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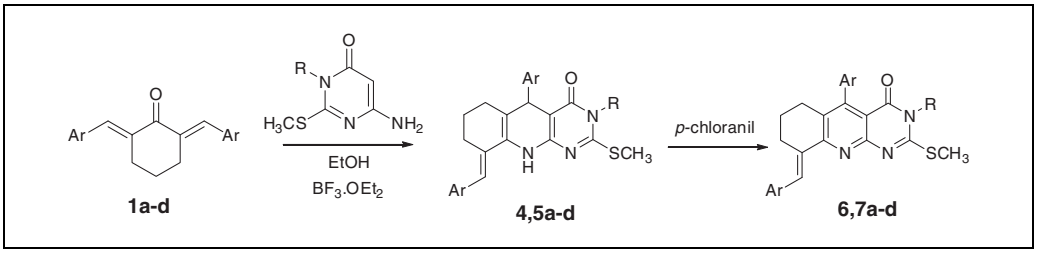


The 5,6,7,8,9,10-hexahydro-2-methylthiopyrimido[4,5-*b*]quinolines **4,5a–d** and their oxidized forms **6,7a–d** were obtained from the reaction of 6-amino-2-(methylthio)pyrimidin-4(3*H*)-one **2** or 6-amino-3-methyl-2-(methylthio)pyrimidin-4(3*H*)-one **3** and α,β-unsaturated ketones **1a–d** using $BF_3.OEt_2$ as catalyst and *p*-chloranil as oxidizing agent. Some of the new compounds were evaluated in the US National Cancer Institute (NCI), where compound **5a** presented remarkable activity against 46 cancer cell lines, with the most important $GI_{50}$ values ranging from 0.72 to 18.4 μM from *in vitro* assays.

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## INTRODUCTION

Some compounds based on pyrimidine and quinoline rings are currently known commercial drugs. Some of them are Imiquimod that have antiviral activity, Enoxacin with antifungal activity, Fluorouracil with antitumor activity, Clioquinol and Sulfadiazine with antibacterial activity (Fig. 1).

Pyrimidoquinoline framework has attracted interest over the years because of its wide range of biological applications displayed by its derivatives [1–5]. Compound **I**, for example, showed comparable activity toward the *Candida albicans* and *Candida gabrata* fungi than the reference drug Nystatin [6], compound **II** was evaluated against *Ehrlich Ascites Carcinoma* cells showing higher activity than Doxorubicin used as reference drug [7], compounds **III** were synthesized and evaluated for antibacterial activity showing moderate to good activity against *Escherichia coli* and *Pseudomonas aeruginosa* [8], whereas chloroquinoline **IV** was evaluated as potential antimalarial showing effective binding to enzyme *Plasmodium falciparum* glutathione reductase [9] (Fig. 2).

Continuing with our current studies on the synthesis of novel heterocyclic structures with potential antitumor activity [10–13], we are reporting here the synthesis and antitumoral evaluation of novel pyrimido[4,5-*b*]quinolin-4-one derivatives **4–7**.

## RESULTS AND DISCUSSION

**Chemistry.** Pyrimidinic monoamines are versatile precursors for the synthesis of heterocyclic compounds of higher complexity [14–16]. For example, 6-amino-2-(methylthio)pyrimidin-4(3***H***)-one **2** and 6-amino-3-methyl-2-(methylthio)pyrimidin-4(3***H***)-one **3** have been used as a essential unit for the synthesis of new pyrrolopyrimidines [17,18], pyridopyrimidines [14,15] and pyrimidoquinolines [2,5,19]. On the basis of the aforementioned reports, we performed the synthesis of new pyrimidoquinolines **4,5a–d** and their oxidized forms **6,7a–d** according to the procedure described in Scheme 1.

Treatment of equimolar amounts of the *bis*-arylidene derivatives **1a–d** and aminopyrimidone **2** in ethanol under reflux and using $BF_3.OEt_2$ as catalyst, led to the formation of compounds **4a–d** in reaction times of 6–9 h. When the process was repeated but starting with aminopyrimidone **3**, the reaction proceeded at room temperature during 24–36 h affording compounds **5a–d**. The corresponding oxidized derivatives **6a–d** and **7a–d** were obtained by treatment of compounds **4a–d** and **5a–d**, respectively with *p*-chloranil as oxidizing agent, under reflux in chloroform during 1–2 h.

The main features in the IR spectra of compounds **4,5a–d** corresponded to NH amine band in the range of 3400–3460 $cm^{-1}$ and the C=O stretching band at 1631–1669 $cm^{-1}$. In the case of compounds **4a–d**, the NH amine band is overlapped by the amidic NH band. The more relevant signal in the $^1H$ NMR spectra of compounds **4,5a–d** corresponded to a singlet at 4.37–4.62 ppm assigned to H-5 proton and a singlet at 8.20–8.44 ppm assigned to the NH amine proton, whereas the C-5 signal is observed at 43.2–44.5 ppm in the $^{13}C$ NMR spectra. For all compounds **4,5a–d**, the molecular ion peaks are well defined in the mass

