One Pot Synthesis of Spiro Pyrimidinethiones/Spiro Pyrimidinones, Quinazolinethiones/Quinazolinones, and Pyrimidopyrimidines

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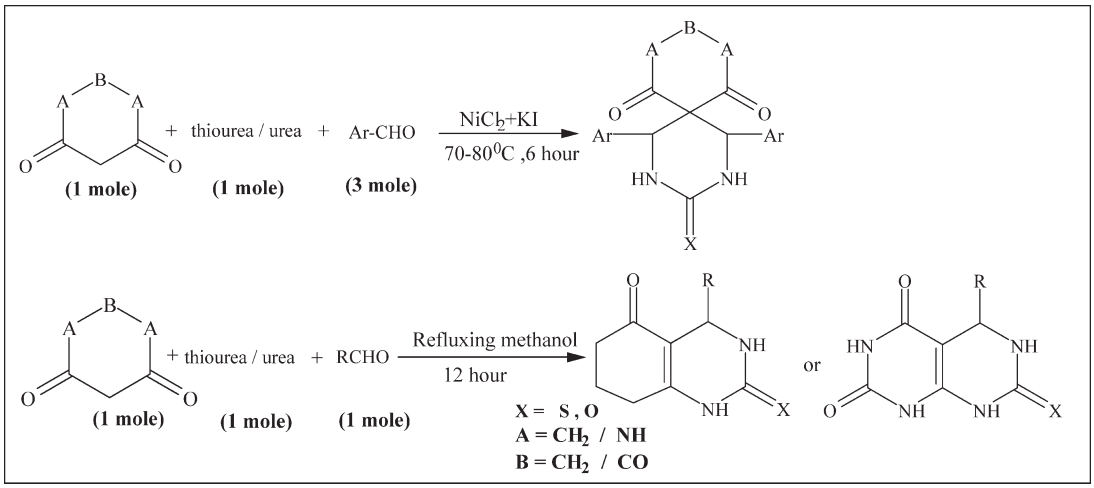

Condensation of cyclohexane-1,3-dione/barbituric acid, thiourea/urea, and aromatic aldehyde in the mole ratio of 1:1:3 in solventless reaction in presence of $NiCl_2$/KI afforded 1,5-diaryl-3-thioxo-2,4-diazaspiro[5.5]undecane-7,11-dione/1,5-diaryl-2,4-diazaspiro[5.5]undecane-3,7,11-trione analogues and 7,11-diaryl-9-thioxo-2,4,8,10-tetraazaspiro[5.5]undecane-1,3,5,-trione/7,11-diaryl-2,4,8,10-tetraazaspiro[5.5] undecane-1,3,5,9-tetraone analogues, respectively. The similar condensation of cyclohexane-1,3-dione/ cyclohexanone, thiourea/urea, and aromatic aldehyde/heteroaromatic aldehyde in the mole ratio of 1:1:1 in refluxing methanol afforded 4-aryl/heteroaryl-2-thioxo-1,2,3,4,5,6,7,8-octahydroquinazolin-5-one, 4-aryl/heteroaryl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione analogues and 4-aryl/heteroaryl-1,2,3,4,5, 6,7,8-octahydroquinazoline-2-thione, 4-aryl/heteroaryl-1,2,3,4,5,6,7,8-octahydroquinazolin-2-one analogues, respectively. Condensation of heterocyclic active methylene compound, barbituric acid, thiourea/ urea, and aromatic aldehydes under similar set of conditions in 1:1:1 mole ratio was carried which afforded 5-aryl-7-thioxo-1,2,3,4,5,6,7,8-octahydropyrimido[4,5-d]pyrimidine-2,4-dione/5-aryl-1,2,3,4,5, 6,7,8-octahydropyrimido[4,5-d]pyrimidine-2,4,7-trione analogues. Similar condensation of an active methine compound, 2-acetylcyclohexanone, thiourea/urea, and aromatic aldehydes in the mole ratio of 1:1:1 produced 5-aryl-1-methyl-3-thioxo-2,4-diazaspiro[5.5]undec-1-en-7-one/5-aryl-1-methyl-2, 4-diazaspiro[5.5]undec-1-ene-3, 7-dione analogues, the spiro compounds of entirely different kind. All these identifications and characterizations have been based on the elemental analysis and spectral data.

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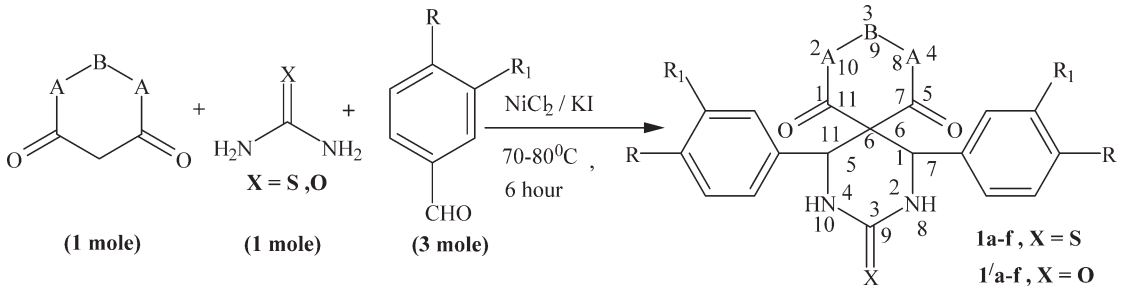
INTRODUCTION

The synthesis of spiro compounds has been a subject of great interest to research workers. Spiro derivatives based on heteropolycyclics have antibacterial, anticonvulsant, antitumor, and anticancer activities. Similarly, condensed heterocyclics containing quinazoline moiety are ranked among the most versatile biologically active compounds possessing pharmacological properties like being anticonvulsant [1, 2], anticoagulant [3], antifibrillatory [4], cardiac stimulant [5], diuretic [6], antibacterial [7], antiviral [8], antifungal [9], antiasthematic, antiallergic [10], and antitubercular [11a]. In addition to its diverse biological activity, the quinazoline nucleus is also a key component in a relatively varied range of colored products [11b]. Compounds possessing pyrimidopyrimidine nucleus show potent biological activities including inhibition of angiogenesis, tumor inhibition [12], and tyrosine kinase inhibitors [13]. Some of the pyrimidopyrimidine derivatives, particularly 3-(2-methylphenyl)-10-phenyl-2-thioxothiazolo[4,5-d]pyrimido[2,1-

Scheme 1



1a , 1′a ; R = CH_3 , R^1 = H , A = B = CH_2

1b , 1′b ; R = OCH_3 , R^1 = H , A = B = CH_2

1c , 1′c ; R = R^1 = OCH_3 , A = B = CH_2

(Internal Numbering)

1d , 1′d ; R = CH_3 , R^1 = H , A = NH , B = CO

1e , 1′e ; R = OCH_3 , R^1 = H, A= NH , B = CO

1f , 1′f ; R = R^1 = OCH_3 , A = NH , B = CO

(External Numbering)

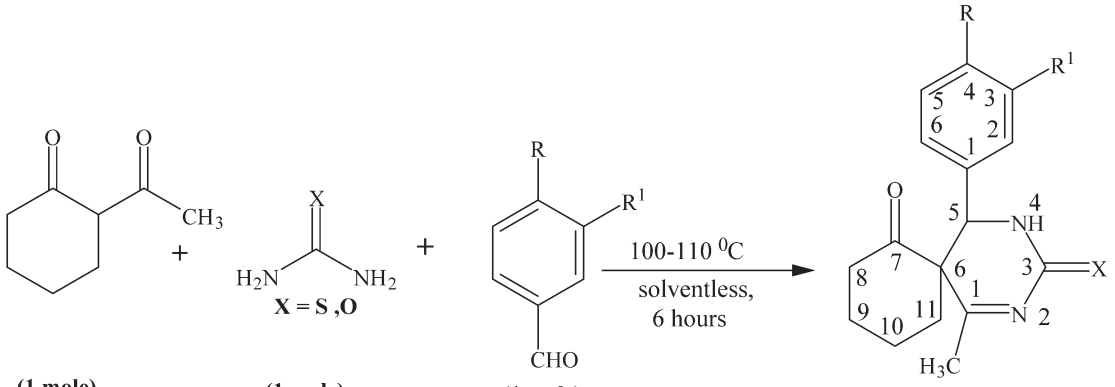
b]pyrimidine [14] have been screened for antifungal activity against *Aspergillus niger* and *Penicillium citrinum*. These promising biological activities encouraged us to prepare some new heterocyclic derivatives.

