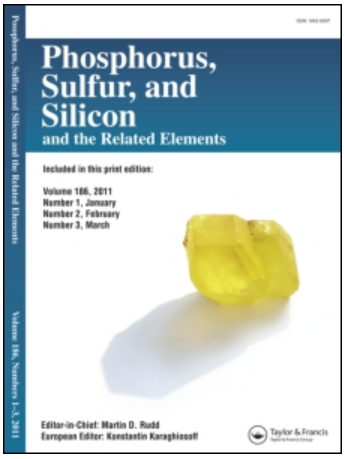

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Synthesis and Reactions of Some New Thiobarbituric Acid Derivatives

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Synthesis and Reactions of Some New Thiobarbituric Acid Derivatives

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*A series of novel thiobarbituric acid derivatives **3a–c**, **5**, and **12** were synthesized via the reaction of 4-benzoyl-1-cyanoacetylthiosemicarbazide (**1**) or its derivatives **2a–c**, **9** with malonic acid and acetyl chloride. Coupling of thiobarbituric acid derivatives **3a-c** and **5** with aromatic diazonium chlorides furnished a new series of the corresponding bisarylhydrazo-thiobarbituric dyes **4a–c**. The reaction of **5** with cyclohexanone and sulfur under Gewald reaction condition afforded thieno[2,3-d]pyrimidine derivative **21**, that condensed with p-anisladehyde to give 5-arylidene thiobarbituric acid derivative **22**. The reaction of **1** with phenyl isothiocyanate afforded the non-isolable adduct **23** which was used as a key intermediate for the synthesis of polyfunctionally substituted thiazolidinone and thiobarbituric ring systems.*

Keywords Azo coupling; pyrimidine; thiazole; thiophene; thiobarbituric; thiosemicarbazide

INTRODUCTION

Pyrimidine is the parent heterocycle of a very important group of compounds that have been extensively studied due to their occurrence in living systems. Pyrimidine moieties were reported to have anti-bacterial, antifungal and anti- HIV activities.[1–5] Certain substituted 2-thiobarbituric acids have long been used as intravenous anesthetics[6] and as intermediates in the preparation of dyes.[7] Recently there has been interest in 2-thiobarbituric acids as antifungal,[8] anticonvulsants,[9] immunotropic and anti-inflammatory compounds,[10] antineoplastic agents,[11] and as platforms in the synthesis of other biologically active compounds.[12] Thiobarbituric acid derivatives were

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also reported to possess antiparkinsonian[13,14] and hypnotic[15] activities. Substituted aminopyrimidines structures are common in marketed drugs, such as anti-atherosclerotic aronixil, anti-histaminic thonzylamine, anti-anxielytic buspirone, anti-psoriatic enazadrem, and other medicinally relevant compounds.[16,17] Thienyl compounds are also reported for their anti-microbial and pharmaceutical activities.[18–21]

In the last few years we have been involved in a program aiming to develop new, simple procedures for the synthesis of functionally substituted heterocycles of anticipated biological activity, from available laboratory starting materials.[22–26] In the context of this program some new functionally substituted thiobarbituric acid derivatives were required. 4-Benzoyl-1-cyanoacetylthiosemicarbazide (**1**)[27] seemed to be a good candidate to fulfil our objective via intermolecular cyclization by the reaction with malonic acid in the presence of acetyl chloride to afford thiobarbituric acid which reacts with suitable reagents.

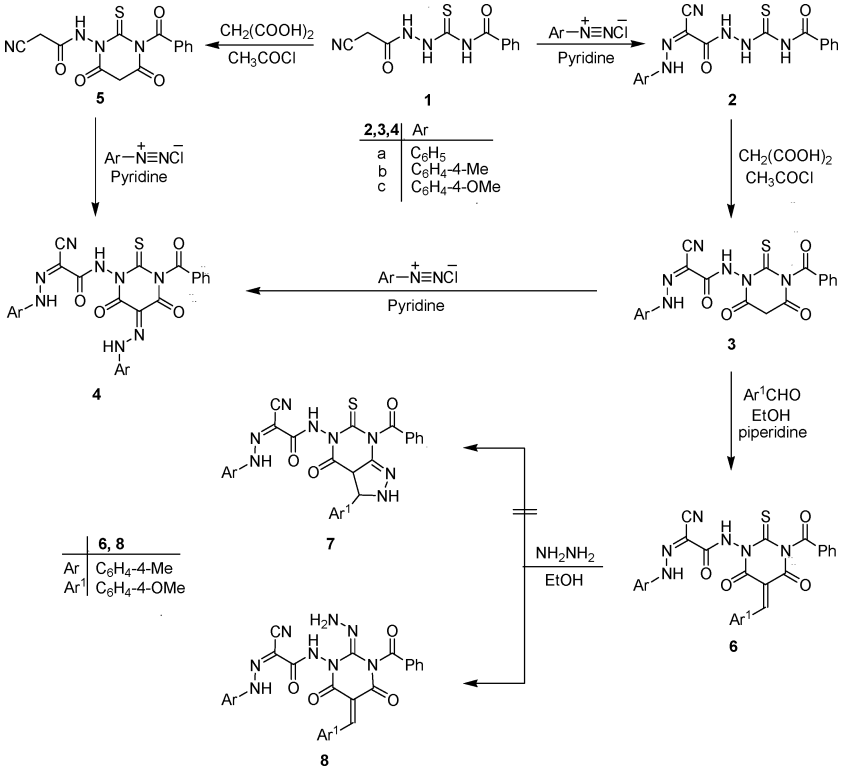
RESULTS AND DISCUSSION

Thus, compound **1** was allowed to couple with an appropriate aromatic diazonium chlorides in pyridine at 0–5°C to afford the colored arylhydrazone derivatives **2a–c**. Elemental analysis and spectral data were in favor of these proposed hydrazo structures. The IR spectra of **2a–c** in general showed absorption bands at 3350–3210 cm^{-1} region due to NH, 2210–2207 cm^{-1} due to conjugated C≡N, 1680 and 1655 cm^{-1} due to two amidic C=O functions. The ^{1}H-NMR spectrum of **2c** as an example displayed a singlet signal at δ 3.90 ppm and multiplet signal at δ 7.17–8.23 ppm region owing to the methoxy and aromatic protons, respectively. Also, the ^{1}H-NMR spectrum showed the absence of activated methylene protons signal which assigned the structure and confirm the formation of hydrazone structure. The mass spectrum of **2c** showed a molecular ion peak (M^+) at $m/z = 396$, corresponding to a molecular formula $C_{18}H_{16}N_6O_3S$.

The thiosemicarbazide derivatives **2a–c** underwent intermolecular cyclization by the reaction with malonic acid in the presence of acetyl chloride and furnished the 2-thiobarbituric acid derivatives **3a–c**. The versatility of the novel synthon **3** was proven by the following transformations. Compounds **3a–c** underwent electrophilic substitution reaction upon coupling with aromatic diazonium chlorides to yield the corresponding bis-arylhydrazonothiobarbituric acid derivatives **4a–c**. The chemical structural of compounds **4a–c** were elucidated on the basis of elemental analysis and spectral data. For example, the IR spectrum of **4c** exhibited absorption bands at 3400 − 3180 cm^{-1} region

characteristic to NH groups, 2205 cm^{-1} characteristic to conjugated C≡N group and 1675, 1665, 1658 and 1650 cm^{-1} characteristic to four amidic C=O groups. The ^{1}H-NMR spectrum of **4c** showed five singlets at δ 3.88, 3.95, 7.13, 10.59 and 11.17 ppm due to two methoxy protons and three NH protons, respectively. The mass spectrum showed a molecular ion peak (M^+) at $m/z = 598$. Compounds **4a–c** could also be obtained and proved chemically by reacting **1** with malonic acid in the presence of acetyl chloride to afford thiobarbituric acid derivative **5** which was then coupled with two equimolar amounts of aromatic diazoinum chlorides in pyridine at 0–5°C.

On the other hand, the condensation of **3b** with p-anislaldehyde in refluxing ethanol containing a catalytic amount of piperidine yielded exclusively the corresponding arylidene derivative **6**. The structure of compound **6** was established on the basis of both analytical and spectral data. The ^{1}H-NMR spectrum of **6** exhibited a new two singlets at δ 3.95 and 8.03 ppm assignable to the methoxy and methine protons,



SCHEME 1

respectively, in addition to the expected agreeable signals. The mass spectrum showed a molecular ion peak at $m/z = 566$ corresponding to the molecular weight of compound **6**. The reaction of **6** with hydrazine hydrate in ethanol, under reflux, furnished a single product. Two possible structures **7** and **8** were considered. The possibility of structure **7** was ruled out on the basis of the chemical tests which revealed the absence of sulfur. Structure **8** was established for the reaction product on the basis of its mass spectrum that revealed a molecular ion peak at $m/z = 564$ corresponding to a molecular formula $C_{29}H_{24}N_8O_5$.