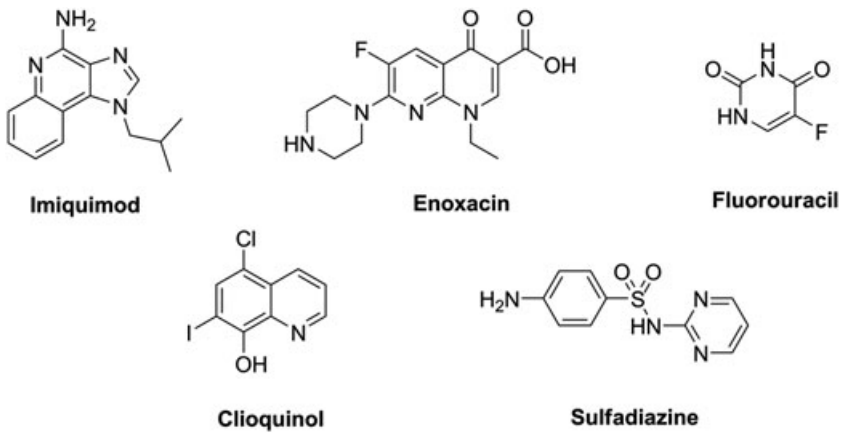



**Figure 1.** Commercial drugs with pyrimidine and quinoline rings.

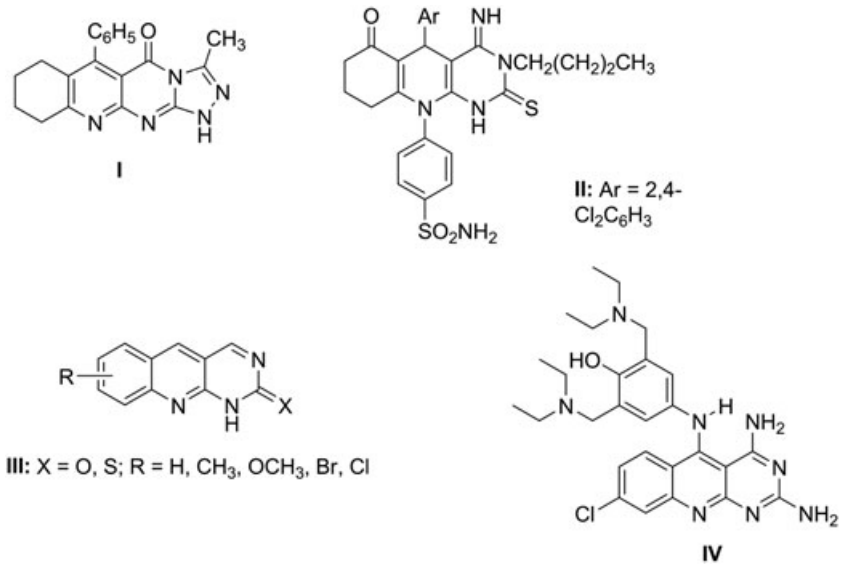



**Figure 2.** Pyrimidoquinolines with important biology activity.

spectra and their base peaks corresponded to the loss of the $C_6H_4X$ (X═H, Cl, Br, $NO_2$) fragment.

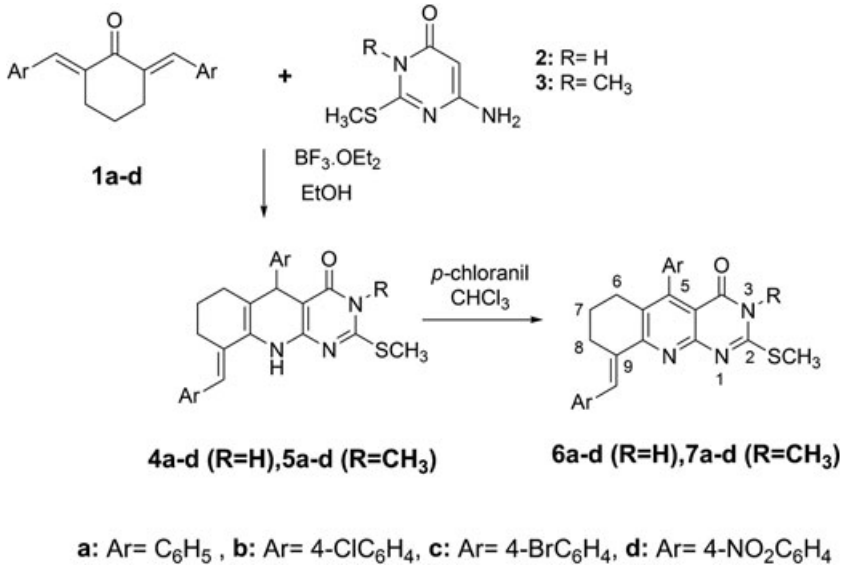
For compounds **6a–d**, the NH amidic band appeared at 3429–3460 $cm^{-1}$ in the IR spectra, whereas C═O stretching bands are observed for all **6,7a–d** compounds. As expected, signals for H-5 and N–H amine protons disappeared in the $^1H$ NMR spectra of compounds **6,7a–d**, and their C-5 signals were shifted to the aromatic region in the $^{13}C$ NMR spectra, confirming that effectively the oxidation process occurred. The molecular ions for these compounds are well defined in the mass spectra along with the $[M^+–H]$ and $[M^+–CH_3]$ ions.

The 9*E*-configuration was determined on the basis of the NOESY experiment, which showed the correlation between the ═CH and NH amine protons and confirmed by X-ray diffraction analysis (Fig. 3) [20].

***In vitro* anticancer activity.** The two-stage screening process started with the evaluation of eight compounds (**4a, 4b, 5a, 5b, 6a, 6b, 7a** and **7b**) selected by NCI, against the 60 cell lines at a single dose of 10.0 μM. The output from the single dose screen was reported as a mean graph available for analysis by the COMPARE program. The results of the primary assay showed that compounds **4a, 4b, 5b, 6a, 6b, 7a** and **7b** were essentially inactive, whereas compound **5a** was active (Table 1).

Then, the second screening was made in order to determine the cytostatic activity of compound **5a** against the 60 cell lines panel representing mainly, melanoma, leukemia

**Scheme 1.** Synthesis of novel pyrimido[4,5-*b*]quinolin-4-ones **(4–7)a–d**.




**a:** Ar= $C_6H_5$ , **b:** Ar= 4-$ClC_6H_4$, **c:** Ar= 4-$BrC_6H_4$, **d:** Ar= 4-$NO_2C_6H_4$

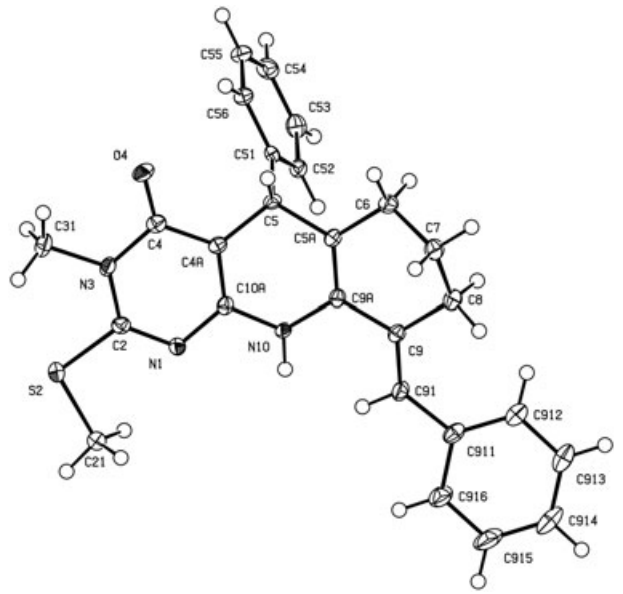



**Figure 3.** ORTEP drawing of the structure of compound **5a**.

and cancers of lung, colon, brain, breast, ovary, kidney and prostate. The compounds were evaluated at five concentration levels (100, 10, 1.0, 0.1 and 0.01 μM). The test consisted of a 48 h continuous drug exposure protocol by using sulforhodamine B (SRB) protein assay to estimate cell growth. Details of this evaluation method and the complementary information related with the activity pattern over all cell lines have been published [21–23]. The compound **5a** shows a remarkable activity against 46 human tumor cell lines, being HL-60(TB) (Leukemia), the most sensitive strains ($GI_{50}$ 0.72 μM ($LC_{50} > 100$ μM)), also showing significant activity in the cell line UO-31 (Renal Cancer) ($GI_{50}$ 1.69 μM ($LC_{50} > 100$ μM)) and SR (Leukemia) ($GI_{50}$ 1.89 μM ($LC_{50} > 100$ μM)). $LC_{50}$ (27.9 μM to > 100 μM) results of this compound have shown that it is a potential antitumor agent.

