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Reaction of Hexahydropyirimidine-2,4,6-trione with Naphthalen-2-amine and Benzaldehydes

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Abstract—Previously unknown 12-aryl-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-diones were synthesized by three-component condensation of naphthalen-2-amine with substituted benzaldehydes and barbituric acid through intermediate 5-benzylidenebarbituric acids.

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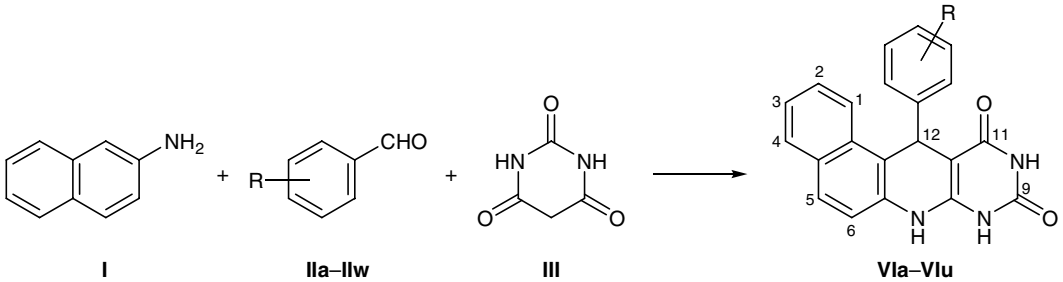
Hexahydropyrimidine-2,4,6-trione (barbituric acid) constitutes a structural base of numerous medical agents exhibiting antispasmodic, soporific, and narcotic activity [1–3]. Apart from medical practice, derivatives of barbituric acid are used as antioxidants and lignin chromophores [4–6]. Therefore, syntheses of new barbituric acid derivatives attract interest from both theoretical and practical viewpoints. Barbituric acid is highly reactive. Its hexahydropyrimidine possesses four labile hydrogen atoms, those attached to C^5 being especially active. Barbituric acid readily undergoes alkylation, and its condensations with ketones and aldehydes are well known [7, 8].

The present work continues our previous studies [9, 10] on cascade heterocyclizations of naphthalen-2-amine with substituted benzaldehydes and CH acids. We examined three-component condensation of naphthalen-2-amine (**I**) with substituted benzaldehydes **IIa**–**IIw** and pyrimidinetrione **III**. The reactions were carried out by heating equimolar amounts of the reactants in boiling butanol for 30–40 min, and the products were 12-aryl-7,8,9,10,11,12-hexahydrobenzo[*f*]-pyrimido[4,5-*b*]quinoline-9,11-diones **VIa**–**VIu** (Scheme 1).

Taking into account our previous data on the three-component condensation involving naphthalen-2-amine, benzaldehydes, and 1,3-diketones [11] and the structure of final products **VI**, two possible reaction pathways were presumed (Scheme 2). Both these are equally probable, for the synthesis of Schiff bases **IV** from naphthalen-2-amine, followed by their heterocyclization with CH acids, and the condensation of aldehydes with barbituric acid to form 5-benzylidene derivatives **V** are well known [12, 13].

The first reaction pathway includes formation of unstable intermediate **A** which then decomposes into

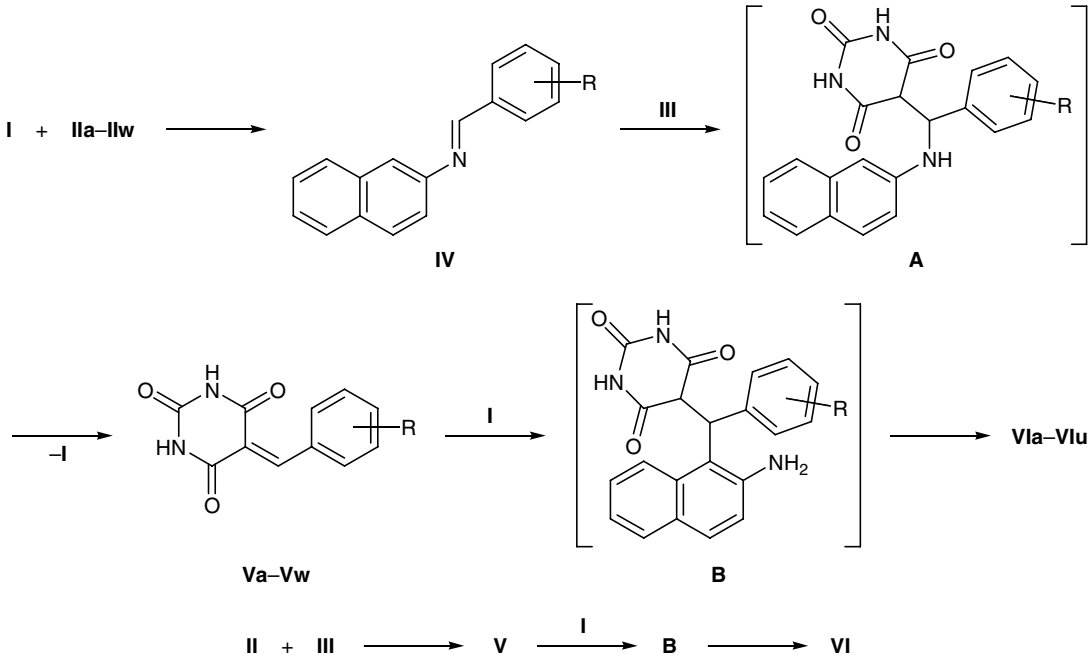
Scheme 1.