To account for the direct formation of the thiobarbituric acid, the mechanism outlined in chart 1 is proposed. According to this mechanism, the reaction starts with the formation of the mixed acid anhydride which undergoes the acid catalyzed cleavage of acetic acid to form malonyl chloride. The latter then undergoes intermolecular nucleophilic cyclization with thiosemicarbazide via elimination of two molecules of HCl to give the thiobarbituric acid derivative.

It was found that when compound **1** reacted with ethyl 2-cyano-3-(4-methoxyphenyl) acrylate in boiling ethanol containing a catalytic amount of piperidine, compound **9** was obtained instead of the expected pyridine-2-one derivative **11**.[28] Formation of **9** was assumed to proceed via the initial Michael addition of the active methylene of **1** to the α,β-unsaturated nitrile to afford the non-isolable acylic Michael adduct **10** which then loses the ethyl cyanoacetate to give the arylidene thiosemicarbazide derivative **9**. Furthermore, the arylidene derivative **9** was identical (TLC, m.p. and mixed m.p.) with an authentic sample synthesized by stirring *p*-anisaldehyde with the thiosemicarbazide derivative

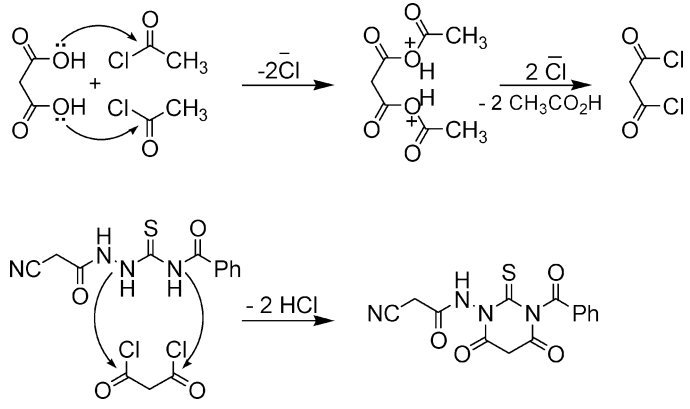
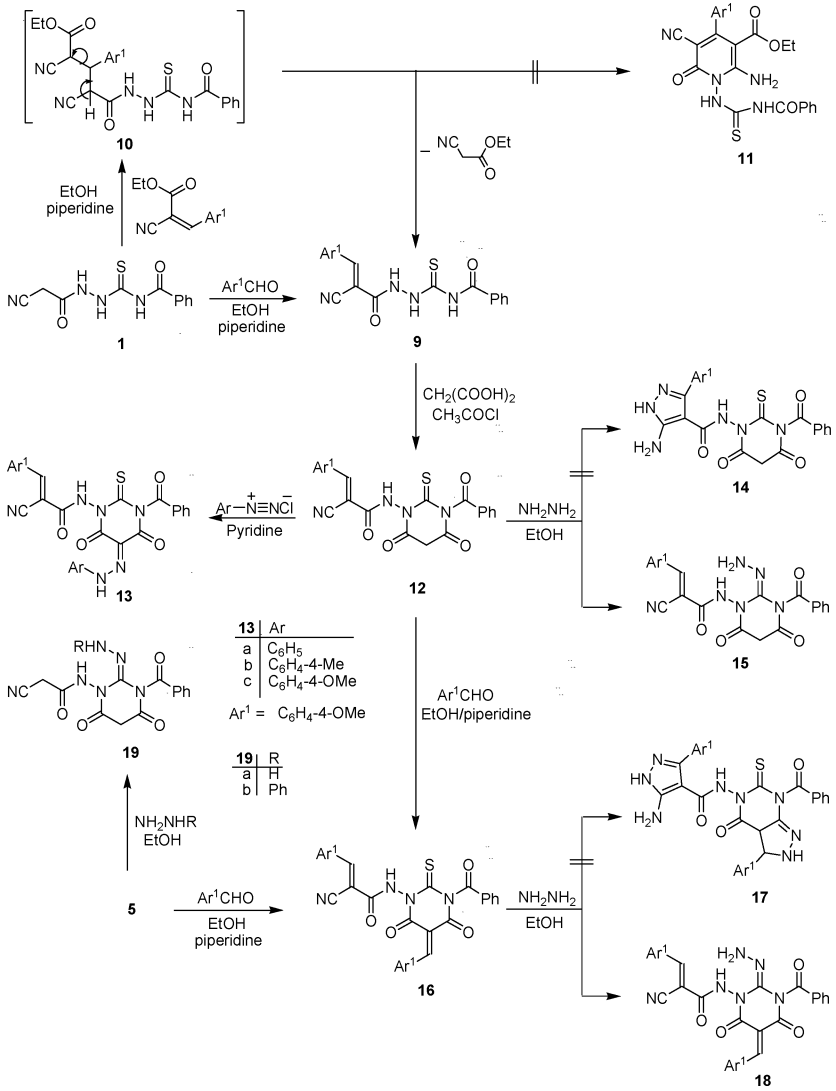


CHART 1



SCHEME 2

1 in refluxing ethanol in the presence of a catalytic amount of piperidine as described in Scheme 2.

Analogous to compound **2**, cyclocondensation of compound **9** with malonic acid in acetyl chloride at 50–60°C afforded the thiobarbituric acid derivative **12**. The reactivity of hydrogen atoms at C-5 is the most outstanding chemical property of thiobarbituric acid derivative

12 which undergoes the characteristic condensation and electrophilic substitution reactions. Thus, coupling of compound **12** with different aromatic diazonium chlorides in pyridine at 0–5°C afforded the corresponding 5-arylhydrazonothiobarbituric acid derivatives **13a–c**. The structures of **13a–c** were identified on the basis of their elemental analysis and spectral data. Thus, the IR spectrum of **13b** as a representive example displayed absorption bands at 3300–3210 cm^{-1} region attributed to two NH functions and at 1590 cm^{-1} attributed to C=N function. Moreover, its ^{1}H-NMR spectrum revealed the presence of two broad signals at δ 11.18 and 12.44 ppm characteristic to two NH protons and three singlet signals at δ 8.03, 3.95, 2.66 ppm characteristic to the methine proton (CH=), OCH_3, and CH_3 protons, respectively. The mass spectrum of **13b** showed a molecular ion peak at $m/z = 566$, corresponding to a molecular formula $C_{29}H_{22}N_6O_5S$.

When compound **12** was treated with an excess of hydrazine hydrate in boiling ethanol aiming to get compound **14**, unfortunately, compound **14** was not formed and 2-hydrazinobarbituric acid derivative **15** was obtained in good yield. Compound **14** was eliminated based on the element test which showed the absence of sulfur indicating that the sulfur was removed via H_2S elimination. Furthermore, the IR spectrum of **15** showed the presence of C≡N stretching band and absence of C=S stretching band. Also, the ^{1}H-NMR spectrum exhibited a broad singlet signal at δ 10.19 ppm assignable to NH_2 protons and a singlet signal at δ 8.01 ppm assignable to the methine proton together with the other expected signals. The mass spectrum showed a molecular ion peak at $m/z = 446$, corresponding to a molecular formula $C_{22}H_{18}N_6O_5$.

The condensation of compound **12** with *p*-anisaldehyde in boiling ethanol containing a catalytic amount of piperidine gave bis-arylidene thiobarbituric derivative **16**. The structure **16** has been proved on the basis of its elemental analysis and spectral data. Analysis of the ^{1}H-NMR spectrum revealed the appearance of a new two singlet signals at δ 8.03 and 8.12 ppm assignable to two methine protons and the disappearance of signals assignable to the methylene protons of thiobarbituric acid. The mass spectrum of **16** showed a molecular ion peak at $m/z = 566$, corresponding to molecular formula $C_{30}H_{22}N_4O_6S$. Further proof for structure **16** was provided by its preparation through another route via the condensation reaction of compound **5** with two equimolar amounts of *p*-anisaldehyde in ethanol containing a catalytic amount of piperidine.

