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Olena V. Il'chenko [a] , Oleg V. Zaremba [b] , Sergiy M. Kovalenko [a] , Aliaksandr A. Sherakov [c] & Valentin P. Chernykh [a]

[a] National University of Pharmacy , Kharkiv, Ukraine

[b] Institute of Combinatorial Organic Chemistry , Kharkiv, Ukraine

[c] Center for Examination and Tests in Health Service, Republican Unitary Enterprise , Minsk, Byelarus

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Synthesis of 3-Substituted 2-Thioxo-2,3-dihydro-1*H*-benzofuro[3,2-*d*] pyrimidin-4(1*H*)-ones

Olena V. Il'chenko
National University of Pharmacy, Kharkiv, Ukraine

Oleg V. Zaremba
Institute of Combinatorial Organic Chemistry, Kharkiv, Ukraine

Sergiy M. Kovalenko
National University of Pharmacy, Kharkiv, Ukraine

Aliaksandr A. Sherakov
Center for Examination and Tests in Health Service, Republican Unitary Enterprise, Minsk, Byelarus

Valentin P. Chernykh
National University of Pharmacy, Kharkiv, Ukraine

Abstract: With the purpose of searching for new biologically active compounds, a method of synthesis of new heterocyclic systems [3-alkyl(aryl)-2-thioxo-2,3-dihydro-1*H*-benzofuro[3,2-*d*]pyrimidin-4(1*H*)-ones] has been developed. The method is based on the interaction of ethyl 3-isothiocyanato-1-benzofurane-2-carboxylate in 2-propanol with amines in the presence of an equimolecular quantity of triethylamine.

Keywords: ethyl 3-isothio-cyanato-1-benzofurane-2-carboxylate, 2-thioxo-2,3-dihydro-1*H*-benzofuro[3,2-*d*]pyrimidin-4(1*H*)-one

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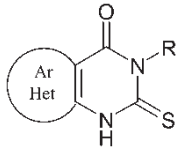
Address correspondence to Sergiy M. Kovalenko, National University of Pharmacy, 53, Pushkinska Str., Kharkiv 61002, Ukraine. E-mail: kosn@ic.kharkov.ua

The present article presents a suitable synthetic route to the novel heterocyclic system of 2-thioxoquinazoline-4-one. Because the systems containing the 2-thioxoquinazoline-4-one moiety do possess many types of physiological activity, they have been extensively studied for several years.[1–6]



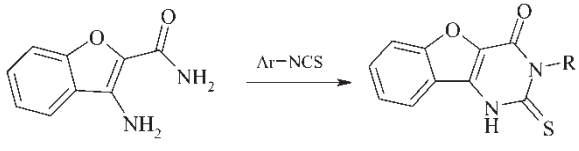
2-Thioxoquinazoline-4-one derivatives are known to exhibit anxiolytic,[7,8] antihypertensive, fungicidal, antidepressant, and antihyperlipaemic, properties.[9]

The synthesis of some novel 4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazolines[10] and thienopyrimidin-4-ones[11] has been recently developed in our laboratory and reported in some papers. The results obtained prompted us to investigate further with the idea of designing molecules containing both benzofuran and pyrimidine moieties.

Among the benzofuran derivatives there are a lot of substances possessing the following activities: anti-inflammatory, antiarythmic, haemostatic, antibacterial, fungicidal, antiviral, antitumor, and antioxidant ones.[12] It should be expected that the newly synthesized related compounds may possibly possess interesting pharmacological properties.

The literature survey shows only one article on the synthesis of 2-thioxo-2,3-dihydro-1*H*-benzofuro[3,2-*d*]pyrimidin-4(1*H*)-ones, which were obtained by the continuous boiling of the mixture of aryl isothiocyanate and 3-amino-1-benzofuran-2-carboxamide in the acetic acid (Scheme 1). However, it should be noted that the aromatic isothiocyanates were used in this reaction and the yield of the products does not exceed the range of 42–58%.[13]

The traditional synthesis of annelated 4-oxo-2-thioxopyrimidine systems is carried out by the condensation of *o*-aminoesters with substituted isothiocyanates.[14] In our investigations, the more effective synthetic route for 4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazolines[10] and thienopyrimidin-4-ones[11] has been developed. It is based on the condensation of the 2-methylcarboxyaryl(thienyl)isothiocyanates with different aliphatic and aromatic amines, aminoacids, hydrazines, hydrazides, sulfohydrazides, and thiosemicarbasides. This method has certain advantages compared with the traditional ones. The first advantage is the possibility of useing the expanded set of



Scheme 1.