I **IIa–IIw** **III** **VIa–VIu**

R = H (**a**), 4-Br (**b**), 4-O_2N (**c**), 4-*i*-Pr (**d**), 4-Ph (**e**), 4-HO (**f**), 4-MeO (**g**), 3-Br (**h**), 3-O_2N (**i**), 3-HO (**j**), 2-Cl (**k**), 2-O_2N (**l**), 2-HO (**m**), 2-MeO (**n**), 2,4-Cl_2 (**o**), 2-Cl-6-F (**p**), 3,4-$(HO)_2$ (**q**), 2,4-$(MeO)_2$ (**r**), 3,4-$(MeO)_2$ (**s**), 3-MeO-4-HO (**t**), 3-EtO-4-HO (**u**), 4-Me_2N (**v**), 4-Et_2N (**w**).

Scheme 1.



5-benzylidenebarbituric acid **V** and naphthalene-2-amine (**I**). The highest electron density in molecule **I** is localized on the carbon atom in the α-position with respect to the amino group; addition at the double C=C bond of **V** gives 5-[2-aminonaphthyl(aryl)methyl]-hexahydropyrimidine-2,4,6-trione **B**, and heterocyclization of the latter with elimination of water molecule yields the final product, 12-aryl-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione **VI**. According to the second pathway, condensation of substituted benzaldehyde with barbituric acid gives 5-benzylidenebarbituric acid **V** having an electrophilic carbon atom at the exocyclic double C=C bond; intermediate **V** is capable of taking up naphthalen-2-amine at the α-carbon atom of the latter with formation of structure **B**. Eventually, the examined three-component condensation of naphthalen-2-amine with benzaldehydes and barbituric acid may be regarded as the reaction of compounds **V** with the amine.

In fact, 5-benzylidenebarbituric acids **Va**–**Vw** were synthesized by reactions of aldehydes **II** with barbituric acid (**III**) in alcohol, and their subsequent treatment with amine **I** under the same conditions gave 12-aryl-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]-quinoline-9,11-diones **VIa**–**VIu**.

Some general relations holding in the examined condensation should be noted. Electron-withdrawing groups in the *para* position of the benzene ring in 5-benzylidenebarbituric acids reduce the electron density on the exocyclic carbon atom at the double C=C bond, thus favoring addition of naphthalene-2-amine, and the yield of compounds **VIb**–**VIe** attains 55–70%. The same substituents in the *meta* position do not affect the reaction to an appreciable extent, so that the yield of products **VIh** and **VIi** is smaller.

Electron-donor substituents in the benzene ring increase the electron density on the electrophilic reaction center of barbituric acid derivatives **V** as a result of π-conjugation with the double bond, and the formation of new C–C bond is hindered. Therefore, the yields of compounds **VIf** and **VIg** are as poor as 30 and 37%, respectively, while 5-benzylidenebarbituric acids **Vv** and **Vw** fail to react with naphthalen-2-amine at all. From the reaction mixtures obtained from naphthalen-2-amine, barbituric acid, and aldehydes **IIv** and **IIw**, only the corresponding barbituric acid derivatives **Vv** and **Vw** were isolated. On the other hand, electron-donor groups in the *meta* position of the benzene ring in compounds **V** do not hamper the process so strongly, and the yield of 12-(3-hydroxyphenyl)-7,8,9,10,-11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione (**VIj**) was greater by 12% than that of 12-(4-hydroxyphenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione (**VIf**). Increase in the yield of final products was observed in the three-component condensation with disubstituted benzaldehydes containing two electron-donor substituents in the *meta* and *para* positions. The yields of

