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Solution phase combinatorial synthesis of a diverse library of 2-aminopyrimidinones and their 6-aza-analogs

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Summary. The solution-phase synthesis of a 150-member library of 2-aminopyrimidinones and their 6-aza-analogs is described. The key intermediates for library generation, S-methylpyrimidinones and S-methyl-6-aza-pyrimidinones, were easily prepared using typical procedures, and subsequent nucleophilic aromatic substitution with various amines was carried out under standardized conditions with high yields.

Keywords: pyrimidines, azapyrimidines, protein kinase inhibitors, arylation, thioazauracils, S-methylpyrimidinones.

Introduction. The pyrimidine core is one of the most widespread structural motifs found in natural products and biologically active compounds. Being present in nature as an important constituent (cytosine, thymine, uracil) of the nucleic acids, vitamins [1] such as thiamine, riboflavin, folic acid, as well as strong toxins and coenzymes [2, 3]. Pyrimidine derivatives exhibit a wide range of pharmacologically important properties, including anticancer, hypnotic, antimicrobial, analgesic, antiallergic, cardiotonic and antihypertensive activities. Some simple biologically active pyrimidines are depicted in Figure 1. Among them, phenobarbital **1a** and cyclobarbital **1b** are the current drugs in the market used as sedative hypnotics [4, 6]. Pyrimidine sulfonamides like sulfadimethoxine **2a** and sulfacytine **2b** have been found to be useful as antiseptics [7, 8], whereas orotic acid **3** has been shown to be useful in metabolic therapy [9]. 5-Fluorouracil **4a** is well known as an antineoplastic agent [10]. Gemcitabine **4b** also shows potent antitumour activity against muscular solid tumours [11].

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Highly efficient protein kinase inhibitors with antitumor activity have also been found among pyrimidine derivatives [12, 13]. We have shown that pyrimidine containing compounds possess inhibitive activity towards protein kinase CK2 [14, 15]. Therefore the development of unambiguous synthetic approach to new pyrimidine derivatives is the important part of current drug discovery and development process.

The synthesis of 2-aminopyrimidinones and their 6-aza-analogs as biologically active compounds by the reaction of S-methyl precursors with amines is described in the literature [16-20]. However, the reactions are provided under various mainly harsh conditions with various ways of product isolation. The main objective of our research is to develop a versatile method of synthesis of 2-aminopyrimidinones and their 6-aza-analogs for combinatorial library synthesis using the reaction of S-methylpyrimidinone derivatives with amines. Synthesized compounds will be subjected to various high-throughput screening assays for the purpose of finding their bioactivity.

Results and discussion. Starting building-blocks 2-S-methylpyrimidin-4-ones **7{1-10}** and their 6-aza-analogs 2-S-methyl-6-azapyrimidin-4-ones **11{1-4}** and 4-S-methyl-6-azapyrimidin-

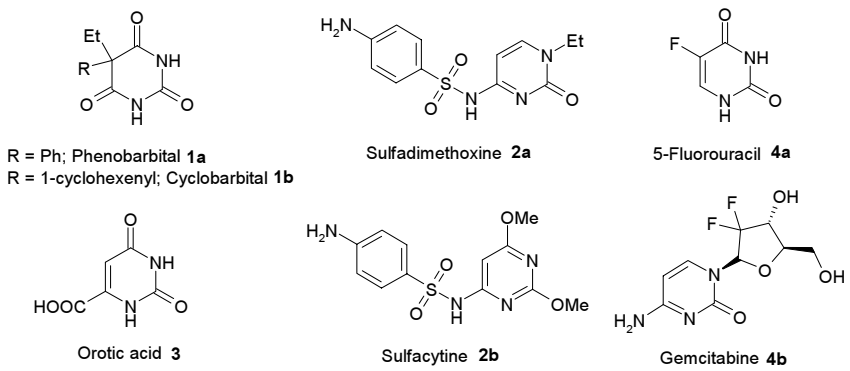


Figure 1. Selected biologically active pyrimidine derivatives.

2-ones **13{1-2}** were synthesized as shown in Scheme 1.

Thiouracils **6{1-9}** were obtained by reacting beta-keto acid methyl esters **5{1-9}** with thiourea in a methanolic solution under alkali conditions. Benzthiouracil **6{10}** was obtained by means of heating methyl anthranilate with ammonium thiocyanate in hydrochloric acid. These thiouracils **6{1-10}** were converted to corresponding 2-S-methylpyrimidin-4-ones **7{1-10}** by methyl iodide in the presence of NaOH.

Thiosemicarbazones **9{1-4}** of alpha-keto acids were synthesized in an aqueous environment by reacting thiosemicarbazide with corresponding alpha-keto acids **8{1-4}**. Then these compounds were treated with aqueous sodium hydroxide to furnish 2-thio-6-azauracils **10{1-4}**. On the next step 2-thio-6-azauracils **10{1-2}** were

Scheme 1

*Synthesis of 2-S-methylpyrimidin-4-ones **7{1-10}**, 2-S-methyl-6-azapyrimidin-4-ones **11{1-4}** and 4-S-methyl-6-azapyrimidin-2-ones **14{1-2}***

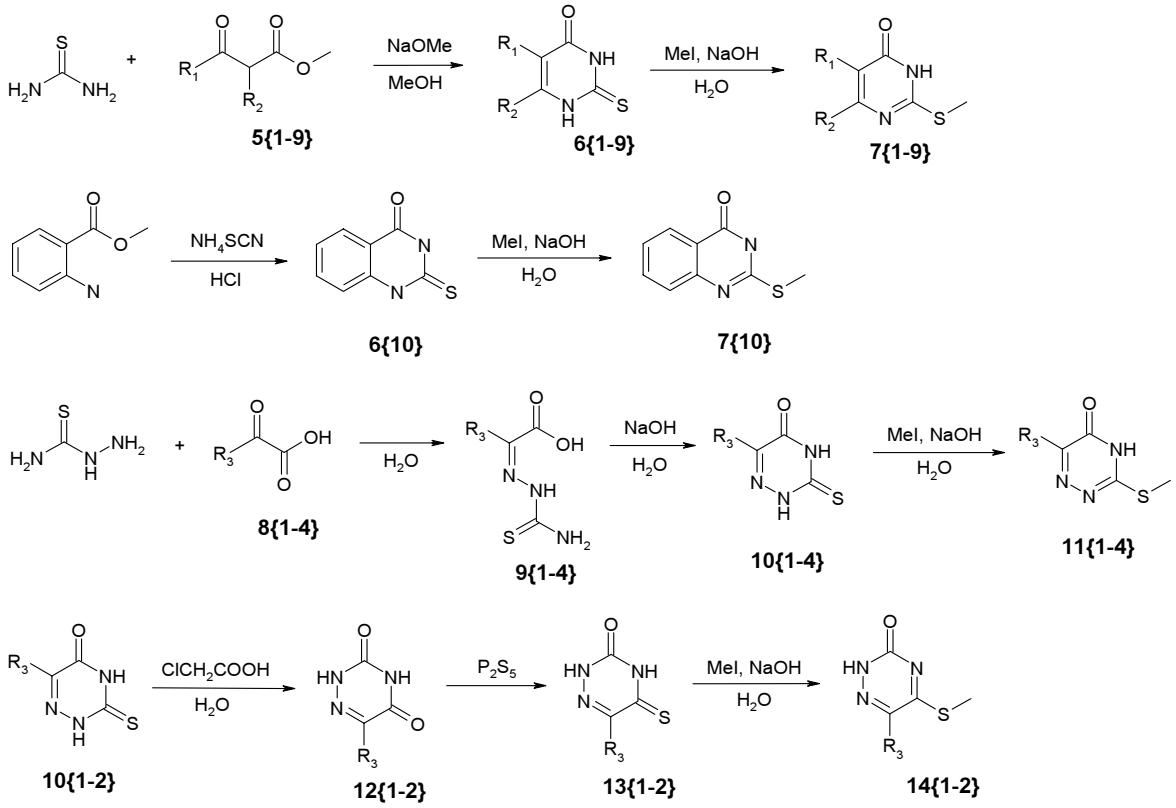
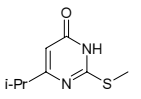
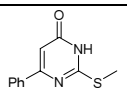
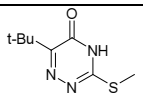
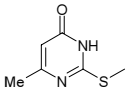
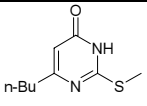
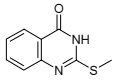
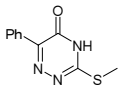
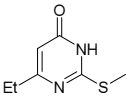
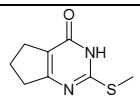
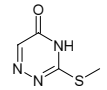
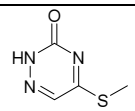
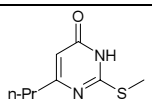
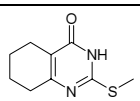
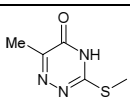
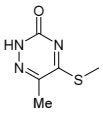