"aminic" components. This approach has been found to be effective for the generation of combinatorial matrixes and synthesis of combinatorial libraries. The next advantages are both the improved yield and the purity of the combinatorial library products with relation to the same characteristics of ordinary synthesized products.

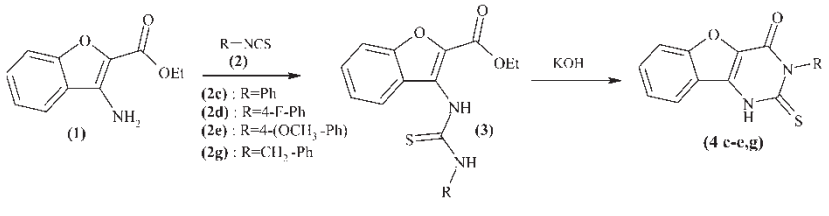
In the present article, we have researched both the traditional and novel synthetic pathways to the 2-thioxo-2,3-dihydro-1*H*-benzofuro[3,2-*d*]pyrimidin-4(1*H*)-ones, which had not been applied to the synthesis of these products before.

According to the first way, the synthesis of 3-substituted-2-thioxo-2,3-dihydro-1*H*-benzofuro[3,2-*d*]pyrimidin-4(1*H*)-ones was been carried out by the interaction of 3-amino-1-benzofuran-2-ethylcarboxylate (**1**) with isothiocyanates (**2**) in dimethylformamide (Scheme 2). The first stage of the reaction is the formation of corresponding N,N′-disubstituted thioureas (**3**), which have not been isolated from the reaction mixture. The thioureas (**3**) were then readily cyclized while heating in the alkaline solution to form the 3-substituted 2-thioxo-2,3-dihydro-1*H*-benzofuro[3,2-*d*]pyrimidin-4(1*H*)-ones (**4c**–**e**, **g**).

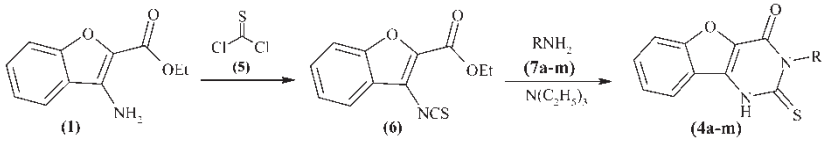
It should be mentioned that the reaction proceeds more readily in the case of aryl- and benzylisothiocyanates than in the case when alkyl ones are utilized. One can see that longer reaction time (3–6 h) was required for alkylisothiocyanates, and the yields of the products were lower (55–68%).

The second method is based on the reaction of 2-ethoxycarbonyl-3-isothiocyanato-1-benzofuran (**6**) with ammonia or primary aliphatic and aromatic amines **7b**–**k** in the presence of triethylamine, which leads to the formation of 3-N-substituted-2-thioxo-2,3-dihydro-1*H*-benzofuro[3,2-*d*]pyrimidin-4(1*H*)-ones **4a**–**m** (Scheme 3). The intermediate compound **6** has been prepared through the interaction of ethyl 3-amino-1-benzofuran-2-carboxylate (**1**) with thiophosgene **5**. The synthesis of **6** has been carried out in binary chloroform–water mixture at room temperature. The hydrogen chloride has been neutralized by aqueous potassium carbonate. The isothiocyanate **6** was used without special purification for further transformations.

^{1}H NMR spectra of the compounds (**4a**–**m**) possess the specific ABCD signals of the system of the benzofuran moiety protons as the combination of the pair of doublets of H-6 protons (7.60–7.82 ppm) and H-9 protons



Scheme 2.



