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Design and Development of Macrocyclization Methods for Compounds with Potential Tuberculocidal Activity to Decrease CYP450 Liver Cytochrome Inhibition

N. I. Vasilevich*, E. A. Aksenova, A. A. Aksenova, and I. I. Afanasyev

New Scientific Technologies, LLC, ul. Geroev Panfilovtsev 20, Moscow, 125480 Russia
**e-mail: nvasilevich@asinex.com*

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Abstract—A procedure for macrocyclization of compounds with potential tuberculocidal activity was developed in order to obtaining compounds with a lower degree of inhibition of the key CYP 3A4 cytochrome.

Keywords: macrocycles, cytochromes CYP 3A4, tuberculocidal activity

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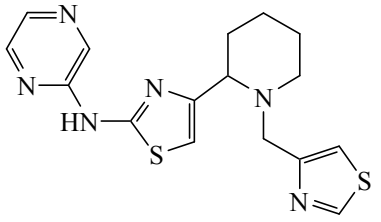
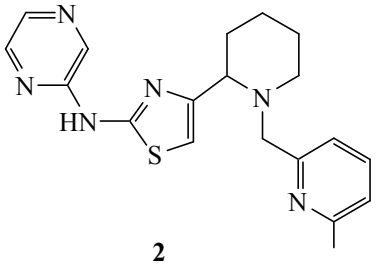
Recently, we have performed a search for a universal pharmacophore combination for serine/threonine kinase class, and have shown a possibility of optimizing this pharmacophore for individual types of kinases to obtain active and selective compounds [1, 2]. As a result of adapting the universal pharmacophore to the mycobacterial serine/threonine kinase PknB, we have obtained compounds **1**–**4** with pronounced bacteriostatic activity against the virulent strain *Mycobacterium tuberculosis* (H37Rv) in a liquid medium [3] (Scheme 1).

Scheme 1.



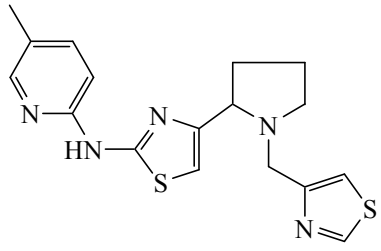
1

H37Rv: MIC 2 μM
CYP3A4: 95% at 10 μM



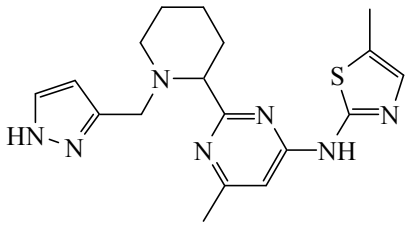
2

H37Rv: MIC 3 μM
CYP3A4: 95% at 10 μM



3

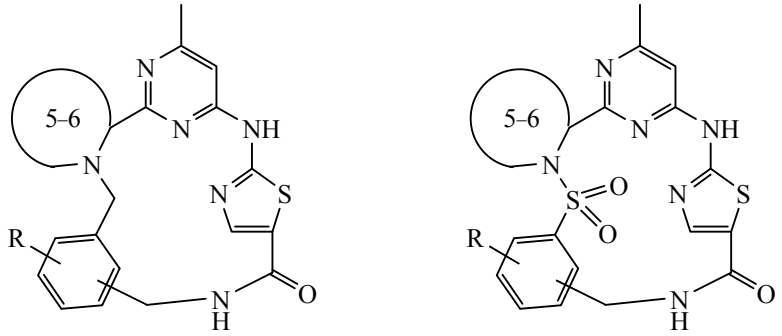
H37Rv: MIC 8 μM
CYP3A4: 94% at 10 μM



4

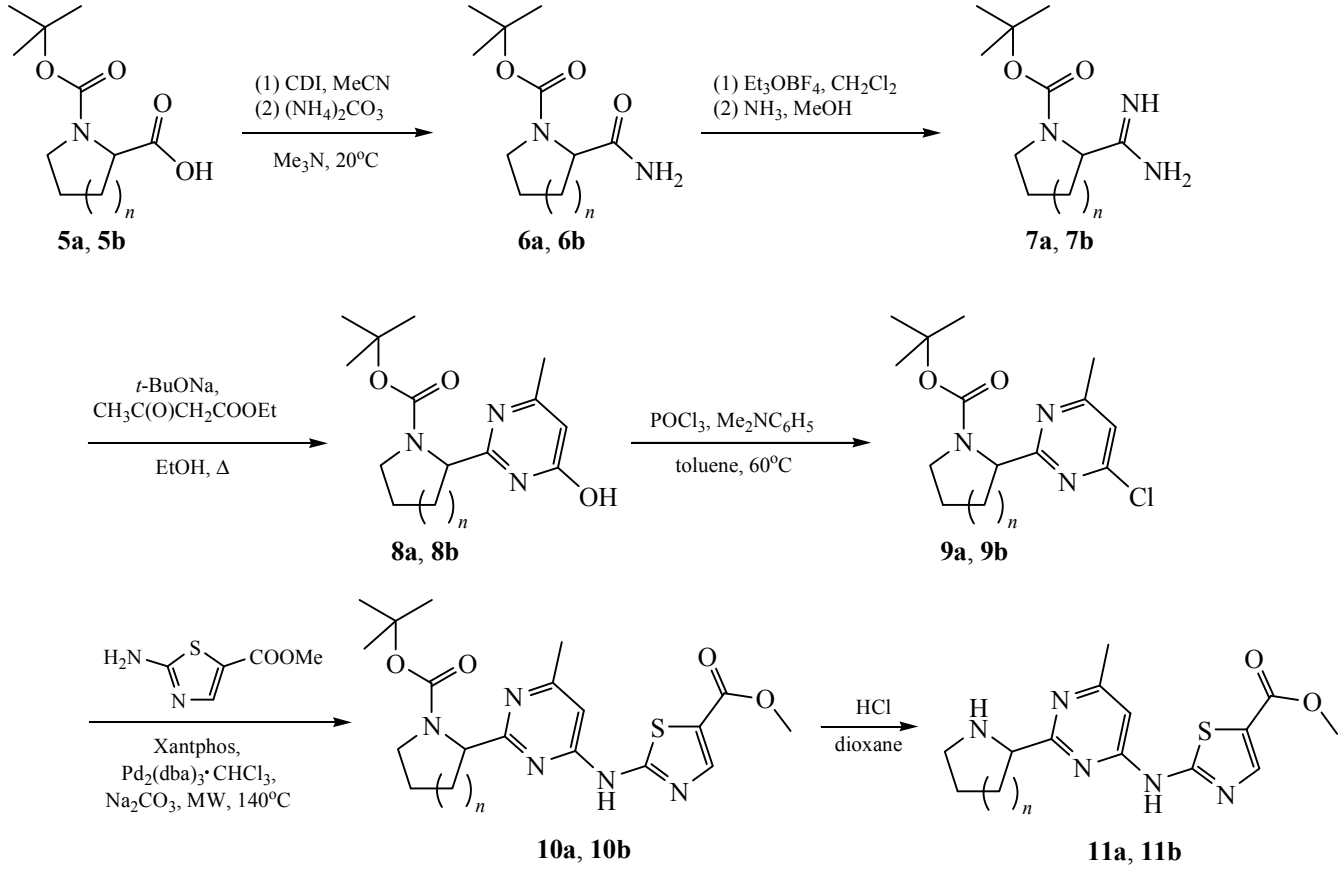
H37Rv: MIC 1 μM
CYP3A4: 97% at 10 μM

Scheme 2.



A **B**

Scheme 3.



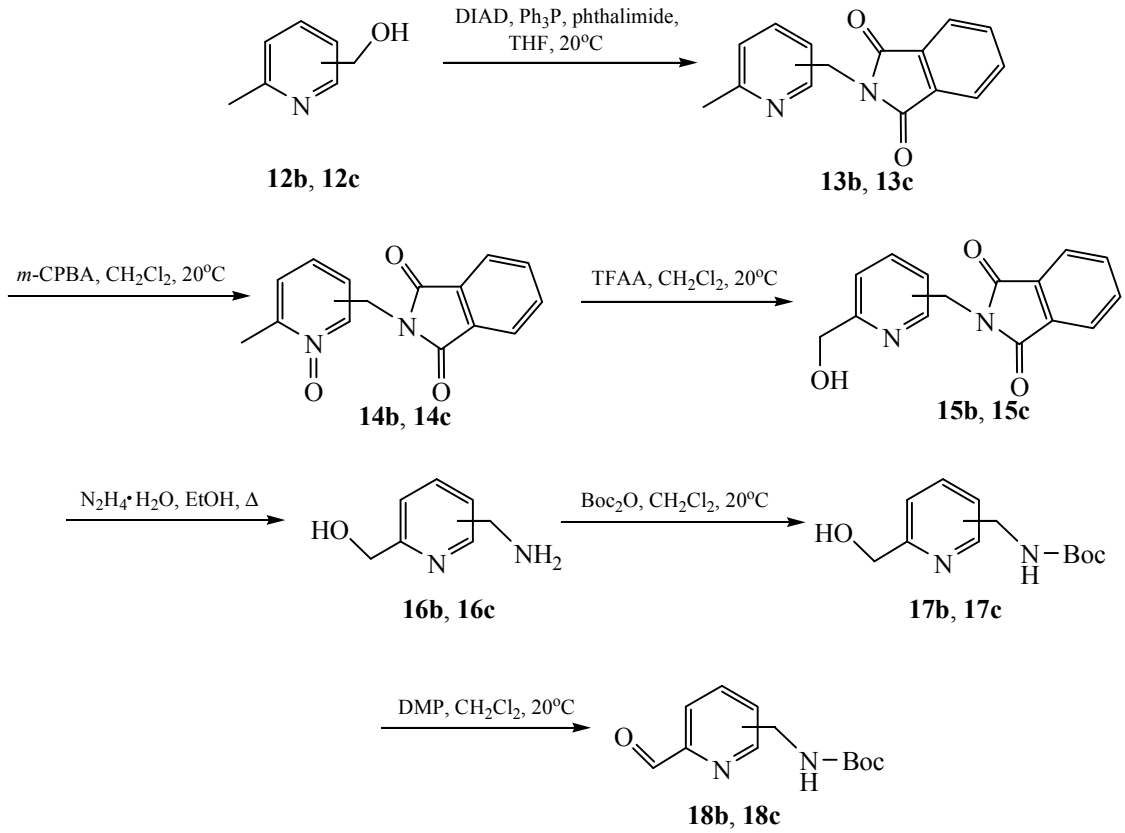
n = 1 (**a**), 2 (**b**).

