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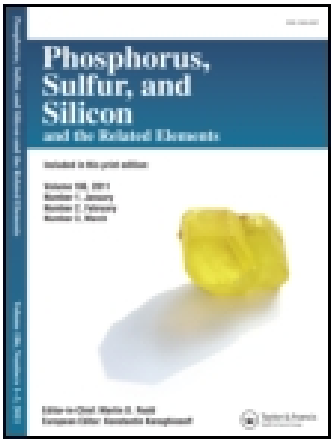

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Synthesis of New Pyrimidine, Quinazoline and Diazatricyclo Derivatives by Multicomponent Reaction and Evaluation of Their Biological Activity

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SYNTHESIS OF NEW PYRIMIDINE, QUINAZOLINE AND DIAZATRICYCLO DERIVATIVES BY MULTICOMPONENT REACTION AND EVALUATION OF THEIR BIOLOGICAL ACTIVITY

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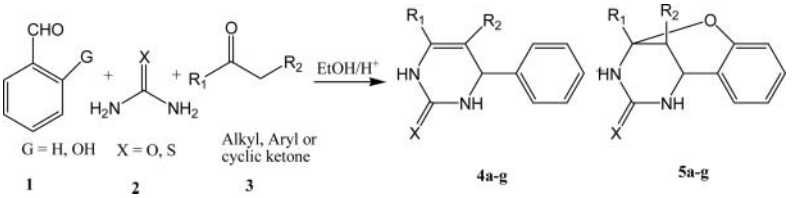
GRAPHICAL ABSTRACT



Abstract *A series of new pyrimidine and quinazoline derivatives was synthesized by a Biginelli-like reaction of urea/thiourea, aldehyde, and ketone in the presence of hydrochloric acid as a catalyst. In a similar way, some novel diazatricyclo derivatives were obtained via a Biginelli-like reaction followed by an intramolecular Michael-type addition. The yields of products were reasonable after recrystallization from ethanol. All newly synthesized compounds were characterized using IR and NMR (^1H and ^{13}C) spectroscopy and elemental analysis. The antibacterial activity of these compounds was investigated against* Staphylococcus aureus *(RTCC, 1885), and* Escherichia Coli *(ATCC, 35922).*

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Keywords Multicomponent reaction; biginelli; michael addition; pyrimidine; quinazoline

INTRODUCTION

Multicomponent reactions (MCRs) are one-step processes in which three or more reactants are reacted together to produce a new product without the isolation of the intermediates, where all or most of the atoms contribute to the structure of new product. These reactions are used as valuable tools for rapid and efficient synthesis of organic and

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Table 1 Synthesis of pyrimidine and quinazolinone derivatives **4a–g**

Entry	Ketone	X	Product **4**	Time (h)	Yield (%)
1	acetone	O	**a**	7	54
2	cyclohexanone	S	**b**	3	73
3	cyclohexane-1,4-dione	O	**c**	6	68
4	1,4-cyclohexadione	S	**d**	4	71
5	2-bromoacetophenone	O	**e**	5	62
6	acetone	S	**f**	6	65
7	acetophenone	S	**g**	7	70

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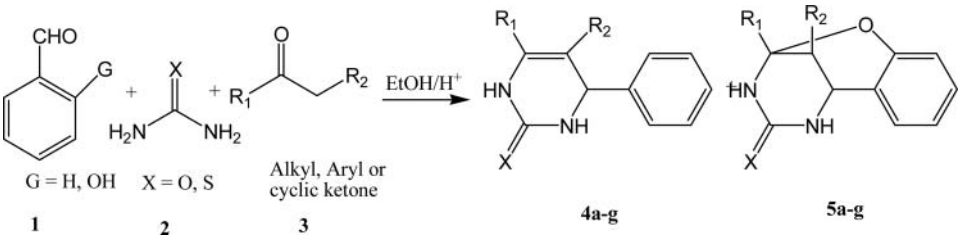
drug-like compounds containing biological screening due to several aspects including minimum preparative work setup and high degree of diversity.[1]