Scheme 3. **(7a)**: R = H, **(7b)**: R = CH_3, **(7c)**: R = Ph, **(7d)**: R = 4-F-Ph, **(7e)**: R = 4-(OCH_3-Ph), **(7f)**: R = C_4H_9 **(7g)**: R = CH_2-Ph, **(7h)**: R = $(CH_2)_2$-OCH_3, **(7i)**: R = CH_2-(4-F-Ph), **(7j)**: R = CH_2-(4-OCH_3-Ph), **(7k)**: R = CH_2-(4-CH_3-Ph), **(71)**: R = CH_2COOH, **(7m)**: R = $(CH_2)_2COOH$.

(7.95–8.24 ppm) and the pair of triplets of H-7 protons (7.50–7.79 ppm) and H-8 protons (7.30–7.67 ppm). The NH group proton's signal appears as the broaded singlet at 13.8–14.0 ppm. The signals of the protons of the substituents in the 3-position are also present as the corresponding multiplets at 6.50–7.46 ppm when the moiety is aromatic and at 0.98–5.6 ppm when it is aliphatic.

The IR spectra of the compounds synthesized show several specific absorption bands. There are the strong band of C═O group of pyrimidinic ring at 1663–1715 cm^{-1} and vibration bands of C═S group at 1214–1288 cm^{-1}. The absorption bands of the C═C group of aromatic rings appear at intervals from 1477 to 1622 cm^{-1}.

The electronic absorption spectra (EAS) of propanol solutions of 3-substituted-2-thioxo-2,3-dihydro-1*H*-benzofuro[3,2-*d*]pyrimidin-4(1*H*)-ones at interval 38000–25000 cm^{-1} show two electronic $\pi \rightarrow \pi^*$ transitions with the maximum at 30540–34760 cm^{-1} and at 29800–30080 cm^{-1}. In the short-wavelength part of the spectra at interval 48000–38000 cm^{-1}, some intensity overlapped bands that are characteristic absorption for π-conjugated systems are observed.

Thus, as a result of a comparative study of two approaches to the synthesis of 3-substituted-2-thioxo-2,3-dihydro-1*H*-benzofuro[3,2-*d*]pyrimidin-4(1*H*)-ones, the interaction of 3-isothiocyanato-1-benzofuran-2-ethylcarboxylate (**6**) with different amines (**7**) in the presence of tryethylamine leads to the formation of 3-N-substituted-2-thioxo-2,3-dihydro-1*H*-benzofuro[3,2-*d*] pyrimidin-4(*1H*)-ones (**4a**–**m**). The application of the given method allowed us to expand considerably a line of derivatives of the given class of compounds and gave us an opportunity of introduction of various aminic components in the reaction.

EXPERIMENTAL

Melting points were measured with a Buchi B-520 melting-point apparatus and are not corrected. Elemental analysis was carried out within +0.4% of the theoretical value. IR spectra were recorded on Bruker Tensor-27

spectrometer in KBr. UV spectra were recorded on Specord M40 spectrometer in 2-propanol. ^{1}H NMR spectra were recorded on Varian WXR-400 (200-MHz) spectrometer in DMSO-d_6 using TMS as an internal standard. The course of reaction was supervised by the thin-layer chromatography (TLC) method on aluminum sheets precoated with Silufol UV_{254} silica gel (5 cm × 15 cm) (Kavalier, Czech Republic), eluent ethyl acetate–toluene system of the solvents 1:2. LC/MS spectra were obtained on a Shimadzu LS–10 VP, Gilson–215 apparatus, the automatic supply of the samples on mass spectrometer API 165EX, detector UV (215 and 254 nm), and ELS on Luna–C 18 column, Phenomenex, 5 cm × 2 mm. According to LC/MS data, all compounds have purity more than 95%.