MIC is the minimum concentration of inhibition, the concentration required to completely inhibit the proliferation of H37Rv in a liquid medium.

A disadvantage of these compounds was a high lipophilicity and almost complete inhibition of the key cytochrome CYP 3A4 at a concentration of 10 μM.

The macrocyclization of molecules allows improving their selectivity, solubility, permeability, metabolism, etc. [4, 5]. In particular, this approach has been successfully applied to improve the properties of kinase inhibitors [6, 7]. The structural analysis of compounds **1**–**4** suggests that they will easily undergo the ring closure by introducing a linker connecting the terminal aromatic moieties. This work is aimed to design and synthesize 15–16-membered macrocyclic compounds that satisfy the requirements of the pharmacophore we have found.

Scheme 4.



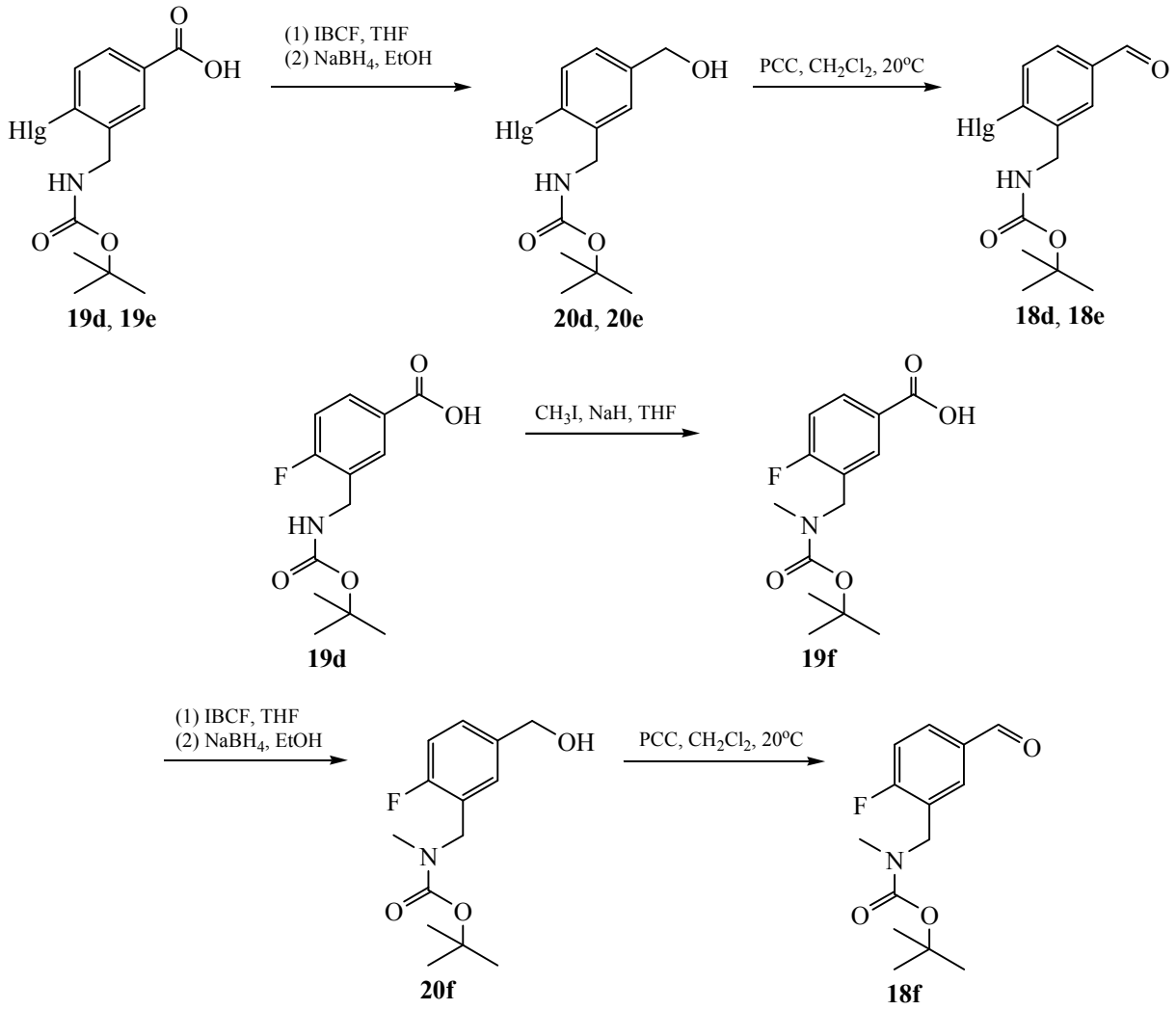
One of the suggested macrocyclic building blocks **A** was designed by connecting the rings with a methyleneaminocarbonyl linker –$CH_2NHC(O)$–. Another building block **B** contained all three necessary aromatic rings; however, unlike the original non-cyclic analogs and compounds including building block **A** one of the aromatic rings was bound to the saturated pyrrolidine or piperidine ring not by a methylene linker but by two sulfamide linkers, which provided the structure with an additional rigidity (Scheme 2).

A computer simulation confirmed the possibility of superimposing the designed macrocyclic compounds with the PknB-pharmacophore which we had found earlier consisting of three hydrophobic regions and projections of the hydrogen bond donor and acceptor [1, 2].

Synthesis of compounds containing the building block **A** was started from the preparation of intermediate **11** (Scheme 3). To this end, Boc-proline **5a** or Boc-pipecolinic acid **5b** was converted to the corresponding amide **6** and then to amidine **7** by successive treatment with an equimolar amount of triethyloxonium tetrafluoroborate and a 10% ammonia solution in methanol. The condensation of amidine **7** with ethyl acetoacetate afforded bicyclic compound **8** which was further converted to chloro derivative **9** by the action of phosphoryl chloride. This compound was brought into a Pd-catalyzed Buchwald–Hartwig reaction with 2-amino-5-carboxymethylthiazole to form compound **10**. Boc deprotection resulted in the formation of compound **11**.

Aldehyde **18a** was obtained by Boc-protection of commercial 3-(aminomethyl)benzaldehyde. Aldehydes **18b** and **18c** were prepared according to Scheme 4. In the first stage the Mitsunobu reaction of the corresponding 6-methylpyridylmethanol **12** with phthalimide in the presence of diisopropyl azodicarboxylate (DIAD) and triphenylphosphine afforded compound **13**. Further oxidation of **13** with *m*-chloroperbenzoic acid in methylene chloride gave rise to pyridinium oxide **14** which was converted to alcohol **15** by the treatment with trifluoroacetic anhydride (TFAA). The removal of the phthalimide protecting group followed by treatment with di-*t*-butyloxycarbonate resulted in the formation of the corresponding Boc-derivative **17**. Dess–Martin oxidation of the latter afforded the desired aldehyde **18**.

Scheme 5.



Hlg = F (**d**), Cl (**e**).

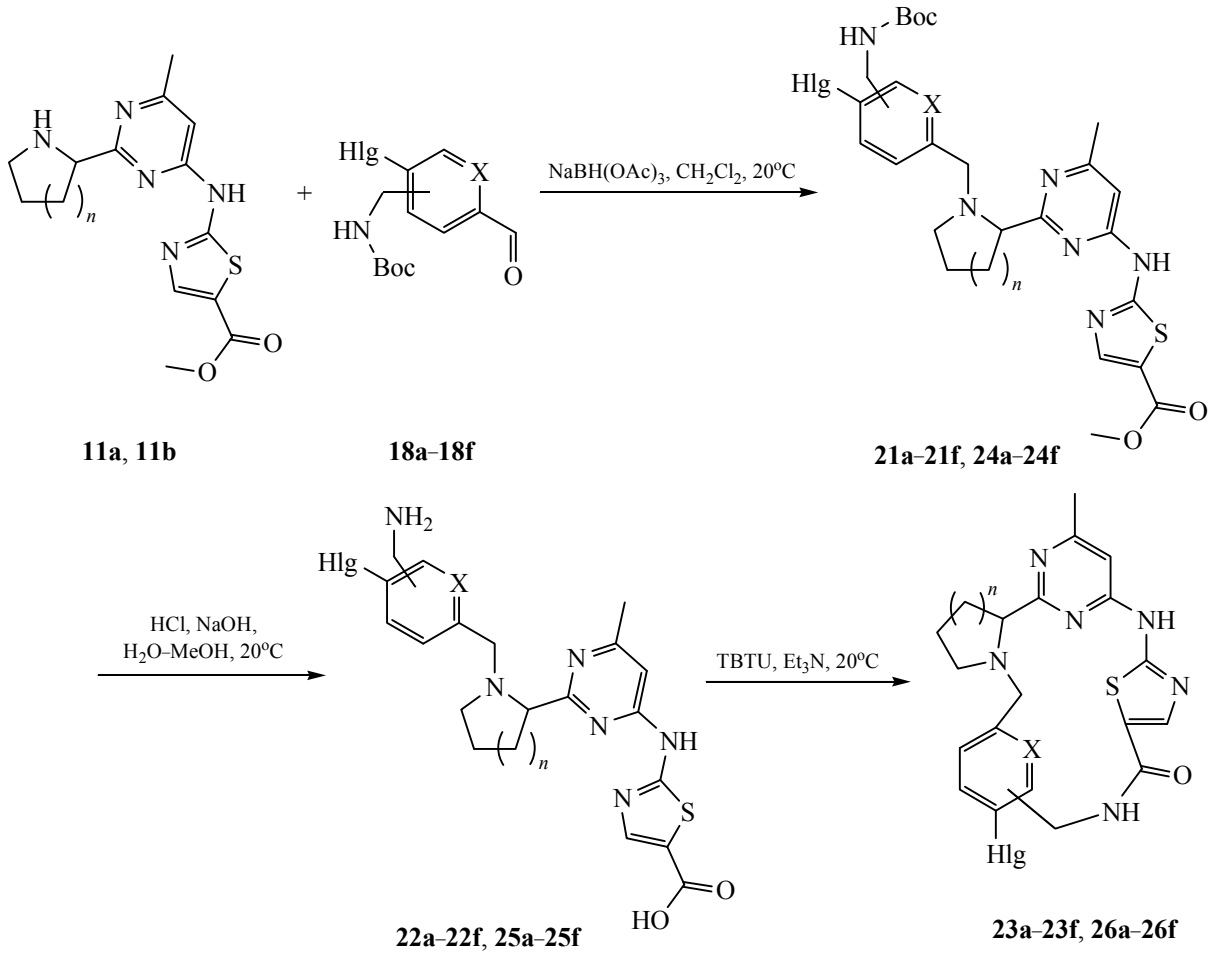
Aldehydes **18d**–**18f** were prepared by reduction of the corresponding benzoic acids **19** to alcohols **20** followed by selective oxidation with pyridinium chlorochromate (Scheme 5). To prepare aldehyde **18f** acid **19b** was initially alkylated with methyl iodide before reduction.

