Modification of biologically active amides and amines with fluorine-containing heterocycles
1. Novel fluorine-containing heterocyclic derivatives of streptocide

V. B. Sokolov, A. Yu. Aksinenko, T. A. Epishina, T. V. Goreva, and I. V. Martynov*

Institute of Physiologically Active Substances, Russian Academy of Sciences, 1 Severnyi proezd, Chernogolovka, 142432 Moscow Region, Russian Federation, Fax: +7 (496) 524 9508. E-mail: alaks@ipac.ac.ru

An approach to the modification of the known antimicrobial drug, streptocide, with fluorine-containing five-membered heterocycles is proposed. The reaction of the generated *in situ* methyl 2-[4-(*N*-acetylamino)phenylsulfonyl]imino-3,3,3-trifluoropropionate with 1,3-*C*,*N*- or 1,3-*N*,*N*-binucleophiles and subsequent hydrolysis of the resulting products furnished different novel fluorine-containing heterocyclic derivatives of streptocide, including fused heterocycles.

Key words: 4-(*N*-acetylamino)benzenesulfonamide, methyl trifluoropyruvate, 6-aminouracils, 6-aminothiouracils, *N*-substituted 3-aminocyclohexenones, *N*-substituted ureas, fluorine-containing dihydro-1*H*-pyrroles, hexahydro-1*H*-indoles, hexahydro-1*H*-pyrrolo[2,3-*d*]-pyrimidines, 2,5-dioxoimidazolidines, cyclocondensation.

Functionalization of biologically active substances (BAS) with fluorine-containing heterocycles is one of the fruitful trends in organic chemistry. In general, the introduction of fluorine-containing substituents into BAS does not influence their biological activities and, at the same time, impart the molecule with unique physicochemical properties, which in turn enhance the pharmacological parameters, and in some cases change them in a controlled fashion.[1—5] The progress in this field is associated mainly with the development of the affordable and effective methods for the introduction of the fluorine-containing, including heterocyclic, substituents in the BAS structure, which could be carried out using highly electrophilic fluorine-containing synthons. The study of the behavior of *N*-substituted imines of methyl trifluoropyruvate and hexafluoroacetone in cyclocondensations with 1,3-*C*,*N*-, 1,3-*C*,*O*- or 1,3-*N*,*N*-binucleophiles and estimation of the synthetic potential of these reactions for the synthesis of various trifluoromethyl-containing five- and six-membered heterocycles,[6—13] allowed us to develop an original approach to the modification of biologically active amides using fluorine-containing heterocycles. In the present paper, a strategy for the modification of streptocide with fluorine-containing five-membered heterocycles is presented.

Despite the advent of penicillin and other antibiotics, sulfonylamides have not lost their significance and are successfully used in therapy of infectious diseases. The currently used sulfonylamide pharmaceuticals differ substantially in the pharmacological parameters (absorption, accumulation in the blood and organs in bacteriostatic concentrations, overcoming the blood brain barrier, excretion time, *etc.*), which is largely due to the nature of the substituents at the nitrogen atom of the sulfamide group.[14] The variation of the substituents at this atom has been, and apparently will be, the main approach to the streptocide modification. From this viewpoint, we proposed a synthetic approach for the introduction of a variety of fluorine-containing five-membered heterocycles at the nitrogen atom of the sulfamide group that involved three-component reaction of 4-(*N*-acetylamino)-benzenesulfonamide with methyl trifluoropyruvate and 1,3-binucleophiles. This strategy may be regarded as an example of a general approach to the modification of biologically active amides with fluorine-containing heterocycles.

The synthesis of the fluorine-containing heterocyclic streptocide derivatives involved two steps: 1) *in situ* generation of 4-(*N*-acetylamino)benzenesulfonylimine of methyl pyruvate by sequential addition of pyridine, methyl trifluoropyruvate (**1**) and thionyl chloride to a solution of 4-(*N*-acetylamino)benzenesulfonamide (**2**) in DMF, the formation of imine **3** being confirmed by ^{19}F NMR spectroscopy (in the ^{19}F NMR spectra of the reaction mixtures, the signal for the trifluoromethyl group at δ 4.9 was observed in the range characteristic of the known methyl trifluoropyruvate imines[15]), 2) cyclocondensation of **3** with 1,3-*C*,*N*- or *N*,*N*-binucleophiles (Scheme 1). Me-

