was established on the basis of its elemental analysis and spectral data (IR, ^{1}H NMR, and MS). Thus, the IR spectrum of the latter product revealed the presence of N–H stretching band at 3165 cm^{-1} and three C=O stretching bands at the range 1672-1689 cm^{-1} besides a broad band at 1620-1625 due to the two C=N stretching. The ^{1}H NMR spectrum of compound **19** exhibited two sharp singlets at 3.21 and 3.22 ppm assignable to two methyl groups, while the olefinic proton was observed as singlet at 6.86 ppm, besides the N–H broad singlet at 10.91 ppm, and aromatic protons in the region of 7.61-7.82 ppm. While, the MS of **19** displayed an intense ion peak at *m/z* 548.00 (M^+, 55%) corresponding to $C_{30}H_{24}N_6O_3S$.

The reactivity of enaminone **19** towards some heterocyclic amines as potential precursors for fused heterocyclic systems was also investigated. Thus, the enaminone **19** treated with equimolar amount of 3-amino-1*H*-1,2,4-triazole in refluxing AcOH, it furnished 2-(5-(((1*H*-1,2,4-triazol-3-yl)amino)-methylene)-4-oxothiazolidin-2-ylidene)hydrazono-1,4-diphenyl-1,2,3,4-tetrahydrobenzo[*g*]quinoxaline-5, 10-dione (**20**) in 65% yield, (**Scheme 5**). The formation of compound **20** was assumed proceeded *via* simple nucleophilic substitution without further cyclocondensation into triazolopyrimidine **21** derivative, as shown in the mass spectrum which declare a molecular ion peak at *m/z* 587.00 corresponding to the molecular formula $C_{30}H_{21}N_9O_3S$. Its, IR spectrum displayed absorption bands at 1620-1625, 1672, 1687 and 3152–3215 cm^{-1} corresponding to the two stretching C=N, three stretching C=O and three N–H groups, respectively. While, the ^{1}H NMR spectrum of **20** showed two doublet signals at δ 6.88 (*d*, 1H, *J* 10.9 Hz, =CH) and 4.21 (*d*, 1H, *J* 10.8 Hz, =CH–NH). (See Experimental Section).



Scheme **5**. Synthesis of 1,2,4-triazolo derivative **20**

When thiazolidinone **5** was coupled with phenyldiazonium chloride afforded 2-((4-oxo-5-(2-phenylhydrazno)thiazolidin-2-ylidene)hydrazono)-1,4-diphenyl-1,2,3,4-tetrahydrobenzo[*g*]quinoxaline-5,10-dione (**22**) in 85% yield, (**Scheme 6**). The structure of the latter compound was in agreement with elemental analysis and spectral data. Its IR spectrum revealed the presence of NH stretching absorption band at 3186–3261 cm^{-1} and three C=O stretching bands at the range 1672-1689 cm^{-1}. Its mass spectrum showed a molecular ion at *m/z* 599.00 corresponding to its molecular formula $C_{33}H_{25}N_7O_3S$. While, the ^1H NMR spectrum showed two D_2O-exchangeable broad singlets at 10.21 and 11.15 ppm for the 2 NH groups. Further, cyclocondensation of the latter product with ethyl cyanoacetate, in boiling EtOH containing catalytic amount of piperidine afforded 6-((5,10-dioxo-1,4-diphenyl-3,4-dihydrobenzo[*g*]quinoxalin-2(1*H*,5*H*,10*H*)-ylidene)hydrazono)-3-oxo-2-phenyl-2,3,5,6-tetrahydrothiazolo[5,4-*c*]pyridazine-4-carbonitrile (**25**) *via* intermediates **23** and **24**. These intermediates were assumed to be formed through initial elimination of EtOH to form **23** followed by cyclocondensation as shown in (**Scheme 6**). The IR spectrum declared the presence of C≡N stretching band at 2217 cm^{-1}, supported imine–enamine tautomerism as a band at 3128 cm^{-1} was still observable. This was further evidenced by its ^1H NMR broad singlet at 10.12 ppm without observation of any signal in the up field region if intermediate **24** was exist.



Scheme **6**. Synthesis of thiazolo[5,4-*c*]pyridazine derivative **25**

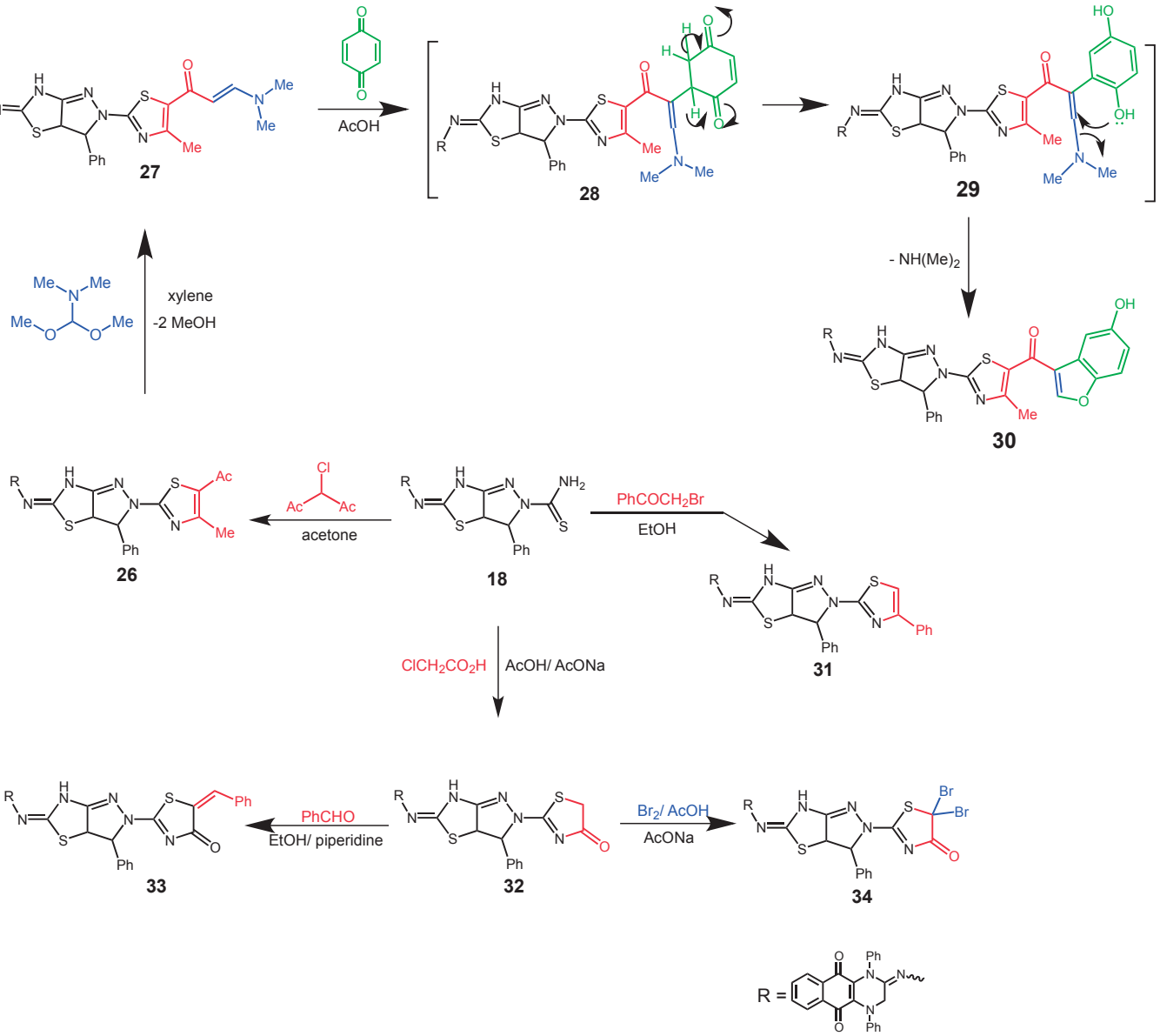
Compound **18** was incorporated in a set of manipulations aiming at exploiting the reactivity of its thioamide tag, to build up the target thiazole architectures. Thus, the thiamido derivative **18** was treated with some α-halocarbonyl using Hantzsch method to afford the target thiazole derivatives **26-34**,[47] (**Scheme 7**). Compound **18** on treating with 3-chloropentane-2,4-dione in refluxing acetone afforded 2-substituted 4-methyl-5-acetylthiazole derivative **26** in yield 80%. The latter compound was treated with dimethyformamide dimethyl acetal (DMF-DMA), in dry xylene, at reflux temperature, afforded the active enamine derivative **27** as a brown crystalline product in 75% yield (**Scheme 7**). Structure of compound **27** was established on the basis of its elemental analysis and spectral data (IR, ^{1}H NMR, and MS). Its, IR spectrum revealed the presence of N–H stretching band at 3202 cm^{-1} and three C=O stretching bands at 1672-1725 cm^{-1}. Its mass spectrum showed the molecular ion at *m/z* 789.00 corresponding to its molecular formula $C_{43}H_{35}N_9O_3S_2$. The ^{1}H NMR spectrum exhibited two sharp singlets at 3.04 and 3.05 ppm assignable to *N,N*-dimethylamino protons, up filed doublet signal due to olefinic proton at δ 5.15 in addition to down field doublet signal due to the azomethine proton (CH=N) at 8.22 ppm and aromatic protons in the region of 7.61-7.82 ppm.