The synthesis of the macrocyclic compounds containing the building block **A** is given in Scheme 6. The reductive amination of intermediate **11** and the corresponding aldehyde **18** led to the formation of the protected amino acid **21**. Further deprotection and cyclization in the presence of *O*- (benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate (TBTU) resulted in the formation of target macrocycles **23** and **26** with yields of 35–88%.

Compounds containing the building block **B** were prepared as shown in Scheme 7. Initially, the intermediate **11a** reacted with the corresponding sulfonyl chloride **27a**–**27c** in the presence of triethylamine to give compounds **28a**–**28c**. Further removal of the protective triflate group followed by intramolecular acylation in the presence of TBTU led to the formation of macrocyclic compounds **30a**–**30c**.

The resulting macrocyclic compounds were tested for inhibitory activity against liver cytochromes CYP450. The data obtained showed that in the vast majority of cases macrocyclization resulted in a significant decrease in inhibition of the key cytochrome CYP3A4 and cytochrome CYP2D6 (see table). However, an unambiguous conclusion about the effect

Scheme 6.



11a, **11b** **18a**–**18f** **21a**–**21f**, **24a**–**24f**

22a–**22f**, **25a**–**25f** **23a**–**23f**, **26a**–**26f**

n = 1 (**11a**, **21a–23f**), 2 (**11b**, **24a–26f**); X = CH (**a**, **d–f**), N (**b**, **c**); Hlg = 0 (**a–c**), F (**d**, **f**), Cl (**e**).

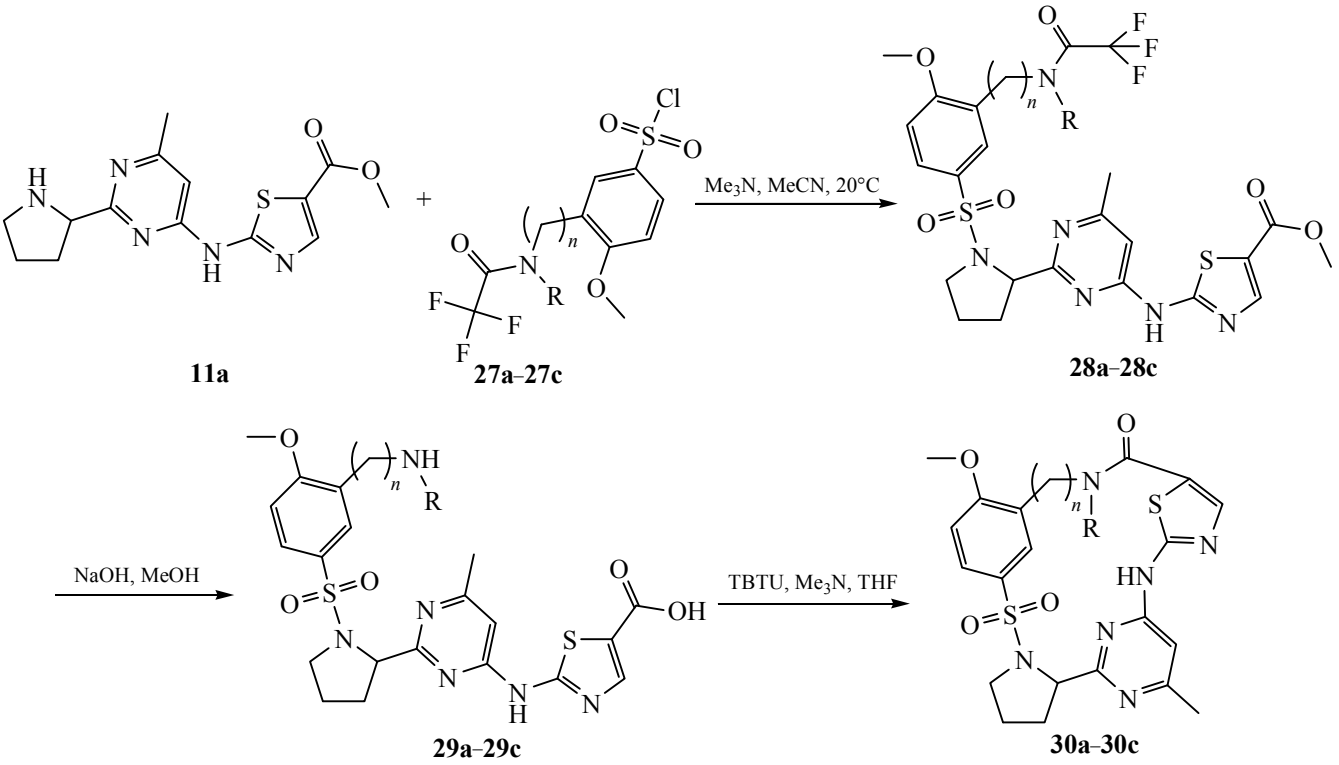
of the structure on the inhibition of cytochromes is difficult to make. In some cases, the pyrrolidine ring (**23d**) was preferable to the piperidine (**26d**). At the same time, the inhibitory effect of compounds with the piperidine ring **26a**–**26c** exceeds those of analogues **23a**–**23c** containing the pyrrolidine ring. The methyltion of the amide linker (**26d**, **26f**, **30a**) resulted in a significant decrease in the inhibition of all cytochromes. In general, compounds containing the building block **A** seem preferable to compounds with the building block **B**, but these differences are not significant. The best compounds in the inhibition parameter of liver cytochromes were compounds **26a** and **26f**.

EXPERIMENTAL

Chromato-mass spectrometric analysis was performed on a Surveyor MSQ (Thermo Fisher Scientific) instrument using chemical ionization at atmospheric pressure (ZORBAX Eclipse XDB-C18 column, 2.1× 15 mm, 1.8 μm, flow rate 750 μL/min, column temperature 25°C; mobile phase: A, 0.1% aqueous solution of formic acid; B, acetonitrile; detection with a photodiode array (PDA), 200–800 nm, photodiode array detector over the entire ultraviolet and visible range from 200 to 800 nm). ^{1}H NMR spectra were recorded on a MERCURY plus 400 MHz Varian spectrometer, internal reference tetramethylsilane.

***tert*-Butyl 2-carbamoylpyrrolidine-1-carboxylate (6a).** To a solution of 20 g (93 mmol) of Boc-proline **5a** in 150 mL of anhydrous acetonitrile were added successively 19.5 g (120 mmol) of 1,1'-carbonyldiimidazole, 21.0 mL (150 mmol) of trimethylamine, and 19.2 g (200 mmol) of ammonium carbonate. The reaction mixture was stirred at room temperature for 24 h. After the reaction completion the mixture was

Scheme 7.



11a **27a–27c** **28a–28c** **29a–29c** **30a–30c**

n = 1, R = Me (**a**); *n* = 2, R = H (**b**); *n* = 3, R = H (**c**).

poured into a saturated solution of potassium carbonate (250 mL) and extracted with dichloromethane (3 × 250 mL). The combined organic extracts were washed with water (2 × 150 mL) and dried with sodium sulfate. After removal of the solvent the reaction product was purified by flash chromatography on silica gel using hexane–ethyl acetate (100 : 0 → 1 : 1). Yield 12.3 g (62%). Mass spectrum, *m*/*z* (I_{rel}, %): 215.1 (100) $[M + H]^+$.

***tert*-Butyl 2-carbamimidoylpyrrolidine-1-carboxylate (7a).** Triethyloxonium tetrafluoroborate (14.6 g, 77 mmol) was added with stirring to a solution of 12.3 g (57.4 mmol) of amide **6a** in 200 mL of anhydrous dichloromethane. The reaction mixture was stirred for 3 h (control by TLC, ethyl acetate–dichloromethane, 1 : 2). The solvent was distilled off in a vacuum at ≤40 °C. The oily residue was treated with 10% ammonia in methanol (150 mL) for 24 h at room temperature. After the removal of methanol the residue was triturated with diethyl ether, then ether was decanted, and the residue was dried at room temperature. Yield 16.3 g (95%). Mass spectrum, *m*/*z* (I_{rel}, %): 214.1 (100) $[M + H]^+$. Amidine **7a** was used in the next step without further purification.