In a similar manner, the reaction of compound **16** with an excess of hydrazine hydrate gave the 2-hydrazinobarbituric acid derivative **18**, instead of compound **17**. The structure **18** seemed to be logical according to elemental analysis and spectral data. Thus, the IR spectrum

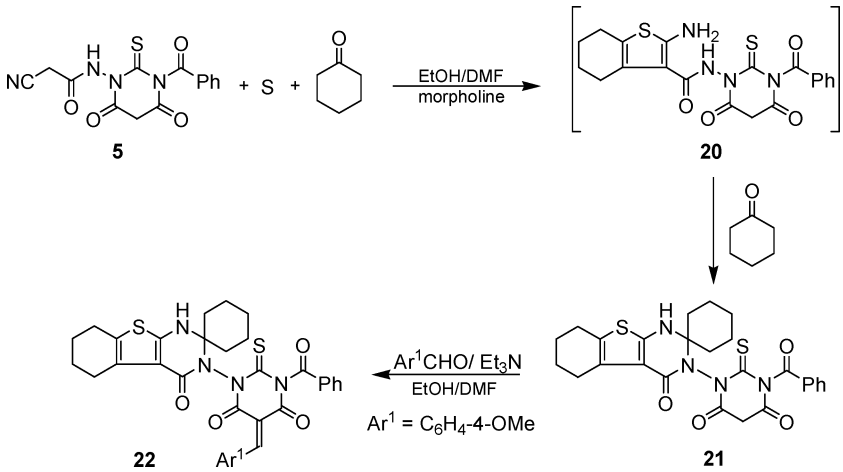
revealed the presence of NH_2 absorption band at 3415–3354 cm^{-1} and conjugated C≡N absorption band at 2205 cm^{-1} and the absence of C=S absorption band. Moreover, the ^{1}H-NMR spectrum displayed two characteristic singlet signals at δ 8.15 and 8.18 ppm for two methine protons, in addition to, a broad singlet signal at δ 6.25 characteristic to NH_2 protons. The mass spectrum of **18** showed a molecular ion peak at m/z = 564, corresponding to a molecular formula $C_{30}H_{24}N_6O_6$.

Similarly, the reaction of compound **5** with equimolar amounts of either hydrazine hydrate or phenyl hydrazine in ethanol solution, under reflux, yielded the corresponding 2-hydrazino or 2-phenylhydrazino barbituric acid derivatives **19a–b**, respectively, via H_2S elimination.

2-Aminothiophenes and thieno[2,3-*d*]pyrimidines have recently received considerable attention because of their synthetic and pharmaceutical importance. In the present work we explore the synthetic potentialities of **5** to obtain some novel thieno[2,3-*d*]pyrimidine derivatives. Thus, the Gewald reaction of thiobarbituric acid derivative **5** with elemental sulfur, cyclohexanone and morpholine as a basic catalyst in a mixture of ethanol and dimethylformamide (1:1) gave compound **21** via the acyclic intermediate **20**. However, the product isolated was assigned the structure **21** on the basis of elemental analysis and spectral data. Thus, its IR spectrum revealed the absence of absorption band characteristic to C≡N function and the presence of absorption bands at 3350 cm^{-1} assignable to NH and at 1682, 1670 and 1662 cm^{-1} for three amidic C=O functions. Moreover, its ^{1}H-NMR spectrum exhibited the disappearance of a signal characteristic to cyanomethylene protons and the appearance of a broad singlet signal at δ 11.21 ppm characteristic to NH proton. The mass spectrum of **21** showed a molecular ion peak at m/z = 522, corresponding to a molecular formula $C_{26}H_{26}N_4O_4S_2$.

The condensation of compound **21** with *p*-anisaldehyde in a mixture of ethanol and dimethylformamide (1:1) containing a catalytic amount of triethylamine under reflux yielded the corresponding arylidene derivative **22**. The assignment of structure **22** was based on analytical and spectral data. The mass spectrum showed a molecular ion peak at m/z = 640, corresponding to a molecular formula $C_{34}H_{32}N_4O_5S$. The ^{1}H-NMR spectrum exhibited a singlet signal at δ 3.96 ppm assignable to the methoxy protons, a singlet signal at δ 8.06 ppm assignable to the methine proton beside a broad singlet signal at δ 11.24 ppm distinctive for the NH proton.

1,3-Thiazole derivatives are considered to be very interesting heterocyclic ring systems because of their biological activities such as antiparasitic, analgesic, antibacterial and CNS depressant.[29,30] Thus, the behaviour of 4-benzoyl-1-cyanoacetylthiosemicarbazide (**1**) itself towards phenyl isothiocyanate as a convenient route to some new thiazole

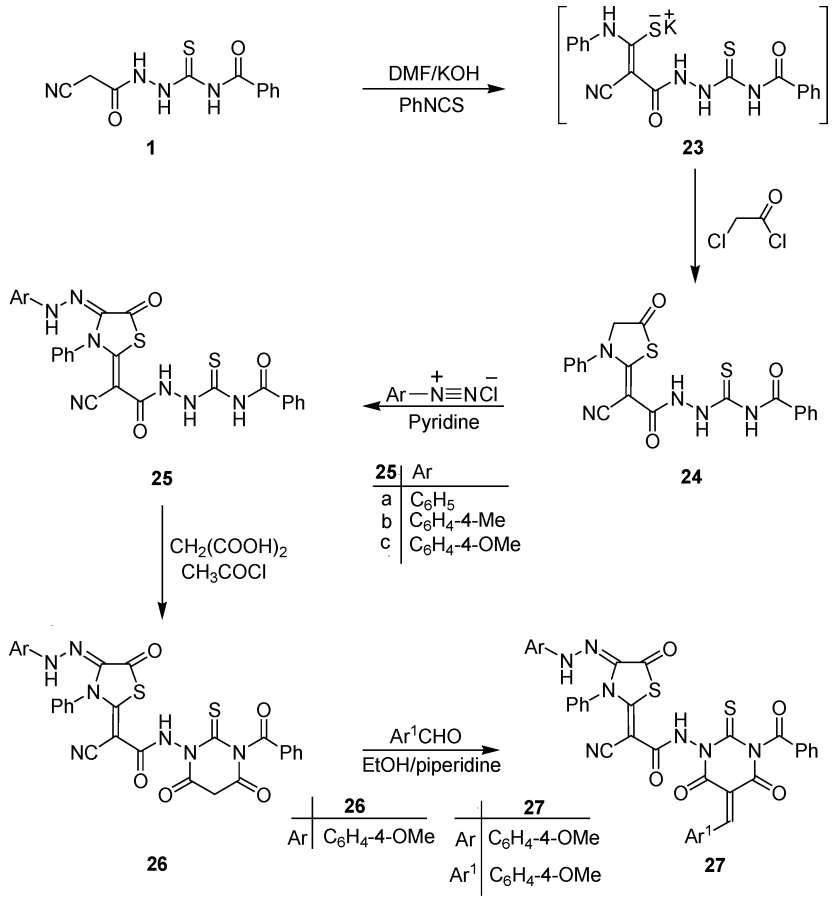


5 20 21 22

SCHEME 3

derivatives was described. The reaction of **1** with an equimolar amount of phenyl isothiocyanate in DMF in the presence of potassium hydroxide gave the non-isolable adduct **23** that reacted with chloroacetyl chloride to give thiazolidin-5-one derivative **24**. The structure **24** was elucidated on the basis of elemental analysis and spectral data. The IR spectrum displayed absorption bands at 3300–3206 cm^{-1} region for NH stretching, at 2202 cm^{-1} for C≡N function, and at 1735 cm^{-1} for thiazolidin-5-one C=O group. The ^{1}H-NMR spectrum revealed the disappearance of cyanomethylene signal and the presence of a new singlet signal at δ 5.25 ppm assignable to the methylene protons of thiazolidin-5-one ring and a multiplet signal at δ 7.18–8.15 ppm due to two phenyl protons. The mass spectrum showed a molecular ion peak at $m/z = 437$, corresponding to a molecular formula $C_{20}H_{15}N_5O_3S_2$.

Coupling of compound **24** with different aromatic diazonium chlorides in pyridine afforded the corresponding arylhydrazone of thiazolidinone derivatives **25a–c**. The structures **25a–c** were supported on the basis of elemental analysis and spectral data. The IR spectrum of **25c** as an example revealed absorption bands at 3420–3160 cm^{-1} region for NH stretching, at 1710 cm^{-1} for thiazolidinone C=O stretching. The ^{1}H-NMR spectrum exhibited the disappearance of a signal belong to the methylene protons of thiazolidinone ring and the appearance of the signal belong to methoxy protons at δ 3.97 ppm. The mass spectrum showed a molecular ion peak at $m/z = 571$, corresponding to a molecular formula $C_{27}H_{21}N_7O_4S_2$.



SCHEME 4

As an extension of our investigation, cyclocondensation of compound **25c** with malonic acid in acetyl chloride at 50–60°C yielded thiobarbituric acid derivative **26**. The structure **26** was elucidated on the basis of elemental analysis and spectral data. It's IR spectrum revealed absorption bands at 3390–3150 cm^{-1} for NH stretching, at 1710 cm^{-1} for thiazolidinone C═O stretching, and at 1662 cm^{-1} for pyrimidinone stretching. Furthermore, its ^{1}H-NMR spectrum exhibited the appearance of an additional a singlet signal belongs to thiobarbituric CH_2 protons at δ 3.11 ppm. The mass spectrum of **26** showed a molecular ion peak at $m/z = 639$, corresponding to a molecular formula $C_{30}H_{21}N_7O_6S_2$.