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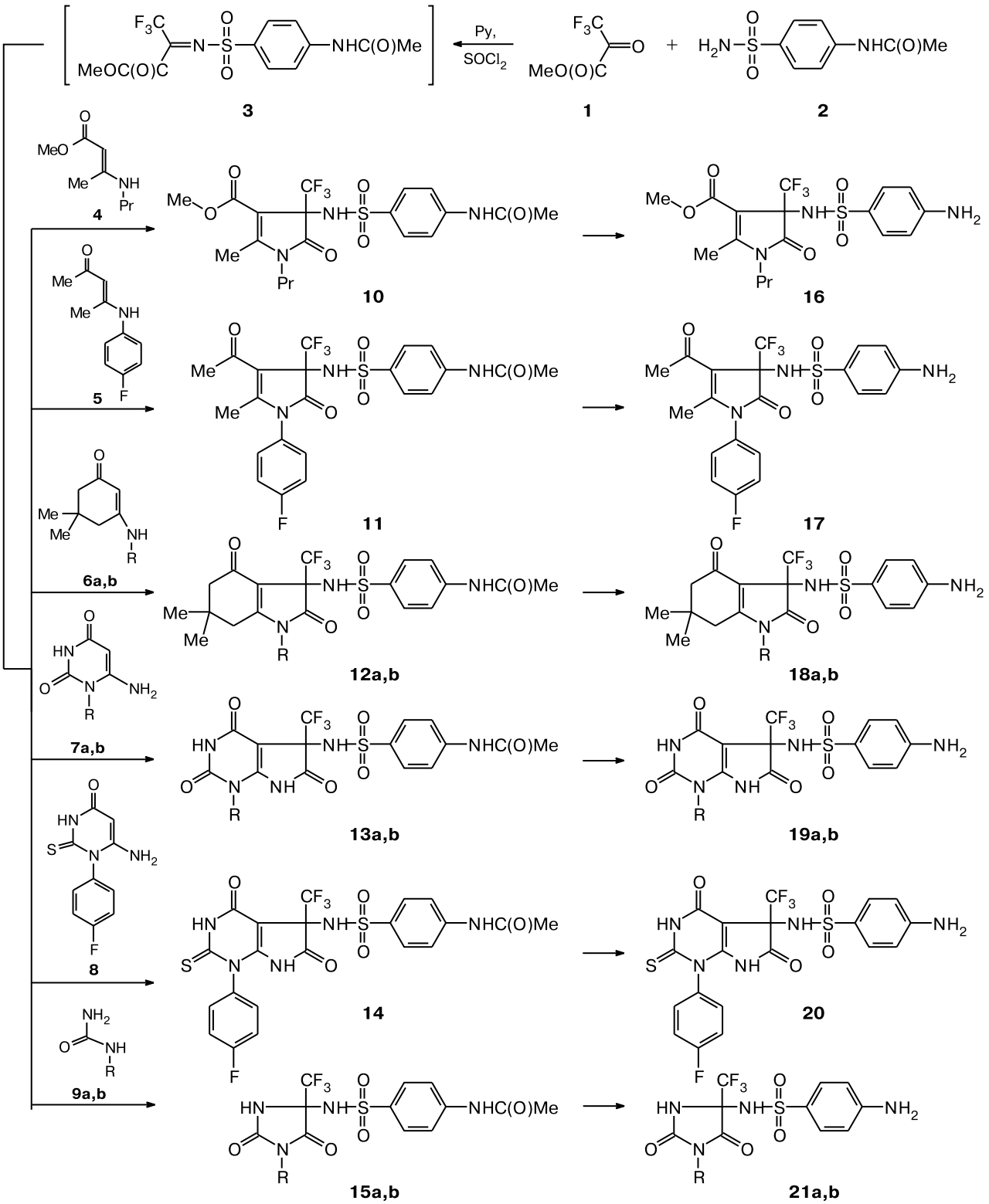
Scheme 1