***tert*-Butyl 2-(4-hydroxy-6-methylpyrimidin-2-yl) pyrrolidine-1-carboxylate (8a).** A solution of 5.9 g (61 mmol) of sodium *t*-butoxide in 150 mL of anhydrous ethanol was added to a solution of 16.3 g (54.5 mmol) of amidine **7a** in ethanol. The resulting mixture was stirred for 10 min, and then 11.7 g (90 mmol) of ethyl acetoacetic acid was added. The reaction mixture was boiled for 10 h, then cooled to room temperature, poured into a saturated solution of ammonium chloride (300 mL), and extracted with dichloromethane (2 × 200 mL). The combined extracts were dried with sodium sulfate, and the solvent was distilled off in a vacuum. The residue was chromatographed on a silica gel column eluting with a 1 : 1 mixture of ethyl acetate and dichloromethane. Yield 8.7 g (57%). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.15 s [9H, $(CH_3)C$], 1.73–1.95 m (2H, CH_2CH_2), 2.06 s (3H, $CH_3C{=}N$), 2.21 m (2H, $CH_2\underline{CH_2}CH$), 3.34 m (1H, $CH_2\underline{CH_2}N$), 3.47 m (1H, $CH_2\underline{CH_2}N$), 4.40 m (1H, $CH_2\underline{CH}N$), 5.99 s (1H, CH=C), 12.15 br.s (1H, OH). Mass spectrum, *m*/*z* (I_{rel}, %): 280.2 (100) $[M + H]^+$. Found, %: C 60.28; H 7.45; N 15.02. $C_{14}H_{21}N_3O_2$. Calculated, %: C 60.20; H 7.58; N 15.04.

Inhibitory effect[a] of compounds **23a**–**23f**, **26a**–**26f,** and **30a**–**30c** on human liver cytochromes CYP450

Compound	CYP3A4, % (IC_{50}, μM)	CYP1A2, % (IC_{50}, μM)	CYP2C9, % (IC_{50}, μM)	CYP2D6, % (IC_{50}, μM)	CYP2C19, % (IC_{50}, μM)
1	95 (0.536)	38	65	83 (1.543)	71 (3.708)
2	95 (0.634)	21	38	69	35
3	94 (0.810)	38	51	92 (1.49)	54
4	96 (0.723)	33	30	82 (2.132)	29
23a	87	–7	14	4	14
23b	97 (0.366)	40	26	46	9
23c	73	16	12	–1	–5
23d	62	13	50	24	70 (4.179)
23e	76	28	19	5	76 (3.161)
23f	88	53	24	56	26
26a	58	3	4	3	5
26b	75	2	17	–4	84 (1.636)
26c	62	7	1	80 (1.226)	14
26d	99 (0.381)	71 (1.562)	80% (3.691)	49	68
26e	92 (0.578)	11	39	69	18
26f	65	9	14	1	3
30a	86	15	83 (1.612)	10	49
30b	59	3	18	–4	97 (0.158)
30c	98 (0.508)	78	89 (1.884)	87 (0.157)	78

[a] At c = 10 μM.

***tert*-Butyl 2-(4-chloro-6-methylpyrimidin-2-yl)pyrrolidine-1-carboxylate (9a).** *N*,*N*-Dimethylaniline (37.0 g, 306 mmol) and phosphoryl chloride (15.6 g, 102 mmol) were successively added to a solution of 8.7 g (31 mmol) of compound **8a** in 200 mL of anhydrous toluene. The mixture was refluxed for 3 h, then cooled to room temperature, and left overnight. The reaction mixture was poured into cold water (300 mL), the organic layer was separated, washed with 1 N HCl (2 × 70 mL) and water (1 × 70 mL), dried with sodium sulfate, and evaporated. The reaction product was isolated on a silica gel column eluting with a 1 : 3 mixture of ethyl acetate and hexane. Yield 6.2 g (67%). Mass spectrum, m/z (I_{rel}, %): 297.9 (100) $[M + H]^+$.

Methyl 2-[2-(1-*t*-butyloxycarbonylpyrrolidin-2-yl)-6-methylpyrimidin-4-ylamino]thiazole-5-carboxylate (10a). A mixture of 2.0 g (6.7 mmol) of chloride **9a**, 0.95 g (6 mmol) of 2-amino-5-carbomethoxythiazole, 4 mol% of 9.9-dimethyl-4,5-bis(diphenylphosphino)xanthene, 2 mol% of $Pd_2(dba)_3 \cdot CHCl_3$ and 0.95 g (9 mmol) of sodium carbonate in 15 mL of a toluene–water (10 : 1) mixture was stirred under argon in a microwave oven at 140 °C for 2 h. After cooling to room temperature 30 mL water was added to the reaction mixture, then the product was extracted with ethyl acetate (2 × 30 ml). The combined organic extracts were dried with sodium sulfate, and the solvent was distilled off in a vacuum. The residue was purified by column chromatography on silica gel (ethyl acetate–hexane, 1 : 2). Yield 2.02 g (80%). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.39–0.85 m [9H, $(CH_3)C$], 1.97–1.73 m (3H, $CH_2\underline{CH_2}$), 2.32 m (1H, $CH_2\underline{CH_2}CH$), 2.36 s (3H, $CH_3C{=}N$), 3.47 m (1H, $CH_2\underline{CH_2}N$), 3.79–3.68 m (1H, $CH_2\underline{CH_2}N$), 3.81 s (3H, CH_3O), 4.72 d (1H, $CH_2\underline{CH}N$, $^3J_{HH}$ = 13.7 Hz), 6.76 d (1H, $C\underline{CH}{=}C$, $^3J_{HH}$ = 12.1 Hz), 8.07 s (1H, C=CHN),

11.99 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 420.3 (100) $[M + H]^+$.

Methyl 2-(6-methyl-2-pyrrolidin-2-yl-pyrimidin-4-ylamino)thiazole-5-carboxylate (11a). To a solution of 2.02 g (4.8 mmol) of the Boc derivative **10a** in 20 mL of methanol was added 16% (by weight) of a solution of hydrogen chloride in 20 mL of dioxane. The mixture was stirred for 5 h at room temperature. Then the solvent was distilled off in a vacuum, the residue was alkalinized with 10% sodium hydroxide solution. The precipitate was filtered off, washed with water, and dried. The yield was quantitative. Mass spectrum, *m*/*z* (I_{rel}, %): 320.4 (100) $[M + H]^+$.

Compound **11b** was prepared similarly to compound **11a**.

***tert*-Butyl 2-carbamoylpiperidine-1-carboxylate (6b)** was prepared from 23.0 g (100 mmol) of Boc-pipecoline-2-carboxylic acid **5b**. Yield 17.6 g (77%). Mass spectrum, *m*/*z* (I_{rel}, %): 229.1 (100) $[M + H]^+$.

***tert*-Butyl 2-carbamimidoylpiperidine-1-carboxylate (7b)** was prepared from 17.6 g (77 mmol) of amide **6b**. Yield 19.2 g (79%). Mass spectrum, *m*/*z* (I_{rel}, %): 228.1 (100) $[M + H]^+$.

***tert*-Butyl 2-(4-hydroxy-6-methylpyrimidin-2-yl)-piperidine-1-carboxylate (8b).** Yield 11.4 g (64%). Mass spectrum, *m*/*z* (I_{rel}, %): 294.2 (100) $[M + H]^+$.

***tert*-Butyl 2-(4-chloro-6-methylpyrimidin-2-yl)-piperidine-1-carboxylate (9b).** Yield 70%. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 1.11 m (1H, $NCH_2\underline{CH_2}CH_2$), 1.36 s [9H, $(CH_3)C$], 1.39–1.67 m (3H, $NCH_2CH_2CH_2$), 1.86 m (1H, $CH\underline{CH_2}$), 2.41 s (3H, $CH_3C{=}N$), 2.45–2.67 m (3H, NCH_2 + $CH\underline{CH_2}$), 5.29 m (1H, NCH), 7.02 s (1H, CH=CCl). Mass spectrum, *m*/*z* (I_{rel}, %): 311.9 (100) $[M + H]^+$.

Methyl 2-[2-(1-*t*-butyloxycarbonylpiperidin-2-yl)-6-methylpyrimidin-4-ylamino]thiazole-5-carboxylate (10b). Yield 82%. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.02–1.22 m (2H, $NCH_2\underline{CH_2}CH_2$), 1.48 s [9H, $(CH_3)C$], 1.56 t (2H, $NCH_2CH_2\underline{CH_2}$, J = 13.7 Hz), 1.87–1.77 m (2H, CH_2), 2.35 s (3H, $CH_3C{=}N$), 2.58 d (1H, $N\underline{CH_2}CH_2$, $^3J_{HH}$ = 13.0 Hz), 3.79 s (3H, CH_3O), 3.95 t (1H, $N\underline{CH_2}CH_2$, J = 12.1 Hz), 5.18 m (1H, NCH), 6.78 s (1H, CH, pyrimidine), 8.09 s (1H, thiazole), 12.00 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 434.2 (100) $[M + H]^+$. Found, %: C 55.48; H 6.40; N 16.07. $C_{20}H_{27}N_5O_4S$. Calculated, %: C 55.41; H 6.28; N 16.15.

Methyl 2-(6-methyl-2-piperidin-2-ylpyrimidin-4-ylamino)thiazole-5-carboxylate (11b). The yield was quantitative. Mass spectrum, *m*/*z* (I_{rel}, %): 334.2 (100) $[M + H]^+$.