## CONCLUSION

The synthesis and biological activity of novel pyrimido [4,5-*b*]quinolines have been performed. Anticancer screening data revealed that among the eight pyrimidoquinolines evaluated, derivative **5a** showed the highest activity against different cancer cell lines with remarkable values in leukemia and renal cancer panels. This compound could be a leader structure for synthesizing new series of pyrimido[4,5-*b*] quinoline analogs with the aim to increase the antitumor activity in this family of compounds.

## EXPERIMENTAL

**Chemistry.** All melting points were measured using a Büchi melting point apparatus and are uncorrected. TLC analyses were performed on Merck TLC-plates aluminum silica gel 60 $F_{254}$. IR spectra (KBr disks) were recorded on a Perkin Elmer 1650 spectrometer (USA). $^1H$ and $^{13}C$ NMR spectra were run on a Bruker DPX 400 spectrometer operating at 400 and 100 MHz, respectively, using dimethyl sulfoxide-$d_6$ as solvent and tetramethylsilane as internal standard. Mass spectra were obtained on a Shimadzu GCMS-QP 2010 spectrometer (equipped with a direct inlet probe) operating at 70 eV. Elemental analyses have been obtained using a LECO CHNS-900 elemental analyzer. Starting materials **1a–d** were prepared according to literature [24].

**Table 1**

*In vitro* testing results expressed as growth inhibition of cancer cell lines for compound **5a**.[a]

| | Number of cell lines | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Giving positive $GI_{50}$ | | | | | |
| | | $GI_{50}$[b] (μM) | | Most sensitive cell lines ($GI_{50} < 20$ μM) | | | |
| Compound | Investigated | No. | Range | Panel | Cell line | $GI_{50}$(μM)[b] | $LC_{50}$(μM)[c] |
| **5a** | 60 | 56 | 0.72–71.7 | | | | |
| | | | | *Leukemia* | CCRF-CEM | 4.62 | >100 |
| | | | | | HL-60(TB) | 0.72 | >100 |
| | | | | | K-562 | 2.86 | >100 |
| | | | | | MOLT-4 | 4.90 | >100 |
| | | | | | RPMI-8226 | 5.31 | >100 |
| | | | | | SR | 1.89 | >100 |
| | | | | *Non-small cell lung cancer* | NCI-H226 | 18.4 | >100 |
| | | | | | NCI-H23 | 7.10 | >100 |
| | | | | | NCI-H460 | 9.87 | >100 |
| | | | | | NCI-H522 | 5.93 | >100 |
| | | | | *Colon cancer* | COLO 205 | 10.3 | >100 |
| | | | | | HCT-116 | 3.41 | 84.4 |
| | | | | | HCT-15 | 4.10 | >100 |
| | | | | | HT29 | 3.58 | >100 |
| | | | | | KM12 | 18.2 | >100 |
| | | | | | SW-620 | 2.53 | 60.4 |
| | | | | *CNS cancer* | SF-268 | 10.7 | >100 |
| | | | | | SF-295 | 4.67 | >100 |
| | | | | | SF-539 | 9.98 | >100 |
| | | | | | SNB-75 | 11.3 | 77.6 |
| | | | | | U251 | 3.99 | >100 |
| | | | | *Melanoma* | LOX IMVI | 3.01 | >100 |
| | | | | | MALME-3 M | 5.87 | >100 |
| | | | | | M14 | 6.56 | >100 |
| | | | | | MDA-MB-435 | 3.99 | >100 |
| | | | | | SK-MEL-2 | 9.48 | >100 |
| | | | | | SK-MEL-5 | 3.58 | >100 |
| | | | | | UACC-257 | 6.62 | >100 |
| | | | | | UACC-62 | 7.95 | >100 |
| | | | | *Ovarian cancer* | IGROV1 | 13.6 | >100 |
| | | | | | OVCAR-3 | 4.41 | >100 |
| | | | | | OVCAR-8 | 3.97 | >100 |
| | | | | | NCI/ADR-RES | 4.07 | >100 |
| | | | | *Renal cancer* | 786-0 | 11.7 | >100 |
| | | | | | A498 | 16.8 | >100 |
| | | | | | ACHN | 3.56 | >100 |
| | | | | | RXF 393 | 2.35 | 27.9 |
| | | | | | UO-31 | 1.69 | >100 |
| | | | | *Prostate cancer* | PC-3 | 7.11 | >100 |
| | | | | | DU-145 | 8.02 | >100 |
| | | | | *Breast cancer* | MCF7 | 7.72 | >100 |
| | | | | | MDA-MB-231/ATCC | 17.4 | >100 |
| | | | | | HS 578 T | 10.2 | >100 |
| | | | | | BT-549 | 11.9 | >100 |
| | | | | | T-47D | 4.15 | >100 |
| | | | | | MDA-MB-468 | 2.84 | >100 |

[a]Data obtained from NCI's *in vitro* disease-oriented human tumor cell lines screen [23].
[b]$GI_{50}$ was the drug concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the drug incubation. Determined at five concentration levels (100, 10, 1.0, 0.1 and 0.01 μM).
[c]$LC_{50}$ is a parameter of cytotoxicity and reflects the molar concentration needed to kill 50% of the cells.

***General procedure for the synthesis of (9E)-5-aryl-9-(arylidene)-2-(methylthio)-5,6,7,8,9,10-hexahydropyrimido[4,5-b]quinolin-4(3H)-ones (4a–d).*** A mixture of **1a–d** (1 mmol) and 6-amino-2-(methylthio)pyrimidin-4(3***H***)-one **2** (1 mmol) was refluxed in ethanol (20 mL) and catalytic amounts of $BF_3{\cdot}OEt_2$ (8 drops) for 6–9 h. The reaction mixture was cooled, the precipitate formed was filtered off, washed with ethanol and crystallized from EtOH : DMF mixture to obtain compounds **4a–d** as yellow solids.