Chemical shifts of carbon nuclei in the ^{13}C NMR spectrum of compound **VIb** (10% solution in DMSO-d_6)

Atom	δ, ppm
C^{1}	122.65 d
C^{2}	127.08 d
C^{3}	123.93 d
C^{4}	128.68 d
C^{4a}	130.43 s
C^{5}	128.53 d
C^{6}	117.49 d
C^{6a}	133.83 s
C^{7a}	145.00 s
C^{9}	150.18 s
C^{11}	162.83 s
C^{11a}	86.21 s
C^{12}	35.85 d
C^{12a}	114.92 s
C^{12b}	130.80 s
$C^{1'}$	145.89 s
$C^{2'}$	129.82 d
$C^{3'}$	130.97 d
$C^{4'}$	119.10 s

12-(3,4-dihydroxyphenyl)-, 12-(3,4-dimethoxyphenyl)-, 12-(4-hydroxy-3-methoxyphenyl)-, and 12-(3-ethoxy-4-hydroxyphenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]-pyrimido[4,5-*b*]quinoline-9,11-diones **VIq**, **VIs**, **VIt**, and **VIu** were 49, 53, 62, and 59%, respectively; i.e., they exceeded the yields of 12-(4-hydroxyphenyl)- and 12-(4-methoxyphenyl)-substituted analogs **VIf** and **VIg**. Presumably, the *meta*-substituent in **Vq**, **Vs**, **Vt**, and **Vu** partially eliminates electronic effect of the *para*-hydroxy or *para*-alkoxy group due to distortion of planar structure of molecule **V** [14].

Substituents in the *ortho* position are likely to exert steric effect on the reaction center in 5-benzylidene-barbituric acids **V**. Thus the yield of *o*-nitrophenyl derivative **VIl** is slightly lower despite positive electronic effect of the nitro group. Steric effect of the *ortho*-substituent is more distinct in 5-(2-methoxybenzylidene)hexahydropyrimidine-2,4,6-trione (**Vn**): the yield of 12-(2-methoxyphenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione (**VIn**) is as low as 14%.

12-Aryl-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido-[4,5-*b*]quinoline-9,11-diones **VIa**–**VIu** were isolated as crystalline substances melting above 320°C. Their structure was confirmed by the ^{1}H NMR spectra. The singlet at δ 5.60–6.20 ppm was assigned to 12-H, and that at δ 8.80–9.29 ppm, to 7-H. A large difference in the chemical shifts of these protons indicates that they are separated by five bonds and that no spin–spin coupling exists between them. The spectra also contained singlets in the regions δ 10.08–10.38 and 10.35–10.65 ppm due to NH protons in the pyrimidine ring of compound **VI**.

Analysis of the ^{1}H–^{1}H and direct ^{13}C–^{1}H coupling constants in the HMBC spectrum of compound **VIb** allowed us to identify signals from carbon atoms in its molecule (see table). The C^{12a} signal appears at δ_C 114.92 ppm; it showed cross peaks due to couplings with protons resonating at δ 5.72 (12-H) and 9.18 ppm (NH proton in the 1,4-dihydropyridine ring). The absence of correlation between 7-H, on the one hand, and C^{12} bearing the aryl group and $C^{1'}$ of the phenyl substituent, on the other, provides an additional proof for the assumed structure.

The IR spectra of **VIa**–**VIu** contained absorption bands corresponding to stretching vibrations of the N–H bonds (3520–3185 cm^{-1}) and carbonyl groups (1729–1701 cm^{-1}). Compounds **VIb** and **VIh** characteristically showed a strong absorption band at 581 and 578 cm^{-1}, respectively, due to stretching vibrations of the C–Br bond; strong bands belonging to symmetric and antisymmetric stretching vibrations of the nitro groups in **VIc**, **VIi**, and **VIl** were located at 1398–1396 and 1545–1542 cm^{-1}, respectively.

The base peak in the mass spectra of **VIa**–**VIu** is that with *m*/*z* 264 ($[M - C_6H_4]^+$, I_{rel} 100%); also, ion peak with *m*/*z* 265 ($[M - C_6H_4 + 1]^+$, I_{rel} 65–70%) is present; the molecular ion peaks $[M]^+$ had a relative intensity of 28 to 35%. Positive fragment ions with *m*/*z* 111 (I_{rel} 28–33%), 134 (I_{rel} 56–60%), 139 (I_{rel} 90–96%), 148 (I_{rel} 72–78%), 153 (I_{rel} 47–55%), 166 (I_{rel} 32–39%), and 222 (I_{rel} 18–23%) are formed from the $[M - C_6H_4]^+$ ion; they are observed in the mass spectra of all compounds **VIa**–**VIu** and therefore are not given in Experimental (except for $[M]^+$).