2-[(6-Methyl-2-pyridyl)methyl]isoindoline-1,3-dione (13b). To a solution of 4.1 g (33.7 mmol) of (6-methyl-2-pyridyl)methanol **12b** in 200 mL of THF was added 9.69 g (37 mmol) of triphenylphosphine and 4.95 g (33.7 mmol) of phthalimide. The mixture was cooled to 0 °C and a solution of 7.47 g (37 mmol) of DIAD in 20 mL of THF was added. The mixture was stirred at room temperature for 8 h. The solvent was distilled off in a vacuum, and the residue was chromatographed on a silica gel column (ethyl acetate–hexane, 1 : 2). Yield 8 g (96%). Mass spectrum, *m*/*z* (I_{rel}, %): 253.2 (100) $[M + H]^+$.

6-Methyl-2-(1,3-dioxoisoindolin-2-yl)methylpyridine-1-oxide (14b). *m*-Chloroperbenzoic acid (7 g, 39 mmol) was added to a solution of 6.6 g (26 mmol) of compound **13b** in 200 mL of anhydrous dichloromethane with cooling to 0 °C. The mixture was stirred at room temperature for 2 h and then poured into a saturated potassium carbonate solution (200 mL). The organic layer was separated, washed with water (1 × 100 mL), dried with sodium sulfate, and evaporated. The residue was recrystallized from hexane. Yield 5.86 g (84%). Mass spectrum, *m*/*z* (I_{rel}, %): 269.2 (100) $[M + H]^+$.

2-[(6-Hydroxymethyl-2-pyridyl)methyl]isoindoline-1,3-dione (15b). To a solution of 5.86 g (21.8 mmol) of compound **14b** in 100 mL of anhydrous THF was added 7.64 mL (55 mmol) of trifluoroacetic anhydride. The reaction mixture was stirred for 3 h. After the reaction completion the solvent was distilled off in a vacuum, the residue was dissolved in dichloromethane (100 mL) and saturated potassium carbonate solution (100 mL) was added. The reaction mixture was vigorously stirred for 3 h, then the organic layer was separated, dried with sodium sulfate, and evaporated. The residue was chromatographed on a silica gel column (ethyl acetate–hexane, 1 : 1). Yield 1.75 g (30%). Mass spectrum, *m*/*z* (I_{rel}, %): 269.2 (100) $[M + H]^+$.

[6-(Aminomethyl)-2-pyridyl]methanol (16b). To a solution of 1.75 g (6.5 mmol) of compound **15b** in 100 mL of ethanol was added 0.325 g (6.5 mmol) of hydrazine hydrate. The mixture was boiled for 4 h and then cooled to room temperature. The precipitate was filtered off, the filtrate was evaporated to dryness to

yield 0.9 g (100%) of compound **16b**, which was used in the next step without further purification. Mass spectrum, *m*/*z* (I_{rel}, %): 139.1 (100) $[M + H]^+$.

***tert*-Butyl *N*-[(6-hydroxymethyl-2-pyridyl)methyl]-carbamate (17b).** To a solution of 0.9 g (6.5 mmol) of compound **16b** in 50 mL of dichloromethane was added 1.53 g (7 mmol) of Boc_2O. The mixture was stirred at room temperature for 4 h. The solvent was distilled off in a vacuum and the residue was purified by flash chromatography on silica gel (ethyl acetate–hexane, 1 : 1). Yield 1.43 g (93%). Mass spectrum, *m*/*z* (I_{rel}, %): 239.0 (100) $[M + H]^+$.

***tert*-Butyl *N*-[(6-formyl-2-pyridyl)methyl]carbamate (18b).** To a solution of 1.43 g (6 mmol) of alcohol **16b** in 100 mL of dichloromethane was added 3.05 g (7.2 mmol) of Dess–Martin periodinane. The resulting suspension was stirred for 48 h. The precipitate was filtered off, the solvent was distilled off in a vacuum and the residue was purified by chromatography on silica gel (ethyl acetate–hexane, 1 : 4). Yield 1.20 g (85%). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 1.47 s [9H, $(CH_3)_3CO$], 4.53 d (2H, Ar-$\underline{CH_2}$NH, $^3J_{HH}$ = 5.6 Hz), 5.49 br.s (1H, NH), 7.49–7.53 m (1H, CH_2, pyrimidine), 7.82–7.87 m (2H, CH_2, pyrimidine), 10.07 s (1H, CHO). Mass spectrum, *m*/*z* (I_{rel}, %): 236.95 (100) $[M + H]^+$.

Aldehyde **18c** was prepared similarly to compound **18b**.

2-[(6-Methyl-3-pyridyl)methyl]isoindoline-1,3-dione (13c). Yield 65%. Mass Spectrum, *m*/*z* (I_{rel}, %): 253.2 (100) $[M + H]^+$.

6-Methyl-3-(1,3-dioxoisoindolin-2-yl)methylpyridine-1-oxide (14c). Yield 45%. Mass spectrum, *m*/*z* (I_{rel}, %): 269.12 (100) $[M + H]^+$.

2-[(6-Hydroxymethyl-3-pyridyl)methyl]isoindoline-1,3-dione (15c). Yield 35%. Mass spectrum, , *m*/*z* (I_{rel}, %): 269.2 (100) $[M + H]^+$.

[6-(Aminomethyl)-3-pyridyl]methanol (16c). The yield was quantitative. Mass spectrum, *m*/*z* (I_{rel}, %): 139.2 (100) $[M + H]^+$.

***tert*-Butyl *N*-[(6-hydroxymethyl-3-pyridyl)methyl]-carbamate (17c).** Yield 95%. Mass spectrum, *m*/*z* (I_{rel}, %): 239.0 (100) $[M + H]^+$.

***tert*-Butyl *N*-[(6-formyl-3-pyridyl)methyl]carbamate (18c).** Yield 91%. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 1.48 s [9H, $(CH_3)_3CO$)], 4.53 m (2H, Ar-$\underline{CH_2}$NH), 5.48 br.s (1H, NH), 7.42–7.48 m (1H, CH_2, pyrimidine), 7.94–8.05 m (1H, CH_2, pyrimidine), 9.43 s (1H, CH_2, pyrimidine), 10.16 s (1H, CHO). Mass spectrum, *m*/*z* (I_{rel}, %): 236.98 (100) $[M + H]^+$.

***tert*-Butyl (2-fluoro-5-hydroxymethylbenzyl)carbaminate (20d).** To a mixture of 538 mg (2.0 mmol) of 3-(*tert*-butoxycarbonylaminomethyl)-4-fluorobenzoic acid **19d** and 222 mg (2.2 mmol) of triethylamine in 30 mL of anhydrous THF at 0 °C was added dropwise 300 mg (2.2 mmol) of isobutyl chloroformate. The reaction mixture was stirred at room temperature for 1.5 h. Triethylamine hydrochloride was filtered off and washed with a small amount of cold THF. To the resulting solution of the mixed anhydride was added 380 mg (10 mmol) of sodium borohydride and 1 mL of ethanol. The suspension was stirred at room temperature for 1 h, then poured into water (100 mL) and extracted with dichloromethane (2 × 100 mL). The organic phase was evaporated, the residue was purified on a silica gel column eluting with dichloromethane–ethyl acetate. Yield 393 mg (77%). Mass spectrum, *m*/*z* (I_{rel}, %): 256.20 (100) $[M + H]^+$.

***tert*-Butyl (2-fluoro-5-formylbenzyl)carbaminate (18d).** Pyridinium chlorochromate (473 mg, 2.2 mmol) was added to a solution of 380 mg (1.5 mmol) of compound **20d** in 20 mL of anhydrous dichloromethane. The resulting mixture was stirred for 1.5 h at room temperature. The solution was decanted, the solvent was distilled off in a vacuum, and the residue was purified by flash chromatography on silica gel (dichloromethane). Yield 340 mg (90%). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 1.37 s [9H, $(CH_3)_3CO$], 4.22 d (2H, Ar-$\underline{CH_2}$NH), 5.48 br.s (1H, NH), 7.32–7.42 m (2H, CH_2, pyrimidine), 7.83–7.90 m (1H, CH_2, pyrimidine), 9.95 s (1H, CHO). Mass spectrum, *m*/*z* (I_{rel}, %): 253.98 (100) $[M + H]^+$.

Aldehyde **18e** was prepared similarly to compound **18d**.

***tert*-Butyl (2-chloro-5-hydroxymethylbenzyl)carbaminate (20e).** Yield 87%. Mass spectrum, *m*/*z* (I_{rel}, %): 272.90 (100) $[M + H]^+$.

***tert*-Butyl (2-chloro-5-formylbenzyl)carbaminate (18e).** Yield 93%. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.44 s [9H, $(CH_3)_3CO$)], 4.25 d (2H, Ar-$\underline{CH_2}$NH, $^3J_{HH}$ = 6.1 Hz), 5.41 br.s (1H, NH), 7.66 d (1H, CH_2, pyrimidine, $^3J_{HH}$ = 8.0 Hz), 7.79 m (2H, CH_2, pyrimidine), 9.99 s (1H, CHO). Mass spectrum, *m*/*z* (I_{rel}, %): 270.77 (100) $[M + H]^+$.

3-[(*t*-Butyloxycarbonylmethylamino)methyl]-4-fluorobenzoic acid (19f). Sodium hydride (480 mg, 12.0 mmol, 60% in mineral oil) was added to a solution of 1.24 g (4.6 mmol) of acid **19d** in 100 mL of anhydrous THF. The resulting mixture was stirred for 15 min and then 1.70 g (12.0 mmol) of methyl iodide was added. The reaction mixture was stirred for 16 h at room temperature, after which 10 mL of a 5% aqueous solution of NaOH was added and stirring was continued for an additional 12 h. After the completion of the reaction the mixture was acidified to pH 5 with a solution of citric acid, extracted with dichloromethane (2 × 150 mL), and evaporated. The residue was triturated with hexane, then filtered off, and dried. Yield 1.19 g (92%). Mass spectrum, *m*/*z* (I_{rel}, %): 283.99 (100) $[M + H]^+$.