The original Biginelli reaction, the synthesis of dihydropyrimidinones, is one of the most useful examples of MCRs, has received considerable attentions in organic synthesis and medicinal chemistry due to their capacity to produce multifunctionalized products including tetrahydropyrimidines, their thiones analogs, and other related heterocyclic compounds.[2] This reaction has developed based on the number of starting materials and in order to obtain derivatives with different structures and biological activities.[3] Dihydropyrimidine,[4] quinazoline,[5,6] and diazatricyclo derivatives[7] have aroused considerable interest because of their pharmacological and therapeutic properties such as antibacterial, antitumor, and antihypertensive activities as well as behaving as calcium channel blockers.[8–19]

In view of these reports and also as a continuation of our work on the synthesis of pyrimidine derivatives and MCRs,[20–26] we have made an attempt to synthesize some biologically active, novel pyrimidine, quinazolinone and diazatricyclo derivatives via a Biginelli-like reaction and an intramolecular Michael-type addition reaction.

RESULTS AND DISCUSSION

The synthetic routes for the preparation of titled compounds are presented in Scheme 1. The good yields of the products, the mild reaction conditions, and the use of simple starting materials are the main advantages of this method. Pyrimidines and quinazolinones **4a–g**, and diazatricyclos **5a–g** were synthesized by a Biginelli-like reaction of benzaldehyde or salicylaldehyde with urea/thiourea and appropriate ketone in the presence of hydrochloric acid as a catalyst. The results are indicated in Tables 1 and 2.



Scheme 1

When salicylaldehyde was used as a starting material, due to existence of an OH group at the ortho position, a bridge oxygen is created with C-6 of the pyrimidine ring.

Table 2 Synthesis of diazatricyclo derivatives **5a–g**

Entry	Ketone	X	Product **5**	Time (h)	Yield (%)
1	acetone	O	**a**	4	80
2	acetone	S	**b**	2	76
3	cyclohexanone	O	**c**	3	65
4	cyclohexanone	S	**d**	2	70
5	acetophenone	O	**e**	3	73
6	acetophenone	S	**f**	4	68
7	4′-bromoacetophenone	O	**g**	5	64

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Steric effects appear to influence the formation of this product. The formation of the oxygen bridge may be due to the effective distance between the ortho-hydroxyl group of phenol and the C-6 atom of pyrimidine ring.[27,28] So, the formation of the oxygen bridge via a Michael addition reaction resulted in the synthesis of diazatricyclo compounds **5a–g** is observed in Biginelli-like reaction when salicylaldehyde is used as a starting material.

The NMR spectra and IR spectra data of all synthesized compounds are consistent with the expected structures. The appearance of two singlets at ∼6.60–9.70 ppm in the ^{1}H NMR spectrum of **4a–g** and **5a–g** due to the resonance of two NH groups (disappeared on D_2O addition) and also the appearance of the absorption bond at ∼3184–3421 cm^{-1} in the IR spectra of these compounds, the characteristic of the NH group, are good evidences in support of expected reactions. In ^{13}C NMR spectra of compounds, the appearance of signals at lowest field is due to resonance of C=O and C=S groups. The other chemical shift of ^{13}C NMR spectra was papered in expected regions.

The verification of antibacterial screening data revealed that 4 out of 15 tested materials showed antibacterial activities against *Stphylococcus aureus* as gram positive and three of these materials showed antibacterial activities against *Escherichia Coli* as gram negative bacteria (Table S31 Supplemental Materials). The maximum activities against *Staphylococcus aureus* and *Escherichia Coli* were related to **4c** and **4g**, respectively.

CONCLUSION

We have been able to synthesize some novel and biological active pyrimidine, quinazolinone, and diazatricyclo derivatives via the Biginelli-like and an intramolecular Michael-type addition reaction of urea/thiourea, aldehyde, and ketone in suitable yields.

EXPERIMENTAL

All reagents and solvents used were commercially available. Melting points were measured using an electro-thermal digital apparatus. IR spectra were performed on a Galaxy series FTIR 5000 spectrometer using KBr discs. The NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer using Dimethylsulfoxide (DMSO-d_6) as a solvent and TMS as an internal standard. Microanalyses were performed by the Elemental Analyzer (Elemental, Vario EL III) at the Arak University. Reactions were monitored by thin layer chromatography using silica gel F_{254} aluminum sheets (Merck). The microbial strains are identified strains and were obtained from the Pasteure Institute of Iran. The

bacterial strains studied are *Staphylococcus aureus* (RTCC, 1885) and *Escherichia Coli* (ATCC, 35922).