Table 1

Chemical structures of building-blocks ***7{1-10}, 11{1-4}, 14{1-2}*** *and their melting points*

compound	structure	m.p., °C	compound	structure	m.p., °C	compound	structure	m.p., °C	compound	structure	m.p., °C
7{1}		198	**7{5}**		121	**7{9}**		241 (dec.)	**11{3}**		195
7{2}		228	**7{6}**		129	**7{10}**		>250 (dec.)	**11{4}**		241 (dec.)
7{3}		151	**7{7}**		178	**11{1}**		212 (dec.)	**14{1}**		171
7{4}		153	**7{8}**		210	**11{2}**		211 (dec.)	**14{2}**		230

hydrolyzed to provide 6-azauracils **12{1-2}** by heating them with chloroacetic acid in water. Subsequently, 6-azauracils **12{1-2}** were treated with phosphorus pentasulfide to give 4-thio-6-azauracils **13{1-2}** which are the isomers of 2-thio-6-azauracils **10{1-2}**.

Both types of thioazauracils **10{1-4}** and **13{1-2}** were methylated under the same conditions as described for the synthesis of compounds **7{1-10}** to afford 2-S-methyl-6-azapyrimidin-4-ones **11{1-4}** and 4-S-methyl-6-azapyrimidin-2-ones **14{1-2}** in moderate and high yields.

As a result of that 16 building-blocks for combinatorial synthesis were synthesized. The chemical structures of these compounds and their melting point are provided in Table 1.

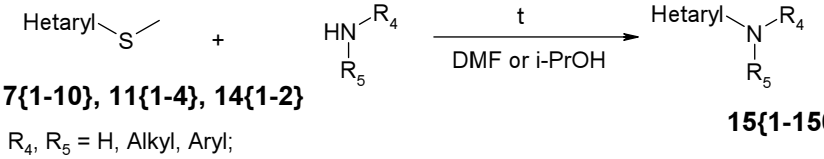
We have developed a simple and versatile combinatorial method of arylation of amines by S-methylpyrimidinone derivatives and have synthesized a 150-member library of 2-aminopyrimidinones and their 6-aza-analogs as well. This procedure was optimized differently for aromatic and aliphatic amines and was used in two variations as method A and method B, respectively. Arylation reaction is depicted in Scheme 2. Library data for compounds **15{1-150}** is described in Table 2. As summarized in Table 2, we have obtained the desired 2-aminopyrimidinone derivatives in moderate and high yields in the range of 42-87 %. All these compounds have had ≥90 % purity.

All of the library members are completely fit for Lipinski's rules [23] (calculated by ChemAxon's Instant JChem [24]). The molecular weight distribution, depicted in Figure 2, shows that all members of the library occupy the desirable molecular weight range.

To the best of our knowledge, 4-Amino-6-azapyrimidine-2-one derivatives are not widely reported in the literature. Their synthesis using the reaction of arylation of amines by 4-S-methyl-6-azapyrimidine-2-ones is described only for 1-methyl-4-S-methyl-6-azapyrimidine-2-one [21] and 4-S-methyl-5-amino-6-azapyrimidine-2-one [22]. The heteroarylation of amines by

Scheme 2

Aminopyrimidinones library generation



7{1-10}, 11{1-4}, 14{1-2}

15{1-150}

R_4, R_5 = H, Alkyl, Aryl;

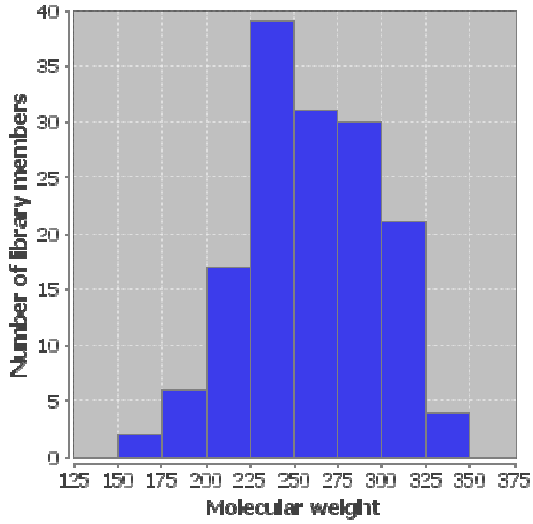


Figure 2. Molecular weight distribution for members of 2-aminopyrimidinone derivatives library.

4-S-methyl-6-azapyrimidine-2-one derivatives **14{1-2}** has been provided by us for the first time.

Conclusions. Thus a simple and versatile combinatorial method of arylation of amines by S-methylpyrimidinone derivatives has been developed in our laboratories. The 150-member library of 2-aminopyrimidinones and their 6-aza-analogs has been obtained. 4-Amino-6-azapyrimidine-2-one derivatives **15{115-150}** have been synthesized by us for the first time using the reaction of arylation of amines by 4-S-methyl-6-azapyrimidine-2-one derivatives **14{1-2}**.

Experimental Section. Starting materials and solvents were purchased from commercial suppliers and were used without further purification. ^{1}H NMR spectra were recorded on a Varian VXR 400 instrument at 400 MHz. ^{13}C NMR spectra were recorded on a Varian VXR 400 instrument at 100 MHz. Chemical shifts are described as parts per million (δ) downfield from an internal standard of tetramethylsilane, and spin multiplicities are given as s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), or m (multiplet). HPLC-MS analysis was performed using the Agilent 1100 LC/MSD SL separations module and Mass Quad G1956B mass detector with electrospray ionization (+ve or -ve ion mode as indicated) and with HPLC performed using Zorbax SB-C18, Rapid Resolution HT Cartridge 4.6×30 mm 1.8-Micron (Agilent P/N:823975-902) i.d. column, at a temperature of 40 °C with gradient elution of 0-100 % CH_3CN (with 1 ml/L HCOOH): H_2O (with 1 ml/L HCOOH) at a flow rate of 3 mL/min and a run time of 2.8 min. Compounds were detected at 215 nm using a Diode Array G1315B detector. All tested compounds gave ≥90 % purity as determined by this method. All purified synthetic intermediates gave ≥95 % purity as determined by this method.