EXPERIMENTAL

The IR spectra were recorded on a Nicolet Protege-460 spectrometer with Fourier transform from samples prepared as thin films of KBr pellets. The NMR spectra were measured on a Bruker AC-500 spectrometer at 500 MHz for ^{1}H and 125 MHz for ^{13}C from 5% solutions in DMSO-d_6 using tetramethylsilane as internal

reference. The mass spectra were run on a Hewlett–Packard HP 5890/5972 GC–MS system (electron impact, 70 eV, HP-5MS column).

5-Benzylidenehexahydropyrimidine-2,4,6-triones Va–Vw were synthesized by heating equimolar amounts of barbituric acid (**III**) and substituted benzaldehyde **IIa–IIw** in boiling alcohol for 20–30 min. Their physical constants coincided with those reported in [15–17].

12-Aryl-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-diones VIa–VIu (*general procedure***).** *a*. A solution of 1.43 g (0.01 mol) of naphthalene-2-amine (**I**), 0.01 mol of substituted benzaldehyde **IIa**–**IIw**, and 1.3 g (0.01 mol) of barbituric acid **III** in 20 ml of butanol was heated under reflux until a solid product began to separate from the solution (30–60 min). After cooling, te precipitate was filtered off, washed with hot water and diethyl ether, and recrystallized from alcohol–benzene (1:1).

b. A solution of 0.01 mol of 5-benzylidenehexahydropyrimidine-2,4,6-trione **Va–Vw** and 0.01 mol of naphthalen-2-amine (**I**) in 20 ml of butanol was heated under reflux until a solid product began to separate from the solution. After cooling, the precipitate was filtered off, and recrystallized from a 1:1 alcohol–benzene mixture.

12-Phenyl-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione (VIa). Yield 60%, colorless crystals. IR spectrum, ν, cm^{-1}: 3191, 3073, 2957, 1705, 1642, 1590, 1541, 1470, 1449, 1390, 1235, 813, 581. ^{1}H NMR spectrum, δ, ppm: 5.70 s (1H, 12-H), 6.80–7.30 m and 7.60–7.90 m (11H, H_{arom}), 8.80 s (1H, 7-H), 10.08 s (1H, NH), 10.35 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 341 (35) $[M]^+$. Found, %: C 73.87; H 4.35; N 12.33. $C_{21}H_{15}N_3O_2$. Calculated, %: C 73.90; H 4.39; N 12.31.

12-(4-Bromophenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione (VIb). Yield 70%, colorless crystals. IR spectrum, ν, cm^{-1}: 3187, 3070, 2952, 1712, 1654, 1597, 1564, 1473, 1441, 1389, 1235, 815, 581. ^{1}H NMR spectrum, δ, ppm: 5.70 s (1H, 12-H); 7.20 m, 7.30–7.50 m, and 7.80–7.90 m (10H, H_{arom}); 9.10 s (1H, 7-H); 10.30 s (1H, NH); 10.60 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 420 (31) $[M]^+$. Found, %: C 60.02; H 3.36; Br 19.00; N 10.04. $C_{21}H_{14}BrN_3O_2$. Calculated, %: C 60.00; H 3.33; Br 19.04; N 10.00.

12-(4-Nitrophenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione (VIc). Yield 65%, yellow crystals. IR spectrum, ν, cm^{-1}: 3388, 3196, 3075, 1707, 1645, 1591, 1545, 1471, 1396, 1349, 1236, 1111, 820, 749, 697, 579. ^{1}H NMR spectrum, δ, ppm: 5.90 s (1H, 12-H), 7.30–8.10 m (10H, H_{arom}), 8.96 s (1H, 7-H), 10.25 s (1H, NH), 10.50 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 386 (30) $[M]^+$. Found, %: C 65.24; H 3.63; N 14.47. $C_{21}H_{14}N_4O_4$. Calculated, %: C 65.28; H 3.65; N 14.50.