Antibacterial Study

The agar disk diffusion method was used for this purpose. The chemically synthesized material (5 mg) was dissolved in DMSO (200 μl) as a solvent and 100 μl of known concentration of the test compounds was introduced onto the disks (7 mm). The disk was saturated with the test compound. Then, the disk was introduced onto the upper layer of the medium with the bacteria. Then, 100 μl of solvent (DMSO) was added to blank disk and implanted as negative control on each plate along with the standard drugs. The plates were incubated overnight at 37°C. The inhibition zones were measured and compared with the controls. Chloramphenicol was used as a standard drug.

General Experimental Procedure for Synthesis of 4 and 5

An equimolar amount of benzaldehyde or salicylaldehyde **1**, urea or thiourea **2**, ketone **3**, and a few drops of hydrochloric acid (37%) in ethanol (20 mL) was refluxed for an appropriate time as indicated in Tables 1a and 2. After completion of reaction, monitored by TLC, the reaction mixture was cooled to room temperature, filtered, washed by hot water and, ethanol and recrystallized from ethanol to afford the pure product of **4** and **5**. Supplemental Materials shows the ^{1}H and ^{13}C NMR spectra for two representative compounds, **4e** and **5e**.

6-Methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (4a). Mp 305–307 °C. IR (KBr), ν (cm^{-1}): 3300 (NH), 3223 (NH), 3068 ($CH_{aromatic}$), 2972 ($CH_{aliphatic}$), 1658 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz), δ (ppm) 1.68 (s, 3H, CH_3), 4.91 (d, J = .0 Hz, 1H, $H_{pyrimidine}$), 5.06 (d, J = 9.0 Hz, 1H, CH), 6.60 (s, 1H, NH), 6.81 (s, 1H, NH), the NH protons disappeared on D_2O addition, 7.06–7.44 (m, 5H, $H_{aromatic}$). ^{13}C NMR (DMSO-d_6, 75 MHz), δ (ppm) 43.8, 49.9, 126.7, 127.7, 127.9, 128.8, 142.1, 143.2, 156.1. Anal cald for: $C_{11}H_{12}N_2O$, C, 70.19; H, 6.43; N, 14.88%. Found: C, 70.29; H, 6.50; N, 14.64%.

4-Phenyl-3,4,5,6,7,8-hexahydroquinazoline-2(1H)-thione (4b). Mp 309–311 °C. IR (KBr), ν (cm^{-1}): 3396 (NH), 3184 (NH), 3082 ($CH_{aromatic}$), 2957 ($CH_{aliphatic}$). ^{1}H NMR (DMSO-d_6, 300 MHz), δ (ppm) 1.03 (m, 2H, CH_2), 1.08 (m, 2H, CH_2), 1.53 (m, 2H, CH_2), 1.60 (m, 2H, CH_2), 4.52 (s, 1H, $H_{pyrimidine}$), 7.23–7.43 (m, 5H, $H_{aromatic}$), 8.61 (s, 1H, NH), 8.92 (s, 1H, NH), the NH protons disappeared on D_2O addition. ^{13}C NMR (DMSO-d_6, 75 MHz), δ (ppm) 18.6, 39.1, 56.6, 57.1, 68.1, 126.4, 127.4, 128.1, 128.5, 129.0, 129.3, 175.4. Anal cald for: $C_{14}H_{16}N_2S$, C, 68.81; H, 6.60; N, 11.46; S, 13.12%. Found: C, 68.73; H, 6.51; N, 11.54; S, 13.24%.

4-Phenyl-3,4,7,8-tetrahydroquinazoline-2,6(1H,5H)-dione (4c). Mp 340–341 °C. IR (KBr), ν (cm^{-1}): 3394 (NH), 3223 (NH), 3082 ($CH_{aromatic}$), 2910 ($CH_{aliphatic}$), 1678 (C=O), 1669 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz), δ (ppm) 2.12–2.59 (m, 6H, $3CH_2$), 4.67 (s, 1H, $H_{pyrimidine}$), 7.04–7.60 (m, 5H, $H_{aromatic}$), 8.09 (s, 1H, NH), 9.07 (s, 1H, NH).), the NH protons disappeared on D_2O addition. ^{13}C NMR (DMSO-d_6, 75 MHz), δ (ppm) 24.4, 27.3, 54.7, 58.9, 127.2, 128.1, 129.0, 129.3, 143.3, 144.3, 152.6, 152.9. Anal cald for: $C_{14}H_{14}N_2O_2$, C, 69.41; H, 5.82; N, 11.56%. Found: C, 69.29; H, 5.60; N, 11.66%.