Ethyl 3-amino-1-benzofuran-2-carboxylate (**1**) was prepared using the described approach.[15]

Ethyl 3-Isothiocyanato-1-benzofuran-2-carboxylate (6)

To a stirred mixture of 100 mL of chloroform and 50 mL of water, 100 mmol (20.5 g) of 3-amino-1-benzofuran-2-ethylcarboxylate (**1**) were added. Then a solution of 110 mmol (12.7 g) of thiophosgene in 50 mL of chloroform was added dropwise. The reaction mixture was stirred at room temperature for 2–3 h, and a solution of 250 mmol (34.5 g) of K_2CO_3 in 50 mL of water was added. The organic phase was washed with water (3 × 100 mL) and dried over $MgSO_4$, and the solvent was evaporated in vacuo. The crude product was crystallized from 2-propanole. Yield 89%.

General Procedure for the Preparation of 3-Alkyl(aryl)-2-tioxo-2,3-dihydro-1*H*-benzofuro[3,2-*d*]pyrimidin-4(1*H*)-ones (4a–k)

Method A (**4c–e**, **g**)

A solution of 5 mmol (1 g) of ethyl 3-amino-1-benzofurane-2-carboxylate (**1**) and 5.5 mmol of appropriated isothiocyanate (**2c–e, g**) in 10 mL of dimethylformamide was heated at reflux for 3–6 h. Then a solution of KOH [4 mmol (0.2 g) in 100 mL of water] was added, and the mixture was refluxed for 1 h. After cooling, the reaction mixture was diluted with 20 mL of water, and the precipitate was filtered and recrystallized from a mixture of 2-propanol and dimethylformamide. Yield 78–91%.

Method B (**4c–e**, **g**, **i**, **j**, **k**)

To a solution of 20 mmol (4.95 g) of 3-isothiocyanato-1-benzofuran-2-ethylcarboxylate (**6**) in 5–7 mL of 2-propanol, 22 mmol of primary amine (**7**) and 22 mmol (2.2 g) of triethylamine were added. The reaction mixture was

heated with stirring at 60–70°C for 3 h. Then 5 mL of acetic acid were added, and the resulting precipitate was filtered, washed with water, and crystallized from a suitable solvent. Yield 70–91%.

Method C (**4a**, **b**, **f**, **h**)

To a solution of 20 mmol (4.95 g) of 3-isothiocyanato-1-benzofuran-2-ethylcarboxylate (**6**) in 5–7 mL of 2-propanol, 22 mmol of primary amine (**7**) and 22 mmol (2.2 g) of triethylamine were added dropwise. The resulting mixture was heated at refluxe for 1 h and cooled, and acetic acid was added to pH = 4–5. The resulting precipitate was filtered, washed with water, and crystallized from a suitable solvent. Yield 75–95%.

Method D (**4l**, **m**)

To a solution of 40 mmol (10.0 g) of 3-isothiocyanato-1-benzofuran-2-ethylcarboxylate (**6**) in 5–7 mL of 2-propanol, a solution of triethylamine salt of amino acid (60 mmol of acid and 11.4 mL triethylamine) in 10 mL of 2-propanole was added. The reaction mixture was heated at reflux for ~1 h. After cooling, the mixture was acidified by hydrochloric acid to pH 2.5–3.0, and the resulting precipitate was filtered and crystallized from dimethylformamide. Yield 82–85%.

Data

2-Thioxo-2,3-dihydro-1*H*-benzofuro[3,2-*d*]pyrimidin-4(1*H*)-one (4a): Yield 95%. Light brown solid, mp 278–280°C; IR (cm^{-1}): 3392, 2999, 2889, 1687, 1616, 1557, 1512, 1218; UV (ν, cm^{-1}, ε 10^{-3}, $L \cdot mol^{-1} \cdot cm^{-1}$): 44060 (16.3), 41640 (15.1), 34760 (16.1); ^1H NMR (200 MHz, DMSO-d_6), δ, ppm: δ 7.70 (d, $J = 9.1$ Hz, 1H), 7.62 (t, $J = 4.5$ Hz, 1H), 7.45 (t, $J = 4.5$ Hz, 1H), 8.12 (d, $J = 9.1$ Hz, 1H), 12.75 (s, 1H, NH), 13.6 (s, 1H, NH). LC/MS (m/z, rel.%): 219 (100) [M +], 203 (60), 185 (8), 150 (18), 130 (55), 115 (48). Anal. calcd. for $C_{10}H_6N_2O_2S$ (218.2): H, 2.77; C, 55.04; N, 12.84; S, 14.69. Found: H, 2.78; C, 55.04; N, 12.82; S, 14.67.