12-(4-Isopropylphenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione (VId). Yield 60%, colorless crystals. IR spectrum, ν, cm^{-1}: 3418, 3185, 3072, 2959, 2870, 1708, 1662, 1647, 1598, 1534, 1469, 1396, 1300, 1232, 814, 591. ^{1}H NMR spectrum, δ, ppm: 1.20 d [6H, $CH(CH_3)_2$, J = 7.0 Hz], 2.26 m [1H, $CH(CH_3)_2$], 5.70 s (1H, 12-H), 7.00 d ($1H_{arom}$, J = 6.9 Hz), 7.19 d ($1H_{arom}$, J = 7.0 Hz), 7.30–7.50 m ($5H_{arom}$), 7.80 and 7.96 m (3H, H_{arom}), 8.90 s (1H, 7-H), 10.28 s (1H, NH), 10.54 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 383 (33) $[M]^+$. Found: % C 75.21; H 5.51; N 11.00. $C_{24}H_{21}N_3O_2$. Calculated, %: C 75.19; H 5.48; N 10.97.

12-(Biphenyl-4-yl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione (VIe). Yield 55%, colorless crystals. IR spectrum, ν, cm^{-1}: 3412, 3176, 2945, 2876, 1714, 1667, 1640, 1591, 1538, 1471, 1396, 1322, 1236, 814, 591. ^{1}H NMR spectrum, δ, ppm: 5.78 s (1H, 12-H); 6.90–7.10 m, 7.20–7.50 m, and 7.60–7.80 m (13H, H_{arom}); 7.80 d (1H, H_{arom}, J = 7.2 Hz); 8.00 d (1H, H_{arom}, J = 6.8 Hz); 9.10 s (1H, 7-H); 10.32 s (1H, NH); 10.60 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 417 (30) $[M]^+$, 154 (43) $[C_6H_5C_6H_5]^+$. Found, %: C 77.65; H 4.54; N 10.10. $C_{27}H_{19}N_3O_2$. Calculated, %: C 77.69; H 4.56; N 10.07.

12-(4-Hydroxyphenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione (VIf). Yield 30%, colorless crystals. IR spectrum, ν, cm^{-1}: 3320, 3182, 3065, 2952, 2864, 1710, 1660, 1657, 1588, 1533, 1462, 1312, 1244, 816, 593. ^{1}H NMR spectrum, δ, ppm: 5.70 s (1H, 12-H); 6.50 d (1H, H_{arom}, J = 6.7 Hz); 6.60–6.90 m, 7.50–7.70 m, and 8.10–8.30 m (9H, H_{arom}, and 1H, OH); 9.08 s (1H, 7-H); 10.28 s (1H, NH); 10.37 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 357 (27) $[M]^+$. Found, %: C 70.57; H 4.24; N 11.79. $C_{21}H_{15}N_3O_3$. Calculated, %: C 70.58; H 4.23; N 11.76.

12-(4-Methoxyphenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione (VIg). Yield 37%, colorless crystals. IR spectrum, ν, cm^{-1}: 3425, 3273, 3250, 3221, 3176, 3090, 2922, 2857, 1708, 1634, 1600, 1552, 1447, 1392, 1294, 1255, 1236, 1110,

1045, 871, 821, 758, 581. ^{1}H NMR spectrum, δ, ppm: 3.60 s (3H, OCH_3), 5.69 s (1H, 12-H), 6.70 d (1H, H_{arom}, J = 6.9 Hz), 7.10–7.42 m and 7.80–7.85 m (8H, H_{arom}), 7.90 d (1H, H_{arom}, J = 7.3 Hz), 8.98 s (1H, 7-H), 10.20 s (1H, NH), 10.50 s (1H, NH). Mass spectrum, m/z (I_{rel}, %): 371 (31) $[M]^+$. Found, %: C 71.19; H 4.53; N 11.56. $C_{22}H_{17}N_3O_3$. Calculated, %: C 71.15; H 4.58; N 11.32.

12-(3-Bromophenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione (VIh). Yield 57%, colorless crystals. IR spectrum, ν, cm^{-1}: 3185, 3064, 2953, 1712, 1656, 1600, 1561, 1478, 1437, 1392, 1235, 815, 578. ^{1}H NMR spectrum, δ, ppm: 5.79 s (1H, 12-H); 7.10–7.18 m, 7.20–7.30 m, and 7.35–7.50 m (10H, H_{arom}); 9.10 s (1H, 7-H); 10.40 s (1H, NH); 10.60 (1H, NH). Mass spectrum, m/z (I_{rel}, %): 420 (34). Found, %: C 59.57; H 3.31; Br 18.97; N 10.05. $C_{21}H_{14}BrN_3O_2$. Calculated, %: C 60.00; H 3.33; Br 19.04; N 10.00.