4-Phenyl-2-thioxo-1,2,3,4,7,8-hexahydroquinazolin-6(5H)-one (4d). Mp 325–327 °C. IR (KBr), ν (cm^{-1}): 3375 (NH), 3210 (NH), 3088 ($CH_{aromatic}$), 2978 ($CH_{aliphatic}$), 1689 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz), δ (ppm) 2.24 (s, 2H, CH_2), 2.60–2.70 (m,

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4H, $2CH_2$,), 4.76 (s, 1H, $H_{pyrimidine}$), 7.11–7.43 (m, 5H, $H_{aromatic}$), 8.76 (s, 1H, NH), 9.58 (s, 1H, NH)), the NH protons disappeared on D_2O addition. ^{13}C NMR (DMSO-d_6, 75 MHz), δ (ppm) 23.6, 26.8, 54.2, 58.2, 125.2, 127.4, 128.4, 128.7, 129.1, 142.8, 142.9, 173.2. Anal cald for: $C_{14}H_{14}N_2OS$, C, 65.09; H, 5.46; N, 10.84; S, 12.41%. Found: C, 65.19; H, 5.40; N, 10.97; S, 12.65%.

5-Bromo-6-hydroxy-4,6-diphenyl-tetrahydropyrimidin-2(1H)-one (4e). Mp 220–222 °C. IR (KBr), ν (cm^{-1}): 3217 (NH), 3190 (NH, OH), 3080 ($CH_{aromatic}$), 2980 ($CH_{aliphatic}$), 1682 (C=O). ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 3.68 (d, $J = 5.6$ Hz, 1H, $H_{pyrimidine}$), 5.05 (d, $J = 5.6$ Hz, 1H, CHBr), 7.27–7.51 (m, 11H, $10H_{aromatic}$, 1H, OH), 8.15 (s, 1H, NH), 8.81 (s, 1H, NH), the NH and OH protons disappeared on D_2O addition. ^{13}C NMR (DMSO-d_6, 75 MHz), δ (ppm) 20.4, 55.5, 66.4, 123.8, 127.2, 128.0, 128.4, 128.9, 132.2, 132.8, 144.1, 153.5. Anal cald for: $C_{16}H_{15}BrN_2O_2$, C, 55.35; H, 4.35; N, 8.07; Br, 23.01%. Found: C, 55.18; H, 4.50; N, 8.19; Br, 23.26%.

6-Hydroxy-6-methyl-4-phenyl-tetrahydropyrimidine-2(1H)-thione (4f). Mp 238–240 °C. IR (KBr), ν (cm^{-1}): 3387 (NH), 3196 (NH, OH), 3082 ($CH_{aromatic}$), 2974 ($CH_{aliphatic}$). ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 0.91 (s, 3H, CH_3), 2.75 (t, $J =$ 5.6 Hz, 1H, $H_{pyrimidine}$), 4.05 (d, $J = 5.6$ Hz, 2H, CH_2), 7.21–7.41 (m, 6H, $5H_{aromatic}$ and 1H, OH), 8.19 (s, 1H, NH), 8.81 (s, 1H, NH), the NH and OH protons disappeared on D_2O addition. ^{13}C NMR (DMSO-d_6, 75 MHz), δ (ppm) 29.1, 43.0, 54.9, 65.0, 127.2, 128.4, 129.1, 140.3, 174.7. Anal cald for: $C_{11}H_{14}N_2OS$, C, 59.43; H, 6.35; N, 12.60; S, 14.42%. Found: C, 59.21; H, 6.44; N, 12.49; S, 14.52%.