***tert*-Butyl (2-fluoro-5-hydroxymethylbenzyl)methylcarbaminate (20f)** was obtained analogously to compound **20d**. Yield 69%. Mass spectrum, *m*/*z* (I_{rel}, %): 270.30 (100) $[M + H]^+$.

***tert*-Butyl (2-chloro-5-formylbenzyl)methyl carbamate (18f)** was obtained analogously to compound **18d**. Yield 97%. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.30 s [9H, $(CH_3)_3CO$)], 2.82 s (3H, CH_3N), 4.46 s (2H, Ar-$\underline{CH_2}$NH), 7.42 d.d (1H, CH_2, pyrimidine, $^3J_{HH}$ = 9.6, 8.7 Hz), 7.79 d (1H, CH_2, pyrimidine, $^3J_{HH}$ = 6.8 Hz), 7.88–7.96 m (1H, CH_2, pyrimidine), 9.91 s (1H, CHO). Mass spectrum, *m*/*z* (I_{rel}, %): 268.27 (100) $[M + H]^+$.

2-{2-[1-(4-Methoxy-3-{[methyl-(2,2,2-trifluoroacetyl)amino]methyl}benzenesulfonyl)pyrrolidin-2-yl]-6-methylpyrimidin-4-ylamino}thiazole-5-carboxylic acid (28a). 4-Methoxy-3-{[methyl-(2,2,2-trifluoroacetyl)amino]methyl}benzenesulfonyl chloride **27a** (345 mg, 1 mmol) and triethylamine (0.17 mL, 1.2 mmol) were added to a solution of 319 mg (1 mmol) of compound **11a** in 10 mL of anhydrous acetonitrile. The mixture was stirred for 4 h, then poured into a saturated solution of potassium carbonate (20 mL), and the product was extracted with dichloromethane. The extract was dried with sodium sulfate. After removing the solvent, the residue was triturated with hexane, filtered off, and dried. Yield 500 mg (80%). Mass spectrum, *m*/*z* (I_{rel}, %): 629.6 (100) $[M + H]^+$.

2-{2-[1-(4-Methoxy-3-methylaminomethylbenzenesulfonyl)pyrrolidin-2-yl]-6-methylpyrimidin-4-ylamino}thiazole-5-carboxylic acid (29a). To a solution of 500 mg (0.8 mmol) of compound **28a** in 10 mL of methanol was added 5 mL of saturated NaOH solution. The resulting mixture was stirred at room temperature for 6 h, then neutralized with concentrated hydrochloric acid to pH 6, and evaporated to dryness. The resulting amino acid was used in the next step without further purification. The yield was quantitative. Mass spectrum, *m*/*z* (I_{rel}, %): 519.6 (100) $[M + H]^+$.

2-(2-{1-[3-(2-Aminoethyl)-4-methoxybenzenesulfonyl]pyrrolidin-2-yl}-6-methylpyrimidin-4-ylamino)thiazole-5-carboxylic acid (29b) was obtained similarly with quantitative yield. Mass spectrum, *m*/*z* (I_{rel}, %): 519.4 (100) $[M + H]^+$.

2-(2-{1-[3-(2-Aminopropyl)-4-methoxybenzenesulfonyl]pyrrolidin-2-yl}-6-methylpyrimidin-4-ylamino)thiazole-5-carboxylic acid (29c) was obtained similarly with quantitative yield. Mass spectrum, *m*/*z* (I_{rel}, %): 532.6 (100) $[M + H]^+$.

General procedure for the synthesis of macrocycles 23a–23f and 26a–26f.

Synthesis of compounds 21a–21f and 24a–24f. To a suspension of 1.00 mmol of compound **11a** or **11b** in 20 mL of dichloromethane was added 1.20 mmol of the corresponding aldehyde **18a**–**18f**. The mixture was stirred for 10–15 min, and then 252 mg (1.20 mmol) of sodium triacetoxyborohydride was added. The reaction mixture was stirred at room temperature for 12 h, then poured into 30 mL of a saturated solution of potassium carbonate and extracted with dichloromethane (50 mL). The organic layer was separated, dried with sodium sulfate, and evaporated. The residue was purified on a silica gel column (ethyl acetate–dichloromethane, 1 : 2).

Methyl 2-(2-{1-(3-[(*tert*-butoxycarbonylamino)-methyl]benzyl}pyrrolidin-2-yl)-6-methylpyrimidin-4-ylamino)thiazole-5-carboxylate (21a). Yield 51%. Mass spectrum, *m*/*z* (I_{rel}, %): 538.2 (100) $[M + H]^+$.

Methyl 2-{2-[1-({6-[(*tert*-butoxycarbonylamino) methyl]pyridin-2-yl}methyl)pyrrolidin-2-yl]-6-methylpyrimidin-4-ylamino}thiazole-5-carboxylate (21b). Yield 74%. Mass spectrum, *m*/*z* (I_{rel}, %): 539.3 (100) $[M + H]^+$.

Methyl 2-{2-[1-({5-[(*tert*-butoxycarbonylamino)-methyl]pyridin-2-yl}methyl)pyrrolidin-2-yl]-6-methylpyrimidin-4-ylamino}thiazole-5-carboxylate (21c). Yield 78%. Mass spectrum, *m*/*z* (I_{rel}, %): 539.2 (100) $[M + H]^+$.

Methyl 2-[2-(1-{3-[(*tert*-butoxycarbonylamino)-methyl]-4-fluorobenzyl}pyrrolidin-2-yl)-6-methyl-

pyrimidin-4-ylamino]thiazole-5-carboxylate (21d). Yield 84%. Mass spectrum, *m*/*z* (I_{rel}, %): 556.3 (100) $[M + H]^+$.

Methyl 2-[2-(1-{3-[(*tert*-butoxycarbonylamino)-methyl]-4-chlorobenzyl}pyrrolidin-2-yl)-6-methyl-pyrimidin-4-ylamino]thiazole-5-carboxylate (21e). Yield 83%. Mass spectrum, *m*/*z* (I_{rel}, %): 572.3 (100) $[M + H]^+$.

Methyl 2-{2-[1-(3-{[*tert*-butoxycarbonyl(methyl)-amino]methyl}-4-fluorobenzyl)pyrrolidin-2-yl]-6-methylpyrimidin-4-ylamino}thiazole-5-carboxylate (21f). Yield 88%. Mass spectrum, *m*/*z* (I_{rel}, %): 570.3 (100) $[M + H]^+$.

Methyl 2-[2-(1-{3-[(*tert*-butoxycarbonylamino)-methyl]benzyl}piperidin-2-yl)-6-methylpyrimidin-4-ylamino]thiazole-5-carboxylate (24a). Yield 66%. Mass spectrum, *m*/*z* (I_{rel}, %): 552.4 (100) $[M + H]^+$.

Methyl 2-{2-[1-({6-[(*tert*-butoxycarbonylamino)-methyl]pyridin-2-yl}methyl)piperidin-2-yl]-6-methyl-pyrimidin-4-ylamino}thiazole-5-carboxylate (24b). Yield 66%. Mass spectrum, *m*/*z* (I_{rel}, %): 553.5 (100) $[M + H]^+$.

Methyl 2-{2-[1-({5-[(*tert*-butoxycarbonylamino)-methyl]pyridin-2-yl}methyl)piperidin-2-yl]-6-methyl-pyrimidin-4-ylamino}thiazole-5-carboxylate (24c). Yield 70%. Mass spectrum, *m*/*z* (I_{rel}, %): 553.5 (100) $[M + H]^+$.

Methyl 2-[2-(1-{3-[(*tert*-butoxycarbonylamino)-methyl]-4-fluorobenzyl}piperidin-2-yl)-6-methyl-pyrimidin-4-ylamino]thiazole-5-carboxylate (24d). Yield 54%. Mass spectrum, *m*/*z* (I_{rel}, %): 570.4 (100) $[M + H]^+$.

Methyl 2-[2-(1-{3-[(*t*-butoxycarbonylamino)methyl]-4-chlorobenzyl}piperidin-2-yl)-6-methylpyrimidin-4-ylamino]thiazole-5-carboxylate (24e). Yield 64%. Mass spectrum, *m*/*z* (I_{rel}, %): 586.3 (100) $[M + H]^+$.

Methyl 2-{2-[1-(3-{[*tert*-butoxycarbonyl(methyl)-amino]methyl}-4-fluorobenzyl)piperidin-2-yl]-6-methylpyrimidin-4-ylamino}thiazole-5-carboxylate (24f). Yield of 57%. Mass spectrum, *m*/*z* (I_{rel}, %): 584.5 (100) $[M + H]^+$.

Synthesis of compounds 22a–22f and 25a–25f. To a solution of 0.5 mmol of compound **21** or **24** in 5 mL of ethanol was added 2 mL of concentrated hydrochloric acid. The mixture was stirred at room temperature for 12 h. The solvents were evaporated to dryness, the residue was dissolved in 3 mL of ethanol and a solution of 200 mg (5.00 mmol) of NaOH in 3 mL of water was added. The resulting mixture was stirred at room temperature for 18 h and then acidified with hydrochloric acid to pH 5–6. After the solvent removal the residue was dried in air at 60°C for 6 h. Amino acid **22** or **25** with an admixture of inorganic salts was prepared, which was used in the next step without further purification.

Synthesis of macrocycles 23a–23f and 26a–26f. To a suspension of 0.5 mmol of compound **22** or **25** in 150 mL of dichloromethane was added 280 μL (2.00 mmol) of triethylamine and 193 mg (0.60 mmol) of TBTU. The mixture was stirred at room temperature for 24 h, then washed with a solution of potassium carbonate, and dried with sodium sulfate. After removal of the solvent the residue was chromatographed on a silica gel column (dichloromethane–methanol, 30 : 1).