General procedures for the synthesis of compounds 6{1-9}. Compounds 6{1-9} were prepared using the following procedure. A solution (7.6 g, 0.10 mol) of thiourea, commercially available beta-keto acid ester **5{2-9}** (0.10 mol) or methyl 3,3-dimethoxypropionate **5{1}** for compound **6{1}** and sodium methoxide (5.9 g, 0.10 mol) in absolute methanol (300 mL) was refluxed for 5 h. The volatiles were removed *in vacuo*, the residue was diluted with hot water (400 mL) and pH was adjusted to 5 using 10% hydrochloric acid at 15 °C. The solids were separated by filtration, washed subsequently with water (200 mL), isopropyl alcohol (50 mL) and air dried to furnish the corresponding product.

2-Thiopyrimidin-4(3H)-one ***6{1}***. Yield 68 % (pale yellow powder). LC-MS *m/z* 129 [M+H$^+$], R_t=1.04 min. ^{1}H NMR (DMSO-d_6) δ 5.74 (d, *J*=7.8 Hz, 1H), 7.30 (d, *J*=7.8 Hz, 1H), 12.18 (s, 1H, NH), 12.27 (s, 1H, NH).

6-Methyl-2-thiopyrimidin-4(3H)-one ***6{2}***. Yield 78 % (white powder). LC-MS *m/z* 143 [M+H$^+$], R_t=1.04 min. ^{1}H NMR (DMSO-d_6) δ 2.19 (s, 3H), 5.69 (s, 1H), 12.22 (s, 1H, NH), 12.27 (s, 1H, NH).

6-Ethyl-2-thiopyrimidin-4(3H)-one ***6{3}***. Yield 77 % (white powder). LC-MS *m/z* 157 [M+H$^+$], R_t=1.06 min. ^{1}H NMR (DMSO-d_6) δ 1.14 (t, *J*=7.6 Hz, 3H), 2.38 (q, *J*=7.6 Hz, 2H), 5.68 (s, 1H), 12.24 (s, 2H, 2NH).

6-Propyl-2-thiopyrimidin-4(3H)-one ***6{4}***. Yield 75 % (white powder). LC-MS *m/z* 171 [M+H$^+$], R_t=1.04 min. ^{1}H NMR (DMSO-d_6) δ 0.93 (t, *J*=7.3 Hz, 3H), 1.65-1.67 (m, 2H), 2.39 (q, *J*=7.3 Hz, 2H), 5.70 (s, 1H), 12.24 (s, 2H, 2NH).

6-Isopropyl-2-thiopyrimidin-4(3H)-one ***6{5}***. Yield 73 % (white powder). LC-MS *m/z* 171 [M+H$^+$], R_t=1.03 min. ^{1}H NMR (DMSO-d_6) δ 1.17 (d, *J*=7.1 Hz, 6H), 2.66-2.67 (m, 2H), 5.56 (s, 1H), 12.08 (s, 1H, NH), 12.17 (s, 1H, NH).

6-Butyl-2-thiopyrimidin-4(3H)-one ***6{6}***. Yield 75 % (white powder). LC-MS *m/z* 185 [M+H$^+$], R_t=1.07 min. ^{1}H NMR (DMSO-d_6) δ 0.93 (t, *J*=7.1 Hz, 3H), 1.35-1.37 (m, 2H), 1.56-1.57 (m,

Table 2

*Library data for compounds **15{1-150}***

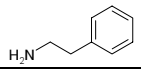
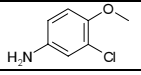
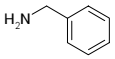
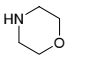
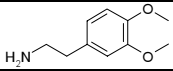
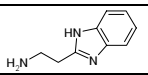
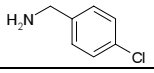
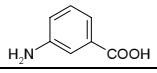
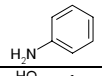
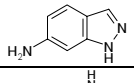
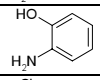
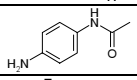
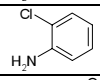
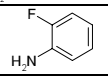
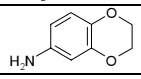
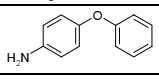
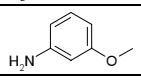
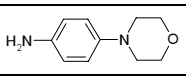
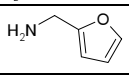
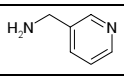
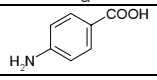
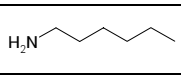
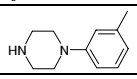
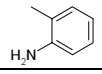
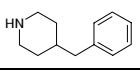
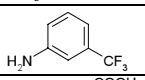
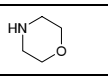
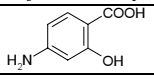
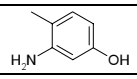
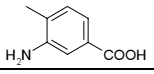
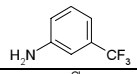
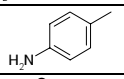
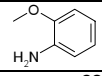
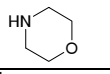
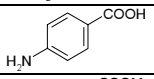
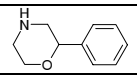
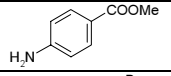
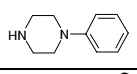
product	reactant	R_3b H N R_3a	method*	yield (%)	entry	reactant	R_3b H N R_3a	method*	yield (%)
1	2	3	4	5	6	7	8	9	10
15{1}	**7**{1}		A	62	**15**{26}	**7**{3}		B	71
15{2}	**7**{1}		A	58	**15**{27}	**7**{4}		A	69
15{3}	**7**{1}		A	61	**15**{28}	**7**{4}		A	61
15{4}	**7**{1}		A	65	**15**{29}	**7**{4}		B	55
15{5}	**7**{1}		B	59	**15**{30}	**7**{4}		B	57
15{6}	**7**{1}		B	55	**15**{31}	**7**{4}		B	62
15{7}	**7**{1}		B	42	**15**{32}	**7**{4}		B	49
15{8}	**7**{1}		B	58	**15**{33}	**7**{4}		B	68
15{9}	**7**{1}		B	63	**15**{34}	**7**{4}		B	73
15{10}	**7**{2}		A	68	**15**{35}	**7**{4}		B	45
15{11}	**7**{2}		A	62	**15**{36}	**7**{4}		B	54
15{12}	**7**{2}		A	60	**15**{37}	**7**{5}		A	72
15{13}	**7**{2}		B	54	**15**{38}	**7**{5}		A	73
15{14}	**7**{2}		B	60	**15**{39}	**7**{5}		A	64
15{15}	**7**{2}		B	48	**15**{40}	**7**{5}		B	66
15{16}	**7**{2}		B	45	**15**{41}	**7**{5}		B	69
15{17}	**7**{2}		B	69	**15**{42}	**7**{5}		B	72
15{18}	**7**{2}		B	63	**15**{43}	**7**{6}		A	67
15{19}	**7**{2}		B	63	**15**{44}	**7**{6}		A	54
15{20}	**7**{2}		B	69	**15**{45}	**7**{6}		A	70
15{21}	**7**{2}		B	75	**15**{46}	**7**{7}		A	68
15{22}	**7**{3}		A	87	**15**{47}	**7**{7}		A	70
15{23}	**7**{3}		A	66	**15**{48}	**7**{7}		A	72
15{24}	**7**{3}		A	68	**15**{49}	**7**{7}		A	72
15{25}	**7**{3}		B	78	**15**{50}	**7**{7}		A	69