***(9E)-9-(benzylidene)-2-(methylthio)-5-phenyl-5,6,7,8,9,10-hexahydropyrimido[4,5-b]quinolin-4(3H)-one (4a).*** It was obtained from **1a** in 40% yield; mp 238 °C (d); FTIR (KBr) $\upsilon = 3448$ (NH), 1651 (C═O) $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta_H$ (ppm): 1.46-1.61 (m, 2H, $CH_2$), 1.90–2.00 (m, 1 H, $CH_2$), 2.01–2.11 (m, 1H, $CH_2$), 2.36–2.46 (m, 1H, $CH_2$), 2.52 (s, 3 H, $SCH_3$), 2.55–2.66 (m, 1H, $CH_2$), 4.37 (s, 1H, 5-CH), 6.97 (s, 1H, ═CH), 7.09–7.16 (m, 1H, phenyl), 7.18–7.27 (m, 5H, phenyl), 7.29–7.40 (m, 4H, phenyl), 8.27 (s, 1H, NH), 11.79–12.06 (br s, 1H, NH); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta_C$ (ppm): 13.1 ($CH_3$), 23.0 ($CH_2$), 27.2 ($CH_2$), 28.5 ($CH_2$), 43.6 (C-5), 93.7 (C), 116.6 (C), 122.2 (CH), 126.6 (CH, phenyl), 126.9 (CH, phenyl), 128.0 (2CH, phenyl), 128.5 (2CH, phenyl), 128.6 (2CH, phenyl), 129.1 (C), 129.6 (2CH, phenyl), 131.6 (C), 137.8 (C), 146.4 (C), 154.0 (C), 159.5 (C), 161.2 (C); MS (EI): *m/z* 413(6) [$M^+$], 336(100), 288(5). *Anal*. Calcd for $C_{25}H_{23}N_3OS$: C, 72.61; H, 5.61; N, 10.16; S, 7.75. Found: C, 72.57; H, 5.68; N, 10.09; S, 7.69.

***(9E)-9-(4-chlorobenzylidene)-5-(4-chlorophenyl)-2-(methylthio)-5,6,7,8,9,10-hexahydropyrimido[4,5-b]quinolin-4(3H)-one (4b).*** It was obtained from **1b** in 51% yield; mp 265 °C (d); FTIR (KBr) $\upsilon = 3435$ (NH), 1631 (C═O) $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta_H$ (ppm): 1.46–1.59 (m, 2H, $CH_2$), 1.85–1.96 (m, 1H, $CH_2$), 1.97–2.09 (m, 1H, $CH_2$), 2.34–2.43 (m, 1H, $CH_2$), 2.51 (s, 3H, $SCH_3$), 2.54–2.62 (m, 1H, $CH_2$), 4.38 (s, 1H, 5-CH), 6.93 (s, 1H, ═CH), 7.23 (d, $J = 8.4$ Hz, 2 H, Ar–H), 7.29 (d, $J = 8.4$ Hz, 2H, Ar–H), 7.33 (d, $J = 7.5$ Hz, 2H, Ar–H), 7.39 (d, $J = 7.5$ Hz, 2 H, Ar–H), 8.26 (s, 1H, NH), 11.72–12.16 (br s, 1H, NH); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta_C$ (ppm): 13.0 ($CH_3$), 22.9 ($CH_2$), 27.0 ($CH_2$), 28.4 ($CH_2$), 43.2 (C-5), 93.2 (C), 100.0 (C), 116.4 (C), 119.7 (C), 120.0 (C), 121.3 (CH), 129.2 (C), 130.2 (2CH, Ar), 131.4 (2CH, Ar), 131.5 (2CH, Ar), 131.7 (2CH, Ar), 132.2 (C), 137.0 (C), 145.6 (C), 154.0 (C), 162.7 (C); MS (EI): *m/z* 485/483/481(1/6/8) [$M^+$], 372/370(41/100), 324/322(2/6). *Anal*. Calcd for $C_{25}H_{21}Cl_2N_3OS$: C, 62.24; H, 4.39; N, 8.71; S, 6.65. Found: C, 62.32; H, 4.44; N, 8.80; S, 6.69.

***(9E)-9-(4-bromobenzylidene)-5-(4-bromophenyl)-2-(methylthio)-5,6,7,8,9,10-hexahydropyrimido[4,5-b]quinolin-4(3H)-one (4c).*** It was obtained from **1c** in 60% yield; mp 289 °C (d); FTIR (KBr) $\upsilon = 3407$ (NH), 1650 (C═O) $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta_H$ (ppm): 1.49–1.60 (m, 2H, $CH_2$), 1.87–1.97 (m, 1H, $CH_2$), 1.99–2.09 (m, 1H, $CH_2$), 2.35–2.45 (m, 1H, $CH_2$), 2.52 (s, 3H, $SCH_3$), 2.53–2.63 (m, 1H, $CH_2$), 4.37 (s, 1H, 5-CH), 6.93 (s, 1H, ═CH), 7.18 (d, $J = 8.4$ Hz, 2H, Ar–H), 7.28 (d, $J = 8.5$ Hz, 2H, Ar–H), 7.44 (d, $J = 8.4$ Hz, 2H, Ar–H), 7.54 (d, $J = 8.5$ Hz, 2H, Ar–H), 8.26 (s, 1H, NH), 11.90–12.08 (br s, 1H, NH); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta_C$ (ppm): 13.2 ($CH_3$), 23.1 ($CH_2$), 27.3 ($CH_2$), 28.5 ($CH_2$), 43.4 (5-CH), 95.5 (C), 101.5 (C), 117.1 (C), 119.6 (C), 119.8 (C), 121.5 (CH), 129.5 (C), 130.0 (2CH, Ar), 130.5 (2CH, Ar), 130.8 (2CH, Ar), 131.8 (2CH, Ar), 133.3 (C), 136.0 (C), 145.6 (C), 155.0 (C), 163.2 (C); MS (EI): *m/z* 573/571/569(3/5/3) [$M^+$], 416/414(99/100), 368/366(5/5). *Anal*. Calcd for $C_{25}H_{21}Br_2N_3OS$: C, 52.56; H, 3.70; N, 7.35; S, 5.61. Found: C, 52.50; H, 3.78; N, 7.39; S, 5.69.