The enaminone **27** reacted with *p*-benzoquinone in AcOH at rt, afforded a product identified as benzo[*b*]furan derivative **30** on the basis of its elemental analysis and spectral data (IR, ^{1}H NMR and MS).

Its IR spectrum showed broad band of the O-H_{str} group at 3425 cm^{-1} and showed three carbonyl absorption bands at 1672-1714 cm^{-1}. Its, mass spectrum showed a peak corresponding to the molecular ion at *m/z* 852.00 (M^+, 25%), the ^1H NMR spectrum of **30** showed characteristic down field singlet signal at δ 8.87 of furan proton and revealed D_2O-exchangeable broad singlet at 9.78 ppm due to hydroxyl group [*cf*. experimental part]. Compound **30** is suggested to be formed *via* an initial addition of the electron-rich moiety C2 of the enaminone to the activated electron-poor double bond system of the quinone to form the intermediate **28** which readily aromatized and cyclized *via* dimethylamine elimination into the final isolable product **30** (**Scheme 7**).

Furthermore, compound **18** was then conveniently cyclized in ethanolic solution to afford 1,4-diphenyl-2-((3-phenyl-2-(4-phenylthiazol-2-yl)-3,3a-dihydro-2*H*-pyrazolo[3,4-*d*]thiazol-5(6*H*)-ylidene)hydrazono)-1,2,3,4-tetrahydrobenzo[*g*]quinoxaline-5,10-dione (**31**), through its treating with phenacyl bromide (**Scheme 7**). The structure of compound **31** was confirmed based on its elemental and spectral data. Its, IR spectrum confirmed the presence of intense absorption bands at 1672 and 3280 cm^{-1} attributed to three C=$O_{str.}$ and N-$H_{str.}$ groups, respectively. The mass spectrum showed a peak at *m/z* 754.00 (M^+, 35%), corresponding to the molecular formula $C_{43}H_{30}N_8O_2S_2$. The ^1H NMR spectrum of **31** showed a singlet at 7.01 ppm attributed to the thiazole-H5 proton [*cf*. experimental part].

In the last part of this work, the 1-thiocarbamoyl **18** was converted to the thiazolone **32** *via* cyclization with chloroacetic acid, then, some chemical manipulations of the thiazolone **32** were investigated (**Scheme 7**). The IR spectrum of **32** revealed the presence of N–H stretching band at 3152 cm^{-1} and three C=O stretching bands at 1672 and 1704 cm^{-1}. Its, mass spectrum showed the molecular ion at *m/z* 694.00 corresponding to its molecular formula $C_{37}H_{26}N_8O_3S_2$. The (NMR) of **32** exhibited a sharp singlet at 3.85 ppm attributed to the thiazolone methylene protons, and its corresponding ^{13}C NMR signal at 40.3. The active methylene group in the thiazolone moiety easily incorporates in condensation reactions with benzaldehyde to give benzylidene derivative **33** in yield 85%. Bromination of compound **32**, performed in AcOH at rt, yielded 2-((2-(5,5-dibromo-4-oxo-4,5-dihydrothiazol-2-yl)-3-phenyl-3,3a-dihydro-2*H*-pyrazolo[3,4-*d*]thiazol-5(6*H*)-ylidene)hydrazono)-1,4-diphenyl-1,2,3,4-tetrahydrobenzo[*g*]quinoxaline-5,10-dione (**34**), (**Scheme 7**).



Scheme **7**. Synthesis of pyrazolo[3,4-*d*]thiazol derivatives **26**- **34**

In the present work, 2-(5,10-dioxo-1,4-diphenyl-3,4-dihydrobenzo[*g*]quinoxalin-2(1*H*,5*H*,10*H*)-ylidene)hydrazinecarbothioamide (**4**) and 2-(4-oxothiazolidin-2-ylidene)hydrazono)- 1,4-diphenyl-1,2,3,4-tetrahydrobenzo[*g*]quinoxaline-5,10-dione (**5**), were prepared as new three–pharmacophoric–motif key intermediates in fair yields. The reactivity of the terminal thioureido as well as 1-thiocarbamoyl moieties were exploited in a series of manipulations encompassing cyclocondensation for the synthesis of new four and/or five–pharmacophoric–motif probes. A study of pharmacological investigations on these new conjugates is going in due course

EXPERIMENTAL

Reagents were purchased from Sigma Aldrich and used without further purification. Reaction progress was monitored by TLC on silica gel precoated F254 Merck plates. Spots were visualized by ultraviolet irradiation. Melting points were determined on a Gallenkamp electrothermal melting point apparatus and are uncorrected. IR spectra were recorded as potassium bromide discs using Bruker-Vector 22 FTIR Spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 300 MHz Bruker WP spectrometer using DMSO–d_6 as solvent, while, TMS was used as internal standard. Mass spectra were recorded on a Hewlett Packard MS–5988 spectrometer at 70 eV. Elemental analyses were carried out at the Micro-analytical Unit of Cairo University, Egypt.

2,3-*Bis*(phenylamino)naphthalene-1,4-dione (2), was prepared as previously reported in literatures.[48-50] Yield (85%) as reddish crystals. mp 215–217 ºC; IR (KBr): (cm^{-1}) 1678 (2 C=O$_{str}$), 3356 (2 N-H$_{str}$); ^{1}H NMR (300 MHz, DMSO–d_6): δ 7.51–7.88 (*m*, 14H, Ar), 9.64 (br, *s*, 2H, 2NH, D$_2$O-exchangeable); MS (*m/z*, %): 340.00 (M$^+$, 50%). Anal. Calcd for $C_{22}H_{16}N_2O_2$ (340.12): C, 77.63; H, 4.74; N, 8.23%. Found: C, 77.35; H, 4.65; N, 8.12%.

1,4-Diphenyl-3,4-dihydrobenzo[*g*]quinoxaline-2,5,10(1*H*)-trione (3). To a well stirred solution of **2** (0.34 g, 1 mmol) and triethylamine (0.5 mL) in dry DMF (20 mL), chloroacetyl chloride (0.02 mol) was added dropwise during 1 h at rt, then the reaction mixture was refluxed for 5 h at 60 ºC, cooled then poured onto ice–cooled H_2O. The precipitate was filtered and then recrystallized from EtOH to afford **3** (65%) as orange crystals. mp 282–284 ºC; IR (KBr): (cm^{-1}) 1665, 1672 (3 C=O$_{str.}$); ^{1}H NMR (300 MHz, DMSO–d_6): δ 4.21 (br. *s*, 2H, CH_2), 7.51–7.80 (*m*, 14H, Ar); ^{13}C NMR (75 MHz, DMSO–d_6): 46.4 (CH_2–Piperaz.), 119.1, 120.7, 126.5, 126.4, 128.0, 128.1, 128.9, 130.1, 135.1, 135.2, 144.2 (C–Ar), 127.6, 132.5 (2 C-Quinone), 162.9, 174.1, 178.4 (3 C=O); MS (*m/z,* %): 380.00 (M$^+$, 62%); Anal. Calcd for $C_{24}H_{16}N_2O_3$ (380.40): C, 75.78; H, 4.24; N, 7.36%. Found: C, 75.61; H, 4.05; N, 7.11%.