In the past decade, dihydropyrimidinones and their derivatives have attracted considerable interest because they exhibit promising activities as calcium channel blockers, antihypertensive agents, α-1a-antagonists [15], and neuropeptide Y (NPY) antagonists. Moreover, several alkaloids containing the dihydropyrimidine core unit have been isolated from marine sources, which also exhibit interesting biological properties [16], most notably among these are the batzellandine alkaloids, which were found to be potent HIV group-120-CD4 inhibitors [17]. The synthesis of the core heterocyclic nucleus of dihydropyrimidinones, tetrahydropyrimidinones, partially reduced quinazolines, and their thio analogues is of much current importance. The most simple and straightforward procedure, first reported by Biginelli in 1893, involves three-component, one pot condensation of a ethyl acetoacetate with an aldehyde and urea under strongly acidic conditions [18]. This procedure is known as the Biginelli reaction. The major drawback associated with this protocol is the low yield, particularly for substituted aromatic and aliphatic aldehydes [19]. Recently, many synthetic methods for preparing dihydropyrimidinones have been reported including classical conditions, with microwave and ultrasound irradiation and by using Lewis acids as well as protic acid promoters such as; H_2SO_4 [20], BF_3 Et_2O/CuCl [21], $InCl_3$ [22], $BiCl_3$ [23], $LiClO_4$ [24], $Ag_3PW_{12}O_{40}$ [25], and $FeCl_3$ $6H_2O$/HCl [26]. Acidic ionic liquids as effective catalysts for this transformation were also utilized [27]. However, some of the reported methods also suffer from drawbacks such as nonrecyclability, harsh reaction conditions, long reaction times, the need of an additive, tedious work-up, and environmental pollution. Moreover, some of the methods are only practical for aromatic aldehydes especially the unsubstituted ones. Therefore, a need still exists for versatile, simple and environment-friendly processes wehereby DHPMs as single ring compounds, as a component in condensed heterocycles and as moieties in spiro heterocyclic systems can be formed under milder and practical conditions. In recent years, multicomponent coupling reactions [28] for the synthesis of the title and closely related compounds have received considerable attention. It is a major attraction to chemists because two or more steps in the synthetic sequence can be carried out without the isolation of intermediates. Thus, the synthesis of compounds containing heterocyclic nucleus is of current interest under this strategy. We, herein, report three component coupling reaction (Biginelli type of reaction), which provides an easy access to spiro and condensed/fused heterocycles in fairly good yield. It is worthwhile to mention here, that we proposed a new one pot method for synthesizing novel spiro pyrimidinethiones/spiro pyrimidinones; varied substituted and reduced quinazolinethiones/quinazolinones and condensed pyrimidopyrimidines. In this work, we describe a general and practical route for the Biginelli type cyclocondensation reactions using $NiCl_2$ + KI as the catalyst. This can serve as a general method which provides an easy access to spiro and condensed systems in excellent yield.

RESULTS AND DISCUSSION

A facile and one pot combination that not only preserves the simplicity of Biginelli's one pot reaction but also consistently produces excellent yields of the spiro

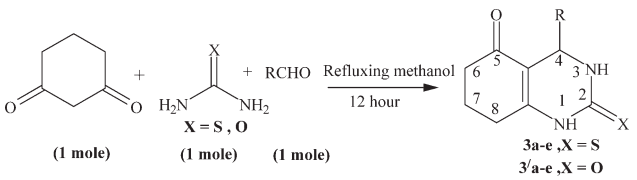
Scheme 2



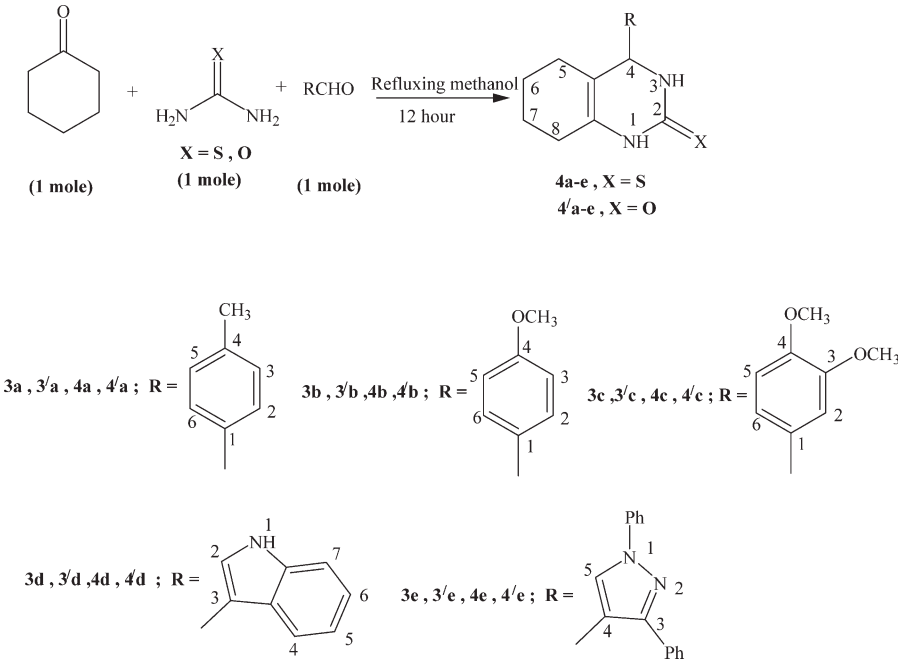
2a , 2′a ; R = R^1 = H
2b , 2′b ; R = CH_3 , R^1 = H
2c , 2′c ; R = OCH_3 , R^1 = H
2d , 2′d ; R = R^1 = OCH_3
2e , 2′e ; R = Cl , R^1 = H

pyrimidinethiones/spiro pyrimidinones (**1a-f/1′a-f**) has been developed as shown in Scheme 1. In a typical general experimental procedure by using highly exceptional conditions, a melt of the mixture of 1,3-dicarbonyl compound (cyclohexane-1,3-dione or barbituric acid), thiourea/urea, an aromatic aldehyde in the mole ratio of 1:1:3 was stirred without using any solvent at 70–80°C in the presence of catalytic amount of $NiCl_2$ + KI for a certain period of time required to complete the reaction (TLC), resulting in the formation of spiro pyrimidinethiones/spiro pyrimidinones. To study the generality of this process, many transformations illustrating this novel and general method for the synthesis of spiro pyrimidinethiones/spiro pyrimidinones were studied and the physical data including elemental analysis of the products is summarized in experimental section. A variety of substituted aromatic aldehydes and the cyclic dicarbonyl compounds afforded high yields of products in high purity. These reactions leading to the formation of spiro pyrimidinethiones/spiro pyrimidinones were confounded from the green perspectives, by the requirements for extractive isolation followed by recrystallization to afford material of a suitable quality. The solvent free approach afforded good yields of products examined during the course of this study. In majority of instances, solvent free approach generated pyrimidinethiones/pyrimidinones of exceptionally good purity. For comparison, condensation of an active methine compound, 2-acetylcyclohexanone (a cyclic β -diketone), thiourea/urea, and aromatic aldehyde in the mole ratio of 1:1:1 produced altogether an unexpected and a novel spiro compound instead of a normal condensed product (a quinazoline analogue), which was characterized as 5-aryl-1-methyl-3-thioxo-2,4-diazaspiro[5.5]undec-1-en-7-one/5-aryl-1-methyl-2,4-diazaspiro[5.5]undec-1-ene-3,7-dione analogue (**2a-e/2′a-e**) as shown in Scheme 2. In another general experimental procedure, condensation of cyclohexane-1,3-dione, thiourea/urea, and aromatic aldehyde/heteroaromatic aldehyde in the mole ratio of 1:1:1 in refluxing methanol for 10–12 h resulted in the formation of 4-aryl/heteroaryl-2-thioxo-1,2,3,4,5,6,7,8-octahydroquinazolin-5-one/4-aryl/heteroaryl-1, 2,3,4,5,6,7,8-octahydro quinazoline-2,5-dione derivatives (**3a-e/3′a-e**) as shown in Scheme 3. Similarly, condensation of cyclohexanone, thiourea/urea, and aromatic or heteroaromatic aldehydes produces 4-aryl/heteroaryl-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione/4-aryl/heteroaryl-1,2,3,4,5,6,7,8 octahydroquinazolin-2-one analogues (**4a-e/4′a-e**) as shown in Scheme 4. Condensation of active methylene heterocyclic compound, barbituric acid, thiourea/urea, and aromatic aldehyde under similar set of conditions afforded 5-aryl-7-thioxo-1,2,3,4,5,6,7,8-pyrimidine-2,4,7-trione derivatives (**5a-d/5′a-d**) as shown in Scheme 5. The physical data of the products of all these reactions has been included in the experimental section. In conclusion, three-component condensation provides an efficient and improved method for the synthesis of spiro and condensed heterocycles. Moreover, this method offers

Scheme 3



Scheme 4



several advantages including high yield, simple work-up procedure and is free from pollution. The structures of all these compounds were established by elemental analysis and spectral studies (IR, ^{1}H NMR, and ^{13}C NMR spectra of some compounds).