***(9E)-2-(methylthio)-9-(4-nitrobenzylidene)-5-(4-nitrophenyl)-5,6,7,8,9,10-hexahydropyrimido[4,5-b]quinolin-4(3H)-one (4d).*** It was obtained from **1d** in 20% yield; mp 238 °C (d); FTIR (KBr) $\upsilon = 3416$ (NH), 1669 (C═O) $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta_H$ (ppm): 1.51–1.60 (m, 2H, $CH_2$), 1.83–1.94 (m, 1H, $CH_2$), 2.03–2.14 (m, 1H, $CH_2$), 2.39–2.46 (m, 1H, $CH_2$), 2.51 (s, 3H, $SCH_3$), 2.57–2.67 (m, 1H, $CH_2$), 4.58 (s, 1H, 5-CH), 7.09 (s, 1H, ═CH), 7.49 (d, $J = 8.5$ Hz, 2H, Ar–H), 7.58 (d, $J = 8.8$ Hz, 2H, Ar–H), 8.12 (d, $J = 8.5$ Hz, 2H, Ar–H), 8.19 (d, $J = 8.8$ Hz, 2H, Ar–H), 8.44 (s, 1H, NH), 11.50–12.50 (br s, 1H, NH); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta_C$ (ppm): 13.1 ($CH_3$), 22.8 ($CH_2$), 27.2 ($CH_2$), 28.4 ($CH_2$), 43.8 (C-5), 92.7 (C), 100.0 (C), 117.4 (C), 121.2 (CH), 123.8 (2CH, Ar), 123.9 (2CH, Ar), 129.2 (2CH, Ar), 129.6 (C), 130.6 (2CH, Ar), 134.8 (C), 144.8 (C), 146.0 (C), 146.6 (C), 153.6 (C), 154.1 (C), 160.1 (C); MS (EI): *m/z* 503(7) [$M^+$], 381(100), 333(5). *Anal*. Calcd for $C_{25}H_{21}N_5O_5S$: C, 59.63; H, 4.20; N, 13.91; S, 6.37. Found: C, 59.57; H, 4.28; N, 13.95; S, 6.31.

***General procedure for the synthesis of (9E)-5-aryl-9-(arylidene)-3-methyl-2-(methylthio)-5,6,7,8,9,10-hexahydropyrimido[4,5-b]quinolin-4(3H)-ones (5a–d).*** A mixture of **1a–d** (1 mmol) and 6-amino-3-methyl-2-(methylthio)pyrimidin-4(3***H***)-one (**3**) (1 mmol) in ethanol (20 mL) and catalytic amounts of $BF_3{\cdot}OEt_2$ (8 drops) was stirred for 24–36 h at room temperature. The solid formed was filtered and recrystallized from EtOH : DMF mixture to obtain **5a–d** as yellow solids.

***(9E)-9-(benzylidene)-3-methyl-2-(methylthio)-5-phenyl-5,6,7,8,9,10-hexahydropyrimido[4,5-b]quinolin-4(3H)-one (5a).*** It was obtained from **1a** in 75% yield; mp 217–220 °C; FTIR (KBr) $\upsilon = 3445$ (NH), 1648 (C═O) $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta_H$ (ppm) 1.44–1.63 (m, 2H, $CH_2$), 1.87–1.99 (m, 1H, $CH_2$), 2.00–2.11 (m, 1H, $CH_2$), 2.36–2.46 (m, 1H, $CH_2$), 2.55–2.67 (m, 1H, $CH_2$), 2.60 (s, 3H, $SCH_3$), 3.26 (s, 3H, $NCH_3$), 4.40 (s, 1H, 5-CH), 6.97 (s, 1H, =CH), 7.08–7.17(m, 1H, phenyl), 7.18–7.28 (m, 5H, phenyl), 7.29–7.39 (m, 4H, phenyl), 8.20 (s, 1H, NH); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta_C$ (ppm): 14.7 ($CH_3$), 23.1 ($CH_2$), 27.2 ($CH_2$), 28.4 ($CH_2$), 29.9 ($CH_3$), 44.3 (C-5), 93.0 (C), 116.5 (C), 122.1 (CH), 126.5 (CH, phenyl), 126.8 (CH, phenyl), 128.1 (2CH, phenyl), 128.4 (2CH, phenyl), 128.5 (2CH, phenyl), 129.1 (C), 129.6 (2CH, phenyl), 131.8 (C), 137.9 (C), 146.3 (C), 152.4 (C), 160.4 (C), 160.9 (C); MS (EI): *m/z* 427(6) [$M^+$], 350(100), 302 (8). *Anal*. Calcd for $C_{26}H_{25}N_3OS$: C, 73.04; H, 5.89; N, 9.83; S, 7.50. Found: C, 72.96; H, 5.82; N, 9.89; S, 7.53.

***(9E)-9-(4-chlorobenzylidene)-5-(4-chlorophenyl)-3-methyl-2-(methylthio)-5,6,7,8,9,10-hexahydropyrimido[4,5-b]quinolin-4(3H)-one (5b).*** It was obtained from **1b** in 58% yield; mp 241–244 °C; FTIR (KBr) $\upsilon = 3433$ (NH), 1661 (C═O) $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta_H$ (ppm): 1.44–1.66 (m, 2H, $CH_2$), 1.85–1.99 (m, 1H, $CH_2$), 2.00–2.14 (m, 1H, $CH_2$), 2.36–2.48 (m, 1H, $CH_2$), 2.55–2.69 (m, 1H, $CH_2$), 2.61 (s, 3H, $SCH_3$), 3.27 (s, 3H, $NCH_3$), 4.43 (s, 1H, 5-CH), 6.97 (s, 1H, ═CH), 7.26 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.32 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.36 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.43 (d, $J = 8.0$ Hz, 2H, Ar–H), 8.27 (s, 1H, NH); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta_C$ (ppm): 14.7 ($CH_3$), 22.9 ($CH_2$), 27.1 ($CH_2$), 28.3 ($CH_2$), 29.9 ($CH_3$), 43.8 (C-5), 92.5 (C), 116.4 (C), 121.3 (CH), 128.5 (2CH, Ar), 128.6 (2CH, Ar), 129.1 (C), 130.0 (2CH, Ar), 131.2 (C), 131.4 (2CH, Ar), 131.5 (C), 132.2 (C), 136.6 (C), 145.2 (C), 152.3 (C), 160.7 (C), 160.8 (C); MS (EI): *m/z* 499/497/495(1/4/6) [$M^+$], 386/384(39/100), 338/336(1/5). *Anal*. Calcd for

$C_{26}H_{23}Cl_2N_3OS$: C, 62.90; H, 4.67; N, 8.46; S, 6.46. Found: C, 62.87; H, 4.68; N, 8.51; S, 6.49.