2-(5,10-Dioxo-1,4-diphenyl-3,4-dihydrobenzo[*g*]quinoxalin-2(1*H*,5*H*,10*H*)-ylidene)hydrazinecarbothioamide (4). A mixture of **3** (0.38 g, 1 mmol), thiosemicarbazide (0.09 g, 1 mmol) and NaOH (0.025 mol) in EtOH (40 mL) was heated under reflux for 6 h. The mixture was filtered while hot and the cooled filtrate was poured onto acidified ice/ water. The precipitate formed was filtered, washed with water, dried well, and recrystallized from EtOH to afford **4** (70%) as brown crystals. mp 203–205 ºC; IR (KBr): (cm^{-1}) 1331 (C=S$_{str}$), 1620 (C=N$_{str.}$), 1672 (2 C=O$_{str.}$) and 3410–3230 (NH and NH$_2$); ^{1}H NMR (300 MHz, DMSO–d_6): δ 3.21 (*s*, 2H, CH_2), 7.32–7.71 (*m*, 14H, Ar-H), 8.21 (*s*, 2H, NH$_{2\text{Deutr. Exch.}}$), 10.21 (*s*, 1H,

N–$H_{Deutr.\ Exch.}$); ^{13}C NMR (75 MHz, DMSO–d_6): 52.3 (CH_2–Piperaz.), 119.2, 120.6, 122.3, 122.9, 126.1, 126.5, 128.9, 130.1, 135.2, 141.4, 144.4 (C–Ar), 127.2, 132.5 (2 C-Quinone), 146.5 (C-2–Piperaz.), 174.1, 178.4 (2 C=O), 181.2 (C=S); MS: *m/z* 453.0 (M^+, 25%). Anal. Calcd for $C_{25}H_{19}N_5O_2S$ (453.52): C, 66.21; H, 4.22; N, 15.44%. Found*:* C, 66.07; H, 4.11; N, 15.12%.

2-((4-Oxothiazolidin-2-ylidene)hydrazono)-1,4-diphenyl-1,2,3,4-tetrahydrobenzo[*g*]quinoxaline-5,10-dione (5). *Method A:* To a well stirred solution of **4** (0.45 g, 1 mmol) and triethylamine (0.5 mL) in dry EtOH (30 mL), chloroacetyl chloride (0.12 mL, 1 mmol) was added dropwise during 1 h at rt, then the reaction mixture was refluxed for 5 h at 60 ºC, cooled then poured onto ice–cooled H_2O. The precipitate was filtered and then recrystallized from MeOH to afford **5** (75%) as brown crystals.

Method B: A mixture of compound **4** (0.45 g, 1 mmol), ethyl bromoacetate (0.16 mL, 1 mmol) and sodium acetate (0.04 mol) in dry EtOH (30 mL) was refluxed for 6 h, the reaction mixture left to cool at rt, diluted with water and allowed to stand overnight; the precipitate was filtered and then recrystallised from EtOH to afford **5** (85%); mp 202–204 ºC; IR (KBr): (cm^{-1}) 1620-1625 (2 C=$N_{str.}$), 1672-1689 (3 C=$O_{str.}$), 3211 (N–$H_{str.}$); ^{1}H NMR (300 MHz, DMSO–d_6): δ 3.82 (br. *s*, 2H, $CH_{2–Thiaz.}$), 4.01 (br. *s*, 2H, $CH_{2–Piperaz.}$), 7.34–7.78 (*m*, 14H, Ar), 11.41 (br. *s*, 1H, N-H); ^{13}C NMR (75 MHz, DMSO–d_6): 32.7 (CH_2–Thiaz.), 51.9 (CH_2–Piperaz.), 119.2, 120.6, 122.3, 122.9, 126.1, 126.5, 128.9, 130.1, 135.2, 141.4, 144.4 (C–Ar), 127.2, 132.5 (2 C-Quinone), 156.5 (C-2–Piperaz.), 158.5 (C-2–Thiaz.), 173.9, 174.1, 178.4 (3 C=O); MS (*m/z,* %): 493.0 (M^+, 45%); Anal. Calcd for $C_{27}H_{19}N_5O_3S$ (493.54): C, 65.71; H, 3.88; N, 14.19%. Found: C, 65.51; H, 3.65; N, 14.09%.

Ethyl 2-(2-((5,10-dioxo-1,4-diphenyl-3,4-dihydrobenzo[*g*]quinoxalin-2(1*H*,5*H*,10*H*)-ylidene)hydrazono)-4-oxothiazolidin-3-yl)acetate (6). A mixture of compound **4** (0.45 g, 1 mmol), ethyl bromoacetate (0.32 mL, 0.02 mol) and sodium acetate (0.04 mol) in dry EtOH (30 mL) was refluxed for 6 h, the reaction mixture left to cool at rt, diluted with water and allowed to stand overnight; the precipitate was filtered and then recrystallized from EtOH to afford **6** (60%) as yellow crystals; mp 219-221 ºC; IR (KBr): (cm^{-1}) 1620-1625 (2 C=$N_{str.}$), 1672, 1689, 1725 (4 C=$O_{str.}$); ^{1}H NMR (300 MHz, DMSO–d_6): δ 1.32 (*t*, *J* = 7.01 *Hz*, 3H, $\underline{CH_3}CH_2$), δ 3.21 (br. *s*, 2H, $CH_{2–Thiaz.}$), 4.01 (br. *s*, 2H, $CH_{2–Piperaz.}$), 4.21 (*q*, *J* = 7.01 *Hz*, 2H, $CH_3\underline{CH_2}$), 4.51 (*s*, 2H, CH_2), 7.34–7.78 (*m*, 14H, Ar); ^{13}C NMR (75 MHz, DMSO–d_6): 14.2 (CH_3), 29.7 (CH_2–Thiaz.), 41.8 (N-CH_2CO), 51.9 (CH_2–Piperaz.), 61.1 (CH_2O), 119.2, 120.6, 122.3, 122.9, 126.1, 126.5, 128.9, 130.1, 135.2, 141.4, 144.4 (C–Ar), 127.2, 132.5 (2 C-Quinone), 156.5 (C-2–Piperaz.), 158.5 (C-2–Thiaz.), 167.6, 172.1, 174.1, 178.4 (4 C=O); MS (*m/z,* %): 579.0 (M^+, 25%); Anal. Calcd for $C_{31}H_{25}N_5O_5S$ (579.63): C, 64.24; H, 4.35; N, 12.08%. Found: C, 64.02; H, 4.21; N, 12.01%.

2-((5-Acetyl-4-methylthiazol-2(3*H*)-ylidene)hydrazono)-1,4-diphenyl-1,2,3,4-tetrahydrobenzo[*g*]quinoxaline-5,10-dione (7). A mixture of the thioureido **4** (0.45 g, 1 mmol) and 3-chloro-2,4-pentanedione (0.13 g, 1 mmol) in acetone (25 mL), was refluxed for 5 h. Then the reaction mixture was cooled down, diluted with water (20 mL), and sodium acetate (0.5 g) was added, and the mixture was stirred for 10 min at r.t. The formed precipitate was filtered off, washed with water and dried, then recrystallized from EtOH to afford **7** (85%); mp 202–204 ºC; IR (KBr): (cm^{-1}) 1620-1625 (2 C=$N_{str.}$), 1672, 1708 (3 C=$O_{str.}$), 3211 (N–$H_{str.}$); ^{1}H NMR (300 MHz, DMSO–d_6): δ 2.72 (*s*, 3H, $CH_{3–Thiaz.}$), 2.78 (*s*, 3H, CH_3CO), 3.21 (br. *s*, 2H, $CH_{2–Piperaz.}$), 7.01–7.78 (*m*, 14H, Ar), 11.20 (br. *s*, 1H, N-H); ^{13}C NMR (75 MHz, DMSO–d_6): 18.2 (CH_3), 25.8 (CH_3CO), 51.8 (CH_2–Piperaz.), 119.2, 120.7, 122.3, 122.9, 126.1, 126.5, 129.4, 130.1, 135.1, 141.4, 144.4 (C–Ar), 127.7, 132.6 (2 C-Quinone), 156.5 (C-2–Piperaz.), 105.4, 158.3, 158.6 (3 C-Thiaz.), 174.1, 178.4, 192.8 (3 C=O); MS (*m/z,* %): 533.0 (M^+, 45%); Anal. Calcd for $C_{30}H_{23}N_5O_3S$ (533.60): C, 65.53; H, 4.34; N, 13.12%. Found: C, 65.21; H, 4.12; N, 13.02%.