In addition, the condensation of compound **26** with *p*-anisaldehyde in boiling ethanol containing a catalytic amount of piperidine afforded

the corresponding arylidene derivative **27**. The structure **27** was supported on the basis of elemental analysis and spectral data. Thus, its IR spectrum revealed absorption bands at 3380–3150 cm^{-1} region for NH stretching, at 1709 cm^{-1} for thiazolidinone C=O stretching, at 1657 cm^{-1} for pyrimidine diketone stretching, and at 1610 cm^{-1} for C=C stretching. Moreover, its ^{1}H-NMR spectrum showed the appearance of two sharp singlet signals at δ 3.97and 3.89 ppm characteristic to two methoxy protons and the disappearance of a signal characteristic to methylene protons of thiobarbituric acid. The mass spectrum of **27** showed a molecular ion peak at $m/z = 741$, corresponding to a molecular formula $C_{38}H_{27}N_7O_6S_2$.

In conclusion, we reported herein a simple and convenient route for the synthesis of some new thiobarbituric acid derivatives with anticipated biological activity starting from readily available 4-benzoyl-1-cyanoacetylthioemicarbazide.

EXPERIMENTAL

Melting points were determined with a Gallenkamp melting point apparatus (capillary method) and were uncorrected. Elemental analyses were carried out at the Microanalytical Unit of the Faculty of Science, Cairo University, and all compounds gave satisfactory elemental analyses. IR spectra (KB_r) were recorded with a Mattson 5000 FTIR spectrometer (not all frequencies are reported). The ^{1}H NMR spectra were acquired using a Bruker WP300 spectrometers at 300 MHz. Mass spectra were obtained on a Finnigan MAT 212 instrument by electron impact at 70 eV. 4-Benzoyl-1-cyanoacetylthiosemicarbazide (**1**) was prepared according to the reported literature procedure.[27]

General Procedure for Coupling Reactions: Synthesis of Compounds (2a–c), (4a–c), (13a–c), and (25a–c)

A solution of sodium nitrite (0.70 g in 10 ml water) was gradually added to a well-cooled (0–5°C) solution of the aromatic amine (10.0 mmol) in concentrated HCl (3.0 ml). The diazonium salt solution was added with continuous stirring to a cold (0–5°C) solution of compounds **1**, **3**, **5**, **12**, and /or **24** (0.01 mol) in pyridine (30 ml). The reaction mixture was allowed to stir at (0–5°C) for 2 hrs, and then the solid was collected by filtration. The crude products thus obtained, were dried and recrystallized from the appropriate solvent to give the corresponding arylhydrazone derivatives.

N-[*N′*-[2-Cyano-2-(phenyl-hydrazono)-acetyl]-hydrazinocarbothioyl]benzamide (2a)

Pale yellow crystal (EtOH-CHCl3); Yield 87%; mp 215–216°C; IR (KBr): $\tilde{\upsilon}_{max.}$ /cm^{-1} = 3330–3210 (4NH), 2208 (C≡N), 1670, 1660 (2C=O),1590 (C=N). ^{1}H-NMR (DMSO–d_6): δ_{ppm} = 6.98 (s, 1H, NH), 7.17–8.23 (m, 10H, Ar-H), 9.85 (s, 1H, NH), 10.51 (s, 1H, NH), 12.44 (s, 1H, NH). Anal. For $C_{17}H_{14}N_6O_2S$ (366.40) Calcd.: C 55.73; H 3.85; N 22.94%, Found: C 55.42; H 3.96; N 22.77%.

N-[*N′*-[2-Cyano-2-(*p*-tolyl-hydrazono)-acetyl]-hydrazinocarbothioyl]benzamide (2b)

Orange crystal (EtOH-DMF); Yield 83%; mp 223–224°C; IR (KBr): $\tilde{\upsilon}_{max.}$ /cm^{-1} = 3320–3205 (4NH), 2208 (C≡N), 1668, 1659 (2C=O), 1585 (C=N). ^{1}H-NMR (DMSO-d_6):δ_{ppm} (2.19 (s, 3H, CH3), 6.96 (s, 1H, 1NH), 7.12, 7.65 (two d, J = 8.0Hz, each 2H, C_6H_4-CH_3), 7.75–8.23 (m, 5H, Ar-H), 9.78 (s, 1H, NH), 10.50 (s, 1H, NH), 12.47 (s, 1H, NH).MS *m/z* (%): 380 (M^+, 14.71), 216 (11.76), 186 (36.75), 159 (29.41), 132 (47.06), 105 (100), 77 (63.23), 51 (17.64). Anal. for $C_{18}H_{16}N_6O_2S$ (380.42) Calcd.: C 56.83; H 4.24; N 22.09%, Found: C 56.72; H 4.19; N 21.97%.

N-[N′-[2-Cyano-2-[(4-methoxy-phenyl)-hydrazono]-acetyl]-hydrazinocarbothioyl] benzamide (2c)

Pale red crystal (EtOH-DMF); Yield 82%; m.p. 234–235°C; IR (KBr): $\tilde{\upsilon}_{max.}$/cm^{-1} = 3300–3190 (4NH), 2206 (C≡N), 1665, 1655 (2C=O), 1582 (C=N). ^{1}H-NMR (dMSO - d_6): δ_{ppm} = 3.90 (s, 3H, OCH_3), 6.97 (s, 1H, 1NH), 7.17, 7.71 (two d, J = 7.8 Hz, each 2H, C_6H_4-OCH_3), 7.75–8.23 (m, 5H, Ar-H), 9.86 (s, 1H, NH), 10.51 (s, 1H, NH), 12.44 (s, 1H, NH).MS *m/z* (%): 396 (M^+, 14.41), 319 (3.23), 276 (19.11), 232 (27.94), 202 (39.70), 174 (47.05), 148 (34.55), 105 (100), 77 (67.67), 51 (32.35). Anal. For $C_{18}H_{16}N_6O_3S$ (396.42) Calcd.: C 54.54; H 4.07; N 21.20%, Found: C 54.85; H 3.95; N 21.41%.

N-[3-Benzoyl-4,6-dioxo-5-(phenyl-hydrazono)-2-thioxo-tetrahydro-pyrimidin-1-yl]-2-cyano-2-(phenyl-hydrazono)-acetamide (4a)

Orange crystal (EtOH-DMF); Yield 84%; mp 275–276°C; IR (KBr): $\tilde{\upsilon}_{max.}$/cm^{-1} = 3410–3195 (3NH), 2208 (C≡N), 1675, 1665, 1660, 1652 (4C=O), 1582 (C=N). ^{1}H-NMR (dMSO-d_6): δ ppm = 7.03 (s, br, 1H, 1NH), 7.26–8.26 (m, 15H, Ar-H), 10.54 (s, 1H, NH), 11.07 (s, br, 1H,

NH). MS *m/z* (%): 538 (M^+, 12.03), 364 (19.14), 319 (27.14), 144 (30.02), 105 (100), 77 (82.86), 51 (17.14). Anal. for $C_{26}H_{18}N_8O_4S$ (538.54) Calcd.: C 57.99; H 3.37; N 20.81%, Found: C 57.78; H 3.45; N 20.70%.

N-[3-Benzoyl-4,6-dioxo-2-thioxo-5-(p-tolyl-hydrazono)-tetrahydro-pyrimidin-1-yl]-2-cyano-2-(p-tolyl-hydrazono) acetamide (4b)

Red crystal (EtOH-$CHCl_3$); Yield 86%; mp 215–217°C; IR (KBr): $\tilde{\upsilon}_{max}$./cm^{-1} = 3398–3192 (3NH), 2208 (C≡N), 1671, 1665, 1658, 1648 (4C=O), 1580 (C=N). ^{1}H-NMR (DMSO–d_6): δ_{ppm} = 2.05 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 7.12 (s, br, 1H, NH), 7.26, 7.66 (two d, J = 7.8Hz, each 2H, C_6H_4-CH_3), 7.35, 7.85 (two d, J = 7.8 Hz, each 2H, C_6H_4-CH_3), 7.87–8.26 (m, 5H, Ar-H), 10.55 (s, br., 1H, NH), 11.14 (s, br,1H, NH).MS *m/z* (%): 566 (M^+, 7.43), 461 (14.29), 347 (17.30), 163 (19.71), 105 (100), 77 (61.43), 51 (17.30). Anal. for $C_{28}H_{22}N_8O_4S$ (566.59) Calcd.: C 59.35; H 3.91; N 19.78%, Found: C 59.13; H 3.98; N 19.87%.