12-(3-Nitrophenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione (VIi). Yield 43%, yellow crystals. IR spectrum, ν, cm^{-1}: 3416, 3237, 3218, 3076, 2924, 1729, 1637, 1589, 1545, 1528, 1469, 1398, 1384, 1355, 1231, 822, 746, 691. ^{1}H NMR spectrum, δ, ppm: 5.90 s (1H, 12-H), 7.30–7.50 m (4H, H_{arom}), 7.70 d (1H, H_{arom}, J = 6.8 Hz), 7.82–7.94 m (4H, H_{arom}), 8.10 s (1H, H_{arom}), 9.29 s (1H, 7-H), 10.40 s (1H, NH), 10.65 s (1H, NH). Mass spectrum, m/z (I_{rel}, %): 386 (34) $[M]^+$. Found, %: C 65.21; H 3.67; N 14.54. $C_{21}H_{14}N_4O_4$. Calculated, %: C 65.28; H 3.65; N 14.50.

12-(3-Hydroxyphenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione (VIj). Yield 42%, colorless crystals. IR spectrum, ν, cm^{-1}: 3320, 3182, 3071, 2954, 2864, 1710, 1665, 1652, 1583, 1531, 1462, 1310, 1248, 815, 591. ^{1}H NMR spectrum, δ, ppm: 5.76 s (1H, 12-H); 6.62–6.90 m, 7.60–7.75 m, and 8.10–8.30 m (10H, H_{arom}, and 1H, OH); 9.14 s (1H, 7-H); 10.26 s (1H, NH); 10.34 s (1H, NH). Mass spectrum, m/z (I_{rel}, %): 357 (26) $[M]^+$. Found, %: C 70.59; H 4.21; N 11.75. $C_{21}H_{15}N_3O_3$. Calculated, %: C 70.58; H 4.23; N 11.76.

12-(2-Chlorophenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione (VIk). Yield 49%, colorless crystals. IR spectrum, ν, cm^{-1}: 3185, 3075, 2954, 1719, 1652, 1608, 1561, 1474, 1431, 1392, 1230, 817, 572. ^{1}H NMR spectrum, δ, ppm: 6.00 s (1H, 12-H); 7.00–7.09 m and 7.10–7.15 m (2H, H_{arom}); 7.28–7.30 m, 7.30–7.38 m, and 7.40–7.46 m (5H, H_{arom}); 7.80–7.86 m (2H, H_{arom}); 8.09 d (1H, H_{arom}, J = 6.4 Hz); 9.10 s (1H, 7-H); 10.28 s (1H, NH); 10.50 s (1H, NH). Mass spectrum, m/z (I_{rel}, %): 375 (29) $[M]^+$. Found, %: C 67.16; H 3.77; Cl 9.38; N 11.24. $C_{21}H_{14}ClN_3O_2$. Calculated, %: C 67.20; H 3.73; Cl 9.33; N 11.20.

12-(2-Nitrophenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione (VIl). Yield 53%, yellow crystals. IR spectrum, ν, cm^{-1}: 3418, 3235, 3214, 3072, 2921, 1728, 1633, 1587, 1542, 1526, 1463, 1398, 1384, 1355, 1230, 821, 743, 690. ^{1}H NMR spectrum, δ, ppm: 5.60 s (1H, 12-H), 7.10–7.40 m and 7.60–7.90 m (9H, H_{arom}), 8.38 d (1H, H_{arom}, J = 7.0 Hz), 9.20 s (1H, 7-H), 10.30 s (1H, NH), 10.60 s (1H, NH). Mass spectrum, m/z (I_{rel}, %): 386 (35) $[M]^+$. Found, %: C 65.29; H 3.65; N 14.52. $C_{21}H_{14}N_4O_4$. Calculated, %: C 65.28; H 3.65; N 14.50.

12-(2-Hydroxyphenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione (VIm). Yield 25%, colorless crystals. IR spectrum, ν, cm^{-1}: 3318, 3190, 3068, 2954, 2873, 1716, 1660, 1653, 1587, 1528, 1460, 1311, 1248, 815, 596. ^{1}H NMR spectrum, δ, ppm: 5.90 s (1H, 12-H); 6.65–6.90 m, 7.40–7.64 m, and 8.00–8.20 m (10H, H_{arom}); 9.24 s (1H, 7-H); 10.10 s (1H, NH); 10.60 s (1H, NH); 10.90 s (1H, OH). Mass spectrum, m/z (I_{rel}, %): 375 (29) $[M]^+$. Found, %: C 70.54; H 4.24; N 11.78. $C_{21}H_{15}N_3O_3$. Calculated, %: C 70.58; H 4.23; N 11.76.