Table 2

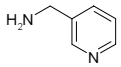
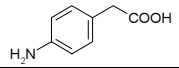
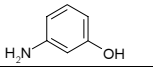
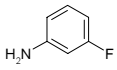
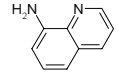
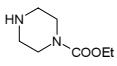
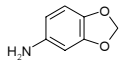
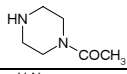
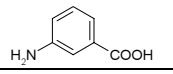
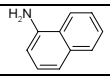
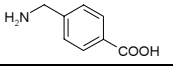
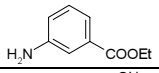
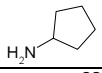
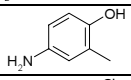
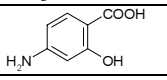
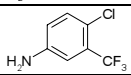
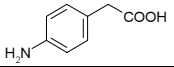
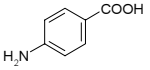
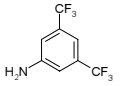
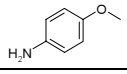
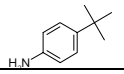
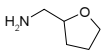
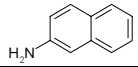
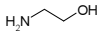
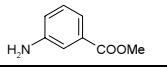
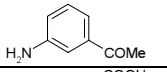
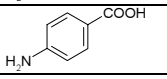
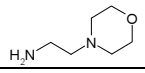
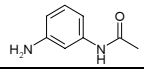
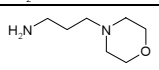
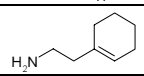
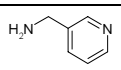
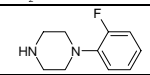
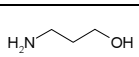
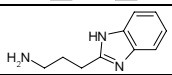
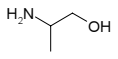
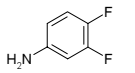
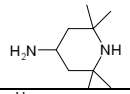
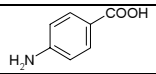
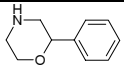
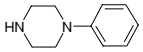
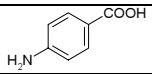
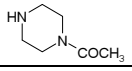
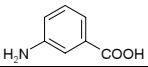
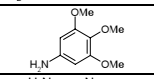
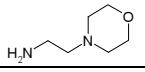
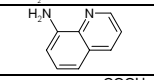
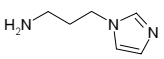
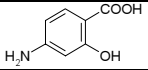
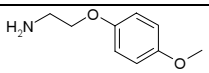
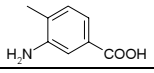
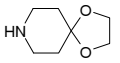
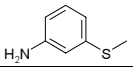
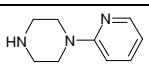
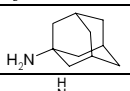
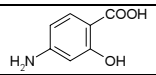
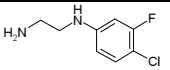
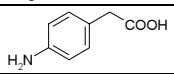
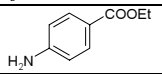
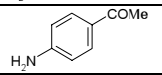
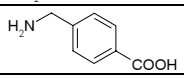
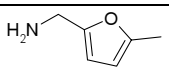
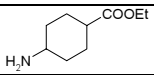
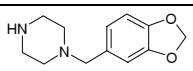
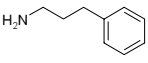
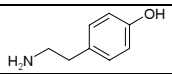
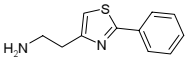
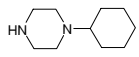
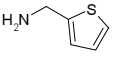
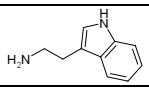
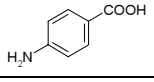
1	2	3	4	5	6	7	8	9	10
15{51}	**7**{7}		A	58	**15**{76}	**7**{10}		B	55
15{52}	**7**{7}		A	67	**15**{77}	**7**{10}		B	68
15{53}	**7**{7}		B	69	**15**{78}	**7**{10}		B	53
15{54}	**7**{8}		A	63	**15**{79}	**7**{10}		B	67
15{55}	**7**{8}		A	65	**15**{80}	**7**{10}		B	56
15{56}	**7**{8}		B	64	**15**{81}	**11**{1}		A	62
15{57}	**7**{8}		B	62	**15**{82}	**11**{1}		A	71
15{58}	**7**{8}		B	64	**15**{83}	**11**{1}		B	53
15{59}	**7**{8}		B	68	**15**{84}	**11**{1}		B	51
15{60}	**7**{8}		B	60	**15**{85}	**11**{1}		B	42
15{61}	**7**{8}		B	73	**15**{86}	**11**{1}		B	64
15{62}	**7**{9}		A	66	**15**{87}	**11**{1}		B	67
15{63}	**7**{9}		A	58	**15**{88}	**11**{1}		B	73
15{64}	**7**{9}		A	63	**15**{89}	**11**{1}		B	47
15{65}	**7**{9}		A	57	**15**{90}	**11**{1}		B	53
15{66}	**7**{9}		A	57	**15**{91}	**11**{1}		B	69
15{67}	**7**{9}		A	55	**15**{92}	**11**{2}		A	61
15{68}	**7**{9}		A	58	**15**{93}	**11**{2}		A	68
15{69}	**7**{9}		A	55	**15**{94}	**11**{2}		A	69
15{70}	**7**{9}		A	57	**15**{95}	**11**{2}		A	57
15{71}	**7**{9}		B	61	**15**{96}	**11**{2}		A	59
15{72}	**7**{10}		A	57	**15**{97}	**11**{2}		A	64
15{73}	**7**{10}		A	59	**15**{98}	**11**{2}		B	58
15{74}	**7**{10}		B	64	**15**{99}	**11**{2}		B	55
15{75}	**7**{10}		B	69	**15**{100}	**11**{2}		B	52

Table 2

1	2	3	4	5	6	7	8	9	10
15{101}	**11**{2}		B	74	**15**{126}	**14**{1}		A	62
15{102}	**11**{2}		B	59	**15**{127}	**14**{1}		A	61
15{103}	**11**{3}		A	71	**15**{128}	**14**{1}		B	57
15{104}	**11**{3}		A	68	**15**{129}	**14**{1}		B	55
15{105}	**11**{4}		A	66	**15**{130}	**14**{1}		B	72
15{106}	**11**{4}		A	69	**15**{131}	**14**{1}		B	61
15{107}	**11**{4}		A	61	**15**{132}	**14**{1}		B	60
15{108}	**11**{4}		A	66	**15**{133}	**14**{1}		B	57
15{109}	**11**{4}		A	61	**15**{134}	**14**{1}		B	68
15{110}	**11**{4}		A	64	**15**{135}	**14**{2}		A	54
15{111}	**11**{4}		B	57	**15**{136}	**14**{2}		A	75
15{112}	**11**{4}		B	55	**15**{137}	**14**{2}		A	65
15{113}	**11**{4}		B	63	**15**{138}	**14**{2}		A	77
15{114}	**11**{4}		B	64	**15**{139}	**14**{2}		A	72
15{115}	**14**{1}		A	62	**15**{140}	**14**{2}		A	75
15{116}	**14**{1}		A	79	**15**{141}	**14**{2}		A	67
15{117}	**14**{1}		A	77	**15**{142}	**14**{2}		A	68
15{118}	**14**{1}		A	66	**15**{143}	**14**{2}		A	72
15{119}	**14**{1}		A	76	**15**{144}	**14**{2}		A	75
15{120}	**14**{1}		A	73	**15**{145}	**14**{2}		B	57
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15{122}	**14**{1}		A	68	**15**{147}	**14**{2}		B	69
15{123}	**14**{1}		A	74	**15**{148}	**14**{2}		B	45
15{124}	**14**{1}		A	64	**15**{149}	**14**{2}		B	52
15{125}	**14**{1}		A	74	**15**{150}	**14**{2}		A	62

** Method A: Hetaryl-SMe (2.0 mmol), amine (1,5 equiv.), i-PrOH (4 mL), heating 1 h at 80 ℃. Method B: Hetaryl-SMe (2.0 mmol), amine (2,0 equiv.), DMF (1 mL), heating 1 h at 140 ℃.*

2H), 2.36 (t, *J*=8.1 Hz, 2H), 5.54 (s, 1H), 12.04 (s, 2H, 2NH).