3-Methyl-2-thioxo-2,3-dihydro-1*H*-benzofuro[3,2-*d*]pyrimidin-4(1*H*)-one (4b): Yield 89%. White solid, mp >300°C; IR (cm^{-1}): 3206, 3088, 3028, 2991, 2920, 1686, 1664, 1622, 1550, 1288; UV (ν, cm^{-1}, ε 10^{-3}, $L \cdot mol^{-1} \cdot cm^{-1}$): 44600 (9.1), 34720 (11.9), 30540 (2.4); ^1H NMR (200 MHz, DMSO-d_6), δ, ppm: δ 7.74 (d, $J = 7.7$ Hz, 1H), 7.63 (t, $J = 6.4$ Hz, 1H), 7.40 (t, $J = 6.4$, 1H), 8.13 (d, $J = 7.7$ Hz, 1H), 13.8 (br s, 1H, NH), 3.55 (s, 3H, NCH_3). Anal. calcd. for $C_{11}H_8N_2O_2S$ (232.3): H, 3.47; C, 56.89; N, 12.06; S, 13.81. Found: H, 3.49; C, 56.90; N, 12.02; S, 13.83.

3-Phenyl-2-thioxo-2,3-dihydro-1*H*-benzofuro[3,2-*d*]pyrimidin-4(1*H*)-one (4c): Yield 91%. White solid, mp 273–275°C; IR (cm^{-1}): 3412, 3143, 3062, 2958, 2894, 1679, 1622, 1544, 1214; UV (ν, cm^{-1}, ε 10^{-3}, $L \cdot mol^{-1} \cdot cm^{-1}$): 43880 (28.3), 34380 (27.9); ^1H NMR (400 MHz, DMSO-d_6), δ, ppm: δ 7.82 (d, $J = 7.9$ Hz, 1H), 7.70 (t, $J = 5.3$ Hz, 1H), 7.42 (t, $J = 5.3$ Hz, 1H), 8.24 (d, $J = 7.9$ Hz, 1H), 13.90 (br s, 1 H, NH), 7.20–7.46 (m, 5H). Anal. calcd. for $C_{16}H_{10}N_2O_2S$ (294.3): H, 3.42; C, 65.29; N, 9.52; S, 10.89. Found: H, 3.41; C, 65.29; N, 9.50; S, 10.87.

3-(4-Fluorophenyl)-2-thioxo-2,3-dihydro-1*H*-benzofuro[3,2-*d*]pyrimidin-4(1*H*)-one (4d): Yield 78%. White solid, mp 283°C; IR (cm^{-1}): 3400, 3104, 3032, 2997, 2890, 1715, 1622, 1544, 1216; UV (ν, cm^{-1}, ε 10^{-3}, $L \cdot mol^{-1} \cdot cm^{-1}$): 43980 (11.8), 34440 (12.3); ^1H NMR (400 MHz, DMSO-d_6), δ, ppm: δ 7.82 (d, $J = 7.7$ Hz, 1H), 7.69 (t, $J = 6.2$ Hz, 1H), 7.50 (t, $J = 6.2$ Hz, 1H), 8.23 (d, $J = 6.2$ Hz, 1H), 14.00 (br s, 1H, NH), 7.24–7.36 (m, 5H). LC/MS (m/z, rel.%): 625 (29) [2M +], 313 (94) [M +], 279 (59), 202 (100), 149 (15), 130 (47). Anal. calcd. for $C_{16}H_9FN_2O_2S$ (312.3): H, 2.90; C, 61.53; N, 8.97; S, 10.27. Found: H, 2.92; C, 61.54; N, 8.99; S, 10.25.