6, **12**, **18**: R = Ph (**a**), 4-$FC_6H_4CH_2$ (**b**);
7, **13**, **19**: R = Me (**a**), 4-$MeOC_6H_4$ (**b**);
9, **15**, **21**: R = 3-ClC_6H_4 (**a**), 3,4-$(MeO)_2C_6H_3CH_2CH_2$ (**b**)

thyl 3-propylaminobyt-2-enoate (**4**), 4-(4-fluoroanilino)-pent-3-en-2-one (**5**), *N*-substituted 3-aminocyclohexenones **6a**,**b**, 6-aminouracils **7a**,**b** and **8**, *N*-substituted ureas **9a**,**b** were involved in the cyclocondensation with imine **3**. The reactions of **3** with 1,3-binucleophiles **4**—**9** were carried out in DMF at 90—100 °C for 2 h in the presence of catalytic amounts of Et_3N. All the reactions resulted in fluorine-containing heterocycles bearing 4-(*N*-acetylamino)phenylsulfonyl residue: the corresponding 4-trifluoromethyl-4,5-dihydro-1*H*-pyrroles **10** and **11**, 2,3,4,5,6,7-hexahydro-1*H*-indoles **12a,b**, 2,4,6-trioxo-5-trifluoromethyl-2,3,4,5,6,7-hexahydro-1*H*-pyrrolo[2,3-*d*]-pyrimidines **13a**,**b**, 4,6-dioxo-2-thioxo-5-trifuoromethyl-2,3,4,5,6,7-hexahydro-1*H*-pyrrolo[2,3-*d*]pyrimidine **14**, and 2,5-dioxo-4-trifluoromethylimidazolidines **15a**,**b**. The *N*-acetylated heterocyclic streptocide derivatives **10**, **11**, **12a**,**b**, **13a**,**b**, **14**, and **15a**,**b** underwent hydrolysis upon reflux in 10% hydrochloric acid for 1 h to give the corresponding trifluoromethyl heterocyclic derivatives **16**, **17**, **18a**,**b**, **19a**,**b**, **20**, and **21a**,**b** (Scheme 1, Table 1).

The data on antimicrobial and antifungal activities of compounds **16**, **17**, **18a,b**, **19b**, **20**, and **21a,b** against *Staphilloccus aureus*, *Salmonella enteritidis*, *Bacillus anthracis*, *Candida albicans*, and *E. coli*, which were obtained by the ´diffusion in agar´ method (Table 2), in several cases indicated significant selective increase in the activity, especially for **18a**, **19b**, and **21b**, relative to the parent structure, streptocide.

Thus, it was found that the three-component reaction of 4-(*N*-acetylanimo)benzenesulfamide with methyl trifluoropyruvate and 1,3-*C*,*N*- or 1,3-*N*,*N*-binucleophiles followed by hydrolysis of the cyclocondensation products resulted in novel fluorine-containing heterocyclic derivatives of streptocide. The introduction of the fluorine-containing heterocyclic substituent at the nitrogen atom

Table 1. Yields and physicochemical data for compounds **10**—**21**

Compound	Yield (%)	m.p. /°C	Molecular formula	Found / Calculated (%)		
				C	H	N
10	71	177—179	$C_{19}H_{22}F_3N_3O_6S$	47.69 47.80	4.81 4.64	8.59 8.80
11	78	194—196	$C_{22}H_{19}F_4N_3O_5S$	51.64 51.46	3.82 3.73	8.01 8.18
12a	69	196—198	$C_{25}H_{24}F_3N_3O_5S$	56.32 56.07	4.26 4.52	7.66 7.85
12b	85	241—243	$C_{26}H_{25}F_4N_3O_5S$	55.33 55.02	4.22 4.44	7.62 7.40
13a	81	237—239	$C_{16}H_{14}F_3N_5O_6S$	41.42 41.65	3.22 3.06	14.95 15.18
13b	77	254—256	$C_{22}H_{18}F_3N_5O_7S$	47.56 47.74	3.03 3.28	12.86 12.65
14	76	247—249	$C_{21}H_{15}F_4N_5O_5S_2$	45.49 45.24	2.88 2.71	12.78 12.56
15a	70	119—121	$C_{18}H_{14}ClF_3N_4O_5S$	44.32 44.05	2.69 2.87	11.59 11.41
15b	82	144—146	$C_{22}H_{23}F_3N_4O_7S$	48.12 48.33	4.02 4.26	10.42 10.29
16	86	142—144	$C_{20}H_{17}F_4N_3O_4S$	51.22 50.96	3.81 3.63	9.12 8.91
17	91	183—185	$C_{19}H_{13}F_4N_5O_4S_2$	44.06 44.27	2.36 2.54	13.42 13.59
18a	78	162—164	$C_{23}H_{22}F_3N_3O_4S$	55.77 55.98	4.72 4.49	8.44 8.51
18b	85	204—206	$C_{24}H_{23}F_4N_3O_4S$	54.66 54.85	4.19 4.41	7.85 8.00
19a	88	227—229	$C_{14}H_{12}F_3N_5O_5S$	40.33 40.10	3.06 2.88	16.49 16.70
19b	93	304—306	$C_{20}H_{16}F_3N_5O_6S$	47.14 46.97	3.38 3.15	13.52 13.69
20	78	221—223	$C_{19}H_{13}F_4N_5O_4S_2$	44.06 44.27	2.36 2.54	13.42 13.59
21a	71	178—180	$C_{16}H_{12}ClF_3N_4O_4S$	42.59 42.82	2.89 2.70	12.22 12.48
21b	85	138—140	$C_{20}H_{21}F_3N_4O_6S$	47.60 47.81	4.42 4.21	11.37 11.15