12-(2-Methoxyphenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione (VIn). Yield 14%, colorless crystals. IR spectrum, ν, cm^{-1}: 3422, 3273, 3250, 3226, 3172, 3083, 2924, 2856, 1701, 1633, 1601, 1558, 1447, 1398, 1291, 1255, 1238, 1113, 1045, 873, 821, 753, 587. ^{1}H NMR spectrum, δ, ppm: 3.90 s (3H, OMe); 6.00 s (1H, 12-H); 6.70–6.75 m, 6.80–6.84 m, 7.00–7.10 m, 7.20–7.25 m, 7.28–7.30 m, 7.40–7.45 m, and 7.70–7.80 m (9H, H_{arom}); 8.19 d (1H, H_{arom}, J = 7.7 Hz); 8.91 s (1H, 7-H); 10.20 s (1H, NH); 10.40 s (1H, NH). Mass spectrum, m/z (I_{rel}, %): 371 (28) $[M]^+$. Found, %: C 71.11; H 4.56; N 11.34. $C_{22}H_{17}N_3O_3$. Calculated, %: C 71.15; H 4.58; N 11.32.

12-(2,4-Dichlorophenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione (VIo). Yield 61%, colorless crystals. IR spectrum, ν, cm^{-1}: 3185, 3079, 2953, 1728, 1670, 1601, 1567, 1472, 1436, 1395, 1230, 823, 572. ^{1}H NMR spectrum, δ, ppm: 5.90 s (1H, 12-H); 7.22 d (1H, H_{arom}, J = 7.00 Hz); 7.30–7.38 m, 7.40–7.47 m, and 7.80–7.85 m (7H, H_{arom}); 8.00 d (1H, H_{arom}, J = 6.8 Hz); 9.24 s (1H, 7-H); 10.30 s (1H, NH); 10.51 s (1H, NH). Mass spectrum, m/z (I_{rel}, %): 409 (33) $[M]^+$. Found, %: C 61.58;

H 3.15; Cl 17.07; N 10.30. $C_{21}H_{13}Cl_2N_3O_2$. Calculated, %: C 61.61; H 3.18; Cl 17.11; N 10.27.

12-(2-Chloro-6-fluorophenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione (VIp). Yield 64%, colorless crystals. IR spectrum, ν, cm^{-1}: 3433, 3272, 3212, 3075, 1706, 1659, 1633, 1601, 1555, 1471, 1445, 1396, 1235, 784, 775. ^{1}H NMR spectrum, δ, ppm: 6.20 s (1H, 12-H); 7.10–7.20 m, 7.24–7.36 m, 7.40–7.48 m, and 7.80–7.85 m (9H, H_{arom}); 9.27 s (1H, 7-H); 10.31 s (1H, NH); 10.50 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 393 (33) $[M]^+$. Found, %: C 64.14; H 3.36; N 10.71. $C_{21}H_{13}ClFN_3O_2$. Calculated, %: C 64.12; H 3.31; N 10.68.

12-(3,4-Dihydroxyphenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione (VIq). Yield 49%, colorless crystals. IR spectrum, ν, cm^{-1}: 3285, 3170, 2951, 2873, 1709, 1665, 1582, 1531, 1464, 1307, 1239, 810, 592. ^{1}H NMR spectrum, δ, ppm: 5.70 s (1H, 12-H); 7.00–7.08 m, 7.12–7.19 m, 7.22–7.30 m, and 7.30–7.48 m (6H, H_{arom}, and 2H, OH); 7.80–7.84 m (2H, H_{arom}); 7.90 d (1H, H_{arom}, J = 7.04 Hz); 9.00 s (1H, 7-H); 10.26 s (1H, NH); 10.54 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 373 (32) $[M]^+$. Found, %: C 68.59; H 4.00; N 11.30. $C_{21}H_{15}N_3O_4$. Calculated, %: C 68.56; H 4.02; N 11.26.