A characteristic multiplet at δ 2.0–2.35 due to six protons of the trimethylene chain of the cyclohexane component of the spiro system; a sharp singlet signal due to two similar benzylic methyl protons corresponding to six protons at δ 2.40 and a downfield singlet around δ 5.0 due to two identical protons at positions 1 and 5 of the spiro system along with the usual appearance of aromatic protons in the ^{1}H NMR spectrum speaks unequivocally of the characterized 1,5-bis(*p*-methylphenyl)-3-thioxo-2,4-diazaspiro[5.5]undecane-7,11-dione structure of the thioxo compound **1a**. The prominent absence of appearance of methylene chain protons, presence of two closely located sharp singlet signals of three protons of each of the two methoxyl groups, one at δ 3.68 and the other at δ 3.72 and more downfield appearance of a signal of two protons due to H-7 and H-11 of the spiro system at δ 5.25 in the ^{1}H NMR spectra of **1f** not only confirmed but distinguished this tetrazaspiro system from the diazaspiro system. Disappearance of a triplet signal due to methine proton of 2-acetylcyclohexanone and appearance of a slightly upfield singlet at δ 1.22 due to methyl group as compared with that of 2-acetylcyclohexanone (δ 2.68); a multiplet due to eight protons of tetramethylene chain at δ 1.79–2.25; a signal at δ 3.70 due to methoxyl protons and a highly downfield singlet at δ 5.18 due to one proton, H-5 in ^{1}H NMR spectrum of **2c** confirmed the generation of a substituted and functionalized cyclohexanespiropyrimidine system, characterized for this compound. The only characteristic difference in the ^{1}H NMR spectra of quinazoline compounds **3** and **4** is that in former we have a slightly downfield multiplet due to six protons of the trimethylene chain and in the latter a slightly up field multiplet due to eight protons of the tetramethylene chain. In compounds **5**, where in the ^{1}H NMR spectra there is a dearth of protons on the carbon atoms of the heterocyclic system, the only prominent singlet characterizing the system is due to a single proton at δ 4.70, supplemented by the elemental analysis data and characteristic IR peaks data as detailed in the experimental part of individual compounds.

In products **1a-f** and **1′a-f**, besides the stereochemistry involved due to spiro system of the 2 six-membered heterocyclic and carbocyclic ring, there are two similar chiral centers on one of the rings of the spiro system. So,

Scheme 5

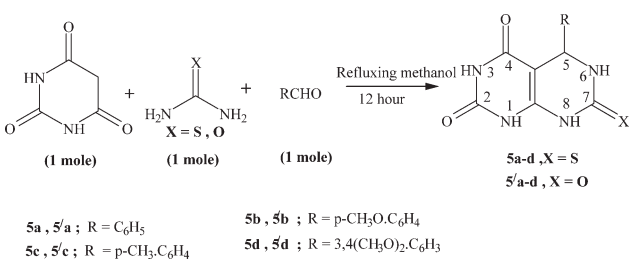


Table 1

Antimicrobial activity of 1,5-diaryl-3-thioxo-2,4-diazaspiro[5.5]undecane-7,11-dione/1,5-diaryl-2,4-diazaspiro[5.5]undecane-3,7,11-trione (**1a-c/1′a-c**) and 7,11-diaryl-9-thioxo-2,4,8,10-tetrazaspiro[5.5]undecane-1,3,5-trione/7,11-diaryl-2,4,8,10-tetrazaspiro[5.5]undecane-1,3,5,9 tetraone (**1d-e/1′d-e**).

	Antibacterial activity			Antifungal activity		
Compd No.	*Escherichia coli*	*Bacillus subtilis*	*Bacillus cereus*	*Aspergillus niger*	*Penicillium* species	*Cladosporium* species
1a	10	–	–	–	–	13
1b	11	–	–	–	–	14
1c	14	–	–	–	–	16
1d	15	–	–	–	–	17
1e	17	–	–	–	–	20
1f	19	–	–	–	–	20
1′a	12	–	–	–	–	14
1′b	10	–	–	–	–	13
1′c	16	–	–	–	–	17
1′d	17	–	–	–	–	16
1′e	19	–	–	–	–	19
1′f	17	–	–	–	–	18

Standard norfloxacin: *Escherichia coli* 28, *Bacillus subtills* 26, *Bacillus cereus* 28; standard fluconazol: *Aspergillus niger* 32, *Penicillium* species 25, *Cladosporium* species 23.

theoretically three distereoisomers (not four distereoisomers and a pair of racemates) should exist including a pair of enantiomers and a meso (optically inactive) stereomer for all these compounds. In this study, it could not be established whether entirely the meso stereomer is formed or one of the optically active enantiomers or a mixture of all the stereomers is formed. However, from the almost zero specific optical rotation values observed for these compounds, it could be summarized that either the only meso stereoisomer or almost a 50:50 racemic mixture is formed. The resolution into enantiomers in this study could not be carried on successfully and is under active study presently. The compounds **2a-e**, **2′a-e**, **3a-e**, **3′a-e**, **4a-e**, **4′a-e**, **5a-d**, and **5′a-d** were all obtained also as racemates.

Antimicrobial activity. Some of the compounds were screened for their antibacterial activity against *Escherichia coli*, *Bacillus sublitis*, and *Bacillus cereus* at concentration of 1000 μg and for antifungal activity against *Aspergillus niger*, Penicillium *species*, and *Cladosporium species* at the same concentration by well diffusion technique [16,17,29–33]. Standard antibacterial norfloxacin and antifungal fluconazole were also screened under similar conditions for a comparison. The zones of inhibition formed were measured [34] in millimeters and are shown in Table 1.

Antimicrobial activity of 1,5-diaryl-3-thioxo-2,4-diazaspiro[5.5]undecane-7,11-dione/1,5-diaryl-2,4-diazaspiro[5.5]undecane-3,7,11-trione (**1a-c/1′a-c)** and 7,11-diaryl-9-thioxo-2,4,8,10-tetrazaspiro[5.5]undecane-1,3, 5-trione/7,11-diaryl-2,4,8,10-tetrazaspiro[5.5]undecane-1,3,5,9 tetraone (**1d-e/1′d-e)**.

It was interesting to observe summarily that all the compounds **1a-f** and **1′a-f** were highly effective against *E. coli* for antibacterial and *Cladosporium* species for antifungal activity and noneffective against other species.

EXPERIMENTAL

General. Melting points were measured in open capillaries on perfit melting point apparatus and are incorrect. IR spectra on KBr were recorded on Brucker-4800 infrared spectrometer. NMR and EIMS/HRMS spectra were recorded on Brucker AC-400 (400 MHz and 100 MHz) and JEOL D-300 mass spectrometer, respectively. Elemental analysis was carried out on simple CHNS analyzer (CHNS-932, LECO Corporation, USA). ^{1}H and ^{13}C chemical shifts are reported in parts per million (ppm) from tetramethylsilane (TMS) as internal standard. All experiments were performed in oven dried glass apparatus. SISCO silica was used as adsorbent for TLC (0.5 mm thick plates) and TLC plates were eluted with 1:9 ratios of ethyl acetate and *n*-hexane. The column chromatography was performed over silica gel (60–120 mesh) with graded solvent systems of ethyl acetate-pet. ether (60–80).

General procedure for the synthesis of 1,5-diaryl-3-thioxo-2,4-diazaspiro[5.5]undecane-7,11-dione/1,5-diaryl-2,4-diazaspiro[5.5]undecane-3,7,11-trione (1a-f/1′a-f). To a magnetically stirred melt of aromatic aldehyde (3 moles) and cyclic active methylene compound (cyclohexane-1,3-dione or barbituric acid) (1 mole) at (70–80°C); thiourea/urea (1 mole) and $NiCl_2$ + KI (0.1 mole) were added at this temperature. The mixture was stirred at 110°C for 6–8 h. After the completion of the reaction as monitored by TLC, the reaction mixture was cooled at room temperature and poured onto crushed ice and again stirred for 10–20 min. The solid thus separated was filtered, washed with cold water and crystallized from ethanol to get **1a-f/1′a-f.**

1,5-Bis-(p-methylphenyl)-3-thioxo-2,4-diazaspiro[5.5] undecane-7,11-dione (1a). Yield 78%; Mp 210–212°C; IR (KBR, v, cm^{-1}): 1185 (C=S), 1650–1710 (C=O), 3360–3430 (NH); ^{1}H NMR ($CDCl_3$) δ: 2.00–2.35 (m, 6H, 3 × CH_2), 2.40 (s, 3H, CH_3), 2.43 (s, 3H, CH_3, 4.99 (s, 2H, 1,5–Hs), 7.00–7.05 (m, 8H, ArHs), and 7.90–8.20 (bs, 2H, NH, D_2O exchangable).

Anal. Calcd. for $C_{23}H_{24}N_2O_2S$: C, 70.40; H, 6.12; N, 7.14; S, 8.16. Found: C, 70.23; H, 6.14; N, 7.16; S, 8.19.