N-[3-Benzoyl-5-[(4-methoxy-phenyl)-hydrazono]-4,6-dioxo-2-thioxo-tetrahydro-pyrimidin-1-yl]-2-cyano-2-[(4-methoxy-phenyl)-hydrazono]-acetamide (4c)

Reddish brown crystal (EtOH-DMF); Yield 82%; m.p. 284–285°C; IR (KBr): $\tilde{\upsilon}_{max}$./cm^{-1} = 3380–3174 (3NH), 2204 (C≡N), 1670, 1660, 1651, 1642 (4C=O), 1573 (C=N). ^{1}H-NMR (DMSO–d6):δ_{ppm} = 3.88 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 7.13 (s, br, 1H, NH), 7.24, 7.65 (two d, J = 8 Hz, each 2H, C_6H_4-OCH_3), 7.37, 7.86 (two d, J (8 Hz, each 2H, C_6H_4-OCH_3), 7.87– 8.29 (m, 5H, Ar-H), 10.59 (s, br., 1H, NH), 11.17 (s, br, 1H, NH).MS *m/z* (%): 598 (M^+, 10.28), 424 (11.43), 202 (21.71), 174 (37.14), 105 (100), 77 (55.71), 51 (20.02). Anal. for $C_{28}H_{22}N_8O_6S$ (598.59) Calcd.: C 56.18; H 3.70; N 18.72%, Found: C 56.47; H 3.46; N 18.51%.

N-[3-Benzoyl-4,6-dioxo-5-(phenyl-hydrazono)-2-thioxo-tetrahydro-pyrimidin-1-yl]-2-cyano-3-(4-methoxy-phenyl) acrylamide (13a)

Yellow crystal (EtOH-DMF); Yield 84%; m.p. 257–258°C; IR (KBr): $\tilde{\upsilon}_{max}$./cm^{-1} = 3300, 3214 (2NH), 2207 (C≡N), 1683, 1672, 1661, 1653 (4C=O), 1617 (C=C), 1592 (C=N). ^{1}H-NMR (DMSO–d_6): δ_{ppm} = 3.95 (s, 3H, OCH_3), 7.15, 7.60 (two d, J = 8.0 Hz, each 2H, C_6H_4-OCH_3), 7.78-8.14 (m, 10H, Ar-H), 8.27 (s,1H, CH=), 11.14 (s, 1H, NH), 12.41 (s, br, 1H, NH). MS *m/z* (%): 552 (M^+, 4.85), 447 (26.28), 333 (23.42), 163 (31.22), 105 (100), 77 (46.57), 51 (19.71). Anal. for $C_{28}H_{20}N_6O_5S$

(552.56). Calcd.: C 60.86; H 3.65; N 15.21%, Found: C 60.71; H 3.72; N 15.31%.

N-[3-Benzoyl-4,6-dioxo-2-thioxo-5-(*p*-tolyl-hydrazono)-tetrahydro-pyrimidin-1-yl]-2-cyano-3-(4-methoxy-phenyl) acrylamide (13b)

Red crystal (EtOH-$CHCl_3$); Yield 83%; m.p. 266–267°C; IR (KBr): $\tilde{v}_{max}$./cm^{-1} = 3270, 3203 (2NH), 2207 (C≡N), 1685, 1669, 1658, 1647 (4C=O), 1612 (C=C), 1584 (C=N). ^{1}H-NMR (DMSO-d_6): δ_{ppm} = 2.66 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 7.17, 7.65 (two d, J = 8.0 Hz, each 2H, C_6H_4-OCH_3), 7.25, 7.78 (two d, J = 8.0 Hz, each 2H, C_6H_4-CH_3), 7.79–8.14 (m, 5H, Ar-H), 8.24 (s, ^{1}H, CH=), 11.17 (s, 1H, NH), 12.44 (s, br, 1H, NH). MS *m/z* (%): 566 (M^+, 9.14), 461 (28.57), 380 (8.04), 163 (30.85), 105 (100), 77 (47.14), 51 (15.71). Anal. for $C_{29}H_{22}N_6O_5S$ (566.59). Calcd.: C 61.48; H 3.91; N 14.83%, Found: C 61.79; H 3.97; N 14.66%.

N-{3-Benzoyl-5-[(4-methoxy-phenyl)-hydrazono]-4,6-dioxo-2-thioxo-tetrahydro-pyrimidin- 1-yl}-2-cyano-3-(4-methoxy-phenyl) acrylamide (13c)

Red crystal (EtOH-DMF); Yield 82%; m.p. 272–273°C; IR (KBr): $\tilde{v}_{max}$./cm^{-1} = 3252, 3185 (2NH), 2203 (C≡N), 1680, 1665, 1652, 1640 (4C=O), 1607 (C=C), 1574 (C=N). ^{1}H-NMR (DMSO-d_6): δ_{ppm} = 3.66 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 7.21, 7.75 (two d, J = 8.0 Hz, each 2H, C_6H_4-OCH_3), 7.27, 7.78 (two d, J = 8.0 Hz, each 2H, C_6H_4-OCH_3), 7.79–8.16 (m, 5H, Ar-H), 8.26 (s, 1H, CH=), 11.19 (s, 1H, NH), 12.43 (s, br, 1H, NH). MS *m/z* (%): 582 (M^+, 7.42), 449 (11.32), 363 (28.21), 186 (31.71), 163 (52.28), 105 (100), 77 (51.42), 51 (14.28). Anal. for $C_{29}H_{22}N_6O_6S$ (582.59). Calcd.: C 59.79; H 3.81; N 14.43%, Found: C 59.92; H 3.84; N14.54%.

N-(N′-2-Cyano-2-[5-oxo-3-phenyl-4-(phenyl-hydrazono)-thiazolidin-2-ylidene] acetyl-hydrazinocarbothioyl) benzamide (25a)

Yellow crystal (EtOH-DMF); Yield 83%; m.p. 265–266°C; IR (KBr): $\tilde{v}_{max}$./cm^{-1} = 3450–3198 (4NH), 2213 (C≡N), 1725 (ring C=O), 1685, 1676 (2C=O), 1622 (C=C), 1235 (C=S). ^{1}H-NMR (DMSO-d_6): δ_{ppm} = 6.86 (s, br, 1H, NH), 7.14 (s, br., 1H, NH), 7.42–8.26 (m, 10H, Ar-H), 10.68 (s, 1H, NH), 11.99 (s, 1H, NH). Anal. for $C_{26}H_{19}N_7O_3S_2$ (541.60) Calcd.: C 57.66; H 3.54; N 18.10%, Found: C 57.98; H 3.38; N 18.19%.

N-(N′-2-Cyano-2-[5-oxo-3-phenyl-4-(p-tolyl-hydrazono)-thiazolidin-2-ylidene]-acetyl-hydrazinocarbothioyl)-benzamide (25b)

Orange crystal (EtOH-$CHCl_3$); Yield 82%; m.p. 272–273°C; IR (KBr): $\tilde{\upsilon}_{max}$./cm^{-1} = 3430–3172 (4NH), 2210 (C≡N), 1715 (ring C=O), 1685, 1672 (2C=O), 1620 (C=C), 1230 (C=S). ^{1}H-NMR (DMSO–d_6): δ_{ppm} = 2.27 (s, 3H, CH_3), 6.80 (s, br, 1H, NH), 7.15 (s, br, 1H, NH), 7.29, 7.38 (two d, J = 7.8 Hz, each 2H, C_6H_4-CH_3), 7.52–7.92 (m, 5H, Ar-H), 10.72 (s, 1H, NH), 11.96 (s, 1H, NH). Anal. for $C_{27}H_{21}N_7O_3S_2$ (555.63) Calcd.: C 58.36; H 3.81; N 17.65%, Found: C 58.17; H 3.87; N 17.77%.

N-[N′-(2-Cyano-2-[4-[2-(4-methoxy-phenyl)-hydrazono]-5-oxo-3-phenyl-thiazolidin-2-ylidene]-acetyl)-hydrazinocarbothioyl] benzamide (25c)

Red crystal (EtOH-DMF); Yield 80%; m.p. 282-283°C; IR (KBr): $\tilde{\upsilon}_{max}$./cm^{-1} = 3420–3160 (4NH), 2205 (C≡N), 1710 (ring C=O), 1682, 1670 (2C=O), 1615 (C=C), 1225 (C=S). ^{1}H-NMR (DMSO–d_6): δ_{ppm} = 3.97 (s, 3H, OCH_3), 6.84 (s, br, 2H, 2NH), 7.17, 7.26 (two d, J = 7.5 Hz, each 2H, C_6H_4-OCH_3), 7.56–7.96 (m, 5H, Ar-H), 10.65 (s, 1H, NH), 11.94 (s, 1H, NH). MS *m/z* (%): 571 (M^+, 9.28), 451 (12.86), 349 (24.28), 244 (30.02), 222 (39.57), 164 (42.85), 105 (100), 77 (71.42), 51 (25.71). Anal. for $C_{27}H_{21}N_7O_4S_2$ (571.63) Calcd.: C 56.73; H 3.70; N 17.15%, Found: C 56.39; H 3.61; N 17.31%.