12-(2,4-Dimethoxyphenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione (VIr). Yield 40%, colorless crystals. IR spectrum, ν, cm^{-1}: 3410, 3200, 3080, 1705, 1647, 1611, 1587, 1540, 1508, 1471, 1397, 1294, 1228, 1210, 1117, 1036, 829, 815, 573. ^{1}H NMR spectrum, δ, ppm: 3.60 s (3H, OCH_3), 3.85 s (3H, OCH_3), 5.90 s (1H, 12-H), 6.35 d (1H, H_{arom}, J = 7.2 Hz), 6.49 s (1H, H_{arom}), 7.10 d (1H, H_{arom}, J = 6.5 Hz), 7.26–7.32 m and 7.35–7.42 m (3H, H_{arom}), 7.70 d (1H, H_{arom}, J = 7.0 Hz), 7.78 d (1H, H_{arom}, J = 7.0 Hz), 8.19 d (1H, H_{arom}, J = 7.2 Hz), 8.90 s (1H, 7-H), 10.15 s (1H, NH), 10.40 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 401 (29) $[M]^+$. Found, %: C 68.77; H 4.78; N 10.50. $C_{23}H_{19}N_3O_4$. Calculated, %: C 68.82; H 4.74; N 10.47.

12-(3,4-Dimethoxyphenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione (VIs). Yield 53%, colorless crystals. IR spectrum, ν, cm^{-1}: 3408, 3215, 3078, 1710, 1642, 1609, 1582, 1547, 1536, 1502, 1473, 1395, 1291, 1226, 1208, 1113, 1039, 831, 815, 572. ^{1}H NMR spectrum, δ, ppm: 3.60 s (3H, OCH_3), 3.65 s (3H, OCH_3), 5.69 s (1H, 12-H), 6.53 d (1H, H_{arom}, J = 6.9 Hz), 6.70 d (1H, H_{arom}, J = 6.8 Hz), 7.08 s (1H, H_{arom}), 7.30–7.40 m and 7.40–7.48 m (3H, H_{arom}), 7.80–7.85 m (2H, H_{arom}), 7.96 d (1H, H_{arom}, J = 6.5 Hz), 9.10 s (1H, 7-H), 10.40 s (1H, NH), 10.60 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 401 (17) $[M]^+$. Found, %: C 68.84; H 4.77; N 10.49. $C_{23}H_{19}N_3O_4$. Calculated, %: C 68.82; H 4.74; N 10.47.

12-(4-Hydroxy-3-methoxyphenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinolin-9,11-dione (VIt). Yield 62%, colorless crystals. IR spectrum, ν, cm^{-1}: 3510, 3210, 3078, 1709, 1642, 1590, 1547, 1512, 1473, 1446, 1393, 1289, 1224, 1113, 817. ^{1}H NMR spectrum, δ, ppm: 3.64 s (3H, OCH_3), 5.63 s (1H, 12-H), 6.47 d (1H, H_{arom}, J = 7.2 Hz), 6.52 d (1H, H_{arom}, J = 7.4 Hz), 7.00 s (1H, H_{arom}), 7.30–7.38 m and 7.40–7.44 m (3H, H_{arom}), 7.79–7.82 m (2H, H_{arom}), 7.96 d (1H, H_{arom}, J = 7.00 Hz), 8.20 s (1H, OH), 8.96 s (1H, 7-H), 10.28 s (1H, NH), 10.53 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 387 (29) $[M]^+$. Found, %: C 68.24; H 4.42; N 10.88. $C_{22}H_{17}N_3O_4$. Calculated, %: C 68.20; H 4.39; N 10.85.

12-(3-Ethoxy-4-hydroxyphenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione (VIu). Yield 59%, colorless crystals. IR spectrum, ν, cm^{-1}: 3520, 3206, 3079, 1707, 1641, 1592, 1514, 1472, 1444, 1397, 1275, 1237, 1114, 816. ^{1}H NMR spectrum, δ, ppm: 1.25 t (3H, $OCH_2C\mathbf{H}_3$), 3.86–3.94 m (2H, $OC\mathbf{H}_2CH_3$), 5.60 s (1H, 12-H), 6.40 d (1H, H_{arom}, J = 7.2 Hz), 6.50–6.54 m (1H, H_{arom}), 6.90 s (1H, H_{arom}), 7.30–7.42 m (3H, H_{arom}), 7.80–7.84 m (2H, H_{arom}), 7.93 d (1H, H_{arom}, J = 6.9 Hz), 8.60 s (1H, OH), 9.08 s (1H, 7-H), 10.38 s (1H, NH), 10.60 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 401 (27) $[M]^+$. Found, %: C 68.87; H 4.76; N 10.51. $C_{23}H_{19}N_3O_4$. Calculated, %: C 68.82; H 4.74; N 10.48.

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