1,4-Diphenyl-2-((4-phenylthiazol-2(3*H*)-ylidene)hydrazono)-1,2,3,4-tetrahydrobenzo[*g*]quinoxaline-5,10-dione (8). An equimolar mixture of compound **4** (0.45 g, 1 mmol), phenacyl bromide (0.19 g, 1 mmol) in dry EtOH (30 mL) containing 0.1 mL of piperidine as catalyst, was refluxed for 6 h, the reaction mixture was evaporated to dryness under reduced pressure. The resultant was separated off, filtered, washed with MeOH and then recrystallized from EtOH to afford **8** (75%); mp 252–254 ºC; IR (KBr): (cm^{-1}) 1621-1627 (2 C=$N_{str.}$), 1672 (2 C=$O_{str.}$), 3231 (N–$H_{str.}$); ^{1}H NMR (300 MHz, DMSO–d_6): δ 3.21 (br. *s*, 2H, $CH_{2–Piperaz.}$), 7.04–7.78 (*m*, 20H, Ar-H & H5-$_{Thiaz.}$), 10.98 (br. *s*, 1H, N-H); ^{13}C NMR (75 MHz, DMSO–d_6): 52.1 (CH_2–Piperaz.), 119.2, 120.9, 122.3, 122.9, 126.3, 126.7, 126.8, 127.9, 128.7, 129.5, 130.1, 134.8, 135.0, 136.7, 141.4, 144.4 (C–Ar), 127.7, 132.6 (2 C-Quinone), 108.5 (C-5–Thiazol.), 158.2 (C-2–Thiazol.), 161.7 (C-4–Thiazol.), 156.5 (C-2–Piperaz.), 174.1, 178.4 (2 C=O); MS (*m/z,* %): 553.00 (M^+, 60%); Anal. Calcd for $C_{33}H_{23}N_5O_2S$ (553.63): C71.59; H, 4.19; N, 12.65%. Found: C, 71.21; H, 4.10; N, 12.32%.

1,4-Diphenyl-2-((4-amino-6-phenyl-1,3-thiazine-5-carbonitril-2-ylidene)hydrazono)-1,2,3,4-tetrahydrobenzo[*g*]quinoxaline-5,10-dione (10). A mixtures of **4** (0.45 g, 1 mmol) and benzylidinemalononitrile (0.15 g, 1 mmol) in dioxane (20 mL) containing few drops of piperidine (0.5 mL) was stirred under reflux for 4 h. Then, the reaction mixture was cooled to rt. The solid formed was filtered, washed with MeOH, and recrystallized from EtOH to afford **10** (69%) as yellow crystals; mp 198–200 ºC; IR (KBr): (cm^{-1}) 1620-1625 (3 C=$N_{str.}$), 1672 (2 C=$O_{str.}$), 2215 (C≡$N_{str.}$), 3452 ($NH_{2.str.}$); ^{1}H

NMR (300 MHz, DMSO–d_6): δ 3.11 (br. *s*, 2H, $CH_{2-Piperaz.}$), 7.04–7.78 (*m*, 19H, Ar-H), 8.71 (br. *s*, 2H, NH_2); ^{13}C NMR (75 MHz, DMSO–d_6): 51.9 (CH_2–Piperaz.), 115.9 (C≡N), 119.2, 120.6, 122.3, 122.9, 126.1, 126.5, 127.8, 128.0, 128.7, 129.5, 130.1, 135.1 136.1, 141.4, 144.5 (C–Ar), 127.2, 132.6 (2 C-Quinone), 156.3 (C-2–Piperaz.), 96.9, 149.7, 158.9, 174.1 (4 C–Thiazine), 174.1, 178.4 (2 C=O); MS (*m/z,* %): 605.0 (M^+, 60%); Anal. Calcd for $C_{35}H_{23}N_7O_2S$ (605.67): 69.41; H, 3.83; N, 16.19%. Found: C, 69.21; H, 3.56; N, 16.02%.

Methyl 2-(2-((5,10-dioxo-1,4-diphenyl-3,4-dihydrobenzo[*g*]quinoxalin-2(1*H*,5*H*,10*H*)-ylidene)hydrazono)-4-oxothiazolidin-5-ylidene)acetate (13). To a well stirred solution of **4** (0.45 g, 1 mmol) in AcOH (50 mL), a solution of dimethyl acetylenedicarboxylate (0.11 mL, 1 mmol) in glacial acetic acid (30 mL) was added dropwise with stirring. The mixture was stirred at room temperature for 1 h, and at reflux for 10 h (the reaction was monitored by TLC analyses). The solvent was evaporated under vacuum and the formed precipitate was filtered and then recrystallized from EtOH to afford **13** (75%) as yellow crystals. mp 182–184 ºC; IR (KBr): (cm^{-1}) 1620-1625 (2 C=$N_{str.}$), 1672, 1689 and 1690 (4 C=$O_{str.}$), 3214 (N–$H_{str.}$); ^{1}H NMR (300 MHz, DMSO–d_6): δ 3.19 (br. *s*, 2H, $CH_{2-Piperaz.}$), 3.51 (*s*, 3H, CH_3), 6.72 (*s*, 1H, C=CH), 7.14–7.78 (*m*, 14H, Ar-H), 11.41 (br. *s*, 1H, N-H); ^{13}C NMR (75 MHz, DMSO–d_6): 51.9 (CH_2–Piperaz.), 52.1 (CH_3), 119.2, 120.6, 122.3, 122.4, 122.9, 126.1, 126.5, 129.3, 130.1, 135.2, 141.4, 144.4 (C–Ar), 127.6, 132.7 (2 C-Quinone), 139.6 (Olefinic), 156.5 (C-2–Piperaz.), 131.3 (C-5–Thiaz.), 158.4 (C-2–Thiaz.), 166.6, 173.9, 174.1, 178.5 (4 C=O); MS (*m/z,* %): 563.0 (M^+, 35%); Anal. Calcd for $C_{30}H_{21}N_5O_5S$ (563.58): C63.93; H, 3.76; N, 12.43%. Found: C, 63.68; H, 3.56; N, 12.32%.

2-((5-Benzylidene-4-oxothiazolidin-2-ylidene)hydrazono)-1,4-diphenyl-1,2,3,4-tetrahydrobenzo[*g*]quinoxaline-5,10-dione (16). *Method A:* A mixtures of **5** (0.49 g, 1 mmol) and benzylidenemalononitrile (0.15 g, 1 mmol) in EtOH (30 mL) containing few drops of piperidine (0.5 mL) was stirred under reflux for 5 h. Then, the reaction mixture was cooled to rt. The solid formed was filtered, washed with hot EtOH, and recrystallized from (dioxane–DMF, 1:2) to afford **16** (90%) as yellow crystals.

Method B: A mixture of **5** (0.98 g, 2.0 mmol) and BzH (0.20 mL, 2.0 mmol) in AcOH (20 mL) containing AcONa (10.0 mmol) was refluxed for 4 h. The reaction mixture was cooled to rt then poured onto ice–cooled H_2O. The precipitate was filtered off, washed with H_2O and the crude product was recrystallized to afford **16** (75%). mp 289–291 ºC; IR: (cm^{-1}) 1620-1625 (2 C=$N_{str.}$), 1672, 1710 (3 C=$O_{str.}$), 3211 (N–$H_{str.}$); ^{1}H NMR (300 MHz, DMSO–d_6): δ 4.01 (br. *s*, 2H, $CH_{2-Piperaz.}$), 6.87 (*s*, 1H, =C-H), 7.31–7.78 (*m*, 19H, Ar-H), 11.41 (br. *s*, 1H, N-H); ^{13}C NMR (75 MHz, DMSO–d_6): 51.9 (CH_2–Piperaz.), 119.2, 120.6, 122.4, 122.8, 126.2, 126.8, 128.5, 128.6, 129.6, 130.1, 135.2, 141.3, 143.4,

144.4 (C–Ar), 116.9 (C-5–Thiazolid.), 158.9 (C-2–Thiazolid.), 127.4, 131.5 (2 C-Quinone), 143.2 (Olefinic), 156.5 (C-2–Piperaz.), 172.8, 173.1, 178.5 (3 C=O); MS (*m/z,* %): 581.0 (M^+, 45%); Anal. Calcd for $C_{34}H_{23}N_5O_3S$ (581.64): C, 70.21; H, 3.99; N, 12.04%. Found: C, 70.11; H, 3.65; N, 11.89%.