Table 2. Antimicrobial and antifungal activities of fluorine-containing *N*-hetaryl-4-aminobenzenesulfonamides **16**—**21**

Compound	*C* (%)	Zones of delayed growth/mm				
		S. aureus	*S. enteritidis*	*B. anthracis*	*Cand.*	*E. Coli*
Streptocide	1.0	51	58	11	11	38
	0.1	35	29	0	0	30
	0.01	22	18	0	0	20
16	1.0	0	0	12	13	0
	0.1	—	—	0	16	—
	0.01	—	—	—	25	—
17	1.0	0	0	0	13	0
	0.1	—	—	—	16	—
	0.01	—	—	—	25	—
18a	1.0	0	0	69	19	25
	0.1	—	—	19	12	20
	0.01	—	—	0	0	19
18b	1.0	11	11	12	17	12
	0.1	0	0	0	29	0
	0.01	0	0	0	30	0
19b	1.0	12	13	24	19	12
	0.1	11	15	16	12	11
	0.01	0	11	0	11	0
20	1.0	16	32	19	17	17
	0.1	12	16	13	11	15
	0.01	0	0	11	0	0
21a	1.0	18	18	17	27	17
	0.1	11	11	12	19	15
	0.01	0	0	0	0	0
21b	1.0	11	12	13	13	11
	0.1	0	0	0	34	0
	0.01	0	0	0	44	0

of the sulfamide group increased the antimicrobial and antifungal activity of the final compounds relative to the parent streptocide structure. This suggests that the developed strategy is a promising approach to the modification of the biologically active amides using fluorine-containing heterocycles.

Experimental

The ^{1}H and ^{19}F NMR spectra were recorded on a Bruker DPX 200 instrument at 200.13 MHz and 188.29 MHz relative to tetramethylsilane (internal standard) and CF_3COOH (external standard), respectively. Melting points were determined in open

Table 3. ^{1}H and ^{19}F NMR spectral data of compounds **10**—**21** in DMSO-d_6