General Procedure for the Synthesis of the Thiobarbituric Acid Derivatives (3), (5), (12), and (26)

To a stirred solution of compounds **1**, **2**, **9** and / or **25*c*** (0.015 mol) in acetyl chloride (10 ml), malonic acid (0.02 mol) was added. The reaction mixture was left for 2 h at ambient temperature and then heated for 4 hrs at 50°–55°C. The contents were then poured onto crushed ice, cooled to 10°C, and the separated solid was filtered off, dried and recrystallized from the appropriate solvent to give the corresponding thiobarbituric acid derivatives.

N-(3-Benzoyl-4,6-dioxo-2-thioxo-tetrahydro-pyrimidin-1-yl)-2-cyano-2-(phenyl-hydrazono) acetamide (3a)

Yellow crystal (Acetic acid); Yield 76%; m.p. 248–249°C; IR (KBr): $\tilde{\upsilon}_{max}$./cm^{-1} = 3310–3165 (2NH), 2207 (C≡N), 1685, 1670, 1660 (3C=O),

1240 (C=S). ^{1}H-NMR (DMSO-d_6): δ_{ppm} = 3.22 (s, 2H, ring CH_2), 7.35–7.88 (m, 10H, Ar-H), 11.15 (s, br, 1H, NH), 12.08 (s, br, 1H, NH). Anal. for $C_{20}H_{14}NO_4S$ (434.43) Calcd.: C 55.29; H 3.25; N 19.35%, Found: C 55.57; H 3.40; N 19.23%.

N-(3-Benzoyl-4,6-dioxo-2-thioxo-tetrahydro-pyrimidin-1-yl)-2-cyano-2-(p-tolyl-hydrazono)acetamide (3b)

Orange crystal (Acetic acid); Yield 78%; m.p. 252–253°C; IR (KBr): $\tilde{\upsilon}_{max}$./cm^{-1} = 3307–3152 (2NH), 2205 (C≡N), 1680, 1667, 1658 (3C=O), 1234 (C=S). ^{1}H-NMR (DMSO-d_6): δ_{ppm} = 2.26 (s, 3H, CH_3), 3.20 (s, 2H, ring CH_2), 7.16, 7.35 (two d, J = 8.0 Hz, each 2H, $C6H_4$-CH_3), 7.46–7.98 (m, 5H, Ar-H), 11.05 (s, br, 1H, NH), 12.11 (s, br, 1H, NH). MS *m/z* (%): 448 (M^+, 13.23), 392 (17.94), 229 (11.91), 186 (22.06), 163 (33.82), 159 (44.12), 105 (100), 77 (69.29), 51 (20.59). Anal. for $C_{21}H_{16}N_6O_4S$ (448.45) Calcd.: C 56.24; H 3.60; N18.74%, Found: C 56.41; H 3.53; N18.85%.

N-(3-Benzoyl-4,6-dioxo-2-thioxo-tetrahydro-pyrimidin-1-yl)-2-cyano-2-[(4-methoxy-phenyl)- hydrazono] acetamide (3c)

Red crystal (EtOH-DMF); Yield 72%; m.p. 257–258°C; IR (KBr): $\tilde{\upsilon}_{max}$./cm^{-1} = 3290–3154 (2NH), 2205 (C≡N), 1680, 1662, 1655 (3C=O), 1235 (C=S). ^{1}H-NMR (DMSO-d_6): δ_{ppm} = 3.19 (s, 2H, ring CH_2), 3.96 (s, 3H, OCH_3), 7.26, 7.42 (two d, J = 8.0 Hz, each 2H, C_6H_4-OCH_3), 7.52–8.34 (m, 5H, Ar-H), 11.02 (s, br, 1H, NH), 12.02 (s, br, 1H, NH). MS *m/z* (%): 464 (M^+, 12.05), 408 (16.18), 245 (30.88), 148 (38.24), 105 (100), 77 (57.35), 51 (11.76). Anal. for $C_{21}H_{16}N_6O_5S$ (464.45) Calcd.: C 54.31; H 3.47; N 18.09%, Found: C 54.07; H 3.38; N 17.96%.

N-(3-Benzoyl-4,6-dioxo-2-thioxo-tetrahydro-pyrimidin-1-yl]-2-cyano-acetamide (5)

Orange crystal (Acetic acid); Yield 80%; m.p. 242–243°C; IR (KBr): $\tilde{\upsilon}_{max}$./cm^{-1} = 3250 (NH), 2235 (C≡N), 1685, 1672, 1662 (4C=O). ^{1}H-NMR (DMSO-d_6): δ_{ppm} = 3.12 (s, 2H, ring CH2), 4.87 (s, 2H, $NCCH_2$), 7.53–8.14 (m, 5H, Ar-H), 11.14 (s, br, 1H, NH). MS *m/z* (%): 330 (M^+, 13.04), 253 (29.13), 163 (27.39), 105 (100), 77 (58.69), 51 (17.39). Anal. for $C_{14}H_{10}N_4O_4S$ (330.32) Calcd.: C 59.91; H 3.05; N 16.96%, Found: C 59.70; H 3.15; N 17.05%.

N-(3-Benzoyl-4,6-dioxo-2-thioxo -tetrahydro-pyrimidin-1-yl)-2-cyano-3-(4-methoxy-phenyl) acrylamide (12)

Orange crystal (EtOH-DMF); Yield 71%; m.p. 226–227°C; IR (KBr): $\tilde{\upsilon}_{max}$./cm^{-1} = 3230 (NH), 2205 (C≡N), 1680, 1662, 1653 (4C=O). ^{1}H-NMR (DMSO-d$_6$): δ_{ppm} = 3.11 (s, 2H, ring CH_2), 3.93 (s, 3H, OCH_3), 7.17, 7.28 (two d, J = 7.8 Hz, each 2H, C_6H_4-OCH_3), 7.56–8.14 (m, 9H, Ar-H), 8.38 (s, 1H, CH=), 11.83 (s, br, 1H, NH). MS *m/z* (%): 448 (M^+, 18.38), 343 (20.88), 186 (34.55), 105 (100), 77 (50.73), 51 (18.23). Anal. for $C_{22}H_{16}N_4O_5S$ (448.45) Calcd.: C 58.92; H 3.60; N 12.49%, Found: C 58.81; H 3.69; N 12.37%.

N-(3-Benzoyl-4,6-dioxo-2-thioxo-tetrahydro-pyrimidin-1-yl)-2-cyano-2-{4-[(methoxy-phenyl)-hydrazono]-5-oxo-3-phenyl-thiazolidin-2-ylidene}acetamide (26)

Reddish brown crystal (EtOH-DMF); Yield 67%; m.p. 295–296°C; IR (KBr): $\tilde{\upsilon}_{max}$./cm^{-1} = 3365, 3203 (2NH), 2205 (C≡N), 1710 (ring C=O), 1680, 1670, 1662 (4C=O), 1220 (C=S). ^{1}H-NMR (DMSO– d$_6$): δ_{ppm} = 3.15 (s, 2H, ring CH_2), 3.96 (s, 3H, OCH_3), 7.25, 7.36 (two d, J = 8.0 Hz, each 2H, C_6H_4-OCH_3), 7.64–8.12 (m, 5H, Ar-H), 10.25 (s, br, 1H, NH), 11.71 (s, br, 1H, NH). Anal. for $C_{30}H_{21}N_7O_6S_2$ (639.66) Calcd.: C 56.33; H 3.31; N 15.33%, Found: C 56.54; H 3.18; N 15.45%.

General Procedure for the synthesis of the arylidene derivatives (6), (16), (22), and (27)

A mixture of the active methylene compounds **3, 5, 21**and / or **26** (0.005 mol) and p-anisaldehyde (0.005 mol) in ethanol (30 ml) containing a catalytic amount of piperidine (3 drops) was boiled under reflux for 3 h. The reaction mixture was cooled and the solid product which precipitated was collected by filtration, dried and crystallized from the appropriate solvent to give the corresponding arylidene derivatives.

N-[3-Benzoyl-5-(4-methoxy-benzylidene)-4,6-dioxo-2-thioxo-tetrahydro-pyrimidin -1-yl]-2-cyano-2-[(p-tolyl-hydrazono) acetamide (6)

Brown crystal (EtOH-$CHCl_3$); Yield 69%; m.p. 288–289°C; IR (KBr): $\tilde{\upsilon}_{max}$./cm^{-1} = 3280, 3142 (2NH), 2206 (C≡N), 1673, 1665, 1657, 1645 (4C=O), 1610 (C=C). ^{1}H-NMR (DMSO-d$_6$): δ_{ppm} = 2.28 (s, 3H, CH_3), 3.96 (s, 3H, OCH_3), 7.13, 7.26 (two d, J (8.0 Hz, each 2H, C_6H_4-OCH_3), 7.18, 7.36 (two d, J = 7.8 Hz, each 2H, C_6H_4-OCH_3), 7.66–8.24 (m, 5H,

Ar-H), 11.15 (s, br, 1H, NH), 11.86 (s, br, 1H, NH). MS *m/z* (%): 566 (M^+, 8.02), 461 (8.57), 380 (20.28), 186 (40.57), 158 (28.57), 105 (100), 77 (55.14), 51 (23.42). Anal. for $C_{29}H_{22}N_6O_5S$ (566.59) Calcd.: C 61.48; H 3.91; N 14.83%, Found: C 61.76; H 3.84; N 14.96%.