Macrocycle 23a. Yield 41%. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.77–1.89 m (2H, CH_2, pyrrolidine), 1.94–2.01 m (1H, CH_2, pyrrolidine), 2.18 d.d (1H, CH_2, pyrrolidine, $^3J_{HH}$ = 18.5, 9.8 Hz), 2.33 d (3H, CH_3-pyrimidine, $^3J_{HH}$ = 13.0 Hz), 3.08 d.d (2H, CH_2, pyrrolidine, $^3J_{HH}$ = 16.3, 8.0 Hz), 3.50 d (1H, CH, pyrrolidine, $^3J_{HH}$ = 13.3 Hz), 3.86 d (1H, CH_2, $^3J_{HH}$ = 13.3 Hz), 3.95 d.d (1H, CH_2, $^3J_{HH}$ = 7.8, 4.4 Hz), 4.39 d.d.d (2H, CH_2, $^3J_{HH}$ = 35.5, 16.3, 6.9 Hz), 6.68 s (1H, pyrimidine), 7.08 d (1H, CH, Ph, $^3J_{HH}$ = 6.8 Hz), 7.21 d.d (2H, CH, Ph, $^3J_{HH}$ = 10.7, 7.3 Hz), 7.75 s (1H, CH, Ph), 7.98 s [1H, C(O)NH], 8.46 t (1H, CH, thiazole, $^3J_{HH}$ = 6.6 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 407.2 (100) $[M + H]^+$. Found, %: C 62.15; H 5.49; N 20.48. $C_{21}H_{22}N_6O$. Calculated, %: C 62.05; H 5.45; N 20.67.

Macrocycle 23b. Yield 35%. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.64–1.92 m (3H, CH_2, pyrrolidine), 2.29 d.d (1H, CH_2, pyrrolidine, $^3J_{HH}$ = 19.4, 9.0 Hz), 2.36 s (3H, CH_3-pyrimidine), 2.87 m (1H, CH_2, pyrrolidine), 3.58–3.33 m (2H, CH_2), 3.97 d (1H, CH_2, pyrrolidine, $^3J_{HH}$ = 21.0 Hz), 4.37 d.d (2H, CH_2NH + CH, pyrrolidine, $^3J_{HH}$ = 17.1, 3.1 Hz), 4.76 d.d (1H, CH_2NH, $^3J_{HH}$ = 17.2, 3.1 Hz), 6.70 s (1H, CH, pyrimidine), 7.24 d.d (2H, CH, Ph, $^3J_{HH}$ = 11.0, 7.7 Hz), 7.70 t (1H, CH, Ph, $^3J_{HH}$ = 7.7 Hz), 7.80 s (1H, NH), 8.10 s (1H, thiazole), 11.69 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 408.3 (100) $[M + H]^+$. Found, %: C 59.02; H 5.29; N 23.91. $C_{20}H_{21}N_7OS$. Calculated, %: C 58.95; H 5.19; N 24.06.

Macrocycle 23c. Yield 35%. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.85–2.26 m (4H, CH_2,

pyrrolidine), 2.24–2.40 m (3H, CH_3-pyrimidine), 2.91–3.23 m (2H, CH_2, pyrrolidine), 3.61–3.86 m (1H, CH_2, pyrrolidine), 3.84–4.53 m (4H, CH_2 + CH_2NH), 6.55 s (1H, CH, pyrimidine), 7.29 m (1H, CH, Ph), 7.61 m (3H, CH, Ph + NH), 8.54–8.32 m (1H, thiazole), 11.50 m (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 408.2 (100) $[M + H]^+$. Found, %: C 59.07; H 5.07; N 23.94. $C_{20}H_{21}N_7OS$. Calculated, %: C 58.95; H 5.19; N 24.06.

Macrocycle 23d was obtained as dihydrochloride by treating with 16% HCl solution in dioxane. Yield 30%. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 2.13 m (2H, CH_2, pyrrolidine), 2.42 s (3H, CH_3-pyrimidine), 2.52–2.69 m (2H, CH_2, pyrrolidine), 3.29 s (1H, CH_2, pyrrolidine), 3.49 s (1H, CH_2, pyrrolidine), 4.54 m (4H, CH_2 + CH_2NH), 4.78 s (1H, CH_2, pyrrolidine), 6.87 s (1H, CH, pyrimidine), 7.28 t (1H, CH, Ph, $^3J_{HH}$ = 9.3 Hz), 7.54 s (1H, NH), 7.82–8.10 m (2H, CH, Ph), 8.38 s (1H, thiazole), 12.18 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 425.1 (100) $[M + H]^+$. Found, %: C 59.47; H 5.12; N 19.99. $C_{21}H_{21}FN_6OS$. Calculated, %: C 59.42; H 4.99; N 19.80.

Macrocycle 23e. Yield 59%. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.63 d (1H, $^3J_{HH}$ = 8.0 Hz, CH_2, pyrrolidine), 1.70–1.83 m (1H, CH_2, pyrrolidine), 1.92 d (1H, CH_2, pyrrolidine, $^3J_{HH}$ = 2.1 Hz), 2.27 d.d (2H, CH_2, pyrrolidine, $^3J_{HH}$ = 19.4, 9.8 Hz), 2.35 s (3H, CH_3-pyrimidine), 3.00–3.12 m (1H, CH_2, pyrrolidine), 3.48 d (1H, CH, pyrrolidine, $^3J_{HH}$ = 13.8 Hz), 4.03 d.d (2H, CH_2, $^3J_{HH}$ = 20.6, 10.7 Hz), 4.34 d.d (1H, CH_2, $^3J_{HH}$ = 16.6, 5.3 Hz), 4.63 d.d (1H, CH_2, $^3J_{HH}$ = 16.7, 7.1 Hz), 4.54 m (4H, CH_2 + CH_2NH), 6.71 s (1H, CH, pyrimidine), 7.10 d (1H, CH, Ph, $^3J_{HH}$ = 7.7 Hz), 7.29 d (1H, CH, Ph, $^3J_{HH}$ = 7.9 Hz), 7.74 s (1H, CH, Ph), 8.43 s (1H, NH), 8.70 s (1H, thiazole), 11.71 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 440.98 (100) $[M + H]^+$. Found, %: C 57.16; H 4.95; N 19.18. $C_{21}H_{21}ClN_6OS$. Calculated, %: C 57.20; H 4.80; N 19.06.

Macrocycle 23f. Yield 49%. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.73–1.93 m (3H, CH_2, pyrrolidine), 2.14 d.t (1H, CH_2, pyrrolidine, $^3J_{HH}$ = 19.5, 8.1 Hz), 2.33 s (3H, CH_3-pyrimidine), 2.41–2.46 m (1H, CH_2, pyrrolidine), 2.87–2.94 m (1H, CH_2, pyrrolidine, $^3J_{HH}$ = 2.1 Hz), 2.98 m (3H, CH_3), 3.43 d (1H, CH_2, $^3J_{HH}$ = 13.2 Hz), 3.78 d (1H, CH_2, $^3J_{HH}$ = 13.2 Hz), 3,89 d.d (1H, CH, pyrrolidine, $^3J_{HH}$ = 4.4, 8.4 Hz), 4.43 d.d (2H, CH_2NH, $^3J_{HH}$ = 15.5, 41.8 Hz), 6.66 s (1H, CH, pyrimidine), 7.07 d.d (1H, CH, Ph, $^3J_{HH}$ = 8.4, 10.4 Hz), 7.20 d.d (1H, CH, Ph, $^3J_{HH}$ = 6.7, 4.2 Hz), 7.63–7.71 m (1H, CH, Ph), 8.38 s (1H, thiazole). Mass spectrum, *m*/*z* (I_{rel}, %): 439.2 (100) $[M + H]^+$. Found, %: C 60.24; H 5.14; N 19.11. $C_{22}H_{23}FN_6OS$. Calculated, %: C 60.26; H 5.29; N 19.16.

Macrocycle 26a. Yield 63%. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.21 s (1H, CH_2, piperidine), 1.51 s (1H, CH_2, piperidine), 1.74 s (2H, CH_2, piperidine), 2.01 s (2H, CH_2, piperidine), 2.34 s (1H, CH_2, piperidine), 2.37 s (3H, CH_3-pyrimidine), 2.95 s (1H, CH_2, piperidine), 3.77–3.93 m (3H, CH_2 + CH, piperidine), 4.37 d.d.d (2H, CH_2NH, $^3J_{HH}$ = 6.8, 16.2, 22.5 Hz), 6.73 s (1H, CH, pyrimidine), 7.18 d.d.d (3H, CH, Ph, $^3J_{HH}$ = 7.2, 14.6, 22.1 Hz), 7.72 s (1H, CH, Ph), 7.94 s (1H, thiazole), 8.47 t (1H, NH, $^3J_{HH}$ = 6.6 Hz), 11.67 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 421.2 (100) $[M + H]^+$. Found, %: C 62.68; H 5.44; N 19.71. $C_{22}H_{24}N_6OS$. Calculated, %: C 62.83; H 5.75; N 19.98.

Macrocycle 26b. Yield 50%. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.18 m (2H, CH_2, piperidine), 1.51 m (2H, CH_2, piperidine), 1.67 m (2H, CH_2, piperidine), 1.98 m (1H, CH_2, piperidine), 2.35 m (1H, CH_2, piperidine), 2.37 s (3H, CH_3-pyrimidine), 2.85 s (1H, CH_2, piperidine), 3.90 m (2H, CH_2), 4.12 d (2H, CH_2NH, $^3J_{HH}$ = 12.5 Hz), 6.68 s (1H, CH, pyrimidine), 7.27 d.d (2H, CH, Ph, $^3J_{HH}$ = 3.2, 7.5 Hz), 7.72 t (1H, CH, Ph, $^3J_{HH}$ = 7.6 Hz), 7.79 s (1H, thiazole), 8.23 t (1H, NH, $^3J_{HH}$ = 5.2 Hz), 11.73 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 422.1 (100) $[M + H]^+$. Found, %: C 59.72; H 5.44; N 23.10. $C_{21}H_{22}N_7OS$. Calculated, %: C 59.84; H 5.50; N 23.26.