Compound	^{1}H NMR (δ, *J*/Hz)	^{19}F NMR (δ)
10	0.98 (t, 3 H, Me, *J* = 7.4); 1.64 (m, 2 H, CH_2); 2.11 (s, 3 H, MeCO); 2.52 (s, 3 H, Me); 3.25 (s, 3 H, MeO); 3.54 (t, 2 H, CH_2, *J* = 7.5); 7.63 (AB-system, 4 H, C_{Ar}, *J* = 11.6); 8.87, 10.11 (both s, 1 H, NH)	5.11 s
11	1.91 (s, 3 H, Me); 2.11 (s, 3 H, MeCO); 2.30 (s, 3 H, Me); 7.27—7.38 (m, 4 H, CH_{Ar}); 7.73 (m, 4 H, CH_{Ar}); 9.44, 10.17 (both s, 1 H, NH)	5.36 s
12a	1.03, 1.10 (both s, 3 H, Me); 2.04 (s, 2 H, CH_2); 2.11 (s, 3 H, MeCO); 2.50 (AB-system, 2 H, CH_2, *J* = 17.8); 7.35 (d, 2 H, CH_{Ar}, *J* = 7.2); 7.56 (m, 3 H, CH_{Ar}); 7.72 (m, 4 H, CH_{Ar}); 9.28, 10.14 (both s, 1 H, NH)	4.86 s
12b	0.95, 1.08 (both s, 3 H, Me); 1.95 (s, 2 H, CH_2); 2.11 (s, 3 H, MeCO); 2.50 (AB-system, 2 H, CH_2, *J* = 17.9); 4.83 (s, 2 H, CH_2); 7.10 (m, 2 H, CH_{Ar}); 7.35 (m, 2 H, CH_{Ar}); 7.64 (m, 4 H, CH_{Ar}); 9.14, 10.12 (both s, 1 H, NH)	4.77 s
13a	2.10 (s, 3 H, MeCO); 3.34 (s, 3 H, MeN); 7.62 (AB-system, 4 H, CH_{Ar}, *J* = 9.1); 9.21 (s, 1 H, NH); 10.17 (s, 1 H, NH); 10.74 (s, 1 H, NH); 12.10 (s, 1 H, NH)	4.65 s
13b	2.12 (s, 3 H, MeCO); 3.89 (s, 3 H, MeO); 7.07 (m, 2 H, CH_{Ar}); 7.26 (m, 2 H, CH_{Ar}); 7.71 (AB-system, 4 H, CH_{Ar}, *J* = 8.8); 9.27 (s, 1 H, NH); 10.20 (s, 1 H, NH); 10.84 (s, 1 H, NH); 11.43 (s, 1 H, NH)	4.74 s
14	2.11 (s, 3 H, MeCO); 7.18—7.48 (m, 4 H, CH_{Ar}); 7.72 (AB-system, 4 H, CH_{Ar}, *J* = 14.2); 9.42, 10.19 (both s, 1 H, NH); 11.56 (s, 1 H, NH); 12.37 (s, 1 H, NH)	4.98 s
15a	2.12 (s, 3 H, MeCO); 7.29—7.57 (m, 4 H, CH_{Ar}); 7.77 (m, 4 H, CH_{Ar}); 9.88 (s, 1 H, NH); 10.08 (s, 1 H, NH); 10.22 (s, 1 H, NH)	0.20 s
15b	2.12 (s, 3 H, MeCO); 2.80 (m, 2 H, CH_2); 3.59 (m, 2 H, CH_2); 3.78 (s, 3 H, MeO); 3.81 (s, 3 H, MeO); 6.77 (m, 3 H, CH_{Ar}); 7.74 (AB-system, 4 H, CH_{Ar}, *J* = 6.5); 9.50 (s, 1 H, NH); 10.05 (s, 1 H, NH); 10.20 (s, 1 H, NH)	−0.16 s