6-Hydroxy-4,6-diphenyl-tetrahydropyrimidine-2(1H)-thione (4g). Mp 285–287 °C. IR (KBr), ν (cm^{-1}): 3387 (NH), 3210 (NH, OH), 3063 ($CH_{aromatic}$), 2949 ($CH_{aliphatic}$).^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 3.15 (d, $J = 5.6$ Hz, 2H, CH_2), 4.14 (t, $J = 5.6$ Hz, 1H, $H_{pyrimidine}$), 6.97–6.99 (m, 5H, $H_{aromatic}$), 7.13–7.15 (m, 6H, 5H, $H_{aromatic}$, 1H, OH), 8.18 (1H, NH), 8.98 (1H, NH), the NH and OH protons disappeared on D_2O addition. ^{13}C NMR (DMSO-d_6, 75 MHz), δ (ppm) 44.7, 55.4, 69.2, 126.9, 127.1, 127.8, 128.0, 128.4, 128.6, 139.4, 140.3, 175.8. Anal cald for: $C_{16}H_{16}N_2OS$, C, 67.58; H, 5.67; N, 9.85; S, 11.28%. Found: C, 67.81; H, 5.50; N, 9.98; S, 11.03%.

9-Methyl-8-oxa-10,12-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-11-one (5a). Mp 291–293 °C. IR (KBr), ν (cm^{-1}): 3310 (NH), 3240 (NH), 3122 ($CH_{aromatic}$), 2891 ($CH_{aliphatic}$), 1687 (C=O). ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 1.59 (s, 3H, CH_3), 2.08 (d, $J = 5.6$ Hz, 2H, CH_2), 4.23 (t, $J = 5.6$ Hz, 1H, $H_{pyrimidine}$), 6.73-7.13 (m, 4H, $H_{aromatic}$), 7.29 (s, 1H, NH), 7.59 (s, 1H, NH), the NH protons disappeared on D_2O addition ^{13}C NMR (DMSO-d_6, 75 MHz), δ (ppm) 26.8, 32.6, 44.9, 82.6, 116.9, 120.5, 126.1, 129.3, 129.4, 151.8, 155.7. Anal cald for: $C_{11}H_{12}N_2O_2$, C, 64.69; H, 5.92; N, 13.72%. Found: C, 64.51; H, 5.99; N, 13.56%.

9-Methyl-8-oxa-10,12-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-11-thione (5b). Mp 225–227 °C. IR (KBr), ν (cm^{-1}): 3210 (NH), 3194 (NH), 3099 ($CH_{aromatic}$), 2968 ($CH_{aliphatic}$). ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 1.66 (s, 3H, CH_3), 2.09 (d, $J =$ 5.6 Hz, 2H, CH_2), 4.30 (t, $J = 5.6$ Hz, 1H, $H_{pyrimidine)}$, 6.78–7.18 (m, 4H, $H_{aromatic}$), 8.80 (s, 1H, NH), 9.01 (s, 1H, NH), the NH protons disappeared on D_2O addition. ^{13}C NMR (DMSO-d_6, 75 MHz), δ (ppm) 25.9, 30.9, 45.5, 81.0, 116.8, 120.9, 124.3, 129.5, 129.7, 151.7, 176.5. Anal cald for: $C_{11}H_{12}N_2OS$, C, 59.97; H, 5.49; N, 12.72; S, 14.56%. Found: C, 59.81; H, 5.60; N, 12.53; S, 14.78%.

2-Oxa-15,17-diazatricyclo[7.5.3.0^{1,10}.0^{3,8}]heptadeca-3,5,7-triene-16-one (5c). Mp 314–316 °C. IR (KBr), ν (cm^{-1}): 3300 (NH), 3230 (NH), 3080 ($CH_{aromatic}$), 2943 ($CH_{aliphatic}$), 1689 (C=O). ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 1.34–2.12 (m, 9H,

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$4CH_2$, 1H, CH), 3.90 (s, 1H, $H_{pyrimidine}$), 6.73–7.13 (m, 4H, $H_{aromatic}$), 7.16 (s, 1H, NH), 7.31 (s, 1H, NH), the NH protons disappeared on D_2O addition. ^{13}C NMR (DMSO-d_6, 75 MHz), δ (ppm) 22.8, 24.4, 25.3, 35.1, 36.2, 48.7, 85.0, 116.8, 120.4, 127.7, 129.2, 129.3, 151.4, 155.5. Anal cald for: $C_{14}H_{16}N_2O_2$, C, 68.83; H, 6.60; N, 11.47%. Found: C, 68.64; H, 6.74; N, 11.31%.