1,5-Bis-(4-methoxyphenyl)-3-thioxo-2,4-diazaspiro[5.5]undecane-7,11-dione (1b). Yield 75%; Mp 204–206°C; IR (KBR, v, cm^{-1}): 1180 (C=S), 1620–1700 (C=O), 3350–3420 (NH); ^1H NMR ($CDCl_3$) δ: 1.90–2.30 (m, 6H, 3 × CH_2), 3.70 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 4.90 (s, 2H, 1,5–Hs), 6.75–7.05 (m, 8H, ArHs), and 7.88–8.00 (bs, 2H, NH); ^{13}C NMR δ: 16.2, 38.5, 47.8, 56.1, 90.5, 114.0, 129.1, 131.0, 159.2, 163.1, 211.1. *Anal*. Calcd. for $C_{23}H_{24}N_2O_4S$: C, 65.09; H, 5.66; N, 6.60; S, 7.54. Found: C, 64.91; H, 5.68; N, 6.53; S, 7.59.

1,5-Bis-(3,4-dimethoxyphenyl)-3-thioxo-2,4-diazaspiro[5.5]undecane-7,11-dione (1c). Yield 75%; Mp 230–232°C; IR (KBR, v, cm^{-1}): 1178 (C=S), 1670–1705 (C=O), 3290–3430 (NH); ^1H NMR($CDCl_3$) δ: 1.95–2.35 (m, 6H, 3 × CH_2), 3.65 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.75 (s, 3H,OCH_3), 4.87 (s, 2H, 1,5-H), 6.60–6.90 (m, 6H, ArHs) and 7.82–8.01 (bs, 2H, NH); ^{13}C NMR δ: 16.4, 38.3, 48.9, 56.1, 90.0, 114.8, 123.5, 130.8, 152.5, 170.1, 211.4. *Anal*. Calcd. for $C_{25}H_{28}N_2O_6S$: C, 61.98; H, 5.78; N, 5.78; S, 6.61. Found: C, 61.80; H, 5.80; N, 5.82; S, 6.55.

7,11-Bis-(p-methylphenyl)-9-thioxo-2,4,8,10-tetrazaspiro[5.5]undecane-1,3,5-trione (1d). Yield 77%; Mp 240–242°C; IR (KBR, v, cm^{-1}): 1175 (C=S), 1670–1705 (C=O), 3290–3430 (NH); ^1H NMR ($CDCl_3$) δ: 2.25 (s, 3H, CH3), 2.30 (s, 3H, CH3), 5.29 (s, 2H, 7, 11–Hs), 7.10–7.20 (m, 8H, ArHs), and 7.89–8.20 (bs, 4H, NH). *Anal*. Calcd. for $C_{21}H_{20}N_4O_3S$: C, 61.76; H, 4.90; N, 13.72; S, 7.84. Found: C, 61.58; H, 4.91; N, 13.75; S, 7.73.

7,11-Bis-(4-methoxyphenyl)-9-thioxo-2,4,8,10-tetrazaspiro[5.5]undecane-1,3,5-trione (1e). Yield 82%; Mp 234–236°C; IR (KBR, v, cm^{-1}): 1182 (C=S), 1660–1700 (C=O), 3280–3425 (NH); ^1H NMR ($CDCl_3$) δ: 3.72 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 5.27 (s, 2H, 7, 11–Hs), 6.90–7.10 (m, 8H, ArHs), and 7.87–8.22 (bs, 4H, NH); ^{13}C NMR δ: 52.2, 56.8, 72.5, 114.3, 122.8, 132.4, 140.5, 146.0, 150.2, 151.7, 163.0, 176.8. *Anal*. Calcd. for $C_{21}H_{20}N_4O_5S$: C, 57.27; H, 4.54; N, 12.72; S, 7.27. Found: C, 57.09; H, 4.55; N, 12.75; S, 7.23.

7,11-Bis-(3,4-dimethoxyphenyl)-9-thioxo-2,4,8,10-tetrazaspiro[5.5]undecane-1,3,5-trione (1f). Yield 86%; Mp 244–246°C; IR (KBR, v, cm^{-1}): 1180 (C=S), 1665–1700 (C=O), 3270–3420 (NH); ^1H NMR ($CDCl_3$) δ: 3.68 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 5.25 (s, 2H, 7,11-H), 6.67–6.90 (m, 6H, ArHs), and 7.89–8.90 (bs,4H,NH); ^{13}C NMR δ: 52.4, 56.2, 71.4, 114.7, 115.0, 121.8, 132.2, 139.2, 144.7, 147.5, 163.1, 176.1. *Anal*. Calcd. for $C_{23}H_{24}N_4O_7S$: C, 55.20; H, 4.8; N, 11.2; S, 6.4. Found: C, 55.01; H, 5.0; N, 11.5; S, 6.9.

1,5-Bis-(p-methylphenyl)-2,4-diazaspiro[5.5]undecane-3,7,11-trione (1′a). Yield 90%; Mp 212–214°C; IR (KBR, v, cm^{-1}): 1660–1700 (C=O), 3382–3470 (NH). ^1H NMR ($CDCl_3$) δ: 2.10–2.25 (m, 6H, 3 × CH_2), 2.43 (s, 3H, CH3), 2.45 (s, 3H, CH_3), 4.87–5.01 (s, 2H, 1,5–Hs), 6.95–7.10 (m, 8H, ArHs), and 7.80–8.15 (bs, 2H, NH). *Anal*. Calcd. for $C_{23}H_{24}N_2O_3$: C, 73.40; H, 6.38; N, 7.44. Found: C, 73.21; H, 6.40; N, 7.38.

1,5-Bis-(4-methoxyphenyl)-2,4-diazaspiro[5.5]undecane-3,7,11-trione (1′b). Yield 80%; Mp 210–211°C; IR (KBR, v, cm^{-1}): 1675–1710 (C=O), 3370–3430 (NH); ^1H NMR ($CDCl_3$) δ: 2.15–2.30 (m, 6H, 3 × CH_2), 3.55 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.97 (s, 2H, 1,5–Hs), 6.90–7.15 (m, 8H, ArHs), and 7.85–8.20 (bs, 2H, NH); ^{13}C NMR δ: 15.5, 40.5, 44.8, 59.7, 92.4, 119.7, 139.3, 142.0, 165.2, 167.6, 218.9. *Anal*. Calcd. for $C_{23}H_{24}N_2O_5$: C, 67.64; H, 5.88; N, 6.86. Found: C, 67.46; H, 5.90; N, 6.74.

1,5-Bis-(3,4-dimethoxyphenyl)-2,4-diazaspiro[5.5]undecane-3,7,11-trione (1′c). Yield 87%; Mp 232–234°C; IR (KBR, v, cm^{-1}): 1670–1705 (C=O), 3390–3440 (NH); ^1H NMR ($CDCl_3$) δ: 2.00–2.10 (m, 6H, 3 × CH_2), 3.60 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 4.83 (s, 2H, 1,5-H), 6.82–7.10 (m, 6H, ArHs), and 7.80–8.15 (bs, 2H, NH); ^{13}C NMR δ: 16.2, 38.5, 49.1, 56.3, 90.3, 115.2, 122.5, 131.4, 147.8, 154.3, 211.2. *Anal*. Calcd. for $C_{25}H_{28}N_2O_7$: C, 64.10; H, 5.98; N, 5.98. Found: C, 63.92; H, 5.96; N, 5.91.

7,11-Bis-(p-methylphenyl)-2,4,8,10-tetrazaspiro[5.5]undecane-1,3,5,9-tetraone (1′d). Yield 80%; Mp 246–248°C; IR (KBR, v, cm^{-1}): 1672–1710 (C=O), 3380–3460 (NH); ^1H NMR ($CDCl_3$) δ: 2.20 (s, 3H, CH3), 2.25 (s, 3H, CH3), 5.15 (s, 2H, 7, 11–Hs), 7.00–7.10 (m, 8H, ArHs), and 7.80–8.15 (bs, 4H, NH). *Anal*. Calcd. for $C_{21}H_{20}N_4O_4$: C, 64.28; H, 5.10; N, 14.28. Found: C, 64.10; H, 5.12; N, 14.25.

7,11-Bis-(4-methoxyphenyl)-2,4,8,10-tetrazaspiro[5.5]undecane-1,3,5,9-tetraone (1′e). Yield 90%; Mp 240–242°C; IR (KBR, v, cm^{-1}): 1680–1720 (C=O), 3270–3420 (NH); ^1H NMR ($CDCl_3$) δ: 3.70 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 5.20 (s, 2H, 7, 11–Hs), 6.80–7.20 (m, 8H, ArHs), and 7.82–8.20 (bs, 4H, NH). *Anal*. Calcd. for $C_{21}H_{20}N_4O_6$: C, 59.43; H, 4.71; N, 13.20. Found: C, 59.25; H, 4.72; N, 13.14.