2-Thioxo-1,2,3,5,6,7-hexahydro-4H-cyclopenta[d]pyrimidin-4-one ***6{7}***. Yield 60 % (white powder). LC-MS *m/z* 169 [M+H$^+$], R_t=1.08 min. ^{1}H NMR (DMSO-d_6) δ 2.00-2.02 (m, 2H), 2.53 (t, *J*=7.1 Hz, 2H), 2.71 (t, *J*=7.6 Hz, 2H, 12.11 (s, 2H, 2NH).

2-Thioxo-2,3,5,6,7,8-hexahydroquinazolin-4(1H)-one ***6{8}***. Yield 66 % (white powder). LC-MS *m/z* 183 [M+H$^+$], R_t=1.05 min. ^{1}H NMR (DMSO-d_6) δ 1.68 (m, 4H), 2.21 (t, *J*=5.4 Hz, 2H), 2.39 (t, *J*=5.4 Hz, 2H), 12.10 (m, 2H, 2NH).

6-Phenyl-2-thiopyrimidin-4(3H)-one ***6{9}***. Yield 68 % (white powder). LC-MS *m/z* 205 [M+H$^+$], R_t=1.04 min. ^{1}H NMR (DMSO-d_6) δ 5.96 (s, 1H), 7.51 (m, 3H), 7.67 (m, 2H), 12.38 (m, 2H, 2NH).

2-Thioxo-2,3-dihydroquinazolin-4(1H)-one ***6{10}***. Concentrated hydrochloric acid (50 mL) was added dropwise to the solution of ammonium thiocyanate (225.0 g, 2.96 mol) and methyl anthranilate (80.0 mL, 0.61 mol) in water (300 mL) at 60-80 ˚C. Then the reaction mixture was stirred and refluxed for 3 hours. Then the precipitate was filtered, washed with water (600 mL), isopropyl alcohol (400 mL) and recrystallized from dioxane. Yield 53 % (yellow powder). LC-MS *m/z* 179 [M+H$^+$], R_t=1.04 min. ^{1}H NMR (DMSO-d_6) δ 7.26 (t, *J*=7.8 Hz, 1H), 7.37 (d, *J*=8.3 Hz, 1H), 7.64 (t, *J*=8.3 Hz, 1H), 7.92 (d, *J*=7.8 Hz, 1H), 12.31 (s, H, 1NH), 12.59 (s, 1H, NH).

General procedures for the synthesis of compounds 7{1-10}: Compounds **7{1-10}** were prepared by the following procedure. Methyl iodide (15.6 g, 0.11 mol) was added dropwise to a solution of compound **6{1-10}** (0.10 mol) and sodium hydroxide (4.4 g, 0.11 mol) in water (400 mL) at room temperature for 3 h. Then the precipitate **7{1-10}** was filtrated, washed with water (200 mL), isopropyl alcohol (40 mL) and air dried to furnish the corresponding products.

2-(Methylthio)pyrimidin-4(3H)-one ***7{1}***. Yield 82 % (white powder). LC-MS *m/z* 143 [M+H$^+$], R_t=1.09 min. ^{1}H NMR (DMSO-d_6) δ 2.17 (s, 3H), 2.47 (s, 3H), δ 5.96 (s, 1H),), δ 12.40 (s, 1H).

6-Methyl-2-(methylthio)pyrimidin-4(3H)-one ***7{2}***. Yield 89 % (white powder). LC-MS *m/z* 157 [M+H$^+$], R_t=1.10 min. ^{1}H NMR (DMSO-d_6) δ 2.17 (s, 3H), 2.47 (s, 3H), δ 5.96 (s, 1H), δ 12.40 (s, 1H).

6-Ethyl-2-(methylthio)pyrimidin-4(3H)-one ***7{3}***. Yield 87 % (white powder). LC-MS *m/z* 171 [M+H$^+$], R_t=1.07 min. ^{1}H NMR (DMSO-d_6) δ 1.14 (t, *J*=7.6 Hz, 3H), 2.38 (q, *J*=7.6 Hz, 2H), 2.47 (s, 3H), 5.68 (s, 1H), 12.24 (s, 1H, NH).

6-Propyl-2-(methylthio)pyrimidin-4(3H)-one ***7{4}***. Yield 78 % (white powder). LC-MS *m/z* 185 [M+H$^+$], R_t=1.10 min. ^{1}H NMR (DMSO-d_6) δ 0.93 (t, *J*=7.3 Hz, 3H), 1.60-1.62 (m, 2H), 2.39 (q, *J*=7.3 Hz, 2H), 2.47 (s, 3H), 5.80 (s, 1H), 12.24 (s, 1H, NH).

6-Isopropyl-2-(methylthio)pyrimidin-4(3H)-one ***7{5}***. Yield 72 % (white powder). LC-MS *m/z* 185 [M+H$^+$], R_t=1.09 min. ^{1}H NMR (DMSO-d_6) δ 1.17 (d, *J*=7.1 Hz, 6H), 2.47 (s, 3H), 2.66-2.68 (m, 2H), 5.56 (s, 1H), 12.17 (s, 1H, NH).

6-Butyl-2-(methylthio)pyrimidin-4(3H)-one ***7{6}***. Yield 75 % (white powder). LC-MS *m/z* 199 [M+H$^+$], R_t=1.09 min. ^{1}H NMR (DMSO-d_6) δ 0.93 (t, *J*=7.3 Hz, 3H), 1.34-1.36 (m, 2H), 1.59-1.61 (m, 2H), 2.41 (t, *J*=7.3 Hz, 2H), 2.47 (s, 3H), 5.81 (s, 1H), 12.32 (s, 1H, NH).

2-(Methylthio)-3,5,6,7-hexahydro-4H-cyclopenta[d]pyrimidin-4-one ***7{7}***. Yield 60 % (white powder). LC-MS *m/z* 183 [M+H$^+$], R_t=1.08 min. ^{1}H NMR (DMSO-d_6) δ 2.00-2.04 (m, 2H), 2.45 (s, 3H), 2.60 (t, *J*=7.3 Hz, 2H), 2.73 (t, *J*=7.8 Hz, 2H, 12.31 (s, 1H, NH).

2-(Methylthio)-5,6,7,8-tetrahydroquinazolin-4(3H)-one ***7{8}***. Yield 66 % (white powder). LC-MS *m/z* 197 [M+H$^+$], R_t=1.10 min. ^{1}H NMR (DMSO-d_6) δ 1.68 (m, 4H), 2.28 (t, *J*=5.6 Hz, 2H), 2.44 (s, 3H), 2.47 (t, *J*=6.6 Hz, 2H), 12.10 (s, 1H, NH).

6-Phenyl-2-(methylthio)pyrimidin-4(3H)-one ***7{9}***. Yield 75 % (white powder). LC-MS *m/z* 219 [M+H$^+$], R_t=1.04 min. ^{1}H NMR (DMSO-d_6) δ 2.62 (s, 3H), 6.56 (s, 1H), 7.44 (m, 3H), 8.00 (m, 2H), 12.54 (s, 1H, NH).

2-(Methylthio)quinazolin-4(3H)-one ***7{10}***. Yield 68 % (pale yellow powder). LC-MS *m/z* 193 [M+H$^+$], R_t=1.04 min. ^{1}H NMR (DMSO-d_6) δ 2.55 (s, 3H), 7.36 (t, *J*=7.8 Hz, 1H), 7.47 (d, *J*=8.3 Hz, 1H), 7.68 (t, *J*=8.3 Hz, 1H), 8.02 (d, *J*=7.8 Hz, 1H), 12.56 (s, 1H, NH).