Macrocycle 26c. Yield 37%. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.48 m (1H, CH_2, piperidine), 1.68 m (2H, CH_2, piperidine), 1.82 m (1H, CH_2, piperidine), 2.20 s (1H, CH_2, piperidine), 2.36–2.38 m (3H, CH_3-pyrimidine), 2.87 d (1H, CH_2, piperidine, $^3J_{HH}$ = 11.0 Hz), 3.21–3.63 m (3H, CH_2, piperidine), 3.76–4.10 m (3H, CH_2 + CH_2NH), 4.31 m (1H, CH_2NH), 6.61 d (1H, CH, pyrimidine, $^3J_{HH}$ = 3.6 Hz), 6.83 d (0.5H, CH, Ph, $^3J_{HH}$ = 8.0 Hz), 7.07 d (0.5H, CH, Ph, $^3J_{HH}$ = 6.5 Hz), 7.47 s (0.5H, CH, Ph), 7.52 m (0.5H, CH, Ph), 7.62–7.73 m (1H, CH, Ph), 8.21–8.39 m (1H, thiazole), 8.45 s (1H, NH), 11.34 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 422.2 (100) $[M + H]^+$. Found, %: C 59.72; H 5.58; N 23.18. $C_{21}H_{22}N_7OS$. Calculated, %: C 59.84; H 5.50; N 23.26.

Macrocycle 26d. Yield 42%. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.10 d (1H, CH_2, piperidine, $^3J_{HH}$ = 12.7 Hz), 1.46 d (2H, CH_2, piperidine,

$^3J_{HH}$ = 31.4 Hz), 1.62–1.76 m (1H, CH_2, piperidine), 1.99 d.d (1H, CH_2, piperidine, $^3J_{HH}$ = 20.1, 7.0 Hz), 2.18–2.30 m (2H, CH_2, piperidine), 2.38 s (3H, CH_3-pyrimidine), 2.84 t (1H, CH_2, piperidine, $^3J_{HH}$ = 10.8 Hz), 3.82 d (1H, CH, piperidine, $^3J_{HH}$ = 13.6 Hz), 3.95 d (2H, CH_2, $^3J_{HH}$ = 13.7 Hz), 4.33 d.d (1H, CH_2NH, $^3J_{HH}$ = 5.6, 16.4 Hz), 4.56 d.d (1H, CH_2NH, $^3J_{HH}$ = 7.2, 16.4 Hz), 6.72 s (1H, CH pyrimidine), 6.98–7.06 m (1H, CH, Ph), 7.13–7.21 m (1H, CH, Ph), 7.71 s (1H, CH, Ph), 8.18 d (1H, thiazole, $^3J_{HH}$ = 7.4 Hz), 8.60 t (1H, NH, $^3J_{HH}$ = 6.1 Hz), 11.72 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 439.2 (100) $[M + H]^+$. Found, %: C 59.99; H 5.38; N 19.21. $C_{22}H_{23}FN_6OS$. Calculated, %: C 60.26; H 5.29; N 19.16.

Macrocycle 26e. Yield 55%. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.05 s (1H, CH_2, piperidine), 1.31 d (1H, CH_2, piperidine, $^3J_{HH}$ = 12.0 Hz), 1.51 s (1H, CH_2, piperidine), 1.68 d (1H, CH_2, piperidine, $^3J_{HH}$ = 12.2 Hz), 2.04 t (1H, CH_2, piperidine, $^3J_{HH}$ = 12.1 Hz), 2.28 d (2H, CH_2, piperidine, $^3J_{HH}$ = 13.6 Hz), 2.38 s (3H, CH_3-pyrimidine), 2.84 t (1H, CH_2, piperidine, $^3J_{HH}$ = 12.4 Hz), 3.86 d (1H, CH, piperidine, $^3J_{HH}$ = 14.1 Hz), 3.98 s (1H, CH_2), 4.08 d (1H, CH_2, $^3J_{HH}$ = 14.1 Hz), 4.31 d.d (1H, CH_2NH, $^3J_{HH}$ = 5.3, 16.8 Hz), 4.64 d.d (1H, CH_2NH, $^3J_{HH}$ = 7.5, 16.9 Hz), 6.78 s (1H, CH, pyrimidine), 7.18 d (1H, CH, Ph, $^3J_{HH}$ = 7.8 Hz), 7.31 d (1H, CH, Ph, $^3J_{HH}$ = 8.0 Hz), 7.72 s (1H, CH, Ph), 8.28 s (1H, thiazole), 8.71 s (1H, NH), 11.84 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 455.0 (100) $[M + H]^+$. Found, %: C 58.19; H 5.08; N 18.22. $C_{22}H_{23}ClN_6OS$. Calculated, %: C 58.08; H 5.10; N 18.47.

Macrocycle 26f. Yield 51%. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.24 d (1H, CH_2, piperidine, $^3J_{HH}$ = 23.9 Hz), 1.45 d (1H, CH_2, piperidine, $^3J_{HH}$ = 23.7 Hz), 1.68 t (1H, CH_2, piperidine, $^3J_{HH}$ = 15.1 Hz), 1.78–2.05 m (3H, CH_2, piperidine), 2.37 s (3H, CH_3-pyrimidine), 2.39–2.44 m (1H, CH_2, piperidine), 2.84 t (1H, CH_2, piperidine, $^3J_{HH}$ = 9.6 Hz), 3.00 s (3H, CH_3), 3.50 d (1H, CH, piperidine, $^3J_{HH}$ = 13.3 Hz), 3.62 d (1H, CH_2, $^3J_{HH}$ = 14.5 Hz), 3.74 t (1H, CH_2, $^3J_{HH}$ = 12.9 Hz), 3.98 s (1H, CH_2), 4.41–4.58 m (2H, CH_2NH), 6.72 s (1H, CH, pyrimidine), 7.03–7.12 m (1H, CH, Ph), 7.20–7.29 m (1H, CH, Ph), 7.73 s (1H, CH, Ph), 8.10 d (1H, thiazole, $^3J_{HH}$ = 7.2 Hz), 11.60 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 453.2 (100) $[M + H]^+$. Found, %: C 61.12; H 5.58; N 18.42. $C_{23}H_{25}FN_6OS$. Calculated, %: C 61.04; H 5.57; N 18.57.

General procedure for the synthesis of macrocycles 30a–30c. To a solution of 0.8 mmol of amino acid **29a**–**29c** in 100 mL of THF was added 321 mg (1.0 mmol) of TBTU and 0.17 mL (1.2 mmol) of triethylamine. The reaction mixture was stirred for 16 h, and then concentrated in a vacuum. A saturated solution of potassium carbonate (25 mL) was added to the residue, and the mixture was extracted with dichloromethane (2 × 25 mL). The organic layer was separated, dried with sodium sulfate, and evaporated. The desired product was isolated by chromatography on a silica gel column (eluent ethyl acetate) and crystallized from hexane.

Macrocycle 30a. Yield 30%. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.8–2.4 m (3H, CH_2, pyrrolidine), 2.28 m (1H, CH_2, pyrrolidine), 3.05 s (3H, CH_3-pyrimidine), 3.41 m (1H, CH_2, pyrrolidine), 3.61 m (1H, CH_2, pyrrolidine), 3.85 s (3H, CH_3N), 4.45 m (2H, CH_2), 4.71 m (1H, CH, pyrrolidine), 6.72 s (1H, CH, pyrimidine), 7.62 m (3H, CH, Ph), 8.17 s (1H, thiazole), 11.75 br.s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 501.2 (100) $[M + H]^+$. Found, %: C 52.62; H 5.00; N 16.58. $C_{22}H_{24}N_6O_4S_2$. Calculated, %: C 52.78; H 4.83; N 16.79.

Macrocycle 30b. Yield 34%. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.76 m (1H, CH_2, pyrrolidine), 2.04–2.20 m (4H, CH_2, pyrrolidine), 2.41 s (3H, CH_3-pyrimidine), 2.90 m (1H, CH_2, pyrrolidine), 3.68 m (4H, CH_2), 3.90 s (3H, CH_3O), 4.59 m (1H, CH, pyrrolidine), 6.75 s (1H, CH, pyrimidine), 7.18 m (1H, CH, Ph), 7.65–7.87 m (4H, CH, Ph + thiazole), 11.76 br.s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 501.4 (100) $[M + H]^+$. Found, %: C 52.72; H 4.99; N 16.67. $C_{22}H_{24}N_6O_4S_2$. Calculated, %: C 52.78; H 4.83; N 16.79.

Macrocycle 30c. Yield 30%. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.72 m (1H, CH_2, pyrrolidine), 1.90 m (3H, CH_2, pyrrolidine), 2.16–2.20 m (3H, CH_2, pyrrolidine + CH_2), 2.40 s (3H, CH_3-pyrimidine), 2.86 m (1H, CH_2), 3.33 m (2H, CH_2), 3.47 m (1H, CH_2), 3.59 m (1H, CH_2), 3.74 s (3H, CH_3O), 4.85 m (1H, CH, pyrrolidine), 6.89 s (1H, CH, pyrimidine), 6.97 m (1H, CH, Ph), 7.37 m (1H, CH, Ph), 7.75 m (2H, CH, Ph + thiazole), 11.76 br.s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 515.4 (100) $[M + H]^+$. Found, %: C 53.72; H 5.16; N 16.43. $C_{23}H_{26}N_6O_4S_2$. Calculated, %: C 53.68; H 5.09; N 16.33.

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