7,11-Bis-(3,4-dimethoxyphenyl)-2,4,8,10-tetrazaspiro[5.5]undecane-1,3,5,9-tetraone (1′f). Yield 87%; Mp 250–252°C; IR (KBR, v, cm^{-1}): 1675–1710 (C=O), 3280–3450 (NH); ^1H NMR ($CDCl_3$) δ: 3.65 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 5.15 (s, 2H, 7,11-H), 6.87–7.10 (m, 6H, ArHs), and 7.60–8.40 (bs, 4H, NH); ^{13}C NMR δ: 55.6, 59.8, 86.4, 118.2, 120.0, 128.8, 138.9, 140.7, 148.8, 150.8, 163.9, 180.1. *Anal*. Calcd. for $C_{23}H_{24}N_4O_8$: C, 57.02; H, 4.95; N, 11.57. Found: C, 56.84; H, 4.97; N, 11.61.

General procedure for the synthesis of 5-aryl-1-methyl-3-thioxo-2,4-diazaspiro[5.5]undec-1-en-7-one/5-aryl-1-methyl-2,4-diazaspiro[5.5]undec-1-ene-3,7-dione (2a-e/2′a-e). These heterocycles were prepared by following the same procedure as mentioned for (**1a-f/1′a-f**) by condensing appropriate aromatic aldehyde, thiourea/urea, and 2-acetylcyclohexanone in the mole ratio of 1:1:1 simply by stirring at 100–110°C for 6 h without using any solvent and catalyst. The work of the reaction was done as usual by pouring ice cold water on to the reaction mixture residue. The spectral characterizations of the synthesized compounds are as follows:

1-Methyl-5-phenyl-3-thioxo-2,4-diazaspiro[5.5]undec-1-en-7-one (2a). Yield 77%; Mp 170–172°C; IR (KBR, v, cm^{-1}): 1180 (C=S), 1680–1700 (C=O), 3420 (NH); ^1H NMR ($CDCl_3$) δ: 1.32 (s, 3H, CH3), 1.95–2.30 (m, 8H, 4 × CH_2), 5.26 (s, 1H, 5-H), 7.01–7.03 (m, 5H, ArHs), and 9.01 (bs, 1H, NH). *Anal*. Calcd. for $C_{16}H_{18}N_2OS$: C, 67.13; H, 6.29; N, 9.79; S, 11.18. Found: C, 66.92; H, 6.30; N, 9.84; S, 11.23.

1-Methyl-5-(p-methylphenyl)-3-thioxo-2,4-diazaspiro[5.5]undec-1-en-7-one (2b). Yield 74%; Mp 178–180°C; IR (KBR, v, cm^{-1}): 1175 (C=S), 1670–1690 (C=O), 3410 (NH); ^1H NMR ($CDCl_3$) δ: 1.30 (s, 3H, CH3), 1.90–2.30 (m, 8H, 4 × CH_2), 5.20 (s, 1H, H-5), 7.01–7.01 (m, 4H, ArHs), and 9.01

(bs, 1H, NH);^{13}C NMR δ: 12.2, 20.6, 22.1, 27.4, 36.9, 38.2, 45.1, 62.0, 128.0, 129.2, 134.7, 136.2, 164.4, 175.0, 211.2. *Anal*. Calcd. for $C_{17}H_{20}N_2OS$: C, 68.0; H, 6.66; N, 9.33; S, 10.66. Found: C, 67.79; H, 6.68; N, 9.35; S, 10.69.

5-(4-Methoxyphenyl)-1-methyl-3-thioxo-2,4-diazaspiro[5.5]undec-1-en-7-one (2c). Yield 70%; Mp 184–186°C; IR (KBR, v, cm^{-1}): 1182 (C=S), 1665–1695 (C=O), 3415 (NH); ^{1}H NMR ($CDCl_3$) δ: 1.22 (s, 3H, CH_3), 1.79–2.25 (m, 8H, 4 × CH_2), 3.70 (s, 3H, OCH_3), 5.18 (s, 1H, H-5), 6.98–7.01 (m, 4H, ArHs), and 8.90 (bs, 1H, NH). *Anal*. Calcd. for $C_{17}H_{20}N_2O_2S$: C, 64.55; H, 6.32; N, 8.86; S, 10.12. Found: C, 64.36; H, 6.34; N, 8.89; S, 10.15.

5-(3,4-Dimethoxyphenyl)-1-methyl-3-thioxo-2,4-diazaspiro[5.5]undec-1-en-7-one (2d). Yield 72%; Mp 192–193°C; IR (KBR, v, cm^{-1}): 1178 (C=S), 1680–1700 (C=O), 3400 (NH); ^{1}H NMR ($CDCl_3$) δ: 1.15 (s, 3H, CH_3), 1.74–2.29 (m, 8H, 4 × CH_2), 3.62 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 5.15 (s, 1H, H-5), 6.98–7.00 (m, 3H, ArHs), and 8.75 (bs, 1H, NH). *Anal*. Calcd. for $C_{18}H_{22}N_2O_3S$: C, 62.42; H, 6.35; N, 8.09; S, 9.24. Found: C, 62.24; H, 6.37; N, 8.14; S, 9.28.

5-(p-Chlorophenyl)-1-methyl-3-thioxo-2,4-diazaspiro[5.5]undec-1-en-7-one (2e). Yield 74%; Mp 220–222°C; IR (KBR, v, cm^{-1}): 1180 (C=S), 1650–1690 (C=O), 3380 (NH); ^{1}H NMR ($CDCl_3$) δ: 1.25 (s, 3H, CH3), 1.80–2.20 (m, 8H, 4 × CH_2), 5.29 (s, 1H, H-5), 7.05–7.25 (m, 4H, ArHs), and 9.05 (bs, 1H, NH);^{13}C NMR δ: 12.8, 22.2, 27.8, 38.6, 39.2, 45.2, 50.2, 128.7, 131.0, 137.5, 164.4, 173.8, 211.5. *Anal*. Calcd. for $C_{16}H_{17}N_2OSCl$: C, 59.90; H, 5.30; N, 8.73; S, 9.98. Found: C, 59.71; H, 5.32; N, 8.79; S, 9.95.

1-Methyl-5-phenyl-2,4-diazaspiro[5.5]undec-1-ene-3,7-dione (2′a). Yield 77%; Mp 172–174°C; IR (KBR, v, cm^{-1}): 1660–1705 (C=O), 3470 (NH); ^{1}H NMR ($CDCl_3$) δ: 1.32 (s, 3H, CH_3), 1.80–2.05 (m, 8H, 4 × CH_2), 5.76 (s, 1H, 5-H), 7.41–7.83 (m, 5H, ArHs), and 9.11 (bs, 1H, NH). *Anal*. Calcd. for $C_{16}H_{18}N_2O_2$: C, 71.11; H, 6.66; N, 10.37. Found: C, 71.19; H, 6.62; N, 10.40.

1-Methyl-5-(p-methylphenyl)-2,4-diazaspiro[5.5]undec-1-ene-3,7-dione (2′b). Yield 76%; Mp 180–182°C; IR (KBR, v, cm^{-1}): 1670–1700 (C=O), 3466 (NH); ^{1}H NMR ($CDCl_3$) δ: 1.20 (s, 3H, CH_3), 1.95–2.20 (m, 8H, 4 × CH_2), 4.90 (s, 1H, H-5), 6.90–7.21 (m, 4H, ArHs), and 9.28 (bs, 1H, NH); ^{13}C NMR δ: 15.2, 22.8, 27.8, 30.4, 34.8, 38.9, 46.2, 60.2, 126.0, 128.1, 139.5, 149.8, 169.8, 185.8, 230.2**.** *Anal*. Calcd. for $C_{17}H_{20}N_2O_2$: C, 71.83; H, 7.04; N, 9.85. Found: C, 71.64; H, 7.06; N, 9.80.

5-(4-Methoxyphenyl)-1-methyl-2,4-diazaspiro[5.5]undec-1-ene-3,7-dione (2′c). Yield 74%; Mp 189–191°C; IR (KBR, v, cm^{-1}): 1675–1692 (C=O), 3410 (NH); ^{1}H NMR ($CDCl_3$) δ: 1.32 (s, 3H, CH_3), 2.10–2.25 (m, 8H, 4 × CH_2), 3.72 (s, 3H, OCH_3), 4.95 (s, 1H, H-5), 6.90–7.00 (m, 4H, ArHs), and 8.72 (bs, 1H, NH). *Anal*. Calcd. for $C_{17}H_{20}N_2O_3$: C, 68.0; H, 6.6; N, 9.33. Found: C, 67.82; H, 6.8; N, 9.38.