3-(4-Methoxyphenyl)-2-thioxo-2,3-dihydro-1*H*-benzofuro[3,2-*d*]pyrimidin-4(1*H*)-one (4e): Yield 82%. White solid, mp 280–281°C; IR (cm^{-1}): 3405, 3096, 2892, 2837, 1711, 1622, 1548, 1510, 1215; UV (ν, cm^{-1}, ε 10^{-3}, $L \cdot mol^{-1} \cdot cm^{-1}$): 43420 (17.8), 34440 (13.9); ^1H NMR (400 MHz, DMSO-d_6), δ, ppm: δ 7.80 (d, $J = 8.8$ Hz, 1H), 7.68 (t, $J = 5.9$ Hz, 1H), 7.49 (t, $J = 5.9$ Hz, 1H), 8.23 (d, $J = 5.9$ Hz, 1H), 13.80 (br s, 1H, NH), 7.01 (d, $J = 11.8$ Hz, 2H), 7.16 (d, $J = 11.8$ Hz, 2H), 3.55 (s, 3H, NCH_3). Anal. calcd. for $C_{17}H_{12}N_2O_3S$ (324.4): H, 3.73; C, 62.95; N, 8.64; S, 9.89. Found: H, 3.72; C, 62.95; N, 8.62; S, 9.88.

3-Butyl-2-thioxo-2,3-dihydro-1*H*-benzofuro[3,2-*d*]pyrimidin-4(1*H*)-one (4f): Yield 86%. White solid, mp 269–271°C; IR (cm^{-1}): 3225, 3079, 2958, 2932, 2868, 1676, 1621, 1549, 1286; UV (ν, cm^{-1}, ε 10^{-3}, $L \cdot mol^{-1} \cdot cm^{-1}$): 44380 (15.3), 40740 (11.5), 34820 (18.7); ^1H NMR (400 MHz, DMSO-d_6), δ, ppm: δ 7.79 (d, $J = 7.5$ Hz, 1H), 7.62 (t, $J = 7.5$ Hz, 1H), 7.46 (t, $J = 6.25$ Hz, 1H), 8.16 (d, $J = 7.5$ Hz, 1H), 13.8 (br s, 1H, NH), 4.30 (t, 2H, N-CH_2), 1.30 (m, 2H, CH_2), 1.70 (m, 2H, CH_2), 0.98 (t, 3H, CH_3). LC/MS (m/z, rel.%): 549 (21) [2M +], 275 (83) [M +], 219 (58), 202 (100), 149 (21), 121 (52). Anal. calcd. for $C_{14}H_{14}N_2O_2S$ (274.3): H, 5.14; C, 61.29; N, 10.21; S, 11.69. Found: H, 5.14; C, 61.31; N, 10.22; S, 11.71.

3-Benzyl-2-thioxo-2,3-dihydro-1*H*-benzofuro[3,2-*d*]pyrimidin-4(1*H*)-one (4g): Yield 78%. White solid, mp 287–288°C; IR (cm^{-1}): 3228, 3076, 3031, 2901, 1678, 1550, 1287; UV (ν, cm^{-1}, ε 10^{-3}, $L \cdot mol^{-1} \cdot cm^{-1}$): 44140 (11.1), 34420 (12.1); ^1H NMR (400 MHz, DMSO-d_6), δ, ppm: δ 7.79

(d, $J = 8.6$ Hz, 1H), 7.69 (t, $J = 5.7$ Hz, 1H), 7.67 (t, $J = 5.7$ Hz, 1H), 8.20 (d, $J = 5.7$ Hz, 1H), 14.00 (br s, 1H, NH), 7.14–7.36 (m, 5H), 5.60 (s, 2H, NCH_2). LC/MS (m/z, rel.%): 617 (14) [2M +], 331 (18), 309 (100) [M +], 149 (18), 122 (55). Anal. calcd. for $C_{17}H_{12}N_2O_2S$ (308.4): H, 3.92; C, 66.22; N, 9.08; S, 10.40. Found: H, 3.93; C, 66.22; N, 9.12; S, 10.39.