5-((5,10-Dioxo-1,4-diphenyl-3,4-dihydrobenzo[*g*]quinoxalin-2(1*H*,5*H*,10*H*)-ylidene)hydrazono)-3-phenyl-3,3a,5,6-tetrahydro-2*H*-pyrazolo[3,4-*d*]thiazole-2-carbothioamide (18). A mixture of **16** (0.58 g, 1 mmol), thiosemicarbazide (0.09 g, 1 mmol) and NaOH (0.025 mol) in EtOH (50 mL) was heated under reflux for 6 h. The mixture was filtered while hot and the cooled filtrate was poured onto acidified ice/ water. The precipitate formed was filtered, washed with water, dried well, and recrystallized from EtOH to afford **18** (70%) as pale yellow crystals. mp 248–250 ºC; IR (KBr): (cm^{-1}) 1332 (C=S_{str}), 1620 -1625 (3 C=$N_{str.}$), 1672 (2 C=$O_{str.}$) and 3480–3235 (NH and NH_2); ^{1}H NMR (300 MHz, DMSO–d_6): δ 3.14 (*s*, 2H, $CH_{2–Piperaz.}$), 3.89 (*d*, *J* = 7.51 *Hz*, 1H, $Pyraz_{(C4)}$-H), 4.42 (*d*, *J* = 7.51 *Hz*, 1H, $Pyraz_{(C3)}$-H), 7.01–7.71 (*m*, 20H, Ar-H.& NH_2), 11.01 (*s*, 1H, N–$H_{Deutr. Exch.}$); ^{13}C NMR (75 MHz, DMSO–d_6): 48.4 (C-5-Thaiaz.), 52.1 (CH_2–Piperaz.), 60.2 (C-3-Pyraz.), 119.2, 120.6, 122.4, 122.8, 126.2, 126.7, 126.8, 126.9, 128.5, 129.6, 130.1, 135.1, 141.3, 143.4, 144.4 (C–Ar), 156.3, 157.1, 158.3 (3 C=N), 127.4, 131.5 (2 C-Quinone), 173.1, 178.5 (2 C=O), 175.9 (C=S); MS: *m/z* 654.00 (M^+, 25%); Anal. Calcd for $C_{35}H_{26}N_8O_2S_2$ (654.76): C, 64.20; H, 4.00; N, 17.11%. Found: C, 64.10; H, 3.85; N, 17.04%.

2-((5-((Dimethylamino)methylene)-4-oxothiazolidin-2-ylidene)hydrazono)-1,4-diphenyl-1,2,3,4-tetrahydrobenzo[*g*]quinoxaline-5,10-dione (19). A mixture of **5** (0.49 g, 1 mmol), DMF–DMA (0.11 mL, 1 mmol) in dry xylene (25 mL) was refluxed for 4 h. The solvent was distilled off *in vacuo* and the residual orange viscous liquid was taken in Et_2O. The resulting yellow crystals were filtered, washed thoroughly with Et_2O, dried then recrystallized from EtOH to afford **19** (79%) as yellow crystals. mp 217–219 ºC; IR (KBr): (cm^{-1}) 1620-1625 (2 C=$N_{str.}$), 1672-1689 (3 C=$O_{str.}$), 3165 (N–$H_{str.}$); ^{1}H NMR (300 MHz, DMSO–d_6): δ 3.21 (*s*, 3H, CH_3), 3.22 (*s*, 3H, CH_3), 3.32 (br. *s*, 2H, $CH_{2–Piperaz.}$), 6.86 (*s*, 1H, =C–H), 7.61–7.82 (*m*, 14H, Ar), 10.91 (br. *s*, 1H, N-H); ^{13}C NMR (75 MHz, DMSO–d_6): 42.4 (2 CH_3), 52.1 (CH_2–Piperaz.), 119.2, 120.6, 122.3, 122.8, 126.5, 128.9, 130.1, 135.2, 141.3, 144.5 (18 C–Ar), 101.7 (C-5–Thiaz.), 158.9 (C-2–Thiaz.), 155.6 (Olefinic), 127.2, 132.5 (2 C-Quinone), 156.5 (C-2–Piperaz.), 173.9, 174.1, 178.4 (3 C=O); MS (*m/z,* %): 548.0 (M^+, 55%); Anal. Calcd for $C_{30}H_{24}N_6O_3S$ (548.61): C, 65.68; H, 4.41; N, 15.32%. Found: C, 65.51; H, 4.25; N, 15.09%.

2-(5-(((1*H*-1,2,4-Triazol-3-yl)amino)methylene)-4-oxothiazolidin-2-ylidene)hydrazono-1,4-diphenyl-1,2,3,4-tetrahydrobenzo[*g*]quinoxaline-5,10-dione (20). A mixture of the enamine **19** (0.54 g, 1 mmol)

and 3-amino-1,2,4-triazol (0.08 g, 1 mmol) in AcOH acid (20 mL) containing anhydrous NaOAc (10 mmol) was refluxed for 10 h. The reaction mixture was cooled to rt, then poured onto ice–cooled water. The precipitate was filtered off and washed with H_2O and the resulting crude product was purified by recrystallization from EtOH as yellow crystals, yield: 65%, mp 256-258 °C; IR (KBr): (cm^{-1}) 1620-1625 (4 C=$N_{str.}$), 1672, 1687 (3 C=$O_{str.}$), 3152-3215 (2 N–$H_{str.}$); ^{1}H NMR (300 MHz, DMSO–d_6): δ 3.32 (br. *s*, 2H, $CH_{2–Piperaz.}$), 4.21 (*d*, 1H, *J* = 7.2 Hz, =CH–NH), 6.88 (*d*, 1H, *J* = 7.2 Hz, =CH), 7.11–7.72 (m, 14H, Ar), 8.14 (br. *s,* 1H, H–$5_{Triaz.}$), 10.03 (br. *s*, 1H, N–$H_{Thiaz.}$), 12.71 (*s*, 1H, N–$H_{Triaz.}$); MS: *m/z,* 587.0 (M^+, 35%). Anal. Calcd for $C_{30}H_{21}N_9O_3S$ (587.61): C, 61.32; H, 3.60; N, 21.45%. Found: C, 61.12; H, 3.28; N, 21.825%.

2-((4-Oxo-5-(2-phenylhydrazono)thiazolidin-2-ylidene)hydrazono)-1,4-diphenyl-1,2,3,4-tetrahydrobenzo[*g*]quinoxaline-5,10-dione (22). $NaNO_2$ (0.76 g, 1 mmol) in cold H_2O (15 mL) was added dropwise during a period of 20 min to a mixture of aniline (0.09 mL, 1 mmol) in EtOH (15 mL) containing conc. HCl (3.0 mL). Then, the mixture was added to a well stirred solution of **5** (0.49 g, 1 mmol) in ice–cooled EtOH (10 mL) containing NaOAc (2.0 g, 0.024 mol) and stirring was continued overnight at rt. The resulting solid was collected by filtration, washed by H_2O and recrystallized from MeOH to afford **22** (85 %) as yellow crystals. mp 156–185 ºC; IR (KBr): (cm^{-1}) 1620-1627 (3 C=$N_{str.}$), 1672-1689 (3 C=$O_{str.}$), 3186-3261 (2 N–$H_{str.}$); ^{1}H NMR (300 MHz, DMSO–d_6): δ 3.21 (s, 2H, $CH_{2–Piperaz.}$), 7.34–7.78 (*m*, 19H, Ar), 10.21 (*s*, 1H, N–$H_{Deutr. Exch.}$), 11.15 (*s*, 1H, N–$H_{Deutr. Exch.}$); ^{13}C NMR (75 MHz, DMSO–d_6): 52.1 (CH_2–Piperaz.), 113.8, 119.4, 120.7, 122.3, 122.9, 126.1, 126.5, 129.2, 130.1, 135.1, 141.4, 143.0, 144.5 (C–Ar), 127.2, 132.5 (2 C-Quinone), 156.3 (C-2–Piperaz.), 158.4, 148.4 (2 C–Thiaz.), 170.9, 174.1, 178.4 (3 C=O); MS (*m/z,* %): 599.0 (M^+, 25%); Anal. Calcd for $C_{33}H_{25}N_7O_3S$ (599.66): C, 66.10; H, 4.20; N, 16.35%. Found: C, 66.01; H, 4.11; N, 16.09%.

6-((5,10-Dioxo-1,4-diphenyl-3,4-dihydrobenzo[*g*]quinoxalin-2(1*H*,5*H*,10*H*)-ylidene)hydrazono)-3-oxo-2-phenyl-2,3,5,6-tetrahydrothiazolo[5,4-c]pyridazine-4-carbonitrile (25). A mixture of **22** (0.59 g, 1 mmol), ethyl cyanoacetate (0.13 mL, 1 mmol) and piperidene (0.1 mL) in EtOH (30 mL) was refluxed for 5 h. The solid product obtained upon cooling was filtered off and recrystallized from EtOH to afford **25** (60%) as brown crystals. mp 236–238 °C; IR (KBr): (cm^{-1}) 1620-1625 (3 C=$N_{str.}$), 1672, 1704 (3 C=$O_{str.}$), 2217 (C≡$N_{str.}$) and 3128 ($NH_{str.}$); ^{1}H NMR (300 MHz, DMSO–d_6): δ 3.42 (*s*, 2H, $CH_{2–Piperaz.}$), 6.91–7.48 (*m*, 19H, Ar-H), 10.12 (*s*, 1H, N–H); ^{13}C NMR (75 MHz, DMSO–d_6): 52.1 (CH_2–Piperaz.), 77.8 (C-4-pyridaz.), 115.9 (C≡N), 118.4, 119.2, 120.6, 122.3, 122.4, 122.8, 126.1, 126.7, 128.1, 128.9, 129.3, 130.1, 135.0, 140.4, 141.3, 144.5 (C–Ar), 127.6, 132.7 (2 C-Quinone), 156.3 (C-2-Piperaz.), 145.6,

156.5, 158.4, (3 C=N), 170.5 (C-5–Thiazol.), 160.6, 174.1, 178.5 (3 C=O); MS (*m/z,* %): 646.00 (M^+, 25%); Anal. Calcd for $C_{36}H_{22}N_8O_3S$ (646.68): C, 66.86; H, 3.43; N, 17.33%. Found: C, 66.61; H, 3.26; N, 17.09%.