16	0.97 (t, 3 H, Me, *J* = 7.2); 1.62 (m, 2 H, CH_2); 2.50 (s, 3 H, Me); 3.32 (s, 3 H, MeO); 3.51 (t, 2 H, CH_2, *J* = 7.2); 5.76 (s, 2 H, NH_2); 6.53 (d, 2 H, CH_{Ar}, *J* = 8.6); 7.28 (d, 2 H, CH_{Ar}, *J* = 8.6); 8.38 (s, 1 H, NH)	4.60 s
17	1.96 (s, 3 H, Me); 2.27 (s, 3 H, Me); 5.82 (s, 2 H, NH_2); 6.60 (d, 2 H, CH_{Ar}, *J* = 8.8); 7.30 (m, 4 H, CH_{Ar}); 7.43 (d, 2 H, CH_{Ar}, *J* = 8.8); 9.03 (s, 1 H, NH)	5.37 s
18a	0.99, 1.07 (both s, 3 H, Me); 2.04 (s, 2 H, CH_2); 2.31 (AB-system, 2 H, CH_2, *J* = 18.6); 5.65 (s, 2 H, NH_2); 6.56 (d, 2 H, CH_{Ar}, *J* = 9.4); 7.30 (d, 2 H, CH_{Ar}, *J* = 6.3); 7.40 (d, 2 H, CH_{Ar}, *J* = 9.4); 7.57 (m, 3 H, CH_{Ar}); 8.81 (s, 1 H, NH)	4.47 s
18b	0.96, 1.09 (both s, 3 H, Me); 1.99 (s, 2 H, CH_2); 2.44 (m, 2 H, CH_2); 4.80 (s, 2 H, CH_2); 5,71 (s, 2 H, NH_2); 7.10 (m, 2 H, CH_{Ar}); 6.55 (d, 2 H, CH_{Ar}, *J* = 9.8); 7.10 (t, 2 H, CH_{Ar}, *J* = 8.6); 7.35 (d, 2 H, CH_{Ar}, *J* = 8.4); 8.57 (s, 1 H, NH)	4.73 s
19a	3.34 (s, 3 H, MeN); 5.65 (s, 2 H, NH_2); 6.54 (d, 2 H, CH_{Ar}, *J* = 8.6); 7.30 (d, 2 H, CH_{Ar}, *J* = 8.6); 8.67 (s, 1 H, NH); 10.81 (s, 1 H, NH); 12.04 (s, 1 H, NH)	4.59 s
19b	3.89 (s, 3 H, MeO); 5.74 (s, 2 H, NH_2); 6.56 (d, 2 H, CH_{Ar}, *J* = 8.6); 7.04 (m, 2 H, CH_{Ar}); 7.22 (m, 2 H, CH_{Ar}); 7.41 (d, 2 H, CH_{Ar}, *J* = 8.6); 8.70 (s, 1 H, NH); 10.89 (s, 1 H, NH); 11.29 (s, 1 H, NH)	4.65 s
20	5.81 (s, 2 H, NH_2); 6.59; 7.41 (d, 2 H, CH_{Ar}, *J* = 8.9); 7.06—7.77 (m, 6 H, CH_{Ar}); 8.78, 11.04 (both s, 1 H, NH); 11.51 (s, 1 H, NH)	4.81 s
21a	5.87 (s, 2 H, NH_2); 6.62 (d, 2 H, CH_{Ar}, *J* = 8.8); 7.28—7.41 (m, 2 H, CH_{Ar}); 7.43—7.61 (m, 4 H, CH_{Ar}); 9.42 (s, 1 H, NH); 10.06 (s, 1 H, NH)	0.25 s
21b	2.79 (m, 2 H, CH_2); 3.56 (m, 2 H, CH_2); 3.78 (s, 3 H, MeO); 3.81 (s, 3 H, MeO); 5.82 (s, 2 H, NH_2); 6.63 (d, 2 H, CH_{Ar}, *J* = 8.6); 6.77 (m, 3 H, CH_{Ar}); 7.43 (d, 2 H, CH_{Ar}, *J* = 8.6); 9.13 (s, 1 H, NH); 9.53 (s, 1 H, NH)	−0.25 s