3-(2-Methoxyethyl)-2-thioxo-2,3-dihydro-1*H*-benzofuro[3,2-*d*]pyrimidin-4(1*H*)-one (4h): Yield 75%. White solid, mp 273–275°C; IR (cm^{-1}): 3215, 3087, 2891, 2831, 1680, 1549, 1477, 1286, 1215; UV (ν, cm^{-1}, ε 10^{-3}, $L \cdot mol^{-1} \cdot cm^{-1}$): 44040 (14.5), 34480 (18.7); ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: δ 7.72 (d, $J = 7.6$ Hz, 1H), 7.69 (t, $J = 5.1$ Hz, 1H), 7.62 (t, $J = 5.1$ Hz, 1H), 8.12 (d, $J = 7.6$ Hz, 1H), 13.80 (br s, 1H, NH), 4.55 (dd, 2H, N-CH_2), 3.65 (dd, 2H, CH_2), 3.30 (s, 3H, OCH_3). LC/MS (m/z, rel.%): 277 (31) [M +], 245 (94), 202 (100), 150 (9), 130 (63), 121 (13). Anal. calcd. for $C_{13}H_{12}N_2O_3S$ (276.3): H, 4.38; C, 56.51; N, 10.14; S, 11.60. Found: H, 4.39; C, 56.52; N, 10.12; S, 11.62.

3-(4-Fluorobenzyl)-2-thioxo-2,3-dihydro-1*H*-benzofuro[3,2-*d*]pyrimidin-4(1*H*)-one (4i): Yield 70%. White solid, mp 285°C; IR (cm^{-1}): 3220, 3079, 3006, 2907, 1663, 1622, 1547, 1284, 1217; UV (ν, cm^{-1}, ε 10^{-3}, $L \cdot mol^{-1} \cdot cm^{-1}$): 43980 (24.6), 34360 (26.7); ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: δ 7.78 (d, $J = 6.1$ Hz,1H), 7.66 (t, $J = 6.1$ Hz, 1H), 7.46 (t, $J = 6.1$ Hz, 1H), 8.19 (d, $J = 9.1$ Hz, 1H), 14.01 (br s, 1H, NH), 7.00–7.43 (m, 4H), 5.60 (s, 2H, CH_2). LC/MS (m/z, rel.%): 327 (49) [M +], 149 (24), 122 (49), 109 (100). Anal. calcd. for $C_{17}H_{11}FN_2O_2S$ (326.3): H, 3.40; C, 62.57; N, 8.58; S, 9.82. Found: H, 3.39; C, 62.57; N, 8.60; S, 9.83.

3-(4-Methoxybenzyl)-2-thioxo-2,3-dihydro-1*H*-benzofuro[3,2-*d*]pyrimidin-4(1*H*)-one (4j): Yield 78%. White solid, mp 276°C; IR (cm^{-1}): 3212, 3086, 3012, 2960, 2907, 1676, 1550, 1511, 1287, 1214; UV (ν, cm^{-1}, ε 10^{-3}, $L \cdot mol^{-1} \cdot cm^{-1}$): 44340 (10.1), 40260 (5.2), 34460 (9.6); ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 7.77 (d, $J = 6.7$ Hz,1H), 7.65 (t, $J = 6.7$ Hz, 1H), 7.45 (t, $J = 6.7$ Hz, 1H), 8.17 (d, $J = 6.7$ Hz, 1H), 13.90 (br s, 1H, NH), 6.50–7.35 (2d, 4H), 5.60 (s, 2H, CH_2), 3.70 (s, 3H, OCH_3). LC/MS (m/z, rel.%): 340 (20) [M +], 149 (15), 121 (100), 115 (8). Anal. calcd. for $C_{18}H_{14}N_2O_3S$ (338.4): H, 4.17; C, 63.89; N, 8.28; S, 9.48. Found: H, 4.17; C, 63.90; N, 8.26; S, 9.49.