2-((2-(5-Acetyl-4-methylthiazol-2-yl)-3-phenyl-3,3a-dihydro-2*H*-pyrazolo[3,4-*d*]thiazol-5(6*H*)-ylidene)hydrazono)-1,4-diphenyl-1,2,3,4-tetrahydrobenzo[*g*]quinoxaline-5,10-dione (26). To a solution of thioureido **18** (0.65 g, 1 mmol) in acetone (30 mL), 3-chloro-2,4-pentanedione (0.13 mL, 1 mmol) was added, and the mixture was refluxed for 6 h. Then the reaction mixture was cooled down, diluted with water (40 mL), and sodium acetate (0.49 g, 6 mmol) was added, and the mixture was stirred for 15 min at rt. The precipitate was filtered off, washed with water and dried. Purification was performed by dissolving crystals in 10% aqueous potassium carbonate, filtering and acidifying the filtrate with acetic acid to pH 6 to afford **26** (80%) as yellow crystals. mp 288–290 °C; IR (KBr): (cm^{-1}) 1335 (C=S_{str}), 1620 -1630 (4 C=$N_{str.}$), 1672, 1710 (3 C=$O_{str.}$) and 3185 ($NH_{str.}$); ^{1}H NMR (300 MHz, DMSO–d_6): δ 2.46 (*s*, 3H, CH_3), 2.51 (*s*, 3H, CH_3CO), 3.15 (*s*, 2H, $CH_{2–Piperaz.}$), 3.84 (*d*, *J* = 7.51 *Hz*, 1H, $Pyraz_{(C4)}$-H), 4.41 (*d*, *J* = 7.51 *Hz*, 1H, $Pyraz_{(C3)}$-H), 7.31–7.92 (*m*, 19H, Ar-H), 10.91 (br. *s*, 1H, N-H); ^{13}C NMR (75 MHz, DMSO–d_6): 16.5, 26.9 (2 CH_3), 48.1 (C-4-Pyraz.), 52.1 (CH_2–Piperaz.), 61.6 (C-3-Pyraz.), 119.2, 120.6, 122.3, 122.7, 126.2, 126.7, 126.8, 126.9, 128.4, 130.1, 135.1, 141.1, 143.2, 144.5 (C-Ar), 132.5 (C-5-Thaiaz.), 156.5 (C-4-Thaiaz.) 156.3, 157.0, 158.1, 167.0 (4 C=N), 173.9, 178.1, 197.1 (3 C=O); MS: *m/z* 734.0 (M^+, 35%). Anal. Calcd for $C_{40}H_{30}N_8O_3S_2$ (734.85): C, 65.38; H, 4.11; N, 15.25%. Found*:* C, 65.12; H, 4.05; N, 15.04%.

2-((2-(5-(3-(Dimethylamino)acryloyl)-4-methylthiazol-2-yl)-3-phenyl-3,3a-dihydro-2*H*-pyrazolo[3,4-*d*]thiazol-5(6*H*)-ylidene)hydrazono)-1,4-diphenyl-1,2,3,4-tetrahydrobenzo[*g*]quinoxaline-5,10-dione (27). A mixture of **26** (0.73 g, 1 mmol) and DMF–DMA (0.11 mL, 1 mmol) in dry xylene (30 mL) was refluxed for 5 h. The solvent was distilled off *in vacuo* and the residual orange viscous liquid was taken in Et_2O. The resulting yellow crystals were filtered, washed thoroughly with Et_2O, dried then recrystallized from EtOH to afford **27** (79%) as yellow crystals. mp 179–181 °C; IR (KBr): (cm^{-1}) 1620-1625 (4 C=$N_{str.}$), 1672-1725 (3 C=$O_{str.}$), 3202 (N–$H_{str.}$); ^{1}H NMR (300 MHz, DMSO–d_6): δ 2.47 (*s*, 3H, CH_3), 3.04 (*s*, 3H, CH_3), 3.05 (*s*, 3H, CH_3), 3.32 (br. *s*, 2H, $CH_{2–Piperaz.}$), 3.82 (*d*, *J* = 7.51 *Hz*, 1H, $Pyraz_{(C4)}$-H), 4.41 (*d*, *J* = 7.51 *Hz*, 1H, $Pyraz_{(C3)}$-H), 5.15 (*d*, *J* = 6.91 Hz, 1H, =C–H), 7.61–7.82 (*m*, 19H, Ar-H), 8.22 (*d*, *J* = 6.91 Hz, 1H, -CH=N), 10.91 (br. *s*, 1H, N-H); ^{13}C NMR (75 MHz, DMSO–d_6): 16.1, 44.2 (3 CH_3), 48.1 (C-4-Pyraz.), 52.1 (CH_2–Piperaz.), 61.3 (C-3-Pyraz.), 119.2, 120.6, 122.3, 122.7, 126.2, 126.7, 126.8, 126.9, 128.3, 128.9, 130.1, 135.2, 141.1, 143.2, 144.5 (C-Ar), 132.5 (C-5-Thaiaz.), 156.5 (C-4-Thaiaz.),

156.3, 157.0, 158.1, 167.0 (4 C=N), 92.2, 155.1 (2 Olefinic), 173.9, 174.1, 187.4 (3 C=O); MS (*m/z,* %): 789.0 (M^+, 45%); Anal. Calcd for $C_{43}H_{35}N_9O_3S_2$ (789.93): C, 65.38; H, 4.47; N, 15.96%. Found: C, 65.11; H, 4.25; N, 15.72%.

2-((2-(5-(5-Hydroxybenzofuran-3-carbonyl)-4-methylthiazol-2-yl)-3-phenyl-3,3a-dihydro-2*H*-pyrazolo[3,4-*d*]thiazol-5(6*H*)-ylidene)hydrazono)-1,4-diphenyl-1,2,3,4-tetrahydrobenzo[*g*]quinoxaline-5,10-dione (30). To a stirred solution of the enaminone **27** (0.78 g, 1 mmol) in AcOH acid (50 mL), 1,4-benzoquinone (0.10 g, 1 mmol) was added and the reaction mixture was stirred overnight at rt. The reaction mixture was evaporated in *vacuo*, and the solid product obtained was filtered off and recrystallized from EtOH/DMF to afford **30** (80%) as brown crystals. mp 259–261 ºC; IR (KBr): (cm^{-1}) 1620-1625 (4 C=$N_{str.}$), 1672-1714 (3 C=$O_{str.}$), 3202 (N–$H_{str.}$), 3425 (O–$H_{str.}$); ^{1}H NMR (300 MHz, DMSO–d_6): δ 2.44 (*s*, 3H, CH_3), 3.32 (br. *s*, 2H, $CH_{2–Piperaz.}$), 5.15 (*d*, *J* = 6.91 Hz, 1H, =C–H), 7.61–7.82 (*m*, 22H, Ar-H), 8.87 (*s*, 1H, furan), 9.78 (*s*, 1H, O-$H_{Deutr. Exch}$), 10.82 (br. *s*, 1H, N-$H_{Deutr. Exch}$); ^{13}C NMR (75 MHz, DMSO–d_6): 16.6 (CH_3), 48.1 (C-4-Pyraz.), 52.1 (CH_2–Piperaz.), 61.6 (C-3-Pyraz.), 107.2, 112.7, 112.8, 119.2, 120.6, 122.3, 122.7, 124.6, 126.2, 126.7, 126.8, 126.9, 128.3, 129.4, 130.1, 135.0, 141.1, 143.2, 144.5 (C-Ar), 132.5 (C-5-Thaiaz.), 156.5 (C-4-Thaiaz.), 125.9 (C-3- Furan.), 160.2 (C-2-Furan.), 156.3, 157.0, 158.4, 167.0 (4 C=N), 173.9, 178.1, 184.4 (3 C=O); MS (*m/z,* %): 852.0 (M^+, 25%); Anal. Calcd for $C_{47}H_{32}N_8O_5S_2$ (852.94): C, 66.18; H, 3.78; N, 13.14%. Found: C, 66.06; H, 3.65; N, 13.02%.