5-(3,4-Dimethoxyphenyl)-1-methyl-2,4-diazaspiro[5.5]undec-1-ene-3,7-dione (2′d). Yield 76%; Mp 191–201°C; IR (KBR, v, cm^{-1}): 1690–1710 (C=O), 3410 (NH); ^{1}H NMR ($CDCl_3$) δ: 1.15 (s, 3H, CH_3), 2.05–2.29 (m, 8H, 4 × CH_2), 3.7 0 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 5.05 (s, 1H, H-5), 6.88–7.10 (m, 3H, ArHs), and 8.76 (bs, 1H, NH). *Anal*. Calcd. for $C_{18}H_{22}N_2O_4$: C, 65.45; H, 6.66; N, 8.48. Found: C, 65.27; H, 6.68; N, 8.54.

5-(p-Chlorophenyl)-1-methyl-2,4-diazaspiro[5.5]undec-1-ene-3,7-dione (2′e). Yield 72%; Mp 221–223°C; IR (KBR, v, cm^{-1}): 1670–1700 (C=O), 3420 (NH); ^{1}H NMR ($CDCl_3$) δ: 1.30 (s, 3H, CH_3), 1.70–2.10 (m, 8H, 4 × CH_2), 4.99 (s, 1H, H-5), 7.00–7.25 (m, 4H, ArHs), and 8.90 (bs, 1H, NH); ^{13}C NMR δ: 15.7, 25.8, 28.9, 39.9, 40.5, 50.8, 54.8, 130.2, 134.6, 150.3, 168.4, 178.8, 220.4. Anal. Calcd. for $C_{16}H_{17}N_2O_2Cl$: C, 63.05; H, 5.58; N, 9.19. Found: C, 62.87; H, 5.59; N, 9.24.

General procedure for the synthesis of reduced 4-aryl/heteroaryl-2-thioxo-quinazolin-5-one, 4-aryl/heteroaryl-quinazoline-2,5-dione (3a-e/3′a-e), 4-aryl/heteroaryl quinazoline-2-thione/4-aryl/heteroaryl-quinazolin-2-one (4a-e/4′a-e), and 5-aryl-7-thioxo pyrimidopyrimidine-2,4-dione/5-aryl-pyrimidopyrimidine-2,4,7-trione (5a–d/5′a-d). A highly grinded and finally powdered homogeneous trinary mixture of appropriate aromatic/hetero aromatic aldehyde (1 mole), thiourea/urea (1 mole), and cyclohexane-1,3-dione/cyclohexanone/barbituric acid (1 mole) in 70–80 mL of methanol was refluxed for 10–12 h. After the completion of reaction as monitored by TLC, the reaction mixture was concentrated to one-third of its volume and was then poured onto ice cold water. The precipitate separated out, filtered, washed, dried, and further recrystallized from ethanol to get the required product.

4-(p-Methylphenyl)-2-thioxo-1,2,3,4,5,6,7,8-octahydroquinazolin-5-one (3a). Yield 80%; Mp 225–227°C; IR (KBR, v, cm^{-1}): 1172 (C=S), 1692 (C=O), 3430–3442 (NH); ^{1}H NMR ($CDCl_3$) δ: 1.60–2.38 (m, 6H, 3 × CH_2), 2.30 (s, 3H, CH3), 4.89 (s, 1H, 4–H), 7.02–7.24 (m, 4H, ArHs), 7.80 (bs, 1H, NH), and 9.60 (bs, 1H, NH); ^{13}C NMR δ: 16.8, 22.4, 26.8, 34.6, 50.2, 115.3, 116.8, 118.2, 118.9, 124.6, 130.4, 135.3, 144.8, 160.6, 197.2. *Anal*. Calcd. for $C_{15}H_{16}N_2OS$: C, 66.66; H, 5.88; N, 10.29; S, 11.76. Found: C, 66.48; H, 5.85; N, 10.29; S, 11.73.

4-(4-Methoxyphenyl)-2-thioxo-1,2,3,4,5,6,7,8-octahydroquinazolin-5-one (3b). Yield 78%; Mp 249–251°C; IR (KBR, v, cm^{-1}): 1190 (C=S), 1620 (C=O), 3435–3445 (NH); ^{1}H NMR ($CDCl_3$) δ: 1.45–2.30 (m, 6H, 3 × CH_2), 3.73 (s, 3H, OCH_3), 4.74 (s, 1H, 4–H), 6.90–7.21 (m, 4H, ArHs), 7.72 (bs, 1H, NH), and 9.56 (bs, 1H, NH). *Anal*. Calcd. for $C_{15}H_{16}N_2O_2S$: C, 62.50; H, 5.55; N, 9.72; S, 11.11. Found: C, 62.34; H, 5.59; N, 9.69; S, 11.08.

4-(3,4-Dimethoxyphenyl)-2-thioxo-1,2,3,4,5,6,7,8-octahydroquinazolin-5-one (3c). Yield 76%; Mp 240–242°C; IR (KBR, v, cm^{-1}): 1178 (C=S), 1620 (C=O), 3435–3445 (NH); ^{1}H NMR ($CDCl_3$) δ: 1.40–2.20 (m, 6H, 3 × CH_2), 3.70 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 4.70 (s, 1H, 4–H), 6.90–7.25 (m, 3H, ArHs), 7.72 (bs, 1H, NH), 9.55 (s, 1H, NH); ^{13}C NMRδ: 16.8, 34.6, 40.6, 48.1, 56.1, 113.4, 114.2, 114.7, 120.6, 135.5, 142.2, 145.4, 147.2, 156.6, 197.4. *Anal*. Calcd. for $C_{16}H_{18}N_2O_3S$: C, 60.37; H, 5.6; N, 8.58; S, 10.06. Found: C, 60.19; H, 5.7; N, 8.55; S, 10.03.

4-(Indol-3-yl)-2-thioxo–1,2,3,4,5,6,7,8-octahydroquinazolin-5-one (3d). Yield 74%; Mp 253–257°C; IR (KBR, v, cm^{-1}): 1180 (C=S), 1680 (C=O), 3390–3445 (NH); ^{1}H NMR ($CDCl_3$) δ: 1.70–2.46 (m, 6H, 3 × CH_2), 5.65 (s, 1H, 4–H), 7.04–8.29 (m, 5H, ArHs), 8.59 (s, 1H, exch. NH), 9.41 (s, 1H, NH), and 10.92 (s, 1H, exch. NH); ^{13}C NMR δ: 19.8, 34.6, 40.2, 52.6, 111.0, 111.2, 112.3, 119.2, 120.2, 121.3, 122.5,

131.4, 136.2, 155.8, 178.0, and 198.0. *Anal*. Calcd. for $C_{16}H_{15}N_3OS$: C, 64.64; H, 5.0; N, 14.14; S, 10.77. Found: C, 64.46; H, 5.2; N, 14.16; S, 10.74.

4-(1,3-Diphenyl-1H-pyrazol-4-yl)-2-thioxo-1,2,3,4,5,6,7,8-octahydroquinazolin-5-one (3e). Yield 72%; Mp 255–257°C; IR (KBR, v, cm^{-1}): 1182 (C=S), 1680 (C=O), 3435–3440 (NH); ^1H NMR ($CDCl_3$) δ: 1.85–2.45 (m, 6H, 3 × CH_2), 5.52 (s, 1H, 4–H), 7.01–7.80 (m, 10H, ArHs), 7.84 (s, 1H, 5′H), 7.90 (s, 1H, NH), 10.80 (s, 1H, NH); ^{13}C NMR δ: 20.0, 35.6, 40.9, 45.2, 111.6, 117.8, 126.0, 128.4, 129.2, 139.8, 155.4, 157.2, 178.4, 197.7. *Anal*. Calcd. for $C_{23}H_{20}N_4OS$: C, 69.0; H, 5.0; N, 14.0; S, 8.0. Found: C, 68.83; H, 5.2; N, 13.96; S, 8.5.

4-(p-Methylphenyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2 5-dione (3′a). Yield 82%; Mp 222–223°C; IR (KBR, v, cm^{-1}): 1660 (C=O), 3430–3442 (NH); ^1H NMR ($CDCl_3$) δ: 1.48–2.20 (m, 6H, 3 × CH_2), 2.35 (s, 3H, CH3), 4.89 (s, 1H, 4–H), 6.98–7.40 (m, 4H, ArHs), 7.70 (bs, 1H, NH), and 9.55 (bs, 1H, NH). *Anal*. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.31; H, 6.25; N, 10.93. Found: C, 70.12; H, 6.23; N, 10.91.

4-(4-Methoxyphenyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione (3′b). Yield 74%; Mp 230–232°C; IR (KBR, v, cm^{-1}): 16,700 (C=O), 3432–3440 (NH); ^1H NMR ($CDCl_3$) δ: 1.40–2.15 (m, 6H, 3 × CH_2), 3.71 (s, 3H, OCH_3), 4.80 (s, 1H, 4–H), 6.92–7.20 (m, 4H, ArHs), 7.70 (bs, 1H, NH), and 9.58 (bs, 1H, NH). *Anal*. Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.17; H, 5.8; N, 10.29. Found: C, 65.98; H, 5.6; N, 10.26.