N-[3-Benzoyl-5-(4-methoxy-benzylidene)-4,6-dioxo-2-thioxo-tetrahydro-pyrimidin-1-yl]-2-cyano-3-(4-methoxy-phenyl) acrylamide (16)

Brown crystal (EtOH-DMF); Yield 71%; m.p. 282–283°C; IR (KBr): $\tilde{\upsilon}_{max}./cm^{-1}$ = 3270 (NH), 2209 (C≡N), 1682, 1668, 1657 (4C=O), 1606 (C=C). ^{1}H-NMR (DMSO-d_6): δ_{ppm} = 3.83 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 7.18, 7.36 (two d, J = 8.0 Hz, each 2H, C_6H_4-OCH_3), 7.24, 7.42 (two d, J = 8.0 Hz, each 2H, C_6H_4-OCH_3), 7.78–7.98 (m, 5H, Ar-H), 8.02 (s, 1H, CH=), 8.12 (s, 1H, CH=), 10.84 (s, 1H, NH). MS *m/z* (%): 566 (M^+, 11.14), 461 (11.71), 386 (17.14), 186 (26.28), 163 (47.14), 131 (31.10), 105 (100), 77 (65.71), 51 (19.14). Anal. for $C_{30}H_{22}N_4O_6S$ (566.58) Calcd.: C 63.60; H 3.91; N 9.89%, Found: C 63.37; H 3.98; N 9.76%.

(5E)-1-Benzoyl-5-(4-methoxybenzylidene)-3-(4-oxo-1,4,5,6,7,8-hexahydro-3H-spiro[1-benzothieno[2,3-d]pyrimidine-2,1′-cyclohexan]-3-yl)-2-thioxodihydro- pyrimidine-4,6(^{1}H,5H)-dione (22)

Brown crystal (EtOH-DMF); Yield 60%; m.p. 292–293°C; IR (KBr): $\tilde{\upsilon}_{max}./cm^{-1}$ = 3340 (NH), 1680, 1667, 1658 (4C=O), 1610 (C=C). ^{1}H-NMR (DMSO-d_6): δ_{ppm} = 1.17–1.67 (m, 10H, cyclohexane), 1.77–2.52 (m, 8H, tetrahydrobenzothiophene), 3.96 (s, 3H, OCH_3), 7.26, 7.38 (two d, J = 7.5 Hz, each 2H, C_6H_4-OCH_3), 7.56–7.89 (m, 5H, Ar-H), 8.26 (s, 1H, CH=), 11.24 (s, br, 1H, NH). Anal. for $C_{34}H_{32}N_4O_5S_2$ (640.77) Calcd.: C 63.73; H 5.03; N 8.74%, Found: C 63.95; H 5.14; N 8.59%.

N-[3-Benzoyl-5-(4-methoxy-benzylidene)-4,6-dioxo-2-thioxo-tetrahydro-pyrimidin-1-yl]-2-cyano-2-{4-[(methoxy-phenyl)-hydrazono]-5-oxo-3-phenyl-thiazolidin-2-ylidene}acetamide (27)

Brown crystal (EtOH-DMF); Yield 61%; m.p. >300°C; IR (KBr): $\tilde{\upsilon}_{max}./cm^{-1}$ = 3357, 3184 (2NH), 2203 (C≡N), 1709 (ring C=O), 1680, 1668, 1657 (4C=O), 1610 (C=C). ^{1}H-NMR (DMSO-d_6): δ_{ppm} = 3.89 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 7.15, 7.38 (two d, J = 8.0 Hz, each 2H,C_6H_4-OCH_3), 7.26, 7.45 (two d, J = 8.0 Hz, each 2H, C_6H_4-OCH_3), 7.76–7.92 (m, 5H, Ar-H), 8.02 (s, 1H, CH=), 11.57 (s, br, 1H, NH), 12.78

(s, br, 1H, NH). Anal. for $C_{38}H_{27}N_7O_7S_2$ (757.79) Calcd.: C 60.23; H 3.59; N 12.94%, Found: C 60.53; H 3.52; N 12.83%.

Synthesis of N-N′-[2-Cyano-3-(4-methoxy-phenyl)-acryloyl]hydrazinocarbothioyl benzamide (9)

Method A

A mixture of **1** (2.62 g, 0.01 mol) and p-anisaldehyde (0.01 mol) in ethanol (30 ml) containing a catalytic amount of piperidine (3 drops) was refluxed for 3 hrs. The reaction mixture was allowed to cool, and then the precipitated product was filtered off, dried well and recrystallized from DMF to give compound **9**.

Method B

A mixture of **1** (2.62 g, 0.01 mol) and ethyl *p*-methoxybenzylidene cyanoacetate (2.31 g, 0.01 mol) in ethanol (30 ml) containing a catalytic amount of piperidine (3 drops) was refluxed for 3 hrs. The precipitated product was formed upon cooling, filtered off, dried well and recrystallized from dMF to give compound **9**.

Yellow crystal; Yield 82%; m.p. 210–211°C; IR (KBr): $\tilde{\upsilon}_{max}$./cm^{-1} = 3320–3236 (3NH), 2210 (C≡N), 1672, 1664 (2C=O), 1610 (C=C), 1238 (C=S). ^{1}H-NMR (DMSO-d$_6$): δ_{ppm} = 3.90 (s, 3H, OCH_3), 7.17, 7.65 (two d, J = 8.0 Hz, each 2H, C_6H_4-OCH_3), 7.82– 8.14 (m, 5H, Ar-H), 8.23 (s, 1H, CH=), 11.14 (s, br, 1H, NH), 11.87 (s, 1H, NH), 12.44 (s, br, 1H, NH). MS *m/z* (%): 380 (M^+, 17.21), 217 (45.50), 186 (67.40), 158 (26.40), 105 (100), 77 (91.80), 51 (54.80). Anal. for $C_{19}H_{16}N_4O_3S$ (380.42) Calcd.: C 59.99; H 4.24; N 14.73%, Found: C 61.28; H 4.13; N 14.81%.

General Procedure for the Synthesis of 2-Hydrazonobarbituric Acid Derivatives (8), (15), and (18)

To a solution of **12** and (or **16** (0.005 mol) in ethanol (20ml), hydrazine hydrate (0.375 g, 0.0075 mol) was added. The reaction mixture was heated under reflux for 4 h (until evolution of hydrogen sulfide ceased), cooled at room temperature, and was left overnight. The precipitate was formed, collected and recrystallized from ethanol to give the corresponding 2-hydrazonobarbituric acid derivatives.

2-(3-Benzoyl-2-hydrazono-5-(4-methoxybenzylidene)-4,6-dioxo-tetrahydro-pyrimidin-1(2*H*)-ylamino)-2-oxo-*N*′-*p*-tolyacetohydrazonyl cyanide (8)

Brown crystal (EtOH-DMF); Yield 65%; m.p. 284–285°C; IR (KBr): $\tilde{\upsilon}_{max}$./cm^{-1} = 3415–3354 (NH_2), 3249 (NH), 2206 (C≡N), 1672, 1661,

1650 (4C=O), 1586 (C=N). ^{1}H-NMR (DMSO-d_6): δ_{ppm} = 3.79 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 5.56 (s, br, 2H, NH_2), 7.20, 7.36 (two d, J = 7.5 Hz, each 2H, C_6H_4-OCH_3), 7.28, 7.78 (two d, J = 7.8 Hz, each 2H, C_6H_4-OCH_3), 7.85–8.05 (m, 5H, Ar-H), 8.16 (s, 1H, CH=), 10.56 (s, br. 1H, NH), 11.12 (s, br, 1H, NH). Anal. for $C_{30}H_{24}N_8O_6$ (580.55) Calcd.: C 60.00; H 4.17; N 19.30%, Found: C 60.02; H 4.15; N 19.27%.