1,4-Diphenyl-2-((3-phenyl-2-(4-phenylthiazol-2-yl)-3,3a-dihydro-2*H*-pyrazolo[3,4-*d*]thiazol-5(6*H*)-ylidene)hydrazono)-1,2,3,4-tetrahydrobenzo[*g*]quinoxaline-5,10-dione (31). An equimolar mixture of **18** (0.65 g, 1 mmol) and 2-bromoacetophenone (0.19 g, 1 mmol) in 20 mL of EtOH containing 0.1 mL of piperidine as catalyst was refluxed for 8 h. The solvent was distilled off *in vacuo*. The resultant was separated off, washed with MeOH and recrystallized from EtOH as brown crystals to afford **31** (75%) as pale yellow crystals. mp 198–200 ºC; IR (KBr): (cm^{-1}) 1620 -1625 (4 C=$N_{str.}$), 1672 (2 C=$O_{str.}$) and 3280 (N–H_{str}); ^{1}H NMR (300 MHz, DMSO–d_6): δ 3.13 (*s*, 2H, $CH_{2–Piperaz.}$), 3.89 (*d*, *J* = 7.51 *Hz*, 1H, $Pyraz_{(C4)}$-H), 4.42 (*d*, *J* = 7.51 *Hz*, 1H, $Pyraz_{(C3)}$-H), 7.01–7.71 (*m*, 25H, Ar-H and $Thiazole_{(C5)}$-H), 11.12 (*s*, 1H, N–$H_{Deutr. Exch.}$); MS: *m/z* 754.0 (M^+, 35%). Anal. Calcd for $C_{43}H_{30}N_8O_2S_2$ (754.88): C, 68.42; H, 4.01; N, 14.84. Found*:* C, 68.31; H, 3.89; N, 14.72.

2-((2-(4-Oxo-4,5-dihydrothiazol-2-yl)-3-phenyl-3,3a-dihydro-2*H*-pyrazolo[3,4-*d*]thiazol-5(6*H*)-ylidene)hydrazono)-1,4-diphenyl-1,2,3,4-tetrahydrobenzo[*g*]quinoxaline-5,10-dione (32). To mixture of **18**

(1.30 g, 2 mmol) and chloroacetic acid (0.18 g, 2 mmol) in AcOH acid (25 mL), anhydrous AcONa (0.5 g) was added. The reaction mixture was heated on water bath for 3 h, and then poured into ice-cold water. The resulting precipitate was filtered off, dried and purified by recrystallization from EtOH to afford **32** (80%) as pale brown crystals. mp 217–219 ºC; IR (KBr): (cm^{-1}) 1620-1625 (4 C=$N_{str.}$), 1672, 1704 (3 C=$O_{str.}$) and 3152 (N–H_{str}); ^{1}H NMR (300 MHz, DMSO–d_6): δ 3.13 (*s*, 2H, $CH_{2–Piperaz.}$), 3.85 (*s*, 2H, $CH_{2–thiazolone}$), 3.91 (*d*, *J* = 7.51 *Hz*, 1H, $Pyraz_{(C4)}$-H), 4.45 (*d*, *J* = 7.51 *Hz*, 1H, $Pyraz_{(C3)}$-H), 6.95–7.71 (*m*, 19H, Ar-H), 11.03 (*s*, 1H, N–$H_{Deutr. Exch.}$); ^{13}C NMR (75 MHz, DMSO–d_6): 36.9 (CH_2), 48.1, 52.4 (CH), 52.1 (CH_2–Piperaz.), 119.2, 122.4, 122.7, 126.1, 126.7, 126.8, 126.9, 128.5, 129.5, 130.0, 135.1, 141.2, 143.3, 144.5 (C–Ar), 156.5, 157.1, 158.1, 158.3 (4 C=N) 173.9, 176.4, 178.1 (3 C=O); MS: *m/z* 754.0 (M^+, 35%). Anal. Calcd for $C_{37}H_{26}N_8O_3S_2$ (694.78): C, 63.96; H, 3.77; N, 16.13. Found*:* C, 63.81; H, 3.62; N, 15.89.

2-((2-(5-Benzylidene-4-oxo-4,5-dihydrothiazol-2-yl)-3-phenyl-3,3a-dihydro-2*H*-pyrazolo[3,4-*d*]thiazol-5(6*H*)-ylidene)hydrazono)-1,4-diphenyl-1,2,3,4-tetrahydrobenzo[*g*]quinoxaline-5,10-dione (33). A mixture of **32** (0.75 g, 1 mmol) and BzH (0.10 mL, 1 mmol) in EtOH (25 mL) containing 0.1 mL of piperidine as catalyst was refluxed for 5 h. The reaction mixture was cooled to rt then poured onto ice–cooled H_2O. The precipitate was filtered off, washed with H_2O and the crude product was recrystallized from EtOH to afford **33** (85%) as brown crystals. mp 187–189 ºC; IR: (cm^{-1}) 1615-1625 (4 C=$N_{str.}$), 1672, 1715 (3 C=$O_{str.}$), 3211 (N–$H_{str.}$); ^{1}H NMR (300 MHz, DMSO–d_6): δ 3.12 (*s*, 2H, $CH_{2–Piperaz.}$), 3.91 (*d*, *J* = 7.51 *Hz*, 1H, $Pyraz_{(C4)}$-H), 4.45 (*d*, *J* = 7.51 *Hz*, 1H, $Pyraz_{(C3)}$-H), 6.95–7.71 (*m*, 24 H, Ar-H), 8.06 (*s*, 1H, =C–H), 11.03 (*s*, 1H, N–$H_{Deutr. Exch.}$); ^{13}C NMR (75 MHz, DMSO–d_6): 48.1, 52.4 (CH), 52.1 (CH_2–Piperaz.), 119.2, 120.7, 122.4, 122.7, 126.1, 126.5, 126.8, 126.9, 127.9, 128.5, 128.6, 129.5, 130.0, 132.6, 135.1, 135.2, 142.2, 143.5, 144.5 (C–Ar), 152.1 (Olefinic), 157.1, 158.3, 160.3, 163.6 (4 C=N), 167.5, 173.9, 178.1 (3 C=O); MS (*m/z,* %): 782.0 (M^+, 15%); Anal. Calcd for $C_{44}H_{30}N_8O_3S_2$ (782.89): C, 67.50; H, 3.86; N, 14.31; O, 6.13; S, 8.19%. Found: C, 67.35; H, 3.73; N, 14.14; O, 6.02; S, 8.10%.

2-((2-(5,5-Dibromo-4-oxo-4,5-dihydrothiazol-2-yl)-3-phenyl-3,3a-dihydro-2*H*-pyrazolo[3,4-*d*]thiazol-5(6*H*)-ylidene)hydrazono)-1,4-diphenyl-1,2,3,4-tetrahydrobenzo[*g*]quinoxaline-5,10-dione (34). To a solution of **32** (0.75 g, 1 mmol) and AcONa (0.24 g, 3 mmol) in AcOH acid (20 mL), bromine (0.79 mL, 10 mmol) was added dropwise. The solution was allowed to stir for 2 h at rt. Upon completion of the reaction (TLC), the reaction mixture was diluted with water (100 mL). The solid was filtered off, washed with water, dried and recrystallized from EtOH to yield **34** (75%) as reddish brown solid, mp 265–267 ºC;

IR (KBr): (cm^{-1}) 1620-1625 (4 C=$N_{str.}$), 1672, 1721 (3 C=$O_{str.}$) and 3152 (N–H_{str}); ^{1}H NMR (300 MHz, DMSO–d_6): δ 3.13 (*s*, 2H, $CH_{2–Piperaz.}$), 3.87 (*d*, *J* = 7.51 *Hz*, 1H, $Pyraz_{(C4)}$-H), 4.39 (*d*, *J* = 7.51 *Hz*, 1H, $Pyraz_{(C3)}$-H), 7.15–7.71 (*m*, 19H, Ar-H), 11.12 (*s*, 1H, N–$H_{Deutr. Exch.}$); ^{13}C NMR (75 MHz, DMSO–d_6): 48.2, 52.4 (CH), 52.1 (CH_2–Piperaz.), 71.0 (C-5-Thiaz.), 119.2, 122.4, 122.7, 126.1, 126.5, 126.8, 126.9, 128.5, 129.5, 130.0, 135.1, 141.2, 143.3, 143.5, 144.5 (C–Ar), 156.5, 157.1, 158.1, 158.3 (4 C=N) 173.9, 176.4, 178.1 (3 C=O); MS: *m/z* 856.0 (M^++4, 20), 854.0 (M^++2, 40), 852.0 (M^+, 20); Anal. Calcd for $C_{37}H_{24}Br_2N_8O_3S_2$ (852.58): C, 52.12; H, 2.84; Br, 18.74; N, 13.14; O, 5.63; S, 7.52%. Found: C, 51.95; H, 2.64; Br, 18.58; N, 13.01; O, 5.49; S, 7.38%.