4-(3,4-Dimethoxyphenyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione (3′c). Yield 80%; Mp 241–243°C; IR (KBR, v, cm^{-1}): 1675 (C=O), 3460–3442 (NH); ^1H NMR ($CDCl_3$) δ: 1.60–2.40 (m, 6H, 3 × CH_2), 3.72 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 5.05 (s, 1H, 4–H), 7.05–7.15 (m, 3H, ArHs), 7.70 (bs, 1H, NH), 9.45 (s, 1H, NH); ^{13}C NMR δ: 15.2, 38.6, 44.8, 50.1, 58.2, 115.7, 120.7, 122.8, 130.6, 140.5, 148.2, 150.5, 155.2, 158.9, 200.7. *Anal*. Calcd. for $C_{16}H_{18}N_2O_4$: C, 63.57; H, 5.96; N, 9.27. Found: C, 63.38; H, 5.98; N, 9.24.

4-(Indol-3-yl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione (3′d). Yield 76%; Mp 256–258°C; IR (KBR, v, cm^{-1}): 1685 (C=O), 3370–3440 (NH); ^1H NMR ($CDCl_3$) δ: 1.90–2.30 (m, 6H, 3 × CH_2), 5.25 (s, 1H, 4–H), 7.10–7.25 (m, 5H, ArHs), 7.92 (s, 1H, exch. NH), 9.42 (s, 1H, NH), and 10.82 (s, 1H, exch. NH); ^{13}C NMR δ: 18.9, 38.9, 42.5, 55.6, 118.0, 120.2, 126.9, 129.2, 130.5, 132.3, 136.5, 139.4, 140.2, 158.8, 188.0, 200.8. *Anal*. Calcd. for $C_{16}H_{15}N_3O_2$: C, 68.32; H, 5.33; N, 14.94. Found: C, 68.14; H, 5.31; N, 14.90.

4-(1,3-Diphenyl-1H-pyrazol-4-yl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione (3′e). Yield 72%; Mp 256–258°C; IR (KBR, v, cm^{-1}): 1620 (C=O), 3435–3445 (NH); ^1H NMR ($CDCl_3$) δ: 1.95–2.40 (m, 6H, 3 × CH_2), 5.25 (s, 1H, 4–H), 7.00–7.60 (m, 10H, ArHs), 7.65 (s, 1H, 5′H), 9.80 (s, 1H, NH), 10.65 (s, 1H, NH); ^{13}C NMR δ: 20.8, 34.2, 42.9, 45.8, 115.6, 118.5, 122.0, 125.4, 130.2, 135.8, 145.4, 155.2, 180.7, 199.8. *Anal*. Calcd. for $C_{23}H_{20}N_4O_2$: C, 71.87; H, 5.20; N, 14.58. Found: C, 71.79; H, 5.21; N, 14.53.

4-(p-Methylphenyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione (4a). Yield 75%; Mp 228–230°C; IR (KBR, v, cm^{-1}): 1181 (C=S), 3438–3445 (NH); ^1H NMR ($CDCl_3$) δ: 1.62–2.32 (m, 8H, 4 × CH_2), 2.35 (s, 3H, CH_3), 4.86 (s, 1H, 4–H), 7.02–7.20 (m, 4H, ArHs), 7.90 (bs, 1H, NH), and 10.7 (bs, 1H, NH). *Anal*. Calcd. for $C_{15}H_{18}N_2S$: C, 69.76; H, 6.9; N, 10.85; S, 12.40. Found: C, 69.68; H, 7.1; N, 10.81; S, 12.20.

4-(4-Methoxyphenyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione (4b). Yield 77%; Mp 256–258°C; IR (KBR, v, cm^{-1}): 1168 (C=S), 3398–3442 (NH); ^1H NMR ($CDCl_3$) δ: 1.42–2.32 (m, 8H, 4 × CH_2), 3.71 (s, 3H, OCH_3), 4.70 (s, 1H, 4–H), 6.92–7.23 (m, 4H, ArHs), 7.70 (bs, 1H, NH), and 9.52 (bs, 1H, NH). *Anal*. Calcd. for $C_{15}H_{18}N_2OS$: C, 65.69; H, 6.56; N, 10.21; S, 11.67. Found: C, 65.51; H, 6.55; N, 10.23; S, 11.70.

4-(3,4-Dimethoxyphenyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione (4c). Yield 78%; Mp 256–258°C; IR (KBR, v, cm^{-1}): 1175 (C=S), 3435–3445 (NH); ^1H NMR ($CDCl_3$) δ: 1.40–2.20 (m, 8H, 4 × CH_2), 3.70 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 4.70 (s, 1H, 4–H), 6.90–7.25 (m, 3H, ArHs), 7.72 (bs, 1H, NH), and 9.55 (bs, 1H, NH). *Anal*. Calcd. for $C_{16}H_{20}N_2O_2S$: C, 63.15; H, 6.57; N, 9.2; S, 10.52. Found: C, 62.96; H, 6.59; N, 9.0; S, 10.59.

4-(Indol-3-yl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione (4d). Yield 72%; Mp 254–256°C; IR (KBR, v, cm^{-1}): 1172 (C=S), 3367–3445 (NH); ^1H NMR ($CDCl_3$) δ: 1.72–2.41 (m, 8H, 4 × CH_2), 5.60 (s, 1H, 4–H), 7.8–8.20 (m, 5H, ArHs), 8.50 (s, 1H, exch. NH), 9.31 (s, 1H, NH), and 10.23 (s, 1H, exch. NH). *Anal*. Calcd. for $C_{16}H_{17}N_3S$: C, 67.84; H, 6.0; N, 14.84; S, 11.30. Found: C, 67.66; H, 6.2; N, 14.89; S, 11.35.

4-(1,3-Diphenyl-1H-pyrazol-4-yl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione (4e). Yield 76%; Mp 260–262°C; IR (KBR, v, cm^{-1}): 1185 (C=S), 3440–3445 (NH); ^1H NMR ($CDCl_3$) δ: 1.92–2.43 (m, 8H, 4 × CH_2), 5.56 (s, 1H, 4–H), 7.02–7.82 (m, 11H, ArHs and 5′H),7.92 (s, 1H, exch. NH), and 10.83 (s, 1H, exch. NH); ^{13}C NMR δ: 21.3, 25.8, 32.2, 38.4, 46.3, 112.2, 115.7, 126.3, 128.3, 129.8, 139.3, 152.8, 157.1, 178.3. *Anal*. Calcd. for $C_{23}H_{22}N_4S$: C, 74.09; H, 5.69; N, 14.50; S, 8.29. Found: C, 73.92; H, 5.7; N, 14.59; S, 8.24.

4-(p-Methylphenyl)-1,2,3,4,5,6,7,8-octahydroquinazolin-2-one (4′a). Yield 78%; Mp 225–227°C; IR (KBR, v, cm^{-1}): 1678 (C=O), 3338–3440 (NH); ^1H NMR ($CDCl_3$) δ: 1.72–2.30 (m, 8H, 4 × CH_2), 2.30 (s, 3H, CH_3), 4.96 (s, 1H, 4–H), 7.00–7.10 (m, 4H, ArHs), 7.95 (bs, 1H, NH), and 10.2 (bs, 1H, NH). *Anal*. Calcd. for $C_{15}H_{18}N_2O$: C, 74.38; H, 7.43; N, 11.57. Found: C, 74.18; H, 7.45; N, 10.62.

4-(4-Methoxyphenyl)-1,2,3,4,5,6,7,8-octahydroquinazolin-2-one (4′b). Yield 75%; Mp 251–253°C; IR (KBR, v, cm^{-1}): 1670 (C=O), 3394–3435 (NH); ^1H NMR ($CDCl_3$) δ: 1.70–2.31 (m, 8H, 4 × CH_2), 3.73 (s, 3H, OCH_3), 4.85 (s, 1H, 4–H), 7.00–7.23 (m, 4H, ArHs), 7.85 (bs, 1H, NH), and 10.5 (bs, 1H, NH). *Anal*. Calcd. for $C_{15}H_{18}N_2O_2$: C, 69.76; H, 6.97; N, 1 0.85. Found: C, 69.68; H, 6.99; N, 10.92.

4-(3,4-Dimethoxyphenyl)-1,2,3,4,5,6,7,8-octahydroquinazolin-2-one (4′c). Yield 80%; Mp 252–254°C; IR (KBR, v, cm^{-1}): 1675 (C=O), 3490–3443 (NH); ^1H NMR ($CDCl_3$) δ: 1.70–2.25 (m, 8H, 4 × CH_2), 3.72 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 4.90 (s, 1H, 4–H), 7.10–7.25 (m, 3H, ArHs), 7.82 (bs, 1H, NH), and 10.2(bs, 1H, NH). *Anal*. Calcd. for $C_{16}H_{20}N_2O_3$: C, 66.66; H, 6.94; N, 9.72. Found: C, 66.48; H, 6.96; N, 9.68.