General procedures for the synthesis of compounds 10{1-4}. The commercially available alpha-keto acid **8{1-4}** (0.10 mol) was added to a solution of thiosemicarbazide (9.1 g, 0.10 mol) in water (300 mL) at 50 ˚C. After cooling the reaction

mixture, precipitate was filtrated, washed with water (100 mL) and added to a solution of sodium hydroxide (5.6 g, 0.14 mol) in water (140 mL) at 90 °C. The reaction mixture was refluxed for 18 min, cooled and pH was adjusted to 5 using 10% aqueous hydrochloric acid. The precipitate was filtrated, washed with water (100 mL), isopropyl alcohol (50 mL) and air dried to give the corresponding product.

3-Thioxo-3,4-dihydro-1,2,4-triazin-5(2H)-one ***10{1}***. Yield 52 % (pale yellow powder). LC-MS *m/z* 130 [M+H$^+$], Rt=1.05 min. ^{1}H NMR (DMSO-d$_6$) δ 7.52 (s, 1H), 13.28 (m, 2H, 2NH).

6-Methyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2H)-one ***10{2}***. Yield 82 % (white powder). LC-MS *m/z* 144 [M+H$^+$], R$_t$=1.04 min. ^{1}H NMR (DMSO-d$_6$) δ 2.26 (s, 3H), 13.23 (m, 2H, 2NH).

6-Tert-butyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2H)-one ***10{3}***. Yield 78 % (white powder). LC-MS *m/z* 186 [M+H$^+$], R$_t$=1.09 min. ^{1}H NMR (DMSO-d$_6$) δ 1.27 (s, 9H), 13.23 (m, 2H, 2NH).

6-Phenyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2H)-one ***10{4}***. Yield 72 % (pale yellow powder). LC-MS *m/z* 206 [M+H$^+$], R$_t$=1.11 min. ^{1}H NMR (DMSO-d$_6$) δ 7.46 (m, 3H), 8.05 (m, 2H), 13.21 (m, 2H, 2NH).

Compounds **11{1-4}** were prepared from compounds **10{1-4}** according to the same method as described for **7{1-10}**.

3-(Methylthio)-3,4-dihydro-1,2,4-triazin-5(2H)-one ***11{1}***. Yield 65 % (white powder). LC-MS *m/z* 144 [M+H$^+$], R$_t$=1.02 min. ^{1}H NMR (DMSO-d$_6$) δ 2.53 (s, 3H), 7.52 (s, 1H), 12.68 (s, 1H, NH).

6-Methyl-3-(methylthio)-1,2,4-triazin-5(4H)-one ***11{2}***. Yield 81 % (white powder). LC-MS *m/z* 158 [M+H$^+$], R$_t$=1.07 min. ^{1}H NMR (DMSO-d$_6$) δ 2.26 (s, 3H), 2.49 (s, 3H), 12.25 (s, 1H, NH).

6-Tert-butyl-3-(methylthio)-3,4-dihydro-1,2,4-triazin-5(2H)-one ***11{3}***. Yield 76 % (white powder). LC-MS *m/z* 200 [M+H$^+$], R$_t$=1.07 min. ^{1}H NMR (DMSO-d$_6$) δ 1.27 (s, 9H), 12.23 (s, 1H, NH).

3-(Methylthio)-6-phenyl-1,2,4-triazin-5(4H)-one ***11{4}***. Yield 75 % (pale yellow powder). LC-MS *m/z* 220 [M+H$^+$], R$_t$=1.09 min. ^{1}H NMR (DMSO-d$_6$) δ 2.55 (s, 3H), 7.46 (m, 3H), 8.05 (m, 2H), 12.21 (s, 1H, NH).

General procedures for the synthesis of compounds 12{1-2}. The suspension of compound **10{1-2}** (0.10 mol) in a solution of chloroacetic acid (10.4 g, 0.15 mol) in water (400 ml) was refluxed for 6 h. After cooling the precipitate was filtrated, washed with water (100 mL), isopropyl alcohol (50 mL) and air dried to provide the desired products.

1,2,4-Triazine-3,5(2H,4H)-dione ***12{1}***. Yield 62 % (white powder). LC-MS *m/z* 130 [M+H$^+$], R$_t$=1.01 min. ^{1}H NMR (DMSO-d$_6$) δ 7.22 (s, 1H), 12.28 (m, 2H, 2NH).

6-Methyl-1,2,4-triazine-3,5(2H,4H)-dione ***12{2}***. Yield 72 % (white powder). LC-MS *m/z* 130 [M+H$^+$], R$_t$=1.07 min. ^{1}H NMR (DMSO-d$_6$) δ 2.24 (s, 3H), 12.09 (m, 2H, 2NH).

General procedures for the synthesis of compounds 13{1-2}. The suspension of compound **12{1-2}** (0.10 mol) and phosphorus pentasulfide (10.4 g, 0.7 mol) in dry dioxane (400 mL) was refluxed for 2 h. The residual phosphorus pentasulfide was removed by filtration. The mother liquor was evaporated *in vacuo*. The residue was recrystallized from isopropyl alcohol and air dried to furnish the corresponding products.

5-Thioxo-4,5-dihydro-1,2,4-triazin-3(2H)-one ***13{1}***. Yield 72 % (white powder). LC-MS *m/z* 130 [M+H$^+$], R$_t$=1.05 min. ^{1}H NMR (DMSO-d$_6$) δ 7.52 (s, 1H), 13.28 (m, 2H, 2NH).

6-Methyl-5-thioxo-4,5-dihydro-1,2,4-triazin-3(2H)-one ***13{2}***. Yield 78 % (white powder). LC-MS *m/z* 144 [M+H$^+$], R$_t$=1.05 min. ^{1}H NMR (DMSO-d$_6$) δ 2.26 (s, 3H), 13.26 (m, 2H, 2NH).

Compounds **14{1-2}** were prepared from compounds **13{1-2}** according to the same method as described for **7{1-10}**.

5-(Methylthio)-1,2,4-triazin-3(2H)-one ***14{1}***. Yield 70 % (white powder). LC-MS *m/z* 144 [M+H$^+$], R$_t$=1.04 min. ^{1}H NMR (DMSO-d$_6$) δ 2.54 (s, 3H), 7.52 (s, 1H), 12.49 (s, 1H, NH).

6-Methyl-5-(methylthio)-4,5-dihydro-1,2,4-triazin-3(2H)-one ***14{2}***. Yield 72 % (white powder). LC-MS *m/z* 158 [M+H$^+$], R$_t$=1.09 min. ^{1}H NMR (DMSO-d$_6$) δ 2.26 (s, 3H), 2.54 (s, 3H), 12.38 (s, 1H, NH).

General procedures for the combinatorial synthesis of compounds 15{1-150}:

Method A. The solution of building-block **7{1-10}**, **11{1-4}**, **14{1-2}** (2.0 mmol) and corresponding aliphatic amine (3.0 mmol) in dry isopropyl alcohol (4 mL) was heated for 1 h at 80 °C.

After cooling the precipitate was filtrated, washed with isopropyl alcohol (0.5 mL) and air dried to furnish the corresponding product. Structures of the aforementioned amines and yields of products are reported in Table 2.

Method B. The solution of building-block **7{1-10}**, **11{1-4}**, **14{1-2}** (2.0 mmol) and corresponding aromatic amines (4.0 mmol) in dry DMF (1 mL) was heated for 1h at 140 ˚C. After cooling the reaction mixture down to 100 ˚C isopropyl alcohol (4 mL) was added. The precipitate was filtrated, washed with isopropyl alcohol (2 mL) and air dried to furnish the corresponding product. Structures of the aforementioned amines and yields of products are reported in Table 2.