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REFERENCES

1. I. H. El Azab and M. R. E Aly, *Heterocycles*, 2015, **91**, 287.
2. I. H. El-Azab and S. H. Abdel-Hafez, *Russ. J. Bioorg. Chem.,* 2015, **41**, 315.
3. I. H. El-Azab and K. M. Khaled, *Russ. J. Bioorg. Chem.,* 2015, **41**, 421.
4. I. H. El-Azab and F. M. Abd El Latif, *Lett. Org. Chem.,* 2015, **12**, 187.
5. I. H. El-Azab and N. A. A. Elkanzy, *Synth. Commun.,* 2014, **44**, 2692.
6. I. H. El-Azab and E. A. El Rady, *Indian J. Chem.,* 2014, **52**(B), 1194.
7. I. H. El-Azab *J. Heterocycl. Chem.,* 2013, **50**, 178.
8. I. H. El-Azab and E. A. El Rady, *J. Heterocycl. Chem.,* 2012, **49**, 135.
9. I. H. El-Azab, M. M. Youssef, and M.A. Amin, *Molecules,* 2014, **19**, 19648.
10. I. H. El-Azab and E. A. El Rady, *Eur. J. Chem.,* 2012, **3**, 81.
11. I. H. El-Azab and F. M. Abd El Latif, *Open J. Synth. Theo. Appl.,* 2012, **1**, 44.
12. I. H. El-Azab and N. A. A. Elkanzy, *J. Heterocycl. Chem*., 2016, **00**, 000 (*Accepted*), DOI 10.1002/jhet.2721.
13. S. Patai and Z. Rappoport, *The Chemistry of Quinonoid Compounds*; Wiley Interscience, New York, 1988, **2**, Part 1, pp. 552–570.
14. M. Tisler, Heterocyclic Quinones in Advances in Heterocyclic Chemistry, Vol. 45, ed. by A. R. Katritzky, Academic Press, London, 1989, pp. 56–63.
15. T. Nogami, K.Yoshihara, and K. Nagakura, *Bull. Chem. Soc. Jpn.*, 1972, **45**, 122.
16. P. C. Dwivedi and R. Agarwal, *Indian J. Chem.*, 1985, **24A**, 100.
17. L. D. Belitskaya and V.T. Kolesnikov, *Zh. Org. Khim.,* 1984, **20**, 1753.

18. W. Gauss, H. Heitzer, and S. Petersen, *Liebigs Ann. Chem.*, 1972, **764**, 131.
19. Y. R. Ibrahim, A. A. Hassan, N. K. Mohamed, and A. E. Mourad, *Arch. Pharm.*, 1992, **325**, 389.
20. A. A. Hassan, N. K. Mohamed, Y. R. Ibrahim, and A. E. Mourad, *Leibigs Ann. Chem.*, 1993, **1993**, 695.
21. A. A. Hassan, N. K. Mohamed, A. A. Aly, and A. E. Mourad, *Bull. Soc. Chim. Belg.*, 1996, **105**, 159.
22. A. A. Hassan, N. K. Mohamed, Y. R. Ibrahim, K. U. Sadek, and A. E. Mourad, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 2612.
23. A. A. Hassan, N. K. Mohamed, A. A. Aly, and A. E. Mourad, *Pharmazie*, 1997, **52**, 23.
24. A. A. Aly, E. K. Ahmed, and K. M. El-Mokadem, *J. Sulfur Chem.*, 2006, **27**, 419.
25. M. A. Metwally, E. Abdel-Latif, F. A. Amer, and G. Kaupp, *J. Sulfur Chem*., 2004, **25**, 63.
26. A. R. Katritzky and W. Q. Fan, *J. Heterocycl. Chem.*, 1988, **25**, 90.
27. M. Matsuoka, A. Iwamato, N. Furukawa, and T. Kitao, *J. Heterocycl. Chem.*, 1992, **29**, 439.
28. A. A. Hassan, N. K. Mohamed, A. A. Aly, and A. E. Mourad, *Monatsh. Chem.*, 1997, **128**, 61.
29. A. J. Lin, L. A. Cosby, C. W. Shansky, and A. C. Sartorelli, *J. Med. Chem*., 1972, **15**, 1247.
30. I. Wilson, P. Wardman, T. S. Lin, and A. C. Sartorelli, *J. Med. Chem.*, 1986, **29**, 1381.
31. P. L. Gutierrez, *Front. Biosci.,* 2000, **5**, 629.
32. G. R. Pettit, J. C. Knight, J. C. Collins, D. L. Herald, R. K. Pettit, M. R. Boyd, and V. G. Young, *J. Nat. Prod*., 2000, **63**, 793.
33. D. J. Milanowski, K. R. Gustafson, J. A. Kelley, and J. B. McMahon, *J. Nat. Prod*., 2004, **67**, 70.
34. U. W. Hawas, M. Shaaban, K. A. Shaaban, M. Speitling, A. Maier, G. Kelter, H. H. Fiebig, M. Meiners, E. Helmke, and H. Laatsh, *J. Nat. Prod.,* 2009, **72**, 2120.
35. W. C. Patt, H. W. Hamilton, M. D. Taylor, M. J. Ryan, D. G. Jr. Taylor, C. J. C. Connolly, A. M. Doherty, S. R. Klutchko, and I. Sircar, *J. Med. Chem.,* 1992, **35***,* 2562.
36. S. K. Agrawal, M. Sathe, A. K. Halve, and M. P. Kaushik, *Tetrahedron Lett.,* 2012, **53***,* 5996.
37. T. K. Venkatachalam, C. Mao, and F. M. Uckun, *Bioorg. Med. Chem.,* 2004, **12**, 4275.
38. G. Zitouni, S. Demirayak, A. Ozdemir, Z. Kaplancikli, and M. Yildiz, *Eur. J. Med. Chem.,* 2004, **39**, 267.
39. O. Kouatly, A. Geronikaki, C. Kamoutsis, D. Hadjipavlou-Litina, and P. Eleftheriou, *Eur. J. Med. Chem.,* 2009, **44**, 1198.
40. J. M. Clough, H. Dube, B. J. Martin, G. Pattenden, K. S. Reddy, and I. R. Waldron, *Org. Biomol. Chem.,* 2006, **4**, 2906.
41. B. C. Chen, R. Zhao, B. Wang, R. Droghini, J. Lajeunesse, P. Sirard, M. Endo, B. Balasubramanian, and J. Barrish, *ARKIVOC,* 2010, **vi**, 32.

42. A. E. Amr, N. M. Sabrry, M. M. Abdalla, and B. F. Abdel-Wahab, *Eur. J. Med. Chem.,* 2009, **44**, 725.
43. F. Guannessi, P. Chiodi, M. Marzi, P. Minetti, P. Pessotto, M. Tinti, P. Carminati, and A. Arduini, *J. Med. Chem.,* 2001, **44***,* 2383.
44. J. Harnett, V. Roubert, C. Dolo, C. Charnet, B. Spinnewyn, S. Cornet, A. Rolland, J. G. Marin, D. Bigg, and P. E. Chabrier, *Bioorg. Med. Chem. Lett.,* 2004, **14**, 157.
45. S. M. Gomha, S. M. Riyadh, E. A. Mahmmoud, and M. M. Elaasser, *Heterocyles*, 2015, **91**, 1227.
46. S. M. Gomha, S. M. Riyadh, I. M. Abbas, and M. A. Bauomi, *Heterocyles*, 2013, **87**, 341.
47. R. Vaickelionienė, V. Mickevičius, G. Vaickelionis, M. Stasevych, O. Komarovska-Porokhnyavets, and V. Novikov, *ARKIVOC*, 2015, **v**, 303.
48. R. F. Silver and H. L. Holmes, *Can. J. Chem.*, 1963, **46**, 1859.
49. W. L. Mosby and R. J. Boyle, *J. Org. Chem.*, 1959, **24**, 374.
50. N. L. Agarwal and W. Schaefer, *J. Org. Chem.*, 1980, **45**, 2155.