4-(Indol-3-yl)-1,2,3,4,5,6,7,8-octahydroquinazolin-2-one (4′d). Yield 78%; Mp 255–257°C; IR (KBR, v, cm^{-1}): 1670 (C=O), 3490–3440 (NH); ^1H NMR ($CDCl_3$) δ: 1.72–2.21 (m, 8H, 4 × CH_2), 5.70 (s, 1H, 4–H), 7.7–8.10 (m, 5H, ArHs), 8.65 (s, 1H, exch. NH), 9.85 (s, 1H, NH), and 10.82 (s, 1H, exch. NH). *Anal*. Calcd. for $C_{16}H_{17}N_3O$: C, 71.91; H, 6.36; N, 15.73. Found: C, 71.72; H, 6.38; N, 15.79.

4-(1,3-Diphenyl-1H-pyrazol-4-yl)-1,2,3,4,5,6,7,8-octahydroquinazolin-2-one (4′e). Yield 78%; Mp 264–266°C; IR (KBR, v, cm^{-1}): 1676 (C=O), 3480–3440 (NH); ^1H NMR ($CDCl_3$) δ: 1.70–2.25 (m, 8H, 4 × CH_2), 5.85 (s, 1H, 4–H), 7.10–8.20 (m, 11H, ArHs and 5′H), 8.50 (s, 1H, exch. NH), and 10.70 (s, 1H, exch. NH). *Anal*. Calcd. for $C_{23}H_{22}N_4O$: C, 74.59; H, 5.94; N, 15.13. Found: C, 72.78; H, 5.95; N, 15.15.

5-Phenyl-7-thioxo-1,2,3,4,5,6,7,8-octahydropyrimido[4,5-d]pyrimidine-2,4-dione (5a). Yield 72%; Mp 228–230°C; IR (KBR, v, cm^{-1}): 1178 (C=S), 1665–1710 (C=O), 3310–3450 (NH); ^1H NMR ($CDCl_3$) δ: 5.20 (s, 1H, 5–H), 7.10–7.21 (m, 5H, ArHs), 8.82–8.98 (bs, 2H, NH at 1, 8), 9.56 (bs, 1H, NH at 3), and 10.54 (bs, 1H, NH at 6). *Anal*. Calcd. for $C_{12}H_{10}N_4O_2S$: C, 52.55; H, 3.64; N, 20.43; S, 11.67. Found: C, 52.38; H, 3.60; N, 20.36; S, 11.61.

5-(4-Methoxyphenyl)-7-thioxo-1,2,3,4,5,6,7,8-octahydropyrimido[4,5-d]pyrimidine-2,4-dione (5b). Yield 77%; Mp 232–234°C; IR (KBR, v, cm^{-1}): 1182 (C=S), 1670–1708 (C=O), 3410–3452 (NH); ^1H NMR ($CDCl_3$) δ: 3.73 (s, 3H, OCH_3), 5.30 (s, 1H, 5–H), 6.70–7.20 (m, 4H, ArHs), 8.72–9.12 (bs, 2H, NH at 1, 8), 9.62 (bs, 1H, NH at 3), and 10.55 (bs, 1H, NH at 6); ^{13}C NMR δ: 47.4, 56.1, 85.7, 113.7, 126.4, 130.6, 142.6, 153.5, 155.8, 162.0, 165.5. *Anal*. Calcd. for $C_{13}H_{12}N_4O_3S$: C, 51.31; H, 3.94; N, 18.42; S, 10.52. Found: C, 51.12; H, 3.96; N, 18.33; S, 11.02.

5-(4-Methylphenyl)-7-thioxo-1,2,3,4,5,6,7,8-octahydropyrimido[4,5-d]pyrimidine-2,4-dione (5c). Yield 82%; Mp 254–256°C; IR (KBR, v, cm^{-1}): 1187 (C=S), 1675–1700 (C=O), 3380–3410 (NH); ^1H NMR ($CDCl_3$) δ: 2.22 (s, 3H, CH3), 4.93 (s, 1H, 5–H), 6.98–7.42 (m, 4H, ArHs), 8.80–9.00 (bs, 2H, NH at 1, 8), 9.51 (bs, 1H, NH at 3), and 10.58 (bs, 1H, NH at 6). *Anal*. Calcd. for $C_{13}H_{12}N_4O_2S$: C, 54.16; H, 4.16; N, 19.44; S, 11.11. Found: C, 53.98; H, 4.18; N, 19.38; S, 11.07.

5-(3,4-Dimethoxyphenyl)-7-thioxo-1,2,3,4,5,6,7,8-octahydropyrimido[4,5-d]pyrimidine-2,4-dione (5d). Yield 74%; Mp 271–273°C; IR (KBR, v, cm^{-1}): 1185 (C=S), 1660–1700 (C=O), 3320–3450 (NH); ^1H NMR ($CDCl_3$) δ: 3.68 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 4.79 (s, 1H, 5–H), 6.87–7.35 (m, 3H, ArHs), 8.90–9.20 (bs, 2H, NH at 1, 8), 9.68 (bs, 1H, NH at 3), and 11.96 (bs, 1H, NH at 6). *Anal*. Calcd. for $C_{14}H_{14}N_4O_4S$: C, 50.29; H, 4.19; N, 16.76; S, 9.58. Found: C, 50.11; H, 4.21; N, 16.79; S, 9.64.

5-Phenyl-1,2,3,4,5,6,7,8-octahydropyrimido[4,5-d]pyrimidine-2,4,7-trione (5′a). Yield 75%; Mp 241–243°C; IR (KBR, v, cm^{-1}): 1685–1710 (C=O), 3330–3440 (NH); ^1H NMR ($CDCl_3$) δ: 5.26 (s, 1H, 5–H), 7.05–7.25 (m, 5H, ArHs), 8.85–8.96 (bs, 2H, NH at 1, 8), 9.90 (bs, 1H, NH at 3), and 10.25 (bs, 1H, NH at 6). *Anal*. Calcd. for $C_{12}H_{10}N_4O_3$: C, 55.81; H, 3.87; N, 21.70. Found: C, 55.62; H, 3.89; N, 7.10; S, 21.66.

5-(4-Methoxyphenyl)-1,2,3,4,5,6,7,8-octahydro pyrimido[4,5-d] pyrimidine-2,4,7-trione (5′b). Yield 80%; Mp 260–262°C; IR (KBR, v, cm^{-1}): 1680–1700 (C=O), 3460–3420 (NH); ^1H NMR ($CDCl_3$) δ: 3.70 (s, 3H, OCH_3), 4.85 (s, 1H, 5–H), 6.90–7.30 (m, 4H, ArHs), 8.72–9.12 (bs, 2H, NH at 1, 8), 9.60 (bs, 1H, NH at 3) and 10.58 (bs, 1H, NH at 6); ^{13}C NMR δ: 45.4, 58.2, 90.7, 115.8, 128.9, 132.5, 140.5, 152.8, 156.9, 160.5, 166.8. *Anal*. Calcd. for $C_{13}H_{12}N_4O_4$: C, 54.16; H, 4.16; N, 19.44. Found: C, 53.98; H, 4.18; N, 19.38.

5-(4-Methylphenyl)-1,2,3,4,5,6,7,8-octahydropyrimido[4,5-d]pyrimidine-2,4,7-trione (5′c). Yield 77%; Mp 252–254°C; IR (KBR, v, cm^{-1}): 1685–1700 (C=O), 3385–3420 (NH); ^1H NMR ($CDCl_3$) δ: 2.20 (s, 3H, CH_3), 4.95 (s, 1H, 5–H), 6.90–7.52 (m, 4H, ArHs), 8.85–9.00 (bs, 2H, NH at 1, 8), 9.58 (bs, 1H, NH at 3), and 10.50 (bs, 1H, NH at 6). *Anal*. Calcd. for $C_{13}H_{12}N_4O_3$: C, 57.35; H, 4.41; N, 20.58. Found: C, 57.17; H, 4.42; N, 20.52.

5-(3,4-Dimethoxyphenyl)-1,2,3,4,5,6,7,8-octahydropyrimido[4,5-d]pyrimidine-2,4,7-trione (5′d). Yield 76%; Mp 270–272°C; IR (KBR, v, cm^{-1}): 1670–1705 (C=O), 3330–3470 (NH); ^1H NMR ($CDCl_3$) δ: 3.72 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 4.90 (s, 1H, 5–H), 6.85–7.30 (m, 3H, ArHs), 8.98–9.30 (bs, 2H, NH at 1, 8), 9.58 (bs, 1H, NH at 3), and 10.58 (bs, 1H, NH at 6). *Anal*. Calcd. for $C_{14}H_{14}N_4O_5$: C, 52.83; H, 4.40; N, 16.66. Found: C, 52.65; H, 4.42; N, 16.61.

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