2-[(2-Phenylethyl)amino]pyrimidin-4(3H)-one ***15{1}***. LC-MS *m/z* 144 [M+H$^+$], R_t=1.18 min. ^{1}H NMR (DMSO-d_6) δ 2.82 (t, *J*=7.6 Hz, 2H), 3.50 (t, *J*=7.6 Hz, 2H), 5.45 (d, *J*=7.8 Hz, 1H), 6.30-6.48 (m, 1H, NH), 7.09-7.36 (m, 5H, Ph), 7.50 (d, *J*=7.8 Hz, 1H), 10.50 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 163.6, 155.9, 139.8, 129.4, 129.0, 126.8, 103.5, 42.3, 35.6.

6-Methyl-2-[(pyridin-3-ylmethyl)amino]pyrimidin-4(3H)-one ***15{11}***. LC-MS *m/z* 217 [M+H$^+$], R_t=1.24 min. ^{1}H NMR (DMSO-d_6) δ 2.04 (s, 3H), 4.50 (d, *J*=7.8 Hz, 2H), 5.37 (s, 1H), 6.70-6.93 (m, 1H, NH), 7.28 (t, *J*=8.3 Hz, 1H), 7.70 (d, *J*=8.3 Hz, 1H), 8.41 (d, *J*=8.3 Hz, 1H), 8.51 (s, 1H), 10.51 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 154.9, 149.6, 148.8, 135.9, 135.5, 124.1, 101.5, 41.9, 24.4.

2-(4-Benzylpiperazin-1-yl)-6-ethylpyrimidin-4(3H)-one ***15{22}***. LC-MS *m/z* 299 [M+H$^+$], R_t=1.15 min. ^{1}H NMR (DMSO-d_6) δ 1.13 (t, *J*=7.6 Hz, 3H), 2.26-2.46 (m, 6H), 3.49 (s, 2H), 3.59-3.67 (m, 4H), 5.41 (s, 1H), 7.17-7.33 (m, 5H, Ph), 10.69 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 171.2, 166.3, 156.5, 138.6, 129.6, 128.9, 127.7, 99.0, 62.6, 52.8, 44.6, 30.8, 12.9.

2-Morpholin-4-yl-6-propylpyrimidin-4(3H)-one ***15{27}***. LC-MS *m/z* 224 [M+H$^+$], R_t=1.22 min. ^{1}H NMR (DMSO-d_6) δ 0.93 (t, *J*=7.3 Hz, 3H), 1.55-1.66 (m, 2H), 2.28 (t, *J*=7.3 Hz, 2H), 3.55-3.72 (m, 8H), 5.46 (s, 1H), 5.52 (s, 1H), 10.90 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 169.9, 166.3, 157.1, 99.1, 66.4, 45.1, 21.5, 14.3.

2-[(4-Hydroxy-2-methylphenyl)amino]-6-isopropylpyrimidin-4(3H)-one ***15{40}***. LC-MS *m/z* 260 [M+H$^+$], R_t=1.19 min. ^{1}H NMR (DMSO-d_6) δ 1.10 (d, *J*=7.1 Hz, 6H), 2.15 (s, 1H), 2.53-2.58 (m, 1H), 2.66-2.67 (m, 2H), 5.43 (s, 1H), 6.48-6.63 (m, 2H), 7.41 (d, *J*=7.8 Hz, 2H), 7.67 (s, 1H, NH), 8.93 (s, 1H, OH), 10.48 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 174.9, 164.0, 155.2, 153.7, 133.6, 128.3, 126.5, 117.5, 113.5, 99.4, 35.7, 26.2, 21.7, 18.6.

6-Butyl-2-(2-phenylmorpholin-4-yl)pyrimidin-4(3H)-one ***15{44}***. LC-MS *m/z* 314 [M+H$^+$], R_t=1.11 min. ^{1}H NMR (DMSO-d_6) δ 0.84 (t, *J*=7.1 Hz, 3H), 1.23-1.43 (m, 4H), 2.26-2,40 (m, 2H), 2.66-2,74 (m, 1H), 2.94-3,00 (m, 1H), 4.00-4,07 (m, 1H), 4.21-4,32 (m, 1H), 4.40-4,48 (m, 2H), 5.54 (s, 1H), 7.20-7.43 (m, 5H, Ph), 11.19 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 140.2, 128.9, 126.8, 77.63, 66.5, 51.2, 44.7, 34.8, 30.7, 22.9, 14.6.

2-[(2-Methoxybenzyl)amino]-3,5,6,7-tetrahydro-4H-cyclopenta[d]pyrimidin-4-one ***15{46}***. LC-MS *m/z* 272 [M+H$^+$], R_t=1.22 min. ^{1}H NMR (CD_3OD) δ 1.80-1.92 (m, 2H), 2.44-2.62 (m, 4H), 3.82 (s, 3H), 4.41 (d, *J*=5.6 Hz, 2H), 6.82-6.95 (m, 2H), 6.99 (d, *J*=7.1 Hz, 1H), 7.19 (d, *J*=7.1 Hz, 1H), 7.25 (t, *J*=7.1 Hz, 1H), 10.67 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 171.2, 161.1, 157.6, 155.60, 129.1, 128.7, 127.2, 120.9, 111.8, 111.3, 56.1, 35.4, 27.2, 21.5.

Ethyl 4-(4-oxo-3,4,5,6,7,8-hexahydroquinazolin-2-yl)piperazine-1-carboxylate ***15{54}***. LC-MS *m/z* 307 [M+H$^+$], R_t=1.24 min. ^{1}H NMR (DMSO-d_6) δ 1.24 (t, *J*=5.1 Hz, 3H), 1.58-1.78 (m, 2H), 2.23-2.40 (m, 4H), 3.36-3.45 (m, 4H), 3.50-3.58 (m, 4H), 3.98-4.11 (m, 2H), 10.88 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 155.3, 153.4, 109.2, 61.5, 44.7, 43.5, 32.1, 22.9, 22.7, 22.0, 15.2.

2-[(2-Hydroxyethyl)amino]-6-phenylpyrimidin-4(3H)-one ***15{63}***. LC-MS *m/z* 232 [M+H$^+$], R_t=1.20 min. ^{1}H NMR (DMSO-d_6) δ 3.48-3.52 (m, 2H), 3.58-3.62 (m, 2H), 6.01 (s, 1H), 6.48-6.64 (m, 1H, NH), 7.33-7.44 (m, 3H), 7.88-7.94 (m, 2H), 10.10 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 164.4, 162.5, 155.5, 138.1, 130.6, 129.1, 127.3, 98.2, 60.4, 43.7.

{4-[(4-Oxo-3,4-dihydroquinazolin-2-yl)amino]phenyl}acetic acid ***15{76}***. LC-MS *m/z* 296 [M+H$^+$], R_t=1.09 min. ^{1}H NMR (DMSO-d_6) δ 3.48 (s, 2H), 7.14-7.21 (m, 3H), 7.37 (d, *J*=7.8 Hz, 1H), 7.59 (t, *J*=7.8 Hz, 1H), 7.65 (d, *J*=8.3 Hz, 2H), 7.94 (d, *J*=7.8 Hz, 1H), 8.47 (s, 1H, NH), 10.70 (s, 1H, NH), 12.16 (s, 1H, COOH); ^{13}C NMR (DMSO-d_6) δ 173.6, 140.6, 138.1, 135.0, 130.4, 126.6, 123.6, 120.2, 119.0.

4-{[(5-Oxo-4,5-dihydro-1,2,4-triazin-3-yl)-amino]methyl}benzoic acid ***15{81}***. LC-MS *m/z* 247 [M+H$^+$], R_t=1.19 min. ^{1}H NMR (DMSO-d_6) δ 3.50 (d, *J*=6.4 Hz, 2H), 7.25 (s, 1H), 7.38 (d, *J*=7.8 Hz, 2H), 7.56-7.72 (m, 3H), 7.94 (d, *J*=7.8 Hz, 2H), 10.67 (s, 1H, NH), 11.98 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6) δ 167.9, 163.7, 155.7, 144.6, 139.6, 130.1, 127.7, 43.2.