capillaries. The starting methyl 3-propylaminobut-2-enoate (**4**), 4-(4-fluoroanilino)pent-3-en-2-one (**5**), *N*-substituted 3-aminocyclohexenones **6a,b** were synthesized in accordance with the known procedure,[16] aminouracils **7a,b** and **8** were obtained by the known method,[17] *N*-substituted ureas **9a,b** and methyl trifluoropyruvate were used as purchased (Aldrich).

Methyl 4-[4-(*N*-Acetylamino)phenylsulfonylamino]-2-methyl-5-oxo-1-propyl-4-trifluoromethyl-4,5-dihydro-1*H*-pyrrole-3-carboxylate (10), *N*-[4-acetyl-1-(4-fluorophenyl)-5-methyl-2-oxo-3-trifluoromethyl-2,3-dihydro-1*H*-pyrrol-3-yl]-4-acetamidobenzenesulfonamide (11), *N*-(6,6-dimethyl-2,4-dioxo-1-phenyl-3-trifluoromethyl-2,3,4,5,6,7-hexahydro-1*H*-indol-3-yl)-4-acetamidobenzenesulfonamide (12a), *N*-[1-(4-fluorobenzyl)-6,6-dimethyl-2,4-dioxo-3-trifluoromethyl-2,3,4,5,6,7-hexahydro-1*H*-indol-3-yl]-4-acetamidobenzenesulfonamide (12b), *N*-[(1-methyl-2,4,6-trioxo-5-trifluoromethyl-2,3,4,5,6,7-hexahydro-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-4-acetamidobenzenesulfonamide (13a), *N*-[1-(4-methoxyphenyl)-2,4,6-trioxo-5-trifluoromethyl-2,3,4,5,6,7-hexahydro-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-4-acetamidobenzenesulfonamide (13b), *N*-[1-(4-fluorophenyl)-4,6-dioxo-5-trifluoromethyl-2-thioxo-2,3,4,5,6,7-hexahydro-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-4-acetamidobenzenesulfonamide (14), *N*-[1-(3-chlorophenyl)-2,5-dioxo-4-trifluoromethylimidazolidin-4-yl]-4-acetamidobenzenesulfonamide (15a), *N*-{1-[2-(3,4-dimethoxyphenyl)ethyl]-2,5-dioxo-4-trifluoromethylimidazolidin-4-yl}-4-acetamidobenzenesulfonamide (15b) (general procedure). To a stirred solution of 4-acetamidobenzenesulfonamide (**2**) (2.14 g, 0.01 mol) in DMF (20 mL), pyridine (1.56 g, 0.01 mol) and methyl trifluoropyruvate **1** (1.56 g, 0.01 mol) was added successively. The reaction mixture was stirred for 30 min, then $SOCl_2$ (1.19 g, 0.01 mol) was added, after 1 h of stirring the corresponding *C*,*N*- or *N*,*N*-binucleophile **4—9** (0.01 mol) and Et_3N (0.1 g) were added. The resulting mixture was stirred at 20 °C for 1 h and at 90—100 °C for 2 h, cooled to room temperature, and poured into water (50 mL). The precipitates that formed were filtered off and recrystallized from 50% EtOH. The yields, melting points, elemental analysis data, and the spectral data of compounds **10**, **11**, **12a,b**, **13a,b**, **14**, and **15a,b** are listed in Tables 1 and 3.

Methyl 4-(4-aminophenylsulfonylamino)-2-methyl-5-oxo-1-propyl-4-trifluorometyl-4,5-dihydro-1*H*-pyrrole-3-carboxylate (16), *N*-[4-acetyl-1-(4-fluorophenyl)-5-methyl-2-oxo-3-trifluoromethyl-2,3-dihydro-1*H*-pyrrol-3-yl]-4-aminobenzenesulfonamide (17), 4-amino-*N*-(6,6-dimethyl-2,4-dioxo-1-phenyl-3-trifluoromethyl-2,3,4,5,6,7-hexahydro-1*H*-indol-3-yl)benzenesulfonamide (18a), 4-amino-*N*-[1-(4-fluorobenzyl)-6,6-dimethyl-2,4-dioxo-3-trifluoromethyl-2,3,4,5,6,7-hexahydro-1*H*-indol-3-yl]benzenesulfonamide (18b), 4-amino-*N*-(1-methyl-2,4,6-trioxo-5-trifluoromethyl-2,3,4,5,6,7-hexahydro-1*H*-pyrrolo-[2,3-*d*]pyrimidin-5-yl)benzenesulfonamide (19a), 4-amino-*N*-[1-(4-methoxyphenyl)-2,4,6-trioxo-5-trifluoromethyl-2,3,4,5,6,7-hexahydro-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]benzenesulfonamide (19b), 4-amino-*N*-[1-(4-fluorophenyl)-4,6-dioxo-5-trifluoromethyl-2-thioxo-2,3,4,5,6,7-hexahydro-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]benzenesulfonamide (20), 4-amino-*N*-[1-(3-chlorophenyl)-2,5-dioxo-4-trifluoromethylimidazolidin-4-yl]benzenesulfonamide (21a), 4-amino-*N*-{1-[2-(3,4-dimethoxyphenyl)ethyl]-2,5-dioxo-4-trifluoromethylimidazolidin-4-yl}benzenesulfonamide (21b) (general procedure). *N*-Acetylated streptocide derivatives **10**, **11**, **12a**,**b**, **13a**,**b**, **14**, and **15a**,**b** (0.005 mol) were refluxed in 10% HCl for 1 h, cooled to room temperature and water (20 mL) was added. The reaction mixtures were neutralized with 10% aqueous ammonia, the precipitates that formed were filtered off and recrystallized from 50% EtOH. The yields, melting points, elemental analysis data, and the spectral data of compounds **16**, **17**, **18a**,**b**, **19a**,**b**, **20**, and **21a**,**b** are listed in Tables 1 and 3.

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