***(9E)-9-(4-bromobenzylidene)-5-(4-bromophenyl)-3-methyl-2-(methylthio)-5,6,7,8,9,10-hexahydropyrimido[4,5-b]quinolin-4(3H)-one (5c).*** It was obtained from **1c** in 65% yield; mp 248 °C (d); FTIR (KBr) $\upsilon = 3420$ (NH), 1662 (C═O) $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta_H$ (ppm): 1.43–1.61 (m, 2H, $CH_2$), 1.83–1.94 (m, 1H, $CH_2$), 1.98–2.09 (m, 1H, $CH_2$), 2.34–2.43 (m, 1H, $CH_2$), 2.51–2.62 (m, 1H, $CH_2$), 2.59 (s, 3H, $SCH_3$), 3.25 (s, 3H, $NCH_3$), 4.39 (s, 1H, 5-CH), 6.92 (s, 1H, ═CH), 7.18 (d, $J = 8.4$ Hz, 2H, Ar–H), 7.28 (d, $J = 8.5$ Hz, 2H, Ar–H), 7.42 (d, $J = 8.4$ Hz, 2H, Ar–H), 7.54 (d, $J = 8.5$ Hz, 2H, Ar–H), 8.26 (s, 1H, NH); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta_C$ (ppm): 14.7 ($CH_3$), 22.9 ($CH_2$), 27.2 ($CH_2$), 28.4 ($CH_2$), 30.0 ($CH_3$), 44.0 (C-5), 92.7 (C), 116.4 (C), 119.7 (C), 120.0 (C), 121.1 (CH), 129.4 (C), 130.3 (2CH, phenyl), 131.3 (2CH, phenyl), 131.5 (2CH, phenyl), 131.6 (2CH, phenyl), 131.8 (C), 137.9 (C), 146.3 (C), 152.4 (C), 160.4 (C), 160.9 (C); MS (EI): *m/z* 587/585/583(4/7/4) [$M^+$], 430/428 (100/99), 382/380(5/5). *Anal*. Calcd for $C_{26}H_{23}Br_2N_3OS$: C, 53.35; H, 3.96; N, 7.18; S, 5.48. Found: C, 53.28; H, 3.98; N, 7.22; S, 5.41.

***(9E)-3-methyl-2-(methylthio)-9-(4-nitrobenzylidene)-5-(4-nitrophenyl)-5,6,7,8,9,10-hexahydropyrimido[4,5-b]quinolin-4(3H)-one (5d).*** It was obtained from **1d** in 42% yield; mp 265 °C (d); FTIR (KBr) $\upsilon = 3400$ (NH), 1656 (C═O) $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta_H$ (ppm): 1.49–1.64 (m, 2H, $CH_2$), 1.82–1.94 (m, 1H, $CH_2$), 2.04–2.18 (m, 1H, $CH_2$), 2.41–2.53 (m, 1H, $CH_2$), 2.57–2.69 (m, 1H, $CH_2$), 2.61 (s, 3H, $SCH_3$), 3.26 (s, 3H, $NCH_3$), 4.62 (s, 1H, 5-CH), 7.12 (s, 1H, ═CH), 7.51 (d, $J = 8.3$ Hz, 2H, Ar–H), 7.60 (d, $J = 8.3$ Hz, 2H, Ar–H), 8.14 (d, $J = 9.0$ Hz, 2H, Ar–H), 8.21 (d, $J = 9.0$ Hz, 2H, Ar–H), 8.42 (s, 1H, NH); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta_C$ (ppm): 14.8 ($CH_3$), 22.8 ($CH_2$), 27.2 ($CH_2$), 28.4 ($CH_2$), 29.9 ($CH_3$), 44.5 (C-5), 91.9 (C), 117.3 (C), 121.3 (CH), 123.8 (2CH, Ar), 123.9 (2CH, Ar), 129.4 (2CH, Ar), 129.5 (C), 130.7 (2CH, Ar), 134.8 (C), 144.8 (C), 146.0 (C), 146.6 (C), 152.4 (C), 153.6 (C), 160.7 (C), 161.3 (C); MS (EI): *m/z* 516(14) [$M^+$-1], 500(100), 395(60), 380(12). *Anal*. Calcd for $C_{26}H_{23}N_5O_5S$: C, 60.34; H, 4.48; N, 13.53; S, 6.20. Found: C, 60.30; H, 4.45; N, 13.59; S, 6.26.

***General procedure for the synthesis of (9E)-5-aryl-9-(arylidene)-2-(methylthio)-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-4(3H)-ones (6a–d) and (9E)-5-aryl-9-(arylidene)-3-methyl-2-(methylthio)-6,7,8,9-tetraahydropyrimido[4,5-b]quinolin-4(3H)-ones (7a–d).*** Pyrimido[4,5-*b*]quinolinones (**6,7)a–d** were obtained by treatment of quinolinones (**4,5)a–d** with *p*-chloranil (1 mmol) in refluxing chloroform (20 mL) for 4–6 h, with TLC control. The reaction mixture was cooled to ambient temperature, the precipitate formed was filtrated and purified by column chromatography on silica gel by using a mixture $CH_2Cl_2$:EtOH (30:1) as eluent.

***(9E)-9-(benzylidene)-2-(methylthio)-5-phenyl-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-4(3H)-one (6a).*** It was obtained from **4a** in 30% yield; mp 286 °C (d); FTIR (KBr) $\upsilon = 3440$ (NH), 1666 (C═O) $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta_H$ (ppm): 1.64–1.73 (m, 2H, $CH_2$), 2.34–2.43 (m, 2H, $CH_2$), 2.65 (s, 3H, $SCH_3$), 2.80–2.88 (m, 2H, $CH_2$), 7.09–7.17 (m, 2H, phenyl), 7.28–7.55 (m, 8H, phenyl), 8.13 (s, 1H, ═CH), 11.93–12.20 (br s, 1H, NH); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta_C$ (ppm): 13.3 ($CH_3$), 22.6 ($CH_2$), 27.5 ($CH_2$), 27.6 ($CH_2$), 127.3 (CH, phenyl), 127.8 (CH, phenyl), 127.9 (2CH, phenyl), 128.2 (2CH, phenyl), 128.8 (2CH, phenyl), 129.9 (C), 130.0 (2CH, phenyl), 130.9 (CH), 135.9 (C), 137.5 (C), 139.0 (C), 149.2 (C), 151.4(C), 151.9(C), 160.2 (C), 161.4 (C), 162.0 (C); MS (EI): *m/z* 412(16), 411(54) [$M^+$], 410(98), 397(31), 396(100), 362(14), 337(13), 334(11). *Anal*. Calcd for $C_{25}H_{21}N_3OS$: C, 72.97; H, 5.14; N, 10.21; S, 7.79. Found: C, 72.92; H, 5.18; N, 10.19; S, 7.71.