3-(4-Methylbenzyl)-2-thioxo-2,3-dihydro-1*H*-benzofuro[3,2-*d*]pyrimidin-4(1*H*)-one (4k): Yield 83%. White solid, mp 282°C; IR (cm^{-1}): 3232, 3076, 2900, 2837, 1676, 1664, 1550, 1518, 1284; UV (ν, cm^{-1}, ε 10^{-3}, $L \cdot mol^{-1} \cdot cm^{-1}$): 44440 (13.7), 34420 (12.7); ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: δ 7.79 (d, $J = 6.6$ Hz, 1H), 7.66 (t, $J = 9.8$ Hz, 1H), 7.47 (t, $J = 9.8$ Hz, 1H), 8.18 (d, $J = 6.6$ Hz, 1H), 14.01 (br s, 1H, NH),

7.08 (d, $J = 6.6$ Hz, 2H), 7.23 (d, $J = 6.6$ Hz, 2H), 5.60 (s, 2H, CH_2), 2.10 (s, 3H, OCH_3). LC/MS (m/z, rel.%): 645 (23) [2M +], 323 (100) [M +], 219 (41), 149 (23), 105 (100). Anal. calcd. for $C_{18}H_{14}N_2O_2S$ (322.4): H, 4.38; C, 67.06; N, 8.69; S, 9.95. Found: H, 4.39; C, 67.06; N, 8.70; S, 9.93.

2-[4-Oxo-2-thioxo-1,4-dihydro-1*H*-benzofuro[3,2-*d*]pyrimidin-3(2*H*)-yl] acetic Acid (4l): Yield 82%. Light brown solid, mp >300°C; IR (cm^{-1}): 3223, 3084, 2942, 2784, 1687, 1626, 1550, 1479, 1269; UV (ν, cm^{-1}, ε 10^{-3}, $L \cdot mol^{-1} \cdot cm^{-1}$): 44580 (39.5), 33780 (45.4), 34660 (52.7); ^1H NMR (400 MHz, DMSO-d_6), δ, ppm: δ 7.78 (d, $J = 8.93$ Hz, 1H), 7.67 (t, $J = 7.14$ Hz, 1H), 7.48 (t, $J = 7.14$ Hz, 1H), 8.17 (d, $J = 8.93$ Hz, 1H), 14.02 (s, 1H, NH), 4.58 (m, 2H, NCH_2), 13.01 (br s, 1H, OH). LC/MS (m/z, rel.%): 553 (16) [2M +], 294 (6), 277 (53) [M +], 259 (31), 202 (100), 149 (19), 130 (81), 121 (31). Anal. calcd. for $C_{12}H_8N_2O_4S$: H, 2.92; C, 52.17; N, 10.14; S, 11.61. Found: H, 2.91; C, 52.17; N, 10.16; S, 11.62.

3-[4-Oxo-2-thioxo-1,4-dihydro-1*H*-benzofuro[3,2-*d*]pyrimidin-3(2*H*)-yl] propanoic acid (4m): Yield 85%. White solid, mp 275°C; IR (cm^{-1}): 3202, 2904, 1682, 1625, 1550, 1477, 1279, 1214; UV (ν, cm^{-1}, ε 10^{-3}, $L \cdot mol^{-1} \cdot cm^{-1}$): 43880 (32.5), 34560 (39.3), 33740 (35.2); ^1H NMR (400 MHz, DMSO-d_6), δ, ppm: δ 7.78 (d, $J = 8.93$ Hz, 1H), 7.66 (t, $J = 7.14$ Hz, 1H), 7.46 (t, $J = 7.14$ Hz, 1H), 8.16 (d, $J = 8.93$ Hz, 1H), 13.90 (br s, 1H, NH), 4.60 (m, 2H, NCH_2), 2.70 (m, 2H, NCH_2CH_2), 12.45 (s, 1H, OH). LC/MS (m/z, rel.%): 291 (40) [M +], 273 (43), 219 (77), 202 (100), 149 (13), 130 (33). Anal. calcd. for $C_{13}H_{10}N_2O_4S$ (290.30): H, 3.47; C, 53.79; N, 9.65; S, 11.05. Found: H, 3.49; C, 53.76; N, 9.66; S, 11.03.

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