3-{[3-(1H-benzimidazol-2-yl)propyl]amino}-6-methyl-1,2,4-triazin-5(4H)-one ***15{94}***. LC-MS *m/z* 285 [M+H$^+$], R_t=1.21 min. ^{1}H NMR (DMSO-d_6) δ 1.92-2.08 (m, 5H), 2.85-2.94 (m, 2H), 3.28-3.37 (m, 2H), 6.93-7.11 (m, 3H), 7.37-7.51 (m, 2H), 12.09-12.35 (m, 2H, NH); ^{13}C NMR (DMSO-d_6) δ 164.0, 156.2, 155.2, 146.7, 121.9, 27.7, 26.3, 17.5.

3-(4-Acetylpiperazin-1-yl)-6-tert-butyl-1,2,4-triazin-5(4H)-one ***15{104}***. LC-MS *m/z* 280 [M+H$^+$], R_t=1.01 min. ^{1}H NMR (DMSO-d_6) δ 1.28 (s, 9H), 2.04 (s, 3H), 3.50-3.55 (m, 6H), 3.56-3.66 (m, 2H), 12.20-12.50 (m, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 169.2, 162.0, 154.4, 154.1, 45.5, 44.0, 43.7, 36.9, 28.2, 21.9.

3-[(2-Morpholin-4-ylethyl)amino]-6-phenyl-1,2,4-triazin-5(4H)-one ***15{106}***. LC-MS *m/z* 302 [M+H$^+$], R_t=1.18 min. ^{1}H NMR (DMSO-d_6) δ 2.40-2.48 (m, 6H), 3.35-3.43 (m, 2H), 3.57-3.64 (m, 4H), 6.75-6.79 (m, 1H, NH), 7.33-7.39 (m, 3H), 7.90-8.04 (m, 2H), 12.22 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 156.3, 144.6, 134.5, 129.6, 128.9, 128.5, 66.9, 57.6, 53.8, 37.5.

5-{[2-(1H-indol-3-yl)ethyl]amino}-1,2,4-triazin-3(2H)-one ***15{120}***. LC-MS *m/z* 256 [M+H$^+$], R_t=1.19 min. ^{1}H NMR (DMSO-d_6) δ 2.97 (t, *J*=7.1 Hz, 2H), 3.58 (q, *J*=6.1 Hz, 2H), 6.95 (t, *J*=7.3 Hz, 1H), 7.03 (t, *J*=7.8 Hz, 2H), 7.11 (s, 1H), 7.28-7.34 (m, 2H), 7.52 (d, *J*=7.8 Hz, 2H), 8.23-8.37 (m, 1H, NH), 10.73 (s, 1H, NH), 11.78 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 158.4, 155.4, 137.0, 127.8, 124.2, 121.7, 119.0, 112.1, 24.7.

1-(3-Oxo-2,3-dihydro-1,2,4-triazin-5-yl)piperidine-4-carboxamide ***15{121}***. LC-MS *m/z* 224 [M+H$^+$], R_t=1.03 min. ^{1}H NMR (DMSO-d_6) δ 1.47-1.63 (m, 2H), 1.76-1.87 (m, 2H), 2.38-2.48 (m, 1H), 2.85-3.00 (m, 1H), 3.10-3.25 (m, 2H), 4.14-4.34 (m, 1H), 4.55-4.74 (m, 1H), 6.67 (s, 1H, NH), 7.19 (s, 1H, NH), 7.89 (s, 1H), 11.93 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 176.4, 156.9, 154.8, 124.6, 45.4, 42.7, 41.7, 29.4, 28.4, 27.1.

4-{2-[(3-Oxo-2,3-dihydro-1,2,4-triazin-5-yl)amino]ethyl}benzenesulfonamide ***15{124}***. LC-MS *m/z* 296 [M+H$^+$], R_t=1.09 min. ^{1}H NMR (DMSO-d_6) δ 2.49 (s, 3H), 2.92 (t, *J*=8.1 Hz, 2H), 3.03 (q, *J*=6.6 Hz, 2H), 6.80-7.30 (m, 2H, NH), 7.36 (t, *J*=13.4 Hz, 1H, NH), 7.42 (d, *J*=8.3 Hz, 2H), 7.75 (d, *J*=8.3 Hz, 2H), 11.08-11.60 (m, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 158.4, 155.3, 149.7, 144.0, 143.4, 142.8, 142.2, 141.5, 136.1, 129.9, 129.8, 127.8, 126.6, 126.4, 34.3, 33.4.

5-({2-[(3-Chloro-4-fluorophenyl)amino]-ethyl}amino)-6-methyl-1,2,4-triazin-3(2H)-one ***15{136}***. LC-MS *m/z* 224 [M+H$^+$], R_t=1.23 min. ^{1}H NMR (DMSO-d_6) δ 2.11 (s, 3H), 3.08-3.28 (m, 2H), 3.44-3.54 (m, 2H), 5.86 (s, 1H, NH), 6.49-6.73 (m, 2H), 6.98 (t, *J*=8.8 Hz, 1H), 7.71 (s, 1H, NH), 11.64 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 157.2, 154.8, 150.0, 147.7, 146.0, 132.9, 119.5, 116.9, 116.7, 111.9, 111.6, 41.2, 16.7.

6-Methyl-5-{[2-(2-phenyl-1,3-thiazol-4-yl)ethyl]amino}-1,2,4-triazin-3(2H)-one ***15{143}***. LC-MS *m/z* 314 [M+H$^+$], R_t=1.21 min. ^{1}H NMR (DMSO-d_6) δ 2.12 (s, 3H), 3.09 (t, *J*=7.3 Hz, 2H), 3.72 (q, *J*=6.8 Hz, 2H), 7.30 (s, 1H),), 7.36-7.50 (m, 3H), 7.78 (t, *J*=4.9 Hz, 1H, NH), 6.95 (d, *J*=7.6 Hz, 2H), 11.62 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 167.2, 157.8, 155.7, 133.9, 133.7, 130.7, 129.9, 126.7, 116.0, 30.6, 17.4.

2-Hydroxy-4-[(6-methyl-3-oxo-2,3-dihydro-1,2,4-triazin-5-yl)amino]benzoic acid ***15{149}***. LC-MS *m/z* 314 [M+H$^+$], R_t=1.21 min. ^{1}H NMR (DMSO-d_6) δ 2.30 (s, 3H), 6.54-6.55 (m, 1H), 7.08-7.11 (m, 2H), 7.25 (s, 1H), 8.80 (s, 1H, NH), 9.30 (s, 1H, OH), 11.86 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 158.0, 156.5, 155.3, 139.3, 134.4, 129.6, 114.7, 112.7, 111.8, 18.0.

Supporting information available. ^{1}H NMR and ^{13}C NMR spectra of a representative 20 library members. This material is available free of charge via the Internet at http://pubs.acs.org.

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Рідиннофазний комбінаторний синтез різноманітної бібліотеки 2-амінопіримідинонів та їхніх 6-азааналогів

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Резюме. Проведено рідиннофазний синтез бібліотеки зі 150 2-амінопіримідинонів та їхніх 6-азааналогів. Ключові інтермедіати для генерації бібліотеки, S-метилпіримідинони і S-метил-6-азапіримідинони, отримано за типовими методиками. Реакції всіх інтермедіатів з різноманітними амінами проведено за стандартних умов з великими виходами.

Ключові слова: піримідини, азапіримідини, інгібітори протеїнкіназ, ацилування, тіоазаурацили, S-метилпіримідинони.

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