***(9E)-9-(4-chlorobenzylidene)-5-(4-chlorophenyl)-2-(methylthio)-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-4(3H)-one (6b).*** It was obtained from **4b**, in 35% yield; mp 318 °C (d); FTIR (KBr) $\upsilon = 3460$ (NH), 1667 (C═O) $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta_H$ (ppm): 1.67–1.75 (m, 2H, $CH_2$), 2.40 (t, $J = 5.7$ Hz, 2H, $CH_2$), 2.65 (s, 3H, $SCH_3$), 2.80–2.86 (m, 2H, $CH_2$), 7.18 (d, $J = 8.3$ Hz, 2H, Ar–H), 7.46 (d, $J = 8.3$ Hz, 2H, Ar–H), 7.48 (d, $J = 8.5$ Hz, 2H, Ar–H), 7.53 (d, $J = 8.5$ Hz, 2H, Ar–H), 8.10 (s, 1H, ═CH), 12.07–12.22 (br s, 1H, NH); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta_C$ (ppm): 13.3 ($CH_3$), 22.5 ($CH_2$), 27.4 ($CH_2$), 27.5 ($CH_2$), 128.3 (2CH, Ar), 128.8 (2CH, Ar), 129.7 (CH), 129.9 (2CH, Ar), 130.0 (C), 131.7 (2CH, Ar), 132.4 (C), 132.6 (C), 133.5 (C), 136.4 (C), 136.6 (C), 137.8 (C), 157.0(C), 158.0(C), 158.1(C), 158.5(C), 160.9 (C); MS (EI): *m/z* 483/481/479(8/41/62) [$M^+$], 482/480/478(22/80/100), 468/466/464(14/63/86), 467/465/463(18/32/13). *Anal*. Calcd for $C_{25}H_{19}Cl_2N_3OS$: C, 62.50; H, 3.99; N, 8.75; S, 6.67. Found: C, 62.57; H, 3.96; N, 8.70; S, 6.61.

***(9E)-9-(4-bromobenzylidene)-5-(4-bromophenyl)-2-(methylthio)-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-4(3H)-one (6c).*** It was obtained from **4c**, in 40% yield; mp 310 °C (d); FTIR (KBr) $\upsilon = 3431$ (NH), 1663 (C═O) $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta_H$ (ppm): 1.67–1.75 (m, 2H, $CH_2$), 2.40 (t, $J = 6.2$ Hz, 2H, $CH_2$), 2.65 (s, 3H, $SCH_3$), 2.79–2.85 (m, 2H, $CH_2$), 7.12 (d, $J = 8.3$ Hz, 2H, Ar–H), 7.46 (d, $J = 8.5$ Hz, 2H, Ar–H), 7.60 (d, $J = 8.3$ Hz, 2H, Ar–H), 7.62 (d, $J = 8.5$ Hz, 2H, Ar–H), 8.06 (s, 1H, ═CH), 12.06–12.23 (br s, 1H, NH); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta_C$ (ppm): 13.3 ($CH_3$), 22.5 ($CH_2$), 27.4 ($CH_2$), 27.5 ($CH_2$), 127.1 (2CH, Ar), 127.5 (2CH, Ar), 128.7 (2CH, Ar), 129.5 (CH), 130.0 (C), 130.1 (2CH, Ar), 131.6 (C), 131.9 (C), 134.2 (C), 136.3 (C), 137.8 (C), 138.2 (C), 140.4 (C), 156.3 (C), 157.0 (C), 160.3 (C), 160.9 (C); MS (EI): *m/z* 571/569/567(25/51/37) [$M^+$], 570/568/566(55/93/47), 557/555/553(15/33/27), 556/554/552(56/100/50), 415/413(11/15), 414/412(16/12), 387/385(10/12), 305(20), 290(17), 279(13). *Anal*. Calcd for $C_{25}H_{19}Br_2N_3OS$: C, 52.74; H, 3.36; N, 7.38; S, 5.63. Found: C, 52.70; H, 3.41; N, 7.31; S, 5.69.

***(9E)-2-(methylthio)-9-(4-nitrobenzylidene)-5-(4-nitrophenyl)-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-4(3H)-one (6d).*** It was obtained from **4d**, in 26% yield; mp 310 °C (d); FTIR (KBr) $\upsilon = 3429$ (NH), 1667 (C═O) $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta_H$ (ppm): 1.68–1.76 (m, 2H, $CH_2$), 2.49 (t, $J = 6.4$ Hz, 2H, $CH_2$), 2.65 (s, 3H, $SCH_3$), 2.90–2.97 (m, 2H, $CH_2$), 7.34 (d, $J = 8.8$ Hz, 2H, Ar–H), 7.52 (d, $J = 8.8$ Hz, 2H, Ar–H), 8.14 (d, $J = 8.8$ Hz, 2H, Ar–H), 8.35 (d, $J = 8.8$, 2 Hz, 2H, Ar–H), 8.39 (s, 1H, ═CH), 12.02–12.90 (br s, 1H, NH); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta_C$ (ppm): 13.5 ($CH_3$), 22.3 ($CH_2$), 27.6 ($CH_2$), 27.9 ($CH_2$), 124.8 (2CH, Ar), 124.9 (2CH, Ar), 127.3 (2CH, Ar), 130.5 (C), 130.6 (CH), 131.1 (2CH, Ar), 133.0 (C), 135.4 (C), 139.3 (C), 143.1 (C), 145.8 (C), 148.2 (C), 150.0(C), 154.5 (C), 158.6 (C), 159.8 (C), 161.2 (C); MS (EI): *m/z* 501(60) [$M^+$], 500(76), 486(100), 484(30), 454(27),440(11). *Anal*. Calcd for $C_{25}H_{19}N_5O_5S$: C, 59.87; H, 3.82; N, 13.96; S, 6.39. Found: C, 59.82; H, 3.86; N, 13.90; S, 6.45.