N-(3-Benzoyl-2-hydrazono-4,6-dioxo-tetrahydro-pyrimidin-1-yl]-2-cyano-3-(4-methoxy-phenyl) acrylamide (15)

Pale brown crystal (EtOH-CHCl3); Yield 61%; m.p. 278–279°C; IR (KBr): $\tilde{v}_{max}$./cm^{-1} (3426–3375 (NH2), 3263 (NH), 2210 (C≡N), 1674, 1665, 1652 (4C= O), 1595 (C=N). ^{1}H-NMR (DMSO-d_6): δ_{ppm} = 3.10 (s, 2H, ring CH_2), 3.94 (s, 3H, OCH_3), 7.18, 7.26 (two d, J = 7.8 Hz, each 2H, C_6H_4-OCH_3), 7.66–7.97 (m, 5H, Ar-H), 8.01 (s, 1H, CH=), 10.19 (s, br, 2H, NH_2), 11.37 (s, br, 1H, NH). MS *m/z* (%): 446 (M^+, 8.82), 390 (14.70), 229 (19.86), 186 (21.17), 161 (28.67), 132 (33.82), 105 (100), 77 (56.18), 51 (17.64). Anal. for $C_{22}H_{18}N_6O_5$ (446.42) Calcd.: C 59.19; H 4.06; N 18.83%, Found: C 58.92; H 4.17; N 18.90%.

N-(3-Benzoyl-2-hydrazono-5-(4-methoxy-benzyliene)-4,6-dioxo-tetrahydro-pyrimidin-1-yl]-2-cyano-3-(4-methoxy-phenyl)acrylamide (18)

Pale brown crystal (EtOH-DMF); Yield 60%; m.p. >300°C; IR (KBr): $\tilde{v}_{max}$./cm^{-1} = 3415–3354 (NH2), 3249 (NH), 2205 (C≡N), 1670, 1660, 1648 (4C=O), 1582 (C=N). ^{1}H-NMR (DMSO-d_6): δ_{ppm} = 3.78 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 5.54 (s, br, 2H, NH_2), 7.23, 7.34 (two d, J = 7.5 Hz, each 2H, C_6H_4-OCH_3), 7. 26, 7.76 (two d, J = 7.8 Hz, each 2H, C_6H_4-OCH_3), 7.84–8.02 (m, 5H, Ar-H), 8.15 (s, 1H, CH=), 8.18 (s, 1H, CH=), 11.08 (s, br, 1H, NH). MS *m/z* (%): 564 (M^+, 12.57), 459 (8.57), 201 (17.42), 161(33.14), 132 (27.71), 105 (100), 77 (62.28), 51 (16.85). Anal. for $C_{30}H_{24}N_6O_6$ (564.55) Calcd.: C 63.82; H 4.28; N 14.89%, Found: C 63.69; H 4.15; N 15.02%.

Synthesis of 2-Hydrazono- & 2-Phenylhydrazonobarbituric Acid Derivatives (19a–b)

To a solution of **5** (3.3 g, 0.01 mol) in ethanol (20 ml), either hydrazine hydrate (0.75 gm, 0.015 mol) or phenyl hydrazine (1.02 gm, 0.015 mol) was added. The reaction mixture was heated under reflux for 6hrs (until evolution of H_2S ceased), cooled at room temperature, and poured into

cold water (20 ml), where upon the solid product thus precipitated was collected by filtration and recrystallized from ethanol-chloroform (2:1) to give **19a–b.**

N-(3-Benzoyl-2-hydrazono-4,6-dioxo-tetrahydro-pyrimidin-1-yl)-2-cyanoacetamide (19a)

Buff crystal; Yield 63%; m.p. 250–251°C; IR (KBr): $\tilde{v}_{max}$./cm^{-1} = 3440–3387 (NH_2), 3274 (NH), 2242 (C≡N), 1680, 1669, 1658 (4C=O), 1592 (C=N). ^{1}H-NMR (DMSO-d_6): δ_{ppm} = 3.18 (s, 2H, ring CH_2), 4.75 (s, 2H, $NCCH_2$), 5.54 (s, br, 2H, NH_2), 7.64–7.85 (m, 5H, Ar-H), 11.08 (s, br, 1H, NH). MS *m/z* (%): 328 (M^+, 13.40), 300 (27.26), 195 (29.13), 161 (42.17), 105 (100), 77 (64.34), 51 (23.91). Anal. for $C_{14}H_{12}N_6O_4$ (328.28) Calcd.: C 51.22; H 3.68; N 25.60%, Found: C 51.54; H 3.60; N 25.72%.

N-[3-Benzoyl-4,6-dioxo-2-(phenyl-hydrazono)-tetrahydro-pyrimidin-1-yl]-2-cyano-acetamide (19b)

Yellow crystal; Yield 59%; m.p. 262–261°C; IR (KBr): $\tilde{v}_{max}$./cm^{-1} = 3386, 3317 (2NH), 3274 (NH), 2238 (C≡N), 1682, 1670, 1662 (4C=O), 1584 (C=N). ^{1}H-NMR (DMSO -d_6): δ_{ppm} = 3.16 (s, 2H, ring CH_2), 4.73 (s, 2H, $NCCH_2$), 7.17–8.14 (m, 10H, Ar-H), 11.15 (s, 1H, NH), 12.47 (s, br, 1H, NH). MS *m/z* (%): 404 (M^+, 11.76), 376 (23.52), 237(29.41), 131 (26.47), 105 (100), 77 (52.79), 51 (23.24). Anal. for $C_{20}H_{16}N_6O_4$ (404.38) Calcd.: C 59.40; H 3.99; N 20.78%, Found: C 59.16; H 4.08; N 20.65%.

Synthesis of 1-Benzoyl-3-(4-oxo-1,4,5,6,7,8-hexahydro-3H-spiro[1-benzothieno [2,3-d]pyrimidine-2,1′-cyclohexan]-3-yl)-2-thioxo-dihydropyrimidine-4,6(^{1}H,5H)-dione (21)

To a mixture of compound **5** (3.3 g, 0.01 mol), cyclohexanone (0.01 mol), finely powdered sulfur (0.013 mol) in ethanol (30 ml) was added dropwise morpholine (0.02 mol). The mixture was stirred for 6hrs at 45–50 -C. After the reaction mixture was cooled, the solid product was filtered off, washed with cold ethanol, dried well and recrystallized from methanol to give **21**.

Green crystal; Yield 63%; m.p. 262–263°C; IR (KBr): $\tilde{v}_{max}$./cm^{-1} = 3350 (NH), 1688, 1682, 1670, 1662 (4C=O). ^{1}H-NMR (DMSO-d_6): δ_{ppm} = 1.17–1.65 (m, 10H, cyclohexane), 1.77–2.67 (m, 8H, tetrahydrobenzothiophene), 3.11 (s, 2H, thiobarbituric ring CH_2), 7.55–8.14 (m, 5H, Ar-H), 11.21 (s, br, 1H, NH). MS *m/z* (%): 522 (M^+, 6.28), 445 (10.15), 303 (14.28), 163 (39.04), 131 (51.42), 105 (100), 77 (54.28), 51 (18.28). Anal.

for $C_{20}H_{16}N_6O_4$ (522.64) Calcd.: C 59.75; H 5.01; N 10.72%, Found: C 59.87; H 4.89; N 10.60%.

Synthesis of N-N′-[2-Cyano-2-(5-oxo-3-phenyl-thiazolidin-2-ylidene)-acetyl] -hydrazinocarbothioyl-benzamide (24)

To a cooled suspension of finally divided potassium hydroxide (0.01 mol) in dimethylformamide (30 ml) were added the cyano methylene compound **1** (2.62 g, 0.01 mol), followed by phenyl isothiocyanate (0.01 mol). The mixture was stirred at room temperature overnight and then treated with chloro acetyl chloride (0.01 mol) and left at room temperature for additional 12hrs. The reaction mixture was then triturated with cold water (50 ml), and few drops of dilute HCl (0.1N, 5drops) was added (till pH = 7). The resultant solid product, so precipitated was collected by filtration, dried well and crystallized from ethanol-dMF to give compound **24.**

Pale brown crystal; Yield 73%; m.p. 232–233°C; IR (KBr): $\tilde{v}_{max}$./cm^{-1} = 3300–3206 (3NH), 2207 (C≡N), 1735 (ring C=O), 1685, 1674 (2C=O), 1620 (C=C). ^{1}H-NMR (DMSO-d_6): δ_{ppm} = 5.25 (s, 2H, thiazolidin-5-one CH_2), 7.18–8.15 (m, 10H, Ar-H), 11.04 (s, 1H, NH), 11.85 (s, 1H, NH), 12.44 (s, br, 1H, NH). MS *m/z* (%): 437 (M^+, 17.64), 317 (13.97), 273 (20.28), 243 (27.94), 187 (35.29), 164 (41.17), 105 (100), 77 (54.41), 51 (22.05). Anal. for $C_{20}H_{16}N_6O_4$ (437.49) Calcd.: C 54.91; H 3.46; N 16.01%, Found: C 54.62; H 3.55; N 15.87%.

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