2-Oxa-15,17-diazatricyclo[7.5.3.0^{1,10}.0^{3,8}] heptadeca-3,5,7-triene-16-thione (5d). Mp 225–227 °C. IR (KBr), ν (cm^{-1}): 3421 (NH), 3194 (NH), 3065 ($CH_{aromatic}$), 2949 ($CH_{aliphatic}$). ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 1.02–2.49 (m, 9H, $4CH_2$, 1H, CH), 3.43 (s, 1H, $H_{pyrimidine}$), 7.11–7.22 (m, 4H, $H_{aromatic}$), 8.64 (s, 1H, NH), 9.02 (s, 1H, NH), the NH protons disappeared on D_2O addition. ^{13}C NMR (DMSO-d_6, 75 MHz), δ (ppm) 19.0, 23.5, 24.4, 31.2, 49.4, 56.5, 83.7, 119.0, 121.6, 124.4, 126.4, 128.5, 154.4, 177.3. Anal cald for: $C_{14}H_{16}N_2OS$, C, 64.58; H, 6.19; N, 10.76; S, 12.32%. Found: C, 64.69; H, 6.01; N, 10.84; S, 12.05%.

9-Phenyl-8-oxa-10,12-diazatricyclo [7.3.1.0^{2,7}]trideca-2,4,6-triene-11-one (5e). Mp 271–273 °C. IR (KBr), ν (cm^{-1}): 3323 (NH), 3219 (NH), 3070 ($CH_{aromatic}$), 2982 ($CH_{aliphatic}$), 1687 (C=O). ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 2.19 (d, $J = 5.6$ Hz, 2H, CH_2), 4.33 (t, $J = 5.6$ Hz, 1H, $H_{pyrimidine}$), 6.81–7.88 (m, 9H, $H_{aromatic}$), 8.64 (s, 1H, NH), 9.70 (s, 1H, NH), the NH protons disappeared on D_2O addition. ^{13}C NMR (DMSO-d_6, 75 MHz), δ (ppm) 35.3, 49.9, 85.2, 121.0, 125.6, 126.2, 126.9, 128.3, 128.7, 129.5, 131.3, 134.6, 151.7, 156.3. Anal cald for: $C_{16}H_{14}N_2O_2$, C, 72.16; H, 5.30; N, 10.52%. Found: C, 72.05; H, 5.21; N, 10.73%.

9-Phenyl-8-oxa-10,12-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-11-thione (5f). Mp 265–267 °C. IR (KBr), ν (cm^{-1}): 3360 (NH), 3210 (NH), 3043 ($CH_{aromatic}$), 2937 ($CH_{aliphatic}$). ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 2.49 (d, $J = 5.6$ Hz, 2H, CH_2), 3.99 (t, $J = 5.6$ Hz, $1H_{pyrimidine}$), 7.04–7.70 (m, 9H, $H_{aromatic}$), 8.85 (s, 1H, NH), 9.62 (s, 1H, NH), the NH protons disappeared on D_2O addition. ^{13}C NMR (DMSO-d_6, 75 MHz), δ (ppm) 36.1, 48.4, 86.7, 122.1, 126.6, 129.1, 129.7, 130.1, 130.4, 132.5, 141.1, 151.5, 153.9, 175.9. Anal cald for: $C_{16}H_{14}N_2OS$, C, 68.06; H, 5.00; N, 9.92; S, 11.36%. Found: C, 68.21; H, 5.12; N, 9.71; S, 11.54%.

9-(4-Bromophenyl)-8-oxa-10,12-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-11-one (5g). Mp 285–287 °C. IR (KBr), ν (cm^{-1}): 3317 (NH), 3221 (NH), 3074 ($CH_{aromatic}$), 2912 ($CH_{aliphatic}$), 1683 (C=O). ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 2.17 (d, $J = 5.6$ Hz, 2H, CH_2), 4.32 (t, $J = 5.6$ Hz, $1H_{pyrimidine}$), 6.93–7.26 (m, 4H, $H_{aromatic}$), 7.41–7.62 (m, 4H, $H_{aromatic}$), 7.65 (s, 1H, NH), 7.89 (s, 1H, NH), the NH protons disappeared on D_2O addition. ^{13}C NMR (DMSO-d_6, 75 MHz), δ (ppm) 35.1, 45.1, 84.9, 121.2, 122.1, 126.0, 128.7, 129.4, 129.6, 131.5, 131.7, 141.4, 151.4, 156.0. Anal cald for: $C_{16}H_{13}BrN_2O_2$, C, 55.67; H, 3.80; N, 8.12; Br, 23.15%. Found: C, 55.51; H, 3.71; N, 7.96; Br, 23.26%.

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