***(9E)-9-(benzylidene)-3-methyl-2-(methylthio)-5-phenyl-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-4(3H)-one (7a).*** It was obtained from **5a**, in 30% yield; mp 224 °C (d); FTIR (KBr) $\upsilon = 1681$ (C═O) $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta_H$ (ppm): 1.67–1.75 (m, 2H, $CH_2$), 2.42 (t, $J = 6.2$ Hz, 2H, $CH_2$), 2.75 (s, 3H, $SCH_3$), 2.81–2.91 (m, 2H, $CH_2$), 3.37 (s, 3H, $NCH_3$), 7.10–7.18 (m, 2H, phenyl), 7.30–7.53 (m, 8H, phenyl), 8.15

(s, 1H, =CH); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta_C$ (ppm): 15.1 ($CH_3$), 22.6 ($CH_2$), 27.6 ($CH_2$), 27.7 ($CH_2$), 30.4 ($CH_3$), 110.7 (C), 127.3 (CH, phenyl), 127.7 (CH, phenyl), 127.8 (2CH, phenyl), 128.3 (2CH, phenyl), 128.8 (2CH, phenyl), 130.0 (2CH, phenyl), 130.1 (C), 131.2 (CH), 136.0 (C), 137.6 (C), 139.2 (C), 152.0 (C), 155.2 (C), 158.0 (C), 160.6 (C), 161.3 (C); MS (EI): *m/z* 426 (14), 425(46) [$M^+$], 424(92), 423(15), 411(30), 410(100), 409 (17), 348(12), 337(20), 307(12),. *Anal*. Calcd for $C_{26}H_{23}N_3OS$: C, 73.38; H, 5.45; N, 9.87; S, 7.54. Found: C, 73.32; H, 5.48; N, 9.91; S, 7.59.

***(9E)-9-(4-chlorobenzylidene)-5-(4-chlorophenyl)-3-methyl-2-(methylthio)-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-4(3H)-one (7b).*** It was obtained from **5b**, in 35% yield; mp 242 °C (d); FTIR (KBr) $\upsilon = 1686$ (C=O) cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta_H$ (ppm): 1.65–1.75 (m, 2H, $CH_2$), 2.40 (t, $J = 6.4$ Hz, 2H, $CH_2$), 2.72 (s, 3H, $SCH_3$), 2.78–2.84 (m, 2H, $CH_2$), 3.35 (s, 3H, $NCH_3$), 7.15 (d, $J = 8.3$ Hz, 2H, Ar–H), 7.44 (d, $J = 8.3$ Hz, 2H, Ar–H), 7.45 (d, $J = 8.3$ Hz, 2H, Ar–H), 7.50 (d, $J = 8.3$ Hz, 2H, Ar–H), 8.42 (s, 1 H, =CH); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta_C$ (ppm): 15.1 ($CH_3$), 22.4 ($CH_2$), 27.5 ($2CH_2$), 30.5 ($CH_3$), 110.7 (C), 120.8 (C), 121.1 (C), 129.9 (CH), 130.0 (C), 130.2 (2CH, Ar), 131.3 (2CH, Ar), 131.7 (2CH, Ar), 131.8 (C), 132.0 (2CH, Ar), 136.7 (C), 138.4 (C), 150.6 (C), 155.1 (C), 157.8 (C), 160.6 (C), 161.5 (C); MS (EI): *m/z* 497/495/493(8/36/57) [$M^+$], 496/494/492(21/79/100), 483/481/479(4/19/34), 482/480/478(15/64/86). *Anal*. Calcd for $C_{26}H_{21}Cl_2N_3OS$: C, 63.16; H, 4.28; N, 8.50; S, 6.49. Found: C, 63.19; H, 4.21; N, 8.53; S, 6.54.

***(9E)-9-(4-bromobenzylidene)-5-(4-bromophenyl)-3-methyl-2-(methylthio)-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-4(3H)-one (7c).*** It was obtained from **5c**, in 37% yield; mp 253 °C (d); FTIR (KBr) $\upsilon = 1682$ (C=O) cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta_H$ (ppm): 1.59–1.69 (m, 2H, $CH_2$), 2.31–2.40 (m, 2H, $CH_2$), 2.67 (s, 3H, $SCH_3$), 2.74–2.82 (m, 2H, $CH_2$), 3.31 (s, 3H, $NCH_3$), 7.10 (d, $J = 7.5$ Hz, 2H, Ar–H), 7.44 (d, $J = 8.3$ Hz, 2H, Ar–H), 7.59 (d, $J = 8.3$ Hz, 2H, Ar–H), 7.61 (d, $J = 7.5$ Hz, 2H, Ar–H), 8.04 (s, 1 H, =CH); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta_C$ (ppm): 15.1 ($CH_3$), 22.5 ($CH_2$), 27.5 ($2CH_2$), 30.5 ($CH_3$), 110.7 (C), 124.4 (2CH, Ar), 128.8 (2CH, Ar), 129.8 (2CH, Ar), 129.9 (CH), 130.1 (C), 131.6 (2CH, Ar), 132.4 (C), 132.7 (C), 136.4 (C), 136.7 (C), 138.0 (C), 150.6(C), 155.2 (C), 157.9 (C), 160.6 (C), 161.5 (C); MS (EI): *m/z* 585/583/581(22/46/34) [$M^+$], 584/582/580(49/83/41), 570/568/566(54/100/51). *Anal*. Calcd for $C_{26}H_{21}Br_2N_3OS$: C, 53.53; H, 3.63; N, 7.20; S, 5.50. Found: C, 53.63; H, 3.68; N, 7.17; S, 5.46.

***(9E)-3-methyl-2-(methylthio)-9-(4-nitrobenzylidene)-5-(4-nitrophenyl)-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-4(3H)-one (7d).*** It was obtained from **5d**, in 23% yield; mp 298 °C (d); FTIR (KBr) $\upsilon = 1682$ (C=O) cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta_H$ (ppm): 1.77–1.89 (m, 2H, $CH_2$), 2.48 (t, $J = 6.0$ Hz, 2H, $CH_2$), 2.83 (s, 3H, $SCH_3$), 2.86–2.96 (m, 2H, $CH_2$), 3.49 (s, 3H, $NCH_3$), 7.36 (d, $J = 9.0$ Hz, 2H, Ar–H), 7.64 (d, $J = 9.0$ Hz, 2H, Ar–H), 8.28 (d, $J = 9.0$ Hz, 2H, Ar–H), 8.38 (d, $J = 9.0$ Hz, 2H, Ar–H), 8.39 (s, 1H, =CH); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta_C$ (ppm): 15.3 ($CH_3$), 22.3 ($CH_2$), 27.6 ($2CH_2$), 30.4 ($CH_3$), 110.5 (C), 123.6 (2CH, Ar), 123.9 (2CH, Ar), 128.2 (2CH, Ar), 129.7 (C), 130.3 (CH), 130.4 (2CH, Ar), 138.0 (C), 144.0 (C), 145.9 (C), 146.7 (C), 147.3 (C), 150.0 (C), 155.2 (C), 158.1 (C), 160.9 (C), 162.6 (C); MS (EI): *m/z* 515(44) [$M^+$], 514(55), 501(32), 500(100). *Anal*. Calcd for $C_{26}H_{21}N_5O_5S$: C, 60.57; H, 4.11; N, 13.58; S, 6.22. Found: C, 60.66; H, 4.08; N, 13.51; S, 6.27.

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